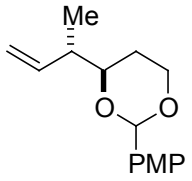
General.

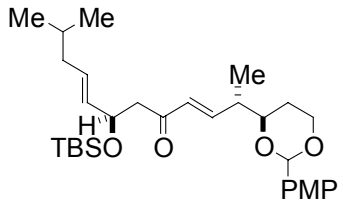
Infrared (IR) spectra were obtained using JASCO P-460 plus FT/IR . Proton and carbon nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on the following instruments: Bruker model Advance 400 (^{1}H at 400 MHz, ^{13}C at 100 MHz), and Bruker model Avance 500 (^{1}H at 500 MHz; ^{13}C at 125 MHz). Optical rotations were determined using a Jasco P-1010 polarimeter. Flash chromatography was carried out using silica get (32 – 63 μm) purchased from Sorbent Technologies. Diethyl ether, tetrahydrafuran (THF), dichloromethane (CH_2Cl_2) were dried by being passed through a column of neutral alumina under nitrogen immediately prior to use. Triethyl amine (Et_3N), pentane, benzene, carbon tetrachloride (CCl_4) were distilled over CaH immediately prior to use. Dimethyl sulfoxide (DMSO) was distilled under reduced pressure from calcium hydride and stored over 4 Å molecular sieves. Methanol (anhydrous) was purchased from ACROS. Commercially available reagents were used without further purification. All air and water sensitive reactions were preformed in flasks flame dried under a positive flow of argon and conducted under an argon atmosphere.



14

1,3-PMP acetal 14. Into a flask with alcohol **13** (2.10g, 8.36 mmol) was added anhydrous methylene chloride (10 mL) followed by 4 Å molecular sieves (2.10g). The reaction was cooled to 0 ºC and DDQ (2.0g, 8.78 mmol) was added in three portions in 5 minutes interval. The reaction was stirred further for 15 minutes before saturated sodium bicarbonate solution and more methylene chloride (100 mL) were added. The layers

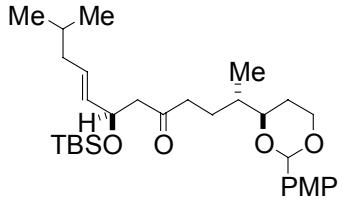
were separated and the organic layer was washed with saturated sodium bicarbonate (2x). The organic layer was dried over Na_2SO_4, filtered and then concentrated *in vacuo*. Purification by flash column chromatography provided the benzylidene acetal **14** (1.6g, 77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, J = 6.9 Hz, 3H), 1.49 (dq, J = 15.6, 3.9, 2.4 Hz, 1H), 1.84 (dq, J = 26.6, 12.5, 5.1 Hz, 1H), 2.39 (app. Sextet, J = 6.9 Hz, 1H), 3.69 (ddd, J = 7.8, 5.4, 2.3, 1H), 3.79 (s, 3H), 3.9 (dt, J = 12.2, 2.6 Hz, 1H), 5.02 -5.08 (m, 2H), 5.44 (s, 1H), 5.85 – 5.94 (m, 1H), 6.86 (dd, J = 6.7, 2.0 Hz, 2H), 7.4 (dd, J = 6.8, 2.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.10, 27.95, 42.42, 55.27, 66.98, 80.33, 100.97, 113.51, 114.81, 127.28, 131.54, 140.21, 159.78; IR(film) 2964, 2838, 1517, 1249, 828; $[\alpha]^{24}_D$ = -16.5 (*c* 0.35, CH_2Cl_2).



20

Enone 20. Alkene **14** (2.38g, 9.55 mmol) was diluted with THF:H_2O (99 ml of 10:1 solution) and then NMO (1.08g, 9.18 mmol) and OsO_4 (4.9 ml of 1g/100ml of H_2O, .19mmol) was added. The reaction was allowed to stir overnight. $NaIO_4$ (4.08g, 19.08g) was added the next day and allowed to stir for 2 h when no diol was observed by TLC. The reaction was then filtered through celite, diluted with ether and then washed with 10% $Na_2S_2O_4$ solution. The organic layer was dried over Na_2SO_4, filtered and the liquid was concentrated *in vacuo*. Purification by flash column chromatography afforded aldehyde **6** (2.0g, 84%) which used immediately in the next reaction.

