Supporting Information

Materials and methods

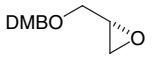
All non-aqueous reactions were carried out in oven or flame-dried glassware under an argon atmosphere, unless otherwise noted. All solvents were reagent grade. Diethyl ether and tetrahydrofuran were freshly distilled from sodium/benzophenone ketyl under argon. The argon was deoxygenated by passing it through an OXICLEAR™ tube from Aldrich. Dichloromethane was freshly distilled from calcium hydride. Anhydrous pyridine was purchased from Aldrich and used without purification. *t*-Butyllithium was purchased from Aldrich and standardized by titration with diphenylacetic acid or *N*-pivaloyl-*o*-toluidine. All other commercially available reagents were used as received.

Except as indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with 0.25-mm E. Merck pre-coated silica gel plates. Flash chromatography was performed with silica gel 60 (particle size 230–400 mesh) supplied by E. Merck. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated.

Infrared spectra were recorded with a Perkin-Elmer Model 283B spectrometer with polystyrene as external standard or Perkin-Elmer 1600 Series FTIR spectrometer, and are reported in cm^{-1} (abs). Proton (^1H) and Carbon (^{13}C) NMR spectra were recorded on a Bruker AM-500 spectrometer. Chemical shifts (δ) are reported in ppm with the solvent resonance as the internal standard relative to chloroform (δ 7.26) and benzene (δ 7.15) for ^1H, and chloroform (δ 77.0) and benzene (δ 128.0) for ^{13}C. Optical rotations were obtained with a Perkin-Elmer model 241 polarimeter with a sodium lamp, and are reported as follows: $[\alpha]_D^{25}$, [c (g/100 mL), solvent]. High resolution mass spectra were measured at the University of Pennsylvania Mass Spectrometry Service Center on either a VG Micromass 70/70H or VG ZAB-E spectrometer.

Preparative Experiments

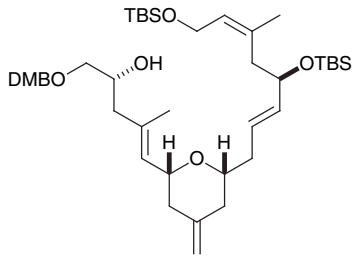
Preparation of Epoxide (+)-4



(+)-**4**

Under argon, a solution of (*S*)-(–)-glycidol (500 mg, 6.75 mmol) in anhydrous tetrahydrofuran (2 mL) was added dropwise *via* cannula to a suspension of sodium hydride (95%, 194.4 mg, 8.1 mmol) in anhydrous tetrahydrofuran (6.6 mL) at 0 °C. During the addition a vigorous evolution of hydrogen gas was observed. The white-cloudy mixture was then stirred at 0 °C for 0.5 h, at which time solid 3,4-dimethoxybenzyl chloride (DMBCl, 1.39 g, 7.43 mmol) was added in one portion followed in turn by solid tetrabutylammonium iodide (73.3 mg, 0.198 mmol). The resultant cloudy mixture was stirred at ambient temperature for 4 h and then at reflux (oil bath temperature at 77 °C) for 15 h. The reaction was then cooled to ambient temperature, quenched with saturated aqueous NH_4Cl solution (2 mL) and poured into water (5 mL). The layers were separated, and the aqueous phase was extracted with diethyl ether (2 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Gradient flash chromatography (hexanes/ethyl acetate, 4:1 $\rightarrow$ 2:1) afforded (+)-**4** (597 mg, 39% yield) as a clear pale yellow oil: $[\alpha]_D^{25}$ +1.8° (*c* 2.25, $CHCl_3$); IR (neat) 2993 (s), 2923 (s), 2842 (s), 1593 (s), 1512 (s), 1462 (s), 1261, (s), 1236 (s), 1156 (s), 1135 (s), 1085 (s), 1025 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.89 (d, J = 1.8 Hz, 1 H), 6.85 (dd, J = 8.2, 1.8 Hz, 1 H), 6.81 (d, J = 8.1 Hz, 1 H), 4.52 (d, J = 11.6 Hz, 1 H), 4.46 (d, J = 11.6 Hz, 1 H), 3.86 (s, 3 H), 3.84 (s, 3 H), 3.72 (dd, J = 11.5, 3.0 Hz, 1 H), 3.39 (dd, J = 11.5, 5.9 Hz, 1 H), 3.17-3.13 (m, 1 H), 2.77 (dd, J = 4.5, 4.5 Hz, 1 H), 2.58 (dd, J = 5.0, 2.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0, 148.6, 130.4, 120.3, 111.1, 110.9, 73.1, 70.5, 55.8, 55.7, 50.7, 44.1; high resolution mass spectrum (ESI) *m/z* 247.0952 [$(M+Na)^+$; calcd for $C_{12}H_{16}O_4Na$: 247.0946].

