# Studies Toward the Synthesis of Spirolide C: Exploration into the Formation of the 23-Membered All-Carbon Macrocyclic Framework

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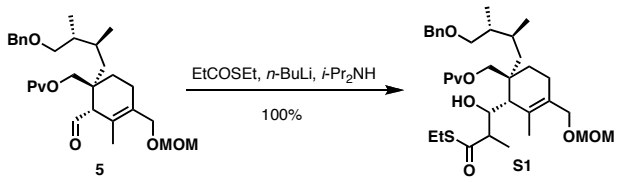
**SUPPORTING INFORMATION 1**

Experimental Procedures

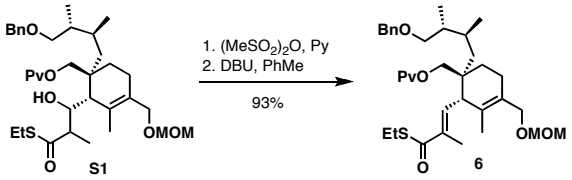
## Supplementary Information

**General Information.** All reactions were carried out under an inert atmosphere of dry argon in oven or flame-dried glassware, unless the reaction procedure states otherwise. Tetrahydrofuran (THF) and ether ($Et_2O$) were distilled from sodium-benzophenone in a continuous still under an atmosphere of argon. Dichloromethane, di-*iso*-propylamine, pyridine, and triethylamine were distilled from calcium hydride in a still under and atmosphere of argon. Reaction temperatures were controlled by IKA-brand fuzzy thermo couples. Room temperature reactions were carried out between 20-25 °C. Analytical thin-layer chromatography (TLC) was performed using pre-coated TLC plates with Silica Gel 60 $F_{254}$ (EMD no. 5715-7) and visualized using combinations of UV, anisaldehyde, ceric ammonium molybdate (CAM), potassium permanganate, and iodine staining. Flash column chromatography was preformed using 40-63 μm silica gel (Merck, Geduran, no. 11567-1) as the stationary phase. Proton magnetic resonance spectra were recorded at 400, and 500 MHz on Varian Unity Inova, and Varian Unity Inova spectrometers, respectively. Carbon magnetic resonance spectra were recorded at 125 MHz on Varian Unity Inova spectrometer. All chemical shifts were reported in δ units relative to tetramethylsilane using residual solvent as reference. Mass spectral data were obtained by the Mass Spectrometry laboratory at the University of California, Santa Barbara.



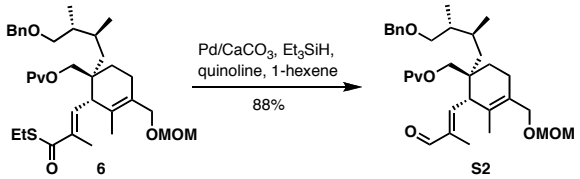

**Thioester S1.** *n*-Butyllithium (2.24 M in hexanes, 0.38 ml, 0.86 mmol) was added to a solution of diisopropylamine (0.12 ml, 0.86 mmol) in THF (0.5 ml) and was stirred for 30 min at -78 °C. *S*-Ethyl thiopropionate (0.12 ml, 1.00 mmol) was added, and the solution was stirred for an additional 30 min. Substrate **5** (36 mg, 72 μmol) in THF (1.0 mL total with rinses) was added dropwise to the reaction mixture at -78 °C, and the solution was stirred for 1 h. The reaction was quenched with saturated aqueous ammonium chloride at -78 °C. The aqueous layer was extracted with ethyl acetate (3x10 ml). The combined organic layers were washed with brine, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 25% ethyl acetate - hexanes) to afford the desired product **S1** (45 mg, 72 μmol, 100%). $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.37-7.26 (m, 5H); 4.66-4.60 (m, 2H); 4.49 (AB, JA=29.0 Hz, JB=12.0 Hz, 2H); 4.22-4.13 (m, 2H); 4.00 (d, J=11.5 Hz, 1H); 3.90 (AB, JA=18.5 Hz, JB=11.0 Hz, 2H); 3.39 (s, 3H); 3.35-3.26 (m, 2H); 2.93 (ddd, J1=J2=J3=7.0 Hz, 2H); 2.90-2.76 (m, 1H); 2.27-2.22 (m, 2H); 2.15 (d, J=10.5 Hz, 1H); 2.06-1.83 (m, 4H); 1.81 (s, 3H); 1.65-1.55 (m, 1H); 1.32-1.19 (m, 2H); 1.28 (dd, J1=J2=7.0 Hz, 3H); 1.22 (s, 9H); 1.19 (d, J=6.5 Hz, 3H); 0.83 (d, J=8.0 Hz, 3H); 0.82 (d, J=7.0 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 203.2, 178.3, 139.0, 134.5, 129.7, 128.6, 128.5, 127.6, 127.6, 127.5, 96.7, 74.4, 73.0, 71.6, 68.1, 66.2, 55.8, 55.6, 47.2, 40.6, 39.4, 39.2, 38.6, 27.5, 26.0,

23.5, 21.4, 16.4, 15.6, 14.9, 11.4. LRMS (ESI) calcd for $C_{35}H_{56}O_7SNa$ [M+Na] 643.37, found 643.37.



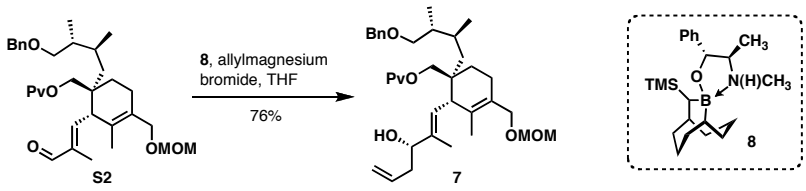

**Thioester 6.** Methanesulfonic anhydride (0.534 g, 3.07 mmol) was added to a solution of substrate **S1** (0.370 g, 0.596 mmol) and pyridine (0.750 ml, 9.12 mmol) in dichloromethane (2.0 ml) at 0 °C. After 5 min, the solution was warmed to rt and stirred for 2 h. Water (3 ml) and dichloromethane (3 ml) were added and the reaction was allowed to stir for 5 min. The aqueous layer was extracted with dichloromethane (3x10ml). The combined organic layers were washed with 1M HCl, water, saturated aqueous sodium bicarbonate, dried with sodium sulfate, concentrated, and the crude residue was submitted to the next step without further purification.

1,8-Diazabicycloundec-7-ene (0.370 ml, 2.46 mmol) was added to a solution of the crude substrate in toluene (12.3 ml) at rt. After 20 min, the reaction was diluted with dichloromethane and water. The aqueous layer was extracted with dichloromethane (3x30ml). The combined organic layers were washed with 1M HCl, water, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 15% ethyl acetate - hexanes to 25% ethyl acetate - hexanes) to afford the desired product **6** (0.334 g, 0.554 mmol, 93% over 2 steps). $[\alpha]_D^{23}$ 159.0° (c 1.0, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$); δ(ppm): 7.37-7.27 (m, 5H); 6.50 (dd, J1=11.2 Hz, J2=1.6 Hz, 1H); 4.61 (s, 2H); 4.48 (AB, JA=20.8 Hz, JB=12.0 Hz, 2H); 4.10 (d, J=11.2 Hz, 1H); 3.97 (AB, JA=19.2 Hz, JB=11.2 Hz, 2H); 3.97 (d, J=11.6 Hz, 1H); 3.38 (s, 3H); 3.30 (dd, J1=9.2 Hz, J2=7.6 Hz, 1H); 3.25 (dd, J1=9.2 Hz, J2=6.4 Hz, 1H); 3.00-2.86 (m, 3H); 2.25 (dd, J1=18.4 Hz, J2=6.0 Hz, 1H); 2.10-1.94 (m, 1H); 1.97 (d, J=1.2 Hz, 3H); 1.88-1.80 (m, 1H); 1.79-1.71 (m, 2H); 1.66-1.56 (m, 1H); 1.58 (s, 3H); 1.39 (dd, J1=14.8 Hz, J2=5.2 Hz, 1H); 1.28 (dd, J1=J2=7.2 Hz, 3H); 1.23 (s, 9H); 1.08 (dd, J1=14.4 Hz, J2=4.4 Hz, 1H); 0.77 (d, J=6.8 Hz, 3H); 0.67 (d, J=6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$); δ(ppm): 194.3, 178.4, 139.6, 139.0, 136.9, 130.5, 128.5, 128.3, 127.6, 95.7, 74.3, 73.0, 67.0, 65.4, 55.5, 46.1, 40.7, 39.6, 39.2, 38.7, 27.4, 26.0, 25.2, 23.6, 18.2, 16.1, 14.8, 13.5, 11.4. LRMS (ESI) calcd for $C_{35}H_{54}O_6SNa$ [M+Na] 625.36, found 625.35.



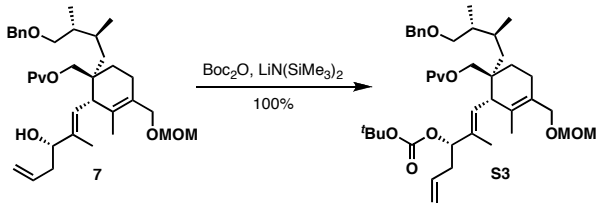

**Aldehyde S2.** Triethylsilane (0.615 ml, 3.86 mmol) was added dropwise to a mixture of substrate **6** (0.465 g, 0.771 mmol), quinoline (0.915 ml, 7.71 mmol), Lindlar catalyst (3.26 g), and 1-hexene (1.90 ml, 15.42 mmol) in dichloromethane (7.7 ml) at rt. Additional triethylsilane (0.615 ml, 3.86 mmol) was added dropwise every 30 min until the reaction was complete (observed by TLC). In total, the solution was stirred for 8 h (in total, 3.08 ml (19.3 mmol) of triethylsilane was added). The

solution was filtered through a short pad of Celite using dichloromethane. The organic layer was washed with 1M HCl (2x10ml), dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 20% ethyl acetate - hexanes) to afford the desired product **S2** (0.369 g, 0.680 mmol, 88%). $[\alpha]_D^{26}$ 183.3° (c 1.0, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$); δ(ppm): 9.48 (s, 1H); 7.38-7.27 (m, 5H); 6.32 (dd, J1=11.2 Hz, J2=1.2 Hz, 1H); 4.61 (s, 2H); 4.48 (AB, JA=23.2 Hz, JB=12.0 Hz, 2H); 4.15 (d, J=11.2 Hz, 1H); 4.00 (AB, JA=24.8 Hz, JB=11.6 Hz, 2H); 3.93 (d, J=11.2 Hz, 1H); 3.38 (s, 3H); 3.27 (dd, J1=9.2 Hz, J2=8.0 Hz, 1H); 3.22 (dd, J1=9.2 Hz, J2=6.0 Hz, 1H); 3.11 (d, J=11.2 Hz, 1H); 2.30 (dd, J1=18.8 Hz, J2=6.4 Hz, 1H); 2.13-2.00 (m, 1H); 1.90-1.57 (m, 4H); 1.85 (d, J=1.2 Hz, 3H); 1.57 (s, 3H); 1.33 (dd, J1=14.8 Hz, J2=5.2 Hz, 1H); 1.24 (s, 9H); 1.11 (dd, J1=14.8 Hz, J2=4.8 Hz, 1H); 0.74 (d, J=6.8 Hz, 3H); 0.65 (d, J=6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$); δ(ppm): 195.5, 178.4, 153.6, 140.0, 138.9, 130.2, 128.9, 128.5, 127.6, 95.9, 74.1, 73.1, 66.9, 65.3, 55.5, 46.6, 41.0, 39.6, 39.2, 38.8, 27.4, 27.3, 25.8, 25.3, 18.8, 16.0, 11.3, 10.3. LRMS (ESI) calcd for $C_{33}H_{50}O_6Na$ [M+Na] 565.36, found 565.35.

