Supporting Information

(+)-Phorboxazole A Synthetic Studies.

A Highly Convergent Second Generation Synthesis of (+)-Phorboxazole A.

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Materials and Methods: All solvents were reagent grade. Diethyl ether (Et₂O) and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone under argon. *n*-Butyllithium and *t*-butyllithium were purchased from Aldrich. 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 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. Proton and carbon-13 NMR spectra were recorded on a Bruker AMX-500 spectrometer. Chemical shifts are reported relative to either chloroform (δ 7.26) or benzene (δ 7.15) for ¹H-NMR and either chloroform (δ 77.0) or benzene (δ 128.0) for ¹³C NMR. 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:

***trans*-Tetrahydropyranone Thiolester (-)-11:** To a solution of enone (-)-10 (6.93 g, 18.2 mmol) and scandium triflate [Sc(OTf)₃] (89.3 mg, 0.182 mmol) in dichloromethane (91.2 mL) under argon was added dropwise, the TMS-enol ether derived from ethylthioacetate (4.83 g, 27.4 mmol) at -78 °C. The reaction mixture was stirred for 15 minutes at -78 °C and then quenched via dropwise addition of methanol/pyridine (1:1, 100 mL) and warmed to room temperature. After one hour and thirty minutes the layers of the biphasic mixture were separated and the aqueous layer was extracted with dichloromethane (70 mL, 3x). The combined organic layers were dried over

Na₂SO₄, filtered and concentrated under reduced pressure. Purification via silica gel chromatography (10% EtOAc/hexanes) afforded *trans*-tetrahydropyranone thiolester (-)-**11** (8.39 g, 95%) as a light yellow oil: $[\alpha]_D^{20}$ -9.1 (c 2.3, CHCl₃); IR (CHCl₃) 2931 (m), 2857 (m), 1719 (s), 1685 (s), 1472 (w), 1428 (m), 1112 (s), 998 (w), 823 (w), 739 (m), 614 (m) cm⁻¹; ¹HNMR (500 MHz, CDCl₃) δ 7.65 (m, 4H), 7.38 (m, 6H), 4.50 (m, 1H), 4.41 (ddd, *J* = 8.6, 5.7, 5.5 Hz, 1H), 3.79 (ddd, *J* = 10.5, 7.8, 5.4 Hz, 1H), 3.71 (m, 1H), 2.84 (m, 3H), 2.65 (dd, *J* = 14.9, 5.8 Hz, 1H), 2.58 (ddd, *J* = 14.5, 5.3, 1.1 Hz, 1H), 2.53 (ddd, *J* = 14.5, 4.7, 1.3 Hz, 1H), 2.33 (ddd, *J* = 14.7, 7.6, 1.1 Hz, 1H), 2.30 (ddd, *J* = 14.5, 6.2, 1.3 Hz, 1H), 1.89 (m, 1H), 1.68 (m, 1H), 1.20 (app t, *J* = 7.4 Hz, 3H), 1.05 (s, 9H); ¹³CNMR (125 MHz, CDCl₃) δ 206.2, 195.7, 135.5, 133.7, 133.6, 129.6, 129.5, 127.7, 70.0, 68.7, 59.9, 48.7, 46.5, 46.2, 36.7, 26.9, 23.5, 19.2, 14.5; high resolution mass spectrum (ES⁺) *m/z* 507.2024 [(M+Na)⁺; calcd for C₂₇H₃₆O₄SSiNa: 507.2001].

***trans*-Tetrahydropyran *exo*-Olefin (-)-12:** To a solution of thiolester (-)-**11** (8.39 g, 17.3 mmol) and ethyl pivalate (0.503 mL, 3.11 mmol) in THF (14.7 mL) under argon at room temperature was added dimethyltitanocene (0.5 M/THF) (62.3 mL, 31.1 mmol) followed by heating to 55 °C with the exclusion of light. After twenty hours, the reaction mixture was cooled to room temperature, diluted with hexanes (6 mL) and filtered through a pad of Celite. The resultant filtrate was then concentrated under reduced pressure. The crude product was dissolved in chloroform (15 mL), washed with 1N hydrogen chloride solution (15 mL, 1x), dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification via silica gel chromatography (2.5% EtOAc/hexanes) afforded *trans*-tetrahydropyran *exo*-olefin (-)-**12** (6.35 g, 76%) as a light yellow oil: $[\alpha]_D^{20}$ -21.2 (c 1.1, CHCl₃); IR (CHCl₃) 3071 (m), 2931 (s), 1689 (s), 1685 (s), 1473 (w), 1428 (s), 1265 (w), 1112 (s), 998 (m), 894 (w), 823 (w), 739 (m), 702 (s) cm⁻¹; ¹HNMR (500 MHz,

CDCl₃) δ 7.66 (m, 4H), 7.40 (m, 6H), 4.79 (s, 2H), 4.24 (m, 1H), 4.01 (m, 1H), 3.75 (m, 1H), 3.72 (m, 1H), 2.82 (m, 2H), 2.80 (dd, J = 14.5, 7.2 Hz, 1H), 2.65 (dd, J = 14.5, 6.4 Hz, 1H), 2.36 (m, 2H), 2.05 (dd, J = 13.2, 6.1 Hz, 1H), 1.99 (dd, J = 13.2, 6.5 Hz, 1H), 1.88 (m, 1H), 1.65 (m, 1H), 1.20 (app t, J = 7.4 Hz, 3H), 1.05 (s, 9H); ¹³CNMR (125 MHz, CDCl₃) δ 196.8, 141.3, 135.5, 134.0, 133.9, 129.5, 129.4, 127.6, 111.0, 69.7, 69.3, 60.6, 47.8, 39.5, 39.1, 36.3, 26.9, 23.3, 19.2, 14.6; high resolution mass spectrum (ES⁺) m/z 505.2229 [(M+Na)⁺; calcd for C₂₈H₃₈O₃SSiNa: 505.2209].

Dioxanone (+)-19: Under argon, a solution of β -hydroxy acid (+)-**17** (14.5 g, 37.6 mmol) in dichloromethane (114 mL) was treated with 1,1,1,3,3,3-hexamethyldisilazane (8.72 mL) at room temperature. After stirring twenty four hours, the reaction was concentrated under reduced pressure followed by drying under vacuum (to remove excess 1,1,1,3,3,3-hexamethyldisilazane) to provide the corresponding bis-silylated β -hydroxy acid that was used without any further purification. Under argon, a solution of the bis-silylated β -hydroxy acid, 2,6-di-*tert*-butyl-4-methylpyridine (2,6-DTBMP) (386 mg, 1.88 mmol) and freshly prepared *E*-C(2-3)-iodomethacrolein **18** (9.94 g, 50.7 mmol) in dichloromethane (150 mL) at -78 °C was treated with trimethylsilyltrifluoromethylsulfonate (TMSOTf) (1.50 mL, 8.26 mmol). After 30 min, trifluoromethanesulfonic acid (TfOH) (300 mL, 3.38 mmol) was added dropwise and the reaction mixture stirred at -78 °C. After two hours, the reaction was quenched via dropwise addition of pyridine (1.16 mL), warmed to room temperature and concentrated under reduced pressure. Purification via silylated silica gel chromatography (50% EtOAc/hexanes) afforded dioxanone (+)-**19** (19.7 g, 93%, 20:1 *dr*) as a light yellow oil: $[\alpha]_D^{20}$ +5.7 (c 1.4, CHCl₃); IR (CHCl₃) 2931 (m),

2857 (m), 1700 (s), 1472 (w), 1428 (m), 1112 (s), 822 (w) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.62 (m, 4H), 7.39 (m, 6H), 6.63 (s, 1H), 5.53 (s, 1H), 4.28 (ddd, J = 8.1, 4.3, 4.3 Hz, 1H), 3.78 (m, 2H), 2.70 (ddd, J = 16.7, 9.3, 5.3 Hz, 1H), 1.83 (d, J = 1.0 Hz, 3H), 1.72 (m, 2H), 1.23 (d, J = 7.3 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.4, 142.5, 135.5, 133.4, 133.3, 129.8, 129.7, 127.8, 102.3, 85.3, 73.4, 59.3, 39.4, 33.9, 26.8, 19.2, 18.7, 12.1; high resolution mass spectrum (ES^+) m/z 587.1093 $[(\text{M}+\text{Na})^+]$; calcd for $\text{C}_{26}\text{H}_{33}\text{O}_4\text{SiNa}$: 587.1091].

