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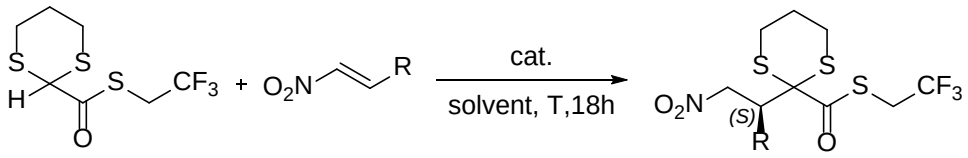
General Methods

Dry solvents were purchased and stored under nitrogen over molecular sieves (bottles with crown caps). Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} pre-coated glass plates (0.25 mm thickness) and visualized using UV light. Flash chromatography was carried out on silica gel (230-400 mesh). Proton NMR spectra were recorded on spectrometers operating at 300 MHz (Bruker Fourier 300 or AMX 300) or at 500 MHz (Bruker Advance 500). Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ δ = 7.26 ppm). ^{13}C NMR spectra were recorded on 300 MHz spectrometers (Bruker Fourier 300 or AMX 300) operating at 75 MHz, or on 500 MHz spectrometers (Bruker Advance 500) operating at 125 MHz, with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ = 77.0 ppm). ^{19}F NMR spectra were recorded on 300 MHz spectrometers (Bruker AMX 300) operating at 282 MHz. Fluorine chemical shifts are reported in ppm (δ) relative to CF_3Cl. Enantiomeric excess determinations were performed under below reported conditions with Agilent 1200 series HPLC. Mass spectra (MS) were performed at CIGA (Centro Interdipartimentale Grandi Apparecchiature), with mass spectrometer APEX II & Xmass software (Bruker Daltonics). Optical rotations were obtained on a polarimeter at 589 nm using 5 mL or 1 mL cell with a length of 1 dm.

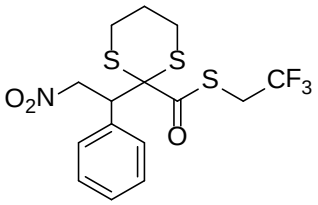
General procedure for organocatalytic reactions



The proper nitrostyrene derivative (0.076 mmol), dithianilthioester (0.152 mmol) and the catalyst (0.0152 mmol, 0.2 eq.) were dissolved in the proper dry solvent - typically, toluene - (1 mL). The reaction mixture was stirred at the desired temperature for 18 hours after which the solvent was removed at reduced pressure. Products were isolated by flash column chromatography on silica gel (9:1 hexane:ethyl acetate). The enantiomeric ratio was determined by HPLC on chiral stationary phase, terms "major" and "minor" being referred respectively to the majority and the minority enantiomer obtained with quinine-derived catalysts, characterized by (*S*) configuration at C9, and with catalysts derived from (*S*,*S*)-diaminocyclohexane. The absolute configuration was determined through chemical correlation.

Characterization of Michael addition products

2,2,2-trifluoroethyl 4-nitro-3-phenyl-2-[(1,3-dithian)2-yl]-butanethioate (**Table 1, compound 9)**



Rf = 0.37 (7:3 hexane:ethyl acetate)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.30 (s, 5H), 5.26 (AB system-part A, J = 13.7, 3.7 Hz, 1H), 5.08 (AB system-part B, J = 13.7, 10.9 Hz,1H), 4.17 (dd, J = 10.9, 3.6 Hz, 1H), 3.51-3.32 (m, 2H), 2.97-2.85 (m, 2H), 2.81-2.77 (m, 2H), δ 2.11-2.028 (m, 1H), 1.93-1.80 (m, 1H).

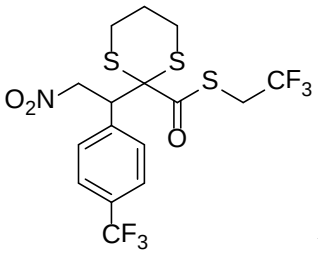
^{19}F-NMR (300 MHz, $CDCl_3$) δ: -65.99 (t, J = 9.2 Hz).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 195.99 (s), 132.29 (s), 129.58 (s), 128.59 (s), 127.97 (s), 124.20 (q, J = 274.6 Hz), 76.96 (s), 66.72 (s), 51.87 (s), 32.85 (q, J = 33.3 Hz), 28.04 (s), 27.54 (s), 22.53 (s).

The enantiomeric excess was determined by HPLC with Phenomenex Lux 3u C ellulose2 column; eluent: 95:5 Hexane/2-Propanol; flow rate: 0.8 mL/min; detection: 210 nm; t_R 8.33 min (major), t_R 9.05 min (minor).

HRMS Mass (ESI+) m/z calc. for $C_{19}H_{19}N_1O_3S_3F_3Na_1^+$: 428.04193, found: 428.04193 [M + Na].

2,2,2-trifluoroethyl 4-nitro-3-[4-(trifluoromethyl)phenyl]-2-[(1,3-dithian)-2-yl]-butanethioate (**Table 4, compound 10)**



Rf = 0.43 (7:3 hexane:ethyl acetate)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.56 (AB system-part A, J = 8.2 Hz, 2H), 7.44 (AB system-part B, J = 8.2 Hz, 2H), 5.26 (AB system-part A, J = 14.0, 3.5 Hz, 1H), 5.05 (AB system-part B, J = 11.0, 3.7 Hz, 1H), 4.22 (dd, J = 11.0, 3.7 Hz, 1H), 3.54-3.35 (m, 2H), 2.99-2.87 (m, 2H), 2.84-2.77 (m, 2H), 2.12-2.04 (m, 1H), 1.95-1.79 (m, 1H).

^{19}F-NMR (300 MHz, $CDCl_3$) δ: -63.35 (s), -66.11 (t, J = 9.7 Hz).

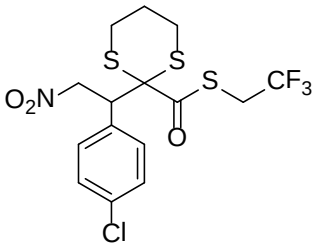
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 195.79 (s), 136.40 (s), 131.00 (s), 129.57 (s), 124.93 (s), 124.04 (q, J = 273.5 Hz), 123.33(q, J = 289.11), 121.40 (s), 76.46 (s), 66.25 (s), 51.45 (s), 32.81 (q, J = 33.6 Hz), 27.96 (s), 27.53 (s), 22.40 (s).

The enantiomeric excess was determined by HPLC on chiral stationary phase with Phenomenex Lux Cellulose2; eluent 9:1 Hexane/2-Propanol; flow 0.8 mL/min; detection: 210 nm; t_R: 9.02 min (major), t_R: 10.52 min (minor).

$[\alpha]_D^{23}$=+ 5. 105 (*c* 0.174, $CHCl_3$, e.e. 53%).

HRMS Mass (ESI+) m/z calc. for $C_{16}H_{15}N_1O_3S_3F_6Na_1^+$: 502.00105, found: 502.00189 [M + Na].

2,2,2-trifluoroethyl 4-nitro-3-[4-(chloro)phenyl]-2-[(1,3-dithian)-2-yl]-butanethioate (**Table 4, compound 11)**



Rf = 0.47 (7:3 hexane:ethyl acetate)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.28 (m, 4H), 5.23 (AB system-part A, J = 13.8, 3.6 Hz, 1H), 5.02 (AB system-part B, J = 13.8, 11.1 Hz, 1H), 4.15 (dd, J = 11.0, 3.5 Hz, 1H), 3.57-3.41 (m, 2H), 3.05-2.88 (m, 2H), 2.86-2.78 (m, 2H), 2.14-2.06 (m, 1H), 1.96-1.81 (m, 1H).

^{19}F-NMR (300 MHz, $CDCl_3$) δ: -66.06 (t).

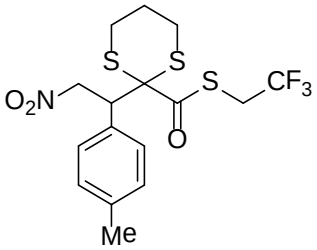
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 196.39 (s), 135.25 (s), 131.31 (s), 130.91 (s), 128.76 (s), 124.65 (q, J = 274.5 Hz), 77.22 (s), 66.97 (s), 51.72 (s), 33.41 (q, j = 33.8 Hz), 28.53 (s), 28.04 (s), 22.98 (s).

The enantiomeric excess was determined by HPLC on chiral stationary phase with Phenomenex Lux Cellulose2; eluent 9:1 Hexane/2-Propanol; flow 0.8 mL/min; detection: 210 nm; t_R: 11.27 min (major), t_R: 12.60 min (minor).

$[\alpha]_D^{23}$= + 8.726 (*c* 0.324, $CHCl_3$, e.e. 69%).

HRMS Mass (ESI+) m/z calc. for $C_{15}H_{15}N_1O_3S_3F_3Na_1^+$: 467.97, found: 467.97582 [M + Na].

2,2,2-trifluoroethyl 4-nitro-3-[4-(methyl)phenyl]-2-[(1,3-dithian)-2-yl]-butanethioate (**Table 4, compound 12)**



Rf = 0.42 (7:3 hexane:ethyl acetate)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.17 (AB system-part A, J = 8.0 Hz, 2H), 7.09 (AB system-part B, J = 8.1 Hz, 2H), 5.20 (AB system-part A, J = 13.6, 3.7 Hz, 1H), 5.03 (AB system-part B, J = 13.5, 10.9 Hz, 1H), 4.12 (dd, J = 10.9, 3.6 Hz, 1H), 3.51-3.38 (m, 2H), 2.97-2.85 (m, 2H), 2.82-2.79 (m, 2H), 2.30 (s, 3H), 2.01-2.08 (m, 1H), 1.93-1.82 (m, 1H).

^{19}F-NMR (300 MHz, $CDCl_3$) δ: -65.98 (t, J = 8.8 Hz).

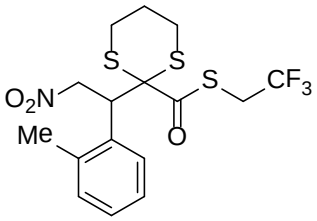
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 196.49 (s), 139.02 (s), 129.61 (s), 129.38 (s), 129.23 (s), 124.73 (q, J = 274.6 Hz), 76.75 (s), 67.40 (s), 52.04 (s), 33.49 (q, J = 33.7 Hz), 28.60 (s), 28.07 (s), 23.11 (s), 21.12 (s).

The enantiomeric excess was determined by HPLC on chiral stationary phase with Phenomenex Lux Cellulose2; eluent 9:1 Hexane/2-Propanol; flow 0.8 mL/min; detection: 210 nm; t_R: 9.24 min (major), t_R: 10.42 min (minor).

$[\alpha]_D^{23}$= + 5.566 (*c* 0.1796, $CHCl_3$, e.e. 73%).

HRMS Mass (ESI+) m/z calc. for $C_{16}H_{18}N_1O_3S_3F_3Na_1^+$ 448.02931, found: 448.03026 [M + Na].

2,2,2-trifluoroethyl 4-nitro-3-[2-(methyl)phenyl]-2-[(1,3-dithian)-2-yl]-butanethioate (**Table 4, compound 13)**



Rf = 0.39 (7:3 hexane:ethyl acetate)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.48-7.45 (m, 1H), 7.23-7.16 (m, 3H), 5.11 (AB system-part A, J = 13.5, 3.5 Hz, 1H), 4.97 (AB system-part B, J = 12.2 Hz, 1H), 4.59 (dd, J = 10.8, 3.2 Hz, 1H), 3.63-3.40 (m, 2H), 3.03-2.88 (m, 2H), 2.83-2.76 (m, 2H), 2.46 (s, 3H), δ 2.11-2.06 (m, 1H), 1.97-1.84 (m, 1H).

^{19}F-NMR (300 MHz, $CDCl_3$) δ: -66.25 (t, J = 9.0 Hz).

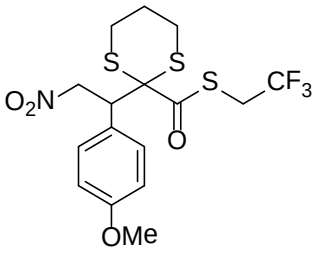
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 197.34 (s), 138.62 (s), 131.90 (s), 131.04 (s), 128.79 (s), 127.75 (s), 126.52 (s), 126.18 (s), 124.69 (q, J = 274.5 Hz), 77.26 (s), 67.77 (s), 46.44 (s), 33.64 (q, J = 33.0 Hz), δ 28.46 (s), 23.02 (s), 20.14 (s).

The enantiomeric excess was determined by HPLC on chiral stationary phase with Phenomenex Lux Cellulose2; eluent 9:1 Hexane/2-Propanol; flow 0.8 mL/min; detection: 210 nm; t_R: 8.89 min (major), t_R: 10.20 min (minor)

$[\alpha]_D^{23}$= - 9.793 (*c* 0.22, $CHCl_3$, e.e. 67%).

HRMS Mass (ESI+) m/z calc. for $C_{16}H_{18}N_1O_3S_3F_3Na_1^+$ 448.02931, found: 448.03034 [M + Na].

2,2,2-trifluoroethyl 4-nitro-3-[4-(methoxy)phenyl]-2-[(1,3-dithian)-2-yl]-butanethioate (**Table 4, compound 14)**



Rf = 0.31 (7:3 hexane:ethyl acetate)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.21 (AB system-part A, J = 8.0 Hz, 2H), 6.80 (AB system-part B, J = 8.1 Hz, 2H), 5.18 (AB system-part A, J = 13.1 Hz, 1H), 5.00 (AB system-part B, J = 12.1 Hz, 1H), 4.09 (d, J = 10.8 Hz, 1H), 3.76 (s, 3H), 3.50-3.38 (m, 2H), 2.96-2.86 (m, 2H), 2.80-2.76 (m, 2H), 2.09-2.04 (m, 1H), 1.92-1.80 (m, 1H).

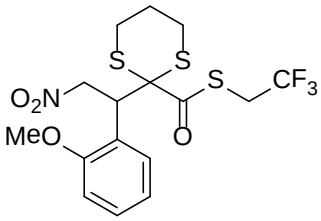
^{19}F-NMR (300 MHz, $CDCl_3$) δ: -65.98 (t, J = 9.6 Hz).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 195.55 (s), 160.04 (s), 130.71 (s), 124.49 (s), 124.73 (q, J = 274.4 Hz), 113.88 (s), 76.86 (s), 67.45 (s), 55.17 (s), 51.77 (s), 33.43 (q, J = 33.5 Hz), 28.59 (s), 28.07 (s), 23.11 (s).

The enantiomeric excess was determined by HPLC on chiral stationary phase with Phenomenex Lux Cellulose2; eluent 9:1 Hexane/2-Propanol; flow 0.8 mL/min; detection: 210 nm; t_R: 13.69 min (major), t_R: 15.78 min (minor).

$[\alpha]_D^{23}$= + 3.062 (*c* 0.288, $CHCl_3$, e.e. 73%). HRMS Mass (ESI+) m/z calc. for $C_{16}H_{18}N_1O_4S_3F_3Na_1^+$ 464.02423, found: 464.02536 [M + Na].

2,2,2-trifluoroethyl 4-nitro-3-[2-(methoxy)phenyl]-2-[(1,3-dithian)-2-yl]-butanethioate (**Table 4, compound 15)**



Rf = 0.41 (7:3 hexane:ethyl acetate)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.37-7.34 (m, 1H), 7.29 (d, J = 7.4 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.87 (d, J = 8.2 Hz, 1H), 5.21 (AB system-part A, J = 13.4, 3.9 Hz, 1H), 5.10 (AB system-part B, 1H), 4.80-4.78 (m, 1H), 3.81 (s, 3H), 3.47 (q, J = 10.0 Hz, 2H), 3.00-2.77 (m, 4H), 2.09-2.03 (m, 1H), 1.92-1.83 (m, 1H).

^{19}F-NMR (300 MHz, $CDCl_3$) δ: -66.09 (t, J = 8.8 Hz).

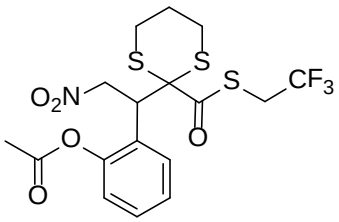
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 196.55 (s), 157.95 (s), 130.20 (s), 124.79 (q, J = 274.6 Hz), 121.75 (s), 120.47 (s), 111.27 (s), 76.33 (s), 67.84 (s), 55.53 (s), 33.60 (q, J = 33.0 Hz), 28.75 (s), 28.11 (s), 23.12 (s).

The enantiomeric excess was determined by HPLC with Daicel Chiralpack AS-3 column; eluent: 9:1 Hex/2-Propanol; flow 0.8 mL/min; detection: 210 nm; t_R: 30.78 min (minor), t_R: 34.22 min (major)

$[\alpha]_D^{23}$= - 11.80 (*c* 0.122, $CHCl_3$, e.e. 71%).

HRMS Mass (ESI+) m/z calc. for $C_{16}H_{18}N_{1O4}S_3F_3Na_1^+$: 464.02423, found: 464.02526 [M + Na].

2,2,2-trifluoroethyl 4-nitro-3-[2-(acetoxy)phenyl]-2-[(1,3-dithian)-2-yl]-butanethioate (**Table 4, compound 16)**



Rf = 0.31 (7:3 hexane:ethyl acetate)

1H-NMR (300 MHz, $CDCl_3$) δ: 7.57 (dd, J = 7.7, 1.1 Hz, 1H), 7.34 (td, J = 7.8, 1.6 Hz 1H), 7.24-7.22 (m, 1H), 7.16 (d, J = 8.1 Hz, 1H), 5.15 (AB system-part A, J = 13.8, 3.8 Hz, 1H), 4.94 (AB system-part B, J = 13.8, 10.3 Hz, 1H), 4.71 (dd, J = 10.1, 3.8 Hz, 1H), 3.37-3.31 (m, 2H), 2.97-2.87 (m, 2H), 2.81-2.73 (m, 2H), 2.38 (s, 3H), 2.09-2.01 (m, 1H), 1.93-1.81 (m, 1H).

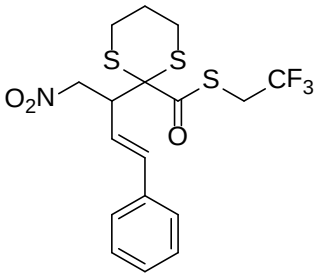
^{19}F-NMR (300 MHz, $CDCl_3$) δ: -66.30 (t).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 196.69, 170.17, 151.34, 131.33, 129.49, 128.12, 127.50, 126.16, 120.36, 76.74, 67.24, 51.60, 32.57 (q), 28.75, 28.11, 23.12, 20.89.

The enantiomeric excess was determined by HPLC on chiral stationary phase with Phenomenex Lux Cellulose2; eluent 9:1 Hexane/2-Propanol; flow 0.8 mL/min; detection: 210 nm; t_R: 18.55 min (minor), t_R: 21.15 min (major)

$[\alpha]_D^{23}$= - 14.82 (*c* 0.244, $CHCl_3$, e.e. 85%).

(*E*)-2,2,2-trifluoroethyl 3-nitromethyl-2-[(1,3-dithian)-2-yl]-5-phenyl-pent-4-en-thioate (compound 17)



Rf = 0.31 (7:3 hexane:ethyl acetate)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.34-7.28 (m, 5H), 6.55 (d, J = 15.6 Hz, 1H), 6.09 (dd, J = 15.6, 9.8 Hz, 1H), 4.98 (AB system-part A, J = 12.8 Hz, 1H), 4.63 (AB system-part B, J = 11.8 Hz, 1H), 3.73-3.55 (m, 3H), 3.02-2.92 (m, 2H), 2.85-2.81 (m, 2H), 2.13-2.10 (m, 1H), 1.95-1.86 (m, 1H).

^{19}F-NMR (300 MHz, $CDCl_3$) δ: -66.31 (t, J = 9.1 Hz).

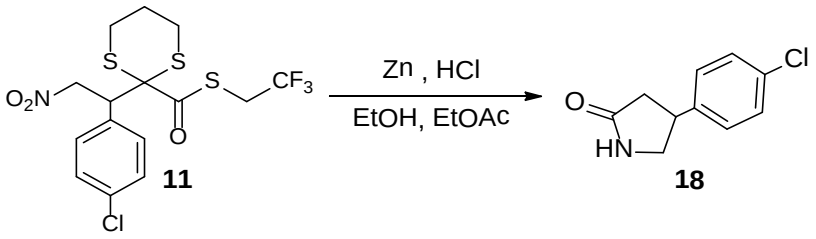
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 195.59 (s), 137.05 (s), 135.08 (s), 128.05 (s), 127.94 (s), 126.33 (s), 124.18 (q, J = 274.4 Hz), 119.93 (s), 76.05 (s), 66.19 (s), 50.05 (s), 32.77 (q, J = 33.6 Hz), 27.82 (s), 27.52 (s), 22.88 (s).

The enantiomeric excess was determined by HPLC on chiral stationary phase with Phenomenex Lux Cellulose2; eluent 9:1 Hexane/2-Propanol; flow 0.8 mL/min; detection: 210 nm; t_R: 9.52 min (major), t_R: 11.45 min (minor).

