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Supporting Information

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TOTAL SYNTHESIS OF PHORBOXAZOLE B

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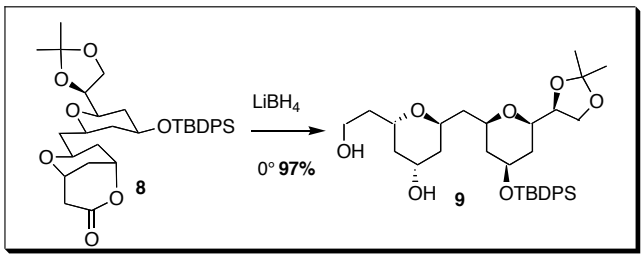
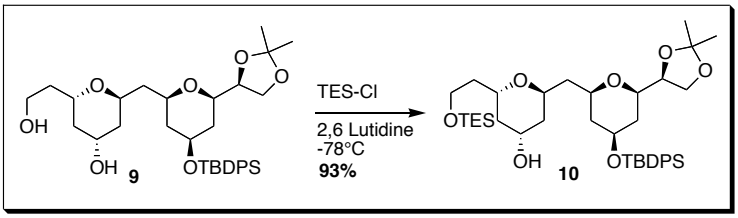
General Procedures. Melting points (mp) are uncorrected. Optical rotations were measured on a digital polarimeter; concentrations (*c*) are reported in g/100 mL. Infrared (IR) spectra are reported in wavenumbers (cm^{-1}) with broad signals denoted by (br). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at 500 MHz in deuterated solvents. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 125 MHz, unless otherwise noted. Chemical shifts for both ^1H and ^{13}C NMR spectra are reported in parts per million (ppm, d). ^1H NMR data are referenced to tetramethylsilane (TMS, d 0.00), and ^{13}C NMR are referenced to the central line of the 1:1:1 triplet of $CDCl_3$ (d 77.0) ^{13}C NMR spectral assignments were aided by Distortionless Enhancement by Polarization Transfer (DEPT) experiments with a phase angle of 135°: (C) not observed; (CH) positive; (CH_2) negative; (CH_3) positive. Mass spectra (MS) were obtained using electrospray ionization.

All moisture-sensitive reactions were performed in flame-dried glassware under a stream of nitrogen, unless indicated otherwise. Bath temperatures were used to record the reaction temperature in all cases. All reactions were stirred magnetically unless otherwise indicated. Analytical thin layer chromatography (TLC) was carried out on E. Merck (Darmstadt) TLC plates pre-coated with silica gel 60 F_{254} (250 m layer thickness). TLC visualization was accomplished using either a UV lamp, iodine adsorbed on silica gel, or charring solution [*p*-anisaldehyde (PAA), phosphomolybdic acid (PMA)]. Concentration *in vacuo* entails evaporation of solvent on a rotary evaporator followed by removal of residual solvent under high vacuum. Flash column chromatography (FCC) was performed on EM Science silica gel 60 (230-400 mesh) purchased from Aldrich.

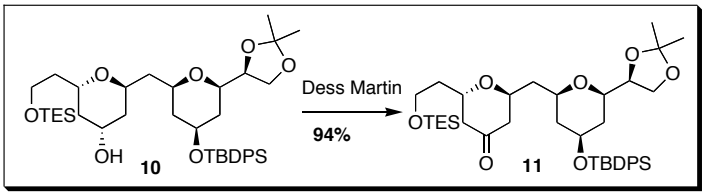
Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl. Toluene, triethylamine (Et_3N), pyridine (py), and dichloromethane (CH_2Cl_2) were distilled from calcium hydride. Methanol (MeOH) was distilled from magnesium methoxide. Hexanes were distilled at atmospheric pressure. Deuterochloroform (chloroform-*d*; $CDCl_3$) was stored over 4 Å molecular sieves (and powdered K_2CO_3 for compound **2**) before use. Deuteromethanol (methanol-d_4) was used as received from Aldrich in glass ampules. All other commercially obtained reagents and solvents were used as received without further purification unless indicated otherwise.



Diol 9: To a solution of bicyclic lactone **8** (790 mg, 1.32 mmol) in 125 mL of anhydrous ether at 0°C was added $LiBH_4$ (0.5 M in ethyl ether, 6.6 mL, 3.3 mmol, 2.5 eq). After stirring at 0°C for 2.5 h, the reaction was quenched with 60 mL of a 1:1 mixture of H_2O / saturated NH_4Cl. The layers were separated and the aqueous layer was extracted with 3 × 100 mL of ether. The combined ether extracts were washed with 50 mL brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (7:3 → 65:35 hexanes/acetone) afforded 770 mg (97%) diol **9**. Data for **9**: $\mathbf{R_f}$ = 0.10 (7:3 hexanes/acetone); **IR** (thin film) 3426, 2932 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.25-1.35 (m, 4H), 1.31 (s, 6H), 1.49-1.59 (m, 3H), 1.69 (m, 1H), 1.75 (m, 3H), 1.91 (m, 3H), 2.45 (br s, 1H), 3.03 (ddd *J* = 11.4, 6.6, 1.7 Hz, 1H), 3.18 (dt *J* = 10.7, 7.0 Hz, 1H), 3.68 (m, 2H), 3.72-3.81 (series of m, 3H), 3.85-3.99 (m, 3H), 4.13 (m, 1H), 7.35-7.45 (series of m, 6H), 7.63 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 19.0 (CH_3), 25.2 (CH_3), 26.6 (CH_3), 37.4 (CH_2), 37.5 (CH_2), 37.6 (CH_2), 40.9 (CH_2), 41.2 (CH_2), 60.8 (CH_2), 64.1 (CH), 66.6 (CH_2), 68.7 (CH), 69.2 (CH), 76.3 (CH), 77.6 (CH), 109.3 (C), 127.6 (CH), 129.64 (CH), 134.1 (C), 134.2 (C), 135.7 (CH) ; **HRMS** (MNa^+) calcd 621.3224 obsd 621.3202; **Optical Rotation** $[\alpha]_D^{25}$ = -23.4 ($CHCl_3$, *c* 1.0).

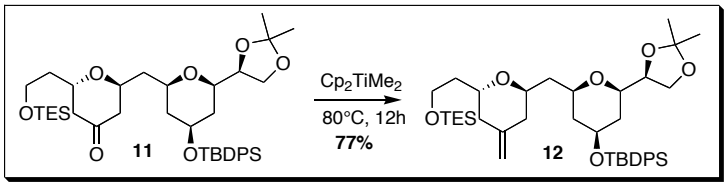


TES-Ether 10: To a solution of diol **9** (110 mg, 0.183 mmol) and 2,6-lutidine (0.096 mL, 0.733 mmol, 4 eq) in 10 mL of dry dichloromethane at –78°C was added TES-Cl (0.034 mL, 0.20 mmol, 1.1 eq). After stirring at –78°C for 75 min, the reaction was quenched with 0.20 mL methanol. After warming to RT, the solvent was removed *in vacuo*. The crude reaction mixture was dissolved in 20 mL ether and the residual solids removed by filtration. The filtrate was concentrated *in vacuo* and purified by column chromatography (9:1 hexanes/acetone) to afford 122 mg (93%) TES-ether **10**. Data for **10**: $\mathbf{R_f}$ = 0.42 (7:3 hexanes/acetone); **IR** (thin film) 3404, 2900 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.56 (q, *J* = 7.8Hz, 6H), 0.92 (t, *J* = 7.8 Hz, 9H), 1.05 (s, 9H), 1.24-1.32 (m, 3H), 1.29 (s, 3H), 1.31 (s, 3H), 1.50 (dt, *J* = 13.8, 6.7 Hz, 1H), 1.55 (ddd, *J* = 13.7, 9.7, 5.2 Hz, 1H), 1.64-1.78 (series of m 4H), 1.82-1.94 (series of m, 4H), 3.00 (ddd, *J* = 11.2, 6.7, 1.4 Hz, 1H), 3.20 (dt, *J* = 11.3, 6.5 Hz, 1H), 3.56-3.66 (m, 2H), 3.76-3.80 (m, 3H), 3.85 (td, *J* = 6.4, 5 Hz, 1H), 3.95 (m, 2H), 4.10 (m, 1H) 7.35-7.45 (series of m, 6H), 7.63 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 4.4 (CH_2), 6.8 (CH_3), 19.0 (C), 25.3 (CH_3), 26.6 (CH_3), 26.9 (CH_3), 37.6 (CH_2), 37.7 (CH_2), 38.2 (CH_2), 38.5 (CH_2), 40.1 (CH_2), 40.9 (CH_2), 59.1 (CH_2), 64.4 (CH), 66.2 (CH), 66.85 (CH_2), 69.3 (CH), 72.7 (CH), 76.3 (CH), 77.8 (CH), 109.3 (C), 127.6 (CH), 129.6 (CH), 134.2 (C),135.69 (CH), 135.72 (CH); **HRMS** (MNa^+) calcd 735.4088 obsd 735.4111; **Optical Rotation** $[\alpha]_D^{25}$ = -22.0 ($CHCl_3$, *c* 1.0).

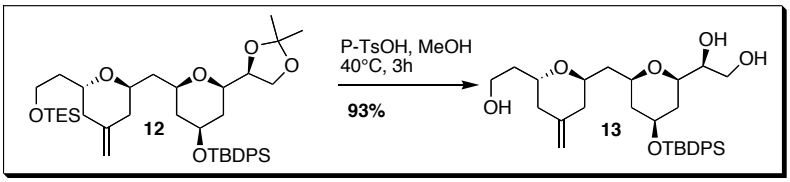


Ketone 11: TES-Ether **10** (63 mg, 0.088 mmol) was dissolved in 4 mL of anhydrous CH_2Cl_2 and Dess-Martin periodinane (112 mg, 0.265 mmol, 3 eq) was added. After stirring at RT for 2 h, 5 mL of 1:1 10% $Na_2S_2O_3$ / saturated $NaHCO_3$ was added, The reaction was stirred for 30 min and diluted with 40 mL CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with 40 mL CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (10:0.75 hexanes/acetone) yielded 59 mg (94%).pure ketone **11**. Data for **11**: $\mathbf{R_f}$ = 0.14 (10:0.5 hexanes/ethyl acetate); **IR** (thin film) 3071, 2952 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.56 (q, *J* = 8.0Hz, 6H), 0.93 (t, *J* = 9.1 Hz, 9H), 1.05 (s, 9H), 1.25-1.35 (m, 2H), 1.29 (s, 3H), 1.31 (s, 3H), 1.51 (ddd *J* = 13.7, 7.0, 5.6 Hz, 1H), 1.61 (m, 1H), 1.76 (m, 2H), 1.86 (ddd *J* =14.1, 7.8, 6.7 Hz, 1H), 2.25 (ddd, *J* = 14.3, 7.0, 0.9 Hz, 1H), 2.27 (ddd, *J* = 14.3, 7.0, 0.9 Hz,1H), 2.45 (ddd, *J* = 14.3 4.3, 0.8 Hz,1H), 2.52

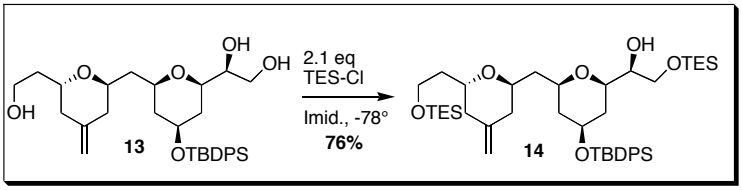
(ddd, *J* = 14.3, 4.9, 0.9 Hz,1H), 3.00 (ddd, *J* = 11.4, 6.6, 2 Hz, 1H), 3.22 (m, 1H), 3.61 (m, 2H), 3.74 (dd, *J* = 8.0, 5.1 Hz, 1H), 3.78 (m, 1H), 3.86 (app q, *J* = 6.2 Hz, 1H), 3.96 (dd, *J* = 8.0, 6.4 Hz, 1H), 4.16 (m, 1H), 4.26 (m, 1H), 7.35-7.45 (series of m, 6H), 7.66 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 4.3 (CH_2), 6.8 (CH_3), 19.0 (C), 25.3 (CH_3), 26.6 (CH_3), 26.9 (CH3), 37.2 (CH_2), 37.6 (CH_2), 40.3(CH_2), 41.3 (CH_2), 46.3 (CH_2), 46.8 (CH_2), 58.6 (CH_2), 66.7 (CH), 68.8 (CH), 69.1 (CH), 69.2 (CH), 71.9 (CH), 76.3 (CH), 77.7 (CH), 109.3 (C), 127.58 (CH), 129.66 (CH), 134.1 (C), 134.2 (C), 135.68 (CH), 135.71 (CH), 207.5 (C). **HRMS** (MNa^+) calcd 733.3932 obsd 733.3956; **Optical Rotation** $[\alpha]_D^{25}$ = -11.4 ($CHCl_3$, *c* =1.0).



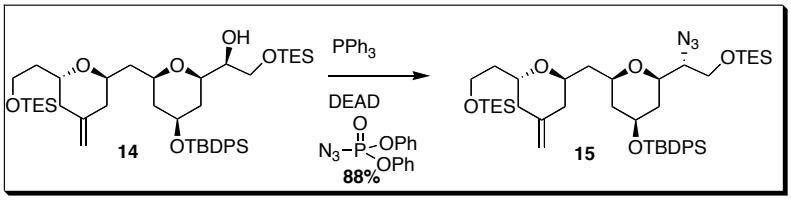
Exo-methylene 12: Ketone **11** (56 mg, 0.078 mmol) was dissolved in 2.4 mL THF and 2.4 mL toluene. Ethyl pivalate (1.2 μL, 0.0078 mmol, 0.1 eq) and Cp_2TiMe_2 (1.2 g of 3.27% solution in 1:1 THF/toluene by wt, 0.2 mmol, 2.5 eq) were added. The reaction was heated to 80°C and protected from light. After 15 h, the reaction was cooled to RT, diluted with 50 mL anhydrous pentane, filtered, and concentrated. Purification by column chromatography (10:0.5 hexanes/ethyl acetate) afforded pure exo-methylene **12** (43 mg, 77% yield). Data for **12**: $\mathbf{R}_f$ = 0.25 (9:1 hexanes/acetone); **IR** (thin film) 2954, 1717 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.58 (q, *J* = 7.6Hz, 6H), 0.93 (t, *J* = 7.8 Hz, 9H), 1.05 (s, 9H), 1.25-1.35 (m, 2H), 1.29 (s, 3H), 1.31 (s, 3H), 1.58 (m, 1H), 1.70-1.85 (series of m, 3H), 1.92 (m, 2H), 1.95 (dd, *J* = 13.0, 5.9 Hz, 1H), 2.25 (dd, *J* = 13.2, 4.2 Hz, 1H), 2.33 (dd, *J* = 13.2, 4.7 Hz, 1H), 2.99 (ddd, *J* = 11.6, 6.8, 1.8 Hz, 1H), 3.20 (dt *J* = 11.5, 6.0 Hz, 1H), 3.59 (app t *J* = 6 Hz , 2H), 3.72-3.83 (series of m, 3H), 3.83-3.92 (series of m, 2H), 3.96 (dd, J = 8.6, 6.2 Hz, 1H), 4.70 (br s, 1H), 4.72 (br s, 1H), 7.35-7.43 (series of m, 6H), 7.66 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 4.4 (CH_2), 6.8 (CH_3), 19.0 (C), 25.3 (CH_3), 26.7 (CH_3), 26.9 (CH_3), 36.1 (CH_2), 37.8 (CH_2), 39.6 (CH_2), 41.4 (CH_2), 59.3 (CH_2), 66.9 (CH_2), 68.4 (CH), 69.1 (CH), 69.3 (CH), 72.4 (CH), 76.3 (CH), 77.7 (CH), 109.2 (C), 110.2 (CH_2), 127.5 (CH), 129.6 (CH), 134.2 (C), 134.3 (C), 135.70 (CH), 135.73 (CH), 142.1 (C); **HRMS** (MNa^+) calcd 731.4139 obsd 731.4174; **Optical Rotation** $[\alpha]_D^{25}$ = -27.7 ($CHCl_3$, *c* 1.0)



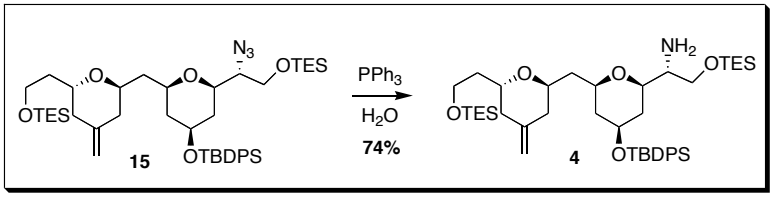
Triol 13: To a solution of **12** (74 mg, 0.104 mmol) in anhydrous methanol (10 mL) was added *p*-TsOH (1.9 mg, 0.01 mmol, 0.1 eq). The reaction was heated to 40°C for 1.5 h, following which, silica gel (350 mg) was added. The solvent was removed *in vacuo* to deposit the crude product on silica gel. The silica gel was transferred to a chromatography column packed and eluted with 7:3 hexanes/acetone to afford 53.4 mg (93%) pure triol **13**. Data for **13**: $\mathbf{R}_f$ = 0.17 (6:4 hexanes/acetone); **IR** (thin film) 3396, 3071, 2940 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.25-1.45 (series of m, 4H), 1.71 (m, 1H), 1.78 (m, 1H), 1.85 (dt, *J* = 15.0, 8.8 Hz, 1H), 1.90-2.00 (series of m, 3H), 2.22 (dd, *J* = 13.1, 4.1 Hz, 1H), 2.37 (dd, *J* = 13.2, 4.8 Hz, 1H), 3.20-3.30 (series of m,3H), 3.40-3.60 (series of m, 4H), 3.68 (m, 2H), 3.75 (m, 2H), 3.84 (tt, *J* = 7.5, 3.5 Hz, 1H), 4.07 (app dq, *J* = 10.1, 5.0 Hz, 1H), 4.73 (br s, 2H), 7.35-7.43 (series of m, 6H), 7.65 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 19.0 (C), 26.9 (CH_3), 33.7 (CH_2), 37.8 (CH_2), 39.4 (CH_2), 40.4 (CH_2), 40.6 (CH_2), 41.9 (CH_2), 60.6 (CH_2), 63.1 (CH_2), 69.0 (CH), 70.8 (CH), 71.8 (CH), 73.2 (CH), 74.9 (CH), 78.7 (CH), 110.2 (CH_2), 127.58 (CH), 129.66 (CH), 129.73 (CH), 134.0 (C), 134.2 (C), 135.7 (CH), 142.2 (C). **HRMS** (MNa^+) calcd 577.2961 obsd 577.2985; **Optical Rotation** $[\alpha]_D^{25}$ = -13.5 ($CHCl_3$, *c* 1.0).