Preparation of Alcohol (–)-6

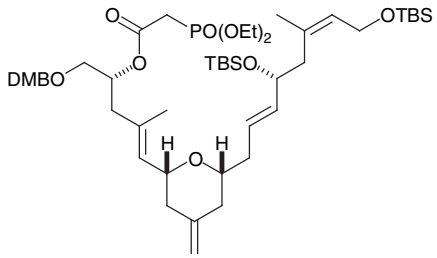


(–)-**6**

Under argon, a suspension of copper (I) cyanide (120.4 mg, 1.34 mmol) in anhydrous tetrahydrofuran (3.8 mL) at –78 °C was treated dropwise with 2-thienyllithium (1.0 *M* solution in tetrahydrofuran, 1.48 mL, 1.48 mmol). The heterogeneous mixture was then transferred to a 0 °C bath, where it quickly became a clear light brown solution, and stirred for 10 min. The reagent was then stored in a 0 °C refrigerator and used later (ca. 0.5 h) without further manipulations. In a separate flask under argon, a solution of vinyl bromide (–)-**AB** (100 mg, 0.167 mmol, azeotropically dried with benzene) in anhydrous diethyl ether (1.1 mL) at –78 °C was treated with *tert*-butyllithium (1.7 *M* solution in pentane, 168 μL, 0.283 mmol). The resultant pale yellow solution was stirred at –45 °C for 15 min, recooled to –78 °C, and treated with the aforementioned cuprate reagent (692 μL, 0.175 mmol). The dark yellow reaction mixture was then stirred at –45 °C for 30 min, after which a solution of epoxide (+)-**4** (55 mg, 0.245 mmol) in anhydrous diethyl ether (1.6 mL) was added dropwise *via* cannula. The resultant reaction mixture was warmed to 0 °C over 45 min, stirred at that temperature for 1 h, and quenched with saturated aqueous NH_4Cl solution (3 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Gradient flash chromatography (hexanes/ethyl acetate, 4:1 → 2:1) furnished (–)-**6** (50 mg, 40% yield) as a pale yellow oil: $[\alpha]_D^{25}$ –15.7° (*c* 1.53 PhH); IR (neat) 3457 (m, br), 2930 (s), 2856 (s), 1647 (m), 1596 (m), 1517 (s), 1470 (s), 1359 (m), 1254 (s), 1064 (s, br), 838 (s), 774 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.88-6.85 (m, 2 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 5.56 (ddd, *J* = 15.4, 7.0, 7.0 Hz, 1 H), 5.44 (dd, *J* = 15.4, 6.5 Hz, 1 H), 5.36 (app dt, *J* = 6.4,

0.9 Hz, 1 H), 5.29 (app dd, J = 7.7, 0.8 Hz, 1 H), 4.71 (s, 2 H), 4.48 (s, 2 H), 4.19-4.09 (complex m, 3 H), 3.98 (ddd, J = 11.2, 7.9, 2.6 Hz, 1 H), 3.96-3.92 (m, 1 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.46 (dd, J = 9.6, 3.4 Hz, 1 H), 3.33 (dd, J = 9.6, 7.1 Hz, 1 H), 3.32-3.27 (m, 1 H), 2.36-2.30 (m, 2 H), 2.28 (dd, J = 13.3, 7.2 Hz, 1 H), 2.20-2.18 (m, 3 H), 2.16-2.09 (m, 3 H), 1.98 (app t, J = 12.3 Hz, 1 H), 1.89 (app t, J = 12.3 Hz, 1 H), 1.72 (d, J = 1.0 Hz, 3 H), 1.70 (d, J = 1.1 Hz, 3 H), 0.89 (s, 9 H), 0.86 (s, 9 H), 0.05 (s, 6 H), 0.01 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.1, 148.7, 144.4, 135.7, 135.0, 133.7, 130.5, 128.7, 127.5, 125.75, 120.4, 111.2, 111.0, 108.55, 78.0, 75.5, 73.7, 73.3, 72.3, 68.5, 60.2, 55.9, 55.8, 43.5, 41.5, 40.7, 39.9, 39.0, 26.0, 25.9, 18.4, 18.15, 17.2, –4.4, –4.8, –5.1; high resolution mass spectrum (ESI) *m/z* 767.4717 [$(M+Na)^+$; calcd for $C_{42}H_{72}O_7Si_2Na$: 767.4714].