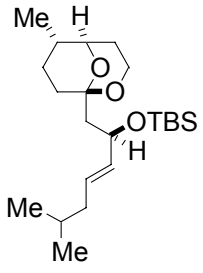
A mixture of the ketophosphonate **7** (3.0g, 7.65 mmol) and $Ba(OH)_2 \cdot 8H_2O$ (2.4g, 7.65 mmol, activated by heating to 100-140 °C for 1-2 h before use) in THF (80 ml) was stirred at room temperature for 1 h. A solution of aldehyde **6** in wet THF (10 ml of 40:1 THF:H_2O solution) was then added and stirring was maintained at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 and wash with saturated $NaHCO_3$ solution. The organic solution was dried over Na_2SO_4, filtered and the liquid was concentrated *in vacuo*. Purification by flash column chromatography provided the enone **20** (3.93g, 90 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.02 (d, J = 2.9 Hz, 6H), 0.8 (s, 9H), 0.84 (dd, J = 7.0, 4.8 Hz, 6H), 1.12 (d, J = 14.6, 8.1 Hz, 1H), 3.76 (dt, J = 14.3, 5.1 Hz, 2H), 2.84 (dd, J = 14.6, 8.1 Hz, 1H), 3.76 (dt, J = 7.7, 2.6 Hz, 1H), 3.8 (s, 3H), 3.9 (dt, J = 12.1, 11.6, 2.6 Hz, 1H), 4.24 (ddd, J = 11.3, 5.1, 1.1 Hz, 1H), 4.6 (app. Quatet, J = 13.5, 7.0 Hz, 1H), 5.37 – 5.41 (m, 1H), 5.40 (s, 1H), 5.55 – 5.59 (m, 1H), 6.13 (dd, 16.1, 1.1 Hz, 1H), 6.84 – 6.90 (m, 3H), 7.37 (dd, J = 8.8, 2.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.93, –4.30, 15.06, 18.13, 22.22, 22.33, 25.85, 28.28, 28.57, 41.44, 41.71, 48.75, 55.28, 66.80, 70.85, 79.75, 101.11, 113.59, 127.28, 129.68, 131.23, 131.75, 133.68, 148.63, 159.92; IR(film) 2956, 1668, 1518, 1249, 1109, 833; $[\alpha]^{26}_D$ = -2.6 (*c* 0.45, CH_2Cl_2).



21

Ketone 21. To a 0 °C solution of THF (5.0 mL) and HMPA (3.0 mL) was added DIBAL-H (3.0 mL of 1.0 M solution in heptane, 3.0 mmol). The solution was allowed to

stir at 0 °C for 30 minutes before enone **20** (1.37g, 2.65 mmol) in THF (5 mL) was added dropwised another 5 mL of THF was added to rinse the flask. The reaction was allowed to stir at 0 °C for another 2 h before quenching with Rochelle salt and warming to room temperature. The reaction mixture was then diluted with Et_2O and the layers were separated. The organic layer was washed with water (2x), brine and dried over Na_2SO_4. After filtration, concentration *in vacuo*, purification by flash column chromatography provided the ketone **21** (1.2 g, 87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.01 (d, J = 1.1 Hz, 6H), 0.82 (s, 9H), 0.84 (dd, J = 6.6, 4.8 Hz, 6H), 0.89 (d, J = 6.9 Hz, 3H), 1.41- 1.48 (m, 2H), 1.55 – 1.64 (m, 2H), 1.76 – 1.89 (m, 4H), 2.35 – 2.55 (m, 3H), 2.64 (dd, J = 14.6, 8.1 Hz, 1H), 3.57 – 3.60 (m, 1H), 3.77 (s, 3H), 3.89 (dt, J = 14.3, 12.1, 1H), 4.24 (ddd, J = 11.0, 4.8, 1.1 Hz), 4.54 (app. Quintet, J = 12.1, 7.3 Hz, 1H), 5.33 – 5.39 (m, 1H), 5.42 (s, 1H), 5.52 – 5.57 (m, 1H), 6.85 (dd, J = 6.6, 2.2 Hz, 2H), 7.38 (dd, J = 6.6, 1.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.96, -4.26, 14.77, 18.07, 22.21, 22.32, 25.83, 26.06, 27.97, 28.29, 37.45, 41.43, 42.61, 51.36, 55.27, 67.04, 70.67, 80.97, 101.09, 113.55, 127.32, 129.78, 131.59, 133.55, 159.84; IR(film) 2956, 1714, 1615, 1249, 1105, 1038, 830; $[\alpha]^{24}_D$ = -7.38 (CH_2Cl_2, c=0.65).

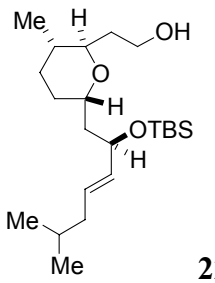


5

Bridged Ketal 5. The ketone **21** (0.33g, 0.64 mmol) was diluted with anhydrous MeOH (7 mL) and catalytic amount of PPTs (.008g, 0.032 mmol) was added. The

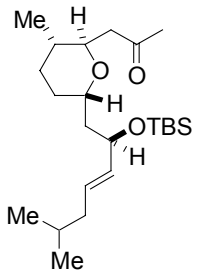
reaction mixture was allowed to stir for an hour and then the reaction was diluted with CH_2Cl_2 and worked up with saturated $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2X). The combined organic fractions were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography provided the methoxy ketal (~0.22g) which was carried forward to the next step immediately.

