Electronic Supporting Information for

Expanded scope of Griesbaum co-ozonolysis for the preparation of structurally diverse sensors of ferrous iron

Jun Chen[†], Ryan L. Gonciarz[†], Adam R. Renslo[†]

[†]Department of Pharmaceutical Chemistry, University of California, San Francisco, 600 16th Street, San Francisco, CA 94143, United States.

Table of Contents

Materials

All chemical reagents were obtained commercially and were used without further purification, unless otherwise stated. Anhydrous solvents were purchased from Sigma-Aldrich and were used without further purification. Solvents used for flash column chromatography and reaction workup procedures were purchased from either Sigma-Aldrich or Fisher Scientific. Column chromatography was performed on Silicycle Sili-prep cartridges using a Biotage Isolera Four automated flash chromatography system.

Instrumentation

NMR spectra were recorded on either a Varian INOVA 400 MHz spectrometer (with 5 mm QuadNuclear Z-Grad Probe), calibrated to CH(D)Cl3 as an internal reference (7.27 and 77.00 ppm for 1 H and 13C NMR spectra, respectively). Data for ^{1}H NMR spectra are reported in terms of chemical shift (δ, ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift (δ, ppm), with multiplicity and coupling constants in the case of C−F coupling. The following abbreviations are used to denote the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent, or combinations of these. UPLC−MS and compound purity were determined using a Waters Acquity QDa mass spectrometer equipped with FTN-H Sample Manager, Evaporative Light Scattering Detector and Photodiode Array Detector. Separations were carried out with Acquity UPLC® BEH C18, 1.7mm, 2.1 x 50 mm column, at 25 °C using a mobile phase of water-acetonitrile containing a constant 0.05 % formic acid.

Plasmodium falciparum EC_{50} Determinations

The growth inhibition assay for *P. falciparum* was conducted as described previously with minor modifications. Briefly, P. falciparum strain W2 synchronized ring-stage parasites were cultured in human red blood cells in 96-well flat-bottom culture plates at 37 °C, adjusted to 1% parasitemia and 2% hematocrit under an atmosphere of 3% O_2, 5% CO_2, and 91% N_2 in a final volume of 0.1 mL per well in RPMI-1640 media supplemented with 0.5% Albumax, 2 mM L-glutamine, and 100 mM hypoxanthine in the presence of various concentrations of inhibitors. Tested compounds were serially diluted 1:3 in the range 10 000−4.6 nM (or 1000−0.006 nM for more potent analogues), with a maximum DMSO concentration of 0.1%. Following 48 h of incubation, the cells were fixed by adding 0.1 mL of 2% formaldehyde in phosphate buffered saline, pH = 7.4 (PBS). Parasite growth was evaluated by flow cytometry on a FACsort (Becton Dickinson) equipped with AMS-1 loader (Cytek Development) after staining with 1 nM of the DNA dye YOYO-1 (Molecular Probes) in 100 mM NH_4Cl, 0.1% Triton x-100 in 0.8% NaCl. Parasitemias were determined from dot plots (forward scatter vs fluorescence) using CELLQUEST software (Becton Dickinson). EC50 values for growth inhibition were determined from plots of percentage control parasitemia over inhibitor concentration using GraphPad Prism software.

Fe(II)-fragmentation assay

To 1 mL of trioxolane analog in DMSO (1 mM) at 37˚C was added 1 mL of Tris containing 50 mM ferrous ammonium sulfate. At various time points, 40 µL aliquots of the resulting mixture were removed and spun down in a mini centrifuge for 20 seconds, 20 uL of the supernatant was removed and 5 uL was injected into the UPLC. The concentration of the fragments was determined by UV from UPLC (290 nm). The resulting UV curves were plotted using GraphPad Prism software.

Synthetic procedures

General procedure A: original conditions for Griesbaum reaction

To an oven-dried 100 mL flask was charged with ketone **2** (1.0 equiv), oxime **1** (3.0 equiv) and CCl_4. The mixture was cooled to 0 °C and ozone was bubbled through the solution. O_2 flow = 1 liter per minute, ozone gauge = 3.5 (This setting amounts to ~6 g/hour ozone production). The reaction mixture was stirred at 0 °C for 4 hours, at which point the reaction was complete based on UPLC-MS. The mixture was then bubbled with N_2 for 10 mins and concentrated. The resulting crude product was purified by flash column chromatography (column was pre-washed with 1% Et_3N in hexane) to yield desired compound.

General procedure B: improved, low temperature conditions for Griesbaum reaction

To an oven-dried 100 mL flask was charged with ketone **2** (1.0 equiv), oxime **1** (3.0 equiv) and hexane. The mixture was cooled to -78 °C and ozone was bubbled through the solution. O_2 flow = 1 liter per minute, ozone gauge = 3.5 (This setting amounts to ~6 g/hour ozone production). For starting materials that are not soluble in hexane, a small amount of dichloromethane can be added to enhance solubility. The reaction flask was wrapped with aluminum foil (protected from light) and the reaction mixture stirred at -78 °C for 4 hours, at which point the reaction was complete based on UPLC-MS. The reaction mixture was then bubbled with N_2 for 10 mins and concentrated. The resulting crude product was purified by flash column chromatography (column was pre-washed with 1% Et_3N in hexane) to yield the desired compound.

General procedure C: Silyl ether deprotection

To a stirred solution of trioxolane **3** (1.0 equiv) in THF (20 mL) was added a solution of tetrabutylammonium fluoride (1.0 M in THF, 5.0 equiv) dropwise while stirring at 0 °C. The reaction mixture was allowed to slowly warm to rt and was stirred for 12 h, at which point conversion was determined to be complete based on TLC and LC/MS analysis. The reaction was then diluted with brine (100 mL) and extracted with EtOAc (2 × 100 mL). The organic layer was then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. The crude material was purified using flash column chromatography ((column was washed with 1% Et_3N in hexane first, 0−50% EtOAc− Hexanes) to yield the desired product **4**.

General procedure D: para-nitrophenyl carbonate formation

To an oven-dried round-bottom flask containing a magnetic stir bar under an Ar (g) atmosphere was added alcohol **4** (1.0 equiv), dichloromethane, *N,N*-diisopropylethylamine (3.0 equiv), and 4-dimethylaminopyridine (1.0 equiv). The mixture was cooled to 0 °C while 4-nitrophenyl chloroformate (3.0 equiv) was added as a solid in two portions. The reaction mixture was allowed to warm to rt and was stirred for 3 h. The reaction was diluted with DI H_2O (100 mL) and extracted with EtOAc (1 × 100 mL). The organic layer was washed repeatedly with 1 M aq. K_2CO_3 solution until the aqueous layer was colorless and no longer yellow (indicating that most of the *p*-nitrophenol had been successfully removed from the organic layer). The organic layer was then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield a viscous yellow oil. The crude material was purified using flash column chromatography (0−25% EtOAc−hexanes; column was pre-washed with 1% Et_3N in hexane) to yield the desired product **5**.

General procedure E: coupling to mefloquine

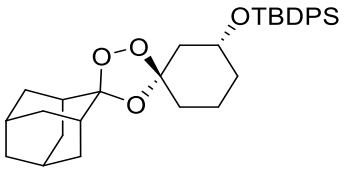
To a solution of **5** (1.0 equiv) in DMF was added *N,N*-diisopropylethylamine (5.0 equiv), dimethylaminopyridine (0.5 equiv) followed by, mefloquine (1.2 equiv) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M aq. NaOH (20 mL) and diluted with EtOAc (30 mL). The organic phase was separated and washed with additional 1 M aq. NaOH (4 × 30 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined aqueous layers were then back extracted with EtOAc (1 × 30 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (0−80% EtOAc−hexanes; column was pre-washed with 1% Et_3N in hexane) to give the desired product **6**.

General procedure F: coupling to morpholine

To a solution of **5** (1.0 equiv) in dichloromethane was added Et_3N (3.0 equiv), followed by, morpholine HCl salt (1.4 equiv) at rt. The bright yellow mixture was allowed to stir at rt for 3 h. The reaction was quenched with 1 M aq. NaOH (20 mL) and diluted with EtOAc (30 mL). The organic phase was separated and washed with additional 1 M aq. NaOH (4 × 30 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined aqueous layers were then back extracted with EtOAc (1 × 30 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (0−80% EtOAc−hexanes; column was pre-washed with 1% Et_3N in hexane) to give the desired product **7**.

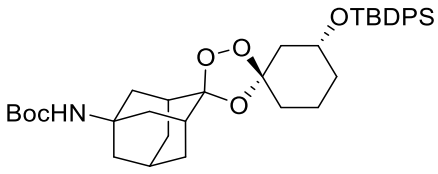
General procedure G: oxime synthesis

To a pressure vessel containing a magnetic stir bar was added ketone (1.0 equiv) followed by MeOH, pyridine (1.5 equiv) and methoxylamine hydrochloride (1.5 equiv). The reaction vessel was then sealed with a teflon screw cap and heated to 90 °C behind a blast shield for 3 h. The mixture was then cooled to rt and the cap was carefully unscrewed. The reaction mixture was then transferred to a flask and concentrated under reduced pressure to a crude semi-solid. The crude residue was diluted with 10% aq. $KHSO_4$ solution (115 mL) and extracted with EtOAc (1 × 200 mL). The organic phase was washed with additional 10% aq. $KHSO_4$ solution (3 × 60 mL) and the aqueous layers back-extracted with EtOAc (1 × 150 mL). The combined organic phases were washed with brine (1 × 150 mL), dried ($MgSO_4$), filtered and concentrated to the desired product **1**, which solidified under high vacuum to give oxime, which was sufficiently pure to be carried onto the next step without further purification.



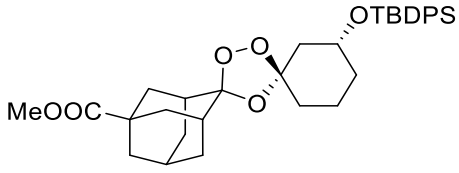
Prepared according to general procedure A using 20 mL CCl_4, ketone **2** (330.0 mg, 0.94 mmol, 1.0 equiv), and oxime **1a** (520.6 mg, 2.88 mmol, 2.5 equiv). Chromatography (0−20% EtOAc/hexanes gradient elution) to afforded 360.0 mg (71%) of **3a** as a white solid (cis: trans = 1: 10).

Prepared according to general procedure B using 20 mL hexane, ketone **2** (50.0 mg, 0.14 mmol, 1.0 equiv), and oxime **1a** (76.3 mg, 0.43 mmol, 3 equiv). Chromatography (0−20% EtOAc/hexanes gradient elution) to afforded 67.5 mg (91%) of **3a** as a white solid (dr > 20:1). ^{1}H NMR (400 MHz, CDCl3): δ 7.69 (td, J = 7.7, 1.5 Hz, 4 H), 7.36−7.46 (m, 6 H), 3.78−3.85 (m, 1 H), 1.47−2.05 (m, 20 H), 1.19−1.36 (m, 2 H), 1.08 (s, 9 H). ^{13}C NMR (100 MHz, CDCl3): δ 135.7 (two peaks), 134.5, 134.4, 129.5 (two peaks), 127.6, 127.5, 111.2, 109.2, 69.8, 43.7, 36.8, 36.3, 36.2, 34.9, 34.8, 34.7, 34.6, 34.4, 33.8, 33.2, 27.0, 26.9, 26.5, 19.9, 19.2. LRMS (ESI) calcd for C32H42NaO4Si $[M + Na]^+$ *m/z* 541.28, found 541.56



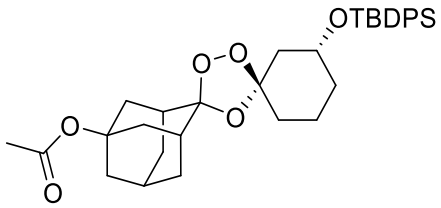
Prepared according to general procedure A using 40 mL CCl_4, ketone **2** (1.00 g, 2.84 mmol, 1.0 equiv, contaminated with 39% TBDPSOH), and oxime **1e** (1.67 g, 5.68 mmol, 2.00 equiv). Chromatography (0−15% EtOAc/hexanes gradient elution) afforded 718.9 mg (contaminated with 57% TBDPSOH by ^{1}HNMR integration, calculated yield 28%) of **3e** as colorless solid.

Prepared according to general procedure B using 30 mL hexane, ketone **2** (100 mg, 0.28 mmol, 1.0 equiv), and oxime **1b** (250 mg, 0.85 mmol, 3.0 equiv). Chromatography (0−20% EtOAc/hexanes gradient elution) to afforded 89.1 mg (50 %) of **3b** as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.71 (m, 4H), 7.34-7.46 (m, 6H), 4.63 (br s, 1H), 3.73-3.83 (m, 1H), 2.04-2.15 (m, 2H), 1.90-2.02 (m, 8H), 1.68-1.84 (m, 6H), 1.54-1.63 (m, 4H), 1.44 (s, 9H), 1.20-1.29 (m, 2H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.4, 135.7 (two peaks), 134.4 (two peaks), 129.5 (two peaks), 127.6 (two peaks), 110.0 (two peaks), 109.5 (two peaks), 69.7 (two peaks), 49.5, 49.2, 43.6 (two peaks), 40.0, 39.9 (two peaks), 38.7, 37.1 (two peaks), 36.8 (two peaks), 34.3, 33.7, 33.5 (two peaks), 28.4, 27.9, 27.5, 27.0, 19.8, 19.1 several minor diastereomer peaks overlapping or not observed; HRMS(ESI) calculated for $C_{37}H_{52}O_6NSiNa$ $[M + Na]^+$ *m/z* 656.3378, found 656.3375



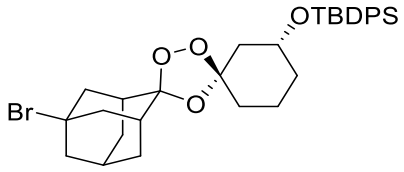
Prepared according to general procedure A using 20 mL CCl_4, ketone **2** (50 mg, 0.14 mmol, 1.0 equiv), and oxime **1c** (101 mg, 0.43 mmol, 3.0 equiv). Chromatography (0−20% EtOAc/hexanes gradient elution) to afforded 19.3 mg (23%) of **3c** as oil (cis: trans = 1: 10).

Prepared according to general procedure B using 30 mL hexane, ketone **2** (400 mg, 1.13 mmol, 1.0 equiv), and oxime **1c** (0.81 g, 3.41 mmol, 3.0 equiv). Chromatography (0−20% EtOAc/hexanes gradient elution) to afforded 501.3 mg (77%) of **3c** as oil (dr > 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.71 (m, 4H), 7.34-7.46 (m, 6H), 3.73-3.83 (m, 1H), 3.64 (app d, 3H), 2.08-2.20 (m, 2H), 1.56-1.98 (m, 17H), 1.20-1.30 (m, 2H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 135.7 (two peaks), 134.3 (two peaks), 129.5 (two peaks), 127.5 (two peaks), 110.0 , 109.5 (two peaks), 69.7, 51.7, 43.6, 39.8, 38.1, 36.3 (two peaks), 36.0, 35.8, 35.7, 34.3, 33.7 (two peaks), 33.5, 27.0, 26.5, 26.1, 24.9, 19.8, 19.1 several minor diastereomer peaks overlapping or not observed; HRMS(ESI) calculated for $C_{34}H_{44}O_6SiNa$ $[M + Na]^+$ *m/z* 599.2805, found 599.2806



Prepared according to general procedure A using 30 mL CCl_4, ketone **2** (50 mg, 0.14 mmol, 1.0 equiv), and oxime **1d** (101 mg, 0.43 mmol, 3.0 equiv). Chromatography (0−5% EtOAc/hexanes gradient elution) to afforded 4.2 mg (5.1%) of **3d** as colorless solid.

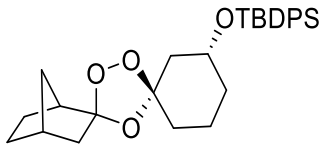
Prepared according to general procedure B using 30 mL hexane, ketone **2** (50 mg, 0.14 mmol, 1.0 equiv), and oxime **1d** (101 mg, 0.43 mmol, 3.0 equiv). Chromatography (0−5% EtOAc/hexanes gradient elution) to afforded 69.3 mg (84%) of **3d** as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 - 7.79 (m, 4H), 7.35 - 7.48 (m, 6H), 3.74 - 3.90 (m, 1H), 2.19 - 2.38 (m, 2H), 2.05 - 2.19 (m, 7H), 1.94 - 2.02 (m, 5H), 1.46 - 1.92 (m, 11H), 1.19 - 1.35 (m, 3H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 135.8 (2 peaks), 134.4 (2 peaks), 129.6 (3 peaks), 127.6 (2 peaks), 109.6 (4 peaks), 78.6, 78.2, 69.7, 43.6 (2 peaks), 40.0 (2 peaks), 38.4, 38.2, 38.0 (2 peaks), 34.3, 33.7 (2 peaks), 33.5 (2 peaks), 33.2 (2 peaks), 29.1, 28.8, 27.0, 22.6 (2 peaks), 19.9, 19.1; HRMS(ESI) calculated for $C_{34}H_{44}O_6SiNa$ $[M + Na]^+$ 599.2799 found m/z: 599.2799.



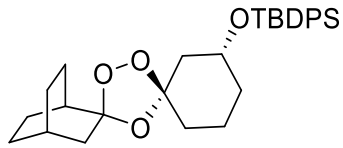
Prepared according to general procedure A using 30 mL CCl_4, ketone **2** (50 mg, 0.14 mmol, 1.0 equiv), and oxime **1e** (101 mg, 0.43 mmol, 3.0 equiv). Chromatography (0−20% EtOAc/hexanes gradient elution) to afforded 15.0 mg (18%) of **3e** as colorless solid.

Prepared according to general procedure B using 30 mL hexane, ketone **2** (50 mg, 0.14 mmol, 1.0 equiv), and oxime **1e** (110 mg, 0.43 mmol, 3.0 equiv). Chromatography (0−20% EtOAc/hexanes gradient elution) to afforded 80.1 mg (94%) of **3e** as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.71 (m, 4H), 7.34-7.47 (m, 6H), 3.77-3.83 (m, 1H), 2.46-2.65 (m, 2H), 2.16-2.37 (m, 4H), 1.46-2.03 (m, 13H), 1.17-1.34 (m, 2H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (two peaks), 134.3 (two peaks), 129.5 (two peaks), 127.5 (two peaks), 109.7 (two peaks), 108.9 (minor diastereomer), 108.8 (major diastereomer), 69.6, 62.5 (minor diastereomer), 62.1 (major diastereomer), 48.4 (two peaks), 45.9, 45.6, 43.5, 45.4, 39.7 (two peaks), 39.5 (two peaks), 34.2, 33.6 (two peaks), 32.9, 32.8, 32.6 (two peaks), 30.8, 30.4, 27.0, 19.7, 19.1

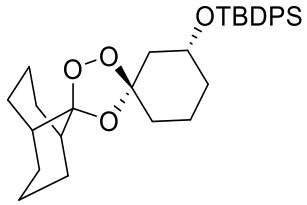
(two peaks) several minor diastereomer peaks overlapping or not observed; HRMS(ESI) calculated for $C_{32}H_{41}O_4BrSiNa$ $[M + Na]^+$ *m/z* 619.1850, found 619.1854



Prepared according to general procedure B using 30 mL hexane, ketone **2** (150 mg, 0.43 mmol, 1.0 equiv), and oxime **1f** (178 mg, 1.28 mmol, 3.0 equiv). Chromatography (0−20% EtOAc/hexanes gradient elution) to afforded 166.2 mg (82%) of **3f** as oil (13:8:1 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.72(m, 4H), 7.35-7.47 (m, 6H), 3.80-3.90 (m, 1H, minor diastereomer), 3.70-3.80 (m, 1H, major diastereomer), 2.22-2.30 (m, 1H), 2.10-2.17 (m, 1H), 1.71-2.02 (m, 4H), 1.12-1.65 (m, 12H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8 (multiple peaks), 134.4 (multiple peaks), 129.6 (multiple peaks), 127.5 (multiple peaks), 115.9, 109.2 (two peaks), 69.7 (two peaks), 45.0, 44.9, 43.8, 43.1, 42.1, 41.0, 37.6, 37.5, 35.4, 35.2, 34.3 (two peaks), 33.8, 33.1, 27.8, 27.7, 27.0 (two peaks), 21.7, 21.6, 19.9, 19.7, 19.1 (two peaks) several minor diastereomer peaks overlapping or not observed; HRMS(ESI) calculated for $C_{29}H_{38}O_4SiNa$ $[M + Na]^+$ *m/z* 501.2432, found 501.2436

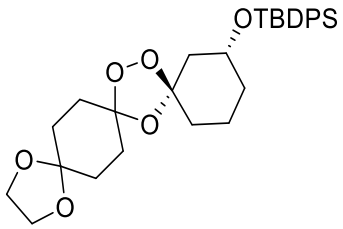


Prepared according to general procedure B using 30 mL hexane, ketone **2** (50 mg, 0.14 mmol, 1.0 equiv), and oxime **1g** (65mg, 0.43 mmol, 3.0 equiv). Chromatography (0−20% EtOAc/hexanes gradient elution) to afforded 31 mg (44%) of **3g** as oil (4:1 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.70 (m, 4H), 7.32-7.46 (m, 6H), 3.80-3.89 (m, 1H, minor diastereomer), 3.69-3.80 (m, 1H, major diastereomer), 1.68-1.88 (m, 9H), 1.57-1.65 (m, 2H), 1.34-1.50 (m, 7H), 1.21-1.29 (m, 2H), 1.08 (app d, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8 (two peaks), 134.4 (two peaks), 129.5 (two peaks), 127.5 (two peaks), 110.1 , 109.1, 69.7, 43.4, 37.7, 34.4, 33.9, 32.7, 27.0, 25.9, 24.2, 21.0, 20.9, 19.8, 19.1 several minor diastereomer peaks overlapping or not observed; HRMS(ESI) calculated for $C_{30}H_{40}O_4SiNa$ $[M + Na]^+$ *m/z* 515.2588, found 515.2594

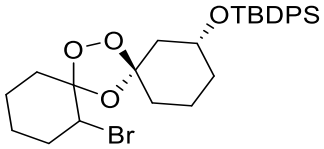


Prepared according to general procedure B using 30 mL hexane, ketone **2** (200 mg, 0.57 mmol, 1.0 equiv), and oxime **1h** (285 mg, 1.70 mmol, 3.0 equiv). Chromatography (0−20% EtOAc/hexanes gradient elution) to afforded 250.1 mg (87%) of **3h** as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.72 (m, 4H), 7.34-7.46 (m, 6H), 3.76-3.83 (m, 1H), 1.92-2.07 (m, 5H), 1.56-1.82 (m, 13H), 1.40-1.51 (m, 2H), 1.20-1.31 (m, 2H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (two peaks), 134.4 (two peaks), 129.5 (two peaks), 127.5 (two peaks), 110.1 , 109.1, 69.8, 43.8, 36.1, 36.0, 34.4, 33.9, 33.4, 33.8, 29.7, 29.4, 29.3, 29.2, 27.9, 27.0, 20.8, 20.4,

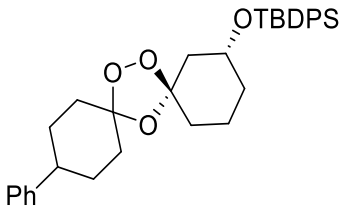
19.9, 19.1 several minor diastereomer peaks overlapping or not observed; HRMS(ESI) calculated for $C_{31}H_{42}O_4SiNa$ $[M + Na]^+$ *m/z* 529.2745, found 529.2751



Prepared according to general procedure B using 30 mL hexane, ketone **2** (100 mg, 0.28 mmol, 1.0 equiv), and oxime **1j** (158 mg, 0.85 mmol, 3.0 equiv). Chromatography (0−20% EtOAc/hexanes gradient elution) to afforded 105.3 mg (71%) of **3j** as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.70 (m, 4H), 7.35-7.47 (m, 6H), 4.17-4.22 (m, 1H, minor diastereomer), 3.90-4.00 (m, 4H), 3.75-3.84 (m, 1H, , major diastereomer), 1.94-2.02 (m, 1H), 1.70-1.88 (m, 10H), 1.55-1.62 (m, 2H), 1.44-1.51 (m, 1H), 1.20-1.31 (m, 2H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8 (two peaks), 134.4 (two peaks), 129.6 (two peaks), 127.6 (two peaks), 109.5, 107.9, 107.7 (minor diastereomer), 69.7, 64.4 (two peaks), 43.5, 34.3, 33.5, 32.1, 31.9, 31.5, 31.3, 27.0, 19.9, 19.1 several minor diastereomer peaks overlapping or not observed; HRMS(ESI) calculated for $C_{30}H_{40}O_6SiNa$ $[M + Na]^+$ *m/z* 547.2486, found 547.2492

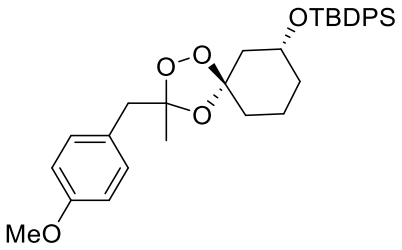


Prepared according to general procedure B using 30 mL hexane, ketone **2** (50 mg, 0.14 mmol, 1.0 equiv), and oxime **1k** (88 mg, 0.43 mmol, 3.0 equiv). Chromatography (0−20% EtOAc/hexanes gradient elution) to afforded 42.3 mg (53%) of **3k** as oil (6:4 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.70 (m, 4H), 7.34-7.50 (m, 6H), 4.23-4.25 (m, 1H, minor diastereomer), 4.03-4.10 (m,1H, major diastereomer), 3.77-3.88 (m, 1H), 1.96-2.22 (m, 4H), 1.71-1.83 (m, 4H), 1.46-1.66 (m, 6H), 1.23-1.34 (m, 2H), 1.08 (app d, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (multiple peaks), 134.3 (multiple peaks), 129.7 (multiple peaks), 127.6 (multiple peaks), 110.4 (two peaks), 107.3 (minor diastereomer), 107.2 (major diastereomer), 69.6, 53.0, 52.7, 43.6, 43.0, 34.2, 33.6, 33.2, 32.6, 31.9, 27.0, 23.2, 23.0, 19.9, 19.6, 19.1 (two peaks) several minor diastereomer peaks overlapping or not observed; HRMS(ESI) calculated for $C_{28}H_{37}O_4BrSiNa$ $[M + Na]^+$ *m/z* 567.1537, found 567.1543

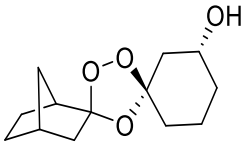


Prepared according to general procedure B using 30 mL hexane, ketone **2** (100 mg, 0.28 mmol, 1.0 equiv), and oxime **1l** (173 mg, 0.85 mmol, 3.0 equiv). Chromatography (0−20% EtOAc/hexanes gradient elution) to afforded 115.5 mg (75%) of **3l** as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74-7.80 (m, 4H), 7.43-7.52 (m, 6H), 7.35-7.40 (m, 2H), 7.25-7.31 (m, 3H), 3.98-4.10 (m, 1H, minor diastereomer), 3.85-3.96 (m, 1H, major

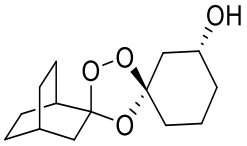
diastereomer), 2.55-2.64 (m, 1H), 2.07-2.23 (m, 2H), 1.83-2.01 (m, 10H), 1.68-1.74 (m, 1H), 1.55-1.64 (m, 1H), 1.32-1.42 (m, 2H),1.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 135.8 (two peaks), 134.4 (two peaks), 129.6 (two peaks), 127.6 (two peaks), 126.9, 126.7, 126.2 (two peaks), 109.6, 109.2 (minor diastereomer), 108.2 (two peaks), 69.7, 43.5, 43.2, 34.6, 34.3, 34.0, 33.6, 31.2, 31.0, 29.7, 27.0, 19.8, 19.1 several minor diastereomer peaks overlapping or not observed; HRMS(ESI) calculated for $C_{34}H_{42}O_4SiNa$ [M + Na]$^+$ *m/z* 565.2745, found 565.2747



Prepared according to general procedure B using 30 mL hexane, ketone **2** (50 mg, 0.14 mmol, 1.0 equiv), and oxime **1q** (82.0 mg, 0.43 mmol). Chromatography (0−20% EtOAc/hexanes gradient elution) to afforded 3 mg (4%) of **3q** as oil (1.4:1 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.70 (m, 4H), 7.32-7.44 (m, 6H), 7.11 (dd, 2H, *J* = 8.8, 13.8 Hz), 6.82 (dd, 2H, *J* = 5.6, 8.5 Hz), 3.69-3.86 (m, 4H), 2.89 (ABq, 1H, *J* = 13.9, 32.9 Hz, minor diastereomer), 2.80 (ABq, 1H, *J* = 14.1, 43.8 Hz, major diastereomer), 1.57-2.04 (m, 6H), 1.21-1.30 (m, 5H), 1.08 (app d, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.44, 135.8 (two peaks), 134.3 (two peaks), 131.4 (two peaks), 129.5 (three peaks), 128.0, 127.5 (three peaks), 113.5, 109.9 (two peaks), 109.2, 69.7 (two peaks), 52.2 (two peaks), 43.4, 43.2, 42.9, 34.3, 33.6, 33.2, 27.0, 22.7, 21.8, 19.8, 19.1 several minor diastereomer peaks overlapping or not observed; HRMS(ESI) calculated for $C_{32}H_{40}O_5SiNa$ [M + Na]$^+$ *m/z* 555.2537, found 555.253.

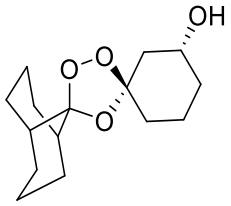


Prepared according to general procedure C using 10 mL THF, trioxloane **3f** (87 mg, 0.18 mmol, 1.0 equiv), and TBAF (1M in THF, 0.91 mL, 0.91 mmol, 5.0 equiv). Chromatography (0−50% EtOAc/hexanes gradient elution) to afforded 25.0 mg (57%) of **4f** as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86-4.04 (m, 1H), 2.25-2.40 (m, 3H), 2.02-2.11 (m, 1H), 1.91-1.99 (m, 1H) 1.60-1.85 (m, 7H), 1.38-1.57 (m, 5H), 1.19-1.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.5 (two peaks), 108.9 (two peaks), 68.0, 44.9 (two peaks), 42.2, 41.5, 41.4, 41.2, 37.6, 35.3 (two peaks), 34.0, 33.2, 33.1, 32.8, 27.7, 21.6, 19.3, 19.0 several minor diastereomer peaks overlapping or not observed; LRMS(ESI) calculated for $C_{13}H_{20}O_4Na$ [M + Na]$^+$ *m/z* 263.13, found 263.09

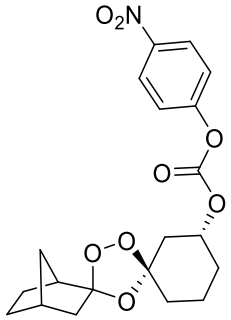


Prepared according to general procedure C using 10 mL THF, trioxolane **3g** (70 mg, 0.14 mmol, 1.0 equiv), and TBAF (1M in THF, 0.71 mL, 0.71 mmol, 5.0 equiv). Chromatography (0−50% EtOAc/hexanes gradient

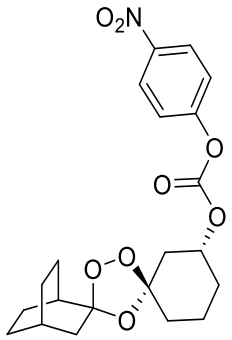
elution) to afforded 20.0 mg (55%) of **4g** as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86-4.03 (m, 1H), 2.38 (br, 1H), 1.39-2.14 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.6, 108.9 (two peaks), 68.0, 42.2, 41.4, 38.1 (two peaks), 34.2, 33.3, 33.1 (two peaks), 32.8 (two peaks), 25.9, 24.4, 24.1, 21.0 (two peaks), 19.3, 19.0 several minor diastereomer peaks overlapping or not observed; LRMS(ESI) calculated for $C_{14}H_{22}O_4Na$ $[M + Na]^+$ *m/z* 277.14, found 277.09



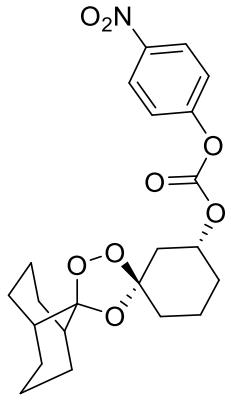
Prepared according to general procedure C using 10 mL THF, trioxolane **3h** (250 mg, 0.49 mmol, 1.0 equiv), and TBAF (1M in THF, 2.47 mL, 2.47 mmol, 5.0 equiv). Chromatography (0−50% EtOAc/hexanes gradient elution) to afforded 132.0 mg (66%) of **4h** as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86-4.03 (m, 1H), 2.69 (br, 1H), 1.35-2.10 (m, 22H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.8, 108.9, 67.9, 41.9, 36.0 (two peaks), 33.8, 33.1, 29.6 (two peaks), 29.3, 20.7, 20.3, 19.1 several minor diastereomer peaks overlapping or not observed; LRMS(ESI) calculated for $C_{15}H_{24}O_4Na$ $[M + Na]^+$ *m/z* 291.16, found 291.09



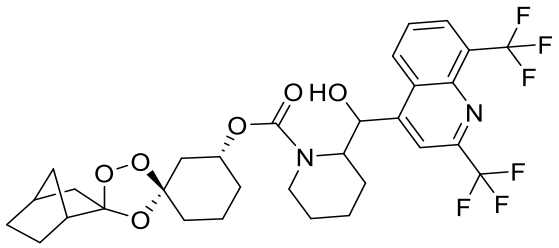
Prepared according to general procedure D using 5 mL DCM, alcohol **4f** (50.0 mg, 0.21 mmol, 1.0 equiv), diisopropylethylamine (80.7 mg, 0.62 mmol, 3.0 equiv), 4-dimethylaminopyridine (25.4 mg, 0.21 mmol, 1.0 equiv) and 4-nitrophenyl chloroformate (126.0 mg, 0.62 mmol, 3.0 equiv). Chromatography (0−50% EtOAc/hexanes gradient elution) to afforded 56.0 mg (66%) of **5f** as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, 2H, *J* = 9.3 Hz), 7.39 (d, 2H, *J* = 9.3 Hz), 4.76-4.90 (m, 1H), 2.29-2.51 (m, 3H), 2.08-2.18 (m, 1H), 1.31-2.00 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 151.3, 145.3, 125.3, 121.7, 116.6 (two peaks), 108.2 (two peaks), 76.1, 45.1, 45.0, 41.6, 41.2, 39.8, 38.9, 37.5 (two peaks), 36.3 (two peaks), 33.6, 32.8, 30.0, 27.7, 21.5, 19.7, 19.4 several minor diastereomer peaks overlapping or not observed; LRMS(ESI) calculated for $C_{20}H_{23}O_8NNa$ $[M + Na]^+$ *m/z* 428.13, found 428.14



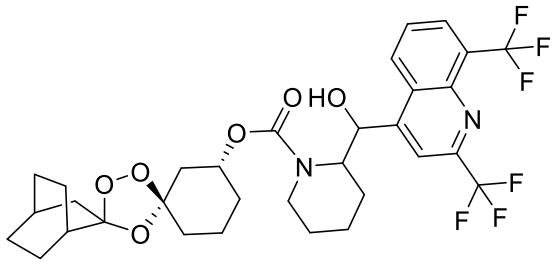
Prepared according to general procedure D using 5 mL DCM, alcohol **4g** (12.0 mg, 0.05 mmol, 1.0 equiv), diisopropylethylamine (18.0 mg, 0.14 mmol, 3.0 equiv), 4-dimethylaminopyridine (5.8 mg, 0.05 mmol, 1.0 equiv) and 4-nitrophenyl chloroformate (29.0 mg, 0.14 mmol, 3.0 equiv). Chromatography (0−50% EtOAc/hexanes gradient elution) to afforded 10.0 mg (51%) of **5g** as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, 2H, *J* = 9.3 Hz), 7.38 (d, 2H, *J* = 9.3 Hz), 4.77-4.94 (m, 1H), 2.21-2.58 (m, 1H), 1.77-2.02 (m, 9H), 1.39-1.59 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 151.5, 145.3, 125.3, 121.7, 111.8 (two peaks), 108.2 (two peaks), 76.1, 39.8, 39.2, 38.2, 38.0, 33.8, 33.2 (two peaks), 30.1, 25.9, 24.4, 24.1, 21.1 (two peaks), 19.3 several minor diastereomer peaks overlapping or not observed; LRMS(ESI) calculated for $C_{21}H_{35}O_8NNa$ $[M + Na]^+$ *m/z* 442.15, found 442.29



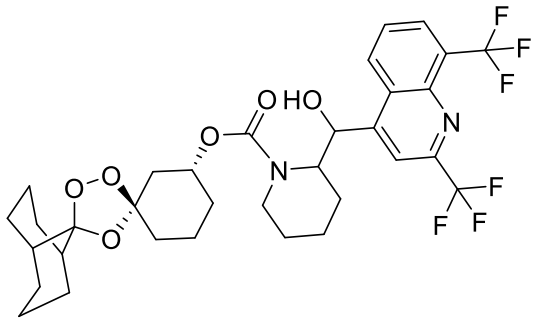
Prepared according to general procedure D using 5 mL DCM, alcohol **4h** (85.0 mg, 0.32 mmol, 1.0 equiv), diisopropylethylamine (123.0 mg, 0.95 mmol, 3.0 equiv), 4-dimethylaminopyridine (38.7 mg, 0.32 mmol, 1.0 equiv) and 4-nitrophenyl chloroformate (192.0 mg, 0.95 mmol, 3.0 equiv). Chromatography (0−50% EtOAc/hexanes gradient elution) to afforded 83.8 mg (61%) of **5h** as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, 2H, *J* = 9.3 Hz), 7.38 (d, 2H, *J* = 9.3 Hz), 4.77-5.04 (m, 1H), 2.34-2.45 (m, 1H), 1.41-2.10 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 151.5, 145.3, 125.2, 121.7, 111.9, 108.1, 76.2, 39.6, 36.2, 36.1, 33.5, 30.0, 29.6, 29.4, 29.3 (two peaks), 20.8, 20.4, 19.5 several minor diastereomer peaks overlapping or not observed; LRMS(ESI) calculated for $C_{22}H_{27}O_8NNa$ $[M + Na]^+$ *m/z* 456.16, found 456.01



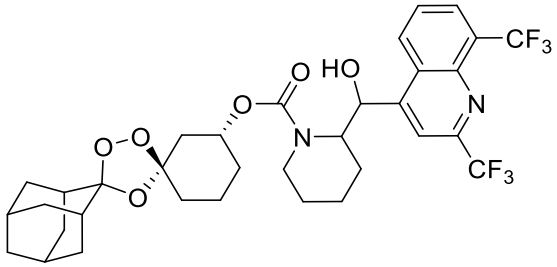
Prepared according to general procedure E using 5 mL DMF, TRX PNP **5f** (10.0 mg, 0.03 mmol, 1.0 equiv), diisopropylethylamine (16.0 mg, 0.12 mmol, 5.0 equiv), 4-dimethylaminopyridine (1.5 mg, 0.01 mmol, 0.5 equiv) and mefloquine (12.0 mg, 0.03 mmol, 1.2 equiv). Chromatography (0−80% EtOAc/hexanes gradient elution) to afforded 8.3 mg (52%) of **6f** as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (dd, 1H, *J* = 3.4, 8.0 Hz), 8.19 (d, 1H, *J* = 7.1 Hz), 8.09 (s, 1H), 7.79 (t, 1H, *J* = 7.1 Hz), 5.93 (br, 1H), 4.69-4.85 (m, 1H), 4.21-4.36 (m, 1H), 3.86-4.02 (m, 1H), 3.29-3.44 (m, 1H), 2.99 (br, 1H), 2.29 (s, 3H), 1.45-1.89 (m, 21H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.3, -67.9; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 150.9, 150.7, 143.7, 129.5, 128.9 (multiple peaks), 128.2 (two peaks), 127.3 (two peaks), 126.7, 122.6, 122.2, 116.5, 116.4, 116.3, 115.4 (two peaks), 109.0 (two peaks), 108.5 (two peaks), 72.2 (two peaks), 71.6, 68.0 (two peaks), 56.9 (multiple peaks), 44.9, 42.2, 41.1-41.6 (multiple peaks), 40.3 (twp peaks), 39.6 (two peaks), 37.5-37.6(multiple peaks), 35.3 (two peaks), 34.0, 33.9 (two peaks), 33.0-33.2 (multiple peaks), 30.6, 29.7 (multiple peaks), 27.7, 24.0 (two peaks), 22.1, 21.6 (two peaks), 19.8, 19.4, 19.0 several minor diastereomer peaks overlapping or not observed; HRMS(ESI) calculated for $C_{31}H_{34}O_6N_2F_6Na$ $[M + Na]^+$ *m/z* 667.2213, found 667.2220



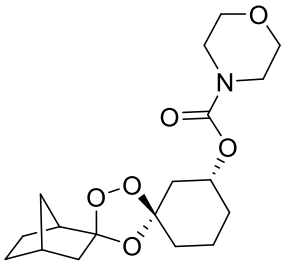
Prepared according to general procedure E using 5 mL DMF, TRX PNP **5g** (10.0 mg, 0.02 mmol, 1.0 equiv), diisopropylethylamine (15.0 mg, 0.12 mmol, 5.0 equiv), 4-dimethylaminopyridine (1.5 mg, 0.01 mmol, 0.5 equiv) and mefloquine (12.0 mg, 0.03 mmol, 1.2 equiv). Chromatography (0−80% EtOAc/hexanes gradient elution) to afforded 7.6 mg (48%) of **6g** as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, 1H, *J* = 8.7 Hz), 8.19 (d, 1H, *J* = 7.3 Hz), 8.11 (s, 1H), 7.79 (app t, 1H, *J* = 7.8 Hz), 5.94 (br, 1H), 4.71-4.88 (m, 1H), 4.23-4.35 (m, 1H), 3.87-4.00 (m, 1H), 3.35-3.47 (m, 1H), 2.80-3.12 (br, 1H), 2.06-2.16 (m, 1H), 1.45-1.94 (m, 25H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.3, -67.9; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 150.8, 150.7, 143.7, 128.9, 128.8, 128.2, 127.3, 126.7, 122.6, 115.4, 111.7, 111.5, 108.6, 108.5, 72.2, 71.6, 68.0, 57.0, 42.2, 41.3, 39.6, 39.5, 38.0-38.2(multiple peaks), 34.1 (two peaks), 33.2, 32.8(multiple peaks), 30.6, 25.9 (two peaks), 24.4, 24.1, 24.0, 21.1, 21.0 (two peaks), 19.9, 19.4, 19.0 several minor diastereomer peaks overlapping or not observed; HRMS(ESI) calculated for $C_{32}H_{36}O_6N_2F_6Na$ $[M + Na]^+$ *m/z* 681.2370, found 681.2386



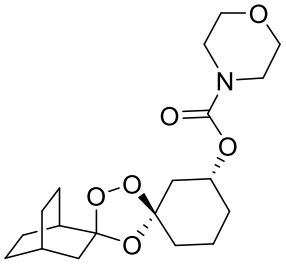
Prepared according to general procedure E using 5 mL DMF, TRX PNP **5g** (10.0 mg, 0.02 mmol, 1.0 equiv), diisopropylethylamine (15.0 mg, 0.12 mmol, 5.0 equiv), 4-dimethylaminopyridine (1.4 mg, 0.01 mmol, 0.5 equiv) and mefloquine (11.5 mg, 0.03 mmol, 1.2 equiv). Chromatography (0−80% EtOAc/hexanes gradient elution) to afforded 7.0 mg (50%) of **6g** as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, 1H, *J* = 8.7 Hz), 8.20 (d, 1H, *J* = 7.1 Hz), 8.11 (app d, 1H, *J* = 3.7 Hz), 7.81 (app t, 1H, *J* = 7.8 Hz), 5.95 (br, 1H), 4.77-4.88 (m, 1H), 4.25-4.39 (m, 1H), 3.91-4.05 (m, 1H), 3.35-3.47 (m, 1H), 2.19-2.28 (m, 1H), 1.45-2.07 (m, 28H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.3, -67.9; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 151.0, 150.8, 143.7, 128.9, 128.8, 128.2 (two peaks), 127.3, 126.8, 122.6, 122.2, 115.4, 111.9, 111.7, 108.9, 108.5, 72.2, 71.6, 68.0, 56.9, 42.2, 41.7, 40.9, 40.0, 36.0-36.2(multiple peaks), 34.1 (two peaks), 33.8, 33.1, 30.6, 29.3-29.7 (multiple peaks), 24.0 (two peaks), 20.9, 20.8, 19.9, 19.5, 19.1 several minor diastereomer peaks overlapping or not observed; HRMS(ESI) calculated for $C_{33}H_{38}O_6N_2F_6Na$ $[M + Na]^+$ *m/z* 695.2526, found 695.2538



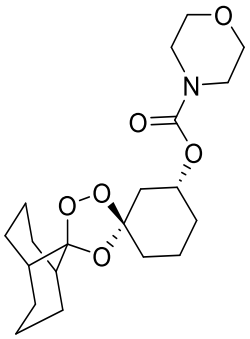
Prepared according to general procedure E using 5 mL DMF, TRX PNP (100.0 mg, 0.22 mmol, 1.0 equiv), diisopropylethylamine (145.0 mg, 1.12 mmol, 5.0 equiv), 4-dimethylaminopyridine (13.7 mg, 0.11 mmol, 0.5 equiv) and mefloquine (112.0 mg, 0.27 mmol, 1.2 equiv). Chromatography (0−80% EtOAc/hexanes gradient elution) to afforded 91.6 mg (60%) of **8** as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (br t, 1H, J = 8.4 Hz), 8.17 (t, 1H, J = 6.5 Hz), 8.10 (d, 1H, J = 5.8 Hz), 7.76 (dt, 1H, J = 11.8, 8.1 Hz), 5.90 (br d, 1H, J = 3.4 Hz), 4.70 - 4.97 (m, 1H), 4.18 - 4.36 (m, 1H), 3.95 (br t, 1H, J = 14.9 Hz), 3.23 - 3.49 (m, 1H), 3.12 (br s, 1H), 2.17 - 2.28 (m, 1H), 1.73 - 2.14 (m, 17H), 1.40 - 1.68 (m, 7H), 1.21 - 1.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 155.6 (several peaks), 151.1, 150.9, 148.4, 148.3, 143.7, 129.4, 129.1, 128.8 (several peaks), 128.2, 128.1, 127.3, 126.8 (2 peaks), 125.4, 124.9 (2 peaks), 123.8, 122.7, 122.2, 121.7, 119.9, 115.4 (several peaks), 111.7, 108.6, 108.6, 77.2, 72.2, 72.0, 71.7, 60.5, 56.8 (several peaks), 42.1 (several peaks), 40.1, 39.9, 36.8, 36.6, 36.3 (3 peaks), 34.9, 34.8 (several peaks), 34.7, 34.0, 33.9, 30.6, 26.9, 26.4, 24.7, 24.0, 22.2, 21.1, 19.8 (several peaks), 19.6 (2 peaks); ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.30, -60.33, -67.87; HRMS (ESI): m/z $[M] + Na^+$ calcd for: $C_{34}H_{38}F_6N_2O_6Na$: 707.2526, found m/z: 707.2529; LRMS (ESI): m/z $[M + Na]^+$ calcd for: $C_{34}H_{38}F_6N_2O_6Na$: 707.25, found m/z: 707.25, retention time (diode array 290 nm) = 6.51 mins.



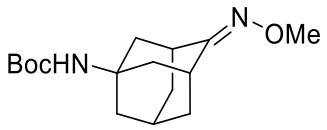
Prepared according to general procedure F using 5 mL DCM, TRX PNP **5f** (18.0 mg, 0.04mmol, 1.0 equiv), triethylamine (13.0 mg, 0.13 mmol, 3.0 equiv), and morpholine HCl salt (7.7 mg, 0.06 mmol, 1.4 equiv). Chromatography (0−50% EtOAc/hexanes gradient elution) to afforded 8.0 mg (51%) of **7f** as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76-4.87 (m, 1H), 3.61-3.70 (m, 4H), 3.42-3.51 (m, 4H), 2.15-2.30 (m, 3H), 1.65-2.00 (m, 7H), 1.24-1.58 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 116.3 (two peaks), 108.5 (two peaks), 71.4, 71.3, 66.6 (br), 45.0 (two peaks), 41.6, 40.1, 39.3, 37.6 (two peaks), 35.3 (two peaks), 34.0, 33.0, 30.6, 27.7 (two peaks), 21.6, 19.7, 19.4 several minor diastereomer peaks overlapping or not observed; HRMS(ESI) calculated for $C_{18}H_{27}O_6NNa$ $[M + Na]^+$ *m/z* 376.1731, found 376.1733



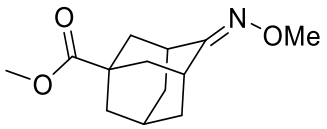
Prepared according to general procedure F using 5 mL DCM, TRX PNP **5g** (12.0 mg, 0.03 mmol, 1.0 equiv), triethylamine (8.7 mg, 0.09 mmol, 3.0 equiv), and morpholine HCl salt (4.9 mg, 0.04 mmol, 1.4 equiv). Chromatography (0−50% EtOAc/hexanes gradient elution) to afforded 6.0 mg (60%) of **7g** as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76-5.03 (m, 1H), 3.61-3.73 (m, 4H), 3.44-3.51 (m, 4H), 2.09-2.35 (m, 1H), 1.40-1.97 (m, 19H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 111.4, 108.5 (two peaks), 71.5, 71.3, 66.6 (two peaks), 40.2, 39.4, 38.3, 38.0, 34.3, 33.4, 32.8 (two peaks), 30.6 (two peaks), 25.9, 24.5, 24.1, 21.0 (three peaks), 19.7, 19.4 several minor diastereomer peaks overlapping or not observed; HRMS(ESI) calculated for $C_{19}H_{29}O_6NNa$ $[M + Na]^+$ *m/z* 390.1889, found 390.1887



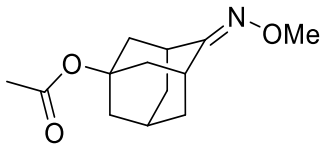
Prepared according to general procedure F using 5 mL DCM, TRX PNP **5h** (25.0 mg, 0.06 mmol, 1.0 equiv), triethylamine (18.0 mg, 0.17 mmol, 3.0 equiv), and morpholine HCl salt (10 mg, 0.08 mmol, 1.4 equiv). Chromatography (0−50% EtOAc/hexanes gradient elution) to afforded 16.0 mg (73%) of **7h** as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78-4.97 (m, 1H), 3.61-3.70 (m, 4H), 3.42-3.51 (m, 4H), 2.20-2.28 (m, 1H), 1.46-2.05 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 111.7, 108.5, 71.4, 66.6 (br), 39.8, 36.2 (two peaks), 34.2, 30.6, 29.7, 29.4, 29.2, 24.7, 20.9, 20.4, 19.4 several minor diastereomer peaks overlapping or not observed; HRMS(ESI) calculated for $C_{20}H_{31}O_6NNa$ $[M + Na]^+$ *m/z* 404.2044, found 404.2049



Prepared according to general procedure G using 35 mL MeOH, tert-butyl ((1S,3R,5S,7S,Z)-4-(methoxyimino)adamantan-1-yl)carbamate (4.61 g, 17.4 mmol, 1.0 equiv), pyridine (2.76 g, 34.8 mmol, 2.0 equiv), and O-methylhydroxylamine hydrochloride (2.23 g, 26.7 mmol, 1.5 equiv). Crude oxime **1b** (5.0 g, 98%) was obtained as solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.43 (br s, 1H), 3.79 (s, 3H), 3.55 (br s, 1H), 2.63 (br s, 1H), 2.14 - 2.21 (m, 1H), 2.00 - 2.14 (m, 5H), 1.92 - 2.00 (m, 2H), 1.83 - 1.89 (m, 1H), 1.67 – 1.83 (m, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 61.0, 50.1, 42.4, 41.1, 37.9, 36.6, 36.4, 29.7, 29.0, 28.4; LRMS(ESI) calculated for $C_{16}H_{27}N_2O_3$ $[M + H]^+$ *m/z* 295.20, found 295.29

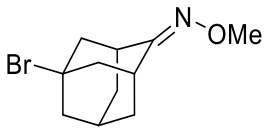


Prepared according to general procedure G using 30 mL MeOH, benzyl 3-oxopyrrolidine-1-carboxylate (1.0 g, 4.4 mmol, 1.0 equiv), pyridine (0.52 g, 6.6 mmol, 1.5 equiv), and O-methylhydroxylamine hydrochloride (0.55 g, 6.6 mmol, 1.5 equiv). Crude oxime **1c** (0.84 g, 82%) was obtained as solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ3.78 (s, 3H), 3.63 (s, 3H), 3.51 - 3.53 (m, 1H), 2.56 - 2.63 (m), 2.09 - 2.14 (m, 1H), 2.03 - 2.09 (m, 1H), 2.00 - 2.03 (m, 1H), 1.94 - 2.00 (m, 4H), 1.87 - 1.94 (m, 1H), 1.79 - 1.85 (m, 2H), 1.72 - 1.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 164.4, 61.0, 51.8, 40.7, 40.0, 38.6, 38.0, 36.5, 35.5, 28.7, 27.6; LRMS(ESI) calculated for $C_{13}H_{20}NO_3$ $[M + H]^+$ *m/z* 238.14, found 237.96

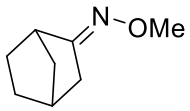


To a 500 mL pressure vessel containing a magnetic stir bar was added 4-oxoadamantan-1-yl acetate (1.18 g, 5.67 mmol, 1.0 equiv) followed by MeOH (17.5 mL), pyridine (917 uL, 11.3 mmol, 2.0 equiv) and methoxylamine hydrochloride (729 mg, 8.73 mmol, 1.5 equiv). The vessel was sealed with a teflon screw cap and heated to 90 °C behind a blast shield for 1.5 h. The mixture was then cooled to rt and the cap carefully unscrewed to allow for slow venting. The reaction mixture was transferred to an rb flask and concentrated under reduced pressure to a crude semi-solid. The crude residue was diluted with 10% aq. $KHSO_4$ solution (60 mL) and extracted with EtOAc (1 × 200 mL). The organic phase was washed with additional 10% aq. $KHSO_4$ solution (3 × 60 mL) and the aqueous layers back-extracted with EtOAc (1 × 150 mL). The combined organic phases were washed with brine (1 × 150 mL), dried ($MgSO_4$), filtered and concentrated to a colorless oil which solidified under high vacuum to give the desired oxime **1d** (1.34 g,

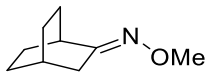
5.65 mmol, 99%), which was sufficiently pure to be carried onto the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 3.60 - 3.69 (m, 1H), 3.19 - 3.20 (m, 1H), 2.54 - 2.81 (m, 1H), 2.22 - 2.35 (m, 6H), 1.97 - 2.19 (m, 5H), 1.98 (s, 3H major diastereomer), 1.97 (s, 3H minor diasteromer), 1.88 - 1.94 (m, 1H), 1.53 - 1.87 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 163.6, 79.4, 78.7, 77.2, 61.1, 41.7, 40.3 (2 peaks), 37.8, 37.5, 37.3, 36.4, 35.0, 32.7, 30.5, 30.3, 29.5, 22.6, 22.5; LRMS (ESI): m/z [M] + H^+ calcd for: $C_{13}H_{20}NO_3$: 238.14 found m/z: 238.20.



