

Supporting information for

**Synthetic Studies Toward Phorboxazole A.  
Stereoselective Synthesis of the C<sub>28</sub>–C<sub>46</sub> Side Chain Fragment.**

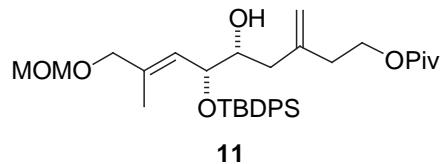
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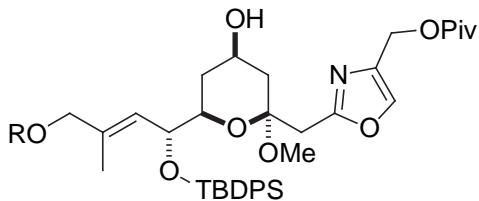
**Experimental Procedures:**



**2,2-Dimethylpropionic acid (5*R*,6*R*)-(E)-5-hydroxy-9-methoxymethoxy-8-methyl-3-methylene-6-*tert*-butyldiphenylsilyloxy-non-7-enyl ester. (11)**

To a 100 mL Schlenk flask containing (*R,R*)-1,2-bis-*para*-toluenesulfonyl-1,2-diphenylethane (0.97 g, 1.88 mmol) under an argon atmosphere was added CH<sub>2</sub>Cl<sub>2</sub> (18 mL). After cooling to 0 °C, the solution was treated with boron tribromide (1.88 mL of a 1M solution in CH<sub>2</sub>Cl<sub>2</sub>, 1.88 mmol). The mixture was stirred at 0 °C for 10 min, warmed to room temperature and stirred for 1 h. After twice removing the solvent and HBr under reduced pressure (0.1 mm Hg), the resulting solid was diluted with CH<sub>2</sub>Cl<sub>2</sub> (18 mL) and cooled to 0 °C. Allylstannane **10** (0.96 g, 2.08 mmol) was added. After stirring for 20 h

at room temperature, the reaction was cooled to  $-78$   $^{\circ}\text{C}$ , and a solution of aldehyde **9** (0.55 g, 1.32 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was added. After stirring for 2 h at  $-78$   $^{\circ}\text{C}$ , the reaction was quenched with pH 7 buffer solution (3 mL) and warmed to room temperature. The mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (100 mL). The organic phase was washed with aqueous saturated  $\text{NaCl}$  (2 x 50 mL). The combined aqueous phases were extracted with  $\text{CH}_2\text{Cl}_2$  (25 mL). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The resulting solid was washed with ether to recover the bisulfonamide chiral auxiliary. The filtrate was concentrated *in vacuo* and purified by flash chromatography (80 g  $\text{SiO}_2$ , 10% EtOAc/hexanes) to afford 740 mg (98%) of a 10:1 ratio of diastereomeric alcohols (**11**-major):  $[\alpha]_D^{23} = -0.2$  (c 2.4,  $\text{CHCl}_3$ );  $R_f = 0.40$  in 25% EtOAc/hexanes; IR (neat) 3529 (bd), 2937, 2860, 1734, 1429, 1159  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.68–7.64 (m, 4H), 7.42–7.33 (m, 6H), 5.40 (d,  $J = 9.6$  Hz, 1H), 4.87 (d,  $J = 7.6$  Hz, 2H), 4.43 (s, 2H), 4.29 (dd,  $J = 8.4, 6.4$  Hz, 1H), 4.15 (t,  $J = 6.8$  Hz, 2H), 3.72–3.66 (m, 1H), 3.66 (s, 2H), 3.27 (s, 3H), 2.64 (d,  $J = 4.0$  Hz, –OH), 2.42–2.32 (m, 2H), 2.23 (d,  $J = 14.4$  Hz, 1H), 2.02 (dd,  $J = 14.4, 9.6$  Hz, 1H), 1.17 (s, 9H), 1.07 (s, 3H), 1.05 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  178.7, 143.0, 136.2, 136.1, 133.9, 133.6, 133.0, 129.8, 127.9, 127.6, 125.8, 113.9, 95.7, 73.9, 73.8, 72.3, 62.7, 55.4, 39.2, 35.1, 27.4, 27.3, 19.6, 14.5; HRMS (FAB, NBA,  $\text{Na}^+$ )  $m/e$  calcd for  $\text{C}_{34}\text{H}_{50}\text{O}_6\text{SiNa}$  ( $\text{M}^+ + \text{Na}$ ) 605.3274, found 605.3282.



