Hemi-Phorboxazole A: Structure Confirmation, Analogue Design and Biological Evaluation

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Supporting Information 1

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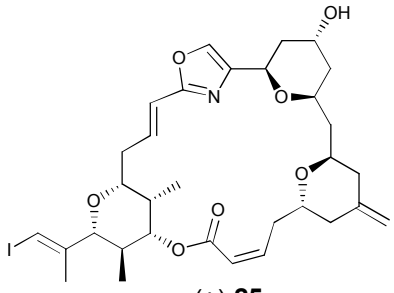
Materials and Methods: All solvents used were reagent grade. Dichloromethane, tetrahydrofuran (THF), and toluene were filtered through an activated alumina and copper purification system (Pure Solv. PS-400) prior to use. All other reagents were purchased from Aldrich or Acros and used as received unless otherwise mentioned. Reactions, carried out in flame-dried or oven-dried glassware, were magnetically stirred under an argon atmosphere and monitored by thin layer chromatography (TLC) with 0.25 mm E. Merck pre-coated silica gel plates. Silica gel chromatography was performed with silica gel 60 (particle size 0.040-0.062 mm) supplied by Silicycle and Sorbent Technologies. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. Infrared spectra were recorded on a Jasco Model FT/IR-480 Plus spectrometer. NMR spectra were recorded on a Bruker AMX-500 spectrometer. Chemical shifts are reported relative to chloroform (δ 7.26 and 77.23 for ^{1}H and ^{13}C NMR, respectively), or benzene (δ 7.16 and 128.39 for ^{1}H and ^{13}C NMR, respectively). Optical rotations were measured on a Perkin-Elmer model 241 polarimeter. High resolution mass spectra were measured at the University of Pennsylvania Mass Spectrometry Service Center.

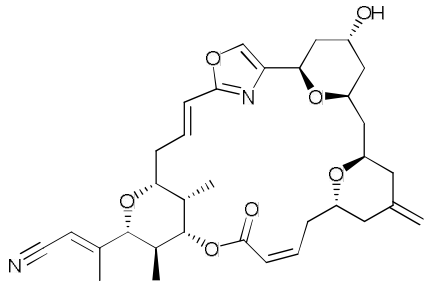
Experimental Procedures:



(+)-**25**

Preparation of alcohol (+)-25: Tetrabutylammonium fluoride (0.3 mL, 1.0 M in THF) was added dropwise to a solution of vinyl iodide (+)-**2** (8.0 mg, 0.01 mmol) in THF (3 mL) at 0 °C. The resultant solution was stirred at 0 °C for 12 h. Brine (3 mL) was added and the mixture was extracted with ethyl acetate (3 × 3 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (25% EtOAc/hexanes) afforded alcohol (+)-**25** (6.4 mg, 94%): $[\alpha]_D^{20}$ + 37.50 (*c* 0.7, $CHCl_3$); IR (thin film, CH_2Cl_2) 3449 (br, w), 3070 (w), 2924 (s), 1719 (s), 1187 (m), 1090 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (s, 1H), 6.66 (ddd, 1H, *J* = 16.2, 9.9, 6.5 Hz), 6.31 (s, 1H), 6.28 (d, 1H, *J* = 15.9 Hz), 5.95-5.89 (m, 2H), 4.98 (s, 1H), 4.73 (dd, 1H, *J* = 10.5, 3.2 Hz), 4.60 (s, 1H), 4.47 (dd, 1H, *J* = 11.2, 4.4 Hz), 4.39 (s, 1H), 4.19-4.15 (m, 1H), 4.07-4.03 (m, 1H), 3.99-3.92 (m, 1H), 3.63 (d, 1H, *J* = 10.2 Hz), 3.52-3.43 (m, 2H), 2.70 (d, 1H, *J* = 12.3 Hz), 2.53-2.47 (m, 1H), 2.43-2.38 (m, 2H), 2.33-2.25 (m, 2H), 2.04 (d, 1H, *J* = 12.8 Hz), 2.01-1.93 (m, 3H), 1.92-1.84 (m, 2H), 1.86 (s, 3H), 1.71 (d, 1H, *J* = 4.0 Hz), 1.62-1.54 (m, 2H) 1.45-1.40 (m, 1H), 0.93 (d, 3H, *J* = 6.9 Hz), 0.72 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 161.5, 145.9, 144.8, 142.3, 142.0, 134.0, 133,9, 121.1, 119.6, 110.3, 88.0, 82.0, 79.2, 78.4, 73.7, 69.3, 68.4,

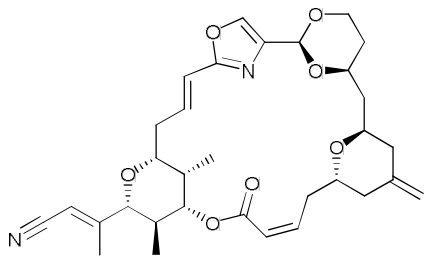
67.1, 64.6, 41.5, 39.2, 37.2, 35.2, 34.5, 32.7, 32.0, 30.7, 19.4, 13.3, 6.2; high resolution mass spectrum (ES+) *m/z* 702.1895 [$(M+Na)^+$; calcd for $C_{32}H_{42}INNaO_7$: 702.1904].



