Synthesis of push-pull-activated ynol ethers and their evaluation in the bioorthogonal hydroamination reaction

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Supporting Information

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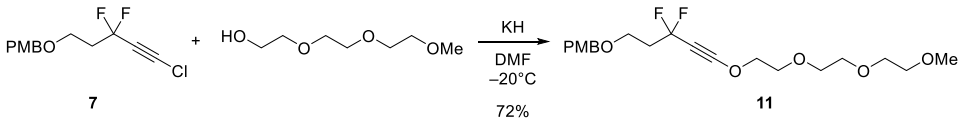
General Chemical Procedures. All reactions were conducted in flame-dried round-bottom flasks under a positive pressure of nitrogen unless otherwise stated. Gas-tight syringes with stainless steel needles or cannulae were used to transfer air- and moisture-sensitive liquids. Flash column chromatography was performed using granular silica gel (60-Å pore size, 40–63 μm, Silicycle). Analytical thin layer chromatography (TLC) was performed using glass plates pre-coated with 0.25 mm silica gel impregnated with a fluorescent indicator (254 nm, Silicycle). TLC plates were visualized by exposure to short wave ultraviolet light (254 nm) and/or an aqueous solution of potassium permanganate ($KMnO_4$). Organic solutions were concentrated at 20 °C on rotary evaporators capable of achieving a minimum pressure of ~2 torr unless otherwise stated. Room temperature is defined as 21.5 ± 2.5 °C. Reaction heating was performed using a UCON fluid heating bath.

General Chemical Materials. All solvents were purchased from Fisher Scientific or Sigma–Aldrich. Unless otherwise stated chemical reagents were purchased from Fisher Scientific, Sigma–Aldrich, Alfa Aesar, Oakwood Chemical, Acros Organics, Combi-Blocks, or TCI America. CMA refers to a solution of 80:18:2 v/v/v chloroform:methanol:ammonium hydroxide (28–30% ammonia solution). Chloroform used in CMA solutions and as co-eluents in silica gel column chromatography were stabilized with 0.75% v/v ethanol. Chloroform used in all hydroamination reactions were stabilized with pentene.

General Chemical Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra, recorded with a 500 MHz Avance III Spectrometer with multi-nuclear Smart probe, are reported in parts per million on the δ scale, and are referenced from the residual protium in the NMR solvent ($CDCl_3$: δ 7.24, CD_3OD: δ 3.31, D_2O: δ 4.79, CD_3CN: δ 1.94). Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, dq = doublet of quartet, td = triplet of doublet, tt = triplet of triplet, ddd = doublet of doublet of doublet), coupling constant(s) in Hertz, integration, assignment]. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra, recorded with a 500 MHz Avance III Spectrometer with multi-nuclear Smart probe, are referenced from the carbon resonances of the solvent ($CDCl_3$: δ 77.23, CD_3OD: δ 49.15). Fluorine-19 nuclear magnetic resonance (^{19}F NMR) is calibrated from the fluorine resonances of the benzotrifluoride ($CDCl_3$: δ –62.76, CD_3OD: δ –64.24, CD_3CN: δ –63.22). Data are reported as follows: chemical shift (assignment). Infrared data (IR) were obtained with a Cary 630 Fourier transform infrared spectrometer equipped with a diamond ATR objective and are reported as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad). High resolution mass spectra (HRMS) were recorded on a Q Exactive™ Plus Hybrid Quadrupole-Orbitrap™ Mass Spectrometer using an electrospray ionization (ESI), atmospheric pressure ionization (API), or electron ionization (EI) source. Automated C_{18} reverse phase chromatography was performed using a Isolera One (Biotage) purification system. High performance liquid chromatography (HPLC) purification was performed using an Agilent 1260 Infinity system.

Synthetic Procedures and Characterizations



14,14-difluoro-18-(4-methoxyphenyl)-2,5,8,11,17-pentaoxaoctadec-12-yne (11):

Chloroalkyne **7** (28.7 mg, 105 µmol, 1 equiv) and potassium hydride (8.42 mg, 210 µmol, 2.00 equiv) were sequentially added to a solution of triethylene glycol monomethyl ether (17.8 µL, 110 µmol, 1.05 equiv) in *N*,*N*-dimethylformamide (1.00 mL) at –20 °C. After 1 h, the reaction was quenched with saturated aqueous ammonium chloride solution (1 mL) at –20 °C then diluted with diethyl ether (15 mL) and washed with saturated aqueous ammonium chloride solution (10 mL). The aqueous layer was extracted with diethyl ether (15 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting crude mixture was purified by flash column chromatography on silica gel (eluent: 20% acetone in hexanes) to provide alkyne **11** (30.3 mg, 72%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC) δ 7.24 (d, *J* = 8.5 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 1H), 4.43 (s, 2H), 4.23–4.19 (m, 2H), 3.78 (s, 3H), 3.76–3.72 (m, 2H), 3.69–3.60 (m, 8H), 3.55–3.52 (m, 2H), 3.36 (s, 3H), 2.34 (tt, J = 7.1 Hz, 2H).

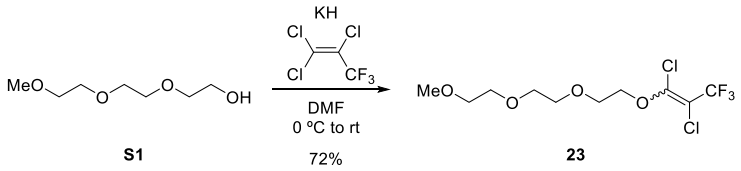
^{13}C NMR (126 MHz, CD_3OD, 25 ºC) δ 161.0, 131.6, 130.7, 116.4 (t, *J* = 230.1 Hz), 114.9, 96.7 (t, *J* = 7.1 Hz), 80.15, 73.8, 73.1, 71.8, 71.7, 71.6, 69.7, 65.6 (t, *J* = 4.6 Hz), 59.2, 55.8, 41.4 (t, *J* = 27.5 Hz), 34.2 (t, *J* = 42.8 Hz).

^{19}F NMR (471 MHz, $CDCl_3$, 25 ºC) δ –76.4.

FTIR (thin film) cm^{-1}: 2873 (b), 2274 (m), 1513 (m), 1245 (m), 1088 (s), 1029 (s), 948 (m), 820 (m).

HRMS (ESI) (*m/z*) calc'd for $C_{20}H_{29}F_2O_6$ $[M+H]^+$: 403.1927, found: 403.1920.

TLC (20% acetone in hexanes) R*f*: 0.46 ($KMnO_4$).



12,13-dichloro-14,14,14-trifluoro-2,5,8,11-tetraoxatetradec-12-ene (23):

1,1,2-Trichloro-3,3,3-trifluoropropene (857 µL, 7.00 mmol, 2.00 equiv) and potassium hydride (421 mg, 10.5 mmol, 3.00 equiv) were sequentially added to a solution of triethylene glycol monomethyl ether (563 µL, 3.50 mmol, 1 equiv) in *N*,*N*-dimethylformamide (14 mL) at 0 °C and allowed to warm to room temperature. After 7.5 h, the reaction was quenched with water (4 mL) at 0 °C then diluted with diethyl ether (100 mL) and washed with water (40 mL). The aqueous layer was extracted with diethyl ether (3 × 25 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography on silica gel (eluent: 5% acetone in hexanes) to provide enol ether **23** (821 mg, 72%, *E*:*Z* 2.15:1) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC) [*E*] δ 4.32–4.27 (m, 2H), 3.79–3.75 (m, 2H), 3.69–3.61 (m, 6H), 3.55–3.51 (m, 2H), 3.36 (s, 3H). [*Z*] δ 4.25–4.21 (m, 2H), 3.76–3.72 (m, 2H), 3.65–3.62 (m, 6H), 3.55–3.51 (m, 2H), 3.36 (s, 3H).

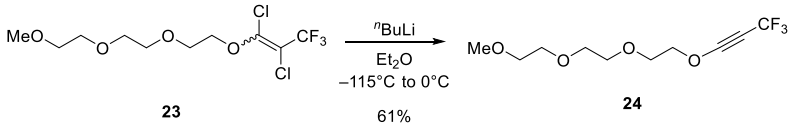
^{13}C NMR (126 MHz, $CDCl_3$, 25 ºC) [*E*] δ 146.0 (q, *J* = 2.5 Hz), 121.3 (q, *J* = 271.0 Hz), 102.2 (q, *J* = 39.4 Hz), 72.1, 71.3, 71.2, 70.8, 70.8, 69.3, 59.2. [*Z*] 150.6 (q, *J* = 2.6 Hz), 121.0 (q, *J* = 272.7 Hz), 106.5 (q, *J* = 38.3 Hz), 72.9, 72.1, 71.0, 70.8, 70.8, 69.1, 59.2.

^{19}F NMR (471 MHz, $CDCl_3$, 25 ºC) [*E*] δ –59.9. [*Z*] δ –60.8.

FTIR (thin film) cm^{-1}: [*E*] 2877 (b), 1625 (m), 1297 (w), 1207 (w), 1122 (s), 1025 (m), 719 (w). [*Z*] 2877 (b), 1628 (m), 1301 (s), 1189 (m), 1125 (s), 1036 (m), 693 (m).

HRMS (ESI) (*m/z*) calc'd for $C_{10}H_{19}Cl_2F_3NO_4$ $[M+NH_4]^+$: 344.0638, 346.0608, found: 344.0634, 346.0603.

TLC (20% acetone in hexanes) [*E*] R*f*: 0.44 ($KMnO_4$). [*Z*] R*f*: 0.46 ($KMnO_4$).



23 **24**

14,14,14-trifluoro-2,5,8,11-tetraoxatetradec-12-yne (24):

n-Butyllithium (160 µL, 399 µmol, 1.30 equiv, 2.5 M in hexanes) was added dropwise to a solution of enol ether **22** (100 mg, 307 µmol, 1 equiv) in diethyl ether (10 mL) at –115 °C. The reaction flask was removed from the cooling bath then allowed to warm to 0 °C over 20 min. The reaction was then quenched with saturated aqueous ammonium chloride solution (1 mL) then diluted with dichloromethane (60 mL) and washed with saturated aqueous ammonium chloride solution (20 mL). The aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting crude mixture was purified by flash column chromatography on silica gel (eluent: gradient, 20→40% ethyl acetate in hexanes) to provide alkyne **24** (47.7 mg, 61%) as a colorless oil.

^{1}H NMR (500 MHz, CD_3OD, 25 ºC) δ 4.46–4.43 (m, 2H), 3.83–3.80 (m, 2H), 3.68–3.63 (m, 6H), 3.57–3.53 (m, 2H), 3.36 (s, 3H).

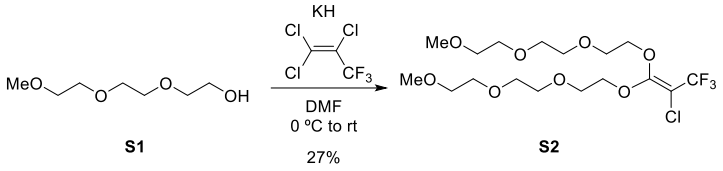
^{13}C NMR (126 MHz, CD_3OD, 25 ºC) δ 117.8 (q, *J* = 253.0 Hz), 96.0 (q, *J* = 6.3 Hz), 81.5, 73.1, 71.9, 71.7, 71.6, 69.7, 59.2, 28.9 (q, *J* = 53.8 Hz).

^{19}F NMR (471 MHz, $CDCl_3$, 25 ºC) δ –46.0.

FTIR (thin film) cm^{-1}: 2878 (b), 2281 (m), 1115 (s), 1077 (s), 939.3 (w), 828 (w).

HRMS (ESI) (*m/z*) calc'd for $C_{10}H_{15}F_3NaO_4$ $[M+Na]^+$: 279.0815, found: 279.0810.

TLC (40% ethyl acetate in hexanes) R*f*: 0.25 ($KMnO_4$).



12-(1-chloro-2,2,2-trifluoroethylidene)-2,5,8,11,13,16,19,22-octaoxatricosane (S2):

1,1,2-Trichloro-3,3,3-trifluoropropene (30.5 µL, 249 µmol, 1 equiv) and potassium hydride (60.0 mg, 1.49 mmol, 6.00 equiv) were sequentially added to a solution of triethylene glycol monomethyl ether (80.5 µL, 498 µmol, 2.00 equiv) in *N*,*N*-dimethylformamide (2 mL) at 0 °C and allowed to warm to room temperature. After 7.5 h, the reaction was quenched with water (1 mL) at 0 °C then diluted with diethyl ether (20 mL) and washed with water (10 mL). The aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography on silica gel (eluent: 20% acetone in hexanes) to provide the enol ether **S2** (62.0 mg, 27%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC) δ 4.23–4.19 (m, 2H), 4.13–4.08 (m, 2H), 3.75–3.71 (m, 2H), 3.71–3.67 (m, 2H), 3.67–3.59 (m, 12H), 3.54–3.50 (m, 4H), 3.36 (s, 3H), 3.35 (s, 3H).

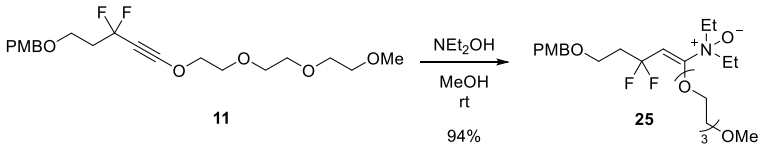
^{13}C NMR (126 MHz, CD_3OD, 25 ºC) δ 161.9 (q, *J* = 2.2 Hz), 124.2 (q, *J* = 268.1 Hz), 89.0 (q, *J* = 111.0 Hz), 73.1, 73.1, 71.9, 71.8, 71.7, 71.7, 71.6, 71.6, 71.5, 70.9, 70.8, 59.2, 59.2.

^{19}F NMR (471 MHz, $CDCl_3$, 25 ºC) δ –60.4.

FTIR (thin film) cm^{-1}: 2874 (b), 1655 (m), 1454 (w), 1316 (m), 1103 (s), 1062 (s), 1025 (2), 980 (m), 850 (w).

HRMS (ESI) (*m/z*) calc'd for $C_{17}H_{30}ClF_3NaO_8$ $[M+Na]^+$: 477.1474, 479.1444, found: 477.1465, 479.1430.

TLC (40% acetone in hexanes) R*f*: 0.45 ($KMnO_4$).



(*Z*)-*N*,*N*-diethyl-14,14-difluoro-18-(4-methoxyphenyl)-2,5,8,11,17-pentaoxaoctadec-12-en-12-amine oxide (25):

N,*N*-Diethylhydroxylamine (5.60 µL, 55.0 µmol, 1.30 equiv) was added to a solution of alkyne **11** (17.0 mg, 42.3 µmol, 1 equiv) in methanol (500 uL) at room temperature. After 1 h, the reaction mixture was diluted with dichloromethane (5 mL) and immediately purified by flash chromatography on silica gel (eluent: gradient, 3→30% CMA in chloroform) to provide enamine *N*-oxide **25** (19.4 mg, 94%) as a colorless oil.

^{1}H NMR (500 MHz, CD_3OD, 25 ºC) δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.44 (t, *J* = 15.1, 1H), 4.44 (s, 2H), 4.39–4.37 (m, 2H), 3.83–3.76 (m, 2H), 3.78 (s, 3H), 3.73–3.71 (m, 2H), 3.66–3.59 (m, 8H), 3.54–3.51 (m, 2H), 3.35 (s, 3H), 3.28–3.23 (m, 2H), 2.38 (tt, *J* = 15.6, 6.5 Hz, 2H), 1.19 (t, *J* = 7.1 Hz, 6H).

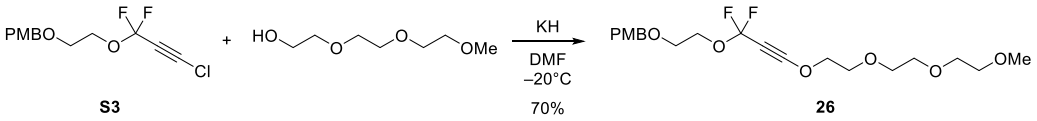
^{13}C NMR (126 MHz, CD_3OD, 25 ºC) δ 161.0, 159.7 (t, *J* = 4.6 Hz), 131.5, 130.7, 122.0 (t, *J* = 238.3 Hz), 114.9, 103.9 (t, *J* = 26.9 Hz), 78.2 (t, *J* = 6.2 Hz), 73.9, 73.2, 71.7, 71.6, 71.6, 71.5, 70.7, 64.8 (t, *J* = 5.3 Hz), 59.2, 55.8, 40.1 (t, *J* = 26.2 Hz), 8.7.

^{19}F NMR (471 MHz, CD_3OD, 25 ºC) δ –87.2.

FTIR (thin film) cm^{-1}: 2874 (b), 1696 (m), 1513 (m), 1245 (m), 1100 (s), 820 (m).

HRMS (ESI) (*m/z*) calc'd for $C_{24}H_{40}F_2NO_7$ $[M+H]^+$: 492.2767, found: 492.2761.

TLC (25% CMA in chloroform) R*f*: 0.30 ($KMnO_4$).



S3 70% **26**

14,14-difluoro-19-(4-methoxyphenyl)-2,5,8,11,15,18-hexaoxanonadec-12-yne (26):

Chloroalkyne **S3** (40.1 mg, 138 µmol, 1 equiv) and potassium hydride (11.1 mg, 276 µmol, 2.00 equiv) were sequentially added to a solution of triethylene glycol monomethyl ether (23.3 µL, 145 µmol, 1.05 equiv) in *N*,*N*-dimethylformamide (1.30 mL) at –20 °C. After 1 h, the reaction was quenched with saturated aqueous ammonium chloride solution (1 mL) at –20 °C then diluted with diethyl ether (15 mL) and washed with saturated aqueous ammonium chloride solution (10 mL). The aqueous layer was extracted with diethyl ether (15 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting crude mixture was purified by flash column chromatography on silica gel (eluent: 20% acetone in hexanes) to provide alkyne **26** (40.2 mg, 70%) as a colorless oil.

^{1}H NMR (500 MHz, CD_3OD, 25 ºC) δ 7.27 (d, *J* = 6.7 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 4.49 (s, 2H), 4.35–4.32 (m, 2H), 4.01–3.99 (m, 2H), 3.79 (s, 3H), 3.79–3.76 (m, 2H), 3.66–3.60 (m, 8H), 3.55–3.52 (m, 2H), 3.31 (s, 3H).

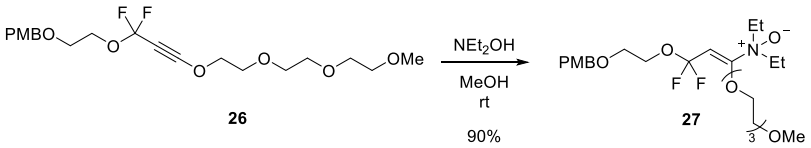
^{13}C NMR (126 MHz, CD_3OD, 25 ºC) δ 161.0, 131.5, 130.7, 117.8 (t, *J* = 239.0 Hz), 114.9, 94.4 (t, *J* = 6.1 Hz), 80.6, 73.9, 73.1, 71.8, 71.7, 71.6, 69.7, 69.1, 66.1 (t, *J* = 3.0 Hz), 59.2, 55.8, 31.8 (t, *J* = 56.2 Hz).

^{19}F NMR (471 MHz, $CDCl_3$, 25 ºC) δ –51.0.

FTIR (thin film) cm^{-1}: 2874 (b), 2277 (m), 1513 (m), 1163 (m), 1096 (s), 1003 (s), 816 (m).

HRMS (ESI) (*m/z*) calc'd for $C_{20}H_{29}F_2O_7$ $[M+H]^+$: 419.1876, found: 419.1868.

TLC (20% acetone in hexanes) Rf: 0.45 ($KMnO_4$).



26 90% **27**

(*Z*)-*N*,*N*-diethyl-14,14-difluoro-19-(4-methoxyphenyl)-2,5,8,11,15,18-hexaoxanonadec-12-en-12-amine oxide (27):

N,*N*-Diethylhydroxylamine (7.70 µL, 79.6 µmol, 1.30 equiv) was added to a solution of alkyne **26** (25.6 mg, 61.2 µmol, 1 equiv) in methanol (500 uL) at room temperature. After 1 h, the reaction mixture was diluted with dichloromethane (5 mL) and immediately purified by flash chromatography on silica gel (eluent: gradient, 3→30% CMA in chloroform) to provide enamine *N*-oxide **27** (28.0 mg, 90%) as a colorless oil.

^{1}H NMR (500 MHz, CD_3OD, 25 ºC) δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.38 (t, *J* = 8.2, 1H), 4.47 (s, 2H), 4.42–4.40 (m, 2H), 4.11–4.09 (m, 2H), 3.79 (s, 3H), 3.82–3.75 (m, 2H), 3.71–3.69 (m, 2H), 3.60–3.57 (m, 4H), 3.56–3.53 (m, 2H), 3.53–3.51 (m, 2H), 3.49–3.47 (m, 2H), 3.35 (s, 3H), 3.28–3.23 (m, 2H), 1.2 (t, *J* = 7.1 Hz, 6H).

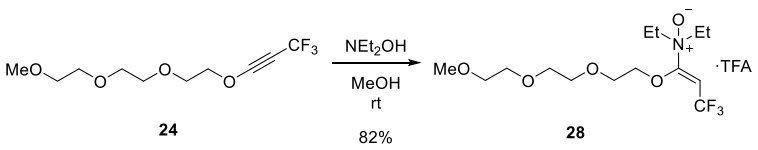
^{13}C NMR (126 MHz, CD_3OD, 25 ºC) δ 161.0, 160.8 (t, *J* = 7.5 Hz), 131.6, 130.7, 123.5 (t, *J* = 253.0 Hz), 115.0, 100.5 (t, *J* = 41.3 Hz), 77.7 (t, *J* = 3.5 Hz), 73.8, 73.2, 71.7, 71.5, 71.5, 70.5, 69.1, 64.7 (t, *J* = 5.5 Hz), 64.1, 59.2, 55.9, 8.6.

