

## Supporting Information-1

### Enantioselective Total synthesis of Peloruside A, a Potent Microtubule Stabilizer

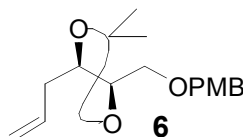
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**General Experimental Methods** All moisture sensitive reactions were carried out under nitrogen or argon atmosphere. Anhydrous solvents were obtained as follows: THF, diethyl ether and benzene, distilled from sodium and benzophenone; dichloromethane, pyridine, triethylamine, and diisopropylethylamine, distilled from CaH<sub>2</sub>. All other solvents were HPLC grade. Column chromatography was performed with 240-400 mesh silica gel under low pressure of 5-10 psi. TLC was carried out with silica gel plates. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on 500 or 400 MHz spectrometers. Infrared spectra were recorded on a FTIR instrument.

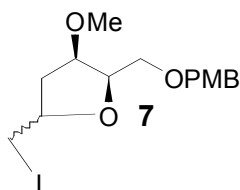


**Olefin (6)** To the solution of (-)-2,3-*O*-isopropylidene-D-threitol (**4**) (5.5 g, 34 mmol) in THF (60 mL) was added NaH (60%, 1.49 g, 37 mmol) at 0°C, and the reaction was warmed up to 23°C over 1 h. PMBCl (4.85 mL, 34 mmol) was added at 23°C and the reaction mixture was stirred for 1.5 h and was quenched with aqueous NH<sub>4</sub>Cl. The mixture was extracted with ether and the organic layer was washed with water and brine. The resulting mixture was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. Purification by column chromatography provided product (7.5 g, 78%).

To a solution of the mono-PMB protected product (87.3 g, 0.31 mol) in THF (700 mL) was added imidazole (52.6 g, 0.77 mol), Ph<sub>3</sub>P (122 g, 0.46 mol) and iodine (118g, 0.46 mol) at 0°C successively. The resulting mixture was warmed up to 23°C over 2 h and stirred overnight and then quenched by 10% aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>. The mixture was extracted with ether and the organic layer was washed with water and brine. The resulting mixture was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. Purification by column chromatography provided (106 g, 88%) iodide as a colorless oil. [ $\alpha$ ]<sub>D</sub><sup>23</sup> = +12.2 (*c* 2.21, CHCl<sub>3</sub>); IR (thin film, cm<sup>-1</sup>) 2986, 1612, 1514, 1091, 821; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.23 (2H, d, *J* = 6.5 Hz), 6.88 (2H, d, *J* = 6.5 Hz), 4.51 (2H, s), 3.94 (1H, dt, *J* = 2.5, 5.0 Hz), 3.83 (1H, dt, *J* = 3.0, 7.5 Hz), 3.81 (3H, s), 3.63 (1H, dd, 10.0, 5.0 Hz), 3.59 (1H, dd, *J* = 10.0, 5.0 Hz), 3.33 (3H, dd, *J* = 5.0, 10.5 Hz), 3.26 (3H, dd, *J* = 5.5, 10.5 Hz), 1.46 (3H, s), 1.41 (3H, s); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  159.3, 129.9, 129.4, 113.9, 109.8, 80.1, 77.7, 73.3, 70.2, 55.3, 27.4, 27.3, 6.5; MS (EI, *m/z*) [*M*]<sup>+</sup> 392.04.

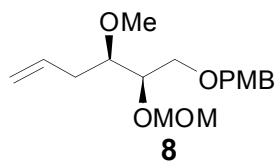
To a solution of thus obtained iodide (34.3 g, 87 mmol) in THF (100 mL) was added HMPA (62 mL) and CuI (3.4 g, 17.2 mmol) at 23°C. The resulting mixture was cooled to -30°C and vinylmagnesium bromide (173 mL, 1M in THF, 173 mmol) was added dropwise at that temperature over 1 h. The resulting mixture was stirred at -30°C for 1 h and then warmed up to 10°C and then quenched with aqueous NH<sub>4</sub>Cl. The organic layer was separated and the aqueous layer was extracted with Et<sub>2</sub>O, the combined organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. Column chromatography provided product **6** (21.6 g, 85%). [ $\alpha$ ]<sub>D</sub><sup>23</sup> = +15.0 (*c* 3.05, CH<sub>2</sub>Cl<sub>2</sub>); IR (thin film, cm<sup>-1</sup>) 3075, 2985, 2933, 2906, 2864, 2838, 1613, 1514, 1369, 1248, 1172, 1086, 1036, 917; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.25 (2H, d, *J* = 8.5 Hz), 6.88 (2H, d, *J* = 8.7 Hz), 5.82 (1H, m), 5.06-5.13 (2H, m), 4.53 (1H, d, *J* = 11.8 Hz), 4.49 (1H, d, *J* = 11.8 Hz), 3.86 (2H, m), 3.79 (3H, s), 2.36 (2H, m), 1.41 (3H, s), 1.40 (3H, s); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  159.1, 133.7, 130.0, 129.2, 117.5, 113.7,

108.8, 79.5, 77.3, 73.1, 70.0, 55.2, 37.3, 27.1, 26.9; MS (ESI,  $m/z$ )  $[M+Na]^+$  315.0; HRMS (ESI)  $[M+Na]^+$  calcd for  $C_{17}H_{24}O_4Na$  315.1572, found 315.1571.



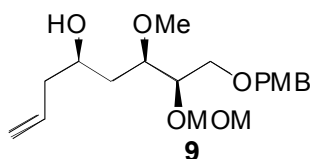
**Methyl ether (7)** To the obtained olefin **6** (31.5 g, 108 mmol) in methanol (500 mL) was added 10% HCl (66 mL) at 0°C and the mixture was stirred at 23°C for 12 h. The reaction was then quenched with  $Na_2CO_3$  (11.4 g, 108 mmol) and concentrated to give the crude diol which was used for the next step without further purification. The crude diol (57 g, 226 mmol) was dissolved in MeCN (1.3 L), and  $NaHCO_3$  (109 g, 1.3 mol) and iodine (125 g, 490 mmol) was added successively at 0°C. The resulting mixture was warmed up to 23°C over 3 h and then quenched by 10% aqueous  $Na_2S_2O_3$  and extracted with ethyl acetate. The combined organic layer was washed with brine and concentrated in vacuo. Column chromatography provided product (70.4 g, 82.4% for 2 steps) as a solid. mp 60-62°C;  $[\alpha]^{23}_D$  -24 ( $c$  2.64,  $CHCl_3$ );  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.30 (2H, m), 6.87 (2H, m), 4.53-4.48 (3H, m), 4.26 (0.75H, m), 4.15 (0.75H, dd,  $J$  = 4.0, 9.0 Hz), 4.09 (0.25H, m), 3.95 (0.25H, dd,  $J$  = 4.5, 9.0 Hz), 3.75 (2H, m), 3.36 (0.5H, m), 3.33-3.27 (1.5H, m), 3.07 (1H, s), 2.35 (0.25H, ddd,  $J$  = 14.0, 7.0, 7.0 Hz), 2.20 (0.75H, dd,  $J$  = 5.5, 14.0 Hz), 1.86 (1H, m);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  159.5, 129.6, 129.5, 114.0, 109.8, 81.7, 81.0, 78.0, 74.0, 73.6, 73.0, 68.7, 68.6, 55.3, 42.3, 40.8, 11.2, 10.7; IR (thin film,  $cm^{-1}$ ) 3440, 2931, 1612, 1513, 1071, 820;