Preparation of Phosphonoester (–)-7

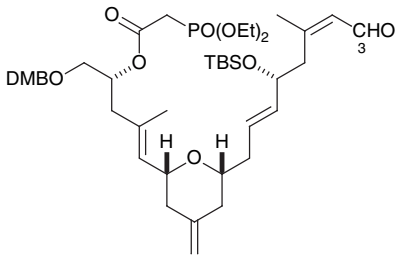


(–)-**7**

Under argon, a solution of alcohol (–)-**6** (44 mg, 59.0 μmol, azeotropically dried with benzene) and diethylphosphonoacetic acid (29 mg, 0.148 mmol) in anhydrous dichloromethane (2.5 mL) at ambient temperature was treated with 4-dimethylaminopyridine (7.2 mg, 59.0 μmol) followed by a solution of 1,3-dicyclohexylcarbodiimide (30.5 mg, 0.148 mmol) in anhydrous dichloromethane (0.5 mL). The cloudy reaction mixture was stirred at ambient temperature for 0.5 h and then concentrated *in vacuo*. The crude residue was taken up in 1:1 hexanes/diethyl ether (5mL), filtered through a pad of celite, and concentrated *in vacuo*. Gradient flash chromatography (hexanes/ethyl acetate, 1:1 → 1:2) gave (–)-**7** (52.3 mg, 96% yield) as a clear, colorless oil: $[\alpha]_D^{25}$ –11.9° (*c* 1.95, PhH); IR (neat) 2930 (s), 2856 (s), 1738 (s), 1655 (m), 1519

(s), 1466 (s), 1263 (s, br), 1064 (s, br), 835 (s), 777 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.87 (d, *J* = 1.6 Hz, 1 H), 6.84 (dd, *J* = 8.1, 1.7 Hz, 1 H), 6.81 (d, *J* = 8.1 Hz, 1 H), 5.54 (ddd, *J* = 15.4, 6.9, 6.9 Hz, 1 H), 5.44 (dd, *J* = 15.5, 6.5 Hz, 1 H), 5.36 (t, *J* = 6.0 Hz, 1 H), 5.25 (app d, *J* = 7.8 Hz, 1 H), 5.21-5.16 (m, 1 H), 4.69 (s, 2 H), 4.47 (d, *J* = 11.7 Hz, 1 H), 4.42 (d, *J* = 11.7 Hz, 1 H), 4.19-4.10 (complex series of m, 7 H), 3.93 (ddd, *J* = 11.1, 7.9, 2.4 Hz, 1 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.52-3.47 (m, 2 H), 3.29-3.24 (m, 1 H), 2.99 (s, 1 H), 2.95 (s, 1 H), 2.38-2.33 (m, 2 H), 2.31-2.26 (m, 2 H), 2.19 (app d, *J* = 13.2 Hz, 1 H), 2.13 (dd, *J* = 14.4, 7.3 Hz, 1 H), 2.10 (dd, *J* = 13.2, 6.1 Hz, 1 H), 2.04 (app d, *J* = 13.2 Hz, 1 H), 1.91 (app t, *J* = 12.1 Hz, 1 H), 1.86 (app t, *J* = 12.1 Hz, 1 H) 1.72 (s, 3 H), 1.69 (s, 3 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 0.88 (s, 9 H), 0.86 (s, 9 H), 0.043 (s, 6 H), 0.004 (s, 3 H), –0.007 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3 (d, *J* = 5.8 Hz, 1 C), 149.0, 148.7, 144.2, 135.8, 133.7, 133.6, 130.4, 129.5, 127.5, 125.6, 120.3, 111.1, 110.9, 108.6, 77.9, 75.4, 73.1, 72.4, 72.3, 70.0, 62.6 (app t, *J* = 6.2 Hz, 2 C), 60.2, 55.9, 55.85, 41.5, 40.75, 40.55, 39.8, 39.0, 34.4 (d, *J* = 134.7 Hz, 1 C), 26.0, 25.9, 24.5, 18.4, 18.15, 17.0, 16.32, 16.27 –4.4, –4.8, –5.1; high resolution mass spectrum (ESI) *m/z* 945.5091[$(M+Na)^+$; calcd for $C_{48}H_{83}O_{11}PSi_2Na$: 945.5109].

Preparation of Aldehyde (–)-3



(–)-**3**

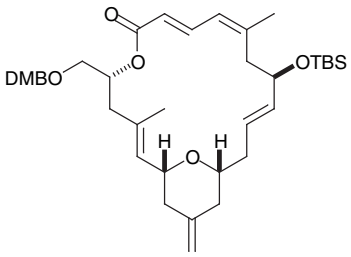
Under argon, a solution of phosphonoester (–)-**7** (46 mg, 50.0 μmol) in tetrahydrofuran (4.3 mL) at ambient temperature was treated with a stock solution of HF·pyridine (1.66 mL) [pyridinium poly(hydrogen fluoride) (3 g); pyridine (10 mL); tetrahydrofuran (20 mL)]. The resultant mixture was stirred at ambient temperature for 4 h, then slowly quenched with saturated