Bis(TES ether) 14: To a solution of triol **13** (26 mg, 0.047 mmol) and imidazole (16 mg, 0.235 mmol, 5 eq) in 5 mL of dry CH_2Cl_2 at –78°C was added TES-Cl (0.016 mL, 0.094 mmol, 2.0 eq). After stirring for 30 min, the reaction was quenched by addition of 0.05 mL of methanol. Silica gel (350 mg) was added, and the crude mixture was concentrated. Purification by column chromatography (10:0.5 hexanes/ethyl acetate) afforded 28 mg (76%) bis(TES ether) **14**. Data for **14**: $\mathbf{R_f}$= 0.10(10:0.5 hexanes/ethyl acetate); **IR** (thin film) 3461, 3071, 2953 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.56 (q, *J* = 8.0 Hz, 6H), 0.58 (q, *J* = 7.8 Hz, 6H), 0.91 (t, *J* = 8.0 Hz, 9H), 0.92 (t, *J* = 8.2 Hz, 9H), 1.05 (s, 9H), 1.28 (app q, *J* = 11.2 Hz, 1H), 1.38 (app q, *J* = 11.6 Hz, 1H), 1.45 (dt, *J* = 12.8, 5.8 Hz, 1H), 1.58 (m, 1H), 1.70-1.81 (series of multiplets, 3H), 1.93 (dd *J* = 13.1, 6.6 Hz, 1H), 2.06 (m, 2H), 2.24 (dd, *J* = 13.0, 4.0 Hz, 1H), 2.31 (dd *J* = 13.1, 4.8 Hz, 1H), 2.42 (d, *J* = 4.2Hz, 1H), 3.07 (ddd, *J* = 11.4, 4.5, 1.4 Hz, 1H), 3.17 (dt, *J* = 11.8, 5.8 Hz, 1H), 3.51 (m, 2H), 3.58 (app t, *J* = 6.0 Hz, 2H), 3.66 (app q, *J* = 6.8 Hz, 1H), 3.80 (m, 2H), 3.90 (m, 1H), 4.69 (br s, 1H), 4.73 (br s, 1H), 7.35-7.43 (series of m, 6H), 7.67 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 4.3 (CH_2), 4.4 (CH_2), 6.7 (CH_3), 6.8 (CH_3), 19.1 (C), 26.9 (CH_3), 36.2 (CH_2), 37.1 (CH_2), 39.3 (CH_2), 39.5 (CH_2), 39.7 (CH_2), 41.5 (CH_2), 59.3 (CH_2), 63.3 (CH_2), 68.4 (CH), 69.1 (CH), 69.5 (CH), 72.2 (CH), 73.5 (CH), 75.5 (CH), 110.1 (CH_2), 127.51 (CH), 127.53 (CH), 129.55 (CH), 134.2 (C), 134.4 (C), 135.7 (CH), 135.72 (CH), 142.1 (C). **HRMS** (MNa^+) calcd 805.4691 obsd 805.4703; **Optical Rotation** $[\alpha]_D^{25}$ = -23.5 ($CHCl_3$, *c* =1.0).

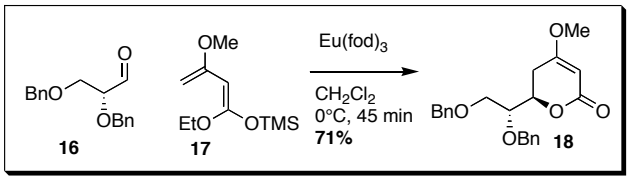


Azide 15: To a round bottom flask containing secondary alcohol **14** (330 mg, 0.42 mmol), PPh_3 (555 mg, 2.12 mmol, 5.05 eq) and DEAD (40 wt % in toluene, 913 mg, 2.10 mmol, 5 eq) in anhydrous THF (40 mL) was added diphenylphosphorylazide (188 μL, 0.84 mmol, 2 eq). The reaction was allowed to stir for 2 h at room temperature. The crude reaction mixture was deposited on silica gel and purified by column chromatography (10:0.5 hexanes/ ethyl ether) to afford 300 mg azide (88%) **15**. Data for **15**: $\mathbf{R_f}$= 0.13 (10:0.5 hexanes/ethyl ether); **IR** (thin film) 2953, 2100 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.56 (q, *J* = 7.9 Hz, 6H), 0.58 (q, *J* = 7.8 Hz, 6H), 0.92 (t, *J* = 8.2 Hz, 18H), 1.05 (s, 9H), 1.30 (app q, *J* = 11.0 Hz, 1H), 1.43-1.60 (series of m, 3H), 1.65 (m, 1H), 1.71-1.88 (series of multiplets, 3H), 1.92 (dd *J* = 13.1, 7.1 Hz, 1H), 1.99 (dd *J* = 13.3, 5.5 Hz, 1H), 2.26 (dd, *J* = 13.1, 4.0 Hz, 1H), 2.33 (dd *J* = 13.1, 4.6 Hz, 1H), 3.19 (m, 2H), 3.26 (ddd *J* = 11.7, 4.8, 2.1 Hz, 1H), 3.59 (app t, *J* = 5.9 Hz, 2H), 3.68 (app d, *J* = 5.5 Hz, 2H), 3.80 (m, 2H), 3.93 (m, 1H), 4.72 (br s, 2H), 7.35-7.44 (series of m, 6H), 7.66 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 4.2 (CH_2), 4.4 (CH_2), 6.7 (CH_3), 6.8 (CH_3), 19.1 (C), 26.9 (CH_3), 35.8 (CH_2), 37.7 (CH_2), 39.3 (CH_2), 39.4 (CH_2), 39.8 (CH_2), 41.0 (CH_2), 59.3 (CH_2), 62.8 (CH_2), 68.1 (CH), 69.2 (CH), 69.3 (CH), 72.3 (CH), 74.5 (CH), 110.1 (CH_2), 127.5 (CH), 129.6 (CH), 134.2 (C), 135.7 (CH), 142.1 (C). **HRMS** (MNa^+) calcd 830.4756 obsd 830.4781; **Optical Rotation** $[\alpha]_D^{25}$ = -19.6 ($CHCl_3$, *c* 1.0)

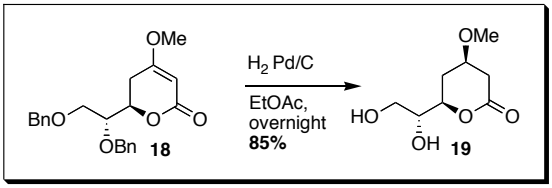


Amine 4: Azide **15** (39 mg, 0.048 mmol) was dissolved in 4 mL of dry THF. To this solution was added PPh_3 (25 mg, 0.096 mmol, 2 eq) and H_2O (17 μL, 0.96 mmol, 20 eq). The solution was heated to reflux for 20 h, cooled to RT, and depositied on 300 mg silica gel. The product was purified by column chromatography: Triphenylphosphine and triphenylphosphine oxide were removed by column chromatography using 10:0.5 hexanes/acetone on silica gel deactivated with Et_3N. Further purification by column chromatography (10:0.3 CH_2Cl_2/MeOH) afforded pure amine **4** (27.7 mg, 74% yield). Data for **4**: $\mathbf{R_f}$= 0.13 (10:0.3 CH_2Cl_2/MeOH); **IR** (thin film) 2953 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.55 (q, *J* = 8.0 Hz, 6H), 0.57 (q, *J* = 8.0 Hz, 6H), 0.92 (t, *J* =8.0 Hz, 9H), 0.93 (t, *J* = 8.1 Hz, 9H), 1.05 (s, 9H), 1.29 (m, 2H), 1.40-1.68 (series of m, 6H), 1.79 (m, 3H), 1.95 (dd *J* = 13.1, 6.6 Hz, 1H), 1.98 (dd *J* = 13.3, 5.9 Hz, 1H), 2.26 (dd, *J* = 13.2, 4.1 Hz, 1H), 2.33 (dd *J* = 13.1, 4.7 Hz, 1H), 2.61 (app q *J* = 5.1 Hz, 1H), 3.04

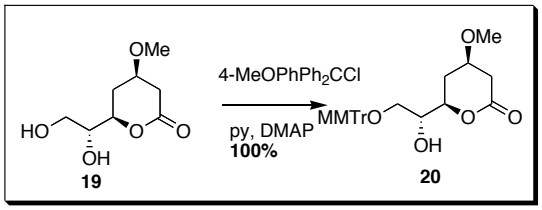
(ddd, J = 11.4, 5.3, 1.5 Hz, 1H), 3.17 (dt, J = 11.5, 6.1 Hz, 1H), 3.39 (AB q, J_{AB} = 9.7, J_{BX} = 6.2 Hz, 1H), 3.50 (ABX, J_{AB} = 9.7 Hz, J_{AX} = 5.0 Hz, 1H), 3.60 (app t, J = 6.6 Hz, 2H), 3.76-3.88 (m, 2H), 3.90 (m, 1H), 4.70 (br s, 1H), 4.72 (br s, 1H), 7.35-7.44 (series of m, 6H), 7.66 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 4.3 (CH_2), 4.4 (CH_2), 6.7 (CH_3), 6.8 (CH_3), 19.1 (C), 26.9 (CH_3), 36.2 (CH_2), 37.9 (CH_2), 39.3 (CH_2), 39.5 (CH_2), 39.8 (CH_2), 41.4 (CH_2), 56.8 (CH), 59.4 (CH_2), 64.5 (CH_2), 68.5 (CH), 69.6 (CH), 72.0 (CH), 75.9 (CH), 110.1 (CH_2), 127.5 (CH), 129.6 (CH), 134.2 (C), 135.70 (CH), 135.72 (CH), 142.2 (C). **HRMS** (MNa^+) calcd 782.5031 obsd 782.5027; **Optical Rotation** $[\alpha]_D^{25}$ = -22.2 (CH_2Cl_2, *c* 1.0).



α,β-Unsaturated lactone 18: To a solution of freshly prepared aldehyde[18] **16** (570 mg, 2.1 mmol) in 4 mL CH_2Cl_2 at 0°C was added Eu(fod)$_3$ (109 mg, 0.105 mmol, 0.05 eq) followed by Brassard diene **17** (500 mg, 2.3 mmol, 1.1 eq).[5,6,13] After stirring for 45 minutes at 0 °C, the reaction was diluted with 25 mL of CH_2Cl_2 and 5 g of silica was added. The solvent was removed *in vacuo* and the reaction mixture was purified by column chromatography (7:3 → 1:1 hexanes/ EtOAc, gradient) to afford 550 mg (71%) of lactone **18**. Data for **18**: $\mathbf{R}_f$ = 0.36 (1:1 hexanes/ EtOAc); **IR** (thin film) 3063, 1716, 1623 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.18 (dd J = 17.2, 4.2 Hz, 1H), 2.78 (ddd J = 17.0, 12.2, 1.4 Hz, 1H), 3.69 (s, 3H), 3.69-3.81 (series of m, 3H), 4.51 (AB q, J_{AB} = 11.7 Hz, 2H), 4.58 (m, 1H), 4.65 (AB q, J_{AB} = 11.7 Hz, 1H), 4.79 (AB q, J_{AB} = 11.9 Hz, 1H), 5.11 (d, J = 1.6 Hz, 1H), 7.3 (m, 10H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 29.0 (CH_2), 56.0 (CH_3), 69.0 (CH_2), 73.1 (CH_2), 75.5 (CH), 77.5 (CH), 90.1 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.3 (CH), 128.4 (CH), 137.8 (C), 137.9 (C), 166.7 (C), 173.1 (C); **HRMS** (MNa^+) calcd 369.1702 obsd 369.1707; **Optical Rotation** $[\alpha]_D^{21}$ = + 41.3 (*c* 1.0, $CHCl_3$).

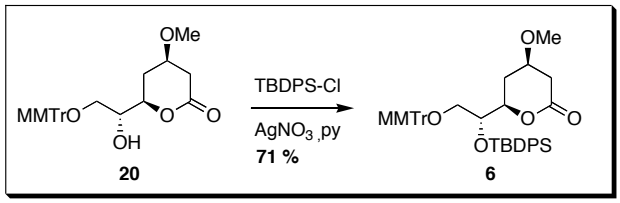


Lactone Diol 19: To a solution of unsaturated lactone **18** (1.55 g, 4.2 mmol) in 80 mL EtOAc was added 10% palladium on carbon (3.0 g). The reaction flask was flushed thoroughly with nitrogen, followed by hydrogen. The reaction was stirred for 16h at RT under a balloon of hydrogen, after which time, the reaction flask was thoroughly purged with nitrogen. The crude reaction mixture was filtered though Celite, rinsed with EtOAc (300 mL), and concentrated *in vacuo*. Purification by column chromatography (7:3 acetone/ hexanes) afforded pure, crystalline **19** (681 mg, 85%). Data for **19**: **m.p.** 55-60°C; $\mathbf{R}_f$ = 0.22 (7:3 acetone/ hexanes); **IR** (thin film) 3396, 1733 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.78 (ddd, J = 13.6, 11.6, 8.3 Hz, 1H), 2.29 (app dt, J = 13.7, 4.6 Hz, 1H), 2.56 ABXY (J_{AB} = 17.0 Hz, J_{BX} = 7.2 Hz, J_{AX} = 0 Hz, 1H), 2.84 (ABXY J_{AB} = 17.0 Hz, J_{AX} = 5.7 Hz, J_{AY} = 1.0 Hz, 1H), 3.10 (br s, 2H), 3.35 (s, 3H), 3.70-3.84 (series of m, 4H), 4.35 (dt, J = 11.7, 3.9 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 30.6 (CH_2), 36.2 (CH_2), 56.1 (CH_3), 62.8 (CH_2), 72.1 (CH), 73.1 (CH), 77.5 (CH), 170.4 (C); **HRMS** (MNa^+) calcd 213.0737 obsd 213.0739; **Optical Rotation** $[\alpha]_D^{23}$ = - 32.5 (*c* 1.0, $CHCl_3$). Crystallographic data for compound **19** can be accessed at the Cambridge Crystallographic Data Center via the internet at www.cdcc.cam.ac.uk (CDCC 617977).