^{19}F NMR (471 MHz, CD_3OD, 25 ºC) δ –61.8.

FTIR (thin film) cm^{-1}: 2874 (b), 1703 (w) 1513 (w), 1345 (m), 1245 (m), 1103 (s), 824 (w).

HRMS (ESI) (*m/z*) calc'd for $C_{24}H_{40}F_2NO_8$ $[M+H]^+$: 508.2717, found: 508.2709.

TLC (20% CMA in chloroform) R*f*: 0.15 ($KMnO_4$).



24 28

(Z)-*N*,*N*-diethyl-14,14,14-trifluoro-2,5,8,11-tetraoxatetradec-12-en-12-amine oxide trifluoroacetate (28):

N,*N*-Diethylhydroxylamine (9.90 µL, 96.3 µmol, 1.35 equiv) was added to a solution of alkyne **24** (18.3 mg, 71.3 µmol, 1 equiv) in methanol (700 µL) at room temperature. After 1 h, the reaction mixture was diluted with water (150 µL), and the resulting solution was purified by automated C_{18} reverse phase column chromatography (30 g C_{18} silica gel, 25 µm spherical particles, eluent: 20% MeCN/H_2O + 0.1% TFA (1 CV), gradient 20→80% MeCN/H_2O + 0.1% TFA (12 CV)). Fractions containing the desired compound were combined, and the solvent was removed under reduced pressure at 0 ºC with a rotary evaporator to provide enamine *N*-oxide **28** (45.8 mg, **28**:TFA of 1:3.8, 82%) as a white solid.

^{1}H NMR (500 MHz, CD_3OD, 25 ºC) δ 6.39 (q, *J* = 8.2 Hz, 1H), 4.60–4.58 (m, 2H), 4.28 (dq, *J* = 14.1, 7.1 Hz, 2H), 3.82 (dq, *J* = 14.1, 7.1 Hz, 2H), 3.81–3.79 (m, 2H), 3.68–3.66 (m, 2H), 3.64–3.59 (m, 4H), 3.55–3.52 (m, 2H), 3.36 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (126 MHz, CD_3OD, 25 ºC) δ 156.6 (q, *J* = 6.1 Hz), 123.7 (q, *J* = 268.3 Hz), 99.3 (q, *J* = 38.6 Hz), 80.9 (q, *J* = 4.1 Hz), 73.2, 71.5, 71.5, 71.4, 70.0, 64.4, 59.2, 8.4 [TFA δ 160.9 (q, *J* = 40.0 Hz), 117.2 (q, *J* = 285.0 Hz)].

^{19}F NMR (471 MHz, CD_3OD, 25 ºC) δ –56.3 [TFA δ –77.5].

FTIR (thin film) cm^{-1}: 2881 (b), 1782 (w), 1707 (w), 1357 (w), 1170 (s), 1133 (s), 947 (w).

HRMS (ESI) (*m/z*) calc'd for $C_{14}H_{27}F_3NO_5$ $[M+H]^+$: 346.1836, found: 346.1832.

TLC (30% CMA in chloroform) R*f*: 0.20 ($KMnO_4$).

Stability Study

Stability experiments for alkynes **11**, **24**, and **26** were carried out in 50% CD_3CN/PBS (pH 7.0) with or without glutathione (2 mM) at room temperature. Reactions were monitored via ^{19}F NMR spectroscopy using α,α,α-benzotrifluoride as an internal standard.

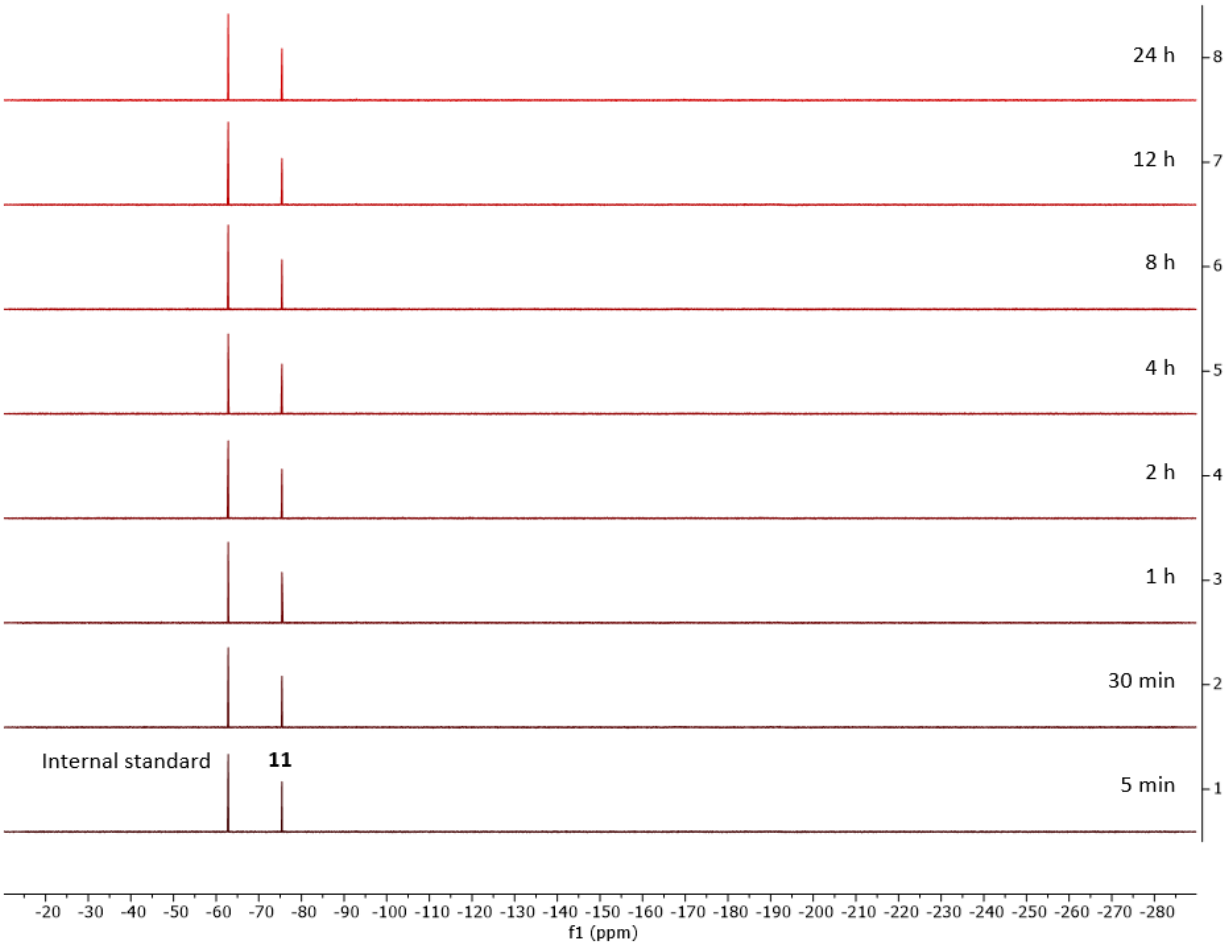


Figure S1. Alkyne **11** (500 µM) is stable in 50% CD_3CN/PBS (pH 7.0) and exhibits no apparent degradation over 24 h.

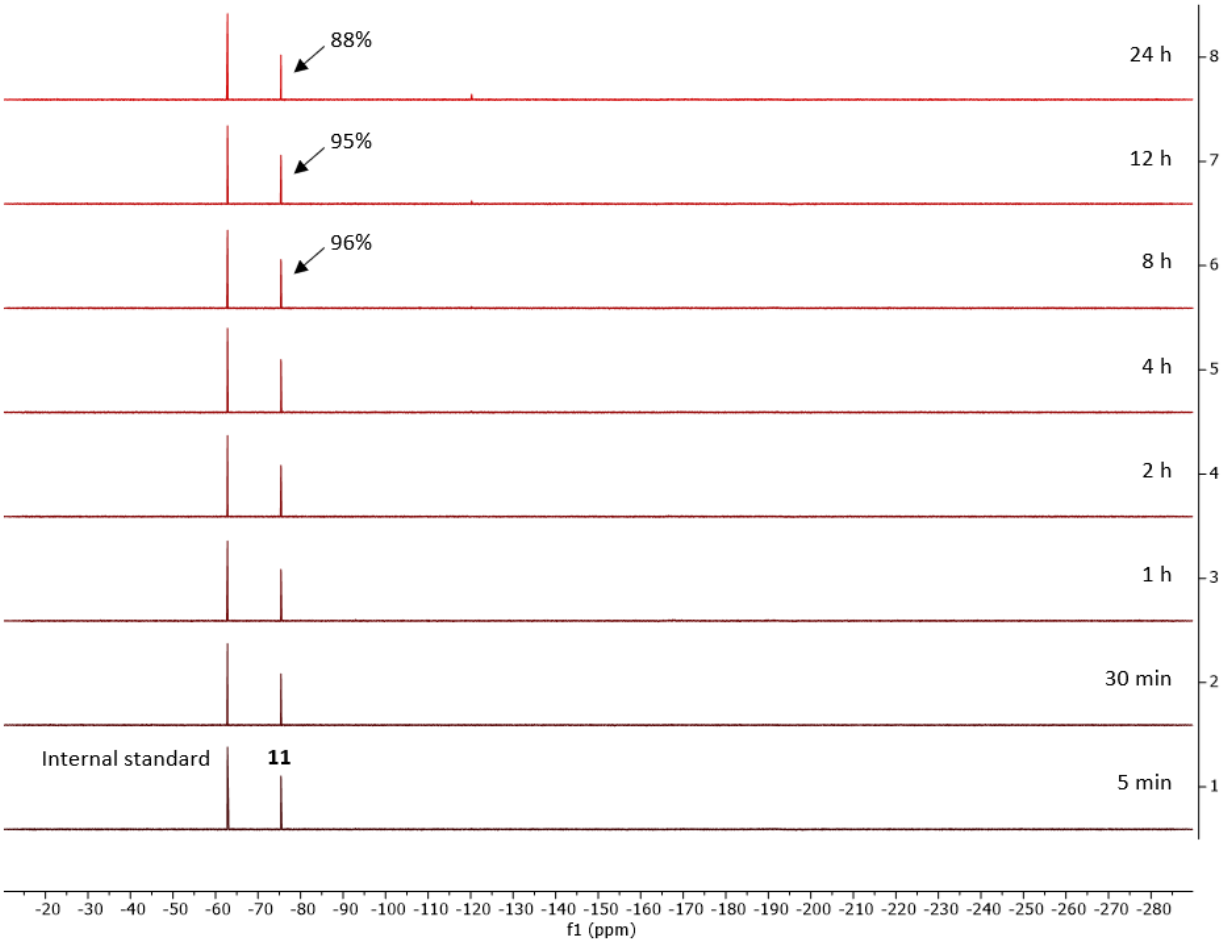


Figure S2. Alkyne **11** (500 µM) has a half-life of 125 h in 50% CD_3CN/PBS (pH 7.0) in the presence of glutathione (2 mM) and exhibits only 5% degradation over 12 h.

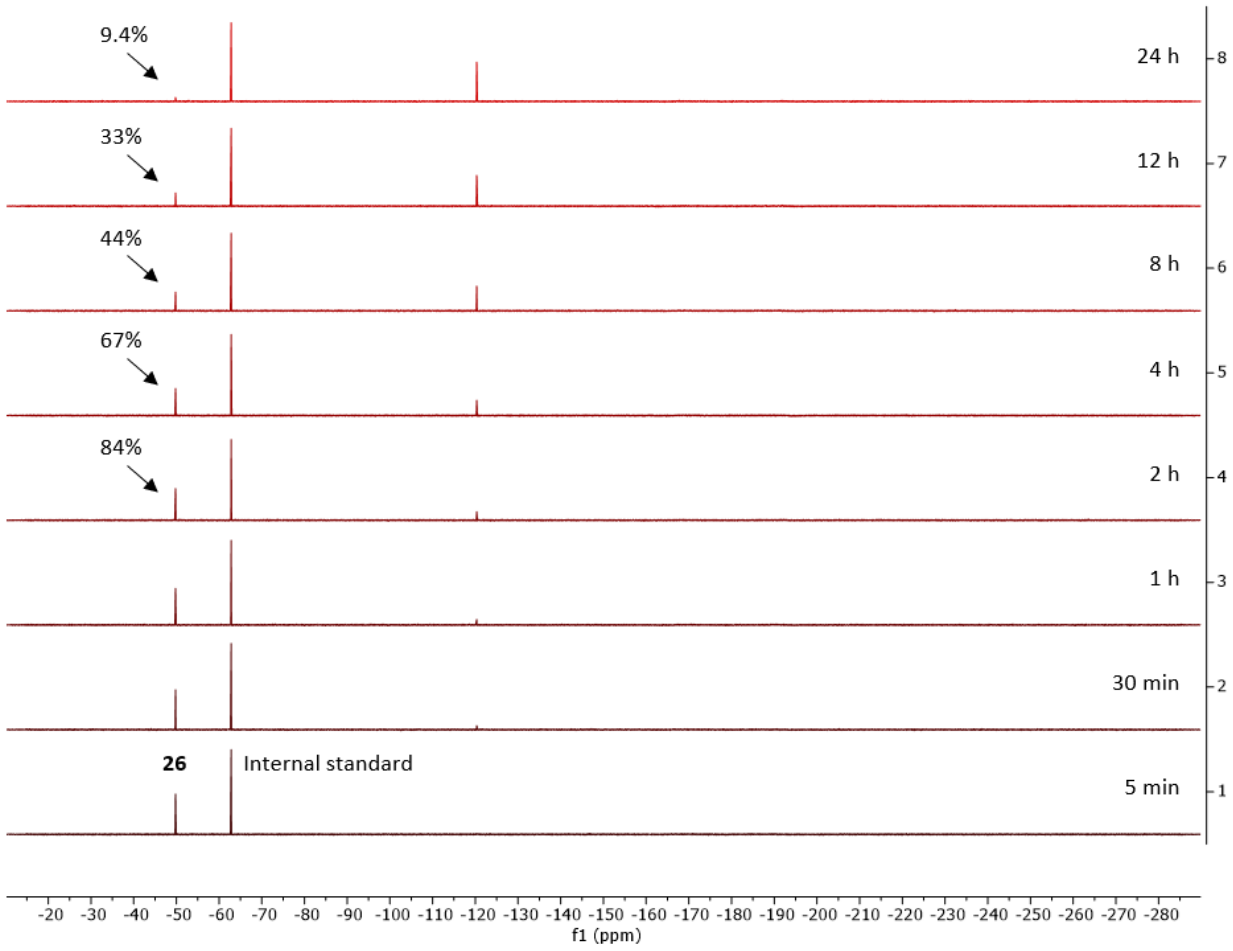


Figure S3. Alkyne **26** (500 µM) has a half-life of 7.1 h in 50% CD_3CN/PBS (pH 7.0).

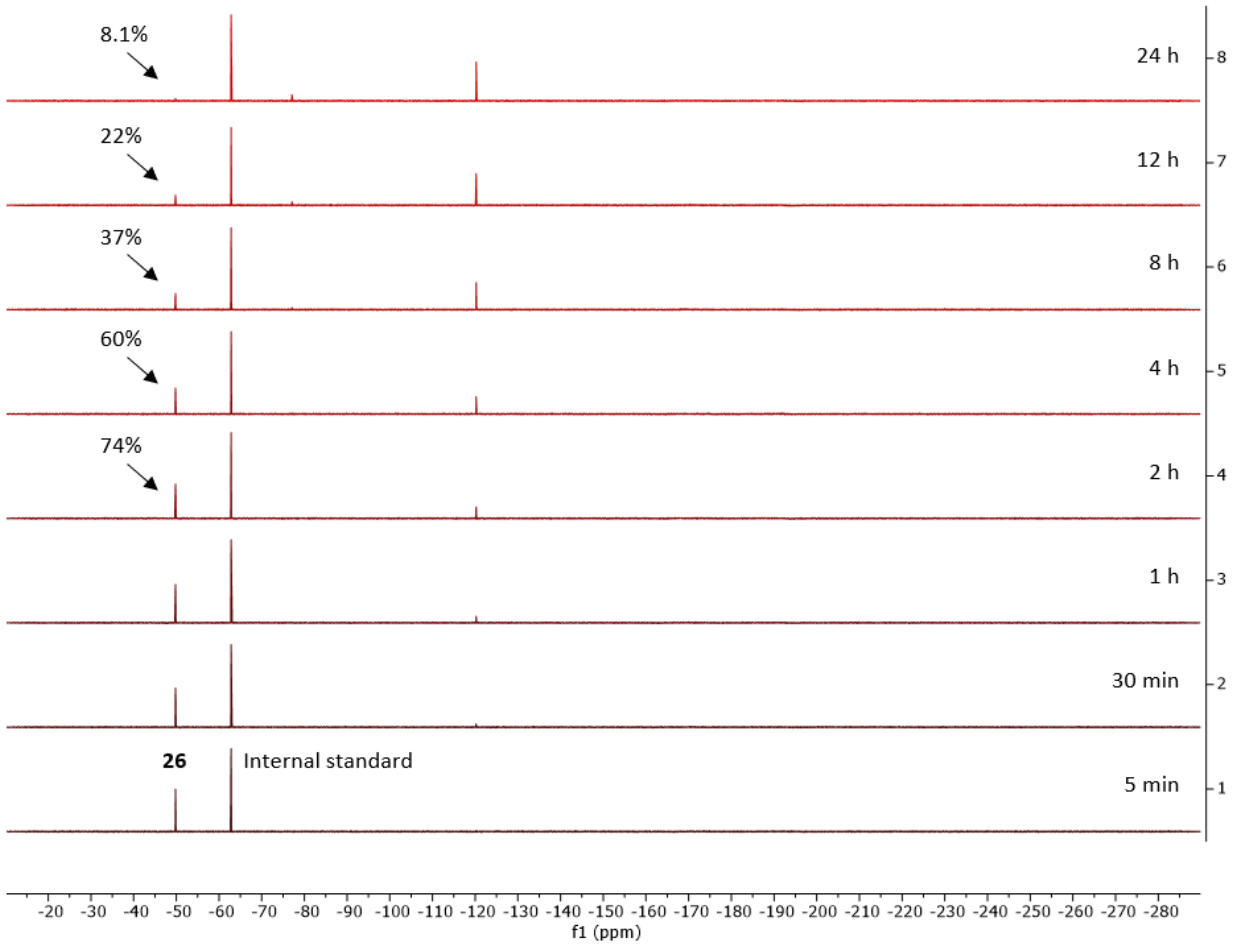


Figure S4. Alkyne **26** (500 µM) has a half-life of 6.5 h in 50% CD_3CN/PBS (pH 7.0) in the presence of glutathione (2 mM).

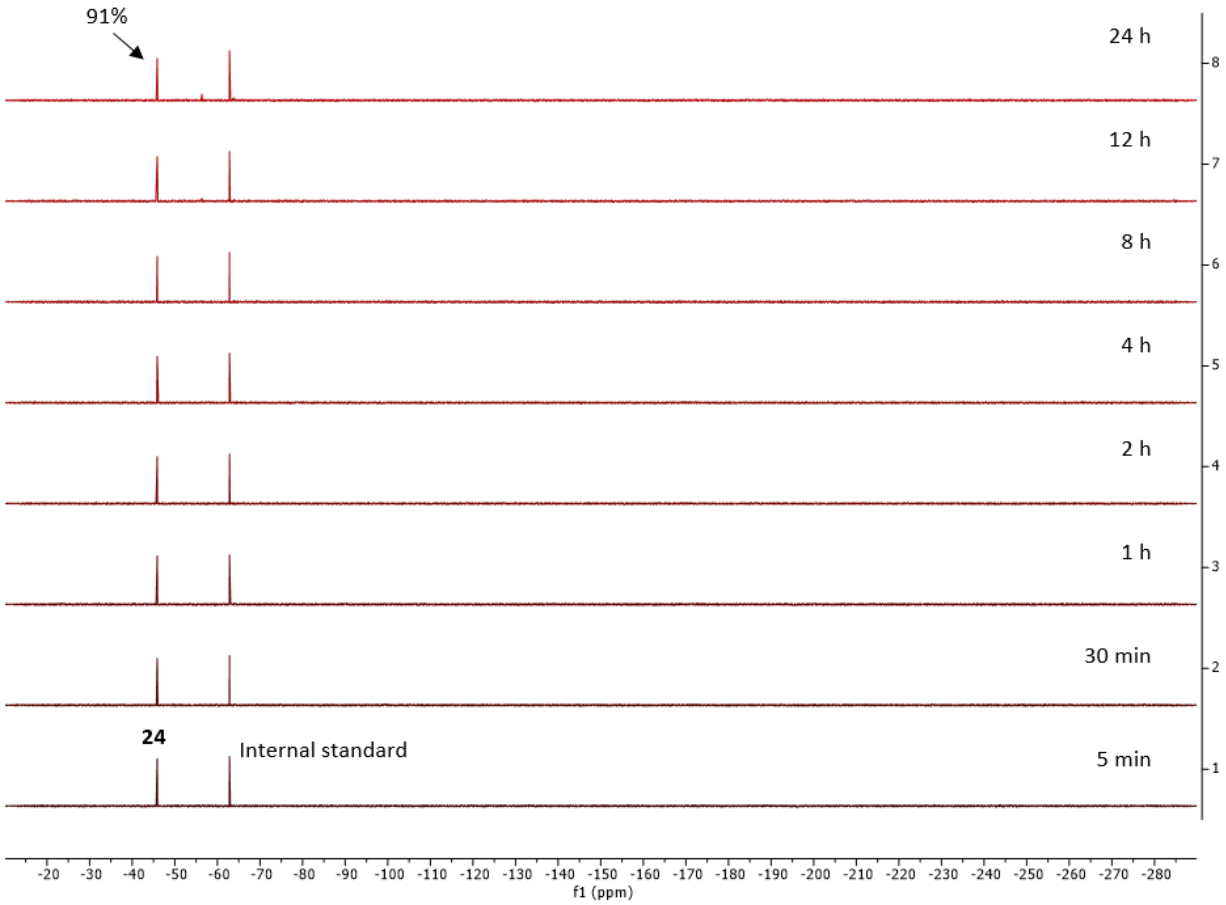


Figure S5. Alkyne **24** (500 μM) has a half-life of 4.6 days in 50% CD_3CN/PBS (pH 7.0) and exhibits no apparent degradation over 24 h.

