Total Synthesis of Cruentaren A

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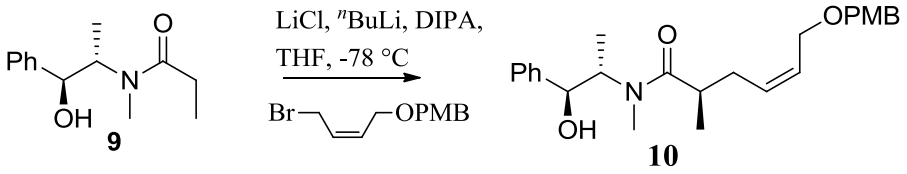
Methods and Experimental

General Methods. All reactions were carried out in flame dried glassware under argon atmosphere unless otherwise stated. Dichloromethane (DCM), diethyl ether, tetrahydrofuran (THF), and toluene were purchased from Sigma Aldrich and were passed through a column of activated alumina prior to use. Anhydrous methanol, acetonitrile, dimethylformamide (DMF), and dimethoxymethane (DME) were purchased from Sigma Aldrich and used without further purification. All reagents and other solvents ethyl acetate (EtOAc) and hexanes were purchased from Sigma Aldrich and were used without further purification unless otherwise stated. Flash column chromatography was performed using silica gel (40–63 mm particle size) from Sorbent Technologies. The ^{1}H and ^{13}C NMR spectra were recorded at 500 and 126 MHz, respectively, on a Bruker AM 500 using $CDCl_3$ or benzene-D_6 purchased from Cambridge Isotope Laboratories, Inc., using solvent as an internal standard ($CDCl_3$ at 7.27 ppm for ^{1}H and 77.16 ppm for ^{13}C, benzene-D_6 at 7.16 ppm for ^{1}H and 128.1 ppm for ^{13}C) or tetramethylsilane (0.00 ppm) unless

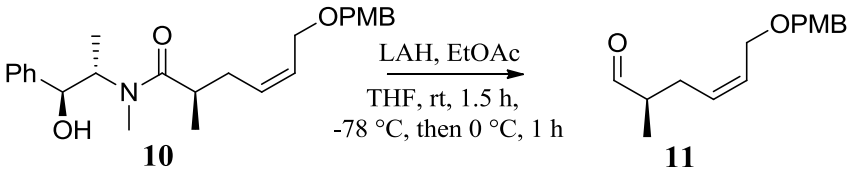
otherwise stated. Data are reported as h = hextet, p = pentet, q = quartet, t = triplet, d = doublet, s = singlet, bs = broad singlet, m = multiplet; coupling constant(s) in Hz. Two-dimensional NMR experiments were run on a Bruker AM 500 at 500 MHz High resolutions mass spectral data were obtained on a Ribermag R10-10 quadrupole, VG Analytical ZA. Optical rotations were recorded with a Perkin Elmer polarimeter at 589 nm at 25 °C with concentration reported as g/mL.

Experimental Section:



(R,Z)-N-((1S,2S)-1-hydroxy-1-phenylpropan-2-yl)-6-((4-methoxybenzyl)oxy)-N,2-dimethylhex-4-enamide (10): A 1 L round bottom flask was flame dried and flushed with argon before THF (82 mL), anhydrous lithium chloride (15.4 g, 363 mmol), and DIPA (17.54 mL, 124 mmol) were added. The solution was cooled to -78 °C and *n*-butyllithium (2.5 M in hexanes, 46.1 mL, 115 mmol) was added slowly to maintain temperature. The reaction mixture was briefly warmed to 0 °C and subsequently cooled back to -78 °C. *N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylpropionamide **9** (13.31 g, 60.4 mmol) was then added in anhydrous THF (192 mL) *via* cannula. The reaction mixture was stirred at -78 °C for 1 h, 0 °C for 20 min, rt for 5 min, and then cooled to 0 °C before (*Z*)-1-(((4-bromobut-2-en-1-yl)oxy)methyl)-4-methoxybenzene **8** (12.6 g, 46.5 mmol) was added in one portion. Stirring was continued for 2 hr at 0 °C, at which point the reaction was quenched by the careful addition of half-saturated, aqueous ammonium chloride (100 mL). The organic layer was collected, and the aqueous layer was extracted with EtOAc (3 X 150 mL). The combined organic layers were collected, dried

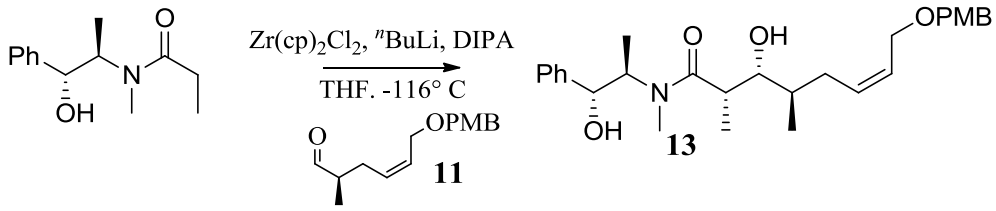
over anhydrous sodium sulfate, and solvent was removed under reduced pressure to afford a yellow oil that was purified by SiO_2 flash chromatography (30% – 5% EtOAc in hexanes) to provide pure **10** as a colorless oil (17.6 g, 93%). $[\alpha]^{25}_D$ = 71.3° (*c* = 0.093, DCM); (*Denotes minor rotamer peak) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 5H), 7.29 – 7.23 (m, 2H), 6.93 – 6.79 (m, 2H), 5.72 – 5.55 (m, 1H), 5.50 – 5.40 (m, 1H), 4.67 – 4.51 (m, 1H), 4.44 (s, 2H), *4.44 (s, 2H), 4.44 (m, 2H), 4.15 – 3.97 (m, 4H), 3.80 (s, 3H), *3.79 (s, 3H), 2.83 (s, 3H), 2.87 – 2.76 (m, 1H), *2.81 (s, 3H), 2.68 – 2.59 (m, 1H), 2.51 (m, 1H), 2.38 – 2.26 (m, 1H), *2.17 – 2.06 (m, 1H), 1.15 – 1.11 (m, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), *1.00 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.4, *176.5, 159.3, 142.66, *141.2, *130.5, 130.5, 129.6, *128.5, 128.5, *127.8, 127.7, *127.1, 127.0, *126.5, 126.4, 113.9, 77.4, 76.6, 72.2, *72.1, *65.8, 65.7, 55.4, 37.0, 32.0, 27.8, 17.2, *14.7, 14.6; HRMS (ESI, *m/z*): calcd for $[C_{25}H_{33}NO_4+Na]^+$, ($[M + Na]^+$): 434.2307, found 434.2306.



10 **11**

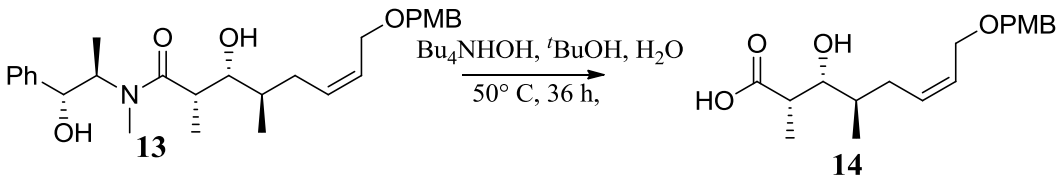
(*R*,*Z*)-6-((4-methoxybenzyl)oxy)-2-methylhex-4-enal (11): A 1 L flask was flame dried and flushed with argon before anhydrous hexanes (170 mL) and solid lithium aluminum hydride (95%, 2.95 g, 73.9 mmol) were added. The suspension was cooled to 0 °C and EtOAc (10.7 mL, 110 mmol) was added by addition funnel over a period of 1.5 h followed by cooling to -78 °C. A solution of amide **10** (10.0 g, 32.1 mmol) in anhydrous THF (110 mL) was added via cannula over 5 min, and the reaction mixture was warmed to 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was transferred by cannula to a solution of trifluoroacetic acid (5 mL, 65 mmol) in 0.5 N aqueous hydrochloric acid solution (400 mL) at 0 °C. The resulting biphasic mixture

was stirred at 0 °C for 20 min and then diluted with 0.1 N aqueous hydrochloric acid solution (700 mL) when the layers were separated. The aqueous layer was extracted with EtOAc (3 X 150 mL). The combined organic layers were neutralized by the cautious addition of saturated aqueous sodium bicarbonate (250 mL). The aqueous layer (pH 7-8) was separated and extracted with EtOAc (100 mL). The combined organic extracts were dried over anhydrous sodium sulfate and solvent was removed under reduced pressure to afford a yellow oil that was purified by SiO_2 flash chromatography (5% – 10% EtOAc in hexanes) to afford aldehyde **11** as a colorless oil (6.7 g, 84 %). $[\alpha]^{25}_{D}$ = -4.6° (*c* = 0.021, DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.20 – 7.15 (m, 2H), 6.82 – 6.74 (m, 2H), 5.66 – 5.57 (m, 1H), 5.51 – 5.42 (m, 1H), 4.36 (s, 2H), 3.96 (dd, *J* = 6.5, 1.4 Hz, 2H), 3.70 (s, 3H), 2.46 – 2.26 (m, 2H), 2.17 – 1.98 (m, 1H), 1.00 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.4, 159.2, 130.24 129.5, 129.4, 128.7, 113.8, 72.0, 65.3, 55.3, 46.2, 28.4, 13.1.

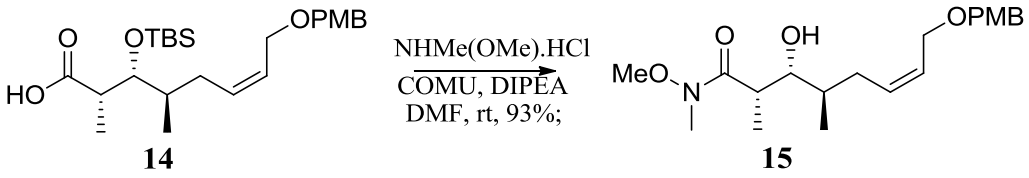


(2S,3R,4R,Z)-3-hydroxy-N-((1R,2R)-1-hydroxy-1-phenylpropan-2-yl)-8-((4-methoxybenzyl)oxy)-N,2,4-trimethyloct-6-enamide (13): A 500 mL flask was flame dried and flushed with argon before anhydrous THF (45 mL) and DIPA (4.78 mL, 33.8 mmol) were added. The solution was cooled to -78 °C and *n*-butyllithium (2.5 M in hexanes, 13.2 mL, 33 mmol) was slowly added. Stirring was continued as the solution was allowed to warm to 0 °C and then cooled back to -78 °C at which point a solution of (*R*,*R*)-pseudoephedrine propionamide **12** (3.56 g, 16.1 mmol) in anhydrous THF (45 mL) was added slowly *via* cannula. Stirring was continued at -78 °C for 2 h, 0 °C for 30 min, and rt for 10 min. The reaction mixture was cooled back to -78

°C followed by the addition of a solution of bis(cyclopentadienyl)zirconium(IV) dichloride (10.34 g, 35.4 mmol) in anhydrous THF (100mmL). The deep orange solution was stirred at -78 °C for 3 h and then cooled to -116 °C when a solution of aldehyde **11** (4 g, 16.1 mmol) in anhydrous THF (10 mL) was added dropwise. Stirring was continued at -116 °C for 3 h at which point the reaction was quenched by the addition of saturated aqueous ammonium chloride (50 mL). The biphasic reaction mixture was warmed to rt and filtered through a pad of celite using EtOAc (300 mL) to rinse. The organic layer was collected, and the aqueous layer was extracted with EtOAc (3 X 100 mL). The combined organic layers were dried over anhydrous sodium sulfate and solvent was removed under reduced pressure to afford an orange oil that was purified by SiO_2 flash chromatography (40% –70%) to provide pure **13** as a colorless oil (6.7 g, 88 %). $[\alpha]^{25}_D$ = -45.6° (c = 0.123, DCM). (*Denotes minor rotamer peak) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 5H), *7.30 – 7.28 (m, 5H), 7.28 – 7.24 (m, 2H), 6.89 – 6.84 (m, 2H), 5.71 – 5.54 (m, 2H), 5.07 (d, *J* = 0.7 Hz, 1H), 4.63 (bs, 1H), 4.68 – 4.56 (m, 1H), *4.54 (d, *J* = 8.2 Hz, 1H), *4.50 (d, *J* = 1.4 Hz, 1H), 4.43 (s, 2H), *4.42 (s, 2H), 4.07 (d, *J* = 6.4 Hz, 2H), *4.04 – 3.97 (m, 1H), 3.79 (s, 3H), *3.77 (s, 3H), 3.45 (dd, *J* = 16.7, 7.7 Hz, 1H), *3.07 – 2.99 (m, 1H), 2.91 (s, 3H), *2.87 (s, 3H), 2.76 – 2.69 (m, 1H), 2.50 – 2.38 (m, 1H), 2.01 (m, 1H), 1.70 – 1.58 (m, 1H), *1.09 (d, *J* = 6.5 Hz, 3H), 1.07 (d, *J* = 7.1 Hz, 3H), 1.06 (d, *J* = 7.3 Hz, 3H), *1.00 (d, *J* = 7.0 Hz, 3H), 0.78 (d, *J* = 5.6 Hz, 3H), *0.77 (d, *J* = 5.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.7, *179.7, 159.3, *159.2, 142.1, *141.5, 131.9, 131.6, *130.7, *130.6, *129.6, 129.5, 129.0, *128.6, 128.6, *128.0, 127.9, *127.7, 126.7, 126.5, 113.8, 76.3, *75.6, 74.6, 72.0, 71.9, 65.8, *58.0, 55.4, 36.8, *35.6, 35.4, 35.4, *31.0, 30.7, *27.3, *15.7, 15.4, *15.2, 14.3, *9.8, 9.3; HRMS (ESI, *m/z*): calcd for $[C_{28}H_{39}NO_5+K]^+$, ($[M + K]^+$): 508.2465, found 508.2466.

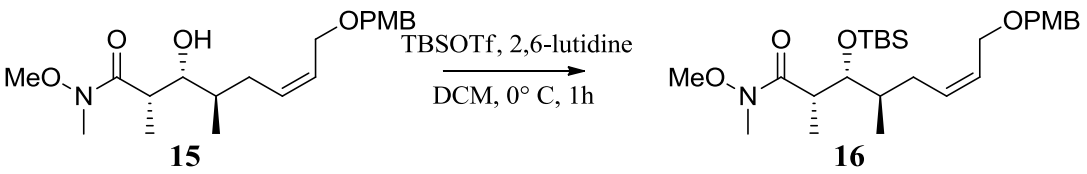


(2S,3R,4R,Z)-3-hydroxy-8-((4-methoxybenzyl)oxy)-2,4-dimethyloct-6-enoic acid (14): A 500 mL flask was charged with amide **13** (8.4 g, 18 mmol), *tert*-butylalcohol (55 mL), and water (180 mL). A 1.5 M aqueous solution of tetrabutylammonium hydroxide (60 mL, 90 mmol) was added and the reaction mixture was heated at reflux for 20 hr. After cooling to rt, the reaction mixture was partitioned between 0.5 N aqueous sodium hydroxide (2.3 L) and diethyl ether (320 mL). The organic layer was removed, and the aqueous layer was extracted with diethyl ether (3 X 320 mL). The aqueous layer was collected, cooled to 0 °C, acidified to pH 3, saturated with sodium chloride, and then extracted with diethyl ether (3 X 300 mL). The organic extracts were collected, dried over anhydrous sodium sulfate, and solvent was removed under reduced pressure to afford pure acid **13** (5.5 g, 95 %). $[\alpha]^{25}_{D}$ = -3.7° (*c* = 0.172, DCM). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.09 (s, 1H), 7.30 – 7.22 (m, 2H), 6.92 – 6.82 (m, 2H), 5.81 – 5.67 (m, 2H), 4.46 (s, 2H), 4.10 (dd, *J* = 11.0, 6.3 Hz, 1H), 3.95 (dd, *J* = 11.1, 6.0 Hz, 1H), 3.81 (s, 3H), 3.68 (dd, *J* = 9.5, 2.6 Hz, 1H), 2.67 (qd, *J* = 7.2, 2.7 Hz, 1H), 2.39 – 2.30 (m, 1H), 2.21 (dt, *J* = 9.1, 4.3 Hz, 1H), 1.83 – 1.72 (m, 1H), 1.19 (d, *J* = 7.2 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.6, 159.6, 132.6, 129.9, 127.1, 114.0, 77.4, 73.8, 72.6, 65.1, 55.5, 41.3, 35.4, 31.0, 15.9, 9.6; HRMS (ESI, *m/z*): calcd for $[C_{36}H_{48}O_{10}+Na]^-$, $[2M+Na–2H]^+$): 665.3302, found 665.3301.



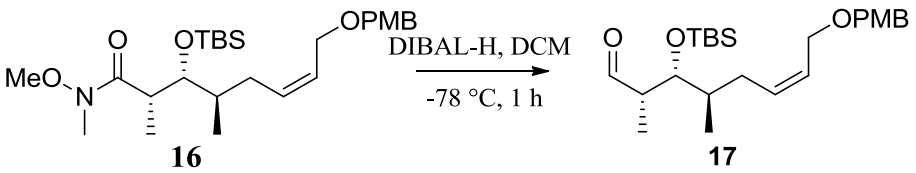
14 **15**

(2*S*,3*R*,4*R*,*Z*)-3-hydroxy-*N*-methoxy-8-((4-methoxybenzyl)oxy)-*N*,2,4-trimethyloct-6-enamide (15): A 250 mL flask was flame dried and flushed with argon before DMF (40 mL), acid **14** (5.50 g, 17.1 mmol), and DIPEA (6.3 mL, 36 mmol) were added. COMU (8.14 g, 1.9 mmol) was then added in one portion and the reaction mixture was stirred at rt for 45 min at which point *N*,*O*-Dimethylhydroxylamine hydrochloride (3.35 g, 34.2 mmol) was added. Stirring was continued for 1 hr and the reaction was quenched by the careful addition of saturated aqueous sodium bicarbonate (30 mL). The resulting slurry was then extracted with EtOAc (3 X 50 mL) and the combined organic portions were dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure to afford a red oil that was purified by SiO_2 flash chromatography (25% – 45% EtOAc in hexanes) to provide pure amide **15** as a yellow oil (5.8 g, 93 %). $[\alpha]^{25}_{D}$ = -2.1° (*c* = 0.01, DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, 2H), 6.88 – 6.83 (m, 2H), 5.71 – 5.55 (m, 2H), 4.43 (s, 2H), 4.11 (bs, 1H), 4.07 (d, *J* = 6.0 Hz, 2H), 3.78 (s, 3H), 3.68 (s, 3H), 3.50 (dd, *J* = 9.2, 1.9 Hz, 1H), 3.18 (s, 3H), 3.10 – 3.03 (m, 1H), 2.48 – 2.39 (m, 1H), 2.05 (dt, *J* = 14.0, 8.5 Hz, 1H), 1.67 (tqd, *J* = 13.6, 6.9, 3.5 Hz, 1H), 1.13 (d, *J* = 7.1 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.7, 159.2, 131.5, 130.6, 129.5, 127.9, 113.8, 77.4, 74.8, 71.9, 65.8, 61.6, 55.3, 35.5, 32.00, 30.7, 15.3, 9.6; HRMS (ESI, *m/*z): calcd for $[C_{20}H_{31}NO_5+K]^+$, ($[M + K]^+$): 404.1839, found 404.1839.



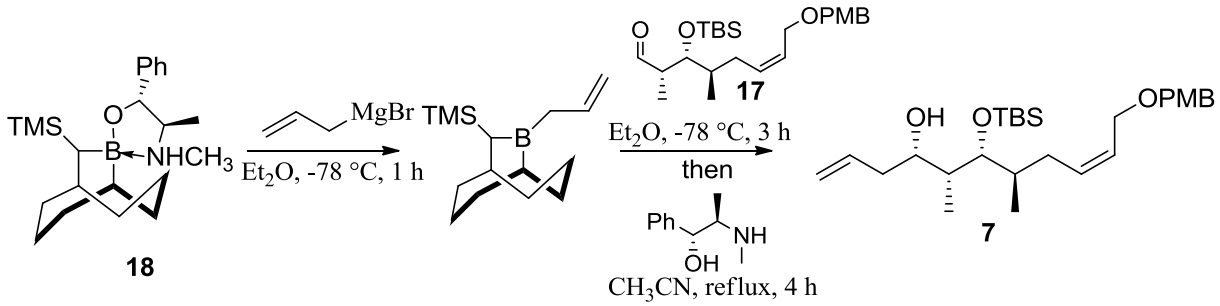
15 **16**

(2*S*,3*R*,4*R*,*Z*)-3-((*tert*-butyldimethylsilyl)oxy)-*N*-methoxy-8-((4-methoxybenzyl)oxy)-*N*,2,4-trimethyloct-6-enamide (16): A flame dried 50 mL flask was flame dried and flushed with argon before DCM (13 mL), amide **15** (1.0 g, 2.7 mmol), and 2-6-lutidine (0.70 mL, 5.94 mmol) were added. The solution was cooled to 0 °C, *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.24 mL, 5.4 mmol) was added dropwise, and stirring was continued for 30 min as the reaction mixture was allowed to warm to rt at which point the reaction was quenched by the addition of saturated aqueous sodium bicarbonate (10 mL). The organic layer was collected, and the aqueous layer was extracted with DCM (3 X 5 mL). The combined organic layers were dried over anhydrous sodium sulfate and solvent was removed under reduced pressure to afford a yellow oil that was purified by SiO_2 flash chromatography (20% EtOAc in hexanes) to provide pure amide **16** as a colorless oil (1.28 g, 98 %). $[\alpha]^{25}_D$ = 4.7° (*c* = 0.031, DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 2H), 6.90 – 6.85 (m, 2H), 5.68 – 5.57 (m, 1H), 5.57 – 5.50 (m, 1H), 4.42 (s, 2H), 4.03 (d, *J* = 6.3 Hz, 2H), 3.86 (dd, *J* = 8.3, 2.7 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 3.14 (s, 3H), 3.21 – 3.01 (m, 1H), 2.19 – 2.08 (m, 1H), 1.85 (dt, *J* = 14.2, 9.7 Hz, 1H), 1.64 – 1.48 (m, 1H), 1.14 (d, *J* = 6.9 Hz, 3H), 0.91 (s, 9H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.1, 159.3, 132.78, 130.6, 129.5, 127.3, 113.9, 77.6, 72.0, 65.9, 61.6, 55.4, 39.0, 38.7, 32.3, 29.5, 26.3, 18.5, 16.7, 15.7, -3.6; HRMS (ESI, *m/z*): calcd for $[C_{26}H_{45}NO_5Si+Na]^+$, ($[M + Na]^+$): 502.2965, found 502.2964.



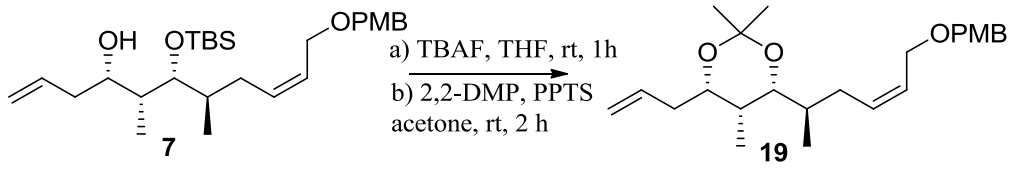
16 **17**

(2*S*,3*R*,4*R*,*Z*)-3-((*tert*-butyldimethylsilyl)oxy)-8-((4-methoxybenzyl)oxy)-2,4-dimethyloct-6-enal (17): A 25 mL flask was flame dried and flushed with argon before DCM (7 mL) and Weinreb amide **16** (400 mg, 0.834 mmol) were added. The solution was cooled to -78 °C and DIBAL-H (180 µL, 1.0 mmol) in DCM (2 mL) was added dropwise over several minutes. The reaction mixture was stirred for 30 min at -78 °C and quenched by the careful addition of half saturated aqueous sodium potassium tartarate (10 mL) and stirred for an additional 4 hours while warming to rt. The organic layer was collected and the aqueous layer was extracted with EtOAc (3 X 10 mL). The combined organic layers were dried over anhydrous sodium sulfate and solvent was removed under reduced pressure to afford a colorless oil that was purified by SiO_2 flash chromatography (5% EtOAc in hexanes) to provide pure aldehyde **17** as a colorless oil (323 mg, 92%). $[\alpha]^{25}_D$ = -3.6° (*c* = 0.014, DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.72 (d, *J* = 0.8 Hz, 1H), 7.30 – 7.24 (m, 10H), 6.88 (m, 2H), 5.70 – 5.51 (m, 2H), 4.44 (s, 2H), 4.02 (d, *J* = 6.9 Hz, 2H), 4.00 (dd, *J* = 5.7, 3.5 Hz, 1H), 3.81 (s, 3H), 2.48 (qd, *J* = 6.9, 0.8 Hz, 1H), 2.24 – 2.14 (m, 1H), 1.89 – 1.76 (m, 1H), 1.76 – 1.65 (m, 1H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.3, 159.3, 132.8, 131.8, 129.6, 127.8, 113.9, 77.4, 75.0, 72.1, 65.7, 55.4, 50.3, 38.4, 30.7, 26.1, 16.2, 8.6, -3.9, -4.0; HRMS (ESI, *m/z*): calcd for $[C_{24}H_{40}O_4Si+Na]^+$, ($[M + Na]^+$): 443.2594, found 443.2591.



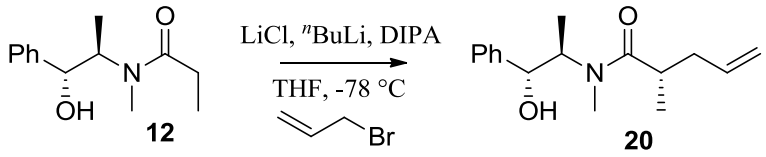
(4*S*,5*R*,6*R*,7*R*,*Z*)-6-((*tert*-butyldimethylsilyl)oxy)-11-((4-methoxybenzyl)oxy)-5,7-dimethylundeca-1,9-dien-4-ol (7): A 25 mL flask was flame dried and flushed with argon before Et_2O (13 mL) and (–)-9-(1*R*,2*R*-Pseudoephedrinyl)-(10*S*)-(trimethylsilyl)-9-borabicyclo[3.3.2]decane **18** (500 mg, 1.34 mmol) were added. The suspension was cooled to -78 °C and allylmagnesium bromide (1M solution in Et_2O, 1.3 mL, 1.3 mmol) was added dropwise. The solution was continually stirred for 1 h, allowed to warm, and then cooled back to -78 °C and a solution of aldehyde **17** (280 mg, 0.67 mmol) in Et_2O (500 mL) was added dropwise. The reaction mixture was stirred for 3 h at -78 °C and then allowed to warm to rt. Solvent was removed under reduced pressure and the resulting white solid was suspended in hexanes and solids removed by filtering through celite with hexanes (100 mL). Solvent was removed under reduced pressure, (*R*,*R*)-pseudoephedrine (222 mg, 1.34 mmol) and ACN (2.7 mL) were added and the solution was heated at reflux for 4 h. After cooling to rt, precipitate was removed by decantation and washed thoroughly with hexanes. Decanted solution was combined with the hexane washes, and solvent was removed under reduced pressure to afford a yellow oil that was purified by SiO_2 flash chromatography (5% – 10% EtOAc in hexanes) to provide diastereomerically pure **7** as a colorless oil (290 mg, 93%). $[\alpha]^{25}_D$ = -14.1° (*c* = 0.011, DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 2H), 6.91 – 6.83 (m, 2H), 5.84 – 5.74 (m, 1H), 5.65 (ddd, *J* = 12.8, 11.7, 6.5 Hz, 1H), 5.61 – 5.53 (m, 1H), 5.18 – 5.05 (m, 2H), 4.44 (s, 2H), 4.03 (d,

J = 6.4 Hz, 2H), 3.80 (s, 3H), 3.67 (dd, *J* = 4.4, 3.5 Hz, 1H), 3.69 – 3.62 (m, 1H), 2.28 – 2.09 (m, 3H), 1.91 – 1.80 (m, 1H), 1.81 – 1.71 (m, 1H), 1.71 – 1.62 (m, 1H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.89 (d, *J* = 7.1 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3, 135.4, 132.6, 130.5, 129.6, 127.3, 117.9, 113.9, 78.2, 77.4, 73.7, 72.1, 65.7, 55.4, 39.9, 39.7, 38.9, 31.0, 26.2, 18.5, 16.3, 9.2, -3.3, -4.0; HRMS (ESI, *m/z*): calcd for $[C_{27}H_{46}O_4Si+Na]^+$, ($[M + Na]^+$): 485.3063, found 485.3070.



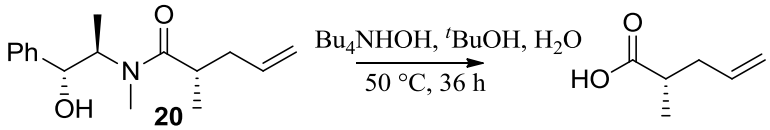
(4*S*,5*R*,6*R*)-4-allyl-6-((*R*,*Z*)-6-((4-methoxybenzyl)oxy)hex-4-en-2-yl)-2,2,5-trimethyl-1,3-dioxane (19): A 1 dram vial was charged with THF (200 µL) and compound **7** (6 mg, 0.013 mmol) and tetrabutylammonium fluoride (1M in THF, 40 µL, 0.04 mmol) was added dropwise. The reaction mixture was stirred at rt for 1 h and quenched by the addition of saturated aqueous ammonium chloride (1 mL) and then diluted with EtOAc (2 mL). The organic layer was collected and the aqueous layer was extracted with EtOAc (3 X, 2 mL). The combined organic layers were dried over anhydrous sodium sulfate and solvent as removed under reduced pressure to afford a yellow oil that was purified by SiO_2 flash chromatography (15% – 30% EtOAc in hexanes) to provide pure 1,3-diol as colorless oil. The oil was dissolved in 2,2-DMP (300 µL) and *p*-toluenesulfonic acid (0.3 mg, 0.001 mmol) was added followed by stirring for 2 h at rt. After 2 h, the reaction was quenched by the addition of sodium bicarbonate (5 mg). Solvent was removed under reduced pressure to afford a white slurry that was purified by SiO_2 flash chromatography (5% – 10% EtOAc in hexanes) to provide pure **19** as a colorless oil (4 mg, 87%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.31 – 7.26 (m, 2H), 6.85 – 6.78 (m, 2H), 5.91 – 5.85 (m, 1H), 5.81 (dddd, *J* = 17.1, 10.2, 7.9, 6.1 Hz, 1H), 5.60 – 5.53 (m, 1H), 5.08 (m, 2H), 4.43 (d, *J* =

1.7 Hz, 2H), 4.16 (dd, *J* = 12.2, 6.4 Hz, 1H), 4.11 (dd, *J* = 12.0, 6.3 Hz, 1H), 3.71 (ddd, *J* = 8.0, 6.0, 2.2 Hz, 1H), 3.29 (s, 3H), 3.24 (dd, *J* = 9.9, 2.1 Hz, 1H), 2.48 – 2.35 (m, 2H), 2.10 – 1.96 (m, 2H), 1.75 – 1.63 (m, 1H), 1.49 (s, 3H), 1.29 (s, 3H), 1.27 – 1.18 (m, 1H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.64 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, C_6D_6) δ 159.7, 135.4, 131.3, 131.0, 129.5, 128.7, 116.7, 114.1, 99.0, 76.9, 73.4, 72.1, 66.1, 54.7, 37.9, 34.8, 32.7, 31.2, 30.4, 19.7, 13.9, 4.8; HRMS (ESI, *m/z*): calcd for $[C_{24}H_{36}O_4+Na]^+$, ($[M + Na]^+$): 411.2511, found 411.2512.