Enol Acetal (+)-S₁: Under argon, a solution of dioxanone (+)-**19** (7.58 g, 13.4 mmol) was treated with dimethyltitanocene (0.5 M/THF) (80.6 mL, 40.3 mmol), and the resultant solution was stirred at 55 °C in the absence of light. After twenty three hours, the reaction mixture was cooled to room temperature and diluted with hexanes (200 mL). The resultant yellow precipitate was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. Flash chromatography on silylated silica gel (7% EtOAc/hexanes) furnished enol acetal (+)-**S₁** (5.98 g, 79%) as a colorless oil: $[\alpha]_{\text{D}}^{20}$ +29.8 (c 2.3, CHCl_3); IR (CHCl_3) 2930 (m), 2857 (m), 1653 (w), 1472 (w), 1428 (m), 1289 (w), 1259 (m), 1112 (s), 997 (m), 823 (w), 738 (m), 701 (s) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.66 (m, 4H), 7.40 (m, 6H), 6.59 (d, J = 0.7 Hz, 1H), 4.97 (s, 1H), 4.45 (s, 1H), 4.24 (s, 1H), 4.06 (m, 1H), 3.80 (ddd, J = 10.2, 10.2, 4.8 Hz, 1H), 3.74 (ddd, J = 10.2, 5.3, 5.0 Hz, 1H), 2.25 (dddd, J = 13.9, 7.0, 7.0, 2.5 Hz, 1H), 1.90 (d, J = 0.9 Hz, 3H), 1.81 (m, 1H), 1.68 (m, 1H), 1.15 (d, J = 7.0 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 162.2, 144.3, 135.5, 133.7, 133.6, 129.7, 129.6, 127.7, 102.6, 92.6, 83.6, 75.7, 59.8, 36.9, 34.9, 26.9, 19.2, 19.1, 13.5; high resolution mass spectrum (ES^+) m/z 585.1324 $[(\text{M}+\text{Na})^+]$; calcd for $\text{C}_{27}\text{H}_{35}\text{O}_3\text{SiNa}$: 585.1298].

Tetrahydropyran (+)-20: Under argon, a solution of enol acetal (+)-**S**₁ (5.27 g, 9.38 mmol) in dichloromethane (94 mL) was treated dropwise with Me₂AlCl (1.0 M/hexane) (11.25 mL, 11.25 mmol) at -78 °C. After stirring for five minutes, the reaction mixture was warmed to 0 °C and stirred for three minutes. The reaction was then recooled to -78 °C and quenched with triethylamine (4.5 mL), followed by treatment with saturated aqueous sodium bicarbonate (70 mL) and warmed to room temperature with stirring. The resulting mixture was diluted with dichloromethane (150 mL) and 1N hydrogen chloride solution (70 mL) and the layers separated. The aqueous layer was extracted with dichloromethane (200 mL, 2x) and the combined organic extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification via silica gel chromatography (5% EtOAc/hexanes) provided tetrahydropyran (+)-**20** (5.26 g, 99%) as a colorless oil: $[\alpha]_D^{20} +66.4$ (c 1.2, CHCl₃); IR (CHCl₃) 2929 (m), 2856 (m), 1719 (s), 1472 (w), 1428 (m), 1112 (s), 822 (w), 738 (m), 702 (s) cm⁻¹; ¹HNMR (500 MHz, CDCl₃) δ 7.64 (m, 4H), 7.40 (m, 6H), 6.36 (dd, *J* = 1.1, 1.0 Hz, 1H), 4.00 (dd, *J* = 11.8, 2.4 Hz, 1H), 3.93 (ddd, *J* = 9.1, 3.3, 2.7 Hz, 1H), 3.82 (ddd, *J* = 10.2, 9.1, 4.7 Hz, 1H), 3.75 (ddd, *J* = 10.2, 5.9, 4.4 Hz, 1H), 2.51 (dd, *J* = 14.5, 11.8 Hz, 1H), 2.36 (m, 1H), 2.34 (ddd, *J* = 14.5, 2.9, 1.2 Hz, 1H), 1.88 (m, 1H), 1.83 (d, *J* = 0.9 Hz, 3H), 1.65 (m, 1H), 1.12 (d, *J* = 7.2 Hz, 3H), 1.03 (s, 9H); ¹³CNMR (125 MHz, CDCl₃) δ 210.4, 146.0, 135.5, 133.7, 133.6, 129.7, 129.6, 127.7, 80.2, 79.2, 75.2, 60.0, 49.0, 42.7, 34.6, 26.8, 20.6, 19.2, 10.9; high resolution mass spectrum (ES⁺) *m/z* 585.1291 [(M+Na)⁺; calcd for C₂₇H₃₅O₃SiNa: 585.1298].

Methylated Tetrahydropyranone (+)-S₂: Under argon, lithium hexamethyldisilazane (LiHMDS) (1.19 M/THF) (9.92 mL, 11.8 mmol) was diluted with THF (9.92 mL) at room temperature and cooled to -78°C . A solution of tetrahydropyranone (+)-**20** (6.03 g, 10.7 mmol) in THF (53.5 mL) was added dropwise via cannula to the diluted lithium hexamethyldisilazane solution under stirring. After stirring for thirty minutes at -78°C , the solution was warmed to -20°C and stirred for one hour. A cooled solution (-20°C) of methyl iodide (2.00 mL, 32.2 mmol) and HMPA (5.60 mL, 32.2 mmol) in THF (21.5 mL) was added dropwise via cannula and the reaction mixture was stirred at -20°C . After two hours, the reaction was quenched with saturated aqueous ammonium chloride (130 mL), warmed to room temperature, stirred for thirty minutes and then extracted with diethyl ether (150 mL, 3x). The combined organic extracts were washed with saturated aqueous ammonium chloride (200 mL) and saturated aqueous sodium chloride (200 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. Purification via silica gel chromatography (2.5% EtOAc/hexanes) furnished methylated tetrahydropyranone (+)-**S₂** (4.20 g, 68%; 91% based on recovered starting material), as a colorless oil and starting material (+)-**20** (1.53 g, 25%); $[\alpha]_{\text{D}}^{20} +12.6$ (c 1.1, CHCl_3); IR (CHCl_3) 2930 (m), 2857 (m), 1715 (s), 1457 (w), 1428 (m), 1282 (w), 1197 (w), 1112 (s), 822 (w), 738 (m), 701 (s) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.64 (m, 4H), 7.40 (m, 6H), 6.25 (d, $J = 0.6$ Hz, 1H), 3.93 (ddd, $J = 8.8, 4.0, 2.4$ Hz, 1H), 3.77 (ddd, $J = 10.0, 10.0, 4.7$ Hz, 1H), 3.70 (ddd, $J = 10.0, 4.9, 4.9$ Hz, 1H), 3.66 (d, $J = 10.5$ Hz, 1H), 2.65 (dddd, $J = 14.4, 10.5, 6.6, 3.9$ Hz, 1H), 2.43 (dddd, $J = 11.8, 7.1, 4.7, 2.4$ Hz, 1H), 1.90 (d, $J = 0.5$ Hz, 3H), 1.85 (m, 1H), 1.64 (m, 1H), 1.15 (d, $J = 7.1$ Hz, 3H), 1.04 (s, 9H), 0.86 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 211.8, 145.5, 135.5, 133.7, 133.6, 129.6, 129.4, 127.7,

88.0, 81.7, 75.7, 60.0, 49.3, 43.2, 34.6, 26.8, 19.2, 18.8, 11.2, 9.3; high resolution mass spectrum (ES⁺) *m/z* 599.1467 [(M+Na)⁺; calcd for C₂₈H₃₇O₃SiNa: 599.1454].