To the solution of the alcohol (24.5 g, 64.8 mmol) in  $CH_2Cl_2$  (240 mL) was added proton sponge (17.3 g, 81 mmol) and  $Me_3OBF_4$  (11.7 g, 79 mmol) at 0°C. The reaction mixture was then warmed up to 23°C and stirred over night. The solid was removed by filtration and the organic layer was washed with aqueous  $NaHCO_3$ , water and brine, and dried over  $Na_2SO_4$  and concentrated in vacuo. Column chromatography provided the methyl ether **7** (22 g, 87%). It's a mixture ( $dr$  4:1).  $[\alpha]^{23}_D$  -41.8 ( $c$  1.83,  $CH_2Cl_2$ ); IR (thin film,  $cm^{-1}$ ) 2929, 2902, 2864, 2835, 1612, 1513, 1462, 1247, 1085, 1034, 820;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.27 (2H, d,  $J$  = 8.1 Hz), 6.87 (2H, d,  $J$  = 8.6 Hz), 4.56 (1H, d,  $J$  = 11.7 Hz), 4.45 (0.2H, d,  $J$  = 11.7 Hz), 4.44 (0.8H, d,  $J$  = 11.7 Hz), 4.23 (0.8H, m), 4.18 (1H, m), 4.06 (0.2H, m), 3.94 (0.8H, m), 3.89 (0.2H, m), 3.79 (3H, s), 3.71-3.67 (0.2H, m), 3.63 (0.8H, dd,  $J$  = 5.0, 9.9 Hz), 3.58 (1H, dd,  $J$  = 6.8, 10.1 Hz), 3.39-3.32 (1.5 H, m), 3.30 (2.4 H, s), 3.28 (0.6H, s), 3.24-3.21 (1H, m), 2.35 (0.8H, m), 2.19 (0.2H, m), 2.04 (0.2H, ddd,  $J$  = 2.3, 4.7, 13.7 Hz), 1.69 (0.8H, ddd,  $J$  = 4.6, 9.1, 13.5 Hz);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  159.1, 130.3, 129.3, 113.6, 82.6, 81.8, 81.7, 80.9, 78.3, 77.2, 76.8, 72.9, 68.7, 68.3, 57.2, 57.1, 55.2, 37.8, 36.2, 11.0, 9.9; MS (ESI,  $m/z$ )  $[M+Na]^+$  415.1; HRMS (ESI)  $m/z$   $[M+Na]^+$  calcd for  $C_{15}H_{21}O_4Na$  415.0382, found 415.0392.



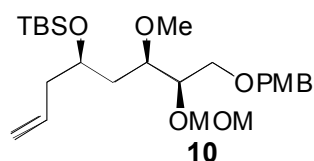
**MOM ether (8)** To a solution of the obtained methyl ether **7** (46.2 g, 118 mmol) in 95% ethanol (610 mL) was added zinc dust (59.4 g, 910 mmol). The reaction mixture was stirred at 80°C for 6 h and cooled down to 23°C. The solid was removed by filtration and rinsed with EtOAc. The filtrate was concentrated in vacuo and purified by column chromatography to provide the product (31 g, 99%) as a colorless oil.  $[\alpha]_D^{23}$  -8.04 (*c* 2.55, CHCl<sub>3</sub>); IR (thin film, cm<sup>-1</sup>) 3457, 2930, 1716, 1612, 1514, 1088, 824; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.25 (2H, d, *J* = 8.4 Hz), 6.88 (2H, d, *J* = 8.4 Hz), 5.82 (1H, m), 5.07 (2H, m), 4.48 (3H, s), 3.76 (3H, m), 3.54-3.46 (2H, m), 3.39 (3H, s), 3.31 (1H, m), 2.38 (1H, m), 2.28 (1H, m); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 159.3, 134.3, 130.1, 129.5, 117.5, 113.7, 80.5, 73.1, 71.4, 70.7, 58.2, 55.3, 34.3; MS (ESI, *m/z*) [M+Na]<sup>+</sup> 289.1.

To a stirred solution of the alcohol (31 g, 116 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (300 mL) was added diisopropylethylamine (69.7 mL 371 mmol) and MOMCl (23.6 mL, 309 mmol) successively and the resulting mixture was stirred over night and quenched with water. The organic layer was separated, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. Column chromatography provided the MOM ether **8** (32 g, 88%) as a colorless oil.  $[\alpha]_D^{23}$  -13.6 (*c* 2.95, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.25 (2H, d, *J* = 9.0 Hz), 6.87 (2H, d, *J* = 9.0 Hz), 5.83 (1H, m), 5.06 (2H, m), 4.78 (1H, d, *J* = 6.5 Hz), 4.69 (1H, d, *J* = 6.5 Hz), 4.78 (1H, A of AB, *J* = 11.5 Hz), 4.45 (1H, B of AB, *J* = 11.7 Hz), 3.80 (s, 3H), 3.77 (1H, m), 3.63 (1H, dd, *J* = 4.5, 9.5 Hz), 3.56 (1H, dd, *J* = 6.0, 10.0 Hz), 3.42 (1H, m), 3.40 (3H, s), 3.38 (3H, s), 2.35 (1H, m), 2.28 (1H, m); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 159.2, 135.3, 130.3, 129.3, 117.1, 113.8, 97.1, 80.5, 73.0, 65.5, 58.7, 55.7, 53.3, 34.5; MS (ESI, *m/z*) [M+Na]<sup>+</sup> 333.0.