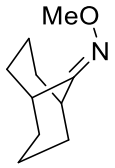
Prepared according to general procedure G using 30 mL MeOH, benzyl 3-oxopyrrolidine-1-carboxylate (1.0 g, 4.4 mmol, 1.0 equiv), pyridine (0.52 g, 6.6 mmol, 1.5 equiv), and O-methylhydroxylamine hydrochloride (0.55 g, 6.6 mmol, 1.5 equiv). Crude oxime **1e** (0.84 g, 82%) was obtained as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 2.66 (br, 1H), 2.38-2.55 (m, 4H), 2.12-2.31 (m, 3H), 1.76-2.00 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 64.3, 62.2, 61.1, 49.5, 49.0, 48.1, 45.0, 39.3, 37.1, 36.8, 35.7, 32.4, 31.8, 31.3; LRMS(ESI) calculated for $C_{11}H_{17}BrON$ $[M + H]^+$ *m/z* 258.05, found 257.99



Prepared according to general procedure G using 300 mL MeOH, bicyclo[2.2.1]heptan-2-one(10.0 g, 90.8 mmol, 1.0 equiv), pyridine (10.8 g, 136.2 mmol, 1.5 equiv), and O-methylhydroxylamine hydrochloride (11.4 g, 136.2 mmol, 1.5 equiv). Crude oxime **1f** (9.8 g, 78%) was obtained as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (S, 3H), 2.79-2.84 (m, 1H), 2.43-2.49 (m, 1H), 2.16-2.25 (m, 1H), 1.96-2.05 (m, 1H), 1.57-1.76 (m, 2H), 1.23-1.51 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 61.2, 61.0, 42.3, 38.9, 38.3, 37.3, 35.2, 35.3, 35.1, 27.6, 27.3, 27.1, 26.1; LRMS(ESI) calculated for $C_8H_{14}ON$ $[M + H]^+$ *m/z* 140.11, found 140.13

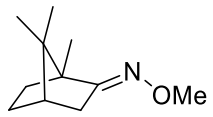


Prepared according to general procedure G using 30 mL MeOH, bicyclo[2.2.2]octan-2-one (1.0 g, 8.1 mmol, 1.0 equiv), pyridine (0.96 g, 12.1 mmol, 1.5 equiv), and O-methylhydroxylamine hydrochloride (1.0 g, 12.1 mmol, 1.5 equiv). Crude oxime **1g** (0.84 g, 68%) was obtained as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 2.28-2.38 (m, 3H), 1.90-1.95 (m, 1H), 1.44-1.75 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 61.0, 31.8, 31.6, 25.4, 25.1, 24.9; LRMS(ESI) calculated for $C_9H_{16}ON$ $[M + H]^+$ *m/z* 154.12, found 154.13

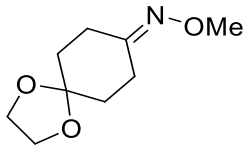


Prepared according to general procedure G using 60 mL MeOH, bicyclo[3.3.1]nonan-9-one (2.0 g, 14.5 mmol, 1.0 equiv), pyridine (1.72 g, 21.7 mmol, 1.5 equiv), and O-methylhydroxylamine hydrochloride (1.81 g, 21.7 mmol, 1.5 equiv). Crude oxime **1h** (2.1 g, 87%) was obtained as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76-3.84 (m, 3H), 3.38 (br, 1H), 2.45 (br, 1H), 1.74-2.07 (m, 10H), 1.44-1.58 (m, 2H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 167.1, 60.8, 36.0, 33.4, 32.0, 29.3, 21.2; LRMS(ESI) calculated for $C_{13}H_{18}ON$ $[M + H]^+$ *m/z* 168.14, found 168.21

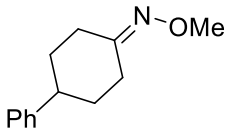


Prepared according to general procedure G using 100 mL MeOH, camphor (5.0 g, 32.8 mmol, 1.0 equiv), pyridine (4.11 g, 49.3mmol, 1.5 equiv), and O-methylhydroxylamine hydrochloride (3.9 g, 49.3 mmol, 1.5 equiv). Crude oxime **1i** (5.14 g, 86%) was obtained as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 2.47 (dt, 1H, *J* = 4.1, 17.8 Hz), 1.97 (d, 1H, *J* = 17.8 Hz), 1.78-1.88 (m, 2H), 1.70 (td, 1H, *J* = 4.1, 12.4 Hz), 1.44 (ddd, 1H, *J* = 4.4, 9.3, 13.4 Hz), 1.21 (ddd, 1H, *J* = 3.9, 9.0, 13.2 Hz), 1.01 (s, 3H), 0.90 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 61.2, 51.6, 48.1, 43.7, 33.6, 32.9, 27.3, 19.4, 18.5, 11.2; LRMS(ESI) calculated for $C_{13}H_{18}ON$ $[M + H]^+$ *m/z* 186.15, found 186.16

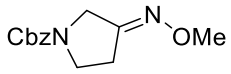


Prepared according to general procedure G using 30 mL MeOH, 1,4-dioxaspiro[4.5]decan-8-one (1.0 g, 6.4 mmol, 1.0 equiv), pyridine (0.76 g, 9.6 mmol, 1.5 equiv), and O-methylhydroxylamine hydrochloride (0.8 g, 9.6 mmol, 1.5 equiv). Crude oxime **1j** (1.0 g, 84%) was obtained as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79-3.99 (m, 4H), 3.20 (s, 3H, minor E/Z isomer), 3.17 (s, 3H, major E/Z isomer), 2.23-2.64 (m, 2H), 1.61-1.90 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 108.5, 108.0, 99.2, 64.4, 64.2, 61.0 (two peaks), 47.8, 34.4, 34.2, 31.2, 29.7, 28.9, 28.7, 21.7; LRMS(ESI) calculated for $C_9H_{16}O_3N$ $[M + H]^+$ *m/z* 186.11, found 186.21

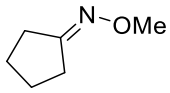
To a pressure vessel containing a magnetic stir bar was added 2-bromocyclohexan-1-one (0.5 g, 2.8 mmol, 1.0 equiv) followed by 20 mL MeOH, pyridine (0.34 g, 4.3 mmol, 1.5 equiv) and methoxylamine hydrochloride (0.35 g, 4.3 mmol, 1.5 equiv). The reaction vessel was then sealed with a teflon screw cap and stirred for 16 h at room temperature. The reaction mixture was then transferred to a flask and concentrated under reduced pressure to a crude oil. The crude residue was diluted with 10% aq. $KHSO_4$ solution (115 mL) and extracted with EtOAc (1 × 200 mL). The organic phase was washed with additional 10% aq. $KHSO_4$ solution (3 × 60 mL) and the aqueous layers back-extracted with EtOAc (1 × 150 mL). The combined organic phases were washed with brine (1 × 150 mL), dried ($MgSO_4$), filtered and concentrated to a colorless oil, which solidified under high vacuum to give oxime **1k** (0.50g, 85%), which was sufficiently pure to be carried onto the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (br, 1H, minor E/Z isomer), 4.91 (br, 1H, major E/Z isomer), 3.88 (s, 3H, minor E/Z isomer), 3.85 (s, 3H, major E/Z isomer), 3.10 (d, 1H, *J* = 14.9 Hz major E/Z isomer), 2.66 (td, 1H, *J* = 4.6, 14.1 Hz minor E/Z isomer), 1.60-2.35 (m, 5H), 1.29-1.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 156.3, 61.6, 51.8, 39.2, 35.9, 34.2, 27.4, 26.0, 24.9, 20.6 (three peaks); LRMS(ESI) calculated for $C_7H_{13}ON$ $[M + H]^+$ *m/z* 206.02, found 206.01



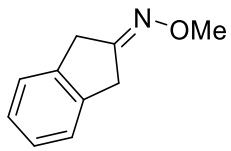
Prepared according to general procedure G using 60 mL MeOH, 4-phenylcyclohexan-1-one (2.0 g, 11.5 mmol, 1.0 equiv), pyridine (1.36 g, 17.2 mmol, 1.5 equiv), and O-methylhydroxylamine hydrochloride (1.44 g, 17.2 mmol, 1.5 equiv). Crude oxime **1l** (1.7 g, 73%) was obtained as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.34 (m, 2H), 7.20-7.25 (m, 3H), 3.88 (s, 3H), 3.40 (ddt, 1H, *J* = 2.2, 4.4, 14.4 Hz), 2.78 (tt, 1H, *J* = 3.4, 15.6 Hz), 2.55 (ddt, 1H, *J* = 2.4, 4.4, 14.1 Hz), 2.26 (td, 1H, *J* = 4.9, 13.9 Hz), 2.01-2.14 (m, 2H), 1.89 (td, 1H, *J* = 4.9, 13.9 Hz), 1.59-1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 145.7, 128.4, 126.4, 126.2, 61.0, 43.6, 34.0, 32.9, 31.9, 24.8; LRMS(ESI) calculated for $C_{13}H_{18}ON$ $[M + H]^+$ *m/z* 204.14, found 204.21



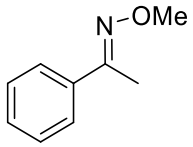
Prepared according to general procedure G using 30 mL MeOH, benzyl 3-oxopyrrolidine-1-carboxylate (0.9 g, 4.1 mmol, 1.0 equiv), pyridine (0.48 g, 6.1mmol, 1.5 equiv), and O-methylhydroxylamine hydrochloride (0.51 g, 6.1 mmol, 1.5 equiv). Crude oxime **1m** (0.84 g, 82%) was obtained as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.40 (m, 5H), 5.16 (d, 2H, *J* = 2.4 Hz), 4.13 (br, 2H), 3.88 (s, 3H, minor E/Z isomer), 3.87 (s, 3H, major E/Z isomer), 3.67 (br, 1H), 2.68-2.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 157.9, 154.6, 154.5, 136.4, 128.3, 130.0 (multiple peaks), 67.0, 61.8 (two peaks), [47.7,47.4, 46.0, 45.6(E/Z isomers & and conformers)], [44.5, 44.2, 44.0, 43.8(E/Z isomers & and conformers)], [28.7, 28.0, 26.1, 25.3 (E/Z isomers & and conformers)] ; LRMS(ESI) calculated for $C_{13}H_{17}O_3N_2$ $[M + H]^+$ *m/z* 249.12, found 249.15



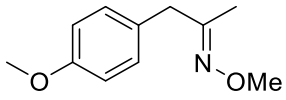
To a pressure vessel containing a magnetic stir bar was added cyclopentanone (2.0 g, 23.8 mmol, 1.0 equiv) followed by 60 mL MeOH, pyridine (2.8 g, 35.7 mmol, 1.5 equiv) and methoxylamine hydrochloride (2.8 g, 35.7 mmol, 1.5 equiv). The reaction vessel was then sealed with a teflon screw cap and stirred for 16 h. The reaction mixture was then transferred to a flask and concentrated under reduced pressure to a crude oil. The crude residue was diluted with 10% aq. $KHSO_4$ solution (115 mL) and extracted with EtOAc (1 × 200 mL). The organic phase was washed with additional 10% aq. $KHSO_4$ solution (3 × 60 mL) and the aqueous layers back-extracted with EtOAc (1 × 150 mL). The combined organic phases were washed with brine (1 × 150 mL), dried ($MgSO_4$), filtered and concentrated to a colorless oil, which solidified under high vacuum to give oxime **1n** (0.45g, 17%), which was sufficiently pure to be carried onto the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 2.29-2.46 (m, 4H), 1.68-1.78 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 61.3, 31.0, 27.5, 25.1, 24.7; LRMS(ESI) calculated for $C_6H_{12}ON$ $[M + H]^+$ *m/z* 204.14, found 204.21



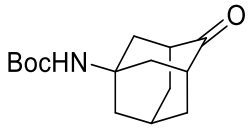
Prepared according to general procedure G using 30 mL MeOH, 1,3-dihydro-2H-inden-2-one (1.0 g, 7.6 mmol, 1.0 equiv), pyridine (0.90 g, 11.3 mmol, 1.5 equiv), and O-methylhydroxylamine hydrochloride (0.95 g, 11.3 mmol, 1.5 equiv). Crude oxime **1o** (1.11 g, 91%) was obtained as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.35 (m, 4H), 3.96 (s, 3H), 3.79-3.84 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 139.1, 139.0, 127.1, 127.0, 125.1, 124.7, 61.7, 36.5, 34.5; LRMS(ESI) calculated for $C_{10}H_{12}ON$ $[M + H]^+$ *m/z* 162.09, found 162.07



Prepared according to general procedure G using 30 mL MeOH, acetophenone (1.0 g, 8.3 mmol, 1.0 equiv), pyridine (0.99 g, 12.5 mmol, 1.5 equiv), and O-methylhydroxylamine hydrochloride (1.0 g, 12.5 mmol, 1.5 equiv). Crude oxime **1p** (1.14 g, 92%) was obtained as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.70 (m, 2H), 7.35-7.41 (m, 3H), 4.02 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 136.6, 129.0, 128.4, 126.0, 61.9, 12.6; LRMS(ESI) calculated for $C_9H_{12}ON$ $[M + H]^+$ *m/z* 150.09, found 150.08

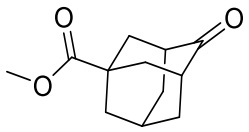


Prepared according to general procedure G using 30 mL MeOH, 4-(4-methoxyphenyl)butan-2-one (1.0 g, 6.1 mmol, 1.0 equiv), pyridine (723.0 mg, 9.1 mmol, 1.5 equiv), and O-methylhydroxylamine hydrochloride (763 mg, 9.1 mmol, 1.5 equiv). Crude oxime **1q** (1.1 g, 94%) was obtained as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09-7.17 (m, 2H), 6.82-6.88 (m, 2H), 3.89 (app d, 3H), 3.80 (s, 3H), 3.62 (s, 2H, minor E/Z isomer), 3.41 (s, 2H, major E/Z isomer), 1.78 (s, 3H, minor E/Z isomer), 1.73 (s, 3H, major E/Z isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 156.8, 130.0, 129.9, 128.9, 114.0, 61.2, 61.1, 55.2, 41.2, 34.4, 19.6, 13.5; LRMS(ESI) calculated for $C_{11}H_{16}O_2N$ $[M + H]^+$ *m/z* 194.12, found 194.11

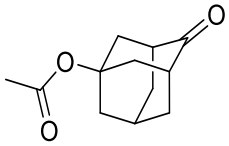


To an oven-dried rb flask equipped with a reflux condenser and magnetic stir bar under an Ar(g) atmosphere was added 4-oxoadamantane-1-carboxylic acid (2.00 g, 10.3 mmol, 1.0 equiv) followed by anhydrous toluene (38 mL) and NEt_3 (1.95 mL, 14.0 mmol, 1.36 equiv). The reaction mixture was cooled to 0 °C and placed behind a blast shield before diphenylphosphoryl azide (2.21 mL, 10.3 mmol, 1.00 equiv) was added dropwise over 5 mins. The reaction mixture was stirred at 0 °C for 5 mins and allowed to warm to rt over 10 mins. The reaction was then gradually heated to 90 °C for 2 h until TLC indicated the reaction was complete. The mixture was then cooled to rt and concentrated under reduced pressure to a viscous pale yellow semi-solid. *tert*-Butanol (42.0 mL, 0.44 mol, 42.6 equiv) was added and the mixture was transferred to a sealed tube with a threaded screw cap and heated to 120 °C behind a blast shield for 16 h. The reaction was then cooled to rt, diluted with 1 M aq. Na_2CO_3 solution (150 mL) and extracted with EtOAc (1 × 150 mL). The aqueous layer was back-extracted with EtOAc (3 × 150 mL) and the combined organic layers washed with brine (1 × 250 mL), dried ($MgSO_4$), filtered and concentrated to a crude residue. Purification via flash column chromatography (0–30% EtOAc–Hexanes) gave the title compound

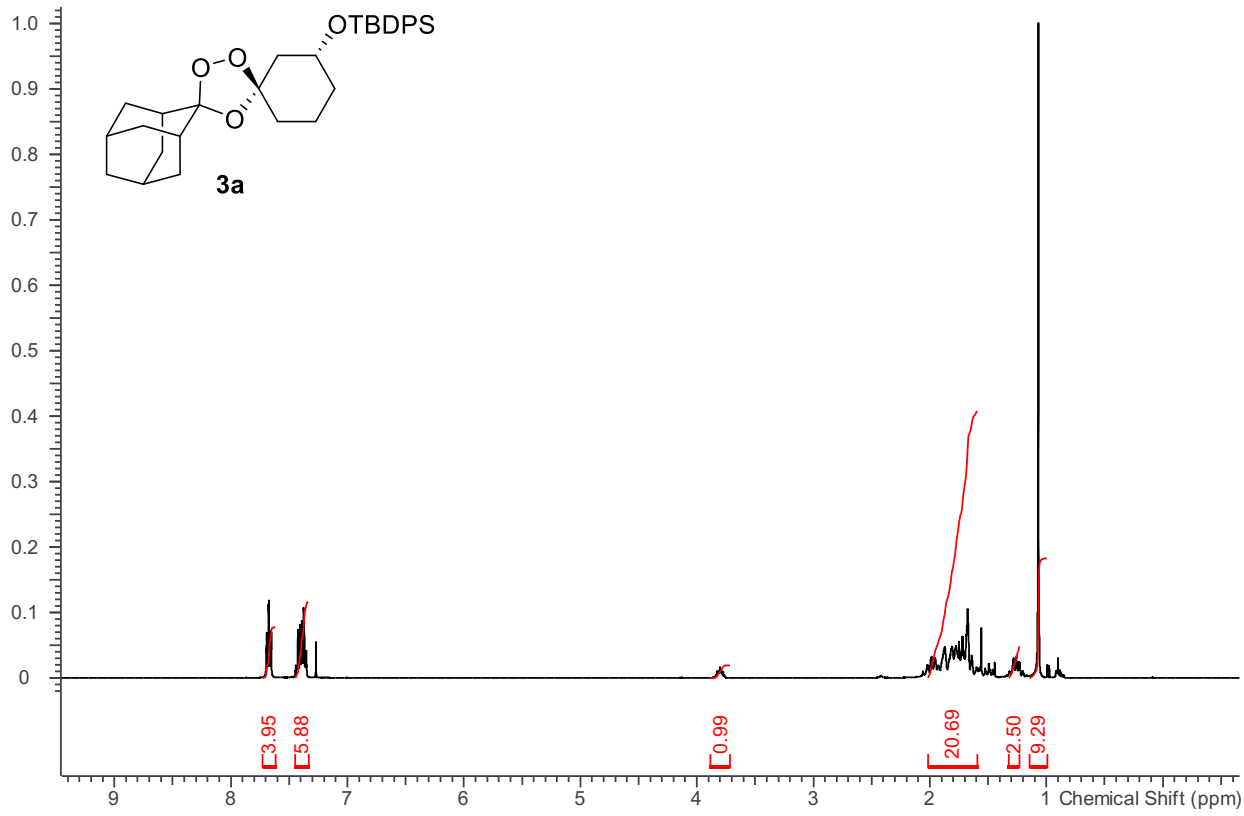
(1.91 g, 7.20 mmol, 70%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52 (br s, 1H), 2.54 (br s, 2H), 2.06 - 2.22 (m, 7H), 1.97 (br d, *J* = 11.7 Hz, 2H), 1.89 (br d, *J* = 12.4 Hz, 2H), 1.34 - 1.53 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.5, 49.5, 46.4, 42.1, 38.2, 28.6, 28.4; LRMS (ESI): m/z [M]-O*t*Bu + H^+ calcd for $C_{11}H_{16}NO_3$: 210.11, found m/z: 210.15.

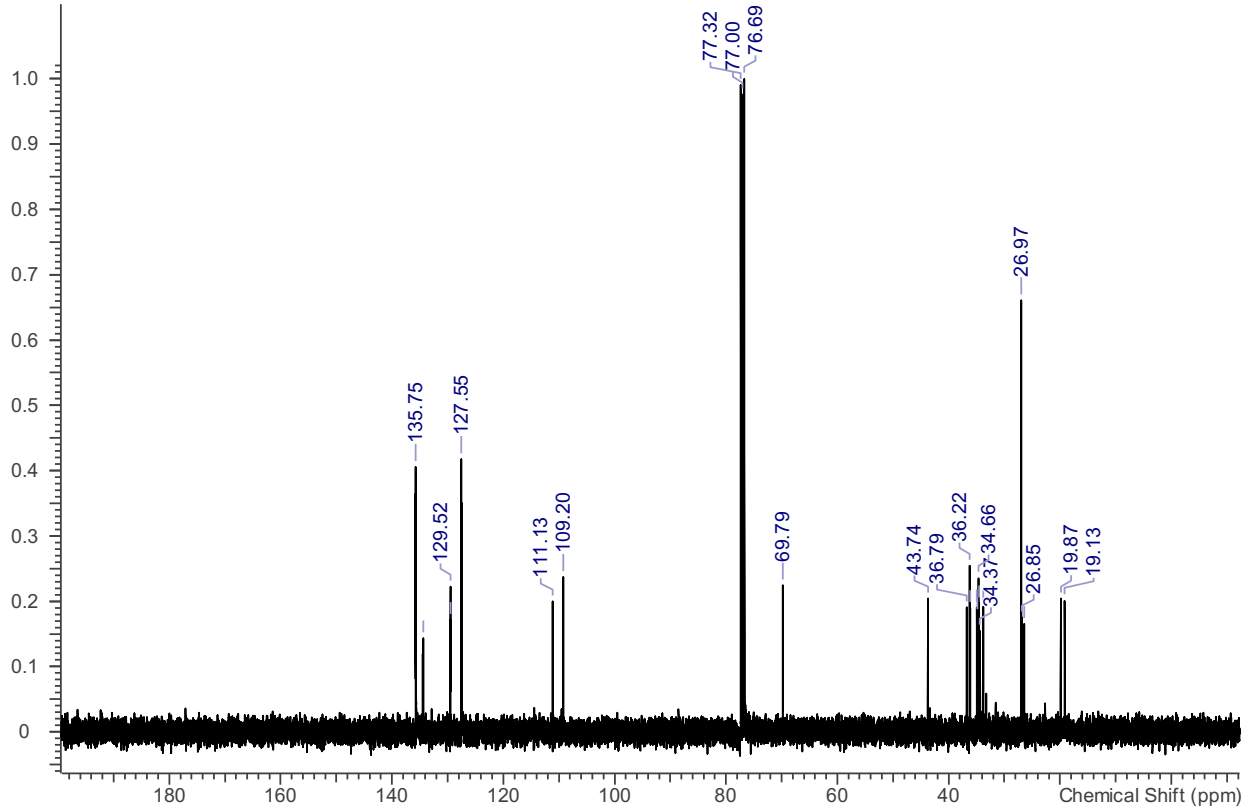


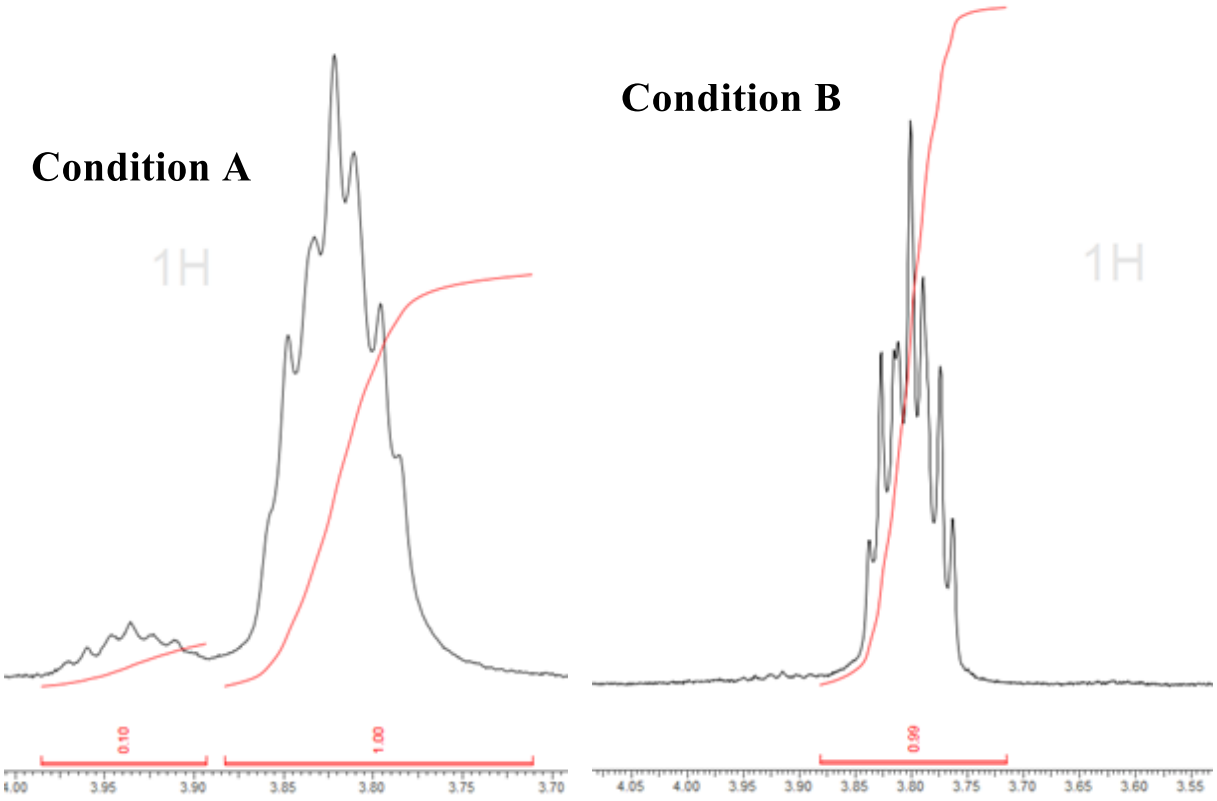
To a rb flask containing a magnetic stir bar under an Ar(g) atmosphere was added 2-adamtanone-5-carboxylic acid (7.50 g, 38.62 mmol, 1.00 equiv), anhydrous DMF (64 mL), K_2CO_3 (8.01 g, 57.92, 1.50 equiv) and iodomethane (3.61 mL, 57.92 mmol, 1.50 equiv). The reaction stirred for 16 h at rt, after which the reaction was judged complete by TLC and was diluted with DI H_2O (100 mL) and extracted with EtOAc (1 x 300 mL). The organic layer was washed with water (6 x 100 mL) and the combined aqueous layers were back-extracted with EtOAc (1 x 200 mL). The combined organic phases were washed with brine (1 x 400 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to a crude brown oil that solidified on cooling to rt. Purification via flash column chromatography (0–50% EtOAc–Hexanes) afforded ester (7.12 g, 34.19 mmol, 89%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 3H), 2.58 (br s, 2H), 2.16 - 2.21 (m, 5H), 2.10 (d, *J* = 2.7 Hz, 2H), 1.95 - 2.06 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.5, 176.2, 52.0, 45.8, 40.3, 40.1, 38.3, 37.8, 27.3; LRMS (ESI): m/z [M] + H^+ calcd for $C_{12}H_{17}O_3$: 209.12, found m/z: 208.96.

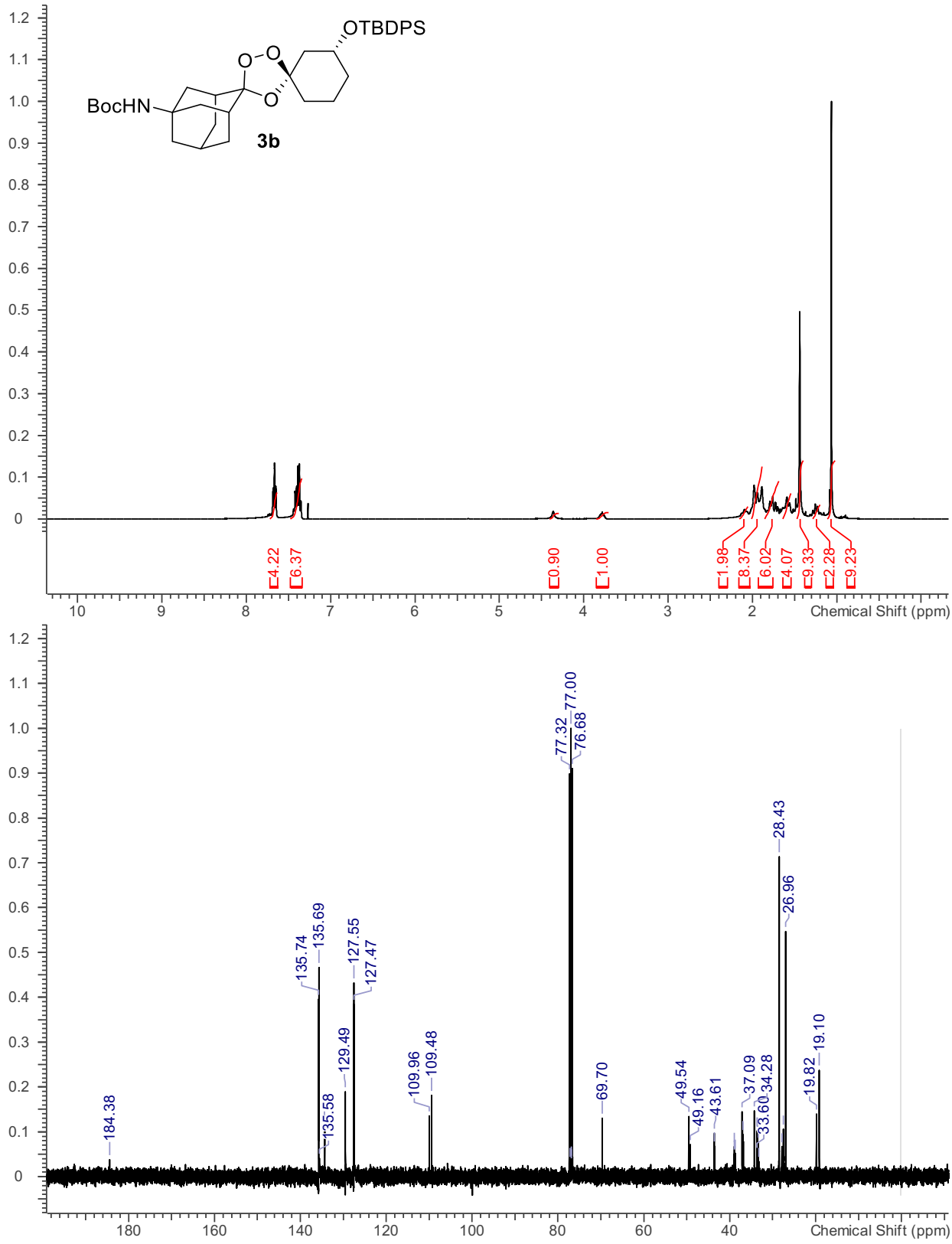


A solution of 5-hydroxy-2-adamantanone (1.00 g, 6.02 mmol, 1.00 equiv) in CH_2Cl_2 (20 mL) was treated with dimethylaminopyridine (0.80 g, 6.55 mmol, 1.09 equiv) and acetic anhydride (0.80 mL, 0.82 mmol, 1.47 equiv) and the reaction stirred overnight at 50 °C. The solvent was removed under reduced pressure and the residue partitioned between DI water (150 mL) and EtOAc (150 mL). The aqueous layer was extracted with EtOAc (2 × 100 mL) and the combined organic layers were washed with satd. aq. $NaCl_2$ solution (1 × 200 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to a crude residue. Purification via flash column chromatography (0–20% EtOAc–Hexanes) afforded the title compound (1.20 g, 5.76 mmol, 96%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.65 (br s, 2H), 2.30 - 2.53 (m, 7H), 1.92 - 2.06 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.6, 170.2, 77.6, 47.0, 41.3, 39.8, 38.2, 29.8, 22.4; LRMS (ESI): m/z [M] + H^+ calcd for $C_{12}H_{17}O_3$: 209.12, found m/z: 209.16.

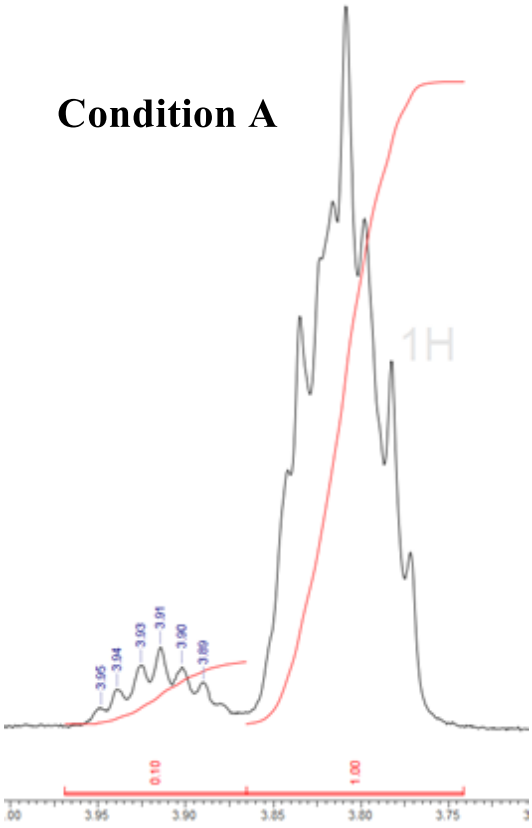

OTBDPS
O
O
O
3a
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
3.95
5.88
0.99
20.69
2.50
9.29
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)


77.32
77.00
76.69
135.75
127.55
129.52
111.13
109.20
69.79
43.74
36.79
36.22
34.37
34.66
26.97
26.85
19.87
19.13
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
180
160
140
120
100
80
60
40
Chemical Shift (ppm)

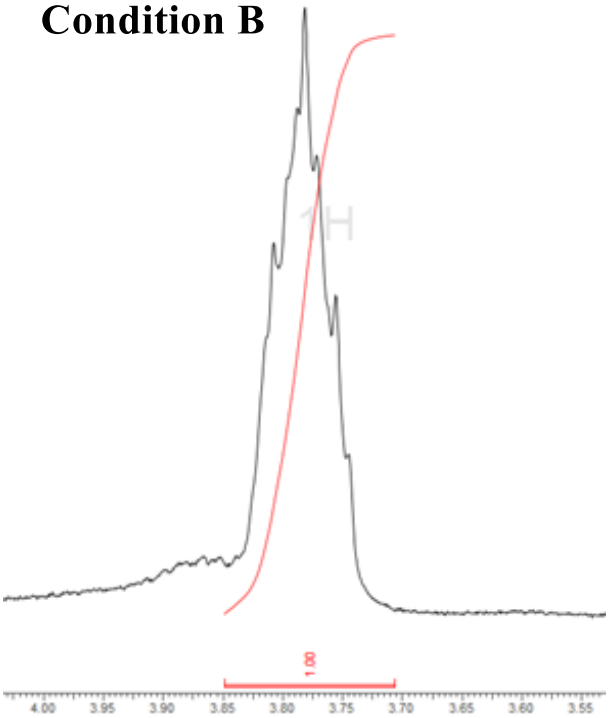

Condition A
1H
0.10
1.00
4.00
3.95
3.90
3.85
3.80
3.75
3.70
Condition B
1H
0.99
4.05
4.00
3.95
3.90
3.85
3.80
3.75
3.70
3.65
3.60
3.55

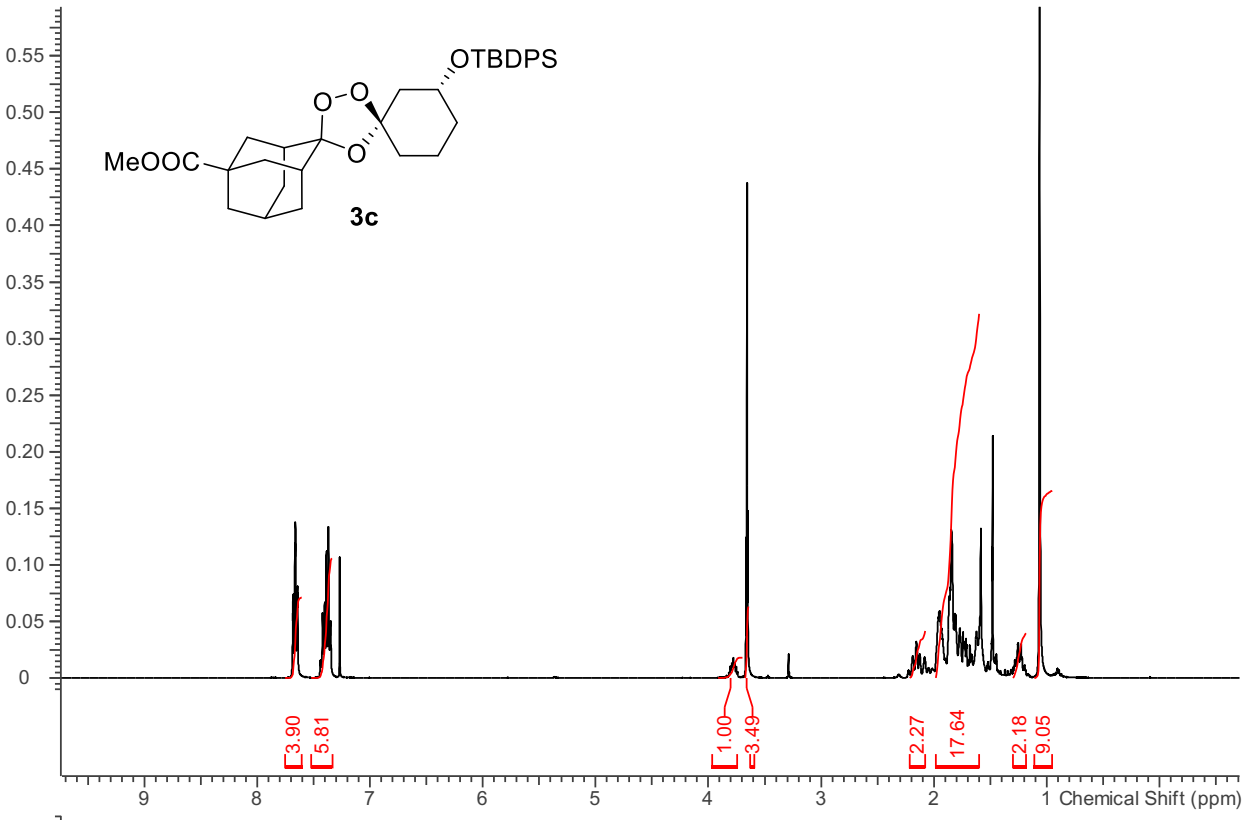

OTBDPS
BocHN
O
O
O
3b
4.22
6.37
0.90
1.00
1.98
8.37
6.02
4.07
9.33
2.28
9.23
Chemical Shift (ppm)
184.38
135.74
135.69
135.58
129.49
127.55
127.47
109.96
109.48
77.32
77.00
76.68
69.70
49.54
49.16
43.61
37.09
34.28
33.60
28.43
26.96
19.82
19.10
Chemical Shift (ppm)

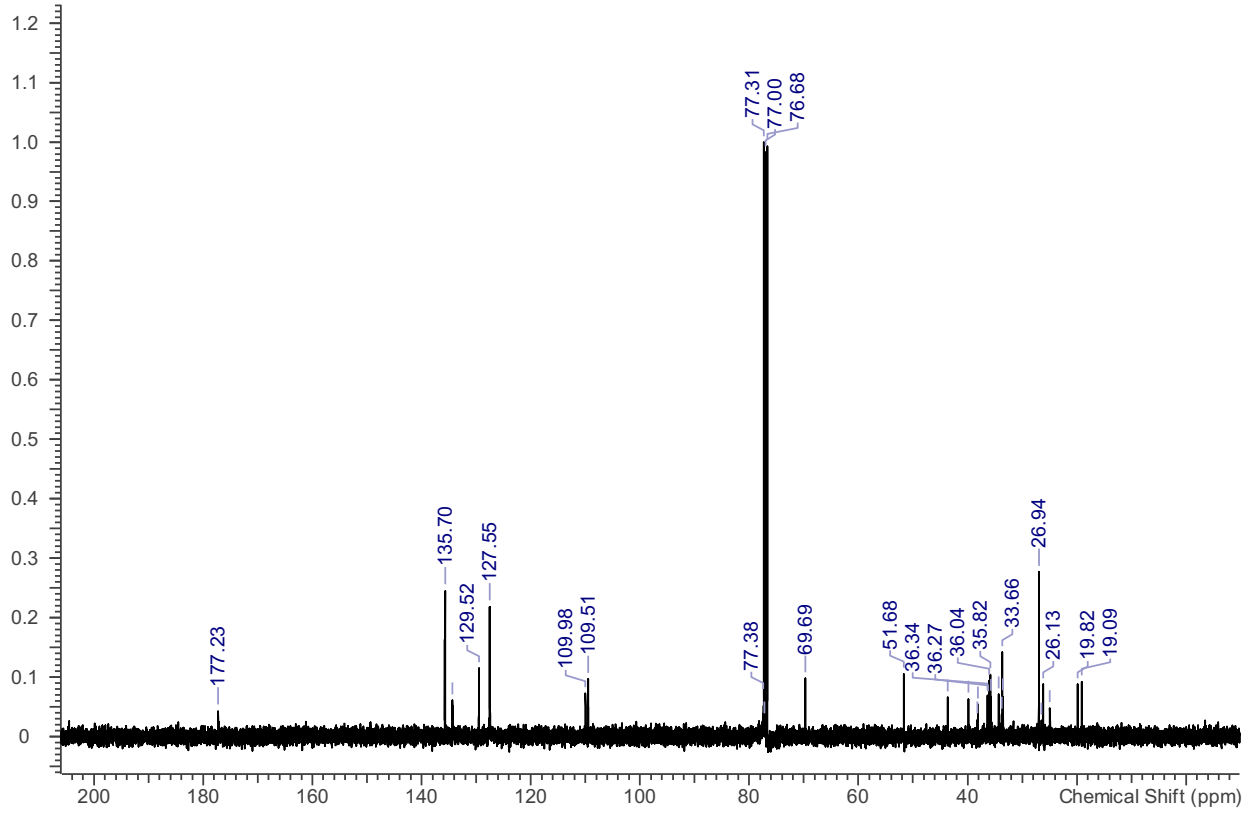
Condition A



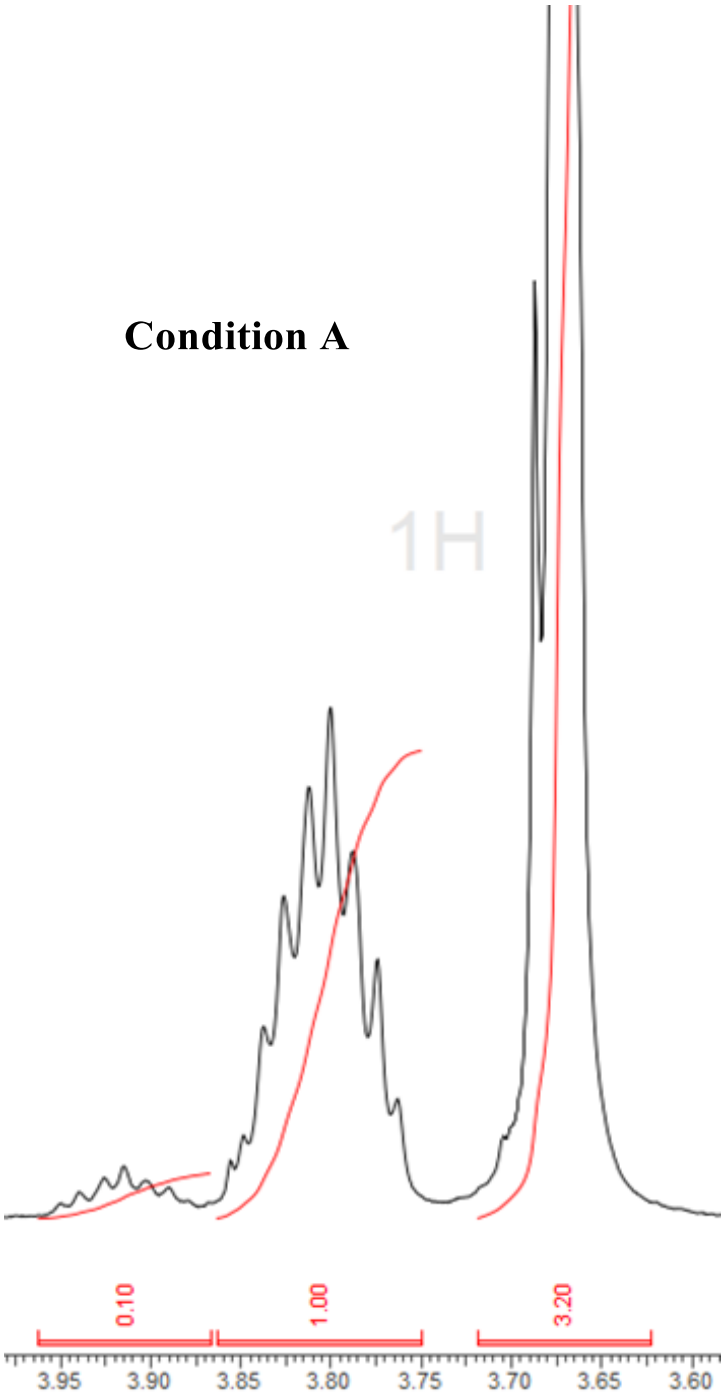
Condition B



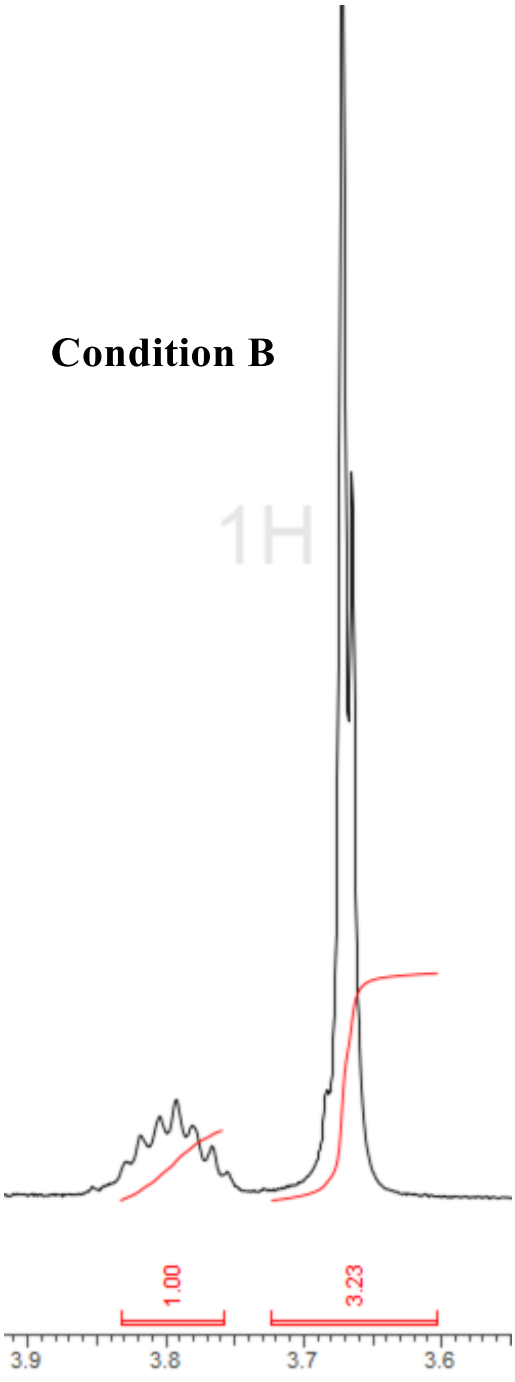

OTBDPS
MeOOC
3c
3.90
5.81
1.00
3.49
2.27
17.64
2.18
9.05
Chemical Shift (ppm)

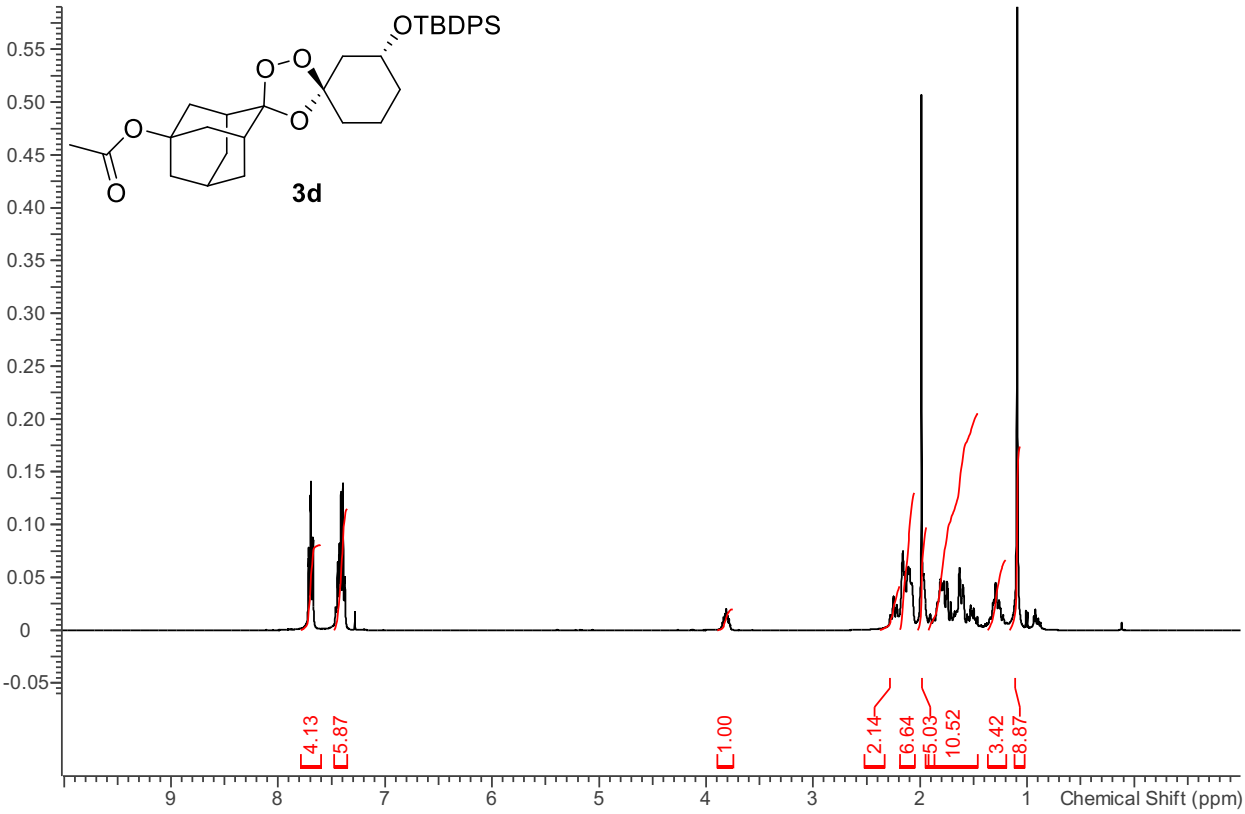

77.31
77.00
76.68
177.23
135.70
129.52
127.55
109.98
109.51
77.38
69.69
51.68
36.34
36.27
36.04
35.82
33.66
26.94
26.13
19.82
19.09
Chemical Shift (ppm)