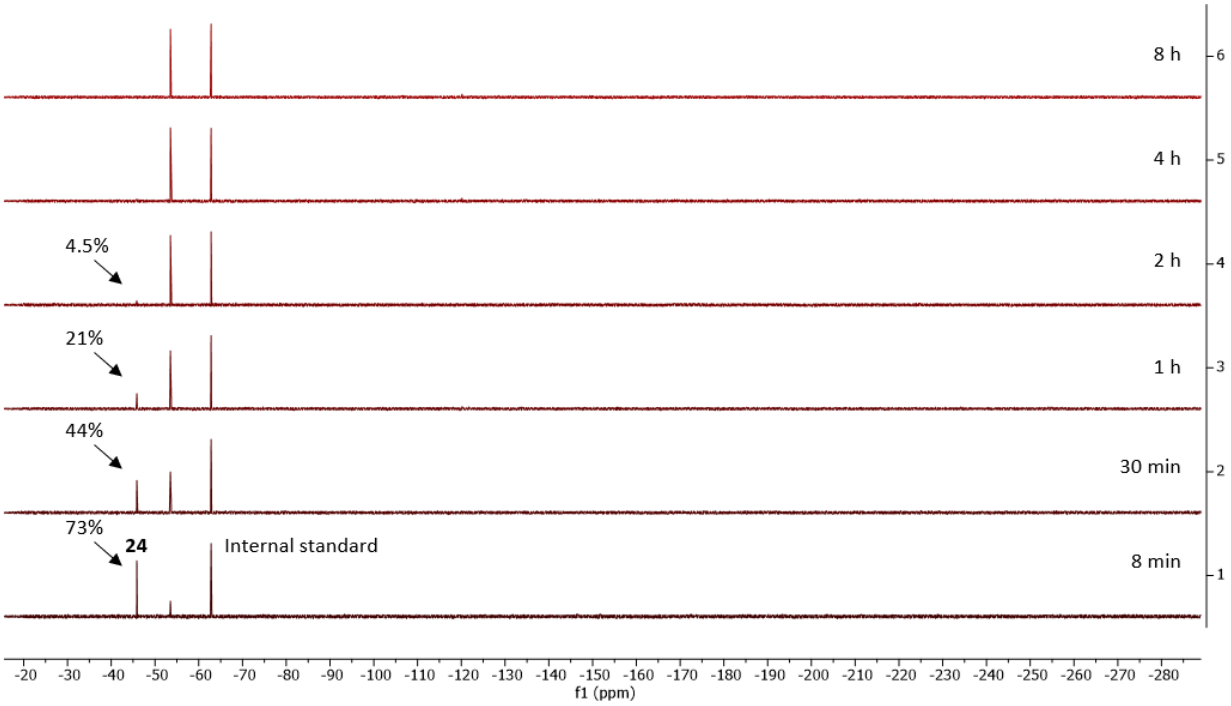


Figure S6. Alkyne **24** (500 μM) has a half-life of 24 min in 50% CD_3CN/PBS (pH 7.0) in the presence of glutathione (2 mM).

Kinetics Study

All kinetics experiments were carried out at room temperature in methanol or CD_3CN. Reactions in CD_3CN were monitored via ^{19}F NMR spectroscopy using α,α,α-benzotrifluoride (5 mM) as an internal standard. Reactions in methanol were monitored by ^{19}F NMR spectroscopy using α,α,α-benzotrifluoride (5 mM) as an internal standard. A capillary NMR tube (diameter 3 mm) filled with D_2O was inserted into each NMR tube (diameter 5 mm) to lock the magnetic field. Second-order kinetics were performed by combining alkynes **11**, **24**, and **26** with *N*,*N*-diethylhydroxylamine in a 1:1 molar ratio to achieve a starting concentration of 5 mM for each compound. The reported errors for rate constants represent the standard deviation of the mean for triplicate experiments.

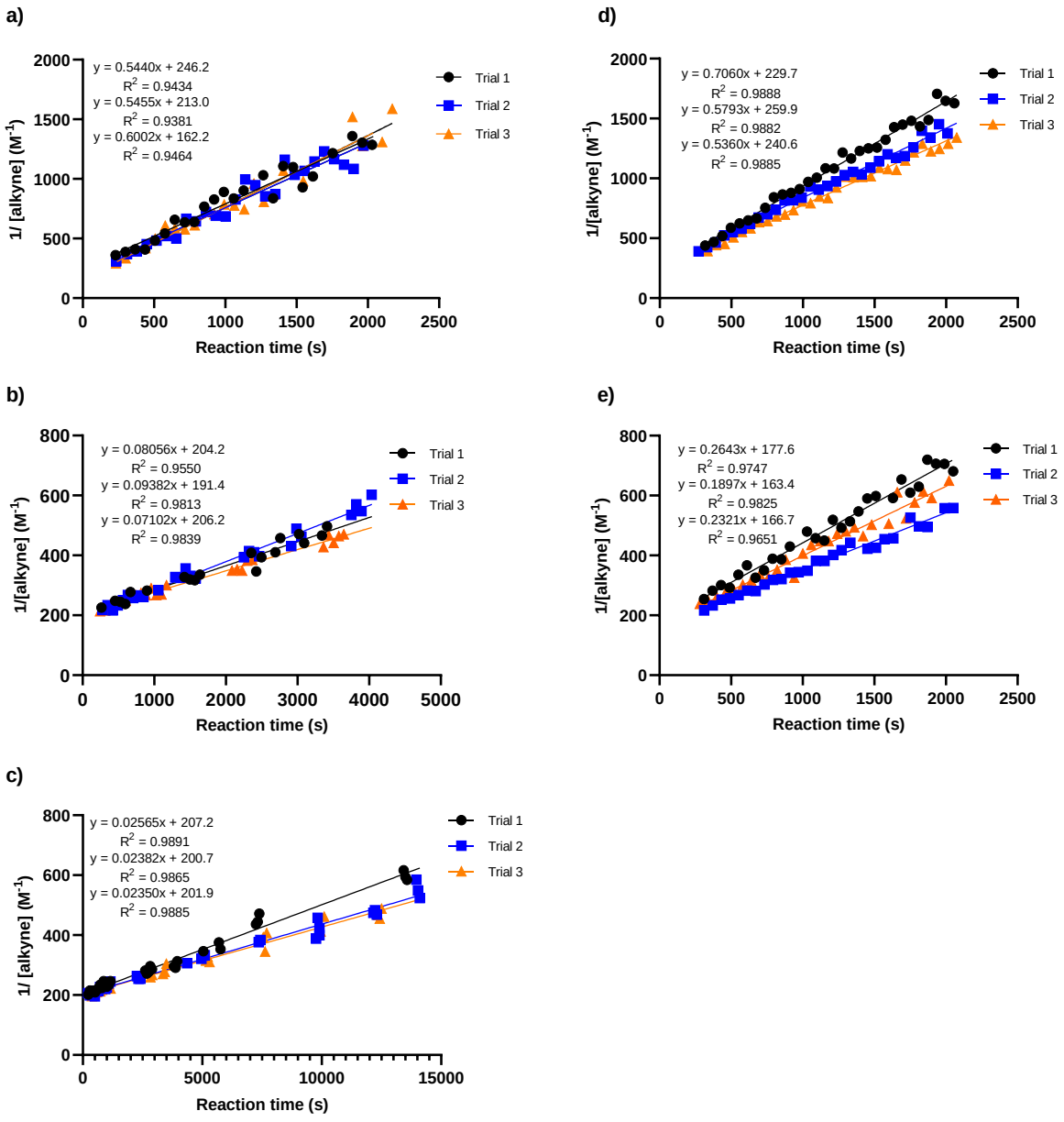


Figure S7. Reaction plots used to calculate second-order rate constants between alkynes **11**, **24**, and **26** (5 mM) and *N*,*N*-diethylhydroxylamine (5 mM). a) Alkyne **24** in methanol; b) Alkyne **26** in methanol; c)

Alkyne **11** in methanol; d) Alkyne **26** in CD_3CN; e) Alkyne **11** in CD_3CN. Each panel shows results performed in triplicate.

Computational Details

All calculations were conducted with Gaussian 09 software.[1] Geometry optimization of all species was performed using the M06-2X functional[2] with the 6-31G(d,p) basis set. Frequency analysis was carried out to ensure the stationary point was either a minimum or a transition state. Intrinsic reaction coordinates were computed for all transition states. Single-point calculations were carried out using the M06-2X functional with the 6-311G(2d,p) basis set. Hybridization was analyzed using natural bond orbital (NBO)[3-4] analysis implemented in Gaussian.

- Cartesian coordinates of optimized structures (Å)

NMe_2OH

N	0.00000000	0.02490000	-0.41697400
C	-1.19858000	-0.64238700	0.06738400
H	-1.22931400	-1.65128600	-0.35177800
H	-1.22122900	-0.70365200	1.16601500
C	1.19858300	-0.64238200	0.06738400
H	1.22932400	-1.65127900	-0.35178200
H	1.22123100	-0.70365100	1.16601500
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H	-0.00000300	1.91418700	-0.55581600
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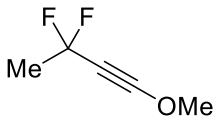
H	-2.07548200	-0.09063900	-0.27480900



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F	1.70023000	-0.86049200	-1.06576600
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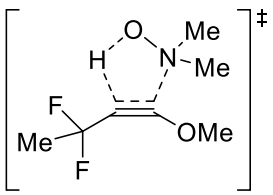
H	-3.18813500	-1.10941700	0.85830800
C	2.18348300	1.19580300	-0.05287100
H	1.94187100	1.75015900	-0.96013100
H	1.96386100	1.81181300	0.81954900
H	3.24097200	0.92533500	-0.05648000



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F	-2.81458400	0.49766800	-0.92881300
F	-2.29772300	-1.57592500	-0.49858700
O	1.19235400	1.69148400	0.01989200
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H	-0.16157700	3.01581600	0.87515600
H	1.22045500	3.71616400	-0.02499600
H	-0.15319500	2.97356800	-0.90859600
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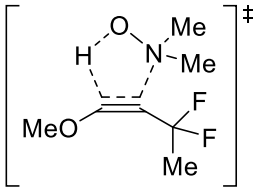

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F	1.55379700	1.18831800	-1.25490300
O	-2.65055200	0.90276600	0.04052100
C	-3.75943400	0.01197000	-0.05874800
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H	-4.65593600	0.63010500	-0.01427000
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H	1.70126000	3.25455300	0.23425600
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C	1.03633500	-1.89779400	1.32004000
H	1.16107600	-2.98599500	1.33899200
H	1.98145400	-1.39937500	1.52700100

H	0.29382400	-1.60206700	2.06273100
C	1.49511100	-1.70001600	-1.07788000
H	2.39124600	-1.11088600	-0.88170600
H	1.74478500	-2.76496500	-1.15140400
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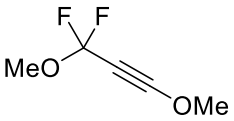

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O	-1.70333400	-0.91221900	-0.05690800
C	-3.10945600	-0.66677800	-0.06377100
H	-3.38928000	-0.06022400	-0.92795800
H	-3.57904200	-1.64642500	-0.12969900
H	-3.41678800	-0.16690800	0.85742400
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F	-1.22001400	1.04140900	-1.02701300
O	2.89548900	-0.77109900	0.04717300
C	3.79695200	0.34321400	-0.06571100
H	4.79826400	-0.08152900	-0.03689800
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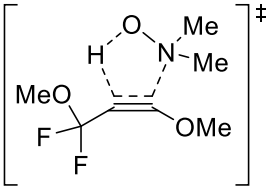

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O	2.25694700	-1.01921300	0.40191300
C	3.67242200	-1.18650900	0.39678200
H	4.15034900	-0.44355100	1.03933000
H	3.85556500	-2.18669100	0.78609500
H	4.06651300	-1.10591800	-0.61903900
F	2.25362200	0.28499200	-1.41007200
F	2.43798100	1.20020300	0.53674400
O	-1.75711400	1.56252400	0.11288600
C	-1.24884100	2.90086900	0.15631900
H	-0.57544000	3.01893900	1.00909000
H	-0.70898300	3.12701500	-0.76679700
H	-2.11650000	3.55095800	0.26010400
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H	-3.49891400	-0.11157600	1.30650600
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H	-3.53304400	-1.79552300	-1.28468400
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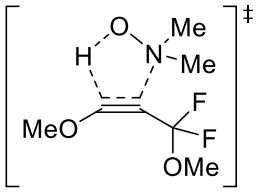
O	-1.22234700	-1.97507100	-0.07613400



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O	-1.95701800	-0.85293700	-0.26475400
C	-2.61891800	-2.11324600	-0.15910000
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H	-3.64678300	-1.93506100	-0.47007100
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F	0.01292100	-1.76359800	-0.80207300
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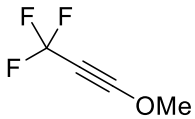
H	1.51685700	1.86852100	0.21054400
N	1.95799600	0.08786100	-0.02188400
C	2.38628500	-0.80313000	1.05331100
H	1.98902400	-1.80047500	0.86099400
H	3.48063900	-0.83372800	1.10844000
H	1.97958400	-0.42189300	1.98940800
C	2.44067600	-0.30762100	-1.34520800
H	3.53218400	-0.22293400	-1.38336200
H	2.12949200	-1.32993300	-1.55354900
H	1.99606600	0.36955600	-2.07576800
O	2.40222200	1.35569100	0.23638100



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C	1.24465500	-0.41101200	-0.00001400
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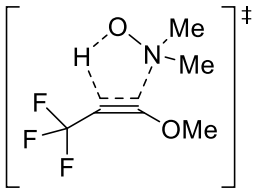
F	-1.95225800	-0.39191100	1.13497100
F	-1.65801000	1.33520100	-0.12577000

O	2.51760800	-0.64622000	0.00081800
C	3.34075800	0.53546500	0.00012500
H	4.36815800	0.17825700	0.00249100
H	3.14189600	1.12481200	-0.89725300
H	3.13892100	1.12797200	0.89475900
F	-1.98684500	-0.60736200	-1.00919400



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F	2.76967700	0.12237000	-1.11489800
F	2.81090800	0.23622200	1.04229800
O	-1.18641500	1.69045500	-0.00143200
C	-0.49979200	2.94905300	0.00060600
H	0.12392200	3.03338600	0.89388300
H	0.12432800	3.03611500	-0.89212200
H	-1.27448800	3.71421600	0.00146700
H	-0.26031800	-1.57970300	0.00869100
N	-1.89829700	-0.70559100	0.00037900
C	-2.68350400	-0.61677400	-1.22438500
H	-3.42114300	-1.42632400	-1.27887600
H	-3.18582800	0.35200800	-1.24375800
H	-1.99832200	-0.69196400	-2.06969200
C	-2.69165300	-0.61061600	1.21939400
H	-3.43006200	-1.41954700	1.27273800
H	-2.01223600	-0.68216300	2.06965200
H	-3.19358100	0.35848400	1.23080200
O	-1.19986100	-1.89816900	0.00569700
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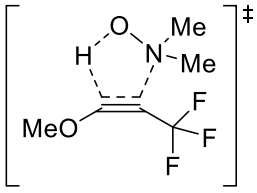

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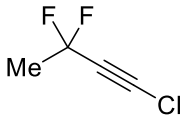
F	-0.78895200	1.77151500	-0.88710400
F	-0.24011100	1.79451000	1.19085700
O	2.33996400	-1.63426600	0.06230500
C	3.41164500	-0.68572700	-0.03771900
H	4.33781300	-1.25913500	-0.02422100
H	3.31972200	-0.12248900	-0.97033900

H	3.37480200	0.00446100	0.80953000
H	-0.23741300	-2.09919000	0.25110000
N	-1.53817500	-0.80575400	0.00365200
C	-2.34710800	-0.24167700	1.08196800
H	-2.52691900	0.81388000	0.87274300
H	-3.29937800	-0.77782200	1.16268000
H	-1.78756600	-0.34137500	2.01161600
C	-2.17705900	-0.74159500	-1.31156300
H	-3.06961800	-1.37612000	-1.32185500
H	-2.44190900	0.29043300	-1.53632100
H	-1.45992800	-1.10764400	-2.04740400
O	-1.25841400	-2.11451700	0.28409100
F	1.28356400	2.02957100	-0.32180400



C	-0.11215400	-0.05054700	-0.00022200
C	-1.31393500	-0.00626600	0.00003600
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F	1.80680300	-0.72641600	1.09095300
F	1.80707500	-0.72660700	-1.09075400
C	1.96234700	1.34154600	-0.00005000
H	1.64189100	1.88247200	-0.89088600
H	1.64191800	1.88244300	0.89081700
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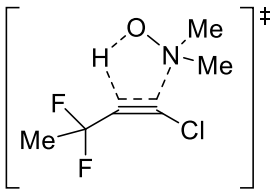

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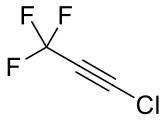
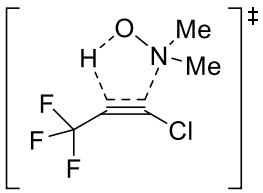
C	-0.30878652	0.69094978	-0.02763188
C	2.22246786	-0.12714374	-0.04357807
F	2.48955495	-1.44190097	-0.33095747
F	2.81993519	0.59070443	-1.03882534
C	2.87614266	0.21614948	1.27606201
H	2.73887714	1.27635980	1.48959400
H	2.43248629	-0.37788619	2.07574769
H	3.94115166	-0.01121440	1.20014937
H	-0.11187646	-1.48566616	-0.02611776
N	-1.80811160	-0.74389330	0.02426074
C	-2.62116393	-0.70585171	-1.18617108
H	-3.30315863	-1.56296015	-1.22178530
H	-3.19239847	0.22444841	-1.20074566
H	-1.94763352	-0.73833168	-2.04325551
C	-2.57272836	-0.68114711	1.26409833

H	-3.14263713	0.24990299	1.28252729
H	-3.25358816	-1.53624541	1.34429151
H	-1.86665100	-0.69775448	2.09510905
O	-1.03683755	-1.87912999	0.02136795
Cl	-1.25542715	2.09201058	-0.02265975



C	-0.09544100	0.00011400	-0.00056100
C	-1.29676200	-0.00038200	0.00037300
C	1.37293600	0.00003900	0.00007200
F	1.85230300	1.01408900	0.72430300
F	1.85224400	-1.13445800	0.51590200
F	1.85289700	0.12035800	-1.23995100
Cl	-2.93537600	0.00008600	-0.00009300



C	0.27682877	0.73522768	0.00206386
C	-0.80109742	0.15258648	0.00472953
H	0.10487413	-1.49652974	0.00874959
N	1.80543236	-0.74936089	0.00058878
C	2.60116878	-0.71062206	1.22140254
H	3.27225478	-1.57565279	1.27805757
H	3.18529933	0.21186146	1.23361875
H	1.91752715	-0.72390646	2.07120799
C	2.59093116	-0.71597596	-1.22699783
H	3.26143917	-1.58132198	-1.28559507
H	1.90013420	-0.73278207	-2.07093840
H	3.17497951	0.20641707	-1.24809393
O	1.02378028	-1.88266179	0.00634433
Cl	1.25473924	2.10167330	0.00024533
C	-2.23773156	-0.11847123	0.00052971
F	-2.86212582	0.50273613	1.00891392
F	-2.50606477	-1.43079903	0.12782303
F	-2.80469190	0.28515394	-1.14300586