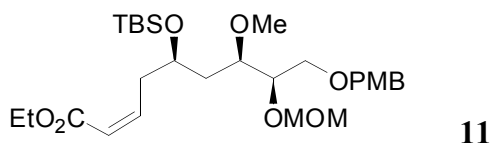


**Alcohol (9)** To the solution of thus obtained MOM ether **8** (7 g, 22.5 mmol) in acetone/H<sub>2</sub>O (106 mL / 13 mL) was added NMO (5.3 g, 45 mmol) and OsO<sub>4</sub> (2.5 w% in <sup>t</sup>BuOH, 8.3 mL, 0.69 mmol). The resulting mixture was stirred at 23°C for 3 h and quenched with saturated aqueous NaHSO<sub>3</sub> (42 mL). The solid was removed by filtration and the filtrate was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. To a solution of 1/3 of the crude diol (2.6 g, 7.49 mmol) in THF/H<sub>2</sub>O (58 mL/ 14 mL) was added NaIO<sub>4</sub> (3.85 g, 18 mmol) at 23°C and stirred for 2 h. The solid was removed by filtration and the filtrate was extracted with Et<sub>2</sub>O. The combined organic layer was washed with buffer solution (pH = 7), water and brine, and dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The aldehyde was used without further purification. To the solution of (+)-Ipc<sub>2</sub>BOMe (2.84 g, 9.0 mmol) in Et<sub>2</sub>O (32 mL) was added allylmagnesium bromide

(1M in Et<sub>2</sub>O, 8.2 mL) dropwise at 0°C. The resulting mixture was warmed up to 23°C over 1 h. The solid was removed by filtration. And to the filtrate was added thus obtained crude aldehyde in Et<sub>2</sub>O (15 mL) via cannul at -78°C over 5 min, and the mixture was stirred for 2 h at -78°C. Then the reaction was quenched with aqueous NaOH (2 M, 12 mL) and H<sub>2</sub>O<sub>2</sub> (30%, 5 mL) and slowly warmed up to 23°C over night. The resulting mixture was extracted with Et<sub>2</sub>O and the combined organic layer was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The crude material was passed through a short column to get the crude product. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.23 (2H, d, *J* = 8.5 Hz), 6.86 (2H, d, *J* = 8.5 Hz), 5.81 (1H, m), 5.09 (2H, m), 4.79 (1H, d, *J* = 6.8 Hz), 4.67 (1H, d, *J* = 6.8 Hz), 4.46 (1H, d, *J* = 11.6 Hz), 4.43 (1H, d, *J* = 11.6 Hz), 3.86 (2H, m), 3.78 (3H, s), 3.62 (2H, m), 3.51 (1H, dd, *J* = 6.6, 10.3 Hz), 3.44 (3H, s), 3.36 (3H, s), 3.28 (1H, br s), 2.21 (2H, m), 1.72 (1H, m), 1.49 (1H, dt, *J* = 14.5, 9.3 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 159.1, 134.7, 130.0, 129.2, 117.4, 113.7, 96.8, 81.3, 77.2, 73.0, 70.3, 69.3, 58.4, 55.6, 55.2, 42.1, 35.8;



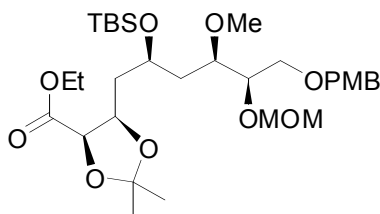
**TBS ether (10)** To a solution of the crude diastereomeric mixture (2.05 g, 5.78 mmol) in DMF (15 mL) was added imidazole (720 mg, 10.6 mmol), DMAP (70 mg, 0.6 mmol) and TBSCl (1.06 g, 7.03 mmol) at 23°C and then the mixture was stirred over night. To the resulting mixture was added water and EtOAc and the organic layer was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo. Column chromatography provided the pure diastereomeric isomer **10** (2.6 g, 74% over 4 steps, *dr* 94:6): [α]<sub>D</sub><sup>23</sup> -4.8 (*c* 2.69, CH<sub>2</sub>Cl<sub>2</sub>); IR (thin film, cm<sup>-1</sup>) 3075, 2953, 2930, 2895, 1856, 1612, 1513, 1249, 1099, 1039, 835; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.24 (2H, d, *J* = 8.6 Hz), 6.86 (2H, d, *J* = 8.6 Hz), 5.82 (1H, m), 5.06 (1H, d, *J* = 6.5 Hz), 5.03 (1H, s), 4.79 (1H, d, *J* = 6.8 Hz), 4.65 (1H, d, *J* = 6.8 Hz), 4.45 (2H, s), 3.81 (2H, m), 3.80 (3H, s), 3.62 (1H, dd, *J* = 4.9, 9.9 Hz), 3.56 (1H, dd, *J* = 6.2, 9.7 Hz), 3.47 (1H, m), 3.37 (3H, s), 3.36 (3H, s), 2.28 (1H, m), 2.23 (1H, m), 1.75 (1H, m), 1.64 (1H, m), 0.87 (9H, s), 0.05 (3H, s), 0.03 (3H, s); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 159.0, 134.9, 130.3, 129.2, 116.9, 113.6, 96.7, 77.5, 72.9, 69.8, 68.9, 58.0, 55.7, 55.2, 41.9, 36.7, 25.8, 17.9, -4.4, -4.6; MS (ESI, *m/z*) [M+Na]<sup>+</sup> 491.18; HRMS (ESI) [M+Na]<sup>+</sup> calcd for C<sub>25</sub>H<sub>44</sub>O<sub>6</sub>SiNa 491.2805, found 491.2806.



**Unsaturated ester (11)** To the solution of thus obtained silyl ether **10** (11 g, 23.5 mmol) in acetone/water (120 mL/ 15 mL) was added OsO<sub>4</sub> (2.5w% in *t*-BuOH, 2.87 mL, 0.24 mmol) and NMO (3.31 g, 28.5 mmol) at 23°C and the reaction mixture was stirred at that temperature for 5 h. The solid was removed and the filtrate was extracted with EtOAc. The combined organic layer was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. To the solution of the crude diol in THF/H<sub>2</sub>O (100

mL/ 25 mL) was added NaIO<sub>4</sub> (6.03 g, 28.2 mmol) and the reaction mixture was stirred at 23°C for 3 h. The solid was removed by filtration and the filtrate was extracted with EtOAc. The combined organic layer was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The crude aldehyde was used without further purification.

To the solution of (*O*-cresol)<sub>2</sub>P(O)CH<sub>2</sub>CO<sub>2</sub>Et (9.29 g, 29.4 mmol) in THF (210 mL) was added NaI (3.45 g, 23 mmol) and NaH (60% in mineral oil, 1.03 g, 25.8 mmol) at 0°C and it was stirred at 0°C for 10 min and cooled down to -78°C. To the resulting mixture was added the aldehyde in THF (50 mL) dropwise at -78°C. The reaction mixture was stirred at -78°C for 2 h and warmed up to -50°C and then quenched with aqueous NH<sub>4</sub>Cl and extracted with EtOAc. The combined organic layer was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. Column chromatography provided the *Z* isomer **11** (9.9 g, 78%) and *E* isomer (1.4 g, 11%). *Z* isomer:  $[\alpha]_D^{23}$  -9.5 (*c* 2.1, CH<sub>2</sub>Cl<sub>2</sub>); IR (thin film, cm<sup>-1</sup>) 2953, 2930, 2897, 2857, 1718, 1514, 1250, 1180, 1098, 1039; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.24 (2H, d, *J* = 8.5 Hz), 6.86 (2H, d, *J* = 8.5 Hz), 6.37 (1H, dt, *J* = 11.6, 7.0 Hz), 5.84 (1H, d, *J* = 11.6 Hz), 4.78 (1H, d, *J* = 6.8 Hz), 4.64 (1H, d, *J* = 6.8 Hz), 4.45 (2H, s), 4.14 (2H, q, *J* = 7.2 Hz), 3.96 (1H, m), 3.79 (3H, s), 3.61 (1H, dd, *J* = 4.7, 9.8 Hz), 3.55 (1H, dd, *J* = 6.3, 9.8 Hz), 3.46 (1H, m), 3.37 (3H, s), 3.36 (3H, s), 2.97 (1H, m), 2.82 (1H, m), 1.68 (2H, m), 1.27 (3H, t, *J* = 7.3 Hz), 0.86 (9H, s), 0.05 (3H, s), 0.04 (3H, s); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 166.2, 159.0, 146.2, 130.3, 129.1, 121.0, 113.6, 96.6, 77.4, 76.5, 72.9, 69.7, 68.4, 59.7, 58.2, 55.7, 55.2, 37.2, 36.1, 25.7, 17.9, 14.2, -4.5, -4.7; MS (ESI, *m/z*) [M+Na]<sup>+</sup> 563.19; HRMS (ESI) [M+Na]<sup>+</sup> calcd for C<sub>28</sub>H<sub>48</sub>O<sub>8</sub>SiNa 563.3016, found 563.3021.