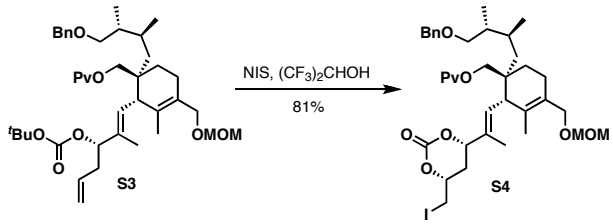



**Homoallylic Alcohol 7.** Allylmagnesium bromide (1.0 M in ether, 0.110 ml, 0.11 mmol) was added to 9-(1*R*,2*R*-pseudoephedrinyl)-(10*S*)-(trimethylsilyl)-9-bora-bicyclo[3.3.2]decane (**8**) (47 mg, 0.127 mmol) in diethyl ether (0.5 ml) at -78 °C. After 15 min, the solution was warmed to rt and stirred for 1 h. The solution was then cooled to -78 °C and substrate **S2** (34.4 mg, 63.4 μmol) in diethyl ether (1.0 ml total with washes) was added dropwise. The solution was stirred at -78 °C for 1 h, warmed to rt and stirred for an additional 1 h. Sodium hydroxide (3.0 M, 0.152 ml, 3.80 mmol), hydrogen peroxide (30%, 45 μl, 1.32 mmol), and additional diethyl ether (2.0 mL) were added and the reaction was refluxed for 1 h. The solution was diluted with water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (3x20ml). The combined organic layers were washed with water, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 20% ethyl acetate - hexanes to 30% ethyl acetate - hexanes) to afford the desired product **7** (28 mg, 47.8 μmol, 76%). $[\alpha]_D^{22}$ 90.1° (c 1.0, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$); δ(ppm): 7.36-7.24 (m, 5H); 5.85-5.74 (m, 1H); 5.34 (d, J=11.2 Hz, 1H); 5.15-5.07 (m, 2H); 4.59 (s, 2H); 4.48 (AB, JA=15.6 Hz, JB=12.4 Hz, 2H); 4.10 (d, J=11.2 Hz, 1H); 4.08-4.02 (m, 1H); 3.93 (d, J=11.2 Hz, 1H); 3.91 (s, 2H); 3.37 (s, 3H); 3.25-3.15 (m, 2H); 2.71 (d, J=10.8 Hz, 1H); 2.40-2.27 (m, 3H); 2.24-2.15 (m, 1H); 2.06-1.84 (m, 2H); 1.71-1.58 (m, 3H); 1.71 (d, J=1.2 Hz, 3H); 1.58 (s, 3H); 1.28-1.24 (m, 1H); 1.21 (s, 9H); 1.13 (dd, J1=14.8 Hz, J2=6.0 Hz, 1H); 0.70 (d, J=7.2 Hz, 3H); 0.66 (d, J=6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$); δ(ppm): 178.6, 138.6, 138.3, 135.1, 133.0, 128.5, 127.9, 127.7, 126.2, 125.8, 117.6, 95.6, 76.2, 74.0, 73.2, 67.1, 55.4, 45.8, 41.6, 40.0, 39.3, 39.2,

39.1, 27.5, 27.3, 25.3, 25.0, 18.1, 15.8, 13.4, 11.0. LRMS (ESI) calcd for $C_{36}H_{56}O_6Na$ [M+Na] 607.40, found 607.42.

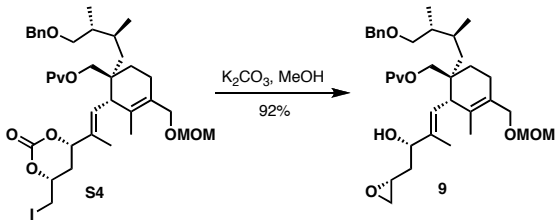



**Carbonate S3.** Lithium bis(dimethylsilyl)amide (1.0 M in toluene, 3.04 ml, 3.04 mmol) was added to a solution of substrate **7** (0.290 g, 0.506 mmol) in THF (8.1 ml) at -78 °C. After 10 min, di-*tert*-butyldicarbonate (0.484 g, 2.78 mmol) in THF (2.0 ml) was added dropwise to the reaction mixture at -78 °C. After 30 min, the reaction was warmed from -30 °C to -20 °C over 1h. The reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with ethyl acetate (3x30ml). The combined organic layers were washed with brine, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 10% ethyl acetate - hexanes to 20% ethyl acetate - hexanes) to afford the desired product **S3** (0.346 g, 0.514 mmol, 100%). $[\alpha]_D^{22}$ 132.9° (c 1.0, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$); δ(ppm): 7.37-7.26 (m, 5H); 5.77-5.67 (m, 1H); 5.29 (d, J=10.8 Hz, 1H); 5.13 (dd, J1=16.8 Hz, J2=1.2 Hz, 1H); 5.09 (d, J=10.4 Hz, 1H); 4.98 (dd, J1=J2=6.8 Hz, 1H); 4.60 (s, 2H); 4.49 (AB, JA=19.2 Hz, JB=12.0 Hz, 2H); 4.06 (d, J=11.6 Hz, 1H); 4.05 (dd, J1=J2=15.2 Hz, 2H); 3.88 (d, J=11.6 Hz, 1H); 3.38 (s, 3H); 3.31 (dd, J1=9.2 Hz, J2=7.6 Hz, 1H); 3.21 (dd, J1=9.2 Hz, J2=6.8 Hz, 1H); 2.82 (d, J=11.2 Hz, 1H); 2.53-2.38 (m, 2H); 2.20-2.12 (m, 1H); 2.08-1.97 (m, 1H); 1.88-1.80 (m, 1H); 1.79-1.68 (m, 1H); 1.72 (s, 3H); 1.67-1.60 (m, 1H); 1.59-1.51 (m, 1H); 1.57 (s, 3H); 1.47 (s, 9H); 1.35-1.29 (m, 1H); 1.22 (s, 9H); 1.11-1.06 (m, 1H); 0.78 (d, J=6.8 Hz, 3H); 0.69 (d, J=6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$); δ(ppm): 178.5, 153.0, 139.0, 133.9, 133.6, 132.5, 129.3, 128.5, 127.5(4), 127.5(1), 126.5, 118.0, 95.5, 82.0, 81.7, 74.5, 73.2, 67.1, 66.1, 55.4, 45.3, 40.7, 39.1, 39.0, 38.9, 37.3, 27.9, 27.5, 27.4, 25.7, 25.3, 18.0, 16.2, 12.8, 11.5. LRMS (ESI) calcd for $C_{41}H_{64}O_8Na$ [M+Na] 707.46, found 707.46.

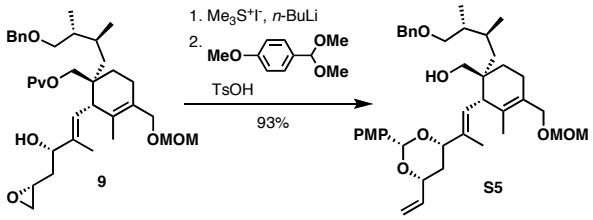



**Iodide S4.** *N*-Iodosuccinimide (76.0 mg, 0.34 mmol) was added to a solution of substrate **S3** (33 mg, 48 μmol) in hexafluoroisopropanol (1.0 ml) at 0 °C. After 30 min, the reaction was diluted with dichloromethane and water. The aqueous layer was extracted with dichloromethane (2x10ml). The combined organic layers were washed with saturated aqueous sodium thiosulfate, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 30% ethyl acetate - hexanes) to afford the desired product **S4** (29 mg, 38 μmol, 81%). $[\alpha]_D^{24}$ 126.3° (c 1.0, $CH_2Cl_2$). $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.34-7.26 (m, 5H);

5.39 (d, J=11.0 Hz, 1H); 4.80 (dd, J1=12.0 Hz, J2=3.5 Hz, 1H); 4.60 (s, 2H); 4.47 (AB, JA=23.5 Hz, JB=11.5 Hz, 2H); 4.44-4.38 (m, 1H); 4.11 (d, J1=11.0 Hz, 1H); 3.94 (AB, JA=19.5 Hz, JB=11.5 Hz, 2H); 3.91 (d, J=11.0 Hz, 1H); 3.40-3.36 (m, 1H); 3.37 (s, 3H); 3.31-3.20 (m, 3H); 2.78 (d, J=11.0 Hz, 1H); 2.32 (ddd, J1=14.0 Hz, J2=J3=2.5 Hz, 1H); 2.21 (dd, J1=18.0 Hz, J2=6.0 Hz, 1H); 2.06-1.96 (m, 1H); 1.90-1.82 (m, 2H); 1.76 (s, 3H); 1.76-1.65 (m, 2H); 1.59 (s, 3H); 1.54-1.48 (m, 1H); 1.30 (dd, J1=14.5 Hz, J2=5.0 Hz, 1H); 1.22 (s, 9H); 1.08 (dd, J1=14.5 Hz, J2=5.0 Hz, 1H); 0.75 (d, J=7.0 Hz, 3H); 0.69 (d, J=7.5 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 178.4, 148.6, 138.9, 132.2, 131.7, 130.8, 128.5, 127.7, 127.6, 127.4, 95.9, 83.3, 74.4, 73.1, 67.0, 65.8, 55.4, 45.3, 40.9, 39.1, 39.0, 32.4, 27.4, 27.3, 25.7, 25.3, 18.1, 16.1, 12.4, 11.4. LRMS (ESI) calcd for $C_{37}H_{55}IO_8Na$ [M+Na] 777.29, found 777.29.



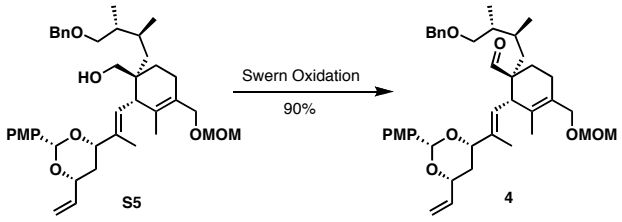

**Epoxide 9.** Potassium carbonate (49 mg, 0.356 mmol) was added to a solution of substrate **S4** (0.134 g, 0.178 mmol) in methanol (3.6 ml) and water (0.36 ml) at rt. After 7.5 h, saturated aqueous sodium bicarbonate was added. The aqueous layer was extracted with ethyl acetate (3x20ml). The combined organic layers were washed with brine, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 40% ethyl acetate - hexanes to 60% ethyl acetate - hexanes) to afford the desired product **9** (98 mg, 0.163 mmol, 92%). $[\alpha]_D^{22}$ 148.2° (c 1.0, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$); δ(ppm): 7.37-7.27 (m, 5H); 5.44 (d, J=11.2 Hz, 1H); 4.60 (s, 2H); 4.50 (AB, JA=14.8 Hz, JB=12.4 Hz, 2H); 4.25-4.20 (m, 1H); 4.10 (d, J=10.8 Hz, 1H); 3.92 (s, 2H); 3.94 (d, J=11.2 Hz, 1H); 3.37 (s, 3H); 3.22-3.20 (m, 2H); 3.06-3.02 (m, 1H); 2.78-2.69 (m, 3H); 2.55-2.53 (m, 1H); 2.26-2.17 (m, 1H); 2.08-1.96 (m, 1H); 1.94-1.88 (m, 1H); 1.84 (ddd, J1=14.4 Hz, J2=J3=5.2 Hz, 1H); 1.78-1.61 (m, 5H); 1.73 (s, 3H); 1.59 (s, 3H); 1.22 (s, 9H); 1.15 (dd, J1=14.4 Hz, J2=6.4 Hz, 1H); 0.71-0.62 (m, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 178.6, 138.5, 138.2, 132.9, 128.6, 128.0, 127.8, 126.4, 125.9, 95.6, 74.9, 73.9, 73.2, 67.4, 67.1, 55.4, 50.4, 47.0, 46.0, 41.9, 39.4, 39.2, 39.0, 38.3, 27.5, 27.3, 25.4, 24.8, 18.0, 15.7, 13.5, 10.8. LRMS (ESI) calcd for $C_{36}H_{56}O_7Na$ [M+Na] 623.40, found 623.42.




**PMP Acetal S5.** *n*-Butyllithium (2.45 M in hexanes, 0.79 ml, 1.91 mmol) was added to a mixture of trimethylsulfonium iodide (0.425 g, 2.08 mmol) in THF (1.5 ml) at -10 °C. After 30 min, substrate **9** (50 mg, 83.2 μmol) in THF (2.7 ml total with washes)

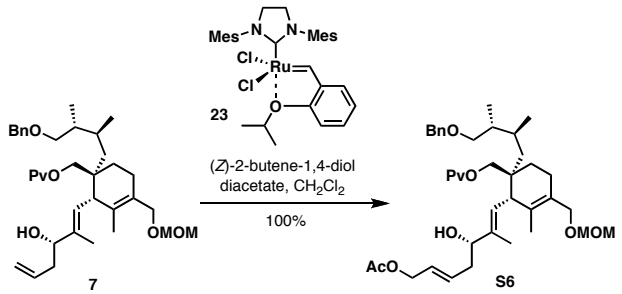
was added to the reaction mixture and stirred for an additional 30 min. The solution was warmed to rt and stirred for 1 h. The reaction was quenched with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with dichloromethane (4x10ml). The combined organic layers were dried with sodium sulfate, concentrated, and the crude residue was submitted to the next step without further purification.

