Supporting Information

(+)-Phorboxazole A Synthetic Studies.

Identification of a Series of Highly Cytotoxic C(45-46) Analogues.

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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 7.16) for ¹HNMR and either chloroform (δ 77.0) or benzene (δ 128.0) for ¹³CNMR. 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:

Alcohol (-)-S₁: Dry copper(I)cyanide (23 mg, 0.259 mmol) was added to a solution of ethylmagnesium bromide (1.0M/THF) (16.2 mL, 16.2 mmol) in freshly distilled THF (26 mL) at 0 °C under argon. After stirring for five minutes, the solution was cooled to -15 °C where known epoxide (+)-**18** (2.45 g, 12.9 mmol) in freshly distilled THF (10.0 mL) was added dropwise via cannula. After stirring for fifteen minutes, the reaction mixture was poured into saturated aqueous ammonium chloride (20 mL), extracted with ethyl acetate (15 mL, 3x), dried over MgSO₄, filtered and concentrated *in vacuo*. Purification via

silica gel chromatography (5% EtOAc/hexanes) afforded alcohol (-)-**S**₁ (2.59 g, 92%) as a colorless oil. $[\alpha]_D^{20}$ -41.7 (c 0.67, CHCl₃); IR (neat) 2927 (m), 1465 (s), 1254 (s), 1097 (s), 838 (s), 780 (s) cm⁻¹; ¹HNMR (500 MHz, CDCl₃) δ 3.64 (m, 1H), 3.62 (dd, *J* = 9.6, 2.3 Hz, 1H), 3.38 (ddd, *J* = 8.9, 7.9, 0.7 Hz, 1H), 2.38 (br s, 1H), 1.41 (m, 4H), 0.93 (app t, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ¹³CNMR (125 MHz, CDCl₃) δ 71.5, 67.2, 34.9, 25.8, 18.7, 18.2, 14.1, -5.3, -5.4; high resolution mass spectrum (CI, NH₃) *m/z* 219.1777 [(M)⁺; calcd for C₁₁H₂₆O₂Si: 219.1701].

(-)-19

TBS Ether (-)-19: To a stirred solution of (-)-**S**₁ (1.24 g, 5.70 mmol) in dichloromethane (9.6 mL) under argon at room temperature was added 2,6-di-*tert*-butyl-4-methylpyridine (2,6-DTBMP) (1.75 g, 8.50 mmol) in one portion followed by the dropwise addition of methyltrifluoromethylsulfonate (3.22 mL, 28.5 mmol). After stirring for seventeen hours at room temperature, the light brown reaction mixture was filtered through a pad of Celite followed by washing with dichloromethane (10 mL, 3x). The filtrate was washed with saturated aqueous sodium bicarbonate (20 mL) and the resultant aqueous layer was extracted with dichloromethane (15 mL, 3x). The combined organic extracts were dried over MgSO₄, filtered and concentrated *in vacuo*. Purification via silica gel chromatography (10% Et₂O/hexanes) afforded (-)-**19** (0.77 g, 58%) as a colorless oil. $[\alpha]_D^{20}$ -32.6 (*c* 0.41, CHCl₃); IR (neat) 2951 (m), 2857 (s), 1463 (s), 1249 (s), 1103 (b), 842 (s), 780 (s) cm⁻¹; ¹HNMR (500 MHz, CDCl₃) δ 3.61 (dd, *J* = 10.5, 5.7 Hz, 1H), 3.54 (dd, *J* = 10.5, 4.9 Hz, 1H), 3.40 (s, 3H), 3.18 (m, 1H), 1.42 (m, 4H), 0.91 (app t, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ¹³CNMR (125 MHz, CDCl₃) δ 82.0, 65.5, 58.1, 33.8, 26.1, 18.8, 14.4, -2.7, -5.1, -5.2; high resolution mass spectrum (CI, NH₃) *m/z* 233.4439 [(M)⁺; calcd for C₁₅H₂₈O₂Si: 233.4441].

(-)-S₂

Alcohol (-)-S₂: To a stirred solution of (-)-**19** (0.12 g, 0.517 mmol) in freshly distilled THF (10.3 mL) at 0 °C under argon was added dropwise, tetrabutylammonium fluoride (1.0 M/THF) (0.78 mL, 0.780 mmol). After stirring for one hour, the reaction was quenched via dropwise addition of saturated aqueous sodium chloride (5 mL) and allowed to warm to room temperature. The layers of the biphasic mixture were separated and the aqueous layer was extracted with ethyl acetate (7 mL, 3x). The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. Purification via silica gel chromatography (40% Et₂O/pentane) afforded alcohol (-)-S₂ (57.9 mg, 95%) as a colorless oil. $[\alpha]_D^{20}$ -32.7 (*c* 0.49, CHCl₃); IR (neat) 3246 (b), 2953 (m), 1463 (s), 1378 (b), 1139 (s), 1095 (b), 1056 (s), 812 (s) cm⁻¹; ¹HNMR (500 MHz, CDCl₃) δ 3.68 (dd, *J* = 11.5, 3.3 Hz, 1H), 3.47 (dd, *J* = 11.5, 6.5 Hz, 1H), 3.41 (s, 3H), 3.26 (m, 2H), 1.92 (br s, 1H), 1.56 (m, 1H), 1.38 (m, 2H), 0.94 (app t, *J* = 7.3, 3H); ¹³CNMR (125 MHz, CDCl₃) δ 81.6, 64.2, 57.3, 32.7, 18.8, 14.5; high resolution mass spectrum (CI, NH₃) *m/z* 119.0991 [(M)⁺; calcd for C₆H₁₄O₂: 119.0994].

(-)-20

Aldehyde (-)-20: To a stirred solution of (-)-S₂ (0.23 g, 1.94 mmol) in dichloromethane (98 mL) at 0 °C under argon was added, in one portion, solid sodium bicarbonate (0.41 g, 4.9 mmol) followed by portion wise addition of Dess-Martin periodinane (4.17 g, 9.80 mmol). After ten minutes, the reaction was warmed to room temperature and stirred for two hours, at which point the reaction was quenched via dropwise addition of saturated aqueous sodium bicarbonate (35 mL). The layers of the biphasic solution

were separated and the aqueous layer extracted with dichloromethane (15 mL, 3x). The combined organic extracts were dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification via silica gel chromatography, (10% Et_2O /pentane) afforded (-)-**20** (0.21 g, 91%) as an amorphous solid. $[\alpha]_{\text{D}}^{20}$ -34.8 (*c* 0.52, CHCl_3); IR (neat) 2925 (m), 1737 (s), 1458 (b), 1098 (b) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.65 (dd, $J = 1.9, 0.7$ Hz, 1H), 3.56 (ddd, $J = 6.2, 5.4, 1.9$ Hz, 1H), 3.44 (d, $J = 0.8$ Hz, 3H), 1.63 (m, 2H), 1.43 (m, 2H), 0.93 (app t, $J = 7.4$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 204.5, 86.0, 58.7, 32.3, 18.4, 14.3; high resolution mass spectrum (CI, NH_3) m/z 117.0143 $[(\text{M})^+]$; calcd for $\text{C}_6\text{H}_{12}\text{O}_2$: 117.0138].

(-)-21

Lactone (-)-21: To a solution of chromium(II)chloride (1.41 g, 11.5 mmol) in freshly distilled THF (4.5 mL) at room temperature under an argon atmosphere was added dropwise, anhydrous DMF (0.87 mL). The resultant brown solution was vigorously stirred for thirty minutes, at which point a solution of aldehyde (-)-**20** (0.13 g, 1.12 mmol) and tributyl(dibromomethyl)stannane ($\text{Bu}_3\text{SnCHBr}_2$) (1.14 g, 2.50 mmol) in freshly distilled THF (4.5 mL) were added dropwise via cannula. The solution was covered with aluminum foil to preclude exposure to light. Flame dried lithium iodide (0.59 g, 4.50 mmol) in freshly distilled THF (4.5 mL) was added dropwise via syringe and the reaction mixture was stirred at room temperature. After twenty four hours, the reaction was quenched via dropwise addition of water (5 mL). The layers of the biphasic solution were separated and the aqueous layer was extracted with diethyl ether (10 mL, 3x). The combined organic layers were washed with water (5 mL), saturated aqueous sodium chloride (5 mL),

dried over MgSO_4 , filtered and concentrated *in vacuo* to afford a light green oil. Due to decomposition upon silica gel chromatography, **15** was carried on crude (78%, 20:1, *E:Z* by ^1H NMR [C_6D_6] analysis of the crude isolate).

Vinylstannane **15** (0.136 g, 0.34 mmol) and vinyl iodide (-)-**16** (0.041 g, 0.084 mmol) were combined in a round bottom flask, azeotroped from benzene (5 mL, 3x) and dried under vacuum for thirty minutes. To the flask under an argon atmosphere were added, $\text{Ph}_2\text{PO}_2\text{NBu}_4$ (0.039 g, 0.084 mmol) and tris(dibenzylideneacetone)dipalladium-chloroform adduct [$\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$] (8.7 mg, 0.0084 mmol) followed by anhydrous DMF (0.85 mL, sparged with argon, one hour). After four hours at room temperature, the reaction was purified directly via silica gel chromatography (20% EtOAc/hexanes) to afford (-)-**21** (0.47 g, 89%) as a colorless oil. $[\alpha]_{\text{D}}^{20}$ -12.0 (*c* 0.05, CHCl_3); IR (neat) 2941 (b), 2868 (s), 1748 (s), 1460 (s), 1371 (b), 1240 (b), 1093 (b), 884 (s), 795 (s), 680 (s) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.16 (d, $J = 15.7$ Hz, 1H), 5.51 (dd, $J = 15.7, 7.8$ Hz, 1H), 5.44 (d, $J = 8.8$ Hz, 1H), 4.79 (dd, $J = 8.8, 4.7$ Hz, 1H), 4.23 (ddd, $J = 8.5, 7.5, 3.4$ Hz, 1H), 3.69 (m, 1H), 3.58 (app q, $J = 6.6$ Hz, 1H), 3.36 (d, $J = 0.9$ Hz, 3H), 3.26 (d, $J = 0.8$ Hz, 3H), 2.89 (dd, $J = 17.2, 5.8$ Hz, 1H), 2.40 (m, 2H), 1.81 (s, 3H), 1.59 (m, 2H), 1.43 (m, 1H), 1.31 (m, 2H), 1.04 (m, 21H), 0.91 (app t, $J = 7.2$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 169.8, 136.2, 136.1, 130.6, 130.0, 82.4, 80.4, 72.7, 70.3, 56.5, 56.2, 37.9, 37.1, 29.8, 18.8, 18.1, 14.2, 13.8, 12.5; high resolution mass spectrum (ES^+) m/z 491.3170 [$(\text{M}+\text{Na})^+$; calcd for $\text{C}_{26}\text{H}_{48}\text{O}_5\text{SiNa}$: 491.3168].