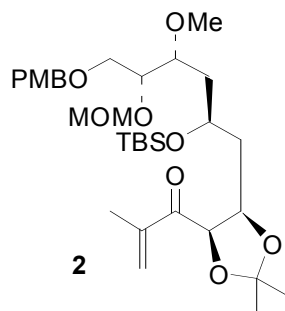


**12**

**Acetonide (12)** To the solution of the *Z* unsaturated olefin **11** (9.89 g, 18.3 mmol) in <sup>t</sup>BuOH/H<sub>2</sub>O (92 mL/ 92 mL) was added AD-mix-α (25.7 g) and CH<sub>3</sub>SO<sub>2</sub>NH<sub>2</sub> (1.74 g) at 0°C. The reaction mixture was stirred at that 0°C for 4 days and then quenched with NaHSO<sub>3</sub> and extracted with EtOAc. The combined organic layer was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The crude material was passed through a short silica gel column to provide the crude diastereomeric mixture (10.2 g, 97%), which could be separated in next step.

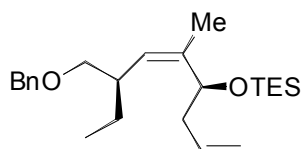
To the solution of crude diol in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was added PPTS (335 mg, 1.33 mmol) and 2-methoxypropene (4.4 mL, 46 mmol) at 23°C and the reaction mixture was stirred for 30 min. The reaction solvent was removed in vacuo and purification by column chromatography provided the major product **11** (8.71 g) and minor product (1.17 g, overall 95%). The major isomer:  $[\alpha]_D^{23}$  +20.0 (*c* 1.89, CH<sub>2</sub>Cl<sub>2</sub>); IR (thin film, cm<sup>-1</sup>) 2982, 2953, 2932, 2896, 2856, 1757, 1513, 1463, 1249, 1099, 1039, 837; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.23 (2H, d, *J* = 8.5 Hz), 6.86 (2H, d, *J* = 8.6 Hz), 4.76 (1H, d, *J* = 6.8 Hz), 4.64 (1H, d, *J* = 6.8 Hz), 4.53 (1H, s), 4.50 (1H, m), 4.44 (2H, s), 4.24-4.14 (2H, m), 4.06 (1H, m), 3.79 (3H, s), 3.76 (1H, m), 3.60 (1H, dd, *J* = 4.5,

10.0 Hz), 3.50 (1H, dd,  $J = 6.5, 9.9$  Hz), 3.43 (1H, m), 3.36 (3H, s), 3.35 (3H, s), 1.71-1.64 (3H, m), 1.58 (3H, s), 1.51 (1H, m), 1.35 (3H, s), 1.25 (3H, t,  $J = 7.2$  Hz), 0.88 (9H, s), 0.07 (3H, s), 0.05 (3H, s);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.4, 159.0, 130.2, 129.1, 113.6, 110.4, 96.5, 77.2, 76.9, 74.1, 72.9, 69.5, 66.4, 60.8, 58.5, 55.6, 55.2, 39.0, 37.6, 27.0, 25.8, 25.7, 17.9, 14.1, -4.3, -4.9; MS (ESI,  $m/z$ )  $[\text{M}+\text{Na}]^+$  637.21; HRMS (ESI)  $[\text{M}+\text{Na}]^+$  calcd for  $\text{C}_{31}\text{H}_{54}\text{O}_{10}\text{SiNa}$  637.3384, found 637.3392.



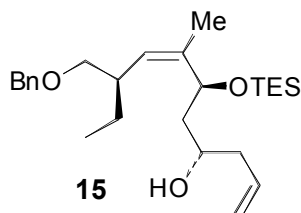
**Enone (2)** To the solution of thus obtained ester **12** (1.47 g, 2.39 mmol) in  $\text{CH}_2\text{Cl}_2$  (30 mL) was added DIBALH (1M in  $\text{CH}_2\text{Cl}_2$ , 2.5 mL, 2.5 mmol) dropwise at  $-78^\circ\text{C}$ . The resulting mixture was stirred at that temperature for 1 h and quenched with  $\text{NH}_4\text{Cl}$ . The solid was removed by filtration and the filtrate was extracted with EtOAc. The combined organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo. The crude material was passed through a short silica gel pad to provide the crude aldehyde, which was then dissolved in THF (50 mL). To the solution was added isopropenylmagnesium bromide (0.5 M in THF, 26.9 mL, 13.4 mmol) dropwise at  $0^\circ\text{C}$  and kept at  $0^\circ\text{C}$  for 15 min before quenched with aqueous  $\text{NH}_4\text{Cl}$ . The resulting mixture was extracted with EtOAc and the combined organic layer was washed with water and brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo. Column chromatography provided the diastereomeric mixture (1.21 g, 86%).

