Total Synthesis of Macquarimicins Using an Intramolecular Diels–Alder Approach Inspired by a Biosynthetic Pathway

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Supporting Information

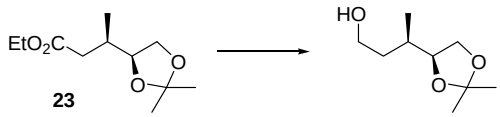
1. Experimental Section

General

Specific rotations were measured in a 10 mm cell. ^{1}H 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.

1.1. Synthesis of Substrates for Stille Coupling Reactions

(3*R*,4*S*)-4,5-(Isopropylidene)dioxy-3-methyl-1-pentanol[1]



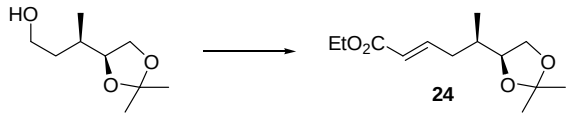
To a cooled (0 °C), stirred solution of **23**[2] (22.9 g, 106 mmol) in Et_2O (230 mL) was added $LiAlH_4$ (4.02 g, 106 mmol). The mixture was stirred at 0 °C for 1 h and $LiAlH_4$ (0.40 g, 11 mmol) was added. The mixture was stirred at 0 °C for 0.5 h and $LiAlH_4$ (0.80 g, 21 mmol) was added. The mixture was stirred at 0 °C for 1 h and then quenched with H_2O (40 mL). This was diluted with an aqueous solution (350 mL) of potassium sodium (+)-tartrate tetrahydrate (82.5 g) was added. The mixture was stirred vigorously for 2.5 h and the organic layer was separated. The aqueous layer 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 1:2) to provide 18.0 g (98%) of the primary alcohol as a colorless oil ; TLC, R_f 0.21 (EtOAc/hexane, 1:2); $[\alpha]^{26}_{D}$ +19.0 (*c* 1.70, $CHCl_3$); ^{1}H NMR (270 MHz) δ 0.99 (d, *J* = 6.6 Hz, 3H), 1.36, 1.42 (2s, 3H × 2), 1.43 (m, 1H), 1.66 (m, 1H), 1.84 (m, 1H), 1.95 (br s, 1H), 3.61–3.80 (m, 3H), 4.01 (m,

[1] This compound had been synthesized by Boeckman et al. in a different route. See: Boeckman, R. K., Jr., Charette, A. B.; Asberom, T.; Johnston, B. H. *J. Am. Chem. Soc.* **1991**, *113*, 5337–5353.

[2] Leonard, J.; Mohialdin, S.; Reed, D.; Ryan, G.; Swain, P. A. *Tetrahedron* **1995**, *51*, 12843–12858.

2H); ^{13}C NMR (75 MHz) δ 15.12, 25.28, 26.38, 32.70, 35.53, 60.30, 67.13, 79.62, 108.73; IR (neat) 3400, 2990 cm^{-1}; HRMS calcd for $C_8H_{15}O_3$ (M^+–CH_3) *m/z* 159.1021, found 159.1024.

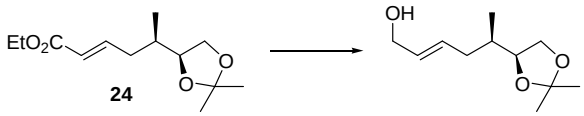
Ethyl (2*E*,5*R*,6*S*)-6,7-(isopropylidene)dioxy-5-methyl-2-heptenoate (24)



To a cooled (0°C), stirred solution of alcohol (18.0 g, 103 mmol) in CH_2Cl_2 (200 mL) was added Dess–Martin periodinane (52.4 g, 124 mmol). The mixture was stirred vigorously for 50 min and diluted with saturated aqueous $NaHCO_3$–10% aqueous $Na_2S_2O_3$ (1:1, 400 mL) and CH_2Cl_2 (200 mL) at 0 °C. The mixture was stirred for 40 min, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried and concentrated in vacuo to give the crude aldehyde, which was used in the next step without purification.

The following reaction was carried out under argon. To a cooled (0 °C), stirred suspension of NaH (60% in oil, 8.24 g, 206 mmol) in THF (200 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (51 mL, 260 mmol). The mixture was stirred for 1 h at room temperature, and a solution of the aldehyde obtained above in THF (20 mL) was added at 0 °C. The mixture was stirred for 2 h and quenched with saturated aqueous NH_4Cl. This was diluted with H_2O (400 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, 1:40) to provide 19.1 g (76%) of **24** as a colorless oil (0.55 g of the *Z*-isomer (2%) was separated from the *E*-isomer **24**); TLC, R_f 0.70 (EtOAc/hexane, 1:2); $[\alpha]^{23}_D$ +5.0 (*c* 1.58, $CHCl_3$); ^{1}H NMR (270 MHz) δ 0.98 (d, *J* = 6.6 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.35, 1.41 (2s, 3H × 2), 1.81 (m, 1H), 2.03 (m, 1H), 2.31 (m, 1H), 3.63 (m, 1H), 3.92–4.04 (m, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 5.85 (dt, *J* = 15.4, 1.5 Hz, 1H), 6.92 (ddd, *J* = 7.0, 8.1, 15.4 Hz, 1H); ^{13}C NMR (68 MHz) δ 14.22, 15.23, 25.28, 26.40, 35.56, 35.68, 60.21, 67.09, 79.13, 108.79, 122.96, 146.89, 166.36; IR (neat) 2990, 1715, 1650 cm^{-1}; HRMS calcd for $C_{13}H_{22}O_4$ (M^+) *m/z* 242.1518, found 242.1518.

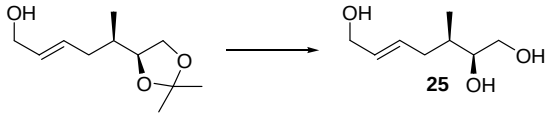
(2*E*,5*R*,6*S*)-6,7-(Isopropylidene)dioxy-5-methyl-2-hepten-1-ol



The following reaction was carried out under argon. To a cooled (–78 °C), stirred solution of **24** (19.1 g, 78.6

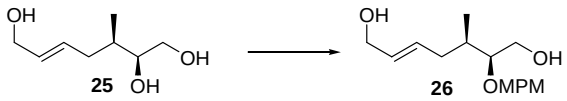
mmol) in CH_2Cl_2 (200 mL) was added Dibal-H (195 mL of 1.0 M in toluene, 195 mmol). The mixture was stirred at –78 °C for 45 min and quenched with H_2O. This was diluted with CH_2Cl_2 (10 mL), and then an aqueous solution (400 mL) of potassium sodium (+)-tartrate tetrahydrate (140 g) was added. The mixture was stirred vigorously for 2.5 h and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried and concentrated in vacuo to give crude the primary alcohol, which was used in the next step without purification. In a small-scale experiment, the pure product was obtained by column chromatography on silica gel (EtOAc/hexane, 1:4) as a colorless oil; TLC, R_f 0.29 (EtOAc/hexane, 1:2); $[\alpha]^{23}_D$ +8.2 (*c* 1.72, $CHCl_3$); ^{1}H NMR (270 MHz) δ 0.97 (d, *J* = 7.0 Hz, 3H), 1.35, 1.40 (2s, 3 H × 2), 1.69 (m, 1H), 1.80–1.93 (m, 2H), 2.15 (m, 1H), 3.62 (t, *J* = 7.3 Hz, 1H), 3.92 (dt, *J* = 7.3, 6.2 Hz, 1H), 4.00 (dd, *J* = 6.2, 7.3 Hz, 1H), 4.10 (m, 2H), 5.62–5.69 (m, 2H); ^{13}C NMR (68 MHz) δ 15.38, 25.43, 26.49, 35.62, 36.34, 63.44, 67.44, 79.59, 108.56, 130.36, 130.91; IR (neat) 3400, 2990 cm^{-1}; HRMS calcd for $C_{11}H_{20}O_3$ (M^+) *m/z* 200.1412, found 200.1401.

(2*S*,3*R*,5*E*)-3-Methyl-5-heptene-1,2,7-triol (25)



To a cooled (0 °C), stirred solution of the crude primary alcohol obtained above in MeOH–H_2O (1:1, 300 mL) was added Amberlyst 15 (3.15 g). The mixture was stirred at 50 °C for 12 h and then the resin was filtered off. The filtrate was concentrated in vacuo to give crude **25**, which was used in the next step without purification. In a small-scale experiment, pure **25** was obtained by column chromatography on silica gel (acetone/toluene, 1:3) as a colorless oil; TLC, R_f 0.22 (acetone/toluene, 1:1); $[\alpha]^{22}_D$ +0.80 (*c* 1.32, MeOH); ^{1}H NMR (270 MHz) δ 0.94 (d, *J* = 6.6 Hz, 3H), 1.68 (m, 1H), 1.78 (br s, 3H), 1.97 (m, 1H), 2.23 (m, 1H), 3.53–3.70 (m, 3H), 4.10–4.12 (m, 2H), 5.66–5.72 (m, 2H); ^{13}C NMR (68 MHz) δ 14.37, 35.56, 36.08, 63.58, 65.05, 74.81, 130.85, 130.94; IR (neat) 3350, 2930 cm^{-1}; HRMS calcd for $C_8H_{14}O_2$ (M^+–H_2O) *m/z* 142.0994, found 142.0993.

(2*E*,5*R*,6*S*)-6-[(4-Methoxyphenyl)methoxy]-5-methyl-2-heptene-1,7-diol (26)

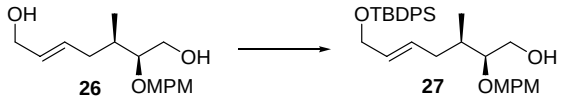


To a cooled (0 °C), stirred solution of the crude **25** obtained above in DMF (130 mL) were added

4-methoxybenzaldehyde dimethylacetal (16 mL, 94 mmol) and $TsOH \cdot H_2O$ (748 mg, 3.93 mmol). The mixture was stirred at 50 °C for 3 h under reduced pressure with aspirator and then 4-methoxybenzaldehyde dimethylacetal (2.7 mL, 16 mmol) was added. The mixture was stirred at 50 °C for 14 h under reduced pressure. This was diluted with saturated aqueous $NaHCO_3$ (400 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, 1:5 to 1:2.5) to provide 18.9 g of the 4-methoxybenzylidene acetal, which was used immediately in the next step.

The following reaction was carried out under argon. To a cooled (–78 °C), stirred solution of the acetal obtained above (18.9 g) in CH_2Cl_2 (200 mL) was added Dibal-H (202 mL of 1.0 M in toluene, 202 mmol). The mixture was stirred at –78 °C for 1.5 h and then Dibal-H (27 mL of 1.0 M in toluene, 27 mmol) was added. The mixture was stirred at –78 °C for 3 h and quenched with H_2O. This was diluted with CH_2Cl_2 (300 mL), and then an aqueous solution (500 mL) of potassium sodium (+)-tartrate tetrahydrate (163 g) was added. The mixture was stirred vigorously for 15 h and the organic layer was separated. The aqueous layer 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 (acetone/hexane, 1:4) to provide 15.6 g (71%, 4 steps from **24**) of **26** as a colorless oil; TLC, R_f 0.50 (acetone/toluene, 1:1); $[\alpha]^{22}_D$ +3.1 (*c* 1.50, $CHCl_3$); ^{1}H NMR (270 MHz) δ 0.94 (d, *J* = 6.2 Hz, 3H), 1.80–1.91 (m, 4H), 2.28 (m, 1H), 3.39 (m, 1H), 3.60 (dd, *J* = 6.2, 11.4 Hz, 1H), 3.67 (dd, *J* = 4.2, 11.4 Hz, 1H), 3.81 (s, 3H), 4.07 (m, 2H), 4.49, 4.56 (2d, *J* = 11.2 Hz, 1H × 2), 5.55–5.70 (m, 2H), 6.89 (m, 2H), 7.27 (m, 2H); ^{13}C NMR (68 MHz) δ 15.26, 34.32, 35.33, 55.26, 62.03, 63.55, 72.13, 82.82, 113.86 × 2, 129.35 × 2, 130.56, 130.65, 131.20, 159.24; IR (neat) 3350, 2940, 1615, 1515 cm^{-1}; HRMS calcd for $C_{16}H_{24}O_4$ (M^+) *m/z* 280.1675, found 280.1677.

(2*S*,3*R*,5*E*)-7-(*t*-Butyldiphenylsilyloxy)-2-[(4-methoxyphenyl)methoxy]-3-methyl-5-hepten-1-ol (27)

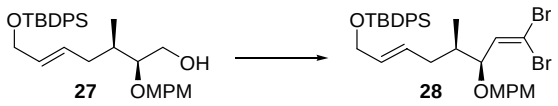


26 **27**

The following reaction was carried out under argon. To a cooled (–78 °C), stirred solution of **26** (1.31 g, 4.69 mmol) in CH_2Cl_2 (40 mL) were added Et_3N (1.1 mL, 8.0 mmol), TBDPSCl (1.0 mL, 4.0 mmol), and a solution of DMAP (57.3 mg, 0.469 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred while gradually wamred to –20 °C over 2 h and then quenched with saturated aqueous $NaHCO_3$. This was diluted with saturated aqueous $NaHCO_3$ (50 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, 1:7) to provide 1.77 g (73%) of **27** as a colorless oil along with 0.18 g of recovered **26** (13%); TLC, R_f 0.43 (EtOAc/hexane, 1:2); $[\alpha]^{21}_D$ +0.8 (*c* 1.89, $CHCl_3$); ^{1}H NMR (270 MHz) δ 0.94 (d, *J* = 6.6 Hz, 3H), 1.06 (s,

9H), 1.63 (br s, 1H), 1.85 (m, 2H), 2.27 (m, 1H), 3.39 (ddd, *J* = 4.0, 4.5, 6.3 Hz, 1H), 3.59 (dd, *J* = 6.3, 11.5 Hz, 1H), 3.67 (dd, *J* = 4.0, 11.5 Hz, 1H), 3.80 (s, 3H), 4.16 (d, *J* = 4.0 Hz, 2H), 4.47, 4.56 (2d, *J* = 11.0 Hz, 1H × 2), 5.49–5.65 (m, 2H), 6.88 (m, 2H), 7.33 (m, 2H), 7.42–7.44 (m, 6H), 7.65–7.71 (m, 4H); ^{13}C NMR (68 MHz) δ 15.02, 19.21, 26.81 × 3, 34.47, 35.33, 55.23, 62.17, 64.45, 72.22, 82.96, 113.86 × 2, 127.60 × 4, 129.18 × 2, 129.35 × 2, 129.55, 130.56, 130.62, 133.82 × 2, 135.52 × 4, 159.21; IR (neat) 3400, 2930, 1615, 1515 cm^{-1}; HRMS calcd for $C_{28}H_{33}O_4Si$ (M^+–*t*-Bu) *m/z* 461.2148, found 461.2139.

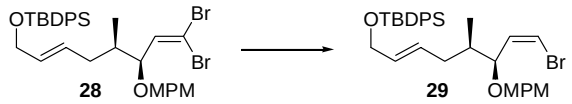
(3*S*,4*R*,6*E*)-1,1-Dibromo-8-(*t*-butyldiphenylsilyloxy)-3-[(4-methoxyphenyl)methoxy]-4-methyl-1,6-octadiene (28)



To a cooled (0°C), stirred solution of **27** (10.1 g, 19.5 mmol) in CH_2Cl_2 (200 mL) was added Dess–Martin periodinane (10.7 g, 25.3 mmol). The mixture was stirred vigorously for 1 h and Dess–Martin periodinane (2.06 g, 4.86 mmol) was added. The mixture was stirred for 1 h and diluted with saturated aqueous $NaHCO_3$–10% aqueous $Na_2S_2O_3$ (1:1, 400 mL) and CH_2Cl_2 (200 mL) at 0 °C. The mixture was stirred for 30 min, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried and concentrated in vacuo to give the crude aldehyde, which was used in the next step without further purification.

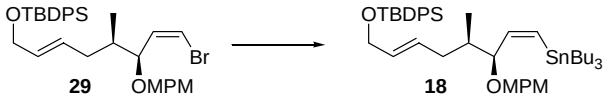
The following reaction was carried out under argon. To a cooled (0°C), stirred solution of CBr_4 (22.6 g, 68.1 mmol) in CH_2Cl_2 (100 mL) was added a solution of PPh_3 (35.8 g, 136 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred at 0 °C for 10 min and a solution of the crude aldehyde obtained above in CH_2Cl_2 (50 mL) was added at –78 °C. The mixture was stirred at –78 °C for 1 h and quenched with saturated aqueous $NaHCO_3$. This was diluted with saturated aqueous $NaHCO_3$ (500 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, 1:50) to provide 12.2 g (93%) of **28**. TLC, R_f 0.74 (EtOAc/hexane, 1:3); $[\alpha]^{26}_D$ –2.2 (*c* 1.48, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.95 (d, *J* = 6.6 Hz, 3H), 1.05 (s, 9 H), 1.74 (m, 1H), 1.87 (m, 1H), 2.22 (m, 1H), 3.78 (s, 3H), 3.91 (dd, *J* = 5.6, 8.5 Hz, 1H), 4.14 (d, *J* = 3.7 Hz, 2H), 4.29, 4.52 (2d, *J* = 11.5 Hz, 1H × 2), 5.48–5.66 (m, 2H), 6.44 (d, *J* = 8.5 Hz, 1H), 6.87 (m, 2H), 7.25 (m, 2H), 7.35–7.41 (m, 6H), 7.64–7.70 (m, 4H); ^{13}C NMR (75 MHz) δ 15.00, 19.21, 26.83 × 3, 35.40, 37.77, 55.22, 64.37, 70.65, 81.84, 91.21, 113.70 × 2, 127.60 × 4, 128.57, 129.44 × 2, 129.56 × 2, 130.28, 130.79, 133.82 × 2, 135.51 × 4, 139.13, 159.17; IR (neat) 3080, 2940, 1610, 1515 cm^{-1}; HRMS calcd for $C_{29}H_{31}O_3Br^{81}BrSi$ (M^+–*t*-Bu) *m/z* 615.0389, found 615.0404.

(1*Z*,3*S*,4*R*,6*E*)-1-Bromo-8-(*t*-butyldiphenylsilyloxy)-3-[(4-methoxyphenyl)methoxy]-4-methyl-1,6-octadiene (29)



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 $Pd(OAc)_2$ (163 mg, 0.724 mmol). The mixture was stirred for 40 min and then **28** (12.2 g, 18.1 mmol) in degassed toluene (80 mL) and Bu_3SnH (5.4 mL, 19.9 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 **29** as a colorless oil; TLC, R_f 0.68 (EtOAc/hexane, 1:3); $[\alpha]^{24}_D$ +3.00 (*c* 1.72, $CHCl_3$); ^{1}H 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 (2d, *J* = 11.5 Hz, 1H×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 × 3, 35.39, 37.78, 55.20, 64.45, 70.38, 79.28, 110.58, 113.63 × 2, 127.60 × 4, 128.98, 129.41 × 2, 129.53 × 2, 130.53, 130.68, 133.85 × 2, 135.11, 135.52 × 4, 159.04; IR (neat) 3080, 2940, 1615, 1515 cm^{-1}; HRMS calcd for $C_{29}H_{32}O_3Si^{81}Br$ (M^+–*t*-Bu) *m*/*z* 537.1284, found 537.1287.

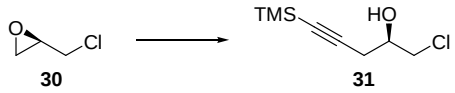
(1*Z*,3*S*,4*R*,6*E*)-8-(*t*-Butyldiphenylsilyloxy)-3-[(4-methoxyphenyl)methoxy]-4-methyl-1-tributylstannyl-1,6-octadiene (18)



The following reaction was carried out under argon. To a cooled (–78 °C), stirred solution of **29** (9.19 g, 15.5 mmol) in Et_2O (180 mL) was added *t*-BuLi (27 mL of 1.40 M in pentane, 37 mmol). The mixture was stirred at –78 °C for 1 h and then Bu_3SnCl (5.1 mL, 18.6 mmol) was added. The mixture was stirred at –78 °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 (Et_3N/hexane, 1:100 then EtOAc/hexane, 1:100) to provide 9.96 g (80%) of **18** as a colorless oil; TLC, R_f 0.77 (EtOAc/hexane, 1:5); $[\alpha]^{24}_D$ +5.23 (*c* 1.99, $CHCl_3$); ^{1}H 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 ×2), 5.51–5.68 (m, 2H), 6.15 (d, *J*= 13.1, $^2J_{Sn\text{-}H}$= 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 10.51×3, 13.68×3, 14.59, 19.20, 26.80×3, 27.34×3, 29.15×3, 36.32, 38.95, 55.24, 64.61, 69.73, 86.15, 113.65 ×2, 127.57×4, 128.78×2, 129.52×2, 129.95, 130.21, 131.25, 132.81, 133.85×2, 135.53×4, 148.49, 158.87; IR (neat) 3080, 2960, 1615, 1515 cm^{-1}; HRMS calcd for $C_{41}H_{59}O_3Si^{118}Sn$ (M^+–Bu) *m*/*z* 745.3252, found 745.3241.

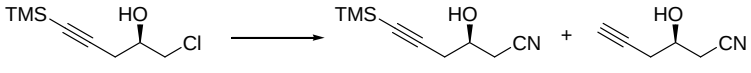
(2*R*)-1-Chloro-5-trimethylsilyl-4-pentyn-2-ol (31)[3]



30 **31**

The following reaction was carried out under argon. To a cooled (–78 °C), stirred solution of trimethylsilylacetylene (5.0 mL, 35 mmol) in THF (45 mL) was added *n*-BuLi (13 mL of 2.66 M in hexane, 35 mmol). The mixture was stirred at –78 °C for 10 min and then (*R*)-epichlorohydrin (**30**) (2.3 mL, 30 mmol) was added. The mixture was stirred at –78 °C for 10 min and then $BF_3{\cdot}Et_2O$ (4.9 mL, 35 mmol) was added. The mixture was stirred while gradually warmed to –30 °C over 2 h and at –30 °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 **31**, which was used in the next step without purification. In a small-scale experiment, pure **31** was obtained by column chromatography on silica gel (EtOAc/hexane, 1:20) as a colorless oil; TLC, R_f 0.60 (EtOAc/hexane, 1:2); $[\alpha]^{19}_D$ –10.7 (*c* 1.69, $CHCl_3$); ^{1}H 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 ×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



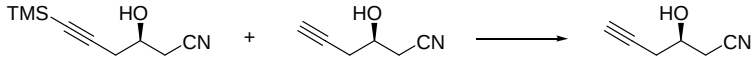
31

To a stirred solution of the crude **31** obtained above in DMSO–H_2O (10:1, 44 mL) were added KCN (2.88 g,

[3] Takano, S.; Kamikubo, T.; Sugihara, T.; Suzuki, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1993**, *4*, 201–204.

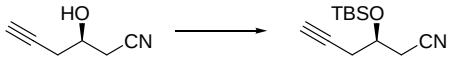
44.3 mmol) and NaI (13.2 g, 88.5 mmol). The mixture was stirred at 80 °C for 5 h and then diluted with EtOAc (250 mL). This was washed with saturated brine. The combined aqueous layers were extracted with EtOAc. The combined organic layers were dried and concentrated in vacuo to give crude mixture of 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); ^{1}H 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 ×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); $[\alpha]^{23}_D$ –22.0 (*c* 2.06, $CHCl_3$); ^{1}H 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 C_6H_8NO (M^++H) *m*/*z* 110.0606, found 110.0628.

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



To a cooled (0 °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 °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.

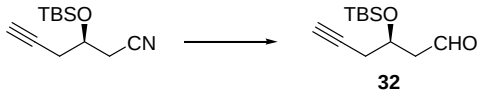
(3*R*)-3-(*t*-Butyldimethylsilyloxy)-5-hexynenitrile



To a cooled (0 °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 **30**) of the TBS ether as a colorless oil; TLC, R_f 0.67 (EtOAc/hexane, 1:2); $[\alpha]^{23}_D$ –16.7 (*c* 2.06, $CHCl_3$); ^{1}H NMR (270 MHz) δ 0.12, 0.15 (2s, 3H ×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 ×3, 27.11, 67.23, 71.67, 79.09, 117.35; IR (neat) 3300, 2930, 2250, 2120 cm^{-1}; HRMS calcd for $C_{12}H_{21}NOSi$ (M^+) *m*/*z* 223.1392, found 223.1373.

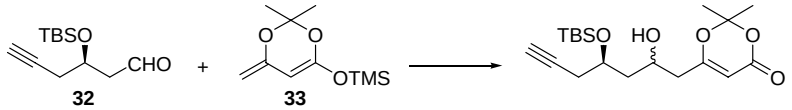
(3*R*)-3-(*t*-Butyldimethylsilyloxy)-5-hexynal (32)



32

The following reaction was carried out under argon. To a cooled (–52 °C), stirred solution of the nitrile (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 °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 **32** as a colorless oil; TLC, R_f 0.69 (EtOAc/hexane, 1:5); $[\alpha]^{21}_D$ –27.1 (*c* 1.11, $CHCl_3$); ^{1}H NMR (270 MHz) δ 0.08, 0.11 (2s, 3H ×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 ×3, 27.64, 50.19, 66.66, 71.10, 80.17, 201.23; IR (neat) 3300, 2930, 2120, 1730 cm^{-1}; HRMS calcd for $C_8H_{13}O_2Si$ (M^+–*t*-Bu) *m*/*z* 169.0685, found 169.0685.