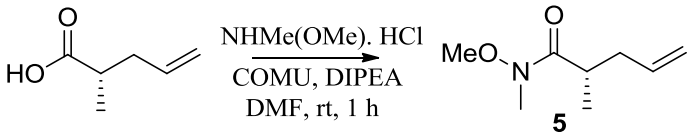
(*S*)-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethylpent-4-enamide (20): A 250 mL flask was flame dried and flushed with argon before anhydrous THF (17 mL), anhydrous lithium chloride (3 g, 68 mmol), and DIPA (4.4 mL, 31 mmol.) were added. The suspension was cooled to -78 °C, butyllithium (2.5 M in hexanes, 11.3 mL, 28 mmol) was added, and stirring was continued as the solution was briefly warmed to 0 °C and then cooled back to -78 °C. An ice cooled solution of *R,R*-pseudoephedrine propionamide (3 g, 13.6 mmol) in anhydrous THF (43 mL) was added *via* cannula followed by a wash with THF (5 mL). Stirring was continued at -78 °C for 2 h, 0 °C for 30 min, and rt for 5 min, before the reaction mixture was finally cooled to 0 °C. Allylbromide (1.77 mL, 20.4 mmol) was then added in one portion, and the reaction mixture was stirred for 2 h at 0 °C. Reaction was quenched at 0 °C by the addition of saturated aqueous ammonium chloride (2 mL) and the mixture was partitioned between saturated aqueous ammonium chloride (130 mL) and EtOAc (50 mL). The organic layer was collected and the aqueous layer was extracted with EtOAc (3 X 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and solvent was removed under reduced pressure to afford a yellow oil that was purified by SiO_2 flash chromatography (30% EtOAc in hexanes) to provide

pure **20** as a colorless oil (96%). Diastereoselectivity (>20:1) was assessed using Myers oxazolium technique (*vide infra*). $[\alpha]^{25}_{D}$ = -71.5° (c = 0.142, DCM); (*Denotes minor rotamer peak) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 5H), *7.29 – 7.23 (m, 5H), *5.80 (ddt, *J* = 17.2, 10.0, 7.0 Hz, 1H), 5.70 (ddt, *J* = 17.2, 10.0, 7.0 Hz, 1H), *5.15 – 5.07 (m, 2H), 5.06 – 4.97 (m, 2H), 4.66 – 4.55 (m, 1H), *4.58 (d, *J* = 8.7 Hz, 1H), 4.52 – 4.24 (m, 1H), *4.13 – 4.02 (m, 1H), *2.92 (s, 3H), 2.86 (s, 3H), 2.74 – 2.63 (m, 1H), *2.58 – 2.47 (m, 1H), *2.47 – 2.40 (m, 1H), 2.40 – 2.28 (m, 1H), *2.24 – 2.13 (m, 1H), 2.14 – 2.01 (m, 1H), 1.11 (d, *J* = 6.8 Hz, 6H), *1.02 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.5, *177.3, 142.6, *141.1, *136.8, 136.1, *128.9, *128.6, 128.5, 127.8, *127.0, 126.5, *116.7, 116.7, 77.4, 76.7, *75.6, *58.2, *38.2, 38.18, 36.7, 35.9, *27.2, *17.7, 17.1, *15.7, 14.6; HRMS (ESI, *m/z*): calcd for $[C_{16}H_{23}NO_2+Na]^+$, ($[M+Na]^+$): 284.1626, found 284.1623.



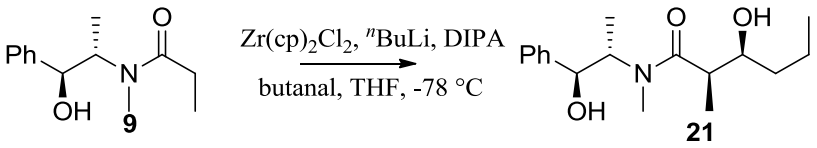
(*S*)-2-methylpent-4-enoic acid: A 500 mL flask was charged with *tert*-butanol (42 mL) and water (136 mL) before amide **20** (3.56 g, 13.6 mmol) and tetrabutylammonium hydroxide (1.5 M in water, 50 mL, 68 mmol) were added. The solution was heated at reflux for 23 h. Once the reaction was complete, the solution was allowed to cool to rt and suspended between 0.5 M aqueous sodium hydroxide (1.76 L) and diethyl ether (250 mL). The organic layer was removed, and the aqueous layer was extracted with diethyl ether (3 X, 250 mL). The aqueous layer was cooled to 0 °C, saturated with sodium chloride, and acidified to pH ~2 with 4 N aqueous HCl. The acid solution was extracted with diethyl ether (4 X 300 mL) and the combined organic extracts were dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure to afford pure title acid compound as a colorless liquid (1.46 g, 94%). $[\alpha]^{25}_{D}$ = +9.6° (*c* = 0.047,

DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H), 5.09 (ddt, *J* = 17.1, 1.7, 1.5 Hz, 1H), 5.06 (ddt, *J* = 10.2, 1.9, 1.0 Hz, 1H), 2.61 – 2.51 (m, 1H), 2.49 – 2.41 (m, 1H), 2.21 (m, 1H), 1.19 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 135.3, 117.3, 39.2, 37.6, 16.5; HRMS (ESI, *m/z*): calcd for $[C_{12}H_{20}O_4+Na]^-$, ($[2M+Na–2H]^-$): 249.1103, found 249.1102.



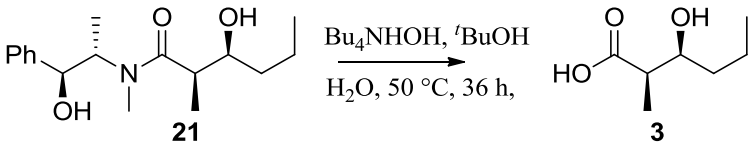
5

(*S*)-*N*-methoxy-*N*,2-dimethylpent-4-enamide (5): A 100 mL flask was flame dried and flushed with argon before DMF (20 mL), above acid (1.20 g, 10.5 mmol), and DIPEA (2.4 mL, 22.1 mmol) were added. COMU (3.13 g, 11.6 mmol) was then added in one portion and the reaction mixture was stirred at rt for 45 min at which point *N*,*O*-dimethylhydroxylamine hydrochloride (1.3 g, 21 mmol) was added. Stirring was continued for 1 h and the reaction was quenched by the careful addition of saturated aqueous sodium bicarbonate (15 mL). The resulting slurry was then extracted with EtOAc (5 X 30 mL) and the combined organic portions were dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure to afford a red oil that was purified by SiO_2 flash chromatography (5% – 15% EtOAc in hexanes) to provide pure amide **5** as a colorless oil (94%). $[\alpha]^{25}_{D}$ = 27.3° (*c* = 0.007, DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (ddt, *J* = 17.0, 10.2, 7.0 Hz, 1H), 5.03 (dd, *J* = 17.1, 1.4 Hz, 1H), 4.97 (dd, *J* = 10.2, 0.9 Hz, 1H), 3.65 (s, 3H), 3.15 (s, 3H), 2.91 (m, 1H), 2.39 (m, 1H), 2.09 (m, 1H), 1.09 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.4, 136.3, 116.5, 61.5, 37.9, 35.2, 17.1; HRMS (ESI, *m/z*): calcd for $[C_8H_{15}NO_2+Na]^+$, ($[M+Na]^+$): 180.1000, found 180.1002.

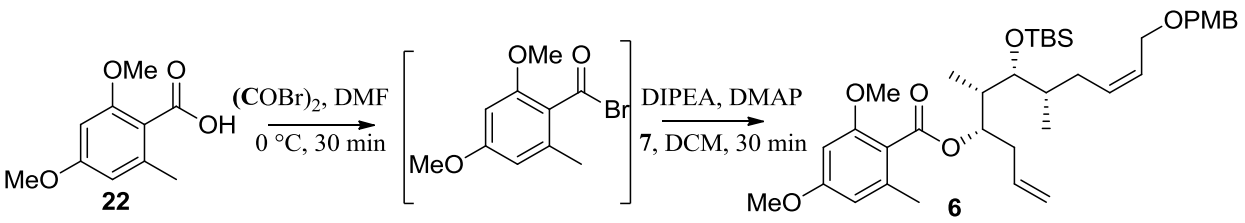


(2*R*,3*S*)-3-hydroxy-*N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethylhexanamide (21): A 250 mL flask was flame dried and flushed with argon before anhydrous THF (25 mL) and DIPA (2.70 mL, 19.0 mmol) were added. The solution was cooled to -78 °C and *n*-butyllithium (2.5 M in hexanes, 7.42 mL, 18.6 mmol) was slowly added. Stirring was continued as the solution was allowed to warm to 0 °C and then cooled back to -78 °C at which point a solution of *S*,*S*-pseudoephedrine propionamide (2.0 g, 9.05 mmol) in anhydrous THF (25 mL) was added slowly *via* cannula. Stirring was continued at -78 °C for 2 hr, 0 °C for 30 min, and rt for 10 min. The reaction mixture was cooled back to -78 °C followed by the addition of a solution of bis(cyclopentadienyl)zirconium(IV) dichloride (5.80 g, 19.9 mmol, 2.2 eq.) in anhydrous THF (56 mL). The deep orange solution was stirred at -78 °C for 3 hr and then cooled to -116 °C when a solution butyraldehyde (2.30 g, 9.05 mmol, 1 eq.) in anhydrous THF (5.6 mL) was added dropwise. Stirring was continued at -116 °C for 3 hr at which point the reaction was quenched by the addition of saturated aqueous ammonium chloride (25 mL). The biphasic reaction mixture was warmed to rt and filtered through a pad of celite using EtOAc (150 mL) to rinse. The organic layer was collected, and the aqueous layer was extracted with EtOAc (3 X 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and solvent was removed under reduced pressure to afford orange oil that was purified by SiO_2 flash chromatography (40% – 70%) to provide pure **21** as colorless oil (84%). $[\alpha]^{25}_{D}$ = 69.7° (*c* = 0.006, DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 5H), 4.66 – 4.62 (m, 1H), 4.61 (d, *J* = 8.0 Hz, 1H), 4.56 (bs, 1H), 4.23 (s, 1H), 4.06 (m, 1H), 3.85 – 3.80 (m, 1H), 3.75 (m, 1H), 2.94 (s, 3H), 2.87 (s, 3H), 2.73 (m, 1H), 2.53 (qd, *J* = 7.0, 2.1 Hz, 1H), 1.56 – 1.41 (m, 2H), 1.40 –

1.29 (m, 1H), 1.29 – 1.18 (m, 1H), 1.16 – 1.03 (m, 6H), 1.01 – 0.88 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.9, 179.2, 142.2, 141.3, 129.0, 128.8, 128.6, 128.0, 126.8, 126.4, 77.4, 76.4, 76.0, 71.4, 71.1, 57.8, 40.0, 39.0, 36.1, 35.9, 27.4, 19.4, 19.4, 15.8, 14.3, 14.3, 14.2, 10.5, 9.7; HRMS (ESI, *m/z*): calcd for $[C_{17}H_{27}NO_3+Na]^+$, ($[M + Na]^+$): 316.1889, found 316.1890.

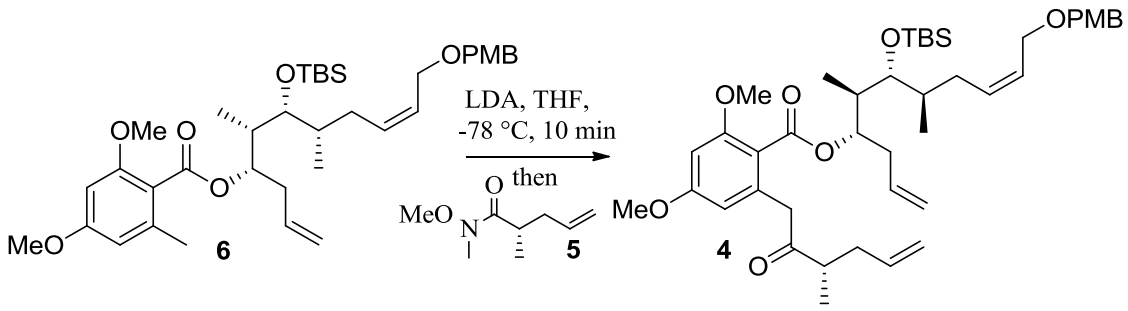


(2*R*,3*S*)-3-hydroxy-2-methylhexanoic acid (3): A 50 mL flask was charged with *tert*-butanol (2 mL) and water (6.3 mL) before amide **21** (200 mg, 0.68 mmol) and tetrabutylammonium hydroxide (1.5 M in water, 2.3 mL, 3.4 mmol) were added. The solution was heated at reflux for 23 h. Once the reaction was complete, the solution was allowed to cool to rt and suspended between 0.5 M aqueous sodium hydroxide (82 mL) and diethyl ether (12 mL). The organic layer was removed, and the aqueous layer was extracted with diethyl ether (3 X, 12 mL). The aqueous layer was cooled to 0 °C, saturated with sodium chloride, and acidified to pH 2 with 4 N HCl. The acid solution was extracted with diethyl ether (4 X 15 mL) and the combined organic extracts were dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure to afford pure acid as a colorless, amorphous solid (94%). $[\alpha]^{25}_D$ = -12.5° (*c* = 0.021, DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.96 (dt, *J* = 8.7, 3.8 Hz, 1H), 3.32 (bs, 1H), 2.63 (qd, *J* = 7.2, 3.5 Hz, 1H), 1.58 – 1.31 (m, 4H), 1.21 (d, *J* = 7.2 Hz, 3H), 0.95 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.7, 71.6, 44.1, 35.7, 19.3, 14.1, 10.7; HRMS (ESI, *m/z*): calcd for $[C_{14}H_{24}O_6+Na]^-$, ($[2M + Na – 2H]^+$): 313.1627, found 313.1627.



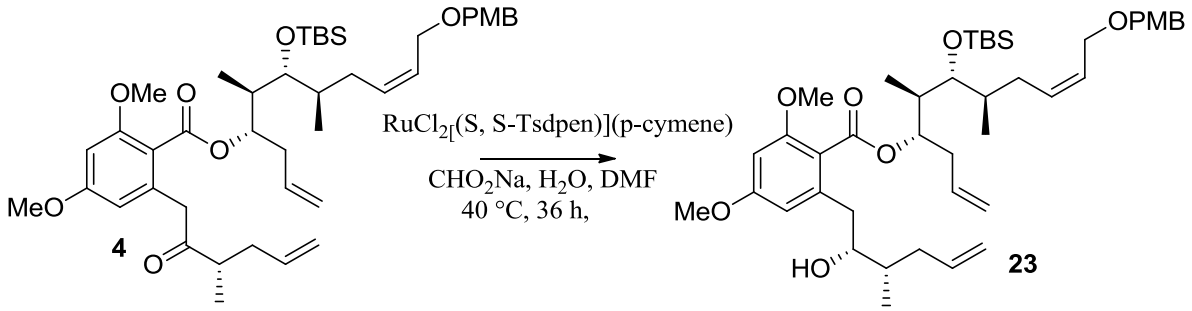
(4*S*,5*R*,6*R*,7*R*,*Z*)-6-((*tert*-butyldimethylsilyl)oxy)-11-((4-methoxybenzyl)oxy)-5,7-dimethylundeca-1,9-dien-4-yl 2,4-dimethoxy-6-methylbenzoate (6): A 25 mL flask was flame dried and flushed with argon before DCM (4.3 mL) and 2,4-dimethoxy-6-methylbenzoic acid **2** (165 mg, 0.86 mmol) were added. The suspension was cooled to 0 °C and oxalyl bromide (85 mL, 0.9 mmol) was added dropwise. The suspension was allowed to warm to rt and stirred until all solid was dissolved at which point 4 drops of anhydrous DMF were added. Stirring was continued at rt for 1 h and the solution was cooled 0 °C before DIPEA (390 mL, 2.2 mmol, 5 eq.) was added. Stirring was continued at 0 °C for 30 min before a solution of alcohol **7** (200 mg, 0.43 mmol, 1 eq.) in DCM (0.5 mL) and DMAP (105 mg, 0.86 mmol, 2 eq.) were added. The reaction mixture was allowed to warm to rt and stirring was continued for 30 min at which point the reaction was quenched by the addition of water (5 mL). The organic layer was collected and the aqueous layer was extracted with DCM (4 X 10 mL). The combined organic layers were dried over anhydrous sodium sulfate and solvent was removed to afford a brown oil that was purified by SiO_2 flash chromatography (5% – 10% EtOAc in hexanes) to provide ester **6** as a colorless oil (264 mg, 96%). $[\alpha]^{25}_D$ = 3.9°, *c* = 0.009, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 2H), 6.92 – 6.80 (m, 2H), 6.31 (d, *J* = 9.9 Hz, 2H), 5.91 – 5.75 (m, 1H), 5.69 – 5.50 (m, 2H), 5.20 (m, 1H), 5.10 (m, 2H), 4.43 (s, 2H), 4.04 (d, *J* = 5.8 Hz, 2H), 3.79 (s, 6H), 3.76 (s, 3H), 3.55 (t, *J* = 4.2 Hz, 1H), 2.58 – 2.38 (m, 2H), 2.29 (s, 3H), 2.23 – 2.14 (m, 1H), 1.99 – 1.81 (m, 2H), 1.81 – 1.68 (m, 1H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 161.2, 159.3, 158.1, 138.0, 135.4, 134.1,

132.7, 130.6, 129.5, 127.4, 117.9, 113.9, 106.6, 96.2, 76.7, 75.5, 72.0, 65.9, 55.7, 55.5, 55.4, 39.9, 38.9, 37.9, 36.8, 30.0, 26.3, 20.2, 17.1, 10.9, -3.4; HRMS (ESI, *m/z*): calcd for $[C_{37}H_{56}O_7Si+Na]^+$, ($[M + Na]^+$): 663.3693, found 663.3698.



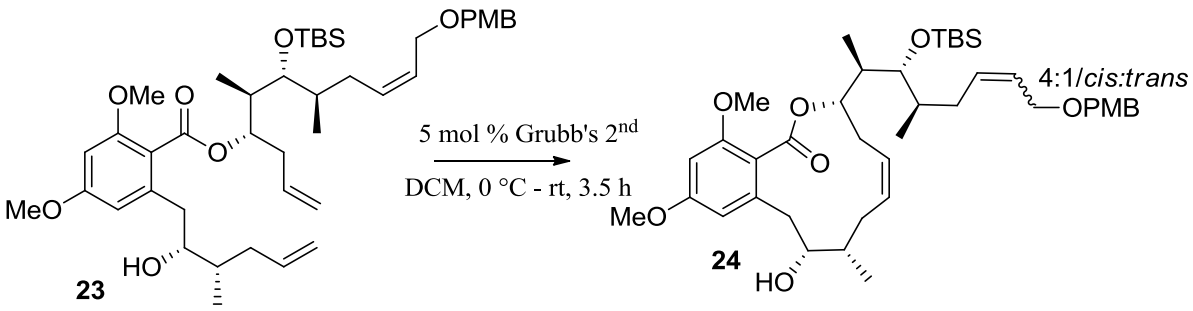
(4*S*,5*R*,6*R*,7*R*,*Z*)-6-((*tert*-butyldimethylsilyl)oxy)-11-((4-methoxybenzyl)oxy)-5,7-dimethylundeca-1,9-dien-4-yl 2,4-dimethoxy-6-((*S*)-3-methyl-2-oxopent-4-en-1-yl)benzoate, (4): A 5 mL flask was flame dried and flushed with argon before THF (600 µL) and compound **6** (150 mg, 0.234 mmol) were added. The solution was cooled to -78 °C and a freshly prepared 1M solution of LDA (468 µL, 0.468 mmol) in THF was added dropwise. After stirring for 5 min at -78 °C, Weinreb amide **5** (92 mg, 0.585 mmol) in THF (200 µL) was added at once and the solution was stirred for an additional 10 min at -78 °C at which point saturated aqueous ammonium chloride (1 mL) was added to quench. Stirring was continued as the heterogeneous mixture was allowed to warm to rt. The organic layer was collected and the aqueous layer was extracted with EtOAc (3 X 5 mL). The combined organic layers were dried with anhydrous sodium sulfate and solvent was evaporated to afford a yellow oil that was purified by SiO_2 flash chromatography (5% – 10% EtOAc in hexanes) to provide pure **97** as a colorless oil (140 mg, 81%). $[\alpha]^{25}_D$ = 10.2° (*c* = 0.005, DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 2H), 6.87 (m, 2H), 6.38 (d, *J* = 2.0 Hz, 1H), 6.27 (d, *J* = 2.0 Hz, 1H), 5.85 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H), 5.71 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H), 5.66 – 5.52 (m, 1H), 5.17 (q, *J* = 6.1 Hz, 1H), 5.14 – 4.98 (m, 2H), 4.43 (s, 2H), 4.04 (d, *J* = 6.2 Hz, 2H), 3.79 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.81 –

3.70 (m, 1H), 3.56 (t, *J* = 4.5 Hz, 1H), 2.73 (h, *J* = 6.9 Hz, 1H), 2.51 (dt, *J* = 12.3, 6.1 Hz, 1H), 2.47 – 2.37 (m, 2H), 2.23 – 2.15 (m, 1H), 2.13 – 2.03 (m, 1H), 1.97 – 1.81 (m, 2H), 1.80 – 1.68 (m, 1H), 1.08 (d, *J* = 7.0 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.92 (s, 9H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.1, 167.6, 161.6, 159.3, 159.0, 135.9, 135.7, 134.3, 132.6, 130.7, 129.5, 127.5, 117.8, 116.9, 113.9, 107.3, 100.1, 97.8, 76.6, 75.7, 72.0, 65.9, 55.8, 55.5, 55.4, 46.6, 45.2, 38.9, 38.1, 38.0, 37.2, 36.9, 30.2, 26.3, 17.0, 16.2, 10.8, -3.3, -3.4; HRMS (ESI, *m/z*): calcd for $[C_{43}H_{64}O_8Si+Na]^+$, ($[M + Na]^+$): 759.4268, found 759.4271.



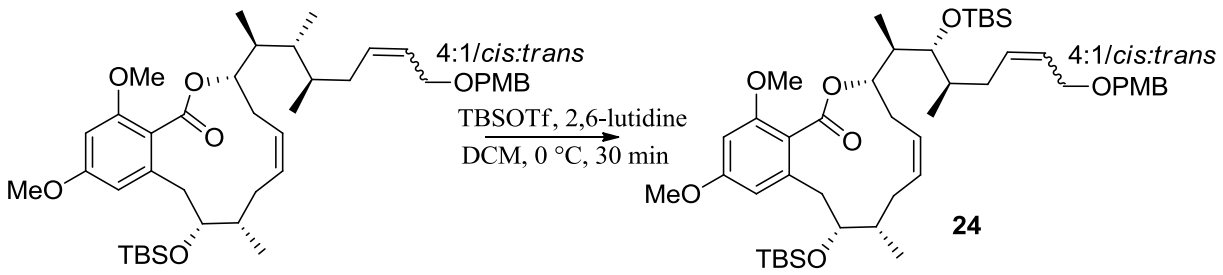
(4*S*,5*R*,6*R*,7*R*,*Z*)-6-((*tert*-butyldimethylsilyl)oxy)-11-((4-methoxybenzyl)oxy)-5,7-dimethylundeca-1,9-dien-4-yl 2-((2*R*,3*S*)-2-hydroxy-3-methylpent-4-en-1-yl)-4,6-dimethoxybenzoate (23): A 5 mL flask was flushed with argon and charged with ketone **4** (110 mg, 0.15 mmol), DMF (250 µL), water (250 µL), sodium formate (156 mg, 2.3 mmol), and RuCl[(S,S)-Tsdpen](p-cymene) (10 mg, 0.015 mmol). The reaction mixture was stirred at 40 °C for 36 h and subsequently quenched by the addition of saturated aqueous ammonium chloride (2 mL) and then diluted with Et_2O (5 mL). The organic layer was collected and the aqueous layer was extracted with Et_2O (4 X 5 mL). The combined organic layers were dried over anhydrous sodium sulfate and solvent was removed under reduced pressure to afford a brown oil that was purified by SiO_2 flash chromatography (5% – 15% EtOAc in hexanes) to provide **23** in a 9:1 diastereomeric mixture as a colorless oil (108 mg, 98%). $[\alpha]^{25}_D$ = 15.3°, *c* = 0.003, DCM);

(*Denotes minor epimeric alcohol product) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.22 (m, 2H), 6.91 – 6.82 (m, 2H), *6.37 (d, *J* = 2.1 Hz, 1H), 6.35 (d, *J* = 2.1 Hz, 1H), 6.33 (d, *J* = 2.1 Hz, 1H), 5.95 – 5.71 (m, 2H), 5.68 – 5.50 (m, 2H), 5.21 (dd, *J* = 12.1, 6.3 Hz, 1H), 5.17 – 4.96 (m, 4H), *4.43 (s, 2H), 4.43 (s, 2H), *4.04 (d, *J* = 6.0 Hz, 2H), 4.03 (d, *J* = 6.3 Hz, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), *3.76 – 3.70 (m, 1H), 3.66 – 3.58 (m, 1H), *3.56 (t, *J* = 4.6 Hz, 1H), 3.51 (t, *J* = 4.5 Hz, 1H), 2.77 (dd, *J* = 13.6, 2.9 Hz, 1H), 2.58 – 2.39 (m, 3H), 2.37 – 2.26 (m, 1H), 2.24 – 2.15 (m, 1H), 2.03 – 1.89 (m, 2H), 1.89 – 1.79 (m, 1H), 1.79 – 1.65 (m, 2H), *1.02 (d, *J* = 6.8 Hz, 3H), *0.96 (d, *J* = 6.2 Hz, 3H), 0.94 (d, *J* = 6.5 Hz, 6H), *0.92 (s, 9H), 0.91 (s, 9H), 0.84 (d, *J* = 6.8 Hz, 3H), *0.10 (s, 3H), 0.07 (s, 3H), *0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 161.9, 159.3, 158.7, 140.9, 137.8, 134.0, 132.5, 130.6, 129.5, 127.5, 117.9, 116.6, 115.9, 113.9, 106.2, 97.1, 77.4, 76.4, 76.4, 72.0, 65.8, 55.7, 55.5, 55.4, 39.5, 38.2, 38.0, 37.6, 37.2, 36.7, 30.4, 26.1, 16.9, 15.1, 10.8, -3.4, -3.5; HRMS (ESI, *m/z*): calcd for $[C_{43}H_{66}O_8Si+Na]^+$, ($[M + Na]^+$): 761.4425, found 761.4420.



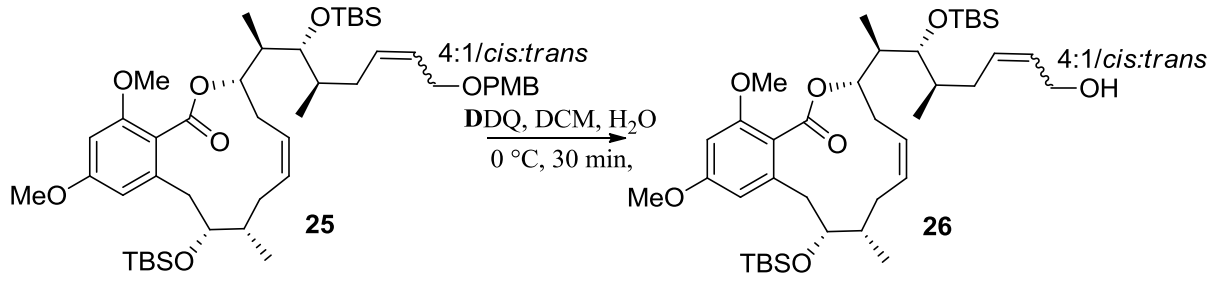
(3*S*,8*S*,9*R*,*Z*)-3-((2*R*,3*R*,4*R*,*Z*)-3-((*tert*-butyldimethylsilyl)oxy)-8-((4-methoxybenzyl)oxy)-4-methyloct-6-en-2-yl)-9-hydroxy-12,14-dimethoxy-8-methyl-3,4,7,8,9,10-hexahydro-1*H*-benzo[*c*][1]oxacyclododecin-1-one (24): A 100 mL flask was flame dried and flushed with argon before DCM (54 mL) and alcohol **23** (20 mg, 0.027 mmol) were added. The solution was cooled to 0 °C, Grubbs' 2nd generation catalyst (1.2 mg, 0.0014 mmol) was added, and the solution was continually stirred while warming to rt for 3.5 h. The reaction mixture was treated

with saturated aqueous potassium carbonate (1 mL), the organic layer was collected and the aqueous layer was extracted with DCM (3X 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and solvent was removed under reduced pressure to afford a brown oil that was purified by SiO_2 flash chromatography (15% – 40% EtOAc in hexanes) to provide **24** in a 4:1 mixture of side chain olefin isomers (4:1/*cis*:*trans*) as a colorless oil (13 mg, 79% based on desired epimeric alcohol). $[\alpha]^{25}_D$ = 9.7°, *c* = 0.002, DCM); (*Denotes minor *trans* side chain olefin isomer) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.22 (m, 2H), 6.91 – 6.82 (m, 2H), 6.35 (d, *J* = 2.2 Hz, 1H), 6.33 (d, *J* = 1.7 Hz, 1H), 5.68 – 5.54 (m, 2H), 5.54 – 5.44 (m, 2H), 5.32 – 5.26 (m, 1H), 4.42 (s, 2H), *4.42 (s, 2H), 4.02 (d, *J* = 5.6 Hz, 2H), *3.91 (d, *J* = 6.0 Hz, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.76 (s, 3H), 3.76 – 3.72 (m, 1H), *3.57 – 3.54 (m, 1H), 3.54 – 3.51 (m, 1H), 3.07 – 2.91 (m, 1H), 2.81 – 2.54 (m, 2H), 2.44 – 2.33 (m, 1H), 2.16 – 2.09 (m, 1H), 2.00 – 1.92 (m, 1H), 1.92 – 1.82 (m, 2H), 1.82 – 1.71 (m, 2H), 1.05 (d, *J* = 6.8 Hz, 3H), *0.97 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.07 (s, 3H), *0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.2, 161.3, 159.2, *158.6, 134.01, 135.9, 133.6, 132.5, *131.1, 130.5, *130.1, 129.4, 127.7, 122.2, 113.8, 106.8, 97.1, 76.2, *75.8, 71.9, 71.5, 70.6, 65.7, 55.9, 55.4, *55.3, 55.3, *40.1, 38.2, 38.1, *38.1, 31.1, *31.1, 29.8, *29.7, 26.2, *26.2, 18.5, *16.6, 16.8, 11.3, -3.6, *-3.7, -3.8; HRMS (ESI, *m/z*): calcd for $[C_{41}H_{62}O_8Si+Na]^+$, ($[M + Na]^+$): 733.4112, found 733.4105.