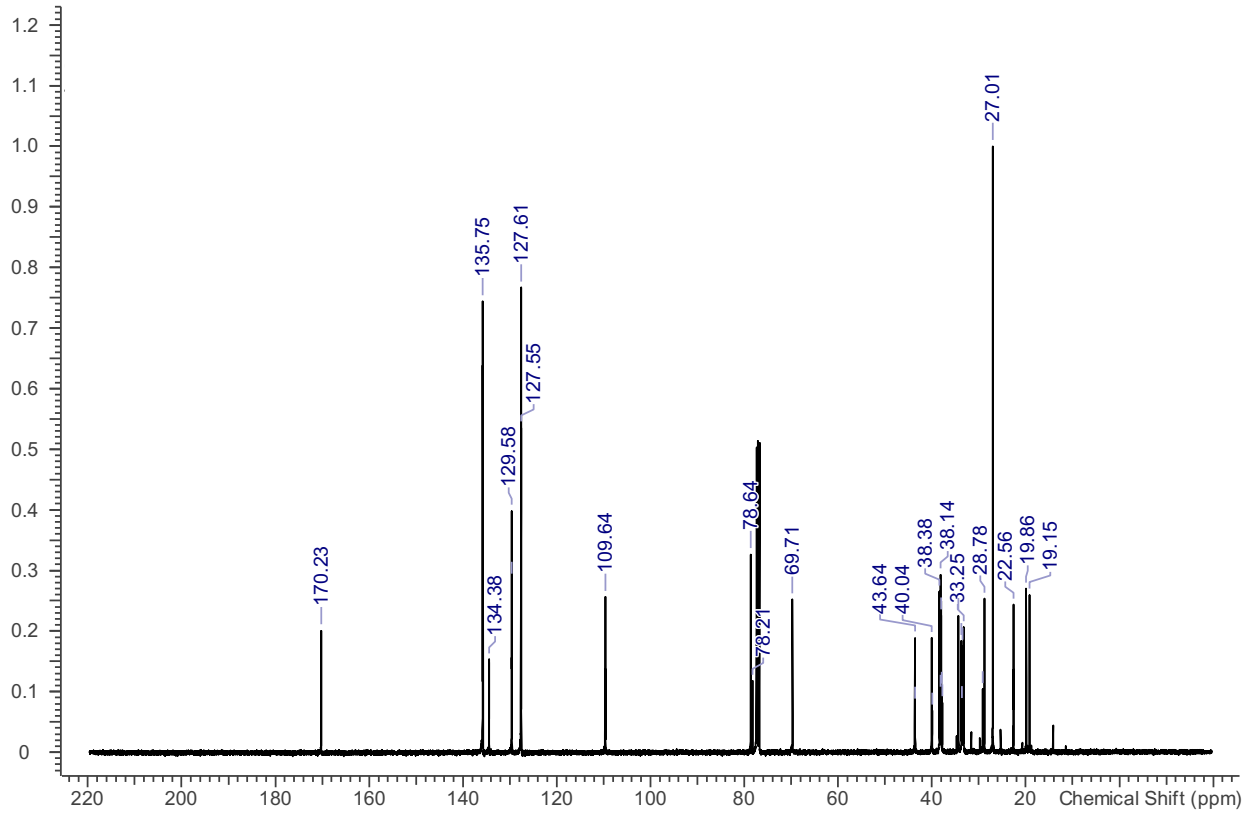
Condition A

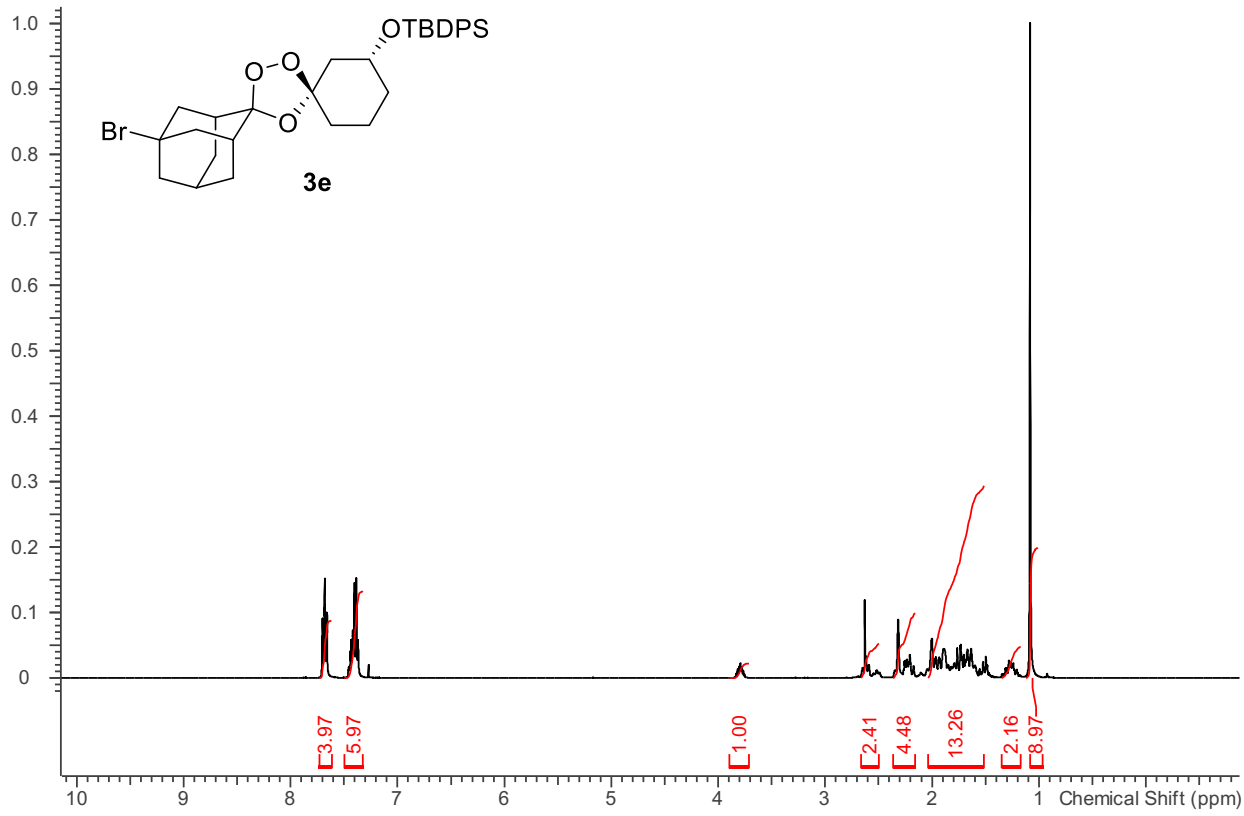


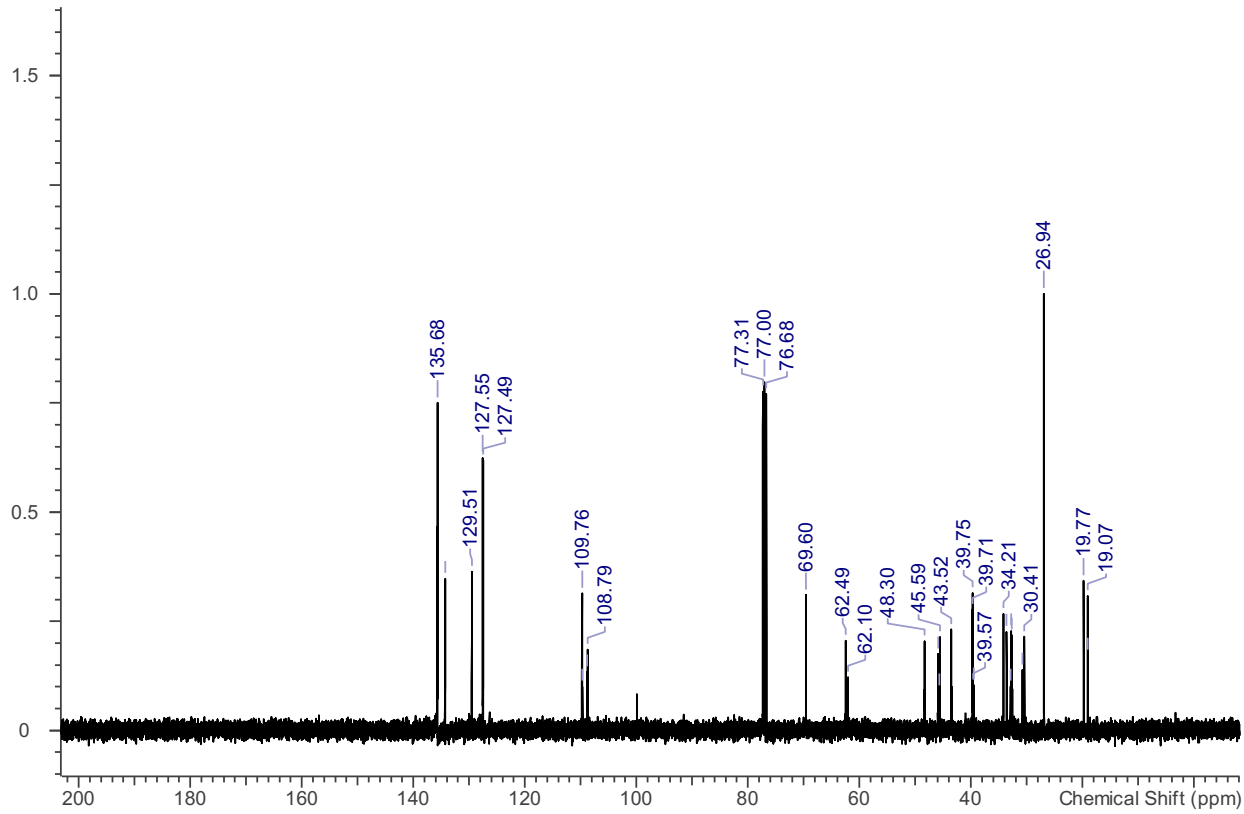
Condition B

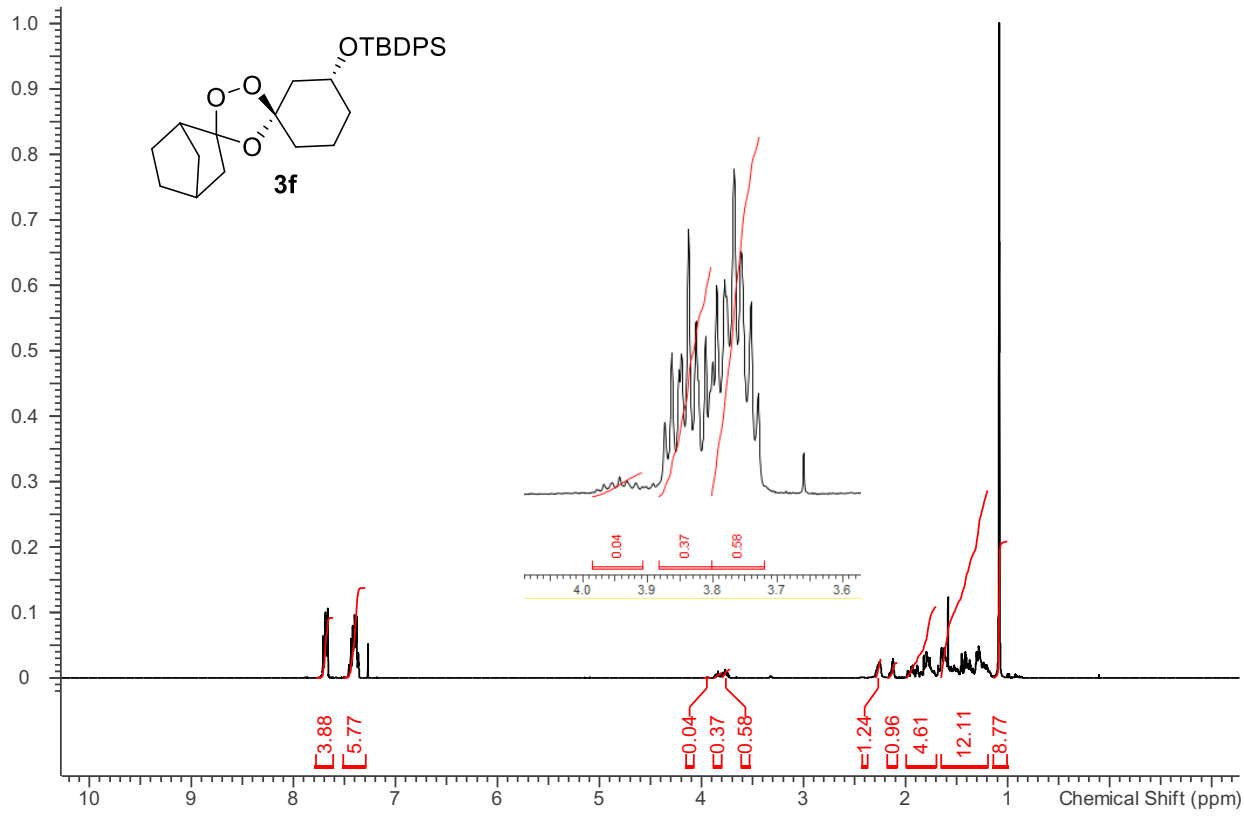


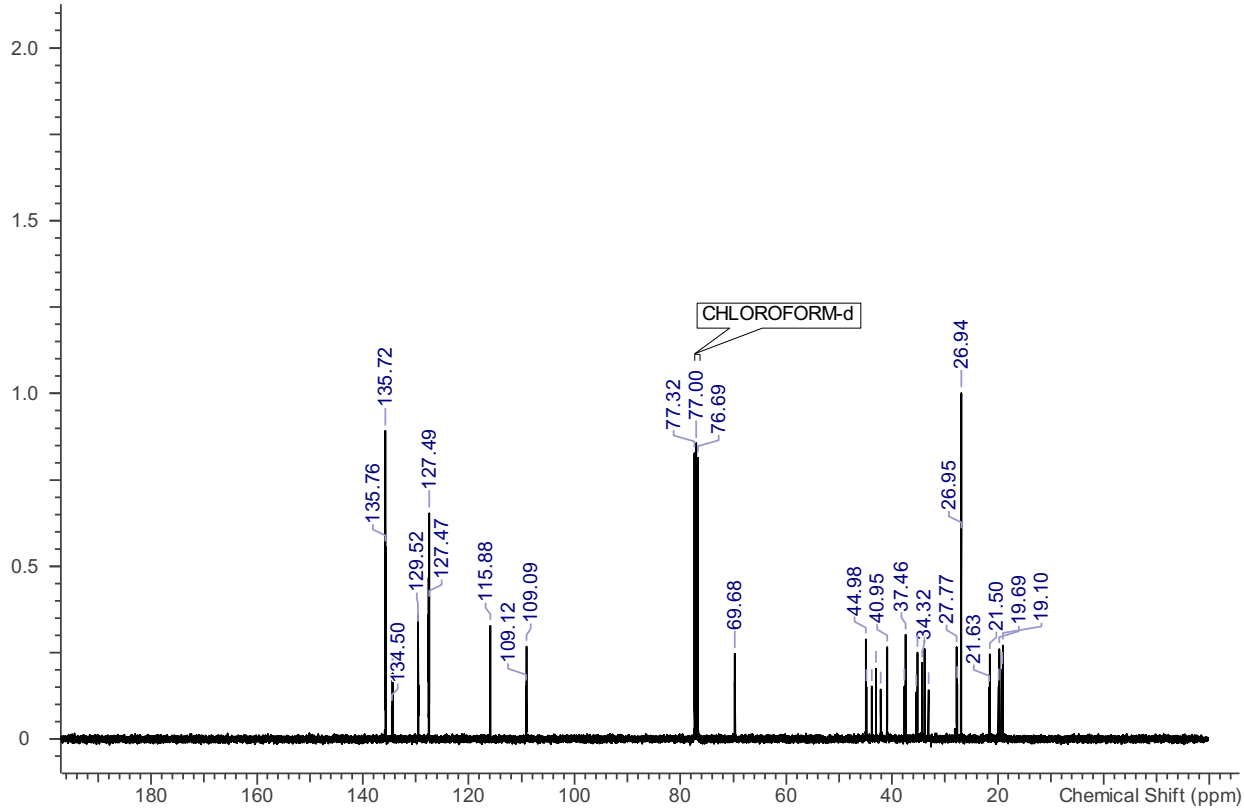

OTBDPS
O
O
O
O
O
3d
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
-0.05
4.13
5.87
1.00
2.14
6.64
5.03
10.52
3.42
8.87
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

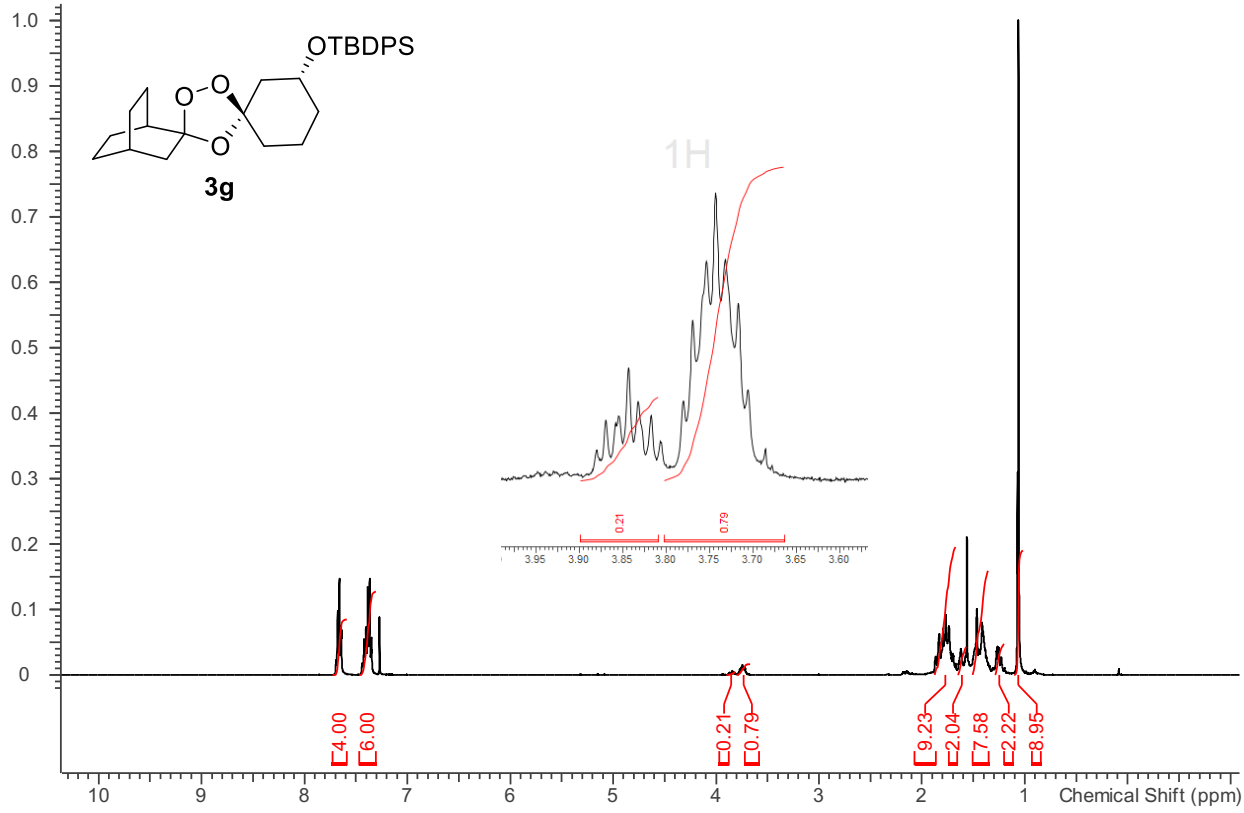

1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
170.23
135.75
134.38
127.61
129.58
127.55
109.64
78.64
78.21
69.71
43.64
40.04
38.38
38.14
33.25
28.78
27.01
22.56
19.86
19.15
220
200
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)

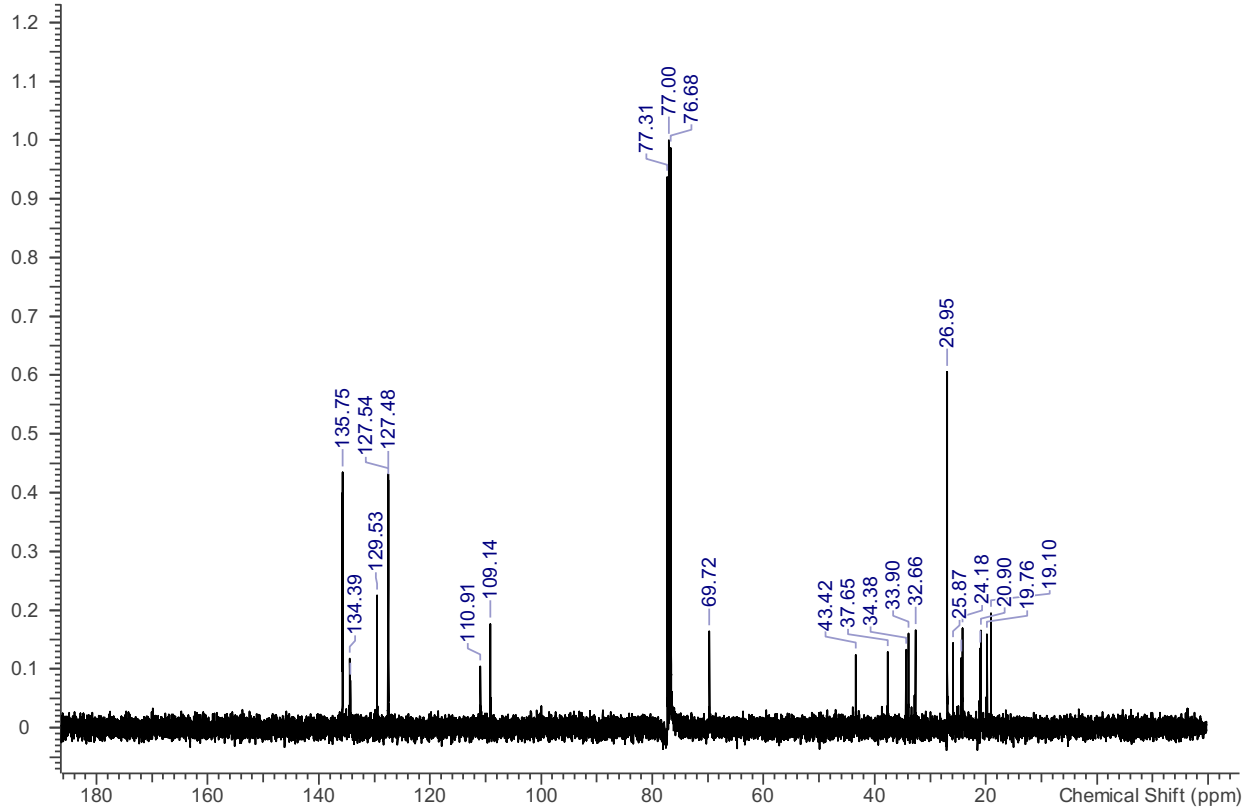

OTBDPS
Br
O
O
O
3e
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
3.97
5.97
1.00
2.41
4.48
13.26
2.16
8.97
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

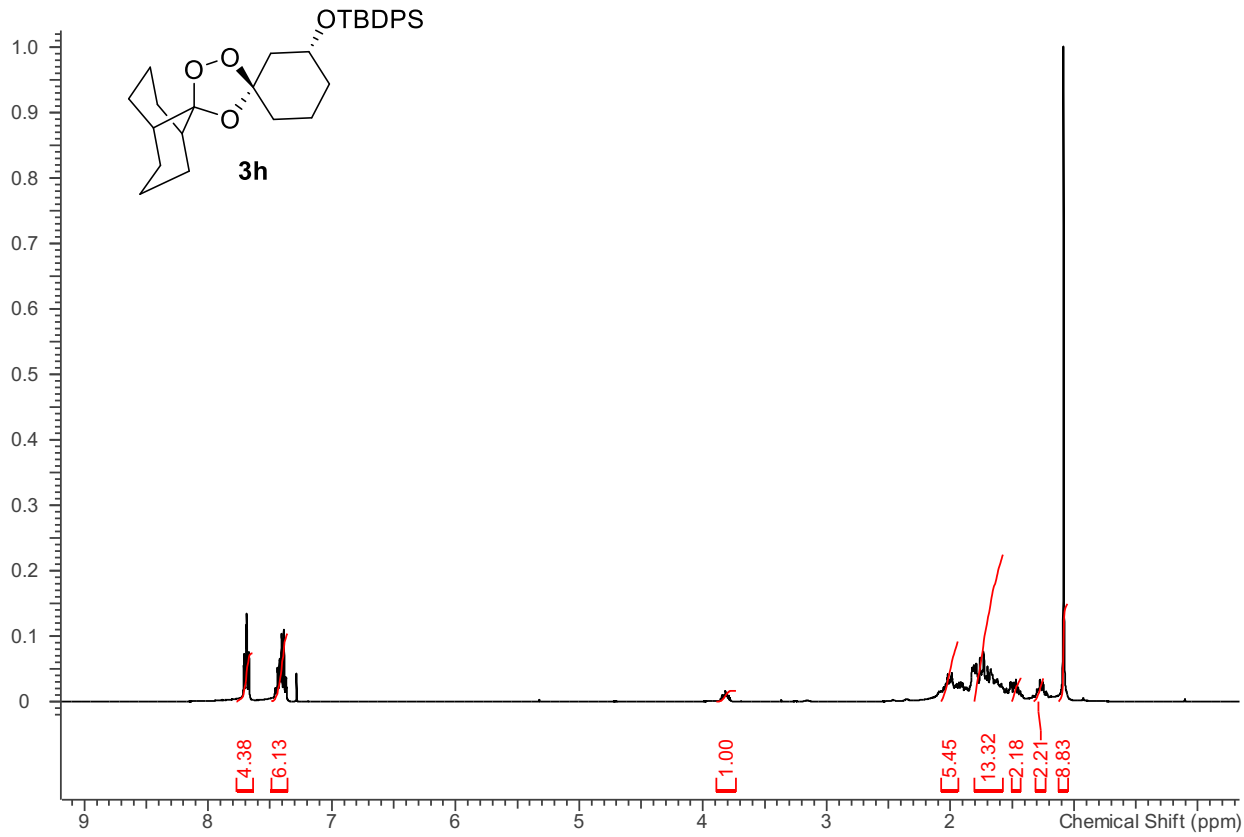

1.5
1.0
0.5
0
135.68
129.51
127.55
127.49
109.76
108.79
77.31
77.00
76.68
69.60
62.49
62.10
48.30
45.59
43.52
39.75
39.71
39.57
34.21
30.41
26.94
19.77
19.07
200
180
160
140
120
100
80
60
40
Chemical Shift (ppm)

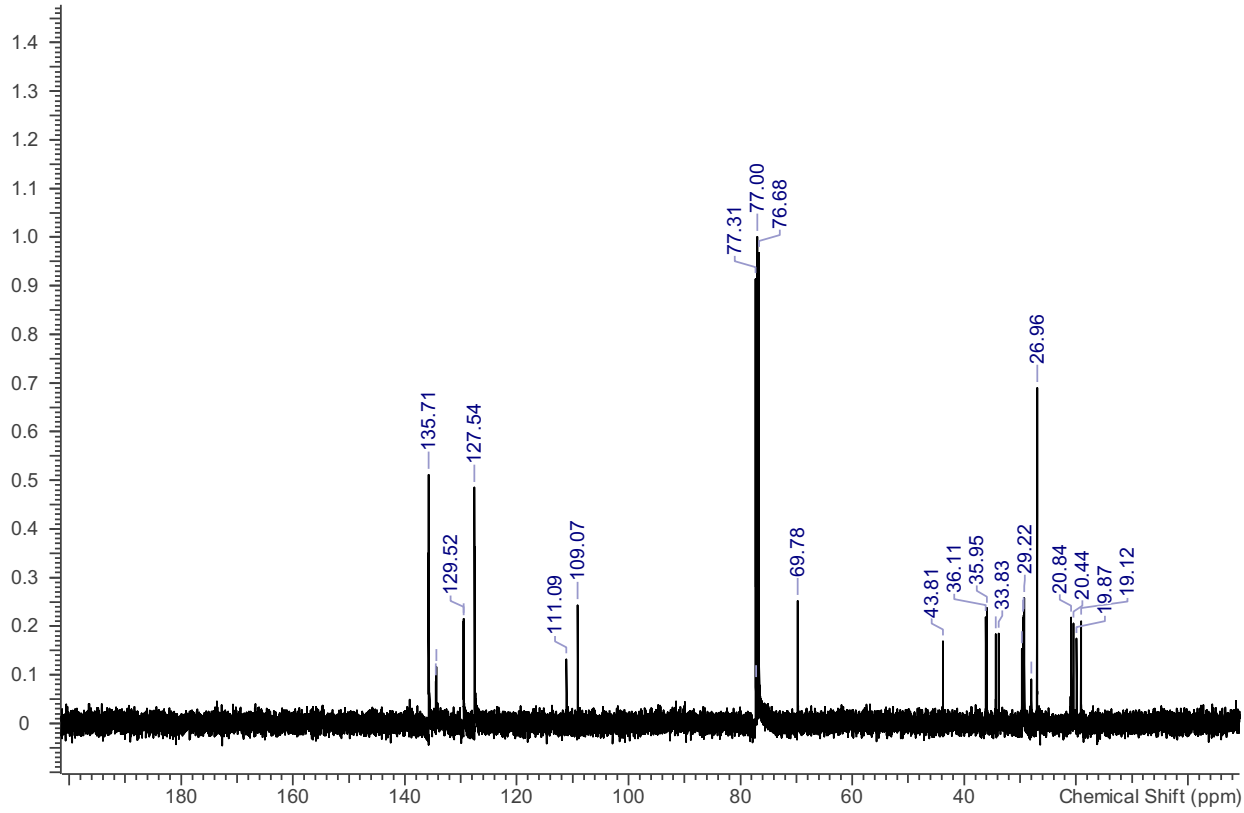

OTBDPS
3f
3.88
5.77
0.04
0.37
0.58
1.24
0.96
4.61
12.11
8.77
Chemical Shift (ppm)

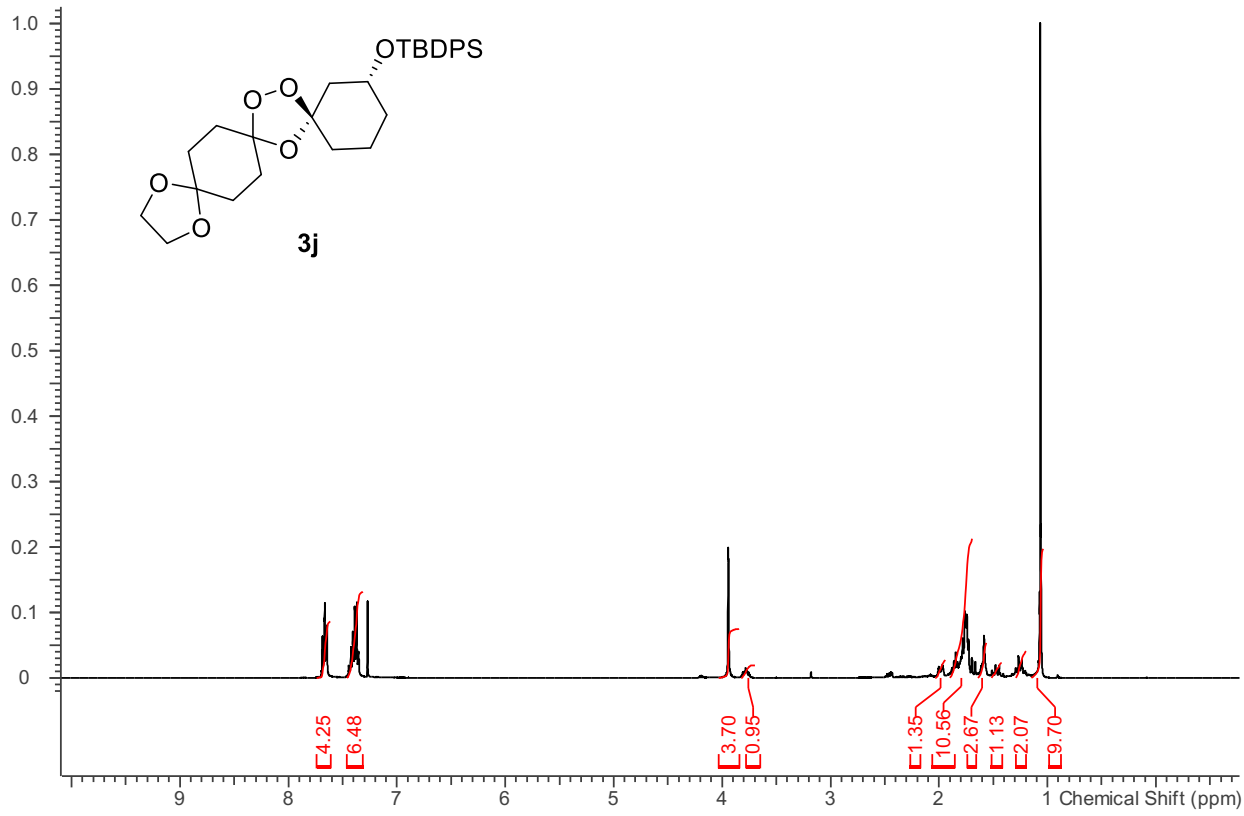

CHLOROFORM-d
135.72
135.76
134.50
129.52
127.49
127.47
115.88
109.12
109.09
77.32
77.00
76.69
69.68
44.98
40.95
37.46
34.32
27.77
26.95
26.94
21.63
21.50
19.69
19.10
Chemical Shift (ppm)

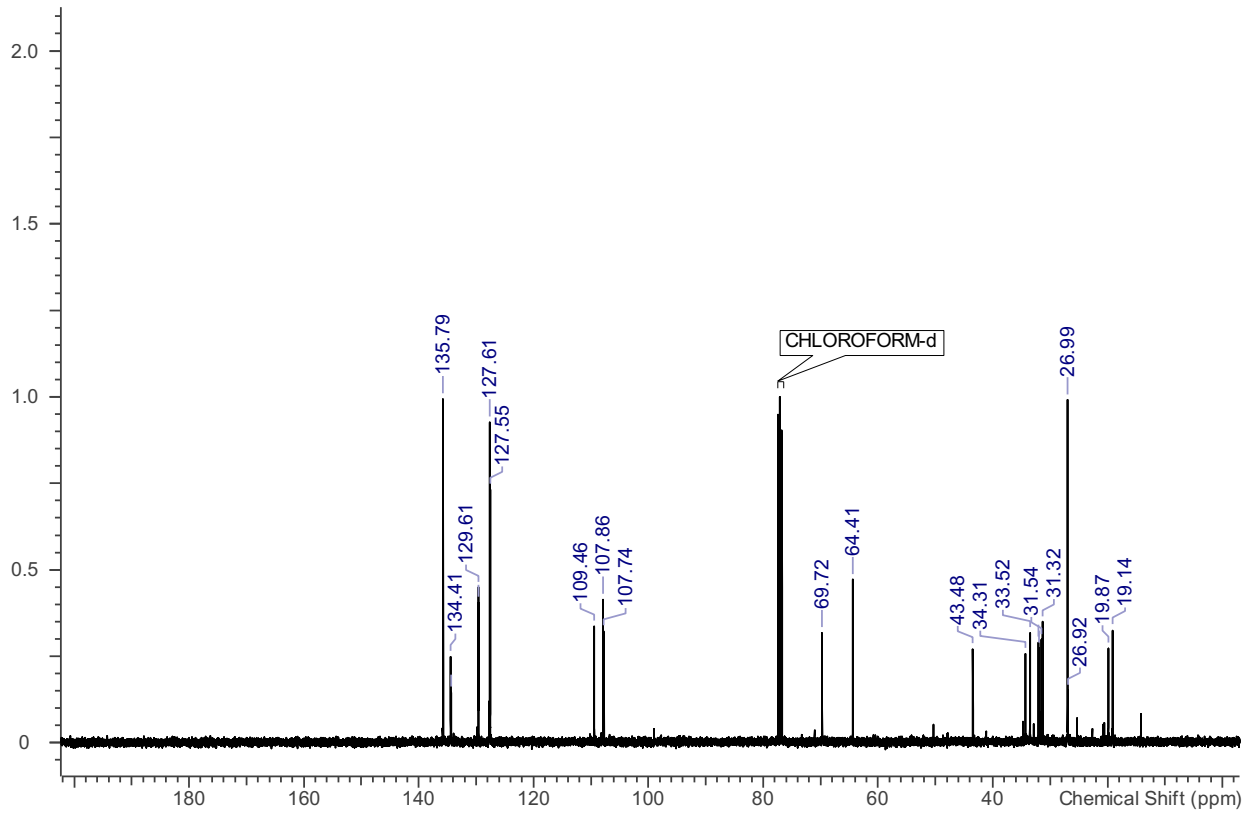

OTBDPS
O
O
O
3g
1H
0.21
0.79
4.00
6.00
0.21
0.79
9.23
2.04
7.58
2.22
8.95
Chemical Shift (ppm)

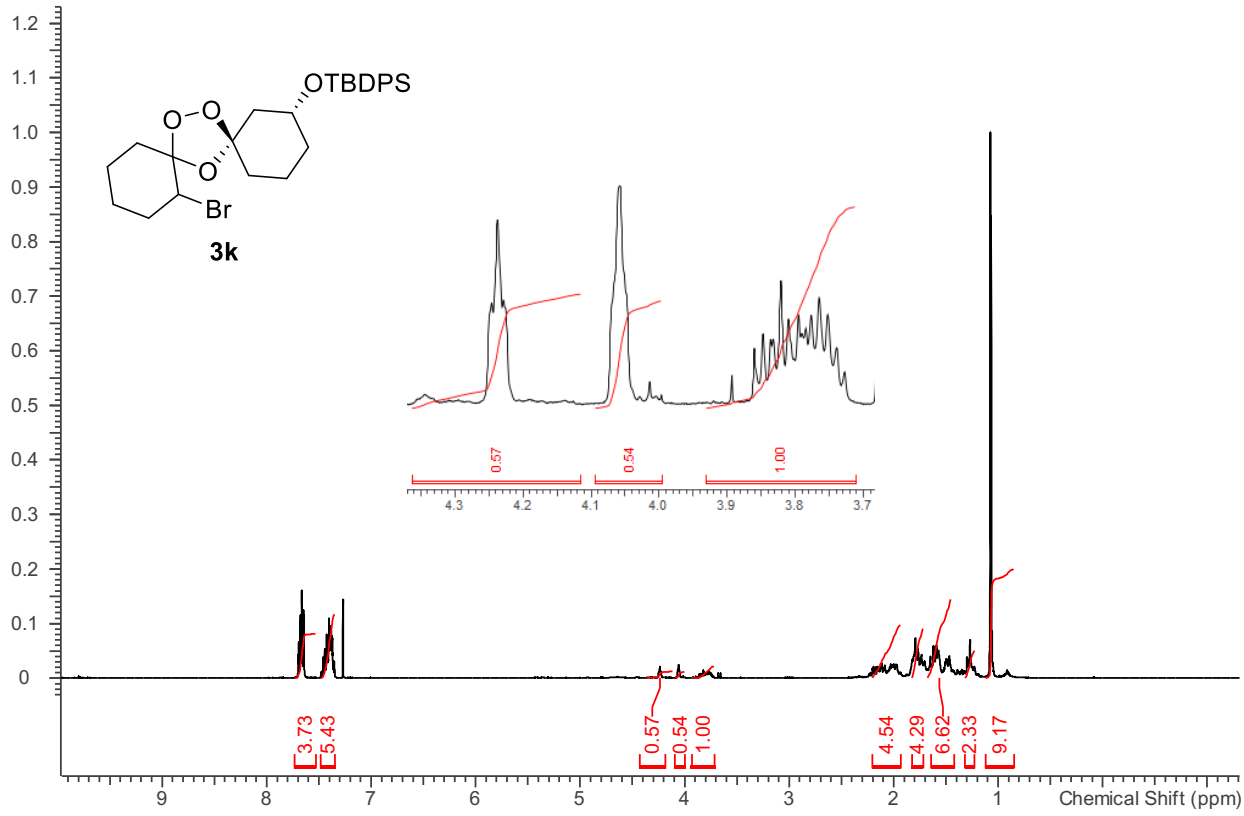

77.31
77.00
76.68
135.75
127.54
127.48
129.53
134.39
110.91
109.14
69.72
43.42
37.65
34.38
33.90
32.66
26.95
25.87
24.18
20.90
19.76
19.10
Chemical Shift (ppm)

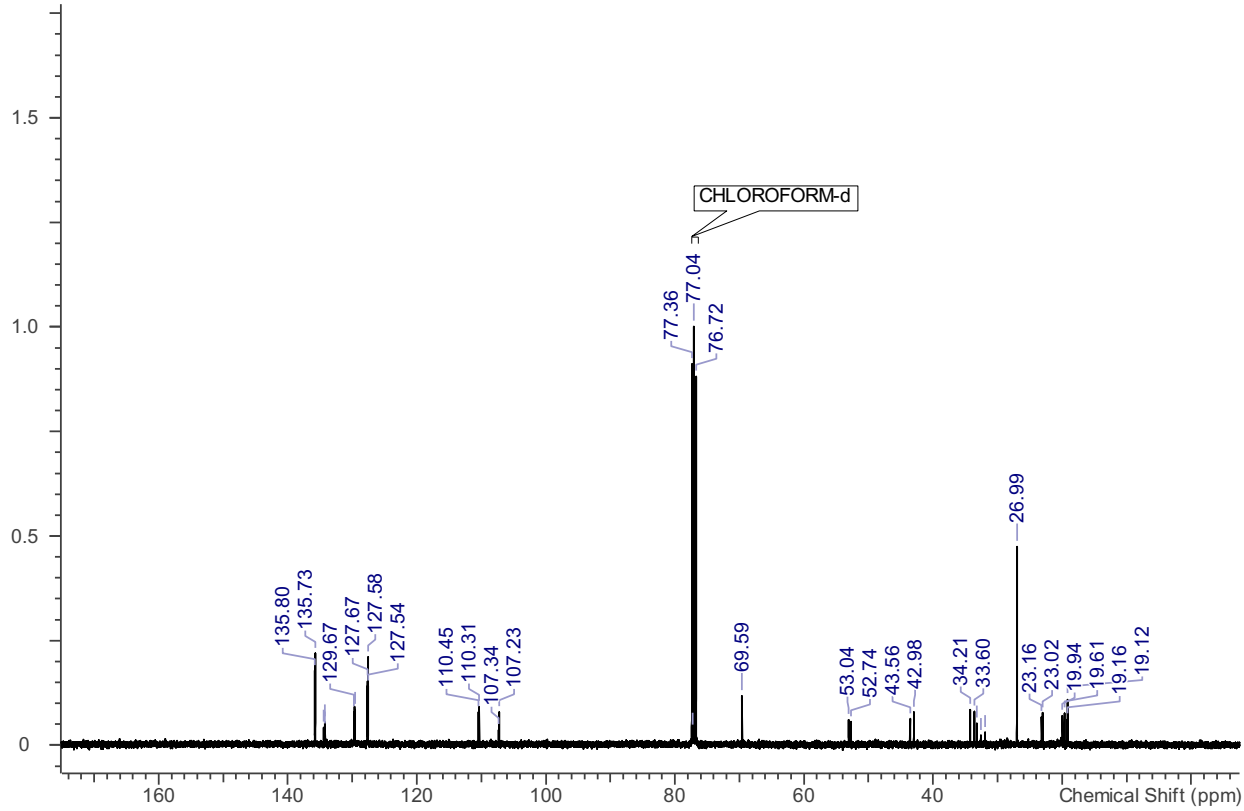

OTBDPS
O
O
O
3h
4.38
6.13
1.00
5.45
13.32
2.18
2.21
8.83
Chemical Shift (ppm)

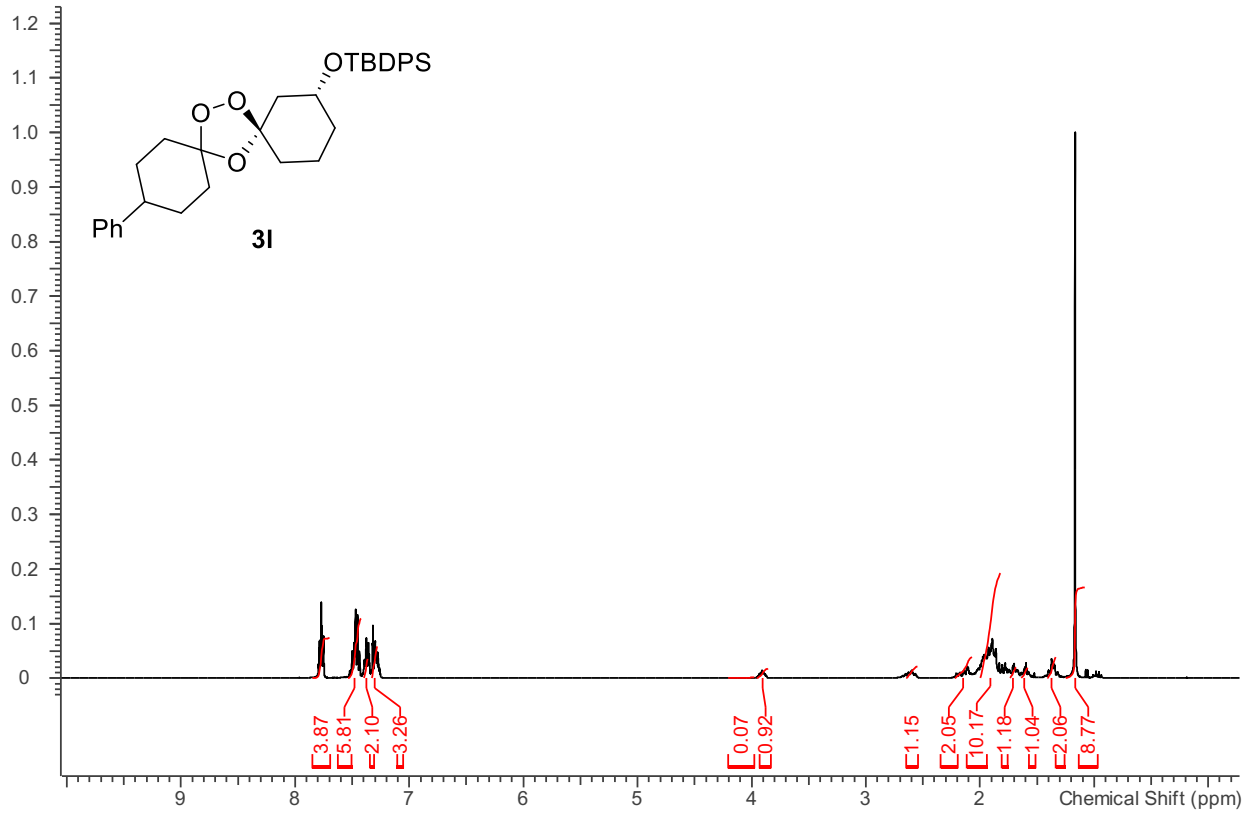

135.71
129.52
127.54
111.09
109.07
77.31
77.00
76.68
69.78
43.81
36.11
35.95
33.83
29.22
26.96
20.84
20.44
19.87
19.12
Chemical Shift (ppm)

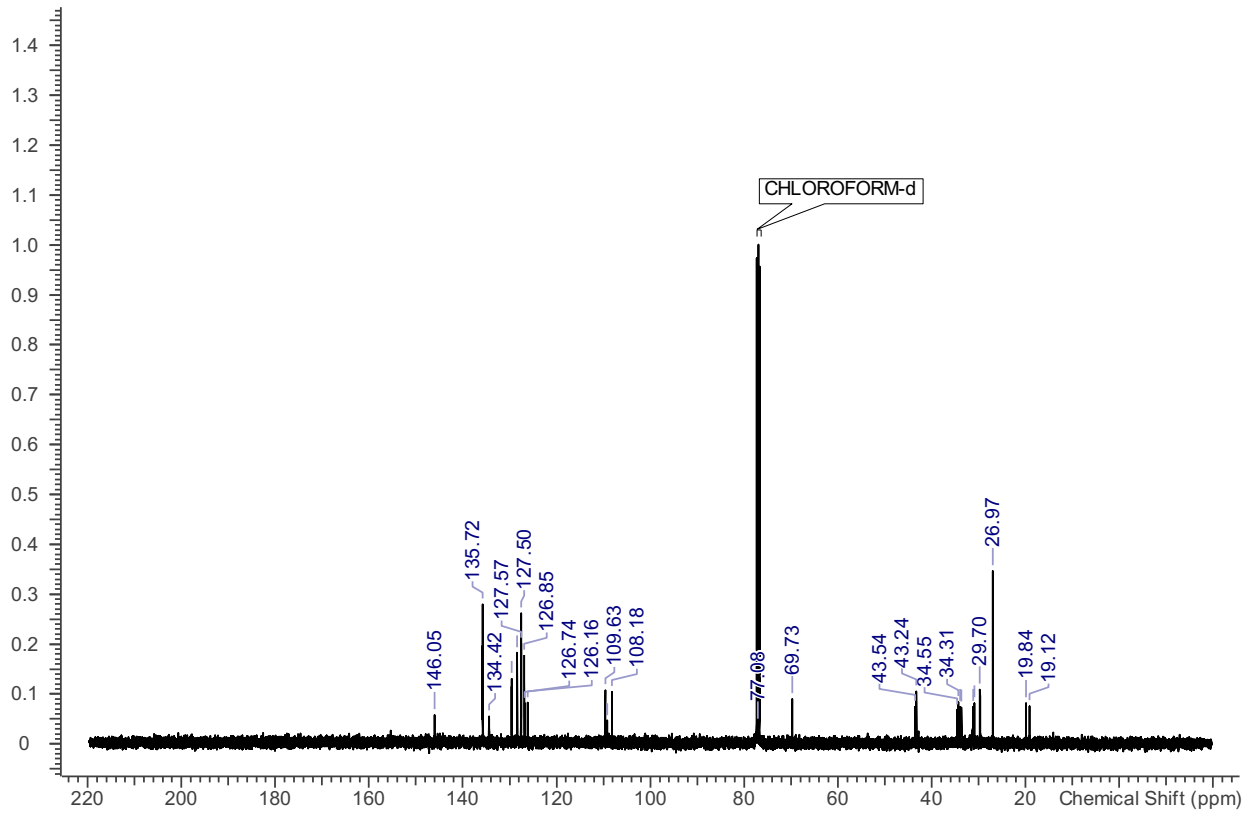

OTBDPS
O
O
O
O
O
3j
4.25
6.48
3.70
0.95
1.35
10.56
2.67
1.13
2.07
9.70
Chemical Shift (ppm)

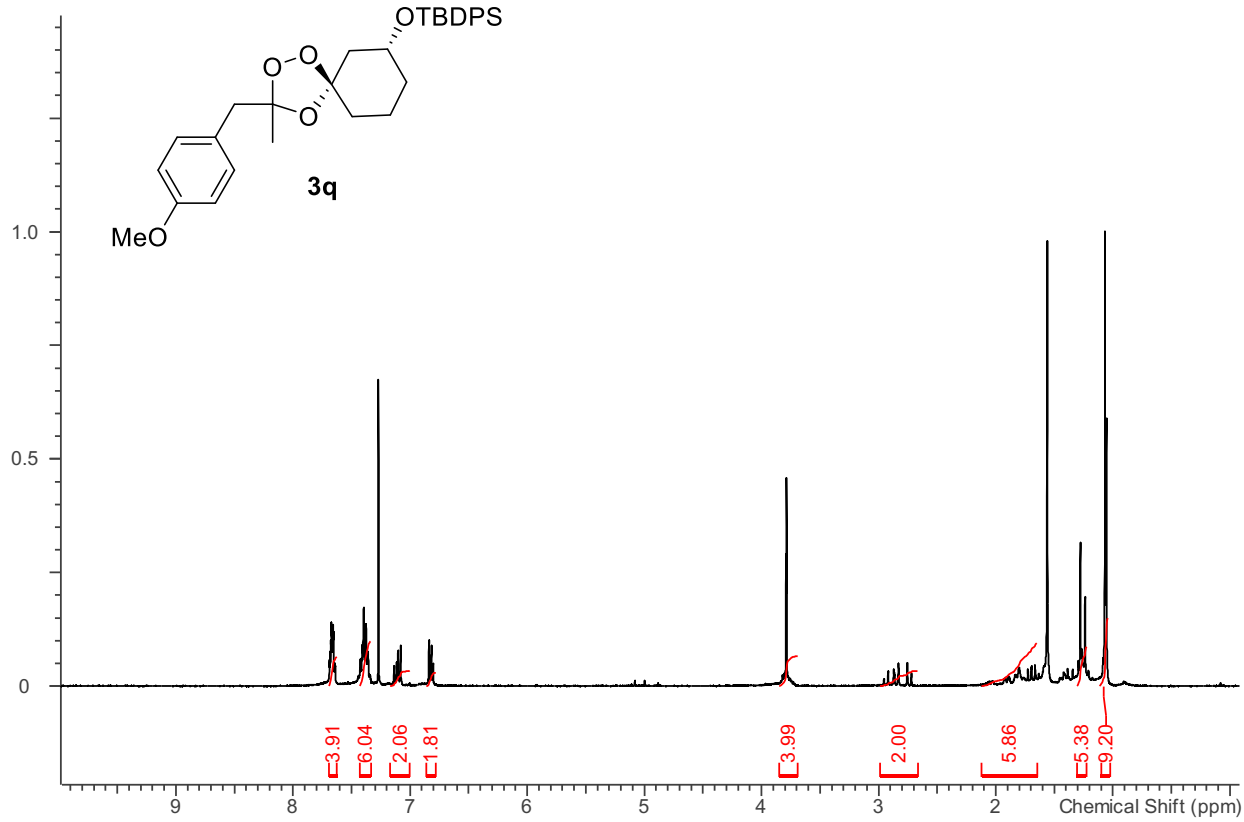

135.79
127.61
127.55
134.41
129.61
109.46
107.86
107.74
CHLOROFORM-d
69.72
64.41
43.48
34.31
33.52
31.54
31.32
26.99
26.92
19.87
19.14
Chemical Shift (ppm)