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



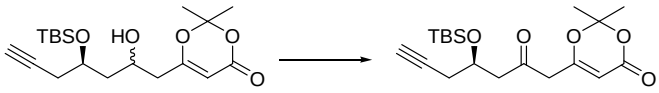
32 **33**

The following reaction was carried out under argon. To a cooled (–78 °C), stirred solution of **32** (5.56 g, 24.6 mmol) in CH_2Cl_2 (100 mL) were added $BF_3{\cdot}Et_2O$ (3.3 mL, 26 mmol) and **33**[4] (6.90 g, 32.2 mmol). The mixture was stirred at –78 °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

[4] Grunwell, J. R.; Karapides, A.; Wigal, C. T.; Heinzman, S. W.; Parlow, J.; Surso, J. A.; Clayton, L.; Fleitz, F. J.; Daffner, M.; Stevens, J. E. *J. Org. Chem.* **1991**, *56*, 91–95.

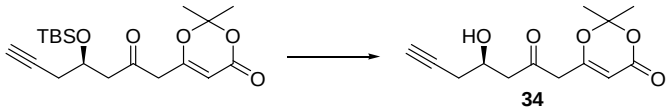
were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to provide 6.65 g (73%) of the secondary alcohol as a colorless oil; TLC, R_f 0.28 (EtOAc/hexane, 1:2); ^{1}H NMR (270 MHz) δ 0.12, 0.14, 0.15 (3s, total 6H) 0.90, 0.91 (2s, total 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 × 1/2), 3.20 (d, *J* = 1.1 Hz, 1H × 1/2), 4.00-4.30 (m, 2H), 5.34, 5.35 (2s, total 1H); IR (neat) 3450, 3300, 2930, 2120, 1735, 1715, 1635 cm^{-1}; HRMS calcd for $C_{18}H_{29}O_5Si$ (M^+–CH_3) *m*/*z* 353.1784, found 353.1810.

(4*R*)-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 (12.6 g, 34.1 mmol) in CH_2Cl_2 (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 $NaHCO_3$–20% aqueous $Na_2S_2O_3$ (1:1, 400 mL) and CH_2Cl_2 (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 CH_2Cl_2. 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); $[\alpha]^{21}_D$ –46.9 (*c* 1.56, $CHCl_3$); ^{1}H 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); ^{13}C 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 $C_{15}H_{21}O_5Si$ (M^+–*t*-Bu) *m*/*z* 309.1158, found 309.1169.

(4*R*)-1-(2,2-Dimethyl-1,3-dioxin-4-one-6-yl)-4-hydroxy-6-heptyn-2-one (34)

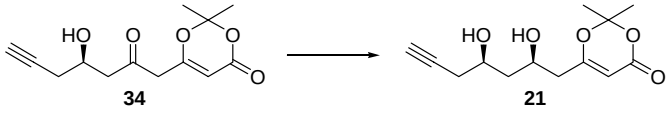


34

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 $NaHCO_3$. This was diluted with saturated aqueous $NaHCO_3$ (400 mL), and extracted with CH_2Cl_2. The

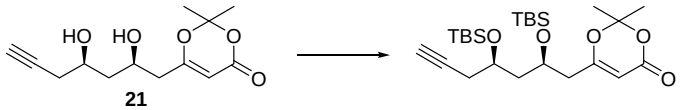
combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) to provide **34** (7.95 g, 92%, 2 steps) as a colorless oil; TLC, R_f 0.15 (EtOAc/hexane, 1:1); $[\alpha]^{22}_D$ –38.3 (*c* 1.21, $CHCl_3$); ^{1}H NMR (270 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); ^{13}C 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, 1725, 1715, 1640 cm^{-1}; HRMS calcd for $C_{13}H_{17}O_5$ (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-heptyne-2,4-diol (21)



The following reaction was carried out under argon. To a cooled (–78 °C), stirred solution of **34** (7.95 g, 31.5 mmol) in THF–MeOH (150 mL) was added Et_2BOMe (38 mL of 1.0 M solution in THF, 38 mmol). The mixture was stirred at –78 °C for 30 min and then $NaBH_4$ (1.70 g, 44.9 mmol) was added. The mixture was stirred at –78 °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 **21** as a colorless oil; TLC, R_f 0.10 (EtOAc/hexane, 1:1); $[\alpha]^{22}_D$ –14.8 (*c* 1.11, $CHCl_3$); ^{1}H 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 (br d, *J* = 10.6 Hz, 1H), 3.68 (br d, *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 $C_{13}H_{19}O_5$ (M^++H) *m*/*z* 255.1233, found 255.1234.

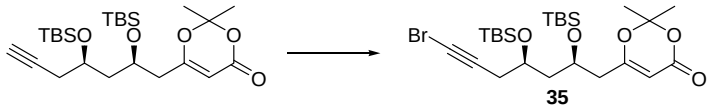
(2*R*,4*R*)-2,4-Bis(*t*-butyldimethylsilyloxy)-1-(2,2-dimethyl-1,3-dioxin-4-one-6-yl)-6-heptyne



To a cooled (0 °C), stirred solution of **21** (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); $[\alpha]^{22}_D$ –40.9 (*c* 1.58, $CHCl_3$); ^{1}H NMR (270 MHz) δ 0.05, 0.07, 0.09, 0.10 (4s, 3H ×4), 0.88, 0.90 (2s, 9H ×2), 1.69 ×2 (2s, 3H ×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 ×2, 17.94 ×2, 24.30, 25.74 ×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 $C_{21}H_{37}O_5Si_2$ (M^+– *t*-Bu) *m*/*z* 425.2180, found 425.2191.

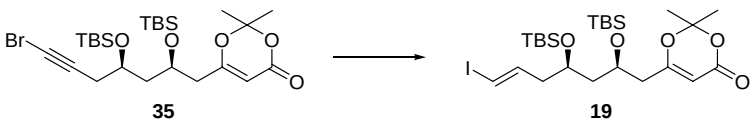
(2*R*,4*R*)-7-Bromo-2,4-bis(*t*-butyldimethylsilyloxy)-1-(2,2-dimethyl-1,3-dioxin-4-one-6-yl)-6-heptyne (35)



35

To a cooled (0 °C), stirred solution of the alkyne (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 **35** as a colorless oil; TLC, R_f 0.52 (EtOAc/toluene, 1:10); $[\alpha]^{21}_D$ –36.3 (*c* 1.38, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.05, 0.08 ×2, 0.10 (4s, 3H ×4), 0.88, 0.90 (2s, 9H ×2), 1.69, 1.70 (2s, 3H ×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 ×2, 24.28, 25.73 ×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 $C_{21}H_{36}{}^{79}BrO_5Si_2$ (M^+–*t*-Bu) *m*/*z* 503.1284, found 503.1288.

(2*R*,4*R*,6*E*)-2,4-Bis(*t*-butyldimethylsilyloxy)-1-(2,2-dimethyl-1,3-dioxin-4-one-6-yl)-7-iodo-6-heptene (19)

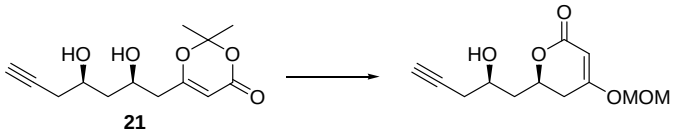


35 **19**

The following reaction was carried out under argon. To a stirred solution of **35** (9.72 g, 17.3 mmol) in argon-bubbled THF (200 mL) were added $Pd_2(dba)_3$ (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 °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 $Na_2S_2O_3$ (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 **19** as a colorless oil; TLC, R_f 0.29 (EtOAc/hexane, 1:5); $[\alpha]^{21}_D$ –16.4 (*c* 1.58, $CHCl_3$); ^{1}H NMR (270 MHz) δ 0.05, 0.06, 0.07 (3s, total 12H), 0.88, 0.90 (2s, 9H ×2), 1.58 (m, 1H), 1.68, 1.70 (2s, 3H ×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 ×2, –4.44, –4.21, 17.94 ×2, 24.42, 25.74 ×3, 25.80 ×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 $C_{21}H_{38}O_5Si_2I$ (M^+–*t*-Bu) *m*/*z* 553.1303, found 553.1297.

(6*R*)-6-[(2*R*)-2-Hydroxypent-4-yn-1-yl]-4-methoxymethoxy-5,6-dihydropyran-2-one

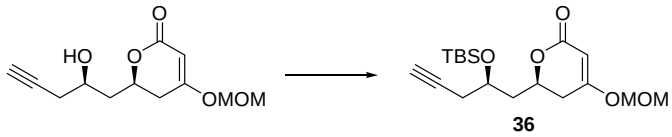


21

To a cooled (0 °C), stirred solution of **21** (155 mg, 0.608 mmol) in MeOH (4 mL) were added $Zn(NO_3)_2{\cdot}6H_2O$ (55.8 mg, 0.188 mmol) and K_2CO_3 (129 mg, 0.936 mmol). The mixture was stirred for 93 h and then K_2CO_3 (43.4 mg, 0.314 mmol) was added. The mixture was stirred for 12 h and then neutralized with Amberlite IR 120 [H^+] ion-exchange regin. The mixture was filtered through sintered grass filter and concentrated in vacuo to give the crude lactone which was used in the next step without purification.

To a cooled (–18 °C), stirred solution of the crude product obtained above in CH_2Cl_2 (5 mL) were added Et_3N (0.34 mL, 2.43 mmol) and chloromethyl methyl ether (0.092 mL, 1.22 mmol). The mixture was stirred for 30 min and then MeOH (1 mL) was added. The mixture was diluted with saturated aqueous $NaHCO_3$ (20 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, 1:1) to provide 143 mg (98%) of the MOM enol ether as a colorless oil; TLC, R_f 0.45 (acetone/toluene, 1:1); $[\alpha]^{26}_D$ –113 (*c* 2.09, $CHCl_3$); ^{1}H NMR (300 MHz) δ 1.95–2.13 (m, 3H), 2.42–2.49 (m, 3H), 2.63 (ddd, *J* = 1.5, 11.7, 17.1 Hz, 1H), 2.79 (br s, 1H), 3.48 (s, 3H), 4.05 (m, 1H), 4.66 (m, 1H), 5.09, 5.13 (2d, *J* = 6.1 Hz, 1H × 2), 5.32 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR (75 MHz) δ 27.19, 32.50, 40.14, 57.10, 66.77, 71.16, 74.15, 80.17, 92.82, 94.45, 166.77, 169.91; IR (neat) 3400, 3290, 2920, 2120, 1695, 1680, 1625 cm^{-1}; HRMS calcd for $C_{12}H_{17}O_5$ (M^++H) *m*/*z* 241.1076, found 241.1096.

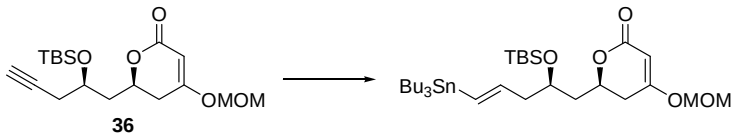
(6*R*)-6-[(2*R*)-2-*t*-Butyldimethylsilyloxypent-4-yne-1-yl]-4-methoxymethoxy-5,6-dihydropyran-2-one (36)



36

To a cooled (0 °C), stirred solution of the secondary alcohol (143 mg, 0.594 mmol) in DMF (1 mL) were added imidazole (165 mg, 2.41 mmol) and TBSCl (189 mg, 1.25 mmol). The mixture was stirred for 11 h and then diluted with saturated aqueous $NaHCO_3$ (20 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, 1:3) to provide 188 mg (89%) of **36** as a colorless oil; TLC, R_f 0.34 (EtOAc/hexane, 1:2); $[\alpha]^{26}_D$ –93.4 (*c* 1.59, $CHCl_3$); ^{1}H NMR (270 MHz) δ 0.08, 0.11 (2s, 3H × 2), 0.89 (s, 9H), 1.94–2.03 (m, 2H), 2.14 (m, 1H), 2.36–2.45 (m, 3H), 2.55 (ddd, *J* = 1.5, 11.4, 17.2 Hz, 1H), 3.47 (s, 3H), 4.08 (m, 1H), 4.60 (m, 1H), 5.08, 5.12 (2d, *J* = 6.2 Hz, 1H × 2), 5.32 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR (75 MHz) δ – 4.90, –4.57, 17.86, 25.63 × 3, 26.84, 32.83, 40.78, 56.96, 66.95, 70.68, 72.82, 80.42, 93.07, 94.32, 166.75, 169.45; IR (neat) 3300, 2930, 2120, 1715, 1635 cm^{-1}; HRMS calcd for $C_{14}H_{21}O_5Si$ (M^+–*t*-Bu) *m*/*zz* 297.1158, found 297.1162.

(6*R*)-6-[(2*R*,4*E*)-2-*t*-Butyldimethylsilyloxy-5-tributylstannylpent-4-en-1-yl]-4-methoxymethoxy-5,6-dihydropyran-2-one

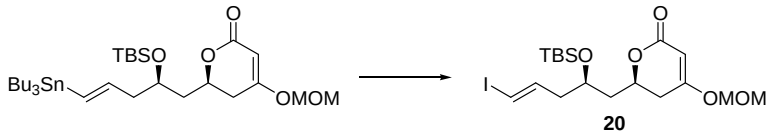


36

The following reaction was carried out under argon. To a stirred solution of **36** (764 mg, 2.91 mmol) in benzene (10 mL) were added Bu_3SnH (0.96 mL, 3.6 mmol) and azobisisobutyronitrile (14.6 mg, 0.0890 mmol). The mixture was refluxed for 46 h and then concentrated in vacuo to give the crude stannylalkene, which was used in the next step without purification. In a small-scale experiment, the pure stannylalkene was obtained by column chromatography on silica gel (EtOAc/hexane, 1:10) as a colorless oil TLC, R_f 0.67 (EtOAc/hexane, 1:2); $[\alpha]^{25}_D$ –48.8 (*c* 0.945, $CHCl_3$); ^{1}H NMR (270 MHz) δ 0.06, 0.08 (2s, 3H × 2), 0.74 –0.99 (m, 24H), 1.32 (m, 6H), 1.49 (m, 6H), 1.78 (dt, *J* = 13.9, 6.2 Hz, 1H), 2.04 (m, 1H), 2.26 –2.56 (m, 4H), 3.46 (s, 3H), 4.00 (m, 1H), 4.55 (m, 1H), 5.07, 5.11 (2d, *J* = 6.2 Hz, 1H×2), 5.32 (d, *J* = 1.5 Hz, 1H), 6.46 –6.56 (m, 2H); ^{13}C NMR (68 MHz) δ –4.64, –4.26, 9.36 × 3, 13.71 × 3, 18.00, 25.80 × 3, 27.27 × 3, 29.11 × 3, 33.06, 41.01, 45.41, 57.04, 68.19, 73.23, 93.21, 94.42, 131.71, 144.56, 167.08, 169.58; IR (neat) 2930, 1715,

1635 cm^{-1}; HRMS calcd for $C_{26}H_{49}O_5SiSn$ (M^+–Bu) *m*/*z* 589.2371, found 589.2373.

(6*R*)-6-[(2*R*,4*E*)-2-*t*-Butyldimethylsilyloxy-5-iodopent-4-enyl]-4-methoxymethoxy-5,6-dihydropyran-2-one (20)



20

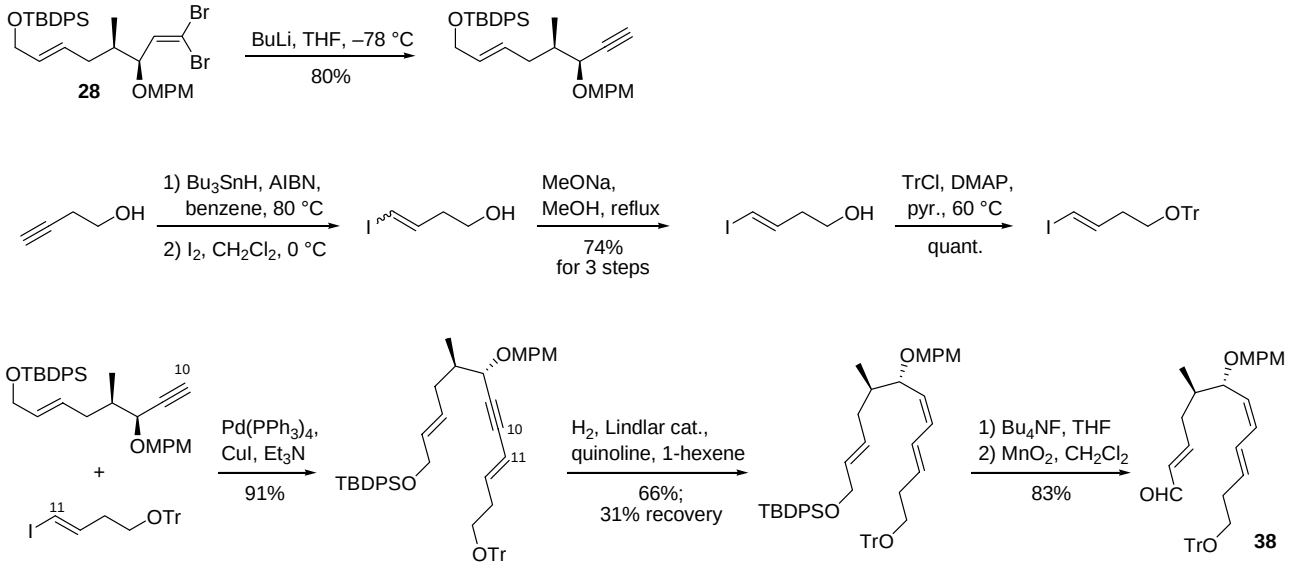
To a cooled (0 °C), stirred solution of the crude stannylalkene obtained above was dissolved in CH_2Cl_2 (10 mL) and stirred at 0 °C. To the solution I_2 (743 mg, 2.93 mmol) was added. The mixture was stirred for 30 min and then diluted with 10% aqueous $Na_2S_2O_3$ (40 mL). This was extracted with CH_2Cl_2. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) to provide 697 mg (81%) of **20** as a colorless oil; TLC, R_f 0.44 (EtOAc/hexane, 1:2); $[\alpha]^{24}_D$ –54.8 (*c* 1.95, $CHCl_3$); ^{1}H NMR (270 MHz) δ 0.06, 0.08 (2s, 3H × 2), 0.88 (s, 9H), 1.75 (m, 1H), 2.03 (m, 1H), 2.18–2.39 (m, 3H), 2.52 (ddd, *J* = 1.8, 11.4, 17.6 Hz, 1H), 3.47 (s, 3H), 4.01 (m, 1H), 4.52 (m, 1H), 5.08, 5.11 (2d, *J* = 6.2 Hz, 1H × 2), 5.32 (d, *J* = 1.8 Hz, 1H), 6.09 (d, *J* = 14.3 Hz, 1H), 6.52 (ddd, *J* = 7.0, 8.1, 14.3 Hz, 1H); ^{13}C NMR (75 MHz) δ –4.70, –4.41, 18.00, 25.77 × 3, 33.14, 41.41, 42.96, 57.13, 67.32, 72.68, 76.54, 93.21, 94.48, 142.31, 166.82, 169.50; IR (neat) 2930, 1715, 1635 cm^{-1}; HRMS calcd for $C_{18}H_{32}O_5ISi$ (M^++H) *m*/*z* 483.1064, found 483.1050.

1.2. Model Study on the Intramolecular Diels–Alder Reaction

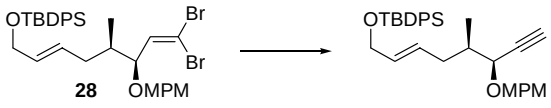
Synthesis of (*E*,*Z*,*E*)-1,6,8-nonatriene 38

The model IMDA substrate **38** was synthesized as shown in Scheme S1.

Scheme S1.



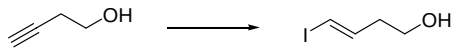
(3*S*,4*R*,6*E*)-8-(*t*-Butyldiphenylsilyloxy)-3-[(4-methoxyphenyl)methoxy]-4-methyl-6-octen-1-yne



The following reaction was carried out under argon. To a cooled (–78 °C), stirred solution of **28** (1.68 g, 2.50 mmol) in THF (30 mL) was added *n*-BuLi (3.1 mL of 2.46 M in hexane, 7.5 mmol). The mixture was stirred at –78 °C for 30 min and quenched with saturated aqueous NH_4Cl. This was diluted with saturated NH_4Cl (100 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, 1:100) to provide 1.02 g (80%) of the alkyne as a colorless oil; TLC, R_f 0.66 (EtOAc/hexane, 1:3); $[\alpha]^{26}_{D}$ –50.9 (*c* 1.62, $CHCl_3$); ^{1}H NMR (270 MHz) δ 0.99 (d, *J* = 7.0 Hz, 3H), 1.05 (s, 9H), 1.82 (m, 1H), 1.95 (m, 1H), 2.34 (m, 1H), 2.46 (d, *J* = 2.0 Hz, 1H), 3.78 (s, 3H), 3.93 (dd, *J* = 2.0, 4.8 Hz, 1H), 4.13 (d, *J* = 4.0 Hz, 2H), 4.39, 4.73 (2d, *J* = 11.4 Hz, 1H × 2), 5.47–5.65 (m, 2H), 6.85 (m, 2H), 7.28 (m, 2H), 7.36–7.42 (m, 6H), 7.64–7.70 (m, 4H); ^{13}C NMR (68

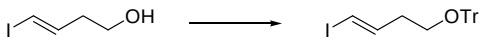
MHz) δ 15.09, 19.21, 26.84 × 3, 35.07, 38.24, 55.23, 64.45, 70.26, 71.67, 74.50, 82.07, 113.72 × 2, 127.60 × 4, 128.81, 129.55 × 2, 129.61 × 2, 130.02, 130.74, 133.87 × 2, 135.52 × 4, 159.19; IR (neat) 3290, 3070, 2930, 1615, 1515 cm^{-1}; HRMS calcd for $C_{33}H_{40}O_3Si$ (M^+) *m/z* 512.2747, found 512.2742.

(*E*)-4-Iodo-3-buten-1-ol[5]



A solution of Bu_3SnH (4.3 mL, 16 mmol), 2,2'-azobisisobutyronitrile (183 mg, 1.11 mmol), and 3-butyn-1-ol (0.74 g, 10.6 mmol) in benzene (5 mL) was stirred at 80 °C for 47 h. After being cooled to ambient temperature, the solution was diluted with CH_2Cl_2 (100 mL). To this solution was added I_2 (4.06 g, 16.0 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min and then washed with 20% aqueous $Na_2S_2O_3$ (50 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were concentrated in vacuo. The residue was dissolved in Et_2O (100 mL) and 10% aqueous KF (50 mL) was added. After being vigorously stirred for 3 h, insoluble precipitates formed were filtered off and washed with Et_2O. From the combined filtrate and washings, the organic layer was separated. The aqueous layer was extracted with Et_2O. The combined organic layers were dried and concentrated in vacuo. The residue was dissolved in MeOH (20 mL) and MeONa (16 mL of 1.0 M in MeOH, 16 mmol) was added. The mixture was heated under reflux for 23 h, and the solvent was removed by evaporation. The residue was diluted with saturated aqueous NH_4Cl (100 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, 1:5) to provide 1.56 g (74%) of the iodoalkene as a colorless oil; TLC, R_f 0.53 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz) δ 1.53 (br s, 1H), 2.33 (ddt, *J* = 1.4, 7.3, 6.2 Hz, 2H), 3.69 (t, *J* = 6.2 Hz, 2H), 6.17 (dt, *J* = 14.5 Hz, 1.4 Hz, 1H), 6.55 (dt, *J* = 14.5, 7.3 Hz, 1H); ^{13}C NMR (68 MHz) δ 39.05, 60.85, 77.23, 142.60; IR (neat) 3400, 2950, 1610 cm^{-1}; HRMS calcd for C_4H_7IO (M^+) *m/z* 197.9542, found 197.9544.