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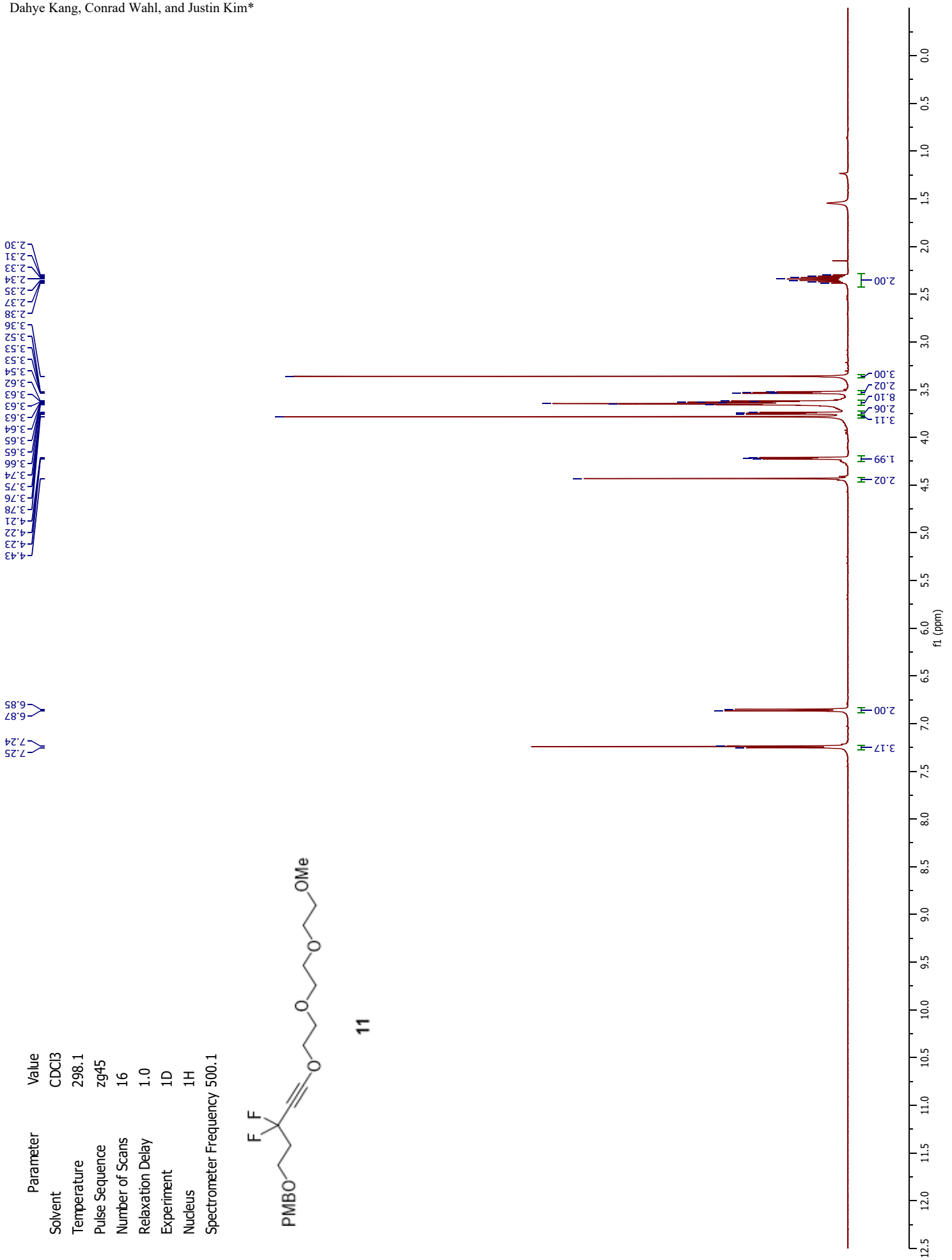
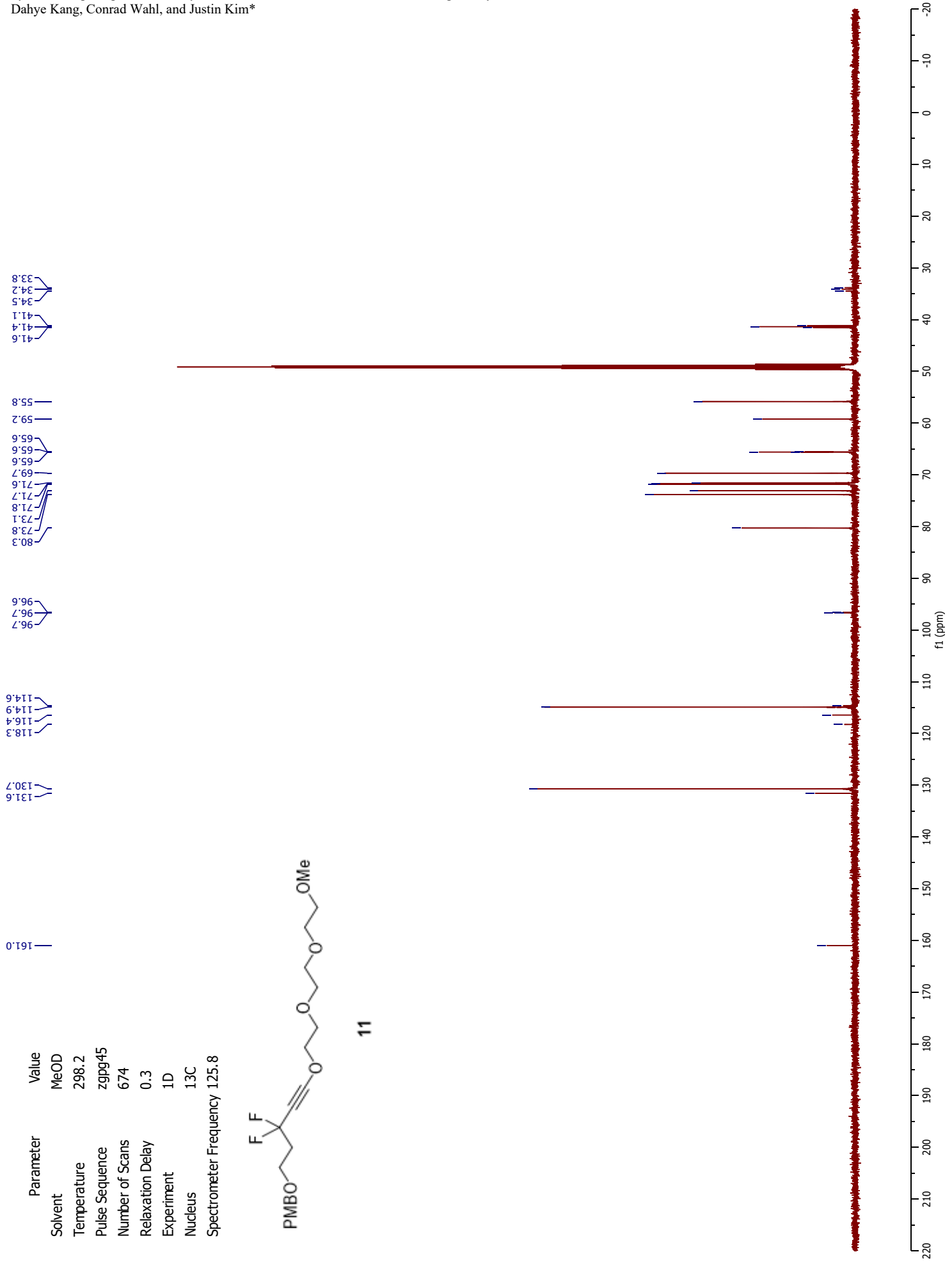
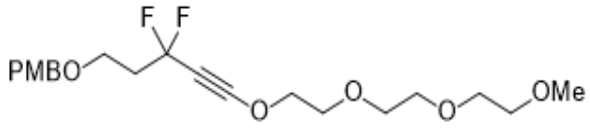
(4) Reed, A. E.; Curtiss, L. A.; Weinhold, F., Intermolecular Interactions from a Natural Bond Orbital, Donor-Acceptor Viewpoint. *Chem. Rev.* **1988,** *88*, 899.


Parameter Value
Solvent CDCl3
Temperature 298.1
Pulse Sequence zg45
Number of Scans 16
Relaxation Delay 1.0
Experiment 1D
Nucleus 1H
Spectrometer Frequency 500.1
PMBO
F F
OMe
11
f1 (ppm)


Parameter Value
Solvent MeOD
Temperature 298.2
Pulse Sequence zgpg45
Number of Scans 674
Relaxation Delay 0.3
Experiment 1D
Nucleus 13C
Spectrometer Frequency 125.8
PMBO
F F
OMe
11
161.0
131.6
130.7
118.3
116.4
114.9
114.6
96.6
96.7
96.7
80.3
73.8
73.1
71.8
71.7
71.6
69.7
65.6
65.6
65.6
59.2
55.8
41.6
41.4
41.1
34.5
34.2
33.8
f1 (ppm)

-76.4

Parameter	Value
Solvent	CDCl3
Temperature	298.1
Pulse Sequence	zgfhigqn.2
Number of Scans	16
Relaxation Delay	1.5
Experiment	1D
Nucleus	19F
Spectrometer Frequency	470.5



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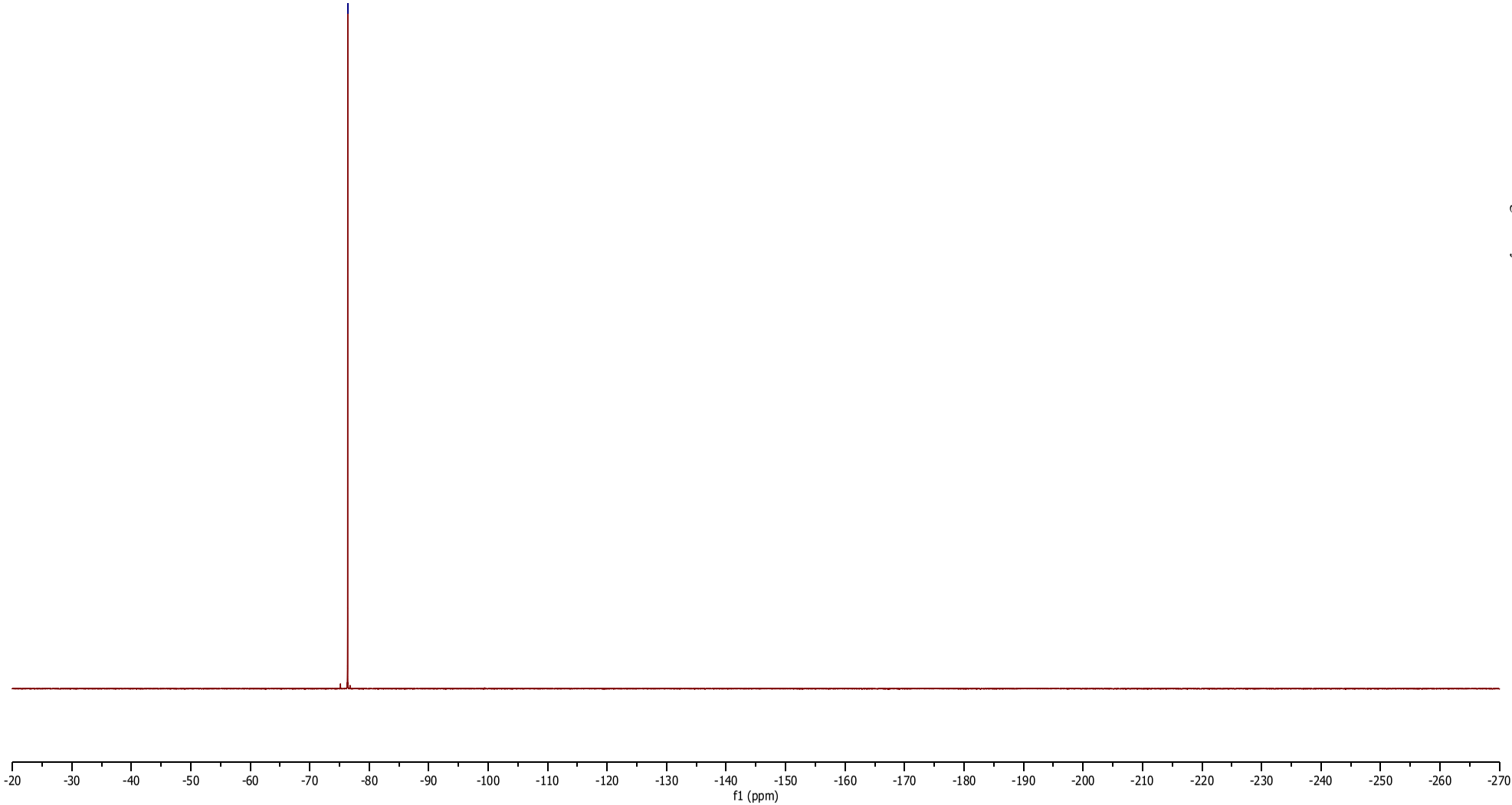

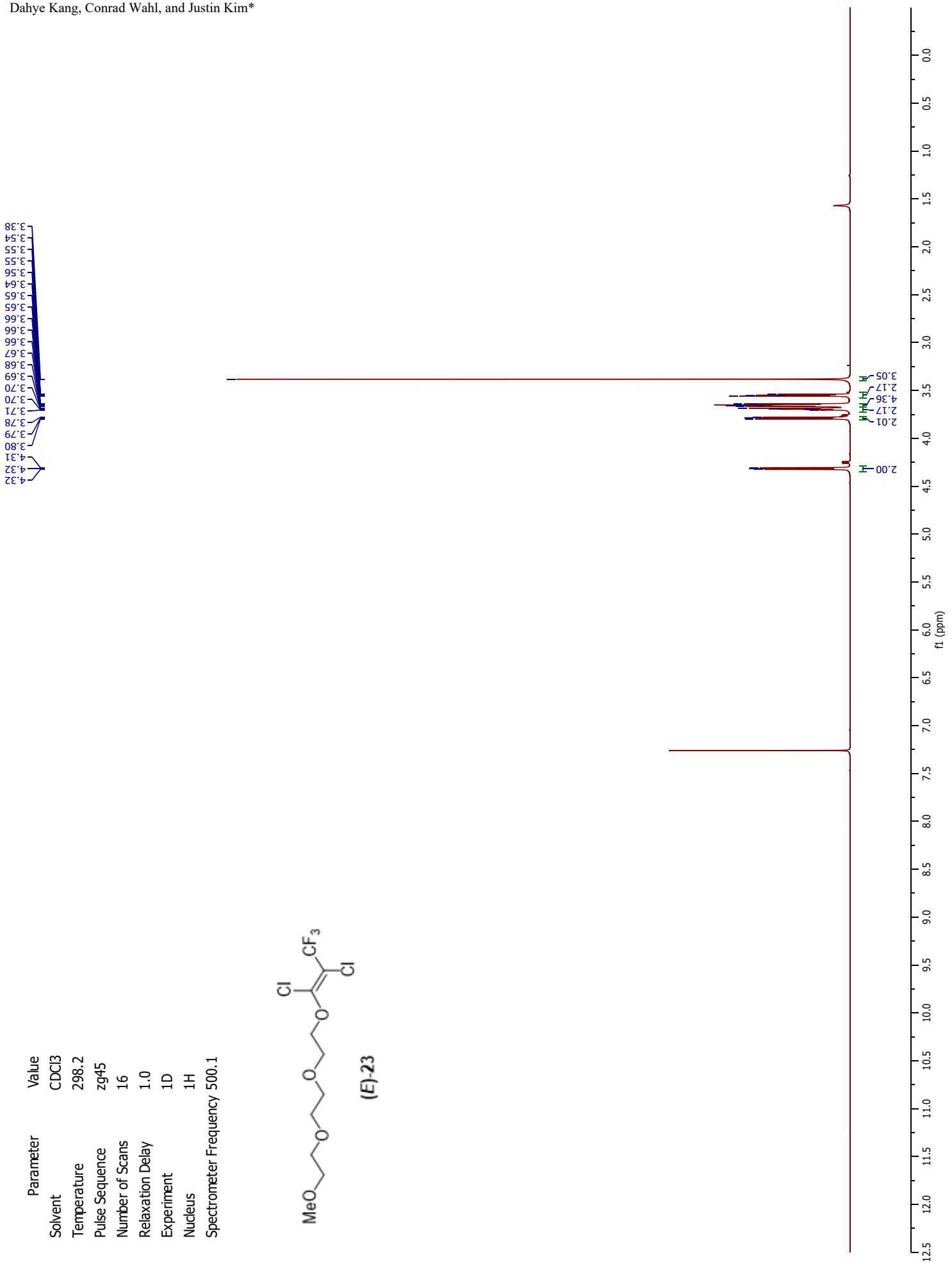
Parameter Value
Solvent CDCl3
Temperature 298.2
Pulse Sequence zg45
Number of Scans 16
Relaxation Delay 1.0
Experiment 1D
Nucleus 1H
Spectrometer Frequency 500.1
MeO
Cl
CF3
Cl
(E)-23
4.32
4.32
4.31
3.80
3.79
3.78
3.71
3.70
3.70
3.69
3.68
3.67
3.66
3.66
3.65
3.65
3.64
3.56
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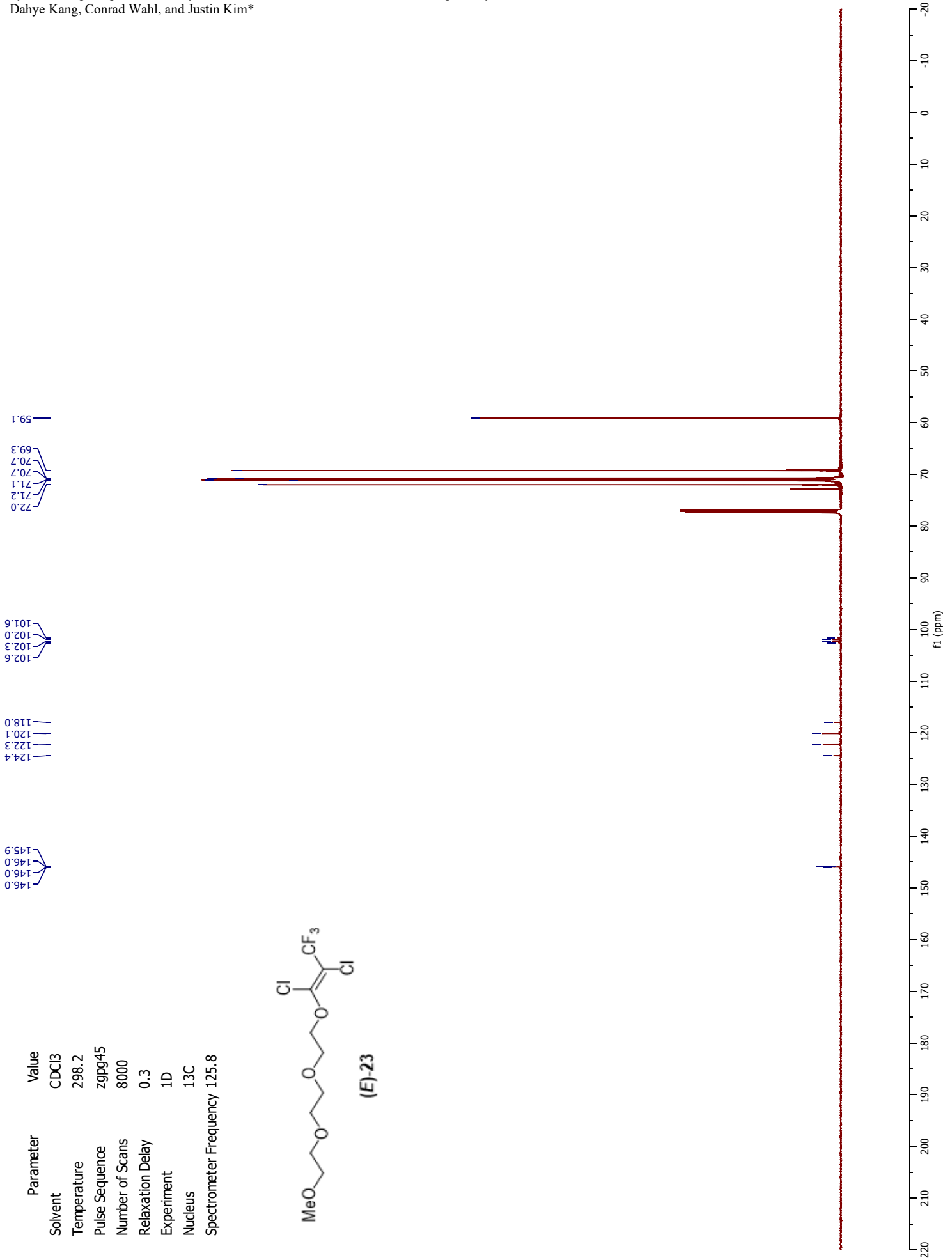
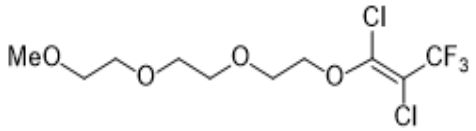
2.17
4.36
2.17
2.01
f1 (ppm)

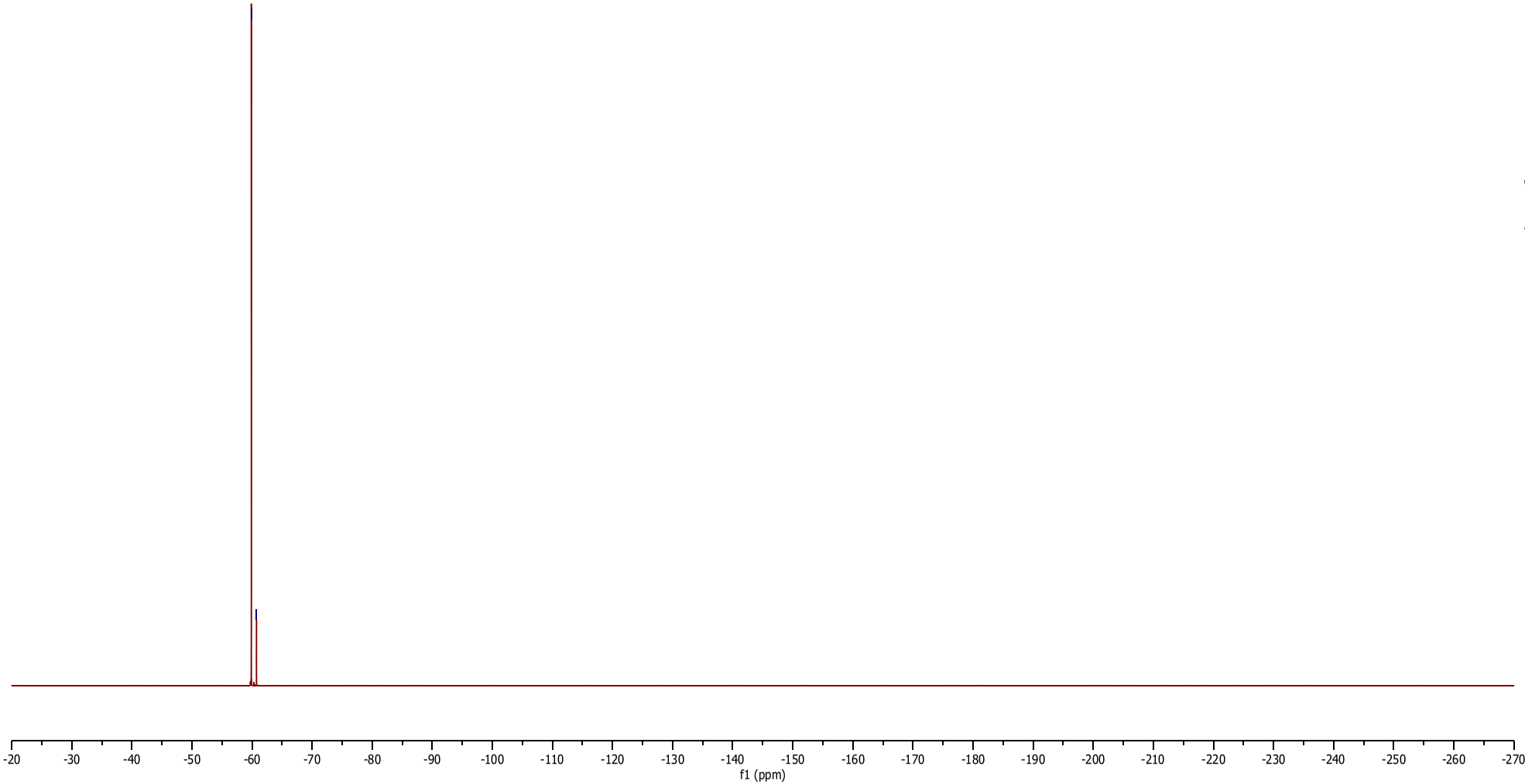

59.1
69.3
70.7
70.7
71.1
71.2
72.0
101.6
102.0
102.3
102.6
118.0
120.1
122.3
124.4
145.9
146.0
146.0
146.0
Parameter Value
Solvent CDCl3
Temperature 298.2
Pulse Sequence zgpg45
Number of Scans 8000
Relaxation Delay 0.3
Experiment 1D
Nucleus 13C
Spectrometer Frequency 125.8
MeO
O
O
O
Cl
Cl
CF3
(E)-23
f1 (ppm)