A solution of the methoxy ketal (0.22g) in anhydrous CH_2Cl_2 (5.0 mL) was treated with catalytic amount of PPTs (0.013 g, 0.053 mmol) and allowed to stir at room temperature for another hour. At which time, the reaction was quenched with saturated $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2X). The combined fractions were dried over Na_2SO_4, filtered and the liquid was concentrated *in vacuo*. Purification by flash column chromatography provided the bridged ketal **5** (0.137g, 56%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (d, J = 10.6 Hz, 6H), 0.85 (s, 9H), 0.83 -0.87 (m, 6H), 1.08 (d, J = 7.0 Hz, 3H), 1.22 – 1.26 (m, 1H), 1.51 – 1.91 (m, 9H), 2.05 – 2.11 (m, 1H), 2.17 – 2.23 (m, 1H), 3.79 – 3.83 (m, 3H), 4.34 (q, d = 12.1, 5.9 Hz, 1H), 5.42 – 5.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.61, -3.99, 18.17, 18.41, 21.90, 22.25, 22.41, 25.96, 28.38, 29.30, 30.10, 32.20, 41.55, 49.89, 57.23, 69.71, 72.11, 97.10, 128.28, 135.61; IR(film) 2954, 1463, 1253, 1083, 971, 836, 775; $[\alpha]^{27}_D$ = -14.54 (*c* 0.5, CH_2Cl_2).



22

Alcohol 22. A solution of the bridged ketal **5** (0.1g, 0.26 mmol) in CCl_4 (3 mL) was cooled to 0 °C and DIBAL-H (1.0 mL of 1.0 M solution in heptane, 1.04 mmol) was added dropwised. The reaction was allowed to stir at 0 °C for 30 min before quenching with Rochelle salt and warming to room temperature. After diluting with CH_2Cl_2, the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic fractions were dried with Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography provided the alcohol **22** (0.093g, 93%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (d, J = 15.6 Hz, 6H), 0.85 (s, 9H), 0.81 – 0.88 (m, 9H), 1.23 – 2.01 (m, 12H), 2.97 (bs, 1H), 3.38 (dt, J = 12.9, 3.6 Hz, 1H), 3.69 – 3.83 (m, 2H), 4.08 – 4.17 (m, 2H), 5.37 – 5.55 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) δ -4.91, -3.93, 18.08, 18.17, 22.30, 22.40, 25.88, 27.28, 28.34, 29.11, 34.80, 35.17, 39.37, 41.49, 61.62, 68.98, 70.84, 76.24, 129.15, 135.05; IR (film) 3053, 2956, 1422, 1265, 1072, 896, 837, 741; $[\alpha]^{25}_D$ = 15.13 (*c* 0.25, CH_2Cl_2).



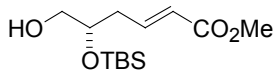
3

Methyl ketone 3. The alcohol **22** (0.40g, 1.00 mmol) was diluted with CH_2Cl_2 (10 mL) and pyridine (0.32mL, 4.01 mmol). Dess-Martin periodinane (0.85g, 2.01 mmol) was then added and the reaction was allowed to stir at room temperature for 1 h. The reaction was quenched with 5:1 $NaHCO_3$:NaS_2O_3 and diluted with Et_2O. The reaction mixture was allowed to stir for an additional 10 minutes. The layers were then

separated and the aqueous layer was extracted with Et_2O (2x). The combined organic fractions were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The aldehyde was dried further by passing through a small column of silica gel and used immediately in the next step.

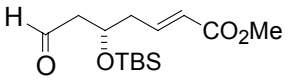
The aldehyde diluted with anhydrous THF (5 mL) was added to a –78 °C solution of MeMgCl (1.0 mL of 3M solution in THF, 3.01 mmol) in THF (5 mL). The reaction was allowed to stir at –78 °C for 1 h before saturated NH_4Cl was added to quench the reaction. The reaction was then diluted with Et_2O and the layers were separated. The aqueous layer was then extracted with Et_2O (2x) and dried over Na_2SO_4. After filtration and concentrating *in vacuo*, the diastereomeric mixture of alcohol was diluted with CH_2Cl_2 (10 mL) and pyridine (0.32mL, 4.01 mmol). Dess-Martin periodinane (0.85g, 2.01 mmol) was then added and the reaction was allowed to stir at room temperature for 1 h. The reaction was quenched with 5:1 $NaHCO_3$:NaS_2O_3 and diluted with Et_2O. The reaction mixture was allowed to stir for an additional 10 minutes. The layers were then separated and the aqueous layer was extracted with Et_2O (2x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography provided the ketone **3** (0.318g, 80 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.01 (d, J = 6.0 Hz, 6H), 0.84 (s, 9H), 0.82 – 0.89 (m, 9H), 1.26 – 1.44 (m, 4H), 1.55 – 1.65 (m, 2H), 1.77 – 1.83 (m, 1H), 1.87 (dt, J = 7.0, 1.1 Hz, 2H), 1.96 (ddd, J = 14.1, 10.1, 2.9 Hz, 1H), 2.16 (s, 3H), 2.49 – 2.58 (m, 2H),3.67 (dt, J = 8.4, 4.4 Hz, 1H), 3.99 – 4.02 (m, 1H), 4.13 (ddd, J = 9.8, 7.3, 2.6 Hz, 1H), 5.38 (ddd, J = 15.3, 8.4, 1.2, 1H), 5.55 – 5.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.85, -4.09, 18.07, 18.15, 22.32, 22.39, 25.92, 27.34, 28.31,29.03, 31.65, 35.09, 39.53, 41.57, 47.42, 68.70, 70.20,

72.32, 128.80, 135.27, 207.97; IR (film) 2954, 1722, 1462, 1069; $[\alpha]^{24}_{D}$ = 9.77 (*c* 0.3, CH_2Cl_2).