(*E*)-1-Iodo-4-(triphenylmethoxy)-1-butene

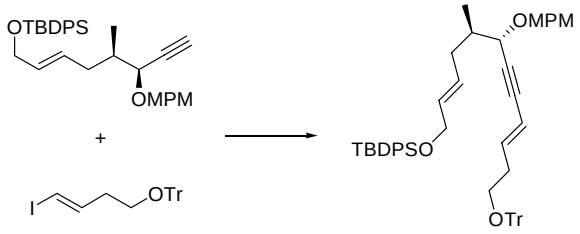


To a cooled (0 °C), stirred solution of the alcohol (323 mg, 1.63 mmol) in pyridine (15 mL) were added

[5] Chong, J. M.; Heuft, M. A. *Tetrahedron* **1999**, *55*, 14243–14250.

chlorotriphenylmethane (546 mg, 1.96 mmol) and DMAP (38.1 mg, 0.312 mmol). The mixture was stirred for 25 h and then chlorotriphenylmethane (95.3 mg, 0.342 mmol) and DMAP (41.6 mg, 0.342 mmol) were added. The mixture was stirred for 12 h at 60 °C and concentrated in vacuo. The residue was diluted with $NaHCO_3$ (50 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, 1:100) to provide 718 mg (100%) of the trityl ether as a colorless oil; TLC, R_f 0.48 (toluene/hexane, 1:2); ^{1}H NMR (300 MHz) δ 2.32 (dt, *J* = 7.1, 6.6 Hz, 2H), 3.11 (t, *J* = 6.6 Hz, 2H), 6.05 (d, *J* = 14.4 Hz, 1H), 6.55 (dt, *J* = 14.4, 7.1 Hz, 1H), 7.19–7.32 (m, 9H), 7.41–7.45 (m, 6H); ^{13}C NMR (75 MHz) δ 36.57, 62.13, 76.49, 86.54, 126.94 × 3, 127.76 × 6, 128.57 × 6, 143.31, 144.00 × 3; IR (neat) 3060, 2920, 1600 cm^{-1}; HRMS calcd for $C_{23}H_{21}IO$ (M^+) *m/z* 440.0637, found 440.0637.

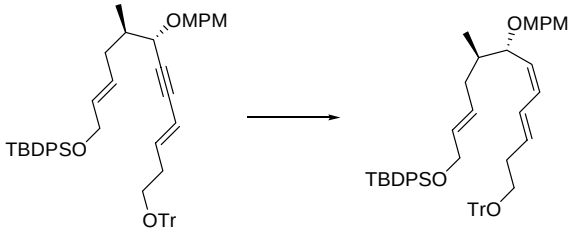
(2*E*,5*R*,6*S*,9*E*)-1-(*t*-Butyldiphenylsilyloxy)-6-[(4-methoxyphenyl)methoxy]-5-methyl-12-(triphenylmethoxy)-2,9-dodecadien-7-yne



The following reaction was carried out under argon. To a stirred solution of the alkyne (85.0 mg, 0.165 mmol) and the iodoalkene (87.2 mg, 0.198 mmol) in Et_3N (2 mL) were added $Pd(PPh_3)_4$ (9.6 mg, 8.3 μmol) and CuI (3.6 mg, 19 μmol). The mixture was stirred for 2.5 h and then diluted with saturated aqueous $NaHCO_3$ (10 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, 1:100) to provide 124 mg (91%) of the coupling product as a colorless oil; TLC, R_f 0.27 (EtOAc/hexane, 1:20); $[\alpha]^{25}_D$ –36.8 (*c* 1.73, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.98 (d, *J* = 6.6 Hz, 3H), 1.04 (s, 9H), 1.81 (m, 1H), 1.96 (m, 1H), 2.30–2.46 (m, 3H), 3.14 (t, *J* = 6.7 Hz, 2H), 3.76 (s, 3H), 4.02 (dd, *J* = 1.2, 4.6 Hz, 1H), 4.12 (d, *J* = 4.1 Hz, 2H), 4.39, 4.71 (2d, *J* = 11.5 Hz, 1H × 2), 5.47–5.65 (m, 3H), 6.18 (dt, *J* = 15.8, 7.1 Hz, 1H), 6.83 (m, 2H), 7.22–7.46 (m, 23H), 7.65–7.69 (m, 4H); ^{13}C NMR (75 MHz) δ 15.26, 19.20, 26.81 × 3, 33.80, 35.22, 38.49, 55.20, 62.74, 64.47, 70.17, 72.41, 85.16, 86.39, 86.56, 110.99, 113.63 × 2, 126.94 × 3, 127.58 × 4, 127.76 × 6, 128.62 × 6, 129.03, 129.56 × 4, 130.25, 130.56, 133.85 × 2, 135.51 × 4, 141.32, 144.13 × 3, 159.07; IR (neat) 3040, 2935, 1615, 1515 cm^{-1}; HRMS calcd for $C_{56}H_{60}O_4Si$ (M^+) *m/z* 824.4261, found 824.4244.

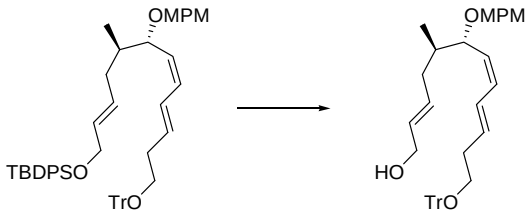
(2*E*,5*R*,6*S*,7*Z*,9*E*)-1-(*t*-Butyldiphenylsilyloxy)-6-[(4-methoxyphenyl)methoxy]-5-methyl-12-(triphenyl-

methoxy)-2,7,9-dodecatriene



A solution of the alkyne (58.9 mg, 0.0714 mmol) in 1-hexene (1 mL) was stirred under atmospheric hydrogen for 2 h in the presence of Lindlar catalyst (5.9 mg) and quinoline (0.003 mL, 0.03 mmol). The catalyst was removed by filtration through a Celite pad, washed with EtOAc and the combined filtrate and washings were concentrated in vacuo. The residue was purified by column chromatography on silica gel (toluene/hexane, 1:1) to provide 38.8 mg (66%) of the triene as a colorless oil. 18.3 mg (31%) of the starting material was recovered; TLC, R_f 0.28 (EtOAc/hexane, 1:20); $[\alpha]^{25}_{D}$ –4.0 (*c* 1.66, $CHCl_3$); ^{1}H NMR (270 MHz) δ 0.93 (d, *J* = 6.2 Hz, 3H), 1.04 (s, 9H), 1.66–1.79 (m, 2H), 2.24 (m, 1H), 2.37 (q, *J* = 6.6 Hz, 2H), 3.11 (t, *J* = 6.6 Hz, 2H), 3.77 (s, 3H), 3.99 (dd, *J* = 6.2, 9.5 Hz, 1H), 4.12 (d, *J* = 4.8 Hz, 2H), 4.20, 4.49 (2d, *J* = 11.7 Hz, 1H × 2), 5.27 (t, *J* = 9.5 Hz, 1H), 5.44–5.65 (m, 2H), 5.75 (m, 1H), 6.18–6.27 (m, 2H), 6.82 (m, 2H), 7.19–7.45 (m, 23H) 7.65–7.69 (m, 4H); ^{13}C NMR (75 MHz) δ 15.23, 19.20, 26.81 × 3, 33.57, 35.45, 38.46, 55.20, 63.17, 64.51, 69.56, 77.43, 86.43, 113.57 × 2, 126.89 × 3, 127.20, 127.58 × 4, 127.71 × 6, 128.64 × 6, 129.13, 129.31 × 2, 129.41, 129.52 × 2, 130.28, 131.02, 132.39, 133.31, 133.85 × 2, 135.50 × 4, 144.21 × 3, 158.92; IR (neat) 3020, 2930, 1615, 1515 cm^{-1}; HRMS calcd for $C_{56}H_{62}O_4Si$ (M^+) *m/z* 826.4417, found 826.4416.

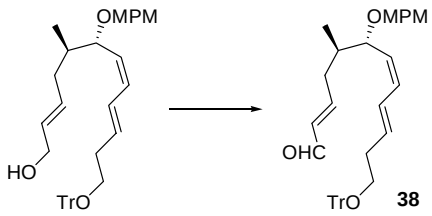
(2*E*,5*R*,6*S*,7*Z*,9*E*)-6-[(4-Methoxyphenyl)methoxy]-5-methyl-12-(triphenylmethoxy)-2,7,9-dodecatrien-1-ol



To a cooled (0 °C), stirred solution of the TBDPS ether (57.5 mg, 0.0695 mmol) in THF (1 mL) was added tetrabutylammonium fluoride (0.077 mL of 1.0 M solution in THF, 0.077 mmol). The mixture was stirred for 2.5 h. This was diluted with H_2O (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, 1:5) to provide 40.9 mg (quant.) of the primary alcohol as a colorless oil; TLC, R_f 0.37

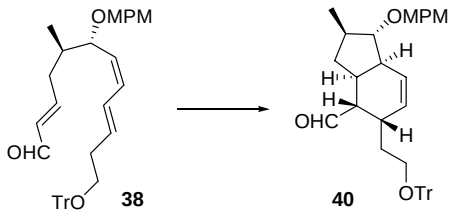
(EtOAc/hexane, 2:1); $[\alpha]^{24}_{D}$ –2.4 (*c* 1.67, $CHCl_3$); ^{1}H NMR (270 MHz) δ 0.93 (d, *J* = 6.6 Hz, 3H), 1.48 (br s, 1H), 1.64–1.86 (m, 2H), 2.24 (m, 1H), 2.41 (q, *J* = 6.5 Hz, 2H), 3.13 (t, *J* = 6.5 Hz, 2H), 3.78 (s, 3H), 3.96–4.02 (m, 3H), 4.19, 4.49 (2d, *J* = 11.7 Hz, 1H × 2), 5.26 (t, *J* = 9.5 Hz, 1H), 5.50–5.64 (m, 2H), 5.76 (m, 1H), 6.18–6.32 (m, 2H), 6.83 (m, 2H), 7.19–7.31 (m, 11H), 7.42–7.46 (m, 6H); ^{13}C NMR (68 MHz) δ 15.26, 33.60, 35.42, 38.30, 55.23, 63.15, 63.73, 69.54, 77.20, 86.45, 113.57 × 2, 126.91 × 3, 127.19, 127.74 × 6, 128.63 × 6, 128.95, 129.38 × 2, 130.48, 130.94, 131.45, 132.46, 133.41, 144.21 × 3, 158.96; IR (neat) 3400, 3030, 2930, 1615, 1515 cm^{-1}; HRMS calcd for $C_{40}H_{44}O_4$ (M^+) *m/z* 588.3240, found 588.3243.

(2*E*,5*R*,6*S*,7*Z*,9*E*)-6-[(4-Methoxyphenyl)methoxy]-5-methyl-12-(triphenylmethoxy)-2,7,9-dodecatrienal (38)



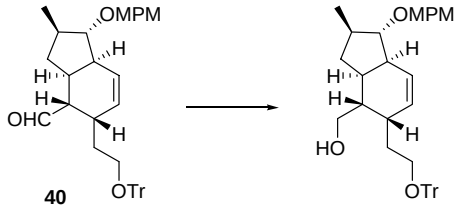
To a cooled (0 °C), stirred solution of the primary alcohol (38.1 mg, 0.0647 mmol) in CH_2Cl_2 (1 mL) was added MnO_2 (411 mg, 4.73 mmol). The mixture was stirred for 30 min, and the insoluble materials were filtered off and washed well with EtOH. The combined filtrate and washings were concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:15) to provide 31.4 mg (83%) of **38** as a colorless oil; TLC, R_f 0.30 (EtOAc/hexane, 1:5); $[\alpha]^{24}_{D}$ –7.9 (*c* 1.52, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.95 (d, *J* = 6.8 Hz, 3H), 1.88 (m, 1H), 2.07 (m, 1H), 2.41 (q, *J* = 6.6 Hz, 2H), 2.52 (m, 1H), 3.14 (t, *J* = 6.6 Hz, 2H), 3.79 (s, 3H), 4.04 (dd, *J* = 5.9, 9.5 Hz, 1H), 4.19, 4.50 (2d, *J* = 11.6 Hz, 1H × 2), 5.26 (t, *J* = 9.5 Hz, 1H), 5.80 (m, 1H), 6.03 (dd, *J* = 7.9, 15.5 Hz, 1H), 6.20–6.32 (m, 2H), 6.73 (m, 1H), 6.83 (m, 2H), 7.18–7.31 (m, 11H), 7.42–7.45 (m, 6H), 9.43 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (75 MHz) δ 15.45, 33.57, 36.04, 37.88, 55.24, 63.03, 69.60, 76.85, 86.46, 113.63 × 2, 126.81, 126.91 × 3, 127.71 × 6, 127.91, 128.62 × 6, 129.43 × 2, 130.58, 133.18, 134.06, 134.18, 144.18 × 3, 157.87, 159.05, 193.99; IR (neat) 3030, 2930, 1690, 1615, 1515 cm^{-1}; HRMS calcd for $C_{40}H_{42}O_4$ (M^+) *m/z* 586.3083, found 586.3066.

Intramolecular Diels–Alder reaction of 38: (1*S*,2*S*,3*S*,4*Z*,6*S*,7*S*,8*R*)-2-Formyl-7-[(4-methoxyphenyl)-methoxy]-8-methyl-3-[2-(triphenylmethoxy)ethyl]bicyclo[4.3.0]non-4-ene (40)



Compound **38** (29.5 mg, 0.0503 mmol) was dissolved in degassed toluene (5 mL), and a crystal of BHT was added. The solution was transferred into a 20 mL sealed tube equipped with a screwed stopper, and the tube was filled with argon. The tube was heated to 150 °C for 5 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, 1:15) to provide 22.1 mg (75%) of **40**; TLC, R_f 0.36 (EtOAc/hexane, 1:5); $[\alpha]^{24}_{D}$ +45.3 (*c* 0.945, $CHCl_3$); ^{1}H NMR (270 MHz) δ 1.05 (d, *J* = 5.8 Hz, 3H), 1.07 (m, 1H), 1.72 (m, 2H), 1.96 (m, 2H), 2.35 (m, 1H), 2.57 (m, 2H), 2.66 (m, 1H), 3.12–3.18 (m, 3H), 3.80 (s, 3H), 4.46, 4.54 (2d, *J* = 11.2 Hz, 1H × 2), 5.56 (m, 1H), 5.73 (m, 1H), 6.87 (m, 2H), 7.23–7.32 (m, 11H), 7.41–7.44 (m, 6H), 9.68 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (68 MHz) δ 18.28, 29.72, 32.42, 33.81, 36.71, 39.62, 43.42, 53.62, 55.23, 61.13, 72.02, 86.50, 92.06, 113.75 × 2, 126.93 × 3, 127.74 × 6, 128.58 × 6, 128.66, 129.21 × 2, 130.36, 130.65, 144.13 × 3, 159.15, 204.92; IR (neat) 3020, 2930, 1720, 1615, 1515 cm^{-1}; HRMS calcd for $C_{40}H_{42}O_4$ (M^+) *m/z* 586.3083, found 586.3083.

(1*R*,2*S*,3*S*,4*Z*,6*S*,7*S*,8*R*)-2-Hydroxymethyl-7-[(4-methoxyphenyl)methoxy]-8-methyl-3-[2-(triphenylmethoxy)ethyl]bicyclo[4.3.0]non-4-ene

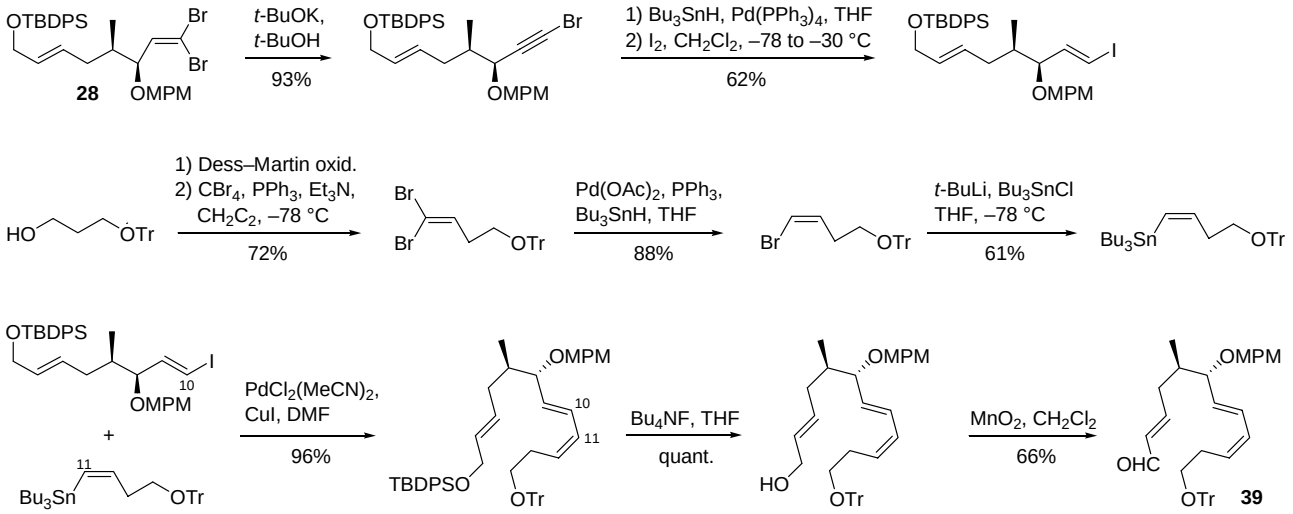


To a cooled (0 °C), stirred solution of **40** (17.8 mg, 0.0303 mmol) in EtOH (1 mL) was added $NaBH_4$ (1.1 mg, 0.029 mmol). The mixture was stirred for 2 h and then quenched with saturated aqueous NH_4Cl. This was diluted with H_2O (10 mL) and extracted with CH_2Cl_2. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) to provide 17.7 mg (99%) of the primary alcohol as a colorless oil; TLC, R_f 0.33 (EtOAc/hexane, 1:3); $[\alpha]^{24}_{D}$ +64.5 (*c* 0.830, $CHCl_3$); ^{1}H NMR (300 MHz) δ 1.04 (d, *J* = 6.6 Hz, 3H), 1.09 (m, 1H), 1.53 (m, 1H), 1.62 (m, 2H), 1.73 (m, 1H), 1.84 (m, 1H), 1.93 (m, 1H), 2.28 (m, 1H), 2.43 (m, 1H), 2.47 (m, 1H), 3.12 (dd, *J* = 6.1, 7.3 Hz, 1H), 3.18 (m, 2H), 3.54 (m, 2H), 3.79 (s, 3H), 4.47, 4.55 (2d, *J* = 11.2 Hz, 1H × 2), 5.48 (m,

1H), 5.66 (m, 1H), 6.87 (m, 2H), 7.20–7.32 (m, 11H), 7.43–7.46 (m, 6H); ^{13}C NMR (75 MHz) δ 18.37, 30.20, 31.52, 34.81, 36.85, 39.72, 42.65, 43.52, 55.24, 61.92, 62.82, 72.05, 86.56, 92.12, 113.73 × 2, 126.88 × 3, 127.73 × 6, 128.64 × 6, 129.23 × 2, 129.44, 129.74, 130.86, 144.26 × 3, 159.07; IR (neat) 3400, 3020, 2930, 1615, 1515 cm^{-1}; HRMS calcd for $C_{40}H_{44}O_4$ (M^+) *m/z* 588.3240, found 588.3233.

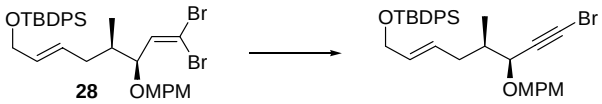
Synthesis of (*E*,*E*,*Z*)-1,6,8-nonatriene 39

The model IMDA substrate **39** was synthesized as shown in Scheme S2.



Scheme S2.

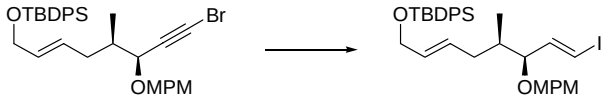
(3*S*,4*R*,6*E*)-1-Bromo-8-(*t*-butyldiphenylsilyloxy)-3-[(4-methoxyphenyl)methoxy]-4-methyl-6-octen-1-yne



To a stirred solution of **28** (608 mg, 0.904 mmol) in *t*-BuOH (10 mL) was added *t*-BuOK (203 mg, 1.81 mmol). The mixture was stirred for 15 h and then diluted with 0.1 M phosphate buffer (20 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, 1:30) to provide 497 mg (93%) of the bromoalkyne as a colorless oil; TLC, R_f 0.67 (EtOAc/hexane, 1:6); $[\alpha]^{26}_D$ –56.0 (*c* 1.95, $CHCl_3$); ^{1}H-NMR (300 MHz) δ 0.98 (d, *J* = 6.8 Hz, 3H), 1.05 (s, 9H), 1.80 (m, 1H), 1.95 (m, 1H), 2.31 (m, 1H), 3.78 (s, 3H), 3.94 (d, *J* = 4.9 Hz, 1H), 4.14 (m, 2H), 4.37, 4.71 (d, *J* = 11.5 Hz, 1H×2), 5.47–5.63 (m, 2H), 6.86 (m, 2H),

7.26 (m, 2H), 7.35–7.42 (m, 6H), 7.66–7.68 (m, 4H); ^{13}C-NMR (75 MHz) δ 15.15, 19.21, 26.83×3, 35.12, 38.39, 45.45, 55.24, 64.42, 70.49, 72.77, 78.74, 113.72 × 2, 127.60 × 4, 128.67, 129.56 × 2, 129.59 × 2, 129.89, 130.81, 133.87 × 2, 135.53 × 4, 159.22; IR (neat) 2930, 2200, 1615, 1515 cm^{-1}; HRMS calcd for $C_{29}H_{30}O_3SiBr$ (M^+–*t*-Bu) *m*/*z* 533.1148, found 533.1143.

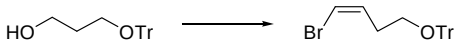
(1*E*,3*S*,4*R*,6*E*)-8-(*t*-Butyldiphenylsilyloxy)-1-iodo-3-[(4-methoxyphenyl)methoxy]-4-methyl-1,6-octadiene



The following reaction was carried out under argon. To a cooled (0 °C), stirred solution of the bromoalkyne (494 mg, 0.835 mmol) in THF (10 mL) was added $Pd(PPh_3)_4$ (48.0 mg, 0.0415 mmol). Then Bu_3SnH (0.77 mL, 2.89 mmol) was added dropwise. The mixture was stirred for 1 h and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:200) to provide 555 mg (72%) of a stannylalkene as a colorless oil.

The following reaction was carried out under argon. To a cooled (–78 °C), stirred solution of the stannylalkene obtained above (555 mg, 0.690 mmol) in CH_2Cl_2 (10 mL) was added iodine (193 mg, 0.759 mmol). The mixture was warmed to –25 °C over 1 h and then diluted with a mixture of saturated aqueous $NaHCO_3$ (7 mL) and 20% $Na_2S_2O_3$ (7 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, 1:150) to provide 398 mg (62%, 2 steps) of the (*E*)-iodoalkene as a colorless oil.; TLC, R_f 0.47 (EtOAc/hexane, 1:8); $[\alpha]^{24}_D$ –30.2 (*c* 1.96, $CHCl_3$); ^{1}H-NMR (270 MHz) δ 0.91 (d, *J* = 6.8 Hz, 3H), 1.05 (s, 9H), 1.67, (1H, m), 1.83, (m, 1H), 2.20 (m, 1H), 3.56 (dd, *J* = 5.4, 7.7 Hz, 1H), 3.79 (s, 3H), 4.14 (m, 2H), 4.24, 4.51 (2d, *J* = 11.5 Hz, 1H × 2), 5.46–5.62 (m, 2H), 6.24 (d, *J* = 14.5 Hz, 1H) , 6.48 (dd, *J* = 7.7, 14.5 Hz, 1H) , 6.86 (m, 2H), 7.23 (m, 2H), 7.34–7.42 (6H, m), 7.66–7.69 (4H, m); ^{13}C-NMR (75 MHz) δ 14.92, 19.23, 26.83×3, 35.40, 37.65, 55.25, 64.45, 70.35, 78.20, 84.40, 113.75 × 2, 127.60 × 4, 128.80, 129.26 × 2, 129.57 × 2, 130.36, 130.69, 133.85 × 2, 135.53 × 4, 145.79, 159.12; IR (neat) 2930, 1615, 1515 cm^{-1}; HRMS calcd for $C_{29}H_{32}O_3SiI$ (M^+–*t*-Bu) *m*/*z* 583.1166, found 583.1168.

(*Z*)-1-Bromo-4-triphenylmethoxy-1-butene

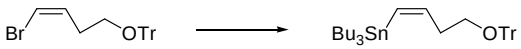


To a stirred solution of the known alcohol[6] (2.18 g, 6.85 mmol) in CH_2Cl_2 (40 mL) were added sodium bicarbonate (1.96 g, 23.8 mmol) and Dess–Martin periodinane (4.94 g, 11.7 mmol). The mixture was stirred for 2.5 h and then diluted with saturated aqueous $NaHCO_3$–20% aqueous $Na_2S_2O_3$ (1:1, 50 mL) at 0 °C. The mixture was stirred for 30 min and then the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried and concentrated in vacuo to give the crude aldehyde.

To a cooled (0 °C), stirred solution of CBr_4 (7.95 g, 24.0 mmol) in CH_2Cl_2 (10 mL) was added a solution of triphenylphosphine (12.6 g, 48.0 mmol) in CH_2Cl_2 (15 mL). The mixture was stirred for 30 min at 0 °C and then Et_3N (8.6 mL, 59.9 mmol) and a solution the crude aldehyde in CH_2Cl_2 were added at –78 °C. The mixture was stirred for 2.5 h at –78 °C and then quenched with saturated aqueous $NaHCO_3$. This was diluted with saturated aqueous $NaHCO_3$ (50 mL) and 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 (Et_3N/EtOAc/hexane, 1:2:100) to provide 2.32 g (72% for 2 steps) of the dibromoalkene as a colorless oil.