Pyridinium *p*-toluenesulfonate (3 mg, 11.9 μmol) was added to a solution of the crude substrate, 1-(dimethoxymethyl)-4-methoxybenzene (70 μl, 0.416 mmol) in dichloromethane (3.0 ml) at rt. After 1 h, the reaction was quenched with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with dichloromethane (3x10ml). The combined organic layers were dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 100% dichloromethane then 30% ethyl acetate - hexanes) to afford the desired product **S5** (50 mg, 77.1 μmol, 93% over 2 steps). $[\alpha]_D^{22}$ 169.1° (c 1.0, $CH_2Cl_2$). $^1H$ NMR (600 MHz, $CDCl_3$); δ(ppm): 7.45-7.43 (m, 2H); 7.36-7.26 (m, 5H); 6.89-6.86 (m, 2H); 5.93 (ddd, J1=16.8 Hz, J2=10.8 Hz, J3=5.4 Hz, 1H); 5.57 (s, 1H); 5.35-5.30 (m, 2H); 5.16 (d, J=10.8 Hz, 1H); 4.60 (s, 2H); 4.52 (d, J=12.0 Hz, 1H); 4.46 (d, J=12.0 Hz, 1H); 4.38-4.35 (m, 1H); 4.25 (dd, J1=10.8 Hz, J2=2.4 Hz, 1H); 4.01 (AB, JA=15.6 Hz, JB=10.8 Hz, 2H); 3.79 (s, 3H); 3.52 (d, J=5.4 Hz 2H); 3.37 (s, 3H); 3.31 (dd, J1=9.0 Hz, J2=8.4 Hz, 1H); 3.25 (dd, J1=8.4 Hz, J2=6.0 Hz, 1H); 2.82 (d, J=10.8 Hz, 1H); 2.17-2.04 (m, 2H); 1.90-1.80 (m, 2H); 1.80 (s, 3H); 1.74-1.56 (m, 5H); 1.56-1.47 (m, 1H); 1.44 (dd, J1=J2=6.0 Hz, 1H); 1.33 (dd, J1=14.4 Hz, J2=5.4 Hz, 1H); 1.06 (dd, J1=14.4 Hz, J2=4.8 Hz, 1H); 0.78 (d, J=6.6 Hz, 3H); 0.73 (d, J=6.6 Hz, 3H). $^{13}C$ NMR (150 MHz, $CDCl_3$); δ(ppm): 160.0, 139.0, 138.1, 135.9, 133.4, 131.6, 128.5, 127.7, 127.6, 127.1, 126.3, 115.7, 113.7, 100.5, 95.8, 81.8, 74.6, 73.2, 67.5, 64.9, 55.5, 55.4, 44.6, 40.6, 40.3, 38.9, 35.9, 27.5, 26.2, 25.6, 18.1, 16.2, 13.6, 11.4. LRMS (ESI) calcd for $C_{40}H_{56}O_7Na$ [M+Na] 671.40, found 671.40.

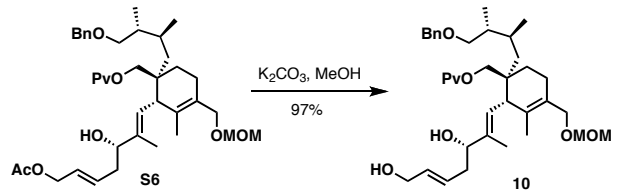



**Aldehyde 4.** Dimethyl sulfoxide (13 μl, 0.173 mmol) was added to a solution of oxalyl chloride (8 μl, 86.4 μmol) in dichloromethane (0.5 ml) at -78 °C. After 15 min, substrate **S5** (18.7 mg, 28.8 μmol) in dichloromethane (1.0 ml total with rinses) was added dropwise and the reaction mixture was stirred for an additional 25 min. Triethylamine (40 μl, 0.259 mmol) was added and the solution was stirred at -78 °C for 10 min, then warmed to 0 °C and stirred for an additional 10 min. The reaction was quenched with 1M HCl. The aqueous layer was extracted with ethyl acetate (3x10ml). The combined organic layers were washed with brine, saturated aqueous sodium bicarbonate, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 25% ethyl acetate - hexanes) to afford the desired product **4** (16.8 mg, 26.0 μmol, 90%). $[\alpha]_D^{23}$ 205.9° (c 1.0, $CH_2Cl_2$). $^1H$ NMR (600 MHz, $CDCl_3$); δ(ppm): 9.53 (s, 1H); 7.48-7.45 (m, 2H);

7.37-7.34 (m, 4H); 7.31-7.28 (m, 1H); 6.92-6.89 (m, 2H); 5.94 (ddd, J1=16.8 Hz, J2=10.2 Hz, J3=5.4 Hz, 1H); 5.60 (s, 1H); 5.35 (d, J=16.8 Hz, 1H); 5.30 (d, J=10.8 Hz, 1H); 5.19 (d, J=10.2 Hz, 1H); 4.56 (AB, JA=10.2 Hz, JB=7.2 Hz, 2H); 4.48 (AB, JA=28.8 Hz, JB=12.0 Hz, 2H); 4.39-4.38 (m, 1H); 4.27 (dd, J1=10.8 Hz, J2=1.8 Hz, 1H); 4.07 (d, J=11.4 Hz, 1H); 3.88 (d, J=11.4 Hz, 1H); 3.82 (s, 3H); 3.36 (s, 3H); 3.29 (dd, J1=9.0 Hz, J2=7.8 Hz, 1H); 3.24-3.20 (m, 2H); 2.19 (dd, J1=18.0 Hz, J2=6.6 Hz, 1H); 2.12-2.06 (m, 1H); 2.00 (dd, J1=13.8 Hz, J2=7.2 Hz, 1H); 1.82 (s, 3H); 1.87-1.83 (m, 1H); 1.70 (s, 3H); 1.76-1.59 (m, 4H); 1.55 (dd, J1=15.0 Hz, J2=6.6 Hz, 1H); 1.24 (dd, J1=14.4 Hz, J2=5.4 Hz, 1H); 0.73 (d, J=6.6 Hz, 3H); 0.64 (d, J=6.6 Hz, 3H). $^{13}$C NMR (150 MHz, $CDCl_3$); δ(ppm): 206.4, 160.1, 138.9, 138.0, 137.8, 133.5, 131.5, 128.5, 128.0, 127.7, 127.7, 124.8, 115.8, 113.7, 100.6, 95.6, 81.7, 74.3, 73.1, 67.0, 55.5, 55.4, 52.1, 43.3, 41.2, 37.7, 36.0, 28.0, 25.5, 25.2, 18.1, 15.8, 13.6, 11.0. LRMS (ESI) calcd for calcd for $C_{40}H_{54}O_7Na$ [M+Na] 669.39, found 669.38.

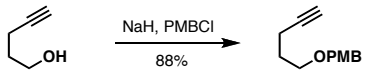



**Allylic Acetate S6.** Hoveyda-Grubbs II catalyst (**23**, 1 mg, 1.58 μmol) was added to a solution of substrate **7** (18.5 mg, 31.7 μmol) and *cis*-1,4-diacetoxy-2-butene (55 mg, 0.371 mmol) in degassed dichloromethane (0.5 ml). The reaction vessel was sealed and heated at 43 °C. After 4 h, the reaction vessel was removed from the oil bath and continued to stir at rt for 12 h. The reaction was concentrated on a rotary evaporator and the residue was purified by column chromatography (silica, 20% to 60% ethyl acetate - hexanes) to afford the desired product **S6** (21 mg, 31.7 μmol, 100%) as an unknown mixture of diastereomers. $^1$H NMR (400 MHz, $CDCl_3$); δ(ppm): 7.36-7.25 (m, 5H); 5.79 (ddd, J1=15.6 Hz, J2=J3=6.4 Hz, 1H); 5.66 (ddd, J1=15.6 Hz, J2=J3=6.4 Hz, 1H); 5.38 (d, J=10.8 Hz, 1H); 4.58 (s, 2H); 4.51 (d, J=6.0 Hz, 2H); 4.52-4.44 (m, 2H); 4.09 (d, J=10.8 Hz, 1H); 4.08-4.01 (m, 1H); 3.94-3.89 (m, 3H); 3.36 (s, 3H); 3.18 (d, J=7.2 Hz, 2H); 2.66 (d, J=10.8 Hz, 1H); 2.56 (bs, 1H); 2.39-2.14 (m, 3H); 2.05 (s, 3H); 2.05-21.82 (m, 2H); 1.69 (s, 3H); 1.70-1.62 (m, 3H); 1.56 (s, 3H); 1.26-1.10 (m, 2H); 1.21 (s, 9H); 0.67 (d, J=6.8 Hz, 3H); 0.64 (d, J=6.8 Hz, 3H). LRMS (ESI) calcd for calcd for $C_{39}H_{60}O_8Na$ [M+Na] 679.42, found 679.43.



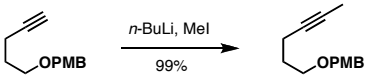

**Allylic Alcohol 10.** Potassium carbonate (22 mg, 0.158 mmol) was added to a solution of the substrate (21 mg, 31.7 μmol) in methanol (0.8 ml) at 0 °C. After 10

min, the reaction was warmed to rt and stirring was for an additional 1 h 20 min. The solution was diluted with water and ethyl acetate. The mixture was extracted with ethyl acetate (4x30 ml), and the organic layers were washed with brine, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 60% → 75% → 100% EtOAc – hexanes) to afford the desired product **10** (18.8 mg, 30.6 μmol, 97%), as a 4.6:1 mixture of diastereomers. $^{1}$H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.36-7.26 (m, 5H); 5.74-5.63 (m, 2H); 5.35 (d, J=11.0 Hz, 1H); 4.60-4.55 (m, 2H); 4.51-4.45 (m, 2H); 4.14-4.02 (m, 4H); 3.96-3.84 (m, 3H); 3.36 (m, 3H); 3.23-3.16 (m, 2H); 2.68 (d, J=11.0 Hz, 1H); 2.59-2.52 (m, 1H); 2.38-2.24 (m, 2H); 2.25-2.16 (m, 1H); 2.04-1.94 (m, 1H); 1.94-1.76 (m, 2H); 1.69 (s, 3H); 11.70-1.58 (m, 3H); 1.58 (s, 3H); 1.21 (s, 9H); 1.28-1.11 (m, 2H); 0.68 (d, J=7.0 Hz, 3H); 0.65 (d, J=6.5 Hz, 3H). LRMS (ESI) calcd for calcd for $C_{37}H_{58}O_7Na$ [M+Na] 637.41, found 637.42.




S7 12

**Alkyne 12.** Sodium hydride (60% in mineral oil, 2.62 g, 65.5 mmol) was added to a solution 4-pentyn-1-ol (**S7**, 5.00 g, 59.5 mmol) in THF (90 ml) at 0 °C. The reaction was warmed to rt and stirred for 2.5 h. The resulting mixture was cooled to 0 °C and 1-(chloromethyl)-4-methoxybenzene (8.88 g, 56.7 mmol) was added, followed by tetrabutylammonium iodide (0.879 g, 2.38 mmol). The reaction mixture was heated at reflux for 4 h and quenched at rt with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with diethyl ether (3x75ml). The combined organic layers were washed with brine, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 2% ethyl acetate - hexanes) to afford the desired product[1] **12** (10.14 g, 49.6 mmol, 88%).

