Total Synthesis and Elucidation of Absolute Configuration of the Diterpene Tonantzitlolone

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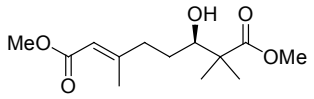
SUPPORTING INFORMATION - EXPERIMENTAL

Supporting Information

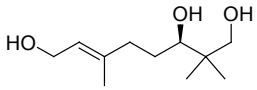
General Methods. ^{1}H NMR, ^{13}C NMR and ^{1}H, ^{13}C-COSY as well as NOESY spectra were measured on Avance 200/DPX (Bruker) with 200 MHz (50 MHz), Avance 400/DPX (Bruker) 400 MHz (100 MHz) and Avance 500/DRX (Bruker) respectively, using tetramethylsilane as the internal standard. If not otherwise noted, $CDCl_3$ is the solvent for all NMR experiments. Multiplicities are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Chemical shift values of ^{13}C NMR spectra are reported as values in ppm relative to residual $CHCl_3$ (77 ppm) or CD_3OD (49) as internal standards. The multiplicities refer to the resonances in the off-resonance spectra and were elucidated using the distortionless enhancement by polarisation transfer (DEPT) spectral editing technique, with secondary pulses at 90° and 135°. Mass spectra were recorded on a type LCT-spectrometer (Micromass) and on a type VG autospec (Micromass). Optical rotations [α] were collected on a Polarimeter 341 (Perkin Elmer) at a wavelength of 589 nm and are given in 10^{-1} deg cm^2 g^{-1}. All solvents used were of reagent grade and were further dried. Reactions were monitored by thin layer chromatography (tlc) on silica gel 60 F^{254} (E. Merck, Darmstadt) and spots were detected either by UV-absorption or by charring with H_2SO_4/4-methoxybenzaldehyde in methanol. Preparative column chromatography was performed on silica gel 60 (E. Merck, Darmstadt).



3

(*E*,6*R*)-Hydroxy-3,7,7-trimethyl-oct-2-enedioic acid dimethylester 3. A flame-dried 3-neck 500 mL round bottom flask equipped with a pressure equalized dropping funnel was charged with *N*-tosylated *L*-valin (7.85 g, 28.9 mmol) and 290 mL of anhydrous CH_2Cl_2. A borane-THF complex solution (28.9 mL, 1 M THF) was added dropwise and the solution was allowed to stir for additional 20 minutes. Then the reaction mixture was cooled to -78°C, and aldehyde **5** (4.52 g, 28.9 mmol) in 30 mL of dry CH_2Cl_2 was introduced, followed by ketene acetal **6** (7.56 g, 43.4 mmol) in 30 mL of dry CH_2Cl_2. After complete addition the solution was warmed slowly to -30°C and *cautiously* terminated with 50 mL of phosphate buffer solution (pH = 7). The mixture was warmed to room temperature and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic solutions were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was treated with hexanes (100 mL) and the solution was filtered to remove the amino acid. The filtrate was concentrated under reduced pressure and taken up in MeOH (50 mL), and a catalytic amount of acetyl chloride was added to cleave the silyl ether. After 15 minutes the solution was concentrated under reduced pressure again and purified by flash chromatography (hexanes/EtOAc, 4:1) to furnish the desired aldol product, 5.45 g (21.1 mmol, 73%), as an oil.

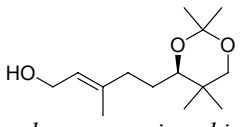
Data are: TLC R_f = 0.17 (hexanes/EtOAc, 4:1); $[\alpha]_D^{20}$ = +20.3° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (dt, *J* = 3.6, 1.2 Hz, 1 H), 3.67 (s, 3 H), 3.65 (s, 3 H), 3.54 (ddd, *J* = 10.8, 6.9, 2.0 Hz, 1 H), 2.69 (d, *J* = 6.9 Hz, 1 H), 2.43 (dddd, *J* = 14.6, 9.7, 4.8, 1.2 Hz, 1 H), 2.17 (dddd, *J* = 14.6, 9.6, 6.7, 1.0 Hz, 1 H), 2.13 (d, *J* = 1.2 Hz, 3 H), 1.58 (dddd, *J* = 13.7, 10.8, 9.7, 6.7, Hz, 1 H), 1.42 (dddd, *J* = 13.7, 9.6, 4.8, 2.0 Hz, 1 H), 1.16 (s, 3 H), 1.15 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 167.1, 159.9, 115.4, 75.8, 51.9, 50.7, 47.0, 37.7, 29.3, 22.2, 20.4, 18.8; IR (neat) ν 3507, 2979, 2951, 1715, 1648, 1435, 1272, 1223, 1146, 1076, 1023, 860; MS (EI) *m/z* (%) 258 (M^+, 28), 243 (25), 226 (33), 211 (38), 195 (55), 176 (46), 157 (59), 144 (65), 125 (100), 102 (100), 97 (81), 87 (67), 70 (98); HRMS (EI) found 258.1466 M^+, calcd 258.1467 for $C_{13}H_{22}O_5$.



7

(*E*,3*R*)-2,6,6-Trimethyl-oct-6-ene-1,3,8-triol 7. A flame-dried 500 mL round bottom flask equipped with a pressure equalized dropping funnel was charged with $LiALH_4$ (4 g, 105 mmol) and 210 mL of anhydrous Et_2O. The reaction mixture was cooled to 0°C, and diester **3** (5.45 g, 21.1 mmol) in 20 mL of anhydrous Et_2O was added dropwise. The mixture was warmed to room temperature in the cold bath and stirred over night. Then H_2O (4 mL) was *cautiously* added, followed by 4 N aqueous NaOH (4 mL) and H_2O (8 mL). After 1 h Na_2SO_4 was added and the mixture was filtered. The residue was washed with EtOAc and the combined organic solutions were concentrated under reduced pressure to deliver the triol, 4.27 g (21.1 mmol, >99%), as an oil.

Data are: tlc R_f = 0.17 (EtOAc); $[\alpha]_D^{20}$ = +23.6° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43-5.46 (m, 1 H), 4.16-4.12 (m, 2 H), 3.57 (d, *J* = 10.8 Hz, 1 H), 3.44 (dd, *J* = 10.6, 1.7 Hz, 1 H), 3.39 (d, *J* = 10.8 Hz, 1 H), 2.27 (ddd, *J* = 14.0, 8.6, 5.3 Hz, 1 H), 2.11-2.07 (m, 1 H), 1.67 (bs, 3 H), 1.66-1.61 (m, 1 H), 1.46 (dddd, *J* = 13.8, 10.6, 8.6, 5.3, Hz, 1 H), 0.89 (s, 3 H), 0.85 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 123.9, 77.9, 71.9, 59.1, 38.5, 36.4, 29.2, 22.5, 18.8, 16.1; IR (neat) ν 3317, 2954, 2873, 1739, 1442, 1381, 1230, 1034, 1000, 932; MS (EI) *m/z* (%) 202 (M^+, 1), 184 (10), 169 (17), 151 (19), 131 (36), 129 (27), 116 (66), 95 (49), 84 (100), 69 (78); HRMS (EI) found 202.1554 M^+, calcd 202.1569 for $C_{11}H_{22}O_3$.

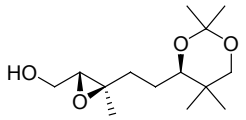


(no compound number was assigned in the manuscript)

(*E*,*R*)-Allyl alcohol. A 250 mL round bottom flask was charged with triol **7** (6.57 g, 32.5 mmol) and 70 mL of anhydrous DMF. 2,2-Dimethoxy propane (20 mL) was added at room temperature, followed by a catalytic amount of *p*TsOH (62 mg, 0.326 mmol). After 30 minutes H_2O (20

mL) was added to terminate the reaction and to cleave the mixed acetal formed as byproduct. Finally K_2CO_3 was added and the layers were separated. The aqueous phase was extracted with MTBE (5 x 25 mL), and the combined organic solutions were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes/EtOAc, 3:1) to afford the title compound, 7.46 g (30.8 mmol, 95%), as an oil.

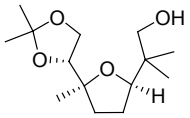
Data are: tlc R_f = 0.41 (hexanes/EtOAc, 2:1); $[\alpha]_D^{20}$ = +25.1° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 5.36 (app dt, *J* = 6.8, 1.3 Hz, 1 H), 4.08 (app d, *J* = 6.8, 2 H), 3.64 (d, *J* = 11.4 Hz, 1 H), 3.54 (dd, *J* = 10.3, 1.7 Hz, 1 H), 3.23 (d, *J* = 11.4 Hz, 1 H), 2.19-2.15 (m, 1 H), 2.01-1.97 (m, 1 H), 1.65 (s, 3 H), 1.58 (dddd, *J* = 13.7, 9.1, 7.5, 1.7 Hz, 1 H), 1.40 (s, 3 H), 1.38-1.34 (m, 1 H), 1.34 (s, 3 H), 0.98 (s, 3 H), 0.73 (s, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 139.2, 125.4, 100.0, 77.5, 73.0, 59.4, 36.9, 33.7, 30.0, 28.2, 21.9, 19.4, 18.5, 16.1; IR (neat) ν 3420, 2990, 2951, 2856, 1463, 1391, 1378, 1360, 1263, 1228, 1198, 1171, 1157, 1102, 1072, 1050, 1004, 937, 921, 904, 848.



8

Epoxide 8. A flame-dried 3-neck 250 mL round bottom flask equipped with a pressure equalized dropping funnel was charged with powdered 4Å molecular sieves (816 mg) and 40 mL of dry CH_2Cl_2. The solution was cooled to -15 to -20°C, and then Ti(*i*PrO)$_4$ (296 µL, 1 mmol) was added, followed by (-)-diethyl-*D*-tartrate (205 µL, 1.2 mmol) in 7 mL of dry CH_2Cl_2 and *t*butyl hydroperoxide (3.64 mL, 5.5 M in CH_2Cl_2). After 30 minutes the suspension was cooled to -25°C before the above synthesized allylic alcohol (2.42 g, 10 mmol) dissolved in 50 mL of dry CH_2Cl_2 was introduced dropwise via a dropping funnel. The reaction was allowed to stir for 16 h at -25°C and then filtered through a plug of celite. The filtrate was mixed with 20 mL of H_2O and warmed to room temperature, then 30 mL of brine-saturated aqueous NaOH (30%) was added and the mixture was vigorously stirred for 1 h. The aqueous layer was separated and extracted with CH_2Cl_2 (5 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (hexanes/EtOAc, 3:1) afforded the title compound as an oil along with a small amount of recovered starting material. The procedure was repeated twice with allylic alcohol (2.42 g, 2.2 g, Σ = 7.04 g, 29 mmol) as described above. A final epoxidation was carried out with the combined recovered starting materials (1.22 g) to deliver an overall yield of 5.97 g (23.1 mmol, 80%).