The following reaction was carried out under argon. To a stirred solution of PPh_3 (268 mg, 1.02 mmol) in degassed toluene (30 mL) was added $Pd(OAc)_2$ (57.0 mg, 0.254 mmol). The mixture was stirred for 30 min and then the dibromoalkene (2.32 g, 4.92 mmol) in degassed toluene (20 mL) and Bu_3SnH (2.3 mL, 8.4 mmol) were added. The mixture was stirred for 4 h and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (Et_3N/hexane, 1:100) to provide 1.70 g (88%) of the (*Z*)-bromoalkene as a colorless oil; TLC, R_f 0.42 (EtOAc/hexane, 1:16); ^{1}H-NMR (300 MHz) δ 2.52 (q, *J* = 6.3 Hz, 2H), 3.15 (t, *J* = 6.3 Hz, 2H), 6.17–6.25 (m, 2H), 7.21–7.33 (m, 9H), 7.43–7.46 (m, 6H); ^{13}C-NMR (68 MHz) δ 30.78, 61.82, 86.56, 109.12, 126.93 × 3, 127.77 × 6, 128.66 × 6, 131.94, 144.15 × 3; IR (neat) 3060, 2930, 1610, 1600 cm^{-1}; HRMS calcd for $C_{23}H_{21}OBr$ (M^+) *m*/*z* 392.0776, found 392.0778.

(*Z*)-1-Tributylstannanyl-4-triphenylmethoxy-1-butene

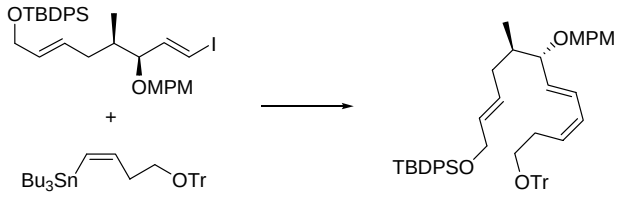


The following reaction was carried out under argon. To a cooled (–78 °C), stirred solution of (*Z*)-bromoalkene (294 mg, 0.747 mmol) in Et_2O (6 mL) was added *t*-BuLi (1.3 mL of 1.40 M in pentane, 1.9 mmol). The mixture was stirred at –78 °C for 1 h and then Bu_3SnCl (0.26 mL, 0.97 mmol) was added. The mixture was stirred at –78 °C for 3 h and then quenched with 0.1 M phosphate buffer. This was diluted with EtOAc (10 mL), and washed with brine. The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (Et_3N/hexane, 1:100) to provide 274 mg (61%) of the (*Z*)-stannylalkene as a colorless oil; TLC, R_f 0.63 (EtOAc/hexane, 1:16); ^{1}H-NMR (300 MHz) δ 0.84–0.92 (m, 15H), 1.28 (m, 6H), 1.48 (m, 6H), 2.38 (q, *J* = 6.8 Hz, 2H), 3.09 (t, *J* = 6.8 Hz, 2H), 5.89 (d, *J* = 12.6 Hz,

[6] Bertolini, G.; Casagrande, C.; Norcini, G.; Santangelo, F. *Synth. Commun.* **1994**, *24*, 1833–1845.

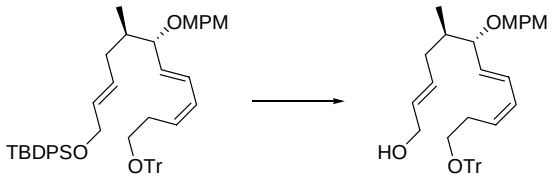
$^2J_{Sn\text{-}H}$= 70.8 Hz, 1H), 6.54 (dt, *J* = 6.8, 12.6 Hz, 1H), 7.20–7.31 (m, 9H), 7.43–7.46 (m, 6H); ^{13}C-NMR (68 MHz) δ 10.19×3, 13.71×3, 27.30×3, 29.17×3, 37.46, 63.47, 86.36, 126.82×3, 127.68×6, 128.69×6, 130.22, 144.30×3, 145.36; IR (neat) 2920, 1600 cm^{-1}; HRMS calcd for $C_{35}H_{48}OSn$ (M^+) *m*/*z* 604.2727, found 604.2722.

(2*E*,5*R*,6*S*,7*E*,9*Z*)-1-(*t*-Butyldiphenylsilyloxy)-6-[(4-methoxyphenyl)methoxy]-5-methyl-12-triphenylmethoxy-2,7,9-dodecatriene



The following reaction was carried out under argon. To a stirred solution of the iodide (119 mg, 0.186 mmol) and the stannane (173 mg, 0.292 mmol) in degassed DMF (5 mL) were added $PdCl_2(MeCN)_2$ (4.8 mg, 0.019 mmol) and CuI (35.3 mg, 0.186 mmol). The mixture was stirred for 20 h and then diluted with saturated aqueous $NaHCO_3$ (10 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 (Et_2O/hexane, 1:70) to provide 145 mg (96%) of the triene as a colorless oil; TLC, R_f 0.38 (EtOAc/hexane, 1:8); $[\alpha]^{26}_D$ –5.2 (*c* 1.27, $CHCl_3$); ^{1}H-NMR (300 MHz) δ 0.91 (d, *J* = 6.6 Hz, 3H), 1.04 (s, 9H), 1.66 (m, 1H), 1.80 (m, 1H), 2.23 (m, 1H), 2.50 (q, *J* = 6.8 Hz, 2H), 3.12 (t, *J* = 6.8 Hz, 2H), 3.61 (dd, *J* = 5.6, 7.8 Hz, 1H), 3.78 (s, 3H), 4.14 (m, 2H), 4.22, 4.49 (2d, *J* = 11.5 Hz, 1H × 2), 5.45–5.64 (m, 4H), 6.11 (t, *J* = 11.1 Hz, 1H), 6.43 (dd, *J* = 11.1, 15.4 Hz, 1H), 6.84 (m, 2H), 7.18–7.46 (m, 23H), 7.66–7.69 (m, 4H); ^{13}C-NMR (68 MHz) δ 15.09, 19.21, 26.81×3, 28.74, 35.68, 38.41, 55.20, 63.15, 64.50, 69.83, 82.93, 86.45, 113.63 × 2, 126.88 × 3, 127.57 × 4, 127.71 × 6, 128.37 × 2, 128.63 × 6, 129.21 × 2, 129.46 × 2, 129.53 × 2, 130.27, 130.99, 133.15, 133.85 × 2, 135.52 × 4, 144.24 × 3, 158.93; IR (neat) 2930, 1610, 1515 cm^{-1}; HRMS calcd for $C_{52}H_{53}O_4Si$ (M^+–*t*-Bu) *m*/*z* 769.3713, found 769.3709.

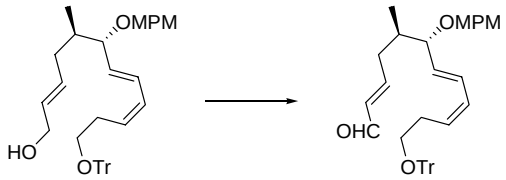
(2*E*,5*R*,6*S*,7*E*,9*Z*)-6-[(4-Methoxyphenyl)methoxy]-5-methyl-12-triphenylmethoxy-2,7,9-dodecatriene-1-ol



To a cooled (0 °C), stirred solution of the TBDPS ether (151 mg, 0.185 mmol) in THF (3 mL) was added

Bu_4NF (0.096 mL of 1.0 M solution in THF, 0.096 mmol) and the mixture was stirred for 5 h. Then Bu_4NF (0.027 mL of 1.0 M solution in THF, 0.027 mmol) was added and stirred for 14 h. The reaction mixture was diluted with brine (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 (Et_3N/EtOAc/hexane, 1:25:75) to provide 105 mg (quant.) of the primary alcohol as a colorless oil; TLC, R_f 0.59 (EtOAc/hexane, 1:1); $[\alpha]^{23}_D$ –9.8 (*c* 0.965, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.92 (d, *J* = 6.8 Hz, 3H), 1.70–1.82 (m, 2H), 2.24 (m, 1H), 2.51 (q, *J* = 6.9 Hz, 2H), 3.14 (t, *J* = 6.9 Hz, 2H), 3.62 (dd, *J* = 5.4, 7.8 Hz, 1H), 3.79 (s, 3H), 4.04–4.06 (m, 2H), 4.22, 4.50 (2d, *J* = 11.5 Hz, 1H × 2), 5.45–5.65 (m, 4H), 6.11 (t, *J* = 10.9 Hz, 1H), 6.44 (dd, *J* = 10.9, 15.1 Hz, 1H), 6.85 (m, 2H), 7.19–7.31 (m, 11H), 7.43–7.46 (m, 6H); ^{13}C NMR (68 MHz) δ 15.15, 28.74, 35.65, 38.27, 55.23, 63.15, 63.75, 69.77, 82.67, 86.47, 113.63 × 2, 126.88 × 3, 127.71 × 6, 128.55 × 2, 128.63 × 6, 129.27 × 2, 129.41, 130.39, 130.94, 131.60, 132.92, 144.21 × 3, 158.96; IR (neat) 3400, 2930, 1610, 1515 cm^{-1}; HRMS calcd for $C_{40}H_{44}O_4$ (M^+) *m/z* 588.3240, found 588.3239.

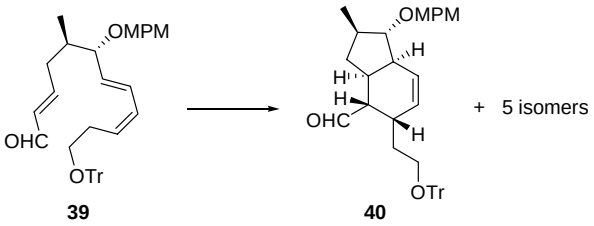
(2*E*,5*R*,6*S*,7*E*,9*Z*)-6-[(4-Methoxyphenyl)methoxy]-5-methyl-12-triphenylmethoxy-2,7,9-dodecatrienal (39)



39

To a cooled (0 °C), stirred solution of the primary alcohol (85.6 mg, 0.145 mmol) in CH_2Cl_2 (1.5 mL) was added MnO_2 (728 mg, 8.37 mmol). The mixture was stirred for 1 h, and the insoluble materials were filtered off and washed well with EtOH. The combined filtrate and washings were concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:100) to provide 56.7 mg (66%) of **39** as a colorless oil; TLC, R_f 0.80 (EtOAc/hexane, 1:1); $[\alpha]^{23}_D$ –15 (*c* 0.38, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.94 (d, *J* = 6.8 Hz, 3H), 1.89 (m, 1H), 2.09 (m, 1H), 2.48–2.55 (m, 3H), 3.14 (t, *J* = 6.6 Hz, 2H), 3.66 (dd, *J* = 5.3, 8.2 Hz, 1H), 3.80 (s, 3H), 4.21, 4.51 (2d, *J* = 11.5 Hz, 1H × 2), 5.49–5.63 (m, 2H), 6.00–6.15 (m, 2H), 6.48 (dd, *J* = 11.4, 15.2 Hz, 1H), 6.75 (dt, *J* = 6.8, 15.2 Hz, 1H), 6.86 (m, 2H), 7.19–7.30 (m, 11H), 7.43–7.46 (m, 6H), 9.45 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (68 MHz) δ 15.35, 28.77, 36.20, 37.87, 55.26, 63.09, 69.83, 82.33, 86.50, 113.72 × 2, 126.91 × 3, 127.74 × 6, 128.63 × 6, 129.18 × 3, 129.35 × 2, 130.56, 131.86, 134.05, 144.21 × 3, 157.89, 159.10, 194.00; IR (neat) 2940, 1695, 1615, 1515 cm^{-1}; HRMS calcd for $C_{40}H_{42}O_4$ (M^+) *m/z* 586.3083, found 586.3085.

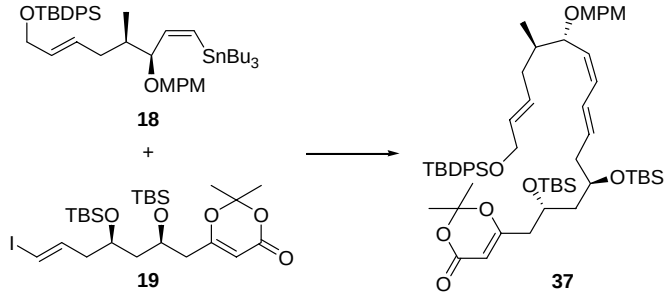
Intramolecular Diels–Alder reaction of 39



Compound **39** (56.2 mg, 0.0959 mmol) was dissolved in degassed toluene (5 mL), and a crystal of BHT was added. The solution was transferred into a 20 mL sealed tube equipped with a screwed stopper, and the tube was filled with argon. The tube was heated to 185 °C for 255 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, 1:30) to provide 39.9 mg (71%) of partly purified mixtures of cycloadducts (1:1:1:0.1:0.1:0.1). The ^{1}H NMR analysis of the mixtures revealed that one of the major cycloadducts is **40**.

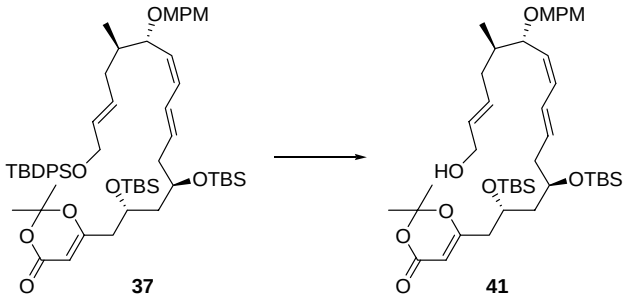
1.3. Synthesis and Examination of IMDA Substrates **14**–**17**

(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 (37)



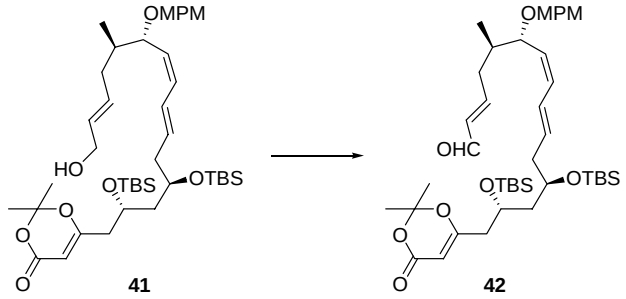
The following reaction was carried out under argon. To a stirred solution of **18** (1.69 g, 2.10 mmol) and **19** (1.06 g, 1.74 mmol) in degassed DMSO-THF (1:1, 40 mL) was added CuCl (254 mg, 2.57 mmol). Then a solution of $Pd(PPh_3)_4$ (101 mg, 0.0877 mmol) in degassed THF (3 mL) was added. The mixture was stirred for 1 h and then $Pd(PPh_3)_4$ (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 **37** as a colorless oil; TLC, R_f 0.57 (EtOAc/hexane, 1:3); $[\alpha]^{21}_D$ –25.9 (*c* 1.36, $CHCl_3$); ^{1}H-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); ^{13}C-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 $C_{55}H_{83}O_7Si_3$ (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 (41)



To a cooled (0 °C), stirred solution of **37** (1.68 g, 1.68 mmol) in MeOH (35 mL) was added NH_4F (351 mg, 9.48 mmol). The mixture was stirred for 14 h and then NH_4F (35.5 mg, 0.958 mmol) was added. The mixture was stirred for 10 h and 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, 1:8 to 1:3) to provide 1.20 g (94%) of **41** as a colorless oil, and 28.8 mg (2%) of **37** was recovered; TLC, R_f 0.53 (EtOAc/hexane, 1:1); $[\alpha]^{20}_D$ –22.8 (*c* 1.17, $CHCl_3$); ^{1}H-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); ^{13}C-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 $C_{39}H_{64}O_7Si_2$ (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)-6-[(4-methoxyphenyl)methoxy]-5-methyl-2,7,9-pentadecatrienal (42)

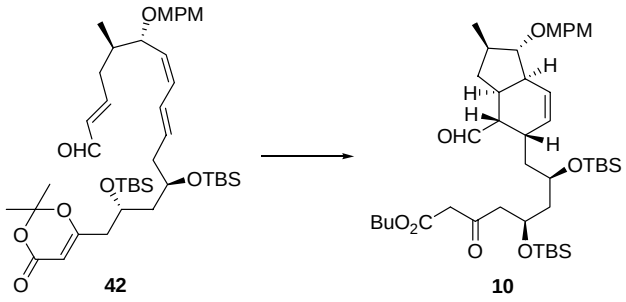


To a cooled (0 °C), stirred solution of **41** (55.6 mg, 0.0732 mmol) in CH_2Cl_2 (1 mL) was added MnO_2 (278 mg, 3.20 mmol). The mixture was stirred for 30 min, and the insoluble materials were filtered off and washed well with CH_2Cl_2. The combined filtrate and washings were concentrated in vacuo. The residue was purified

by column chromatography on silica gel (EtOAc/hexane, 1:4) to provide 49.5 mg (89 %) of **42** as a colorless oil; TLC, R_f 0.55 (EtOAc/hexane, 1:2); $[\alpha]^{23}_D$ –37.6 (*c* 1.47, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.05, 0.07 (2s, total 12H), 0.87, 0.90 (2s, 9H × 2), 0.97 (d, *J* = 6.6 Hz, 3H), 1.54–1.83 (m, 8H), 1.90 (m, 1H), 2.11 (m, 1H), 2.20–2.36 (m, 3H), 2.42 (dd, *J* = 4.3, 13.8 Hz, 1H), 2.55 (m, 1H), 3.77–3.86 (m, 4H), 4.05–4.14 (m, 2H), 4.21, 4.51 (2d, *J* = 11.7 Hz, 1H × 2), 5.26–5.33 (m, 2H), 5.72 (dt, *J* = 7.6, 13.6 Hz, 1H), 6.06 (dd, *J* = 7.9, 15.5 Hz, 1H), 6.13–6.17 (m, 2H), 6.78 (dt, *J* = 7.7, 15.5 Hz, 1H), 6.87 (m, 2H), 7.22 (m, 2H), 9.46 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (75 MHz) δ –4.72, –4.61, –4.46, –4.13, 15.35, 17.85, 17.93, 24.31, 25.68 × 3, 25.78 × 4, 35.94, 37.87, 41.09, 41.70, 44.86, 55.17, 66.59, 68.86, 69.58, 76.82, 95.56, 106.26, 113.62 × 2, 127.65, 128.27, 129.29 × 2, 130.51, 132.80, 134.03 × 2, 157.65, 159.03, 160.86, 168.97, 193.79; IR (neat) 2930, 1730, 1695, 1620, 1515 cm^{-1}; HRMS calcd for $C_{38}H_{59}O_8Si_2$ (M^+– *t*-Bu) *m*/*z* 699.3748, found 699.3734.

Intramolecular Diels–Alder rection of 42:

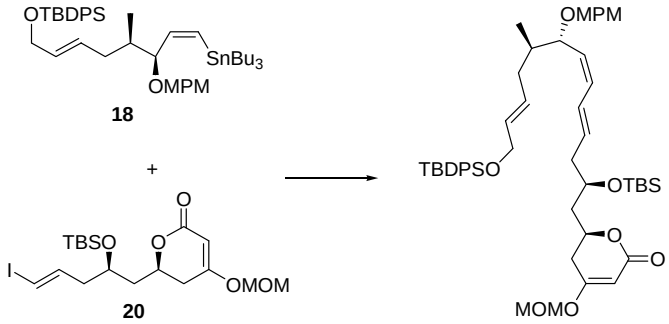
(1*S*,2*S*,3*S*,4*Z*,6*S*,7*S*,8*R*)-2-Formyl-7-[(4-methoxyphenyl)methoxy]-8-methyl-3-[(2*R*,4*R*)-7-butoxy-carbonyl-2,4-bis(*t*-butyldimethylsilyloxy)-6-oxoheptyl]bicyclo[4.3.0]non-4-ene (10)



The compound **42** (50.0 mg, 0.0660 mmol) was dissolved in degassed 1-butanol (3 mL), and a crystal of BHT was added. The solution was transferred into a 20 mL sealed tube equipped with a screwed stopper, and the tube was filled with argon. The tube was heated to 150 °C for 6 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, 1:20 to 1:8) to provide 33.5 mg (66%) of **10** as a colorless oil; TLC, R_f 0.44 (EtOAc/hexane, 1:5); $[\alpha]^{24}_D$ –43.0 (*c* 1.26, $CHCl_3$); ^{1}H NMR (300 MHz, keto/enol = 3:1) δ 0.03, 0.06, 0.06 (3s, total 12H), 0.88 (s, 18H), 0.93 (t, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 6.0 Hz, 3H), 1.09 (m, 1H), 1.34–1.50 (m, 3H), 1.53–1.75 (m, 5H), 1.93–2.07 (m, 2H), 2.31 (d, *J* = 6.0 Hz, 2H × 1/4, enol form), 2.41 (m, 1H), 2.61–2.76 (m, 3H + 2H × 3/4, keto form), 3.16 (m, 1H), 3.45 (s, 2H × 3/4, keto form), 3.80, (s, 3H), 3.88 (m, 1H), 4.07 (m, 1H × 1/4, enol form), 4.13 (t, *J* = 6.6 Hz, 2H), 4.20 (m, 1H × 3/4, keto form), 4.47, 4.56 (2d, *J* = 11.3 Hz, 1H × 2), 4.99 (s, 1H × 1/4, enol form), 5.73 (br d, *J* = 10.2 Hz, 1H), 5.81 (br d, *J* = 10.2 Hz, 1H), 6.88 (m, 2H), 7.27 (m, 2H), 9.72 (d, *J* = 2.1 Hz, 1H), 12.04 (s, 1H × 1/4, enol form); ^{13}C NMR (75 MHz, keto + enol form) δ –4.57, –4.51, –4.48, –4.10, 13.64, 17.88, 17.95, 18.34, 19.01, 25.81 × 3, 25.84 × 3, 28.75, 29.67 30.48, 30.66 (enol), 33.93, 36.80, 39.59, 43.56, 43.84 (enol), 45.68, 50.42, 50.76, 54.56, 54.71 (enol), 55.25, 63.84 (enol), 65.21, 65.98, 66.85, 72.10, 91.46 (enol), 92.22, 113.77 × 2, 128.60, 129.21× 2, 130.63,

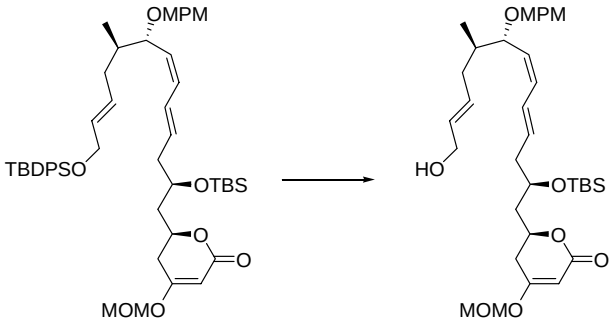
130.71, 159.15, 167.01, 172.54 (enol), 175.04 (enol), 201.31, 204.83; IR (neat) 2950, 1720, 1615, 1515 cm^{-1}; HRMS calcd for $C_{43}H_{72}O_8Si_2$ (M^+) *m*/*z* 772.4766, found 772.4749.

(2*E*,5*R*,6*S*,7*Z*,9*E*,12*R*)-12-(*t*-Butyldimethysilyloxy)-1-(*t*-butyldiphenylsilyloxy)-13-[(6*R*)-4-methoxy-methoxy-5,6-dihydropyran-2-one-6-yl]-6-[(4-methoxyphenyl)methoxy]-5-methyl-2,7,9-tridecatriene



The following reaction was carried out under argon. To a stirred solution of **18** (991.1 mg, 1.23 mmol) and **20** (396.6 mg, 0.822 mmol) in degassed DMSO (15 mL) were added CuCl (122 mg, 1.23 mmol) and $PdCl_2(MeCN)_2$ (21.3 mg, 0.0822 mmol). The mixture was stirred for 10 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, concentrated in vacuo, and filtered through a short silica-gel column to give the crude triene, which was used in the next step without purification. In a small-scale experiment, the pure triene was obtained by column chromatography on silica gel (EtOAc/hexane, 1:2) as a colorless oil; TLC, R_f 0.69 (acetone/toluene, 1:5); $[\alpha]^{23}_D$ –45.3 (*c* 1.24, $CHCl_3$); ^{1}H NMR (270 MHz) δ 0.05, 0.06 (2s, 3H × 2), 0.88 (s, 9H), 0.94 (d, *J* = 6.6 Hz, 3H), 1.04 (s, 9H), 1.65–1.84 (m, 3H), 2.03 (m, 1H), 2.21–2.39 (m, 4H), 2.51 (ddd, *J* = 1.5, 11.4, 17.0 Hz, 1H), 3.44 (s, 3H), 3.79 (s, 3H), 3.95–4.05 (m, 2H), 4.14 (m, 2H), 4.22, 4.49 (2d, *J* = 11.7 Hz, 1H × 2), 4.55 (m, 1H), 5.05, 5.09 (2d, *J* = 6.2 Hz, 1H × 2), 5.26–5.33 (m, 2H), 5.47–5.76 (m, 3H), 6.18–6.32 (m, 2H), 6.86 (m, 2H), 7.24 (m, 2H), 7.33–7.45 (m, 6H), 7.66–7.70 (m, 4H); ^{13}C NMR (68 MHz) δ –4.64, –4.29, 15.17, 18.00, 19.21, 25.80 × 3, 26.84 × 3, 33.09, 35.45, 38.47, 40.23, 41.55, 55.23, 57.04, 64.53, 68.22, 69.66, 72.97, 77.75, 93.24, 94.42, 113.63 × 2, 127.60 × 4, 128.23, 129.24 × 2, 129.47, 129.53 × 3, 130.27, 131.05, 131.97, 132.15, 133.87 × 2, 135.52 × 4, 158.96, 166.90, 169.50; IR (neat) 2930, 1715, 1610, 1515 cm^{-1}; HRMS calcd for $C_{47}H_{63}O_8Si_2$ (M^+–*t*-Bu) *m*/*z* 811.4061, found 811.4062.