Mixed Methyl Ketal (-)-S₃: To lactone (-)-**21** (29.0 mg, 0.063 mmol) in a flame dried round bottom flask under argon at room temperature in freshly distilled THF (3.0 mL) was added oxazole **17** (0.12 g, 0.380 mmol) and the solution cooled to 0 °C. *iso*-Propylmagnesium chloride (2.0 M/THF, 0.079 mL, 0.157 mmol) was then added dropwise over thirty minutes. After stirring for twenty minutes, another addition of *iso*-propylmagnesium chloride (2.0 M/THF, 0.04 mL, 0.076 mmol) was introduced over twenty minutes. After a third addition of *iso*-propylmagnesium chloride (0.04 mL, 0.076 mmol) and stirring for thirty minutes, the reaction was quenched via dropwise addition of saturated aqueous sodium bicarbonate (3 mL). The solution was warmed to room temperature, at which point the layers of the biphasic mixture were separated and the aqueous layer was extracted with ethyl acetate (5 mL, 3x). The combined organic extracts were dried over MgSO₄, filtered and concentrated *in vacuo*. The resultant pale yellow oil was then dissolved in anhydrous methanol (7.3 mL) followed by the addition of *p*-TsOH•H₂O (7 mg, 0.038 mmol) under an argon atmosphere. After stirring for twenty hours at room temperature, the reaction was quenched via dropwise addition of aqueous saturated sodium bicarbonate (8 mL). The biphasic mixture was extracted with ethyl acetate (5 mL, 3x) and the combined organic extracts were dried over MgSO₄, filtered and concentrated *in vacuo*. Purification via silica gel chromatography (20% EtOAc/hexanes) afforded (-)-**S₃** (21.1 mg, 47%) over the two steps as a colorless oil. $[\alpha]_D^{20}$ -13.2 (*c* 0.61, CHCl₃); IR (neat) 2935 (b), 2867 (s), 1593 (s), 1433 (s), 1375 (b), 1224 (s), 1137 (s), 1098 (b), 860 (b) cm⁻¹; ¹HNMR (500 MHz, CDCl₃) δ 7.60 (s, 1H), 6.15 (d, *J* = 15.7 Hz, 1H), 5.47 (dd, *J* = 15.7, 7.9 Hz, 1H), 5.38 (d, *J* = 8.9, Hz,

1H), 4.64 (dd, $J = 8.9, 6.2$ Hz, 1H), 3.56 (m, 3H), 3.31 (s, 3H), 3.30 (s, 3H), 3.27 (s, 3H), 3.26 (d, $J = 15.5$ Hz, 1H), 2.99 (d, $J = 14.9$ Hz, 1H), 2.17 (dddd, $J = 12.6, 4.6, 4.6, 1.5$ Hz, 1H), 1.99 (dd, $J = 12.2, 4.3$, Hz, 1H), 1.77 (d, $J = 0.9$ Hz, 3H), 1.62 (m, 1H), 1.44 (m, 1H), 1.34 (m, 3H), 1.07 (m, 22H), 0.92 (app t, $J = 7.3$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 159.0, 145.0, 136.6, 134.6, 132.3, 129.8, 127.1, 99.9, 82.6, 74.4, 73.6, 71.9, 56.4, 55.8, 48.1, 39.4, 37.9, 36.2, 32.3, 18.8, 18.2, 18.1, 14.2, 13.8, 12.6; high resolution mass spectrum (ES^+) m/z 736.3152 [$(\text{M}+\text{Na})^+$; calcd for $\text{C}_{32}\text{H}_{54}\text{NO}_9\text{SSiNa}$: 736.3137].

C(45-46)-Alkyl Stannane Sidechain (-)-10: Oxazole triflate (-)-**S**₃ (42 mg, 0.059 mmol) was combined with hexamethylditin (0.017 mL, 0.082 mmol) in a sealed tube (100 mL), azeotroped from benzene (5 mL, 3x) and dried under vacuum for one hour. To the sealed tube in a glove bag under an argon atmosphere was added flame dried lithium chloride (40 mg, 0.940 mmol), tetrakis(triphenylphosphine)palladium [$\text{Pd}(\text{PPh}_3)_4$] (10 mg, 0.008 mmol) and anhydrous dioxane (0.60 mL, freeze pump thawed, 3x). The tube was sealed and the reaction vessel heated to 90 °C behind a blast shield. After twelve hours, the reaction was cooled to room temperature and purified directly via silica gel chromatography (15% EtOAc/hexanes) to afford (-)-**10** (27.5 mg, 64%) as a colorless oil. $[\alpha]_{\text{D}}^{20}$ -14.6 (c 0.57, CH_2Cl_2); IR (neat) 2930 (b), 2870 (s), 1462 (s), 1378 (b), 1087 (b), 879 (s), 775 (b); ^1H NMR (500 MHz, C_6D_6) δ 7.21 (s, 1H), 6.23 (d, $J = 15.7$ Hz, 1H), 5.56 (dd, $J = 15.7, 7.7$ Hz, 1H), 5.53 (d, $J = 8.4$ Hz, 1H), 4.73 (dd, $J = 8.8, 6.3$

Hz, 1H), 3.74 (m, 1H), 3.67 (m, 1H), 3.52 (app q, $J = 6.8$ Hz, 1H), 3.46 (d, $J = 14.9$ Hz, 1H), 3.43 (s, 3H), 3.17 (s, 3H), 3.06 (s, 3H), 3.05 (d, $J = 14.7$ Hz, 1H), 2.57 (dddd, $J = 12.6, 4.5, 4.4, 1.4$ Hz, 1H), 2.14 (dd, $J = 12.2, 2.2$ Hz, 1H), 1.73 (s, 3H), 1.68 (app q, $J = 6.5$ Hz, 1H), 1.47 (m, 2H), 1.35 (m, 3H), 1.14 (m, 21H), 0.88 (app t, $J = 7.3$ Hz, 3H), 0.24 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 161.5, 145.4, 136.7, 135.1, 133.1, 130.9, 100.9, 82.8, 74.7, 74.2, 72.9, 56.5, 55.6, 48.3, 40.6, 38.8, 36.4, 33.2, 19.4, 18.7, 18.6, 14.6, 14.1, 13.2, -9.3; high resolution mass spectrum (ES^+) m/z 752.3370 $[(\text{M}+\text{Na})^+]$; calcd for $\text{C}_{34}\text{H}_{63}\text{NO}_6\text{SiSnNa}$: 752.3345].

Terminal Alkyne Sidechain (-)-22: To a solution of oxazole triflate (-)-14 (43 mg, 0.055 mmol) under an argon atmosphere in freshly distilled THF (1 mL), absolute ethanol (1 mL), and water (1 mL) was added 2,6-lutidine (0.086 ml) at room temperature. After stirring for five minutes, silver nitrate (93.0 mg, 0.550 mmol) was added as one portion. After fifteen hours, the reaction was quenched via dropwise addition of 1N potassium dihydrogenphosphate (KH_2PO_4) (5 mL). After stirring for five minutes at room temperature, the yellow biphasic mixture was poured into saturated aqueous sodium chloride (10 mL) and extracted with ethyl acetate (10 mL, 3x). The combined organic extracts were dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification via silica gel chromatography (30% EtOAc/hexanes) afforded terminal alkyne sidechain (-)-22 (35.5 mg, 91%) as a pale yellow oil. $[\alpha]_{\text{D}}^{20}$ -31.1 (c 0.09, CHCl_3); IR (neat) 2941

(b), 2868 (s), 1591 (s), 1434 (s), 1230 (s), 1141 (s), 1093 (s), 1015 (s), 858 (s), 800 (b); ^1H NMR (500 MHz, CDCl_3) δ 7.60 (s, 1H), 6.25 (d, J = 15.7 Hz, 1H), 5.57 (dd, J = 15.6, 7.7 Hz, 1H), 5.43 (d, J = 8.9 Hz, 1H), 4.61 (dd, J = 8.9, 6.3 Hz, 1H), 3.79 (app q, J = 6.0 Hz, 1H), 3.56 (m, 2H), 3.32 (s, 3H), 3.31 (s, 3H), 3.30 (s, 3H), 3.25 (d, J = 14.9 Hz, 1H), 2.98 (d, J = 14.9 Hz, 1H), 2.49 (m, 2H), 2.17 (dddd, J = 12.6, 4.6, 4.5, 1.7, Hz, 1H), 1.99 (app t, J = 2.6 Hz, 1H), 1.78 (d, J = 1.1 Hz, 3H), 1.37 (dd, J = 12.6, 11.1 Hz, 1H), 1.06 (m, 23H); ^{13}C NMR (125 MHz, CDCl_3) δ 158.9, 144.9, 137.7, 134.4, 133.2, 127.5, 127.1, 99.9, 80.8, 80.6, 74.3, 73.5, 71.8, 70.1, 56.8, 55.8, 48.2, 39.3, 36.1, 32.2, 25.9, 18.2, 18.1, 13.8, 12.6; high resolution mass spectrum (ES^+) m/z 732.2795 [$(\text{M}+\text{Na})^+$; calcd for $\text{C}_{32}\text{H}_{50}\text{F}_3\text{NO}_9\text{SSiNa}$: 732.2826].

