SUPPORTING INFORMATION

Convergent Route to the Spirohexenolide Macrocycle

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Synthetic studies were conducted by B.D.J., J.J.L, and M.D.B.

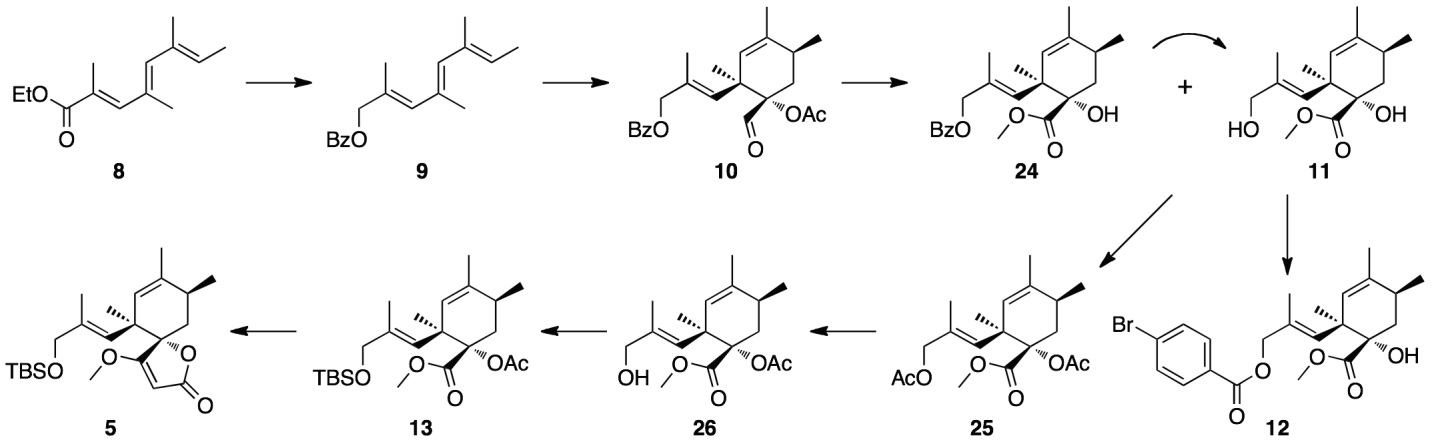
X-ray crystallography was performed by C.F.M. and A.L.R.

This file contains the experimental procedures for preparation of each intermediate and product. An additional file containing copies of spectral data, pages S23–S48 has been provided and can be downloaded online at http://pubs.acs.org.

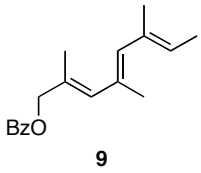
General materials and methods.

Unless otherwise noted, all reagents and chemical compounds were purchased from commercial sources and used without further purification. High purity anhydrous solvents (tetrahydrofuran, dichloromethane, diethyl ether, and toluene) were obtained by passing through a solvent column composed of activated A–1 alumina. Anhydrous *N*,*N*–dimethylformamide was obtained by passage over activated molecular sieves and a subsequent sodium isocyanate column to remove traces of dimethylamine. Triethylamine (Et_3N) was dried over sodium and freshly distilled. Ethyl–*N*,*N*–diisopropylamine (*i*–Pr_2NEt) was distilled from ninhydrin, then from potassium hydroxide. Anhydrous acetonitrile was obtained by distillation from calcium hydride. All air or moisture sensitive reactions were performed under positive pressure of dry argon in oven–dried glassware sealed with septa. Reactions were magnetically stirred with Teflon coated stir bars. Flash chromatography was performed on Geduran Silica Gel 60 (40–63 mesh) from EM Biosciences according to the method of Still.[S1] Analytical TLC was performed on Silica Gel 60 F254 pre–coated glass plates. Visualization was achieved with UV light and/or an appropriate stain (I_2 on SiO_2, $KMnO_4$, bromocresol green, dinitrophenylhydrazine, ninhydrin, and ceric ammonium molybdate). Yields and characterization data correspond to isolated, chromatographically and spectroscopically homogeneous materials unless otherwise noted. ^{1}H NMR spectra were recorded on Varian Mercury 300 MHz or 400 MHz spectrometers, or a Varian Mercury Plus 400 MHz spectrometer, or a JEOL ECA 500 MHz spectrometer, or a Varian VX 500 MHz spectrometer. ^{13}C NMR spectra were recorded at 125 MHz on the JEOL ECA 500 instrument or the Varian VX500 spectrometer, or at 100 MHz on either Varian Mercury or Varian Mercury Plus instrument, or at 75 MHz on a Varian Mercury spectrometer. Chemical shifts for ^{1}H NMR and ^{13}C NMR analyses were referenced to the reported values of Gottlieb,[S2] using the signal from the residual protonated solvent for ^{1}H spectra, or to the ^{13}C signal from the deuterated solvent. Chemical shift δ values for ^{1}H and ^{13}C spectra are reported in parts per million (ppm) relative to these referenced values, and multiplicities are abbreviated as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. All ^{13}C NMR spectra were recorded with complete proton decoupling. FID files were processed using MestraNova 6.0.2. (MestreLab Research). Electrospray (ESI) mass spectrometric analyses were performed using a ThermoFinnigan LCQ Deca mass spectrometer, and high–resolution analyses were conducted using a ThermoFinnigan MAT900XL mass spectrometer with electron impact (EI) ionization. A Thermo Scientific LTQ Orbitrap XL mass spectrometer was used for high–resolution electrospray ionization mass spectrometry analysis (HR–ESI–MS). FTIR spectra were obtained on a Nicolet magna 550 series II spectrometer with samples prepared as thin films on either KBr or NaCl discs, and peaks are reported in wavenumbers (cm^{-1}). Spectral data and procedures are provided for all new compounds and copies of select spectra have been provided.

Synthesis of tetronate component 5. The route depicted in Scheme S1, and Scheme 2 in the manuscript, was used to prepare component **5** in 9 steps from ester **8** in 18% yield overall. The following sections describe the methods for preparation of intermediates **9**–**13** and **24**–**26** used in this route.



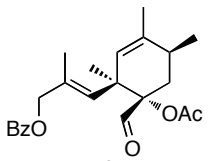
Scheme S1. Synthesis of tetronate component **5**.



Benzoate 9. DIBAL–H (60.6 mL of a 1.5 M solution in toluene, 90.8 mmol) was added slowly via syringe to a stirred solution of the (2*E*,4*E*,6*E*)–ethyl 2,4,6–trimethylocta–2,4,6–trienoate (**8**) (8.60 g, 41.3 mmol) in Et_2O (150 mL) at 0 °C. The reaction was stirred for 1.5 h at this temperature. The reaction was quenched by the dropwise addition of MeOH (~2 mL, until gas evolution ceased) followed by a saturated aqueous Rochelle's salt solution (250 mL). The mixture was allowed to warm to rt with stirring. Once the layers had separated, the aqueous layer was extracted twice with additional Et_2O (2 x 100 mL), and the combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue (6.8 g) was dissolved in CH_2Cl_2 (300 mL) and treated with DMAP (512 mg, 4.70 mmol) and Et_3N (10.5 mL, 75.6 mmol). After cooling to 0 °C, BzCl (5.73 mL, 49.9 mmol) was added dropwise syringe until the alcohol intermediate (R_f < 0.1 in 5:1 hexanes / Et_2O) was consumed, and benzoate **9** (R_f = 0.5 in 5:1 hexanes / Et_2O) was the predominant component of the mixture. The mixture was then diluted with additional CH_2Cl_2 (100 mL) and saturated $NaHCO_3$ (200 mL), and the aqueous layer was extracted with additional portions CH_2Cl_2 (2 x 100 mL). The combined organic layers were washed with deionized H_2O (200 mL), brine (200 mL), and then dried over

Na_2SO_4. The organic layer was then filtered and concentrated under reduced pressure, and the residue was purified by flash chromatography (8:1 to 6:1 hexanes / Et_2O) to provide the benzoate **9** (11.0 g, 99% over 2 steps from **8**).

Benzoate **9**: TLC (5:1 hexanes / Et_2O): R_f = 0.5; ^{1}H–NMR ($CDCl_3$, 400 MHz) δ 8.07 (d, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 6.05 (s, 1H), 5.84 (s, 1H), 5.45 (q, *J* = 6.8 Hz, 1H), 4.76 (s, 2H), 1.92 (s, 6H), 1.77 (s, 3H), 1.71 (d, *J* = 6.8 Hz, 3H); ^{13}C–NMR ($CDCl_3$, 100 MHz) δ 166.6, 135.0, 133.9, 133.5, 133.0, 131.2, 130.5, 129.9, 129.8, 128.5, 125.2, 71.5, 18.8, 16.9, 16.0, 14.0; FTIR (film) νmax 2969, 2917, 2855, 1719, 1449, 1265, 1178, 1108, 1020, 715 cm^{-1}; ESI–MS *m/z* 292.79 $[M+Na]^+$; HR–ESI–MS *m/z* calcd. for $C_{18}H_{22}O_2Na_1$ $[M+Na]^+$: 293.1512, found 293.1513.

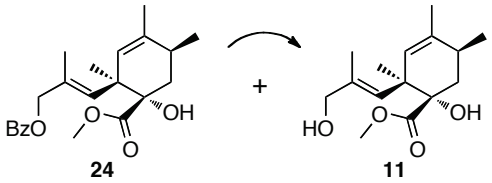


10

Diels–Alder adduct 10. $MeAlCl_2$ (40 mL of a 1.0 M solution in hexanes, 40 mmol) was added slowly via syringe solution of the benzoate **9** (11.0 g, 40.6 mmol) and α–acetoxyacrolein (12.7 g, 111 mmol) in CH_2Cl_2 (400 mL) cooled to -78 °C. The solution was stirred at this temperature for 0.5 h, then quenched by the addition of a saturated aqueous $NaHCO_3$ solution (100 mL) and allowed to warm to rt. The mixture was then partitioned between deionized H_2O (200 mL) and CH_2Cl_2 (100 mL), and the aqueous layer was extracted with additional CH_2Cl_2 (2 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (4:1 to 3:1 hexanes / Et_2O) to provide a mixture of byproducts (3.14 g) with higher R_f than the product, and NMR analysis indicated that they were not aldehydes, followed by the Diels–Alder adduct **10** (11.75 g, 75%), as a single diastereomer.