Secondary Alcohol (+)-S₃: To a solution of methylated tetrahydropyranone (+)-S₂ (5.88 g, 10.2 mmol) in ethanol (51 mL) at -10 °C under argon was added sodium borohydride (772 mg, 20.4 mmol) in one portion. After stirring for thirty minutes, the reaction mixture was treated with saturated aqueous ammonium chloride (80 mL) followed by dilution with chloroform (100 mL). The resulting layers were separated, and the aqueous layer was extracted with chloroform (100 mL, 2x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification via silica gel chromatography (10% EtOAc/hexanes → 20% EtOAc/hexanes) afforded secondary alcohol (+)-S₃ (4.80 g, 81%, 6.8:1 *dr*) as a colorless oil and the secondary alcohol epimer (-)-S₄ (0.68 g, 12%). (+)-S₃: [α]_D²⁰ +15.9 (*c* 1.2, CHCl₃); IR (CHCl₃) 3446 (b), 2959 (m), 2929 (m), 2857 (m), 1471 (w), 1428 (m), 1389 (w), 1279 (w), 1112 (s), 1088 (s), 1053 (m), 822 (w), 737 (m), 701 (s) cm⁻¹; ¹HNMR (500 MHz, CDCl₃) δ 7.65 (m, 4H), 7.40 (m, 6H), 6.19 (d, *J* = 0.6 Hz, 1H), 3.77 (ddd, *J* = 10.1, 8.3, 5.0 Hz, 1H), 3.69 (ddd, *J* = 10.1, 5.5, 5.0 Hz, 1H), 3.67 (m, 1H), 3.44 (d, *J* = 10.3 Hz, 1H), 3.43 (d, *J* = 10.1 Hz, 1H), 1.82 (m, 2H), 1.81 (d, *J* = 1.0 Hz, 3H), 1.64 (m, 2H), 1.05 (s, 9H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.81 (d, *J* = 6.5 Hz, 3H); ¹³CNMR (125 MHz, CDCl₃) δ 146.5, 135.5, 133.9, 133.8, 129.7, 129.6, 127.6, 87.2, 80.6, 76.7, 75.0, 60.4, 38.4, 35.5, 34.7, 26.9, 19.3, 19.2, 13.2, 5.7; high resolution mass spectrum (ES⁺) *m/z* 601.1626 [(M+Na)⁺; calcd for C₂₈H₃₉O₃SiNa: 601.1611].

(-)-S₄; a light yellow oil; $[\alpha]_D^{20}$ -2.4 (c 1.8, CHCl_3); IR (CHCl_3) 3474 (b), 3070 (w), 2960 (s), 2930 (s), 2857 (s), 1617 (w), 1589 (w), 1473 (m), 1428 (s), 1390 (m), 1278 (m), 1112 (s), 982 (m), 823 (m), 738 (m), 701 (s) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.67 (m, 4H), 7.38 (m, 6H), 6.19 (d, J = 0.7 Hz, 1H), 4.12 (m, 1H), 3.94 (d, J = 10.6 Hz, 1H), 3.73 (m, 3H), 1.81 (d, J = 1.0 Hz, 3H), 1.80 (m, 2H), 1.62 (m, 2H), 1.46 (br s, 1H), 1.06 (s, 9H), 0.93 (d, J = 7.1 Hz, 3H), 0.76 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 147.1, 135.6, 134.0, 133.9, 129.5, 129.4, 127.6, 82.8, 80.2, 75.0, 70.0, 60.7, 39.3, 35.4, 32.0, 26.9, 19.3, 19.2, 13.3, 10.9; high resolution mass spectrum (ES^+) m/z 601.1617 [$(\text{M}+\text{Na})^+$; calcd for $\text{C}_{28}\text{H}_{39}\text{O}_3\text{SiNa}$: 601.1611].

DMB Ether (+)-21: To a solution of the alcohol (+)-S₃ (3.04 g, 5.26 mmol) in THF (52 mL) at 0 °C under argon was added 15-crown-5 (316 mL, 1.58 mmol), 35% potassium hydride (1.21 g, 10.5 mmol) and 3,4-dimethoxybenzyl chloride (1.47 g, 7.89 mmol) followed by warming to 65 °C. After ten minutes, the reaction mixture was cooled to 0 °C and quenched with saturated aqueous ammonium chloride (70 mL). The resultant mixture was extracted with chloroform (100 mL, 3x) and the combined organic extracts were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. Purification via silica gel chromatography (50% CHCl_3 /hexanes $\rightarrow$ 100%

CHCl₃) afforded a mixture of the desired DMB ether (+)-**21** and 3,4-dimethoxybenzyl alcohol. A second silica gel flash chromatography (10% EtOAc/hexanes) provided pure DMB ether (+)-**21** (3.52 g, 92%) as a colorless oil. $[\alpha]_D^{20} +29.8$ (c 1.8, CHCl₃); IR (CHCl₃) 2930 (m), 2856 (m), 1516 (s), 1463 (m), 1389 (w), 1266 (s), 1238 (m), 1156 (m), 1112 (s), 1030 (s), 822 (w), 738 (m), 702 (s) cm⁻¹; ¹HNMR (500 MHz, CDCl₃) δ 7.66 (m, 4H), 7.40 (m, 6H), 6.87 (m, 3H), 6.17 (d, J = 1.1 Hz, 1H), 4.57 (d, J = 11.2 Hz, 1H), 4.30 (d, J = 11.2 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.78 (ddd, J = 10.2, 8.6, 4.9 Hz, 1H), 3.72 (ddd, J = 10.6, 10.2, 5.4 Hz, 1H), 3.63 (ddd, J = 8.2, 4.8, 1.9 Hz, 1H), 3.43 (d, J = 10.3 Hz, 1H), 3.17 (dd, J = 10.4, 4.7 Hz, 1H), 2.08 (m, 1H), 1.83 (m, 1H), 1.80 (d, J = 1.0 Hz, 3H), 1.77 (m, 1H), 1.68 (m, 1H), 1.06 (s, 9H), 0.93 (d, J = 6.9 Hz, 3H), 0.80 (d, J = 6.5 Hz, 3H); ¹³CNMR (125 MHz, CDCl₃) δ 149.0, 148.6, 146.7, 135.6, 133.9, 133.8, 131.1, 129.6, 129.4, 127.6, 120.2, 111.2, 110.9, 87.5, 83.2, 80.5, 74.9, 69.8, 60.6, 55.9, 55.8, 35.7, 34.2, 33.4, 26.9, 19.2, 19.1, 13.6, 6.0; high resolution mass spectrum (ES⁺) m/z 751.2320 [(M+Na)⁺; calcd for C₃₇H₄₉O₅SiNa: 751.2292].

Primary Alcohol (+)-S₅: To a solution of BPS-protected tetrahydropyran (+)-**21** (155.0 mg, 0.213 mmol) in THF (2.1 mL) under argon was added tetrabutylammonium fluoride (1.0 M/THF) (426 mL, 0.426 mmol) at room temperature. After stirring for one hour, the reaction mixture was treated with saturated aqueous sodium chloride (5 mL) and the solution was extracted with chloroform (10 mL, 3x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification via silica gel chromatography (33% EtOAc/hexanes) afforded primary alcohol (+)-**S₅** (101.4 mg, 97%) as a colorless oil. $[\alpha]_D^{20} +51.4$ (c 0.8, CHCl₃); IR (CHCl₃) 3452 (b), 2934 (m), 2879 (m), 1594 (w), 1516 (s), 1464 (m), 1419 (m),

1387 (m), 1265 (s), 1238 (s), 1156 (s), 1139 (s), 1093 (m), 1028 (s), 807 (w), 766 (w) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.86 (m, 3H), 6.24 (d, J = 0.9 Hz, 1H), 4.57 (d, J = 11.3 Hz, 1H), 4.31 (d, J = 11.3 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.76 (m, 2H), 3.62 (ddd, J = 9.8, 2.5, 2.3 Hz, 1H), 3.55 (d, J = 10.3 Hz, 1H), 3.18 (dd, J = 10.4, 4.7 Hz, 1H), 2.31 (br s, 1H), 2.04 (m, 1H), 1.97 (m, 1H), 1.80 (d, J = 1.0 Hz, 3H), 1.79 (m, 1H), 1.53 (m, 1H), 0.98 (d, J = 6.9 Hz, 3H), 0.80 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 149.0, 148.7, 146.1, 130.9, 120.2, 111.2, 110.9, 87.6, 82.6, 81.2, 78.7, 69.9, 61.7, 55.9, 55.8, 35.1, 34.8, 33.2, 19.1, 13.5, 6.2; high resolution mass spectrum (ES^+) m/z 513.1096 $[(\text{M}+\text{Na})^+]$; calcd for $\text{C}_{21}\text{H}_{31}\text{O}_5\text{INa}$: 513.1114].