(+)-**1**

Preparation of hemi-phorboxazole A [(+)-1]: To a solution of vinyl iodide (+)-**25** (4.0 mg, 0.0059 mmol) in anhydrous benzene (0.3 mL) was added copper iodide (0.2 mg, 0.0010 mmol), tetrakis(triphenylphosphine)palladium(0) (2.0 mg, 0.0018 mmol) and tributyltin cyanide (2.1 mg, 0.0071 mmol) sequentially. The mixture was heated at reflux in a sealed tube for 2 h. The solvent was removed *in vacuo* and the crude oil was purified directly by flash chromatography (25% EtOAc/hexanes) to provide hemi-phorboxazole (3.0 mg, 90%): $[\alpha]_D^{20}$ + 42.30 (*c* 0.2, $CHCl_3$); IR (thin film, CH_2Cl_2) 3436 (br, w), 3070 (w), 2930 (s), 2220 (m), 1718 (s), 1187 (s), 1093 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (s, 1H), 6.65 (ddd, 1H, *J* = 16.0, 9.7, 6.3 Hz), 6.29 (d, 1H, *J* = 16.0 Hz), 5.98-5.89 (m, 2H), 5.32 (s, 1H), 4.97 (s, 1H), 4.74 (dd, 1H, *J* = 10.9, 3.0 Hz), 4.60 (s, 1H), 4.48 (dd, 1H, *J* = 11.2, 4.4 Hz), 4.42-4.38 (m, 1H), 4.19-4.14 (m, 1H), 4.08-4.03 (m, 1H), 4.01-3.94 (m, 1H), 3.56 (d, 1H, *J* = 10.2 Hz), 3.53-3.44 (m, 2H), 2.70 (d, 1H, *J* = 12.4 Hz), 2.53-2.47 (m, 1H), 2.44-2.37 (m, 2H), 2.36-2.32 (m, 2H), 2.10 (s, 3H), 2.07 (d, 1H, *J* = 13.1 Hz), 2.01-1.93 (m, 3H), 1.92-1.88 (m, 2H), 1.71 (d, 1H, *J* = 13.7 Hz), 1.64-1.54 (m, 2H), 1.43 (ddd, 1H, *J* =13.3, 10.0, 3.1 Hz), 0.93 (d, 3H, *J* = 6.9 Hz), 0.76 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 161.3, 161.0, 145.0, 142.3, 142.0, 133.9,

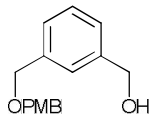
133.5, 120.9, 120.0, 116.3, 110.1, 99.1, 86.3, 78.7, 78.6, 73.6, 69.3, 68.8, 67.1, 64.6, 41.4, 39.2, 39.1, 37.1, 35.1, 34.3, 32.6, 32.0, 30.7, 16.6, 13.1, 6.0; high resolution mass spectrum (ES+) *m/z* 601.2899 [$(M+Na)^+$; calcd for $C_{33}H_{42}N_2NaO_7$: 601.2992].



(+)-3

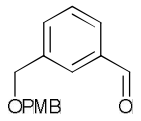
Preparation of hemi-phorboxazole analogue (+)-3. To a solution of vinyl iodide (+)-**15** (4.6 mg, 0.0069 mmol) in anhydrous benzene (0.4 mL) was added copper iodide (0.3 mg, 0.00158 mmol), tetrakis(triphenylphosphine)palladium(0) (2.4 mg, 0.0021 mmol) and tributyltin cyanide (2.6 mg, 0.0083 mmol) sequentially. The mixture was heated at reflux in a sealed tube for 2 h. The solvent was removed *in vacuo* and the crude oil was purified directly by flash chromatography (25% to 33% EtOAc/hexanes) to provide (+)-**3** (3.0 mg, 90%): $[\alpha]_D^{20}$ + 43.90 (*c* 0.2, $CHCl_3$); IR (thin film, CH_2Cl_2) 2934 (s), 2857 (s), 2221 (m), 1717 (s), 1639 (m), 1234 (m), 1192 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60 (s, 1H), 6.67 (ddd, 1H, *J* = 16.2, 10.5, 6.1 Hz), 6.29 (d, 1H, *J* = 15.9 Hz), 5.99-5.90 (m, 2H), 5.47 (s, 1H), 5.32 (s, 1H), 4.93 (s, 1H), 4.62 (s, 1H), 4.47 (dd, 1H, *J* = 11.2, 4.3 Hz), 4.24 (dd, 1H, *J* = 11.5, 4.6 Hz), 4.20-4.16 (m, 1H), 4.03-3.98 (m, 1H), 3.96-3.89 (m, 2H), 3.56 (d, 1H, *J* = 10.3 Hz), 3.51 (dd, 1H, *J* = 10.7, 5.2 Hz), 3.40 (ddd, 1H, *J* = 14.0, 12.3, 9.5 Hz), 2.61 (d, 1H, *J* = 12.3 Hz), 2.53-2.47 (m, 1H), 2.45-2.34 (m, 4H), 2.10 (s, 3H), 2.05 (d, 1H, *J* = 11.4 Hz), 2.02-1.81 (m, 5H), 1.52 (d, 1H, *J* = 13.2 Hz), 0.93 (d, 3H, *J* = 6.9 Hz), 0.76 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 161.3, 161.0, 145.0, 141.7, 139.9, 135.0, 133.9, 120.9, 119.5, 116.3, 110.3, 99.2, 97.2, 86.4, 78.9, 78.7, 73.5, 73.5,

68.5, 67.2, 41.4, 39.3, 37.1, 34.2, 32.6, 32.1, 30.6, 16.6, 13.1, 6.0; high resolution mass spectrum (ES+) *m/z* 587.2733 [$(M+Na)^+$; calcd for $C_{32}H_{40}N_2NaO_7$: 587.2722].