Diels–Alder adduct **10**: TLC (3:1 hexanes / Et_2O): R_f = 0.2; ^{1}H–NMR ($CDCl_3$, 400 MHz) δ 9.66 (s, 1H), 8.06 (d, *J* = 7.5 Hz, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 5.33 (s, 1H), 5.20 (s, 1H), 4.62 (d, *J* = 12.5 Hz, 1H), 4.58 (d, *J* = 12.5 Hz, 1H), 2.52 (dd, *J* = 14.0, 5.3 Hz, 1H), 2.11 (s, 3H), 2.05–1.95 (m, 1H), 1.89 (dd, *J* = 14.0, 11.3 Hz, 1H), 1.83 (s, 3H), 1.73 (s, 3H), 1.29 (s, 3H), 1.05 (d, *J* = 6.9 Hz, 3H); ^{13}C–NMR ($CDCl_3$, 100 MHz) δ 199.4, 170.7, 166.4, 135.9, 133.1, 132.8, 130.9, 130.3, 129.8, 128.5, 127.7, 86.3, 71.6, 44.9, 31.9, 30.5, 23.1, 21.0, 18.1, 15.3; FTIR (film) νmax 2966, 2932,

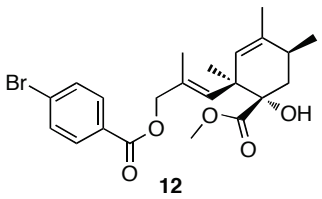
2878, 1663, 1602, 1448, 1374, 1112, 1025, 716 cm^{-1}; ESI–MS *m/z* 407.15 $[M+Na]^+$, 384.92 $[M+H]^+$; HR–ESI–MS *m/z* calcd. for $C_{23}H_{28}O_5Na_1$ $[M+Na]^+$: 407.1829, found 407.1833.



Diol 11. KOH (305 mL of a 0.78 M solution in MeOH, 238 mmol) and I_2 (153 mL of a 0.78 M solution in MeOH, 119 mmol) were added sequentially to a solution of Diels–Alder adduct **10** (11.75 g, 30.6 mmol) in MeOH (310 mL) cooled to 0 °C. The darkened solution stirred at this temperature for 1 h. At this time, 285 mL of a 2 N solution of H_2SO_4 (570 mmol) was added at 0 °C. The mixture was allowed to warm to rt and then diluted with deionized H_2O (200 mL) and Et_2O (200 mL). The aqueous layer was extracted with additional portions of Et_2O (3 x 200 mL). The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$, then brine, then were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (5:2 hexanes / Et_2O to 100% Et_2O) to provide the benzoate **24** (6.43 g, 56%) and diol **11** (1.40 g, 17%). Benzoate **24** was then methanolized to afford additional quantities of diol **11**. KOH (172 mL of a 1.0 M solution in MeOH, 172 mmol) was added to a solution of benzoate **24** (6.43 g, 17.2 mmol) in MeOH (340 mL) at 0 °C. This solution was stirred at 0 °C for 2 h, then at rt for 2 h. The reaction was then diluted with deionized H_2O (200 mL) and EtOAc (300 mL) and the aqueous layer was washed with additional portions of EtOAc (3 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (1:1 hexanes / EtOAc) provided the diol **11** (4.42 g, 96%).

Benzoate **24**: TLC (1:1 hexanes / Et_2O): R_f = 0.4; ^1H–NMR ($CDCl_3$, 400 MHz) δ 8.05 (d, *J* = 8.0 Hz, 2H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 2H), 5.31 (s, 1H), 5.19 (s, 1H), 4.64 (d, *J* = 12.8 Hz, 1H), 4.60 (d, *J* = 12.8 Hz, 1H), 3.68 (s, 3H), 3.12 (s, 1H), 2.41–2.28 (m, 1H), 1.94–1.87 (m, 2H), 1.84 (s, 3H), 1.75 (s, 3H), 1.19 (s, 3H), 1.05 (d, *J* = 7.1 Hz, 3H); ^{13}C–NMR ($CDCl_3$, 100 MHz) δ 176.0, 166.4, 136.0, 133.1, 133.0, 130.8, 130.5, 129.7, 128.5, 127.6, 78.1, 72.1, 52.5, 45.7, 37.3, 30.3, 22.8, 21.1, 18.3, 15.0; FTIR (film) νmax 3429 br, 2959, 2872, 1716, 1643, 1448, 1367, 1273, 1112, 1031, 716 cm^{-1}; ESI–MS *m/z* 395.05 $[M+Na]^+$, 389.90 $[M+NH_4]^+$, HR–ESI–MS *m/z* calcd. for $C_{22}H_{28}O_5Na_1$ $[M+Na]^+$: 395.1829, found 395.1825.

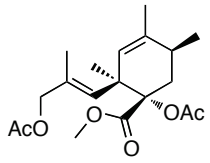
Diol **11**: TLC (1:1 hexanes / EtOAc): R_f = 0.3; ^{1}H–NMR ($CDCl_3$, 500 MHz) δ 5.17 (s, 2H), 3.89 (d, *J* = 5.8 Hz, 2H), 3.75 (s, 3H), 3.04 (s, 1H), 2.39–2.28 (m, 1H), 1.90–1.87 (m, 2H), 1.76 (s, 3H), 1.74 (s, 3H), 1.18 (s, 3H), 1.05 (d, *J* = 6.9 Hz, 3H); ^{13}C–NMR ($CDCl_3$, 125 MHz) δ 175.8, 135.6, 135.5, 130.1, 127.9, 78.3, 70.8, 52.4, 45.5, 37.3, 30.2, 22.9, 21.1, 18.3, 14.8; FTIR (film) νmax 3456 br, 2959, 2872, 1723, 1441, 1381, 1260, 1152, 1125, 1025, 863, 756; ESI–MS *m/z* 307.09 $[M+K]^+$, 291.07 $[M+Na]^+$, 285.90 $[M+NH_4]^+$, 268.90 $[M+H]^+$; HR–ESI–MS *m/z* calcd. for $C_{15}H_{24}O_4Na_1$ $[M+Na]^+$: 291.1567, found 291.1570.



12

4–Bromobenzoate 12. A reaction flask as charged with 4–bromobenzoic acid (32 mg, 0.160 mmol), CSA (18 mg, 0.080 mmol), DMAP (21 mg, 0.168 mmol) and a solution of the diol **11** (43 mg, 0.160 mmol) in CH_2Cl_2 (5 mL). DCC (53 mg, 0.256 mmol) was added in one portion to the stirred mixture at rt. After 3 h at rt, the mixture was diluted with CH_2Cl_2 (10 mL) and 10% aqueous citric acid (10 mL). The layers were separated, and the organic layer was washed successively with saturated aqueous $NaHCO_3$ (10 mL), deionized H_2O (10 mL), and then brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (5:3 hexanes / Et_2O) to provide the *p*–bromobenzoate **12** (57 mg, 80%). Diffraction quality crystals were obtained by perfusion of hexanes into an EtOAc solution of **12**, and a neat sample of **12** solidified in the freezer (mp of the amorphous solid = 49–51 °C (uncorrected).

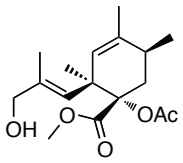
4–Bromobenzoate **12**: TLC (5:3 hexanes / Et_2O): R_f = 0.2; ^{1}H–NMR ($CDCl_3$, 500 MHz) δ 7.91 (d, *J* = 8.6 Hz, 2H), 7.59 (d, *J* = 8.6 Hz, 2H), 5.30 (s, 1H), 5.18 (s, 1H), 4.63 (d, *J* = 11.5 Hz, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 3.69 (s, 3H), 3.11 (s, 1H), 2.40–2.29 (m, 1H), 1.91–1.87 (m, 2H), 1.83 (s, 3H), 1.75 (s, 3H), 1.19 (s, 3H), 1.05 (d, *J* = 6.9 Hz, 3H); ^{13}C–NMR ($CDCl_3$, 100 MHz) δ 175.8, 165.7, 136.1, 133.4, 131.9, 131.2, 130.6, 129.4, 128.2, 127.5, 78.1, 72.5, 52.5, 45.7, 37.4, 30.3, 22.8, 21.1, 18.3, 15.1; ESI–MS *m/z* 474.95 $[M+Na]^+$, 467.76 $[M+H]^+$; HR–ESI–MS *m/z* calcd. for $C_{22}H_{27}Br_1O_5Na_1$ $[M+Na]^+$: 473.0934, found 473.0929.



25

Bis–acetate 25. $Sc(OTf)_3$ (4.05 g dissolved in 35 mL MeCN, 8.24 mmol) was added via a cannula to a stirred solution of diol **11** (4.42 g, 16.5 mmol) in Ac_2O (140 mL, 1.48 mol) at 0 °C. The solution stirred for 30 s at this temperature. The reaction was quenched by the slow addition of a saturated aqueous $NaHCO_3$ solution (150 mL) and was transferred to a 2 L beaker so that the gas evolution could be more easily controlled. Solid $NaHCO_3$ (50 g) was also added and the mixture was stirred until gas evolution ceased. The mixture was then diluted with Et_2O (600 mL) and deionized H_2O (300 mL), and the aqueous layer was extracted with additional portions of Et_2O (3 x 250 mL). The combined organic layers were washed with brine (250 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (3:2 hexanes / EtOAc, isocratic) to provide the bis–acetate **25** (4.6 g, 79%).