16: R = TBMPS  
17: R = H

**2,2-Dimethylpropionic acid 2-((2S, 4R, 6R)-6-[(R)-(E)-1-(tert-butyldiphenylsilyl)oxy)-4-(tert-butyloxymethoxyphenylsilyl)oxy]-3-but-2-enyl]-4-hydroxy-2-methoxytetrahydropyran-2-ylmethyl)oxazol-4-ylmethyl ester. (16)**

A solution of SmI<sub>2</sub> in THF was prepared by addition of CH<sub>2</sub>I<sub>2</sub> (0.09 mL, 1.08 mmol) to a suspension of Sm<sup>o</sup> powder (0.17 g, 1.08 mmol) in anhydrous, degassed THF (2 mL). This mixture was stirred in the dark for 2 h at room temperature. A pre-mixed solution of aldehyde **14** (0.24 mg, 0.27 mmol) and oxazole iodide **15** (0.10 g, 0.30 mmol) in degassed THF (1 mL) was introduced dropwise to the stirring solution of SmI<sub>2</sub>. After stirring for 15 min at room temperature, the reaction mixture was diluted with ether (50 mL) and brine (80 mL). The biphasic mixture was separated. The aqueous phase was back extracted with ether (30 mL). The combined organic phases were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (15 g SiO<sub>2</sub>, 8% EtOAc/hexanes) to afford 220 mg (76%) of the β-hydroxyoxazole (90-95% purity) as a 1:1:1:1 mixture of diastereomers. The alcohol mixture was immediately used in the next step.

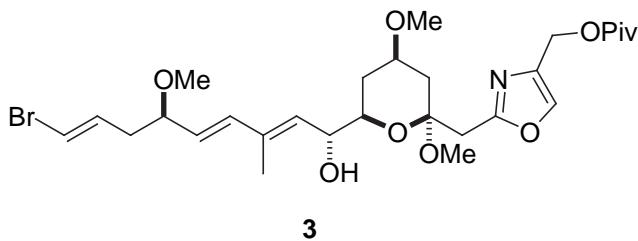
To a cold (−78 °C) solution of trifluoroacetic anhydride (0.06 mL, 0.44 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added dimethylsulfoxide (0.06 mL, 0.88 mmol). The resulting slurry was maintained at −78 °C for 15 min. A solution of the β-hydroxyoxazole (0.19 g, 0.17 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) was then added dropwise to the TFAA/DMSO adduct, and the resulting yellow slurry stirred another 20 min at −78 °C. At this time

triethylamine (0.20 mL, 1.42 mmol) was added in one portion and the reaction was gradually warmed to  $-30$   $^{\circ}\text{C}$ . The solution was diluted with ether (80 mL) and then washed with aqueous saturated  $\text{NaHCO}_3$  (2 x 50 mL). The combined aqueous phases were back extracted with ether (40 mL). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (10 g  $\text{SiO}_2$ , 8% EtOAc/hexanes) to afford 134 mg (71%) of the  $\beta$ -ketooxazole:  $R_f = 0.43$  in 20% EtOAc/hexanes;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.72-7.58 (m, 6H), 7.52 (s, 1H), 7.43-7.22 (m, 9H), 5.86 (dd,  $J = 7.2, 6.8$  Hz, 1H), 5.00 (s, 1H), 4.99 (s, 1H), 4.34-4.31 (m, 2H), 4.03-3.80 (m, 4H), 3.55 (s, 1.5H), 3.54 (s, 1.5H), 3.51 (dd,  $J = 12.0, 5.2$  Hz, 1H), 2.74-2.66 (m, 2H), 2.17-2.04 (m, 1H), 1.67-1.50 (m, 3H), 1.20 (s, 9H), 1.06 (d,  $J = 10.4$  Hz, 3H), 1.03 (s, 9H), 0.95 (s, 9H), 0.87 (s, 4.5H), 0.86 (s, 4.5H), 0.75 (s, 4.5H), 0.73 (s, 4.5H), 0.13 (s, 1.5H), 0.11 (s, 1.5H), 0.05 (s, 1.5H), 0.04 (s, 1.5H), -0.04 (s, 3H), -0.24 (s, 3H).