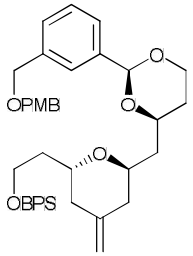
26

Preparation of PMB-ether 26: Sodium hydride (460.2 mg, 11.50 mmol) was added to a solution of 1,3-benzenedimethanol (1.58 g, 11.44 mmol) in DMF (15 mL) at 0 °C. After 10 min, the ice bath was removed and stirring continued at rt for 1 h. The reaction was then re-cooled to 0 °C and dropwise addition of 4-methoxybenzyl bromide (1.65 mL, 11.44 mmol) was followed by addition of tetrabutylammonium iodide (421.5 mg, 1.14 mmol). The resultant mixture was warmed to rt and stirring continued for 16 h. Hydrochloric acid (5 mL, 1 M) was added and the reaction mixture diluted with ethyl acetate (80 mL). The organic layer was separated, washed with brine (x 3), dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (20% to 50% EtOAc/hexanes) afforded **26** as colorless oil (1.22 g, 41%), (the di-protected compound was also isolated in 23% yield): IR (neat) 3389 (br, m), 2934 (m), 2860 (m), 2836 (m), 1612 (m), 1515 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.35-7.26 (m, 6H), 6.91 (d, 2H, *J* = 8.5 Hz), 4.62 (s, 2H), 4.53 (s, 2H), 4.51 (s, 2H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.3, 141.3, 138.6, 130.3, 129.6, 128.6, 127.0, 126.4, 126.3, 113.9, 72.0, 71.8, 65.0, 55.3; high resolution mass spectrum (ES^+) *m/z* 281.1146 [$(M+Na)^+$; calcd for $C_{16}H_{18}O_3Na$: 281.1154].



16

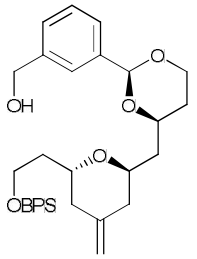
Preparation of aldehyde 16: Manganese dioxide (2.57 g, 29.56 mmol) was added to a solution of alcohol **26** (743.9 mg, 2.88 mmol) in dichloromethane (50 mL). The reaction was stirred at rt for 16 h. Flash chromatography on silica gel (20% to 50% EtOAc/hexanes) afforded **16** as colorless oil (695.7 mg, 94%): IR (neat) 2930 (m), 2851 (m), 2837 (m), 1701 (m), 1607 (m), 1513 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 10.0 (s, 1H), 7.87 (s, 1H), 7.81 (d, 1H, *J* = 7.5 Hz), 7.63 (d, 1H, *J* = 7.5 Hz), 7.52 (t, 1H, *J* = 7.5 Hz), 7.30 (d, 2H, *J* =8.4 Hz), 6.90 (d, 2H, *J* = 8.4 Hz), 4.59 (s, 2H), 4.54 (s, 2H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 192.5, 159.6, 139.9, 136.7, 133.8, 130.1, 129.7, 129.3, 129.1, 129.0, 114.1, 72.5, 71.2, 55.5; high resolution mass spectrum (ES^+) *m/z* 279.0991 [$(M+Na)^+$; calcd for $C_{16}H_{16}O_3Na$: 279.0997].



(–)-19

Preparation of acetal (–)-19: 10-Camphorsulfonic acid (4.4 mg, 17.6 μmol) and sodium sulfate (238.5 mg, 1.89 mmol) were added to a solution of diol (–)-**18** (49.8 mg, 0.11 mmol) and aldehyde **16** (38.0 mg, 0.15 mmol) in toluene (4 mL). The reaction was heated at 90 °C for 24 h. The reaction mixture was cooled to rt, diluted with ethyl acetate and washed with phosphate buffer pH 7. The organic layer was dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (5% to 10% EtOAc/hexanes)

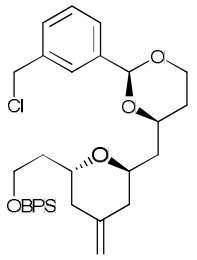
afforded (–)-**19** as colorless oil (73.3 mg, 94%): $[\alpha]_D^{29}$ –22.2 (*c* 0.22, $CHCl_3$); IR (neat) 2935 (m), 2856 (m), 1513 (m), 1248 (m), 1109 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.71-7.66 (m, 4H), 7.44-7.34 (m, 10H), 7.30-7.28 (m, 2H), 6.90-6.88 (m, 2H), 5.40 (s, 1H), 4.77 (s, 2H), 4.53 (s, 2H), 4.47 (s, 2H), 4.18 (dd, 1H, *J* = 11.2, 4.9 Hz), 4.06-4.04 (m, 1H), 3.96-3.89 (m, 2H), 3.81 (s, 3H), 3.78-3.76 (m, 2H), 3.72-3.69 (m, 1H), 2.36 (dt, 2H, *J* = 13.2, 4.8 Hz), 2.13 (ddd, 1H, *J* = 13.9, 9.2, 5.7), 2.03 (ddd, 2H, *J* = 20.5, 13.2, 6.3 Hz), 1.89-1.84 (m, 1H), 1.78-1.66 (m, 2H), 1.56-1.51 (m, 2H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 159.4, 142.1, 139.1, 138.6, 135.7, 134.0, 130.6, 129.8, 129.6, 128.5, 128.2, 127.9, 125.6, 125.5, 114.0, 110.7, 101.3, 74.2, 71.9, 71.8, 69.1, 68.1, 67.1, 60.8, 55.5, 40.0, 39.8, 39.4, 36.6, 31.1, 27.1, 19.4; high resolution mass spectrum (ES^+) *m/z* 729.3607 [$(M+Na)^+$; calcd for $C_{44}H_{54}O_6SiNa$: 729.3587].



