Synthesis of the Macrocyclic Core of Iriomoteolide-1a

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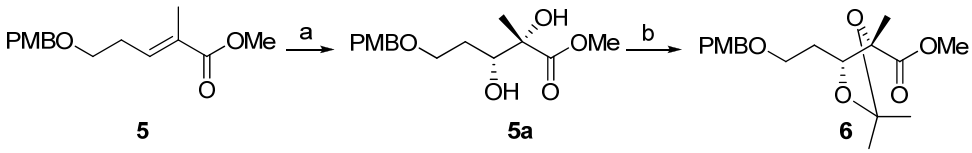
General experimental

All non-aqueous reactions were run under an inert atmosphere (nitrogen or argon) with rigid exclusion of moisture from reagents, and all reaction vessels were oven-dried. Solvents were distilled prior to use: THF and toluene from Na/benzophenone, dichloromethane, DMF, triethylamine, diisoproylethylamine and 2,6-lutidine from CaH_2. NMR spectra were recorded on Bruker Avance AV500 MHz spectrometer. Chemical shifts are reported in parts per million (ppm), relative to either a tetramethylsilane internal standard or the signals due to the solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad), coupling constants, and integration. Low- and high- resolution ESI mass spectra were obtained using a Q-star Elite mass spectrometer. Optical rotations were recorded on a Perkin Elmer 343 Polarimeter. TLC was carried out using pre-coated sheets (Qingdao silica gel 60-F_{250}, 0.2mm) which, after development, were visualized at 254nm, and/or staining in p-anisole, ninhydrin or phosphomolybdic acid solution followed by heating. Flash column chromatography was performed using the indicated solvents (with R_f = 1.5-3.0 for the desired component) on silica gel 60 (Qingdao, 230-400 mesh ASTM).

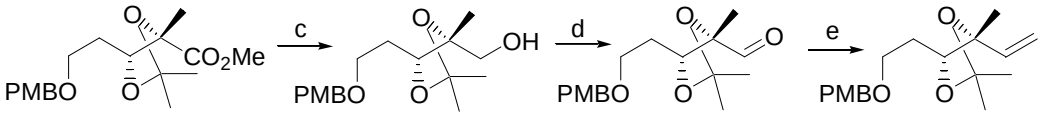
Experimental procedures



A 500-mL round bottom (RB) flask was charged with $K_3Fe(CN)_6$ (14.80 g, 45.0 mmol), K_2CO_3 (6.21 g, 45.0 mmol), $MeSO_2NH_2$ (1.42 g, 15 mmol), *tert*-BuOH (75 mL), and H_2O (75 mL). The reaction mixture was stirred for 10 min, after $(DHQ)_2$-PHAL (233.7 mg, 0.3 mmol) and K_2OsO_4 (99.6 mg, 0.3 mmol) were added, stir was continued for an additional 30 min prior to the addition of ester **5** (5.28 g, 20.0 mmol). The reaction mixture was allowed to stir for 3 days at 0 °C. Sodium bisulfite (5 g) was slowly added at 0 °C to quench the reaction. Volatiles were removed under reduced pressure, and the aqueous residue was extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (200 mL), dried over sodium sulfate, and concentrated under reduced pressure to give a crude oil. Flash column chromatographic purification on a silica gel column, eluting with 40% ethyl acetate-hexane, afforded **5a** (5.84 g, 98%) as colorless oil. $[\alpha]_D^{25}$ = +13.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500MHz, $CDCl_3$): δ_H 7.24 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.44 (s, 2H), 4.00-3.96 (m, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.76-3.71 (m, 1H), 3.66-3.63 (m, 1H), 3.49 (brs, 1H), 3.28 (d, *J* = 4.9 Hz, 1H), 1.85-1.81 (m, 2H), 1.31 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 176.3, 159.3, 129.9, 129.2, 113.8, 77.1, 74.9, 72.9, 68.2, 55.2, 52.7, 29.7, 21.4 ppm. HRMS (ESI) for $C_{15}H_{22}NaO_6$ $[M+Na]^+$: calculated 321.1314, found 321.1312.

To a stirred solution of **5a** (3.60 g, 12.0 mmol) in 2,2-dimethoxy propane (20 mL) and benzene (100 mL) was added *p*-TsOH·H_2O (114.30 mg, 0.6 mmol) at room temperature. The reaction mixture was allowed to reflux for 16 h. After the starting material was consumed, the reaction was quenched with saturated aqueous solution of $NaHCO_3$ (80 mL) and extracted with CH_2Cl_2 (200 mL x 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by flash chromatography on silica gel column, eluting with 2% ethyl acetate-hexane, to give product **6** as colorless oil (3.98 g, 99%). $[\alpha]_D^{25}$ = +6.5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500MHz, $CDCl_3$): δ_H 7.26 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 4.45 (dd, *J* = 17.2, 11.6 Hz, 2H), 4.35 (dd, *J* = 9.7, 3.4 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H),

3.64-3.56 (m, 2H), 2.01-1.94 (m, 1H), 1.91-1.84 (m, 1H), 1.47 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 173.5, 159.2, 130.6, 129.2, 113.8, 109.0, 82.5, 77.2, 72.6, 67.1, 55.3, 52.4, 30.1, 28.3, 25.6, 19.9 ppm. HRMS (ESI) for $C_{18}H_{26}NaO_6$ $[M+Na]^+$: calculated 361.1627, found 361.1623.

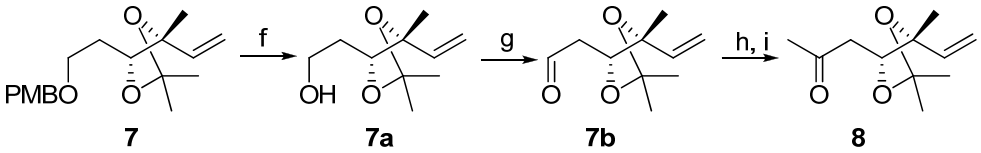


To a solution of the ester **6** (3.40 g, 10.0 mmol) in THF (100 mL) was added DIBAL-H (30.0 mL, 30.0 mmol, 1.0 M in hexane) at -78 ^{o}C, then the resultant mixture was slowly warmed to room temperature within 1 h. The reaction was carefully quenched with MeOH (10 mL) followed by addition of saturated aqueous Rochelle's salt (80 mL). The reaction mixture was vigorously stirred until it became clear. Volatiles were removed under reduced pressure; the aqueous phase was extracted with diethyl ether (100 mL x 3). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and concentrated in *vacuo* to produce **6a**, which was used in next step without further purification.

To a solution of the above crude alcohol **6a** and $NaHCO_3$ (1.68 g, 20.0 mmol) in dry CH_2Cl_2 (100 mL) was added Dess-Martin Periodinane (17.00 g, 40.0 mmol) at 0 ^{o}C. The reaction was monitored by TLC. Upon the consumption of the starting material, the reaction was quenched with saturated aqueous solution of ammonium chloride (100 mL). Layers were separated and the aqueous phase was extracted with diethyl ether (200 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated in *vacuo* to give aldehyde **6b,** which was used in next step without further purification.

To a stirred solution of CH_3PPh_3I (16.16 g, 40.0 mmol) in THF (150 mL) was added *n*-BuLi (13.6 mL, 30.0 mmol, 2.2 M in hexanes) at -78 ^{o}C. 1 h later, a solution of aldehyde **6b** in THF (30 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. Water (15 mL) was then added to quench the reaction. Volatiles were removed under reduced pressure and the aqueous layer was extracted with diethyl ether (200 mL x 3). The combined organic extracts were washed with brine (150 mL), dried over Na_2SO_4, and concentrated in *vacuo*. The crude product was purified by flash chromatography on a silica gel

column eluting with 5% ethyl acetate-hexane to give **7** as colorless oil (2.48 g, 81% over 3 steps). $[\alpha]_D^{25}$ = +2.5 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500MHz, $CDCl_3$): δ_H 7.25 (d, *J* = 7.8 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.84 (dd, *J* = 17.5, 10.5 Hz, 1H), 5.31 (dd, *J* = 17.5, 1.1 Hz, 1H), 5.12 (dd, *J* = 10.5, 1.2 Hz, 1H), 4.45 (dd, *J* = 15.0, 7.0 Hz, 2H), 3.92 (dd, *J* = 9.5, 6.0 Hz, 1H), 3.81 (s, 3H), 3.61-3.57 (m, 1H), 3.56-3.52 (m, 1H), 1.86-1.80 (m, 1H), 1.79-1.72 (m, 1H), 1.46 (s, 3H), 1.37 (s, 3H), 1.19 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 159.3, 141.2, 130.6, 129.2, 114.4, 113.9, 107.5, 82.2, 79.4, 72.7, 67.4, 55.3, 29.5, 28.5, 26.6, 20.3 ppm. HRMS (ESI) for $C_{18}H_{26}NaO_4$ $[M+Na]^+$: calculated 329.1729, found 329.1721.