18

Alcohol 18. The alcohol **17** (1.25g, 5.78 mmol) was diluted with CH_2Cl_2 (20 ml) and degassed for fifteen minutes. Methyl acrylate (1.30 ml, 14.44 mmol freshly distilled) was then added to the reaction flask followed by G2 (0.089g, 0.12 mmol). The reaction was allowed to reflux for twenty hours under argon, at which time, it was allowed to oxidize by opening the reaction to air and stirring overnight. The dark brown solution was then concentrated and purified by flash column chromatography to give the α,β - unsaturated ester **18** (1.35g, 85 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (d, J = 6.01 Hz, 6H), 0.87 (s, 9H), 1.84 (t, J = 6.2 Hz, 1H), 2.37 – 2.42 (m, 2H), 3.42 – 3.48 (m, 1H), 3.51 -3.56 (m, 1H), 3.70 (s, 3H), 3.71 – 3.85 (m, 1H), 5.85 (app. d, J = 15.7 Hz, 1H), 6.91 (dt, J = 15.3, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.67, -4.64, 18.02, 25.73, 36.89, 51.45, 66.01, 71.62, 123.34, 145.11, 166.66; IR (film) 3474, 2953, 2858, 1724, 1659, 1257, 1100, 838, 735; $[\alpha]^{25}_{D}$ = -11.82 (*c* 0.28, CH_2Cl_2).



4

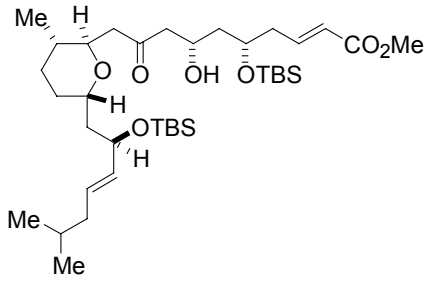
Aldehyde 4. To a flask containing the alcohol **18** (0.241g, 0.89 mmol) in CH_2Cl_2 (5 mL) and pyridine (0.28 ml, 3.5 mmol) was added Dess-Martin periodinane (0.75g,

1.76mmol) in one portion. After 1h the white slurry was quench by the addition of a 5:1 solution of $NaHCO_3/Na_2S_2O_3$ and diluted with ether. The reaction mixture was allowed to stir for 10 min. The organic layer was separated and the aqueous layer was extracted with Et_2O (2x). The combined organic fractions were dried over Na_2SO_4, filtered and then concentrated *in vacuo*. The oil was dried further by passing through a plug of silica and used directly without further purification.

Into a flamed dried flask was added the $MeOCH_2PPh_3Cl$ (0.722g, 2.11mmol) and placed on the high vac pump for an hour to rid off any possible moisture. Into the flask was added anhydrous THF (3 mL) and the reaction flask was cooled to – 78 °C. *sec*-BuLi (1.25 mL of a 1.4 M solution in THF, 1.76 mmol) was then added dropwise and the reaction was allowed to stir at –78 °C for 30 min. The aldehyde **19** (0.195 g, 0.702 mmol) in THF (1 mL) was added to the reaction flask and stirring continued for another 30 min before the dry ice bath is replaced with a 0 °C bath. The reaction mixture was allowed to stir at 0°C for 30 min before saturated $NaHCO_3$ was added, at which time it was allowed to warm to room temperature. The reaction was then diluted with Et_2O and the layers were separated. The aqueous layer was extracted further with Et_2O (2X). The combined organic fractions were dried over Na_2SO_4, filtered and the liquid was concentrated *in vacuo*. Purification by flash column chromatography provided methyl enol ether (0.182g, 86 %) as a mixture of E/Z isomer. The enol ether was quite unstable and was used immediately.

The methyl enol ether (0.1g, 0.33 mmol) was diluted with $THF:H_2O$ (3 ml of a 10:1 solution) and $Hg(OAc)_2$ (0.32g, 1.0 mL) was added. The reaction was allowed to stir at room temperature for 1h. Saturated KI was then added and stirred for another 10

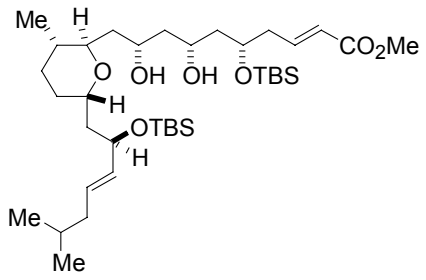
min. After the 10 min, the reaction mixture was diluted with Et_2O and the layers were separated. The organic layer was then washed with saturated KI, brine and dried over Na_2SO_4. The crude aldehyde **4** (0.076g, 80 %) was purified by flash column chromatography; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (d, J = 7.3 Hz, 6H), 0.85 (s, 9H), 2.42 (q, J = 12.1, 5.5 Hz, 2 H), 2.53-2.57 (m, 2H), 5.85 (d, J = 15.4 Hz, 1H), 6.91 (dt, J = 15.0, 7.3 Hz, 1H), 9.77 (t, J = 1.8 Hz, 1H).