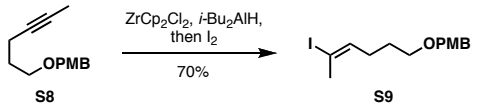



12 S8

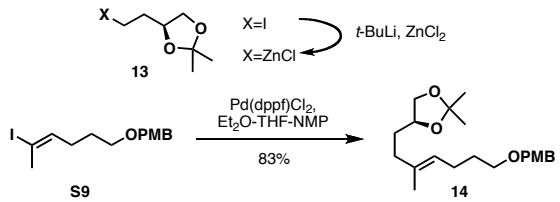
**Alkyne S8.** *n*-Butyllithium (2.43 M in hexanes, 17.7 ml, 43.1 mmol) was added dropwise to a solution of substrate **12** (8.02 g, 29.2 mmol) in THF (80 ml) at -78 °C over 20 min. After 1 h, hexamethylphosphoamidate (7.5 ml, 43.1 mmol) was added, followed by methyl iodide (3.67 ml, 58.8 mmol). The mixture was stirred at for an additional 1 h then warmed rt and continued to stir for 10 h. The reaction was quenched with saturated aqueous ammonium chloride at 0 °C. The aqueous layer was extracted with ethyl acetate/hexanes (50 ml), then with ethyl acetate (50 ml). The combined organic layers were washed with brine, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 2% ethyl acetate - hexanes) to afford the desired product **S8** (8.50 g, 38.9 mmol, 99%). $^{1}$H NMR (400 MHz, $CDCl_3$); δ(ppm): 7.30-7.26 (m, 2H); 6.92-6.88 (m, 2H); 4.46 (s, 2H); 3.82 (s, 3H); 3.54 (dd, J1=J2=6.4 Hz, 2H); 2.27-2.22 (m, 2H); 1.81-1.74 (m, 5H). $^{13}$C NMR (100 MHz, $CDCl_3$); δ(ppm): 159.2, 130.8, 129.4, 113.9, 78.7, 75.8,

[1] Toró, A.; Lemelin, C.; Préville, P.; Bélanger, G.; Deslongchamps, P., *Tetrahedron*, **1999**, *9*, 4655-4684.

72.7, 68.8, 55.4, 29.3, 15.7, 3.6. LRMS (ESI) calcd for $C_{14}H_{18}O_2Na$ [M+Na] 241.13, found 241.12.

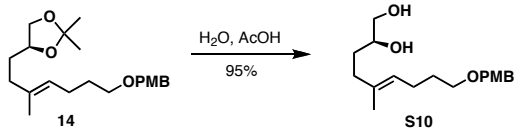



**Iodoalkene S9.** A solution of diisobutylaluminum hydride (5.69 g, 40.0 mmol) in THF (30 ml) was added dropwise to a solution of bis(cyclopentadienyl)zirconium dichloride (11.7 g, 40.0 mmol) in THF (40 ml) at 0 °C over 1 h. After 2 h, substrate **S8** (4.37 g, 20.0 mmol) in THF (20 ml total with rinses) was added to the reaction mixture. After addition, the reaction was heated at 50 °C for 1 h. The reaction mixture was then cooled to -78 °C and a solution of iodine (7.62 g, 30 mmol) in THF (30 ml) was added. After addition, the reaction was warmed to 0 °C for 10 min. The reaction was quenched carefully at 0 °C with the addition of saturated aqueous sodium thiosulfate followed by saturated aqueous Rochelle's salt and was allowed to stir at rt for 3 h. The aqueous layer was extracted with ethyl acetate (3x100ml). The combined organic layers were washed with brine, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 5% ethyl acetate - hexanes) to afford the desired product **S9** (4.86 g, 14.0 mmol, 70%) which was immediately submitted to the next reaction. $^1$H NMR (400 MHz, $CDCl_3$); δ(ppm): 7.28-7.23 (m, 2H); 6.91-6.86 (m, 2H); 6.14 (dd, J1=7.6 Hz, J2=J3=J4=1.2 Hz, 1H); 4.42 (s, 2H); 3.81 (s, 3H); 3.43 (dd, J1=J2=6.4 Hz, 2H); 2.36 (dd, J1=J2=0.8 Hz, 3H); 2.15-2.05 (m, 2H); 1.70-1.58 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$); δ(ppm): 159.3, 140.7, 130.6, 129.4, 113.9, 94.3, 72.8, 69.0, 55.4, 29.0, 27.6, 27.4. LRMS (ESI) calcd for $C_{14}H_{19}IO_2Na$ [M+Na] 369.04, found 369.05.

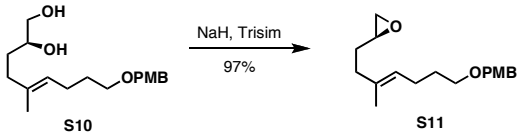



**Acetonide 14.** (*S*)-4-(2-Iodoethyl)-2,2-dimethyl-1,3-dioxolane (**13**) (5.38 g, 21.0 mmol) in diethyl ether (15 ml total with rinses) was added dropwise to a solution of *t*-butyllithium (1.66 M in pentane, 25.3 ml, 42.0 mmol) in diethyl ether (15 ml) at -78 °C. After stirring for 1.5 h, zinc chloride (1.0 M in THF, 23.1 ml, 23.1 mmol) was added, and the solution was allowed to warm to rt. After 10 min, THF (35 ml) and additional *N*-methylpyrrolidin-2-one (NMP) (35 ml) were added, followed by the addition substrate **S9** (4.85 g, 14.0 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.286 g, 0.35 mmol). After 4 h, the reaction mixture was diluted with ethyl acetate (150 ml). The organic layer was washed with brine (3x), dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 10% ethyl acetate - hexanes) to afford the desired product **14** (4.05 g, 11.6 mmol, 83%). $[\alpha]_D^{22}$ 10.4° (c 1.0, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$); δ(ppm): 7.27-7.23 (m, 2H); 6.89-6.85 (m, 2H); 5.13 (ddd, J1=J2=7.2 Hz, J3=1.2 Hz, 1H); 4.42 (s, 2H); 4.06-4.00 (m, 2H); 3.79 (s, 3H); 3.53-3.48 (m, 1H); 3.42 (dd, J1=J2=6.8 Hz, 2H);

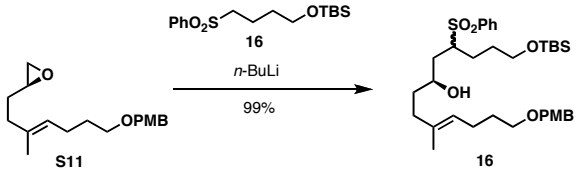
2.11–2.03 (m, 3H); 2.01–1.93 (m, 1H); 1.78–1.70 (m, 1H); 1.67–1.53 (m, 3H); 1.60 (s, 3H); 1.41 (s, 3H); 1.35 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$); δ(ppm): 159.1, 135.0, 130.9, 129.4, 124.5, 113.9, 108.7, 76.0, 72.8, 69.8, 69.6, 55.5, 35.8, 32.1, 30.0, 27.2, 26.0, 24.7, 16.2. LRMS (ESI) calcd for $C_{21}H_{32}O_4Na$ [M+Na] 371.23, found 371.23.



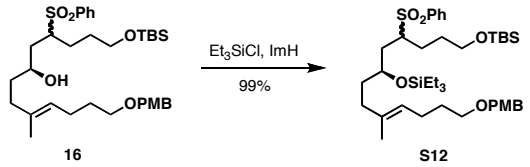

**Diol S10.** Acetic acid (40 ml, 0.70 mol) was added to a solution of substrate **14** (4.30 g, 12.3 mmol) in THF (40 ml) and water (40 ml). The reaction was heated at 50 °C for 5 h. After cooling to rt, THF and acetic acid were removed under reduced pressure. The residue was diluted with saturated aqueous sodium bicarbonate, and ethyl acetate (200ml). The aqueous layer was extracted with ethyl acetate (3x75ml). The combined organic layers were washed with brine, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 50% ethyl acetate - hexanes) to afford the desired product **S10** (3.61 g, 11.7 mmol, 95%). $[\alpha]_D^{22}$ -2.2° (c 1.0, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$); δ(ppm): 7.28–7.24 (m, 2H); 6.90–6.85 (m, 2H); 5.17 (dd, J1=J2=6.8 Hz, 1H); 4.42 (s, 2H); 3.80 (s, 3H); 3.70–3.61 (m, 2H); 3.47–3.41 (m, 1H); 3.43 (dd, J1=J2=6.4 Hz, 2H); 2.17–2.02 (m, 5H); 1.95–1.86 (m, 1H); 1.69–1.56 (m, 2H); 1.61 (s, 3H); 1.56–1.50 (m, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 159.3, 135.3, 130.9, 129.5, 124.8, 114.0, 72.7, 72.3, 69.7, 66.7, 55.5, 35.9, 31.4, 29.9, 24.7, 16.0. LRMS (ESI) calcd for $C_{18}H_{28}O_4Na$ [M+Na] 331.19, found 331.20.




**Epoxide S11.** Substrate **S10** (4.00 g, 13.0 mmol) in THF (20 ml total with rinses) was added dropwise to a suspension of sodium hydride (60% in mineral oil, 1.30 g, 32.4 mmol) in THF (260 ml) at 0 °C. After stirring for 1.5 h, the reaction mixture was cooled to -78 °C and 1-[(2,4,6-triisopropylphenyl)sulfonyl]-1*H*-imidazole (4.56 g, 13.6 mmol) was added. The mixture was allowed to warm to 0 °C and stirred for 1 h. The solid was filtered off and to the filtrate was added saturated aqueous ammonium chloride. The aqueous layer was extracted with ethyl acetate (3x75ml). The combined organic layers were washed with water, brine, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 10% ethyl acetate - hexanes) to give the desired product **S11** (3.65 g, 12.6 mmol, 97%). $[\alpha]_D^{22}$ -1.9° (c 1.0, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$); δ(ppm): 7.27–7.23 (m, 2H); 6.88–6.84 (m, 2H); 5.15 (ddd, J1=J2=7.2 Hz, J3=1.6 Hz, 1H); 4.41 (s, 2H); 3.79 (s, 3H); 3.42 (dd, J1=J2=6.4 Hz, 2H); 2.91–2.86 (m, 1H); 2.73 (dd, J1=4.8 Hz, J2=4.0 Hz, 1H); 2.46 (dd, J1=4.8 Hz, J2=2.8 Hz, 1H); 2.16–2.03 (m, 4H); 1.68–1.56 (m, 4H), 1.60 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$); δ(ppm): 159.2, 134.6, 130.9, 129.4, 124.7, 113.9, 72.7, 69.7, 55.4, 52.2, 47.3, 36.0, 31.1, 29.9, 24.6, 16.1. LRMS (ESI) calcd for $C_{18}H_{26}O_3Na$ [M+Na] 313.19, found 313.18.

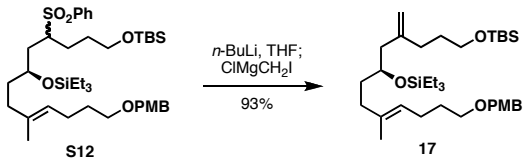



**Sulfone 16.** *n*-Butyllithium (2.50 M in hexanes, 20.9 ml, 52.4 mmol) was added dropwise to a solution of the sulfone[2] (**16**) (18.1 g, 55.1 mmol) in THF (100 ml) at -78 °C over 20 min. After 2 h, the substrate **S11** (8.00 g, 27.6 mmol) in THF (40 ml total with rinses) was added dropwise to the reaction mixture. After addition, the reaction mixture was allowed to warm to 0 °C over 4 h. The reaction was quenched carefully with saturated aqueous ammonium chloride. The aqueous layer was extracted with ethyl acetate (3x200ml). The combined organic layers were washed with brine, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 25% ethyl acetate - hexanes) to afford the desired product **16** (17.0 g, 27.5 mmol, 99%). $^1$H NMR (400 MHz, $CDCl_3$); δ(ppm): 7.90-7.86 (m, 2H); 7.66-7.62 (m, 1H); 7.57-7.53 (m, 2H); 7.27-7.23 (m, 2H); 6.89-6.85 (m, 2H); 5.16-5.11 (m, 1H); 4.42-4.41 (m, 2H); 3.80 (s, 3H); 3.70-3.62 (m, 1H); 3.57-3.52 (m, 2H); 3.44-3.40 (m, 2H); 3.36-3.33 (m, 1H); 2.42-2.28 (m, 1H); 2.14-1.82 (m, 5H); 1.72-1.46 (m, 9H); 1.58 (s, 3H); 0.87-0.80 (m, 9H); 0.00— -0.03 (m, 6H). LRMS (ESI) calcd for $C_{34}H_{54}O_6SSiNa$ [M+Na] 641.34, found 641.33.

