Supporting Information for

Iriomoteolides: Novel Chemical Tools to Study Actin Dynamics

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1. Synthesis of Iriomoteolide 3a and analogues

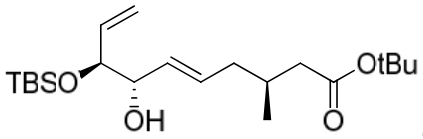
General information

All reactions were carried out under a nitrogen atmosphere using Standard Schlenk-lines or gloveboxes (Mecaplex or Innovative Technology). All reagents were used as received unless otherwise noted. Solvents were purchased in the best quality available, degassed by purging thoroughly with nitrogen and dried over activated molecular sieves of appropriate size. Alternatively, they were purged with argon and passed through alumina columns in a solvent purification system (Innovative Technology). Reactions were monitored by thin layer chromatography (TLC) using Merck TLC silica gel 60 F_{254}. Flash column chromatography was performed over silica gel (230-400 mesh). NMR spectra were recorded on AV2 400 or AV2 500 MHz Bruker spectrometers. Chemical shifts are given in ppm. The spectra are calibrated to the residual ^{1}H and ^{13}C signals of the solvents. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), apparent triplet (at), doublet apparent triplet (dat), doublet-doublet (dd), triplet-doublet (td), doublet-doublet-doublet (ddd), doublet-doublet-doublet-doublet (dddd), multiplet (m), and broad (br). High-resolution electrospray ionization mass spectrometry was performed on a Finnigan MAT 900 (Thermo Finnigan, San Jose, CA; USA) doublefocusing magnetic sector mass spectrometer. A mass accuracy ≤ 2 ppm was obtained in the peak matching acquisition mode by using a solution containing 2 <l PEG200, 2 <l PPG450, and 1.5 mg NaOAc (all obtained from Sigma-Aldrich, CH-Buchs) dissolved in 100ml MeOH (HPLC Supra grade, Scharlau, E-Barcelona) as internal standard. GC-MS analysis was done on a Finnigan Voyager GC8000 Top. Optical rotations were measured at 25 ºC on a Jasco P-2000 Polarimeter using a a filtered Hg lamp (λ = 589 nm).

The following compounds: **3, 4**, **5a-d** and **6** were prepared according to our previously reported synthesis of iriomoteolide 3a.[1]

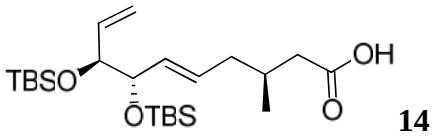
Synthesis of Iriomoteolide-3a and derivatives thereof following the sequence described in Scheme 1B

Synthesis of Iriomoteolide-3a (1)



26

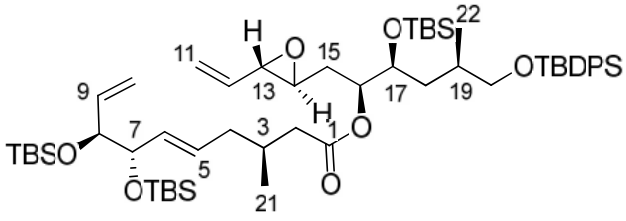
(*E*)-(3*S*,7*S*,8*S*)-8-(*tert*-Butyl-dimethyl-silanyloxy)-7-hydroxy-3-methyl-deca-5,9-dienoic acid *tert*-butyl ester (26) To a solution of *tert*-butylester **13** (150 mg, 0.81 mmol) and diene **5d** (371 mg, 1.62 mmol) in toluene (3 mL), was added Grubb's II generation catalyst **11** (7 mg, 1 % mmol). The reaction mixture was heated at 50 °C for 8 h, during which time further diene **5d** (371 mg, 1.62 mmol) and Grubb's II generation catalyst **11** (27 mg, 4 % mmol) were added by portions until complete conversion of the starting material (TLC, hexanes/EtOAc 80:20, *Rf* = 0.65) into a major product (*Rf* = 0.32) was observed. The solvent was evaporated under reduced pressure to give the crude material which was purified by silica gel flash column chromathography (hexanes/EtOAc 95: 5→ 80:20) to provide **26** (248 mg, 82 %)**.** Colourless oil: $[\alpha]_D^{25}$ +6.2 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.79 (ddd, *J* = 17.1, 10.4, 6.4 Hz, 1H), 5.66 (dat, *J* = 15.3, 7.5 Hz, 1H), 5.43 (dd, *J* = 15.4, 6.5, Hz, 1H), 5.22 (dat, *J* = 17.1, 1.6, Hz,1H), 5.17 (dat, *J* = 10.4, 1.6, Hz, 1H), 3.94 (at, *J* = 6.4 Hz, 1H), 3.90 (at, *J* = 6.5 Hz, 1H), 2.53 (br s, 1H, 7-OH), 2.22 (dd, *J* = 17.6, 8.8, Hz, 1H), 2.11-2.04 (m, 1H), 2.03-1.89 (m, 3H), 1.44 (s, 9H), 0.91 (s, 12H), 0.08, 0.05 (2 x s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 137.9, 131.0, 130.6, 116.9, 80.0, 77.8, 75.7, 42.5, 39.4, 30.4, 28.1, 25.8, 19.3, 18.1, -4.1, -4.8; IR (film): $\tilde{\upsilon}$ = 3500, 2956, 2929, 2857, 1729, 1461, 1366, 1253, 1150, 835, 777 cm^{-1}; HRMS (ES^+) m/z: Calcd. for $C_{21}H_{40}O_4NaSi$ (MNa^+) 407.2594. Found 407.2595.



14

(*E*)-(3*S*,7*S*,8*S*)-7,8-Bis-(*tert*-butyl-dimethyl-silanyloxy)-3-methyl-deca-5,9-dienoic acid (14) To a solution of *tert*-butylester **26** (100 mg, 0.26 mmol) in CH_2Cl_2 (6 ml) at 0 °C were added 2,6-lutidine (2.6 mmol, 302 µL) and *tert*-butyldimethylsilyl triflate (302 µL, 1.3 mmol). The reaction mixture was stirred for 2 h at 0 °C then diluted with

EtOAc and washed with aq. 0.01 M HCl. The organic layer was dried over magnesium sulfate and the solvent evaporated under reduced pressure to give a crude residue which was dissolved in a mixture of EtOAc/methanol/water 1:8:1, (10 mL) and treated with Na_2CO_3 (275 mg, 2.6 mmol) at room temperature. After 1 h the mixture was concentrated under reduced pressure to ¼ of its volume, diluted with EtOAc (20 mL), washed with with aq. 0.01 M HCl. The organic layer was dried over $MgSO_4$ and the solvent evaporated under reduced pressure to give a crude residue which was purified by rapid filtration on silica gel (hexanes/EtOAc 70 : 30) to give acid **14** (91 mg, 78%). Colourless oil: $[\alpha]_D^{20}$ = -30.7 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.88 (ddd, *J* = 17.2, 10.5, 4.4 Hz, 1H, H-9), 5.55-5.41 (m, 2H, H-5, H-6), 5.18 (dat, *J* = 17.2, 1.7 Hz, 1H, H-10a), 5.10 (dat, *J* = 10.5, 1.4 Hz, 1H, H-10b), 4.10-4.05 (m, 2H, H-8, H-7), 2.39 (dd, *J* = 14.9, 5.0 Hz, 1H, H-2a), 2.13-1.94 (m, 4H, H-3, H-4, H-2b), 0.96 (d, *J* = 6.2 Hz, 3H, 3-CH_3), 0.90, 0.89 (2 x s, 18H, 2 x $SiC(CH_3)_3$), 0.06, 0.03 (2 x s, 12H, 4 x $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.2 (s, *C*=O), 137.3 (d, C-9), 131.5, 128.9 (2 x d, C-5, C-6), 115.0 (t, C-10), 76.2, 75.9 (2 x d, C-8, C-7), 40.6 (t, C-2), 39.3 (t, C-4), 30.1 (d, C-3), 25.8 (6 x q, 2 x $SiC(CH_3)_3$), 19.4 (q, 3-CH_3), 18.2 (2 x s, 2 x Si*C*), -4.5, -4.6, -4.7, -4.8 (4 x q, 4 x $SiCH_3$); IR (film): $\tilde{\upsilon}$ = 2956, 2929, 2857, 1709, 1472, 1407, 1253, 1133, 835, 775 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{23}H_{46}O_4NaSi_2$ (M^+ + Na): 465.2832, found: 465.2837.

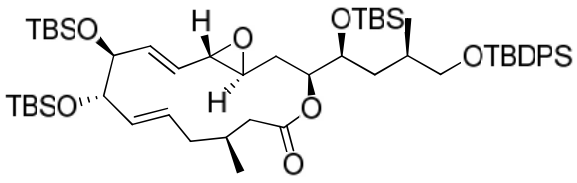


15

Ring-Closing Metathesis precursor 15. Acid **14** (230 mg, 0.52 mmol) was dissolved in CH_2Cl_2 (5 mL). To the solution, 4-pyrrolidino-pyridine (200 mg, 1.35 mmol) and EDC·HCl (250 mg, 1.30 mmol) were added, followed by alcohol **3** (295 mg, 0.52 mmol). The reaction mixture was stirred at room temperature for 24 h, after which time the solvent was evaporated under reduced pressure and the crude residue was purified by flash chromatography (hexanes/EtOAc 95 : 5) to give ester **15** (416 mg, 84%). Colorless oil: *Rf* = 0.56 (toluene 100%); $[\alpha]_D^{20}$ = -29.5 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65-7.62 (m, 4H, aromatics), 7.44-7.35 (m, 6H,

aromatics), 5.86 (ddd, *J* = 17.2, 10.5, 4.6 Hz, 1H, H-9), 5.53 (ddd, *J* = 17.2, 9.9, 7.3 Hz, 1H, H-12), 5.48-5.37 (m, 3H, H-11a, H-6, H-5), 5.24 (dd, *J* = 9.9, 1.7 Hz, 1H, H-11b), 5.17 (dt, *J* = 17.2, 1.8 Hz, 1H, H-10a), 5.08 (dt, *J* = 10.2, 1.8 Hz, 1H, H-10b), 5.01 (dat, *J* = 10.0, 3.3 Hz, 1H, H-16), 4.09-4.03 (m, 2H, H-7, H-8), 3.83 (ddd, *J* = 8.1, 5.3, 3.3 Hz, 1H, H-17), 3.47 (dd, *J* = 9.8, 4.9 Hz, 1H, H-20a), 3.41 (dd, *J* = 9.8, 5.9 Hz, 1H, H-20b), 3.06 (dd, *J* = 7.3, 2.0 Hz, 1H, H-13), 2.84 (ddd, *J* = 7.3, 5.9, 2.0 Hz, 1H, H-14), 2.25 (dd, *J* = 14.3, 4.5 Hz, 1H, H-2a), 2.05-1.92 (m, 4H, H-2b, H-3, H-4a, H-15a), 1.85-1.78 (m, 2H, H-4b, H-19), 1.71 (ddd, *J* = 14.6, 10.0, 5.9 Hz, 1H, H-15b), 1.65-1.63 (m, 1H, H-18a) 1.25-1.22 (m, 1H, H-18b), 1.05 (s, 9H, SiC$(CH_3)_3$), 0.97 (d, *J* = 6.7 Hz, 3H, 22-CH_3), 0.90 (s, 9H, SiC$(CH_3)_3$), 0.89 (s, 9H, SiC$(CH_3)_3$), 0.87 (s, 9H, SiC$(CH_3)_3$), 0.82 (d, *J* = 6.2 Hz, 3H, 21-CH_3), 0.09 (s, 3H, SiCH_3), 0.07 (s, 3H, SiCH_3), 0.06 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3), 0.03 (s, 3H, SiCH_3), 0.02 (s, 3H, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.43 (s, *C*=O), 137.3 (d, C-9), 135.6 (4 x d, 4 x Ar*C*H), 135.5 (d, C-12), 133.8 (s, Ar*C*), 133.7 (s, Ar*C*), 133.7 (d, C-5), 129.1 (d, C-6), 129.5 (2 x d, 2 x Ar*C*H), 127.6 (4 x d, 4 x Ar*C*H), 119.3 (t, C-11), 115.8 (t, C-10), 76.2 (d, C-8), 75.9 (d, C-7), 72.7 (d, C-16), 70.1 (d, C-17), 68.3 (t, C-20), 59.0 (d, C-13), 57.7 (d, C-14), 41.2 (t, C-2), 39.5 (t, C-4), 35.5 (t, C-18), 32.0 (d, C-19), 31.6 (t, C-15), 30.0 (d, C-3), 26.9 (q, SiC(*C*$H_3)_3$), 25.9 (2 x q, 2 x SiC(*C*$H_3)_3$), 25.8 (q, SiC(*C*$H_3)_3$), 19.3 (q, C-21), 19.3 (s, Si*C*), 18.2 (s, Si*C*), 18.2 (s, Si*C*), 10.0 (q, C-22), 17.9 (s, Si*C*), -4.3 (q, Si*C*H_3), -4.5 (q, Si*C*H_3), -4.6 (q, Si*C*H_3), -4.7 (q, Si*C*H_3), -4.8 (2 x q, 2 x Si*C*H_3); IR (film): $\tilde{\upsilon}$ = 2955, 2929, 2857, 1737, 1472, 1428, 1361, 1254, 1111, 1078, 835, 776, 701, 506 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{56}H_{96}NaO_7Si_4$ (M^+ + Na): 1015.6131, found: 1015.6143.

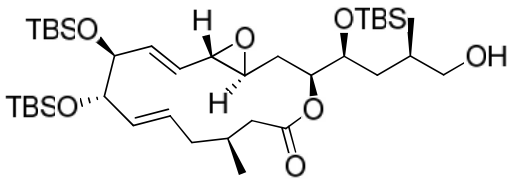
Compound **15** intercepts with our previously reported synthesis and was processed as previously described[1] to give iriomoteolide 1a (**1**).



12

Ring Closing Metathesis Product 12. To a solution of **15** (25 mg, 0.025 mmol) in toluene (55 mL) was added Grubbs II generation catalyst **11** (2.5 mg, 5% mol) in 2 portions over a period of 30 h. The reaction was stirred at room temperature till LC-MS analysis showed complete conversion of the starting material (ESI, m/z ($M+Na^+$) = 1015.84) into a single peak (ESI, m/z ($M+Na^+$) = 987.84). Evaporation of the

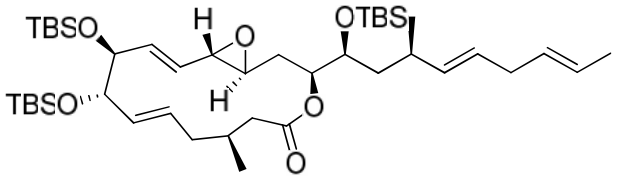
solvent under reduced pressure and purification of the crude residue by flash chromatography (toluene 100%) gave compound **12** (18 mg, 81%). Colorless oil: $[\alpha]_D^{20}$ = +8.9 (*c* = 2.00 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.65-7.61 (m, 4H, aromatics), 7.42-7.35 (m, 6H, aromatics), 5.64 (dd, *J* = 15.8, 7.9 Hz, 1H, H-9), 5.46 (dat, *J* = 15.6, 6.2 Hz, 1H, H-5), 5.35 (dd, *J* = 15.6, 5.7 Hz, 1H, H-6), 5.11 (dd, *J* = 15.8, 8.8 Hz, 1H, H-10), 5.00 (ddd, *J* = 12.0, 4.3, 1.9 Hz, 1H, H-14), 4.02-3.97 (m, 2H, H-7, H-8), 3.82 (dat, *J* = 8.2, 4.1 Hz, 1H, H-15), 3.45 (d, *J* = 4.9 Hz, 2H, H-18), 2.98 (dd, *J* = 8.7, 2.0 Hz, 1H, H-11), 2.77 (dat, *J* = 9.8, 2.0 Hz, 1H, H-12), 2.38 (dat, *J* = 14.1, 2.3 Hz, 1H, H-13a), 2.33-2.29 (m, 1H, H-4a), 2.27 (dd, *J* = 18.2, 6.3 Hz, 1H, H-2a), 2.12-2.08 (m, 1H, H-3), 1.86 (dd, *J* = 18.2, 6.0 Hz, 1H, H-2b), 1.81-1.76 (m, 2H, H-4b, H-17), 1.69-1.62 (m, 1H, H-16a), 1.28-1.24 (m, 1H, H-13b) 1.23-1.16 (m, 1H, H-16b), 0.97 (d, *J* = 6.7 Hz, 3H, H-19), 1.04, 0.89, 0.87, 0.86 (4 x s, 39H, 4 x $SiC(CH_3)_3$, H-20), 0.09 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5 (s, *C*=O), 137.0 (d, C-9), 135.6 (4 x d, 4 x Ar*C*H), 133.8 (s, Ar*C*), 133.7 (s, Ar*C*), 132.3 (d, C-6), 129.5 (2 x d, 2 x Ar*C*H), 129.3 (2 x d, C-5, C-10), 127.6 (4 x d, 4 x Ar*C*H), 77.7 (d, C-8), 77.5 (d, C-7), 72.1 (d, C-14), 70.0 (d, C-15), 67.7 (t, C-18), 59.4 (d, C-11), 57.7 (d, C-12), 37.9 (t, C-2), 37.5 (t, C-4), 34.9 (t, C-16), 31.8 (d, C-17), 31.6 (t, C-13), 28.1 (d, C-3), 26.9 (q, $SiC(CH_3)_3$), 26.0 (q, $SiC(CH_3)_3$), 25.9 (q, $SiC(CH_3)_3$), 25.8 (q, $SiC(CH_3)_3$), 21.0 (q, C-19), 19.3 (s, Si*C*), 18.2 (s, Si*C*), 18.2 (s, Si*C*), 18.1 (s, Si*C*), 17.9 (q, C-20), -4.2 (q, $SiCH_3$), -4.3 (q, $SiCH_3$), -4.4 (q, $SiCH_3$), -4.5 (q, $SiCH_3$), -4.6 (q, $SiCH_3$), -4.7 (q, $SiCH_3$); IR (film): $\tilde{\upsilon}$ = 2955, 2929, 2857, 1739, 1472, 1428, 1253, 1111, 1060, 835, 776 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{54}H_{92}NaO_7Si_4$ (M^+ + Na): 987.5818, found: 987.5815.



27

Compound 27 To a solution of intermediate **12** (170 mg, 0.17 mmol) in a mixture of THF/ MeOH (1 : 10, 7 mL) was added NH_4F (651 mg, 1.70 mmol). The mixture was stirred at 25ºC for 96 h and monitored by TLC till partial conversion of the starting material into a major more polar spot was observed (hexanes/EtOAc 4:1, *Rf* = 0.25). The solvents were evaporated under reduced pressure to ¼ of their volume and the

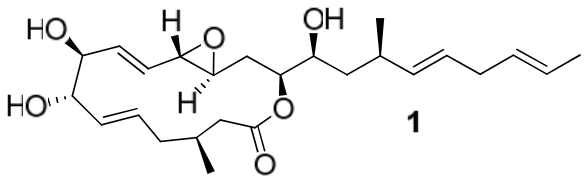
mixture was diluted with brine and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and the solvents were evaporated under reduced pressure to give the crude material which was purified by flash chromatography (hexanes/EtOAc 90 :10) to give recovered starting material (90 mg, 53%), and by further elution alcohol **27** (49 mg, 38%). Recycling of the starting material under the same reaction conditions, gave further alcohol **27** (26 mg, 58% overall yield). Colorless oil: $[\alpha]_D^{20}$ = +6.7 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.65 (dd, *J* = 15.7, 7.8 Hz, 1H, H-9), 5.48 (dat, *J* = 15.6, 6.5 Hz, 1H, H-5), 5.36 (dd, *J* = 15.6, 5.6 Hz, 1H, H-6), 5.14-5.08 (m, 2H, H-10, H-14), 4.02-3.97 (m, 2H, H-7, H-8), 3.82 (dat, *J* = 6.3, 5.0 Hz, 1H, H-15), 3.46-3.38 (m, 2H, H-18), 2.99 (dd, *J* = 8.7, 2.0 Hz, 1H, H-11), 2.77 (dat, *J* = 9.8, 2.0 Hz, 1H, H-12), 2.38 (dd, *J* = 18.1, 5.6 Hz, 1H, H-2a), 2.35-2.28 (m, 2H, H-4a, H-13a), 2.18-2.12 (m, 1H, H-3), 1.95 (dd, *J* = 18.1, 6.6 Hz, 1H, H-2b), 1.83-1.76 (m, 2H, H-4b, H-17), 1.60-1.52 (m, 1H, H-16a), 1.31-1.24 (m, 2H, H-13b, H-16b), 0.98 (d, *J* = 6.8 Hz, 3H, H-19), 0.92 (d, *J* = 6.7 Hz, 3H, H-20), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.11 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7 (s, *C*=O), 137.2 (d, C-9), 132.2 (d, C-6), 129.4 (d, C-5), 129.1 (d, C-10), 77.6 (2 x d, C-8, C-7), 71.8 (d, C-14), 70.8 (d, C-15), 67.8 (t, C-18), 59.4 (d, C-11), 57.5 (d, C-12), 38.2 (t, C-2), 37.6 (t, C-4), 31.8 (t, C-16), 32.6 (t, C-13), 32.0 (d, C-17), 28.3 (d, C-3), 26.0 (q, $SiC(CH_3)_3$), 25.9 (q, $SiC(CH_3)_3$), 25.7 (q, $SiC(CH_3)_3$), 21.2 (q, C-19), 18.2 (s, Si*C*), 18.1 (s, Si*C*), 17.9 (s, Si*C*), 17.9 (q, C-20), -4.2 (q, $SiCH_3$), -4.3 (q, $SiCH_3$), -4.4 (q, $SiCH_3$), -4.4 (q, $SiCH_3$), -4.5 (q, $SiCH_3$), -4.5 (q, $SiCH_3$) ; IR (film): $\tilde{\upsilon}$ = 3500, 2954, 2928, 2857, 1739, 1472, 1361, 1251, 1073, 835, 775 cm^{-1}; HRMS (ES$^+$): *m/z*: Calcd. for $C_{38}H_{74}NaO_7Si_3$ (M^+ + Na): 749.4640, found: 749.4629.



28

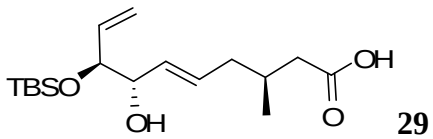
Compound 28. To a solution of alcohol **27** (21 mg, 28 μmol) in wet CH_2Cl_2 (1 mL) was added Dess-Martin periodinane (18 mg, 42 μmol). The resulting suspension was stirred for 45 min at 25ºC, the solvent was evaporated under reduced pressure and the crude residue was purified through a pad containing Florisil® (60-100 mesh,

hexanes/EtOAc 9:1), to give the intermediate aldehyde (18 mg, 88%), which was directly used in the next step without further purification. To a solution of previously reported $BTSO_2CH_2CHCHCH_3$ [1] (**6**) (7 mg, 24 μmol) in THF (0.6 mL) at -78°C, was added a solution of KHMDS (10 mg, 48 μmol) in DMF (0.4 mL). The resulting yellow-orange mixture was stirred at -78°C for 40 min, before a solution of the aldehyde obtained in the previous step in THF (0.5 mL) was slowly added. After 45 min, the mixture was slowly warmed to 25ºC and quenched with aq. sat. NH_4Cl solution. The mixture was diluted with EtOAc, the organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude residue which was purified by flash chromatography (toluene 100%) to give compound **28** (14 mg, 76%). Colorless oil: $[\alpha]_D^{20}$ = +14.7 (*c* = 1.00 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 5.64 (dd, *J* = 15.7, 7.8 Hz, 1H, H-9), 5.48 (dat, *J* = 15.6, 6.3 Hz, 1H, H-5), 5.42-5.29 (m, 4H, H-6, H-19, H-21, H-22), 5.13 (ddt, *J* = 15.4, 7.9, 1.3 Hz, 1H, H-18), 5.11 (dd, *J* = 15.7, 8.7 Hz, 1H, H-10), 4.94 (ddd, *J* = 12.1, 4.2, 1.8 Hz, 1H, H-14), 4.00-3.97 (m, 2H, H-7, H-8), 3.74 (dat, *J* = 8.5, 4.1 Hz, 1H, H-15), 2.99 (dd, *J* = 8.7, 2.0 Hz, 1H, H-11), 2.74 (dat, *J* = 9.7, 2.0 Hz, 1H, H-12), 2.65-2.62 (m, 2H, H-20), 2.40 (dat, *J* = 13.8, 2.2 Hz, 1H, H-13a), 2.35 (dd, *J* = 18.2, 6.2 Hz, 1H, H-2a), 2.32-2.29 (m, 1H, H-4a), 2.26-2.15 (m, 2H, H-3, H-17), 1.93 (dd, *J* = 18.2, 5.9 Hz, 1H, H-2b), 1.84-1.80 (m, 1H, H-4b), 1.66-1.63 (m, 3H, H-23), 1.35-1.25 (m, 2H, H-16), 1.24-1.16 (m, 1H, H-13b), 0.99 (d, *J* = 6.8 Hz, 3H, H-25 or H-24), 0.96 (d, *J* = 6.7 Hz, 3H, H-25 or H-24), 0.92 (s, 9H, $SiC(CH_3)_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.11 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3 (s, *C*=O), 136.9 (d, C-9), 135.9 (d, C-18), 132.0 (d), 129.6 (d), 127.9 (d), 125.5 (d), 129.3 (d, C-10), 129.2 (d, C-5), 77.6 (d, C-8), 77.0 (d, C-7), 72.2 (d, C-14), 69.5 (d, C-15), 59.5 (d, C-11), 57.6 (d, C-12), 38.9 (t, C-16), 38.2 (t, C-2), 37.9 (t, C-4), 35.6 (t, C-20), 32.8 (d, C-3 or C-17), 31.1 (t, C-13), 28.0 (d, C-3 or C-17), 25.9 (q, $SiC(CH_3)_3$), 25.9 (q, $SiC(CH_3)_3$), 25.8 (q, $SiC(CH_3)_3$), 22.1 (q, C-25), 21.2 (q, C-24), 18.2 (s, Si*C*), 18.1 (s, Si*C*), 17.9 (s, Si*C*), 17.8 (q, C-23), -4.2 (q, $SiCH_3$), -4.2 (q, $SiCH_3$), -4.3 (q, $SiCH_3$), -4.4 (q, $SiCH_3$), -4.4 (q, $SiCH_3$), -4.6 (q, $SiCH_3$); IR (film): $\tilde{\upsilon}$ = 2954, 2929, 2857, 1741, 1472, 1361, 1251, 1124, 1061, 965, 835, 775 cm^{-1}; HRMS (ES^+): *m/z*: Calcd. for $C_{43}H_{80}O_6NaSi_3$ (M^+ + Na): 799.5160, found: 799.5164.



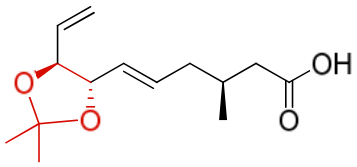
Iriomoteolide-3a (1). To a solution of protected iriomoteolide-3a **28** (19 mg, 18 μmol) in THF (1 mL), was added TBAF (1M in THF, 57 μL, 57 μmol). The reaction mixture was stirred at 25ºC for 3 h. A major more polar spot (TLC hexanes/EtOAc 1:9, *Rf* = 0.25) was observed. The solvent was removed under a flow of nitrogen, and the crude residue was purified by flash chromatography (hexanes/EtOAc 1:9 → EtOAc 100%) to give Iriomoteolide-3a **1** (9 mg, 86%). Amorphous solid: $[\alpha]_D^{20}$ = +30.5 (*c* = 0.33 in $CHCl_3$), (Lit.[1] +24.0, $CHCl_3$). The spectroscopic data are in full agreement with those of the natural product reported in the literature [2]. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.79 (m, 1H), 5.77 (m, 1H), 5.45 (m, 1H), 5.40 (m, 2H), 5.38 (m, 1H), 5.25 (dd, *J* = 15.5, 9.3 Hz, 1H), 5.20 (dd, *J* =15.5, 8.5 Hz, 1H), 5.11 (ddd, *J* = 12.0, 3.4, 2.2 Hz, 1H), 3.96 (m, 1H), 3.95 (m, 1H), 3.59 (brm, 1H), 3.00 (dd, *J* = 9.2, 2.0 Hz, 1H), 2.89 (dd, *J* = 10.2, 2.0 Hz, 1H), 2.66 (m, 2H), 2.38 (dd, *J* = 17.9, 4.9 Hz, 1H), 2.35 (m, 1H), 2.32 (m, 1H), 2.26 (dt, *J* = 14.0, 2.3 Hz, 1H), 2.10 (m, 1H), 1.98 (dd, *J* = 17.9, 8.1 Hz, 1H), 1.82 (ddd, *J* = 14.0, 8.9, 5.9 Hz, 1H), 1.64 (d, *J* = 4.7 Hz, 3H), 1.48 (ddd, *J* = 14.0, 10.4, 10.0 Hz, 1H), 1.39 (ddd, *J* = 13.9, 10.0, 4.0 Hz, 1H), 1.27 (dd, *J* = 13.9, 10.1, 2.7 Hz, 1H), 1.01 (d, *J* = 6.6 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.5, 135.4, 135.3, 133.6, 133.0, 131.2, 129.5, 128.7, 125.6, 76.8, 76.7, 72.8, 70.9, 58.9, 57.6, 40.7, 37.7, 36.0, 35.5, 34.4, 33.3, 29.9, 21.7, 20.8, 17.9; HRMS (ES^+): *m/z*: Calcd. for $C_{25}H_{38}O_6Na$ (M^+ + Na): 457.2561, found: 457.2558.

Synthesis of 7,8-O-Isopropylidene Iriomoteolide-3a. Analogue 2



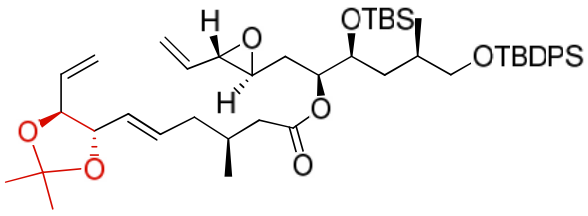
(*3S,7S,8S,E*)-8-(*tert*-butyldimethylsilyloxy)-7-hydroxy-3-methyldeca-5,9-dienoic acid (29) Following an identical procedure to the one described for compound **14**, starting from previously synthetized (*S*)-3-methylhex-5-enoic acid [1] (**4**) (100 mg, 0.78 mmol) and diene **5d** (711 mg, 3.1 mmol), diene **29** was obtained (166 mg, 65 %)**.** Colourless oil: $[\alpha]_D^{25}$ +5.2 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.78 (ddd, *J* = 17.2, 10.4, 6.9 Hz, 1H), 5.67 (dat, *J* = 15.1, 7.2 Hz, 1H), 5.45 (dd, *J* = 15.1,

6.4 Hz, 1H), 5.22 (dat, *J* = 17.2, 1.6 Hz, 1H), 5.17 (dat, *J* = 10.4, 1.6 Hz, 1H), 3.94 (at, *J* = 6.4 Hz, 1H), 3.90 (at, *J* = 6.4 Hz, 1H), 2.37 (dd, *J* = 14.8, 5.3 Hz, 1H), 2.17-1.96 (m, 4H), 0.96 (d, *J* = 6.2 Hz, 3H), 0.91 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.0, 137.8, 131.1, 130.9, 117.0, 77.8, 75.7, 40.6, 39.4, 30.1, 25.8, 19.5, 18.2, -4.1, -4.8; IR (film): ν = 3500, 2956, 2929, 2857, 1708, 1461, 1361, 1252, 1086, 925, 835 cm^{-1}; HRMS (ES^+) m/z: Calcd. for $C_{17}H_{32}O_4Si$ (M^+) 328.2070. Found 328.2076.



30

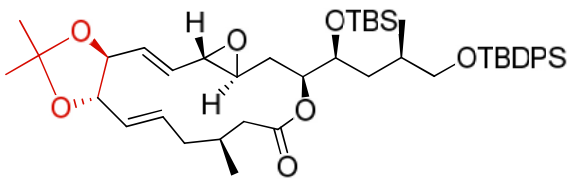
(*S*,*E*)-6-((*4S*,*5S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-3-methylhex-5-enoic acid (30) Diene **29** (166 mg, 0.50 mmol) was dissolved in THF (4 mL) and treated with TBAF (1M in THF, 600 µL, 0.60 mmol) for 1h. The solvent was removed under reduced pressure and the residue was filtered on silica gel eluting with AcOEt 100%. The intermediate diol was dissolved in acetone dimethylacetal (25 mL) and triflic acid was added (0.13 µL, 0.5%). The reaction mixture was stirred at r.t. for 2h, after which time triethylamine (2 µL) was added. The solvents were removed under reduced pressure and the residue was purified by flash chromatography (hexanes/AcOEt 80 : 20) to give acid **30** (71 mg, 56%). Colourless oil: $[\alpha]_D^{25}$ +5.2 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.82-5.69 (m, 2H), 5.67 (dd, *J* = 15.1, 7.2 Hz, 1H), 5.33 (dd, *J* = 17.3, 1.0 Hz, 1H), 5.23 (dd, *J* = 10.2, 1.0 Hz,1H), 4.08-4.03 (m, 2H), 2.35 (dd, *J* = 15.1, 5.7 Hz, 1H), 2.16-2.11 (m, 2H), 2.08-1.96 (m, 2H), 1.44 (s, 3H), 1.43 (s, 3H), 0.96 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.9, 134.2, 133.5, 128.2, 118.7, 109.0, 82.3, 82.0, 40.7, 39.2, 29.8, 27.0, 26.9, 19.4; IR (film): ν = 2986, 2933, 1707, 1456, 1372, 1238, 1053, 929, 879 cm^{-1}; HRMS (ES^+) m/z: Calcd. for $C_{14}H_{22}O_4Na$ (MNa^+) 277.1410. Found 277.1411.



31

Ring Closing Metathesis precursor 31. Following an identical procedure to the one described for the synthesis of compound **15**, starting from acid **30** (99 mg, 0.39 mmol) and alcohol **3** (221 mg, 0.39 mmol), ester **31** was obtained (243 mg, 77 %). Colourless

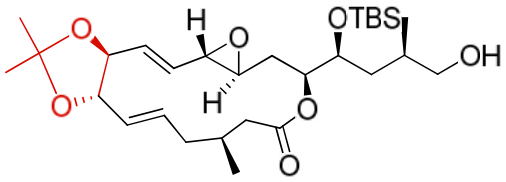
oil: $[\alpha]_D^{20}$ = +1.0 (*c* = 1.00 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.68-7.61 (m, 4H, aromatics), 7.43-7.36 (m, 6H, aromatics), 5.78 (ddd, *J* = 17.0, 12.0, 6.5 Hz, 1H, H-9), 5.66 (dat, *J* = 15.0, 7.1 Hz, 1H, H-5), 5.53 (ddd, *J* = 17.2, 10.0, 7.5 Hz, 1H, H-12), 5.46-5.39 (m, 2H, H-11a, H-6), 5.32 (d, *J* = 17.0 Hz, 1H, H-10a), 5.25 (dd, *J* = 11.3, 1.1 Hz, 1H, H-11b), 5.22 (dd, *J* = 10.2, 1.0 Hz, 1H, H-10b), 5.02 (dat, *J* = 9.8, 3.3 Hz, 1H, H-16), 4.06-4.02 (m, 2H, H-7, H-8), 3.87-3.82 (m, 1H, H-17), 3.47 (dd, *J* = 9.8, 4.9 Hz, 1H, H-20a), 3.41 (dd, *J* = 9.8, 5.7 Hz, 1H, H-20b), 3.07 (dd, *J* = 7.5, 1.7 Hz, 1H, H-13), 2.84 (td, *J* = 7.3, 2.0 Hz, 1H, H-14), 2.24 (dd, *J* = 14.2, 4.5 Hz, 1H, H-2a), 2.07 (dat, *J* = 12.5, 5.7 Hz, 1H, H-4a), 2.02 (m, 3H, H-2b, H-3, H-15a), 1.92-1.86 (m, 1H, H-4b), 1.82-1.76 (m, 1H, H-19), 1.73 (ddd, *J* = 15.7, 9.9, 6.2 Hz, 1H, H-15b), 1.68-1.63 (m, 1H, H-18a), 1.43 (s, 6H, $OC(CH_3)_2$), 1.26-1.20 (m, 1H, H-18b), 1.05 (s, 9H, $SiC(CH_3)_3$), 0.98 (d, *J* = 6.7 Hz, 3H, 22-CH_3), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.82 (d, *J* = 6.2 Hz, 3H, 21-CH_3), 0.09, 0.03 (2 x s, 6H, 2 x $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1 (s, *C*=O), 135.6 (4 x d, 4 x Ar*C*H), 135.5 (d, C-12), 134.2 (d, C-9), 133.8, 133.7 (2 x s, 2 x Ar*C*), 133.6 (d, C-5), 129.5 (2 x d, 2 x Ar*C*H), 128.1 (d, C-6), 127.6 (4 x d, 4 x Ar*C*H), 119.4 (t, C-11), 118.6 (t, C-10), 108.9 (s, $C(CH_3)_2$, 82.3, 82.1 (2 x d, C-8, C-7), 72.7 (d, C-16), 70.1 (d, C-17), 68.2 (t, C-20), 59.0 (d, C-13), 57.6 (d, C-14), 41.0 (t, C-2), 39.4 (t, C-4), 35.5 (t, C-18), 32.0 (d, C-19), 31.6 (t, C-15), 29.8 (d, C-3), 27.0, 26.9 (2 x q, 2 x CH_3), 26.8, 25.8 (4 x q, 2 x $SiC(CH_3)_3$), 19.3 (q, C-21), 19.3 (s, Si*C*), 18.0 (s, Si*C*), 17.9 (q, C-22), -4.3, -4.6, (2 x q, 2 x $SiCH_3$); IR (film): ν = 2956, 2930, 2857, 1735, 1472, 1428, 1251, 1111, 1078, 835, 777, 704, 502 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{47}H_{72}O_7NaSi_2$ (M^+ + Na): 827.47088, found: 827.47069.



32

Ring Closing Metathesis product 32. To a solution of ester **31** (236 mg, 0.29 mmol) in toluene (580 mL) was added Grubb's II generation catalyst **11** (27 mg, 11 % mol) in 4 portions of 7 mg each over a period of 20 h stirring at room temperature. Evaporation of the solvent under reduced pressure and purification of the crude residue by silica gel flash column chromatography (toluene/AcoEt 97 : 3) gave compound **32** (154 mg, 68 %). Colourless oil: $[\alpha]_D^{20}$ = +42.7 (*c* = 0.7 in $CHCl_3$); ^1H

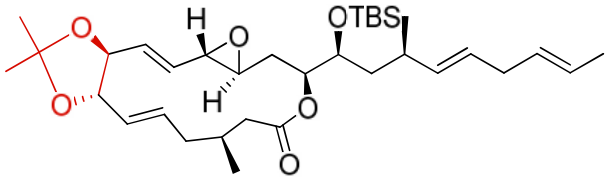
NMR (400 MHz, $CDCl_3$): δ = 7.65-7.62 (m, 4H, aromatics) 7.45-7.35 (m, 6H, aromatics), 5.86 (dd, *J* = 15.3, 9.2 Hz, 1H, H-9), 5.79 (ddd, *J* = 15.4, 8.5, 6.2 Hz, 1H, H-5), 5.45 (dd, *J* = 15.4, 8.4 Hz, 1H, H-6), 5.32 (dd, *J* = 15.3, 9.4 Hz, 1H, H-10), 5.18 (ddd, *J* = 12.1, 3.7, 2.5 Hz, 1H, H-14), 4.02 (d, *J* = 8.6 Hz, 1H, H-7), 3.92 (d, *J* = 8.6 Hz, 1H, H-8), 3.78-3.74 (m, 1H, H-15), 3.50-3.42 (m, 2H, H-18), 3.03 (dd, *J* = 9.5, 1.7 Hz, 1H, H-11), 2.83 (dat, *J* = 9.5, 1.7 Hz, 1H, H-12), 2.34 (dd, *J* = 13.4, 2.1 Hz, 1H, H-2a), 2.27 (dat, *J* = 14.3, 1.7 Hz, 1H, H-13a), 2.19 (ddd, *J* = 13.0, 8.5, 3.6 Hz, 1H, H-4a), 1.85-1.61 (m, 5H, H-17, H-16a, H-4b, H-3, H-2b), 1.44-1.42 (m, 1H, H-13b), 1.44 (s, 3H, CCH_3), 1.42 (s, 3H, CCH_3), 1.26 (m, 1H, H-16b), 1.04 (s, 9H, $SiC(CH_3)_3$), 0.98 (d, *J* = 6.7 Hz, 3H, H-19 or H-20), 0.94 (d, *J* = 6.7 Hz, 3H, H-19 or H-20), 0.85 (s, 9H, $SiC(CH_3)_3$), 0.05, -0.01 (2 x s, 6H, 2 x $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5 (s, *C*=O), 135.6 (4 x d, 4 x Ar*C*H), 135.5 (d, C-5), 134.9 (d, C-10), 133.8, 133.6 (2 x s, 2 x Ar*C*), 132.5 (d, C-9), 129.6, 129.5 (2 x d, 2 x Ar*C*H), 127.6 (4 x d, 4 x Ar*C*H), 127.3 (d, C-6), 109.5 (s, *C*CH_3), 83.0 (d, C-7), 81.4 (d, C-8), 72.4 (d, C-14), 70.6 (d, C-15), 68.0 (t, C-18), 59.2 (d, C-11), 58.1 (d, C-12), 37.0 (t, C-2), 36.4 (t, C-4), 35.8 (t, C-16), 33.2 (d, C-3 or C17), 32.0 (t, C-13), 31.7 (d, C-3 or C-17), 27.0, 26.9 (2 x q, 2 x C*C*H_3), 26.8 (3 x q, $SiC(CH_3)_3$), 25.8 (3 x q, $SiC(CH_3)_3$), 21.0 (q, C19 or C20), 19.3 (s, Si*C*), 18.0 (q, C-19 or C-20), 17.9 (s, Si*C*), -4.3, -4.5, (2 x q, 2 x Si*C*H_3); IR (film): $\tilde{\upsilon}$ = 2955, 2930, 2857, 1736, 1472, 1428, 1369, 1217, 1055, 776 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{45}H_{68}O_7NaSi_2$ (M^+ + Na): 799.43958, found: 799.43883.



33

Alcohol 33. To a solution of **32** (154 mg, 0.19 mmol) in a mixture of THF/ MeOH (1 : 10, 7 mL) was added NH_4F (700 mg, 19.0 mmol). The mixture was stirred at room temperature for 96 h, after which time partial conversion of the starting material into a major more polar spot was observed on TLC. The solvents were evaporated under reduced pressure to ¼ of their volume and the mixture was diluted with brine and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and the solvents were evaporated under reduced pressure to give the crude material which was purified by flash chromatography (hexanes/EtOAc 90 :10) to give recovered starting material (90 mg, 61%), and by further elution alcohol **33** (30 mg, 29%). Successive recycling of

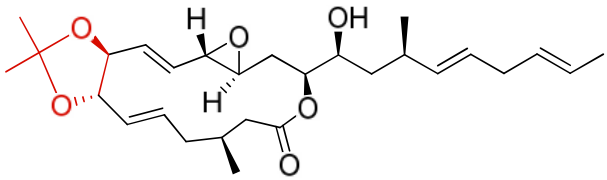
the starting material under the same reaction conditions, gave further alcohol **33** (35 mg, 63% overall). Colourless oil: $[\alpha]_D^{20}$ = +45.7 (*c* = 0.5 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 5.62 (dd, *J* = 15.4, 9.1 Hz, 1H, H-9), 5.82 (ddd, *J* = 15.3, 8.6, 6.3 Hz, 1H, H-5), 5.45 (dd, *J* = 15.3, 8.4 Hz, 1H, H-6), 5.32 (dd, *J* = 15.4, 9.0 Hz, 1H, H-10), 5.32-5.29 (m, 1H, H-14), 4.02 (at, *J* = 8.5 Hz, 1H, H-7), 3.92 (at, *J* = 8.7 Hz, 1H, H-8), 3.80 (dd, J = 11.0, 5.4 Hz, 1H, H-15), 3.47-3-37 (m, 2H, H-18), 3.04 (dd, *J* = 9.4, 1.7 Hz, 1H, H-11), 2.86 (dat, *J* = 9.7, 1.7 Hz, 1H, H-12), 2.44 (dd, J = 14.7, 2.0 Hz, 1H, H-2a), 2.25-2.16 (m, 2H, H-13a, H-4a), 1.95-1.66 (m, 5H, H-17, H13b, H-4b, H-3, H-2b), 1.58-1.52 (m, 1H, H-16a), 1.47 (s, 3H, CCH_3), 1.42 (s, 3H, CCH_3), 1.38-1.29 (m, 1H, H-16b), 1.02 (d, *J* = 6.1 Hz, 3H, H-17 or H-3), 0.91 (d, *J* = 6.7 Hz, 3H, H-17 or H-3), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.04, (s, 6H, 2 x $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6 (s, *C*=O), 135.6 (d, C-5), 134.8 (d, C-9), 132.7 (d, C-6), 127.4 (d, C-10), 109.6 (s *C*CH_3), 83.0 (d, C-7), 81.3 (d, C-8), 72.1 (d, C-15), 71.5 (d, C-14), 68.0 (t, C-18), 59.2 (d, C-11), 57.8 (d, C-12), 37.5 (t, C-16), 37.3 (t, C-2), 36.5 (t, C-4), 33.4 (t, C-17 or C-3), 33.0 (d, C-13), 31.9 (d, C-17 or C-3), 27.0 (2 x q, 2 x C*C*H3), 25.7 (3 x q, $SiC(CH_3)_3$), 21.1 (q, C-20 or, C-19), 18.0 (q, C-20 or, C-19), 17.9 (s,Si*C*), -4.4, -4.5 (2 x q, 2 x Si*C*H_3); IR (film): $\tilde{\upsilon}$ = 2958, 2929, 2857, 1734, 1459, 1370, 1252, 1171, 1051, 837 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{29}H_{50}O_7NaSi$ (M^+ + Na): 561.32180, found: 561.32163.



34

Compound 34 To a solution of alcohol **33** (65 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) was added Dess-Martin periodinane (61 mg, 0.13 mmol). The resulting suspension was stirred for 45 min at room temperature, the solvent was evaporated under reduced pressure and the crude residue was rapidly passed through a pad containing Fluorisil® (60-100 mesh, hexanes/EtOAc 80 : 20), to give the intermediate crude aldehyde (59 mg, 91%), which was directly reacted in the next step. To a solution of previously reported $BTSO_2CH_2CHCHCH_3$ [1] (**6**) (29 mg, 0.11 mmol) and the previously obtained aldehyde, in THF (2 mL) at -78 °C, was slowly added KHMDS (44 mg, 0.22 mmol) dissolved in DMF (0.7 mL). The resulting yellow orange mixture was stirred at -78 °C for 40 min., After 45 min, the mixture was slowly warmed to room temperature and quenched with aq. sat. NH_4Cl. The mixture was diluted with EtOAc, the organic

layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude residue which was purified by flash chromatography (toluene 100%) to give compound **34** (41 mg, 63%). Colourless oil: $[\alpha]_D^{20}$ = +65.0 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.86 (dd, *J* = 15.46, 9.1 Hz, 1H, H-9), 5.81 (ddd, *J* = 15.5, 8.5, 6.2 Hz, 1H, H-5), 5.45 (dd, *J* = 15.5, 8.4 Hz, 1H, H-6), 5.41-5.29 (m, 4H, H-22, H-21, H-19, H-10), 5.19-5.12 (m, 2H, H-18, H-14), 4.02 (at, *J* = 8.6 Hz, 1H, H-7), 3.92 (at, *J* = 8.6 Hz, 1H, H-8), 3.70 (dt, *J* = 10.0, 4.0 Hz, 2H, H-15), 3.04 (dd, *J* = 9.3, 1.9 Hz, 1H, H-11), 2.81 (dat, *J* = 10.0, 1.9 Hz, 1H, H-12), 2.65-2.62 (m, 2H, H-20), 2.41 (dd, J = 22.0, 8.3 Hz, 1H, H2a), 2.29 (dat, *J* = 14.0, 2.2 Hz, 1H, H-13a), 2.27-2.18 (m, 4H, H-17, H-13a, H-4a), 1.93-1.84 (m, 1H, H-4b), 1.65-1.63 (m, 3H, H-23), 1.44 (s, 3H, CCH_3), 1.42 (s, 3H, CCH_3), 1.39-1.28 (m, 2H, H-16), 1.04 (d, *J* = 6.0 Hz, 3H, H-24), 0.97 (d, *J* = 6.8 Hz, 3H, H-25), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.08 (s, 3H, $SiCH_3$), 0.07, (s, 3H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4 (s, *C*=O), 136.0 (d, C-18), 135.3 (d, C-5), 134.9 (d, C-10), 132.5 (d, C-9), 129.9, 129.6, 128.0, 125.5 (4 x d, C-22, C-21, C-19, C-6), 109.5 (s, *C*CH_3), 83.0 (d, C-7), 81.4 (d, C-8), 72.5 (d, C-14), 70.4 (d, C-15), 59.2 (d, C-11), 58.2 (d, C-12), 39.6 (t, C-16), 37.3 (t, C-2), 36.4 (t, C-4), 35.6 (t, C-20), 33.1 (d, C-17), 32.8 (d, C-3), 31.7 (t, C-13), 27.0 (2 x q, 2 x C*C*H_3), 25.8 (3 x q, $SiC(CH_3)_3$), 22.0 (q, C-25), 19.5 (q, C-24), 18.2, 18.1, 18.0 (s, Si*C*), 17.8 (q, C-23), -4.3, (2 x q, 2 x Si*C*H_3); IR (film): $\tilde{\upsilon}$ = 2955, 2930, 2857, 1737, 1456, 1370, 1219, 1171, 1055, 967, 836, 774 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{34}H_{56}O_6NaSi$ (M^+ + Na): 611.37384, found: 611.37379.

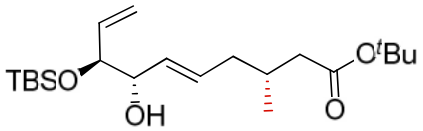


2

Iriomoteolide 3a-7,8-O-acetonide. Analogue (2) To a solution of **34** (41 mg, 70 µmol) in THF (2 mL), was added TBAF (1M in THF, 95 µL, 95 µmol). The reaction mixture was stirred at room temperature for 3 h. The solvent was removed under nitrogen flow, and the crude residue was purified by flash chromatography (hexanes/EtOAc 70 : 30) to give acetonide **2** (28 mg, 84%). Colourless amorphous solid: $[\alpha]_D^{20}$ = +45.2 (*c* = 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 5.86 (dd, *J* = 15.3, 9.1 Hz, 1H, H-9), 5.82 (dd, *J* = 15.4, 8.6, 6.1 Hz, 1H, H-5), 5.49-5.38 (m, 4H, H-22, H-21, H-19, H-6), 5.32 (dd, *J* = 15.3, 9.3 Hz, 1H, H-10), 5.23 (m, 2H, H-18, H-

14), 4.02 (at, *J* = 8.5 Hz, 1H, H-7), 3.93 (at, *J* = 8.8 Hz, 1H, H-8), 3.63-3.56 (m, 1H, H-15), 3.05 (dd, *J* = 9.4, 1.7 Hz, 1H, H-11), 2.86 (dt, *J* = 10.0, 1.7 Hz, 1H, H-12), 2.69-2.63 (m, 2H, H-20), 2.48 (dd, *J* = 17.2, 1.7 Hz, 1H, H-2a), 2.40-2.33 (m, 3H, H-17), 2.26-2.18 (m, 2H, H-13a, H-4a), 1.94 (dd, *J* = 17.2, 10.6 Hz, 1H, H-2b), 1.91-1.81 (m, 1H, H-3), 1.67-1.64 (m, 3H, H-23), 1.60-1.55 (m, 1H, H-13b), 1.43 (s, 3H, CCH_3), 1.42 (s, 3H, CCH_3), 1.42-1.37 (m, 1H, H-16a), 1.28 (ddd, *J* = 15.5, 9.9, 2.7 Hz, 1H, H-16b), 1.01 (d, *J* = 6.2 Hz, 3H, H-24), 1.00 (d, *J* = 6.7 Hz, 3H, H.25); ^{13}C NMR (125 MHz, CD_2Cl_2): δ = 172.7 (s, *C*=O), 135.6 (d, C-18), 135.2 (d, C-5), 134.8 (d, C-10), 132.7 (d, C-9), 129.5, 128.8, 127.6, 125.6 (4 x d, C-22, C-21, C-19, C-6), 109.6 (s, *C*CH_3), 83.0 (d, C-7), 81.4 (d, C-8), 73.3 (d, C-14), 70.8 (d, C-15), 59.1 (d, C-11), 57.5 (d, C-12), 40.6 (t, C-16), 37.1 (t, C-2), 36.5 (t, C-2), 35.5 (t, C-20), 34.1 (t, C-13), 33.6 (d, C-3), 33.3 (d, C-3), 27.0 (2 x q, 2 x C*C*H_3), 21.6 (q, C-25), 21.2 (q, C-24), 17.9 (q, C-23); IR (film): $\tilde{\upsilon}$ = 3950, 2984, 2957, 2930, 2871, 1733, 1455, 1371, 1218, 1171, 1054, 969, 878 cm^{-1}; HRMS (ES$^+$): *m/z*: Calcd. for $C_{28}H_{42}O_6Na$ (M^+ + Na): 497.28736, found: 497.28727.

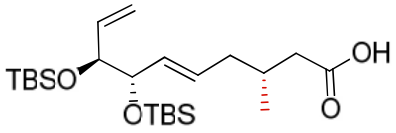
Synthesis of the C-3 epimer of iriomoteolide 3a. Analogue 17



35

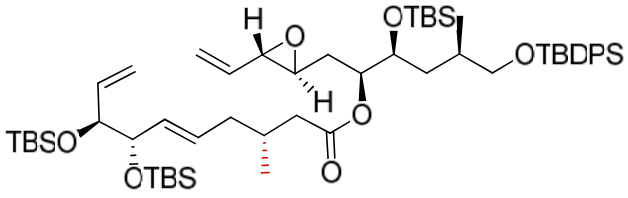
(*E*)-(3*R*,7*S*,8*S*)-8-(*tert*-Butyl-dimethyl-silanyloxy)-7-hydroxy-3-methyl-deca-5,9-dienoic acid *tert*-butyl ester (35) Following an identical procedure to the one described for compound **26**, starting from *ent*-ester **13** (200 mg, 0.87 mmol), *tert*butyl ester **35** (252 mg, 75%) was obtained. Colourless oil: $[\alpha]_D^{20}$ = +11.0 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82 (ddd, *J* = 17.2, 10.4, 6.6 Hz, 1H, H-9), 5.67 (dat, *J* = 15.4, 6.3 Hz, 1H, H-5), 5.43 (dd, *J* = 15.4, 6.4 Hz, 1H, H-6), 5.21 (dat, *J* = 17.2, 1.6 Hz, 1H, H-10a), 5.17 (dat, *J* = 10.4, 1.6 Hz, 1H, H-10b), 3.94 (at, *J* = 6.3 Hz, 1H, H-8), 3.93-3.87 (m, 1H, H-7), 2.53 (d, *J* = 4.0 Hz, 1H, 7-OH), 2.22 (dd, *J* = 17.5, 8.1 Hz, 1H, H-2a), 2.05-1.94 (m, 4H, H-2b, H-3, H-4), 1.44 (s, 9H, $OC(CH_3)_3$,), 0.93 (d, *J* = 5.7 Hz, 3H, 3-CH_3), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.08, 0.05 (2 x s, 6H, 2 x $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5 (s, *C*=O), 137.9 (d, C-9), 131.4 (d, C-5), 130.6 (d, C-6), 116.9 (t, C-10), 80.0 (s, O*C*$(CH_3)_3$), 77.8 (d, C-8), 75.7 (d, C-7), 42.4 (t, C-2), 39.4 (t, C-4), 30.4 (d, C-3), 28.1 (3 x q, $OC(CH_3)_3$), 25.8 (3 x q,

SiC(CH_3)$_3$), 19.5 (q, 3-CH_3), 18.1 (s, Si*C*), -4.1, -4.8 (2 x q, 2 x SiCH_3); IR (film): $\tilde{\upsilon}$ = 3500, 2956, 2929, 2857, 1729, 1461, 1366, 1253, 1149, 835, 776 cm^{-1}; HRMS (ES$^+$): m/z: Calcd for $C_{21}H_{40}O_4NaSi$ (M^+ + Na): 407.2594, found: 407.2593.



36

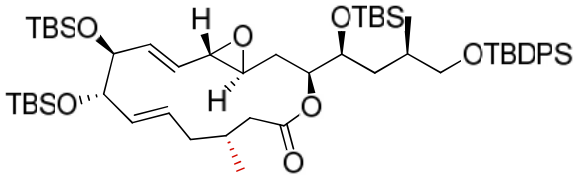
(*E*)-(3*R*,7*S*,8*S*)-7,8-Bis-(*tert*-butyl-dimethyl-silanyloxy)-3-methyl-deca-5,9-dienoic acid (36) Following an identical procedure to the one described for compound **14**, starting from *tert*butyl ester **35** (242 mg, 0.63 mmol), acid **36** was obtained (226 mg, 81%). Colourless oil: $[\alpha]_D^{20}$ = -41.6 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.88 (ddd, *J* = 17.2, 10.5, 6.4 Hz, 1H, H-9), 5.51 (dat, *J* = 15.6, 8.6 Hz, 1H, H-5), 5.43 (dd, *J* = 15.6, 5.5 Hz, 1H, H-6), 5.18 (dat, *J* = 17.2, 1.7 Hz, 1H, H-10a), 5.09 (dat, *J* = 10.5, 1.4 Hz, 1H, H-10b), 4.10-4.04 (m, 2H, H-8, H-7), 2.42 (dd, *J* = 14.6, 4.2 Hz, 1H, H-2a), 2.09-1.99 (m, 4H, H-3, H-4, H-2b), 0.97 (d, *J* = 6.1 Hz, 3H, 3-CH_3), 0.90, 0.89 (2 x s, 18H, 2 x SiC(CH_3)$_3$), 0.06, 0.03, 0.01 (4 x s, 12H, 4 x SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.2 (s, *C*=O), 137.3 (d, C-9), 131.5, 129.0 (2 x d, C-5, C-6), 115.1 (t, C-10), 76.2, 75.9 (2 x d, C-8, C-7), 40.3 (t, C-2), 39.4 (t, C-4), 30.2 (d, C-3), 25.8 (4 x q, 4 x SiCCH_3), 19.6 (q, 3-CH_3), 18.2 (2 x s, 2 x Si*C*), -4.5, -4.6, -4.7, -4.8 (4 x q, 4 x SiCH_3); IR (film): $\tilde{\upsilon}$ = 2956, 2929, 2857, 1709, 1407, 1253, 1133, 1077, 835, 775 cm^{-1}; HRMS (ES$^+$): *m/z*: Calcd for $C_{23}H_{46}O_4NaSi$ (M^+ + Na): 465.2832, found: 465.2835.



37

Ring Closing Metathesis precursor 37. Following an identical procedure to the one described for compound **15**, starting from alcohol **3** (282 mg, 0.49 mmol) and acid **36** (220 mg, 0.63 mmol), ester **37** was obtained (405 mg, 81%). Colourless oil: $[\alpha]_D^{20}$ = -25.5 (*c* = 1.50 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65-7.62 (m, 4H, aromatics), 7.43-7.37 (m, 6H, aromatics), 5.86 (ddd, *J* = 17.2, 10.5, 4.5 Hz, 1H, H-9), 5.57 (ddd, *J* = 17.2, 10.0, 7.4 Hz, 1H, H-12), 5.51-5.38 (m, 3H, H-11a, H-6, H-5), 5.24 (dd, *J* = 10.0, 1.6 Hz, 1H, H-11b), 5.16 (dat, *J* = 17.2, 1.6 Hz, 1H, H-10a), 5.07 (dt, *J* = 10.5, 1.8 Hz, 1H, H-10b), 5.02 (dat, *J* = 9.9, 3.2 Hz, 1H, H-16), 4.09-4.03 (m,

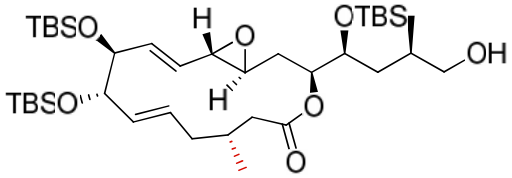
2H, H-7, H-8), 3.85-3.81 (m, 1H, H-17), 3.47 (dd, *J* = 9.7, 4.9 Hz, 1H, H-20a), 3.41 (dd, *J* = 9.7, 5.8 Hz, 1H, H-20b), 3.06 (dd, *J* = 7.3, 2.0 Hz, 1H, H-13), 2.84 (td, *J* = 5.9, 2.0 Hz, 1H, H-14), 2.23 (dd, *J* = 14.6, 4.6 Hz, 1H, H-2a), 2.04-1.91 (m, 4H, H-2b, H-3, H-4a, H-15a), 1.87-1.78 (m, 2H, H-4b, H-19), 1.72 (ddd, *J* = 14.5, 9.9, 5.9 Hz, 1H, H-15b), 1.67-1.60 (m, 1H, 18a), 1.25-1.18 (m, 1H, H-18b), 1.04 (s, 9H, SiC(CH_3)$_3$), 0.97 (d, *J* = 6.7 Hz, 3H, H-22), 0.99, 0.88, 0.87 (3 x s, 27H, 3 x SiC(CH_3)$_3$), 0.84 (d, *J* = 6.2 Hz, 3H, H-21), 0.09, 0.06, 0.05, 0.03, 0.02 (6 x s, 18H, 6 x SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.4 (s, *C*=O), 137.4 (d, C-9), 135.6 (4 x d, 4 x Ar*C*H), 135.5 (d, C-12), 133.8, 133.7 (2 x s, 2 x Ar*C*), 131.3, 128.9 (2 x d, C-5, C-6), 129.5 (2 x d, 2 x Ar*C*H), 127.6 (4 x d, 4 x Ar*C*H), 119.3 (t, C-11), 115.1 (t, C-10), 76.3, 75.9 (2 x d, C-8, C-7), 72.7 (d, C-16), 70.1 (d, C-17), 68.3 (t, C-20), 59.0 (d, C-13), 57.7 (d, C-14), 41.3 (t, C-2), 39.5 (t, C-4), 35.5 (t, C-18), 32.0 (d, C-19), 31.6 (t, C-15), 30.3 (d, C-3), 26.9, 25.9 (4 x q, 4 x SiC(*C*H_3)$_3$), 19.3 (q, C-21), 19.3 (s, Si*C*), 18.2 (2 x s, 2 x Si*C*), 17.9 (q, C-22), 17.9 (s, Si*C*), -4.3, -4.5, -4.6, -4.7, -4.8 (6 x q, 6 x Si*C*H_3); IR (film): $\tilde{\upsilon}$ = 2955, 2929, 2857, 1735, 1472, 1361, 1253, 1078, 835, 775, 701 cm^{-1}; HRMS (ES$^+$): *m/z*: Calcd for $C_{56}H_{96}O_7NaSi_4$ (M^+ + Na): 1015.6131, found: 1015.6136.



38

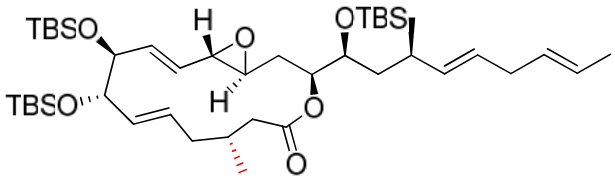
Ring Closing Metathesis product 38. Following an identical procedure to the one described for compound **12**, starting from open precursor **37** (200 mg, 0.20 mmol), compound **38** was obtained (152 mg, 79%). Colourless oil: $[\alpha]_D^{20}$ = +9.6 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66-7.61 (m, 4H, aromatics) 7.43-7.35 (m, 6H, aromatics), 5.62 (dd, *J* = 15.6, 8.6 Hz, 1H, H-9), 5.31 (ddd, *J* = 15.5, 10.0, 3.7 Hz, 1H, H-5), 5.19 (dd, *J* = 15.5, 8.6 Hz, 1H, H-6), 5.07 (dd, *J* = 15.6, 8.9 Hz, 1H, H-10), 5.07-5.03 (m, 1H, H-14), 3.99-3.91 (m, 2H, H-7, H-8), 3.78-3.73 (m, 1H, H-15), 3.49 (d, *J* = 9.8, 4.5 Hz, 1H, H-18a), 3.38 (dd, *J* = 9.8, 5.5 Hz, 1H, H-18b), 2.94 (dd, *J* = 8.8, 2.0 Hz, 1H, H-11), 2.77 (dat, *J* = 9.8, 2.0 Hz, 1H, H-12), 2.33-2.28 (m, 1H, H-13a), 2.23-2.13 (m, 2H, H-2), 2.11-1.98 (m, 1H, H-4a), 1.82-1.69 (m, 2H, H-3, H-17), 1.58 (dat, *J* = 13.7, 6.1 Hz, 2H, H-4b, H-16a), 1.38-1.20 (m, 2H, H-13b, H-16b), 1.04 (s, 9H, SiC(CH_3)$_3$), 0.97, 0.90 (2 x d, *J* = 6.7 Hz, 6H, H-19, H-20), 0.88,

0.87 (3 x s, 27H, 3 x SiC(CH_3)$_3$), 0.08, 0.06, 0.05, 0.04, 0.02, 0.01 (6 x s, 18H, 6 x SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1 (s, *C*=O), 137.0 (d, C-9), 135.6 (4 x d, 4 x Ar*C*H), 133.8, 133.7 (2 x s, 2 x Ar*C*), 133.0, 132.1 (2 x d, C-5, C-6), 129.9 (d, C-10), 129.5 (2 x d, 2 x Ar*C*H), 127.6 (4 x d, 4 x Ar*C*H), 79.1, 78.7 (2 x d, C-8, C-7), 71.1 (d, C-14), 70.5 (d, C-15), 68.1 (t, C-18), 58.9 (d, C-11), 58.1 (d, C-12), 37.5 (t, C-4), 36.9 (t, C-2), 35.6 (t, C-16), 32.3 (t, C-13) 31.8, 30.4 (2 x d, C-3, C-17), 26.9, 26.0, 25.8 (12 x q, 4 x SiC(*C*H_3)$_3$), 19.3, 18.2, 18.2, 18.1, 17.9 17.8 (4 x s, 4 x Si*C*, 2 x q, C-19, C-20), -4.2, -4.3, -4.4, -4.7 (6 x q, 6 x Si*C*H_3); IR (film): $\tilde{\upsilon}$ = 2955, 2929, 2857, 1737, 1558, 1540, 1472, 1428, 1251, 1361, 1111, 1077, 776 cm^{-1}; HRMS (ES$^+$): *m/z*: Calcd for $C_{54}H_{92}O_7NaSi_4$ (M^+ + Na): 987.5818, found: 987.5816.



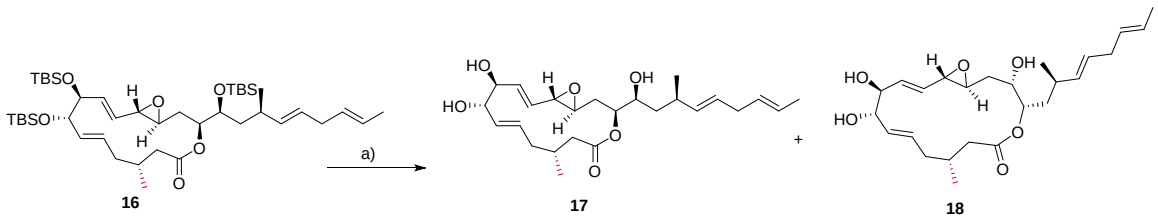
39

Alcohol 39. Following an identical procedure to the one described for compound **27**, starting from protected compound **38** (180 mg, 0.18 mmol), alcohol **39** was obtained (73 mg, 57%). Colourless amorphous solid: $[\alpha]_D^{20}$ = +6.7 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.63 (dd, *J* = 15.6, 8.5 Hz, 1H, H-9), 5.34 (ddd, *J* = 15.5, 10.2, 3.1 Hz, 1H, H-5), 5.19 (dd, *J* = 15.5, 8.2 Hz, 1H, H-6), 5.15-5.10 (m, 1H, H-14), 5.07 (dd, *J* = 15.6, 8.6 Hz, 1H, H-10), 3.98-3.93 (m, 2H, H-7, H-8), 3.82-3.78 (m, 1H, H-15), 3.44-3.39 (m, 2H, H-18), 2.95 (dd, *J* = 8.7, 2.1 Hz, 1H, H-11), 2.77 (dat, *J* = 9.7, 2.1 Hz, 1H, H-12), 2.34-2.23 (m, 4H, H-2, H-4a, H-13a), 2.06-2.02 (m, 1H, H-4b), 1.83-1.72 (m, 2H, H-3, H-17), 1.57 (dat, *J* = 13.9, 6.2 Hz, 1H, H-16a,), 1.35 (ddd, *J* = 13.9, 11.8, 9.7 Hz, 1H, H-13b), 1.28-1.23 (m, 1H, H-16b), 1.04, 0.93 (2 x d, *J* = 6.8, 6.7 Hz, 6H, H-19, H-20), 0.89, 0.87, 0.86 (3 x s, 27H, 3 x SiC(CH_3)$_3$), 0.10, 0.09, 0.06, 0.05, 0.03, 0.02 (6 x s, 18H, 6 x SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4 (s, *C*=O), 137.1 (d, C-9), 133.1 (d, C-6), 132.0 (d, C-5), 129.7 (d, C-10), 79.0, 78.5 (2 x d, C-8, C-7), 70.9 (2 x d, C-14, C-15), 67.9 (t, C-18), 59.0 (d, C-11), 57.9 (d, C-12), 37.5 (t, C-4), 37.1 (t, C-2), 36.5 (t, C-16), 32.8 (t, C-13), 32.0, 28.3 (2 x d, C-3, C-17), 26.0, 25.7 (3 x q, 3 x SiC(*C*H_3)$_3$), 19.5, 18,2, 18.1, 17.9 (3 x s, 3 x Si*C*, 2 x q, C-19, C-20), -3.9, - 4.2, -4.5 (6 x q, 6 x Si*C*H_3); IR (film): $\tilde{\upsilon}$ = 3500, 2954, 2929, 2857, 1733, 1558, 1540, 1472, 1457, 1361, 1251, 1218, 835, 773 cm^{-1}; HRMS (ES$^+$): *m/z*: Calcd for $C_{38}H_{74}O_7NaSi_3$ (M^+ + Na): 749.4629, found: 749.4632.



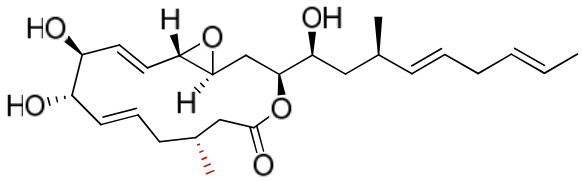
16

Compound 16. Following an identical procedure to the one described for compound **28**, starting from alcohol **39** (73 mg, 0.10 mmol), compound **16** was obtained (51 mg, 66%). Colourless oil: $[\alpha]_D^{20}$ = +14.7 (*c* = 1.00 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 5.63 (dd, *J* = 15.6, 8.5 Hz, 1H, H-9), 5.43-5.32 (m, 4H, H-19, H-5, H-21, H-22), 5.20 (dd, *J* = 15.4, 7.9 Hz, 1H, H-6), 5.14 (dd, *J* = 15.4, 8.0 Hz, 1H, H-18), 5.08 (dd, *J* = 15.6, 8.8 Hz, 1H, H-10) 5.02 (ddd, *J* = 12.0, 3.8, 1.7 Hz, 1H, H-14), 3.98-3.93 (m, 2H, H-7, H-8), 3.71-3.68 (m, 1H, H-15), 2.94 (dd, *J* = 8.8, 1.6 Hz, 1H, H-11), 2.74 (dat, *J* = 9.8, 1.6 Hz, 1H, H-12), 2.64-2.61 (m, 2H, H-20), 2.35 (dat, *J* = 13.3, 2.0 Hz, 1H, H-13a), 2.30-2.20 (m, 4H, H-2, H-4a, H-17), 2.05 (dat, *J* = 14.0, 3.9 Hz, 1H, H-4b), 1.82-1.75 (m, 1H, H-3), 1.66-1.64 (m, 3H, H-23), 1.33 (ddd, *J* = 14.0, 9.2, 3.4 Hz, 1H, H-13b), 1.30-1.25 (m, 2H, H-16), 1.04 (d, *J* = 6.8 Hz, 3H, H-24), 0.97 (d, *J* = 6.7 Hz, 3H, H-25), 0.89, 0.87, 0.86 (3 x s, 27H, 3 x $SiC(CH_3)_3$), 0.10, 0.07, 0.06, 0.05, 0.04, 0.02 (6 x s, 18H, 6 x $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.05 (s, *C*=O), 137.2 (d, C-9), 135.9 (d, C-18), 133.0 (d, C-6), 132.0 (d, C-5), 129.9 (d, C-10), 129.6, 128.0, 125.5 (3 x d, C-22, C-21 C-19), 79.1, 78.5 (2 x d, C-7, C-8), 71.3 (d, C-14), 70.0 (d, C-15), 59.1 (d, C-11), 58.1 (d, C-12), 38.1 (t, C-16), 37.6 (t, C-4), 37.4 (t, C-2), 35.6 (t, C-20), 32.8 (d, C-17), 31.4 (t, C-13), 30.5 (d, C-3), 26.0, 25.8 (9 x q, 3 x $SiC(CH_3)_3$), 22.0 (q, C-25), 19.5 (q, C-24), 18.2, 18.1, 17.8 (3 x s, 3 x SiC), 18.0 (q, C-23), -3.9, -4.0, -4.3, -4.4 (6 x q, 6 x $SiCH_3$); IR (film): $\tilde{\upsilon}$ = 2955, 2928, 2856, 1739, 1471, 1386, 1251, 1113, 1079, 1059, 964, 833, 774 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{43}H_{80}O_6NaSi_3$ (M^+ + Na): 799.5160, found: 799.5165.



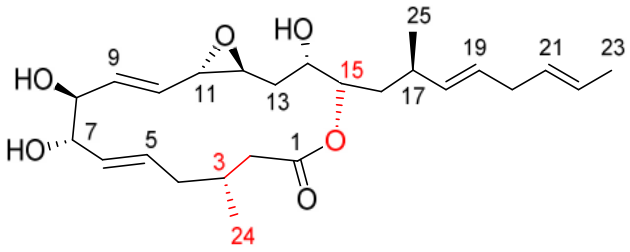
To a solution of protected compound **16** (51 mg, 65 µmol) in THF (1 mL), was added TBAF (1 M in THF, 210 µL, 0.210 mmol). The reaction mixture was stirred at room

temperature for 3 h, after which time complete conversion of the starting material and of the intermediate byproducts into two more polar spots (EtOAc 100%, *Rf* = 0.45, 0.40, respectively) was observed. The mixture was concentrated under nitrogen flow, and the crude residue was purified flash chromatography (hexanes/EtOAc 10 : 90) to give triol **17** (19 mg, 63%), and triol **18** (4.5 mg, 15%).



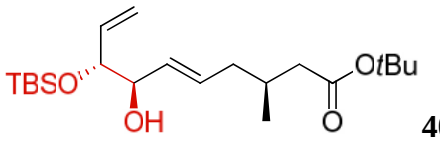
17

Analogue 17. Colourless amorphous solid: $[\alpha]_D^{20}$ = +70.0 (*c* = 0.24 in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 5.77 (dd, *J* = 15.3, 8.8 Hz, 1H, H-9), 5.55-5.53 (m, 1H, H-5), 5.49-5.35 (m, 3H, H-22, H-21, H-19), 5.36-5.24 (m, 2H, H-10, H-6), 5.20 (dd, *J* = 15.4, 8.3 Hz, 1H, H-18), 5.06 (dat, *J* =6.7, 3.2 Hz, 1H, H-14), 4.02-3.93 (m, 2H, H-7, H-8), 3.63-3.57 (m, 1H, H-15), 2.99 (dd, *J* = 9.6, 1.4 Hz, 1H, H-11), 2.85 (dt, *J* = 10.5, 2.1 Hz, 1H, 1H, H-12), 2.70-2.62 (m, 2H, H-20), 2.44-2.30 (m, 3H, H-17, H-2), 2.23-2.12 (m, 3H, H-13a, H-4), 1.91-1.84 (m, 1H, H-3), 1.70-1.62 (m, 3H, H-23), 1.57-1.46 (m, 1H, H-13b), 1.38 (ddd, *J* = 14.0, 9.6, 4.4 Hz, 1H, H-16a), 1.32-1.25 (m, 1H, H-16b), 1.03, 1.00 (2 x d, *J* = 6.8 Hz, 6H, H-24, H.25); ^{13}C NMR (125 MHz, CD_2Cl_2): δ = 172.1 (s, *C*=O), 136.0 (d, C-18), 135.9 (d, C-9), 135.6 (d, C-5), 133.8, 131.5, 130.2, 129.0, 126.0, (5 x d, C-22, C-21, C-19, C-10, C-6), 78.0, 77.4 (2 x d, C-7, C-8), 73.3 (d, C-14), 71.5 (d, C-15), 59.4 (d, C-11), 58.1 (d, C-12), 41.4 (t, C-16), 38.5 (t, C-4), 37.9 (t, C-2), 36.0 (t, C-20), 34.5 (t, C-13), 33.8 (d, C-17), 30.5 (d, C-3), 22.0, 19.6 (2 x q, C-24, C-25), 18.2 (q, C-23); IR (film): $\tilde{\upsilon}$ = 3446, 2959, 2932, 2890, 1728, 1386, 1193, 1155, 1056, 964 cm^{-1}; HRMS (ES^+): *m/z*: Calcd. for $C_{25}H_{38}O_6Na$ (M^+ + Na): 457.2561, found: 457.2565.