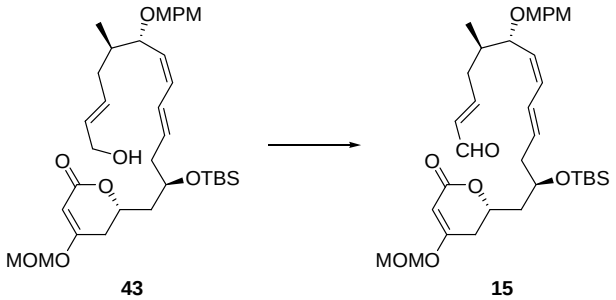
(2*E*,5*R*,6*S*,7*Z*,9*E*,12*R*)-12-(*t*-Butyldimethysilyloxy)-13-[(6*R*)-4-methoxymethoxy-5,6-dihydro-pyran-2-one-6-yl]-6-[(4-methoxyphenyl)methoxy]-5-methyl-2,7,9-tridecatrien-1-ol (43)



43

To a cooled (0 °C), stirred solution of the TBDPS ether obtained above in pyridine–THF (1:2, 20 mL) was added HF-pyridine complex (2 mL). The mixture was stirred for 12 h, and quenched with saturated aqueous $NaHCO_3$. This was diluted with saturated aqueous $NaHCO_3$ (50 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 (acetone/toluene, 1:10) to provide 356 mg (65%, 2 steps) of **43** as a colorless oil; TLC, R_f 0.28 (acetone/toluene, 1:5); $[\alpha]^{24}_{D}$ –44.4 (*c* 1.40, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.06, 0.07 (2s, 3H × 2), 0.88 (s, 9H), 0.96 (d, *J* = 6.8 Hz, 3H), 1.67 (br s, 1H), 1.68–1.89 (m, 3H), 2.04 (m, 1H), 2.19–2.41 (m, 4H), 2.52 (ddd, *J* = 1.5, 11.6, 17.2 Hz, 1H), 3.45 (s, 3H), 3.80 (s, 3H), 3.96–4.07 (m, 4H), 4.21, 4.49 (2d, *J* = 11.4 Hz, 1H × 2), 4.57 (m, 1H), 5.06, 5.10 (2d, *J* = 6.1 Hz, 1H × 2), 5.26–5.36 (m, 2H), 5.52–5.76 (m, 3H), 6.18–6.32 (m, 2H), 6.86 (m, 2H), 7.23 (m, 2H); ^{13}C NMR (68 MHz) δ –4.73, –4.38, 15.17, 17.94, 25.74 × 3, 32.97, 35.42, 38.24, 40.23, 41.52, 55.17, 56.99, 63.47, 68.28, 69.60, 72.91, 77.29, 93.10, 94.39, 113.54 × 2, 128.20, 129.24 × 2, 129.55, 130.74, 130.79, 130.91, 131.97, 132.03, 158.90, 167.02, 169.58; IR (neat) 3450, 2930, 1715, 1610, 1515 cm^{-1}; HRMS calcd for $C_{35}H_{54}O_8Si$ (M^+) *m*/*z* 630.3588, found 630.3587.

(2*E*,5*R*,6*S*,7*Z*,9*E*,12*R*)-12-(*t*-Butyldimethysilyloxy)-13-[(6*R*)-4-methoxymethoxy-5,6-dihydropyran-2-one-6-yl]-6-[(4-methoxyphenyl)methoxy]-5-methyl-2,7,9-tridecatrienal (15)

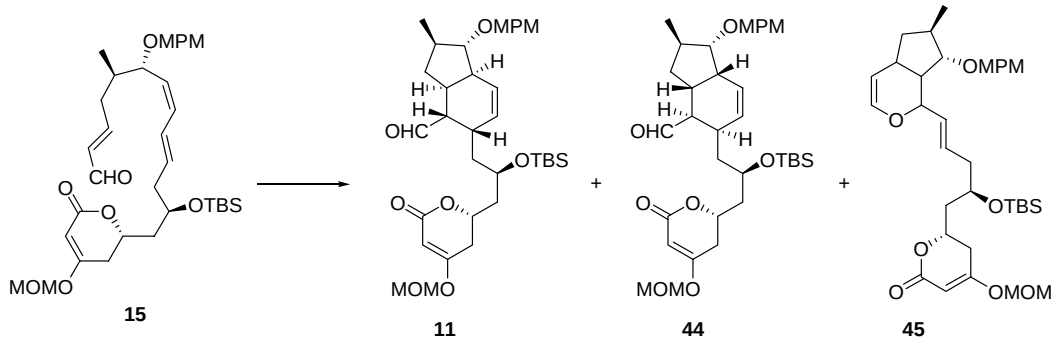


43 **15**

To a cooled (0 °C), stirred solution of **43** (96.4 mg, 0.153 mmol) in CH_2Cl_2 (2 mL) was added MnO_2 (482 mg, 5.54 mmol). The mixture was stirred for 30 min, and the insoluble materials were filtered off and washed well with EtOH. The combined filtrate and washings were concentrated in vacuo. The residue was purified

by column chromatography on silica gel (EtOAc/hexane, 1:4) to provide 90.4 mg (94%) of **15** as a colorless oil; TLC, R_f 0.52 (EtOAc/hexane, 1:1); $[\alpha]^{24}_D$ –61.3 (*c* 1.26, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.06, 0.07 (2s, 3H × 2), 0.88 (s, 9H), 0.97 (d, *J* = 6.8 Hz, 3H), 1.76 (dt, *J* = 14.1, 5.9 Hz, 1H), 1.90 (m, 1H), 2.01–2.18 (m, 2H), 2.25–2.44 (m, 3H), 2.49–2.59 (m, 2H), 3.46 (s, 3H), 3.81 (s, 3H), 3.97–4.11 (m, 2H), 4.21, 4.51 (2d, *J* = 11.5 Hz, 1H × 2), 4.57 (m, 1H), 5.06, 5.11 (2d, *J* = 6.1 Hz, 1H × 2), 5.26–5.32 (m, 2H), 5.75 (m, 1H), 6.07 (dd, *J* = 8.1, 15.6, 1H), 6.20–6.31 (m, 2H), 6.79 (ddd, *J* = 6.6, 8.1, 15.6 Hz, 1H), 6.87 (m, 2H), 7.22 (m, 2H), 9.47 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (68 MHz) δ –4.76, –4.43, 15.26, 17.88, 25.69 × 3, 33.01, 35.99, 37.82, 40.14, 41.42, 55.14, 56.95, 68.17, 69.58, 72.76, 76.87, 93.07, 94.34, 113.57 × 2, 127.75, 128.34, 129.24 × 2, 130.51, 132.73 × 2, 133.98, 157.75, 158.97, 166.77, 169.46, 193.86; IR (neat) 2930, 1715, 1695, 1615, 1515 cm^{-1}; HRMS calcd for $C_{35}H_{52}O_8Si$ (M^+) *m*/*z* 628.3431, found 628.3435.

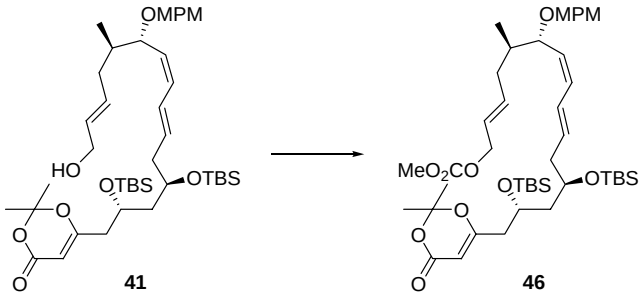
Intramolecular Diels–Alder reaction of 15



The compound **15** (75.2 mg, 0.0120 mmol) was dissolved in degassed toluene (6 mL), and a crystal of BHT was added. The solution was transferred into a 20 mL sealed tube equipped with a screwed stopper, and the tube was filled with argon. The tube was heated to 150 °C for 9 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 61.2 mg (81%) of **11**, 4.2 mg (5.6%) of **44**, and 6.5 mg (8.6%) of **45** as colorless oils; Compound **11**: TLC, R_f 0.45 (EtOAc/hexane, 1:1); $[\alpha]^{24}_D$ –2.1 (*c* 0.970, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.06, 0.08 (2s, 3H × 2), 0.88 (s, 9H), 1.05 (d, *J* = 5.9 Hz, 3H), 1.12 (m, 1H), 1.46 (m, 1H), 1.62–1.76 (m, 2H), 1.93–2.12 (m, 3H), 2.33–2.72 (m, 6H), 3.17 (dd, *J* = 4.3, 6.7 Hz, 1H), 3.47 (s, 3H), 3.81 (s, 3H), 4.09 (m, 1H), 4.43–4.53 (m, 2H), 4.56 (d, *J* = 11.2 Hz, 1H), 5.07, 5.11 (2d, *J* = 6.2 Hz, 1H × 2), 5.32 (d, *J* = 1.2 Hz, 1H), 5.73 (br d, *J* = 10.1 Hz, 1H), 5.81 (br d, *J* = 10.1 Hz, 1H), 6.88 (m, 2H), 7.27 (m, 2H), 9.70 (d, *J* = 2.7 Hz, 1H); ^{13}C NMR (75 MHz) δ –4.69, –4.23, 17.86, 18.29, 25.73 × 3, 28.46, 33.29, 34.31, 36.68, 39.12, 39.46, 42.83, 43.39, 54.61, 55.19, 57.03, 65.96, 71.97, 72.62, 92.18, 93.15, 94.39, 113.72 × 2, 127.93, 129.18 × 2, 130.56, 130.81, 159.08, 166.65, 169.38, 204.91; IR (neat) 2930, 1715, 1615, 1515 cm^{-1}; HRMS calcd for $C_{35}H_{52}O_8Si$ (M^+) *m*/*z* 628.3431, found 628.3425. Compound **44**: TLC, R_f 0.46 (EtOAc/hexane, 1:1); $[\alpha]^{22}_D$ –112 (*c* 0.245, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.06, 0.06 (2s, 3H × 2), 0.87 (s, 9H), 0.97 (d, *J* = 6.6 Hz, 3H), 1.52–1.73 (m, 4H), 1.80 (dt, *J* = 14.6, 5.5 Hz, 1H), 1.89–2.12 (m, 2H), 2.37 (dd, *J* = 4.0, 17.3 Hz, 1H),

2.43–2.68 (m, 4H), 2.80 (m, 1H), 3.43 (m, 1H), 3.47 (s, 3H), 3.81 (s, 3H), 4.05 (m, 1H), 4.45 (d, *J* = 11.2 Hz, 1H), 4.48–4.62 (m, 2H), 5.07, 5.11 (2d, *J* = 6.1 Hz, 1H × 2), 5.32 (d, *J* = 1.5 Hz, 1H), 5.78–5.86 (m, 2H), 6.88 (m, 2H), 7.26 (m, 2H), 9.72 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR (75 MHz) δ –4.38, –4.31, 17.96, 18.37, 25.81 × 3, 29.00, 31.94, 33.26, 34.25, 36.37, 38.46, 39.20, 41.53, 54.09, 55.27, 57.11, 67.08, 71.47, 72.61, 87.38, 93.25, 94.47, 113.75 × 2, 127.57, 129.11 × 2, 130.71, 131.15, 159.12, 166.72, 169.43, 205.06; IR (neat) 2930, 1715, 1615, 1515 cm^{-1}; HRMS calcd for $C_{35}H_{52}O_8Si$ (M^+) *m*/*z* 628.3431, found 628.3427. Compound **45** (ca. 3:2 mixture of dastereomers): TLC, R_f 0.55 (EtOAc/hexane, 1:1); ^{1}H NMR (300 MHz, signals for 2 diastereomers) δ 0.04, 0.06, 0.08 (3s, total 6H), 0.87 (s, 0.4 × 9H), 0.88 (s, 0.6 × 9H), 1.11 (d, *J* = 7.1 Hz, 0.6 × 3H), 1.14 (d, *J* = 6.8 Hz, 0.4 × 3H), 1.42 (m, 0.6H), 1.62–1.79 (m, 2H), 1.93–2.55 (m, 8H), 2.71 (m, 0.4 H), 3.25 (dd, *J* = 4.6, 9.3 Hz, 0.4H), 3.46 (s, 0.4 × 3H), 3.47 (s, 0.6 × 3H), 3.66 (dd, *J* = 5.0, 8.1 Hz, 0.6H), 3.72 (m, 0.4H), 3.79 (s, 0.6 × 3H), 3.80 (s, 0.4 × 3H), 3.95 (m, 0.6H), 4.34–4.62 (m, 4H), 4.72 (d, *J* = 6.1 Hz, 0.6 H), 4.83 (m, 0.4H), 5.04–5.12 (m, 2H), 5.30 (dd, *J* = 1.3, 9.9 Hz, 1H), 5.47 (dd, *J* = 15.4, 6.1 Hz, 0.4 H), 5.64–5.76 (m, 0.6 × 2H + 0.4H), 6.22 (dd, *J* = 2.0, 6.1 Hz, 0.6H), 6.30 (dd, *J* = 1.6, 6.0 Hz, 0.4H), 6.84–6.89 (m, 2H), 7.25 (m, 2H); ^{13}C NMR (75 MHz, signals for 2 diastereomers) δ –4.71, –4.67, –4.34, –4.28, 17.99, 22.12, 22.37. 25.81 × 3, 28.59, 29.69, 32.88, 33.00, 33.06, 34.08, 36.06, 37.70, 39.18, 39.40, 39.89, 40.00, 41.11, 41.25, 50.12, 52.03, 55.29, 57.05, 68.13, 68.25, 71.74, 71.80, 72.92, 73.10, 75.65, 86.20, 86.89, 93.19, 93.27, 94.39, 94.45, 100.56, 102.91, 107.71, 113.75, 113.81, 127.52, 127.71, 128.90 129.10, 129.21, 129.49, 130.12, 130.71, 130.92, 131.79, 141.71, 142.63, 159.17, 166.90, 169.46, 169.51; IR (neat) 2930, 1715, 1615, 1515 cm^{-1}; HRMS calcd for $C_{35}H_{52}O_8Si$ (M^+) *m*/*z* 628.3431, found 628.3435.

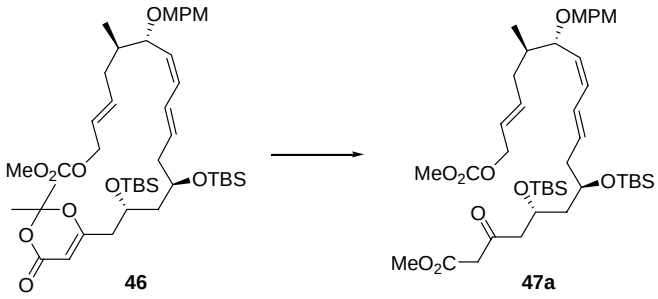
(2*E*,5*R*,6*S*,7*Z*,9*E*,12*R*,14*R*)-12,14-Bis(*t*-butyldimethylsilyloxy)-15-(2,2-dimethyl-1,3-dioxin-4-one-6-yl)-1-(methoxycarbonyl)oxy-6-[(4-methoxyphenyl)methoxy]-5-methyl-2,7,9-pentadecatriene (46)



To a cooled (0 °C), stirred solution of **41** (1.21 g, 1.59 mmol) in CH_2Cl_2 (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 (Et_3N/hexane, 1:100 to EtOAc/hexane, 1:5) to provide 1.29 g (quant.) of **46** as a colorless oil; TLC, R_f 0.63 (EtOAc/hexane, 1:1); $[\alpha]^{25}_D$ –23.9 (*c* 1.77, $CHCl_3$); ^{1}H-NMR (270 MHz) δ 0.04, 0.05, 0.07 (3s, total 12H), 0.86, 0.90 (2s, 9H×2),

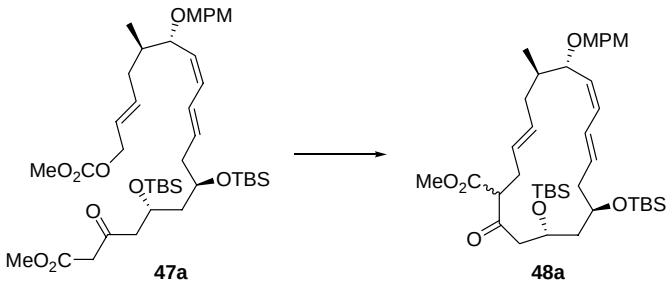
0.92 (d, *J* = 6.6 Hz, 3H), 1.67, 1.68 (2s, 3H×2), 1.54-1.83 (m, 4H), 2.17-2.32 (m, 4H), 2.43 (dd, *J* = 4.4, 13.9 Hz, 1H), 3.77 (s, 3H), 3.77 (m, 1H), 3.80 (s, 3H), 4.02 (dd, *J* = 5.7, 9.5 Hz, 1H), 4.10 (m, 1H), 4.20, 4.49 (2d, *J* = 11.7 Hz, 1H×2), 4.54 (d, *J* = 6.2 Hz, 2H), 5.27 (s, 1H), 5.28 (t, *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); ^{13}C-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 $C_{40}H_{63}O_{10}Si_2$ (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-(methoxycarbonyl)oxy-13-[(4-methoxyphenyl)methoxy]-14-methyl-3-oxo-9,11,16-octadecatriene-1-carboxylate (47a)



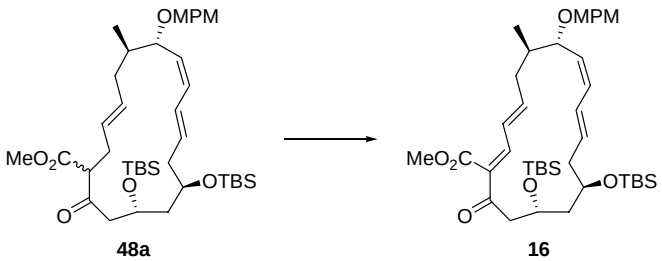
Compound **46** (1.29 g 1.59 mmol) was dissolved in degassed toluene–MeOH (8:1, 25 mL). The solution was transferred into three 20 mL sealed tubes equipped with a screwed stopper, and the tubes were filled with argon. The tubes were heated to 110 °C for 3 h. After being cooled to ambient temperature, 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 **47a** as a colorless oil; TLC, R_f 0.74 (EtOAc/hexane, 1:2); $[\alpha]^{26}_D$ –22.3 (*c* 1.11, $CHCl_3$); ^{1}H-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 + enol form) δ –4.81, –4.52×2, –4.21, 15.17, 17.88, 17.97, 25.83×6, 35.48, 38.21, 40.92, 43.57 (enol), 44.78, 45.09 (enol), 50.05, 50.68, 51.08 (enol), 52.21, 54.65, 55.23, 66.49, 67.01 (enol), 68.56, 68.91, 69.56, 77.29, 91.17 (enol), 113.60×2, 124.63, 127.74 (enol), 127.86, 128.92 (enol), 129.01, 129.30×2, 130.97, 132.43, 132.55, 132.78 (enol), 135.80, 155.64, 158.98, 167.45, 172.81 (enol), 175.66 (enol), 201.60; IR (neat) 2930, 1750, 1615, 1515 cm^{-1}; HRMS (FAB) calcd for $C_{42}H_{70}O_{10}Si_2Na$ (M^++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 (48a, *ca*. 3:2 diastereomeric mixture)



To a stirred solution of $Pd(PPh_3)_4$ (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 **47a** (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 **48a** as a colorless oil; TLC, R_f 0.66 (EtOAc/hexane, 1:4); $[\alpha]^{24}_D$ +28.8 (*c* 1.48, $CHCl_3$); ^{1}H-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, signals for 2 diastereomers) 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 $C_{40}H_{66}O_7Si_2$ (M^+) *m*/*z* 714.4347, found 714.4342.

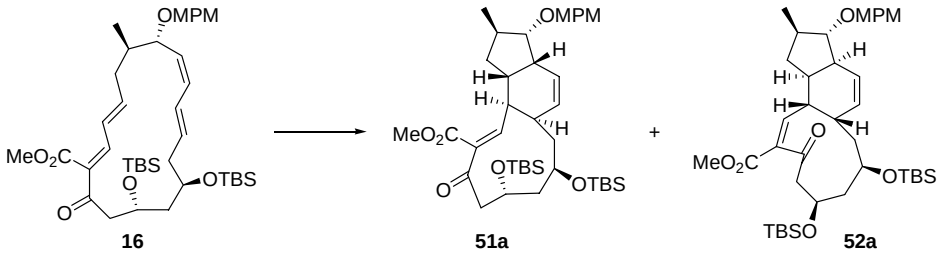
(2*Z*,4*E*,7*R*,8*S*,9*Z*,11*E*,14*R*,16*R*)-14,16-Bis(*t*-butyldimethylsilyloxy)-2-methoxycarbonyl-8-[(4-methoxyphenyl)methoxy]-7-methyl-2,4,9,11-cycloheptadecatetraen-1-one (16)



The following reaction was carried out under argon. To a cooled (–78 °C) stirred solution of **48a** (113.2 mg, 0.158 mmol) in THF (2.5 mL) was added NaHMDS (1.0 M in THF, 0.32 mL, 0.32 mmol). The mixture was stirred for 1 h at –78 °C, and a solution of PhSeCl (83.3 mg, 0.413 mmol) in toluene (1.2 mL) was added. After being stirred at –78 °C for 5 h, the solution was quenched with saturated aqueous NH_4Cl. This was diluted with saturated aqueous NH_4Cl (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 (toluene/hexane, 1:3 to toluene) to provide 123.0 mg (89%) of the selenide as a colorless oil.

The following reaction was carried out under argon. To a cooled (–78 °C), stirred solution of the selenide (123.0 mg, 0.141 mmol) in CH_2Cl_2 (2.5 mL) was added a solution of mCPBA (50.3 mg, 0.291 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred for 1 h at –78 °C, and quenched with 20% aqueous $Na_2S_2O_3$ and MeOH. This was diluted with 20% aqueous $Na_2S_2O_3$ (20 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/toluene, 1:100) to provide 61.9 mg (66%) of **16** as a colorless oil; TLC, R_f 0.28 (EtOAc/hexane, 1:5); $[\alpha]^{24}_D$ –15.2 (*c* 1.19, $CHCl_3$); ^{1}H-NMR (270 MHz) δ 0.063, 0.080 (2s, total 12H), 0.88, 0.89 (2s, 9H×2), 1.17 (d, *J* = 6.8 Hz, 3H), 1.71 (m, 2H), 1.90 (m, 1H), 2.19-2.49 (m, 4H), 2.86 (dd, *J* = 7.6, 12.9 Hz, 1H), 2.94 (dd, *J* = 5.6, 12.9 Hz, 1H), 3.77-3.86 (m, 1H), 3.80 (s, 3H), 3.82 (s, 3H), 3.86 (dd, *J* = 8.3, 10.0 Hz, 1H), 4.18 (d, *J* = 11.7 Hz, 1H), 4.24 (m, 1H), 4.47 (d, *J* = 11.7 Hz, 1H), 5.27 (t, *J* = 10.0 Hz, 1H), 5.73 (ddd, *J* = 6.4, 9.8, 14.4 Hz, 1H), 6.12-6.28 (m, 3H), 6.54 (dd, *J* = 11.2, 14.9 Hz, 1H), 6.86 (m, 2H), 7.07 (d, *J* = 11.2 Hz, 1H), 7.23 (m, 2H); ^{13}C-NMR (75 MHz) δ –4.74, –4.49, –4.44×2, 17.07, 18.01 × 2, 25.89×6, 36.94, 37.52, 42.83, 43.97, 47.21, 51.93, 55.20, 67.33, 69.42, 69.47, 76.46, 113.68 × 2, 127.80, 128.22, 129.05, 129.28×2, 130.82, 132.47, 132.76, 133.26, 146.37, 146.89, 159.07, 165.91, 198.04; IR (neat) 2930, 1730, 1690, 1630, 1585, 1515 cm^{-1}; HRMS calcd for $C_{40}H_{64}O_7Si_2$ (M^+) *m*/*z* 712.4191, found 712.4187.