(-)-11

C(45-46)-Alkenyl Stannane Sidechain (-)-11: To a stirring solution of alkyne (-)-22 (37.0 mg, 0.052 mmol) in acetone (3.5 mL) and 1-hexene (3.5 mL) at room temperature under an argon atmosphere were added quinoline (0.061 mL, 0.520 mmol), and Lindlar's catalyst (5% Pd/ CaCO_3 , poisoned with Pb) (20 mg, 0.010 mmol). Under vigorous stirring, the reaction vessel was fitted with a hydrogen balloon and stirred at room temperature. After three hours, the reaction was quenched with 1N hydrogen chloride solution (5 mL) and allowed to stir for one minute. The biphasic solution was filtered through a pad of Celite, and washed with acetone (10 mL, 3x). The layers of the biphasic mixture were separated and the aqueous layer was extracted with ethyl acetate (10 mL, 3x). The combined organic extracts were dried over

MgSO₄, filtered and concentrated under reduced pressure. Crude C(45-46)-alkene **S**₄ (27 mg, 0.038 mmol) was then combined with hexamethylditin (0.011 mL, 0.053 mmol) in a sealed tube (100 mL), azeotroped from benzene (5 mL, 3x) and dried under vacuum for one hour. In a glove bag under an inert argon atmosphere was added flame dried lithium chloride (25 mg, 0.600 mmol), tetrakis(triphenylphosphine)palladium [Pd(PPh₃)₄] (6 mg, 0.006 mmol) and dioxane (0.5 mL, freeze pump thawed, 3x). The tube was sealed and heated to 90 °C behind a blast shield. After fifteen hours, the reaction was cooled to room temperature and the reaction mixture was introduced directly onto a silica gel column, (15% EtOAc/hexanes) to afford (-)-**11** (26.4 mg, 69%, 2-steps) as a colorless oil. $[\alpha]_D^{20}$ -12.6 (*c* 0.92, CH₂Cl₂); IR (neat) 2935 (s), 2867 (s), 1559 (s), 1457 (s), 1300 (b), 1093 (s), 966 (s), 882 (s), 775 (b) cm⁻¹; ¹HNMR (500 MHz, C₆D₆) δ 7.21 (s, 1H), 6.21 (d, *J* = 15.7 Hz, 1H), 5.90 (m, 1H), 5.54 (dd, *J* = 15.7, 7.7 Hz, 1H), 5.51 (d, *J* = 7.2 Hz, 1H), 5.06 (s, 1H), 5.04 (d, *J* = 2.0 Hz, 1H), 4.72 (dd, *J* = 8.8, 6.3 Hz, 1H), 3.73 (dd, *J* = 10.2, 6.2 Hz, 1H), 3.67 (m, 1H), 3.55 (dd, *J* = 13.6, 6.5 Hz, 1H), 3.44 (d, *J* = 18.2 Hz, 1H), 3.42 (s, 3H), 3.13 (s, 3H), 3.05 (s, 3H), 3.04 (d, *J* = 12.7 Hz, 1H), 2.56 (dd, *J* = 12.7, 3.0 Hz, 1H), 2.43 (m, 1H), 2.28 (m, 1H), 2.12 (d, *J* = 10.0 Hz, 1H), 1.71 (s, 3H), 1.67 (app t, *J* = 12.6 Hz, 1H), 1.30 (app q, *J* = 11.9 Hz, 1H), 1.13 (m, 21 H), 0.24 (s, 9H); ¹³CNMR (125 MHz, C₆D₆) δ 161.7, 145.6, 138.6, 137.2, 135.7, 135.1, 133.5, 130.2, 117.3, 101.1, 82.8, 74.9, 74.4, 73.1, 56.6, 55.8, 48.5, 41.3, 40.7, 36.6, 33.4, 18.8, 18.7, 14.3, 13.4; high resolution mass spectrum (ES⁺) *m/z* 750.3220 [(M+Na)⁺; calcd for C₃₄H₆₁NO₆SiSnNa: 750.3213].

C(45-46)-*E*-Chloroalkene (-)-S₅: To a solution of terminal alkyne (-)-**22** (32 mg, 0.045 mmol) in anhydrous benzene (1.3 mL) at room temperature under an argon atmosphere was added 2,2'-azobis(2-methylpropionitrile) (AIBN) (1 mg, 0.009 mmol) in one portion, followed by the dropwise addition of tri-*n*-butyltinhydride (0.024 mL, 0.09 mmol) and the reaction was heated to 85 °C. After four hours, the reaction was cooled to room temperature, diluted with dichloromethane (3 mL) and concentrated *in vacuo*. The resultant crude vinyl stannane (26 mg, 0.026 mmol), as a colorless oil, was then dissolved in freshly distilled THF (1 mL). Copper(II)chloride (8 mg, 0.057 mmol) was added in one portion and the resultant yellow solution was stirred at room temperature under an argon atmosphere. After fifteen hours, the reaction was quenched via dropwise addition of saturated aqueous sodium bicarbonate (5 mL). The layers of the resultant biphasic mixture were separated and the aqueous layer was extracted with dichloromethane (5 mL, 4x). The combined organic extracts were dried over MgSO₄, filtered and concentrated *in vacuo*. Purification via silica gel chromatography, (25% EtOAc/hexanes) afforded C(45-46)-*E*-chloroalkene (-)-**S**₅ (21.5 mg, 64%, 13:1, *E*:*Z*, 2 steps) as a colorless oil. $[\alpha]_D^{20}$ -31.3 (c 0.41, CHCl₃); IR (neat) 2942 (b), 2864 (s), 1594 (s), 1432 (s), 1231 (s), 1138 (s), 1094 (b), 854 (b); ¹HNMR (500 MHz, CDCl₃) δ 7.60 (s, 1H), 6.17 (d, *J* = 15.7 Hz, 1H), 6.00 (d, *J* = 13.3 Hz, 1H), 5.89 (m, 1H), 5.45 (dd, *J* = 15.7, 7.8 Hz, 1H), 5.42 (d, *J* = 9.4 Hz, 1H), 4.60 (dd, *J* = 8.8, 6.2 Hz, 1H), 3.64 (app q, *J* = 6.5 Hz, 1H), 3.56 (m, 2H), 3.31 (s, 3H), 3.30 (s, 3H), 3.27 (s, 3H), 3.25 (d, *J* = 14.9 Hz, 1H), 2.98 (d, *J* = 14.9 Hz, 1H), 2.37 (m, 1H), 2.27 (m, 1H), 2.17 (dd, *J* = 12.6, 3.5 Hz, 1H), 1.99 (ddd, *J* = 10.0, 4.2, 2.1 Hz, 1H), 1.76 (s,

3H), 1.38 (d, $J = 12.3$ Hz, 1H), 1.36 (d, $J = 11.4$ Hz, 1H), 1.06 (m, 21H); ^{13}C NMR (125 MHz, CDCl_3) δ 159.0, 145.0, 137.4, 134.3, 133.1, 129.8, 128.3, 127.1, 119.1, 99.9, 81.7, 74.3, 73.5, 71.8, 56.5, 55.7, 48.1, 39.3, 37.4, 36.1, 32.2, 18.2, 18.1, 13.8, 12.6; high resolution mass spectrum (ES^+) m/z 769.3469 $[(\text{M}+\text{Na})^+]$; calcd for $\text{C}_{32}\text{H}_{51}\text{F}_3\text{NO}_9\text{SSiClNa}$: 769.3474].

(-)-12

C(45-46)-*E*-Chloroalkenyl Stannane Sidechain (-)-12: C(45-46)-*E*-chloroalkene (-)-**S₅** (0.42 g, 0.059 mmol) was combined with hexamethylditin (0.017 mL, 0.082 mmol) in a sealed tube (100 mL), azeotroped from benzene (5 mL, 3x) and dried for one hour under vacuum. In a glove bag under an inert argon atmosphere was added flame dried lithium chloride (39 mg, 0.941 mmol) followed by tetrakis(triphenylphosphine)palladium $[\text{Pd}(\text{PPh}_3)_4]$ (10 mg, 0.009 mmol) and dioxane (0.6 mL, freeze pump thawed, 3x). The tube was sealed and the reaction mixture heated to 80 °C behind a blast shield. After twelve hours, the reaction was cooled to room temperature and introduced directly onto a silica gel column, (15% EtOAc/hexanes) to afford C(45-46)-*E*-chloroalkene stannane sidechain (-)-**12** (30.5 mg, 68%) as a colorless oil. $[\alpha]_{\text{D}}^{20}$ -28.4 (c 0.32, CH_2Cl_2); IR (neat) 2940 (s), 2863 (s), 1556 (s), 1460 (s), 1378 (b), 1244 (s), 1095 (b), 990 (s), 883 (s), 773 (s), 681 (s); ^1H NMR (500 MHz, C_6D_6) δ 7.21 (s, 1H) 6.12 (d, $J = 15.7$ Hz, 1H), 5.90 (ddd, $J = 13.3, 7.5, 7.4$ Hz, 1H), 5.69 (d, $J = 13.3$ Hz, 1H), 5.51 (d, $J = 8.9$ Hz, 1H), 5.38 (dd, $J = 15.7, 7.8$ Hz, 1H), 4.72 (dd, $J = 8.8, 6.3$ Hz, 1H), 3.74 (m, 1H), 3.66 (m, 1H), 3.45

(d, $J = 14.9$ Hz, 1H), 3.43 (s, 3H), 3.35 (app q, $J = 6.4$ Hz, 1H), 3.06 (s, 3H), 3.03 (s, 3H), 2.56 (dd, $J = 12.7, 3.0$ Hz, 1H), 2.12 (m, 2H), 1.99 (app q, $J = 6.1$ Hz, 1H), 1.68 (s, 3H), 1.30 (dd, $J = 23.6, 11.9$ Hz, 2H), 1.14 (m, 22H), 0.24 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 161.5, 145.4, 137.5, 134.7, 133.8, 130.5, 129.3, 119.5, 100.9, 81.9, 74.7, 74.2, 72.8, 56.4, 55.6, 48.3, 40.5, 37.8, 36.4, 33.2, 18.7, 18.6, 14.1, 13.2, -9.3; high resolution mass spectrum (ES^+) m/z 784.2787 $[(\text{M}+\text{Na})^+]$; calcd for $\text{C}_{34}\text{H}_{60}\text{ClNO}_6\text{SiSnNa}$: 784.2645].