To a solution of the ketone (0.11 g, 0.10 mmol) in  $\text{MeOH}$  (1.5 mL) was added pyridinium *para*-toluenesulfonate (0.02 g, 0.10 mmol). The reaction mixture was then heated at  $50$   $^{\circ}\text{C}$  for 40 h. The mixture was diluted with EtOAc (40 mL) and aqueous saturated  $\text{NaHCO}_3$  (40 mL). The layers were separated and the aqueous phase was back extracted with EtOAc (20 mL). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (10 g  $\text{SiO}_2$ , 33% EtOAc/hexanes to elute **16** and 100% EtOAc to elute **17**) to afford 36 mg (42%) of alcohol **16** along with 18 mg (21%) of diol **17**.

Spectral data for alcohol **16**:  $R_f = 0.50$  in 50% EtOAc/hexanes;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.77-7.55 (m, 7H), 7.42-7.28 (m, 9H), 5.54 (dd,  $J = 9.2, 8.8$  Hz, 1H), 5.00 (s, 2H), 4.48 (dd,  $J = 8.8, 6.8$  Hz, 1H), 4.00-3.92 (m, 3H), 3.60-3.53 (m, 1H), 3.55 (s, 1.5H), 3.54 (s, 1.5H), 3.30 (dd,  $J = 14.4, 3.6$  Hz, 1H), 3.26 (s, 3H), 3.25 (d,  $J = 14.4$  Hz, 1H), 2.92 (d,  $J = 14.4$  Hz, 1H), 2.11 (dd,  $J = 12.8, 3.2$  Hz, 1H), 1.96-1.87 (m, 1H), 1.45-1.25 (m, 2H), 1.20 (s, 9H), 1.07 (s, 3H), 1.06 (s, 9H), 0.94 (s, 9H).

Spectral data for diol **17**:  $R_f = 0.13$  in 50% EtOAc/hexanes;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.77-7.76 (m, 4H), 7.57 (s, 1H), 7.43-7.32 (m, 6H), 5.22 (d,  $J = 10.2$  Hz, 1H), 5.01 (s, 2H), 4.49 (dd,  $J = 8.8, 6.8$  Hz, 1H), 4.22 (ddd,  $J = 17.8, 10.8, 6.0$  Hz, 1H), 4.06-3.95 (m, 1H), 3.69-3.57 (m, 2H), 3.30 (s, 3H), 3.25 (d,  $J = 14.8$  Hz, 1H), 3.02 (d,  $J = 14.8$  Hz, 1H), 2.12 (ddd,  $J = 12.4, 4.4, 2.0$  Hz, 1H), 1.89 (ddd,  $J = 12.0, 2.0, 2.0$  Hz, 1H), 1.49-1.25 (m, 2H), 1.20 (s, 9H), 1.12 (s, 3H), 1.05 (s, 9H).

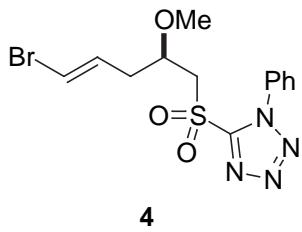


**2,2-Dimethyl propionic acid 2-[(2S, 4R, 6R)-6-((1R, 6R)-(2E,4E,8E)-9-bromo-1-hydroxy-6-methoxy-3-methylnona-2,4,8-trienyl)-2,4-dimethoxy-tetrahydropyran-2-ylmethyl]-oxazol-4-ylmethyl ester. (3)**

To a solution of (*E,Z*)-diene **19** (2 mg) in *d*6-benzene (1.2 mL) in a NMR tube was added a trace amount of iodine. A sun lamp (250 W) was then shined on the reaction sample and the conversion of **19** to **3** was monitored via  $^1\text{H}$  NMR (500 MHz) at 30 min intervals. After 3 h, the reaction was quenched by pouring into aqueous saturated  $\text{NaHSO}_3$  (10 mL). The aqueous phase was extracted with ether (2 x 10 mL). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (pipette column, 66% EtOAc/hexanes) to afford 2 mg of the side chain **3**:  $R_f = 0.31$  in 66% EtOAc/hexanes;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.60 (s, 1H), 6.22 (d,  $J = 16.0$  Hz, 1H), 6.13 (ddd,  $J = 13.5, 6.5, 6.5$  Hz, 1H), 6.10 (ddd,  $J = 13.6, 1.0, 1.0$  Hz, 1H), 5.51 (dd,  $J = 16.0, 8.0$  Hz, 1H), 5.48 (d,  $J = 11.0$  Hz, 1H), 5.03 (s, 2H), 4.22 (ddd,  $J = 11.0, 7.5, 7.5$  Hz, 1H), 3.66 (ddd,  $J = 11.5, 7.5, 2.0$