(–)-**27**

Preparation of alcohol (–)-27: A solution of PMB-ether (–)-**19** (278.3 mg, 0.39 mmol) in dichloromethane (39 mL) and water (2.5 mL) was cooled to 0 °C. DDQ (133.5 mg, 0.59 mmol) was added in one portion. After 10 min the ice bath was removed and stirring continued at rt for 16 h. The reaction was quenched by the addition of saturated sodium bicarbonate solution (15 mL) and the organic layer was separated. The aqueous layer was extracted with dichloromethane (30 mL); the combined organic layers were dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (25% to 50% EtOAc/hexanes) afforded (–)-**27** as colorless oil (222.8 mg, 97%): $[\alpha]_D^{29}$ –18.9 (*c* 0.47,

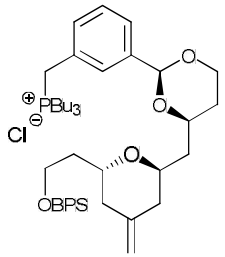
$CHCl_3$); IR (neat) 3421 (br, w), 2930 (m), 2857 (m), 1109 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.70-7.65 (m, 4H), 7.46 (s, 1H), 7.42-7.32 (m, 9H), 5.39 (s, 1H), 4.76 (s, 2H), 4.68 (s, 2H), 4.17 (dd, 1H, *J* = 11.3, 4.6 Hz), 4.05-4.03 (m, 1H), 3.94-3.90 (m, 2H), 3.80-3.75 (m, 2H), 3.70-3.66 (m, 1H), 2.35 (ddd, 2H, *J* = 13.1, 8.0, 4.7 Hz), 2.12 (ddd, 1H, *J* = 14.1, 9.1, 5.5 Hz), 2.05-1.95 (m, 2H), 1.86-1.83 (m, 1H), 1.78-1.63 (m, 2H), 1.60 (bs, 1H), 1.57-1.51 (m, 2H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.1, 141.1, 139.3, 135.8, 134.1, 129.9, 128.7, 127.9, 127.9, 127.5, 125.7, 124.8, 110.7, 101.2, 74.3, 69.1, 68.2, 67.2, 65.6, 60.9, 40.0, 39.9, 39.4, 36.7, 31.1, 27.1, 19.4; high resolution mass spectrum (ES^+) *m/z* 609.2998 [$(M+Na)^+$; calcd for $C_{36}H_{46}O_5SiNa$: 609.3012].



(–)-**20**

Preparation of chloride (–)-20: Carbon tetrachloride (3 mL) and triphenylphosphine (907.1 mg, 3.46 mmol) were added to a solution of alcohol (–)-**27** (202.2 mg, 0.34 mmol) in dichloromethane (15 mL) at rt. Stirring continued at rt for 1.5 h. The reaction mixture was poured onto saturated sodium bicarbonate solution (10 mL) and extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (5% EtOAc/hexanes) afforded (–)-**20** as colorless oil (186.9 mg, 91%): $[\alpha]_D^{29}$ –23.2 (*c* 0.18, $CHCl_3$); IR (neat) 2930 (m), 2857 (m), 1110 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.69-7.65 (m, 4H), 7.46 (s, 1H), 7.42-7.34 (m, 9H), 5.37 (s, 1H), 4.76 (s, 2H), 4.57 (s, 2H), 4.17 (dd, 1H, *J* = 11.4, 4.3 Hz), 4.07-4.01 (m, 1H), 3.96-3.87 (m, 2H), 3.80-3.75 (m, 2H), 3.72-3.67 (m,

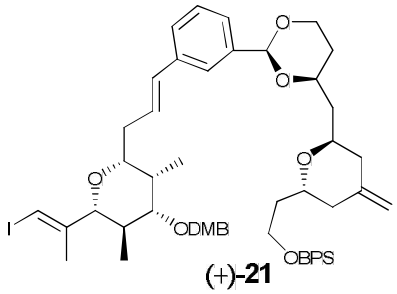
1H), 2.38-2.33 (m, 2H), 2.13-2.09 (m, 1H), 2.05-1.98 (m, 2H), 1.88-1.84 (m, 1H), 1.75-1.65 (m, 2H), 1.57-1.51 (m, 2H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.1, 139.5, 137.6, 135.8, 134.0, 129.9, 129.0, 128.8, 127.9, 127.8, 126.5, 126.4, 110.7, 100.9, 74.3, 69.1, 68.2, 67.1, 60.8, 46.3, 40.0, 39.8, 39.4, 36.7, 31.1, 27.1, 19.4; high resolution mass spectrum (ES$^+$) *m/z* 627.2657 [(M+Na)$^+$; calcd for $C_{36}H_{45}O_4SiClNa$: 627.2673].