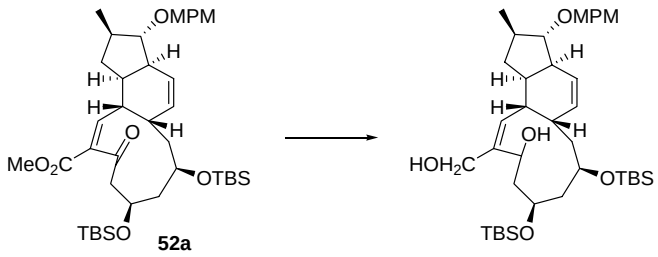
Intramolecular Diels–Alder reaction of 16



Compound **16** (30.2 mg, 0.0424 mmol) was dissolved in degassed toluene (6 mL), and a crystal of BHT was added. The solution was transferred into a 20 mL sealed tube equipped with a screwed stopper, and the tube was filled with argon. The tube was heated to 130 °C for 72.5 h. After being cooled to ambient temperature, the solution was concentrated in vacuo. The residue was purified by column chromatography on silica gel

(EtOAc/toluene, 1:150 to 1:50) to provide 8.7 mg (29%) of **51a** as a colorless oil and 3.3 mg (10%) of **52a** as a colorless oil; Compound **51a**: TLC, R_f 0.54 (EtOAc/hexane, 1:3); $[\alpha]^{22}_D$ –62 (c 0.28, $CHCl_3$); ^{1}H-NMR (300 MHz) δ 0.0024, 0.037, 0.084, 0.096 (4s, 3H×4), 0.86, 0.88 (2s, 9H×2), 0.97 (d, *J* = 6.8 Hz, 3H), 1.46 (m, 1H) 1.58-1.67 (m, 2H), 1.82 (m, 1H), 1.97-2.12 (m, 3H), 2.22 (m, 1H), 2.70 (m, 2H), 2.79 (dd, *J* = 2.6, 12.8 Hz, 1H), 3.06 (dd, *J* = 9.6, 12.8 Hz, 1H), 3.14 (m, 1H), 3.45 (t, *J* = 5.6 Hz, 1H), 3.74–3.90 (m, 2H), 3.74 (s, 3H), 3.81 (s, 3H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.51 (d, *J* = 11.7 Hz, 1H), 5.76 (br d, *J* = 9.3 Hz, 1H), 5.85 (br d, *J* = 9.3 Hz, 1H), 6.74 (d, *J* = 11.0 Hz, 1H), 6.88 (m, 2H), 7.25 (m, 2H); ^{13}C-NMR (68 MHz) δ –4.75 × 2, –4.50 × 2, 17.68, 17.97, 19.21, 25.74 × 3, 25.83 × 3, 35.50, 36.11, 37.00, 37.15, 40.17, 41.93, 42.33, 50.28, 50.91, 52.09, 55.26, 69.00, 70.09, 71.18, 87.28, 113.69×2, 125.09, 128.89 × 2, 130.97, 132.09, 137.91, 154.92, 158.05, 165.75, 197.00; IR (neat) 2930, 1730, 1705, 1670, 1615, 1515 cm^{-1}; HRMS calcd for $C_{40}H_{64}O_7Si_2$ (M^+) *m*/*z* 712.4191, found 712.4202. Compound **33**: TLC, R_f 0.54 (EtOAc/hexane, 1:3); $[\alpha]^{27}_D$ –70 (c 0.13, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.012, 0.015, 0.025 (3s, total 12H), 0.86, 0.87 (2s, 9H × 2), 1.05 (d, *J* = 6.8 Hz, 3H), 1.25 (m, 1H) 1.50-1.74 (m, 4H), 1.82 (m, 1H), 1.94 (m, 1H), 2.26 (m, 1H), 2.56 (dd, *J* = 12.0, 13.7 Hz, 1H), 2.60 (m, 1H), 2.80-2.83 (m, 2H), 3.15 (dd, *J* = 3.7, 13.7 Hz, 1H), 3.24 (dd, *J* = 2.4, 6.1 Hz, 1H), 3.79 (s, 3H), 3.80 (s, 3H), 3.94–4.01 (m, 2H), 4.40 (d, *J* = 11.2 Hz, 1H), 4.53 (d, *J* = 11.2 Hz, 1H), 5.15 (br d, *J* = 10.1 Hz, 1H), 5.63 (br d, *J* = 10.1 Hz, 1H), 6.88 (m, 2H), 6.94 (d, *J* = 12.2 Hz, 1H), 7.26 (m, 2H); ^{13}C-NMR (75 MHz) δ –4.97 × 2, –4.82, –4.67, 17.76, 18.08, 18.93, 25.59×3, 25.78 × 3, 27.47, 36.14, 37.60, 39.53, 40.05, 40.53, 41.76, 45.52, 52.21, 53.51, 55.27, 66.23, 67.80, 71.14, 92.18, 113.78 × 2, 129.16×2, 129.82, 130.15, 130.69, 135.10, 149.36, 159.08, 164.17, 202.25; IR (neat) 2930, 1730, 1705, 1615, 1515 cm^{-1}; HRMS calcd for $C_{40}H_{64}O_7Si_2$ (M^+) *m*/*z* 712.4191, found 712.4200.

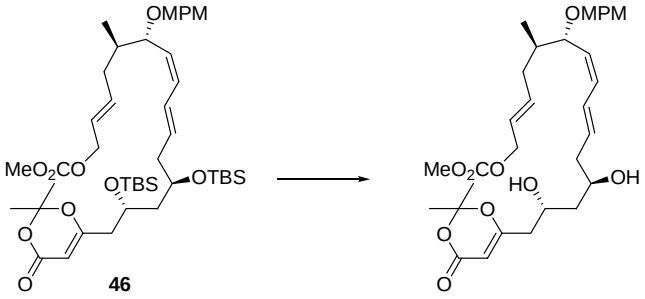
(1*S*,2*E*,6*R*,8*R*,10*S*,11*Z*,13*S*,14*S*,15*R*,17*R*)-6,8-Bis(*t*-butyldimethylsilyloxy)-3-hydroxymethyl-14-[(4-methoxyphenyl)methoxy]-15-methyltricyclo[8.7.0.0^{13,17}]heptadeca-2,11-dien-4-ol



The following reaction was carried out under argon. To a cooled (–78 °C), stirred solution of **52a** (1.2 mg, 0.0017 mmol) in CH_2Cl_2 (1 mL) was added Dibal-H (1.0 M solution in toluene, 2 drops). The mixture was stirred at –78 °C for 1.5 h and then Dibal-H (1.0 M solution in toluene, 3 drops) was added. This was stirred at –78 °C for 1 h and then Dibal-H (1.0 M solution in toluene, 3 drops) was added. This was stirred at –78 °C for 1.5 h and quenched with 10% aqueous potassium sodium (+)-tartarate tetrahydrate. This was diluted with

10% aqueous solution potassium sodium (+)-tartarate tetrahydrate (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, 1:3) to provide 1.2 mg (quant.) of the diol as a colorless oil; TLC, R_f 0.46 (EtOAc/hexane, 1:1); $[\alpha]^{27}_D$ –9.6 (*c* 0.080, $CHCl_3$); ^{1}H-NMR (300 MHz) δ –0.02 –0.01, 0.02, 0.04 (4s, 3H × 4), 0.86, 0.87 (2s, 9H × 2), 1.06 (d, *J* = 6.6 Hz, 3H), 1.25 (m, 1H) 1.58–2.05 (m, 7H), 2.20 (m, 1H), 2.59 (m, 1H), 2.65 (t, *J* = 13.9 Hz, 1H), 2.82 (m, 1H), 3.26 (dd, *J* = 2.2, 6.5 Hz, 1H), 3.61 (m, 1H), 3.80 (s, 3H), 3.90–4.00 (m, 2H), 3.95 (s, 2H), 4.43 (d, *J* = 11.2 Hz, 1H), 4.52 (d, *J* = 11.2 Hz, 1H), 4.74 (d, *J* = 5.1 Hz, 1H), 5.15 (br d, *J* = 10.0 Hz, 1H), 5.56 (br d, *J* = 10.0 Hz, 1H), 5.60 (d, *J* = 12.2 Hz, 1H), 6.88 (m, 2H), 7.26 (m, 2H); ^{13}C-NMR (68 MHz) δ –4.87, –4.67, –4.61, –4.15, 19.23 × 2, 25.74 × 3, 25.89 × 3, 27.76, 29.69, 35.94, 36.40, 37.17, 39.77, 41.84, 42.01, 42.44, 44.03, 55.26, 67.73, 67.90, 68.53, 70.78, 71.10, 92.44, 113.75 × 2, 129.01, 129.18 × 2, 130.82, 131.28, 132.64, 138.42, 159.07; IR (neat) 3400, 2930, 1730, 1615, 1515 cm^{-1}; HRMS calcd for $C_{39}H_{66}O_6Si_2$ (M^+) *m*/*z* 686.4398, found 686.4428.

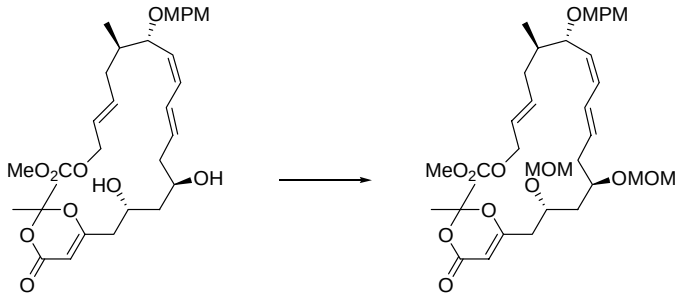
(2*R*,4*R*,6*E*,8*Z*,10*S*,11*R*,13*E*)-1-(2,2-Dimethyl-1,3-dioxin-4-one-6-yl)-15-methoxycarbonyloxy-10-[(4-methoxyphenyl)methoxy]-11-methyl-6,8,13-pentadecatrien-2,4-diol



To a cooled (0 °C), stirred solution of **46** (522 mg, 0.639 mmol) in pyridine (10 mL) was added HF-pyridine complex (1 mL). The mixture was stirred for 45 h, and quenched with saturated aqueous $NaHCO_3$. This was diluted with saturated aqueous $NaHCO_3$ (50 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, 2:1 to EtOAc) to provide 384 mg (quant.) of the diol as a colorless oil; TLC, R_f 0.25 (EtOAc/hexane, 2:1); $[\alpha]^{25}_D$ –8.8 (*c* 1.76, $CHCl_3$); ^{1}H-NMR (300 MHz) δ 0.94 (d, *J* = 6.6 Hz, 3H), 1.53-1.89 (m, 4H), 1.70 × 2 (2s, 3H × 2), 2.22-2.45 (m, 5H), 2.80 (m, 1H), 3.77 (s, 3H), 3.77 (m, 1H), 3.80 (s, 3H), 3.94 (m, 1H), 4.01(dd, *J* = 6.8, 9.4 Hz, 1H), 4.18 (m, 1H), 4.22, (d, *J* = 11.4 Hz, 1H), 4.50 (d, *J* = 11.4 Hz, 1H), 4.54 (d, *J* = 6.3 Hz, 2H), 5.33 (t, *J* = 9.4 Hz, 1H), 5.34 (s, 1H), 5.52 (dt, *J* = 15.4, 6.3 Hz, 1H), 5.64-5.78 (m, 2H), 6.18-6.33 (m, 2H), 6.86 (m, 2H), 7.22 (m, 2H); ^{13}C-NMR (68 MHz) δ 15.06, 24.71, 25.17, 35.36, 38.04, 41.44, 41.90, 42.04, 54.65, 55.17, 68.45, 69.17, 69.54, 71.79, 76.77, 95.06, 106.55, 113.54 × 2, 124.72, 128.92, 129.27 × 2, 129.93, 130.65, 130.99, 131.74, 135.46, 155.56, 158.93, 161.17, 168.86; IR (neat) 3440,

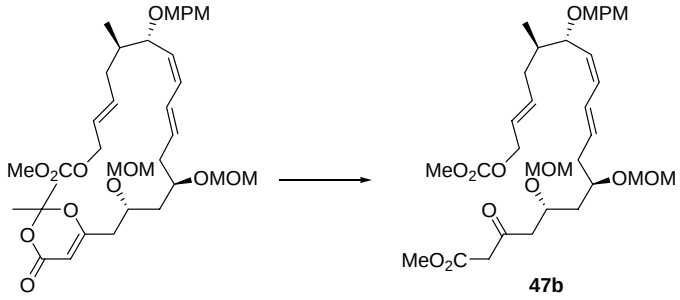
2960, 1750, 1730, 1640, 1615, 1515 cm^{-1}; HRMS (FAB) calcd for (M^++H) *m*/*z* 589.3013, found 389.3005.

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



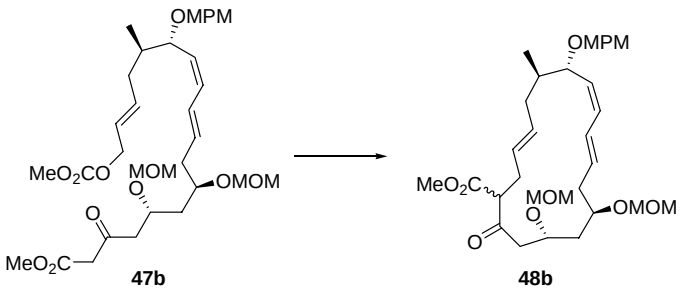
To a cooled (0 °C), stirred solution of the diol (384 mg, 0.653 mmol) in CH_2Cl_2 (10 mL) were added *i*Pr_2NEt (2.3 mL, 13 mmol) and MOMCl (0.50 mL, 6.5 mmol). The mixture was stirred for 23 h and *i*Pr_2NEt (1.2 mL, 6.9 mmol) and MOMCl (0.25 mL, 3.3 mmol) were added. This was stirred for 14.5 h, and *i*Pr_2NEt (0.4 mL, 2.3 mmol) and MOMCl (0.10 mL, 1.3 mmol) were added. This was refluxed for 3.5 h and quenched with saturated aqueous $NaHCO_3$. This was diluted with saturated aqueous NH_4Cl (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, 2:3) to provide 405 mg (94%) of the di-MOM ether as a colorless oil; TLC, R_f 0.55 (EtOAc/hexane, 2:1); $[\alpha]^{24}_D$ –30.2 (*c* 1.67, $CHCl_3$); ^{1}H-NMR (270 MHz) δ 0.93 (d, *J* = 6.9 Hz, 3H), 1.68 (s, 6H), 1.62–1.97 (m, 4H), 2.23–2.57 (m, 5H), 3.35, 3.38 (2s, 3H × 2), 3.74 (m, 1H), 3.76 (s, 3H), 3.80 (s, 3H), 4.00 (m, 2H), 4.21, (d, *J* = 11.7 Hz, 1H), 4.49 (d, *J* = 11.7 Hz, 1H), 4.54 (d, *J* = 6.2 Hz, 2H), 4.61 (d, *J* = 7.0 Hz, 1H), 4.63 (s, 2H), 4.69 (d, *J* = 7.0 Hz, 1H), 5.30 (t, *J* = 9.5 Hz, 1H), 5.33 (s, 1H), 5.52 (dt, *J* = 15.4, 6.2 Hz 1H), 5.66–5.78 (m, 2H), 6.18-6.33 (m, 2H), 6.87 (m, 2H), 7.22 (m, 2H); ^{13}C-NMR (68 MHz) δ 15.00, 24.91, 24.99, 35.33, 37.78, 38.04, 38.90, 39.28, 54.51, 55.06, 55.63 × 2, 68.36, 69.43, 71.73, 73.57, 76.89, 95.11, 95.17, 95.55, 106.29, 113.49 × 2, 124.63, 128.20, 129.21 × 2, 129.35, 130.65, 131.45, 132.00, 135.46, 155.47, 158.90, 160.77, 168.66; IR (neat) 2960, 1750, 1730, 1640, 1615, 1515 cm^{-1}; HRMS (FAB) calcd for (M^++H) *m*/*z* 677.3537, found 677.3539.

Methyl (5*R*,7*R*,9*E*,11*Z*,13*S*,14*R*,16*E*)-18-(Methoxycarbonyl)oxy-5,7-di(methoxymethoxy)-13-[(4-methoxyphenyl)methoxy]-14-methyl-3-oxo-9,11,16-octadecatriene-1-carboxylate (47b)



The dioxinone (405 mg 0.598 mmol) was dissolved in degassed toluene–MeOH (8:1, 8 mL). The solution was transferred into a 20 mL sealed tube equipped with a screwed stopper, and the tube was filled with argon. The tube was heated to 110 °C for 5 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, 1:2) to provide 372 mg (96%) of **47b** as a colorless oil; TLC, R_f 0.55 (EtOAc/hexane, 2:1); $[\alpha]^{23}_{D}$ –29.4 (*c* 2.76, $CHCl_3$); ^{1}H-NMR (270 MHz) δ 0.93 (d, *J* = 6.1 Hz, 3H), 1.60–1.94 (m, 4H), 2.23–2.46 (m, 3H, 2H×1/10, enol form), 2.75 (dd, *J* = 4.9, 15.9 Hz, 1H×9/10, keto form), 2.84 (dd, *J* = 6.7, 15.9 Hz, 1H×9/10, keto form), 3.33, 3.34 (2s, total 3H), 3.37, 3.38 (2s, total 3H), 3.49 (s, 2H×9/10, keto form), 3.73 (s, 3H), 3.75 (m, 1H), 3.77 (s, 3H), 3.80 (s, 3H), 4.01 (dd, *J* = 5.8, 9.0 Hz, 1H), 4.21, (d, *J* = 11.6 Hz, 1H), 4.21 (m, 1H), 4.49 (d, *J* = 11.6 Hz, 1H), 4.54 (d, *J* = 6.1 Hz, 2H), 4.59–4.68 (m, 4H), 5.07 (s, 1H × 1/10, enol form), 5.28 (t, *J* = 9.5 Hz, 1H), 5.53 (dt, *J* = 15.3, 6.1 Hz, 1H), 5.68–5.78 (m, 2H), 6.19–6.33 (m, 2H), 6.87 (m, 2H), 7.23 (m, 2H), 12.04 (s, 1H × 1/10, enol form); ^{13}C-NMR (68 MHz, keto + enol form) δ 15.09, 35.42, 37.89, 38.10, 39.28, 47.83, 49.90, 51.09 (enol), 52.24, 54.60, 55.17, 55.64, 55.72 × 2, 68.48, 69.51, 71.39, 71.82 (enol), 73.80, 90.91 (enol), 95.34, 95.52 (enol), 95.98, 113.54 × 2, 124.66, 128.17, 129.24, 129.30 × 2, 130.79, 131.71, 131.83 (enol), 132.20, 135.63, 155.56, 158.96, 167.39, 175.25 (enol), 201.00; IR (neat) 2950, 1750, 1615, 1515 cm^{-1}; HRMS calcd for $C_{34}H_{50}O_{12}$ (M^+) *m*/*z* 650.3302, found 650.3297.

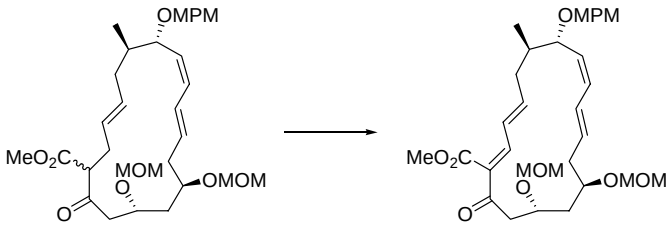
(2*RS*,4*E*,7*R*,8*S*,9*Z*,11*E*,14*R*,16*R*)-2-Methoxycarbonyl-14,16-di(methoxymethoxy)-8-[(4-methoxyphenyl)-methoxy]-7-methyl-4,9,11-cycloheptadecatrien-1-one (48b, *ca*. 3:2 diastereomeric mixture)



To a stirred solution of **47b** (98.0 mg, 0.151 mmol) in degassed THF (50 mL) were added $Pd(PPh_3)_4$ (32.2 mg,

0.0279 mmol) and dppe (11.0 mg, 0.0279 mmol) in THF (6 mL). The mixture was stirred for 3 h, and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2 to 1:1) to provide 73.1 mg (84%) of **48b** as a colorless oil; TLC, R_f 0.61 (EtOAc/hexane, 2:1); $[\alpha]^{21}_D$ +30.2 (*c* 1.26, $CHCl_3$); ^{1}H-NMR (300 MHz) δ 0.96 (d, *J* = 6.9 Hz, 3H), 1.57 (m, 1H), 1.74–1.95 (m, 3H), 2.17 (m, 1H), 2.35–2.92 (m, 6H), 3.33, 3.34, 3.39 (3s, total 6H), 3.36 (m, 1H × 3/5), 3.52 (m, 1H × 2/5), 3.67, 3.71, 3.74 (3s, total 3H), 3.81, 3.82 (2s, total 3H), 3.87 (m, 1H), 4.04–4.22 (m, 3H), 4.46–4.68 (m, 5H), 5.25 (m, 1H), 5.35-5.45 (m, 2H), 5.75 (m, 1H), 5.98–6.24 (m, 1H + 1H × 3/5), 6.39 (dd, *J* = 11.7, 15.0 Hz, 1H×2/5), 6.88 (m, 2H), 7.25 (m, 2H), [enol: 12.84 (s, 1H × 3/5)]; ^{13}C-NMR (68 MHz, signals for two diastereomeric keto tautomer + one enol tautomer) δ 14.78, 14.86, 15.33, 27.57, 30.75, 30.79, 35.65, 36.25, 36.36, 36.45, 36.81, 37.85, 37.91, 38.53, 38.89, 39.26, 39.31, 40.86, 47.98, 48.60, 51.62, 52.31, 52.35, 55.07, 55.14, 55.18, 55.24, 55.43, 55.46, 55.49, 55.55, 55.61, 55.64, 55.87, 57.46, 57.98, 69.30, 69.64, 71.04, 71.35, 71.84, 72.95, 72.98, 73.41, 73.55, 74.22, 74.34, 94.89, 94.97, 95.14, 96.09, 96.34, 113.57, 113.60, 124.93, 126.63,127.36, 127.47, 128.42, 128.45, 129.23, 129.35, 129.64, 129.78, 130.71, 130.89, 130.94, 130.98, 131.03, 131.20, 131.34, 131.61, 131.90, 132.05, 132.19, 132.63, 158.92, 158.95, 169.55, 169.66, 173.60, 202.52, 202.91; IR (neat) 2930, 1750, 1715, 1650, 1615, 1585, 1515 cm^{-1}; HRMS calcd for $C_{32}H_{46}O_9$ (M^+) *m*/*z* 574.3141, found 574.3147.

(2*Z*,4*E*,7*R*,8*S*,9*Z*,11*E*,14*R*,16*R*)-2-Methoxycarbonyl-14,16-di(methoxymethoxy)-8-[(4-methoxyphenyl)-methoxy]-7-methyl-2,4,9,11-cycloheptadecatetraen-1-one (49)

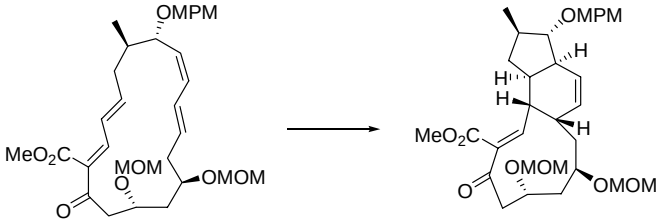


The following reaction was carried out under argon. To a cooled (–78 °C), stirred solution of **48b** (274 mg, 0.477 mmol) in THF (6 mL) was added NaHMDS (1.0 M in THF, 1.0 mL, 1.0 mmol). The mixture was stirred for 1 h at –78 °C and a solution of PhSeCl (245 mg, 1.21 mmol) in toluene (2 mL) was added. After being stirred at –78 °C for 2 h, the solution was quenched with saturated aqueous NH_4Cl. This was diluted with saturated aqueous NH_4Cl (60 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 (toluene/hexane, 1:3 to EtOAc /hexane, 1:4) to provide 331 mg (95%) of the selenide as a colorless oil.

The following reaction was carried out under argon. To a cooled (–78 °C), stirred solution of the selenide (331 mg, 0.453 mmol) in CH_2Cl_2 (8 mL) was added a solution of mCPBA (164.0 mg, 0.950 mmol) in CH_2Cl_2

(3 mL). The mixture was stirred for 3 h at –78 °C and quenched with 20% aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. This was diluted with saturated aqueous $NaHCO_3$ (50 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/toluene, 1:6) to provide 140.3 mg (54%) of **49** (*Z*/*E* > 20:1) as a colorless oil; TLC, R_f 0.43 (EtOAc/hexane, 1:1); $[\alpha]^{22}_D$ –83.5 (*c* 1.76, $CHCl_3$); ^{1}H-NMR (270 MHz) δ 1.18 (d, *J* = 7.0 Hz, 3H), 1.72 (m, 2H), 1.88 (m, 1H), 2.12–2.29 (m, 2H), 2.37–2.52 (m, 2H), 2.79 (dd, *J* = 8.4, 13.2 Hz, 1H), 3.20 (dd, *J* = 4.4, 13.2 Hz, 1H), 3.37, 3.38 (2s, 3H×2), 3.63 (m, 1H), 3.81 (s, 3H), 3.82 (m, 1H), 3.82 (s, 3H), 3.98 (m, 1H), 4.17 (d, *J* = 11.4 Hz, 1H), 4.47 (d, *J* = 11.4 Hz, 1H), 4.60–4.72 (m, 4H), 5.25 (t, *J* = 10.3 Hz, 1H), 5.69 (ddd, *J* = 4.8, 9.9, 14.7 Hz, 1H), 6.07 (dd, *J* = 11.0, 14.7 Hz, 1H), 6.17–6.27 (m, 2H), 6.54 (dd, *J* = 11.5, 14.8 Hz, 1H), 6.87 (m, 2H), 7.07 (d, *J* = 11.5 Hz, 1H), 7.22 (m, 2H); ^{13}C-NMR (68 MHz) δ 17.00, 37.15, 37.43, 39.97, 40.08, 45.27, 51.95, 55.20, 55.60, 55.72, 69.14, 72.08, 74.26, 75.85, 95.29, 95.37, 113.60 × 2, 127.97, 128.03, 129.30 × 2, 130.71 × 2, 131.40, 132.38, 132.78, 146.29, 147.12, 159.04, 165.78, 197.95; IR (neat) 2950, 1730, 1680, 1630, 1585, 1515 cm^{-1}; HRMS calcd for $C_{32}H_{44}O_9$ (M^+) *m*/*z* 572.2985, found 572.2980.