$[\alpha]_D^{23}$= + 50.55 (*c* 0.182, $CHCl_3$, e.e. 71%).

HRMS Mass (ESI+) m/z calc. for $C_{17}H_{18}N_1O_3S_3\ F_3Na_1^+$: 460.02931, found: 460.03053.

Baclofen (compound 19) synthesis



Compound **11** (1.34 mmol) was dissolved in ethanol and 53.8 mL) and ethyl acetate (40 mL); the solution was cooled to 0 °C and stirred for 10 minutes, after which 6M HCl (11.6 mL) was added. The solution was vigorously stirred while powder zinc (66.8 mmol) was added in three portions over 10 min. The reaction mixture was stirred at room temperature for 2 hours; after this period powder zinc (33.4 mmol) was added in one portion and the resultant grey suspension was stirred at room temperature for a further 1 hour. The organic solvent was removed under vacuum and the aqueous solution was quenched with an oversaturated solution of $NaHCO_3$. The aqueous layer was washed five times with ethyl acetate. The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Purification through flash column chromatography on silica gel (98:2 CH_2Cl_2:MeOH) afforded the desired product **18** as a white solid (0.926 mmol, 69% yield).

The reaction was performed also on 5 mmols scale of starting material.

Rf = 0.38 (94:6 CH_2Cl_2:MeOH)

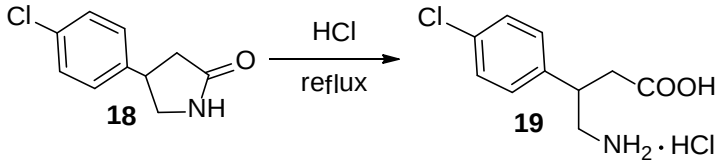
^{1}H-NMR (300 MHz, $CDCl_3$):δ: 7.34 (AB system-part A, J = 8.3 Hz, 2H), 7.17 (AB system-part B, J = 8.2 Hz, 2H), 3.74 (t, 1H), 3.65 (m, 1H), 3.38 (t, 1H), 2.75 (AB system-part A, 1H), 2.43 (AB system-part B, 1H).

^{19}F-NMR (300 MHz, $CDCl_3$): no signal

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 177.90, 140.69, 129.24, 128.98, 128.12, 49.55, 39.59, 38.01.

$[\alpha]_D^{23}$= + 18.35 (c 0.306, $CHCl_3$).

MS Mass (ESI+) m/z calc. for $C_{10}H_{10}Cl_1N_1O_1Na_1^+$ 218.23, experimental 218.10.



A solution of product **18** (1.34 mmol) in 6M HCl (3.3 mL) was refluxed for 18 hours. After this period the solvent was removed under reduced pressure and baclofen hydrochloridric salt **19** was isolated as a white solid (0.48 mmol, 73% yield).

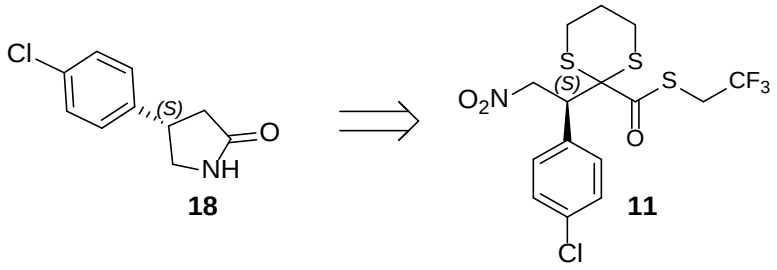
^{1}H-NMR (300 MHz, CD_3OD) δ: 7.35 (m, 4H), 3.32 (m, 2H), 3.18 (m, 1H), 2.80 (AB system-part A, 1H), 2.67 (AB system-part B, 1H).

^{13}C-NMR (75 MHz, CD_3OD) δ: 173.95, 138.63, 134.25,δ 130.20, 129.80,44.36,40.57, 38.74.

HMRS Mass (FAB +) m/z calc. for: $C_{10}H_{13}Cl_2N0_2^+$: 214.06, found: 214.0637.

Determination of the absolute configuration

The sense of enantioselection the stereoselective organocatalyzed conjugate addition reaction was determined through chemical correlation.



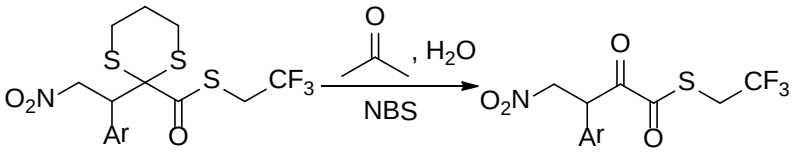
2,2,2-trifluoroethyl 4-nitro-3-[4-(chloro)phenyl]-2-[(1,3-dithian)-2-yl]-butanethioate (compound **11**), obtained with quinine-derived catalyst A, was transformed into the known compound **18** (direct precursor of baclofen, compound **19**) through one-pot nitro group reduction and lactonization and simultaneous loss of the dithiane moiety.

Optical rotation of the product was measured ($[\alpha]_D^{23}$= + 18.35, *c* 0.306, $CHCl_3$) and compared with literature data ($[\alpha]_D^{23}$= +21.8, *c* 0.5, CH_2Cl_2).[1]

Compound **18** - and, as a consequence, compound **11** - was assigned (*S*)-configuration.

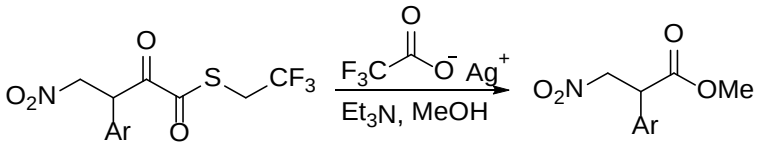
General procedure for the synthesis of β-aryl-α-ketothioesters and of the corresponding β-nitro-α-aryl-esters

Step 1[2]



To a stirred solution of *N*-bromosucinimide (10 eq.) in aqueous 97% acetone (1.85 mL for 1 mmol of NBS) at 0 ° C a solution of the proper 2,2,2-trifluoroethyl 4-nitro-3-aryl-2-[(1,3-dithian)2-yl]-butanethioate (1 eq.) in acetone (4 mL for 1 m mol of carboxythioester) was added dropwise. The solution turned yellow to limpid orange and after some minutes faded to pale yellow. The reaction mixture was allowed to warm to room temperature and stirred for 4 hours. After this period, the reaction mixture was treated with an oversatured aqueous solution of Na_2SO_3 and extracted with ethyl acetate. The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Products were used in the subsequent step without further purification.

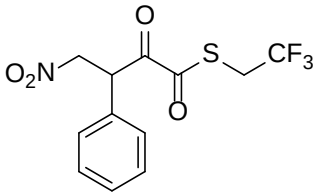
Step 2[3]



To a stirred solution in dry methanol (0.1 mL for 0.057 m mol of substrate), of the β-nitro-α-ketothioester (1 eq.), obtained in the previous step, CF_3CO_2Ag (1.2 eq.) and triethylamine (1 eq.) were added at room temperature. A yellow precipitate was formed. After ten minutes, water was added and the crude reaction product was extracted three times with ethyl acetate The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure.

Characterization of β-aryl-α-ketothioesters and of the corresponding β-nitro-α-aryl-esters

2,2,2-trifluoroethyl 4-nitro-3-phenyl-2-oxo-butanethioate (compound 20)



Rf = 0.53 (8:2 hexane:ethyl acetate))

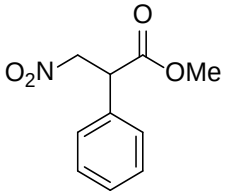
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42-7.39 (m, 3H), 7.27-7.24 (m, 2H), 5.36 (dd, J = 10.3, 4.4 Hz, 1H), 5.23 (dd, J = 14.8, 10.3 Hz, 1H), 4.68 (dd, J = 14.8, 4.4 Hz, 1H), 3.60 (q, J = 9.6 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.71 (s), 186.04 (s), 133.00 (s), 129.33 (s), 128.90 (s), 128.33 (s), 127.61 (s), 127.40 (q, J = 274.9 Hz), 73.97 (s), 48.10 (s), 30.04 (q, J = 34.5 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ: -66.45 (t, J = 9.6 Hz).

$[\alpha]_D^{23}$= + 7.55, *c* 0.1, $CHCl_3$

Methyl 3-nitro-2-phenylpropanoate (compound 23)[4]



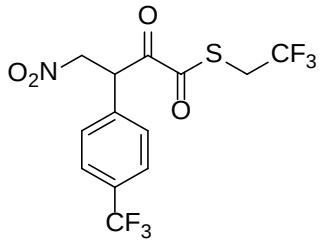
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40-7.36 (m, 3H), 7.30-7.27 (m, 2H), 5.13 (dd, J = 14.5, 9.8 Hz, 1H), 4.57 (dd, J = 14.5, 5.2 Hz, 1H), 4.47 (dd, J = 9.8, 5.2 Hz, 1H), 3.76 (s, 3H).

The enantiomeric excess was determined by HPLC on chiral stationary phase with Daicel Chiralcell OD-H column, eluent 95:5 Hexane/2-Propanol; flow 1 mL/min; detection: 210 nm; t_R: 23.00 min (major), t_R: 59.40 min (minor).

$[\alpha]_D^{23}$= - 141.45, *c* 0.300, $CHCl_3$ (in lit., ref. 4, $[\alpha]_D^{23}$= –134.9 (*c* 1.8, $CHCl_3$, 82% ee).

Alternative HPLC analysis conditions: column: Phenomenex Lux Cellulose2; eluent 8:2 Hexane/2-Propanol; flow 0.8 mL/min; detection: 210 nm; t_R: 9.07 min (minor), t_R: 11.41 min (major).

2,2,2-trifluoroethyl 4-nitro-3-[4-(trifluoromethyl)phenyl]-2-oxo-butanethioate (compound 21)



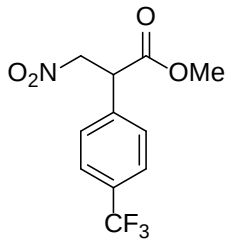
Rf = 0.60 (8:2 hexane:ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.68 (AB system-part A, J = 8.2 Hz, 2H), 7.42 (AB system-part B, J = 8.2 Hz, 2H), 5.44 (dd, J = 10.0, 4.8 Hz, 1H), 5.24 (dd, J = 15.0, 10.0 Hz, 1H), 4.75-4.67 (m, 1H), 3.61 (q, J = 9.6 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.88 (s), 186.46 (s), 135.36 (s), 133.81 (s), 129.32 (s), 130.20 (q, J = 16.3), 129.127.88 (q, J = 276.80 Hz), 127.56 (q, J = 284.8 Hz), 126.83 (s), 74.27 (s), 48.32 (s), 30.64 (q, J = 34.8 Hz).

$[\alpha]_D^{23}$= + 8.06, *c* 0.15, $CHCl_3$

Methyl 3-nitro-2-[4-(trifluoromethyl)-phenyl]-propanoate (compound 24)



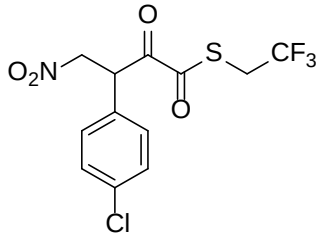
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.67 (AB system-part A, *J* = 8.1 Hz, 2H), 7.44 (AB system-part B, *J* = 8.0 Hz, 2H), 5.14 (dd, *J* = 14.2, 8.9 Hz, 1H), 4.61 (dd, *J* = 19.3, 5.1 Hz, 1H), 4.60-4.52 (m ,2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.24 (s), 136.99 (s), 128.46 (s), 126.41 (s), 125.83 (s), 75.36 (s), 52.97 (s), 48.41(s).

^{19}F NMR (282 MHz, $CDCl_3$) δ: -76.20 (s).

$[\alpha]_D^{23}$= - 131,5, *c* 0.1, $CHCl_3$

2,2,2-trifluoroethyl 4-nitro-3-[4-(chloro)phenyl]-2-oxo-butanethioate (compound 22)



Rf = 0.63 (8:2 hexane:ethyl acetate)

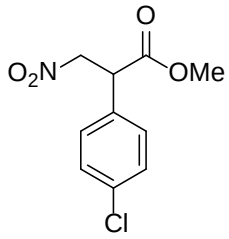
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 8.5 Hz, 2H), 5.31 (dd, J = 10.0, 4.7 Hz, 1H), 5.16 (dd, J = 14.8, 10.0 Hz, 1H), 4.64 (dd, J = 14.9, 4.8 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.41 (s), 185.98 (s), 135.26 (s), 133.61 (s), 129.60 (s), 73.79 (s), 47.39 (s), 30.06 (q, J = 34.6 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ: -66.44 (t, J = 9.6 Hz).

$[\alpha]_D^{23}$= + 5.70, *c* 0.15, $CHCl_3$

Methyl 3-nitro-2-[4-(chloro)phenyl]-propanoate (compound 25)



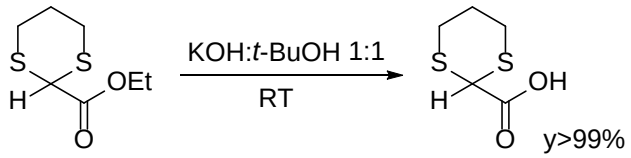
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37 (AB system-part A, J = 8.5 Hz, 1H), 7.23 (AB system-part B, J = 8.5 Hz, 1H), 5.09 (dd, J = 14.6, 9.5 Hz, 1H), 4.56 (dd, J = 14.6, 5.5 Hz, 1H), 4.44 (dd, J = 9.5, 5.6 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.69 (s), 135.33 (s), 131.59 (s), 129.61 (s), 129.29 (s), 75.33 (s), 53.02 (s), 48.00 (s).

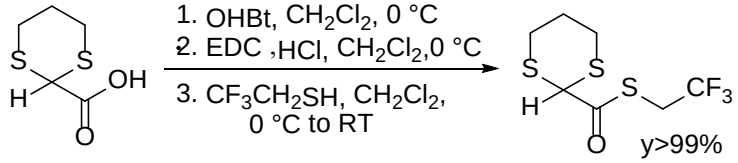
$[\alpha]_D^{23}$= - 137.05, *c* 0.15, $CHCl_3$

The enantiomeric excess was determined by HPLC on chiral stationary phase with Phenomenex Lux Cellulose2; eluent 8:2 Hexane/2-Propanol; flow 0.8 mL/min; detection: 210 nm; t_R: 9.81 min (minor), t_R: 13.69 min (major).

2,2,2-trifluoroethyl 2-[(1,3-dithian)-2-yl]-ethanthioate (compound 8) preparation



A solution of ethyl 2-[(1,3-dithian)-2-yl]-acetate (1.92 g, 10 mmol) in a 1:1 mixture of 1N KOH (10 mL) and *tert*-butanol (10 mL) was stirred overnight at room temperature. The alcohol was removed under reduced pressure and the aqueous phase was acidified with 2N HCl. The mixture was extracted with ethyl acetate (4 x 50 mL) and the solvent was removed under reduced pressure to give 1.5 g of solid dithiane carboxylic acid (mp 115-116°C). The ^{1}H NMR spectra was in agreement with that reported in the literature.



To a solution of carboxylic acid (821 mg, 5 mmol) in dry CH_2Cl_2 (25 mL) HOBt (709 mg, 5.25 mmol) was added at 0 °C, and the resulting solution was stirred for 10 minutes at the same temperature. After this period, EDC•HCl (1.01 g, 5.25 mmol) was added at 0 °C and the mixture was stirred for 30 minutes at the same temperature. Finally, 2,2,2-trifluoroethanethiol (638 mg, 5.50 mmol) was added at 0 °C, and the mixture was allowed to warm to room temperature. After being stirred overnight, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and H_2O (30 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic phases were washed with water (2 × 10 mL) and brine (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the desired compound was obtained as a white solid (1.25 g, 95%).

Mp: 56-57 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.62 (q, J = 9.8 Hz, 2H), 3.16-3.24 (m, 2H), 2.60-2.68 (m, 2H), 1.96-2.20 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 192.7 (s), 124.0 (q, J = 272.0 Hz), 49.5 (s), 31.8 (q, J = 1.4 Hz), 26.4 (s), 24.7 (s).

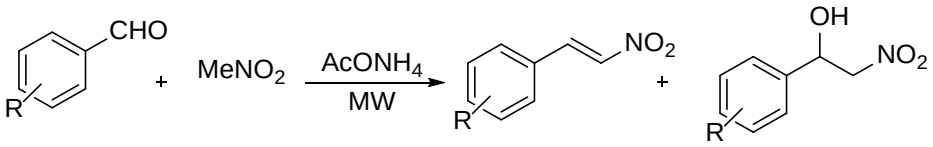
^{19}F-NMR (282 MHz, $CDCl_3$) δ: -67.2 (t).

ν (cm^{-1}) (KBr) 2998, 2970, 2934, 2907, 1698, 1686, 1400, 1307, 1270, 1237, 1131, 1081, 1009, 992, 910, 764.

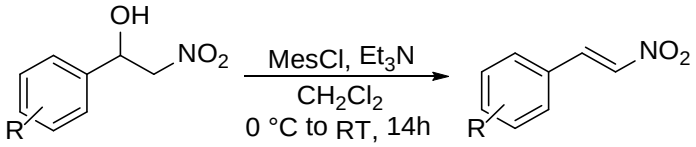
$C_7H_9F_3OS_3$ (262.34): calc. C, 32.05, H, 3.46; found C, 32.14, H, 3.47.

Nitrostyrene derivatives preparation

Compounds 1-15 synthesis



A stirred mixture of the proper aldehyde (1 eq.), ammonium acetate (0.3 eq.) and nitromethane (55 eq.) was subjected to 200W microwave irradiation and heated to 90 °C for 1 hour. Constant microwave irradiation and simultaneous air-cooling (2 bar) were applied during the entire reaction time. After this period, the mixture was treated with an oversaturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. This procedure typically brought to the formation of a mixture of the desired nitrostyrene derivative and of the nitroalcohol; the two products were separated through flash column chromatography on silica gel (9:1 hexane:ethyl acetate) and nitroalcohols were subjected to subsequent dehydration.

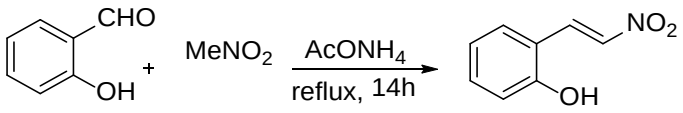


The proper nitroalcohol was dissolved in CH_2Cl_2; the solution was cooled to 0 °C and stirred for 10 minutes. After this period, triethylamine (4 eq.) and methanesulfonyl chloride (3 eq.) were added dropwise. The resulting mixture was stirred at room temperature for 14 hours, after which the reaction mixture was quenched with water; the aqueous layer was separated and washed three times with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography on silica gel (9:1 hexane:ethyl acetate).

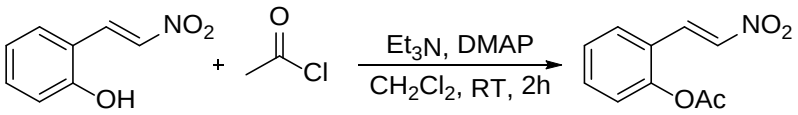
Products' analytical data were in agreement with literature.

Compound	R	Yield (%)
10	*p*- CF_3	51
11	*p*- Cl	52
12	*p*- CH_3	53
13	*o*- CH_3	79
14	*p*- OMe	37
15	*o*- OMe	>99

Compound 16 synthesis

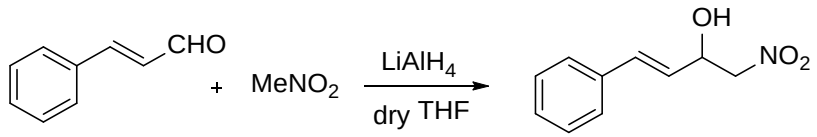


A stirred mixture of the salicylic aldehyde (1 eq.), ammonium acetate (1.1 eq.) and nitromethane (100 eq.) was refluxed for 14 hours. After this period, nitromethane was removed under reduced pressure and the mixture was treated with H_2O and extracted with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. After purification through flash column chromatography on silica gel (9:1 hexane:ethyl acetate) the desired nitrostyrene derivative (*E*)-2-(2-nitrovinyl)phenol was obtained as yellow solid (46% yield).

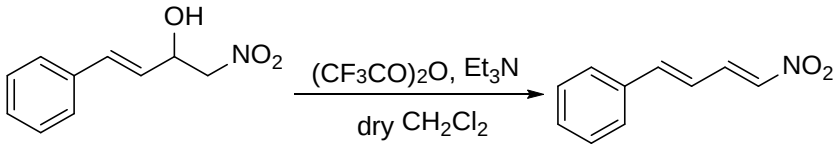


To a stirred solution of the previously prepared nitrostyrene derivative (*E*)-2-(2-nitrovinyl)phenol (1 eq.) 4-dimethylaminopyridine (0.1 eq.), triethylamine (2 eq.) and acetyl chloride (1.5 eq.) were added dropwise at 0 °C. The mixture was stirred for 2 hours and after this period it was quenched with an oversaturated solution of $NaHCO_3$; the aqueous layer was separated and washed diethyl ether. The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Purification though flash column chromatography on silica gel (9:1 hexane:ethyl acetate) afforded compound **16** as a yellow solid (36% yield).