Aldehyde (+)-5: To a solution of primary alcohol (+)-**S**₅ (0.415 g, 0.848 mmol) in dichloromethane (8.5 mL) under argon was added methylsulfoxide (0.902 mL, 12.7 mmol) and triethylamine (0.589 mL, 4.2 mmol) followed by cooling to 0 °C. $\text{SO}_3\cdot\text{Pyridine}$ complex (0.337 g, 2.10 mmol) was added in one portion and after stirring for ten minutes, the reaction was warmed to room temperature. After two hours, the reaction was quenched with water (5 mL), and extracted with diethyl ether (10 mL, 3x). The combined organic extracts were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. Purification via silica gel chromatography (40% EtOAc/hexanes) afforded aldehyde (+)-**5** (0.384 g, 92%) as a white solid. mp. 98-100 °C; $[\alpha]_{\text{D}}^{20}$ +36.7 (c 0.3, CHCl_3); IR (CHCl_3) 2959 (w), 2926 (m), 2848 (m), 1725 (s), 1516 (s), 1464 (m), 1263 (s), 1157 (m), 1075 (m), 1029 (s) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.74 (app t, J = 1.9 Hz, 1H), 6.84 (m, 3H), 6.22 (d, J = 1.0 Hz, 1H), 4.56 (d, J = 11.3 Hz, 1H), 4.30 (d, J = 11.3 Hz, 1H), 3.95 (ddd, J = 8.6, 4.5, 2.2 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.53 (d, J = 10.3 Hz, 1H), 3.20 (dd, J = 10.4, 4.6 Hz, 1H), 2.74 (ddd, J = 16.8, 8.6, 1.9 Hz, 1H), 2.42 (ddd, J = 16.8, 4.5, 1.9 Hz,

36.7, 27.0, 26.0, 19.4, 18.2, -4.5, -4.6; high resolution mass spectrum (ES⁺) m/z 806.3529 [(M+Na)⁺; calcd for C₄₁H₆₁NO₈SSi₂Na: 806.3517].

(+)-22

C(19-20)-*E*-Olefin (+)-22: To a solution of mesylate (-)-6 (0.707 g, 0.901 mmol) in anhydrous DMF (192 mL) at room temperature under argon was added dropwise, tri-*n*-butylphosphine (0.901 mL, 3.61 mmol). After thirty six hours at room temperature, aldehyde (+)-5 (0.439 g, 0.901 mmol) in anhydrous DMF (103 mL) was added dropwise via cannula followed by dropwise addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.272 mL, 1.80 mmol). After stirring at room temperature for three hours, the reaction mixture was diluted with diethyl ether (80 mL) and poured into water (120 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (50 mL, 5x). The combined organic extracts were washed with saturated aqueous sodium chloride (50 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. Purification via silica gel chromatography (20% EtOAc/hexanes) afforded the C(19-20)-*E*-olefin product (+)-22 (1.01 g, 96%, 20:1, *E:Z*) as a white foam. $[\alpha]_D^{20} +22.7$ (*c* 1.0, CHCl₃); IR (neat) 2967 (b), 2930 (s), 1487 (m), 1258 (s), 1110 (s), 776 (s) cm⁻¹; ¹HNMR (500 MHz, CDCl₃) δ 7.64 (m, 4H), 7.35 (m, 6H), 6.89 (d, *J* = 1.9 Hz, 1H), 6.82 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.58 (m, 1H), 6.32 (d, *J* = 16.0 Hz, 1H), 6.23 (s, 1H), 4.82 (dd, *J* = 11.2, 1.9 Hz, 1H), 4.70 (s, 2H), 4.56 (d, *J* = 11.2 Hz, 1H), 4.26 (d, *J* = 11.2 Hz, 1H), 4.24, (m, 1H), 3.95 (m, 3H), 3.87 (s, 3H), 3.65 (m, 2H),

3.50 (d, $J = 10.4$ Hz, 1H), 3.45 (ddd, $J = 14.1, 7.1, 1.8$ Hz, 1H), 3.12 (dd, $J = 10.4, 4.5$ Hz, 1H), 2.52 (m, 1H), 2.34 (m, 3H), 2.08 (m, 1H), 2.00 (dd, $J = 13.0, 7.0$ Hz, 1H), 1.93 (dd, $J = 13.0, 7.0$ Hz, 1H), 1.86 (m, 2H), 1.82 (s, 3H), 1.80 (m, 2H), 1.75 (m, 4H), 1.61 (m, 3H), 1.48 (m, 3H), 1.06 (s, 9H), 0.97 (d, $J = 6.7$ Hz, 3H), 0.91 (s, 9H), 0.76 (d, $J = 6.3$ Hz, 3H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 160.7, 149.0, 148.6, 146.3, 143.3, 142.3, 135.6, 135.5, 135.1, 134.2, 133.9, 133.8, 130.9, 129.5, 127.6, 120.2, 118.8, 111.1, 110.1, 87.5, 82.8, 80.9, 77.4, 77.2, 69.9, 69.0, 68.8, 67.4, 64.7, 60.6, 55.9, 55.7, 39.6, 39.3, 39.2, 38.9, 38.2, 36.6, 36.2, 33.7, 33.5, 33.3, 30.3, 26.8, 25.8, 19.1, 18.0, 13.5, 5.7, -4.8, -4.9; high resolution mass spectrum (ES^+) m/z 1182.4735 $[(\text{M}+\text{Na})^+]$; calcd for $\text{C}_{61}\text{H}_{86}\text{INO}_9\text{Si}_2\text{Na}$: 1182.4886].

Primary Alcohol (+)-S₇: Under an argon atmosphere, a solution of C(19-20)-*E*-olefin product (+)-**23** (0.153 g, 0.132 mmol) in THF (18 mL) was added dropwise via cannula to a solution of potassium hydroxide (0.627 g, 11.0 mmol), and 18-crown-6 (1.04 g, 3.95 mmol) in THF (20 mL) and water (1.5 mL) at 0 °C. After forty minutes, the solution was warmed to room temperature and after five hours, the reaction mixture was poured over saturated aqueous sodium chloride (25 mL) and extracted with ethyl acetate (15 mL, 3x). The combined organic extracts were dried over MgSO_4 and concentrated *in vacuo*. Purification via silica gel chromatography (40% EtOAc/hexanes) afforded primary alcohol (+)-**S₇** (0.106 g, 87%) as a colorless oil. $[\alpha]_{\text{D}}^{20} +25.0$ (c 1.0, CHCl_3); IR (neat) 2927 (b), 2831 (s), 1516 (s), 1464 (m), 1258 (b), 1031 (m), 835 (s) cm^{-1} ;

^1H NMR (500 MHz, CDCl_3) δ 7.46 (s, 1H), 6.82 (m, 3H), 6.59 (ddd, J = 15.6, 8.6, 6.7 Hz, 1H), 6.33 (d, J = 16.0 Hz, 1H), 6.23 (s, 1H), 4.83 (dd, J = 10.8, 2.6 Hz, 1H), 4.76 (s, 1H), 4.72 (s, 1H), 4.56 (d, J = 11.5 Hz, 1H), 4.27 (m, 1H), 4.26 (d, J = 11.2 Hz, 1H), 4.06 (m, 1H), 4.01 (m, 1H), 3.95 (m, 1H), 3.87 (s, 6H), 3.71 (m, 2H), 3.50 (d, J = 10.1 Hz, 1H), 3.45 (ddd, J = 13.1, 6.7, 1.9 Hz, 1H), 3.13 (dd, J = 10.1, 4.5 Hz, 1H), 2.52 (m, 1H), 2.33 (m, 3H), 2.26 (dd, J = 13.4, 4.1 Hz, 1H), 2.08 (m, 1H), 2.00 (m, 2H), 1.92 (m, 1H), 1.82 (s, 3H), 1.76 (m, 4H), 1.48 (m, 4H), 0.95 (d, J = 7.1 Hz, 3H), 0.91 (s, 9H), 0.78 (d, J = 6.7 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 161.3, 149.0, 148.6, 146.5, 142.8, 142.1, 141.8, 136.6, 134.6, 131.2, 120.5, 118.5, 111.5, 111.3, 110.6, 87.8, 83.1, 81.1, 77.7, 77.3, 70.8, 70.2, 70.1, 67.3, 65.0, 60.4, 56.2, 56.0, 40.3, 39.4, 39.0, 38.9, 38.1, 36.5, 36.4, 33.9, 33.5, 26.1, 19.4, 18.1, 13.7, 5.9, -4.6; high resolution mass spectrum (ES^+) m/z 944.3605 [$(\text{M}+\text{Na})^+$; calcd for $\text{C}_{45}\text{H}_{66}\text{INO}_9\text{SiNa}$: 944.3652].