(–)-**28**

Preparation of Wittig salt (–)-28: Tri-*n*-butylphosphine (0.07 mL, 0.28 mmol) was added to a solution of chloride (–)-**20** (155.3 mg, 0.26 mmol) in DMF (7.5 mL). After stirring at rt for 16 h, additional tri-*n*-butylphosphine (0.12 mL, 0.49 mmol) was added. The reaction was stirred at rt for a further 48 h. The solvent was removed under reduced pressure. Silica gel chromatography (5% to 10% methanol/dichloromethane) afforded (–)-**28** as colorless oil (205.9 mg, 98%): $[\alpha]_D^{28}$ –28.0 (*c* 0.10, $CHCl_3$); IR (neat) 2952 (m), 2930 (m), 2871 (m), 2868 (m), 1110 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.66-7.64 (m, 4H), 7.51-7.50 (m, 1H), 7.41-7.33 (m, 8H), 7.30 (s, 1H), 5.35 (s, 1H), 4.76 (s, 1H), 4.75 (d, 1H, *J* = 4.1 Hz), 4.19 (quintet, 2H, *J* = 15.4 Hz), 4.12 (dd, 1H, *J* = 11.3, 4.7 Hz), 4.03-4.01 (m, 1H), 3.91-3.88 (m, 2H), 3.77-3.73 (m, 2H), 3.69-3.66 (m, 1H), 2.41-2.32 (m, 8H), 2.09-2.06 (m, 1H), 2.03-1.97 (m, 2H), 1.85-1.82 (m, 1H), 1.69-1.65 (m, 2H), 1.53-1.45 (m, 14H), 1.03 (s, 9H), 0.94-0.91 (m, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.0, 135.7, 134.0, 131.1, 129.8, 129.6, 128.5, 127.9, 127.8, 127.4, 126.5, 110.7, 100.4, 74.3, 69.1, 68.1, 67.1, 60.8, 39.9, 39.8, 39.4, 36.7, 31.1, 27.1, 24.2, 24.1, 24.0, 23.9, 19.4,

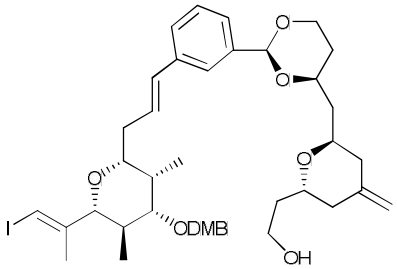
19.0, 18.6, 13.6; high resolution mass spectrum (ES^+) *m/z* 772.5005 [$(M+H)^+$-Cl; calcd for $C_{48}H_{73}O_4Si$: 772.5016].



(+)-**21**

Preparation of styrene (+)-21: Potassium *tert*-butoxide (0.18 mL, 1 M in THF) was added dropwise to a solution of Wittig salt (–)-**28** (115.3 mg, 0.14 mmol) and aldehyde (+)-**17** (70.9 mg, 0.15 mmol) in toluene (18 mL) at 0 °C. Stirring continued at 0 °C for 4.5 h. The reaction was quenched by the addition of water (5 mL) and the organic layer separated. The aqueous layer was extracted with ethyl acetate (10 mL) and the combined organic layers were dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (20% EtOAc/hexanes) afforded **21** as colorless oil (137.6 mg, 94%, *E*:*Z* = 4/1). Separation of *E*/*Z*-isomers was not achieved at this stage and the product was carried forward as a mixture of isomers until after macrocyclization. An analytically pure sample of (+)-**21** (*E*-isomer) was obtained by chromatography on silver nitrate impregnated silica gel (20% EtOAc/hexanes): $[\alpha]_D^{17}$ +12.1 (*c* 0.28, $CDCl_3$); IR (neat): 2925 (m), 2854 (m), 1461 (m), 1108 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.69-7.65 (m, 4H), 7.44 (s, 1H), 7.41-7.37 (m, 6H), 7.31-7.28 (m, 3H), 6.89-6.86 (m, 2H), 6.82-6.81 (m, 1H), 6.45 (d, 1H, *J* = 15.9 Hz), 6.25 (s, 1H), 6.15 (ddd, 1H, *J* = 15.9, 8.7, 8.0 Hz), 5.37 (s, 1H), 4.76 (s, 2H), 4.57 (d, 1H, *J* = 11.2 Hz), 4.27 (d, 1H, *J* = 11.2 Hz), 4.18 (dd, 1H, *J* = 11.2, 4.9 Hz), 4.07-4.02 (m, 1H), 3.95-3.88 (m, 2H), 3.86 (s, 6H), 3.81-3.75 (m, 2H), 3.72-3.67 (m, 1H), 3.52 (d, 1H, *J* = 10.2 Hz), 3.46 (t, 1H, *J* = 7.2 Hz), 3.15 (dd,

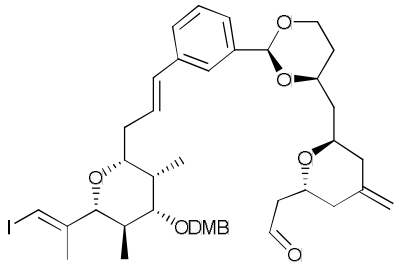
1H, J = 10.3, 4.6 Hz), 2.56-2.51 (m, 1H), 2.38-2.32 (m, 3H), 2.15-2.08 (m, 2H), 2.06-1.98 (m, 2H), 1.88-1.78 (m, 2H), 1.84 (s, 3H), 1.76-1.64 (m, 2H), 1.58-1.55 (m, 2H), 1.05 (s, 9H), 0.98 (d, 3H, J = 7.0 Hz), 0.81 (d, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.2, 148.8, 146.7, 142.1, 139.2, 137.7, 135.8, 134.0, 132.3, 131.2, 129.9, 128.6, 127.9, 127.8, 126.7, 126.4, 125.2, 123.9, 120.4, 111.3, 111.2, 110.7, 101.4, 87.8, 83.3, 81.3, 78.5, 74.3, 70.1, 69.2, 68.2, 67.2, 60.9, 56.1, 56.0, 40.0, 39.9, 39.5, 36.6, 33.6, 33.5, 31.1, 27.1, 19.4, 19.4, 13.8, 5.9; high resolution mass spectrum (ES^+) *m/z* 1063.4034 [$(M+Na)^+$; calcd for $C_{57}H_{73}O_8SiINa$: 1063.4017].