aqueous $NaHCO_3$ solution (6 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Gradient flash chromatography (ethyl acetate/hexanes, 2:1 → 4:1 → 1:5) provided recovered (–)-**7** (15 mg) and the C(3) alcohol (25 mg, 62% yield; 92% yield based on the recovery of the starting material) as a clear, colorless oil: $[\alpha]_D^{25}$ –10.7° (*c* 1.25, PhH); IR (neat) 3425 (s, br), 2922 (s), 2850 (s), 1737 (s), 1516 (s), 1460 (m), 1260 (s, br), 1054 (s), 833 (s), cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.90 (d, *J* = 1.9 Hz, 1 H), 6.86 (dd, *J* = 8.1, 1.9 Hz, 1 H), 6.62 (d, *J* = 8.1 Hz, 1 H), 5.70 (ddd, *J* = 15.4, 7.0, 7.0 Hz, 1 H), 5.63 (app dt, *J* = 6.8, 0.9 Hz, 1 H), 5.52 (dd, *J* = 15.5, 6.7 Hz, 1 H), 5.44-5.38 (m, 2 H), 4.75 (s, 2 H), 4.43 (d, *J* = 11.7 Hz, 1 H), 4.36 (d, *J* = 11.7 Hz, 1 H), 4.27-4.23 (m, 1 H), 4.20-4.12 (m, 2 H), 4.02-3.94 (complex m, 5 H), 3.52 (s, 3 H), 3.49 (app d, *J* = 4.8 Hz, 2 H), 3.42 (s, 3 H), 3.32-3.27 (m, 1 H), 2.94 (s, 1 H), 2.90 (s, 1 H), 2.48 (dd, *J* = 13.2, 7.8 Hz, 1 H), 2.34 (app d, *J* = 6.9 Hz, 2 H), 2.32-2.25 (m, 1 H), 2.16-2.11 (m, 2 H), 2.09 (app d, *J* = 14.4, Hz, 1 H), 2.06 (app d, *J* = 14.1 Hz, 1 H), 2.00 (app t, *J* = 12.3 Hz, 1 H), 1.92 (app t, *J* = 12.2 Hz, 1 H), 1.71 (d, *J* = 0.5 Hz, 3 H), 1.61 (d, *J* = 1.0 Hz, 3 H), 1.05 (t, *J* = 7.1 Hz, 3 H), 1.05 (t, *J* = 7.1 Hz, 3 H), 0.99 (s, 9 H), 0.10 (s, 6 H); ^{13}C NMR (125 MHz, C_6D_6) δ 165.6 (d, *J* = 5.8 Hz, 1 C), 150.4, 149.9, 144.9, 136.2, 135.2, 133.6, 131.2, 130.3, 128.4, 126.5, 120.6, 112.5, 112.1, 108.7, 78.1, 75.9, 73.4, 72.7, 72.3, 70.5, 62.4 (app t, *J* = 5.0 Hz, 2 C), 59.0, 55.69, 55.67, 41.7, 41.2, 41.0, 40.4, 39.3, 34.9 (d, *J* = 133.4 Hz, 1 C), 26.2, 24.5, 18.5, 16.9, 16.4 (app d, *J* = 5.9 Hz, 2 C), –4.1, –4.5; high resolution mass spectrum (ESI) *m/z* 831.4271[$(M+Na)^+$; calcd for $C_{42}H_{69}O_{11}PSiNa$: 831.4245].

Under argon, a solution of the C(3) alcohol from the previous step (35.4 mg, 42.6 μmol) in anhydrous dichloromethane (2 mL) at ambient temperature was treated with pyridine (21 μL, 0.255 mmol) and Dess–Martin periodinane (40 mg, 93.8 μmol). The cloudy white solution was stirred at ambient temperature for 40 min and then quenched with a 1:1 mixture of 10% aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ solutions (1 mL). The resultant biphasic mixture was stirred for 5 min and poured into water (2 mL). The layers were separated, and the aqueous