Aldehyde (+)-S₈: To a solution of alcohol (+)-S₇ (61.0 mg, 0.066 mmol) in dichloromethane (24 mL) under argon at 0 °C was added solid sodium bicarbonate (5.5 mg, 0.066 mmol) followed by Dess-Martin periodinane (56.0 mg, 0.132 mmol). After thirty minutes, the reaction was warmed to room temperature and after two total hours of reaction, the solution was poured into saturated aqueous sodium bicarbonate (15 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (15 mL, 3x), dried over MgSO_4 and concentrated under reduced pressure. Purification via silica gel chromatography (30% EtOAc/hexanes) afforded aldehyde (+)-

S₈ (59.4 mg, 98%) as a colorless oil. $[\alpha]_D^{20} +35.0$ (*c* 1.0, CHCl₃); IR (neat) 2931 (b), 2851 (s), 1724 (s), 1510 (s), 1461 (s), 1366 (m), 1257 (b), 1098 (b), 1028 (s), 914 (b), 834 (s) cm⁻¹; ¹HNMR (500 MHz, CDCl₃) δ 9.74 (app t, *J* = 2.6 Hz, 1H), 7.47 (s, 1H), 6.82 (m, 3H), 6.59 (m, 1H), 6.32 (s, 1H), 4.83 (dd, *J* = 8.9, 5.2 Hz, 1H), 4.79 (s, 1H), 4.77 (s, 1H), 4.56 (d, *J* = 11.2 Hz, 1H), 4.31 (m, 1H), 4.25 (d, *J* = 10.8 Hz, 1H), 4.24 (m, 1H), 4.00 (m, 2H), 3.87 (s, 6H), 3.49 (d, *J* = 10.4 Hz, 1H), 3.45 (ddd, *J* = 7.4, 7.4, 1.8 Hz, 1H), 3.12 (dd, *J* = 10.0, 4.8 Hz, 1H), 2.64 (dd, *J* = 7.8, 3.0 Hz, 1H), 2.61 (dd, *J* = 7.8, 2.6 Hz, 1H), 2.52 (m, 1H), 2.48 (dd, *J* = 6.0, 2.2 Hz, 1H), 2.45 (dd, *J* = 6.0, 1.9 Hz, 1H), 2.32 (m, 3H), 2.08 (m, 2H), 1.95 (m, 2H), 1.82 (s, 2H), 1.75 (m, 3H), 1.43 (m, 3H), 0.95 (d, *J* = 7.1 Hz, 3H), 0.91 (s, 9H), 0.79 (d, *J* = 6.7 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ¹³CNMR (125 MHz, CDCl₃) δ 200.9, 160.9, 149.0, 148.6, 146.3, 143.1, 140.9, 136.1, 135.3, 134.2, 131.9, 120.2, 118.7, 111.1, 110.9, 87.5, 82.8, 80.9, 77.4, 77.1, 69.9, 69.6, 69.1, 67.3, 67.2, 64.6, 55.9, 55.7, 47.7, 39.6, 38.9, 38.8, 38.0, 36.2, 33.6, 33.3, 29.6, 25.8, 19.1, 13.5, 5.7, -4.9, -5.0; high resolution mass spectrum (ES⁺) *m/z* 942.3552 [(M+Na)⁺; calcd for C₄₅H₆₆INO₉SiNa: 942.3455].

Secondary Alcohol-Aldehyde (+)-23: To a solution of aldehyde (+)-**S₈** (59.4 mg, 0.064 mmol) in dichloromethane (10 mL) and pH 7 buffer (2.7 mL) under an argon atmosphere at room temperature was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (29.3 mg, 0.129 mmol). After stirring for four hours, the reaction was poured over saturated aqueous sodium bicarbonate (10 mL), extracted with dichloromethane (8 mL, 3x), dried over MgSO₄, filtered and

concentrated under reduced pressure. Purification via silica gel chromatography (25% EtOAc/hexanes) afforded secondary alcohol-aldehyde (+)-**23** (50.6 mg, 95%) as a colorless oil. $[\alpha]_D^{20} +34.0$ (c 0.1, CHCl_3); IR (neat) 3429 (b), 2924 (s), 2853 (s), 1725 (s), 1461 (s), 1377 (m), 1252 (s), 1098 (s), 1049 (b), 900 (b), 835 (s), 776 (s) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.74 (app t, $J = 2.2$ Hz, 1H), 7.45 (s, 1H), 6.56 (m, 1H), 6.30 (d, $J = 16.0$ Hz, 1H), 6.24 (s, 1H), 4.81 (app t, $J = 7.4$ Hz 1H), 4.79 (s, 1H), 4.77 (s, 1H), 4.31 (m, 1H), 4.24 (br s, 1H), 3.99 (m, 2H), 3.48 (m, 1H), 3.47 (d, $J = 10.3$ Hz, 1H), 3.41 (dd, $J = 10.4, 4.8$ Hz, 1H), 2.64 (dd, $J = 7.8, 2.6$ Hz, 1H), 2.51 (m, 1H), 2.48 (dd, $J = 6.0, 2.2$ Hz, 1H), 2.39 (dd, $J = 6.0, 1.9$ Hz, 1H), 2.29 (m, 3H), 1.96 (m, 3H), 1.88 (m, 1H), 1.83 (s, 3H), 1.80 (m, 2H), 1.44 (m, 4H), 0.94 (d, $J = 6.7$ Hz, 3H), 0.91 (s, 9H), 0.80 (d, $J = 6.7$ Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 200.9, 161.3, 146.6, 143.6, 135.8, 134.7, 119.2, 111.6, 87.8, 81.4, 78.2, 70.1, 69.6, 67.8, 67.7, 65.1, 48.2, 40.1, 39.5, 39.4, 39.3, 39.1, 38.6, 38.4, 36.4, 35.1, 30.1, 26.3, 19.7, 18.5, 13.6, 5.9, -4.3, -4.4; high resolution mass spectrum (ES^+) m/z 792.2767 $[(\text{M}+\text{Na})^+]$; calcd for $\text{C}_{36}\text{H}_{56}\text{INO}_7\text{SiNa}$: 792.2736].