Bis–acetate **25**: TLC (1:1 hexanes / EtOAc): R_f = 0.5; ^{1}H–NMR ($CDCl_3$, 400 MHz) δ 5.15 (s, 1H), 5.10 (s, 1H), 4.36 (d, *J* = 12.4 Hz, 1H), 4.30 (d, *J* = 12.4 Hz, 1H), 3.69 (s, 3H), 2.60 (dd, *J* = 14.0, 4.9 Hz, 1H), 2.06 (s, 3H), 2.05 (s, 3H), 1.98–1.87 (m, 1H), 1.82 (dd, *J* = 14.0, 11.6 Hz, 1H), 1.74 (s, 3H), 1.70 (s, 3H), 1.28 (s, 3H), 1.01 (d, *J* = 6.9 Hz, 3H); ^{13}C–NMR ($CDCl_3$, 100 MHz) δ 171.0, 170.9, 170.3, 135.4, 132.2, 131.1, 127.7, 83.4, 71.5, 52.0, 45.1, 34.0, 30.6, 23.2, 21.1, 20.8, 18.0, 14.9; FTIR (film) νmax 2948, 1736, 1440, 1370, 1230, 1111, 1021, 913, 733 cm^{-1}; ESI–MS *m/z* 375.05 $[M+Na]^+$, 369.91 $[M+NH_4]^+$; HR–ESI–MS *m/z* calcd. for $C_{19}H_{28}O_6Na$ $[M+Na]^+$: 375.1778, found 375.1782.

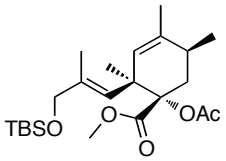


26

Mono–acetate 26. DIBAL–H (34.1 mL of a 1.5 M solution in toluene, 51 mmol) was added slowly via syringe over 10 min to a bis–acetate **25** (4.50 g, 12.8 mmol) in THF (75 mL) at -78 °C. The resulting mixture was stirred for 2 h at this temperature. The reaction was quenched by the dropwise addition of MeOH (~5 mL, until gas evolution ceased) followed by a saturated aqueous solution of Rochelle's salt (150 mL), followed by warming to rt. When the layers had separated, the mixture was diluted with deionized H_2O (100 mL) and EtOAc (200 mL), and the aqueous layer was extracted with additional portions of EtOAc (2 x 150 mL). The combined organic layers were washed with brine (100 mL), dried over

Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography of the residue (3:1 to 1:1 hexanes / EtOAc) provided the mono–acetate **26** (3.01 g, 76%).

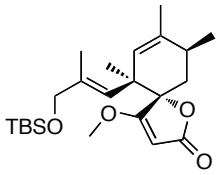
Mono–acetate **26**: TLC (1:1 hexanes / EtOAc): R_f = 0.3; ^{1}H–NMR ($CDCl_3$, 400 MHz) δ 5.16 (s, 1H), 5.08 (s, 1H), 3.88 (d, *J* = 6.0 Hz, 2H), 3.71 (s, 3H), 2.59 (dd, *J* = 13.8, 4.7 Hz, 1H), 2.06 (s, 3H), 2.00–1.86 (m, 1H), 1.85 (dd, *J* = 13.8, 11.6 Hz, 1H), 1.75 (s, 3H), 1.71 (s, 3H), 1.43 (t, *J* = 6.0 Hz, 1H), 1.28 (s, 3H), 1.02 (d, *J* = 6.8 Hz, 3H); ^{13}C–NMR ($CDCl_3$, 100 MHz) δ 171.3, 170.4, 137.1, 135.1, 128.2, 128.1, 83.6, 70.6, 52.0, 45.0, 34.0, 30.6, 23.4, 21.1, 20.8, 18.0, 14.7; FTIR (film) νmax 2949, 1734, 1438, 1370, 1268, 1016, 909, 732 cm^{-1}; ESI–MS *m/z* 348.97 $[M+K]^+$, 333.06 $[M+Na]^+$, 327.94 $[M+NH_4]^+$, 292.87 $[M+H–H_2O]^+$; HR–ESI–MS *m/z* calcd. for $C_{17}H_{26}O_5Na_1$ $[M+Na]^+$: 333.1672, found 333.1675.



13

Silyl ether 13. Imidazole (1.65 g, 24.2 mmol) and TBSCl (2.93 g, 19.4 mmol) were added to a stirred solution of the mono–acetate **26** (3.01 g, 9.7 mmol) in DMF (100 mL) at rt. The mixture was stirred until only the product was visible by TLC. Once complete, the mixture was diluted with saturated aqueous $NaHCO_3$ (30 mL) and 1:1 hexanes / Et_2O (200 mL). The aqueous layer was extracted with an additional portion of the solvent mixture (100 mL), and the combined organic layers were washed with deionized H_2O (50 mL) and brine (50 mL), then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography of the residue (5:1 to 3:1 hexanes / EtOAc) provided the silyl ether **13** (4.0 g, 97%).

Silyl ether **13**: TLC (1:1 hexanes / EtOAc): R_f = 0.7; ^{1}H–NMR ($CDCl_3$, 400 MHz) δ 5.18 (s, 1H), 5.12 (s, 1H), 3.88 (s, 2H), 3.69 (s, 3H), 2.59 (dd, *J* = 13.3, 4.2 Hz, 1H), 2.05 (s, 3H), 2.01–1.80 (m, 2H), 1.70 (s, 3H), 1.67 (s, 3H), 1.28 (s, 3H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C–NMR ($CDCl_3$, 100 MHz) δ 171.1, 170.4, 136.3, 134.6, 128.6, 126.3, 83.7, 69.7, 52.0, 44.9, 34.0, 30.6, 26.1, 23.3, 21.2, 20.8, 18.5, 18.1, 14.5, -5.1, -5.2; FTIR (film) νmax 2956, 2857, 1738, 1437, 1370, 1256, 1106, 908, 837, 777, 733 cm^{-1}; ESI–MS *m/z* 447.09 $[M+Na]^+$, 441.87 $[M+NH_4]^+$; HR–ESI–MS *m/z* calcd. for $C_{23}H_{40}O_5Si_1Na_1$ $[M+Na]^+$: 447.2537, found 447.2540.

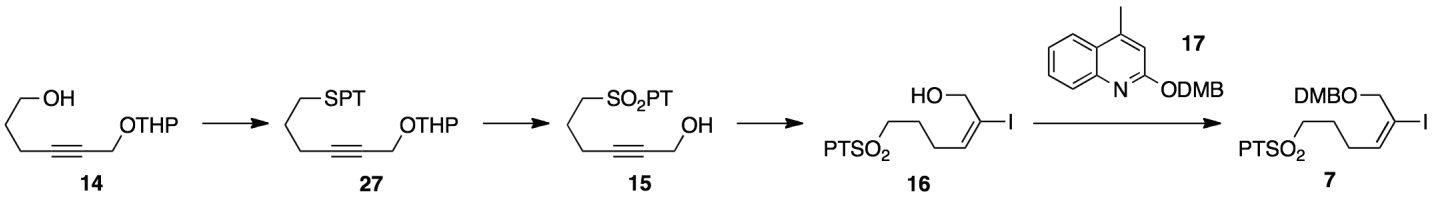


5

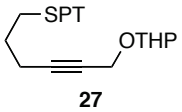
Spirotetronate 5. A solution of LiHMDS (20.4 mL of a 1.06 M solution in THF, 21.6 mmol) was added slowly via syringe to a stirred -78 °C solution of the silyl ether **13** (4.0 g, 9.42 mmol) in THF (100 mL) and freshly distilled HMPA (35 mL). The reaction was stirred at this temperature for 30 min, and then allowed to warm to rt over 1 h. After 15 min at rt, $(MeO)_2SO_2$ (2.23 mL, 23.5 mmol) was added via syringe. The reaction stirred for an additional 2 h at rt before being partitioned between deionized H_2O (150 mL) and Et_2O (200 mL). The aqueous layer was extracted with two portions of additional Et_2O (2 x 100 mL), and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (4:1 to 1:1 hexanes / EtOAc) to provide the spirotetronate **5** (2.75 g, 72%).

Spirotetronate **5**: TLC (1:1 hexanes / EtOAc): R_f = 0.6; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.54 (s, 1H), 5.30 (s, 1H), 5.06 (s, 1H), 3.91 (s, 2H), 3.82 (s, 3H), 2.50–2.36 (m, 1H), 1.96 (dd, *J* = 13.7, 10.5 Hz, 1H), 1.78 (dd, *J* = 13.7, 6.4 Hz, 1H), 1.70 (s, 3H), 1.66 (s, 3H), 1.06 (s, 3H), 1.01 (d, *J* = 7.1 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 184.7, 172.1, 135.1, 134.6, 128.4, 127.4, 89.6, 88.0, 69.7, 59.5, 44.3, 37.2, 31.6, 26.1, 22.3, 21.1, 18.5, 18.4, 14.8, -5.1, -5.1; FTIR (film) νmax 2957, 2858, 1747, 1625, 1440, 1361, 1253, 1207, 1173, 1093, 1019, 961, 909, 837, 808, 778, 732 cm^{-1}; ESI–MS *m/z* 429.08 $[M+Na]^+$, 406.82 $[M+H]^+$; HR–ESI–MS *m/z* calcd. for $C_{23}H_{38}O_4Si_1Na_1$ $[M+Na]^+$: 429.2432, found 429.2436.

Synthesis of vinyl iodide component 7. The route depicted in Scheme S2, and Scheme 3 in the manuscript, was developed to prepare component **7** in 4 steps from **14** in 15% yield overall. The following sections describe the methods for preparation of compounds **14–16** and **27** used in this route.

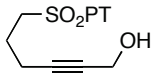


Scheme S2. Synthesis of component **7**.



Sulfide 27. A reaction flask was charged PPh_3 (30.45 g, 116.1 mmol), 1–phenyl–*1H*–tetrazole–5–thiol (20.70 g, 116.1 mmol), and the primary alcohol **14** (15.35 g, 77.4 mmol) dissolved in dissolved in THF (500 mL) and cooled to 0 °C. DIAD (27.44 mL, 139.4 mmol) was added slowly via syringe to this solution. The reaction was allowed to warm to rt slowly over 12 h. The mixture was then partitioned between saturated aqueous $NaHCO_3$ (300 mL) and EtOAc (300 mL) and the aqueous layer was extracted with an additional portion of EtOAc (2 x 300 mL). The combined organic layers were washed with deionized water (300 mL), brine (300 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes to 3:1 hexanes / EtOAc followed by a second column of hexanes to 4:1 hexanes / EtOAc) to provide the sulfide **27** (24.2 g, 87%).