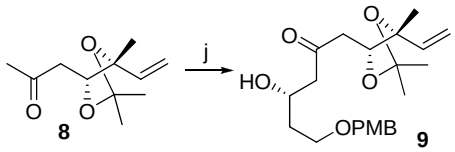


DDQ (7.42 g, 32.7 mmol) was added to a solution of **7** (4.00 g, 13.1 mmol) in CH_2Cl_2-H_2O (130 mL, v/v 10:1) at 0 ^oC. The mixture was vigorously stirred for 2 h, and then quenched with saturated aqueous sodium bicarbonate (200 mL). Layers were separated and the aqueous phase was extracted with CH_2Cl_2 (200 mL x 3). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated. Purification of the residue by chromatography on silica gel column, eluting with 10% ethyl acetate-hexane, gave the primary alcohol **7a** as a colorless oil (2.07 g, 85%). $[\alpha]_D^{25}$ = -3.1 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500MHz, $CDCl_3$): δ_H 5.85 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.32 (d, *J* = 17.6, 0.8 Hz, 1H), 5.14 (dd, *J* = 10.8, 0.8 Hz, 1H), 3.91 (dd, *J* = 9.8, 2.7 Hz, 1H), 3.81-3.78 (m, 2H), 2.12 (brs, 1H), 1.85-1.78 (m, 1H), 1.69-1.60 (m, 1H), 1.47 (s, 3H), 1.38 (s, 3H), 1.20 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 140.9, 114.7, 108.0, 82.4, 81.4, 61.3, 31.4, 28.5, 26.7, 20.4 ppm. HRMS (ESI) for $C_{10}H_{18}NaO_3$ $[M+Na]^+$: calculated 209.1154, found 209.1151.

To a solution of alcohol **7a** (1.86 g, 10.0 mmol) and $NaHCO_3$ (1.68 g, 20.0 mmol) in dry CH_2Cl_2 (100 mL) was added Dess-Martin Periodinane (17.00 g, 40.0 mmol) at 0 ^oC. When all the starting material was consumed, the reaction was quenched with saturated ammonium chloride (100 mL). The organic layer was separated and the aqueous phase was extracted with diethyl ether (100 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated to give aldehyde **7b,** which was pure enough for use in the next step.

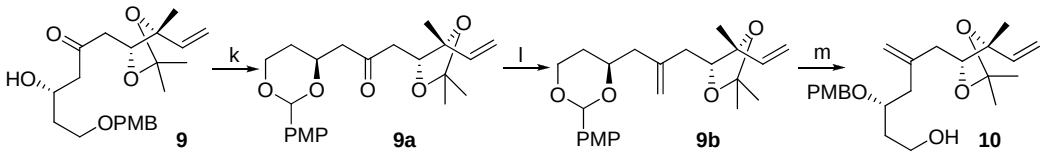
$[\alpha]_D^{25}$ = -22.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500MHz, $CDCl_3$): δ_H 9.80 (t, *J* = 2.0 Hz, 1H), 5.87 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.33 (dd, *J* = 17.2, 0.9 Hz, 1H), 5.18 (dd, *J* = 10.8, 1.0 Hz, 1H), 4.28 (dd, *J* = 9.5, 3.1 Hz, 1H), 2.71 (ddd, *J* = 16.0, 9.4, 2.0 Hz, 1H), 2.41 (ddd, *J* = 16.0, 3.3, 2.0 Hz, 1H), 1.47 (s, 3H), 1.40 (s, 3H), 1.20 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 199.4, 140.4, 115.2, 108.4, 82.0, 43.3, 28.3, 26.5, 20.5 ppm.

Aldehyde **7b** (1.84 g 10.0 mmol) was dissolved in dry Et_2O (100 mL). To this solution, MeMgBr (30 mL, 30.0 mmol, 1.0 M in THF) was added slowly at -78 ^oC; and the reaction mixture was allowed to warm to 0 ^oC over 2h period. After the starting material was consumed, the reaction was quenched with saturated solution of NH_4Cl (80 mL) and extracted with Et_2O (200 mL x 3). The combined organic extracts were washed with brine (80 mL), dried over anhydrous Na_2SO_4 and concentrated to give the corresponding alcohol. This alcohol, without purification, was dissolved in CH_2Cl_2 (100 mL) at 0 ^oC and treated with Dess-Martin periodinane (17.0 g, 40.0 mmol) and $NaHCO_3$ (1.68 g, 20.0 mmol). The reaction process was monitored by TLC. When starting material was consumed, the reaction was quenched with saturated aqueous solution of ammonium chloride (100 mL). The organic layer was separated and the aqueous phase was extracted with diethyl ether (100 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel column, eluting with 10% ethyl acetate-hexane, to give compound **8** as colorless oil (1.64 g, 83% over 3 steps). $[\alpha]_D^{25}$ = -22.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500MHz, $CDCl_3$): δ_H 5.86 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.31 (dd, *J* = 17.3, 1.0 Hz, 1H), 5.15 (dd, *J* = 10.8, 1.0 Hz, 1H), 4.24 (dd, *J* = 9.4, 3.3 Hz, 1H), 2.71 (dd, *J* = 16.0, 9.4 Hz, 1H), 2.41 (dd, *J* = 16.0, 3.3 Hz, 1H), 2.22 (s, 3H); 1.46 (s, 3H), 1.39 (s, 3H), 1.19 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 205.7, 140.7, 114.8, 107.9, 81.9, 78.0, 43.1, 30.5, 28.4, 26.5, 20.5 ppm. HRMS (ESI) for $C_{11}H_{18}NaO_3$ $[M+Na]^+$: calculated 221.1154, found 221.1154.



To a solution of ketone **8** (1.98 g, 10.0 mmol) and *i*-Pr_2NEt (2.26 mL, 13.0 mmol) in Et_2O (100 mL) at -78 °C, $(c\text{-Hex})_2BCl$, (12 mL, 12.0 mmol, 1.0 M in hexane) was dropwise added. The

reaction mixture was stirred at -78 °C for 1 h, before the addition of a solution of aldehyde **11** (2.52 g, 14.0 mmol) in Et_2O (10 mL) over a period of 15 min. The reaction was stirred at -78 °C for 16 h and then quenched by the addition of a solution of pH 7 buffer-MeOH (70 mL, v/v, 1/6). This resulting clear solution was cooled at 0°C followed by the addition of 30% H_2O_2 solution-MeOH (30 mL, v/v, 1/2). The reaction mixture was stirred at room temperature for 1 h before being diluted with Et_2O (100 mL) and water (100 mL). Layers were separated, the aqueous phase was extracted with Et_2O (100 x 3 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (100 mL), brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on a silica gel column, eluting with 15% ethyl acetate-hexane, to afford **9** as colorless oil (3.33 g, 85%). $[\alpha]_D^{25}$ = +8.1 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500MHz, $CDCl_3$): δ_H 7.24 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.85 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.31 (dd, *J* = 17.8, 1.0 Hz, 1H), 5.15 (dd, *J* = 10.8, 1.0 Hz, 1H), 4.44 (s, 2H), 4.27 (brs, 1H), 4.24 (dd, *J* = 9.5, 3.1 Hz, 1H), 3.80 (s, 3H), 3.67-3.59 (m, 2H), 3.37 (brs, 1H), 2.72 (dd, *J* = 16.0, 9.5 Hz, 1H), 2.66-2.65 (m, 2H), 2.42 (dd, *J* = 16.2, 2.6 Hz, 1H), 1.81-1.73 (m, 2H), 1.45 (s, 3H), 1.38 (s, 3H), 1.18 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 208.1, 159.3, 140.5, 130.2, 129.3, 114.8, 113.9, 108.0, 81.9, 77.8, 72.9, 67.6, 66.6, 55.2, 50.3, 43.1, 36.1, 28.3, 26.5, 20.5 ppm. HRMS (ESI) for $C_{22}H_{32}NaO_6$ $[M+Na]^+$: calculated 415.2097, found 415.2101.