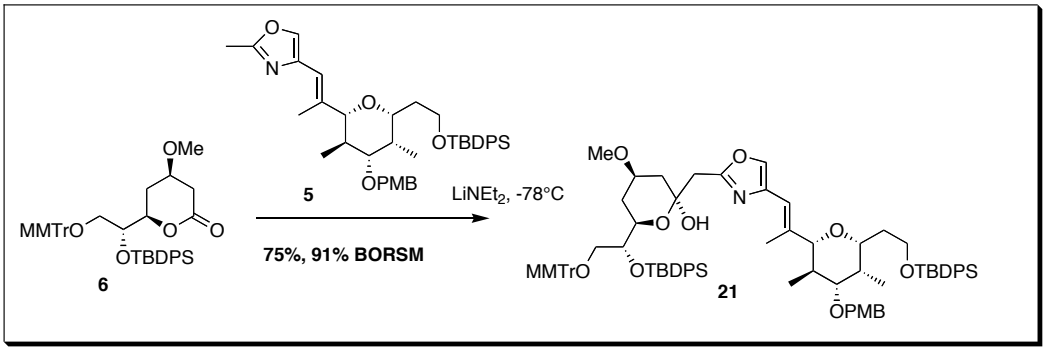


Monomethoxytrityl lactone 20: Lactone **19** (285 mg, 1.5 mmol) was dissolved in 25 mL of anhydrous CH_2Cl_2, followed by addition of DMAP (18 mg, 0.15 mmol, 0.1 eq), pyridine (0.194 mL, 2.4 mmol, 1.6 eq), and monomethoxytritylchloride (602 mg, 1.95 mmol, 1.3 eq). The reaction was stirred at room

temperature for 1 h and quenched by addition of 10 mL of saturated NH_4Cl solution. The aqueous layer was extracted with 1 × 15 mL of CH_2Cl_2 and 1 × 15 mL of EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (1:1 hexanes/ EtOAc) afforded 680 mg (100%) of pure **20**. Data for **20**: $\mathbf{R}_f$ = 0.16 (1:1 hexanes/EtOAc); **IR** (thin film) 3446, 2933, 1735 cm^{-1}; **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 1.68 ddd, *J* = 13.8, 11.5, 7.8 Hz, 1H), 2.11 (dddd, *J* = 13.8, 5.8, 3.5, 1.0 Hz, 1H), 2.48 (m, 2H), 2.78 (dd *J* = 16.8, 5.6 Hz, 1H), 3.22 (A<u>B</u>X, J_{AB} = 9.8, J_{BX} = 5.7 Hz, 1H), 3.30 (s, 3H), 3.33 (<u>A</u>BX, J_{AB} = 9.8, J_{AX} = 5.3 Hz, 1H), 3.74 (m, 2H), 3.80 (s, 3H), 4.39 (dt *J* = 11.7, 3.5 Hz, 1H), 6.86 (m, 2H), 7.25 (m, 2H), 7.33 (m, 6H), 7.45 (m, 6H); **^{13}C NMR** (125 MHz, CD_2Cl_2) δ 31.1, 36.8, 55.8, 56.4, 64.3, 72.8, 77.5, 87.1, 113.7, 127.6, 128.5, 128.8, 130.9, 135.7, 144.8, 144.9, 159.4, 170.1; **HRMS** (MNa^+) calcd 485.1940 obsd 485.1926; **Optical Rotation** $[\alpha]_D^{23}$ = - 20.8 (*c* 1.0, CH_2Cl_2).



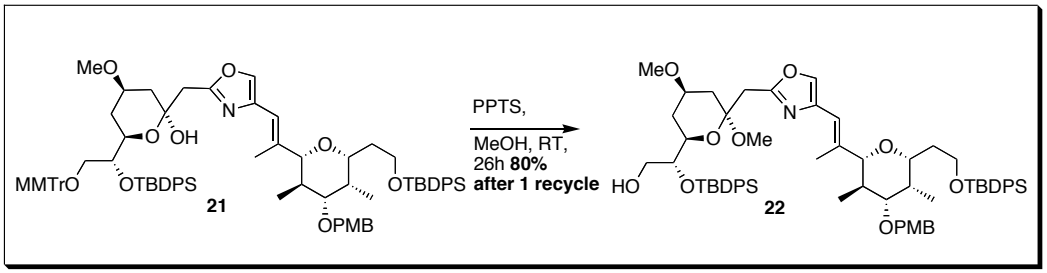
TBDPS Lactone 6: Monomethoxytrityl lactone **20** (230 mg, 0.5 mmol) was dissolved in pyridine (5 mL) and the reaction flask was shielded from light. Silver nitrate (422 mg, 2.5 mmol, 5 eq) and TBDPS-Cl (0.65 mL, 2.5 mmol, 5 eq) were added sequentially with vigorous stirring. The reaction was heated at 50°C for 2 h in the dark, after which time, the reaction was cooled to room temperature and diluted with Et_2O (200 mL). The organic layer was washed with 4 × 20 mL sat. $CuSO_4$ and 1 × 25 mL brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* Purification by column chromatography (8:2 hexanes/ethyl acetate) afforded pure **6** (250 mg, 71%). Data for **6**: $\mathbf{R}_f$ = 0.16 (8:2 hexanes/ acetone); **IR** (thin film) 2933, 1742 cm^{-1}; **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 1.01 (s, 9H), 1.68 (A<u>B</u>XY, J_{AB} = 13.1 Hz, J_{BX} = 9.3 Hz, J_{AY} = 0 Hz, 1H), 1.95 (<u>A</u>BXY J_{AB} = 13.3 Hz, J_{AX} = 13.2 Hz, J_{AY} = 1.1 Hz, 1H), 2.35 (A<u>B</u>XY, J_{AB} = 17.2 Hz, J_{BX} = 8.0 Hz, J_{AY} = 0 Hz,1H), 2.81 (<u>A</u>BXY, J_{AB} = 17.2 Hz, J_{AX} = 6.1 Hz, J_{AY} = 1.1 Hz, 1H), 3.09 (A<u>B</u>X, J_{AB} = 9.6, 4.7 Hz, 1H), 3.27 (s, 3H), 3.36 (<u>A</u>BX, J_{AB} = 9.4 Hz, J_{AX} = 7.6 Hz, 1H), 3.66 (ddt, *J* = 9.4, 8.0, 5.9 Hz, 1H), 3.78 (s, 3H), 3.80 (ddd, *J* = 7.6, 4.9, 3.0 Hz, 1H), 4.39 (dt, *J* = 12.1, 2.9 Hz, 1H), 6.74 (m, 2H), 7.11 (m, 2H), 7.20-7.36 (series of m, 16H), 7.55 (m, 4H); **^{13}C NMR** (125 MHz, CD_2Cl_2) δ 19.8, 27.3, 31.2, 37.4, 55.7, 56.2, 63.8, 73.0, 73.8, 76.7, 87.2, 113.5, 137.4, 128.0, 128.2, 128.30, 128.32, 130.3, 130.4, 130.8, 133.5, 134.0, 135.7, 136.4, 136.5, 144.8, 145.0, 159.2, 170.2; **HRMS** (MNa^+) calcd 723.3118 obsd 723.3104; **Optical Rotation** $[\alpha]_D^{23}$ = - 26.5 (*c* 1.0, CH_2Cl_2).



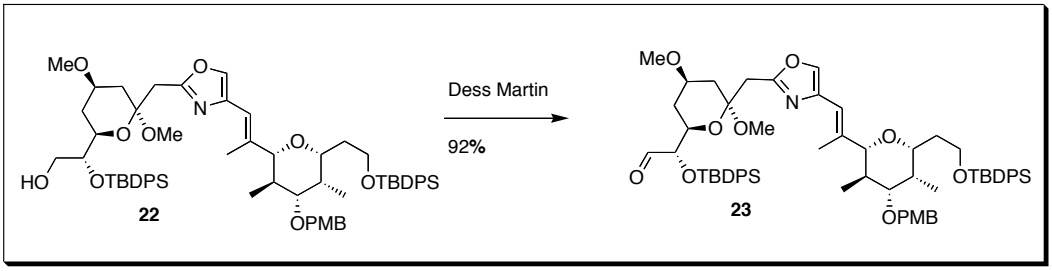
Hemiketal 21: A stock solution of lithium diethylamide was prepared as follows: To a flame-dried flask under nitrogen was added diethylamine (885 μL, 8.56 mmol) and anhydrous THF (2.4 mL). The solution was cooled to –78°C and n-butyllithium (1.7 M in hexanes, 4.7 mL, 8.00 mmol) was added dropwise. The reaction was warmed to 0°C over 10 minutes and titrated (0.98 M).

C20-C32 subunit **5** (440 mg, 0.672 mmol, 1 eq) was dissolved in anhydrous THF (3 mL) and cooled to –78°C. Freshly prepared $LiNEt_2$ (0.98 M, 755μL, 0.74 mmol, 1.1 eq) was added dropwise and the resulting orange solution was stirred at –78°C for 10 min. Lactone **6** (472 mg, 0.672 mmol, 1.0 eq) in THF (2 mL) was added via cannula., followed by a THF rinse (2 mL). The reaction was stirred at –78°C for 45 min and quenched with 20 mL of H_2O. After warming to room temperature, the layers were separated and the aqueous layer was extracted with 3 × 50 mL of EtOAc. The organic layers were dried

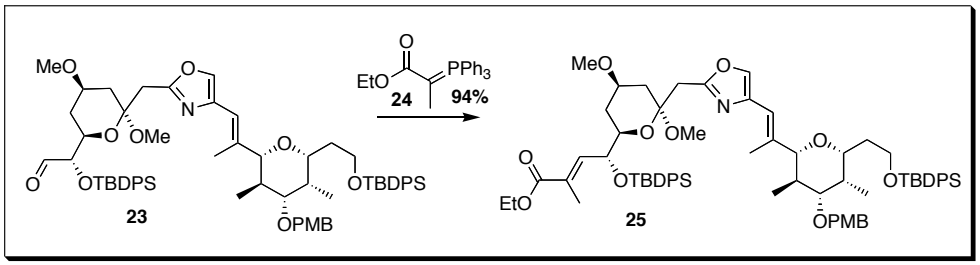
over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (100% CH_2Cl_2 → 10:1 CH_2Cl_2/ EtOAc gradient) afforded 70 mg recovered **5** (16%) and 690 mg **21** (75%, 91% BORSM). Data for **21**: $\mathbf{R}_f$ = 0.23 (8:2 hexanes/EtOAc); **IR** (thin film) 3300(br), 2930 cm^{-1}; **^{1}H NMR** (500 MHz, acetone-d_6) δ 0.80 (d, *J*= 6.3 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 1.00 (s, 9H), 1.05 (s, 9H), 1.10 (m, 1H), 1.35 (app t, *J* = 11.1 Hz, 1H), 1.78 (m, 2H), 1.86 (m, 2H), 1.94 (s, 3H), 2.20 (m, 2H), 2.87 (br m, 2H), 3..02 (s, 2H), 3.08 (dd, *J* = 9.7, 6.1 Hz, 1H), 3.20 (s, 3H), 3.29 (dd, *J* = 10.3, 4.7 Hz, 1H), 3.34 (dd, *J* = 9.6, 5.3 Hz, 1H), 3.47 (d, *J* = 10.5 Hz, 1H), 3.57 (tt, *J* = 11.2, 4.3 Hz, 1H), 3.78 (s, 3H), 3.80 (s, 3H), 3.80 (m, 2H), 3.85 (m, 1H), 3.90 (app q, *J* = 5.4 Hz, 1H), 4.10 (ddd, *J* = 12.0, 3.6, 1.8 Hz, 1H), 4.34 (A<u>B</u>q, J_{AB} = 11.2 Hz, 1H), 4.60 (<u>A</u>Bq, J_{AB} = 11.6 Hz, 1H), 6.17 (s, 1H), 6.79 (m, 2H), 6.91 (m, 2H), 7.20 (series of m, 9H), 7.30-7.45 (series of m, 19H), 7.68 (m, 10 H). **^{13}C NMR** (125 MHz, acetone-d_6) δ; 6.5 (CH_3), 14.2 (CH_3), 14.5 (CH_3), 19.8 (C), 20.1 (C), 27.4 (CH_3), 27.5 (CH_3), 33.1 (CH_2), 34.2 (CH), 35.2 (CH), 36.9 (CH_2), 41.1 (CH_2), 41.4 (CH_2), 55.4 (CH_3), 55.6 (CH_3), 61.6 (CH_2), 65.66 (CH_2), 70.1 (CH_2), 70.4 (CH), 74.4 (CH), 75.4 (CH), 75.7 (CH), 84.1 (CH), 87.4 (C), 89.8 (CH), 97.6 (C), 113.8 (CH), 114.5 (CH), 118.9 (CH), 127.5 (CH), 128.3 (CH), 128.5 (CH), 128.7 (CH), 129.3 (CH), 129.4 (CH), 130.1 (CH), 130.6 (CH), 131.4 (CH), 132.1 (CH), 134.6 (C), 134.7 (C), 134.9 (C), 136.3 (CH), 136.5 (C), 136.7 (CH), 136.8 (CH), 137.2 (CH), 138.8 (C), 139.1 (C), 145.7 (C), 145.9 (C), 159.6 (C), 160.2 (C), 161.1 (C). **HRMS** (MNa^+) calcd 1376.6654 obsd 1376.6675; **Optical Rotation** $[\alpha]_D^{23}$ = + 17.3 (*c* 1.0, CH_2Cl_2).



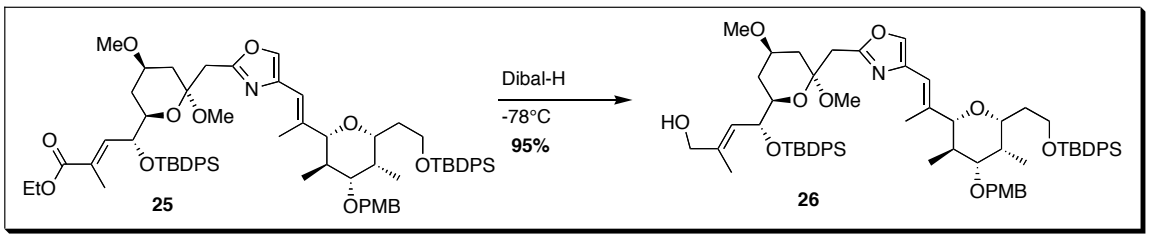
Mixed Methyl Ketal 22: Hemiketal **21** (249 mg, 0.188 mmol) was slurried in 15 mL of dry MeOH at 30°C. Anhydrous CH_2Cl_2 (4 mL) was added to dissolve **21**. Next, PPTS (46 mg, 0.188 mmol, 1 eq) was added and the reaction mixture was stirred at 30°C for 26 h. The solvent was removed *in vacuo* and replaced with EtOAc (150 mL). The organic layer was washed with 20 mL of saturated $NaHCO_3$, and the aqueous layer was back extracted with 2 × 20 mL of EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (8:2 → 7:3 hexanes/ EtOAc) afforded 151 mg **22** 75%) and 22 mg (11%) of an intermediate des-MMTr hemiketal. The intermediate was recycled to product using 1 eq PPTS (as above) to afford an additional 12.5 mg of **22** (55% yield, 81% total after 1 recycle). Data for **22**: $\mathbf{R}_f$ = 0.16 (8:2 hexanes/ethyl acetate); **IR** (thin film) 3400(br), 2958, 1111 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.80 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 7.1 Hz, 3H), 1.06 (s, 9H), 1.09 (s, 9H), 1.19-1.31 (m, 2H), 1.69 (qt, *J* = 8.0, 6.0 Hz, 1H), 1.74-1.90 (series of m, 2H), 1.85 (s, 3H), 2.10 (m, 2H), 2.14 (ddd, *J* = 12.4, 3.9, 1.3 Hz, 1H), 3.04 (ABq, 2H), 3.06 (3H), 3.19 (dd, *J* =10.4, 4.6 Hz, 1H), 3.30 (s, 3H), 3.41 (d, *J* = 10.3 Hz, 1H), 3.50 (tt *J* = 10.9, 4.7 Hz, 1H), 3.60 (m, 2H), 3.65 (ddd, *J* = 7.2, 5.1, 1.9 Hz, 1H), 3.68-3.80 (series of m, 3H), 3.80 (s, 3H), 3.95 (dt, *J* = 5.9, 4.1 Hz, 1H), 4.29 (A<u>B</u>q, J_{AB} = 10.9 Hz, 1H), 4.58 (<u>A</u>Bq, J_{AB} = 11.0 Hz, 1H), 6.18 (s, 1H), 6.83 (m, 2H), 7.28 (m, 4H), 7.40 (series of m, 12H), 7.50 (s, 1H), 7.63 (series of m, 8H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 6.0, 13.7, 14.2, 19.2,19.3, 26.8, 27.0, 30.6, 33.2, 34.1, 35.4, 35.7, 39.1, 47.8, 55.2, 55.5, 69.6, 71.4, 73.1, 73.5, 74.8, 83.4, 88.8, 99.9, 113.7, 118.5, 127.6, 127.7, 127.7, 129.4, 129.5, 129.9, 129.9, 130.7, 133.4, 133.6, 133.8, 134.0, 135.5, 135.6, 135.7, 135.8, 138.1, 138.5, 158.9, 159.1; **HRMS** (MH^+) calcd 1096.5790 obsd 1096.5784; **Optical Rotation** $[\alpha]_D^{23}$ = + 16.2 (*c* 1.0, $CHCl_3$).