(+)-**29**

Preparation of alcohol (+)-29: Tetrabutylammonium fluoride (0.11 mL, 1 M in THF) was added to a solution of tetracycle **21** (108.7 mg, 0.10 mmol) in THF (2.5 mL) at rt. Stirring continued at rt for 1.5 h. The reaction was quenched by dropwise addition of brine and diluted with ethyl acetate (5 mL). The organic layer was separated, dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (20% to 80% EtOAc/hexanes) afforded **29** as colorless oil (75.7 mg, 95%). Complete separation of *E*/*Z*-isomers (from Wittig reaction) was not achieved at this stage, however an analytically pure sample of (+)-**29** was obtained by chromatography on silver nitrate impregnated silica gel (50% EtOAc/hexanes): $[\alpha]_D^{29}$ +23.5 (*c* 0.38, $CDCl_3$); IR (neat) 3414 (br, w), 2929 (m), 2851 (m), 1516 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.49 (s, 1H), 7.34-7.30 (m, 3H), 6.90-6.86 (m, 2H), 6.83-6.81 (m, 1H), 6.46 (d, 1H, J = 16.1 Hz),

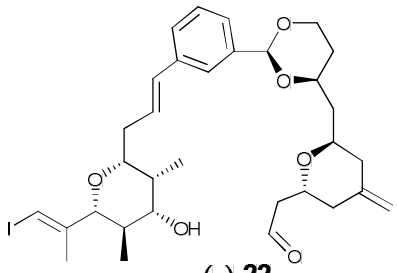
6.25 (s, 1H), 6.20-6.14 (m, 1H), 5.51 (s, 1H), 4.80 (s, 1H), 4.76 (s, 1H), 4.58 (d, 1H, J = 11.3 Hz), 4.30-4.27 (m, 1H), 4.28 (d, 1H, J = 11.3 Hz), 4.18-4.14 (m, 1H), 4.01-3.94 (m, 3H), 3.86 (s, 6H), 3.75-3.71 (m, 2H), 3.53 (d, 1H, J = 10.5 Hz), 3.46 (t, 1H, J = 6.9 Hz), 3.15 (dd, 1H, J = 10.5, 4.6 Hz), 2.56-2.51 (m, 1H), 2.47-2.44 (m, 1H), 2.38-2.28 (m, 3H), 2.23-2.13 (m, 2H), 2.09-2.01 (m, 2H), 1.88-1.80 (m, 3H), 1.84 (s, 3H), 1.65-1.59 (m, 3H), 0.98 (d, 3H, J = 7.0 Hz), 0.81 (s, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.2, 148.8, 146.7, 141.5, 139.1, 137.7, 132.3, 131.2, 128.7, 126.8, 126.5, 125.3, 124.0, 120.4, 111.3, 111.1, 111.0, 101.6, 87.8, 83.3, 81.3, 78.5, 74.7, 71.6, 70.1, 69.5, 67.3, 61.3, 56.1, 56.0, 40.4, 39.1, 38.4, 36.7, 36.6, 33.6, 33.5, 31.4, 19.4, 13.8, 5.9; high resolution mass spectrum (ES$^+$) *m/z* 803.3016 [(M+H)$^+$; calcd for $C_{41}H_{56}O_8I$: 803.3020].



(+)-30

Preparation of aldehyde (+)-30: Dess–Martin periodinane (84.4 mg, 0.20 mmol) and sodium bicarbonate (7.9 mg, 0.094 mmol) were added to a solution of alcohol **29** (75.7 mg, 0.094 mmol) in dichloromethane (35 mL) at 0 °C. After 10 min the ice bath was removed and stirring continued at rt for 4 h. The reaction was quenched by the dropwise addition of saturated sodium bicarbonate solution (10 mL). The organic layer was separated; the aqueous layer further extracted with dichloromethane (25 mL), and the combined organic layers dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (20% to 50% EtOAc/hexanes) afforded **30** as colorless oil (69.9 mg, 93%). Complete separation of *E*/*Z*-isomers (from Wittig reaction) was not achieved at