23a

β-hydroxy-ketone 23a. A flask containing (-) DIPCl (0.43g, .119 mmol) was diluted with pentane (1 mL). The reaction flask was cooled down to 0 °C and then Et_3N (0.18 mL, 0.130 mmol) was added. The white cloudy solution was allowed to stir for 10 min before a solution of ketone (0.43 g, 0.108 mmol) in pentane (1 mL) was added dropwise. The milky white suspension was stirred for 90 min at 0 °C and then cooled further to –78 °C. A solution of aldehyde (0.31g, 0.108 mmol) in pentane (1 mL) was then added slowly. The reaction mixture was allowed to stir at –78°C for 3 h. The reaction was quenched by carefully adding MeOH/pH 7 buffer (1 mL of a 1:1 solution) and then allowed to warm to 0 °C. Oxidation was accomplished by adding 30% aqueous H_2O_2/pH7 buffer (1 mL of a 1:1 solution) and stirred for 1 h. Then the reaction was diluted with Et_2O, the layers were separated and the organic layer was washed with water and brine. The crude aldol reaction mixture was dried over Na_2SO_4 and concentrated *in*

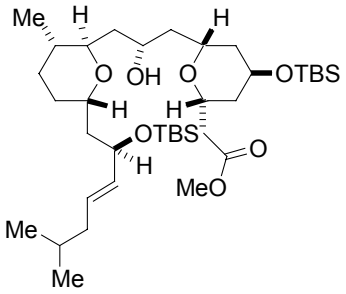
vacuo. Purification by flash column chromatography provided the aldol adduct **23** (0.61g as a 15:1 anti:syn ratio determined by ^{1}H NMR analysis, 81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.09 (d, J = 3. 0 Hz, 6H), 0.05 (d, J = 3.6 Hz, 6H), 0.82 – 0.89 (m, 27H), 1.38 – 1.97 (m, 12H), 2.32 – 2.36 (m, 1H), 2.43 – 2.58 (m, 5H), 3.29 (d, J = 2.4 Hz, 1H), 3.70 (s, 3H), 3.67 – 3.71 (m, 1H), 3.97 – 4.00 (m, 1H), 4.05 – 4.08 (m, 1H), 4.12 – 4.17 (m, 2H), 5.39 (dd, J = 15.3, 7.1 Hz, 1H), 5.56 – 5.61 (m, 1H0, 5.83 (dd, J = 14.5, 1.2 Hz, 1H), 6.96 (dt, J = 15.3, 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.74, -.59, -4.48, -4.03, 17.97, 18.08, 18.15, 22.33, 22.41, 25.81, 25.93, 27.24, 28.35, 28.97, 34.95, 39.62, 41.57, 43.29, 47.33, 51.34, 65.19, 69.01, 69.32, 70.37, 72.01, 123.30, 128.90, 135.22, 145.60, 166.66, 210.15; IR (film) 3443, 2954, 1726, 1257, 1072, 836, 776, 740; $[\alpha]^{23}_D = 9.10$ (*c* = 0.41, CH_2Cl_2).



24

Diol 24. Ketone **23a** (0.06g, 0.09 mmol) was diluted with THF/H_2O (2.25 ml of a 4:1 solution mixture) and cooled to –78 °C. Et_2BOMe (0.1 ml of 1 M solution in ether, 0.1 mmol) was then added dropwise to the reaction and allowed to stir for 15 min. $NaBH_4$ (0.004g, 0.097 mmol) was added and stirring continued for another 1 h at –78 °C. At which time the reaction was quenched with Rochelle salt, allowed to warm to room temperature and continued stirring for another hour. The reaction was then diluted with EtOAc and the layers were separated. The organic layer was dried over Na_2SO_4 and then

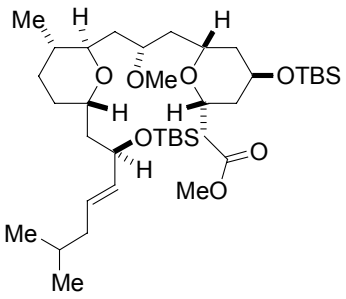
concentrated in vacuo. The crude diol was azeotroped with MeOH several times to hydrolyze the boronate intermediate. In a few instances, the reaction mixture was quenched as in the boron aldol reaction described previously in order to hydrolyze the boronate. Flash chromatography provided the diol **24** (0.051g, 85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.022 (d, J = 15.1 Hz, 6H), 0.06 (d, J = 2.2 Hz, 6H), 0.08 (d, J = 6.5 Hz, 3H), 0.85 (s, 9H), 0.86 (d, 6.7 Hz, 6H), 0.87 (s, 9H),1.27 – 1.72 (m, 12H), 1.82 – 1.88 (m, 3H0, 2.01 (ddd, J = 13.7, 10.1, 3.0 Hz, 1H), 2.36 – 2.47 (m, 2H), 3.48 (dt, J = 10.1 Hz, 3.0 Hz, 1H), 3.71 (s, 3H), 4.04 (t, J = 6.3 Hz, 1H), 4.08 – 4.23 (m, 6H), 5.40 (dd, J = 15.3, 7.2 Hz, 1H), 5.52 – 5.58 (m, 1H), 5.84 (d, J = 15.7 Hz, 1H), 6.95 (app. quintet, J = 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.81, -4.63, -4.39, -4.00, 17.94, 18.06, 18.20, 22.30, 22.42, 25.79, 25.90, 27.48, 28.32, 29.26, 34.72, 38.91, 39.36, 39.97, 41.52, 43.81, 44.29, 51.42, 69.11, 69.44, 69.77, 70.27, 70.61, 72.96, 123.28, 129.13, 134.94, 145.55, 166.73; IR (film) 3458, 2952, 2857, 1727, 1658, 1462, 1361, 1254, 1073, 836, 809, 776, 667; $[\alpha]^{25}_{D} = 10.2$ (*c* = 0.34, CH_2Cl_2).