phase was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Gradient flash chromatography (ethyl acetate/hexanes, 2:1 → 4:1) afforded (–)-**3** (32.6 mg, 95% yield) as a clear, colorless oil: $[\alpha]_D^{25}$ –8.0° (*c* 1.63, PhH); IR (neat) 2928 (s), 2856 (s), 1735 (s), 1675 (s), 1516 (s), 1465 (m), 1260 (s, br), 1055 (s), 1025 (s), 968 (m), 840 (m), 778 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 9.98 (d, *J* = 7.9 Hz, 1 H), 6.90 (d, *J* = 1.8 Hz, 1 H), 6.86 (dd, *J* = 8.0, 1.8 Hz, 1 H), 6.62 (d, *J* = 8.0 Hz, 1 H), 5.91 (app dd, *J* = 7.8, 1.0 Hz, 1 H), 5.67 (ddd, *J* = 15.4, 7.1, 7.1 Hz, 1 H), 5.44-5.35 (m, 3 H), 4.76 (br d, *J* = 1.3 Hz, 2 H), 4.43 (d, *J* = 11.7 Hz, 1 H), 4.36 (d, *J* = 11.7 Hz, 1 H), 4.17-4.13 (m, 1 H), 4.01 (ddd, *J* = 11.3, 7.9, 2.4 Hz, 1 H), 4.00-3.94 (m, 4 H), 3.52 (s, 3 H), 3.49 (d, *J* = 4.8 Hz, 2 H), 3.42 (s, 3 H), 3.29-3.24 (m, 1 H), 2,91 (s, 1 H), 2.87 (s, 1 H), 2.62 (dd, *J* = 13.0, 7.8 Hz, 1 H), 2.36 (d, *J* = 6.9 Hz, 2 H), 2.28-2.22 (m, 2 H), 2.12-2.04 (m, 3 H), 1.99 (app t, *J* = 12.3 Hz, 1 H), 1.90 (app t, *J* = 12.1 Hz, 1 H), 1.61 (d, *J* = 1.0 Hz, 3 H), 1.59 (d, *J* = 1.2 Hz, 3 H), 1.05 (t, *J* = 7.1 Hz, 6 H), 0.93 (s, 9 H), 0.02 (s, 3 H), –0.003 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 190.2 (d, *J* = 5.0 Hz, 1 C), 165.6 (d, *J* = 5.9 Hz, 1 C), 158.0, 150.3, 149.9, 144.7, 135.2, 133.5, 131.2, 130.6, 130.2, 127.5, 120.6, 112.5, 112.1, 108.8, 78.0, 75.9, 73.4, 72.75, 72.4, 70.4, 62.3 (d, *J* = 6.0 Hz, 2 C), 55.7, 55.67, 41.6, 41.2, 40.95, 40.4, 39.2, 35.0 (d, *J* = 133.8 Hz, 1 C), 26.05, 25.8, 18.3, 17.0, 16.4 (d, *J* = 5.8 Hz, 2 C), –4.2, –4.7; high resolution mass spectrum (ESI) *m/z* 829.4060 [$(M+Na)^+$; calcd for $C_{42}H_{67}O_{11}PSiNa$: 829.4088].

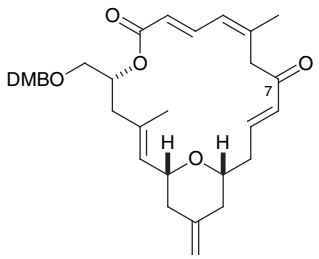
Preparation of Macrocycle (–)-8



(–)-**8**

Under argon, a solution of aldehyde (–)-**3** (27.3 mg, 33.8 μmol, azeotropically dried with benzene) in anhydrous tetrahydrofuran (5.1 mL) at –78 °C was treated dropwise with sodium bis(trimethylsilyl)amide (1.0 *M* solution in tetrahydrofuran, 40 μL, 40.0 μmol). The pale yellow reaction mixture was stirred at –78 °C for 10 min, then at 0 °C for 75 min, quenched with saturated aqueous NH_4Cl solution (2 mL), and poured into water (2 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Gradient flash chromatography (hexanes/ethyl acetate 4:1 → 2:1) furnished (–)-**8** (15.8 mg, 72% yield) as a clear, colorless oil: $[\alpha]_D^{25}$ –45.9° (*c* 0.79, PhH); IR (neat) 2930 (s), 2858 (s), 1715 (s), 1633 (s), 1514 (s), 1463 (m), 1359 (m), 1256 (s, br), 1158 (s), 1059 (s), 837 (s), 775 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 15.1, 11.6 Hz, 1 H), 6.88 (d, *J* = 1.7 Hz, 1 H), 6.85 (dd, *J* = 8.1, 1.8 Hz, 1 H), 6.82 (d, *J* = 8.1 Hz, 1 H), 5.99 (d, *J* = 11.6 Hz, 1 H), 5.79 (d, *J* = 15.1 Hz, 1 H), 5.68-5.62 (m, 1 H), 5.43 (app dd, *J* = 15.6, 5.2 Hz, 1 H), 5.39-5.34 (m, 1 H), 5.18 (d, *J* = 7.8 Hz, 1 H), 4.69 (br s, 2 H), 4.51 (d, *J* = 11.7 Hz, 1 H), 4.47 (d, *J* = 11.7 Hz, 1 H), 4.34-4.30 (m, 1 H), 3.93 (ddd, *J* = 11.1, 7.8, 2.5 Hz, 1 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.58 (dd, *J* = 10.3, 6.1 Hz, 1 H), 3.53 (dd, *J* = 10.3, 5.3 Hz, 1 H), 3.36-3.30 (m, 1 H), 2.90 (dd, *J* = 13.2, 8.7 Hz, 1 H), 2.27-2.05 (complex series of m, 7 H), 1.94 (app t, *J* = 12.3 Hz, 2 H), 1.85 (s, 3 H), 1.71 (d, *J* = 1.0 Hz, 3 H), 0.89 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 149.1, 148.6, 146.0, 144.7, 140.6, 132.9, 132.1, 130.7, 129.7, 127.6, 125.4, 120.2, 119.3, 111.1, 110.9, 108.3, 77.7, 75.7, 73.1, 71.2 ,71.15, 69.3, 55.9, 55.8, 42.0, 41.3, 41.1, 40.7, 39.3, 25.9, 24.4, 18.2, 17.1, –4.5, –4.8; high resolution mass spectrum (ESI) *m/z* 675.3668 [$(M+Na)^+$; calcd for $C_{38}H_{56}O_7SiNa$: 675.3693].