Analogue 18: Colourless amorphous: $[\alpha]_D^{20}$ = +33.0 (*c* = 0.44 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.80 (dd, *J* = 15.5, 8.2 Hz, 1H, H-9), 5.59 (ddd, *J* = 15.2, 10.9, 3.8 Hz, 1H, H-5), 5.45-5.25 (m, 5H, H-22, H-21, H-19, H-10, H-6), 5.21 (dd, *J* = 15.5, 8.3 Hz, 1H, H-18), 4.97-4.92 (m, 1H, H-15), 3.96-3.85 (m, 3H, H-14, H-7, H-8), 3.08 (dd *J* = 8.0, 2.0 Hz, 1H, H-11), 3.07-3.04 (m, 2H, H-12), 2.68-2.63 (m, 2H, H-20), 2.37 (dd, *J* = 17.8, 1.3 Hz, 1H, H-2a), 2.28-2.23 (m, 2H, H-13a, H-4a), 2.18-2.14 (m, 1H, H-17), 2.05-1.95 (m, 2H, H-3), 1.75 (dd, *J* = 17.8, 12.2 Hz, 1H, H-2b), 1.68-1.59 (m, 6H, H-23, H-16, H-4b), 1.49-1.43 (m, 1H, H-13b), 1.02 (d, *J* = 6.7 Hz, 3H, H-24), 0.98 (d, *J* = 6.4 Hz, 3H, H-25); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6 (s, *C*=O), 135.4 (d, C-18), 134.2 (d, C-9), 134.9, 132.4, 130.6, 129.5, 128.7, 125.6 (6 x d, C-22, C-21, C-19, C-10, C-5, C-6,) 76.5, 76.2 (2 x d, C-7, C-8), 74.6 (d, C-15), 68.9 (d, C-14), 57.5 (d, C-11), 56.2 (d, C-12), 40.0 (t, C-4), 38.9 (t, C-2), 36.1 (t, C-13), 35.4 (2 x t, C-20, C-16), 33.6 (d, C-17), 28.5 (d, C-3), 21.5 (q, C-24), 21.0 (q, C-25), 17.8 (q, C-23); IR (film): $\tilde{\upsilon}$ = 3450, 2969, 1736, 1558, 1540, 1455, 1373, 1228, 970 cm^{-1}; HRMS (ES$^+$): *m/z*: Calcd for $C_{25}H_{38}O_6Na$ (M^+ + Na): 457.2561, found: 457.2567.

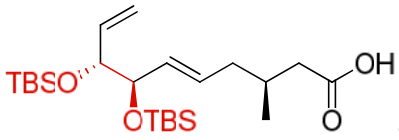
Synthesis of the (7*R*, 8*R*)-diastereoisomer of Iriomoteolide 3a. Analogue 20.



40

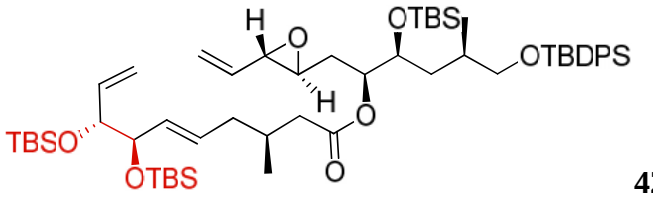
(*E*)-(3*R*,7*R*,8*R*)-8-(*tert*-Butyl-dimethyl-silanyloxy)-7-hydroxy-3-methyl-deca-5,9-dienoic acid *tert*-butyl ester (40). Following an identical procedure to the one described for compound **26**, starting from *tert*-butyl ester **13** (250 mg, 0.87 mmol), and *ent*-diene **5d** [3] (900 mg, 3.94 mmol), ester **40** (252 mg, 75%) was obtained. Colourless oil: $[\alpha]_D^{20}$ = +11.0 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ =

5.82 (ddd, *J* = 17.2, 10.4, 6.6 Hz, 1H, H-9), 5.67 (dat, *J* = 15.4, 6.3 Hz, 1H, H-5), 5.43 (dd, *J* = 15.4, 6.4 Hz, 1H, H-6), 5.21 (dat, *J* = 17.2, 1.6 Hz, 1H, H-10a), 5.17 (dat, *J* = 10.4, 1.6 Hz, 1H, H-10b), 3.94 (at, *J* = 6.3 Hz, 1H, H-8), 3.93-3.87 (m, 1H, H-7), 2.53 (d, *J* = 4.0 Hz, 1H, 7-OH), 2.22 (dd, *J* = 17.5, 8.1 Hz, 1H, H-2a), 2.05-1.94 (m, 4H, H-2b, H-3, H-4), 1.44 (s, 9H, $OC(CH_3)_3$), 0.93 (d, *J* = 5.7 Hz, 3H, 3-CH_3), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.08, 0.05 (2 x s, 6H, 2 x $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5 (s, *C*=O), 137.9 (d, C-9), 131.4 (d, C-5), 130.6 (d, C-6), 116.9 (t, C-10), 80.0 (s, O*C*$(CH_3)_3$), 77.8 (d, C-8), 75.7 (d, C-7), 42.4 (t, C-2), 39.4 (t, C-4), 30.4 (d, C-3), 28.1 (3 x q, OC(*C*$H_3)_3$), 25.8 (3 x q, SiC(*C*$H_3)_3$), 19.5 (q, 3-CH_3), 18.1 (s, Si*C*), -4.1, -4.8 (2 x q, 2 x Si*C*H_3); IR (film): $\tilde{\upsilon}$ = 3500, 2956, 2929, 2857, 1729, 1461, 1366, 1253, 1149, 835, 776 cm^{-1}; HRMS (ES^+): m/z: Calcd for $C_{21}H_{40}O_4NaSi$ (M^+ + Na): 407.2594, found: 407.2593.



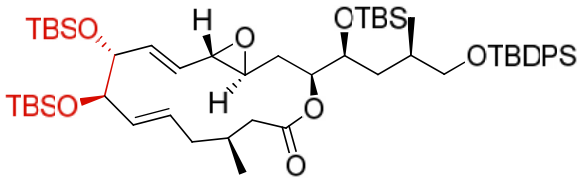
41

(*E*)-(3*S*,7*R*,8*R*)-7,8-Bis-(*tert*-butyl-dimethyl-silanyloxy)-3-methyl-deca-5,9-dienoic acid (41). Following an identical procedure to the one described for compound **14**, starting from compound **40** (302 mg, 0.79 mmol), acid **41** (283 mg, 82%) was obtained. Colourless amorphous solid: $[\alpha]_D^{20}$ = +17.7 (*c* = 1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 5.88 (ddd, *J* = 16.7, 10.5, 4.4 Hz, 1H, H-9), 5.55-5.41 (m, 2H, H-5, H-6), 5.18 (d, *J* = 17.2 Hz, 1H, H-10a), 5.10 (d, *J* = 10.5 Hz, 1H, H-10b), 4.09-4.05 (m, 2H, H-8, H-7), 2.43 (d, *J* = 11.7 Hz, 1H, H-2a), 2.10-2.00 (m, 4H, H-3, H-4, H-2b), 0.96 (d, *J* = 4.1 Hz, 3H, 3-CH_3), 0.90, 0.89 (2 x s, 18H, 2 x $SiC(CH_3)_3$), 0.06, 0.03 (2 x s, 12H, 4 x $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.5, 137.3, 131.6, 129.1, 115.1, 76.2, 76.0, 40.6, 39.4, 30.2, 26.0, 19.6, 18.2, -4.5, -4.7, -4.7, -4.8; IR (film): $\tilde{\upsilon}$ = 2956, 2929, 2892, 2857, 1709, 1472, 1463, 1407, 1388, 1361,1253, 1220, 1136, 1077, 1033, 1055, 971, 922, 900, 835, 813, 774, 673 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{23}H_{46}O_4NaSi_2$ (M^+ + Na): 465.28268, found: 465.28219.



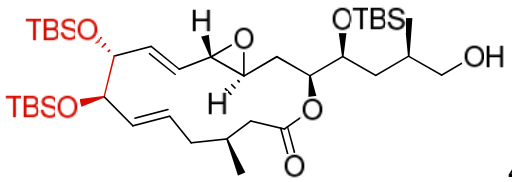
42

Ring Closing Metathesis precursor 42. Following an identical procedure to the one described for compound **15**, starting from alcohol **3** (150 mg, 0.26 mmol) and acid **41** (116 mg, 0.26 mmol), ester **42** was obtained (201 mg, 81%). Colourless oil: $[\alpha]_D^{20}$ = +9.07 (*c* = 1 in $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 7.66-7.62 (m, 4H, aromatics), 7.43-7.35 (m, 6H, aromatics), 5.85 (ddd, *J* = 17.2, 10.5, 4.6 Hz, 1H, H-9), 5.53 (ddd, *J* = 17.3, 10.1, 7.5 Hz, 1H, H-12), 5.50-5.40 (m, 3H, H-11a, H-6, H-5), 5.24 (dd, *J* = 10.1, 1.6, 1H, H-11b), 5.16 (dd, *J* = 17.3, 1.6 Hz, 1H, H-10a), 5.07 (dd, *J* = 10.5, 2.1 Hz, 1H, H-10b), 5.00 (dat, *J* = 9.8, 3.1 Hz, 1H, H-16), 4.08-4.04 (m, 2H, H-7, H-8), 3.86-3.83 (m, 1H, H-17), 3.46 (dd, *J* = 9.8, 4.8 Hz, 1H, H-20a), 3.40 (dd, *J* = 9.8, 5.9 Hz, 1H, H-20b), 3.05 (dd, *J* = 7.4, 2.0 Hz, 1H, H-13), 2.84 (td, *J* = 5.9, 2.0 Hz, 1H, H-14), 2.26 (dd, *J* = 14.4, 4.5 Hz, 1H, H-2a), 2.20-1.92 (m, 4H, H-19, H-15a, H-4a, H-2b), 1.89-1.84 (m, 1H, H-4b), 1.83-1.77 (m, 1H, H-15a), 1.71 (ddd, *J* = 14.5, 9.9, 6.0 Hz), 1H, H-15b), 1.63 (ddd, *J* = 13.8, 6.2, 5.5, 1H, H-18a), 1.27-1.19 (m, 1H, H-18b), 1.04 (s, 9H, $SiC(CH_3)_3$), 0.97 (d, *J* = 6.7 Hz, 3H, H-22), 0.90, 0.89, 0.87 (3 x s, 27H, 3 x $SiC(CH_3)_3$), 0.81 (d, *J* = 6.1 Hz, 3H, H-21), 0.09, 0.06, 0.05,0.03, 0.02, 0.02 (6 x s, 18H, 6 x $SiCH_3$); ^{13}-NMR (125 MHz, $CDCl_3$): δ= 172.4 (s, C=O), 137.4 (s, C-9), 135.6 (d, ArCH), 135.5 (s, ArC), 133.8 (d, C-12), 131.3 (s, C-5), 129.6 (s, ArC), 128.9 (s, C-6), 127.6 (s, ArCH), 119.3 (s, C-11), 115.1 (s, C-10), 76.3 (s, C-7), 75.9 (s, C-8), 72.7 (s, C-16), 70.1 (s, C-17), 68.3 (s, C-20), 59.1 (s, C-13), 57.7 (s, C-14), 41.2 (s, C-2), 39.5 (s, C-4), 35.5 (s, C-18), 32.0 (s, C-19), 31.6 (s, C-15), 30.2 (s, C-3), 26.9, 26.0 (4 x s, 4 x $Si(CH_3)_3$, 19.3 (s, C-21), 19.3 (s, SiC), 18.2 (2 x s, 2 x SiC) 18.0 (s, C-22), 18.0 (s, SiC), -4.3, -4.5, -4.6, -4.6 , -4.7, -4.8 (6 x s, 6 x $SiCH_3$); IR(film): ῡ = 2956, 2929, 2895, 2857, 1737, 1472, 1463, 1428, 1405, 1388, 1362, 1254, 1216, 1112, 1077, 1033, 1055, 923, 901, 836, 807, 774, 758, 703, 689, 651 cm^{-1}. HRMS (ES^+), *m/z*: calcd for $C_{56}H_{96}NaO_7Si_4$ (M^+ + Na): 1015.6131, found: 1015.61301.



43

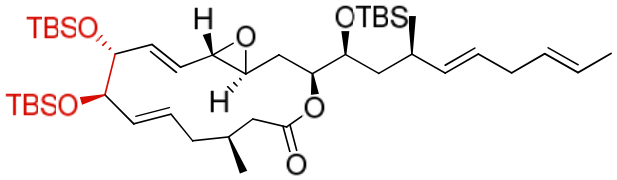
Ring Closing Metathesis product 43. Following an identical procedure to the one described for compound **12**, starting from compound **42** (190 mg, 0.19 mmol), diene **43** was obtained (126 mg, 68%). Colourless oil: $[\alpha]_D^{20}$ = +27.26 (*c* = 1.00 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.66-7.59 (m, 4H, aromatics) 7.48-7.35 (m, 6H, aromatics), 6.05 (dd, *J* = 15.5, 1.9 Hz, 1H, H-9), 5.67-5.59 (m, 1H, H-5), 5.51 (dd, *J* = 15.5, 1.9 Hz, 1H, H-6), 5.25 (ddd, *J* = 15.5, 9.4, 1.7 Hz, 1H, H-10), 5.10-5.05 (m, 1H, H-14), 4.24-4.20 (m, 1H, H-8), 4.18-4.13 (m, 1H, H-7), 3.81-3.75 (m, 1H, H-15), 3.48-3.42 (m, 2H, H-18), 3.07 (dd, *J* = 9.4, 1.6 Hz, 1H, H-11), 2.83 (dat, *J* = 9.7, 1.8 Hz, 1H, H-12), 2.41-2.27 (m, 3H, H-13a, H-4a, H-2a), 2.10-2.02 (m, 1H, H-3), 1.87-1.75 (m, 3H, H-3, H-4b, H-2b), 1.71-1.63 (m, 1H, H-16a), 1.33-1.15 (m, 2H, H-13b, H-16b), 1.05 (s, 9H, $SiC(CH_3)_3$), 0.97 (d, *J* = 6.7 Hz, 3H, H-20), 0.94, 0,90 (2 x s, 18H, 2 x $SiC(CH_3)_3$), 0.87 (d, *J* = 6.7 Hz, 3H, H-19) 0.86 (s, 9H, $SiC(CH_3)_3$) 0.09, 0.08, 0.07 (6 x s, 18H, 6 x $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4 (s, *C*=O), 136.3 (d, C-9), 135.6 (4 x d, 4 x Ar*C*H), 133.8, 133.7 (2 x s, 2 x Ar*C*), 132.4 (d, C-6), 129.6 (2 x d, 2 x Ar*C*H), 127.6 (4 x d, 4 x Ar*C*H), 126.7 (d, C-5), 125.6 (d, C-10), 74.4 (d, C-8), 74.0 (d, C-7), 71.9 (d, C-14), 70.2 (d, C-15), 67.7 (t, C-18), 59.9 (d, C-11), 58.3 (d, C-12), 37.5 (t, C-4), 36.1 (t, C-2), 35.2 (t, C-16), 32.8 (t, C-17), 31.8 (t, C-13), 31.7 (d, C-3), 28.6, 26.9, 26.0, 25.8 (12 x q, 4 x $SiC(CH_3)_3$), 20.4 (q, C-20), 19.4, 18.2, 18.1, 17.9 (4 x s, 4 x Si*C*) 17.9 (q, C-19), -4.3, -4.7, -4.8 (6 x q, 6 x $SiCH_3$); IR (film): $\tilde{\upsilon}$ = 2955, 2929, 2857, 1739, 1472, 1362, 1256, 1113, 1073, 835 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{54}H_{92}O_7NaSi_4$ (M^+ + Na): 987.58123, found: 987.58215.



44

Alcohol 44. Following an identical procedure to the one described for compound **27**, starting from compound **43** (126 mg, 0.18 mmol), alcohol **44** was obtained (50 mg, 53%). Colourless amorphous solid: $[\alpha]_D^{20}$ = +74.2 (*c* = 1.00 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 6.06 (dd, *J* = 15.4, 1.9 Hz, 1H, H-9), 5.70-5.61 (m, 1H, H-5), 5.52

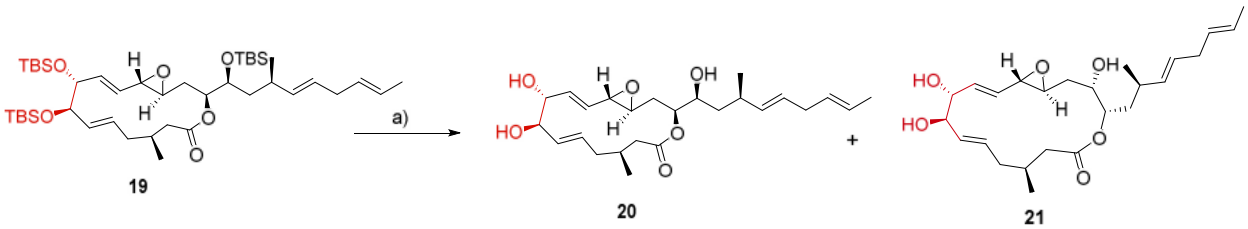
(dd, *J* = 15.5, 2.0 Hz, 1H, H-6), 5.23 (ddd, *J* = 15.4, 9.5, 2.2 Hz, 1H, H-10), 5.20-5.14 (m, 1H, H-14), 4.23-4.20 (m, 1H, H-8), 4.18-4.14 (m, 1H, H-7), 3.83-3.77 (m, 1H, H-15), 3.45-3.38 (m, 2H, H-18), 3.06 (dd, *J* = 9.5, 1.8 Hz, 1H, H-11), 2.85 (dat, *J* = 9.7, 2.1 Hz, 1H, H-12), 2.47 (dd, *J* = 18.0, 6.8 Hz, 1H, H-2a), 2.36-2.28 (m, 2H, H-13a, H-4a), 2.16-2.07 (m, 1H, H-3), 1.93 (dd, *J* = 18.0, 6.6 Hz, 1H, H-2b), 1.88-1.76 (m, 2H, H-17, H-4b), 1.60-1.52 (m, 1H, H-16a), 1.36-1.21 (m, 2H, H-13b, H-16b), 0.98 (d, *J* = 6.8 Hz, 3H, H-19), 0.94 (s, 9H, 2 x $SiC(CH_3)_3$), 0.92 (d, *J* = 6.8 Hz, 3H, H-20), 0.90, 0.88 (2 x s, 18H, 2 x $SiC(CH_3)_3$), 0.11, 0.09, 0.07, 0.05 (6 x s, 18H, 6 x $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6 (s, *C*=O), 136.5 (d, C-9), 131.5 (d, C-6), 126.7 (d, C-5), 125.8 (d, C-10), 74.4 (d, C-8), 74.1 (d, C-7), 71.7 (d, C-14), 71.0 (d, C-15), 68.0 (t, C-18), 59.9 (d, C-11), 58.1 (d, C-12), 37.8 (t, C-2), 36.8 (t, C-16), 36.2 (t, C-4), 32.8 (t, C-13), 32.0 (d, C-3), 28.9 (d,C-17), 25.9, (9 x q, 3 x $SiC(CH_3)_3$), 20.6 (q, C-19), 18.2, 18.1, 18.0 (3 x s, 3 x Si*C*) 18.0 (q, C-20), -4.3, -4.4, -4.7, -4.8 (6 x q, 6 x $SiCH_3$); IR (film): $\tilde{\upsilon}$ = 3500, 2954, 2929, 2857, 1739, 1472, 1361, 1255, 1118, 835, 775 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{38}H_{74}O_7NaSi_3$ (M^+ + Na): 749.46346, found: 749.46307.



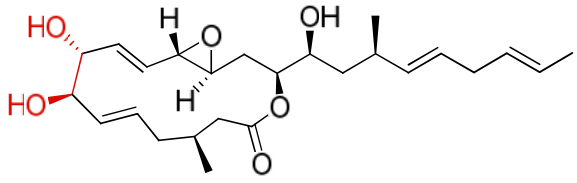
19

Compound 19. Following an identical procedure to the one described for compound **28**, starting from alcohol **44** (48 mg, 0.066 mmol), compound **19** was obtained (35 mg, 68%). Colourless oil: $[\alpha]_D^{20}$ = +84.1 (*c* = 1.00 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 6.04 (dd, *J* = 15.5, 2.2 Hz, 1H, H-9), 5.69-5.60 (m, 1H, H-5H), 5.51 (dd, *J* = 15.5, 1.4 Hz, 1H, H-6), 5.45-5.29 (m, 3H, H-22, H-21, H-19), 5.24 (ddd, *J* = 15.4, 9.3, 1.9 Hz, 1H, H-10), 5.14 (dd, *J* = 15.4, 7.9 Hz, 1H, H-18), 5.05-4.14 (m, 1H, H-14), 4.23-4.20 (m, 1H, H-7), 4.16-4.13 (m, 2H, H-8), 3.73-3.68 (m, 1H, H-15), 3.06 (dd, *J* = 9.5, 1.8 Hz, 1H, H-11), 2.80 (dat, *J* = 10.0, 2.2 Hz, 1H, H-12), 2.65-2.61 (m, 2H, H-20), 2.43 (dd, *J* = 18.1, 7.7 Hz, 1H, H-2a), 2.42-2.30 (m, 2H, H-13a, H-4a), 2.26-2.18 (m, 1H, H-17) , 2.18-2.10 (m, 1H, H-3), 1.95-1.84 (m, 2H, H-4b, H-2b), 1.66-1.63 (m, 2H, H-23), 1.38-1.19 (m, 3H, H-16, H-13b), 0.99 (d, *J* = 6.9 Hz, 3H, H-24), 0.96 (d, *J* = 6.7 Hz, 3H, H-25), 0.94, 0.90, 0.88 (3 x s, 27H, 3 x $SiC(CH_3)_3$), 0.11, 0.09, 0.07, 0.05 (6 x s, 18H, 6 x $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2 (s,

C=O), 136.2 (d, C-9), 136.0 (d, C-18), 131.4 (d, C-6), 129.6, 127.9, 125.5 (3 x d, C-22, C-21,C-19), 127.6 (d, C-10), 125.5 (d, C-5), 74.3 (d, C-8), 74.15 (d, C-7), 71.9 (d, C-14), 69.7 (d, C-15), 59.9 (d, C-11), 58.3 (d, C-12), 39.1 (t, C-16), 37.7 (t, C-2), 36.04 (t, C-4), 35.6 (t, C-20), 32.8 (d, C-17), 31.3 (t, C-13), 28.4 (d, C-3), 25.9, 25.8 (9 x q, 3 x SiC(CH_3)$_3$), 22.2 (q, C-25), 20.5 (q, C-24), 18.2, 18.1, 18.0 (3 x s, 3 x Si*C*), 18.0 (q, C-23), -4.3, -4.5, -4.7, -4.8, -4.9 (6 x q, 6 x SiCH_3); IR (film): $\tilde{\upsilon}$ = 2954, 2929, 2857, 1741, 1476, 1255, 1101, 1078, 965, 834, 775 cm^{-1}; HRMS (ES$^+$): *m/z*: Calcd for $C_{43}H_{80}O_6NaSi_3$ (M^+ + Na): 799.51549, found: 799.51561.



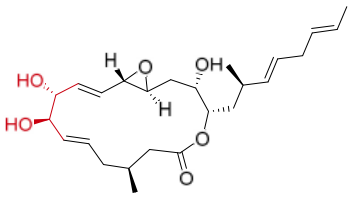
To a solution of **19** (35 mg, 45 µmol) in THF (1 mL), was added TBAF (1 M in THF, 160 µL, 0.16 mmol). The reaction mixture was stirred at room temperature for 3 h, after which time complete conversion of the starting material and of the intermediate byproducts into two more polar spots (EtOAc 100%, *Rf* = 0.66, 0.62, respectively) was observed. The mixture was concentrated under nitrogen flow, and the crude residue was purified flash chromatography (hexanes/EtOAc 10 : 90) to give triol **20** (10 mg, 52%), and triol **21** (3.5 mg, 18%).



20

Analogue 20. Colourless amorphous solid: $[\alpha]_D^{20}$ = +48.6 (*c* = 0.75 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.00 (dd, *J* = 15.8, 3.9 Hz, 1H, H-9), 5.57 (ddd, *J* = 15.7, 8.6, 4.4 Hz, 1H, H-5), 5.49-5.37 (m, 5H, H-22, H-21, H-19, H-10, H-6), 5.21 (dd, *J* = 15.5, 8.3 Hz, 1H, H-18), 5.03 (ddd, *J* = 15.7, 8.6, 4.4 Hz, 1H, H-14), 4.25-4.19 (m, 1H, H-8), 4.04-3.98 (m, 1H, H-7), 3.63-3.54 (m, 1H, H-15), 3.04 (dd *J* = 8.3, 1.6 Hz, 1H, H-11), 2.84 (dd *J* = 9.8, 2.1 Hz, 1H, H-12), 2.69-2.63 (m, 2H, H-20), 2.44 (dd, *J* = 17.8, 1.3 Hz, 1H, H-2a), 2.40-2.16 (m, 3H, H-17, H-13a, H-4a), 2.15-2.05 (m, 1H, H-3), 1.98 (dd, *J* = 18.1, 7.7 Hz, 1H, H-2b), 1.79-1.65 (m, 1H, H-4b),

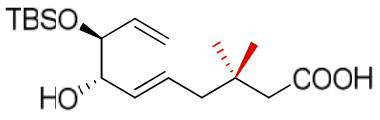
1.65-1.63 (m, 3H, H-23), 1.46-1.24 (m, 3H, H-16, H-13b), 0.99 (2 x d, J = 6.7 Hz, 6H, H-24, H-25), 0.98 (d, J = 6.4 Hz, 3H, H-25); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6 (s, *C*=O), 136.0 (d, C-18), 135.6 (d, C-9), 133.2 (d, C-5), 131.0, 130.2, 129.0, 128.5, 126.0 (5 x d, C-22, C-21, C-19, C-10, C-6,) 77.3, (d, C-7), 74.6 (d, C-8), 73.8 (d, C-14), 71.5 (d, C-15), 59.7 (d, C-11), 57.8 (d, C-12), 41.1 (t, C-16), 39.1 (t, C-4), 38.9 (t, C-2), 36.0 (t, C-20), 34.7 (t, C-13), 33.9 (d, C-17), 29.4 (d, C-3), 22.1, 21.9 (2 x q, C-25, C-24), 18.2 (q, C-23); IR (film): $\tilde{\upsilon}$ = 3410, 2956, 2925, 1735, 1455, 1376, 1162, 970 cm^{-1}; HRMS (ES$^+$): *m/z*: Calcd for $C_{25}H_{38}O_6Na$ (M^+ + Na): 457.25606, found: 457.25560.



21

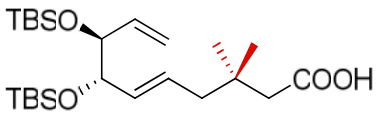
Analogue 21. Colourless amorphous: $[\alpha]_D^{20}$ = -57.2 (*c* = 0.75 in CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 5.84 (dd, J = 15.3, 3.4 Hz, 1H, H-10), 5.62 (dd, J = 15.3, 7.3 Hz 1H, H-9), 5.55 (ddd, J = 15.2, 9.7, 4.4 Hz 1H, H-5), 5.47-5.34 (m, 3H, H-22, H-21, H-19), 5.27-5.19 (m, 2H, H-18, H-6), 4.94-4.89 (m, 1H, H-15), 3.93-3.83 (m, 3H, H-14, H-8, H-7), 2.97 (at, J = 2.0 Hz, 1H, H-11), 2.88 (ddd, J = 8.5, 3.6, 2.1 Hz, 1H, H-12), 2.68-2.64 (m, 2H, H-20), 2.44 (dd, J = 14.2, 2.8 Hz, 1H, H-2a), 2.29 (ddd, J = 14.2, 10.5, 3.7 Hz 1H, H-13a), 2.24-2.17 (m, 1H, H-4a), 2.16-2.07 (m, 1H, H-17), 1.94-1.85 (m, 1H, H-3), 1.71-1.60 (m, 7H, H-23, H-16, H-4b, H-2b), 1.38-1.29 (m, 1H, H-13b), 1.03 (d, J = 6.7 Hz, 3H, H-24), 0.98 (d, J = 6.6 Hz, 3H, H.25); ^{13}C NMR (125 MHz, CD_2Cl_2): δ = 172.5 (s, *C*=O), 135.7 (d, C-18), 134.1 (d, C-5), 132.2 (d, C-6), 131.4 (d, C-10), 130.1 (d, C-9), 130.1, 129.4, 126.0, (3 x d, C-22, C-21, C-19), 76.7, 76.1 (2 x d, C-7, C-8), 74.8 (d, C-15), 69.2 (d, C-14), 59.4 (d, C-12), 55.7 (d, C-11), 41.6 (t, C-2), 40.7 (t, C-4), 37.3 (t, C-13), 36.0 (t, C-20), 35.4 (t, C-16), 34.1 (t, C-17), 31.0 (d, C-3), 22.3 (q, C-24), 20.9 (q, C-25), 18.2 (q, C-23); IR (film): $\tilde{\upsilon}$ = 3411, 2956, 2919, 2870, 1734, 1455, 1372, 1258, 1216, 1013, 970 cm^{-1}; HRMS (ES$^+$): *m/z*: Calcd. for $C_{25}H_{38}O_6Na$ (M^+ + Na): 457.25606, found: 457.25613.

Synthesis of C3-dimethyl substituted iriomoteolide-3a. Analogue (22)



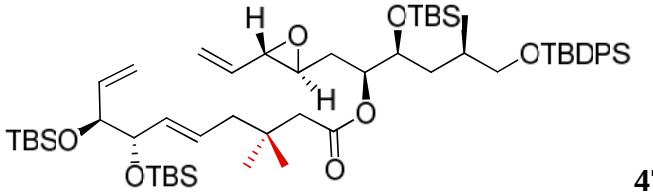
45

(*E*)-(7*R*,8*R*)-8-(*tert*-Butyl-dimethyl-silanyloxy)-7-hydroxy-3-dimethyl-deca-5,9-dienoic acid (45). Following an identical procedure to the one described for compound **26**, starting from 3,3-dimethylhex-5-enoic acid [4] (750 mg, 5.45 mmol) and alcohol **5d** (250 mg, 1.09 mmol), diene **45** (215 mg, 58%) was obtained. Colourless oil: $[\alpha]_D^{20}$ = +9.9 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.78 (ddd, *J* = 17.0, 10.4, 6.4 Hz, 1H), 5.74-5.69 (m, 1H), 5.46 (dd, *J* = 15.4, 6.4 Hz, 1H), 5.22 (d, *J* = 17.0 Hz, 1H), 5.17 (dat, *J* = 10.0 Hz, 1H), 3.94 (at, *J* = 6.5 Hz, 1H), 3.90 (at, *J* = 6.2 Hz, 1H), 2.20 (s, 2H), 2.11-2.06 (m, 2H), 1.02 (s, 6H), 0.90 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.2, 137.8, 131.9, 129.5, 117.1, 77.8, 75.7, 45.3, 44.9, 33.5, 27.1, 26.6, 25.8, 18.2, -4.1, -4.6; IR (film): $\tilde{\upsilon}$ = 3500, 2956, 2930, 2857, 1706, 1471,1252, 1217, 1092, 837, 775 cm^{-1}; HRMS (ES$^+$): m/z: Calcd for $C_{18}H_{34}O_4NaSi$ (M^+ + Na): 365.21186, found: 365.21177.



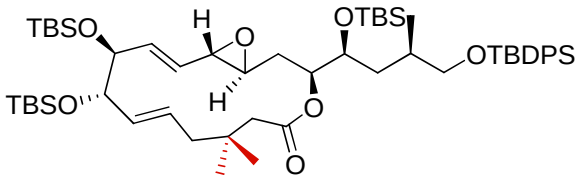
46

(*E*)-(7*R*,8*R*)-8-(*tert*-Butyl-dimethyl-silanyloxy)-7-hydroxy-3-dimethyl-deca-5,9-dienoic acid (46). Following an identical procedure to the one described for compound **14**, starting from acid **45** (200 mg, 0.58 mmol), diene **46** (191 mg, 72%) was obtained. Colourless oil: $[\alpha]_D^{20}$ = -69.3 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.88 (ddd, *J* = 17.3, 10.7, 4.3 Hz, 1H), 5.58 (dat, *J* = 15.4, 7.2 Hz, 1H), 5.45 (dd, *J* = 15.4, 5.3 Hz, 1H), 5.17 (dt, *J* = 17.3, 1.7 Hz, 1H) 5.09 (dt, *J* = 10.7, 1.7 Hz, 1H), 4.11-4.05 (m, 2H), 2.20 (s, 2H), 2.10-2.01 (m, 2H), 1.01 (s, 6H), 0.90, 0.89 (2 x s, 18H), 0.08, 0.06, 0.03 (4 x s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4, 137.2, 132.5, 127.3, 115.0, 76.1, 75.9, 45.3, 44.9, 33.6, 27.0, 26.9, 25.9, 25.8, 18.2, 18.1, -4.5, -4.6, -4.7, -4.8; IR (film): $\tilde{\upsilon}$ = 2955, 2929, 2857, 1706, 1472, 1253, 1082, 835, 775 cm^{-1}; HRMS (ES$^+$): m/z: Calcd for $C_{24}H_{48}O_4NaSi_2$ (M^+ + Na): 479.29833, found: 479.29808.



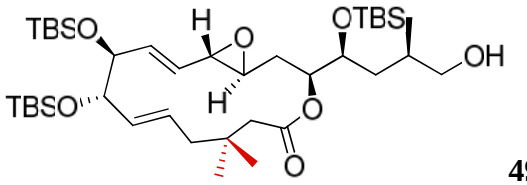
47

Ring Closing Metathesis precursor 47. Following an identical procedure to the one described for compound **15**, starting from alcohol **3** (152 mg, 0.27 mmol) and acid **46** (122 mg, 0.27 mmol), ester **47** was obtained (205 mg, 78%). Colourless oil: $[\alpha]_D^{20}$ = -30.1 (*c* = 1.50 in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.67-7.63 (m, 4H, aromatics), 7.43-7.35 (m, 6H, aromatics), 5.87 (ddd, *J* = 17.2, 10.6, 4.3 Hz, 1H, H-9), 5.58-5.48 (m, 2H, H-12, H-5), 5.45-5.41 (m, 2H, H-11a, H-6), 5.24 (dd, *J* = 10.0, 1.6 Hz, 1H, H-11b), 5.16 (dat, *J* = 17.2, 1.7 Hz, 1H, H-10a), 5.08 (dt, *J* = 10.6, 1.7 Hz, 1H, H-10b), 5.00 (dat, *J* = 9.7, 3.6 Hz, 1H, H-16), 4.11-4.05 (m, 2H, H-7, H-8), 3.85-3.81 (m, 1H, H-17), 3.49 (dd, *J* = 9.7, 4.7 Hz, 1H, H-20a), 3.39 (dd, *J* = 9.7, 6.3 Hz, 1H, H-20b), 3.07 (dd, *J* = 7.5, 1.8 Hz, 1H, H-13), 2.84 (td, *J* = 5.8, 1.8 Hz, 1H, H-14), 2.10, 2.09 (2 x s, 2H, H-2), 2.01-1.94 (m, 3H, H-15a, H-4), 1.85-1.76 (m, 1H, H-19), 1.74 (ddd, *J* = 15.2, 9.5, 5.8 Hz, 1H, H-15b), 1.67-1.59 (m, 1H, 18a), 1.26-1.19 (m, 1H, H-18b), 1.05 (s, 9H, $SiC(CH_3)_3$), 0.99 (d, *J* = 6.6 Hz, 3H, H-23), 0.99, 0.88, 0.87 (5 x s, 33H, 3 x $SiC(CH_3)_3$, H-21, H-22), 0.10, 0.06, 0.04, 0.03 (6 x s, 18H, 6 x $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.5 (s, *C*=O), 137.4 (d, C-9), 135.6 (4 x d, 4 x Ar*C*H), 135.5 (d, C-12 or C-5), 133.8, 133.7 (2 x s, 2 x Ar*C*), 132.4 (d, C-6), 129.5 (2 x d, 2 x Ar*C*H), 127.6 (4 x d, 4 x Ar*C*H), 127.3 (d, C-12 or C-5), 119.2 (t, C-11), 115.1 (t, C-10), 76.3, 75.9 (2 x d, C-8, C-7), 72.5 (d, C-16), 70.1 (d, C-17), 68.3 (t, C-20), 59.0 (d, C-13), 57.7 (d, C-14), 46.2 (t, C-2), 45.4 (t, C-4), 35.5 (t, C-18), 33.5 (s, C-3), 32.1 (d, C-19), 31.6 (t, C-15), 26.9, 26.8, 26.7, 25.9 (6 x q, 4 x $SiC(CH_3)_3$, C-21, C-22), 19.3 (q, C-23), 19.3, 18.2, 17.9 (4 x s,4 x Si*C*), -4.3, -4.4, -4.6, -4.7, -4.8 (6 x q, 6 x $SiCH_3$); IR (film): $\tilde{\upsilon}$ = 2955, 2929, 2857, 1734, 1472, 1361, 1253, 1112, 1078, 835, 775 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{57}H_{98}O_7NaSi_4$ (M^+ + Na): 1029.62818, found: 1029.62874.



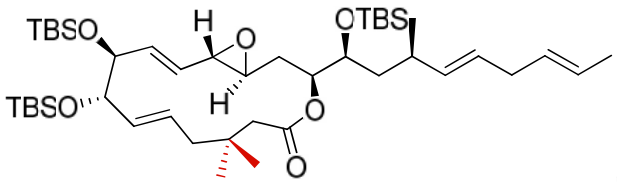
48

Ring Closing Metathesis product 48. Following an identical procedure to the one described for compound **12**, starting from compound **47** (205 mg, 0.20 mmol), diene **48** was obtained (140 mg, 72%). Colourless oil: $[\alpha]_D^{20}$ = +10.5 (*c* = 1.00 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.66-7.62 (m, 4H, aromatics) 7.44-7.34 (m, 6H, aromatics), 5.61 (dd, *J* = 15.6, 8.4 Hz, 1H, H-9), 5.41 (ddd, *J* = 15.0, 10.7, 3.9 Hz, 1H, H-5), 5.24 (dd, *J* = 15.0, 8.1 Hz, 1H, H-6), 5.10 (dd, *J* = 15.6, 8.8 Hz, 1H, H-10), 5.07-5.03 (m, 1H, H-14), 4.01-3.94 (m, 2H, H-7, H-8), 3.76-3.72 (m, 1H, H-15), 3.47 (dd, *J* = 9.8, 4.4 Hz, 1H, H-18a), 3.42 (dd, *J* = 9.8, 5.4 Hz, 1H, H-18b), 2.92 (dd, *J* = 8.8, 1.8 Hz, 1H, H-11), 2.79 (dat, *J* = 9.9, 1.8 Hz, 1H, H-12), 2.66 (dd, *J* = 13.8, 10.7 Hz, 1H, H-4a), 2.31 (dat, *J* = 13.7, 2.6 Hz, 1H, H-13a), 2.19 (d, *J* = 16.7 Hz, 1H, H-2a), 1.94 (d, *J* = 16.7 Hz, 1H, H-2b), 1.80-1.73 (m, 2H, H-17, H-4b), 1.62 (dat, *J* = 13.6, 6.1 Hz, 1H, H-16a), 1.34-1.20 (m, 2H, H-16b, H-13b), 1.05 (s, 9H, $SiC(CH_3)_3$), 0.99 (d, *J* = 6.6 Hz, 1H, H-21), 0.89-0.85 (m, 33H, 3 x $SiC(CH_3)_3$, H-19, H-20), 0.07, 0.06, 0.04, 0.01 (6 x s, 18H, 6 x $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8 (s, *C*=O), 136.4 (d, C-9), 135.6 (4 x d, 4 x Ar*C*H), 133.9 (d, C-5), 133.8, 133.7 (2 x s, 2 x Ar*C*), 130.1 (d, C-6), 129.6 (d, C-10), 129.5 (2 x d, 2 x Ar*C*H), 127.6 (4 x d, 4 x Ar*C*H), 79.3, 78.9 (2 x d, C-8, C-7), 70.9 (d, C-15), 70.6 (d, C-14), 68.1 (t, C-18), 58.5 (d, C-11), 58.3 (d, C-12), 42.3 (t, C-4), 41.9 (t, C-2), 35.6 (t, C-16), 32.8 (t, C-13), 32.8 (s, C-3), 31.8 (d, C-17), 28.8, 27.3 (2 x q, C-19, C-20), 26.9, 26.0, 25.8 (12 x q, 4 x $SiC(CH_3)_3$), 19.3, 18.2, 18.1, 18.0 (4 x s, 4 x Si*C*), 17.7 (q, C-21), -3.9, -4.0, -4.1, -4.4, -4.5 (6 x q, 6 x $SiCH_3$); IR (film): $\tilde{\upsilon}$ = 2955, 2929, 2857, 1739, 1472, 1361, 1253, 1111, 1072, 835, 775 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{55}H_{94}O_7NaSi_4$ (M^+ + Na): 1001.59688, found: 1001.59705.



49

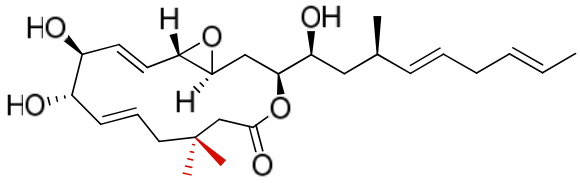
Alcohol 49. Following an identical procedure to the one described for compound **27**, starting from compound **48** (117 mg, 0.12 mmol), alcohol **49** was obtained (39 mg, 45%). Colourless oil: $[\alpha]_D^{20}$ = +18.4 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.62 (dd, *J* = 15.6, 8.1 Hz, 1H, H-9), 5.42 (ddd, *J* = 15.4, 10.7, 4.0 Hz, 1H, H-5), 5.24 (dd, *J* = 15.4, 8.6 Hz, 1H, H-6), 5.10 (dd, *J* = 15.8, 8.6 Hz, 1H, H-10), 5.07-5.03 (m, 1H, H-14), 4.01-3.94 (m, 2H, H-7, H-8), 3.80-3.75 (m, 1H, H-15), 3.41 (at, *J* = 5.8 Hz, 2H, H-18), 2.94 (dd, *J* = 8.6, 2.0 Hz, 1H, H-11), 2.79 (dat, *J* = 9.7, 2.0 Hz, 1H, H-12), 2.66 (dd, *J* = 13.8, 10.6 Hz, 1H, H-4a), 2.31 (dat, *J* = 13.7, 2.2 Hz, 1H, H-13a), 2.24 (d, *J* = 16.7 Hz, 1H, H-2a), 2.04 (d, *J* = 16.7 Hz, 1H, H-2b), 1.82-1.77 (m, 2H, H-17, H-4b), 1.66-1.54 (m, 1H, H-16a), 1.35-1.24 (m, 2H, H-16b, H-13b), 1.01, 0.96 (2 x s, 6H, H-20, H-19), 0.93 (d, *J* = 6.6 Hz, 3H, H-21), 0.89, 0.88, 0.86 (3 x s, 3 x $SiC(CH_3)_3$), 0.09, 0.08, 0.07, 0.06, 0.04 (6 x s, 18H, 6 x $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0 (s, *C*=O), 136.4 (d, C-9), 134.0 (d, C-5), 129.8 (d, C-10), 129.6 (d, C-6), 79.2, 78.7 (2 x d, C-8, C-7), 71.2 (d, C-15), 70.4 (d, C-14), 68.0 (t, C-18), 58.5 (d, C-11), 58.2 (d, C-12), 42.4 (t, C-4), 42.1 (t, C-2), 36.7 (t, C-16), 33.4 (s, C-3) 32.9 (t, C-13), 32.0 (d, C-17), 28.8, 27.4 (2 x q, C-19, C-20), 26.0, 25.9, 25.7 (9 x q, 3 x $SiC(CH_3)_3$), 18.2, 18.1, 17.9 (3 x s, 3 x Si*C*), 17.4 (q, C-21), -3.9, -4.0, -4.1, -4.2, -4.5 (6 x q, 6 x $SiCH_3$); IR (film): $\tilde{\upsilon}$ = 2954, 2929, 2857, 1735, 1472, 1361, 1251, 1218, 1112, 835, 775 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{39}H_{76}O_7NaSi_3$ (M^+ + Na): 763.47911, found: 763.47943.



50

Compound 50. Following an identical procedure to the one described for compound **28**, starting from alcohol **49** (35 mg, 0.048 mmol), compound **50** was obtained (25 mg, 66%). Colourless oil: $[\alpha]_D^{20}$ = +22.0 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.62 (dd, *J* = 15.6, 8.5 Hz, 1H, H-9), 5.47-5.31 (m, 4H, H-22, H-21, H-19, H-5), 5.26 (dd, *J* = 15.5, 8.9 Hz, 1H, H-6), 5.16 (dd, *J* = 15.3, 7.9 Hz, 1H, H-18),

5.10 (dd, *J* = 15.6, 8.5 Hz, 1H, H-10), 5.02-4.99 (m, 1H, H-14), 4.00-3.94 (m, 2H, H-7, H-8), 3.70-3.65 (m, 1H, H-15), 2.92 (dd, *J* = 8.5, 1.7 Hz, 1H, H-11), 2.77 (dat, *J* = 9.9, 1.7 Hz, 1H, H-12), 2.69-2.62 (m, 3H, H-20, H-4a), 2.36 (dat, *J* = 13.9, 2.0 Hz, 1H, H-13a), 2.24-2.20 (m, 2H, H-17, H-4a), 1.99 (d, *J* = 16.7 Hz, 1H, H-2b), 1.84-1.78 (m, 1H, H-4b), 1.66-1.64 (m, 3H, H-23), 1.39 (ddd, *J* = 13.0, 8.9, 3.6 Hz, 1H, H-16a), 1.31-1.17 (m, 2H, H-16b, H-13b), 1.07,0.97 (2 x s, 6H, H-25, H-24), 0.97 (d, *J* = 6.7 Hz, 3H, H-26), 0.89, 0.87, 0.86 (3 x s, 27H, 3 x SiC(CH_3)$_3$), 0.09, 0.06, 0.05, 0.04 (6 x s, 18H, 6 x SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6 (s, *C*=O), 136.5 (d, C-9), 135.9 (d, C-18), 133.9 (d, C-6), 130.2 (d, C-10), 129.7, 129.6, 127.8, 125.5 (4 x d, C-22, C-21 C-19, C-5), 79.3, 78.8 (2 x d, C-7, C-8), 70.8 (d, C-14), 70.4 (d, C-15), 58.6 (d, C-11), 58.2 (d, C-12), 42.4 (t, C-4), 42.2 (t, C-2), 39.1 (t, C-16), 35.6 (t, C-20), 32.9 (d, C-17), 32.7 (s, C-3), 31.9 (t, C-13), 28.9, 27.5 (2 x q, C-25, C-24), 26.0, 25.8 (9 x q, 3 x SiC(*C*H_3)$_3$), 21.8 (q, C-26), 18.2, 18.1, 18.0 (3 x s, 3 x Si*C*), 17.8 (q, C-23), -3.9, -4.0, -4.1, -4.3, -4.4 (6 x q, 6 x Si*C*H_3); IR (film): $\tilde{\upsilon}$ = 2955, 2928, 2857, 1742, 1472, 1360, 1251, 1113, 1060, 969, 835 cm^{-1}; HRMS (ES$^+$): *m/z*: Calcd for $C_{44}H_{82}O_6NaSi_3$ (M^+ + Na): 813.53114, found: 813.53055.

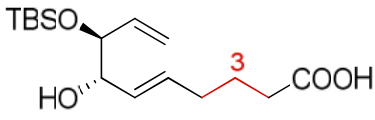


22

Analogue 22. Following an identical procedure to the one described for the synthesis of **1**, starting from compound **50** (15 mg, 19 μmol), triol **22** (7 mg, 82%) was obtained. Colourless oil: $[\alpha]_D^{20}$ = +23.1 (*c* = 0.25 in $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 5.75-5.65 (m, 2H, H-9, H-5), 5.47-5.34 (m, 4H, H-22, H-21, H-19, H-6), 5.25 (dd, *J* = 15.4, 9.2 Hz, 1H, H-10), 5.20 (ddt, *J* = 15.3, 8.2, 1.4 Hz, 1H, H-18), 5.00 (ddd, *J* = 11.8, 3.6, 1.9 Hz, 1H, H-14), 4.02-3.93 (m, 2H, H-7, H-8), 3.63-3.57 (m, 1H, H-15), 2.97 (dd, *J* = 9.3, 1.7 Hz, 1H, H-11), 2.87 (dt, *J* = 10.4, 2.2 Hz, 1H, H-12), 2.68-2.64 (m, 2H, H-20a, H-20b), 2.63 (dd, *J* = 14.0, 10.3 Hz, 1H, H-4a), 2.39-2.24 (m, 2H, H-17, H-13a), 2.22 (d, *J* = 16.6 Hz, 1H, H-2a), 2.08 (d, *J* = 16.6 Hz, 1H, H-2b), 1.93-1.87 (m, 1H, H-4b), 1.66-1.64 (m, 3H, H-23), 1.50-1.41 (m, 1H, H-13b), 1.39-1.27 (m, 2H, H-16a, H-16b), 1.21-0.98 (m, 9H, H-24, H-25, H-26). ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 170.9 (s, C=O), 135.2 (s, C-18), 134.2 (s, C-9), 133.7 (s, C-10), 133.5 (s, C-5), 131.5 (s, C-6), 129.5 (s, C-21), 128.7 (s, C-19), 125.7 (s, C-22),

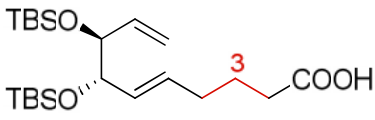
77.0 (C-7, C-8), 72.3 (s, C-15), 71.2 (s, C-14), 58.2 (s, C-11), 58.1 (s, C-12), 42.5 (s, C-4), 42.1 (s, C-2), 40.8 (s, C-16), 35.5 (s, C-20), 34.5 (s, C-13), 33.2 (s, C-17), 33.0 (s, C-3), 28.9 (s, C-24), 27.1 (s, C-25), 21.6 (s, C-26), 17.9 (s, C-23). IR(film): ϑ = 3405, 2969, 2925, 2853, 1738, 1435, 1366, 1228, 1217, 1003, 968, 874, 770 cm^{-1}. HRMS (ES^+), *m/z*: calcd for $C_{26}H_{40}NaO_6$ (M^+ + Na): 471.27171, found: 471.27173.

Synthesis of C3-unsubstituted iriomoteolide-3a. Analogue (23)



51

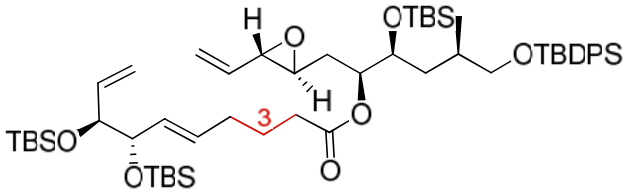
(*E*)-(7*R*,8*R*)-8-(*tert*-Butyl-dimethyl-silanyloxy)-7-hydroxy-deca-5,9-dienoic acid (51). Following an identical procedure to the one described for compound **26**, starting from commercially available 5-hexenoic acid (625 mg, 5.5 mmol) and diene **5d** (250 mg, 1.09 mmol), acid **51** was obtained (192 mg, 56%). Colourless oil: $[\alpha]_D^{20}$ = +9.7 (*c* = 1.00 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 5.78 (ddd, *J* = 17.2, 10.4, 6.5 Hz, 1H), 5.68 (dat, *J* = 15.5, 6.7 Hz, 1H), 5.45 (dd, *J* = 15.5, 6.3 Hz, 1H), 5.22 (dat, *J* = 17.2, 1.2 Hz, 1H), 5.17 (dat, *J* = 10.4, 1.2 Hz, 1H), 3.94 (at, *J* = 6.3 Hz, 1H), 3.87 (at, *J* = 6.3 Hz, 1H 1H), 2.43 (t, *J* = 7.4 Hz, 2H), 2.13-2.07 (m, 2H), 1.76-1.68 (m, 2H), 0.90 (s, 9H), 0.08, 0.05 (2 x s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.2, 137.8, 132.2, 129.7, 116.9, 77.7, 75.5, 33.2, 31.5, 25.8, 23.9, 18.2, -4.1, -4.8; IR (film): $\tilde{\upsilon}$ = 3500, 2963, 2929, 2857, 1709, 1472, 1252, 1085, 835, 777 cm^{-1}; HRMS (ES^+): m/z: Calcd for $C_{16}H_{30}O_4NaSi$ (M^+ + Na): 337.18056, found: 337.18049.



52

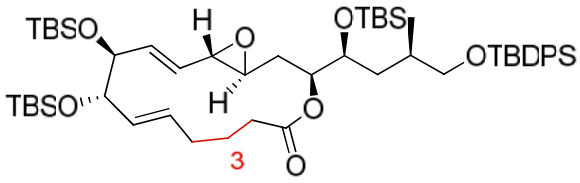
(*E*)-(7*S*,8*S*)-7,8-Bis-(*tert*-butyl-dimethyl-silanyloxy)-deca-5,9-dienoic acid (52). Starting from diene **51** (365 mg, 1.2 mmol) and performing the same protocol described for compound **14**, acid **52** (392 mg, 76%) was obtained. Colourless oil: $[\alpha]_D^{20}$ = -35.6 (*c* = 1.00 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 5.88 (ddd, *J* = 17.2, 10.5, 4.6 Hz, 1H), 5.55-5.39 (m, 2H), 5.18 (ddd, *J* = 17.2, 2.2, 1.7 Hz, 1H), 5.10 (ddd, *J* = 10.5, 2.2, 1.6 Hz, 1H), 4.09-4.04 (m, 2H), 2.34 (t, *J* = 7.6 Hz, 2H), 2.13-2.03 (m, 2H), 1.73-1.75 (m, 2H), 0.90, 0.89 (2 x s, 18H), 0.06, 0.04, 0.03, 0.02 (4 x s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.6, 137.3, 130.4, 130.3, 115.1, 76.2,

75.9, 32.9, 31.5, 25.8, 24.1, 18.2, 18.2, -4.6, -4.7, -4.7, -4.8 ; IR (film): $\tilde{\upsilon}$ = 2954, 2929, 2885, 1710, 1472, 1462, 1407, 1252, 1129, 1074, 834, 774 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{22}H_{44}O_4NaSi_2$ (M^+ + Na): 451.26703. Found 451.26718.



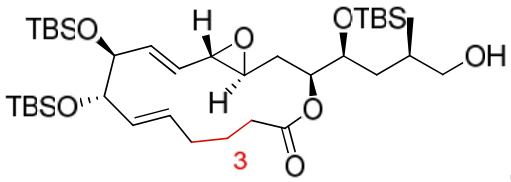
53

Ring Closing Metathesis precursor 53. Following an identical procedure to the one described for compound **15**, starting from alcohol **3** (265 mg, 0.46 mmol) and acid **52** (200 mg, 0.46 mmol), ester **53** was obtained (282 mg, 65%). Colourless oil: $[\alpha]_D^{20}$ = -23.9 (*c* = 1.50 in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.65-7.62 (m, 4H, aromatics), 7.43-7.37 (m, 6H, aromatics), 5.86 (ddd, *J* = 17.3, 10.5, 4.7 Hz, 1H, H-9), 5.57-5.38 (m, 4H, H-12, H-11a, H-6, H-5), 5.25 (dd, *J* = 9.9, 1.7 Hz, 1H, H-11b), 5.17 (dat, *J* = 17.3, 1.7 Hz, 1H, H-10a), 5.08 (dat, *J* = 10.5, 1.7 Hz, 1H, H-10b), 5.02 (dat, *J* = 9.9, 3.2 Hz, 1H, H-16), 4.08-4.02 (m, 2H, H-7, H-8), 3.88-3.83 (m, 1H, H-17), 3.48-3.41 (m, 2H, H-20), 3.06 (dd, *J* = 7.4, 1.9 Hz, 1H, H-13), 2.85 (td, *J* = 5.9, 1.9 Hz, 1H, H-14), 2.26-2.12 (m, 2H, H-2), 2.04-1.94 (m, 3H, H-4, H-15a), 1.75-1.71 (m, 1H, H-19), 1.71-1.50 (m, 4H, H-18a, H-15b, H-3), 1.26-1.17 (m, 1H, H-18b), 1.05 (s, 9H, $SiC(CH_3)_3$), 0.97 (d, *J* = 6.6 Hz, 3H, H-21), 0.90, 0.89, 0.87 (3 x s, 27H, 3 x $SiC(CH_3)_3$), 0.09, 0.06, 0.05, 0.04, 0.02, 0.02 (6 x s, 18H, 6 x $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.9 (s, *C*=O), 137.4 (d, C-9), 135.6, 135.5 (4 x d, 4 x Ar*C*H), 135.5 (d, C-12), 133.8, 133.7 (2 x s, 2 x Ar*C*), 130.5, 130.0 (2 x d, C-5, C-6), 129.5 (2 x d, 2 x Ar*C*H), 127.6 (4 x d, 4 x Ar*C*H), 119.3 (t, C-11), 115.1 (t, C-10), 76.2, 75.9 (2 x d, C-8, C-7), 72.6 (d, C-16), 70.1 (d, C-17), 68.1 (t, C-20), 59.0 (d, C-13), 57.7 (d, C-14), 35.4 (t, C-18), 33.7 (t, C-2), 31.9 (d, C-19), 31.8 (t, C-4), 31.7 (t, C-15), 26.8, 25.8 (4 x q, 4 x $SiC(CH_3)_3$), 24.4 (t, C-3), 19.3 (s, Si*C*), 18.1 (2 x s, 2 x Si*C*), 18.0 (q, C-21), 18.0 (s, Si*C*), -4.3, -4.4, -4.6, -4.7, -4.7, 4.7 (6 x q, 6 x $SiCH_3$); IR (film): $\tilde{\upsilon}$ = 2955, 2929, 2893, 1736, 1472, 1428, 1253, 1219, 1078, 773, cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{55}H_{94}O_7NaSi_4$ (M^+ + Na): 1001.59688, found: 1001.59817.



54

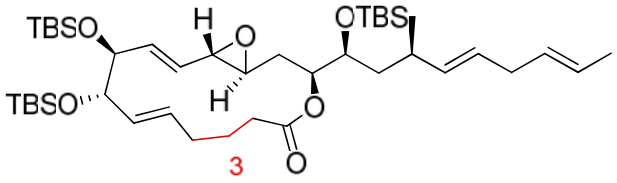
Ring Closing Metathesis product 54. Following an identical procedure to the one described for compound **12**, starting from compound **53** (223 mg, 0.23 mmol), intermediate **54** was obtained (159 mg, 73%). Colourless oil: $[\alpha]_D^{20}$ = +9.8 (*c* = 1.00 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.64-7.61 (m, 4H, aromatics) 7.44-7.36 (m, 6H, aromatics), 5.64 (dd, *J* = 15.6, 8.1 Hz, 1H, H-9), 5.32-5.23 (m, 2H, H-6, H-5), 5.07 (dd, *J* = 15.6, 8.9 Hz, 1H, H-10), 4.97 (dd, *J* = 11.8, 3.7 Hz, 1H, H-14), 3.98-3.94 (m, 2H, H-7, H-8), 3.82-3.79 (m, 1H, H-15), 3.47-3.40 (m, 2H, H-18), 3.01 (d, *J* = 8.8 Hz, 1H, H-11), 2.76 (d, *J* = 9.9 Hz, 1H, H-12), 2.40 (d, *J* = 13.8 Hz, H-13a), 2.26-2.21 (m, 1H, H-4a), 2.19-2.11 (m, 2H, H-2), 2.10-2.03 (m, 1H, H-4b), 1.85-1.75 (m, 2H, H-3a, H-17), 1.65 (ddd, *J* = 12.8, 7.0, 4.2 Hz, 1H, H-16a), 1.43-1.35 (m, 1H, H-3b), 1.30-1.22 (m, 1H, H-13b), 1.16 (ddd, *J* = 14.3, 8.5, 6.4 Hz, 1H, H-16b), 1.04 (s, 9H, $SiC(CH_3)_3$), 0.97 (d, *J* = 6.7 Hz, 3H, H-19), 0.88, 0.87, 0.86 (3 x s, 27H, 3 x $SiC(CH_3)_3$), 0.10, 0.06, 0.05, 0.05, 0.02, 0.01 (6 x s, 18H, 6 x $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6 (s, *C*=O), 136.9 (d, C-9), 135.6 (4 x d, 4 x Ar*C*H), 133.8, 133.6 (2 x s, 2 x Ar*C*), 132.5 (d, C-5 or C-6), 131.18 (d, C-5 or C-6), 129.8 (d, C-10), 129.5 (2 x d, 2 x Ar*C*H), 127.6 (4 x d, 4 x Ar*C*H), 78.4, 78.0 (2 x d, C-8, C-7), 72.1 (d, C-14), 69.7 (d, C-15), 67.5 (t, C-18), 59.1 (d, C-11), 57.7 (d, C-12), 34.6 (t, C-16), 31.8 (d, C-17), 31.1 (t, C-13), 30.0 (t, C-2), 29.7 (t, C-4), , 26.9, 26.0, 25.8 (12 x q, 4 x $SiC(CH_3)_3$), 22.0 (t, C-3), 19.3 (q, C-19), 18.3, 18.2, 18.1, 17.9 (4 x s, 4 x Si*C*), -4.0, -4.1, -4.2, -4.3, -4.4, -4.7 (6 x q, 6 x $SiCH_3$); IR (film): $\tilde{\upsilon}$ = 2954, 2929, 2857, 2893, 1740, 1472, 1462, 1251, 1361, 1112, 835, 775 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{53}H_{90}O_7NaSi_4$ (M^+ + Na): 973.56558, found: 973.56582.



55

Alcohol 55. Following an identical procedure to the one described for compound **27,** starting from protected **54** (200 mg, 0.20 mmol), alcohol **55** was obtained (152 mg, 79%). Colourless oil: $[\alpha]_D^{20}$ = +16.5 (*c* = 0.3 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$):

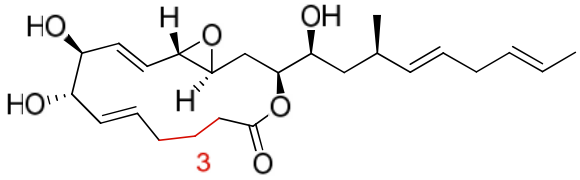
δ = 5.64 (dd, *J* = 15.5, 8.4 Hz, 1H, H-9), 5.36-5.23 (m, 2H, H-5, H-6), 5.11-5.05 (m, 1H, H-14), 5.08 (dd, *J* = 15.7, 8.7 Hz, 1H, H-10), 3.98-3.96 (m, 2H, H-7, H-8), 3.84-3.80 (m, 1H, H-15), 3.44-3.39 (m, 2H, H-18), 3.01 (dd, *J* = 8.8, 2.0 Hz, 1H, H-11), 2.77 (dat, *J* = 9.8, 2.0 Hz, 1H, H-12), 2.35 (dat, *J* = 13.9, 2.2 Hz, 1H, H-13a), 2.30-2.24 (m, 3H, H-2, H-4a), 2.12-2.05 (m, 1H, H-4b), 1.94-1.83 (m, 1H, H-3a), 1.82-1.76 (m, 1H, H-17), 1.73 (br t, *J* = 5.6 Hz, 18-OH), 1.57-1.48 (m, 2H, H-16a, H-13b), 1.31-1.22 (m, 2H, H-16b, H-13b), 0.92 (d, *J* = 6.8 Hz, 3H, H-19), 0.89, 0.88, 0.87 (3 x s, 27H, 3 x SiC(CH_3)$_3$), 0.12, 0.09, 0.06, 0.05, 0.04, 0.02 (6 x s, 18H, 6 x SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8 (s, *C*=O), 137.0 (d, C-9), 132.6 (d, C-5 or C-6), 131.7 (d, C-5 or C-6), 129.6 (d, C-10), 78.4 (d, C-8 or C-7), 78.0 (d, C-8 or C-7), 71.9 (d, C-14), 70.5 (d, C-15), 67.7 (t, C-18), 59.2 (d, C-11), 57.6 (d, C-12), 36.2 (t, C-16), 32.0 (t, C-13), 32.0 (d, C-17), 30.2 (t, C-2), 29.7 (t, C-4), 26.9, 25.9, 25.7 (9 x q, 3 x SiC(*C*H_3)$_3$), 22.1 (t, C-13), 18.2, 18.1, 18.0 (4 x s, 4 x Si*C*), 17.9 (q, C-19), -4.0, -4.1, -4.2, -4.5, -4.6 (6 x q, 6 x Si*C*H_3); IR (film): $\tilde{\upsilon}$ = 2953, 2928, 2885, 1740, 1471, 1462, 1410, 1251, 1215, 1118, 1052, 833, 774 cm^{-1}; HRMS (ES$^+$): *m/z*: Calcd for $C_{37}H_{72}O_7NaSi_3$ (M^+ + Na): 735.44781, found: 735.44750.



56

Compound 56. Following an identical procedure to the one described for compound **28**, starting from alcohol **55** (55 mg, 0.077 mmol), compound **56** was obtained (35 mg, 59%, two steps). Colourless oil: $[\alpha]_D^{20}$ = +16.2 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.63 (dd, *J* = 15.6, 8.4 Hz, 1H, H-9), 5.43-5.32 (m, 5H, H-22, H-21, H-19, H-5, H-6). 5.14 (dd, *J* = 15.4, 8.0 Hz, 1H, H-18), 5.08 (dd, *J* = 15.6, 8.9 Hz, 1H, H-10), 4.92 (ddd, *J* = 12.0, 4.0, 1.4 Hz, 1H, H-14), 3.99-3.94 (m, 2H, H-7, H-8), 3.75-3.71 (m, 1H, H-15), 3.00 (dd, *J* = 8.8, 2.0 Hz, 1H, H-11), 2.75 (dat, *J* = 9.8, 2.0 Hz, 1H, H-12), 2.64-2.60 (m, 2H, H-20), 2.42 (dat, *J* = 13.3, 2.0 Hz, 1H, H-13a), 2.27-2.20 (m, 4H, H-2, H-4a, H-17), 2.16-2.06 (m, 1H, H-4b), 1.95-1.86 (m, 1H, H-3a), 1.65-1.64 (m, 3H, H-23), 1.57-1.48 (m, 1H, H-3b), 1.31-1.25 (m, 3H, H-16, H-13b), 0.96 (d, *J* = 6.8 Hz, 3H, H-24), 0.89, 0.88, 0.86 (3 x s, 27H, 3 x SiC(CH_3)$_3$), 0.12, 0.07, 0.06, 0.05, 0.04, 0.02 (6 x s, 18H, 6 x SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3 (s, *C*=O), 136.9 (d, C-9), 135.8 (d, C-18), 132.5, 131.7, 129.8,

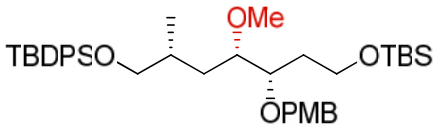
129.6, 128.1, 125.5 (6 x d, C-22, C-21, C-19, C-10, C-5, C-6), 78.4, 78.0 (2 x d, C-7, C-8), 72.3 (d, C-14), 69.3 (d, C-15), 59.2 (d, C-11), 57.7 (d, C-12), 38.8 (t, C-16), 35.5 (t, C-20), 32.9 (d, C-17), 30.7 (t, C-2), 30.2 (t, C-13), 29.8 (t, C-4), 26.0, 25.9, 25.8 (9 x q, 3 x SiC(CH_3)$_3$), 22.3 (t, C-3), 22.0 (q, C-24), 18.2, 18.1, 17.9 (3 x s, 3 x Si*C*), 17.8 (q, C-23), -4.0, -4.1, -4.1, -4.2, -4.3, -4.5 (6 x q, 6 x SiCH_3); IR (film): $\tilde{\upsilon}$ = 2954, 2929, 2857, 1742, 1472, 1251, 1120, 1059, 835, 776 cm^{-1}; HRMS (ES$^+$): *m/z*: Calcd for $C_{42}H_{78}O_6NaSi_3$ (M^+ + Na): 785.49984, found: 785.50004.



23

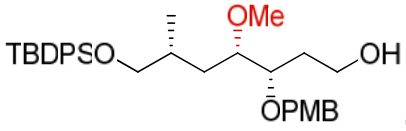
Analogue 23. Following an identical procedure to the one described for compound **1**, starting from protected **56** (25 mg, 0.032 mmol), analogue **23** was obtained (10 mg, 74%). White amorphous solid: $[\alpha]_D^{20}$ = +46.9 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.76 (dd, *J* = 15.3, 8.8 Hz, 1H, H-9), 5.62 (ddd, *J* = 15.1, 9.0, 4.6 Hz, 1H, H-5), 5.47-5.30 (m, 4H, H-22, H-21, H-19, H-6), 5.24 (dd, *J* = 15.3, 9.2 Hz, 1H, H-10), 5.18 (dd, *J* = 15.3, 8.4 Hz, 1H, H-18), 5.07 (dat, *J* = 12.3, 3.2 Hz, 1H, H-14), 3.97-3.92 (m, 2H, H-7, H-8), 3.63-3.54 (m, 1H, H-15), 3.03 (dd, *J* = 9.9, 1.3 Hz, 1H, H-11), 2.85 (dat, *J* = 9.9, 1.3 Hz, 1H, H-12), 2.67-2.63 (m, 2H, H-20), 2.45-2.22 (m, 5H, H-17, H-13a, H-4a, H-2), 2.17-2.08 (m, 1H, H-4b), 1.87-1.78 (m, 1H, H-3a), 1.66-1.60 (m, 4H, H-23, H-3a), 1.53-1.44 (m, 1H, H-13b), 1.38-1.26 (m, 2H, H-16), 1.00 (d, *J* = 6.7 Hz, 3H, H-24); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9 (s, *C*=O), 135.7 (d, C-9), 135.2 (d, C-5), 135.0 (d, C-18), 133.2 (d, C-10), 130.8 (d, C-6), 129.4, 128.8, 125.6 (3 x d, C-22, C-21 C-19), 77.3, 76.7 (2 x d, C-7, C-8), 72.9 (d, C-14), 71.0 (d, C-15), 58.9 (d, C-11), 57.5 (d, C-12), 40.6 (t, C-16), 35.5 (t, C-20), 33.9 (t, C-13), 33.4 (d, C-17), 30.1 (t, C-2), 28.8 (t, C-4), 23.1 (t, C-3), 21.7 (q, C-24), 18.4 (q, C-23); IR (film): $\tilde{\upsilon}$ = 3477, 2869, 2363, 1731, 1180, 1098, 1054, 963 cm^{-1}; HRMS (ES$^+$): *m/z*: Calcd for $C_{24}H_{36}O_6Na$ (M^+ + Na): 443.2404, found: 443.2402.

Synthesis of the C_{15}-OMe- Iriomoteolide 3a. Analogue 24.



57

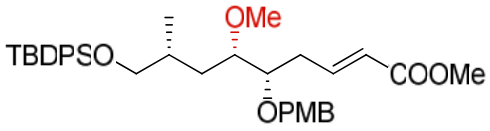
(2*R*,4*S*,5*S*)-7-(*tert*-butyl-dimethyl-silanyloxy)-1-(*tert*-butyl-diphenyl-silanyloxy)-4-(methoxy)-5-(4-methoxy-benzyloxy)-2-methyl-heptane (57). A solution of the corresponding secondary alcohol[1] (931 mg, 1,43 mmol) in THF (20 mL) was cooled to 0 °C and NaH (60 % dispersion in mineral oil, 86 mg, 2,15 mmol) was added. After 15 min MeI (267 µL, 4,29 mmol) was added and the mixture was stirred for additional 30 min then allowed to warm to room temperature. After 7 h the reaction was cooled to 0 °C and water was added, THF was removed *in vacuo* and the residue was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure and purification of the crude material by flash chromatography (hexanes/EtOAc 20:1 → 10:1) provided methylether **57** (768 mg, 80%). Colorless oil: $[\alpha]_D^{20}$ = -26.9 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69-7.67 (m, 4H), 7.42-7.35 (m, 6H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 4.49 (d, *J* = 11.1 Hz, 1H), 4.43 (d, *J* = 11.1 Hz, 1H), 3.77 (s, 3H), 3.69-3.65 (m, 3H), 3.57 (dd, *J* = 9.8, 5.0 Hz, 1H), 3.46 (dd, *J* = 9.8, 6.6 Hz, 1H), 3.30 (s, 3H), 3.27-3.22 (m, 1H), 1.89-1.55 (m, 4H), 1.25 (ddd, *J* = 14.2, 8.4, 5.7 Hz, 1H), 1.07 (s, 9H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 135.6, 135.6, 134.0, 134.0, 131.0, 129.5, 129.5, 127.6, 127.6, 113.7, 80.3, 75.4, 72.3, 68.8, 59.7, 57.9, 55.2, 33.5, 33.1, 32.9, 26.9, 25.9, 19.3, 18.2, 18.0, -5.3; -5.4 IR (film): $\tilde{\upsilon}$ = 2953, 2928, 2856, 1612, 1513, 1463, 1428, 1389, 1361, 1302, 1248, 1173, 1087, 1038, 1007, 938, 832, 775, 740, 701, 663, 613, 503 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{39}H_{60}NaO_5Si_2$ (M^+ + Na): 687.38715, found: 687.38678.



58

(3*S*,4*S*,6*R*)-7-(*tert*-butyl-diphenyl-silanyloxy)-4-(methoxy)-3-(4-methoxy-benzyloxy)-6-methyl-heptan-1-ol (58). To a solution of **57** (1.67 g, 2.51 mmol) in EtOH (23 mL) was added pyridinium *p*-toluensulfonate (694 mg, 2.76 mmol). The reaction mixture was stirred for 5 h, concentrated under reduced pressure, diluted with

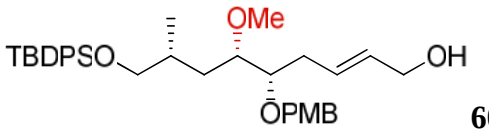
EtOAc and washed with aq. sat. $NaHCO_3$ solution and brine. The aqueous layers were extracted with EtOAc and the combined organic extracts were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure and purification of the crude material by flash chromatography (hexanes/EtOAc 4:1 → 2:1) provided alcohol **58** (1.33 g, 95%). Colorless oil: $[\alpha]_D^{20}$ = -27.6 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69-7.65 (m, 4H), 7.44-7.34 (m, 6H), 7.19 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 4.52 (d, *J* = 11.2 Hz, 1H), 4.41 (d, *J* = 11.2 Hz, 1H), 3.78 (s, 3H), 3.70-3.61 (m, 3H), 3.56 (dd, *J* = 9.9, 5.3 Hz, 1H), 3.47 (dd, *J* = 9.9, 6.4 Hz, 1H), 3.36-3.32 (m, 1H), 3.32 (s, 3H), 2.33 (t, *J* = 5.5 Hz, 1H), 1.91-1.82 (m, 1H), 1.81-1.74 (m, 1H), 1.72-1.63 (m, 2H), 1.28 (ddd, *J* = 14.5, 8.5, 5.6 Hz, 1H), 1.06 (s, 9H), 1.00 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 135.6, 135.6, 133.9, 133.9, 130.3, 129.6, 129.5, 127.6, 127.6, 113.8, 80.2, 77.9, 72.0, 68.7, 60.8, 58.1, 55.2, 33.5, 33.0, 32.3, 26.9, 19.3, 18.1; IR (film): $\tilde{\upsilon}$ = 3442, 2930, 2858, 1612, 1513, 1463, 1428, 1389, 1302, 1249, 1109, 1081, 1038, 824, 741, 703, 503 cm^{-1}; HRMS (ES$^+$): *m/z*: Calcd for $C_{33}H_{46}NaO_5Si$ (M^+ + Na): 573.30067, found: 573.30039.