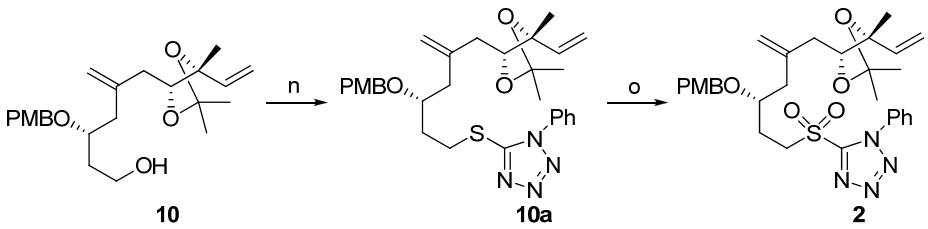
4 Å molecular sieves (MS) (2.8 g) was added to a solution of **9** (1.96 g, 5.0 mmol) in CH_2Cl_2 (50 mL) at 0 °C. 30 min later, DDQ (1.36 g, 6.0 mmol) was added in portions. The reaction mixture was warmed to room temperature and stirred for 16 h. The reaction was quenched with saturated aqueous solution of $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were washed with saturated solution of $NaHCO_3$ (2 x 100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel, eluting with 10-15% ethyl acetate - hexane, to produce **9a** as a colorless oil (1.68 g, 86%). $[\alpha]_D^{25}$ = +5.7^o (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500MHz, $CDCl_3$): δ_H 7.36 (d,

J = 8.2 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.82 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.46 (s, 1H), 5.27 (dd,, *J* = 17.8, 0.9 Hz, 1H), 5.11 (dd, *J* = 10.5, 0.9 Hz, 1H), 4.36-4.31 (m, 1H), 4.25-4.21 (m, 2H), 3.98-3.92 (m, 1H), 3.77 (s, 3H), 2.88 (dd, *J* = 15.8, 7.3 Hz, 1H), 2.73 (dd, *J* = 16.2, 9.2 Hz, 1H), 2.62 (dd, *J* = 16.2, 5.3 Hz, 1H), 2.48 (dd, *J* = 16.2, 3.3 Hz, 1H), 1.83-1.75 (m, 1H), 1.59 (dd, *J* = 13.2, 1.2 Hz, 1H), 1.44 (s, 3H), 1.37 (s, 3H), 1.14 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 205.4, 159.8, 140.5, 130.9, 127.2, 114.6, 113.4, 107.8, 101.0, 81.8, 77.6, 73.2, 66.6, 55.1, 49.2, 43.5, 31.0, 28.2, 26.4, 20.4 ppm. HRMS (ESI) for $C_{22}H_{30}NaO_6$ $[M+Na]^+$: calculated 413.1940, found 413.1940.

n-BuLi (2.2 M, 6.82 mL, 15.0 mmol) was added to a stirred solution of CH_3PPh_3I (8.08 g, 20.0 mmol) in THF (100 mL) at -78 ^{o}C. 1 h later, a solution of **9a** (1.37 g, 3.5 mmol) in THF (30 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for 16 h before being quenched with water (15 mL). Volatiles were removed in *vacuo*, the aqueous residue was extracted with diethyl ether (200 mL x 3). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The crude product was purified by flash chromatography on silica gel column, eluting with 5% ethyl acetate-hexane, to provide **9b** as colorless oil (0.93 g, 68 %). $[\alpha]_D^{25}$ = +13.1 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500MHz, $CDCl_3$): δ_H 7.40 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.80 (dd, *J* = 17.3, 11.3 Hz, 1H), 5.46 (s, 1H), 5.30 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.09 (dd, *J* = 10.8, 1.2 Hz, 1H), 5.01 (s, 1H), 4.96 (s, 1H), 4.25 (dd, *J* = 10.9, 4.8 Hz, 1H), 4.01-3.92 (m, 3H), 3.80 (s, 3H), 2.48 (dd, *J* = 14.3, 6.7 Hz, 1H), 2.35-2.29 (m, 2H), 2.23 (dd, *J* = 15.1, 3.4 Hz, 1H), 1.84-1.76 (m, 1H), 1.55 (brs, 1H), 1.47 (s, 3H), 1.37 (s, 3H), 1.19 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 160.0, 142.6, 141.1, 131.5, 127.3, 114.4, 114.2, 113.6, 107.4, 101.2, 82.4, 80.7, 76.4, 67.0, 55.3, 42.8, 36.0, 31.1, 28.5, 26.6, 20.2 ppm. HRMS (ESI) for $C_{23}H_{32}NaO_5$ $[M+Na]^+$: calculated 411.2147, found 411.2151.

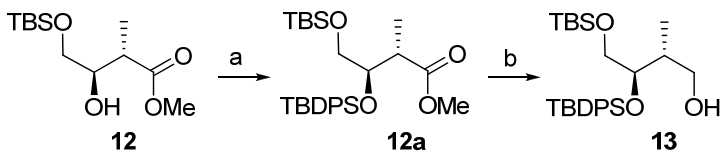
DIBAL-H (6 mL, 6.0 mmol, 1.0 M in hexane) was added to a solution of **9b** (1.94 g, 5.0 mmol) in CH_2Cl_2 (50 mL) at -20 ^{o}C. The reaction mixture was stirred at this temperature for 2 h and quenched with MeOH (5 mL). After saturated aqueous solution of Rochelle's salt (50 mL) was added, the mixture was vigorously stirred until it became clear. Layers were separated and the aqueous phase was extracted with CH_2Cl_2 (100 mL x 3). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel to give alcohol **10** (1.85 g, 95 %) as an oil. $[\alpha]_D^{25}$ =

-15.5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500MHz, $CDCl_3$): δ_H 7.26 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.81 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.31 (dd, *J* = 17.4, 1.2 Hz, 1H), 5.12 (dd, *J* = 10.8, 1.2 Hz, 1H), 4.96 (s, 1H), 4.90 (s, 1H), 4.57 (d, *J* = 11.2 Hz, 1H), 4.44 (d, *J* = 11.2 Hz, 1H), 3.89 (dd, *J* = 9.4, 3.0 Hz, 1H), 3.79 (s, 3H), 3.78-3.73 (m, 2H), 3.71-3.67 (m, 1H), 2.61 (dd, *J* = 13.9, 5.1 Hz, 1H), 2.43 (brs, 1H), 2.26-2.19 (m, 2H), 2.11 (dd, *J* = 15.0, 2.6 Hz, 1H), 1.85-1.79 (m, 1H), 1.71-1.65 (m, 1H), 1.47 (s, 3H), 1.37 (s, 3H), 1.19 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 159.3, 143.1, 140.9, 130.4, 129.4, 114.6, 114.5, 113.9, 107.5, 82.3, 81.2, 76.3, 70.6, 60.5, 55.2, 40.6, 36.0, 35.5, 28.5, 26.5, 20.1 ppm. HRMS (ESI) for $C_{23}H_{34}NaO_5$ $[M+Na]^+$: calculated 413.2304, found 413.2302.



To a solution of the **10** (1.21 g, 3.1 mmol), PPh_3 (1.6 g, 6.1 mmol) and PTSH (1.36 g, 7.7 mmol) in THF (40 mL), diisopropyl azodicarboxylate (1.52 mL, 7.7 mmol) was added at 0 ^{o}C. The reaction mixture was stirred at room temperature for 16 h and then was poured into water (10 mL). The solution was extracted with diethyl ether (100 mL x 3). The organic layers were combined, washed with saturated solution of $NaHCO_3$ (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude product was purified by flash chromatography on silica gel column, eluting with 10-15% ethyl acetate-hexane, to give **10a** as colorless oil (1.66 g, 98 %). $[\alpha]_D^{25}$ = -7.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500MHz, $CDCl_3$): δ_H 7.55 (brs, 5H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.80 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.30 (d, *J* = 17.3, 1.2 Hz, 1H), 5.10 (dd, *J* = 10.8, 1.2 Hz, 1H), 4.96 (s, 1H), 4.90 (s, 1H), 4.56 (d, *J* = 11.2 Hz, 1H), 4.42 (d, *J* = 11.2 Hz, 1H), 3.88 (dd, *J* = 9.4, 3.0 Hz, 1H), 3.79 (s, 3H), 3.74-3.69 (m, 1H), 3.51-3.46 (m, 1H), 3.45-3.39 (m, 1H), 2.59 (dd, *J* = 14.1, 5.2 Hz, 1H), 2.26-2.20 (m, 2H); 2.14-2.07 (m, 2H), 1.97-1.91 (m, 1H), 1.46 (s, 3H), 1.37 (s, 3H), 1.17 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 159.9, 142.5, 141.1, 132.3 (2C), 131.4, 128.5, 128.4, 127.3, 114.4, 114.1, 113.6, 107.4, 101.1, 82.4, 80.7, 76.3, 67.0, 55.3, 42.8, 36.0, 31.1, 28.5, 26.6, 20.2 ppm. HRMS (ESI) for $C_{30}H_{38}N_4NaO_4S$ $[M+Na]^+$: calculated 573.2511, found 573.2509.

To the solution of **10a** (1.50 g, 2.72 mmol) in ethanol (40 mL) was added $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (1.00 g, 0.8 mmol) dissolved in 30% H_2O_2 solution (4 mL, 35.3 mmol) at 0 ^oC. The reaction mixture was stirred at room temperature for 18 h, then it was poured into 10% aqueous solution of $Na_2S_2O_3$ (50 mL). Volatiles were removed; the aqueous residue was extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with saturated solution of $NaHCO_3$ (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude product was purified by flash chromatography on silica gel column, eluting with 10-15% ethyl acetate-hexane, to give the desired sulfone **2** as colorless oil (1.57 g, 99 %). $[\alpha]_D^{25}$ = -8.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500MHz, $CDCl_3$): δ_H 7.67-7.65 (m, 2H), 7.62-7.56 (m, 3H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.81 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.31 (dd, *J* = 17.4, 1.2 Hz, 1H), 5.11 (dd, *J* = 10.8, 1.2 Hz, 1H), 4.98 (s, 1H), 4.91 (s, 1H), 4.55 (d, *J* = 11.3 Hz, 1H), 4.43 (d, *J* = 11.3 Hz, 1H), 3.79 (s, 3H), 3.78-3.68 (m, 4H), 2.63 (dd, *J* = 14.1, 5.2 Hz, 1H), 2.23-2.10 (m, 4H); 2.04-1.97 (m, 2H), 1.47 (s, 3H), 1.37 (s, 3H), 1.19 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 159.4, 153.5, 142.6, 140.9, 133.1, 131.4, 130.1, 129.7, 129.5, 125.1, 115.1, 114.6, 114.0, 107.6, 82.4, 81.4, 74.3, 70.6, 55.3, 52.7, 40.5, 35.5, 28.5, 26.6, 26.2, 20.1 ppm. HRMS (ESI) for $C_{30}H_{38}N_4NaO_6S$ $[M+Na]^+$: calculated 605.2410; found 605.2410.