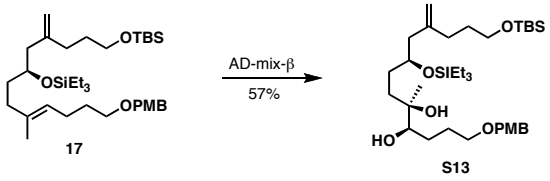



**TES Ether S12.** Chlorotriethylsilane (9.2 ml, 55.1 mmol) was added to a solution of substrate **16** (17.0 g, 27.5 mmol) and imidazole (7.51 g, 100.2 mmol) in dichloromethane (150 ml) at 0 °C. The resulting mixture was stirred at rt for 2 h. The reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with ethyl acetate (3x150ml). The combined organic layers were washed with brine, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 10% ethyl acetate - hexanes) to afford the desired product **S12** (20.0 g, 27.3 mmol, 99%). $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.88-7.86 (m, 2H); 7.65-7.61 (m, 1H); 7.58-7.53 (m, 2H); 7.27-7.24 (m, 2H); 6.89-6.86 (m, 2H); 5.11-5.06 (m, 1H); 4.42 (s, 2H); 3.95-3.76 (m, 1H); 3.80 (s, 3H); 3.60-3.52 (m, 2H); 3.45-3.40 (m, 2H); 3.23-3.06 (m, 1H); 2.10-2.02 (m, 2H); 1.96-1.84 (m, 3H); 1.78-1.42 (m, 9H); 1.60 (s, 3H); 0.99-0.83 (m, 18H); 0.62-0.49 (m, 6H); 0.01— -0.01 (m, 6H). LRMS (ESI) calcd for $C_{40}H_{68}O_6SSi_2Na$ [M+Na] 755.43, found 755.43.

[2] Nystroem, J. E.; McCanna, T. D.; Helquist, P.; Iyer, R. S. *Tetrahedron Letters*, **1985**, *26*, 5393—5396.

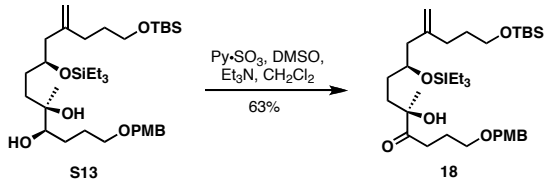



**Alkene 17.** Isopropylmagnesium chloride (2.0 M in THF, 46.8 ml, 93.6 mmol) was added dropwise to a solution of diiodomethane (6.9 ml, 85.1 mmol) in THF (100 ml) at -78 °C. The reaction mixture was stirred at the same temperature for 1 h. In a separate flask, *n*-butyllithium (2.51 M in hexanes, 14.7 ml, 36.9 mmol) was added to a solution of substrate **S12** (20.8 g, 27.6 mmol) in THF (100 ml) at -78 °C. After 1 h, the mixture was transferred to the above iodomethylmagnesium chloride solution via cannula. After 2 h, the reaction mixture was quenched with saturated aqueous ammonium chloride at -78 °C. After warming to rt, the aqueous layer was extracted with ethyl acetate (3x200ml). The combined organic layers were washed with brine, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 5% ethyl acetate - hexanes) to afford the desired product **17** (15.6 g, 25.8 mmol, 93%). $[\alpha]_D^{22}$ -2.7° (c 1.0, $CH_2Cl_2$). $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.27-7.25 (m, 2H); 6.89-6.86 (m, 2H); 5.11 (ddd, J1=J2=6.5 Hz, J3=1.0 Hz, 1H); 4.76 (d, J=14.5 Hz, 2H); 4.42 (s, 2H); 3.80 (s, 3H); 3.80-3.76 (m, 1H); 3.61 (dd, J1=J2=6.5 Hz, 2H); 3.43 (dd, J1=J2=7.0 Hz, 2H); 2.23-2.14 (m, 2H); 2.10-2.03 (m, 5H); 1.98-1.92 (m, 1H); 1.68-1.54 (m, 5H); 1.58 (s, 3H); 1.49-1.40 (m, 1H); 0.96 (dd, J1=J2=8.0 Hz, 9H); 0.89 (s, 9H); 0.60 (ddd, J1=J2=J3=8.5 Hz, 6H); 0.07-0.04 (m, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 159.3, 146.6, 135.9, 131.0, 129.4, 123.9, 113.9, 111.9, 72.8, 71.1, 70.0, 63.1, 55.5, 44.7, 35.7, 35.6, 32.8, 31.2, 30.1, 26.2, 24.7, 18.6, 16.3, 7.2, 5.3, -5.1. LRMS (ESI) calcd for $C_{35}H_{64}O_4Si_2Na$ [M+Na] 627.43, found 627.45.



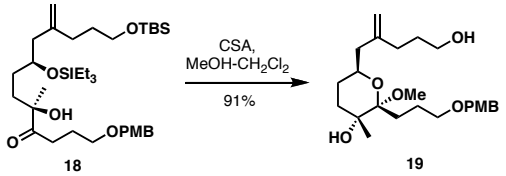

**Diol S13.** A mixture of AD-mix-β (8.50 g, 9.01 mmol) and methanesulfonamide (1.57 g, 16.5 mmol) in *t*-butanol (41.3 ml) and water (31.3 ml) was stirred at rt until both phases became clear. The mixture was cooled to 0 °C, and substrate **17** (5.00 g, 8.25 mmol) in *t*-butanol (10 ml total with rinses) was added to the reaction mixture. After stirring at 0 °C for 60 h, the reaction was quenched with saturated aqueous sodium thiosulfate. The aqueous layer was extracted with ethyl acetate (3x250ml). The combined organic layers were washed with brine, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 25% ethyl acetate - hexanes) to afford the desired product **S13** (3.01 g, 4.71 mmol, 57%). Additionally 1.38 g (2.28 mmol, 28%) of starting material **17** was recovered from the reaction. $[\alpha]_D^{22}$ 5.2° (c 1.0, $CH_2Cl_2$). $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.27-7.24 (m, 2H); 6.89-6.85 (m, 2H); 4.77 (d, J=13.0 Hz, 2H); 4.45 (s, 2H); 3.88-3.80 (m, 1H); 3.80 (s, 3H); 3.61 (dd, J1=J2=6.0 Hz, 2H); 3.50 (dd, J1=J2=6.0 Hz, 2H); 3.38 (d, J1=10.5 Hz, 1H); 3.06 (bs, 1H); 2.72 (bs, 1H); 2.26-

2.17 (m, 2H); 2.04 (dd, J1=J2=7.5 Hz, 2H); 1.87-1.80 (m, 1H); 1.75-1.47 (m, 8H); 1.39-1.31 (m, 1H); 1.07 (s, 3H); 0.96 (dd, J1=J2=8.0 Hz, 9H); 0.89 (s, 9H); 0.60 (ddd, J1=J2=J3=8.0 Hz, 6H); 0.05 (s, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 159.4, 146.3, 130.4, 129.5, 114.0, 112.1, 74.3, 72.9, 71.4, 70.4, 63.0, 55.4, 44.2, 33.9, 32.6, 31.1, 30.0, 28.9, 27.2, 26.1, 21.0, 18.5, 7.1, 5.1, -5.5. LRMS (ESI) calcd for $C_{35}H_{66}O_6Si_2Na$ [M+Na] 661.44, found 661.47.




S13 18

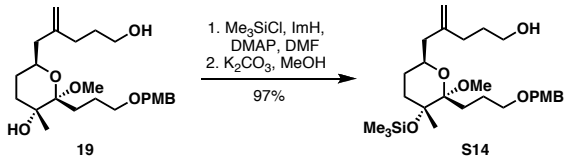
**Ketone 18.** Pyridine sulfur trioxide (3.18 g, 20.0 mmol) was added to a solution of substrate **S13** (6.39 g, 10.0 mmol), triethylamine (13.9 ml, 99.7 mol) and dimethyl sulfoxide (14.2 ml, 0.20 mol) in dichloromethane (100 ml). The resulting mixture was stirred at 35 °C. After 48 h, the mixture was diluted with dichloromethane (100 ml). The organic layer was washed with brine, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 25% ethyl acetate - hexanes) to afford the desired product **18** (4.00 g, 6.27 mmol, 63%). Additionally 0.68 g (1.07 mmol, 11%) of starting material **S13** was recovered from the reaction. $[\alpha]_D^{22}$ -6.6° (c 1.0, $CH_2Cl_2$). $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.26-7.22 (m, 2H); 6.88-6.85 (m, 2H); 4.74 (d, J=17.5 Hz, 2H); 4.41 (s, 2H); 3.87 (s, 1H); 3.83-3.78 (m, 1H); 3.80 (s, 3H); 3.60 (dd, J1=J2=6.0 Hz, 2H); 3.44 (dd, J1=J2=6.0 Hz, 2H); 2.69 (ddd, J1=18.0 Hz, J2=8.0 Hz, J3=7.0 Hz, 1H); 2.56 (ddd, J1=18.0 Hz, J2=8.0 Hz, J3=6.0 Hz, 1H); 2.21-2.12 (m, 2H); 2.02 (dd, J1=J2=8.0 Hz, 2H); 1.96-1.83 (m, 2H); 1.81-1.74 (m, 1H); 1.71-1.60 (m, 3H); 1.52-1.45 (m, 1H); 1.32-1.25 (m, 1H); 1.31 (s, 3H); 0.94 (dd, J1=J2=8.0 Hz, 9H); 0.89 (s, 9H); 0.57 (ddd, J1=J2=J3=8.0 Hz, 6H); 0.04 (s, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 214.7, 159.4, 146.2, 130.6, 129.5, 114.0, 112.2, 78.7, 72.8, 70.8, 69.0, 63.0, 55.5, 44.2, 34.6, 32.8, 32.6, 31.1, 30.3, 26.2, 25.4, 24.0, 18.5, 7.2, 5.2, -5.1. LRMS (ESI) calcd for $C_{35}H_{64}O_6Si_2Na$ [M+Na] 659.42, found 659.46.




18 19

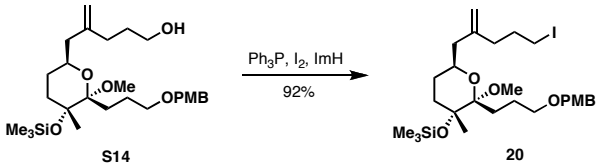
**Acetal 19.** (±)-10-Camphorsulfonic acid (0.40 g, 1.73 mmol) was added to a solution of substrate **18** (5.50 g, 8.63 mmol) in methanol (69 ml) and dichloromethane (17 ml) at rt. After 1.5 h, the reaction was quenched with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with ethyl acetate(3x150ml). The combined organic layers were washed with brine, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 30% to 50% ethyl acetate - hexanes) to afford the desired product **19** (3.30 g, 7.81 mmol, 91%). $[\alpha]_D^{22}$ 46.9° (c 1.0, $CH_2Cl_2$). $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.30-7.23 (m, 2H); 6.92-6.85 (m, 2H); 4.81 (d, J1=10.5 Hz, 2H); 4.43 (s, 2H); 3.80 (s, 3H);

3.65 (dd, J1=J2=6.5 Hz, 2H); 3.63-3.58 (m, 1H); 3.45-3.36 (m, 2H); 3.23-3.19 (m, 3H); 2.26-2.20 (m, 2H); 2.16-2.07 (m, 3H); 2.06-1.97 (m, 1H); 1.96-1.89 (m, 1H); 1.77-1.67 (m, 4H); 1.65-1.51 (m, 4H); 1.36-1.25 (m, 1H); 1.27 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 159.2, 146.5, 131.0, 129.5, 113.9, 112.0, 102.0, 72.6, 72.5, 70.6, 69.4, 62.9, 55.5, 48.0, 42.3, 36.6, 33.1, 30.9, 30.0, 29.1, 24.7, 22.1. LRMS (ESI) calcd for $C_{24}H_{38}O_6Na$ [M+Na] 445.27, found 445.31.