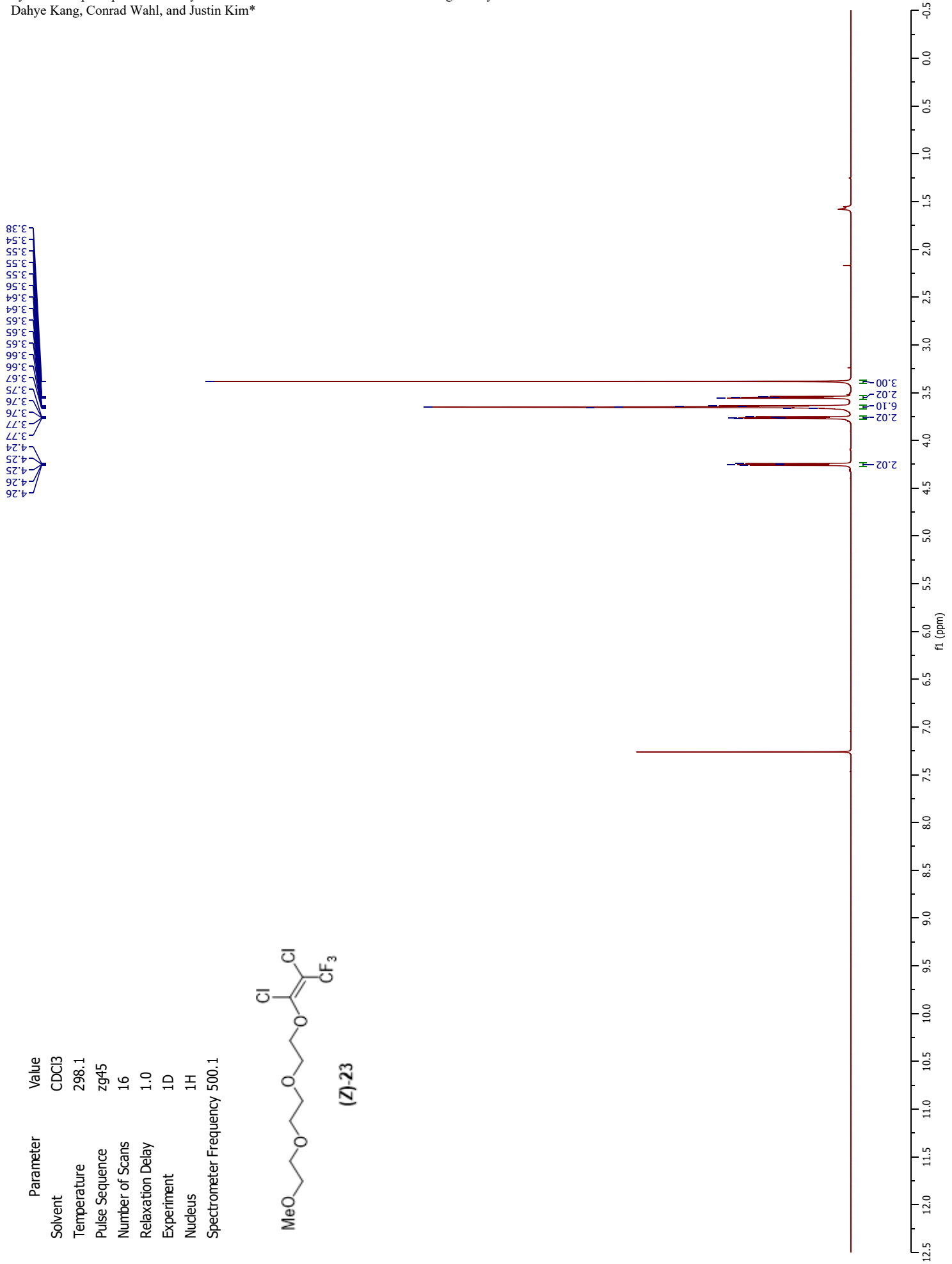
-59.9
-60.8

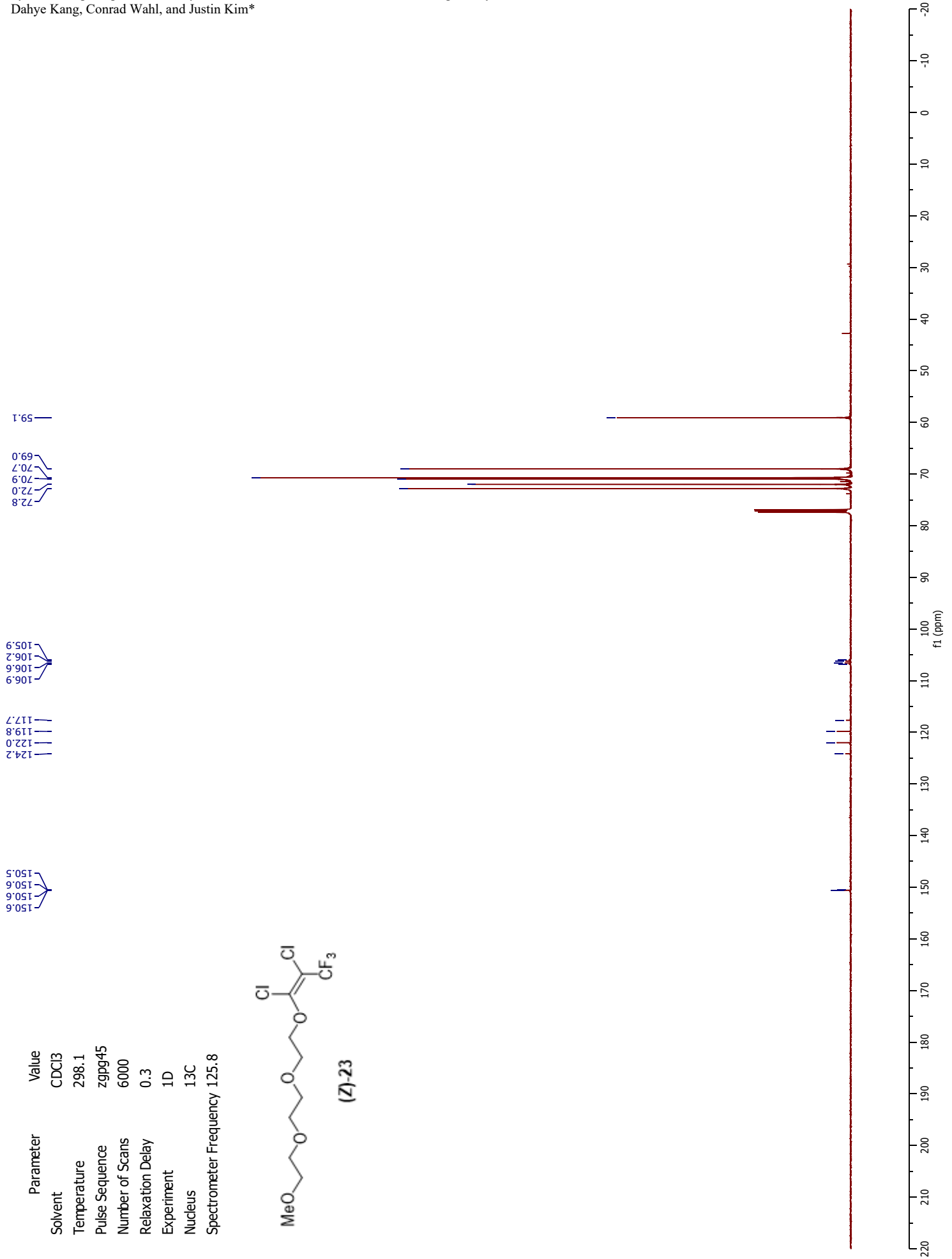
Parameter	Value
Solvent	CDCl3
Temperature	298.2
Pulse Sequence	zgfhigqn.2
Number of Scans	32
Relaxation Delay	1.5
Experiment	1D
Nucleus	19F
Spectrometer Frequency	470.5



(*E*)-**23**




Parameter Value
Solvent CDCl3
Temperature 298.1
Pulse Sequence zg45
Number of Scans 16
Relaxation Delay 1.0
Experiment 1D
Nucleus 1H
Spectrometer Frequency 500.1
MeO
Cl
Cl
CF3
(Z)-23
3.00
2.02
6.10
2.02
2.02
f1 (ppm)

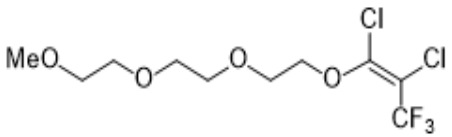


Parameter	Value
Solvent	CDCl3
Temperature	298.1
Pulse Sequence	zgpg45
Number of Scans	6000
Relaxation Delay	0.3
Experiment	1D
Nucleus	13C
Spectrometer Frequency	125.8

(*Z*)-23

-60.8

Parameter	Value
Solvent	CDCl3
Temperature	298.2
Pulse Sequence	zgfhigqn.2
Number of Scans	32
Relaxation Delay	1.5
Experiment	1D
Nucleus	19F
Spectrometer Frequency	470.5



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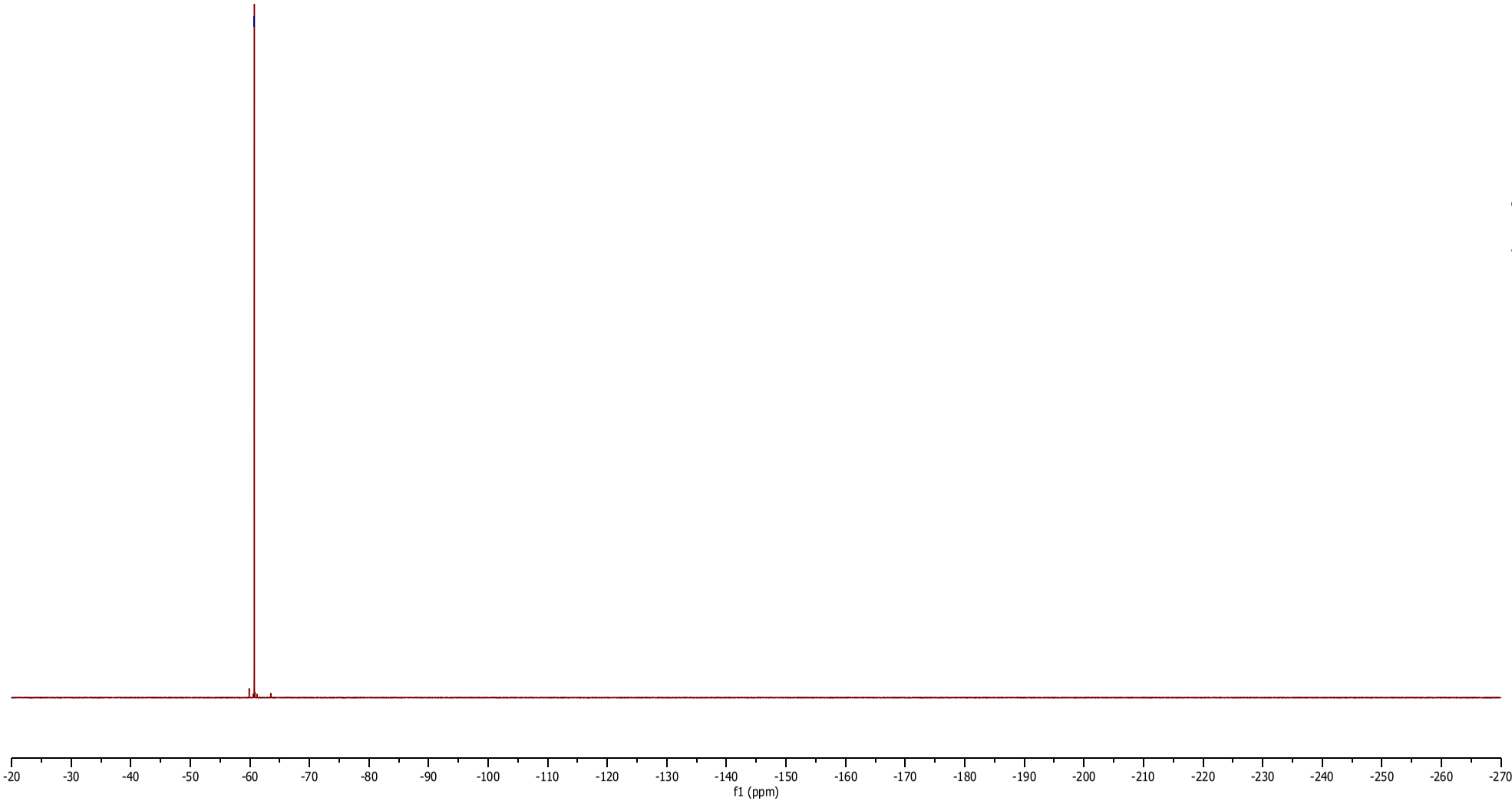
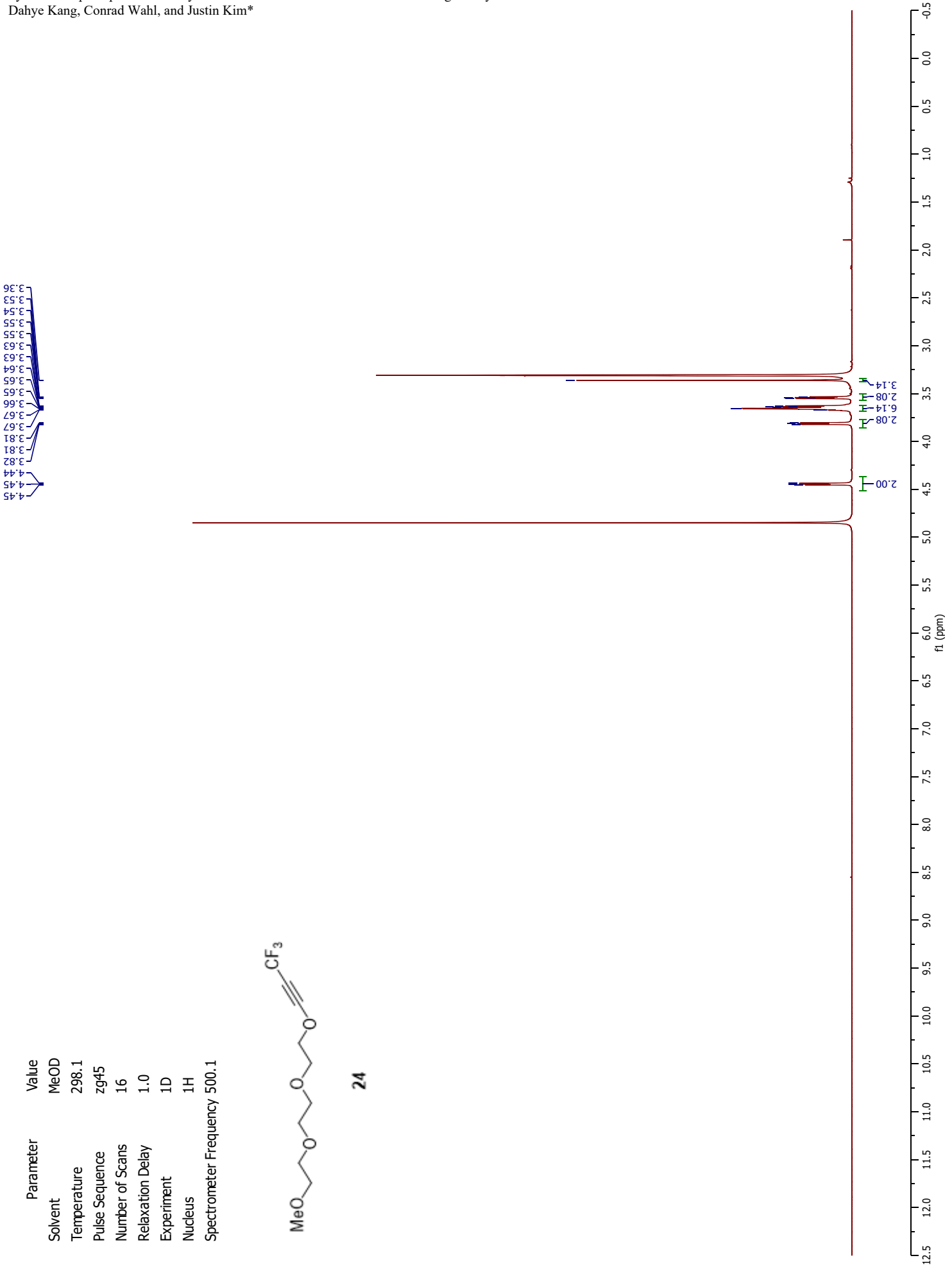
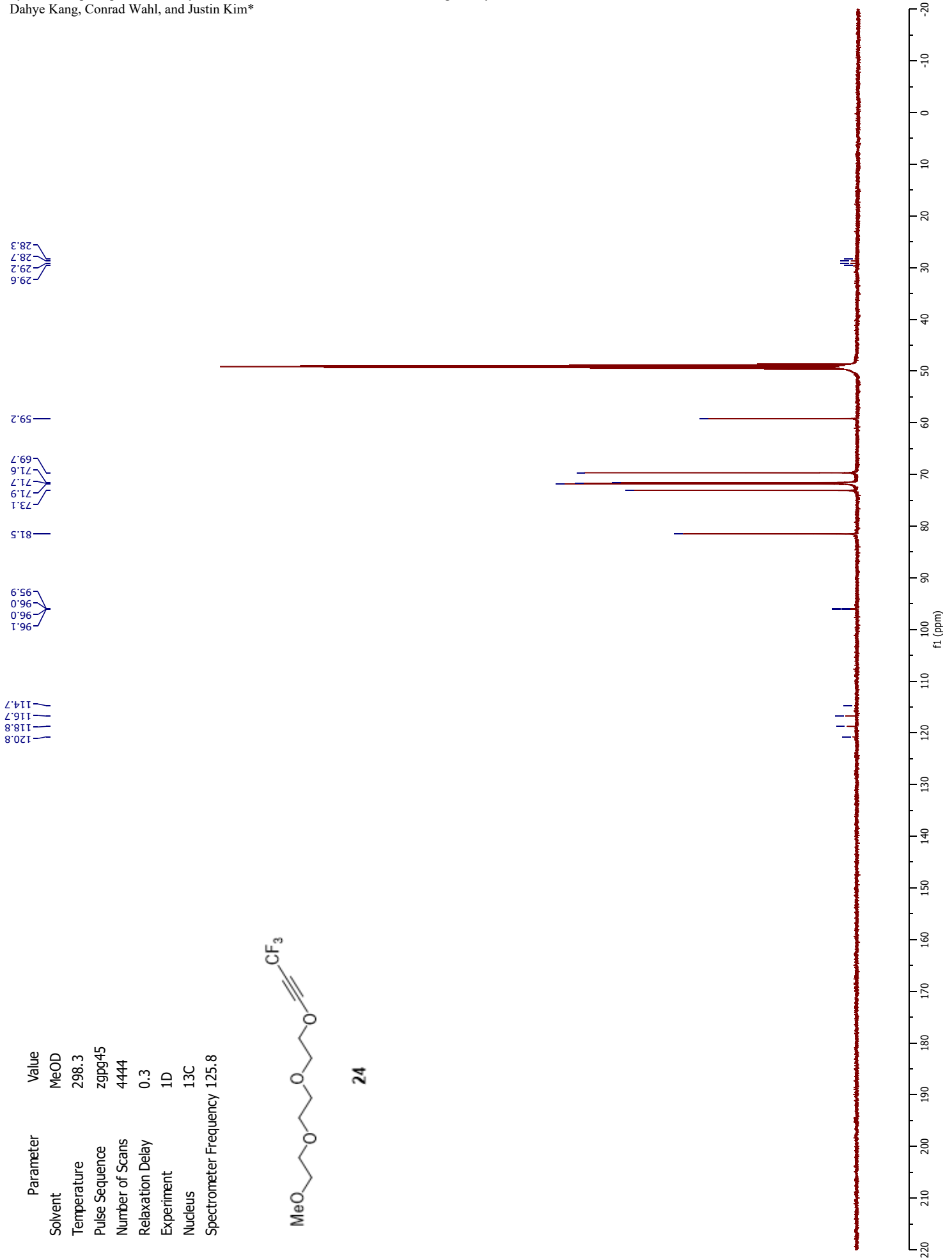