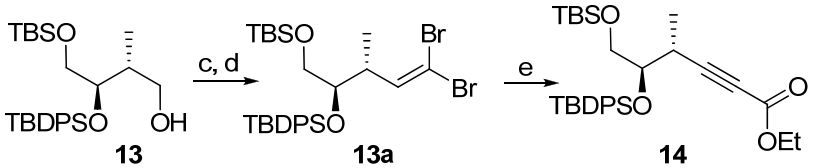


To a solution of compound **12** [1] (1.37 g, 5.2 mmol) in DMF (20 mL) was added DMAP (61.0 mg, 0.3 mmol) and imidazole (0.71 g, 10.4 mmol) at 0 ^oC, followed by addition of TBDPSCl (1.74 g, 6.2 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 16 h before it was poured into saturated solution of ammonium chloride (100 mL) followed by extraction with diethyl ether (100 mL x 3). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated in *vacuo*. The residue was purified by flash chromatography, using 5% ethyl acetate-hexane as eluent, on silica gel to produce **12a** (2.58 g, 99%) as an oil. $[\alpha]_D^{25}$ = +41.2 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500MHz, $CDCl_3$): δ_H 7.72-7.67 (m, 4H), 7.43-7.36 (m, 6H), 4.07 (dd, *J* = 11.0, 5.1 Hz, 1H), 3.61 (s, OCH_3, 3H), 3.53

[1] (a) Thomast, E. J.; Williams, A. C. *J. Chem. Soc. Perkin Trans. 1* **1995**, 351-358. (b) Fox, M. E.; Jackson, M.; Lennon, I. C.; McCague, R. A. *J. Org. Chem.* **2005**, *70*, 1227-1236.

(dd, *J* = 10.4, 6.2 Hz, 1H), 3.44 (dd, *J* = 5.8, 4.5 Hz, 1H), 2.82 (dq ,1H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.04 (s, 9H), 0.80 (s, 9H), -0.12 (s, 3H), -0.14 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 174.6, 135.9 (2C), 134.3, 133.8, 129.7, 129.5, 127.6, 127.5, 75.3, 64.1, 51.2, 43.1, 26.9, 25.8, 19.4, 18.2, 12.1, -5.6, -5.8 ppm. HRMS (ESI) for $C_{28}H_{44}NaO_4Si_2$ $[M+Na]^+$: calculated 523.2676, found 523.2686.

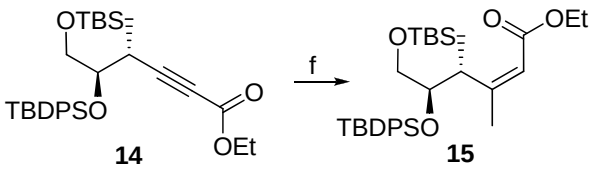
DIBAL-H (15.0 mL, 15.0 mmol, 1.0 M in hexane) was added to a solution of **12a** (2.50 g, 5.0 mmol) in THF at -78 ^{o}C; and the reaction mixture was then allowed to warm to room temperature and stirred for 16 h. The reaction was carefully quenched with MeOH (5 mL). After saturated aqueous solution of Rochelle's salt (80 mL) was added, the mixture was vigorously stirred until it became clear. Volatiles were removed; the aqueous residue was extracted with diethyl ether (60 mL x 3). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by flash column chromatography using with 10% ethyl acetate-hexane as eluent on silica gel to give alcohol **13** (2.20 g, 95%) as an oil. $[\alpha]_D^{25}$ = +27.0 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (500MHz, $CDCl_3$): δ_H 7.69-7.67 (m, 4H), 7.44-7.37 (m, 6H), 3.82 (dd, *J* = 7.0, 4.0 Hz, 1H), 3.66 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.62-3.58 (m, 2H), 3.41 (dd, *J* = 10.0, 4.0 Hz, 1H), 2.87 (t , *J* = 5.8 Hz, 1H), 2.05-2.03 (m, 1H), 1.08 (s, 9H), 1.06 (d, *J* = 7.5 Hz, 3H), 0.79 (s, 9H), -0.12 (s, 3H), -0.17 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 136.1, 136.0, 134.2, 133.5, 130.0, 129.9, 127.8, 127.7, 76.8, 64.8, 64.0, 38.9, 27.2, 25.9, 19.6, 18.3, 12.5, -5.7, -5.8 ppm. HRMS (ESI) for $C_{27}H_{44}NaO_3Si_2$ $[M+Na]^+$: calculated 495.2727, found 495.2730.



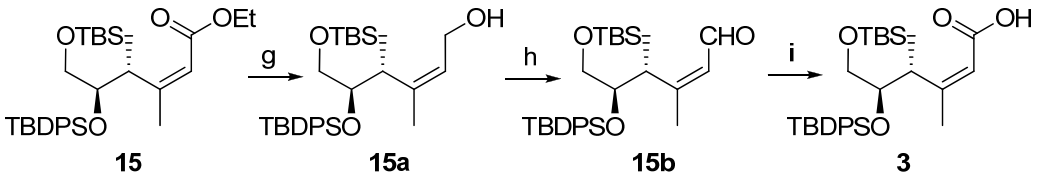
To a solution of alcohol **13** (2.56 g, 5.4 mmol) and $NaHCO_3$ (0.91 g, 10.8 mmol) in dry CH_2Cl_2 (100 mL) was added Dess-Martin Periodinane (8.48 g, 20.0 mmol) at 0 ^{o}C. When all the starting material was consumed, the reaction was quenched with saturated ammonium chloride (100 mL). The organic layer was separated and the aqueous phase was extracted with diethyl ether (100 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated to give aldehyde, which was pure enough for next step without further purification.

PPh_3 (6.50 g, 24.8 mmol) was added to a solution of CBr_4 (4.12 g, 12.4 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min and cooled to -20 °C, before a solution of the above aldehyde and Et_3N (2.25 mL, 16.2 mmol) in CH_2Cl_2 (10 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for 4 h before it was filtered through a pad of silica gel and eluted with CH_2Cl_2 (150 mL). The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel column, eluting with 2% ethyl acetate-hexanes, to afford **13a** (2.72 g, 82%). $[\alpha]_D^{25}$ = +38.5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500MHz, $CDCl_3$): δ_H 7.69-7.64 (m, 4H); 7.44-7.36 (m, 6H); 6.57 (d, J = 9.5 Hz,1H), 3.69-3.66 (m, 1H), 3.37-3.33 (m, 2H), 2.88-2.81 (m, 1H), 1.07 (s, 9H), 1.06 (d, *J* = 7.5 Hz, 3H); 0.78 (s, 9H), -0.13 (s, 3H), -0.19 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 140.5, 136.0, 135.9, 134.3, 133.6, 129.8, 129.7, 127.7, 127.5, 88.2, 64.5, 41.3, 27.1, 25.8, 19.5, 18.1, 15.4, -5.7, -5.8 ppm. HRMS (ESI) for $C_{28}H_{42}Br_2NaO_2Si_2$ $[M+Na]^+$: calculated 647.0988, found 647.0983.

n-Butyllithium (8.86 mL, 13.3 mmol, 1.5 M in hexanes) was dropwise added to a solution of **13a** (2.72 g, 4.4 mmol) in THF (30 mL) at -78 °C. 20 min later, the reaction mixture was cooled at -95 °C and a solution of ethyl chloroformate (0.85 mL, 8.9 mmol) in THF (10 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for 16 h before it was quenched with saturated aqueous solution of ammonium chloride (30 mL). After volatiles were removed in *vacuo*, the aqueous residue was extracted with ethyl acetate (70 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column, eluting with 2% ethyl acetate-hexane, to produce **14** as a colorless oil (2.15 g, 90%). $[\alpha]_D^{25}$ = +37.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500MHz, $CDCl_3$): δ_H 7.73-7.72 (m, 4H), 7.44-7.37 (m, 6H), 4.24 (q, J = 7.2 Hz, 2H), 3.73-3.71 (m, 1H), 3.58 (dd, *J* = 10.0, 7.6 Hz, 1H), 3.46 (dd, *J* = 10.0, 4.7 Hz, 1H), 2.95 (dq , 1H), 1.30 (t, *J* = 6.7 Hz, 3H), 1.22 (d, *J* = 7.2 Hz, 3H), 1.08 (s, 9H), 0.79 (s, 9H), -0.10 (s, 3H), -0.14 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 154.0, 136.0 (2C), 134.3, 133.8, 129.9, 129.8, 127.8, 127.7, 90.7, 76.0, 74.9, 64.7, 61.7, 29.9, 27.1, 26.0, 19.7, 18.3, 16.5, 14.2, -5.6, -5.7 ppm. HRMS (ESI) for $C_{31}H_{46}NaO_4Si_2$ $[M+Na]^+$: calculated 561.2832, found 561.2830.