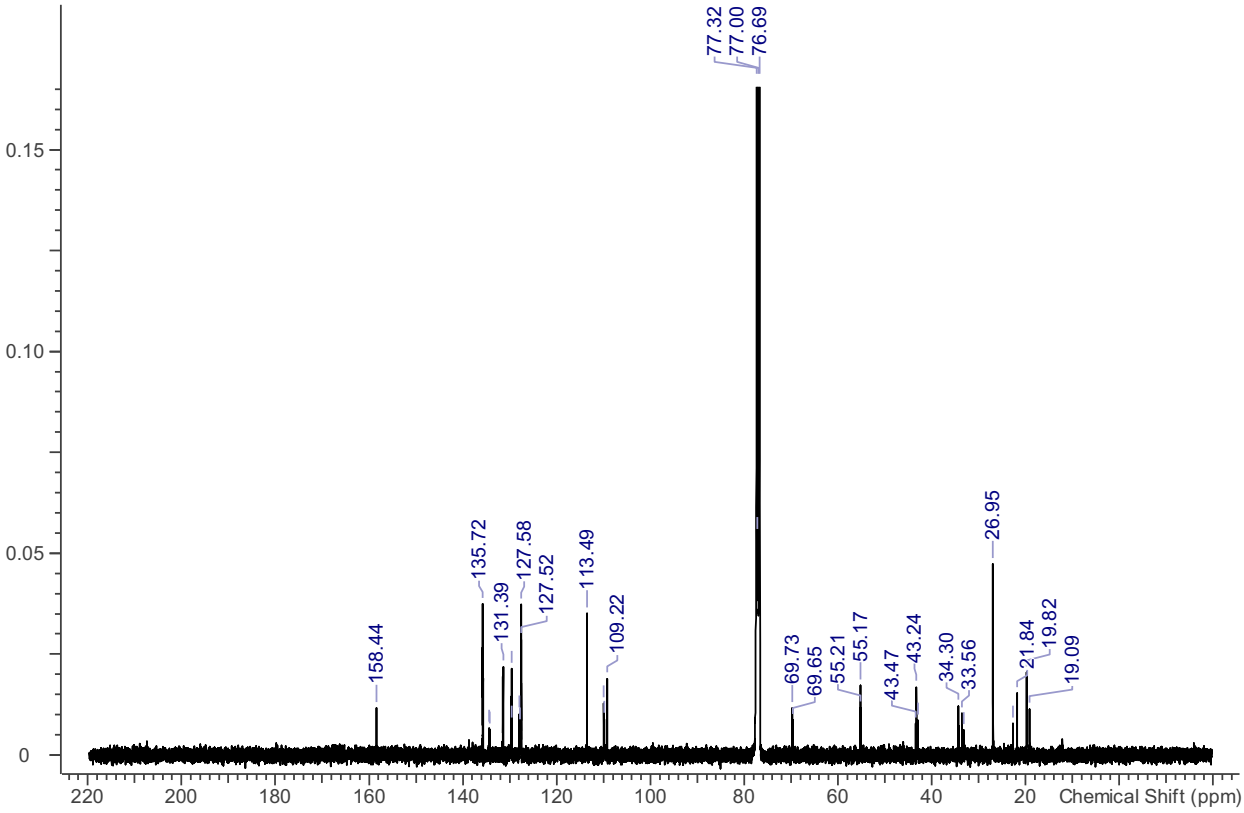

OTBDPS
O
O
O
Br
3k
0.57
0.54
1.00
4.3
4.2
4.1
4.0
3.9
3.8
3.7
3.73
5.43
0.57
0.54
1.00
4.54
4.29
6.62
2.33
9.17
Chemical Shift (ppm)

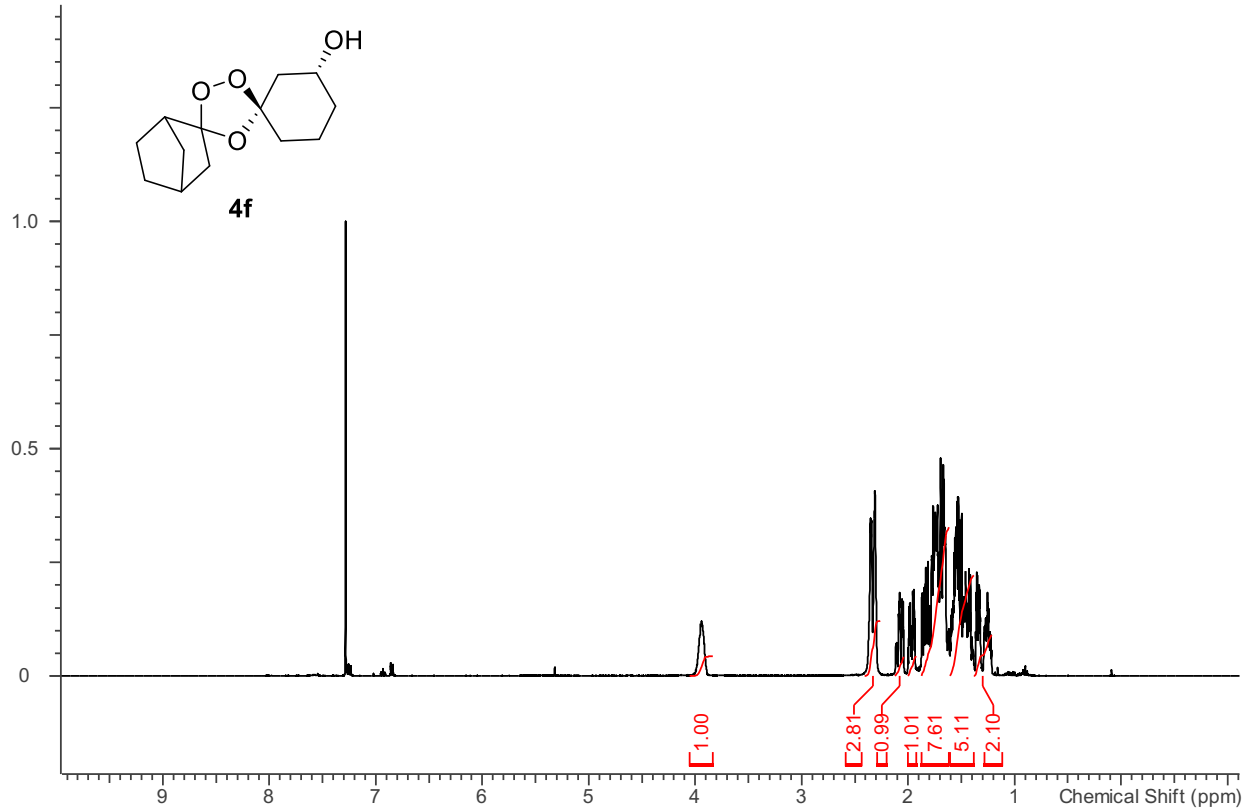

CHLOROFORM-d
77.36
77.04
76.72
135.80
135.73
129.67
127.67
127.58
127.54
110.45
110.31
107.34
107.23
69.59
53.04
52.74
43.56
42.98
34.21
33.60
26.99
23.16
23.02
19.94
19.61
19.16
19.12
Chemical Shift (ppm)

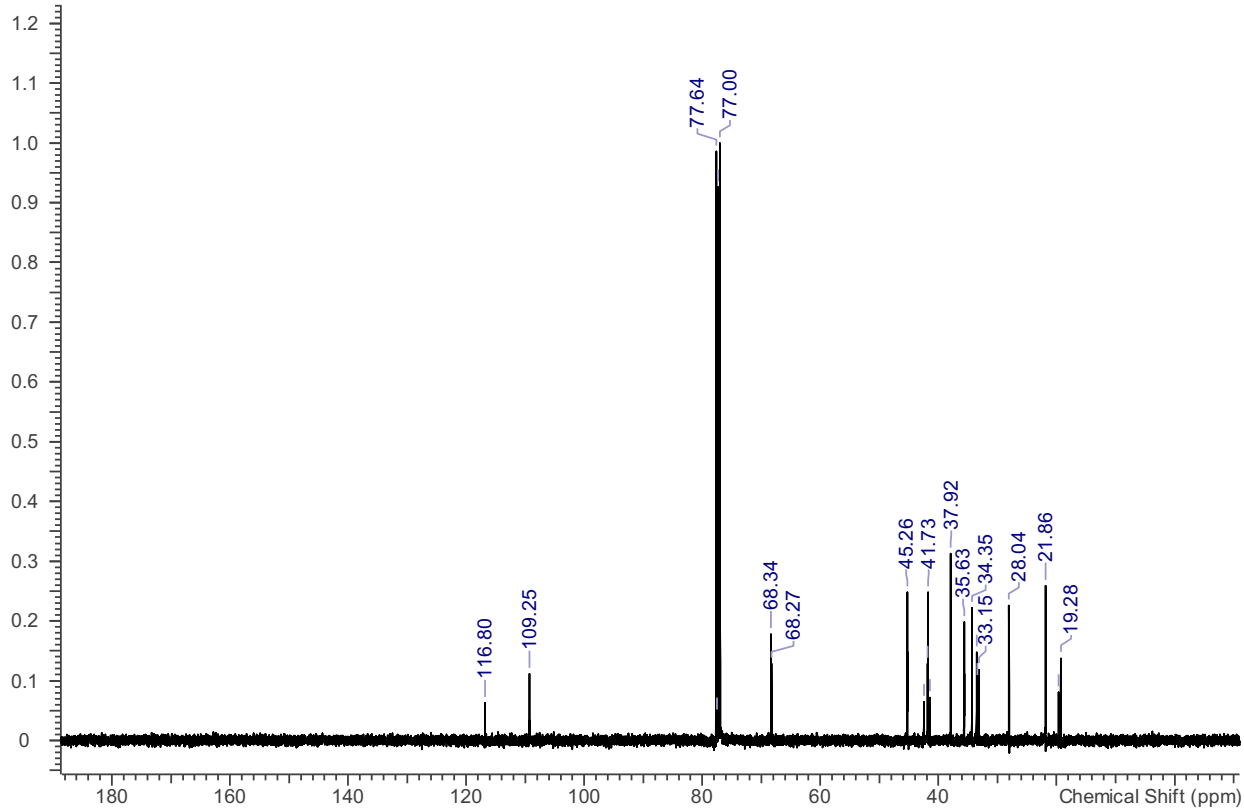

OTBDPS
O
O
O
Ph
3.87
5.81
2.10
3.26
0.07
0.92
1.15
2.05
10.17
1.18
1.04
2.06
8.77
Chemical Shift (ppm)

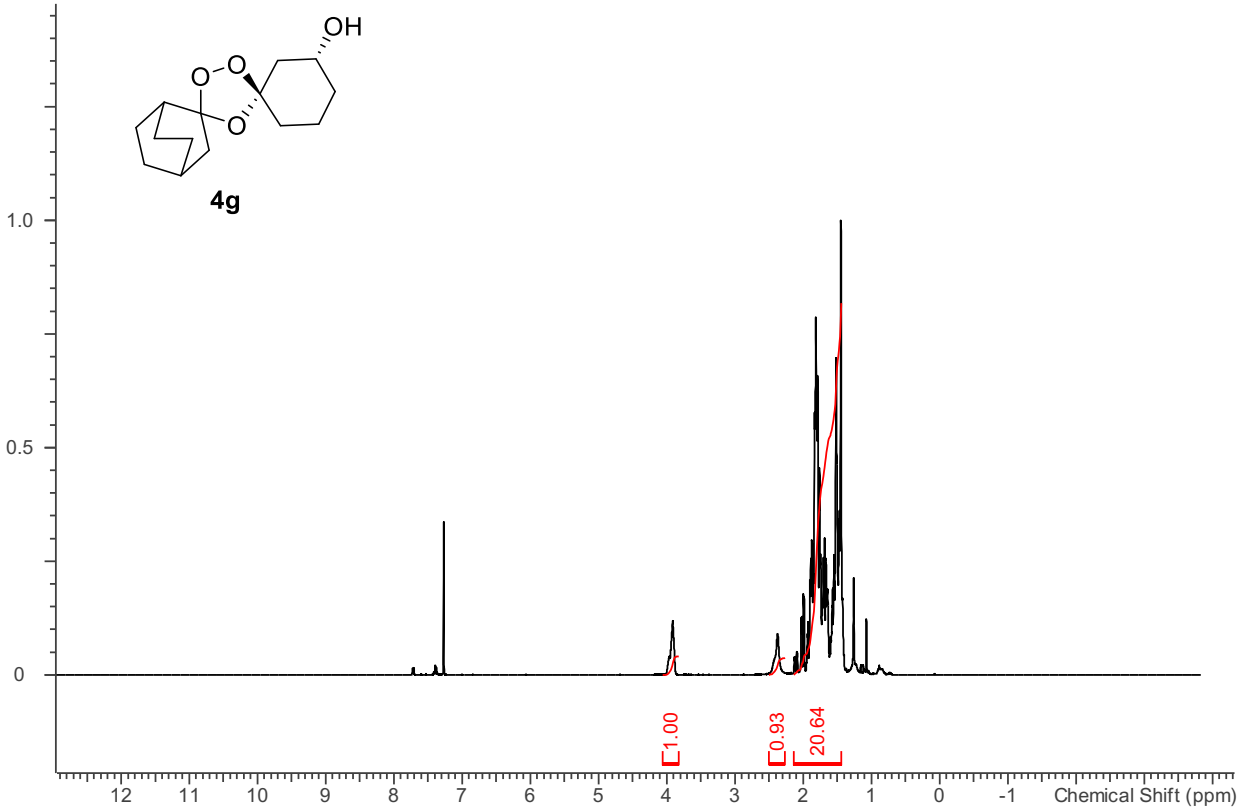

CHLOROFORM-d
146.05
135.72
134.42
127.57
127.50
126.85
126.74
126.16
109.63
108.18
77.08
69.73
43.54
43.24
34.55
34.31
29.70
26.97
19.84
19.12
Chemical Shift (ppm)

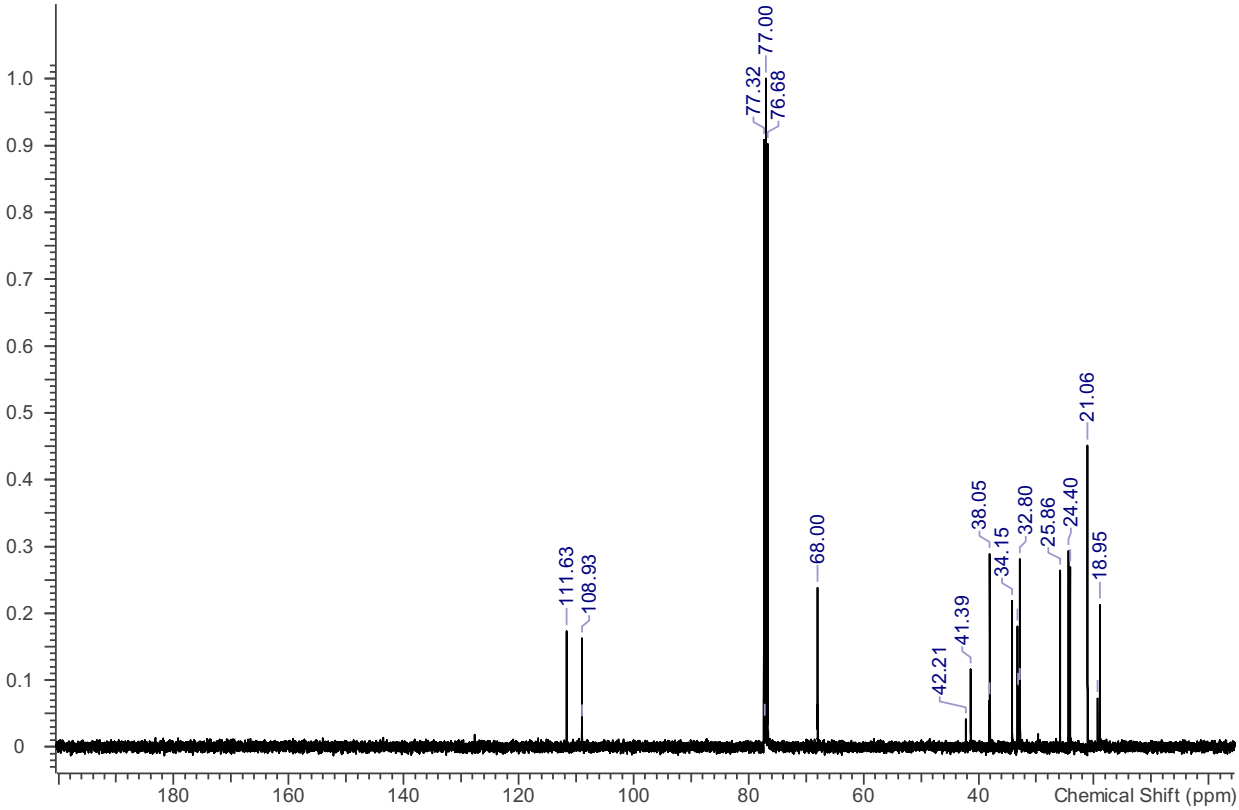

OTBDPS
O
O
O
3q
MeO
1.0
0.5
0
3.91
6.04
2.06
1.81
3.99
2.00
5.86
5.38
9.20
9
8
7
6
5
4
3
2
Chemical Shift (ppm)

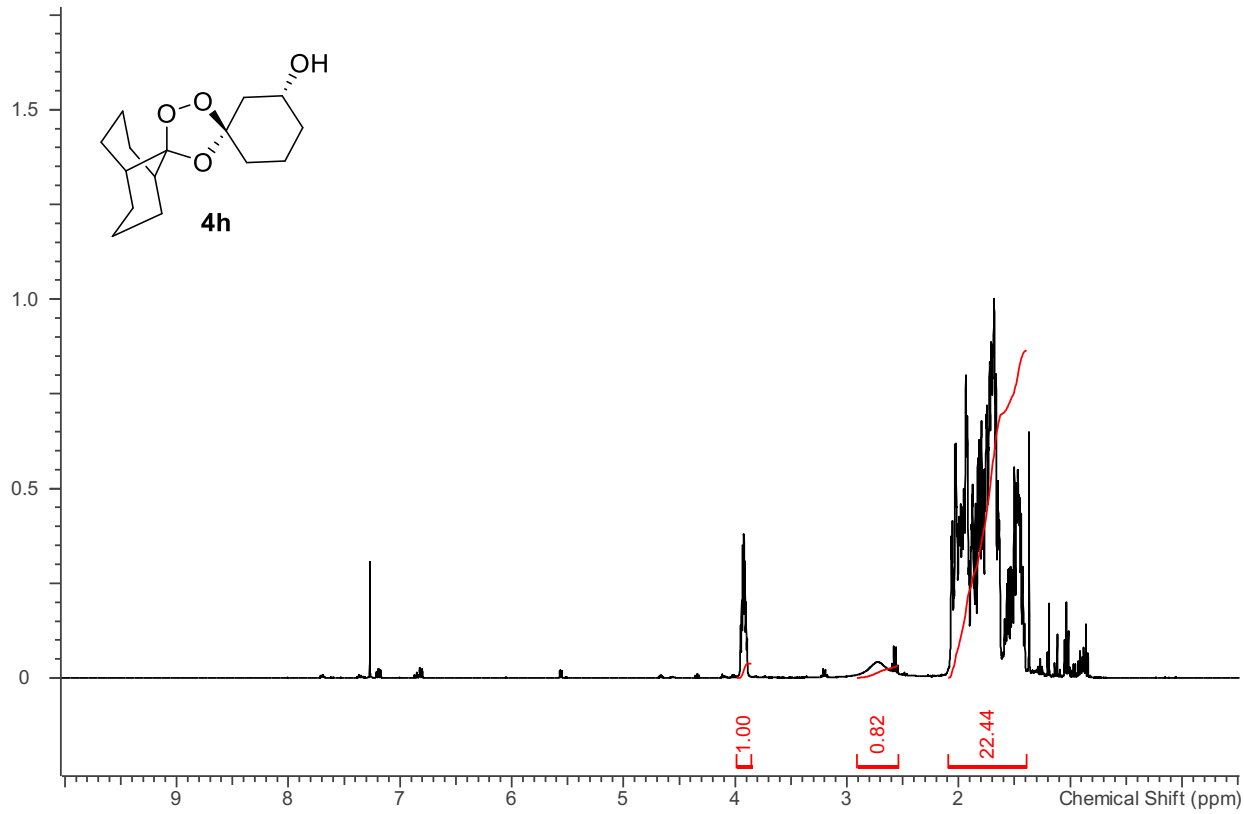

0.15
0.10
0.05
0
77.32
77.00
76.69
158.44
135.72
131.39
127.58
127.52
113.49
109.22
69.73
69.65
55.21
55.17
43.47
43.24
34.30
33.56
26.95
21.84
19.82
19.09
220
200
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)

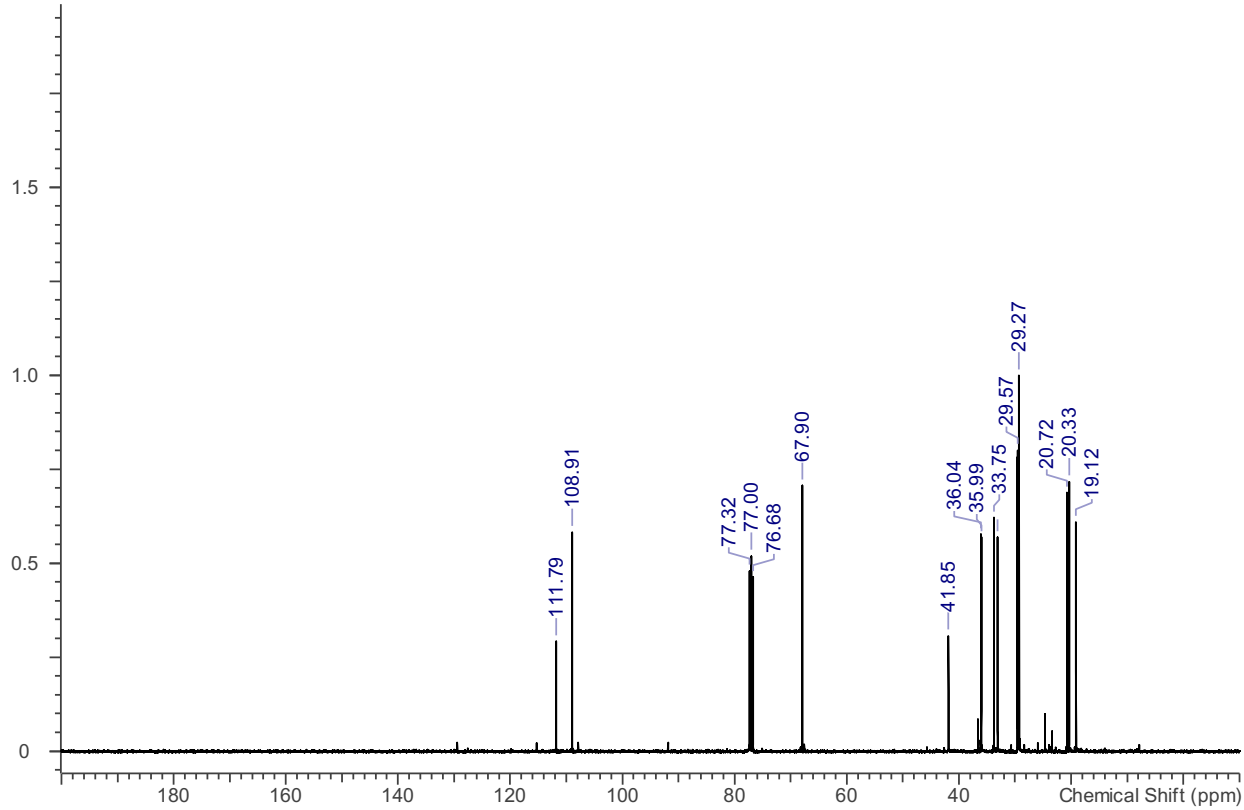

OH
O
O
O
4f
1.0
0.5
0
1.00
2.81
0.99
1.01
7.61
5.11
2.10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

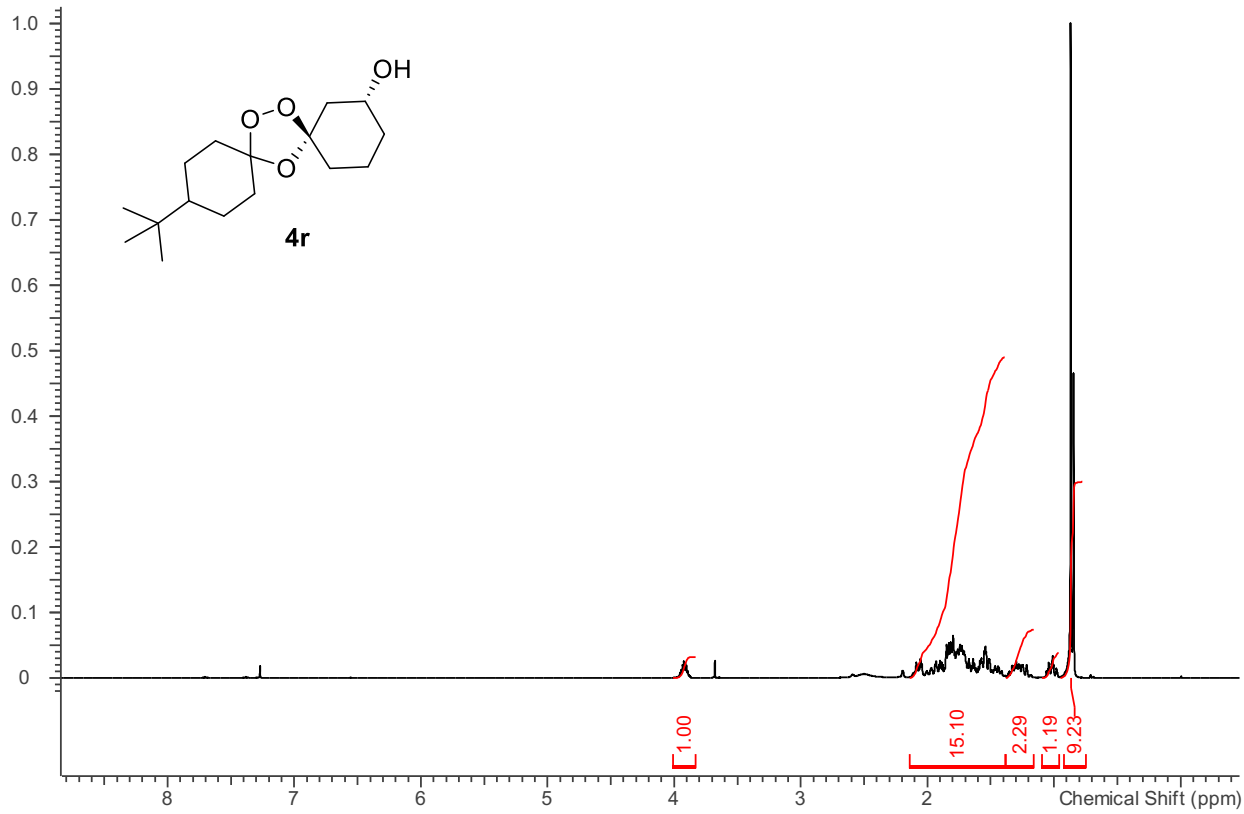

1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
77.64
77.00
116.80
109.25
68.34
68.27
45.26
41.73
37.92
35.63
34.15
34.35
28.04
21.86
19.28
180
160
140
120
100
80
60
40
Chemical Shift (ppm)

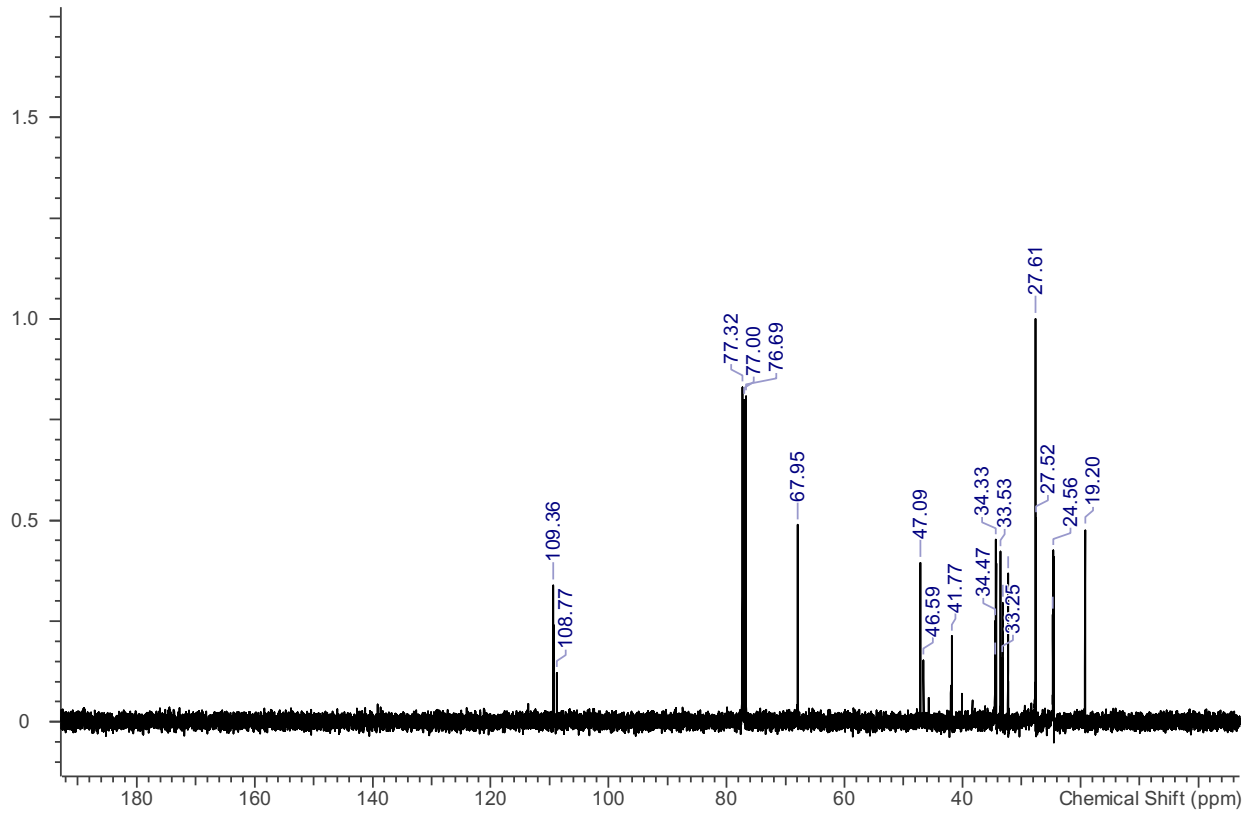

OH
O
O
O
4g
1.0
0.5
0
1.00
0.93
20.64
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
Chemical Shift (ppm)

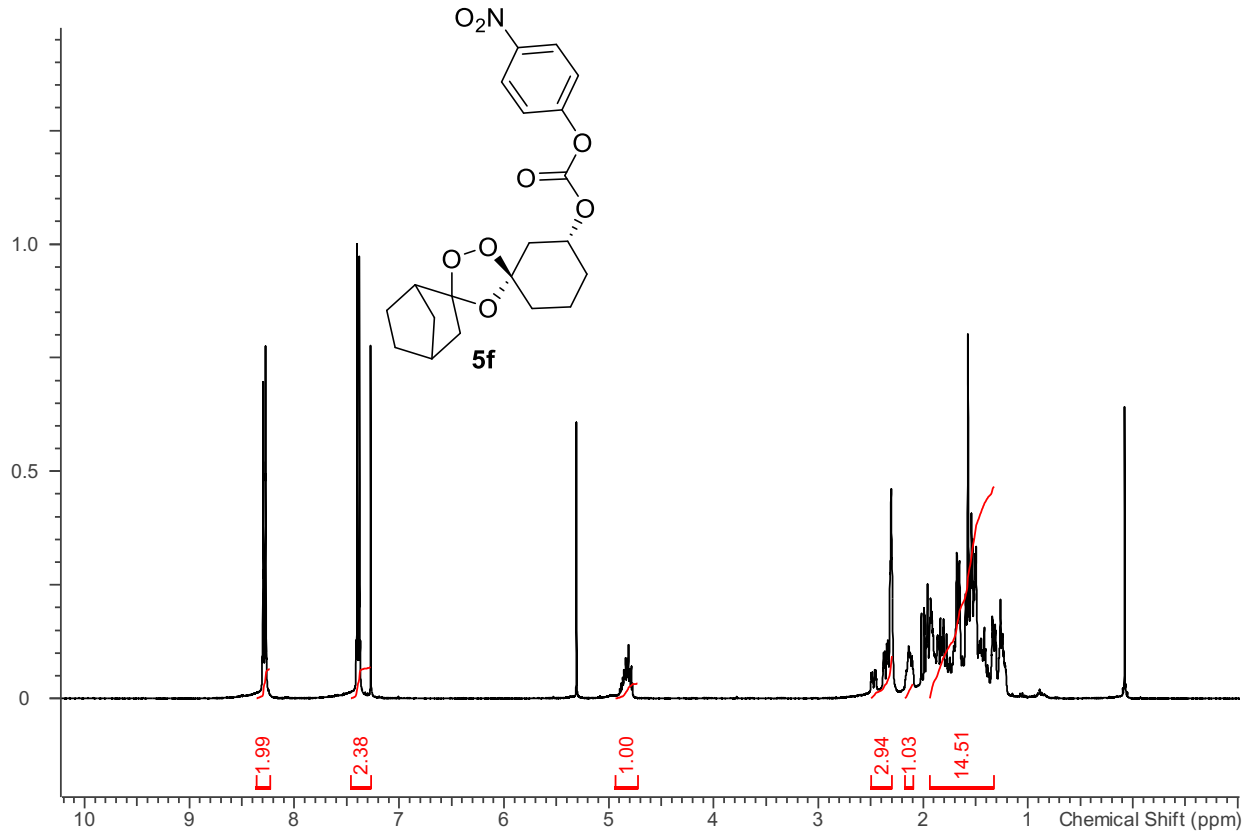

1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
77.32
77.00
76.68
111.63
108.93
68.00
42.21
41.39
38.05
34.15
32.80
25.86
24.40
21.06
18.95
180
160
140
120
100
80
60
40
Chemical Shift (ppm)

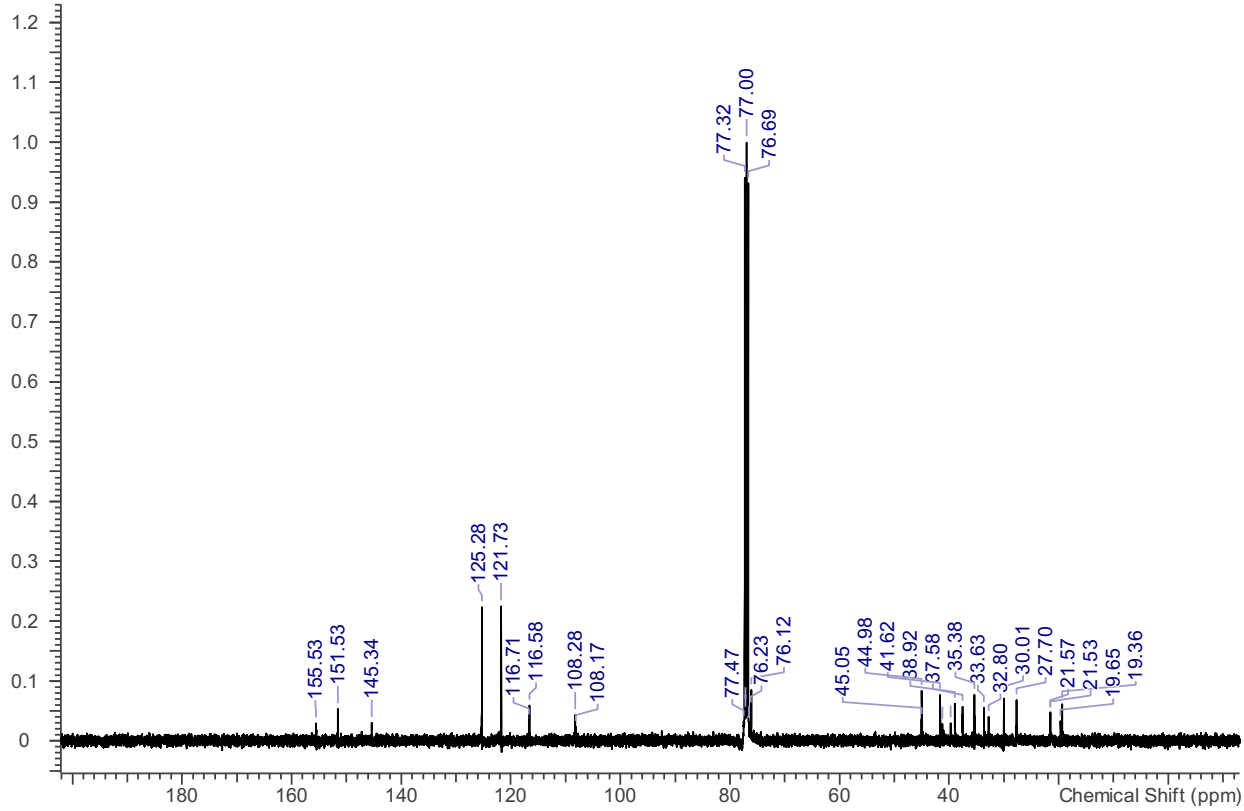

OH
O
O
O
4h
1.5
1.0
0.5
0
1.00
0.82
22.44
9
8
7
6
5
4
3
2
Chemical Shift (ppm)

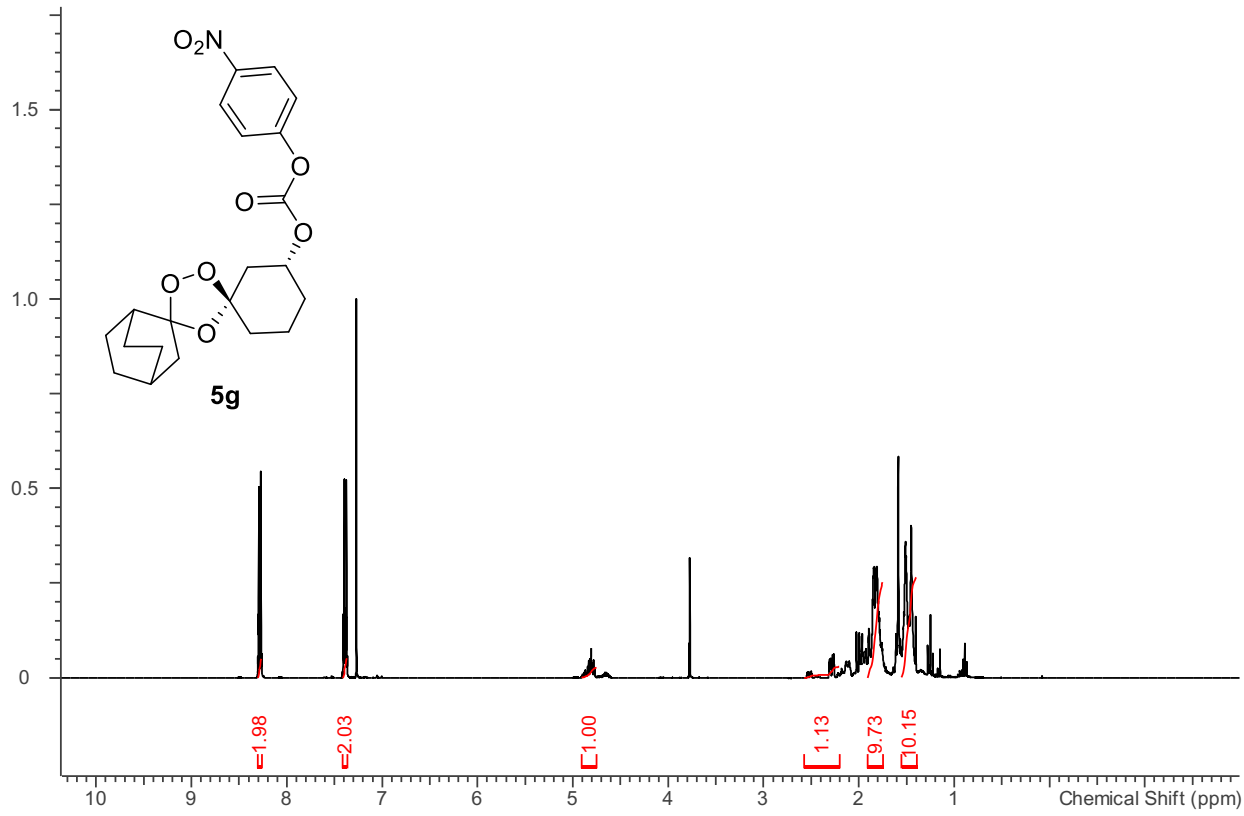

1.5
1.0
0.5
0
111.79
108.91
77.32
77.00
76.68
67.90
41.85
36.04
35.99
33.75
29.57
29.27
20.72
20.33
19.12
180
160
140
120
100
80
60
40
Chemical Shift (ppm)

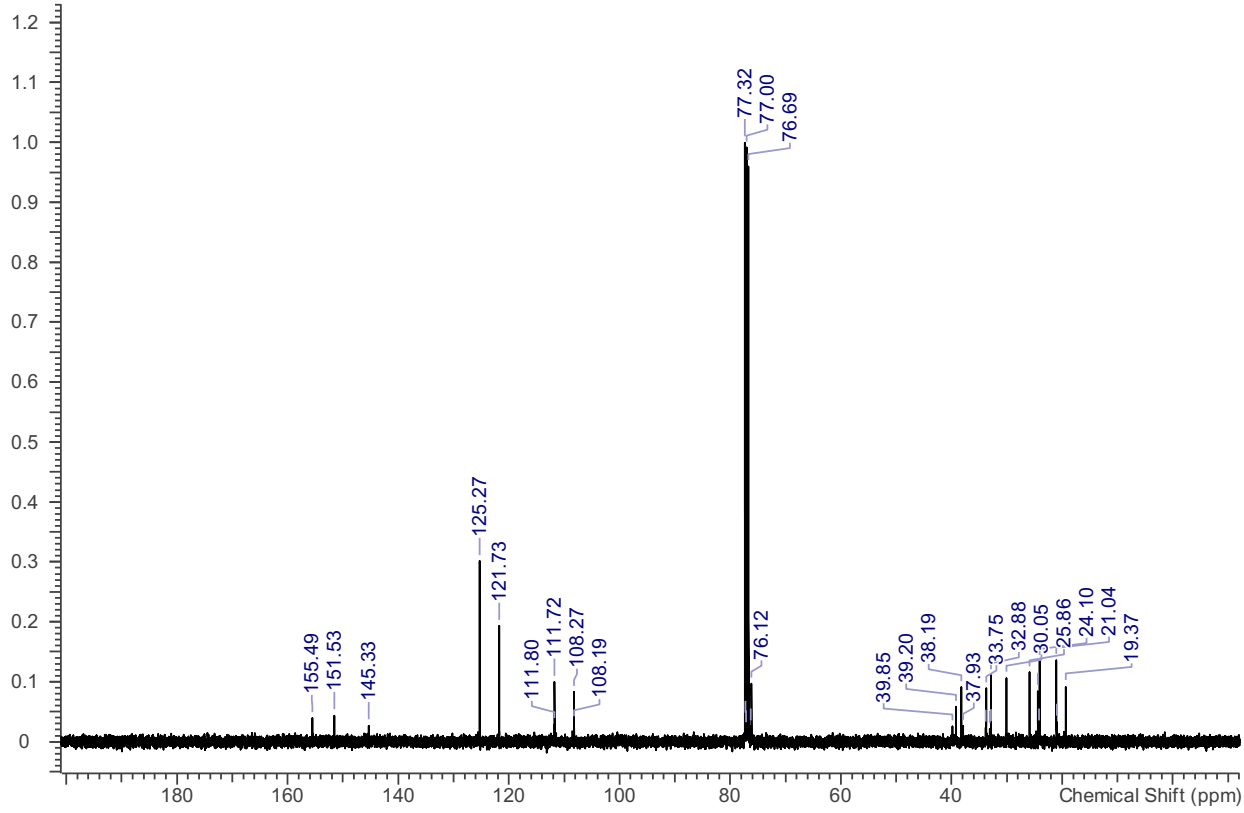

OH
O
O
O
4r
1.00
15.10
2.29
1.19
9.23
Chemical Shift (ppm)

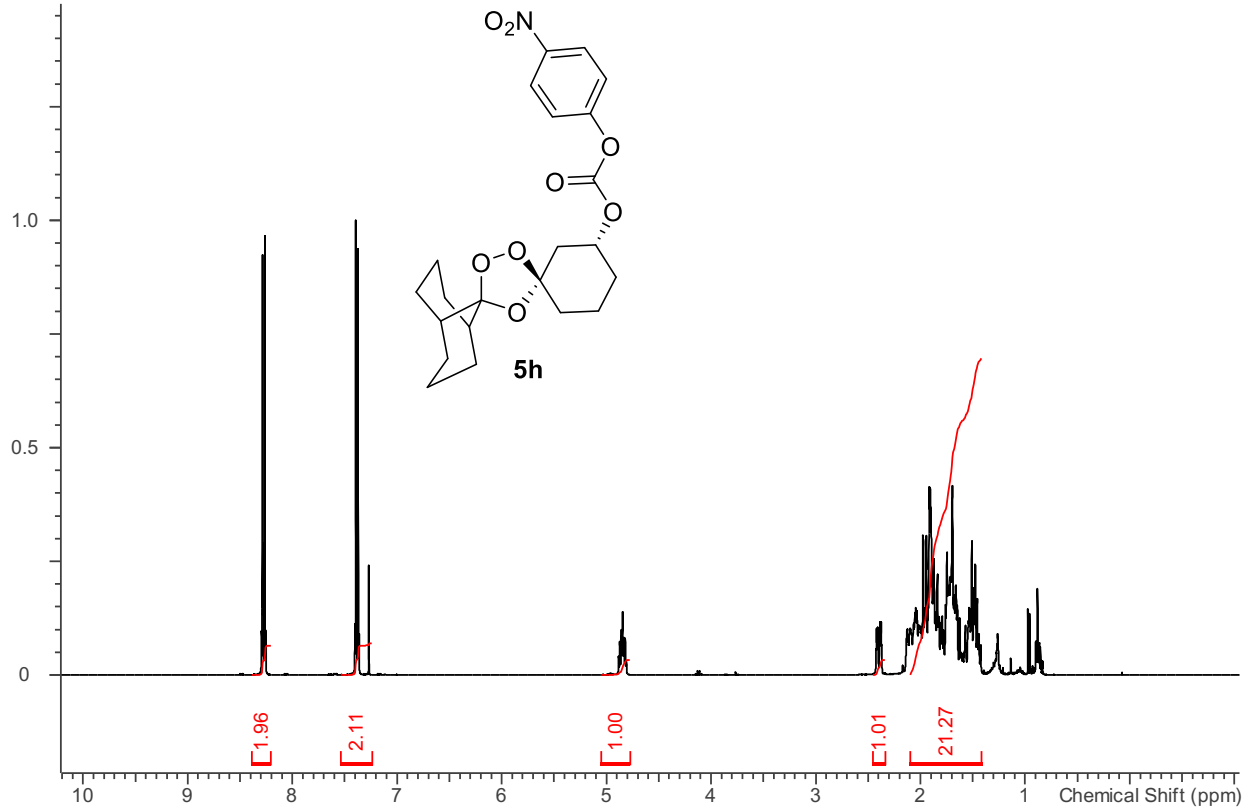

109.36
108.77
77.32
77.00
76.69
67.95
47.09
46.59
41.77
34.47
34.33
33.53
33.25
27.61
27.52
24.56
19.20
Chemical Shift (ppm)

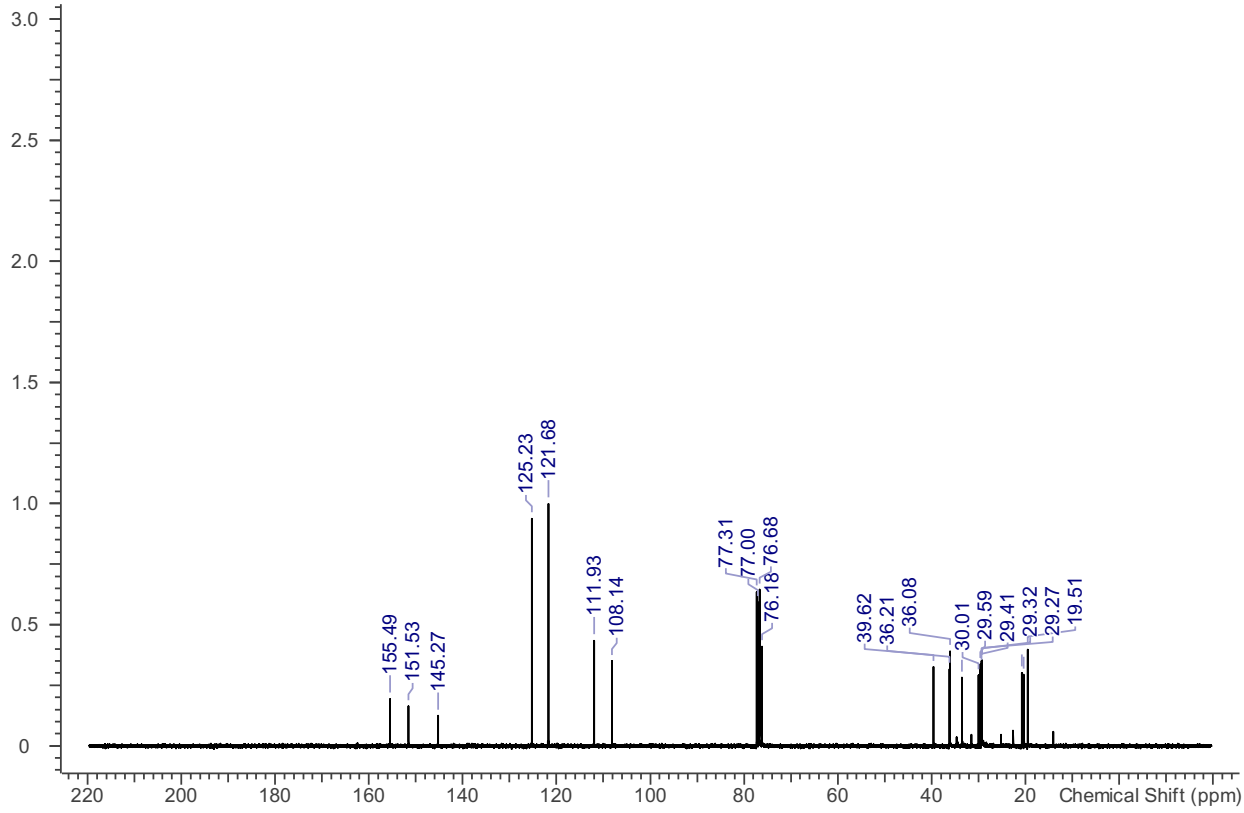

O2N
O
O
O
O
O
O
5f
1.0
0.5
0
1.99
2.38
1.00
2.94
1.03
14.51
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

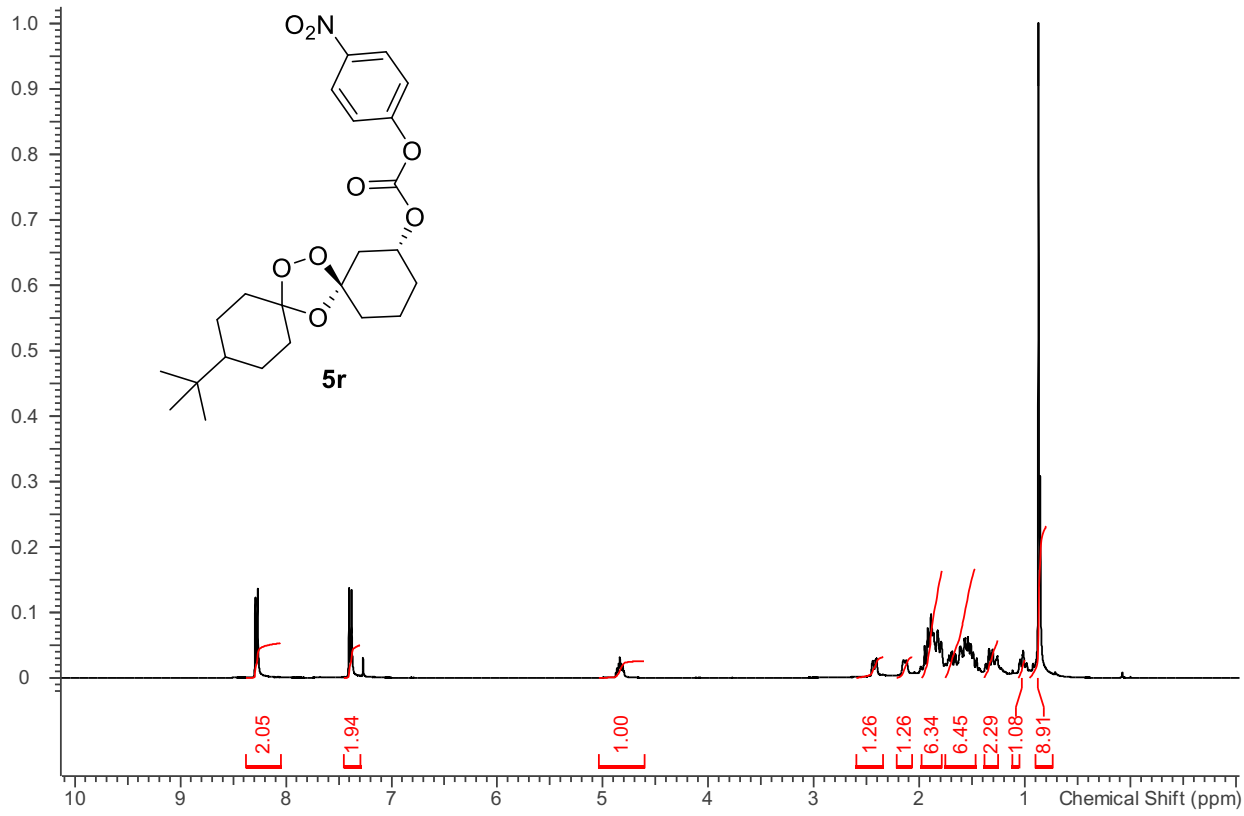

1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
77.32
77.00
76.69
125.28
121.73
155.53
151.53
145.34
116.71
116.58
108.28
108.17
77.47
76.23
76.12
45.05
44.98
41.62
38.92
37.58
35.38
33.63
32.80
30.01
27.70
21.57
21.53
19.65
19.36
180
160
140
120
100
80
60
40
Chemical Shift (ppm)