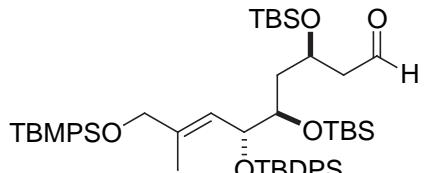
Hz, 1H), 3.60 (dddd,  $J$  = 11.5, 11.5, 5.0, 5.0 Hz, 1H), 3.50 (ddd,  $J$  = 15.5, 7.0, 7.0 Hz, 1H), 3.33 (s, 3H), 3.30 (s, 3H), 3.26 (s, 3H), 3.25 (d,  $J$  = 14.5 Hz, 1H), 3.15 (d,  $J$  = 14.5 Hz, 1H), 2.34 (m, 1H), 2.20 (m, 3H), 1.83 (s, 3H), 1.39 (m, 1H), 1.16 (m, 1H).

**Characterization data:**



**(E)-((R)-5-Bromo-2-methoxy-pent-4-ene-1-sulfonyl)-1-phenyl-1H-tetrazole. (4)**

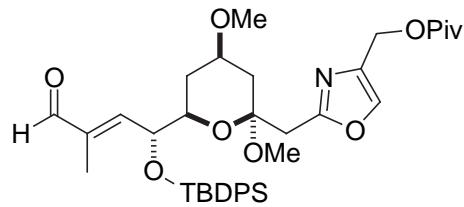
$[\alpha]_D^{23} = -14.5$  (c 1.3, CHCl<sub>3</sub>); R<sub>f</sub> = 0.46 in 33% EtOAc/hexanes; IR (neat) 3075, 2936, 2843, 1740, 1628, 1503, 1351 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.65-7.60 (m, 5H), 6.17 (d,  $J$  = 13.6 Hz, 1H), 6.06 (ddd,  $J$  = 14.4, 7.2, 7.2 Hz, 1H), 3.93 (dddd,  $J$  = 8.4, 8.4, 8.4, 4.8 Hz, 1H), AB of ABX ( $\delta_A$  = 3.63,  $\delta_B$  = 3.55,  $J_{AB}$  = 15.0 Hz,  $J_{AX}$  = 8.4 Hz,  $J_{BX}$  = 3.6 Hz, 2H), 3.42 (s, 3H), 2.48-2.34 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  154.4, 133.2, 131.9, 131.3, 129.9, 126.0, 109.1, 74.2, 59.4, 57.6, 36.0; MS (Cl/CH<sub>4</sub>) 387 (3), 355 (3), 307 (16), 267 (76), 239 (34), 161 (75), 117 (100); HRMS *m/e* calcd for C<sub>13</sub>H<sub>15</sub>N<sub>4</sub>O<sub>2</sub>S (M<sup>+</sup> + H) 387.0127, found 387.0118.



14

(E)- (3S, 5R, 6R)-3,5-bis(*tert*-butyldimethylsilyloxy)-6-(*tert*-butyldiphenylsilyloxy)-9-(*tert*-butylmethoxyphenylsilyloxy)-8-methyl-non-7-enal. (14)

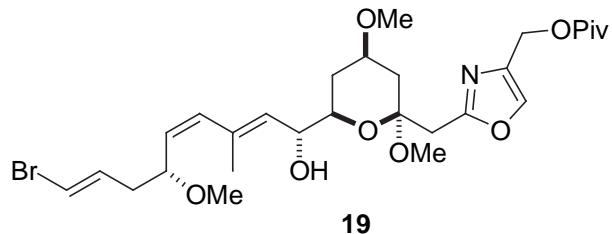
$[\alpha]_D^{23} = -6.4$  (c 1.3,  $\text{CHCl}_3$ );  $R_f = 0.59$  in 20%  $\text{EtOAc/hexanes}$ ; IR (neat) 2939, 2858, 1736, 1473, 1255, 1105  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.81 (dd,  $J = 2.0, 2.0$  Hz, 0.5H), 9.75 (dd,  $J = 2.0, 2.0$  Hz, 0.5H), 7.71 (m, 6H), 7.45-7.30 (m, 9H), 5.63 (dd,  $J = 10.8, 10.8$  Hz, 1H), 4.46-4.37 (m, 2H), 4.05 (s, 2H), 3.89-3.85 (m, 1H), 3.57 (s, 1.5H), 3.56 (s, 1.5H), 2.71-2.61 (m, 1H), 2.57-2.45 (m, 1H), 2.27-2.17 (m, 1H), 1.76-1.61 (m, 1H), 1.11 (d,  $J = 10.8$  Hz, 1H), 1.05 (s, 9H), 0.97 (s, 9H), 0.90 (s, 4.5H), 0.88 (s, 4.5H), 0.78 (s, 4.5H), 0.76 (s, 4.5H), 0.15 (s, 1.5H), 0.13 (s, 1.5H), 0.12 (s, 1.5H), 0.10 (s, 1.5H), -0.03 (s, 3H), -0.20 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  202.5, 138.0, 137.9, 136.2, 136.1, 135.5, 135.4, 134.4, 134.2, 134.0, 131.8, 130.1, 130.0, 129.8, 127.9, 127.7, 122.4, 122.2, 73.7, 72.5, 68.1, 68.0, 67.2, 67.1, 52.1, 51.7, 41.0, 27.3, 26.4, 26.1, 19.5, 19.0, 18.2, 18.1, 14.4, -3.6, -3.9, -4.0, -4.4; HRMS (FAB, NBA,  $\text{Na}^+$ )  $m/e$  calcd for  $\text{C}_{49}\text{H}_{80}\text{O}_6\text{Si}_4\text{Na}$  899.4957, found 899.4962.