To the solution of the obtained alcohol mixture (7.02 g, 11.4 mmol) in  $\text{CH}_2\text{Cl}_2$  (40 mL) was added Dess-Martin periodinane (5.83 g, 13.7 mmol) and  $\text{NaHCO}_3$  (3.46 g, 41.2 mmol) at  $23^\circ\text{C}$ . The reaction mixture was stirred for 30 min and quenched with saturated aqueous  $\text{Na}_2\text{S}_2\text{O}_3$  (20 mL) and saturated aqueous  $\text{NaHCO}_3$  (30 mL). The aqueous layer was extracted with  $\text{Et}_2\text{O}$  and the combined organic layer was washed with water and brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo. Column chromatography provided the enone **2** (6.28 g, 90%).  $[\alpha]_D^{23} +29.3$  ( $c$  2.4,  $\text{CH}_2\text{Cl}_2$ ); IR (thin film,  $\text{cm}^{-1}$ ) 2953, 2931, 2894, 2856, 1693, 1513, 1378, 1249, 1100, 1073, 835;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.22 (2H, d,  $J = 8.5$  Hz), 6.85 (2H, d,  $J = 8.6$  Hz), 5.88 (1H, s), 5.84 (1H, d,  $J = 1.1$  Hz), 5.29 (1H, d,  $J = 7.1$  Hz), 4.74 (1H, d,  $J = 6.8$  Hz), 4.62 (1H, d,  $J = 6.8$  Hz), 4.58 (1H, m), 4.43 (2H, s), 4.01 (1H, m), 3.78 (3H, s), 3.73 (1H, dt,  $J = 6.7, 4.1$  Hz), 3.58 (1H, dd,  $J = 4.2, 9.9$  Hz), 3.48 (1H, dd,  $J = 6.6, 9.9$  Hz), 3.37 (1H, m), 3.34 (3H, s), 3.32 (3H, s), 1.87 (3H, s), 1.60 (1H, m), 1.58 (3H, s), 1.40 (1H, m), 1.37 (3H, s), 0.87 (9H, s), -0.07 (3H, s), -0.04 (3H, s);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  197.0, 159.0, 144.0, 130.2, 129.1, 125.3, 113.6, 109.6, 96.6, 78.6, 77.2, 76.9, 74.5, 72.9, 69.5, 66.3, 58.5, 55.6, 55.1, 39.0, 38.1, 27.3, 25.8, 25.5, 17.9, 17.8, -4.3, -4.9; MS (ESI,  $m/z$ )  $[\text{M}+\text{Na}]^+$  633.16; HRMS (ESI)  $[\text{M}+\text{Na}]^+$  calcd for  $\text{C}_{32}\text{H}_{54}\text{O}_9\text{SiNa}$  633.3435, found 633.3433.



**14**

**TES ether (14)** To the solution of the alcohol **5** (390 mg, 1.41 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was added 2,6-lutidine (0.63 mL, 5.36 mmol) and TESOTf (0.80 mL, 3.55 mmol). The resulting mixture was stirred for 5 min and water and EtOAc was added. The organic layer was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The crude material was passed through a silica gel pad to provide the crude silyl ether (495 mg, 90%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.34 (4H, m), 7.28 (1H, m), 5.81 (1H, m), 5.13-5.07 (2H, m), 4.92 (1H, d, *J* = 10.2 Hz), 4.54 (1H, dd, *J* = 5.0, 8.1 Hz), 4.51 (2H, s), 3.32 (3H, m), 2.57 (1H, m), 2.37 (1H, m), 2.16 (1H, m), 1.71 (3H, d, *J* = 1.0 Hz), 1.66 (1H, m), 1.23 (2H, m), 0.94 (9H, t, *J* = 7.8 Hz), 0.85 (3H, t, *J* = 7.5 Hz), 0.56 (6H, q, *J* = 7.8 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 139.2, 138.6, 135.8, 128.2, 127.5, 127.4, 126.7, 116.3, 73.5, 73.0, 70.6, 41.5, 39.1, 25.3, 17.9, 11.6, 6.8, 4.7;

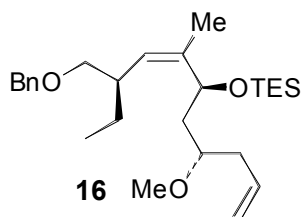


**15**

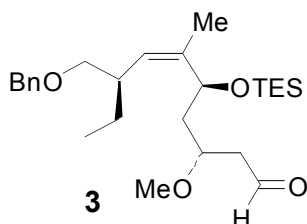
**Alcohol (15)** The TES ether was dissolved in *t*-BuOH/Acetone/H<sub>2</sub>O (4 mL/4 mL/1 mL). To the solution was added NMO (0.41 g, 3.53 mmol) and OsO<sub>4</sub> (2.5 w% in *t*-BuOH, 0.88 mL, 0.074 mmol) at 0°C and it was stirred at this temperature for 2 h before quenched with aqueous NaHSO<sub>3</sub>. The resulting mixture was extracted with EtOAc and the organic layer was washed with brine, concentrated in vacuo and dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL). To the solution was added pyridine (0.3 mL, 3.7 mmol) and Pb(OAc)<sub>4</sub> (0.66 g, 1.49 mmol) at 23°C and stirred for 30 min. The solid was removed by filtration and the filtrate was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The crude material was passed through a silica gel pad to give crude aldehyde (374 mg, 74%, 2 steps).

To the solution of (-)-Ipc<sub>2</sub>BOMe (788 mg, 2.49 mmol) in Et<sub>2</sub>O (12 mL) was added allylmagnesium bromide (1 M in Et<sub>2</sub>O, 2.22 mL, 2.22 mmol) dropwise at 0°C. The resulting mixture was warmed up to 23°C over 2 h. The solid was removed by filtration and the filtrate was cooled down to -78°C. To the filtrate was added thus obtained crude aldehyde in Et<sub>2</sub>O (5 mL) via cannul at -78°C over 5 min, and the mixture was stirred for 2 h at -78°C and then quenched with buffer (pH = 7) and H<sub>2</sub>O<sub>2</sub> (30%, 5 mL). The resulting mixture was slowly warmed up to 23°C over night and extracted with Et<sub>2</sub>O. The combined organic layer was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. Column chromatography provided major isomer (374 mg, 83%, *dr* 5:1).