59

(*E*)-(5*S*,6*S*,8*R*)-9-(*tert*-butyl-diphenyl-silanyloxy)-6-(methoxy)-5-(4-methoxy-benzyloxy)-8-methyl-non-2-enoic acid methyl ester (59). To a solution of oxalyl chloride (283 µL, 3.61 mmol) in CH_2Cl_2 (26 mL) at -78 °C was added DMSO (502 µL, 7.70 mmol) dropwise. After 30 min, a solution of alcohol **58** (1.33 g, 2.41 mmol) in CH_2Cl_2 (40 mL) was added to the reaction mixture, which was stirred for 1 h at -78°C. The mixture was quenched with Et_3N (1.65 mL, 11.98 mmol), stirred at -78°C for additional 30 min, allowed to warm to room temperature and washed with aq. sat. NH_4Cl solution and water. The organic phase was dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The crude residue was dissolved in CH_2Cl_2 (150 mL), and $Ph_3PCHCOOMe$ (1.67 g, 4.80 mmol) was added as a solid. The mixture was stirred for 19 h at room temperature. Then, the solvent was evaporated under reduced pressure and the crude residue was purified by flash chromatography (hexanes/EtOAc 9:1 → 5:1) to provide **59** (1.34 g, 92%). Colorless oil: $[\alpha]_D^{20}$ = -15.9 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69-7.66 (m, 4H), 7.45-7.34

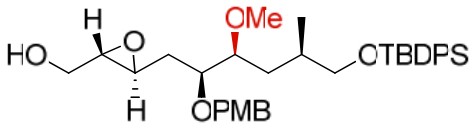
(m, 6H), 7.17 (d, *J* = 8.6 Hz, 2H), 6.96 (dat, *J* = 15.6, 7.4 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 2H), 5.82 (dat, *J* = 15.6, 1.3 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.57-3.44 (m, 3H), 3.31-3.23 (m, 1H), 3.29 (s, 3H), 2.46 (dddd, *J* = 14.6, 7.3, 3.0, 1.3 Hz, 1H), 2.33 (dddd, *J* = 14.6, 9.4, 7.3, 1.3 Hz, 1H), 1.87-1.76 (m, 1H), 1.69 (ddd, *J* = 14.0, 7.0, 4.4 Hz, 1H), 1.27 (ddd, *J* = 14.0, 8.4, 6.0 Hz, 1H), 1.06 (s, 9H), 0.98 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 159.2, 146.6, 135.6, 135.6, 133.9, 133.9, 130.2, 129.5, 127.6, 127.6, 122.6, 113.7, 80.0, 77.8, 72.2, 68.7, 58.0, 55.2, 51.4, 33.3, 33.1, 32.8, 26.9, 19.3, 17.9; IR (film): $\tilde{\upsilon}$ = 2930, 2858, 2360, 2341, 1723, 1656, 1612, 1513, 1463, 1428, 1320, 1248, 1172, 1109, 1037, 822, 741, 703, 614, 503 cm^{-1}; HRMS (ES$^+$): *m/z*: Calcd for $C_{36}H_{48}NaO_6Si$ (M^+ + Na): 627.31124, found: 627.31122.



60

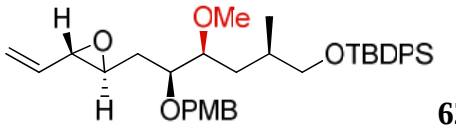
(*E*)-(5*S*,6*S*,8*R*)-9-(*tert*-butyl-diphenyl-silanyloxy)-6-(methoxy)-5-(4-methoxy-benzyloxy)-8-methyl-non-2-en-1-ol (60). To a solution of methyl ester **59** (1.31 g, 2.17 mmol) in CH_2Cl_2 (60 mL) at -78 °C was slowly added DIBAL-H (1M in hexanes, 5.50 mL, 5.50 mmol). The mixture was stirred for 5 min at -78 °C, quenched by slow addition of EtOAc (200 mL) and allowed to warm to room temperature. Aq. sat. potassium tartrate solution was added (200 mL) and stirring was continued until clear separation of two phases. The aqueous phase was extracted with EtOAc and the combined organic extracts were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure and purification of the crude residue by filtration on silica gel (hexanes/EtOAc 2:1 → 1.5:2.5) gave alcohol **60** (1.20 g, 96%). Colorless oil: $[\alpha]_D^{20}$ = -12.0 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69-7.65 (m, 4H), 7.44-7.34 (m, 6H), 7.19 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 5.67-5.64 (m, 2H), 4.47 (d, *J* = 11.4 Hz, 1H), 4.42 (d, *J* = 11.4 Hz, 1H), 4.06-4.02 (m, 2H), 3.77 (s, 3H), 3.55 (dd, *J* = 9.8, 5.1 Hz, 1H), 3.45 (dd, *J* = 9.8, 6.4 Hz, 1H), 3.42-3.37 (m, 1H), 3.31 (s, 3H), 3.27-3.22 (m, 1H), 2.34-2.28 (m, 1H), 2.26-2.17 (m, 1H), 1.87-1.76 (m, 1H), 1.67 (ddd, *J* = 14.1, 7.1, 4.4 Hz, 1H), 1.55 (br s, 1H), 1.28 (ddd, *J* = 14.1, 8.4, 6.3 Hz, 1H), 1.06 (s, 9H), 0.98 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 135.6, 135.6, 134.0, 134.0, 131.1, 129.8, 129.5, 127.6, 127.6, 113.6, 80.3, 79.1, 72.1,

68.8, 63.7, 58.2, 55.3, 33.6, 33.0, 32.8, 26.9, 19.3, 18.0; IR (film): $\tilde{\upsilon}$ = 3400, 2958, 2930, 2857, 1612, 1512, 1471, 1462, 1428, 1249, 1111, 1076, 834, 774, 702, 505 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{35}H_{48}NaO_5Si$ (M^+ + Na): 599.31632, found: 599.31642.



61

4-[(1*S*,2*S*,4*R*)-5-(*tert*-butyl-diphenyl-silanyloxy)-2-(methoxy)-1-((2*S*,3*S*)-3-hydroxymethyl-oxiranylmethyl)-4-methyl-pentyloxymethyl]-phenol (61). To a solution of (+)-DIPT (57 mg, 0.24 mmol) in CH_2Cl_2 (11 mL) containing 4Å activated molecular sieves (300 mg) at -30°C was added titanium tetraisopropoxide (61 µL, 0.204 mmol). After stirring for 30 min, allylic alcohol **60** (1.18 g, 2.04 mmol) was added and the mixture was stirred for additional 30 min. *tert*-Butyl hydroperoxide (5.5 M in decane, 0.82 mL, 4.50 mmol) was slowly added and the reaction mixture was stirred for 5 h at -30°C, warmed up to 0°C and quenched with 20 mL of an ice-cold aqueous solution of $FeSO_4 \cdot 7\ H_2O$ (4.9 g) and tartaric acid (1.6 g). After stirring for 10 min, the mixture was diluted with EtOAc, the layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and the solvent evaporated under reduced pressure to give the crude material which was purified by flash chromatography (hexanes/EtOAc 1:1) to give **61** (839 mg, 69%). Colorless oil: $[\alpha]_D^{20}$ = -34.7 (*c* = 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.69-7.65 (m, 4H), 7.44-7.34 (m, 6H), 7.19 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 4.52 (d, *J* = 11.2 Hz, 1H), 4.45 (d, *J* = 11.2 Hz, 1H), 3.86 (ddd, *J* = 12.5, 5.5, 2.7 Hz 1H), 3.77 (s, 3H), 3.69-3.64 (m, 1H), 3.61-3.53 (m, 2H), 3.46 (dd, *J* = 9.9, 6.4 Hz, 1H), 3.31-3.26 (m, 1H), 3.29 (s, 3H), 3.06 (ddd, *J* = 7.1, 4.6, 2.4 Hz, 1H), 2.92 (dat, *J* = 4.5, 2.4 Hz, 1H), 1.88-1.80 (m, 1H), 1.76 (ddd, *J* = 14.2, 9.6, 4.6 Hz, 1H), 1.70-1.61 (m, 2H), 1.60 (br s, 1H), 1.23 (ddd, *J* = 14.2, 8.8, 6.2 Hz, 1H), 1.06 (s, 9H), 0.99 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 135.6, 135.6, 133.9, 133.9, 130.5, 129.5, 129.5, 127.6, 127.6, 113.8, 80.0, 76.4, 72.5, 68.7, 61.6, 59.1, 58.0, 55.2, 53.7, 33.3, 32.9, 32.5, 26.9, 19.3, 18.0; IR (film): $\tilde{\upsilon}$ = 3440, 3070, 3050, 2954, 2930, 2857, 1612, 1587, 1513, 1463, 1427, 1389, 1362, 1302, 1247, 1173, 1105, 1082, 1035, 822, 741, 701, 613, 503 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{35}H_{48}NaO_6Si$ (M^+ + Na): 615.31124, found: 615.31127.

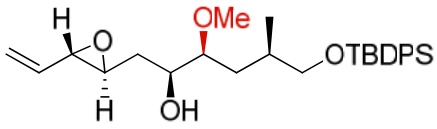


62

(2*S*,3*S*)-2-[(2*S*,3*S*,5*R*)-6-(*tert*-butyl-diphenylsilanoxy)-3-(methoxy)-2-(4-methoxy-benzyloxy)-5-methyl-hexyl]-3-vinyl-oxirane (62). To a solution of oxalyl chloride (162 µL, 2.07 mmol) in CH_2Cl_2 (16 mL) at -78°C was slowly added DMSO (287 µL, 4.41 mmol). After 30 min, a solution of alcohol **61** (817 mg, 1.38 mmol) in CH_2Cl_2 (16 mL) was added to the reaction mixture. After stirring for 1 h at -78°C the mixture was quenched with Et_3N (956 µL, 6.89 mmol), stirred at -78°C for 30 min and then warmed up to 25ºC and washed aq. sat. NH_4Cl solution and water. The organic extracts were dried over $MgSO_4$, the solvent was evaporated under reduced pressure to give the crude aldehyde which was used without further purification in the next step.

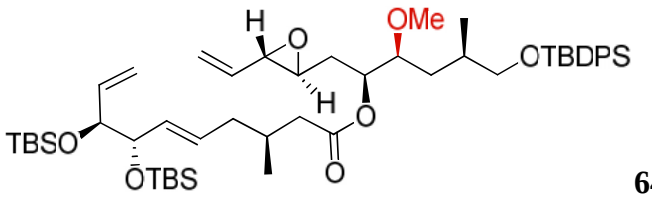
To a suspension methyltriphenylphosphonium bromide (1.23 g, 3.45 mmol) in THF (5 mL) cooled to 0°C was added NaHMDS (632 mg, 3.45 mmol). After stirring for 45 min at 0°C a solution of the previous aldehyde in THF (5 mL) was added dropwise. The reaction mixture was stirred for 20 min at 0°C and quenched with aq. sat. NH_4Cl solution. The mixture was diluted with EtOAc and washed with brine. The organic extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to give a crude residue which was purified by flash chromatography (hexanes/EtOAc 7:1 → 4:1) to give intermediate **62** (434 mg, 53%). Colorless oil: $[\alpha]_D^{20}$ = -22.1 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69-7.64 (m, 4H), 7.45-7.34 (m, 6H), 7.19 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 5.57 (ddd, *J* = 17.4, 10.2, 7.5 Hz, 1H), 5.44 (dd, *J* = 17.4, 1.5 Hz, 1H), 5.26 (dd, *J* = 10.2, 1.6 Hz, 1H), 4.51 (d, *J* = 11.1 Hz, 1H), 4.46 (d, *J* = 11.1 Hz, 1H), 3.77 (s, 3H), 3.69-3.64 (m, 1H), 3.56 (dd, *J* = 9.9, 5.2 Hz, 1H), 3.46 (dd, *J* = 9.9, 6.4 Hz, 1H), 3.32-3.25 (m, 4H), 3.12 (dd, *J* = 7.5, 2.1 Hz, 1H), 2.95 (ddd, *J* = 7.0, 4.8, 2.1 Hz, 1H), 1.88-1.81 (m, 1H), 1.76 (ddd, *J* = 14.2, 9.6, 4.8 Hz, 1H), 1.69-1.61 (m, 2H), 1.23 (ddd, *J* = 14.2, 8.5, 5.7 Hz, 1H), 1.06 (s, 9H), 0.99 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 135.8, 135.6, 135.6, 133.9, 133.9, 130.5, 129.5, 129.5, 127.6, 127.6, 119.1, 113.7, 80.1, 76.4, 72.5, 68.8, 59.5, 58.2, 58.0, 55.3, 33.3, 32.9, 26.9, 19.3, 18.0; IR (film): $\tilde{\upsilon}$ = 3070, 2929, 2857, 1612, 1587, 1513, 1463, 1427, 1389, 1362, 1302,

1247, 1173, 1108, 1090, 1037, 922, 877, 822, 740, 702, 613, 503, 488 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{36}H_{48}NaO_5Si$ (M^+ + Na): 611.31632, found: 611.31599.



63

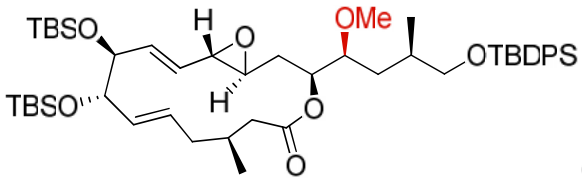
(2*S*,3*S*,5*R*)-6-(*tert*-butyl-diphenyl-silanyloxy)-3-(methoxy)-5-methyl-1-[(2*S*,3*S*)-3-vinyl-oxiranyl]-hexan-2-ol (63). To a solution of **62** (425 mg, 0.73 mmol) in CH_2Cl_2 (50 mL) containing aqueous phosphate buffer solution (pH 7, 0.75 mL) was added DDQ (331 mg, 1.46 mmol). The reaction mixture was vigorously stirred at 25ºC for 20 min, diluted with EtOAc and washed with aq. sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and the solvent evaporated under reduced pressure to give a residue which was purified by flash chromatography (Toluene/EtOAc 10:1) to give alcohol **63** (239 mg, 70%). Colorless oil: $[\alpha]_D^{20}$ = -11.5 (*c* = 1.00 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.68-7.65 (m, 4H), 7.45-7.36 (m, 6H), 5.60 (ddd, *J* = 17.3, 10.1, 7.4 Hz, 1H), 5.47 (dd, *J* = 17.3, 1.6 Hz, 1H), 5.27 (dd, *J* = 10.1, 1.6 Hz, 1H), 3.74-3.68 (m, 1H), 3.57-3.47 (m, 2H), 3.34 (s, 3H), 3.16 (dd, *J* = 7.4, 2.2 Hz, 1H), 3.11-3.04 (m, 2H), 2.29 (d, *J* = 5.7 Hz, 1H), 1.87 (ddd, *J* = 14.1, 9.7, 4.2 Hz, 1H), 1.81-1.75 (m, 1H), 1.73-1.66 (m, 1H), 1.57 (ddd, *J* = 14.1, 7.0, 3.2 Hz, 1H), 1.36-1.29 (m, 1H), 1.06 (s, 9H), 0.98 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.6, 135.6, 135.6, 133.8, 133.8, 129.6, 127.6, 127.6, 119.2, 82.1, 70.4, 68.7, 58.9, 58.0, 58.0, 36.1, 33.6, 32.5, 26.9, 19.3, 17.7; IR (film): $\tilde{\upsilon}$ = 3451, 2930, 2857, 1471, 1427, 1389, 1188, 1105, 1090, 985, 921, 880, 823, 740, 701, 613, 502, 487 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{28}H_{40}NaO_4Si$ (M^+ + Na): 491.25881, found: 491.25887.



64

Ring Closing Metathesis precursor 64. Following an identical procedure to the one described for compound **15**, starting from alcohol **63** (282 mg, 0.49 mmol) and acid **14** (220 mg, 0.63 mmol), ester **64** was obtained (405 mg, 81%). Colourless oil: $[\alpha]_D^{20}$

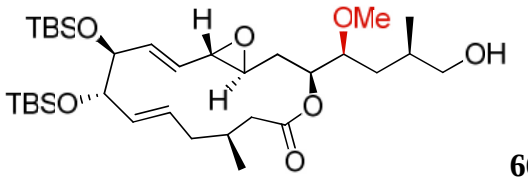
= -30.8 (*c* = 0.50 in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.67-7.63 (m, 4H, aromatics), 7.44-7.34 (m, 6H, aromatics), 5.87 (ddd, *J* = 17.2, 10.5, 4.5 Hz, 1H, H-9), 5.53 (ddd, *J* = 17.2, 10.3, 7.3 Hz, 1H, H-12), 5.48-5.37 (m, 3H, H-11a, H-6, H-5), 5.25 (dd, *J* = 10.0, 1.6 Hz, 1H, H-11b), 5.19-5.14 (m, 2H, H-16, H-10a), 5.08 (dat, *J* = 10.5, 1.6 Hz, 1H, H-10b), 4.09-4.02 (m, 2H, H-7, H-8), 3.53-3.43 (m, 2H, H-20), 3.34 (s, 3H, OCH_3), 3.33-3.28 (m, 1H, H-17), 3.08 (dd, *J* = 7.3, 2.0 Hz, 1H, H-13), 2.86 (td, *J* = 5.9, 2.0 Hz, 1H, H-14), 2.30 (dd, *J* = 14.8, 5.3 Hz, 1H, H-2a), 2.03-1.94 (m, 3H, H-4a, H-3, H-2b), 1.94-1.70 (m, 4H, H-19, H-15, H-4b), 1.60-1.53 (m, 1H, H-18a), 1.36-1.25 (m, 1H, H-18b), 1.05 (s, 9H, $SiC(CH_3)_3$), 0.96 (d, *J* = 6.7 Hz, 3H, H-22), 0.99, 0.88 (2 x s, 18H, 2 x $SiC(CH_3)_3$), 0.85 (d, *J* = 6.3 Hz, 3H, H-21), 0.06, 0.05, 0.03, 0.02 (4 x s, 12H, 6 x $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.5 (s, *C*=O), 137.3 (d, C-9), 135.6 (4 x d, 4 x Ar*C*H), 135.4 (d, C-12), 133.8, 133.7 (2 x s, 2 x Ar*C*), 131.3, 129.0 (2 x d, C-5, C-6), 129.6 (2 x d, 2 x Ar*C*H), 127.6 (4 x d, 4 x Ar*C*H), 119.4 (t, C-11), 115.1 (t, C-10), 79.4 (d, C-17), 76.2, 75.9 (2 x d, C-8, C-7), 70.7 (d, C-16), 68.6 (t, C-20), 58.9 (d, C-13), 58.1 (q, OCH_3), 57.4 (d, C-14), 41.2 (t, C-2), 39.5 (t, C-4), 33.3 (t, C-18), 32.6 (d, C-19), 32.6 (t, C-15), 30.1 (d, C-3), 26.9, 25.9 (3 x q, 3 x $SiC(CH_3)_3$), 19.3 (q, C-21), 19.3 (s, Si*C*), 18.2 (2 x s, 2 x Si*C*), 17.6 (q, C-22), -4.5, -4.6, -4.7, -4.8 (4 x q, 4 x $SiCH_3$); IR (film): $\tilde{\upsilon}$ = 2956, 2929, 2857, 1734, 1472, 1428, 1361, 1254, 1219, 835, 775 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{51}H_{84}O_7NaSi_3$ (M^+ + Na): 915.54171, found: 915.54189.



65

Ring Closing Metathesis product 65. Following an identical procedure to the one described for compound **12,** starting from compound **64** (272 mg, 0.30 mmol), ring closing metathesis product **65** was obtained (182 mg, 70%). Colourless oil: $[\alpha]_D^{20}$ = +28.2 (*c* = 0.5 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67-7.61 (m, 4H, aromatics) 7.44-7.34 (m, 6H, aromatics), 5.65 (dd, *J* = 15.9, 8.0 Hz, 1H, H-9), 5.48 (dat, *J* = 15.6, 6.5 Hz, 1H, H-5), 5.34 (dd, *J* = 15.6, 6.0 Hz, 1H, H-6), 5.20 (ddd, *J* = 12.6, 3.6, 2.1 Hz, 1H, H-14), 5.07 (dd, *J* = 15.9, 8.7 Hz, 1H, H-10), 4.03-3.97 (m, 2H, H-7, H-8), 3.50 (d, *J* = 10.2 Hz, 1H, H-18a), 3.38 (dd, *J* = 10.2 Hz, 1H, H-18b), 3.34 (s, 3H, OC*H*$_3$), 3.29-3.24 (m, 1H, H-15), 2.99 (dd, *J* = 8.7, 1.9 Hz, 1H, H-11), 2.80

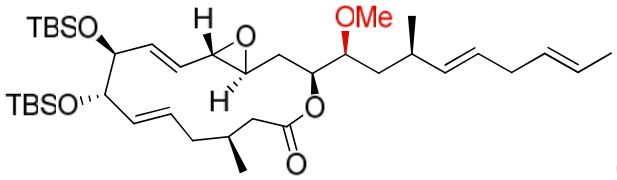
(dat, *J* = 9.8, 2.4 Hz, 1H, H-12), 2.36 (dd, *J* = 18.1, 5.6 Hz, 1H, H-2a), 2.35-2.38 (m, 1H, H-4a), 2.26 (dat, *J* = 13.9, 2.4 Hz, 1H, H-13a), 2.15-2.06 (m, 1H, H-3), 1.90 (dd, *J* = 18.1, 6.7 Hz, 1H, H-2b), 1.85-1.73 (m, 2H, H-17, H-4b), 1.60-1.53 (m, 1H, H-16a), 1.40-1.20 (m, 2H, H-16b, H-13b), 1.04 (s, 9H, $SiC(CH_3)_3$), 0.96 (d, *J* = 6.7 Hz, 3H, H-19), 0.90 (d, *J* = 5.8 Hz, 3H, H-20), 0.88, 0.87 (2 x s, 18H, 2 x $SiC(CH_3)_3$), 0.06, 0.05, 0.04, 0.02 (4 x s, 12H, 4 x $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6 (s, *C*=O), 137.2 (d, C-9), 135.6 (4 x d, 4 x Ar*C*H), 133.8, 133.7 (2 x s, 2 x Ar*C*), 132.4 (d, C-6), 129.6 (2 x d, 2 x Ar*C*H), 129.5 (C-5), 129.4 (d, C-10), 127.6 (4 x d, 4 x Ar*C*H), 79.8, (d, C-15), 77.7, 77.5 (2 x d, C-8, C-7), 69.8 (d, C-14), 68.4 (t, C-18), 59.4 (d, C-11), 58.4 (q, O*C*H_3), 57.4 (d, C-12), 38.0 (t, C-2), 37.4 (t, C-4), 33.5 (t, C-16), 32.9 (t, C-13), 32.4 (d, C-17), 28.4 (d, C-3), 26.9, 26.0, 25.9 (9 x q, 3 x $SiC(CH_3)_3$), 21.0 (q, C-19), 19.3, 18.2, 18.1 (3 x s, 3 x Si*C*), 17.7 (q, C-20), -4.1, -4.2, -4.2, -4.3 (4 x q, 4 x Si*C*H_3); IR (film): $\tilde{\upsilon}$ = 2955, 2929, 2857, 1738, 1472, 1461, 1428, 1251, 1110, 1086, 835, 776 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{49}H_{80}O_7NaSi_3$ (M^+ + Na): 887.51041, found: 887.51063.



66

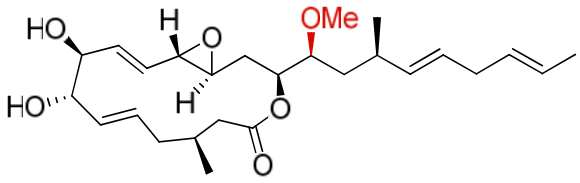
Alcohol 66. Following an identical procedure to the one described for compound **27,** starting from compound **65** (141 mg, 0.163 mmol), alcohol **66** was obtained (49mg, 43%). Colourless oil: $[\alpha]_D^{20}$ = +21.4 (*c* = 1.00 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 5.65 (dd, *J* = 15.7, 7.6 Hz, 1H, H-9), 5.481 (dat, *J* = 15.6, 6.5 Hz, 1H, H-5), 5.35 (dd, *J* = 15.6, 5.6 Hz, 1H, H-6), 5.25 (ddd, *J* = 12.8, 3.8, 2.2 Hz, 1H, H-14), 5.12 dd, (*J* = 15.6, 5.6 Hz, 1H, H-10), 4.04-3.97 (m, 2H, H-7, H-8), 3.78-3.73 (m, 2H, H-18), 3.43 (s, 3H, O*C*H_3), 3.35-3.30 (m, 1H, H-15), 3.00 (dd, *J* = 8.7, 2.0 Hz, 1H, H-11), 2.80 (dat, *J* = 9.8, 2.4 Hz, 1H, H-12), 2.42 (dd, *J* = 18.2, 5.4 Hz, 1H, H-2a), 2.34-2.25 (m, 2H, H-13a, H-4a), 2.19-2.09 (m, 1H, H-3), 1.98 (dd, *J* = 18.2, 6.8 Hz, 1H, H-2b), 1.88-1.75 (m, 2H, H-17, H-4b), 1.56-1.48 (m, 1H, H-13b), 1.45-1.34 (m, 2H, H-16), 0.98 (2d, *J* = 6.8 Hz, 3H, H-19), 0.92 (d, *J* = 6.8 Hz, 3H, H-20), 0.88, 0.86 (2 x s, 18H, 2 x $SiC(CH_3)_3$), 0.06, 0.05, 0.04, 0.02 (4 x s, 12H, 4 x $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9 (s, *C*=O), 137.3 (d, C-9), 132.2 (d, C-6), 129.4 (d, C-5), 129.0 (d, C-10), 79.3 (d, C-15), 77.6 (2 x d, C-8, C-7), 69.6 (d, C-14),

67.6 (t, C-18), 58.4 (d, C-11), 58.1 (q, OCH_3), 57.3 (d, C-12), 38.1 (t, C-2), 37.6 (t, C-4), 33.0 (t, C-13), 32.9 (t, C-16) 32.4 (d, C-17), 28.4 (d, C-3), 26.0, 25.9 (6 x q, 3 x $SiC(CH_3)_3$), 21.0 (q, C-19), 18.2 (2 x s, 2 x SiC), 17.0 (q, C-20), -4.2, -4.3, (4 x q, 4 x $SiCH_3$); IR (film): $\tilde{\upsilon}$ = 2955, 2929, 2857, 1737, 1472, 1428, 1251, 1375, 1251, 1086, 965, 835, 775 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{33}H_{62}O_7NaSi_2$ (M^+ + Na): 649.39263, found: 649.39274.



67

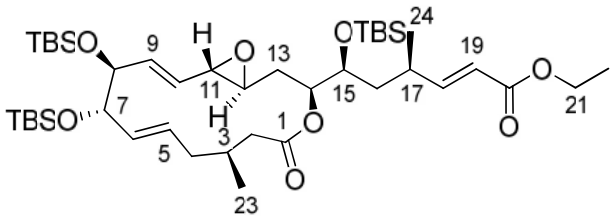
Compound 67. Following an identical procedure to the one described for compound **28,** starting from alcohol **66** (49 mg, 0.078 mmol), compound **67** was obtained (28 mg, 53% overall). Colourless oil: $[\alpha]_D^{20}$ = +24.2 (*c* = 1.00 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 5.64 (dd, *J* = 15.9, 7.6 Hz, 1H, H-9), 5.48 (dat, *J* = 15.6, 6.7 Hz, 1H, H-5), 5.43-5.33 (m, 4H, H-22, H-21, H-19, H-6), 5.22-5.15 (m, 2H, H-18, H-14), 5.10 (dd, *J* = 15.9, 8.7 Hz, 1H, H-10), 4.02-3.98 (m, 2H, H-7, H-8), 3.40 (s, 3H, OCH_3), 3.26-3.21 (m, 1H, H-15), 2.99 (dd, *J* = 8.7, 1.2 Hz, 1H, H-11), 2.80 (dat, *J* = 9.9, 2.4 Hz, 1H, H-12), 2.67-2.63 (m, 2H, H-20), 2.40 (dd, *J* = 18.1, 5.5 Hz, 1H, H-2a), 2.35-2.25 (m, 3H, H-13a, H-4a, H-17), 2.19-2.09 (m, 1H, H-3), 1.96 (dd, *J* = 18.1, 6.8 Hz, 1H, H-2b), 1.84-1.75 (m, 2H, H-17, H-4b), 1.66-1.63 (m, 1H, H-20), 1.42-1.33 (m, 1H, H-13b), 1.32-1.20 (m, 2H, H-16), 0.98 (d, *J* = 6.7 Hz, 3H, H-24), 0.97 (d, *J* = 6.8 Hz, 3H, H-25), 0.88, 0.86 (2 x s, 18H, 2 x $SiC(CH_3)_3$), 0.06, 0.05, 0.04, 0.02 (4 x s, 12H, 4 x $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6 (s, *C*=O), 137.3 (d, C-9), 135.8 (d, C-18), 132.5 (d, C-6), 129.6, 129.5, 129.2, 128.4, 125.5 (5 x d, C-22, C-21, C-19, C-10, C-5), 79.4 (d, C-15), 77.7 (2 x d, C-8, C-7), 70.2 (d, C-14), 59.4 (d, C-11), 58.7 (q, OCH_3), 57.4 (d, C-12), 38.2 (t, C-2), 37.7 (t, C-16), 37.6 (t, C-4), 35.5 (t, C-20), 33.5 (t, C-17), 33.0 (t, C-13), 28.4 (d, C-3), 26.0, 25.9 (9 x q, 3 x $SiC(CH_3)_3$), 21.8 (q, C-24), 21.1 (q, C-25), 18.2, 18.1 (2 x s, 2 x SiC), 17.9 (q, C-23), -4.2, -4.3, (4 x q, 4 x $SiCH_3$); IR (film): $\tilde{\upsilon}$ = 2955, 2929, 2857, 1740, 1472, 1456, 1251, 1084, 965, 835, 775 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{38}H_{68}NaO_6Si_2$ (M^+ + Na): 699.44707, found: 699.44526.



24

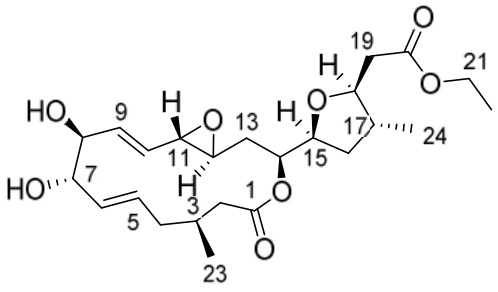
Analogue 24. Following an identical procedure to the one described for compound **1,** starting from compound **67** (28 mg, 0.041 mmol), gave diol **24** (14 mg, 76%). Colourless amorphous solid: $[\alpha]_D^{20}$ = +79.8 (*c* = 1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.81-5.72 (m, 2H, H-9, H-5), 5.46-5.34 (m, 4H, H-22, H-21, H-19, H-6), 5.29-5.21 (m, 2H, H-18, H-14), 5.17 (dd, *J* = 15.3, 8.3 Hz, 1H, H-10), 3.96-3.91 (m, 2H, H-7, H-8), 3.40 (s, 3H, OC*H*$_3$), 3.23-3.18 (m, 1H, H-15), 3.00 (dd, *J* = 9.2, 1.8 Hz, 1H, H-11), 2.87 (dat, *J* = 10.1, 2.1 Hz, 1H, H-12), 2.68-2.64 (m, 4H, H-20), 2.45-2.22 (m, 4H, H-17, H-13a, H-2, H-4), 2.16-2.03 (m, 1H, H-3), 1.97 (dd, *J* = 17.8, 6.7 Hz, 1H, H-2b), 1.88-1.79 (m, 1H, H-4b), 1.67-1.63 (m, 1H, H-20), 1.45-1.34 (m, 2H, H-16a, H-13b), 1.32-1.20 (m, 1H, H-16b), 1.00 (d, *J* = 6.7 Hz, 3H, H-24), 0.98 (d, *J* = 6.8 Hz, 3H, H-25); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3 (s, *C*=O), 135.8 (d, C-18), 135.2 (d, C-9), 133.4 (d, C-5), 133.1 (d, C-10), 131.2, 129.6, 128.5, 125.6, (4 x d, C-22, C-21, C-19, C-6), 79.6 (d, C-15), 76.9, 76.7 (2 x d, C-8, C-7), 70.4 (d, C-14), 58.9 (d, C-11), 58.8 (q, OCH_3), 57.8 (d, C-12), 37.8 (t, C-16), 37.7 (t, C-2), 35.9 (t, C-4), 35.5 (t, C-20), 33.5 (t, C-17), 33.2 (t, C-13), 29.7 (d, C-3), 21.8 (q, C-25), 20.7 (q, C-24), 17.9 (q, C-23); IR (film): $\tilde{\upsilon}$ = 3396, 2956, 2932, 1736, 1455, 1375, 1084, 967 cm^{-1}; HRMS (ES$^+$): *m/z*: Calcd for $C_{26}H_{40}O_6Na$ (M^+ + Na): 471.27171, found: 471.27214.

Synthesis of the C_{15}-THF- Iriomoteolide 3a. Analogue 25.



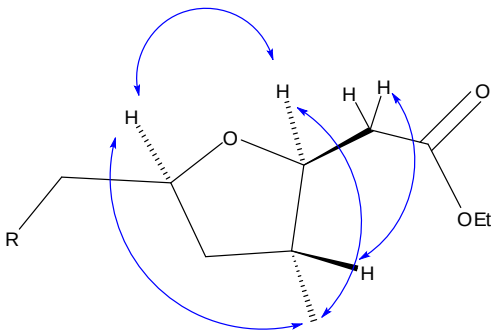
Ester 68. Alcohol **27** was converted into the corresponding aldehyde following an identical procedure to the one described for the synthesis of compound **28**. To a solution of triethyl phosphonoacetate (7.5 μL, 0.034 mmol) in THF (1 mL) at 0 °C was added NaHMDS (7 mg, 0.034 mmol), the mixture was stirred for 30 min at 0 °C, and a solution of the previously prepared aldehyde (12 mg, 0.016 mmol) in THF (0.5

mL) was slowly added. The mixture was stirred for 45 min, after which time complete conversion of the starting material (TLC hexanes/EtOAc 5 : 1, *Rf* = 0.55) into a single less polar spot (*Rf* = 0.59) was observed. The reaction mixture was quenched with aq. sat. NH_4Cl and extracted with Et_2O, the organic layer was dried oved $MgSO_4$ and the solvent evaporated under reduced pressure. The crude residue was purified by flash chromatography to give ester **68** (10 mg, 75%). Colourless oil: $[\alpha]_D^{20}$ = +8.4 (*c* = 0.50 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.77 (dd, *J* = 15.7, 8.0 Hz, 1H, H-18), 5.75 (dd, *J* = 15.7, 0.9 Hz, 1H, H-19), 5.63 (dd, *J* = 15.7, 7.8 Hz, 1H, H-9), 5.47 (dat, *J* = 15.5, 6.3 Hz, 1H, H-5), 5.36 (dd, *J* = 15.5, 5.7 Hz, 1H, H-6), 5.10 (dd, *J* = 15.7, 8.7 Hz, 1H, H-10), 4.97 (ddd, *J* = 12.1, 4.2, 1.7 Hz, 1H, H-14), 4.17 (q, *J* = 7.1 Hz, 2H, H-21), 4.02-3.96 (m, 2H, H-7, H-8), 3.67 (dat, *J* = 9.0, 3.0 Hz, 1H, H-15), 2.99 (dd, *J* = 8.8, 2.0 Hz, 1H, H-11), 2.75 (dat, *J* = 9.7, 2.0 Hz, 1H, H-12), 2.49-2.43 (m, 1H, H-17), 2.40 (dat, *J* = 13.8, 2.2 Hz 1H, H-13a), 2.33 (dat, *J* = 18.2, 6.4 Hz, 1H, H-2a), 2.35-2.28 (m, 1H, H-4a), 2.20-2.14 (m, 1H, H-3), 1.99 (dd, *J* = 18.2, 5.9 Hz, 1H, H-2b), 1.85-1.79 (m, 1H, H-4b), 1.49 (ddd, *J* = 13.8, 9.0, 3.0 Hz, 1H, H-16a), 1.37 (ddd, *J* = 13.8, 9.0, 4.3 Hz, 1H, H-16b), 1.27 (t, *J* = 7.1 Hz, 3H, H-22), 1.22-1.17 (m, 1H, H-13b), 1.05 (d, *J* = 6.8 Hz, 3H, H-24), 0.99 (d, *J* = 6.8 Hz, 3H, H-23), 0.89, 0.88, 0.87 (3 x s, 27H, 3 x $SiC(CH_3)_3$), 0.12, 0.07, 0.06, 0.04, 0.02 (6 x s, 18H, 6 x $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.4 (s, *C*=O), 166.6 (s, *C*=O), 153.4 (d, C-18), 137.1 (d, C-9), 132.0 (d, C-6), 129.2, 129.1 (2 x d, C-5, C-10), 120.3 (d, C-19), 77.6 (2 x d, C-7, C-8), 71.8 (d, C-14), 69.5 (d, C-15), 60.2 (t, C-21), 59.4 (d, C-11), 57.5 (d, C-12), 38.0, 37.8 (3 x t, C-2, C-4, C-16), 32.6 (d, C-17), 31.0 (t, C-13), 28.0 (d, C-3), 25.9, 25.7 (3 x q, 3 x $SiC(CH_3)_3$), 22.1 (q, C-23), 20.8 (q, C-24), 18.2, 18.1, 17.9 (3 x s, 3 x Si*C*), 14.2 (q, C-22), -4.2, -4.3, -4.4, -4.5 (6 x q, 6 x $SiCH_3$); IR (film): $\tilde{\upsilon}$ = 2955, 2929, 2857, 1744, 1721, 1472, 1253,1219, 984, 835, 774 cm^{-1}; HRMS (ES^+): *m/z*: Calcd for $C_{43}H_{78}O_8NaSi_3$ (M^+ + Na): 817.4897, found: 817.4901.



Analogue (25). To a solution of protected compound **68** (10 mg, 0.012 mmol) in THF (1 mL), was added TBAF (1M in THF, 39 μL, 0.038 mmol). The reaction mixture

was stirred at room temperature for 3 h, after which time complete conversion of the starting material and of the intermediate byproducts into a major more polar spot (EtOAc 100%, *Rf* = 0.34) was observed. The mixture was concentrated under nitrogen flow, and the crude residue was purified by flash chromatography (hexanes/EtOAc 10 : 90 → EtOAc 100%) to give compound **25** as a solid, which was triturated with a mixture of hexanes/Et_2O to give tetrahydrofuran **25** (4 mg, 74%). White solid: m. p. = 82 °C; $[\alpha]_D^{20}$ = +36.3 (*c* = 0.25 in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ = 5.80-5.76 (m, 2H, H-5, H-9), 5.39 (dd, *J* = 15.6, 8.1 Hz, 1H, H-6), 5.25 (dd, *J* = 15.4, 9.7 Hz, 1H, H-10), 5.13 (ddd, *J* = 12.2, 5.0, 2.2 Hz, 1H, H-14), 4.15 (q, *J* = 6.7 Hz, 2H, H-21), 4.00 (dat, *J* = 10.2, 5.2 Hz, 1H, H-15), 3.96-3.93 (m, 2H, H-7, H-8), 3.84 (aq, *J* = 6.6 Hz, 1H, H-18), 3.00 (dd, *J* = 9.1, 2.0 Hz, 1H, H-11), 2.86 (dd, *J* = 10.2, 2.0 Hz, 1H, H-12), 2.48 (d, *J* = 6.3 Hz, 2H, H-19), 2.40-2.31 (m, 2H, H-2a, H-4a), 2.23 (dat, *J* = 13.9, 2.1 Hz, 1H, H-13a), 2.13-2.08 (m, 1H, H-3), 1.97 (dd, *J* = 17.9, 7.8 Hz, 1H, H-2b), 1.95-1.89 (m, 1H, H-17), 1.88-1.80 (m, 2H, H-4b, H-16a), 1.64 (dat, *J* = 12.5, 7.9 Hz, 1H, H-16b), 1.39-1.31 (m, 1H, H-13b), 1.26 (t, *J* = 6.7 Hz, 3H, H-22), 1.03, (d, *J* = 6.5 Hz, 3H, H-24), 1.00 (d, *J* = 6.8 Hz, 3H, H-23); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.4, 171.3 (2 x s, 2 x *C*=O), 135.3, 133.6 (2 x d, C-5, C-9), 133.1 (d, C-10), 131.05 (d, C-6), 82.3 (d, C-18), 78.4 (d, C-15), 76.8, 76.7 (2 x d, C-7, C-8), 71.3 (d, C-14), 60.5 (t, C-21), 58.8 (d, C-11), 57.6 (d, C-12), 39.6 (t, C-19), 38.4 (d, C-17), 37.7 (t, C-2), 35.9 (2 x t, C-16, C-4), 34.1 (t, C-13), 29.7 (d, C-3), 20.7 (q, C-23), 17.0 (q, C-24), 14.2 (q, C-22); IR (film): $\tilde{\upsilon}$ = 3411, 2966, 2892, 1733, 1558, 1541, 1510, 1456, 1169, 1035, 971 cm^{-1}; HRMS (ES^+): *m/z*: Calcd. for $C_{24}H_{36}O_8Na$ (M^+ + Na): 475.2302, found: 475.2301.



Observed NOE interactions for assignment of the stereochemistry of the tetrahydrofuran ring in compound **N**. For other examples of Michael addition promoted by TBAF see ref. 5.

2. Molecular Dynamic simulations for 1 and 17

Each molecule was simulated by molecular dynamics with the Merck Molecular Force Field (MMFF94) in the CHARMM program. A dielectric constant of 80 was used to simulate the effect of water. The simulations were carried out at 1000 K during 1 ns and 500 frames were extracted from the trajectory at 2 ps intervals. Each frame was minimized by 750 steps of the steepest descent (SD) algorithm in CHARMM. The resulting 500 conformations were clustered to determine the main conformations. The lowest energy conformation (LEC) is taken as representative of the first cluster, and all conformations having a root-mean-square deviation (RMSD) lower than 1.5 Å are also compiled into that cluster. Then, the LEC of the remaining conformations is taken as starting point for the second cluster, and this process is iteratively repeated till the 500 conformers have been clustered. The two sets of clusters were caped by means of a 10 kcal/mol maximum energy difference with the corresponding global minimum. This restriction afforded 62 clusters for the natural product and 31 for the epimer.

For the two molecules investigated, the lower energy clusters (clusters 1-5 with a max. ΔE = 2 Kcal/mol and comprising more than 1/3 of the total number of conformers) present a rather distinct conformational blueprint (Figure 1 in the maintext). Especially remarkable is the influence that the methyl at C3 exerts on the dihedral angle O1-C14-C15-OH, which is shifted from -63º in the natural compound to +62º in **17**. The relative disposition of the lateral chain compared to macrocycle is thus strongly affected, with the dihedral C1-O1-C14-C15 going from -5º in **1** to -44º in the synthetic analogue **17**. This effect also translates into a macrocycle "folding" in **17** compared to the relatively flat structure observed in the parent compound **1**.

Interestingly, these clusters present several structural features matching the NMR data recorded for these compounds in different organic solvents. Thus, the resonance for H_9 appears at higher field for compound **17** than for the natural molecule, which reflects a shielding effect in the former case as this hydrogen is pointing towards the interior of the macrocyclic cavity.

3. Cell proliferation assay

General

Muscle NIH/3T3 (myc-) cells from the UZH Cancer Institute were cultured using Dulbelcco's modified Eagle's medium and EBV- positive lymphoma cells (Daudi and Akata) were cultured using RPMI medium. All the media were suplemented with 10% (v/v) fetal bovine serum, 100 units/mL of penicillin, 100µg/mL of streptomycin, 4.5 g/L glucose, 0.11 g/L sodium pyrubate and 2 mM glutamine and the cells were grown at 37 ºC in 5% CO_2 atmosphere with 80% relative humidity.

A 5mM stock solution of the drugs in DMSO was prepared and kept at -20 ºC.

In order to asses the cytotoxicity of Iriomoteolide 3a and analogues cell proliferation was measured in vitro using a fluorimetric assay with resazurin as fluorescent dye for the three cell lines mentioned above. Resazurin is a non-toxic metabolic indicator of viable cells that becomes fluorescent upon mitochondrial reduction.[6]

In 96-well microtiter plates, 20 000 lymphoma cells/well were seeded in 100 µL of RMPI media. After 24 hours, 12.5 µL of a 10 fold concentrated drug or DMSO solution in RMPI media was added in every well. After 72 hours, cell viability was studied by measuring their ability to process resazurin. Resazurin was added to every well to obtain a final concentration of 86 µM, and after 3 hours, the fluorescence was quantified using a fluorescence microplate reader (Biotek, FLx800^{TM}) at the respective excitation and emission wavelength of 560 and 590nm. The activity of mitochondrial dehydrogenases was determined by the decrease in absorbance. The measured fluorescence values were corrected from the control samples containing DMSO and normalized to 0-100% cell viability.

Two different set-ups for the cell proliferation assay were performed in the case of NIH/3T3 cell line. In 96-well microtiter plates, 5000 cells/well were seeded in 100 µL of the appropiate cell culture media, whereas in 24-well plates 40 000 cells/well were seeded in 1 mL media. Cells were allowed to attach overnight, the old media was removed, the cells were washed with PBS (phosphate-buffered saline) and fresh media, together with the corresponding concentration of the drug or DMSO as a control. The cells were incubated during different time periods (2, 8 and 24 h), the media was once more removed and the cells were washed with PBS, to then be incubated with media containing 86 µM resazurin. After 3 hours, the fluorescence was quantified using a fluorescence microplate reader (Biotek, FLx800^{TM}) at the respective excitation and emission wavelength of 560 and 590 nm. The measured

fluorescence values were corrected from the control samples containing DMSO and normalized to 0-100% cell viability.

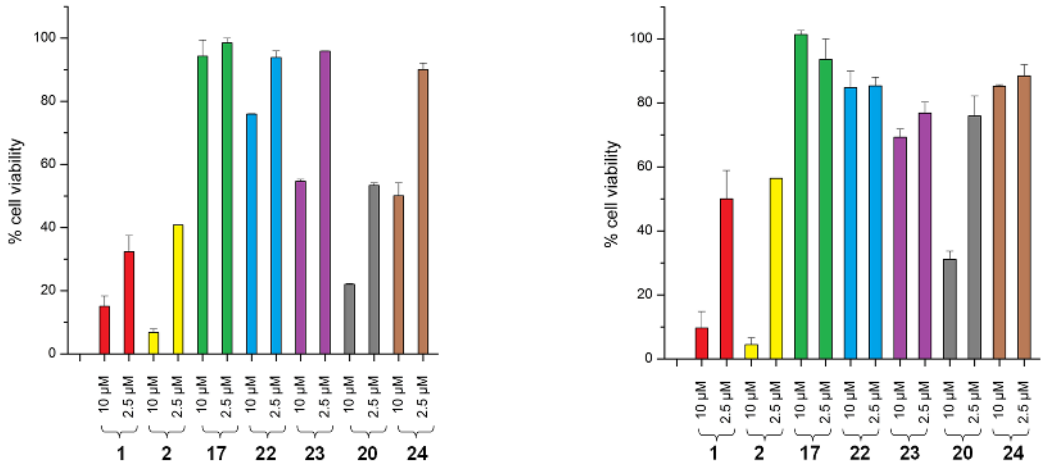


Figure S1 Left: Cytotoxicity of the synthesized compounds for DAUDI cells upon exposure of the drugs at 10 and 2.5 µM.
Right: Cytotoxicity of the synthesized compounds for AKATA cells upon exposure of the drugs at 10 and 2.5 µM. The results are presented as mean ± SEM of independent experiments.

GI_{50} values were calculated for DAUDI cell lines after 3 day incubation for the following compounds:

Compound **1**: 0.99 uM, 0.98 uM (two repeats)

Compound **2**: 0.45 uM (single measurement)

Compound **20**: 4.72 uM, 3.57 uM (two repeats)

Compound **24**: n.d. (ca. 10 uM, i.e. highest concentration tested).

4. Fluorescent visualization of F-actin and tubulin

10 000 cells per well in 90 µL cell culture media were seeded in MEZEL diagnostic slides (PTFE coating around 10 wells of 6.7 mm diameter each) and grown overnight. The cells were incubated with 4 µM, 1 µM and 250 nM for 2 h or 8 h of the corresponding compound. For the recovery experiments, the cells were incubated for 2h and allowed to recover in fresh media for 22 h.

The cells were washed with PBS and fixed with a solution of 4% paraformaldehyde in PBS for 10 minutes. Actin filaments were stained for 1h with a solution of 0.1 µM

tetramethyl rhodamine isothiocyanate TRITC labelled phalloidin (P1951, Sigma Aldrich) in PBS and cell nuclei were stained with a 1 µg/mL DAPI (2-(4-amidinophenyl)-6-indolecarbamidine dihydrochloride) solution in PBS. The cells were mounted in Glycergel® mounting medium (Dako) after several PBS washes. Cells were visualized and photographed using a 40 x oil objective, A4 (nuclei) and TX2 (actin) filter cubes in a Leica wide field microscope (Hamamatsu EM-CCD).

According to the cytotoxicity assay, as we have more than 75% cell viability for the range of concentrations used in the cell-based experiments, we can conclude that the morphological changes seen in the actin cytoeskeleton are due to effect of drug and not to its toxicity.

For indirect immunostainings to visualize tubulin, the cells were first incubated for 1 h with a 3 µg/mL solution of tubulin β mouse monoclonal antibody (Invitrogen) in a humid atmosphere, followed by a 1h incubation of a 4 µg/mL solution of goat anti-mouse IgG conjugated to Cy5 (Invitrogen), 0.1 µM TRITC labelled phalloidin and 1 µg/mL DAPI. Cells were always rinsed with PBS between both incubations. The pictures were taken using a Leica confocal laser scanning microscope.

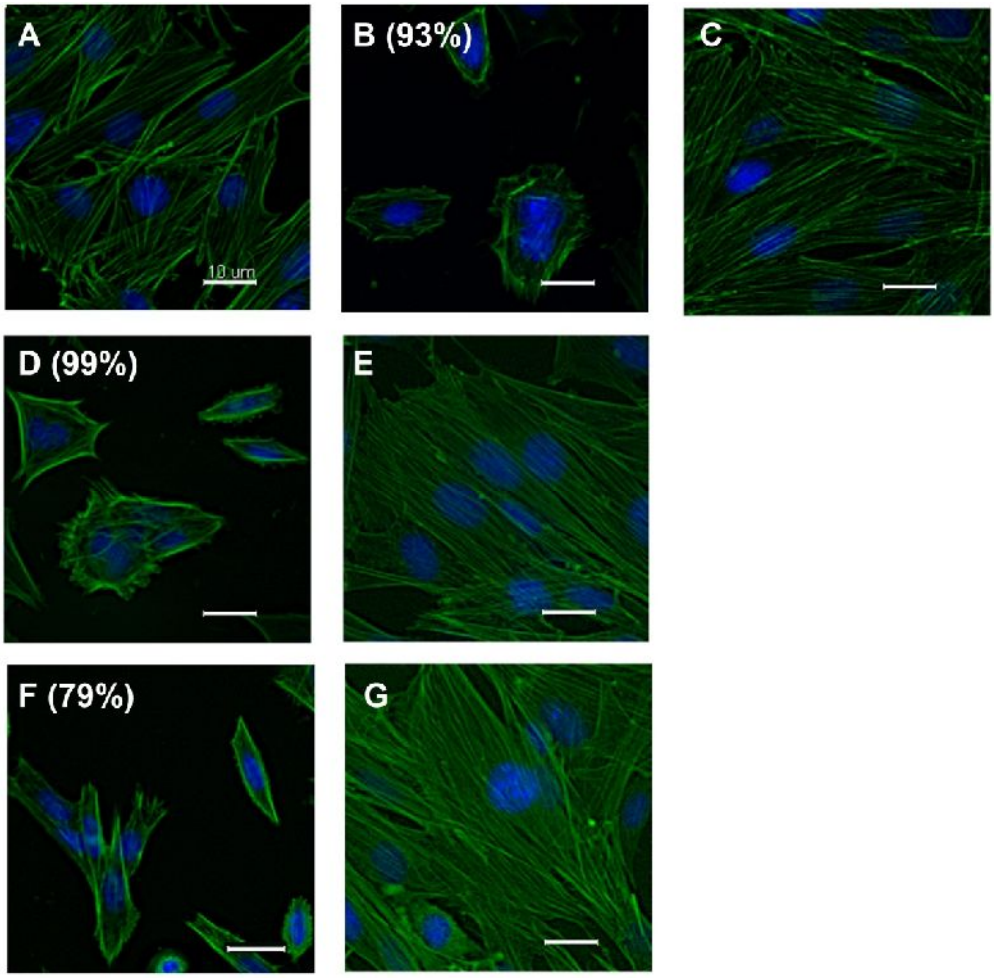


Figure S2 Effect of iriomoteolide-3a (**1**) on the actin cytoeskeleton of NIH/3T3 cells. Actin cytoeskeleton is stained with FITC-phalloidin (green) and nuclei with DAPI (blue). The value in (%) indicates the percentage of viable cells.

(**A)** Control cells. (**B**) Cells incubated with iro-3a (**1**) at 250 nM for 2 hours and (**C**) after removal of the drug and recovery for 22 h. (**D**) Cells incubated with iro-3a (**1**) at 1 μM for 2 hours and (**E**) after removal of the drug and recovery for 22 h. (**F**) Cells incubated with iro-3a (**1**) at 4 μM for 2 hours and (**G**) after removal of the drug and recovery for 22 h.

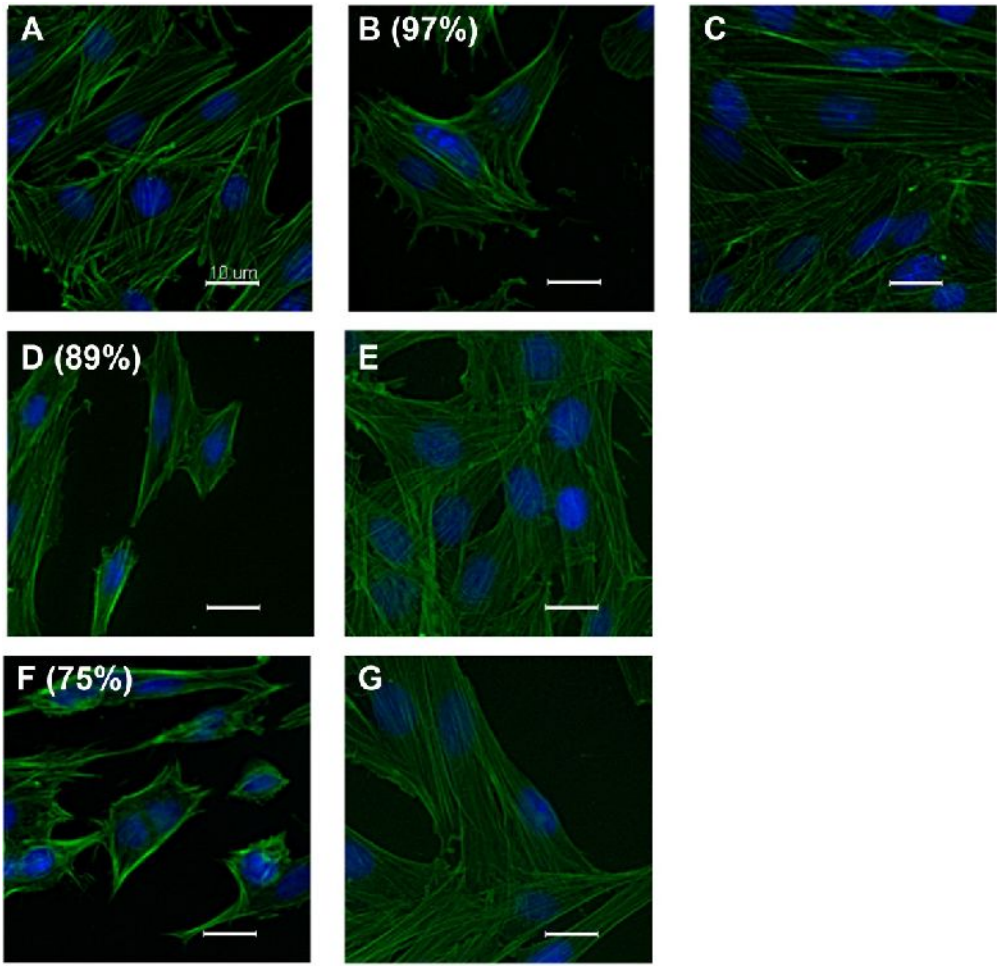


Figure S3 Effect of acetonide **2** on the actin cytoeskeleton of NIH/3T3 cells. Actin cytoeskeleton is stained with FITC-phalloidin (green) and nuclei with DAPI (blue). The value in (%) indicates the percentage of viable cells.

(**A**) Control cells. (**B**) Cells incubated with acetonide (**2**) at 250 nM for 2 hours and (**C)** after removal of the drug and recovery for 22h. (**D**) Cells incubated with **2** at 1μM for 2 hours and (**E**) after removal of the drug and recovery for 22h. (**F**) Cells incubated with **2** at 4 μM for 2 hours and (**G**) after removal of the drug and recovery for 22h.

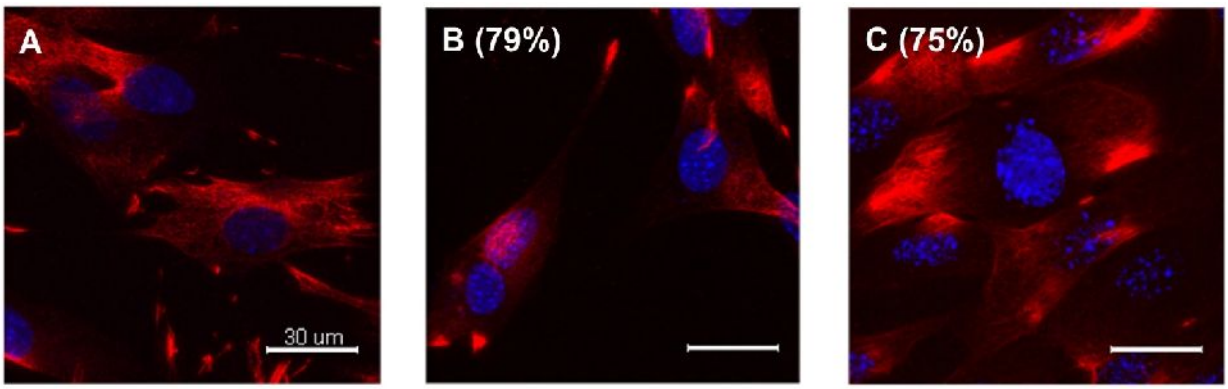


Figure S4 Effect of 4µM iriomoteolide 3a (**B**) and acetonide **2** (**C**) on the tubulin cytoeskeleton of NIH/3T3 cells after 2 hours of drug incubation. The value in (%) indicates the percentage of viable cells.

5. Cell migration assay/wound healing assay [7]

The experiments were done in triplicate using DMEM media supplemented with 2% calf serum in order to minimize cell proliferation. A cell monolayer was created by seeding 80000 NIH/3T3 cells per well on Lab-Tek™ II Chambered Coverglasses (Nunc). The cells were allowed to attach for 4h, a wound was created by scratching a p200 pipet tip and pictures were taken (0 h).

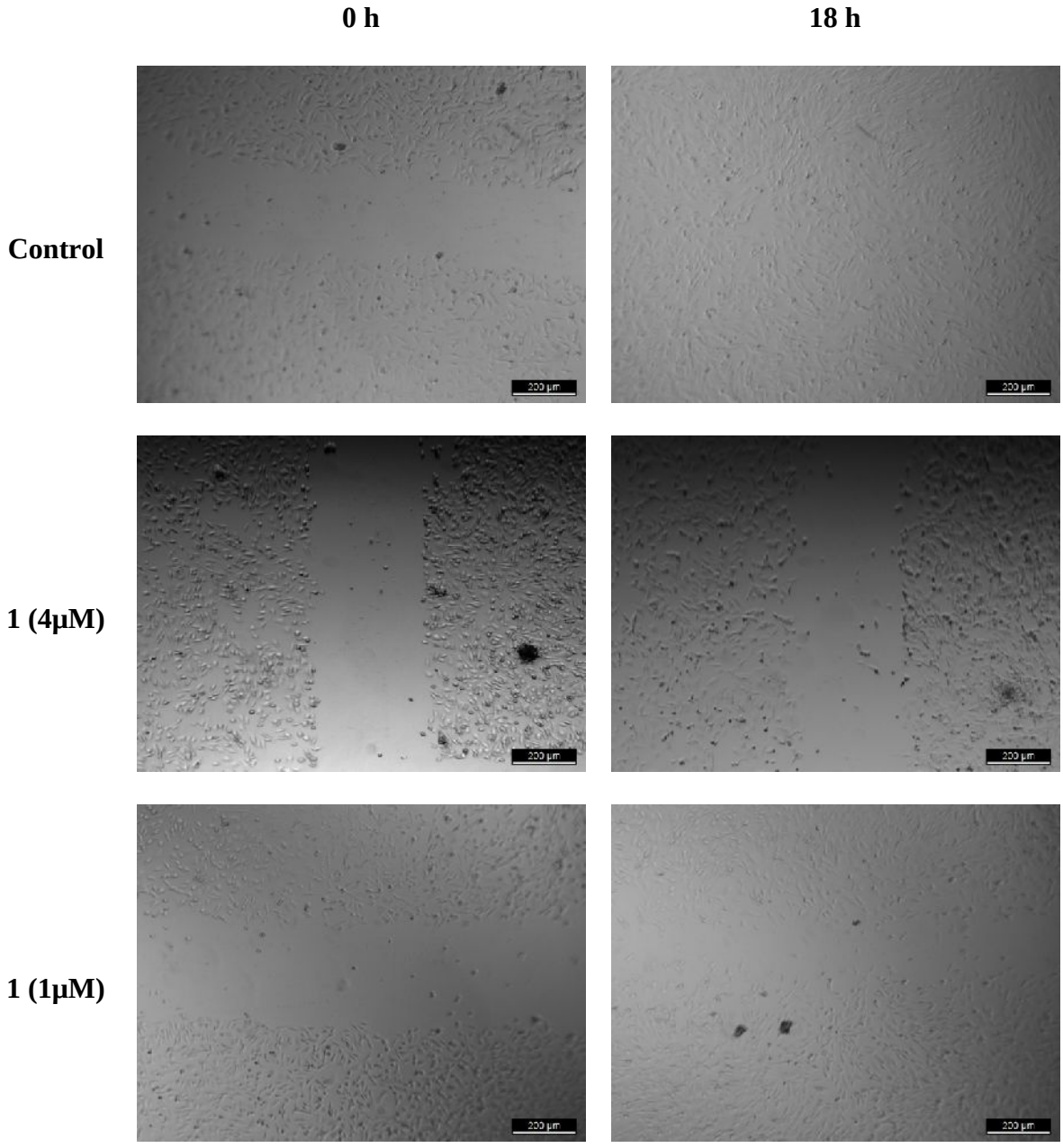
The cells were incubated for 18 h with the corresponding drug concentration of **1**, **2** and **20** compounds. The cells were washed with PBS and pictures were taken using a 5x magnification in a Leica photomicrosope.

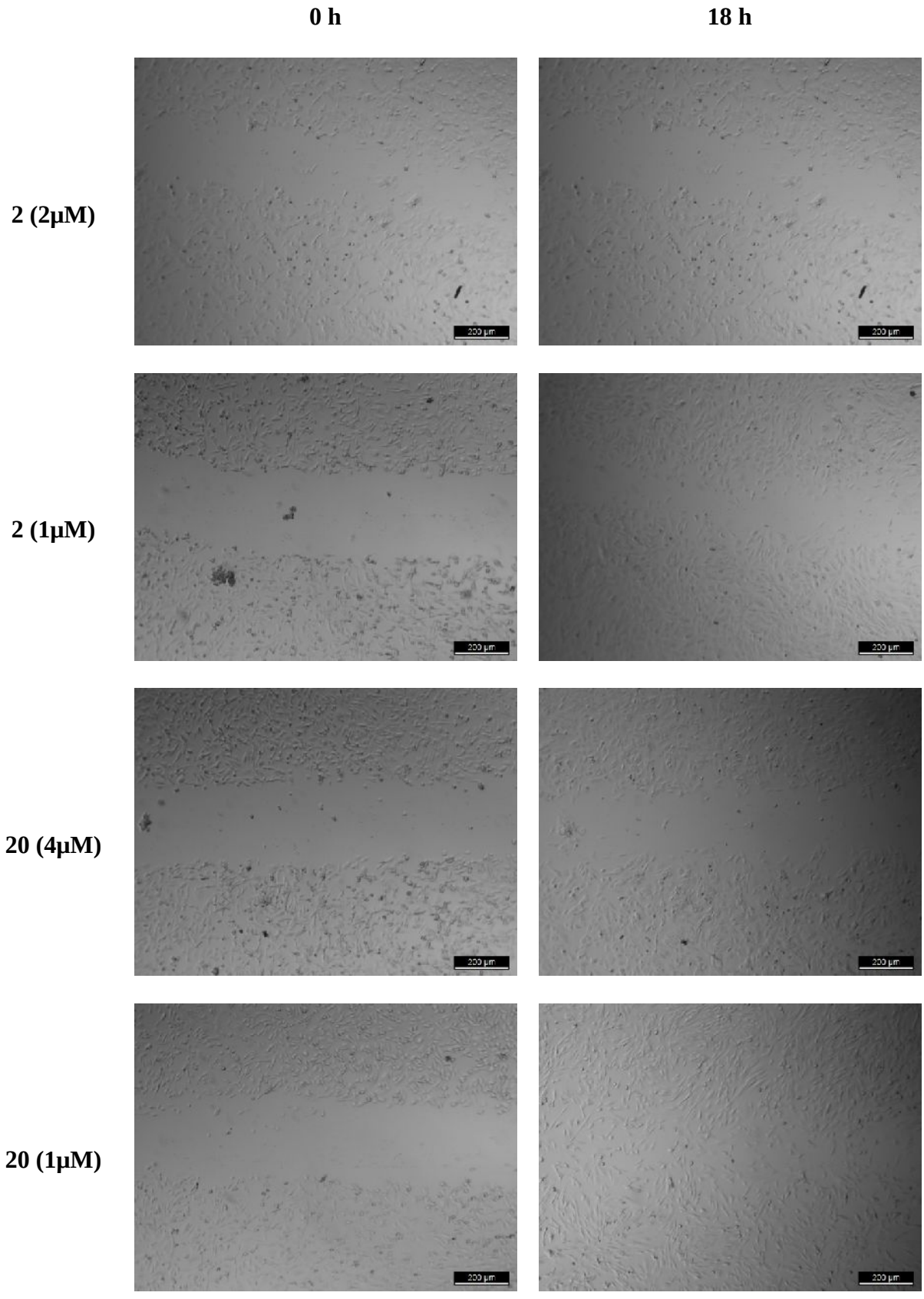
Cell migration was quantified with ImageJ by measuring the % wound coverage that can be defined as follows [8]:

$$\%\ \text{wound coverage} = \frac{[\text{Wound Area (0h)} - \text{Wound Area(18h)}]}{\text{Wound Area (0h)}} \text{x}100 \qquad (1)$$

GI_{50} values for compounds **1**, **2** and **20** on NIH/3T3 healthy mice fibroblast cells after 24 hours of compound incubation were determined to be (see section 3 for experimental set up) 23.5, 12.5 and 10.8 µM respectively. Thus, a cytotoxic effect or substantial cell death in the wound healing assay can be ruled out.

Figure S5 Determination of the effects of **1**, **2** and **20** on cell migration. An initial scratch carried out on NIH/3T3 cells (t=0 h) and the colonization of the wound surface by the cells after an 18 h treatment with different concentrations of the compounds can be seen.




0 h
18 h
2 (2μM)
2 (1μM)
20 (4μM)
20 (1μM)

6. In vitro actin experiments

a) Polymerization and depolymerization assays

To eludicidate the mode of action of Iriomoteolide 3a and analogues, their interactions with G and F actin were studied in vitro. In the polymerization experiments pyrene labeled muscle actin (Cytoeskeleton) was depolymerized on ice cold G-buffer (5 mM Tris-HCl pH 8.0, 0.2 mM $CaCl_2$ and 0.2 mM ATP) at a concentration of 8.2 μM. Actin concentration was determined by the Bradford protein assay[9] using BSA as a standard.

Actin was polymerized at 24 ºC at the corresponding actin concentrations in a 96 well-plate (200 μL/well). All the wells contained the same DMSO concentration (less than 5%). The fluorescence of pyrene labeled actin with the drug was monitored for 20 min to establish a baseline. Actin polymerization was induced by the addition of actin polymerization buffer (50 mM KCl, 2 mM $MgCl_2$ and 1 mM ATP, final concentrations). The polymerization process was measured by monitoring the fluorescence once every 30s for a total of 1 h-1.5 h in a Tecan Infinite® M1000 microplate reader with an excitation and emission wavelength of 350 nm and 407 nm respectively. Plotting and statistical analysis was performed using Origin.

To study the effect of the compounds on the depolymerization of actin, pyrene labeled muscle actin was polymerized at a 23.3 μM concentration in G buffer by adding 2.5 μL of actin polymerization buffer (500 mM KCl, 20 mM $MgCl_2$ and 10 mM ATP). Actin was let to assemble at room temperature for one hour. It was then diluted with G-buffer to reach a final concentration of 2.3 μM. The compounds and an equivalent volume of DMSO were added to the controls and the fluorescence was monitored at 24 ºC once every 30s for a total of 1 h-1.5 h in a Tecan Infinite® M1000 microplate reader with an excitation and emission wavelength of 350 nm and 407 nm respectively.

b) MALDI-TOF to monitor the interaction of iriomoteolide 3a with G-actin

The MALDI-TOF experiments were carried out as previously described.[10]

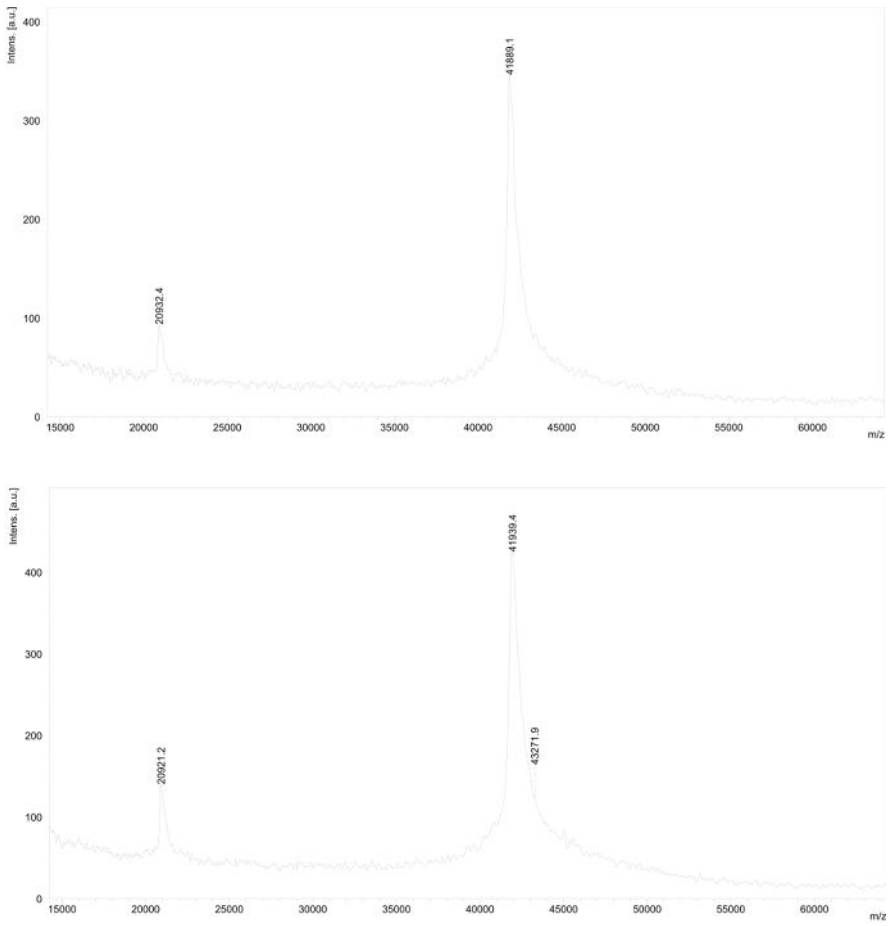


Figure S6. MALDI-TOF on actin (top) and actin in the presence of iriomoteolide-3a (bottom).

7. Computational Analysis of Iriomoteolide-3a binding to Actin - Methods

Coordinates for monomeric G-actin in complex with gelsolin, ATP, and calcium (Ca) were downloaded from the protein databank (PDB-ID: 1EQY).[11] Gelsolin, water, and co-solvent molecules were manually removed from 1EQY. Missing atoms from 1EQY G-actin residues ranging from 5 to 375 were added via CHARMM.[12-14] Parameters for all amino acids were created with the *pdb2gmx* module of GROMACS (version 3.3.6) for the CHARMM 27 protein force field parameters.[15-17] Parameters for calcium and ATP where also taken from the CHARMM 27 force field. For both systems (actin, ATP, CA, and iriomoteolide) threonine 6 was capped with an n-terminal acetyl cap while the C-terminal phenyl alanine 375 was charged negatively.[18] The 3-dimensional structure of iriomoteolide 3a was generated via Pymol and transformed into a TRIPOS MOL2 file manually.[19, 20] Parameters for iriomoteolide 3a were obtained via uploading the manually generated MOL2 files to

paramchem.org.[21-24] To make CGenFF parameter stream files (.str) compatible with simulations run in GROMACS (.itp), bond, angle, dihedral, improper units were converted from kcal/mol to kJ/mol and Ångstrom to nanometers respectively. All 1-4 interactions were enumerated and pre-calculated via unit conversion of the original CHARMM parameters as previously outlined in the literature.[25]

Deploying the GROMACS package *editconf*, a dodecahedric box the actin-ATP-complex was created with a periodic boundary 1.2 nm distanced from the most outlying atoms of G-actin. Iriomoteolide was then placed at random positions within the box by deploying the GROMACS *genbox* package. Subsequently, the system was filled with repetitive units of pre-equilibrated SPC water coordinates parameterized for the TIP3P water mode[26-28] via the GROMACS package *genbox*. To neutralize the system sodium and chlorine ions were added at a concentration of 150 mM via the *genion* module of GROMACS.

Each system was then minimized for 10,000 steps via the steepest descent minimizer or prematurely stopped if the total energy of the system was lower than 10 kcal. A minimization step size of 0.01 kcal/mol was selected. After energy minimization, the system was equilibrated in a simulation for 1 ns with random velocities and at constant temperature, pressure and number of particles (NPT) in which restraints were applied to all heavy atoms of G-actin, iriomoteolide, and the ATP/calcium complex while the remainder of the system could be propagated unrestrained. All subsequent production runs were started with new initial, random velocities and no restraints.

All simulations (including equilibration) were performed with a velocity rescaling thermostat and a Parinello-Rahman barostat at 1 atmospheric pressure unit and a temperature of 310 K.[29-31] The time step of the simulation was set to 2 fs. Long range vdW and electrostatic interactions were calculated with simple cut-off scheme and a particle mesh Ewald (PME) cut-off scheme at 1.2 nm respectively.[32, 33] The LINCS algorithm implemented in GROMACS was applied to constrain all atoms in the system.[34] For the 25 and 5 single iriomoteolide simulations, the simulation times were 100 ns and 700 ns respectively. The positions of iriomoteolide in the 25 100 ns simulations are identical to the 5 700 ns simulations each started 5 times with random velocities. Out of 25 100 ns iriomoteolide simulations, 5 simulations were prolonged to a total of 300 ns.

Each simulation was performed on 64 Xeon 5560 processors clocked at 2.8 GHz each via MPI for GROMACS 3.3.6 on 64 cores per simulation.

Prior to trajectory analysis, all waters and solvent ions were removed so that only G-actin, ATP/Ca and iriomoteolide were contained in within the system. Movement of atoms across the periodic boundary was removed in three steps via the *trjconv* GROMACS module: First, single atomic movement over the PBC was removed so that if a single atom would cross the periodic boundary the entire molecule would be moved (*-pbc mol*). In a second *trjconv* step G-Actin, ATP/Ca, and iriomoteolide were clustered (*-pbc cluster*) in the respective frame. Finally, only the actin protein was centered in the box and all ATP/Ca, irio3a movement is relative to the centered protein (*-center*). Finally, all trajectories were concatenated into a single non-overlapping trajectory via *trjcat* module implemented in GROMACS.

The center of mass distances between iriomoteolide 3a and every residue of actin were calculated via *g_dist* in GROMACS. The number of contacts N_i between irio3a and the respective residue was calculated by evaluating if the center of mass distances $\mathbf{d_{COM}}$ between irio3a and each residue was equal to or lower than 1 nm ($d_{COM}[irio,res_i] \leq 1$ nm : $N_i + 1$). If this threshold was crossed for one snapshot the number of contacts **N** for residue **i** would be incremented. The relative contact frequency (RCF) for each residue for the given iriomoteolide simulations (5x700 ns, single iriomoteolide; 25x100 ns, single iriomoteolide) was then calculated by:

$$rCFi = \frac{N_i}{max(N_{1..n})} \tag{2}$$

where $\mathbf{rCF_i}$ is the relative contact frequency for residue **i**. $\mathbf{N_i}$ for each residues **i** is the number of snapshots for which $d_{COM}[irio,res_i]$ was smallor or equal to 1. **max(N1..n)** is the largest $\mathbf{N_i}$. All contact frequencies are thus annotated relative to the contact frequency of the "most visited" residue which has a rCF of 100%. rCF heat maps projected onto the protein surface of 1EQY were then generated via Pymol by manually substituting the b-factor column with the relative contact frequencies for all atoms of the individual residues and applying a green, yellow, and red color scheme (*spectrum b*) with a maximum of 1.0 and a minimum of 0.0.[32]

Prior to the cluster analysis and cut-based free energy profile (cFEP) generation all alpha carbons of G-actin were aligned to the reference structure 1EQY.[35, 36] Cluster

analysis was performed by application of the tree-based clustering included in CAMPARI, taking into accounts all 700 ns simulations for which iriomoteolide traversed the system to the barbed end of G-actin.[37, 38] RMSD-based clustering was performed with threshold radius (*CRADIUS*) of 2.5 Å, a tree height (*BIRCHHEIGHT*) of 9 and a coarsest threshold (*CMAXRAD*) of 14 Å. This procedure was repeated for the combined simulations including the original 3 x 700 ns simulations plus 5 x 300 ns simulations which were elongated from the 25 x 100 ns simulations. The clustering was performed on all heavy atoms of iriomoteolide. The cluster representatives were then visually inspected (Figure 6 main text)

The free energy profile was generated by deploying a method based on the equilibrium kinetic network which preserves the free energy barriers.[35, 36, 39] This methods emulates the cuts in flow-networks, and the computed profile thus has been named cut-based free energy profile (cFEP). The nodes and links of the equilibrium kinetic network are the clusters which were generated via the tree-based clustering as outlined above and the direct transitions between them sampled along the MD runs, respectively. For each node, all nodes are partitioned into two groups A and B by applying the mean first passage time (MFPT) to the reference node as an order parameter. The free energy is related to the maximum flow between sets A and B and calculated as $G = -kT \ln(Z_{AB}/Z)$, where Z_{AB}/Z is the relative partition function which represents the statistical weight of the transitions between sets A and B. The result is a one-dimensional profile along the reaction coordinate Z_A/Z (i.e., the relative partition function representing the statistical weight of set A) which preserves the barrier height between the free energy basins (Figure S9).