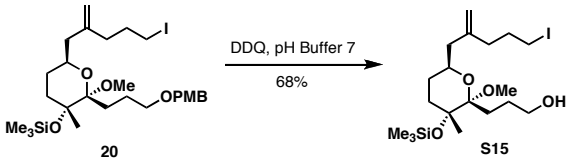

**TMS Ether S14.** Trimethylsilylchloride (7.10 ml, 55.9 mmol) was added to a solution of substrate **19** (5.90 g, 14.0 mmol), imidazole (7.61 g, 0.11 mol) and dimethylaminopyridine (0.85 g, 6.98 mmol) in dimethylformamide (70 ml) at 0 °C. After 10 min, the solution was heated at 40 °C for 12 h. The reaction mixture was quenched with water. The aqueous layer was extracted with ethyl acetate (3x100ml). The combined organic layers were washed with water, brine, dried with sodium sulfate, concentrated, and the crude residue was submitted to the next step without further purification.

Potassium carbonate (0.385 g, 2.79 mmol) was added to a solution of the crude residue in methanol (60 ml) at 0 °C. After 30 min, the reaction mixture was diluted with ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (3x100ml). The combined organic layers were washed with brine, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 20% ethyl acetate - hexanes) to afford the desired product **S14** (6.73 g, 13.6 mmol, 97%). $[\alpha]_D^{22}$ 35.6° (c 1.0, $CH_2Cl_2$). $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.28-7.24 (m, 2H); 6.89-6.86 (m, 2H); 4.80 (d, J=7.0 Hz, 2H); 4.43 (s, 2H); 3.80 (s, 3H); 3.69-3.62 (m, 3H); 3.45-3.38 (m, 2H); 3.17 (s, 3H); 2.22-2.11 (m, 4H); 2.07 (dd, J1=14.0 Hz, J2=6.0 Hz, 1H); 1.94-1.86 (m, 1H); 1.74-1.60 (m, 5H); 1.58-1.52 (m, 1H); 1.50-1.42 (m, 2H); 1.31 (s, 3H); 0.09 (s, 9H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 159.2, 146.6, 131.2, 129.3, 113.9, 111.8, 101.9, 76.3, 72.5, 70.9, 68.7, 62.9, 55.5, 47.2, 42.5, 35.1, 33.0, 30.9, 30.0, 28.7, 25.8, 24.7, 3.1. LRMS (ESI) calcd for $C_{27}H_{46}O_6SiNa$ [M+Na] 517.31, found 517.32.

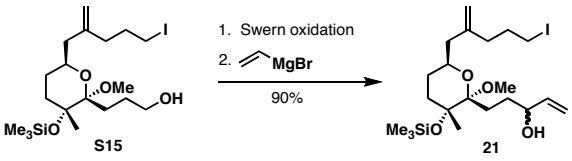



**Iodide 20.** Iodine (27.9 mg, 0.11 mmol) was added to a solution of substrate **S14** (44 mg, 89 μmol), triphenylphosphine (28 mg, 0.106 mmol), imidazole (28 mg, 0.111 mmol) in dichloromethane (3.0 ml) at 0 °C. After 10 min, the mixture was allowed to warm to rt and stirred for 1 h. Hexanes (3 ml) was added and the mixture was filtered through a short silica plug. The resulting solution was concentrated and the residue was purified by column chromatography (silica, 10% ethyl acetate -

hexanes) to afford the desired product **20** (49 mg, 81 μmol, 92%). $[\alpha]_D^{22}$ 26.8° (c 1.0, $CH_2Cl_2$). $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.29-7.25 (m, 2H); 6.89-6.86 (m, 2H); 4.82 (s, 2H); 4.45-4.42 (m, 2H); 3.80 (s, 3H); 3.67-3.62 (m, 1H); 3.44-3.39 (m, 2H); 3.22-3.15 (m, 5H); 2.23-2.14 (m, 4H); 2.04 (dd, J1=14.0 Hz, J2=6.0 Hz, 1H); 1.99-1.87 (m, 3H); 1.70-1.61 (m, 3H); 1.58-1.52 (m, 1H); 1.50-1.44 (m, 1H); 1.36-1.26 (m, 1H); 1.32 (s, 3H); 0.17-0.05 (s, 9H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 159.2, 145.0, 131.1, 129.4, 129.2, 113.9, 112.6, 102.0, 72.6, 72.5, 71.0, 68.7, 55.5, 48.1, 42.3, 37.3, 35.1, 31.5, 30.0, 28.7, 25.7, 24.7, 6.8, 3.0, 2.9. LRMS (ESI) calcd for $C_{27}H_{45}IO_5SiNa$ [M+Na] 627.21, found 627.20.



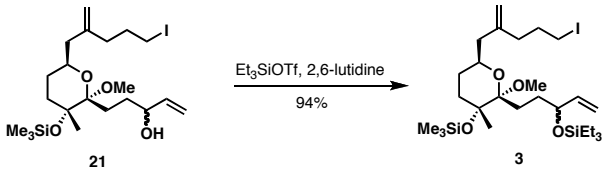

**Alcohol S15.** 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (1.97 g, 8.68 mmol) was added to a solution of substrate **20** (2.10 g, 3.47 mmol) in pH buffer 7 (40 ml) and dichloromethane (60 ml) at 0 °C. After stirring for 15 min, the reaction was quenched with 1:1 saturated aqueous sodium thiosulfate:saturated aqueous sodium bicarbonate. The aqueous layer was extracted with dichloromethane (3x100ml). The combined organic layers were dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 100% dichloromethane then 1% triethylamine in 30% ethyl acetate – hexanes) to afford the desired product **S15** (1.14 g, 2.35 mmol, 68%). $[\alpha]_D^{22}$ 10.4° (c 1.0, $CH_2Cl_2$). $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 4.81 (s, 2H); 3.70-3.64 (m, 1H); 3.62-3.57 (m, 2H); 3.21-3.14 (m, 5H); 2.21 (dd, J1=13.5 Hz, J2=5.0 Hz, 1H); 2.18-2.13 (m, 3H); 2.04 (dd, J1=14.0 Hz, J2=5.5 Hz, 1H); 1.97-1.91 (m, 2H); 1.89-1.81 (m, 1H); 1.75-1.60 (m, 4H); 1.57-1.54 (m, 1H); 1.51-1.46 (m, 1H); 1.37-1.28 (m, 4H); 0.17-0.04 (m, 9H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 144.9, 112.7, 101.9, 76.4, 68.7, 63.8, 48.4, 42.3, 37.3, 35.0, 31.5, 30.0, 28.4, 27.6, 25.7, 6.8, 3.0. LRMS (ESI) calcd for $C_{19}H_{37}IO_4SiNa$ [M+Na] 507.15, found 507.15.



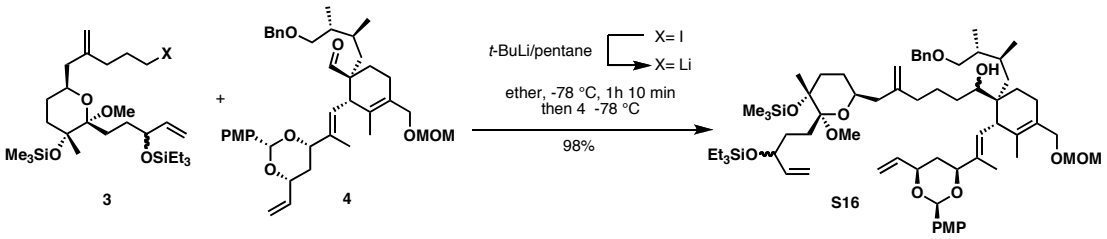

**Allylic Alcohol 21.** Dimethylsulfoxide (7 μl, 95 μmol) was added to a solution of oxalyl chloride (4 μl, 48 μmol) in dichloromethane (0.5 ml) at -78 °C. After 15 min, substrate **S15** (7.7 mg, 15.9 μmol) in dichloromethane (0.3 ml total with rinses) was added. The solution was stirred for 25 min and triethylamine (20 μl, 0.143 mmol) was added. After 10 min, the reaction was warmed to 0 °C and stirred for 10 min. The reaction was quenched with pH buffer 7. The aqueous layer was extracted with ethyl acetate (3x10 ml). The combined organic layers were washed with brine:saturated sodium bicarbonate (1:1), dried with sodium sulfate,

concentrated, and the product was submitted directly to the next step without further purification.

Vinylmagnesium bromide (1 M in THF, 50 µl, 50 µmol) was added to a solution of the crude substrate in THF (0.8 ml) at -78 °C. After 10 min, the reaction was placed in a -35 °C ice bath and allowed to warm to -20 °C over 50 min. The reaction was quenched with pH buffer 7. The aqueous layer was extracted with ethyl acetate (3x10 ml). The combined organic layers were washed with 1:1 brine:saturated aqueous sodium bicarbonate, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 15% ethyl acetate - hexanes) to afford the desired product **21** (7.3 mg, 14.2 µmol, 90%). $^1$H NMR (400 MHz, $CDCl_3$); δ(ppm): 5.86 (ddd, J1=16.4 Hz, J2=9.6 Hz, J3=6.0 Hz, 1H); 5.26-5.21 (m, 1H); 5.12-5.08 (m, 1H); 4.82 (s, 2H); 4.08-4.02 (m, 1H); 3.70-3.58 (m, 1H); 3.23-3.14 (m, 5H); 2.24-2.12 (m, 4H); 2.10-2.00 (m, 1H); 1.98-1.91 (m, 2H); 1.89-1.42 (m, 6H); 1.32 (s, 3H); 1.37-1.21 (m, 2H); 0.15-0.05 (m, 9H). LRMS (ESI) calcd for $C_{21}H_{39}IO_4SiNa$ [M+Na] 533.16, found 533.15.

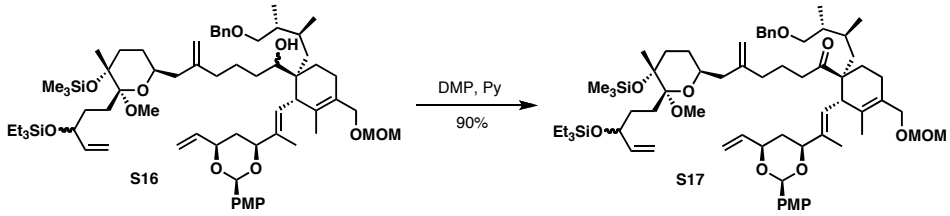



**TES Ether 3.** Triethylsilyl trifluoromethanesulfonate (0.37 ml, 1.63 mmol) was added to a solution of substrate **21** (0.278 g, 0.545 mmol) and 2,6-lutidine (0.565 ml, 4.91 mmol) in dichloromethane (10.9 ml) at 0 °C. After 10 min, the reaction was warmed to rt and stirred for an additional 10 min. The reaction was quenched with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with dichloromethane (3x20 ml). The combined organic layers were dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 100% hexanes then 2% ethyl acetate - hexanes) to afford the desired product **3** (0.320 g, 0.648 mmol, 94%). $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 5.84-5.77 (m, 1H); 5.16-5.11 (m, 1H); 5.04-5.00 (m, 1H); 4.81 (s, 2H); 4.08-4.00 (m, 1H); 3.66-3.61 (m, 1H); 3.22-3.14 (m, 5H); 2.20-2.14 (m, 4H); 2.04 (dd, J1=13.5 Hz, J2=5.5 Hz, 1H); 1.98-1.79 (m, 3H); 1.71-1.41 (m, 5H); 1.35-1.26 (m, 1H); 1.30 (s, 3H); 0.95 (dd, J1=J2=8.0 Hz, 9H); 0.59 (ddd, J1=J2=J3=8.0 Hz, 6H); 0.14-0.05 (m, 9H). LRMS (ESI) calcd for $C_{27}H_{53}IO_4Si_2Na$ [M+Na] 647.25, found 647.25.