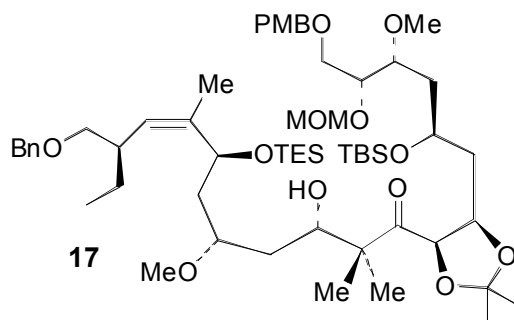




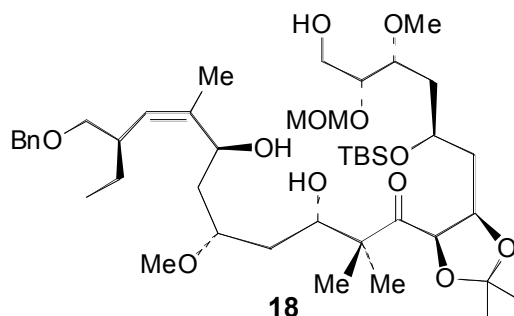
**Methyl ether (16)** To the solution of the thus made homoallylic alcohol (165 mg, 0.38 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 mL) was added proton sponge (333 mg, 1.56 mmol) and  $\text{Me}_3\text{OBF}_4$  (173 mg, 1.17 mmol) at  $23^\circ\text{C}$ . The reaction mixture was stirred for 3 h and the solid was removed by filtration. The filter cake was washed with hexane and the filtrate was washed with  $\text{NaHCO}_3$ , water and brine. The organic phase was dried over  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo. Column chromatography provided methyl ether **13** (153 mg, 93%):  $[\alpha]_D^{23}$  -35.3 (*c* 1.21,  $\text{CH}_2\text{Cl}_2$ ); IR (thin film,  $\text{cm}^{-1}$ ) 3075, 3066, 3029, 2955, 2936, 2876, 2825, 1454, 1239, 1089, 1005, 741;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34 (4H, m), 7.27 (1H, m), 5.86 (1H, m), 5.13-5.07 (2H, m), 4.94 (1H, d,  $J = 10.1$  Hz), 4.60 (1H, dd,  $J = 4.6, 8.8$  Hz), 4.50 (2H, s), 3.33 (3H, m), 3.32 (3H, s), 2.56 (1H, m), 2.38 (1H, m), 2.23 (1H, m), 1.94 (1H, ddd,  $J = 4.9, 8.9, 13.8$  Hz), 1.69 (3H, d,  $J = 1.0$  Hz), 1.62 (1H, m), 1.44 (1H, ddd,  $J = 4.5, 7.5, 12.2$  Hz), 1.24 (1H, m), 0.92 (9H, t,  $J = 8.0$  Hz), 0.84 (3H, t,  $J = 7.4$  Hz), 0.56 (6H, q,  $J = 7.9$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  138.9, 138.6, 134.7, 128.2, 127.5, 127.4, 127.2, 116.9, 77.4, 73.3, 73.0, 67.5, 55.9, 40.1, 39.0, 37.4, 25.3, 17.8, 11.4, 6.9, 4.8; MS (ESI, *m/z*)  $[\text{M}+\text{Na}]^+$  469.21; HRMS (ESI)  $[\text{M}+\text{Na}]^+$  calcd for  $\text{C}_{27}\text{H}_{46}\text{O}_3\text{SiNa}$  469.3114, found 469.3123.



**Aldehyde (3)** To the solution of the methyl ether **16** (133 mg, 0.30 mmol) in  $t\text{BuOH}/\text{Acetone}/\text{H}_2\text{O}$  (1.0 mL/1.0 mL/0.25 mL) was added NMO (0.07 g, 0.60 mmol) and  $\text{OsO}_4$  (2.5w% in  $t\text{BuOH}$ , 0.15 mL, 0.013 mmol) at  $0^\circ\text{C}$  and it was stirred at this temperature for 2 h before quenched with aqueous  $\text{NaHSO}_3$ . The resulting mixture was extracted with EtOAc and the organic layer was washed with brine, concentrated in vacuo and dissolved in  $\text{CH}_2\text{Cl}_2$  (3 mL). To the solution was added pyridine (0.068 mL, 0.75 mmol) and  $\text{Pb}(\text{OAc})_4$  (145 mg, 0.052 mmol) at  $23^\circ\text{C}$  and stirred for 30 min. The solid was removed by filtration and the filtrate was extracted with EtOAc. The organic layer was washed with water and brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo. The crude material was purified by column chromatography to give the aldehyde **3** (100 mg, 75%, 2 steps):  $[\alpha]_D^{23}$  -40.1 (*c* 1.16,  $\text{CH}_2\text{Cl}_2$ ); IR (thin film,  $\text{cm}^{-1}$ ) 3029, 2956, 2935, 2876, 1727, 1455, 1085, 1005, 742;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.80 (1H, t,  $J = 1.9$  Hz), 7.36-7.25 (5H, m), 4.94 (1H, d,  $J = 10.3$  Hz), 4.58 (1H, dd,  $J = 3.6, 9.1$  Hz), 4.49 (2H, s), 3.82 (1H, m), 3.34 (3H, s), 3.32 (2H, m), 2.64 (1H, ddd,  $J = 1.6, 4.1, 16.3$  Hz), 2.57 (1H, ddd,  $J = 2.7, 7.6, 16.5$  Hz), 2.51 (1H, m), 2.08 (1H, m), 1.71 (3H, s), 1.64 (1H, m), 1.45 (1H, ddd,  $J = 3.6, 8.2, 13.7$  Hz), 1.21 (1H, dt,  $J = 13.6, 7.7$  Hz), 0.92 (9H, t,  $J = 8.0$  Hz), 0.82 (3H, t,  $J = 7.7$  Hz), 0.56 (6H, q,  $J = 7.7$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  201.4, 138.6, 138.5, 128.2, 127.5, 127.4, 73.7, 73.3, 73.0, 67.1, 56.2, 47.7, 40.1, 39.3, 25.3, 17.9, 11.6, 6.8, 4.7.

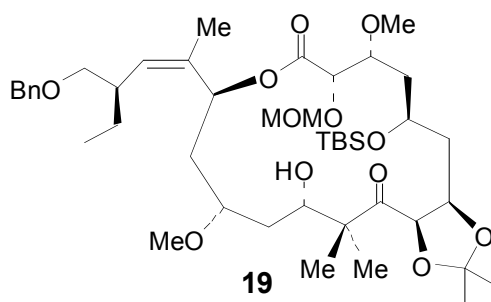


**Aldol product (17)** To the solution of the enone **2** (645 mg, 1.06 mmol) in Et<sub>2</sub>O (200 mL) was added L-Selectride (lithium tri-*sec*-butylborohydride, 1.0 M in THF, 1.1 mL, 1.1 mmol) at -78°C and the reaction was kept at that temperature for 10-15 min. To the solution was added thus obtained aldehyde **3** (520 mg, 1.2 mmol) in Et<sub>2</sub>O (20 mL) at -78°C. The reaction mixture was stirred at -78°C for 1 h and quenched with NH<sub>4</sub>Cl. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. Column chromatography provided the major isomer **17** and minor isomer (823 mg and 206 mg respectively, 92%, *dr* 4:1). Major isomer:  $[\alpha]_D^{23}$  -13.9 (*c* 1.15, CH<sub>2</sub>Cl<sub>2</sub>); IR (thin film, cm<sup>-1</sup>) 2956, 2936, 2879, 2859, 1714, 1514, 1463, 1379, 1249, 1098, 1078, 1038, 836; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.30-7.25 (5H, m), 7.22 (2H, d, *J* = 8.5 Hz), 6.84 (2H, d, *J* = 8.5 Hz), 5.12 (1H, d, *J* = 6.7 Hz), 4.92 (1H, d, *J* = 10.1 Hz), 4.75 (1H, d, *J* = 6.7 Hz), 4.63 (1H, d, *J* = 6.8 Hz), 4.54 (2H, m), 4.46 (2H, s), 4.43 (2H, s), 4.01 (2H, m), 3.75 (3H, s), 3.59 (2H, dd, *J* = 4.3, 10.0 Hz), 3.48 (1H, dd, *J* = 6.7, 9.9 Hz), 3.39 (1H, m), 3.35 (6H, s), 3.30 (2H, m), 3.29 (3H, s), 2.51 (1H, m), 2.05 (1H, m), 1.69 (3H, s), 1.64-1.61 (4H, m), 1.57-1.42 (2H, m), 1.50 (3H, s), 1.33 (3H, s), 1.23 (2H, m), 1.18 (3H, s), 1.10 (3H, s), 0.94 (1H, m), 0.89 (9H, t, *J* = 8.0 Hz), 0.87 (12H, s), 0.83 (3H, t, *J* = 7.5 Hz), 0.54 (6H, q, *J* = 8.0 Hz), 0.08 (3H, s), 0.05 (3H, s); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 210.2, 159.0, 138.9, 138.5, 130.2, 129.1, 128.2, 127.4, 127.3, 127.2, 113.6, 109.1, 96.6, 79.2, 77.3, 76.9, 76.5, 74.3, 73.2, 73.0, 72.9, 72.8, 69.5, 67.3, 66.4, 58.5, 56.2, 55.6, 55.0, 51.3, 39.14, 39.05, 33.3, 27.6, 25.8, 25.3, 20.8, 18.8, 17.94, 17.87, 11.6, 6.8, 4.7, -4.3, -4.9; MS (ESI, *m/z*) [M+Na]<sup>+</sup> 1083.32; HRMS (ESI) [M+Na]<sup>+</sup> calcd for C<sub>58</sub>H<sub>100</sub>O<sub>13</sub>Si<sub>2</sub>Na 1083.6600, found 1083.6611.