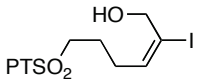
Sulfide **27**: TLC (1:1 hexanes / EtOAc): R_f = 0.5; ^{1}H–NMR ($CDCl_3$, 500 MHz) δ 7.64–7.49 (m, 5H), 4.78 (t, *J* = 3.5 Hz, 1H), 4.27 (dt, *J* = 15.3, 2.1 Hz, 1H), 4.18 (dt, *J* = 15.3, 2.1 Hz, 1H), 3.82 (m, 1H), 3.53 (m, 1H), 3.50 (t, *J* = 7.1 Hz, 2H), 2.41 (tt, *J* = 6.8, 2.1 Hz 2H), 2.06 (p, *J* = 7.1 Hz, 2H), 1.82 (m, 1H), 1.72 (m, 1H), 1.57 (m, 4H) ; ^{13}C–NMR ($CDCl_3$, 125 MHz) δ 154.2, 133.8, 130.3, 129.9, 124.0, 96.9, 84.5, 62.2, 54.7, 32.3, 30.4, 27.9, 25.5, 19.2, 17.9; FTIR (film) νmax 2946, 2865, 1602, 1501, 1387, 1119, 1022, 765, 693 cm^{-1}; ESI–MS *m/z* 396.94 $[M+K]^+$, 380.99 $[M+Na]^+$, 358.78 $[M+H]^+$; HR–ESI–MS *m/z* calcd. for $C_{18}H_{22}N_4O_2S_1Na_1$ $[M+Na]^+$: 381.1356, found 381.1357.



15

Sulfone 15. Sulfide **27** (8.07 g, 22.5 mmol) was dissolved in EtOH (130 mL) and the solution was stirred and cooled to 0 °C. A solution of $(NH_4)_6Mo_7O_{24} \bullet 4H_2O$ (5.24 g, 42.0 mmol) in 30% w/w aqueous H_2O_2 (36.1 mL) was added and stirred for 3 h at 0 °C. The solution was slowly warmed to rt over 12 h. The mixture was partitioned between EtOAc (400 mL) and brine (400 mL), and the aqueous layer was extracted with additional portions of EtOAc (2x 400 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered through 30 g pad of SiO_2 and concentrated under reduced pressure. The residue was purified by flash chromatography (3:1 to 1:1 hexanes / EtOAc followed by a second column of 10:1 to 3:1 CH_2Cl_2 / EtOAc) to provide the sulfone **15** (6.64 g, 96%). On smaller scales, the reaction often provided significant quantities of the corresponding THP ether, which was converted to **15** by warming with PPTS in EtOH.

Sulfone **15**: TLC (1:1 hexanes / EtOAc): $R_f = 0.3$; ^{1}H–NMR ($CDCl_3$, 400 MHz) δ 7.69 (m, 2H), 7.62 (m, 3H), 4.26 (dt, *J* = 6.1, 2.1 Hz, 2H), 3.89 (dd, *J* = 6.8, 8.7 Hz, 2H), 2.49 (tt, *J* = 2.1, 6.8 Hz, 2H), 2.19 (m, 2H), 1.72 (t, *J* = 6.1 Hz, 1H); ^{13}C–NMR ($CDCl_3$, 125 MHz) δ 153.5, 133.1, 131.7, 129.9, 125.2, 83.1, 81.0, 55.1, 51.3, 21.5, 17.7; FTIR (film) νmax 3369 br, 2912, 1723, 1495, 1340, 1155, 1014, 765, 691; ESI–MS *m/z* 344.80 $[M+K]^+$, 328.90 $[M+Na]^+$, 306.91 $[M+H]^+$; HR–ESI–MS *m/z* calcd. for $C_{13}H_{15}N_4O_3S_1$ $[M+H]^+$: 307.0859, found 307.0861.

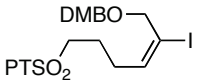


16

Iodide 16. A reaction flask was charged $(PPh_3)_2PdCl_2$ (772 mg, 1.10 mmol) and propargylic alcohol **15** (6.83 g, 22.0 mmol) in THF (250 mL). The solution was stirred as n–Bu_3SnH (7.20 mL, 26.8 mmol) was added slowly via syringe at rt. After vigorously stirring the dark solution for 20 min, the reaction mixture was concentrated under reduced pressure, dissolved in CH_2Cl_2 (300 mL), and cooled to 0 °C. A solution of I_2 (5.6 g, 22.0 mmol) in CH_2Cl_2 (250 mL) was added slowly via cannula to the chilled solution, and the reaction mixture was allowed to slowly warm to rt, and stirred at rt for 30 min. Solid KF on Celite (10 g of a 50% w/w mixture[S3], 455 mg / mmol) was added to remove the organotin byproducts.[S4] The suspension stirred an additional 2 h at rt. The suspension was filtered and the resulting solution was concentrated under reduced pressure. Flash chromatography of the residue (2:1 to 1:1 hexanes / EtOAc) provided the

iodide **16** (1.69 g, 18%), followed by mixed fractions containing the desired product with undesired byproducts and regioisomers (3.24 g).

Iodide **16**: TLC (1:1 hexanes / EtOAc): R_f = 0.4; ^{1}H–NMR ($CDCl_3$, 500 MHz) δ 77.67 (m, 2H), 7.61 (m, 3H), 6.29 (t, *J* = 7.8 Hz, 1H), 4.23 (d, *J* = 6.6 Hz, 2H), 3.69 (m, 2H), 2.40 (q, *J* = 7.4 Hz, 2H), 2.11 (p, *J* = 7.5 Hz, 2H), 1.94 (t, *J* = 6.4 Hz, 1H); ^{13}C–NMR ($CDCl_3$, 125 MHz) δ 153.5, 140.2, 133.1, 131.7, 129.9, 125.2, 105.2, 65.3, 55.0, 29.2, 21.7; FTIR (film) νmax 3402 br, 2946, 1730, 1496, 1341, 1157, 1043, 769, 691; ESI–MS *m/z* 456.79 $[M+Na]^+$, 451.70 $[M+NH_4]^+$, 434.78 $[M+H]^+$, 416.71 $[M–H_2O+H]^+$; HR–ESI–MS *m/z* calcd. for $C_{13}H_{15}I_1N_4O_3S_1Na_1$ $[M+Na]^+$: 456.9802, found 456.9797.

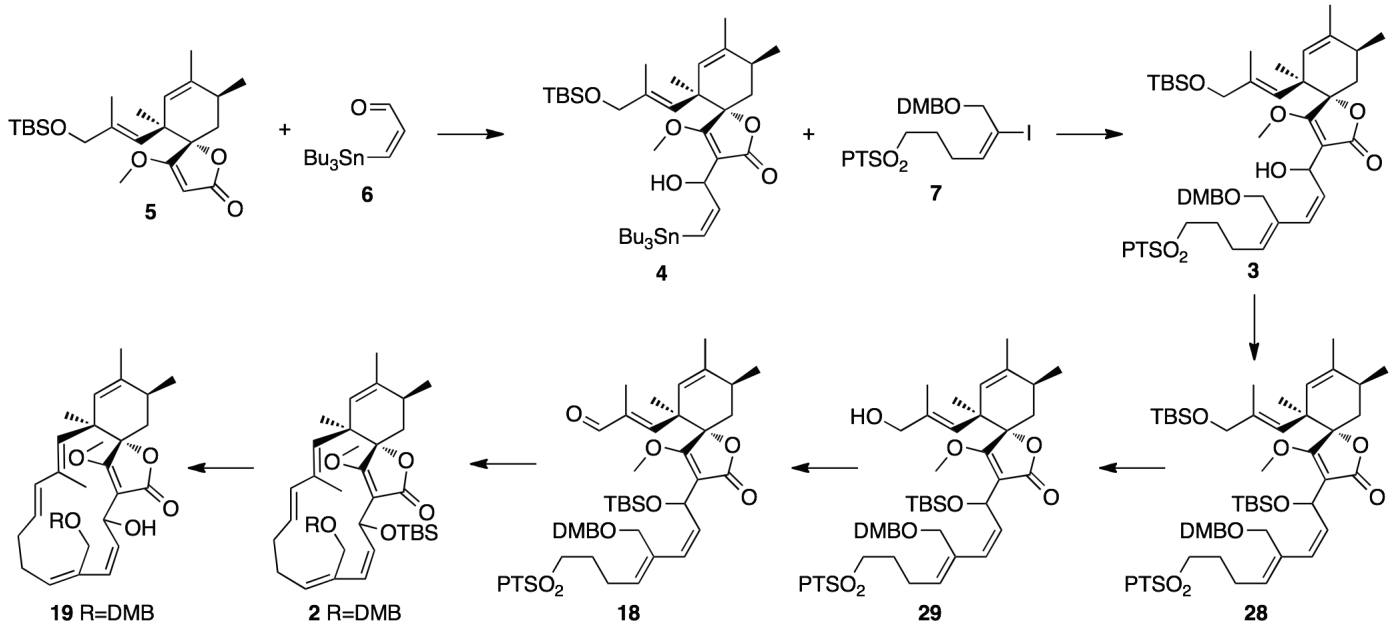


7

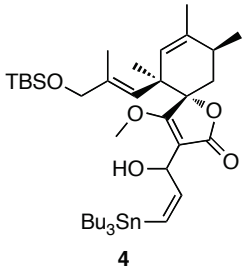
Component 7. (±)–10–Camphorsulfonic acid (90 mg, 0.389 mmol) was added a single portion to a solution of the iodide **16** (1.69 g, 3.89 mmol) and lepidine **17** (2.52 g, 7.78 mmol) in CH_2Cl_2 (50 mL) at rt. After 36 h at rt, a yellow precipitate had formed and TLC analysis confirmed the consumption of starting material. The reaction mixture was partitioned between aqueous $NaHCO_3$ (25 mL), water (25 mL) and CH_2Cl_2 (25 mL), the layers were separated, and the aqueous layer was extracted twice with additional CH_2Cl_2 (2x 25 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, then filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes / EtOAc gradient) to provide the component **7** (1.68 g, 74%), as a clear oil.

