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Supporting Information

Scalable Total Synthesis, IP3R Inhibitory Activity of Desmethylxestospongin B, and Effect on Mitochondrial Function and Cancer Cell Survival

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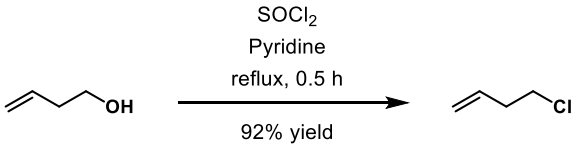
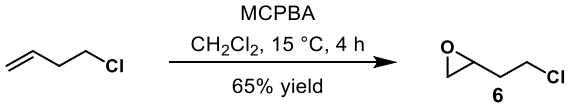
General Information. All reactions were carried out under an inert atmosphere of dry argon in oven or flame-dried glassware unless the reaction procedure states otherwise. Tetrahydrofuran (THF) and diethyl ether (Et2O) were distilled from sodium-benzophenone in a continuous still under an atmosphere of argon. Dichloromethane, di-iso-propylamine, triethylamine, and acetonitrile were distilled from calcium hydride in a continuous still under an atmosphere of argon. Reaction temperature was controlled by IKA ETS-D4 fuzzy thermo couples. Analytical normal-phase thin-layer chromatography (TLC) was performed using pre-coated TLC plates with Silica Gel 60 F254 (EMD no. 5715-7) and visualized using combinations of UV, anisaldehyde, ceric ammonium molybdate (CAM), and potassium permanganate staining. Normal-phase flash column chromatography was performed using 40-63 μm silica gel (EMD, Geduran, no. 1.11567.9026) as the stationary phase. Analytical reverse-phase thin-layer chromatography was performed using pre-coated TLC plates with Silica gel 60 RP-18 F254s (Merck, no. 1.15685.0001). Reverse-phase flash column chromatography was performed using C18-Reversed phase silica gel, fully end-capped (Fluka, no. 60756). Proton nuclear magnetic resonance spectra were recorded at 400, 500, and 600 MHz on Varian Unity Inova. Carbon nuclear magnetic resonance spectra were recorded at 101 MHz, 126 MHz, and 151 MHz on Varian Unity Inova, and Varian Unity Inova spectrometers. All chemical shifts were reported in □ units relative to tetramethylsilane. Optical rotations were measured on a Rudolph Autopol III polarimeter. High-resolution mass spectral data were obtained by the Mass Spectrometry laboratory at the University of California, Santa Barbara.



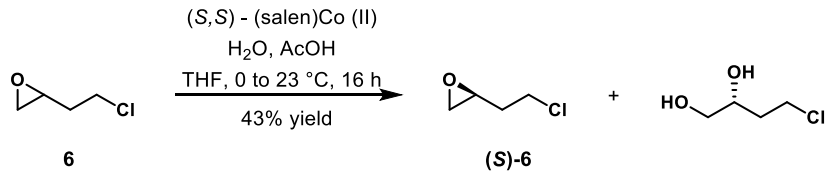
4-Chlorobut-1-ene: Prepared according to a modification of the literature procedure[1]: A mixture containing but-3-en-1-ol (83.65 g, 1.16 mol) and freshly distilled pyridine (0.50 mL, 6.50 mmol, 0.7 mol%) was cooled to 0 °C. After thionyl chloride (67.80 mL, 1.16 mol, 1.0 equiv) was added, reaction was heated at reflux for 0.5 h. The crude material was distilled under atmospheric pressure to afford 4-chlorobut-1-ene (96.57 g, 1.07 mol, 92% yield) as a clear liquid. ^{1}H and ^{13}C NMR spectral data matched that reported in the literature.[2]



2-(2-Chloroethyl)oxirane 6: 4-Chlorobut-1-ene (50 g, 0.55 mol) was dissolved in 135 mL of CH_2Cl_2 in a 1 L three neck flask equipped with a mechanical stirrer, reflux condenser and thermometer. After the mixture was cooled to 0 °C, MCPBA (75% wt, 140 g, 0.61 mol, 1.10

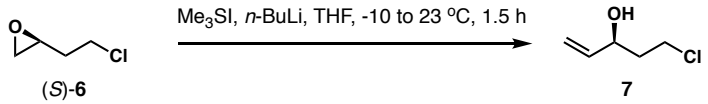
equiv) was added in 5 portions maintaining temperature below 10 °C. The mixture was warmed to 15 °C and stirred for 4 h. The white precipitate was removed by filtration and washed with 100 mL of cold CH_2Cl_2. The filtrate was placed in a freezer for 1 h and white solid was filtered and washed with 100 mL of cold dichoromethane again. The filtrate was cooled to 0 °C and dimethylsulfide (52 mL, 0.72 mol, 1.30 equiv) was added slowly. The mixture was allowed to warm to room temperature and stirred for 20 min. (Peroxide test showed the absence of peroxides. The peroxide test: 1 mL of the mixture was added to a fresh solution of 100 mg of the sodium iodide dissolved in 1 mL of glacial acetic acid. The solution remained clear.) The mixture was washed with 3M aqueous NaOH (3x200 mL) and brine (300 mL), then dried with Na_2SO_4. The organic solvent was distilled off under atmospheric pressure and the crude residue was then distilled under reduced pressure (bp 52 °C/30 mmHg) to afford 2-(2-chloroethyl)oxirane (38.10 g, 0.358 mol, 65% yield) as a clear liquid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.69 – 3.64 (m, 2H), 3.10 (dtt, J = 6.7, 4.2, 2.1 Hz, 1H), 2.82 (dd, J = 4.9, 3.9 Hz, 1H), 2.56 (dd, J = 4.9, 2.6 Hz, 1H), 2.06 (dtd, J = 14.5, 7.4, 4.4 Hz, 1H), 1.93 (dq, J = 14.7, 5.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 49.64, 46.88, 41.15, 35.44. HRMS (TOF MS EI) calcd for C_4H_7ClO $[M]^+$ 106.0185, found 106.0184.



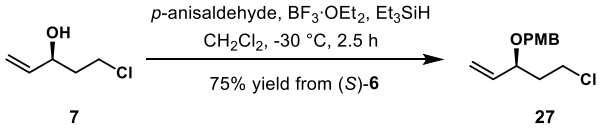
(*S*)-2-(2-Chloroethyl)oxirane (*S*)-6: Prepared according to a modification of the literature procedure[3]. 2-(2-chloroethyl)oxirane (165 g, 1.51 mol) was treated with (*S,S*)-(salen)Co (II) (4.56 g, 7.55 mmol, 0.005 equiv), AcOH (0.86 mL, 15.10 mmol, 0.01 equiv), and THF (15 mL). After the mixture was cooled to 0 °C, H_2O (15 mL, 0.83 mmol, 0.55 equiv) was added in one portion. The reaction was allowed to warm to room temperature and stir for 16 h. The (*S*)-2-(2-chloroethyl)oxirane and volatile materials were isolated by vacuum distillation at 0.2 mmHg into a cooled (–78 °C) receiving flask. The recovered epoxide was dried with Na_2SO_4 and washed with distilled CH_2Cl_2. Organic solvents were distilled off under atmospheric pressure and the crude residue was then distilled under reduced pressure (bp 52 °C/30 mmHg) to afford (*S*)-2-(2-chloroethyl)oxirane (69 g, 0.648 mol, 43% yield) as a clear liquid.

$[\alpha]_D^{25}$ –31.1˚ (*c* 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.69 – 3.64 (m, 2H), 3.10 (dtt, J = 6.7, 4.2, 2.1 Hz, 1H), 2.82 (dd, J = 4.9, 3.9 Hz, 1H), 2.56 (dd, J = 4.9, 2.6 Hz, 1H), 2.06 (dtd, J = 14.5, 7.4, 4.4 Hz, 1H), 1.93 (dq, J = 14.7, 5.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 49.64, 46.88, 41.15, 35.44. $[M]^+$ 106.0185, found 106.0184. Er was determined after derivatization to (–)-**23**.



(*S*)-**6** **7**

(*S*)-5-Chloropent-1-en-3-ol 7: *n*-Butyllithium (2.50 M in hexanes, 273 mL, 0.681 mol, 2.90 equiv) was added to solution of trimethylsulfonium iodide (144 g, 0.70 mol, 3.0 equiv) in THF (1 L) at –30 °C under argon and the resulting solution was stirred for 30 min. A solution of epoxide **(*S*)-6** (25 g, 0.235 mol) in THF (175 mL) was then added and the mixture was allowed to warm to room temperature and stir for 1 h. The reaction mixture was quenched with saturated aqueous ammonium chloride (100 mL) at 0 °C and then warmed to room temperature. It was extracted with Et_2O (3x800 mL). The combined organic layers were washed with brine (500 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. This yielded the alcohol **7** with minor impurities (29 g) as a pale-yellow liquid which was submitted to the next step without further purification.



7 **27**

(*S*)-Chloride 27: Boron trifluoride diethyl etherate (30.9 mL, 0.25 mol, 1.05 equiv) was added to the mixture of *p*-anisaldehyde (30.4 mL, 0.25 mol, 1.05 equiv) in CH_2Cl_2 (700 mL) under argon at –40 °C and the resulting solution was stirred for 5 min. A solution of crude alcohol **7** from the previous step (~29 g, ~0.235 mol) in CH_2Cl_2 (790 mL) was then added followed by triethylsilane (125.10 mL, 0.785 mol, 3.30 equiv) and the mixture turned orange. It was warmed to –30 °C and stirred for 2.5 h. The reaction mixture was quenched with H_2O (500 mL) and then warmed to room temperature. The layers were separated, and the organic layer was washed with saturated aqueous sodium bicarbonate, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (4% EtOAc in hexanes) to provide alkene **27** (42.85 g, 0.178 mol, 76% yield from epoxide **(*S*)-6**) as a pale-yellow oil after three reaction cycles with recovery of the starting material.

$[\alpha]_D^{25}$ –58.5° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 2H), 6.91 – 6.85 (m, 2H), 5.75 (ddd, J = 17.0, 10.3, 7.7 Hz, 1H), 5.33 – 5.24 (m, 2H), 4.54 (d, J = 11.2 Hz, 1H), 4.30 (d, J = 11.2 Hz, 1H), 3.99 (td, J = 8.0, 4.8 Hz, 1H), 3.81 (s, 3H), 3.68 (ddd, J = 10.7, 8.1, 6.1 Hz, 1H), 3.62 – 3.54 (m, 1H), 2.08 (ddt, J = 14.2, 8.4, 5.9 Hz, 1H), 1.91 (dddd, J = 14.4, 8.1, 6.5, 4.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.11, 137.91, 130.37, 129.32, 117.78, 113.73, 77.00, 70.08, 55.17, 41.27, 38.32. HRMS (TOF MS EI) calcd for $C_{13}H_{17}ClO_2$ $[M]^+$ 240.0917, found 240.0914. Er 96:4 (Chiralcel® OD-H; 0.5% i-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 220 nm; t1 = 6.05 min (major); t2 = 6.55 min (minor).

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SHIMADZU LabSolutions **Analysis Report**

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Batch Filename	:		
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Date Acquired	: 8/13/2020 1:27:20 PM	Acquired by	: Masa Podunavac
Date Processed	: 8/13/2020 1:36:25 PM	Processed by	: Masa Podunavac

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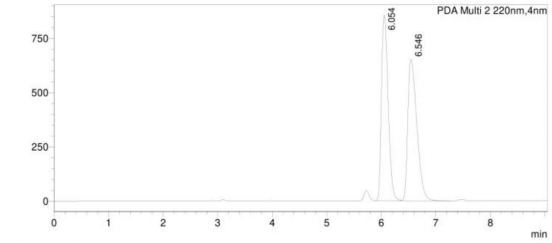

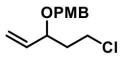

(±) **27**

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PDA Ch2 220nm

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8/13/2020 1:54:41 PM Page 1 / 1

SHIMADZU LabSolutions **Analysis Report**

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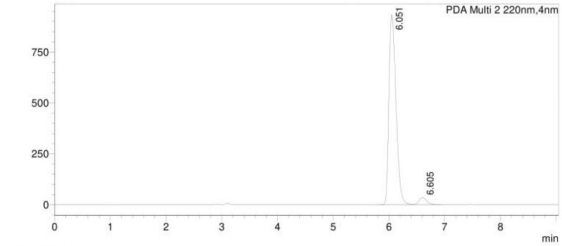

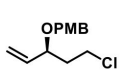

(–) **27**

<Peak Table>

PDA Ch2 220nm

Peak#	Ret. Time	Area	Height	Conc.	Area%
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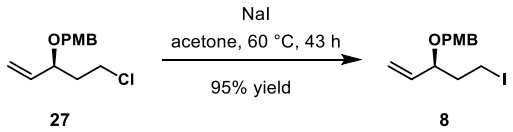
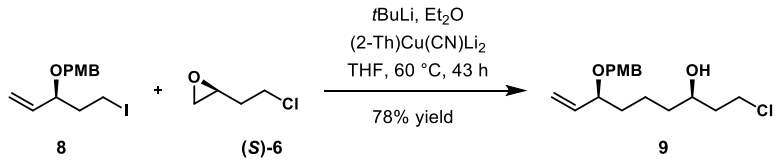


(*S*)-Iodide 8: Sodium iodide (57.2 g, 0.38 mol, 2.0 equiv) was added to the solution of chloride **27** (46 g, 0.19 mol) in dry acetone (190 mL) and the resulting solution was heated to 60 °C and stirred for 43 h. The reaction mixture was concentrated *in vacuo*. The residue was diluted with EtOAc (200 mL), washed with aqueous saturated sodium thiosulfate (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (4% EtOAc in hexanes) to provide iodide **8** (60.02 g, 0.181 mol, 95% yield) as a clear oil.

$[\alpha]_D^{25}$ –51.2° (*c* 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, 2H), 6.93 – 6.82 (m, 2H), 5.74 (ddd, J = 17.2, 10.3, 7.6 Hz, 1H), 5.36 – 5.26 (m, 2H), 4.54 (d, J = 11.1 Hz, 1H), 4.30 (d, J = 11.1 Hz, 1H), 3.88 (td, J = 7.8, 4.7 Hz, 1H), 3.81 (s, 3H), 3.32 – 3.19 (m, 2H), 2.11 (dddd, J = 15.0, 8.1, 7.0, 5.7 Hz, 1H), 2.02 – 1.95 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.11, 137.63, 130.33, 129.39, 117.88, 113.75, 79.79, 70.12, 55.21, 39.10, 2.41. HRMS (TOF MS EI) calcd for $C_{13}H_{17}IO_2$ $[M]^+$ 332.0273, found 332.0260.



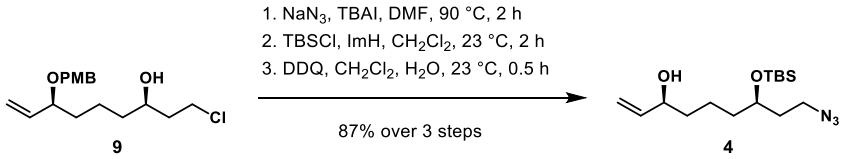
Alcohol 9: Prepared according to a modification of the literature procedure[4]: *n*-Butyllithium (2.50 M in hexanes, 83.60 mL, 0.209 mol, 1.20 equiv) was added to a solution of thiophene (16.70 mL, 0.209 mol, 1.20 equiv) in THF (170 mL) was added at –78 °C. The temperature was slowly raised to 0 °C and the mixture was stirred for 30 min. Copper(I) cyanide (17 g, 0.190 mol, 1.10 equiv) was added to the mixture at –78°C and the reaction mixture was stirred for 30 min at 0 °C.

t-Buthyllithium (1.70 M in pentane, 223.50 mL, 0.380 mol, 2.20 equiv) was added to a solution of iodide **8** (63.10 g, 0.190 mol, 1.10 eq) in Et_2O (525 mL) at –78 °C and it was stirred for 1 h. The mixture was added via cannula to a solution of (2-Th)Cu(CN)Li_2 at –78 °C (105 mL wash with Et_2O) and the mixture was stirred for 30 min at 0 °C.

Previously cooled (–30 °C) solution of epoxide **(*S*)-6** (18.40 g, 0.173 mol) in THF (460 mL) was added via cannula to the cuprate at –78 °C and then stirred for 1 h at 0 °C. The reaction mixture was quenched with 500 mL of 90% NH_4Cl (satd)/10% NH_4OH (conc) solution, diluted with H_2O (500 mL) and let to stir for 3 h until two layers formed. The aqueous layer was extracted with EtOAc (3x500 mL). The combined organic layers were washed with brine, dried

over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (15% EtOAc-hexanes) to afford alcohol **9** (42.0 g, 0.134 mol, 78% yield) as a clear oil.

$[\alpha]_D^{25}$ –44.7° (*c* 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 – 7.21 (m, 2H), 6.91 – 6.83 (m, 2H), 5.73 (ddd, J = 17.1, 10.4, 7.8 Hz, 1H), 5.26 – 5.18 (m, 2H), 4.53 (d, J = 11.5 Hz, 1H), 4.27 (d, J = 11.5 Hz, 1H), 3.80 (s, 3H), 3.74 – 3.62 (m, 3H), 1.90 – 1.78 (m, 2H), 1.63 (m, 2H), 1.57 – 1.48 (m, 2H), 1.46 – 1.42 (m, 2H), 1.41 – 1.33 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.00, 138.88, 130.61, 129.34, 117.12, 113.68, 79.80, 69.62, 68.58, 55.19, 41.91, 39.68, 37.21, 35.18, 21.20. HRMS (TOF MS EI) calcd for $C_{17}H_{25}ClO_3$ $[M+Na]^+$ 335.1390, found 335.1392.



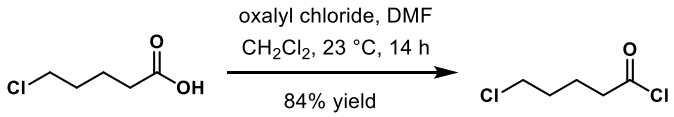
Azide 4: Sodium azide (15.20 g, 0.234 mol, 1.10 equiv) and tetrabutylammonium iodide (0.71 g, 1.92 mmol, 0.9 mol%) were added to the solution of chloride **9** (66.50 g, 0.213 mol) in DMF (133 mL) and the resulting solution was heated to 90 °C and stirred for 2 h. The reaction mixture was diluted with 20% EtOAc / 80% Hex solution (20 mL). The organic layer was washed with water (5 x 100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The light-yellow oil residue was submitted to the next step without further purification.

The crude residue from the previous step was dissolved in CH_2Cl_2 (136 mL) and imidazole (43.50 g, 0.64 mol, 3.0 equiv) and *tert*-butyldimethylsilyl chloride (48.20 g, 0.320 mol, 1.50 equiv) were added at 0 °C. The reaction mixture was warmed up to room temperature and stirred for 0.5 h. The mixture was diluted with CH_2Cl_2 (150 mL), and the organic layer was washed with water, then brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The light-yellow oil residue was submitted to the next step without further purification.

The crude material from the previous step was dissolved in 1:1 mixture of CH_2Cl_2 – water (700 mL), and DDQ (53.10 g, 0.234 mol, 1.10 equiv) was added. Reaction was let to stir for 0.5 h and then quenched by addition of 3M sodium sulfite in water (250 mL). The mixture was washed with saturated aqueous sodium bicarbonate (200 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (100 % CH_2Cl_2 to 15% EtOAc-hexanes) to afford azide **4** (58.10 g, 0.185 mol, 87% yield over 3 steps) as a clear oil.

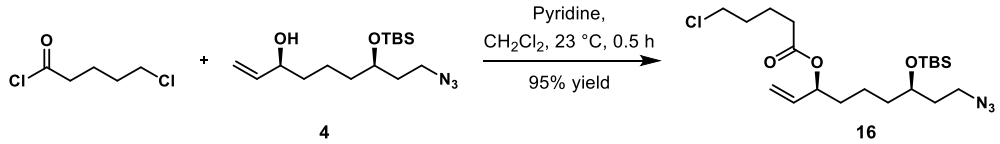
$[\alpha]_D^{25}$ –17.0° (*c* 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.86 (ddd, J = 17.0, 10.4, 6.3 Hz, 1H), 5.22 (dt, J = 17.2, 1.4 Hz, 1H), 5.11 (dt, J = 10.4, 1.3 Hz, 1H), 4.10 (dt, J = 9.1, 4.6 Hz, 1H), 3.78 (dtd, J = 7.2, 5.7, 4.4 Hz, 1H), 3.41 – 3.29 (m, 2H), 1.77 – 1.64 (m, 2H), 1.56 – 1.45 (m, 4H), 1.45

– 1.39 (m, 1H), 1.35 (m, 1H), 0.88 (s, 9H), 0.05 (d, J = 1.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.09, 114.72, 73.06, 69.23, 47.96, 37.11, 36.96, 35.51, 25.81, 20.77, 18.00, -4.39, -4.72. HRMS (TOF MS EI) calcd for $C_{15}H_{31}N_3O_2Si$ $[M+Na]^+$ 336.2085, found 336.2085.



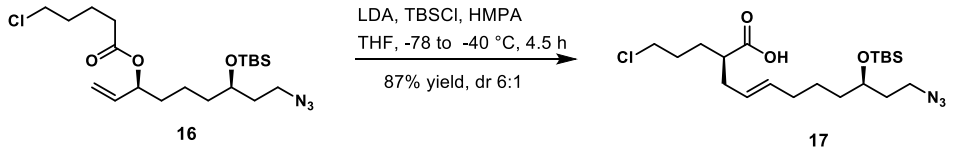
5-Chloropentanoyl chloride: Oxalyl chloride (8.80 mL, 0.103 mol, 1.10 equiv) was added to a solution of 5-chlorovaleric acid (11.0 mL, 94.16 mmol), dimethylformamide (10 µL), in CH_2Cl_2 (32 mL). The solution was stirred at room temperature for 14 h, and then concentrated *in vacuo*. The residue was purified by distillation under reduced pressure (bp 54 °C/2.50 mmHg) to afford 5-chloropentanoyl chloride (12.25 g, 79.02 mmol, 84% yield) as a pale-yellow liquid that was used immediately without further purification.

^{1}H NMR (500 MHz, C_6D_6) δ 3.45 (dd, J = 6.6, 5.5 Hz, 2H), 2.85 (t, J = 6.8 Hz, 2H), 1.83 – 1.70 (m, 4H).



Ester 16: 5-Chloropentanoyl chloride (6.10 mL, 47.22 mmol, 1.20 equiv) was added dropwise to the solution of alcohol **4** (12.30 g, 39.35 mmol) and pyridine (6.30 mL, 78.70 mmol, 2.0 eqiv) in CH_2Cl_2 (80 mL) at 0 °C. Reaction mixture was warmed up to room temperature after participate formed and reaction turned pink. The reaction mixture was stirred for 30 min, then diluted with CH_2Cl_2 (100 mL), and quenched with 1M aqueous HCl in water (30 mL). The organic layer was washed with water (100 mL), saturated aqueous sodium bicarbonate (100 mL), water again (100 mL), and finally with brine (100 mL). It was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (5% EtOAc-hexanes) to afford ester **16** (16.10 g, 37.26 mmol, 95% yield) as a clear oil.

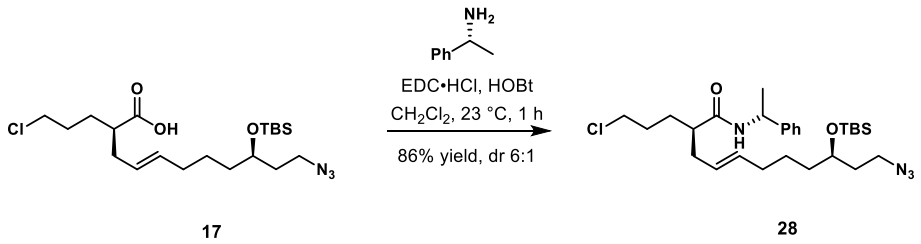
$[\alpha]_D^{25}$ –12.6° (*c* 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (ddd, J = 17.2, 10.5, 6.4 Hz, 1H), 5.28 – 5.22 (m, 2H), 5.17 (dt, J = 10.5, 1.2 Hz, 1H), 3.79 – 3.73 (m, 1H), 3.55 (t, J = 6.2 Hz, 2H), 3.40 – 3.29 (m, 2H), 2.36 (t, J = 7.0 Hz, 2H), 1.90 – 1.75 (m, 3H), 1.72 – 1.55 (m, 3H), 1.46 (ddd, J = 8.6, 7.2, 5.4 Hz, 2H), 1.42 – 1.27 (m, 1H), 0.88 (s, 8H), 0.05 (d, J = 4.6 Hz, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.33, 136.33, 116.85, 74.62, 69.14, 47.91, 44.40, 36.94, 35.62, 34.27, 33.61, 31.83, 25.80, 22.27, 20.61, 18.00, -4.41, -4.68. HRMS (TOF MS EI) calcd for $C_{20}H_{38}ClN_3O_3Si$ $[M+Na]^+$ 454.2269, found 454.2268.



Acid 17: *n*-Butyllithium (2.50M in hexanes, 21.80 ml, 54.62 mmol, 2.0 equiv) was added to a solution of diisopropylamine (8.30 mL, 59.26 mmol, 2.17 equiv) in THF (160 ml) at –78 °C, and the mixture was stirred for 20 min. The solution was cooled to –78 °C and a solution of ester **16** (11.80 g, 27.31 mmol) in THF (92 mL then 3 x 6.0 mL rinses) was added. The solution was stirred 0.5 h at –78 °C, when *tert*-butyldimethylsilyl chloride (9.60 g, 63.63 mmol, 2.33 equiv) followed by HMPA (48.20 mL, 15 %vol) were added. The solution was stirred 0.5 h at –78 °C, then 0.5 h at –40 °C, and finally 0.5 h at –15 °C. The reaction mixture was then poured into a separatory funnel containing 1M aqueous HCl (100 mL) and the layers were separated. The aqueous layer was extracted with hexanes (2 x 250 mL), the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The precooled solution of LiOH (1.64 g, 68.47 mmol, 2.50 equiv) in water (38 mL) was added to the mixture of the residue in THF (103 mL) at 0 °C. The mixture was stirred for 0.5 h and then diluted with EtOAc (200 mL) and washed with 1M aqueous HCl (100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes) to give acid **17** (10.21 g, 23.63 mmol, 87% yield, dr 6:1) as a clear oil.

$[\alpha]_D^{25}$ –9.13° (*c* 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.48 (dt, J = 14.9, 6.6 Hz, 1H), 5.41 – 5.31 (m, 1H), 3.83 – 3.72 (m, 1H), 3.54 (qd, J = 6.4, 5.4, 1.5 Hz, 2H), 3.40 – 3.28 (m, 2H), 2.44 (m, 1H), 2.36 (dt, J = 14.0, 7.1 Hz, 1H), 2.22 (dt, J = 13.7, 6.7 Hz, 1H), 1.99 (q, J = 6.9 Hz, 2H), 1.91 – 1.62 (m, 5H), 0.89 (s, 9H), 0.06 (d, J = 1.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.19, 133.18, 126.42, 69.24, 47.97, 44.82, 44.58, 36.64, 35.62, 34.96, 32.48, 30.15, 28.42, 25.83, 24.74, 18.03, -4.36, -4.69. HRMS (TOF MS EI) calcd for $C_{20}H_{38}ClN_3O_3Si$ $[M+Na]^+$ 454.2269, found 454.2271.

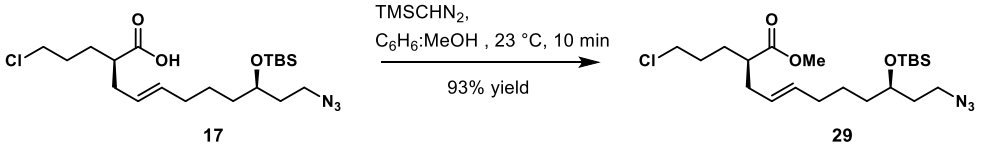
Determination of the diastereomer ratio for acid 24:



Amide 28: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (20 mg, 0.104 mmol, 1.5 equiv), (*R*)-(+)-alpha-methylbenzylamine (13 µL, 0.104 mmol, 1.5 equiv), and HOBt (14 mg, 0.104 mmol, 1.5 equiv) were added sequentially to a solution of acid **17** (30 mg, 0.069 mmol) in CH_2Cl_2

(0.40 mL). The solution was stirred at room temperature for 1h, then diluted with CH_2Cl_2 (5 mL) and washed with saturated aqueous sodium bicarbonate (5 mL) and brine (5 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography (15% EtOAc-hexanes) to give amide **28** (48 mg, 0.089 mmol, 86% yield, dr 6:1) as a clear oil.

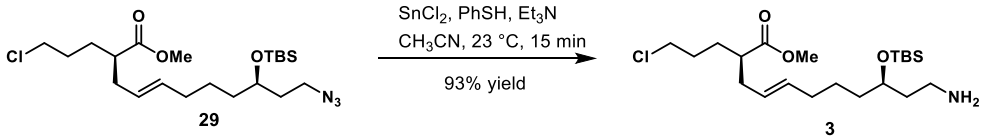
$[\alpha]_D^{25}$ +12.1° (*c* 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.29 (overlapping m, 4.60H), 7.27 (t, J = 1.7 Hz, 0.5H), 5.64 (d, J = 7.9 Hz, 1H), 5.47 (dt, J = 14.2, 6.7 Hz, 0.17H), 5.44 – 5.37 (m, 1H), 5.35 (dd, J = 15.0, 7.3 Hz, 0.16H), 5.30 – 5.23 (m, 1H), 5.15 (overlapping h, J = 7.3 Hz, 1.16H), 3.74 (overlapping dtd, J = 7.1, 5.7, 4.3 Hz, 1.16H), 3.55 (overlapping dt, J = 10.8, 6.3 Hz, 1.16H), 3.52 – 3.43 (overlapping m, 1.32H), 3.38 – 3.29 (overlapping m, 2.32H), 2.28 (overlapping dt, J = 14.5, 7.5 Hz, 1.16H), 2.12 (overlapping dt, J = 13.3, 6.4 Hz, 1.16H), 2.08 – 2.02 (overlapping m, 1.16H), 1.98 (q, J = 7.3 Hz, 0.32H), 1.90 (q, J = 7.2 Hz, 2H), 1.84 – 1.78 (m, 1H), 1.77 – 1.59 (overlapping m, 5H), 1.49 (overlapping d, J = 6.9 Hz, 3.5H), 1.46 – 1.35 (overlapping m, 2.5H), 1.30 (overlapping p, J = 7.7 Hz, 2.16H), 0.88 (overlapping d, J = 2.2 Hz, 10.5H), 0.05 (overlapping d, J = 4.4 Hz, 7H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.60, 143.10, 132.78, 132.73, 128.59, 128.52, 127.29, 127.23, 127.07, 126.12, 126.08, 69.13, 48.46, 48.35, 47.93, 47.39, 47.23, 44.79, 36.72, 36.67, 36.00, 35.53, 35.51, 32.54, 32.43, 30.40, 30.28, 29.57, 29.48, 25.80, 24.68, 24.61, 21.64, 17.98, -4.38, -4.74. HRMS (TOF MS EI) calcd for $C_{28}H_{47}ClN_4O_2Si$ $[M+Na]^+$ 557.3055, found 557.3051.



17 29

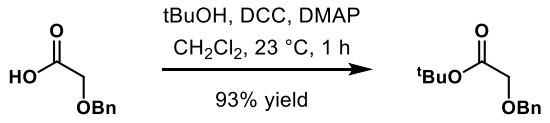
Methyl Ester 29: Trimethylsilyldiazomethane (3.30M in hexanes, 9.20 mL, 30.39 mmol, 1.30 equiv) was added to a solution of acid **17** (10.1 g, 23.38 mmol) in benzene (116 ml) and methanol (29 mL) at 0 °C. The mixture was warmed up to room temperature and stirred for 10 min. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (10% EtOAc-hexanes) to give ester **29** (9.30 g, 20.85 mmol, 89% yield) as a clear oil.

$[\alpha]_D^{25}$ –13.3° (*c* 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.44 (dtt, J = 14.8, 6.7, 1.3 Hz, 1H), 5.32 (dtt, J = 15.3, 7.0, 1.3 Hz, 1H), 3.76 (dtd, J = 7.2, 5.7, 4.4 Hz, 1H), 3.67 (s, 3H), 3.52 (td, J = 6.4, 3.0 Hz, 2H), 3.40 – 3.30 (m, 2H), 2.46 – 2.37 (m, 1H), 2.35 – 2.27 (m, 1H), 2.22 – 2.14 (m, 1H), 2.02 – 1.92 (m, 2H), 1.83 – 1.62 (m, 5H), 1.43 (dq, J = 10.1, 5.9 Hz, 1H), 1.38 – 1.31 (m, 1H), 0.88 (s, 8H), 0.05 (d, J = 2.1 Hz, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.62, 132.83, 126.64, 69.19, 51.42, 47.94, 44.99, 44.97, 44.56, 36.65, 35.61, 35.26, 32.49, 30.26, 28.78, 25.81, 24.75, 24.74, 18.00, -4.39, -4.72. HRMS (TOF MS EI) calcd for $C_{21}H_{42}ClN_3O_3Si$ $[M+H]^+$ 446.2527, found 44.2525.



Amine 3: Prepared according to a modification of the literature procedure[5]: thiophenol (8.20 mL, 80.70 mmol, 6.0 equiv) and triethylamine (8.40 mL, 60.52 mmol, 4.50 equiv) were added to a solution of anhydrous $SnCl_2$ (3.83 g, 20.17 mmol, 1.5 equiv) in acetonitrile (80 mL). The mixture turned bright yellow and was let to stir at room temperature for 15 min. Solution of azide **29** (5.60 g, 12.50 mmol) in acetonitrile (46 mL then 3 x 3.0 mL rinses) was added and the mixture was stirred at room temperature for 15 min when it was concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 (20 mL) and washed with 2M aqueous NaOH (20 mL). The extract was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc-CH_2Cl_2 then 20% MeOH-1% NH_4OH-CH_2Cl_2) to afford amine **3** (4.89 g, 11.64 mmol, 93% yield) as a pale-yellow oil.

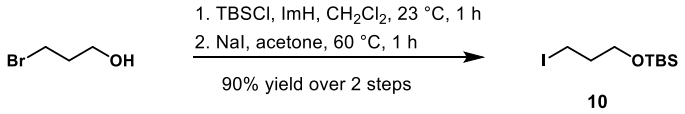
$[\alpha]_D^{25}$ –4.5˚ (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 5.44 (dt, J = 13.7, 6.6 Hz, 1H), 5.31 (dt, J = 14.7, 6.9 Hz, 1H), 3.74 (p, J = 5.7 Hz, 1H), 3.67 (s, 3H), 3.52 (t, J = 6.5 Hz, 2H), 2.77 (t, J = 7.4 Hz, 2H), 2.47 – 2.36 (m, 1H), 2.30 (dt, J = 14.4, 7.3 Hz, 1H), 2.17 (dt, J = 13.6, 6.6 Hz, 1H), 1.96 (q, J = 7.0 Hz, 2H), 1.84 – 1.63 (m, 6H), 1.59 (q, J = 6.8 Hz, 2H), 1.48 – 1.30 (m, 3H), 0.88 (s, 9H), 0.04 (d, J = 2.8 Hz, 6H). ^{13C} NMR (126 MHz, $CDCl_3$) δ 175.60, 132.88, 126.51, 70.25, 51.40, 44.95, 44.53, 36.60, 35.23, 32.50, 30.23, 28.74, 25.80, 24.88, 17.97, -4.46, -4.60. HRMS (TOF MS EI) calcd for $C_{21}H_{42}ClN_3O_3Si$ $[M+H]^+$ 420.2701, found 420.2702.



Benzyloxyacetic acid t-butylester: N,N′-Dicyclohexylcarbodiimide (45.0 g, 0.218 mol, 1.30 eq) was added to a solution of 2-(benzyloxy)acetic acid (28 g, 0.168 mol), 4-dimethylaminopyridine (2.26 g, 18.50 mmol, 0.11 equiv), *t*-butyl alcohol(31.90 mL, 0.336 mmol, 2 equiv)in CH_2Cl_2 (560 mL) at 0 °C. The mixture was warmed up to room temperature and stirred for 1 h. The white solid was filtered off, and the filtrate was washed with saturated sodium bicarbonate (50 mL), then brine (50 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was dissolved in 100 mL of Et_2O:hexanes (1:1) and it was stirred for 1 h at room temperature. Precipitate was filtered out and the filtrate was concentrated *in vacuo*. The crude residue was then distilled under reduced pressure (bp 100 °C/0.2 mmHg) to afford benzyloxyacetic acid t-butylester (34.81 g, 0.156 mol, 93% yield) as a clear liquid.

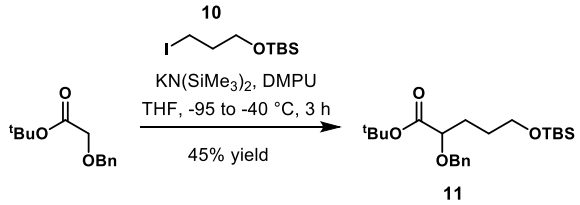
^1H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 5H), 7.32 – 7.28 (m, 1H), 4.63 (d, J = 1.2 Hz, 2H), 3.99 (d, J = 1.2 Hz, 2H), 1.49 (d, J = 1.4 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.40, 137.25,

137.24, 128.29, 127.89, 127.75, 81.41, 73.05, 67.60, 27.98. HRMS (TOF MS EI) calcd for $C_{13}H_{18}O_3$ $[M+Na]^+$ 245.1154, found 245.1152.



Iodide 10: Imidazole (64.70 g, 0.950 mol, 2.20 equiv) and TBSCl (68.30 g, 0.453 mol, 1.05 equiv) were added to a precooled solution (0 °C) of 3-bromo-1-propanol (60.0 g, 0.432 mol) in CH_2Cl_2 (270 mL). The mixture was warmed up to room temperature and stirred for 1 h. It was washed with water (2 x 300 mL), then brine (200 mL) and the organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The clear liquid residue (123.0 g) was submitted to the next step without further purification.

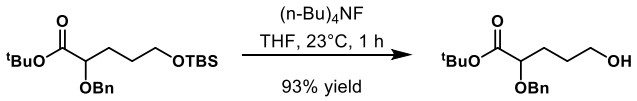
The crude material from the previous step was dissolved in dry acetone (432 mL), and sodium iodide (130 g, 0.864 mol, 2.0 equiv) was added. The resulting solution was heated to 60 °C and stirred for 1 h. The reaction mixture was concentrated *in vacuo*. The residue was diluted with EtOAc (200 mL), washed with aqueous saturated sodium thiosulfate (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by distillation under reduced pressure (bp 74 °C/0.2 mmHg) to afford **10** (116.8 g, 0.389 mol, 90% yield over 2 steps) as a pale-yellow liquid. ^{1}H and ^{13}C NMR spectral data matched that reported in the literature [6].



Ester 11: Precooled solution (–78 °C) of benzyloxyacetic acid t-butylester (24.20 g, 0.109 mol) in THF (175 mL) was added dropwise via cannula to the solution of $KN(SiMe_3)_2$ (47.84 g, 0.240 mol, 2.20 equiv), DMPU (18.50 mL, 5% v/v to THF) in THF (370 mL) at –95 °C. The reaction mixture was stirred for 0.5 h when precooled (–78 °C) neat iodide **10** (81.8 g, 0.273 mol, 2.50 equiv) was added dropwise. Reaction mixture was stirred for 0.5 h at –95 °C, then 0.5 h at –78 °C, and finally 2 h at –40 °C. The reaction mixture was quenched with an addition of sat. aq. NH_4Cl (100 mL) and warmed up to 0 °C. The product was extracted with EtOAc (3 x 300 mL), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (5% EtOAc-hexanes) to give ester **11** (19.30 g, 48.91 mmol, 45% yield) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 4H), 7.30 – 7.27 (m, 1H), 4.70 (d, J = 11.6 Hz, 1H), 4.40 (d, J = 11.6 Hz, 1H), 3.82 (dd, J = 8.0, 4.7 Hz, 1H), 3.59 (t, J = 6.3 Hz, 2H), 1.83 (dddd, J = 14.5, 10.4, 6.1, 4.7 Hz, 1H), 1.79 – 1.72 (m, 1H), 1.71 – 1.63 (m, 1H), 1.60 (dtd, J = 13.4, 6.4, 3.7

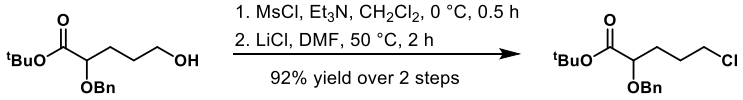
Hz, 1H), 1.49 (s, 9H), 0.88 (d, J = 0.5 Hz, 9H), 0.03 (d, J = 0.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.02, 137.86, 128.30, 127.95, 127.67, 81.19, 78.28, 71.98, 62.57, 29.44, 28.49, 28.09, 25.92, 18.29, -5.34. HRMS (TOF MS EI) calcd for $C_{22}H_{38}O_4Si$ [M+Na]$^+$ 417.2437, found 417.2440.



11 12

Alcohol 12: Tetra-*n*-butylammonium fluoride (1M in THF, 74.0 mL, 73.37 mmol, 1.50 equiv) was added to a flask containing ester **11** (19.30 g, 48.91 mmol) at 0 °C. The reaction mixture was warmed up to 23 °C for 1 h, then quenched with saturated aq. NH_4Cl (4 mL), and the mixture was extracted with CH_2Cl_2 (2 x 80 mL). The combined organic layers were washed with water (5 x 30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc-hexanes then 40% EtOAc-hexanes) to give alcohol **12** (12.81 g, 45.69 mmol, 93% yield) as clear liquid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.32 (m, 4H), 7.29 (t, J = 7.6 Hz, 1H), 4.72 (d, J = 11.4 Hz, 1H), 4.40 (dd, J = 11.4, 1.0 Hz, 1H), 3.85 (ddd, J = 7.8, 4.5, 1.1 Hz, 1H), 3.62 (dp, J = 8.7, 4.7 Hz, 2H), 1.94 – 1.76 (m, 2H), 1.76 – 1.63 (m, 2H), 1.49 (d, J = 1.2 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.78, 137.47, 128.37, 128.05, 127.83, 81.51, 78.30, 72.18, 62.35, 29.54, 28.62, 28.07. HRMS (TOF MS EI) calcd for $C_{16}H_{24}O_4$ [M+Na]$^+$ 303.1572, found 303.1574.

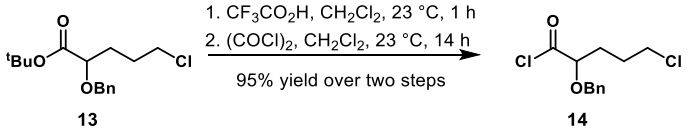


12 13

Chloride 13: Methanesulfonyl chloride (4.60 mL, 59.35 mmol, 1.30 equiv) was added to the solution of alcohol **12** (12.80 g, 45.66 mmol), triethylamine(16.60 mL, 0.119 mol, 2.60 equiv) in CH_2Cl_2 (114 mL) at 0 °C. Water (20 mL) was added to the reaction mixture after 0.5 h at 0 °C. The mixture was washed with water (2 x 50 mL), then 1M aqueous HCl (50 mL), then saturated aqueous sodium bicarbonate (50 mL), and finally with brine (50 mL). It was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The clear oil residue was submitted to the next step without further purification.

Lithium chloride (19.37 g, 0.457 mol, 10 equiv) was added to the solution of crude material from the previous step in DMF (46 mL). The reaction mixture was heated for 2 h at 50 °C. The mixture was diluted with EtOAc (80 mL), washed with water (4 x 150 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (10% EtOAc-hexanes) to give chloride **13** (12.50 g, 41.83 mmol, 92% yield over two steps) as clear oil.

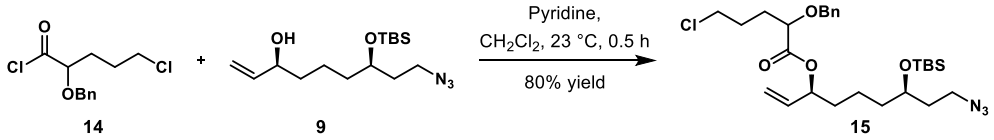
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 4H), 7.32 – 7.28 (m, 1H), 4.72 (d, J = 11.5 Hz, 1H), 4.40 (d, J = 11.5 Hz, 1H), 3.83 (dd, J = 7.3, 3.4 Hz, 1H), 3.53 (t, J = 5.5 Hz, 2H), 1.97 – 1.78 (m, 4H), 1.50 (d, J = 0.9 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.44, 137.55, 128.29, 127.89, 127.72, 81.45, 77.51, 72.00, 44.56, 30.14, 28.34, 28.00. HRMS (TOF MS EI) calcd for $C_{22}H_{38}O_4Si$ $[M+H]^+$ 299.1336, found 299.1334.



Acyl chloride 14: Ester **14** (12.50 g, 41.83 mmol) was dissolved in TFA (105 mL) and CH_2Cl_2 (210 mL), and the mixture and stirred for 1 h at 23 °C. The reaction mixture was concentrated *in vacuo*. The residue was diluted with toluene (30 mL) and concentrated *in vacuo*. This was repeated 3 times to provide the light-yellow oil residue (10.0 g) that was submitted to the next step without further purification.