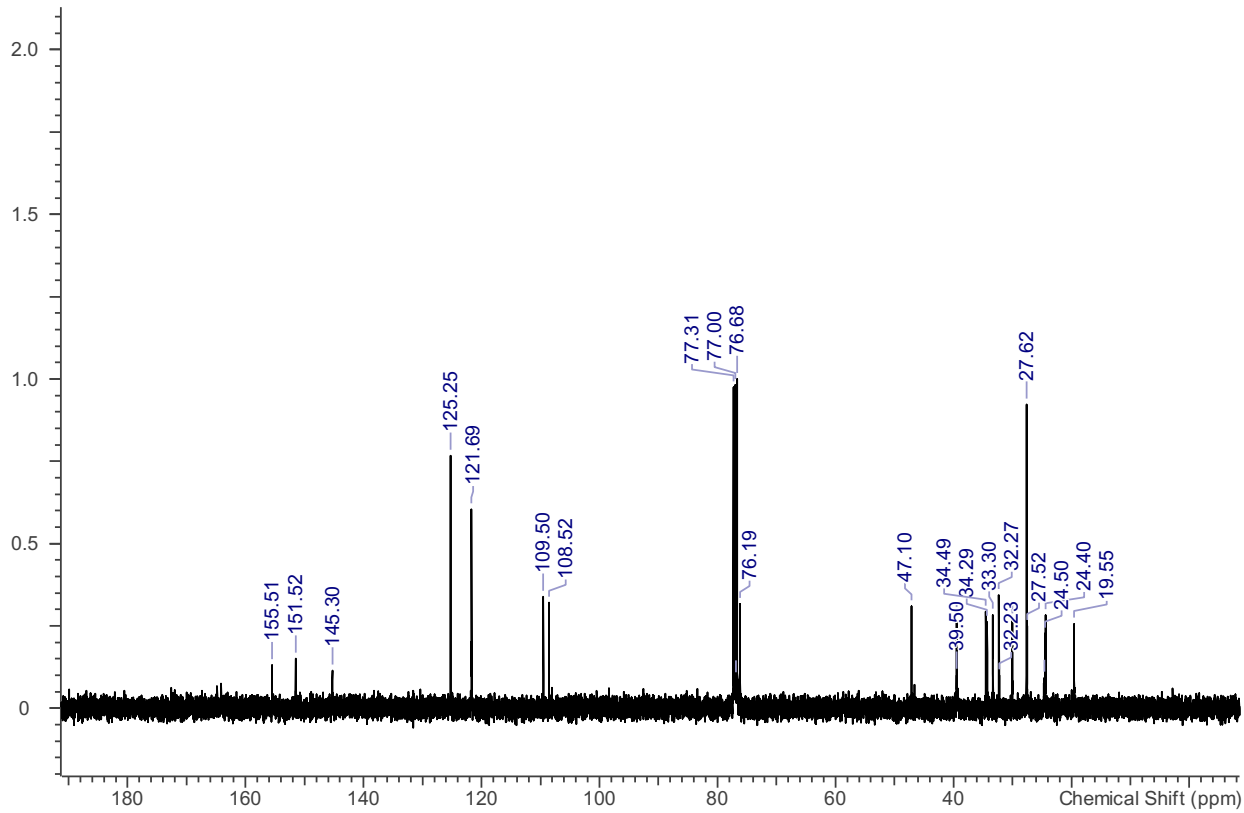

O2N
O
O
O
O
O
O
5g
1.98
2.03
1.00
1.13
9.73
10.15
Chemical Shift (ppm)

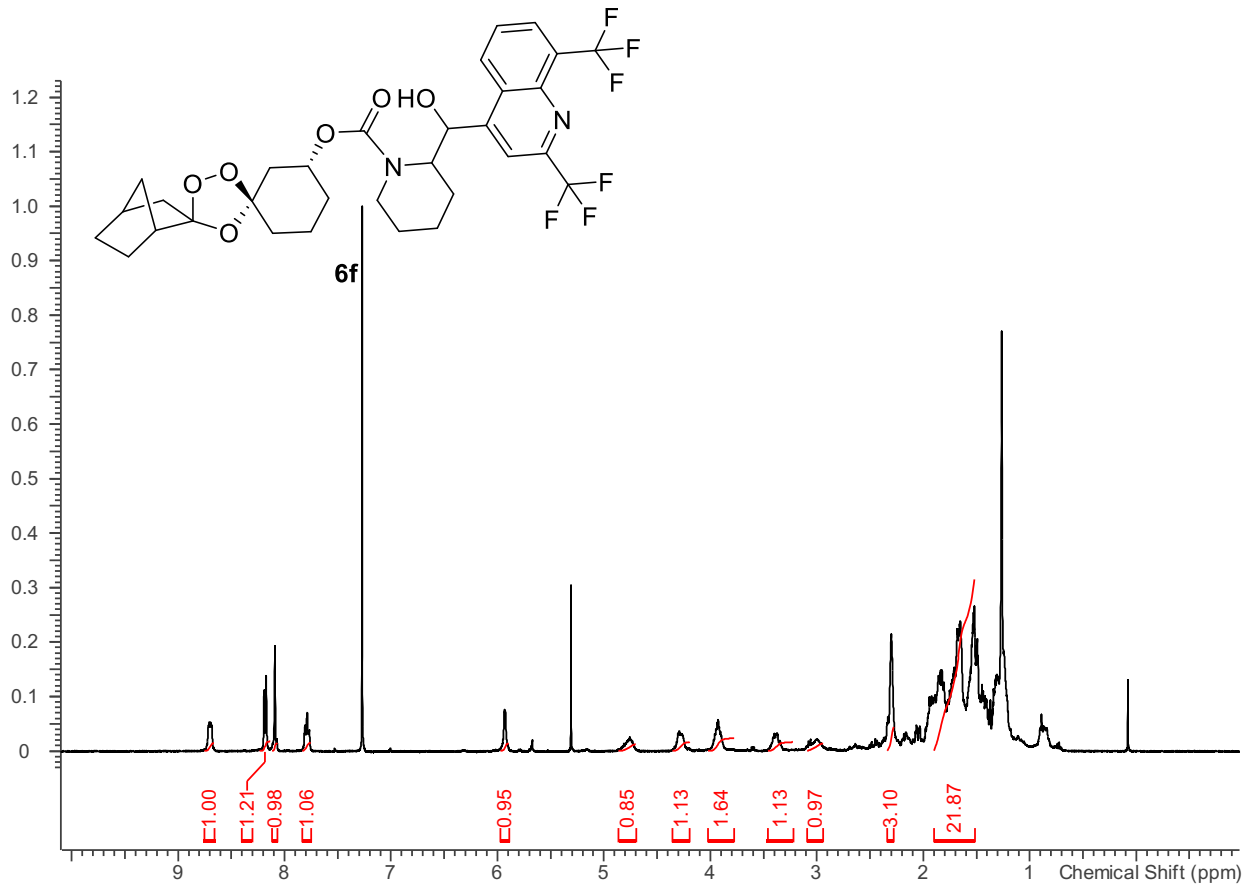

77.32
77.00
76.69
125.27
121.73
155.49
151.53
145.33
111.80
111.72
108.27
108.19
76.12
39.85
39.20
38.19
37.93
33.75
32.88
30.05
25.86
24.10
21.04
19.37
Chemical Shift (ppm)

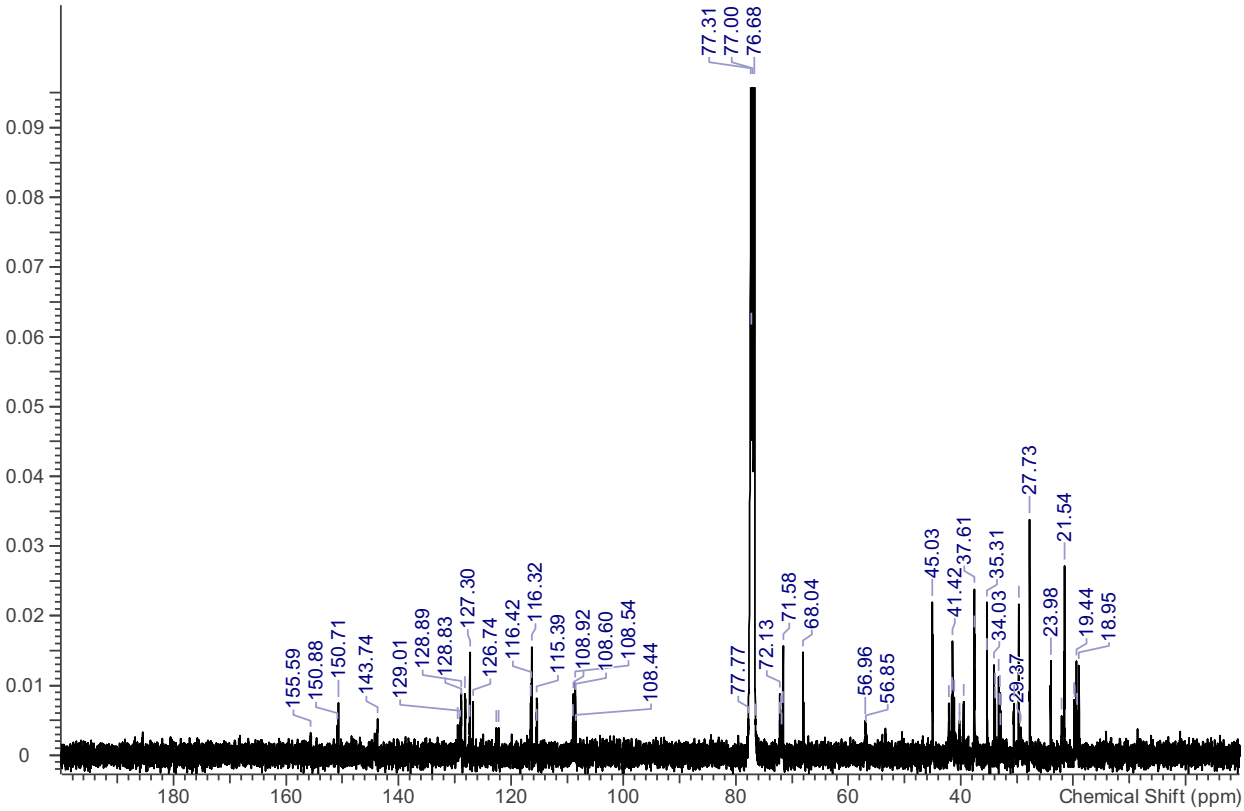

O2N
O
O
O
O
O
O
5h
1.96
2.11
1.00
1.01
21.27
Chemical Shift (ppm)

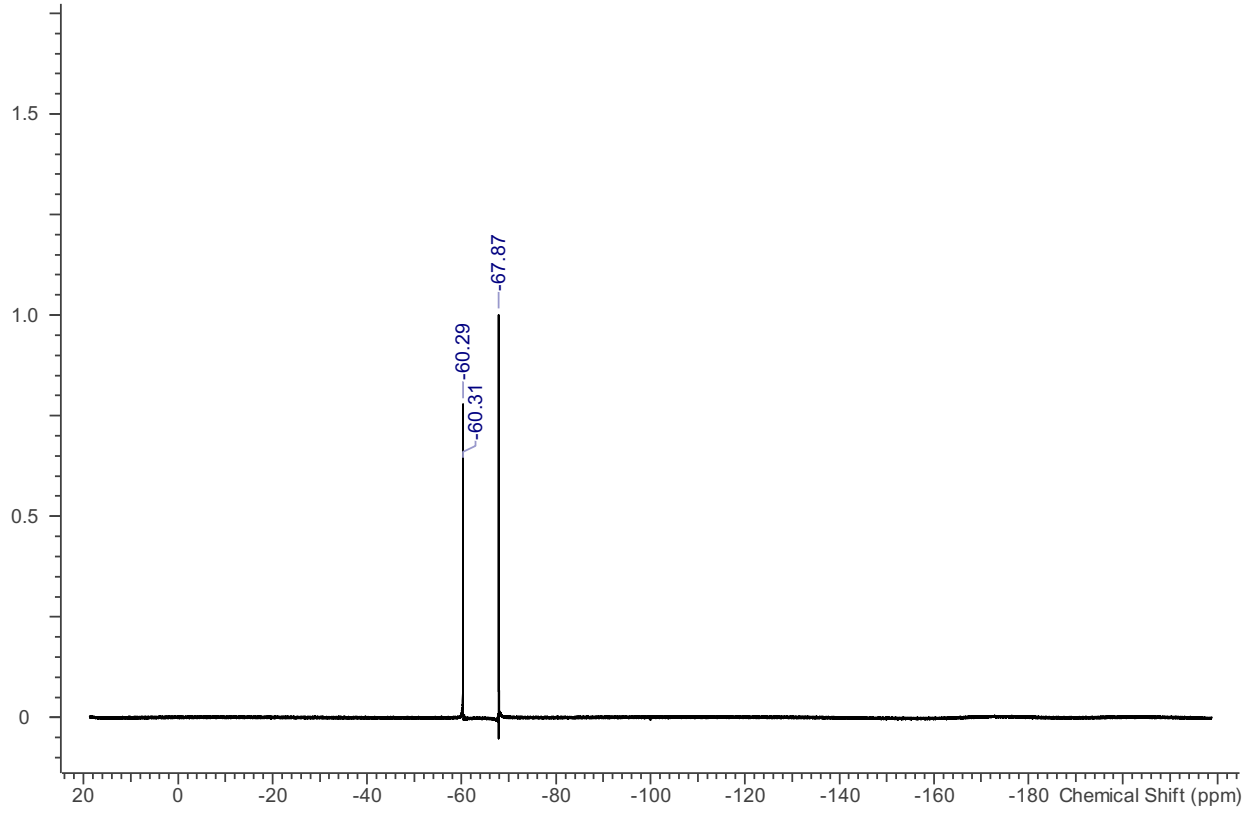

155.49
151.53
145.27
125.23
121.68
111.93
108.14
77.31
77.00
76.68
76.18
39.62
36.21
36.08
30.01
29.59
29.41
29.32
29.27
19.51
Chemical Shift (ppm)

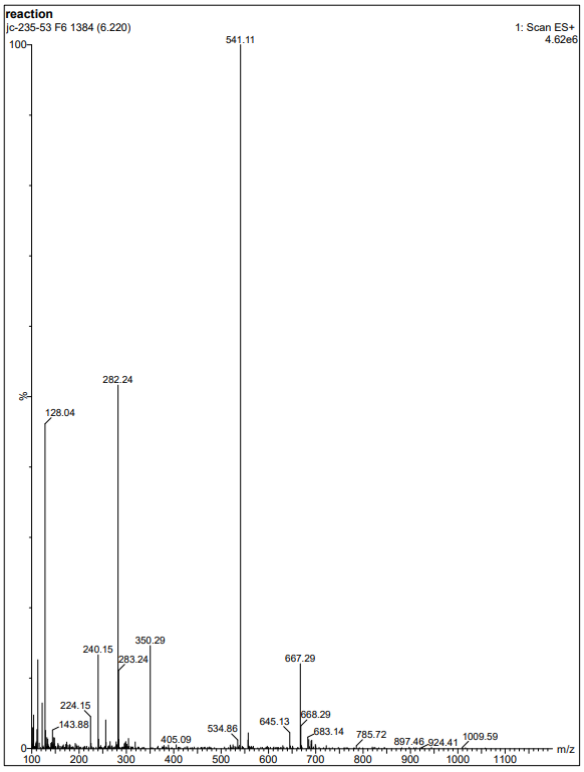

O2N
O
O
O
O
O
O
5r
2.05
1.94
1.00
1.26
1.26
6.34
6.45
2.29
1.08
8.91
Chemical Shift (ppm)

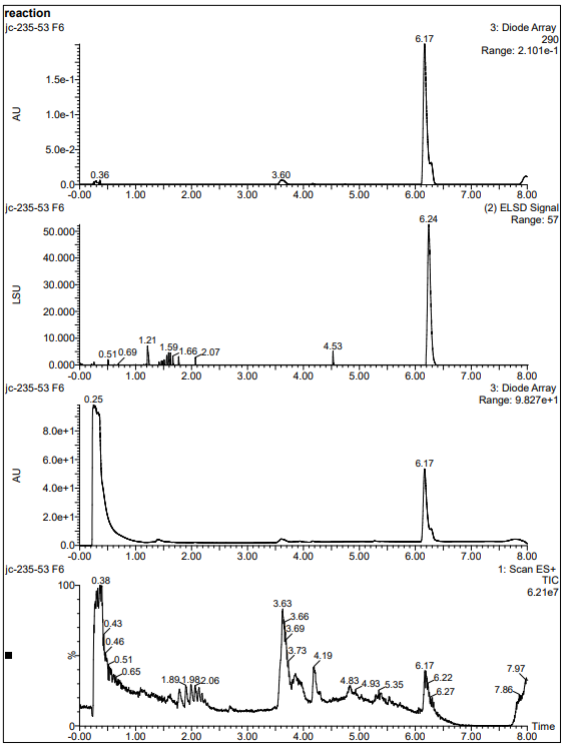

155.51
151.52
145.30
125.25
121.69
109.50
108.52
77.31
77.00
76.68
76.19
47.10
34.49
34.29
33.30
32.27
27.62
27.52
24.50
24.40
19.55
Chemical Shift (ppm)

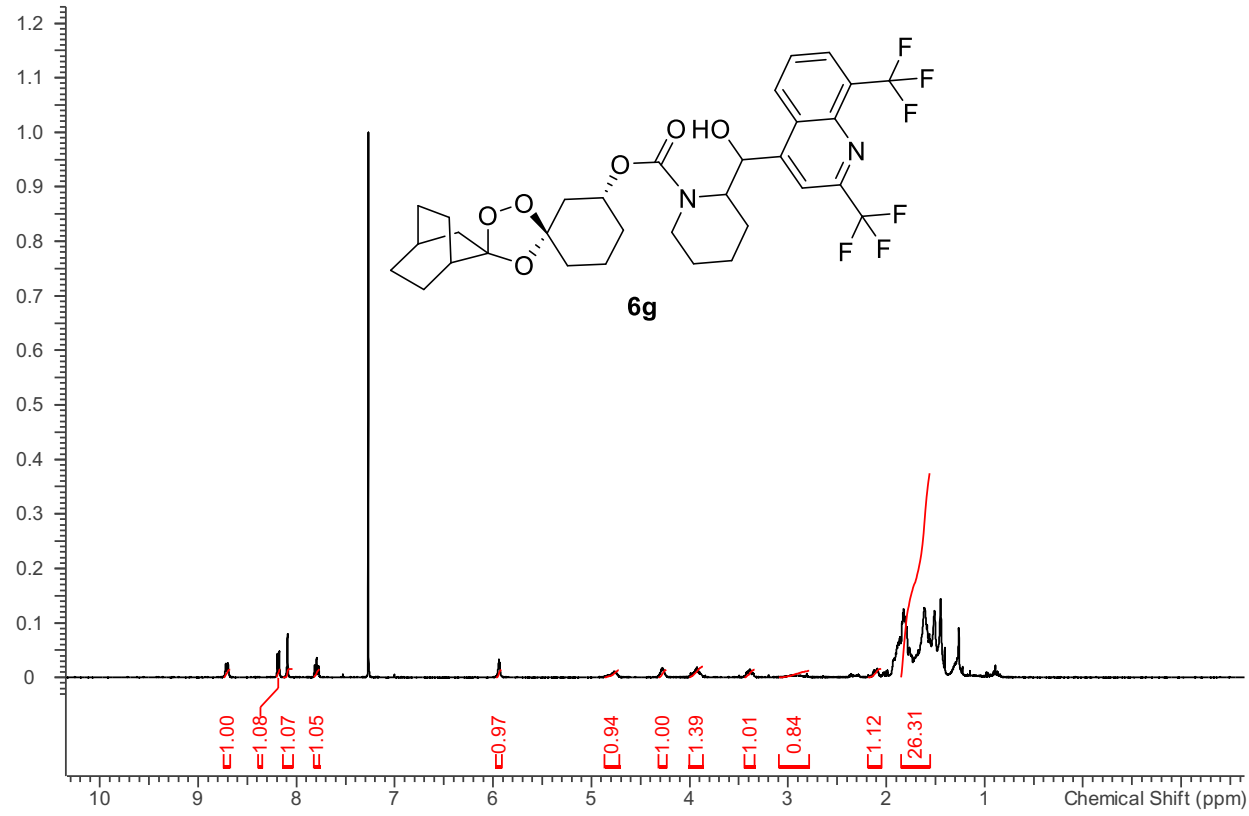

6f
1.00
1.21
0.98
1.06
0.95
0.85
1.13
1.64
1.13
0.97
3.10
21.87
Chemical Shift (ppm)

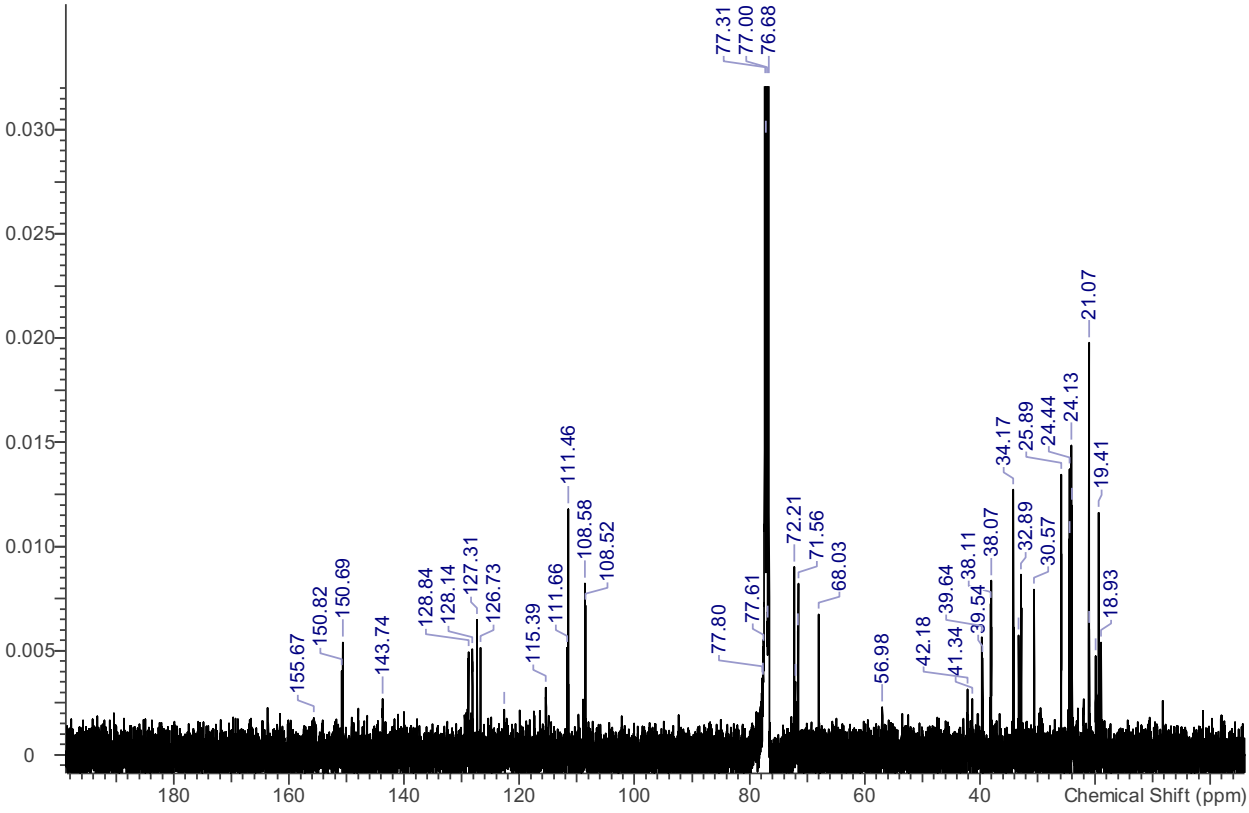

77.31
77.00
76.68
155.59
150.88
150.71
143.74
129.01
128.89
128.83
127.30
126.74
116.42
116.32
115.39
108.92
108.60
108.54
108.44
77.77
72.13
71.58
68.04
56.96
56.85
45.03
41.42
37.61
35.31
34.03
29.37
27.73
23.98
21.54
19.44
18.95
Chemical Shift (ppm)

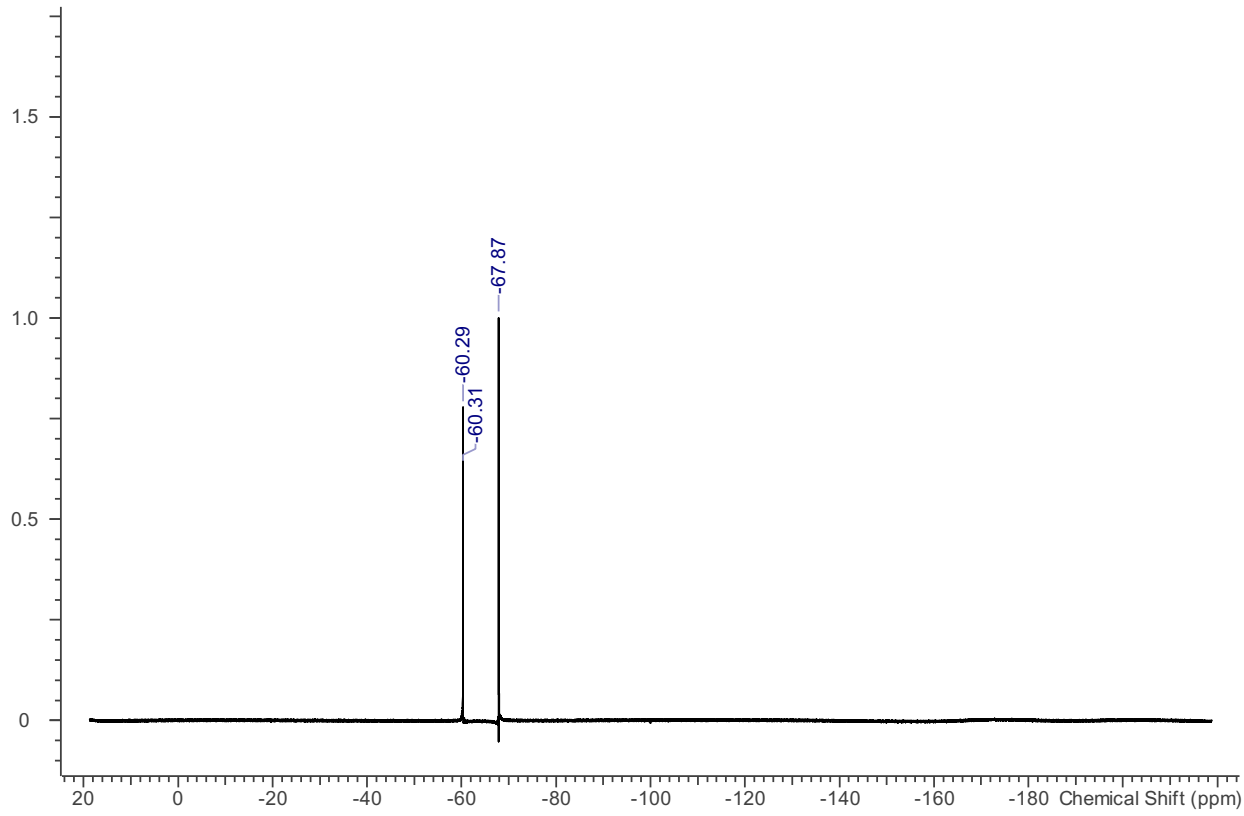

-67.87
-60.29
-60.31
Chemical Shift (ppm)

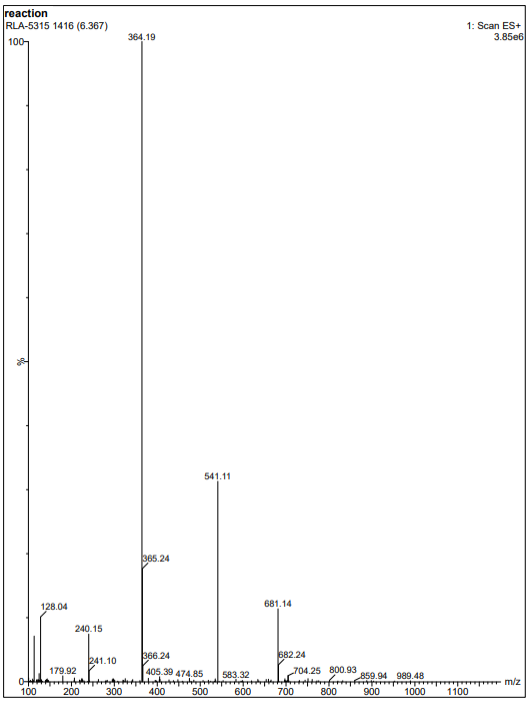

reaction
jc-235-53 F6 1384 (6.220)
1: Scan ES+
4.62e6
541.11
282.24
128.04
m/z

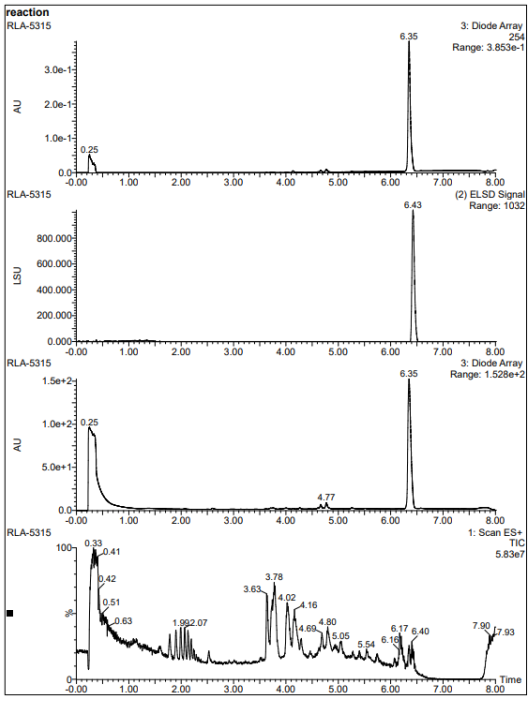

reaction
jc-235-53 F6
3: Diode Array
Range: 2.101e-1
6.17
AU
(2) ELSD Signal
Range: 57
6.24
LSU
3: Diode Array
Range: 9.827e+1
0.25
1: Scan ES+
TIC
6.21e7
Time

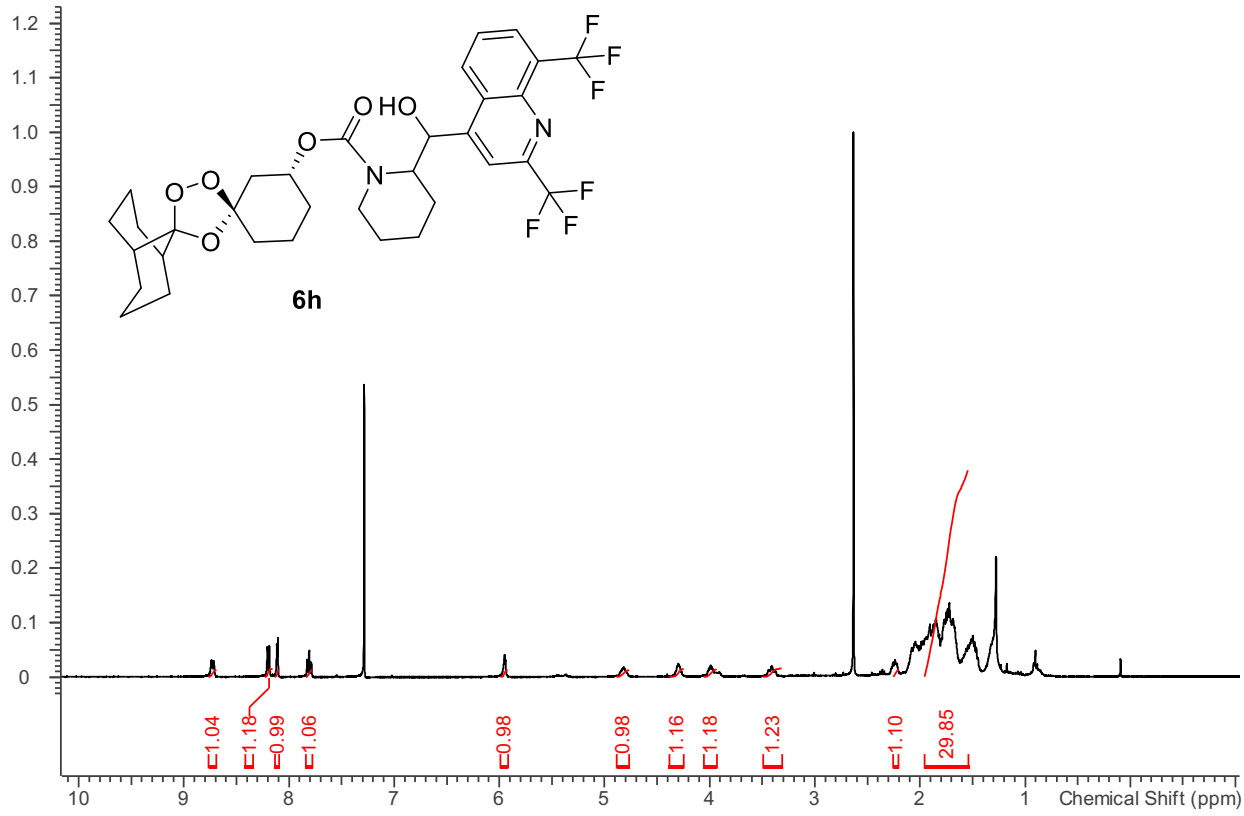

6g
Chemical Shift (ppm)

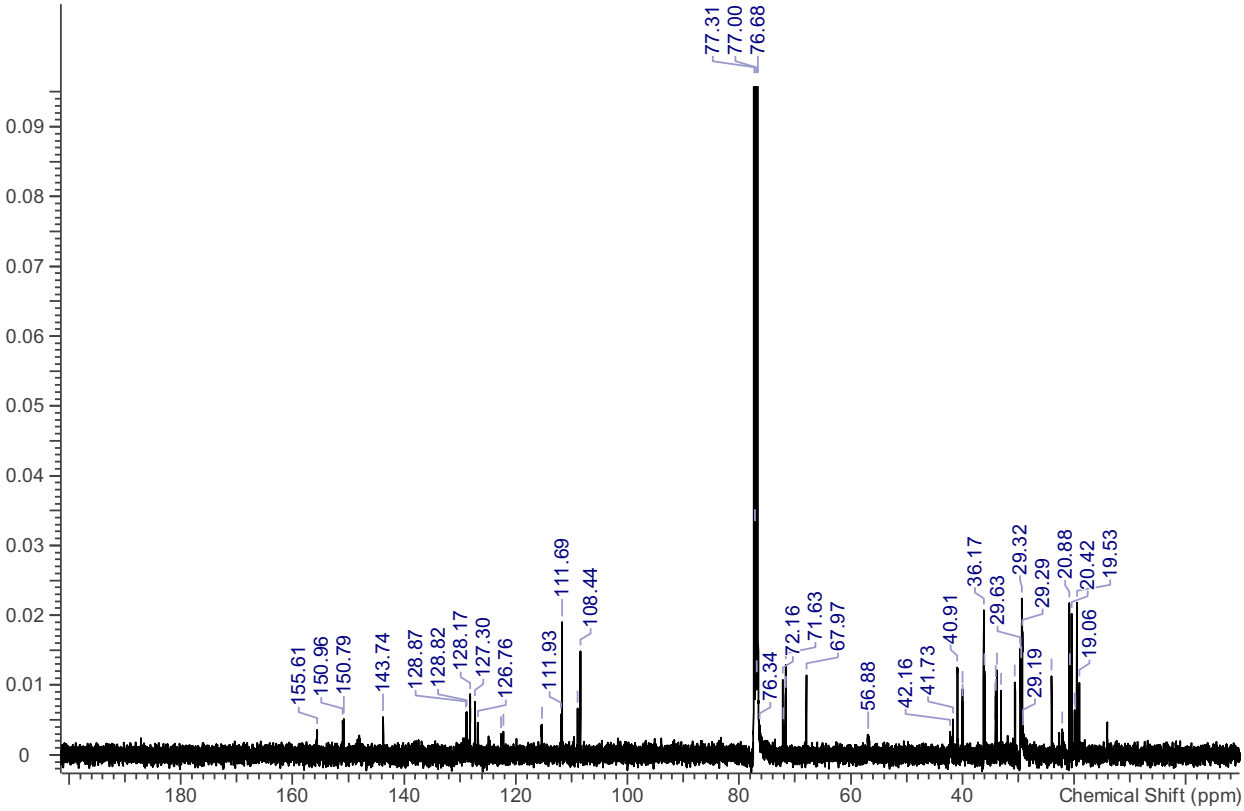

Chemical Shift (ppm)

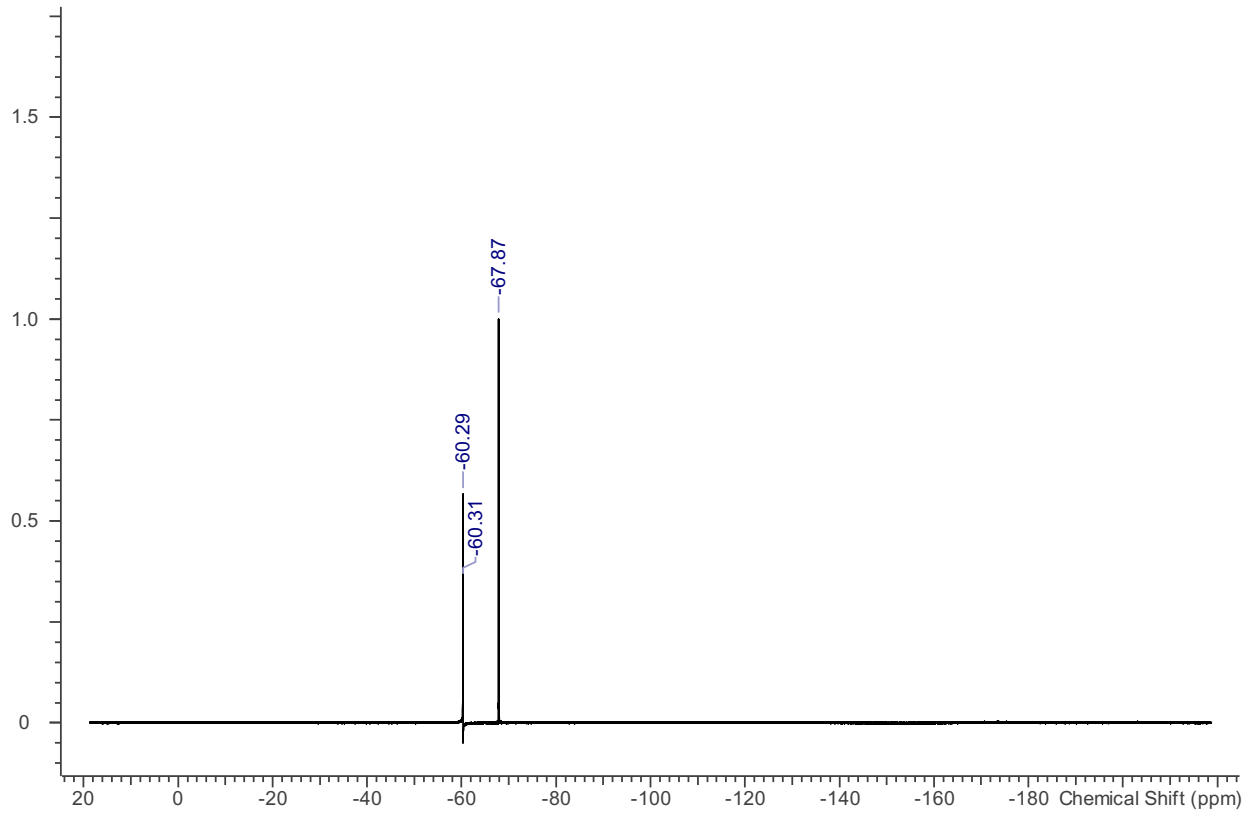

-67.87
-60.29
-60.31
Chemical Shift (ppm)

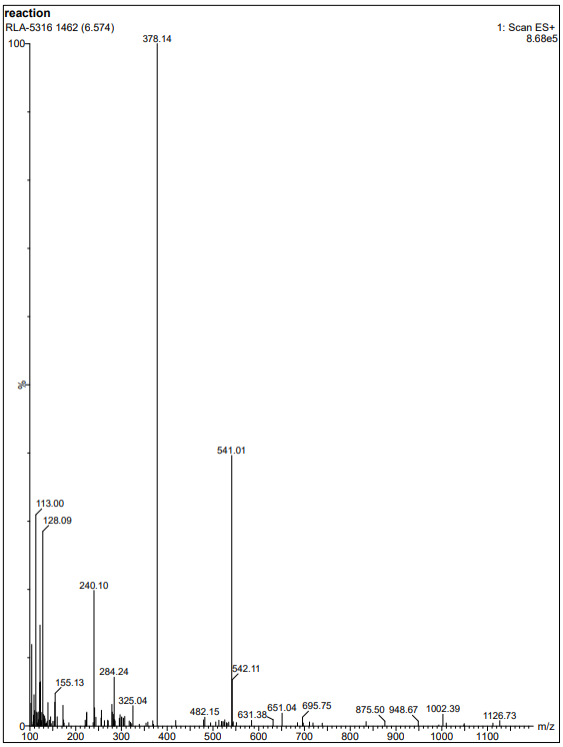

reaction
RLA-5315 1416 (6.367)
1: Scan ES+
3.85e6
364.19
541.11
365.24
128.04
681.14
240.15
241.10
366.24
682.24
179.92
405.39
474.85
583.32
704.25
800.93
859.94
989.48
m/z

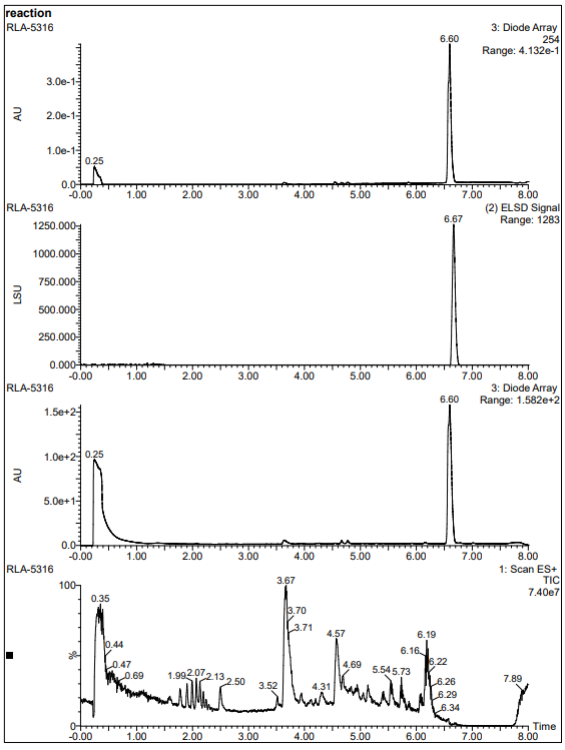

reaction
RLA-5315
3: Diode Array
254
Range: 3.853e-1
6.35
0.25
AU
RLA-5315
(2) ELSD Signal
Range: 1032
6.43
LSU
RLA-5315
3: Diode Array
Range: 1.528e+2
6.35
0.25
4.77
AU
RLA-5315
1: Scan ES+
TIC
5.83e7
0.33
0.41
0.42
0.51
0.63
1.99
2.07
3.63
3.78
4.02
4.16
4.69
4.80
5.05
5.54
6.16
6.17
6.40
7.90
7.93
Time

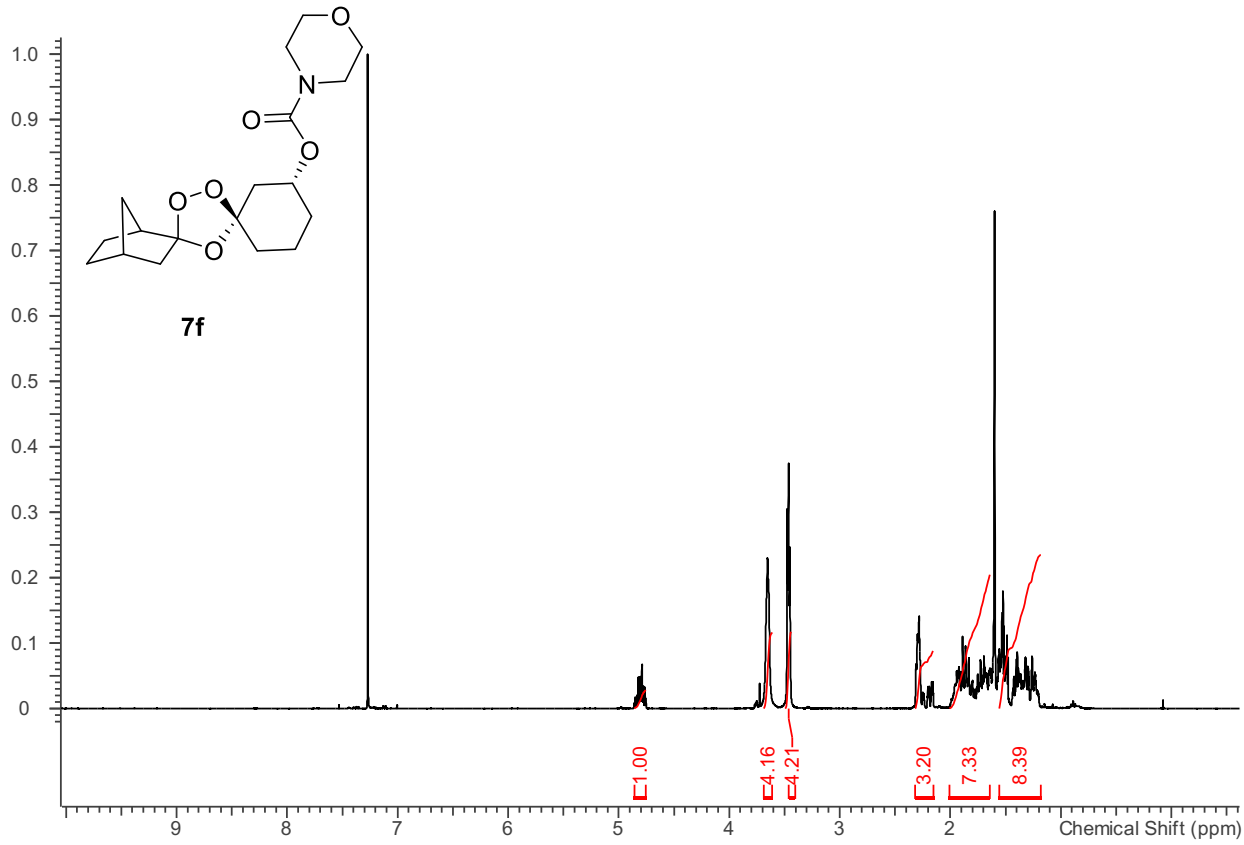

6h
1.04
1.18
0.99
1.06
0.98
0.98
1.16
1.18
1.23
1.10
29.85
Chemical Shift (ppm)

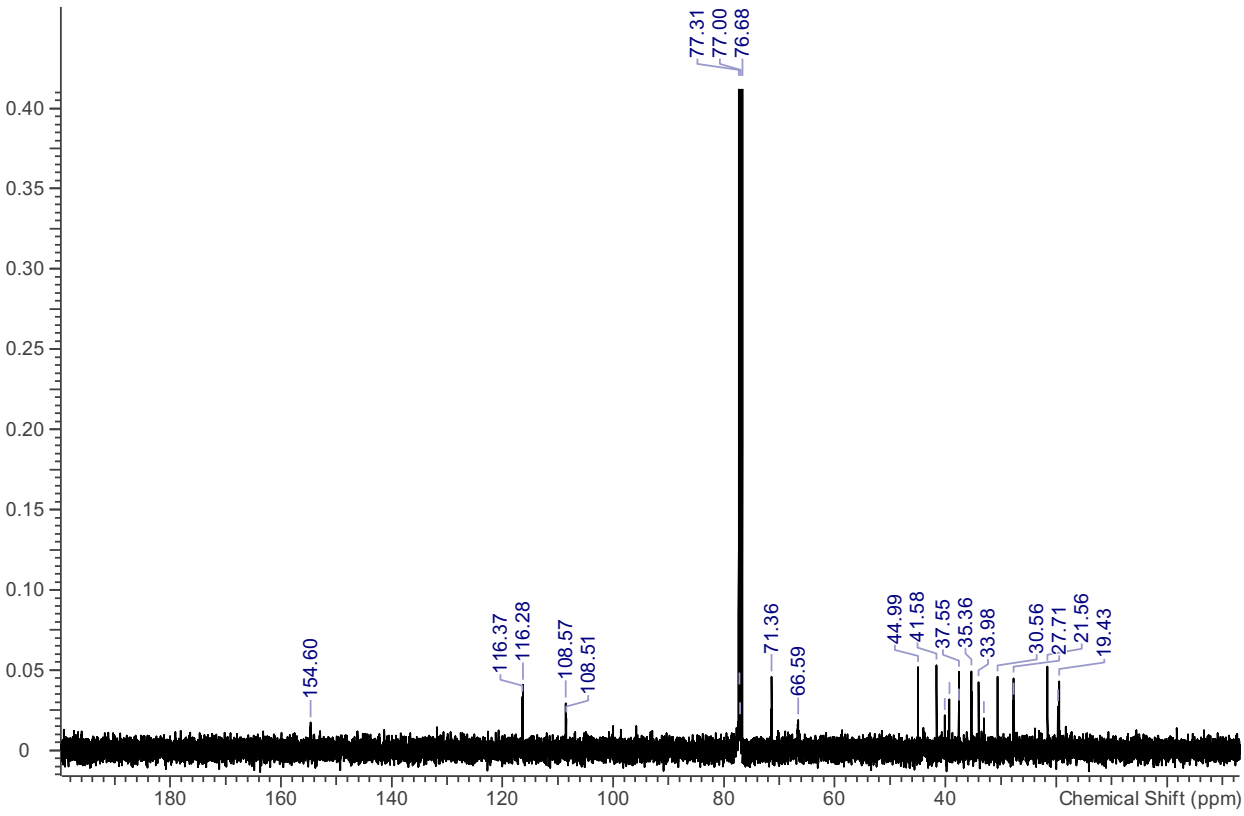

77.31
77.00
76.68
155.61
150.96
150.79
143.74
128.87
128.82
128.17
127.30
126.76
111.93
111.69
108.44
76.34
72.16
71.63
67.97
56.88
42.16
41.73
40.91
36.17
29.63
29.32
29.29
29.19
20.88
20.42
19.53
19.06
Chemical Shift (ppm)

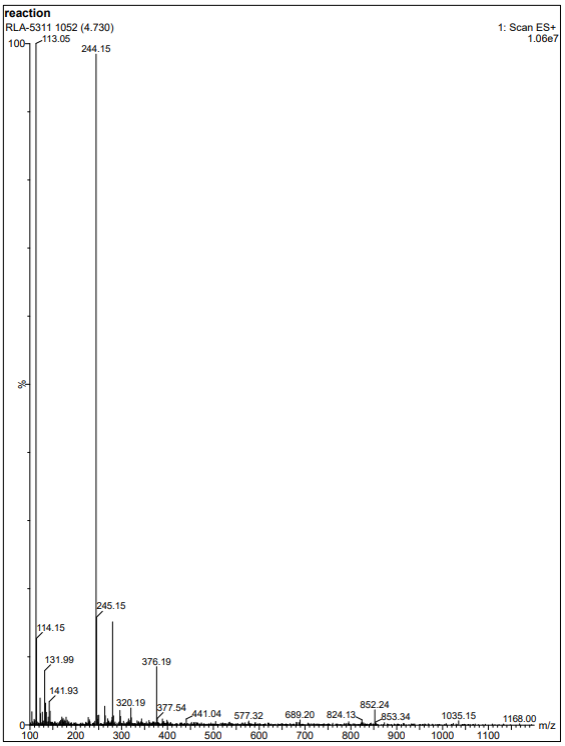

1.5
1.0
0.5
0
-67.87
-60.29
-60.31
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
Chemical Shift (ppm)

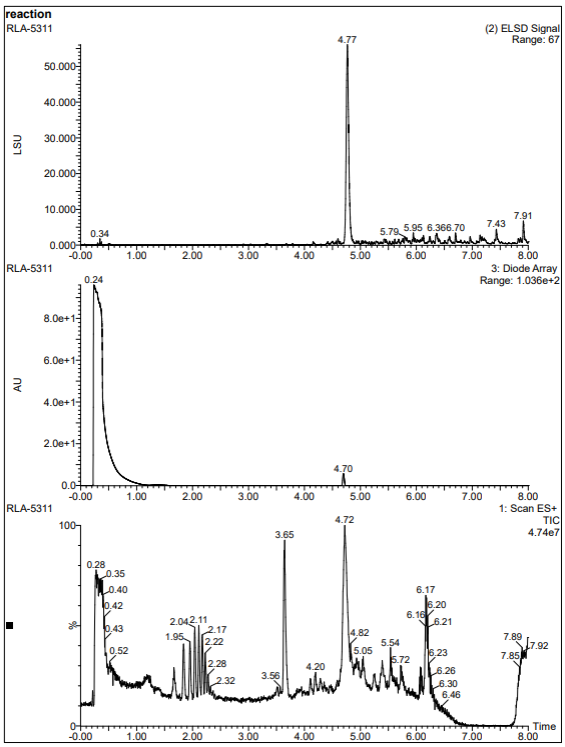

reaction
RLA-5316 1462 (6.574)
1: Scan ES+
8.68e5
100
%
0
378.14
541.01
113.00
128.09
240.10
155.13
284.24
325.04
542.11
482.15
631.38
651.04
695.75
875.50
948.67
1002.39
1126.73
100
200
300
400
500
600
700
800
900
1000
1100
m/z