Compound 17 synthesis[5]



A solution of lithium aluminium hydride (0.179 mmol) in dry tetrahydrofuran (7 mL) was cooled to 0 °C and stirred for 30 minutes. After this period, nitromethane (0.485 mL) was added and the reaction mixture was stirred at 0 °C for 30 minutes. Cinnamaldehyde (1.79 mmol) was added dropwise and the reaction mixture was stiredr at 0 °C for 14 hours, after which the reaction mixture was quenched with 1M HCl; the aqueous layer was separated and extracted with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The product was purified by flash column chromatography on silica gel (9:1 hexane:ethyl acetate). The desired nitroalcohol was obtained as a yellow oil (1.29 mmol, 72% yield).



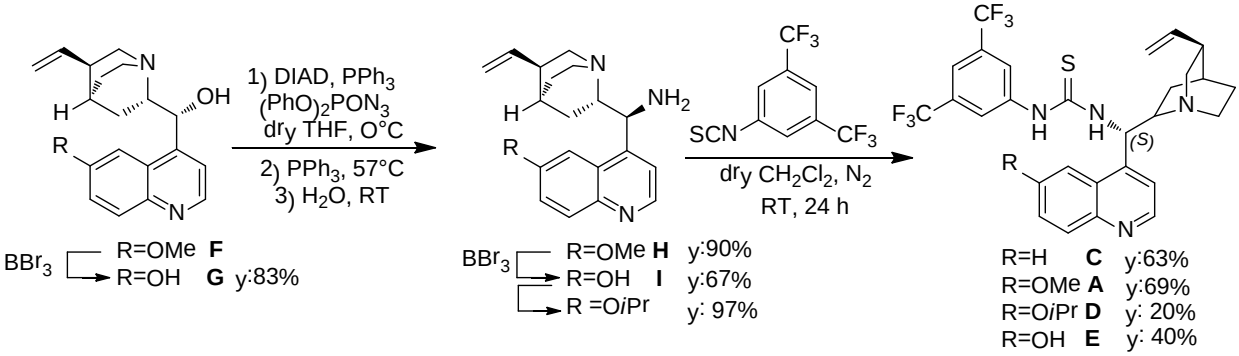
Nitroalcohol (1.29 mmol) was dissolved under inert atmosphere in CH_2Cl_2; the solution was cooled to 0 °C and stirred for 10 minutes. After this period, 2,2,2-trifluoroacetic anhydride (1.37 mmol) and triethylamine (2.73 mmol) were added. The reaction mixture was stirred under inert atmosphere at room temperature for 2 hours, after which it was treated with an oversaturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2. The combined organic phases were washed with an oversaturated solution of NaCl and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude was purified by flash column chromatography on silica gel (9:1 hexane:ethyl acetate). Nitrostyrene derivative **17** was isolated as a yellow solid.

Product's analytical data were in agreement with literature.

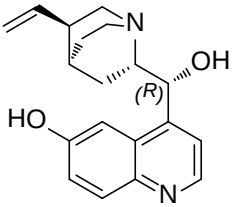
Catalysts preparation

Synthesis of thiourea-based bifunctional catalysts derived from Cinchona alkaloids

Products were prepared according to literature procedures; analytical data were in agreement with literature ones.



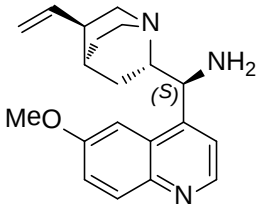
Catalyst G[6]



Rf = 0.33 (CH_2Cl_2/MeOH = 95/5 + 1mL NH_4OH)

^{1}H-NMR (300 MHz, CD_3OD) δ: 8.56 (d, J = 4.6 Hz, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.58 (d, J = 4.6 Hz, 1H), 7.32-7.27 (m, 2H), δ 5.76-5.65 (m, 1H), 5.51 (d, J = 3.3 Hz, 1H), 4.95-4.84 (m, 2H), 3.71-3.62 (m, 1H), 3.10-3.02 (m, 1H), 2.73-2.60 (m, 2H), 2.37-2.23 (bs, 1H), δ 1.88-1.75 (m, 3H), 1.77 (br s, 1H), 1.59-1.51 (m, 1H), 1.45-1.36 (m, 1H).

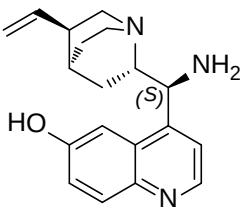
Catalyst H[7]



Rf = 0.41 (EtOAc/MeOH = 50/50 + 1mL NH_4OH)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.69 (d, J = 4.4 Hz, 1H), 7.97 (d, J = 9.2 Hz, 1H), 7.65 (bs, 1H), 7.40 (d, J = 4.4 Hz, 1H), 7.32 (dd, J = 9.2, 2.4 Hz, 1H), 5.80-5.7 (m, 1H), δ 4.97-4.89 (dd, J = 13.6, 9.9 Hz, 2H), 4.53 (d, J = 10.1 Hz, 1H), 3.90 (s, 3H), 3.26-3.16 (m, 2H), 2.98-3.07 (m, 1H), δ 2.79-2.69 (m, 2H), 2.22 (br s, 1H), 2.03 (bs, 2H), 1.56-1.50 (m, 3H), 1.36-1.43 (m, 1H), 0.80-0.68 (m, 1H).

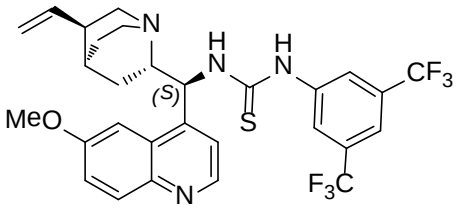
Catalyst I[8]



Rf = 0.22 (CH_2Cl_2/MeOH = 50/50 + 1mL NH_4OH)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.59-8.56 (m, 1H), 7.95 (dd, J = 9.1, 1.9 Hz, 1H), 7.53 (bs, 1H), 7.31-7.25 (m, 2H), 7.29 (dd, 1H), 5.77-5.63 (m, 1H), 4.45-4.12 (m), 3.19-3.11 (m, 1H), 3.07-2.94 (m, 2H), 2.73-2.60 (m, 2H), 2.19 (bs, 1H), 1.49-1.36 (m, 4H), 0.65-0.59 (m, 1H).

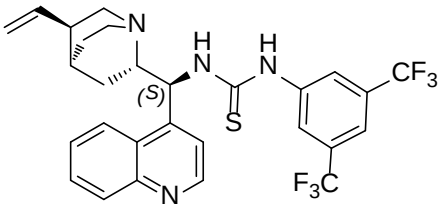
Catalyst A[9]



Rf = 0.6 (CH_2Cl_2/MeOH = 96/4)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.69 (d, J = 4.5 Hz, 1H), 8.05 (d, J = 9.2 Hz, 1H), 7.86 (s, 2H), 7.68 (s, 2H), 7.42 (dd, J = 9.2, 2.6 Hz, 1H), 7.29 (s, 1H), 5.93 (bs, 1H), 5.76-5.65 (m, 1H), 5.07 (d, J = 4.9, 1H), 5.03 (bs, 1H), 3.99 (s, 3H), 3.46 (bs, 2H), 3.24 (dd, *J* = 13.8, 10.1 Hz, 1H), 2.90-2.79 (m, 2H), 2.42 (bs, 1H), 1.78-1.74 (m, 3H), 1.53-1.43 (m, 1H), 1.04-0.99 (m, 1H).

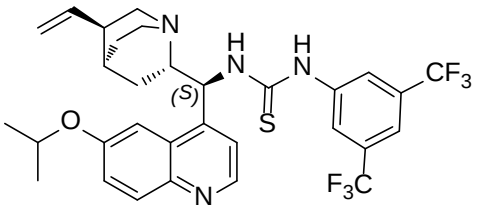
Catalyst C[7]



Rf = 0.35 (CH_2Cl_2/MeOH = 95/5)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.73 (bs, 1H), 8.40 (d, J = 6.3 Hz, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.81 (s, 2H), 7.71-7.66 (m, 1H), 7.63-7.57 (m, 2H), 7.24 (d, J = 5.4 Hz, 1H), 5.86 (bs, 1H), 5.68-5.57 (m, 1H), 4.97-4.91 (m, 2H), 3.30-3.20 (m, 3H), 3.14-3.06 (m, 1H), 2.73-2.68 (bs, 2H), 2.28 (bs, 1H), 1.72-1.62 (m, 3H), 0.95-0.83 (m, 1H).

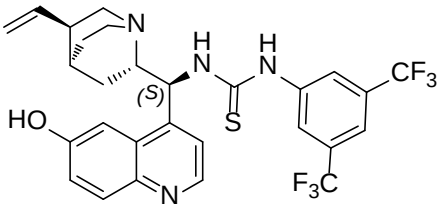
Catalyst D[10]



Rf = 0.33 (CH_2Cl_2/MeOH = 94/6)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.72 (d, J = 4.5 Hz, 1H), 8.02 (d, J = 9.2 Hz, 1H), 7.97 (s, 2H), 7.72 (bs, 1H), 7.60 (s, 1H), 7.44 (d, J = 4.4 Hz, 1H), 7.37 (d, J = 9.3, 2.2 Hz, 1H), 6.19 (bs, 1H), 5.68-5.56 (m, 1H), 5.06-5.00 (m, 2H), 4.79-4.71 (m, 1H), 3.77-3.60 (m, 2H), 3.32 (dd, J = 13.6, 10.5 Hz, 1H), 2.97-285 (m, 2H), 2.48-2.46 (m, 1H), 1.85 (bs, 3H), 1.49-1.59 (m, 1H), 1.42 (d, J = 6.0 Hz, 6H), 1.07 (d, J = 11.1 Hz, 1H).

Catalyst E[11]

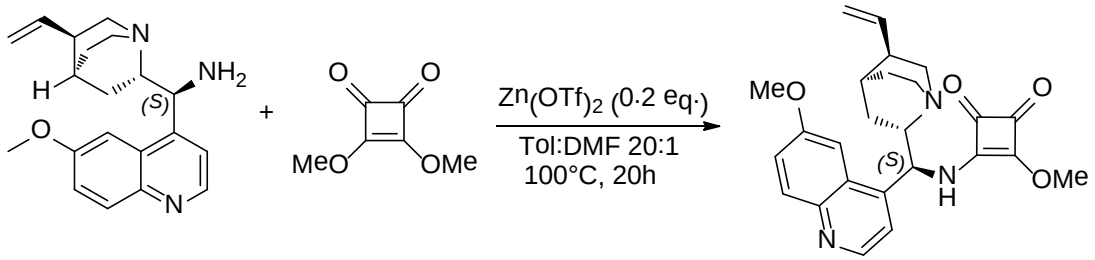


Rf = 0.37 (CH_2Cl_2/MeOH = 94/6)

^{1}H NMR (300 MHz, CD_3OD) δ: 8.67 (s, 1H), 8.20 (s, 2H), 7.90 (s, 2H), 7.74 (s, 1H), 7.60 (s, 1H), 7.38 (d, J = 8.5 Hz, 1H), 6.77 (d, J = 9.4 Hz, 1H), 5.84 (bs, 1H), 5.21-5.08 (m, 2H), 4.29-4.17 (m, 2H), 3.66-5.87 (m, 1H), 3.40-3.28 (m, 3H), 2.74 (bs, 1H), 1.99-1.91 (m, 3H), 1.70 (bs, 1H), 1.18-1.12 (m, 1H).

Synthesis of squaramide-based bifunctional catalysts derived from Cinchona alkaloids

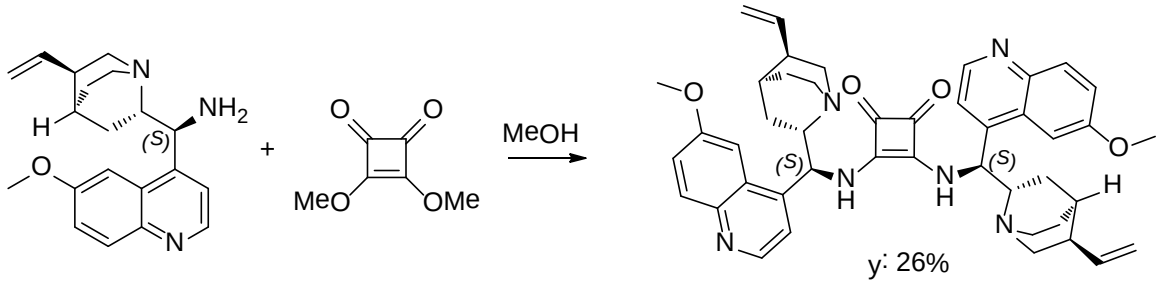
Catalyst L



^{1}H NMR (300 MHz, CD_3OD) δ: 8.72 (d, *J* = 4.7 Hz, 1H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.91 (d, *J* = 2.6 Hz, 1H), 7.61 (d, *J* = 4.8 Hz, 1H), 7.44 (dd, *J* = 9.2, 2.6 Hz, 1H), 6.36 (d, *J* = 11.2 Hz, 1H), 6.04-5.95 (m, 1H), 5.23-5.14 (m, 2H), 4.00 (s, 6H), 3.59-3.52 (m, 1H), 3.00-3.17 (m, 2H), 2.69 (bs, 1H), 1.82-1.93 (m, 5H), 0.99-0.92 (m, 1H).

^{1}H NMR (300 MHz, CD_3OD) δ: 189.22 (s), 188.07 (s), 167.90 (s), 159.35 (s), 147.02 (s), 135.91 (s), 130.36 (s), 129.36 (s), 123.13 (s), 118.96 (s), 116.85 (s), 100.36 (s), 67.58 (s), 66.02 (s), 55.36 (s), 51.88 (s), 48.32, 37.54, 29.16, 26.01 (s), 24.17 (s).

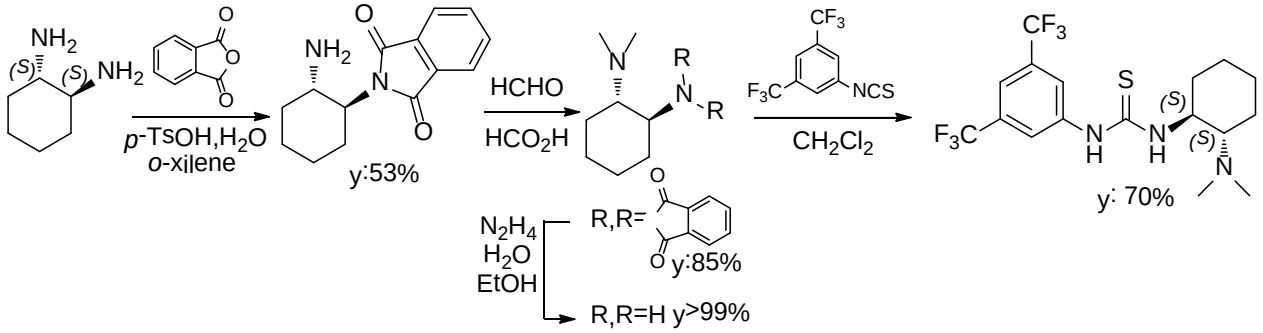
Catalyst M[12]



^{1}H NMR (300 MHz, DMSO) δ: 8.81 (d, J = 4.2 Hz, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.87-7.79 (m, 2H), 7.58 (d, *J* = 4.4 Hz, 1H), 7.46 (d, J = 9.1 Hz, 1H), 6.01-5.84 (m, 2H), 5.01-4.93 (m, 2H), 3.94 (s, 3H), 3.25-3.12 (m, 3H), 3.08-3.01 (m, 1H), 2.50 (bs, 1H), 2.24-2.15 (m, 1H), 1.52-1.43 (m, 4H), 0.56-0.44 (m, 1H).

Synthesis of bifunctional catalysts derived from diaminocyclohexane

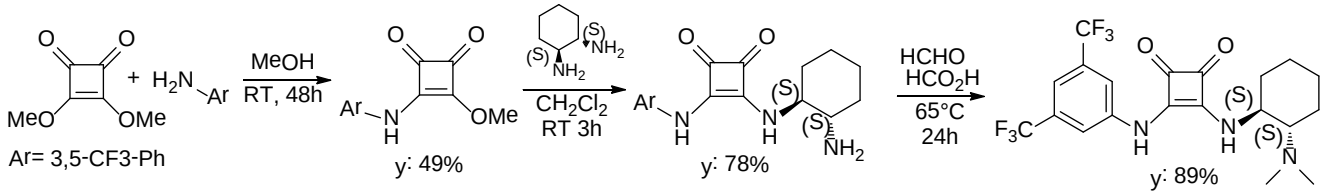
Catalyst B (Takemoto catalyst)[13]



Rf = 0.23 (CH_2Cl_2/MeOH = 9/1)

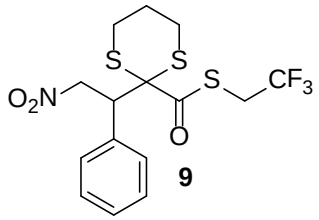
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.92 (s, 2H), 7.63 (s, 1H), 3.99 (bs, 1H), 2.68 (bs, 1H), 2.45 (s, 7H), 2.40 (s, 1H), 2.00-1.97 (m, 1H), 1.93-1.89 (m, 1H), 1.82-1.78 (m, 1H), 1.40-1.17 (m, 4 H).

Catalyst N[14]