Protected C(45-46)-TMS-Alkynyl-Phorboxazole (+)-25: Vinyl iodide macrocycle (+)-**13** (13.8 mg, 0.017 mmol) and C(45-46)-TMS-alkyne stannane sidechain (-)-**9** (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 was 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. $[\alpha]_D^{20} +1.36$ (c 0.22, CHCl_3); IR (neat)

2925.8 (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].

(-)-26

Protected C(45-46)-Alkyl-Phorboxazole (-)-26: To a flame dried round bottom flask (5 mL), vinyl iodide macrocycle (+)-**13** (10.7 mg, 0.013 mmol) was combined with the C(45-46)-alkyl sidechain (-)-**10** (14.7 mg, 0.020 mmol), azeotroped from benzene (3 mL, 3x) and dried under vacuum. After two hours, under an argon atmosphere, tris(dibenzylideneacetone)dipalladium-chloroform adduct $[\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3]$ (2.8 mg, 0.0027 mmol), triphenylarsine (AsPh_3) (4.9 mg, 0.016 mmol) and $\text{Ph}_2\text{PO}_2\text{NBu}_4$ (9.3 mg, 0.020 mmol) were added followed by anhydrous DMF (0.14 mL, sparged with argon, one hour) and diisopropylethylamine (0.002 mL, 0.014 mmol). After two minutes, the black solution turned light brown and was stirred at room temperature. After sixteen hours, the light brown reaction mixture was purified directly via silica gel chromatography, (25% EtOAc/hexanes) to afford protected C(45-46)-alkyl-phorboxazole (-)-**26** (13.5 mg, 82%) as an off white foam. $[\alpha]_{\text{D}}^{20}$ -7.3 (*c* 0.65, CHCl_3); IR (neat) 2930 (s), 2865 (s), 1717 (s), 1459 (b), 1382 (b), 1188 (s), 1095 (s), 1055 (b), 881 (s), 837 (s); ^1H NMR (500 MHz, C_6D_6) δ 7.14 (s, 1H), 6.95 (s, 1H), 6.89 (m, 1H), 6.36 (s, 1H), 6.24 (d, *J* = 15.7 Hz, 1H), 6.18 (d, *J* = 15.9 Hz, 1H), 5.78 (dd, *J* = 11.1, 2.5 Hz, 1H), 5.57 (dd, *J* = 11.1, 2.5 Hz, 1H), 5.54 (d, *J* = 9.1 Hz, 1H), 5.43 (ddd, *J* = 10.7, 10.7, 2.6 Hz, 1H), 5.19 (s, 1H), 4.95 (d, *J* = 11.2 Hz, 1H), 4.74 (m, 2H), 4.61 (dd, *J* = 15.5, 4.3 Hz, 1H), 4.39 (br s, 1H), 4.24 (app t, *J* = 10.3 Hz, 1H), 4.07 (m, 1H), 4.01 (d, *J* = 2.8 Hz, 1H), 3.96 (m, 1H), 3.77 (dd, *J* = 6.2, 1.7 Hz, 1H), 3.71 (m, 1H), 3.52 (dd, *J* = 12.7, 6.8 Hz, 1H), 3.43 (d, *J* = 12.6 Hz, 1H), 3.41 (s, 3H), 3.39 (m, 2H), 3.35 (d, *J* = 14.8 Hz, 1H), 3.17 (s, 3H), 3.06 (s, 3H), 2.94 (d, *J* = 14.8 Hz, 1H), 2.65 (app t, *J* = 5.7 Hz, 1H), 2.57 (dd, *J* = 12.7, 3.5 Hz, 1H), 2.39 (m, 4H), 2.17 (dd, *J* = 10.1, 7.9 Hz,

1H), 2.08 (s, 3H), 2.04 (m, 2H), 1.97 (app t, $J = 14.2$ Hz, 1H), 1.74 (s, 3H), 1.65 (m, 3H), 1.48 (m, 3H), 1.37 (m, 4H), 1.15 (m, 23H), 1.04 (d, $J = 6.8$ Hz, 3H), 0.92 (s, 9H), 0.89 (app t, $J = 7.3$ Hz, 3H), 0.76 (d, $J = 6.4$ Hz, 3H), 0.01 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 165.9, 161.9, 160.2, 145.8, 144.0, 143.2, 139.4, 138.4, 137.0, 136.9, 135.3, 134.5, 134.0, 133.2, 131.1, 121.6, 120.4, 119.7, 110.7, 101.0, 90.2, 83.0, 80.4, 78.9, 74.9, 74.4, 73.9, 72.9, 70.1, 69.4, 67.9, 66.1, 56.7, 55.8, 48.5, 42.6, 40.7, 40.6, 40.2, 39.0, 38.1, 36.5, 35.1, 33.4, 33.3, 32.6, 31.3, 30.7, 26.6, 26.5, 19.6, 18.9, 18.7, 14.8, 14.3, 13.9, 13.3, 6.8, -4.2, -4.3; high resolution mass spectrum (ES^+) m/z 1253.7355 $[(\text{M}+\text{Na})^+]$; calcd for $\text{C}_{69}\text{H}_{110}\text{N}_2\text{O}_{13}\text{Si}_2\text{Na}$: 1253.7442].

(+)-27

Protected C(45-46)-Alkenyl-Phorbaxazole (+)-27: In a flame dried round bottom flask (5 mL), vinyl iodide macrocycle (+)-**13** (7.0 mg, 0.009 mmol) and C(45-46)-alkenyl sidechain (-)-**11** (9.6 mg, 0.013 mmol) were combined, azeotroped from benzene (3 mL, 3x) and dried under reduced pressure. After one hour, under an inert argon atmosphere, tris(dibenzylideneacetone)dipalladium-chloroform adduct $[\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3]$ (1.8 mg, 0.0017 mmol), triphenylarsine (AsPh_3) (3.2 mg, 0.011 mmol) and $\text{Ph}_2\text{PO}_2\text{NBu}_4$ (6.1 mg, 0.013 mmol) were added followed by anhydrous DMF (0.1 mL, sparged with argon, one hour), and diisopropylethylamine (0.001 mL, 0.009 mmol). After one minute, the black solution turned light brown and was stirred at room temperature. After sixteen hours, the reaction mixture was purified directly

via silica gel chromatography, (20% EtOAc/hexanes) to afford protected C(45-46)-alkenyl-phorboxazole (+)-**27** (8.4 mg, 77%) as an off white foam. $[\alpha]_D^{20} +7.4$ (*c* 0.17, CHCl₃); IR (neat) 2989 (b), 2865 (s), 1721 (s), 1646 (b), 1463 (b), 1384 (b), 1252 (b), 1187 (s), 1098 (s), 1061 (b) cm⁻¹; ¹HNMR (500 MHz, C₆D₆) δ 7.12 (s, 1H), 6.95 (s, 1H), 6.88 (m, 1H), 6.35 (s, 1H), 6.22 (d, *J* = 16.1 Hz, 1H), 6.19 (d, *J* = 17.4 Hz, 1H), 5.91 (m, 1H), 5.78 (d, *J* = 11.2 Hz, 1H), 5.56 (dd, *J* = 15.7, 7.6 Hz, 1H), 5.53 (d, *J* = 7.8 Hz, 1H), 5.45 (app t, *J* = 10.5 Hz, 1H), 5.17 (s, 1H), 5.06 (d, *J* = 12.2 Hz, 1H), 4.94 (d, *J* = 10.1 Hz, 1H), 4.74 (s, 1H), 4.61 (dd, *J* = 11.2, 4.2 Hz, 1H), 4.38 (br s, 1H), 4.25 (app t, *J* = 10.6 Hz, 1H), 4.06 (br s, 1H), 4.02 (s, 1H), 3.94 (m, 1H), 3.75 (m, 1H), 3.69 (m, 1H), 3.57 (app q, *J* = 6.6 Hz, 1H), 3.44 (d, *J* = 10.0 Hz, 1H), 3.41 (s, 3H), 3.34 (d, *J* = 14.8 Hz, 1H), 3.14 (s, 3H), 3.07 (s, 3H), 3.06 (m, 1H), 2.95 (d, *J* = 14.8 Hz, 1H), 2.65 (br s, 1H), 2.56 (d, *J* = 12.4 Hz, 1H), 2.41 (m, 5H), 2.30 (m, 2H), 2.16 (d, *J* = 10.1 Hz, 2H), 2.08 (s, 3H), 1.74 (s, 3H), 1.64 (m, 4H), 1.48 (d, *J* = 13.6 Hz, 1H), 1.34 (m, 6H), 1.17 (m, 22H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.93 (s, 9H), 0.76 (d, *J* = 6.4 Hz, 3H), 0.01 (s, 3H), -0.01 (s, 3H); ¹³CNMR (125 MHz, C₆D₆) δ 165.8, 161.7, 160.0, 145.5, 143.8, 143.0, 139.2, 138.2, 136.9, 136.8, 135.5, 135.0, 134.5, 133.8, 133.2, 130.1, 121.4, 120.1, 119.5, 117.2, 110.5, 100.9, 90.0, 82.6, 80.3, 78.8, 74.7, 74.2, 73.8, 72.8, 69.9, 69.3, 67.7, 65.9, 56.4, 55.6, 48.3, 42.4, 41.1, 40.5, 40.5, 40.0, 37.9, 36.4, 36.3, 34.9, 33.1, 32.4, 31.2, 30.5, 26.3, 18.7, 18.6, 14.6, 14.1, 13.7, 13.2, 6.6, -4.4, -4.5; high resolution mass spectrum (ES⁺) *m/z* 1251.7268 [(M+Na)⁺; calcd for C₆₉H₁₀₈N₂O₁₃Si₂Na: 1251.7286].