25

Alcohol 25. Diol **24** (0.043g, 0.063 mmol) was diluted with anhydrous THF (1.5 mL) and cooled to 0 °C. A solution of KO*t*-Bu (1.0 mg, 0.006 mmol) in THF (0.5 mL) was then added dropwise. The reaction was allowed to stir at 0 °C for 10 min before quenching with saturated NH_4Cl. After warming to room temperature, the reaction was

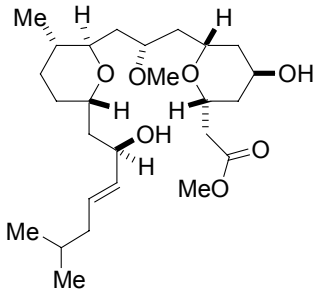
extracted with EtOAc (3x), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography provided the alcohol **25** (0.034 as 9:1 mixture of cis:trans isomers by ^{1}H NMR analysis, 80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (d, J = 3.7 Hz, 6H), 0.06 (d, J = 17.2 Hz, 6H), 0.82 – 0.87 (m, 27 H), 1.22 – 1.87 (m, 17 H), 2.02 (ddd, J = 13.3, 10.1, 2.9 Hz, 1H), 2.35 (dd, J = 15.0, 5.2 Hz, 1H), 2.45 (dd, J = 15.0, 8.0 Hz, 1H), 3.44 (t, J = 8.1 Hz, 1H), 3.65 (s, 3H), 3.79 (s, 1H), 4.11 – 4.29 (m, 5H), 4.32 (dt, 9.4, 2.5 Hz, 1H), 5.4 (dd, J = 15.4, 7 Hz, 1H), 5.54 – 5.60 (m 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.94, -4.90, -4.76, -4.03, 17.97, 18.13, 22.35, 22.44, 25.76, 25.99, 27.68, 28.32, 29.24, 35.63, 38.71, 39.35, 39.46, 40.97, 41.14, 41.63, 43.31, 51.66, 64.45, 68.00, 68.46, 68.57, 70.21, 71.06, 73.52, 128.56, 135.54, 171.35; IR (film) 3511, 2953, 1744, 1252, 1063, 836, 775, 734; $[\alpha]^{22}_D$ = -23.8 (*c* = 0.06, CH_2Cl_2).



26

Methyl ether 26. 4 Å molecular sieves (0.11g) was added to alcohol **25** (.022g, 0.32 mmol) in CH_2Cl_2 (2.2 mL) and then cooled to 0 °C. 2,6-di-*tert*-butyl-4-methylpyridine (0.79g, .385 mmol) was then added and allowed to stir for 10 min before Me_3OBF_4 was added. The reaction was allowed to stir for 10 h while warming to room temperature slowly. Work up involved filtration and washing the organic layer with saturated $NaHCO_3$. After drying over Na_2SO_4, filtration, and concentration *in vacuo*, the crude reaction mixture was purified by flash column chromatography to afford methyl

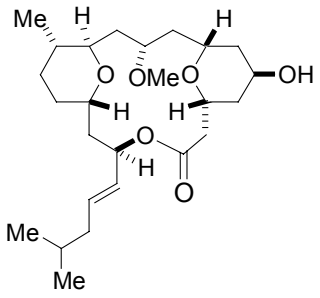
ether **26** (0.02g, 87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (d, J = 3.1 Hz, 6H), 0.04 (d, J = 11.4 Hz, 6H), 0.84 – 0.87 (m, 27 H), 1.21 – 1.49 (m, 9H), 1.53 – 1.62 (m, 3H), 1.69 – 1.88 (m, 3H), 1.95 (ddd, J = 12.5, 9.0, 3.1 Hz, 3H), 2.33 (dd, J = 14.8, 6.4 Hz, 1H), 2.51 (dd, J = 14.8, 7.0 Hz, 1H), 3.29 (s, 3H), 3.35 (t, J = 8.2 Hz, 1H), 3.56 – 3.60 (m, 1H), 3.64 (s, 3H), 3.93 – 4.20 (m, 5H), 5.39 (dd, J = 15.4, 6.7 Hz, 1H), 5.47 – 5.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.89, -4.85, -4.56, -3.96, 18.04, 18.19, 18.34, 22.26, 22.38, 25.79, 25.92, 27.55, 28.35, 29.24, 35.47, 38.88, 39.32, 39.45, 39.95, 40.47, 41.38, 41.56, 51.49, 56.46, 64.92, 68.52, 68.81, 70.47, 71.33, 74.14, 128.54, 135.29, 171.60; IR (film) 2952, 1745, 1462, 1252, 1069, 836, 774; $[\alpha]^{23}_D = 8.95$ (*c* = 0.19, CH_2Cl_2).