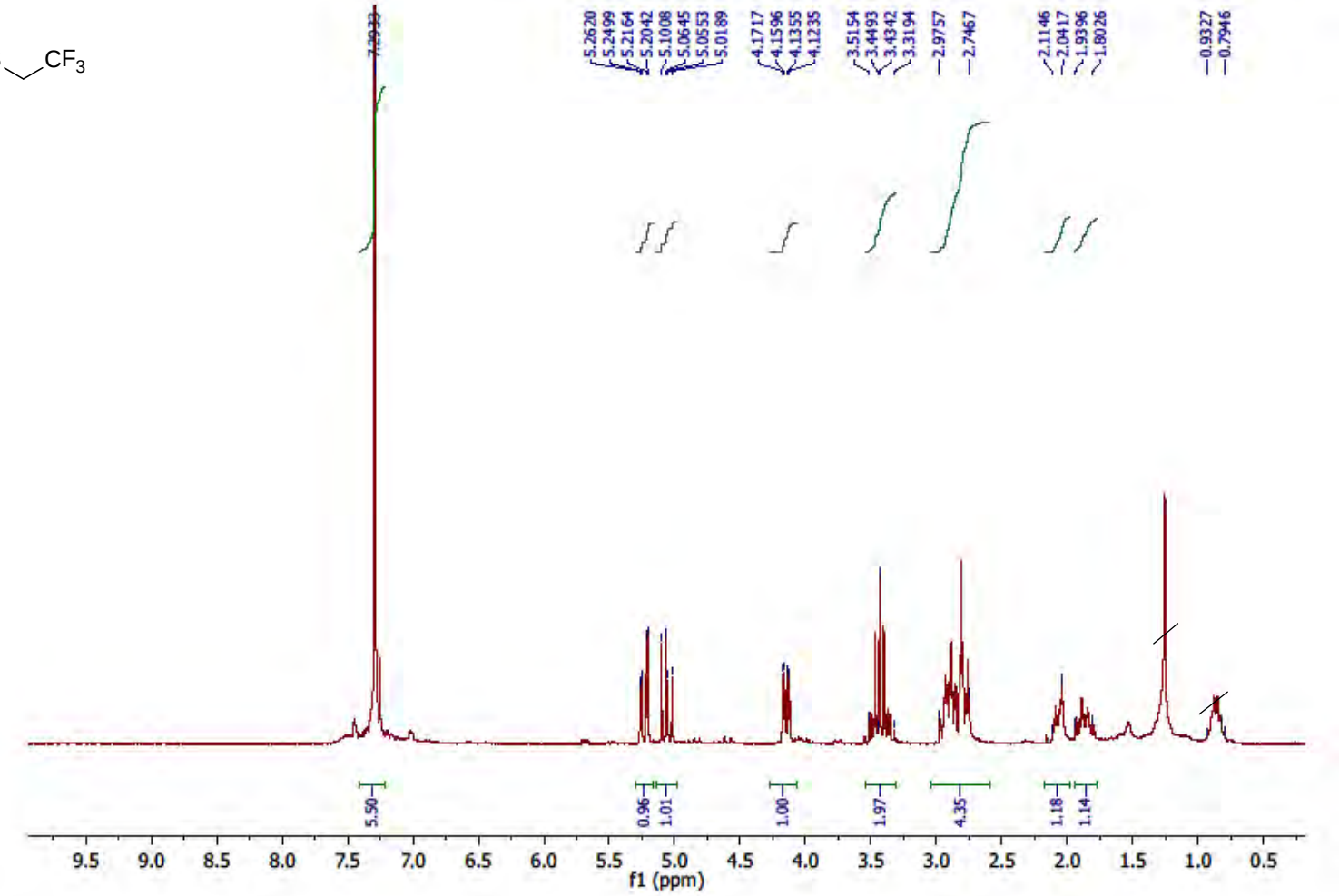


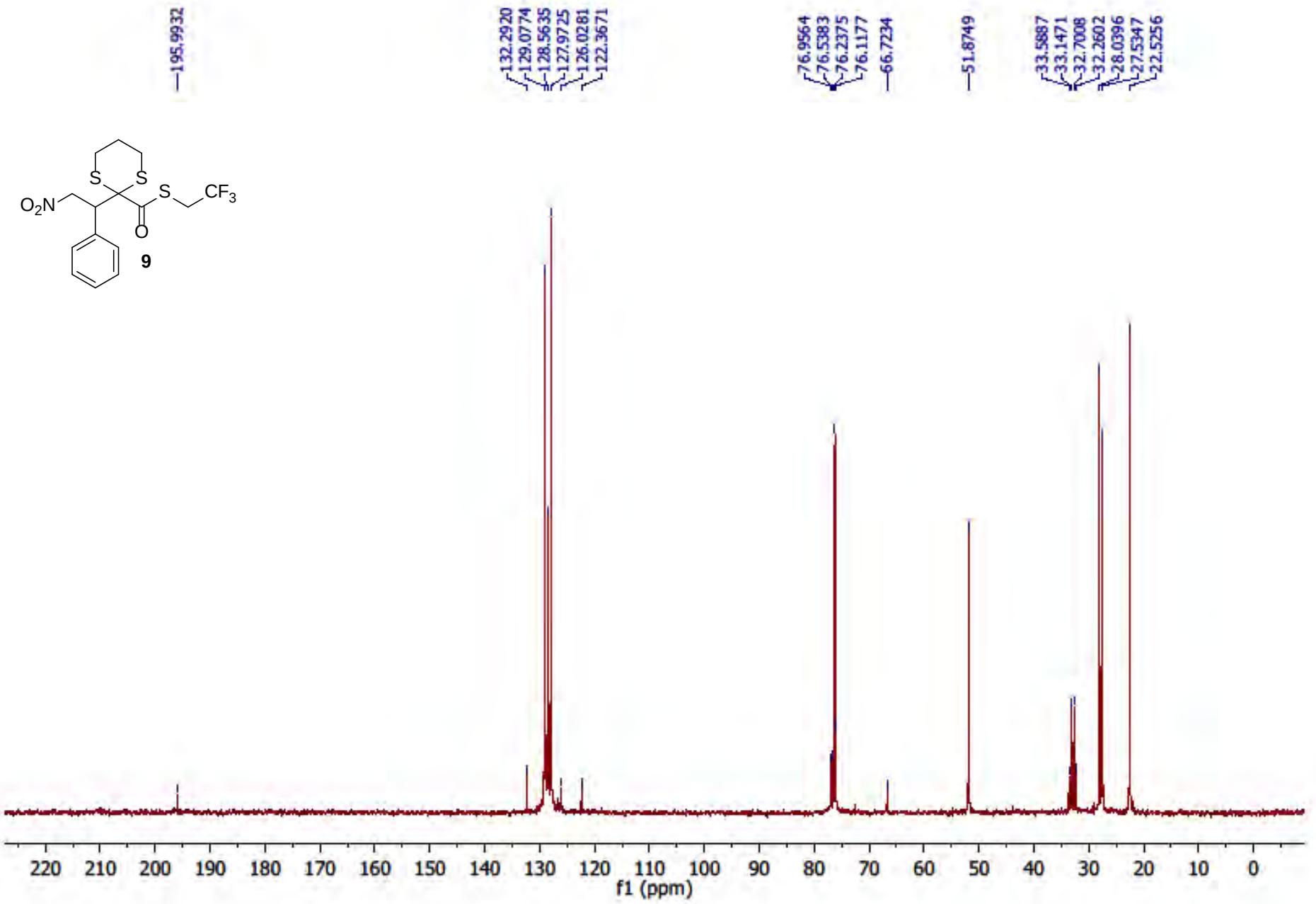
^{1}H NMR (300 MHz, CD_3OD) δ 7.81 (s, 2H), 7.33 (s, 1H), 4.11-3.94 (m, 1H), 2.57-2.44 (m, 1H), 2.30-2.27 (m, 1H), 2.33 (s, 3H), 1.98-1.75 (m, 3H), 1.60-1.49 (m, 1H), 1.45-1.27 (m, 1H).

^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra



9

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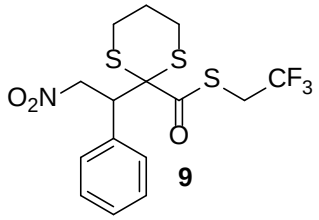
129.0774
128.5635
127.9725
126.0281
122.3671
76.9564
76.5383
76.2375
76.1177
66.7234
51.8749
33.5887
33.1471
32.7008
32.2602
28.0396
27.5347
22.5256
O2N
S
S
S
CF3
O
9
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


S
S
S
CF3
O2N
O

9

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-65.9893
-66.0193
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-30
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-50
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-100
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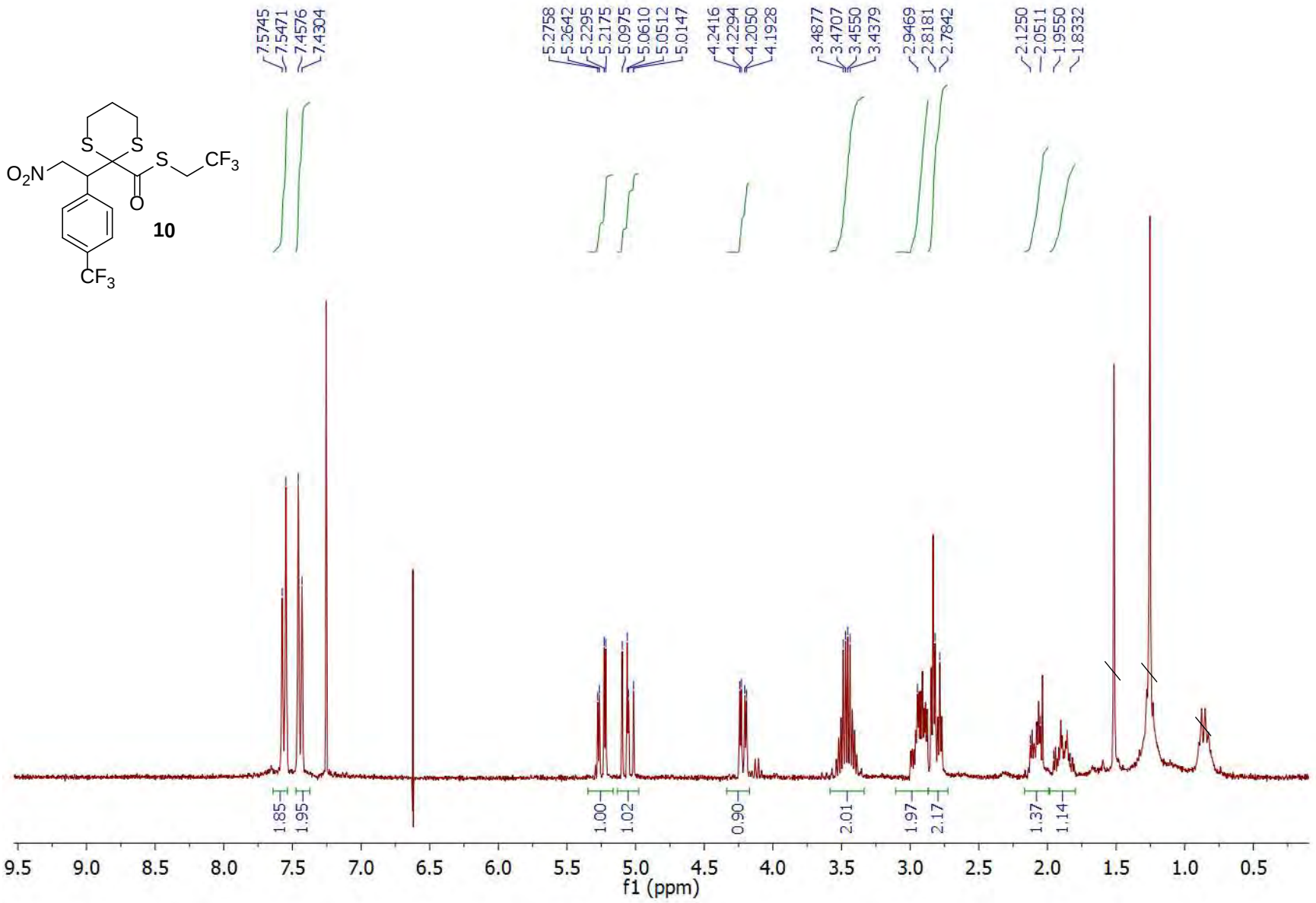
-110
-115
-120
-125
f1 (ppm)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7.4304
5.2758
5.2642
5.2295
5.2175
5.0975
5.0610
5.0512
5.0147
4.2416
4.2294
4.2050
4.1928
3.4877
3.4707
3.4550
3.4379
2.9469
2.8181
2.7842
2.1250
2.0511
1.9550
1.8332
1.85
1.95
1.00
1.02
0.90
2.01
1.97
2.17
1.37
1.14
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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3.5
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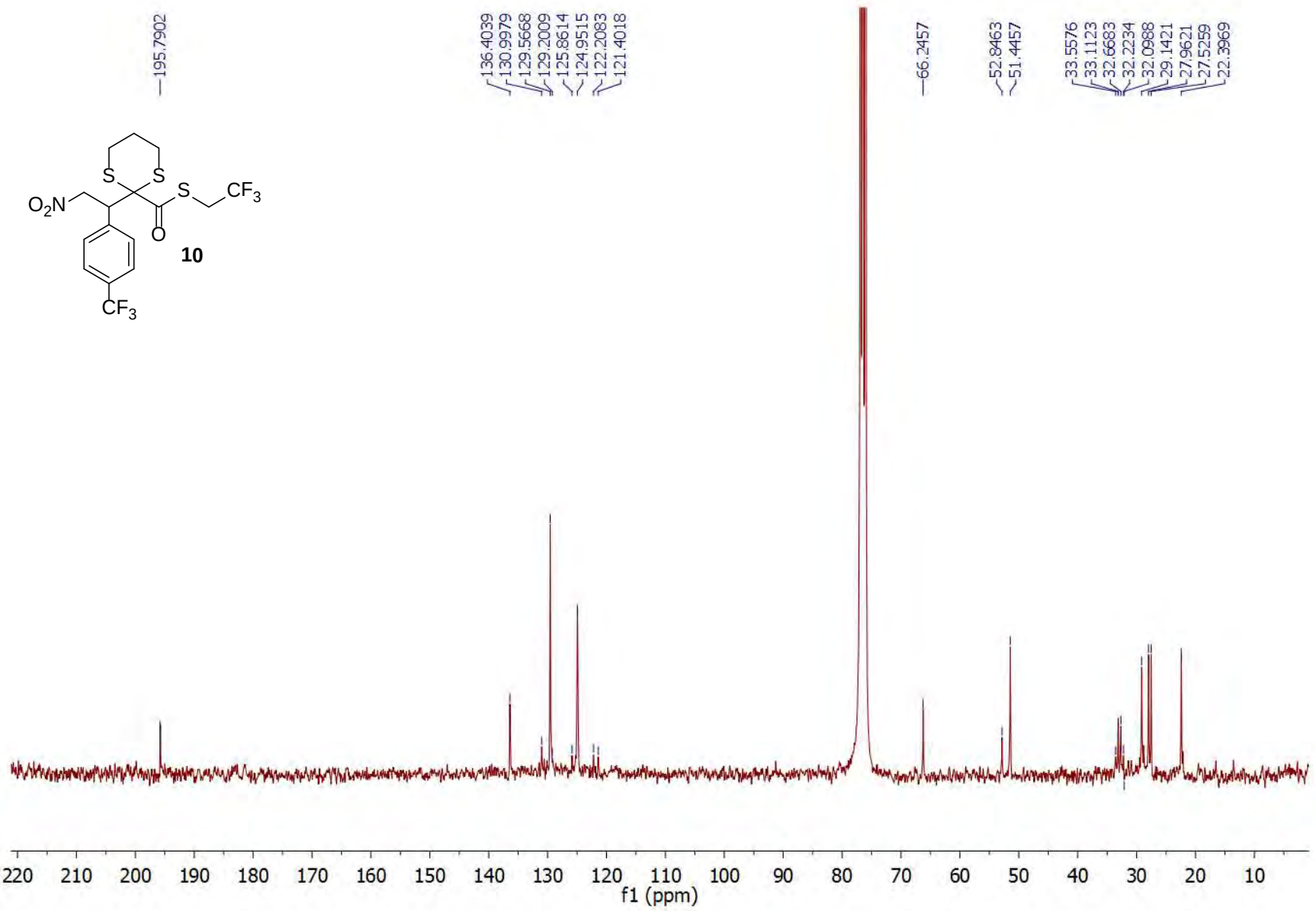
2.0
1.5
1.0
0.5
f1 (ppm)

10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130.9979
129.5668
129.2009
125.8614
124.9515
122.2083
121.4018
66.2457
52.8463
51.4457
33.5576
33.1123
32.6683
32.2234
32.0988
29.1421
27.9621
27.5259
22.3969
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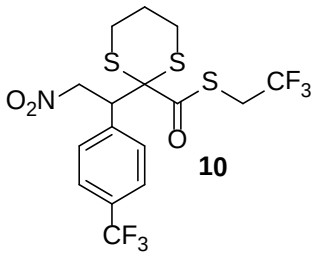
S
S
CF_3
O_2N
O
CF_3
10
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


S
S
S
CF3
O2N
O
CF3

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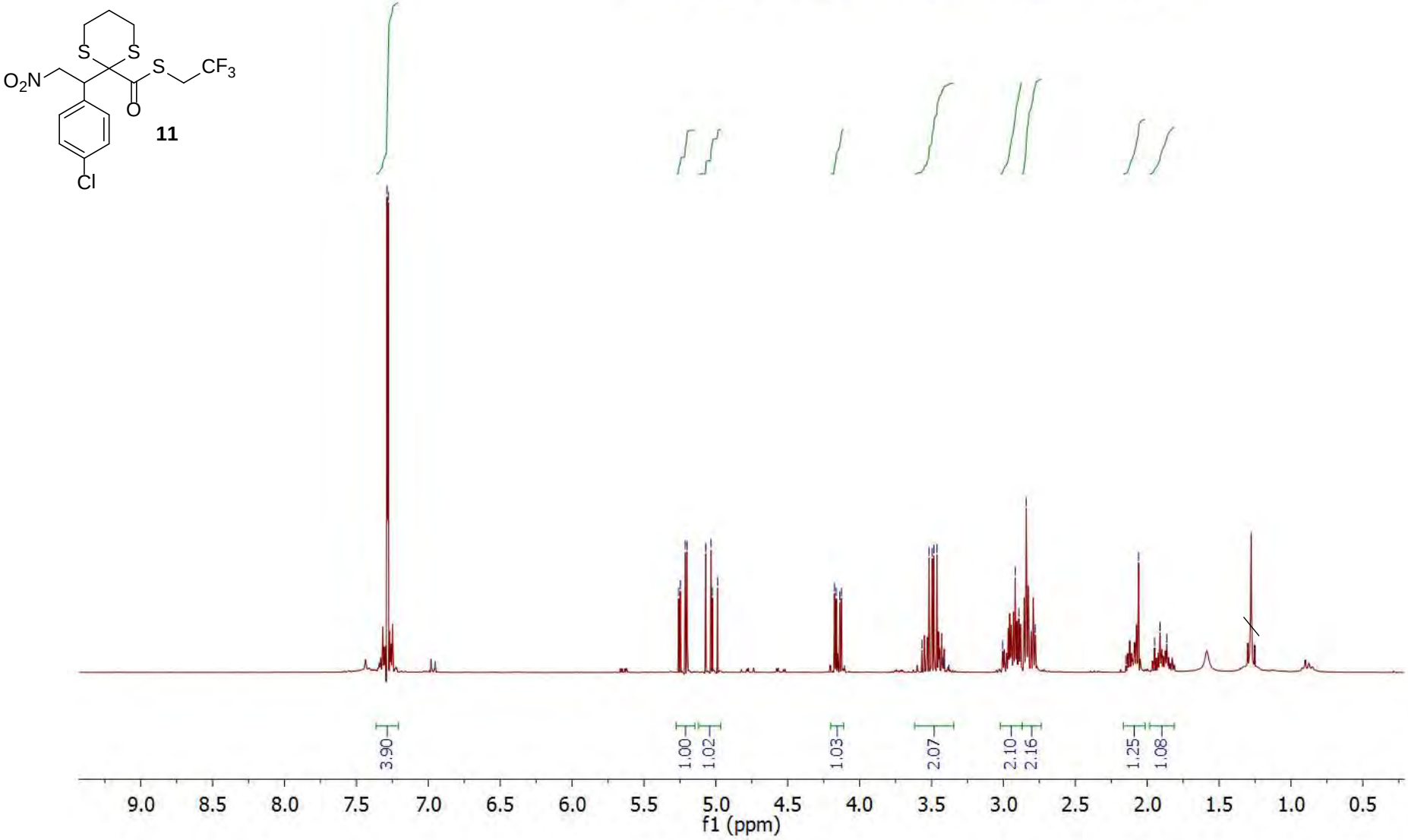
-100
-105
-110
f1 (ppm)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5.2466
5.2128
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5.0704
5.0336
5.0246
4.9878
4.1748
4.1627
4.1380
4.1264
3.5170
3.4948
3.4839
2.9179
2.8926
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2.7786
2.1478
2.0598
1.9488
1.9106
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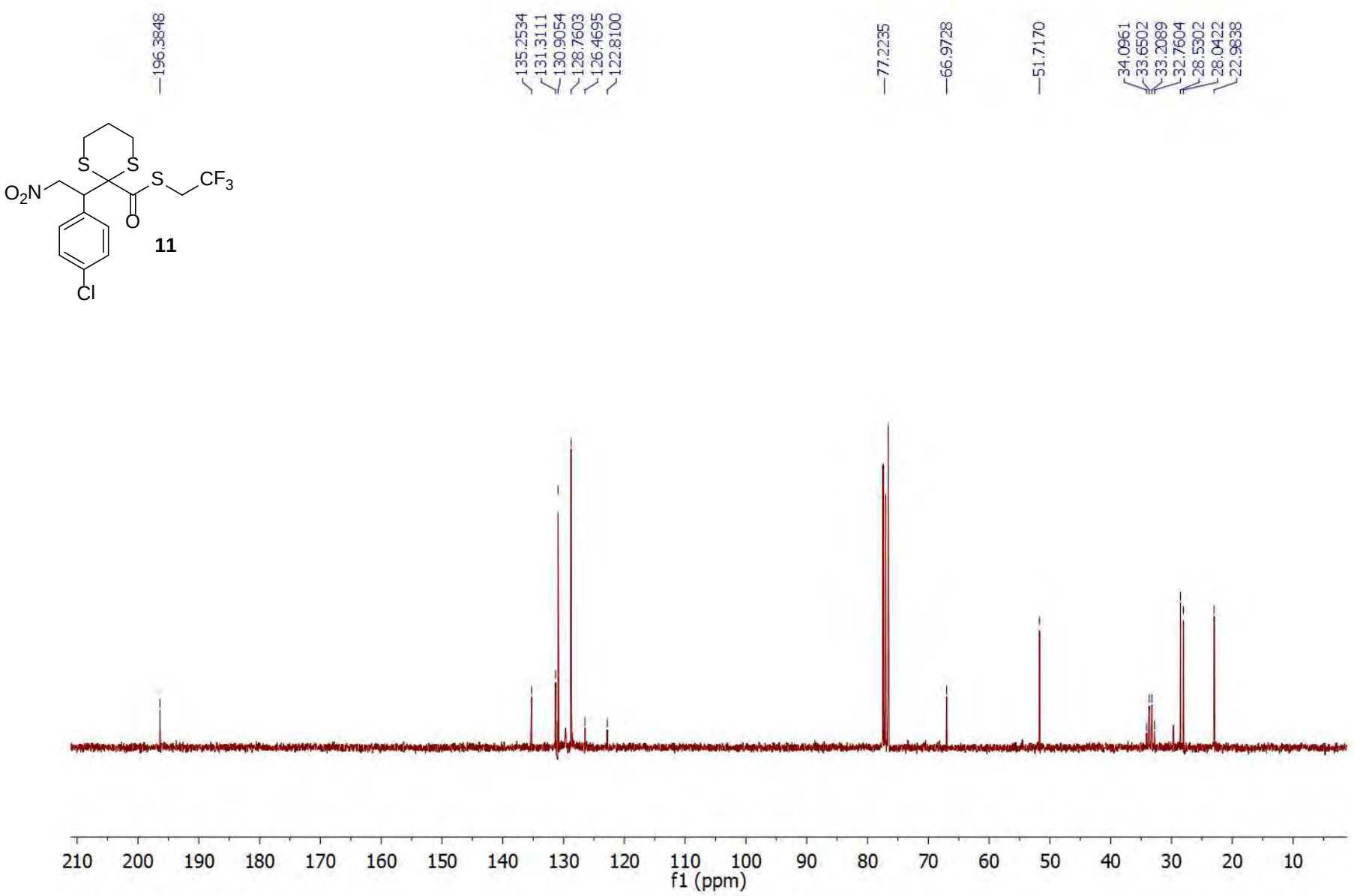
1.03
2.07
2.10
2.16
1.25
1.08
f1 (ppm)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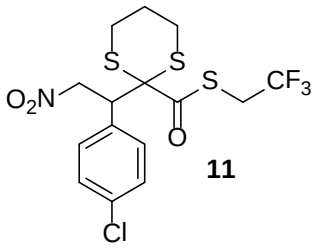
34.0961
33.6502
33.2089
32.7604
28.5302
28.0422
22.9838
S
S
S
CF3
O2N
O
Cl
11
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