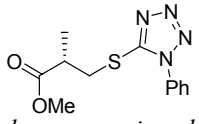
Data are: tlc R_f = 0.27 (hexanes/EtOAc, 2/1); $[\alpha]_D^{20}$ = +22.9° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 3.70 (dd, *J* = 12.2, 5.0 Hz, 1 H), 3.65 (d, *J* = 11.4 Hz, 1 H), 3.61 (dd, *J* = 12.2, 6.3 Hz, 1 H), 3.56 (dd, *J* = 9.9, 1.8 Hz, 1 H), 3.23 (d, *J* = 11.4 Hz, 1 H), 2.91 (dd, *J* = 6.3, 5.0 Hz, 1 H), 1.89-1.80 (m, 1 H), 1.59-1.50 (m, 1 H), 1.42 (bs, 3 H), 1.41-1.35 (m, 2 H), 1.33 (bs, 3 H), 1.26 (s, 3 H), 0.99 (s, 3 H), 0.75 (s, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 100.0, 78.0, 72.9, 64.2, 61.8, 61.7, 35.9, 33.8, 30.0, 25.7, 21.9, 19.4, 18.4, 17.0; IR (neat) ν 3427, 2990, 2958, 2862, 1462, 1392, 1378, 1360, 1262, 1198, 1157, 1105, 1078, 1041, 1009, 920, 899, 855.



9

South fragment 9. A 250 mL round bottom flask was charged with epoxide **8** (2.72 g, 10.5 mmol) and 100 mL of dry CH_2Cl_2. A solution of ethylene glycol (704 µL, 12.6 mmol) in 55 mL of dry CH_2Cl_2/THF (10:1) was added, followed by dry *p*TsOH (181 mg, 1.05 mmol). After 30 minutes, complete conversion of the starting material was observed before 2,2-dimethoxy propane (17 mL) was introduced. The solution was allowed to stir for 16 h and then terminated by addition of saturated $NaHCO_3$ solution (30 mL). The aqueous layer was separated and extracted with MTBE (5 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (hexanes/EtOAc, 2:1) afforded the title compound, 2.19 g (8.48 mmol, 81%), as an oil.

Data are: tlc R_f = 0.34 (hexanes/EtOAc, 2/1); $[\alpha]_D^{20}$ = -4.5° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02-3.98 (m, 2 H), 3.83 (dd, *J* = 9.4, 6.1 Hz, 1 H), 3.76 (dd, *J* = 6.8, 4.6 Hz, 1 H), 3.47 (dd, *J* = 11.3, 6.9 Hz, 1 H), 3.40 (dd, *J* = 11.3, 5.1 Hz, 1 H), 3.16 (dd, *J* = 6.8, 5.3 Hz, 1 H), 2.00 (ddd, *J* = 12.3, 8.5, 3.7 Hz, 1 H), 1.84-1.76 (m, 2 H), 1.63 (dt, *J* = 12.3, 8.7 Hz, 1 H), 1.43 (bs, 3 H), 1.33 (bs, 3 H), 1.17 (s, 3 H), 0.90 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.4, 86.5, 83.3, 80.1, 71.7, 65.7, 37.3, 33.8, 27.1, 26.2, 24.8, 22.9, 22.1; IR (neat) ν 3458, 2965, 2873, 1457, 1370, 1261, 1211, 1156, 1058, 900, 854; HRMS (ESI) found 281.1738 $[M + Na]^+$, calcd 281.1729 for $C_{19}H_{32}O_3Na^+$.

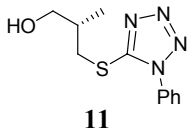


(no compound number was assigned in the manuscript)

(2*S*)-Methyl-3-(1-phenyl-1*H*-tetrazol-5-ylsulfanyl)-propionic acid methyl ester. A flame-dried 100 mL round bottom flask equipped with a pressure equalized dropping funnel was charged with (-)-methyl D-β-hydroxyisobutyrate **10** (1 g, 8.47 mmol), triphenylphosphine (3.33 g, 12.7 mmol) and 20 mL of anhydrous THF. The solution was cooled to 0°C and a solution of DIAD (2.57 g, 12.7 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (2.26 g, 12.7 mmol) in 20 mL of anhydrous THF was added dropwise via the dropping funnel. After warming to room temperature within 2 h the solution was stirred for additional 3 h. Then 40 mL H_2O and 100 mL MTBE were added. The aqueous layer was separated and extracted with MTBE (2 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (hexanes/EtOAc,

2.5:1) afforded the title compound, 2.31 g (8.29 mmol, 98%), as an oil.

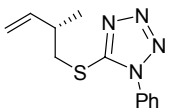
Data are: tlc R_f = 0.33 (hexanes/EtOAc, 2.5:1); $[\alpha]_D^{20}$ = -89.5° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.53 (m, 5 H), 3.70 (s, 3 H), 3.58 (dm, *J* = 6.9 Hz, 2 H), 3.16-3.06 (m, 1 H), 1.35 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 154.0, 133.4, 130.0, 129.7, 123.6, 51.9, 39.4, 35.5, 16.8; IR (neat) ν 3068, 2979, 2953, 2879, 2854, 1732, 1597, 1500, 1460, 1434, 1411, 1387, 1357, 1302, 1279, 1239, 1220, 1171, 1114, 1090, 1075, 1042, 1015, 981, 916, 860, 825, 762, 694; MS (EI) *m/z* (%) 278 (M^+, 14), 204 (29), 162 (39), 145 (50), 133 (39), 120 (32), 118 (71), 101 (17), 85 (14), 77 (20), 76 (100), 73 (19). HRMS (EI) found 278.0836 M^+, calcd 278.0838 for $C_{12}H_{14}N_4SO_2$.



11

(2*S*)-Methyl-3-(1-phenyl-1*H*-tetrazol-5-ylsulfanyl)-propan-1-ol 11. A 500 mL round bottom flask equipped with a pressure equalized dropping funnel was charged with the thioether (11.8 g, 42.4 mmol) described above and 150 mL of anhydrous THF. The solution was then cooled to 0°C and $LiEt_3BH$ (93 mL, 1.0 M THF) was cautiously added during 1 h via dropping funnel. After an additional hour 70 mL of saturated NH_4Cl solution was added. THF was distilled off under reduced pressure and the resulting mixture was extracted with CH_2Cl_2 (3 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. Flash chromatography (hexanes/EtOAc, 2.5:1) afforded the title compound, 9.91 g (39.6 mmol, 93%), as an oil.

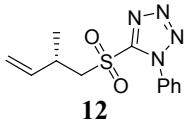
Data are: tlc R_f = 0.09 (hexanes/EtOAc, 2.5:1); $[\alpha]_D^{20}$ = -10.4° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.52 (m, 5 H), 3.67 (dd, *J* = 11.5, 4.3 Hz, 2 H), 3.55-3.44 (m, 3 H), 2.27-2.15 (m, 1 H), 1.06 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 133.5, 130.2, 129.8, 123.9, 64.6, 36.8, 36.3, 15.9; IR (neat) ν 3391, 3066, 2960, 2930, 2874, 2337, 1596, 1498, 1460, 1409, 1385, 1317, 1278, 1240, 1176, 1089, 1073, 1038, 1014, 984, 941, 915, 841, 814, 759, 713, 685, 552, 516; MS (EI) *m/z* (%) 250 (M^+, 6), 220 (66), 208 (22), 203 (17), 179 (42), 178 (91), 163 (27), 150 (36), 135 (45), 119 (47), 118 (100), 117 (68), 104 (83), 91 (54), 77 (75), 65 (30); HRMS (EI) found 250.0894 M^+, calcd 250.0888 for $C_{11}H_{14}N_4SO_2$.



(no compound number was assigned in the manuscript)

5-[(2*S*)-Methyl-but-3-enylsulfanyl]-1-phenyl-1*H*-tetrazole. A 250 mL round bottom flask was charged with alcohol **11** (2.28 g, 9.1 mmol) and 80 mL of anhydrous CH_2Cl_2. The solution was then cooled to 0°C and $NaHCO_3$ (2.28 g, 27.3 mmol) was added, followed by Dess-Martin periodinane (4.96 g, 11.7 mmol) in portions. After 30 minutes the mixture is poured in 100 mL of saturated $NaHCO_3$ solution and diluted with 200 mL hexanes. The organic layer was washed twice with $NaHCO_3$ solution (100 mL), and the combined aqueous layers were reextracted once with hexanes (100 mL). The combined hexane solutions were dried over Na_2SO_4, filtered, and concentrated to furnish the crude aldehyde. A flame-dried 3-neck 250 mL round bottom flask equipped with a pressure equalized dropping funnel was charged with methyl triphenylphosphonium bromide (6.5 g, 18.2 mmol) and 100 mL of anhydrous THF. This mixture was cooled to 0°C and LDA (9 mL, 2 M THF/heptane) was introduced via syringe in portions. After 30 minutes the crude aldehyde, dissolved in 25 mL of anhydrous THF, was added slowly via dropping funnel. After 30 minutes the reaction was terminated with 50 mL of saturated NH_4Cl solution. THF was distilled of in vacuum and the resulting mixture was extracted with CH_2Cl_2 (3 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. Flash chromatography (hexanes/EtOAc, 10:1) delivers the desired olefin, 1.70 g (6.9 mmol, 76%), as an oil.