Parameter Value
Solvent MeOD
Temperature 298.1
Pulse Sequence zg45
Number of Scans 16
Relaxation Delay 1.0
Experiment 1D
Nucleus 1H
Spectrometer Frequency 500.1
MeO
O
O
O
O
CF3
24
3.36
3.53
3.54
3.55
3.55
3.63
3.63
3.64
3.65
3.65
3.66
3.67
3.67
3.81
3.81
3.82
4.44
4.45
4.45
3.14
2.08
6.14
2.08
2.00
f1 (ppm)

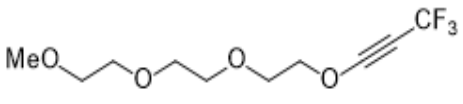


Parameter	Value
Solvent	MeOD
Temperature	298.3
Pulse Sequence	zgpg45
Number of Scans	4444
Relaxation Delay	0.3
Experiment	1D
Nucleus	13C
Spectrometer Frequency	125.8

24

-46.0

Parameter	Value
Solvent	CDCl3
Temperature	298.2
Pulse Sequence	zgfhigqn.2
Number of Scans	8
Relaxation Delay	1.5
Experiment	1D
Nucleus	19F
Spectrometer Frequency	470.5



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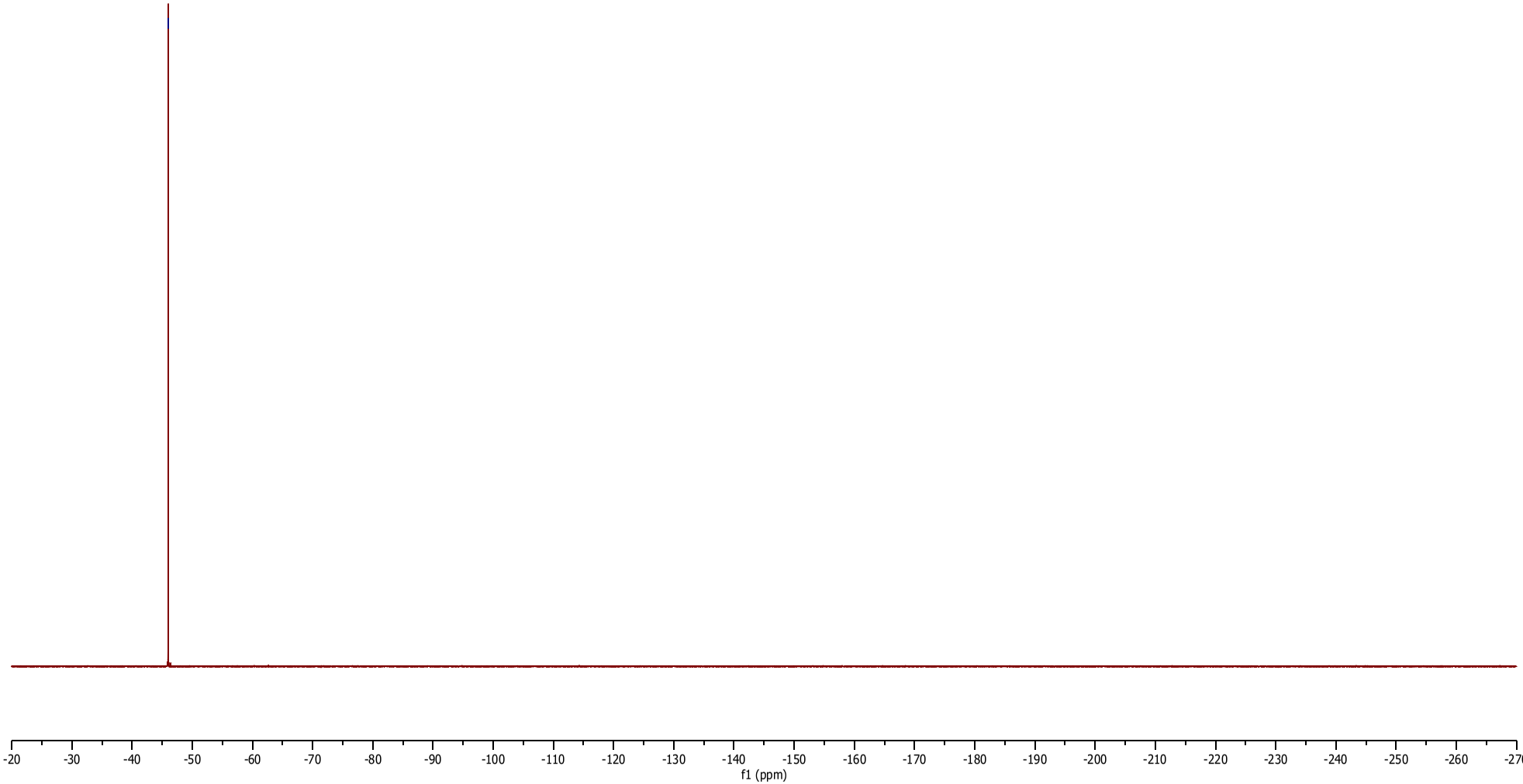
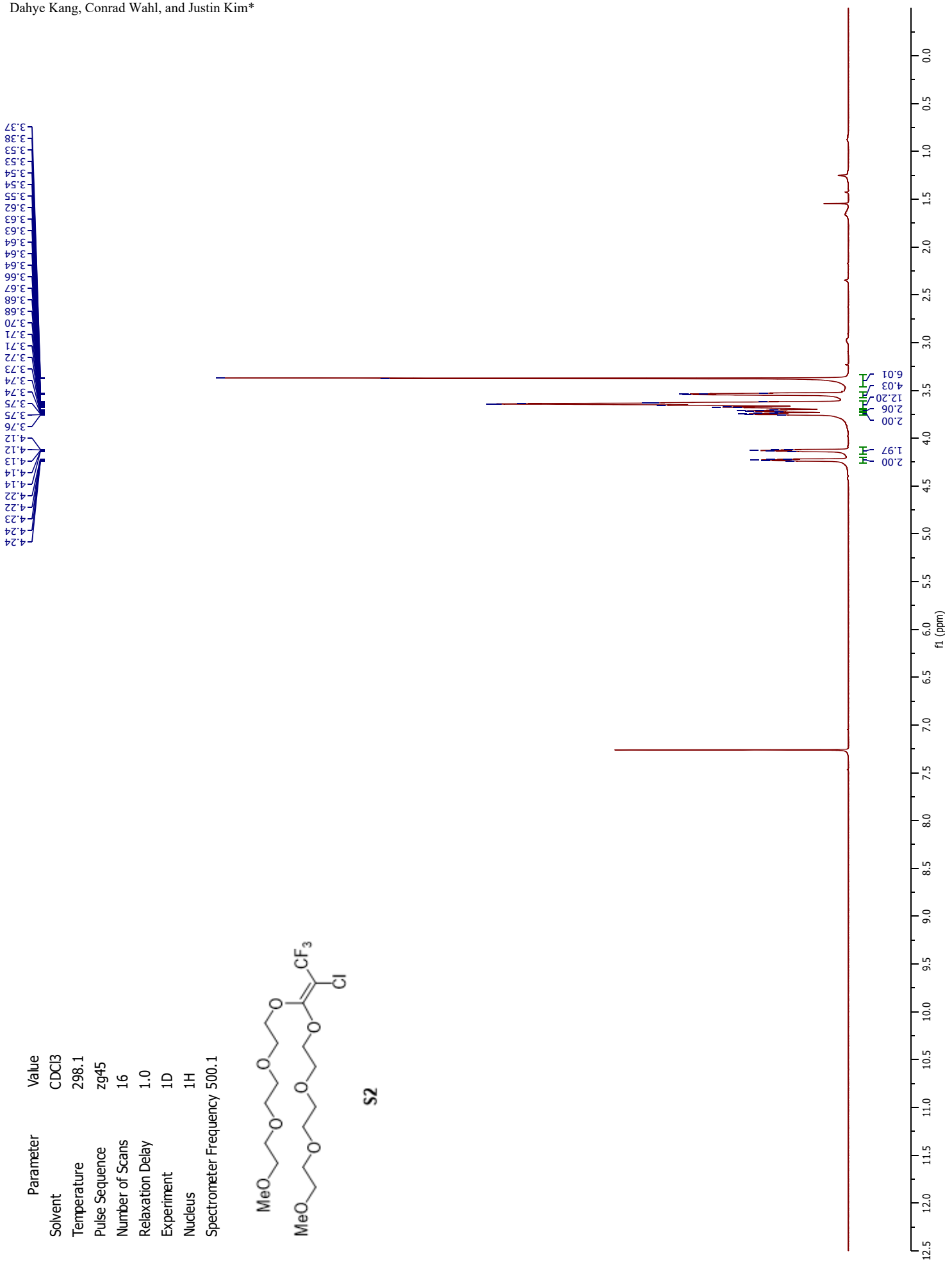
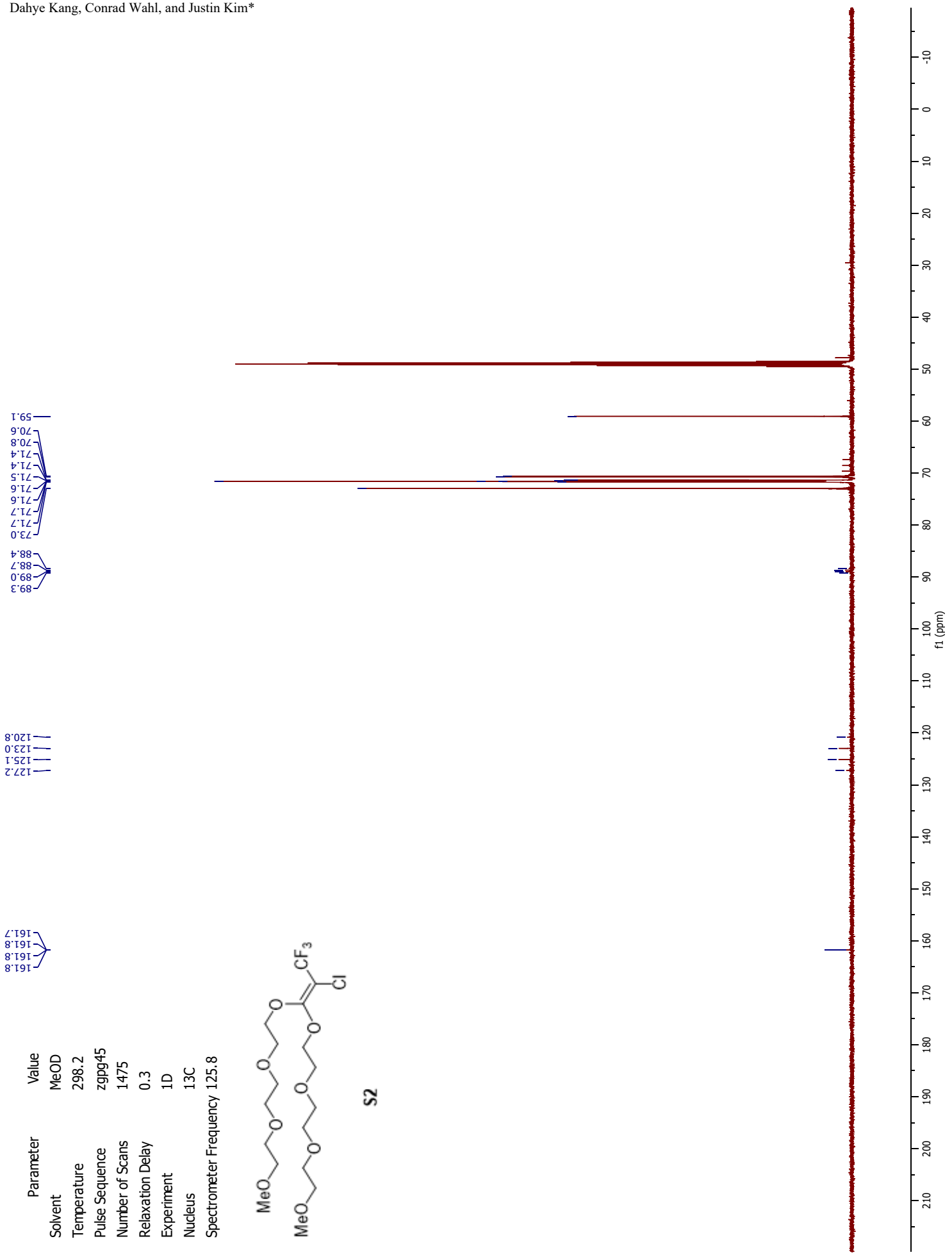
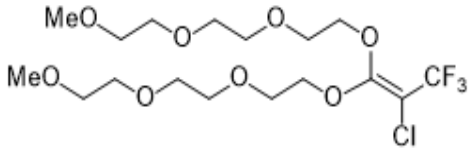



Parameter Value
Solvent CDCl3
Temperature 298.1
Pulse Sequence zg45
Number of Scans 16
Relaxation Delay 1.0
Experiment 1D
Nucleus 1H
Spectrometer Frequency 500.1
MeO
MeO
CF3
Cl
S2
6.01
4.03
12.20
2.06
2.00
1.97
2.00
f1 (ppm)

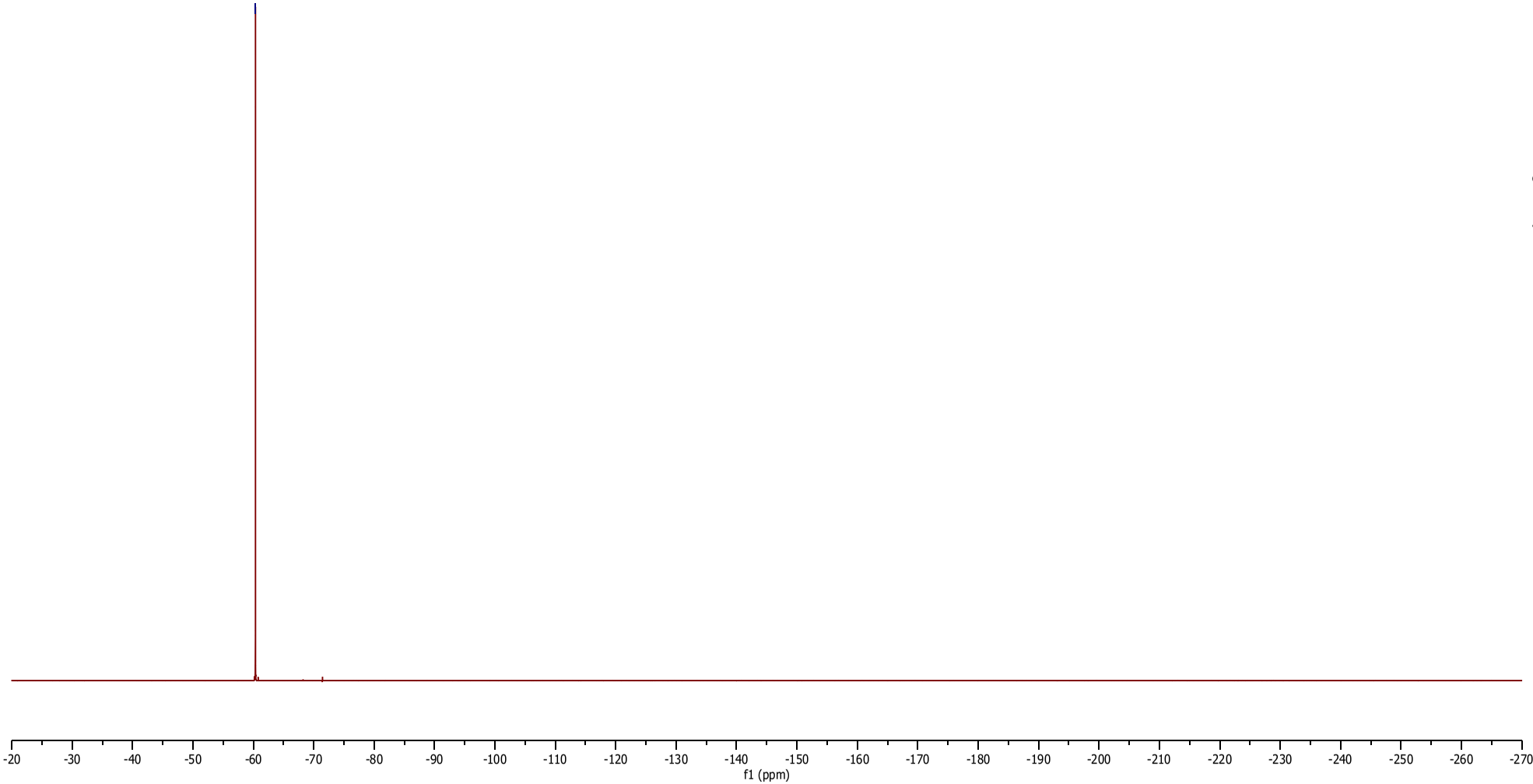

Parameter Value
Solvent MeOD
Temperature 298.2
Pulse Sequence zgpg45
Number of Scans 1475
Relaxation Delay 0.3
Experiment 1D
Nucleus 13C
Spectrometer Frequency 125.8
161.7
161.8
161.8
161.8
127.2
125.1
123.0
120.8
89.3
89.0
88.7
88.4
73.0
71.7
71.6
71.6
71.5
71.4
71.4
70.8
70.6
59.1
MeO
MeO
CF3
Cl
S2
f1 (ppm)