Intramolecular Diels–Alder reaction of 49

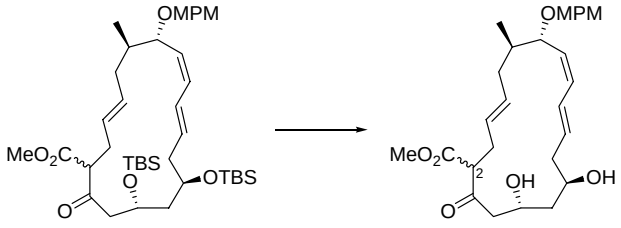


49 **50**

The compound **49** (31.8 mg, 0.0555 mmol) was dissolved in degassed toluene (8 mL), and a crystal of BHT was added. The solution was transferred into a 20 mL sealed tube equipped with a screwed stopper, and the tube was filled with argon. The tube was heated to 130 °C for 80 h. After being cooled to ambient temperature, the solution was concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/toluene, 1:7) to provide 9.1 mg (29%) of **50** as a colorless oil; TLC, R_f 0.32 (EtOAc/toluene, 1:1); $[\alpha]^{22}_D$ –0.5 (c 0.840, $CHCl_3$); ^{1}H-NMR (270 MHz) δ 1.06 (d, *J* = 6.6 Hz, 3H), 1.68 (m, 2H) 1.82–2.18 (m, 5H), 2.26 (m, 1H), 2.52 (m, 1H), 2.65 (m, 1H), 2.85 (dd, *J* = 6.2, 13.6 Hz, 1H), 3.03 (td, *J* = 10.3, 4.7 Hz, 1H), 3.16 (m, 1H), 3.22 (t, *J* = 7.7 Hz, 1H), 3.37 (s, 6H), 3.66 (m, 1H), 3.81 (s, 3H), 3.82 (s, 3H), 3.93 (m, 1H), 4.50–4.70 (m, 6H), 5.74 (m, 1H), 5.87 (m, 1H), 6.44 (br d, *J* = 10.3 Hz, 1H), 6.88 (m, 2H), 7.28 (m, 2H); ^{13}C-NMR (75 MHz) δ 18.79, 29.68, 35.80, 36.39, 39.68, 43.46, 44.80, 52.33, 55.26, 55.57, 71.76, 72.58, 73.04, 91.53, 94.64, 95.02, 113.79 × 2, 129.22 × 3, 130.81 × 2, 137.56, 153.40, 159.15, 164.96, 198.63 (4 carbons were not detected, but the structure was confirmed by a ^{1}H-^{1}H COSY analysis.); IR (neat) 2950,

1730, 1700, 1670, 1615, 1515 cm^{-1}; HRMS calcd for $C_{32}H_{44}O_9$ (M^+) *m*/*z* 572.2985, found 572.2988.

(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]-7-methyl-4,9,11-cycloheptadecatrien-1-one

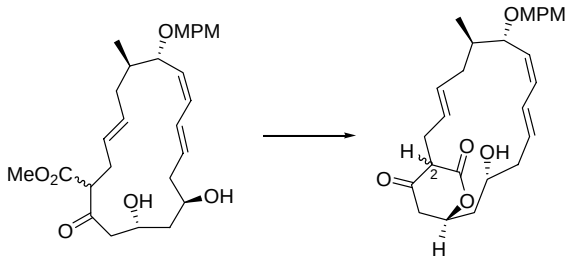


48a

To a cooled (0 °C), stirred solution of **48a** (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 $NaHCO_3$. This was diluted with saturated aqueous $NaHCO_3$ (60 mL), and extracted with CH_2Cl_2. 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 $C_{28}H_{38}O_7$ (M^+) *m*/*z* 486.2618, found 486.2618.

This compound showed a complicated ^{1}H-NMR spectrum, making its analysis extremely difficult. We attribute this complication to the presence of tautomers such as a hemiketal form and/or rotamers, in addition to diastereomers concening C(2).

(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

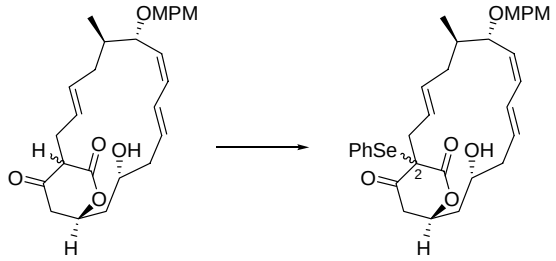


To a cooled (0 °C), stirred solution of the crude diol obtained above in MeOH (5 mL) was added *i*Pr_2NEt (0.5 mL). The mixture was stirred for 24 h, and then azeotroped with toluene to give the crude lactone, which was

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 $C_{27}H_{34}O_6$ (M^+) *m*/*z* 454.2355, found 454.2353.

This compound showed a complicated ^{1}H-NMR spectrum, making its analysis extremely difficult. We attribute this complication to the presence of tautomers such as a hemiketal form and/or rotamers, in addition to diastereomers concening C(2).

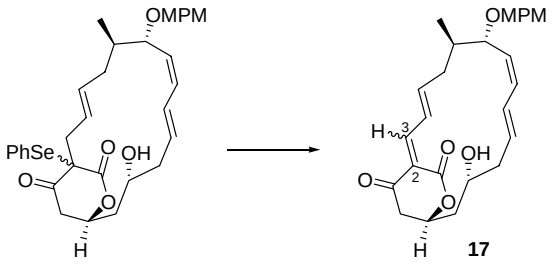
(1*RS*,3*E*,6*R*,7*S*,8*Z*,10*E*,13*R*,15*R*)-13-Hydroxy-7-[(4-methoxyphenyl)methoxy]-6-methyl-1-phenylselenyl-16-oxabicyclo[13.2.2]nonadeca-3,8,10-triene-17,18-dione



The following reaction was carried out under argon. To a stirred solution of the crude lactone obtained above in CH_2Cl_2 (2 mL) was added Et_3N (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 CH_2Cl_2 (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 CH_2Cl_2 (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, CH_2Cl_2, 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 **48a**) of the phenylselenide as an amorphous solid; TLC, R_f 0.57 (acetone/toluene, 1:2), HRMS calcd for $C_{33}H_{38}O_6Se$ (M^+) *m*/*z* 610.1833, found 610.1842.

This compound showed a complicated ^{1}H-NMR spectrum, making its analysis extremely difficult. We attribute this complication to the presence of tautomers such as a hemiketal form and/or rotamers, in addition to diastereomers concening C(2).

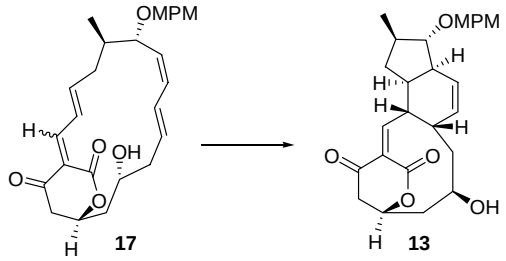
(1*EZ*,3*E*,6*R*,7*S*,8*Z*,10*E*,13*R*,15*R*)-13-Hydroxy-7-[(4-methoxyphenyl)methoxy]-6-methyl-16-oxabicyclo-[13.2.2]nonadeca-1,3,8,10-tetraene-17,18-dione (17)



The following reaction was carried out under argon. To a cooled (–50 °C) stirred solution of the selenide (159 mg, 0.260 mol) in CH_2Cl_2 (5mL) was added mCPBA (125 mg, 0.724 mmol). The mixture was stirred for 3.5 h at –50 °C, and quenched with Me_2S. The mixture was stirred for 0.5 h and then diluted with saturated aqueous $NaHCO_3$ (20 mL). This was extracted with CH_2Cl_2, and the combined organic layers were dried and concentrated in vacuo. The residue was filtered through silica gel to provide 118 mg of **17** 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 $C_{27}H_{32}O_6$ (M^+) *m*/*z* 452.2199, found 452.2195.

This compound showed a complicated ^{1}H-NMR spectrum, making its analysis extremely difficult. We attribute this complication to the presence of tautomers such as a hemiketal form and/or rotamers, in addition to geometrical isomers regarding C(2)–C(3) double bond.

(1*Z*,3*S*,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-oxa-tetracyclo[13.2.2.0^{3,11}.0^{4,8}]nonadeca-1,9-diene-17,18-dione (13)

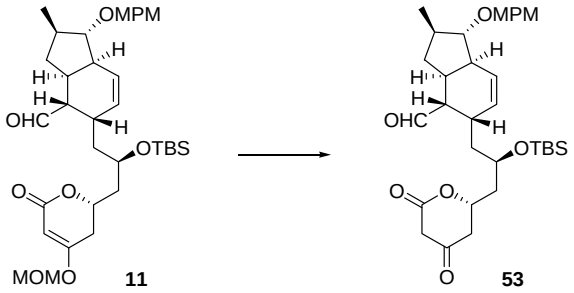


The compound **17** (118 mg, 0.260 mmol) was dissolved in degassed toluene (16 mL), and a crystal of BHT was added. The solution was divided into two 20 mL sealed tubes equipped with a screwed stopper, and the tubes were filled with argon. The tubes were heated to 130 °C for 26 h. After being cooled 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 **13** as a colorless oil; TLC, R_f 0.31 (acetone/toluene, 1:2); $[\alpha]^{23}_D$ +37.5 (*c* 0.625, $CHCl_3$); ^{1}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 ×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}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, 113.83×2, 124.83, 129.27×2, 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 $C_{27}H_{32}O_6$ (M^+) *m*/*z* 452.2199, found 452.2195.

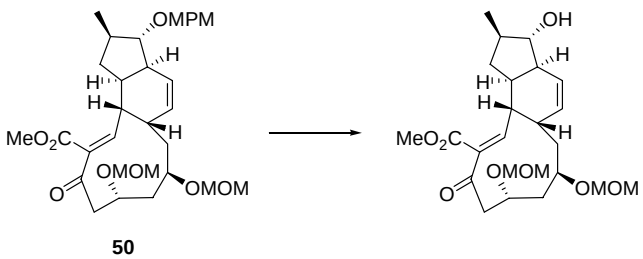
1.4. Completion of the Total Synthesis

(1*S*,2*S*,3*S*,4*Z*,6*S*,7*S*,8*R*)-3-{(2*R*)-2-(*t*-Butyldimethylsilyloxy)-3-[(6*R*)-2,4-dioxopyran-6-yl]propyl}-2-formyl-7-[(4-methoxyphenyl)methoxy]-8-methylbicyclo[4.3.0]non-4-ene (53)



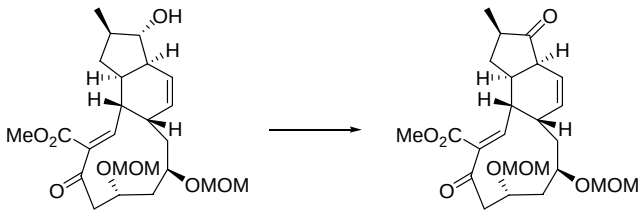
To a cooled (0 °C), stirred solution of **11** (32.3 mg, 0.0514 mmol) in Et_2O (1 mL) were added EtSH (0.019 mL, 0.257 mmol) and $MgBr_2{\cdot}OEt_2$ (13.3 mg, 0.0514 mmol). The mixture was stirred for 8 h and quenched with saturated aqueous $NaHCO_3$. This was diluted with saturated aqueous $NaHCO_3$ (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, 1:1) to provide 19.1 mg (64%) of **53** as a colorless oil; TLC, R_f 0.23 (EtOAc/hexane, 1:1); $[\alpha]^{24}_D$ +28.3 (*c* 0.40, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.07, 0.08 (2s, 3H × 2), 0.88 (s, 9H), 1.06 (d, *J* = 6.5 Hz, 3H), 1.11 (m, 1H), 1.50 (m, 1H), 1.61–1.84 (m, 2H), 1.97–2.12 (m, 3H), 2.39–2.52 (m, 2H), 2.63–2.77 (m, 4H), 3.18 (dd, *J* = 4.4, 6.9 Hz, 1H), 3.44, 3.62 (2d, *J* = 19.0 Hz, 1H × 2), 3.81 (s, 3H), 4.07 (m, 1H), 4.48, 4.56 (2d, *J* = 11.0 Hz, 1H × 2), 4.76 (m, 1H), 5.71 (br d, *J* = 10.5 Hz, 1H), 5.83 (br d, *J* = 10.5 Hz, 1H), 6.89 (m, 2H), 7.27 (m, 2H), 9.70 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (75 MHz) δ –4.64, –4.15, 17.94, 18.37, 25.77 × 3, 28.56, 34.09, 36.80, 39.10, 39.56, 42.62, 43.54, 44.09, 47.17, 54.65, 55.26, 65.88, 72.11, 72.25, 92.15, 113.80 × 2, 127.80, 129.27 × 2, 130.59, 130.97, 159.19, 166.85, 199.53, 204.71; IR (neat) 2950, 1715, 1615, 1515 cm^{-1}; HRMS calcd for $C_{32}H_{48}O_5Si$ (M^+–CO_2) *m*/*z* 540.3271, found 540.3252.

(1*S*,2*Z*,6*R*,8*R*,10*S*,11*Z*,13*S*,14*S*,15*R*,17*R*)-14-Hydroxy-3-methoxycarbonyl-6,8-di(methoxymethoxy)-15-methyltricyclo[8.7.0.0^{13,17}]heptadeca-2,11-dien-4-one



To a stirred solution of **50** (12.6 mg, 0.022 mmol) in CH_2Cl_2 (1 mL) was added H_2O (0.05 mL). This was stirred for 30 min and then DDQ (8.1 mg, 0.036 mmol) was added at 0 °C. The mixture was stirred for 3 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 (acetone/toluene, 1:7) to provide 9.0 mg (90%) of the secondary alcohol as a colorless oil; TLC, R_f 0.46 (acetone/toluene, 1:2); $[\alpha]^{22}_D$ +2.74 (c 0.660, $CHCl_3$); ^{1}H-NMR (270 MHz) δ 0.86 (m, 1H), 1.04 (d, *J* = 6.2 Hz, 3H), 1.59 (m, 1H), 1.71–1.84 (m, 4H), 2.08–2.36 (m, 4H), 2.62 (m, 1H), 2.88 (dd, *J* = 7.3, 13.6 Hz, 1H), 3.03 (td, *J* = 10.3, 4.4 Hz, 1H), 3.10 (dd, *J* = 2.6, 13.6 Hz, 1H), 3.28 (t, *J* = 9.2 Hz, 1H), 3.37 (s, 6H), 3.72 (m, 1H), 3.81 (s, 3H), 3.86 (m, 1H), 4.56 (d, *J* = 7.0 Hz, 1H), 4.60 (d, *J* = 7.0 Hz, 1H), 4.68 (d, *J* = 7.0 Hz, 1H), 4.69 (d, *J* = 7.0 Hz, 1H), 5.83–5.91 (m, 2H), 6.35 (d, *J* = 10.3 Hz, 1H); ^{13}C-NMR (68 MHz) δ 17.33, 33.40, 35.10, 36.28, 37.89, 41.38, 44.35, 45.58, 46.27, 52.35, 55.60, 71.59, 73.03, 83.65, 94.65, 94.91, 126.99, 127.05, 131.77, 137.70, 153.63, 164.72, 198.90 (1 carbon was not detected, but the structure was confirmed by a COSY analysis.); IR (neat) 3460, 2950, 1730, 1690, 1670, 1615 cm^{-1}; HRMS calcd for $C_{24}H_{36}O_8$ (M^+) *m*/*z* 452.2410, found 452.2425.

(1*S*,2*Z*,6*R*,8*R*,10*S*,11*Z*,13*S*,15*R*,17*R*)-3-Methoxycarbonyl-6,8-di(methoxymethoxy)-15-methyltricyclo-[8.7.0.0^{13,17}]heptadeca-2,11-diene-4,14-dione (54)

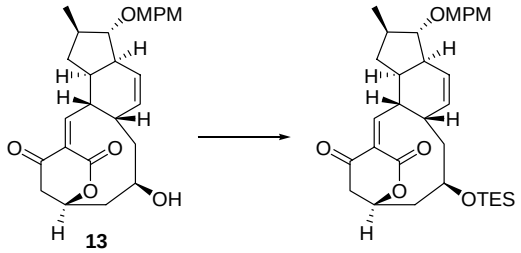


54

To a cooled (0 °C), stirred solution of the secondary alcohol (8.2 mg, 0.018 mmol) in CH_2Cl_2 (1 mL) was added Dess–Martin periodinane (16.0 mg, 0.035 mmol). The mixture was stirred for 2 h and then diluted with saturated aqueous $NaHCO_3$-20% aqueous $Na_2S_2O_3$ (1:1, 10 mL) and CH_2Cl_2 (5 mL) at 0 °C. The mixture was stirred for 30 min and the organic layer was separated. The aqueous layer 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/toluene, 1:1) to provide 8.1 mg (99%) of **54** as a colorless oil; TLC, R_f 0.44 (acetone/toluene, 1:3); $[\alpha]^{25}_D$ +96 (*c* 0.40, $CHCl_3$); ^{1}H-NMR (270 MHz) δ 1.11 (d, *J* = 6.6 Hz, 3H), 1.45 (m, 1H), 1.80 (m, 1H), 1.97–2.12 (m, 3H), 2.32 (m, 2H), 2.54 (m, 1H), 2.76–2.87 (m, 2H), 2.95 (m, 1H), 3.09 (m, 1H), 3.23 (m, 1H), 3.38 (s, 6H), 3.56 (m, 1H), 3.83 (s, 3H), 4.01 (m, 1H), 4.61 (d, *J* = 7.3 Hz, 1H), 4.62 (d, *J* = 7.0 Hz, 1H), 4.66 (d, *J* = 7.0 Hz, 1H), 4.70 (d, *J* = 7.3 Hz, 1H), 5.76–5.86 (m, 2H), 6.53 (d, *J* = 10.6

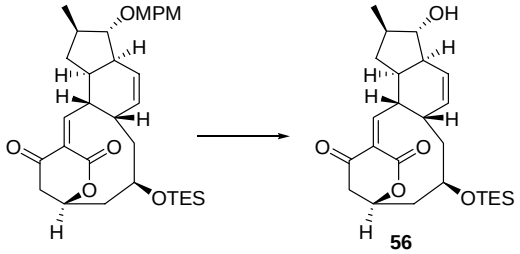
Hz, 1H); ^{13}C-NMR (68 MHz) δ 14.17, 33.29, 34.90, 35.01, 41.32, 41.38, 55.58, 55.66, 71.96, 73.00, 94.65, 95.26, 124.23, 128.80, 138.02 × 2, 151.07 × 2, 198.29, 217.64 (4 carbons were not detected, but the structure was confirmed by ^{1}H-^{1}H COSY analysis.); IR (neat) 2940, 1730, 1680, 1640 cm^{-1}; HRMS calcd for $C_{24}H_{34}O_8$ (M^+) *m*/*z* 450.2253, found 450.2240.

(1*Z*,3*S*,4*R*,6*R*,7*S*,8*S*,9*Z*,11*S*,13*R*,15*R*)-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 **13** (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); $[\alpha]^{23}_{D}$ +47 (*c* 0.40, $CHCl_3$); ^{1}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 ×2), 4.87 (m, 1H), 5.65 (d, *J* = 10.4 Hz, 1H), 5.71 (d, *J* = 10.4 Hz, 1H), 6.90 (m, 3H), 7.30 (m, 2H); ^{13}C-NMR (68 MHz) δ 5.35 ×3, 6.88 ×3, 18.86, 35.56×2, 37.64, 39.65, 39.82, 41.47, 41.81, 42.30, 45.61, 55.26, 67.79, 71.59, 72.77, 92.61, 113.80×2, 125.52, 129.27×2, 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 $C_{33}H_{46}O_6Si$ (M^+) *m*/*z* 566.3064, found 566.3061.

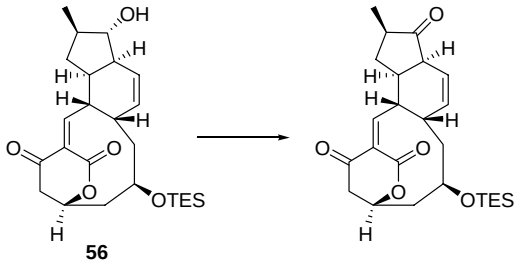
(1*Z*,3*S*,4*R*,6*R*,7*S*,8*S*,9*Z*,11*S*,13*R*,15*R*)-7-Hydroxy-6-methyl-13-triethylsilyloxy-16-oxatetracyclo[13.2.2.0^{3,11}.0^{4,8}]nonadeca-1,9-diene-17,18-dione (56)



56

To a stirred solution of the MPM ether (35.9 mg, 0.0633 mmol) in CH_2Cl_2 (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 $NaHCO_3$. This was diluted with saturated aqueous $NaHCO_3$ (15 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 1:1) to provide 26.1 mg (92%) of **56** as a colorless oil; TLC, R_f 0.30 (EtOAc/hexane, 1:1); $[\alpha]^{22}_D$ +65.9 (*c* 0.33, $CHCl_3$); ^{1}H-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); ^{13}C-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 $C_{25}H_{38}O_5Si$ (M^+) *m*/*z* 446.2489, found 446.2497.

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

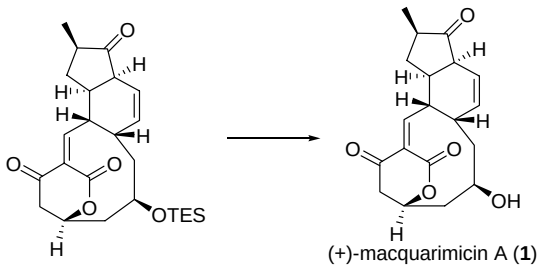


56

To a cooled (0 °C), stirred solution of **56** (23.5 mg, 0.0526 mmol) in CH_2Cl_2 (3 mL) were added $NaHCO_3$ (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 $NaHCO_3$–20% aqueous $Na_2S_2O_3$ (1:1, 10 mL) and CH_2Cl_2 (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 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 22.0 mg (94%) of the ketone as a colorless oil; TLC, R_f 0.55 (EtOAc/hexane, 1:1); $[\alpha]^{23}_D$ +182 (*c* 0.26, $CHCl_3$); ^{1}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}C-NMR (68 MHz) δ 5.33 ×3, 6.85 ×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 $C_{25}H_{36}O_5Si$ (M^+) *m*/*z* 444.2332, found 444.2331.

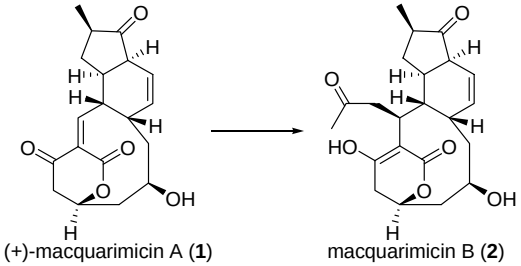
(+)-Macquarimicin A (1)



(+)-macquarimicin A (**1**)

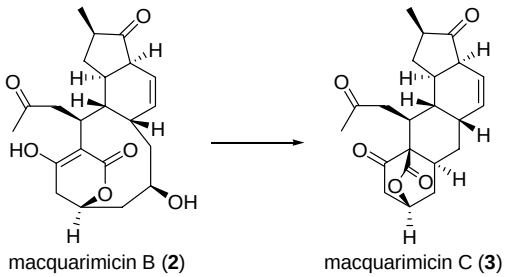
To a cooled (0 °C), stirred solution of the TES ether (22.0 mg, 0.0495 mmol) in MeOH (3 mL) was added PPTS (1.0 mg, 0.0040 mmol). The mixture was stirred for 2 h and then $NaHCO_3$ (6.0 mg, 0.071 mmol) was added at 0 °C. This was azeotroped with EtOAc and the residue was purified by column chromatography 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); $[\alpha]^{23}_D$ +270 (*c* 0.20, MeOH), $[\alpha]^{23}_D$ +285 (*c* 0.780, MeOH); ^{1}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}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 $C_{19}H_{22}O_5$ (M^+) *m*/*z* 330.1467, found 330.1457.