Component **7**: ^{1}H–NMR ($CDCl_3$, 500 MHz) δ 7.71–7.56 (m, 5H), 6.99–6.79 (m, 3H), 6.39 (t, 1H, *J* = 7.7 Hz), 4.46 (s, 2H), 4.14 (s, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.71–3.68 (m, 2H), 2.32 (q, 2H, *J* = 7.6 Hz), 2.06 (p, 2H, *J* = 7.6 Hz); ^{13}C–NMR ($CDCl_3$, 125 MHz) δ 153.4, 149.2, 148.9, 142.0, 133.1, 131.7, 130.1, 129.9, 125.1, 120.6, 111.4, 111.0, 100.9, 71.8, 71.2, 56.0, 56.0, 55.1, 29.5, 21.7; FTIR (film) νmax 2932, 2851, 1723, 1596, 1516, 1496, 1463, 1340, 1266, 1236, 1155, 1027, 764, 690 cm^{-1}; ESI–MS *m/z* 584.92 $[M+H]^+$, 601.91 $[M+NH_4]^+$, 606.93 $[M+Na]^+$, 622.92 $[M+K]^+$; HR–ESI–MS *m/z* calcd. for $C_{22}H_{25}I_1N_4O_5S_1Na_1$ $[M+Na]^+$: 607.0483, found 607.0487.

Component assembly. The route depicted in Scheme S3, and Scheme 4 in the manuscript, was developed to prepare alcohol **19**. The following sections describe the methods for preparation of compounds **3**, **4**, **18**, **19**, **28** and **29** used in these studies.

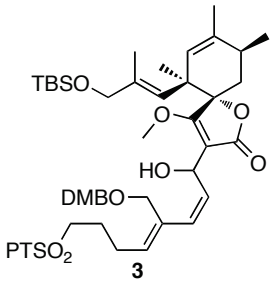


Scheme S3. Assembly of components **5**, **6** and **7**.



Vinyl stannanes 4. *t*–BuLi (1.40 mL of a 1.5 M solution in pentane, 2.09 mmol) was added slowly via syringe to a solution of the spirotetronate **5** (707 mg, 1.74 mmol) in THF (20 mL) cooled to -78 °C. The solution turned lemon yellow. The lithiation was allowed to proceed at this temperature for 30 min, and then the aldehyde **6** (650 mg dissolved in 5 mL of THF, 1.88 mmol) was added via syringe, and the reaction stirred at -78 °C for 20 min. The reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (5 mL) and allowed to warm to rt. The mixture was partitioned between deionized H_2O (30 mL) and EtOAc (30 mL), and the aqueous layer was extracted twice with additional EtOAc (2x 20 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (20:1 to 5:1 hexanes / EtOAc) to provide vinyl stannanes **4** (1.19 g, 91%) as a 1:1 mixture of diastereomers.

Vinyl stannanes **4**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.75 (t, *J* = 4.4 Hz, 1H), 6.71 (t, *J* = 4.4 Hz, 1H), 6.19 (dd, *J* = 2.7, 2.0 Hz, 1H), 6.16 (dd, *J* = 2.7, 2.0 Hz, 1H), 5.47 (s, 1H), 5.28–5.21 (m, 1H), 5.26 (s, 1H), 4.06 (s, 3H), 4.05 (s, 3H), 3.91 (s, 2H), 3.61 (d, *J* = 3.6 Hz, 1H), 3.59 (d, *J* = 3.3 Hz, 1H), 2.46–2.34 (m, 1H), 1.96 (dd, *J* = 15.5, 5.9 Hz, 1H), 1.93 (dd, *J* = 15.5, 5.9 Hz, 1H), 1.80–1.69 (m, 1H), 1.69 (s, 3H), 1.66 (s, 3H), 1.56–1.44 (m, 6H), 1.37–1.22 (m, 9H), 1.08–0.82 (m, 24H), 0.07–0.05 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.4, 176.0, 173.5, 173.4, 147.5, 147.5, 135.0, 134.9, 134.4, 134.3, 132.9, 132.8, 128.6, 128.5, 127.4, 127.3, 104.6, 104.5, 87.1, 87.1, 69.8, 69.8, 67.8, 67.7, 60.9, 60.9, 44.8, 44.8, 37.2, 36.9, 34.8, 31.7, 31.7, 31.6, 29.4, 29.4, 29.3, 27.5, 26.1, 26.1, 25.4, 22.8, 22.5, 22.4, 21.1, 21.0, 18.5, 18.4, 18.3, 14.7, 14.7, 14.3, 13.9, 11.2, -5.1; FTIR (film) νmax 3429, 2959, 2925, 2858, 1730, 1636, 1461, 1374, 1253, 1078, 830, 776, 736 cm^{-1}; ESI–MS *m/z* 775.19 $[M+Na]^+$, 752.95 $[M+H]^+$; HR–ESI–MS *m/z* calcd. for $C_{38}H_{68}O_5Si_1Sn_1Na_1$ $[M+Na]^+$: 775.3750, found 775.3763.

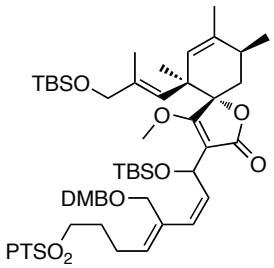


3

Stille adducts 3. A reaction flask was charged with LiCl (157 mg, 3.72 mmol) that was dried under high vacuum (0.1 mm Hg) with a Fisher burner for 10 min. After cooling to rt under argon, $AsPh_3$ (760 mg, 2.48 mmol) and Pd_2dba_3 (284 mg, 0.310 mmol) were added, followed by a solution of stannanes **4** (933 mg, 1.24 mmol) and vinyl iodide **7** (908 mg, 1.55 mmol) in freshly distilled *N*–methylpyrrolidone (15 mL). Care was taken to conduct this transformation under a strict Ar atmosphere using degassed syringe additions of solutions and degassing after additions of solids. The mixture stirred for 12 h at rt, after which it was partitioned between Et_2O (50 mL) and deionized H_2O (20 mL), and the aqueous layer was extracted with additional portions of Et_2O (2 x 20 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (hexanes / Et_2O gradient) of the resulting residue afforded the Stille adducts **3** (809 mg, 71%).

Stille adducts **3**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73–7.56 (m, 5H), 6.88–6.80 (m, 3H), 6.08–6.02 (m, 1H), 5.91–5.80 (m, 2H), 5.66 (t, *J* = 9.3 Hz, 1H), 5.63 (t, *J* = 9.3 Hz, 1H), 5.47–5.41 (m, 1H), 5.26 (br s, 1H), 4.47–4.38 (m, 2H), 4.21–3.98 (m, 4H), 3.93–3.83 (m, 9H), 3.78–3.70 (m, 2H), 2.44–2.32 (m, 3H), 2.15–2.04 (m, 2H), 1.96–1.86 (m, 1H), 1.81–1.73 (m,

1H), 1.69 (overlapping s, 3H), 1.65 (s, 3H), 1.63 (s, 3H), 1.06–0.98 (m, 6H), 0.88 (s, 9H), 0.88 (s, 9H), 0.03 (overlapping s, 3H), 0.02 (overlapping s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.1, 175.7, 173.6, 173.5, 153.5, 149.1, 149.1, 148.8, 135.2, 135.1, 135.0, 134.9, 134.7, 134.4, 134.4, 134.0, 133.6, 133.1, 132.9, 132.7, 131.8, 131.7, 131.6, 130.4, 129.9, 129.5, 128.6, 128.4, 128.4, 127.5, 127.4, 125.2, 125.2, 120.6, 120.6, 111.2, 110.9, 104.3, 104.3, 87.2, 87.2, 72.7, 72.7, 69.9, 69.9, 66.8, 66.8, 62.3, 60.8, 60.7, 56.1, 56.0, 55.4, 44.7, 37.1, 36.7, 31.6, 31.6, 28.0, 27.0, 26.6, 26.6, 26.0, 22.3, 22.2, 22.1, 21.1, 21.1, 18.5, 18.4, 18.3, 14.7, 14.7, -5.1; FTIR (film) νmax 2959, 2932, 2858, 1734, 1639, 1516, 1463, 1340, 1260, 1158, 1075, 1024, 839, 764, 737, 690 cm^{-1}; ESI–MS *m/z* 941.30 $[M+Na]^+$, 957.27 $[M+K]^+$; HR–ESI–MS *m/z* calcd. for $C_{48}H_{66}N_4O_{10}S_1Si_1Na_1$ $[M+Na]^+$: 941.4161, found 941.4156.

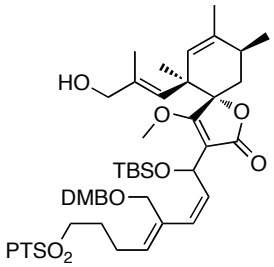


28

Bis–silyl ethers 28. *i*–Pr_2NEt (691 μL, 3.96 mmol) and TBSOTf (404 μL, 1.76 mmol) were added sequentially via syringe to a solution of the Stille adducts **3** (809 mg, 0.880 mmol) in CH_2Cl_2 (10 mL) cooled to 0 °C. The reaction stirred at this temperature for 2 h, and then was partitioned between CH_2Cl_2 (20 mL) and saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was extracted with additional CH_2Cl_2 (2 x 10 mL), and the combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. The solution was filtered and concentrated under reduced pressure, and the residue was purified by flash chromatography to provide the bis–silyl ethers **28** (427 mg, 47%).