S
S
S
O_2N
CF_3
O
Cl

11

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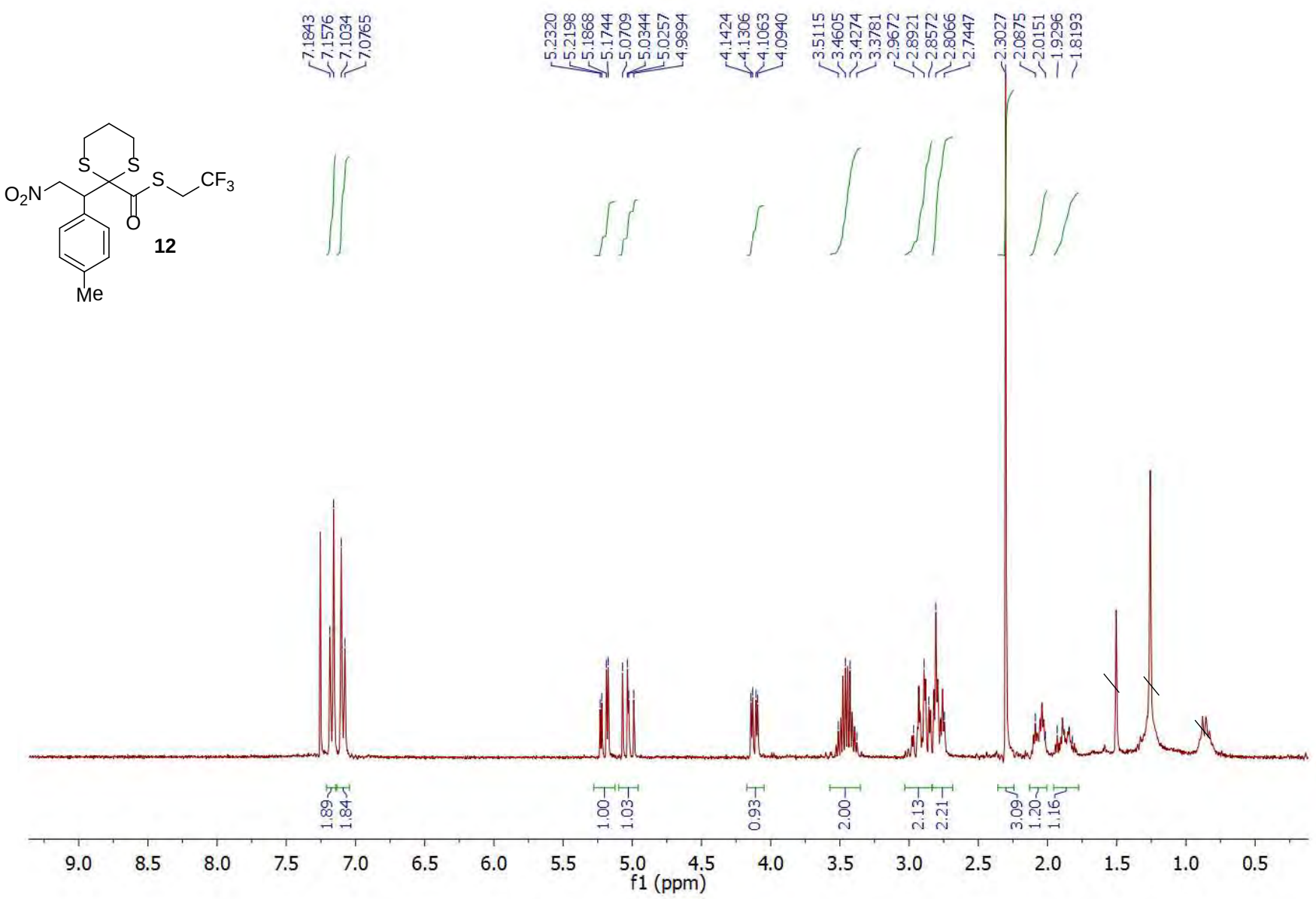
-220
f1 (ppm)


O2N
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S
S
CF3
O
Me
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5.1868
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5.0709
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1.8193
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0.93
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7.0
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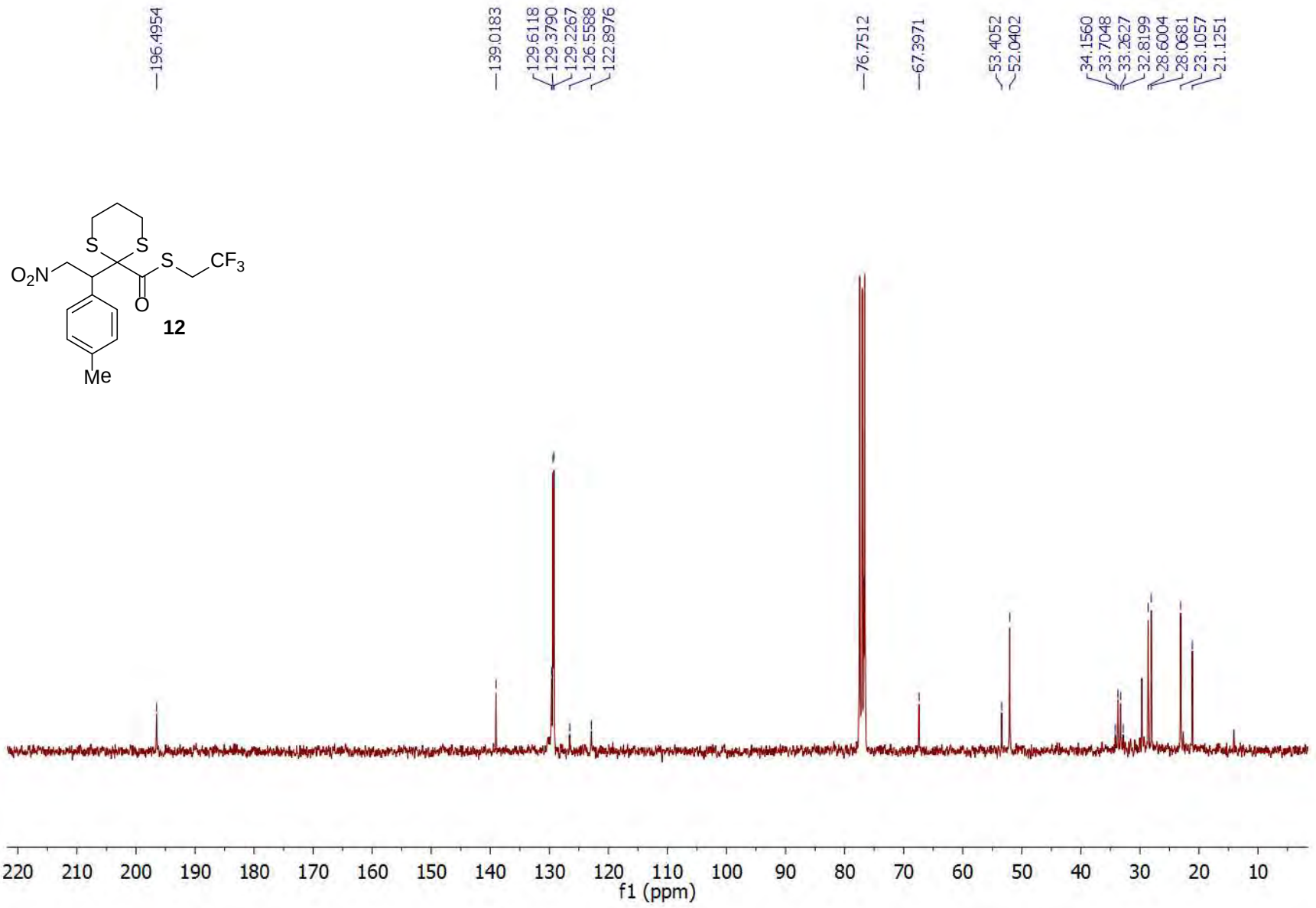
0.5
f1 (ppm)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34.1560
33.7048
33.2627
32.8199
28.6004
28.0681
23.1057
21.1251
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S
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O
O_2N
CF_3
Me
12
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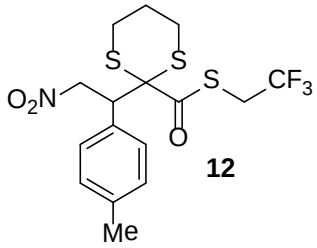
f1 (ppm)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S
S
CF3
O2N
O
Me

12

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-60
-65
-70
-75
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-85
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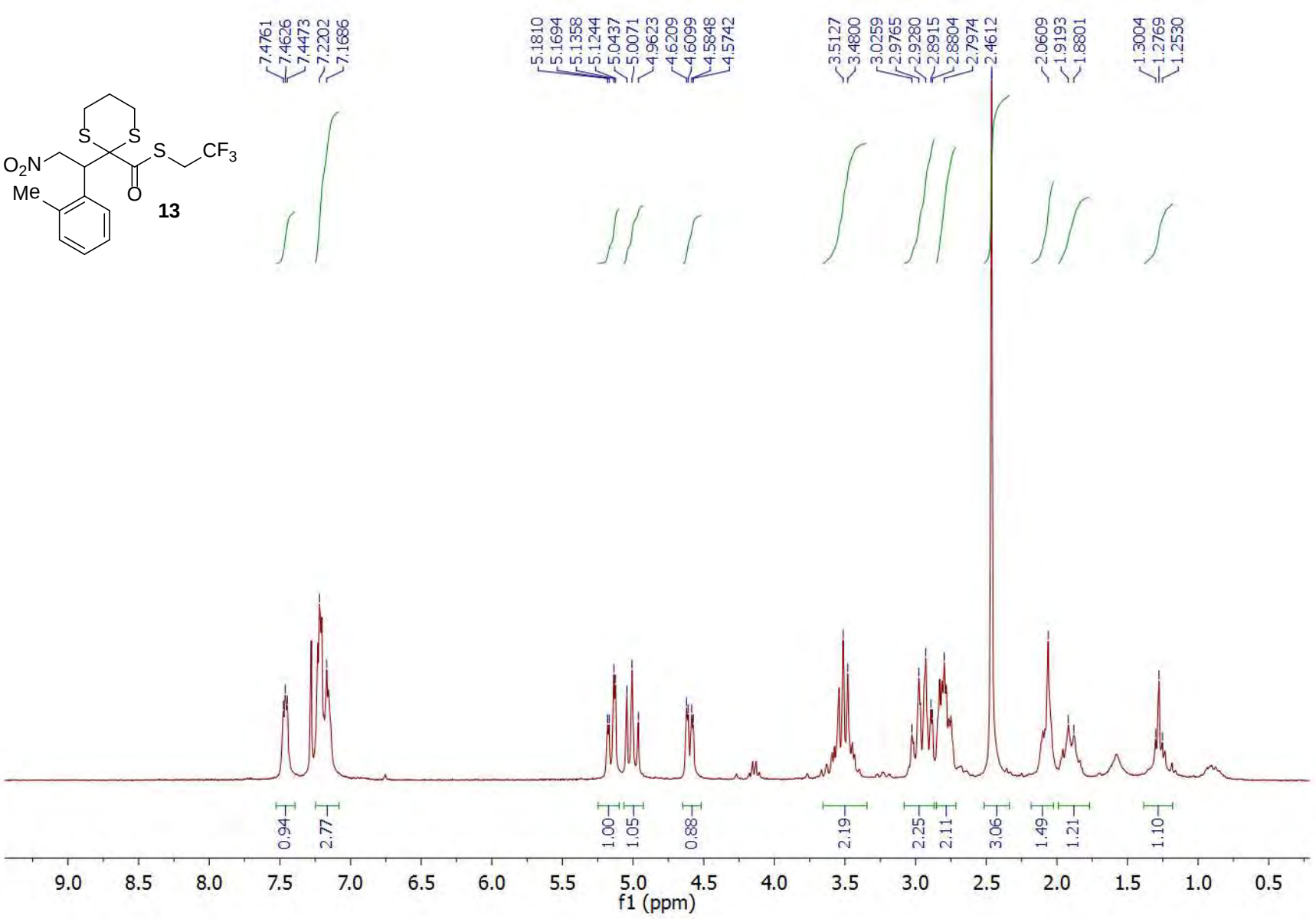
-95
-100
-105
-110
f1 (ppm)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5.1694
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5.1244
5.0437
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4.9623
4.6209
4.6099
4.5848
4.5742
3.5127
3.4800
3.0259
2.9765
2.9280
2.8915
2.8804
2.7974
2.4612
2.0609
1.9193
1.8801
1.3004
1.2769
1.2530
0.94
2.77
1.00
1.05
0.88
2.19
2.25
2.11
3.06
1.49
1.21
1.10
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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4.0
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2.5
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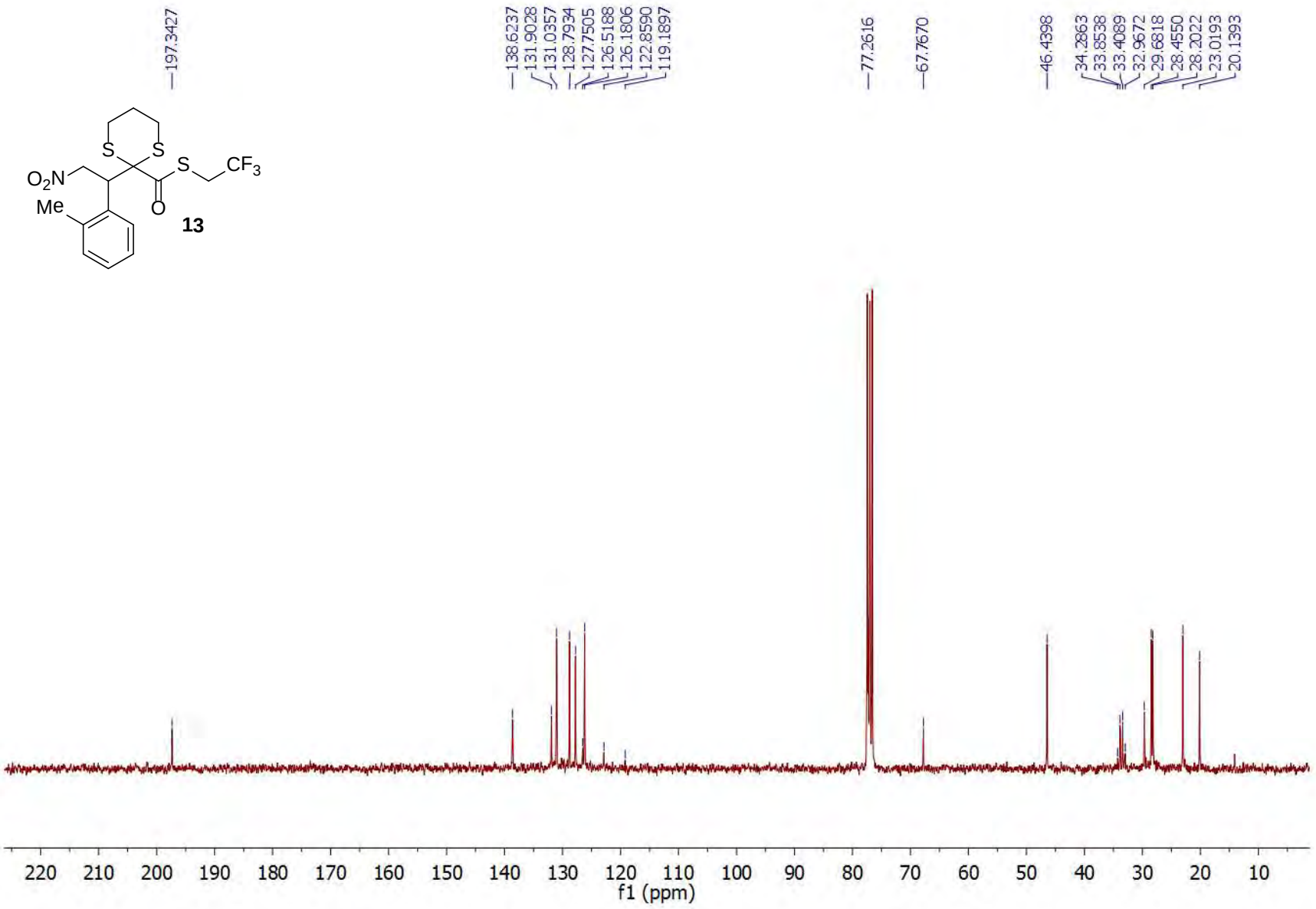
1.5
1.0
0.5
f1 (ppm)