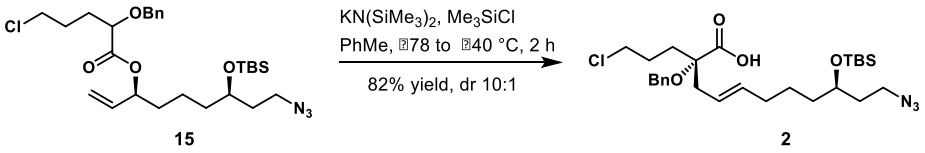
Oxalyl chloride (3.50 mL, 41.20 mmol, 1 equiv) was added to a solution of the crude material from the previous step (10.0 g, 41.20 mmol), dimethylformamide (10 µL), in CH_2Cl_2 (14 mL). The solution was stirred at room temperature for 14 h, and then concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 (15 mL) and concentrated *in vacuo*. This was repeated 3 times to provide the light-yellow oil residue (10.24 g, 39.21 mmol, 95% yield) that was used immediately in the next step without further purification.

^{1}H NMR (500 MHz, C_6D_6) δ 7.16 – 6.98 (m, 5H), 4.45 (d, *J* = 11.1 Hz, 1H), 3.98 (dd, *J* = 11.4, 1.7 Hz, 1H), 3.79 (dt, *J* = 6.3, 2.7 Hz, 1H), 2.96 (td, *J* = 6.4, 2.4 Hz, 2H), 1.81 – 1.60 (m, 2H), 1.56 – 1.41 (m, 2H).



Ester 15: Acyl chloride **14** (11.90 g, 38.07 mmol) was added dropwise to the solution of alcohol **9** (10.24 g, 39.21 mmol, 1.03 equiv) and pyridine (15.40 mL, 0.190 mol, 5.0 eqiv) in CH_2Cl_2 (15.40 mL) at 0 °C. Reaction was warmed up to room temperature. After a participate formed the reaction turned pink. The mixture was stirred for 30 min, then diluted with CH_2Cl_2 (100 mL), and quenched with 1M aqueous HCl in water (30 mL). The organic layer was washed with water (100 mL), saturated aqueous sodium bicarbonate (100 mL), water again (100 mL), and finally with brine (100 mL). It was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (5% EtOAc-hexanes) to afford ester **15** (16.32 g, 30.32 mmol, 80% yield) as a clear oil.

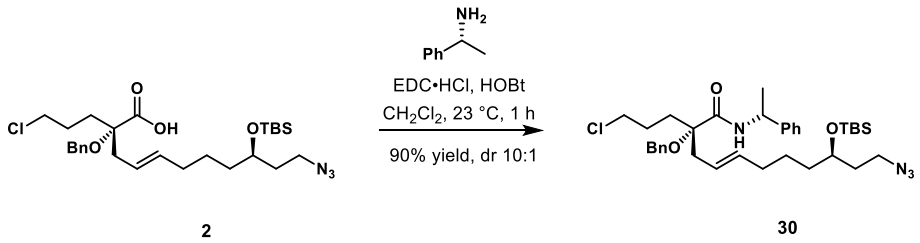
$[\alpha]_D^{25}$ –7.1˚ (*c* 1.00, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 4H), 7.32 – 7.28 (m, 1H), 5.78 (dddd, J = 17.3, 11.4, 10.6, 6.8 Hz, 1H), 5.37 – 5.25 (m, 2H), 5.22 (dq, J = 10.5, 1.3 Hz, 1H), 4.73 (dd, J = 11.6, 5.2 Hz, 1H), 4.39 (d, J = 11.6 Hz, 1H), 3.99 – 3.93 (m, 1H), 3.76 (ddt, J = 10.2, 6.9, 5.7 Hz, 1H), 3.52 (td, J = 5.9, 2.0 Hz, 2H), 3.39 – 3.28 (m, 2H), 2.00 – 1.84 (m, 3H), 1.74 – 1.58 (m, 3H), 1.51 – 1.45 (m, 2H), 1.43 – 1.27 (m, 1H), 0.88 (d, J = 2.7 Hz, 9H), 0.05 (dd, J = 5.6, 4.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.70, 171.50, 137.29, 137.28, 135.87, 135.77, 128.32, 127.88, 127.87, 127.82, 117.70, 117.32, 77.10, 75.38, 75.31, 72.13, 72.12, 69.02, 68.98, 47.81, 44.45, 36.82, 35.53, 35.45, 34.16, 30.77, 30.17, 30.12, 28.29, 28.26, 25.72, 20.53, 20.51, 17.92, 17.91, -4.45, -4.47, -4.77, -4.80. HRMS (TOF MS EI) calcd for $C_{27}H_{44}ClN_3O_4Si$ $[M+Na]^+$ 560.2687, found 560.2687.



Carboxylic acid 2: Prepared according to a modification of the literature procedure[7]: flame-dried 500 mL round bottom flask was brought into a nitrogen-filled glove box and charged with $KN(SiMe_3)_2$ (18.85 g, 94.49 mmol, 2.2 equiv). The flask was capped, removed from the glove box, attached to a Schlenk line, and backfilled with argon three times. Toluene (148 mL) was then added to the flask and the solution was cooled to –78 °C. A solution of ester **15** (23.12 g, 42.95 mmol) in PhMe (128 then 2 x 10 mL rinses) was added dropwise and the resulting solution was stirred 30 min. Chlorotrimethylsilane (10.90 mL, 9.33 g, 85.90 mmol, 2 equiv) was then added dropwise, and the solution was stirred 1h at –78 °C and 1h at –40 °C, The solution was then poured into a separatory funnel containing 1M aqueous HCl (100 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 80 mL), the combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes) to give acid **2** (18.91 g, 35.14 mmol, 82% yield, dr 10:1) as a clear oil.

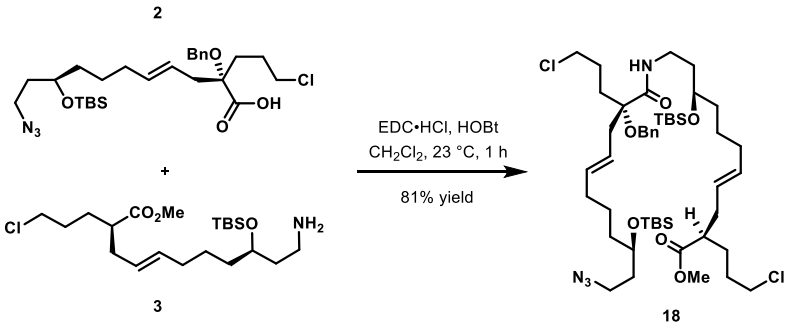
$[\alpha]_D^{25}$ –0.7˚ (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.31 (m, 5H), 5.65 – 5.55 (m, 1H), 5.41 – 5.32 (m, 1H), 4.57 (d, J = 10.2 Hz, 1H), 4.50 (d, J = 10.2 Hz, 1H), 3.78 – 3.72 (m, 1H), 3.61 (dt, J = 11.1, 5.6 Hz, 1H), 3.50 (ddd, J = 10.8, 8.4, 4.9 Hz, 1H), 3.38 – 3.28 (m, 2H), 2.70 – 2.59 (m, 2H), 2.14 (ddd, J = 15.4, 12.0, 4.2 Hz, 1H), 2.06 – 1.97 (m, 3H), 1.87 (dddd, J = 19.4, 12.4, 8.6, 4.3 Hz, 1H), 1.82 – 1.73 (m, 1H), 1.71 – 1.63 (m, 2H), 1.46 – 1.32 (m, 4H), 0.88 (s, 9H), 0.05 (d, J = 5.2 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.99, 136.88, 135.52, 128.56, 128.12, 127.87, 122.58, 83.10, 69.19, 65.34, 47.92, 44.73, 37.96, 36.61, 35.61, 32.64, 31.77, 26.50, 25.81, 24.61, 18.01, -4.38, -4.70. HRMS (TOF MS EI) calcd for $C_{27}H_{44}ClN_3O_4Si$ $[M+Na]^+$ 560.2687, found 560.2686.

Determination of diastereomer ratio for carboxylic acid 26:



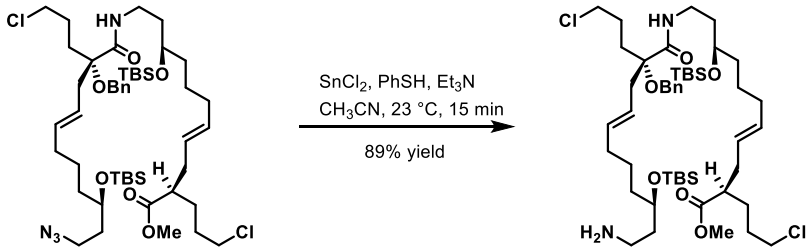
Amide 30: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (21 mg, 0.111 mmol, 1.5 equiv), (*R*)-(+)-alpha-methylbenzylamine (14 µL, 0.111 mmol, 1.5 equiv), and HOBt (15 mg, 0.111 mmol, 1.5 equiv) were added sequentially to a solution of acid **2** (40 mg, 0.074 mmol) in CH_2Cl_2 (0.42 mL). The solution was stirred at room temperature for 1h, then diluted with CH_2Cl_2 (5 mL) and washed with saturated aqueous sodium bicarbonate (5 mL), brine (5 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography (15% EtOAc-hexanes) to give amide **30** (43 mg, 0.067 mmol, 90% yield, dr 10:1) as a clear oil.

$[\alpha]_D^{25}$ –15.5° (*c* 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.27 (overlapping m, 11 H), 7.11 (overlapping d, J = 8.5 Hz, 1.10H), 5.55 (dt, J = 14.4, 7.1 Hz, 0.10H), 5.45 (dt, J = 14.1, 6.7 Hz, 1H), 5.37 (dt, J = 15.1, 7.3 Hz, 0.10H), 5.21 (dt, J = 14.8, 7.1 Hz, 1.10H), 5.13 (overlapping q, J = 7.4 Hz, 1.10H), 4.51 (overlapping d, J = 10.7 Hz, 1.10H), 4.45 (overlapping d, J = 10.7 Hz, 1.10H), 3.70 (overlapping dt, J = 10.7, 5.3 Hz, 1.10H), 3.60 (overlapping dt, J = 11.2, 5.8 Hz, 1.10H), 3.48 (overlapping ddd, J = 10.8, 8.3, 5.6 Hz, 1.10H), 3.41 – 3.24 (overlapping m, 2.20H), 2.62 (overlapping dd, J = 15.0, 6.5 Hz, 1.10H), 2.54 (overlapping dd, J = 14.9, 7.5 Hz, 1.10H), 2.01 (overlapping ddd, J = 9.5, 5.8, 3.3 Hz, 2.20H), 1.85 (overlapping p, J = 8.5, 7.8 Hz, 2.20H), 1.82 – 1.70 (overlapping m, 1.10H), 1.63 (overlapping dq, J = 11.6, 6.7 Hz, 2.20H), 1.45 (overlapping d, J = 7.0 Hz, 3.30H), 1.42 – 1.33 (overlapping m, 2.20H), 1.27 (overlapping h, J = 8.0, 7.4 Hz, 3.30H), 0.87 (overlapping s,9.90), 0.03 (overlapping d, J = 7.5 Hz, 6.60H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.69, 143.19, 137.79, 133.99, 128.51, 128.43, 127.67, 127.30, 127.14, 127.07, 125.96, 125.87, 123.59, 82.86, 69.06, 63.99, 48.28, 48.05, 47.87, 44.91, 37.99, 36.75, 36.68, 35.53, 35.47, 34.57, 32.72, 32.53, 31.68, 31.56, 31.49, 29.60, 26.58, 26.41, 25.76, 25.19, 24.63, 24.49, 22.56, 21.96, 17.94, 14.04, -4.41, -4.78. HRMS (TOF MS EI) calcd for $C_{35}H_{53}ClN_4O_3Si$ $[M+Na]^+$ 663.3473, found 663.3472.



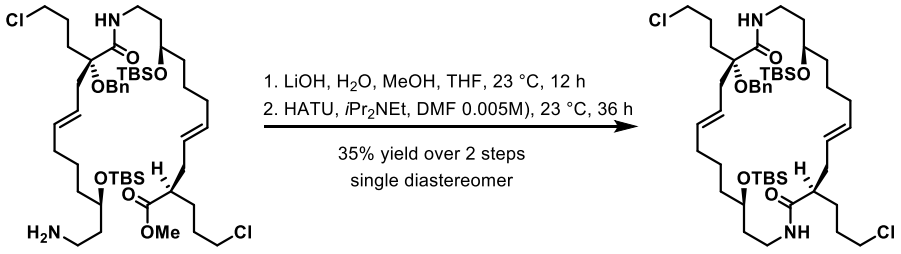
Amide 18: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (3.76 g, 19.64 mmol, 1.5 equiv), amine **3** (5.0 g, 12.09 mmol, 1.0 equiv), and HOBt (2.67 g, 19.64 mmol, 1.5 equiv) were added sequentially to a solution of acid **2** (7.05 g, 12.09 mmol) in CH_2Cl_2 (75 mL). The solution was stirred at room temperature for 1h, then diluted with CH_2Cl_2 (25 mL) and washed with saturated aqueous sodium bicarbonate (50 mL), brine (50 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography (15% EtOAc-hexanes) to give amide **18** (9.23 g, 9.82 mmol, 81% yield) as a clear oil.

$[\alpha]_D^{25}$ –11.1° (*c* 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 5H), 6.85 (t, J = 6.0 Hz, 1H), 5.51 (dt, J = 15.0, 6.7 Hz, 1H), 5.42 (dtt, J = 13.3, 6.6, 1.2 Hz, 1H), 5.36 – 5.25 (m, 2H), 4.50 (d, J = 10.4 Hz, 1H), 4.42 (d, J = 10.4 Hz, 1H), 3.76 – 3.72 (m, 1H), 3.66 (overlapping m and s, 4H), 3.58 (dt, J = 11.5, 5.8 Hz, 1H), 3.51 (td, J = 6.4, 2.3 Hz, 2H), 3.45 (ddd, J = 10.7, 8.5, 5.6 Hz, 1H), 3.38 – 3.29 (m, 3H), 3.22 – 3.16 (m, 1H), 2.64 (dd, J = 15.0, 7.5 Hz, 1H), 2.55 (dd, J = 15.0, 7.5 Hz, 1H), 2.41 (tt, J = 8.1, 5.9 Hz, 1H), 2.33 – 2.27 (m, 1H), 2.20 – 2.13 (m, 1H), 2.02 – 1.91 (m, 6H), 1.82 – 1.60 (m, 9H), 1.53 (dtd, J = 13.1, 8.3, 6.0 Hz, 1H), 1.45 – 1.38 (m, 4H), 1.38 – 1.27 (m, 4H), 0.86 (d, J = 16.3 Hz, 18H), 0.04 (d, J = 6.5 Hz, 6H), -0.02 (d, J = 14.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.60, 172.46, 137.71, 133.83, 132.87, 128.44, 127.78, 127.76, 126.51, 123.84, 123.78, 82.92, 69.97, 69.88, 69.09, 64.04, 51.39, 47.90, 44.94, 44.89, 44.53, 38.07, 36.70, 36.65, 36.57, 35.73, 35.55, 35.24, 32.69, 32.51, 31.59, 30.24, 28.75, 26.71, 25.79, 24.81, 24.66, 17.96, -4.39, -4.44, -4.66, -4.75. HRMS (TOF MS EI) calcd for $C_{48}H_{84}Cl_2N_4O_6Si_2$ $[M+Na]^+$ 961.5204, found 961.5212.



Amine 27: Prepared according to a modification of the literature procedure[5]: thiophenol (4.50 mL, 44.04 mmol, 6.0 equiv) and triethylamine (4.60 mL, 33.03 mmol, 4.50 equiv) were added to a solution of anhydrous $SnCl_2$ (2.10 g, 11.01 mmol, 1.50 equiv) in acetonitrile (43 mL). The mixture turned bright yellow and was let to stir at room temperature for 15 min. Solution of azide **18** (6.90 g, 7.34 mmol) in acetonitrile (30 mL) was added and the mixture was stirred at room temperature for 15 min when it was concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 (30 mL) and washed with 2M aqueous NaOH (20 mL). It was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified using 3.5-inch silica plug (20% EtOAc-CH_2Cl_2 then 20% MeOH-1% NH_4OH-CH_2Cl_2) to afford amine **19** (5.97 g, 6.53 mmol, 89% yield) as a pale-yellow oil.

$[\alpha]_D^{25}$ –5.6° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.30 (m, 4H), 6.85 (t, J = 6.0 Hz, 1H), 5.54 – 5.47 (m, 1H), 5.46 – 5.39 (m, 1H), 5.35 – 5.26 (m, 2H), 4.49 (d, J = 10.4 Hz, 1H), 4.41 (d, J = 10.4 Hz, 1H), 3.76 – 3.69 (m, 1H), 3.65 (s, 3H), 3.65 – 3.62 (m, 1H), 3.57 (dt, J = 11.5, 5.8 Hz, 1H), 3.51 (td, J = 6.4, 2.2 Hz, 2H), 3.45 (ddd, J = 10.7, 8.5, 5.6 Hz, 1H), 3.35 (ddt, J = 13.0, 8.6, 6.0 Hz, 1H), 3.22 – 3.13 (m, 1H), 2.80 (s, 2H), 2.66 – 2.60 (m, 1H), 2.54 (dd, J = 15.1, 7.5 Hz, 1H), 2.40 (tt, J = 8.0, 5.7 Hz, 1H), 2.30 (dt, J = 13.9, 7.4 Hz, 1H), 2.21 – 2.12 (m, 1H), 2.06 – 1.88 (m, 6H), 1.83 – 1.58 (m, 4H), 1.56 – 1.46 (m, 1H), 1.40 (ddd, J = 11.6, 6.0, 3.7 Hz, 4H), 1.36 – 1.22 (m, 4H), 0.85 (d, J = 14.9 Hz, 18H), 0.03 (d, J = 9.2 Hz, 6H), -0.02 (d, J = 15.0 Hz, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.60, 172.48, 137.71, 133.94, 132.87, 128.43, 127.77, 126.49, 123.74, 123.69, 82.91, 70.27, 69.86, 64.05, 51.40, 44.94, 44.89, 44.53, 38.08, 36.64, 36.55, 35.71, 35.23, 32.73, 32.50, 31.59, 30.23, 28.74, 26.70, 25.81, 25.79, 24.86, 24.81, 17.96, -4.43, -4.59, -4.66. HRMS (TOF MS EI) calcd for $C_{48}H_{86}Cl_2N_2O_6Si_2$ $[M+Na]^+$ 913.5480, found 913.5471.



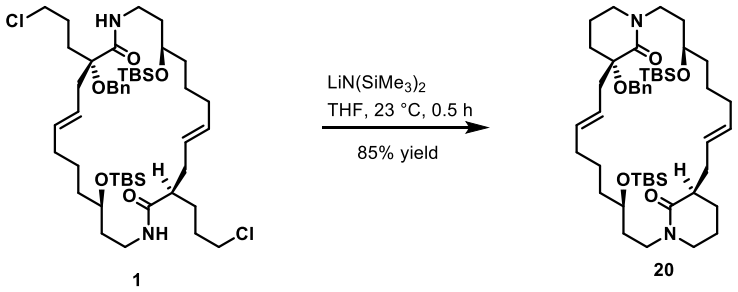
19 1

Macrocyclic bis-lactam 1: Lithium hydroxide (0.93 g, 22.21 mmol, 10 equiv) was added to a solution of ester **19** (2.0 g, 2.22 mmol) in MeOH (15 mL) and water (5 mL) at 0 °C. The mixture was warmed up to room temperature and THF (20 mL) was added. Reaction was cooled down back to 0 °C after 12 h, diluted with THF (20 mL) and quenched with 1M aqueous HCl (23 mL). The mixture was concentrated *in vacuo* and the residue was purified using 3.5 inch silica plug (20% MeOH-1% NH_4OH-CH_2Cl_2), concentrated *in vacuo* and submitted to the next step.

Amino acid from the previous step (6.36 g) was dissolved in anhydrous *N*,*N*-dimethylformamide (2.4 L) under argon. *N*,*N*-Diisopropylethylamine (4.90 mL, 28.28 mmol, 4.0 equiv) and HATU (4.0 g, 10.61 mmol, 1.5 equiv) were added, the mixture turned bright yellow and was let to stir at room temperature for 36 h. DMF was distilled off under reduced pressure (0.2 mmHg) into a receiving flask cooled to –78 °C. The residue was dissolved in EtOAc (30 mL) and washed with water (3x100 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (40% EtOAc-hexanes) to give of macrolactam **1** (2.15 g, 2.44 mmol, 35% yield over two steps) as a single diastereomer, and as a white foam.

$[\alpha]_D^{25}$ +13.6° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.30 (m, 5H), 6.91 (dd, J = 7.9, 4.4 Hz, 1H), 6.25 (t, J = 4.9 Hz, 1H), 5.53 (dt, J = 15.2, 6.4 Hz, 1H), 5.43 (dt, J = 15.0, 6.4 Hz, 1H), 5.30 (dq, J = 15.0, 7.3 Hz, 2H), 4.49 (d, J = 10.5 Hz, 1H), 4.43 (d, J = 10.5 Hz, 1H), 3.87 –

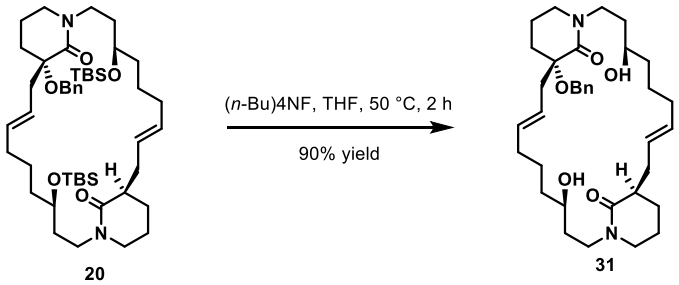
3.79 (m, 1H), 3.73 (dq, J = 9.5, 5.2 Hz, 1H), 3.58 (dt, J = 11.1, 5.7 Hz, 1H), 3.55 – 3.41 (m, 3H), 3.36 (ddt, J = 14.2, 9.8, 5.1 Hz, 1H), 3.30 – 3.21 (m, 1H), 3.02 (ddt, J = 13.2, 8.8, 5.3 Hz, 1H), 2.56 (qd, J = 14.8, 7.0 Hz, 2H), 2.25 (ddd, J = 13.8, 10.6, 7.5 Hz, 1H), 2.10 (dt, J = 13.6, 5.1 Hz, 1H), 1.96 (dtd, J = 38.4, 14.4, 12.6, 6.1 Hz, 7H), 1.83 – 1.66 (m, 4H), 1.62 (ddq, J = 13.4, 9.2, 4.7 Hz, 1H), 1.58 – 1.26 (m, 7H), 0.86 (d, J = 18.6 Hz, 18H), 0.05 (s, 3H), 0.01 (d, J = 5.7 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) 174.12, 172.24, 137.72, 133.59, 132.33, 128.40, 127.70, 127.68, 126.76, 123.37, 83.21, 71.38, 70.56, 63.88, 47.80, 47.78, 44.92, 44.71, 38.09, 37.47, 36.54, 36.29, 36.26, 36.20, 35.82, 34.57, 32.87, 32.64, 31.24, 30.60, 30.01, 26.61, 25.81, 25.79, 24.88, 24.46, 17.94, 17.87, -4.47, -4.62, -4.67. HRMS (TOF MS EI) calcd for $C_{47}H_{82}Cl_2N_2O_5Si_2$ $[M+Na]^+$ 903.5037, found 903.5037.



1 20

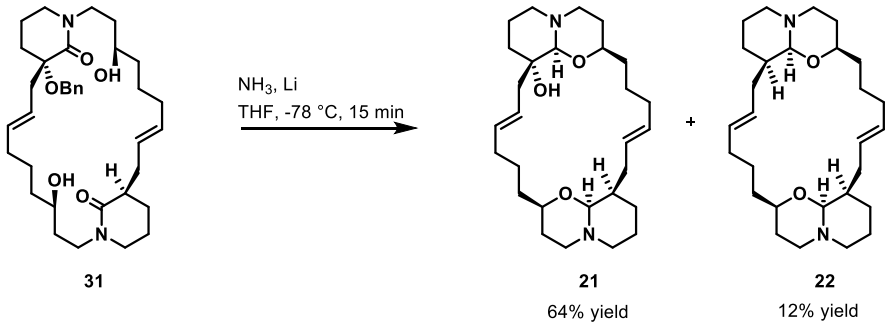
Bis-Lactam 20: Lithium bis(trimethylsilyl)amide (0.5M in THF, 5.25 mL, 2.63 mmol, 2.10 equiv) was added dropwise to a solution of macrocyclic bis-macrolactam **1** (1.10 g, 1.25 mmol) in anhydrous THF (6.20 mL) under argon. Saturated aq. NH_4Cl (6 mL) was added, and the mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc-hexanes) to give bis-lactam **20** (0.86 g, 1.06 mmol, 85% yield) as a white foam.

$[\alpha]_D^{25}$ +18.1° (*c* 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 4H), 7.25 – 7.20 (m, 1H), 5.49 (ddt, J = 28.1, 15.3, 6.4 Hz, 2H), 5.40 (dt, J = 15.3, 6.7 Hz, 1H), 5.26 (ddd, J = 15.0, 8.1, 6.3 Hz, 1H), 4.67 (d, J = 11.6 Hz, 1H), 4.53 (d, J = 11.7 Hz, 1H), 3.79 (ddd, J = 13.1, 8.9, 6.3 Hz, 1H), 3.68 (dq, J = 11.9, 5.7 Hz, 2H), 3.43 (dt, J = 13.9, 7.1 Hz, 1H), 3.36 (dt, J = 13.6, 7.0 Hz, 1H), 3.29 (ddd, J = 11.9, 10.4, 4.9 Hz, 1H), 3.21 (dddd, J = 16.2, 11.9, 9.5, 4.6 Hz, 3H), 3.06 – 2.96 (m, 2H), 2.42 (dt, J = 13.2, 6.5 Hz, 1H), 2.37 – 2.27 (m, 2H), 2.20 (dd, J = 13.1, 8.2 Hz, 1H), 2.17 – 2.09 (m, 1H), 1.97 (tq, J = 8.2, 5.4, 4.5 Hz, 5H), 1.92 – 1.82 (m, 3H), 1.79 – 1.62 (m, 5H), 1.62 – 1.53 (m, 1H), 1.50 (ddd, J = 12.1, 9.4, 6.3 Hz, 1H), 1.40 (dddd, J = 20.9, 19.0, 11.4, 4.7 Hz, 6H), 1.32 – 1.23 (m, 1H), 0.88 (d, J = 1.1 Hz, 18H), 0.04 (d, J = 8.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) 171.45, 168.13, 139.38, 134.43, 132.27, 128.00, 127.76, 127.25, 126.91, 124.91, 77.34, 70.51, 70.12, 65.76, 48.44, 48.05, 43.84, 43.81, 41.71, 38.80, 36.21, 35.55, 34.93, 33.93, 33.65, 32.46, 31.92, 26.37, 25.79, 25.02, 24.95, 22.06, 18.75, 17.96, -4.47, -4.52. HRMS (TOF MS EI) calcd for $C_{47}H_{80}N_2O_5Si_2$ $[M+Na]^+$ 831.5504, found 831.5507.



Macrocyclic diol 31: Tetra-*n*-butylammonium fluoride (1M in THF, 4.0 mL, 3.96 mmol, 4 equiv) was added to the flask with macrolactam **20** (0.80 g, 0.99 mmol) at 0 °C. The reaction mixture was heated to 50 °C for 2 h, when it was quenched with saturated aq. NH_4Cl (4 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with water (5 x 10 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (30% acetone-hexanes to 50% acetone-hexanes) to give macrolactam **31** (0.52 g, 0.891 mmol, 90% yield) as a white foam.

$[\alpha]_D^{25}$ +19.1˚ (*c* 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (d, J = 6.5 Hz, 4H), 7.20 (t, J = 6.7 Hz, 1H), 5.47 (dddt, J = 27.5, 22.0, 15.4, 6.3 Hz, 3H), 5.21 (ddd, J = 15.0, 8.8, 5.5 Hz, 1H), 4.64 (d, J = 11.6 Hz, 1H), 4.51 (d, J = 11.6 Hz, 1H), 3.82 (dt, J = 13.7, 6.9 Hz, 1H), 3.64 (ddd, J = 13.9, 9.9, 3.8 Hz, 1H), 3.54 (dq, J = 10.3, 6.0 Hz, 1H), 3.37 (qd, J = 10.3, 8.9, 4.2 Hz, 2H), 3.25 (td, J = 11.2, 9.4, 4.6 Hz, 2H), 3.21 – 3.16 (m, 2H), 3.11 (dd, J = 12.9, 5.4 Hz, 1H), 3.03 (dt, J = 13.3, 6.4 Hz, 1H), 2.33 (tq, J = 15.7, 6.7, 5.7 Hz, 3H), 2.13 (dq, J = 18.6, 7.1, 6.6 Hz, 1H), 2.07 – 1.98 (m, 4H), 1.91 (dddd, J = 28.1, 19.1, 10.6, 3.6 Hz, 5H), 1.75 (dd, J = 10.9, 4.8 Hz, 1H), 1.68 (dh, J = 13.8, 6.9 Hz, 3H), 1.59 (pd, J = 9.8, 4.0 Hz, 3H), 1.55 – 1.36 (m, 8H). ^{13}C NMR (126 MHz, $CDCl_3$) □ 172.86, 168.62, 139.22, 134.54, 132.09, 128.02, 127.71, 127.18, 126.96, 124.64, 77.38, 77.20, 68.83, 66.68, 65.63, 48.48, 47.86, 44.43, 43.58, 41.73, 39.17, 35.85, 35.72, 35.08, 34.95, 34.64, 31.72, 31.64, 31.60, 26.60, 24.76, 24.49, 21.93, 18.55. HRMS (TOF MS EI) calcd for $C_{35}H_{52}N_2O_5$ $[M+Na]^+$ 603.3774, found 603.3779.

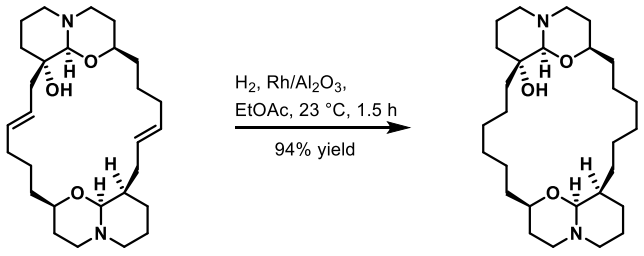


Bis-1-oxaquinolizidine 21 and 22: The outlet of the ammonia lecture bottle (anhydrous, ≥99.98%, Sigma Aldrich) was connected through a Teflon tube to a 25 mL round recovery flask with a glass stirring bar serving as a receiving vessel. The receiving flask was cooled to –78 °C and 5.0 mL of ammonia was condensed. Small pieces of lithium (46 mg, 6.63 mmol, 30 equiv)

were added in portions and solution immediately turned deep blue. The mixture was stirred for 4 h at –40 °C, then cooled back to –78 °C. THF was added (2.50 mL), followed with macrocyclic diol **31** (0.13 g, 0.221 mmol) in THF (2.50 mL). The reaction mixture stayed deep blue and was stirred for 15 min at –78 °C before it was quenched with solid NH_4Cl (2 g), diluted with THF (5.0 mL), warmed to room temperature. Water (3 mL) was carefully added and the solution was transferred to a separatory funnel containing 1M aqueous NaOH (7 mL), extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by reverse column chromatography (10% water-MeOH) to give **21** (65 mg, 0.140 mmol, 64% yield) and **22** (12 mg, 0.026 mmol, 12% yield) both as a clear oil.

21: $[\alpha]_D^{25}$ –5.8° (*c* 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.55 (t, J = 4.3 Hz, 2H), 5.50 – 5.43 (m, 1H), 5.37 (ddd, J = 14.8, 9.0, 5.1 Hz, 1H), 4.20 (d, J = 3.3 Hz, 1H), 3.94 (s, 1H), 3.54 – 3.40 (m, 2H), 3.19 – 3.11 (m, 1H), 3.09 – 2.99 (m, 3H), 2.99 – 2.90 (m, 2H), 2.50 (s, 1H), 2.39 (dt, J = 10.7, 3.3 Hz, 1H), 2.36 – 2.30 (m, 2H), 2.16 – 2.01 (m, 4H), 1.96 – 1.84 (m, 3H), 1.82 – 1.23 (m, 19H), 1.08 – 0.97 (m, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 134.26, 132.03, 127.48, 123.96, 87.43, 76.82, 76.54, 71.02, 52.67, 52.51, 45.19, 41.29, 40.40, 35.85, 35.66, 35.52, 32.30, 31.97, 26.19, 25.95, 25.68, 25.33, 25.26, 20.93. HRMS (TOF MS EI) calcd for $C_{28}H_{46}N_2O_3$ $[M+H]^+$ 459.3586, found 459.3586.

22: $[\alpha]_D^{25}$ -22.1° (*c* 0.50, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.52 – 5.43 (m, 2H), 5.35 (ddd, J = 14.8, 9.0, 5.1 Hz, 2H), 4.20 (d, J = 3.2 Hz, 2H), 3.45 (ddt, J = 14.7, 9.7, 2.8 Hz, 2H), 3.15 (td, J = 13.4, 3.5 Hz, 2H), 3.05 (ddd, J = 12.3, 10.6, 3.1 Hz, 2H), 2.94 (ddd, J = 13.7, 4.5, 1.6 Hz, 2H), 2.39 (dt, J = 10.8, 3.3 Hz, 2H), 2.20 – 2.01 (m, 4H), 1.89 (ddt, J = 31.9, 12.8, 5.5 Hz, 4H), 1.78 – 1.41 (m, 14H), 1.40 – 1.20 (m, 6H), 1.01 (dp, J = 13.2, 1.8 Hz, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 132.21, 127.34, 87.43, 76.50, 52.67, 45.17, 40.33, 32.08, 29.68, 26.18, 25.89, 25.41. HRMS (TOF MS EI) calcd for $C_{28}H_{46}N_2O_2$ $[M+H]^+$ 443.3629 found 443.3629.

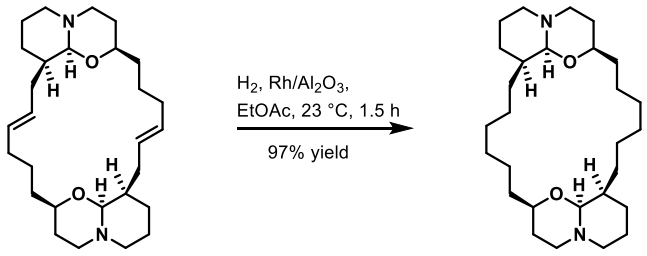


21 (+)-dmXe B

(+)-Desmethylxestospongin B: Bis-1-oxaquinolizidine **21** (36 mg, 0.0785 mmol) was dissolved in dry EtOAc (3.60 mL), and 5 wt. % Rh/Al_2O_3 (18 mg) was added. The atmosphere in the flask was exchanged with hydrogen (a hydrogen balloon was inserted into the flask along with a hypodermic needle; the hypodermic needle was removed after 5 min). The solution was stirred for at room temperature for 1.5 h under a hydrogen atmosphere, then filtered through syringe

filter (Acrodics, 13 mm, 0.2µm PFTE) and concentrated *in vacuo* to give (+)-desmethylxestospongin B (34.3 mg, 0.0741 mmol, 94% yield) as a white foam.

$[\alpha]_D^{25}$ +5.1° (*c* 0.40, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 4.28 (d, J = 3.2 Hz, 1H), 4.03 (s, 1H), 3.52 (dt, J = 22.1, 10.8 Hz, 2H), 3.17 (td, J = 14.0, 13.5, 3.5 Hz, 1H), 3.12 – 2.98 (m, 3H), 2.94 (ddd, J = 13.1, 7.4, 4.6 Hz, 2H), 2.45 (s, 1H), 2.39 (dd, J = 10.5, 3.6 Hz, 1H), 2.35 – 2.28 (m, 1H), 1.75 (dtt, J = 23.0, 11.5, 6.1 Hz, 3H), 1.69 (s, 1H), 1.62 – 1.45 (m, 9H), 1.44 – 1.22 (m, 16H), 1.20 – 1.06 (m, 6H), 1.05 – 0.97 (m, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 90.32, 87.42, 76.40, 76.15, 70.72, 52.46, 52.40, 45.09, 44.20, 40.04, 38.45, 36.17, 36.07, 32.84, 32.19, 31.63, 31.50, 29.50, 29.41, 27.06, 26.13, 26.05, 25.95, 25.20, 24.81, 24.80, 22.65, 20.87. HRMS (TOF MS El) calcd for $C_{28}H_{50}N_2O_3$ $[M+H]^+$ 463.3900, found 463.3900.



22 **(⍰)-Ar B**

(–)-Araguspongine B: Bis-1-oxaquinolizidine **22** (16 mg, 0.0361 mmol) was dissolved in dry EtOAc (1.60 mL), and 5 wt. % Rh/Al_2O_3 (8 mg) was added. The atmosphere in the flask was exchanged with hydrogen (a hydrogen balloon was inserted into the flask along with a hypodermic needle; the hypodermic needle was removed after 5 min). The solution was stirred for at room temperature for 1.5 h under a hydrogen atmosphere, then filtered through syringe filter (Acrodics, 13 mm, 0.2µm PFTE) and concentrated *in vacuo* to give (–)-araguspongine B (15.6 mg, 0.0349 mmol, 97% yield) as a white solid.

$[\alpha]_D^{25}$ –12.5° (*c* 0.44, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 4.29 (d, J = 3.2 Hz, 2H), 3.52 (tt, J = 10.8, 2.3 Hz, 2H), 3.17 (td, J = 13.4, 3.5 Hz, 2H), 3.05 (ddd, J = 12.8, 10.8, 3.1 Hz, 2H), 2.95 (ddd, J = 13.8, 4.6, 1.6 Hz, 2H), 2.39 (dt, J = 10.9, 3.3 Hz, 2H), 1.78 – 1.70 (m, 2H), 1.67 (ddt, J = 16.1, 6.2, 3.7 Hz, 2H), 1.57 (ddt, J = 13.6, 9.2, 4.2 Hz, 8H), 1.47 (qd, J = 12.0, 4.4 Hz, 2H), 1.43 – 1.22 (m, 15H), 1.13 (dddd, J = 26.1, 18.2, 9.9, 4.0 Hz, 7H), 1.02 (ddt, J = 13.2, 3.6, 1.8 Hz, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 87.36, 75.96, 52.73, 45.17, 40.41, 36.22, 32.98, 31.74, 29.46, 27.32, 26.48, 26.24, 25.74, 24.74. HRMS (TOF MS El) calcd for $C_{28}H_{50}N_2O_2$ $[M+H]^+$ 447.3951, found 447.3944.

Table S1: Comparison of ^1H NMR Data for Natural[8] and Synthetic (+)-desmethylxestospongin B in C_6D_6:

Proton	Natural dmXeB (250 MHz)	Synthetic dmXeB (600 MHz)

H-2	3.40 (br t, J=10.8 Hz)	3.46 – 3.34 (m)
H-3α	0.65 (br d, J=13.5 Hz)	0.64 (dt, J = 13.5, 2.7 Hz)
H-4α	2.80 - 2.60 (m)	2.70 – 2.57 (m)
H-4β	2.95 - 2.80 (m)	2.95 – 2.83 (m)
H-6α	3.20 - 3.00 (m)	3.09 (td, J = 11.2, 5.2 Hz)
H-6β	2.33 (ddd, J=10.3, 2.3, 2.3 Hz)	2.33 (dd, J = 10.4, 3.6 Hz)
H-10	4.18 (s)	4.15 (s)
H-2′	3.40 (br t, J=10.8 Hz)	3.46 – 3.34 (m)
H-3′α	0.65 (br d, J=13.5 Hz)	0.70 (dt, J = 14.6, 2.8 Hz)
H-4′α	2.80 - 2.60 (m)	2.79 (ddd, J = 13.8, 4.6, 1.5 H)
H-4′β	2.95 - 2.80 (m)	2.95 – 2.83 (m)
H-6′α	3.30 - 2.90 (m)	3.09 (td, J = 11.2, 5.2 Hz)
H-6′β	2.09 (br d, J=10.2 Hz)	2.07 (dt, J = 10.9, 2.9 Hz)
H-10′	4.41 (br d, J=1.5 Hz)	4.38 (s)

Table S2: Comparison of ^{13}C NMR Data for Natural[8] and Synthetic (+)-desmethylxestospongin B in C_6D_6:

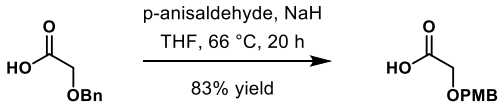
Carbon	Natural dmXeB (250 MHz)	Synthetic dmXeB (600 MHz)
C-2	76.5	76.7
C-4	52.7	53.0
C-6	45.6	45.9
C-9	70.7	71.0
C-10	91.2	91.4
C-2′	76.2	76.4
C-4′	53.0	53.3
C-6′	45.5	44.8
C-9′	40.7	40.9
C-10′	87.9	88.2

Table S3: Comparison of ^{1}H NMR Data for Natural[9] and Synthetic (–)-araguspongine B in $CDCl_3$:

Proton	Natural ArB (250 MHz)	Synthetic ArB (600 MHz)
H-2	3.53 (br t, J=11.0 Hz)	3.52 (tt, J = 10.8, 2.3 Hz)
H-4α	2.95 (ddd, J=13.7, 3.1, 1.5 Hz)	2.95 (ddd, J = 13.8, 4.6, 1.6 Hz)
H-4β	3.18 (ddd, J=13.7, 13.4, 3.1 Hz)	3.17 (td, J = 13.4, 3.5 Hz)
H-10	4.30 (d, J=2.8 Hz)	4.29 (d, J = 3.2 Hz)

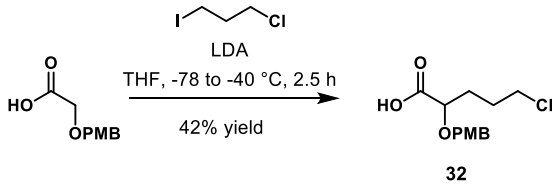
Table S4: Comparison of ^{13}C NMR Data for Natural[9] and Synthetic (–)-araguspongine B in $CDCl_3$:

Carbon	Natural ArB (250 MHz)	Synthetic ArB (600 MHz)
C-2	76.0	75.96
C-4	52.8	52.73
C-6	45.3	45.17
C-9	40.5	40.41
C-10	87.5	87.36



2-((4-methoxybenzyl)oxy)acetic acid: Prepared according to a modification of the literature procedure[10]: Sodium hydride (1.54 g, 38.4 mmol, 2.4 equiv) was added in portions to a solution of bromoacetic acid (2.20 g, 16.0 mmol) and p-anisaldehyde (2.0 mL, 16.0 mmol) in THF (29 mL) at 0 °C under argon. The suspension was heated at reflux for 20 h when it was quenched with methanol (2 mL) and concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL) and washed with water (3 x 20 mL). The combined aqueous layers were acidified with 1 M HCl to pH=4, and the resulting solution was extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue afforded 2-((4-methoxybenzyl)oxy)acetic acid (2.60 g, 13.25 mmol, 83% yield) as a clear oil that was used immediately without further purification.

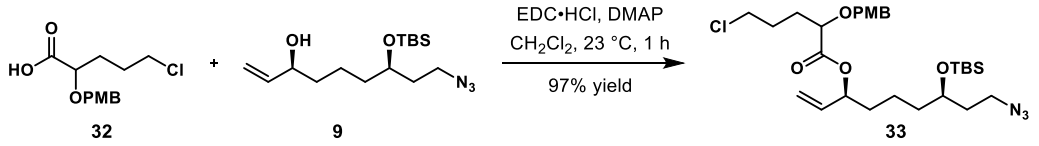
^1H and ^{13}C NMR spectral data matched that reported in the literature.[9]



Acid 32: *n*-Butyllithium (2.40M in hexanes, 16.35 ml, 39.25 mmol, 2.20 equiv) was added to a solution of diisopropylamine (5.77 mL, 41.03 mmol, 2.30 equiv) in THF (53 ml) at –78 °C, and the mixture was stirred for 20 min. Solution of 2-((4-methoxybenzyl)oxy)acetic acid (3.50 g, 17.84 mmol) in THF (30 mL then 3 x 2.0 mL rinses) was added. The solution was stirred 1 h at –78 °C, when 1-chloro-3-iodopropane (5.75 mL, 53.52 mmol, 3 equiv) was added. The solution was stirred 0.5 h at –78 °C, then 2 h at –40 °C. The reaction mixture was then diluted with EtOAc (30 mL) and washed with 1M aqueous HCl (50 mL), brine (50 mL), dried over Na_2SO_4,

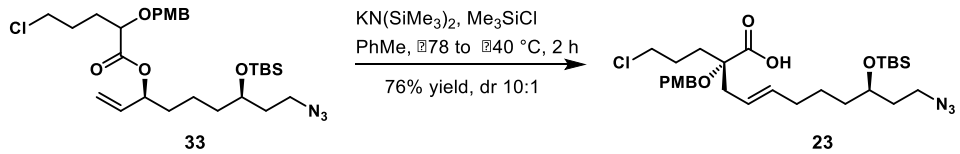
filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (60% EtOAc-hexanes to 60% EtOAc-1% AcOH-hexanes) to give acid **32** (2.06 g, 7.55 mmol, 42% yield) as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 11.26 (s, 1H), 7.34 – 7.19 (m, 2H), 6.98 – 6.80 (m, 2H), 4.69 (d, J = 11.2 Hz, 1H), 4.41 (d, J = 11.3 Hz, 1H), 4.00 (dd, J = 7.2, 4.1 Hz, 1H), 3.81 (s, 3H), 3.55 – 3.41 (m, 2H), 2.07 – 1.74 (m, 4H).^{13}C NMR (126 MHz, $CDCl_3$) δ 178.02, 159.50, 129.80, 128.87, 113.88, 76.11, 72.14, 55.23, 44.38, 29.85, 28.16. HRMS (TOF MS EI) calcd for $C_{13}H_{17}ClO_4$ $[M+Na]^+$ 295.0708, found 295.0708.