(+)-28

Protected C(45-46)-*E*-Chloroalkenyl-Phorboxazole (+)-28: In a round bottom flask (5 mL), vinyl iodide macrocycle (+)-**13** (11.4 mg, 0.014 mmol) and C(45-46)-*E*-chloroalkene sidechain (-)-**12** (16.4 mg, 0.021 mmol) were combined, azeotroped from benzene (3 mL, 3x) and dried under vacuum. After one hour, under an inert argon atmosphere, tris(dibenzylideneacetone)dipalladium-chloroform adduct $[\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3]$ (2.9 mg, 0.0028 mmol), triphenylarsine (AsPh_3) (5.3 mg, 0.017 mmol) and $\text{Ph}_2\text{PO}_2\text{NBu}_4$ (9.9 mg, 0.021 mmol) were added followed by anhydrous DMF (0.14 mL, sparged with argon, one hour), and diisopropylethylamine (0.002 mL, 0.014 mmol). After one minute, the black solution turned light brown and was allowed to stir at room temperature. After seventeen hours, the light brown solution was purified directly via silica gel chromatography (20% EtOAc/hexanes $\rightarrow$ 25% EtOAc/hexanes) to afford protected C(45-46)-*E*-chloroalkenyl-phorboxazole (+)-**28** (15.8 mg, 87%) as an off white foam. $[\alpha]_D^{20} +14.3$ (c 0.37, CHCl_3); IR (neat) 2933 (s), 2866 (s), 1716 (s), 1644 (b), 1461 (b), 1370 (b), 1254 (s), 1187 (s), 1153 (s), 1096 (s), 1043 (b), 879 (s), 836 (s), 807 (b) cm^{-1} ; ^1H NMR (500 MHz, C_6D_6) δ 7.15 (s, 1H), 6.96 (s, 1H), 6.87 (m, 1H), 6.35 (s, 1H), 6.19 (d, $J = 15.8$ Hz, 1H), 6.14 (d, $J = 15.8$ Hz, 1H), 5.91 (m, 1H), 5.79 (dd, $J = 11.5, 2.9$ Hz, 1H), 5.70 (d, $J = 13.3$ Hz, 1H), 5.53 (d, $J = 8.6$ Hz, 1H), 5.45 (ddd, $J = 10.6, 10.6, 2.8$ Hz, 1H), 5.41 (dd, $J = 15.7, 7.7$ Hz, 1H), 5.17 (s, 1H), 4.94 (d, $J = 11.2$ Hz, 1H), 4.73 (m, 2H), 4.61 (dd, $J = 11.2, 4.4$ Hz, 1H), 4.38 (br s, 1H), 4.24 (app t, $J = 10.7$ Hz, 1H), 4.06 (m, 1H), 4.02 (s, 1H), 3.94 (m, 1H), 3.77 (dd, $J = 6.1, 1.9$ Hz, 1H), 3.69 (m, 1H), 3.43 (d, $J = 10.0$ Hz, 1H), 3.40 (s, 3H), 3.37 (d, $J = 6.7$ Hz, 1H), 3.33 (d, $J = 14.8$ Hz, 1H), 3.07 (s, 3H), 3.04 (s, 3H), 2.94 (d, $J = 14.8$ Hz, 1H), 2.64 (app

t, $J = 5.8$ Hz, 1H), 2.56 (dd, $J = 13.0, 4.4$ Hz, 1H), 2.39 (m, 3H), 2.13 (m, 2H), 2.08 (s, 3H), 2.00 (m, 3H), 1.70 (s, 3H), 1.63 (m, 2H), 1.48 (d, $J = 13.2$ Hz, 1H), 1.32 (m, 5H), 1.14 (m, 25H), 1.03 (d, $J = 6.8$ Hz, 3H), 0.92 (s, 9H), 0.76 (d, $J = 6.4$ Hz, 3H), 0.01 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 165.9, 161.8, 160.2, 145.8, 144.0, 143.2, 139.4, 138.4, 137.7, 136.9, 134.9, 134.5, 134.0, 133.9, 130.7, 121.6, 120.4, 120.1, 119.7, 119.6, 110.7, 101.0, 90.2, 82.1, 81.6, 80.4, 78.9, 74.9, 74.3, 73.9, 72.9, 70.1, 69.4, 67.9, 66.1, 56.6, 55.8, 48.5, 42.6, 40.7, 40.6, 40.1, 38.1, 38.0, 36.5, 35.1, 33.3, 32.6, 31.3, 30.7, 26.5, 18.9, 18.7, 14.8, 14.2, 13.9, 13.3, 6.8, -4.2, -4.3; high resolution mass spectrum (ES^+) m/z 1285.7001 [$(\text{M}+\text{Na})^+$; calcd for $\text{C}_{69}\text{H}_{107}\text{ClN}_2\text{O}_{13}\text{Si}_2\text{Na}$: 1285.6997].

(+)-29

Protected *E*-C(2-3)-C(45-46)-Alkynyl-Phorboxazole (+)-29: In a flame dried round bottom flask (5 mL), *E*-C(2-3)-vinyl iodide macrocycle (+)-**23** (9.1 mg, 0.012 mmol) was combined with C(45-46)-TMS-alkynyl sidechain (-)-**9** (13.7 mg, 0.017 mmol), azeotroped from benzene (2 mL, 3x) and dried under vacuum. After one hour, under an inert argon atmosphere, tris(dibenzylideneacetone)dipalladium-chloroform adduct [$\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$] (2.4 mg, 0.0023 mmol), triphenylarsine (AsPh_3) (4.2 mg, 0.014 mmol) and $\text{Ph}_2\text{PO}_2\text{NBu}_4$ (8 mg, 0.017 mmol) were added followed by anhydrous DMF (0.12 mL, sparged with argon, one hour), and diisopropylethylamine (0.002 mL, 0.011 mmol). After one minute, the black solution turned light brown and the reaction was stirred at room temperature. After twenty hours, the reaction mixture

was purified directly via silica gel chromatography, (20% EtOAc/hexanes → 30% EtOAc/hexanes) to afford protected *E*-C(2-3)-C(45-46)-alkynyl-phorboxazole (+)-**29** (9.7 mg, 66%) as an off white foam. $[\alpha]_D^{20} +10.6$ (c 0.31, CHCl₃); IR (neat) 2936 (b), 1718 (s), 1653 (s), 1464 (b), 1351 (b), 1250 (s), 1151 (s), 1087 (s), 843 (s) cm⁻¹; ¹HNMR (500 MHz, C₆D₆) δ 7.13 (s, 1H), 6.92 (s, 1H), 6.89 (m, 1H), 6.30 (d, *J* = 15.7 Hz, 1H), 6.27 (s, 1H), 6.14 (d, *J* = 16.0 Hz, 1H), 6.04 (d, *J* = 15.2 Hz, 1H), 5.67 (dd, *J* = 15.7, 7.3 Hz, 1H), 5.55 (d, *J* = 8.9 Hz, 1H), 5.08 (dd, *J* = 10.8, 3.7 Hz, 1H), 4.95 (d, *J* = 11.7 Hz, 1H), 4.75 (dd, *J* = 8.7, 6.1 Hz, 1H), 4.68 (s, 1H), 4.59 (s, 1H), 4.34 (br s, 1H), 4.00 (s, 1H), 3.92 (br s, 1H), 3.75 (dd, *J* = 11.7, 6.1 Hz, 1H), 3.68 (m, 2H), 3.42 (m, 3H), 3.39 (s, 3H), 3.37 (d, *J* = 9.8 Hz, 1H), 3.31 (d, *J* = 14.9 Hz, 1H), 3.08 (s, 3H), 3.07 (s, 3H), 2.92 (d, *J* = 14.7 Hz, 1H), 2.83 (br s, 1H), 2.57 (dd, *J* = 16.7, 5.7 Hz, 1H), 2.56 (m, 1H), 2.47 (br s, 1H), 2.43 (dd, *J* = 16.8, 6.8 Hz, 1H), 2.26 (m, 2H), 2.13 (m, 4H), 2.05 (s, 3H), 1.90 (d, *J* = 12.6 Hz, 1H), 1.82 (d, *J* = 13.6 Hz, 1H), 1.75 (s, 3H), 1.67 (m, 5H), 1.33 (m, 4H), 1.15 (m, 21H), 0.96 (s, 9H), 0.84 (app t, *J* = 7.4 Hz, 6H), 0.23 (s, 9H), 0.00 (s, 3H), -0.01 (s, 3H); ¹³CNMR (125 MHz, C₆D₆) δ 167.5, 162.6, 160.1, 147.5, 143.8, 142.8, 139.5, 138.5, 137.5, 136.9, 135.2, 134.5, 134.1, 133.8, 132.4, 130.1, 128.0, 124.3, 119.4, 119.1, 111.4, 104.8, 101.0, 86.9, 81.2, 79.3, 77.3, 74.9, 74.3, 72.9, 71.0, 66.4, 66.2, 59.2, 59.1, 56.9, 55.8, 48.4, 41.3, 40.6, 40.4, 38.8, 38.6, 38.4, 36.5, 35.6, 33.2, 30.7, 28.0, 26.5, 24.6, 20.5, 19.0, 18.9, 18.8, 14.7, 14.4, 14.3, 13.4, 0.84, -4.2; high resolution mass spectrum (ES⁺) *m/z* 1321.7463 [(M+Na)⁺; calcd for C₇₂H₁₁₄N₂O₁₃Si₃: 1321.7524].