Preparation of Ketone (+)-9



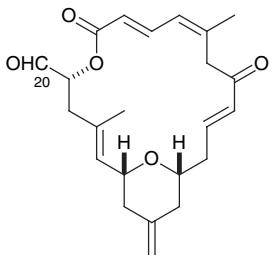
(+)-**9**

Under argon, a solution of macrocycle (–)-**8** (17.2 mg, 26.3 μmol) in anhydrous tetrahydrofuran (2 mL) at ambient temperature was treated with tetrabutylammonium fluoride (1.0 *M* solution in tetrahydrofuran, 66 μL, 66.0 μmol). The light brown mixture was stirred at ambient temperature for 0.5 h, after which it was treated with additional tetrabutylammonium fluoride (50 μL, 50.0 μmol) and stirred further for 0.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution (1 mL) and poured into water (2 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Gradient flash chromatography (hexanes/ethyl acetate, 2:1 → 1:2) gave the C(7) alcohol (8.8 mg, 62% yield) as a clear, colorless oil: $[\alpha]_D^{25}$ –51.7° (*c* 0.88, PhH); IR (neat) 3440 (s, br), 2934 (s), 2851 (s), 1713 (s), 1635 (s), 1517 (s), 1455 (m), 1372 (m), 1264 (s, br), 1155 (s), 1026 (s), 892 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.82 (dd, *J* = 15.1, 11.6 Hz, 1 H), 6.86 (d, *J* = 1.9 Hz, 1 H), 6.82 (dd, *J* = 8.1, 1.9 Hz, 1 H), 6.59 (d, *J* = 8.1 Hz, 1 H), 5.93 (d, *J* = 15.1 Hz, 1 H), 5.76 (d, *J* = 11.6 Hz, 1 H), 5.71-5.62 (m, 2 H), 5.49 (app dd, *J* = 15.7, 5.2 Hz, 1 H), 5.39 (d, *J* = 7.7 Hz, 1 H), 4.71 (br d, *J* = 1.4 Hz, 2 H), 4.43 (d, *J* = 11.9 Hz, 1 H), 4.34 (d, *J* = 11.9 Hz, 1 H), 4.08-4.04 (m, 1 H), 4.01 (ddd, *J* = 11.1, 7.8, 2.6 Hz, 1 H), 3.57 (dd, *J* = 10.0, 6.1 Hz, 1 H), 3.46 (dd, *J* = 10.2, 5.3 Hz, 1 H), 3.45 (s, 3 H), 3.40 (s, 3 H), 3.28-3.23 (m, 1 H), 2.57 (dd, *J* = 13.4, 7.9 Hz, 1 H), 2.32 (dd, *J* = 13.7, 9.1 Hz, 1 H), 2.22-2.08 (complex m, 4 H), 1.99 (app t, *J* = 12.3 Hz, 1 H), 1.93-1.88 (m, 2 H), 1.83 (app t, *J* = 12.0 Hz, 1 H), 1.67 (s, 3 H), 1.57 (s, 3 H);^{13}C NMR (125 MHz, C_6D_6) δ 166.0, 150.3, 149.8, 146.3, 144.9, 140.6, 133.6, 133.0, 131.3, 130.2, 125.6, 120.5, 120.2, 112.2, 112.1, 108.6, 78.1, 76.0, 73.2,

71.35, 70.2, 69.8, 55.6, 55.5, 42.2, 41.5, 41.1, 40.4, 39.8, 24.1, 17.2; high resolution mass spectrum (FAB) *m/z* 561.2824 [(M+Na)$^+$; calcd for $C_{32}H_{42}O_7Na$: 561.2828].