Aldehyde 23: Dess-Martin periodinane (940 mg, 2.22 mmol, 4 eq) was added to a solution of mixed methyl ketal **22** (600 mg, 0.554 mmol) in CH_2Cl_2 (55 mL) at room temperature. The reaction was stirred for 30 min, then H_2O (10 μL, 0.554 mmol, 1 eq) was added. After 20 min, the reaction was quenched with 55 mL of a 1:1 solution of 10% $Na_2S_2O_3$ / saturated $NaHCO_3$. The reaction was allowed to stir for an additional 30 min before being transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with 3 × 50 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concetrated *in vacuo*. Purification by column chromatography (8:2 hexanes/ ethyl acetate) provided pure aldehyde **23** (550 mg, 92%). Data for **23**: $\mathbf{R_f}$ = 0.34 (8:2 hexanes/ethyl acetate); **IR** (thin film) 2958, 1734, 1111 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.4 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H), 1.06 (s, 9H), 1.12 (s, 9H), 1.39 (app q, *J* = 11.9 Hz, 1H), 1.42 (dd, *J* = 12.5, 11.1 Hz, 1H), 1.70 (m, 1H), 1.78-1.88 (series of m, 3H), 1.88 (s, 3H), 2.11 (m, 1H), 2.20 (ddd, *J* = 12.6, 4.2, 1.2 Hz, 1H), 3.03 (A<u>B</u>q, J_{AB} = 14.8 Hz, 1H), 3.13 (s, 3H), 3.20 (<u>A</u>Bq, J_{AB} = 14.9 Hz, 1H), 3.21 (m, 1H), 3.25 (s, 3H), 3.41 (d, *J* = 10 Hz, 1H), 3.55 (tt, *J* = 11.0, 4.6 Hz, 1H), 3.66 (m, 1H), 3.70-3.85 (series of m, 3H), 3.81 (s, 3H), 4.10 (dd, *J* = 3.8, 1.4 Hz, 1H), 4.30 (A<u>B</u>q, J_{AB} = 11.0 Hz, 1H), 4.57 (<u>A</u>Bq, J_{AB} = 11.0 Hz, 1H), 6.20 (br s, 1H), 6.89 (m, 2H), 7.29 (m, 2H), 7.40 (m, 12H), 7.52 (s, 1H), 7.67 (m, 8H), 9.63 (d, *J* = 1.1 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 6.0, 13.8, 14.2, 19.2, 19.5, 26.8, 26.9, 32.1, 33.3, 34.1, 35.3, 35.8, 39.0, 48.0, 55.2, 55.5, 60.7, 69.6, 71.6, 72.8, 74.8, 79.3, 83.5, 88.9, 100.1, 113.7, 118.5, 127.6, 127.8, 129.3, 129.5, 130.1, 130.7, 132.7, 132.8, 133.8, 133.9, 135.52, 135.54, 135.8, 135.9, 136.0, 138.0, 138.4, 158.8, 159.1, 203.2; **HRMS** (MH^+) calcd 1094.5634 obsd 1094.5674; **Optical Rotation** $[\alpha]_D^{23}$ = + 2.3 (*c* 1.0, $CHCl_3$).

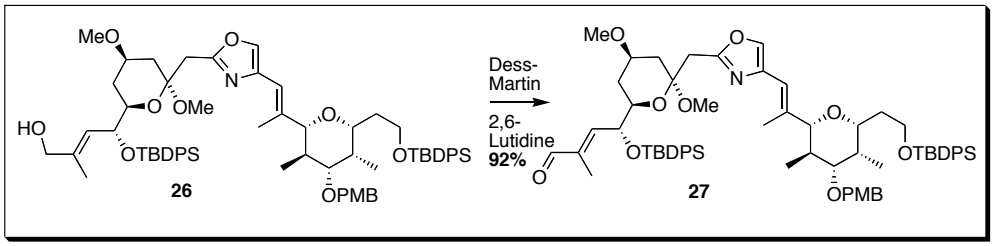


Ester 25: To a solution of aldehyde **23** (300 mg, 0.274 mmol) in dry toluene (10 mL) was added (1-ethoxycarbonylethylidene)triphenylphosphorane **24** (297 mg, 0.822 mmol, 3 eq). The reaction was heated to 80°C for 24 h, cooled to RT, and concentrated *in vacuo*. Purification by column chromatography (7:3 hexanes/Et_2O) afforded 305 mg (94%) of ester **25**. Data for **25**: $\mathbf{R}_f$ = 0.19 (9:1 hexanes/ acetone); **IR** (thin film) 3400(br), 2958, 1111 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.84 (d, *J* = 6.4 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H), 1.07 (s, 9H), 1.08 (m, 1H), 1.09 (s, 9H),1.27 (t, *J* = 7.3 Hz, 3H), 1.35 (d, *J* = 1.5 Hz, 3H), 1.40 (m, 1H), 1.70 (m, 1H), 1.80-1.90 (m, 2H), 1.90 (d, *J* = 0.9Hz, 3H), 1.96 (qdd *J* = 6.9, 5.0, 1.4 Hz, 1H), 2.23 (ddd, *J* = 12.5, 4.5, 1.3 Hz, 1H), 2.98 (A<u>B</u>q, J_{AB} = 14.6 Hz, 1H), 3.20 (dd, *J* = 10.4, 5.7 Hz, 1H), 3.27 (s, 3H), 3.29 (s, 3H), 3.26-3.30 (m, 1H), 3.41 (d, *J* = 10.0 Hz, 1H), 3.59 (tt, *J* = 10.8, 4.5 Hz, 1H), 3.66 (m, 2H), 3.75 (m, 1H), 3.80 (m, 1H), 3.81 (s, 3H), 4.13 (<u>AB</u>X_3 , J_{AX} = J_{BX} = 7.2 Hz, J_{AB} = 10.5 Hz, ν_a = 4.15, ν_b = 4.12, 2H), 4.30 (A<u>B</u>q, J_{AB} = 11.0 Hz, 1H), 4.53 (dd, *J* = 9.4, 6.2 Hz, 1H), 4.58 (<u>A</u>Bq, J_{AB} = 10.9 Hz, 1H), 6.21 (s, 1H), 6.58 (dd, *J* = 9.1, 1.2 Hz, 1H), 6.89 (m, 2H), 7.29 –7.42 (series of m, 14H), 7.52 (s, 1H), 7.66 (m, 6H), 7.75 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 6.0, 12.9, 13.7, 14.2, 19.2, 19.3, 26.8, 26.9, 31.7, 33.3, 34.1, 35.4, 35.8, 39.1, 47.9, 55.2, 55.6, 60.5, 60.7, 69.5, 72.1, 72.9, 73.2, 74.8, 83.5, 88.9, 99.9, 113.7, 118.5, 127.3, 127.5, 127.6, 129.3, 129.5, 129.6, 129.7, 130.7, 133.4, 133.6, 133.9, 135.50, 135.53, 135.9, 138.0, 138.3, 139.1, 158.9, 159.1, 167.4; **HRMS** (MH^+) calcd 1178.6209 obsd 1178.6178; **Optical Rotation** $[\alpha]_D^{23}$ = -1.5 (*c* 1.0, $CHCl_3$).

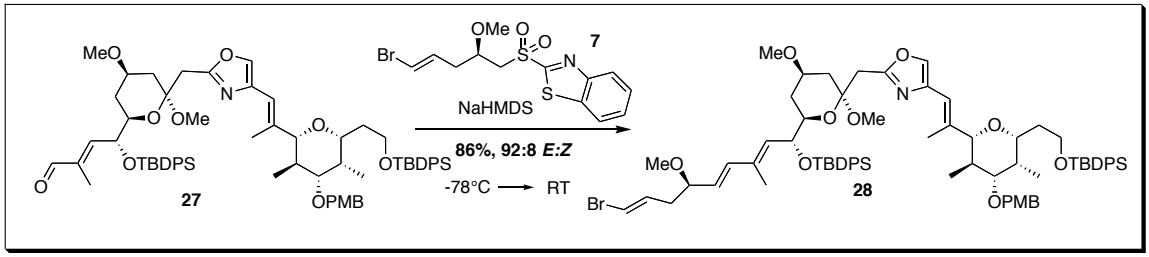


Allylic alcohol 26: Ester **25** (295 mg, 0.25 mmol) was dissolved in 25 mL of CH_2Cl_2 and cooled to –78°C. To this solution was added Dibal-H (1.5 M in toluene, 0.67 mL, 1 mmol, 4 eq). The reaction was stirred at –78°C for 1 h and quenched with 1 mL of MeOH. After warming to RT, 10 mL of saturated NH_4Cl and 20

mL of saturated Rochelle's salt were added and the biphasic mixture was stirred for 30 min. The layers were separated and the aqueous layer was extracted with 1 × 50 mL and 2 × 30 mL portions of CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (8.5:1.5 hexanes/ acetone) afforded 271.5 mg (95%) allylic alcohol **26**. Data for **26**: $\mathbf{R}_f$ = 0.22 (8:2 hexanes/ acetone); **IR** (thin film) 3450(br), 2958, 1111 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.84 (d, *J* = 6.3 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 1.07 (s, 9H), 1.073 (s, 9H), 1.04-1.10 (m, 1H), 1.13 (s, 3H), 1.41 (dd, *J* = 12.5, 11.0 Hz, 1H), 1.71 (m, 1H), 1.80-1.95 (series of m, 3H), 1.91 (s, 3H), 2.12 (m, 1H), 2.22 (dd, *J* = 8.4, 1.3 Hz, 1H), 3.03 (A<u>B</u>q, J_{AB} = 14.7, 1H), 3.21 (dd, *J* = 10.3, 4.6 Hz, 1H), 3.29 (s, 3H), 3.33 (<u>A</u>Bq, J_{AB} = 14.6 Hz, 1H), 3.35 (s, 3H), 3.43 (d, *J* = 10.3 Hz, 1H), 3.55-3.82 (series of m, 7H), 3.81 (s, 3H), 4.30 (A<u>B</u>q, J_{AB} = 11.0 Hz, 1H), 4.52 (dd, *J* = 9.1, 6.7 Hz, 1H), 4.58 (<u>A</u>Bq, J_{AB} = 11.0 Hz, 1H), 5.25 (dd, *J* = 9.2, 1.2 Hz, 1H), 6.21 (s, 1H), 6.90 (m, 2H), 7.28-7.45 (m, 14H), 7.54 (s, 1H), 7.68 (m, 6H), 7.79 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 6.0, 13.7, 14.0, 14.2, 19.2, 19.3, 26.8, 26.9, 32.1, 33.2, 34.1, 35.5, 35.7, 39.1, 47.9, 55.2, 55.6, 60.7, 67.8, 69.5, 72.2, 73.4, 74.8, 83.5, 88.9, 99.8, 113.7, 118.5, 124.3, 127.2, 127.4, 127.6, 129.3, 129.4, 129.5, 130.7, 133.8, 133.9, 134.8, 135.5, 135.5, 135.9, 136.0, 137.9, 138.0, 138.4, 159.1; **HRMS** (MNa^+) calcd 1158.5923 obsd 1158.5955; **Optical Rotation** $[\alpha]_D^{23}$ + 11.1 (*c* 1.0, $CHCl_3$).

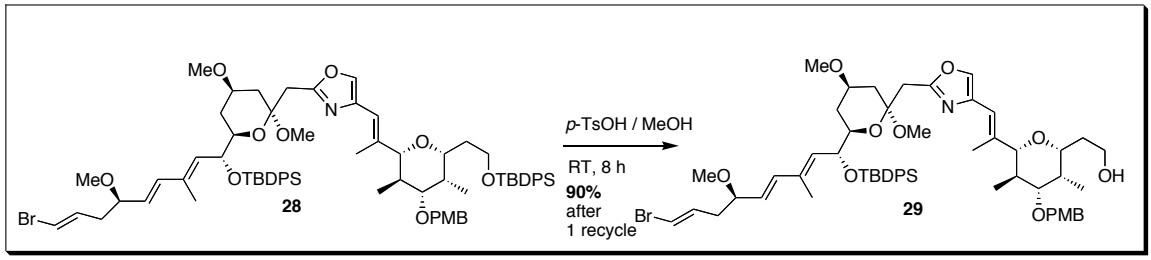


Aldehyde 27: Allylic alcohol **26** (265 mg, 0.23 mmol) was dissolved in 23 mL of dry CH_2Cl_2. Dess-Martin periodinane (400 mg, 0.93 mmol, 4 eq) and 2,6-lutidine (27 μL, 0.23 mmol, 1 eq) were added to the reaction flask. After 30 min, H_2O (4 μL, 0.23 mmol, 1 eq) was added. The reaction was stirred for an additional 1 min before being quenched with 30 mL of a 1:1 solution of 10% $Na_2S_2O_3$ / saturated $NaHCO_3$. After stirring for 30 min, the reaction was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with 2 × 30 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (9:1 hexanes/ acetone) afforded 244 mg (92%) of aldehyde **27**. Data for **27**: $\mathbf{R}_f$ = 0.31 (8:2 hexanes/acetone); **IR** (thin film) 2958, 1694, 1111 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.3 Hz, 3H), 0.94 (d, *J* = 7.2 Hz, 3H), 1.05 (s, 9H), 1.09 (s, 9H), 1.15 (app q, *J* = 12.3 Hz, 1H), 1.31 (s, 3H), 1.39 (dd, *J* = 12.4, 10.9 Hz, 1H), 1.70 (m, 1H), 1.80-1.90 (series of m, 3H), 1.88 (d, *J* = 1.0 Hz, 3H), 2.01 (m, 1H), 2.11 (m, 1H), 2.24 (ddd, *J* = 12.8, 4.7, 1.7 Hz, 1H), 2.96 (A<u>B</u>q, J_{AB} = 14.9 Hz, 1H), 3.20 (m, 2H), 3.20 (s, 3H), 3.29 (s, 3H), 3.40 (d, *J* = 10.3 Hz, 1H), 3.56 (tt, *J* = 10.9, 4.5 Hz, 1H), 3.64-3.80 (series of m, 3H), 3.80 (s, 3H), 4.29 (A<u>B</u>q, J_{AB} = 11 Hz, 1H), 4.57 (<u>A</u>Bq, J_{AB} = 11 Hz, 1H), 4.70 (dd, *J* = 8.8, 5.6Hz, 1H), 6.18 (s, 1H), 6.26 (dd, *J* = 8.6, 1.1 Hz, 1H), 6.88 (m, 2H), 7.29-7.43 (series of m, 14H), 7.47 (s, 1H), 7.60-7.72 (series of m, 8H), 9.20 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 6.0, 9.6, 13.8, 14.2, 19.24, 19.29, 26.8, 26.9, 31.6, 33.3, 34.1, 35.4, 35.8, 39.1, 47.8, 55.2, 55.6, 60.7, 69.6, 71.6, 72.7, 73.1, 74.8, 83.5, 88.9, 100.0, 113.7, 118.4, 127.6, 127.7, 129.3, 129.5, 129.9, 130.0, 130.7, 133.0, 133.4, 133.8, 133.9, 135.52, 135.55, 135.8, 135.9, 136.0, 138.0, 138.5, 139.9, 150.8, 158.8, 159.1, 194.7; **HRMS** (MNa^+) calcd 1156.5766 obsd 1156.5746; **Optical Rotation** $[\alpha]_D^{23}$ + 2.5 (*c* 1.0, $CHCl_3$).