Bis–silyl ethers **28**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71–7.54 (m, 5H), 6.90–6.80 (m, 3H), 5.98–5.93 (m, 1H), 5.80–5.73 (m, 1H), 5.57–5.41 (m, 3H), 5.24 (br s, 1H), 4.41 (s, 2H), 4.27 (s, 3H), 4.25 (s, 3H), 4.02–3.89 (m, 4H), 3.87 (overlapping s, 6H), 3.80–3.68 (m, 2H), 2.47–2.23 (m, 3H), 2.16–2.03 (m, 2H), 1.99–1.81 (m, 2H), 1.69 (s, 3H), 1.68 (s, 3H), 1.64 (overlapping s, 3H), 1.02 (d, *J* = 7.1 Hz, 3H), 1.00 (overlapping s, 3H), 0.98 (d, *J* = 7.1 Hz, 3H), 0.91–0.90 (m, 18H), 0.06–0.00 (m, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.8, 178.5, 172.7, 172.4, 153.6, 153.6, 149.1, 149.1, 148.7, 148.7, 135.5, 135.0, 134.9, 134.7, 134.3, 134.3, 134.2, 134.1, 134.0, 133.8, 133.3, 133.0, 132.8, 131.5, 130.8, 130.8, 130.2, 130.0, 129.9, 129.7, 128.9, 128.7, 128.4, 127.7, 127.5, 125.4, 125.4, 120.6, 120.6, 111.3, 111.3, 111.0, 111.0, 105.5, 105.4, 86.4, 86.3, 72.3, 72.3, 69.9, 69.8, 68.1, 67.2, 67.1, 62.3, 62.3, 62.0, 61.8, 56.1, 56.0, 55.6, 55.6, 45.1, 44.9, 37.1,

37.0, 31.6, 31.6, 26.6, 26.5, 26.1, 26.1, 25.9, 25.9, 25.8, 25.8, 22.4, 22.4, 21.9, 21.8, 21.1, 21.0, 18.5, 18.5, 18.3, 18.3, 18.1, 18.0, 14.7, 14.6, -3.4, -4.5, -4.6, -4.7, -4.7, -5.1, -5.1, -5.1; FTIR (film) νmax 2966, 2925, 2858, 1740, 1639, 1519, 1466, 1343, 1263, 1158, 845, 782, 693 cm^{-1}; ESI–MS *m/z* 1050.23 $[M+NH_4]^+$, 1055.40 $[M+Na]^+$, 1071.26 $[M+K]^+$; HR–ESI–MS *m/z* calcd. for $C_{54}H_{80}N_4O_{10}S_1Si_2Na_1$ $[M+Na]^+$: 1055.5026, found 1055.5036.

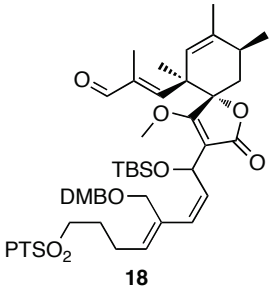


29

Primary alcohols 29. HF • pyridine (450 μL of a 70% w/w solution) was added mixture of pyridine (1 mL) and THF (4 mL) providing a stock 3.2 M HF • pyridine solution. An aliquot of this stock solution (2.6 mL, 20 eq.) was added to bis–silyl ethers **28** (427 mg, 0.413 mmol) in THF (3 mL) and pyridine (1 mL) at rt. The mixture was stirred at rt for 12 h, after which time it was partitioned between saturated aqueous $NaHCO_3$ (20 mL) and EtOAc (20 mL), and the aqueous layer was extracted with additional portions of EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to provide the primary alcohols **29** (299 mg, 79%).

Primary alcohols **29**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.72–7.53 (m, 5H), 6.93–6.78 (m, 3H), 5.99–5.92 (m, 1H), 5.82–5.73 (m, 1H), 5.58–5.46 (m, 2H), 5.42–5.36 (m, 1H), 5.21 (br s, 1H), 4.48–4.37 (m, 2H), 4.28 (s, 3H), 4.24 (s, 3H), 4.02–3.88 (m, 4H), 3.87 (overlapping s, 6H), 3.81–3.67 (m, 2H), 2.47–2.22 (m, 3H), 2.15–2.02 (m, 2H), 1.96–1.81 (m, 1H), 1.74 (overlapping s, 3H), 1.69 (overlapping s, 3H), 1.68–1.59 (m, 1H), 1.38–1.28 (m, 1H), 1.02 (d, *J* = 7.2 Hz, 3H), 1.01–0.96 (m, 6H), 0.84 (s, 9H), 0.83 (s, 9H), 0.03 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.4, 178.0, 172.5, 172.3, 153.6, 149.0, 148.7, 148.7, 135.5, 135.4, 134.8, 134.6, 134.3, 134.3, 134.2, 133.2, 132.9, 132.7, 131.5, 130.7, 130.7, 130.2, 130.0, 129.8, 129.6, 128.4, 128.2, 125.4, 125.4, 120.6, 120.6, 111.3, 111.2, 110.9, 105.7, 105.7, 86.1, 86.1, 72.4, 72.3, 70.9, 70.8, 67.2, 67.0, 62.4, 62.3, 61.8, 61.7, 60.6, 56.0, 56.0, 55.5, 55.5, 45.2, 45.0, 37.0, 37.0, 31.6, 31.5, 26.5, 25.9, 25.9, 22.7, 22.6, 21.8, 21.2, 21.1, 21.0, 18.3, 18.0, 14.9, 14.3, -4.5, -4.6, -4.7, -4.7; FTIR (film) νmax 3496, 2959, 2939, 2865, 1743, 1636, 1522, 1468, 1340, 1266, 1159, 1025, 769, 729 cm^{-1}; ESI–MS *m/z*

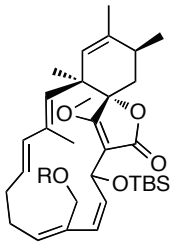
936.07 $[M+NH_4]^+$, 941.25 $[M+Na]^+$, 957.13 $[M+K]^+$; HR–ESI–MS *m/z* calcd. for $C_{48}H_{66}N_4O_{10}S_1Si_1Na_1$ $[M+Na]^+$: 941.4161, found 941.4152.



18

Aldehydes 18. *N*–Methylmorpholine *N*–oxide (57 mg, 0.488 mmol), powdered 4 Å molecular sieves (100 mg), and primary alcohol **29** (299 mg, 0.325 mmol) in CH_2Cl_2 (3 mL) were added to a cooled and dried flask. TPAP (6 mg, 0.016 mmol) was added to this solution as a sold. The color of the suspension changed from green to black over a few minutes, along with consumption of **29**, as observed by TLC analysis. Filtration of the reaction mixture through a short silica gel plug with 4:1 CH_2Cl_2 : EtOAc and concentration of the filtrate under reduced pressure provided the aldehyde **18** (298 mg, 99%).

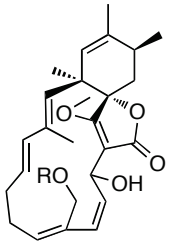
Aldehydes **18**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.32 (s, 1H), 9.30 (s, 1H), 7.69–7.56 (m, 5H), 6.86–6.80 (m, 3H), 6.50 (s, 1H), 6.49 (s, 1H), 5.98 (d, *J* = 12.0 Hz, 1H), 5.97 (d, *J* = 12.0 Hz, 1H), 5.76 (t, *J* = 12.0 Hz, 1H), 5.74 (t, *J* = 12.0 Hz, 1H), 5.59–5.46 (m, 2H), 5.24 (br s, 1H), 4.47–4.37 (m, 2H), 4.30 (s, 3H), 4.25 (s, 3H), 4.02–3.92 (m, 2H), 3.87 (s, 3H), 3.87 (s, 3H), 3.81–3.69 (m, 2H), 2.50–2.25 (m, 3H), 2.15–2.04 (m, 1H), 1.92–1.80 (m, 2H), 1.83 (overlapping s, 3H), 1.72 (s, 3H), 1.71 (s, 3H), 1.07–1.03 (m, 6H), 1.01 (d, *J* = 7.5 Hz, 3H), 0.84 (s, 9H), 0.83 (s, 9H), 0.06–0.00 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.7, 196.6, 177.5, 177.2, 172.2, 171.9, 171.3, 157.6, 157.3, 153.6, 149.1, 149.1, 148.8, 148.8, 138.1, 137.9, 137.9, 134.3, 134.2, 134.1, 133.8, 133.3, 132.9, 132.8, 131.5, 130.7, 130.6, 130.4, 129.8, 125.8, 125.7, 125.4, 125.3, 120.6, 120.6, 111.3, 111.3, 110.0, 110.0, 106.1, 105.8, 85.2, 85.1, 72.5, 72.4, 67.2, 65.0, 62.4, 62.2, 62.1, 62.0, 61.9, 60.5, 56.1, 56.0, 55.6, 55.5, 46.2, 46.0, 37.3, 37.3, 31.7, 31.6, 25.9, 25.8, 21.9, 21.8, 21.1, 20.9, 18.5, 18.4, 18.0, 18.0, 14.4, 14.3, 10.4, 10.4, -4.5, -4.7; FTIR (film) νmax 2966, 2939, 2858, 1746, 1687, 1639, 1519, 1463, 1340, 1266, 1155, 842, 779, 764 cm^{-1}; ESI–MS *m/z* 934.13 $[M+NH_4]^+$, 939.23 $[M+Na]^+$, 941.22 $[M+K]^+$; HR–ESI–MS *m/z* calcd. for $C_{48}H_{64}N_4O_{10}S_1Si_1Na_1$ $[M+Na]^+$: 939.4005, found 939.4008.



2 R=DMB

Macrocycle 2. KHMDS (780 μL of a 0.5 M solution in toluene, 0.390 mmol) was added via syringe to a solution of aldehyde **18** (298 mg, 0.325 mmol) in THF (30 mL) at -78 °C. The solution was stirred for 0.5 h at -78 °C and then allowed to slowly warm to rt over 1 h. After an additional 0.5 h at rt, the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (5 mL). The mixture was partitioned between EtOAc (20 mL) and deionized H_2O (5 mL), and the aqueous layer was extracted with additional portions of EtOAc (2 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography of the residue (1:1 to 1:2 hexanes / diethyl ether) provided the pure macrocycle **2** (33 mg, 15%) as a single diastereomer.