8. Computational Analysis of Iriomoteolide-3a binding to Actin - Results

To analyze interactions of iriomoteolide 3a (**1**) with G-actin molecular dynamic simulations with explicit water were performed in a 1:1 iriomoteolide 3a (**1**):actin ratio with different positions of iriomoteolide 3a (**1**) within the box. A total of 30 simulations were conducted resulting in a cumulative simulation time of 7 µs.

The initial five simulations of 700 ns each were evaluated for the distance of iriomoteolide 3a (**1**) with Gly168, a central residue located at the barbed end of G-actin. The distance analysis showed that out of the five simulations, three (Figure S7)

showed binding of iriomoteolide 3a (**1**) to the barbed end of actin within 200 ns, resulting in a cumulative residence time of ~ 1.75 µs at the barbed end. No association of iriomoteolide 3a (**1**) to the barbed end was observed in simulations 1 (Figure S7, black) and 5 (Figure S7, yellow), which revealed two distinct interaction sites located around the residues Met283 and Met355, located in subdomains 4 and 3 of actin respectively.

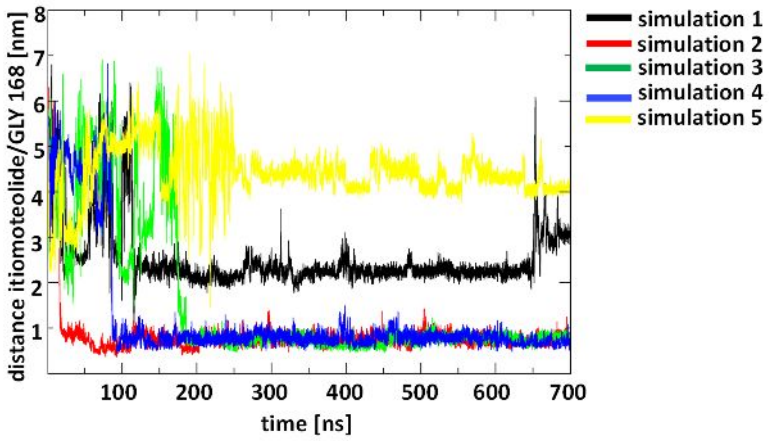


Figure S7. Distances of iriomoteolide 3a (1) with Gly168, a central residue located at the barbed end of actin, for the 5 x 700 ns simulations with an iriomoteolide 3a (1):actin ratio of 1 : 1. Simulations 2-4 show center of mass distances between iriomoteolide 3a (1) and Gly168 smaller than 1 nm after 20 ns, 90 ns, and 170 ns respectively. Simulations 1 and 5 bind in a second and third interaction site after 120 ns and 250 ns respectively. Distances were plotted in GRACE (5.1.23, Evgeny Stambulchik).

To further evaluate all residues for possible interactions with iriomoteolide 3a (**1**) a heat map displaying all contact frequencies was generated for the 5x700 ns and 25x100 ns simulations (Figure S7 A,B). The relative contact frequencies show a significant hot spot for interaction at the barbed end with Phe352 (RCF_{352} of 100%) representing the residue for which most of the interaction with iriomoteolide 3a (**1**) was observed. Secondary hot spots, albeit very weak in comparison, were located at Met227 and Met283 (located in the subdomains 4 and 3 of G-actin respectively). Overall the results indicate that the system was sufficiently equilibrated and that the barbed end represented the site of preferred interaction of iriomoteolide 3a (**1**) with actin.

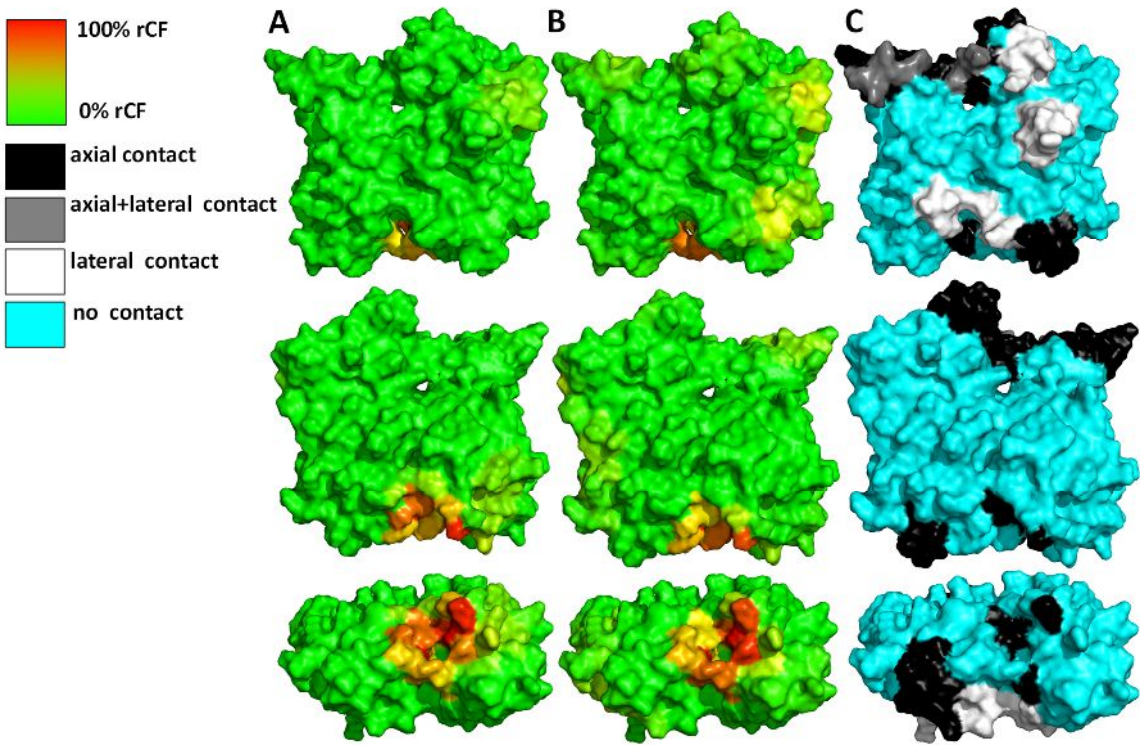


Figure S8. Summary view of the relative contact frequencies for all actin iriomoteolide simulation schemes. (A, B) Heat map of relative contact frequencies for the two distinct simulation schemes. Top and middle panel represent front and back of G-actin, the bottom panel shows a top-down view of the barbed end. (A) and (B) show high similarity in the distribution and intensity of the respective high contact residues, primarily in the barbed end. (C) Annotation of axial/lateral contacts in F-actin with the adjacent monomers according to the Oda 2009 model. The pointed end and the barbed end of the next monomer are interfaces where obstruction would lead to an effective sequestering of monomers.

Out of all three interaction sites the barbed end with Gly168 (close to Phe352) represents a viable site for inhibiting G-actin polymerization. Several reports have already shown that actin binding natural product macrolides bind at the barbed end while having *in vitro* properties that lead to the sequestering of monomers, fibril disruption and polymerization inhibition.[3, 10, 14, 40-49] The second site of interaction, around Met283, is located outside the barbed end in subdomain 1, which features axial contacts with other actin monomers. The third interaction site, Met227, is on the periphery of several lateral contacts between actin monomers. Thus, this hotspot is

considered the least likely to interfere with nucleation or polymerization of actin given the Oda et al. 2009 model.[50]

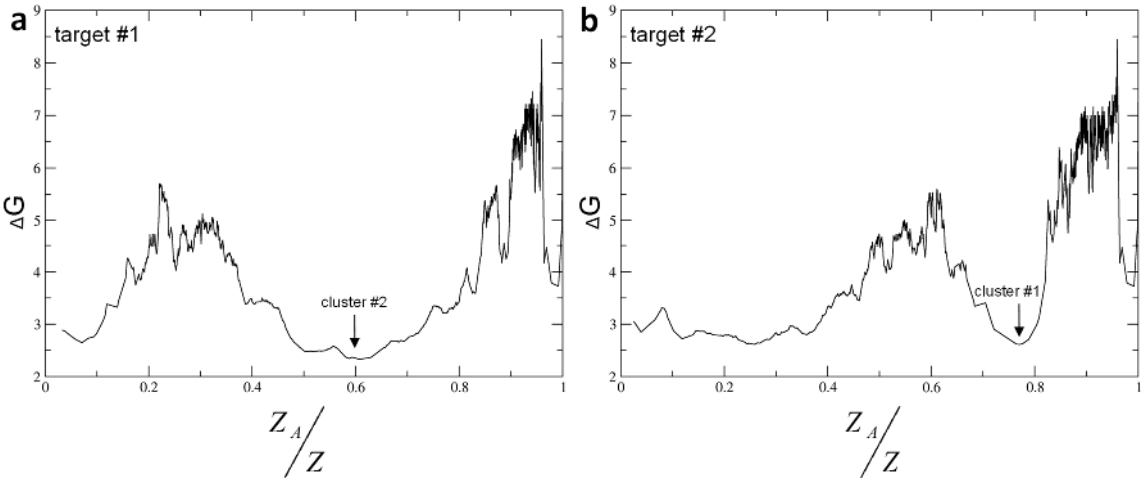


Figure S9. Cut-based free energy profiles for the combined simulations. The cFEP reveals two distinct free energy basins with energy barriers at height of 5.5 kcal. The representaties of the two respective clusters are located at the respective minima of the basins (Figure 6).

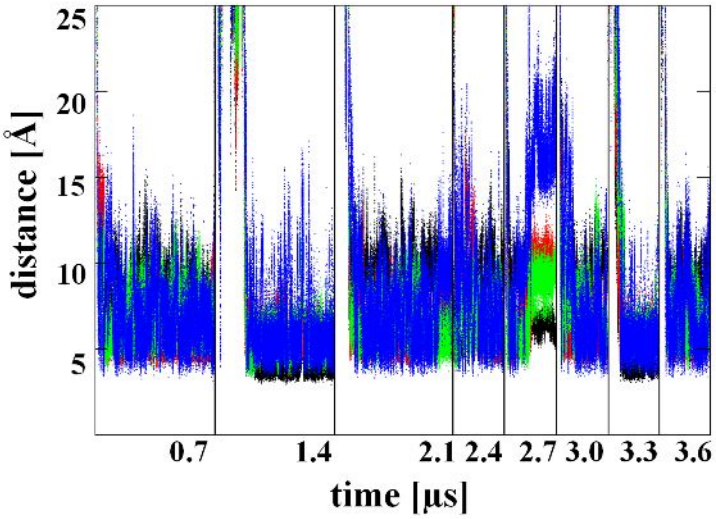


Figure S10. Overview of selected contacts between the barbed end of G-actin and iriomoteolide 3a. Black shows the distances between the geometric center of the iriomoteolide ring and the geometric center of the Tyr143 phenol side chain. Red shows the distances between the 4-terminal carbons of the iriomoteolide 3a tail and the gamma carbon of Ile346. Green denotes the distance between the 6th carbon of the iriomoteolide tail and the geometric center of the Phe352 side chain while blue shows the distance between the 4 terminal carbons of the iriomoteolide tail and the C4

carbon of the Phe375 side chain. Although the fluctuations vary upon reaching the respective clusters the average values indicate close contacts for the majority of the 3.6 µs simulation.

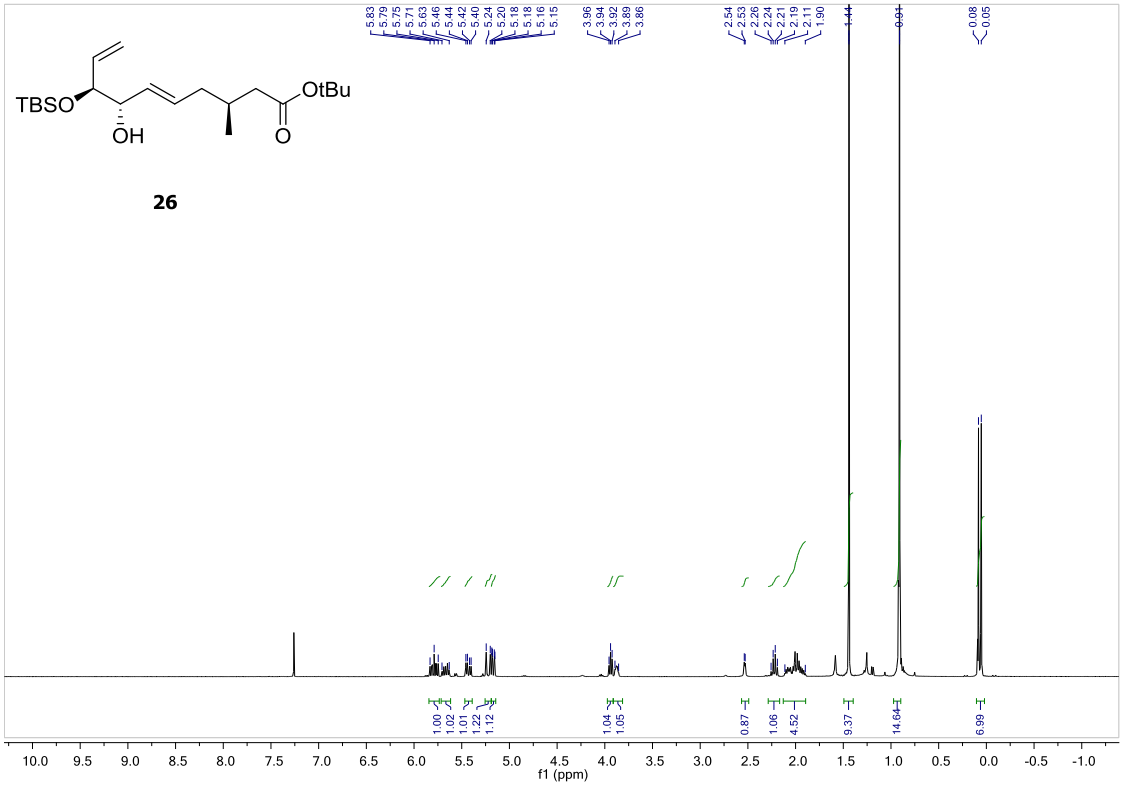
References

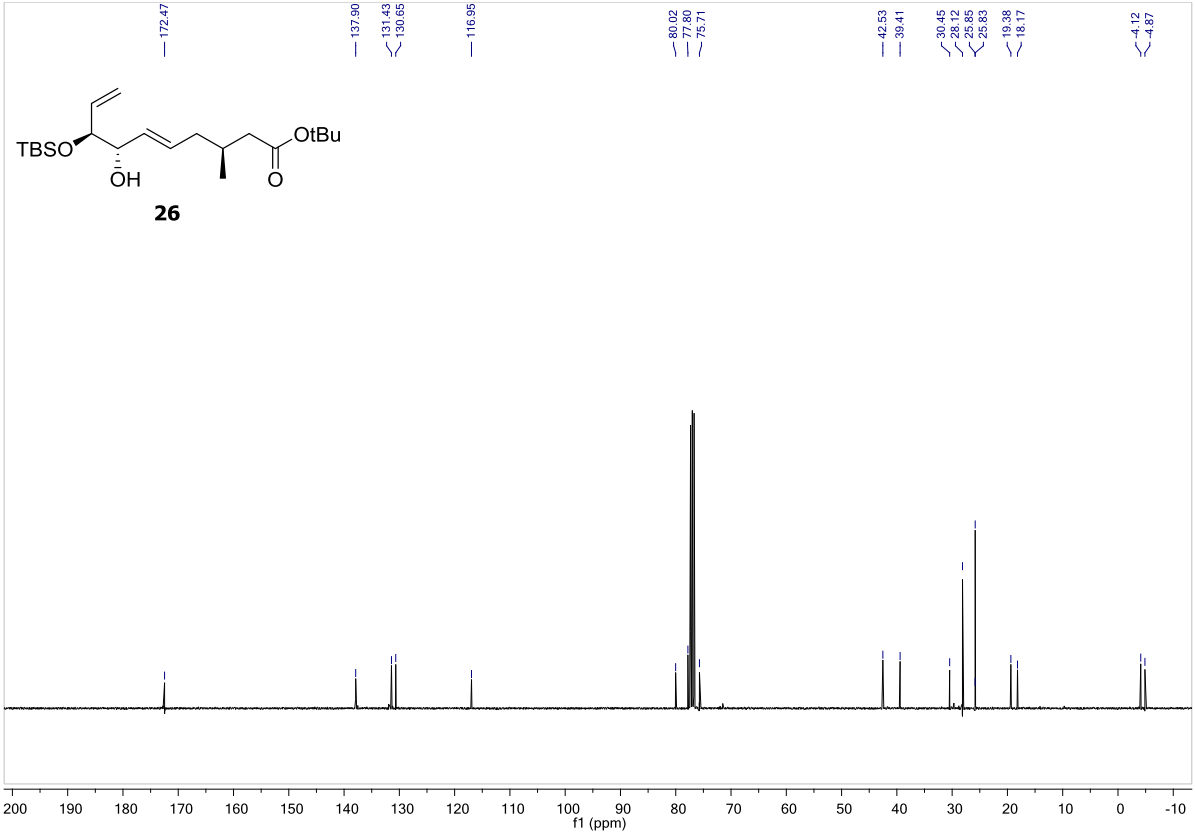
1. R. Cribiu, C. Jager and C. Nevado, *Angew. Chem. Int. Ed.*, 2009, **48**, 8780-8783.
2. K. Oguchi, M. Tsuda, R. Iwamoto, Y. Okamoto, J. Kobayashi, E. Fukushi, J. Kawabata, T. Ozawa, A. Masuda, Y. Kitaya and K. Omasa, *J. Org. Chem.*, 2008, **73**, 1567-1570.
3. J. S. Allingham, A. Zampella, M. V. D'Auria and I. Rayment, *Proc. Natl. Acad. Sci. U.S.A*, 2005, **102**, 14527-14532.
4. A. Jellal and M. Santelli, *Tetrahedron Lett.*, 1980, **21**, 4487-4490.
5. R. H. Bates, J. B. Shotwell and W. R. Roush, *Org. Lett.*, 2008, **10**, 4343-4346.
6. M. M. Nociari, A. Shalev, P. Benias and C. Russo, *J. Immunol. Methods*, 1998, **213**, 157-167.
7. C. C. Liang, A. Y. Park and J. L. Guan, *Nat. Protoc.*, 2007, **2**, 329-333.
8. C. U. Niesler and K. P. Goetsch, *Anal. Biochem.*, 2011, **411**, 158-160.
9. M. M. Bradford, *Anal. Biochem.*, 1976, **72**, 248-254.
10. S. A. Rizvi, D. S. Courson, V. A. Keller, R. S. Rock and S. A. Kozmin, *Proc. Natl. Acad. Sci. U.S.A*, 2008, **105**, 4088-4092.
11. P. J. Mclaughlin, J. T. Gooch, H. G. Mannherz and A. G. Weeds, *Nature*, 1993, **364**, 685-692.
12. B. R. Brooks, R. E. Bruccoleri, B. D. Olafson, D. J. States, S. Swaminathan and M. Karplus, *J. Comput. Chem.*, 1983, **4**, 187-217.
13. A. D. MacKerell, B. Brooks, C. L. Brooks, L. Nilsson, B. Roux, Y. Won and M. Karplus, in *Encyclopedia of Computational Chemistry*, John Wiley & Sons, Ltd, 2002, DOI: 10.1002/0470845015.cfa007.
14. B. R. Brooks, C. L. Brooks, A. D. Mackerell, L. Nilsson, R. J. Petrella, B. Roux, Y. Won, G. Archontis, C. Bartels, S. Boresch, A. Caflisch, L. Caves, Q. Cui, A. R. Dinner, M. Feig, S. Fischer, J. Gao, M. Hodoscek, W. Im, K. Kuczera, T. Lazaridis, J. Ma, V. Ovchinnikov, E. Paci, R. W. Pastor, C. B. Post, J. Z. Pu, M. Schaefer, B. Tidor, R. M. Venable, H. L. Woodcock, X. Wu, W. Yang, D. M. York and M. Karplus, *J. Comput. Chem.*, 2009, **30**, 1545-1614.
15. H. J. C. Berendsen, D. Vanderspoel and R. Vandrunen, *Comput. Phys. Commun.*, 1995, **91**, 43-56.
16. D. Van der Spoel, E. Lindahl, B. Hess, G. Groenhof, A. E. Mark and H. J. C. Berendsen, *J. Comput. Chem.*, 2005, **26**, 1701-1718.
17. P. Bjelkmar, P. Larsson, M. A. Cuendet, B. Hess and E. Lindahl, *J. Chem. Theory Comput.*, 2010, **6**, 459-466.
18. A. D. Mackerell, M. Feig and C. L. Brooks, *J. Comput. Chem.*, 2004, **25**, 1400-1415.
19. *The PyMOL Molecular Graphics System, Version 1.7.4 Schrödinger, LLC.*
20. M. Clark, R. D. Cramer and N. Vanopdenbosch, *J. Comput. Chem.*, 1989, **10**, 982-1012.

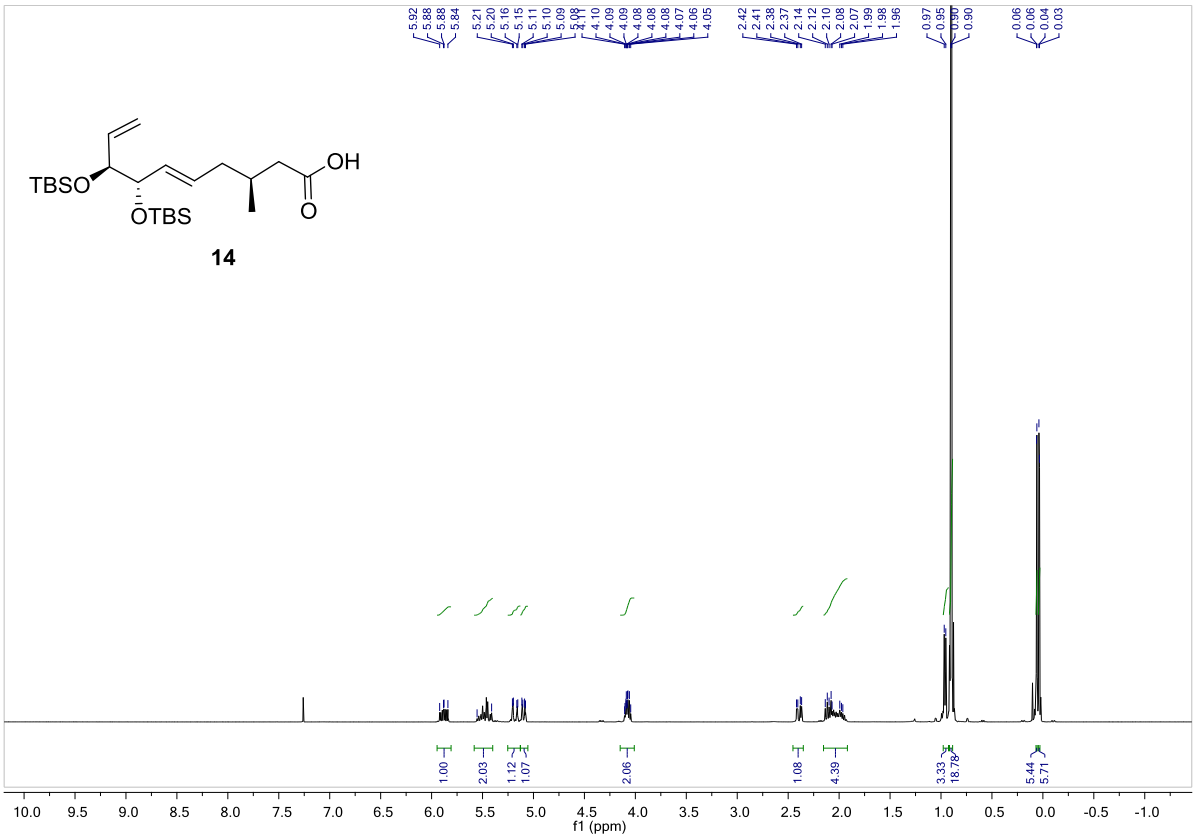
21. K. Vanommeslaeghe, E. Hatcher, C. Acharya, S. Kundu, S. Zhong, J. Shim, E. Darian, O. Guvench, P. Lopes, I. Vorobyov and A. D. MacKerell, *J. Comput. Chem.*, 2010, **31**, 671-690.
22. K. Vanommeslaeghe and A. D. MacKerell, *J. Chem. Inf. Model.*, 2012, **52**, 3144-3154.
23. K. Vanommeslaeghe, E. P. Raman and A. D. MacKerell, *J. Chem. Inf. Model.*, 2012, **52**, 3155-3168.
24. W. B. Yu, X. B. He, K. Vanommeslaeghe and A. D. MacKerell, *J. Comput. Chem.*, 2012, **33**, 2451-2468.
25. *GROMACS Manual 4.5.6 Chapter 5 (Topologies).*
26. W. L. Jorgensen, J. Chandrasekhar, J. D. Madura, R. W. Impey and M. L. Klein, *J. Chem. Phys.*, 1983, **79**, 926-935.
27. K. Toukan and A. Rahman, *Phys. Rev. B*, 1985, **31**, 2643-2648.
28. E. Neria, S. Fischer and M. Karplus, *J. Chem. Phys.*, 1996, **105**, 1902-1921.
29. G. Bussi, D. Donadio and M. Parrinello, *J. Chem. Phys.*, 2007, **126**.
30. G. Bussi and M. Parrinello, *Comput. Phys. Commun.*, 2008, **179**, 26-29.
31. G. Bussi, T. Zykova-Timan and M. Parrinello, *J. Chem. Phys.*, 2009, **130**.
32. T. Darden, D. York and L. Pedersen, *J. Chem. Phys.*, 1993, **98**, 10089-10092.
33. U. Essmann, L. Perera, M. L. Berkowitz, T. Darden, H. Lee and L. G. Pedersen, *J. Chem. Phys.*, 1995, **103**, 8577-8593.
34. B. Hess, H. Bekker, H. J. C. Berendsen and J. G. E. M. Fraaije, *J. Comput. Chem.*, 1997, **18**, 1463-1472.
35. S. V. Krivov and M. Karplus, *J. Phys. Chem. B*, 2006, **110**, 12689-12698.
36. S. V. Krivov and M. Karplus, *Proc. Natl. Acad. Sci. U.S.A*, 2008, **105**, 13841-13846.
37. A. Vitalis and A. Caflisch, *J. Chem. Theory Comput.*, 2012, **8**, 1108-1120.
38. A. Vitalis and R. V. Pappu, *Annu. Rep. Comput. Chem.*, 2009, **5**, 49-76.
39. M. Seeber, M. Cecchini, F. Rao, G. Settanni and A. Caflisch, *Bioinformatics*, 2007, **23**, 2625-2627.
40. V. A. Klenchin, J. S. Allingham, R. King, J. Tanaka, G. Marriott and I. Rayment, *Nat. Struct. Biol.*, 2003, **10**, 1058-1063.
41. V. A. Klenchin, R. King, J. Tanaka, G. Marriott and I. Rayment, *Chem. Biol.*, 2005, **12**, 287-291.
42. K. Hirata, S. Muraoka, K. Suenaga, T. Kuroda, K. Kato, H. Tanaka, M. Yamamoto, M. Takata, K. Yamada and H. Kigoshi, *J. Mol. Biol.*, 2006, **356**, 945-954.
43. S. A. Rizvi, V. Tereshko, A. A. Kossiakoff and S. A. Kozmin, *J. Am. Chem. Soc.*, 2006, **128**, 3882-3883.
44. D. R. Terry, I. Spector, T. Higa and M. R. Bubb, *J. Biol. Chem.*, 1997, **272**, 7841-7845.
45. M. V. Dauria, L. G. Paloma, L. Minale, A. Zampella, J. F. Verbist, C. Roussakis, C. Debitus and J. Patissou, *Tetrahedron*, 1994, **50**, 4829-4834.
46. X. Q. Zhang, L. Minale, A. Zampella and C. D. Smith, *Cancer Res.*, 1997, **57**, 3751-3758.
47. S. Wada, S. Matsunaga, S. Saito, N. Fusetani and S. Watabe, *J. Biochem.*, 1998, **123**, 946-952.
48. S. Y. Saito, S. Watabe, H. Ozaki, H. Kigoshi, K. Yamada, N. Fusetani and H. Karaki, *J. Biochem.*, 1996, **120**, 552-555.
49. A. V. Statsuk, R. Bai, J. L. Baryza, V. A. Verma, E. Hamel, P. A. Wender and S. A. Kozmin, *Nat. Chem. Biol.*, 2005, **1**, 383-388.