Data are: tlc R_f = 0.50 (hexanes/EtOAc, 2.5:1); $[\alpha]_D^{20}$ = -15.9° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.49 (m, 5 H), 5.75 (ddd, *J* = 17.3, 10.2, 7.2 Hz, 1 H), 5.12-5.02 (m, 2 H), 3.42 (d, *J* = 2.5 Hz, 1 H), 3.41 (d, *J* = 3.1 Hz, 1 H), 2.68 (app sept, *J* = 7.0 Hz, 1 H), 1.17 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 140.9, 133.8, 130.1, 129.8, 123.9, 115.3, 39.5, 37.4, 19.3; IR (neat) ν 3073, 2966, 2930, 2870, 2361, 2338, 1752, 1737, 1641, 1597, 1499, 1459, 1410, 1386, 1332, 1316, 1279, 1238, 1176, 1159, 1088, 1075, 1055, 1041, 1014, 994, 918, 860, 821, 760, 694, 608, 553, 521, 503; MS (EI) *m/z* (%) 246 (M^+, 74), 231 (20), 203 (27), 199 (95), 185 (19), 178 (34), 176 (53), 171 (18), 163 (73), 150 (30), 145 (60), 135 (74), 117 (100), 104 (29), 101 (74), 91 (74), 85 (32), 77 (86), 69 (28), 67 (74), 65 (74); HRMS (EI) found 246.0934 M^+, calcd 246.0939 for $C_{12}H_{14}N_4S$.

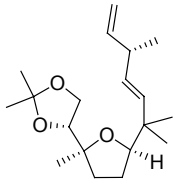


12

5-[(2*S*)-methyl-but-3-ene-1-sulfonyl]-1-phenyl-1*H*-tetrazole 12. A 250 mL round bottom flask was charged with the olefin from the Wittig reaction (2.81 g, 11.4 mmol) and 75 mL of EtOH. The solution was then cooled to 0°C and $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (1.41 g, 1.14 mmol) in 35% H_2O_2 (10 mL, 114 mmol) was added. The reaction was warmed to room temperature and stirred for 24 h. Then 75 mL H_2O and 150 mL CH_2Cl_2 were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL), and the combined organic solutions were dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (hexanes/EtOAc, 2.5:1) furnished the desired sulfon, 2.92 g (10.5 mmol, 92%), as a colourless solid.

Data are: tlc R_f = 0.49 (hexanes/EtOAc, 2.5:1); mp = 62°C; $[\alpha]_D^{20}$ = -19.4° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.55 (m, 5 H), 5.74 (ddd, *J* = 17.3, 10.3, 7.5 Hz, 1 H),

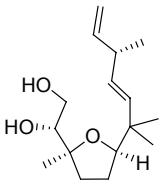
5.09 (dm, J = 17.3 Hz, 1 H), 5.02 (dm, J = 10.3 Hz, 1 H), 3.90 (dd, J = 14.6, 7.1 Hz, 1 H), 3.68 (dd, J = 14.6, 6.4 Hz, 1 H), 3.02 (app sep, J = 7.0 Hz, 1 H), 1.24 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 139.5, 133.0, 131.4, 129.6, 125.2, 115.7, 61.3, 32.7, 19.9; IR (neat) ν 3081, 2971, 2934, 2873, 1643, 1595, 1497, 1460, 1422, 1399, 1347, 1295, 1255, 1205, 1152, 1098, 1075, 1045, 1015, 995, 921, 876, 808, 763, 690, 623, 574, 545, 523; MS (EI) *m/z* (%) 278 (M^+, 39), 145 (55), 131 (30), 123 (12), 119 (35), 118 (100), 117 (68), 91 (37), 77 (55), 69 (72), 68 (29), 67 (20), 65 (55); HRMS (EI) found 278.0837 M^+, calcd 278.0838 for $C_{12}H_{14}N_4SO_2$; Anal. calcd for $C_{12}H_{14}N_4SO_2$: C, 51.78, H 5.07, N 20.13, found: C, 51.47, H 5.10, N 20.09.



13

Julia product 13. A 100 mL round bottom flask was charged with alcohol **9** (1.64 g, 6.35 mmol) and 40 mL of dry CH_2Cl_2. Subsequently powdered 4Å molecular sieves (1.04 g), NMO (1.11 g, 9.52 mmol) and TPAP (112 mg, 0.318 mmol) were added at room temperature. After 1 h, the reaction mixture was filtered over a plug of silica gel, washed, and the resulting filtrate was concentrated under reduced pressure. The obtained aldehyde (1.37 g, 5.35 mmol, 84%) was directly subjected to the following olefination prodcedure without further purification. A flame-dried 100 mL round bottom flask was charged with sulfone **12** (1.93 g, 6.95 mmol) and 35 mL of dry THF. The solution was cooled to -78°C, then LDA (4 mL, 2 M THF/heptane) was added dropwise via syringe. After 20 minutes, the aldehyde mentioned above (1.37 g, 5.35 mmol) in 5 mL of dry THF was added. The solution was allowed to warm to room temperature and stirred for 16 h, and was then refluxed over 4 h before cooling to room temperature. The reaction mixture was terminated with half-saturated NH_4Cl solution (20 mL), and the aqueous layer was extracted with MTBE (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (hexanes/EtOAc, 10:1) afforded the title compound, 1.50 g (4.86 mmol, 91%, 76% over 2 steps), as an oil.

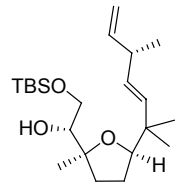
Data are: tlc R_f = 0.46 (hexanes/EtOAc 10/1); $[\alpha]_D^{20}$ = +25.4° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddd, J = 17.1, 10.4, 6.6 Hz, 1 H), 5.43 (dd, J = 15.9, 0.9 Hz, 1 H), 5.31 (dd, J = 15.9, 6.5 Hz, 1 H), 4.90-5.02 (m, 2 H), 3.87-4.03 (m, 3 H), 3.65-3.70 (m, 1 H), 2.77-2.87 (m, 1 H), 1.85-1.97 (m, 1 H), 1.72-1.80 (m, 1 H), 1.59-1.69 (m, 2 H), 1.42 (s, 3 H), 1.33 (s, 3 H), 1.16 (s, 3 H), 1.08 (d, J = 6.9 Hz, 3 H), 0.99 (s, 3 H), 0.94 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 135.2, 131.6, 112.5, 109.1, 86.3, 82.5, 80.0, 65.6, 40.5, 38.9, 35.9, 26.9, 26.3, 24.9, 24.5, 24.3, 21.1, 20.1; IR (neat) ν 3081, 2964, 2930, 2872, 1784, 1715, 1635, 1602, 1494, 1454, 1380, 1369, 1262, 1210, 1155, 1069, 1019, 995, 979, 911, 855, 798, 747, 699; HRMS (ESI) found 331.2244 $[M + Na]^+$, calcd 331.2249 for $C_{19}H_{32}O_3Na^+$.



(no compound number was assigned in the manuscript)

1,2-Diol. A 100 mL round bottom flask was charged with Julia product **13** (640 mg, 2.07 mmol) and 30 mL of MeOH. After addition of *p*TsOH (79 mg, 0.415 mmol) the solution was warmed to 50°C for 18 h and then cooled to room temperature. The reaction was stopped by addition of saturated $NaHCO_3$ solution (20 mL), and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried over Na_2SO_4 and the crude product was purified over a short column (hexanes/EtOAc, 10:1 → EtOAc) to provide the desired diol, 405 mg (1.51 mmol, 73%), as an oil, along with recovered starting material, 168 mg (545 μmol, >26%).

Data are: tlc R_f = 0.04 (hexanes/ EtOAc, 10:1); $[\alpha]_D^{20}$ = +9.9° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddd, J = 17.1, 10.4, 6.6 Hz, 1 H), 5.44 (d, J = 15.9 Hz, 1 H), 5.38 (dd, J = 15.9, 5.8 Hz, 1 H), 5.03-4.91 (m 2 H), 3.74-3.63 (m, 3 H), 3.56 (dd, J = 10.8, 7.0 Hz, 1 H), 2.89-2.79 (m, 1 H), 2.75 (br s, 2 H), 1.97-1.78 (m, 2 H), 1.70-1.59 (m, 1 H), 1.55-1.46 (m, 1 H), 1.15 (s, 3 H), 1.09 (d, J = 6.9 Hz, 3 H), 1.04 (s, 3 H), 0.96 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 134.4, 132.7, 112.7, 84.9, 84.1, 76.6, 63.2, 40.4, 38.9, 32.5, 26.9, 24.6, 24.5, 22.1, 20.0; HRMS (ESI) found 291.1949 $[M + Na]^+$, calcd 291.1936 for $C_{16}H_{28}O_3Na^+$.

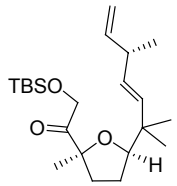


(no compound number was assigned in the manuscript)

TBS-alcohol. A 100 mL round bottom flask was charged with the deprotected 1,2-diol (660 mg, 2.46 mmol) and 30 mL of dry CH_2Cl_2. Then imidazole (330 mg, 4.85 mmol) was added, followed by TBS-Cl (580 mg, 3.85 mmol) and DMAP (15 mg, 0.123 mmol). After 30 minutes the reaction was terminated by addition of saturated NH_4Cl solution (10 mL). The aqueous layer was extracted once with CH_2Cl_2 (10 mL), and the combined organic solutions were dried over Na_2SO_4 and concentrated under reduced pressure. Filtration over silica gel (hexanes/EtOAc, 10:1) afforded the TBS-protected alcohol, 929 mg (2.43 mmol, 99%), as an oil.

Data are: tlc R_f = 0.49 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = +21.0° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddd, J = 17.1, 10.4, 6.5 Hz, 1 H), 5.43 (dd, J = 15.9, 0.6 Hz, 1 H), 5.33 (dd, J =15.9, 6.5 Hz, 1 H), 5.00-4.90 (m 2

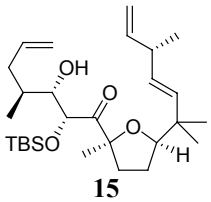
H), 3.76 (dd, *J* = 10.3 Hz, 3.9 Hz, 1 H), 3.69 (dd, *J* = 8.0, 6.7 Hz, 1 H), 3.62 (dd, *J* = 10.3, 7.0 Hz, 1 H), 3.51 (ddd, *J* = 7.0, 3.9, 2.5 Hz, 1 H), 2.82 (app sex, *J* = 6.5 Hz, 1 H), 2.64 (d, *J* = 2.5 Hz, 1 H), 2.02-1.94 (m, 1 H), 1.84-1.75 (m, 1 H), 1.67-1.50 (m, 2 H), 1.14 (s, 3 H), 1.07 (d, *J* = 6.9 Hz, 3 H), 1.01 (s, 3 H), 0.95 (s, 3 H), 0.90 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 135.0, 132.1, 112.6, 85.5, 83.7, 76.6, 63.7, 40.4, 39.0, 34.2, 26.9, 25.9, 24.5, 24.3, 21.7, 20.1, 18.3, -5.36, -5.37; IR (neat) ν 3575, 3080, 2958, 2930, 2858, 2711, 1636, 1463, 1408, 1385, 1362, 1327, 1253, 1096, 1061, 1024, 994, 938, 910, 834, 776, 741, 677; HRMS (ESI) found 405.2817 $[M + Na]^+$, calcd 408.2801 for $C_{22}H_{42}O_3SiNa^+$.