27

Diol 27. The silyl ether **26** (0.04g, 0.057mmol) was diluted with THF (2.0 mL) and TBAF (0.23 mL, 0.230 mmol of 1M solution in THF) was added. The reaction was stirred overnight and then quenched with saturated NH_4Cl. EtOAc was added and the layers were separated. The aqueous layer was extracted with EtOAc (3X) and the combined organic fractions were dried over Na_2SO_4. After filtration and concentration *in vacuo*, the crude mixture was purified by flash column chromatography to provide the diol **27** (.023g, 85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (dd, J = 6.6, 2.9 Hz, 6H), 0.98 (d, J = 6.6 Hz, 3H), 1.33 – 1.90 (m, 20 H), 2.35 (dd, J = 15.1, 4.9 Hz, 1H), 2.49 (dd, J = 15.1, 8.5 Hz, 1H), 3.29 (s, 3H), 3.35 – 3.60 (m, 2H), 3.65 (s, 3H), 3.82 – 3.87 (m, 1H),

3.97 – 4.01 (m, 1H), 4.19 – 4.24 (m, 2H), 4.33 (app. triplet, J = 6.8 Hz, 1H), 5.47 (dd, J = 15.4, 6.2 Hz, 1H), 5.60- 5.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.48, 22.25, 22.32, 26.20, 27.69, 28.27, 33.27, 37.87, 38.13, 38.74, 40.15, 40.66, 41.16, 41.65, 51.69, 56.45, 64.54, 66.91, 68.40, 68.63, 68.87, 73.27, 74.84, 129.22, 134.45, 171.83; IR (film) 3433, 2926, 1740, 1438, 1383, 1161, 1061, 972; $[\alpha]^{24}_D = 27.28$ (*c* = 0.35, CH_2Cl_2).

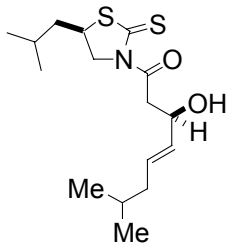


2

Macrolactone 2. The methyl ester **27** (6 mg, 0.013 mmol) was diluted with Et_2O (3 mL) and TMSOK (5 mg, 0.038 mmol) was added. The reaction was allowed to stir at room temperature overnight. The reaction was quenched with 0.1 M $NaHSO_4$ until pH = 2 and the mixture was extracted with CH_2Cl_2 (6x). The combined organic layer was dried over $MgSO_4$, filtered and then concentrated *in vacuo*.

The crude acid **28** was diluted with benzene (60 mL) and Et_3N (80 μL, 0.57 mmol) was added followed by trichlorobenzoyl chloride (82 μL, 0.523 mmol) and then DMAP(16 mg, 0.13 mmol). The reaction was stirred for 1h and more DMAP (16 mg, 0.13 mmol) was added. The reaction was allowed to stir at room temperature for 48 h. The reaction was diluted with CH_2Cl_2 and quenched with $NaHSO_4$ (0.1 M). The layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic fractions were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash column chromatography afforded macrolactone **2** (3 mg, 54%); ^{1}H NMR (500 MHz,

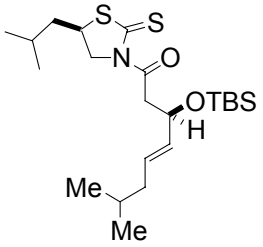
C_5D_5N) δ .0.79 (d, J = 6.6 Hz, 3H), 0.80 (d, J = 6.6 Hz, 3H), 1.02 – 1.12 (m, 2H), 1.08 (d, J = 7.1 Hz, 3H), 1.18-1.98 (m, 14H), 2.12 (t, J =11.5 Hz, 1H), 2.47 – 2.54 (m, 2H), 2.69 (dd, J = 13.0 Hz, 3.7 Hz, 1H), 3.38 (s, 3H), 3.76 (t, J = 10.8 Hz, 1H), 3.94 (t, J = 10.7 Hz, 1H), 4.07 (d, J = 11.4 Hz, 1H), 4.19 (t, J = 11.5 Hz, 1H), 4.43 (m, 1H), 4.63-4.67 (m, 1H), 5.53-5.58 (dd, J = 15.5 Hz, 6.9 Hz, 1H), 5.74-5.82 (m, 2 H); ^{13}C NMR (125 MHz, C_5D_5N) δ 18.43, 22.25, 22.29, 24.25, 27.38, 28.32, 35.86, 39.49, 39.65, 39.92, 41.73, 43.38, 43.94, 56.66, 56.67, 63.13, 63.76, 69.68, 69.86, 70.90, 73.85, 73.90, 131.52, 131.92, 170.29;IR (film) 3437, 1731; $[\alpha]^{23}_D$ = 32.1 (*c* = 0.1, EtOH).