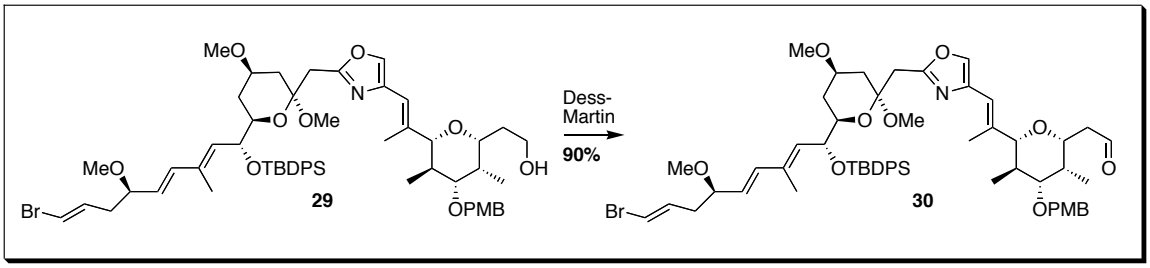


C20-C46 Fragment 28 : Aldehyde **27** (240 mg, 0.216 mmol, 1 eq) and sulfone **7** (87.5 mg, 0.232 mmol, 1.1 eq) were combined in a 10 mL round-bottomed flask and azeotroped with 2 × 3 mL of anhydrous benzene. The combined solids were then dissolved in anhydrous THF (2 mL) and placed in a –78°C bath.

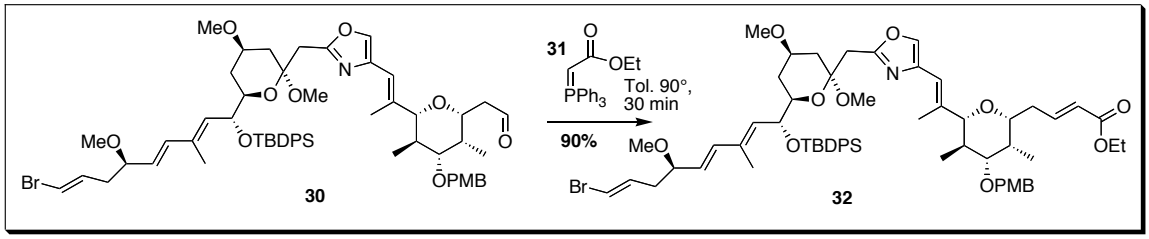
To this solution was added NaHMDS (1 M in THF, 230 μL, 0.232 mmol, 1.1 eq) via dropwise addition. The reaction was allowed to stir at –78°C for 30 min, warmed to 0°C for 15 min, then warmed to RT for 30 min. The reaction was quenched by addition of 10 mL of a pH = 7 buffer solution and extracted with 4 × 20 mL of ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture typically consists of desired product C41-C42 *E* **28**, its undesired C41-C42 *Z* isomer, unreacted aldehyde **28**, unreacted sulfone **7**, and 2-hydroxybenzothiazole. Clean C41-C42 *E* **28** is obtained by the following purification sequence: The crude reaction mixture is loaded onto a silica gel column packed with 8:2 CH_2Cl_2/ hexanes. An 8:2 CH_2Cl_2/ hexanes → 100% CH_2Cl_2 gradient is run to elute unreacted sulfone **7**. The solvent is then switched to 10:0.2 CH_2Cl_2/ EtOAc to elute 2-hydroxybenzothiazole. After the 2-hydroxybenzothiazole has eluted, the solvent is again switched to 10:0.6 hexanes/ acetone to isolate 242 mg (86%) **28** (92:8 *E* : *Z*) and 30 mg of residual aldehyde **27** (12%, 97% **28** BORSM). Pure *E* **28** can be obtained by preparative HPLC (Phenomenex Sphereclone® Silica10 mm × 250 mm, 88/12 hexanes/ethyl acetate). Data for pure *E* **28** : $\mathbf{R}_f$ = 0.31 (9:1 hexanes/acetone); **IR** (thin film) 2930, 1111 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.84 (d, *J* = 6.4 Hz, 3H), 0.95 (d *J* = 6.9 Hz, 3H), 1.05 (s, 9H), 1.06 (s, 9H), 1.20 (s, 3H), 1.36 (dd, *J* = 12.4, 11.2 Hz, 1H), 1.70 (m, 1H), 1.72-1.95 (series of m, 3H), 1.90 (s, 3H), 2.11 (m, 1H), 2.23 (m, 2H), 2.32 (dt, *J* = 13.6, 6.6 Hz, 1H), 2.95 (A<u>B</u>q, J_{AB} = 14.7 Hz, 1H), 3.20 (m, 1H), 3.21 (s, 3H), 3.28 (s, 3H), 3.30 (s, 3H), 3.33 (<u>A</u>Bq J_{AB} = 14.7 Hz, 1H), 3.42 (d, *J* = 10.1 Hz, 1H), 3.51-3.80 (series of m, 6H), 3.81 (s, 3H), 4.30 (A<u>B</u>q, J_{AB} = 11.0 Hz, 1H), 4.54 (dd, *J* =9.1, 6.6 Hz, 1H), 4.57 (<u>A</u>Bq, J_{AB} = 11.0 Hz, 1H), 5.23 (dd, *J* = 15.4, 7.9 Hz, 1H), 5.37 (d, *J* = 9.1 Hz, 1H), 6.00 (d, *J* = 15.5 Hz, 1H), 6.10 (d, *J* = 13.6 Hz, 1H), 6.20 (dt, *J* = 13.6, 6.9 Hz,1H), 6.21 (s, 1H), 6.88 (m, 2H), 7.27-7.42 (series of m, 14H), 7.53 (s, 1H), 7.64 (m, 6H), 7.75 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 6.0, 12.9, 13.8, 14.2, 19.2, 19.3, 26.8, 26.9, 32.2, 33.3, 34.1, 35.4, 35.8, 39.1, 39.2, 47.9, 55.2, 55.6, 56.2, 60.7, 69.6, 72.4, 73.4, 73.5, 74.8, 81.1, 83.5, 88.8, 99.9, 106.2, 113.8, 118.2, 127.2, 127.4, 127.6, 127.8, 129.3, 129.4, 129.5, 130.7, 131.5, 133.8, 134.0, 134.1, 135.5, 135.6, 136.0, 136.1, 137.3, 137.7, 138.8, 159.1, 159.2; **HRMS** (MNa^+) calcd 1316.5654 obsd 1316.5651; **Optical Rotation** $[\alpha]_D^{23}$ = -13.9 (*c* 1.0, $CHCl_3$).



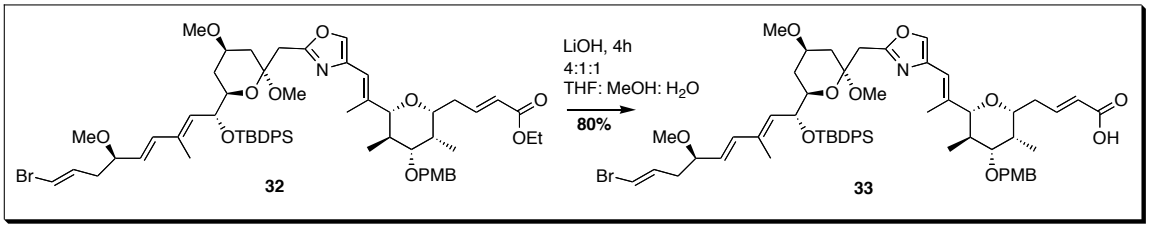
Primary Alcohol 29 : TBDPS-ether **28**(140 mg, 0.108 mmol) was slurried in 10 mL of anhydrous MeOH. Dichloromethane (1 mL) was added to dissolve **28**, followed by addition of *p*-TsOH (20 mg, 0.108 mmol, 1 eq). The reaction mixture was stirred at RT for 8h and quenched with 10 mL of saturated $NaHCO_3$ solution. Ether (100 mL) was added and the layers were separated. The aqueous layer was extracted with 2 × 50 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (8.5 :1.5 hexanes / acetone) afforded 95 mg (83%) **29** and 12 mg (8.6 %) recovered **28**. Recovered **28** was resubjected to the above reaction conditions to afford an additional 7 mg (71%, 90% total after 1 recycle) **29**. Data for **29**: $\mathbf{R}_f$ = 0.10 (8:2 hexanes/acetone); **IR** (thin film) 3455(br), 2958, 1110 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.84 (d, *J* = 6.4 Hz, 3H), 1.00 (d, *J* = 7.3 Hz, 3H), 1.06 (s, 9H), 1.20 (s, 3H), 1.35 (dd, *J* = 12.6, 11.2, 1H), 1.40 (m, 1H), 1.51 (m, 1H), 1.83 (m, 1H), 1.90 (s, 3H), 1.92 (m, 1H), 2.00 (m, 1H), 2.07 (qdd, *J* = 6.9, 4.8, 2.1 Hz, 1H), 2.21 (m, 2H), 2.33 (dt, *J* =14.0, 6.7 Hz, 1H), 2.96 (d, *J* = 15.1 Hz, 1H), 3.21 (s, 3H), 3.23 (m, 1H), 3.27 (s, 3H), 3.28 (s, 3H), 3.30 (m, 1H), 3.53 –3.61 (series of m, 3H), 3.51 (d, *J* = 10.3 Hz, 1H), 3.66 (dt, *J* = 9.9, 1.9 Hz, 1H), 3.74 - 3.80 (m, 2H), 3.81 (s, 3H), 4.30 (A<u>B</u>q, J_{AB} = 11.2 Hz, 1H), 4.53 (dd, *J* = 9.1, 6.8 Hz, 1H), 4.58 (<u>A</u>Bq, J_{AB} = 11.1 Hz, 1H), 5.24 (dd, *J* = 15.7, 8.2 Hz, 1H), 5.36 (d, *J* = 9.1 Hz, 1H), 6.00 (d, *J* = 15.6 Hz, 1H), 6.10 - 6.19 (m, 2H), 6.21 (s, 1H), 6.90 (m, 2H), 7.27-7.42 (series of m, 8H), 7.51 (s, 1H), 7.62 (m, 2H), 7.74 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 6.2, 12.9, 13.6, 14.0, 19.4, 26.9, 32.2, 33.1, 34.9, 35.1, 35.4, 39.1, 39.2, 47.9, 55.3, 55.6, 56.2, 62.0, 69.7, 72.4, 73.4, 73.5, 78.9, 81.1, 82.8, 89.1, 99.8, 106.2, 113.8, 118.7, 127.2, 127.4, 127.7, 129.3, 129.4, 129.5, 130.5, 131.5, 133.8, 134.1, 134.9, 136.0, 136.1, 136.2, 137.3, 137.6, 159.2, 159.3 ppm; **HRMS** (MNa^+) calcd 1078.4476 obsd 1078.4447; **Optical Rotation** $[\alpha]_D^{23}$ = -15.0 (*c* 1.0, $CHCl_3$).



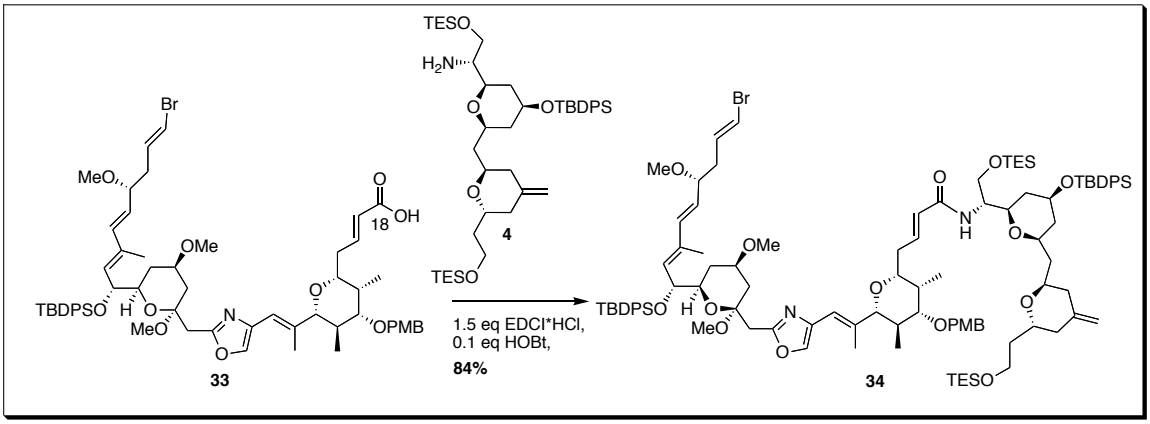
Aldehyde 30: To a solution of 1° alcohol **29** (50 mg, 0.047 mmol) in 4.7 mL of CH_2Cl_2 was added Dess-Martin periodinane (80 mg, 0.110 mmol, 4 eq). After 20 min, H_2O (1 μL, 0.055 mmol, 1.2 eq) was added. The reaction was stirred for an additional 5 min, and quenched with 3 mL of a 1:1 solution of 10% $Na_2S_2O_3$ / saturated $NaHCO_3$, followed by stirring for 20 min. The crude reaction mixture was diluted with CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with 2 × 10 mL portions of CH_2Cl_2 and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* Purification by column chromatography (8.5:1.5 hexanes/ acetone) afforded 45 mg (90%) of pure **30** as a white foam. Data for **30** : $\mathbf{R}_f$ = 0.19 (8:2 hexanes/acetone); **IR** (thin film), 2931, 1727, 1110 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.84 (d, *J* = 6.4 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H), 1.06 (m, 1H), 1.06 (s, 9H), 1.20 (s, 3H), 1.36 (dd, *J* = 12.8, 11.2 Hz, 1H), 1.85 (tq, *J* = 10.4, 6.4 Hz, 1H), 1.90 (s, 3H), 1.91 (qdd, *J* = 6.8, 4.6, 1.8 Hz, 1H), 2.14 (m, 1H), 2.25 (m, 2H), 2.31 (dt, *J* = 13.8, 6.9 Hz, 1H), 2.43 (A<u>B</u>XY, J_{AB} = 16.8 Hz, J_{BX} = 4.6 Hz, J_{BY} = 2.1 Hz, 1H), 2.75 (<u>A</u>BXY, J_{AB} = 16.8 Hz, J_{AX} = 8.7 Hz, J_{AY} = 1.9 Hz, 1H), 2.98 (d, *J* = 14.7 Hz, 1H), 3.21 (s, 3H), 3.25-3.31 (m, 2H), 3.27 (s, 3H), 3.28 (s, 3H), 3.50-3.61 (series of m, 4H), 3.81 (s, 3H), 4.02 (ddd *J* = 8.5, 4.7, 1.7 Hz, 1H), 4.31 (A<u>B</u>q, J_{AB} = 10.8 Hz, 1H) 4.52 (dd, *J* = 9.2, 5.9 Hz, 1H), 4.59 (<u>A</u>Bq J_{AB} = 11.3 Hz, 1H), 5.22 (dd, *J* = 15.4, 7.9 Hz, 1H), 5.37 (d, *J* = 9.2 Hz, 1H), 6.00 (d, *J* = 15.8 Hz, 1H), 6.09-6.19 (series of m, 2H), 6.21 (s, 1H), 6.90 (m, 2H), 7.28-7.42 (m, 8H), 7.52 (s, 1H), 7.62 (m, 2H), 7.73 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 6.1, 12.9, 13.6, 14.1, 19.3, 26.9, 32.2, 33.0, 34.2, 35.4, 39.1, 39.2, 46.9, 47.9. 55.2, 55.6, 56.2, 69.8, 72.4, 73.4, 73.5, 81.1, 82.6, 89.1, 99.8, 106.2, 113.8, 118.6, 127.2, 127.4, 127.7, 129.3, 129.4, 129.5, 130.4, 131.5, 133.8, 134.1, 134.9, 136.0,136.1,136.2,137.3, 137.5, 137.9, 159.2, 159.3, 201.2; **HRMS** (MNa^+) calcd 1076.4320 obsd 1076.4296; **Optical Rotation** $[\alpha]_D^{23}$ = -14.1 (*c* 1.0, $CHCl_3$).