14

TBS-ketone 14. A 100 mL round bottom flask was charged with the TBS protected alcohol (875 mg, 2.29 mmol) and 20 mL of dry CH_2Cl_2. The solution was cooled to 0°C, then Dess-Martin periodinane (1.5 g, 3.54 mmol) was added. After addition the reaction mixture was warmed to room temperature and stirred for 2 h, before saturated $NaHCO_3$ solution (20 mL) and $Na_2S_2O_3$ solution (10 mL) were added. The aqueous layer was separated and extracted once with CH_2Cl_2 (10 mL). The combined organic solutions were dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (hexanes/EtOAc, 40:1) afforded the desired ketone, 828 mg (2.17 mmol, 95%), as an oil.

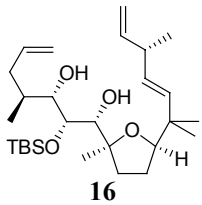
Data are: tlc R_f = 0.53 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = -12.3° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (ddd, *J* = 17.1, 10.4, 6.6 Hz, 1 H), 5.42 (d, *J* = 16.0 Hz, 1 H), 5.34 (dd, *J* = 16.0, *J* = 6.6 Hz, 1 H), 5.01-4.90 (m 2 H), 4.69 (br s, 2 H), 3.75 (dd, *J* = 8.2, 6.1 Hz, 1 H), 2.82 (ps sex, *J* = 6.6 Hz, 1 H), 2.03-1.98 (m, 1 H), 1.85-1.72 (m, 2 H), 1.58-1.49 (m, 1 H), 1.29 (s, 3 H), 1.07 (d, *J* = 6.9 Hz, 3 H), 1.03 (s, 3 H), 0.99 (s, 3 H), 0.92 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6, 143.1, 134.7, 132.2, 112.7, 87.8, 86.8, 66.5, 40.5, 38.8, 35.8, 26.4, 25.8, 24.3, 24.2, 23.8, 20.1, 18.6, -5.4, -5.5; IR (neat) ν 3081, 2958, 2929, 2857, 1736, 1636, 1463, 1421, 1387, 1363, 1253, 1160, 1100, 1047, 1002, 938, 912, 835, 777, 735, 681; HRMS (ESI) found 387.2907 $[M + Li]^+$, calcd 387.2902 for $C_{22}H_{40}O_3SiLi^+$.



15

Aldol product 15. A 100 mL round bottom flask was charged with the alcohol precursor from aldehyde **B**[6] (700 mg, 7.13 mmol) and 40 mL of dry CH_2Cl_2. The solution was cooled to 0°C and Dess-Martin periodinane (3.56 g, 8.39 mmol) was added. After 15 minutes the mixture was warmed to room temperature. After 1 h an additional small amount Dess-Martin periodinane was added, and after 2 h the reaction was terminated by addition of an aqueous 10% $Na_2S_2O_3$/saturated $NaHCO_3$ solution (50 mL). The organic layer was separated and successively washed with this solution (4 x 50 mL). The combined aqueous phases were then reextracted once with CH_2Cl_2 (25 mL), and the combined organic solutions were dried over $MgSO_4$ and concentrated cautiously under reduced pressure (p = 600 mbar). The volatile aldehyde obtained was directly subjected to the following aldol prodcedure. A 100 mL round bottom flask was charged with ketone **14** (650 mg, 1.71 mmol) and 40 mL of dry THF. The solution was cooled to -78°C, before KHMDS (3.42 mL, 0.5 M toluene) was introduced dropwise. After 30 minutes the aldehyde **B** in dry THF (5 mL) was added and the solution was stirred for 2 h. The reaction was then terminated by careful addition of MeOH, followed by saturated NH_4Cl solution (10 mL). The flask was warmed to room temperature in the cold bath, then the aqueous layer was separated and extracted with MTBE (3x 10 mL). The combined organic solutions were dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (hexanes/EtOAc, 40:1) furnished the desired aldol product, 807 mg (1.69 mmol, 99%), as an oil.

Data are: tlc R_f = 0.42 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = -43.6° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87-5.74 (m, 1 H), 5.76 (ddd, *J* = 17.1, 10.4, 6.5 Hz, 1 H), 5.44 (d, *J* = 16.1 Hz, 1 H), 5.35 (dd, *J* = 16.1, 6.7 Hz, 1 H), 5.08 (br s, 1 H), 5.08-4.89 (m, 4 H), 3.88 (t, *J* = 10.6 Hz, 1 H), 3.79 (dd, *J* = 7.8, 6.8 Hz, 1 H), 2.80 (app hex, *J* = 6.7 Hz, 1 H), 2.61-2.52 (m, 1 H), 2.00-1.69 (m, 6 H), 1.56-1.45 (m, 1 H), 1.34 (s, 3 H), 1.06 (d, *J* = 6.8 Hz, 3 H), 1.03 (s, 3 H), 1.00 (s, 3 H), 0.96 (d, *J* = 6.8 Hz, 3 H), 0.92 (s, 9 H), 0.10 (s, 3 H), -0.03 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.7, 143.1, 137.2, 134.8, 132.2, 116.1, 112.7, 88.6, 86.3, 76.2, 75.0, 40.5, 38.8, 37.27, 37.26, 36.2, 25.9, 25.6, 24.2, 24.05, 24.03, 20.1, 18.5, 15.9, -4.2, -5.3; IR (neat) ν 3572, 3077, 2959, 2930, 2858, 1727, 1638, 1462, 1387, 1363, 1253, 1214, 1160, 1100, 1043, 1022, 999, 967, 909, 860, 836, 807, 777, 672; HRMS (ESI) found 479.3577 $[M + H]^+$, calcd 479.3557 for $C_{28}H_{50}O_4SiH^+$.

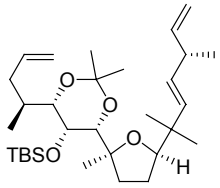


16

***Syn*-diol 16.** A 25 mL round bottom flask was charged with aldol product **15** (200 mg, 418 μmol) and 10 mL of anhydrous CH_2Cl_2 and cooled to –78°C, before DIBAL-H (2.1 mL, 1 M hexane) was added. Additional DIBAL-H (0.8 mL) was added after 2.5 h, and a final portion (0.5 mL) 30 minutes thereafter. After 4.5 h the reaction mixture was allowed to warm to -30°C and was then terminated with H_2O (340 μL). 340 μL of a 4 M NaOH solution was

introduced after reaching room temperature, followed by H_2O (680 µL). After 15 minutes Na_2SO_4 was added and the mixture was filtered. The residue was washed and the combined organic solutions were concentrated under reduced pressure. Flash chromatography delivered the diol, 140 mg (291 µmol, 70%), as an oil, along with recovered starting material (56 mg, 117 µmol, 28%).

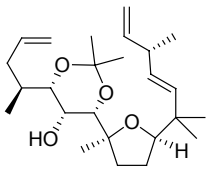
Data are: tlc R_f = 0.45 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = +27.7° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86-5.72 (m, 1 H), 5.77 (ddd, *J* = 17.1, 10.4, 6.7 Hz, 1 H), 5.43 (d, *J* = 15.9, 1 H), 5.37 (dd, *J* = 15.9, 5.9 Hz, 1 H), 5.08-4.89 (m, 4 H), 3.78 (d, *J* = 6.5 Hz, 1 H), 3.71 (dd, *J* = 8.7, 6.2 Hz, 1 H), 3.46 (dd, *J* = 4.5 u. 6.5 Hz, 1 H), 3.17 (t, *J* = 8.6 Hz, 1 H), 2.88 (d, *J* = 8.6 Hz, 1 H), 2.84 (app hex, *J* = 6.3 Hz, 1 H), 2.73 (d, *J* = 4.5 Hz, 1 H), 2.53-2.44 (m, 1 H), 2.14-2.06 (m, 1 H), 1.97 (dt, *J* = 13.7, 8.3 Hz, 1 H), 1.87-1.74 (m, 2 H), 1.72-1.55 (m, 2 H), 1.21 (s, 3 H), 1.08 (d, *J* = 6.9 Hz, 3 H), 1.03 (s, 3 H), 0.95 (s, 3 H), 0.90 (s, 9 H), 0.83 (d, *J* = 6.8 Hz, 3 H), 0.15 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 137.2, 134.4, 132.8, 116.1, 112.7, 85.5, 83.9, 77.3, 73.7, 73.6, 40.4, 38.7, 37.1, 35.6, 35.3, 27.3, 26.2, 24.6, 24.5, 21.5, 20.0, 18.6, 15.8, -3.5, -4.76; IR (neat) ν 3551, 3077, 2959, 2930, 2857, 1639, 1462, 1386, 1362, 1329, 1249, 1215, 1116, 1071, 1037, 994, 959, 937, 910, 892, 858, 834, 802, 776, 681; HRMS (ESI) found 481.3733 $[M + H]^+$, calcd 481.3713 for $C_{28}H_{53}O_4SiH^+$.



(no compound number was assigned in the manuscript)

1,3-Acetonide. A 25 mL round bottom flask was charged with the 1,3-diol **16** (56 mg, 117 µmol) and 3 mL of 2,2-dimethoxy propane. *p*TsOH (8.5 mg, 44.7 µmol) was added, and after 4 h the reaction was stopped by addition of 3 mL of saturated $NaHCO_3$ solution. The solution was transferred to a separating funnel and extracted twice with CH_2Cl_2 (5 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. A short filtration over silica gel (hexanes/EtOAc, 40:1) afforded the desired product, 60 mg (115 µmol, 99%), as an oil.