13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126.5188
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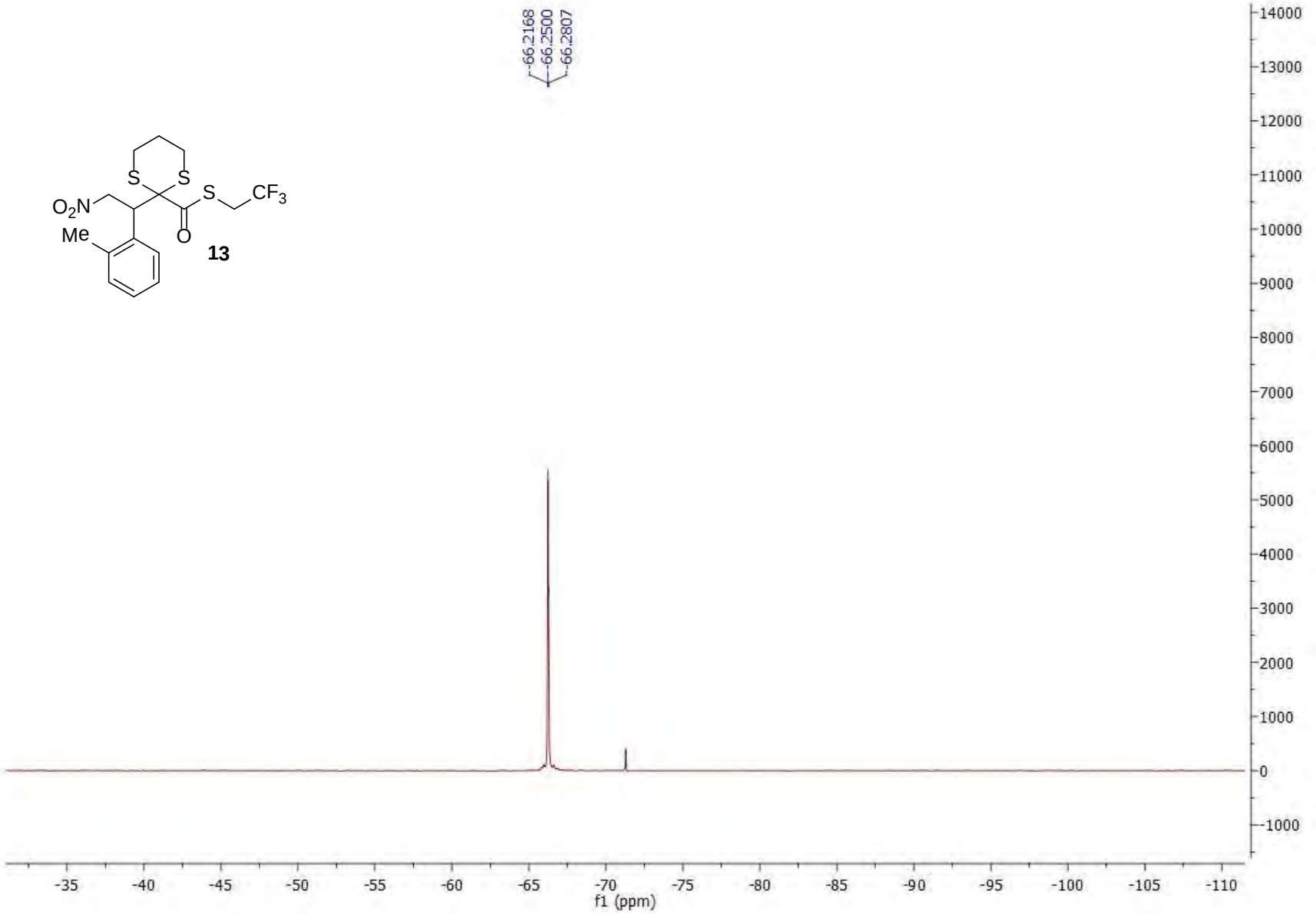
122.8590
119.1897
77.2616
67.7670
46.4398
34.2863
33.8538
33.4089
32.9672
29.6818
28.4550
28.2022
23.0193
20.1393
S
S
S
CF3
O2N
Me
O
13
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)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S
S
CF3
O2N
Me
O
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14000
13000
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11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-35
-40
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-60
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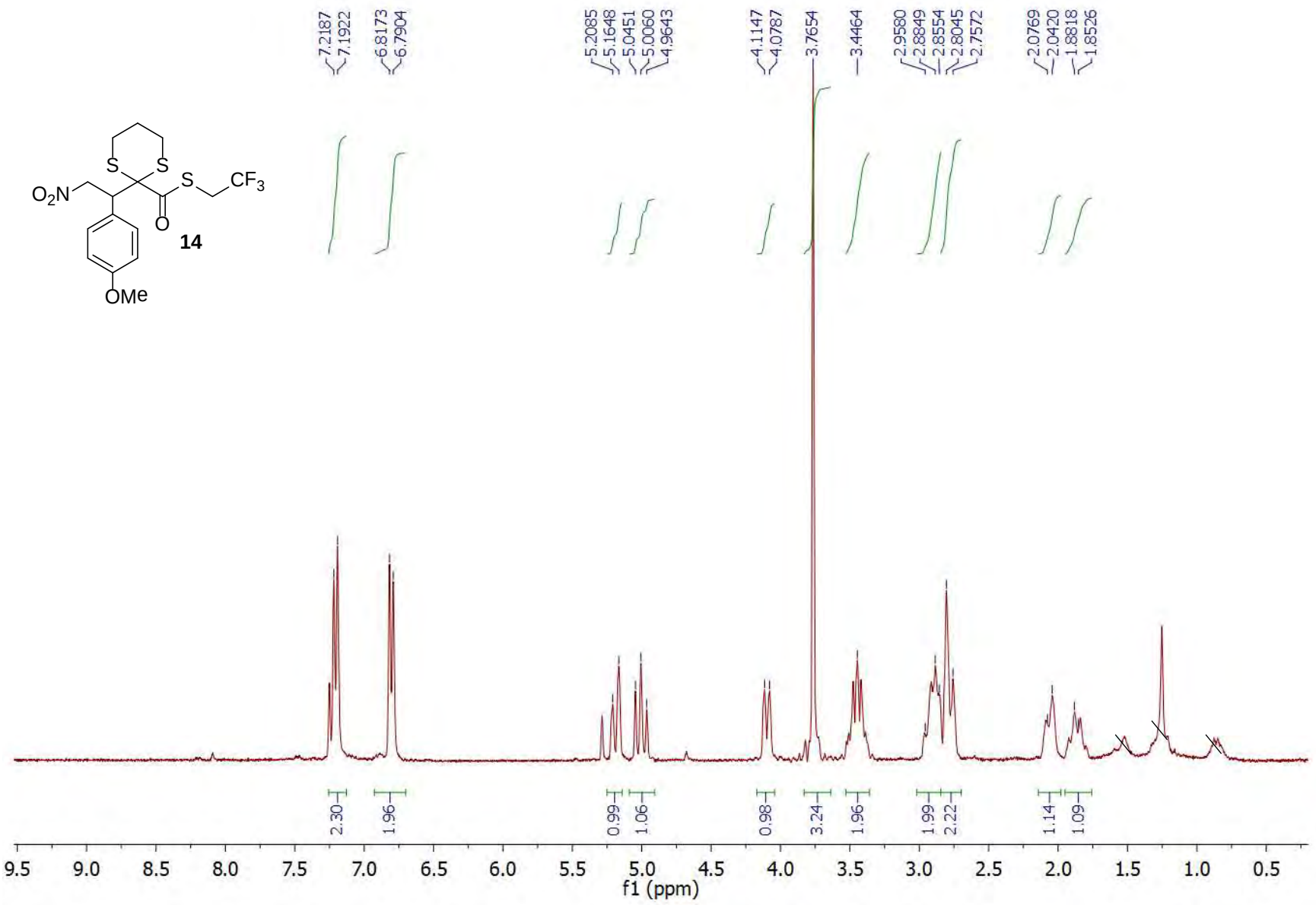
-70
-75
-80
-85
-90
-95
-100
-105
-110
f1 (ppm)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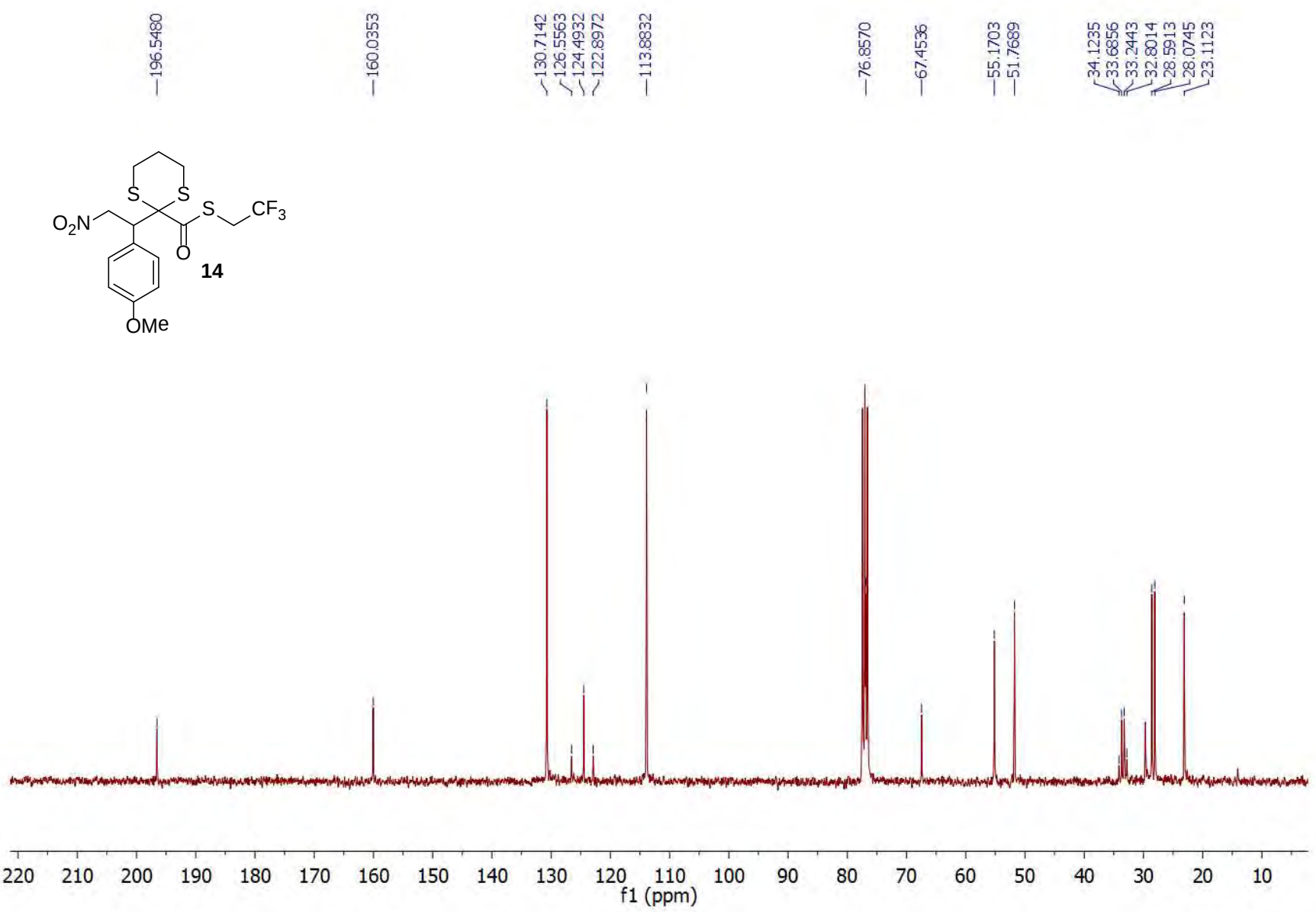
3.7654
3.4464
2.9580
2.8849
2.8554
2.8045
2.7572
2.0769
2.0420
1.8818
1.8526
2.30
1.96
0.99
1.06
0.98
3.24
1.96
1.99
2.22
1.14
1.09
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
S
S
S
CF3
O2N
O
OMe
14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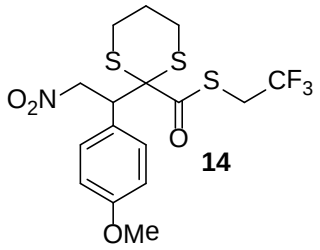
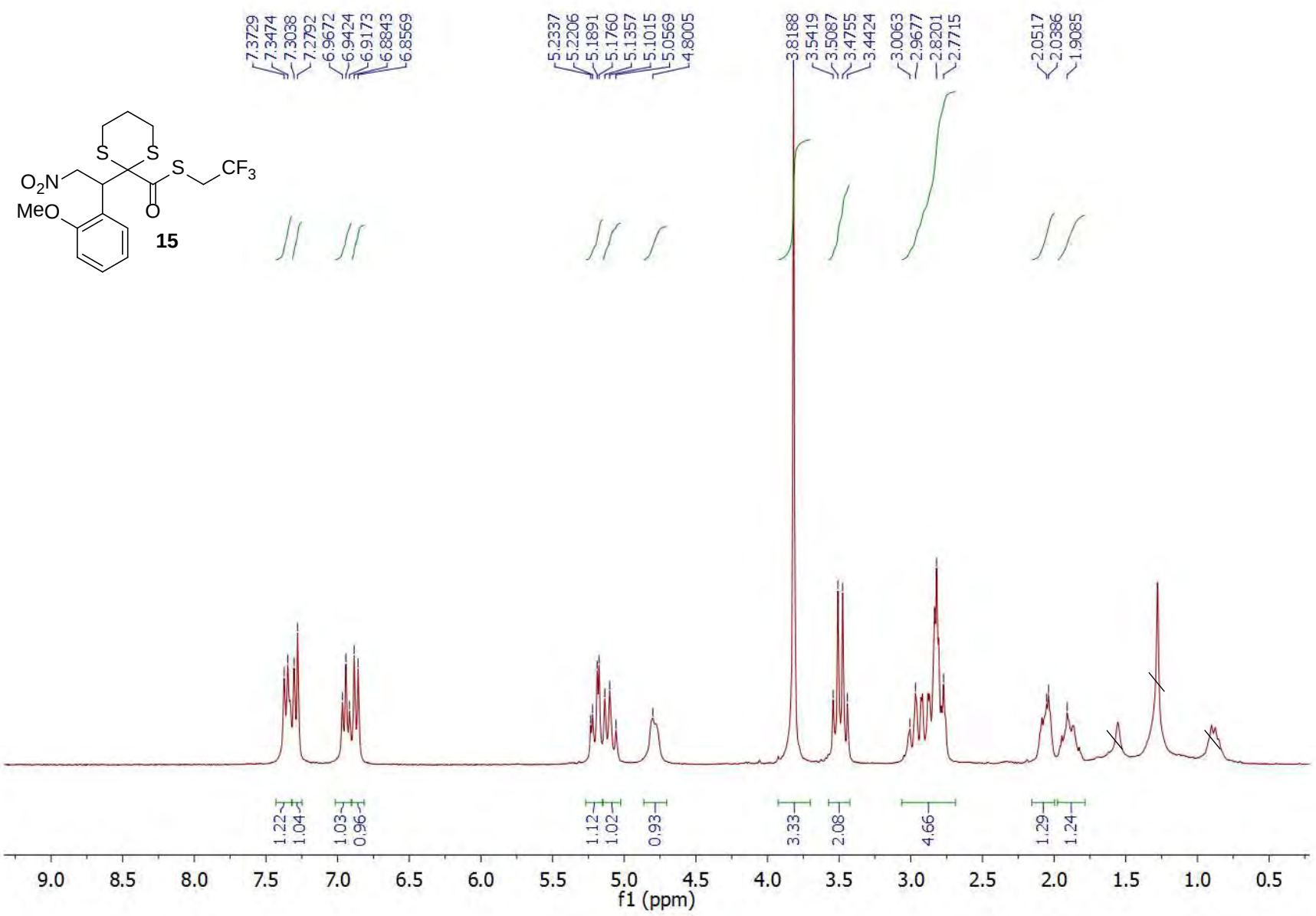
130.7142
126.5563
124.4932
122.8972
113.8832
76.8570
67.4536
55.1703
51.7689
34.1235
33.6856
33.2443
32.8014
28.5913
28.0745
23.1123
S
S
S
CF3
O2N
O
OMe
14
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


S
S
S
O_2N
CF_3
O
OMe

14

-65.9407
-65.9759
-66.0089
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
f1 (ppm)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7.3474
7.3038
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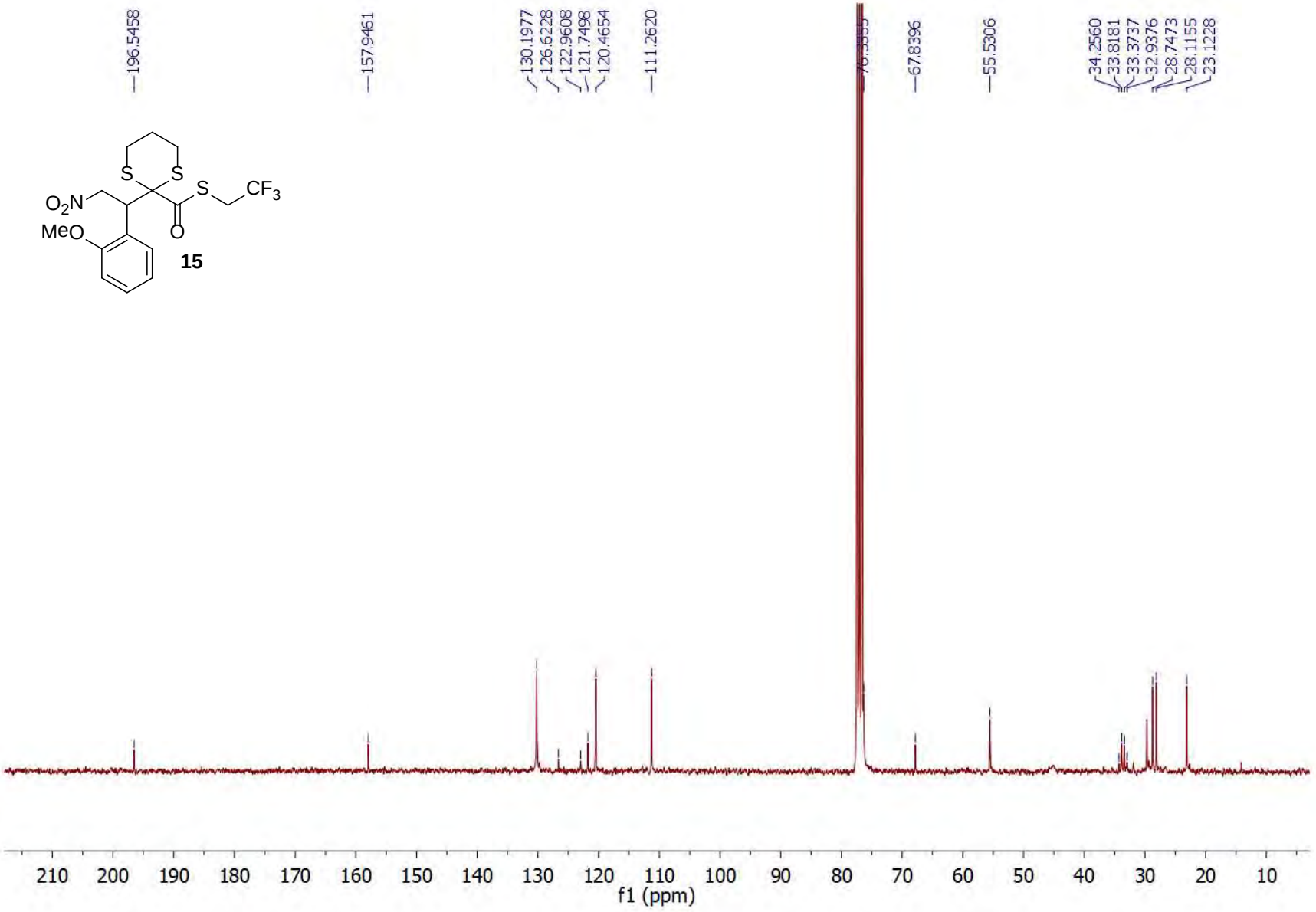
6.9672
6.9424
6.9173
6.8843
6.8569
5.2337
5.2206
5.1891
5.1760
5.1357
5.1015
5.0569
4.8005
3.8188
3.5419
3.5087
3.4755
3.4424
3.0063
2.9677
2.8201
2.7715
2.0517
2.0386
1.9085
S
S
S
CF3
O2N
MeO
O
15
1.22
1.04
1.03
0.96
1.12
1.02
0.93
3.33
2.08
4.66
1.29
1.24
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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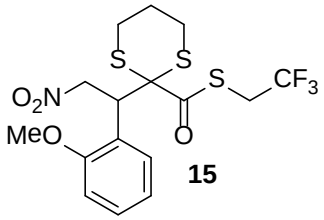
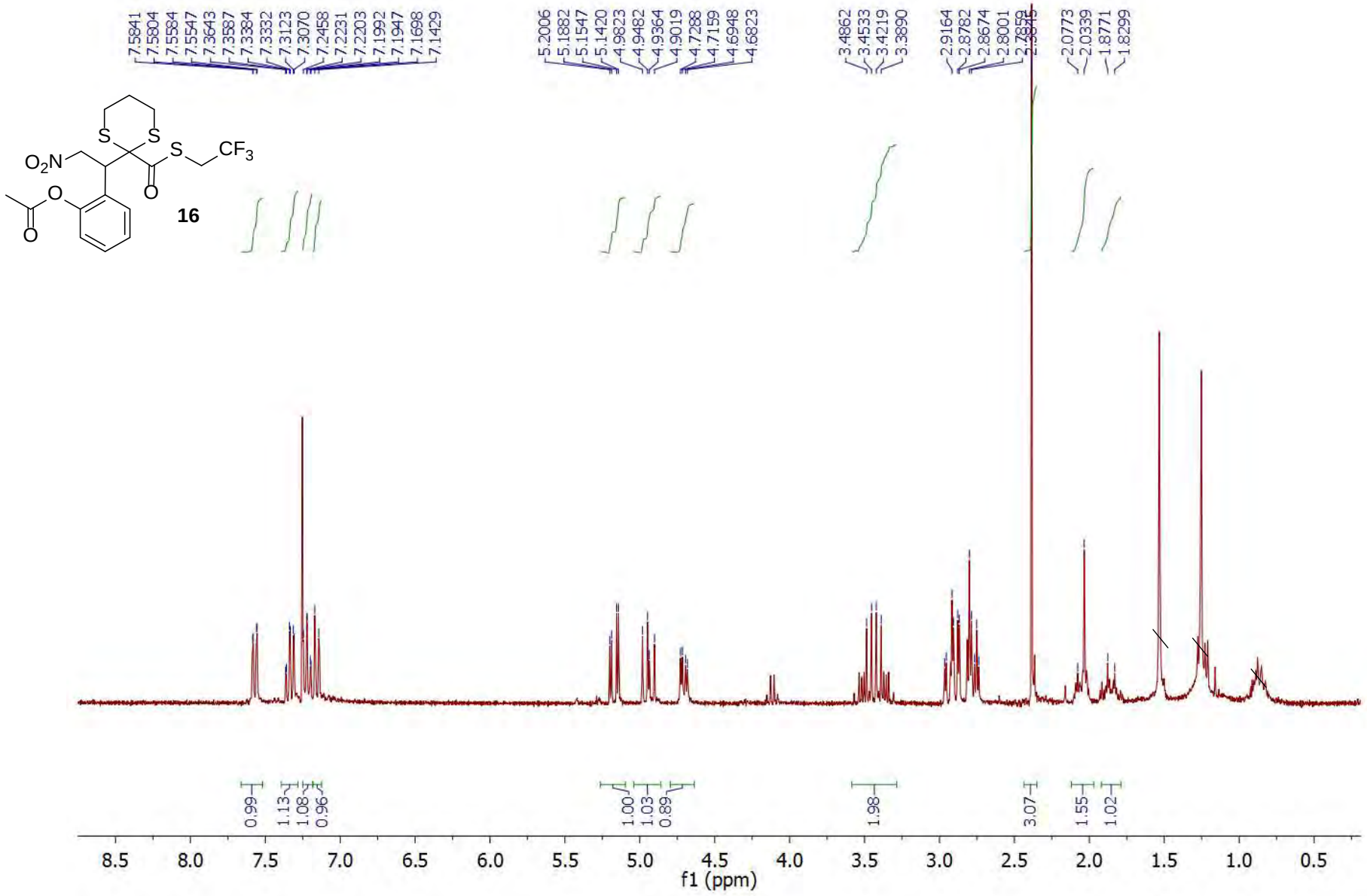
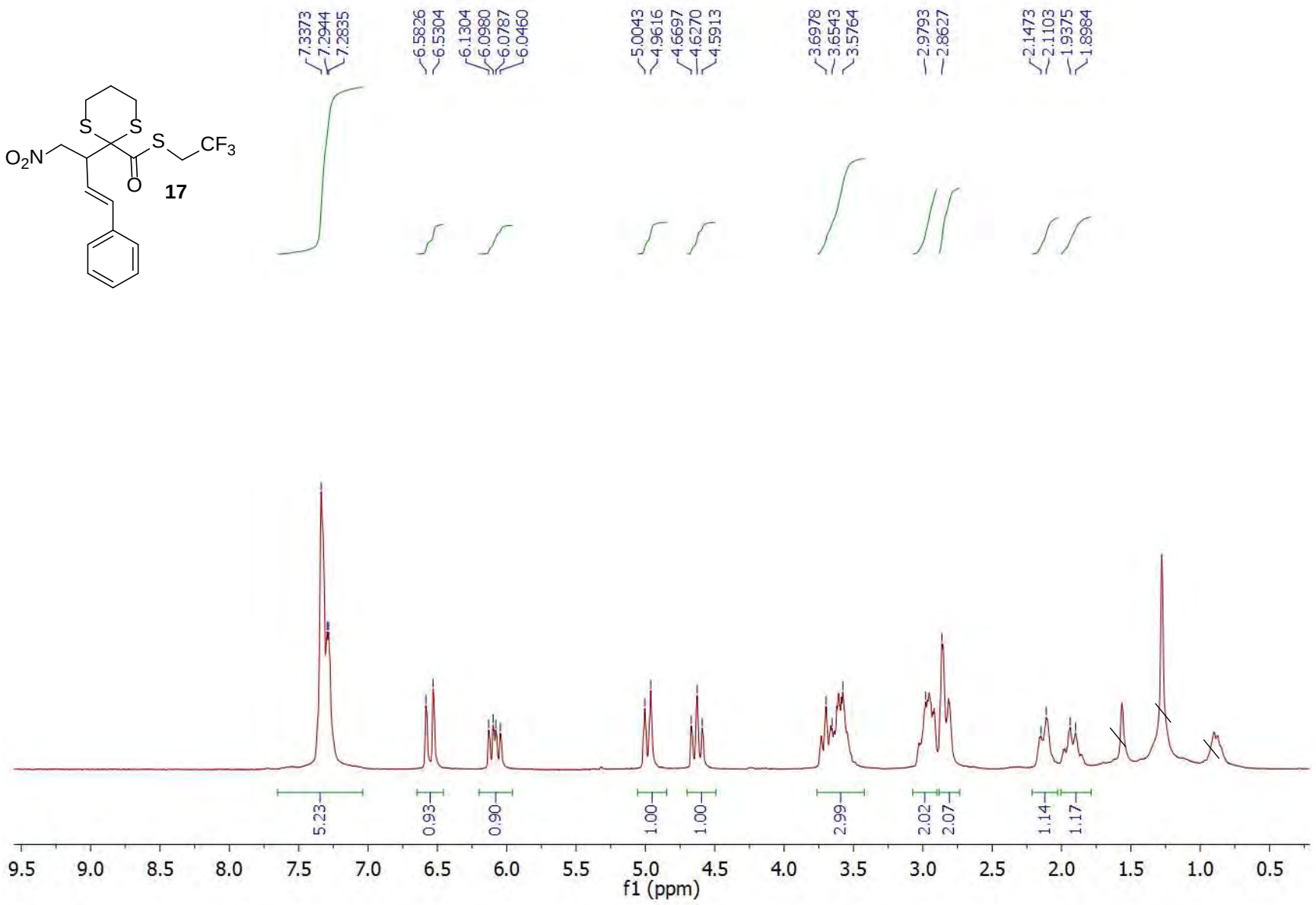
130.1977
126.6228
122.9608
121.7498
120.4654
111.2620
67.8396
55.5306
34.2560
33.8181
33.3737
32.9376
28.7473
28.1155
23.1228
S
S
S
CF3
O2N
MeO
O
15
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