Ester 32: Aldehyde **30** (126 mg, 0.119 mmol) and (carbethoxymethylene) triphenylphosphorane **31** (165 mg, 0.476 mmol, 4 eq) were dissolved in 12 mL dry toluene and heated to 90°C for 30 min. The reaction was cooled to RT and the toluene was removed under vacuum. Purification by column chromatography (10:1 → 9:1 hexanes/ acetone) afforded 121 mg (90%) of pure ester **32**. Data for **32** : $\mathbf{R}_f$ = 0.28 (8:2 hexanes/ acetone); **IR** (thin film), 2931, 1717, 1105 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.3 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 1.05 (m, 1H), 1.06 (s, 9H),1.20 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.35 (dd, *J* = 12.6, 11.3 Hz, 1H), 1.84 (m, 1H), 1.90 (s, 3H), 1.91 (m, 1H), 2.10 (m, 1h), 2.20-2.38 (series of m, 4H), 2.55 (dtd, *J* = 14.0, 7.2, 1.5 Hz, 1H), 2.98 (d, *J* = 12.1 Hz, 1H), 3.19 (m, 1H), 3.21 (s, 3H), 3.27 (s, 3H), 3.28 (s, 3H), 3.29 (m, 1H), 3.47 (d, *J* = 10.6 Hz, 1H), 3.55 (m, 4H), 3.81 (s, 3H), 4.20 (q, *J* = 7.4 Hz, 2H), 4.30 (A<u>B</u>q, J_{AB} = 11.0 Hz, 1H), 4.52 (dd, *J* = 9.2, 6.0 Hz, 1H), 4.58 (<u>A</u>Bq, J_{AB} = 10.9 Hz, 1H), 5.24 (dd, *J* = 15.4, 7.7 Hz, 1H), 5.36 (d, *J* = 9.1 Hz, 1H), 5.90 (d, *J* = 15.8 Hz, 1H), 6.00 (d, *J* = 16.1 Hz, 1H), 6.09-6.20 (m, 2H), 6.22 (s, 1H), 6.89 (m, 2H), 6.92 (ddd, *J* = 15.7, 8.1, 6.4 Hz, 1H), 7.28-7.42 (series of m, 8H), 7.53 (s, 1H), 7.63 (m, 2H), 7.75 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 5.7, 12.9, 13.7, 14.1, 14.2, 19.3, 26.9, 32.2, 33.2, 33.8, 35.4, 35.8, 39.1, 39.2, 47.9, 55.2, 55.5, 56.1, 60.2, 69.7, 72.4, 73.3, 76.7, 81.1, 83.0, 89.0, 99.8, 106.2, 113.8, 118.6, 123.3, 127.2, 127.4, 127.7, 129.3, 129.4, 129.5, 130.5, 131.5, 133.8, 134.1, 134.9, 135.99, 136.04, 136.13, 137.3, 137.7, 138.1, 145.0, 159.16, 159.19, 166.4; **HRMS** (MNa^+) calcd 1146.4738 obsd 1146.4778; **Optical Rotation** $[\alpha]_D^{23}$ = -8.1 (*c* 1.0, $CHCl_3$).

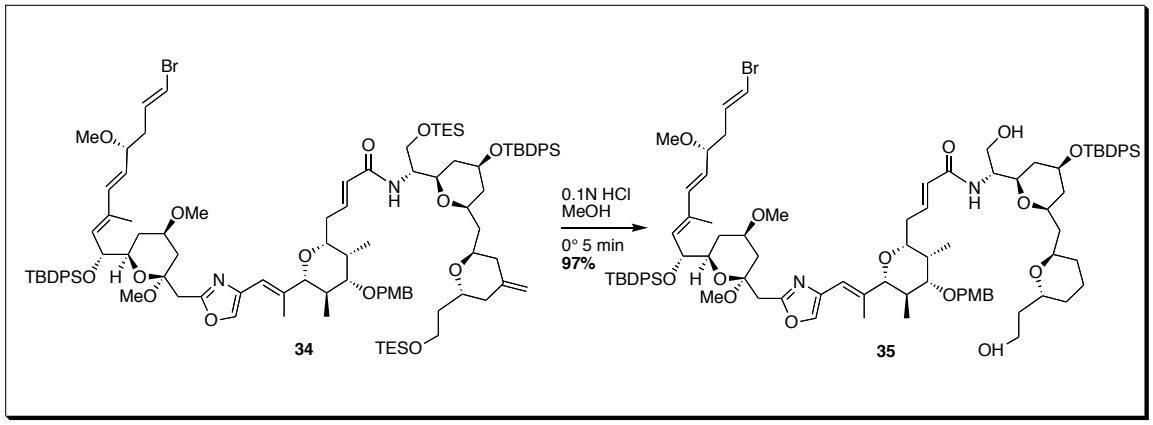


C18-C46 Acid 33: Ethyl ester **32** (70 mg, 0.0622 mmol) was dissolved in 4 mL of THF, 1 mL of MeOH, and 1 mL of H_2O. Lithium hydroxide (1 M solution in H_2O, 2 mL, 2 mmol, 32 eq) was added dropwise. The reaction was stirred at RT for 4 h, diluted with 10 mL H_2O, and the pH was carefully adjusted to 5 using 1 N HCl. Ethyl acetate (50 mL) was added, the layers were separated, and the aqueous layer was extracted with 2 × 50 mL of EtOAc. The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (7:3 hexanes/ acetone) afforded 54 mg (80%) of acid **33**. Data for **33**: $\mathbf{R}_f$ = 0.15 (7:3 hexanes/acetone); **IR** (thin film), 2931, 1699, 1110 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.83 (d, *J* = 6.5 Hz, 3H), 0.98 (d, *J* = 7.1 Hz, 3H), 1.06 (m, 1H), 1.06 (s, 9H), 1.20 (s, 3H), 1.30 (dd, *J* = 12.7, 11.3 Hz, 1H), 1.84 (m, 1H), 1.90 (s, 3H), 1.91 (m, 1H), 2.09 (m, 1H), 2.20-2.40 (series of m, 4H), 2.56 (dt, *J* = 13.7, 6.6 Hz, 1H), 2.98 (ABq, J_{AB} = 15.2 Hz, 1H), 3.20 (m, 1H), 3.21 (s, 3H), 3.27 (s, 3H), 3.28 (s, 3H), 3.31 (ABq J_{AB} = 14.8 Hz, 1H), 3.47 (d, *J* = 10.5 Hz, 1H), 3.52-3.61 (series of m, 4H), 3.80 (s, 3H), 4.30 (ABq, J_{AB} = 11.0 Hz, 1H), 4.52 (dd, *J* = 9.0, 6.5 Hz, 1H), 4.57 (ABq, J_{AB} = 11.1 Hz, 1H), 5.24 (dd, *J* = 15.4, 7.8 Hz, 1H), 5.36 (d, *J* = 9.3 Hz, 1H), 5.90 (d, *J* = 15.8 Hz, 1H), 6.00 (d, *J* = 16.0 Hz, 1H), 6.09-6.19 (m, 2H), 6.22 (s, 1H), 6.88 (m, 2H), 7.03 (ddd, *J* = 15.4, 8.5, 6.6 Hz, 1H), 7.28-7.42 (series of m, 8H), 7.52 (s, 1H), 7.62 (m, 2H), 7.75 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 5.7, 12.9, 13.7, 14.1, 19.3, 26.9, 32.1, 33.2, 33.9, 35.4, 35.9, 39.0, 39.1, 47.9, 55.2, 55.5, 56.2, 69.8, 72.4, 73.39, 73.44, 76.4, 81.1, 83.0, 89.0, 99.8, 106.2, 113.8, 118.6, 122.6, 127.2, 127.4, 127.7, 129.3, 129.4, 129.5, 130.5, 131.5, 133.8, 134.0, 134.9, 135.9, 136.0, 136.1, 137.3, 137.7, 137.9, 147.6 159.1, 159.2, 170.7. **HRMS** (MNa^+) calcd 1118.4425 obsd 1118.4390; **Optical Rotation** $[\alpha]_D^{23}$ = -8.8 (*c* 1.0, $CHCl_3$).

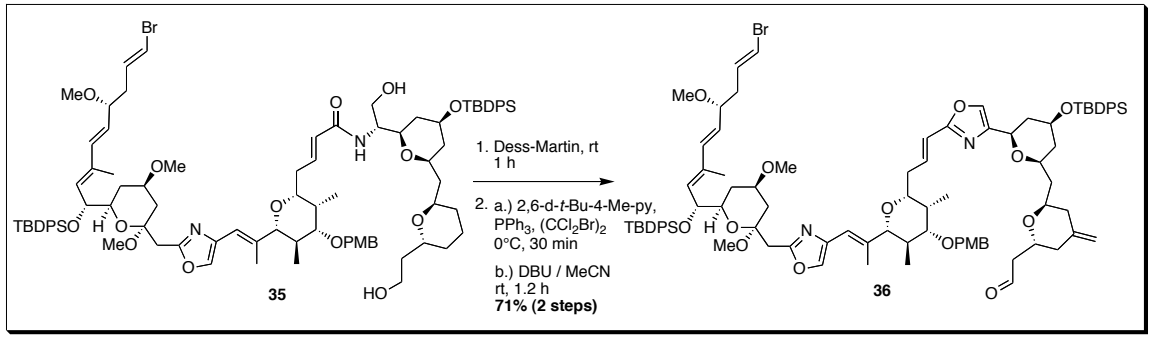


Bis-TES amide 34: To a solution of C3-C17 amine **4** (41.5 mg, 0.053 mmol, 1 eq) and C18-C46 acid **33** (58mg, 0.053 mmol, 1 eq) in 5.3 mL of CH_2Cl_2 was added EDCI•MeI (23.6 mg, 0.080 mmol, 1.5 eq) and HOBt (1.4 mg, 0.010 mmol, 0.2 eq). After stirring at RT for 3 h, the reaction mixture was deposited on SiO_2 (800 mg) and purified by column chromatography (9:1 hexanes/ acetone) to afford 83 mg (84%) of bis-TES amide **34**. Data for **34**: $\mathbf{R}_f$ = 0.12 (9:1 hexanes/ acetone); **IR** (thin film) 2953, 1683, 1652, 1513, 1427 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.58 (q, *J* = 8.0 Hz, 6H), 0.59 (q, *J* = 7.8 Hz, 6H), 0.84(d, *J* = 6.0 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 9H), 0.95 (t, *J* = 7.8 Hz, 9H), 1.01 (d, *J* = 6.8 Hz, 3H), 1.04 (s, 9H), 1.07 (s, 9H), 1.20 (s, 3H), 1.26 (m, 2H), 1.35 (app t, *J* = 12.2 Hz, 1H), 1.42-1.68 (series of m, 4H), 1.70-1.80 (m, 4H), 1.86 (m, 1H), 1.92 (s, 3H), 1.93-2.02 (series of m, 3H), 2.16-2.36 (series of m, 6H), 2.42 (dt, *J* = 15.1, 7.7 Hz, 1H), 2.54 (dt, *J* = 14.9, 5.4 Hz, 1H), 2.96 (d, *J* = 14.8 Hz, 1H), 3.20 (m, 2H), 3.21 (s, 3H), 3.26 (s, 3H), 3.28 (s, 3H), 3.30 (m, 1H), 3.45-3.63 (series of m, 10H), 3.80 (s, 3H), 3.81-3.90 (series of m, 4H), 4.28 (ABq, J_{AB} = 11.1 Hz, 1H), 4.53 (dd, *J* = 8.8, 6.2 Hz, 1H), 4.60 (ABq, J_{AB} = 11.0 Hz, 1H), 4.70 (br s, 1H), 4.74 (br s, 1H), 5.24 (dd, *J* = 15.8, 7.9 Hz, 1H), 5.36 (d, *J* = 9.3 Hz, 1H), 5.71 (d, *J* = 8.6 Hz, 1H), 5.88 (d, *J* = 15.1 Hz, 1H), 6.00 (d, *J* = 15.3 Hz, 1H), 6.11 (d, *J* = 13.5 Hz, 1H), 6.16 (dt, *J* = 13.3, 6.9 Hz, 1H),

6.21 (br s, 1H), 6.84 (dt, *J* = 15.3, 7.7 Hz, 1H), 6.88 (m, 2H), 7.28-7.44 (series of m, 14H), 7.52 (s, 1H), 7.65 (m, 6H), 7.75 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 4.2, 4.3, 5.6, 6.7, 6.8, 12.9, 13.7, 14.0, 14.1, 18.9, 19.3, 26.8, 26.9, 31.5, 32.2, 33.2, 33.3, 35.4, 35.6, 36.3, 37.9, 39.0, 39.1, 39.2, 39.5, 39.7, 41.3, 47.9, 53.7, 55.2, 55.5, 56.1, 59.3, 60.7, 68.4, 69.2, 69.3, 69.7, 71.5, 72.2, 72.4, 73.38, 73.42, 77.0, 81.1, 83.1, 89.0, 99.9, 106.2, 110.2, 113.8, 118.8, 125.6, 127.2, 127.4, 127.5, 127.6, 127.7, 129.3, 129.4, 129.5, 129.6, 129.7 130.6, 131.5, 133.8, 133.9, 134.1, 134.3, 134.9, 135.7, 136.0, 136.06, 136.12, 137.3, 137.89, 137.94, 140.5, 142.0, 159.1, 159.2, 165.4; **HRMS** $[MNa]^+$ calcd 1881.9273 obsd 1881.9364; **Optical Rotation** $[\alpha]_D^{23}$ = - 14.4 (*c* 1.0, CH_2Cl_2).



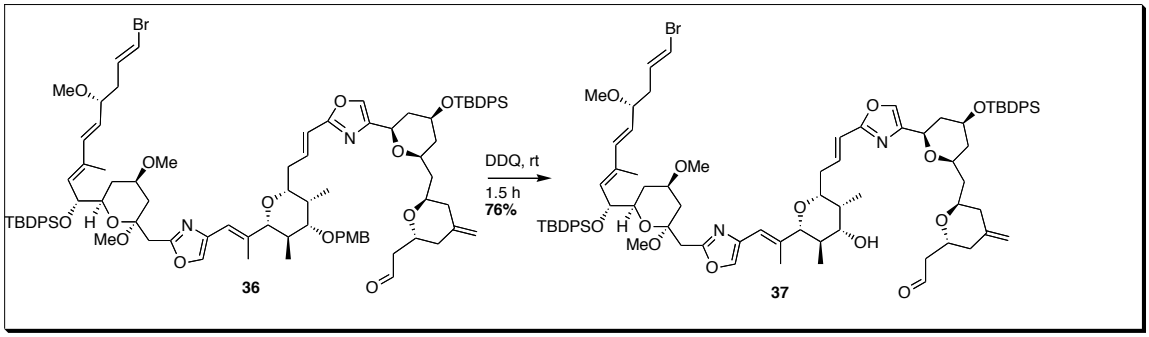
Des-silyl amide 35: Bis-TES amide **34** (101 mg, 0.054 mmole) was dissolved in 10 mL of a 1:1 mixture of CH_2Cl_2/ MeOH and cooled to 0°C. To this was added 2.0 mL of methanolic HCl (prepared from 1 mL of conc. HCl diluted to 100 mL with MeOH, ~0.12 N). After 5 min, solid $NaHCO_3$ (600 mg) was added, followed by 50 mL of CH_2Cl_2. The solution was filtered and concentrated *in vacuo*. Purification by column chromatography (65:35 → 60:40 hexanes/ acetone) afforded 86 mg (97%) of des-silyl amide **35**. Data for **35**: $\mathbf{R}_f$ = 0.13 (7:3 hexanes/ acetone); **IR** (thin film) 3420, 3070, 2931, 1652, 1513, 1427, 1110 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.84 (d, *J* = 6.5 Hz, 3H), 1.02 (m, 3H), 1.03 (s, 9H), 1.06 (s, 9H), 1.20 (s, 3H), 1.25-1.45 (series of m, 5H), 1.49 (app q, *J* = 11.3 Hz, 1H), 1.62 (m, 1H), 1.72-2.00 (series of m, 8H), 1.93 (s, 3H), 2.20 (series of m, 4H), 2.31 (dt, *J* = 13.5, 7.4 Hz, 1H), 2.44 (m, 2H), 2.56 (dt, *J* = 14.3, 6.9 Hz, 1H), 2.96 (d *J* = 15.1 Hz, 1H), 3.19-3.32 (series of m, 3H), 3.21 (s, 3H), 3.26 (s, 3H), 3.28 (s, 3H), 3.49 (d, *J* = 9.7 Hz, 1H), 3.52-3.66 (series of m, 9 H), 3.70-3.79 (m, 4H), 3.80 (s, 3H), 4.00 (m, 1H), 4.12 (m, 1H), 4.29 (A<u>B</u>q, J_{AB} = 10.6 Hz, 1H), 4.53 (dd *J* = 9.3, 6.6 Hz, 1H), 4.60 (<u>A</u>Bq, J_{AB} = 11.1 Hz, 1H), 4.71 (s, 1H), 4.74 (s, 1H), 5.23 (dd, *J* = 15.5, 7.9 Hz, 1H), 5.37 (d, *J* = 9.1 Hz, 1H), 5.95 (d, *J* = 15.3 Hz, 1H), 6.00 (d, *J* = 15.5 Hz, 1H), 6.10 (d, *J* = 13.7 Hz, 1H), 6.16 (dt, *J* = 13.7, 7.1 Hz, 1H), 6.23 (s, 1H), 6.32 (d, *J* = 9.2 Hz, 1H), 6.87 (m, 2H), 7.28-7.45 (series of m, 14H), 7.53 (s, 1H), 7.64 (m, 6H), 7.75 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 5.7, 12.8, 13.7, 14.1, 18.9, 19.3, 26.8, 26.9, 32.2, 33.4, 33.5, 35.4, 36.6, 37.5, 38.9, 39.0, 39.1, 40.6, 41.1, 41.7, 47.9, 52.0, 55.2, 55.5, 56.1, 59.3, 65.2, 68.6, 69.7, 70.6, 70.8, 72.4, 73.3, 73.4, 75.4, 77.0, 77.6, 81.1, 83.1, 90.0, 99.8, 106.2, 110.4, 113.7, 118.6, 125.7, 127.2, 127.4, 127.5, 127.6, 127.7, 129.3, 129.4, 129.5, 129.6, 129.7, 130.6, 131.5, 133.6, 133.8, 134.1, 134.2, 134.9, 135.7, 135.9, 136.0, 136.1, 137.3, 137.8, 140.7, 141.1, 159.1, 165.8; **Optical Rotation** $[\alpha]_D^{23}$ = - 15.5 (*c* 1.0, CH_2Cl_2). **HRMS** $[MNa]^+$ calcd 1653.7543 obsd 1653.753.