Protected C(45-46)-Alkenyl-C(22-26)-Central Tetrahydropyran (-)-30: To a flame dried round bottom flask (5 mL), C(22-26)-central tetrahydropyran (+)-**24** (12.1 mg, 0.016 mmol) was combined with C(45-46)-alkenyl sidechain (-)-**11** (18.0 mg, 0.025 mmol), azeotroped from benzene (2 mL, 3x) and dried under vacuum. After one hour, under an argon atmosphere, tris(dibenzylideneacetone)dipalladium-chloroform adduct $[\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3]$ (3.4 mg, 0.0033 mmol), triphenylarsine (AsPh_3) (6.1 mg, 0.020 mmol) and $\text{Ph}_2\text{PO}_2\text{NBu}_4$ (11.4 mg, 0.025 mmol) were added followed by anhydrous DMF (0.17 mL, sparged with argon, one hour), and diisopropylethylamine (0.003 mL, 0.016 mmol). After one minute, the black solution turned light brown and was allowed to stir at room temperature. After twenty hours, the reaction mixture was purified directly via silica gel chromatography (10% EtOAc/hexanes $\rightarrow$ 30% EtOAc/hexanes) to afford protected C(45-46)-alkenyl-C(22-26)-central tetrahydropyran phorbolboxazole (-)-**30** (12.9 mg, 69%) as a white foam. $[\alpha]_D^{20}$ -2.3 (*c* 0.064, CHCl_3); IR (neat) 2940 (b), 2863 (s), 1585 (b), 1513 (s), 1460 (s), 1383 (b), 1263 (b), 1100 (b), 801 (b), 701 (s) cm^{-1} ; ^1H NMR (500 MHz, C_6D_6) δ 7.81 (m, 3H), 7.28 (m, 2H), 7.25 (m, 2H), 7.14 (s, 1H), 6.97 (d, J = 1.8 Hz, 1H), 6.92 (dd, J = 8.1, 1.8 Hz, 1H), 6.7 (d, J = 8.1 Hz, 1H), 6.38 (s, 1H), 6.22 (d, J = 15.7 Hz, 1H), 5.90 (m, 1H), 5.56 (dd, J = 15.7, 7.7 Hz, 1H), 5.53 (d, J = 8.7 Hz, 1H), 5.07 (d, J = 13.5 Hz, 1H), 5.04 (d, J = 13.9 Hz, 1H), 4.73 (dd, J = 8.8, 6.2 Hz, 1H), 4.53 (d, J = 11.4 Hz, 1H), 4.21 (d, J = 11.4 Hz, 1H), 3.97 (m, 1H), 3.84 (m, 1H), 3.75 (m, 2H), 3.69 (m, 1H), 3.56 (app q, J = 6.5 Hz, 1H), 3.51 (s, 3H), 3.47 (d, J = 10.2 Hz, 1H), 3.45 (s, 3H), 3.40 (s, 3H), 3.34 (d, J = 14.8 Hz, 1H), 3.16 (dd, J = 10.3, 4.6 Hz, 1H), 3.13 (s, 3H), 3.06 (s, 3H), 2.93 (d, J = 14.8 Hz, 1H), 2.57 (dd, J = 12.7, 3.2 Hz, 1H), 2.44 (m, 1H), 2.49 (m, 1H), 2.15 (ddd, J = 10.2, 4.4, 2.0 Hz, 1H), 2.07 (s, 3H), 1.99 (m,

3H), 1.74 (m, 1H), 1.73 (s, 3H), 1.65 (dd, $J = 12.6, 11.0$ Hz, 1H), 1.33 (m, 2H), 1.21 (s, 9H), 1.15 (m, 23H), 1.10 (d, $J = 6.4$ Hz, 3H), 0.96 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 160.1, 150.9, 150.4, 139.6, 139.2, 137.1, 136.8, 136.6, 136.5, 135.6, 135.2, 134.9, 134.9, 133.4, 132.7, 130.6, 130.3, 120.8, 119.3, 117.3, 113.0, 112.9, 101.1, 90.1, 84.4, 82.8, 75.5, 74.9, 74.3, 72.9, 70.4, 61.8, 56.6, 56.3, 56.2, 55.8, 48.5, 51.3, 40.7, 37.1, 36.5, 35.6, 34.4, 33.3, 27.7, 20.1, 18.9, 18.8, 14.8, 14.5, 14.3, 13.3, 3.6; high resolution mass spectrum (ES^+) m/z 1186.6799 $[(\text{M}+\text{Na})^+]$; calcd for $\text{C}_{68}\text{H}_{101}\text{NO}_{11}\text{Si}_2\text{Na}$: 1186.6809].

C(45-46)-Alkynyl-Phorboxazole (+)-3: Fully protected C(45-46)-alkynyl-phorboxazole (+)-**25** (3.8 mg, 0.003 mmol) was introduced into a flame dried round bottom flask, azeotroped from benzene (2 mL, 3x) and dried under vacuum. After one hour, (+)-**25**, under an argon atmosphere was dissolved in freshly distilled THF (0.7 mL) and cooled to 0 °C. After five minutes, tetrabutylammonium fluoride (1.0 M/THF) (0.009 mL, 0.009 mmol) was added dropwise. After one hour, the reaction was quenched via dropwise addition of saturated aqueous sodium chloride (1 mL) and allowed to stir for thirty seconds. The layers of the biphasic mixture were separated and the aqueous layer extracted with ethyl acetate (4 mL, 4x). The combined organic extracts were dried over MgSO_4 , filtered and concentrated under reduced pressure. The resultant crude amorphous solid, under an inert argon atmosphere was then dissolved in freshly distilled THF (2.1 mL) followed by dropwise addition of 6% hydrogen chloride solution (0.82 mL). After

thirty six hours at room temperature, the reaction was cooled to 0 °C, poured into saturated aqueous sodium bicarbonate (3 mL), extracted with dichloromethane (3 mL, 3x) followed by extraction with ethyl acetate (3 mL, 2x). The combined organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. Purification via silica gel chromatography, (100% EtOAc → 10% CH₃OH/EtOAc) afforded C(45-46)-alkynyl-phorboxazole (+)-**3** (1.7 mg, 64%) as a white amorphous solid. $[\alpha]_D^{20} +64.1$ (*c* 0.64, CH₂Cl₂); IR (neat) 3431 (b), 2920 (s), 1643 (b), 1189 (s), 1091 (s); ¹HNMR (500 MHz, C₆D₆) δ 7.03 (s, 1H), 6.90 (s, 1H), 6.86 (m, 1H), 6.23 (d, *J* = 15.7 Hz, 1H), 6.21 (d, *J* = 15.8 Hz, 1H), 6.20 (s, 1H), 5.79 (dd, *J* = 11.2, 2.3 Hz, 1H), 5.59 (dd, *J* = 15.7, 7.5 Hz, 1H), 5.56 (d, *J* = 9.9 Hz, 1H), 5.46 (ddd, *J* = 13.1, 13.1, 2.7 Hz, 1H), 5.38 (s, 1H), 5.22 (s, 1H), 4.78 (d, *J* = 9.4 Hz, 1H), 4.77 (s, 1H), 4.61 (dd, *J* = 11.2, 4.4 Hz, 1H), 4.35 (app t, *J* = 6.8 Hz, 1H), 4.02 (m, 2H), 3.92 (m, 2H), 3.77 (m, 2H), 3.64 (app q, *J* = 6.3 Hz, 1H), 3.42 (m, 1H), 3.40 (d, *J* = 10.1 Hz, 1H), 3.11 (d, *J* = 13.8 Hz, 1H), 3.09 (s, 3H), 3.07 (s, 3H), 2.97 (d, *J* = 11.0 Hz, 1H), 2.84 (d, *J* = 15.4 Hz, 1H), 2.69 (d, *J* = 15.4 Hz, 1H), 2.63 (m, 1H), 2.41 (m, 5H), 2.29 (m, 2H), 2.03 (m, 4H), 1.94 (s, 3H), 1.66 (d, *J* = 0.9 Hz, 3H), 1.51 (m, 4H), 1.29 (m, 7H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.74 (d, *J* = 6.5 Hz, 3H); ¹³CNMR (125 MHz, C₆D₆) δ 165.8, 161.7, 145.7, 143.8, 143.1, 139.1, 137.8, 137.2, 136.3, 134.4, 133.8, 131.9, 127.9, 121.4, 120.2, 118.7, 110.4, 97.2, 89.7, 81.3, 81.0, 80.1, 78.8,, 73.8, 73.3, 71.4, 70.7, 69.9, 69.1, 67.5, 64.7, 56.6, 55.7, 42.3, 41.5, 40.2, 40.1, 39.6, 37.9, 35.5, 34.9, 33.9, 33.1, 32.4, 32.0, 31.2, 30.5, 30.1, 26.6, 23.4, 14.7, 13.7, 6.6; high resolution mass spectrum (ES⁺) *m/z* 965.4766 [(M+Na)⁺; calcd for C₅₃H₇₀N₂O₁₃: 965.4776].

C(45-46)-Alkyl-Phorboxazole (-)-4: Fully protected C(45-46)-alkyl-phorboxazole (-)-**26** (13.1 mg, 0.010 mmol) was introduced into a flame dried round bottom flask, azeotroped from benzene (3 mL, 3x) and dried under vacuum. After one hour, under an argon atmosphere, (-)-**26** was dissolved in freshly distilled THF (2.7 mL) and cooled to 0 °C. Tetrabutylammonium fluoride (1.0 M/THF) (0.030 mL, 0.030 mmol) was then added dropwise and after one hour, the reaction was quenched via dropwise addition of saturated aqueous sodium chloride (2 mL) and the layers of the biphasic mixture were separated. The aqueous layer was extracted with ethyl acetate (3 mL, 4x) and the combined organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. At room temperature under an argon atmosphere, the resultant amorphous solid was dissolved in freshly distilled THF (7.4 mL) followed by dropwise addition of 6% hydrogen chloride solution (2.9 mL). After thirty seven hours, the reaction mixture was cooled to 0 °C, stirred for five minutes and poured into saturated aqueous sodium bicarbonate (5 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (5 mL, 4x) followed by extraction with ethyl acetate (5 mL, 2x). The combined organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. Purification via silica gel chromatography (100% EtOAc → 10% CH₃OH/EtOAc) afforded C(45-46)-alkyl-phorboxazole (-)-**4** (8.1 mg, 86%) as an off white amorphous solid. $[\alpha]_D^{20}$ -51.0 (c 0.19, CH₂Cl₂); IR (neat) 3401 (b), 2921 (b), 1715 (s), 1451 (b), 1374 (b), 1186 (s), 1157 (s), 1090 (s); ¹HNMR (500 MHz, C₆D₆) δ 7.02 (s, 1H), 6.91 (s, 1H), 6.87 (m, 1H), 6.23 (d, *J* = 15.8 Hz, 1H), 6.22 (s, 1H), 6.21 (d, *J* = 15.6 Hz, 1H), 5.79 (dd, *J* = 11.4, 2.7