Phosphonate Ester (+)-S₉: To a solution of secondary alcohol-aldehyde (+)-**23** (30.5 mg, 0.039 mmol) in dichloromethane (7.3 mL) under an argon atmosphere at room temperature was added dropwise via cannula, trifluoroethyl-phosphonate acid **24** (59.0 mg, 0.195 mmol) as a solution in dichloromethane (7.3 mL) and allowed to stir for five minutes. 1-[3-(dimethylamino)propyl]-3-

ethylcarbodiimide methiodide (EDCI•MeI) (58.9 mg, 0.198 mmol) followed by hydroxybenzotriazole (HOBT) (catalytic) were added and the reaction was allowed to stir at room temperature. After thirty minutes, the reaction solution was concentrated under reduced pressure to 1/2 volume and purified directly via silica gel chromatography (40% EtOAc/hexanes) to afford phosphonate ester (+)-**S₉** (38.3 mg, 93%) as a colorless oil. $[\alpha]_D^{20} +20.0$ (c 0.1, CHCl₃); IR (neat) 2928 (b), 1734 (s), 1268 (b), 1174 (s), 1098 (m), 963 (s), 893 (b), 835 (s), 775 (s) cm⁻¹; ¹HNMR (500 MHz, CDCl₃) δ 9.74 (app t, J = 2.2 Hz, 1H), 7.45, (s, 1H), 6.53 (m, 1H), 6.29 (d, J = 16 Hz, 1H), 6.28 (s, 1H), 4.82 (app t, J = 7.1 Hz, 1H), 4.79 (s, 1H), 4.77 (s, 1H), 4.72 (dd, J = 11.2, 4.8 Hz, 1H), 4.39 (m, 4H), 4.31 (m, 1H), 4.24 (br s, 1H), 3.99 (m, 2H), 3.56 (m, 2H), 3.19 (s, 1H), 3.14 (s, 1H), 2.64 (dd, J = 7.4, 2.6 Hz, 1H), 2.60 (dd, J = 7.8, 2.9 Hz, 1H), 2.55 (m, 1H), 2.45 (m, 2H), 2.25 (m, 3H), 2.07 (m, 2H), 1.96 (m, 4H), 1.86 (m, 2H), 1.84 (m, 2H), 1.83 (s, 3H), 1.61 (m, 2H), 1.46 (m, 3H), 0.95 (d, J = 6.7 Hz, 3H), 0.91, (s, 9H), 0.72 (d, J = 6.4 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ¹³CNMR (125 MHz, CDCl₃) δ 200.9, 163.9, 160.7, 145.3, 143.1, 140.8, 134.6, 134.2, 119.0, 111.1, 87.1, 81.7, 80.5, 77.1, 77.0, 69.6, 69.0, 67.3, 67.2, 64.6, 62.5, 62.4, 47.7, 39.6, 38.9, 38.8, 38.7, 38.1, 35.8, 35.2, 34.6, 33.5, 32.0, 29.6, 25.8, 19.1, 18.0, 12.9, 6.0, -4.9, -5.0; high resolution mass spectrum (ES⁺) m/z 1078.2700 [(M+Na)⁺; calcd for C₄₅H₆₈INO₉SiNa: 1078.2657].

Z-C(2-3)-Macrocycle (+)-4: To a flask charged with freshly distilled toluene (34 mL) at room temperature under argon was added 18-crown-6 (0.710 g, 2.70 mmol) and potassium carbonate (79.0 mg, 0.576 mmol). After stirring for three hours, a solution of phosphonate ester (+)-**S**₉ (50.7 mg, 0.048 mmol) in toluene (34 mL) was added dropwise via cannula and allowed to stir at room temperature. After three hours, the reaction mixture was poured into saturated aqueous sodium chloride (30 mL) and the resultant layers of the biphasic mixture were separated. The aqueous layer was extracted with ethyl acetate (20 mL, 3x) and the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Purification by preparative thin layer chromatography (30% EtOAc/hexanes) afforded Z-C(2-3)-macrocycle (+)-**4** (22.2 mg, 68% yield) as a white foam and E-C(2-3)-macrocycle (+)-**S**₁₀ (10.5 mg, 29%) as a light yellow oil. Total (32.7 mg, 96%, 2.5:1 Z:E). **Z-C(2-3)-Macrocycle (+)-4:** $[\alpha]_{\text{D}}^{20} +47.5$ (*c* 0.3, CHCl₃); IR (neat) 2926 (s), 2854 (s), 1718 (s), 1252 (s), 1186 (s), 1091 (s), 1034 (m), 835 (s) cm⁻¹; ¹HNMR (500 MHz, C₆D₆) δ 6.94 (s, 1H), 6.84 (m, 1H), 6.16 (d, *J* = 15.9 Hz, 1H), 6.02 (s, 1H), 5.76 (dd, *J* = 13.4, 11.2 Hz, 1H), 5.43 (ddd, *J* = 10.4, 10.4, 2.8 Hz, 1H), 5.16 (s, 1H), 4.95 (d, *J* = 11.3 Hz, 1H), 4.72 (s, 1H), 4.48 (dd, *J* = 15.5, 11.2 Hz, 1H), 4.38 (m, 1H), 4.24 (app t, *J* = 10.8 Hz, 1H), 4.06 (m, 1H), 4.00 (app t, *J* = 2.5 Hz, 1H), 3.94 (m, 1H), 3.27 (m, 1H), 3.24 (d, *J* = 10.2 Hz, 1H), 3.04 (d, *J* = 11.9 Hz, 1H), 2.57 (app t, *J* = 6.4 Hz, 1H), 2.41 (d, *J* = 3.1 Hz, 1H), 2.32 (m, 2H), 2.09 (ddd, *J* = 13.1, 11.8, 5.0 Hz, 1H), 1.99 (app t, *J* = 11.8 Hz, 1H), 1.94 (d, *J* = 12.9 Hz, 1H), 1.84 (m, 1H), 1.79 (d, *J* = 0.9 Hz, 3H), 1.63 (m, 3H), 1.47 (d, *J* = 13.4 Hz, 1H), 1.33 (m, 2H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.92 (s, 9H), 0.57 (d, *J* = 6.5 Hz, 3H), 0.00 (s, 3H), -0.01 (s, 3H); ¹³CNMR (125 MHz, C₆D₆) δ 165.7, 161.6, 146.7, 145.8, 143.8,

143.0, 134.1, 133.8, 121.2, 120.2, 110.4, 88.1, 81.5, 79.7, 78.8, 73.6, 69.9, 69.3, 67.6, 65.8, 42.4, 40.5, 39.9, 37.9, 36.3, 34.7, 33.0, 32.3, 31.1, 26.3, 19.6, 18.6, 13.3, 6.5, -4.4, -4.5; high resolution mass spectrum (ES⁺) m/z 816.2741 [(M+Na)⁺; calcd for C₃₈H₅₆INO₇SiNa: 816.2763].

***E*-C(2-3)-Macrocycle (+)-S₁₀:** $[\alpha]_D^{20}$ +26.7 (c 0.9, CHCl₃); IR (neat) 2933 (b), 2794 (s), 1718 (s), 1654 (s), 1252 (m), 1152 (s), 1087 (m), 1024 (s), 833 (s), 775 (s) cm⁻¹; ¹HNMR (500 MHz, C₆D₆) δ 7.20 (m, 1H), 6.90 (s, 1H), 6.83 (m, 1H), 6.11 (d, J = 15.7 Hz, 1H), 6.01 (d, J = 15.2 Hz, 1H), 5.95 (s, 1H), 4.93 (d, J = 11.6 Hz, 1H), 4.94 (m, 1H), 4.67 (s, 1H), 4.58 (s, 1H), 4.34 (br s, 1H), 3.99 (s, 1H), 3.90 (app q, J = 7.1 Hz, 1H), 3.37 (app t, J = 9.1 Hz, 1H), 3.31 (m, 1H), 3.19 (d, J = 10.0 Hz, 1H), 2.41 (d, J = 13.9 Hz, 1H), 2.26 (m, 2H), 2.12 (d, J = 10.6 Hz, 1H), 2.08 (d, J = 10.5 Hz, 1H), 2.02 (m, 1H), 1.89 (dd, J = 13.0, 2.6 Hz, 1H), 1.80 (m, 3H), 1.75 (d, J = 1.0 Hz, 3H), 1.67 (m, 3H), 1.61 (m, 1H), 1.35 (m, 2H), 0.96 (m, 9H), 0.74 (d, J = 6.7 Hz, 3H), 0.66 (d, J = 6.5 Hz, 3H), 0.00 (s, 3H), -0.01 (s, 3H); ¹³CNMR (125 MHz, C₆D₆) δ 167.3, 162.4, 147.6, 146.9, 143.9, 142.8, 135.7, 134.6, 124.1, 119.2, 111.4, 88.1, 81.5, 78.8, 77.4, 71.0, 70.0, 68.7, 66.4, 66.2, 41.6, 41.3, 40.4, 38.8, 38.6, 38.5, 35.8, 35.3, 33.2, 26.6, 26.5, 19.8, 18.8, 13.6, 6.1, -4.2; high resolution mass spectrum (ES⁺) m/z 816.2788 [(M+Na)⁺; calcd for C₃₈H₅₆INO₇SiNa: 816.2763].