**Alcohol (18)** To the solution of the major aldol product **17** (30 mg, 0.028 mmol) in THF/H<sub>2</sub>O (9:1, 1.8 mL) was added DDQ (2 mg, 0.01 mmol). The reaction mixture was stirred for 3 h at 23°C and CH<sub>2</sub>Cl<sub>2</sub> (7 mL), buffer (pH=7, 1.2 mL) and DDQ (30 mg, 0.13 mmol) was added. The resulting mixture was stirred for 8 h at 23°C and aqueous NaHCO<sub>3</sub> was added. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic phase was washed with dilute aqueous NaHCO<sub>3</sub>, water and brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. Column

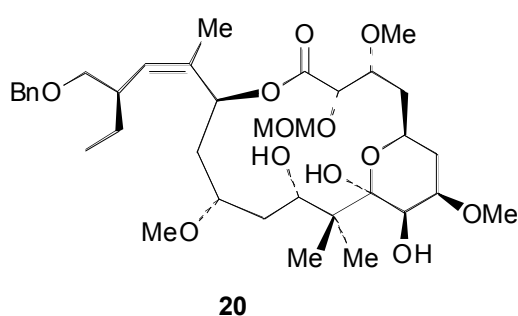
chromatography gave the alcohol **18** (16 mg, 70%):  $[\alpha]_D^{23} +17.9$  (*c* 1.3, CHCl<sub>3</sub>); IR (thin film, cm<sup>-1</sup>) 3443, 2956, 2928, 2855, 1713, 1462, 1378, 1252, 1097, 1074, 836; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.34-7.24 (5H, m), 5.10 (1H, d, *J* = 6.6 Hz), 4.95 (1H, d, *J* = 9.5 Hz), 4.71 (1H, d, *J* = 6.9 Hz), 4.65 (1H, d, *J* = 6.9 Hz), 4.59 (1H, dd, *J* = 4.8, 8.5 Hz), 4.52 (1H, m), 4.47 (2H, m), 4.02-3.95 (2H, m), 3.69 (1H, m), 3.63-3.53 (3H, m), 3.42-3.36 (2H, m), 3.40 (3H, s), 3.35 (3H, s), 3.32 (3H, s), 3.12 (1H, t, *J* = 9.1 Hz), 2.65 (1H, m), 2.02 (1H, m), 1.72 (3H, s), 1.69-1.55 (6H, m), 1.50 (3H, s), 1.20 (2H, m), 1.18 (3H, s), 1.13 (1H, m), 1.09 (3H, s), 0.87 (9H, s), 0.82 (3H, t, *J* = 7.4 Hz), 0.07 (3H, s), 0.05 (3H, s); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  210.6, 139.3, 137.6, 130.9, 128.4, 127.7, 109.2, 97.3, 81.1, 79.1, 78.1, 77.9, 74.3, 73.7, 73.4, 73.2, 66.3, 65.7, 62.4, 58.2, 56.9, 55.7, 51.4, 39.3, 38.9, 38.6, 36.5, 33.5, 29.6, 27.6, 25.8, 24.7, 20.8, 18.9, 18.1, 17.9, 11.8, -4.3, -4.9; MS (ESI, *m/z*) [M+Na]<sup>+</sup> 849.2; HRMS (ESI) [M+Na]<sup>+</sup> calcd for C<sub>44</sub>H<sub>78</sub>O<sub>12</sub>SiNa 849.5160, found 849.5154.



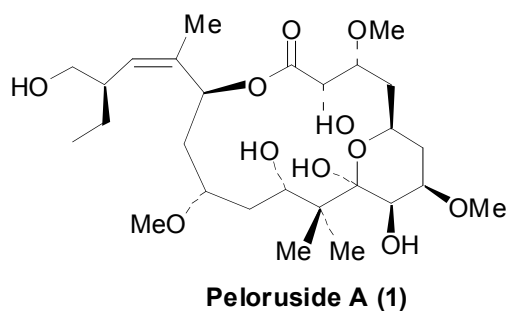
**Macrolactone (19)** To the solution of the alcohol **18** (17.3 mg, 0.021 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.9 mL) was added 4Å molecular sieve, NMO (2.2 mg, 0.021 mmol) and TPAP (1.2 mg, 0.004 mmol) at 0°C. The resulting mixture was stirred at 0°C for 1 h. The solid was removed by filtration and EtOAc was added to the filtrate. The organic phase was washed with aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, water and brine, concentrated in vacuo and dissolved in *t*-BuOH (3.3 mL). To the solution was added 2-methyl-2-butene (0.4 mL) and a solution of NaClO<sub>2</sub> (32 mg, 0.35 mmol) and NaH<sub>2</sub>PO<sub>4</sub> (35 mg, 0.29 mmol) in H<sub>2</sub>O (3.3 mL). The resulting mixture was stirred at 23°C for 25 min. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic phase was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The crude product was passed through a short silica gel column to obtain the crude seco-acid 9 mg.