Macrocycle **2**: ^{1}H–NMR ($CDCl_3$, 500 MHz) δ 6.87–6.76 (m, 3H), 6.16 (dd, *J* = 12.6, 8.0 Hz, 1H), 5.98 (d, *J* = 8.0 Hz, 1H), 5.88 (d, *J* = 12.6 Hz, 1H), 5.60 (d, *J* = 15.5 Hz, 1H), 5.57–5.51 (m, 2H), 5.24 (ddd, *J* = 5.2, 10.3, 15.5 Hz, 1H), 5.09 (s, 1H), 4.41 (d, *J* = 12.0 Hz, 1H), 4.21 (d, *J* = 12.0 Hz, 1H), 4.09 (s, 3H), 3.98 (d, *J* = 13.2 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.68 (d, *J* = 13.2 Hz, 1H), 2.62 (dd, *J* = 9.5, 14.5 Hz, 1H), 2.50–2.20 (m, 3H), 1.96–1.86 (m, 1H), 1.81 (s, 3H), 1.76–1.68 (m, 1H), 1.72 (s, 3H), 1.53 (d, *J* = 14.9 Hz, 1H), 1.21 (s, 3H), 1.12 (d, *J* = 7.4 Hz, 3H), 0.83 (s, 9H), 0.01 (s, 3H), -0.09 (s, 3H); ^{13}C–NMR ($CDCl_3$, 100 MHz) δ 177.9, 171.3, 148.9, 148.6, 140.4, 134.7, 134.5, 133.2, 132.7, 132.1, 131.0, 128.6, 127.9, 124.3, 120.6, 111.3, 110.9, 105.7, 85.7, 70.1, 64.5, 62.7, 59.2, 56.0, 55.9, 43.9, 36.2, 32.7, 31.7, 28.4, 27.5, 25.9, 22.1, 20.5, 18.0, 12.9, -3.1, -4.4; FTIR (film) νmax 2925, 2858, 1757, 1646, 1518, 1461, 1263, 806, 732 cm^{-1}; ESI–MS *m/z* 713.38 $[M+Na]^+$; HR–ESI–MS *m/z* calcd. for $C_{41}H_{58}O_7Si_1Na_1$ $[M+Na]^+$: 713.3844, found 713.3849.



19 R=DMB

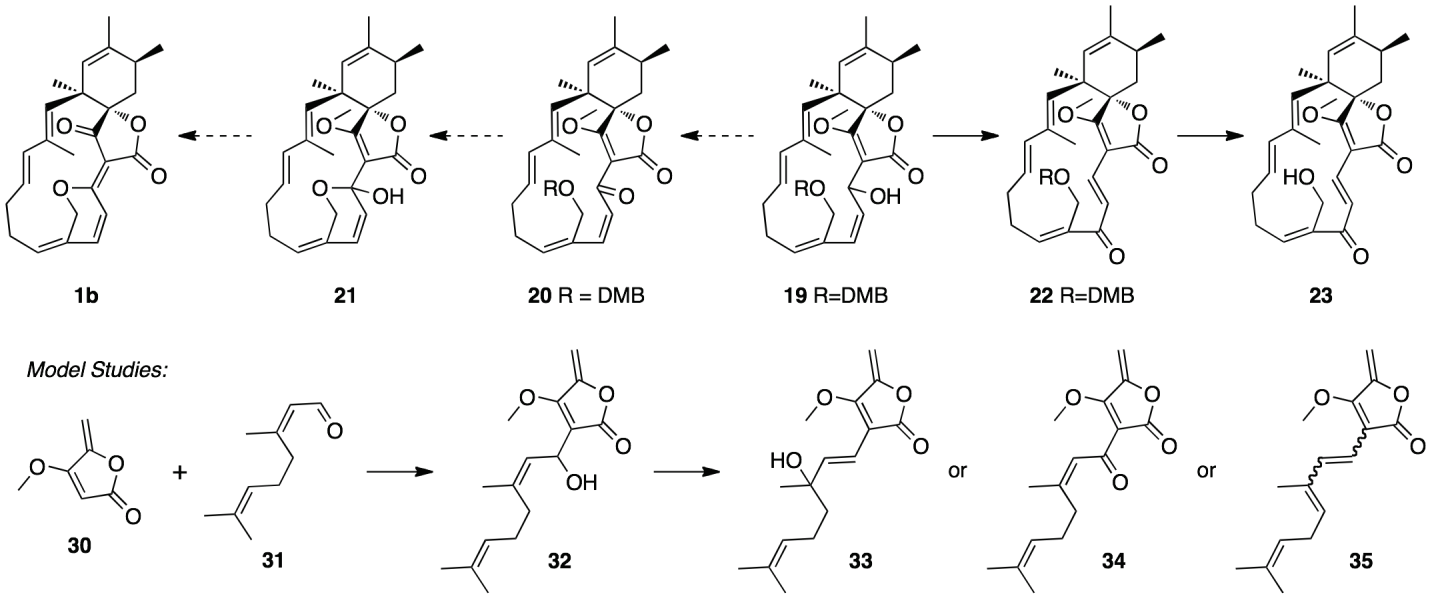
Macrocyclic alcohol 19. TBAF (96 μL of a 1.0 M solution in THF, 0.096 mmol) was added to a solution of macrocycle **2** (33 mg, 0.048 mmol) in THF (1 mL) in a plastic vial. After 2 h at rt, TLC analysis indicated the consumption of starting material. The reaction mixture was partitioned between deionized H_2O (1 mL) and EtOAc (2 mL), and the aqueous layer was extracted with additional EtOAc (2 x 2 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (2:1 EtOAc / hexanes) to provide the alcohol **19** (16 mg, 58%) as a colorless amorphous solid.

Macrocyclic alcohol **19**: TLC (2:1 EtOAc / hexanes): R_f = 0.2; ^{1}H–NMR ($CDCl_3$, 400 MHz) δ 6.88–6.74 (m, 3H), 6.11 (dd, 1H, *J* = 12.0, 8.0 Hz), 6.04–5.96 (m, 1H), 5.92 (d, 1H, *J* = 12.0 Hz), 5.60 (dd, 1H, *J* = 9.8, 6.9 Hz), 5.57 (d, 1H, *J* = 16.0 Hz), 5.51 (s, 1H), 5.28 (ddd, 1H, *J* = 16.0, 10.3, 5.8 Hz), 5.08 (s, 1H), 4.44 (d, 1H, *J* = 11.5 Hz), 4.15 (d, 1H, *J* = 11.5 Hz), 4.12 (s, 3H), 4.03 (d, 1H, *J* = 13.5 Hz), 3.87 (s, 3H), 3.87 (s, 3H), 3.71 (d, 1H, *J* = 13.5 Hz), 2.63 (dd, 1H, *J* = 14.3, 9.2 Hz), 2.49–2.36 (m, 1H), 2.44–2.35 (m, 1H), 2.29–2.20 (m, 1H), 2.09–2.00 (m, 1H), 1.81 (s, 3H), 1.79–1.66 (m, 1H), 1.73 (s, 3H), 1.61 (d, 1H, *J* = 14.3 Hz), 1.21 (s, 3H), 1.13 (d, 3H, *J* = 7.4 Hz); ^{13}C–NMR ($CDCl_3$, 100 MHz) δ 178.8, 172.1, 149.1, 148.6, 140.5, 135.9, 135.0, 134.5, 133.6, 131.1, 130.4, 130.4, 129.7, 127.9, 124.3, 120.0, 111.1, 110.9, 104.4, 86.7, 70.0, 64.3, 62.1, 60.0, 56.1, 56.0, 43.8, 35.8, 32.8, 31.8, 28.6, 27.7, 22.0, 20.5, 13.0; ESI–MS *m/z* 593.92 $[M+NH_4]^+$; HR–ESI–MS *m/z* calcd. for $C_{35}H_{44}O_7Na_1$ $[M+Na]^+$: 599.2979, found 599.2981.

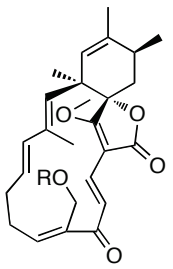
Table S1. NMR analysis of compound **19** in $CDCl_3$ at 500 MHz.

C/H no.	δC (ppm)	δH (ppm), mult., *J* (Hz)	COSY	HMBC
1	172.1	–	–	–
2		–	–	–
3	62.11	6.04–5.96 (m)	3–OH, 4	1
4	130.41	6.11, dd, (12, 8)	3,5	3,6
5	129.65	5.92, d (12)	3,4, 21a	3,4,7,21
6	134.96	–	–	–
7	135.88	5.60, dd (9.8, 6.9)	8a, 8b	5,8,21
8a	27.72	2.29–2.20, m	7, 9a, 9b	6,7,10
8b		2.09–2.00, m	7, 9a, 9b	7
9a	31.81	2.44–2.35, m	8a, 8b, 10	10,11
9b		1.79–1.66, m	8a, 8b, 10	nd
10	124.32	5.28, ddd (16.0, 10.3, 5.8)	9a, 9b, 11	9
11	140.46	5.57, d (16.0)	10	13,22
12	133.57	–	–	–
13	134.52	5.08,s	22	11,12,14,15,19,22,23
14	43.83	–	–	–
15	127.9	5.51, s	24	14,17,19,24
16	130.41	–	–	–
17	32.79	2.49–2.36, m	18a, 18b, 25	16,19,25
18a	35.84	2.63, dd, (14.3, 9.2)	17, 18b	17,19,20,24
18b		1.61, d, (14.3)	18a	14,17,19,20,24
19	86.67	–	–	–
20	178.83	–	–	–
21a	64.25	4.03, d, (13.5)	21b	DMB (CH_2), 5, 6
21b		3.71, d, (13.5)	21a	DMB (CH_2), 5, 6
22	12.99	1.81, s	13	
23	28.55	1.21, s	–	
24	21.99	1.73, s	15	
25	20.46	1.13, d, (7.4)	17	
DMB	70.04	4.13, d, and 4.15, d		
DMB	110.89			
DMB	111.11			
DMB	120.03	}6.88–6.74, m, 3H		
DMB	131.13			
DMB	148.61			
DMB	149.13			
DMB	55.98	3.87, s		
DMB	56.07	3.87, s		
OMe	60	4.12, s		

Oxidation of carbinol 19. A series of oxidants were screened using the model bis–allylic alcohol **32**.



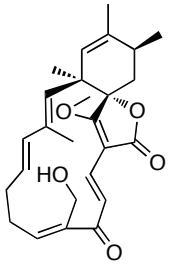
Scheme S4. Oxidation studies including model studies (bottom) and application (top).



Ketone 22. Dess–Martin periodinane (7 mg, 0.017 mmol) was added to alcohol **19** (5 mg, 0.0087 mmol) in CH_2Cl_2 (0.5 mL) containing solid $NaHCO_3$ (3.5 mg, 0.043 mmol). The suspension was stirred at rt for 20 min, at which point TLC of the reaction mixture indicated the consumption of the starting material. The reaction mixture was then filtered through a short silica gel plug with 2:1 CH_2Cl_2 / EtOAc and a short Celite plug with the same solvent in order to remove the insoluble Dess–Martin periodinane byproducts. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography (4:1 CH_2Cl_2 : EtOAc) to provide dienone **22** (4 mg, 80%).