MeLi (26.7 mL, 42.7 mmol, 1.6 M in Et_2O) was added to a stirred solution of copper (I) iodide (4.06 g, 21.3 mmol) in THF (50 mL) at 0 °C. 15 min later, the resulting solution was cooled to –50 °C. After a solution of **14** (3.83 g, 7.1 mmol) in THF (20 mL) was added, stir was continued for additional 3 h at this temperature. The reaction was warmed to –45 °C and quenched by the addition of glacial acetic acid (1.2 mL) and saturated solution of NH_4Cl (20 mL). Volatiles were removed; the aqueous residue was extracted with Et_2O (60 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel, using 1-2% ethyl acetate-hexane, to produce **15** (3.74 g, 94%) as oil. $[\alpha]_D^{25}$ = + 5.8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500MHz, $CDCl_3$): δ_H 7.71-7.65 (m, 4H), 7.41-7.32 (m, 6H), 5.69 (s,1H), 4.24 (q, J = 7.2 Hz, 1H), 4.13-4.08 (m, 2H), 3.76 (dd, *J* = 5.8, 5.0 Hz, 1H), 3.47 (dd, *J* = 5.2, 1.8 Hz, 2H), 1.91 (s, 3H); 1.24 (t, *J* = 7.1 Hz, 3H), 1.05 (d, *J* = 7.5 Hz, 3H), 1.02 (s, 9H), 0.74 (s, 9H), -0.22 (s, 3H), -0.27 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 166.1, 161.7, 136.2, 135.9, 135.0, 133.7, 129.6, 129.3, 127.5, 127.2, 118.0, 77.3, 66.0, 59.3, 37.9, 27.0, 25.9, 21.6, 19.5, 18.2, 15.8, 14.3, -5.8, -5.9 ppm. HRMS (ESI) for $C_{32}H_{50}NaO_4Si_2$ $[M+Na]^+$: calculated 577.3145, found 577.3142.



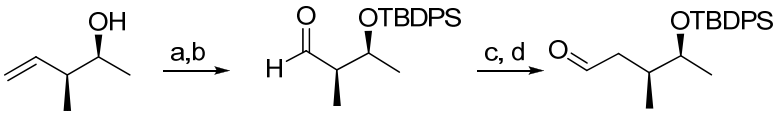
DIBAL-H (15.0 mL, 15.0 mmol, 1.0 M in hexane) was added to a solution of **15** (2.80 g, 5.0 mmol) in THF at -78 ^oC; the reaction mixture was allowed to warm to room temperature within 4 h period and then quenched with MeOH (5 mL). After saturated aqueous solution of Rochelle's salt (80 mL) was added, the reaction mixture was vigorously stirred until it became clear. Volatiles were removed in *vacuo*, the aqueous residue was extracted with diethyl ether (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by flash column chromatography using with 10%

ethyl acetate-hexane as eluant on silica gel to give **15a** (2.43 g, 95%) as an oil. $[\alpha]_D^{25}$ = +42.9 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500MHz, $CDCl_3$): δ_H 7.71-7.67 (m, 4H), 7.44-7.36 (m, 6H), 5.68 (t, *J* = 7.6 Hz, 1H), 4.17-4.13 (m, 1H), 3.88-3.82 (m, 1H), 3.60-3.57 (m, 1H), 3.47-3.40 (m, 2H), 3.15-3.10 (m, 1H), 2.40 (d, *J* = 6.4 Hz, 1H), 1.83 (s, 3H), 1.06 (d, *J* = 7.1 Hz, 3H), 1.05 (s, 9H), 0.77 (s, 9H), -0.24 (s, 3H), -0.25 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 141.8, 136.2, 136.0, 134.3, 133.1, 129.8, 129.6, 127.7, 127.5, 127.0, 77.2, 64.7, 57.8, 35.3, 27.0, 25.8, 20.9, 19.5, 18.2, 16.1, -5.6, -5.7 ppm. HRMS (ESI) for $C_{30}H_{48}NaO_3Si_2$ $[M+Na]^+$: calculated 535.3040, found 577.3030.

To a solution of **15a** (2.43 g, 4.75 mmol) in CH_2Cl_2 (50 mL) was added MnO_2 (2.10 g, 24.1 mmol) at room temperature. When all starting material was consumed, the reaction mixture was filtered through a pad of celite and the cake was rinsed with CH_2Cl_2 (30 mL x 3). The combined filtrate was concentrated in *vacuo* to give the crude aldehyde **15b,** which was used in next step without further purification. Analytical data were collected after purification of a part of the crude aldehyde with chromatography on silica gel, eluting with 15% ethyl acetate in hexane. $[\alpha]_D^{25}$ = +18.1 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500MHz, $CDCl_3$): δ_H 9.99 (d, *J* = 8.2 Hz, 1H), 7.68-7.63 (m, 4H), 7.44-7.36 (m, 6H), 5.95 (d, *J* = 8.2 Hz, 1H), 4.17-4.13 (m, 1H), 3.86-3.81 (m, 1H), 3.68-3.65 (m, 1H), 3.44-3.36 (m, 2H), 1.99 (d, *J* = 1.0 Hz, 3H), 1.16 (d, *J* = 7.1 Hz, 3H), 1.03 (s, 9H), 0.76 (s, 9H), -0.19 (s, 3H), -0.23 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 191.1, 164.8, 136.1, 135.9, 134.2, 133.0, 130.9, 129.9, 129.7, 127.7, 127.5, 77.0, 64.3, 36.7, 27.0, 25.8, 21.9, 19.5, 18.1, 15.9, -5.6, -5.8 ppm.

Aqueous solution of $NaClO_2$ (1.84 g, 20 mmol, 80%) was adjusted to pH 7 with a solution of NaH_2PO_4 in water, this mixture was then added to a solution of aldehyde **15b** (2.37 g, 4.7 mmol) in *tert*-butanol/water (40 mL, 1:1) at 0 ^{o}C. After $CH_3SO_2NH_2$ (950.0 mg, 10.0 mmol) was added, the reaction mixture was stirred for 16 h before it was poured into ethyl acetate (50 mL). Layers were separated; the aqueous phase was further extracted with ethyl acetate (50 mL x 2). The combined extracts were washed with brine (30 mL x 2), dried over Na_2SO_4 and concentrated *in vacuo* to furnish the desired acid **3** (2.16 g, 82% over two steps). ^{1}H NMR (500MHz, $CDCl_3$): δ_H 7.72-7.69 (m, 4H), 7.44-7.35 (m, 6H), 5.76 (s, 1H), 4.20 (dd, *J* = 13.7, 6.9 Hz, 1H), 3.72 (dd, *J* = 10.6, 4.8 Hz, 1H), 3.52-3.46 (m, 2H), 1.93 (d, *J* = 1.0 Hz, 3H), 1.06 (d, *J* = 7.8 Hz, 3H), 1.05 (s, 9H), 0.79 (s, 9H), -0.17 (s, 3H), -0.20 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 170.7, 162.9,

136.1, 135.9, 134.5, 133.3, 129.7, 129.4, 127.6, 127.3, 118.2, 77.0, 65.2, 37.7, 27.0, 25.8, 21.6, 19.5, 18.2, 15.6, -5.8, -5.9 ppm. HRMS(ESI) for $C_{30}H_{46}NaO_4Si_2$ $[M+Na]^+$: calculated 549.2832, found 549.2832.



16 **17** **18**

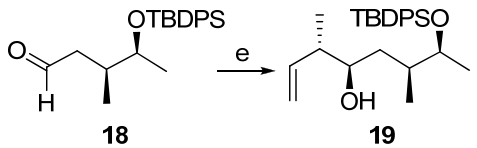
Homoallylic alcohol **16** [2] (2.50 g, 25.0 mmol) was dissolved in DMF (80 mL) at 0 ^oC, after DMAP (158.6 mg, 1.3 mmol), imidazole (3.40 g, 50.0 mmol) and TBDPSCl (7.8 mL, 30.0 mmol) were sequentially added, the reaction mixture was allowed to warm to room temperature and stirred for 16 h. Saturated aqueous solution of ammonium chloride (80 mL) was used to quench the reaction, followed by extraction with diethyl ether (100 mL x 3). The combined organic layers were washed with water (80 mL) and brine (80 mL), dried over $MgSO_4$ and concentrated in *vacuo*. The residue was purified by flash chromatography, using with 2% ethyl acetate-hexane as eluant, on silica gel to produce the desired silyl ether intermediate (8.02 g, 95%).