To the solution of thus obtained seco-acid in toluene (2.4 mL) was added DIPEA (0.05 mL, 0.29 mmol) and 2,4,6-trichlorobenzoyl chloride (18.8  $\mu$ L, 0.12 mmol) at 23°C. The reaction was stirred for 15 h at that temperature and was added dropwise to a solution of DMAP (22.4 mg, 0.18 mmol) in toluene (25 mL) at 23°C over 10 h. The resulting mixture was stirred at 23°C for 36 h and water was added. The organic layer was separated and the aqueous was extracted with EtOAc. The combined organic phase was wash with 0.18% HCl, water and brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. Column chromatography provided product **19** (5.7 mg, 64%):  $[\alpha]_D^{23} -45.7$  (*c* 0.88, CHCl<sub>3</sub>); IR (thin film, cm<sup>-1</sup>) 2956, 2929, 2856, 1730, 1463, 1379, 1256, 1095, 1076, 1027, 971, 837; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.35-7.22 (5H, m), 5.78 (1H, d, *J* = 8.0 Hz), 5.06 (1H, d, *J* = 10.2 Hz), 4.90 (1H, d, *J* = 6.9 Hz), 4.70 (1H,

d,  $J = 6.7$  Hz), 4.68 (1H, d,  $J = 6.7$  Hz), 4.63 (1H, m), 4.53 (1H, d,  $J = 12.1$  Hz), 4.47 (1H, d,  $J = 12.1$  Hz), 4.08 (1H, m), 3.98 (1H, d,  $J = 5.1$  Hz), 3.81 (1H, m), 3.59 (1H, dd,  $J = 4.1, 9.3$  Hz), 3.49 (1H, m), 3.40 (3H, s), 3.37 (3H, s), 3.34 (6H, s), 3.20 (1H, m), 2.75 (1H, m), 2.05 (1H, ddd,  $J = 15.2, 5.5, 1.1$  Hz), 1.97 (1H, ddd,  $J = 15.2, 9.1, 1.3$  Hz), 1.88 (1H, ddd,  $J = 14.5, 6.3, 4.3$  Hz), 1.72 (2H, m), 1.66 (3H, s), 1.63 (1H, m), 1.59 (3H, s), 1.53 (1H, m), 1.42 (3H, s), 1.37 (3H, s), 1.32 (1H, m), 1.22 (1H, m), 1.18 (3H, s), 0.88 (9H, s), 0.84 (3H, t,  $J = 7.5$  Hz), 0.09 (3H, s), 0.08 (3H, s);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  216.1, 168.8, 138.9, 134.0, 129.8, 128.1, 127.5, 127.2, 110.2, 96.4, 79.4, 77.4, 76.7, 75.4, 74.0, 72.7, 70.6, 66.0, 58.4, 57.4, 56.2, 50.4, 39.5, 39.3, 38.5, 37.9, 35.7, 29.6, 26.7, 25.8, 25.5, 25.2, 24.9, 21.0, 17.9, 11.6, -4.2, -5.0; MS (ESI,  $m/z$ )  $[\text{M}+\text{Na}]^+$  845.24; HRMS (ESI)  $[\text{M}+\text{Na}]^+$  calcd for  $\text{C}_{44}\text{H}_{74}\text{O}_{12}\text{SiNa}$  845.4847, found 845.4840.



**Methyl ether (20)** The macrolactone **19** (13 mg, 0.016 mmol) was dissolved in a mixture of THF (3.6 mL) and 1N HCl (3.6 mL). The resulting mixture was stirred at 23°C for 9 h. The aqueous layer was extracted with EtOAc and the combined organic phase was washed with aqueous  $\text{NaHCO}_3$ , water and brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo. The crude material was passed through a silica gel pad to give the crude product which was then dissolved in  $\text{CH}_2\text{Cl}_2$ . To the solution was added 2,6-di-tert-butylpyridine (60  $\mu\text{L}$ ),  $\text{Me}_3\text{OBF}_4$  (24 mg) at 0°C. The reaction was stirred for 4 h and quenched with aqueous  $\text{NaHCO}_3$ . The organic phase was separated and the aqueous layer was extracted with EtOAc. Combined organic phase was washed with water and brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo. A simple silica gel column gave 8 mg crude product, which may contains both the macrolactone form and the semi-ketal form. The NMR spectra seem complicated. MS (ESI,  $m/z$ )  $[\text{M}+\text{Na}]^+$  705.29;



To the solution of the methyl ether (4 mg) in methanol (2 mL) was added formic acid (0.1 mL) and 10% Pd/C (a spatula) at 23°C and the resulting mixture was stirred for 1 h. Celite was added and the solid was removed by filtration. The filtrate

was concentrated in vacuo and was dissolved in THF/4N HCl (1.5 mL/ 1.5 mL) and was stirred for 3.5 h at 23°C. The reaction mixture was extracted with EtOAc and the combined organic layer was washed with NaHCO<sub>3</sub>, water and brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. Column chromatography provided the (+)-Peloruside A (**1**) (1.6 mg, 50%, 2 steps) [ $\alpha$ ]<sub>D</sub><sup>23</sup> +15.1 (*c* 0.1, CH<sub>2</sub>Cl<sub>2</sub>); IR (thin film, cm<sup>-1</sup>) 2957, 2923, 2852, 1742, 1463, 1378, 1151, 1086, 1037, 722; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  6.79 (1H, br s), 5.69 (1H, d, *J* = 10.6 Hz), 5.05 (1H, d, *J* = 10.5 Hz), 4.91 (1H, m), 4.54 (1H, br d, *J* = 8.2 Hz), 4.47 (1H, s), 4.28 (1H, ddd, *J* = 11.3, 4.4, 2.5 Hz), 4.23 (1H, dd, *J* = 10.6, 5.4 Hz), 4.02 (1H, d, *J* = 2.8 Hz), 3.99 (1H, m), 3.82 (1H, ddd, *J* = 11.5, 5.0, 3.0 Hz), 3.65 (1H, br d, *J* = 10.5), 3.48 (3H, s), 3.39 (3H, s), 3.36 (1H, m), 3.31 (3H, s), 3.01 (1H, br s), 2.70 (1H, d, *J* = 9.3 Hz), 2.62 (1H, m), 2.27 (1H, br s), 2.14 (1H, m), 2.05 (1H, m), 1.79 (1H, ddd, *J* = 12.5, 4.9, 2.5 Hz), 1.78 (1H, m), 1.68 (3H, d, *J* = 1.1 Hz), 1.53 (1H, q, *J* = 12.0 Hz), 1.46-1.40 (2H, m), 1.17 (1H, m), 1.13 (3H, s), 1.10 (3H, s), 0.87 (3H, t, *J* = 7.5 Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  174.0, 136.1, 131.2, 102.0, 78.3, 78.0, 76.0, 73.9, 70.9, 70.3, 67.0, 66.9, 63.5, 59.1, 56.1, 55.7, 43.6, 43.4, 35.8, 33.9, 32.6, 31.7, 24.7, 20.9, 17.5, 15.8, 12.3; MS (ESI, *m/z*) [M+Na]<sup>+</sup> 571.17; HRMS (ESI) [M+Na]<sup>+</sup> calcd for C<sub>27</sub>H<sub>48</sub>O<sub>11</sub>Na 571.3094, found 571.3102.