Ester 33: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (1.47 g, 9.44 mmol, 2 equiv), was added to a solution of acid **32** (2.06 g, 7.55 mmol, 1.6 equiv) in CH_2Cl_2 (17 mL). A solution of alcohol **9** (1.50 g, 4.72 mmol) in CH_2Cl_2 (10 mL, then 3 x 1 mL rinses) was then added, followed by the addition of 4-dimethylaminopyridine (0.120 g, 0.944 mmol, 0.2 equiv). The solution was stirred at room temperature for 1 h, then diluted with additional CH_2Cl_2 (40 mL) and washed with brine (50 mL). The organic layer was dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (6% EtOAc-hexanes) to give ester **33** (2.60 g, 4.58 mmol, 97% yield) as a clear oil.

$[\alpha]_D^{25}$ –4.1° (*c* 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.22 (m, 2H), 6.96 – 6.78 (m, 2H), 5.79 (dddd, J = 17.2, 10.4, 8.0, 6.7 Hz, 1H), 5.36 – 5.25 (m, 2H), 5.23 (dt, J = 10.5, 1.1 Hz, 1H), 4.66 (dd, J = 11.3, 5.0 Hz, 1H), 4.33 (d, J = 11.2 Hz, 1H), 3.94 (dq, J = 5.3, 1.6 Hz, 1H), 3.81 (s, 3H), 3.77 (qd, J = 6.9, 3.5 Hz, 1H), 3.51 (td, J = 5.7, 1.9 Hz, 2H), 3.35 (tdt, J = 10.2, 7.3, 3.8 Hz, 2H), 2.00 – 1.80 (m, 4H), 1.73 – 1.58 (m, 4H), 1.53 – 1.44 (m, 2H), 1.37 (dttd, J = 20.9, 14.1, 10.5, 10.0, 7.0 Hz, 2H), 0.89 (d, J = 2.4 Hz, 9H), 0.06 (t, J = 4.0 Hz, 6H).^{13}C NMR (126 MHz, $CDCl_3$) δ 171.67, 159.37, 135.93, 135.83, 129.62, 129.38, 129.36, 117.77, 117.38, 113.78, 75.39, 75.32, 71.82, 69.07, 69.04, 55.20, 47.87, 44.51, 36.88, 35.58, 35.51, 34.21, 30.22, 30.17, 28.37, 28.34, 25.78, 20.59, 20.57, 17.97, -4.39, -4.41, -4.62, -4.71, -4.74. HRMS (TOF MS EI) calcd for $C_{28}H_{46}ClN_3O_5Si$ $[M+Na]^+$ 590.2793, found 590.2793.

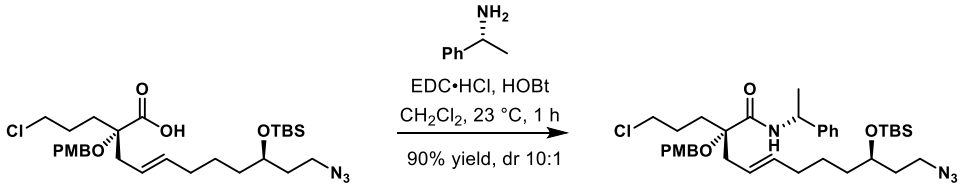


Carboxylic acid 23: Prepared according to a modification of the literature procedure[7]: flame-dried 100 mL round bottom flask was brought into a nitrogen-filled glove box and charged with $KN(SiMe_3)_2$ (2.00 g, 10.08 mmol, 2.2 equiv). The flask was capped, removed from the

glove box, attached to a Schlenk line, and backfilled with argon three times. Toluene (16 mL) was then added to the flask and the solution was cooled to –78 °C. A solution of ester **33** (2.60 g, 4.58 mmol) in PhMe (14 mL then 2 x 1 mL rinses) was added dropwise and the resulting solution was stirred 30 min. Chlorotrimethylsilane (1.20 mL, 1.03 g, 9.16 mmol, 2 equiv) was then added dropwise, and the solution was stirred 1h at –78 °C and 1h at –40 °C, The solution was then poured into a separatory funnel containing 1M aqueous HCl (10 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 15 mL), the combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes) to give acid **23** (1.98 g, 3.48 mmol, 76% yield, dr 10:1) as a clear oil.

$[\alpha]_D^{25}$ +0.2° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 2H), 6.94 – 6.88 (m, 2H), 5.60 (ddd, *J* = 15.0, 7.4, 6.1 Hz, 1H), 5.41 – 5.32 (m, 1H), 4.50 (d, *J* = 9.8 Hz, 1H), 4.42 (d, *J* = 9.8 Hz, 1H), 3.82 (s, 3H), 3.79 – 3.73 (m, 1H), 3.62 (dt, *J* = 11.0, 5.6 Hz, 1H), 3.50 (ddd, *J* = 10.8, 8.6, 4.9 Hz, 1H), 3.37 – 3.30 (m, 2H), 2.70 – 2.57 (m, 2H), 2.14 (ddd, *J* = 14.3, 11.9, 4.2 Hz, 1H), 2.06 – 1.96 (m, 3H), 1.86 (dddd, *J* = 20.2, 13.8, 7.2, 4.6 Hz, 1H), 1.81 – 1.72 (m, 1H), 1.72 – 1.63 (m, 2H), 1.47 – 1.33 (m, 4H), 0.88 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.57, 159.58, 135.49, 129.57, 128.85, 122.60, 113.99, 83.09, 69.19, 64.95, 55.27, 47.93, 44.71, 38.00, 36.62, 35.63, 32.64, 31.69, 26.52, 25.82, 24.63, 18.01, -4.38, -4.70. HRMS (TOF MS EI) calcd for $C_{28}H_{46}ClN_3O_5Si$ $[M+Na]^+$ 590.2793, found 590.2781.

Determination of diastereomer ratio for carboxylic acid 23:

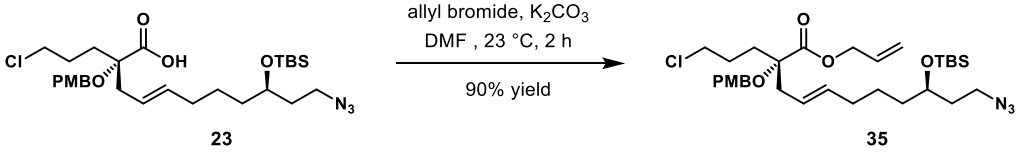


23 **34**

Amide 34: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (10 mg, 0.053 mmol, 3 equiv), (*R*)-(+)-alpha-methylbenzylamine (7 µL, 0.058 mmol, 3 equiv), and HOBt (7 mg, 0.053 mmol, 3 equiv) were added sequentially to a solution of acid **23** (10 mg, 0.018 mmol) in CH_2Cl_2 (0.10 mL). The solution was stirred at room temperature for 1h, then diluted with CH_2Cl_2 (2 mL) and saturated aqueous sodium bicarbonate (2 mL), brine (2 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography (15% EtOAc-hexanes) to give amide **34** (11 mg, 0.016 mmol, 90% yield, dr 10:1) as a clear oil.

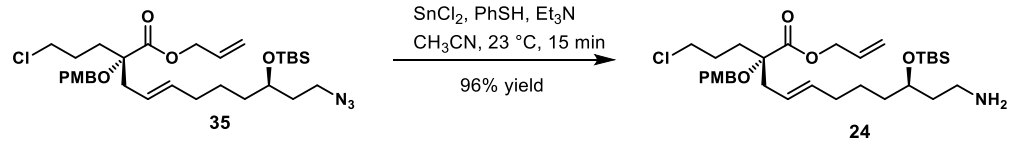
$[\alpha]_D^{25}$ +14.5° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.35 – 7.17 (overlapping m, 11H), 7.09 (overlapping d, J = 8.5 Hz, 1H), 6.93 – 6.85 (overlapping m, 2.20H), 5.54 (dq, J = 15.0, 7.8, 7.3 Hz, 0.10H), 5.45 (dt, J = 15.2, 6.8 Hz, 1H), 5.26 – 5.17 (m, 1H), 5.17 – 5.06 (overlapping m, 1.10H), 4.43 (overlapping d, J = 10.1 Hz, 1.10H), 4.37 (overlapping d, J = 10.2 Hz, 1.10H), 3.82

(overlapping s, 3.30H), 3.77 – 3.67 (m, 1H), 3.61 (dt, J = 11.2, 5.8 Hz, 1H), 3.48 (overlapping ddd, J = 10.7, 8.4, 5.6 Hz, 1.10H), 3.39 – 3.23 (overlapping m, 2.20H), 2.66 – 2.57 (overlapping m, 1.10H), 2.53 (overlapping dd, J = 14.9, 7.4 Hz, 1.10H), 2.07 – 1.93 (overlapping m, 2.20H), 1.87 (overlapping q, J = 7.3 Hz, 2.20H), 1.82 (ddd, J = 11.0, 8.3, 5.4 Hz, 1H), 1.79 (overlapping s, 1.10H), 1.69 – 1.60 (m, 2H), 1.60 (overlapping s, 2.20H), 1.45 (overlapping d, J = 6.9 Hz, 3.30H), 1.41 – 1.33 (overlapping m, 2.20H), 1.32 – 1.23 (overlapping m, 3.30H), 0.87 (overlapping s, 9.90H), 0.04 (overlapping d, J = 7.8 Hz, 6.60H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.93, 159.28, 143.25, 134.02, 129.91, 129.03, 128.50, 127.15, 126.07, 125.07, 123.75, 113.92, 110.83, 82.82, 69.19, 64.16, 63.82, 55.28, 48.24, 48.12, 47.98, 45.04, 38.05, 36.80, 35.59, 32.65, 31.77, 29.69, 26.68, 25.85, 24.64, 22.00, 18.04, 17.90, 17.86, 11.85, 11.82, -4.32, -4.69. HRMS (TOF MS EI) calcd for $C_{36}H_{55}ClN_4O_4Si$ $[M+Na]^+$ 693.3579, found 693.3589.



Allyl Ester 35: Potassium carbonate (0.20 g, 1.41 mmol, 1.10 equiv) was added to a solution of acid **23** (0.73 g, 1.28 mmol) and allyl bromide (0.33 mL, 3.84 mmol, 3 equiv) in DMF (2.60 mL). The solution was stirred at room temperature for 2 h, then diluted with water (5 mL) and hexanes (5 mL) and washed with 1M HCl (5 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (5% EtOAc-hexanes) to give allyl ester **35** (0.70 g, 1.15 mmol mmol, 90% yield) as a clear oil.

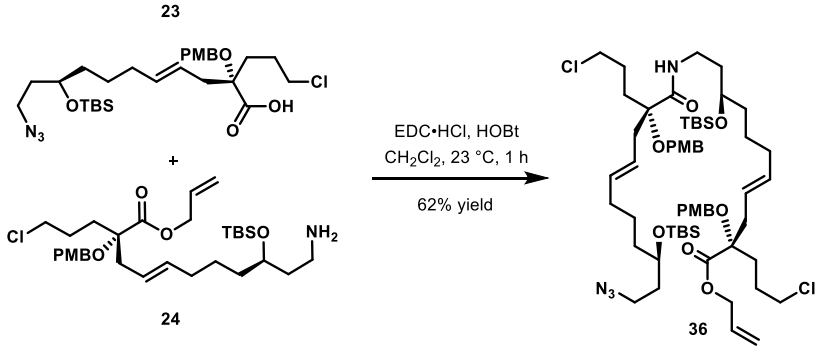
$[\alpha]_D^{25}$ –4.9° (*c* 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H), 6.92 – 6.81 (m, 2H), 5.94 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.57 – 5.49 (m, 1H), 5.42 – 5.33 (m, 2H), 5.27 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.65 (dt, *J* = 5.8, 1.4 Hz, 2H), 4.47 – 4.34 (m, 2H), 3.80 (s, 3H), 3.75 (ddd, *J* = 7.1, 6.0, 4.5 Hz, 1H), 3.59 – 3.45 (m, 2H), 3.33 (tt, *J* = 12.2, 6.8 Hz, 2H), 2.65 – 2.52 (m, 2H), 2.03 – 1.94 (m, 4H), 1.93 – 1.85 (m, 1H), 1.82 – 1.73 (m, 1H), 1.73 – 1.61 (m, 2H), 1.44 (dq, *J* = 9.7, 5.7 Hz, 2H), 1.40 – 1.31 (m, 2H), 0.88 (s, 9H), 0.05 (d, *J* = 2.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.77, 159.07, 134.59, 131.81, 130.31, 129.07, 123.54, 118.78, 113.64, 82.18, 69.15, 65.96, 65.45, 55.16, 47.88, 45.06, 37.72, 36.67, 35.60, 32.64, 31.87, 26.40, 25.78, 24.70, 17.96, -4.41, -4.74. HRMS (TOF MS EI) calcd for $C_{31}H_{50}ClN_3O_5Si$ $[M+Na]^+$ 630.3106, found 630.3096.



Amine 24: Prepared according to a modification of the literature procedure[5]: thiophenol (0.70 mL, 6.90 mmol, 6.0 equiv) and triethylamine (0.72 mL, 5.17 mmol, 4.50 equiv) were added to a solution of anhydrous $SnCl_2$ (0.33 g, 1.72 mmol, 1.5 equiv) in acetonitrile (7 mL). The mixture

turned bright yellow and was let to stir at room temperature for 15 min. Solution of azide **35** (0.70 g, 1.15 mmol) in acetonitrile (3 mL then 3 x 0.5 mL rinses) was added and the mixture was stirred at room temperature for 15 min when it was concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 (15 mL) and washed with 2M aqueous NaOH (10 mL). The extract was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc-CH_2Cl_2 then 20% MeOH-1% NH_4OH-CH_2Cl_2) to afford amine **24** (0.64 g, 1.10 mmol, 96% yield) as a pale-yellow oil.

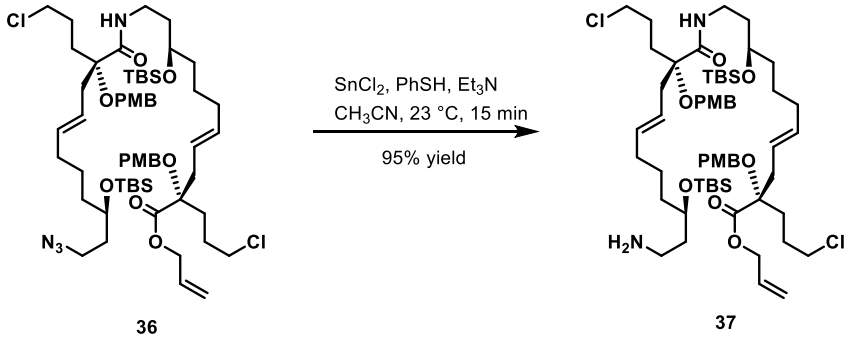
$[\alpha]_D^{25}$ –1.9° (*c* 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 6.90 – 6.81 (m, 2H), 5.94 (ddt, J = 17.1, 10.4, 5.8 Hz, 1H), 5.52 (dt, J = 13.4, 3.8 Hz, 1H), 5.41 – 5.33 (m, 2H), 5.27 (dq, J = 10.4, 1.3 Hz, 1H), 4.65 (dt, J = 5.9, 1.3 Hz, 2H), 4.48 – 4.35 (m, 2H), 3.80 (s, 3H), 3.73 (q, J = 5.7 Hz, 1H), 3.58 – 3.46 (m, 2H), 2.84 – 2.69 (m, 2H), 2.64 – 2.53 (m, 2H), 2.18 – 2.03 (m, 2H), 1.99 (tdd, J = 10.5, 7.8, 5.5 Hz, 4H), 1.92 – 1.84 (m, 1H), 1.76 (dddd, J = 19.7, 12.4, 9.2, 5.6 Hz, 1H), 1.59 (qd, J = 7.0, 6.0, 1.4 Hz, 2H), 1.47 – 1.29 (m, 4H), 0.88 (s, 9H), 0.04 (d, J = 5.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) ? 172.81, 159.05, 134.78, 131.80, 130.32, 129.08, 123.35, 118.81, 113.64, 82.18, 70.36, 65.97, 65.46, 55.18, 45.08, 40.07, 38.46, 37.71, 36.75, 32.72, 31.88, 26.41, 25.82, 24.90, 17.98, -4.42, -4.57. HRMS (TOF MS EI) calcd for $C_{31}H_{52}ClNO_5Si$ $[M+H]^+$ 582.2381, found 582.3386.



Amide 36: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.21 g, 1.34 mmol, 1.5 equiv), amine **24** (0.52 g, 0.89 mmol, 1 equiv), and HOBt (0.18 g, 1.34 mmol, 1.5 equiv) were added sequentially to a solution of acid **23** (0.51 g, 0.89 mmol) in CH_2Cl_2 (5 mL). The solution was stirred at room temperature for 1h, then diluted with CH_2Cl_2 (3 mL) and washed with saturated aqueous sodium bicarbonate (5 mL), brine (5 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc-hexanes) to give amide **36** (0.62 g, 0.547 mmol, 62% yield) as a clear oil.

$[\alpha]_D^{25}$ –6.8° (*c* 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 7.25 (d, J = 8.8 Hz, 2H), 6.87 (ddd, J = 16.8, 9.4, 7.3 Hz, 5H), 5.93 (ddt, J = 16.5, 10.4, 5.8 Hz, 1H), 5.51 (dq, J = 12.5, 6.3 Hz, 2H), 5.43 – 5.29 (m, 3H), 5.28 – 5.23 (m, 1H), 4.64 (dt, J = 5.8, 1.4 Hz, 2H), 4.47 – 4.30 (m, 4H), 3.81 (s, 3H), 3.79 (s, 3H), 3.75 (dt, J = 10.6, 5.2 Hz, 1H), 3.65 (tq, J = 10.8, 5.7, 4.6 Hz, 1H), 3.61 – 3.42 (m, 4H), 3.38 – 3.29 (m, 3H), 3.17 (tt, J = 13.6, 6.2 Hz, 1H), 2.71 – 2.49 (m,

4H), 1.96 (dp, J = 14.2, 5.7, 5.0 Hz, 8H), 1.89 (tt, J = 11.3, 5.6 Hz, 1H), 1.76 (dtd, J = 19.3, 7.4, 3.7 Hz, 2H), 1.72 – 1.59 (m, 4H), 1.59 – 1.48 (m, 1H), 1.42 (qd, J = 7.3, 4.1 Hz, 4H), 1.39 – 1.29 (m, 4H), 0.86 (d, J = 18.9 Hz, 18H), 0.05 (d, J = 5.4 Hz, 6H), -0.02 (d, J = 14.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.83, 172.58, 159.31, 159.08, 134.73, 133.76, 131.83, 130.34, 129.83, 129.40, 129.12, 123.90, 123.43, 118.83, 113.85, 113.67, 82.79, 82.20, 69.89, 69.14, 66.00, 65.48, 63.72, 55.22, 55.21, 47.93, 45.10, 44.95, 38.08, 37.73, 36.73, 36.60, 35.71, 35.59, 32.77, 32.71, 31.88, 31.59, 29.63, 26.73, 26.43, 25.81, 24.86, 24.71, 17.98, -4.36, -4.41, -4.64, -4.73. HRMS (TOF MS EI) calcd for $C_{59}H_{96}Cl_2N_4O_9Si_2$ $[M+Na]^+$ 1153.5991, found 1153.6012.

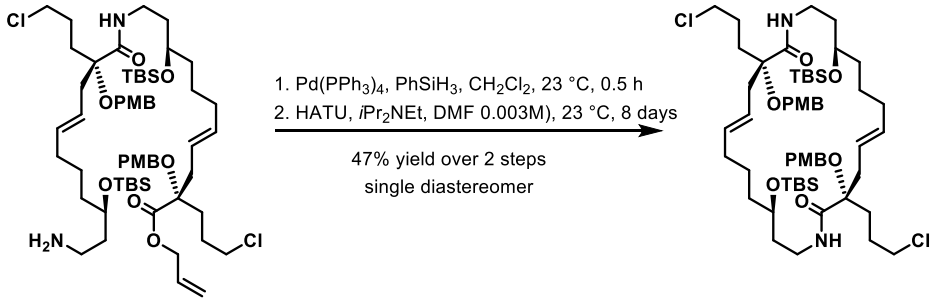


36 37

Amine 37: Prepared according to a modification of the literature procedure[5]: thiophenol (0.40 mL, 3.92 mmol, 6.0 equiv) and triethylamine (0.41 mL, 2.94 mmol, 4.50 equiv) were added to a solution of anhydrous $SnCl_2$ (0.19 g, 0.98 mmol, 1.50 equiv) in acetonitrile (4 mL). The mixture turned bright yellow and was let to stir at room temperature for 15 min. Solution of azide **36** (0.74 g, 0.65 mmol) in acetonitrile (2.5 mL) was added and the mixture was stirred at room temperature for 15 min when it was concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 (5 mL) and washed with 2M aqueous NaOH (5 mL). It was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc-CH_2Cl_2 then 20% MeOH-1% NH_4OH-CH_2Cl_2) to afford amine **37** (0.69 g, 0.62 mmol, 95% yield) as a pale-yellow oil.

$[\alpha]_D^{25}$ –5.7° (*c* 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 – 7.18 (m, 4H), 6.95 – 6.78 (m, 5H), 5.99 – 5.88 (m, 1H), 5.51 (dt, J = 14.4, 6.9 Hz, 2H), 5.42 – 5.27 (m, 3H), 5.27 – 5.22 (m, 1H), 4.69 – 4.60 (m, 2H), 4.48 – 4.29 (m, 4H), 4.11 – 3.87 (m, 2H), 3.80 (two singlets, 6H), 3.73 (p, J = 5.8 Hz, 1H), 3.64 (h, J = 6.1 Hz, 1H), 3.60 – 3.40 (m, 4H), 3.38 – 3.28 (m, 1H), 3.20 – 3.09 (m, 1H), 2.79 (q, J = 6.8 Hz, 2H), 2.67 – 2.48 (m, 4H), 2.06 – 1.82 (m, 10H), 1.82 – 1.57 (m, 8H), 1.51 (ddt, J = 12.6, 9.7, 6.4 Hz, 2H), 1.42 (h, J = 5.4 Hz, 4H), 1.37 – 1.19 (m, 14H), 1.08 – 1.01 (m, 1H), 0.96 (dd, J = 6.7, 1.5 Hz, 1H), 0.91 – 0.80 (m, 18H), 0.04 (dd, J = 7.1, 1.5 Hz, 6H), -0.02 (dd, J = 15.5, 1.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.85, 172.60, 159.32, 159.10, 134.76, 133.88, 131.84, 130.36, 129.87, 129.43, 129.14, 123.85, 123.44, 118.84, 113.87, 113.68, 82.80, 82.22, 70.39, 69.89, 66.02, 65.50, 63.76, 55.24, 55.22, 45.11, 44.96, 38.11, 37.97, 37.75, 36.74, 36.69, 36.62, 35.71, 34.63, 34.48, 32.79, 31.90, 31.62, 31.54, 29.02, 26.76, 26.45, 25.85, 25.83,

25.24, 24.95, 24.89, 22.61, 20.66, 18.72, 18.00, 14.07, 11.38, -4.39, -4.57, -4.62. HRMS (TOF MS EI) calcd for $C_{59}H_{98}Cl_2N_2O_9Si_2$ $[M+H]^+$ 1105.6266, found 1105.6281.

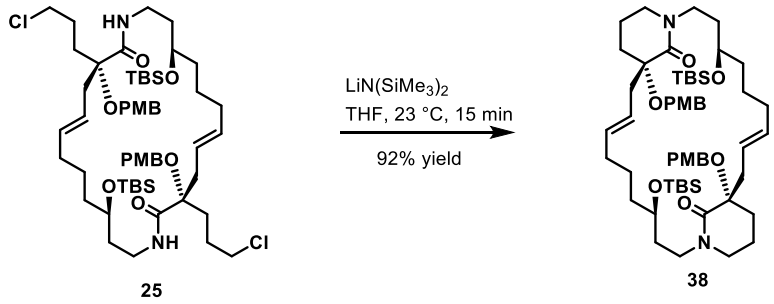


37 25

Macrocyclic bis-lactam 25: Tetrakis(triphenylphosphine)-palladium(0) (22 mg, 0.019 mmol, 0.03 equiv) was added to a solution of amine **37** (0.69 g, 0.62 mmol) and phenylsilane (0.31 mL, 0.27 g, 2.50 mmol, 4 equiv) in CH_2Cl_2 (3.10 mL). The mixture was stirred at room temperature for 30 min when it was concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc-Hex then 20% MeOH-1% NH_4OH-CH_2Cl_2), concentrated *in vacuo* and submitted to the next step.

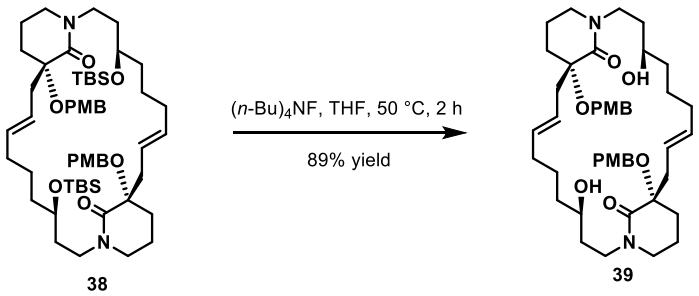
Amino acid from the previous step (0.70 g) was dissolved in anhydrous *N*,*N*-dimethylformamide (208 mL) under argon. *N*,*N*-Diisopropylethylamine (0.43 mL, 2.50 mmol, 4.0 equiv) and HATU (0.36 g, 0.94 mmol, 1.5 equiv) were added, the mixture turned bright yellow and was let to stir at room temperature for 8 days. DMF was distilled off under reduced pressure (0.2 mmHg) into a receiving flask cooled to –78 °C. The residue was dissolved in EtOAc (10 mL) and washed with water (3x50 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc-hexanes) to give of macrolactam **25** (0.31 g, 0.29 mmol, 47% yield over two steps) as a single diastereomer, and as a white foam.

$[\alpha]_D^{25}$ +11.6° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.30 – 7.18 (m, 5H), 6.93 (dd, J = 7.8, 4.5 Hz, 2H), 6.90 – 6.76 (m, 4H), 5.50 (dt, J = 15.2, 6.5 Hz, 2H), 5.28 (dt, J = 14.8, 6.9 Hz, 2H), 4.43 (d, J = 10.1 Hz, 2H), 4.36 (d, J = 10.1 Hz, 2H), 3.74 (s, 6H), 3.70 (dq, J = 9.7, 5.4 Hz, 2H), 3.60 (dt, J = 11.1, 5.8 Hz, 2H), 3.51 – 3.37 (m, 4H), 3.05 – 2.90 (m, 2H), 2.55 (qd, J = 14.7, 7.1 Hz, 4H), 2.08 – 1.96 (m, 4H), 1.92 (q, J = 7.3 Hz, 4H), 1.78 (tdd, J = 14.0, 9.8, 4.7 Hz, 2H), 1.70 (ddt, J = 19.5, 11.3, 5.6 Hz, 3H), 1.63 – 1.53 (m, 2H), 1.46 – 1.20 (m, 11H), 0.84 (s, 18H), 0.01 (d, J = 6.7 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) 172.47, 159.21, 133.90, 129.93, 129.42, 129.28, 123.42, 113.84, 83.12, 70.33, 63.53, 55.17, 45.09, 38.22, 37.44, 36.68, 36.23, 33.02, 31.34, 26.75, 25.85, 24.58, 18.02, -4.42, -4.57. HRMS (TOF MS EI) calcd for $C_{56}H_{92}Cl_2N_2O_8Si_2$ $[M+Na]^+$ 1069.5667, found 1069.5673.



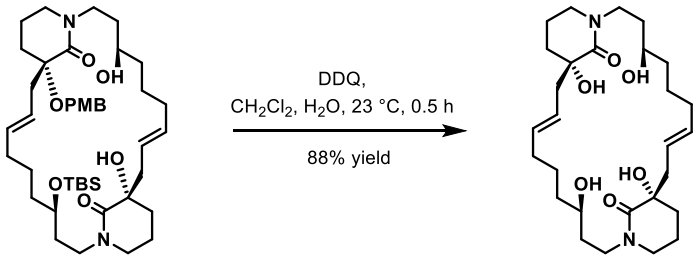
Bis-Lactam 38: Lithium bis(trimethylsilyl)amide (0.5M in THF, 1.20 mL, 0.59 mmol, 2.20 equiv) was added dropwise to a solution of macrocyclic bis-macrolactam **25** (0.28 g, 0.27 mmol) in anhydrous THF (1.30 mL) that was heated at reflux under argon. After 15 min, saturated aq. NH_4Cl (1 mL) was added, and the mixture was extracted with EtOAc (2 x 4 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc-hexanes) to give bis-lactam **38** (0.24 g, 0.25 mmol, 92% yield) as a white foam.

$[\alpha]_D^{25}$ +1.01˚ (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) 7.33 – 7.15 (m, 5H), 6.89 – 6.69 (m, 4H), 5.55 (dt, J = 15.4, 6.6 Hz, 2H), 5.37 – 5.18 (m, 2H), 4.60 (d, J = 11.1 Hz, 2H), 4.46 (d, J = 11.1 Hz, 2H), 3.77 (overlapping m and s, 8H), 3.65 (h, J = 6.3, 5.9 Hz, 2H), 3.28 – 3.13 (m, 4H), 3.12 – 2.96 (m, 4H), 2.15 (td, J = 14.6, 13.9, 7.4 Hz, 4H), 2.07 – 1.77 (m, 8H), 1.77 – 1.52 (m, 8H), 1.47 – 1.29 (m, 6H), 0.89 (s, 18H), 0.05 (d, J = 9.0 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) 13C NMR (126 MHz, cdcl3) 168.23, 158.73, 134.43, 131.53, 128.89, 124.87, 113.52, 77.42, 70.15, 65.58, 55.16, 48.35, 43.59, 38.89, 35.70, 33.47, 32.33, 32.00, 25.81, 25.20, 18.85, 18.00, -4.43. HRMS (TOF MS EI) calcd for $C_{56}H_{90}N_2O_8Si_2$ $[M+Na]^+$ 997.6133, found 997.6152.



Macrocyclic diol 39: Tetra-n-butylammonium fluoride (1M in THF, 0.62 mL, 0.62 mmol, 4 equiv) was added to the flask with macrolactam **38** (0.15 g, 0.15 mmol) at 0 °C. The reaction mixture was heated to 50 °C for 2 h, when it was quenched with saturated aq. NH_4Cl (1 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 x 2 mL). The combined organic layers were washed with water (5 x 2 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (40% acetone-hexanes to 50% acetone-hexanes) to give macrocyclic diol **39** (0.10 g, 0.14 mmol, 89% yield) as a white foam.

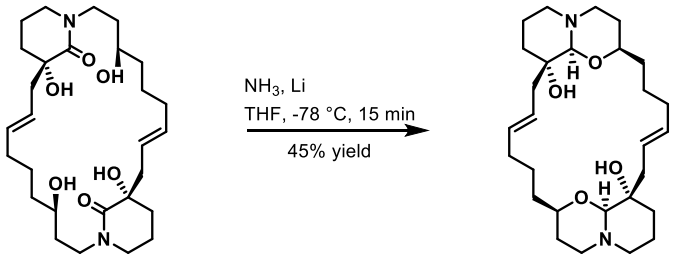
$[\alpha]_D^{25}$ –10.9° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) 7.22 (d, J = 8.3 Hz, 5H), 6.83 (d, J = 8.3 Hz, 4H), 5.59 (dt, J = 15.5, 5.8 Hz, 2H), 5.27 (dq, J = 15.3, 7.4, 6.7 Hz, 2H), 4.59 (d, J = 11.1 Hz, 2H), 4.45 (d, J = 11.0 Hz, 2H), 4.06 (ddd, J = 14.0, 9.5, 4.0 Hz, 2H), 3.77 (s, 6H), 3.48 (t, J = 7.5 Hz, 2H), 3.43 – 3.24 (m, 4H), 3.13 (td, J = 12.5, 10.7, 5.7 Hz, 4H), 2.87 (dt, J = 14.0, 5.3 Hz, 2H), 2.20 – 2.00 (m, 6H), 1.92 (dtt, J = 18.7, 13.5, 4.9 Hz, 6H), 1.82 – 1.64 (m, 6H), 1.64 – 1.51 (m, 4H), 1.46 (qt, J = 15.8, 7.7 Hz, 2H), 1.28 (dtd, J = 21.5, 12.3, 10.9, 6.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) 168.81, 158.76, 134.64, 131.35, 128.80, 124.32, 113.57, 77.40, 68.74, 65.41, 55.19, 48.28, 44.19, 39.10, 36.60, 35.03, 32.04, 31.77, 25.07, 18.44. HRMS (TOF MS EI) calcd for $C_{44}H_{62}N_2O_8$ $[M+Na]^+$ 769.4404, found 769.4413.



39 **26**

Tetrahydroxy macrocycle 26: Macrocyclic diol **39** (0.10 g, 0.134 mmol) was dissolved in 10:1 mixture of CH_2Cl_2 – water (2.40 mL), and DDQ (76 mg, 0.34 mol, 2.50 equiv) was added. Reaction was let to stir for 0.5 h. The mixture was diluted with CH_2Cl_2 (2 mL), washed with 1:1 mixture of saturated aqueous sodium bicarbonate-brine (2 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (100% acetone-hexanes to 10 % MeOH-CH_2Cl_2) to afford tetrahydroxy macrocycle **26** (60 mg, 0.118 mol, 88% yield) as a clear oil.

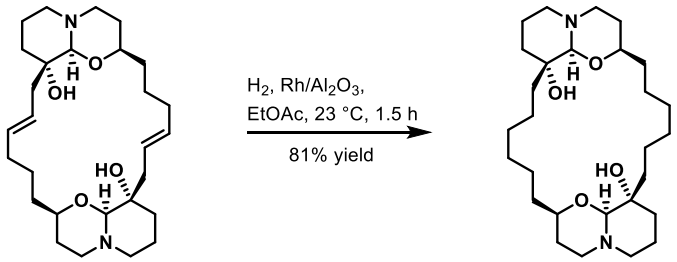
$[\alpha]_D^{25}$ –11° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) 5.48 (dt, J = 15.2, 6.6 Hz, 2H), 5.36 (dt, J = 15.1, 7.3 Hz, 2H), 3.61 (s, 2H), 3.50 (q, J = 7.3, 6.5 Hz, 4H), 3.41 – 3.31 (m, 2H), 3.27 (dt, J = 9.4, 4.4 Hz, 4H), 2.42 – 2.28 (m, 4H), 2.03 (h, J = 8.0, 7.3 Hz, 4H), 1.98 – 1.88 (m, 4H), 1.84 (tt, J = 11.0, 6.8 Hz, 4H), 1.74 – 1.64 (m, 2H), 1.58 – 1.39 (m, 10H). ^{13}C NMR (126 MHz, CDCl3) δ 173.67, 134.74, 124.57, 72.33, 67.55, 48.31, 44.34, 43.59, 35.31, 34.66, 32.70, 31.58, 24.39, 19.34. HRMS (TOF MS EI) calcd for $C_{28}H_{46}N_2O_6$ $[M+Na]^+$ 529.3254, found 529.3246.



26 **40**

Bis-1-oxaquinolizidine 40: The outlet of the ammonia lecture bottle (anhydrous, ≥99.98%, Sigma Aldrich) was connected through a Teflon tube to a 25 mL round recovery flask with a glass stirring bar serving as a receiving vessel. The receiving flask was cooled to –78 °C and 2.0 mL of ammonia was condensed. Small pieces of lithium (20 mg, 2.88 mmol, 27 equiv) were added in portions and solution immediately turned deep blue. The mixture was stirred for 1 h at –40 °C, then cooled back to –78 °C. THF was added (1 mL), followed with tetrahydroxy macrocycle **26** (55 mg, 0.11 mmol) in THF (1 mL). The reaction mixture stayed deep blue and was stirred for 15 min at –78 °C before it was quenched with solid NH_4Cl (0.5 g), diluted with THF (3 mL), warmed to room temperature. Water (1 mL) was carefully added, and the solution was transferred to a separatory funnel containing 1M aqueous NaOH (2 mL), extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by reverse column chromatography (10% water-MeOH) to give **40** (28 mg, 0.059 mmol, 45% yield) as a white foam.

$[\alpha]_D^{25}$ +8.9° (*c* 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) □ 5.65 – 5.43 (m, 4H), 3.93 (s, 2H), 3.54 – 3.44 (m, 2H), 3.13 – 2.90 (m, 6H), 2.58 – 2.47 (m, 2H), 2.38 – 2.26 (m, 2H), 2.14 – 2.00 (m, 4H), 1.98 – 1.86 (m, 2H), 1.75 (tdd, J = 17.4, 10.3, 3.5 Hz, 4H), 1.69 – 1.58 (m, 4H), 1.57 – 1.45 (m, 8H), 1.44 – 1.37 (m, 2H), 1.34 – 1.25 (m, 2H), 1.06 (d, J = 13.7 Hz, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 134.14, 124.14, 76.91, 71.01, 52.52, 41.24, 40.31, 35.73, 32.23, 31.93, 28.75, 25.63, 25.24, 20.95.HRMS (TOF MS EI) calcd for $C_{28}H_{46}N_2O_4$ $[M+H]^+$ 475.3536, found 475.3527.



40 (+)-Ar C

(+)-Araguspongine C: Bis-1-oxaquinolizidine **40** (25 mg, 0.053 mmol) was dissolved in dry EtOAc (2.5 mL), and 5 wt. % Rh/Al_2O_3 (12 mg) was added. The atmosphere in the flask was exchanged with hydrogen (a hydrogen balloon was inserted into the flask along with a hypodermic needle; the hypodermic needle was removed after 5 min). The solution was stirred for at room temperature for 1 h under a hydrogen atmosphere, then filtered through syringe filter (Acrodics, 13 mm, 0.2µm PFTE) and concentrated *in vacuo* to give (+)-araguspongine C (20 mg, 0.043 mmol, 81% yield) as a white foam.

$[\alpha]_D^{25}$ +25.2° (*c* 0.32, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.05 (s, 2H), 3.55 (tt, J = 10.9, 2.2 Hz, 2H), 3.16 – 3.07 (m, 2H), 3.03 (ddd, J = 13.4, 10.6, 2.9 Hz, 2H), 2.97 (ddd, J = 13.8, 4.7, 1.5 Hz, 2H), 2.51 (s, 1H), 2.37 – 2.29 (m, 2H), 1.77 (dtdd, J = 13.0, 11.2, 9.1, 4.5 Hz, 4H), 1.64 – 1.58 (m, 2H), 1.53 (dddd, J = 17.3, 14.7, 9.6, 5.5 Hz, 6H), 1.45 – 1.34 (m, 6H), 1.33 – 1.24 (m, 8H),

1.20 (tdd, J = 12.5, 9.3, 2.7 Hz, 2H), 1.17 – 1.08 (m, 2H), 1.10 – 0.97 (m, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 90.33, 76.49, 70.75, 52.51, 44.24, 38.48, 36.28, 32.28, 31.48, 29.60, 26.00, 24.95, 22.58, 20.91. HRMS (TOF MS EI) calcd for $C_{28}H_{50}N_2O_4$ $[M+H]^+$ 479.3849, found 479.3847.

Table **S5**: Comparison of ^{1}H NMR Data for Natural[9] and Synthetic (+)-araguspongine C in $CDCl_3$:

Proton	Natural ArC (250 MHz)	Synthetic ArC (600 MHz)
H-2	3.56 (br t, J=10.7 Hz)	3.55 (tt, J = 10.9, 2.2 Hz)
H-4α	2.97 (br dd, J=13.7, 3.4 Hz)	2.97 (ddd, J = 13.8, 4.7, 1.5 Hz)
H-4β	3.11 (br t, J=13.7 Hz)	3.16 – 3.07 (m)
H-6α	2.34 (br d, J=10.0)	2.37 – 2.29 (m)
H-6β	3.03 (ddd, J=10.0, 10.0, 3.1 Hz)	3.03 (ddd, J = 13.4, 10.6, 2.9 Hz)
H-7β	1.72 (m)	1.77 (dtdd, J = 13.0, 11.2, 9.1, 4.5 Hz)
H-10	4.06 (s)	4.05 (s)

Table **S6** Comparison of ^{13}C NMR Data for Natural[9] and Synthetic (+)-araguspongine C in $CDCl_3$:

Carbon	Natural ArC (250 MHz)	Synthetic ArC (600 MHz)
C-2	76.5	76.49
C-4	52.6	52.51
C-6	44.3	45.24
C-9	70.8	70.75
C-10	90.4	90.33

BIOLOGICAL STUDIES SECTION

Material and Methods

Reagents

Oligomycin A, FCCP, Rotenone, and Antimycin A used to obtain the bioenergetic profiles were purchased from Sigma-Aldrich Corp. (St. Louis, MO, USA) as well as ATP. The Xestospongine B (Xe B), extracted and purified from the *Xestospongia exigua* marine sponge, was provided by Dr. Jordi Molgo (France).

Cell Culture

Breast cell line MCF10A was maintained in DMEM/F12 supplemented with 5% (v/v) horse serum, 10 µg/ml insulin, 20 ng/ml EGF, 100 ng/ml cholera toxin and 0.5 µg/ml hydrocortisone. MCF7, MDA-MB-231, ZR75-1 and BT549 cell lines were maintained in DMEM supplemented with 10% (v/v) FBS (Hyclone, Logan, UT, USA). All cells were grown in the presence of 100 U/ml penicillin,100 µg/ml streptomycin and 0.25 µg/ ml fungizone (Gibco) at 37°C (95%/5% air/CO2).

Cytoplasmic Ca^{2+} Measurement

Imaging of cytoplasmic Ca2+ signals was accomplished by confocal microscopy using a Nikon A1R confocal microscope equipped with Perfect Focus in a Tokai Hit incubation chamber. Cells were loaded with freshly prepared Fluo-4 (5 µM) and imaged at 37 °C and 5% CO_2. After 10 seconds of basal $[Ca^{2+}]_c$ measurement, ATP-Mg (100 µM) was added and images were recorded every 3 s at 488 nm using a 20X objective. Images were analyzed and quantified using ImageJ (NIH).

Cellular Oxygen Consumption in Real Time

Oxygen consumption rate (OCR) as measurements of oxidative phosphorylation (OXPHOS) was measured at 37 °C using an XFe96 extracellular analyzer (Agilent, USA). 1.5 x 10^4 cells per well were seeded onto poly-lysine (Sigma-Aldrich, USA) pre-treated plates and allowed to attach for 24 h. When indicated, MCF10A and MDA-MB-231 cells were exposed to increasing concentration of either Xe B or dmXe B for 24 h and then loaded into the analyzer in fresh un-buffered Seahorse media, and basal OCR was determined. Sequential injections of 1 µM oligomycin, 250 nM FCCP and 1 µM rotenone/antimycin A were used to reveal different parameters of cellular respiration. The data were normalized for protein concentration by lysing samples after each experiment.

Cell Viability

Cell death was determined by propidium iodide (PI) incorporation (Molecular Probes) through flow cytometry. The culture medium from each well was collected in an Eppendorf tube to preserve dead cells present in the medium. Then, the plates were washed with PBS and the

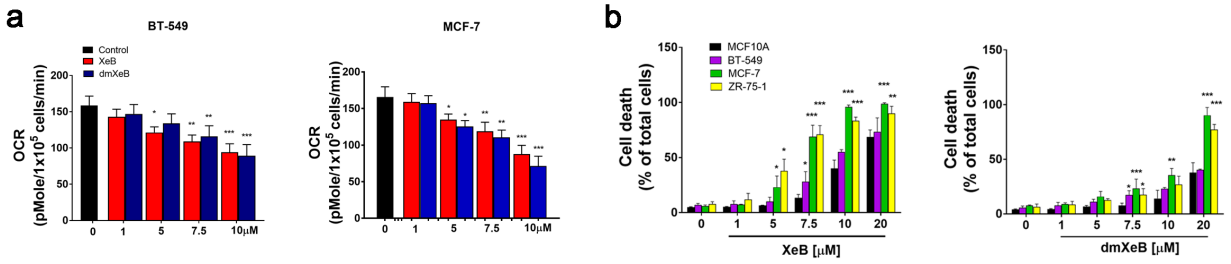
cells detached and collected in the respective Eppendorf tubes. The tubes were centrifuged at 2,500 rpm for 5 min at 4 °C and the supernatant was discarded. The cells pellet was resuspended in a PI solution (5 mg/mL) in 1X PBS and transferred to BD cytometer tubes. Fluorescence was detected using a BD FACSaria III flow cytometer.