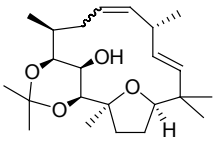
Data are: tlc R_f = 0.70 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = +7.5° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79-5.69 (m, 1 H), 5.78 (ddd, *J* = 17.1, 10.3, 6.5 Hz, 1 H), 5.41 (dd, *J* = 15.9, 0.6 Hz, 1 H), 5.30 (dd, *J* = 15.9, 6.5 Hz, 1 H), 5.05-4.91 (m, 4 H), 3.78 (dd, *J* = 8.3, 4.6 Hz, 1 H), 3.74 (s, 1 H), 3.52 (s, 1 H), 3.18 (d, *J* = 9.7 Hz, 1 H), 2.82 (ps hex, *J* = 6.5 Hz, 1 H), 2.37-2.27 (m, 1 H), 1.98-1.85 (m, 3 H), 1.72-1.61 (m, 1 H), 1.60-1.54 (m, 2 H), 1.46 (s, 3 H), 1.39 (s, 3 H), 1.22 (s, 3 H), 1.07 (d, *J* = 6.9 Hz, 3 H), 0.99 (s, 3 H), 0.94 (s, 3 H), 0.91 (s, 9 H), 0.81 (d, *J* = 6.5 Hz, 3 H), 0.10 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 136.7, 135.6, 131.5, 116.2, 112.5, 99.1, 85.1, 84.4, 80.7, 78.3, 66.0, 40.5, 39.6, 36.3, 33.8, 31.4, 29.5, 26.4, 26.3, 24.8, 23.8, 21.2, 20.2, 19.1, 18.9, 15.3, -1.6, -2.3; IR (neat) ν 3077, 2961, 2930, 2892, 2857, 2708, 1826, 1638, 1462, 1414, 1377, 1305, 1252, 1198, 1159, 1101, 1058, 1029, 979, 936, 909, 860, 834, 804, 771, 725, 696, 675; HRMS (ESI) found 521.4025 $[M + H]^+$, calcd 521.4026 for $C_{31}H_{56}O_4SiH^+$.



(no compound number was assigned in the manuscript)

2-deprotected 1,3-Acetonide. A 25 mL round bottom flask was charged with the TBS-protected acetonide (59 mg, 113 µmol) and 1 mL of anhydrous THF. TBAF (158 mg, 501 µmol) in 3 mL of anhydrous THF was added, and after 16 h the reaction was stopped by addition of 3 mL of saturated NH_4Cl solution. The solution was directly filtered through a short column charged with silica gel (hexanes/EtOAc, 40:1) to afford the desired alcohol, 46 mg (113 µmol, >99%), as an oil.

Data are: tlc R_f = 0.48 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = +21.7° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84-5.74 (m, 1 H), 5.78 (ddd, *J* = 17.0, 10.5 u. 6.9 Hz, 1 H), 5.49 (dd, *J* = 15.9, 0.6 Hz, 1 H), 5.28 (dd, *J* = 15.9, 6.9 Hz, 1 H), 5.04-4.87 (m, 4 H), 4.09 (d, *J* = 2.6 Hz, 1 H), 3.80-3.76 (m, 1 H), 3.71 (dd, *J* = 8.0 u. 7.1 Hz, 1 H), 3.47 (s, 1 H), 3.24 (d, *J* = 9.5 Hz, 1 H), 2.81 (app hex, *J* = 7.0 Hz, 1 H), 2.42-2.33 (m, 1 H), 2.14-1.90 (m, 3 H), 1.76-1.65 (m, 2 H), 1.57-1.48 (m, 1 H), 1.45 (s, 3 H), 1.36 (s, 3 H), 1.26 (s, 3 H), 1.05 (d, *J* = 6.9 Hz, 3 H), 1.00 (s, 3 H), 0.99 (s, 3 H), 0.91 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 136.8, 136.1, 131.2, 116.4, 112.3, 98.8, 86.8, 84.7, 76.5, 75.6, 63.7, 40.5, 39.1, 36.8, 35.2, 32.4, 29.7, 26.9, 24.7, 23.7, 23.2, 20.2, 18.9, 14.3; IR (neat) ν 3478, 3076, 2968, 2934, 2872, 1729, 1638, 1462, 1377, 1262, 1202, 1175, 1156, 1120, 1086, 1062, 1025, 993, 982, 910, 863, 814; HRMS (ESI) found 429.2985 $[M + Na]^+$, calcd 429.2981 for $C_{25}H_{42}O_4Na^+$.

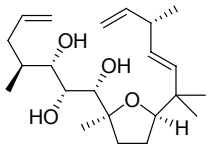


17

Metathesis product 17. A 50 mL round bottom flask with a reflux condenser was charged with the deprotected alcohol (22 mg, 54.1 µmol) and 27 mL of anhydrous CH_2Cl_2. Then Grubbs II catalyst (4.6 mg, 5.42 µmol) was added and the reaction was refluxed over 2h before cooling to room temperature. The solution was saturated with air and silica gel (100 mg) was added. After concentration the resulting solid was purified by flash column chromatography (hexanes/EtOAc, 10:1) to afford the macrocycle **17**, 14.5 mg (38.3 µmol, 71%), as a colourless solid (*Z*:*E* ≈ 6:1).

Data are: tlc R_f = 0.43 (hexanes/EtOAc, 10:1); mp = 138°C; $[\alpha]_D^{20}$ = +37.2° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (*Z*-isomer) 5.60 (d, *J* = 15.6 Hz, 1 H), 5.28-5.17 (m, 3 H),

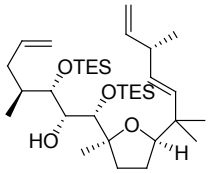
3.92 (d, J = 11.3 Hz, 1 H), 3.69 (d, J = 6.1 Hz, 1 H), 3.54 (dd, J = 11.8, 4.4 Hz, 1 H), 3.28 (br s, 1 H), 3.34-3.23 (m, 1 H), 2.55-2.42 (m, 2 H), 2.12-2.06 (m, 1 H), 2.06-1.91 (m, 2 H), 1.86-1.77 (m, 1 H), 1.70-1.62 (m, 1 H), 1.44 (s, 3 H), 1.39 (s, 3 H), 1.35-1.27 (m, 1 H), 1.15 (s, 3 H), 1.11 (s, 3 H), 1.09 (d, J = 7.0 Hz, 3 H), 1.01 (d, J = 6.6 Hz, 3 H), 0.90 (s, 3 H); δ (*E*-isomer) 5.72 (ddd, J = 15.1, 11.0, 3.2 Hz, 1 H), 5.59 (d, J = 15.9 Hz, 1 H), 5.38 (ddd, J = 15.1, 9.6, 2.2 Hz, 1 H), 5.36 (dd, J = 15.9, 6.7 Hz, 1 H), 4.17 (d, J = 10.4 Hz, 1 H), 3.65 (d, J = 9.9 Hz, 1 H), 3.50 (dd, J = 11.2, 5.0 Hz, 1 H), 3.44 (br s, 1 H), 2.92-2.83 (m, 1 H), 2.55-2.42 (m, 2 H), 2.12-2.06 (m, 1 H), 2.06-1.91 (m, 2 H), 1.86-1.77 (m, 1 H), 1.70-1.62 (m, 1 H), 1.41 (s, 3 H), 1.39 (s, 3 H), 1.35-1.27 (m, 1 H), 1.20 (d, J = 7.4 Hz, 3 H), 1.15 (s, 3 H), 1.11 (s, 3 H), 1.04 (d, J = 7.3 Hz, 3 H), 0.91 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (*Z*-isomer) 134.7, 132.8, 132.3, 125.7, 99.5, 86.4, 82.3, 77.7, 74.3, 63.6, 38.2, 36.7, 35.9, 33.1, 31.7, 29.9, 28.1, 28.0, 26.2, 25.9, 21.3, 19.1, 16.2; δ (*E*-isomer) 135.5, 133.3, 132.8, 125.1, 99.4, 86.3, 82.0, 77.8, 77.4, 65.6, 41.4, 38.1, 36.4, 36.0, 32.7, 29.9, 28.2, 28.0, 27.0, 25.2, 21.4, 19.1, 13.4; IR (neat) ν 3582, 2962, 2936, 2871, 2840, 1728, 1679, 1602, 1578, 1510, 1453, 1397, 1381, 1360, 1304, 1258, 1201, 1170, 1101, 1086, 1071, 1056, 1035, 1000, 985, 907, 865, 835, 810, 732, 703; HRMS (ESI) found 379.2841 $[M + H]^+$**,** calcd 379.2848 for $C_{23}H_{39}O_4^+$.



(no compound number was assigned in the manuscript)

Triol. A 25 mL round bottom flask was charged with the TBS-protected diol **16** (141 mg, 293 μmol) and 5 mL of anhydrous THF. TBAF (215 mg, 682 μmol) was added, and after 4 h the reaction was directly filtered through a short column with silica gel (hexanes/EtOAc, 10:1) to afford the desired triol, 104 mg (284 μmol, 97%), as an oil.

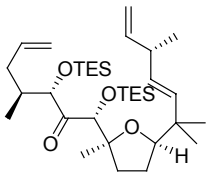
Data are: tlc R_f = 0.08 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = +14.4° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87-5.73 (m, 2 H), 5.45 (d, J = 15.9 Hz, 1 H), 5.38 (dd, J = 15.9, 6.1 Hz, 1 H), 5.08-4.90 (m, 4 H), 3.98 (br s, 1 H), 3.74 (dd, J = 8.9, 6.5 Hz, 1 H), 3.68-3.64 (m, 1 H), 3.48-3.39 (m 2 H), 3.15-3.04 (m, 2 H), 2.83 (app hex, J = 6.5 Hz, 1 H), 2.42-2.34 (m, 1 H), 2.18 (ddd, J = 12.1, 9.4, 4.7 Hz, 1 H), 2.03-1.94 (m, 1 H), 1.89-1.76 (m, 2 H), 1.76-1.66 (m, 1 H), 1.64-1.54 (m, 1 H), 1.23 (s, 3 H), 1.08 (d, J = 6.9 Hz, 3 H), 1.03 (s, 3 H), 0.96 (s, 3 H), 0.95 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 137.8, 134.4, 132.8, 116.0, 112.8, 86.7, 86.1, 77.8, 76.8, 69.2, 40.5, 38.8, 36.3, 35.4, 34.9, 27.0, 24.6, 24.4, 23.6, 20.0, 16.1; IR (neat) ν 3457, 3076, 2962, 2929, 2871, 1727, 1638, 1458, 1384, 1272, 1073, 1054, 1024, 993, 911, 849, 792, 743, 670; HRMS (ESI) found 389.2667 $[M + Na]^+$**,** calcd 389.2668 for $C_{22}H_{38}O_4Na^+$.