C(45-46)-TMS-Alkynyl Sidechain (-)-3: Oxazole triflate, **(-)-S₁₁** (69.6 mg, 0.089 mmol) was combined with hexamethylditin (0.026 mL, 0.125 mmol) in a 100 mL sealed tube and azeotroped from benzene (5 mL, 3x) followed by drying under vacuum for one hour. In a glove bag, under an inert argon atmosphere to the sealed tube was added, flame dried lithium chloride (60.0 mg, 1.40 mmol), tetrakis(triphenylphosphine)palladium [Pd(PPh₃)₄] (15.0 mg, 0.013 mmol) and dioxane (0.90 mL), (freeze pump thawed, 3x). The reaction was heated to 90 °C behind a blast shield and after fifteen hours, the reaction was cooled to room temperature and purified directly via silica gel chromatography (15% EtOAc/hexanes) to afford C(45-46)-TMS-alkynyl sidechain **(-)-3** (46.4 mg, 64%) as a colorless oil. $[\alpha]_D^{20}$ -37.5 (*c* 0.1, CH₂Cl₂); IR (neat) 2927 (s), 2865 (s), 1462 (m), 1248 (s), 1093 (b), 843 (s) cm⁻¹; ¹HNMR (500 MHz, CDCl₃) δ 7.45 (s, 1H), 6.24 (d, *J* = 15.7 Hz, 1H), 5.55 (dd, *J* = 15.6, 7.6 Hz, 1H), 5.43 (d, *J* = 8.8 Hz, 1H), 4.63 (dd, *J* = 8.7, 6.1 Hz, 1H), 3.78 (app q, *J* = 3.2 Hz, 1H), 3.57 (m, 3H), 3.34 (s, 3H), 3.31 (s, 3H), 3.29 (s, 3H), 3.03 (d, *J* = 14.9 Hz, 1H), 2.58 (dd, *J* = 16.7, 5.7 Hz, 1H), 2.44 (dd, *J* = 16.7, 6.8 Hz, 1H), 2.20 (dddd, *J* = 12.7, 4.6, 4.5, 1.6 Hz, 1H), 2.00 (dd, *J* = 12.2, 4.4 Hz, 1H), 1.78 (d, *J* = 0.9 Hz, 3H), 1.37 (dd, *J* = 12.6, 11.2 Hz, 1H), 1.06 (m, 22H), 0.31 (s, 9H), 0.14 (s, 9H); ¹³CNMR (125 MHz, CDCl₃) δ 160.9, 145.1, 137.2, 134.1, 133.0, 127.4, 103.2, 99.9, 86.4, 80.6, 73.8, 73.5, 71.7, 56.5, 55.5, 47.8, 39.2, 35.6, 32.0, 29.6, 27.0, 18.0, 17.9, 13.6, 12.3, 0.04; high resolution mass spectrum (ES⁺) *m/z* 820.3400 [(M+Na)⁺; calcd for C₃₇H₆₇NO₆Si₂SnNa: 820.3426].

(+)-25

Protected C(45-46)-TMS-Alkynyl-Phorboxazole (+)-25: Vinyl iodide macrocycle (+)-**4** (13.8 mg, 0.017 mmol) and C(45-46)-TMS-alkynyl sidechain (-)-**3** (21.0 mg, 0.026 mmol) were combined in a flame dried round bottom flask (5 mL), azeotroped from benzene (2 mL, 3x) and dried under vacuum for two hours. To the flask under an argon atmosphere were added tris(dibenzylideneacetone)dipalladium-chloroform adduct $[\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3]$ (3.6 mg, 0.003 mmol), triphenylarsine (AsPh_3) (6.4 mg, 0.021 mmol) and $\text{Ph}_2\text{PO}_2\text{NBu}_4$ (12 mg, 0.026 mmol) followed by introduction of DMF (0.17 mL, sparged with argon, thirty minutes) and diisopropylethylamine (0.003 mL, 0.017 mmol). After the reaction was allowed to stir for sixteen hours at room temperature, the light brown reaction mixture was introduced directly onto a silica gel column, (20% EtOAc/hexanes $\rightarrow$ 30% EtOAc/hexanes) to afford protected C(45-46)-TMS-alkynyl-phorboxazole (+)-**25** (14.9 mg, 68%) as a light yellow oil. $[\alpha]_D^{20} +1.3$ (c 0.2, CHCl_3); IR (neat) 2925 (b), 1718 (s), 1456 (b), 1250 (s), 1187 (s), 1091 (s), 1053 (b), 840 (s) cm^{-1} ; ^1H NMR (500 MHz, C_6D_6) δ 6.96 (s, 1H), 6.90 (m, 1H), 6.37 (s, 1H), 6.32 (d, $J = 15.7$ Hz, 1H), 6.20 (d, $J = 15.9$ Hz, 1H), 5.79 (dd, $J = 11.2, 2.3$ Hz, 1H), 5.69 (dd, $J = 15.7, 7.3$ Hz, 1H), 5.57 (d, $J = 8.9$ Hz, 1H), 5.47 (ddd, $J = 10.7, 10.5, 2.9$ Hz, 1H), 5.18 (s, 1H), 4.96 (dd, $J = 11.3, 2.0$ Hz, 1H), 4.77 (m, 2H), 4.62 (dd, $J = 11.2, 4.4$ Hz, 1H), 4.39 (m, 1H), 4.25 (app t, $J = 10.4$ Hz, 1H), 4.08 (m, 1H), 4.03 (d, $J = 2.6$ Hz, 1H), 3.95 (m, 1H), 3.76 (m, 1H), 3.69 (app t, $J = 6.9$ Hz, 1H), 3.68 (m, 1H),

3.52 (dd, $J = 9.4, 4.6$ Hz, 1H), 3.45 (d, $J = 10.1$ Hz, 1H), 3.41 (s, 3H), 3.34 (d, $J = 14.7$ Hz, 1H), 3.28 (app t, $J = 4.8$ Hz, 1H), 3.23 (app t, $J = 5.0$ Hz, 1H), 3.09 (s, 3H), 3.08 (s, 3H), 3.04 (d, $J = 11.4$ Hz, 1H), 2.95 (d, $J = 14.8$ Hz, 1H), 2.66 (app t, $J = 6.3$ Hz, 1H), 2.60 (m, 1H), 2.58 (dd, $J = 16.7, 5.7$ Hz, 1H), 2.44 (dd, $J = 16.7, 6.8$ Hz, 1H), 2.42 (m, 2H), 2.37 (dd, $J = 12.8, 5.5$ Hz, 1H), 2.17 (dd, $J = 10.0, 7.7$ Hz, 1H), 2.10 (m, 1H), 2.09 (d, $J = 0.6$ Hz, 3H), 2.02 (d, $J = 11.8$ Hz, 1H), 1.98 (d, $J = 13.0$ Hz, 1H), 1.77 (d, $J = 0.8$ Hz, 3H), 1.65 (m, 3H), 1.49 (d, $J = 13.2$ Hz, 1H), 1.35 (m, 3H), 1.17 (m, 22H), 1.05 (d, $J = 6.9$ Hz, 3H), 0.94 (s, 9H), 0.77 (d, $J = 6.5$ Hz, 3H), 0.24 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 165.8, 161.7, 160.0, 145.5, 143.8, 143.0, 139.2, 138.2, 137.3, 136.8, 135.0, 134.4, 133.8, 133.5, 121.4, 120.1, 119.5, 110.5, 104.6, 100.8, 90.0, 86.8, 81.0, 80.2, 78.7, 74.7, 74.1, 73.7, 72.7, 69.9, 69.3, 67.7, 65.9, 56.7, 55.6, 48.3, 42.4, 40.5, 40.4, 40.0, 37.9, 36.4, 36.3, 34.9, 33.1, 32.4, 31.2, 30.5, 27.9, 26.3, 18.7, 18.6, 14.6, 14.1, 13.7, 13.2, 6.6, 1.7, 0.6, -4.5, -4.4; high resolution mass spectrum (ES^+) m/z 1321.7641 $[(\text{M}+\text{Na})^+]$; calcd for $\text{C}_{72}\text{H}_{114}\text{N}_2\text{O}_{13}\text{Si}_3\text{Na}$: 1321.7626].