Hz, 1H), 5.58 (d, J = 10.1 Hz, 1H), 5.53 (dd, J = 7.8, 4.1 Hz, 1H), 5.44 (ddd, J = 10.8, 10.7, 2.6 Hz, 1H), 5.25 (s, 1H), 4.81 (dd, J = 11.2, 2.1 Hz, 1H), 4.78 (s, 1H), 4.61 (dd, J = 11.2, 4.4 Hz, 1H), 4.38 (dd, J = 15.7, 7.2 Hz, 1H), 4.35 (br s, 1H), 4.08 (m, 2H), 3.97 (m, 2H), 3.79 (m, 2H), 3.52 (dd, J = 12.5, 6.1 Hz, 1H), 3.41 (m, 2H), 3.18 (s, 3H), 3.14 (m, 1H), 3.10 (dd, J = 5.9, 2.2 Hz, 1H), 3.07 (s, 3H), 3.01 (d, J = 10.6 Hz, 1H), 2.86 (d, J = 15.3 Hz, 1H), 2.74 (d, J = 15.3 Hz, 1H), 2.65 (br s, 1H), 2.42 (m, 4H), 2.30 (dd, J = 13.0, 5.4 Hz, 1H), 2.02 (m, 5H), 1.93 (s, 3H), 1.80 (m, 1H), 1.68 (d, J = 0.8 Hz, 3H), 1.56 (m, 5H), 1.42 (m, 2H), 1.29 (m, 4H), 1.04 (d, J = 6.8 Hz, 3H), 0.90 (app t, J = 5.8 Hz, 3H), 0.74 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 165.9, 161.8, 161.3, 145.9, 143.9, 143.3, 139.2, 138.6, 137.7, 137.1, 136.5, 134.5, 134.0, 131.4, 131.3, 128.0, 127.9, 121.5, 120.4, 118.9, 110.7, 97.4, 89.9, 83.0, 80.3, 79.0, 73.9, 73.5, 71.6, 70.1, 69.3, 67.7, 64.8, 56.6, 55.8, 42.5, 41.6, 40.4, 40.2, 39.8, 39.1, 38.1, 35.6, 35.1, 34.1, 33.3, 32.6, 31.3, 19.6, 14.9, 14.0, 13.9, 6.8; high resolution mass spectrum (ES^+) m/z 969.5174 [$(\text{M}+\text{Na})^+$; calcd for $\text{C}_{53}\text{H}_{74}\text{N}_2\text{O}_{13}\text{Na}$: 969.5189].

C(45-46)-Alkenyl-Phorbboxazole (+)-5: Fully protected C(45-46)-alkenyl-phorbboxazole (+)-27 (3.8 mg, 0.003 mmol) was introduced into a flame dried round bottom flask, azeotroped from benzene (3 mL, 3x) and dried under vacuum. After one hour, under an argon atmosphere, (+)-27 was dissolved in freshly distilled THF (1 mL), cooled to 0 °C and tetrabutylammonium fluoride (1.0 M/THF) (0.009 mL, 0.009

mmol) was added dropwise. After one hour, the reaction was quenched via dropwise addition of saturated aqueous sodium chloride (2 mL) and the layers of the biphasic mixture were separated. The aqueous layer was extracted with ethyl acetate (3 mL, 4x) and the combined organic extracts were dried over MgSO_4 , filtered and concentrated under reduced pressure. At room temperature under an argon atmosphere, the resultant amorphous solid was dissolved in freshly distilled THF (5 mL) followed by dropwise addition of 6% hydrogen chloride solution (2.0 mL). After thirty seven hours, the reaction mixture was cooled to 0 °C, stirred for five minutes and poured into saturated aqueous sodium bicarbonate (5 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (5 mL, 4x) followed by extraction with ethyl acetate (5 mL, 2x). The combined organic extracts were dried over MgSO_4 , filtered and concentrated under reduced pressure. Purification via silica gel chromatography, (100% EtOAc $\rightarrow$ 10% $\text{CH}_3\text{OH}/\text{EtOAc}$) afforded C(45-46)-alkenyl-phorboxazole (+)-**5** (1.9 mg, 67%) as an off white amorphous solid. $[\alpha]_{\text{D}}^{20} +49.7$ (c 0.51, CH_2Cl_2); IR (neat) 3404 (b), 2927 (b), 1716 (s), 1661 (b), 1441 (b), 1372 (b), 1188 (s), 1161 (s), 1092 (s); ^1H NMR (500 MHz, C_6D_6) δ 7.02 (s, 1H), 6.89 (s, 1H), 6.85 (m, 1H), 6.21 (d, $J = 12.7$ Hz, 1H), 6.20 (s, 1H), 6.18 (d, $J = 15.8$ Hz, 1H), 5.93 (m, 1H), 5.79 (dd, $J = 11.2, 2.4$ Hz, 1H), 5.55 (d, $J = 8.6$ Hz, 1H), 5.53 (dd, $J = 15.7, 7.6$ Hz, 1H), 5.45 (app t, $J = 10.4$ Hz, 1H), 5.23 (s, 1H), 5.07 (s, 1H), 5.06 (d, $J = 10.1$ Hz, 1H), 4.79 (d, $J = 8.8$ Hz, 1H), 4.78 (s, 1H), 4.61 (dd, $J = 11.1, 4.4$ Hz, 1H), 4.37 (m, 2H), 4.06 (m, 2H), 3.93 (m, 2H), 3.78 (m, 2H), 3.56 (app q, $J = 6.4$ Hz, 1H), 3.41 (m, 1H), 3.39 (d, $J = 9.9$ Hz, 1H), 3.14 (s, 3H), 3.13 (m, 1H), 3.07 (s, 3H), 2.99 (d, $J = 11.5$ Hz, 1H), 2.83 (d, $J = 15.3$ Hz, 1H), 2.69 (d, $J = 15.4$ Hz, 1H), 2.65 (app t, $J = 6.5$ Hz, 1H), 2.40 (m, 4H), 2.27 (m, 2H), 2.04 (m, 2H), 1.98 (d, $J = 12.3$ Hz, 2H), 1.93 (s, 3H), 1.67 (d, $J = 0.8$ Hz, 3H), 1.49 (m, 5H), 1.28 (m, 6H), 1.04 (d, $J = 6.9$ Hz, 3H), 0.73 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 165.8, 161.7, 161.2, 145.7, 143.7, 143.1, 139.0, 138.4, 137.4, 137.2, 136.3, 135.5, 134.3, 133.8, 131.4, 130.4, 130.3, 121.3, 120.2, 118.7, 117.2, 110.5, 97.3, 89.7, 82.6, 80.1, 78.8, 73.7, 73.3, 71.4, 69.9, 69.1, 67.5, 64.7, 56.4, 55.7, 42.3, 41.4, 41.3, 40.2, 40.0, 39.6, 37.9, 35.5, 34.9, 33.9, 33.1, 32.4, 31.2, 14.7, 13.8, 13.7, 6.6; high resolution mass spectrum (ES^+) m/z 967.4971 $[(\text{M}+\text{Na})^+]$; calcd for $\text{C}_{53}\text{H}_{72}\text{N}_2\text{O}_{13}\text{Na}$: 967.4931].

C(45-46)-*E*-Chloroalkenyl-Phorboxazole (+)-6: Fully protected C(45-46)-*E*-chloroalkenyl-phorboxazole (+)-**28** (8.2 mg, 0.006 mmol) was introduced into a flame dried round bottom flask, azeotroped from benzene (3 mL, 3x) and dried under vacuum. After one hour, under an inert argon atmosphere, (+)-**28** was dissolved in freshly distilled THF (5.3 mL), cooled to 0 °C and tetrabutylammonium fluoride (1.0 M/THF) (0.018 mL, 0.018 mmol) was added dropwise. After one hour, the reaction was quenched via dropwise addition of saturated aqueous sodium chloride (5 mL) and allowed to stir for one minute. The layers of the biphasic mixture were separated and the aqueous layer extracted with ethyl acetate (5 mL, 4x). The combined organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. The resultant off white amorphous solid, under an argon atmosphere was dissolved in freshly distilled THF (7.4 mL) followed by dropwise addition of 6% hydrogen chloride solution (2.9 mL). After stirring for thirty six hours at room temperature, the reaction was cooled to 0 °C and poured into saturated aqueous sodium bicarbonate (5 mL). The resultant layers were separated and the aqueous layer extracted with dichloromethane (5 mL, 4x) followed by ethyl acetate (5 mL, 2x). The combined organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. Purification via silica gel chromatography, (100% EtOAc → 10% CH₃OH/EtOAc) afforded C(45-46)-*E*-chloroalkenyl-phorboxazole (+)-**6** (3.8 mg, 61%) as a white amorphous solid. $[\alpha]_D^{20} +47.8$ (c 0.39, CH₂Cl₂); IR (neat) 3411 (b), 2926 (s), 1720 (s), 1647 (b), 1443 (b), 1375 (b), 1186 (s), 1156 (s), 1088 (s), 991 (b); ¹HNMR

(500 MHz, C₆D₆) δ 7.04 (s, 1H), 6.91 (s, 1H), 6.87 (m, 1H), 6.22 (d, J = 15.7 Hz, 1H), 6.21 (s, 1H), 6.10 (d, J = 15.7 Hz, 1H), 5.98 (m, 1H), 5.80 (dd, J = 11.0, 2.9 Hz, 1H), 5.74 (d, J = 13.3 Hz, 1H), 5.55 (d, J = 8.8 Hz, 1H), 5.45 (ddd, J = 12.7, 12.6, 1.2 Hz, 1H), 5.37 (dd, J = 15.7, 7.8 Hz, 1H), 5.24 (s, 1H), 4.81 (d, J = 11.1 Hz, 1H), 4.78 (s, 1H), 4.61 (dd, J = 11.1, 4.3 Hz, 1H), 4.37 (m, 2H), 4.08 (m, 2H), 3.96 (m, 2H), 3.80 (m, 2H), 3.41 (m, 1H), 3.39 (d, J = 9.9 Hz, 1H), 3.36 (app q, J = 7.3 Hz, 1H), 3.08 (s, 3H), 3.04 (s, 3H), 3.00 (dd, J = 11.1, 0.9 Hz, 1H), 2.86 (d, J = 15.3 Hz, 1H), 2.74 (d, J = 15.3 Hz, 1H), 2.65 (app t, J = 5.2 Hz, 1H), 2.42 (m, 4H), 2.30 (dd, J = 12.1, 4.3 Hz, 1H), 2.11 (m, 1H), 2.01 (m, 6H), 1.92 (d, J = 0.5 Hz, 3H), 1.63 (d, J = 0.9 Hz, 3H), 1.54 (m, 4H), 1.29 (m, 6H), 1.05 (d, J = 6.8 Hz, 3H), 0.73 (d, J = 6.4 Hz, 3H); ¹³CNMR (125 MHz, C₆D₆) δ 165.1, 161.0, 160.5, 145.1, 143.1, 142.4, 138.4, 137.7, 136.6, 135.6, 133.6, 133.2, 131.2, 129.9, 127.2, 120.7, 119.6, 119.2, 118.1, 109.8, 96.6, 89.1, 81.1, 79.4, 78.1, 73.1, 72.6, 70.7, 69.3, 68.5, 66.9, 64.0, 55.7, 55.0, 41.6, 40.7, 39.5, 39.4, 39.0, 37.4, 37.3, 34.8, 34.3, 33.6, 33.2, 32.4, 31.7, 30.5, 14.1, 14.0, 13.1, 6.0; high resolution mass spectrum (ES⁺) m/z 1002.5813 [(M+Na)⁺ calcd for C₅₃H₇₁ClN₂O₁₃Na: 1002.5801].