Colony Formation Assay

Briefly, MDA-MB-231 cells were treated with 7.5 μM of either Xe B or dmXe B for 24 h. Then, the cells were trypsinized and counted. One thousand cells were seeded and left undisturbed for 1 week. Finally, colonies obtained were fixed and stained with 6% glutaraldehyde and 0.5% crystal violet, analyzed and counted.

Analysis and Statistics

All statistical analyses were performed using Graph Pad Prism 4.03 (GraphPad Software, San Diego, California, USA). The data are expressed as mean ± SEM of three or more independent experiments, each one performed in technical triplicate. Statistical analysis was performed using unpaired t-tests, one-way ANOVA with Bonferroni's post-test for pairwise comparisons or two-way ANOVA. The data were considered statistically significant at the 95% level ($p < 0.05$).



Supplementary figure S1. a. Basal oxygen consumption rate (OCR) of BT-549 (left panel) and MCF7 (right panel) cells incubated for 24 h with increasing concentration of either Xe B (red) or dmXe B (blue). The black bar represents cells basal OCR without treatment. Mean ± SEM of 3 independent experiments with 10 replicates each. *p < 0.05, **p < 0.01, ***p < 0.001 compared to respective control. **b.** MCF10A (black), BT-549 (purple), MCF7 (green) and ZR-75-1 (yellow) were treated with increasing concentrations of either Xe B (lef panel) or dmXe B (right panel) for 24 h and cell death was determined by propidium iodide incorporation by flow cytometer. Mean ± SEM of 3 independent experiments, each in triplicate. *p < 0.05, ***p < 0.001 compared to respective control.

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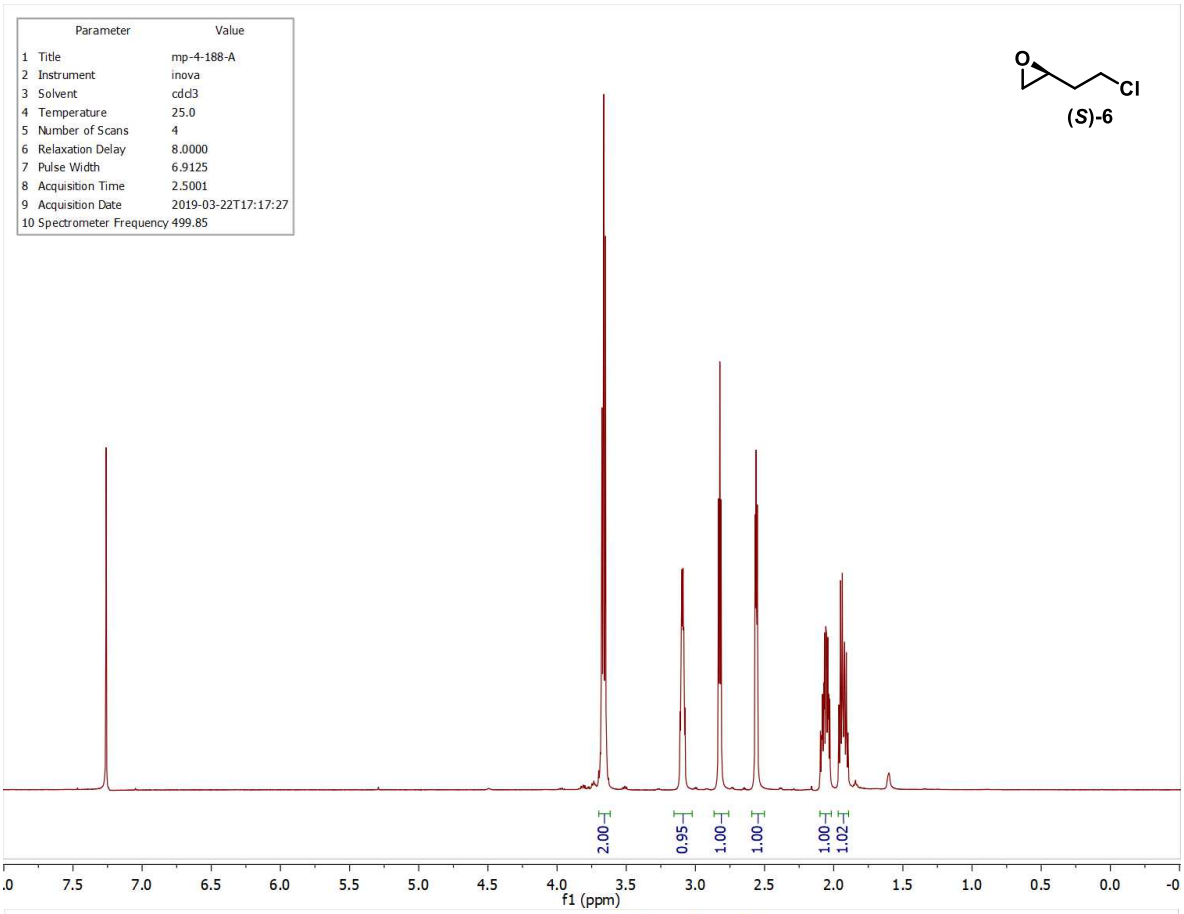
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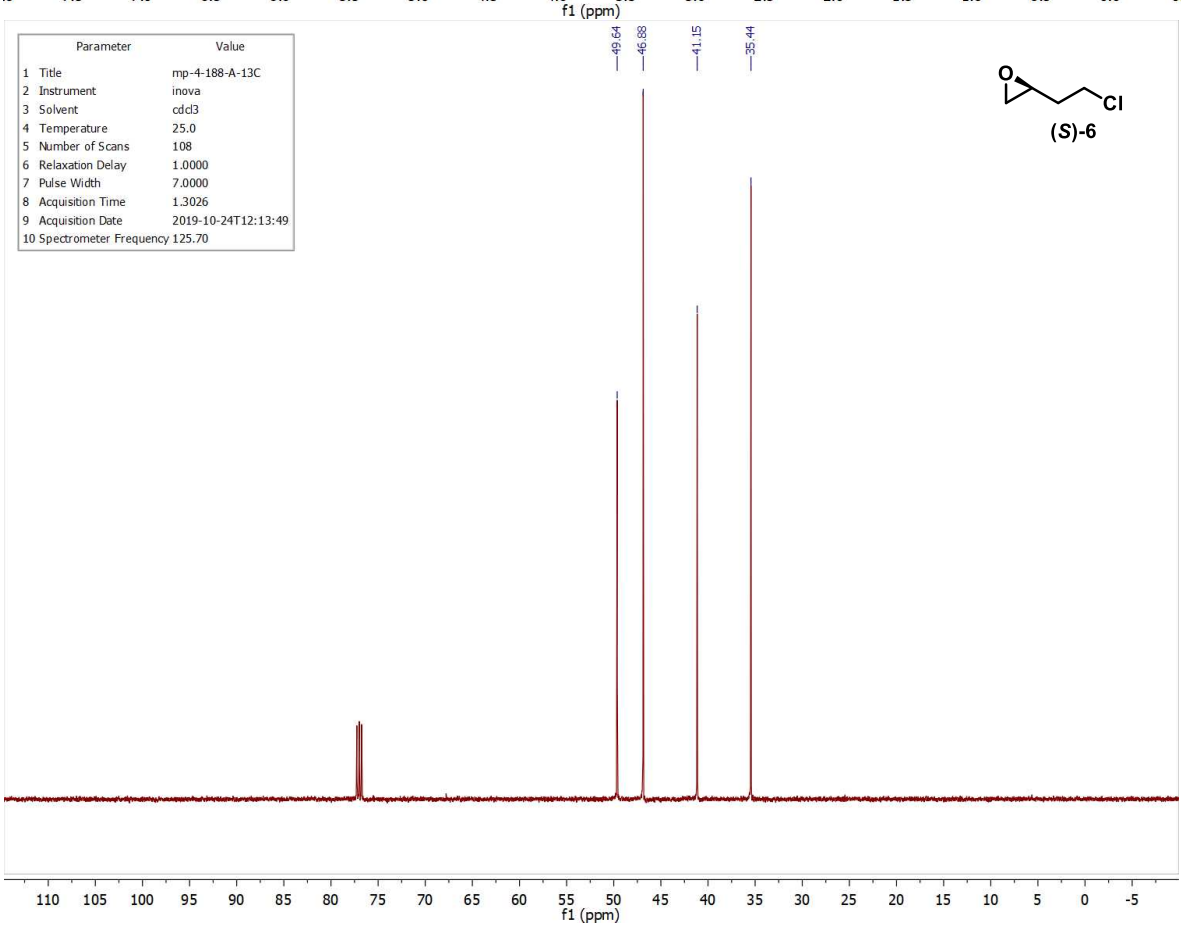
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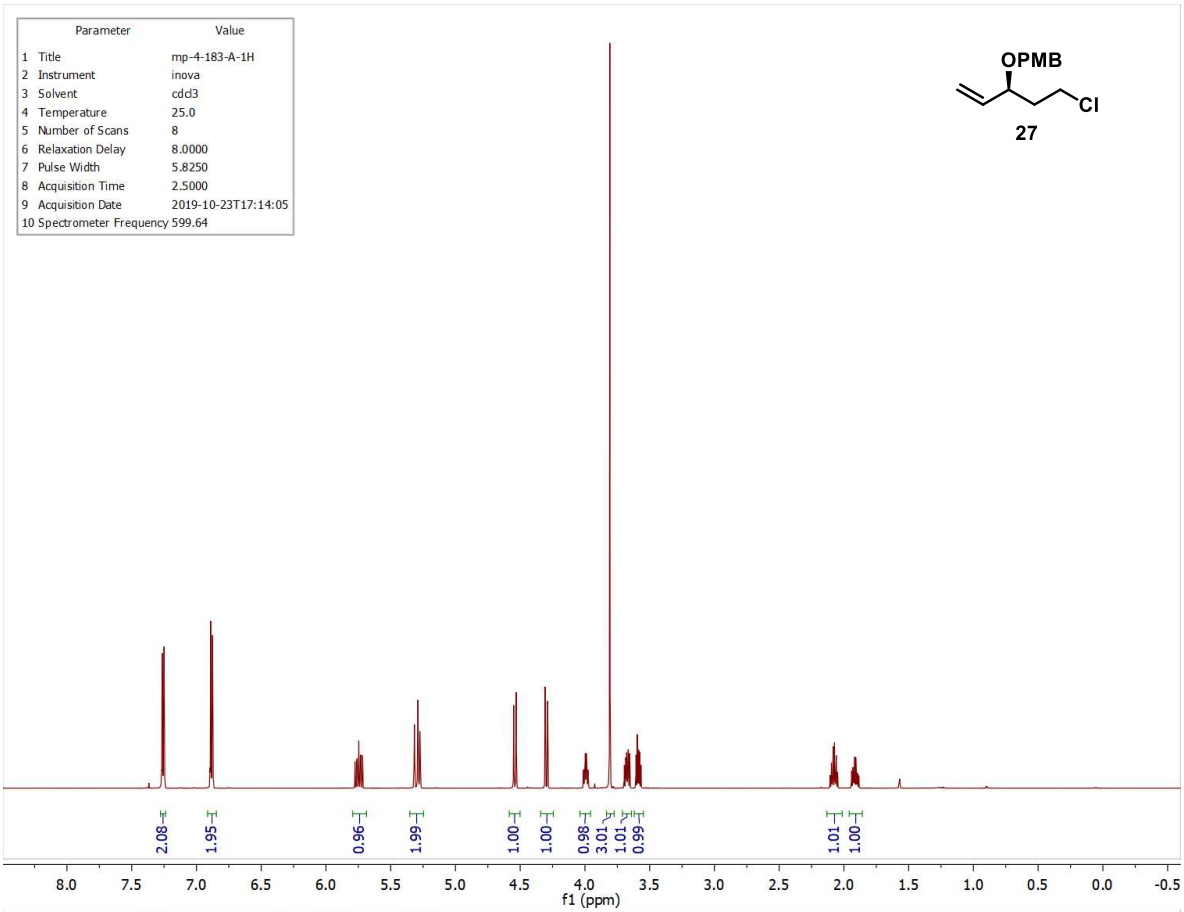
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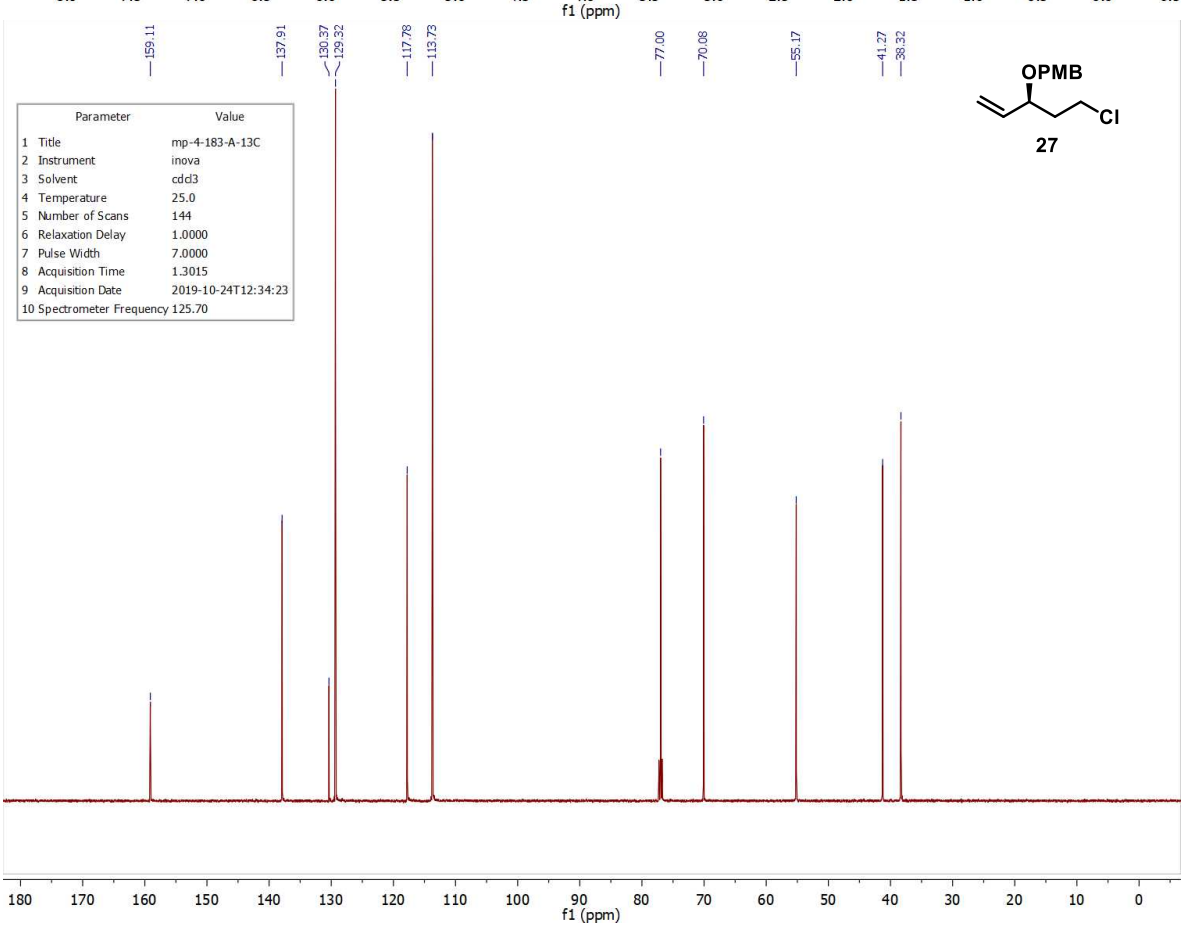
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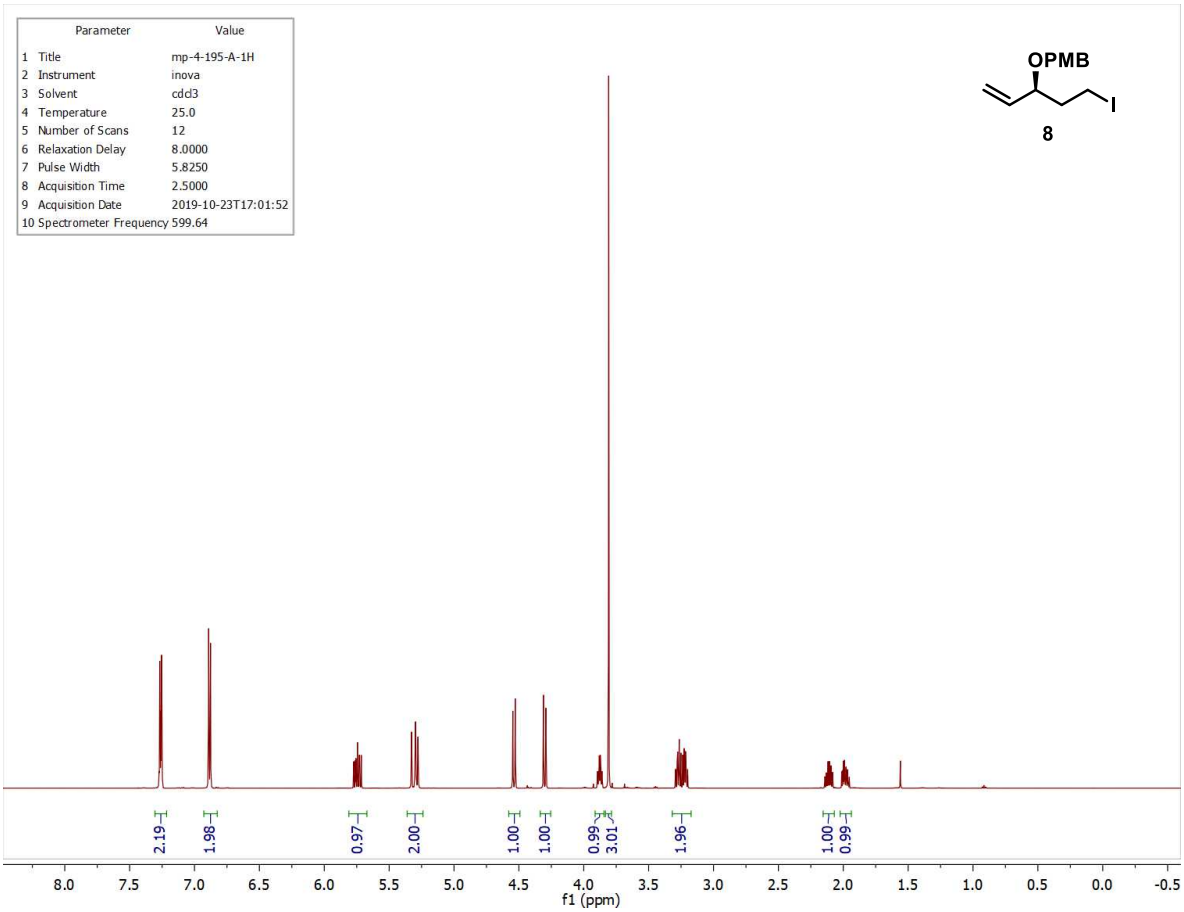
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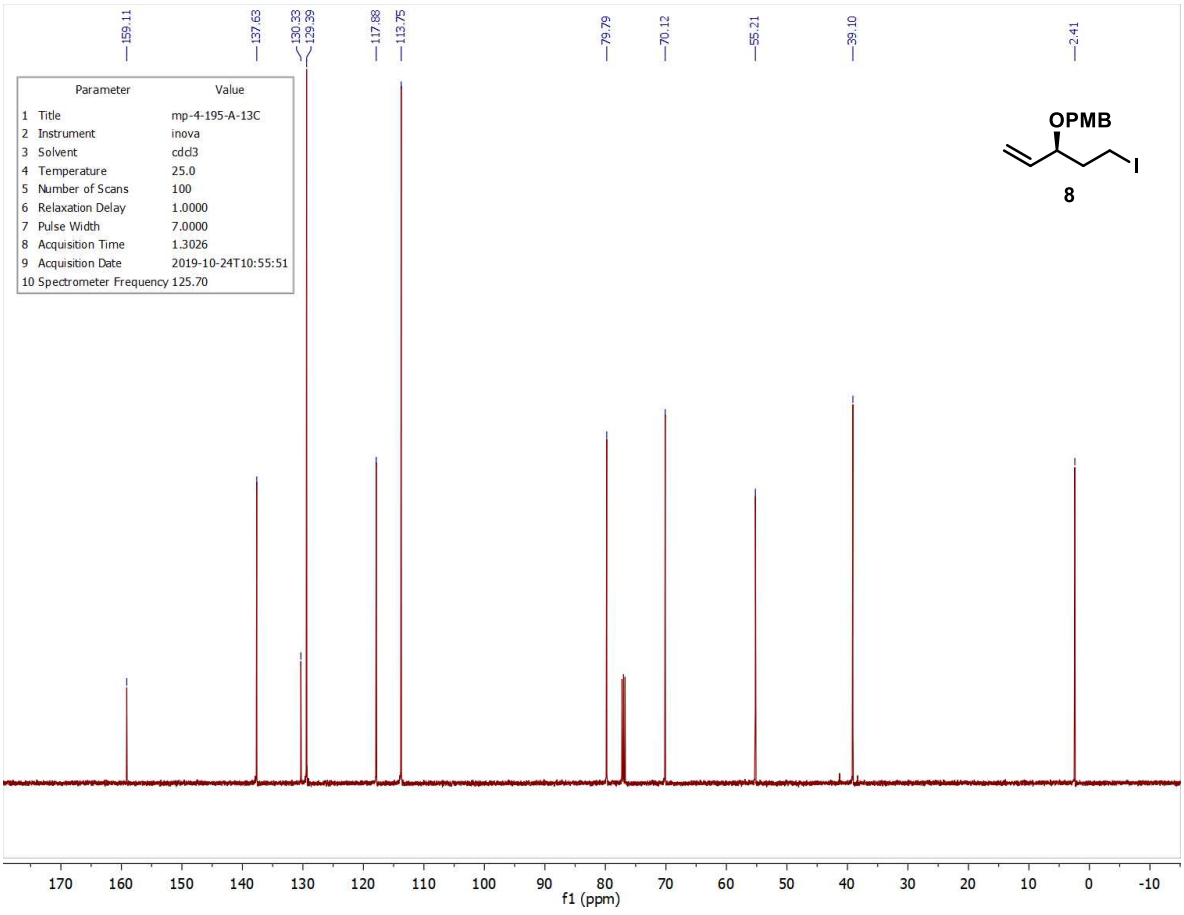
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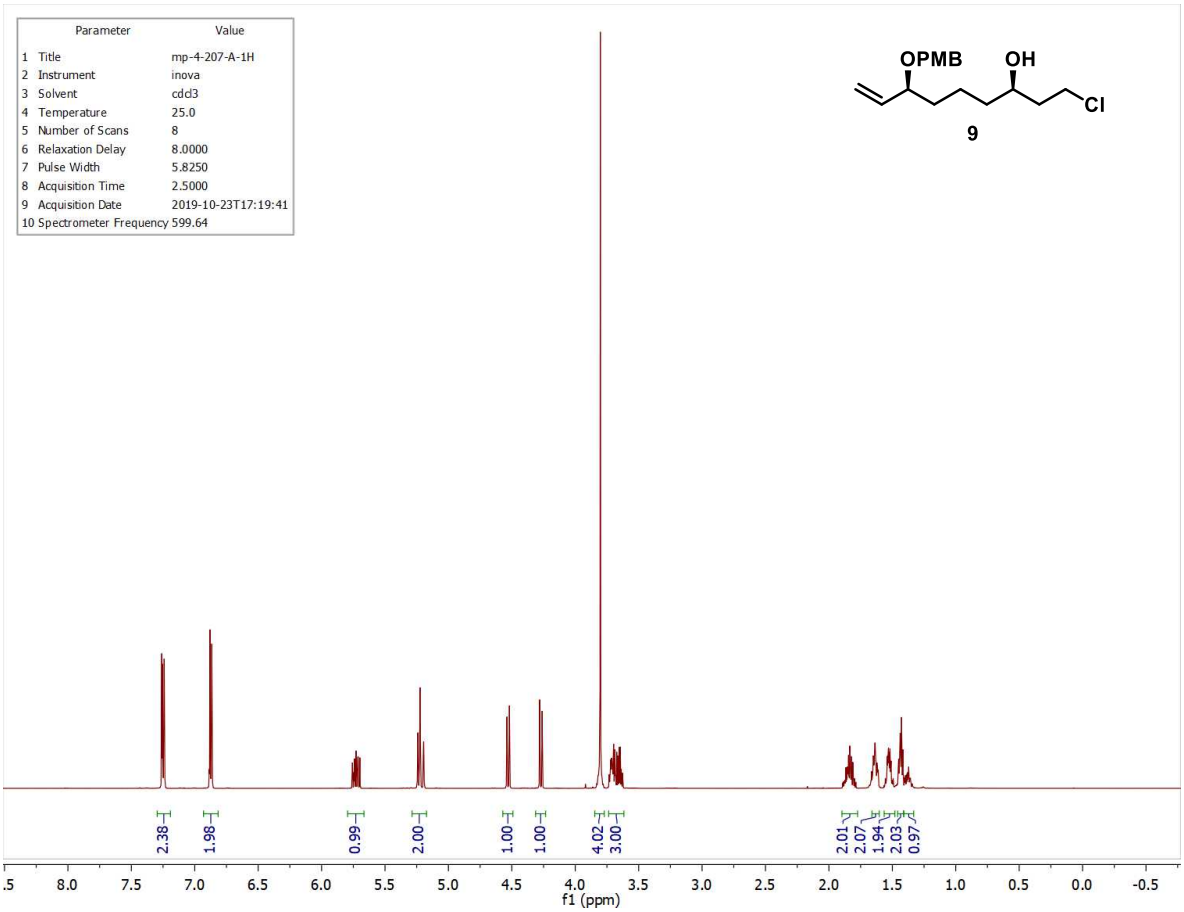
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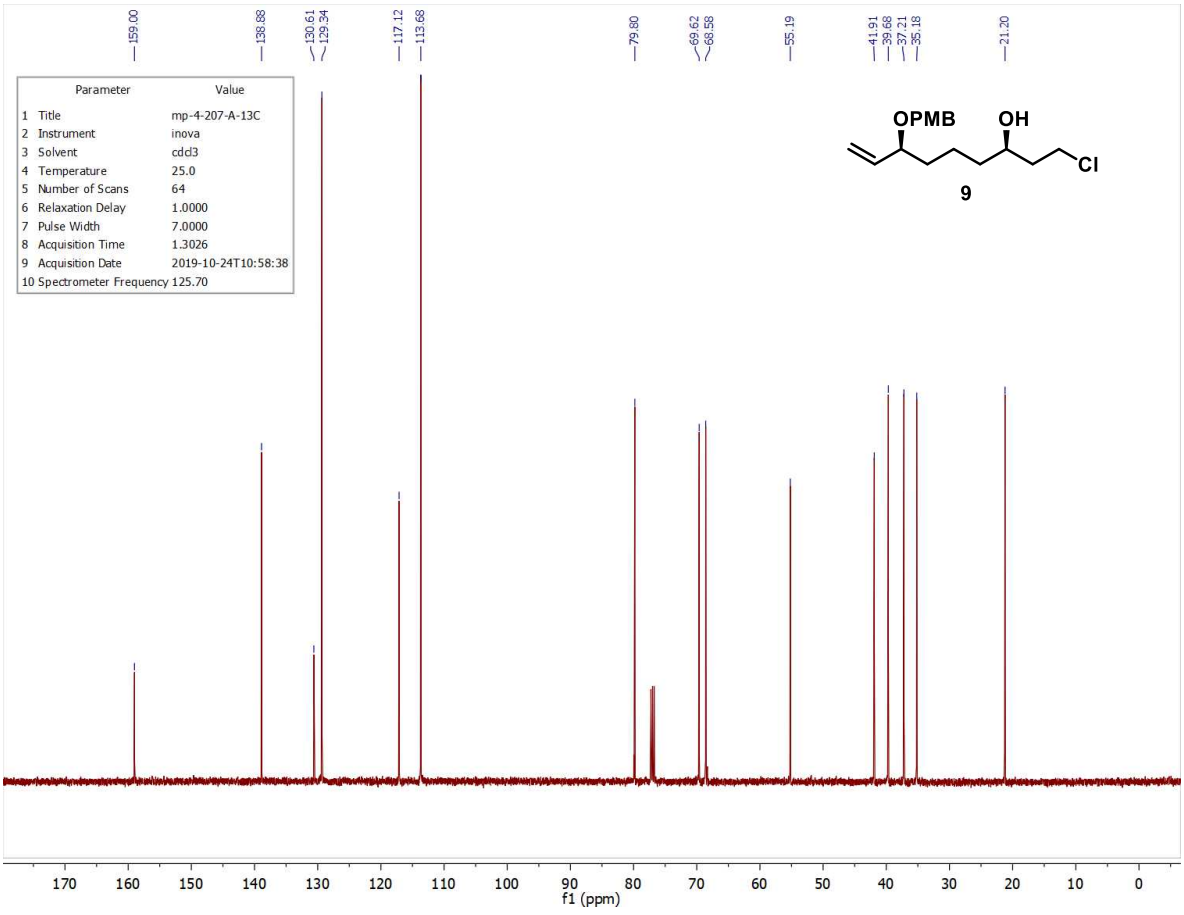
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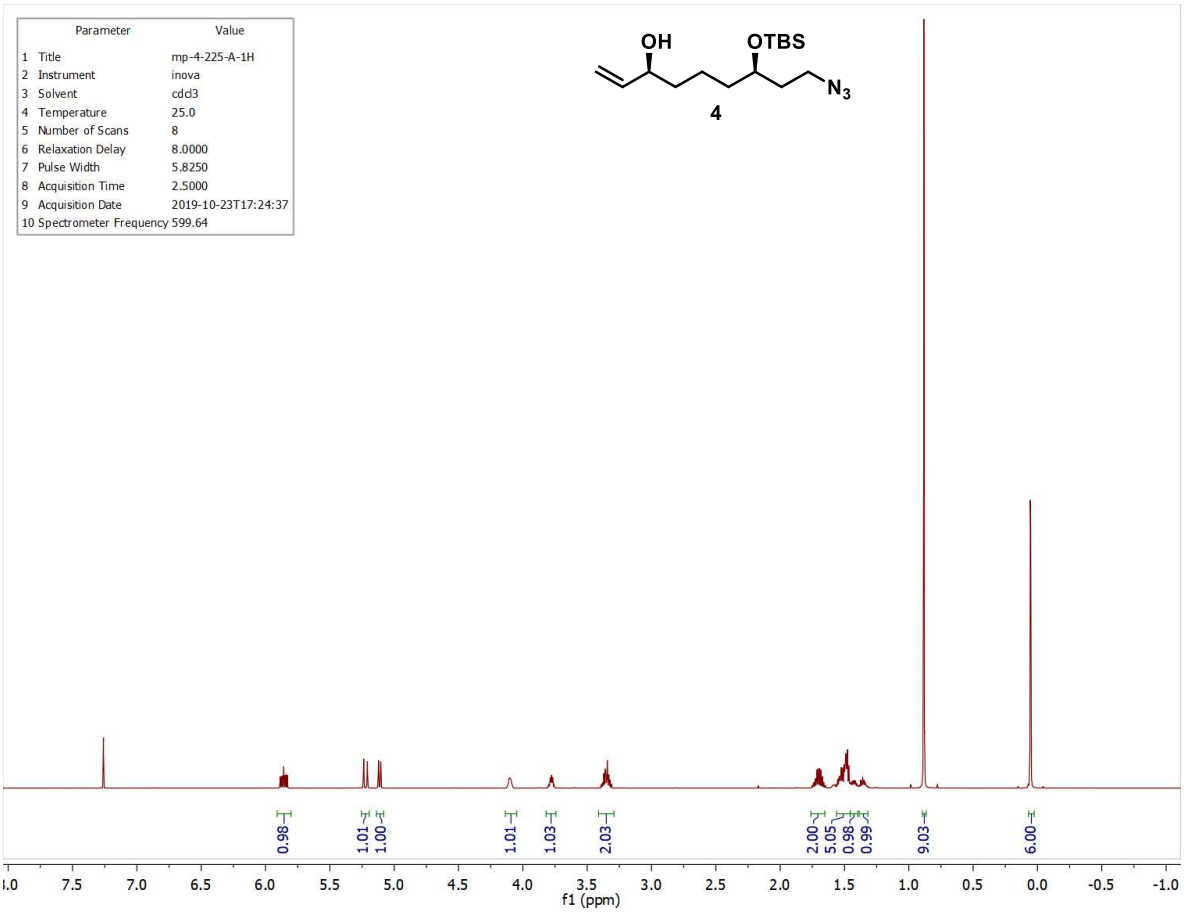
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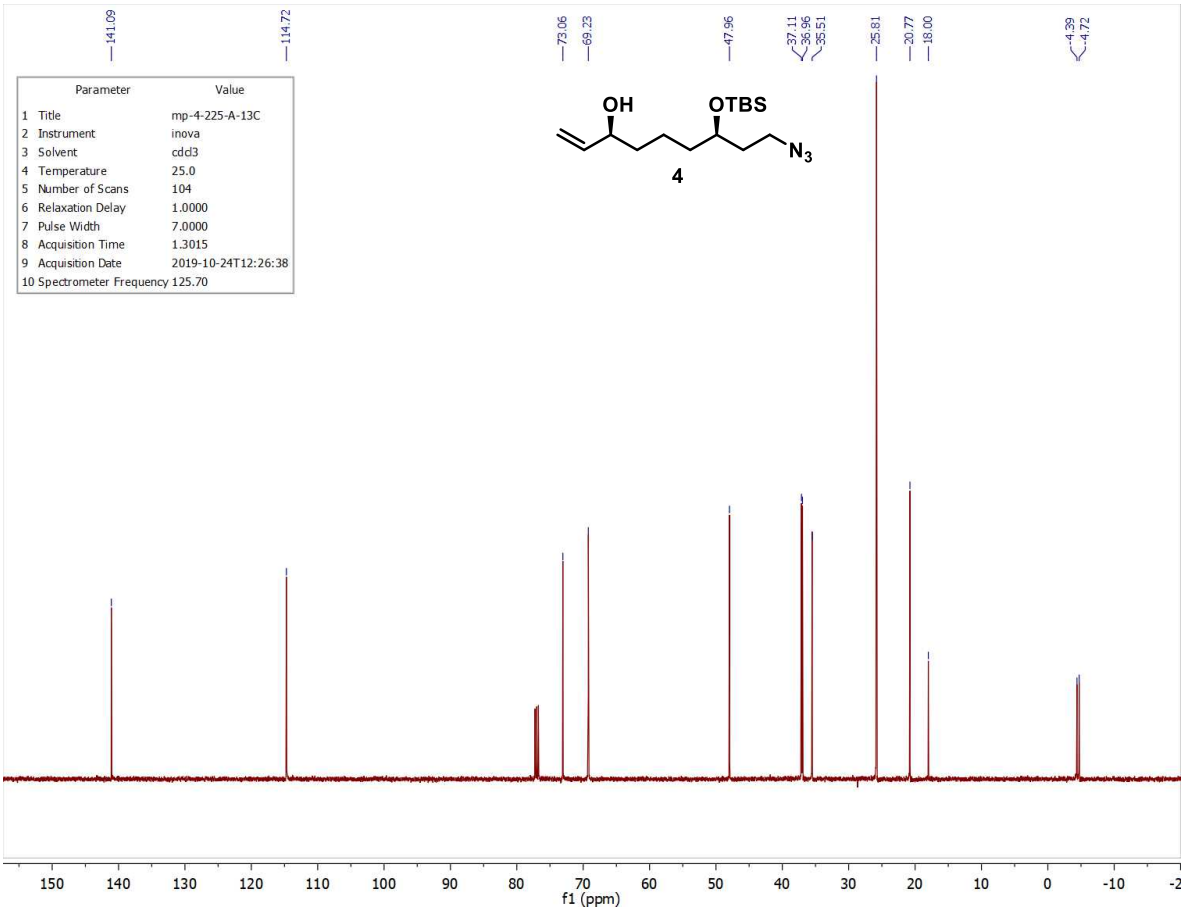
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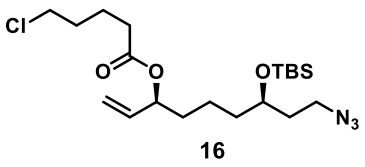

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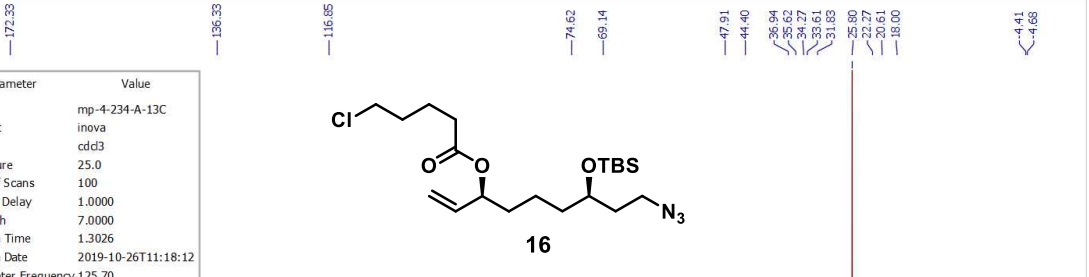

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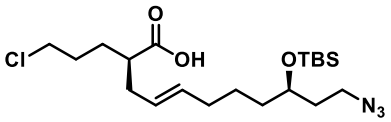
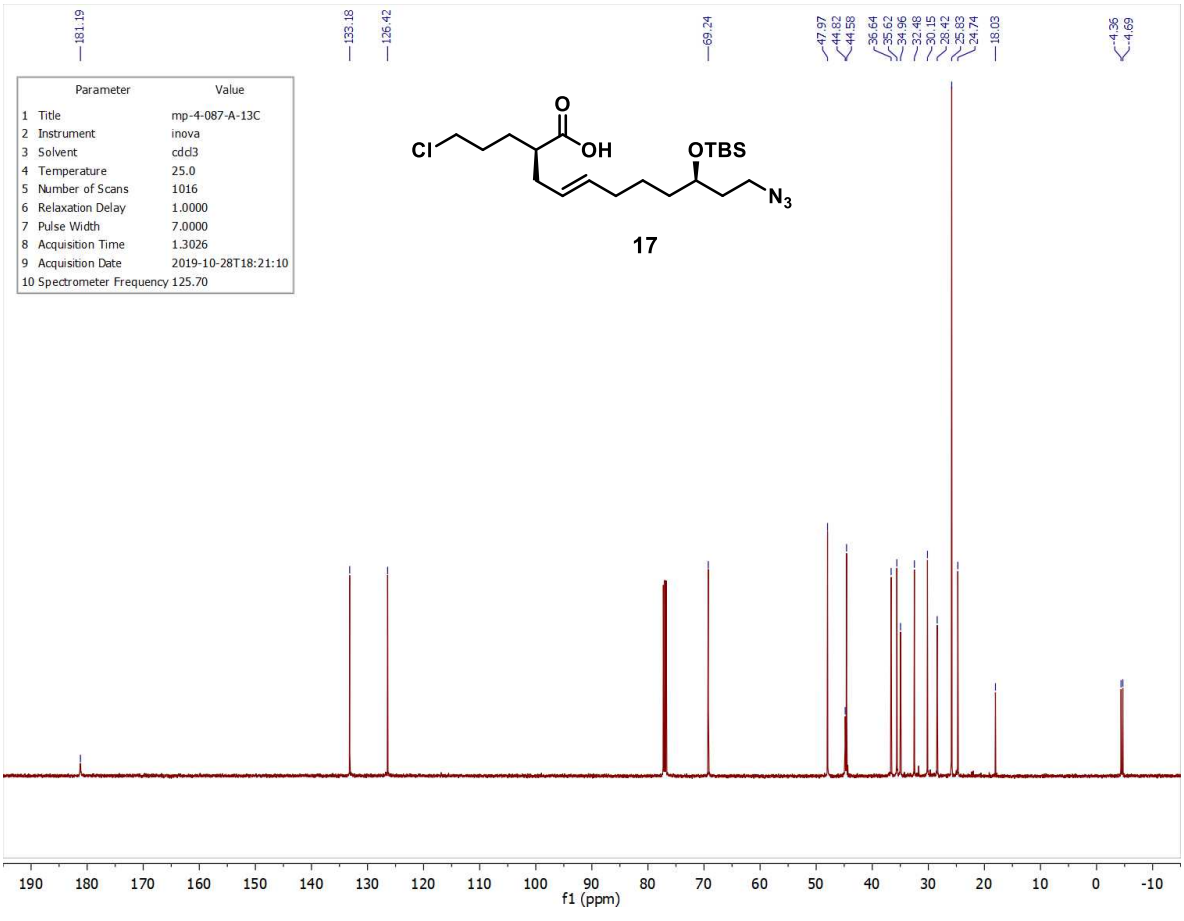
10	Spectrometer Frequency	499.85

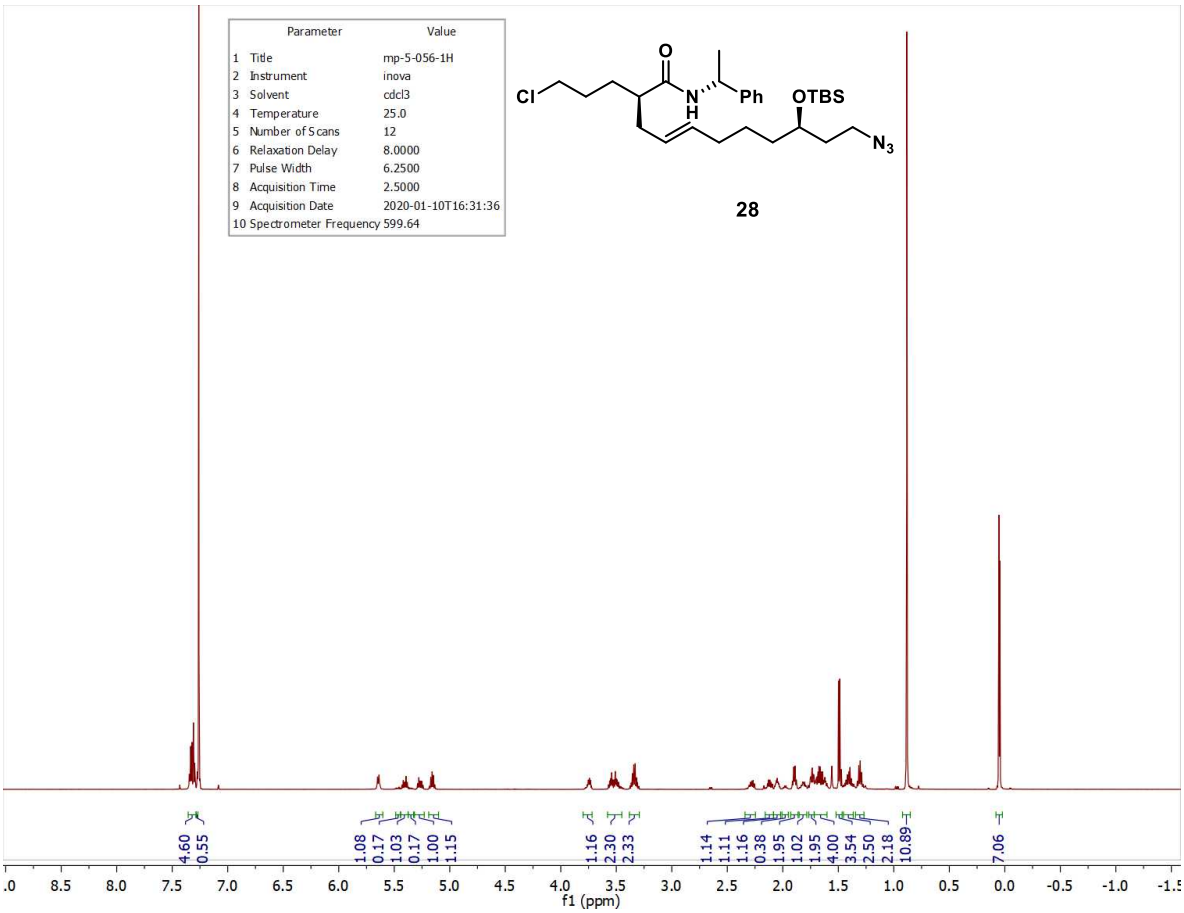


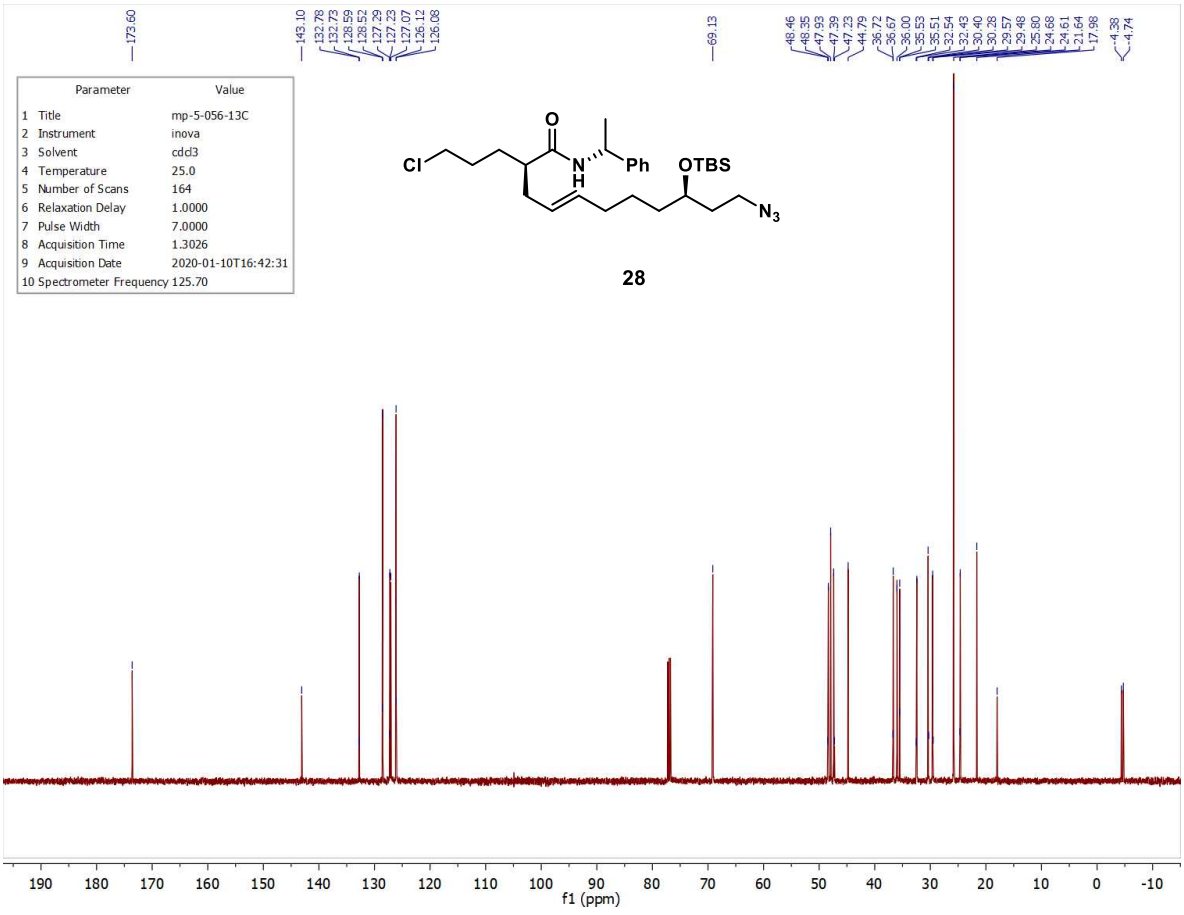
17



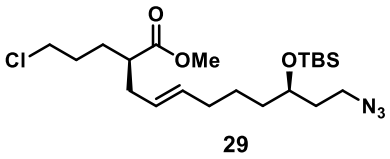
	Parameter	Value
1	Title	mp-4-087-A-13C
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	1016
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2019-10-28T18:21:10
10	Spectrometer Frequency	125.70