Oxazole 36: Des-silyl amide **35** (35 mg, 0.021 mmol) was dissolved in 6 mL of anhydrous CH_2Cl_2. Dess-Martin periodinane (54.5 mg, 0.128 mmol, 6 eq) was added. After stirring for 1 h at RT, H_2O (3 μL) was

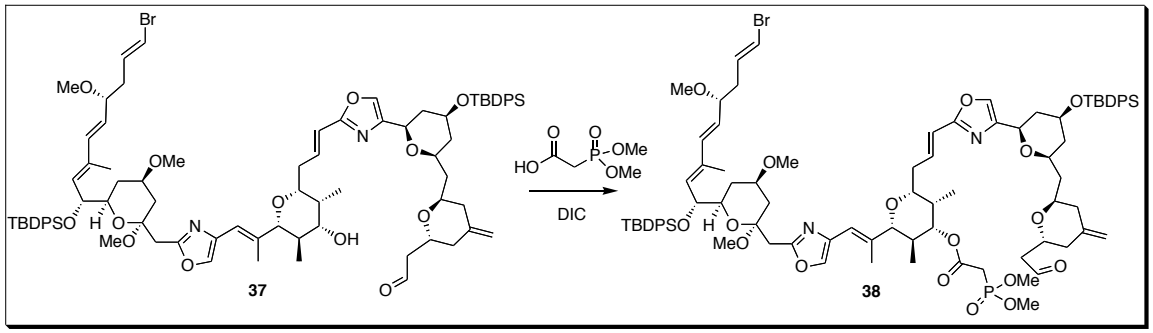
added and the solution was stirred for an additional 15 min. The reaction was filtered through Celite® and rinsed with 10 mL of CH_2Cl_2 and 20 mL of 1:1 hexanes/acetone. The combined rinses were concentrated *in vacuo* and crudely purified by column chromatography (7:3 hexanes/acetone). The dialdehyde was used in the next step after removal of solvent under high vacuum for 2 h.

To a round bottomed flask containing the intermediate dialdehyde **3** was added via syringe a solution of 2,6-di-*t*-butyl 4-methyl pyridine (50.2 mg, 0.24 mmol, 10 eq) in 1.2 mL anhydrous CH_2Cl_2, followed by a solution of PPh_3 (32 mg, 0.12 mmol, 5 eq) in 0.6 mL of anhydrous CH_2Cl_2. The reaction was cooled to 0°C, and a solution of dibromotetrachloroethane (40 mg, 0.12 mmol, 5 eq) in 0.6 mL of CH_2Cl_2 was added dropwise. After 30 min, anhydrous acetonitrile (2.4 mL) was added, followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 74 μL, 0.48 mmole, 20 eq). The reaction was warmed to RT and stirred for 1 h 15 min, and then diluted with 75 mL of Et_2O. The organic layers were washed with 4 × 2 mL of 0.1 M aqueous NH_4Cl and 1 × 5 mL of brine, dried over $MgSO_4$, filtered, and concentrated in *vacuo*. Purification by column chromatography (7:3 hexanes/EtOAc) afforded 24 mg (71%) of oxazole **36**. Data for **36**: $\mathbf{R}_f$ = 0.26 (7:3 hexanes/EtOAc); **IR** (thin film) 2931, 2856, 1725, 1513, 1427, 1247, 1110 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.82, (d, *J* = 6.4 Hz, 3H), 0.98 (d, *J* = 6.5 Hz, 3H), 1.04 (s, 9H), 1.06 (s, 9H), 1.20 (s, 3H), 1.36 (m, 2H), 1.45 (m, 1H), 1.73 (app q, *J* = 11.7 Hz, 1H), 1.81 (m, 2H), 1.90 (s, 3H), 1.91-2.03 (series of m, 5H), 2.12 (m, 2H), 2.21 (m, 2H), 2.30-2.45 (series of m, 5H), 2.51-2.62 (m, 2H), 2.96 (d, *J* = 14.8 Hz, 1H), 3.19-3.21 (m, 1H), 3.20 (s, 3H), 3.26 (s, 3H), 3.28 (s, 3H), 3.35 (m, 2H), 3.46 (d, *J* = 10.2 Hz, 1H), 3.55 (m, 4H), 3.80 (s, 3H), 3.88 (m, 2H), 4.20 (d, *J* = 10.7 Hz, 1H), 4.29 (m, 2H), 4.52 (dd, *J* = 9.5, 6.5 Hz, 1H), 4.58 (d, *J* = 11.0 Hz, 1H), 4.74 (s, 1H), 4.76 (s, 1H), 5.23 (dd, *J* = 15.8, 7.9 Hz, 1H), 5.36 (d, *J* = 9.2 Hz, 1H), 6.00 (d, *J* = 15.3 Hz, 1H), 6.11 (d, *J* = 13.9 Hz, 1H), 5.15 (dt, *J* = 13.9, 6.9 Hz, 1H), 6.35 (d, *J* = 15.9 Hz, 1H), 6.66 (dt, *J* = 16.5, 6.7 Hz, 1H), 6.88 (m, 2H), 7.28-7.44 (series of m, 15H), 7.53 (s, 1H), 7.60-7.70 (series of m, 6H), 7.60 (m, 2H), 9.65 (t, *J* = 1.9 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 5.7, 12.9, 13.7, 14.1, 19.1, 19.3, 26.86, 26.92, 32.2, 33.2, 33.6, 35.4, 36.4, 38.8, 39.0, 39.1, 39.4, 40.1, 40.8, 47.5, 47.9, 55.2, 55.5, 56.2, 67.2, 69.1, 69.8, 69.7, 70.8, 72.4, 72.8, 73.3, 73.4, 77.0, 81.1, 83.1, 89.0, 99.9, 106.2, 111.3, 113.8, 127.2, 127.4, 127.5, 127.6, 127.8, 129.3, 129.4, 129.5, 129.6, 130.6, 131.5, 133.8, 134.1, 134.2, 134.3, 134.9, 135.72, 135.75, 136.0, 136.07, 136.10, 137.3, 140.7, 159.2, 160.9, 200.7; **HRMS** $[MNa]^+$ calcd 1631.7141 obsd 1631.7161 **Optical Rotation** $[\alpha]_D^{23}$ = - 19 (*c* 0.5, $CHCl_3$).

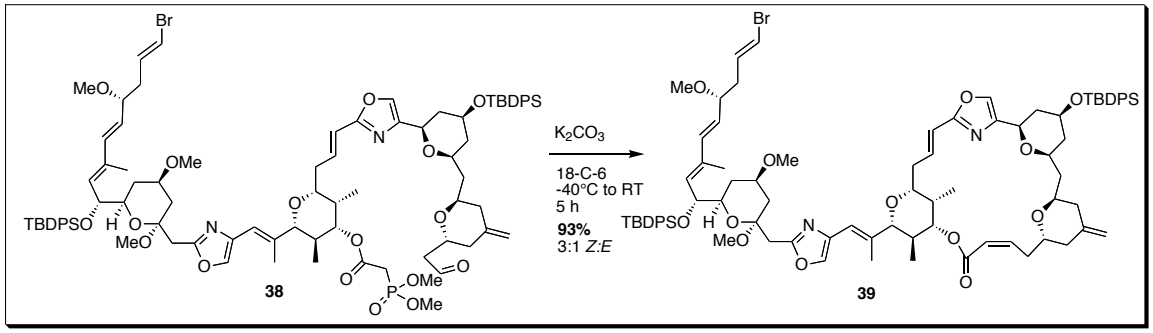


Des-PMB oxazole aldehyde 37: To a round bottomed flask containing oxazole **36** (10 mg, 0.0062 mmol) was added CH_2Cl_2 (5 mL), pH 7 buffer (0.5 mL), and DDQ (7 mg, 0.031 mmol, 5 eq). The reaction was vigorously stirred for 3 h, filtered through Celite®, and rinsed with 20 mL of CH_2Cl_2. The organic layers were washed with 1 × 2 mL of saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (8:2 hexanes/acetone) afforded 7 mg (76%) of des-PMB oxazole aldehyde **37**. Data for **37**: $\mathbf{R}_f$ = 0.26 (7:3 hexanes/EtOAc); **IR** (thin film) 2931, 1725, 1513, 1427, 1247, 1110 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.86 (d, *J* = 6.4 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H), 1.04 (s, 9H), 1.06 (s, 9H), 1.20 (s, 3H), 1.30-1.41 (m, 2H), 1.45 (dt, *J* = 13.7, 5.8 Hz, 1H), 1.70-1.81 (series of m, 4H), 1.90-2.05 (series of m, 11H), 2.12 (m, 1H), 2.25 (m, 2H), 2.27-2.39 (m, 4H), 2.42 (ddd, *J* = 16.2, 5.5, 1.8 Hz, 1H), 2.52-2.60 (m, 2H), 2.96 (A<u>B</u>q, J_{AB} = 14.7 Hz, 1H), 3.21 (s, 3H), 3.27 (s, 3H), 3.29 (s, 3H), 3.31 (m, 1H), 3.32 (<u>A</u>Bq J_{AB} = 14.7 Hz, 1H), 3.48 (m, 2H), 3.52-3.62 (series of m, 4H), 3.80-3.94 (m, 2H), 4.19 (d, *J* = 11.5 Hz, 1H), 4.29 (m, 1H), 4.52 (dd, *J* = 9.1, 6.8 Hz, 1H), 4.74 (s, 1H), 4.76 (s, 1H), 5.28 (dd, *J* = 15.5, 7.9 Hz, 1H), 5.36 (d, *J* = 9.0 Hz, 1H), 6.00 (d, *J* = 15.0 Hz, 1H), 6.10 (d, *J* = 13.4 Hz, 1H), 6.15 (dt, *J* = 13.6, 7.0 Hz, 1H), 6.25 (s, 1H), 6.35 (d, *J* = 16.3 Hz, 1H), 6.68 (ddd, *J* = 14.7, 7.5, 6.4 Hz, 1H), 7.29-7.44 (series of m, 13H), 7.52 (s, 1H), 7.62-7.70 (series of m, 2H), 9.65 (t, *J* = 2.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 5.5, 12.9, 13.4, 14.3, 19.1, 19.3, 26.8, 26.9, 32.2, 34.6, 35.4, 36.1, 37.9, 38.9, 39.0,

39.1, 39.4, 40.1, 40.8, 47.5, 47.9, 55.5, 56.2, 67.2, 69.1, 69.4, 70.8, 72.4, 72.8, 73.4, 73.5, 76.1, 77.4, 81.1, 88.7, 99.9, 106.2, 111.3, 118.1, 118.5, 127.2, 127.4, 127.5, 127.6, 127.7, 129.4, 129.5, 129.6, 131.5, 133.8, 134.0, 134.1, 134.2, 134.3, 134.9, 135.7, 136.0, 136.1, 136.2, 136.7, 137.3, 137.6, 138.0, 140.7, 141.8, 159.3, 160.9, 200.8; **HRMS** $[MNa]^+$ calcd 1511.6549 obsd 1511.6519; **Optical Rotation** $[\alpha]_D^{23}$ = - 25 (*c* 0.5, $CHCl_3$).

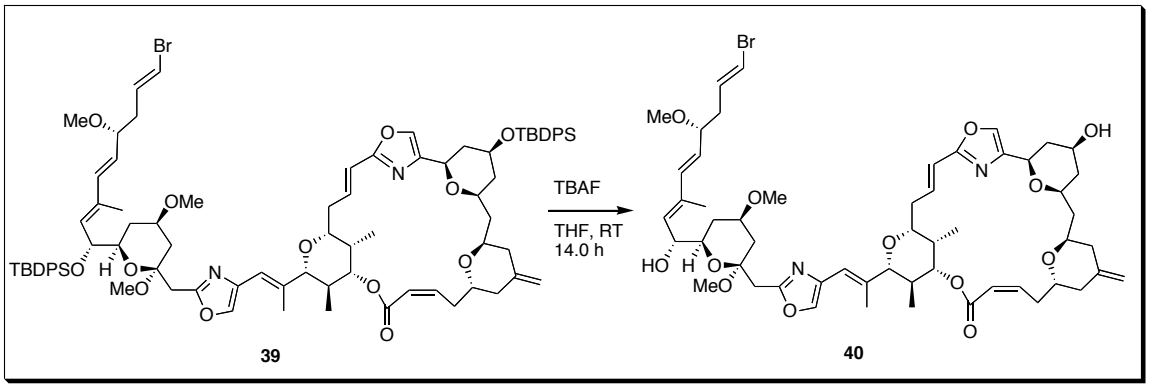


Dimethylphosphonoacetate 38: To a solution of des-PMB oxazole aldehyde **37** (10 mg, 0.0067 mmol) in $CH_2Cl_2$was added dimethyl phosophonoacetic acid (67μL of a 0.2M solution in CH_2Cl_2,0.0134 mmol, 2 eq) followed by DIC (67μL of a 0.2M solution in CH_2Cl_2, 0.0134 mmol, 2 eq). The reaction was stirred at RT for 30 min and deposited on 150 mg of SiO_2. Purification by column chromatography (7:3 hexanes/acetone) afforded 10 mg (91%) of dimethylphosphonoacetate **38**. Data for **38**: $\mathbf{R}_f$ = 0.12 (7:3 hexanes/acetone); **IR** (thin film) 2931, 1731, 1272, 1111 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.78 (d, *J* = 6.3 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 1.04 (s, 9H), 1.06 (s, 9H), 1.20 (s, 3H), 1.31-1.40 (m, 2H), 1.46 (dt, *J* = 14.3, 5.9 Hz, 1H), 1.76 (app q, *J* = 12.0 Hz, 1H), 1.79 (m, 1H), 1.90-2.02 (series of m, 11H), 1.95 (s, 3H), 2.10 (m, 2H), 2.22 (m, 2H), 2.31 (m, 4H), 2.42 (ddd, *J* = 16.0, 5.2, 1.2 Hz, 1H), 2.55 (m, 2H), 2.97 (d, *J* = 14.3, 1H), 3.01 (d, *J* = 21.4 Hz, 1H), 3.21 (s, 3H), 3.27 (s, 3H), 3.29 (s, 3H), 3.31 (m, 2H), 3.50-3.68 (series of m, 5H), 3.80 (d, *J* = 11.0 Hz, 3H), 3.81 (d, *J* = 11.1 Hz, 3H), 3.85 (m, 2H), 4.19 (d, *J* = 11.5 Hz, 1H), 4.26 (m, 1H), 4.52 (dd, *J* = 9.4, 6.6 Hz, 1H), 4.75 (m, 3H), 5.22 (dd, *J* = 15.3, 8.0 Hz, 1H), 5.36 (d, *J* = 9.1 Hz, 1H), 6.01 (d, *J* =15.9 Hz, 1H), 6.10 (d, J = 13.7 Hz, 1H), 6.15 (dt, *J* = 13.5, 7.1 Hz, 1H), 6.25 (s, 1H), 6.34 (d, *J* = 16.1 Hz, 1H), 6.62 (dt , *J* = 15.2, 8.0 Hz, 1H), 7.29-7.42 (series of m, 13H), 7.54 (s, 1H), 7.60-7.70 (m, 6H), 7.74 (m, 2H), 9.65 (br s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 6.1, 12.9, 13.1, 14.3, 19.0, 19.3, 26.8, 26.9, 32.1, 32.9, 34.0, 35.3, 35.4, 36.0, 38.8, 39.0, 39.1, 39.4, 40.1, 40.8, 47.5, 47.7, 53.0, 53.1, 55.6, 56.2, 67.2, 69.1, 69.4, 70.8 72.4, 72.8, 73.3, 73.4, 76.2, 76.8, 80.1, 81.1, 88.6, 99.9, 106.2, 111.3, 118.3, 127.2, 127.4, 127.5, 127.6, 127.8, 129.4, 129.5, 129.6, 131.5, 133.8, 134.0, 134.1, 134.2, 134.3, 134.9, 135.7, 136.0, 136.1, 136.3, 137.2, 137.6, 140.7, 159.3, 160.7, 200.7; **HRMS** $[MNa]^+$ calcd 1661.6631 obsd 1661.6614 **Optical Rotation** $[\alpha]_D^{23}$ = - 35 (*c* 0.1, $CHCl_3$).