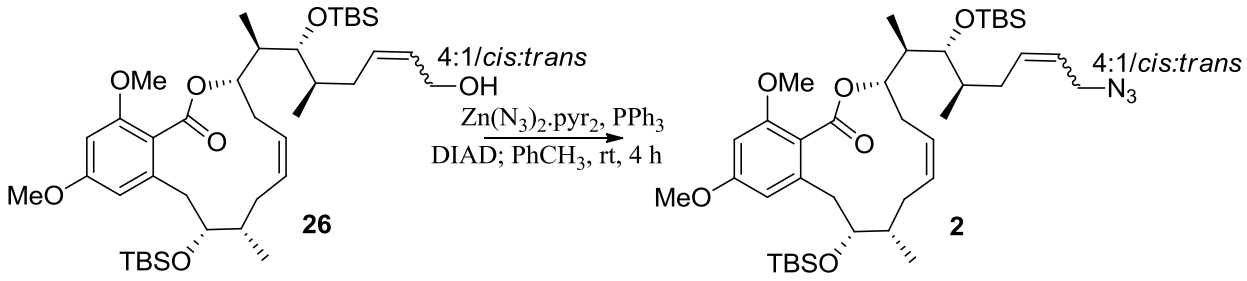
(3*S*,8*S*,9*R*,*Z*)-9-((*tert*-butyldimethylsilyl)oxy)-3-((2*R*,3*R*,4*R*,*Z*)-3-((*tert*-butyldimethylsilyl)oxy)-8-((4-methoxybenzyl)oxy)-4-methyloct-6-en-2-yl)-12,14-dimethoxy-8-methyl-3,4,7,8,9,10-hexahydro-1*H*-benzo[*c*][1]oxacyclododecin-1-one (25): A 5 mL flask was flame dried and flushed with argon before DCM (200 µL), **24** (18 mg, 0.024 mmol), and DIPEA (18 µL, 0.094 mmol) were added. The solution was cooled to 0 °C and *tert*-butyldimethylsilyl trifluoromethanesulfonate (19.2 µL, 0.084 mmol) was added dropwise. Stirring was continued for 30 min as the reaction mixture was allowed to warm to rt at which point the reaction was quenched by the addition of saturated aqueous ammonium chloride (1 mL). The biphasic mixture was diluted with DCM (5 mL), the organic layer was collected and the aqueous layer was extracted with DCM (3 X 5 mL). The combined organic layers were dried over anhydrous sodium sulfate and solvent was removed under reduced pressure to afford a colorless oil that was purified by SiO_2 flash chromatography (5% – 10% EtOAc in hexanes) to provide **25** in a 4:1 mixture of side chain olefin isomers (*cis*:*trans*) as a colorless oil (18 mg, 91%). $[\alpha]^{25}_D$ = 4.7° (*c* = 0.002, DCM); (*Denotes minor *trans* side chain olefin isomer) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 2H), 6.90 – 6.84 (m, 2H), 6.31 (d, *J* = 2.2 Hz, 1H), 6.29 (d, *J* = 1.7 Hz, 1H), 5.71 – 5.52 (m, 3H), 5.39 – 5.30 (m, 1H), 5.29 – 5.22 (m, 1H), 4.43 (s, 2H), *4.42 (s, 2H), 4.03 (d, *J* = 5.0 Hz, 2H), *3.93 (m, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.77 – 3.74 (m, 1H), 3.74 (s, 3H), 3.52 – 3.41 (m, 1H), 3.13 (d, *J* = 12.9 Hz, 1H), 2.74 – 2.60 (m, 1H), 2.28 – 2.09 (m, 3H), 2.09 – 2.01 (m, 1H), 1.98 – 1.70 (m, 5H), 1.01 (d, *J* = 6.8 Hz, 3H), *0.96 (d, *J* =

6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.88 (d, *J* = 7.2 Hz, 3H), 0.76 (s, 9H), *0.01 (s, 3H), -0.00 (s, 3H), -0.01 (s, 3H), -0.19 (s, 3H), -0.61 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.4, 160.5, 159.3, 158.8, 140.8, 134.0, 132.8, *130.7, 130.7, *129.6, 129.5, *127.8, 127.7, 127.2, 116.6, 113.9, 109.2, 97.2, 77.4, 72.8, 72.0, 71.6, 65.8, 56.2, *55.4, 55.4, 55.4, *53.6, 41.6, 40.2, 37.8, 34.2, 32.5, 32.2, 31.7, 29.8, 29.5, 26.3, 26.4, 18.6, 18.0, *17.4, 11.3, -3.5, -3.7, *-3.7, -5.0, -5.7; HRMS (ESI, *m/z*): calcd for $[C_{47}H_{76}O_8Si_2+Na]^+$, ($[M + Na]^+$): 847.4976, found 847.4983.



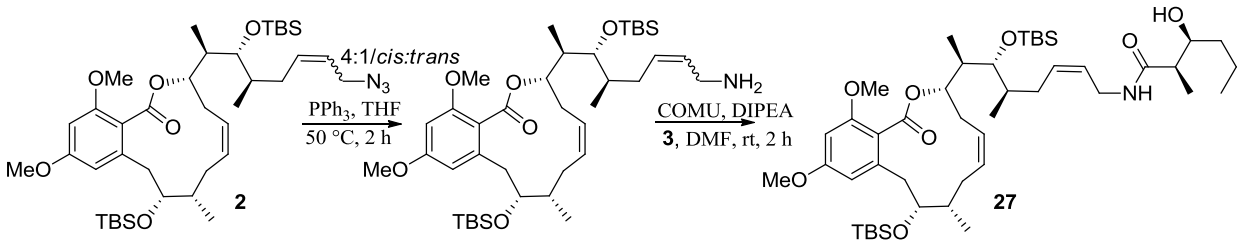
(3*S*,8*S*,9*R*,*Z*)-9-((*tert*-butyldimethylsilyl)oxy)-3-((2*R*,3*R*,4*R*,*Z*)-3-((*tert*-butyldimethylsilyl)oxy)-8-hydroxy-4-methyloct-6-en-2-yl)-12,14-dimethoxy-8-methyl-3,4,7,8,9,10-hexahydro-1*H*-benzo[*c*][1]oxacyclododecin-1-one (26): A 5 mL flask was charged with DCM (400 µL), water (26 µL), and **25** (10.5 mg, 0.0126 mmol). DDQ (4.8 mg, 0.02 mmol) was added in one portion and the reaction mixture was stirred at rt for 30 min and subsequently quenched by the addition of saturated aqueous sodium bicarbonate (2 mL). The biphasic mixture was diluted with DCM (2 mL), the organic layer was collected, and the aqueous layer was extracted with DCM (3 X 5 mL). The combined organic layers were dried over anhydrous sodium sulfate and solvent was removed under reduced pressure to afford an orange oil that was purified by SiO_2 flash chromatography (15% – 30% EtOAc in hexanes) to provide **25** in a 4:1 mixture of side chain olefin isomers (*cis*:*trans*) as a colorless oil (8.8 mg, 98%). $[\alpha]^{25}_D$ = 7.7°, c = 0.001, DCM). (*Denotes minor *trans* side chain olefin isomer) ^{1}H NMR (500

MHz, $CDCl_3$) δ 6.32 (d, *J* = 2.3 Hz, 1H), 6.30 (d, *J* = 1.9 Hz, 1H), 5.69 – 5.51 (m, 3H), 5.40 – 5.22 (m, 2H), 4.22 (dd, *J* = 12.2, 5.6 Hz, 1H), 4.13 (dd, *J* = 12.2, 6.6 Hz, 1H), 4.10 – 4.01 (m, 1H), 3.79 (s, 3H), *3.75 (s, 3H), 3.74 (s, 3H), 3.76 – 3.71 (m, 1H), *3.51 (dd, *J* = 5.3, 3.5 Hz, 1H), 3.46 (dd, *J* = 5.9, 3.1 Hz, 1H), 3.12 (d, *J* = 12.7 Hz, 1H), 2.79 – 2.61 (m, 1H), *2.55 – 2.44 (m, 1H), 2.28 – 2.11 (m, 3H), 2.11 – 2.02 (m, 1H), 1.98 – 1.74 (m, 4H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 7.1 Hz, 3H), *0.95 (d, *J* = 7.7 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), *0.87 (s, 9H), 0.76 (s, 9H), 0.01 (s, 3H), *-0.00 (s, 3H), -0.03 (s, 3H), *-0.07 (s, 3H), -0.20 (s, 3H), -0.62 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6, 160.6, 158.8, 140.9, *132.3, 132.2, *130.6, *129.7, 129.5, 127.6, *126.5, 116.5, 109.2, 97.2, 75.8, 72.8, 64.0, 58.8, 56.2, *56.2, 55.4, 41.5, 40.2, 38.0, 34.1, 32.6, 32.1, 30.1, 29.8, 29.3, 26.3, *26.2, 26.0, 18.0, 13.8, 11.4, *11.2, -3.6, -3.8, *-4.0, -5.0, -5.7; HRMS (ESI, *m/z*): calcd for $[C_{39}H_{68}O_7Si_2+Na]^+$, ($[M + Na]^+$): 727.4401, found 727.4410.



(3*S*,8*S*,9*R*,*Z*)-3-((2*R*,3*R*,4*R*,*Z*)-8-azido-3-((*tert*-butyldimethylsilyl)oxy)-4-methyloct-6-en-2-yl)-9-((*tert*-butyldimethylsilyl)oxy)-12,14-dimethoxy-8-methyl-3,4,7,8,9,10-hexahydro-1*H*-benzo[*c*][1]oxacyclododecin-1-one (2): A 5 mL flask was flame dried and flushed with argon before anhydrous toluene (0.5 mL), alcohol **26** (8.8 mg, 0.012 mmol), PPh_3 (12 mg, 0.048 mmol), and freshly synthesized $Zn(N_3)_2(C_5H_5N)_2$ (18 mg, 0.06 mmol) were added. The suspension was cooled to 0 °C and DIAD (10 mg, 0.05 mmol) was added dropwise over 15 min and the reaction mixture was stirred at this temperature for an additional 10 min before warming

to rt, followed by an additional 30 min of stirring. Precipitate was removed by filtering through SiO_2 with Et_2O (50 mL) and solvent was removed under reduced pressure to afford an amorphous white solid that was purified by SiO_2 flash chromatography (5% – 10% EtOAc in hexanes) to provide **2** in a 4:1 mixture of side chain olefin isomers (*cis*:*trans*) as a colorless oil (8 mg, 89 %). $[\alpha]^{25}_D$ = 1.9°, *c* = 0.001, DCM); (*Denotes minor *trans* side chain olefin isomer) ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.32 (d, *J* = 2.2 Hz, 1H), 6.30 (d, *J* = 2.2 Hz, 1H), 5.80 – 5.66 (m, 1H), 5.63 – 5.43 (m, 2H), 5.40 – 5.31 (m, 1H), 5.30 – 5.22 (m, 1H), 3.80 (s, 3H), 3.78 – 3.72 (m, 2H), 3.75 (s, 3H), 3.66 (dd, *J* = 7.6, 3.8 Hz, 1H), 3.49 (ddd, *J* = 11.4, 5.7, 3.2 Hz, 1H), 3.14 (d, *J* = 12.8 Hz, 1H), 2.69 (dd, *J* = 24.3, 11.2 Hz, 1H), 2.33 – 2.13 (m, 3H), 2.12 – 2.03 (m, 2H), 1.99 – 1.75 (m, 4H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 3.5 Hz, 3H), *0.90 (s, 9H), 0.90 (s, 9H), 0.75 (s, 9H), *0.08 – 0.05 (s, 3H), 0.02 (s, 3H), -0.01 (s, 3H), -0.19 (s, 3H), -0.61 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.4, 160.6, 158.8, 140.8, 135.5, 129.7, 129.0, 127.6, 116.5, 109.3, 97.2, 76.8, 76.4, 72.8, 56.2, 55.4, 53.6, 53.0, 47.4, 41.6, 40.2, 37.7, 34.2, 32.2, 30.1, 29.8, 26.3, 26.0, 18.6, 14.3, 11.4, -3.5, -3.7, -5.0, -5.7; HRMS (ESI, *m/z*): calcd for $[C_{39}H_{67}N_3O_6Si_2+Na]^+$, ([M + Na]$^+$): 752.4466, found 752.4459.



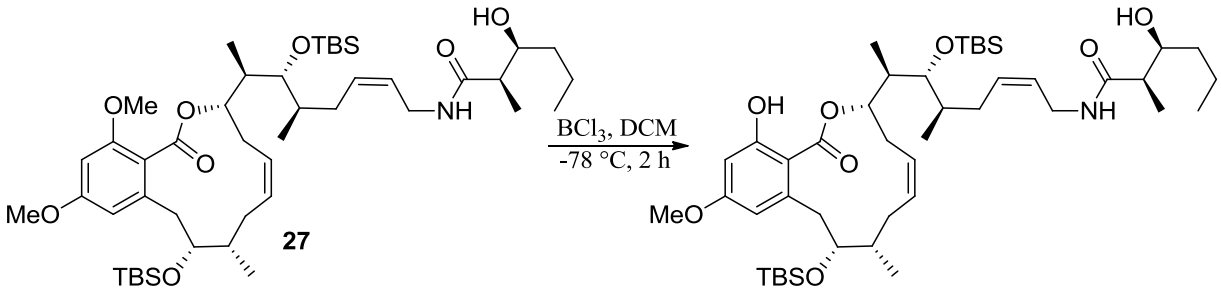
(2*R*,3*S*)-*N*-((5*R*,6*R*,7*R*,*Z*)-6-((*tert*-butyldimethylsilyl)oxy)-7-((3*S*,8*S*,9*R*,*Z*)-9-((*tert*-butyldimethylsilyl)oxy)-12,14-dimethoxy-8-methyl-1-oxo-3,4,7,8,9,10-hexahydro-1*H*-benzo[*c*][1]oxacyclododecin-3-yl)-5-methyloct-2-en-1-yl)-3-hydroxy-2-methylhexanamide (27): *Flask A*: A 5 mL flask was flame dried and flushed with argon before THF (400 µL),

compound **3** (8 mg, 0012 mmol), and PPh_3 (8 mg, 0.03 mmol) were added. The reaction mixture was heated at 50 °C for 2 h and then allowed to cool to rt.

Flask B: A separate 5 mL flask was flame dried and flushed with argon before DMF (200 µL), acid **3** (3.4 mg, 0.024 mmol), DIPEA (21 µL, 0.12 mmol), and COMU (11 mg, 0.025 mmol) were sequentially added. The reaction mixture was stirred for 30 min at rt.

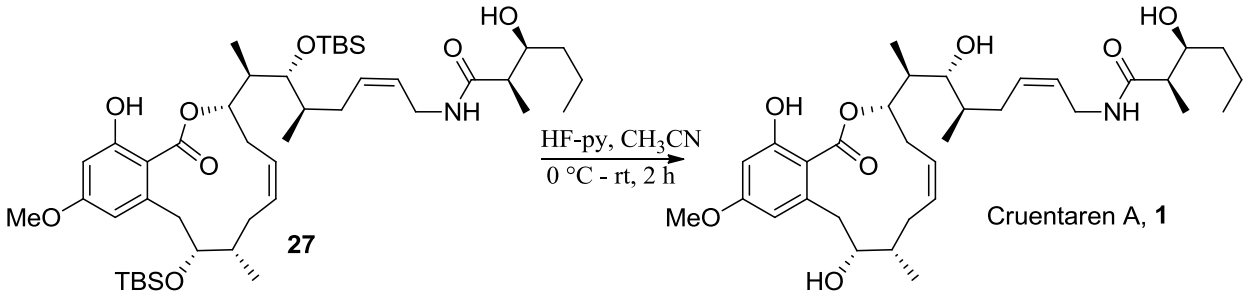
After stirring the reaction mixtures for the designated time, the contents of flask B were added to flask A (rinse with 100 µL DMF), and the combined reaction mixtures were stirred for 1 h at rt. Reaction was quenched by the addition of saturated aqueous sodium bicarbonate (1 mL). The resultant slurry was partitioned between Et_2O (3 mL) and water (1 mL). The organic layer was collected and the aqueous layer was extracted with Et_2O (5 X 3 mL) and the combined organic extracts were dried over anhydrous sodium sulfate followed by the removal of solvent under reduced pressure to afford a red oil that was purified by SiO_2 flash chromatography (5% – 10% EtOAc in hexanes) to provide **27** as a colorless oil (7.9 mg, 79%). $[\alpha]^{25}_D$ = 2.2°, *c* = 0.001, DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.32 (d, *J* = 2.3 Hz, 1H), 6.30 (d, *J* = 2.2 Hz, 1H), 6.25 (s, 1H), 5.62 (m, 1H), 5.55 (ddd, *J* = 10.7, 3.0, 1.1 Hz, 1H), 5.48 (ddd, *J* = 10.8, 4.5, 2.0 Hz, 1H), 5.38 – 5.24 (m, 2H), 3.99 (dddd, *J* = 14.7, 7.1, 5.9, 1.6 Hz, 1H), 3.92 – 3.85 (m, 1H), 3.86 – 3.77 (m, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.67 (d, *J* = 2.5 Hz, 1H), 3.43 (dd, *J* = 5.9, 3.0 Hz, 1H), 3.10 (d, *J* = 12.6 Hz, 1H), 2.74 (dt, *J* = 14.1, 11.3 Hz, 1H), 2.33 – 2.12 (m, 5H), 2.08 – 2.01 (m, 1H), 1.98 – 1.82 (m, 2H), 1.83 – 1.74 (m, 1H), 1.61 – 1.40 (m, 2H), 1.38 – 1.18 (m, 2H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.0 Hz 3H), 0.89 (d, *J* = 7.2 Hz, 6H), 0.88 (s, 9H), 0.76 (s, 9H), 0.00 (s, 3H), -0.04 (s, 3H), -0.20 (s, 3H), -0.62 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.0, 172.2, 169.99, 166.9, 158.7, 132.9, 127.6, 126.2, 109.2, 106.5, 97.1, 77.7, 72.9, 72.8, 71.7, 56.1, 55.4, 44.5, 40.2, 40.1, 38.3, 36.4, 36.4, 35.9, 34.0, 32.1,

32.1, 29.8, 29.0, 26.3, 25.9, 19.4, 17.9, 14.2, 13.7, 11.5, 11.2, -3.6, -3.8, -5.0, -5.7; HRMS (ESI, *m/z*): calcd for $[C_{46}H_{81}NO_8Si_2+Na]^+$, ($[M + Na]^+$): 854.5398, found 854.5401.



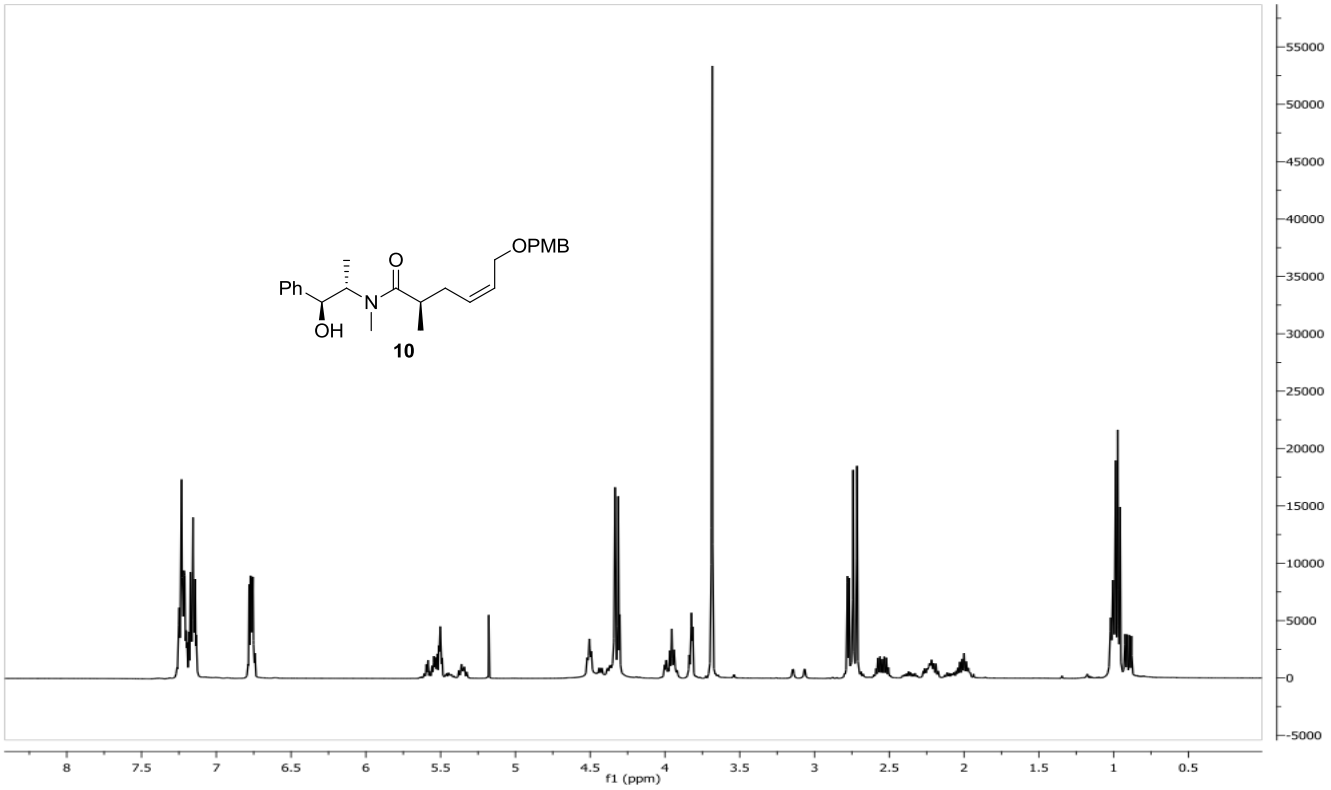
(2*R*,3*S*)-*N*-((5*R*,6*R*,7*R*,*Z*)-6-((*tert*-butyldimethylsilyl)oxy)-7-((3*S*,8*S*,9*R*,*Z*)-9-((*tert*-butyldimethylsilyl)oxy)-14-hydroxy-12-methoxy-8-methyl-1-oxo-3,4,7,8,9,10-hexahydro-1*H*-benzo[*c*][1]oxacyclododecin-3-yl)-5-methyloct-2-en-1-yl)-3-hydroxy-2-methylhexanamide: A 5 mL flask was flame dried and flushed with argon before DCM (200 µL) and compound **27** (7.6 mg, 0.003 mmol) were added. The solution was cooled to -78 °C and boron trichloride (1M in DCM, 12 µL, 0.012 mmol) was added dropwise over 10 min. Stirring was continued at -78 °C for 2 h at which point the reaction was quenched by the addition of saturated aqueous sodium acetate (2 mL) and subsequently diluted with DCM (2 mL). The organic layer was collected and the aqueous layer was extracted with DCM (4 X 2 mL). The combined organic layers were dried over anhydrous sodium sulfate and solvent was removed under reduced pressure to afford a light yellow oil that was purified by SiO_2 flash chromatography (35% – 50% EtOAc in hexanes) to provide isomerically pure title compound as an amorphous solid (6.5 mg, 78 %). $[\alpha]^{25}_D$ = 10.2°, *c* = 0.001, DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.56 (s, 1H), 6.31 (d, *J* = 2.6 Hz, 1H), 6.29 (d, *J* = 2.6 Hz, 1H), 5.73 (bt, 1H), 5.47 (dd, *J* = 20.6, 10.4 Hz, 1H), 5.40 – 5.32 (m, 2H), 5.31 – 5.25 (m, 1H), 5.11 (dd, *J* = 11.3, 4.5 Hz, 1H), 3.90 – 3.81 (m, 2H), 3.78 (s, 3H), 3.78 – 3.72 (m, 2H), 3.67 (dd, *J* = 14.5, 6.7 Hz, 1H), 3.59 (d, *J* = 11.8 Hz, 1H), 3.49 (bs, 1H), 2.73 (dd, *J* = 25.1, 10.9 Hz, 1H), 2.27 (dt, *J* = 16.3, 12.6 Hz,

2H), 2.22 – 2.13 (m, 2H), 2.11 – 2.05 (m, 2H), 1.97 – 1.93 (m, 1H), 1.93 – 1.82 (m, 2H), 1.80 – 1.71 (m, 2H), 1.67 – 1.59 (m, 3H), 1.17 (d, *J* = 7.2 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 7.2 Hz, 3H), 0.91 (s, 9H), 0.88 (t, *J* = 7.0 Hz, 3H), 0.74 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H), -0.21 (s, 3H), -0.67 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.6, 171.7, 165.2, 163.4, 144.9, 132.2, 131.6, 126.4, 125.9, 114.2, 105.3, 99.6, 78.3, 76.6, 73.6, 71.8, 55.4, 44.6, 40.2, 39.9, 38.2, 36.3, 35.9, 33.2, 32.1, 29.6, 29.4, 29.2, 26.2, 25.9, 24.9, 22.8, 19.4, 14.3, 14.2, 11.2, -3.2, -4.3, -4.8, -5.8; HRMS (ESI, *m/z*): calcd for $[C_{45}H_{79}NO_8Si_2+Na]^+$, ($[M + Na]^+$): 840.5242, found 840.5245.



Cruentaren A (1): A Teflon reaction vessel was equipped with a stir bar and charged with ACN (500 µL) and the above compound (6 mg, 0.0084 mmol). The solution was cooled to 0 °C and aqueous HF (48 % *w*/*w*, 500 µL) and stirring was continued for 1 h at 0 °C then continued for 1 h at rt. The reaction mixture was cooled back to 0 °C and was quenched by the addition of saturated aqueous sodium bicarbonate (5 mL) and diluted with EtOAc (5 mL). The organic layer was collected and the aqueous layer was extracted with EtOAc (3 X, 5 mL). The combined organic layers were dried over anhydrous sodium sulfate and solvent was removed under reduced pressure to afford an orange oil that was purified by thin-layer chromatography (20% acetone in DCM) to afford cruentaren A (**1**) as a colorless amorphous solid (2.7 mg, 76%). $[\alpha]^{25}_D$ = - 2.8°, *c* =0.0006 , DCM). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.50 (br s, 1H), 6.37 (d, *J* = 2.7 Hz, 1H), 6.31 (d, *J* = 2.6 Hz, 1H), 6.09 (t, *J* = 5.4 Hz, 1H), 5.56 (dddt, *J* = 10.8, 8.6, 7.1, 1.4 Hz,