17

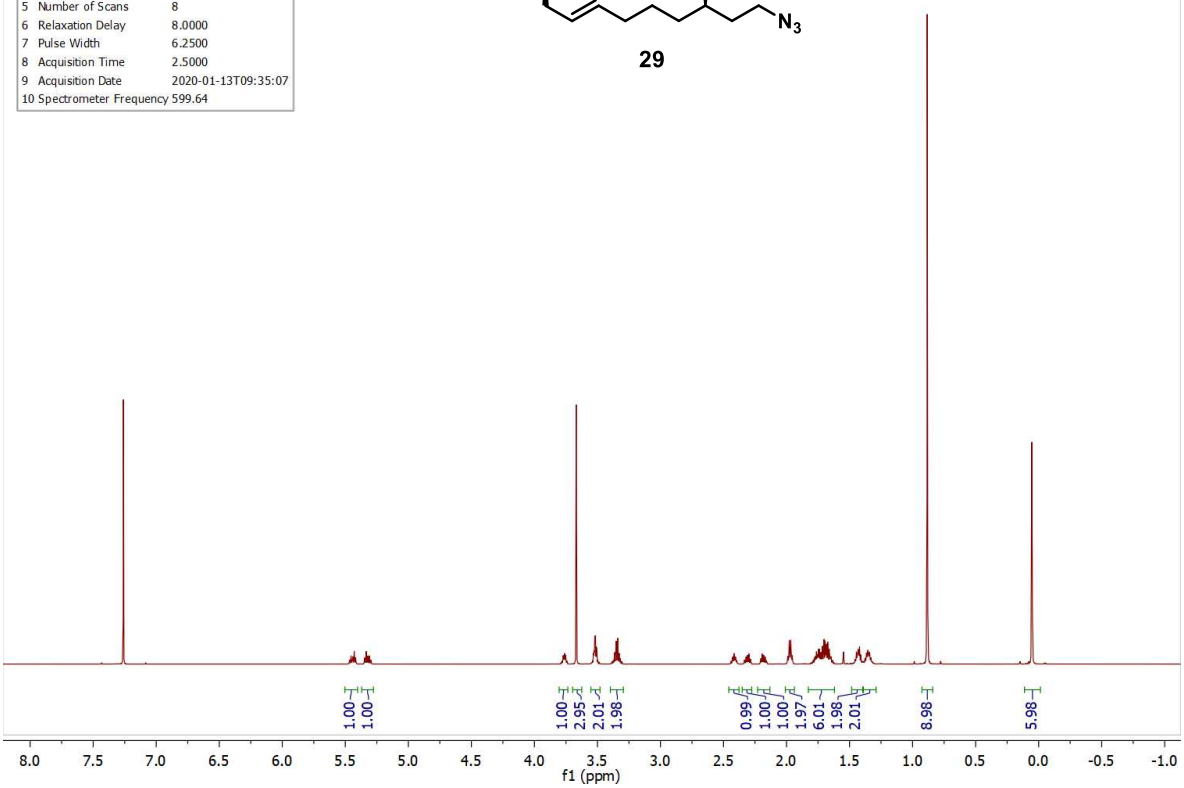

Parameter Value
1 Title mp-5-056-1H
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 6.2500
8 Acquisition Time 2.5000
9 Acquisition Date 2020-01-10T16:31:36
10 Spectrometer Frequency 599.64
Cl
O
N
H
Ph
OTBS
N3
28
4.60 0.55 1.08 0.17 1.03 0.17 1.00 1.15 1.16 2.30 2.33 1.14 1.11 1.16 0.38 1.95 1.02 1.95 4.00 3.54 2.50 2.18 10.89 7.06
f1 (ppm)

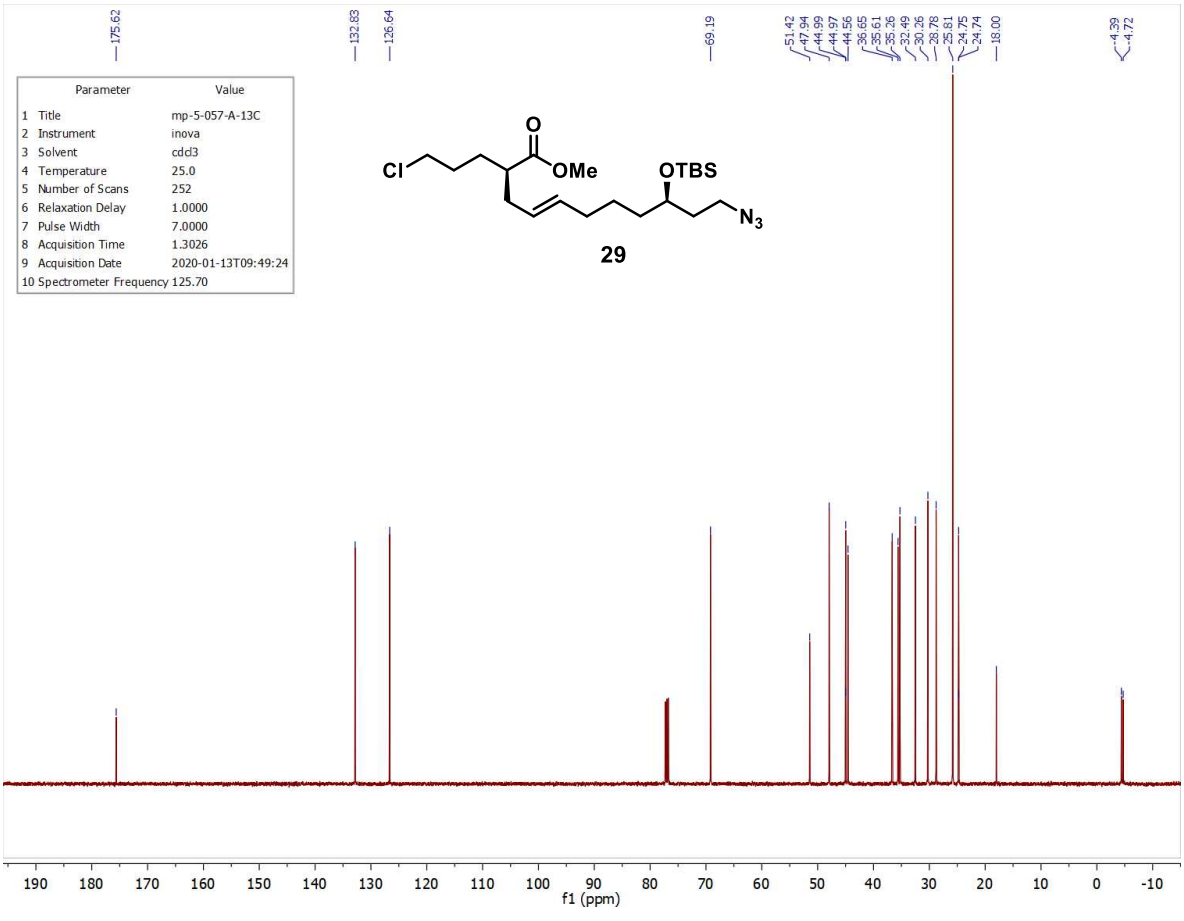

173.60 143.10 132.78 132.73 128.59 128.52 127.29 127.23 127.07 126.12 126.08 69.13 48.46 48.35 47.93 47.39 47.23 44.79 36.72 36.67 36.00 35.53 35.51 32.54 32.43 30.40 30.28 29.57 29.48 25.80 24.68 24.61 21.64 17.98 -4.38 -4.74
Parameter Value
1 Title mp-5-056-13C
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 164
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2020-01-10T16:42:31
10 Spectrometer Frequency 125.70
Cl
O
N
H
Ph
OTBS
N3
28
f1 (ppm)

	Parameter	Value
1	Title	mp-5-057-A-1H
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	8
6	Relaxation Delay	8.0000
7	Pulse Width	6.2500
8	Acquisition Time	2.5000
9	Acquisition Date	2020-01-13T09:35:07
10	Spectrometer Frequency	599.64



29

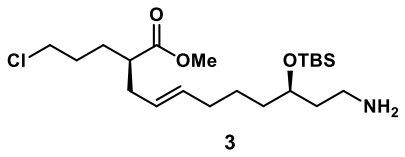




	Parameter	Value
1	Title	mp-5-057-A-13C
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	252
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2020-01-13T09:49:24
10	Spectrometer Frequency	125.70

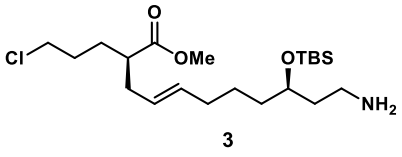
29

	Parameter	Value
1	Title	mp-4-247-A-1H
2	Instrument	vnmrs
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	12
6	Relaxation Delay	8.0000
7	Pulse Width	9.1625
8	Acquisition Time	2.5001
9	Acquisition Date	2019-08-01T12:38:08
10	Spectrometer Frequency	399.78



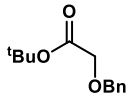
3

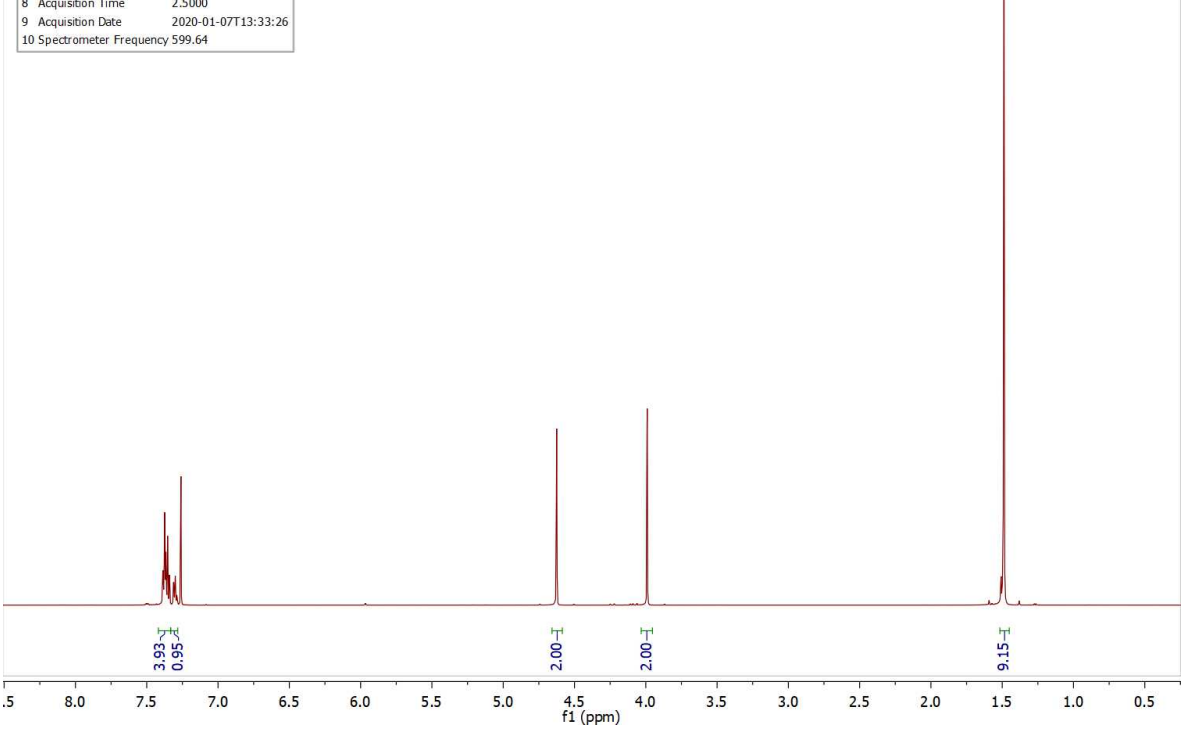
	Parameter	Value
1	Title	mp-5-058-A-13C
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	384
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2020-01-16T11:14:31
10	Spectrometer Frequency	125.70

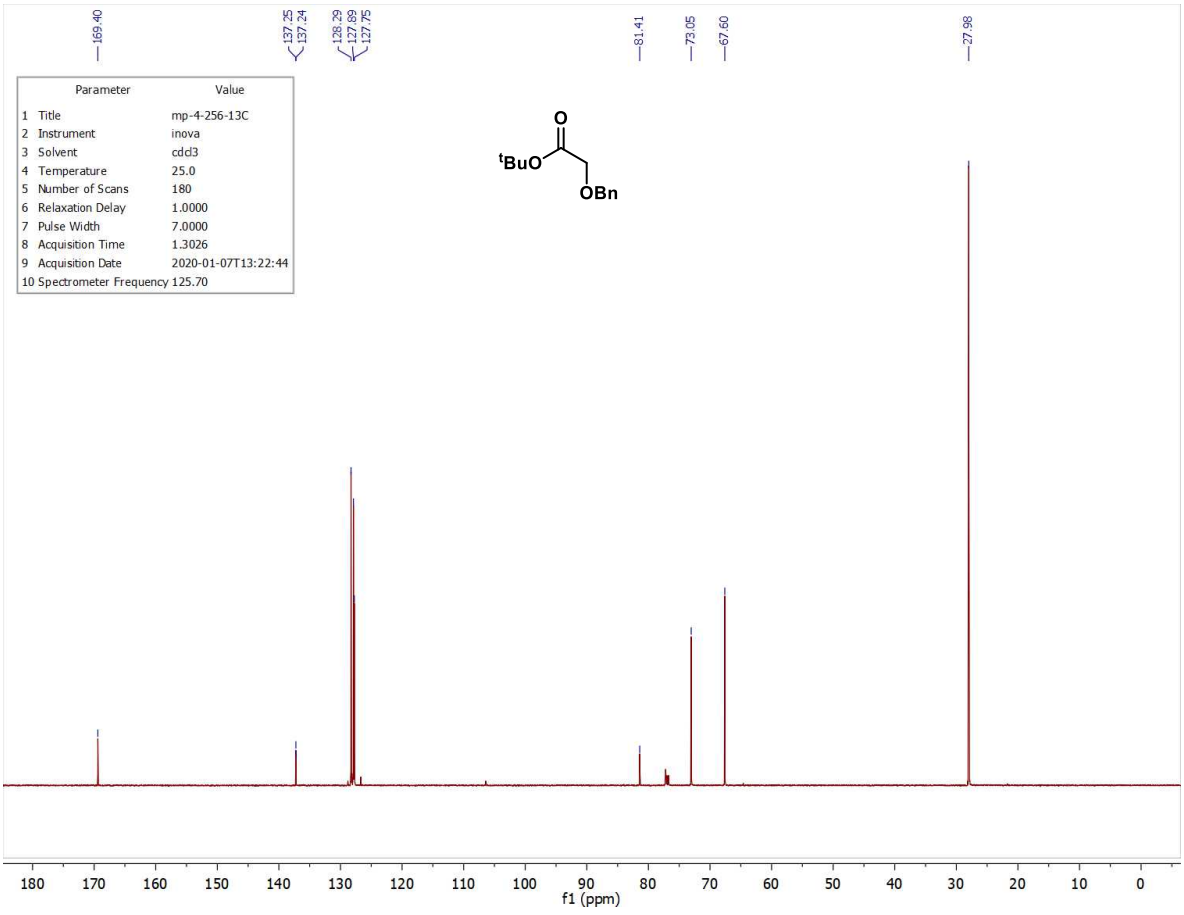


3

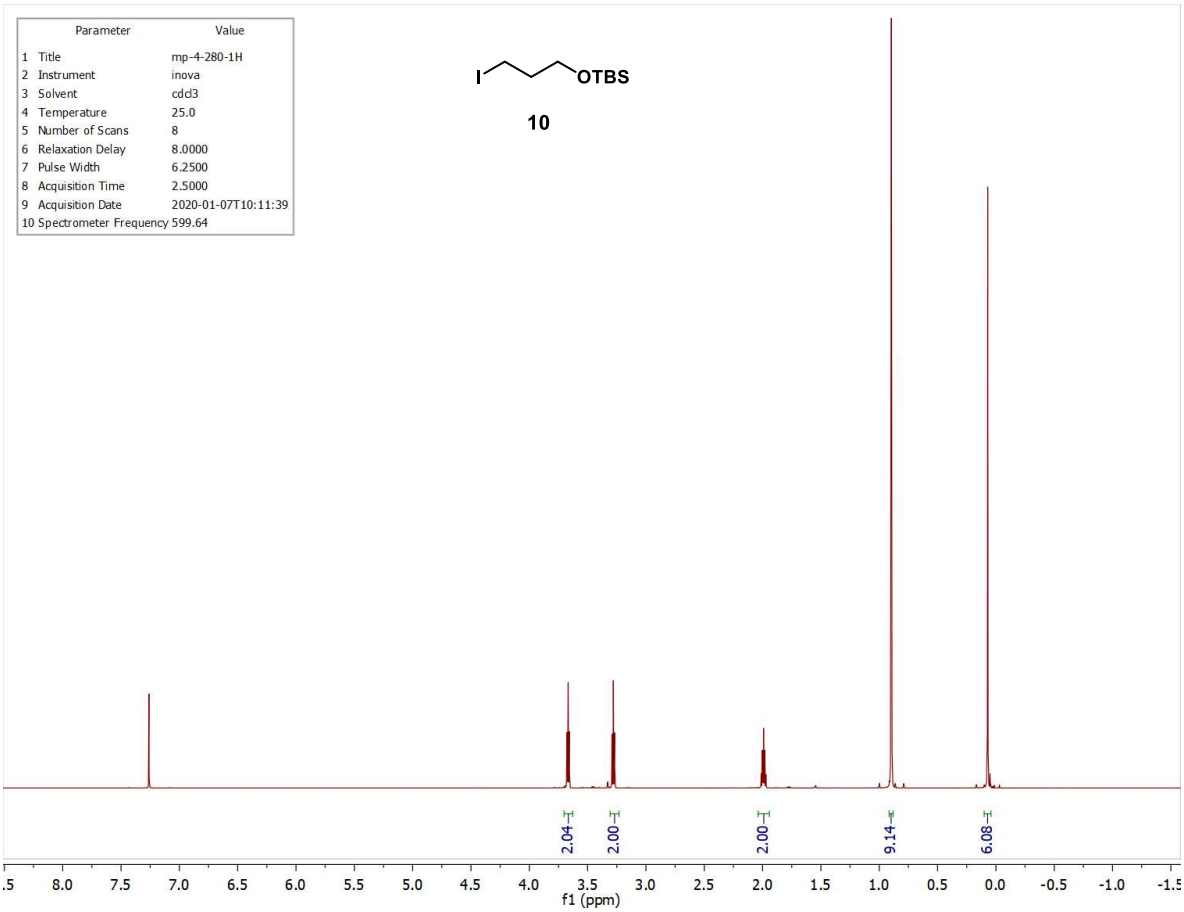
	Parameter	Value
1	Title	mp-4-256-1H
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	20
6	Relaxation Delay	8.0000
7	Pulse Width	6.2500
8	Acquisition Time	2.5000
9	Acquisition Date	2020-01-07T13:33:26
10	Spectrometer Frequency	599.64

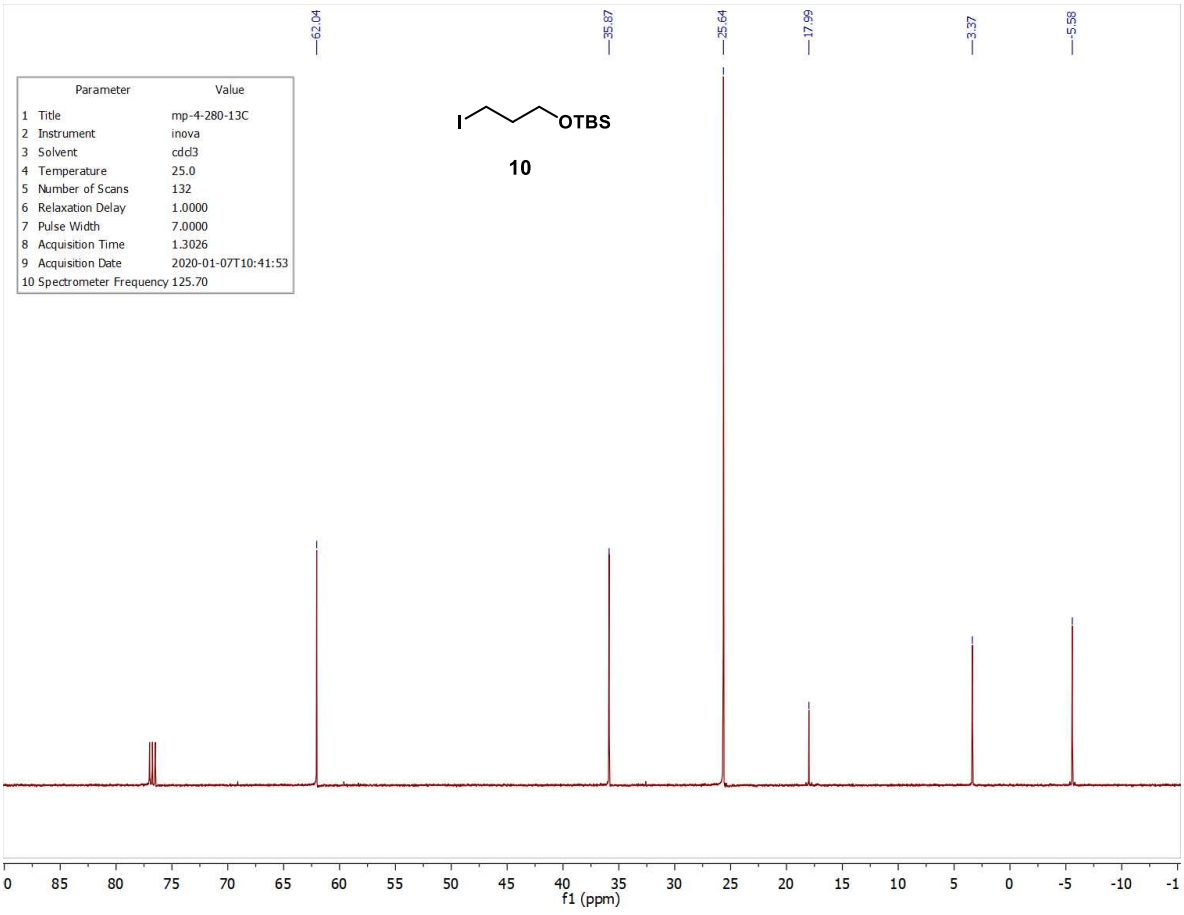




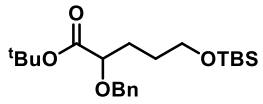


	Parameter	Value
1	Title	mp-4-256-13C
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	180
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2020-01-07T13:22:44
10	Spectrometer Frequency	125.70

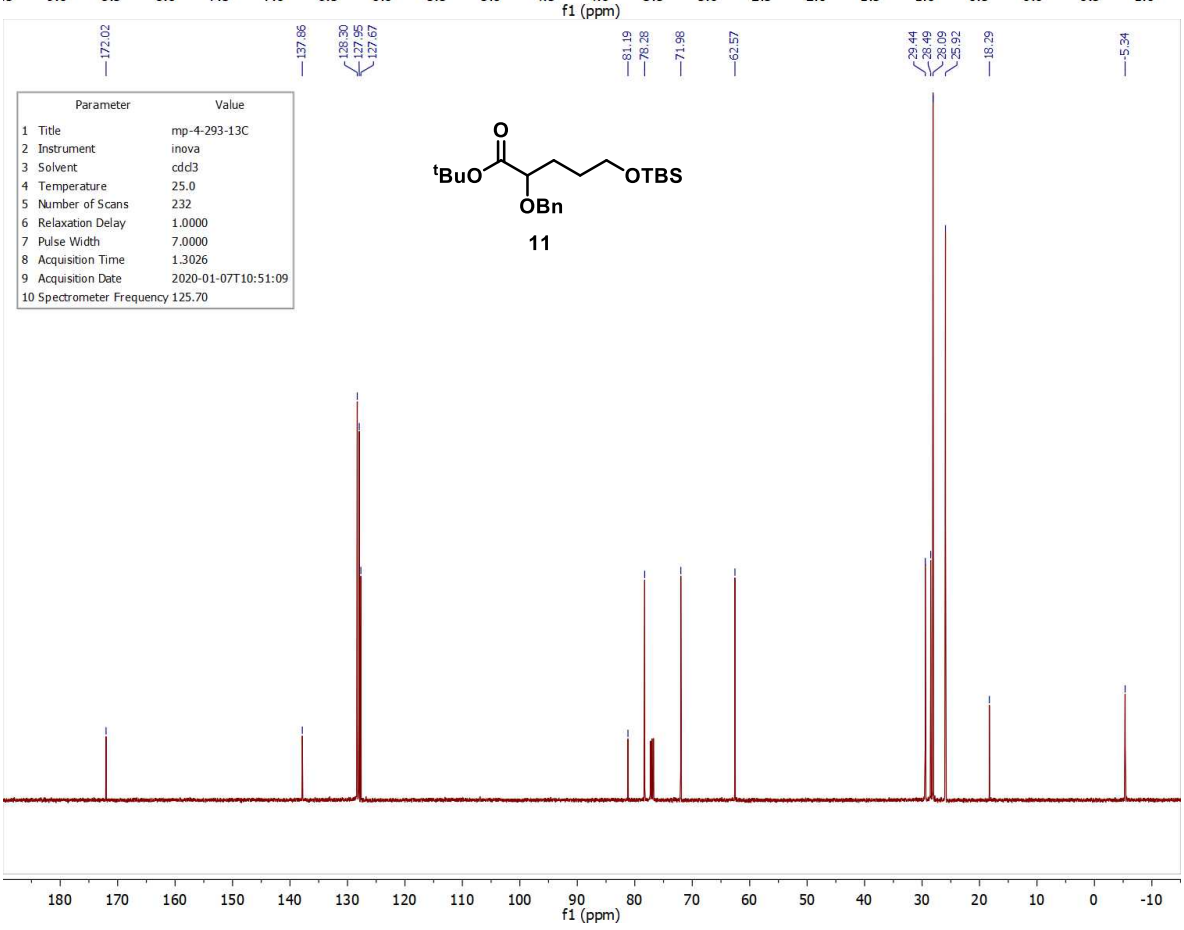

Parameter Value
1 Title mp-4-280-1H
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 6.2500
8 Acquisition Time 2.5000
9 Acquisition Date 2020-01-07T10:11:39
10 Spectrometer Frequency 599.64
I
OTBS
10
2.04
2.00
2.00
9.14
6.08
f1 (ppm)


62.04
35.87
25.64
17.99
3.37
-5.58
Parameter Value
1 Title mp-4-280-13C
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 132
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2020-01-07T10:41:53
10 Spectrometer Frequency 125.70
I
OTBS
10
f1 (ppm)

	Parameter	Value
1	Title	mp-4-293-1H
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	12
6	Relaxation Delay	8.0000
7	Pulse Width	6.2500
8	Acquisition Time	2.5000
9	Acquisition Date	2020-01-07T10:16:47
10	Spectrometer Frequency	599.64

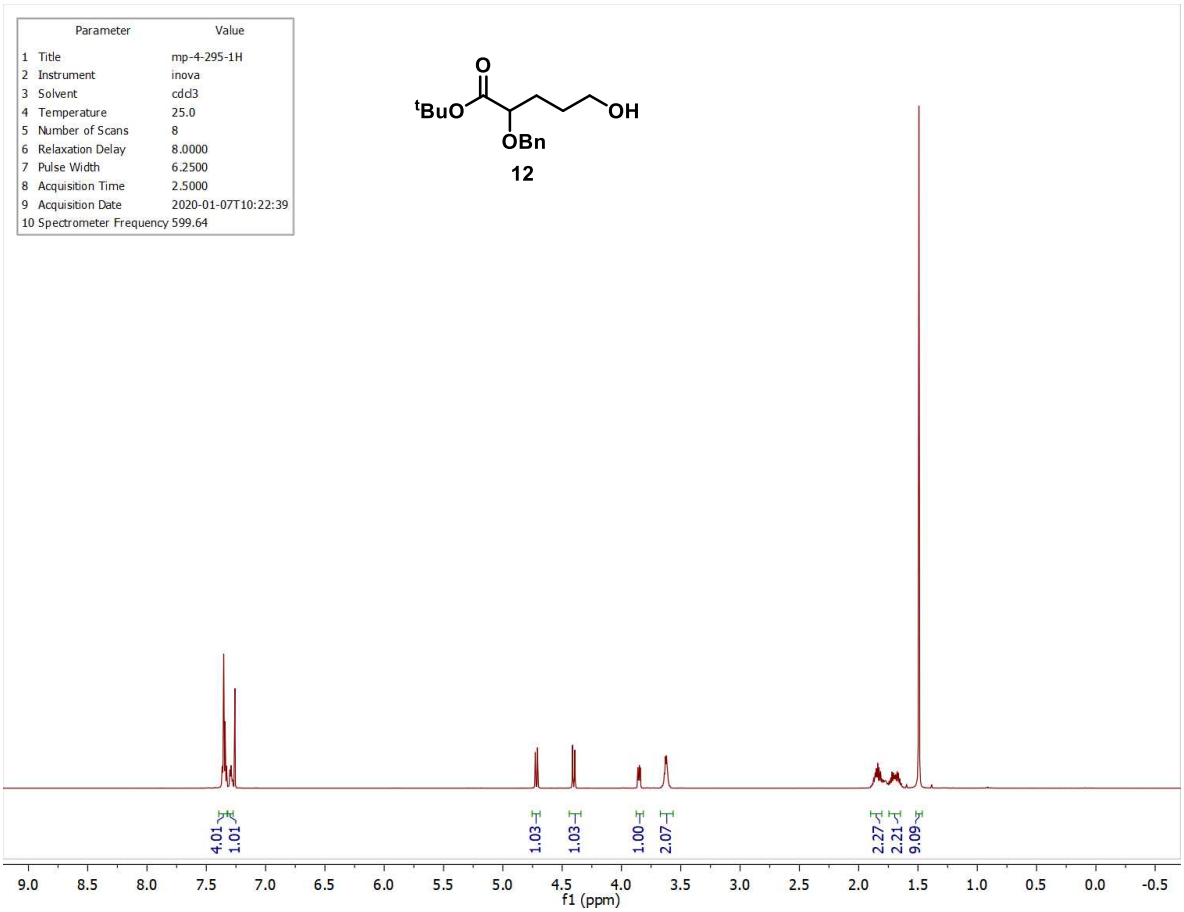


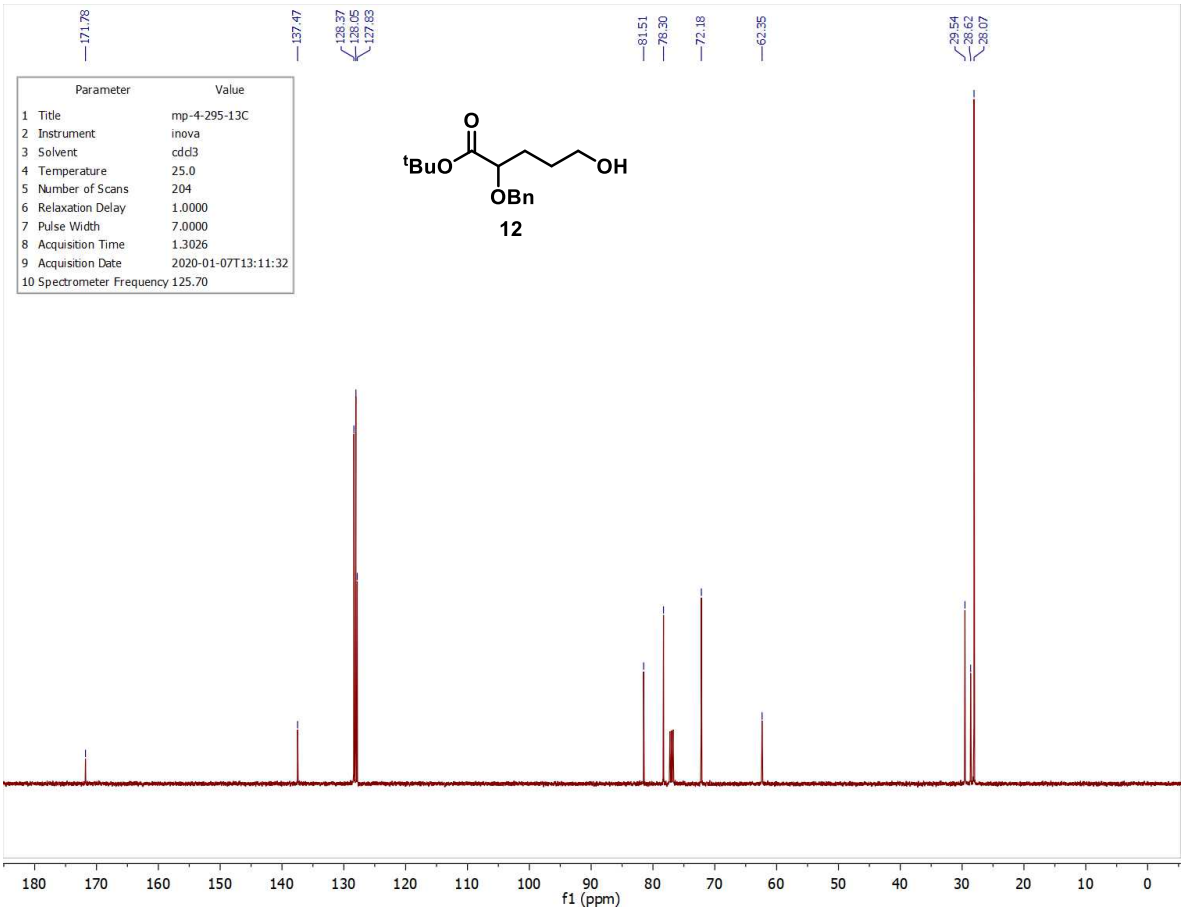
11



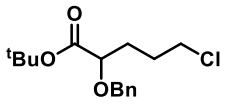
	Parameter	Value
1	Title	mp-4-293-13C
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	232
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2020-01-07T10:51:09
10	Spectrometer Frequency	125.70

11

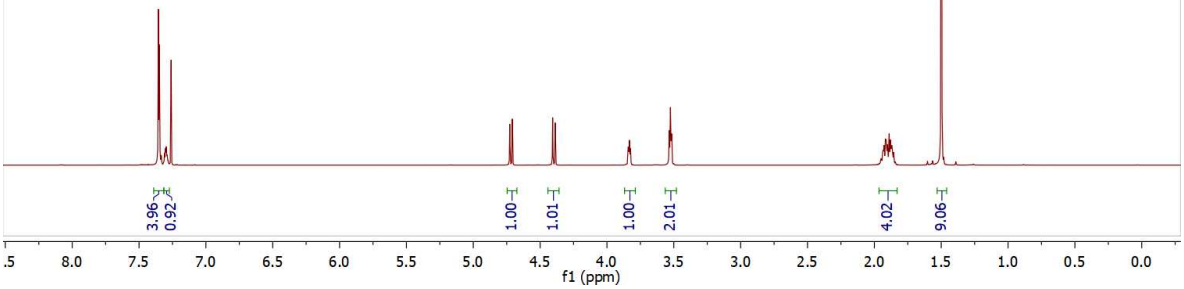

Parameter Value
1 Title mp-4-295-1H
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 6.2500
8 Acquisition Time 2.5000
9 Acquisition Date 2020-01-07T10:22:39
10 Spectrometer Frequency 599.64
tBuO
O
OH
OBn
12
4.01
1.01
1.03
1.03
1.00
2.07
2.27
2.21
9.09
f1 (ppm)


171.78
137.47
128.37
128.05
127.83
81.51
78.30
72.18
62.35
29.54
28.62
28.07
Parameter Value
1 Title mp-4-295-13C
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 204
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2020-01-07T13:11:32
10 Spectrometer Frequency 125.70
tBuO
O
OH
OBn
12
f1 (ppm)

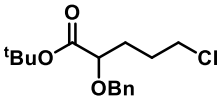
	Parameter	Value
1	Title	mp-4-296-1H
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	24
6	Relaxation Delay	8.0000
7	Pulse Width	6.2500
8	Acquisition Time	2.5000
9	Acquisition Date	2020-01-07T10:27:50
10	Spectrometer Frequency	599.64



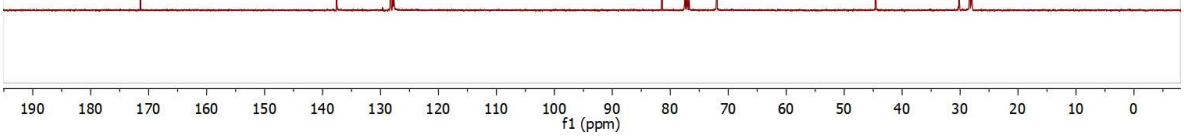
13

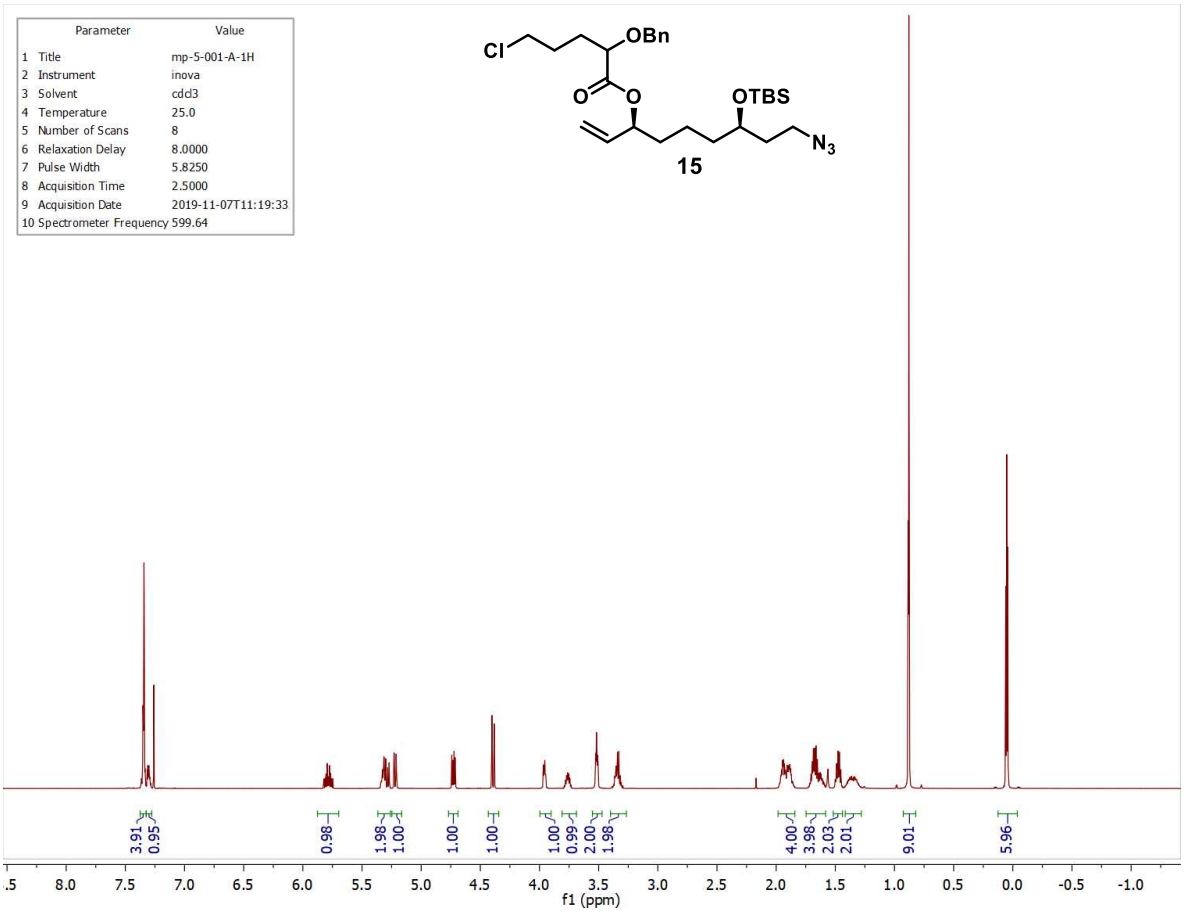


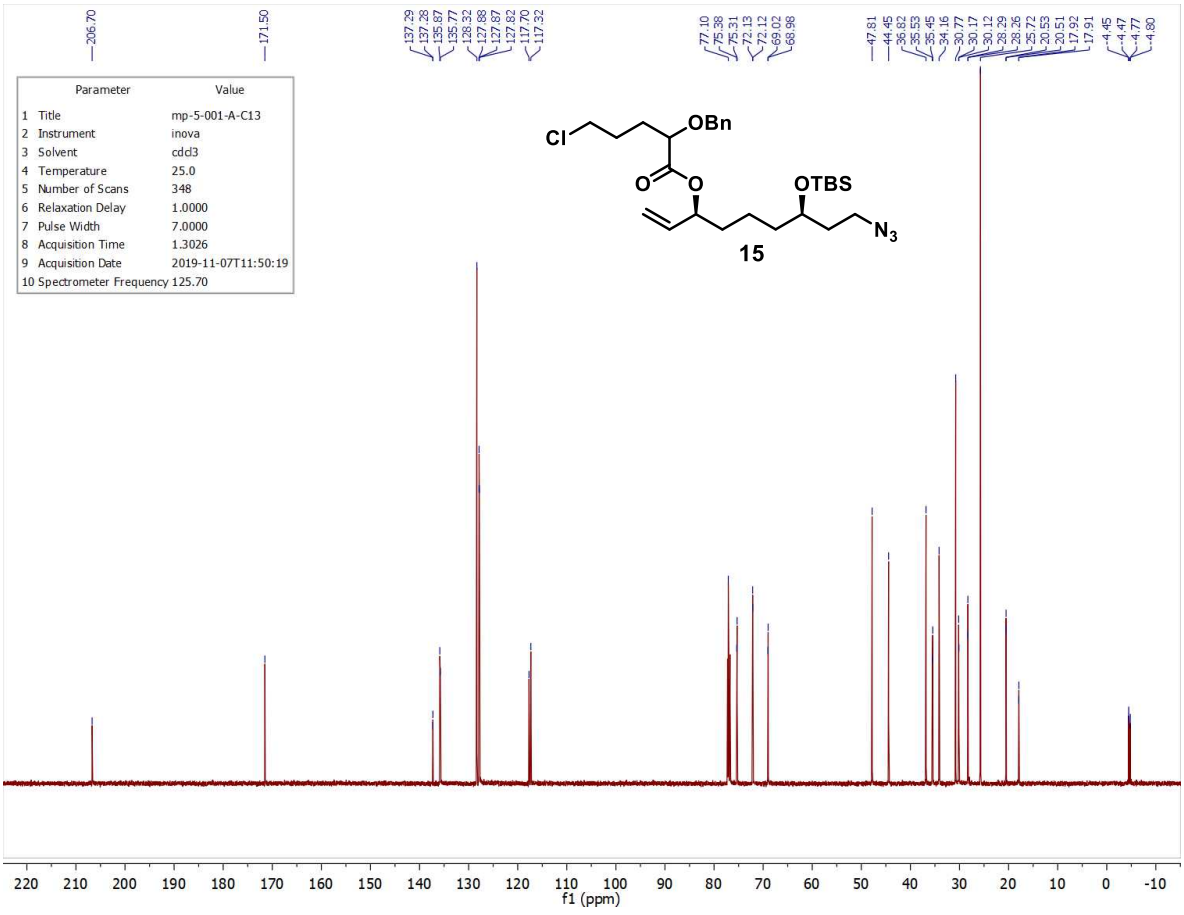
	Parameter	Value
1	Title	mp-4-296-13C
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	132
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2020-01-07T11:03:32
10	Spectrometer Frequency	125.70