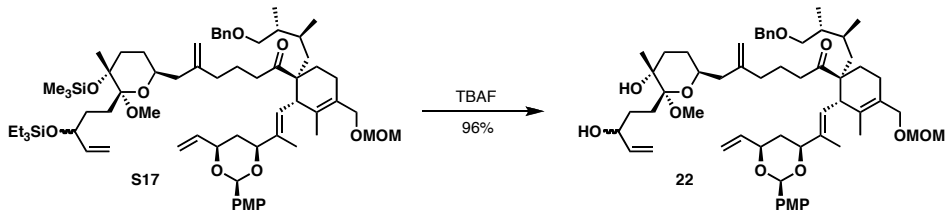



**Alcohol S16.** A solution of iodide **3**(0.171 g, 0.274 mmol) in diethyl ether (1.5 ml) was added dropwise to freshly titrated *t*-butyllithium (1.20 M in pentane, 0.460 ml, 0.551 mmol) in diethyl ether (0.7 ml) at -78 °C. After 1 h, a solution of aldehyde **4** (71 mg, 0.110 mmol) in diethyl ether (1.5 ml) was added to the reaction

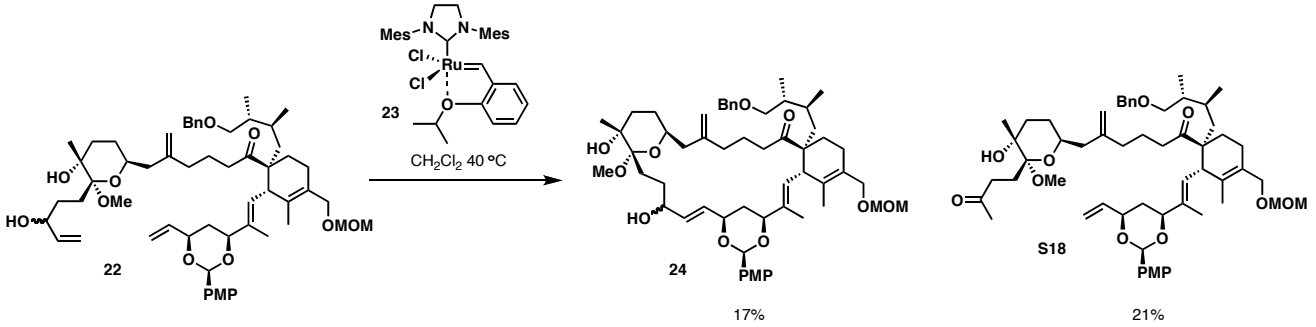
mixture dropwise and stirred at -78 °C. After 1 h, the solution was placed in a 0 °C ice bath and stirred for an additional 2 min. The reaction was quenched with saturated aqueous ammonium chloride and diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate (4x20 ml). The combined organic layers were washed with a saturated aqueous solution of sodium bicarbonate, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 10% ethyl acetate - hexanes then 20% ethyl acetate - hexanes) to afford the desired product **S16** (0.123 g, 0.107 mmol, 98%). $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.47-7.43 (m, 2H); 7.35-7.29 (m, 4H); 7.28-7.24 (m, 1H); 6.89-6.86 (m, 2H); 5.90 (ddd, J1=17.0 Hz, J2=10.5 Hz, J3=5.0 Hz, 1H); 5.84-5.76 (m, 1H); 5.53-5.42 (m, 2H); 5.33-5.28 (m, 1H); 5.16-5.11 (m, 2H); 5.02-5.00 (m, 1H); 4.81-4.74 (m, 2H); 4.61-4.59 (m, 2H); 4.45-4.41 (m, 2H); 4.32-4.26 (m, 1H); 4.23-4.18 (m, 1H); 4.06-3.97 (m, 2H); 3.81-3.79 (m, 3H); 3.68-3.57 (m, 3H); 3.37 (s, 3H); 3.31-3.27 (m, 1H); 3.21-3.14 (m, 4H); 2.74 (d, J=11.0 Hz, 1H); 2.25-1.99 (m, 8H); 1.94-1.10 (m, 18H); 1.77 (s, 3H); 1.57 (s, 3H); 1.30 (s, 3H); 0.95 (dd, J1=J2=8.0 Hz, 9H); 0.77-0.69 (m, 6H); 0.58 (ddd, J1=J2=J3=8.0 Hz, 6H); 0.14-0.05 (m, 9H). LRMS (ESI) calcd for $C_{67}H_{108}O_{11}Si_2Na$ [M+Na] 1167.74, found 1167.74.




**Ketone S17.** Dess-Martin periodinane (18.5 mg, 43.6 μmol) was added to a solution of substrate **S16** (10 mg, 8.7 μmol) and pyridine (10 μl, 0.134 mmol) in dichloromethane (1.0 ml) at rt. After 15 min, the reaction was quenched with 1:1 saturated aqueous sodium thiosulfate:saturated aqueous sodium bicarbonate. The aqueous layer was extracted with dichloromethane (3x10 ml). The combined organic layers were dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 1% triethylamine in 10% ethyl acetate - hexanes then 1% triethylamine in 20% ethyl acetate - hexanes) to afford the desired product **S17** (9.0 mg, 7.87 μmol, 90%). $^1$H NMR (400 MHz, $CDCl_3$); δ(ppm): 7.46-7.42 (m, 2H); 7.33-7.31 (m, 5H); 6.90-6.85 (m, 2H); 5.92 (ddd, J1=17.2 Hz, J2=10.8 Hz, J3=5.6 Hz, 1H); 5.84-5.75 (m, 1H); 5.57 (s, 1H); 5.32 (d, J=17.2 Hz, 1H); 5.26 (d, J=10.0 Hz, 1H); 5.17-5.11 (m, 2H); 5.01 (d, J=10.4 Hz, 1H); 4.77 (s, 1H); 4.74 (s, 1H); 4.52 (AB, JA=9.6 Hz, JB=6.4 Hz, 2H); 4.44 (AB, JA=18.4 Hz, JB=12.0 Hz, 2H); 4.42-4.34 (m, 1H); 4.24 (d, J=11.2 Hz, 1H); 4.07-3.99 (m, 2H); 3.81-3.79 (m, 4H); 3.66-3.56 (m, 1H); 3.38-3.33 (m, 5H); 3.28-3.24 (m, 1H); 3.18-3.14 (m, 4H); 2.56-2.48 (m, 1H); 2.42-2.33 (m, 1H); 2.22-1.70 (m, 10H); 1.82 (s, 3H); 1.76-1.19 (m, 15H); 1.66 (s, 3H); 1.29 (s, 3H); 0.95 (dd, J1=J2=8.0 Hz, 9H); 0.71 (d, J=6.8 Hz, 4H); 0.58 (ddd, J1=J2=J3=8.0 Hz, 6H); 0.13-0.04 (m, 9H). LRMS (ESI) calcd for $C_{67}H_{106}O_{11}Si_2Na$ [M+Na] 1165.73, found 1165.75.

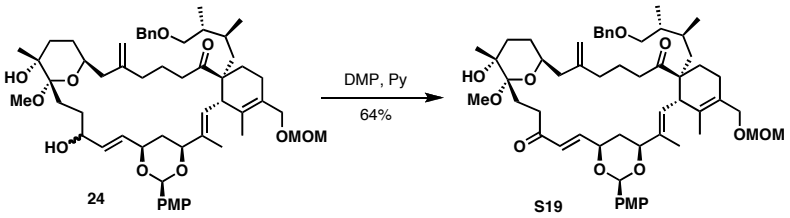



**Diol 22.** Tetrabutylammonium fluoride (1 M in THF, 90 µl, 90 µmol) was added to a solution of substrate **S17** (16.1 mg, 14 µmol) in THF (2.0 ml) at rt. After 45 min, the reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with ethyl acetate (3x10 ml). The combined organic layers were washed with a saturated aqueous solution of sodium bicarbonate, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 40% ethyl acetate - hexanes then 60% ethyl acetate - hexanes) to afford the desired product **22** (13.0 mg, 13.6 µmol, 96%). $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.47-7.43 (m, 2H); 7.35-7.31 (m, 4H); 7.29-7.26 (m, 1H); 6.89-6.87 (m, 2H); 5.95-5.83 (m, 2H); 5.57 (s, 1H); 5.34-5.31 (m, 1H); 5.28-5.26 (m, 1H); 5.25-5.21 (m, 1H); 5.16 (d, J=11.0 Hz, 1H); 5.10 (d, J=9.5 Hz, 1H); 4.78 (s, 1H); 4.77 (s, 1H); 4.52 (AB, JA=10.5 Hz, JB=6.5 Hz, 2H); 4.45 (AB, JA=20.5 Hz, JB=12.0 Hz, 2H); 4.40-4.34 (m, 1H); 4.25 (dd, J1=11.0 Hz, J2=2.0 Hz, 1H); 4.09-4.00 (m, 2H); 3.83-3.79 (m, 1H); 3.80 (s, 3H); 3.60-3.56 (m, 1H); 3.37 (d, J=11.0 Hz, 1H); 3.33 (s, 3H); 3.25 (dd, J1=9.0 Hz, J2=7.0 Hz, 1H); 3.22-3.15 (m, 4H); 2.53 (ddd, J1=18.0 Hz, J2=9.0 Hz, J3=5.5 Hz, 1H); 2.40 (ddd, J1=17.5 Hz, J2=9.0 Hz, J3=6.0 Hz, 1H); 2.22-1.88 (m, 9H); 1.82 (s, 3H); 1.75-1.46 (m, 14H); 1.66 (s, 3H); 1.34-1.20 (m, 6H); 0.72 (d, J=7.0 Hz, 3H); 0.57 (d, J=7.0 Hz, 3H). LRMS (ESI) calcd for $C_{58}H_{84}O_{11}Na$ [M+Na] 979.60, found 979.62.



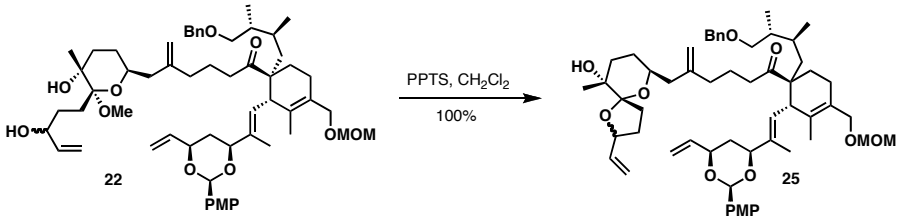

**Macrocycle 24.** Hoveyda-Grubbs II catalyst **23** (12.0 mg, 19.3 µmol) was added to a solution of substrate **22** (37 mg, 38.6 µmol) in degassed dichloromethane (7.7 ml) and heated at 40 °C. After 16 h, the solvent was removed under reduced pressure and the residue was purified by column chromatography (silica, 30%→40%→50%→60%→70% ethyl acetate - hexanes) to afford the desired product **24** (6.3 mg, 6.79 µmol, 17%) along with methyl ketone **S18** (7.6 mg, 8.11 µmol, 21%). $^1$H NMR (600 MHz, $CDCl_3$); δ(ppm): 7.45-7.40 (m, 2H); 7.37-7.30 (m, 4H); 7.30-7.25 (m, 1H); 6.89-6.86 (m, 2H); 5.95-5.87 (m, 1H); 5.77-5.72 (m, 1H); 5.63-5.52 (m, 1H); 5.28-5.12 (m, 1H); 4.78-4.67 (m, 2H); 4.62-4.58 (m, 2H); 4.52-4.34 (m, 4H); 4.29-4.24 (m, 1H); 4.18-4.03 (m, 1H); 3.95-3.82 (m, 1H); 3.79 (s, 3H); 3.62-3.45 (m, 1H); 3.39-3.29 (m, 2H); 3.37 (s, 3H); 3.29-3.24 (m, 3H); 2.99-2.95 (m, 1H); 2.75-1.18 (m, 35H); 0.89-0.45

(m, 8H). LRMS (ESI) calcd for $C_{56}H_{80}O_{11}Na$ [M+Na] 951.53, found 951.56. **Methyl Ketone S18.** $[\alpha]_D^{24}$ 94.1° (c 1.0, $CH_2Cl_2$). $^1H$ NMR (500 MHz, $CDCl_3$); δ(ppm): 7.46-7.41 (m, 2H); 7.35-7.21 (m, 5H); 6.90-6.86 (m, 2H); 5.92 (ddd, J1=17.0 Hz, J2=10.5 Hz, J3=5.5 Hz, 1H); 5.57 (s, 1H); 5.32 (ddd, J1=17.0 Hz, J2=J3=1.5 Hz, 1H); 5.27 (d, J=10.5 Hz, 1H); 5.16 (ddd, J1=10.5 Hz, J2=J3=1.5 Hz, 1H); 4.78 (s, 1H); 4.77 (s, 1H); 4.52 (AB, JA=10.0 Hz, JB=6.5 Hz, 2H); 4.44 (AB, JA=20.0 Hz, JB=12.0 Hz, 2H); 4.38-4.35 (m, 1H); 4.25 (d, J=11.0 Hz, 1H); 4.04 (d, J=10.5 Hz, 1H); 3.82-3.80 (m, 1H); 3.80 (s, 3H); 3.58-3.53 (m, 1H); 3.38-3.33 (m, 1H); 3.33 (s, 3H); 3.30-3.16 (m, 2H); 3.16 (s, 3H); 2.92 (ddd, J1=17.5 Hz, J2=11.5 Hz, J3=5.5 Hz, 1H); 2.52 (ddd J1=18.0 Hz, J2=9.0 Hz, J3=6.0 Hz, 1H); 2.44-2.38 (m, 2H); 2.17-1.83 (m, 6H); 2.14 (s, 3H); 1.83 (s, 3H); 1.74-1.50 (m, 15H); 1.66 (s, 3H); 1.35-1.20 (m, 2H); 1.24 (s, 3H); 0.72 (d, J=7.0 Hz, 3H); 0.57 (d, J=7.5 Hz, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$); δ(ppm): 213.7, 208.5, 160.1, 146.0, 139.0, 138.0, 137.3, 134.2, 131.5, 128.5, 127.8, 127.6, 127.2, 126.0, 115.8, 113.7, 112.3, 101.6, 100.6, 95.5, 74.3, 73.0, 72.6, 69.4, 66.9, 55.5, 55.4, 54.2, 48.0, 44.2, 43.0, 42.1, 38.8, 37.8, 36.7, 36.5, 36.1, 35.9, 30.3, 30.0, 28.3, 26.6, 26.0, 25.6, 22.4, 22.1, 21.7, 18.3, 16.0, 13.8, 11.4. LRMS (ESI) calcd for $C_{57}H_{82}O_{11}Na$ [M+Na] 965.59, found 965.56.