50. T. Oda, M. Iwasa, T. Aihara, Y. Maeda and A. Narita, *Nature*, 2009, **457**, 441-445.

9. NMR traces of selected compounds



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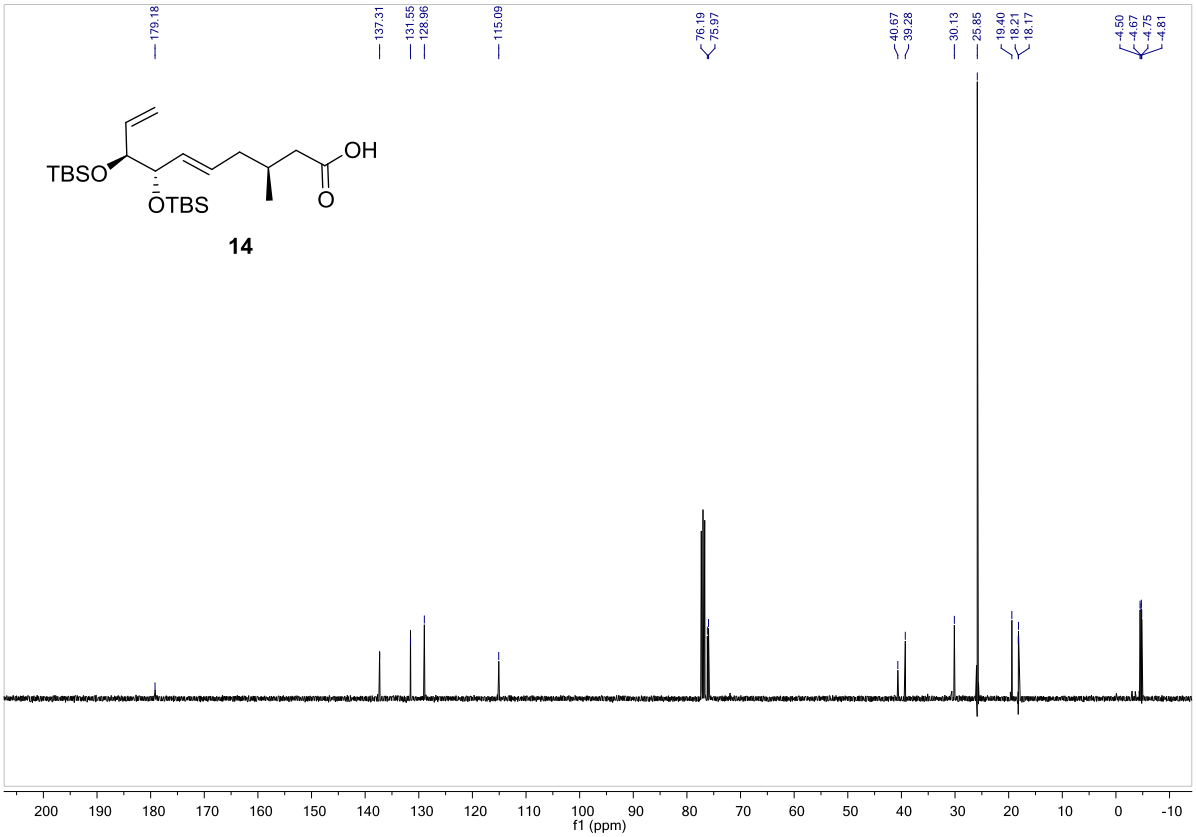
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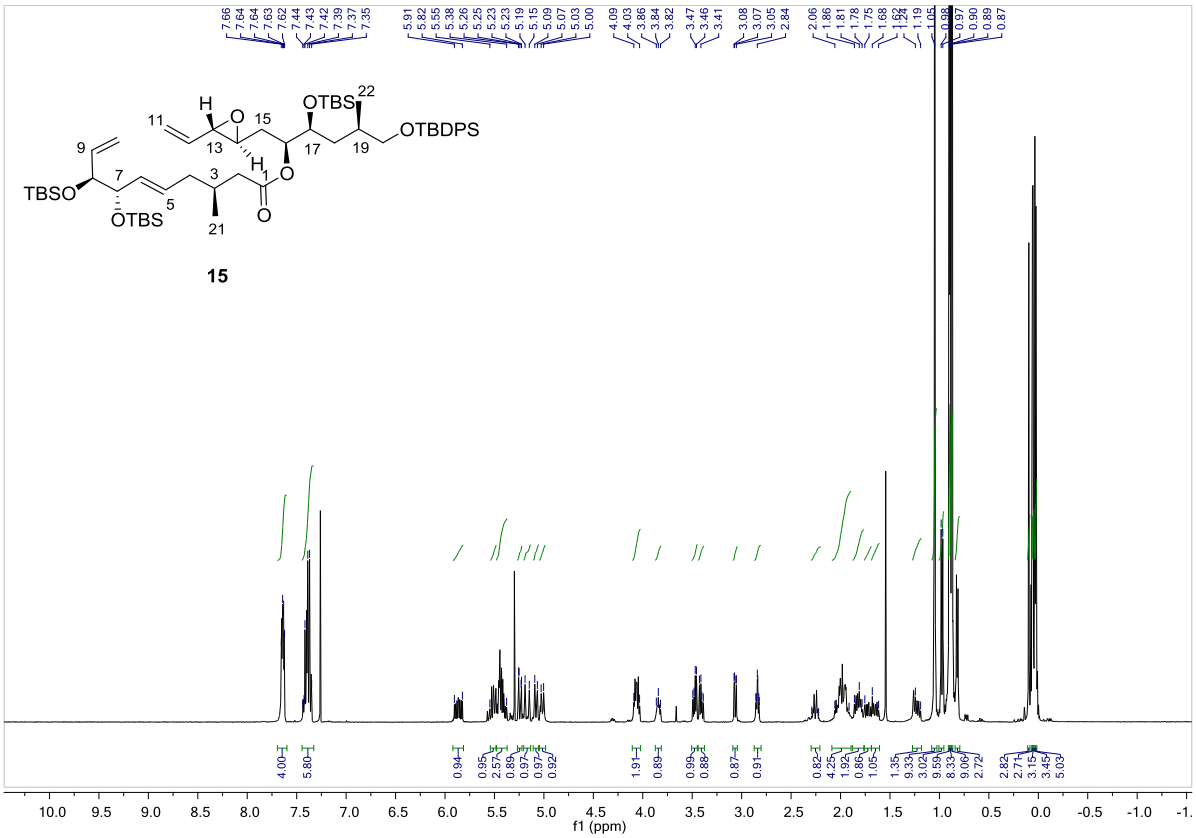
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OTBS
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3
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9
11
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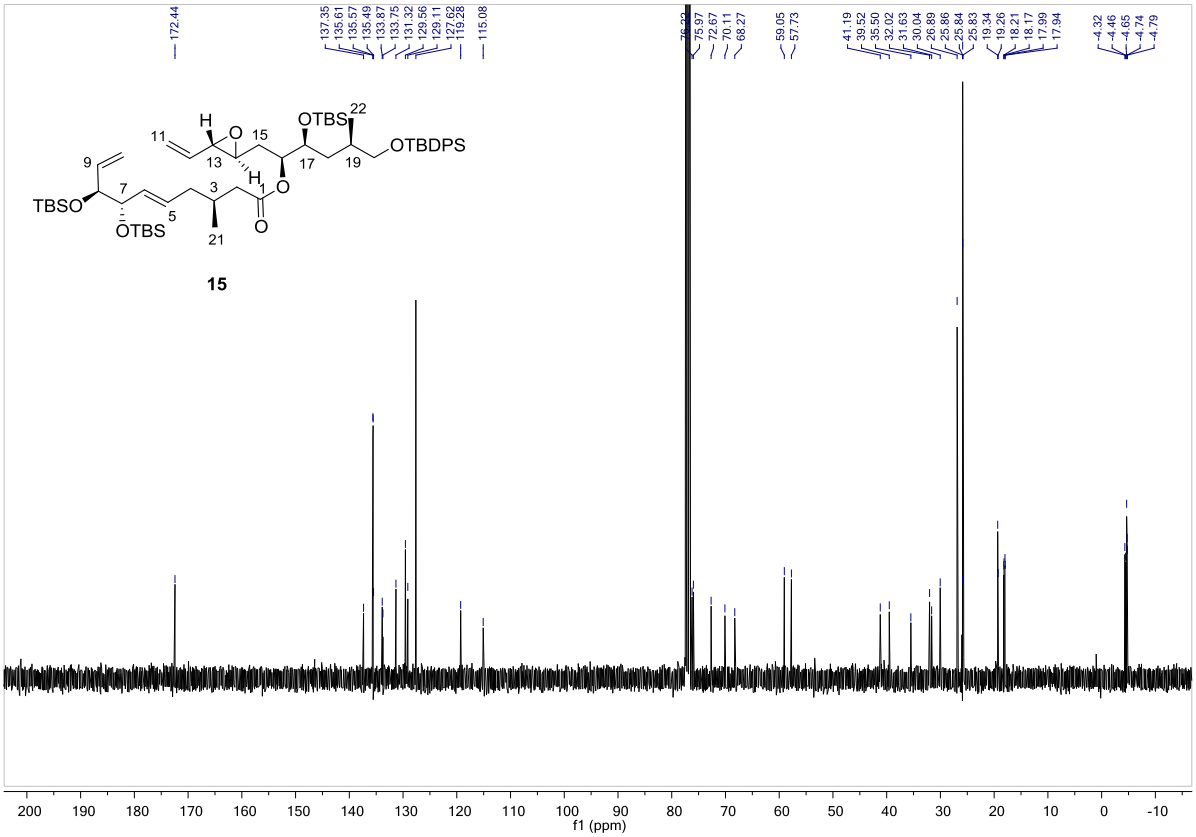
19
21
22
15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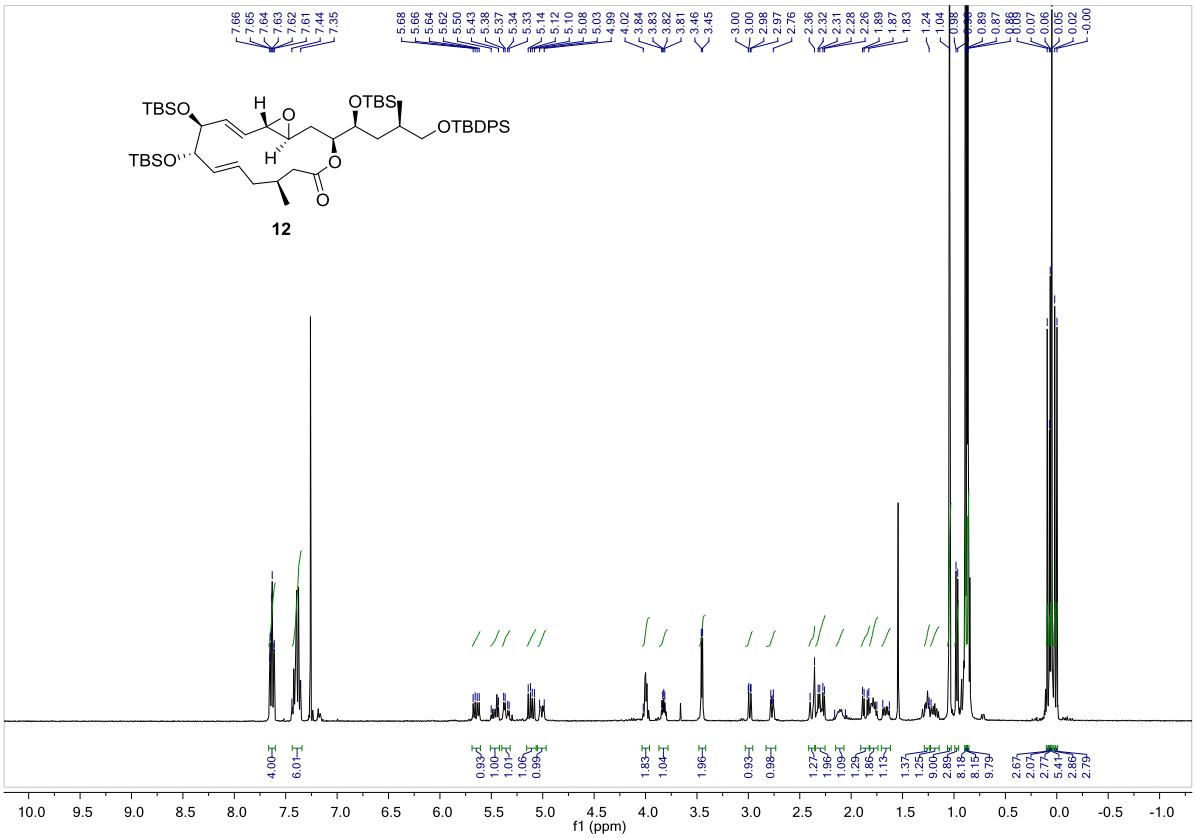
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O
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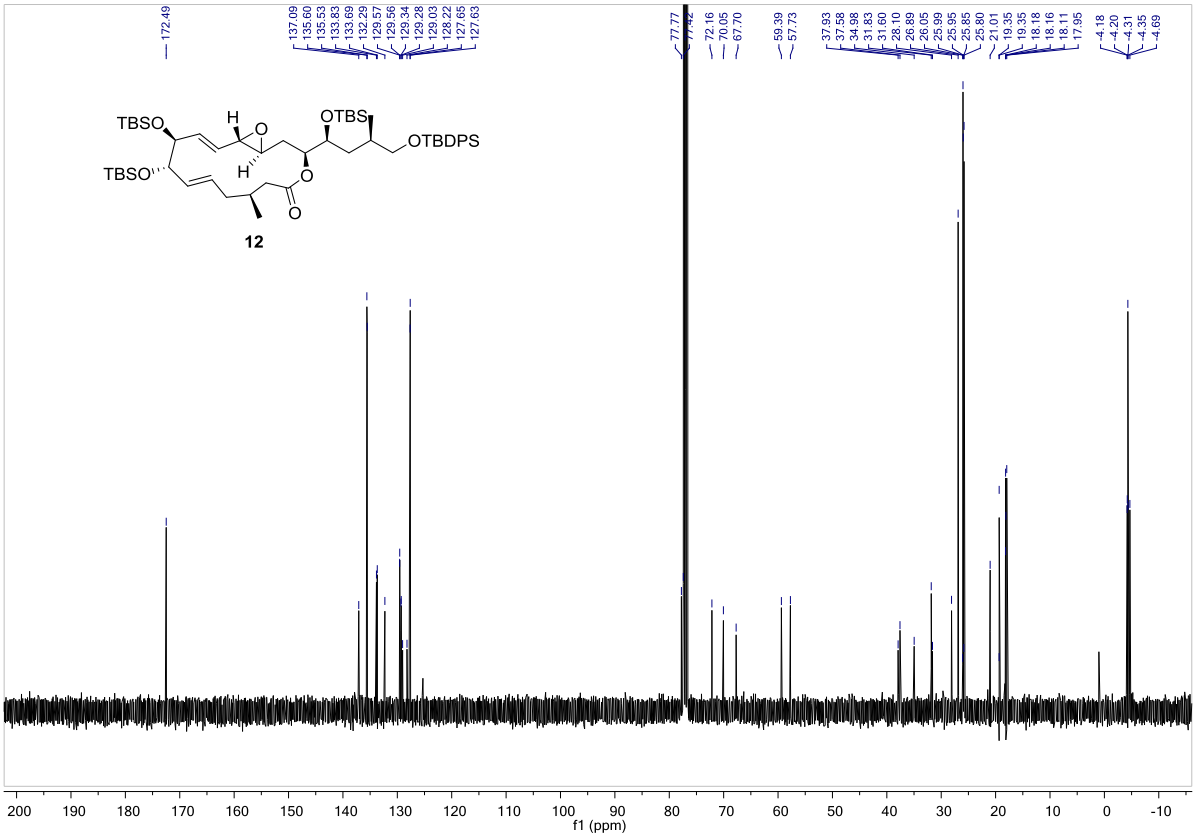
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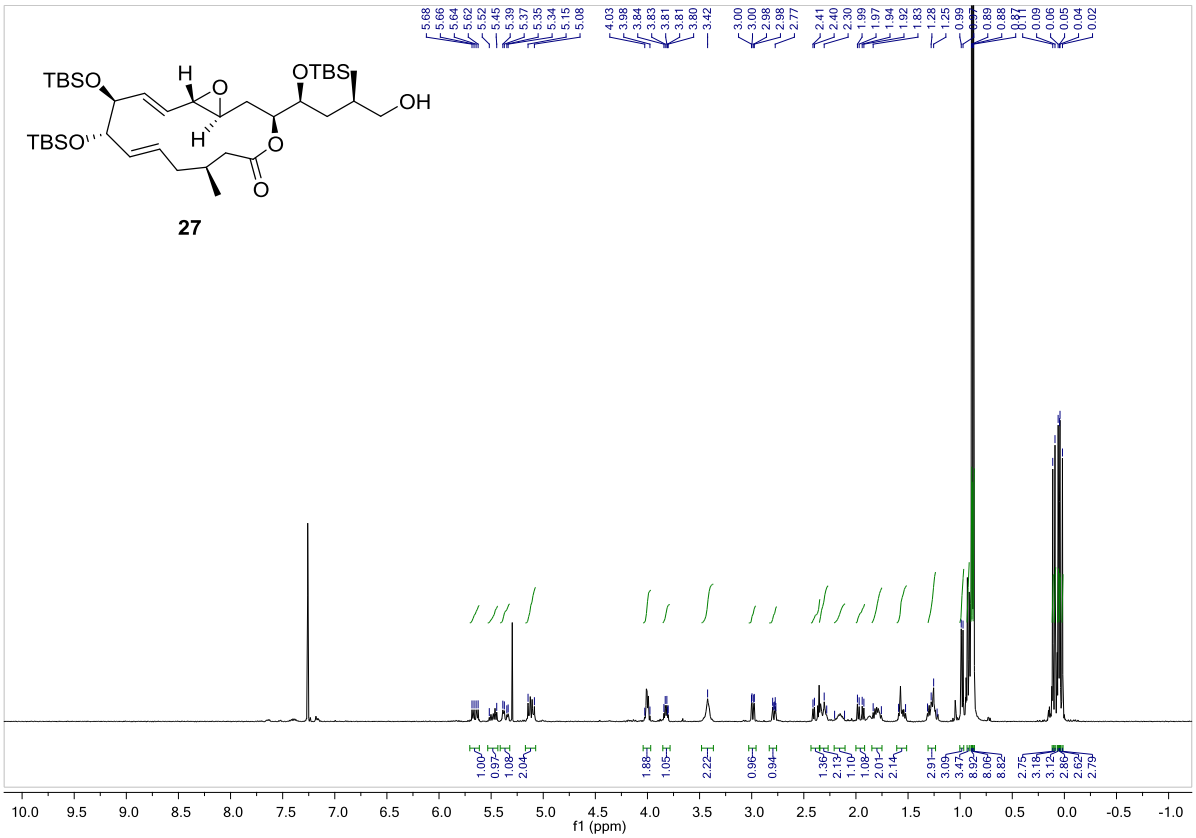
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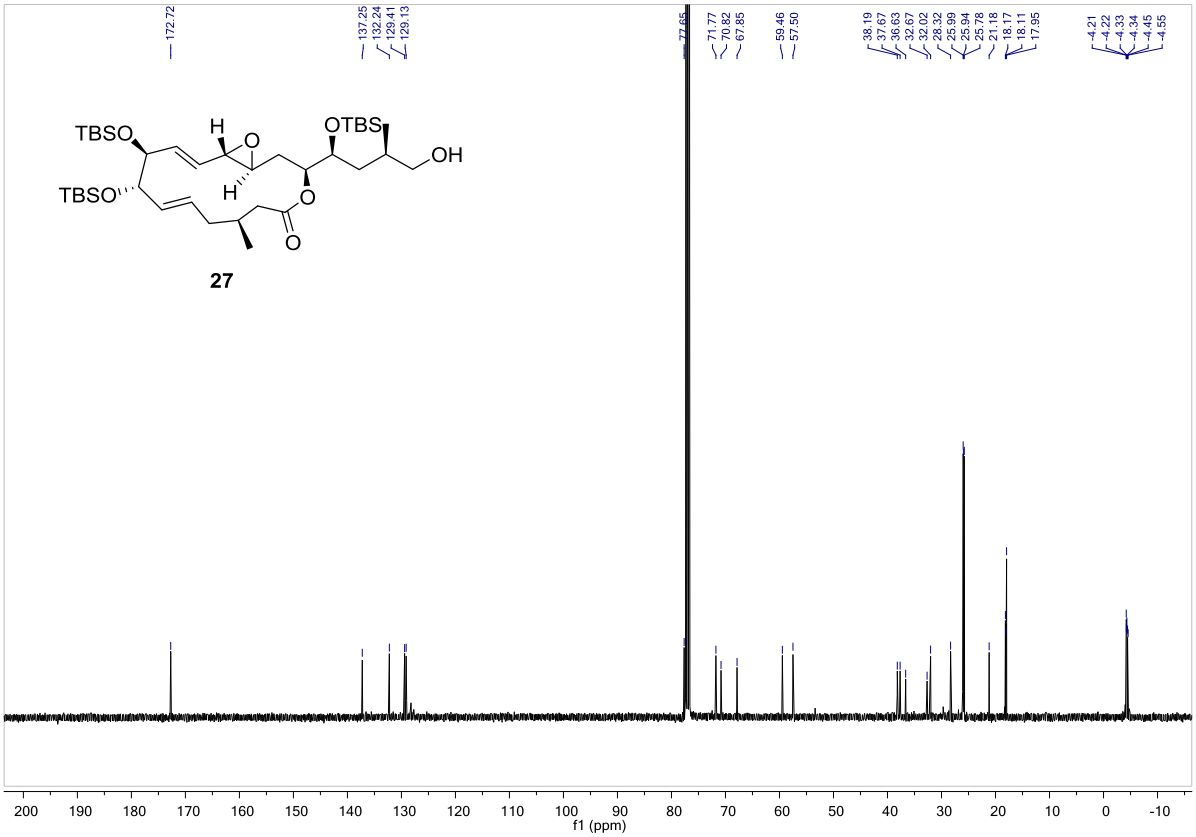
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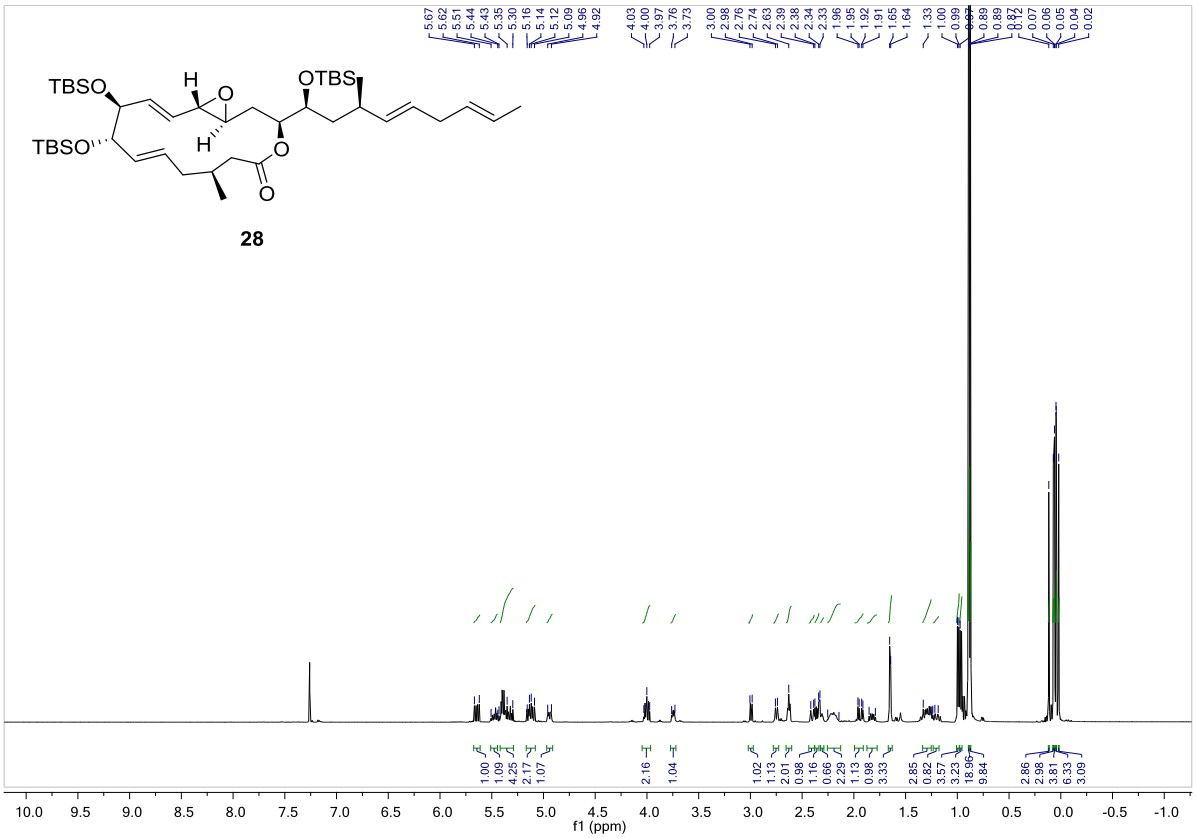
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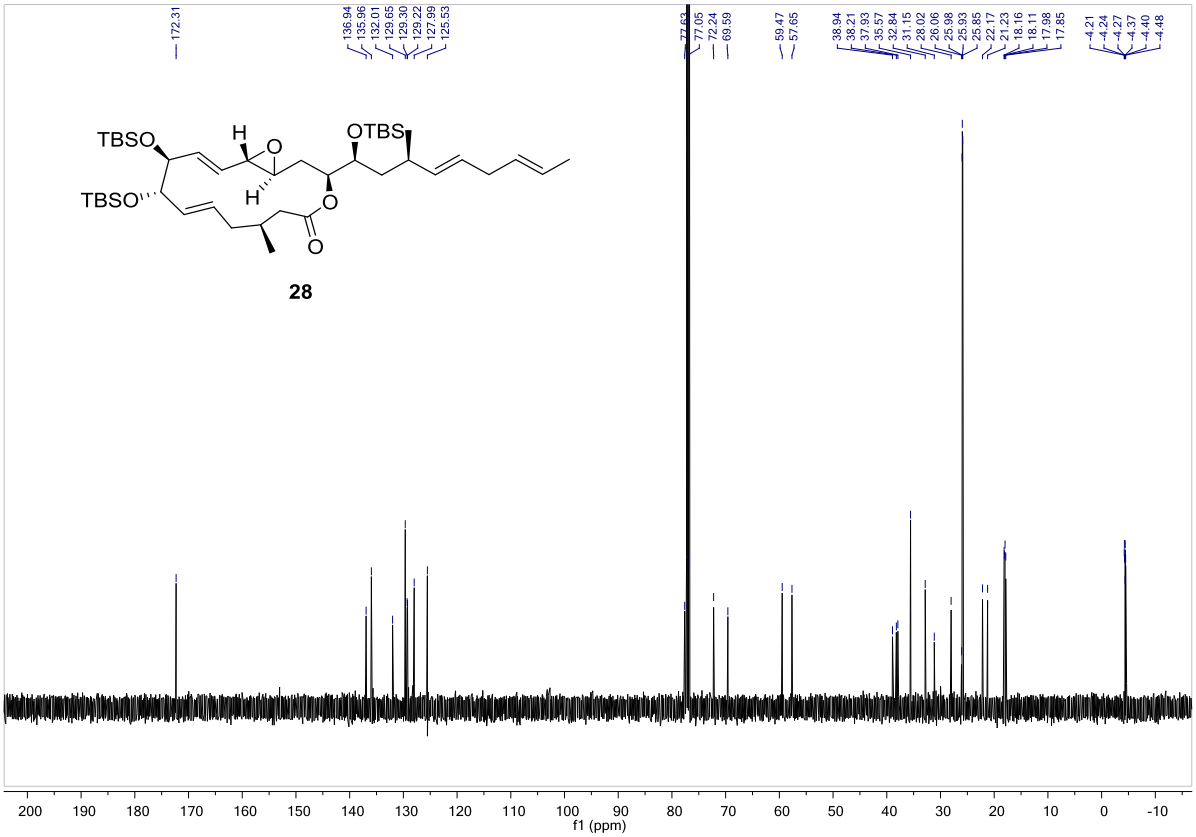
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O
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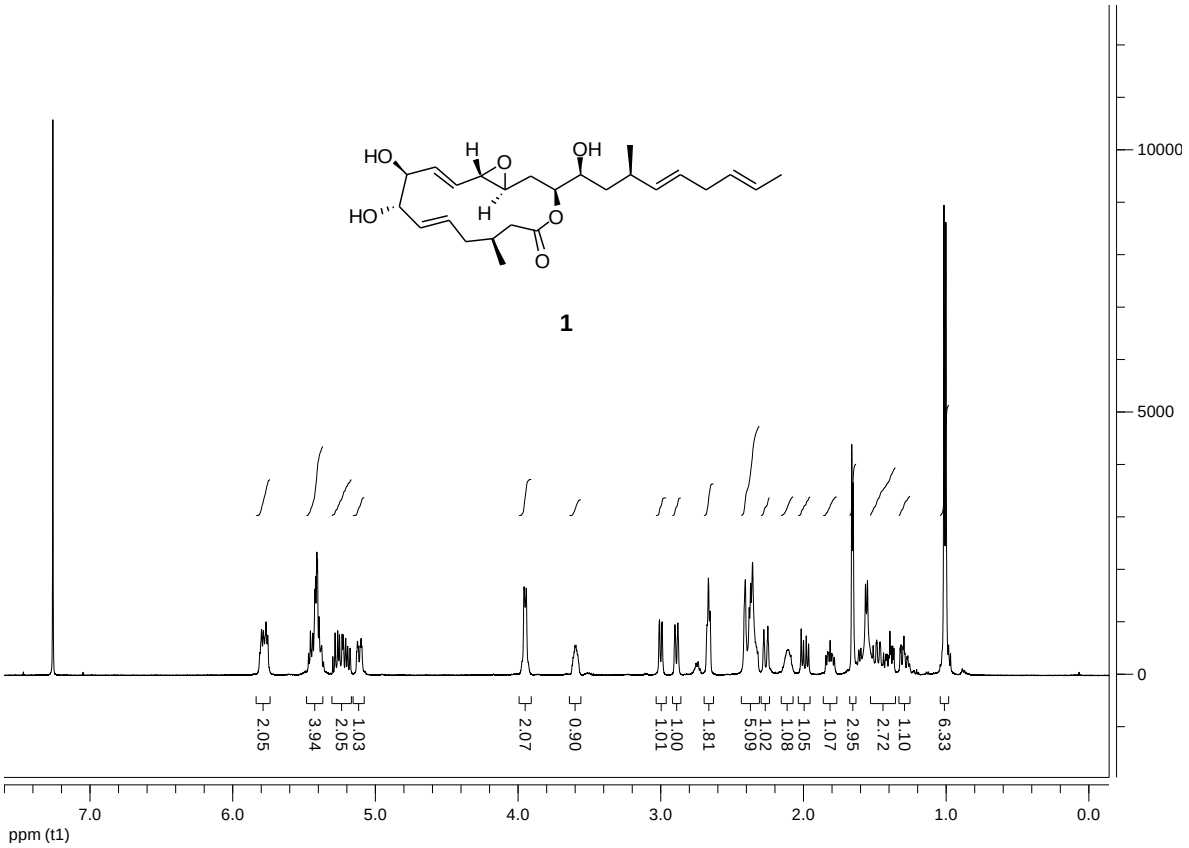
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2.07
0.90
1.01
1.00
1.81
5.09
1.02
1.08
1.05
1.07
2.95
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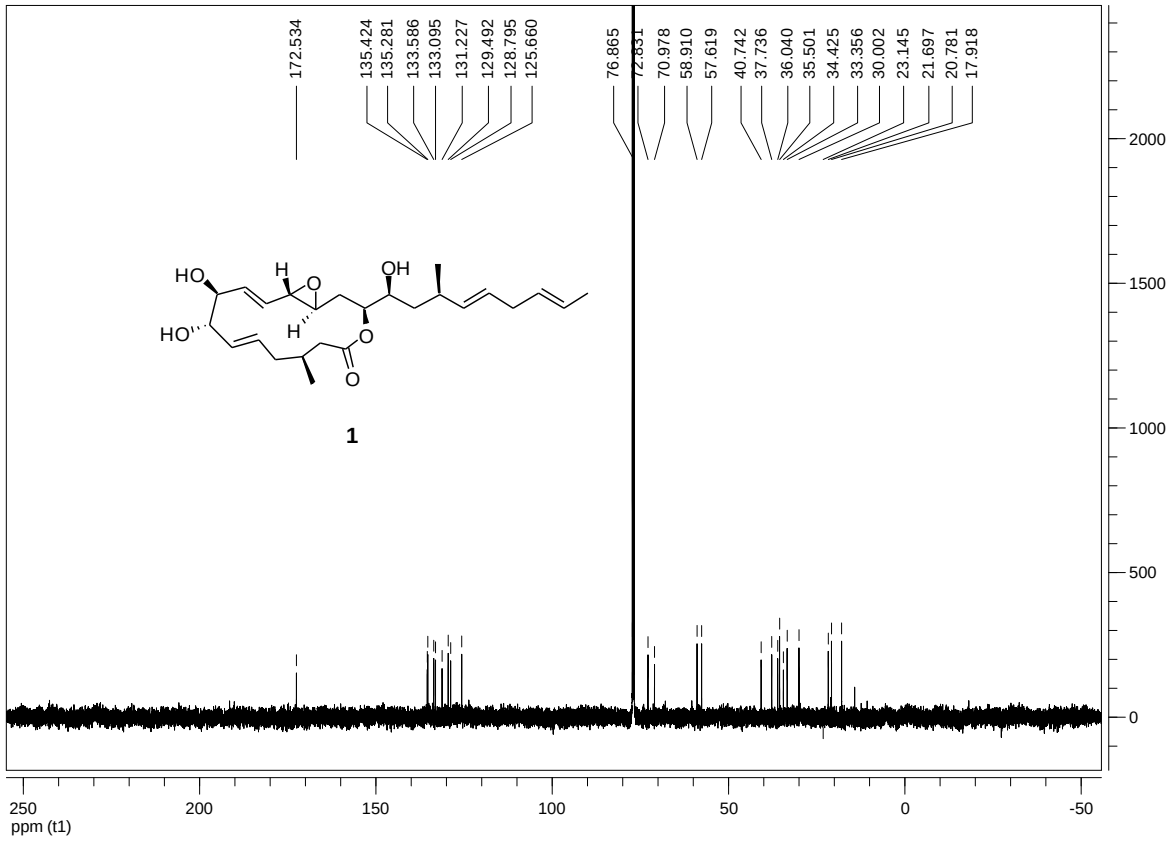
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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17.918
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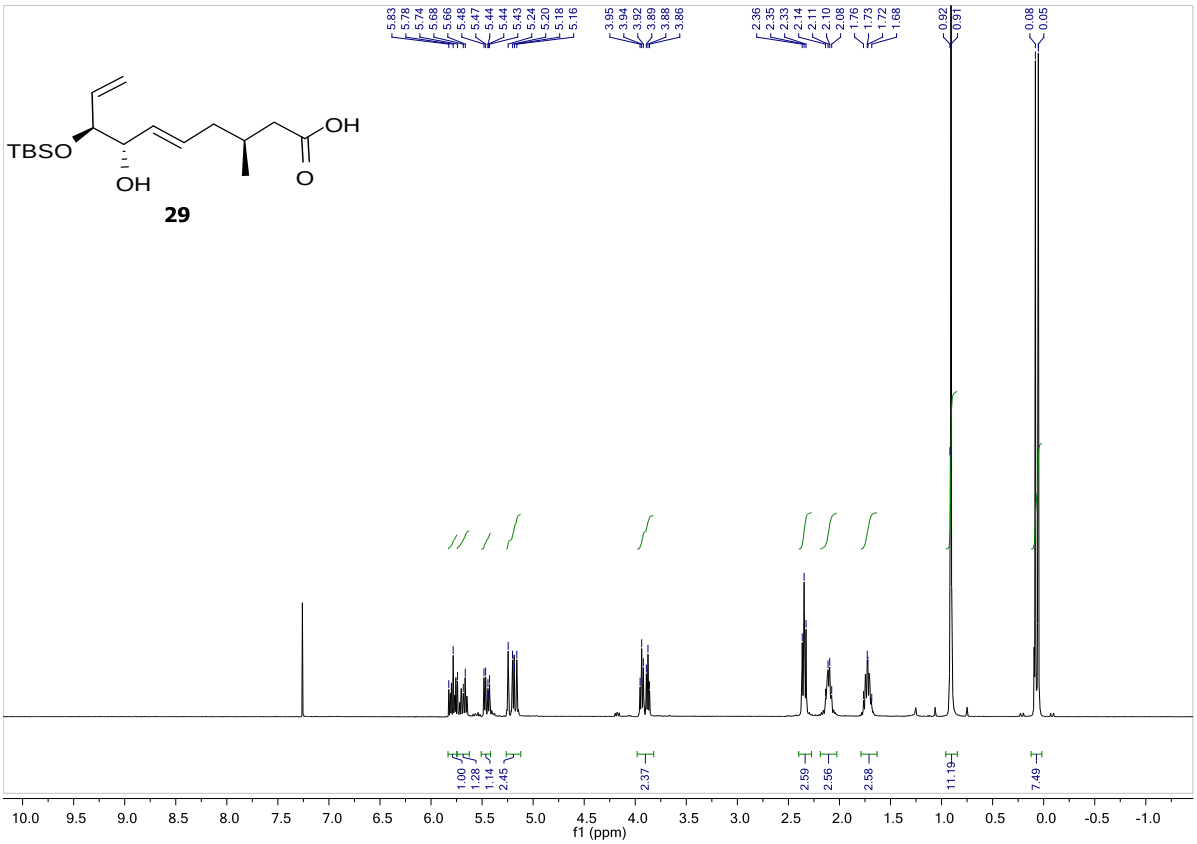
ppm (t1)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5.43
5.24
5.20
5.18
5.16
3.95
3.94
3.92
3.89
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2.14
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1.68
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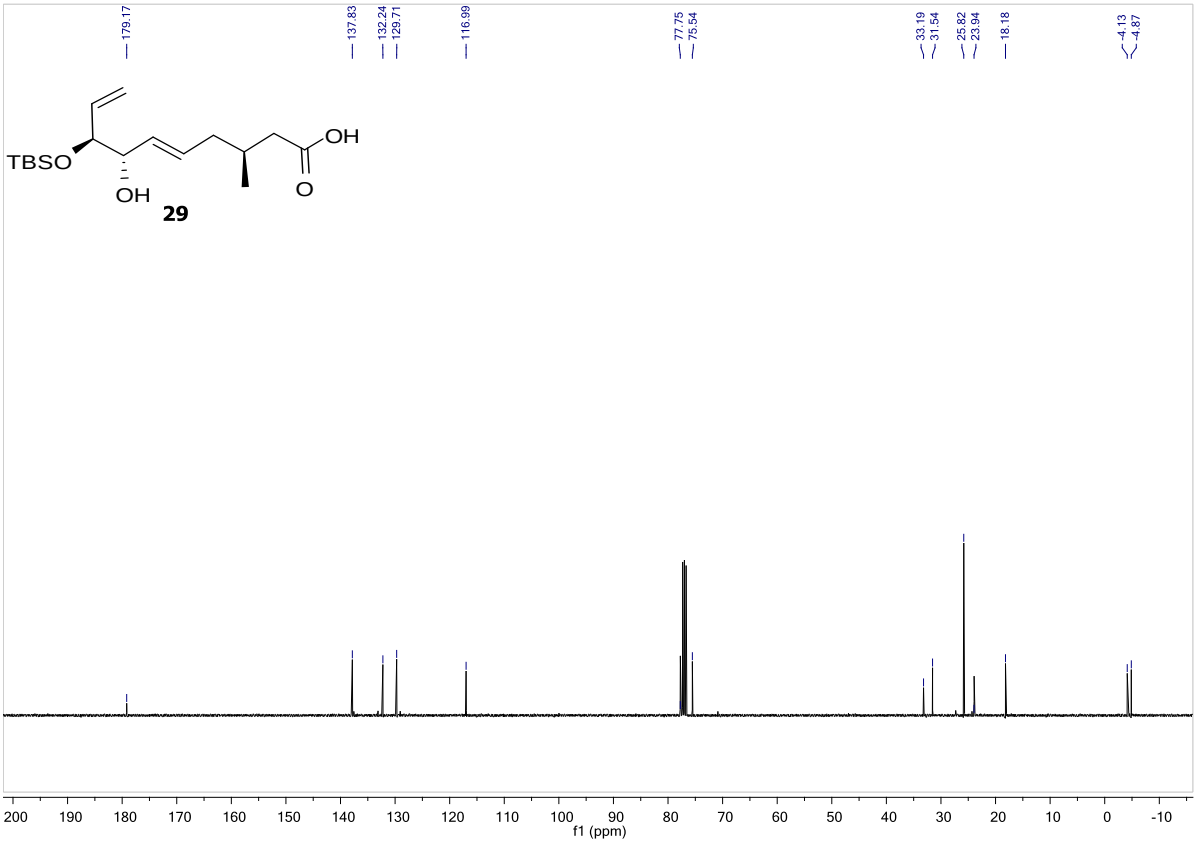
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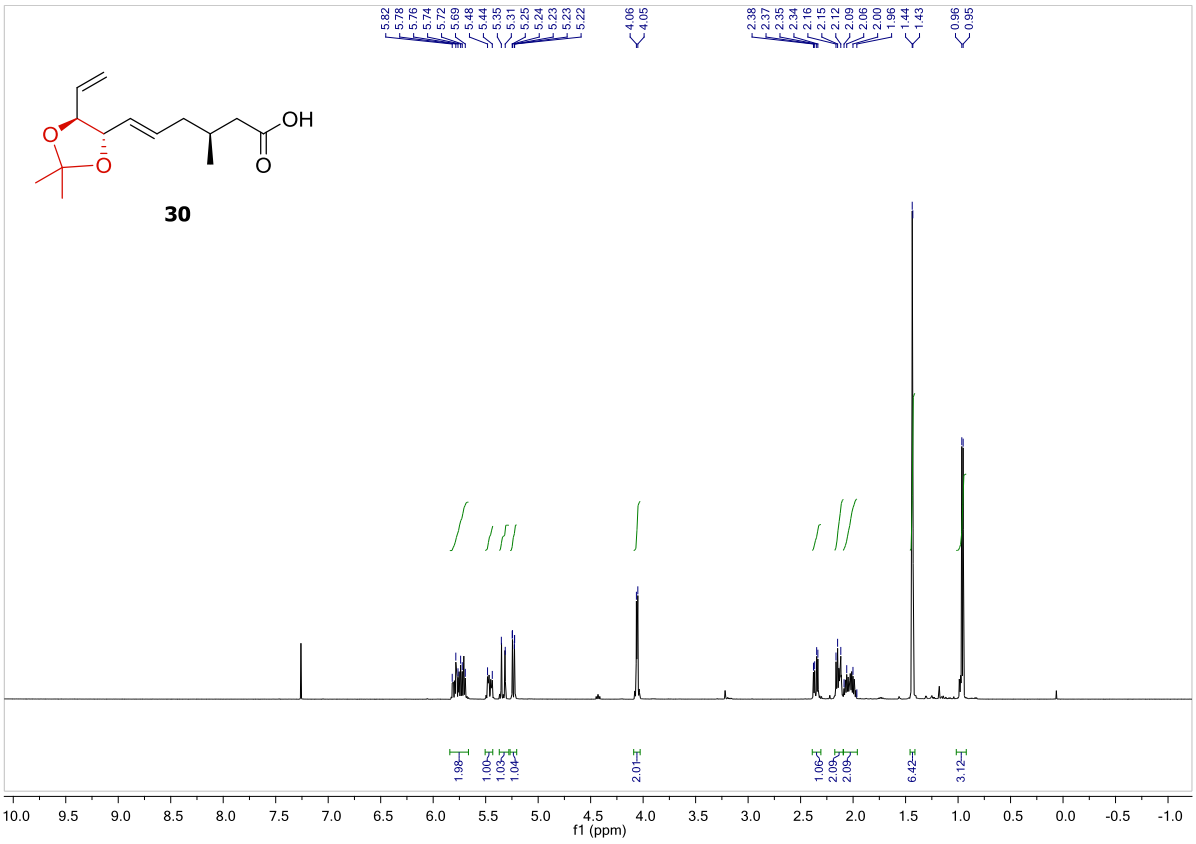
f1 (ppm)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5.23
5.22
4.06
4.05
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2.35
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1.06
2.05
2.09
6.42
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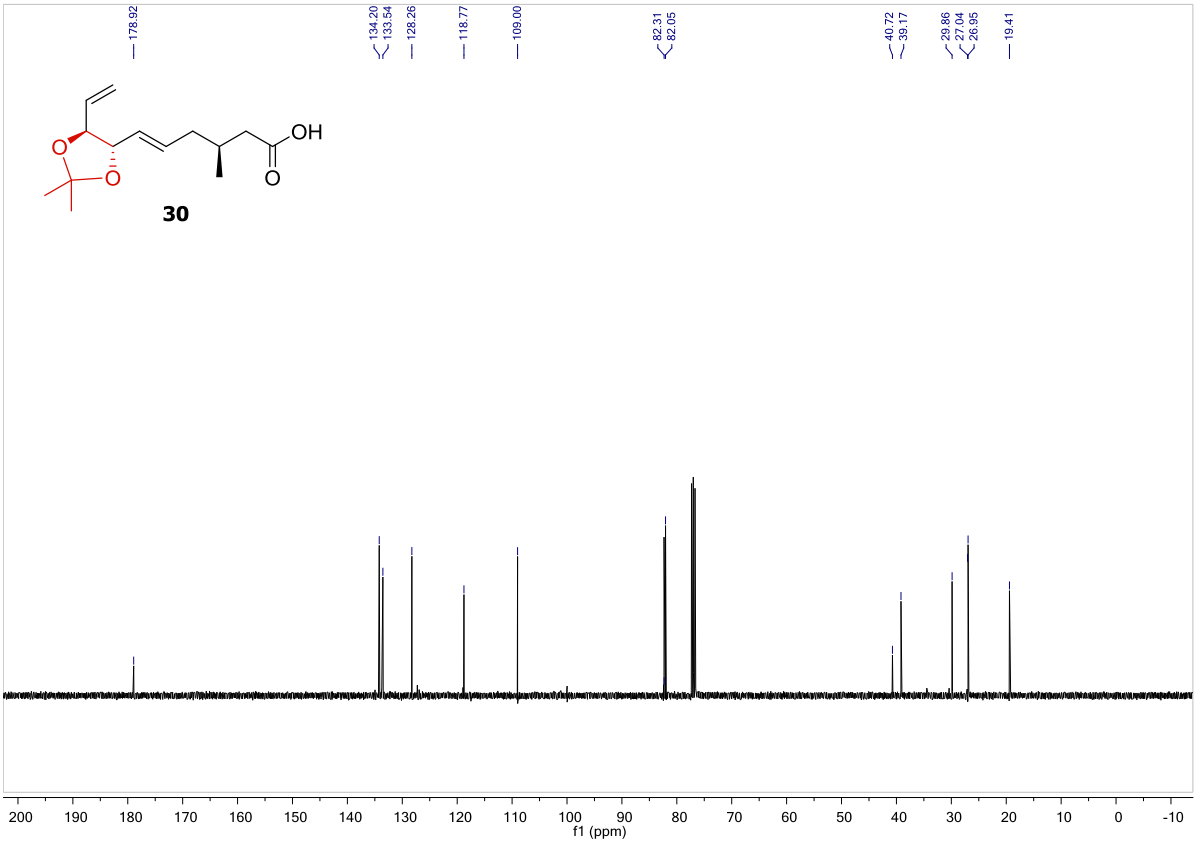
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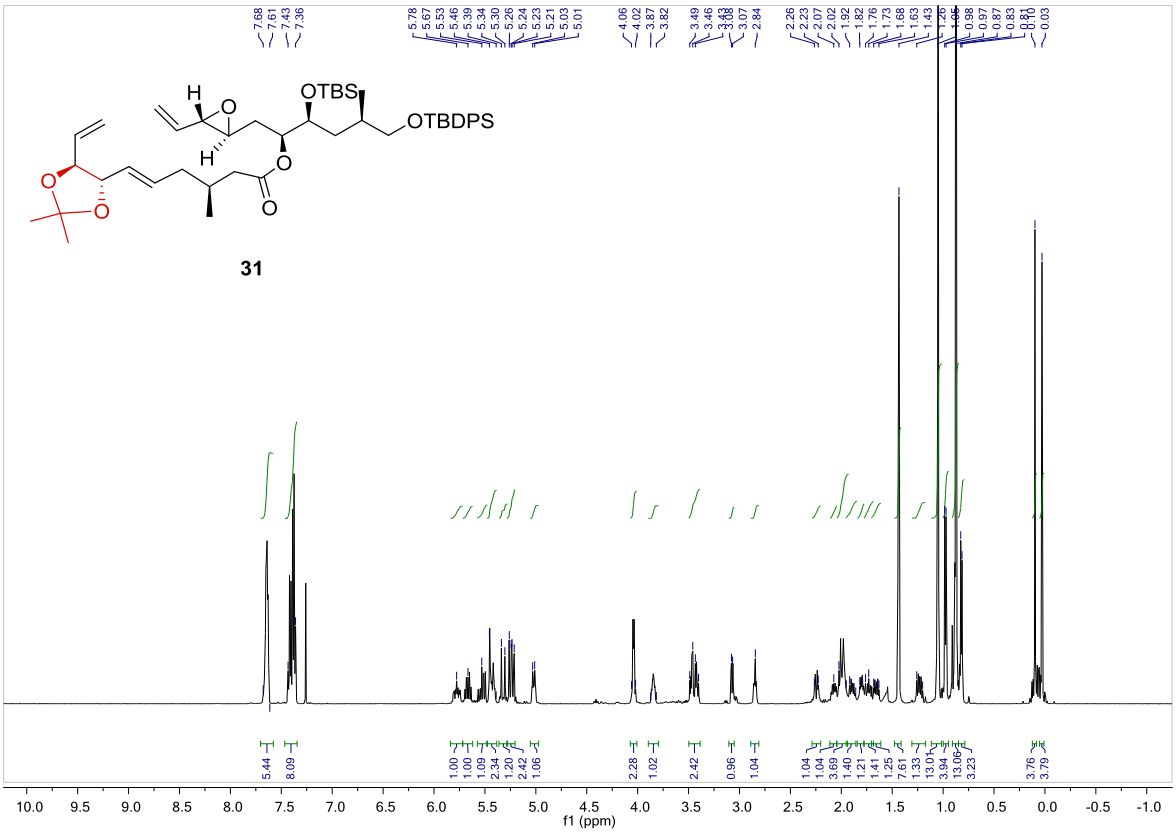
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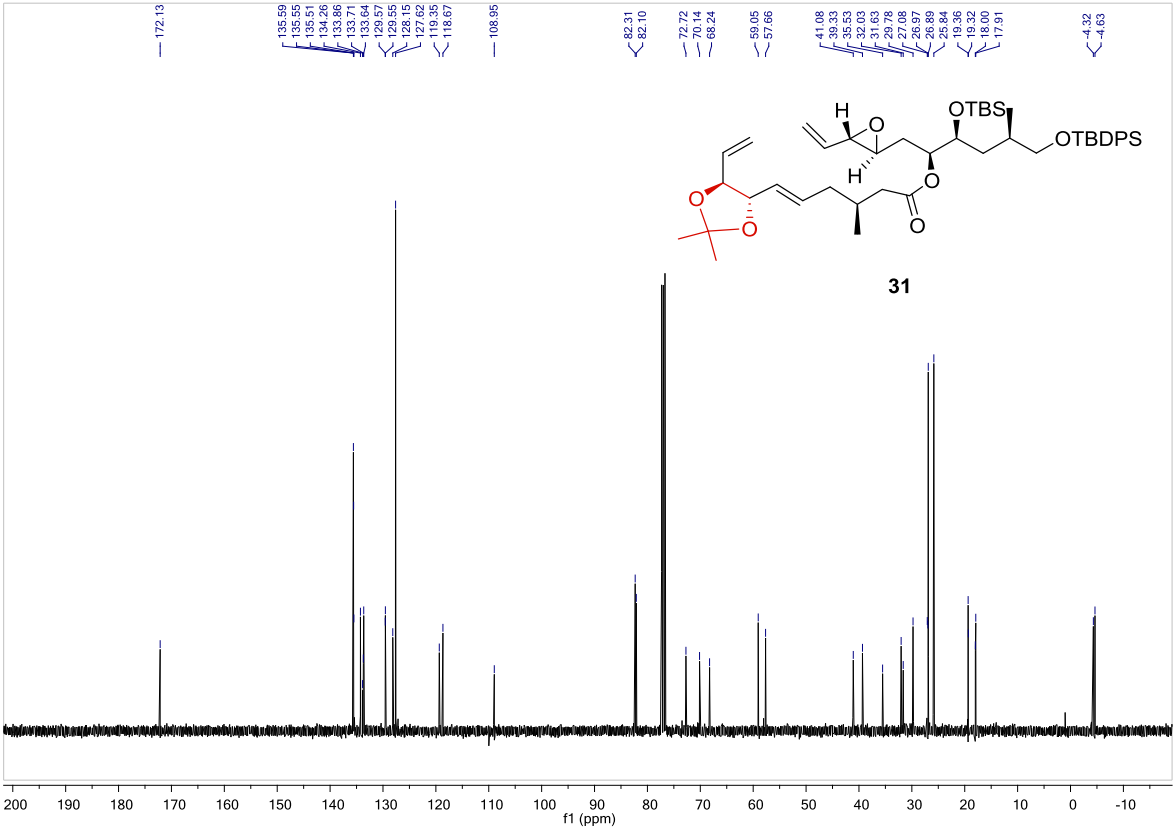
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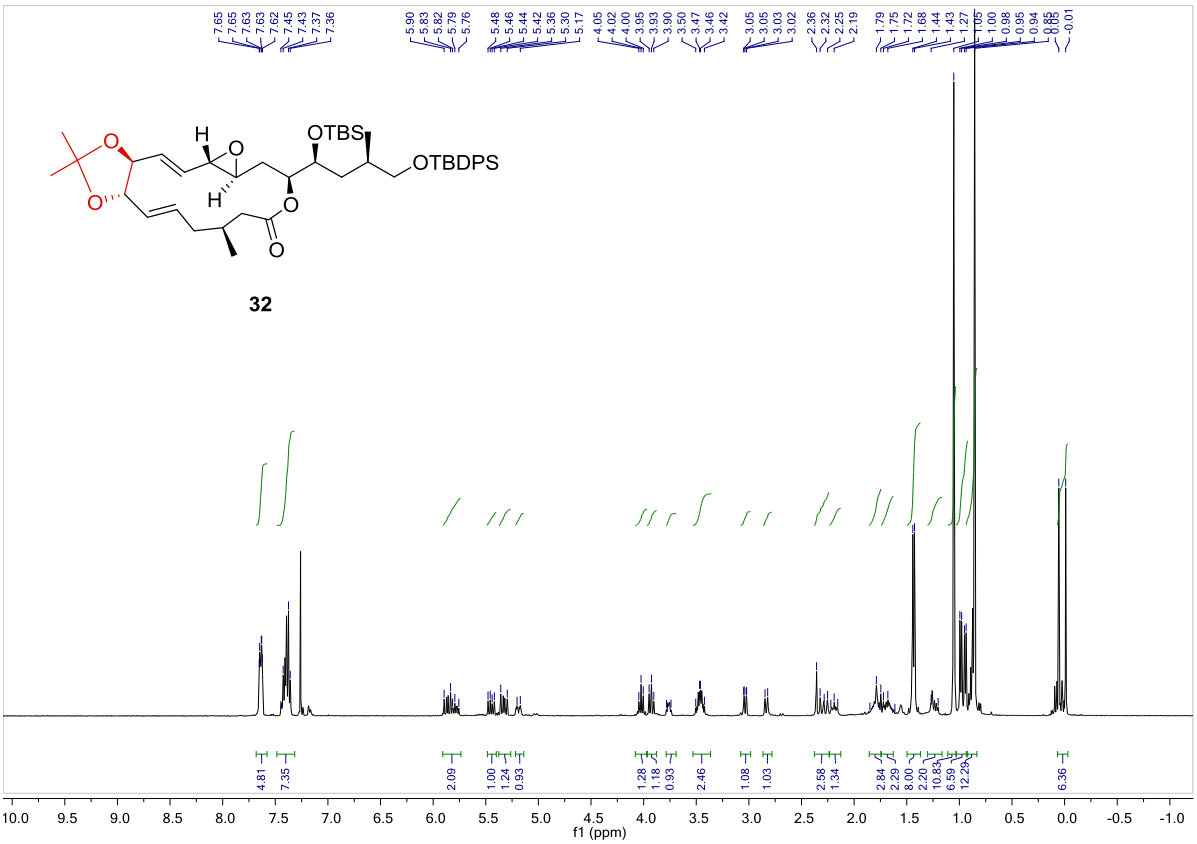
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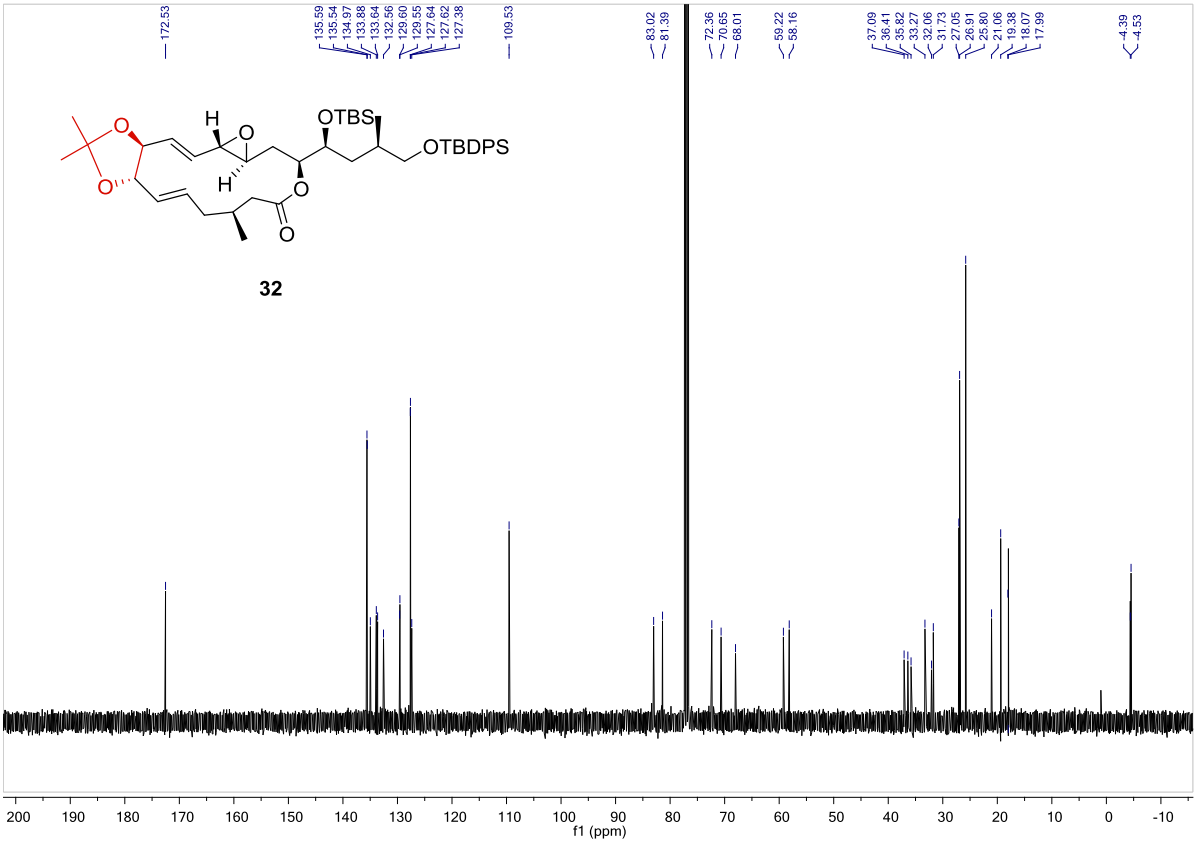
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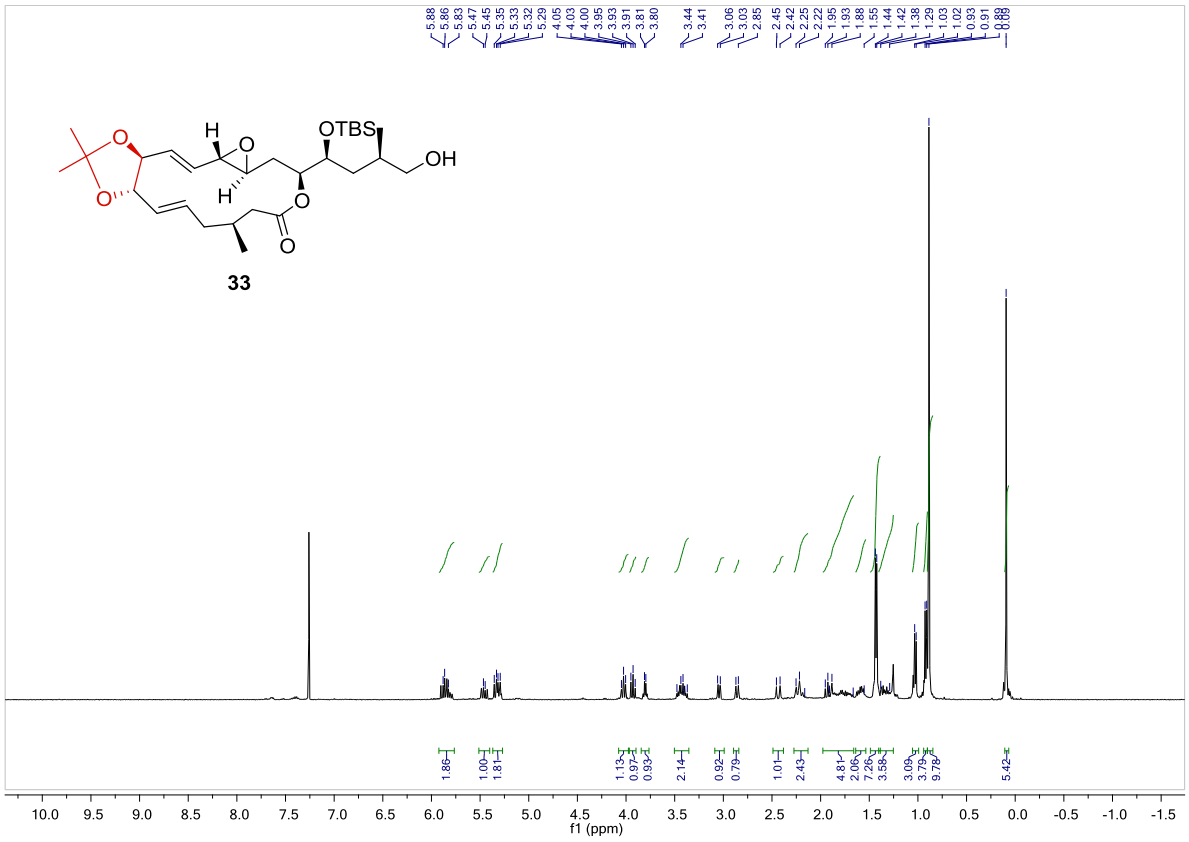
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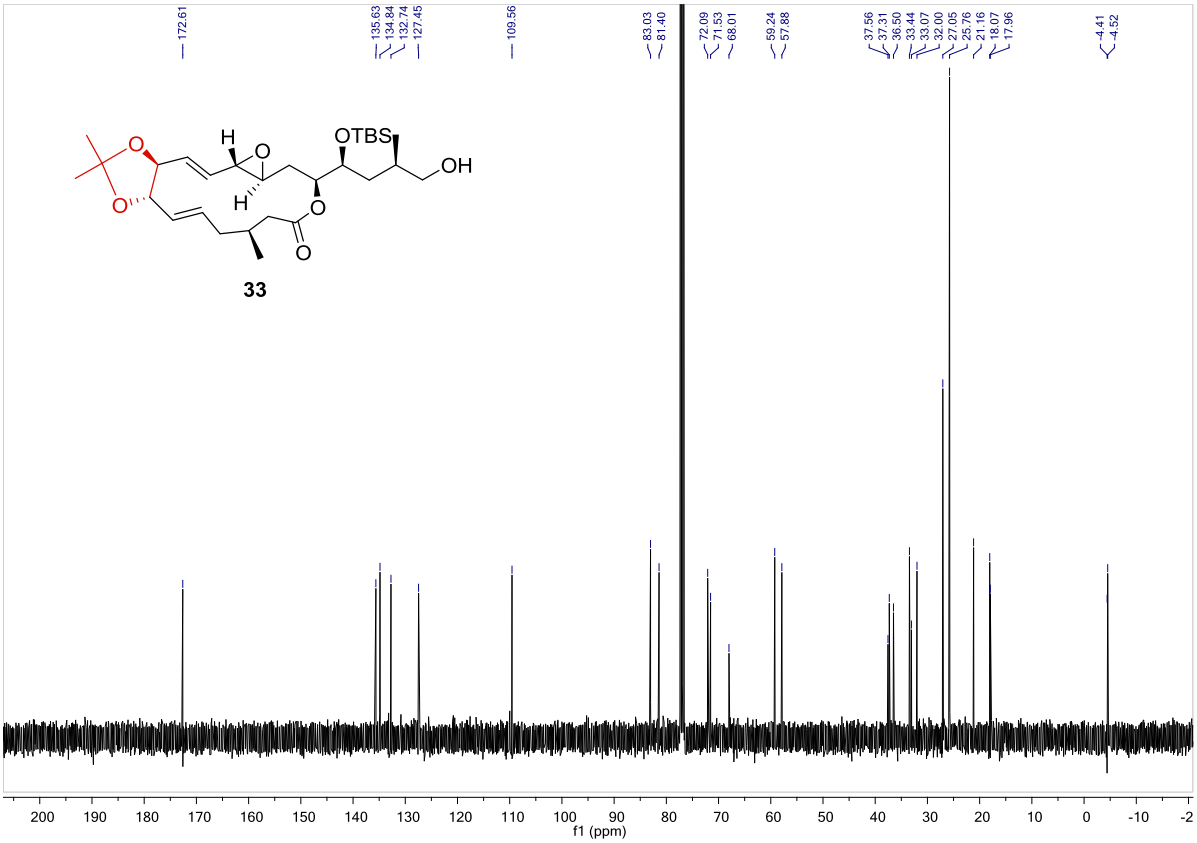
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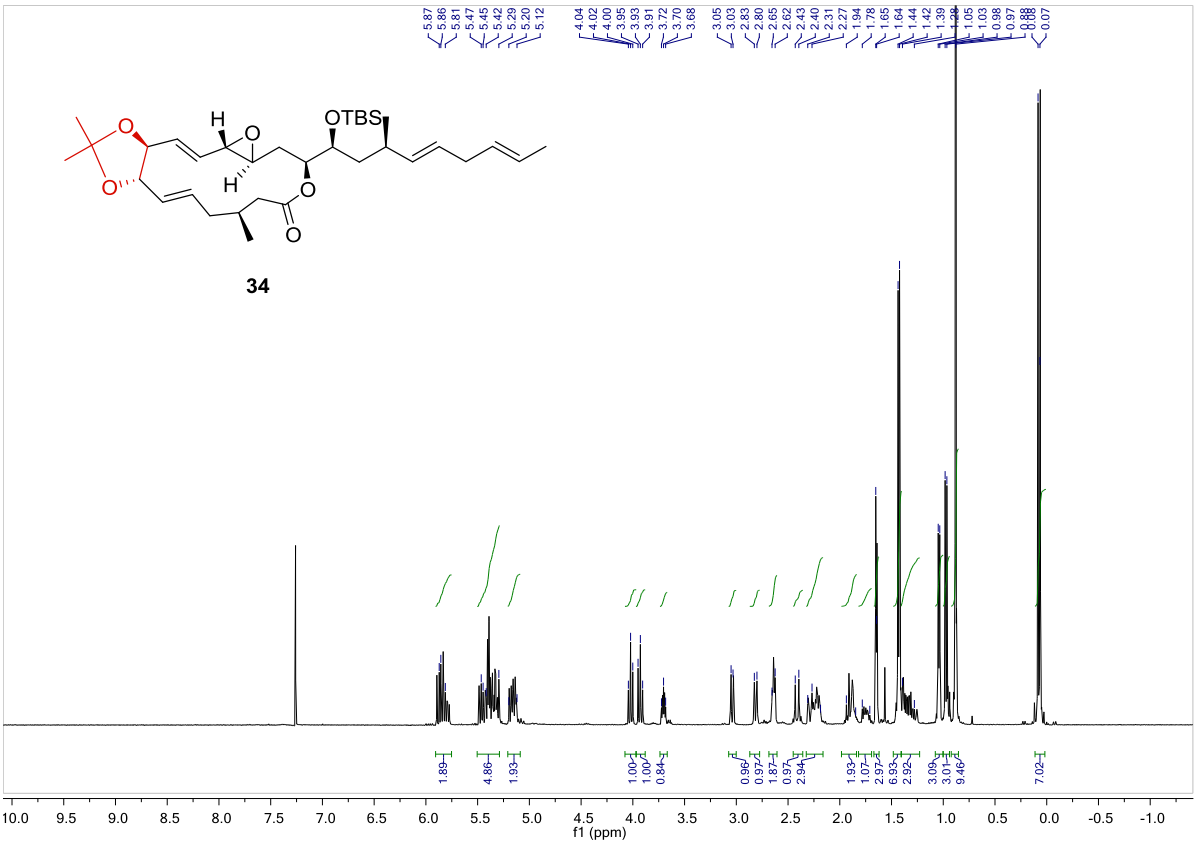
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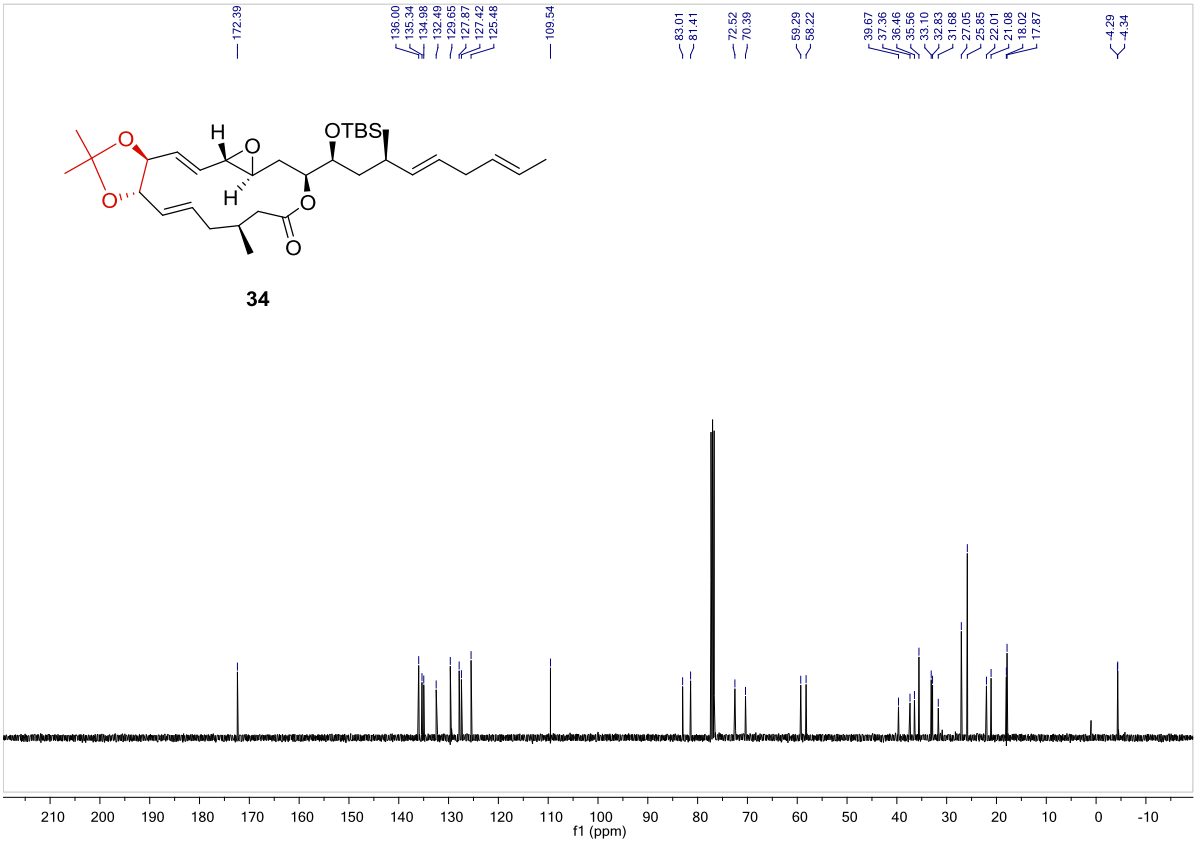
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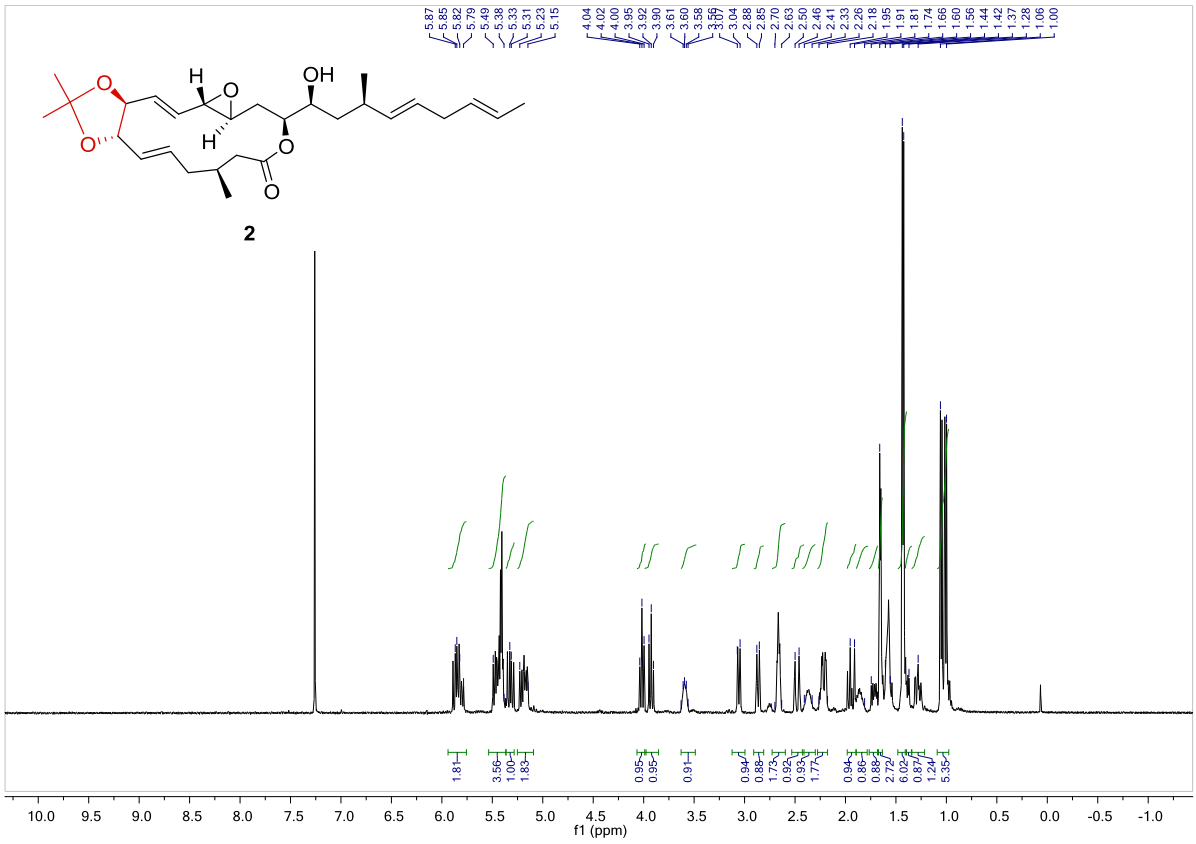
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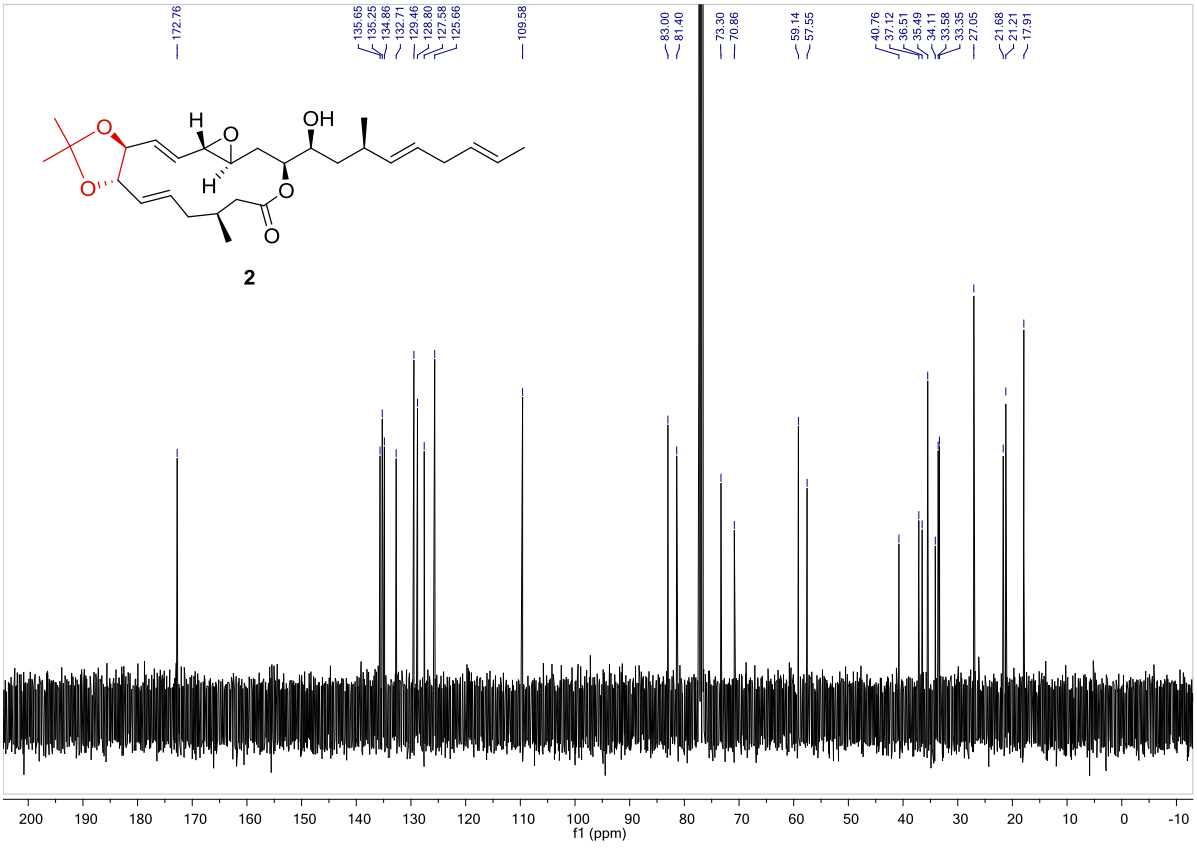
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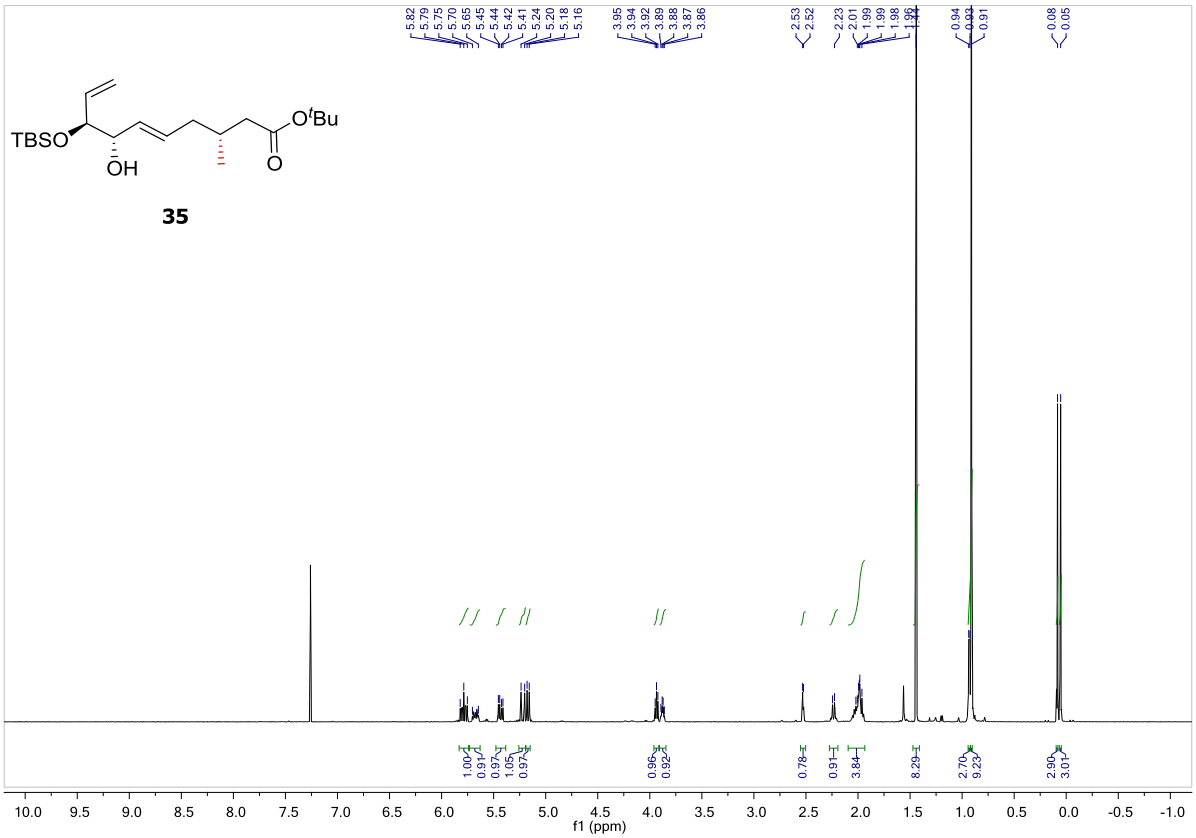
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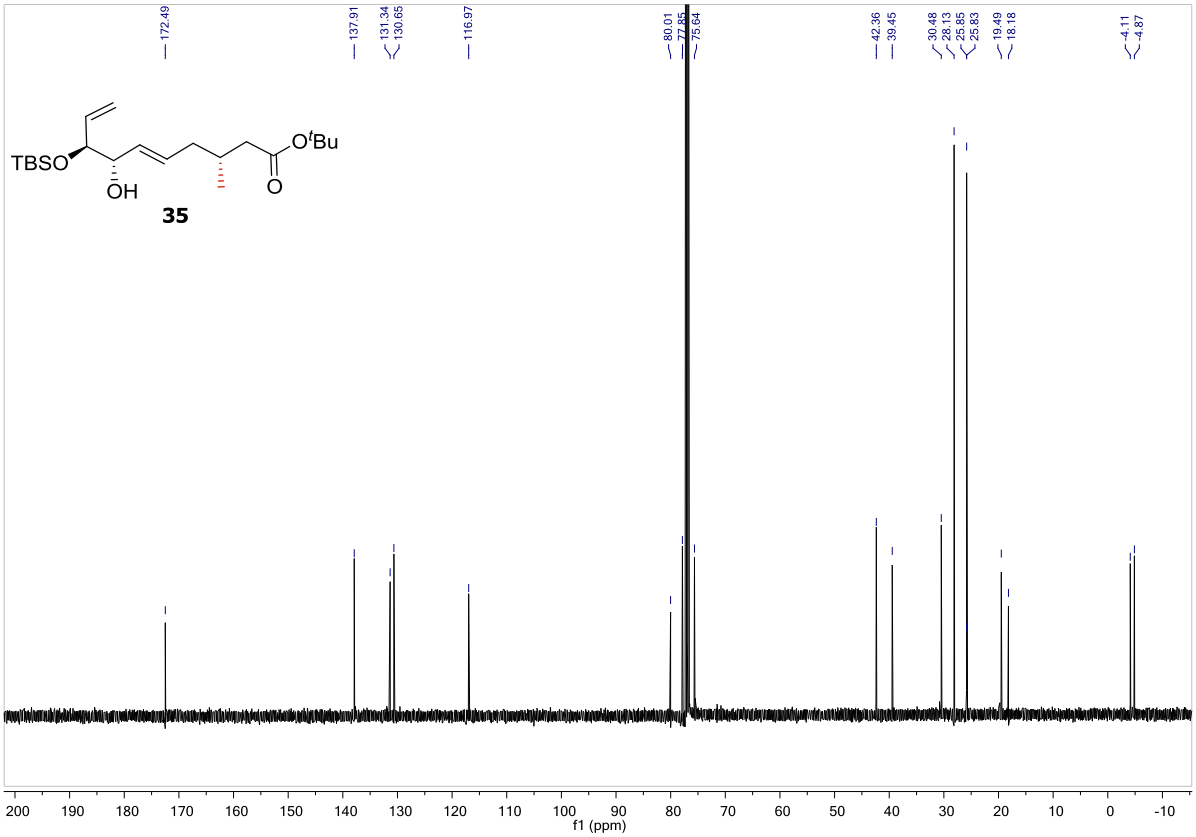
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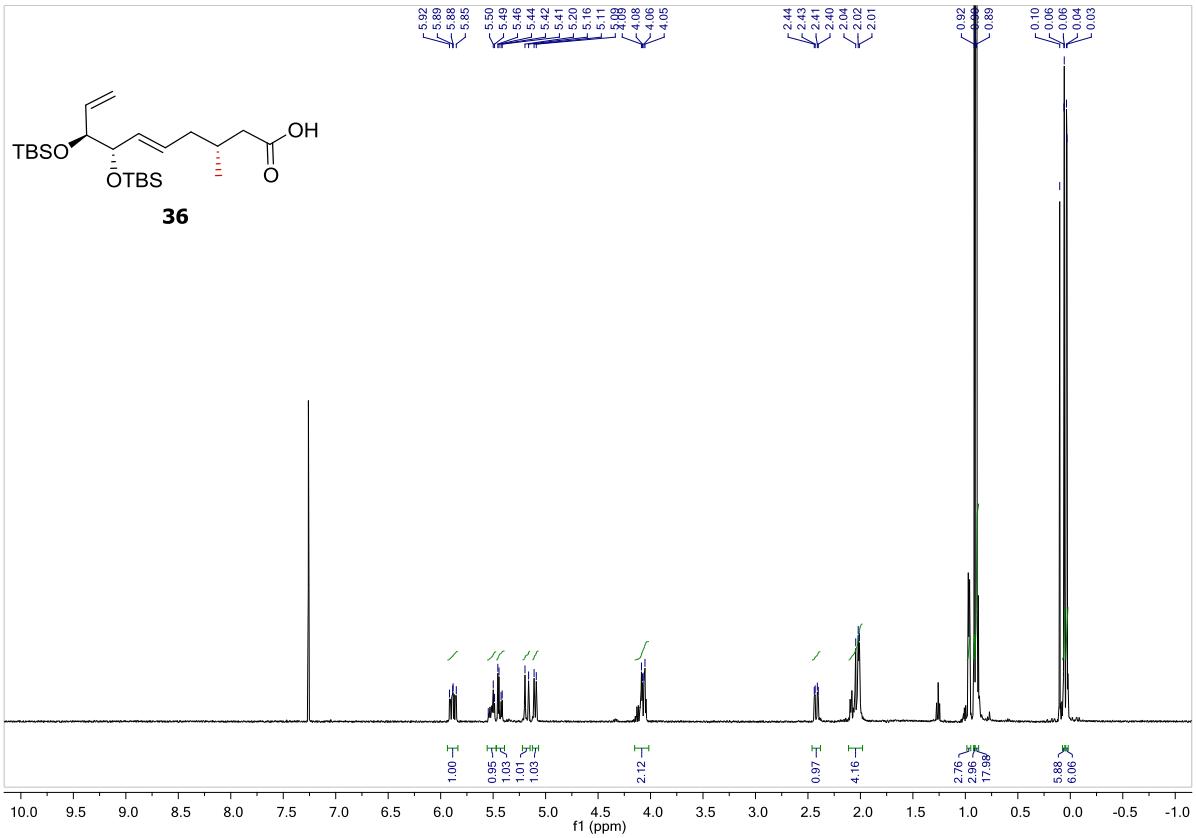
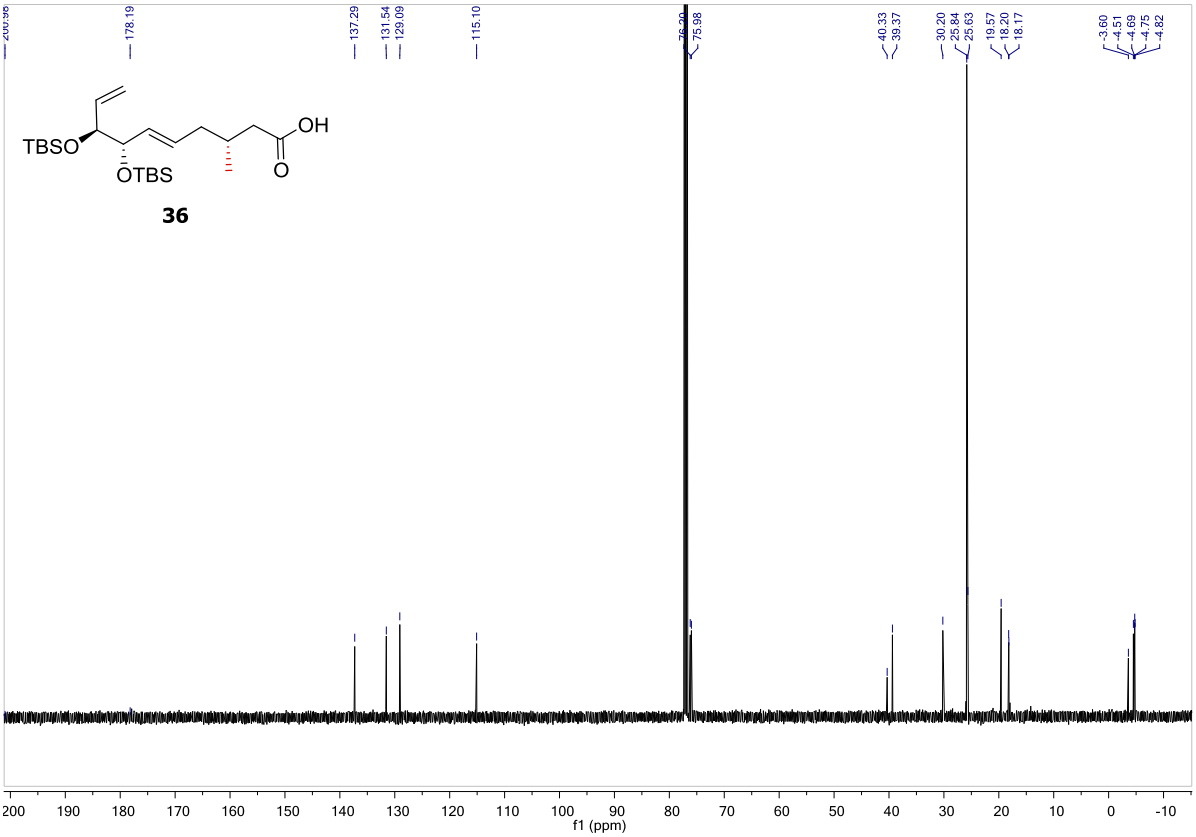
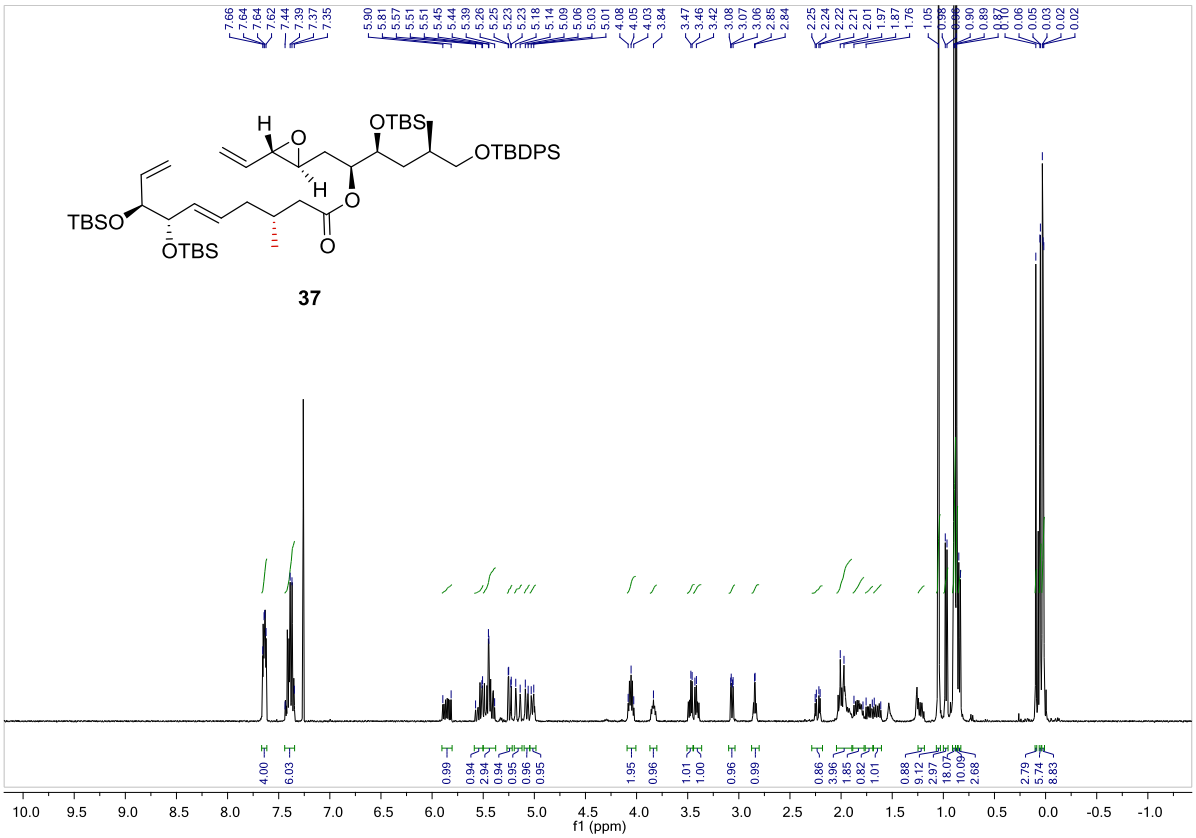
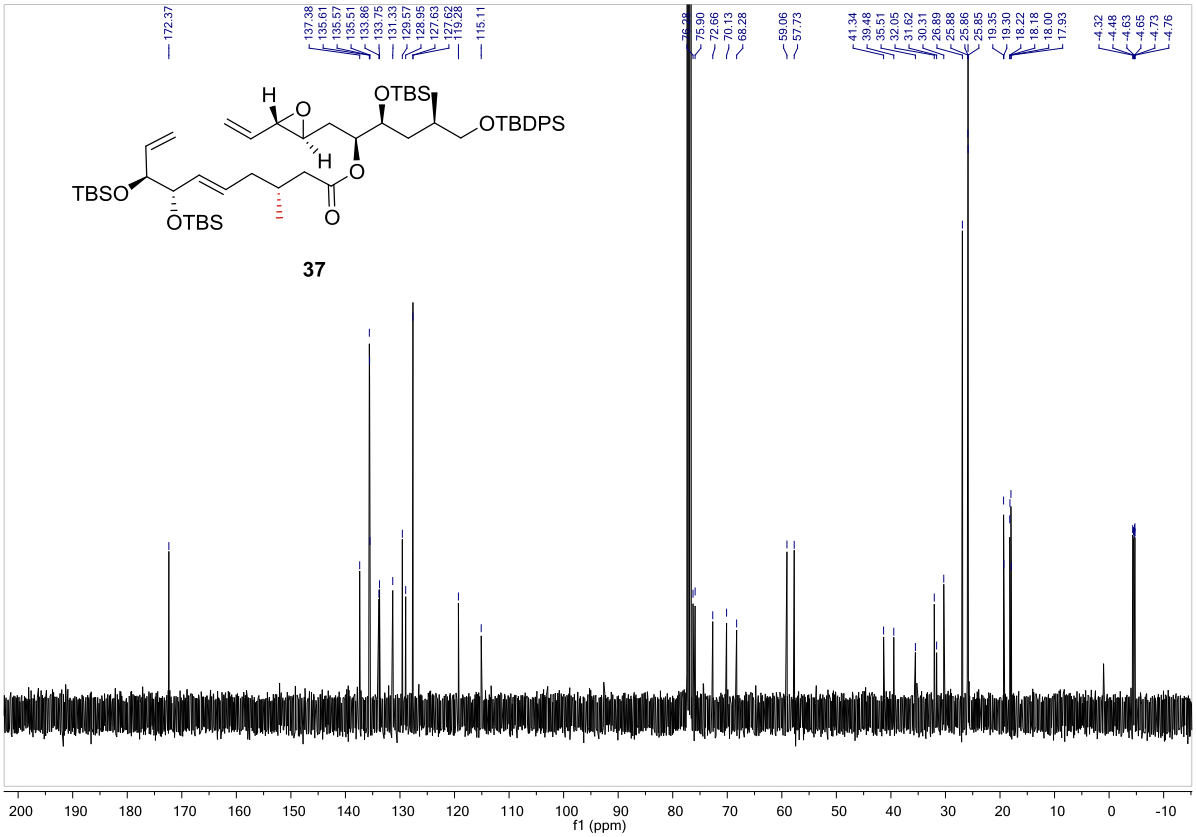
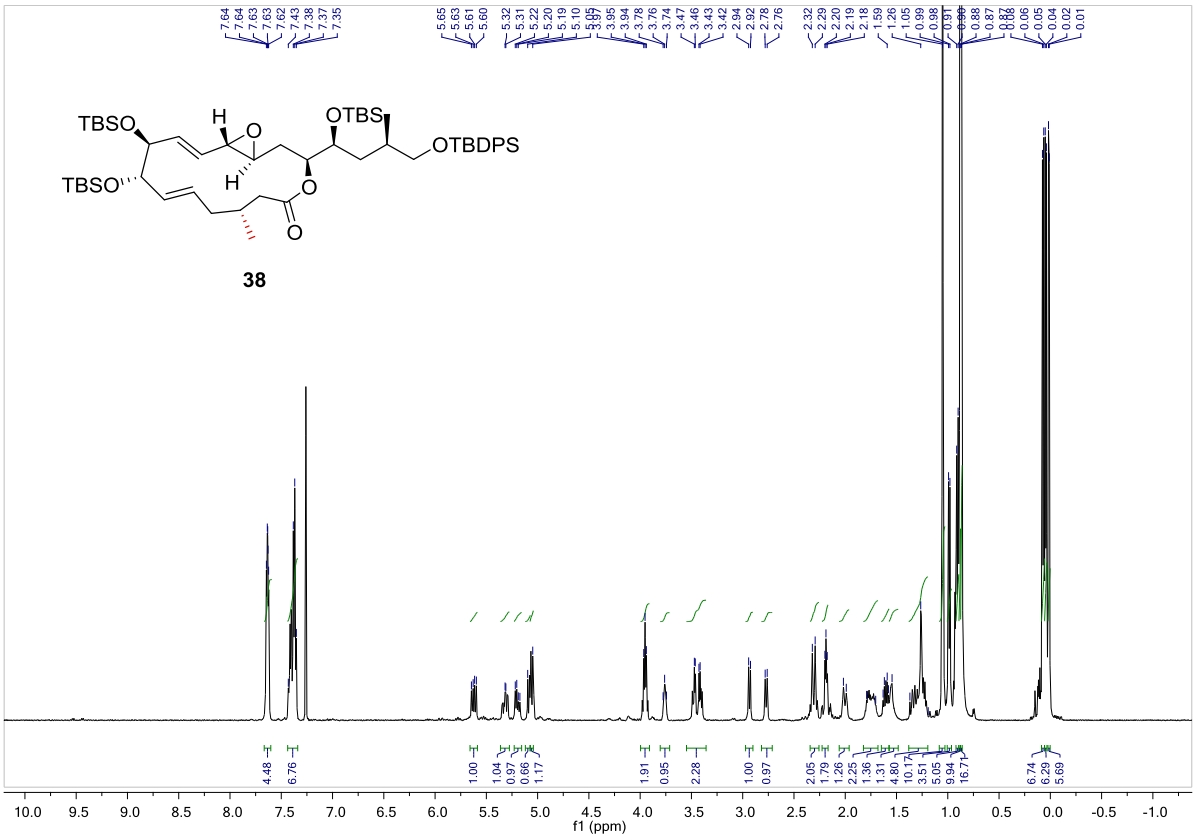
35
f1 (ppm)

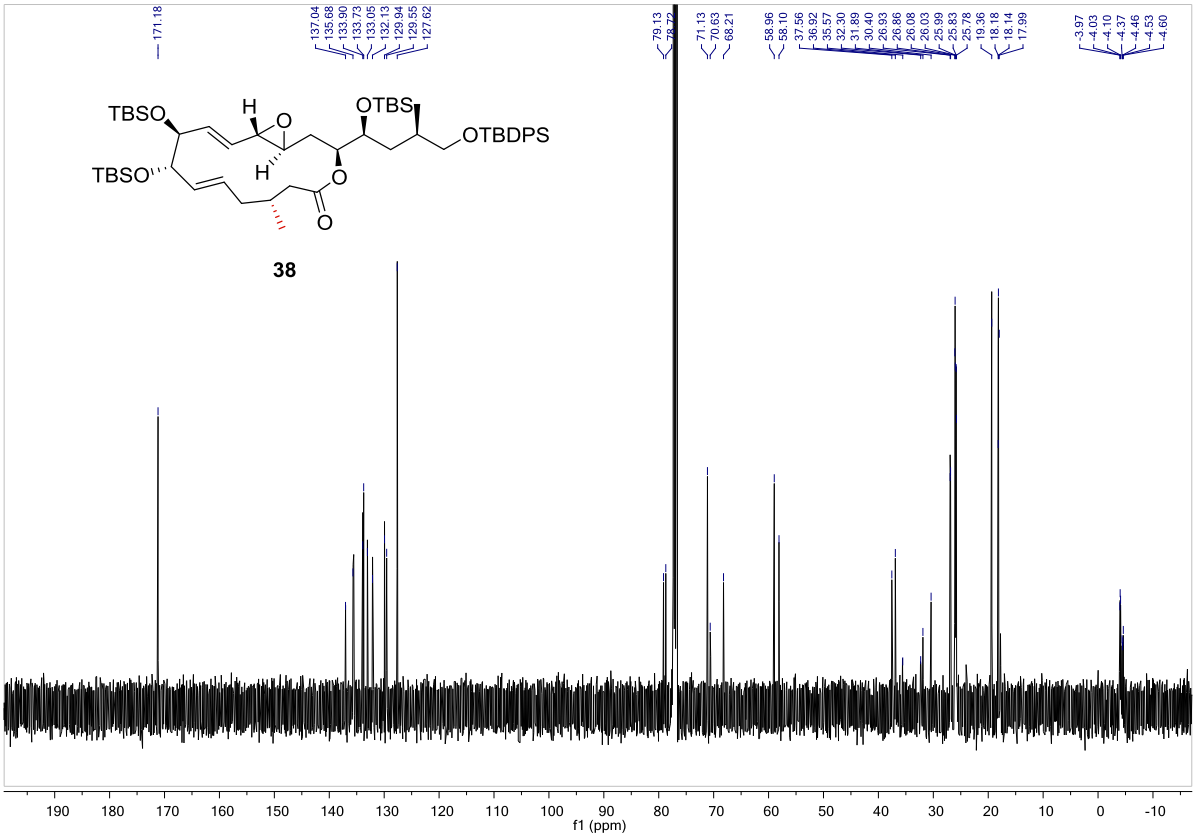

TBSO
OTBS
OH
O
36
f1 (ppm)

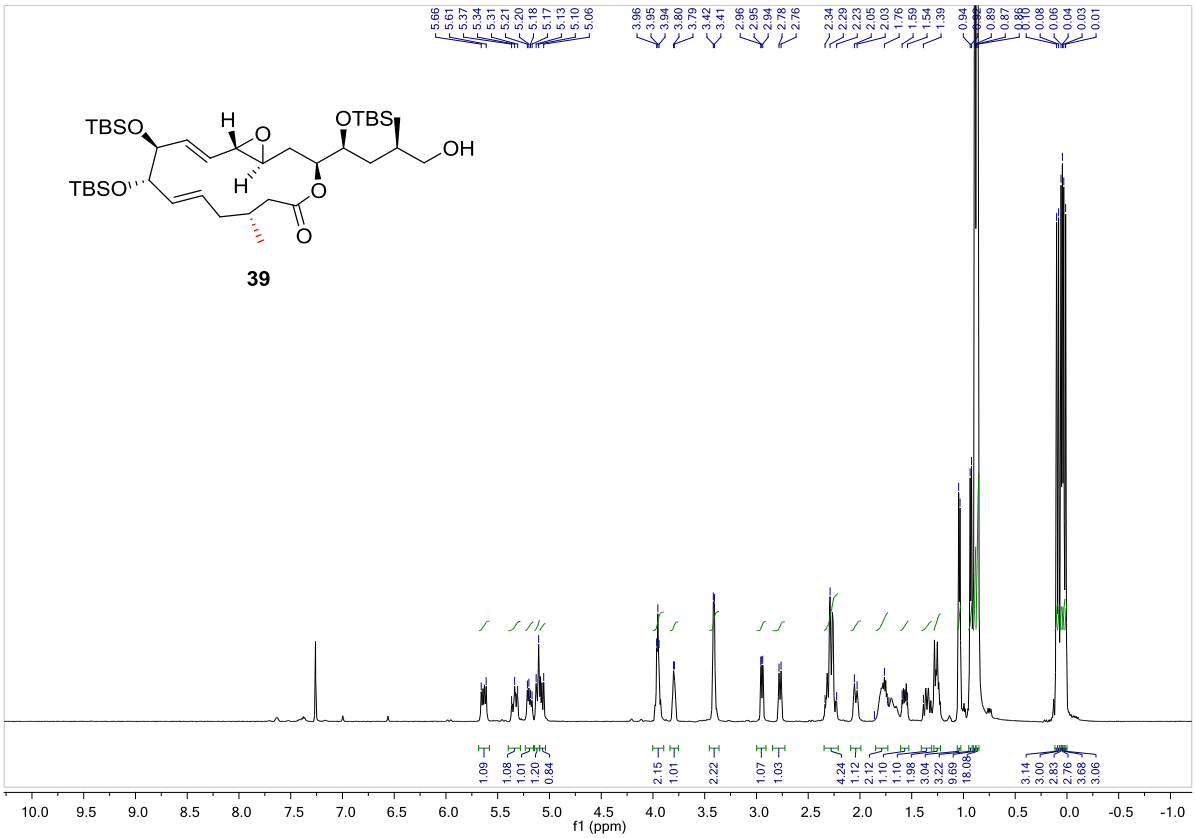

TBSO
OTBS
OH
O
36
f1 (ppm)

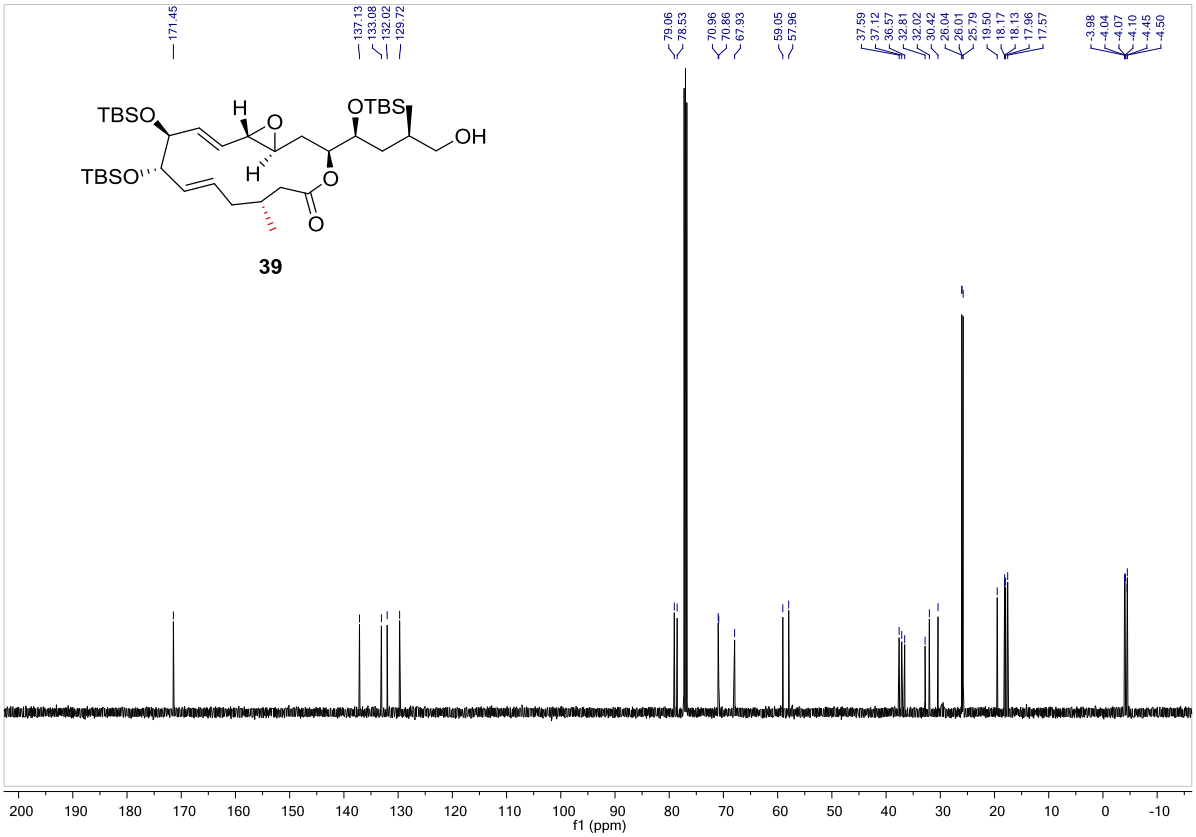

H
O
OTBS
OTBDPS
H
O
TBSO
OTBS
O
37
f1 (ppm)

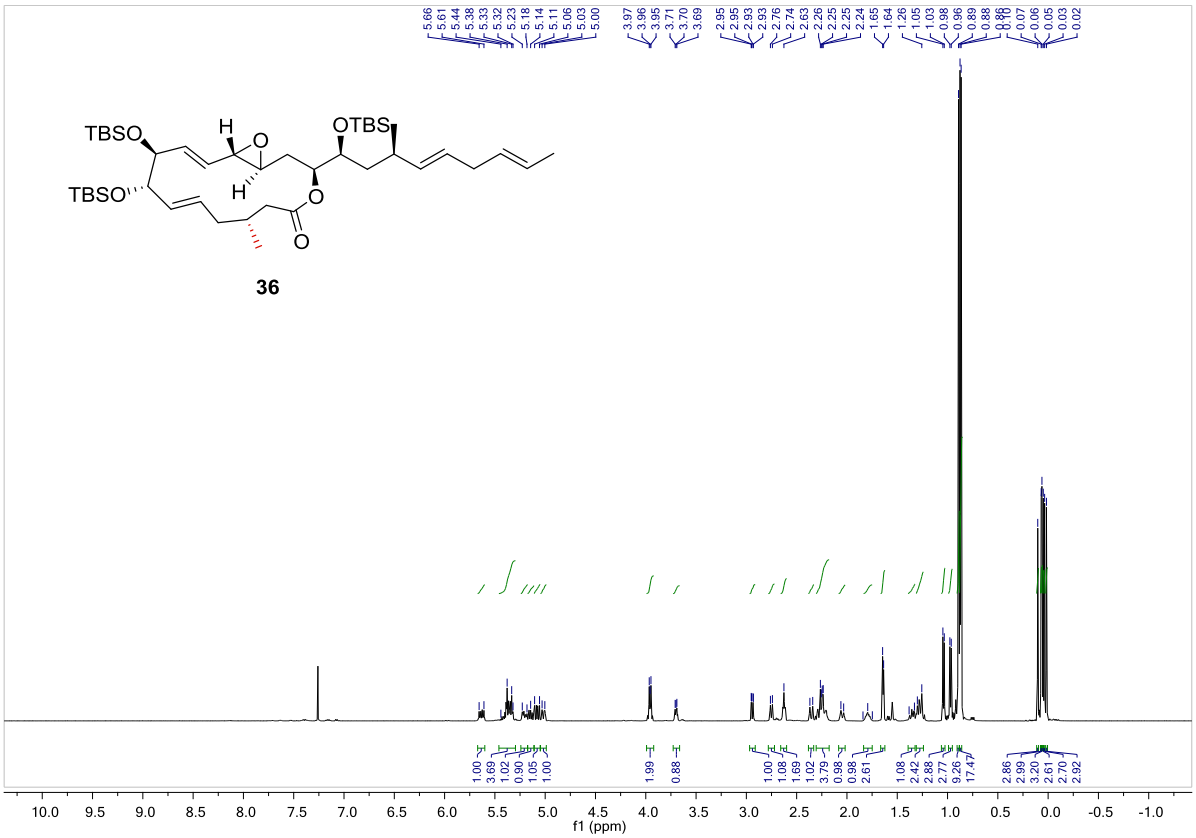

H
O
OTBS
OTBDPS
H
O
TBSO
OTBS
O
37
f1 (ppm)

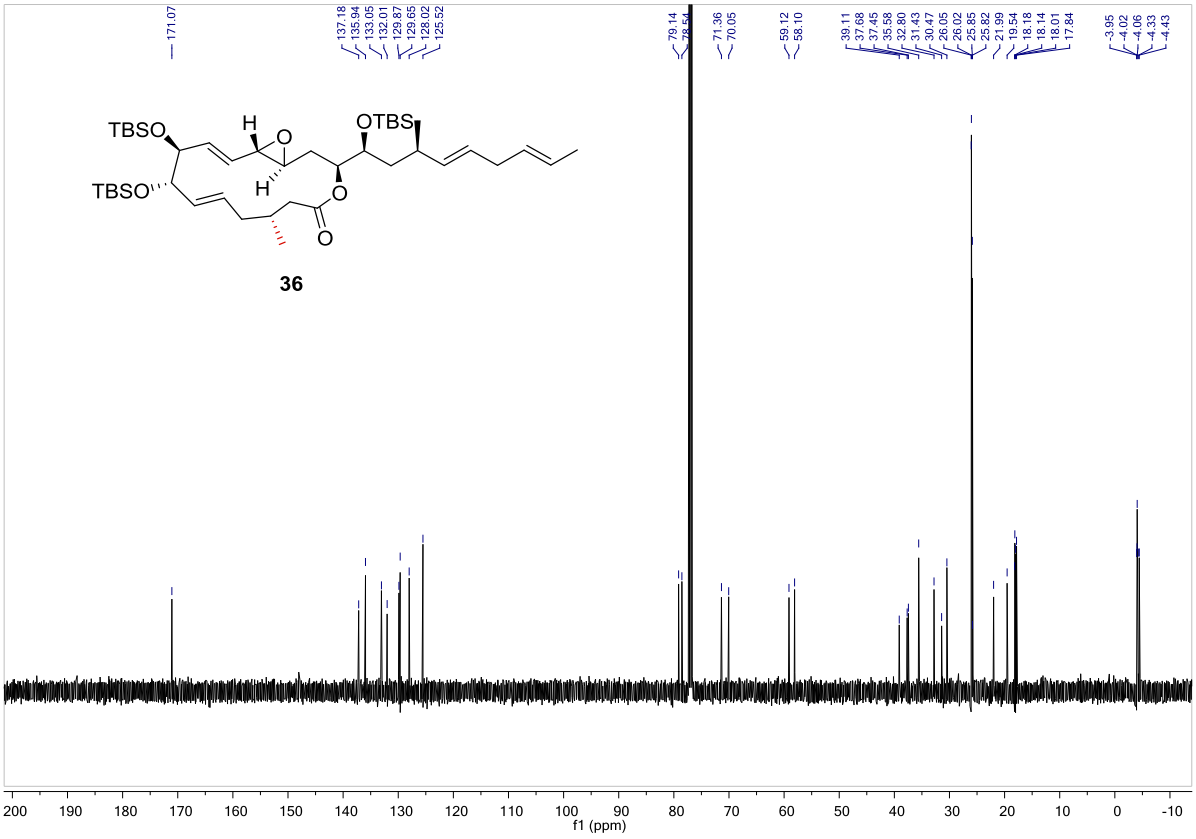

TBSO
H
O
OTBS
OTBDPS
TBSO
H
O
O
38
f1 (ppm)

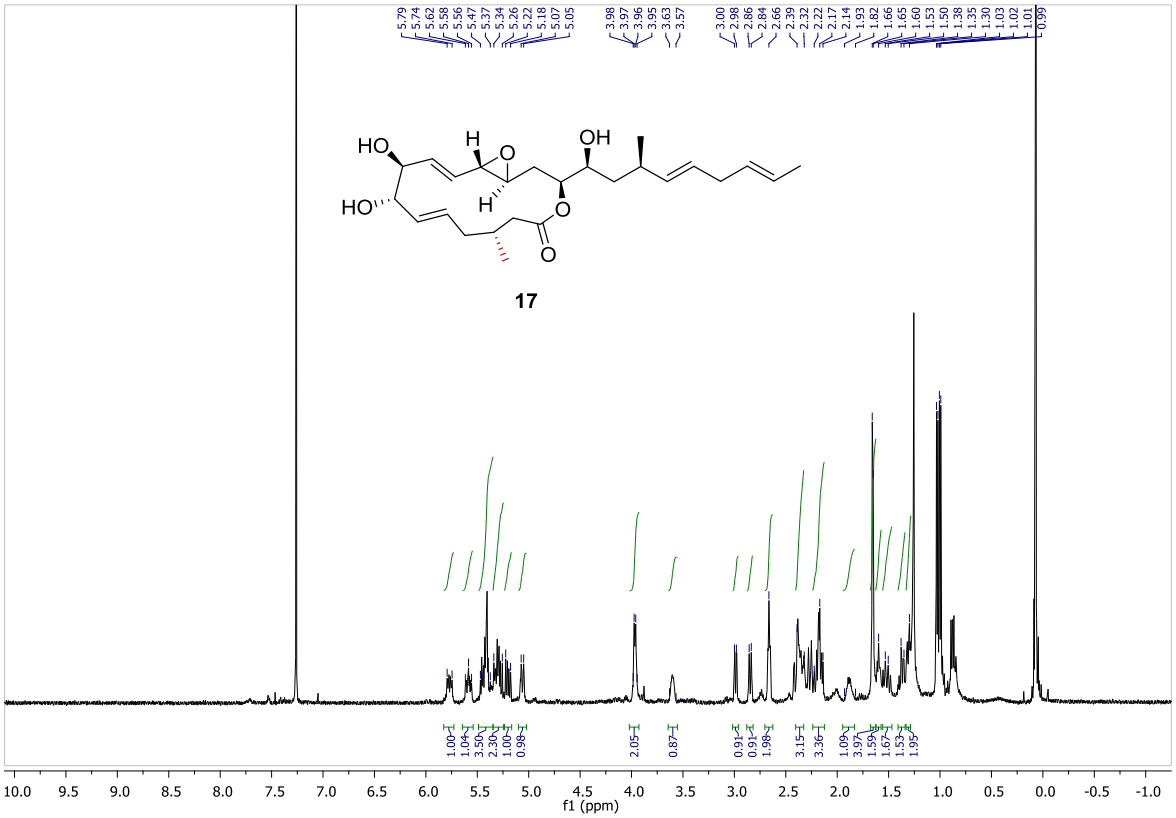

TBSO
H
O
OTBS
OTBDPS
TBSO
H
O
O
38
f1 (ppm)

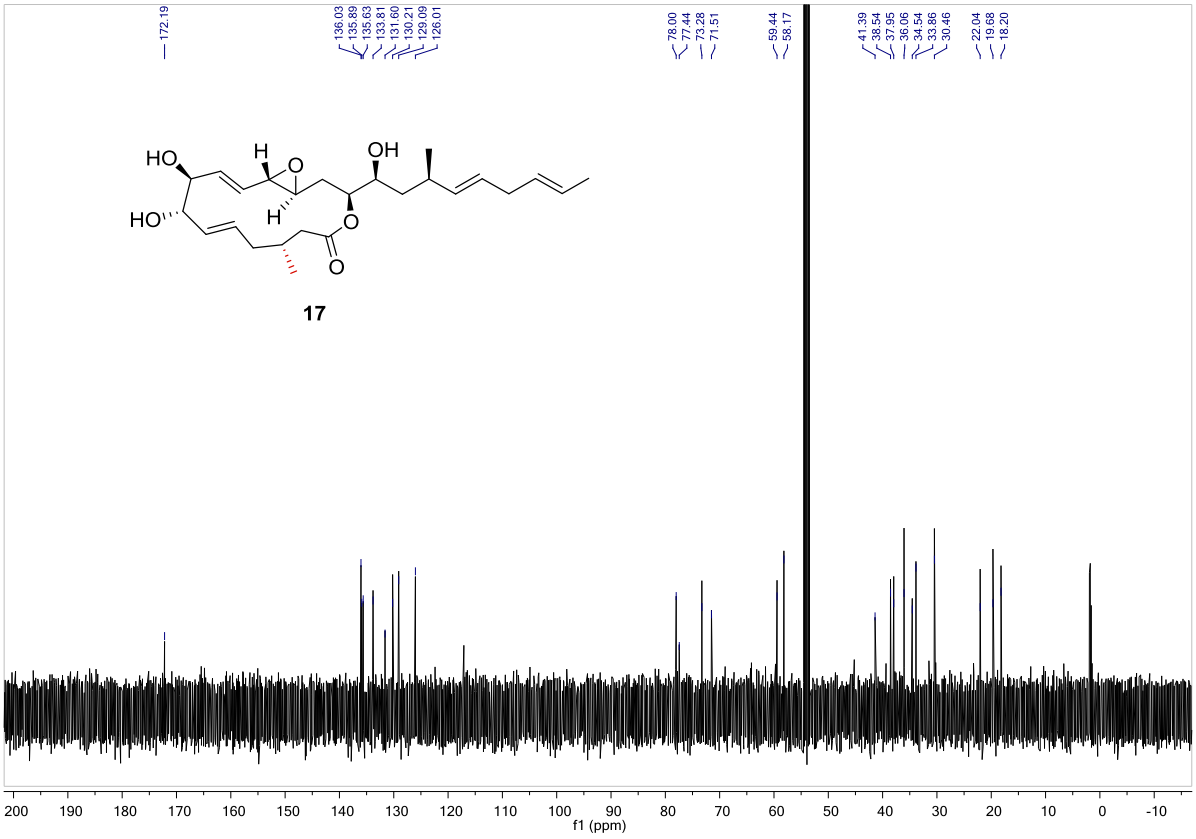

TBSO
H
O
OTBS
OH
TBSO
H
O
O
O
39
f1 (ppm)