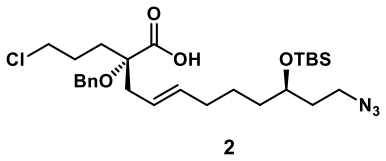
13



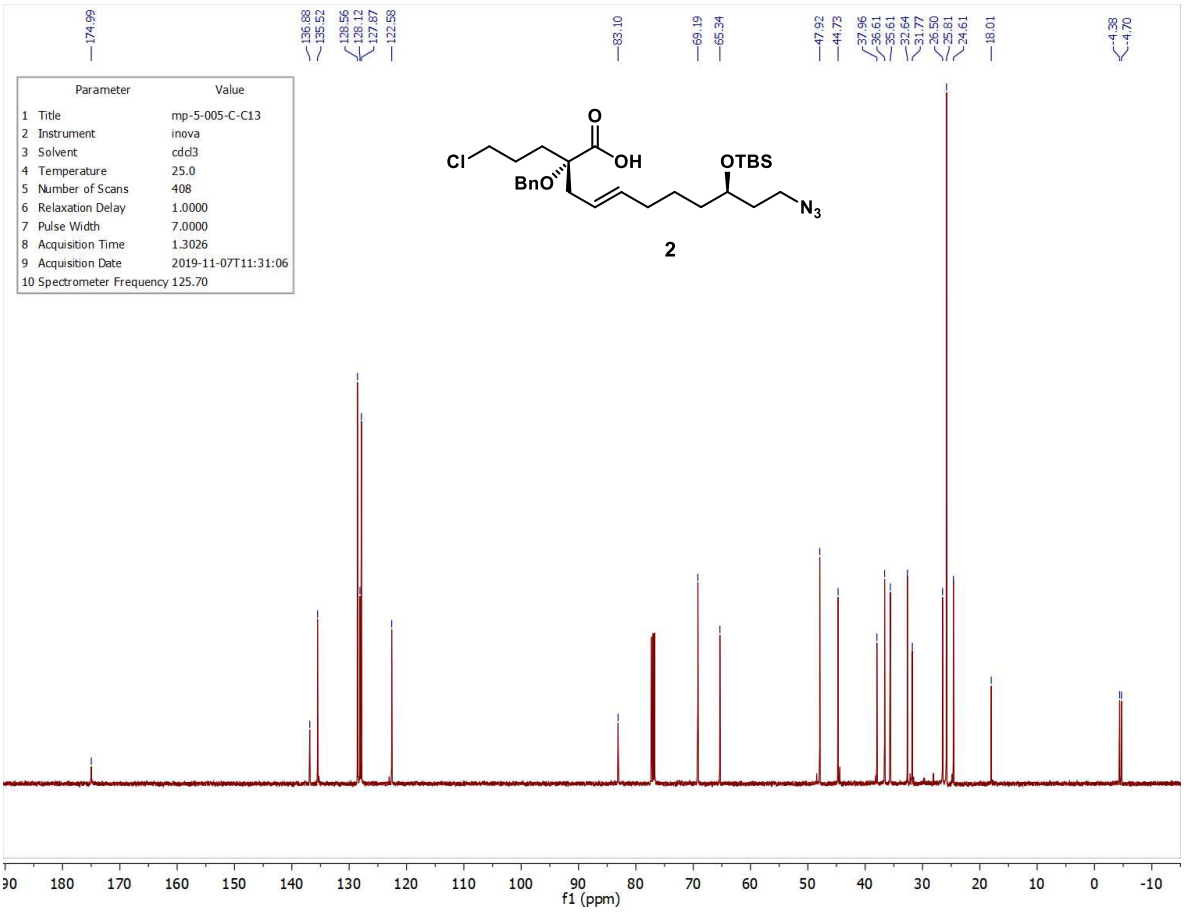

Parameter Value
1 Title mp-5-001-A-1H
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 5.8250
8 Acquisition Time 2.5000
9 Acquisition Date 2019-11-07T11:19:33
10 Spectrometer Frequency 599.64
Cl
OBn
O
O
OTBS
N3
15
3.91
0.95
0.98
1.98
1.00
1.00
1.00
1.00
0.99
2.00
1.98
4.00
3.98
2.03
2.01
9.01
5.96
f1 (ppm)


206.70
171.50
137.29
137.28
136.87
135.77
128.32
127.88
127.87
127.82
117.70
117.32
77.10
75.38
75.31
72.13
72.12
69.02
68.98
47.81
44.45
36.82
35.53
35.45
34.16
30.77
30.17
30.12
28.29
28.26
25.72
20.53
20.51
17.92
17.91
-4.45
-4.47
-4.77
-4.80
Parameter Value
1 Title mp-5-001-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 348
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2019-11-07T11:50:19
10 Spectrometer Frequency 125.70
Cl
OBn
O
O
OTBS
N3
15
f1 (ppm)

	Parameter	Value
1	Title	mp-5-005-C-1H
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	8
6	Relaxation Delay	8.0000
7	Pulse Width	5.8250
8	Acquisition Time	2.5000
9	Acquisition Date	2019-11-07T11:14:34
10	Spectrometer Frequency	599.64

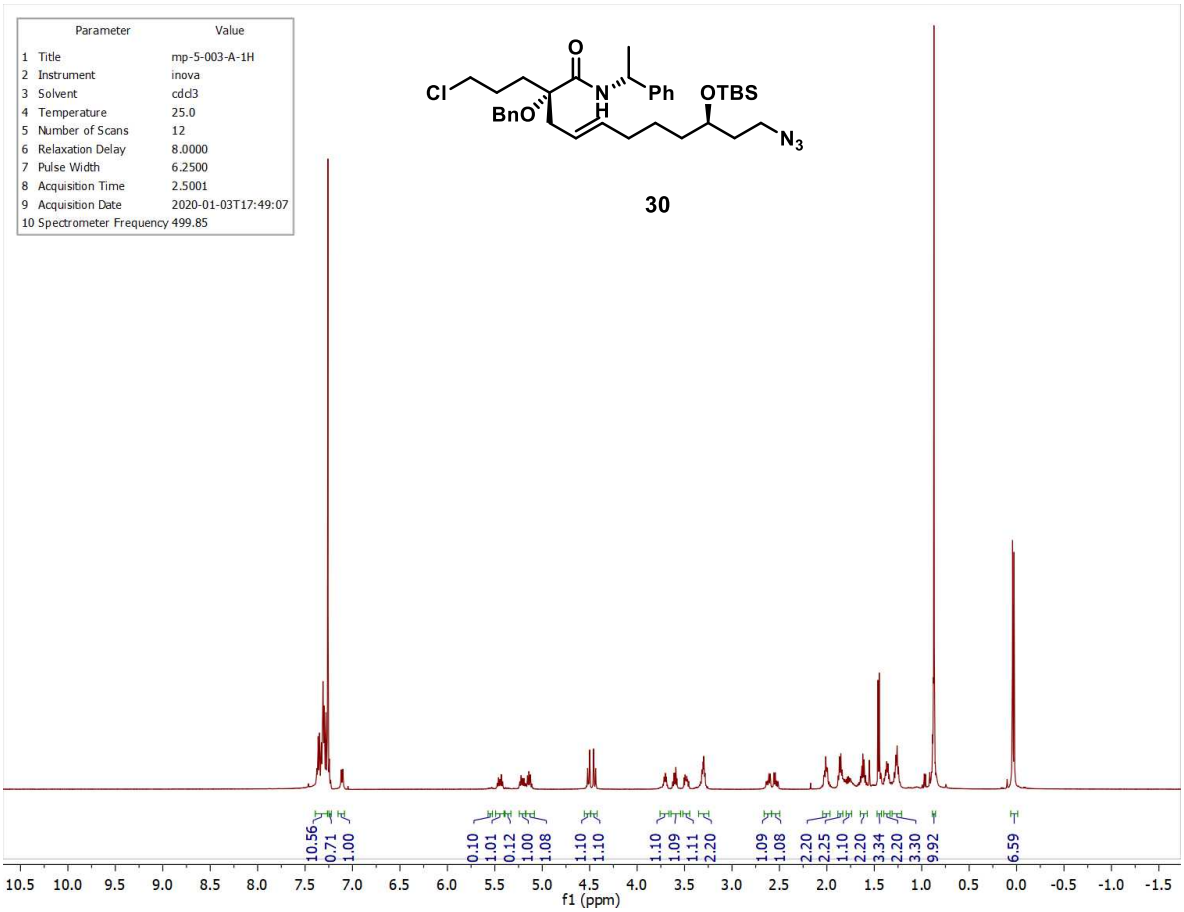


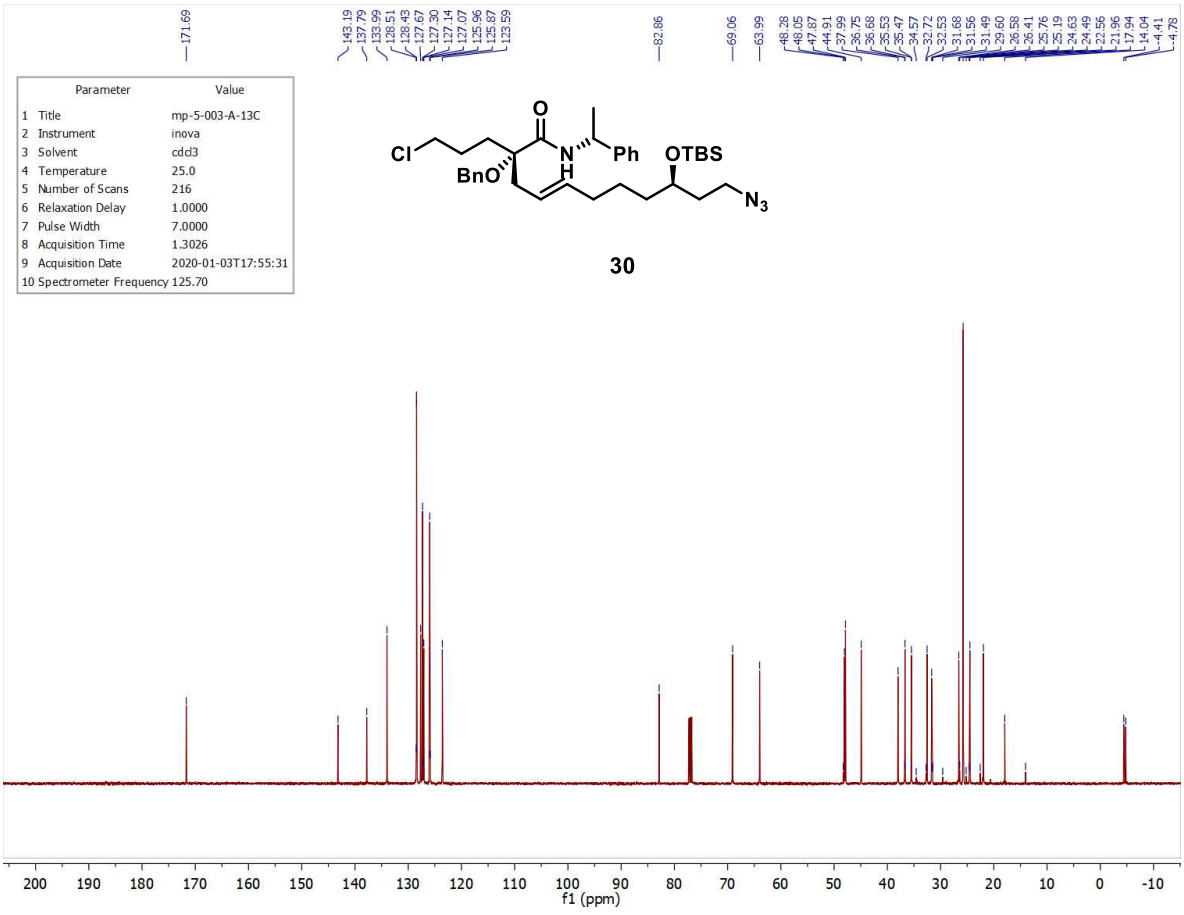
2



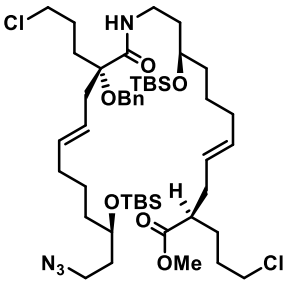
	Parameter	Value
1	Title	mp-5-005-C-C13
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	408
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2019-11-07T11:31:06
10	Spectrometer Frequency	125.70

2

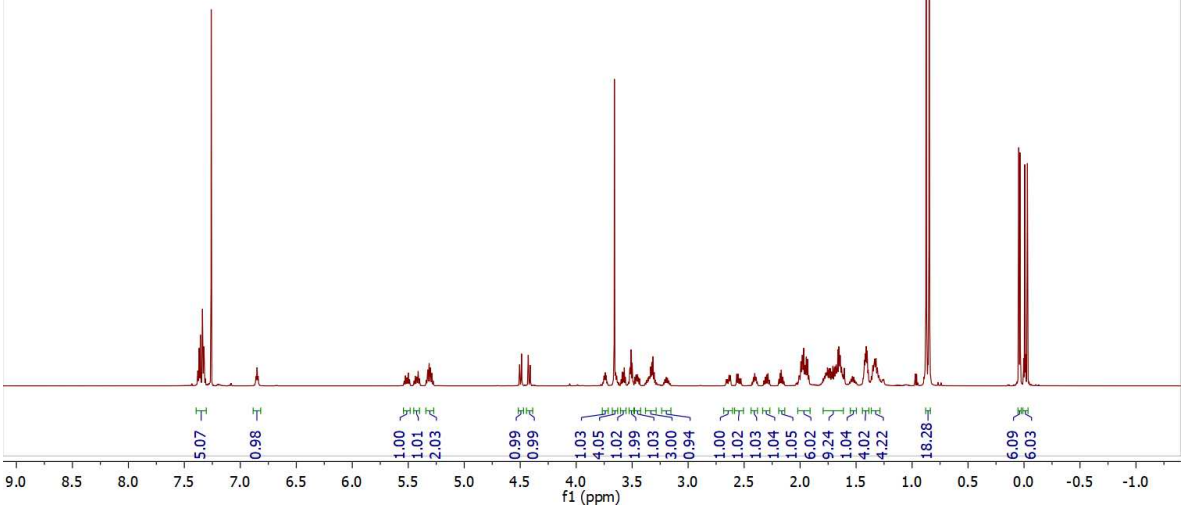

Parameter Value
1 Title mp-5-003-A-1H
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 6.2500
8 Acquisition Time 2.5001
9 Acquisition Date 2020-01-03T17:49:07
10 Spectrometer Frequency 499.85
Cl
O
N
H
Ph
OTBS
BnO
N3
30
10.56 0.71 1.00 0.10 1.01 0.12 1.00 1.08 1.10 1.10 1.10 1.09 1.11 2.20 1.09 1.08 2.20 2.25 1.10 2.20 3.34 2.20 3.30 9.92 6.59
f1 (ppm)


171.69
143.19 137.79 133.99 128.51 128.43 127.67 127.30 127.14 127.07 125.96 125.87 123.59
82.86
69.06
63.99
48.28 48.05 47.87 44.91 37.99 36.75 36.68 35.53 35.47 34.57 32.72 32.53 31.68 31.56 31.49 29.60 26.58 26.41 25.76 25.19 24.63 24.49 22.56 21.96 17.94 14.04 -4.41 -4.78
Parameter Value
1 Title mp-5-003-A-13C
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 216
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2020-01-03T17:55:31
10 Spectrometer Frequency 125.70
Cl
O
N
H
Ph
OTBS
BnO
N3
30
f1 (ppm)

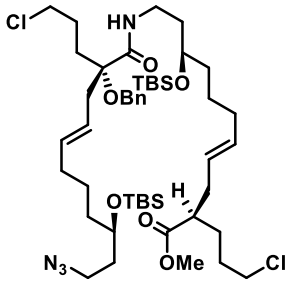
	Parameter	Value
1	Title	mp-5-004-A-1H
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	8
6	Relaxation Delay	8.0000
7	Pulse Width	6.2500
8	Acquisition Time	2.5000
9	Acquisition Date	2020-01-18T13:13:13
10	Spectrometer Frequency	599.64



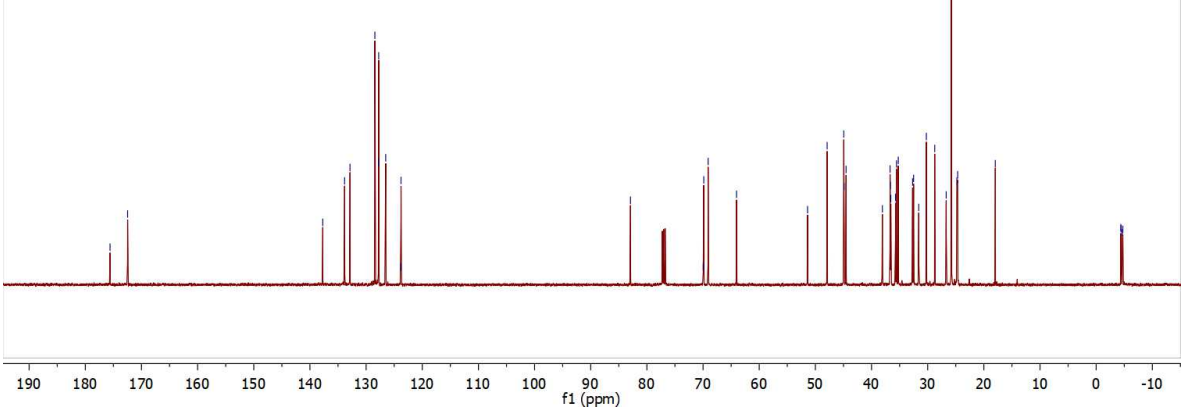
18



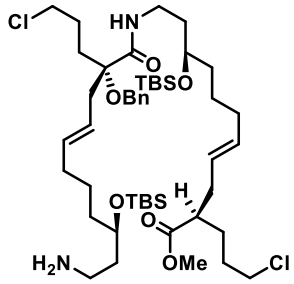
	Parameter	Value
1	Title	mp-5-004-A-13C
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	352
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2020-01-18T13:20:31
10	Spectrometer Frequency	125.70



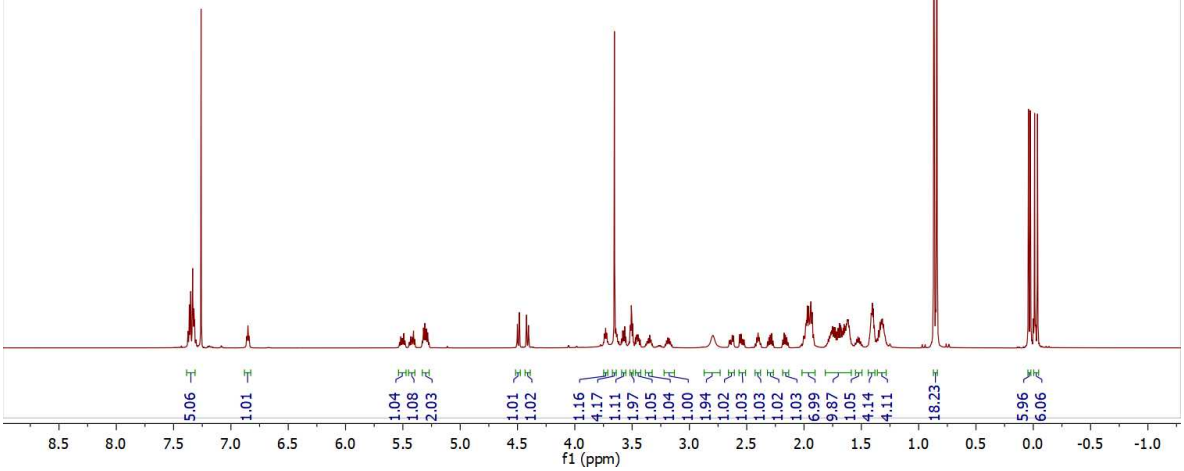
18



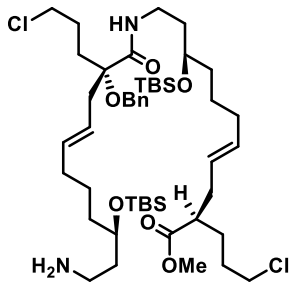
	Parameter	Value
1	Title	mp-5-059-A-1H
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	20
6	Relaxation Delay	8.0000
7	Pulse Width	6.2500
8	Acquisition Time	2.5000
9	Acquisition Date	2020-01-21T11:03:44
10	Spectrometer Frequency	599.64



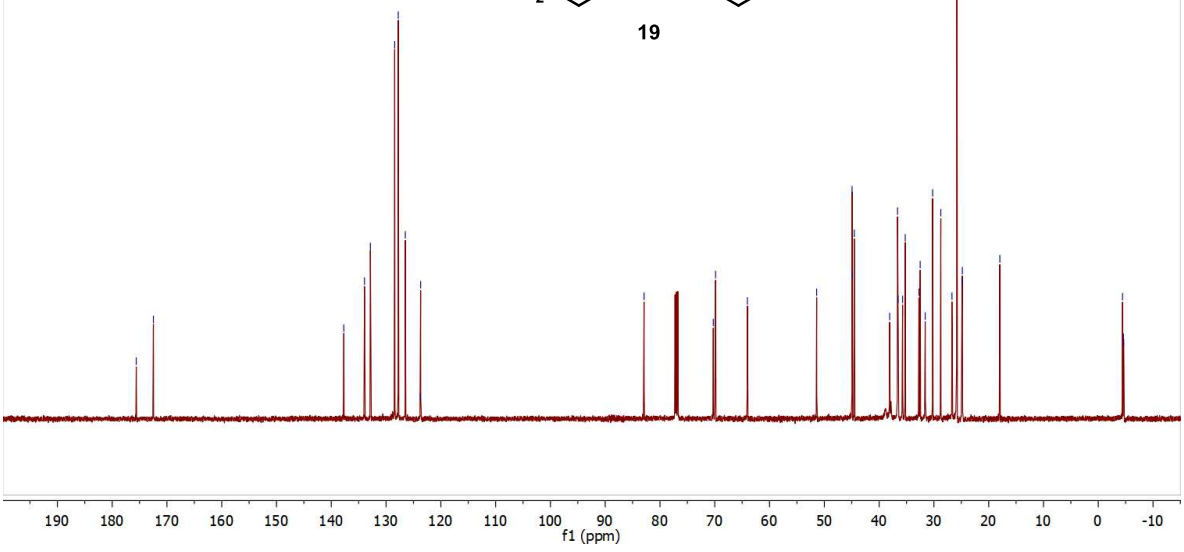
19



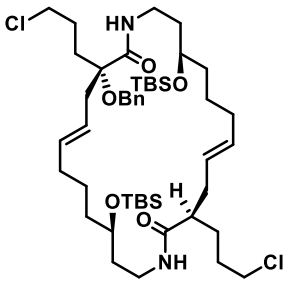
	Parameter	Value
1	Title	mp-5-059-A-13C
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	368
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2020-01-21T11:13:48
10	Spectrometer Frequency	125.70



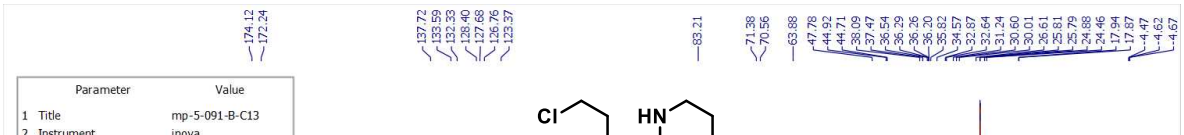
19



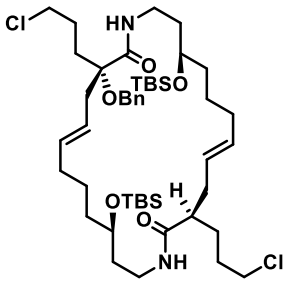
	Parameter	Value
1	Title	mp-5-091-B-1H
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	8
6	Relaxation Delay	8.0000
7	Pulse Width	6.2500
8	Acquisition Time	2.5000
9	Acquisition Date	2020-06-30T17:31:56
10	Spectrometer Frequency	599.64



1

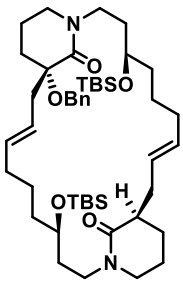


	Parameter	Value
1	Title	mp-5-091-B-C13
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	364
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2020-06-30T17:23:12
10	Spectrometer Frequency	125.70



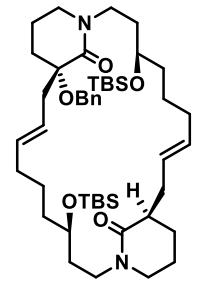
1

	Parameter	Value
1	Title	mp-5-092-A-1H
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	8
6	Relaxation Delay	8.0000
7	Pulse Width	6.2500
8	Acquisition Time	2.5000
9	Acquisition Date	2020-07-03T20:22:48
10	Spectrometer Frequency	599.64

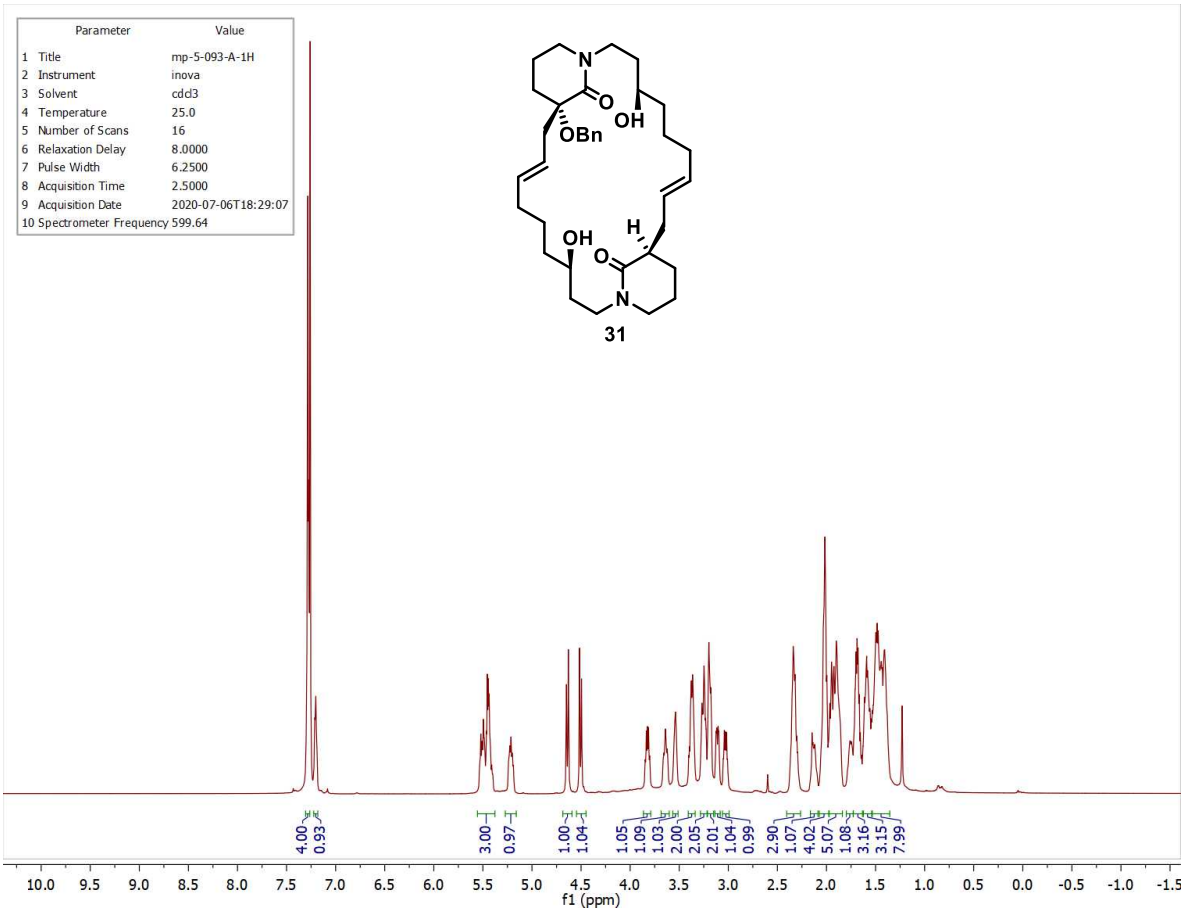


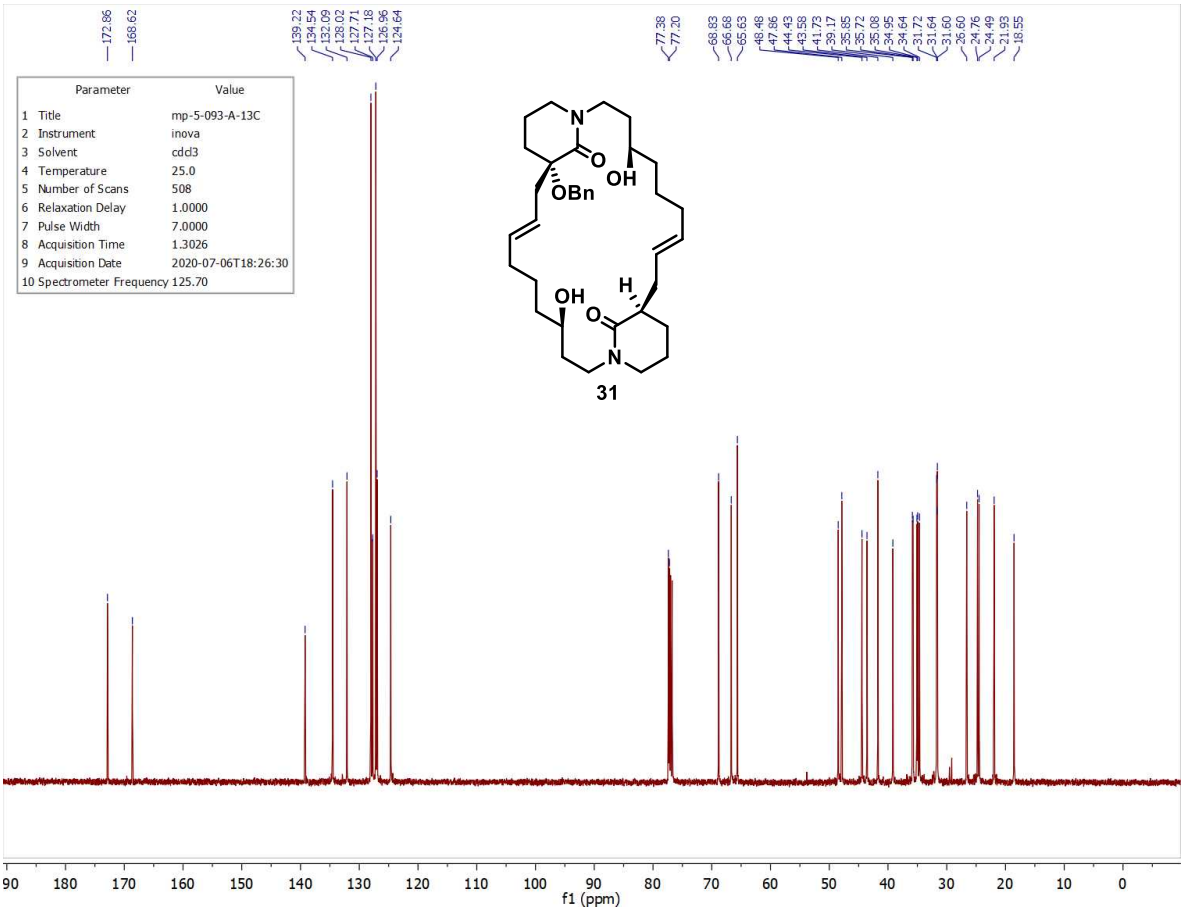
20

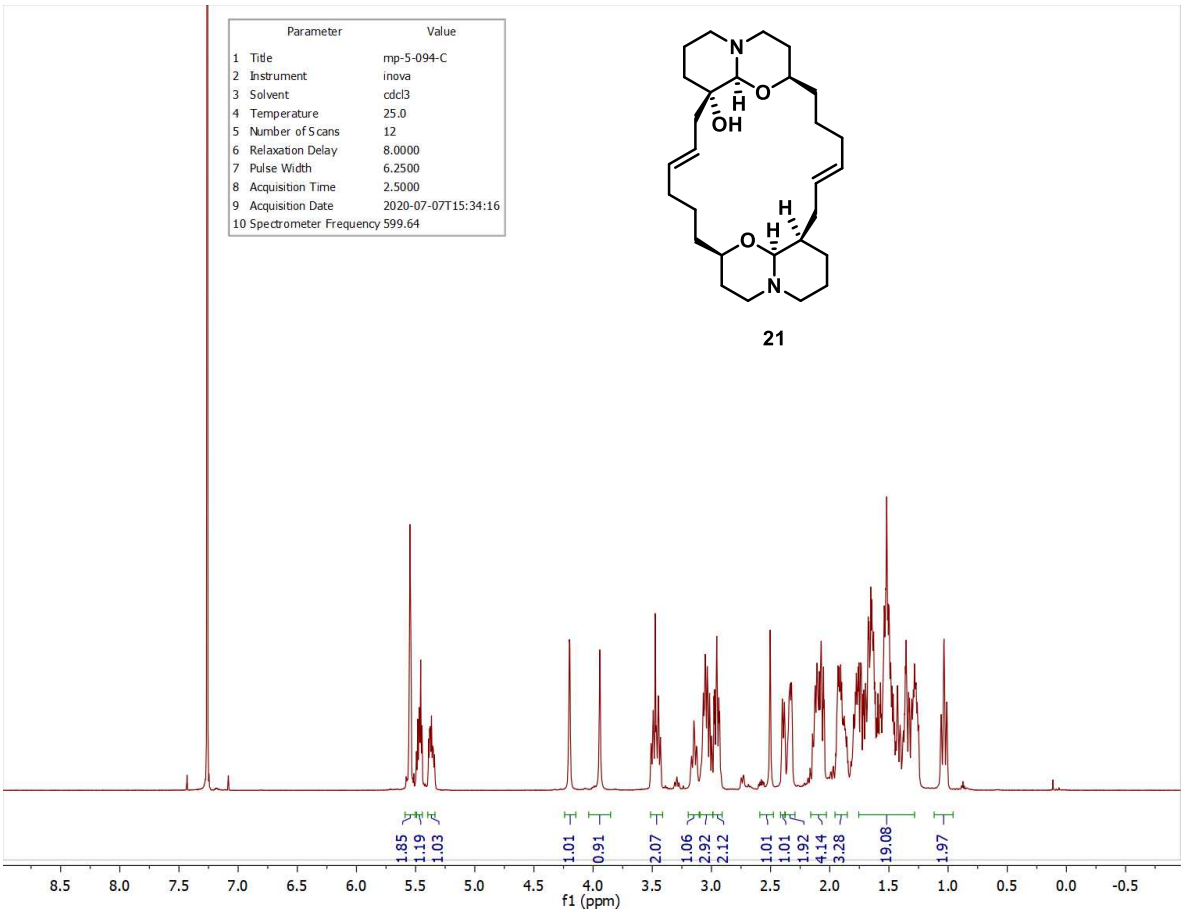
	Parameter	Value
1	Title	mp-5-092-A-C13
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	308
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2020-07-03T20:20:02
10	Spectrometer Frequency	125.70

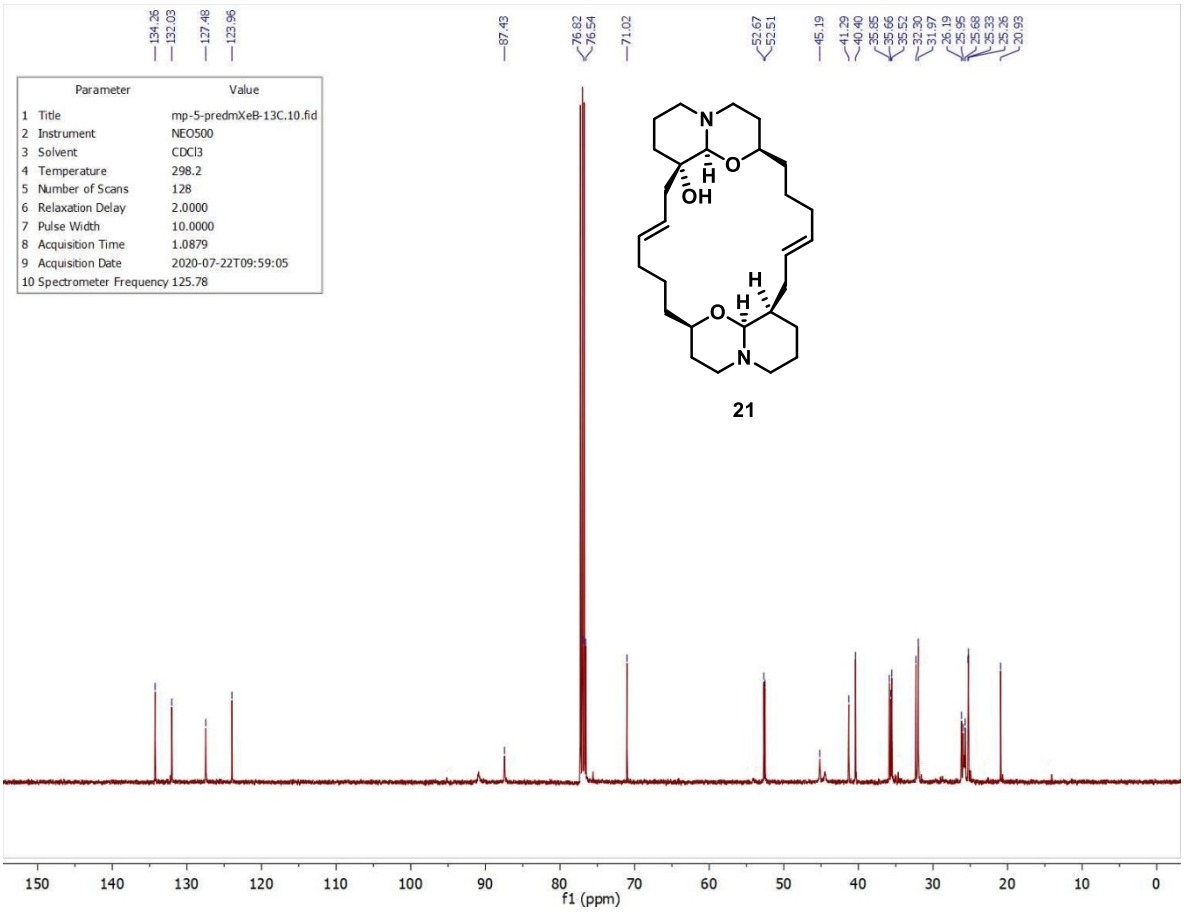


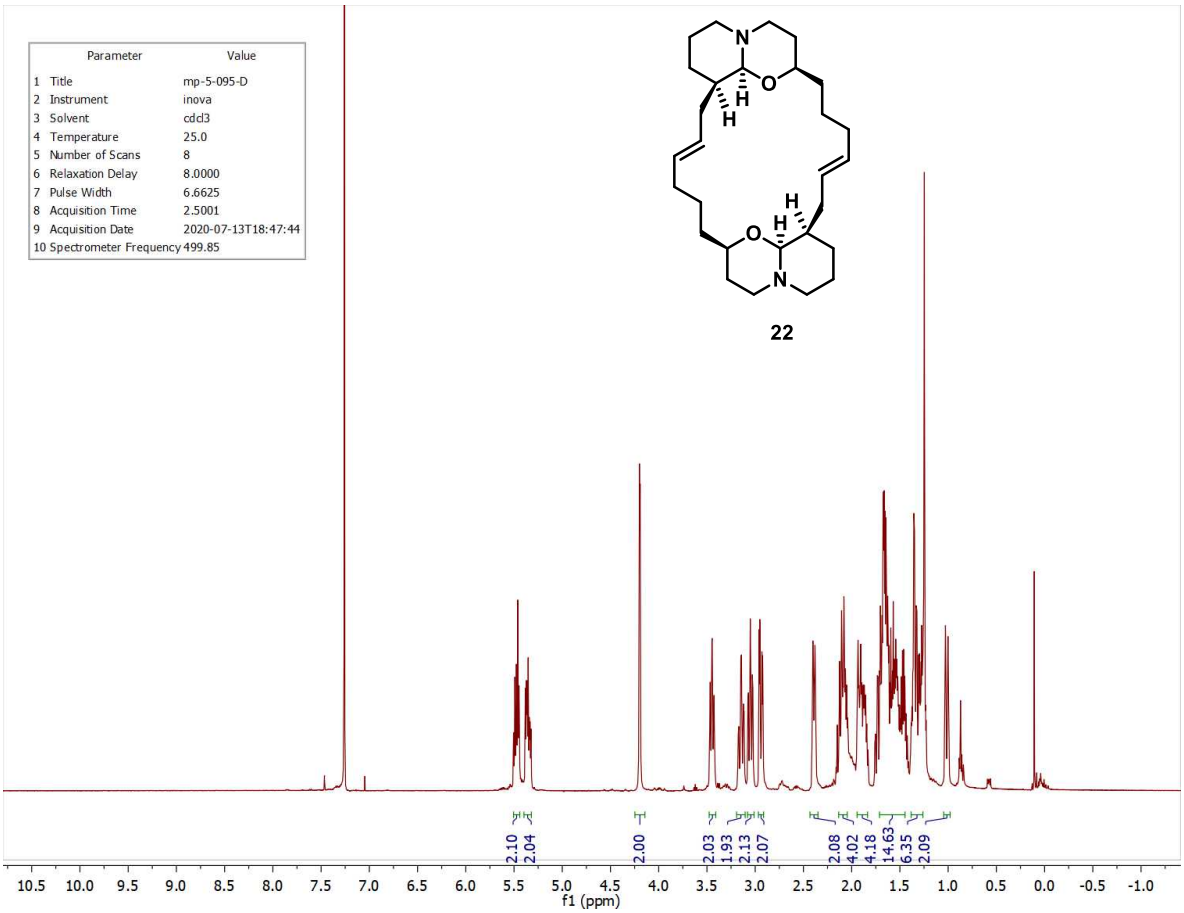
20

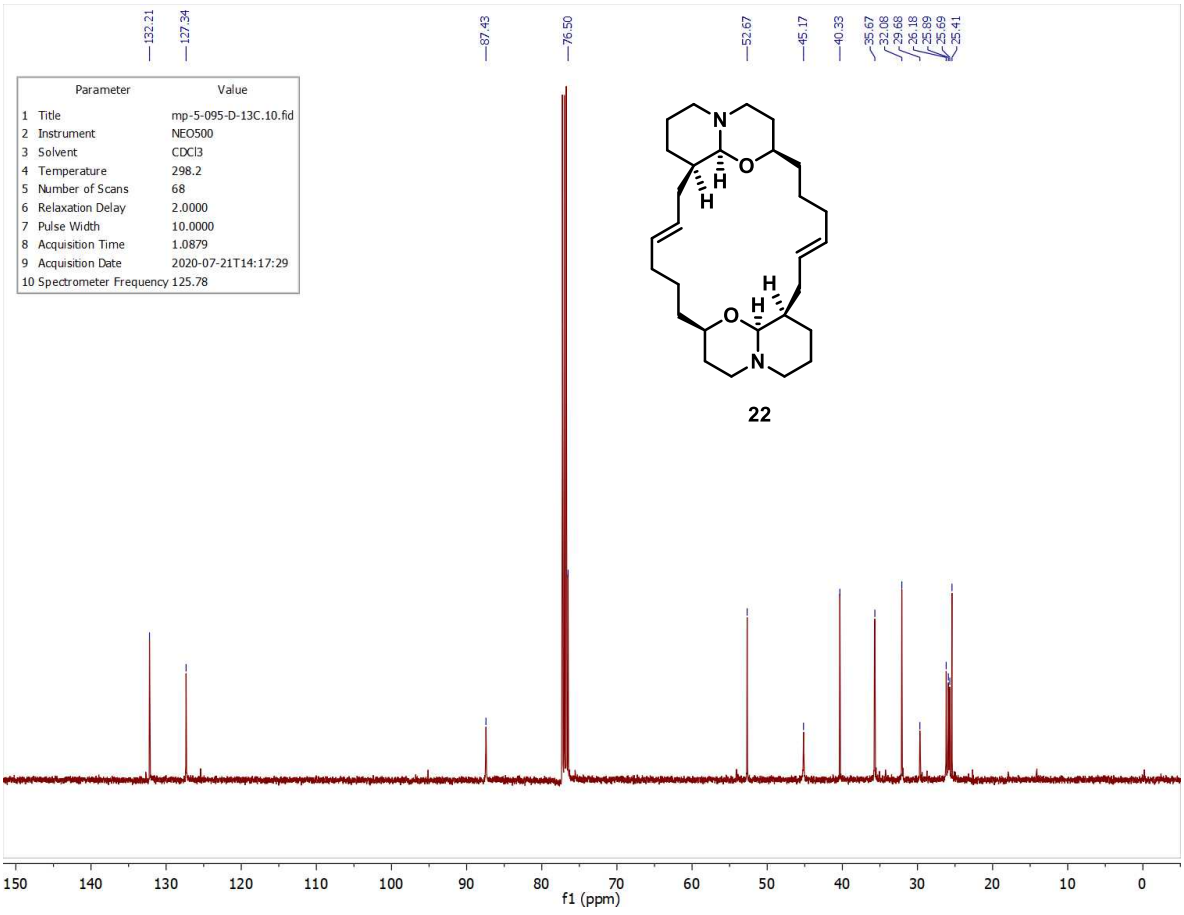

Parameter Value
1 Title mp-5-093-A-1H
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 16
6 Relaxation Delay 8.0000
7 Pulse Width 6.2500
8 Acquisition Time 2.5000
9 Acquisition Date 2020-07-06T18:29:07
10 Spectrometer Frequency 599.64
OBn
OH
OH
H
O
N
31
4.00 0.93 3.00 0.97 1.00 1.04 1.05 1.09 1.03 2.00 2.05 2.01 1.04 0.99 2.90 1.07 4.02 5.07 1.08 3.16 3.15 7.99
f1 (ppm)