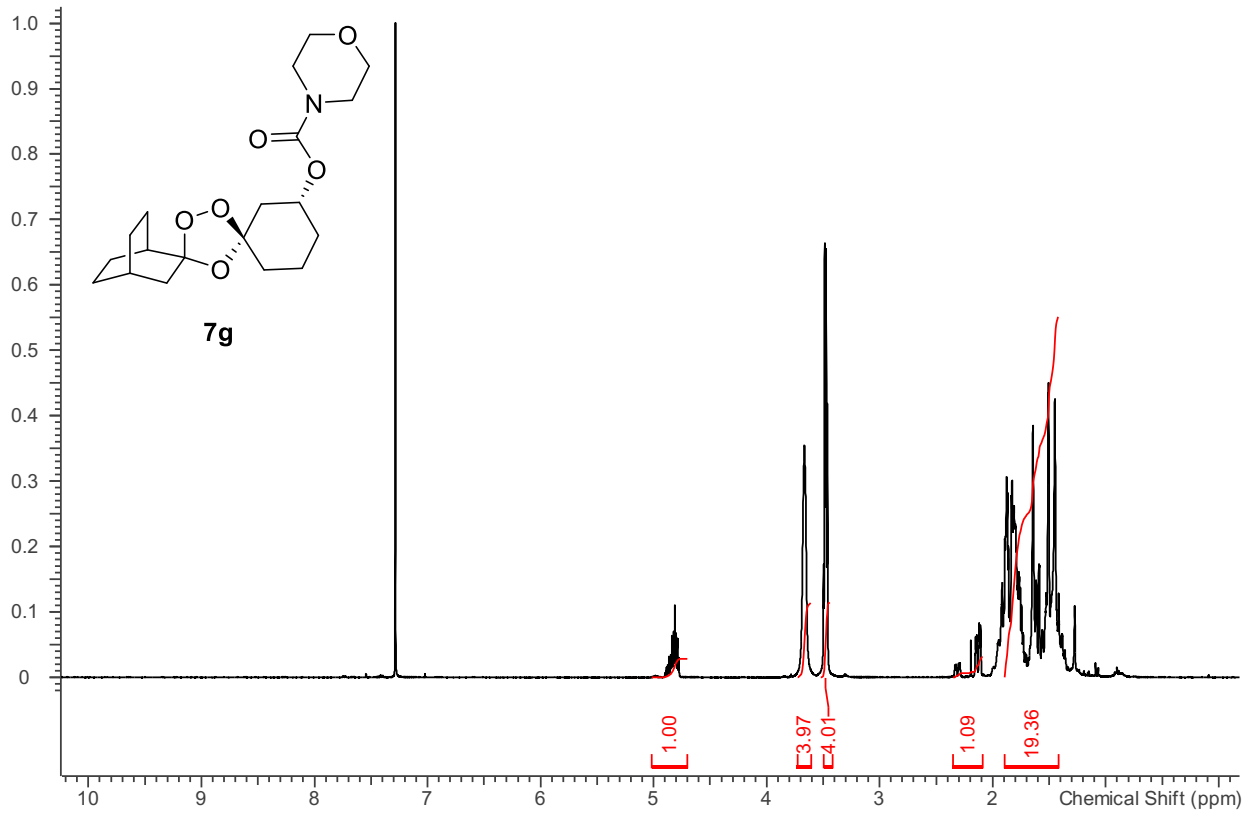

reaction
RLA-5316
3: Diode Array
254
Range: 4.132e-1
6.60
AU
3.0e-1
2.0e-1
1.0e-1
0.0
0.25
RLA-5316
(2) ELSD Signal
Range: 1283
6.67
LSU
1250.000
1000.000
750.000
500.000
250.000
0.000
RLA-5316
3: Diode Array
Range: 1.582e+2
6.60
AU
1.5e+2
1.0e+2
5.0e+1
0.0
0.25
RLA-5316
1: Scan ES+
TIC
7.40e7
100
%
0
3.67
0.35
3.70
3.71
0.44
4.57
0.47
0.69
4.69
6.19
6.16
1.99
2.07
2.13
2.50
3.52
4.31
5.54
5.73
6.22
6.26
6.29
6.34
7.89
Time
-0.00
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00

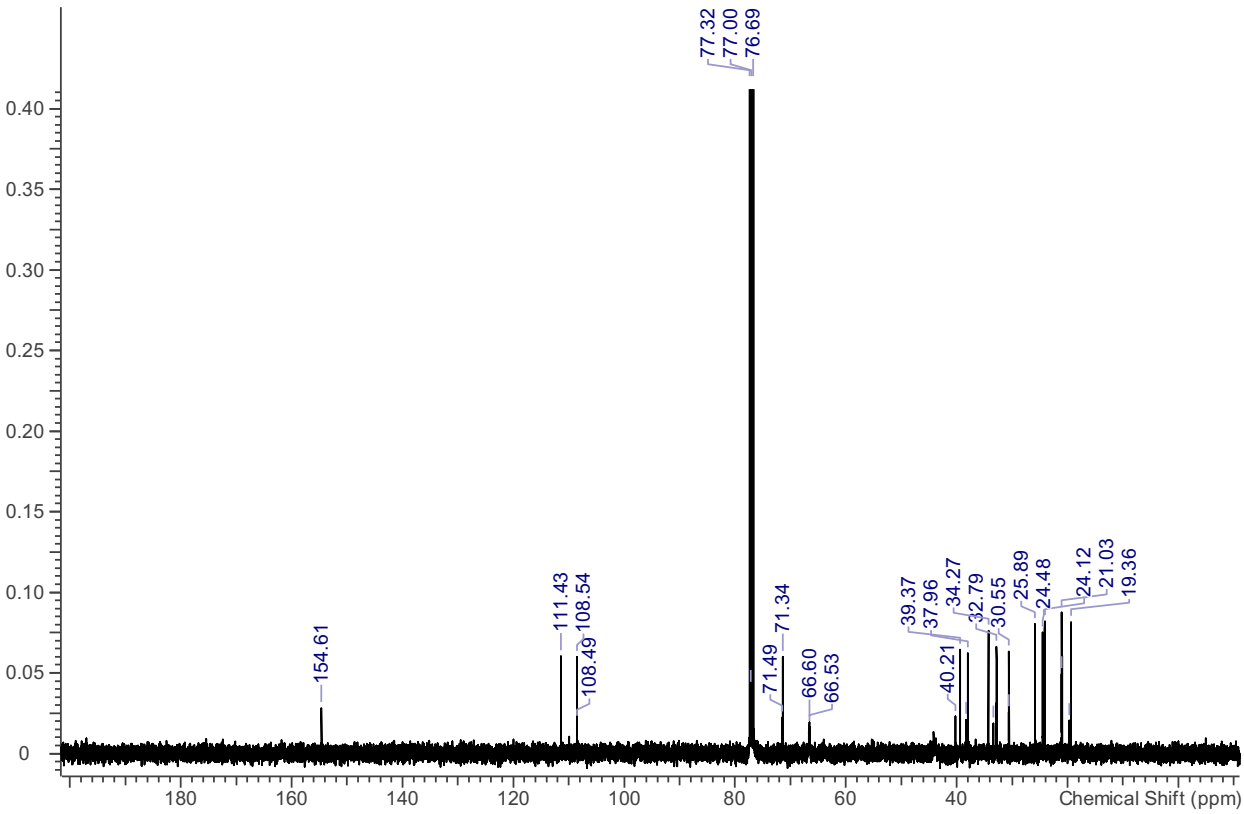

7f
1.00
4.16
4.21
3.20
7.33
8.39
Chemical Shift (ppm)

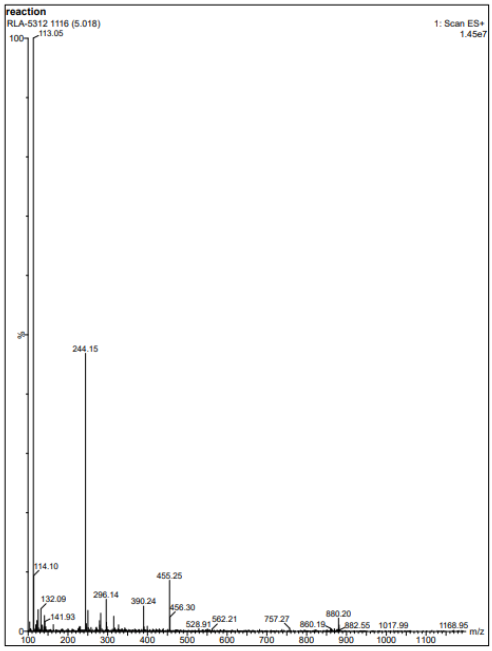

77.31
77.00
76.68
154.60
116.37
116.28
108.57
108.51
71.36
66.59
44.99
41.58
37.55
35.36
33.98
30.56
27.71
21.56
19.43
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
180
160
140
120
100
80
60
40
Chemical Shift (ppm)

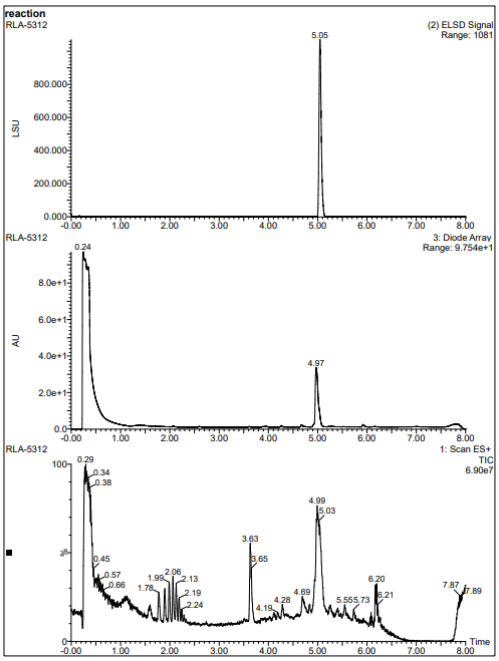

reaction
RLA-5311 1052 (4.730)
1: Scan ES+
1.06e7
100
%
0
113.05
244.15
245.15
114.15
131.99
141.93
320.19
376.19
377.54
441.04
577.32
689.20
824.13
852.24
853.34
1035.15
1168.00
100 200 300 400 500 600 700 800 900 1000 1100
m/z

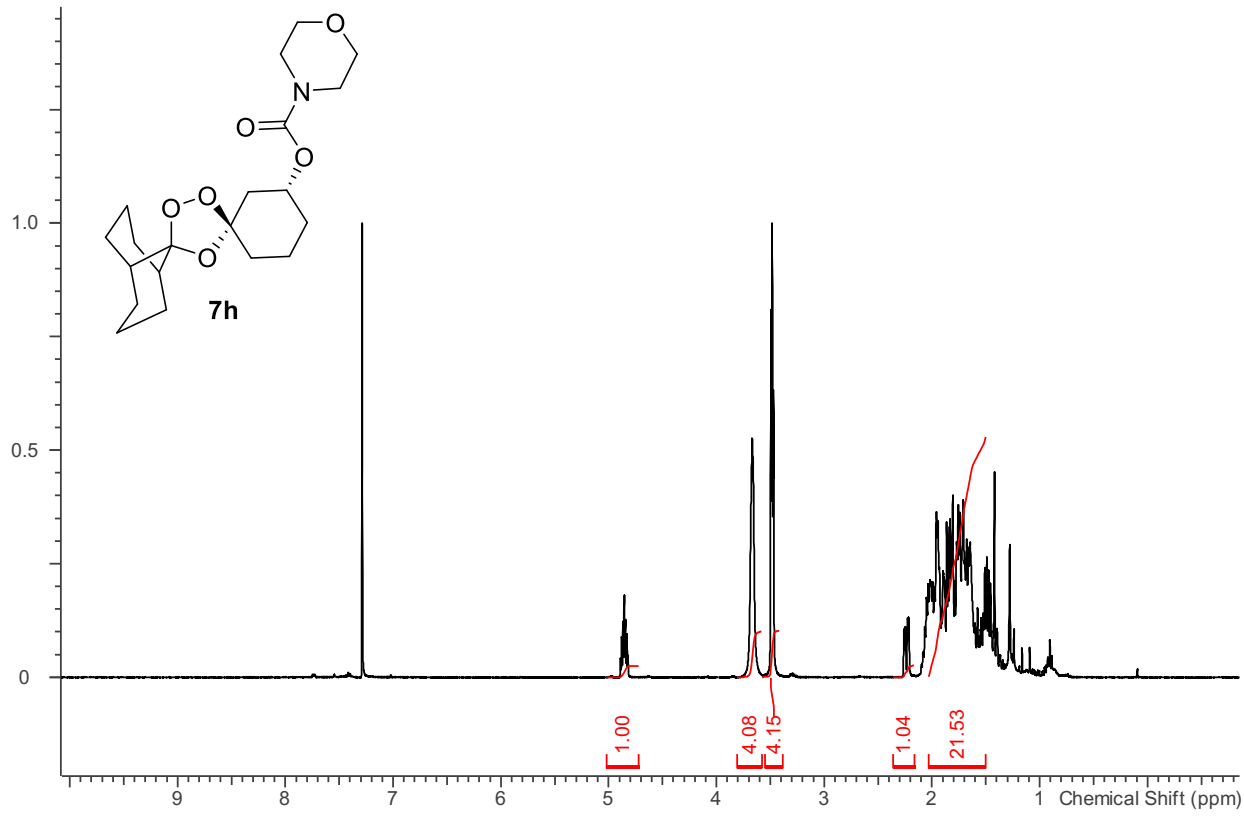

reaction
RLA-5311
(2) ELSD Signal
Range: 67
LSU
50.000
40.000
30.000
20.000
10.000
0.000
4.77
0.34
5.79
5.95
6.36
6.70
7.43
7.91
-0.00 1.00 2.00 3.00 4.00 5.00 6.00 7.00 8.00
RLA-5311
3: Diode Array
Range: 1.036e+2
AU
8.0e+1
6.0e+1
4.0e+1
2.0e+1
0.0
0.24
4.70
-0.00 1.00 2.00 3.00 4.00 5.00 6.00 7.00 8.00
RLA-5311
1: Scan ES+
TIC
4.74e7
100
%
0
0.28
0.35
0.40
0.42
0.43
0.52
1.95
2.04
2.11
2.17
2.22
2.28
2.32
3.56
3.65
4.20
4.72
4.82
5.05
5.54
5.72
6.17
6.20
6.18
6.21
6.23
6.26
6.30
6.46
7.89
7.85
7.92
-0.00 1.00 2.00 3.00 4.00 5.00 6.00 7.00 8.00
Time

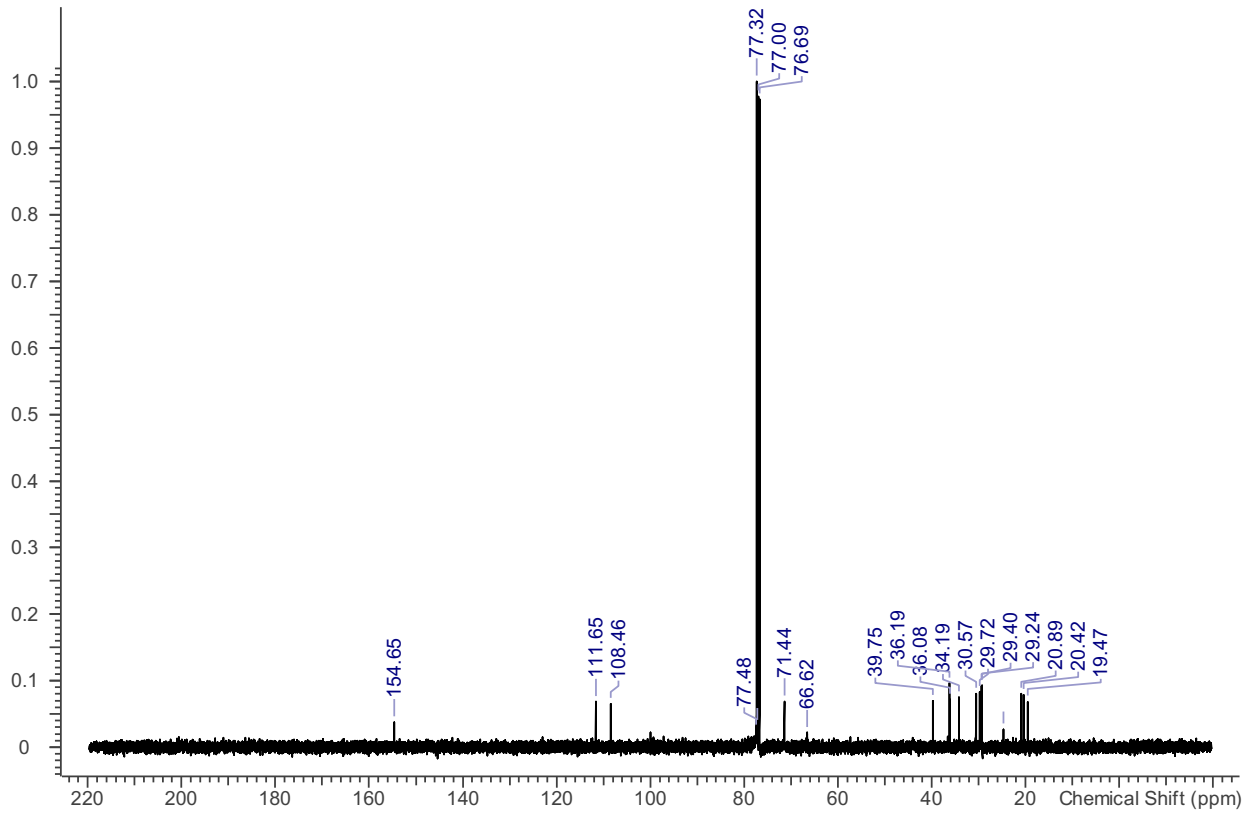

7g
1.00
3.97
4.01
1.09
19.36
Chemical Shift (ppm)

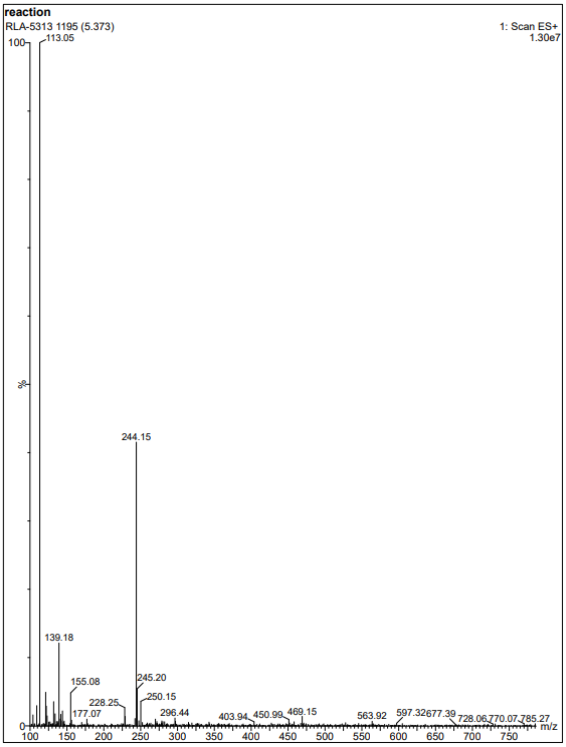

77.32
77.00
76.69
154.61
111.43
108.54
108.49
71.49
71.34
66.60
66.53
40.21
39.37
37.96
34.27
32.79
30.55
25.89
24.48
24.12
21.03
19.36
Chemical Shift (ppm)

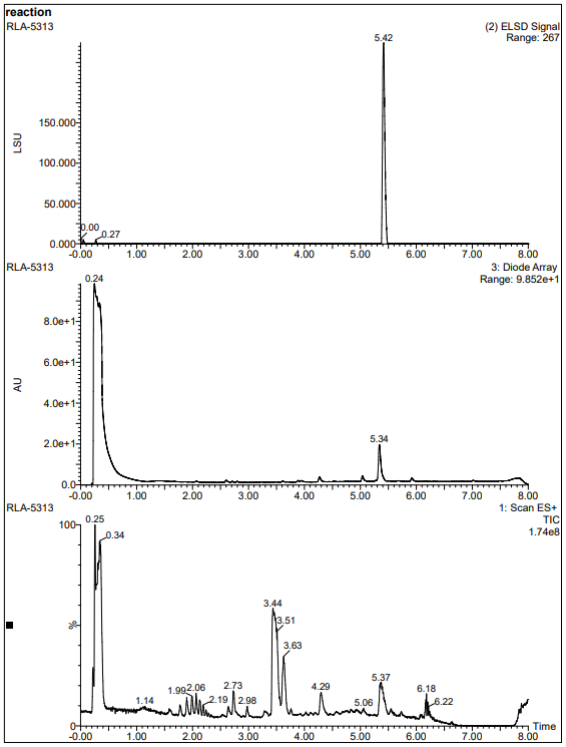

reaction
RLA-5312 1116 (5.018)
1: Scan ES+
1.45e7
113.05
244.15
114.10
132.09
141.93
296.14
390.24
455.25
456.30
528.97
562.21
757.27
860.19
880.20
882.55
1017.99
1168.95
m/z

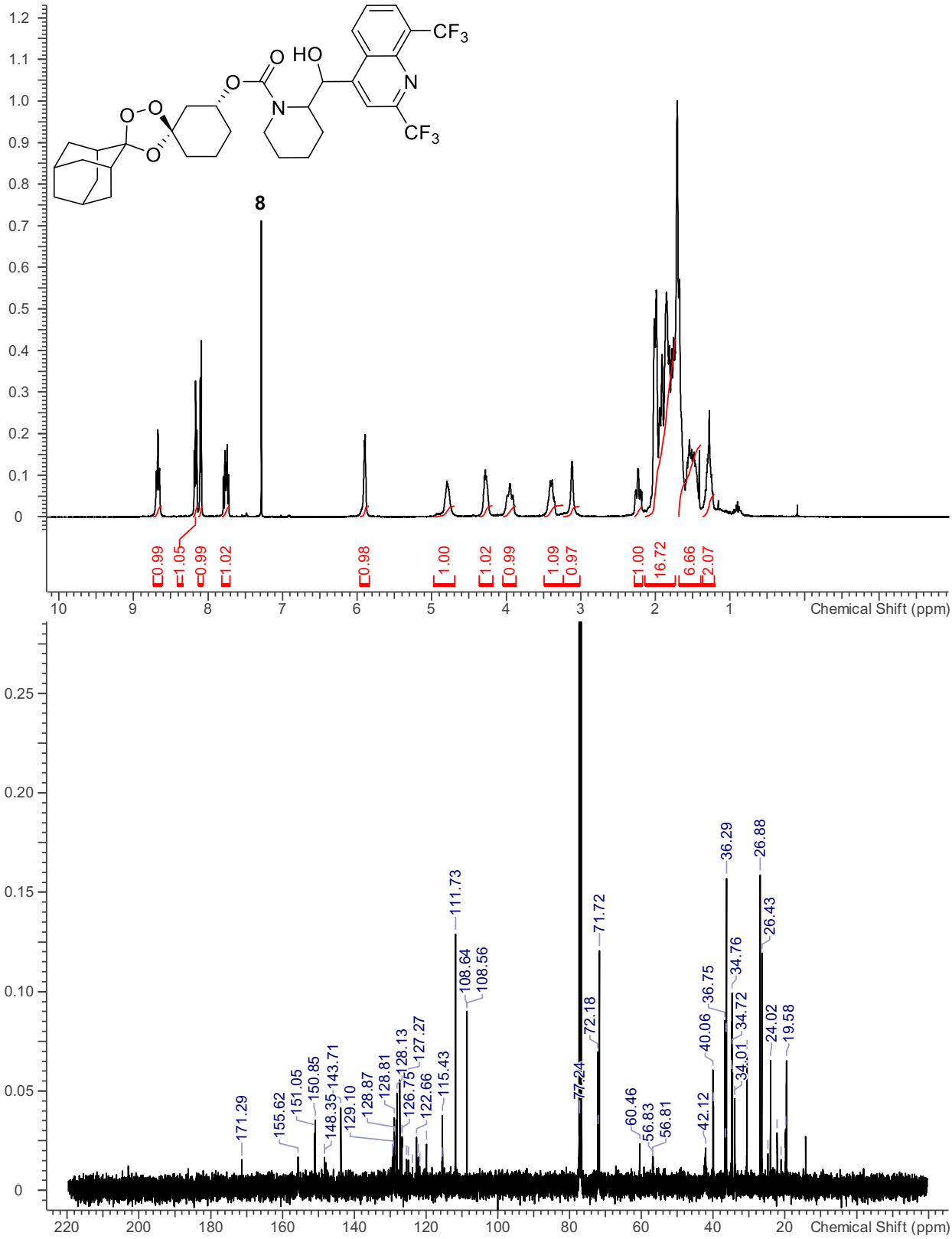

reaction
RLA-5312
(2) ELSD Signal
Range: 1081
5.05
LSU
RLA-5312
3: Diode Array
Range: 9.754e+1
0.24
4.97
AU
RLA-5312
1: Scan ES+
TIC
6.90e7
0.29
0.34
0.38
0.45
0.57
0.66
1.78
1.99
2.06
2.13
2.19
2.24
3.63
3.65
4.19
4.28
4.69
4.99
5.03
5.55
5.73
6.20
6.21
7.87
7.89
Time

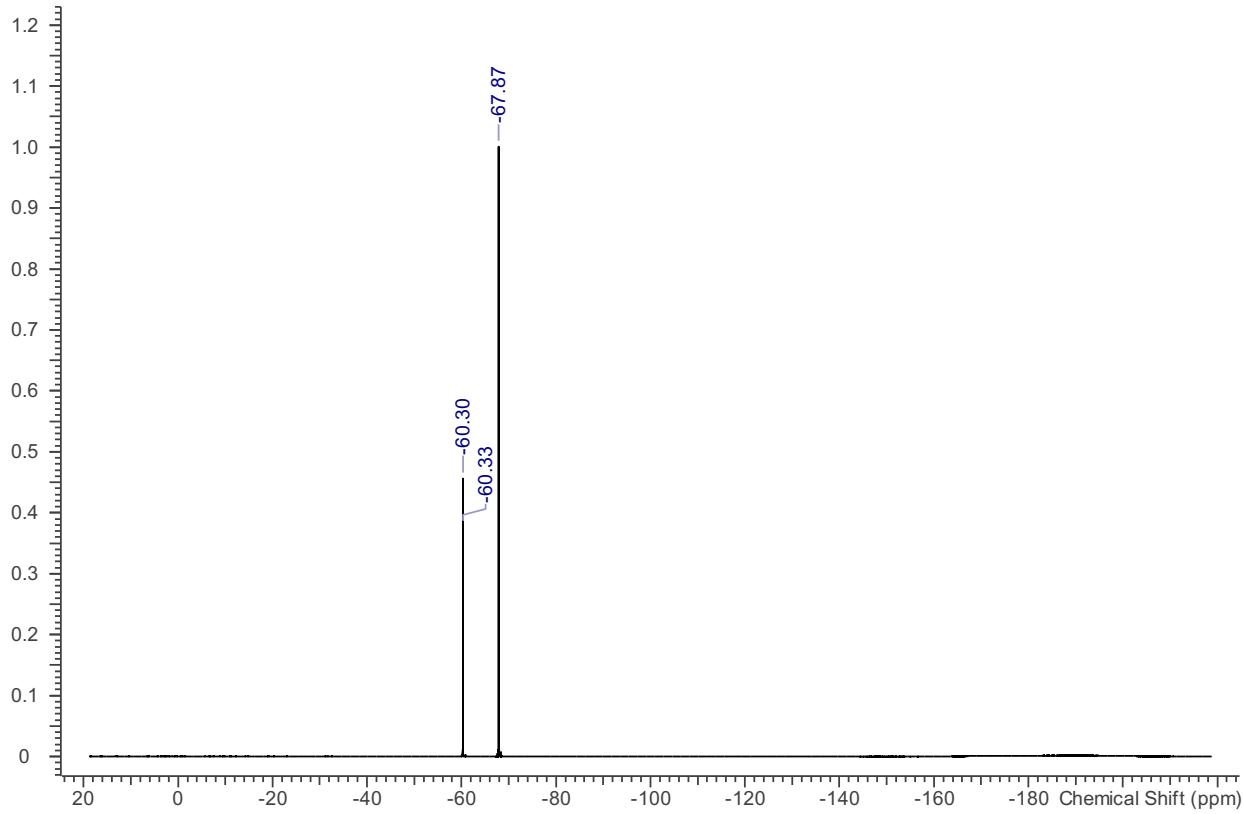

7h
1.00
4.08
4.15
1.04
21.53
Chemical Shift (ppm)

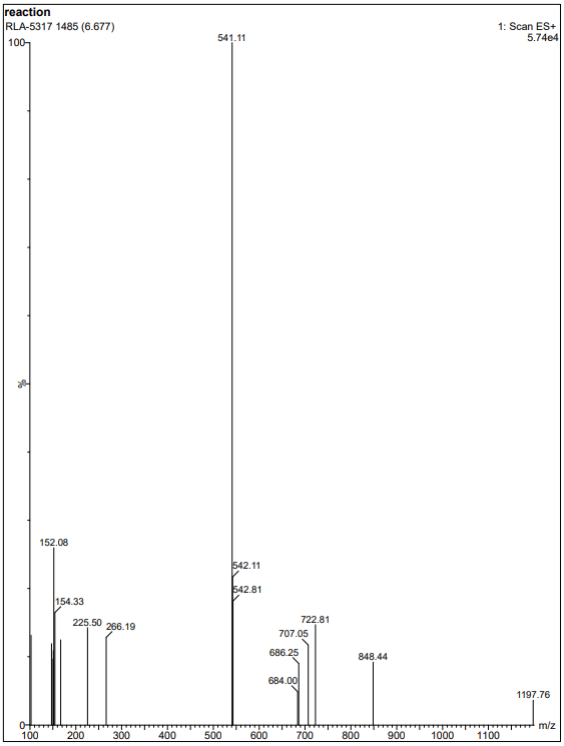

77.32
77.00
76.69
154.65
111.65
108.46
77.48
71.44
66.62
39.75
36.19
36.08
34.19
30.57
29.72
29.40
29.24
20.89
20.42
19.47
Chemical Shift (ppm)

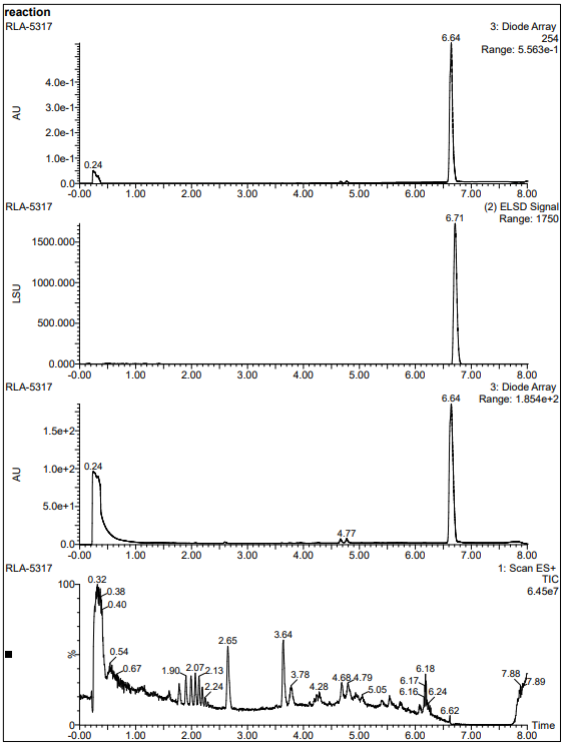

reaction
RLA-5313 1195 (5.373)
1: Scan ES+
1.30e7
113.05
244.15
139.18
155.08
245.20
228.25
250.15
177.07
296.44
403.94
450.99
469.15
563.92
597.32
677.39
728.06
770.07
785.27
m/z

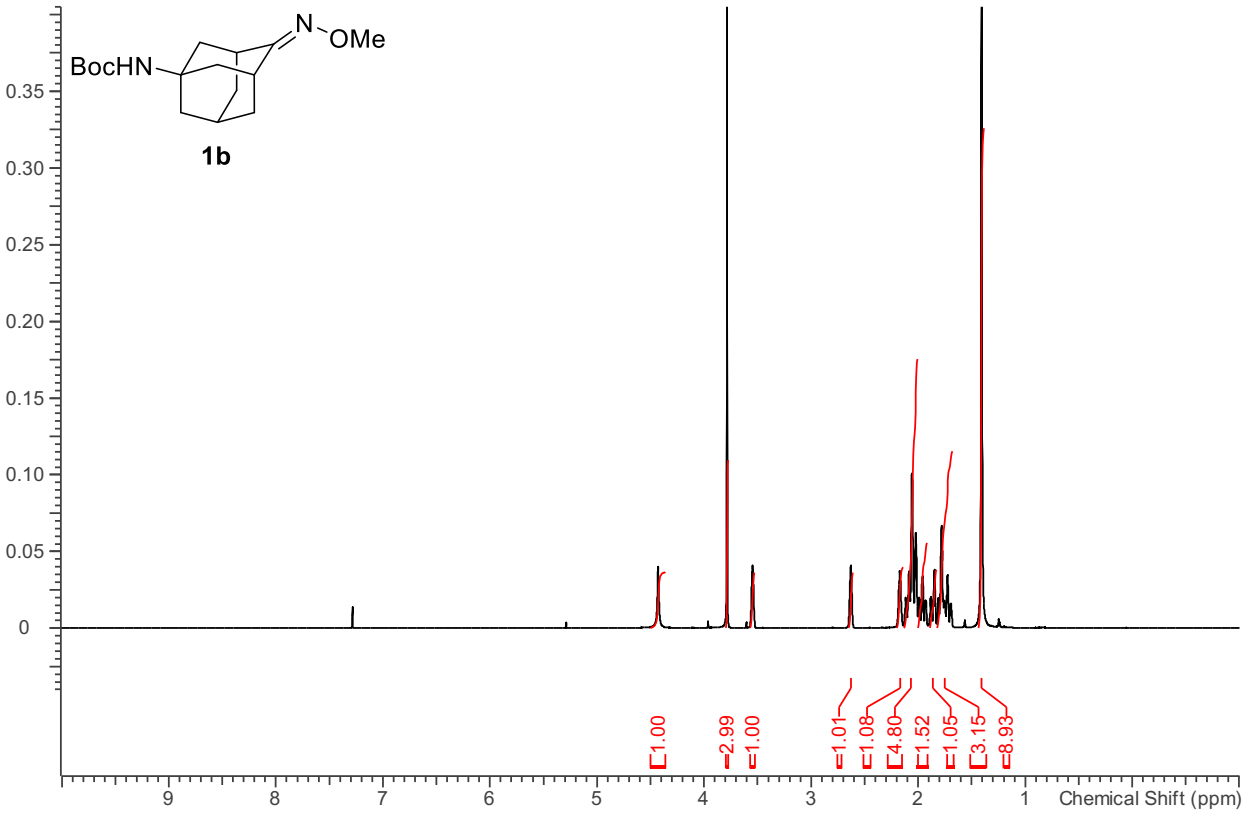

reaction
RLA-5313
(2) ELSD Signal
Range: 267
5.42
LSU
0.27
RLA-5313
3: Diode Array
Range: 9.852e+1
0.24
5.34
AU
RLA-5313
1: Scan ES+
TIC
1.74e8
0.25
0.34
3.44
3.51
3.63
1.14
1.99
2.06
2.19
2.73
2.98
4.29
5.06
5.37
6.18
6.22
Time

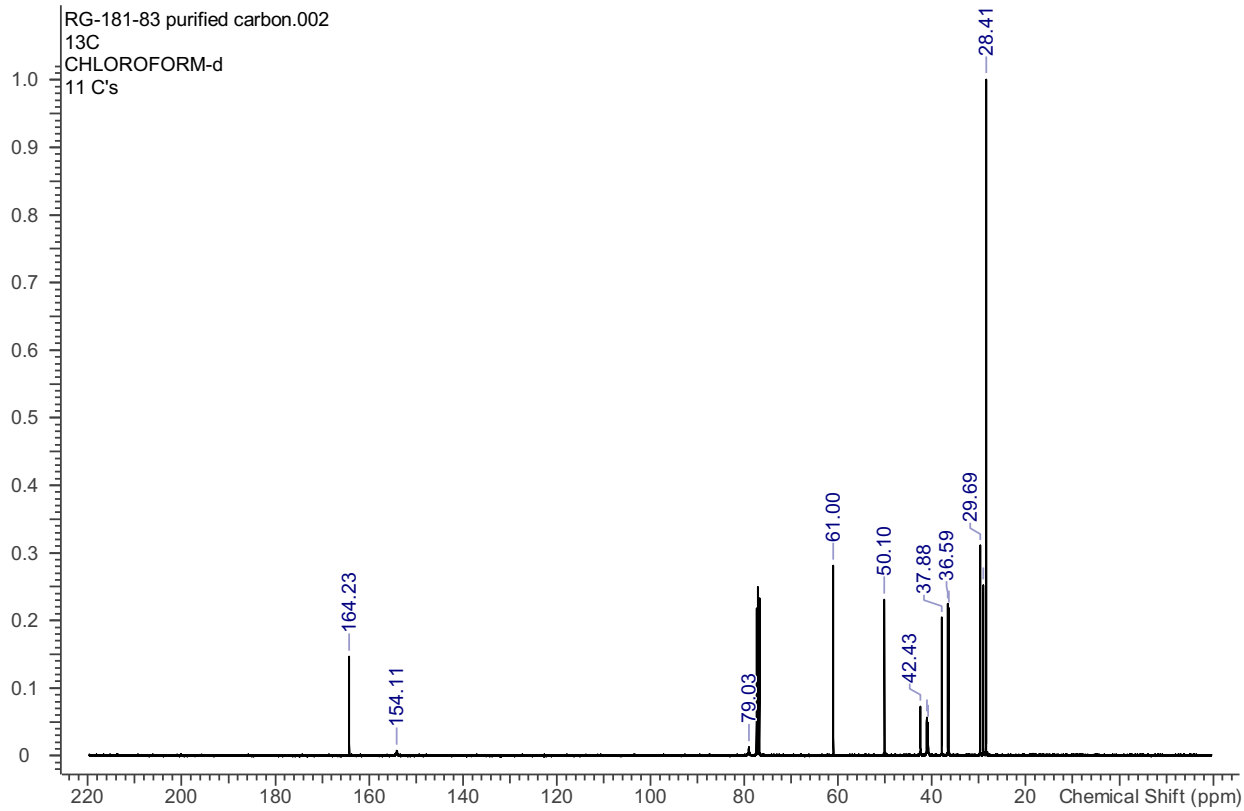

8
0.99
1.05
0.99
1.02
0.98
1.00
1.02
0.99
1.09
0.97
1.00
16.72
6.66
2.07
Chemical Shift (ppm)
171.29
155.62
151.05
150.85
148.35
143.71
129.10
128.87
128.81
128.13
126.75
127.27
122.66
115.43
111.73
108.64
108.56
77.24
72.18
71.72
60.46
56.83
56.81
42.12
40.06
36.75
36.29
34.76
34.72
34.01
26.88
26.43
24.02
19.58
Chemical Shift (ppm)

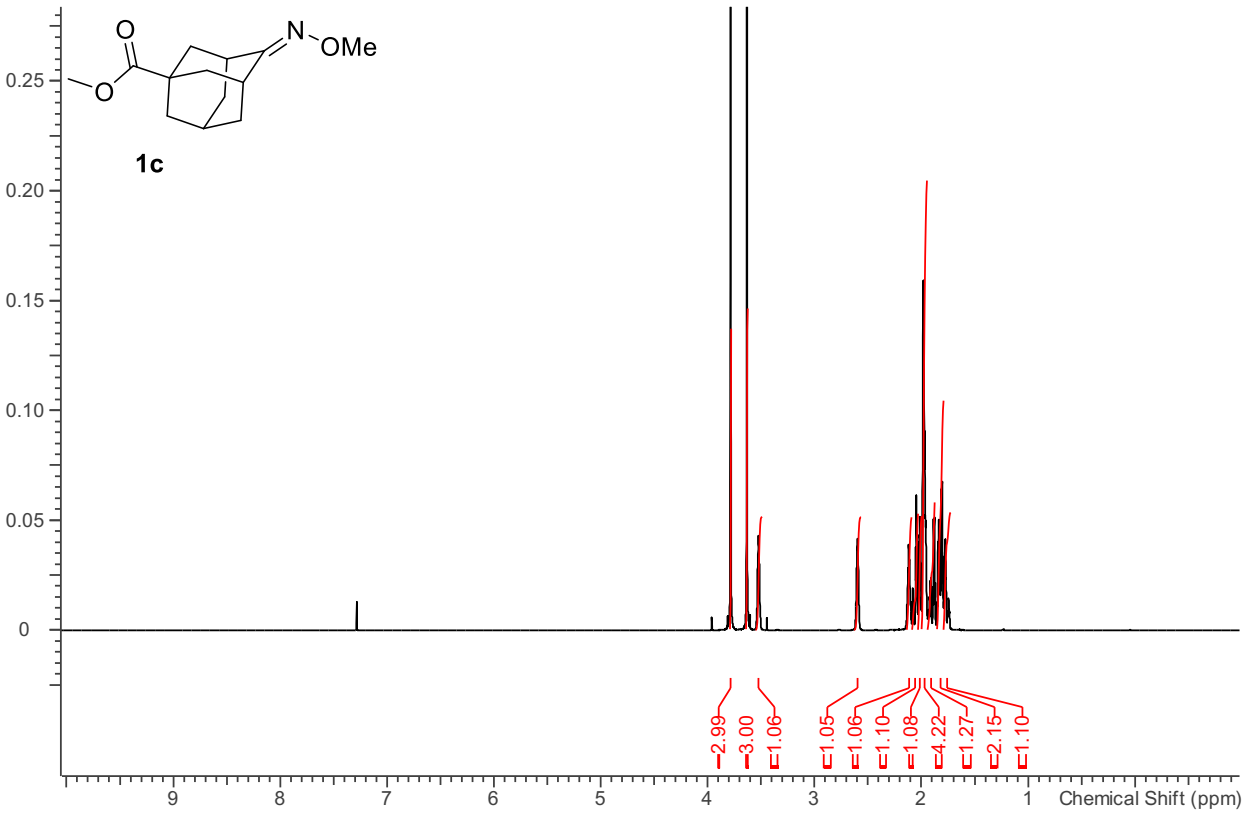

67.87
60.30
60.33
Chemical Shift (ppm)

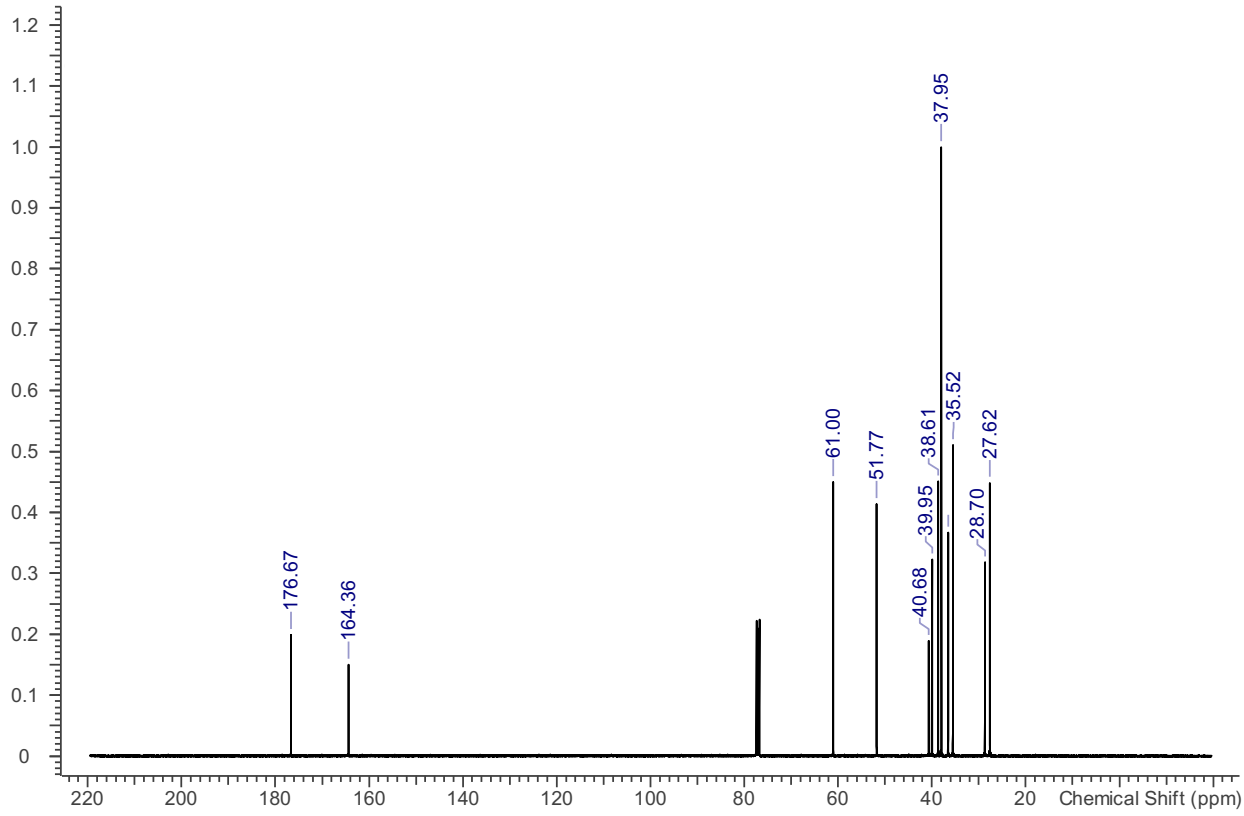

reaction
RLA-5317 1485 (6.677)
1: Scan ES+
5.74e4
541.11
152.08
154.33
225.50
266.19
542.11
542.81
707.05
722.81
686.25
684.00
848.44
1197.76
m/z

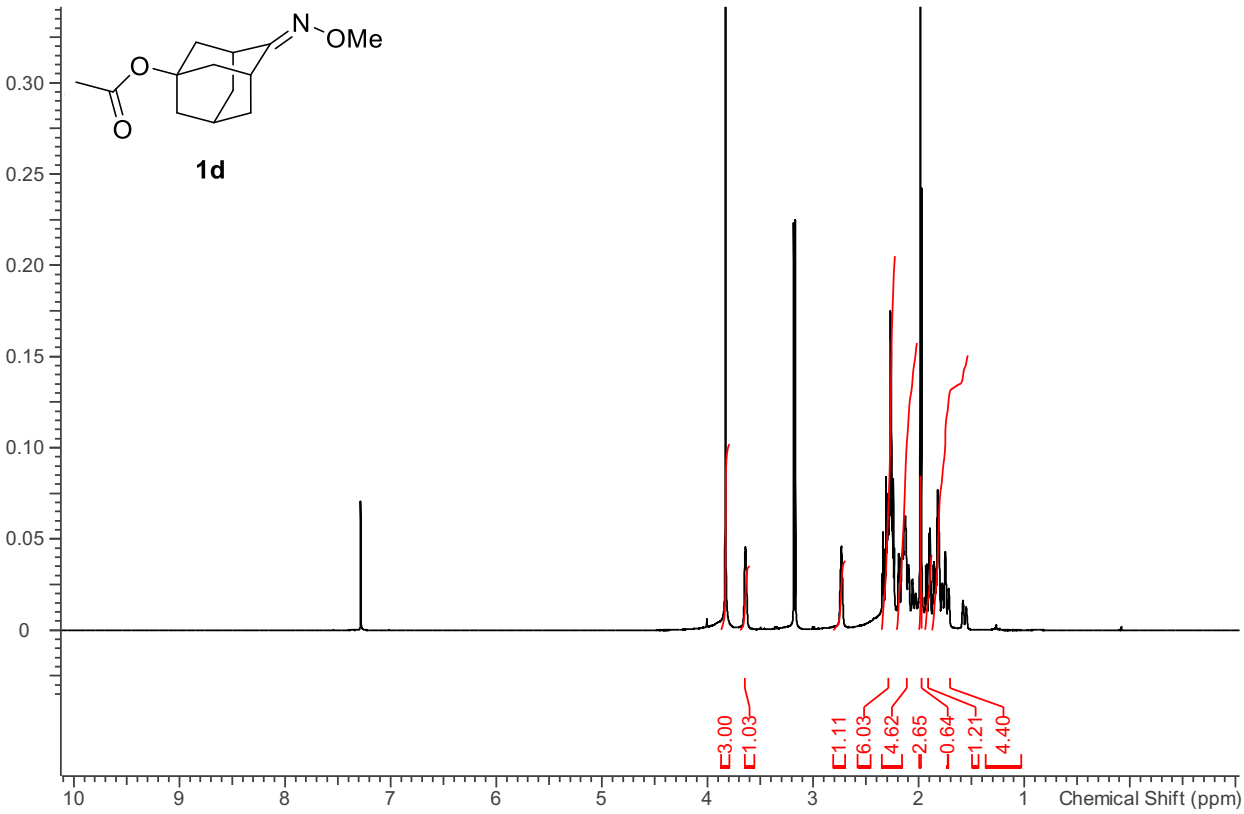

reaction
RLA-5317
3: Diode Array
254
Range: 5.563e-1
6.64
0.24
AU
RLA-5317
(2) ELSD Signal
Range: 1750
6.71
LSU
RLA-5317
3: Diode Array
Range: 1.854e+2
6.64
0.24
4.77
AU
RLA-5317
1: Scan ES+
TIC
6.45e7
0.32
0.38
0.40
0.54
0.67
1.90
2.07
2.13
2.24
2.65
3.64
3.78
4.28
4.68
4.79
5.05
6.16
6.17
6.18
6.24
6.62
7.88
7.89
Time

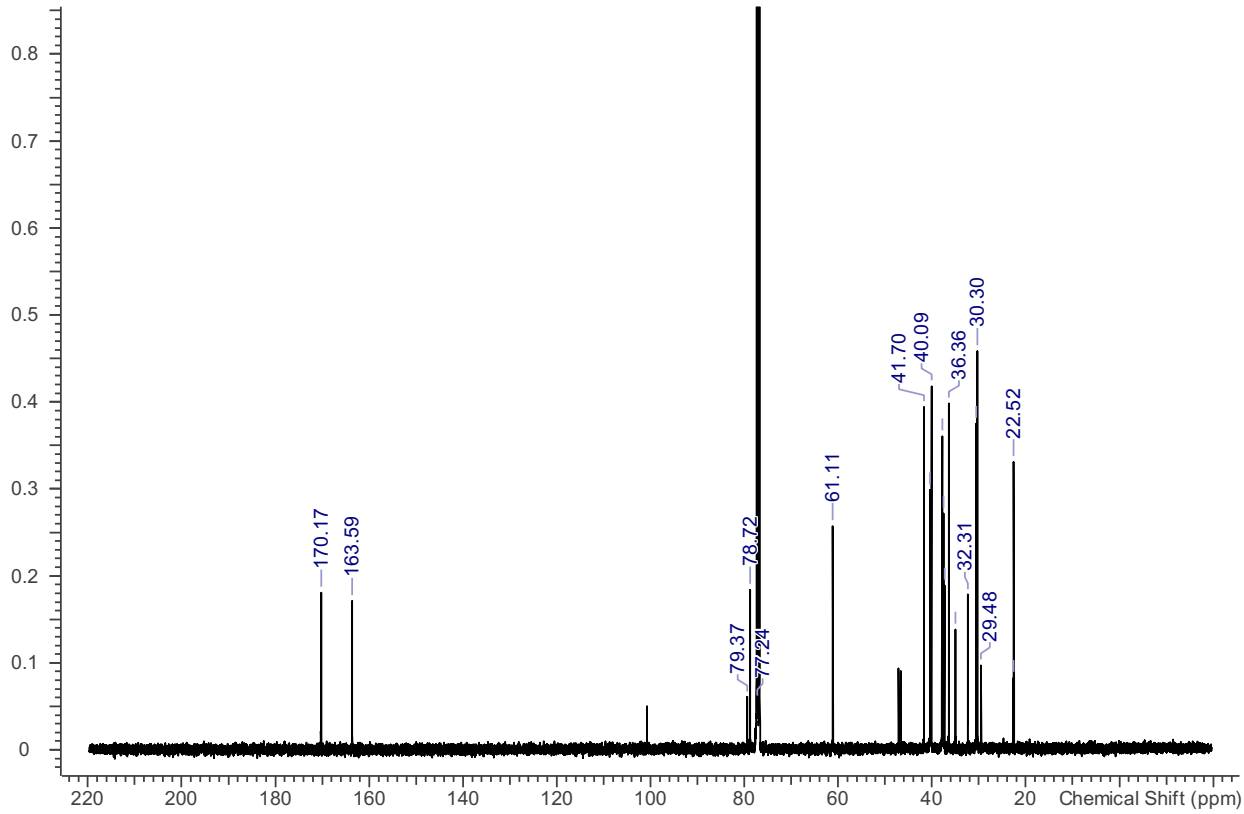

BocHN
N
OMe
1b
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
1.00
2.99
1.00
1.01
1.08
4.80
1.52
1.05
3.15
8.93
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

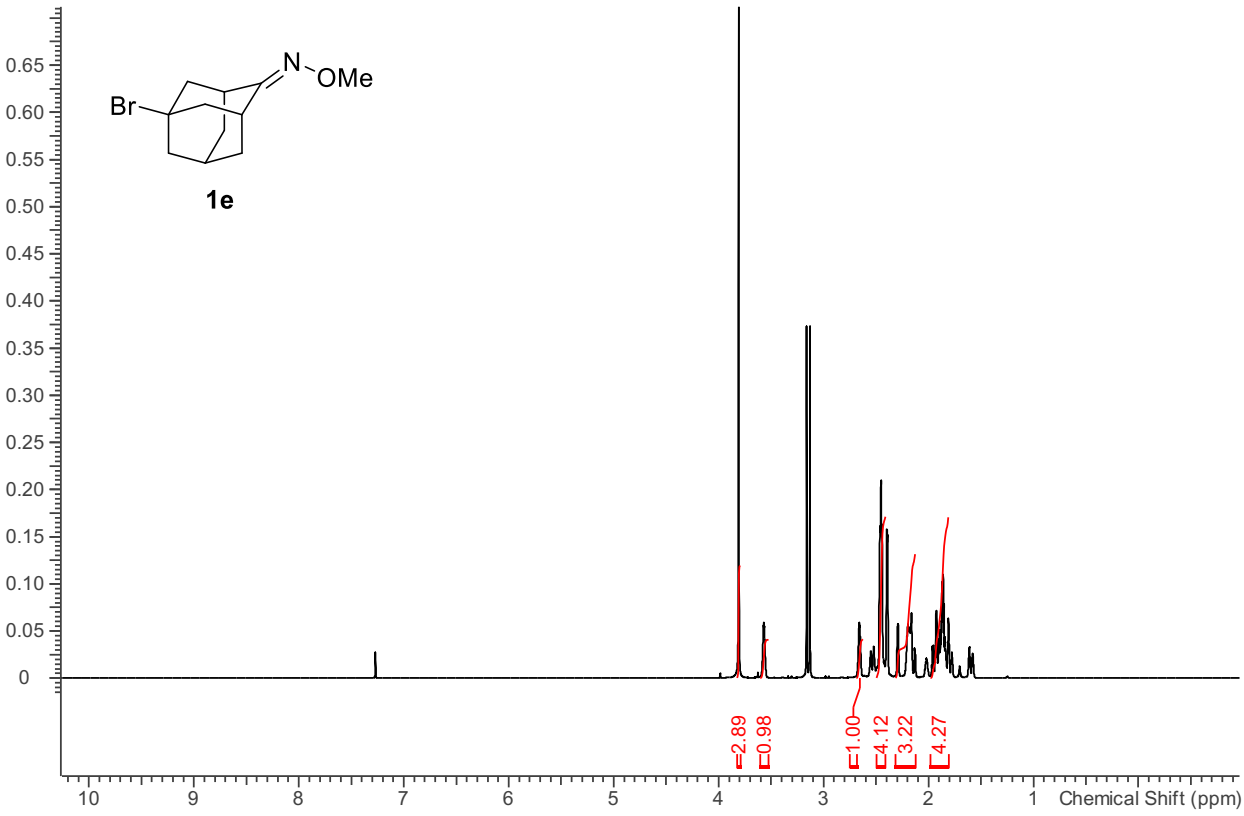

RG-181-83 purified carbon.002
13C
CHLOROFORM-d
11 C's
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
164.23
154.11
79.03
61.00
50.10
42.43
37.88
36.59
29.69
28.41
220
200
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)