1H), 5.46 – 5.52 (m, 1H), 5.44 (ddd, *J* = 11.1, 4.5, 1.6 Hz, 1H), 5.40 (dddd, *J* = 11.0, 11.0, 4.5, 2.0 Hz, 1H), 5.30 (ddd, *J* = 11.6, 5.6, 1.9 Hz, 1H), 3.91 (dddd, *J* = 14.9, 7.5, 5.8, 1.3, 1H), 3.80 – 3.87 (m, 2H), 3.80 (s, 3H), 3.74 (dd, *J* = 12.8, 1.6 Hz, 1H), 3.64 (ddd, *J* = 10.8, 2.9, 1.7 Hz, 1H), 3.45 (ddd, *J* = 9.1, 6.7, 2.1 Hz, 1H), 3.10 (d, *J* = 3.3 Hz, 1H), 2.83 (dt, *J* = 14.1, 11.5 Hz, 1H), 2.75 (d, *J* = 6.7 Hz, 1H), 2.34 (dt, *J* = 14.3, 11.6 Hz, 1H), 2.27 (dq, *J* = 7.2, 2.9 Hz, 1H) 2.20 – 2.28 (m, 4H), 1.95 – 2.05 (m, 3H), 1.70 (dddq, *J* = 9.1, 6.8, 6.8, 4.7 Hz, 1H), 1.42 – 1.51 (m, 2H), 1.27 – 1.35 (m, 3H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5, 171.4, 165.7, 163.5, 143.6, 132.1, 130.9, 126.7, 125.7, 112.3, 104.9, 99.6, 78.0, 74.6, 73.0, 71.8, 55.4, 44.8, 39.2, 38.2, 36.8, 36.6, 36.5, 35.7, 31.6, 30.6, 29.8, 29.7, 19.2, 16.1, 14.1, 14.0, 11.2, 8.5. HRMS (ESI, *m/z*): calcd for $[C_{33}H_{51}NO_8+Na]^+$, ($[M + Na]^+$): 612.3506, found 612.3508.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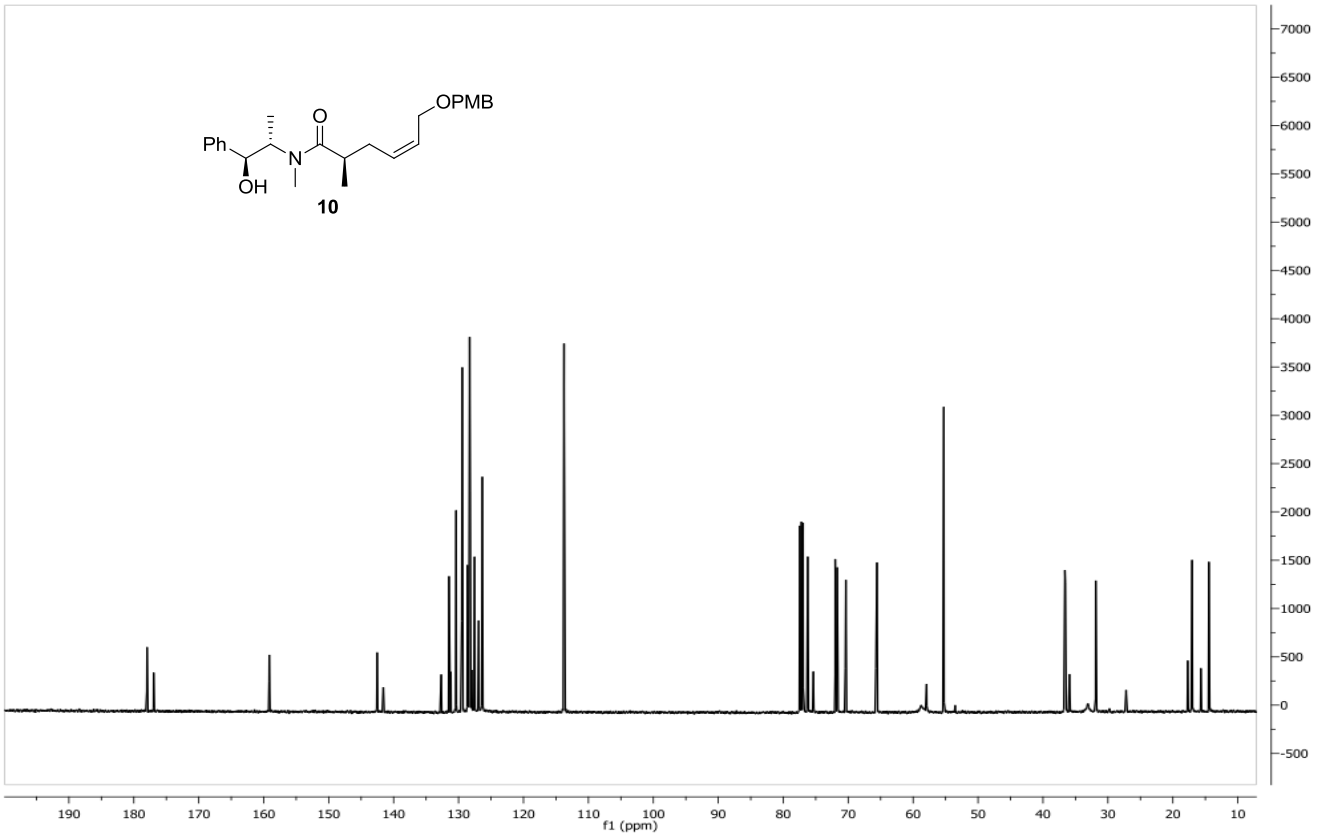
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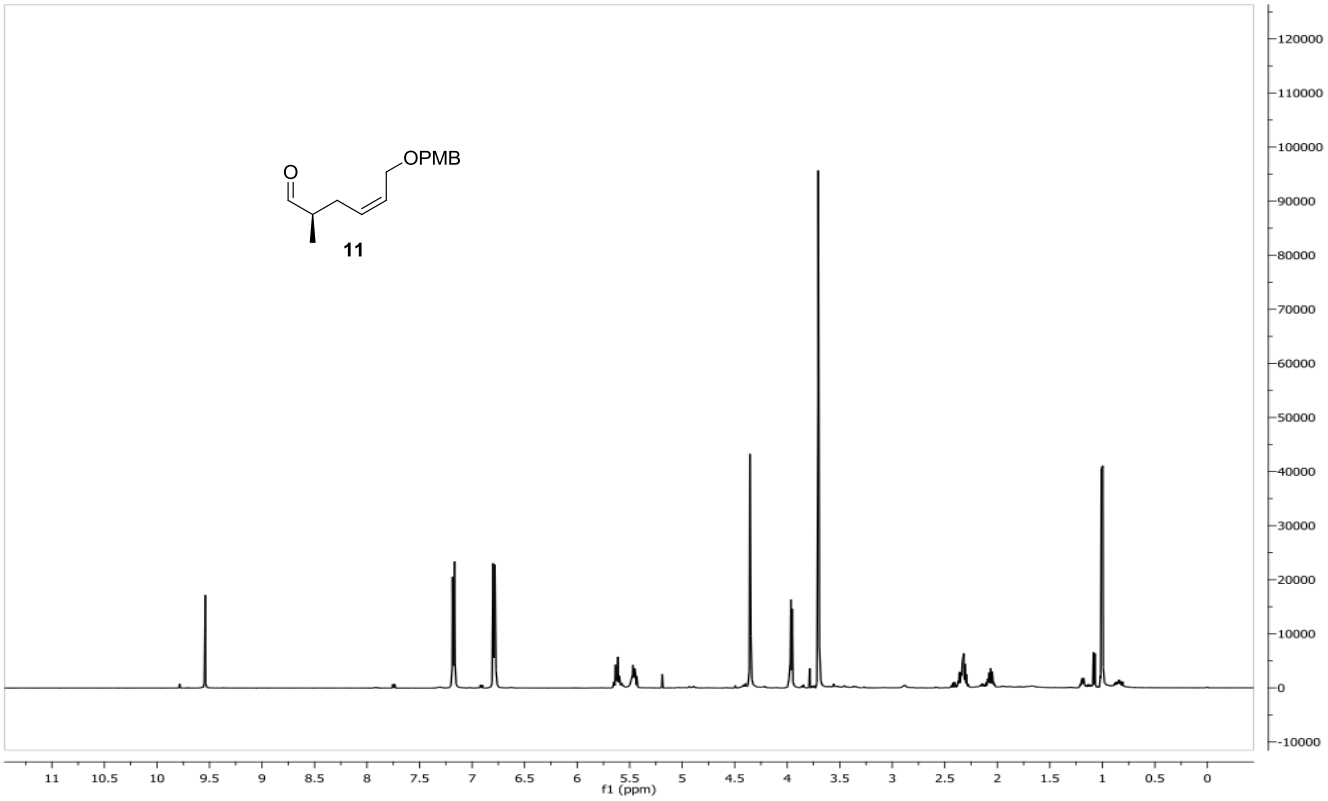
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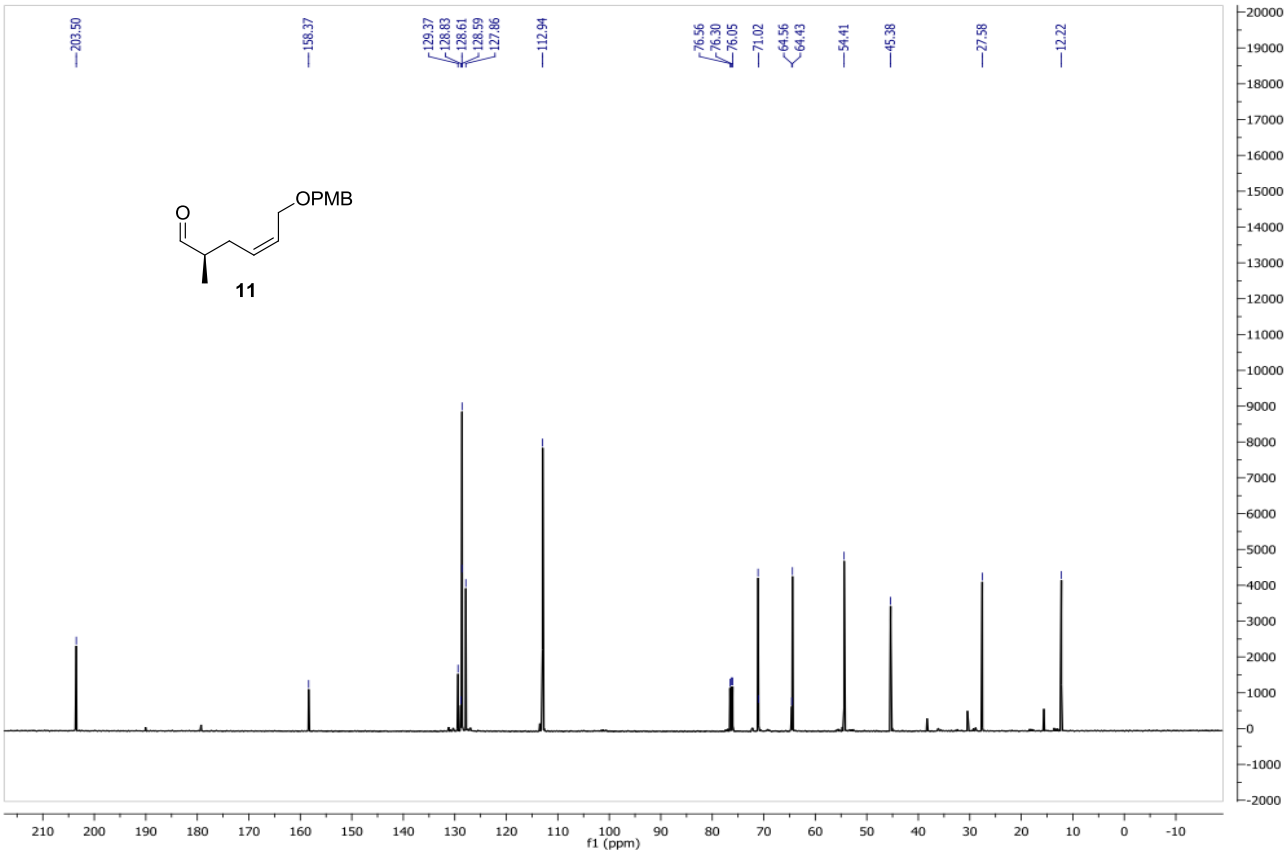
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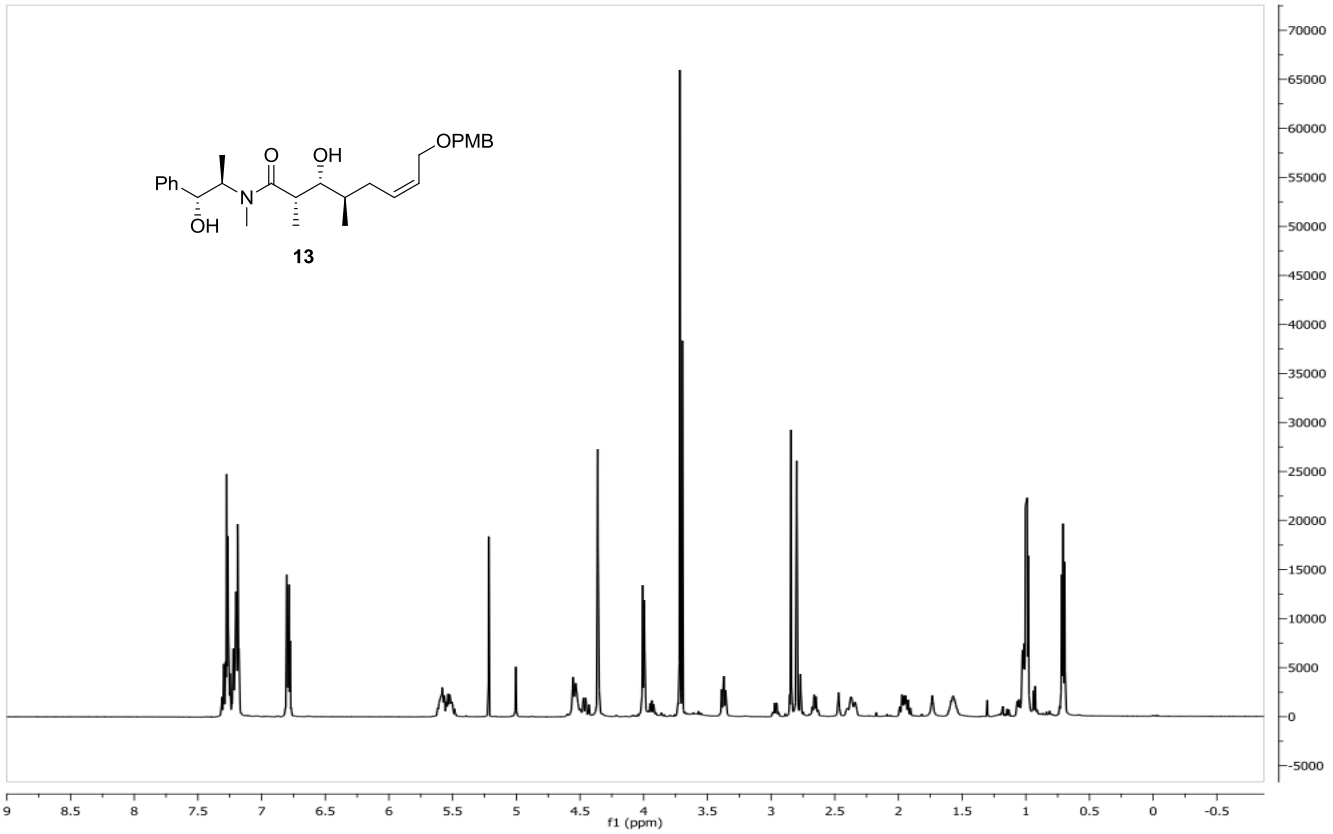
f1 (ppm)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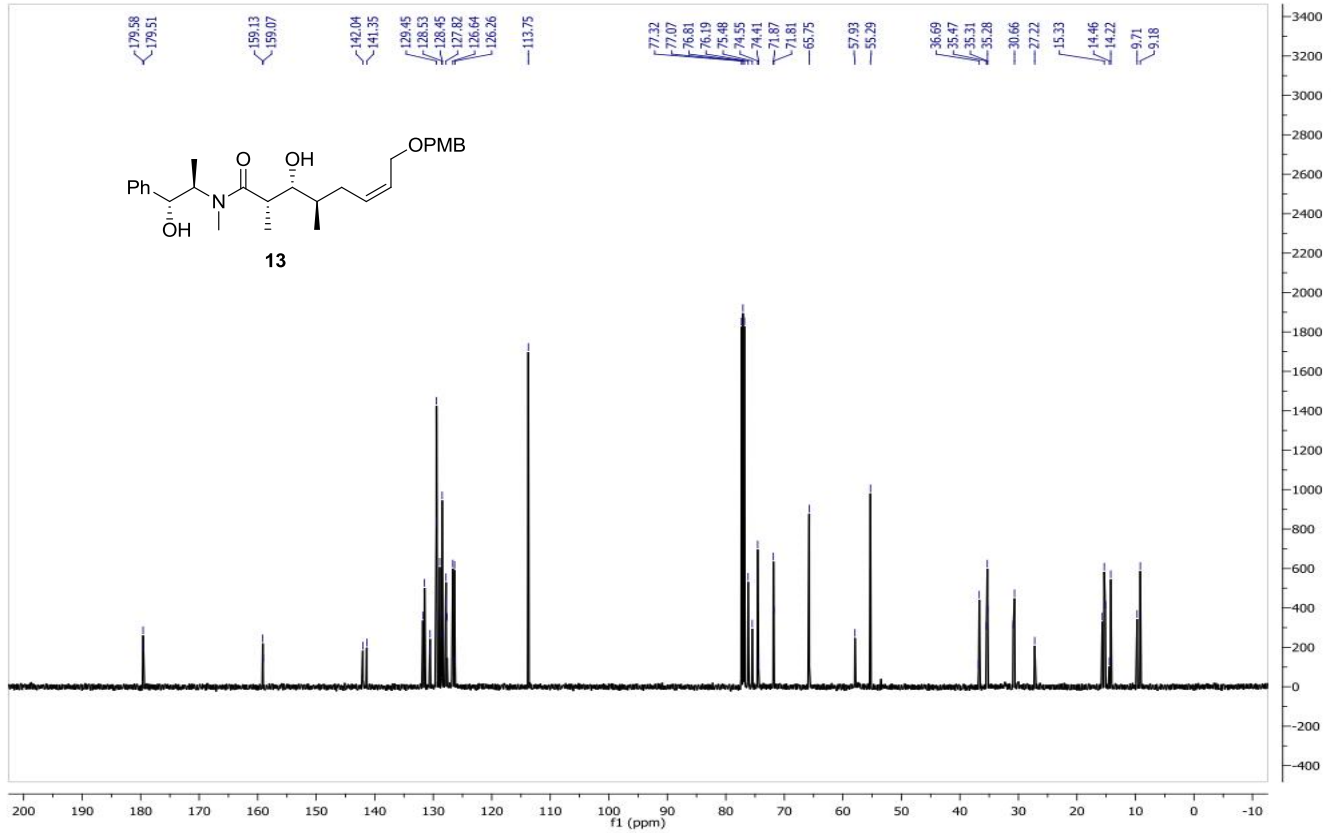
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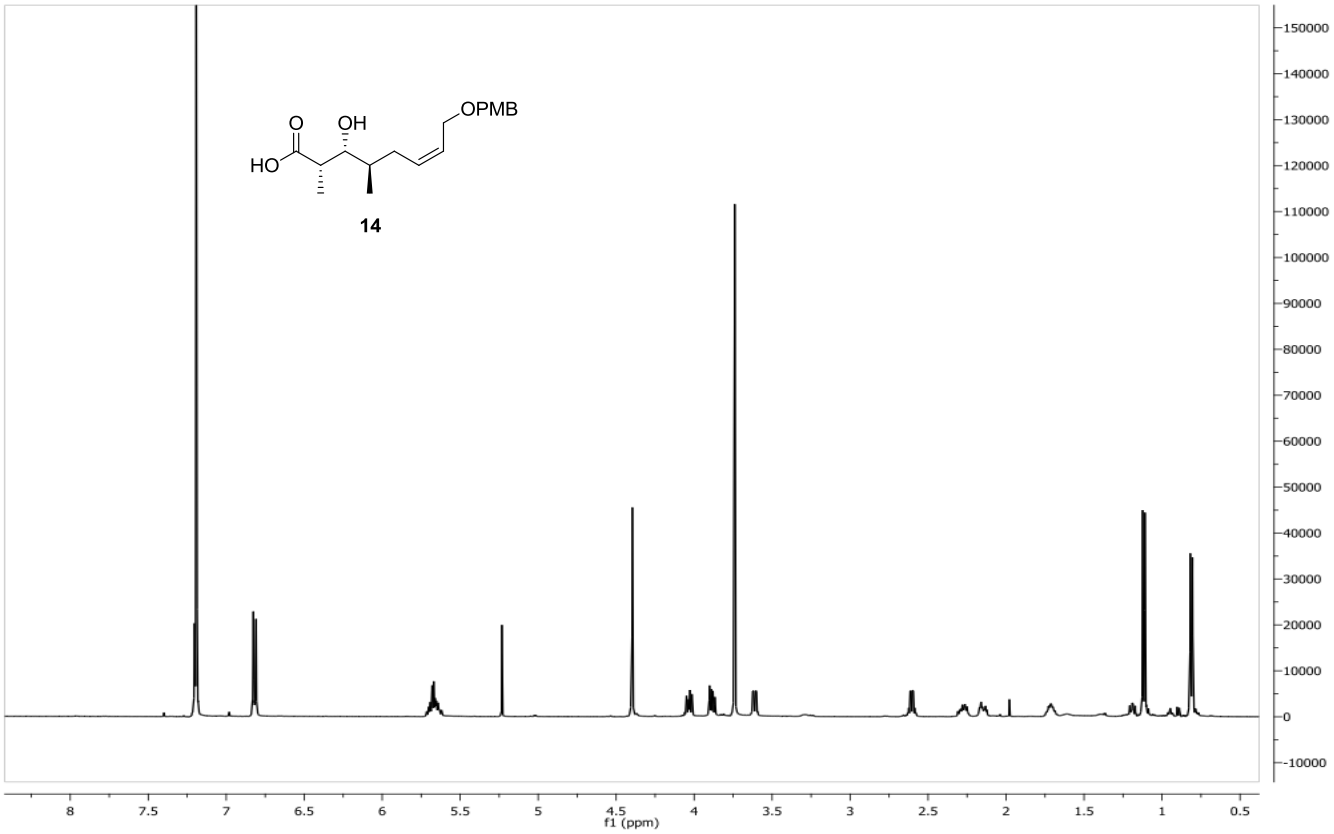
f1 (ppm)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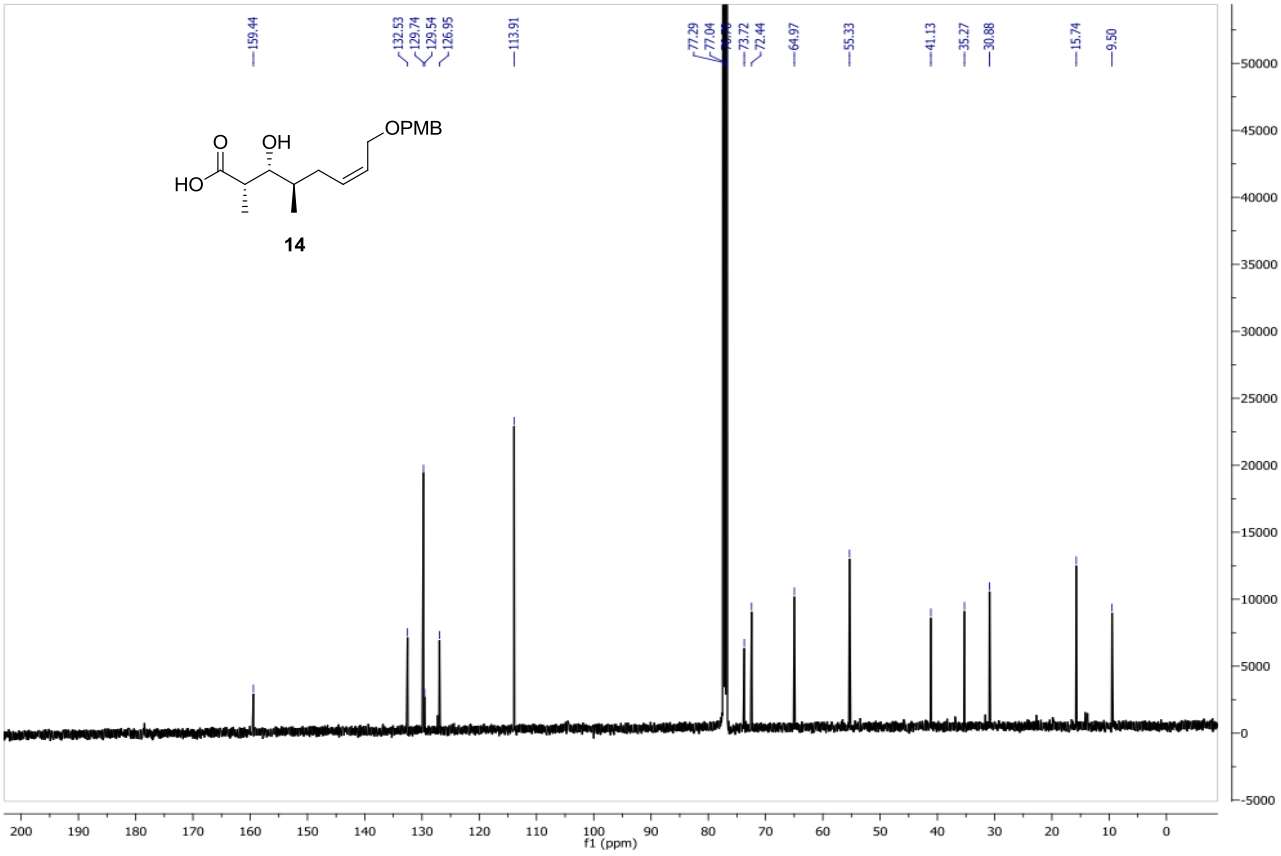
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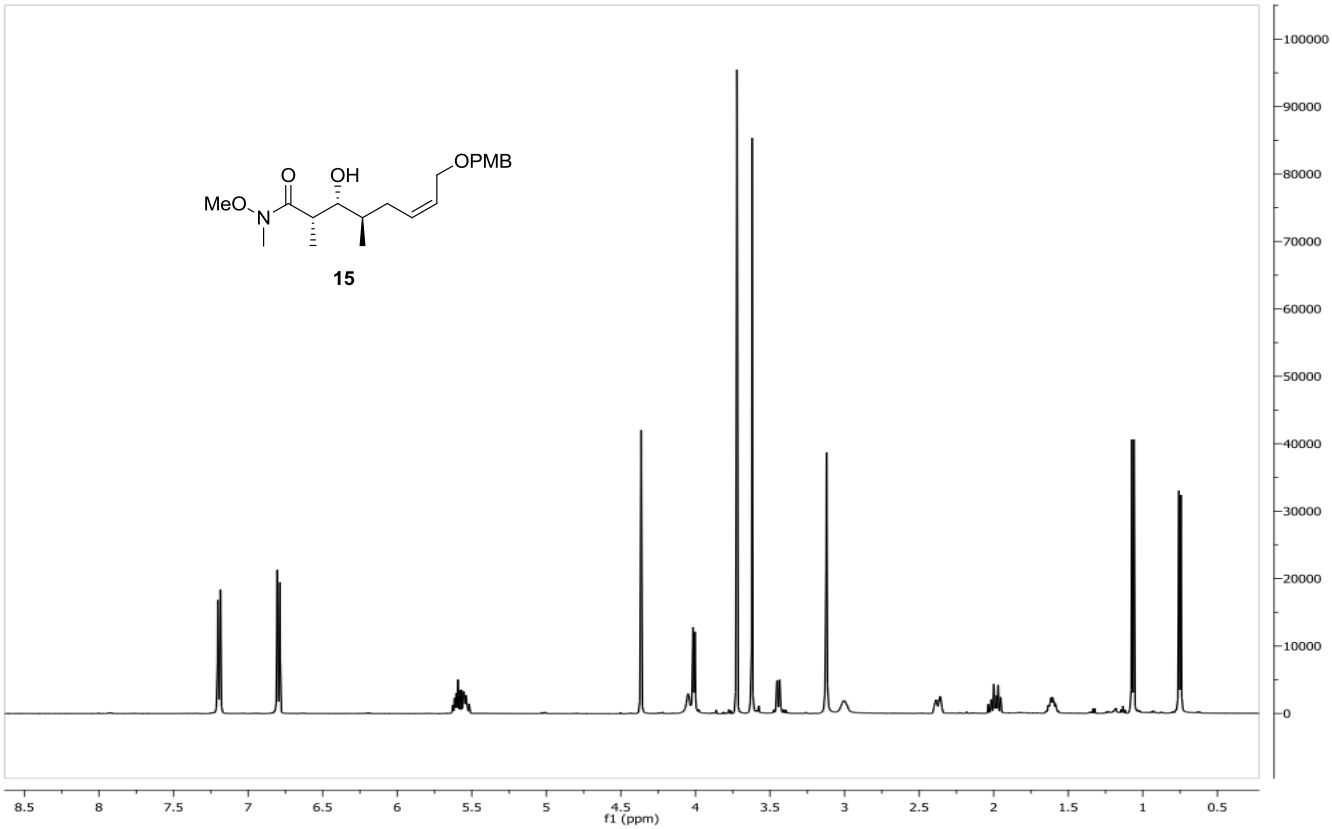