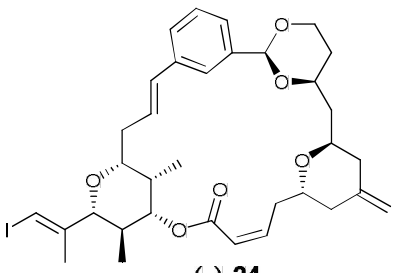
this stage, however an analytically pure sample of (+)-**30** was obtained by chromatography on silver nitrate impregnated silica gel (25% EtOAc/hexanes): $[\alpha]_D^{18}$ +5.5 (*c* 0.24, C_6D_6); IR (neat) 2927 (m), 2851 (m), 1724 (m), 1516 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.75 (s, 1H), 7.48 (s, 1H), 7.34-7.27 (m, 3H), 6.91-6.87 (m, 2H), 6.83-6.81 (m, 1H), 6.46 (d, 1H, *J* = 15.7 Hz), 6.25 (s, 1H), 6.17 (ddd, 1H, *J* = 15.7, 8.4, 5.6 Hz), 5.51 (s, 1H), 4.82 (s, 2H), 4.57 (d, 1H, *J* = 11.2 Hz), 4.45-4.40 (m, 1H), 4.30-4.27 (m, 1H), 4.28 (d, 1H, *J* = 11.2 Hz), 4.03-3.94 (m, 3H), 3.86 (s, 6H), 3.53 (d, 1H, *J* = 10.2 Hz), 3.46 (t, 1H, *J* = 7.2 Hz), 3.16 (dd, 1H, *J* = 10.5, 4.6 Hz), 2.72 (ddd, 1H, *J* = 16.1, 8.5, 3.2 Hz), 2.56-2.46 (m, 2H), 2.44-2.32 (m, 3H), 2.17-2.11 (m, 2H), 2.09-2.03 (m, 2H), 1.84 (s, 3H), 1.83-1.79 (m, 2H), 1.63-1.57 (m, 2H), 0.98 (d, 3H, *J* = 6.9 Hz), 0.81 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.8, 149.2, 148.8, 146.7, 140.9, 139.2, 137.7, 132.3, 131.2, 128.7, 126.8, 126.5, 125.3, 123.9, 120.4, 111.7, 111.3, 111.2, 101.6, 87.8, 83.3, 81.3, 78.5, 74.4, 70.1, 69.0, 67.5, 67.3, 56.2, 56.0, 47.8, 39.6, 39.5, 39.3, 36.6, 33.6, 33.5, 31.2, 19.4, 13.8, 5.9; high resolution mass spectrum (ES^+) *m/z* 823.2714 [$(M+Na)^+$; calcd for $C_{41}H_{53}O_8INa$: 823.2683].



(–)-**22**

Preparation of hydroxy-aldehyde (–)-22: DDQ (5.8 mg, 0.026 mmol) was added to a solution of DMB-ether **30** (20.6 mg, 0.026 mmol) in phosphate buffer pH 7 (0.19 mL) and toluene (3.71 mL) at 0 °C. After 10 min, the reaction was allowed to warm to rt and stirring continued for 18 h. The reaction mixture was diluted with buffer solution (pH 7)

and extracted with ethyl acetate. The organic layer was separated, dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (20% to 50% EtOAc/hexanes) afforded **22** as colorless oil (11.2 mg, 66%). Starting material **30** was also recovered in 12% yield. Complete separation of *E*/*Z*-isomers (from Wittig reaction) was not achieved at this stage, however an analytically pure sample of (–)-**22** was obtained by chromatography on silver nitrate impregnated silica gel (25% EtOAc/hexanes): $[\alpha]_D^{18}$ –5.1 (*c* 0.24, $CDCl_3$); IR (neat) 3405 (br, w), 2924 (m), 1722 (m), 1104 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.76 (s, 1H), 7.45 (s, 1H), 7.30-7.27 (m, 3H), 6.44 (d, 1H, *J* = 15.8 Hz), 6.26 (s, 1H), 6.14 (ddd, 1H, *J* = 15.8, 8.3, 6.9 Hz), 5.50 (s, 1H), 4.82 (s, 2H), 4.45-4.39 (m, 1H), 4.29-4.26 (m, 1H), 4.04-3.94 (m, 3H), 3.54-3.49 (m, 2H), 3.46-3.43 (m, 1H), 2.72 (ddd, 1H, *J* = 16.2, 8.5, 3.0 Hz), 2.53-2.47 (m, 2H), 2.44-2.39 (m, 2H), 2.36-2.30 (m, 1H), 2.16-1.96 (m, 4H), 1.85 (s, 3H), 1.83-1.80 (m, 2H), 1.62-1.57 (m, 2H), 0.98 (d, 3H, *J* = 6.9 Hz), 0.82 (d, 3H, *J* = 6.4 Hz) [O*H* not observed]; ^{13}C NMR (C_6D_6, 125 MHz) δ 199.7, 147.4, 141.8, 140.6, 138.2, 132.9, 128.9, 127.1, 126.9, 126.1, 124.8, 111.4, 102.1, 87.9, 81.0, 79.0, 76.7, 74.7, 69.1, 67.6, 67.4, 47.9, 39.9, 39.8, 38.4, 36.9, 35.1, 32.6, 31.6, 19.8, 13.6, 6.0; high resolution mass spectrum (ES^+) *m/z* 673.2007 [$(M+Na)^+$; calcd for $C_{32}H_{43}O_6INa$: 673.2002].



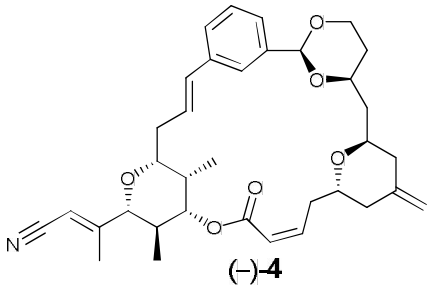
(–)-**24**

Preparation of vinyl iodide (–)-24: A solution of hydroxy-aldehyde **22** (13.4 mg, 0.02 mmol) and 2-[*bis*-(2,2,2-trifluoroethoxy)phosphoryl]acetic acid (32.3 mg, 0.11 mmol) in

dichloromethane (4.1 mL) was stirred at rt for 20 min. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide methiodide (30.1 mg, 0.10 mmol) and 1-hydroxybenzotriazole (0.6 mg, 4.44 μmol) were added and stirring continued at rt for 5 h. The reaction mixture was filtered directly through a short plug of silica (50% EtOAc/hexanes) and concentrated to provide the phosphonate ester, which was used without further purification.