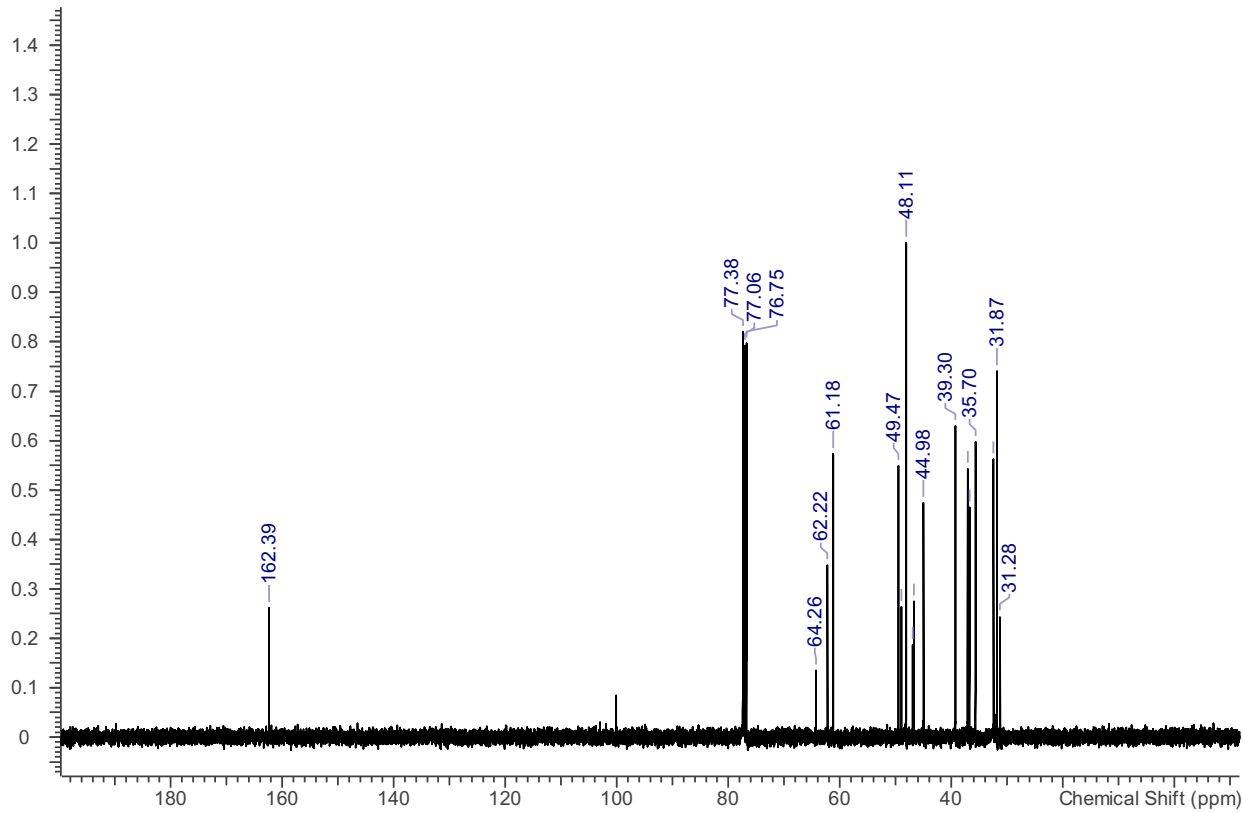

O
N
OMe
O
1c
0.25
0.20
0.15
0.10
0.05
0
2.99
3.00
1.06
1.05
1.06
1.10
1.08
4.22
1.27
2.15
1.10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

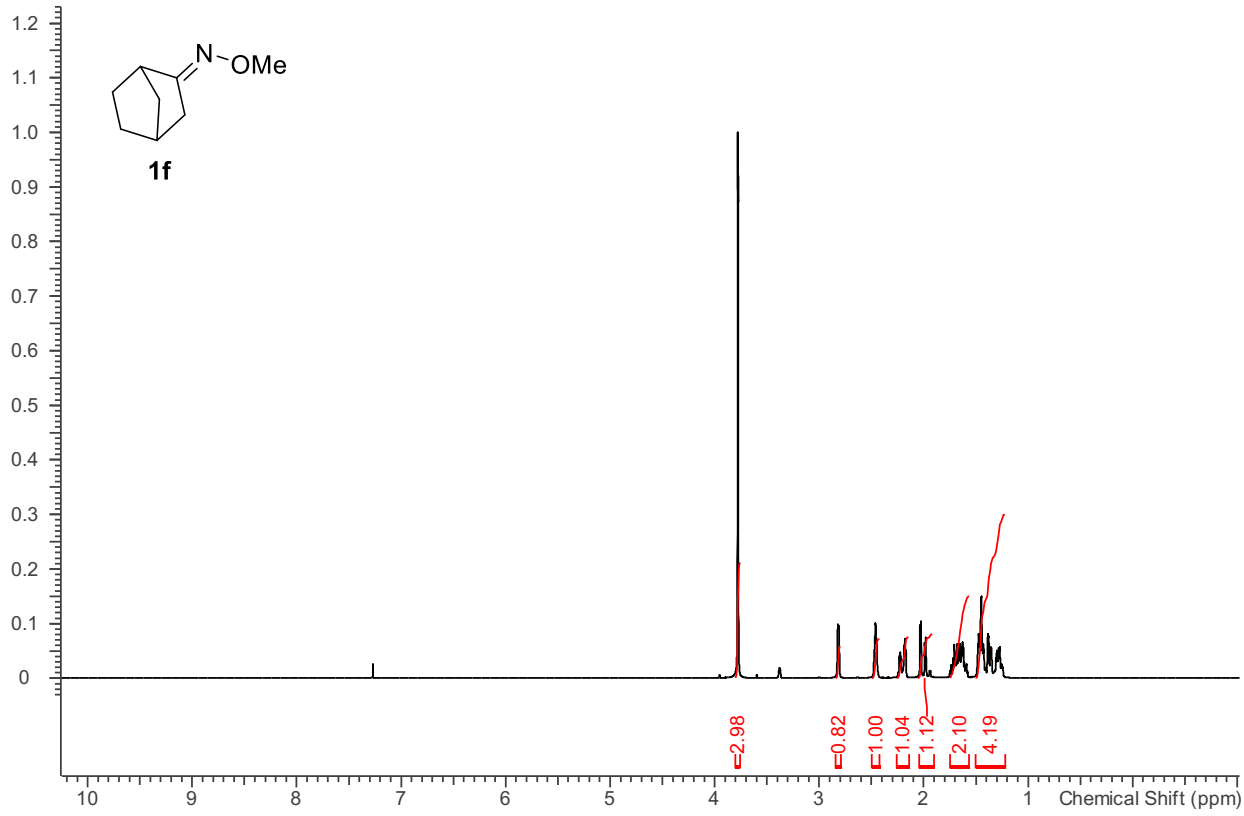

1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
176.67
164.36
61.00
51.77
40.68
39.95
38.61
37.95
35.52
28.70
27.62
220
200
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)

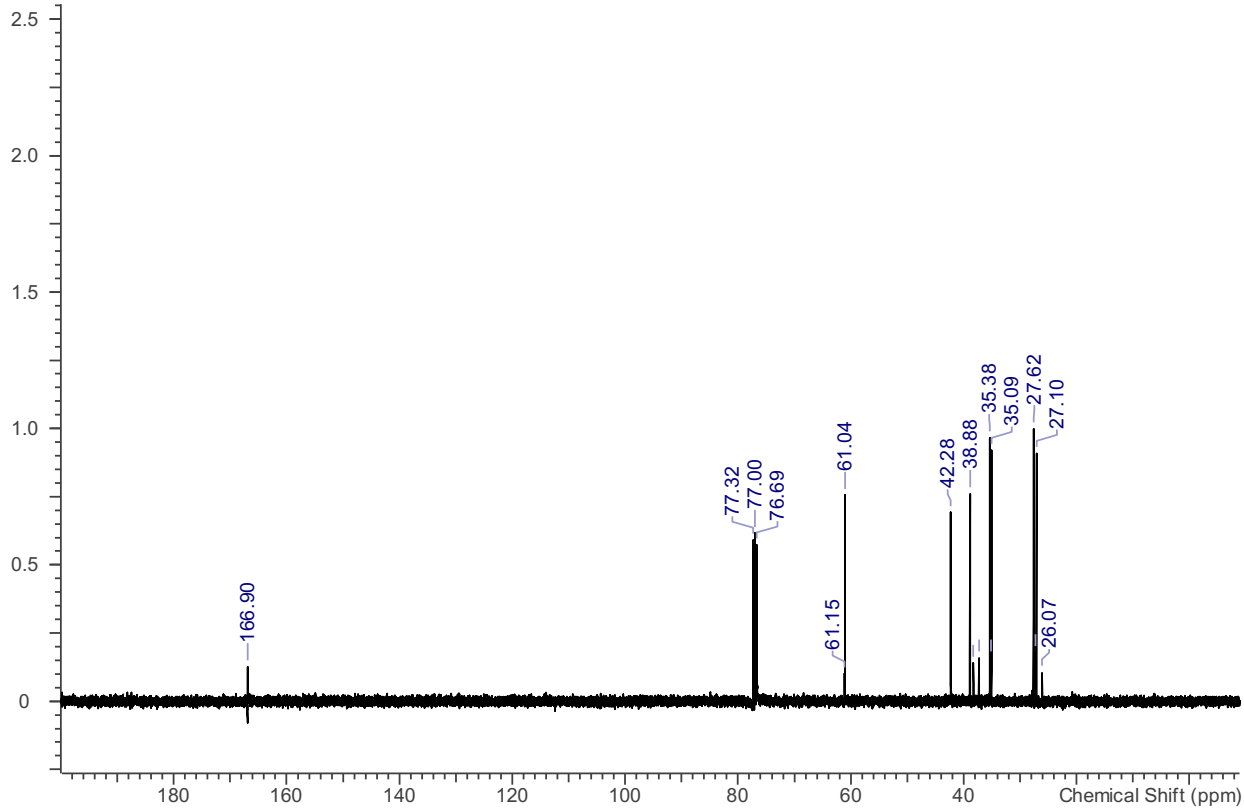

N
OMe
O
O
1d
0.30
0.25
0.20
0.15
0.10
0.05
0
3.00
1.03
1.11
6.03
4.62
2.65
0.64
1.21
4.40
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

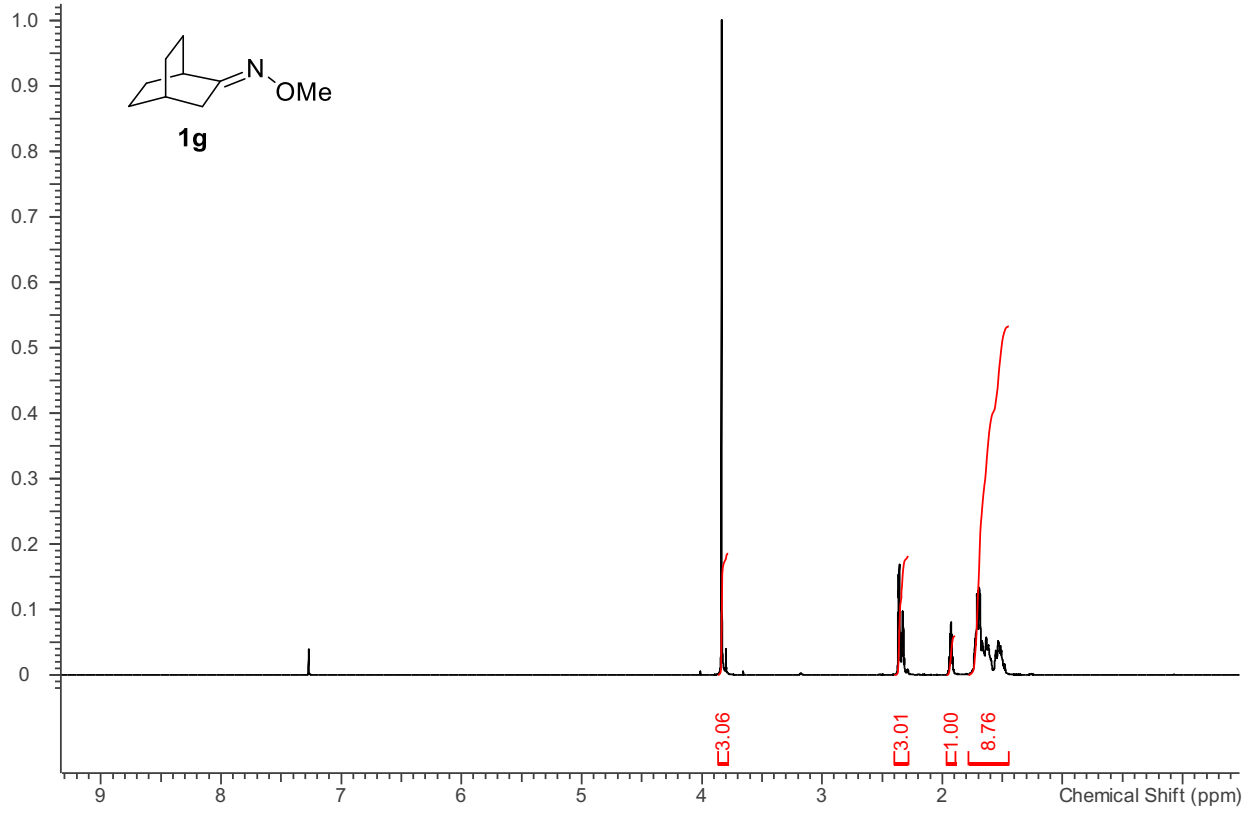

0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
170.17
163.59
79.37
78.72
77.21
61.11
41.70
40.09
36.36
30.30
32.31
29.48
22.52
220
200
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)

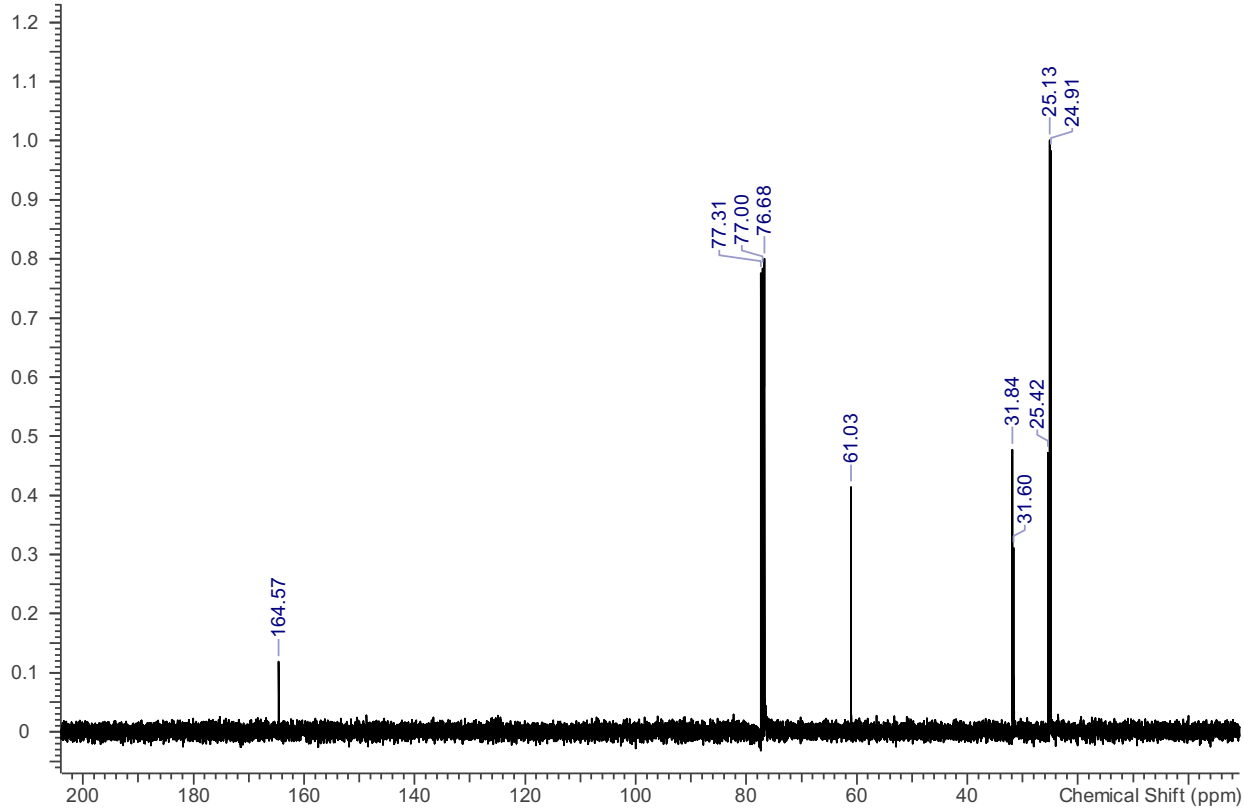

Br
N
OMe
1e
2.89
0.98
1.00
4.12
3.22
4.27
Chemical Shift (ppm)

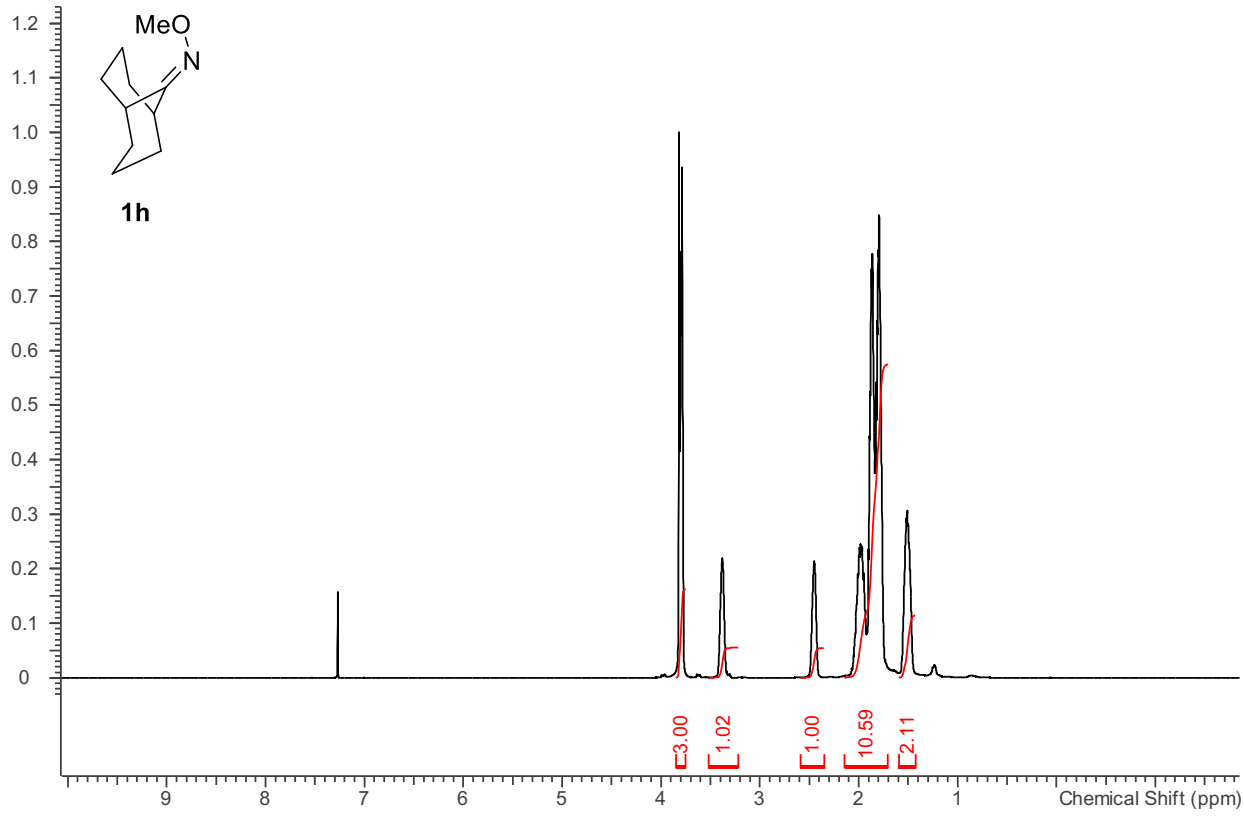

162.39
77.38
77.06
76.75
64.26
62.22
61.18
49.47
48.11
44.98
39.30
35.70
31.87
31.28
Chemical Shift (ppm)

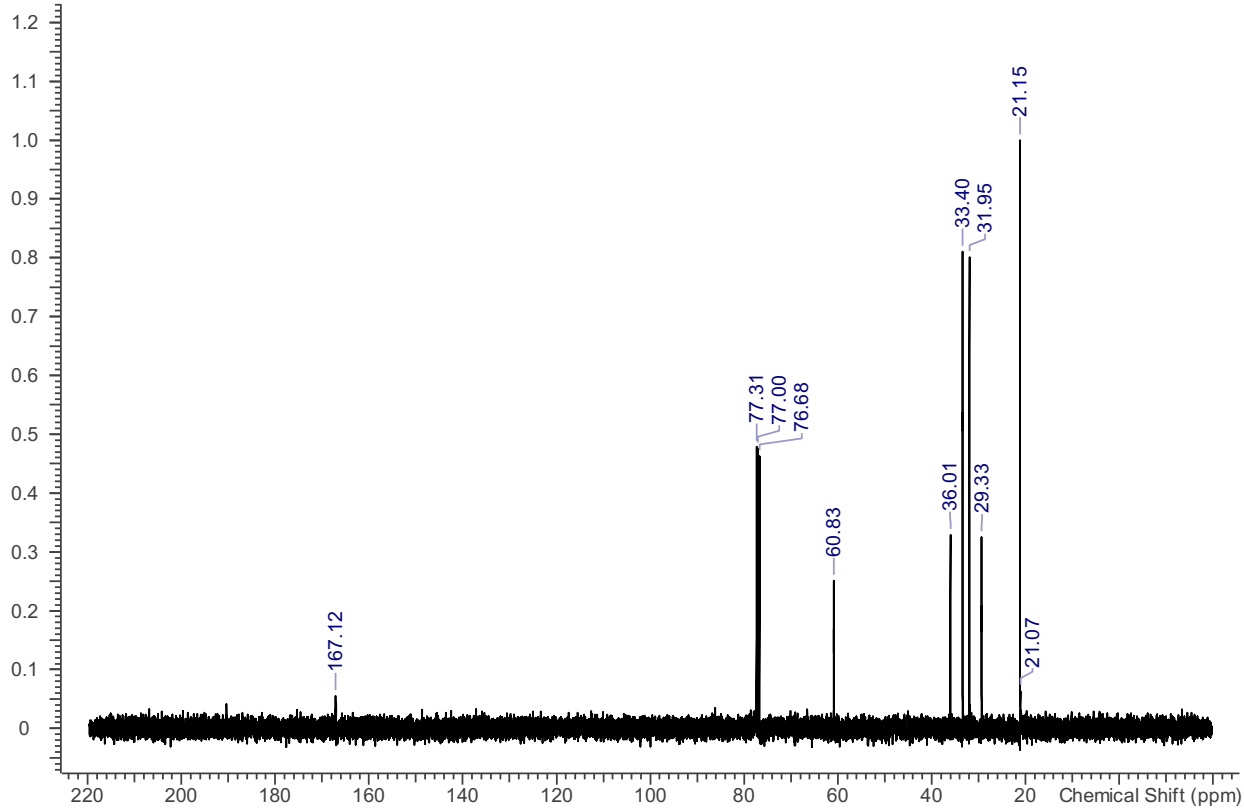

N
OMe
1f
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
2.98
0.82
1.00
1.04
1.12
2.10
4.19
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

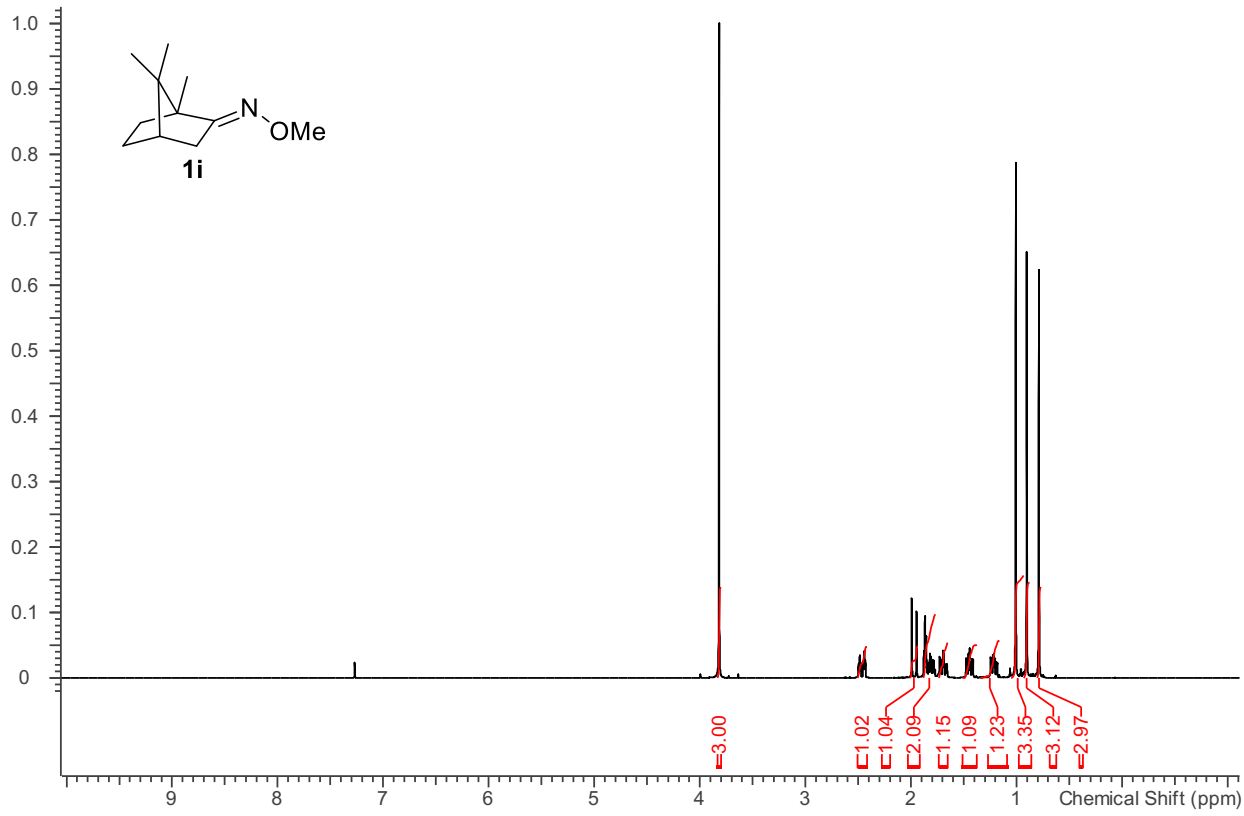

2.5
2.0
1.5
1.0
0.5
0
166.90
77.32
77.00
76.69
61.15
61.04
42.28
38.88
35.38
35.09
27.62
27.10
26.07
180
160
140
120
100
80
60
40
Chemical Shift (ppm)

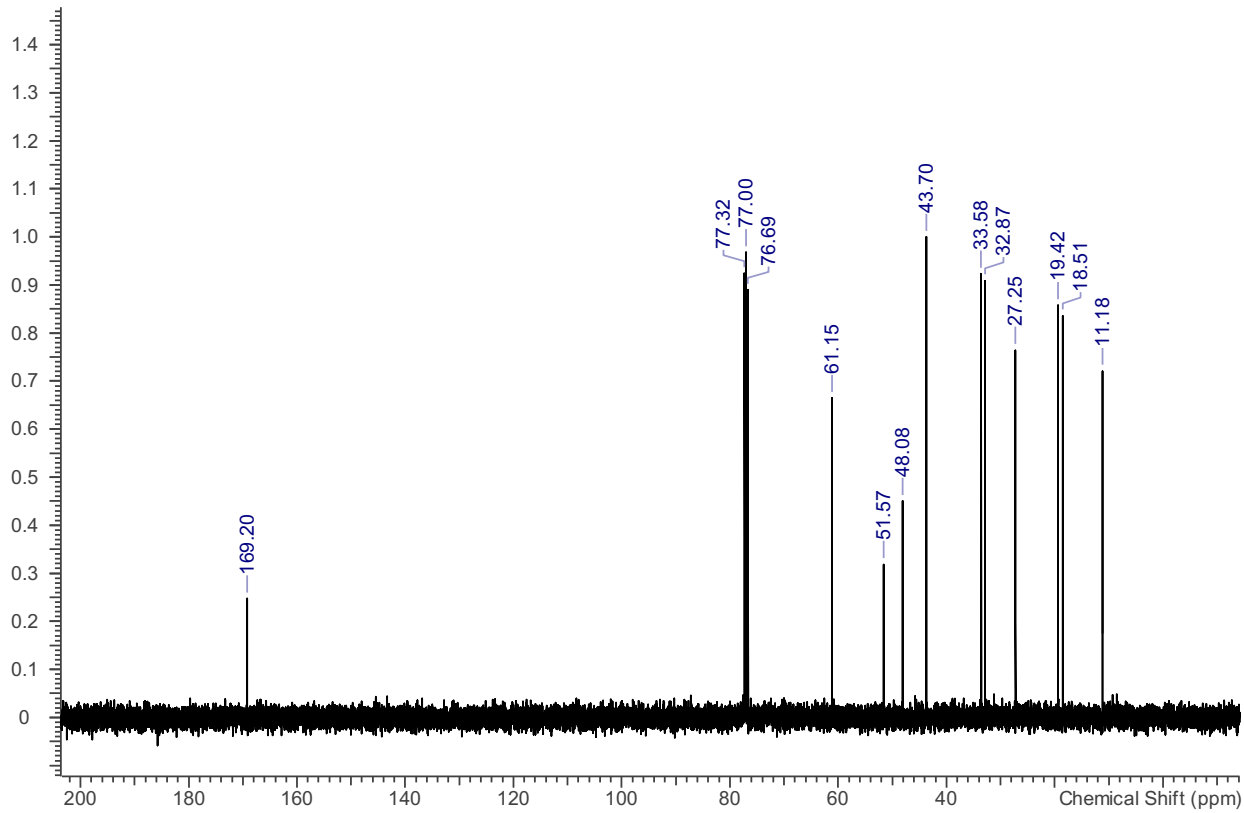

N
OMe
1g
3.06
3.01
1.00
8.76
Chemical Shift (ppm)

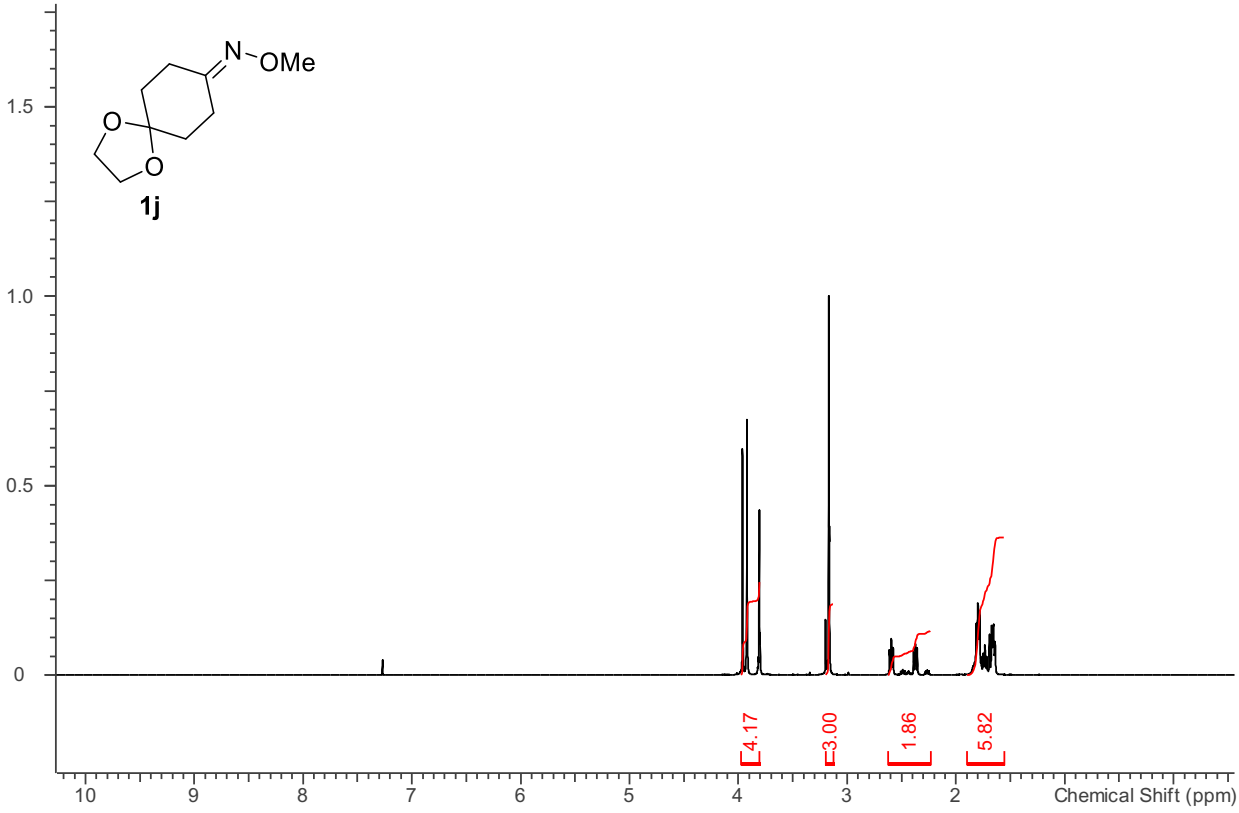

164.57
77.31
77.00
76.68
61.03
31.84
31.60
25.42
25.13
24.91
Chemical Shift (ppm)

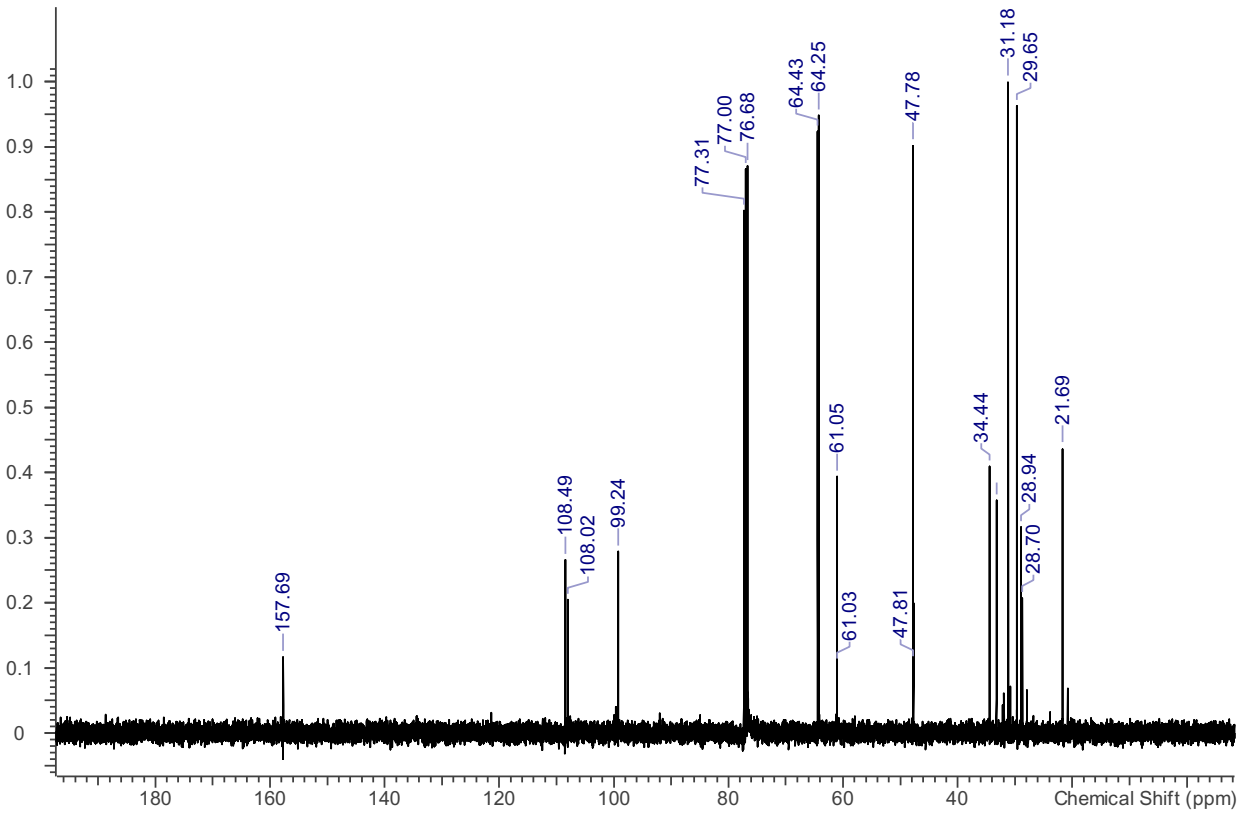

MeO
N
1h
3.00
1.02
1.00
10.59
2.11
Chemical Shift (ppm)

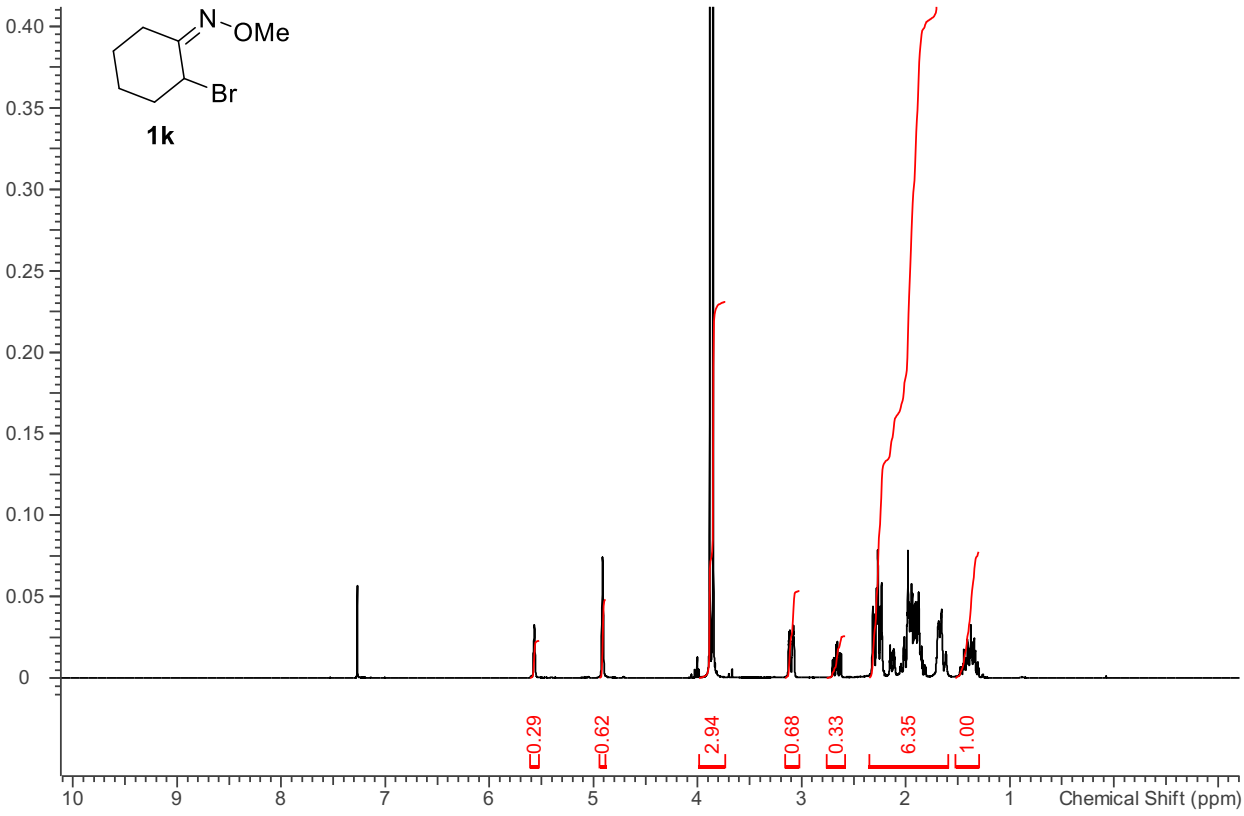

167.12
77.31
77.00
76.68
60.83
36.01
33.40
31.95
29.33
21.15
21.07
Chemical Shift (ppm)

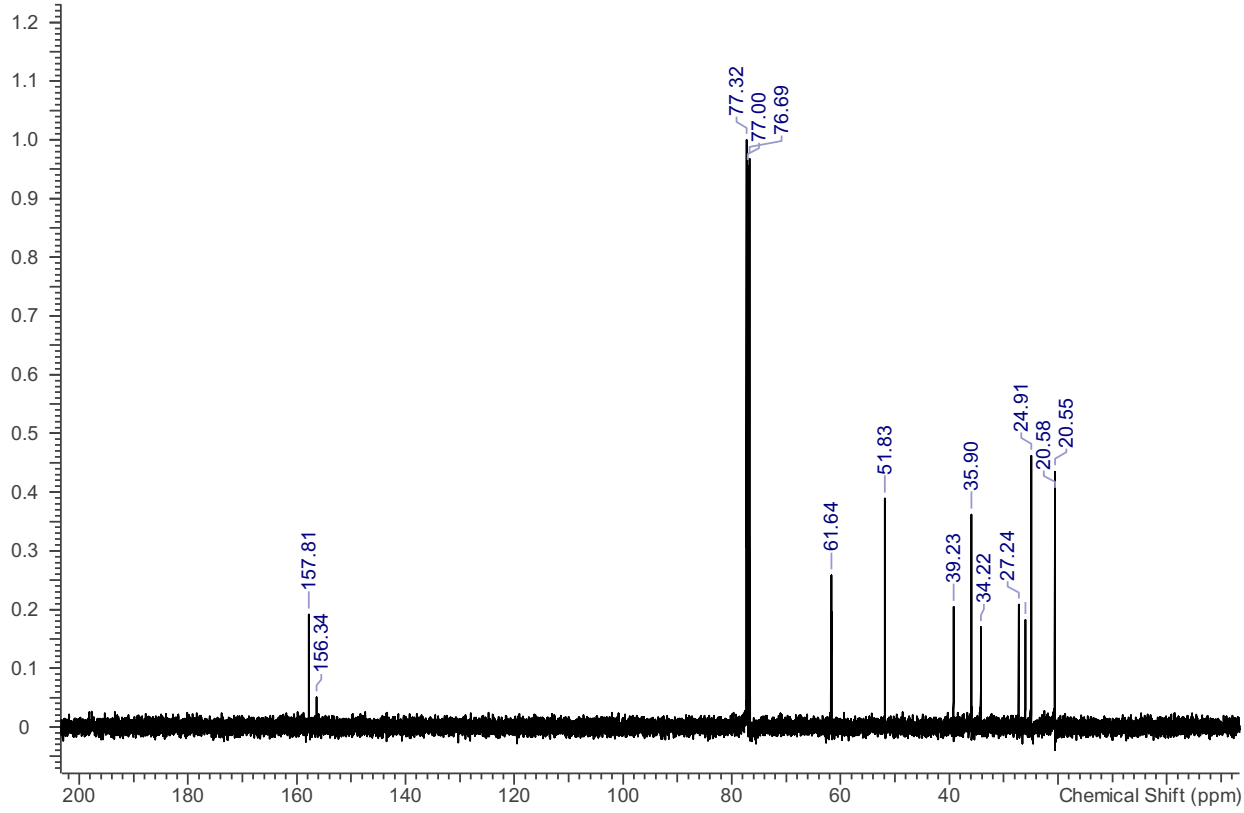

N
OMe
1i
3.00
1.02
1.04
2.09
1.15
1.09
1.23
3.35
3.12
2.97
Chemical Shift (ppm)

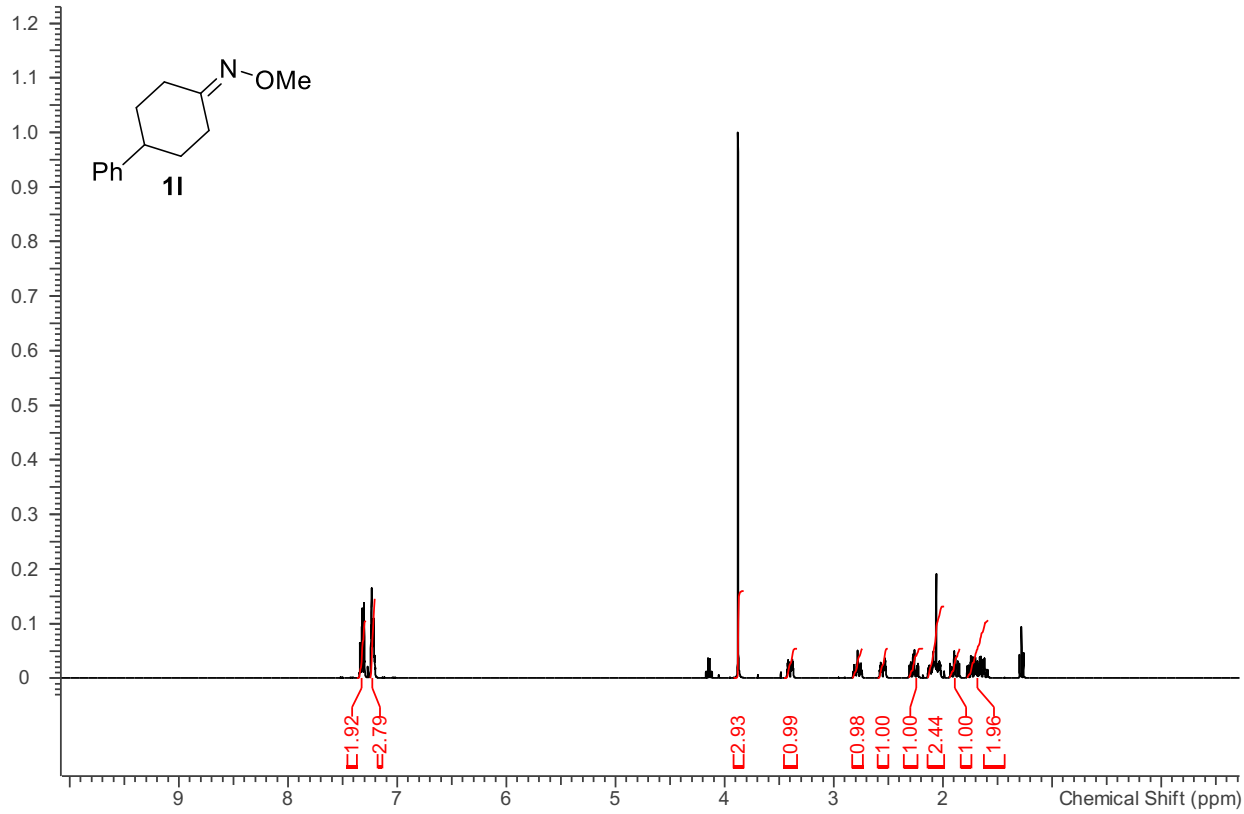

169.20
77.32
77.00
76.69
61.15
51.57
48.08
43.70
33.58
32.87
27.25
19.42
18.51
11.18
Chemical Shift (ppm)

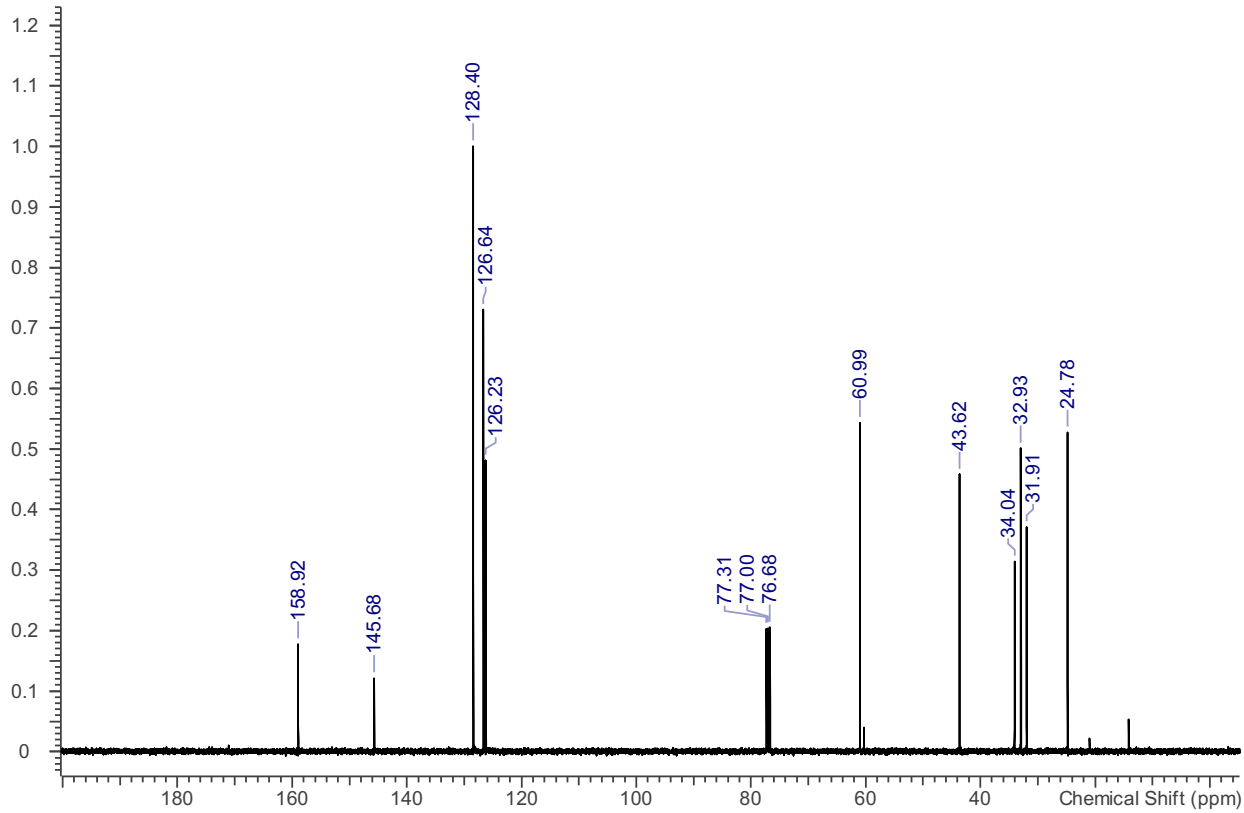

N
OMe
O
O
1j
1.5
1.0
0.5
0
4.17
3.00
1.86
5.82
10
9
8
7
6
5
4
3
2
Chemical Shift (ppm)

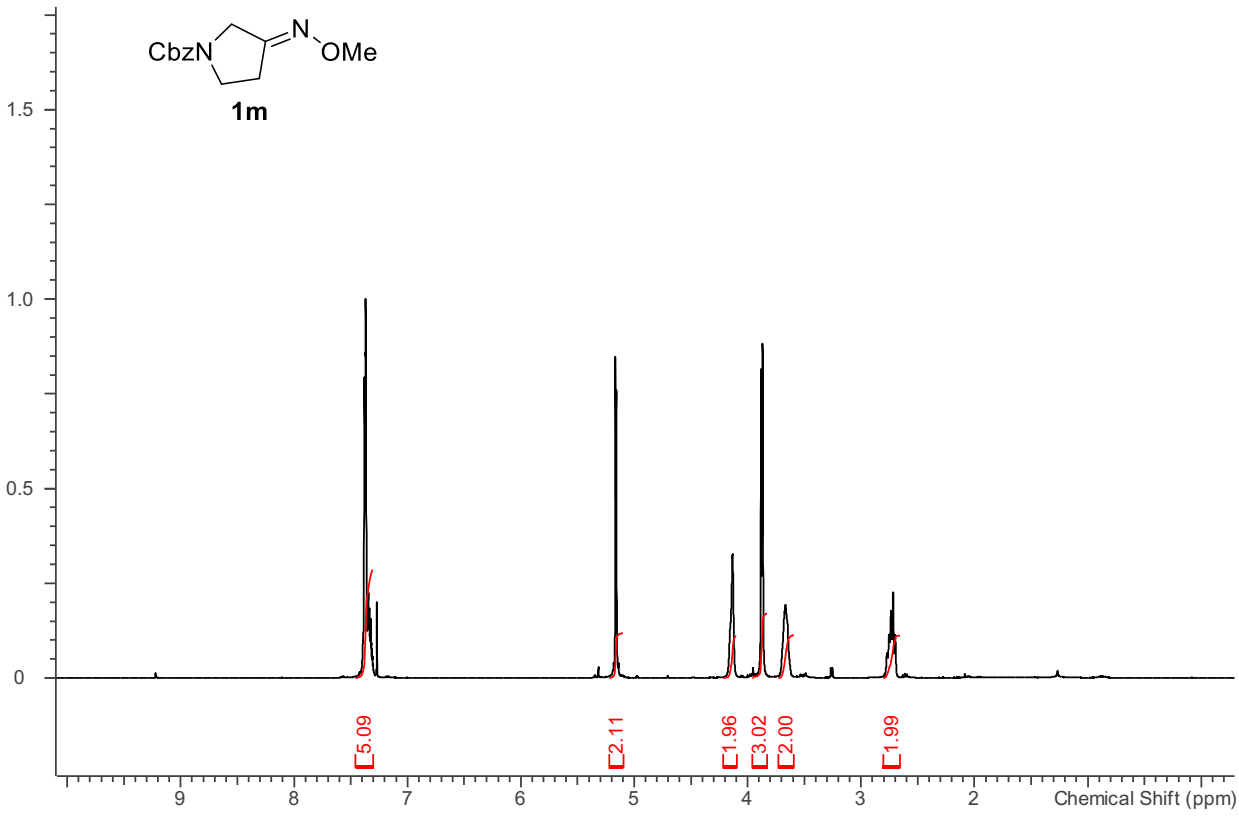

1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
157.69
108.49
108.02
99.24
77.31
77.00
76.68
64.43
64.25
61.05
61.03
47.81
47.78
34.44
31.18
29.65
28.94
28.70
21.69
180
160
140
120
100
80
60
40
Chemical Shift (ppm)