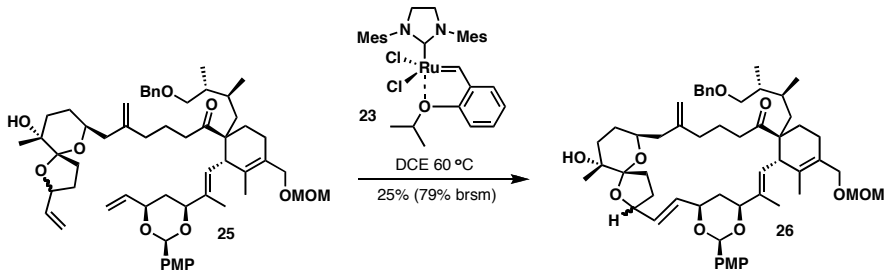



**Enone S19.** Dess-Martin periodinane (17 mg, 40.7 μmol) was added to a solution of substrate **24** (6.3 mg, 6.78 μmol) and pyridine (11 μl, 0.136 mmol) in dichloromethane (1.0 ml) at rt. After 30 min, the reaction was quenched with 1:1 saturated aqueous sodium thiosulfate:saturated aqueous sodium bicarbonate. The aqueous layer was extracted with dichloromethane (3x10 ml). The combined organic layers were dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 40% ethyl acetate - hexanes) to afford the desired product **S19** (4.0 mg, 4.32 μmol, 64%). $[\alpha]_D^{22}$ 26.0° (c 1.0, $CH_2Cl_2$). $^1H$ NMR (600 MHz, $CDCl_3$); δ(ppm): 7.48-7.45 (m, 2H); 7.36-7.31 (m, 4H); 7.29-7.23 (m, 1H); 6.92-6.90 (m, 2H); 6.82 (dd, J1=16.2 Hz, J2=4.8 Hz, 1H); 6.35 (dd, J1=16.2 Hz, J2=1.2 Hz, 1H); 5.59 (s, 1H); 5.25 (d, J1=11.4 Hz, 1H); 4.75 (s, 1H); 4.69 (s, 1H); 4.64-4.59 (m, 1H); 4.61 (AB, JA=9.0 Hz, JB=6.6 Hz, 2H); 4.49 (AB, JA=28.8 Hz, JB=12.0 Hz, 2H); 4.38 (dd, J1=11.4 Hz, J2=3.0 Hz, 1H); 4.17 (d, J=10.2 Hz, 1H); 3.87 (d, J=10.8 Hz, 1H); 3.81 (s, 3H); 3.60-3.54 (m, 1H); 3.37 (s, 3H); 3.37-3.26 (m, 2H); 3.30 (s, 3H); 3.17-3.13 (m, 1H); 2.73 (ddd, J1=15.6 Hz, J2=9.6 Hz, J3=4.8 Hz, 1H); 2.52 (ddd, J1=18.6 Hz, J2=J3=6.0 Hz, 1H); 2.39-2.32 (m, 2H); 2.30-2.20 (m, 3H); 2.19-1.83 (m, 12H); 1.76-1.18 (m, 17H); 0.88 (d, J=6.6 Hz, 3H); 0.53 (d, J=6.6 Hz, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$); δ(ppm): 212.5, 200.8, 160.3, 145.5, 143.8, 139.0, 138.7, 131.6, 131.1, 128.6, 128.5, 128.0, 127.7, 127.6, 125.2, 113.8, 111.0, 102.0, 100.2, 96.0, 82.1, 75.2, 74.3, 73.1, 72.4, 68.5, 67.5, 55.5, 55.4, 53.0, 48.9, 46.9, 43.1, 39.6, 36.3, 36.1, 35.9, 35.6, 35.3, 31.3, 30.5, 30.1,

29.9, 27.1, 25.9, 25.3, 21.6, 21.3, 17.5, 15.8, 12.9, 11.9. LRMS (ESI) calcd for $C_{56}H_{78}O_{11}Na$ [M+Na] 949.55, found 949.53.

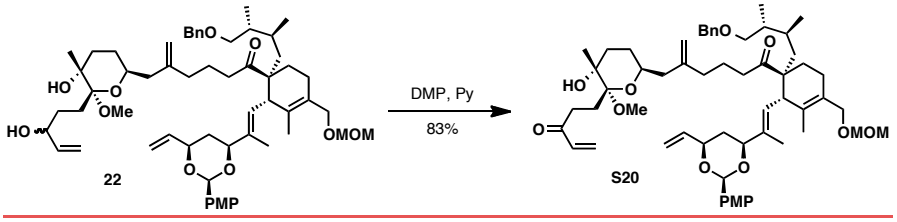



**Ketal 25.** Pyridinium *p*-toluenesulfonate (2.0 mg, 7.95 μmol) was added to a solution of substrate **22** (5.0 mg, 5.22 μmol) in dichloromethane (1.0 ml) at 0 **°C.** After 20 min, additional pyridinium *p*-toluenesulfonate (2 mg, 7.95 μmol) was added, and the reaction was stirred for 15 min at rt. The reaction was quenched with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with dichloromethane (3x10 ml). The combined organic layers were dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 25% ethyl acetate - hexanes then 30% ethyl acetate - hexanes) to afford the desired product **25** (5.0 mg, 5.22 μmol, 100%). $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.47-7.43 (m, 2H); 7.34-7.22 (m, 5H); 6.89-6.87 (m, 2H); 5.95-5.80 (m, 2H); 5.57 (s, 1H); 5.34-5.29 (m, 1H); 5.28-5.26 (m, 1H); 5.24-5.20 (m, 1H); 5.17-5.15 (m, 1H); 5.12-5.07 (m, 1H); 4.81-4.74 (m, 2H); 4.52 (AB, JA=10.5 Hz, JB=6.5 Hz, 2H); 4.44 (AB, JA=20.5 Hz, JB=12.0 Hz, 2H); 4.38-4.35 (m, 1H); 4.27-4.23 (m, 1H); 4.08-4.02 (m, 1H); 3.98-3.89 (m, 1H); 3.84-3.79 (m, 1H); 3.79 (s, 3H); 3.36 (d, J=11.0 Hz, 1H); 3.33 (s, 3H); 3.26 (dd, J1=9.0 Hz, J2=7.5 Hz, 1H); 3.16 (dd, J1=9.0 Hz, J2=6.5 Hz, 1H); 2.53 (ddd, J1=18.0 Hz, J2=9.0 Hz, J3=6.0 Hz, 1H); 2.43-2.34 (m, 1H); 2.25-1.99 (m, 7H); 1.83 (s, 3H); 1.90-1.51 (m, 12H); 1.66 (s, 3H); 1.42-1.17 (m, 10H); 0.72 (d, J=7.0 Hz, 3H); 0.57 (d, J=7.0 Hz, 3H). LRMS (ESI) calcd for $C_{57}H_{80}O_{10}Na$ [M+Na] 947.58, found 947.58.




**Macrocycle 26.** Hoveyda-Grubbs II catalyst **23** (1.3 mg, 2.1 μmol) was added to a solution of substrate **25** (5.0 mg, 5.22 μmol) in degassed dichloroethane (1.05 ml), and heated at 60 °C. After 24 h, the solvent was removed under reduced pressure and the residue was purified by column chromatography (silica, 35% ethyl acetate - hexanes) to afford the desired product **26** (1.2 mg, 1.29 μmol, 25%). Additionally, 2.7 mg (2.91 μmol, 54%) of the starting material was recovered. $^1$H NMR (600 MHz, $CDCl_3$); δ(ppm): 7.45-7.42 (m, 2H); 7.34-7.23 (m, 5H); 6.89-6.86 (m, 2H); 5.95-5.89 (m, 1H); 5.59-5.57 (m, 1H); 5.34-5.23 (m, 1H); 5.20-5.14 (m, 1H); 4.82-4.79 (m, 2H); 4.62-4.35 (m, 5H); 4.26-4.21 (m, 1H); 4.14-4.12 (m, 1H); 4.08-4.04 (m, 1H); 3.91-3.84 (m, 1H); 3.80 (s, 3H); 3.44-3.18 (m, 6H); 3.05-3.02 (m, 1H); 2.67-2.60

(m, 1H); 2.44-1.51 (m, 25H); 1.40-1.20 (m, 10H); 0.91-0.58 (m, 6H). LRMS (ESI) calcd for $C_{55}H_{76}O_{10}Na$ [M+Na] 919.54, found 919.55.




**Enone S20.** Dess-Martin periodinane (26 mg, 61.3 μmol) was added to a solution of substrate **22** (6 mg, 6.27 μmol) and pyridine (16 μl, 0.198 mmol) in dichloromethane (1.0 ml) at rt. After 30 min, the reaction was quenched with 1:1 saturated aqueous sodium thiosulfate:saturated aqueous sodium bicarbonate. The aqueous layer was extracted with dichloromethane (3x10 ml). The combined organic layers were dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica, 40% ethyl acetate - hexanes) to afford the desired product **S20** (5 mg, 5.23 μmol, 83%). $^1$H NMR (400 MHz, $CDCl_3$); δ(ppm): 7.46-7.42 (m, 2H); 7.33-7.25 (m, 5H); 6.90-6.86 (m, 2H); 6.35 (dd, J1=17.6 Hz, J2=10.4 Hz, 1H); 6.23 (d, J=17.2 Hz, 1H); 5.92 (ddd, J1=17.2 Hz, J2=10.8 Hz, J3=5.6 Hz, 1H); 5.57 (s, 1H); 5.32 (d, J=17.2 Hz, 1H); 5.26 (d, J=10.4 Hz, 1H); 5.15 (d, J=10.4 Hz, 1H); 4.78 (s, 1H); 4.77 (s, 1H); 4.52 (AB, JA=9.2 Hz, JB=6.4 Hz, 2H); 4.44 (AB, JA=18.0 Hz, JB=12.0 Hz, 2H); 4.40-4.34 (m, 1H); 4.24 (d, J=11.2 Hz, 1H); 4.03 (d, J=10.4 Hz, 1H); 3.82-3.78 (m, 1H); 3.79 (s, 3H); 3.61-3.52 (m, 1H); 3.39-3.33 (m, 1H); 3.33 (s, 3H); 3.28-3.22 (m, 1H); 3.19-3.06 (m, 2H); 3.17 (s, 3H); 2.60-2.46 (m, 2H); 2.44-2.34 (m, 1H); 2.20-1.80 (m, 11H); 1.83 (s, 3H); 1.76-1.50 (m, 10H); 1.66 (s, 3H); 1.40-1.20 (m, 6H); 0.71 (d, J=6.8 Hz, 3H); 0.57 (d, J=6.8 Hz, 3H). LRMS (ESI) calcd for $C_{58}H_{82}O_{11}Na$ [M+Na] 977.59, found 977.58.