(no compound number was assigned in the manuscript)

***Bis*-TES protected alcohol**. A 25 mL round bottom flask was charged with the deprotected triol (84 mg, 229 μmol) and 12 mL of anhydrous DMF. Then imidazole (95 mg, 1.40 mmol) was added, followed by TES-Cl (120 μL, 108 mg, 715 μmol). After 20h the mixture was warmed to 30°C and a second portion TES-Cl (80 μL, 72 mg, 477 μmol) was introduced. The reaction was terminated after 6 h at 30°C by addition of saturated NH_4Cl solution (10 mL) and hexanes (20 mL). Then, the aqueous layer was separated and extracted with hexanes (3 x 20 mL). The combined organic solutions were dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (hexanes/EtOAc, 40:1) furnished the desired alcohol, 132 mg (222 μmol, 97%), as an oil.

Data are: tlc R_f = 0.29 (hexanes/EtOAc, 40:1); $[\alpha]_D^{20}$ = +9.3° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83-5.69 (m, 2 H), 5.46 (dd, J = 15.9, 1.1 Hz, 1 H), 5.33 (dd, J = 15.9, 6.5 Hz), 5.03-4.89 (m, 4 H), 3.75 (dd, J = 8.7, 5.8 Hz, 1 H), 3.65 (br s, 1 H), 3.46 (dd, J = 8.8, 1.8 Hz, 1 H), 3.39 (t, J = 8.8 Hz, 1 H), 2.80 (app hex, J = 6.7 Hz, 1 H), 2.63 (d, J = 8.8 Hz, 1 H), 2.19-2.10 (m, 1 H), 1.97-1.81 (m, 2 H), 1.71-1.56 (m, 3 H), 1.32 (q, J = 10.4 Hz, 1 H), 1.17 (s, 3 H), 1.07 (d, J = 6.9 Hz, 3 H), 1.01-0.93 (m, 27 H), 0.69-0.59 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 138.0, 135.4, 131.6, 115.5, 112.5, 86.1, 84.6, 79.1, 77.2, 72.8, 40.4, 39.3, 34.86, 34.85, 34.3, 26.0, 24.2, 24.1, 20.0, 18.4, 18.0, 7.1, 7.0; IR (neat) ν 3508, 3077, 2956, 2911, 2875, 1731, 1639, 1459, 1414, 1378, 1269, 1238, 1139, 1114, 1093, 1066, 1006, 976, 911, 846, 811, 741, 673; HRMS (ESI) found 617.4381 $[M + Na]^+$**,** calcd 617.4397 for $C_{34}H_{66}Si_2O_4Na^+$.

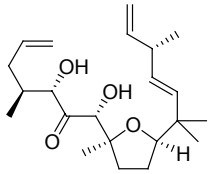


(no compound number was assigned in the manuscript)

TES ketone. A 50 mL round bottom flask was charged with the TES alcohol (115 mg, 193 μmol) and 15 mL of dry CH_2Cl_2. The solution was then charged with Dess-Martin periodinane (342 mg, 806 μmol) and stirred for 1.5 h. The reaction mixture was terminated by addition of saturated $NaHCO_3$ solution (3 mL) and saturated $Na_2S_2O_3$ solution (3 mL) and vigorously stirred for 30 minutes. The aqueous layer was separated and extracted once with CH_2Cl_2 (5 mL). The organic solutions were dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (hexanes/EtOAc, 40:1) afforded the desired ketone, 106 mg (179 μmol, 93%), as an oil.

Data are: tlc R_f = 0.39 (hexanes/EtOAc, 40:1), 0.74 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = +40.1° (*c* 1, $CHCl_3$); ^{1}H NMR (400 NHz, $CDCl_3$) δ 5.82-5.64 (m, 2 H), 5.44 (dd, J

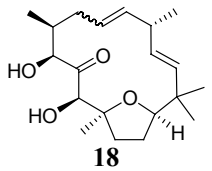
= 15.9 Hz, 0.8 Hz, 1 H), 5.32 (dd, *J* = 15.9, 6.7 Hz, 1 H), 5.01-4.89 (m, 4 H), 4.66 (d, *J* = 2.6 Hz, 1 H), 4.20 (br s, 1 H), 3.68 (dd, *J* = 7.8, 6.3 Hz, 1 H), 2.80 (app hex, *J* = 6.7 Hz, 1 H), 2.13-2.03 (m, 1 H), 2.02-1.94 (m, 1 H), 1.93-1.78 (m, 3 H), 1.64-1.53 (m, 1 H), 1.49-1.36 (m, 1 H), 1.09 (s, 3 H), 1.07 (d, *J* = 6.9 Hz, 3 H), 1.03-0.92 (m, 27 H), 0.80-0.71 (m, 6 H), 0.64-0.55 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2, 143.3, 137.4, 135.5, 131.6, 115.9, 112.5, 84.8, 84.1, 81.5, 79.4, 40.4, 39.1, 36.3, 34.6, 34.5, 26.2, 24.4, 24.1, 20.0, 18.1, 17.0, 7.0, 6.8, 5.0, 4.9; IR (neat) ν 3078, 2957, 2911, 2876, 1733, 1640, 1459, 1415, 1372, 1330, 1239, 1170, 1095, 1006, 976, 912, 836, 742, 683; HRMS (ESI) found 615.4268 $[M + Na]^+$, calcd 615.4241 for $C_{34}H_{64}Si_2O_4Na^+$.



(no compound number was assigned in the manuscript)

Hydroxy ketone. A 10 mL round bottom flask was charged with the TES ketone (205 mg, 346 μmol) and 3 mL of anhydrous THF. After cooling to 0°C TBAF (298 mg, 944 μmol) in 3 mL of dry THF was added, and after 30 minutes the reaction was stopped by direct filtration of the mixture (silica gel; hexanes/EtOAc, 10:1) to furnish the desired hydroxyl ketone, 125 mg (343 μmol, 99%), as an oil.

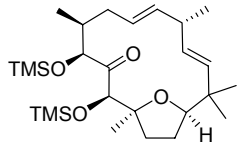
Data are: tlc R_f = 0.32 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = -64.1° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (ddd, *J* = 17.2, 10.4, 6.7 Hz, 1 H), 5.74-5.63 (m, 1 H), 5.37 (dd, *J* = 15.8 Hz, 5.6 Hz, 1 H), 5.31 (d, *J* = 15.8 Hz, 1 H), 5.06-4.91 (m, 4 H), 4.49 (d, *J* = 6.2 Hz, 1 H), 4.31 (br s, 1 H), 4.15 (br s, 1 H), 3.81 (t, *J* = 7.0 Hz, 1 H), 3.18 (d, *J* = 6.2 Hz, 1 H), 2.81 (app hex, *J* = 6.6 Hz, 1 H), 2.22-2.12 (m, 1 H), 2.10-2.02 (m, 1 H), 2.02-1.92 (m, 1 H), 1.89-1.77 (m, 2 H), 1.68-1.52 (m, 2 H), 1.30 (s, 3 H), 1.08 (d, *J* = 6.9 Hz, 3 H), 1.02 (d, *J* = 6.9 Hz, 3 H), 0.98 (s, 3 H), 0.92 (s, 3 H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.0, 142.9, 136.9, 134.2, 132.9, 116.4, 112.8, 86.4, 85.6, 79.8, 78.4, 40.4, 38.8, 37.2, 35.3, 32.0, 25.3, 24.8, 23.6, 23.3, 19.9, 16.5; IR (neat) ν 3459, 3078, 2969, 2932, 2873, 1709, 1640, 1456, 1374, 1265, 1123, 1071, 1022, 995, 913, 851; HRMS (ESI) found 387.2521 $[M + Na]^+$, calcd 387.2511 for $C_{22}H_{36}O_4Na^+$.



18

***Trans* olefin 18**. A 500 mL round bottom flask with a reflux condenser was charged with the deprotected hydroxyl ketone (125 mg, 343 μmol) and 200 mL of anhydrous CH_2Cl_2. Then Grubbs II catalyst (27.8 mg, 32.7 μmol) was added and the reaction was refluxed over 1.5 h before cooling to room temperature. The solution was saturated with air and silica gel (400 mg) was added. After concentration the resulting solid was purified by flash column chromatography (hexanes/EtOAc, 10:1) to afford the macrocycle **18**, 98 mg (290 μmol, 85%), as an oil (*E*:*Z* ≈ 5:1).

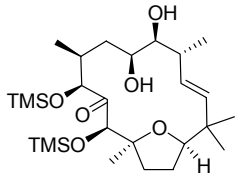
Data are: tlc R_f = 0.13 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = +48.2° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (dd, *J* = 15.5, 8.8 Hz, 1 H), 5.33 (d, *J* = 15.4 Hz, 1 H), 5.27 (dd, *J* = 15.4 Hz, 7.9 Hz, 1 H), 5.24-5.16 (m, 1 H), 4.57 (br s, 1 H), 4.35 (br s, 1 H), 3.81 (dd, *J* = 8.0, 3.0 Hz, 1 H), 3.54 (br s, 1 H), 2.80-2.67 (m, 2 H), 2.57-2.47 (m, 1 H), 2.09-1.97 (m, 2 H), 1.95-1.74 (m, 4 H), 1.17 (d, *J* = 7.0 Hz, 3 H), 1.09 (s, 3 H), 1.05 (s, 3 H), 1.03 (d, *J* = 6.7 Hz, 3 H), 0.88 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.4, 137.2, 133.8, 132.7, 127.8, 88.2, 85.4, 81.8, 77.9, 42.0, 40.3, 39.6, 34.6, 32.3, 26.7, 25.7, 24.2, 21.3, 21.0, 20.4; IR (neat) ν 3477, 2961, 2930, 2871, 1707, 1454, 1374, 1327, 1239, 1156, 1121, 1074, 1059, 1024, 982, 910, 883, 829, 769, 726, 666; HRMS (ESI) found 359.2202 $[M + Na]^+$, calcd 359.2198 for $C_{20}H_{32}O_4Na^+$.



(no compound number was assigned in the manuscript)

TMS olefin. A 25 mL round bottom flask was charged with olefin **18** (28 mg, 83.2 μmol) and 10 mL of anhydrous DMF. The solution was cooled to 0°C before NEt_3 (80 μL, 58.4 mg, 577 μmol) and TMS-Cl (50 μL, 43 mg, 395 μmol) were added consecutively. After 1 h saturated NH_4Cl solution (5 mL) was added, followed by H_2O (15 mL) and hexanes/EtOAc (10:1; 30 mL). The organic layer was washed twice with H_2O (20 mL), and the combined aqueous phases were reextracted once with hexanes/EtOAc (10:1; 20 mL). Then, the organic solutions were combined, dried over Na_2SO_4 and concentrated under reduced pressure. A short filtration over silica gel (hexanes/EtOAc, 10:1) afforded the TMS-protected diol, 39.8 mg (82.8 μmol, >99%), as an oil.