f1 (ppm)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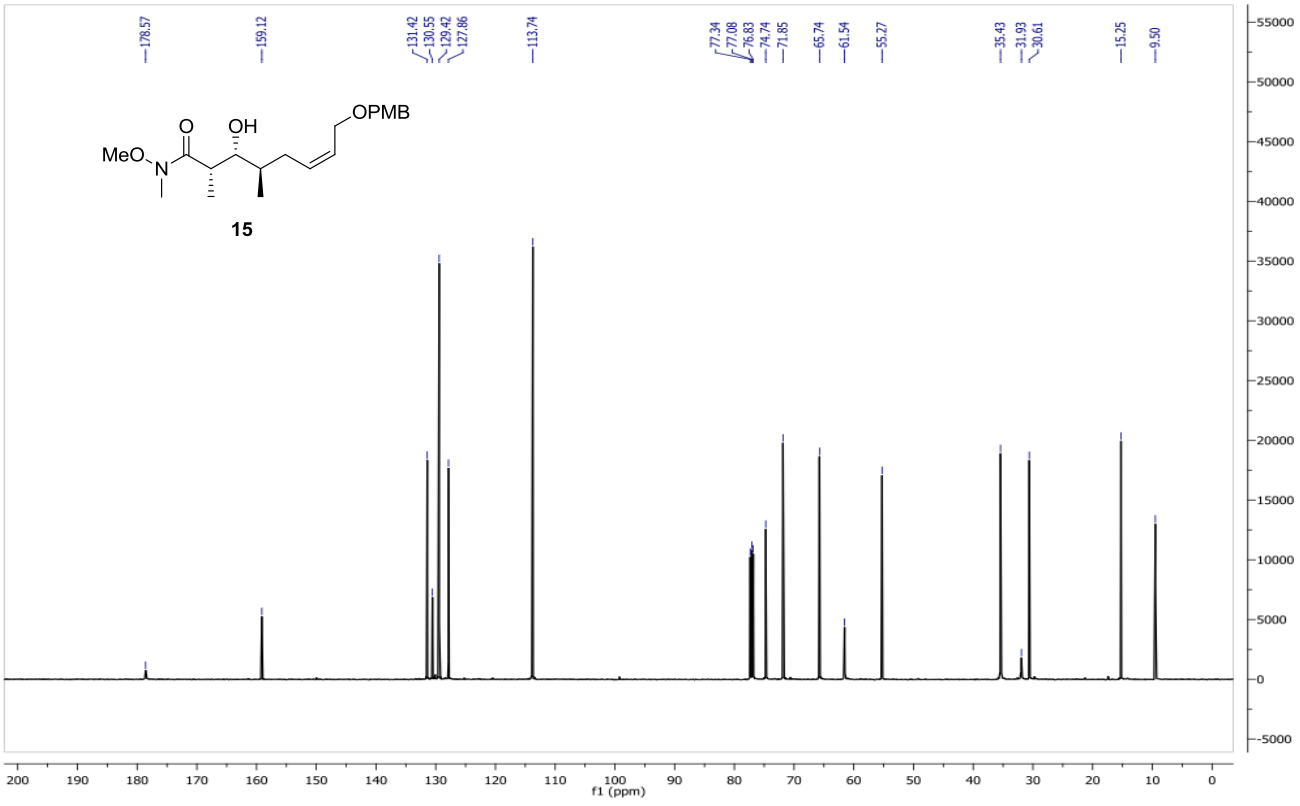
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MeO
N
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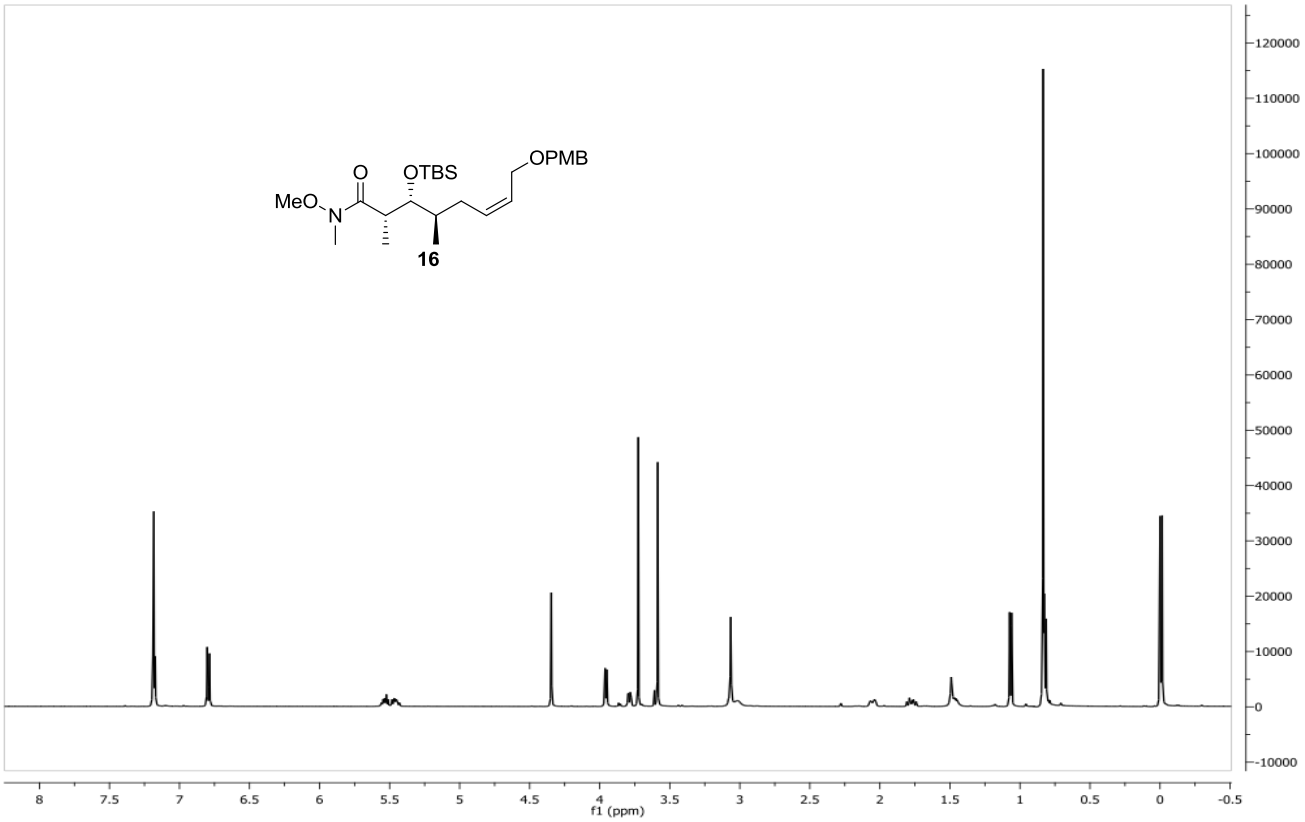
f1 (ppm)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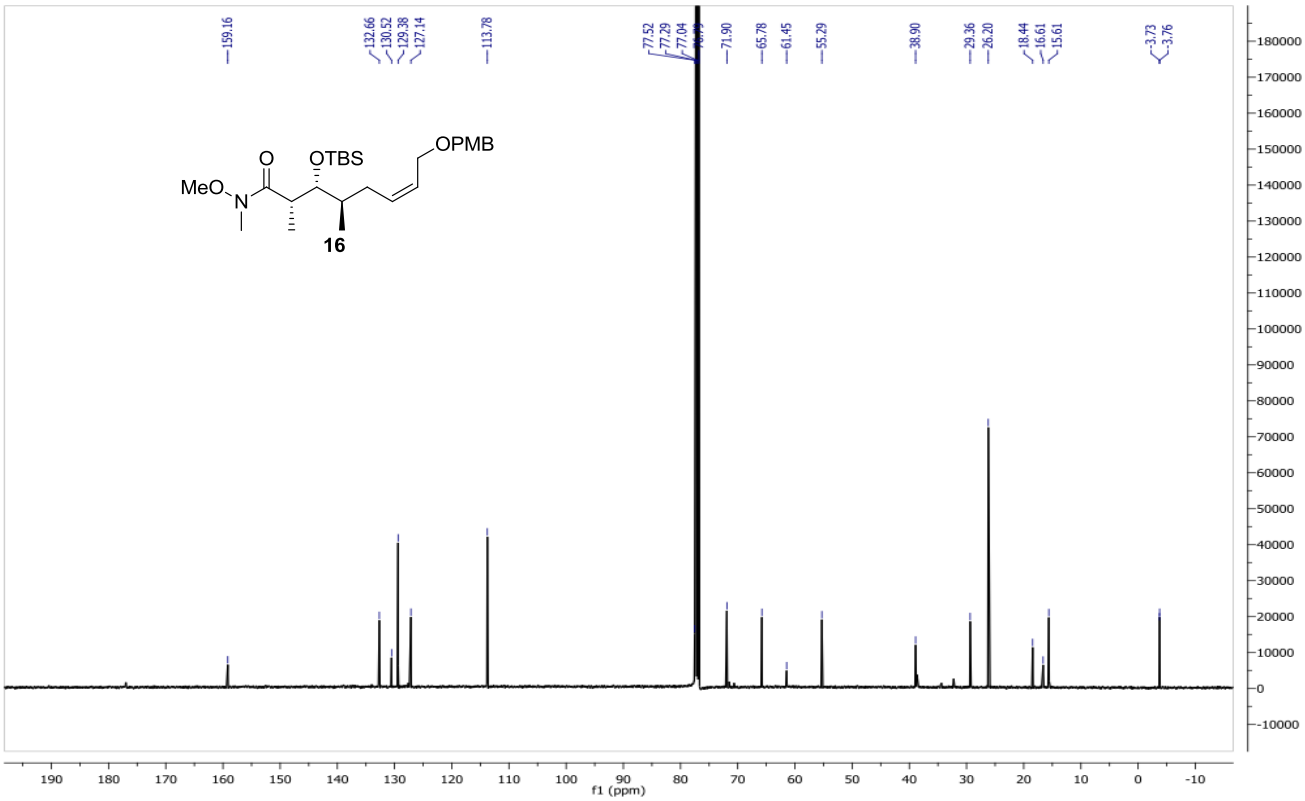
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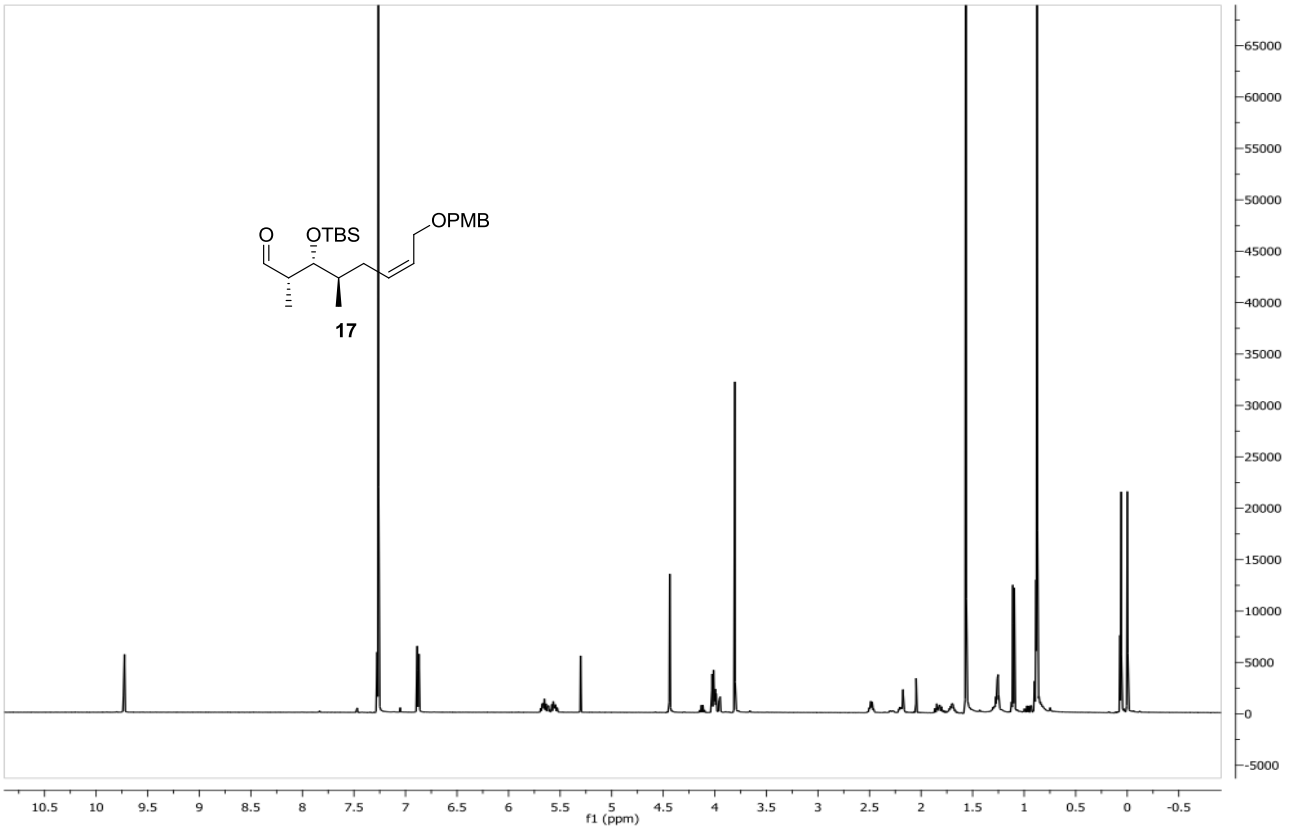
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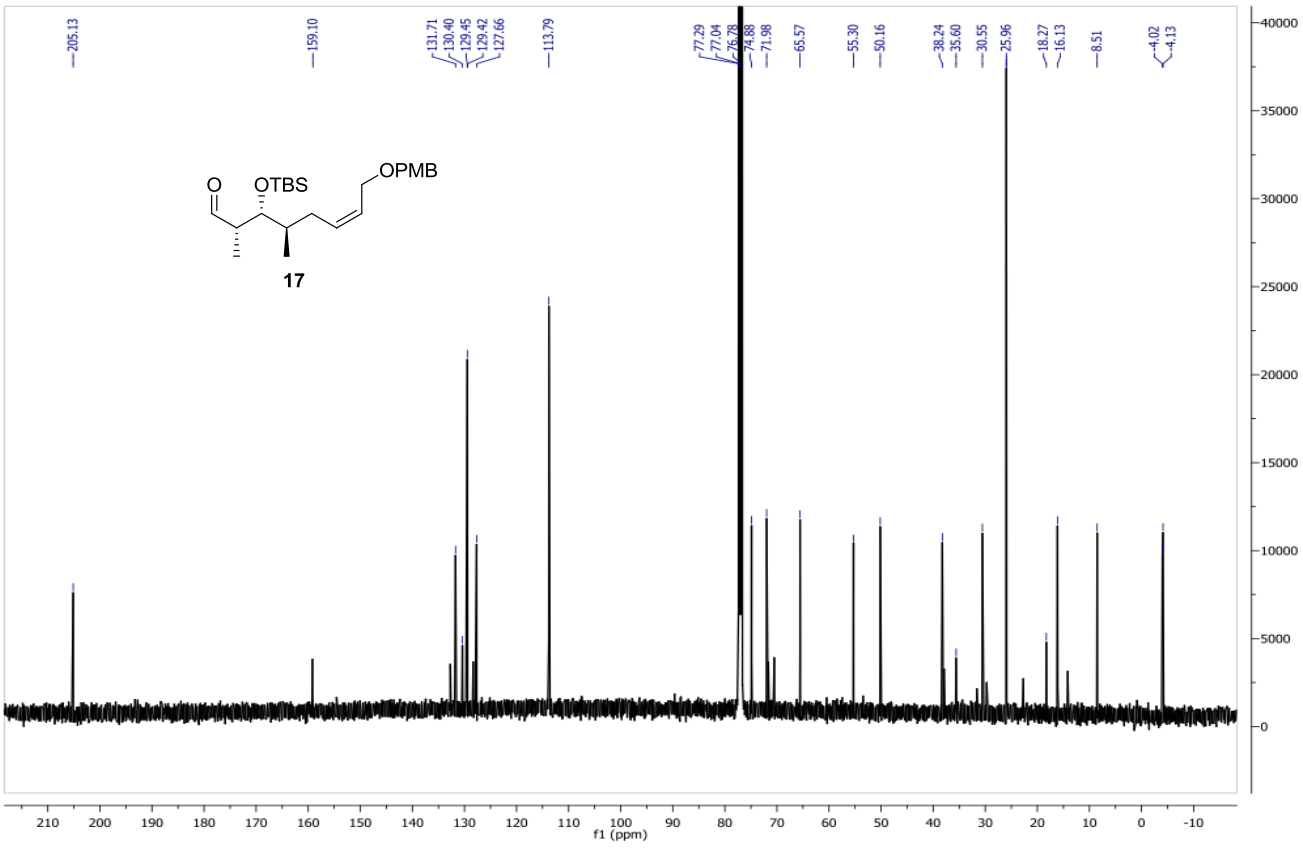
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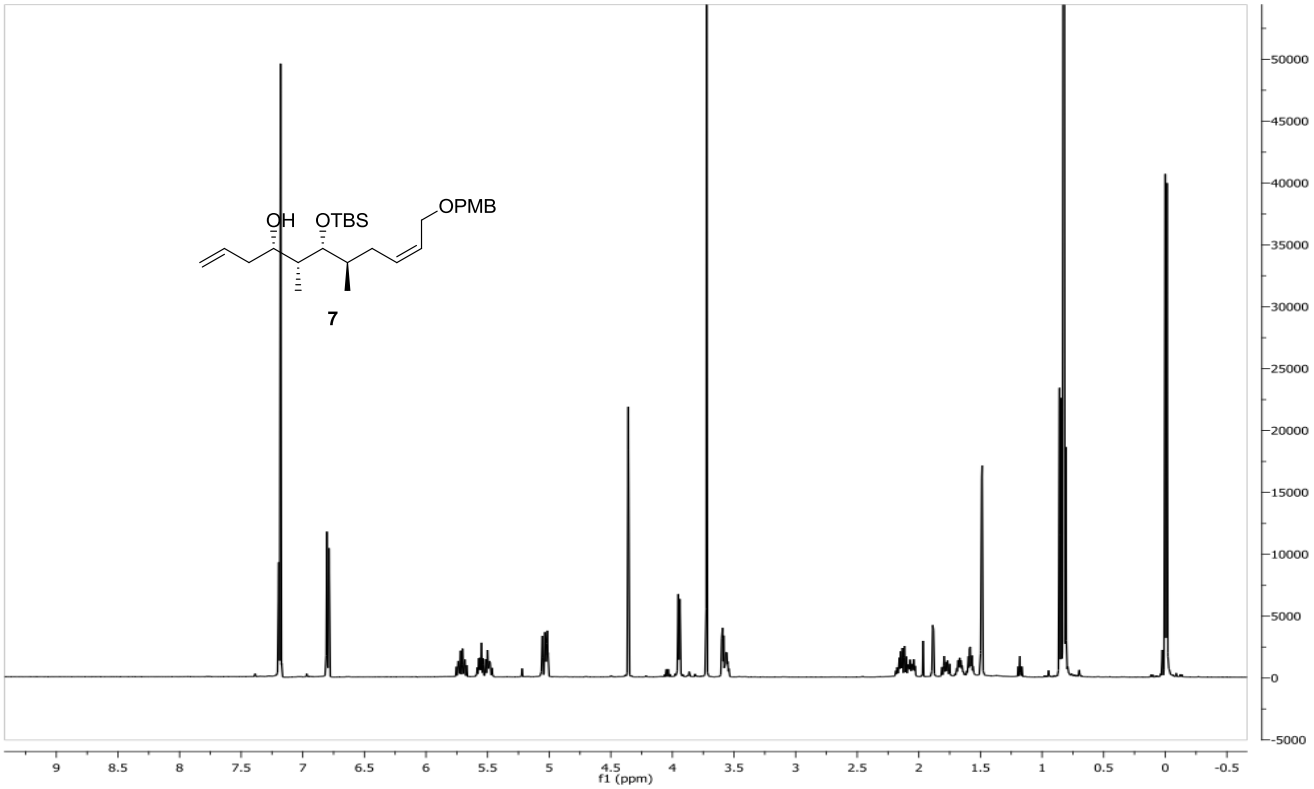
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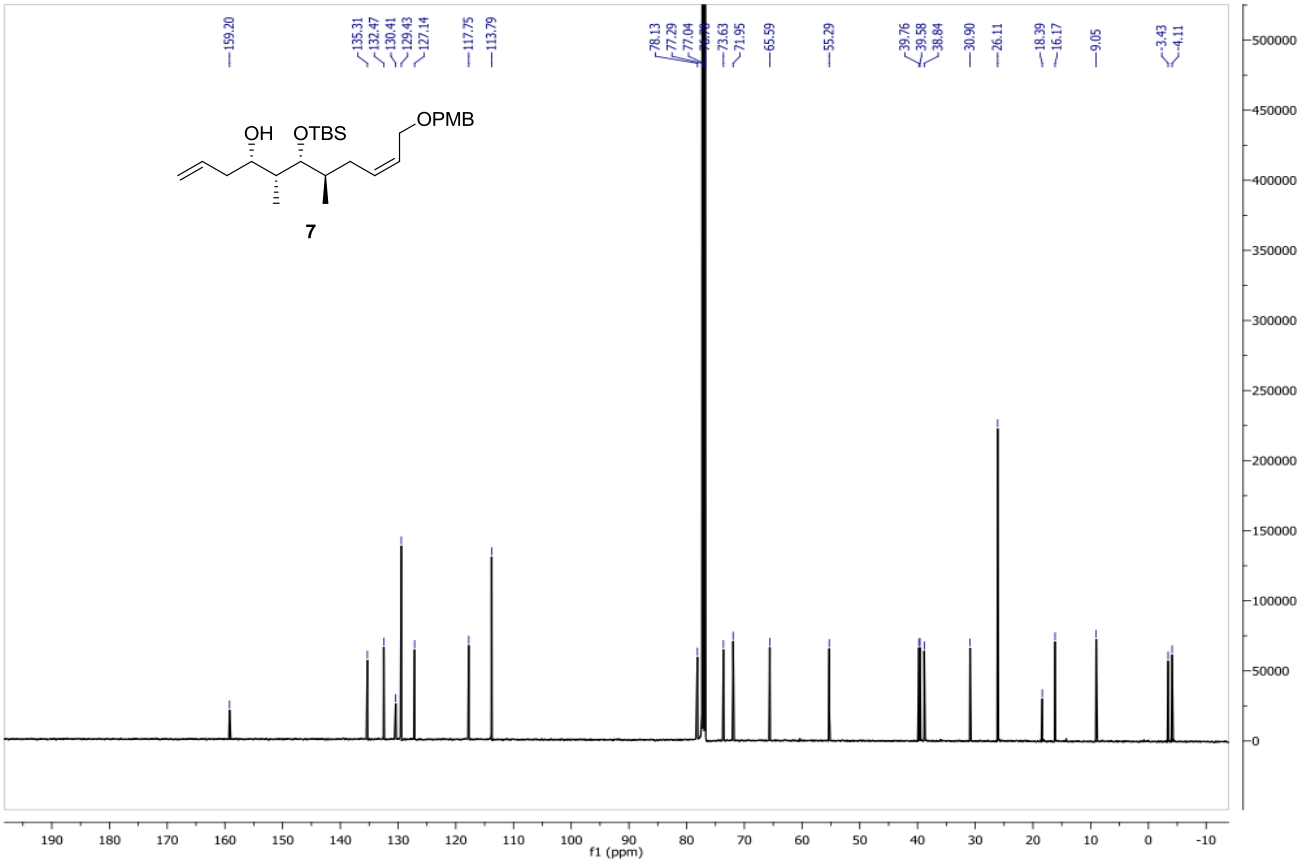
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OPMB
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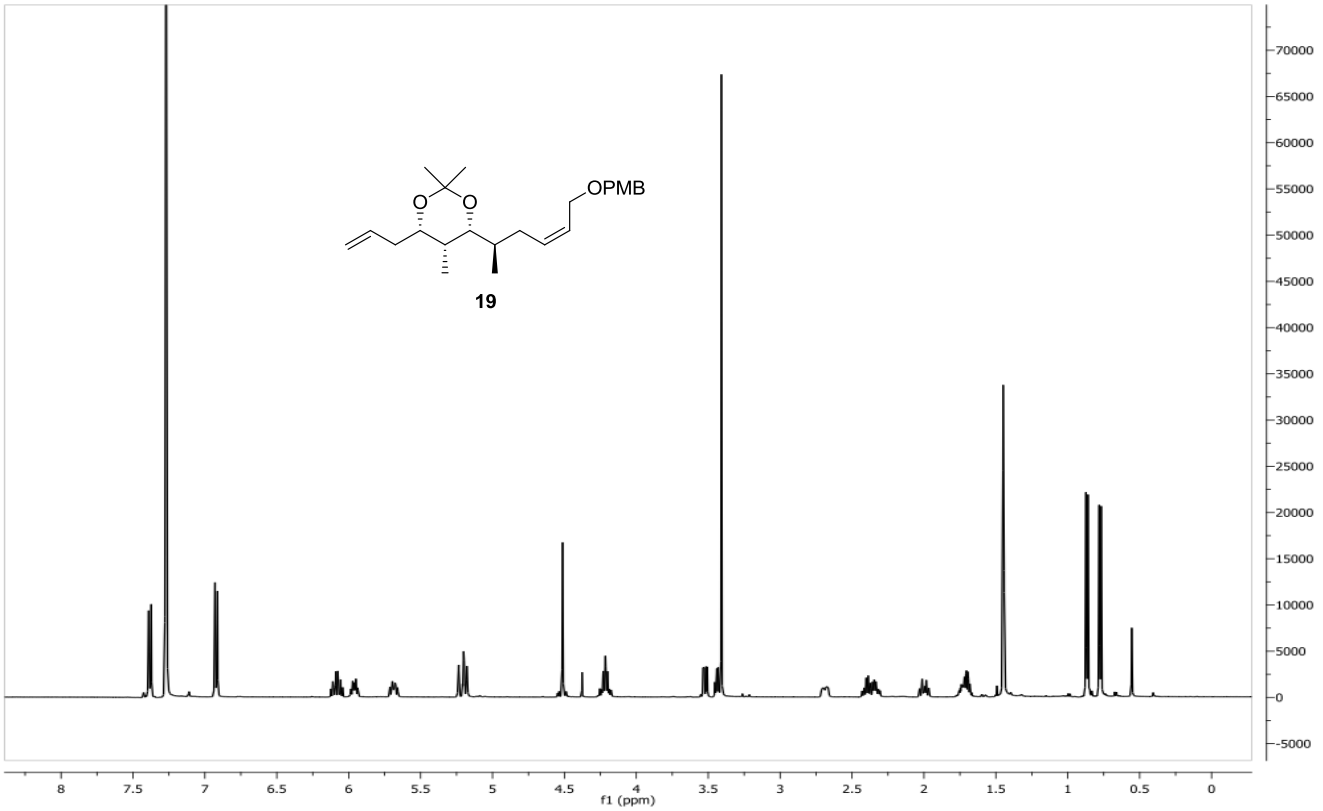
f1 (ppm)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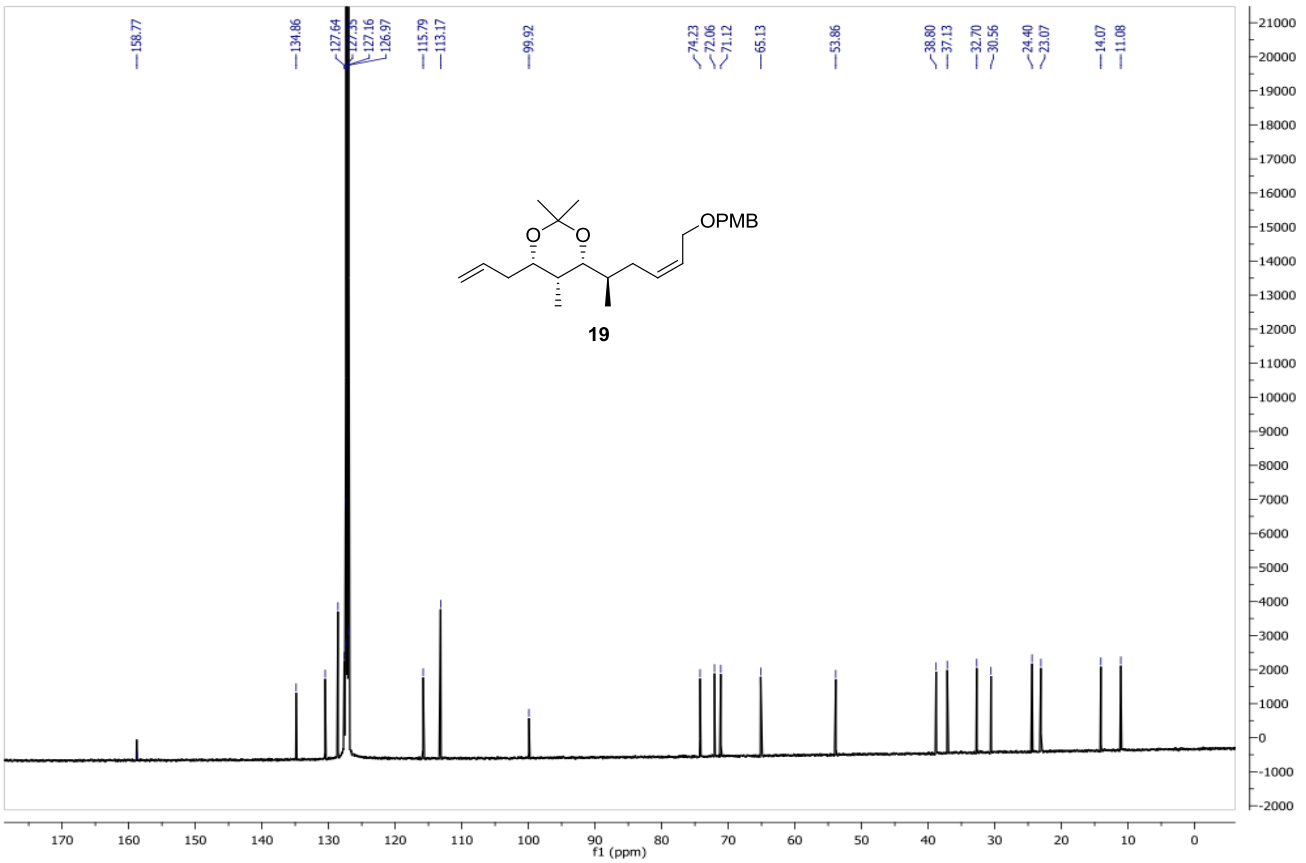
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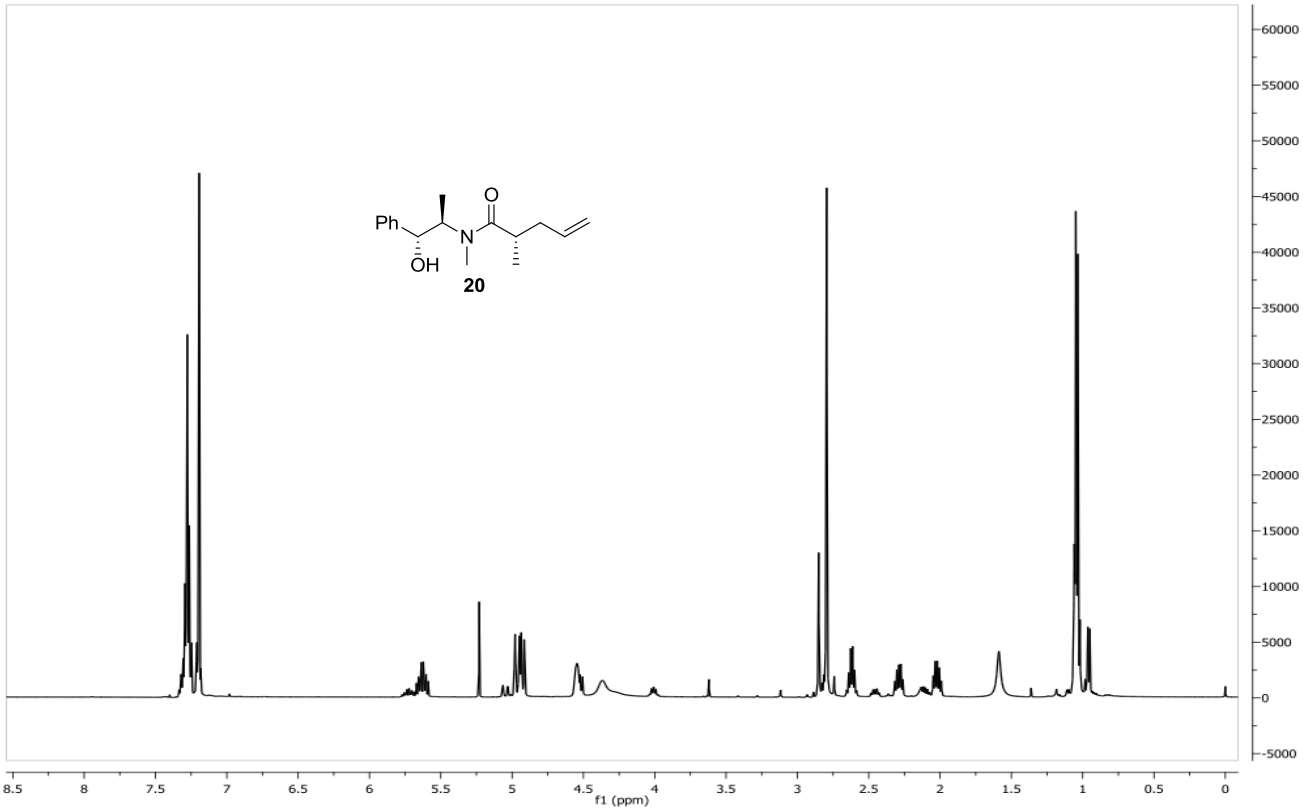
f1 (ppm)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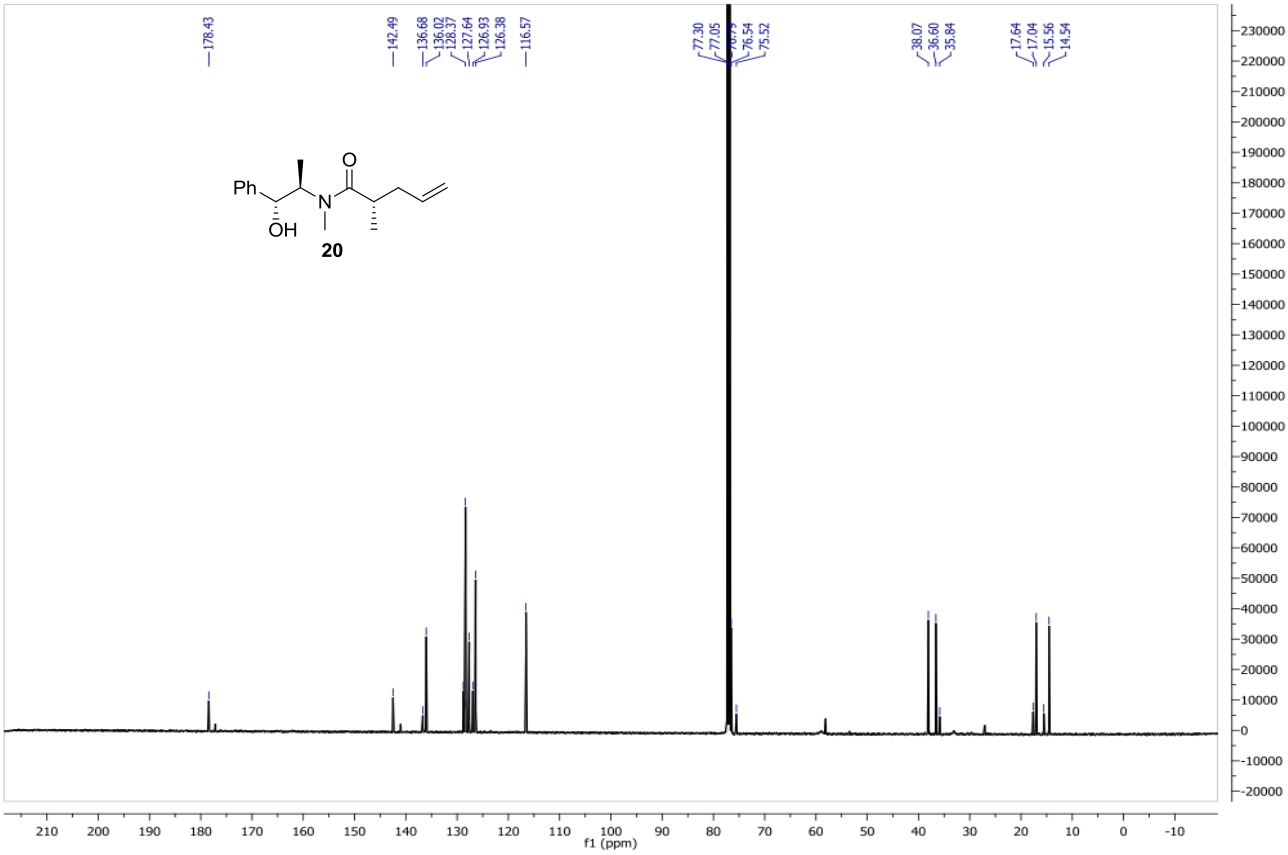
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Ph
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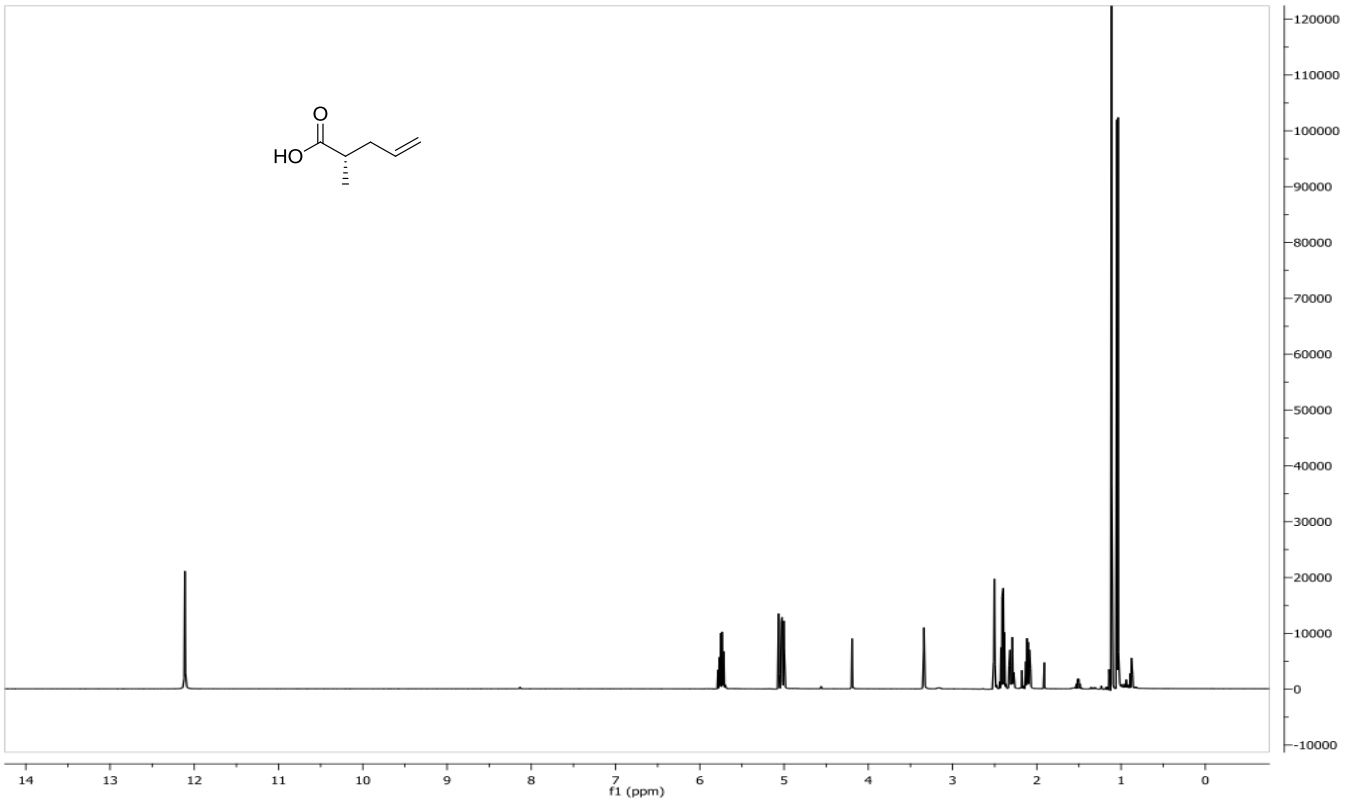
f1 (ppm)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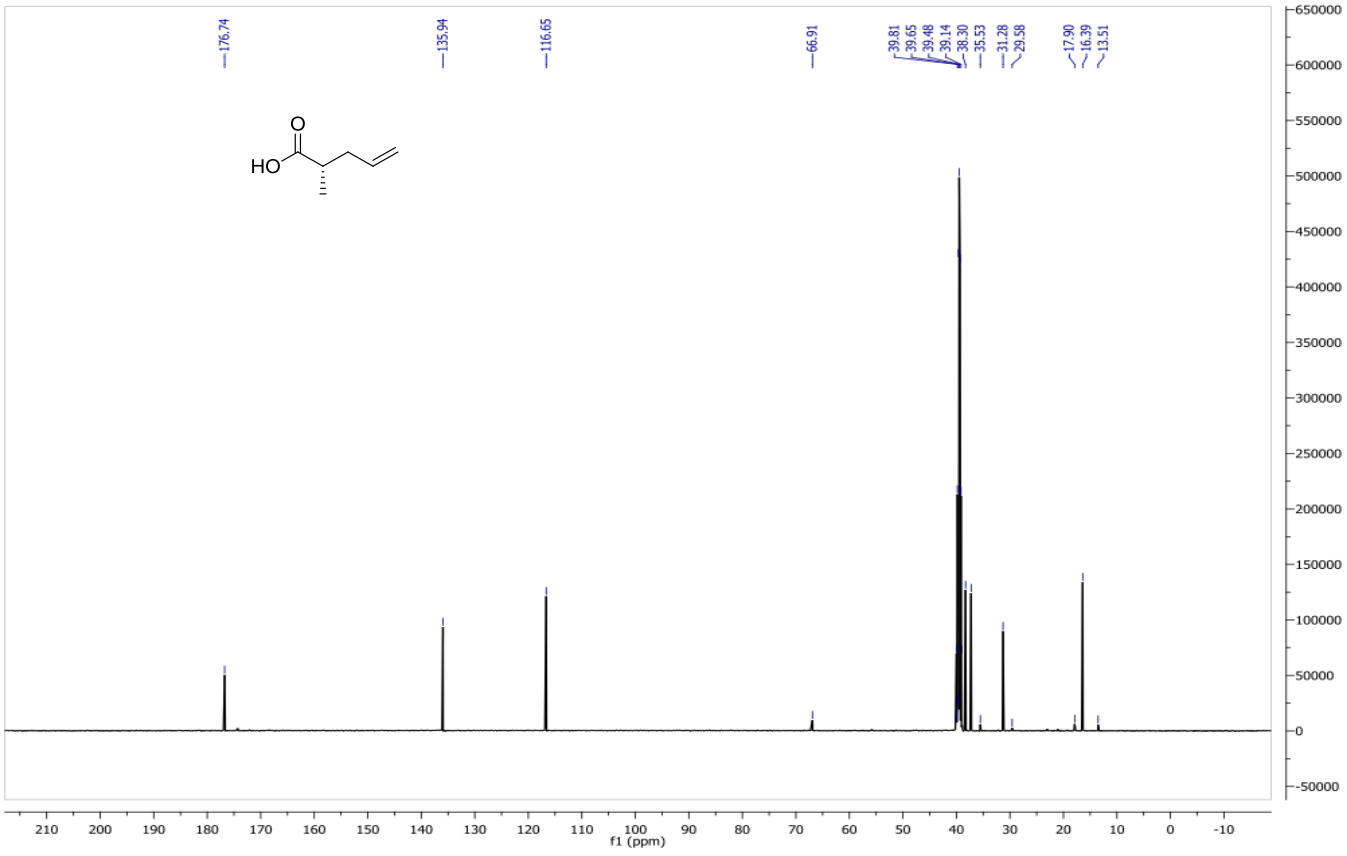
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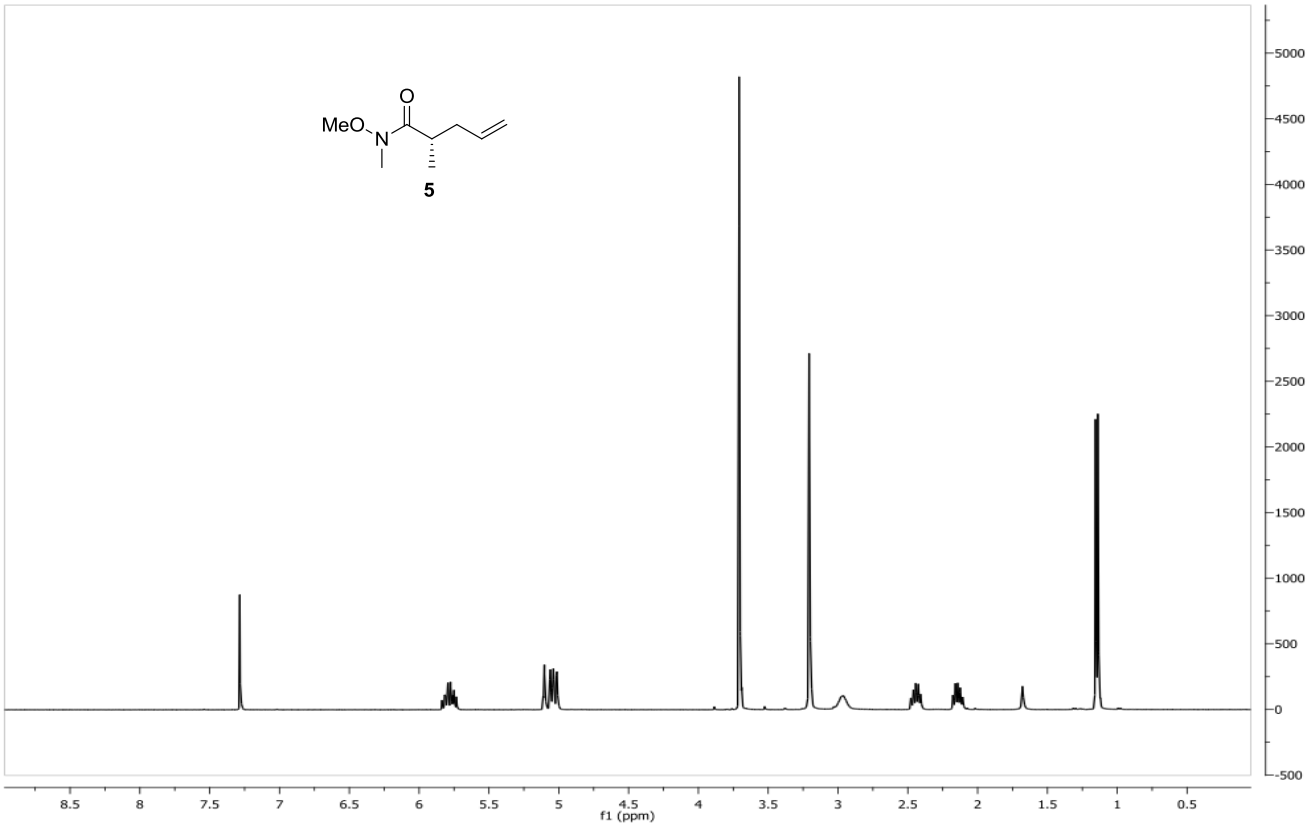
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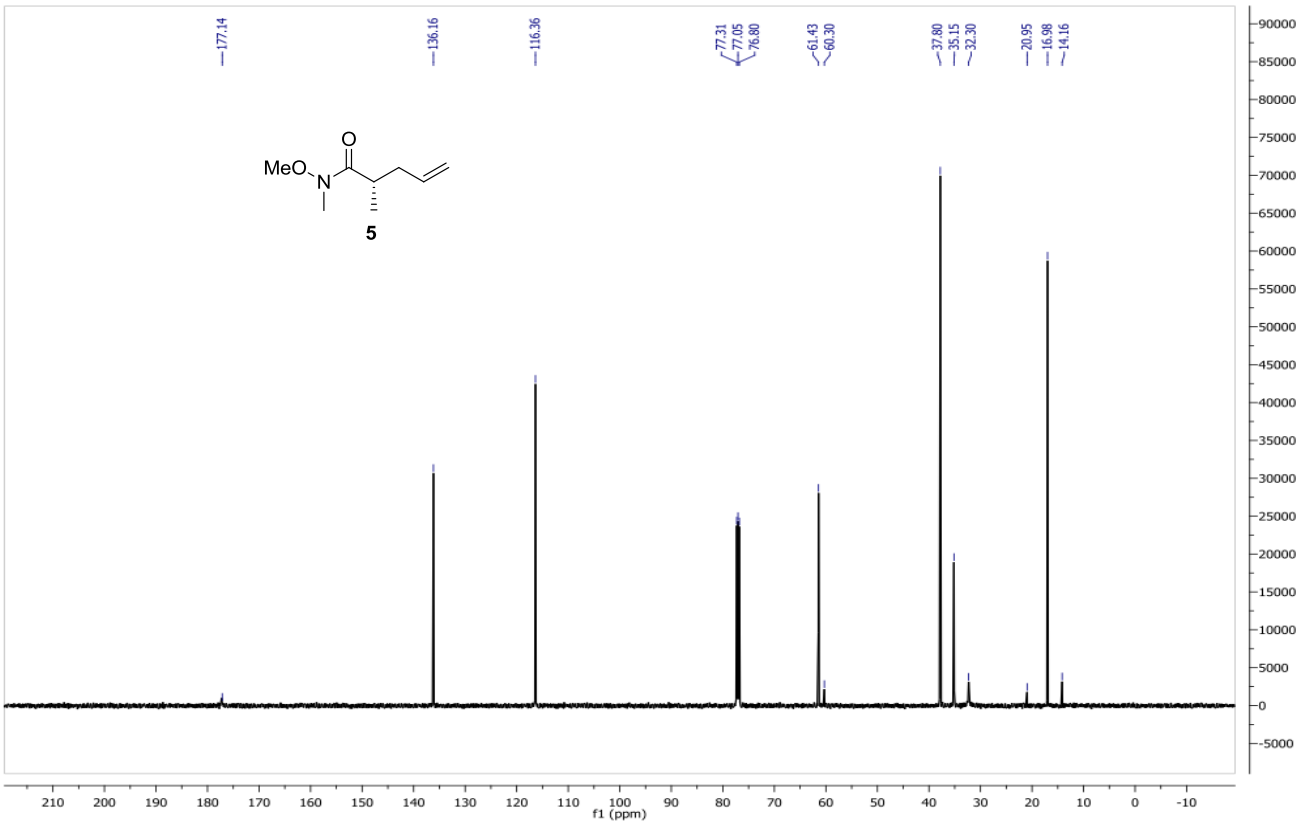
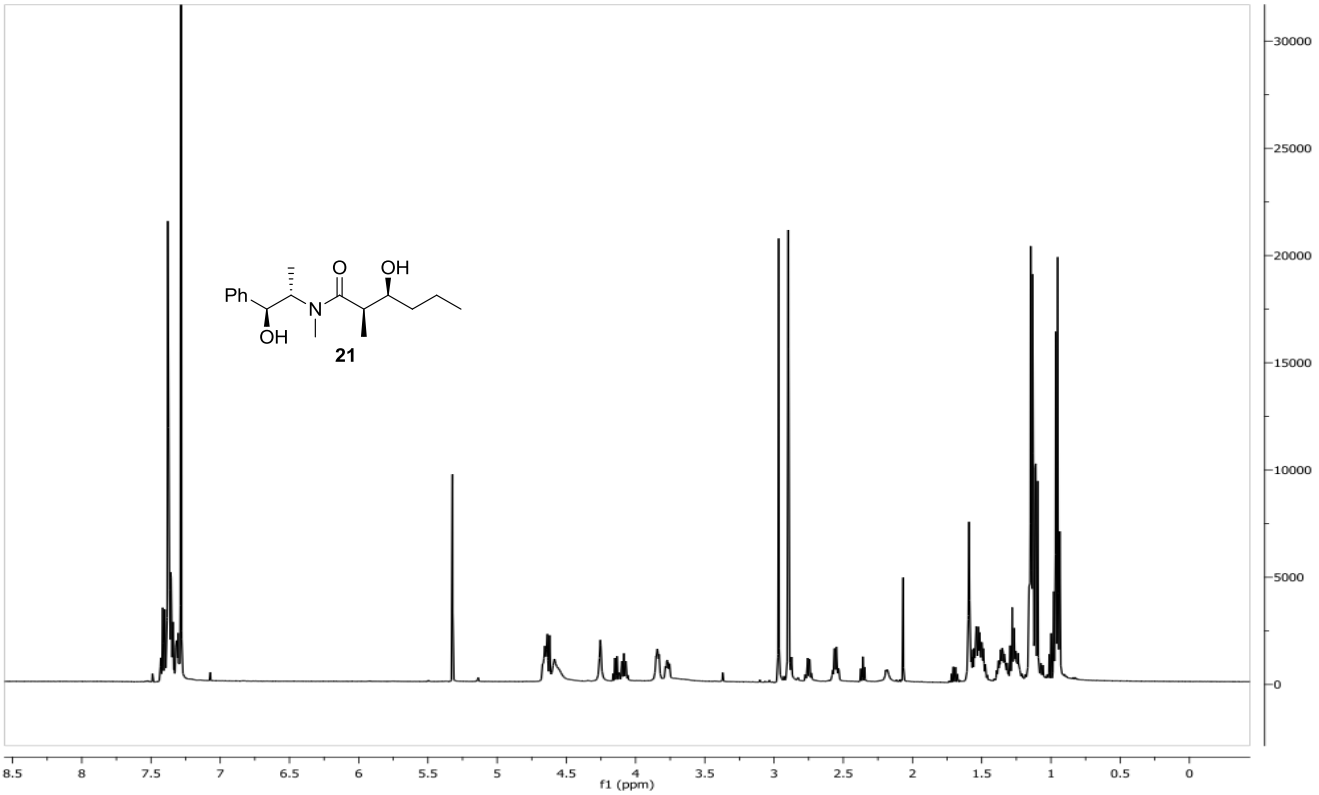
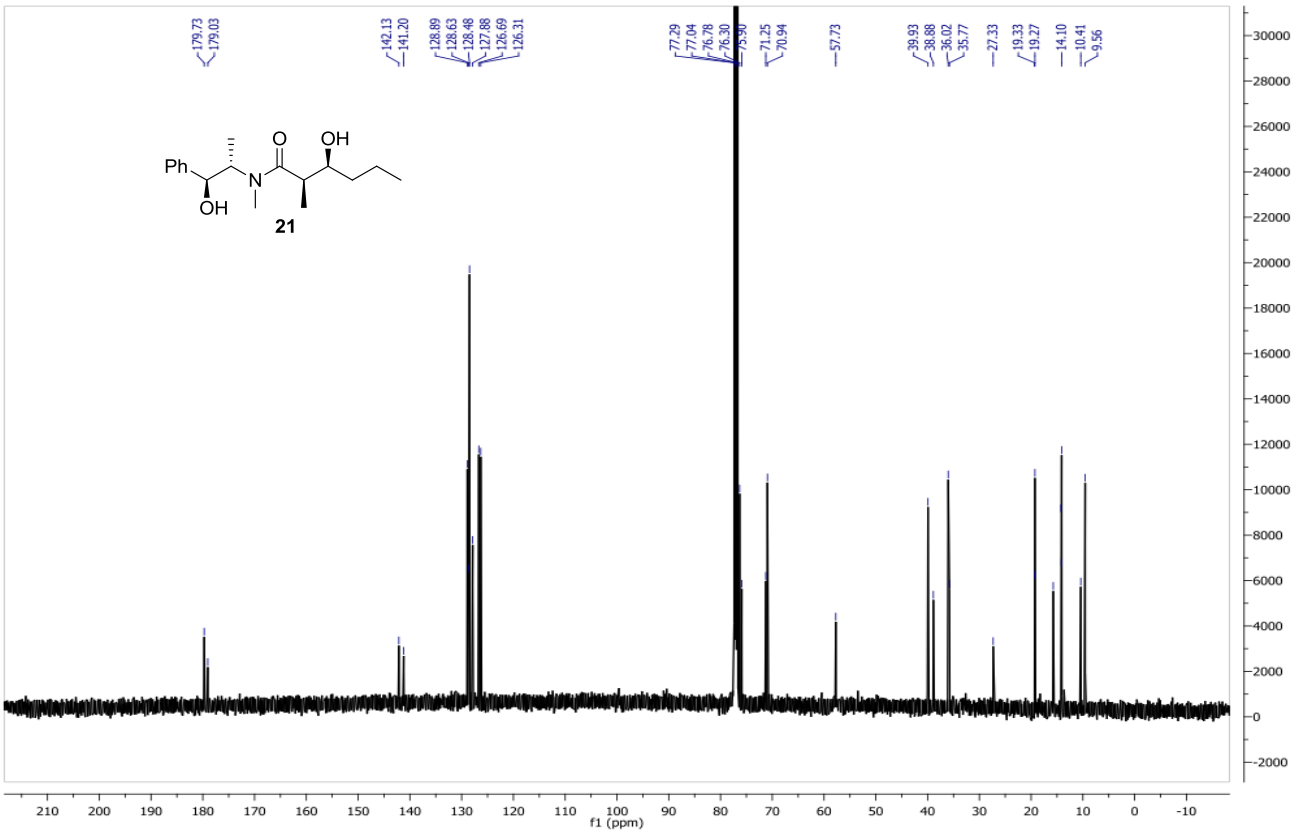
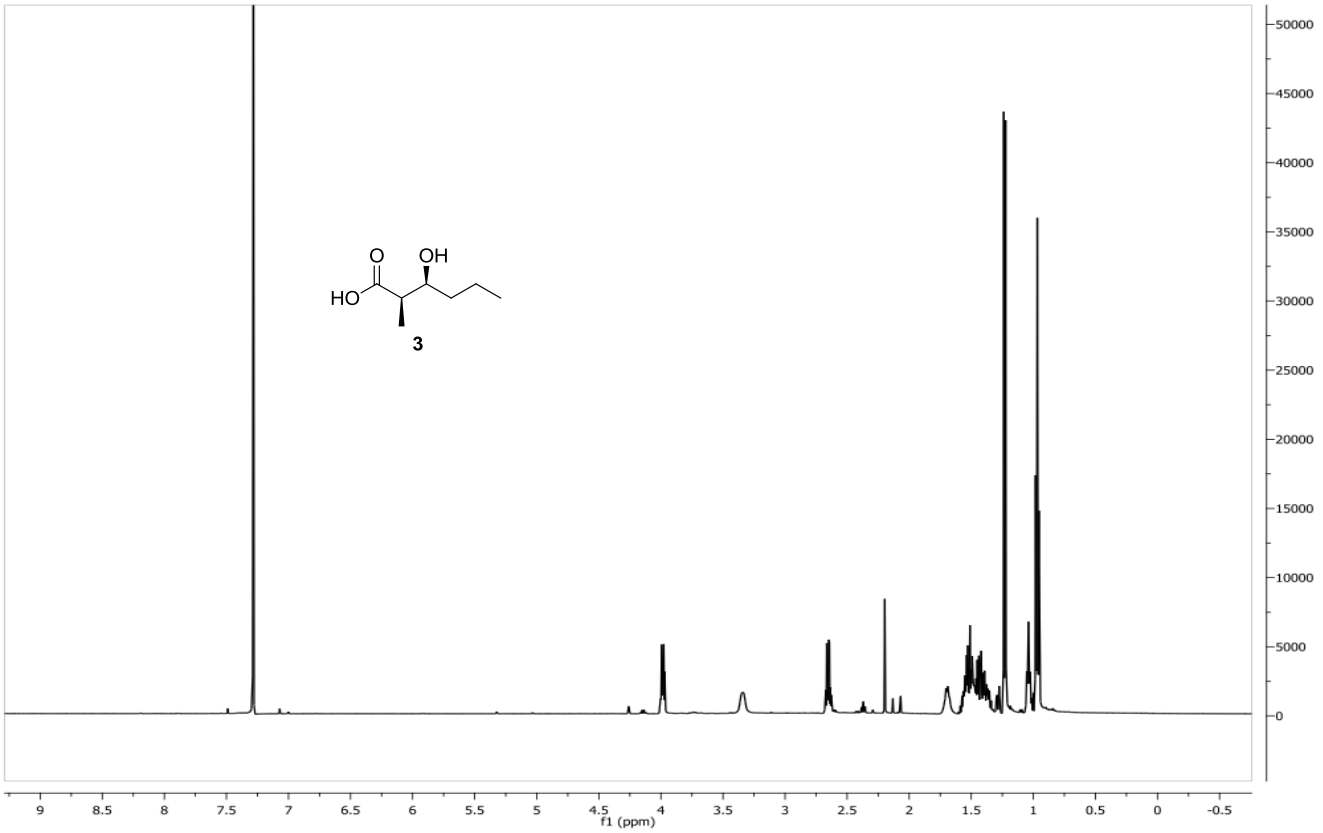
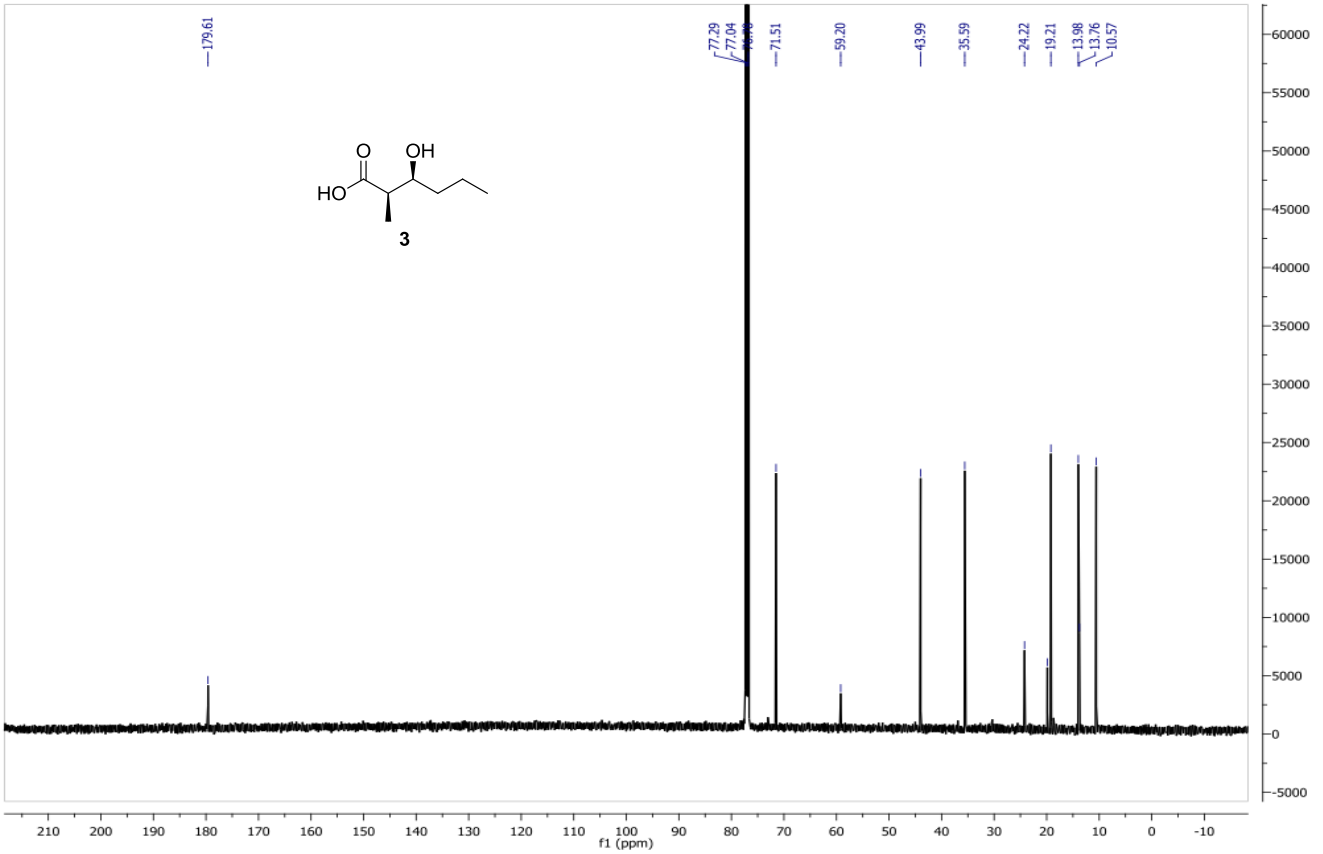
5
f1 (ppm)