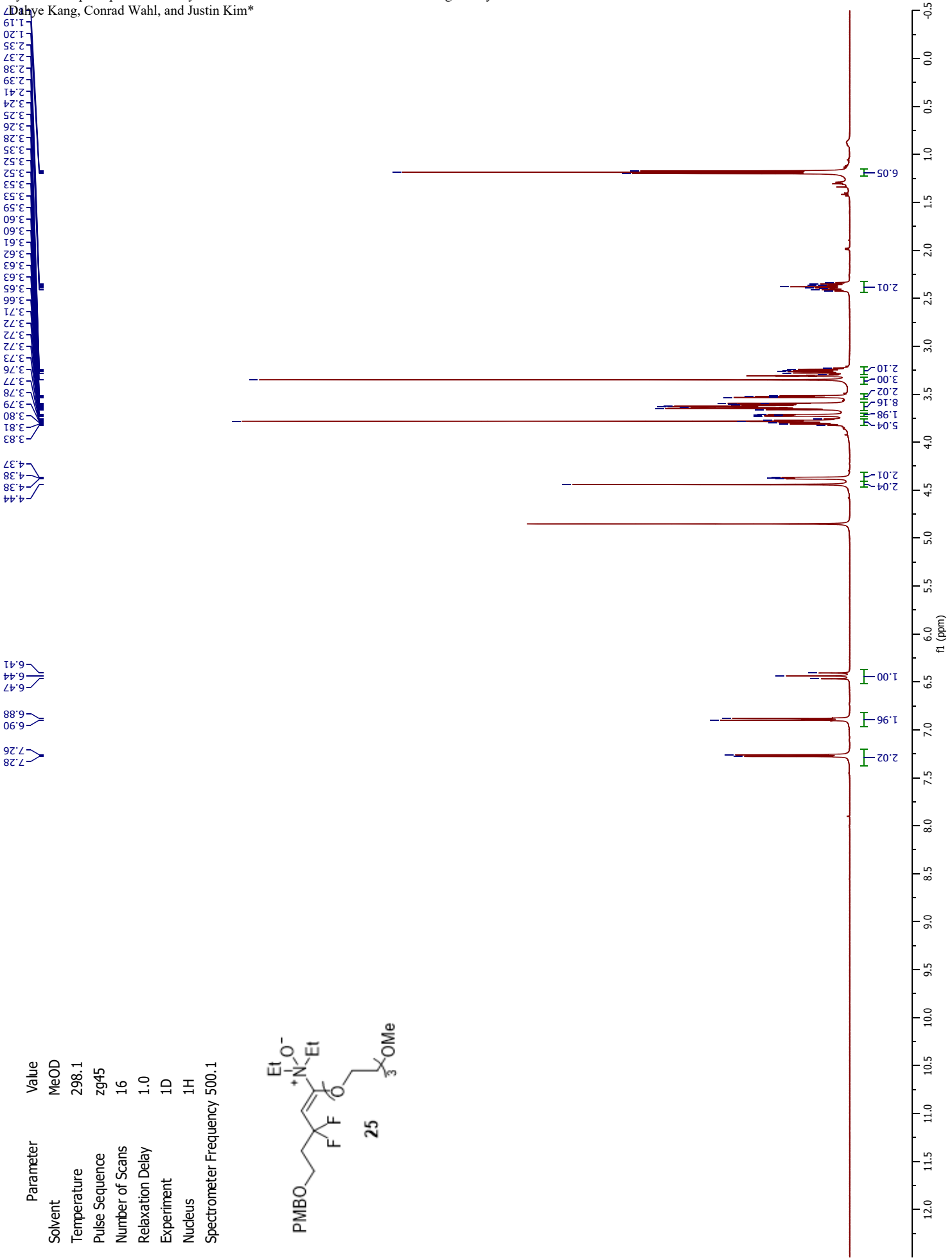
-60.4

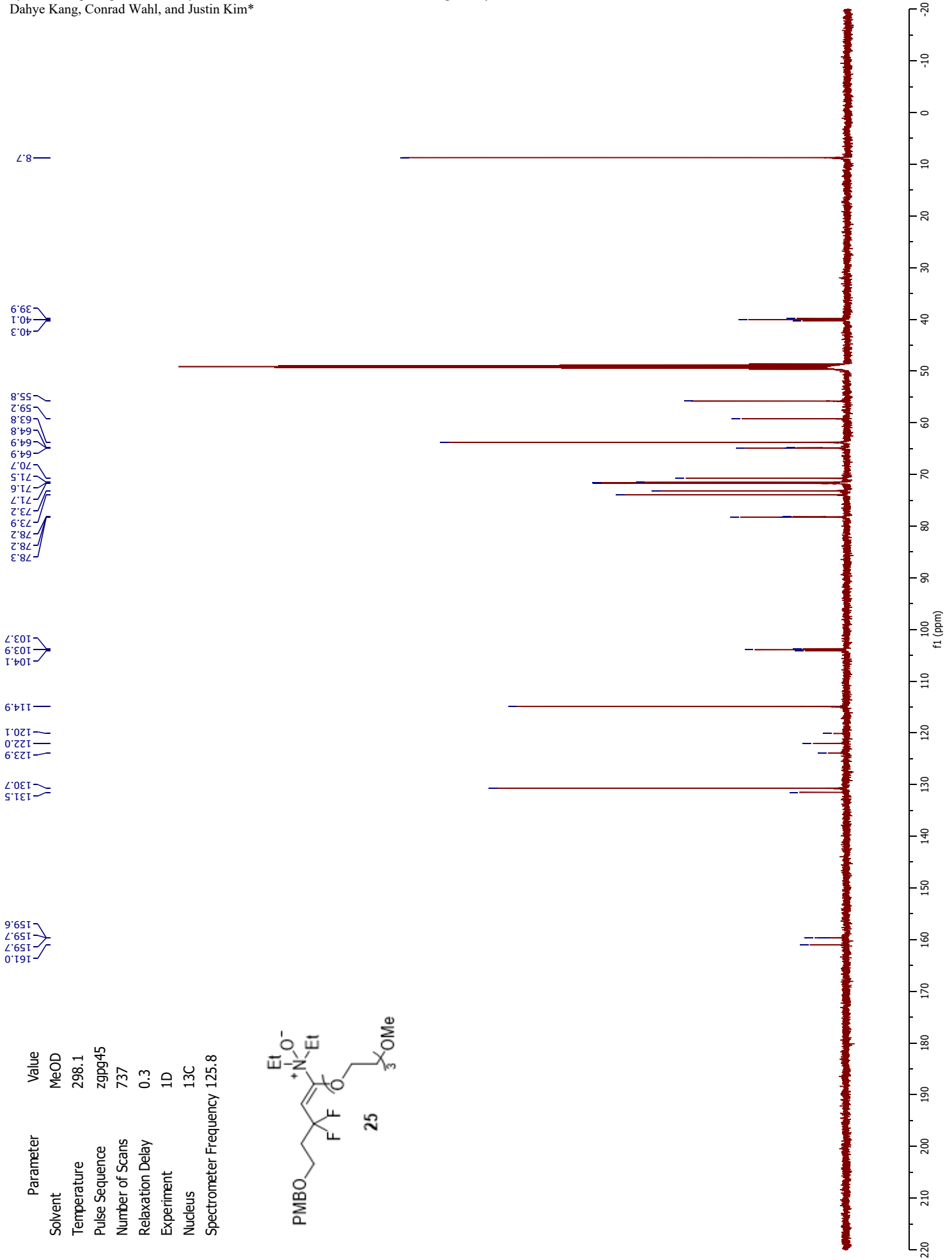
Parameter	Value
Solvent	CDCl3
Temperature	298.2
Pulse Sequence	zgfhigqn.2
Number of Scans	32
Relaxation Delay	1.5
Experiment	1D
Nucleus	19F
Spectrometer Frequency	470.5



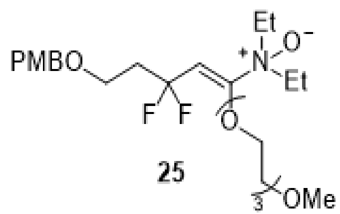
S2




Parameter Value
Solvent MeOD
Temperature 298.1
Pulse Sequence zg45
Number of Scans 16
Relaxation Delay 1.0
Experiment 1D
Nucleus 1H
Spectrometer Frequency 500.1
PMBO
F F
Et O⁻
+N
Et
O
3
OMe
25
f1 (ppm)


8.7
39.9
40.1
40.3
55.8
59.2
63.8
64.8
64.9
64.9
70.7
71.5
71.6
71.7
73.2
73.9
78.2
78.2
78.3
103.7
103.9
104.1
114.9
120.1
122.0
123.9
130.7
131.5
159.6
159.7
159.7
161.0
f1 (ppm)
Parameter Value
Solvent MeOD
Temperature 298.1
Pulse Sequence zgpg45
Number of Scans 737
Relaxation Delay 0.3
Experiment 1D
Nucleus 13C
Spectrometer Frequency 125.8
PMBO
Et
O⁻
N⁺
Et
F
F
OMe
3
25

Parameter	Value
Solvent	MeOD
Temperature	298.2
Pulse Sequence	zgfhigqn.2
Number of Scans	8
Relaxation Delay	1.5
Experiment	1D
Nucleus	19F
Spectrometer Frequency	470.5



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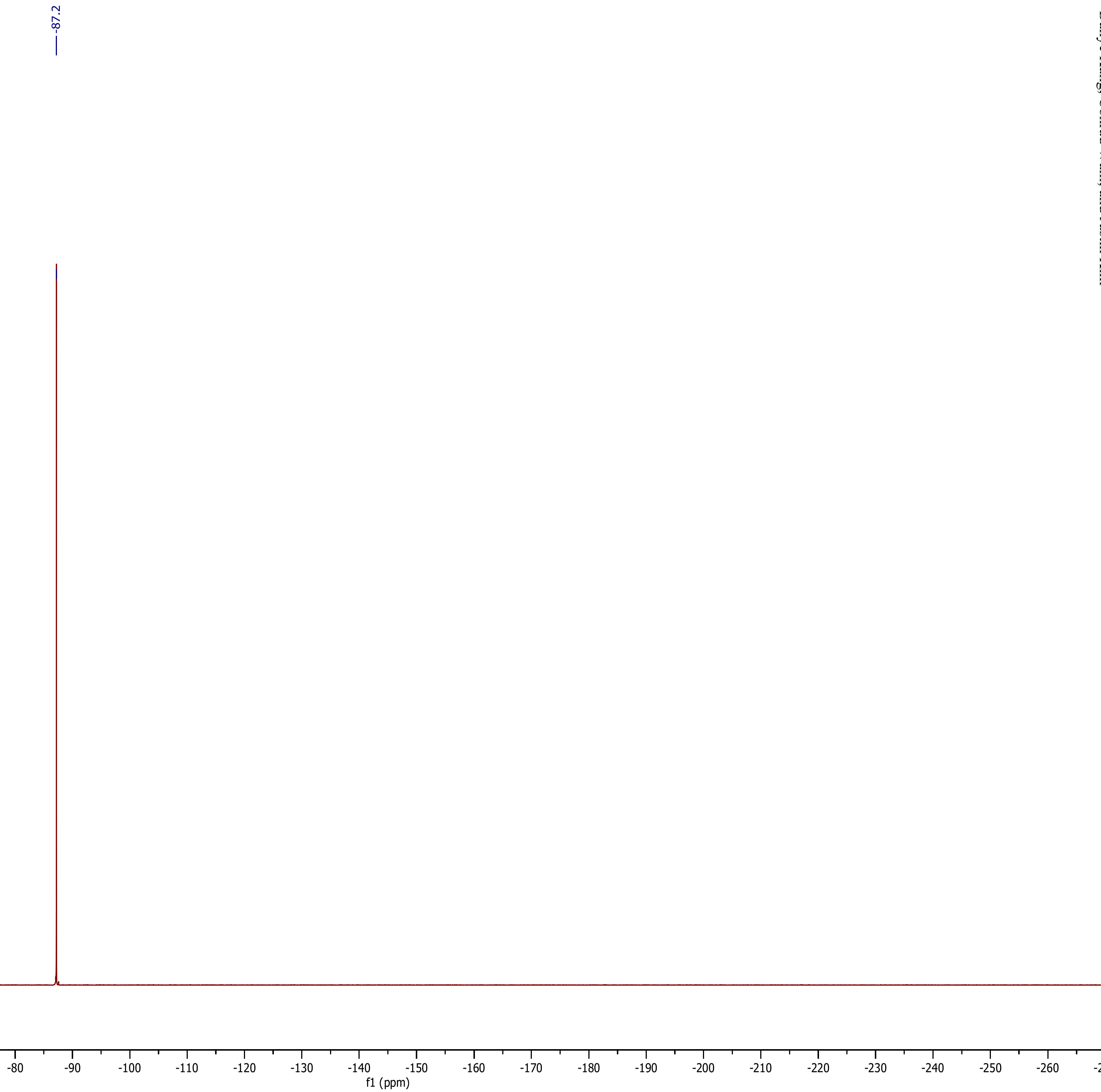
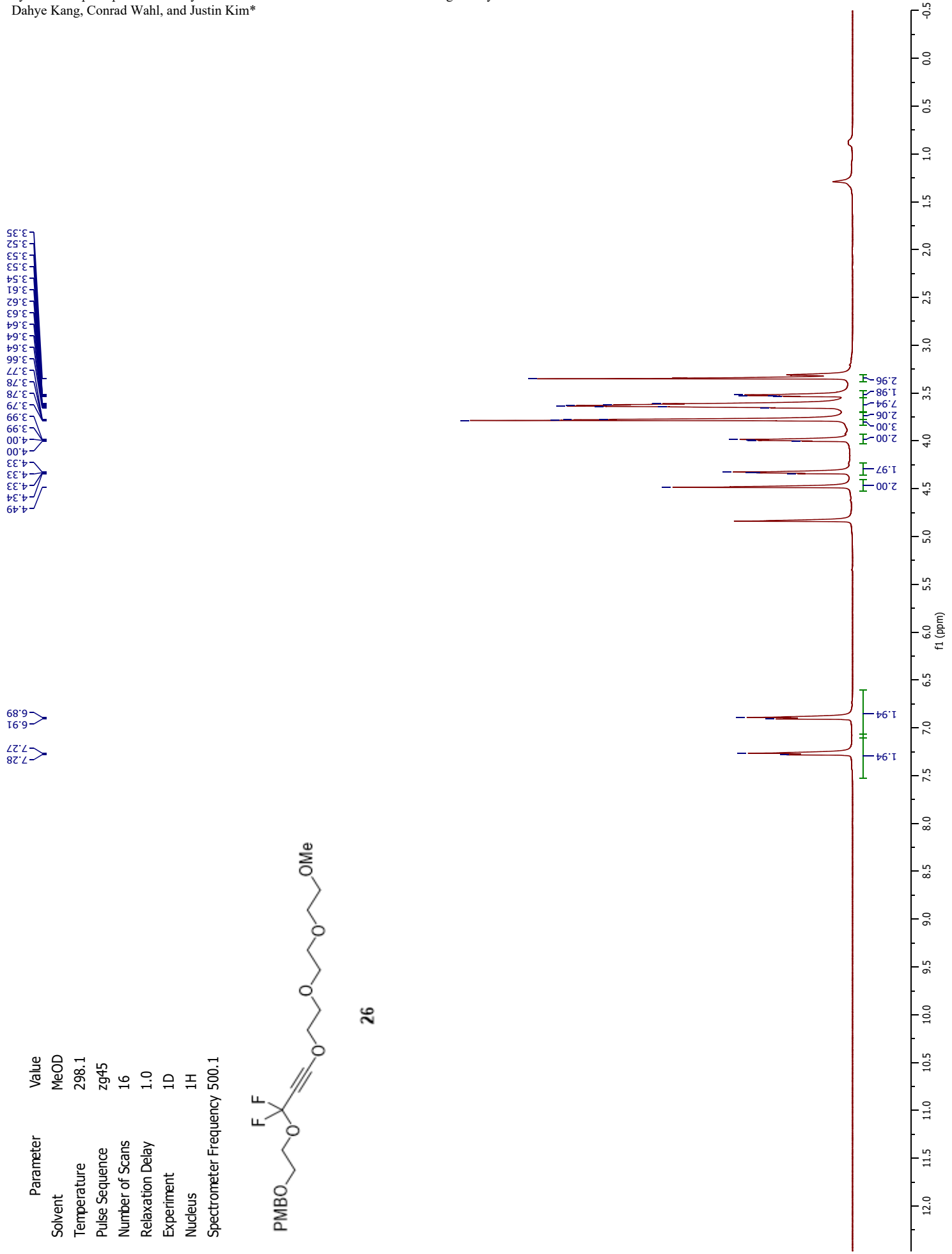
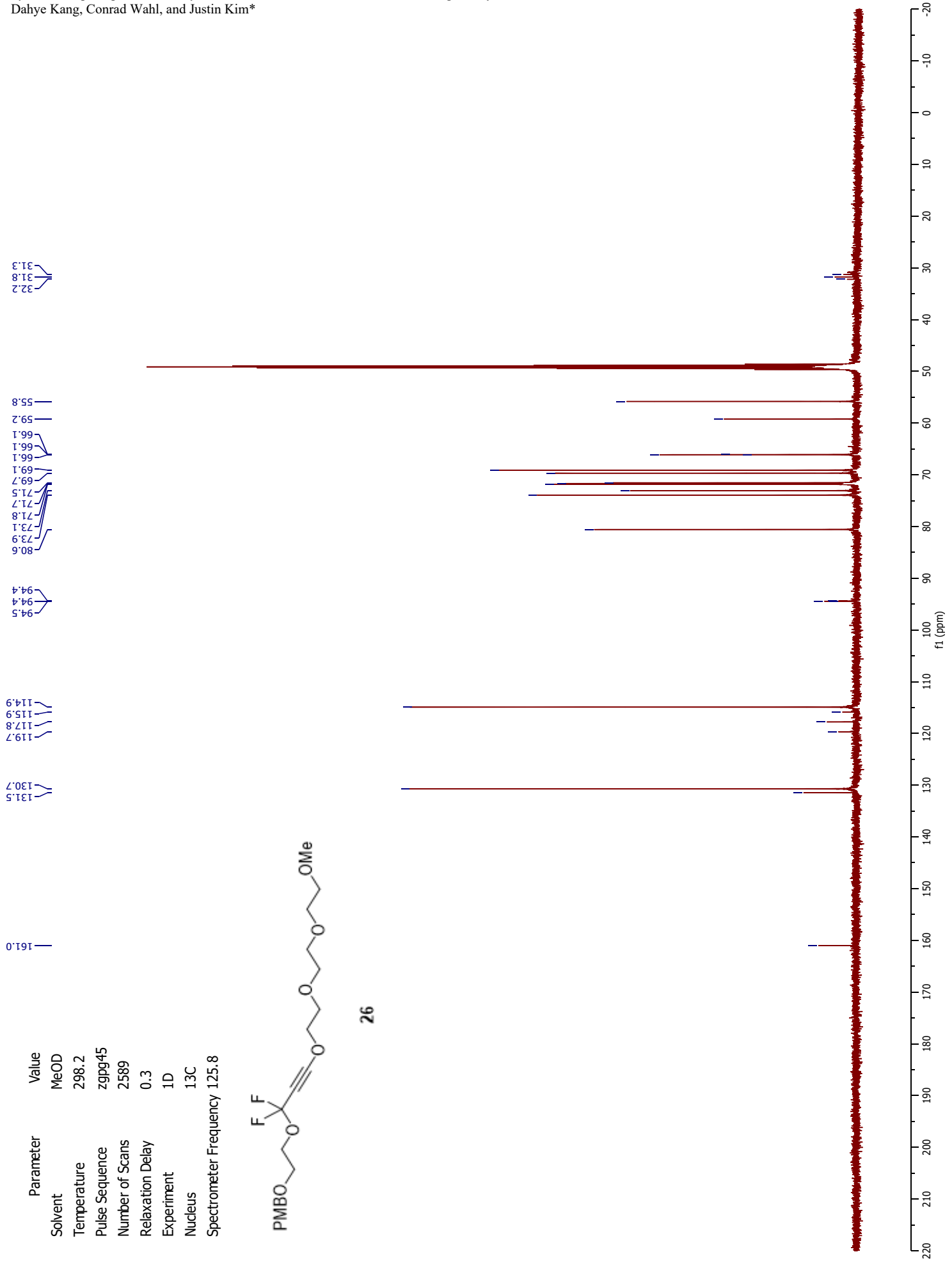
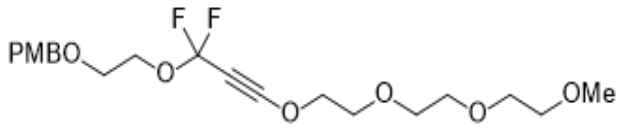



Parameter Value
Solvent MeOD
Temperature 298.1
Pulse Sequence zg45
Number of Scans 16
Relaxation Delay 1.0
Experiment 1D
Nucleus 1H
Spectrometer Frequency 500.1
PMBO
F F
OMe
26
f1 (ppm)


Parameter Value
Solvent MeOD
Temperature 298.2
Pulse Sequence zgpg45
Number of Scans 2589
Relaxation Delay 0.3
Experiment 1D
Nucleus 13C
Spectrometer Frequency 125.8
PMBO
F F
OMe
26
161.0
131.5
130.7
119.7
117.8
115.9
114.9
94.5
94.4
94.4
80.6
73.9
73.1
71.8
71.7
71.5
69.7
69.1
66.1
66.1
66.1
59.2
55.8
32.2
31.8
31.3
f1 (ppm)

Parameter	Value
Solvent	CDCl3
Temperature	298.1
Pulse Sequence	zgfhigqn.2
Number of Scans	64
Relaxation Delay	1.5
Experiment	1D
Nucleus	19F
Spectrometer Frequency	470.5