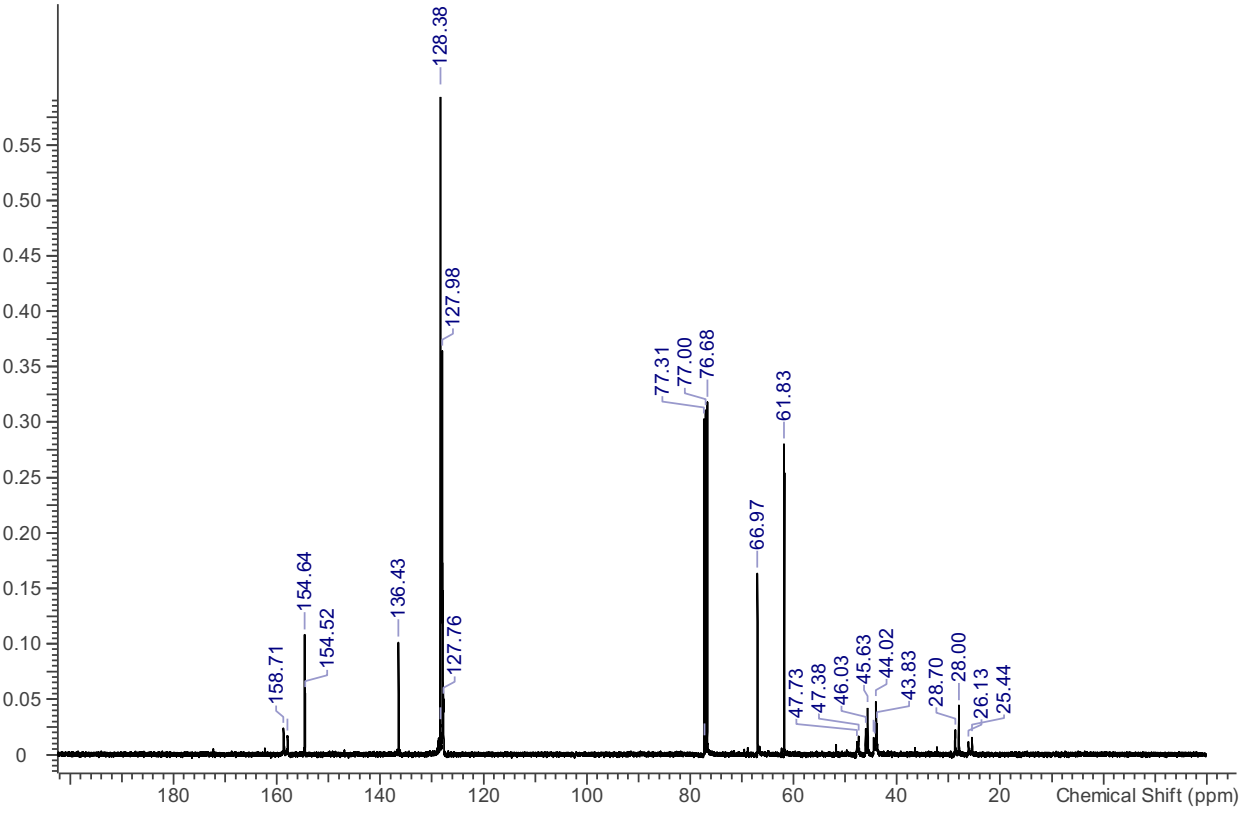

N
OMe
Br
1k
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0.29
0.62
2.94
0.68
0.33
6.35
1.00
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

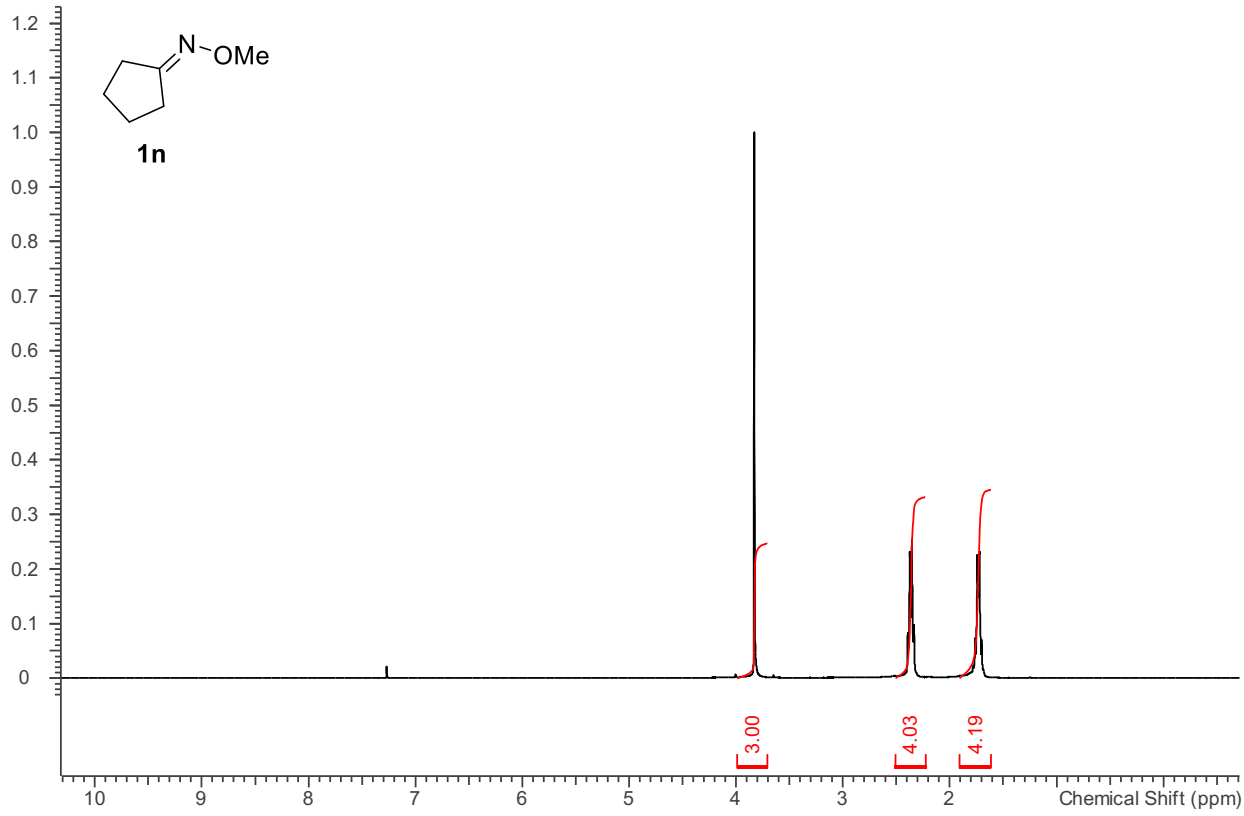

1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
77.32
77.00
76.69
157.81
156.34
61.64
51.83
39.23
35.90
34.22
27.24
24.91
20.58
20.55
200
180
160
140
120
100
80
60
40
Chemical Shift (ppm)

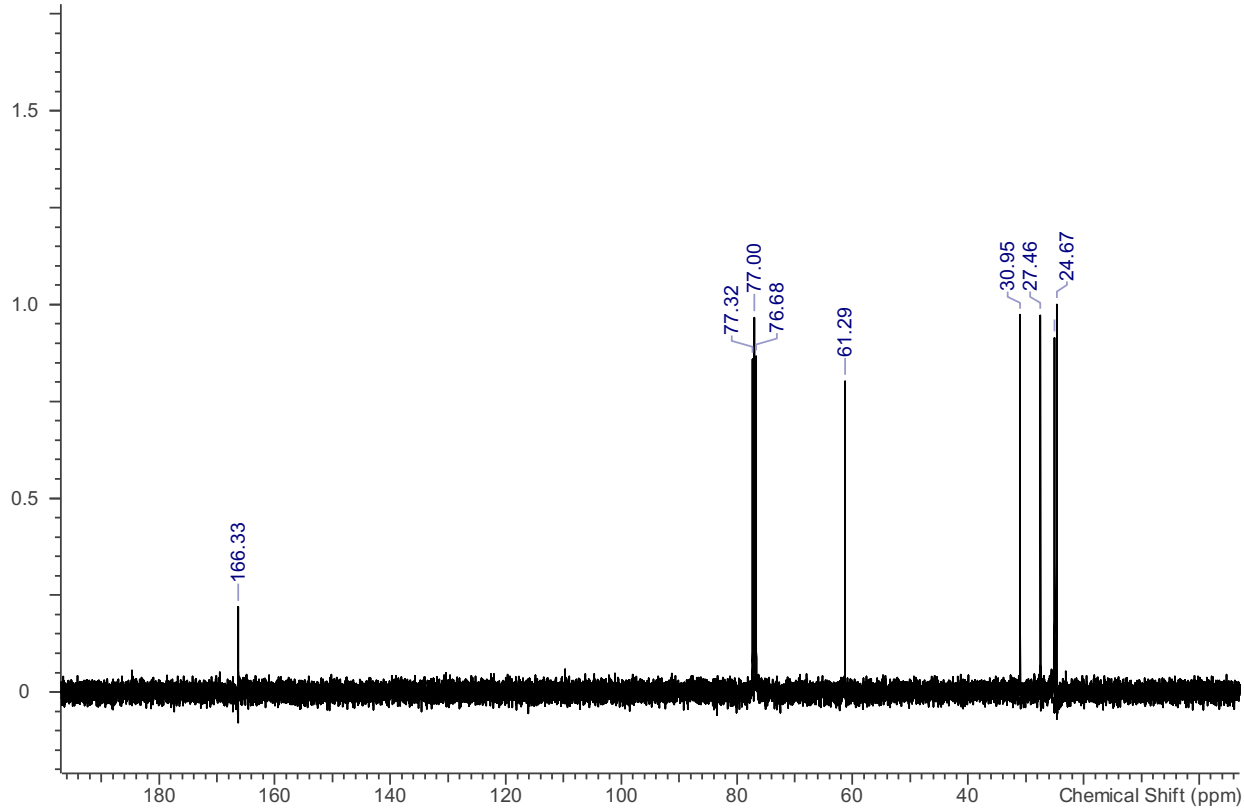

N
OMe
Ph
1l
1.92
2.79
2.93
0.99
0.98
1.00
1.00
2.44
1.00
1.96
Chemical Shift (ppm)

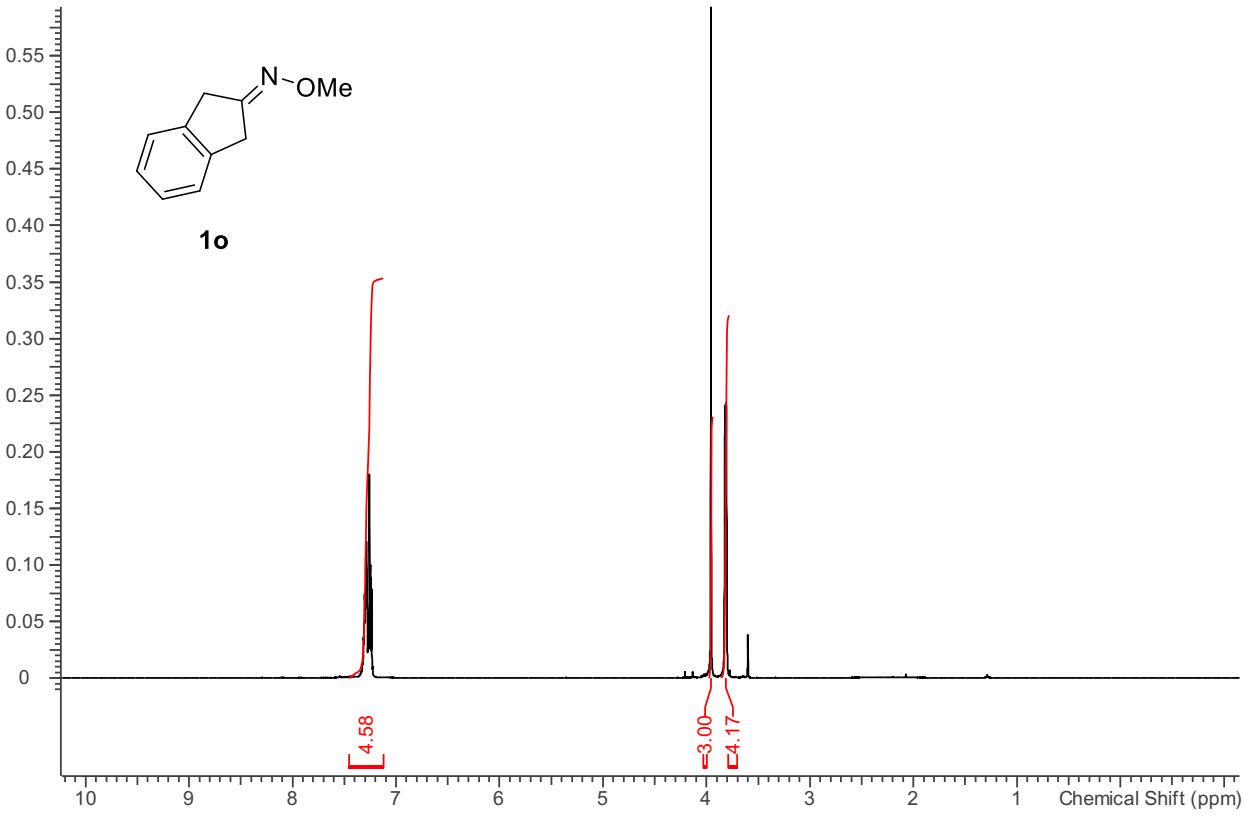

128.40
126.64
126.23
158.92
145.68
77.31
77.00
76.68
60.99
43.62
34.04
32.93
31.91
24.78
Chemical Shift (ppm)

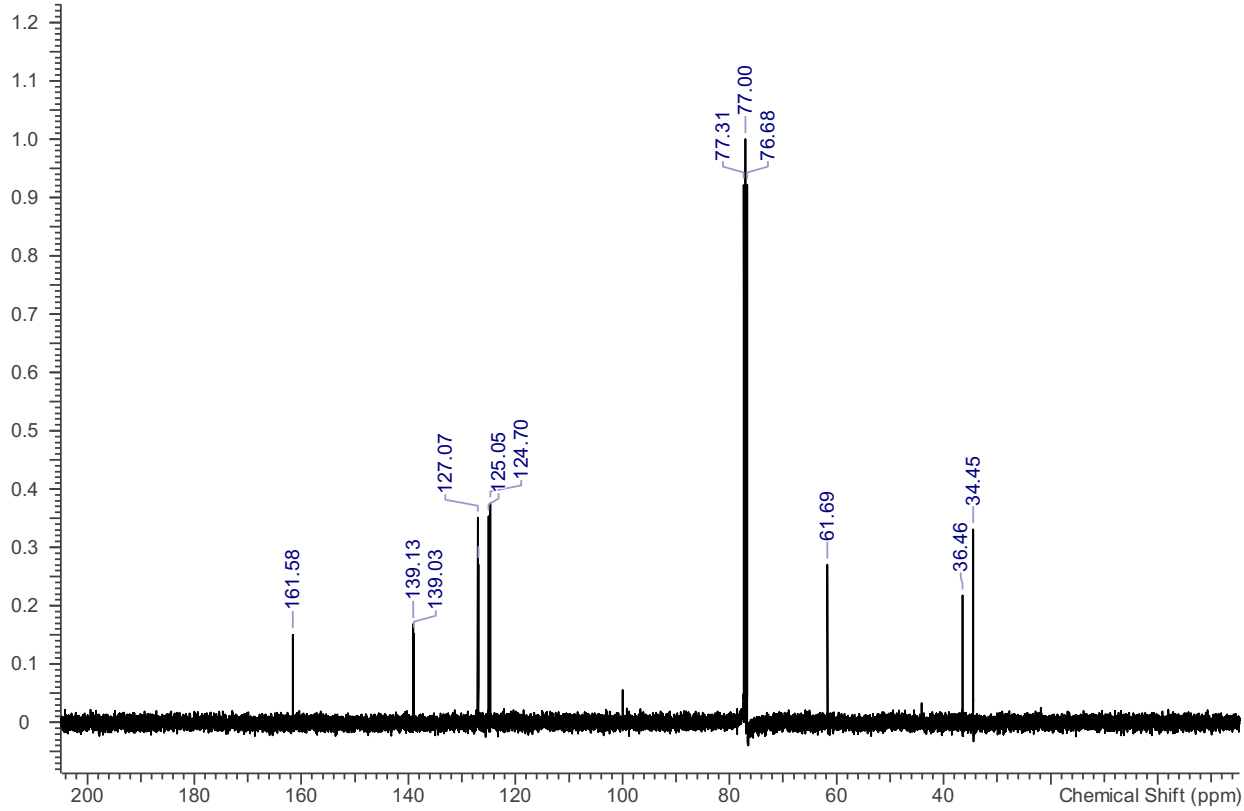

CbzN
N
OMe
1m
1.5
1.0
0.5
0
5.09
2.11
1.96
3.02
2.00
1.99
9
8
7
6
5
4
3
2
Chemical Shift (ppm)

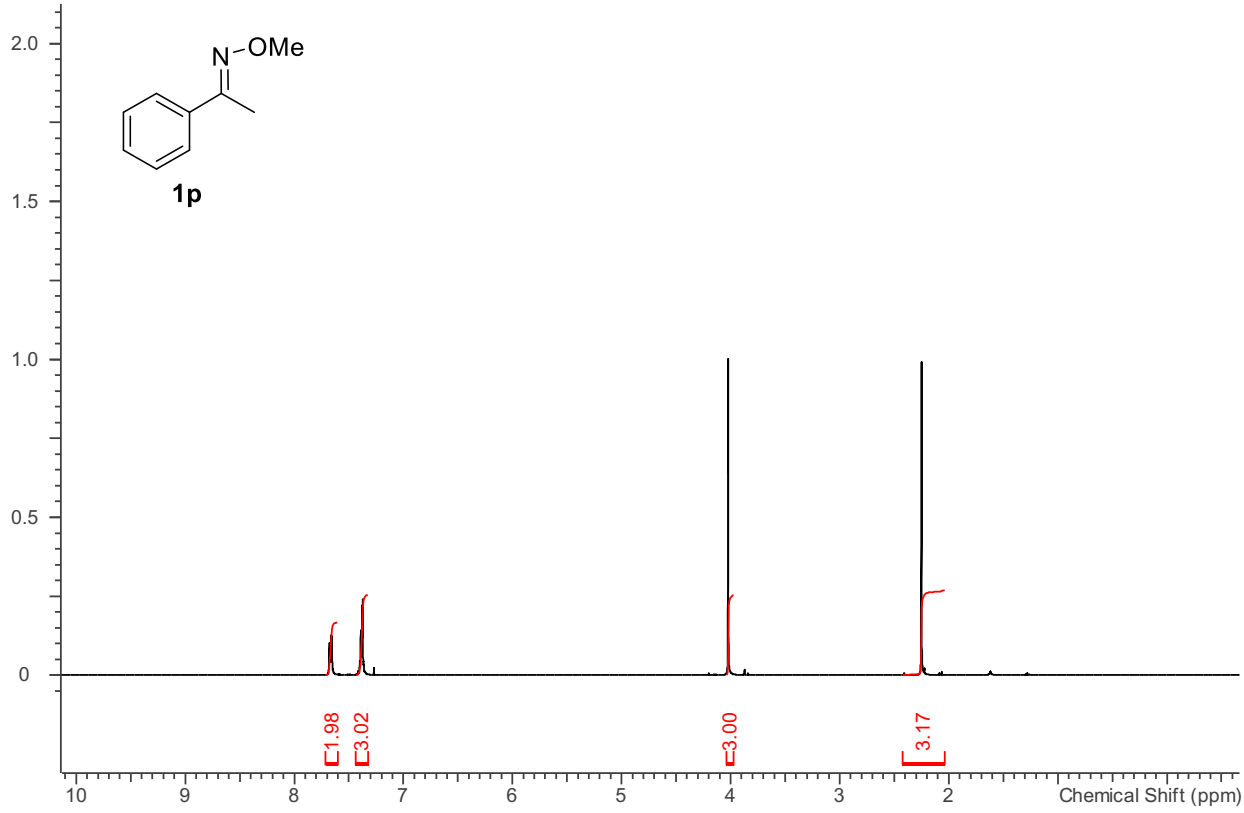

128.38
127.98
127.76
158.71
154.64
154.52
136.43
77.31
77.00
76.68
66.97
61.83
47.73
47.38
46.03
45.63
44.02
43.83
28.70
28.00
26.13
25.44
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)

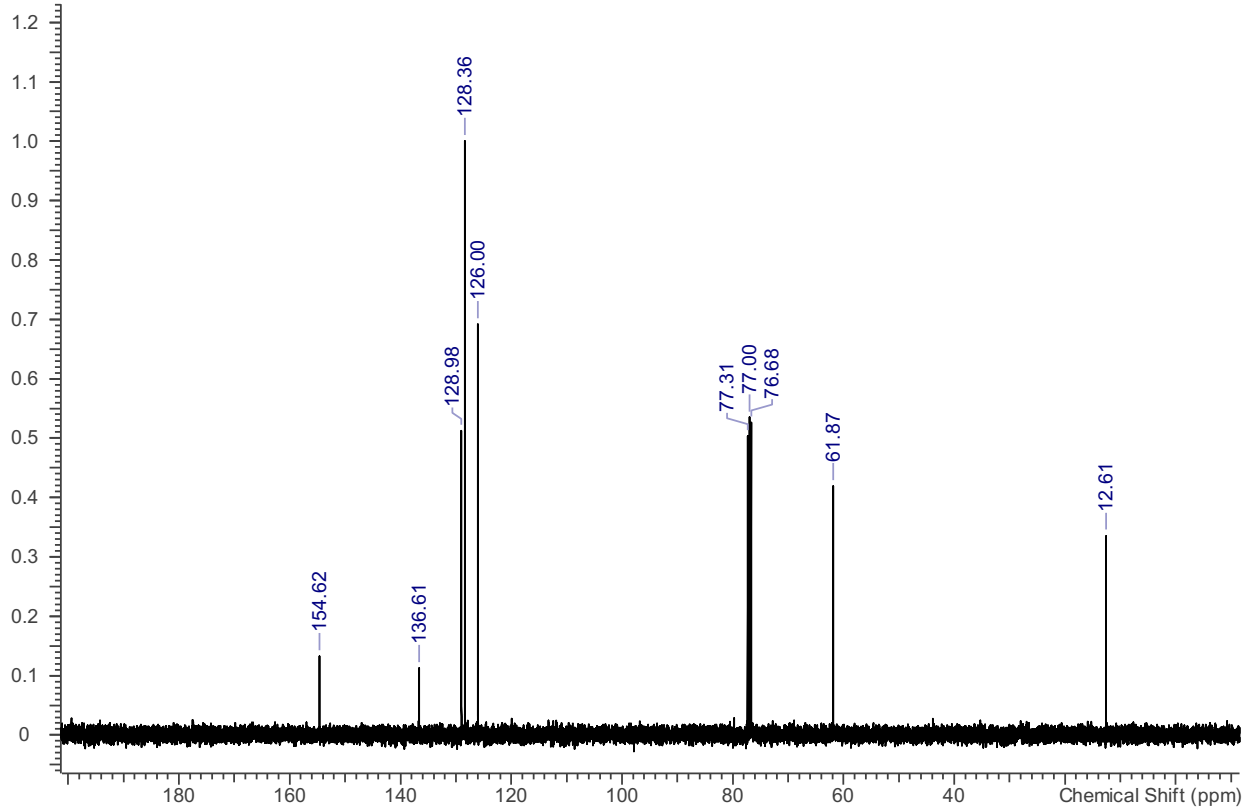

N
OMe
1n
3.00
4.03
4.19
Chemical Shift (ppm)

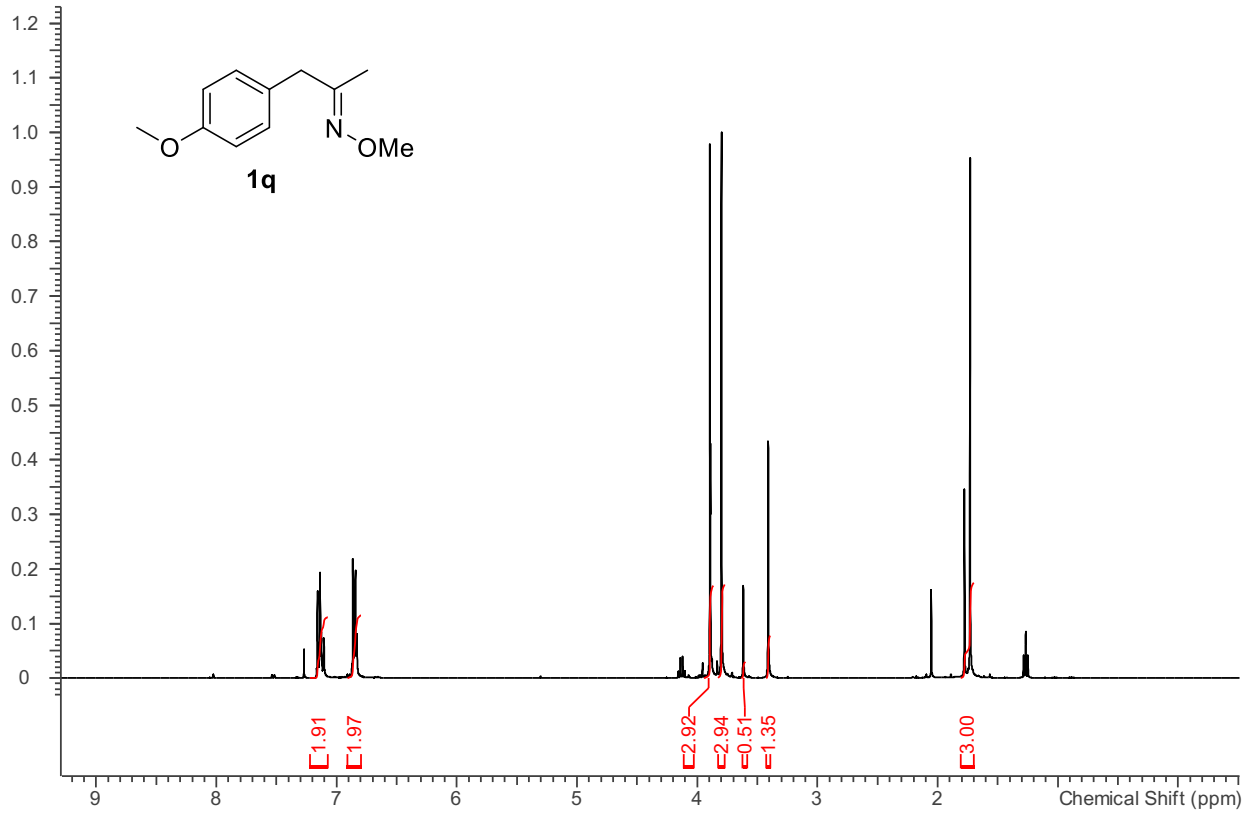

166.33
77.32
77.00
76.68
61.29
30.95
27.46
24.67
Chemical Shift (ppm)

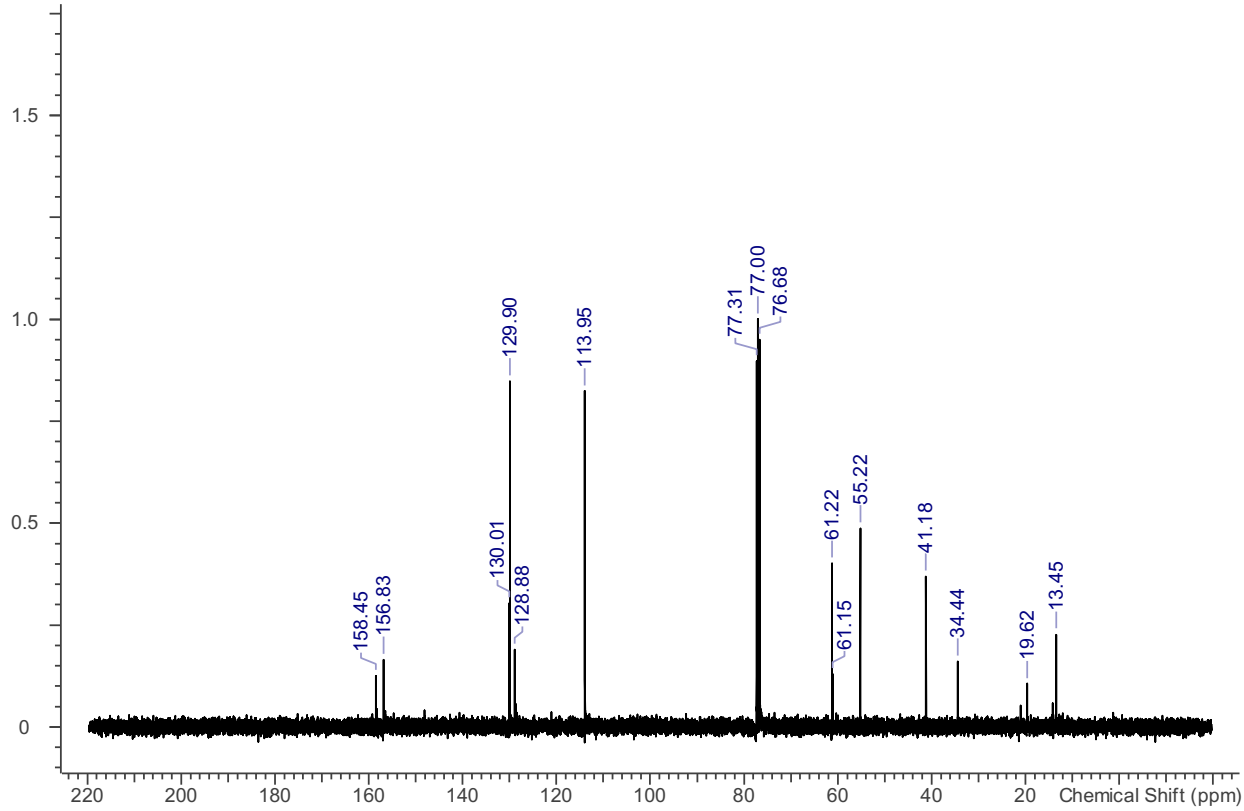

N
OMe
1o
4.58
3.00
4.17
Chemical Shift (ppm)

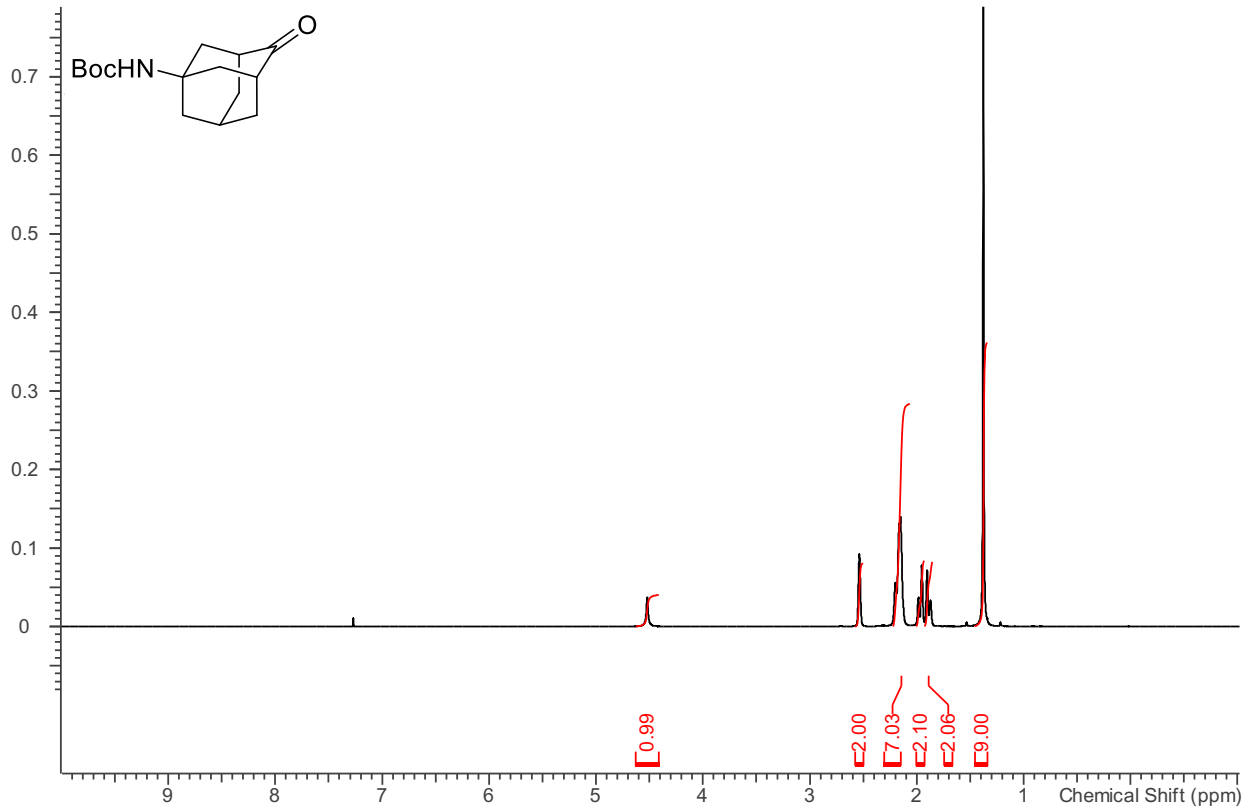

77.31
77.00
76.68
161.58
139.13
139.03
127.07
125.05
124.70
61.69
36.46
34.45
Chemical Shift (ppm)

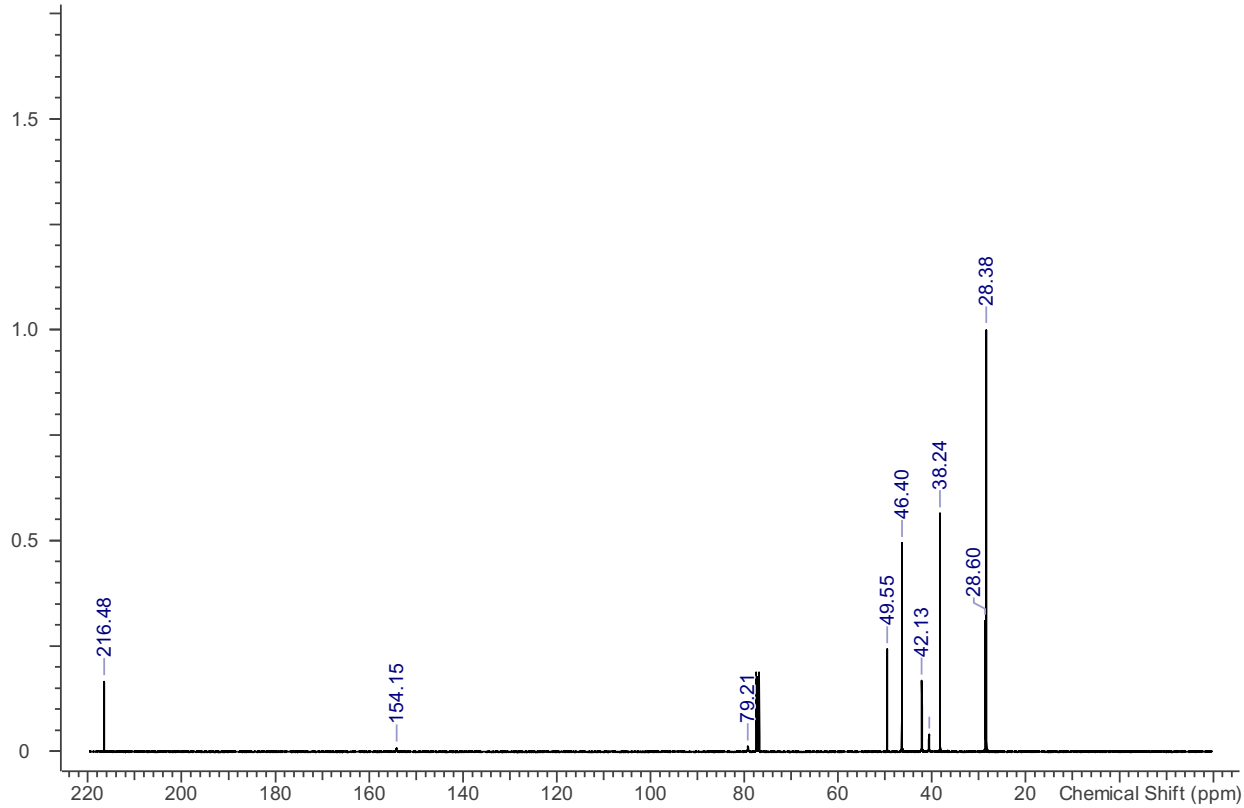

N–OMe
1p
1.98
3.02
3.00
3.17
Chemical Shift (ppm)

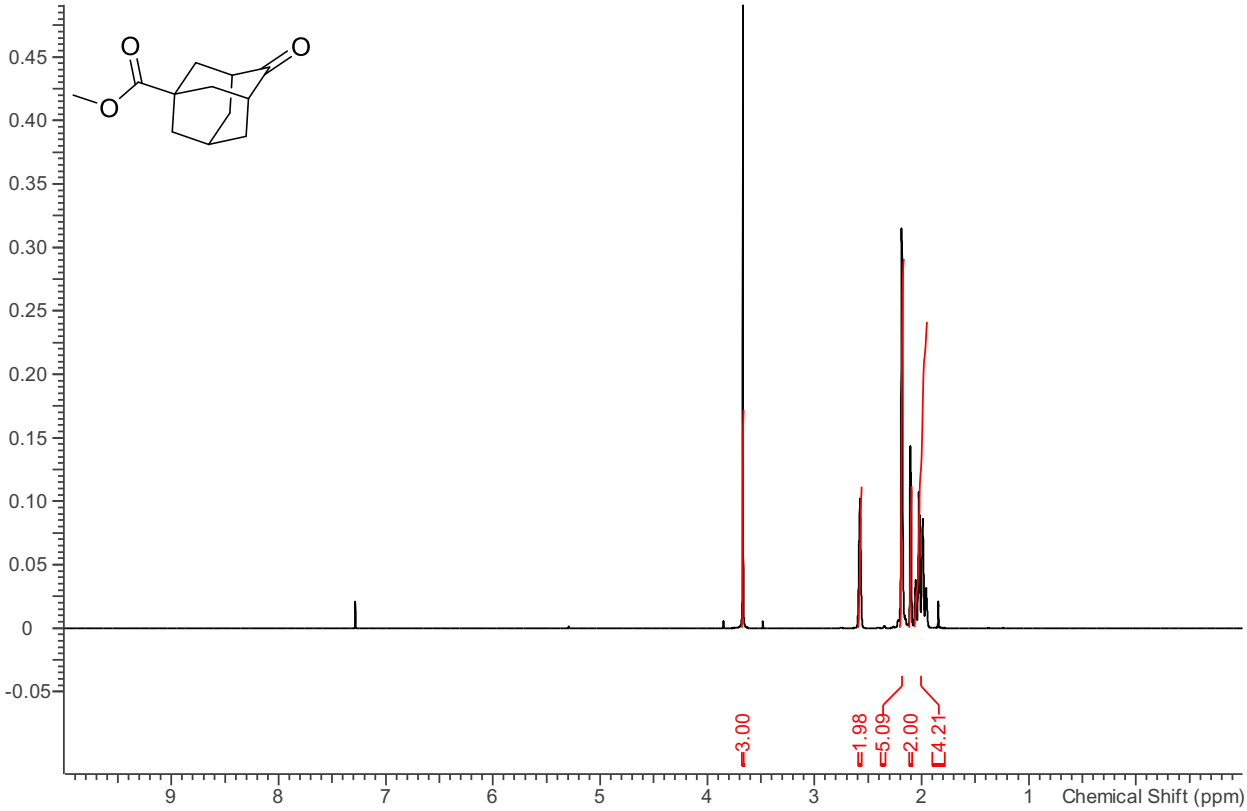

128.36
126.00
128.98
77.31
77.00
76.68
61.87
12.61
154.62
136.61
Chemical Shift (ppm)

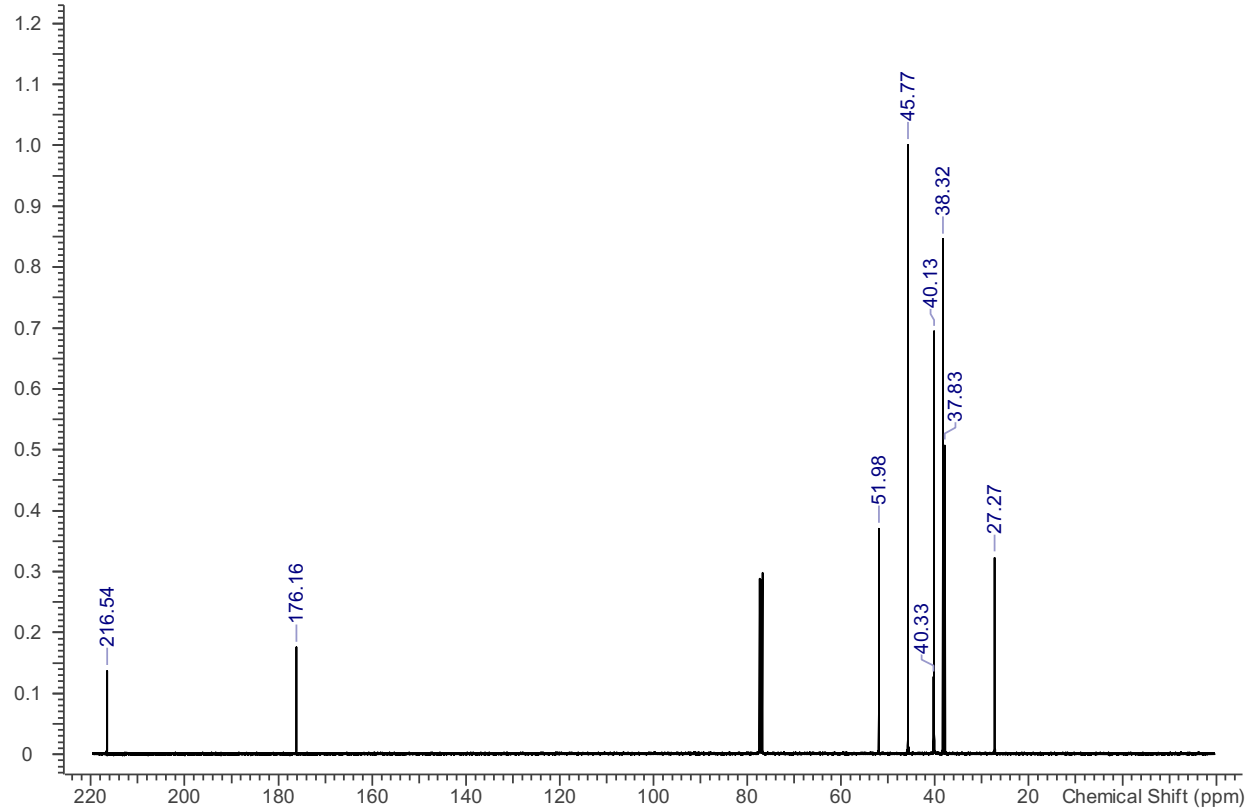

1q
O
N
OMe
1.91
1.97
2.92
2.94
0.51
1.35
3.00
Chemical Shift (ppm)

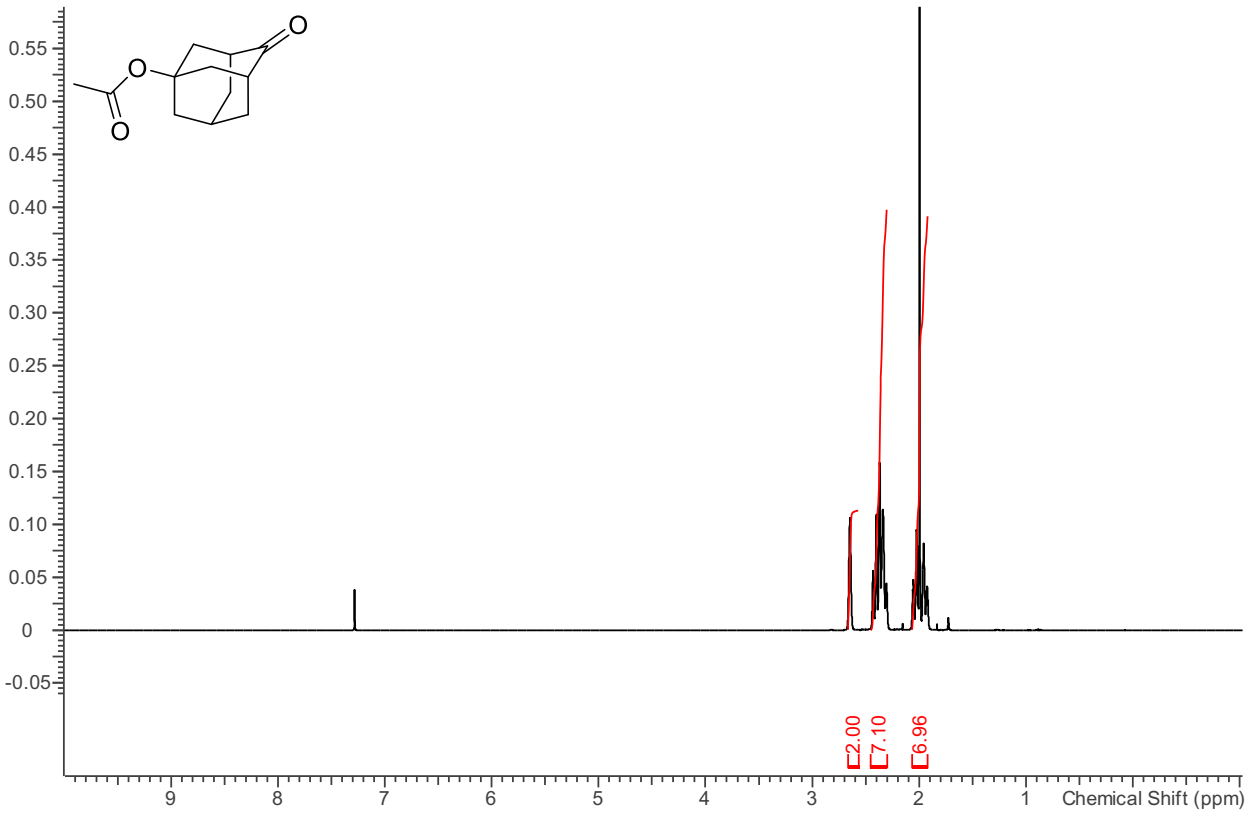

158.45
156.83
130.01
129.90
128.88
113.95
77.31
77.00
76.68
61.22
61.15
55.22
41.18
34.44
19.62
13.45
Chemical Shift (ppm)

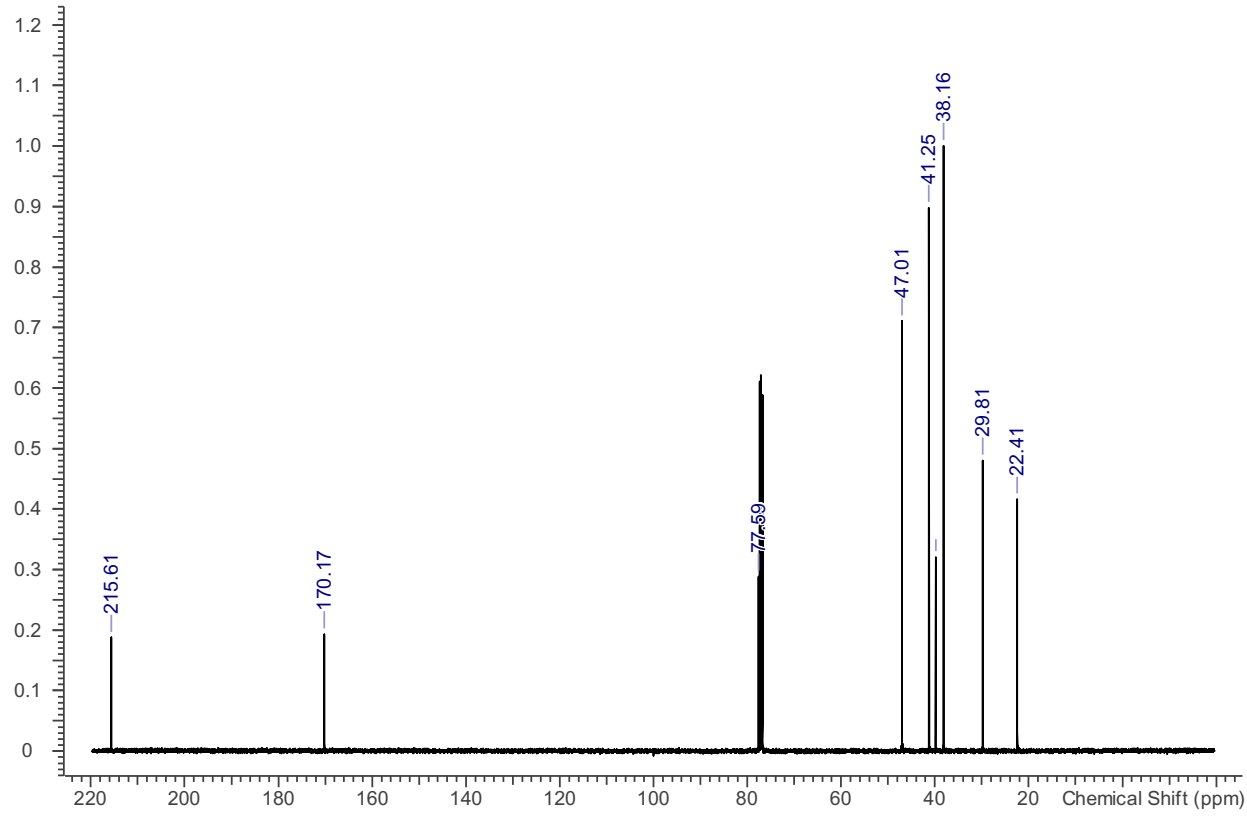

BocHN
O
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.99
2.00
7.03
2.10
2.06
9.00
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)


1.5
1.0
0.5
0
216.48
154.15
79.21
49.55
46.40
42.13
38.24
28.60
28.38
220
200
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)


0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
-0.05
3.00
1.98
5.09
2.00
4.21
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)


1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
216.54
176.16
51.98
45.77
40.33
40.13
38.32
37.83
27.27
220
200
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)


0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
-0.05
2.00
7.10
6.96
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)


1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
215.61
170.17
77.59
47.01
41.25
38.16
29.81
22.41
220
200
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)

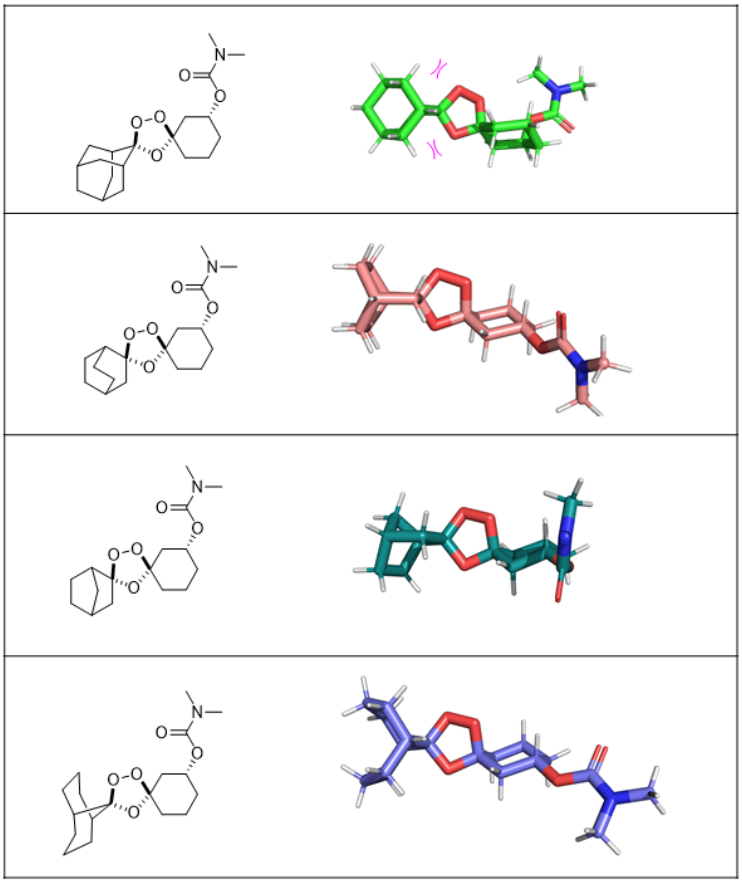


Figure S1. Representative low-energy conformations of putative bridged bicyclic trioxolane adducts, modelled as the *N,N*-dimethyl carbamates, using MarvinSketch (v19.10).