***E*-C(2-3)-C(45-46)-Alkynyl-Phorboxazole (+)-7:** Fully protected *E*-C(2-3)-C(45-46)-alkynyl-phorboxazole (+)-**29** (6.8 mg, 0.005 mmol) was introduced into a flame dried round bottom flask, azeotroped from benzene (3 mL, 3x) and dried under vacuum. After one hour, under an inert argon

atmosphere, (+)-**29** was dissolved in freshly distilled THF (1.3 mL) followed by dropwise introduction of tetrabutylammonium fluoride (1.0 M/THF) (0.015 mL, 0.015 mmol). After one hour, the reaction was quenched via dropwise addition of saturated aqueous sodium chloride (2 mL). After stirring for one minute at 0 °C, the layers of the biphasic mixture were separated and the aqueous phase was extracted with ethyl acetate (5 mL, 4x). The combined organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. The resultant amorphous solid, under an inert argon atmosphere was dissolved in freshly distilled THF (4.7 mL) followed by dropwise introduction of 6% hydrogen chloride solution (1.9 mL) and allowed to stir at room temperature. After thirty six hours, the reaction was cooled to 0 °C and poured into saturated aqueous sodium bicarbonate (5 mL). The biphasic mixture was separated and the aqueous layer was extracted with dichloromethane (5 mL, 4x) followed by extraction with ethyl acetate (5 mL, 2x). The combined organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. Purification via silica gel chromatography, 100% EtOAc → 10% CH₃OH/EtOAc afforded *E*-C(2-3)-C(45-46)-alkynyl-phroboxazole (+)-**7** (3.3 mg, 69%) as an off white amorphous solid. $[\alpha]_D^{20} +51.6$ (c 0.31, CH₂Cl₂); IR (neat) 3431 (b), 2924 (s), 1695 (s), 1195 (b), 993 (s); ¹HNMR (500 MHz, C₆D₆) δ 7.00 (s, 1H), 6.93 (s, 1H), 6.86 (m, 1H), 6.23 (d, *J* = 15.7 Hz, 1H), 6.15 (d, *J* = 14.5 Hz, 1H), 6.13 (s, 1H), 6.05 (d, *J* = 15.1 Hz, 1H), 5.59 (dd, *J* = 15.6, 7.5 Hz, 1H), 5.56 (d, *J* = 8.9 Hz, 1H), 5.47 (s, 1H), 5.07 (dd, *J* = 10.8, 3.8 Hz, 1H), 4.82 (dd, *J* = 11.7, 2.1 Hz, 1H), 4.7 (s, 1H), 4.62 (s, 1H), 4.35 (app t, *J* = 7.3 Hz, 1H), 4.31 (br s, 1H), 3.97 (dd, *J* = 10.4, 7.6 Hz, 1H), 3.83 (m, 3H), 3.63 (app q, *J* = 6.7 Hz, 1H), 3.45 (br s, 1H), 3.37 (m, 1H), 3.34 (d, *J* = 10.0 Hz, 1H), 3.09 (s, 3H), 3.08 (s, 3H), 2.84 (d, *J* = 15.3 Hz, 1H), 2.70 (d, *J* = 16.0 Hz, 1H), 2.51 (br s, 1H), 2.45 (dd, *J* = 5.7, 2.6 Hz, 1H), 2.35 (dd, *J* = 6.6, 2.6 Hz, 1H), 2.27 (m, 4H), 2.11 (m, 3H), 1.96 (m, 4H), 1.89 (s, 3H), 1.79 (m, 2H), 1.70 (m, 2H), 1.66 (d, *J* = 3.4 Hz, 3H), 1.48 (d, *J* = 12.6 Hz, 1H), 1.32 (m, 4H), 1.22 (m, 3H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.5 Hz, 3H); ¹³CNMR (125 MHz, C₆D₆) δ 167.5, 162.5, 161.2, 147.6, 143.8, 142.8, 139.3, 138.6, 138.0, 137.4, 136.4, 134.5, 132.2, 128.0, 127.9, 124.2, 119.1, 118.8, 111.4, 100.9, 99.2, 97.4, 89.7, 81.5, 81.2, 79.2, 77.3, 74.0, 73.9, 73.4, 71.6, 71.0, 70.9, 66.1, 64.9, 56.8, 55.9, 41.6, 41.3, 40.3, 39.5, 38.6, 38.5, 38.3, 38.0, 35.5, 34.0, 30.7, 26.7, 26.7, 14.8, 13.9, 6.1; high resolution mass spectrum (ES⁺) *m/z* 965.4831 [(M+Na)⁺; calcd for C₅₃H₇₀N₂O₁₃Na: 965.4843].

(-)-8

C(45-46)-Alkenyl-C(22-26)-Central Tetrahydropyran Phorboxazole (-)-8: Fully protected C(45-46)-alkenyl-C(22-26)-central tetrahydropyran phorboxazole (-)-**30** (12.9 mg, 0.011 mmol) was introduced into a flame dried round bottom flask, azeotroped from benzene (5 mL, 3x) and dried under vacuum. After one hour, under an argon atmosphere, (-)-**30** was dissolved in freshly distilled THF (2.7 mL), followed by cooling to 0 °C and dropwise addition of tetrabutylammonium fluoride (1.0 M/THF) (0.022 mL, 0.022 mmol). After one hour, the reaction was warmed to room temperature and after 2.5 total hours of reacting, the reaction was quenched via dropwise addition of saturated aqueous sodium chloride (3 mL). The layers of the biphasic mixture were separated and the aqueous layer was extracted with ethyl acetate (5 mL, 4x). The combined organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. The resultant off white amorphous solid, under an argon atmosphere was dissolved in freshly distilled THF (7.1 mL) followed by dropwise introduction of 6% hydrogen chloride solution (2.8 mL). After stirring at room temperature for thirty six hours, the reaction was cooled to 0 °C and poured into saturated aqueous sodium bicarbonate (5 mL). The layers of the resultant biphasic mixture were separated and the aqueous layer was extracted with dichloromethane (5 mL, 4x) followed by extraction with ethyl acetate (5 mL, 2x). The combined organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. Purification via silica gel chromatography, (100% EtOAc → 10% CH₃OH/EtOAc) afforded C(45-46)-alkenyl-C(22-26)-central tetrahydropyran phorboxazole (-)-**8** (7.1 mg,

66%) as an off white amorphous solid. $[\alpha]_D^{20}$ -69.0 (*c* 0.16, CH₂Cl₂); IR (neat) 2921 (b), 1515 (s), 1454 (b), 1420 (s), 1376 (b), 1260 (s), 1238 (s), 1152 (s), 1087 (b), 1027 (s), 966 (s); ¹HNMR (500 MHz, C₆D₆) δ 6.99 (s, 1H), 6.97 (d, *J* = 1.8 Hz, 1H), 6.92 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.19 (s, 1H), 6.18 (d, *J* = 15.7 Hz, 1H), 5.92 (m, 1H), 5.54 (d, *J* = 8.6 Hz, 1H), 5.52 (dd, *J* = 15.6, 7.6 Hz, 1H), 5.40 (s, 1H), 5.08 (d, *J* = 15.9 Hz, 2H), 5.05 (d, *J* = 10.1 Hz, 1H), 4.52 (d, *J* = 11.4 Hz, 1H), 4.36 (app t, *J* = 7.3 Hz, 1H), 4.21 (d, *J* = 11.4 Hz, 1H), 3.96 (dddd, *J* = 11.8, 6.9, 5.0, 4.8 Hz, 1H), 3.77 (m, 1H), 3.64 (m, 2H), 3.56 (app q, *J* = 6.5 Hz, 1H), 3.52 (s, 3H), 3.44 (s, 3H), 3.35 (d, *J* = 10.3 Hz, 1H), 3.14 (s, 3H), 3.07 (s, 3H), 3.06 (m, 2H), 2.84 (d, *J* = 15.4 Hz, 1H), 2.70 (d, *J* = 15.5 Hz, 1H), 2.44 (m, 2H), 2.29 (m, 2H), 1.97 (d, *J* = 14.5 Hz, 1H), 1.91 (m, 3H), 1.88 (d, *J* = 0.9 Hz, 3H), 1.66 (d, *J* = 1.1 Hz, 3H), 1.31 (m, 4H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.4 Hz, 3H); ¹³CNMR (125 MHz, C₆D₆) δ 161.0, 150.7, 150.2, 139.4, 138.3, 137.3, 137.3, 136.2, 135.5, 132.2, 131.5, 130.1, 120.5, 118.7, 117.2, 112.6, 112.5, 97.2, 89.5, 83.4, 82.6, 77.7, 73.7, 73.3, 71.4, 70.2, 61.2, 56.4, 56.1, 56.0, 55.7, 41.5, 41.2, 40.1, 36.3, 35.4, 33.9, 33.9, 14.6, 14.3, 13.7, 6.8; high resolution mass spectrum (ES⁺) *m/z* 778.4134 [(M+Na)⁺; calcd for C₄₂H₆₁NO₁₁Na: 778.4141].