A solution of the above silyl ether (7.44 g, 22.0 mmol) in dioxane-water (80 mL, v/v 3:1) was treated with OsO_4 (13.5 mL, 0.7 mmol, 2.5% wt in *tert*-BuOH) and $NaIO_4$ (11.0 g, 49 mmol) in the presence of 2,6-lutidine (4.28 g, 44.0 mmol) at 0 ^oC. After the starting material was consumed, the reaction was quenched with saturated Na_2SO_3 solution (150 mL). Stir was continued for an additional 30 min and then the volatiles were removed in *vacuo*. The aqueous residue was extracted with CH_2Cl_2 (100 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated in *vacuo* to produce aldehyde **17** [3] (6.95 g, 93%), which was subjected to next reaction without purification.

NaHMDS (25.0 mL, 50.0 mmol, 2.0 M in THF) was added to a solution of $MeOCH_2PPh_3Cl$ (17.20 g, 50.0 mmol) in THF (150 mL) at -78 ^oC. 1 h later, a solution of aldehyde **17** (6.40 g, 18.8 mmol) in THF (30 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for 16 h before it was quenched with saturated aqueous solution of NH_4Cl (50 mL). Volatiles were removed in *vacuo*, the aqueous residue was extracted with diethyl ether

[2] Brown, H.C.; Bhat, K.S. *J. Am. Chem. Soc.* **1986**, *108*, 293-294.
[3] Masahiro, T.; Noriko, Y.; Youichi, N.; Keiichiro, F. *Heterocycles* **1995**, *40*, 115-117.

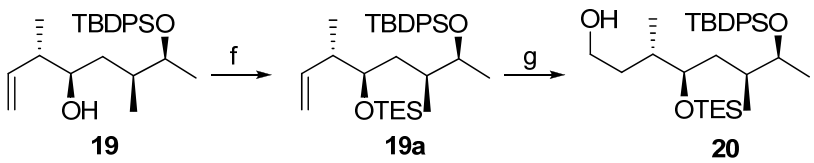
(200 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The residue, without purification, was dissolved in CH_2Cl_2-THF (200 mL, v/v 4/1) at 0 ^oC, HCl (20 mL, 5 M solution in water) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for 16 h and then diluted with water (100 mL). Layers were separated; the aqueous phase was extracted with CH_2Cl_2 (200 mL x 3). The combined extracts were washed with saturated aqueous solution of $NaHCO_3$ (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel column, eluting with 2% ethyl acetate-hexane, to give compound **18**[4] as colorless oil (5.6 g, 83% over two steps).



Potassium *tert*-butoxide (1.68 g, 15.0 mmol, dried at 0.5 mmHg / 80 ^oC for 8 h) was dissolved in THF **(**15 mL) at -78 ^oC; after *trans*-2-butene (1.68 g, 30.0 mmol) was introduced, *n*-BuLi (6.8 mL, 15.0 mmol, 2.2 M in hexane) was added slowly. The resulting orange solution was then stirred at -45 ^oC for 10 min and re-cooled to -78 ^oC before (-)-methoxydiisopinocampheylborane (15.8 mL, 15.8 mmol, derived from (+)-α-pinene, 1.0 M in THF) was dropwise added. 30 min later, boron trifluoride etherate (2.1 mL, 16.5 mmol) was added, followed by the solution of aldehyde **18** (3.56 g, 10 mmol) in THF (10 mL). The reaction mixture was stirred at -78 ^oC for 6 h and then treated with NaOH (6 mL, 18.0 mmol, 3.0 M in water) and H_2O_2 (3.0 mL, 30% solution) under refluxing temperature for 1 h. Volatiles were removed *in vacuo*, the aqueous residue was extracted with Et_2O (100 mL x 3). The combined extracts were washed with water (60 mL) and brine (60 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel chromatography, using 5% ethyl acetate-hexane as eluant, to provide the **19** (3.22 g, 78%) as an oil. $[\alpha]_D^{25}$ = -7.6 (*c* 0.5, CH_2Cl_2); ^1H NMR (500MHz, $CDCl_3$): δ_H 7.72-7.68 (m, 4H), 7.46-7.37 (m, 6H), 5.85-5.74 (m, 1H), 5.13-5.07 (m, 2H), 3.90-3.85 (m, 1H), 3.52 (brs, 1H), 2.21-2.14 (m, 1H), 1.83-1.74 (m, 2H); 1.63 (brs, 1H), 1.28-1.19 (m, 1H), 1.07 (s, 9H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 140.3, 136.0

[4] Giorgio, D. S.; Cutignano, A.; Fontana, A.; Spinella, A.; Calabrese, G.; Coll, A. D.; d'Ippolito, G.; Carmela, D. M.; Cimino, G. *Tetrahedron* **2007**, *63*, 7256-7263.

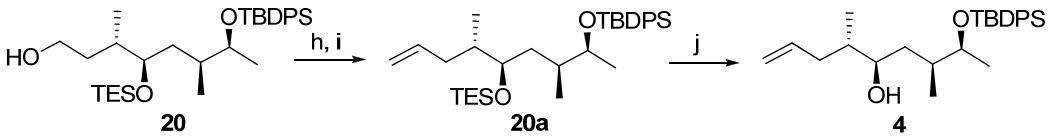
(2C), 135.9 (2C), 134.8, 134.2, 129.6, 129.5, 127.6 (2C), 127.4 (2C), 115.8, 73.4, 72.5, 44.2, 37.1, 36.9, 27.1 (3C), 19.3, 19.1, 16.5, 16.3. HRMS (ESI) for $C_{26}H_{38}NaO_2Si$ $[M+Na]^+$: calculated 433.2539, found 433.2531.



TESOTf (2.62 mL, 12.15 mmol) was dropwise added to a solution of **19** (2.50 g, 6.1 mmol) and 2,6-lutidine (2.12 mL, 18.3 mmol) in CH_2Cl_2 (60 mL) at -30 ^oC. Upon the completion of addition, the reaction mixture was stirred at -30 ^oC for 10 min, and then allowed to slowly warm to room temperature. 6 h later, the reaction was quenched with saturated aqueous solution of NH_4Cl (50 mL) and extracted with CH_2Cl_2 (100 mL x 3). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel column, eluting with 2% ethyl acetate-hexane, to produce **19a** as colorless oil (3.13 g, 98%). $[\alpha]_D^{25}$ = -7.0 (*c* 1.0, CH_2Cl_2); ^1H NMR (500MHz, $CDCl_3$): δ_H 7.71-7.68 (m, 4H); 7.44-7.41 (m, 2H); 7.39-7.35 (m, 4H); 5.80-5.73 (m, 1H), 4.95-4.85 (m, 2H), 3.80-3.76 (m, 1H), 3.65-3.62 (m, 1H), 2.27-2.23 (m, 1H), 1.74-1.69 (m, 1H), 1.58-1.53 (m, 1H), 1.27-1.22 (m, 1H), 1.07 (s, 9H), 1.02 (d, *J* = 7.9 Hz, 3H); 0.96-0.92 (m,15H), 0.56 (q, *J* = 8.1 Hz, 6H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 140.5, 136.0, 135.9, 135.2, 134.3, 129.4, 129.3, 127.5, 127.3, 114.5, 74.5, 72.5, 43.1, 37.0, 36.6, 27.1, 20.2, 19.4, 15.7, 15.1, 7.0, 5.3 ppm. HRMS (ESI) for $C_{32}H_{52}NaO_2Si_2$ $[M+Na]^+$: calculated 547.3404, found 547.3407.

9-BBN (22.8 mL, 11.4 mmol, 0.5 M solution in THF) was dropwise added to a solution of **19a** (3.00 g, 5.7 mmol) in THF (50 mL) at 0 ^oC over 30 min. The reaction mixture was stirred at 0 ^oC for 1 h, and then at room temperature for 16 h. After it was re-cooled to 0 ^oC, the reaction was carefully quenched by addition of a pre-mixed aqueous solution of NaOH (15 mL3 M) and H_2O_2 (15 mL, 30% in water). The reaction mixture was refluxed for 1 h and then cooled to room temperature again. Brine (100 mL) was added for dilution, volatiles were removed in *vacuo*. The aqueous residue then was extracted with Et_2O (80 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel column, eluting with 5% ethyl acetate-hexane, to

afford **20** as a colorless oil (2.73 g, 88%). $[\alpha]_D^{25}$ = -3.5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500MHz, $CDCl_3$): δ_H 7.70-7.66 (m, 4H), 7.43-7.41 (m, 2H), 7.40-7.35 (m, 4H), 3.81-3.77 (m, 1H), 3.66-3.61 (m, 2H), 3.51-3.47 (m, 1H), 2.51 (brs, 1H), 1.88-1.82 (m, 1H), 1.74-1.70 (m, 1H), 1.64-1.58 (m, 1H), 1.49-1.42 (m, 1H), 1.33-1.24 (m, 2H), 1.05 (s, 9H), 0.96-0.93 (m, 15H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.58 (q, *J* = 8.1 Hz, 6H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 136.0, 135.9, 135.1, 134.5, 129.5, 129.4, 127.5, 127.4, 75.1, 72.9, 59.8, 37.1, 36.4, 34.0, 33.4, 27.1, 19.8, 19.4, 16.1, 15.0, 6.9, 5.2 ppm. HRMS (ESI) for $C_{32}H_{54}NaO_3Si_2$ $[M+Na]^+$: calculated 565.3509, found 565.3513.