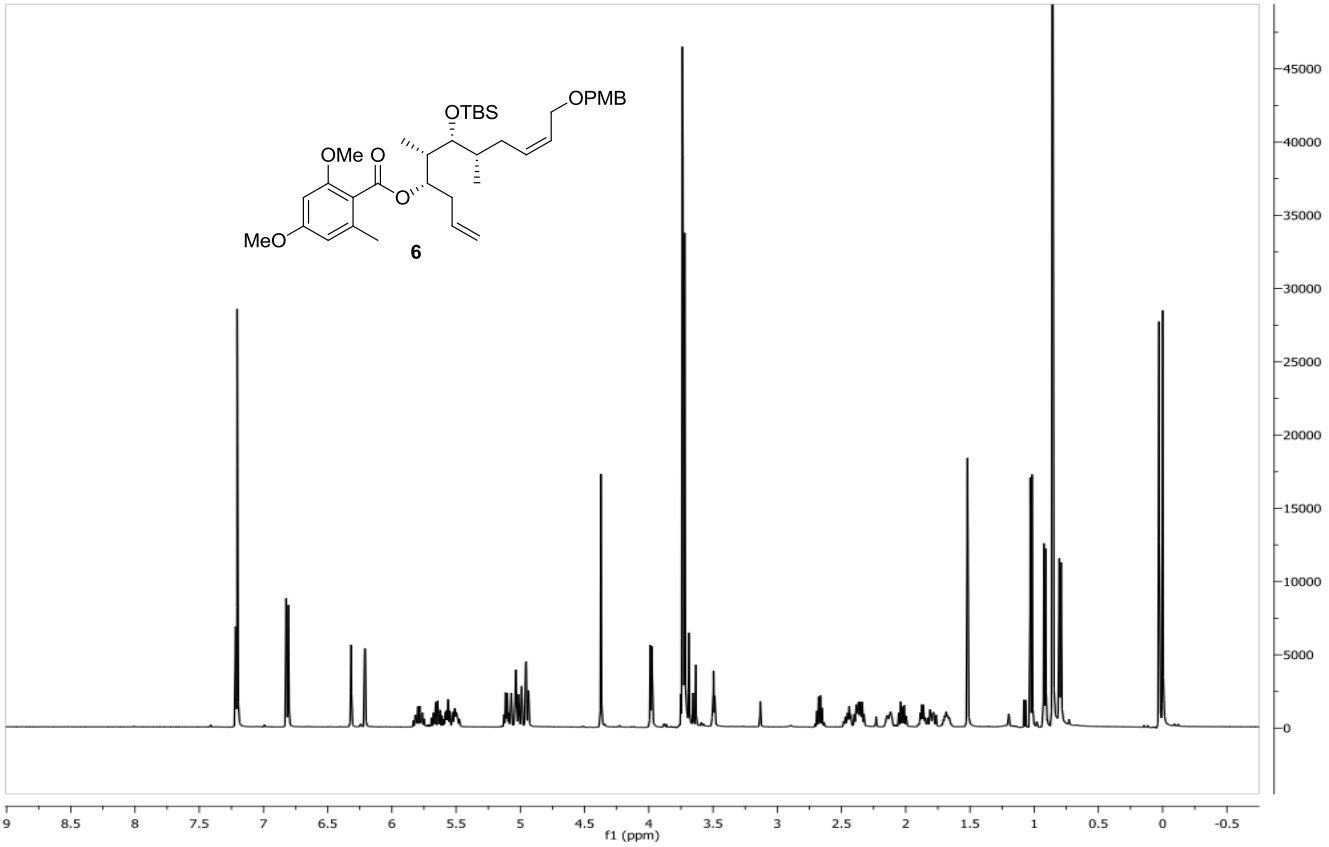

177.14
136.16
116.36
77.31
77.05
76.80
61.43
60.30
37.80
35.15
32.30
20.95
16.98
14.16
MeO
N
O
5
f1 (ppm)

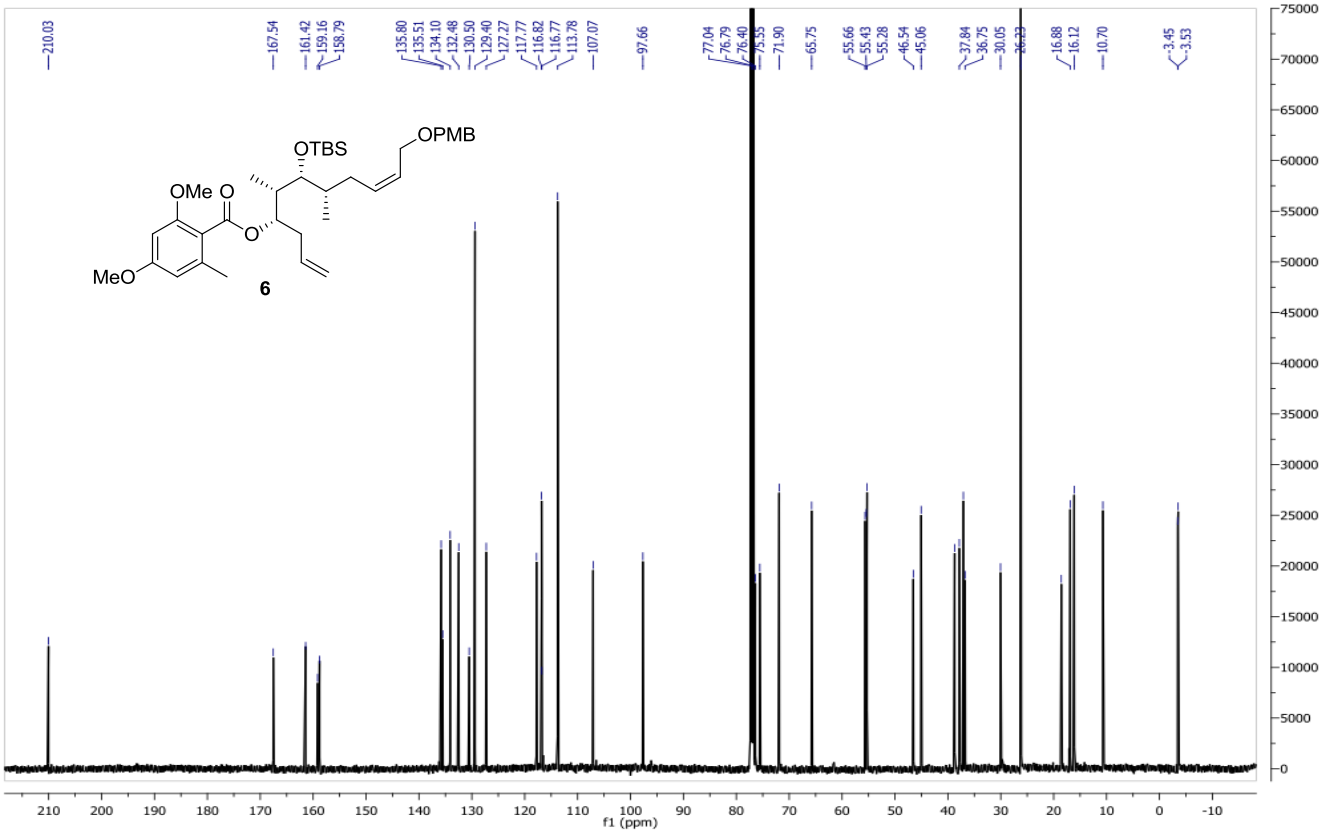

Ph
OH
N
O
OH
21
f1 (ppm)