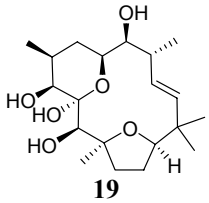
Data are: tlc R_f = 0.67 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = -23.4° (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54-5.24 (m, 4 H), 4.75-4.63 (m, 1 H), 4.50 (br d, *J* = 1.8 Hz, 1 H), 3.62 (br t, *J* = 6.0 Hz, 1 H), 2.74 (app hex, *J* = 6.5 Hz, 1 H), 2.52-2.33 (m, 1 H), 2.13-1.98 (m, 1 H), 1.96-1.66 (m, 4 H), 1.64-1.46 (m, 1 H), 0.87 (s, 3 H), 1.08-0.98 (m, 12 H), 0.18 (s, 9 H), 0.12 (s, 9 H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 134.6, 132.3, 127.3, 87.2, 86.4, 85.6, 78.3, 40.2, 39.0, 34.0, 32.1, 26.3, 26.1, 24.9, 24.6, 21.9, 20.1, 15.5, 0.7, 0.1, C=O was not observed, the NMR spectra display a strong line broadening due to a slow conformational equilibrium; IR (neat) ν 2960, 2871, 1727, 1453, 1371, 1305, 1251, 1099, 1051, 1027, 999, 980, 880, 842, 753; HRMS (ESI) found 503.2986 $[M + Na]^+$, calcd 503.2989 for $C_{26}H_{48}O_4Si_2Na^+$.



(no compound number was assigned in the manuscript)

TMS diol. A 10 mL round bottom flask was charged with the TMS ether of **18** (62 mg, 129 μmol), *t*BuOH (4 mL) and H_2O (4 mL). Then *α*-DHQ-CLB (21.8 mg, 46.9 μmol), K_2CO_3 (55.5 mg, 402 μmol), $K_3Fe(CN)_6$ (129 mg, 392 μmol) and MSA (37 mg, 389 μmol) were added consecutively. When the mixture became a clear the solution was cooled to 0°C and an OsO_4 solution (2.5 wt-% in *t*BuOH, 162 μL, 131 mg, 12.9 μmol) was introduced dropwise. After 2.5 h the reaction was terminated by addition of an halfsaturated aqueous $Na_2S_2O_3$ solution. The mixture was extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (hexanes/EtOAc, 5:1) afforded the title compound, 55 mg (107 μmol, 83%), as an oil.

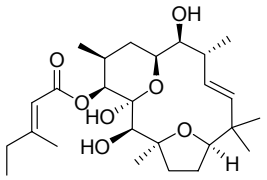
Data are: tlc R_f = 0.17 (hexanes/EtOAc, 5:1); $[\alpha]_D^{20}$ = +4.8°, $[\alpha]_{365}^{20}$ = -12.0° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 (d, *J* = 15.8 Hz, 1 H), 5.12 (dd, *J* = 15.8, 9.2 Hz, 1 H), 4.65 (br s, 1 H), 4.29 (br s, 1 H), 3.67 (br s, 1 H), 3.56 (dd, *J* = 9.6, 5.6 Hz, 1 H), 3.15 (br t, *J* = 9.6 Hz, 1 H), 2.40-2.20 (m, 2 H), 2.00-1.88 (m, 2 H), 1.88-1.62 (m, 4 H), 1.51-1.41 (m, 1 H), 1.18 (s, 3 H), 1.11 (s, 3 H), 1.08 (d, *J* = 6.7 Hz, 3 H), 0.98 (d, *J* = 6.5 Hz, 3 H), 0.88 (s, 3 H), 0.16 (s, 9 H), 0.13 (s, 9 H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 131.6, 86.3, 84.1, 77.6, 77.2, 74.6, 68.7, 40.6, 38.1, 35.6, 34.0, 31.2, 27.5, 26.0, 25.5, 25.4, 18.2, 16.6, 0.4, 0.3, C=O signal was not detected because the NMR spectra display a strong line broadening for which we make a slow conformational equilibrium responsible; IR (neat) ν 3424, 2960, 2872, 1726, 1453, 1372, 1251, 1097, 1049, 997, 925, 878, 842, 754 ; HRMS (ESI) found 537.3060 $[M + Na]^+$**,** calcd 537.3044 for $C_{26}H_{50}O_6Si_2Na^+$.



19

Triol 19. A 5 mL round bottom flask was charged with the protected dihydroxylated product (17.7 mg, 34.4 μmol) and 1 mL of dry THF. The solution was cooled to 0°C before a solution of TBAF (13.2 mg, 41.8 μmol) in 0.5 mL of dry THF was added. After 10 minutes the complete mixture was directly filtered over a short plug of silica gel (hexanes/EtOAc, 1:1) and the resulting solution was concentrated under reduced pressure. The colourless oil was dried in vacuum to afford the title compound, 12.7 mg (34.3 μmol, >99%).

Data are: tlc R_f = 0.17 (hexanes/EtOAc, 1:1), 0.27 (EtOAc); $[\alpha]_D^{20}$ = +30.6° (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, d_4-MeOH) δ 5.49 (d, *J* = 15.3 Hz, 1 H), 5.36 (dd, *J* = 15.3, 9.3 Hz, 1 H), 4.12 (dt, *J* = 12.3, 2.3 Hz, 1 H), 3.86 (dd, *J* = 7.8, 6.2 Hz, 1 H), 3.72 (br s, 1 H), 3.34 (d, *J* = 2.4 Hz, 1 H), 3.27 (dd, *J* = 6.3, 2.3 Hz, 1 H), 2.35-2.15 (m, 3 H), 2.08-1.92 (m, 2 H), 1.74 (q, *J* = 12.3 Hz, 1 H), 1.61 (ddd, *J* = 12.2, 7.2, 5.1 Hz, 1 H), 1.31 (s, 3 H), 1.13-1.04 (m, 1 H), 1.09 (d, *J* = 7.0 Hz, 3 H), 1.07 (s, 3 H), 0.94 (d, *J* = 7.0 Hz, 3 H), 0.92 (s, 3 H), ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45 (d, *J* = 15.4 Hz, 1 H), 5.31 (dd, *J* = 15.4, 9.2 Hz, 1 H), 4.56 (br s, 1 H), 4.12 (dt, *J* = 12.1, 2.1 Hz, 1 H), 3.88 (bs, 1 H), 3.81 (t, *J* = 7.2 Hz, 1 H), 3.67 (br s, 1 H), 3.40 (bs, 1 H), 3.27 (bd, *J* = 4.6 Hz, 1 H), 2.39-2.26 (m, 3 H), 1.98-1.84 (m, 2 H), 1.74 (ps q, *J* = 12.9 Hz, 1 H), 1.66-1.54 (m, 2 H), 1.30 (s, 3 H), 1.22-1.14 (m, 1 H), 1.11 (d, *J* = 7.0 Hz, 3 H), 1.08 (s, 3 H), 0.97 (d, *J* = 7.0 Hz, 3 H), 0.91 (s, 3 H), ^{13}C NMR (100 MHz, d_4-MeOH) δ 136.0, 131.6, 98.6, 89.46, 89.44, 81.4, 79.5, 76.1, 70.5, 46.7, 39.8, 35.6, 31.0, 30.2, 27.9, 26.8, 26.6, 24.7, 21.5, 17.8; IR (neat) ν 3348, 2963, 2927, 2870, 1719, 1665, 1611, 1547, 1455, 1369, 1286, 1225, 1120, 1098, 1059, 1024, 991, 870, 778, 702; HRMS (ESI) found 393.2260 $[M + Na]^+$**,** calcd 393.2253 for $C_{20}H_{34}O_6Na^+$.

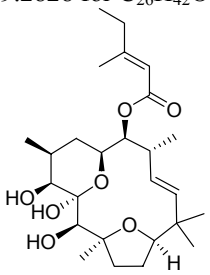


20b

20b. A 5 mL round bottom flask was charged with **19** (5.5 mg, 14.8 μmol), the side chain (25.2 mg, 221 μmol) and 1.2 mL of dry CH_2Cl_2. DIC (33 μL, 26.9 mg, 213 μmol) was added via syringe, followed by DMAP (2.1 mg, 17.2 μmol) after 1h. The reaction mixture was allowed to stir for 28h at room temperature and then directly filtered over silica gel (hexanes/EtOAc, 1:1). The resulting filtrate was reduced and purified by flash column chromatography (hexanes/EtOAc, 10:1 → 5:1 → 2.5:1) to afford **20b** and **20c**, 4.8 mg (70%), as an oil and inseparable, along with **20a**, 1.5 mg (22%), as an oil. **20a** was fully characterized, but tends to spontaneously rearrange to the desired **20b**, thereby furnishing **20b** as pure material. **20c** was obtained as sole product under Yamaguchi conditions, so that the following spectroscopical data for **20a-c** were all recorded for pure samples.

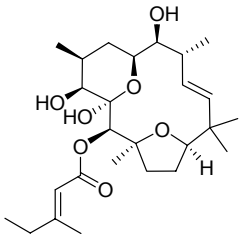
Data are (**20b**): tlc R_f = 0.63 (hexanes/EtOAc, 1:1); $[\alpha]_D^{20}$ = +16.3° (*c* 0.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (s, 1 H), 5.70 (q, *J* = 1.2 Hz, 1 H), 5.50 (d, *J* = 15.3 Hz, 1 H), 5.28 (dd, *J* = 15.3, 9.3 Hz, 1 H), 4.92 (d, *J* = 2.5 Hz, 1 H), 4.20 (dt, *J* = 12.0, 2.3 Hz, 1 H), 3.70 (dd, *J* = 9.5, 5.9 Hz, 1 H), 3.46 (d, *J* = 6.4 Hz, 1 H), 3.38 (ddd, *J* = 8.5, 6.3, 2.3 Hz, 1 H), 3.07 (d, *J* = 6.4 Hz, 1 H), 2.48-2.27 (m, 3 H), 2.24-2.11 (m, 5 H), 1.94-1.83 (m, 1 H), 1.82-1.72 (m, 2 H), 1.49 (ddd, *J* = 12.4, 9.9, 7.3 Hz, 1 H), 1.32 (s, 3 H), 1.20-1.16 (m, 1 H), 1.12 (d, *J* = 7.0 Hz, 3 H), 1.10 (s, 3 H), 1.07 (t, *J* = 7.5 Hz, 3 H), 0.90 (s, 3 H), 0.84 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 135.0, 130.4, 114.1, 96.8, 88.0, 87.9, 78.3, 78.1, 73.5, 68.4, 45.5, 38.4, 36.2, 33.9, 30.0, 29.1, 28.0, 27.3, 26.0, 25.2, 20.9, 19.0, 17.3, 11.9, C-3´ was not detected; IR (neat) ν 3354, 2969, 2925,

2855, 1741, 1670, 1653, 1456, 1374, 1261, 1227, 1216, 1144, 1074, 1023, 798, 696 ; HRMS (ESI) found 489.2840 $[M + Na]^+$, calcd 489.2828 for $C_{26}H_{42}O_7Na^+$.