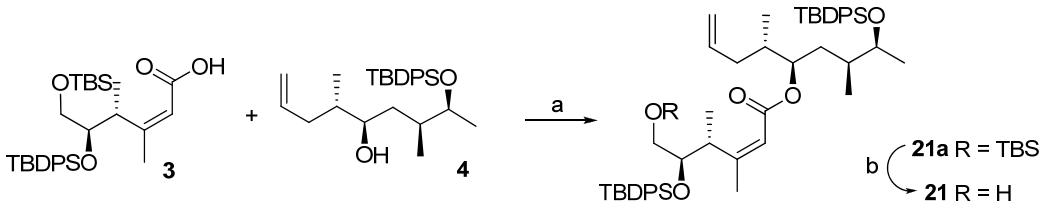


To a stirred solution of **20** (2.50 g, 4.6 mmol) in CH_2Cl_2 (50 mL) at 0 ^{o}C, $NaHCO_3$ (773.0 mg, 9.2 mmol) and Dess-Martin Periodinane (7.80 g, 18.4 mmol) were sequentially added. When all starting material was consumed, the reaction mixture was filtered through a pad of silica gel and eluted with diethyl ether (50 mL x 3). The filtrate was washed with brine (50 mL), dried over $MgSO_4$ and concentrated to give the corresponding crude aldehyde.

n-BuLi (6.82 mL, 15.0 mmol, 2.2 M in hexane) was added to a stirred solution of Ph_3PCH_3I (8.08 g, 20 mmol) in THF (100 mL) at -78 ^{o}C. 1 h later, a solution of the above aldehyde (2.45 g, 4.5 mmol) in THF (30 mL) was added at -78 ^{o}C. Then the reaction mixture was allowed to warm to room temperature and stirred overnight. Water (30 mL) was added to quench the reaction. Volatiles were removed in *vacuo*, and the aqueous residue was extracted with diethyl ether (100 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel column, eluting with 5% ethyl acetate-hexane, to produce **20a** as colorless oil (2.17 g, 87% over 2 steps). $[\alpha]_D^{25}$ = -7.8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500MHz, $CDCl_3$): δ_H 7.69-7.66 (m, 4H), 7.43-7.40 (m, 2H), 7.39-7.35 (m, 4H), 5.77-5.69 (m, 1H), 4.96-4.92 (m, 2H), 3.81-3.77 (m, 1H), 3.62-3.59 (m, 1H), 2.10-2.03 (m, 1H), 1.81-1.71 (m, 2H), 1.24-1.18 (m, 3H), 1.05 (s, 9H), 0.95-0.93 (m, 12H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 7.8 Hz, 3H), 0.53 (q, *J* = 7.9 Hz, 6H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 138.3, 136.0, 135.9, 135.2, 134.4, 129.5, 129.4, 127.5, 127.3, 115.2, 75.0, 72.7, 38.1, 37.4, 35.9, 35.6, 27.1, 19.9, 19.4, 15.4, 15.3, 7.0, 5.4 ppm. HRMS (ESI) for $C_{33}H_{54}NaO_2Si_2$

$[M+Na]^+$: calculated 565.3560, found 565.3554.

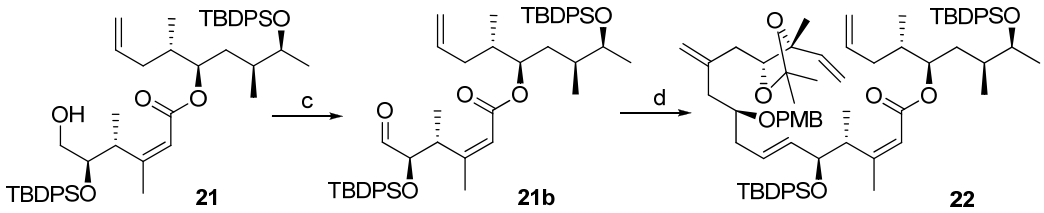
20a (1.62 g, 3.0 mmol) was dissolved in CH_2Cl_2-THF (50 mL, v/v 4/1) at 0 ^oC, cold solution of HCl (5 mL, 3.0 M in water) was added. The reaction mixture was then allowed to warm to room temperature and stirred for 12 h. The reaction was quenched with cold saturated solution $NaHCO_3$, until the pH of the solution reached 7. The mixture was concentrated *in vacuo* to remove all volatiles. The aqueous layer was extracted with CH_2Cl_2 (100 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The crude product was purified by flash chromatography on silica gel column, eluting with 2% ethyl acetate-hexane, to provide **4** as colorless oil (1.27 g, 99 %). $[\alpha]_D^{25}$ = -2.5 (*c* 1.0, CH_2Cl_2); ^1H NMR (500MHz, $CDCl_3$): δ_H 7.68-7.67 (m, 4H), 7.43-7.41 (m, 2H), 7.39-7.36 (m, 4H), 5.85-5.76 (m, 1H), 5.04-4.99 (m, 2H), 3.87-3.83 (m, 1H), 3.60-3.57 (m, 1H), 2.33-2.29 (m, 1H), 2.18 (d, *J* = 5.5 Hz, 1H), 1.96-1.90 (m, 2H), 1.76-1.71 (m, 1H), 1.60-1.55 (m, 1H), 1.30-1.24 (m, 1H), 1.07 (s, 9H), 0.93 (d, *J* = 6.0 Hz, 3H), 0.88 (d, *J* = 7.8 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 137.8, 136.0, 135.9, 134.6, 133.9, 129.7, 129.6, 127.7, 127.5, 115.8, 73.8, 73.2, 38.9, 36.8, 36.5 (2C), 27.1, 19.3, 18.3, 17.5, 15.6 ppm. HRMS (ESI) for $C_{27}H_{40}NaO_2Si$ $[M+Na]^+$: calculated 447.2695, found 447.2699.



To a solution of acid **3** (930.0 mg, 1.8 mmol) in toluene (20 mL) was added triethylamine (1.23 mL, 8.8 mmol), followed by 2,4,6-trichlorobenzoyl chloride (863.0 mg, 3.5 mmol) at 0 ºC. The reaction mixture was stirred at room temperature for 1 h, and then cooled to 0 ºC; a solution of DMAP (432.0 mg, 3.5 mmol) and alcohol **4** (754.0 mg, 1.8 mmol) in toluene (15 mL) was added to the solution. This reaction mixture was stirred at room temperature for 20 h before it was diluted with ethyl acetate (150 mL) and washed with saturated aqueous solution of NH_4Cl (50 mL), saturated aqueous solution of $NaHCO_3$ (50 mL) and brine (50 mL). The organic phase was dried over anhydrous Na_2SO_4, concentrated under reduced pressure to leave a residue, which was purified by flash column chromatography on silica gel column, eluting with 1-2% ethyl

acetate-hexane, to provide the ester **21a** (1.35 g, 82 %) as a colorless oil. $[\alpha]_D^{25}$ = -16.7 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500MHz, $CDCl_3$): δ_H 7.73-7.66 (m, 8H), 7.43-7.32 (m, 12H), 5.76-5.70 (m, 1H), 5.66 (d, *J* = 1.2 Hz, 1H), 4.99 (s, 1H), 4.96 (s, 1H), 4.88-4.85 (m, 1H), 4.30-4.26 (m, 1H), 3.87-3.83 (m, 1H), 3.77-3.74 (m, 1H), 3.55 (dd, *J* = 10.6, 4.7 Hz, 1H), 3.50 (dd, *J* = 10.6, 4.6 Hz, 1H), 2.23-2.17 (m, 1H), 1.90 (s, 3H), 1.91-1.86 (m, 1H), 1.86-1.79 (m, 1H), 1.76-1.72 (m, 1H), 1.57-1.53 (m, 1H), 1.37-1.32 (m, 1H), 1.07 (s, 9H), 1.03 (d, *J* = 7.1 Hz, 3H), 1.01 (s, 9H), 0.93 (d, *J* = 6.1 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.75 (s, 9H), -0.21 (s, 3H), -0.27 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 165.7, 162.3, 137.3, 136.1, 135.9 (3C), 135.0 (2C), 134.3, 133.7, 129.5 (2C), 129.3, 129.2, 127.5, 127.4, 127.3, 127.2, 117.9, 115.7, 77.0, 75.7, 72.4, 66.3, 38.3, 37.8, 36.4, 36.3, 32.6, 27.1, 27.0, 25.9, 21.4, 19.5 (2C), 19.3, 18.2, 15.8, 15.5, 15.2, -5.8, -5.9 ppm. HRMS (ESI) for $C_{57}H_{84}NaO_5Si_3$ $[M+Na]^+$: calculated 955.5524, found 955.5527.