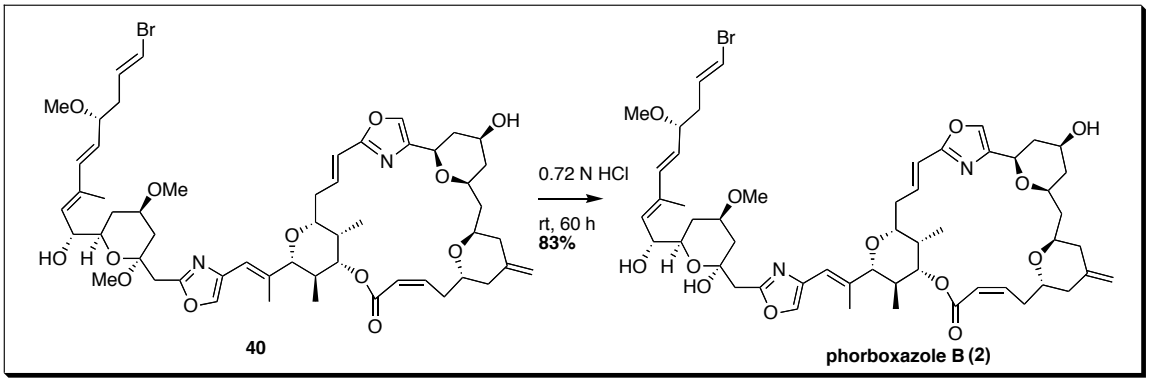


***Z*-macrocycle 39**: Potassium carbonate (8.4 mg, 0.061 mmol, 10 eq) and 18-crown-6 (80.5 mg, 0.305 mmol, 50 eq) were slurried in anhydrous toluene for 2 h at RT and cooled to –40°C. To this mixture was added dimethylphosphonoacetate **38** (10 mg, 0.0061 mmol) in 1 mL of anhydrous toluene via cannula, followed by 2 × 1 mL toluene rinses. The reaction mixture was allowed to slowly warm to RT over 1 hour, and stirred for 4 h at RT. The crude mixture was transferred to a separatory funnel and rinsed with 5 mL of EtOAc. The organic layer was washed with 2 × 3 mL of brine. The aqueous layer was back extracted with 2 × 3 mL of EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (9:1 hexanes/acetone) afforded 8.6 mg (93%) of a 3:1 *Z*: *E* mixture of isomers. The isomers can be separated by column chromatography using

400 g SiO_2 / 1g of mixture, eluted with 75:25 hexanes/ EtOAc or by preparative HPLC. In this example, purification by HPLC (Phenomenex Sphericlone Silica, 250 mm × 10 mm, 75:25 hexanes/ EtOAc, 6 mL/min, 260 nm observe. R_T *Z* **39** = 8.6 min, R_T **39** *E* =10.2 min) afforded 5.6 mg (62%) of pure *Z*-**39**. Data for **39**: $\mathbf{R}_f$ = 0.22 (75:25 hexanes/ EtOAc); **IR** (thin film) 3070, 2931, 1718, 1111 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.78 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 1.06 (s, 9H), 1.07 (s, 9H), 1.20 (s, 3H), 1.30-1.45 (series of m, 4H), 1.70 (app q, *J* = 12.2 Hz, 1H), 1.76 (m, 2H), 1.82 (m, 2H), 1.96 (s, 3H), 2.06 (m, 4H), 2.10-2.40 (series of m, 8H), 2.51 (m, 2H), 2.96 (d, *J* = 14.9 Hz, 1H), 3.21 (s, 3H), 3.27, (s, 3H), 3.29 (s, 3H), 3.30-3.36 (m, 2H), 3.40-3.46 (m, 2H), 3.90 (m, 2H), 3.99 (d, *J* = 12 Hz, 1H), 4.14 (dt, *J* = 11.2, 4.9 Hz, 1H), 4.51 (m, 2H), 4.56 (br s, 1H), 4.90 (br s, 1H), 5.24 (dd, *J* = 15.7, 8.2 Hz, 1H), 5.36 (d, *J* = 9.2 Hz, 1H), 5.80 (m, 2H), 6.00 (d, *J* = 16.0 Hz, 1H), 6.11 (d, *J* = 13.8 Hz, 1H), 6.15 (dt, *J* = 13.6, 7.1 Hz, 1H), 6.25 (d, *J* = 15.9 Hz, 1H), 6.26 (s, 1H), 6.63 (ddd *J* = 16.1, 9.7, 6.5 Hz, 1H), 7.29-7.42 (series of m, 13H), 7.54 (s, 1H), 7.63 (m, 2H), 7.68 (m, 4H), 7.76 (m, 2H); **HRMS** $[MNa]^+$ calcd 1535.6549 obsd 1535.6591 **Optical Rotation** $[\alpha]_D^{23}$ = - 16 (*c* 0.2, $CHCl_3$).

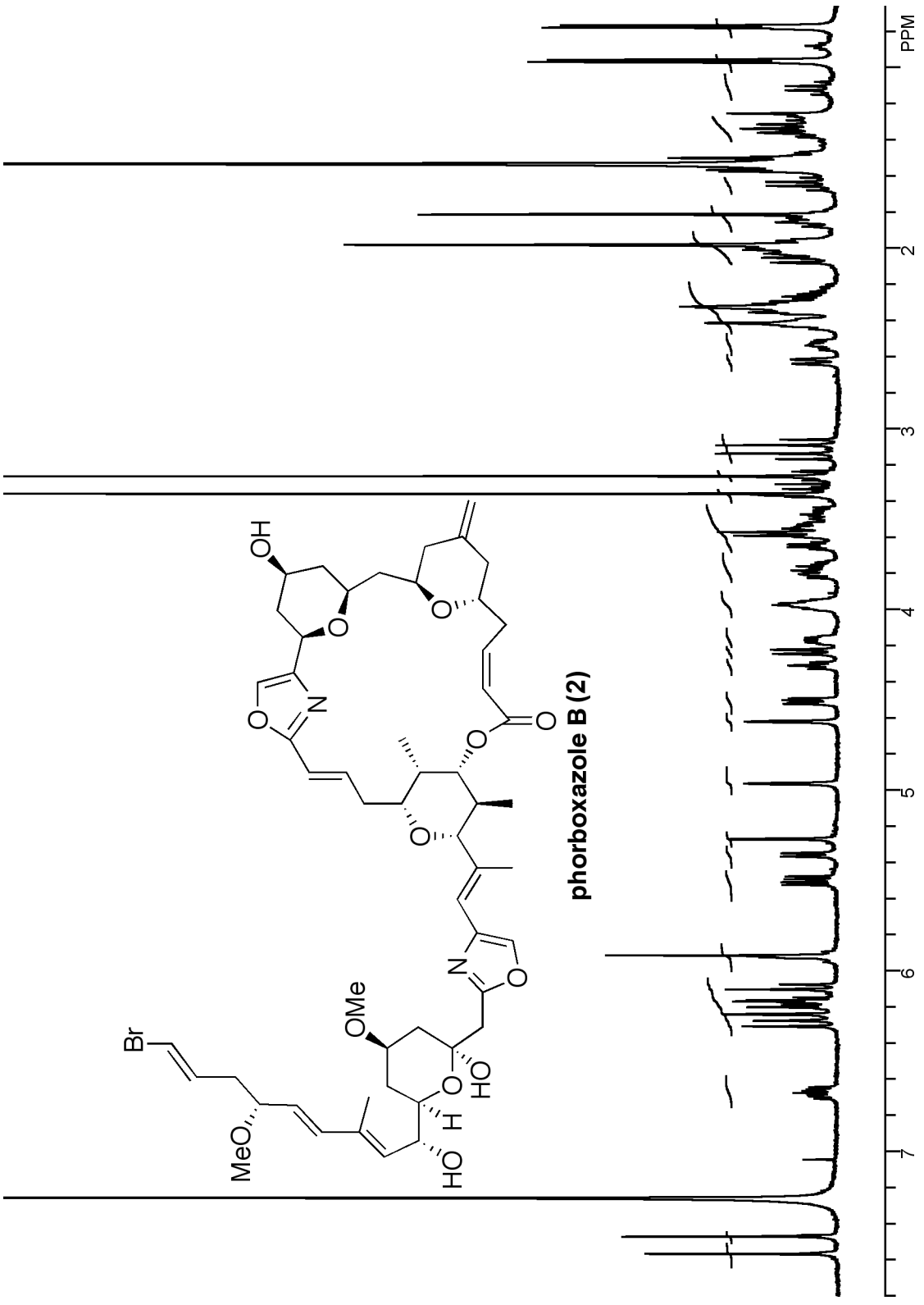


C33-OMe Phorboxazole B 40: TBDPS protected *Z*-macrocycle **39** (5.4 mg, 0.036 mmol) was dissolved in 1.5 mL of anhydrous THF and cooled to 0°C. TBAF (1M in THF, 36 μL, 0.036 mmol,10 eq) was added. After 10 min, the solution was warmed to RT and stirred for 14 h. The crude reaction mixture was filtered through a short pad of silica gel and rinsed with 16 mL of 15:1 EtOAc/ MeOH (v/v). The filtrate was concentrated and purified by column chromatography (10:0.35 CH_2Cl_2/ MeOH) to afford 2.3 mg (62%) of C33-OMe phorboxazole B **40**. Data for **40**: $\mathbf{R}_f$ = 0.19 (10:0.5 CH_2Cl_2/ MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.79 (d, *J* = 6.5 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H), 1.15 (app q, *J* = 11.5 Hz, 1H), 1.32 (app q, *J* = 11.7 Hz, 1H), 1.40 (dd, *J* = 12.1, 11.0 Hz, 1H), 1.50 (m, 1H), 1.62 (m, 1H), 1.80 (s, 3H), 1.90-2.09 (m, 6H), 1.98 (s, 3H), 2.24-2.36 (series of m, 6H), 2.40 (m, 2H), 2.55 (m, 1H), 2.62 (d, *J* = 12.6 Hz, 1H), 2.74 (br s, 1H), 3.10 (d, *J* = 14.5 Hz, 1H), 3.26 (S, 3H), 3.27 (d, J = 14.5 Hz, 1H), 3.30 (s, 3H), 3.33 (s, 3H), 3.44-3.66 (series of m, 8H), 3.96 (m, 2H), 4.16 (m, 1H), 4.24 (d, *J* = 11.9 Hz, 1H), 4.40 (t, *J* = 7.2 Hz, 1H), 4.52 (dd, *J* = 11.2, 4.8 Hz, 1H), 4.62 (br s, 1H), 4.97 (br s, 1H), 5.49 (d, *J* = 9.5 Hz, 1H), 5.53 (dd, *J* = 15.7, 7.9 Hz, 1H), 5.91 (m, 2H), 6.08-6.32 (series of m, 5H), 6.69 (ddd, *J* = 16.2, 10.2, 6.9 Hz, 1H), 7.47 (s, 1H), 7.56 (s, 1H); **HRMS** (MNa^+) calcd 1059.4194 obsd 1059.4177.



Phorboxazole B (2): To a solution of C33-OMe phorboxazole B **40** (3.3 mg, 0.0032 mmol) in 2.0 mL of anhydrous THF at 0°C was added 0.72 N HCl (0.69 mL). The solution was warmed to RT. After 60 h, the solution was cooled to 0°C and quenched carefully with 3.0 mL of saturated $NaHCO_3$ solution. The

reaction was extracted with 3 × 20 mL of CH_2Cl_2, 1 × 10 mL of Et_2O, and 1 × 20 mL of EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (150:1 EtOAc/MeOH) afforded 2.7 mg (83%) synthetic **phorboxazole B (2)**. Data for **phorboxazole B (2)**: $\mathbf{R}_f$ = 0.45 (6% MeOH in EtOAc), $\mathbf{R}_f$ = 0.18 (5% MeOH in CH_2Cl_2); **IR** (thin film) 3411, 2918, 2849, 1718, 1158, 1089 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.77 (d, *J* = 6.6 Hz, 3H), 0.96 (d *J* = 7.0 Hz, 3H), 1.11 (ddd, (app q) *J* = 11.3, 11.3, 11.3 Hz, 1H), 1.34 (ddd, (app q) *J* = 11.4, 11.4, 11.4 Hz, 1H), 1.36 (app t, *J* = 11.9 Hz, 1H), 1.50 (ddd, *J* = 13.5, 7.3, 3.3 Hz, 1H), 1.63 (ddd (app q), *J* = 11.7, 11.7, 11.7 Hz, 1H), 1.81 (s, 3H), 1.86 (dd (app t), *J* = 11.5 Hz, 11.5 Hz, 1H), 1.95 (m, 3H), 1.96 (s, 3H), 2.06 (d, *J* = 13.6, 1H), 2.24-2.45 (series of m, 8H), 2.53 (ddd, *J* = 12.7, 10.4, 5.6 Hz, 1H), 2.62 (br d, *J* = 11.9 Hz, 1H), 3.12 (ABq, J_{AB} = 15.8 Hz, $\Delta\nu_{AB}$ = 35 Hz, 2H), 3.26 (s, 3H), 3.36 (s, 3H), 3.35-3.60 (series of m, 3H), 3.58 (d, *J* = 10.1 Hz, 1H), 3.65 (dt, *J* = 7.5, 6.4 Hz, 1H), 3.76 (tt, *J* = 11.1, 4.4 Hz, 1H), 3.80 (ddd, *J* = 11.8, 7.9, 1.8 Hz, 1H), 3.96 (m, 2H), 4.17 (dt, *J* = 11.3, 4.6 Hz, 1H), 4.23 (br d, *J* = 11.6 Hz, 1H), 4.31 (td, *J* = 8.0, 2.0 Hz, 1H), 4.50 (dd, *J* = 11.3, 4.3 Hz, 1H), 4.62 (br s, 1H), 4.97 (br s, 1H), 5.30 (d, *J* = 2.5 Hz, 1H), 5.36 (d, *J* =9.0 Hz, 1H), 5.50 (dd, *J* = 15.8, 8.0 Hz, 1H), 5.92 (m, 2H), 6.09 (dd, *J* = 13.7, 0.9 Hz, 1H), 6.15-6.19 (m, 2H), 6.24 (s, 1H), 6.29 (d, *J* = 15.8 Hz, 1H), 6.68 (ddd, *J* = 16.4, 9.9, 6.5 Hz, 1H), 7.48 (s, 1H), 7.57 (s, 1H); **HRMS** (MNa^+) calcd 1045.4037 obsd 1045.4028. **Optical Rotation** $[\alpha]_D^{22}$ = + 31 (c 0.1, MeOH).


phorboxazole B (2)
PPM
1
2
3
4
5
6
7
OH
O
N
O
O
O
O
O
N
O
OMe
HO
H
HO
MeO
Br