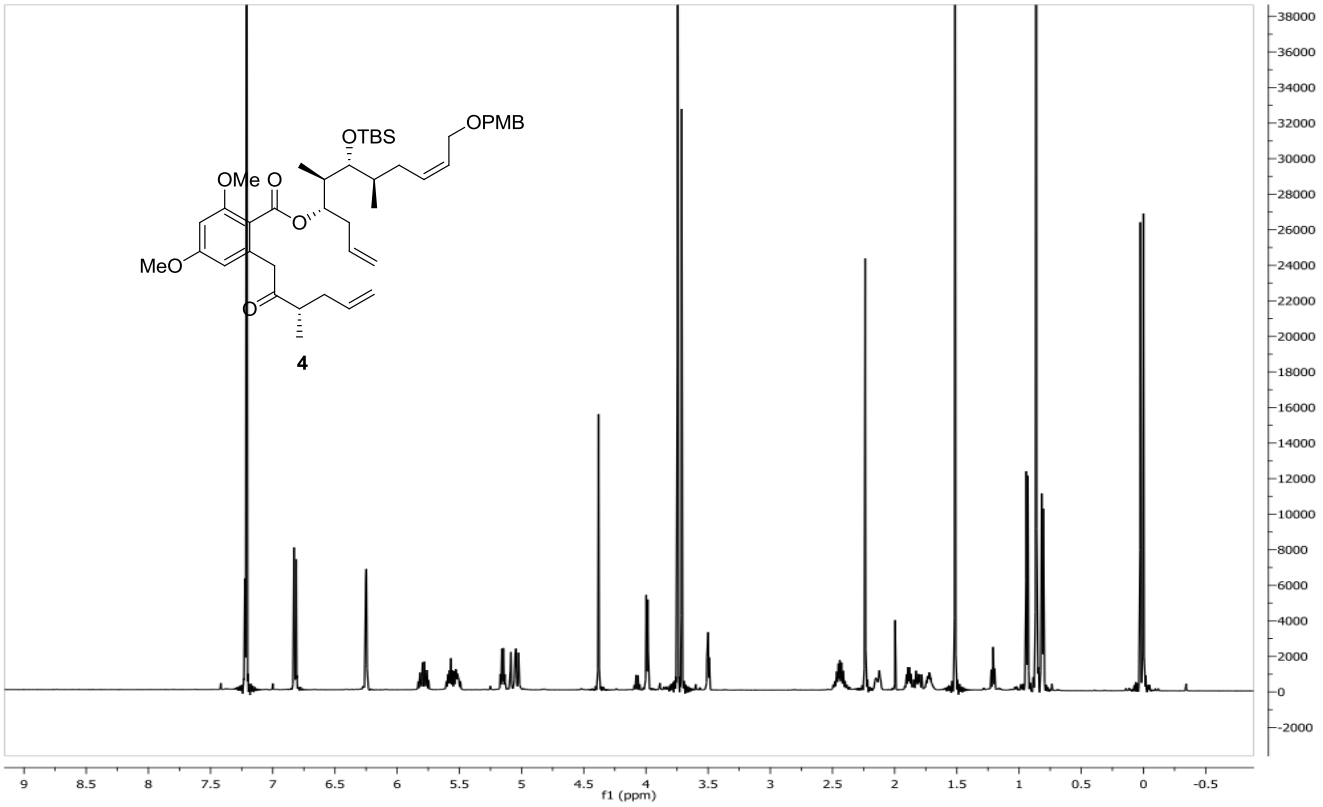

179.73
179.03
142.13
141.20
128.89
128.63
128.48
127.88
126.69
126.31
77.29
77.04
76.78
76.30
75.90
71.25
70.94
57.73
39.93
38.88
36.02
35.77
27.33
19.33
19.27
14.10
10.41
9.56
Ph
OH
N
O
OH
21
f1 (ppm)

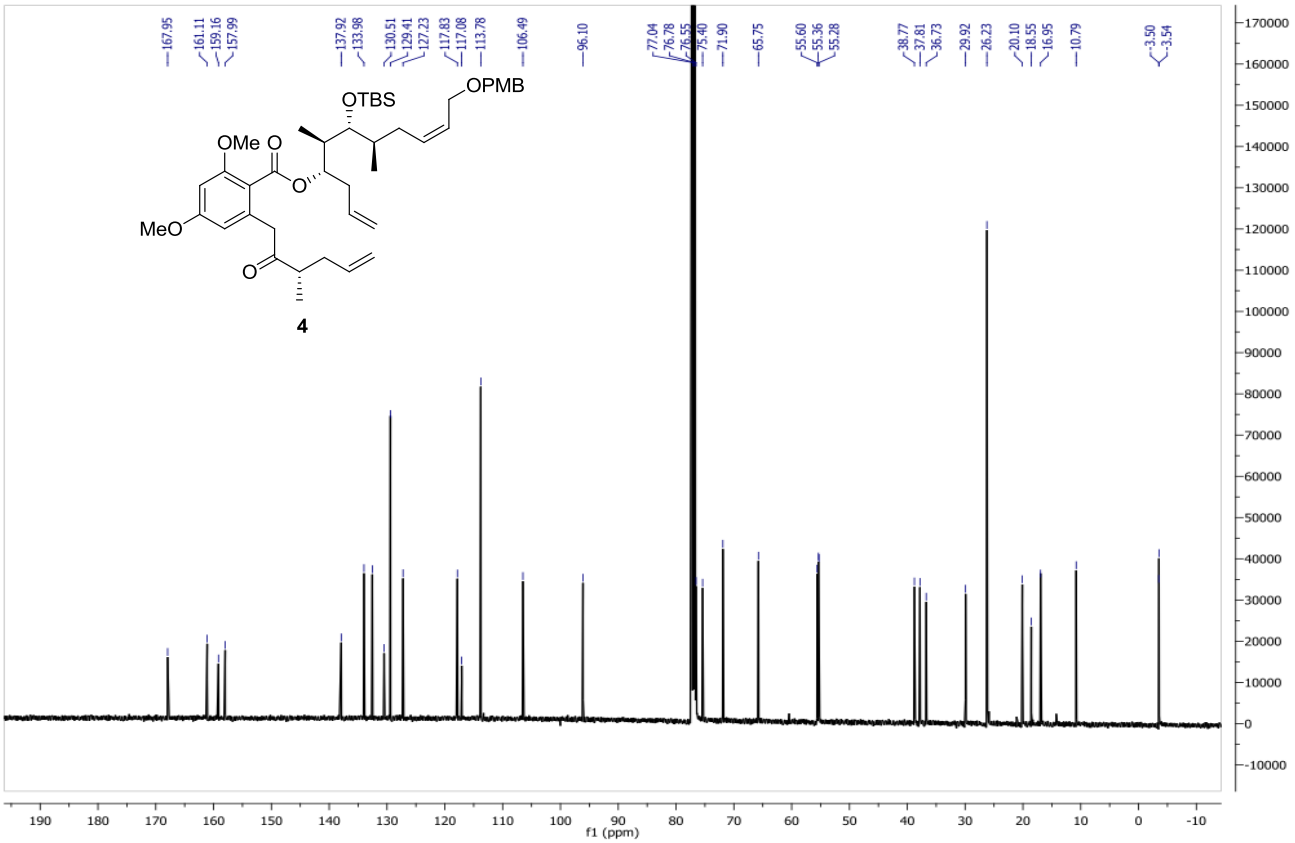

O
OH
HO
3
f1 (ppm)

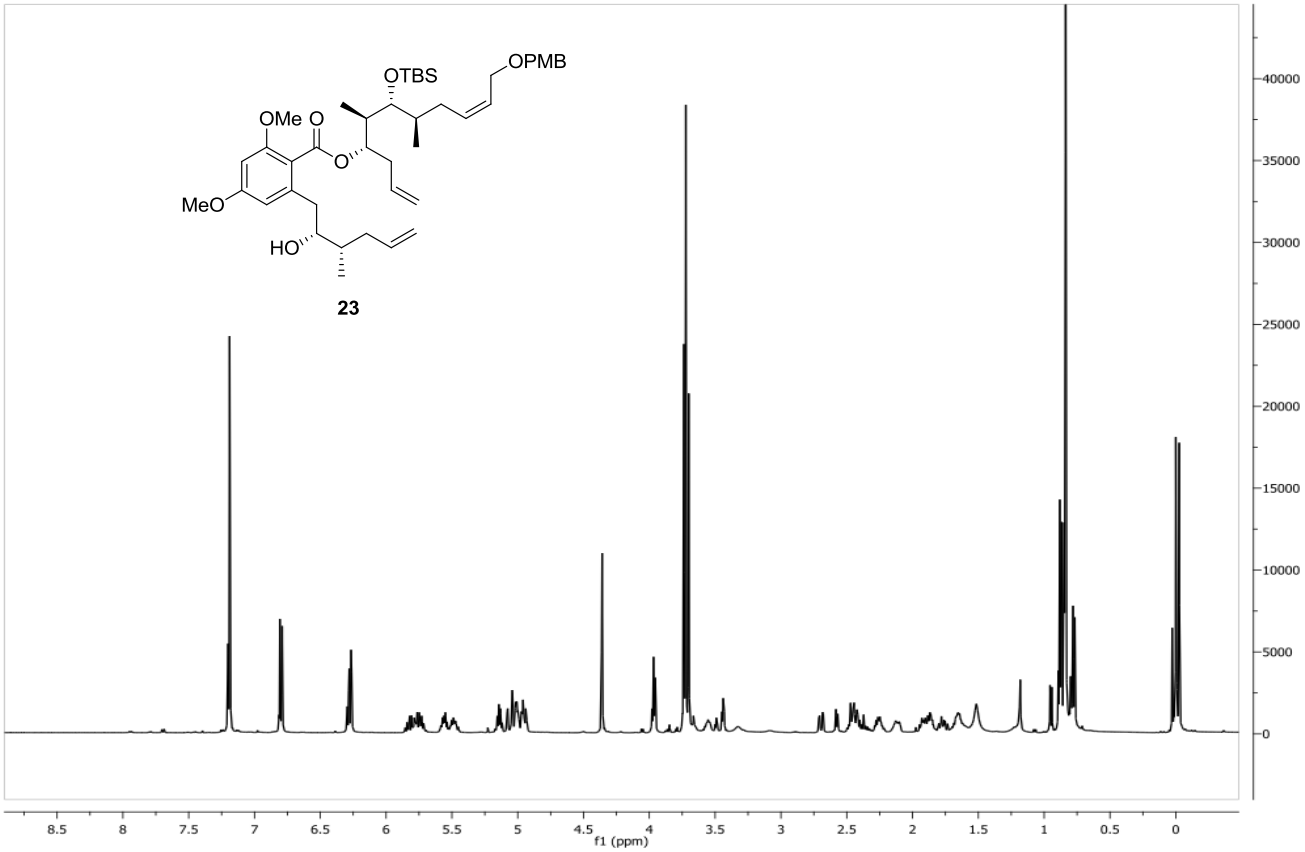

179.61
77.29
77.04
71.51
59.20
43.99
35.59
24.22
19.21
13.98
13.76
10.57
O
OH
HO
3
f1 (ppm)

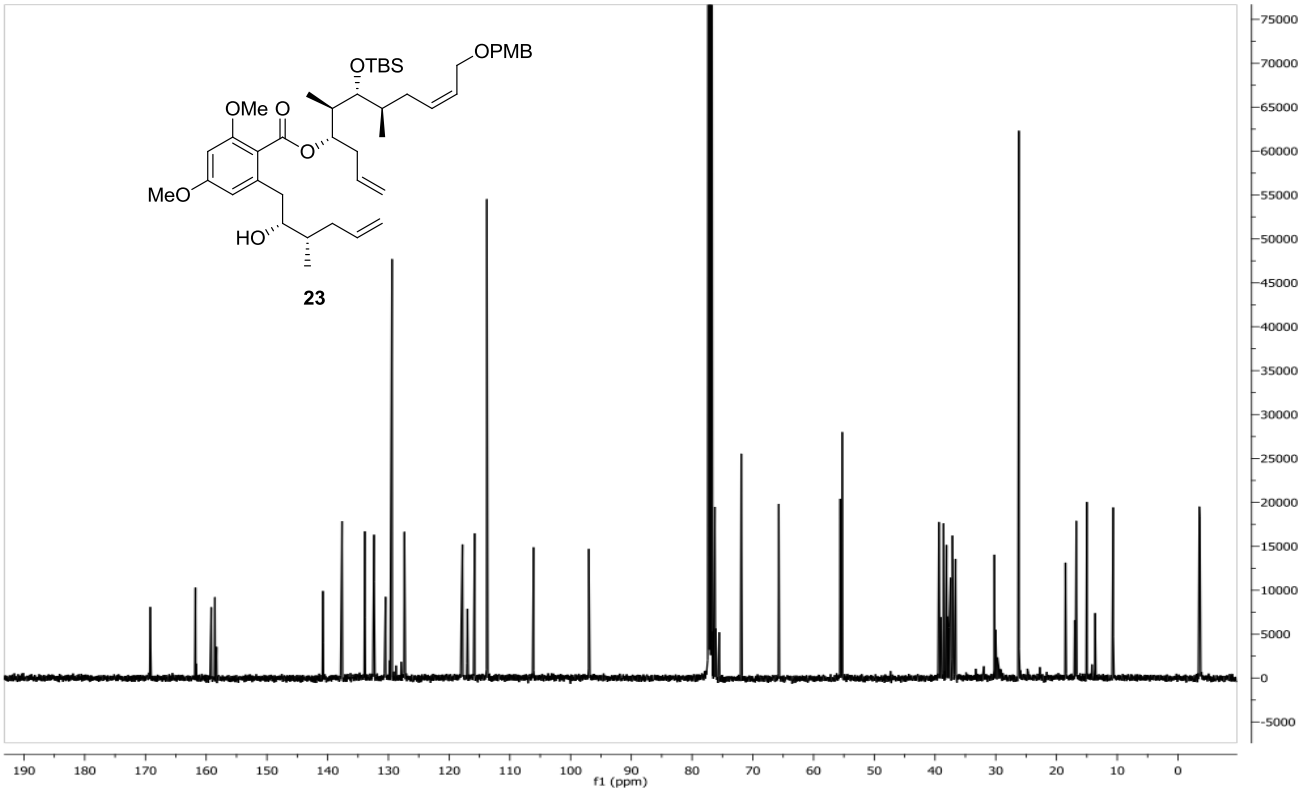

OTBS
OPMB
OMe O
O
MeO
6
f1 (ppm)

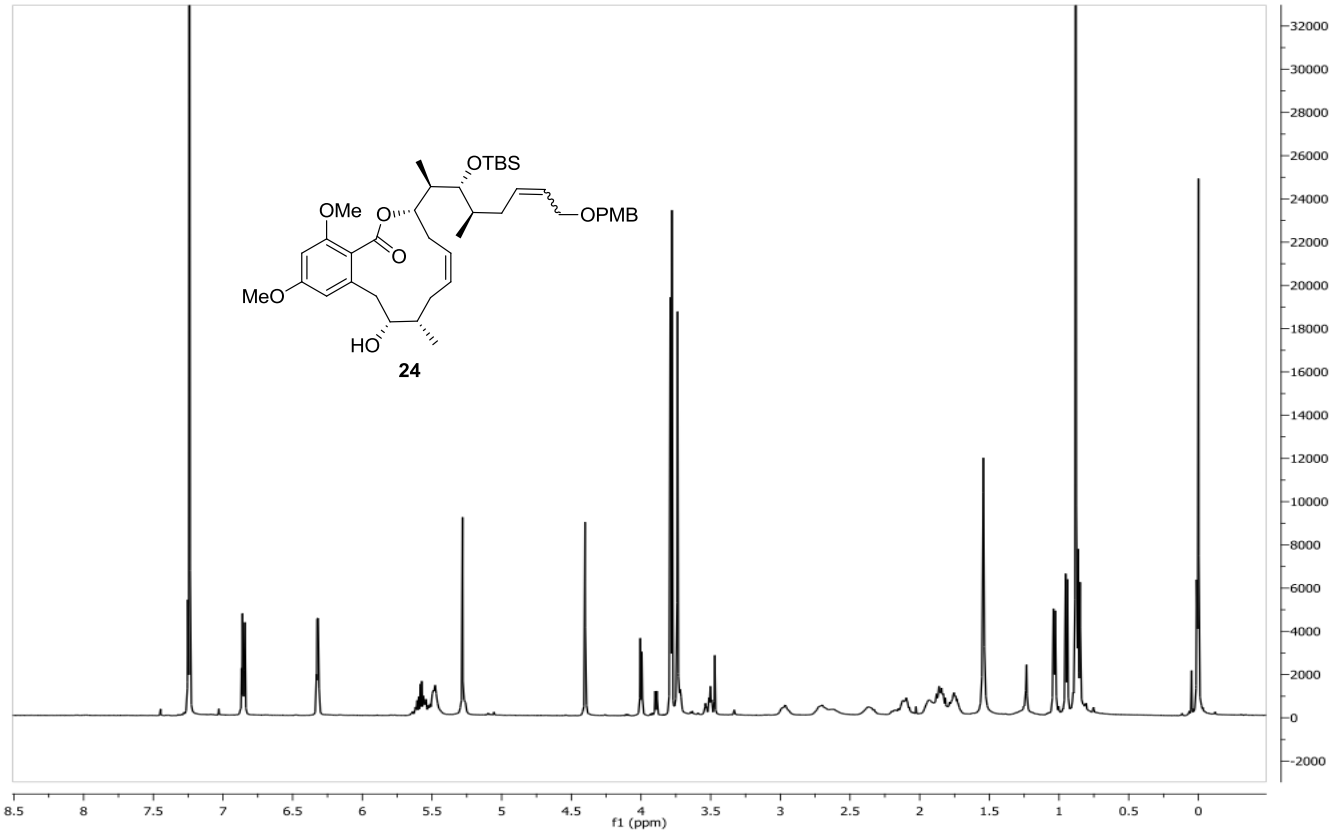

210.03
167.54
161.42
159.16
158.79
135.80
135.51
134.10
132.48
130.50
129.40
127.27
117.77
116.82
116.77
113.78
107.07
97.66
77.04
76.79
76.40
75.55
71.90
65.75
55.66
55.43
55.28
46.54
45.06
37.84
36.75
30.05
26.23
16.88
16.12
10.70
-3.45
-3.53
OTBS
OPMB
OMe O
O
MeO
6
f1 (ppm)

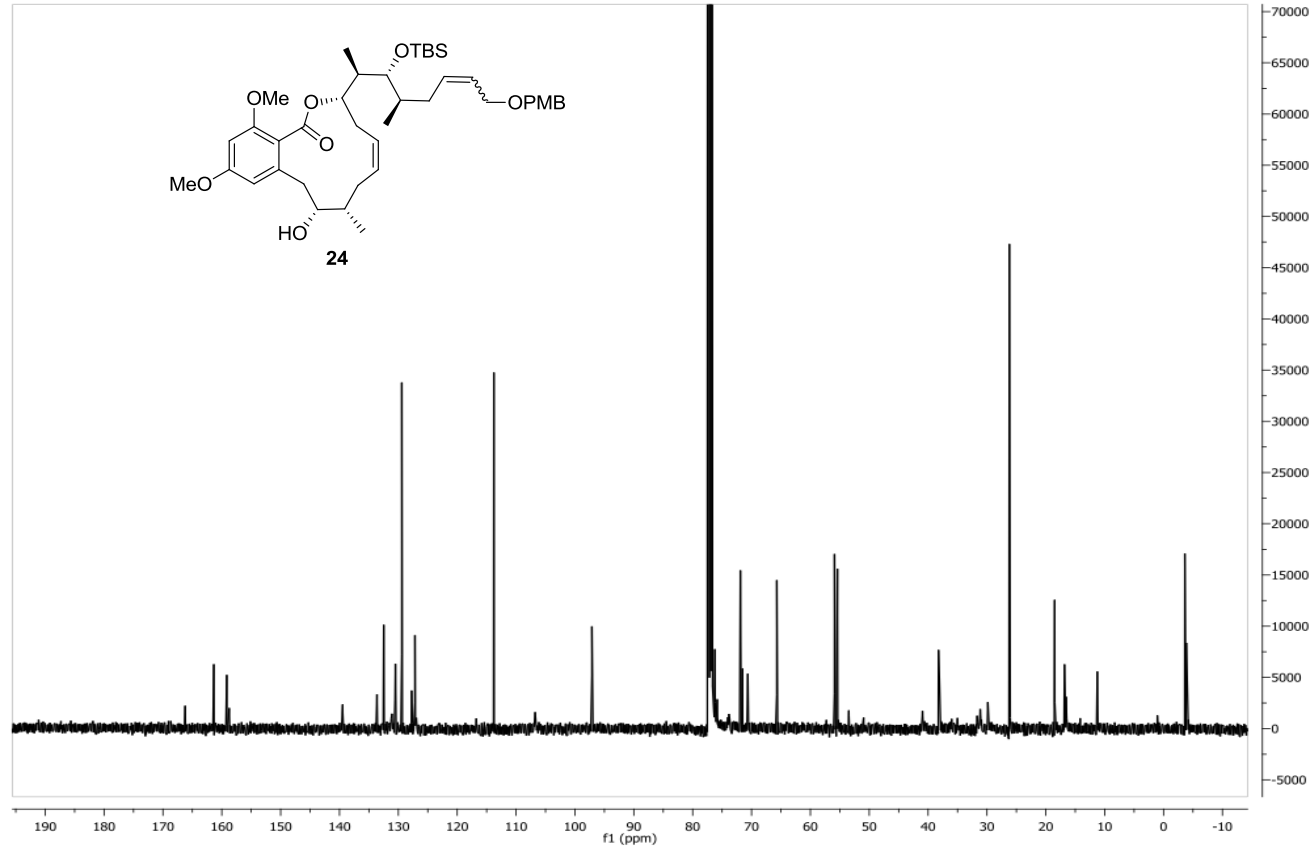

OTBS
OPMB
OMe O
O
MeO
O
4
f1 (ppm)

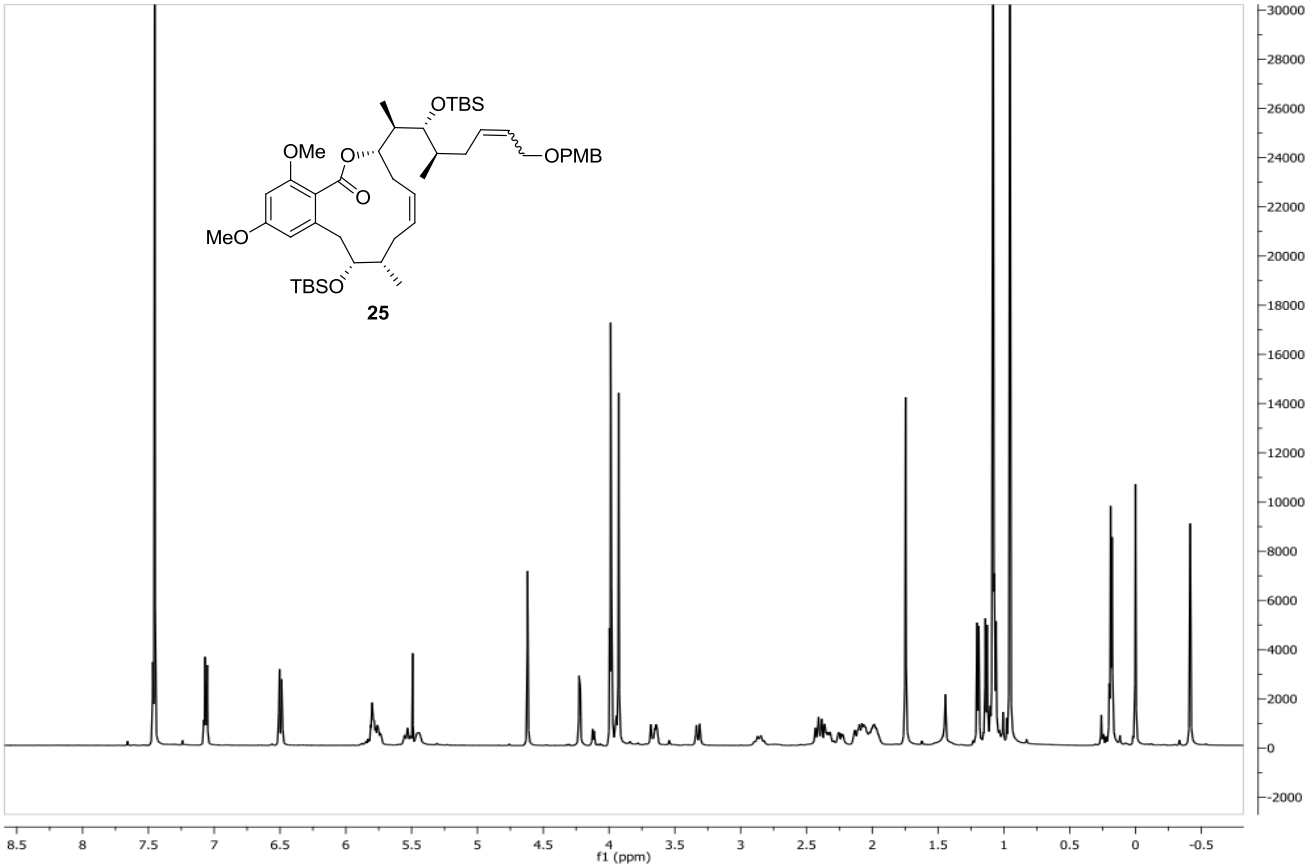

167.95
161.11
159.16
157.99
137.92
133.98
130.51
129.41
127.23
117.83
117.08
113.78
106.49
96.10
77.04
76.78
76.55
75.40
71.90
65.75
55.60
55.36
55.28
38.77
37.81
36.73
29.92
26.23
20.10
18.55
16.95
10.79
-3.50
-3.54
OTBS
OPMB
OMe O
O
MeO
O
4
f1 (ppm)

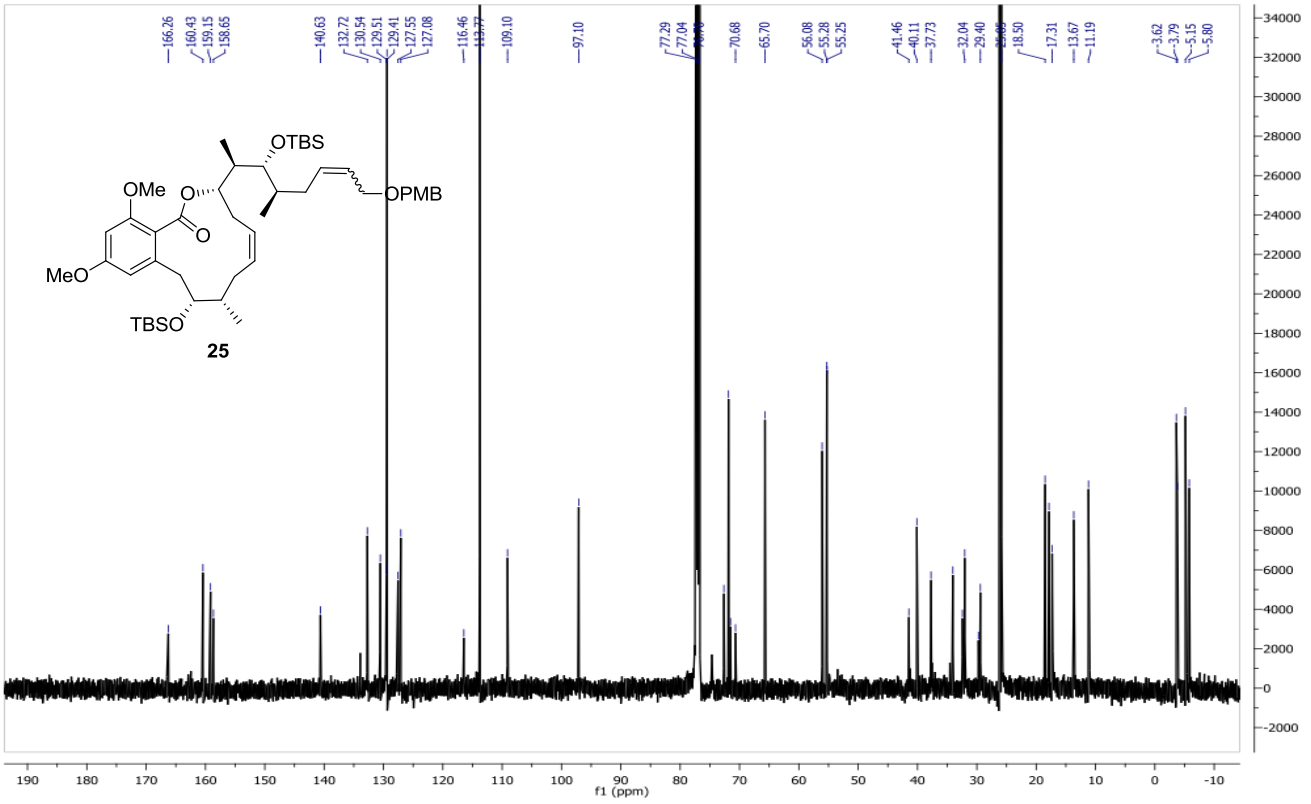

OTBS
OPMB
OMe O
O
MeO
HO
23
f1 (ppm)

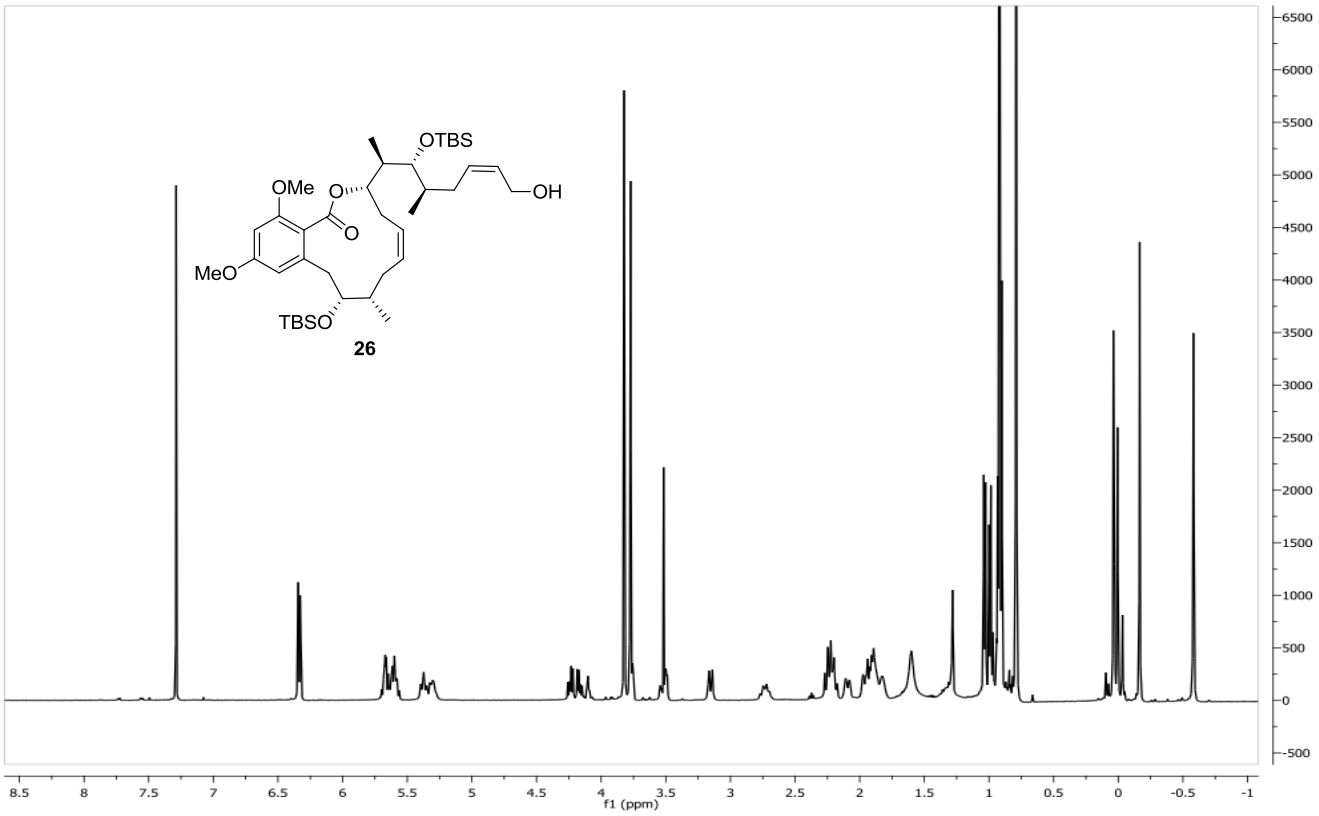

OTBS
OPMB
OMe O
O
MeO
HO
23
f1 (ppm)