Under argon, a solution of the C(7) alcohol from the previous step (17.6 mg, 32.7 μmol) in anhydrous dichloromethane (3 mL) at ambient temperature was treated with solid sodium bicarbonate (10 mg, 0.120 mmol) followed by Dess-Martin periodinane (30.5 mg, 71.9 μmol). The cloudy-white reaction mixture was stirred at ambient temperature for 0.5 h, diluted with diethyl ether, filtered through a pad of celite, and concentrated *in vacuo*. Gradient flash chromatography (hexanes/ethyl acetate, 2:1 → 1:1) provided (+)-**9** (14 mg, 80% yield) as a clear, colorless oil: $[\alpha]_D^{25}$ +100.0° (*c* 0.70, PhH); IR (neat) 2919 (s), 2848 (s), 1715 (s), 1669 (s), 1630 (s), 1517 (s), 1461 (m), 1416 (m), 1360 (m), 1259 (s), 1157 (s), 1087 (s), 1026 (s), 803 (s) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.78 (dd, *J* = 15.0, 11.6 Hz, 1 H), 6.88-6.84 (m, 2 H), 6.81(ddd, *J* = 16.3, 9.6, 4.6 Hz, 1 H), 6.62 (d, *J* = 8.0 Hz, 1 H), 5.94 (d, *J* = 15.0 Hz, 1 H), 5.92 (d, *J* = 16.3 Hz, 1 H), 5.68 (d, *J* = 11.6 Hz, 1 H), 5.67-5.63 (m, 1 H), 5.37 (d, *J* = 7.8 Hz, 1 H), 4.69 (br d, *J* = 1.6 Hz, 1 H), 4.67 (br d, *J* = 1.6 Hz, 1 H), 4.42 (d, *J* = 11.8 Hz, 1 H), 4.38 (d, *J* = 11.8 Hz, 1 H), 4.01 (ddd, *J* = 11.1, 7.8, 2.6 Hz, 1 H), 3.65 (d, *J* = 13.5 Hz, 1 H), 3.53 (dd, *J* = 10.0, 6.0 Hz, 1 H), 3.46 (s, 3 H), 3.44 (dd, *J* = 10.1, 5.1 Hz, 1 H), 3.41 (s, 3 H), 3.14-3.09 (m, 1 H), 2.69 (d, *J* = 13.5 Hz, 1 H), 2.29 (dd, *J* = 13.5, 10.8 Hz, 1 H), 2.16 (d, *J* = 13.5 Hz, 1 H), 2.09-2.03 (m, 2 H), 1.93 (app t, *J* = 12.2 Hz, 1 H), 1.78-1.73 (m, 2 H), 1.69 (s, 3 H), 1.67-1.64 (m, 1 H), 1.54 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 196.5, 166.55, 150.4, 150.0, 145.3, 144.3, 142.9, 139.7, 133.0, 131.9, 131.2, 130.1, 125.6, 121.5, 120.5, 112.4, 112.2, 108.9, 76.8, 76.2, 73.4, 71.8, 69.6, 55.7, 55.6, 44.8, 43.0, 41.11, 41.06, 40.1, 23.3, 16.7; high resolution mass spectrum (FAB) *m/z* 559.2682 [(M+Na)$^+$; calcd for $C_{32}H_{40}O_7Na$: 559.2672].

Preparation of (+)-Dactylolide (1)



(+)-**1**

A solution of ketone (+)-**9** (14 mg, 26.0 μmol) in dichloromethane (2 mL) at ambient temperature was treated with pH 7 buffer (3 drops) followed by freshly recrystallized 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (17.9 g, 78.3 μmol). The resultant green biphasic mixture was stirred at ambient temperature for 1 h, then quenched with saturated aqueous $NaHCO_3$ solution (1 mL) and poured into water. The layers were separated, and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Gradient flash chromatography (hexanes/ethyl acetate, 2:1 → 1:1) afforded the C(20) alcohol (9 mg, 90% yield) as a clear, colorless oil: $[\alpha]_D^{25}$ +128.9° (*c* 0.45, PhH); IR (neat) 3440 (s, br), 2926 (s), 2854 (s), 1713 (s), 1670 (s), 1634 (s), 1517 (s), 1434 (m), 1359 (m), 1281 (s), 1148 (s), 1051 (s), 979 (s), 890 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.78 (dd, *J* = 15.0, 11.6 Hz, 1 H), 6.81 (ddd, *J* = 16.3, 9.5, 4.6 Hz, 1 H), 5.93 (d, *J* = 16.4 Hz, 1 H), 5.89 (d, *J* = 15.0 Hz, 1 H), 5.72 (d, *J* = 11.6 Hz, 1 H), 5.33-5.27 (m, 2 H), 4.69 (app d, *J* = 1.7 Hz, 1 H), 4.67 (app d, *J* = 1.7 Hz, 1 H), 4.00 (ddd, *J* = 11.2, 7.8, 2.6 Hz, 1 H), 3.66 (d, *J* = 13.5 Hz, 1 H), 3.43 (dd, *J* = 11.5, 6.0 Hz, 1 H), 3.38 (dd, *J* = 11.5, 4.6 Hz, 1 H), 3.13-3.08 (m, 1 H), 2.72 (d, *J* = 13.5 Hz, 1 H), 2.15 (dd, *J* = 13.5, 11.0 Hz, 1 H), 2.09-2.05 (m, 2 H), 1.97-1.90 (m, 2 H), 1.78-1.73 (m, 2 H), 1.69-1.66 (m, 1 H), 1.66 (d, *J* = 0.8 Hz, 3 H), 1.57 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 196.5, 166.7, 145.3, 144.2, 143.1, 139.8, 133.0, 131.9, 129.9, 125.6, 121.4, 108.9, 76.8, 76.1, 71.8, 65.0, 44.8, 42.3, 41.1, 41.05, 40.1, 23.4, 16.7; high resolution mass spectrum (ESI) *m/z* 409.1999 [$(M+Na)^+$; calcd for $C_{23}H_{30}O_5Na$: 409.1991].