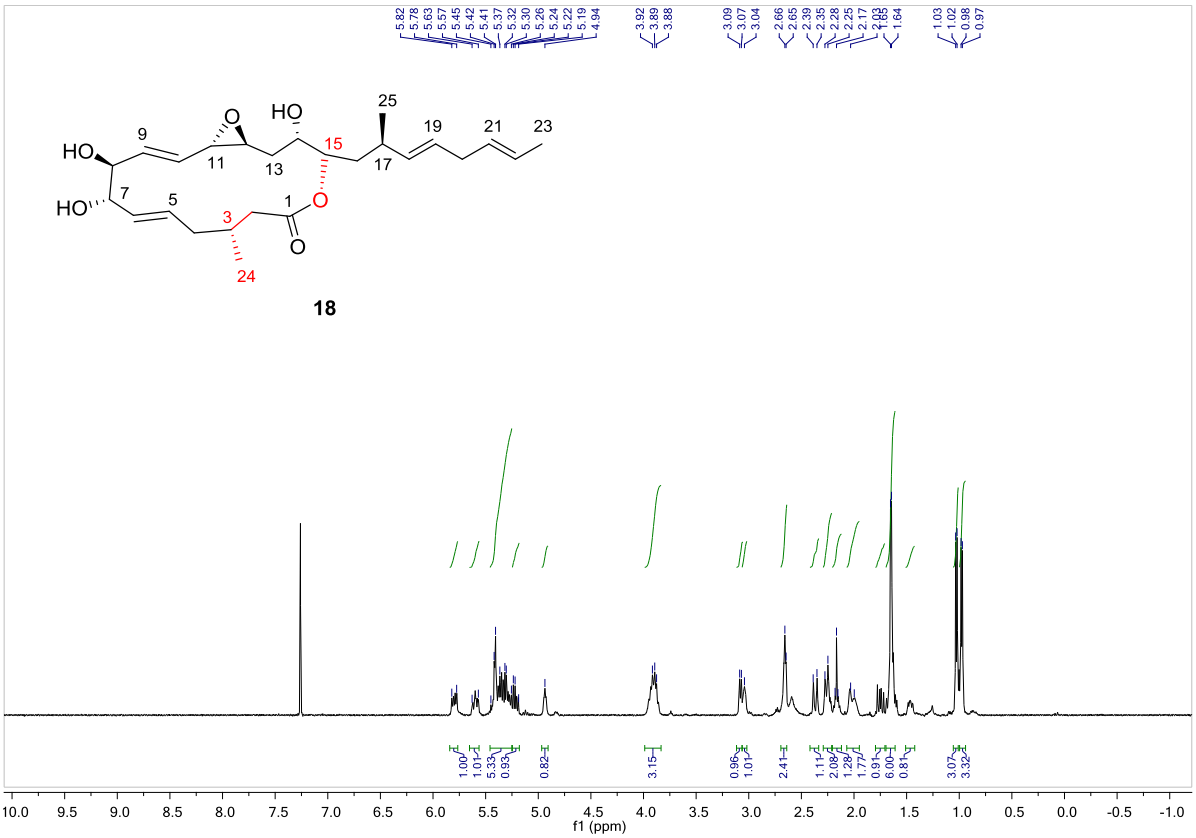

TBSO
H
O
OTBS
OH
TBSO
H
O
O
O
39
f1 (ppm)

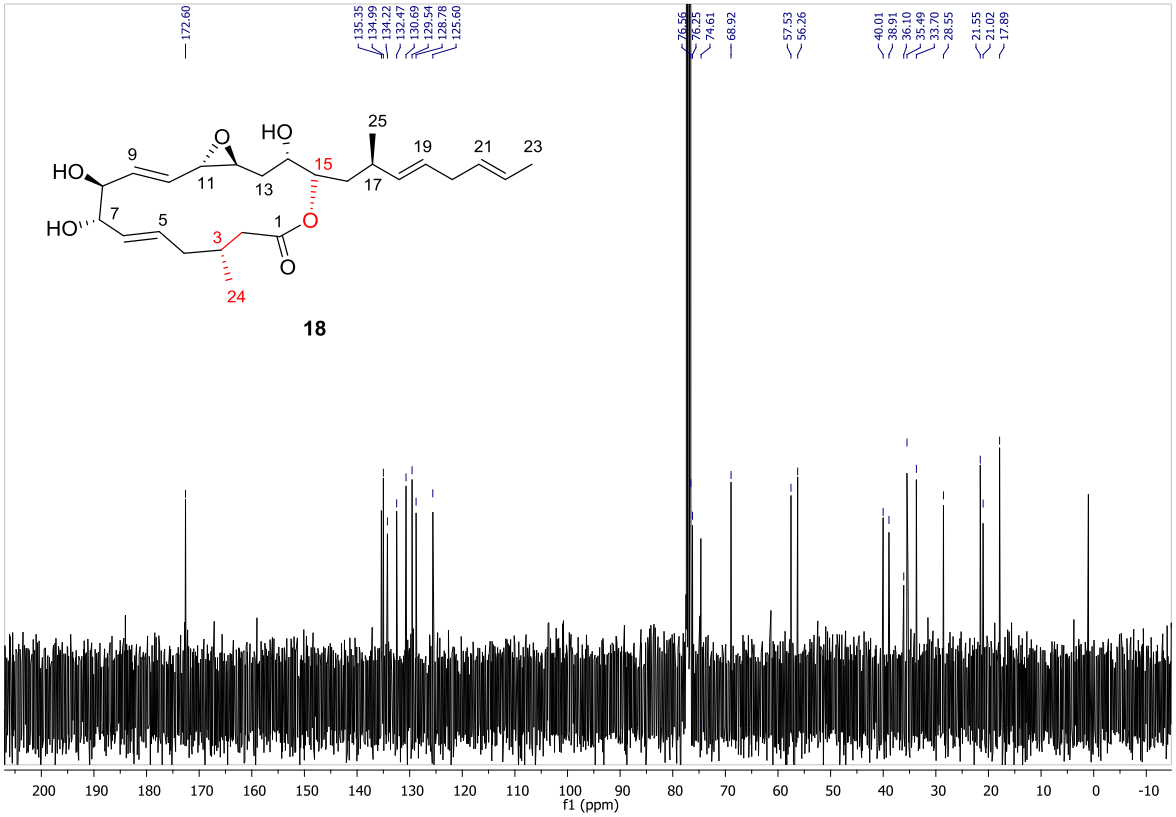

TBSO
H
O
OTBS
TBSO
H
O
O
36
f1 (ppm)

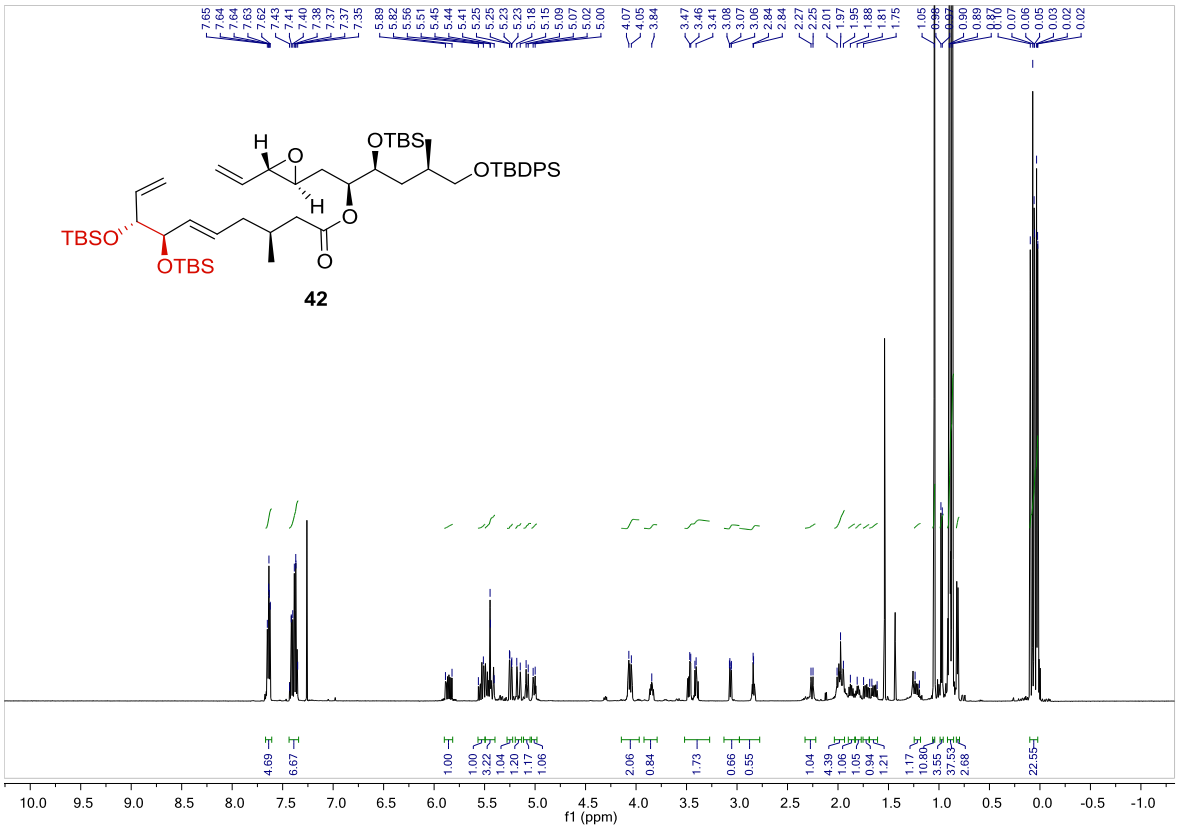

TBSO
H
O
OTBS
TBSO
H
O
O
36
f1 (ppm)

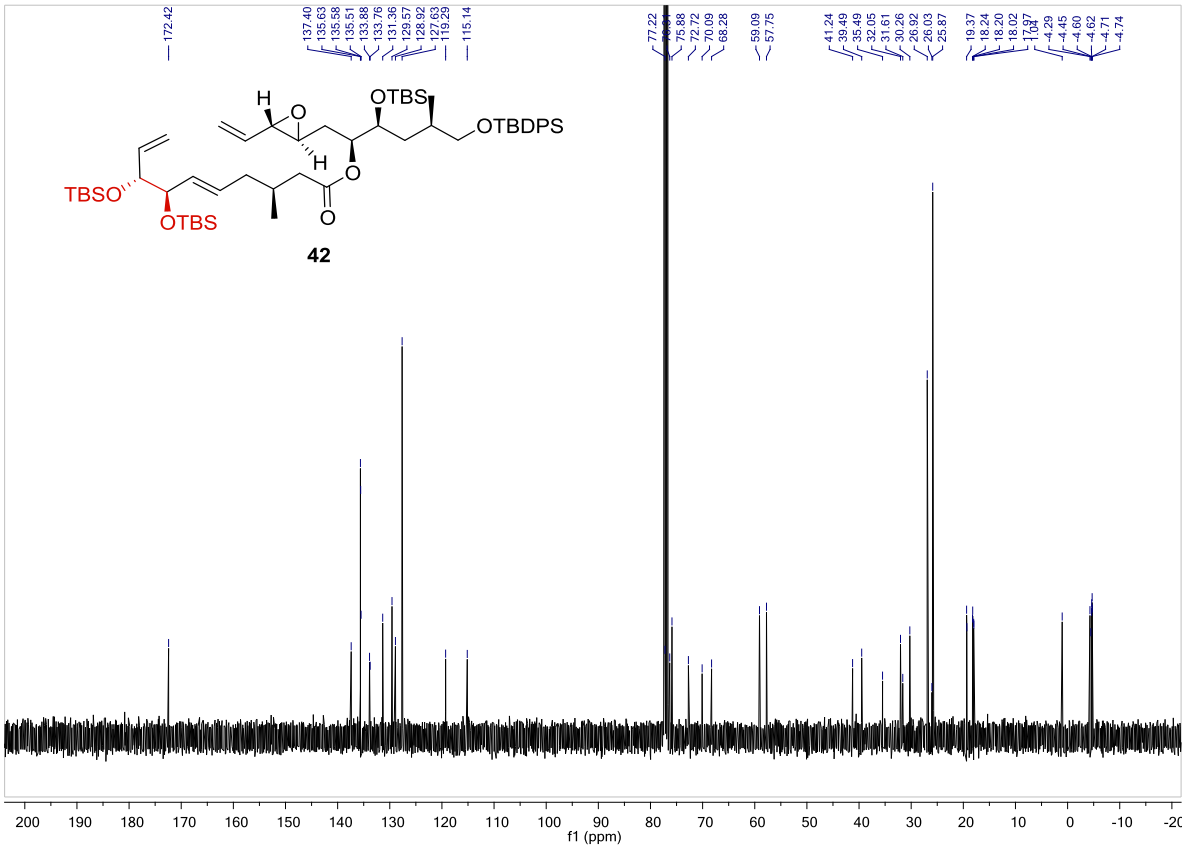

HO
H
O
OH
HO
H
O
O
17
f1 (ppm)

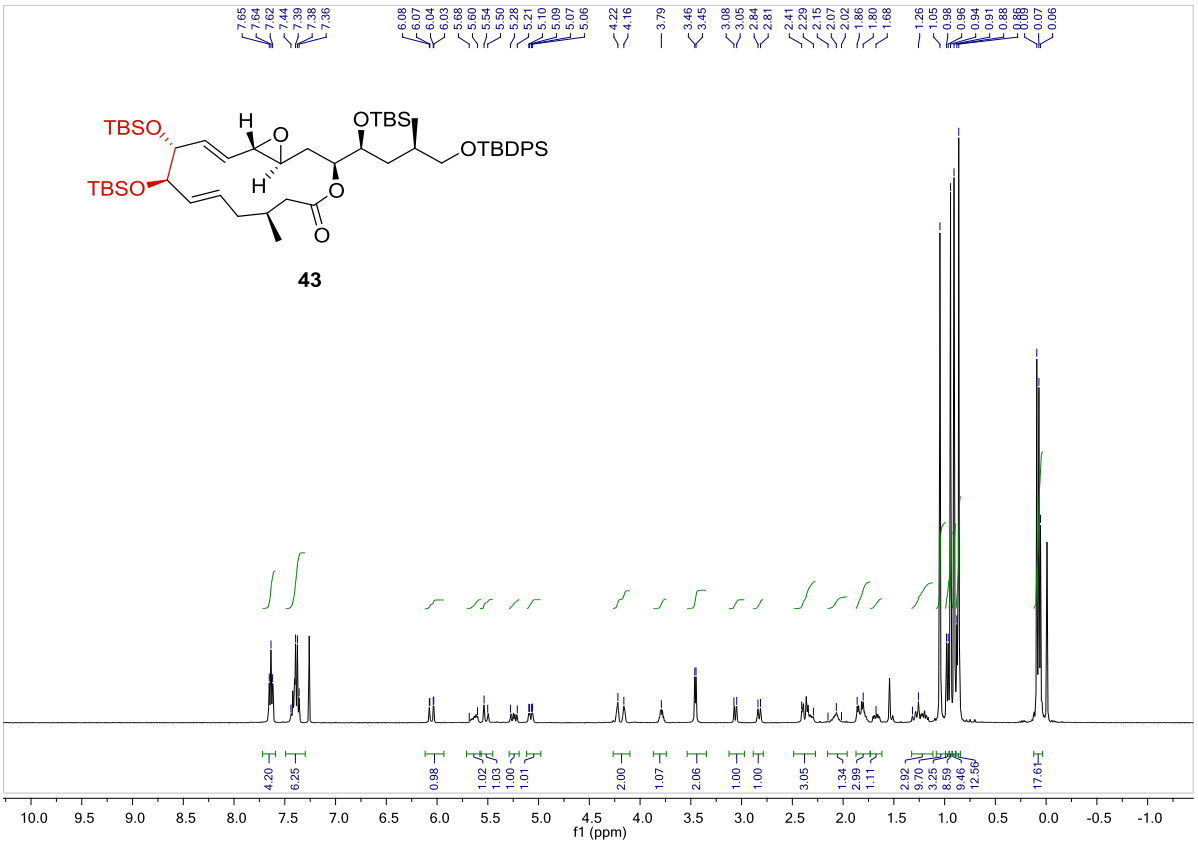

HO
H
O
OH
HO
H
O
O
17
f1 (ppm)

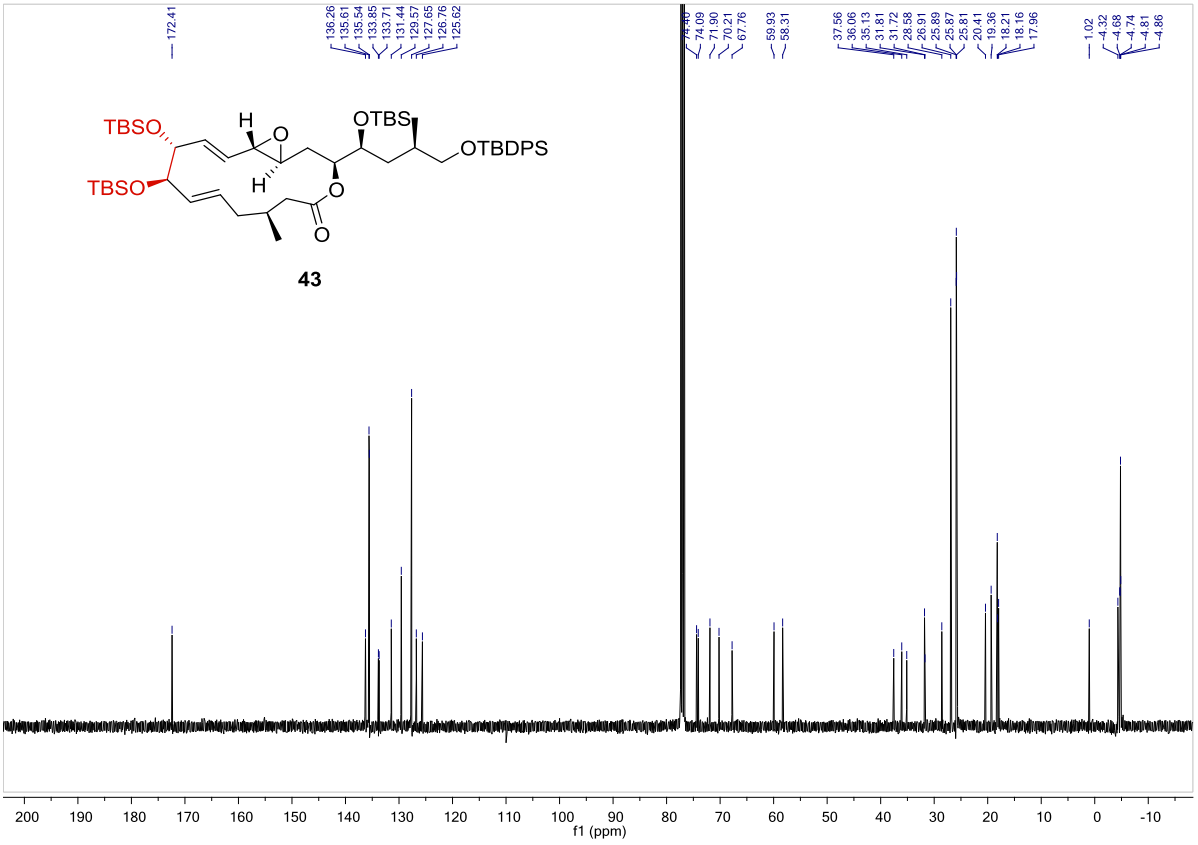

18
f1 (ppm)

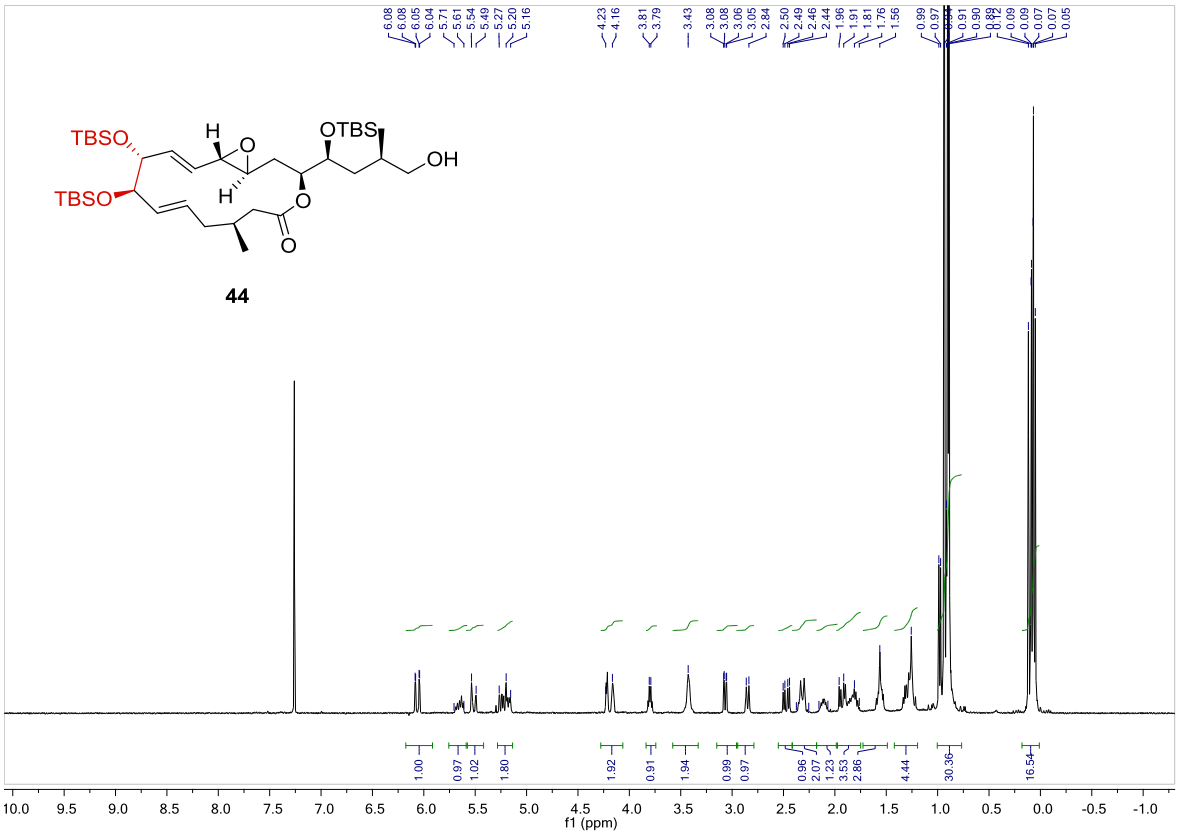

18
f1 (ppm)

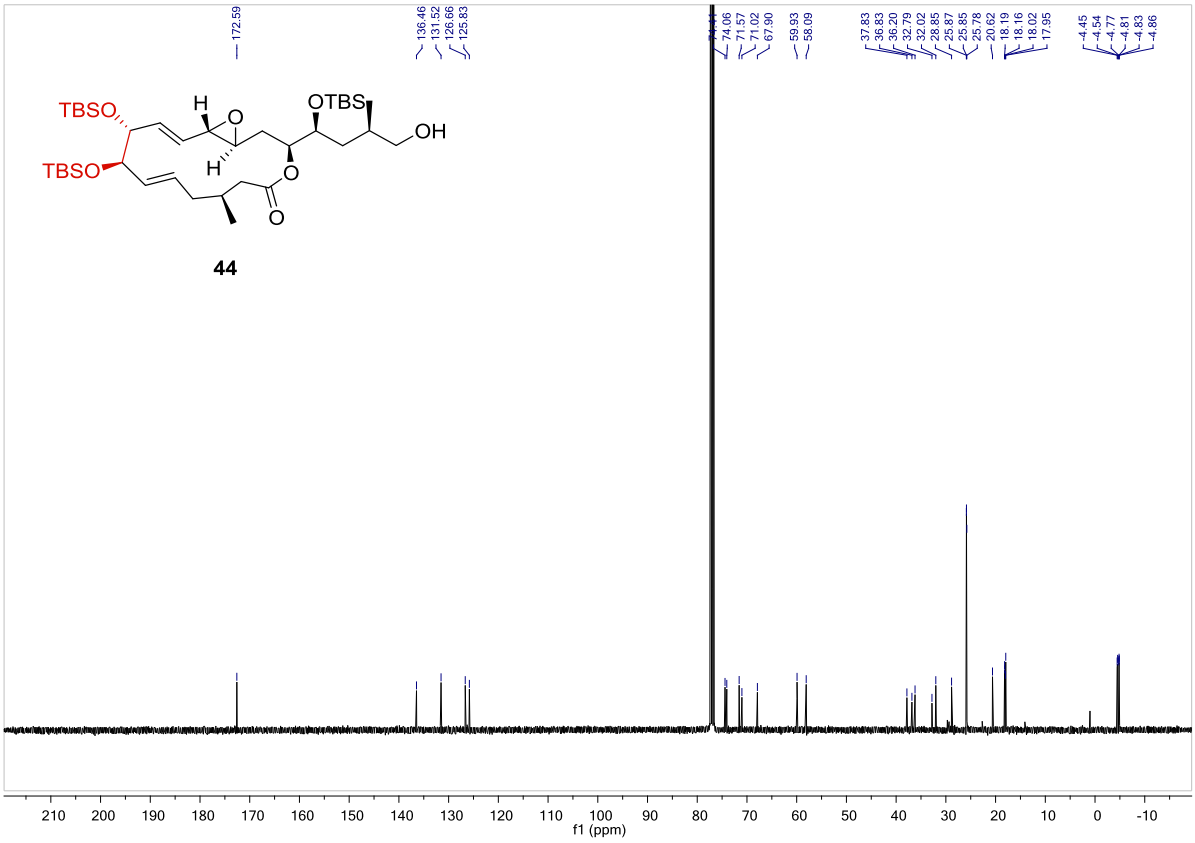

H
O
OTBS
OTBDPS
H
O
TBSO
OTBS
O
42
f1 (ppm)

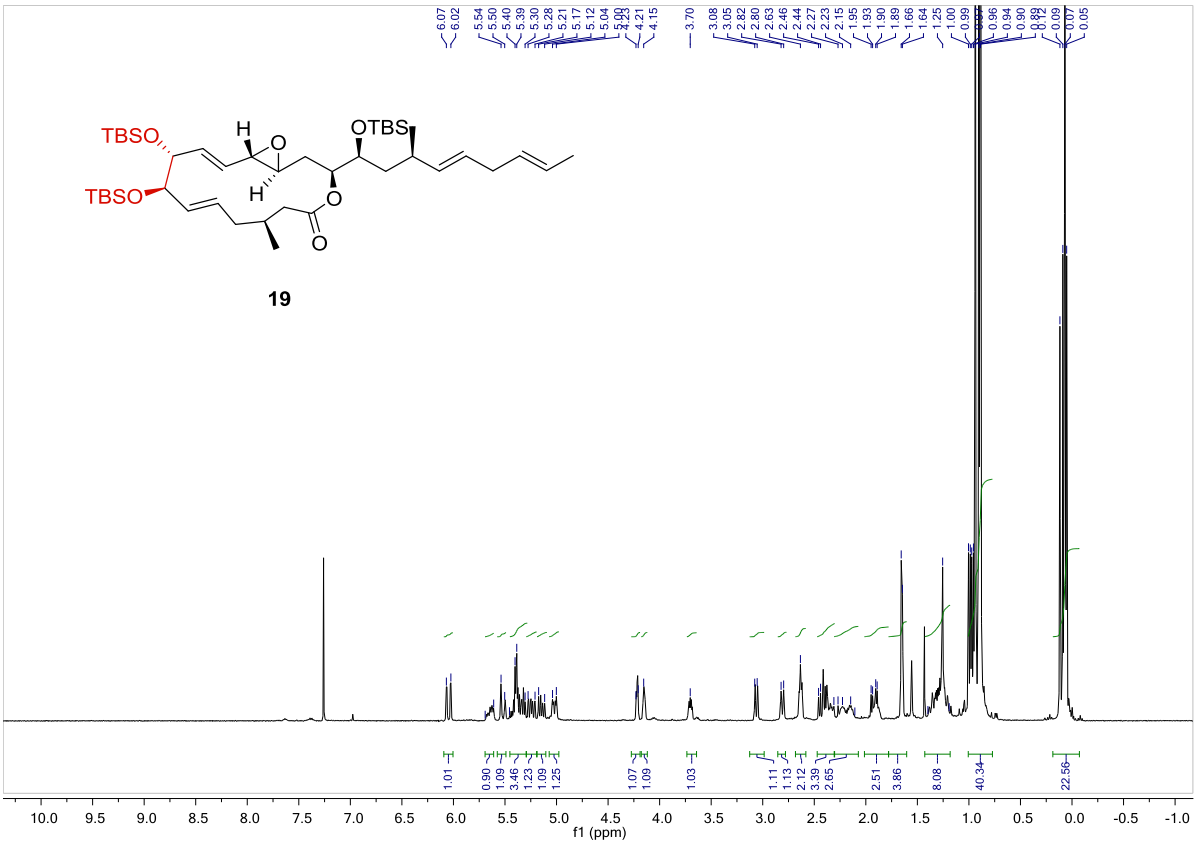

H
O
OTBS
OTBDPS
H
O
TBSO
OTBS
O
42
f1 (ppm)

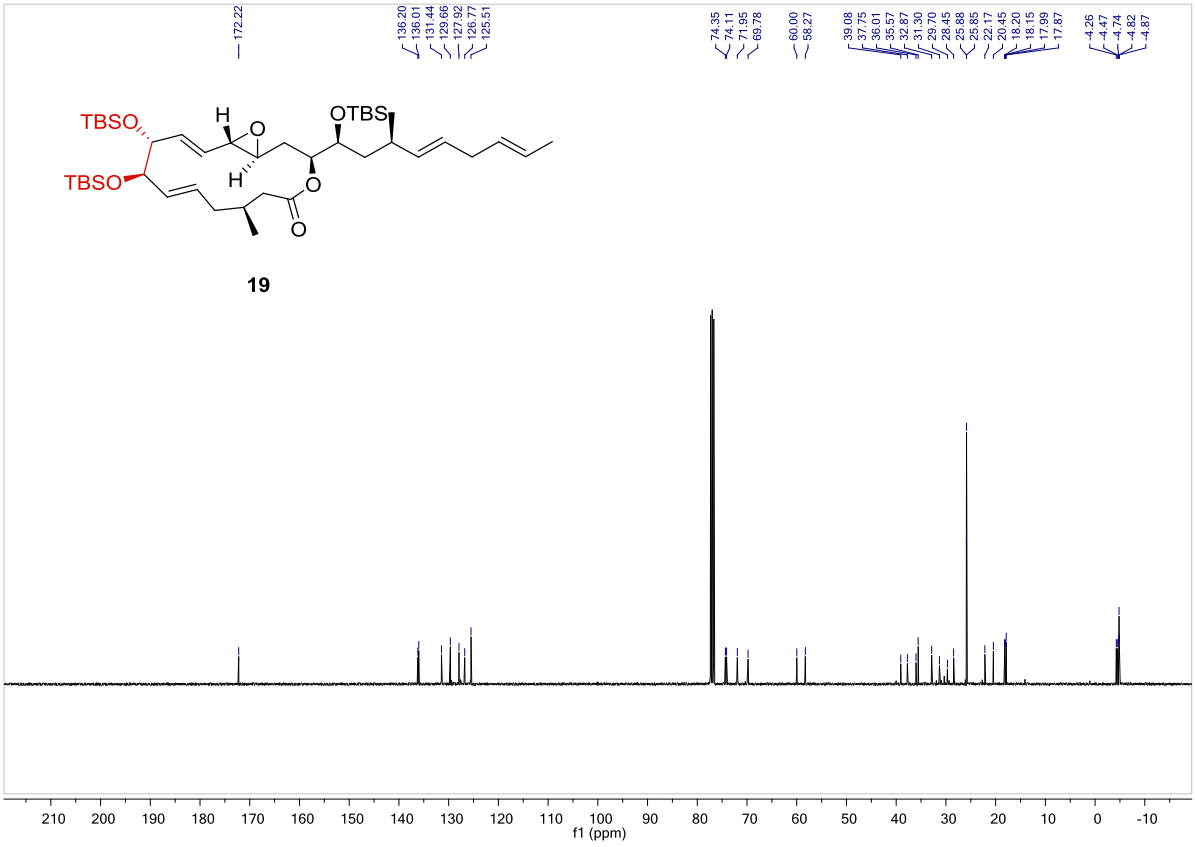

TBSO
TBSO
H
O
H
OTBS
OTBDPS
O
O
43
f1 (ppm)

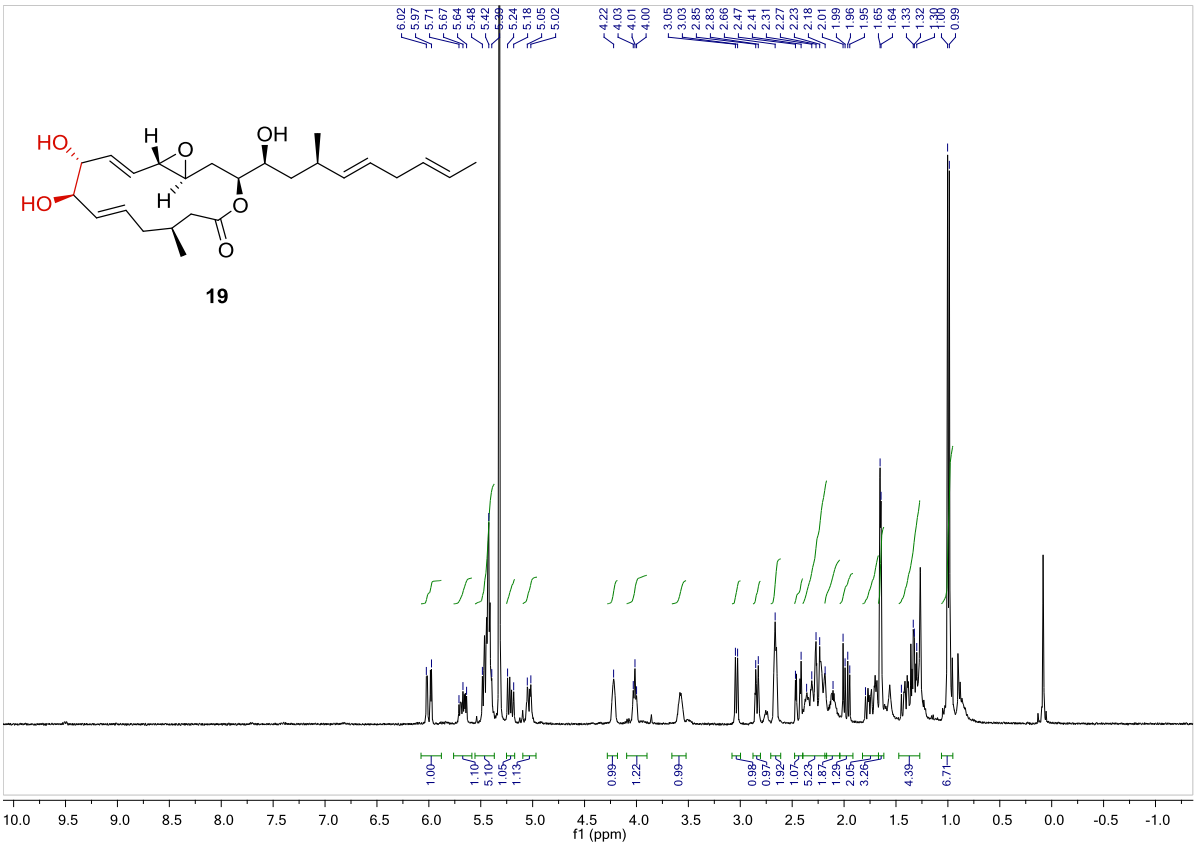

TBSO
TBSO
H
O
H
OTBS
OTBDPS
O
O
43
f1 (ppm)

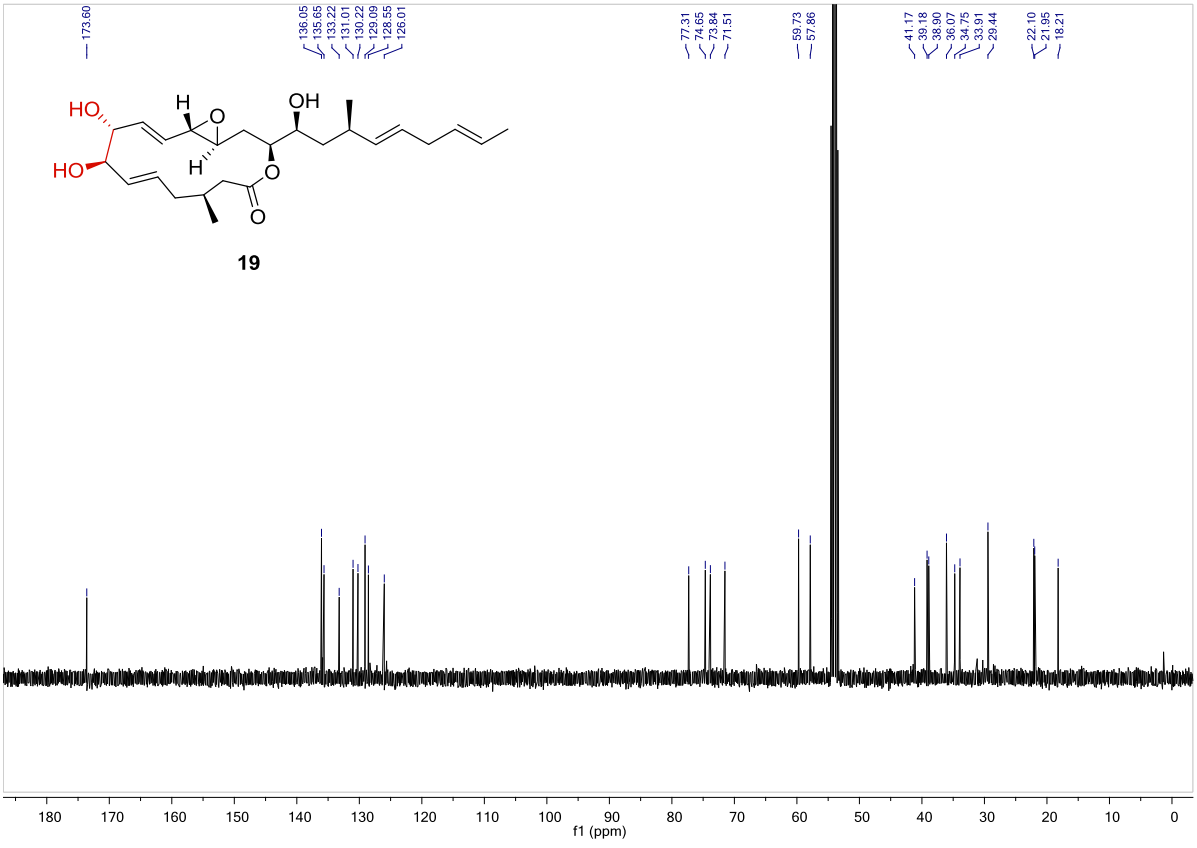

TBSO
TBSO
H
O
OTBS
OH
H
O
O
44
f1 (ppm)

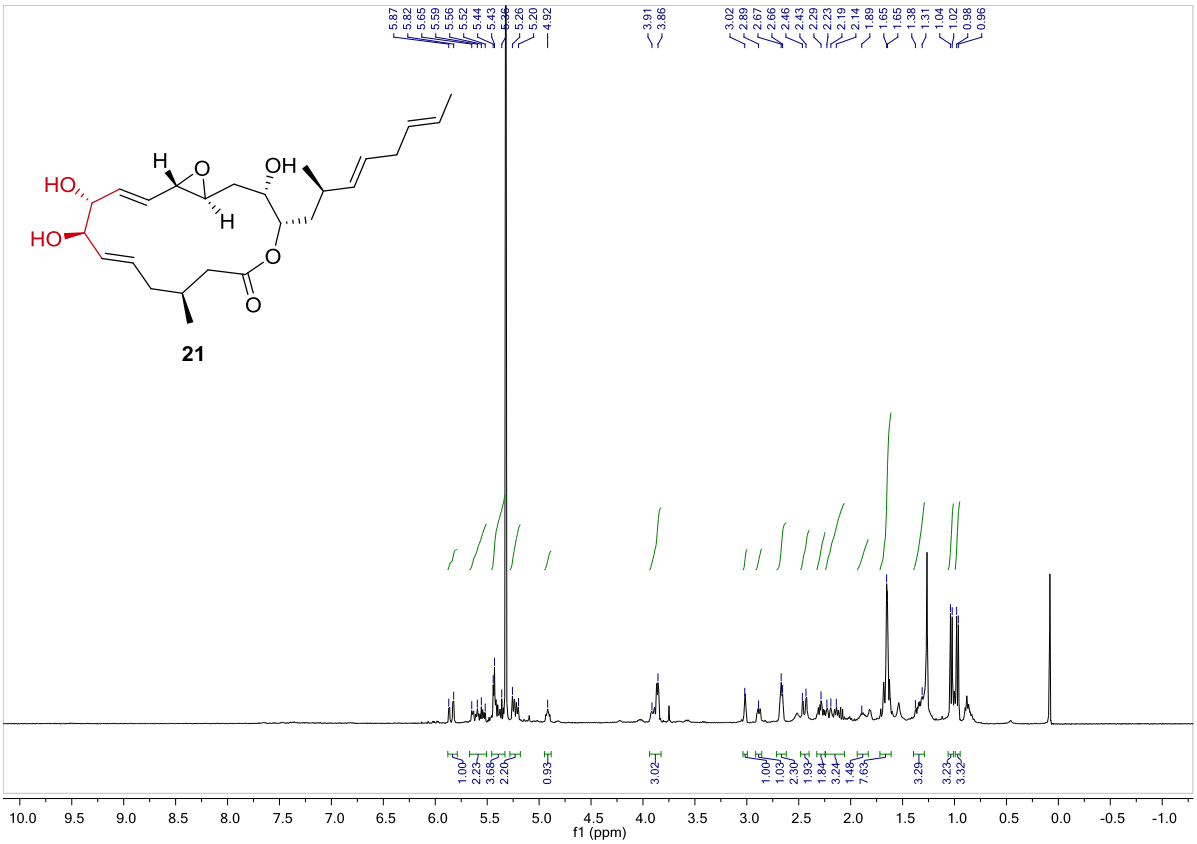

TBSO
TBSO
H
O
OTBS
OH
H
O
O
44
f1 (ppm)

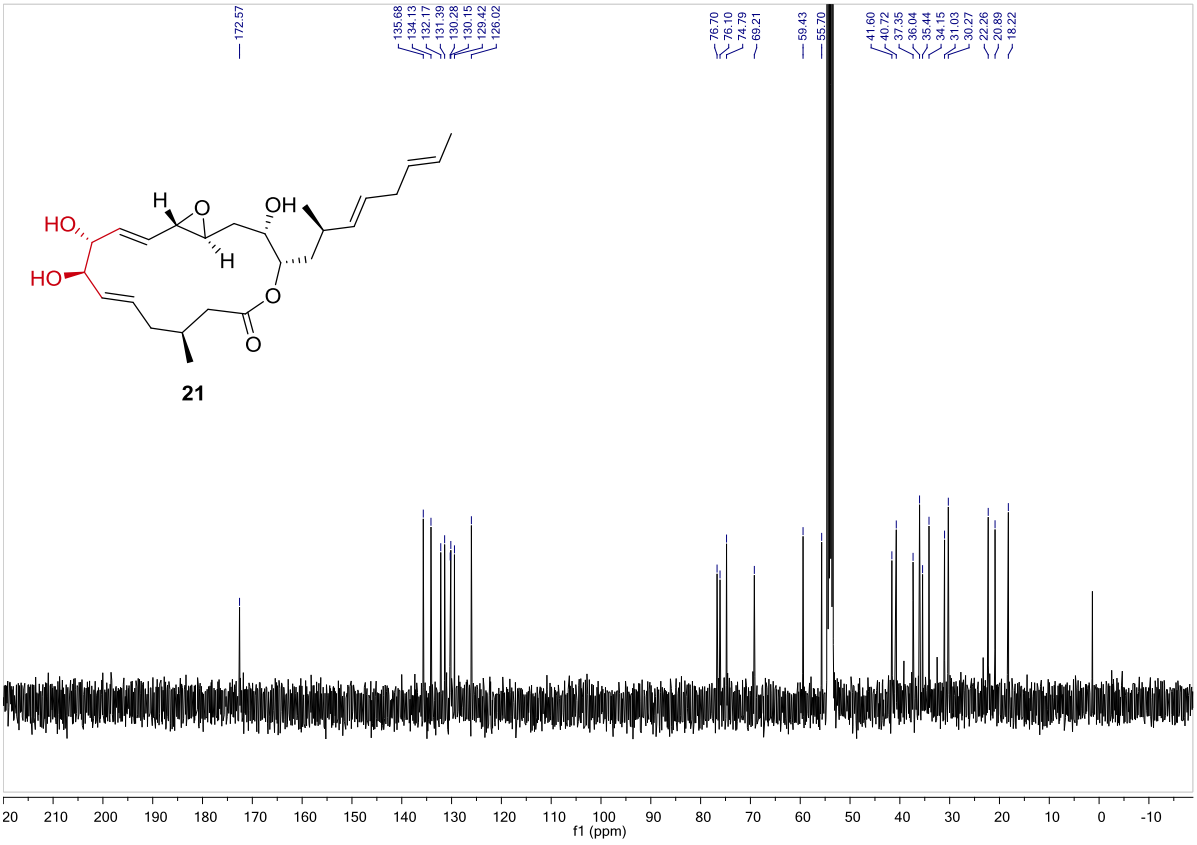

TBSO
TBSO
H
O
OTBS
H
O
O
19
f1 (ppm)

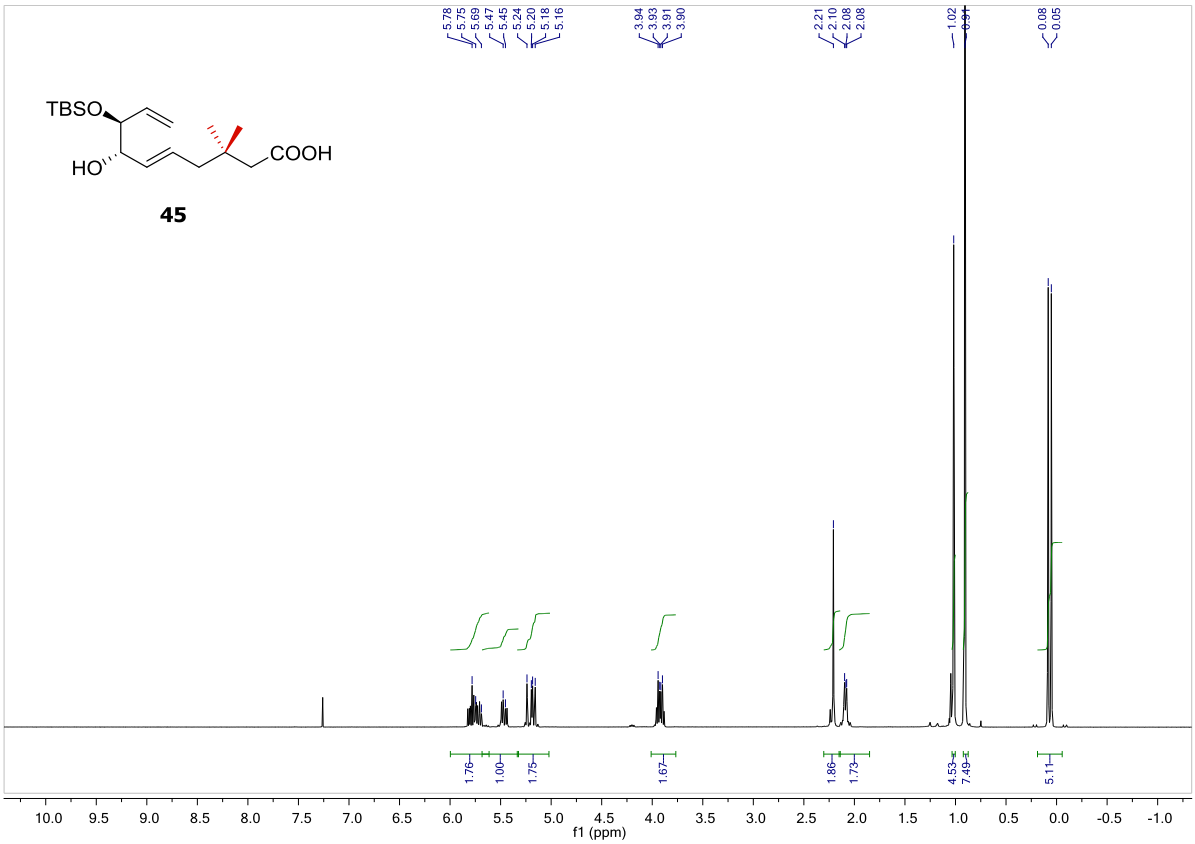

TBSO
TBSO
H
O
OTBS
H
O
O
19
f1 (ppm)

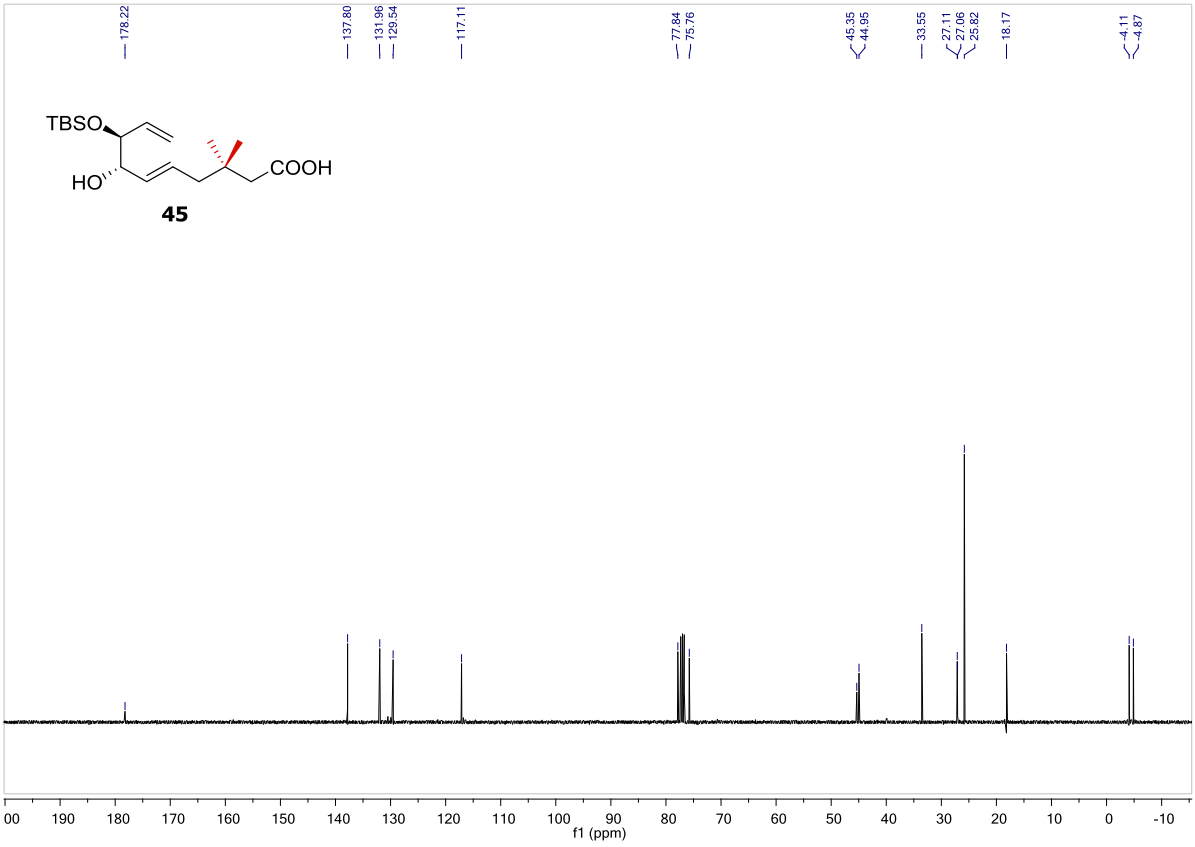

HO
HO
H
O
OH
H
O
O
O
19
6.02
5.97
5.71
5.67
5.64
5.48
5.42
5.39
5.24
5.18
5.05
5.02
4.22
4.03
4.01
4.00
3.05
3.03
2.85
2.83
2.66
2.47
2.41
2.31
2.27
2.23
2.18
2.01
1.99
1.96
1.95
1.65
1.64
1.33
1.32
0.99
1.00
1.10
5.10
1.05
1.13
0.99
1.22
0.99
0.98
0.97
1.92
1.07
5.23
1.87
1.29
2.05
3.26
4.39
6.71
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

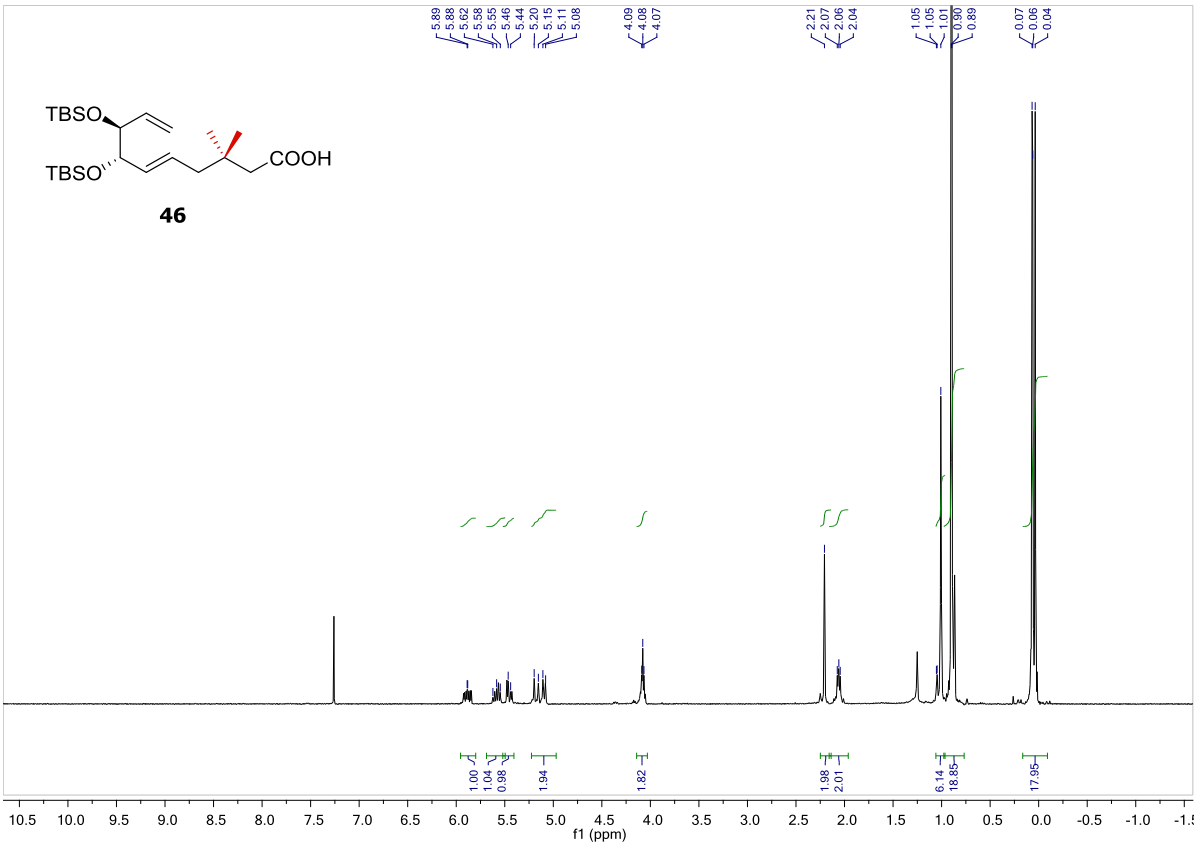

HO
HO
H
O
OH
H
O
O
O
19
173.60
136.05
135.65
133.22
131.01
130.22
129.09
128.55
126.01
77.31
74.65
73.84
71.51
59.73
57.86
41.17
39.18
38.90
36.07
34.75
33.91
29.44
22.10
21.95
18.21
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

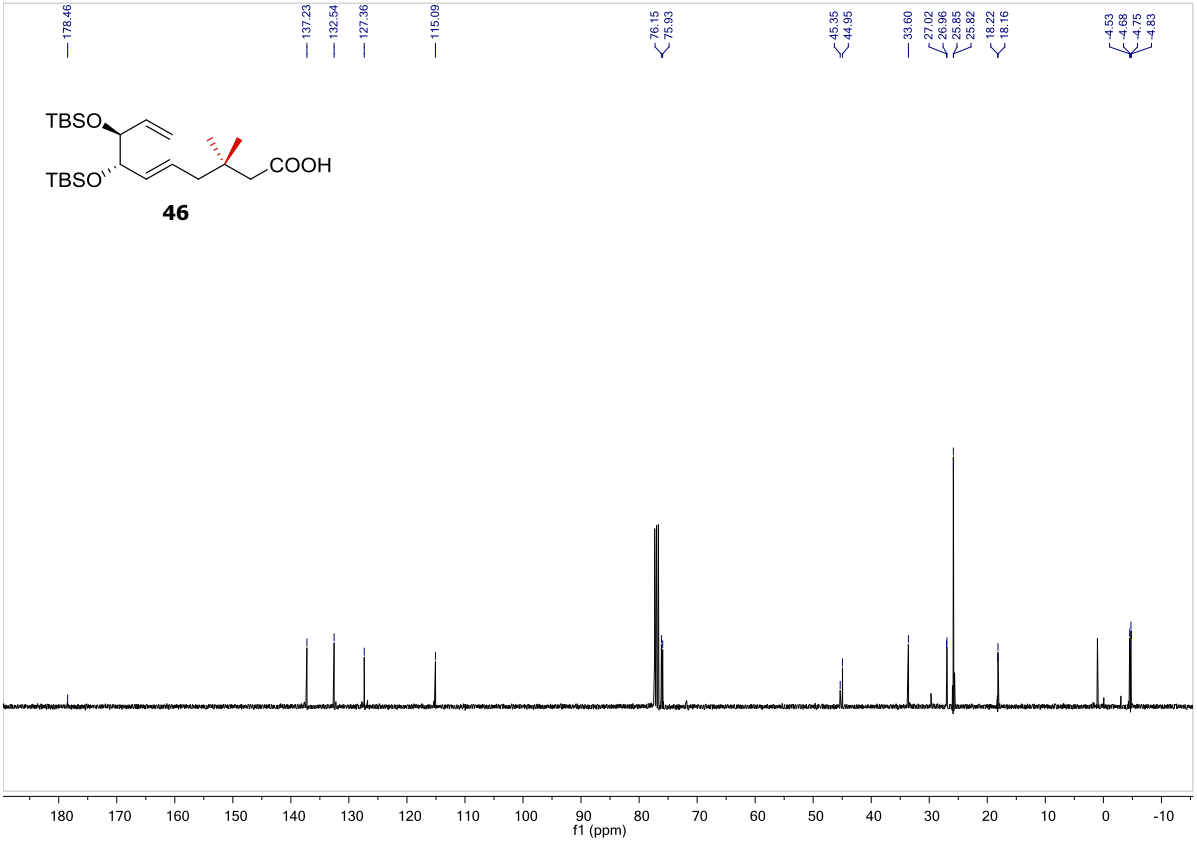

HO
HO
H
O
OH
H
O
O
21
f1 (ppm)

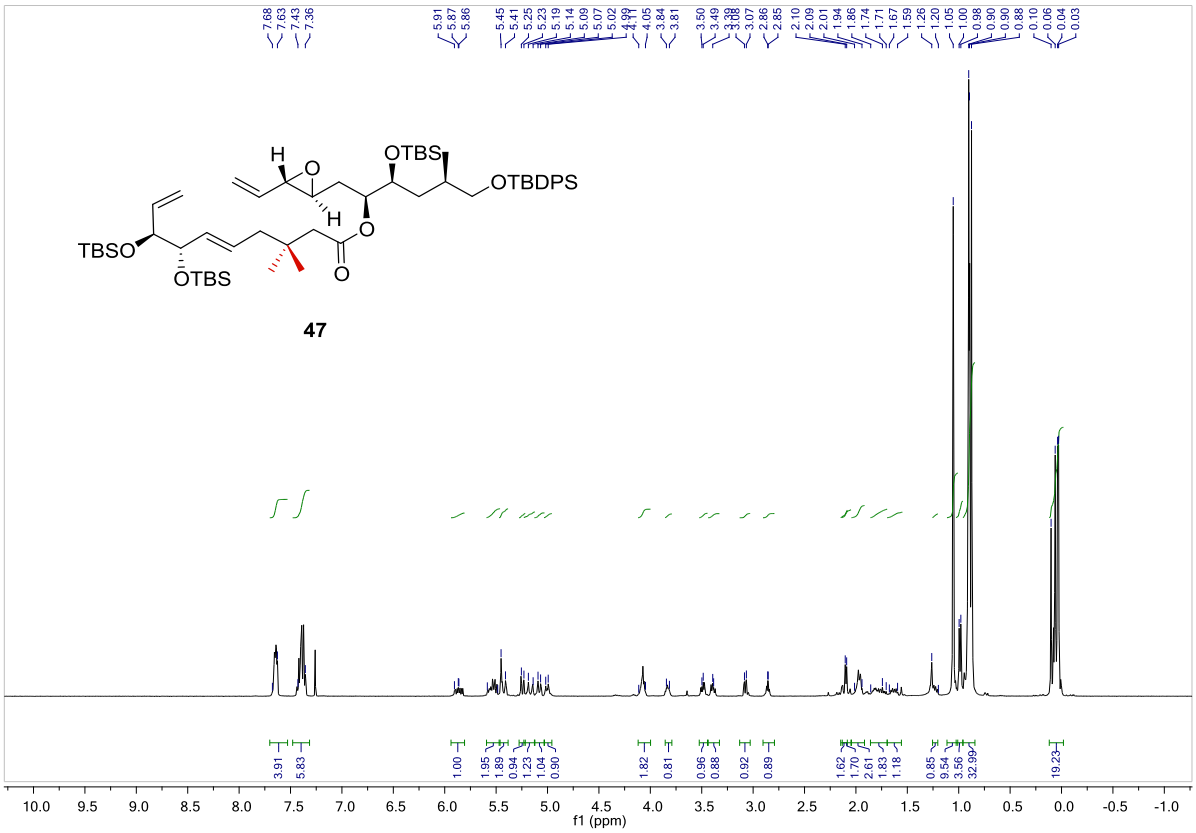

HO
HO
H
O
OH
H
O
O
21
f1 (ppm)


TBSO
HO
COOH
45
5.78
5.75
5.69
5.47
5.45
5.24
5.20
5.18
5.16
3.94
3.93
3.91
3.90
2.21
2.10
2.08
2.08
1.02
0.91
0.08
0.05
1.76
1.00
1.75
1.67
1.86
1.73
4.53
7.49
5.11
f1 (ppm)

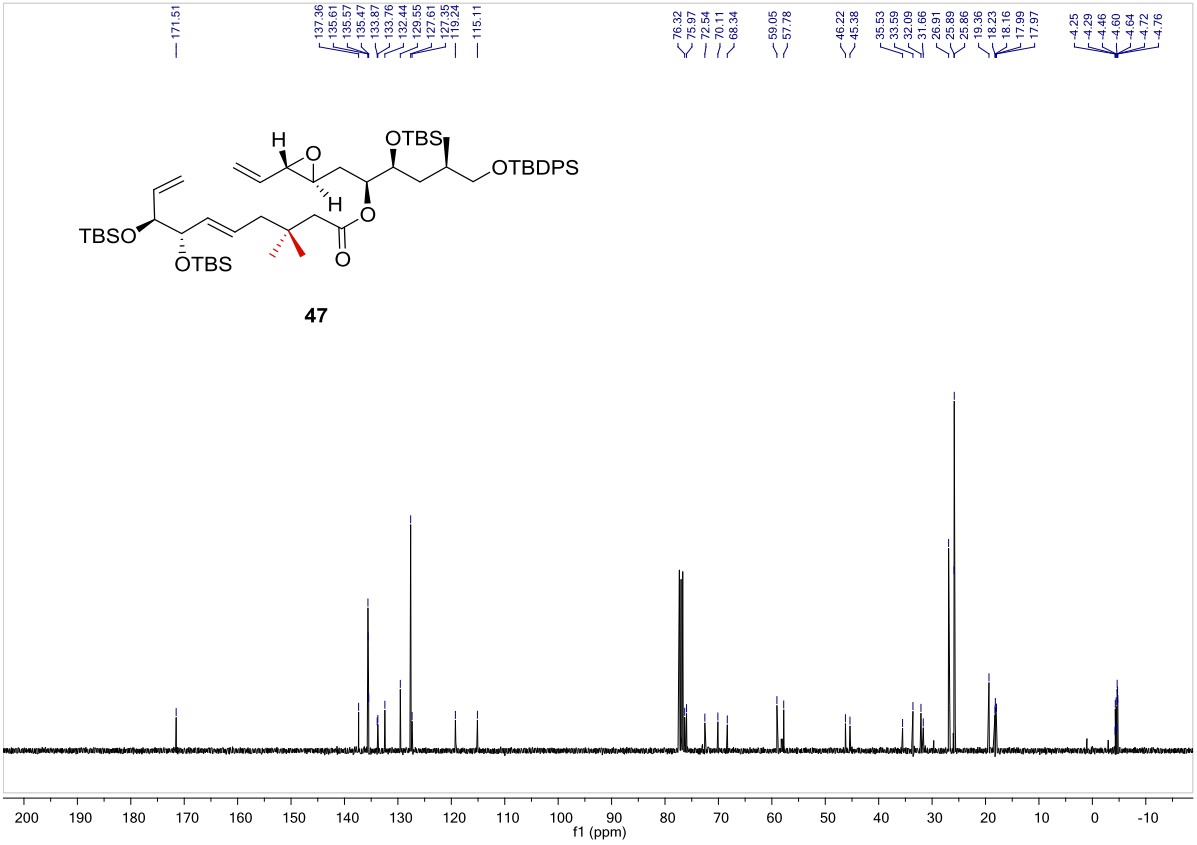

TBSO
HO
COOH
45
178.22
137.80
131.96
129.54
117.11
77.84
75.76
45.35
44.95
33.55
27.11
27.06
25.82
18.17
-4.11
-4.87
f1 (ppm)


TBSO
TBSO
COOH
46
5.89
5.88
5.62
5.58
5.55
5.46
5.44
5.20
5.15
5.11
5.08
4.09
4.08
4.07
2.21
2.07
2.06
2.04
1.05
1.05
1.01
0.90
0.89
0.07
0.06
0.04
1.00
1.04
0.98
1.94
1.82
1.98
2.01
6.14
18.85
17.95
f1 (ppm)

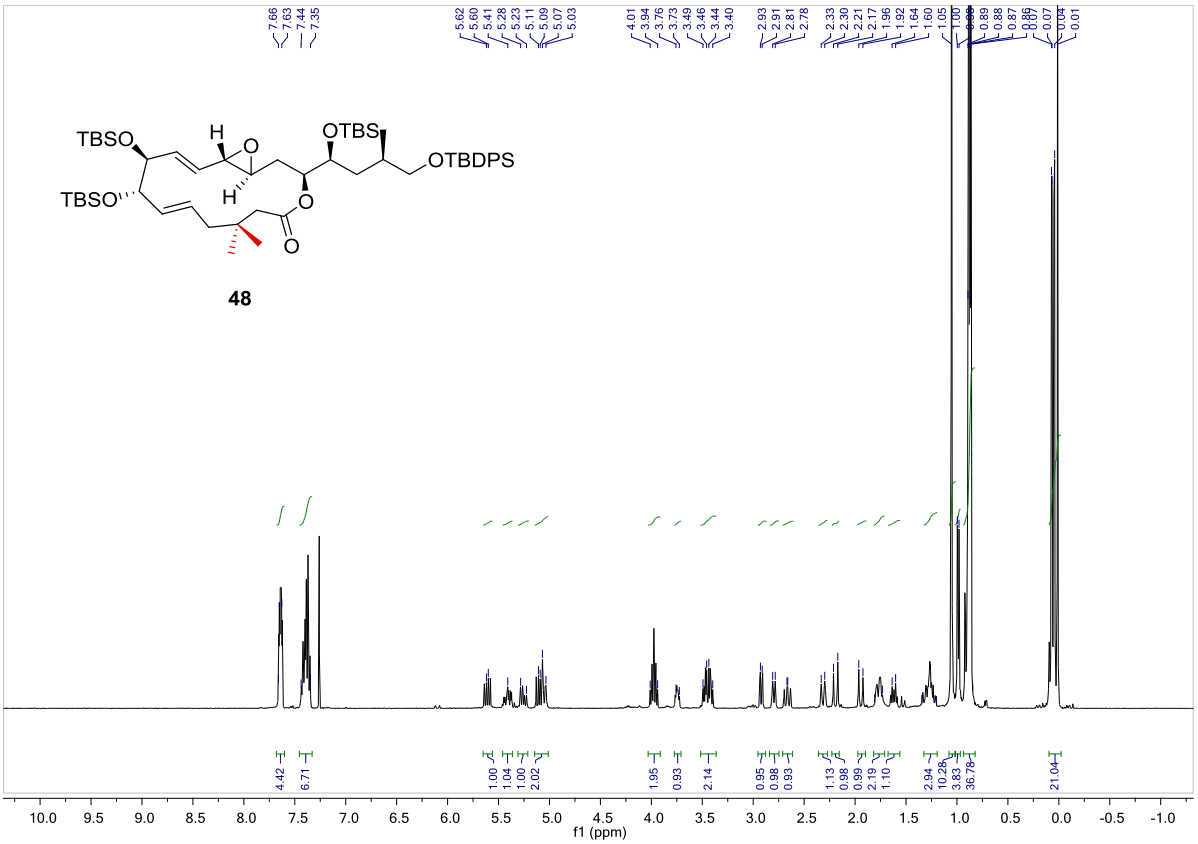

TBSO
TBSO
COOH
46
178.46
137.23
132.54
127.36
115.09
76.15
75.93
45.35
44.95
33.60
27.02
26.96
25.85
25.82
18.22
18.16
-4.53
-4.68
-4.75
-4.83
f1 (ppm)

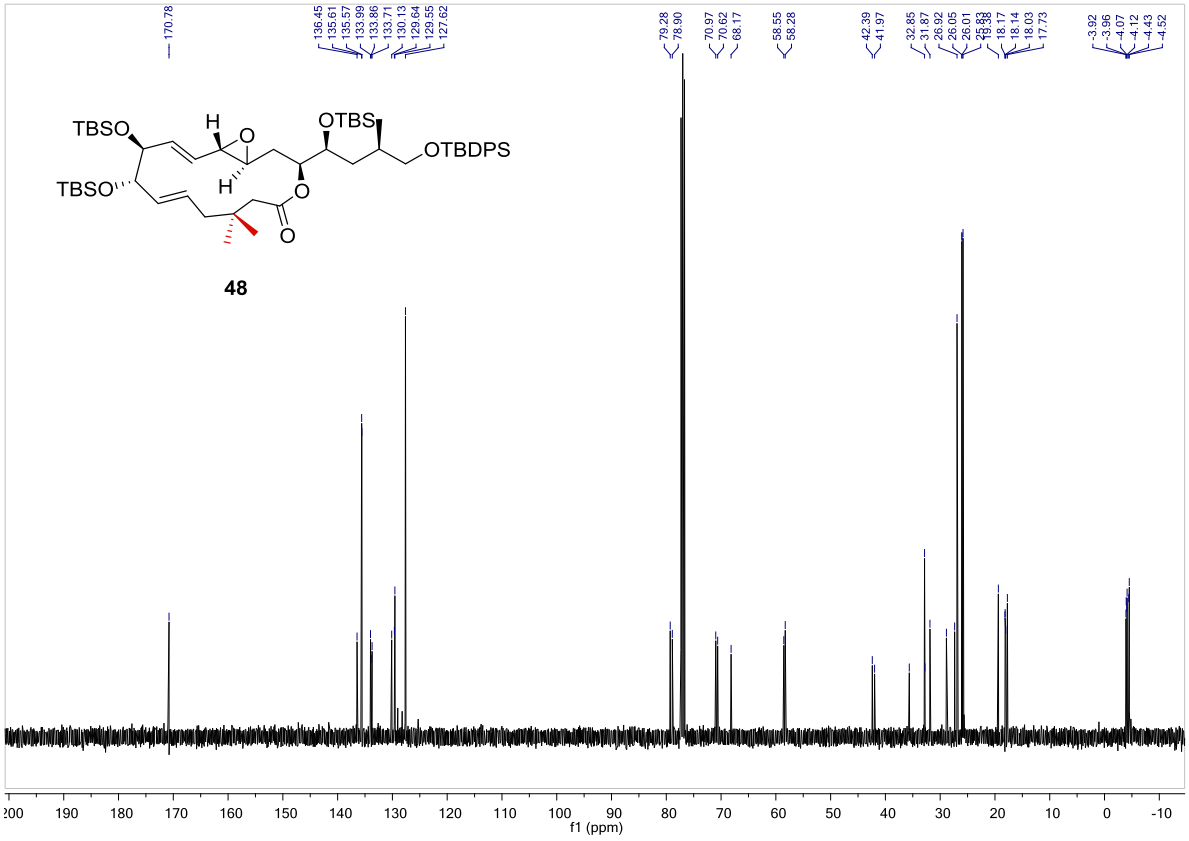


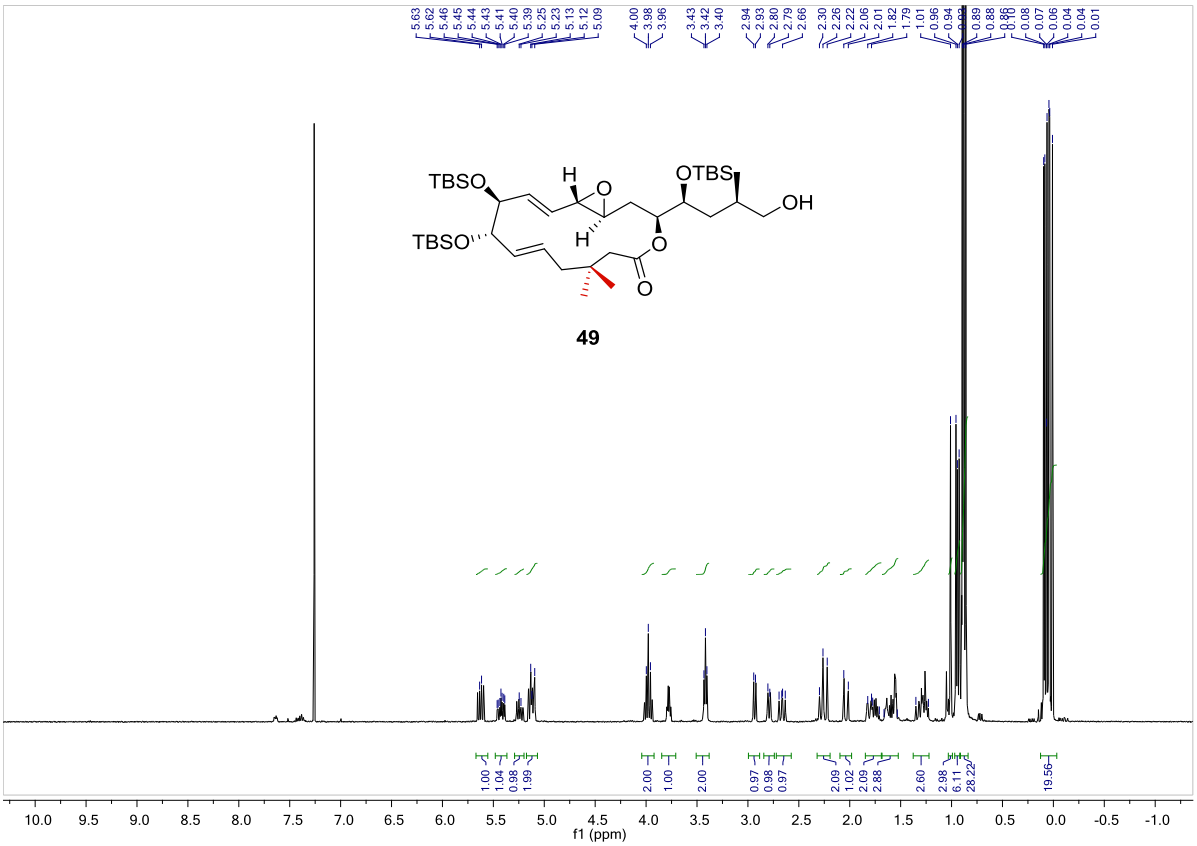
47

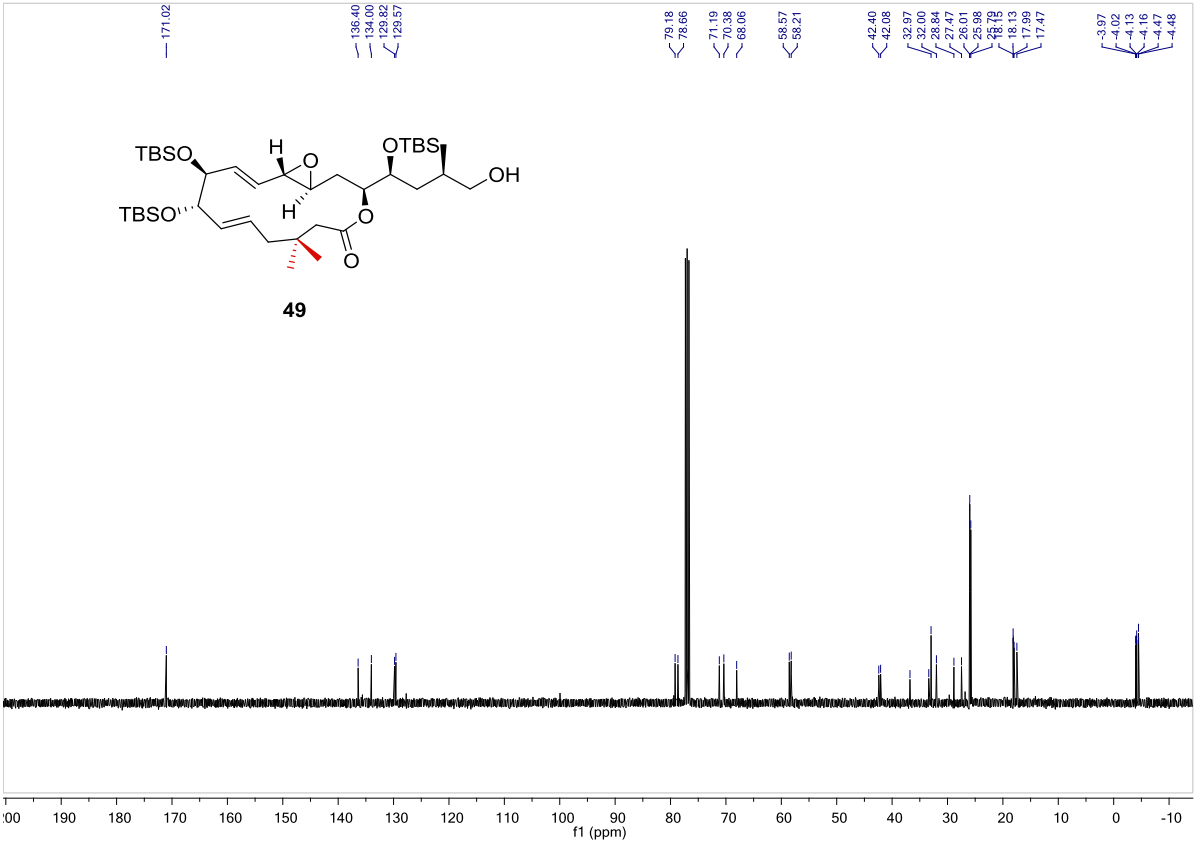


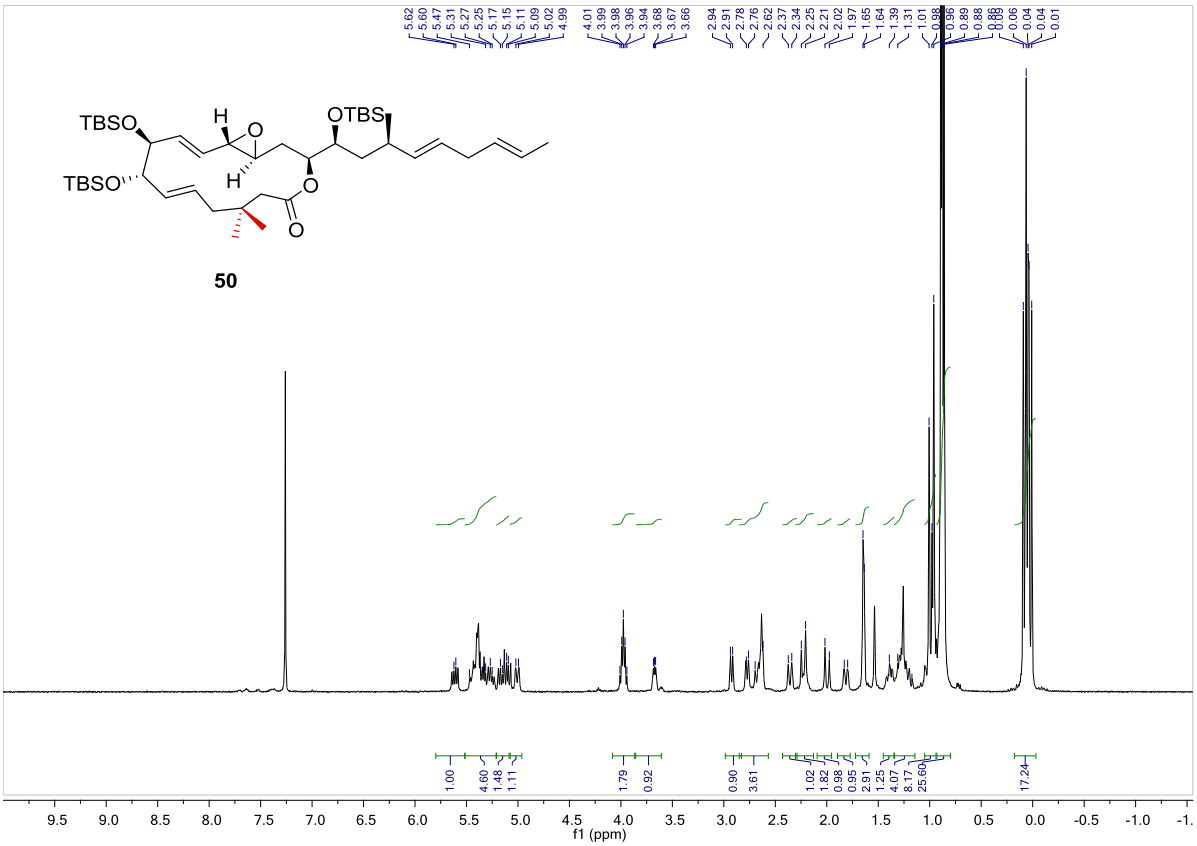
47

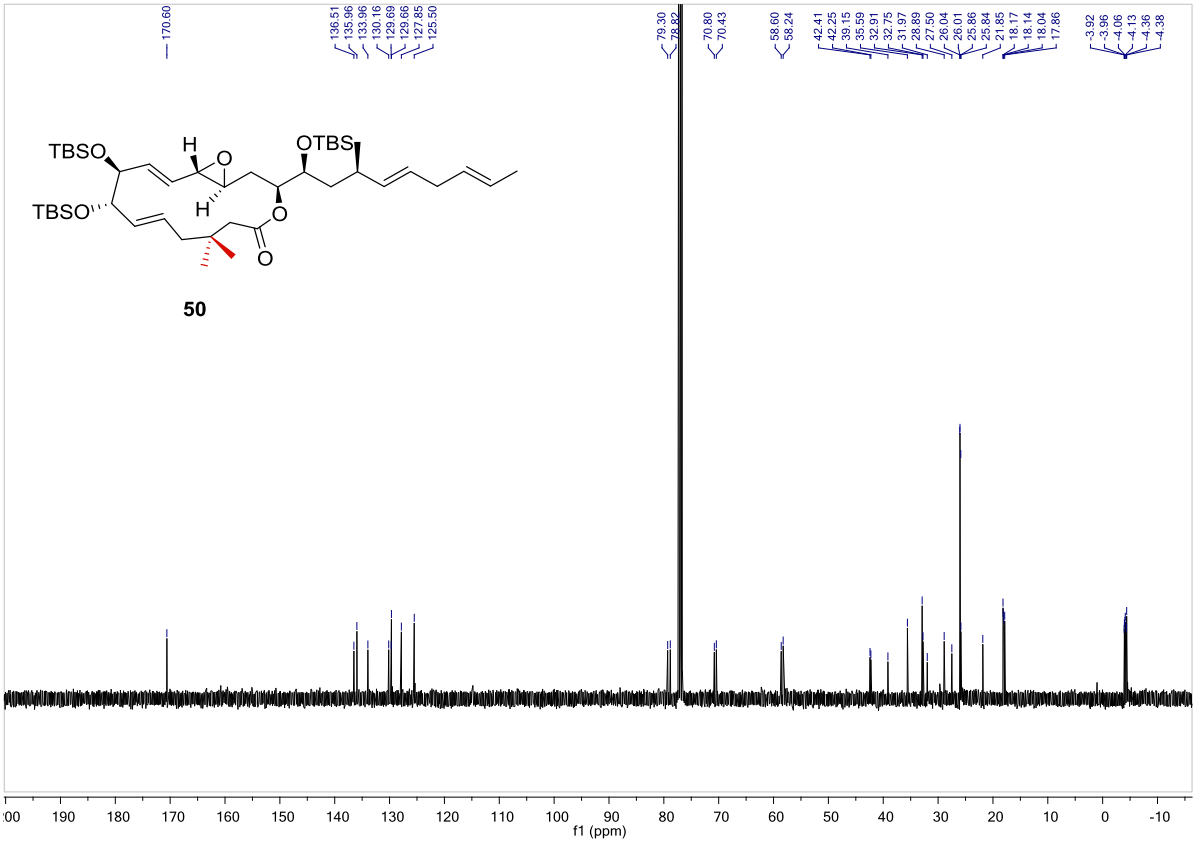

TBSO
H
O
OTBS
OTBDPS
TBSO
H
O
O
O
48
f1 (ppm)