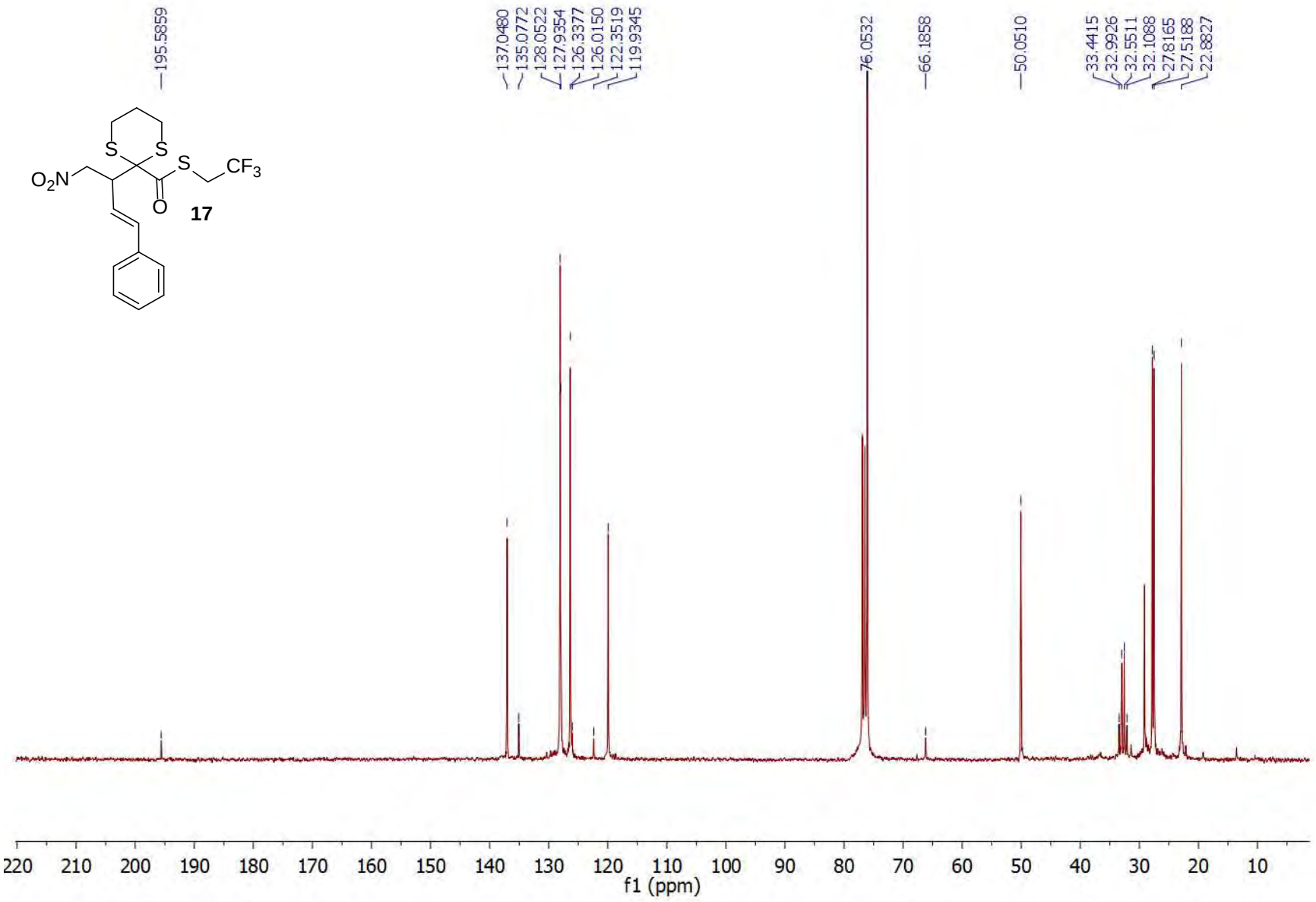

S
S
S
CF3
O2N
MeO
O

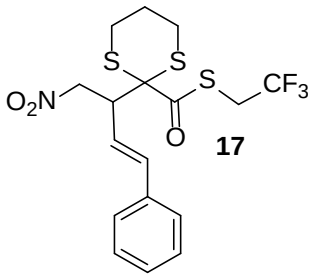
15

-66.0538
-66.0853
-66.1162
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
f1 (ppm)


7.5841
7.5804
7.5584
7.5547
7.3643
7.3587
7.3384
7.3332
7.3123
7.3070
7.2458
7.2231
7.2203
7.1992
7.1947
7.1698
7.1429
5.2006
5.1882
5.1547
5.1420
4.9823
4.9482
4.9364
4.9019
4.7288
4.7159
4.6948
4.6823
3.4862
3.4533
3.4219
3.3890
2.9164
2.8782
2.8674
2.8001
2.7859
2.7815
2.0773
2.0339
1.8771
1.8299
O2N
S
S
S
CF3
O
O
O
16
0.99
1.13
1.08
0.96
1.00
1.03
0.89
1.98
3.07
1.55
1.02
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

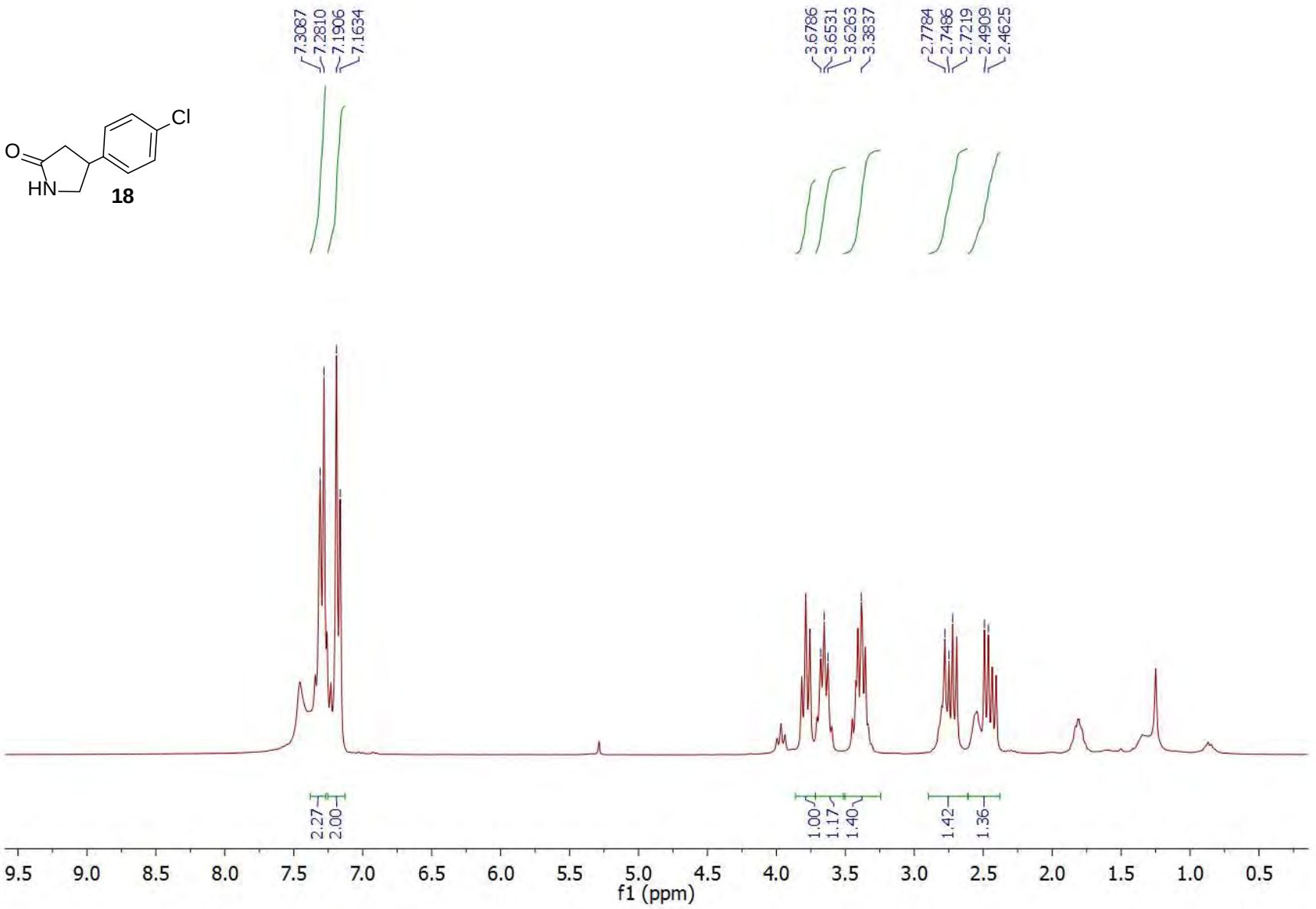

7.3373
7.2944
7.2835
6.5826
6.5304
6.1304
6.0980
6.0787
6.0460
5.0043
4.9616
4.6697
4.6270
4.5913
3.6978
3.6543
3.5764
2.9793
2.8627
2.1473
2.1103
1.9375
1.8984
O2N
S
S
S
CF3
O
17
5.23
0.93
0.90
1.00
1.00
2.99
2.02
2.07
1.14
1.17
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

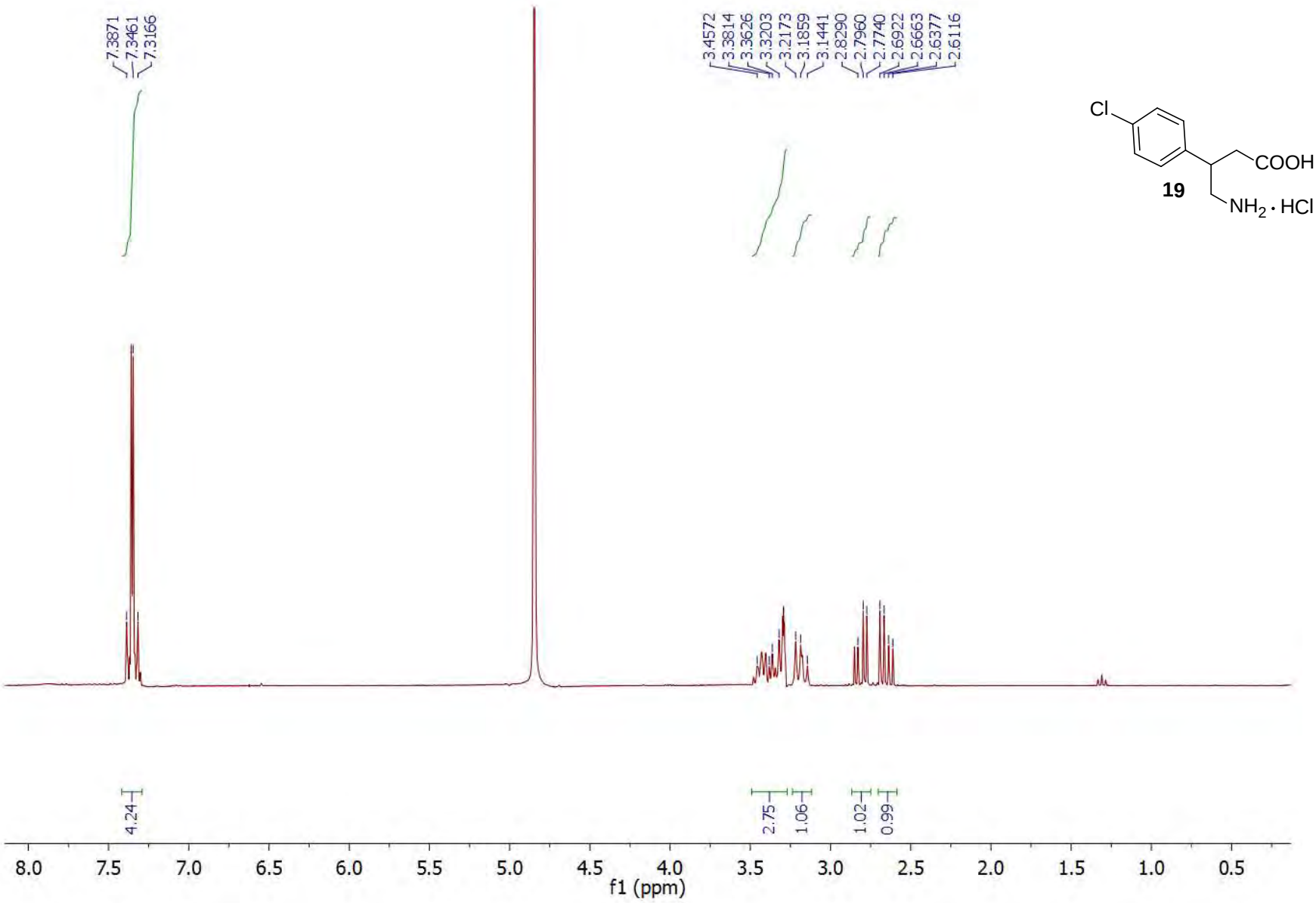

195.5859
137.0480
135.0772
128.0522
127.9354
126.3377
126.0150
122.3519
119.9345
76.0532
66.1858
50.0510
33.4415
32.9926
32.5511
32.1088
27.8165
27.5188
22.8827
S
S
S
CF_3
O_2N
O
17
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