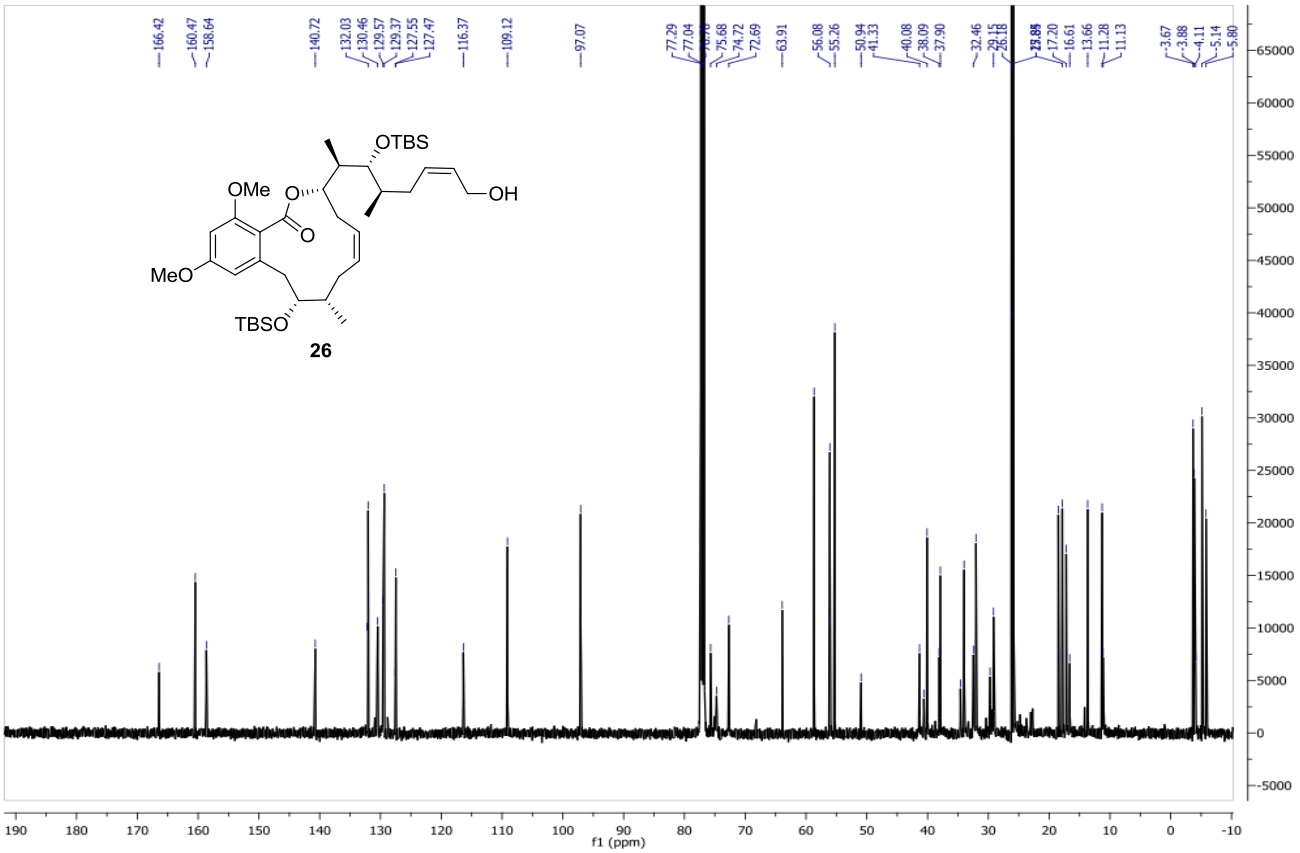

OTBS
OMe
O
OPMB
O
MeO
HO
24
f1 (ppm)

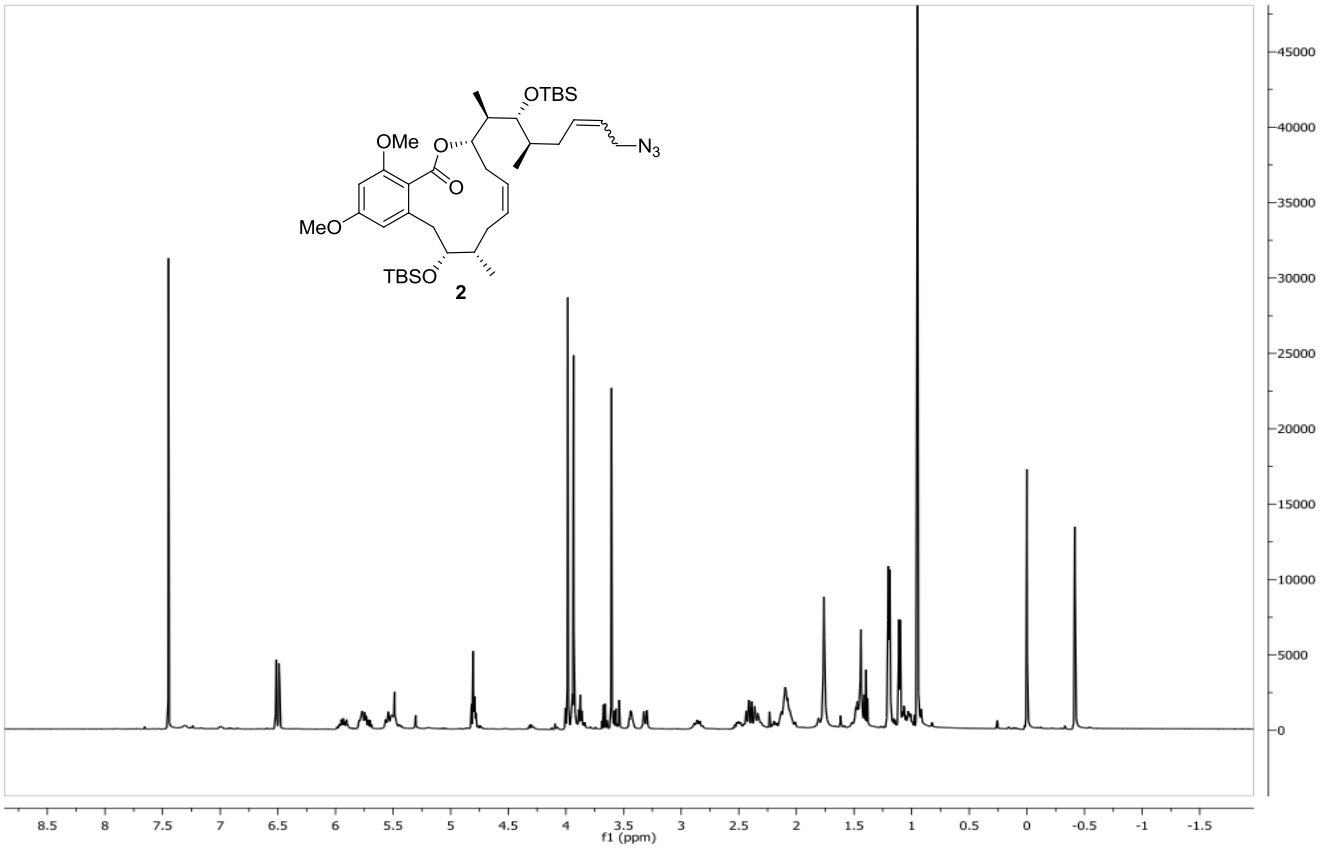

OTBS
OMe
O
OPMB
O
MeO
HO
24
f1 (ppm)

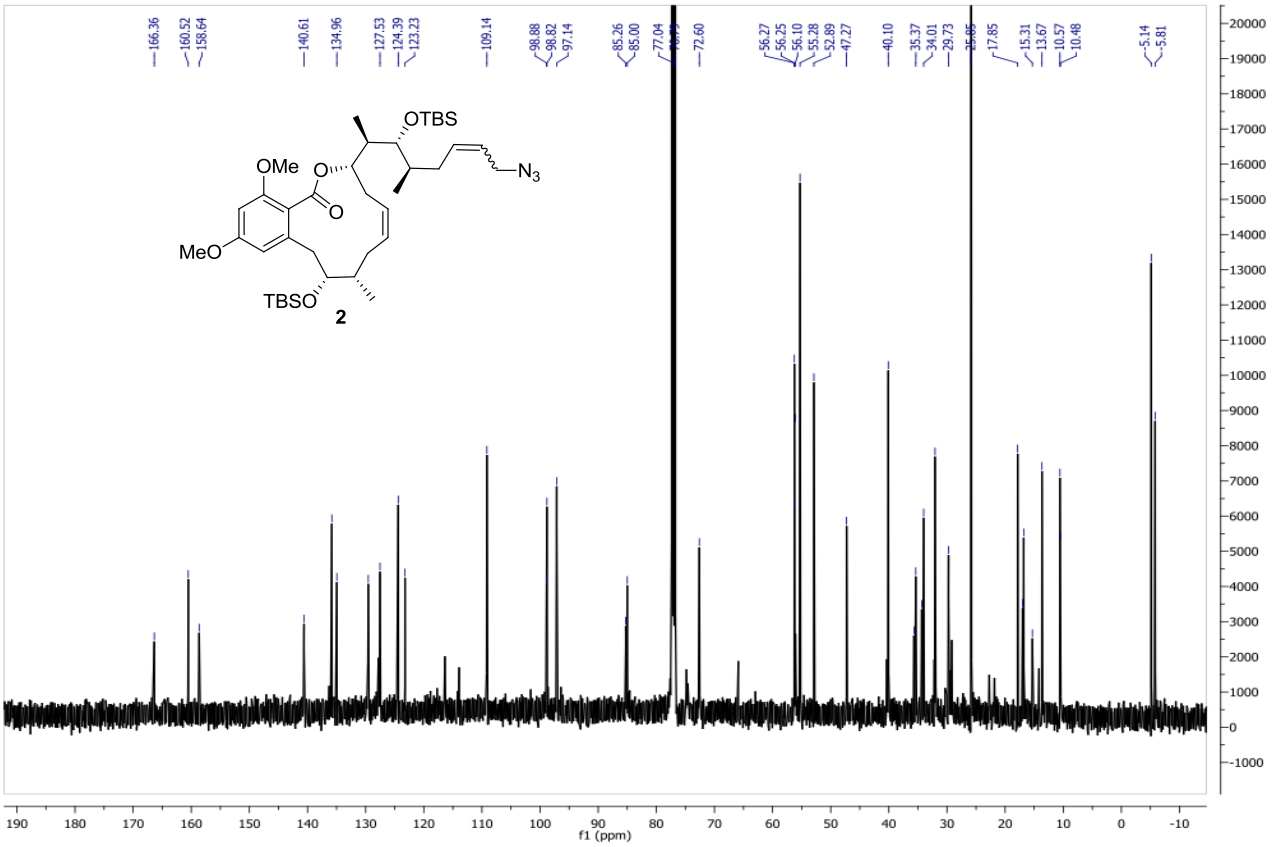

OTBS
OMe
O
OPMB
O
MeO
TBSO
25
f1 (ppm)

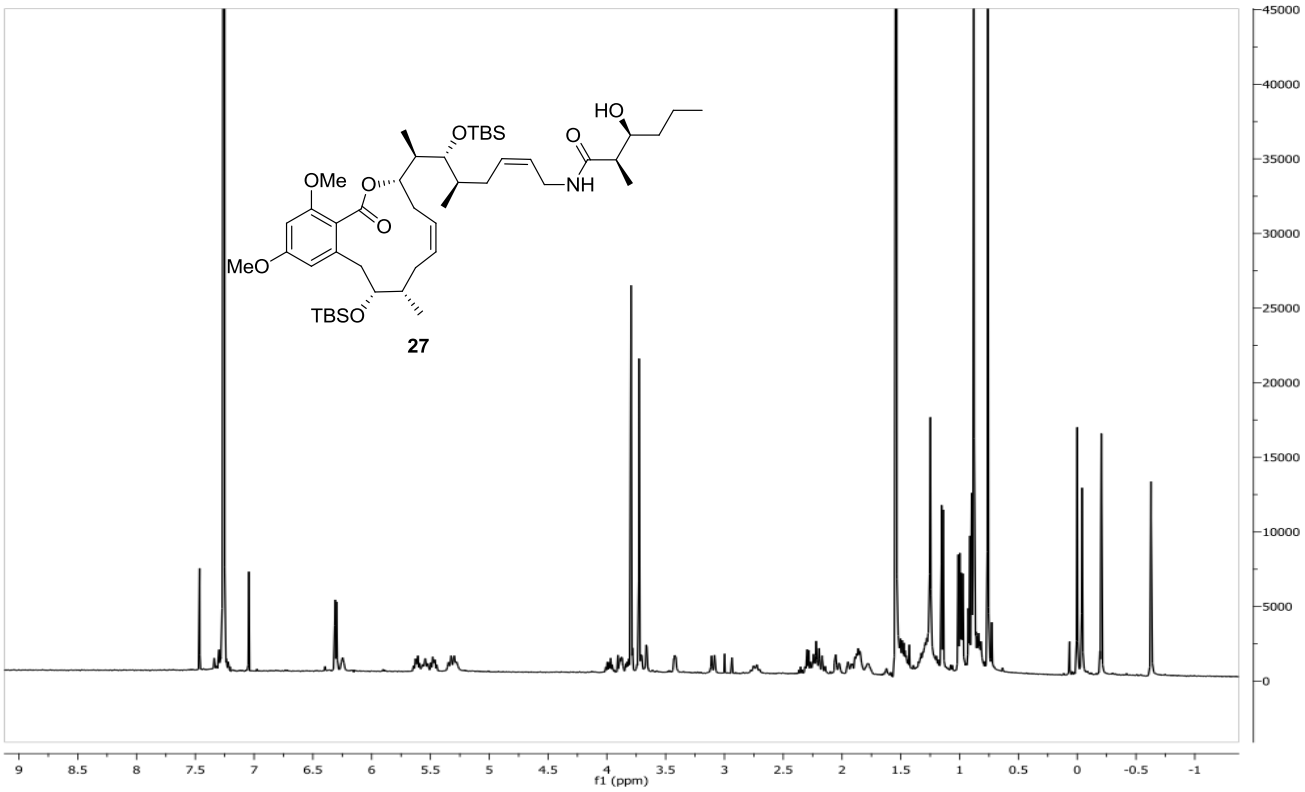

166.26
160.43
159.15
158.65
140.63
132.72
130.54
129.51
129.41
127.55
127.08
116.46
113.77
109.10
97.10
77.29
77.04
70.68
65.70
56.08
55.28
55.25
41.46
40.11
37.73
32.04
29.40
18.50
17.31
13.67
11.19
3.62
-3.79
-5.15
-5.80
OTBS
OMe
O
OPMB
O
MeO
TBSO
25
f1 (ppm)

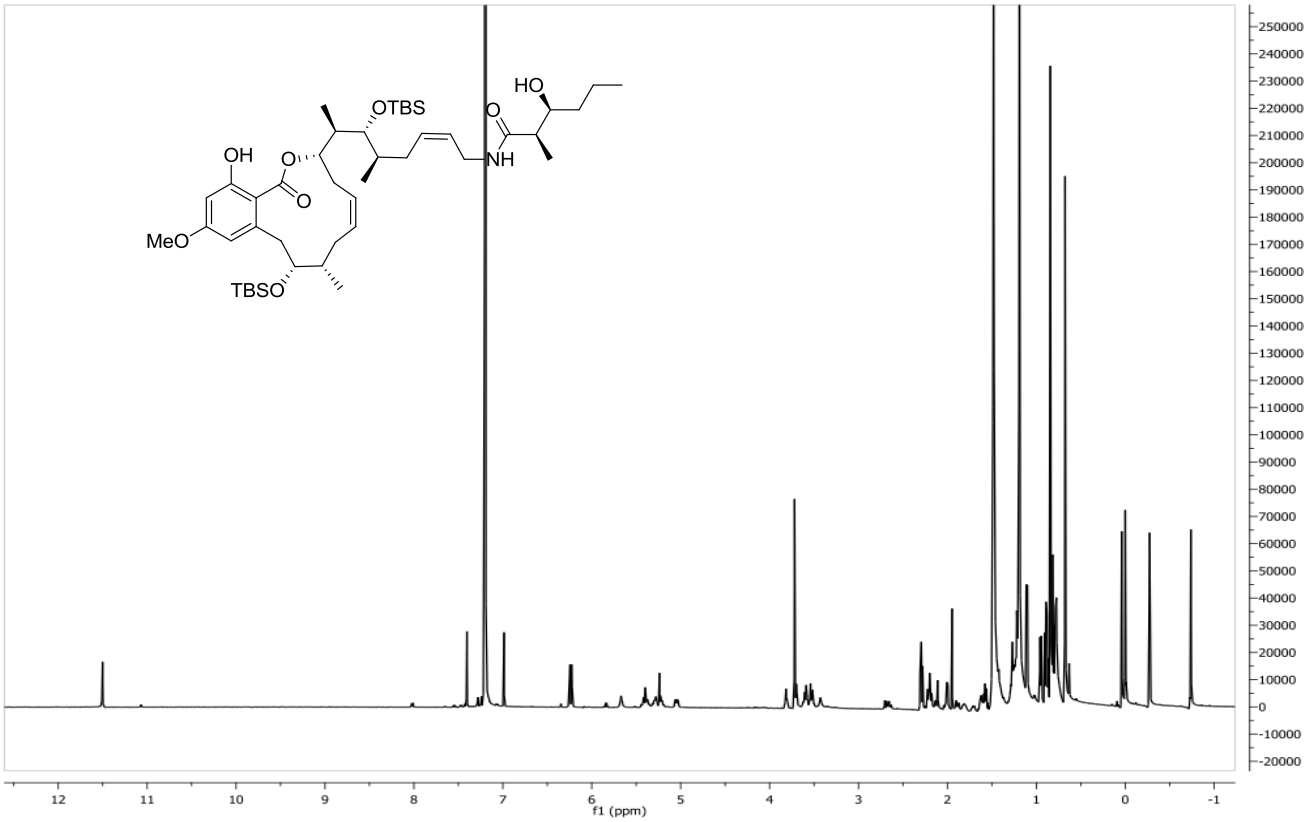

OTBS
OMe
O
O
OH
MeO
TBSO
26
f1 (ppm)

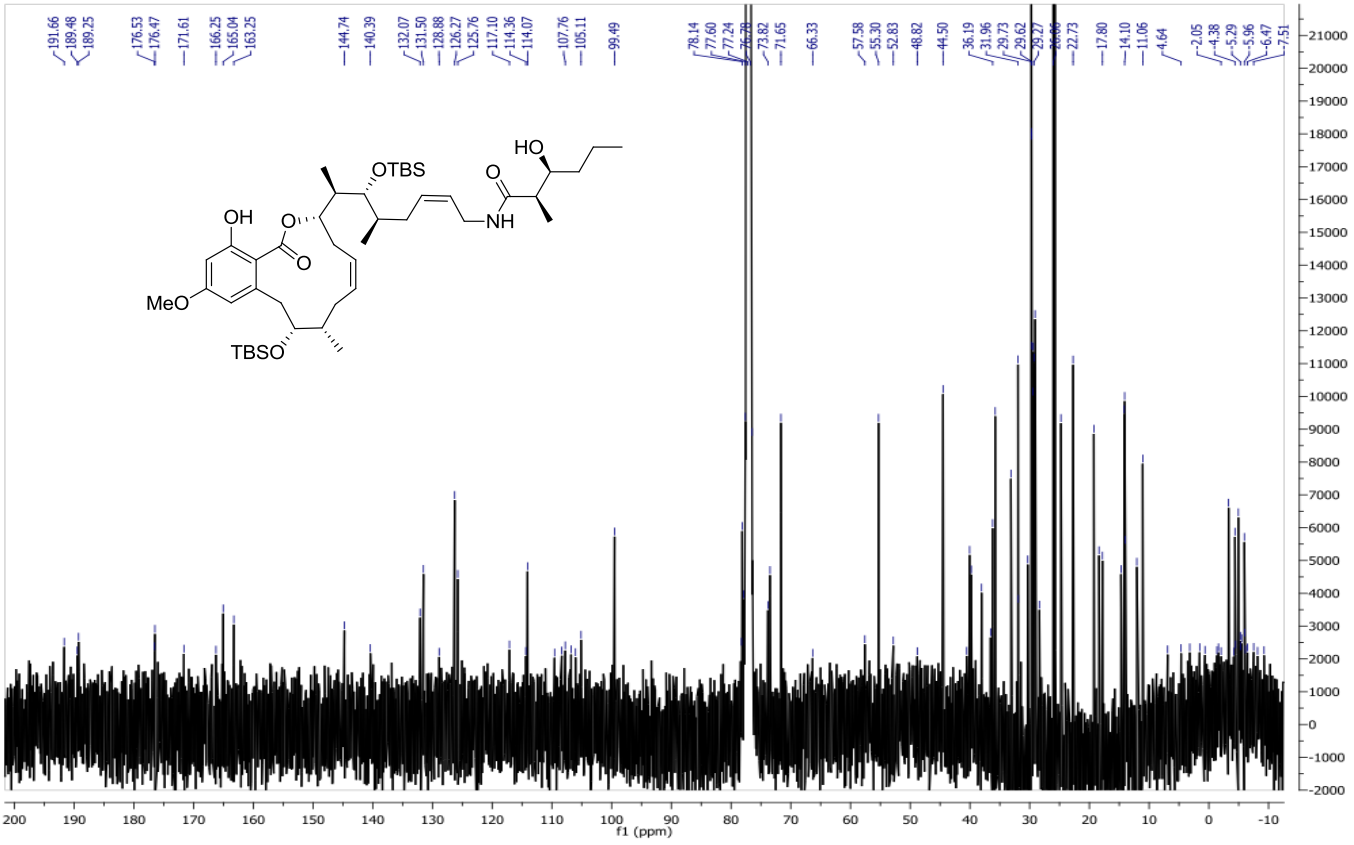

166.42
160.47
158.64
140.72
132.03
130.46
129.57
129.37
127.55
127.47
116.37
109.12
97.07
77.29
77.04
76.76
75.68
74.72
72.69
63.91
56.08
55.26
50.94
41.33
40.08
38.09
37.90
32.46
25.88
25.18
17.20
16.61
13.66
11.28
11.13
-3.67
-3.88
-4.11
-5.14
-5.80
OTBS
OMe
O
O
OH
MeO
TBSO
26
f1 (ppm)

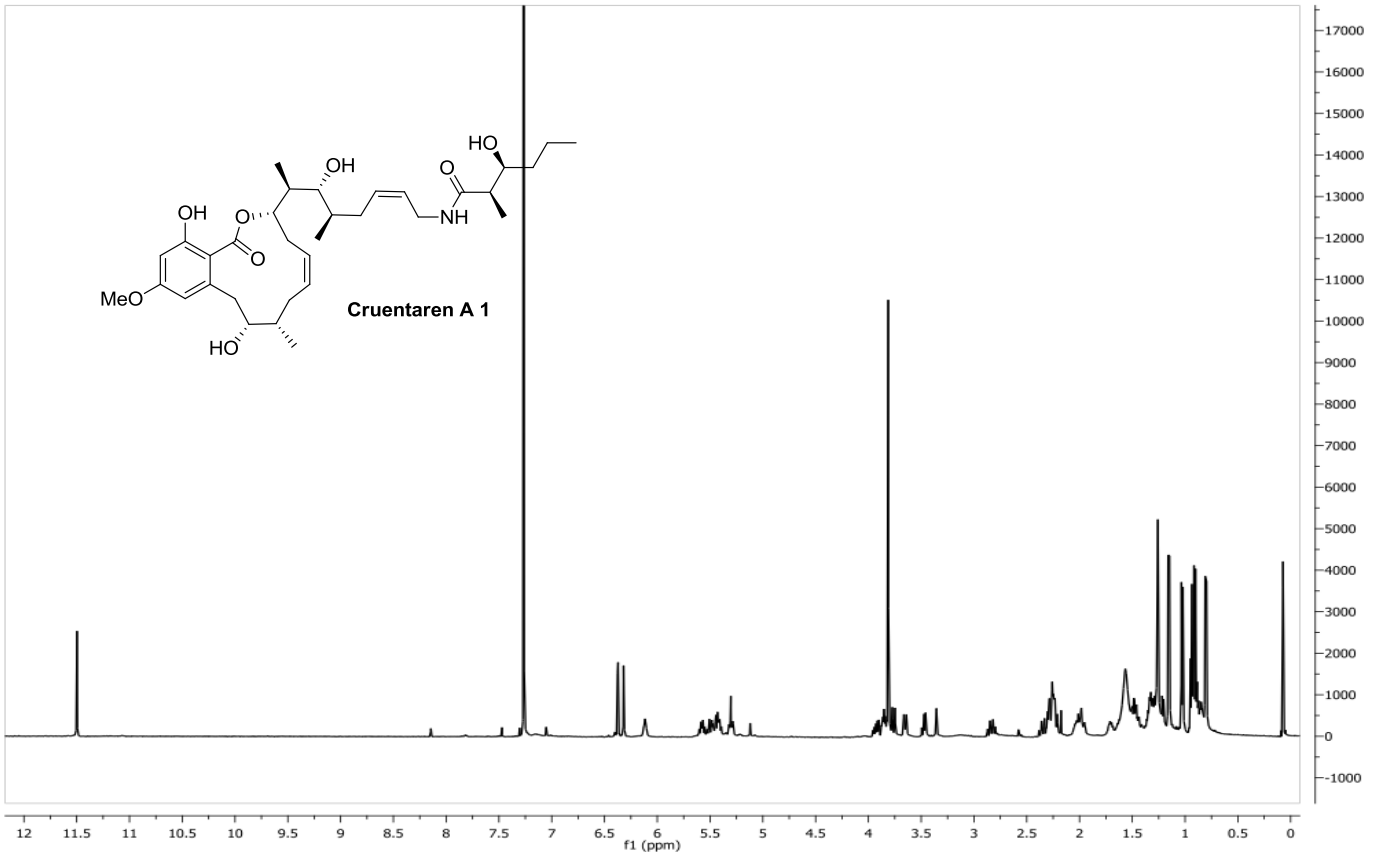

OTBS
OMe
O
O
N3
MeO
TBSO
2
f1 (ppm)

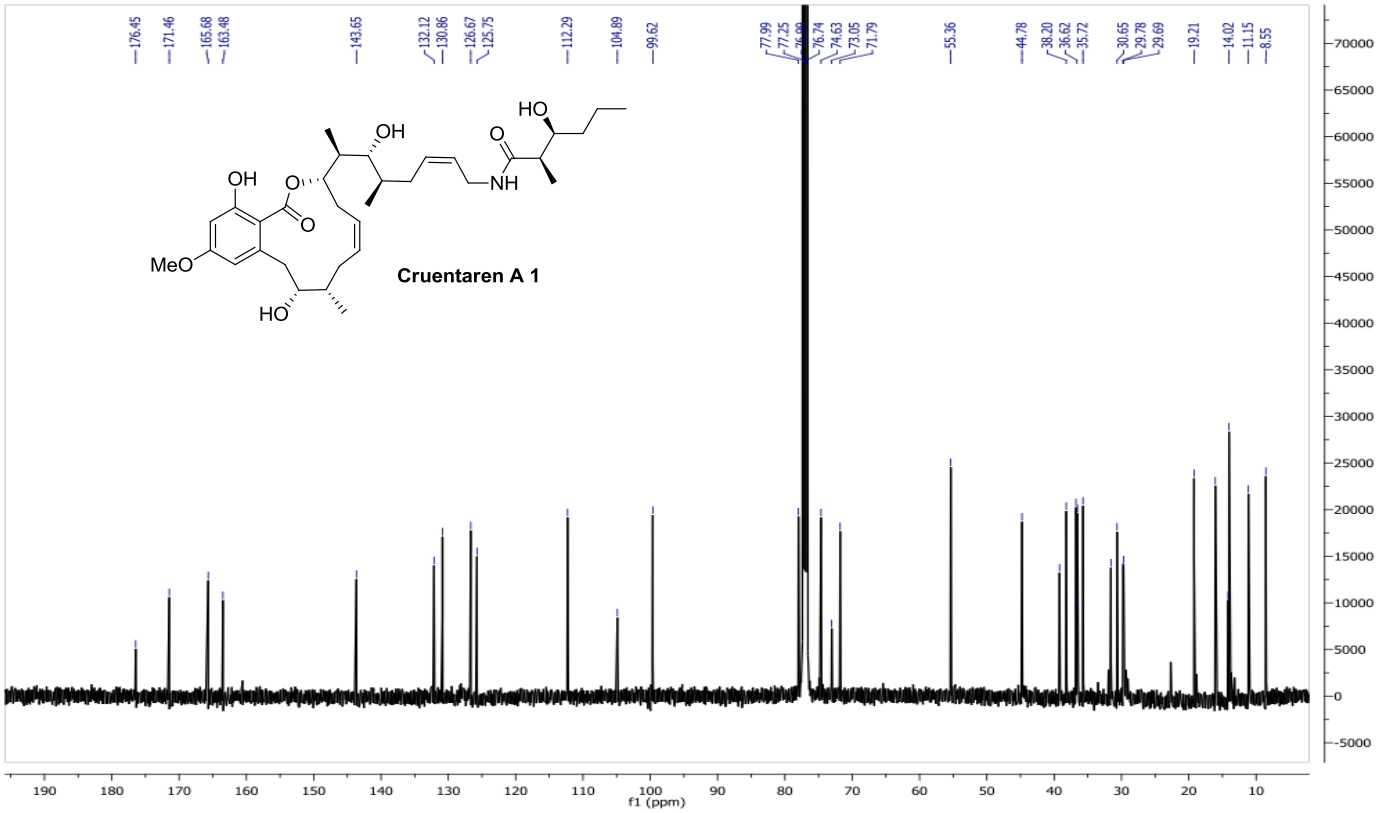

166.36
160.52
158.64
140.61
134.96
127.53
124.39
123.23
109.14
98.88
98.82
97.14
85.26
85.00
77.04
72.60
56.27
56.25
56.10
55.28
52.89
47.27
40.10
35.37
34.01
29.73
17.85
15.31
13.67
10.57
10.48
5.14
5.81
OTBS
OMe
O
O
N3
MeO
TBSO
2
f1 (ppm)


HO
OTBS
O
NH
OMe
O
O
MeO
TBSO
27
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
9
8.5
8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
-0.5
-1
f1 (ppm)


OTBS
HO
O
NH
OH
O
O
MeO
TBSO
f1 (ppm)


191.66
189.48
189.25
176.53
176.47
171.61
166.25
165.04
163.25
144.74
140.39
132.07
131.50
128.88
126.27
125.76
117.10
114.36
114.07
107.76
105.11
99.49
78.14
77.60
77.24
76.78
73.82
71.65
66.33
57.58
55.30
52.83
48.82
44.50
36.19
31.96
29.73
29.62
29.27
22.73
17.80
14.10
11.06
4.64
-2.05
-4.38
-5.29
-5.96
-6.47
-7.51
OTBS
HO
O
NH
OH
O
O
MeO
TBSO
f1 (ppm)


Cruentaren A 1
f1 (ppm)


176.45
171.46
165.68
163.48
143.65
132.12
130.86
126.67
125.75
112.29
104.89
99.62
77.99
77.25
76.89
76.74
74.63
73.05
71.79
55.36
44.78
38.20
36.62
35.72
30.65
29.78
29.69
19.21
14.02
11.15
8.55
Cruentaren A 1
f1 (ppm)