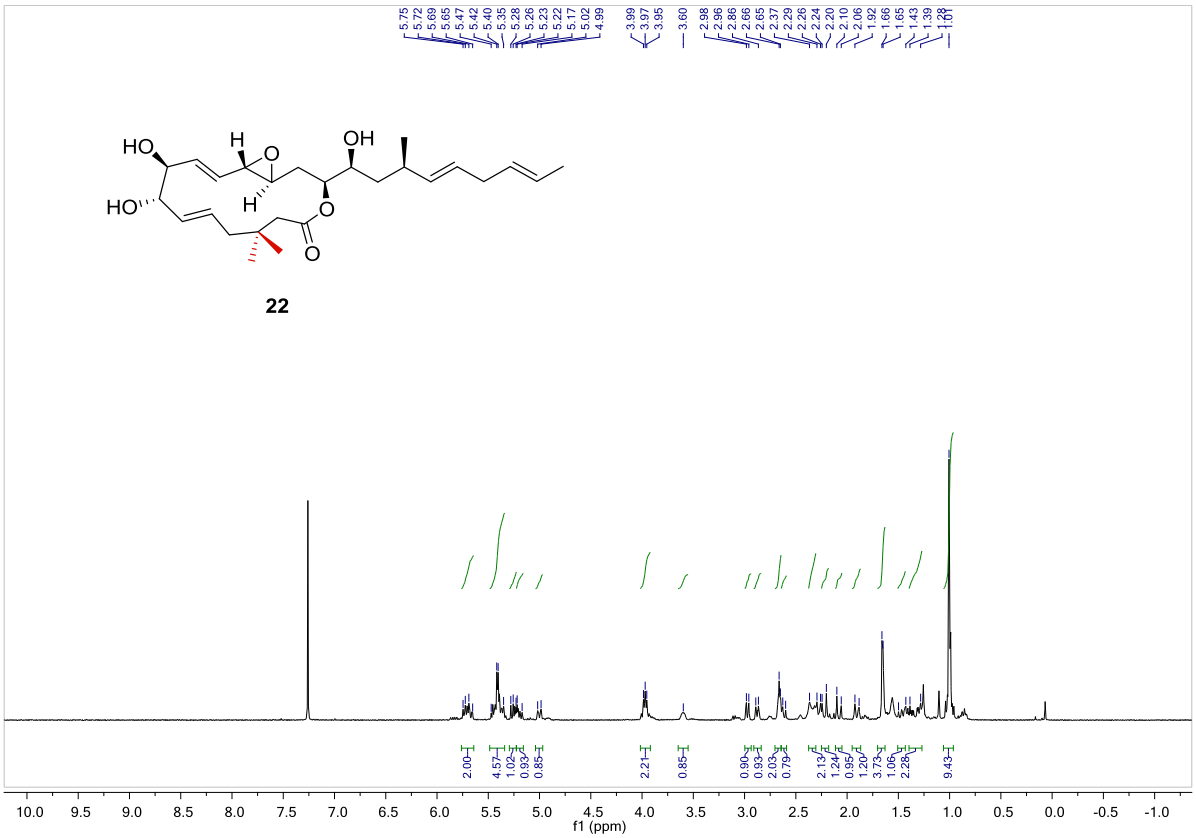

TBSO
H
O
OTBS
OTBDPS
TBSO
H
O
O
O
48
f1 (ppm)

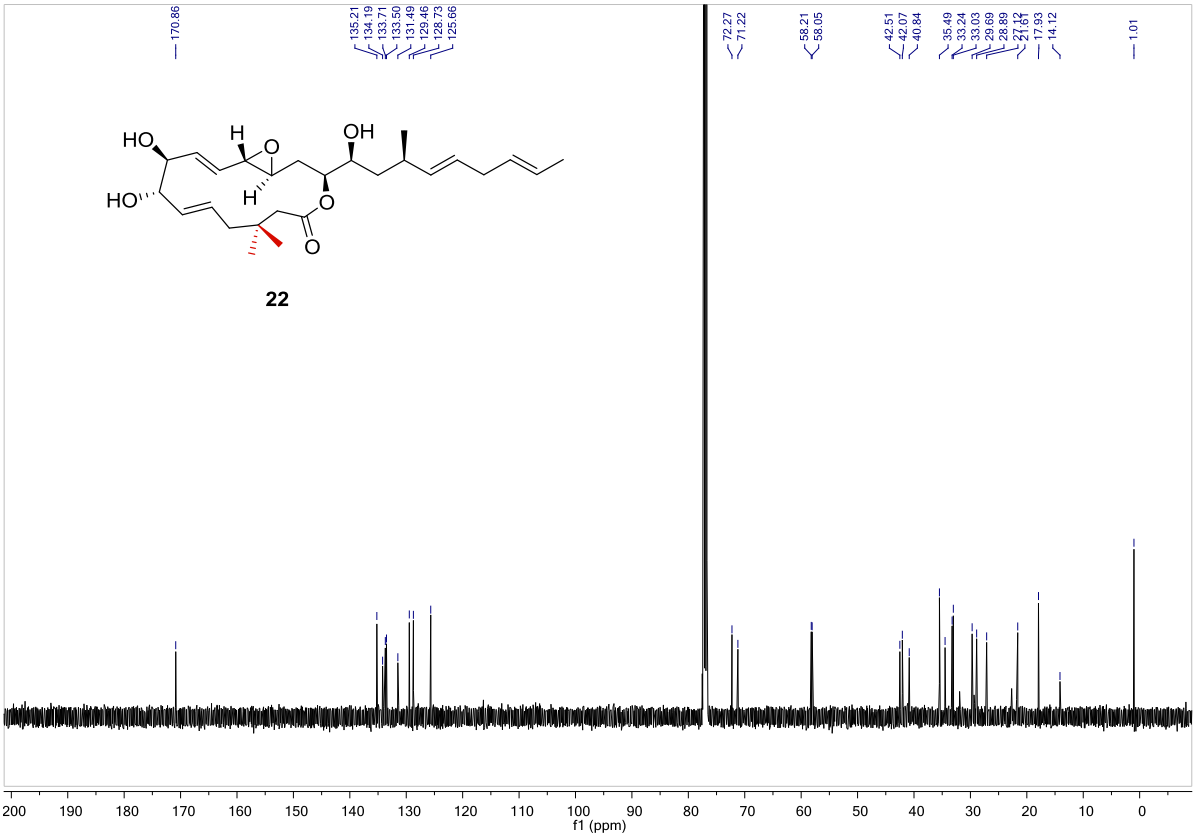

TBSO
H
O
OTBS
OH
TBSO
H
O
O
O
49
f1 (ppm)

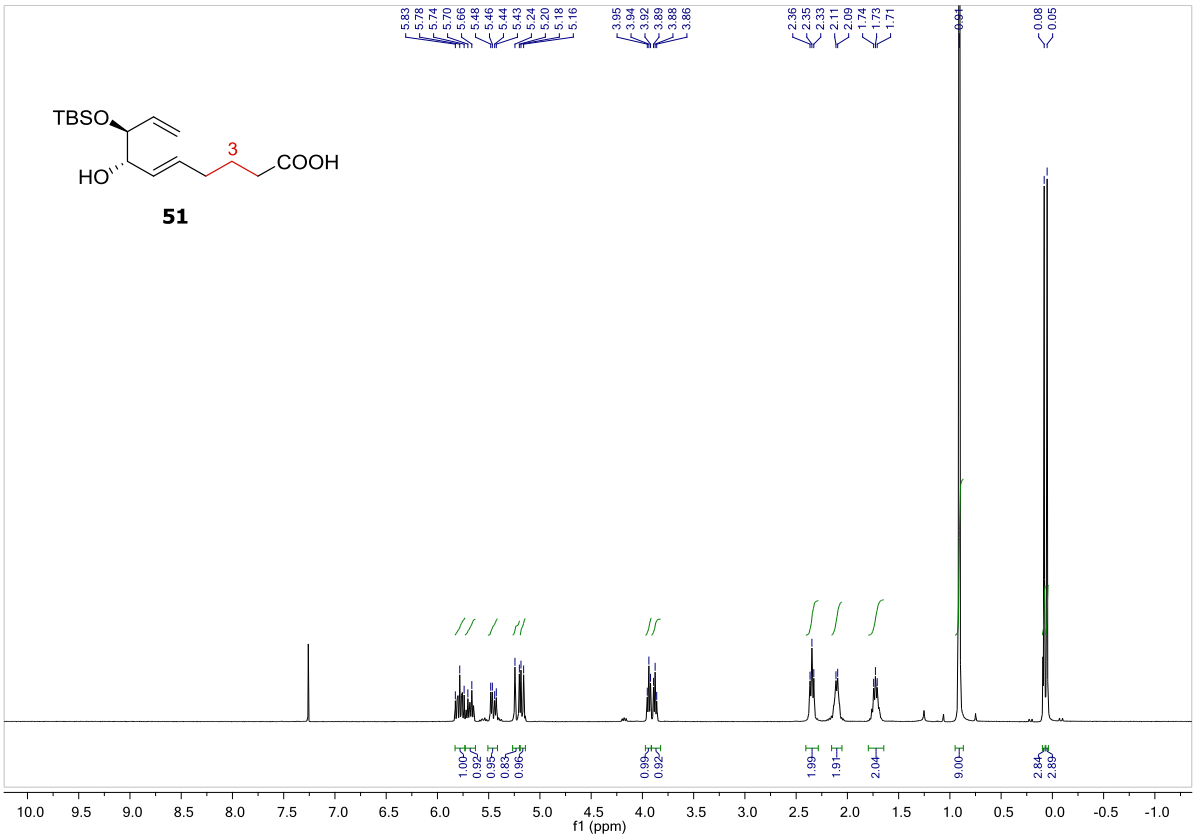

TBSO
H
O
OTBS
OH
TBSO
H
O
O
O
49
f1 (ppm)

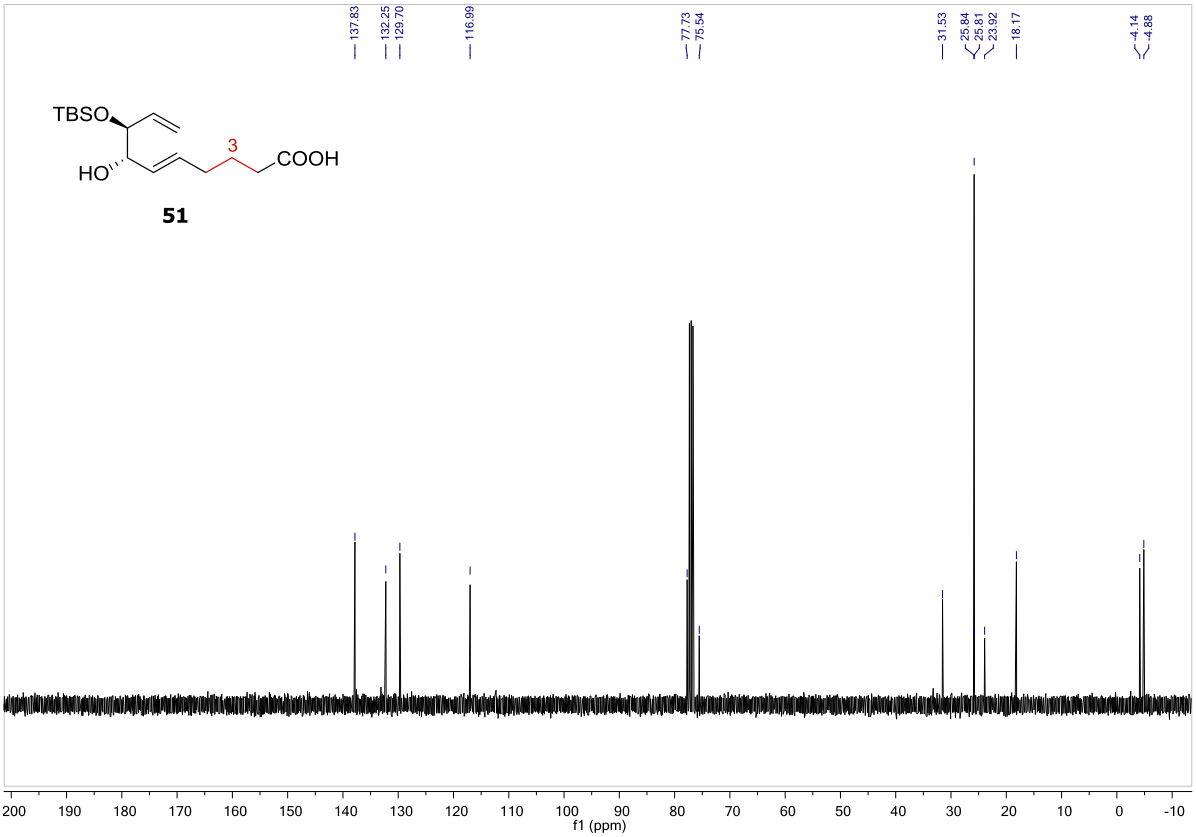

TBSO
H
O
OTBS
TBSO
H
O
O
50
f1 (ppm)

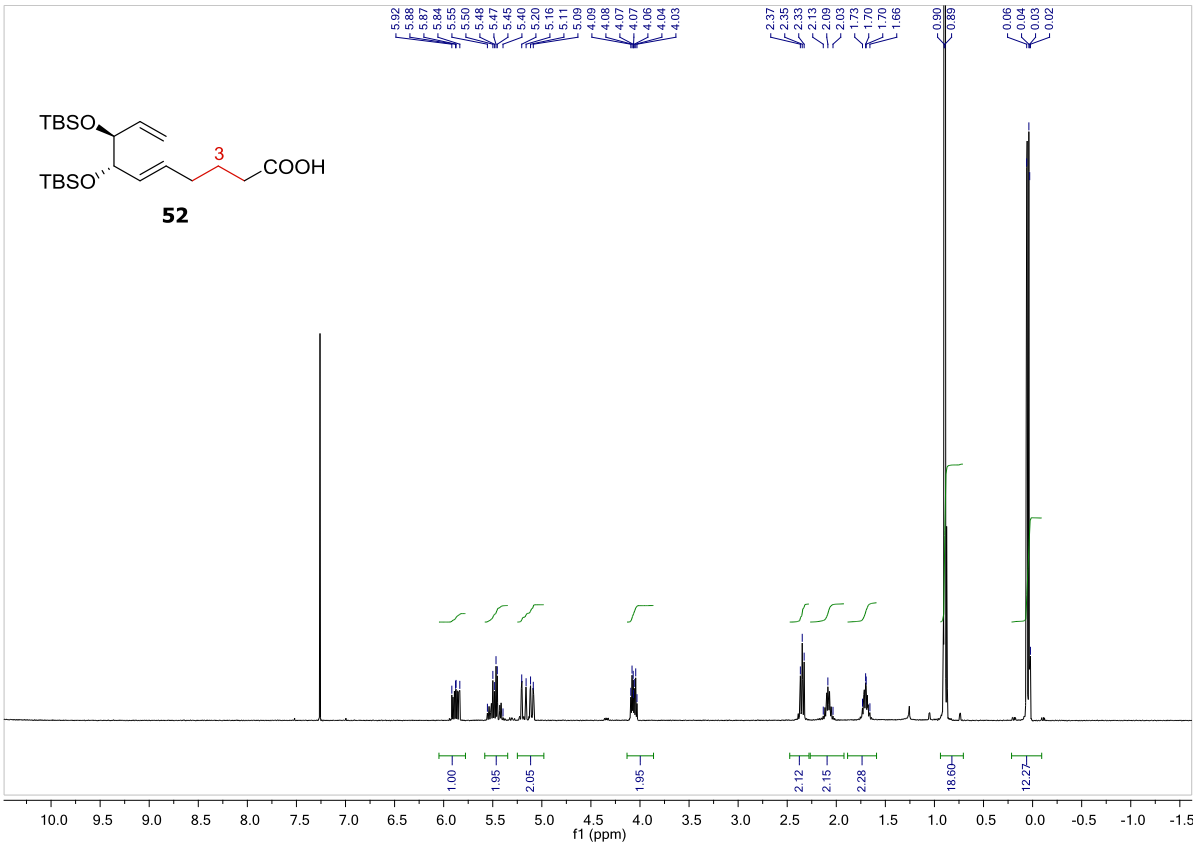

TBSO
H
O
OTBS
TBSO
H
O
O
50
f1 (ppm)

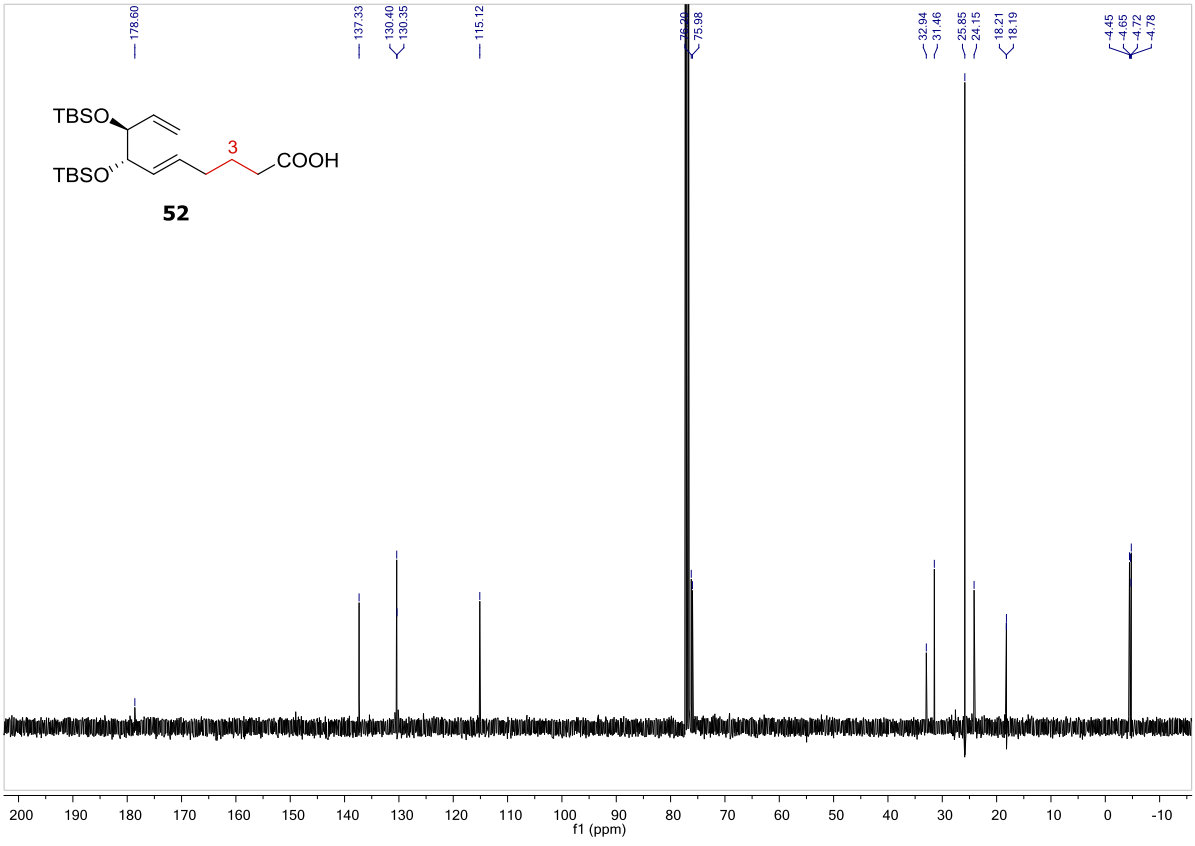

HO
H
O
OH
HO
H
O
O
22
f1 (ppm)


HO
H
O
OH
HO
H
O
O
22
f1 (ppm)


TBSO
HO
3
COOH
51
5.83
5.78
5.74
5.70
5.66
5.48
5.46
5.44
5.43
5.24
5.20
5.18
5.16
3.95
3.94
3.92
3.89
3.88
3.86
2.36
2.35
2.33
2.11
2.09
1.74
1.73
1.71
0.91
0.08
0.05
1.00
0.92
0.95
0.83
0.96
0.99
0.92
1.99
1.91
2.04
9.00
2.84
2.89
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


TBSO
HO
3
COOH
51
137.83
132.25
129.70
116.99
77.73
75.54
31.53
25.84
25.81
23.92
18.17
-4.14
-4.88
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


TBSO
TBSO
3
COOH
52
5.92
5.88
5.87
5.84
5.55
5.50
5.48
5.47
5.45
5.40
5.20
5.16
5.11
5.09
4.09
4.08
4.07
4.07
4.06
4.04
4.03
2.37
2.35
2.33
2.13
2.09
2.03
1.73
1.70
1.70
1.66
0.90
0.89
0.06
0.04
0.03
0.02
1.00
1.95
2.05
1.95
2.12
2.15
2.28
18.60
12.27
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)


TBSO
TBSO
3
COOH
52
178.60
137.33
130.40
130.35
115.12
76.90
75.98
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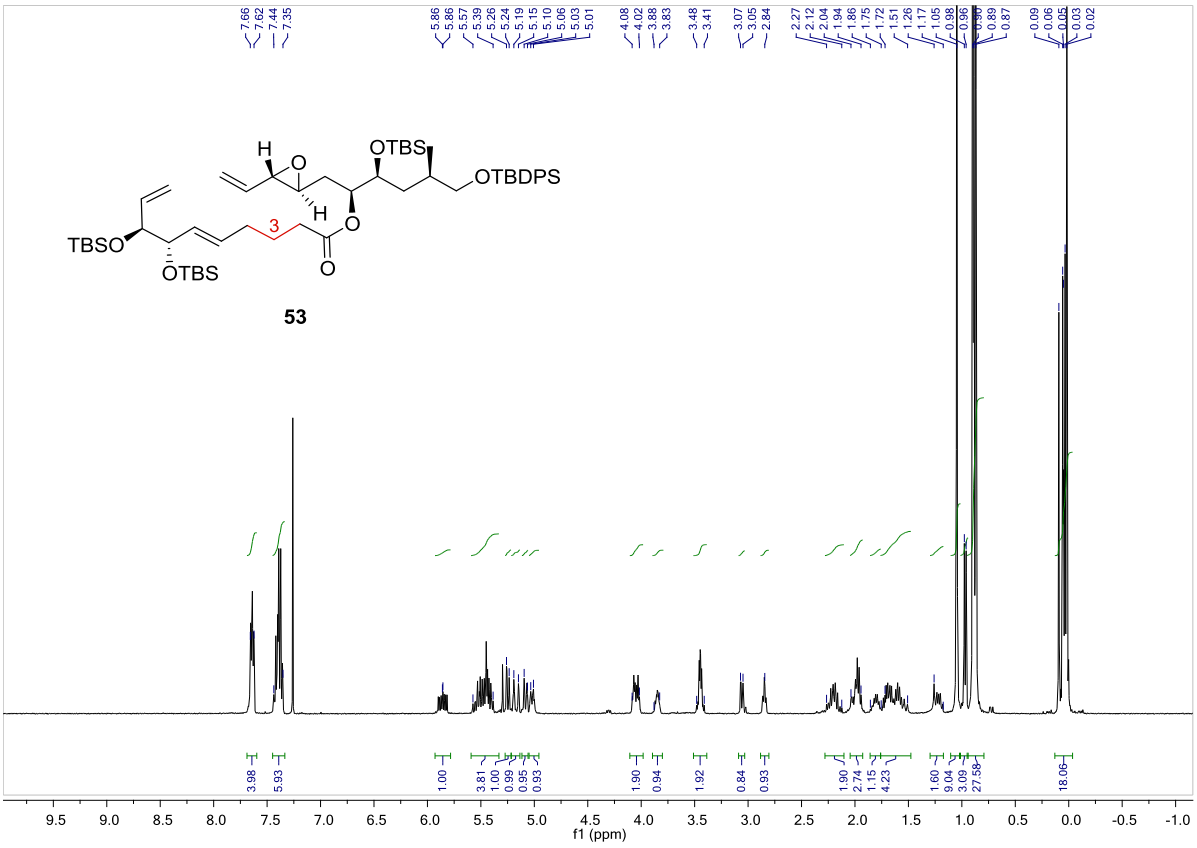
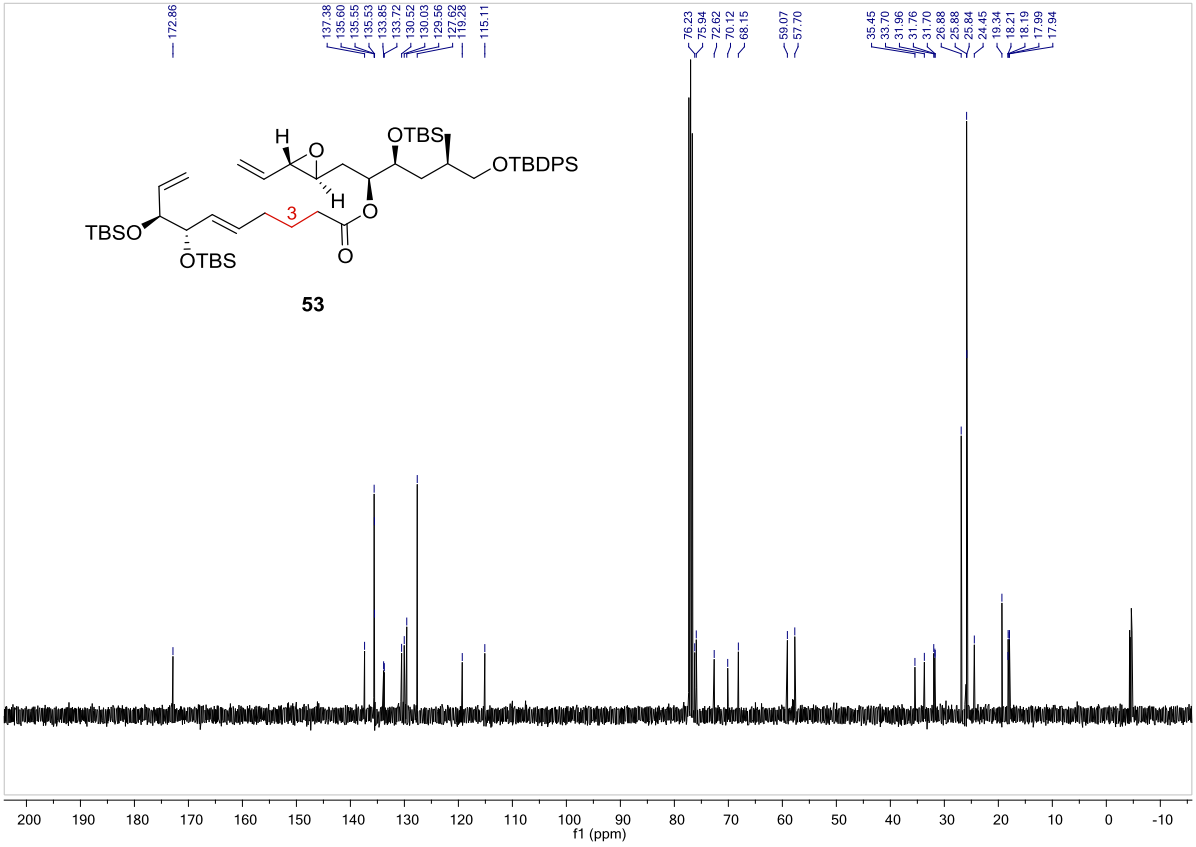
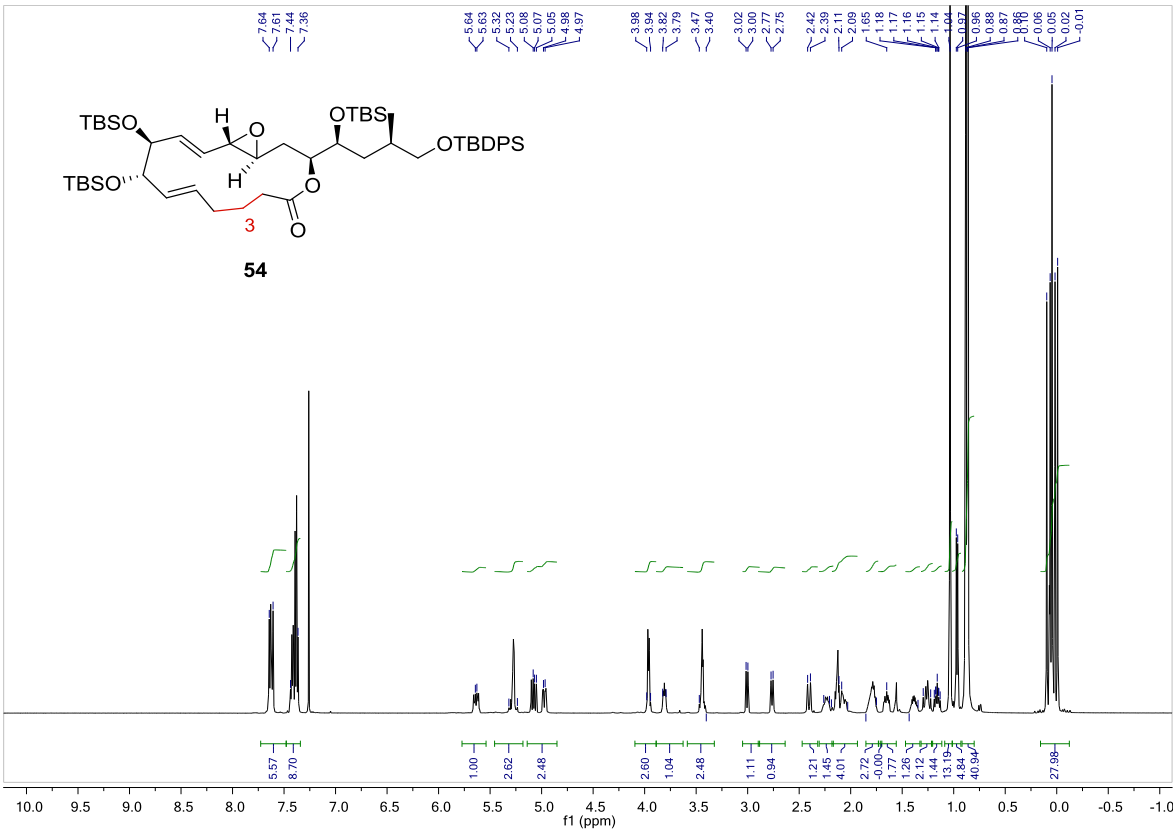
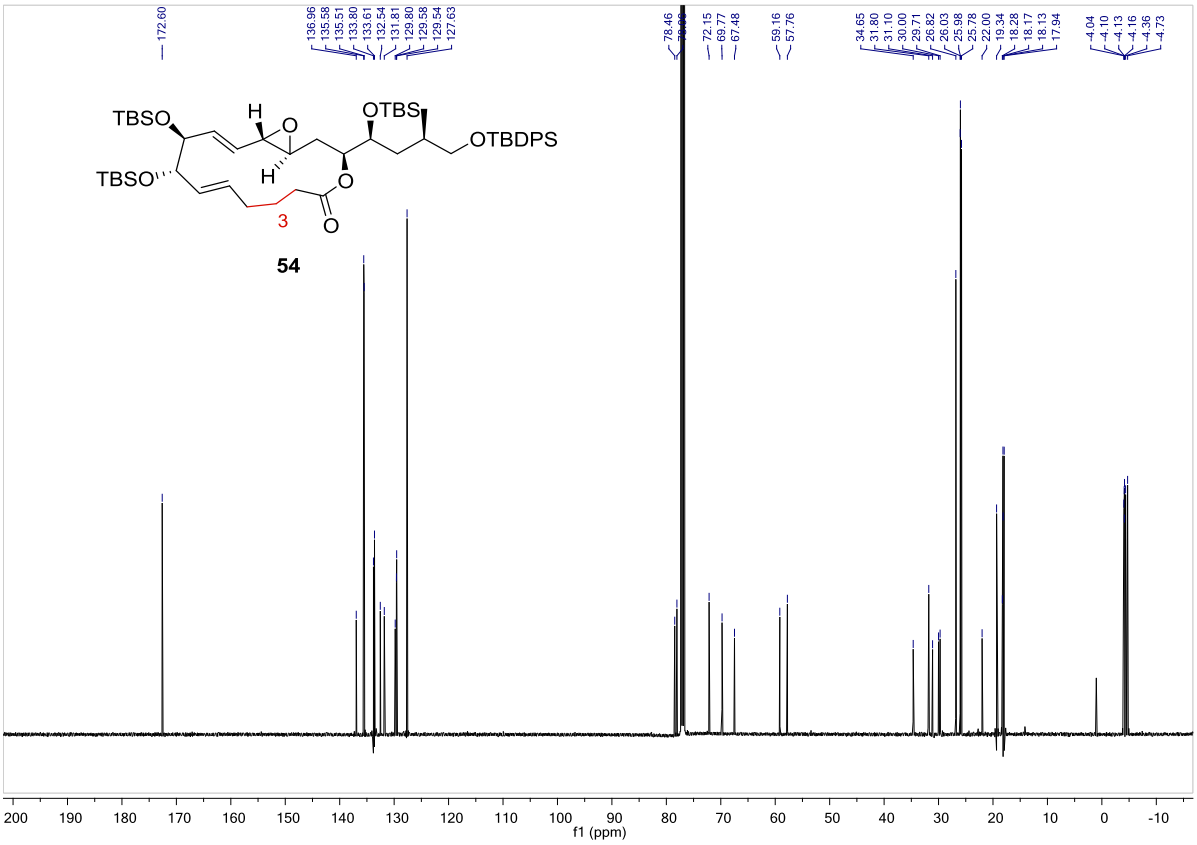
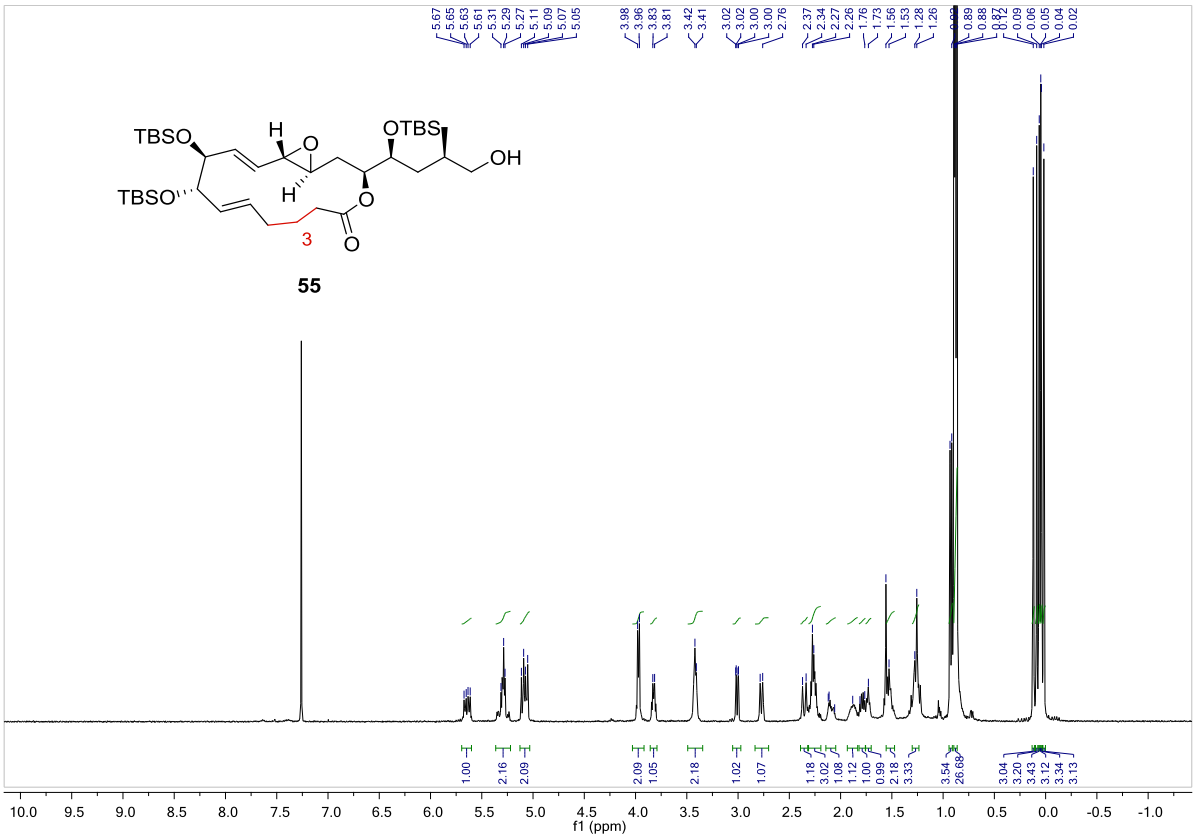
31.46
25.85
24.15
18.21
18.19
-4.45
-4.65
-4.72
-4.78
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

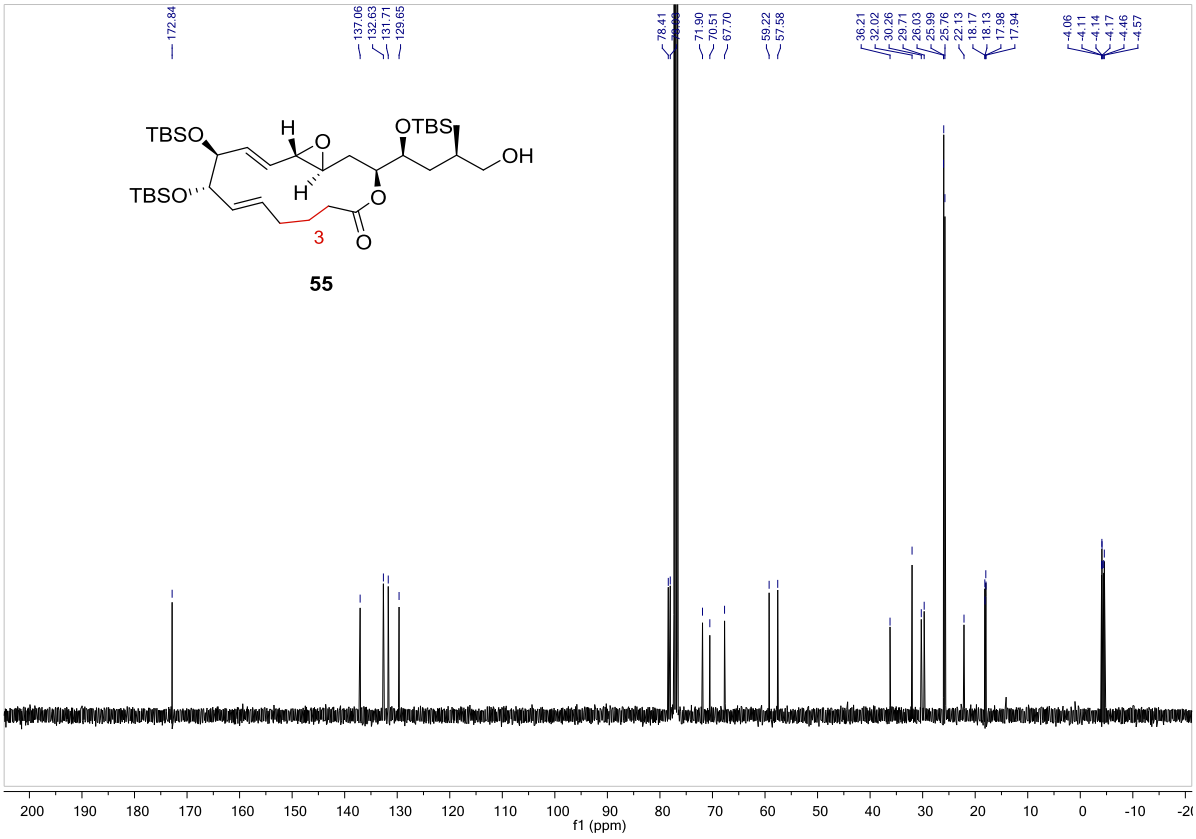

H
O
OTBS
OTBDPS
H
O
3
TBSO
OTBS
O
53
f1 (ppm)

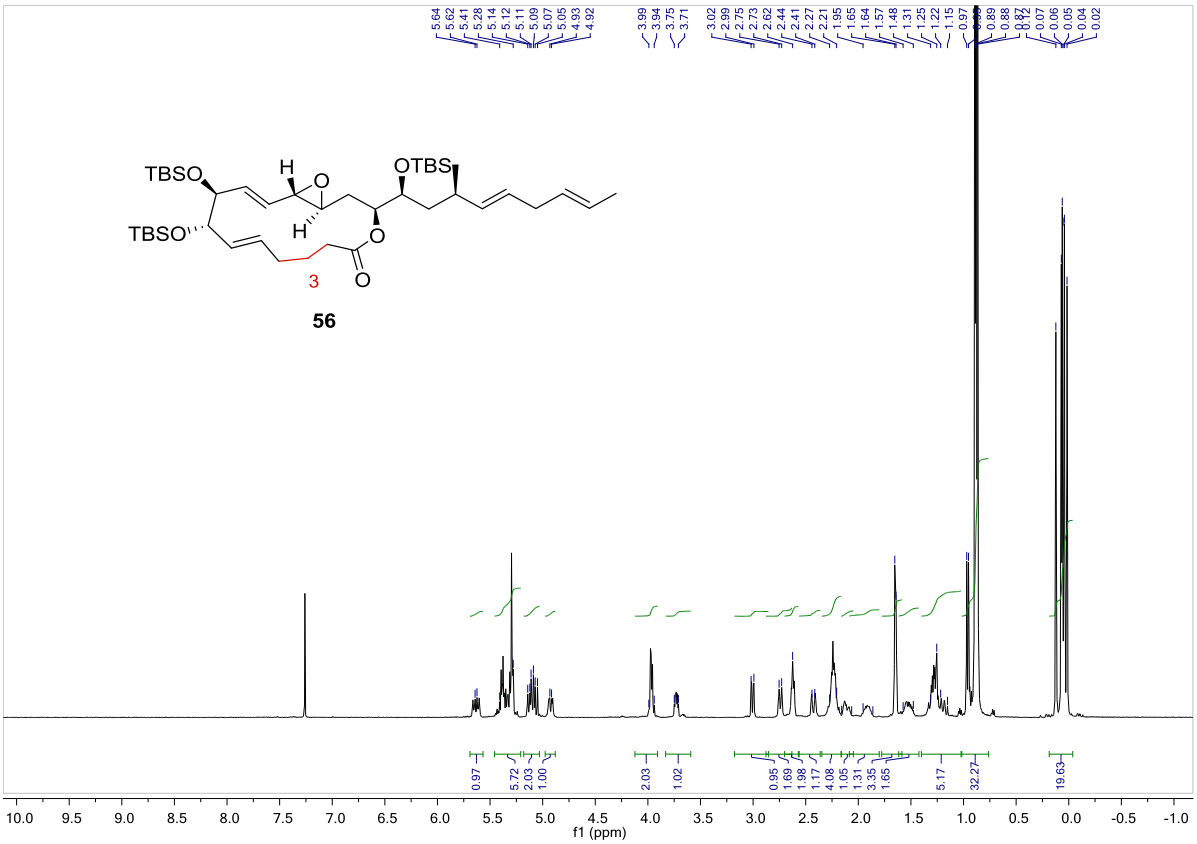

H
O
OTBS
OTBDPS
H
O
3
TBSO
OTBS
O
53
f1 (ppm)

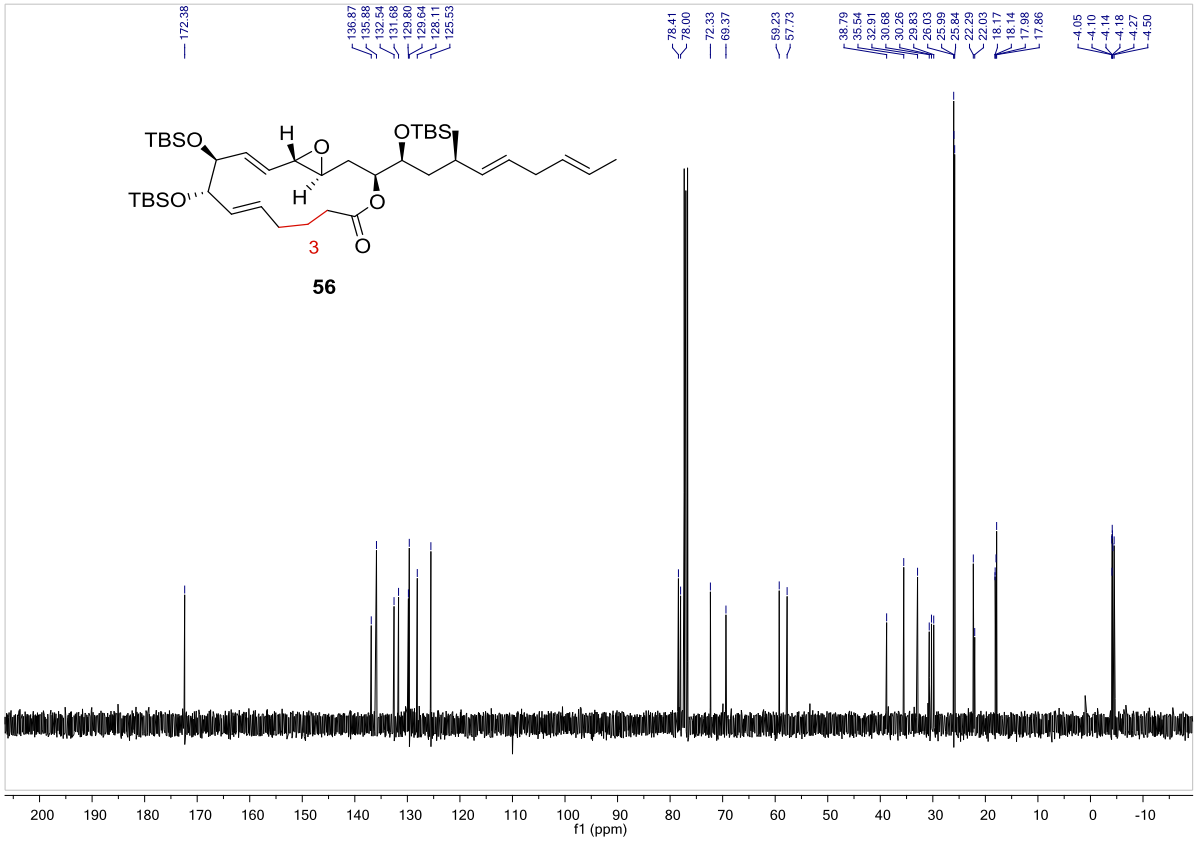

TBSO
H
O
OTBS
OTBDPS
TBSO
H
O
3
O
54
f1 (ppm)

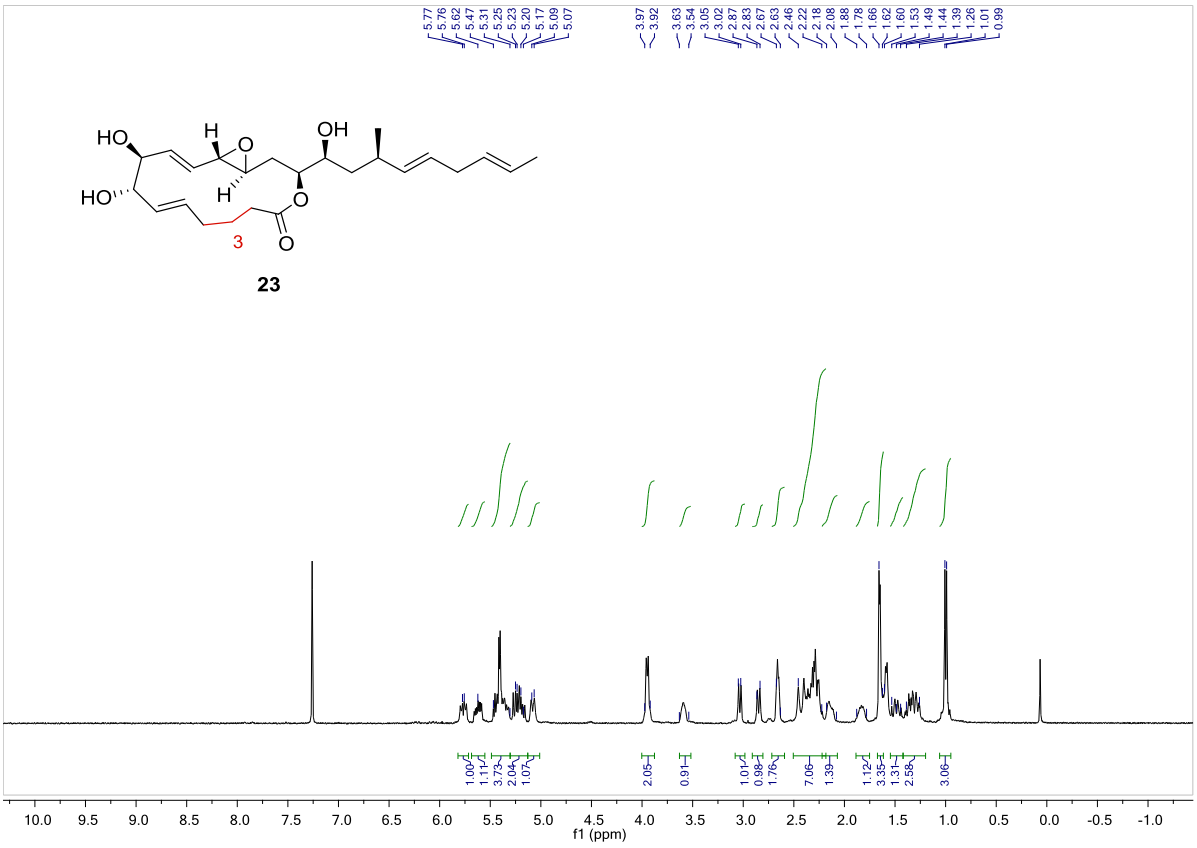

TBSO
H
O
OTBS
OTBDPS
TBSO
H
O
3
O
54
f1 (ppm)

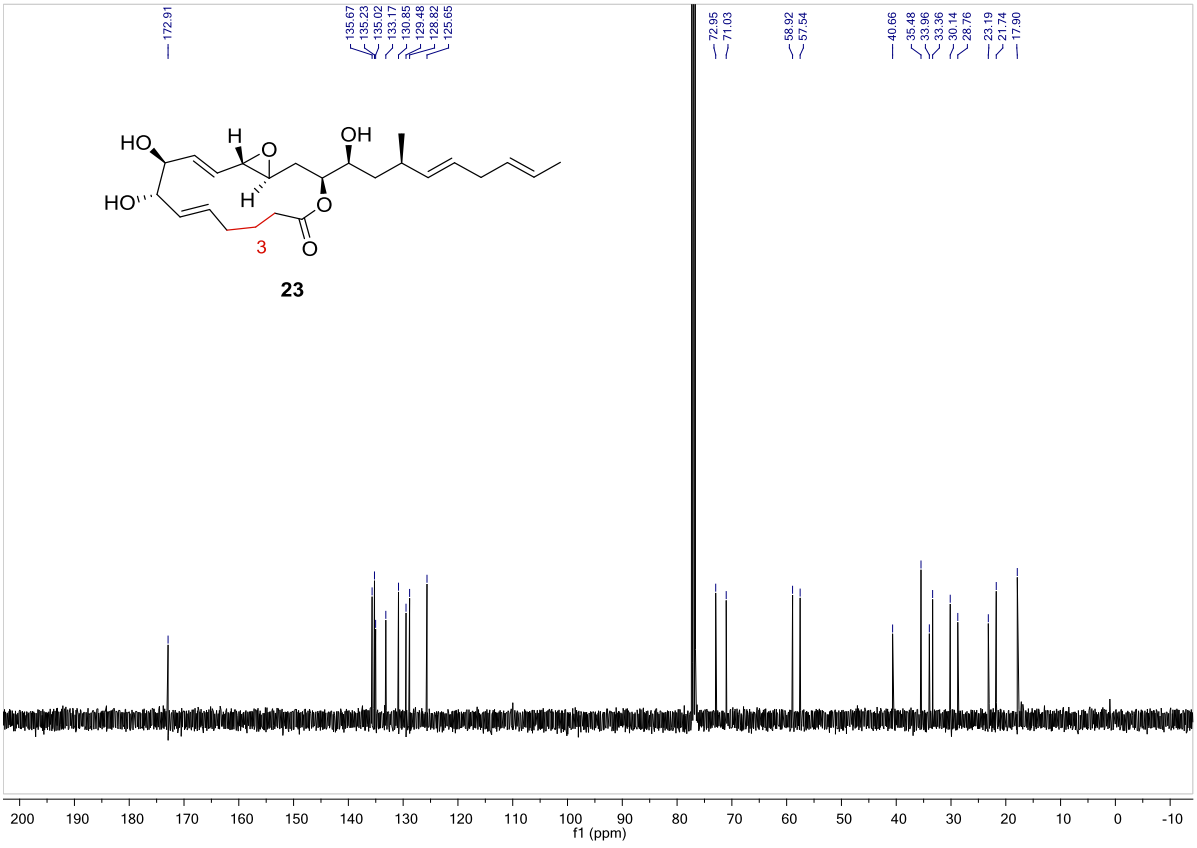

TBSO
H
O
OTBS
OH
TBSO
H
O
3
O
55
f1 (ppm)

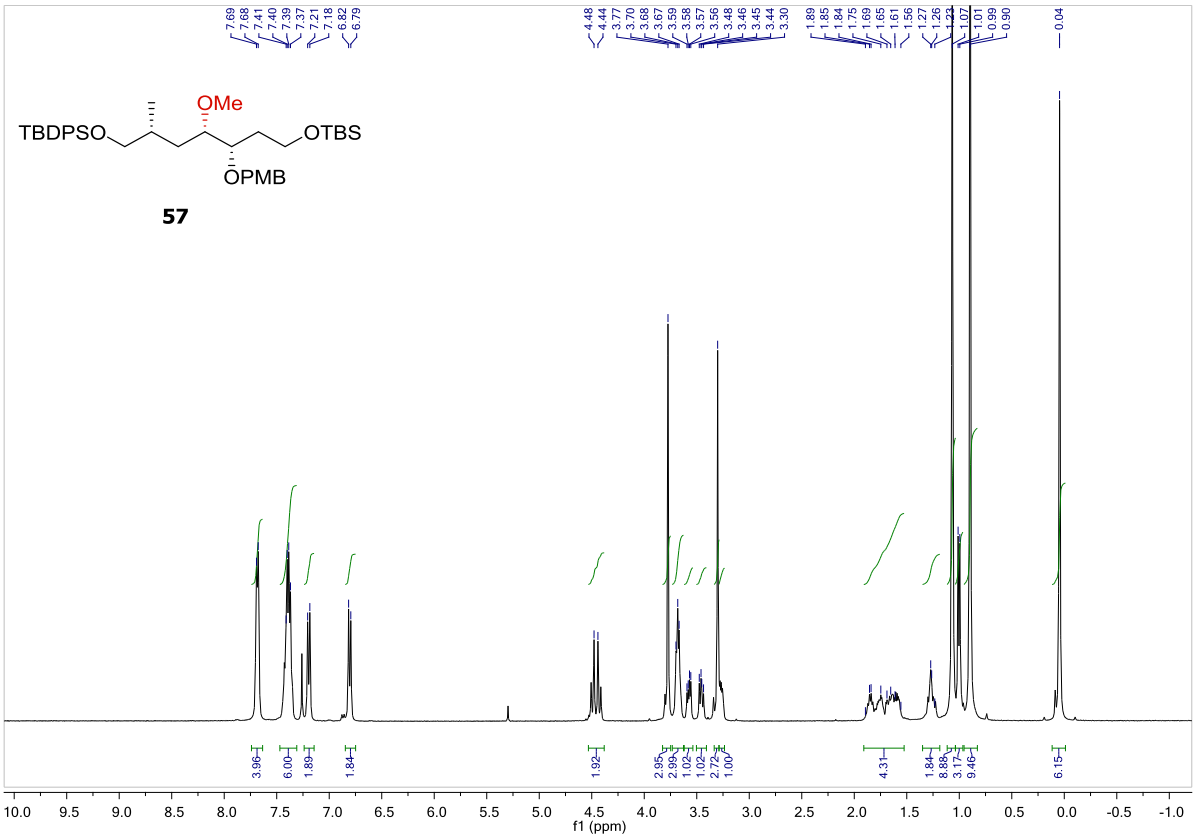

TBSO
H
O
OTBS
OH
TBSO
H
O
3
O
55
f1 (ppm)

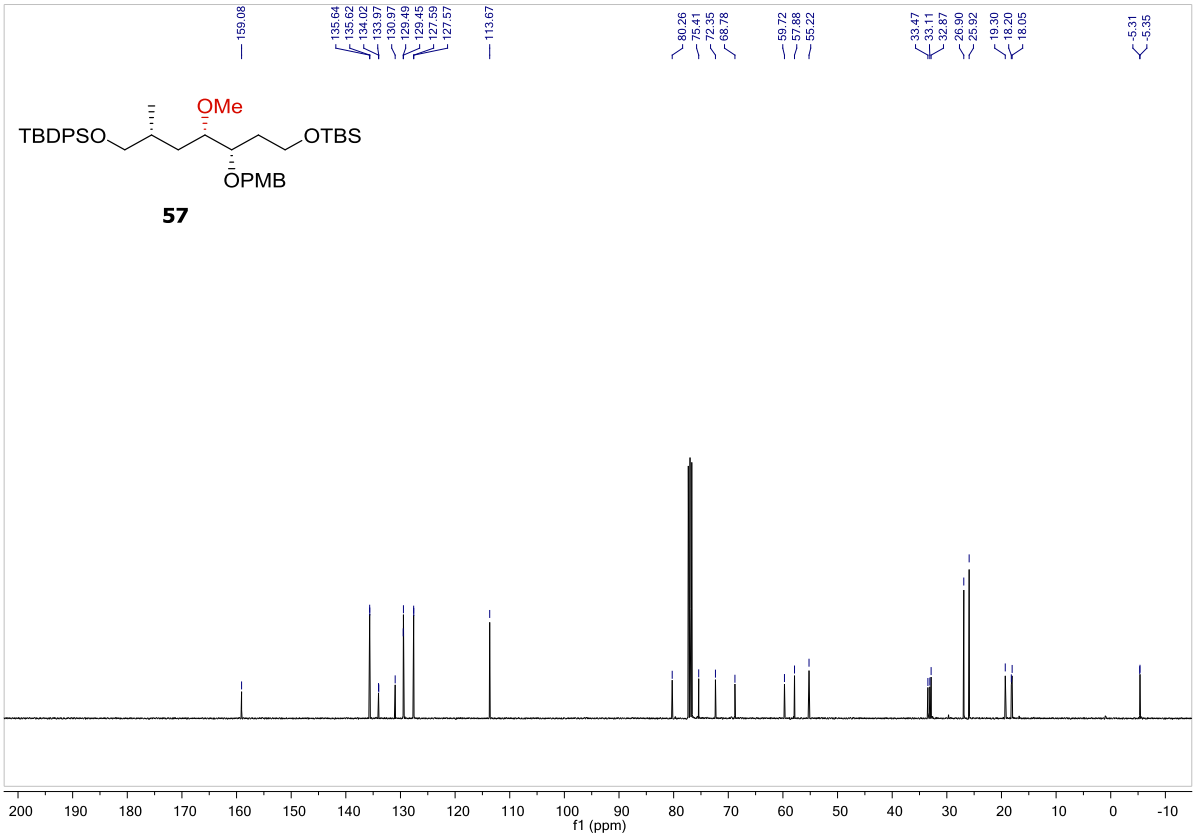

TBSO
H
O
OTBS
TBSO
H
O
O
3
O
56
f1 (ppm)

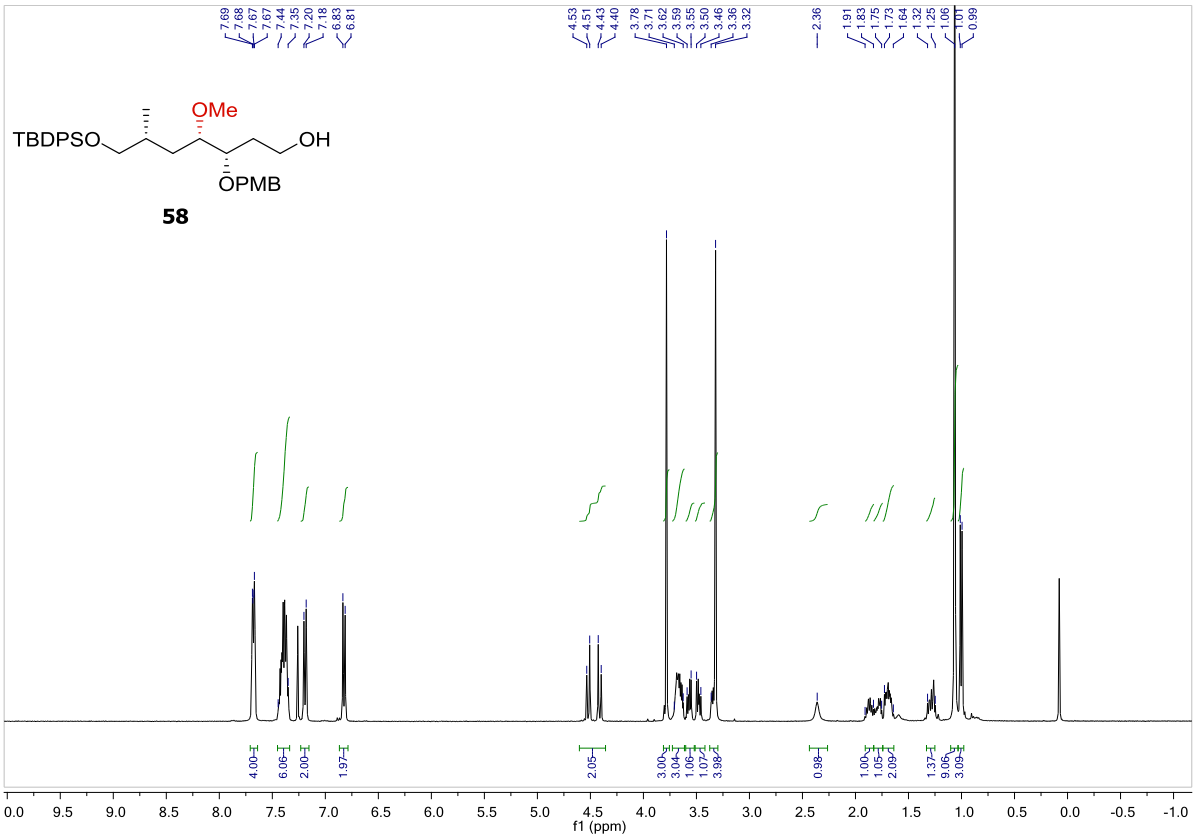

TBSO
H
O
OTBS
TBSO
H
O
O
3
O
56
f1 (ppm)

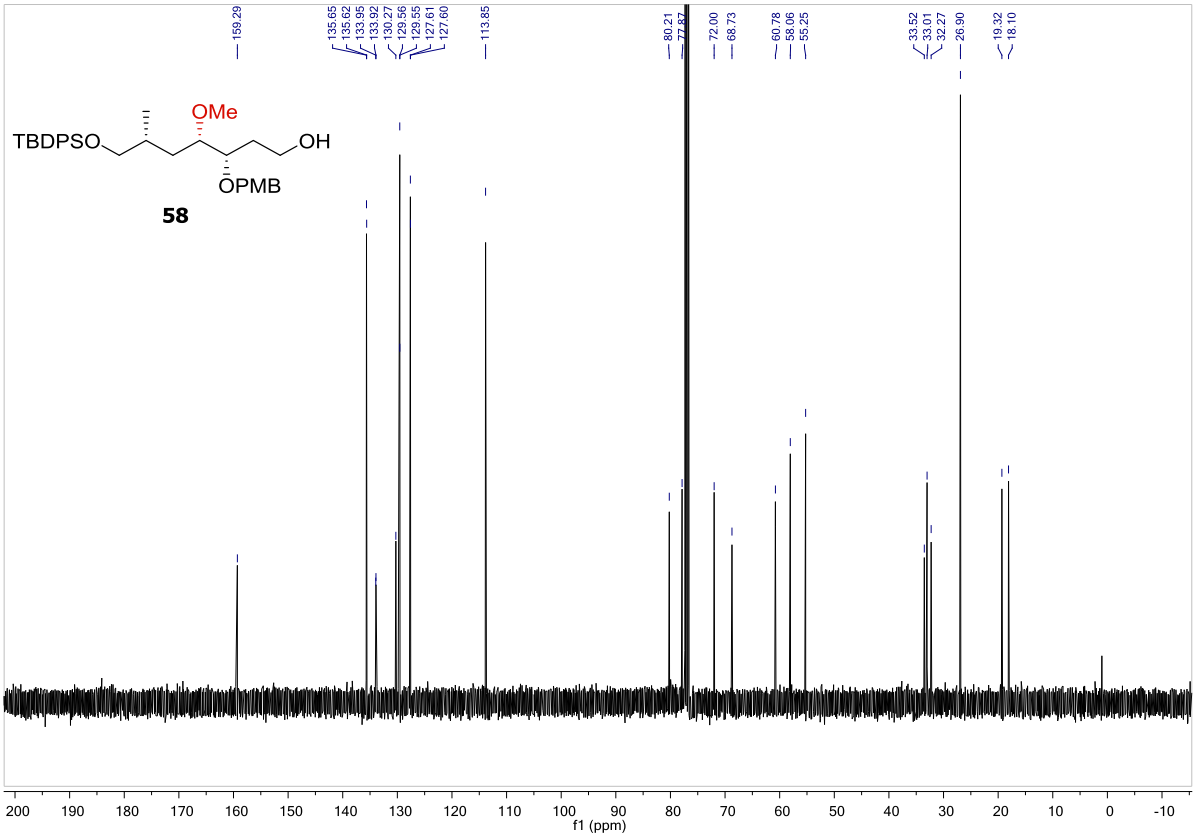

HO
H
O
OH
HO
H
O
3
O
23
f1 (ppm)

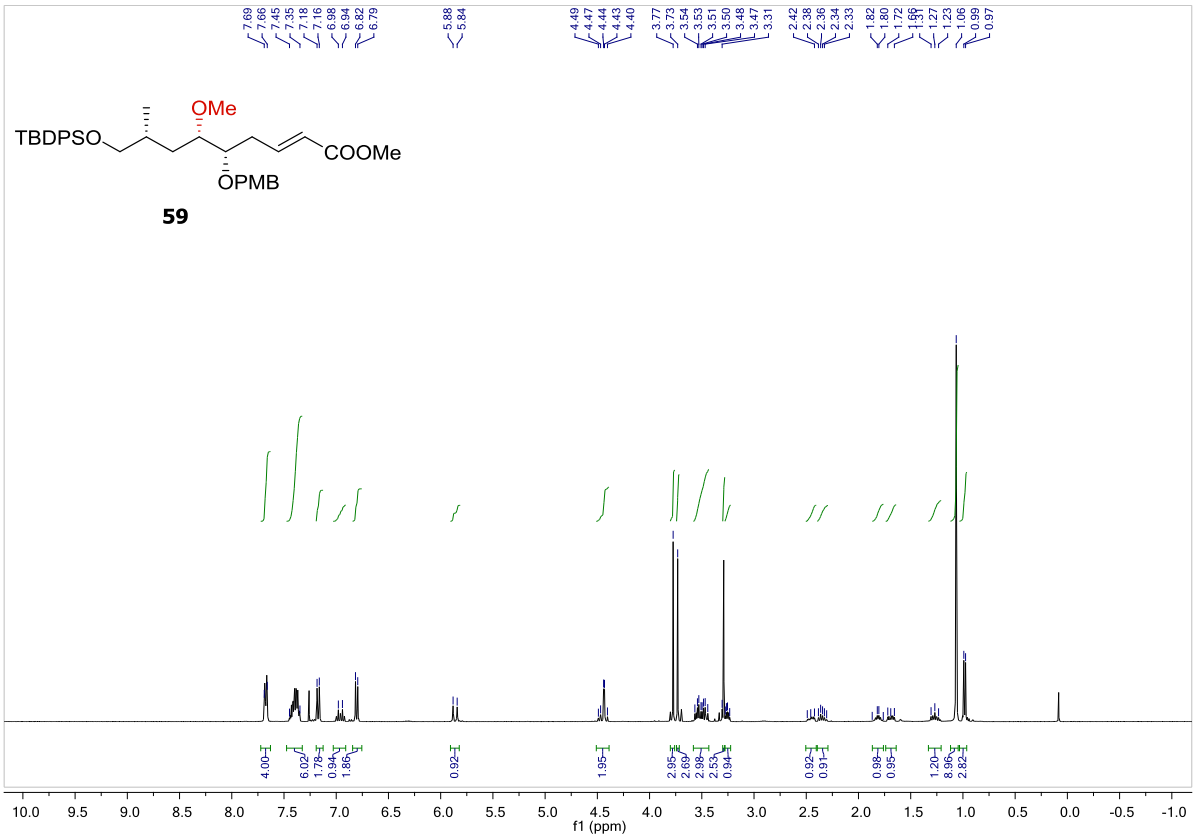

HO
H
O
OH
HO
H
O
3
O
23
f1 (ppm)