10

Alcohol 10. To a solution of acetylthiazolidine thione **9** (7.42g, 34.14 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added $TiCl_4$ (3.41 mL, 31.04 mmol) followed by DIEA (5.40 mL, 31.04 mmol). The reaction was stirred for 1 h at 0 °C before cooling to –78 °C and aldehyde **8** (3.48g, 31.04 mmol) in CH_2Cl_2 (100 mL) was added slowly. The reaction was allowed to stir at –78 °C for 2 h, before saturated NH_4Cl solution was added to quench the reaction and then it was warmed to room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic fractions were then dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash column chromatography provided the aldol adduct **10** (6.75g, 60 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (dd, J = 6.7, 1.9 Hz, 6H), 0.96 (dd, J = 6.7, 3.9 Hz, 6H), 1.49 – 1.64 (m, 3H), 1.84

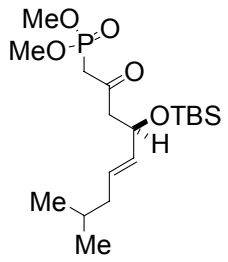
– 1.90 (m, 3H), 2.65 (d, J = 4.3 Hz, 1H), 2.88 (d, J = 11.3 Hz, 1H), 3.26 (dd, J = 17.6, 9.0 Hz, 1H), 3.49 – 3.55 (m, 2H), 4.57 – 4. 61 (m, 1H0, 5.21 – 5.27 (m, 1H0, 5.45 – 5.51 (m, 1H), 5.63 – 5.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.28, 22.16, 22.20, 23.44, 25.34, 28.08, 33.17, 39.59, 41.42, 45.72, 65.84, 65.58, 131.09, 131.67, 172.30, 201.56; IR (film)3436, 2956, 1694, 1465, 1269, 1161, 909, 734; $[\alpha]^{26}_{D}$ = 228.6 (*c* = 0.7, CH_2Cl_2).



11

Silyl ether 11. To a 0 °C solution of alcohol **10** (5.02g, 15.78 mmol) in CH_2Cl_2 was added 2,6-lutidine (5.5 mL, 47.3 mmol) followed by TBSOTf (7.25 mL, 33.38 mmol). The reaction was allowed to stir for 1 h at 0 °C. MeOH (0.5 mL) was added and reaction was warmed to room temperature. H_2O and CH_2Cl_2 were then added and the layers were separated. The aqueous layer was then extracted with CH_2Cl_2 (2x). The combined organic fractions were dried over Na_2SO_4, filtered and then concentrated *in vacuo*. Purification by flash column chromatography provided silyl ether **11** (7.3g, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (d, J = 7.0 Hz, 6H), 0.83 (s, 9H), 0.85 (dd, J = 6.7, 3.1 Hz, 6H), 0.96 (dd, J = 6.6, 3.5 Hz, 6H), 1.54 – 1.64 (m, 3H), 1.85 – 1.91 (m, 3H), 2.88 (d, J = 11.3 Hz, 1H), 3.04 (dd, J = 16.0, 3.9 Hz, 1H), 3.48 (dd, J = 11.3, 7.0 Hz, 1H), 3.61 (dd, J = 16.0, 8.6 Hz, 1H), 4.65 – 4.70 (m, 1H), 5.08 – 5.13 (m, 1H), 5.42 (dd, J = 15.3, 7.0 Hz, 1H), 5.55 – 5.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.94, -4.12, 18.06, 21.26, 22.26, 22.36, 23.56, 25.45, 25.80, 28.29, 33.50, 39.37, 41.42, 46.84, 66.32,

70.85, 130.22, 133.34, 171.55, 20.1.38; IR (film) 3955, 1701, 1466, 1339, 1251, 1163, 936, 777; $[\alpha]^{25}_{D} = 189.51$ ($c = 0.6$, CH_2Cl_2).



7

Methyl phosphonate 7. *n* -BuLi (22.5 mL of 1.6 M solution in Hexane) was added to flask with methyl phosphonate (4.80mL, 43.3 mmol) in THF (35 mL) and the reaction was cooled to –78 °C and allowed to stir for 1 h. Amide **11** (6.4g, 14.4 mmol) in THF (3 +2 mL) was added to the reaction flask and allowed to stir for an additional hour. Reaction turned from yellow to clear and was quenched with saturated NH_4Cl. After warming to room temperature, the crude mixture was extracted with Et_2O (3x). The combined organic fractions were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash column chromatography provided the phosphonate **7** (5.1g, 90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.01 (d, J = 3.5 Hz, 6H), 0.81 (s, 9H), 0.79 – 0.84 (m, 6H), 1.56 (septet, J = 20.0, 13.3, 6.7 Hz, 1H), 1.81 – 1.86 (m, 2H), 2.59 (dd, J = 15.3, 5.1 Hz, 1H), 2.81 (dd, J = 15.3, 7.8 Hz, 1H), 3.01 – 3.75 (m, 2H), 3.73 (dd, J = 11.0, 1.2 Hz, 6H), 4.51 (dd, J = 11.7, 7.0 Hz, 1H), 5.34 (dd, J = 15.3, 7.0 Hz, 1H), 5.51 – 5.57 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.0, -4.26, 18.07, 22.23, 22.35, 25.80, 28.26, 41.39, 42.10, 43.37, 52.40, 52.91, 52.96, 53.02, 70.45, 130.30, 133.00, 200.47, 200.53; IR (film) 2957, 2248, 1715, 1464, 1255, 1038, 909, 732; $[\alpha]^{26}_{D} = 20.50$ ($c = 1.5$, CH_2Cl_2).