Ketone **22**: ^{1}H–NMR ($CDCl_3$, 500 MHz) δ 7.03 (d, 1H, *J* = 16.0 Hz), 6.88–6.80 (m, 3H), 6.78 (d, 1H, *J* = 16.0 Hz), 6.35 (dd, 1H, *J* = 6.2, 4.4 Hz), 6.01 (d, 1H, *J* = 15.4 Hz), 5.56 (s, 1H), 5.45 (ddd, 1H, *J* = 15.4, 10.3, 4.4 Hz), 5.10 (s, 1H), 4.44 (s, 2H), 4.30 (d, 1H, *J* = 11.0 Hz), 4.17 (d, 1H, *J* = 11.0 Hz), 3.88 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 2.64 (dd, 1H, *J* =

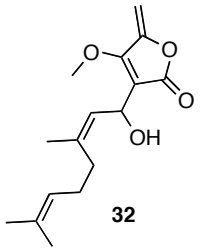
14.7, 9.5 Hz), 2.51–2.41 (m, 4H), 2.14–2.05 (m, 1H), 1.86 (s, 3H), 1.74 (s, 3H), 1.65 (d, 1H, J = 14.7 Hz), 1.31 (s, 3H), 1.12 (d, 3H, J = 7.5 Hz); ^{13}C–NMR ($CDCl_3$, 125 MHz) δ 197.8, 181.9, 170.1, 149.1, 148.7, 148.5, 140.2, 138.4, 134.5, 134.4, 133.7, 131.1, 130.8, 130.0, 127.3, 126.2, 120.3, 111.3, 111.0, 98.5, 86.2, 73.0, 64.1, 60.8, 56.1, 56.0, 45.5, 34.0, 32.6, 31.9, 27.6, 27.1, 22.0, 20.5, 13.1; ESI–MS m/z 575.43 $[M+H]^+$, 597.47 $[M+Na]^+$; HR–ESI–MS m/z calcd. for $C_{35}H_{42}O_7Na_1$ $[M+Na]^+$: 597.2823, found 597.2822.



23

Alcohol 23. DDQ (2 mg, 0.0088 mmol) was added to dienone **22** (3 mg, 0.0052 mmol) in CH_2Cl_2 (0.5 mL) and deionized H_2O (30 μL). The mixture was stirred at rt for 10 min and then filtered through a short plug of silica gel with 1:1 CH_2Cl_2 / EtOAc and then a short plug of Celite with the same solvent. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography (2:1 CH_2Cl_2 / EtOAc) to provide the alcohol **23** (2 mg, 91%) as a colorless crystalline solid. Diffraction quality crystals were obtained by slow evaporation of a $CHCl_3$ / hexanes solution of **23**.

Alcohol **23**: ^{1}H–NMR ($CDCl_3$, 500 MHz) δ 7.02 (d, 1H, J = 16.0 Hz), 6.74 (d, 1H, J = 16.0 Hz), 6.40 (t, 1H, J = 5.3 Hz), 6.03 (d, 1H, J = 15.4 Hz), 5.58 (s, 1H), 5.44 (ddd, 1H, J = 15.4, 10.5, 4.6 Hz), 5.12 (s, 1H), 4.42 (dd, 1H, J = 13.0, 5.0 Hz), 4.27 (dd, 1H, J = 13.0, 6.5 Hz), 3.98 (s, 3H), 2.77 (br t, 1H, $J \approx$ 6.5 Hz), 2.65 (dd, 1H J = 14.7, 9.5 Hz), 2.55–2.31 (m, 4H), 2.15–1.97 (m, 1H), 1.88 (s, 3H), 1.75 (s, 3H), 1.66 (d, 1H, J = 14.7 Hz), 1.32 (s, 3H), 1.14 (d, 3H, J = 7.5 Hz); ^{13}C–NMR ($CDCl_3$, 125 MHz) δ 199.4, 182.1, 170.1, 148.0, 140.7, 139.9, 134.5, 134.5, 133.7, 130.7, 128.8, 127.2, 125.8, 98.3, 86.2, 61.0, 58.6, 45.6, 34.0, 32.6, 31.7, 27.7, 26.5, 22.1, 20.5, 13.1; ESI–MS m/z 425.36 $[M+H]^+$, 447.45 $[M+Na]^+$; HR–ESI–MS m/z calcd. for $C_{26}H_{32}O_5Na_1$ $[M+Na]^+$: 447.2142, found 447.2141.



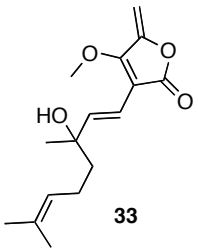
32

Model bis–allylic alcohol 32. n–BuLi (1.2 mL of a 1.6 M solution in hexanes, 1.90 mmol) was added to a solution of freshly distilled *i*–Pr_2NH (267 μL, 1.90 mmol) in THF (10 mL) at 0 °C. The solution stirred at this temperature for 30 min. A reaction flask was charged with tetronate **30**[S5] (200 mg, 1.59 mmol) and THF (5 mL), and the stirred solution was cooled to -78 °C. The LDA solution was slowly cannulated into the reaction flask over 1 min, and the deprotonation was allowed to proceed for 10 min at -78 °C before a solution of neral **31**[S6] (500 mg, 3.0 mmol) in THF (2 mL) was added slowly via syringe. The reaction mixture stirred for 1 h at -78 °C, and then was quenched by the addition of a saturated aqueous solution of NH_4Cl (5 mL), and warmed to rt. The mixture was diluted with deionized H_2O (15 mL) and EtOAc (20 mL), and the aqueous layer was extracted with additional portions of EtOAc (2x 10 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes / ethyl acetate gradient) to provide the model bis–allylic alcohol **32** (240 mg, 55%) as a yellow oil.

Bis–allylic alcohol 32: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.63 (d, 1H, *J* = 8.9 Hz), 5.53 (dd, 1H, *J* = 7.4, 8.9 Hz), 5.12–5.06 (m, 1H), 5.06 (d, 1H, *J* = 2.1 Hz), 5.05 (d, 1H, *J* = 2.1 Hz), 4.18 (s, 3H), 2.71 (d, 1H, *J* = 7.4 Hz), 2.25–2.05 (m, 4H), 1.76 (s, 3H), 1.68 (s, 3H), 1.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.4, 161.2, 149.7, 140.7, 132.6, 125.7, 123.6, 107.3, 93.2, 64.3, 61.9, 60.7, 32.4, 26.4, 25.8, 23.4, 17.8; ESI–MS *m/z* 301.37 $[M+Na]^+$; HR–ESI–MS m/z calcd. for $C_{16}H_{22}O_4Na_1$ $[M+Na]^+$: 301.1410, found 301.1413.

Table S2. Exemplary conditions evaluated in model studies and for the oxidation of alcohol **19**.

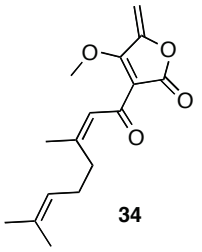
Oxidant	Model Product	Reaction with compound **19**
Dess–Martin periodinane / $NaHCO_3$	**34**	**22**
RuO_2*xH_2O, O_2 atmosphere	Complex Mixture	–
TPAP / NMO	**34**	Complex mixture
DDQ / Dioxane	**33**	–
$(COCl)_2$, DMSO, Et_3N	**35**	–
PDC / CH_2Cl_2	**33**	–
PDC / DMF	**33**	–
DMSO / Ac_2O	**35**	–
IBX	**34**	**22**
TEMPO / $PhI(OAc)_2$	**34**	No reaction
$PhI(OAc)_2$ / I_2	Complex Mixture	–
TEMPO / Oxone / *n*–Bu_4NBr	**33** + Complex mixture	–
PCC / NaOAc	**33**	–
$CHDFe(CO)_3$ / Me_3NO	–	No reaction



33

Tertiary alcohol 33. PDC (12 mg, 0.032 mmol) was added in a single portion to a stirred solution of alcohol **32** (7.2 mg, 0.026 mmol) in DMF (150 μL) at 0 °C. The mixture stirred at this temperature for 1 h, and then was filtered through a short plug of silica gel with 2:1 hexanes / ethyl acetate, and the filtrate was concentrated under reduced pressure to provide the rearrangement product **33** (5 mg, 69%) as a yellow oil.

Tertiary alcohol **33**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.81 (d, 1H, *J* = 15.8 Hz), 6.60 (d, 1H, *J* = 15.8 Hz), 5.15–5.08 (m, 1H), 5.03 (d, 1H, *J* = 2.6 Hz), 5.01 (d, 1H, *J* = 2.6 Hz), 4.19 (s, 3H), 2.42 (s, 1H), 2.20–1.90 (m, 2H), 1.67 (s, 3H), 1.70–1.60 (m, 2H), 1.59 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.0, 160.0, 149.3, 143.1, 132.5, 124.3, 112.9, 103.9, 92.7, 74.0, 60.5, 42.4, 28.8, 25.9, 23.1, 20.0, 17.9.



34

Ketone **34**. Dess–Martin periodinane (42 mg, 0.099 mmol) was added to a stirred solution of alcohol **32** (23 mg, 0.082 mmol) in CH_2Cl_2 (1 mL) containing suspended $NaHCO_3$ (35 mg, 0.41 mmol). The mixture stirred for 15 min at rt, and then was filtered through a short plug of Celite and then a silica gel plug using CH_2Cl_2 as the eluent. The filtrate was concentrated under reduced pressure to provide the ketone **34** as a yellow oil.

Ketone **34**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.63 (s, 1H), 5.22 (d, 1H, J = 2.5 Hz), 5.17 (d, 1H, *J* = 2.5 Hz), 5.19–5.12 (m, 1H), 4.13 (s, 3H), 2.65 (t, 2H, *J* = 7.6 Hz), 2.17 (q, 2H, *J* = 7.6 Hz), 1.98 (s, 3H), 1.68 (s, 3H), 1.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.1, 167.5, 166.7, 163.4, 149.2, 132.5, 124.1, 123.7, 107.2, 95.1, 62.8, 34.9, 26.8, 26.4, 25.9, 17.8.

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