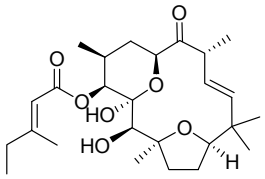
20c

Data are (**20c**): tlc R_f = 0.59 (hexanes/EtOAc, 1:1); $[\alpha]_D^{20}$ = +25.2° (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (s, 1 H), 5.72 (q, *J* = 1.2 Hz, 1 H), 5.54 (d, *J* = 15.3 Hz, 1 H), 5.33 (dd, *J* = 15.3, 9.4 Hz, 1 H), 4.92 (dd, *J* = 7.7, 3.1 Hz, 1 H), 4.31 (dt, *J* = 11.9, 3.1 Hz, 1 H), 3.75 (dd, *J* = 9.0, 6.0 Hz, 1 H), 3.68-3.63 (m, 1 H), 3.32 (br s, 1 H), 2.51-2.39 (m, 2 H), 2.25-2.13 (m, 4 H), 2.18 (d, *J* = 1.2 Hz, 3 H), 1.97-1.73 (m, 4 H), 1.34 (s, 3 H), 1.30-1.21 (m, 1 H), 1.12 (s, 3 H), 1.10 (t, *J* = 7.5 Hz, 3 H), 1.01 (d, *J* = 6.9 Hz, 3 H), 0.93 (d, *J* = 6.9 Hz, 3 H), 0.90 (s, 3 H), the ^{1}H NMR spectrum shows slightly broadened signals for which we make conformational equilibrium responsible; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 162.5, 135.6, 129.7, 114.3, 97.1, 88.1, 87.9, 79.1, 77.2, 77.9, 68.4, 42.3, 38.5, 36.0, 33.9, 29.3, 28.4, 27.9, 27.3, 25.8, 24.8, 20.6, 18.9, 17.3, 11.9; IR (neat) ν 3500, 3351, 2963, 2926, 2872, 1713, 1648, 1456, 1375, 1261, 1217, 1144, 1099, 1070, 1034, 995, 866, 761; HRMS (ESI) found 489.2830 $[M + Na]^+$, calcd 489.2828 for $C_{26}H_{42}O_7Na^+$.



20a

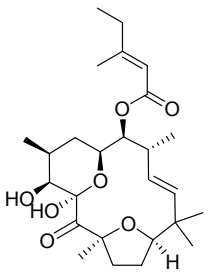
Data are (**20a**): tlc R_f = 0.32 (hexanes/EtOAc, 1:1); $[\alpha]^{20}_D$ = +4.5°, $[\alpha]^{20}_{365nm}$ = +30.7° (*c* 0.31, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (s, 1 H), 5.64 (q, *J* = 1.3 Hz, 1 H), 5.46 (d, *J* = 15.8 Hz, 1 H), 5.33 (dd, *J* = 15.8, 8.2 Hz, 1 H), 5.18 (s, 1 H), 4.09 (dd, *J* = 12.4, 2.2 Hz, 1 H), 3.78 (t, *J* = 7.3 Hz, 1 H), 3.41 (dd, *J* = 8.3, 2.2 Hz, 1 H), 3.29 (br s, 1 H), 3.11-2.97 (br s, 1 H), 2.45-2.32 (m, 1 H), 2.27-2.14 (m, 6 H), 2.11-1.99 (m, 1 H), 1.94-1.76 (m, 3 H), 1.71-1.63 (m, 2 H), 1.25 (s, 3 H), 1.11 (s, 3 H), 1.08 (t, *J* = 7.5 Hz, 3 H), 1.03 (d, *J* = 7.2 Hz, 3 H), 0.95 (s, 3 H), 0.92 (d, *J* = 6.9 Hz, 3 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 163.9, 133.7, 131.6, 113.9, 98.0, 87.8, 86.2, 78.1, 77.2, 73.8, 66.9, 43.3, 38.4, 35.3, 33.9, 30.7, 29.9, 27.2, 26.8, 25.78, 25.75, 19.4, 19.0, 17.3, 11.9; IR (neat) ν 3366, 2962, 2924, 2872, 2854, 1716, 1649, 1458, 1377, 1274, 1218, 1142, 1097, 1072, 1029, 994, 865 ; HRMS (ESI) found 489.2837 $[M + Na]^+$, calcd 489.2828 for $C_{26}H_{42}O_7Na^+$.



***ent*-1**

***ent*-1**. A 5 mL round bottom flask was charged with **20b**/**20c** (3.2 mg, 6.86 μmol), powdered 4Å molecular sieve (12 mg), NMO (10 mg, 85.5 μmol) and 1 mL of dry CH_2Cl_2. TPAP (1 mg, 2.85 μmol) was added and the reaction was stirred at room temperature for 1 h. Then the mixture was cautiously reduced and directly purified by flash column chromatography (hexanes/EtOAc, 10:1) to afford *ent*-**1**, 1.4 mg (3.0 μmol, 44%), as an oil, and the product of **20c** oxidation, 1.3 mg (2.80 μmol, 41%), as an oil.

Data are (***ent*-1**): tlc R_f = 0.66 (hexanes/EtOAc, 2.5:1); $[\alpha]^{20}_D$ = -119.0° (*c* 0.056, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (d, *J* = 15.3 Hz, 1 H), 5.70 (q, *J* = 1.3 Hz, 1 H), 5.66 (s, 1 H), 5.24 (dd, *J* = 15.3, 9.7 Hz, 1 H), 4.90 (d, *J* = 2.6 Hz, 1 H), 4.63 (dd, *J* = 11.8, 2.9 Hz, 1 H), 3.77 (dd, *J* = 11.3, 5.1 Hz, 1 H), 3.43 (d, *J* = 6.4 Hz, 1 H), 3.34 (dq, *J* = 9.7, 6.8 Hz, 1 H), 3.11 (d, *J* = 6.4 Hz, 1 H), 2.44 (dd, *J* = 12.7, 7.2 Hz, 1 H), 2.38-2.29 (m, 1 H), 2.21 (q, *J* = 7.6 Hz, 2 H), 2.16 (d, *J* = 1.3 Hz, 3 H), 2.09-1.97 (m, 1 H), 1.85 (ddd, *J* = 13.6, 3.9, 2.9 Hz, 1 H), 1.77 (ddd, *J* = 12.0, 7.2, 5.1 Hz, 1 H), 1.58-1.51 (m, 1 H), 1.41-1.36 (m, 1 H), 1.36 (s, 3 H), 1.14 (s, 3 H), 1.12 (d, *J* = 6.8 Hz, 3 H), 1.07 (t, *J* = 7.6 Hz, 3 H), 0.91 (s, 3 H), 0.85 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3, 166.6, 162.9, 140.1, 126.9, 113.9, 97.2, 88.9, 87.7, 78.3, 74.2, 73.2, 49.6, 38.8, 37.4, 33.9, 29.1, 28.9, 28.14, 28.10, 25.5, 25.1, 19.0, 17.0, 16.0, 11.9; IR (neat) ν 3368, 2956, 2924, 2854, 1717, 1649, 1460, 1379, 1260, 1215, 1142, 1098, 1073, 1024, 980, 852, 795, 701; HRMS (ESI) found 487.2693 $[M + Na]^+$, calcd 487.2672 for $C_{26}H_{40}O_7Na^+$.



Data are (**20c** oxidized product): tlc R_f = 0.58 (hexanes/EtOAc, 2.5:1); $[\alpha]^{20}_D$ = -16.0°, $[\alpha]^{20}_{365nm}$ = -185.6° (*c* 0.063, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (s, 1 H), 5.77 (br s, 1 H), 5.48 (d, *J* = 15.2 Hz, 1 H), 5.40 (dd, *J* = 15.2, 9.1 Hz, 1 H), 4.93 (dd, *J* = 7.8, 2.8 Hz, 1 H), 4.32 (dt, *J* = 12.3, 2.8 Hz, 1 H), 3.96 (t, *J* = 7.2 Hz, 1 H), 3.86 (br s, 1 H), 3.53 (br s, 1 H), 2.54-2.46 (m, 1 H), 2.34 (dq, *J* = 12.5, 8.1 Hz, 1 H), 2.22-2.16 (m, 1 H), 2.17 (q, *J* = 7.4 Hz, 1 H), 2.14 (br s, 3 H), 2.03-1.92 (m, 2 H), 1.81 (ddd, *J* = 12.5, 7.5, 5.7 Hz, 1 H), 1.63 (q, *J* = 12.3 Hz, 1 H), 1.42 (s, 3 H), 1.18 (s, 3 H), 1.14-1.08 (m, 1H), 1.08 (t, *J* = 7.4 Hz, 3 H), 1.00 (d, *J* = 6.9 Hz, 3 H), 0.97 (d, *J* =

6.9 Hz, 3 H), 0.94 (s, 3 H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.7, 167.1, 162.2, 135.1, 130.0, 114.4, 97.0, 91.1, 89.2, 76.9, 70.9, 68.8, 41.7, 38.7, 36.1, 33.8, 29.2, 28.5, 26.0, 25.2, 24.42, 24.39, 20.4, 18.9, 17.3, 11.9; IR (neat) ν 3360, 2962, 2926, 2872, 1714, 1650, 1457, 1377, 1311, 1263, 1216, 1143, 1095, 1030, 995, 977, 866, 803; HRMS (ESI) found 487.2683 $[M + Na]^+$, calcd 487.2672 for $C_{26}H_{40}O_7Na^+$.