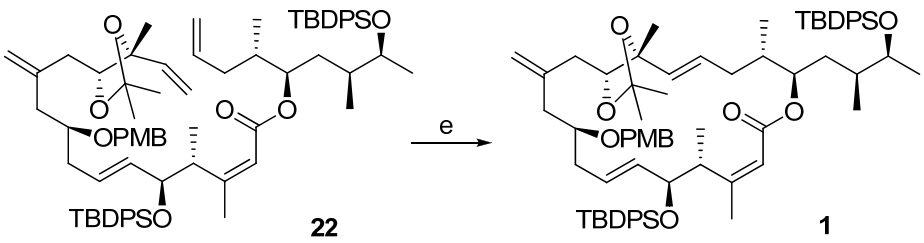
Compound **4** (680.0 mg, 0.7 mmol) was dissolved in EtOH-THF (15 mL, v/v 2/1) at room temperature. After CAS (51 mg, 0.07 mmol) was added, the reaction mixture was refluxed for 12 h and was then poured into saturated aqueous solution of $NaHCO_3$ (50 mL). Volatiles were removed in *vacuo*. The aqueous residue was extracted with diethyl ether (100 mL x 3). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel column, eluting with 5% ethyl acetate-hexane, to afford **21** as a colorless oil (585.0 mg, 98 %). $[\alpha]_D^{25}$ = -42.5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500MHz, $CDCl_3$): δ_H 7.79-7.67 (m, 8H), 7.48-7.38 (m, 12H), 5.87 (s, 1H), 5.80-5.72 (m, 1H), 5.04 (s, 1H), 5.02 (s, 1H), 4.90-4.86 (m, 1H), 4.04-3.99 (m, 1H), 3.89-3.85 (m, 1H), 3.85-3.82 (m, 1H), 3.64-3.61 (m, 1H), 3.45-3.42 (m, 2H), 2.24-2.19 (m, 1H), 2.08 (s, 3H), 1.96-1.91 (m, 1H), 1.90-1.86 (m, 1H), 1.78-1.74 (m, 1H), 1.56-1.52 (m, 1H), 1.41-1.36 (m, 1H), 1.14 (d, *J* = 7.5 Hz, 3H), 1.12 (s, 9H), 1.10 (s, 9H), 0.96 (d, *J* = 6.3 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 167.5, 161.4, 137.0, 136.1, 135.9, 135.8, 135.7, 134.9, 134.4, 134.1, 132.8, 129.9, 129.6, 129.5, 129.4, 127.8, 127.5 (2C), 127.3, 118.8, 116.0, 78.1, 76.8, 72.0, 64.5, 37.5, 36.5, 36.1 (2C), 32.9, 27.1 (2C), 22.6, 19.5 (2C), 19.3, 16.4, 15.4, 15.3 ppm. HRMS (ESI) for $C_{51}H_{70}NaO_5Si_2$ $[M+Na]^+$: calculated 841.4659, found 841.4669.



To a solution of **21** (414.0 mg, 0.5 mmol) in CH_2Cl_2 (20 mL), $NaHCO_3$ (84.0 mg, 1.0 mmol) and Dess-Martin Periodinane (1.27 g, 3.0 mmol) were added at 0 ^oC. When starting material was consumed, the reaction mixture was filtered through a pad of silica gel and eluted with diethyl ether (50 mL x 3). The combined filtrate was washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated in *vacuo* to give aldehyde **21b,** which was used in next step without further purification.

LiHMDS (0.5 mL, 0.5 mmol, 1.0 M in THF) was added to a solution of sulfone **2** (291.0 mg, 0.5 mmol) in DMF/HMPA (5 mL, v/v 3/1) at -50 ^oC, followed by dropwise addition of a solution of aldehyde **21b** in DMF/HMPA (5 mL, v/v 3/1). The reaction mixture was allowed to warm to room temperature and stirred for 16 h, before it was poured into water (60 mL) and extracted with diethyl ether (100 mL x 3). The combined organic layers were washed with saturated aqueous solution of NH_4Cl (50 mL) and brine (50 mL x 2), dried over $MgSO_4$ and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel column, eluting with 5% ethyl acetate-hexane, to produce **22** as colorless oil (440.0 mg, 75 %). $[\alpha]_D^{25}$ = +6.7 (*c* 1.0, CH_2Cl_2); ^1H NMR (500MHz, $CDCl_3$): δ_H 7.70-7.71 (m, 8H), 7.42-7.30 (m, 12H), 7.15 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.79-5.71 (m, 2H), 5.72 (s, 1H), 5.45-5.40 (m, 1H), 5.29 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.11-5.05 (m, 2H), 4.99 (brs, 1H), 4.96 (d, *J* = 12.0 Hz, 1H), 4.93-4.88 (m, 1H), 4.91 (s, 1H), 4.78 (s, 1H), 4.21 (s, 2H), 4.20-4.16 (m, 1H), 3.99 (t, *J* = 8.9 Hz, 1H), 3.88-3.84 (m, 2H), 3.80 (s, 3H), 3.28-3.24 (m, 1H), 2.24-2.14 (m, 3H), 2.05-2.01 (m, 1H), 1.99-1.90 (m, 4H), 1.86-1.81 (m, 1H), 1.77-1.72 (m, 1H), 1.75 (s, 3H), 1.48-1.44 (m, 1H), 1.47 (s, 3H), 1.39-1.34 (m, 1H), 1.36 (s, 3H), 1.16 (s, 3H), 1.07 (s, 9H), 0.96 (s, 9H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 6H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 165.9, 161.8, 159.1, 143.3, 141.0, 137.3, 136.1, 136.0, 135.9 (2C), 135.1, 134.8, 134.3, 134.2, 134.0, 130.9, 129.9, 129.6, 129.5, 129.4, 129.3, 129.1 (2C), 127.7, 127.5, 127.3 (2C), 127.1, 118.4, 115.8, 114.3, 113.8, 113.7, 107.3, 82.3, 80.8, 78.0, 75.9, 72.5, 70.4, 55.2, 40.9, 40.8, 37.8, 36.4, 36.2, 35.6, 32.7, 28.5, 27.1, 26.9,

26.6, 26.5, 20.2, 20.0, 19.5, 19.4, 19.3 (2C), 15.6, 15.4, 15.2 ppm. HRMS (ESI) for $C_{74}H_{100}NaO_8Si_2$ $[M+Na]^+$: calculated 1195.6854, found 1195.6870.



Compound **22** (130.0 mg, 0.11 mmol) was dissolved in toluene (120 mL, degassed). After the 2nd generation Hoveyda-Grubbs' catalyst (22.7 mg, 0.033 mmol) was added, the reaction was warmed to 80 °C. Three additional portions of the catalyst (each 15.7 mg, 0.025 mmol) were added at the time of 24 h, 48 h and 64 h respectively. After the reaction mixture was stirred for 96 h, it was concentrated in *vacuo* and the residue was purified by flash column chromatography on silica gel column, eluting with 2-5% ethyl acetate-hexane, to produce the macrocycle **1** (64 mg, 51%). $[\alpha]_D^{25}$ = -15.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500MHz, $CDCl_3$): δ_H 7.71-7.64 (m, 8H), 7.43-7.30 (m, 12H), 7.15 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 5.69 (s, 1H), 5.61-5.55 (m, 1H), 5.35 (dd, *J* = 15.6, 8.1 Hz, 1H), 5.29 (d, *J* = 15.6 Hz, 1H), 5.20-5.14 (m, 1H), 4.98 (s, 1H), 4.75 (s, 1H), 4.75-4.72 (m, 1H), 4.17 (d, *J* = 11.0 Hz, 1H), 4.10-4.05 (m, 3H), 3.86-3.81 (m, 2H), 3.80 (s, 3H), 3.21-3.15 (m, 1H), 2.28 (dd, *J* = 14.6, 7.2 Hz, 1H), 2.17(dd, *J* = 15.4, 6.1 Hz, 1H), 2.09-2.05 (m, 2H), 2.00-1.91 (m, 4H), 1.93 (s, 3H), 1.68-1.62 (m, 1H), 1.56-1.51 (m, 1H), 1.47 (s, 3H), 1.37 (s, 3H), 1.32-1.27 (m, 2H), 1.16 (s, 3H), 1.06 (s, 18H), 0.92 (d, *J* = 6.3 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.78 (d, *J* = 6.7 Hz, 6H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 165.8, 160.5, 159.1, 142.6, 136.3, 136.2, 135.9 (2C), 135.1, 134.8, 134.7, 134.3, 133.5, 132.9, 130.9, 129.6, 129.5 (2C), 129.4, 129.3, 129.1, 128.9, 127.6, 127.5, 127.4, 127.2, 118.4, 114.0, 113.8, 107.0, 81.9, 80.1, 77.9, 76.3, 72.2, 70.5, 55.3, 40.5, 40.3, 37.9, 37.7, 37.0, 35.7, 35.3, 34.3, 29.7, 28.5, 27.2, 27.1, 26.7, 22.7, 22.2, 19.8, 19.7, 19.5, 19.4, 15.8, 15.6 ppm. HRMS (ESI) for $C_{72}H_{96}NaO_8Si_2$ $[M+Na]^+$: calculated 1167.6541, found 1167.6563.

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