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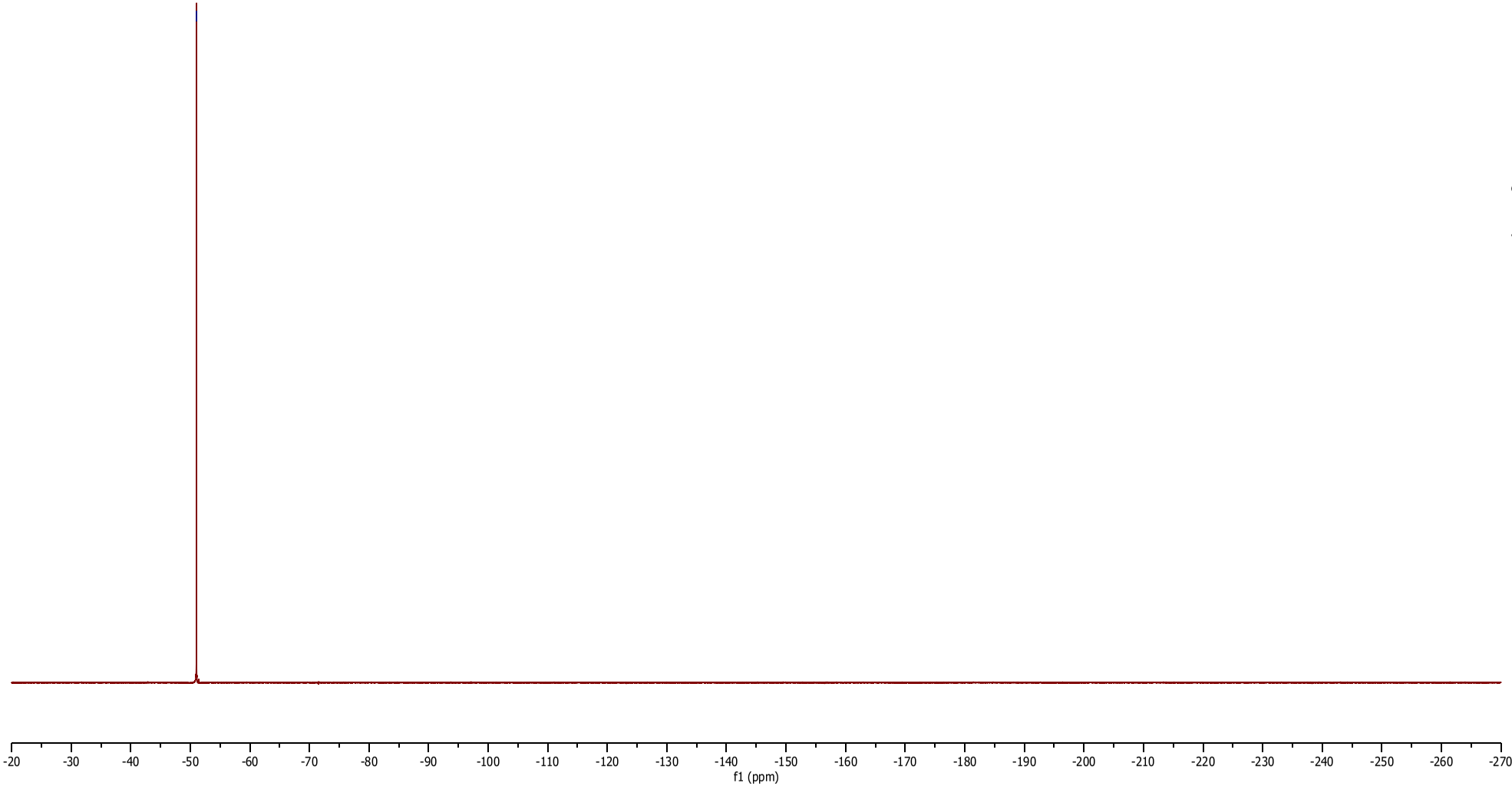
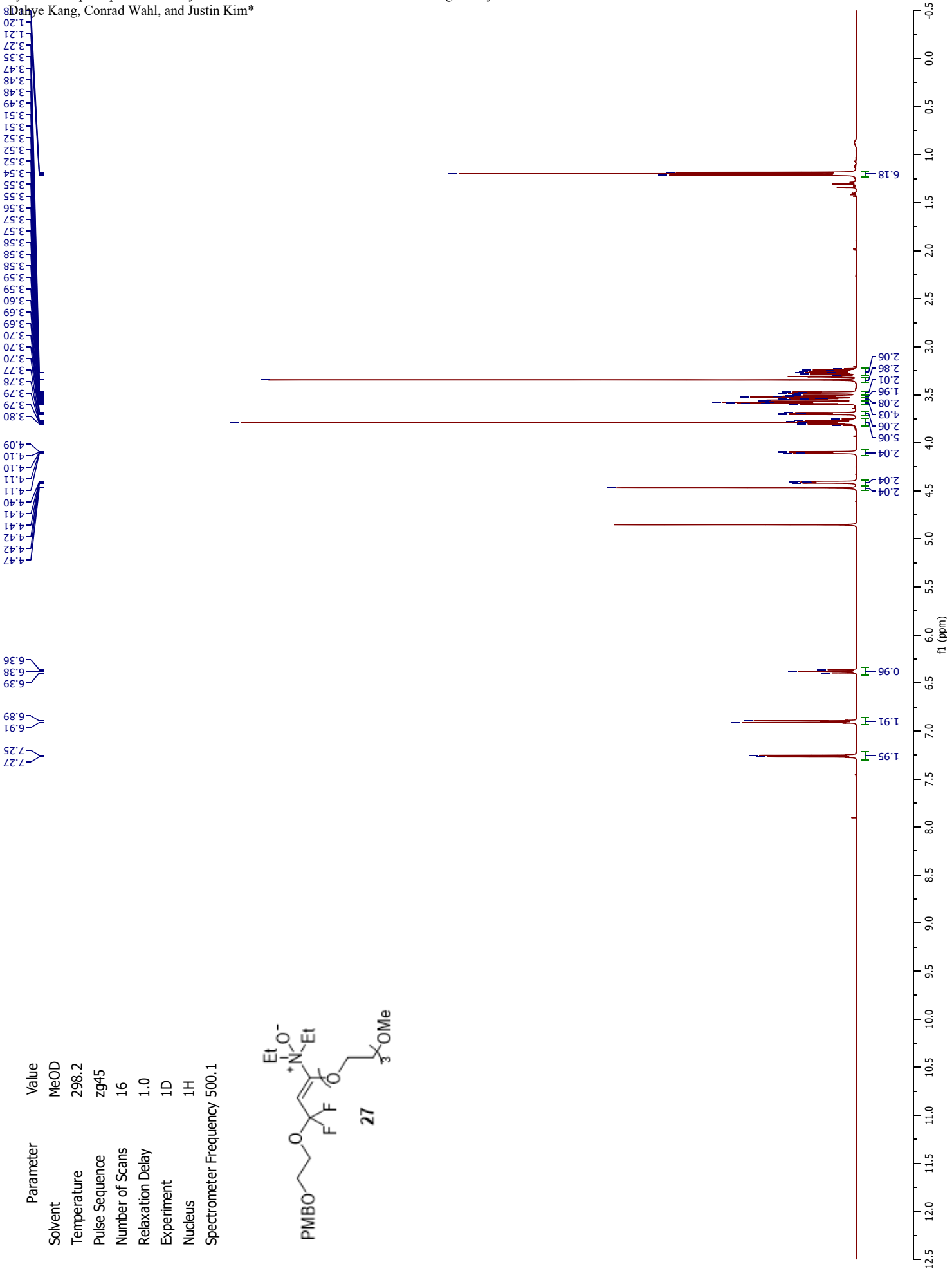
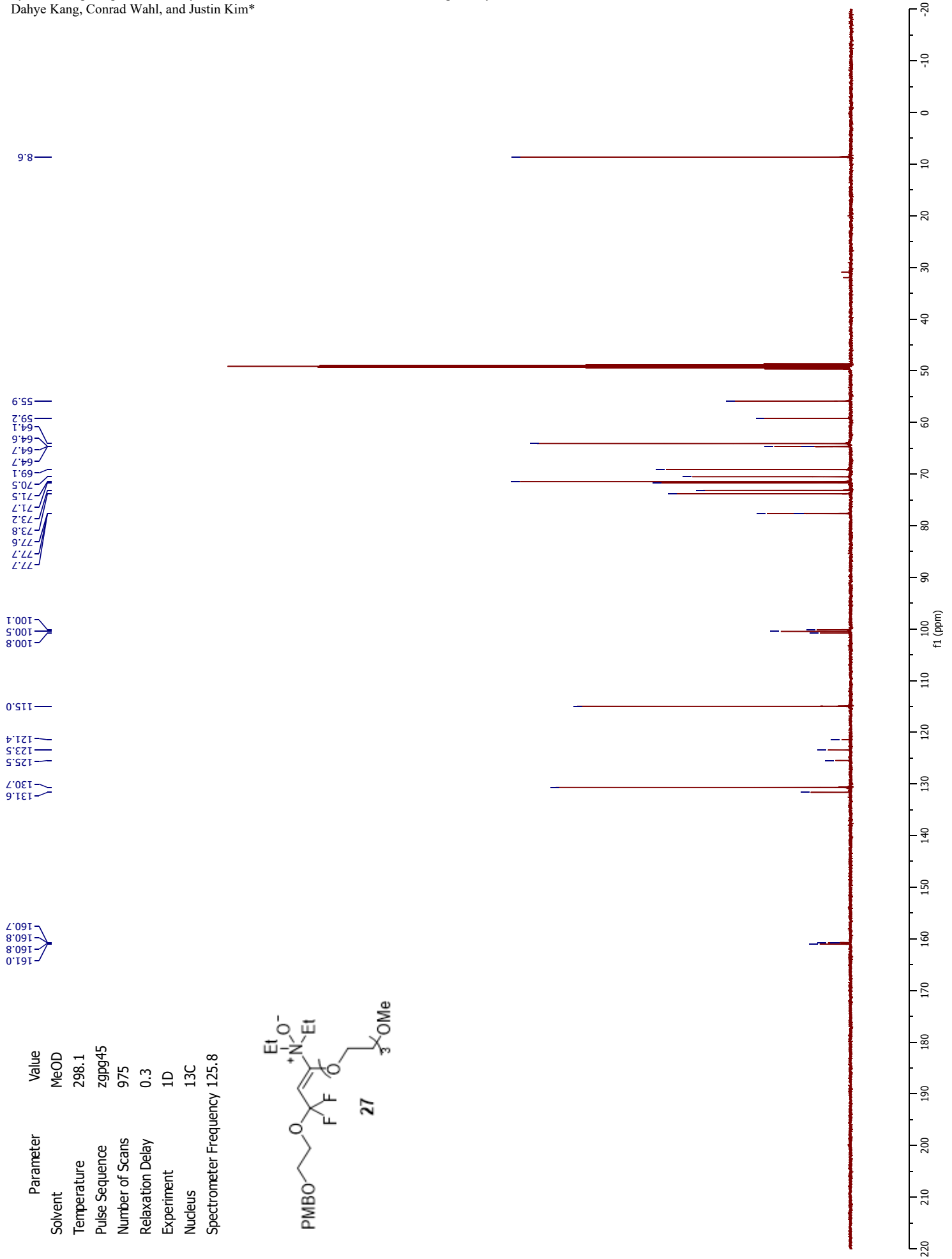
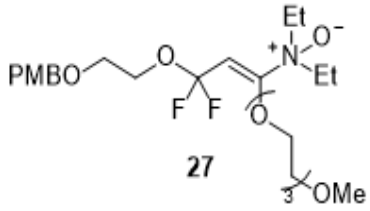



Parameter Value
Solvent MeOD
Temperature 298.2
Pulse Sequence zg45
Number of Scans 16
Relaxation Delay 1.0
Experiment 1D
Nucleus 1H
Spectrometer Frequency 500.1
PMBO
Et
O
N
Et
F
F
OMe
27
f1 (ppm)


8.6
55.9
59.2
64.1
64.6
64.7
64.7
69.1
70.5
71.5
71.7
73.2
73.8
77.6
77.7
77.7
100.1
100.5
100.8
115.0
121.4
123.5
125.5
130.7
131.6
160.7
160.8
160.8
161.0
f1 (ppm)
Parameter Value
Solvent MeOD
Temperature 298.1
Pulse Sequence zgpg45
Number of Scans 975
Relaxation Delay 0.3
Experiment 1D
Nucleus 13C
Spectrometer Frequency 125.8
PMBO
Et
O
N
Et
F
F
OMe
27

-61.8

Parameter	Value
Solvent	MeOD
Temperature	298.2
Pulse Sequence	zgfhigqn.2
Number of Scans	8
Relaxation Delay	1.5
Experiment	1D
Nucleus	19F
Spectrometer Frequency	470.5



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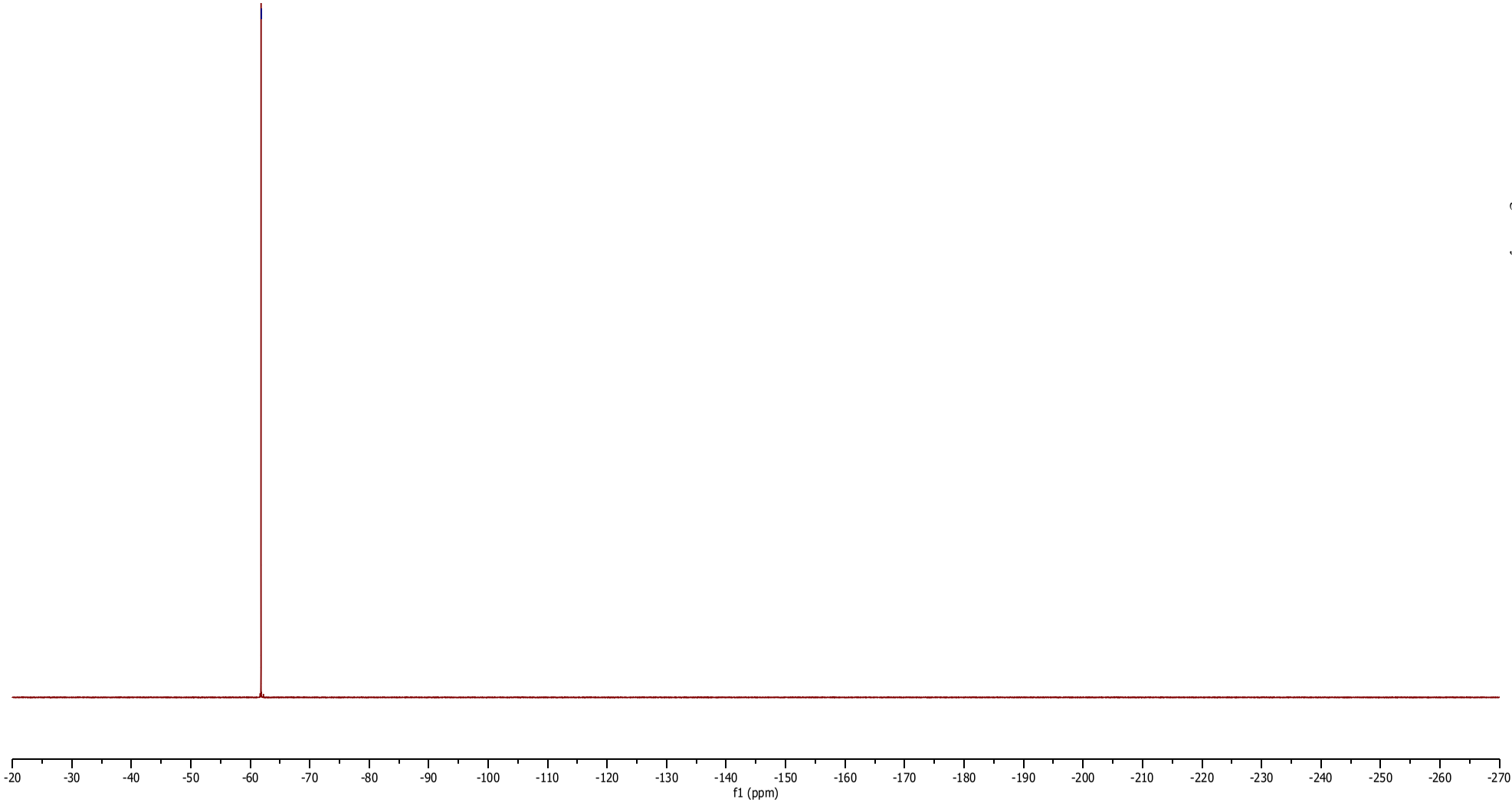
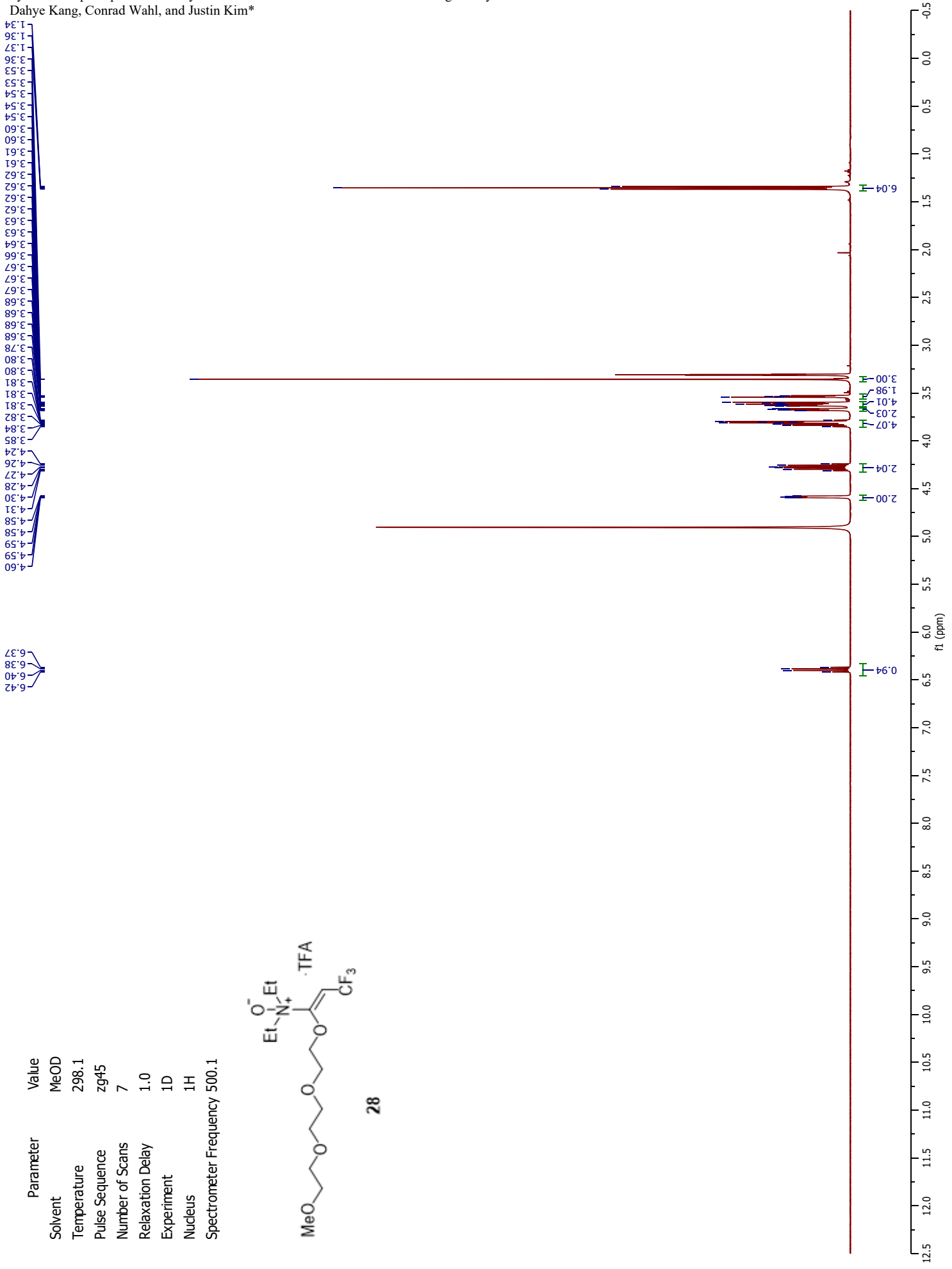
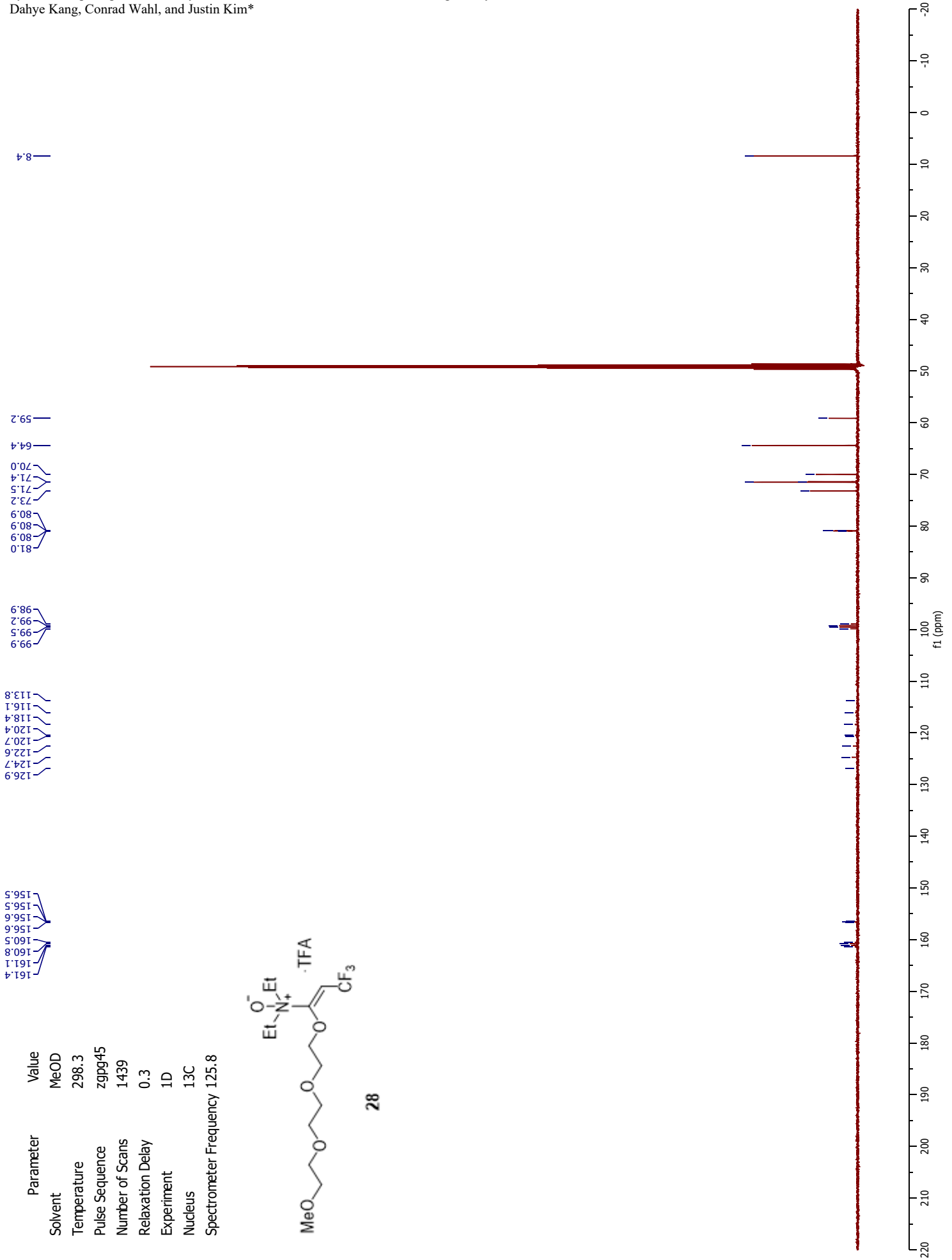
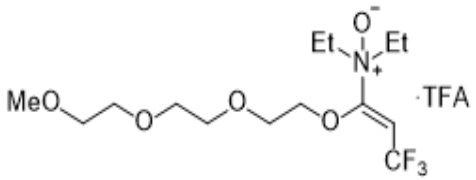



Parameter Value
Solvent MeOD
Temperature 298.1
Pulse Sequence zg45
Number of Scans 7
Relaxation Delay 1.0
Experiment 1D
Nucleus 1H
Spectrometer Frequency 500.1
MeO
Et
Et
·TFA
CF3
28
6.04
3.00
1.98
4.01
2.03
4.07
2.04
2.00
0.94
f1 (ppm)


8.4
59.2
64.4
70.0
71.4
71.5
73.2
80.9
80.9
80.9
81.0
98.9
99.2
99.5
99.9
113.8
116.1
118.4
120.4
120.7
122.6
124.7
126.9
156.5
156.5
156.6
156.6
160.5
160.8
161.1
161.4
Parameter
Value
Solvent
MeOD
Temperature
298.3
Pulse Sequence
zgpg45
Number of Scans
1439
Relaxation Delay
0.3
Experiment
1D
Nucleus
13C
Spectrometer Frequency
125.8
MeO
Et
Et
TFA
CF3
28
f1 (ppm)

-56.3
-77.5

Parameter	Value
Solvent	MeOD
Temperature	298.2
Pulse Sequence	zgfhigqn.2
Number of Scans	8
Relaxation Delay	1.5
Experiment	1D
Nucleus	19F
Spectrometer Frequency	470.5



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