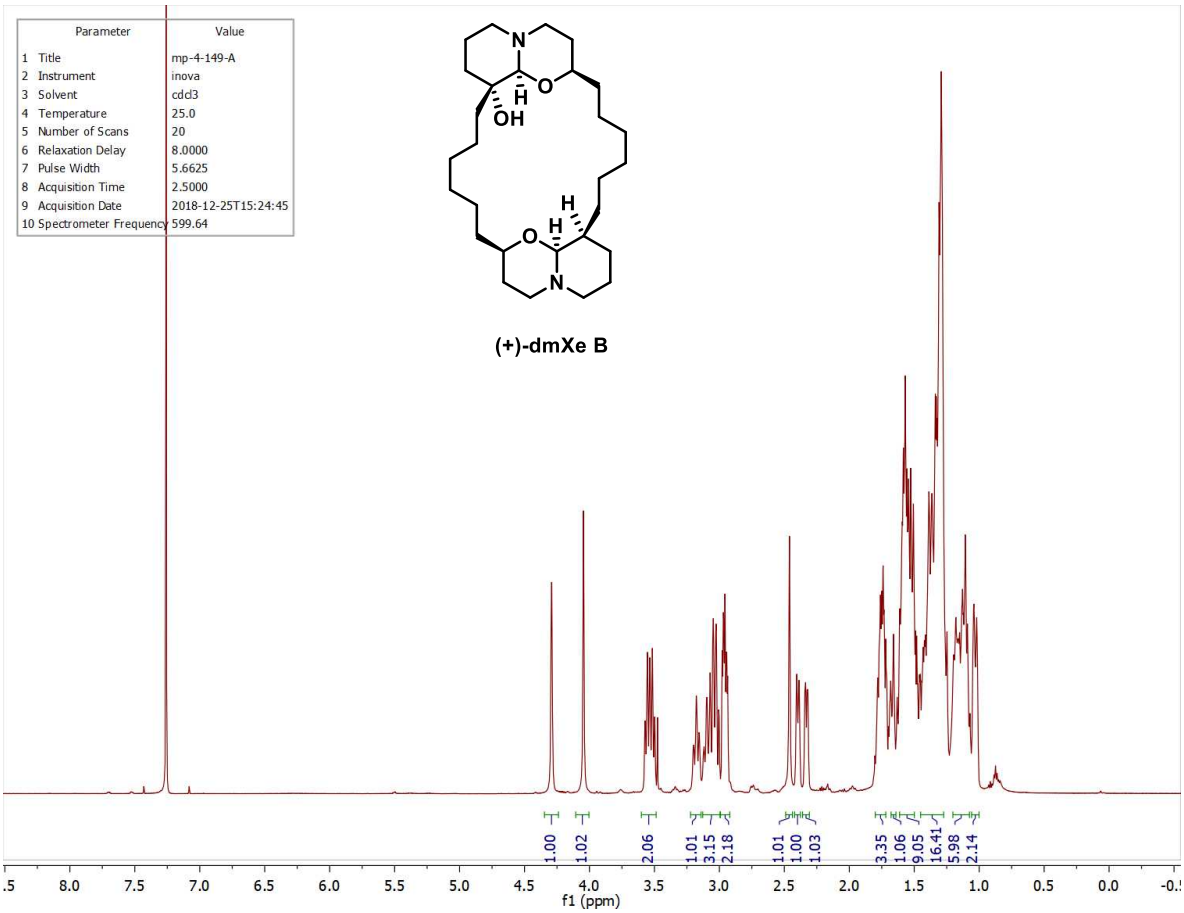

172.86 168.62 139.22 134.54 132.09 128.02 127.71 127.18 126.96 124.64 77.38 77.20 68.83 66.68 65.63 48.48 47.86 44.43 43.58 41.73 39.17 35.85 35.72 35.08 34.95 34.64 31.72 31.64 31.60 26.60 24.76 24.49 21.93 18.55
Parameter Value
1 Title mp-5-093-A-13C
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 508
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2020-07-06T18:26:30
10 Spectrometer Frequency 125.70
OBn
OH
OH
H
O
N
31
f1 (ppm)

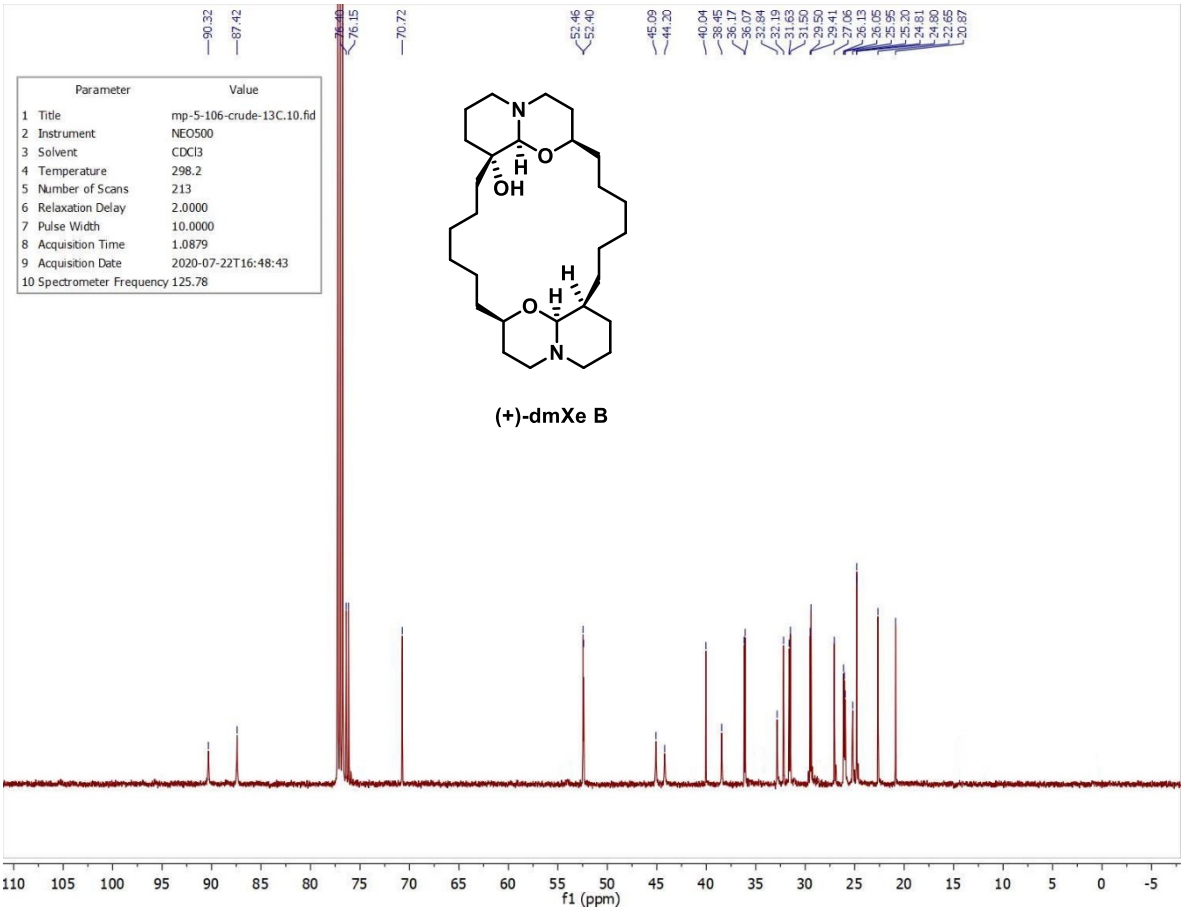

Parameter Value
1 Title mp-5-094-C
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 6.2500
8 Acquisition Time 2.5000
9 Acquisition Date 2020-07-07T15:34:16
10 Spectrometer Frequency 599.64
N
O
H
OH
H
H
O
N
21
1.85
1.19
1.03
1.01
0.91
2.07
1.06
2.92
2.12
1.01
1.01
1.92
4.14
3.28
19.08
1.97
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
f1 (ppm)

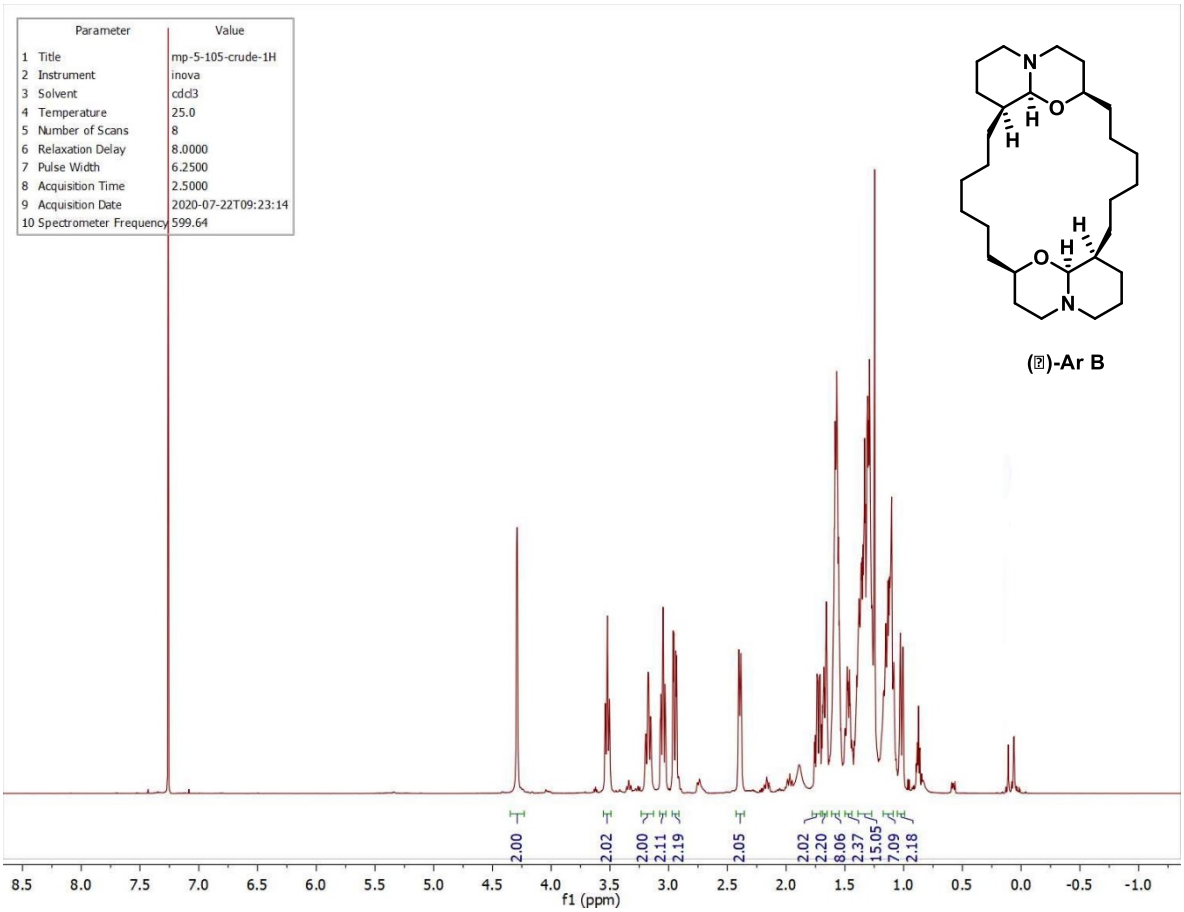

134.26
132.03
127.48
123.96
87.43
76.82
76.54
71.02
52.67
52.51
45.19
41.29
40.40
35.85
35.66
35.52
32.30
31.97
26.19
25.95
25.68
25.33
25.26
20.93
Parameter Value
1 Title mp-5-predmXeB-13C.10.fid
2 Instrument NEO500
3 Solvent CDCl3
4 Temperature 298.2
5 Number of Scans 128
6 Relaxation Delay 2.0000
7 Pulse Width 10.0000
8 Acquisition Time 1.0879
9 Acquisition Date 2020-07-22T09:59:05
10 Spectrometer Frequency 125.78
N
O
H
OH
H
H
O
N
21
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

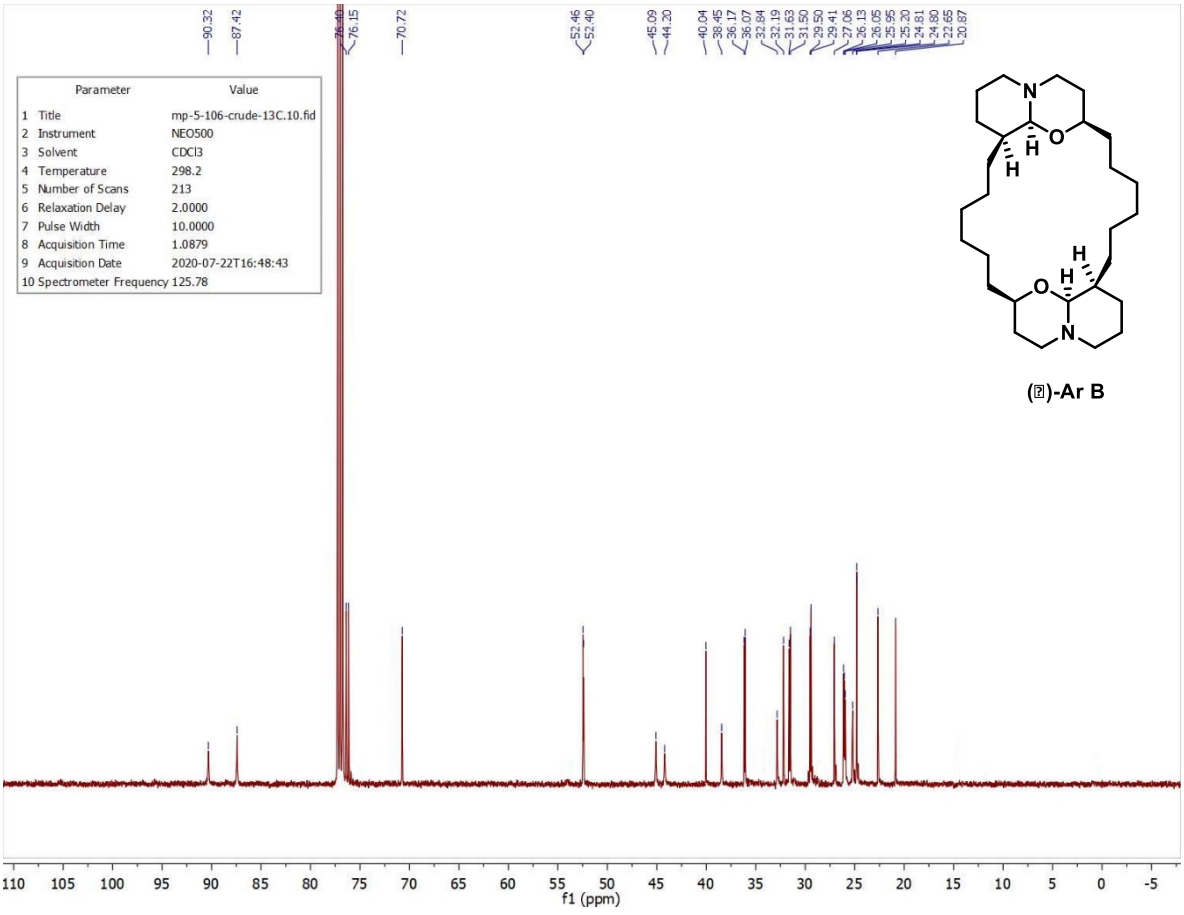

Parameter Value
1 Title mp-5-095-D
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 6.6625
8 Acquisition Time 2.5001
9 Acquisition Date 2020-07-13T18:47:44
10 Spectrometer Frequency 499.85
22
2.10 2.04 2.00 2.03 1.93 2.13 2.07 2.08 4.02 4.18 14.63 6.35 2.09
f1 (ppm)


132.21 127.34 87.43 76.50 52.67 45.17 40.33 35.67 32.08 29.68 26.18 25.89 25.69 25.41
Parameter Value
1 Title mp-5-095-D-13C.10.fid
2 Instrument NEO500
3 Solvent CDCl3
4 Temperature 298.2
5 Number of Scans 68
6 Relaxation Delay 2.0000
7 Pulse Width 10.0000
8 Acquisition Time 1.0879
9 Acquisition Date 2020-07-21T14:17:29
10 Spectrometer Frequency 125.78
22
f1 (ppm)

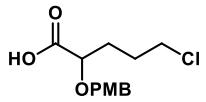

Parameter Value
1 Title mp-4-149-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 20
6 Relaxation Delay 8.0000
7 Pulse Width 5.6625
8 Acquisition Time 2.5000
9 Acquisition Date 2018-12-25T15:24:45
10 Spectrometer Frequency 599.64
(+)-dmXe B
1.00 1.02 2.06 1.01 3.15 2.18 1.01 1.00 1.03 3.35 1.06 9.05 16.41 5.98 2.14
f1 (ppm)


90.32 87.42 76.15 70.72 52.46 52.40 45.09 44.20 40.04 38.45 36.17 36.07 32.84 32.19 31.63 31.50 29.50 29.41 27.06 26.13 26.05 25.95 25.20 24.81 24.80 22.65 20.87
Parameter Value
1 Title mp-5-106-crude-13C.10.fid
2 Instrument NEO500
3 Solvent CDCl3
4 Temperature 298.2
5 Number of Scans 213
6 Relaxation Delay 2.0000
7 Pulse Width 10.0000
8 Acquisition Time 1.0879
9 Acquisition Date 2020-07-22T16:48:43
10 Spectrometer Frequency 125.78
(+)-dmXe B
f1 (ppm)

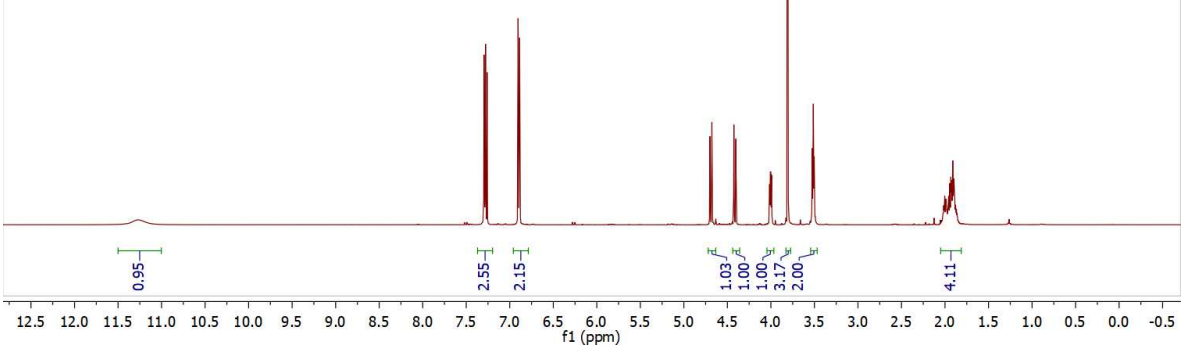

Parameter Value
1 Title mp-5-105-crude-1H
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 6.2500
8 Acquisition Time 2.5000
9 Acquisition Date 2020-07-22T09:23:14
10 Spectrometer Frequency 599.64
(±)-Ar B
2.00 2.02 2.00 2.11 2.19 2.05 2.02 2.20 8.06 2.37 15.05 7.09 2.18
f1 (ppm)

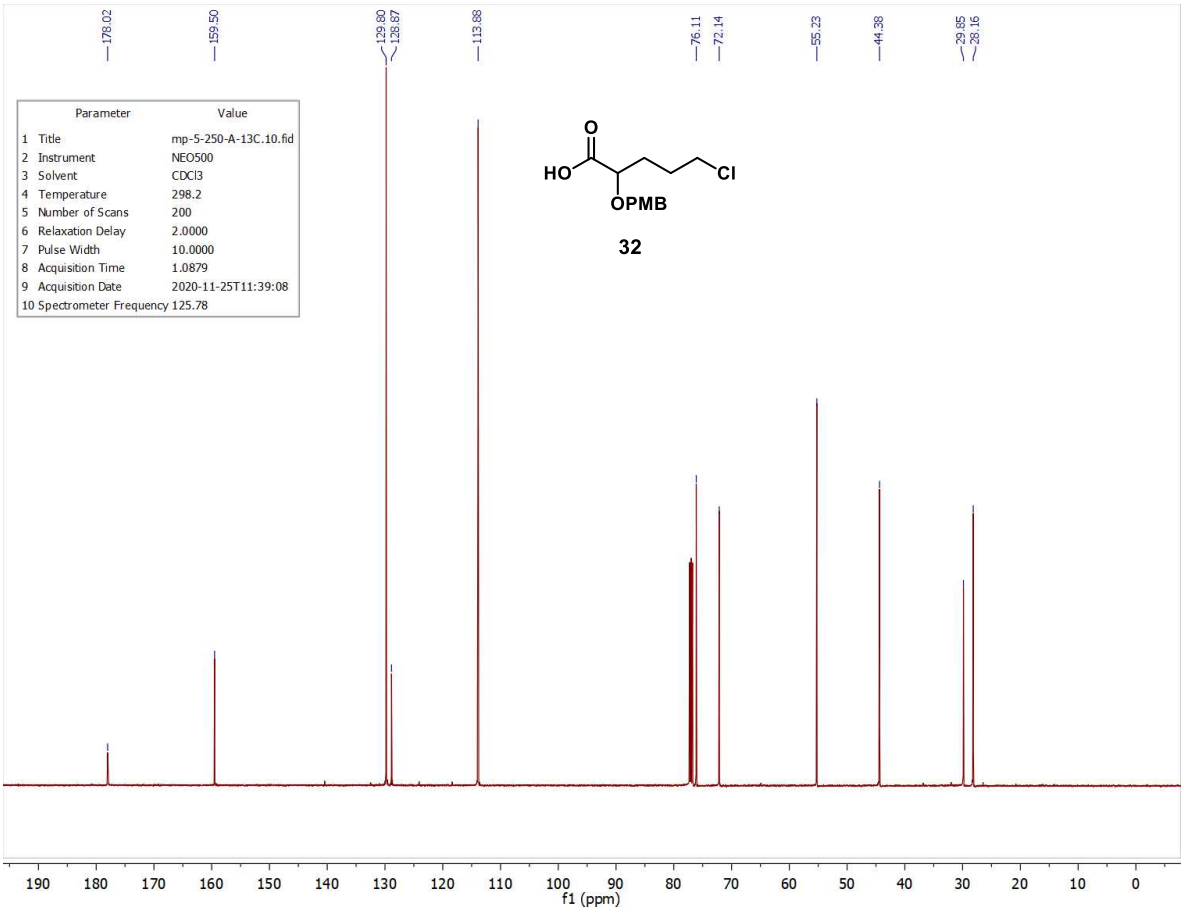

90.32 87.42 76.15 70.72 52.46 52.40 45.09 44.20 40.04 38.45 36.17 36.07 32.84 32.19 31.63 31.50 29.50 29.41 27.06 26.13 26.05 25.95 25.20 24.81 24.80 22.65 20.87
Parameter Value
1 Title mp-5-106-crude-13C.10.fid
2 Instrument NEO500
3 Solvent CDCl3
4 Temperature 298.2
5 Number of Scans 213
6 Relaxation Delay 2.0000
7 Pulse Width 10.0000
8 Acquisition Time 1.0879
9 Acquisition Date 2020-07-22T16:48:43
10 Spectrometer Frequency 125.78
(±)-Ar B
f1 (ppm)

	Parameter	Value
1	Title	mp-5-250-A-1H.10.fid
2	Instrument	NEO500
3	Solvent	CDCl3
4	Temperature	298.1
5	Number of Scans	16
6	Relaxation Delay	8.0000
7	Pulse Width	12.0000
8	Acquisition Time	3.2768
9	Acquisition Date	2020-11-25T11:26:50
10	Spectrometer Frequency	500.15



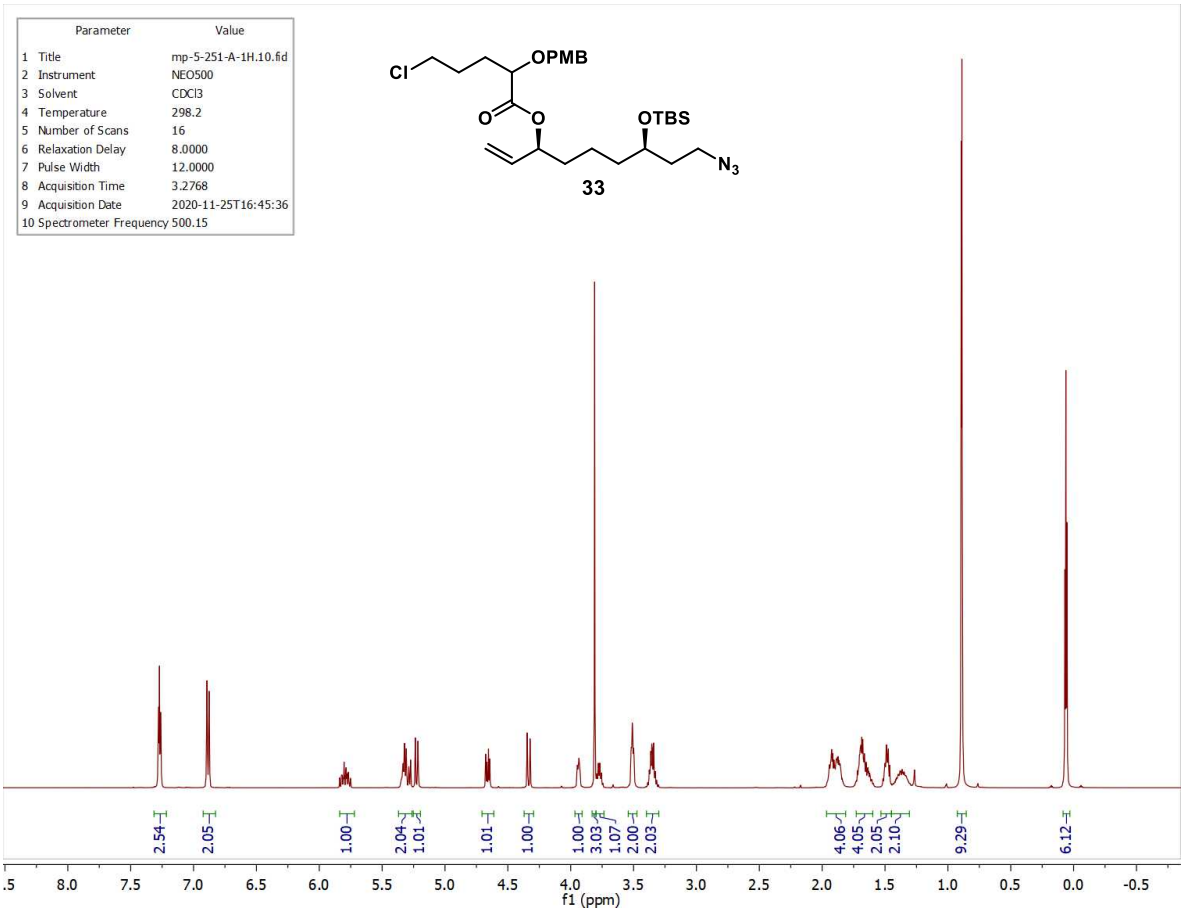
32

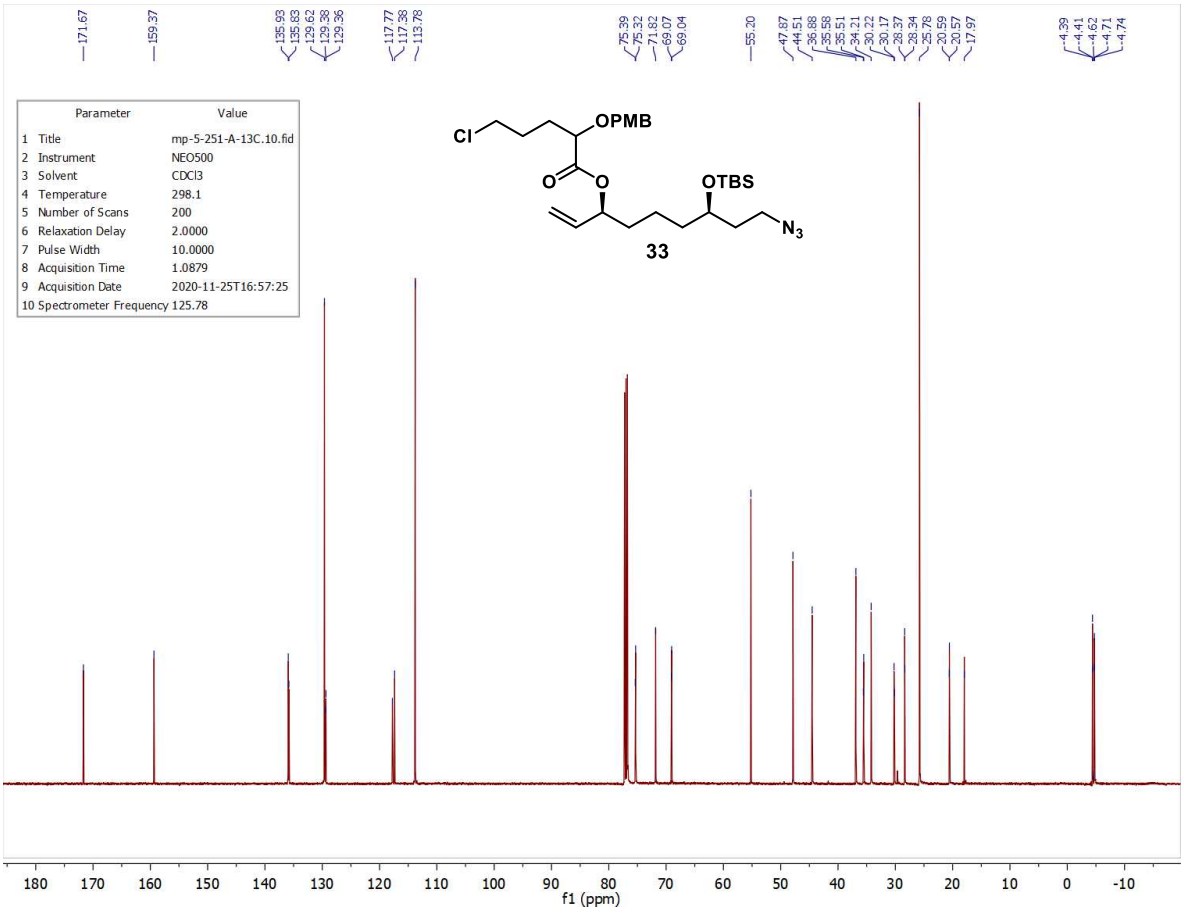


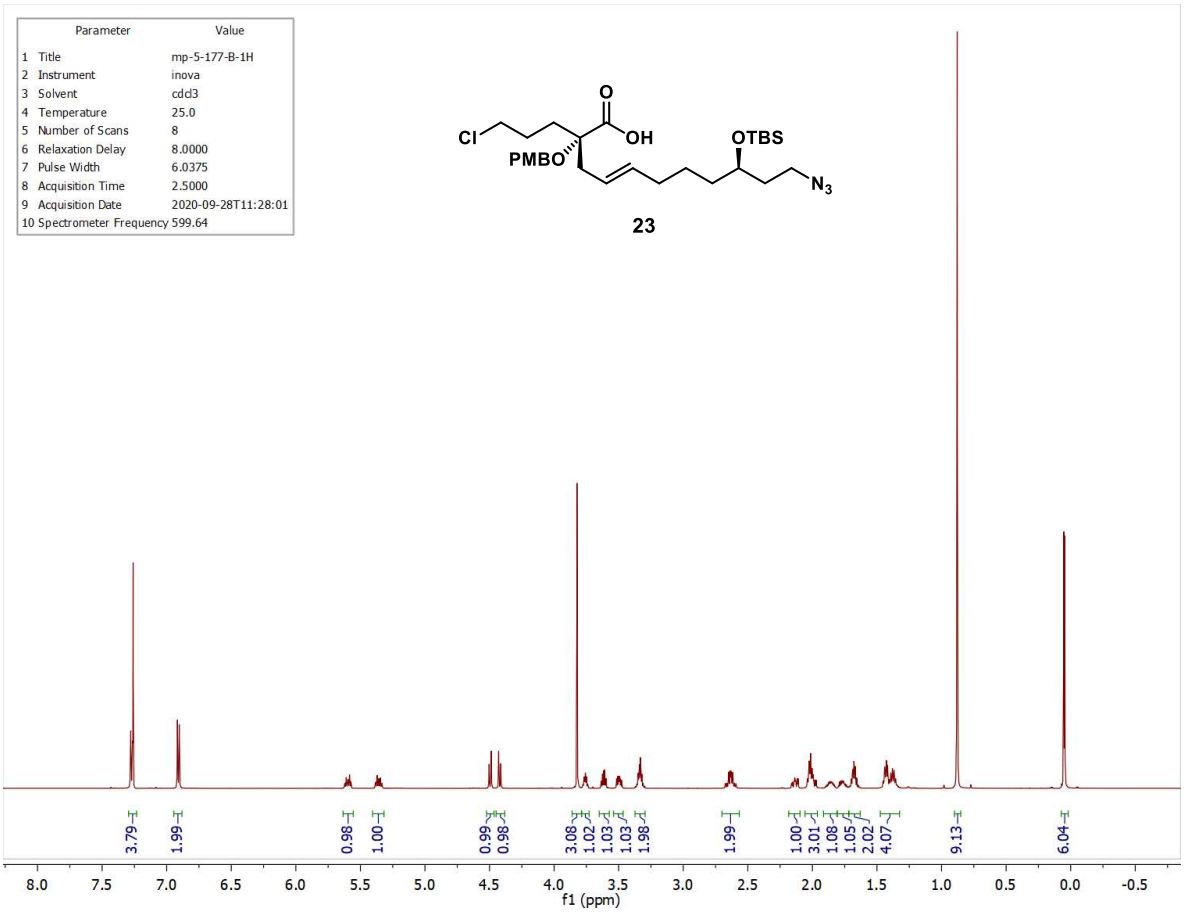


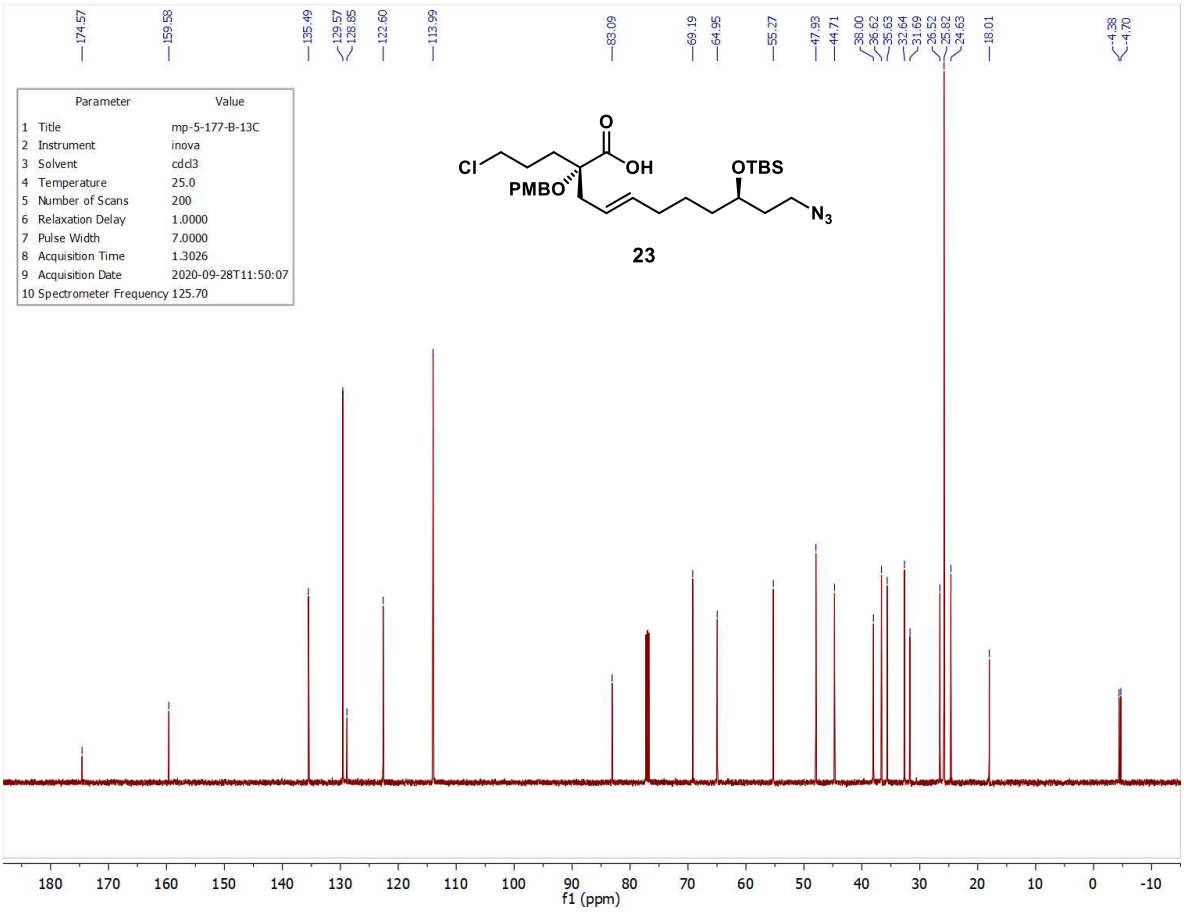
	Parameter	Value
1	Title	mp-5-250-A-13C.10.fid
2	Instrument	NEO500
3	Solvent	CDCl3
4	Temperature	298.2
5	Number of Scans	200
6	Relaxation Delay	2.0000
7	Pulse Width	10.0000
8	Acquisition Time	1.0879
9	Acquisition Date	2020-11-25T11:39:08
10	Spectrometer Frequency	125.78

32

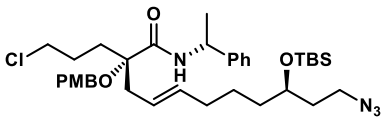

Parameter Value
1 Title mp-5-251-A-1H.10.fid
2 Instrument NEO500
3 Solvent CDCl3
4 Temperature 298.2
5 Number of Scans 16
6 Relaxation Delay 8.0000
7 Pulse Width 12.0000
8 Acquisition Time 3.2768
9 Acquisition Date 2020-11-25T16:45:36
10 Spectrometer Frequency 500.15
Cl
OPMB
O
O
OTBS
N3
33
2.54
2.05
1.00
2.04
1.01
1.01
1.00
1.00
3.03
1.07
2.00
2.03
4.06
4.05
2.05
2.10
9.29
6.12
f1 (ppm)


171.67
159.37
135.93
135.83
129.62
129.38
129.36
117.77
117.38
113.78
75.39
75.32
71.82
69.07
69.04
55.20
47.87
44.51
36.88
35.58
35.51
34.21
30.22
30.17
28.37
28.34
25.78
20.59
20.57
17.97
4.39
4.41
4.62
4.71
4.74
Parameter Value
1 Title mp-5-251-A-13C.10.fid
2 Instrument NEO500
3 Solvent CDCl3
4 Temperature 298.1
5 Number of Scans 200
6 Relaxation Delay 2.0000
7 Pulse Width 10.0000
8 Acquisition Time 1.0879
9 Acquisition Date 2020-11-25T16:57:25
10 Spectrometer Frequency 125.78
Cl
OPMB
O
O
OTBS
N3
33
f1 (ppm)

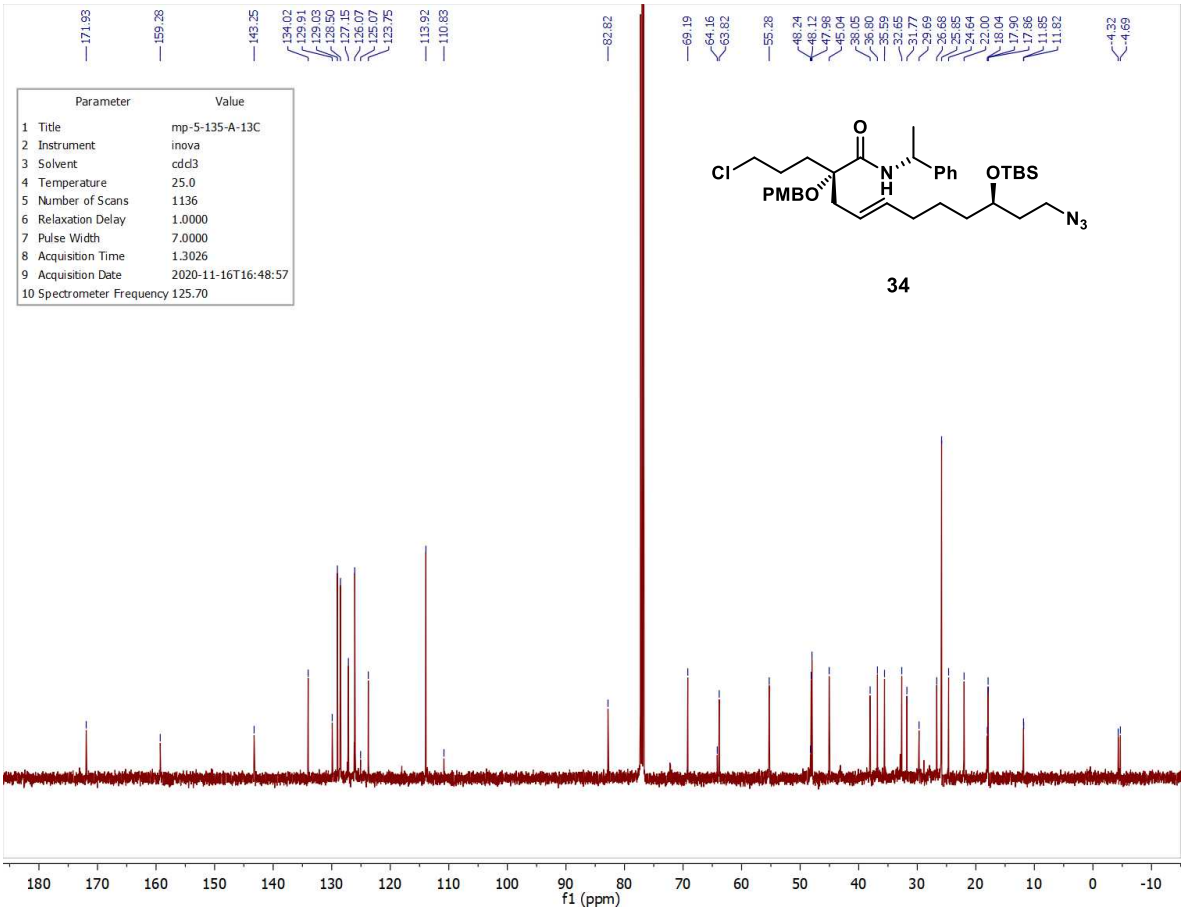

Parameter Value
1 Title mp-5-177-B-1H
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 6.0375
8 Acquisition Time 2.5000
9 Acquisition Date 2020-09-28T11:28:01
10 Spectrometer Frequency 599.64
Cl
O
OH
PMBO
OTBS
N3
23
3.79 1.99 0.98 1.00 0.99 0.98 3.08 1.02 1.03 1.03 1.98 1.99 1.00 3.01 1.08 1.05 2.02 4.07 9.13 6.04
f1 (ppm)