A solution of potassium carbonate (37.3 mg, 0.27 mmol) and 18-crown-6 (300.4 mg, 1.14 mmol) in toluene (18 mL) was stirred at rt for 3 h. To this solution was added dropwise a solution of the phosphonate ester (from above) in toluene (16 mL) and stirring continued at rt for 14 h. The reaction was quenched with brine (10 mL), the organic layer was separated and the aqueous layer was extracted with ethyl acetate (20 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (20% EtOAc/hexanes) afforded (–)-**24** as colorless oil (6.0 mg, 44%, *Z*-isomer), (the *E*-macrolide was also isolated in 15% yield): $[\alpha]_D^{29}$ –5.2 (*c* 0.17, $CDCl_3$); IR (neat) 2920 (m), 2850 (m), 1719 (m) cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 7.71 (s, 1H), 7.64 (d, 1H, *J* = 7.6 Hz), 7.24-7.04 (m, 2H), 6.41 (d, 1H, *J* = 15.6 Hz), 6.02 (s, 1H), 5.92 (dt, 1H, *J* = 15.6, 7.6 Hz), 5.86 (d, 1H, *J* = 10.4 Hz), 5.61 (dt, 1H, *J* = 10.4, 4.6 Hz), 5.31 (s, 1H), 4.82 (s, 1H), 4.74 (s, 1H), 4.66 (dd, 1H, *J* = 11.0, 4.5 Hz), 4.22-4.18 (m, 1H), 3.98-3.93 (m, 2H), 3.66-3.59 (m, 2H), 3.53-3.44 (m, 2H), 3.13 (d, 1H, *J* = 10.1 Hz), 3.13-3.29 (m, 1H), 2.53-2.51 (m, 1H), 2.46-2.41 (m, 3H), 2.27-2.24 (m, 1H), 1.97-1.86 (m, 3H), 1.83 (d, 3H, *J* = 1.0 Hz), 1.65-1.55 (m, 3H), 0.98 (d, 3H, *J* = 6.8 Hz), 0.79-0.77 (m, 1H), 0.64 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (C_6D_6, 125 MHz, cryogenic probe) δ 165.8, 146.8, 144.9, 142.9, 140.4, 138.4, 134.0, 130.5, 127.8, 125.7, 125.5, 124.1, 122.2, 110.6, 101.1, 88.0, 81.7, 79.5, 78.2, 74.4, 73.0, 69.0, 67.2, 41.5, 40.3, 38.2, 35.5, 33.6, 32.7, 32.0,

31.9, 19.6, 14.7, 13.5; high resolution mass spectrum (ES^+) *m/z* 697.1984 [$(M+Na)^+$; calcd for $C_{34}H_{43}O_6INa$: 697.2002].



(–)-**4**

Preparation of hemi-phorboxazole analogue (–)-4: Vinyl iodide (–)-**24** (3.8 mg, 5.63 μmmol), copper iodide (0.6 mg, 3.15 μmmol), tetrakis(triphenylphosphine)palladium(0) (1.8 mg, 1.56 μmmol) and tributyltin cyanide (2.1 mg, 6.64 μmmol) were placed in a sealed tube and anhydrous benzene (0.4 mL) added. The reaction was heated at 80 °C for 3.5 h. After cooling to rt, silica gel chromatography (20% to 50% EtOAc/hexanes) afforded (–)-**4** as colorless oil (3.0 mg, 93%): $[\alpha]_D^{30}$ –4.1 (*c* 0.30, C_6D_6); IR (neat) 2958 (m), 2923 (m), 2850 (m), 2219 (w), 1716 (m) cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 7.73 (s, 1H), 7.63 (d, 1H, *J* = 7.3 Hz), 7.19-7.09 (m, 2H), 6.42 (d, 1H, *J* = 15.6 Hz), 5.90 (dt, 1H, *J* = 15.6, 7.7 Hz), 5.85 (d, 1H, *J* = 10.6 Hz), 5.64 (dt, 1H, *J* = 10.6, 4.7 Hz), 5.32 (s, 1H), 4.81 (s, 1H), 4.72 (s, 1H), 4.67 (s, 1H), 4.58 (dd, 1H, *J* = 11.1, 4.3 Hz), 4.23-4.17 (m, 1H), 3.97-3.93 (m, 2H), 3.64-3.58 (m, 2H), 3.52-3.45 (m, 2H), 3.21 (ddd, 1H, *J* = 10.3, 5.3, 1.8 Hz), 3.00 (d, 1H, *J* = 10.4 Hz), 2.49-2.35 (m, 5H), 2.26-2.22 (m, 1H), 1.97-1.86 (m, 2H), 1.78 (d, 3H, *J* = 1.0 Hz), 1.68-1.53 (m, 3H), 0.90 (d, 3H, *J* = 6.7 Hz), 0.80-0.78 (m, 1H), 0.48 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (C_6D_6, 125 MHz, cryogenic probe) δ 165.7, 160.6, 145.2, 142.9, 140.4, 138.3, 134.1, 128.9, 127.9, 125.6, 125.3, 124.0, 122.0, 116.6, 110.6, 101.1, 99.4, 86.4, 79.0, 78.3, 74.4, 72.9, 69.0, 67.2, 41.3, 40.2, 38.3, 35.3, 33.5,

32.6, 32.0, 31.9, 16.2, 14.1, 13.2; high resolution mass spectrum (ES^+) *m/z* 596.2986 [$(M+Na)^+$; calcd for $C_{35}H_{43}NO_6Na$: 596.2988].