Bromoalkyne (+)-S₁₂: Protected C(45-46)-TMS-alkynyl-phorboxazole (+)-**25** (4.4 mg, 0.0034 mmol) was introduced into a flame dried round bottom flask, azeotroped from benzene (2 mL, 3x) and dried under vacuum. After one hour, under an argon atmosphere, (+)-**25** was stirred in HPLC grade acetone (2.1 mL) at 0 °C. After five minutes, silver nitrate (catalytic) followed by N-

bromosuccinimide (NBS) (3.3 mg, 0.018 mmol) were added and after thirty minutes, the reaction mixture was warmed to room temperature. After two hours and thirty minutes of total reaction time, the reaction solution was recooled to 0 °C and quenched via dropwise addition of saturated aqueous sodium thiosulfate (2 mL), stirred until the initial yellow color dissipated and then poured into saturated aqueous sodium bicarbonate (5 mL). The layers of the biphasic mixture were separated and the aqueous layer was extracted with dichloromethane (8 mL, 3x), dried over MgSO₄, filtered and concentrated under reduced pressure. Purification via silica gel chromatography (40% EtOAc/hexanes) afforded bromoalkyne (+)-**S**₁₂ (4.2 mg, 95%) as a white amorphous solid. $[\alpha]_D^{20} +3.1$ (c 0.04, CH₂Cl₂); IR (neat) 2921 (b), 2861 (s), 1719 (s), 1461 (m), 1371 (m), 1187 (s), 1093 (s), 884 (w); ¹HNMR (500 MHz, C₆D₆) δ 7.20 (s, 1H), 6.95 (s, 1H), 6.88 (m, 1H), 6.35 (s, 1H), 6.23 (d, *J* = 15.8 Hz, 1H), 6.19 (d, *J* = 15.8 Hz, 1H), 5.79 (dd, *J* = 11.2, 2.5 Hz, 1H), 5.54 (d, *J* = 10.7 Hz, 1H), 5.53 (dd, *J* = 15.3, 7.3 Hz, 1H), 5.45 (ddd, *J* = 10.7, 10.7, 2.7 Hz, 1H), 5.17 (s, 1H), 4.95 (d, *J* = 11.2 Hz, 1H), 4.74 (s, 1H), 4.73 (m, 1H), 4.61 (dd, *J* = 11.2, 4.3 Hz, 1H), 4.39 (m, 1H), 4.23 (m, 1H), 4.06 (m, 1H), 4.02 (m, 1H), 3.97 (m, 1H), 3.75 (ddd, *J* = 12.1, 7.8, 1.8 Hz, 1H), 3.69 (m, 1H), 3.54 (dd, *J* = 13.2, 6.6 Hz, 1H), 3.43 (d, *J* = 9.9 Hz, 1H), 3.40 (s, 3H), 3.33 (d, *J* = 14.7 Hz, 1H), 3.07 (s, 3H), 3.04 (s, 3H), 2.94 (d, *J* = 14.8 Hz, 1H), 2.65 (m, 1H), 2.56 (dd, *J* = 12.9, 3.3 Hz, 1H), 2.42 (m, 4H), 2.37 (dd, *J* = 16.7, 5.7 Hz, 1H), 2.24 (dd, *J* = 16.6, 6.7 Hz, 1H), 2.14 (m, 1H), 2.08 (s, 3H), 2.03 (d, *J* = 11.4 Hz, 1H), 1.97 (m, 1H), 1.70 (d, *J* = 0.8 Hz, 3H), 1.63 (m, 5H), 1.48 (d, *J* = 13.3 Hz, 1H), 1.34 (m, 5H), 1.16 (m, 21H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.92 (s, 9H), 0.76 (d, *J* = 6.4 Hz, 3H), 0.09 (s, 3H), -0.01 (s, 3H); ¹³CNMR (125 MHz, C₆D₆) δ 165.1, 161.1, 159.4, 144.9, 143.2, 142.3, 138.7, 137.6, 137.1, 136.1, 134.1, 133.9, 133.2, 133.1, 120.8, 119.6, 118.8, 109.8, 100.3, 89.4, 80.2, 79.6, 78.2, 77.1, 74.1, 73.1, 72.0, 69.3, 68.6, 67.1, 65.3, 56.0, 55.0, 47.7, 47.6, 41.8, 39.9, 39.8, 39.7, 39.3, 37.3, 35.7, 35.5, 34.3, 32.5, 31.8, 30.5, 29.9, 26.9, 25.7, 18.0, 17.8, 13.9, 13.4, 13.1, 12.7, 6.0, -5.0, -5.1; high resolution mass spectrum (ES⁺) *m/z* 1327.6339 [(M+Na)⁺; calcd for C₆₉H₁₀₅O₁₃N₂Si₂BrNa: 1327.6343].

Phorboxazole A (+)-1: In a flame dried round bottom flask, bromoalkyne (+)-**S**₁₂ (4.2 mg, 0.0032 mmol) was azeotroped from benzene (2 mL, 3x) and dried under vacuum. After one hour, under an argon atmosphere at room temperature, (+)-**S**₁₂ was dissolved in freshly distilled THF (1.5 mL) followed by the addition of bis(triphenylphosphine)palladium(II)chloride [PdCl₂(PPh₃)₂] (0.25 mL, 0.0006 mmol of stock solution; 2.0 mg/1.0 mL THF) and tri-*n*-butyltinhydride (0.002 mL, 0.0071 mmol). After fifteen minutes, tri-*n*-butyltinhydride (0.002 mL, 0.0071 mmol) was added and allowed to stir for twenty minutes at which time, the reaction was quenched via dropwise addition of saturated aqueous sodium bicarbonate (5 mL). The layers of the bisphasic mixture were separated and the aqueous layer was extracted with dichloromethane (8 mL, 3x). The combined organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. Filtration through a plug of silica gel (20% EtOAc/hexanes) and concentration under reduced pressure afforded vinylstannane **S**₁₃.

Vinylstannane **S**₁₃, under an argon atmosphere was dissolved in anhydrous acetonitrile (2.0 mL) and cooled to 0 °C. After five minutes, N-bromosuccinimide (NBS) (1.8 mg, 0.001 mmol) was added and following thirty minutes, the reaction was quenched via dropwise addition of saturated aqueous sodium thiosulfate (3 mL) and stirred until the resultant yellow color dissipated. The solution was poured into saturated aqueous sodium bicarbonate (5 mL) and extracted with dichloromethane (5 mL, 4x). The combined organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. Filtration through a plug of silica gel (40%

EtOAc/hexanes) and concentration under reduced pressure afforded protected phorboxazole A **S₁₄**.

Protected phorboxazole A **S₁₄** under an argon atmosphere was dissolved in freshly distilled THF (1.7 mL) followed by the dropwise addition of 6% HCl (0.67 mL) at room temperature. After ninety six hours, the reaction mixture was cooled to 0 °C and poured into saturated aqueous sodium bicarbonate (5 mL) and extracted with dichloromethane (5 mL, 3x) followed by ethyl acetate (5 mL, 3x). The combined organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. Purification via silica gel chromatography (100% EtOAc → 10% methanol/EtOAc) afforded phorboxazole A (+)-**1** (1.1 mg, 6:1-C(46):C(45) vinyl bromide). Further purification via reverse phase HPLC (Zorbax C₁₈ column, acetonitrile/H₂O (55/45) eluent) afforded phorboxazole A (+)-**1** (0.90 mg, 35% over 3-steps after HPLC purification) which matched the ¹HNMR, [α]_D²⁰, and high resolution mass spectrum of natural (+)-phorboxazole A: [α]_D²⁰ +43.4 (c 0.04, CH₂Cl₂), high resolution mass spectrum (ES⁺) *m/z* 1045.4029 [(M+Na)⁺; calcd for C₅₃H₇₁N₂O₁₃Na: 1045.4037].