Under argon, a solution of the C(20) alcohol from the previous step (3 mg, 7.76 μmol) in anhydrous dichloromethane (1 mL) at ambient temperature was treated with pyridine (4.0 μL,

46.6 μmol) followed by Dess-Martin periodinane (7.6 mg, 17.8 μmol). The cloudy reaction mixture was stirred at ambient temperature for 0.5 h, diluted with diethyl ether, filtered through a 0.2 μm polypropylene syringe filter, and concentrated *in vacuo*. Flash chromatography (hexanes/ethyl acetate, 1:1) provided (+)-dactylolide (**1**) (2.3 mg, 77% yield) as a clear, colorless glass: $[\alpha]_D^{25}$ +235° (*c* 0.52, MeOH); IR (neat) 2924 (m), 2848 (w), 1713 (s), 1667 (s), 1633 (s), 1434 (m), 1359 (m), 1281 (s), 1144 (s), 1083 (s), 1049 (s), 977 (s), 889 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.66 (s, 1 H), 7.63 (dd, *J* = 15.1, 11.6 Hz, 1 H), 6.85 (ddd, *J* = 16.1, 8.5, 6.0 Hz, 1 H), 6.16 (d, *J* = 11.6 Hz, 1 H), 6.01 (d, *J* = 16.3 Hz, 1 H), 5.96 (d, *J* = 15.2 Hz, 1 H), 5.31 (dd, *J* = 11.3, 2.5 Hz, 1 H), 5.24 (d, *J* = 8.0 Hz, 1 H), 4.75 (br s, 2 H), 3.97 (ddd, *J* = 11.1, 8.0, 2.5 Hz, 1 H), 3.94 (d, *J* = 14.2 Hz, 1 H), 3.33 (dddd, *J* = 11.4, 9.3, 2.3, 2.3 Hz, 1 H), 3.24 (d, *J* = 14.3 Hz, 1 H), 2.55 (br d, *J* = 13.9 Hz, 1 H), 2.37-2.28 (complex m, 3 H), 2.19-2.15 (m, 1 H), 2.13-2.09 (m, 1 H), 1.96 (br t, *J* = 12.4 Hz, 2 H), 1.87 (s, 3 H), 1.72 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.0, 197.3, 166.3, 145.9, 144.0, 143.5, 140.4, 131.5, 130.95, 130.6, 125.6, 119.8, 109.3, 76.5, 75.75, 75.4, 44.9, 40.8, 40.5, 39.7, 39.6, 24.1, 16.0; high resolution mass spectrum (ESI) *m/z* 407.1853 [$(M+Na)^+$; calcd for $C_{23}H_{28}O_5Na$: 407.1834].

Thermolysis of (+)-Zampanolide (2) and (+)-C(20)-*Epi*-Zampanolide

Under argon, a solution of a ca. 1.3:1 mixture of synthetic (+)-zampanolide (**2**) and (+)-C(20)-*epi*-zampanolide (2.2 mg, 4.44 μmol) in benzene (1.5 mL) was heated at reflux (oil bath temperature at 85 °C) until the starting material was no longer detected by TLC and LRMS (105 min). The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. ^1H NMR analysis of the crude reaction mixture revealed a mixture of **1** and hexa-2*Z*,4*E*-dienoic acid amide (**10**). Flash chromatography (hexanes/ethyl acetate, 1:1) provided (+)-dactylolide (**1**) (1.7 mg, 100% yield) as a clear and colorless glass, which displayed spectral data identical in all respects (500 MHz ^1H and 125 MHz ^{13}C NMR, HRMS, and optical rotation) to that reported for synthetic (+)-dactylolide (**1**) obtained from vinyl bromide (–)-**AB**.

Thermolysis of (+)-Zampanolide (2)

Under argon, a solution of synthetic (+)-zampanolide (0.5 mg, 1.01 μmol) in benzene (1 mL) was heated at reflux (oil bath temperature at 85 °C) until the starting material was no longer detected by TLC and LRMS (105 min). The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. ^{1}H NMR analysis of the reaction mixture revealed **1**.