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**2,2-Dimethylpropionic acid 2-[(2S, 4R, 6R)-6-[(R)-(E)-1-(tert-butyldiphenylsilyl)oxy]-3-but-2-en-4-yl]-2,4-dimethoxy-tetrahydropyran-2-ylmethyl]-oxazol-4-ylmethyl ester. (5)**

$R_f = 0.60$  in 50% EtOAc/hexanes;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.19 (s, 1H), 7.71-7.59 (m, 4H), 7.51 (s, 1H), 7.44-7.30 (m, 6H), 6.24 (dd,  $J = 8.8, 1.2$  Hz, 1H), 4.99 (s, 2H), 4.69 (dd,  $J = 8.8, 5.6$  Hz, 1H), 3.66 (ddd,  $J = 12.0, 5.6, 2.0$  Hz, 1H), 3.59-3.51 (m, 1H), 3.29 (s, 3H), 3.20 (d,  $J = 6.8$  Hz, 1H), 3.18 (s, 3H), 2.97 (d,  $J = 6.8$  Hz, 1H), 2.20 (ddd,  $J = 12.8, 4.4, 3.2$  Hz, 1H), 2.01 (ddd,  $J = 12.8, 2.4, 2.4$  Hz, 1H), 1.42-1.25 (m, 2H), 1.31 (d,  $J = 1.2$  Hz, 3H), 1.20 (s, 9H), 1.08 (s, 9H).



**2,2-Dimethyl propionic acid 2-[(2*S*, 4*R*, 6*R*)-6-((1*R*, 6*R*)-(2*E*,4*Z*,8*E*)-9-bromo-1-hydroxy-6-methoxy-3-methylnona-2,4,8-trienyl)-2,4-dimethoxy-tetrahydropyran-2-ylmethyl]-oxazol-4-ylmethyl ester. (19)**

$R_f = 0.31$  in 66% EtOAc/hexanes;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.59 (s, 1H), 6.24-6.09 (m, 3H), 5.27 (d,  $J = 9.5$  Hz, 1H), 5.29-5.24 (m, 1H), 5.02 (s, 2H), 4.32 (dd,  $J = 7.5, 7.5$  Hz, 1H), 4.12 (ddd,  $J = 15.5, 6.5, 6.5$  Hz, 1H), 3.63 (dddd,  $J = 11.5, 11.5, 5.0, 5.0$  Hz, 1H), 3.51 (ddd,  $J = 11.5, 7.5, 2.0$  Hz, 1H), 3.34 (s, 3H), 3.32 (s, 3H), 3.23 (s, 3H), 3.25 (d,  $J = 14.5$  Hz, 1H), 3.10 (d,  $J = 14.5$  Hz, 1H), 2.39-2.21 (m, 4H), 1.83 (s, 3H), 1.39 (m, 1H), 1.16 (m, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  178.5, 160.3, 137.6, 137.5, 136.8, 136.4, 134.1, 130.9, 128.7, 106.8, 100.3, 76.2, 73.5, 73.1, 71.5, 58.6, 56.5, 56.1, 48.6, 39.5, 39.4, 36.1, 33.3, 27.5, 18.2; HRMS (FAB, NBA,  $\text{Na}^+$ )  $m/e$  calcd for  $\text{C}_{28}\text{H}_{42}\text{BrNO}_8\text{Na}$  622.1992, found 622.1981.