174.57 159.58 135.49 129.57 128.85 122.60 113.99 83.09 69.19 64.95 55.27 47.93 44.71 38.00 36.62 35.63 32.64 31.69 26.52 25.82 24.63 18.01 -4.38 -4.70
Parameter Value
1 Title mp-5-177-B-13C
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 200
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2020-09-28T11:50:07
10 Spectrometer Frequency 125.70
Cl
O
OH
PMBO
OTBS
N3
23
f1 (ppm)

	Parameter	Value
1	Title	mp-5-178-A
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	8
6	Relaxation Delay	8.0000
7	Pulse Width	6.2500
8	Acquisition Time	2.5000
9	Acquisition Date	2020-09-01T16:00:41
10	Spectrometer Frequency	599.64

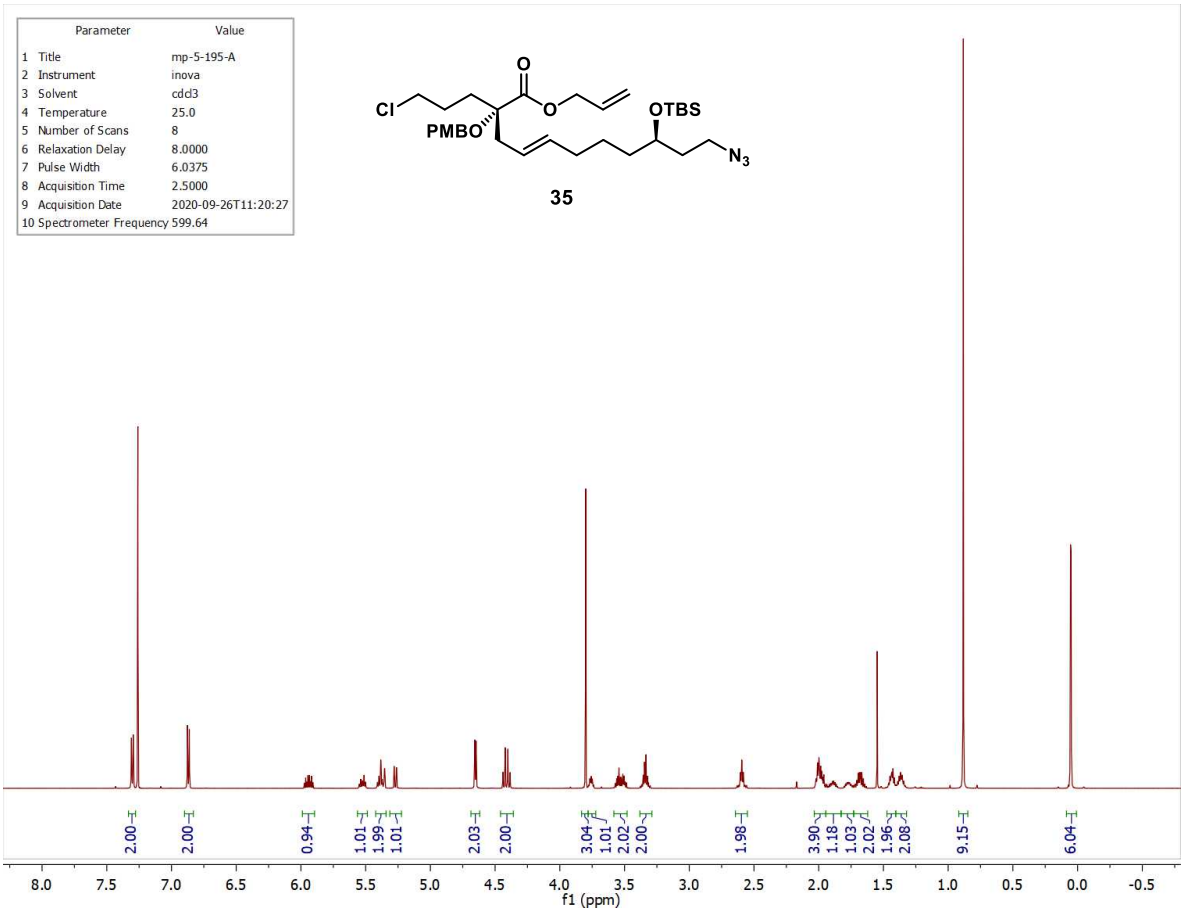


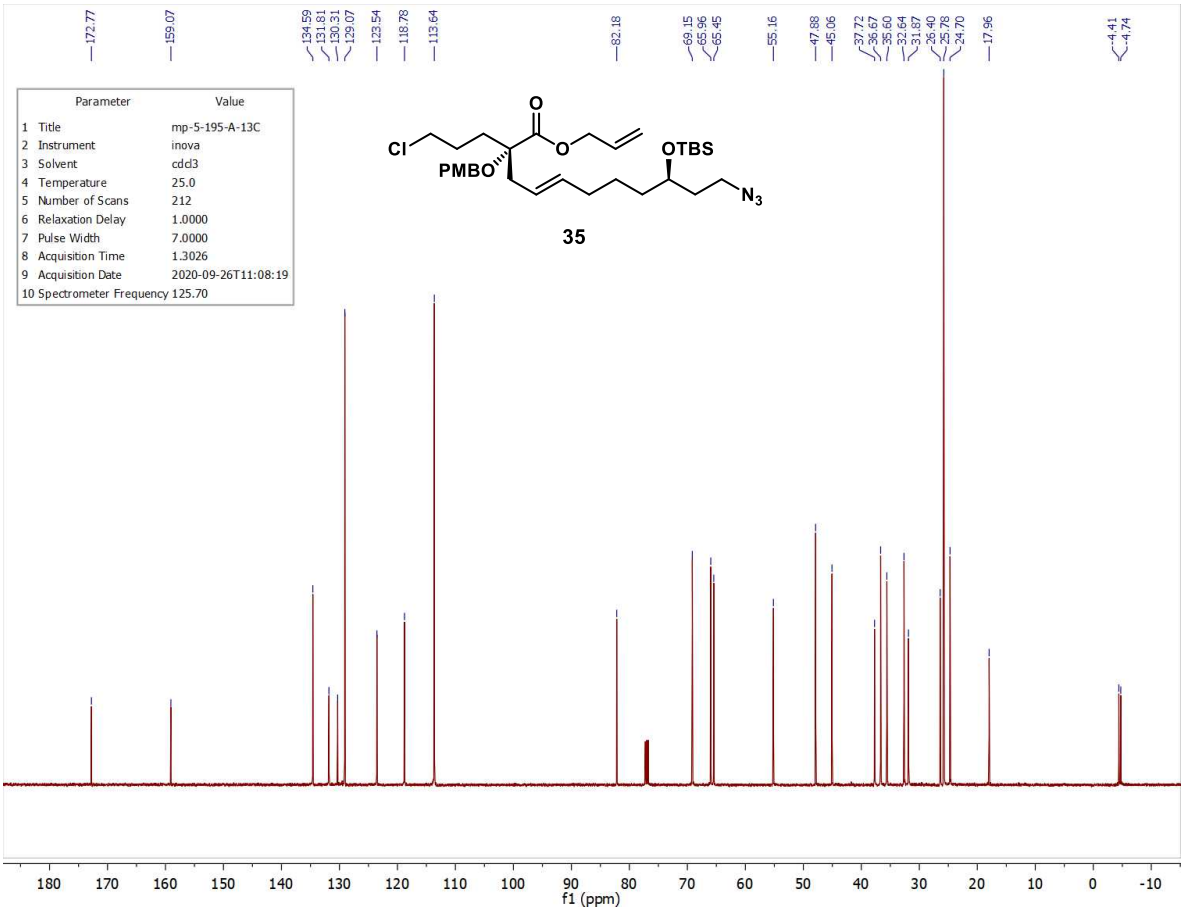
34



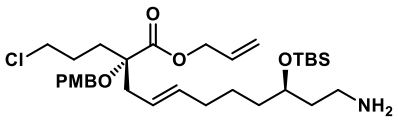
	Parameter	Value
1	Title	mp-5-135-A-13C
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	1136
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2020-11-16T16:48:57
10	Spectrometer Frequency	125.70

34

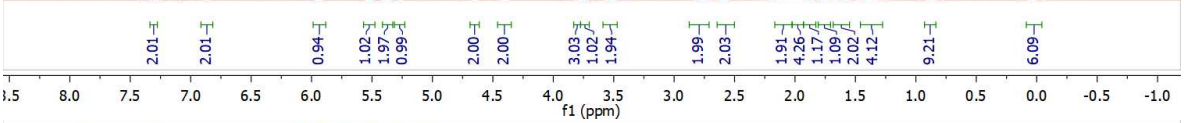

Parameter Value
1 Title mp-5-195-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 6.0375
8 Acquisition Time 2.5000
9 Acquisition Date 2020-09-26T11:20:27
10 Spectrometer Frequency 599.64
Cl
PMBO
O
O
OTBS
N3
35
2.00 2.00 0.94 1.01 1.99 1.01 2.03 2.00 3.04 1.01 2.02 2.00 1.98 3.90 1.18 1.03 2.02 1.96 2.08 9.15 6.04
f1 (ppm)

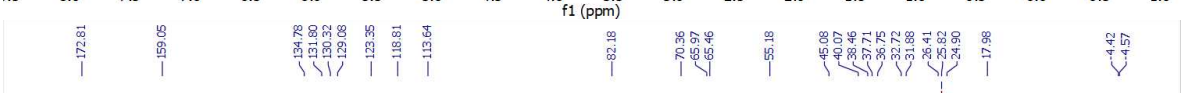

172.77 159.07 134.59 131.81 130.31 129.07 123.54 118.78 113.64 82.18 69.15 65.96 65.45 55.16 47.88 45.06 37.72 36.67 35.60 32.64 31.87 26.40 25.78 24.70 17.96 -4.41 -4.74
Parameter Value
1 Title mp-5-195-A-13C
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 212
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2020-09-26T11:08:19
10 Spectrometer Frequency 125.70
Cl
PMBO
O
O
OTBS
N3
35
f1 (ppm)

	Parameter	Value
1	Title	mp-5-196-A
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	8
6	Relaxation Delay	8.0000
7	Pulse Width	6.0375
8	Acquisition Time	2.5000
9	Acquisition Date	2020-09-28T11:33:27
10	Spectrometer Frequency	599.64

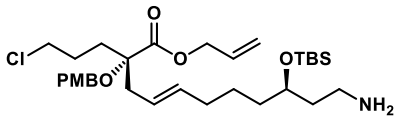


24





	Parameter	Value
1	Title	mp-5-196-A-13C
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	200
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2020-09-28T11:39:36
10	Spectrometer Frequency	125.70



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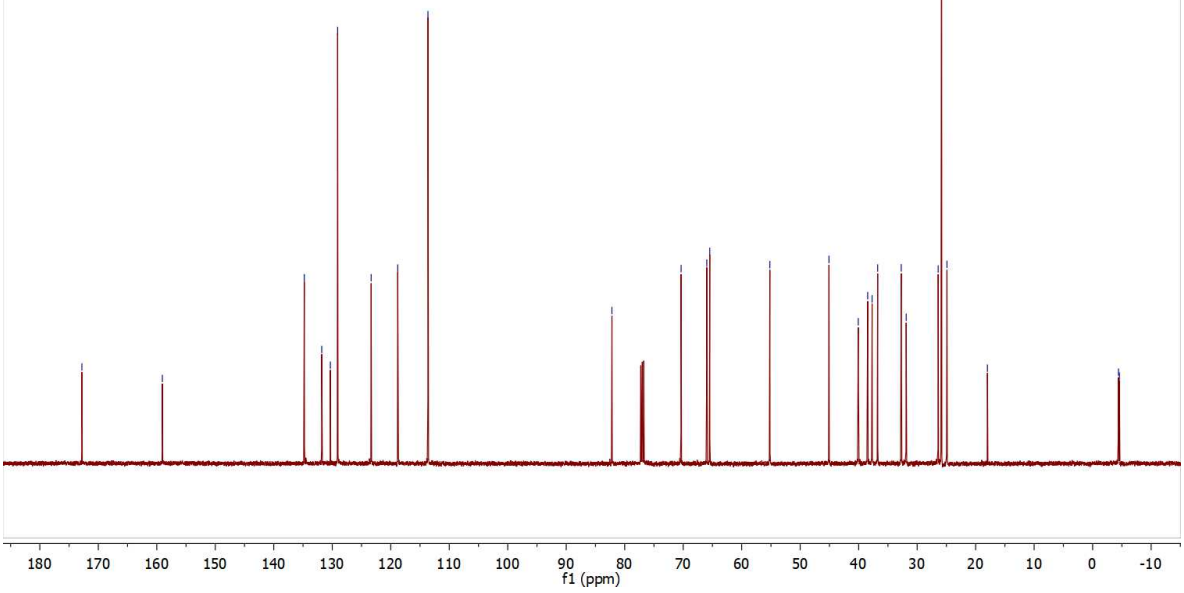
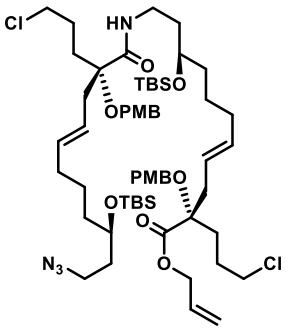
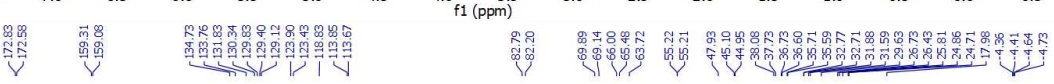


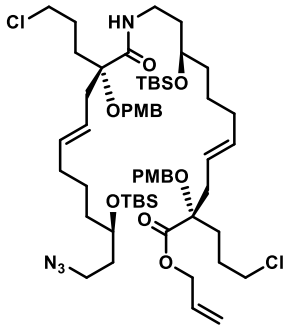
	Parameter	Value
1	Title	mp-5-197-A-1H
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	8
6	Relaxation Delay	8.0000
7	Pulse Width	6.0375
8	Acquisition Time	2.5000
9	Acquisition Date	2020-10-06T10:15:19
10	Spectrometer Frequency	599.64



36

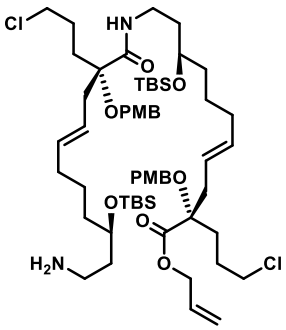


	Parameter	Value
1	Title	mp-5-197-A-13C
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	252
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2020-10-06T10:23:30
10	Spectrometer Frequency	125.70

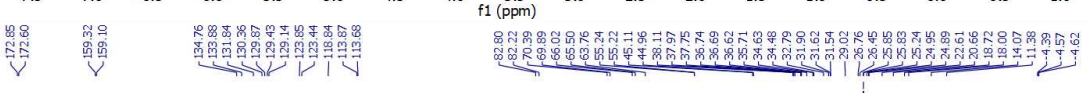


36

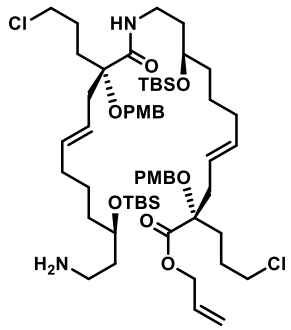
	Parameter	Value
1	Title	mp-5-187-A-1H
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	12
6	Relaxation Delay	8.0000
7	Pulse Width	6.2500
8	Acquisition Time	2.5000
9	Acquisition Date	2020-09-15T18:20:56
10	Spectrometer Frequency	599.64



37

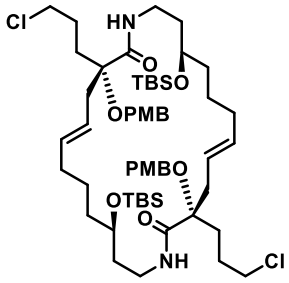


	Parameter	Value
1	Title	mp-5-187-A-13C
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	368
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2020-09-15T18:29:47
10	Spectrometer Frequency	125.70

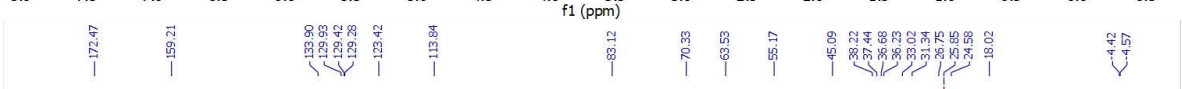


37

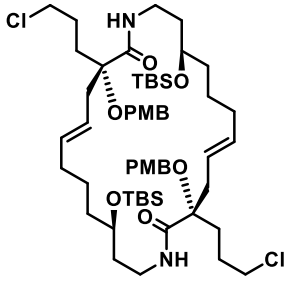
	Parameter	Value
1	Title	mp-5-189-A
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	12
6	Relaxation Delay	8.0000
7	Pulse Width	6.0375
8	Acquisition Time	2.5000
9	Acquisition Date	2020-09-21T14:49:25
10	Spectrometer Frequency	599.64



25

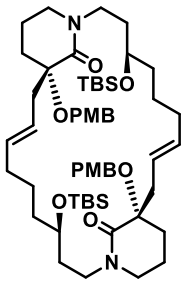


	Parameter	Value
1	Title	mp-5-208-B-13C
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	168
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2020-10-16T13:50:38
10	Spectrometer Frequency	125.70

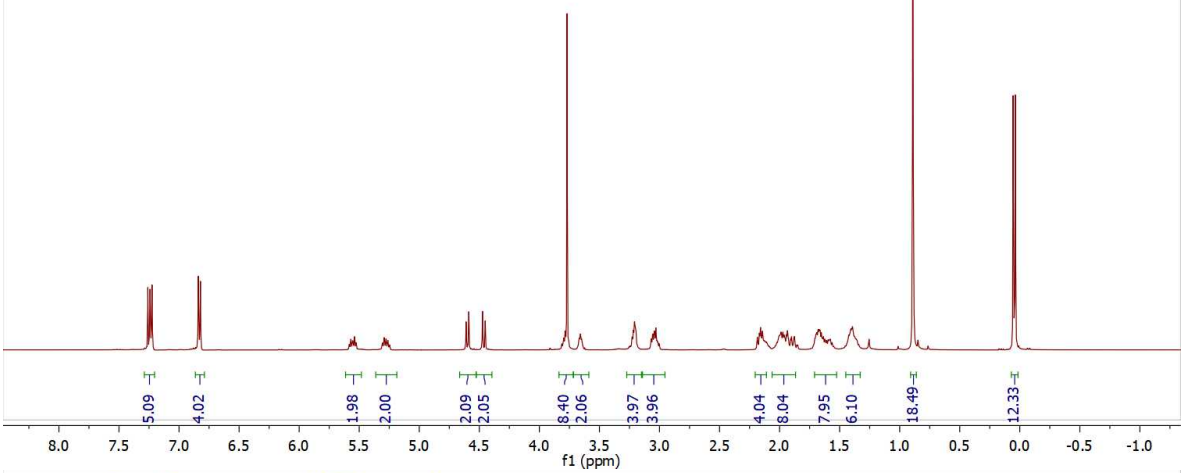


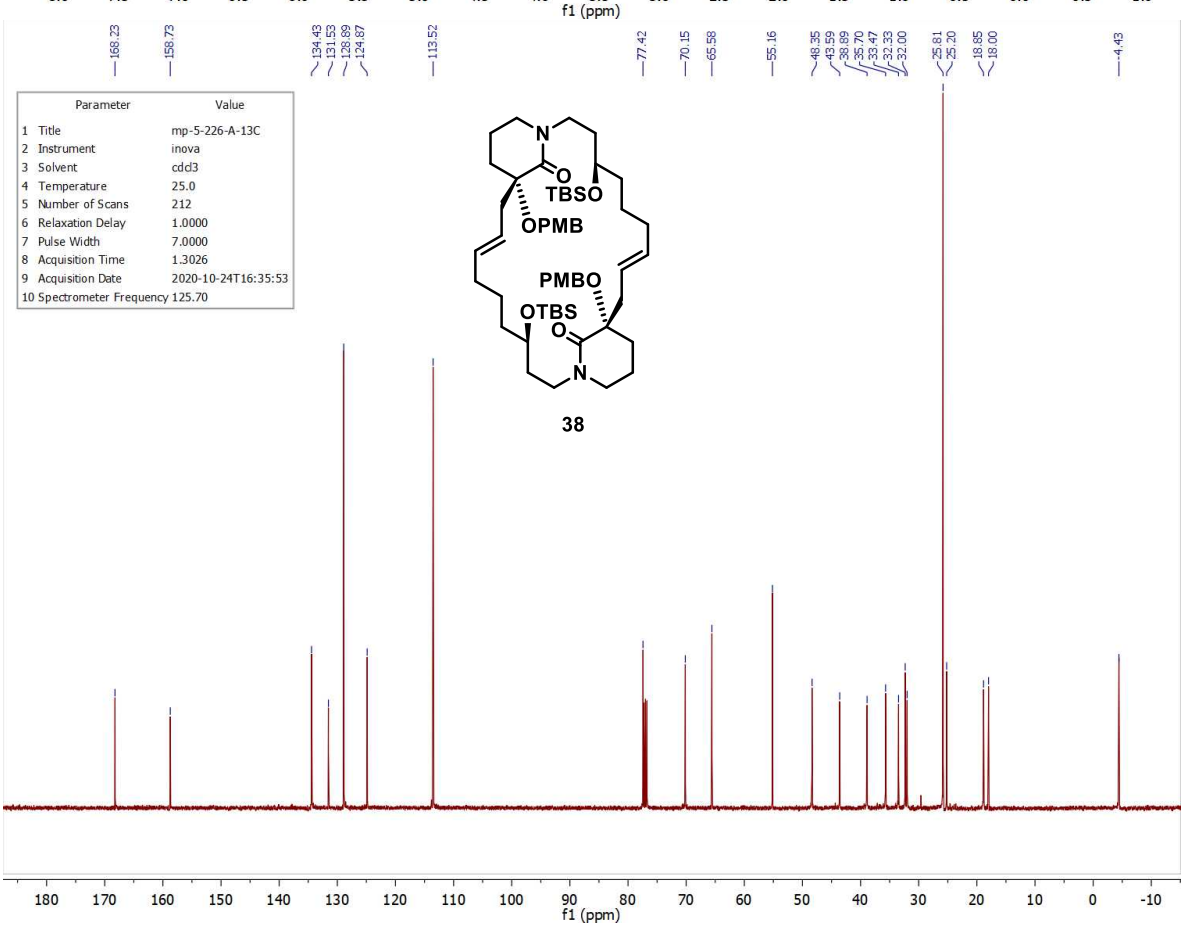
25

	Parameter	Value
1	Title	mp-5-226-A-1H
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	12
6	Relaxation Delay	12.0000
7	Pulse Width	6.6625
8	Acquisition Time	2.5001
9	Acquisition Date	2020-10-24T16:28:45
10	Spectrometer Frequency	499.85



38

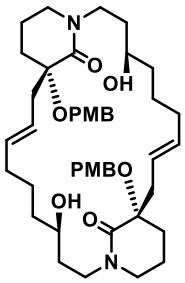




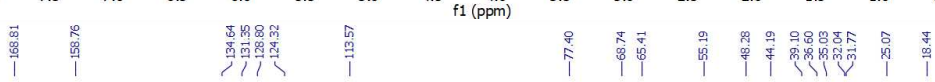
	Parameter	Value
1	Title	mp-5-226-A-13C
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	212
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2020-10-24T16:35:53
10	Spectrometer Frequency	125.70

38

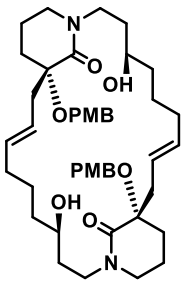
	Parameter	Value
1	Title	mp-5-238-A-1H
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	8
6	Relaxation Delay	8.0000
7	Pulse Width	6.0375
8	Acquisition Time	2.5000
9	Acquisition Date	2020-10-28T09:26:23
10	Spectrometer Frequency	599.64



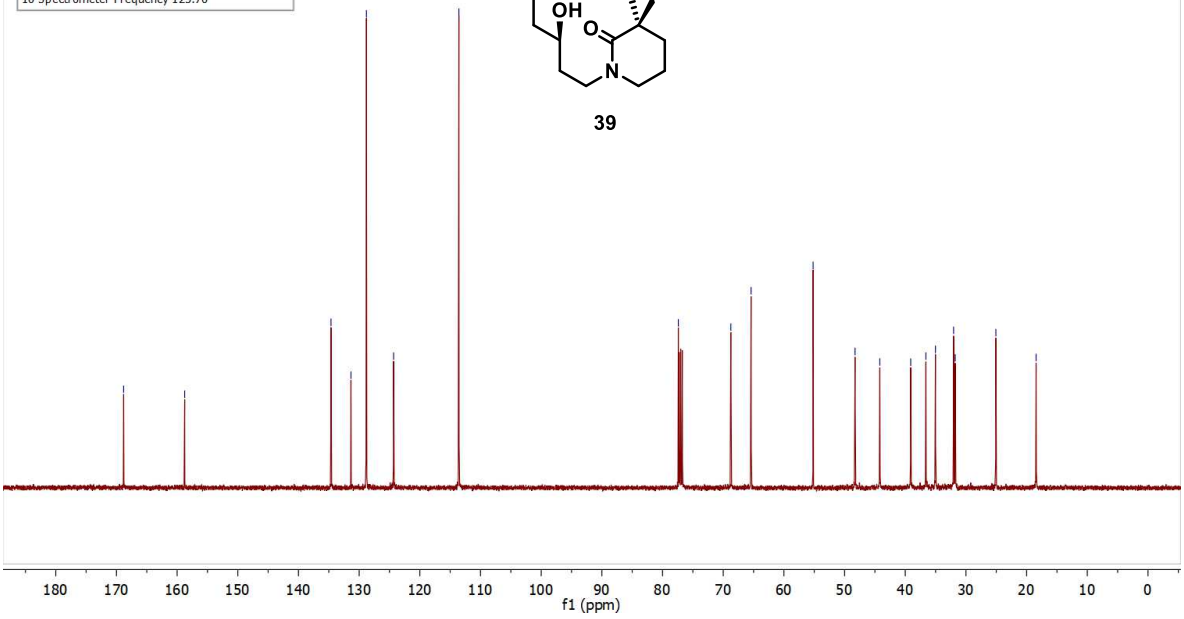
39



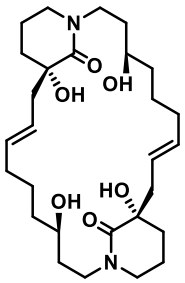
	Parameter	Value
1	Title	mp-5-238-A-13C
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	268
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2020-10-28T09:39:22
10	Spectrometer Frequency	125.70



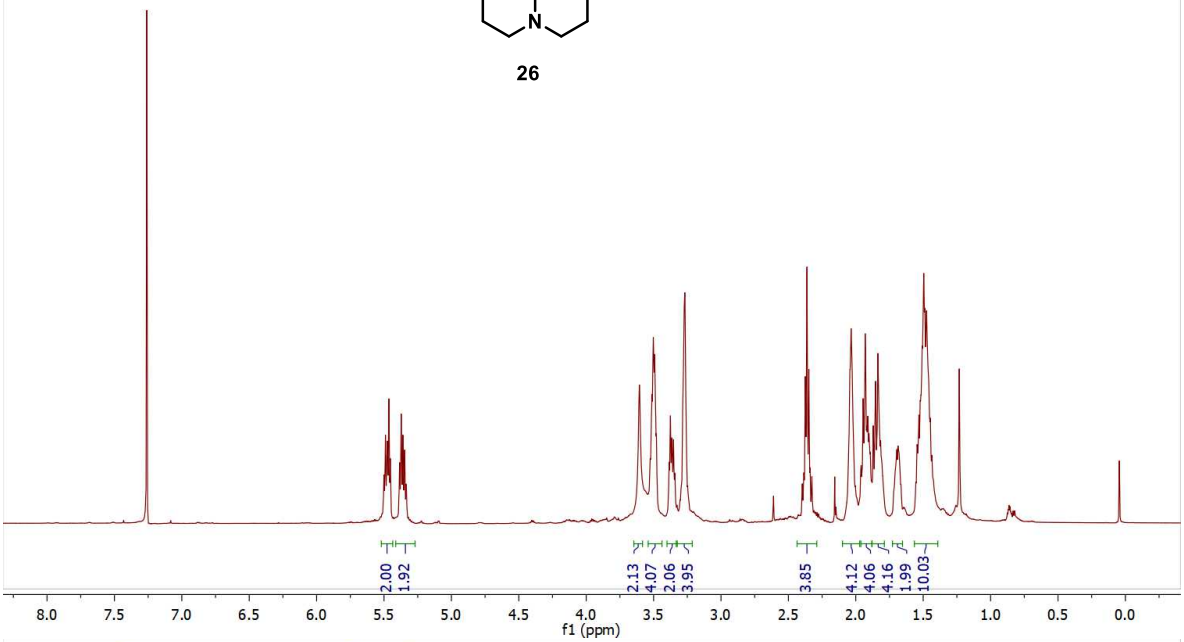
39

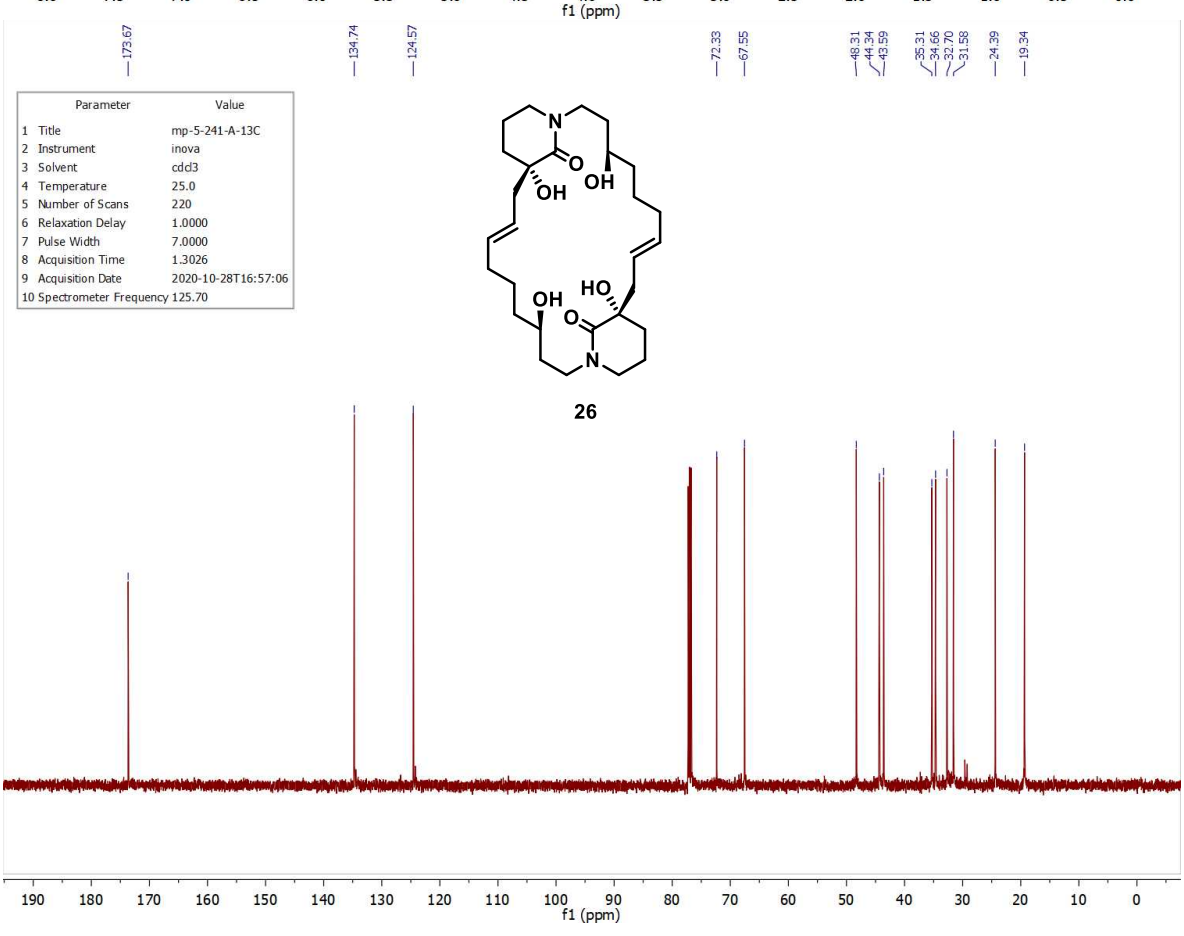


	Parameter	Value
1	Title	mp-5-241-A-1H
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	12
6	Relaxation Delay	8.0000
7	Pulse Width	6.0375
8	Acquisition Time	2.5000
9	Acquisition Date	2020-10-28T16:43:37
10	Spectrometer Frequency	599.64



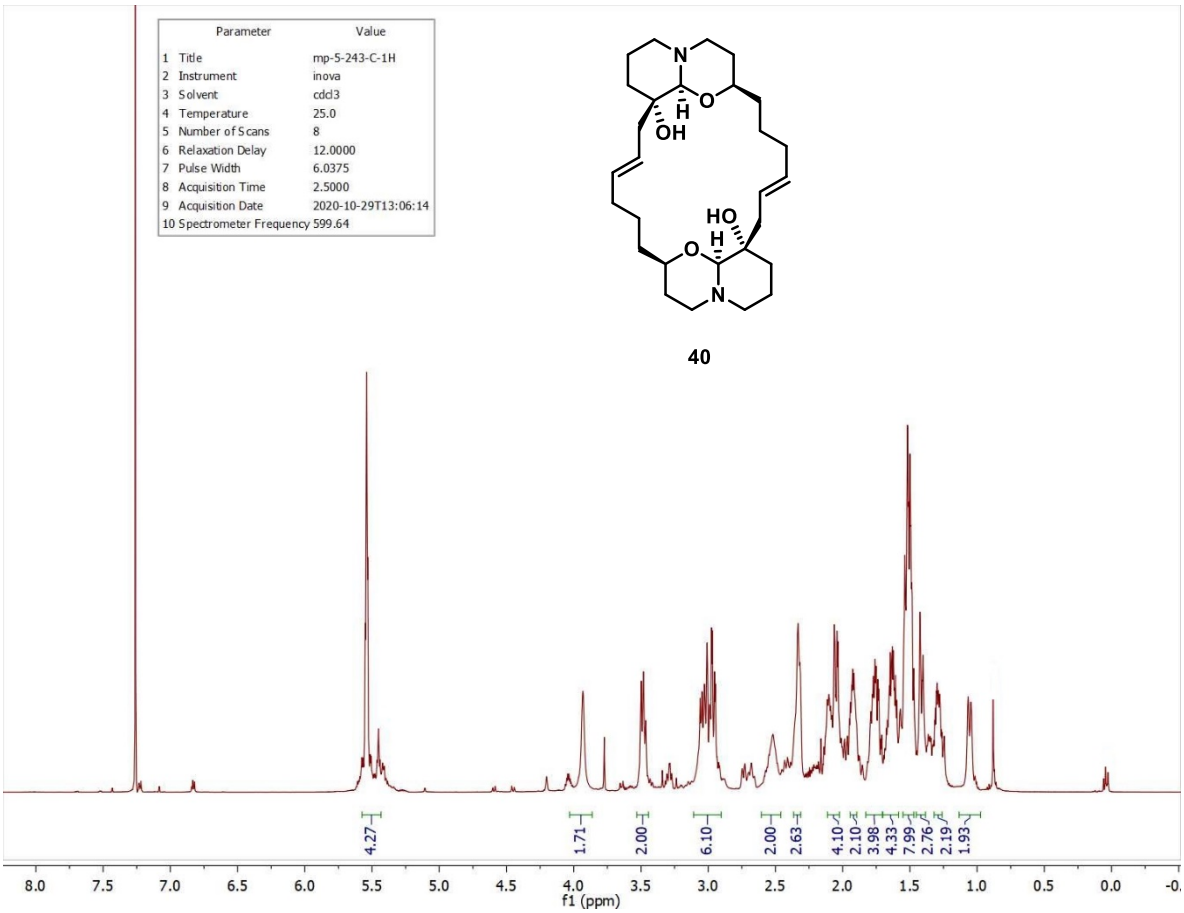
26



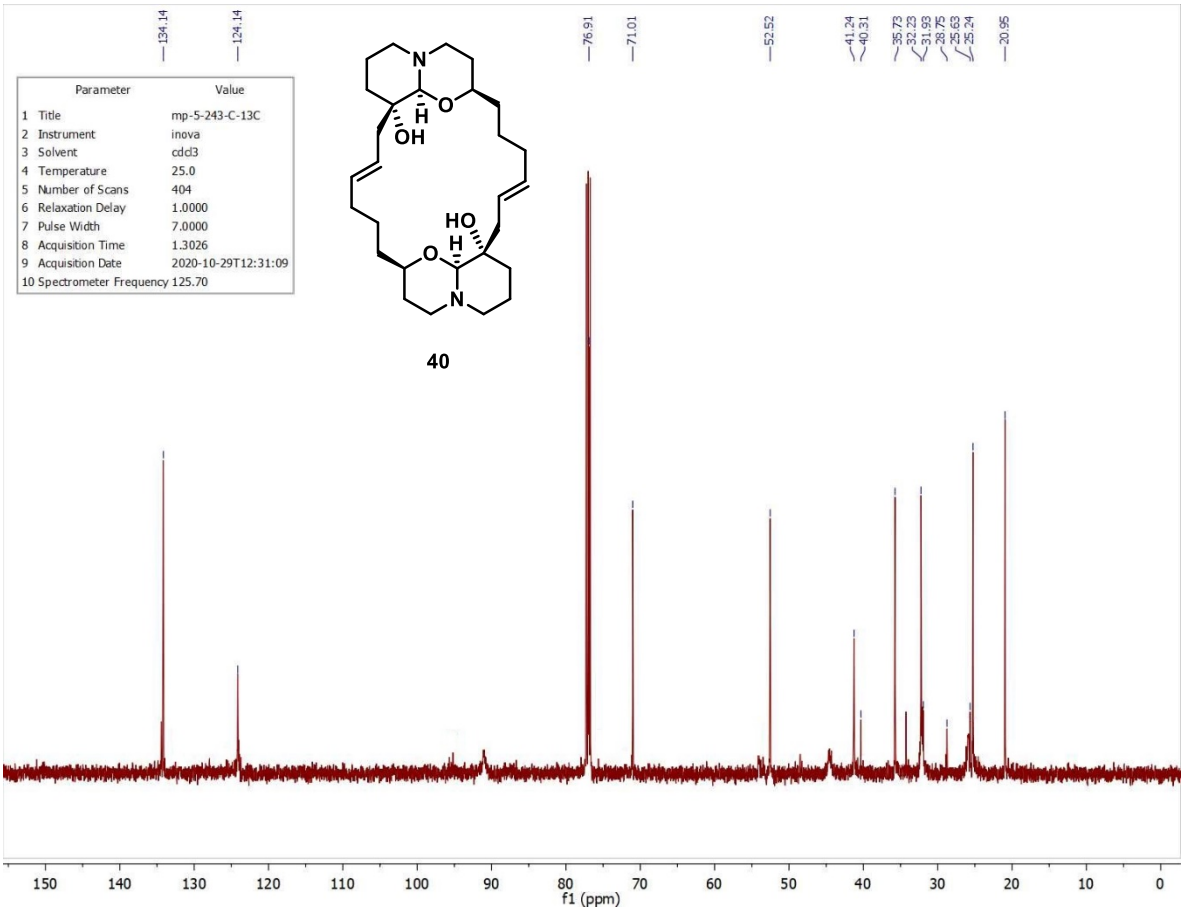


	Parameter	Value
1	Title	mp-5-241-A-13C
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	220
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2020-10-28T16:57:06
10	Spectrometer Frequency	125.70

26

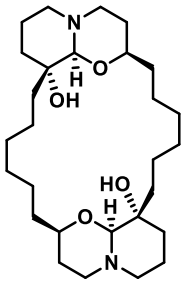

Parameter Value
1 Title mp-5-243-C-1H
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 12.0000
7 Pulse Width 6.0375
8 Acquisition Time 2.5000
9 Acquisition Date 2020-10-29T13:06:14
10 Spectrometer Frequency 599.64
OH
H
HO
H
4.27
1.71
2.00
6.10
2.00
2.63
4.10
2.10
3.98
4.33
7.99
2.76
2.19
1.93
f1 (ppm)

40

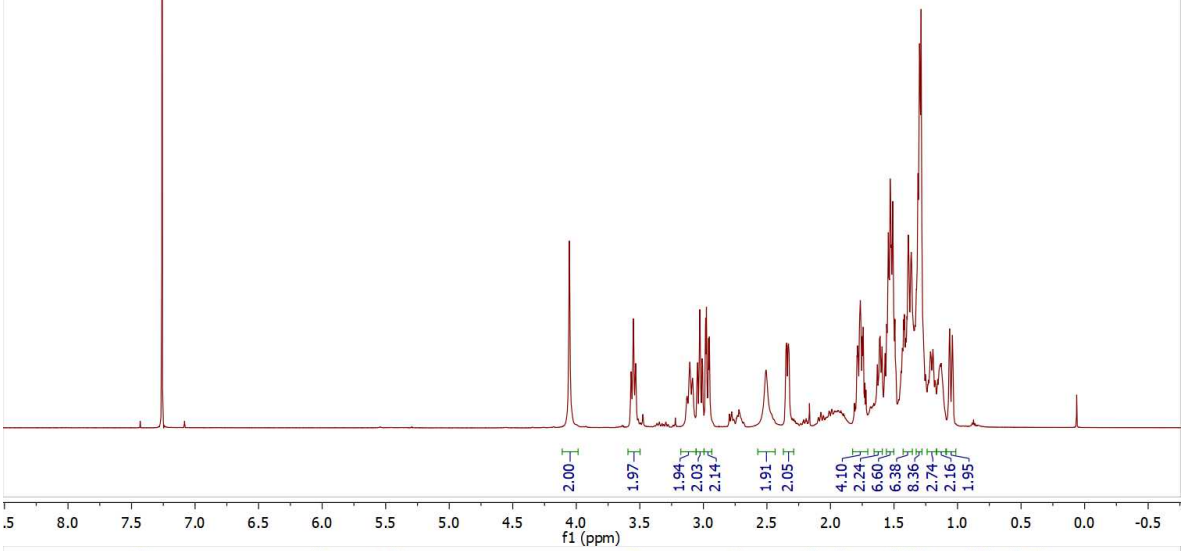

134.14
124.14
76.91
71.01
52.52
41.24
40.31
35.73
32.23
31.93
28.75
25.63
25.24
20.95
Parameter Value
1 Title mp-5-243-C-13C
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 404
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2020-10-29T12:31:09
10 Spectrometer Frequency 125.70
OH
H
HO
H
f1 (ppm)

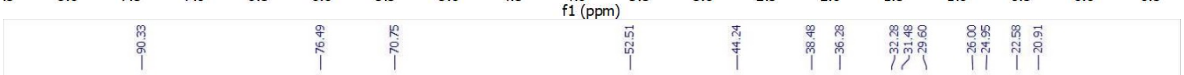
40

	Parameter	Value
1	Title	mp-5-244-A-1H
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	8
6	Relaxation Delay	12.0000
7	Pulse Width	6.0375
8	Acquisition Time	2.5000
9	Acquisition Date	2020-10-29T18:22:41
10	Spectrometer Frequency	599.64

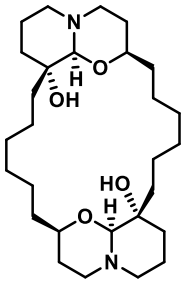


(+)-Ar C





	Parameter	Value
1	Title	mp-5-244-A-13C
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	684
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2020-10-29T18:30:05
10	Spectrometer Frequency	125.70



(+)-Ar C