(+)-Macquarimicin B (2)



To a cooled (0°C), stirred solution of **1** (7.6 mg, 0.0230 mmol) in THF-H_2O (5:1, 1 mL) was added isopropenyl methyl ether (0.2 mL). The mixture was stirred for 3 h, and azeotroped with acetone. The residue was purified by column chromatography on silica gel (acetone/toluene, 1:2 to acetone) to provide 7.4 mg (83%) of the (+)-macquarimicin B (**2**) as white powder; TLC, R_f 0.30 (acetone/toluene, 1:1); $[\alpha]^{25}_D$ +325 (*c* 0.25, MeOH); ^{1}H-NMR (300 MHz) δ 1.09 (d, *J* = 6.6 Hz, 3H), 1.49 (q, *J* = 12.2 Hz, 1H), 1.74 (d, *J* = 14.9 Hz, 1H), 1.84 (d, *J* = 17.1 Hz, 1H), 1.98 (ddd, *J* = 5.1, 9.5, 17.1 Hz, 1H), 2.09–2.28 (m, 3H), 2.21 (s, 3H), 2.34 (d, *J* = 18.0 Hz, 1H), 2.43–2.53 (m, 2H), 2.77 (m, 1H), 2.89–3.01 (m, 4H), 3.49 (dd, *J* = 10.5, 20.0 Hz, 1H), 3.84 (m, 1H), 4.60 (m, 1H), 5.63 (dt, *J* = 10.6, 3.4 Hz, 1H), 6.01 (d, *J* = 10.6 Hz, 1H), 9.11 (s, 1H); ^{13}C-NMR (68 MHz) δ 13.99, 28.62, 30.12, 31.59, 31.85, 34.44, 36.40, 38.15, 40.57, 43.51, 45.24, 46.22, 46.36, 67.84, 71.53, 106.60, 122.96, 128.72, 164.48, 167.19, 214.30, 217.79; IR (KBr disk) 3530, 3130, 1725, 1685, 1660, 1635 cm^{-1}; HRMS calcd for $C_{22}H_{28}O_6$ (M^+) *m*/*z* 388.1886, found 388.1893.

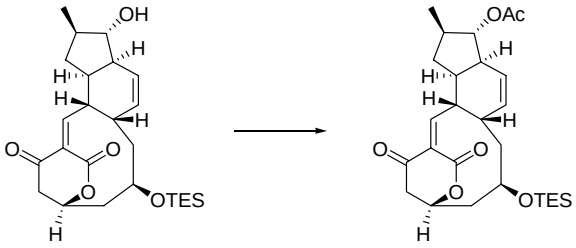
(+)-Macquarimicin C (3)



To a cooled (0°C), stirred solution of **2** (1.9 mg, 0.0049 mmol) in CH_2Cl_2 (1 mL) was added CSA (1.0 mg, 0.0043 mmol). The mixture was stirred for 2 h and CSA (3.0 mg, 0.013 mmol) was added. This was stirred for 7.5 h and CSA (1.5 mg, 0.0065 mmol) was added. This was stirred for 2 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 (acetone/toluene, 1:5) to provide 1.9 mg (quant.) of (+)-macquarimicin C (**3**) as an amorphous solid. TLC, R_f 0.53 (acetone/toluene, 1:1); $[\alpha]^{24}_D$ +250 (*c* 0.25, MeOH); ^{1}H-NMR (270 MHz) δ 1.06 (d, *J* = 6.6 Hz, 3H), 1.39 (q, *J* = 12.0 Hz, 1H), 1.59 (m, 1H), 1.85 (m, 1H), 1.90 (d, *J* = 14.0 Hz, 1H),

2.01–2.22 (m, 6H), 2.13 (s, 3H), 2.42 (dd, *J* = 2.2, 19.3 Hz, 1H), 2.45 (dd, *J* = 1.2, 19.0 Hz, 1H), 2.48 (m, 1H), 2.66 (m, 1H), 2.71 (dt, *J* = 19.0, 3.2 Hz, 1H), 2.82 (dd, *J* = 5.9, 19.3 Hz, 1H), 3.28 (m, 1H), 4.98 (m, 1H), 5.34 (d, *J* = 10.0 Hz, 1H), 5.73 (dt, *J* = 10.0, 3.3 Hz, 1H); ^{13}C-NMR (75 MHz) δ 13.88, 28.26, 29.89, 30.30, 31.88, 33.36, 34.08, 34.59, 36.89, 37.90, 41.91, 43.77, 46.30, 48.38, 65.89, 73.10, 125.94, 128.68, 169.36, 202.89, 206.75, 218.53; IR (neat) 2930, 1730, 1650, cm^{-1}; HRMS calcd for $C_{22}H_{26}O_5$ (M^+) *m*/*z* 370.1780, found 370.1777.

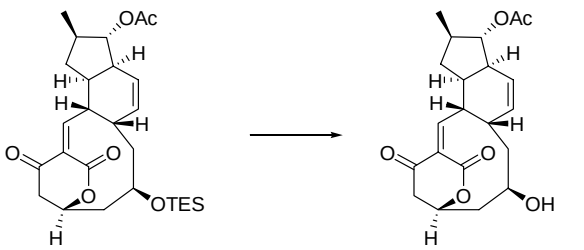
16-*O*-TES-9-*epi*-cochleamycin A



56

To a cooled (–18 °C), stirred solution of **56** (10.4 mg, 0.0233 mmol) in CH_2Cl_2 (1 mL) were added Ac_2O (0.010 mL, 0.11 mmol) and 4-dimethylaminopyridine (4.3 mg, 0.035 mmol). The mixture was stirred for 1.5 h and then filtered through a pad of silica gel. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) to provide 10.7 mg (94%) of 16-*O*-TES-9-epi-cochleamycin A as a colorless oil; TLC, R_f 0.69 (EtOAc/hexane, 1:2); $[\alpha]^{21}_D$ +44.9 (*c* 0.535, $CHCl_3$); ^{1}H-NMR (270 MHz) δ 0.52 (q, *J* = 7.8 Hz, 6H), 0.91 (t, *J* = 7.8 Hz, 9H), 1.07 (d, *J* = 7.0 Hz, 3H), 1.30 (q, *J* = 11.7 Hz, 1H), 1.60–1.74 (m, 2H), 1.88 (m, 1H), 2.02–2.19 (m, 2H), 2.09 (s, 3H), 2.33–2.56 (m, 2H), 2.62 (d, *J* = 18.7 Hz, 1H), 2.70 (m, 1H), 2.84 (m, 1H), 3.12 (dd, *J* = 6.8, 18.7 Hz, 1H), 3.34 (ddd, *J* = 2.2, 5.5, 11.4 Hz, 1H), 3.65 (dd, *J* = 6.2, 10.3 Hz, 1H), 4.46 (dd, *J* = 2.2, 6.2 Hz, 1H), 4.87 (m, 1H), 5.75 (br d, *J* = 10.6, 1H), 5.89 (m, 1H), 6.83 (d, *J* = 11.4 Hz, 1H); ^{13}C-NMR (68 MHz) δ 5.33 × 3, 6.88 × 3, 18.51, 21.28, 35.33, 35.50, 37.95, 38.87, 39.31, 41.44, 42.24, 42.82, 45.61, 67.73, 72.82, 86.76, 126.16, 128.86, 136.06, 156.68, 165.72, 171.37, 194.09; IR (neat) 2960, 1740, 1710, 1610 cm^{-1}; HRMS calcd for $C_{27}H_{40}O_6Si$ (M^+) *m*/*z* 488.2594, found 488.2596.

9-*Epi*-cochleamycin A (57)

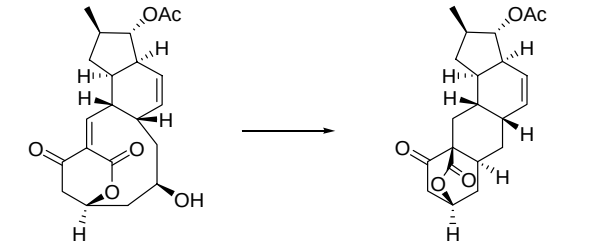


9-*epi*-cochleamycin A (**57**)

To a cooled (0 °C), stirred solution of 16-*O*-TES-9-epi-cochleamycin A (10.7 mg, 0.0219 mmol) in MeOH (1

mL) was added PPTS (1.7 mg, 0.0066 mmol). The mixture was stirred for 4 h and then $NaHCO_3$ (10.0 mg, 0.119 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 8.2 mg (quant.) of 9-*epi*-cochleamycin A (**57**) as an amorphous solid; TLC, R_f 0.38 (acetone/toluene, 1:2); $[\alpha]^{21}_D$ +42 (*c* 0.44, $CHCl_3$); ^{1}H-NMR (300 MHz) δ 1.07 (d, *J* = 6.6 Hz, 3H), 1.31 (q, *J* = 11.8 Hz, 1H), 1.71 (d, *J* = 17.3 Hz, 1H), 1.79 (d, *J* = 15.6 Hz, 1H), 1.85–2.12 (m, 4H), 2.08 (s, 3H), 2.44–2.56 (m, 2H), 2.68 (d, *J* = 18.7 Hz, 1H), 2.69 (m, 1H), 2.87 (m, 1H), 3.13 (dd, *J* = 7.4, 18.7 Hz, 1H), 3.36 (dd, *J* = 5.8, 11.1 Hz, 1H), 3.64 (m, 1H), 4.45 (d, *J* = 6.3 Hz, 1H), 4.90 (m, 1H), 5.78 (br d, *J* = 10.4, 1H), 5.90 (br d, *J* = 10.4 Hz, 1H), 6.82 (d, *J* = 11.1 Hz, 1H); ^{13}C-NMR (68 MHz) δ 18.49, 21.25, 35.22, 35.30, 37.95, 38.93, 39.33, 41.24 × 2, 42.76, 45.55, 66.84, 72.77, 86.65, 125.49, 129.61, 136.15, 156.48, 165.69, 171.28, 194.29; IR (neat) 3450, 2930, 1710, 1705, 1620 cm^{-1}; HRMS calcd for $C_{21}H_{26}O_6$ (M^+) *m*/*z* 374.1729, found 374.1723.

9-*Epi*-cochleamycin B (58)



9-*epi*-cochleamycin A (**57**) 9-*epi*-cochleamycin B (**58**)

To a cooled (0 °C), stirred solution of **57** (4.0 mg, 0.011 mmol) in MeOH (1 mL) were added $NaBH_4$ (4.0 mg, 0.11 mmol). The mixture was stirred for 6 h and then quenched with sat. aq. NH_4Cl (1 mL). This was diluted with brine and extracted with CH_2Cl_2. The combined organic layers were dried and concentrated in vacuo to give a crude product, which was immediately used in the next step without purification. To a cooled (0 °C), stirred solution of the product obtained above in CH_2Cl_2 (1 mL) were added CSA (0.5 mg, 0.002 mmol). The mixture was stirred for 1 h and then quenched with pH7 phosphate buffer (1 mL). This was diluted with brine 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, 1:2) to provide 2.7 mg (71%) of 9-*epi*-cochleamycin B (**58**) as an amorphous solid; TLC, R_f 0.61 (acetone/toluene, 1:1); $[\alpha]^{21}_D$ +73 (*c* 0.14, $CHCl_3$); ^{1}H-NMR (300 MHz) δ 1.04 (d, *J* = 6.8 Hz, 3H), 1.21 (q, *J* = 12.0 Hz, 1H), 1.45 (dt, *J* = 4.5, 13.2 Hz, 1H), 1.68 (t, *J* = 13.5 Hz, 1H), 1.76–1.94 (m, 4H), 1.98–2.12 (m, 2H), 2.07 (s, 3H), 2.15–2.30 (m, 3H), 2.37–2.52 (m, 3H), 2.73 (dt, *J* = 19.3, 3.0 Hz, 1H), 4.38 (dd, *J* = 2.7, 6.3 Hz, 1H), 4.99 (m, 1H), 5.27 (br d, *J* = 10.2, 1H), 5.90 (dt, *J* = 10.2, 2.7 Hz, 1H); ^{13}C-NMR (68 MHz) δ 18.46, 21.31, 24.53, 29.57, 30.38, 30.55, 33.14, 35.68, 38.04, 38.93, 41.32, 41.75, 42.99, 60.13, 73.03, 86.99, 127.16, 130.27, 170.10, 171.37, 203.42; IR (neat) 2925, 1765, 1735, 1720 cm^{-1}; HRMS (FAB) calcd for $C_{21}H_{27}O_5$ (M^++H) *m*/*z* 359.1859, found

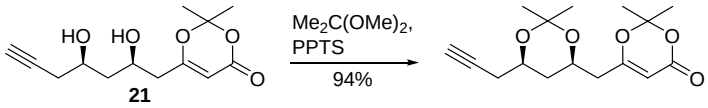
359.1853.

2. Determination of Stereochemistry

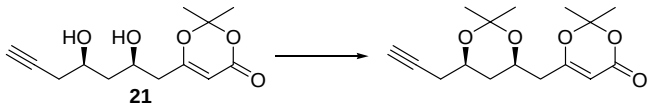
2.1. Stereochemistry of *syn*-1,3-Diol **21**

Stereochemistry of **21** was determined to be *syn* based on the ^{13}C-NMR analysis of its acetonide, of which synthesis is shown below (Scheme S3). The ^{13}C-NMR shifts of newly formed (CH$_3$)$_2$C= were δ 19.64 and 29.86 ppm. As the difference of the two methyl shifts was 10.22 ppm, we assigned **21** to be *syn*-isomers based on the empirical rule reported by Rychnovsky et al.[7]

Scheme S3



6-[(4*R*,6*R*)-2,2-Dimethyl-6-(2-propynyl)-1,3-dioxan-4-yl]methyl-2,2-dimethyl-1,3-dioxin-4-one



To a stirred solution of **21** (18.4 mg, 0.0724 mmol) in 2,2-dimethoxypropane (1 mL) was added PPTS (0.7 mg, 0.003 mmol). The mixture was stirred for 9 h and then Et_3N (0.05 mL) was added. The mixture was concentrated in vacuo and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to provide 20.1 mg (94%) of the acetonide as a colorless oil; TLC, R_f (EtOAc/hexane, 1:1); $[\alpha]^{23}_D$ –46.5 (*c* 1.01, $CHCl_3$); ^{1}H NMR (270 MHz) δ 1.26 (q, *J*= 12.2 Hz, 1H), 1.37, 1.43, 1.68, 1.70 (4s, 3H × 4), 1.80 (dt, *J*= 12.2, 2.4 Hz, 1H), 2.02 (t, *J*= 2.6 Hz, 1H), 2.23–2.53 (m, 4H), 4.00 (m, 1H), 4.15 (m, 1H), 5.32 (s, 1H); ^{13}C NMR (68 MHz) δ 19.64, 24.48, 25.60, 26.06, 29.86, 35.56, 40.43, 65.77, 67.44, 70.09, 79.82, 95.29, 99.06, 106.49, 161.06, 168.23; IR (neat) 3000, 2950, 1735, 1635 cm^{-1}; HRMS calcd for $C_{16}H_{22}O_5$ (M^+) *m*/*z* 294.1467, found 294.1487.

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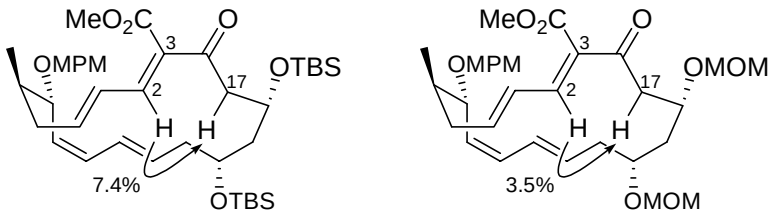
[7] Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511–3515.

2.2. C(2)–C(3) Geometry of TADA Substrates **16** and **49**

The C(2)–C(3) geometry of **16** and **49** was determined to be *Z* by NOE experiments as shown in Figure S1. In both cases, irradiation at H(2) enhanced one of two signals for H(17), establishing *cis*-relationship of H(2)–H(17).



16 **49**

Figure S1. NOE experiments on TADA substrates **16** and **49**.

2.3. Determination of the Stereochemistry of the Cycloadducts **40**, **10**, **11**, **44**, **50**, **51a**, and **52a**

Stereochemistry of each cycloadduct was determined unambiguously by analysis of ^{1}H NMR spectrum and NOE difference experiments of the cycloadduct and its derivative if required. The syntheses of the derivatives are described in the Experimental Section (pages 22 and 39 for reduction of **40** and **52a**, respectively).

Results of the NOE experiments on the cycloadducts produced via IMDA reactions are illustrated in Figure S2. The stereochemistry of **40**, the cycloadduct obtained from model substrate **38**, was determined as follows. The signal enhancement between substituents at angular positions established expected *cis*-*anti*-*cis* ring fusion. The π-facial selectivity of the reaction was determined by *syn* relationship H(7) and H(5). Likewise, stereochemistry of **10** and **11**, cycloadducts with the same stereochemistry, was determined. On the other hand, NOE experiments revealed that **44** also have *cis*-*anti*-*cis* ring fusion, while it was established that the opposite π-facial selectivity provided **44** by *syn* relationship H(8) and H(9). These results indicate that all cycloadducts are derived from (*E*,*Z*,*E*)-1,6,8-nonatrienes. Thus alkene isomerization was not observed.

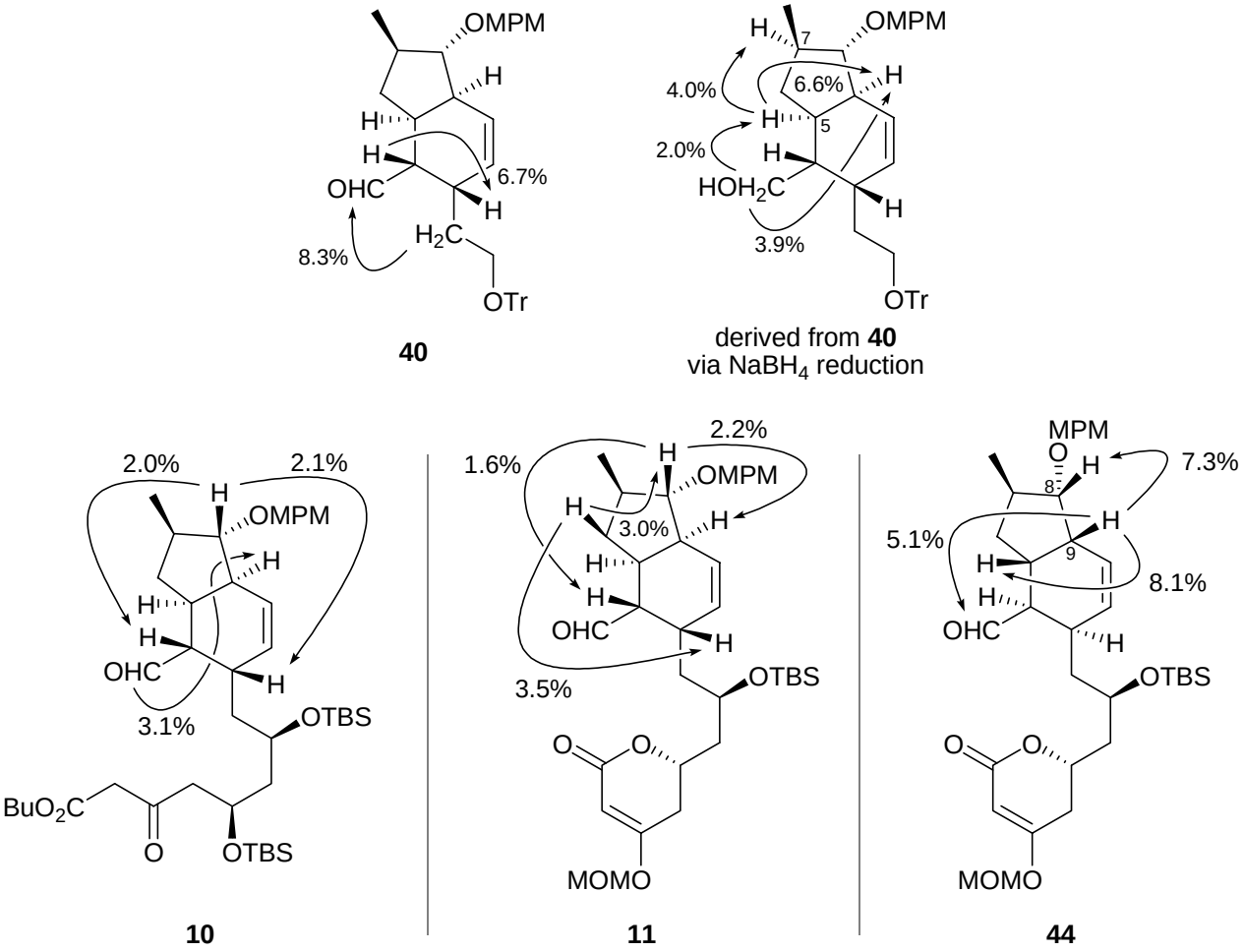


Figure S2. NOE experiments on the cycloadducts of the IMDA reactions

The stereochemistry of cycloadducts **50**, **51a**, and **52a**, obtained from TADA reactions of **16** and **49** are established as shown in Figure S3. The cycloadduct **50**, afforded from **49**, proved to have the same stereochemistry as macquarimicins. On the other hand, the NOE experiments on **51a** revealed the opposite π-facial selectivity by *syn* relationship of H(8) and H(9). In the case of cycloadduct **52a**, C(2)–C(3) geometry was determined to be *E*, revealing involvement of alkene isomerization.

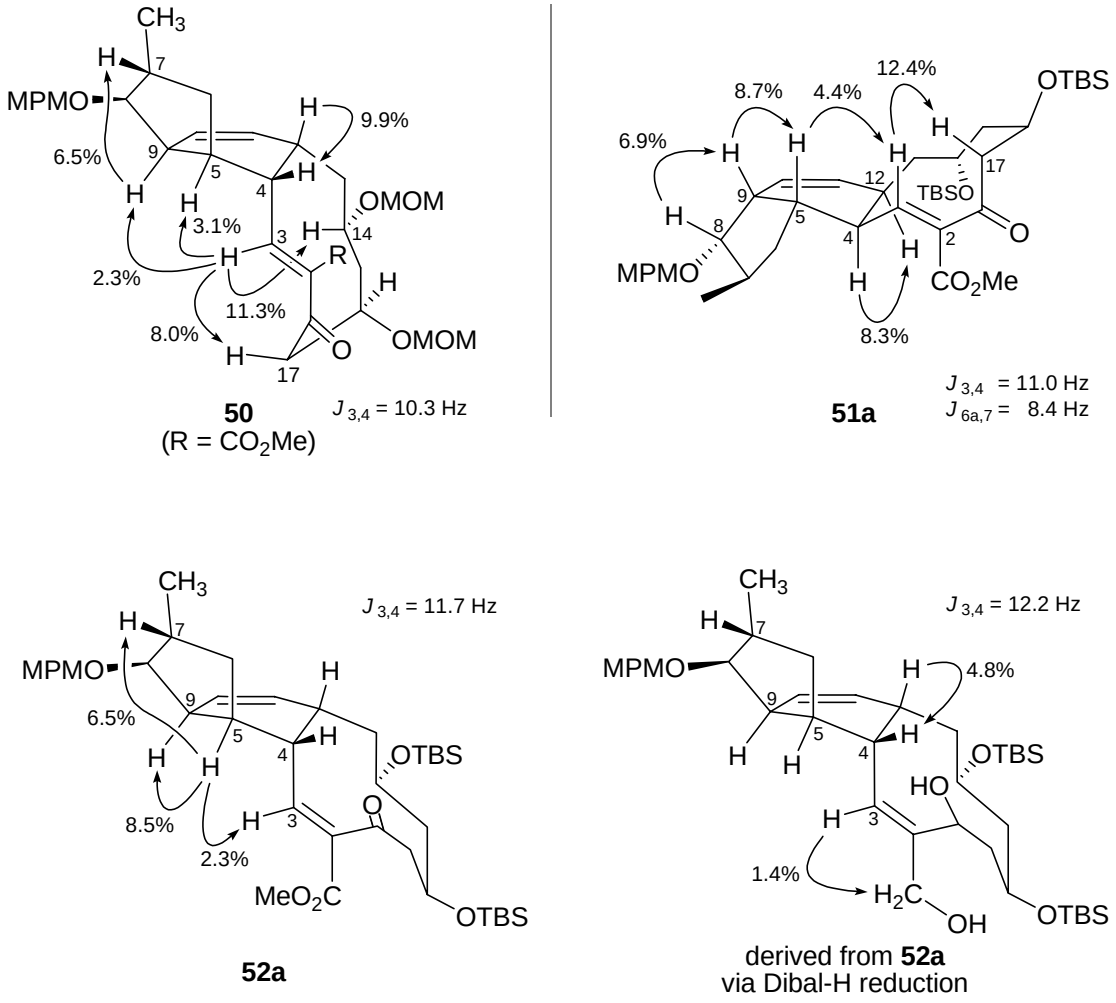


Figure S3. NOE experiments on the cycloadducts of the TADA reactions