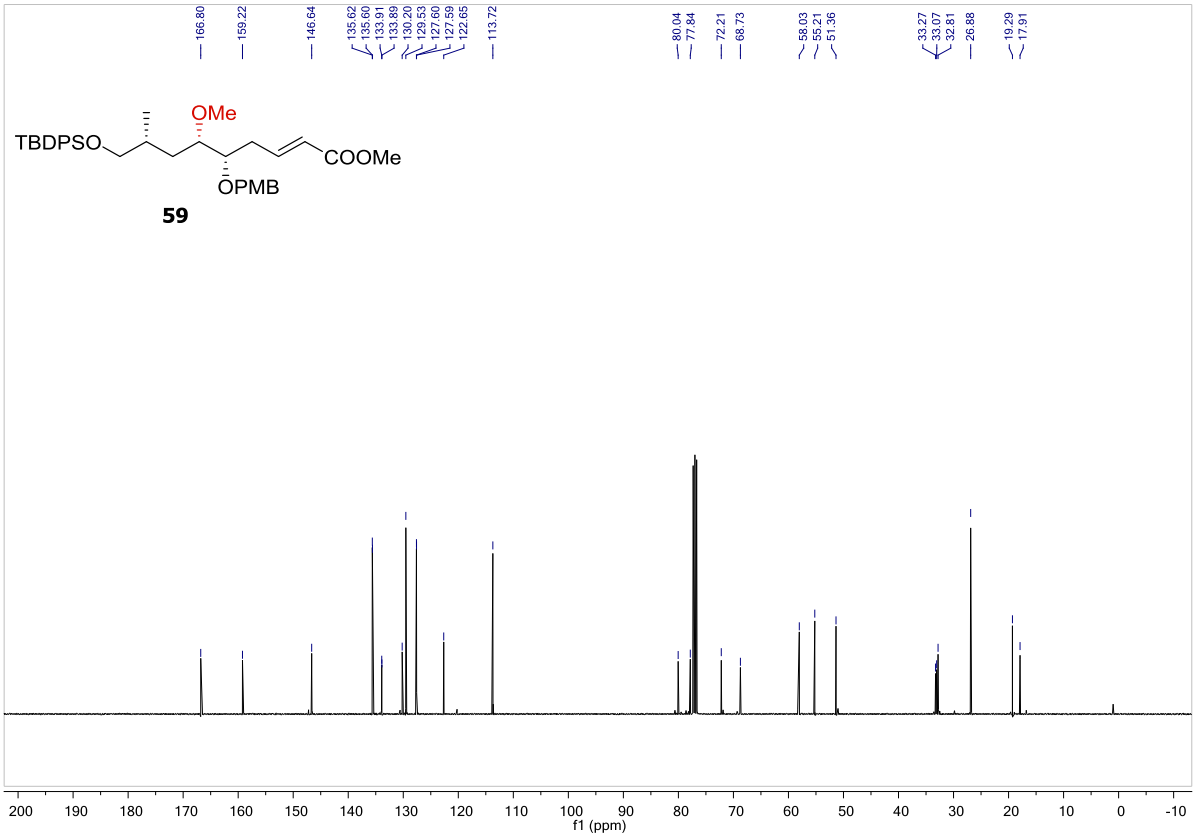

TBDPSO
OMe
OTBS
OPMB
57
f1 (ppm)

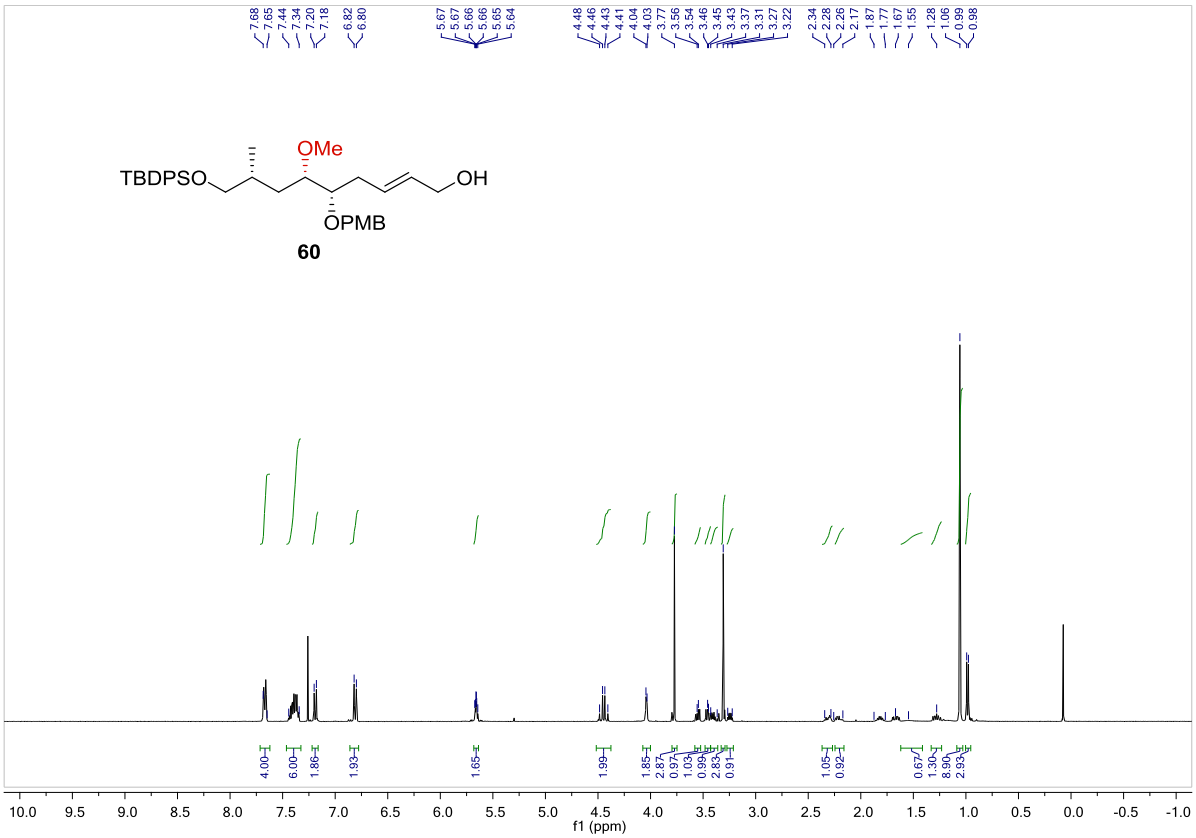

TBDPSO
OMe
OTBS
OPMB
57
f1 (ppm)

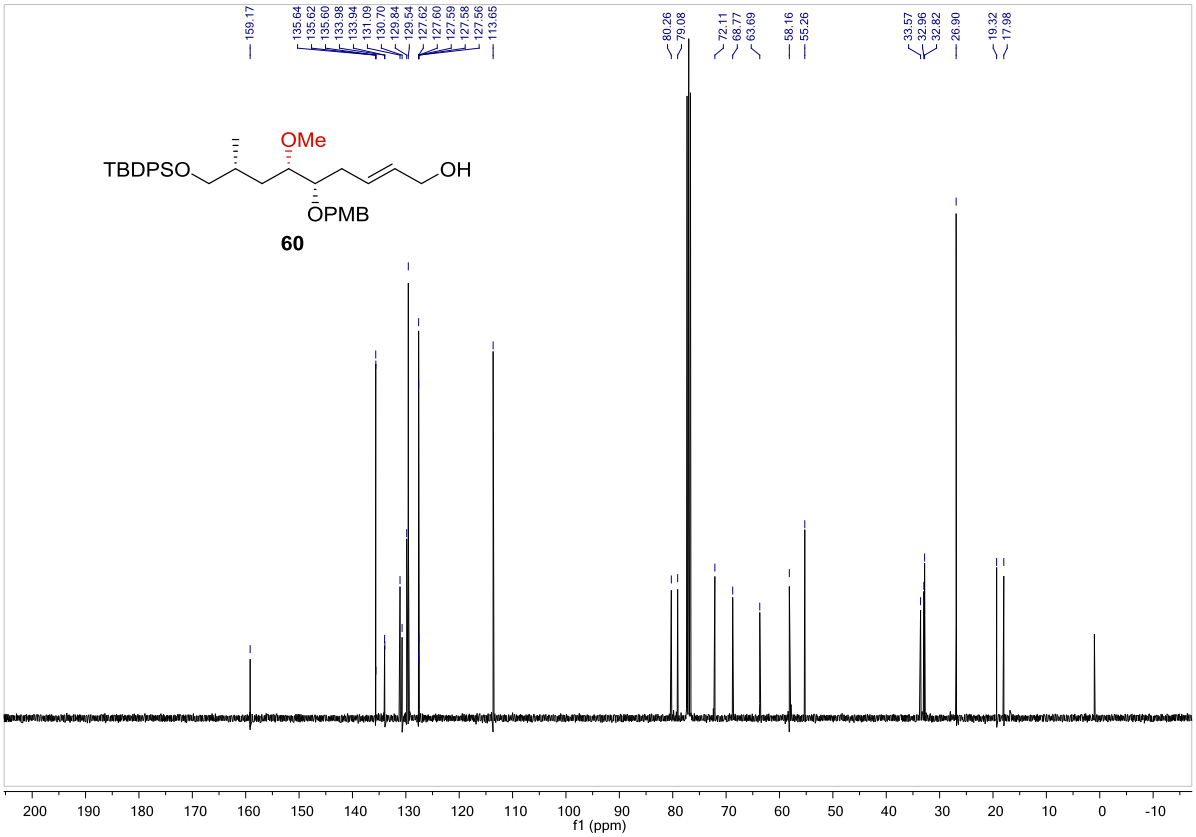

TBDPSO
OMe
OH
OPMB
58
f1 (ppm)

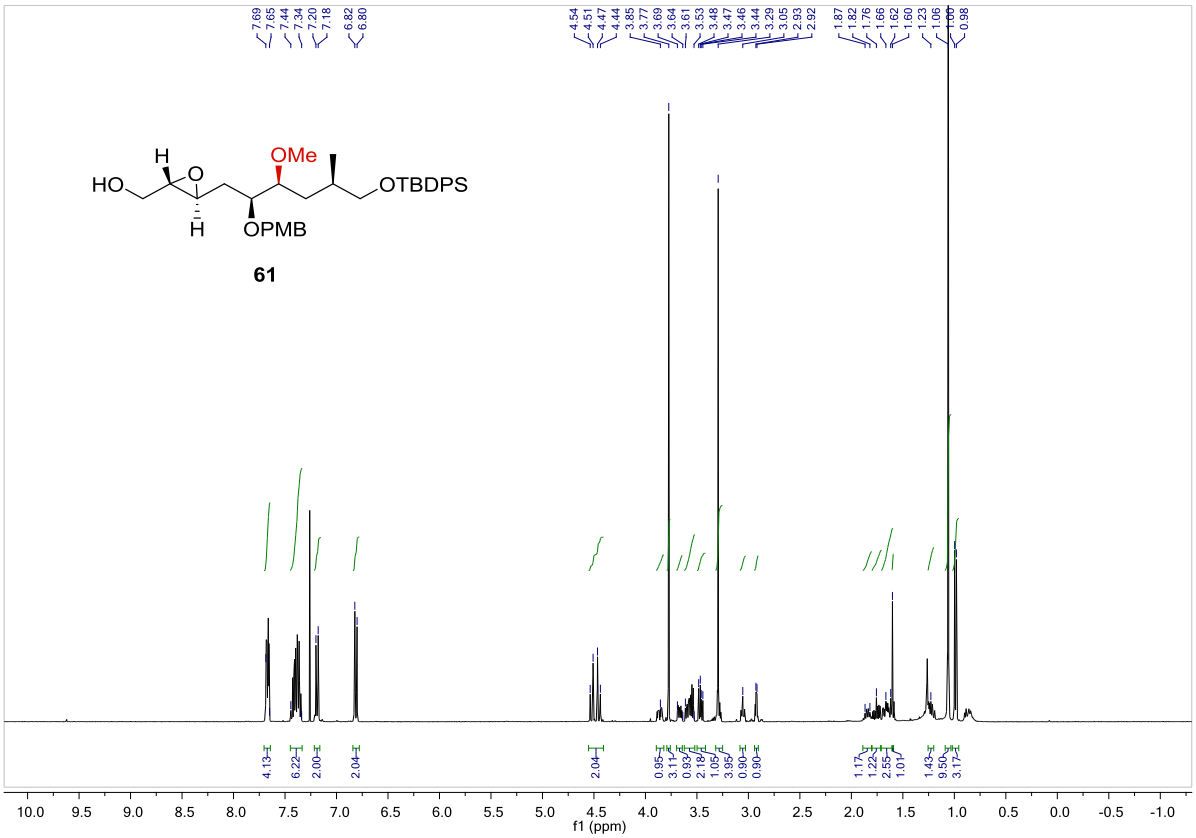

TBDPSO
OMe
OH
OPMB
58
f1 (ppm)

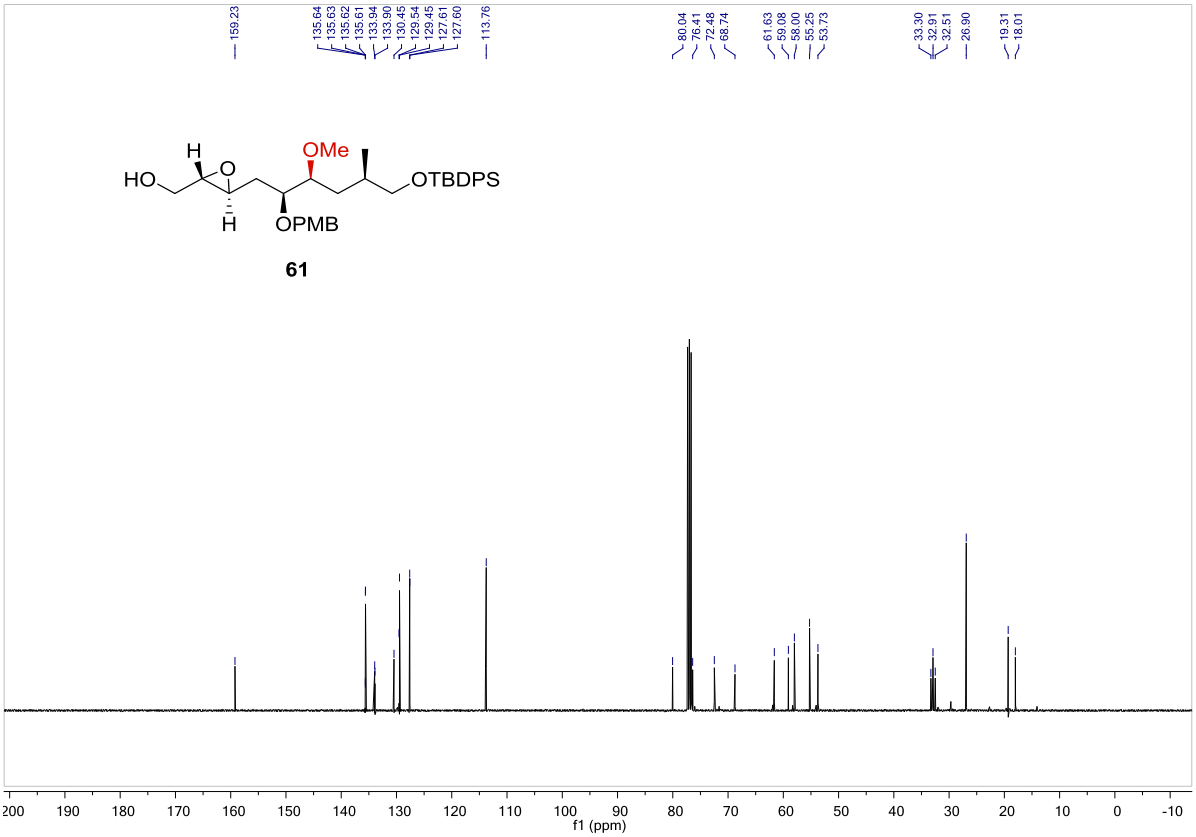

7.69
7.66
7.45
7.35
7.18
7.16
6.98
6.94
6.82
6.79
5.88
5.84
4.49
4.47
4.44
4.43
4.40
3.77
3.73
3.54
3.53
3.51
3.50
3.48
3.47
3.31
2.42
2.38
2.36
2.34
2.33
1.82
1.80
1.72
1.66
1.31
1.27
1.23
1.06
0.99
0.97
OMe
TBDPSO
COOMe
OPMB
59
4.00
6.02
1.78
0.94
1.86
0.92
1.95
2.95
2.69
2.98
2.53
0.94
0.92
0.91
0.98
0.95
1.20
8.96
2.82
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

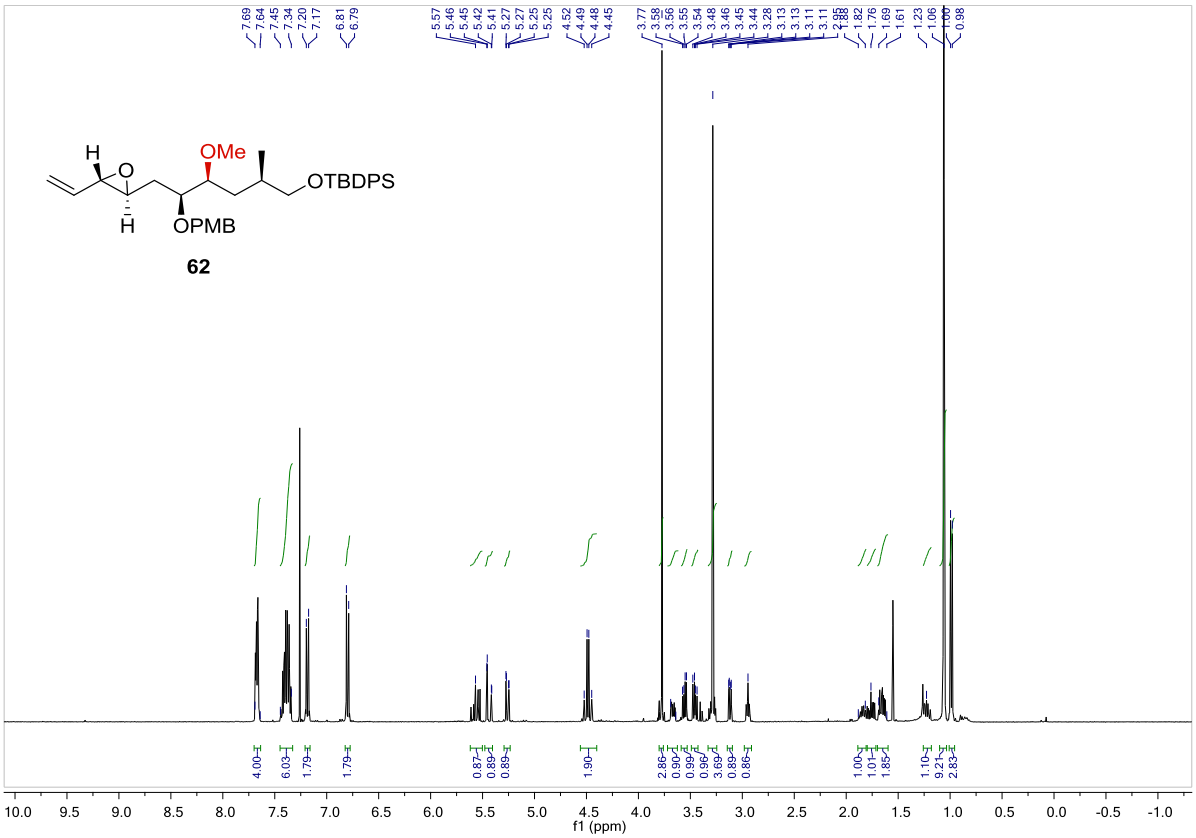

166.80
159.22
146.64
135.62
135.60
133.91
133.89
130.20
129.53
127.60
127.59
122.65
113.72
80.04
77.84
72.21
68.73
58.03
55.21
51.36
33.27
33.07
32.81
26.88
19.29
17.91
OMe
TBDPSO
COOMe
OPMB
59
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.68
7.65
7.44
7.34
7.20
7.18
6.82
6.80
5.67
5.67
5.66
5.66
5.65
5.64
4.48
4.46
4.43
4.41
4.04
4.03
3.77
3.56
3.54
3.46
3.45
3.43
3.37
3.31
3.27
3.22
2.34
2.28
2.26
2.17
1.87
1.77
1.67
1.55
1.28
1.06
0.99
0.98
OMe
TBDPSO
OH
OPMB
60
4.00
6.00
1.86
1.93
1.65
1.99
1.85
2.87
0.97
1.03
0.99
2.83
0.91
1.05
0.92
0.67
1.30
8.90
2.93
f1 (ppm)

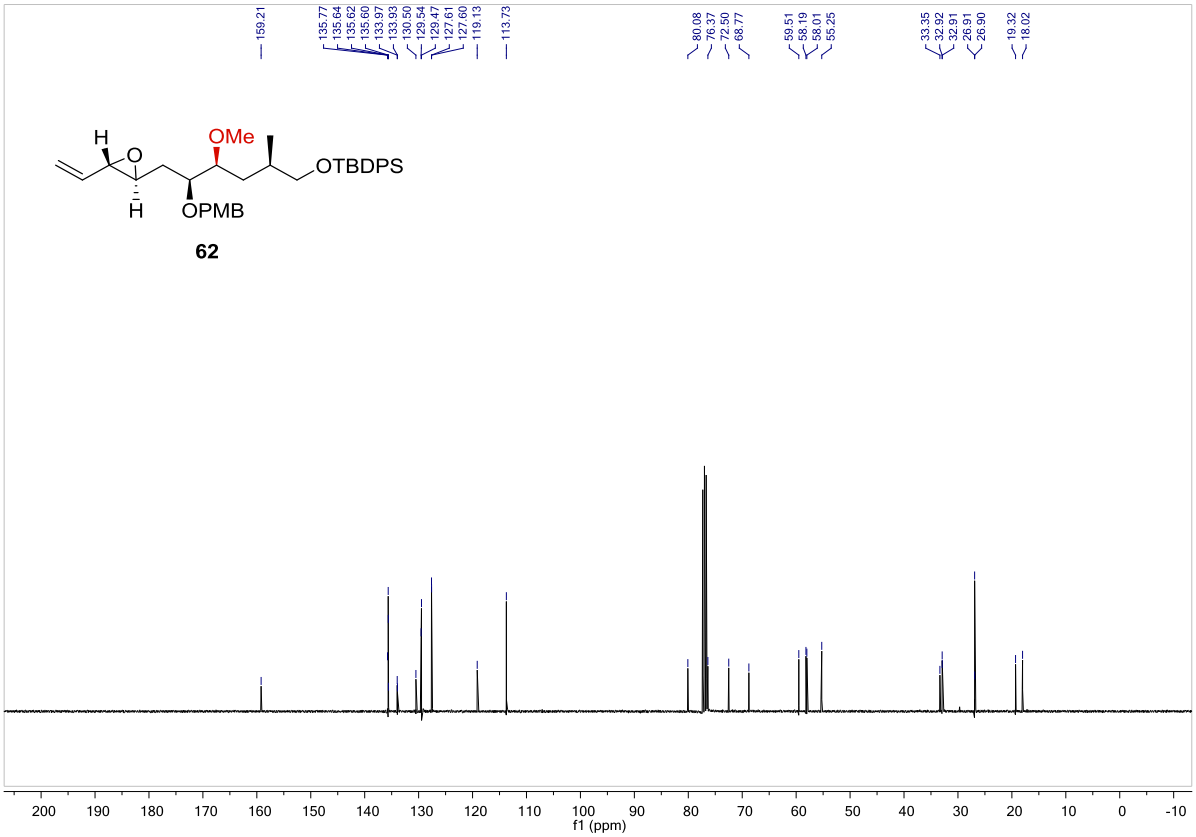

159.17
135.64
135.62
135.60
133.98
133.94
131.09
130.70
129.84
129.54
127.62
127.60
127.59
127.58
127.56
113.65
80.26
79.08
72.11
68.77
63.69
58.16
55.26
33.57
32.96
32.82
26.90
19.32
17.98
OMe
TBDPSO
OH
OPMB
60
f1 (ppm)


HO
H
O
H
OMe
OPMB
OTBDPS
61
f1 (ppm)

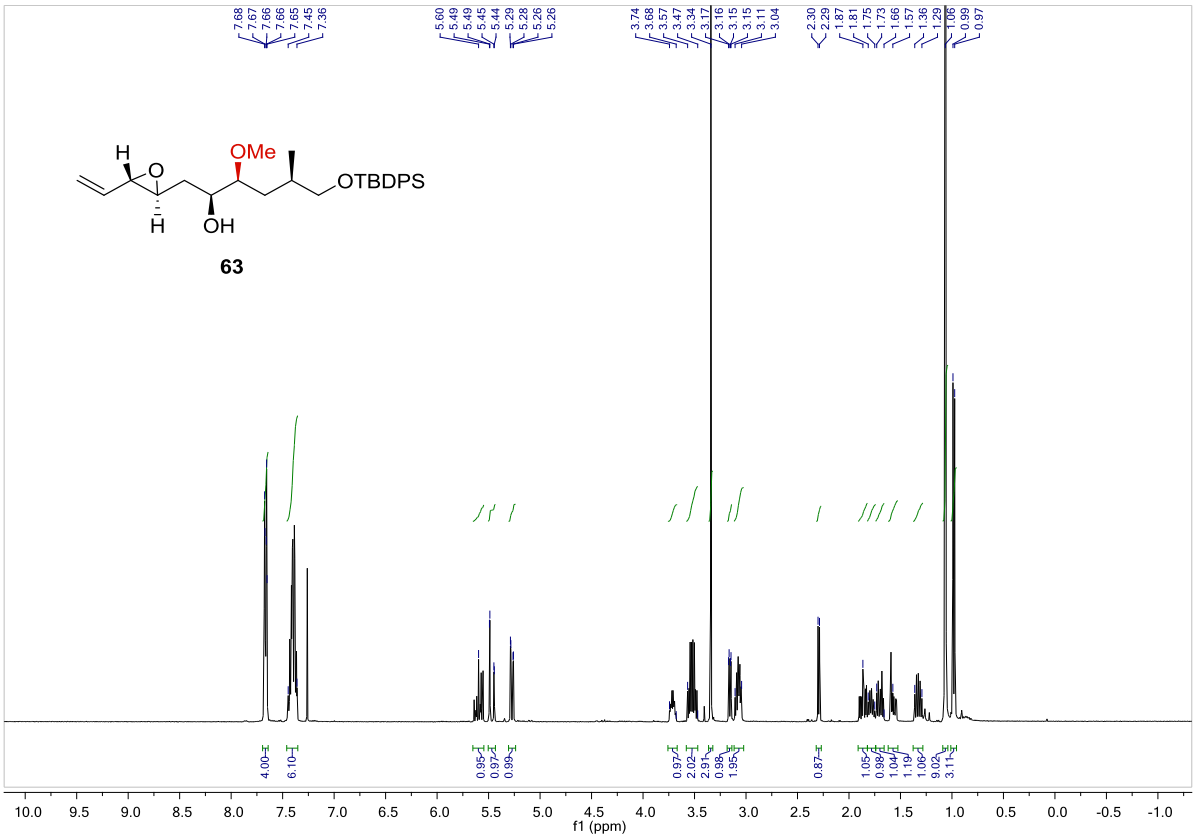

HO
H
O
H
OMe
OPMB
OTBDPS
61
f1 (ppm)

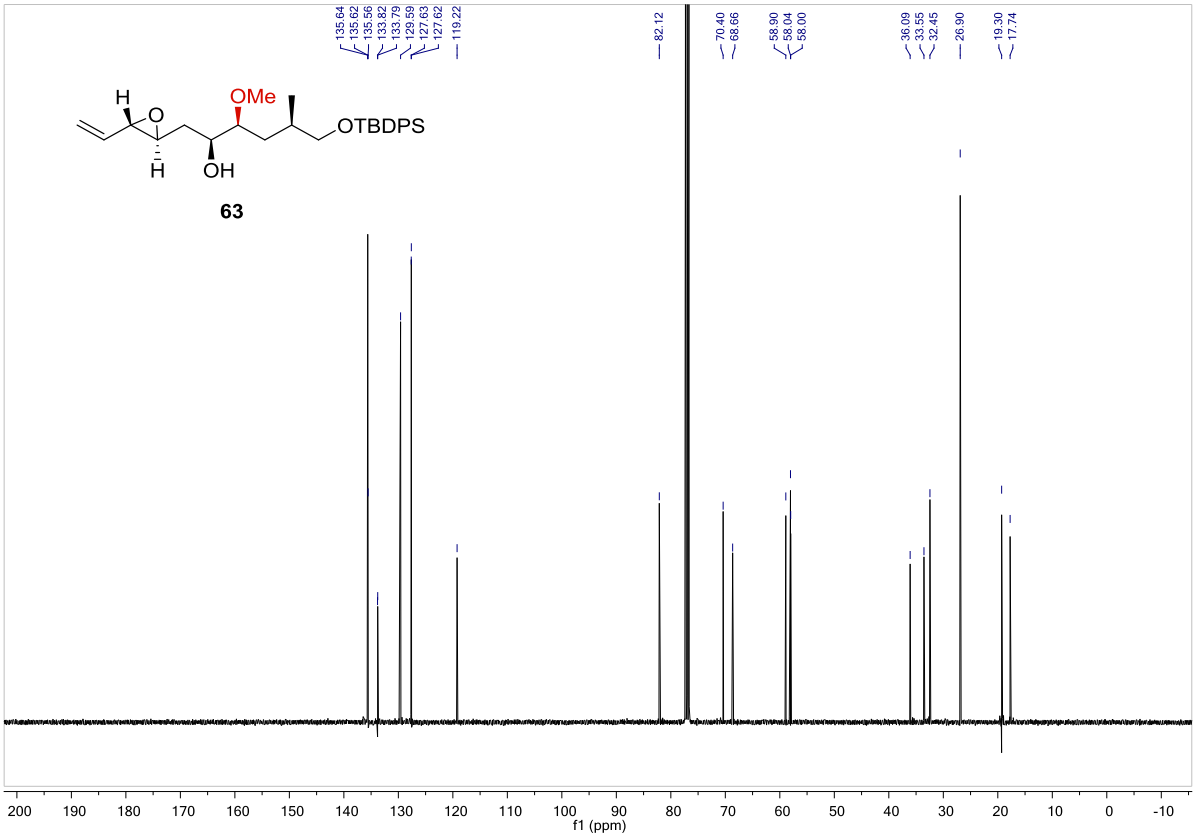


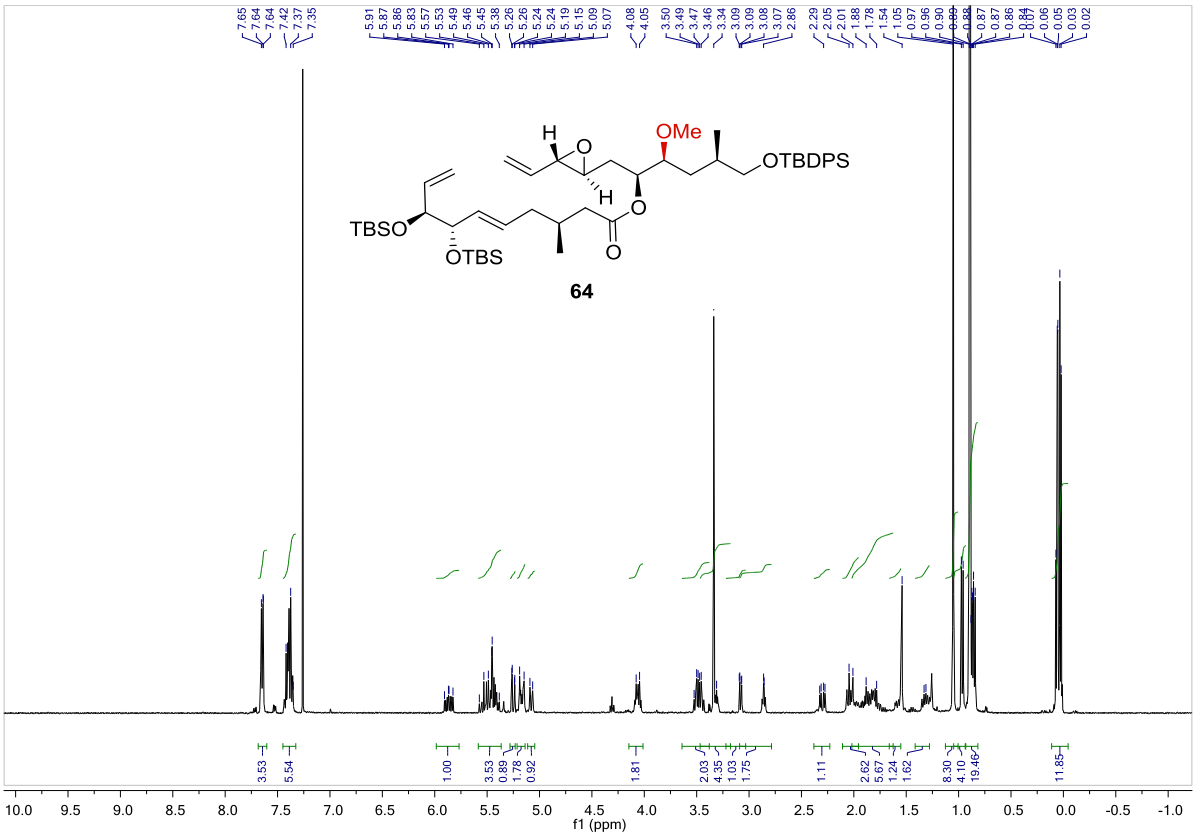
62

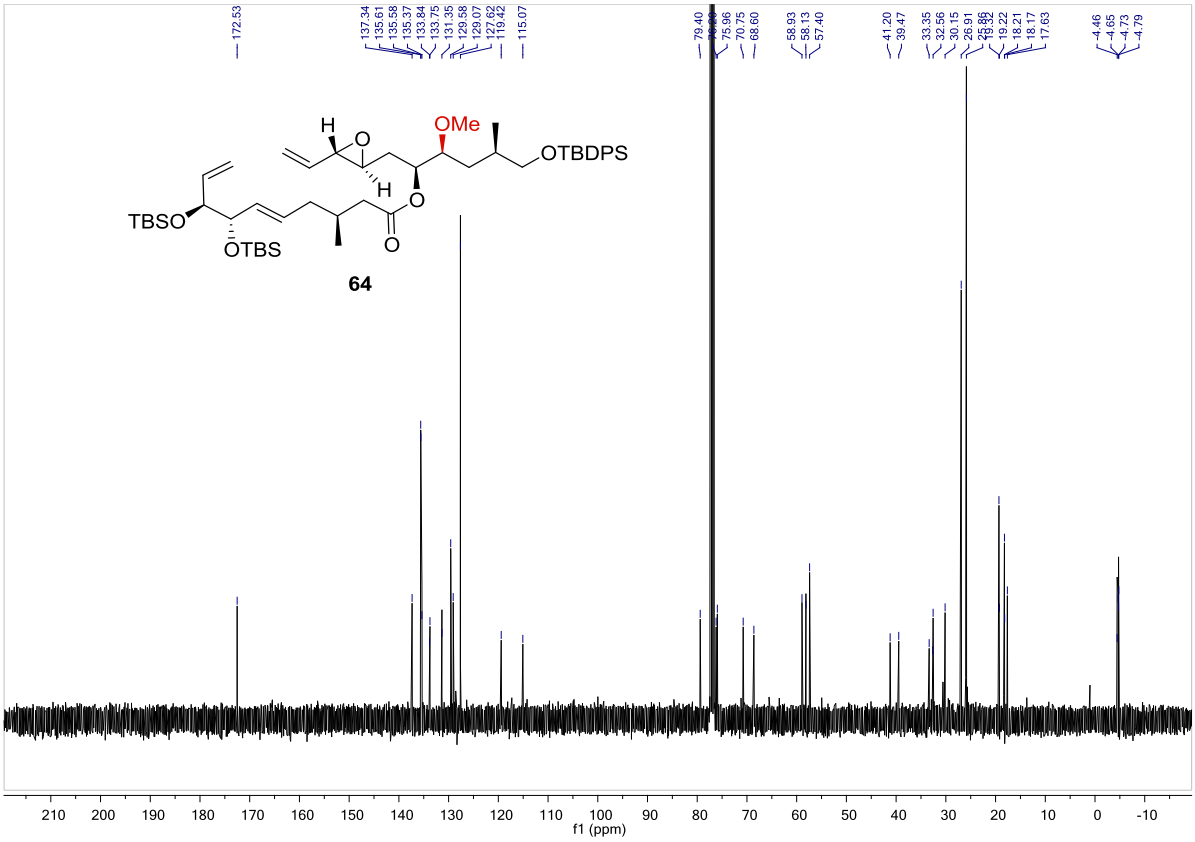


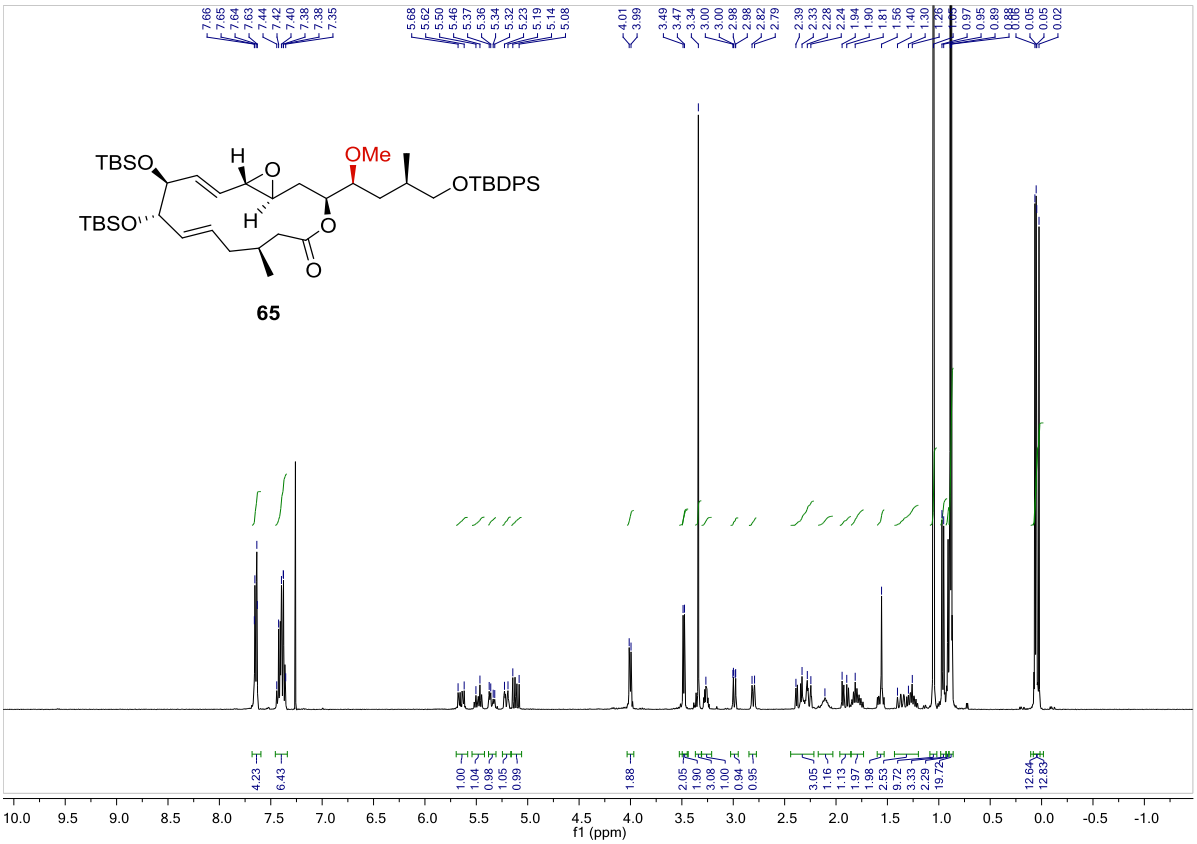
62

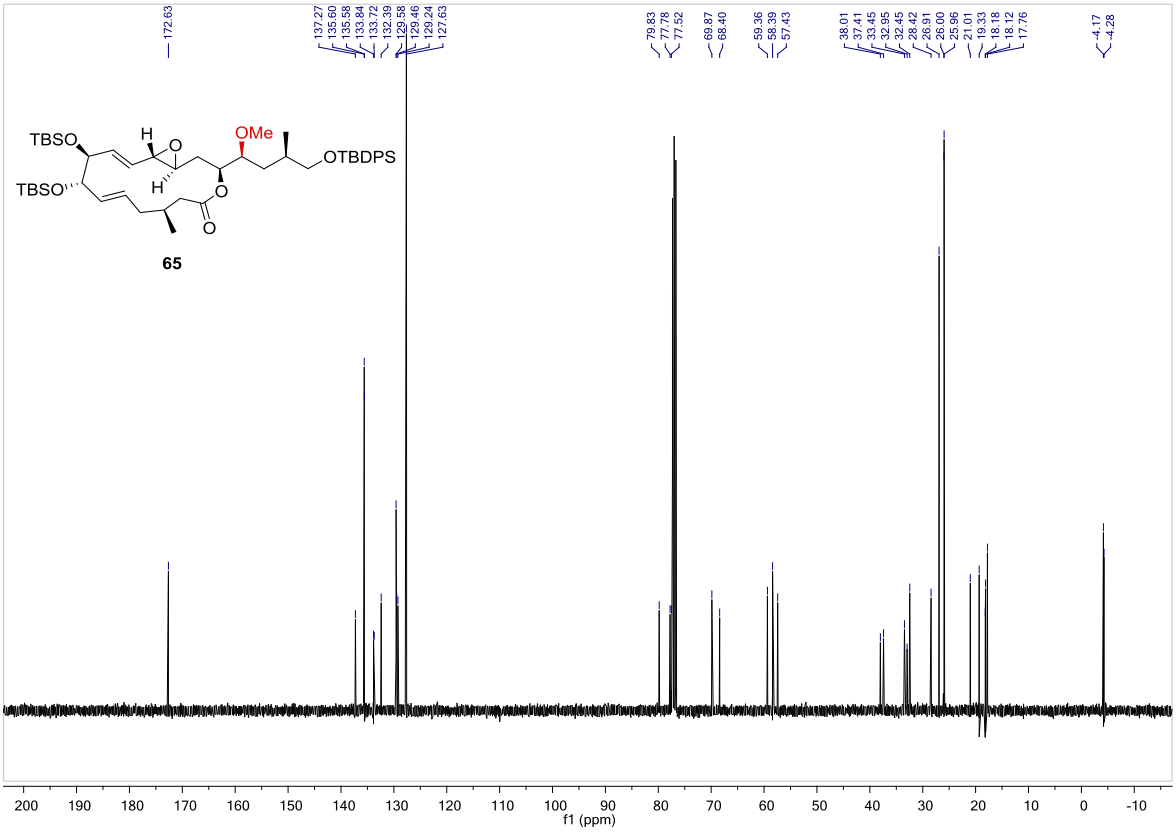

H
O
H
OMe
OH
OTBDPS
63
7.68
7.67
7.66
7.66
7.65
7.45
7.36
5.60
5.49
5.49
5.45
5.44
5.29
5.28
5.26
5.26
3.74
3.68
3.57
3.47
3.34
3.17
3.16
3.15
3.15
3.11
3.04
2.30
2.29
1.87
1.81
1.75
1.73
1.66
1.57
1.36
1.29
1.08
0.99
0.97
4.00
6.10
0.95
0.97
0.99
0.97
2.02
2.91
0.98
1.95
0.87
1.05
0.98
1.04
1.19
1.06
9.02
3.11
f1 (ppm)

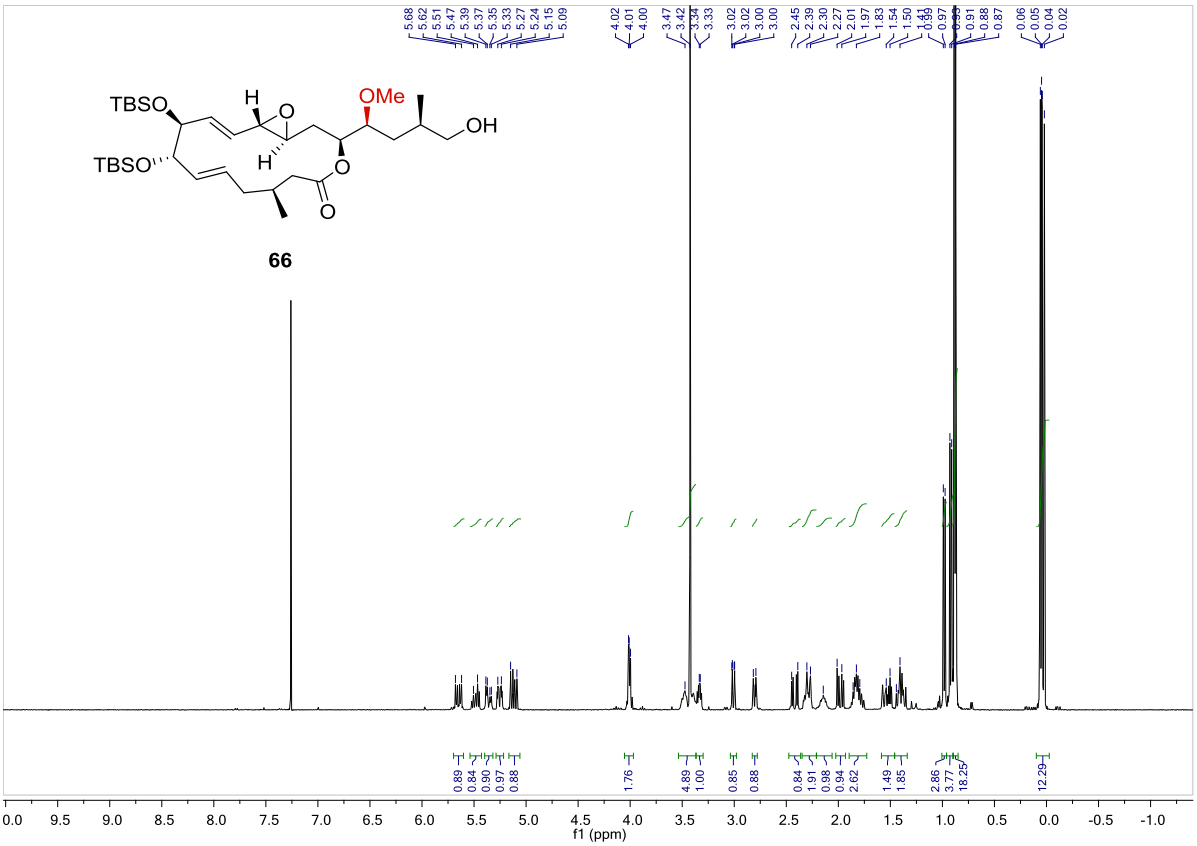

H
O
H
OMe
OH
OTBDPS
63
135.64
135.62
135.56
133.82
133.79
129.59
127.63
127.62
119.22
82.12
70.40
68.66
58.90
58.04
58.00
36.09
33.55
32.45
26.90
19.30
17.74
f1 (ppm)

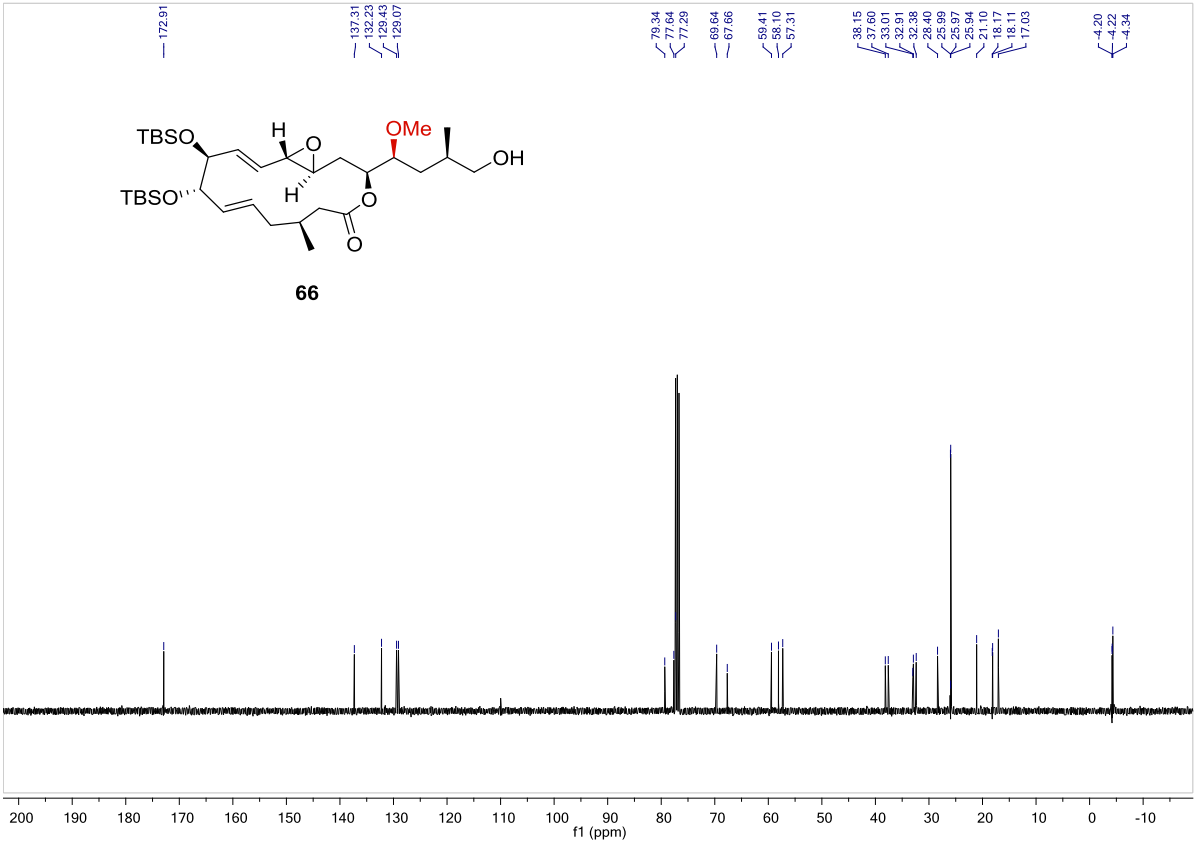

H
O
OMe
OTBDPS
H
O
TBSO
OTBS
O
64
f1 (ppm)

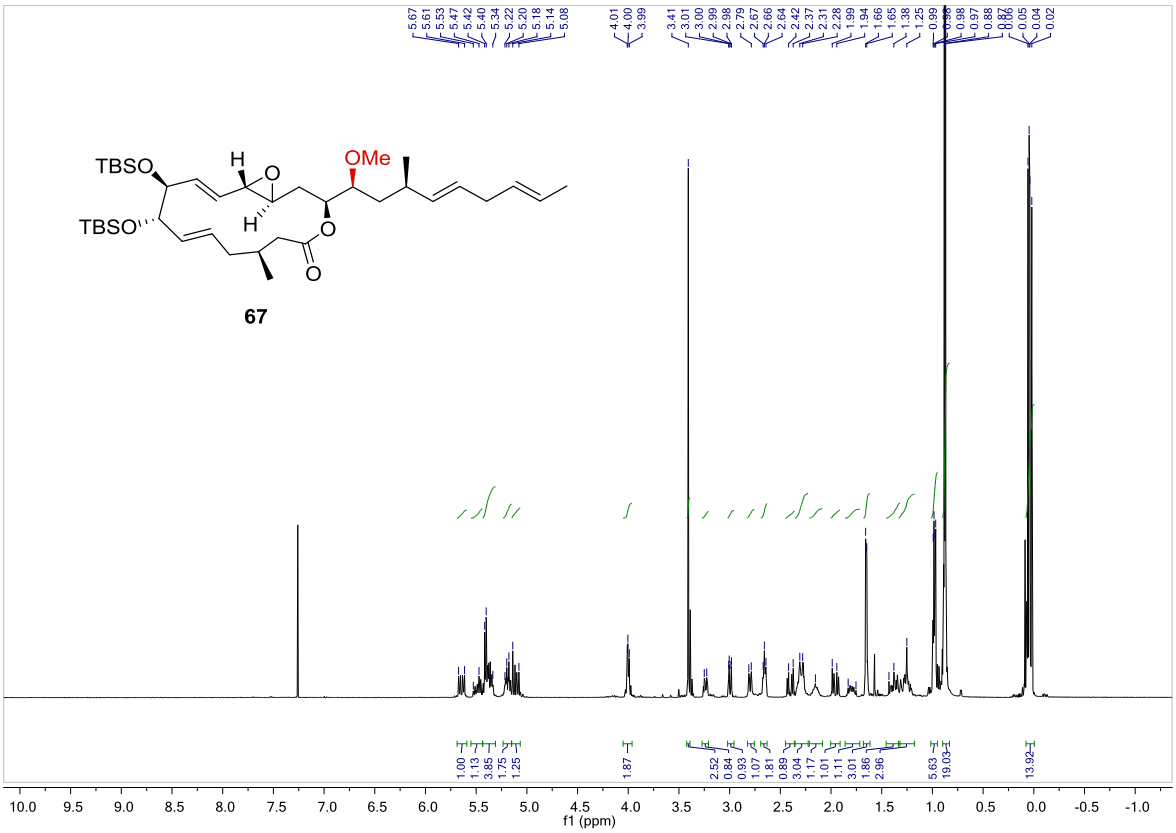

H
O
OMe
OTBDPS
H
O
TBSO
OTBS
O
64
f1 (ppm)

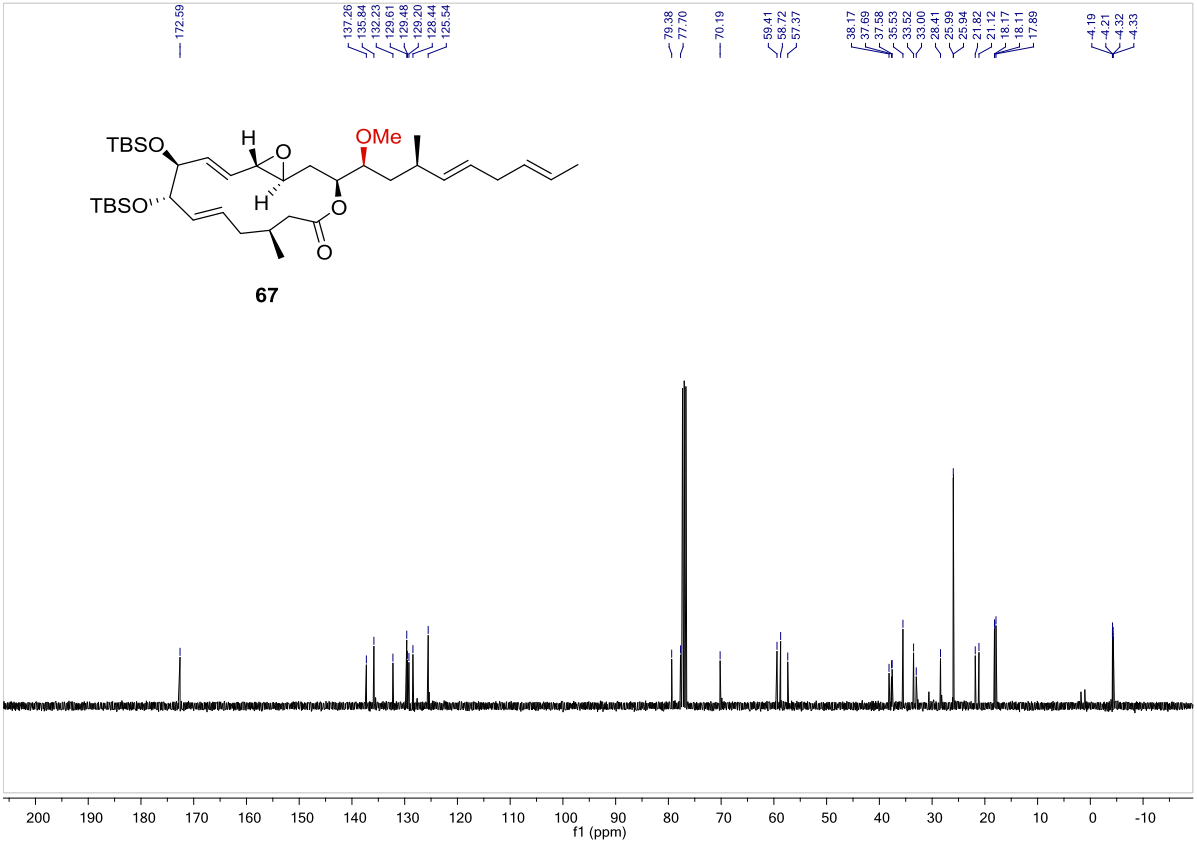

TBSO
H
O
OMe
OTBDPS
TBSO
H
O
O
O
65
f1 (ppm)

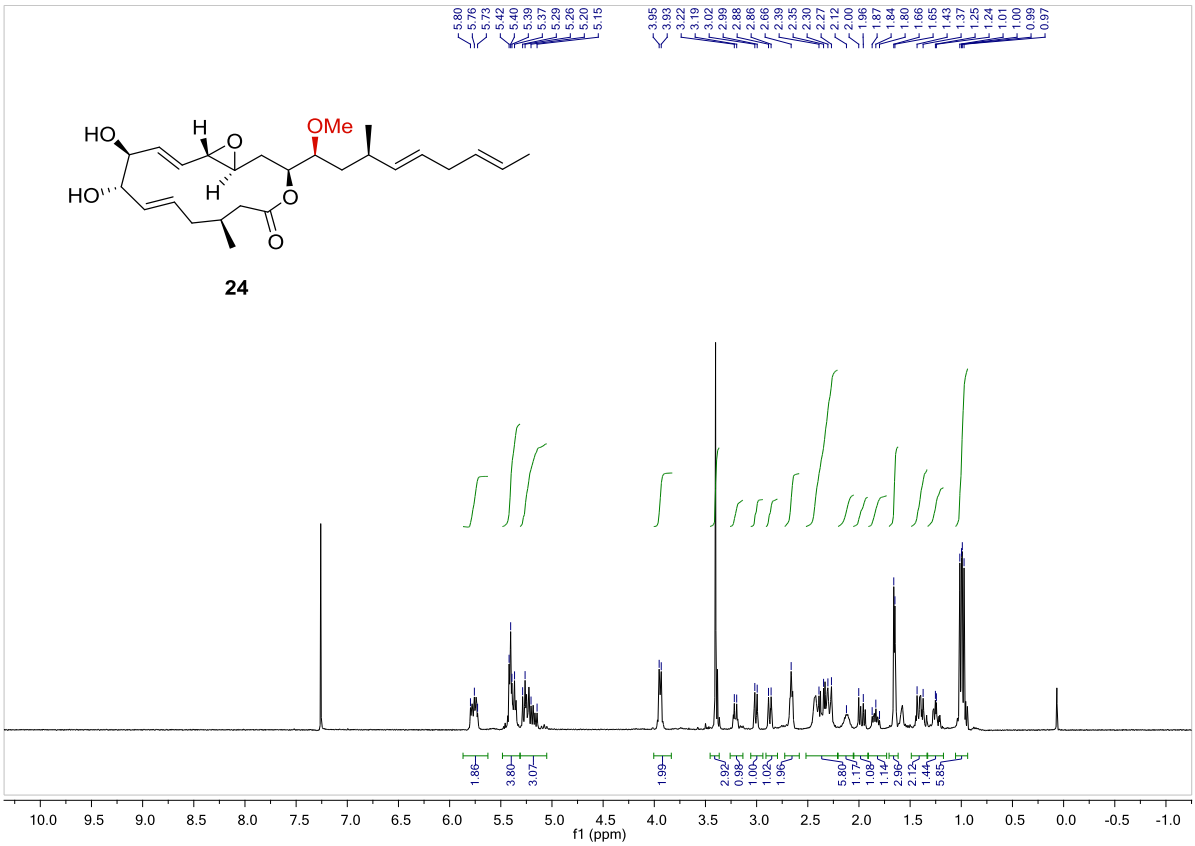

TBSO
H
O
OMe
OTBDPS
TBSO
H
O
O
65
f1 (ppm)

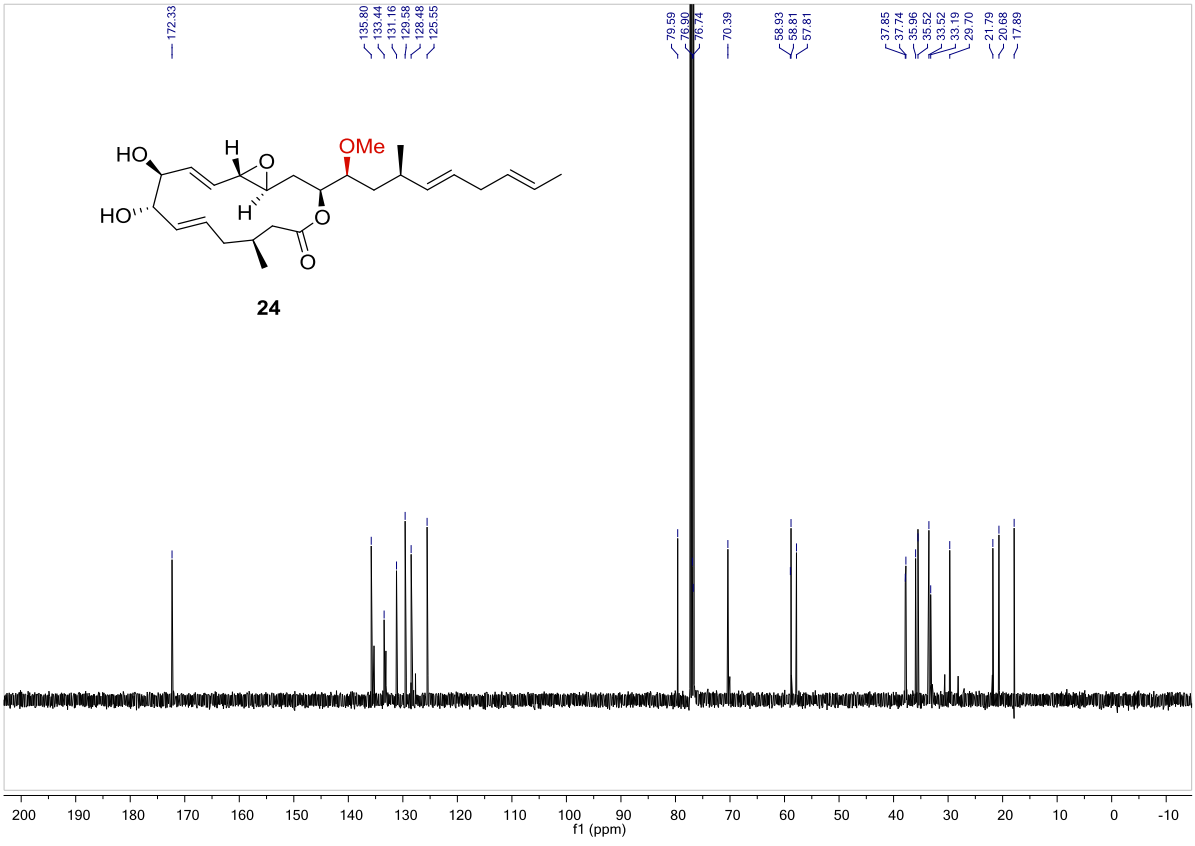

TBSO
H
O
OMe
OH
TBSO
H
O
O
66
f1 (ppm)

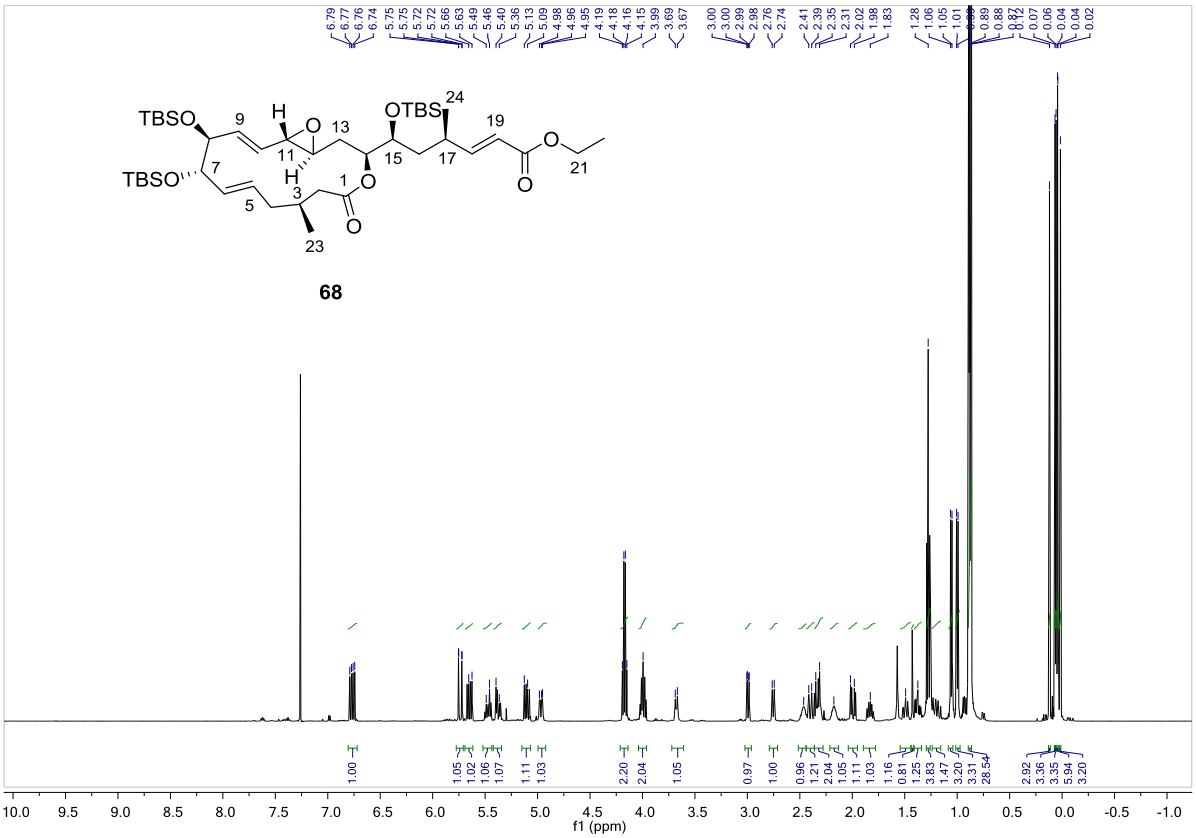

TBSO
H
O
OMe
OH
TBSO
H
O
O
66
f1 (ppm)

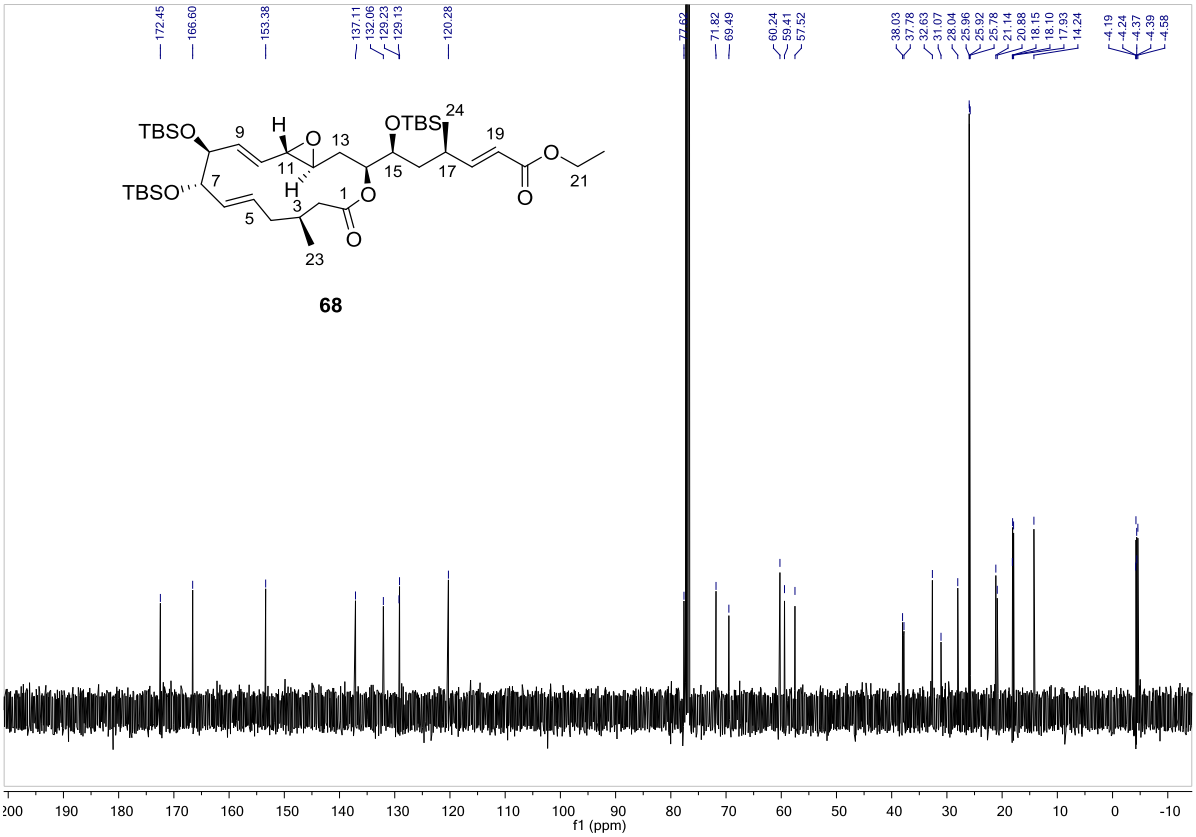

TBSO
TBSO
H
O
H
OMe
O
O
67
f1 (ppm)

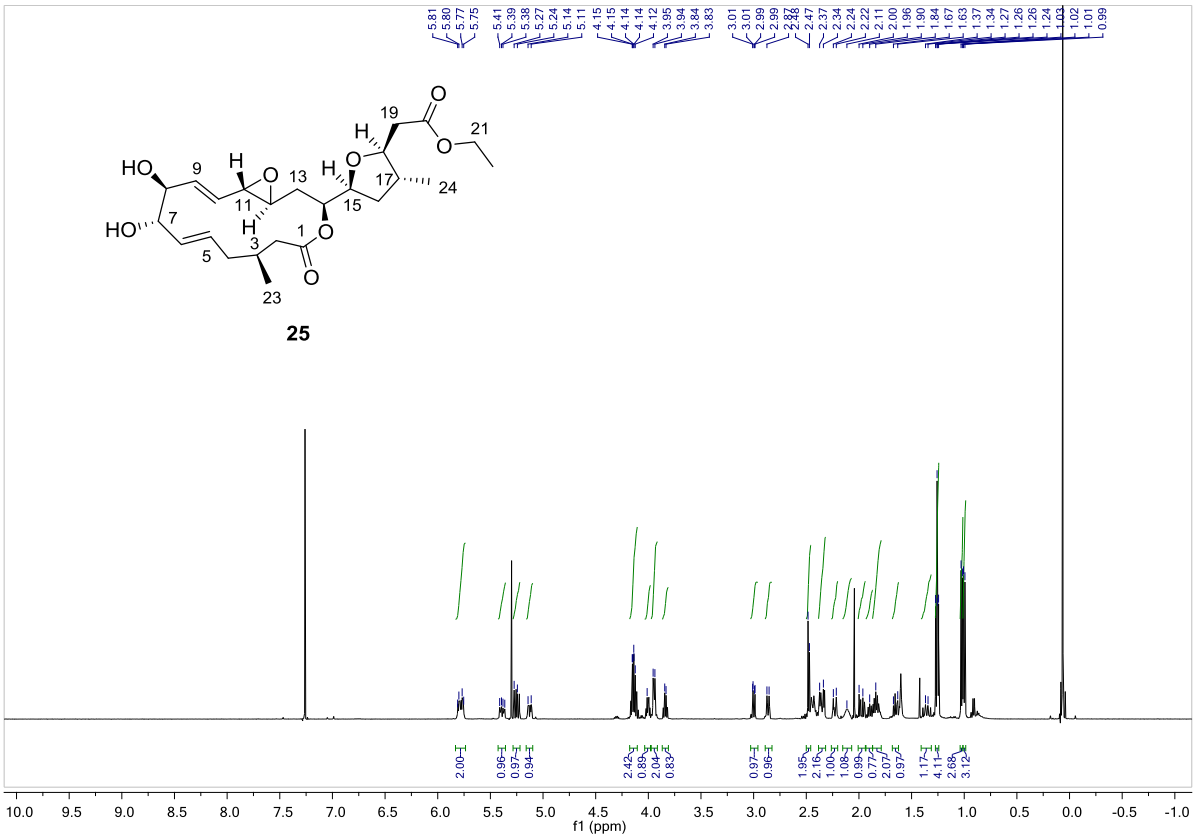

TBSO
TBSO
H
O
H
OMe
O
O
67
f1 (ppm)


HO
H
O
OMe
HO
H
O
O
O
24
f1 (ppm)

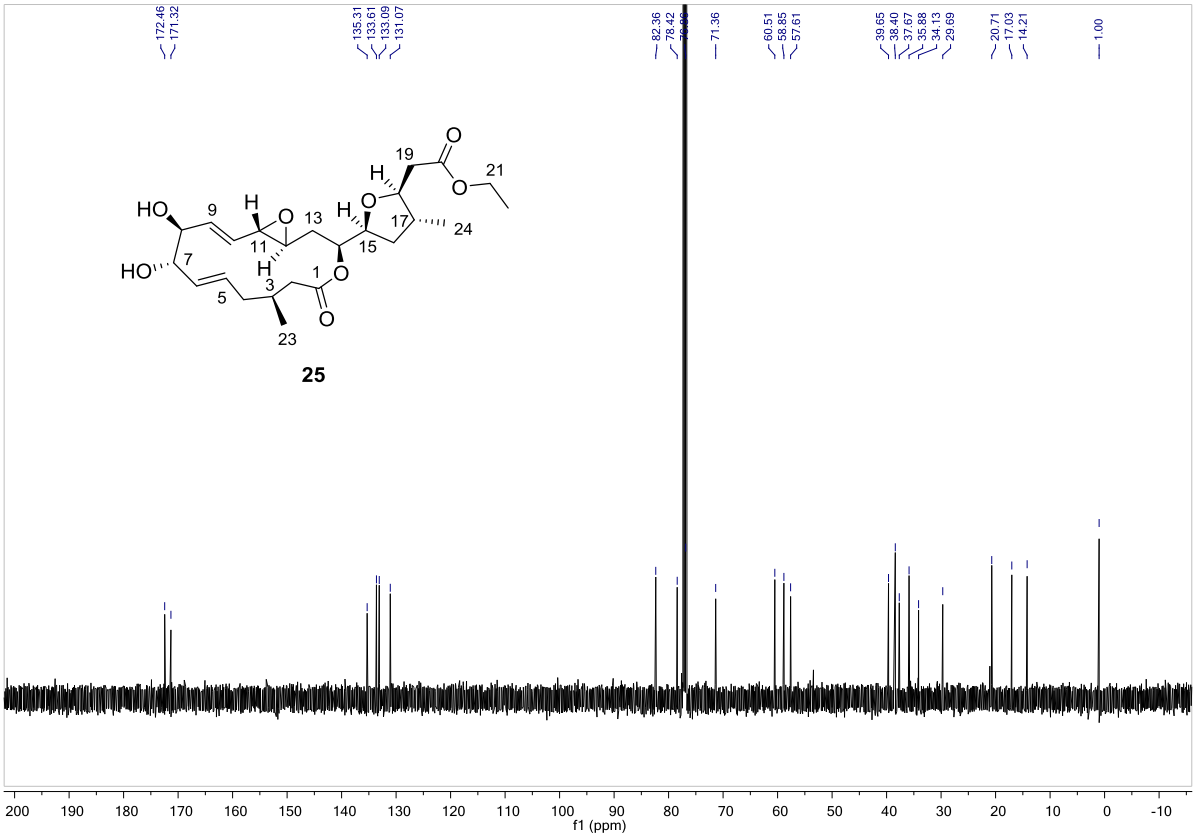

HO
H
O
OMe
HO
H
O
O
O
24
f1 (ppm)


TBSO
TBSO
OTBS
O
H
H
O
O
O
O
O
1
3
5
7
9
11
13
15
17
19
21
23
24
68
f1 (ppm)


TBSO
TBSO
OTBS
O
H
H
O
O
O
O
O
1
3
5
7
9
11
13
15
17
19
21
23
24
68
f1 (ppm)


5.81
5.80
5.77
5.75
5.41
5.39
5.38
5.27
5.24
5.14
5.11
4.15
4.15
4.14
4.14
4.12
3.95
3.94
3.84
3.83
3.01
3.01
2.99
2.99
2.87
2.48
2.47
2.37
2.34
2.24
2.22
2.11
2.00
1.96
1.90
1.84
1.67
1.63
1.37
1.34
1.27
1.26
1.26
1.24
1.03
1.02
1.01
0.99
HO
HO
O
O
O
O
O
H
H
H
H
1
3
5
7
9
11
13
15
17
19
21
23
24
2.00
0.96
0.97
0.94
2.42
0.89
2.04
0.83
0.97
0.96
1.95
2.16
1.00
1.08
0.99
0.77
2.07
0.97
1.17
4.11
2.68
3.12
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

25


172.46
171.32
135.31
133.61
133.09
131.07
82.36
78.42
76.66
71.36
60.51
58.85
57.61
39.65
38.40
37.67
35.88
34.13
29.69
20.71
17.03
14.21
1.00
HO
HO
O
O
O
O
O
H
H
H
H
1
3
5
7
9
11
13
15
17
19
21
23
24
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

25