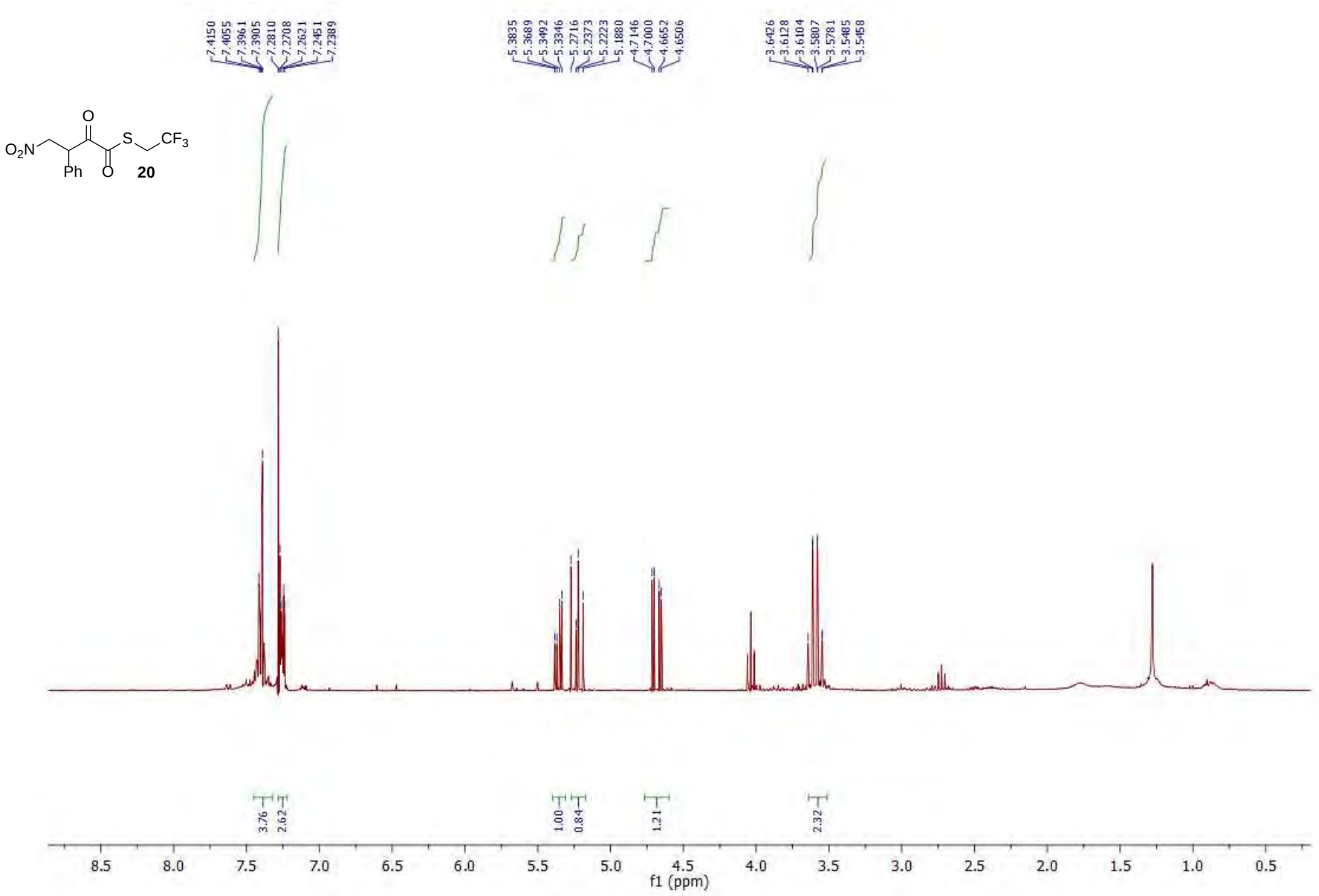

S
S
S
CF_3
O_2N
O

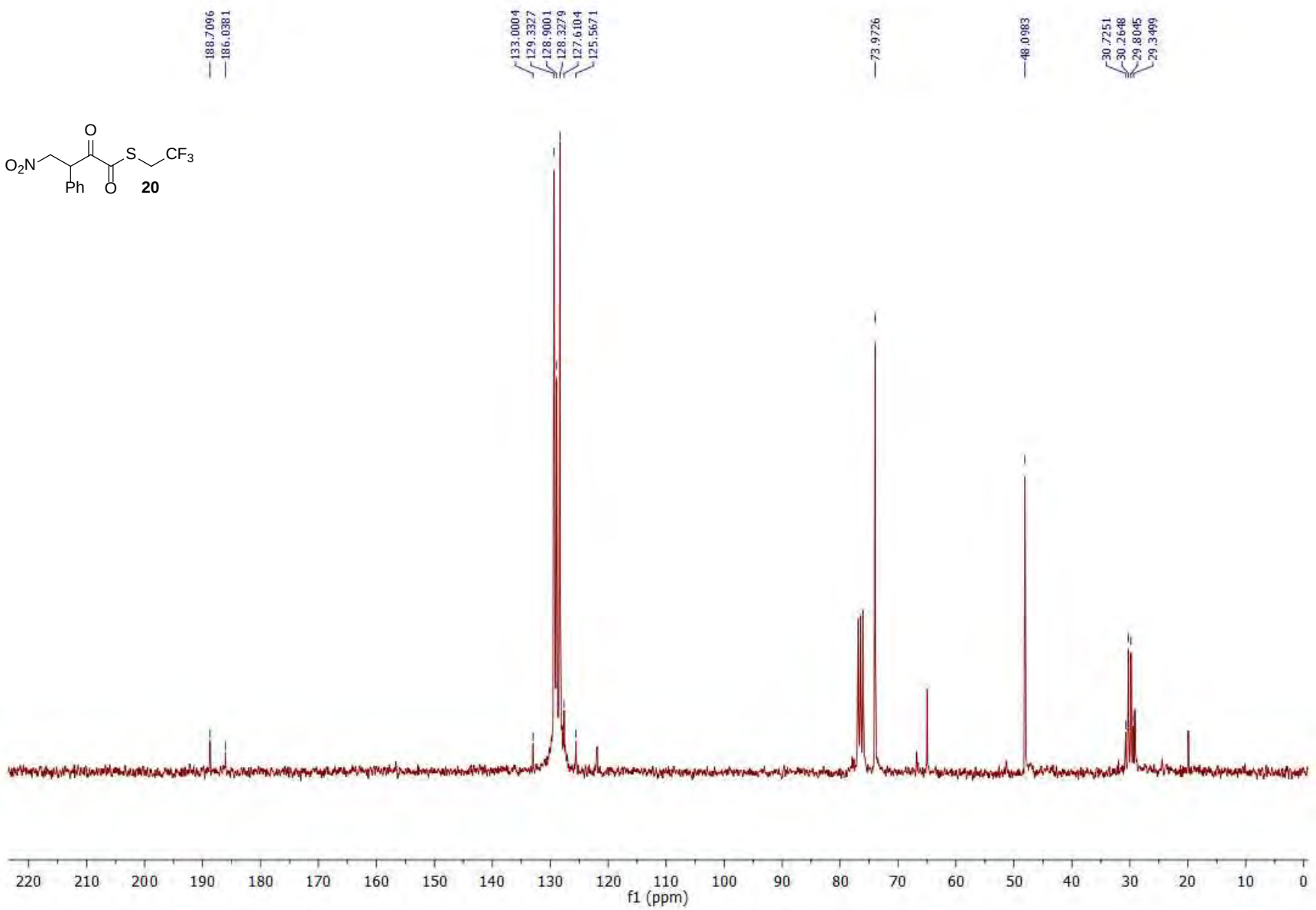
17

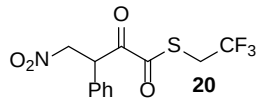
-66.3072
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
f1 (ppm)


O
HN
Cl
18
7.3087
7.2810
7.1906
7.1634
3.6786
3.6531
3.6263
3.3837
2.7784
2.7486
2.7219
2.4909
2.4625
2.27
2.00
1.00
1.17
1.40
1.42
1.36
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


7.3871
7.3461
7.3166
3.4572
3.3814
3.3626
3.3203
3.2173
3.1859
3.1441
2.8290
2.7960
2.7740
2.6922
2.6663
2.6377
2.6116
Cl
COOH
19
NH2 · HCl
4.24
2.75
1.06
1.02
0.99
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

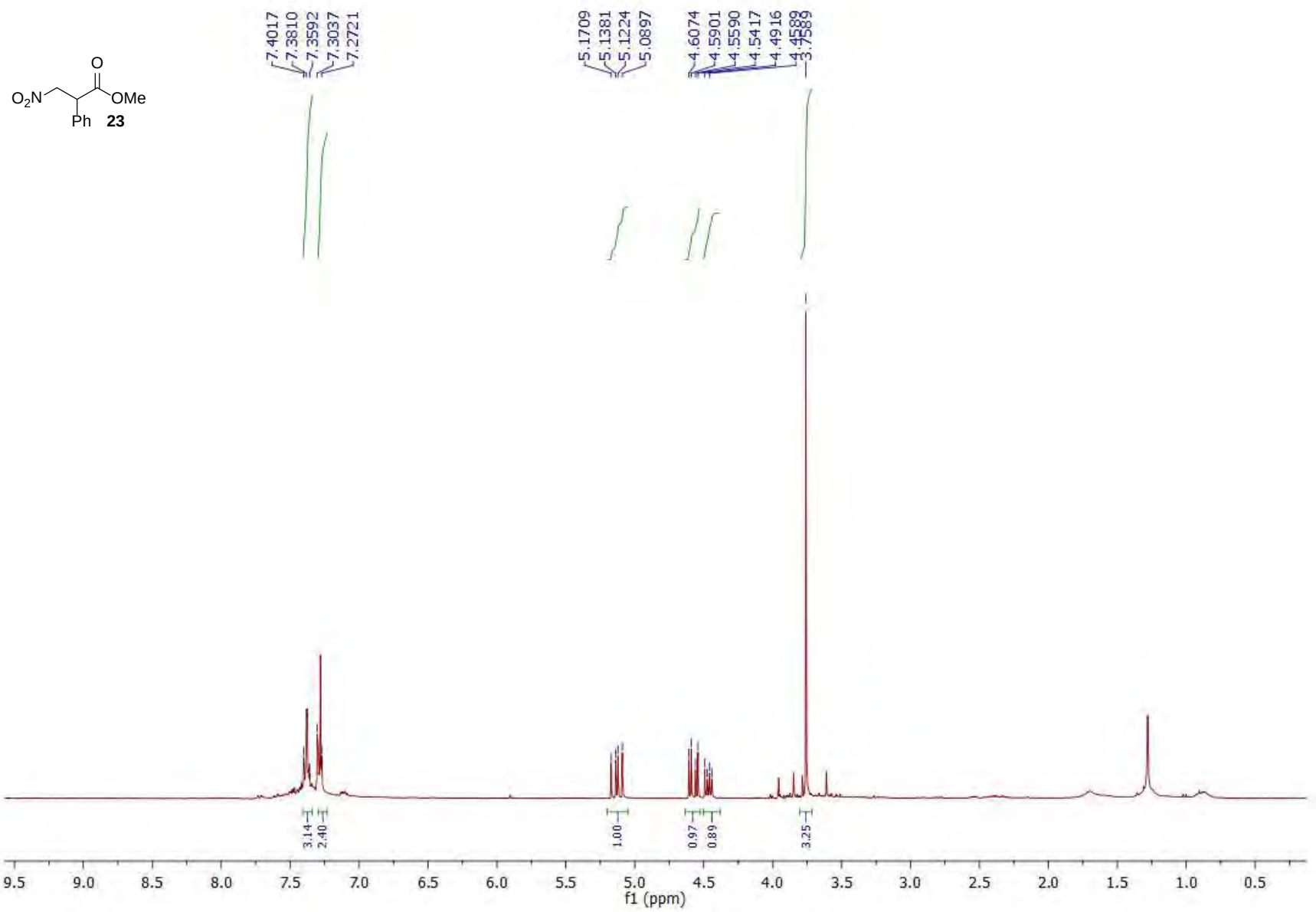

7.4150
7.4055
7.3961
7.3905
7.2810
7.2708
7.2621
7.2451
7.2389
5.3835
5.3689
5.3492
5.3346
5.2716
5.2373
5.2223
5.1880
4.7146
4.7000
4.6652
4.6506
3.6426
3.6128
3.6104
3.5807
3.5781
3.5485
3.5458
O
O2N
S
CF3
Ph
O
20
3.76
2.62
1.00
0.84
1.21
2.32
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


188.7096
186.0381
133.0004
129.3327
128.9001
128.3279
127.6104
125.5671
73.9726
48.0983
30.7251
30.2648
29.8045
29.3499
O
O2N
S
CF3
Ph
O
20
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
O_2N
S
CF_3
Ph
O

20

-66.42
-66.45
-66.49
-42
-44
-46
-48
-50
-52
-54
-56
-58
-60
-62
-64
-66
-68
-70
-72
-74
-76
-78
-80
-82
-84
-86
-88
-90
f1 (ppm)


O
O2N
OMe
Ph
23
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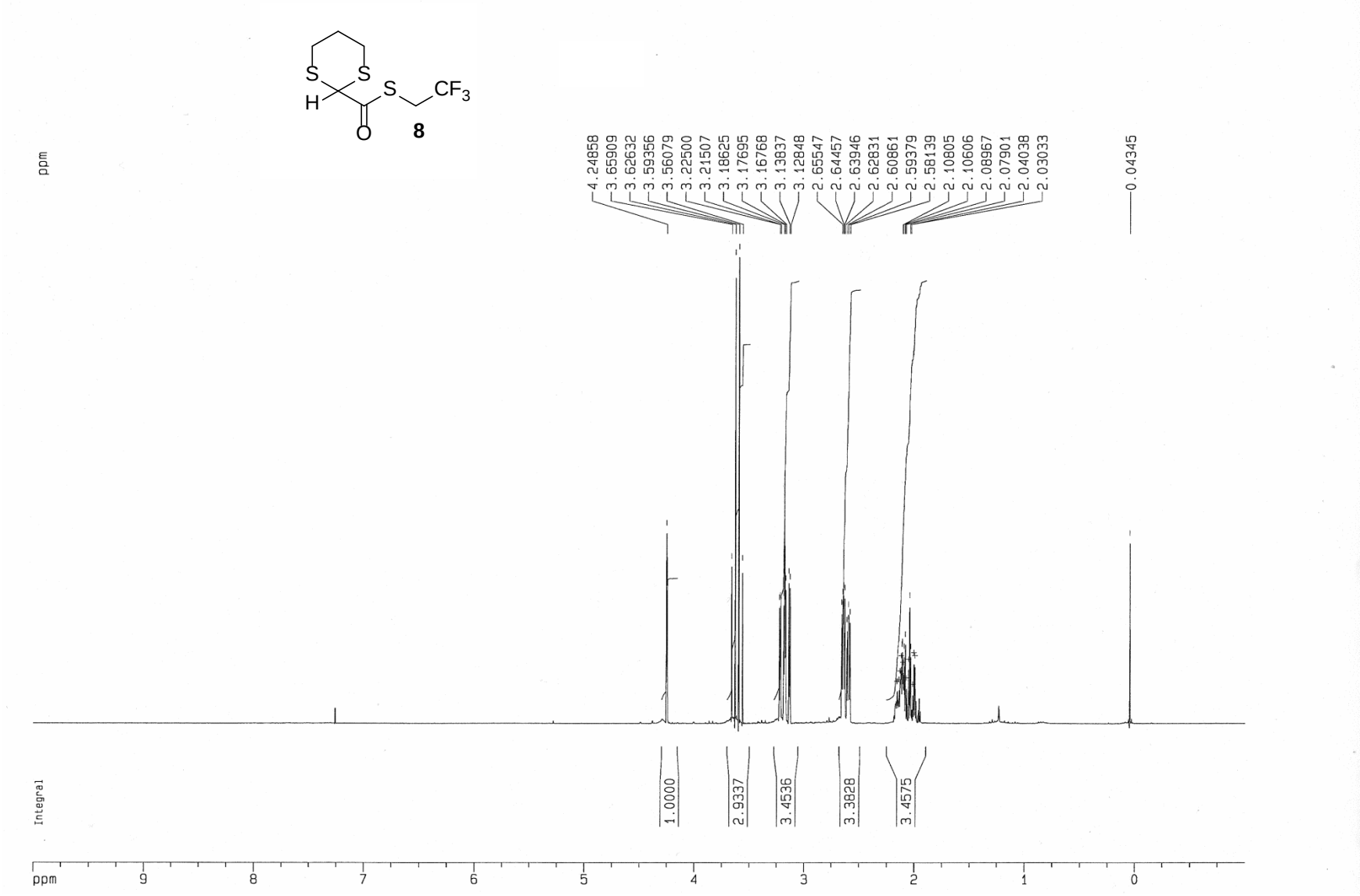
7.3592
7.3037
7.2721
5.1709
5.1381
5.1224
5.0897
4.6074
4.5901
4.5590
4.5417
4.4916
3.7589
3.14
2.40
1.00
0.97
0.89
3.25
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


S
S
H
O
S
CF3
8
ppm
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3.65909
3.62632
3.59356
3.56079
3.22500
3.21507
3.18625
3.17695
3.16768
3.13837
3.12848
2.65547
2.64457
2.63946
2.62831
2.60861
2.59379
2.58139
2.10805
2.10606
2.08967
2.07901
2.04038
2.03033
0.04345
Integral
1.0000
2.9337
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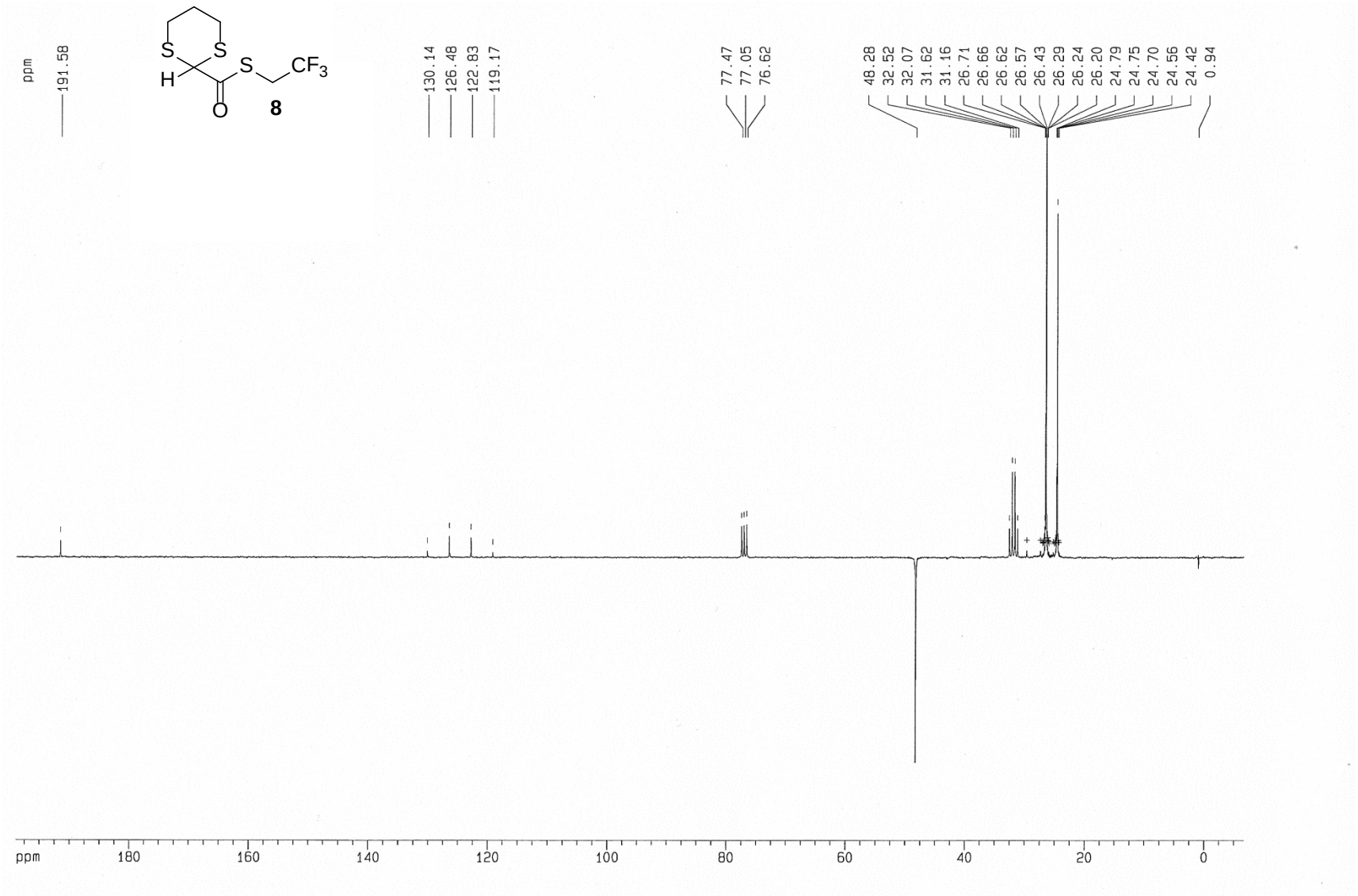
3.3828
3.4575
ppm
9
8
7
6
5
4
3
2
1
0


ppm
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126.48
122.83
119.17
77.47
77.05
76.62
48.28
32.52
32.07
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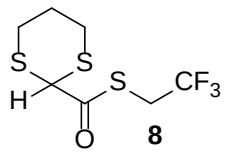
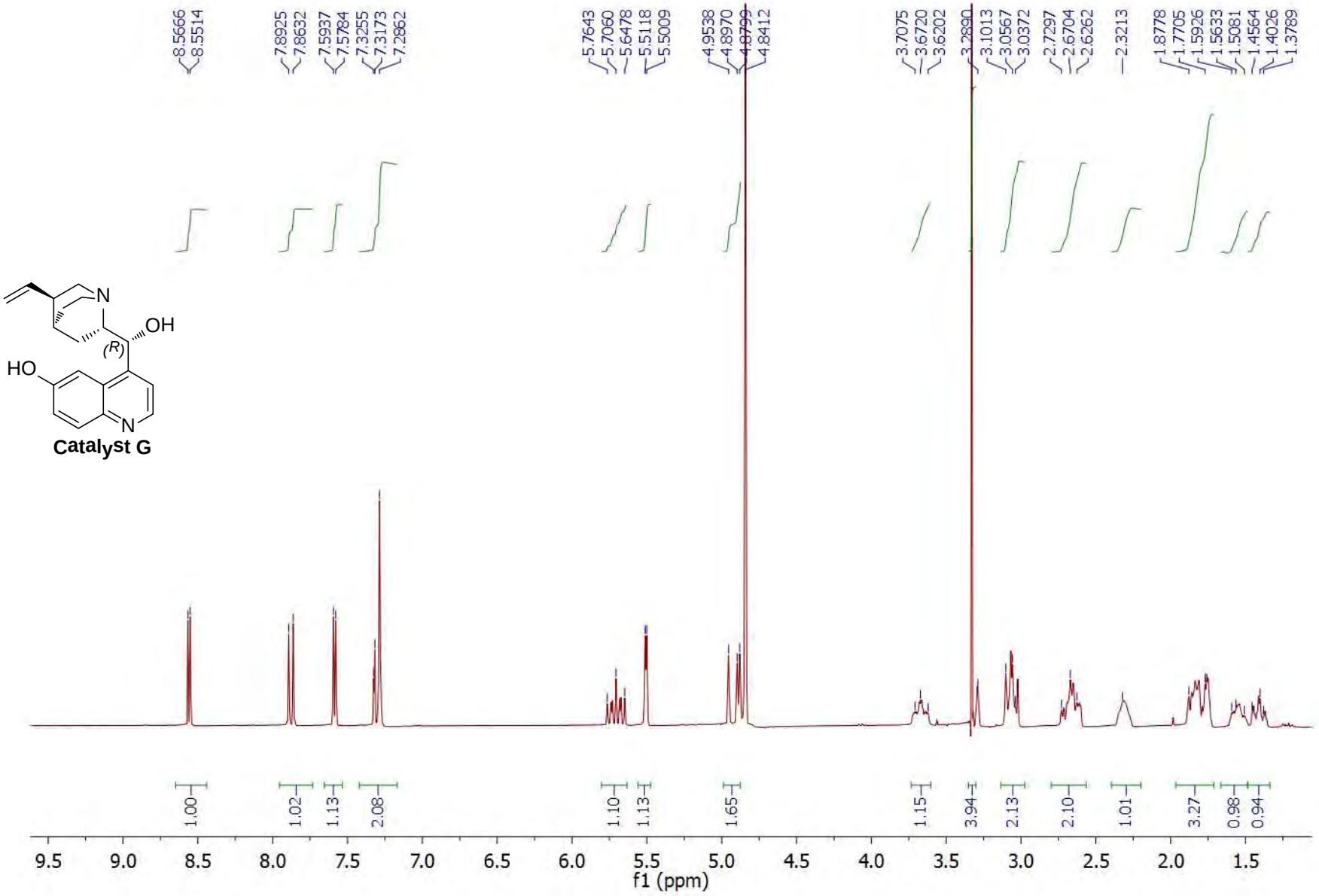
31.16
26.71
26.66
26.62
26.57
26.43
26.29
26.24
26.20
24.79
24.75
24.70
24.56
24.42
0.94
S
S
H
O
S
CF3
8
ppm
180
160
140
120
100
80
60
40
20
0


S
S
H
S
CF3
O

8

-66.6325
-30
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
f1 (ppm)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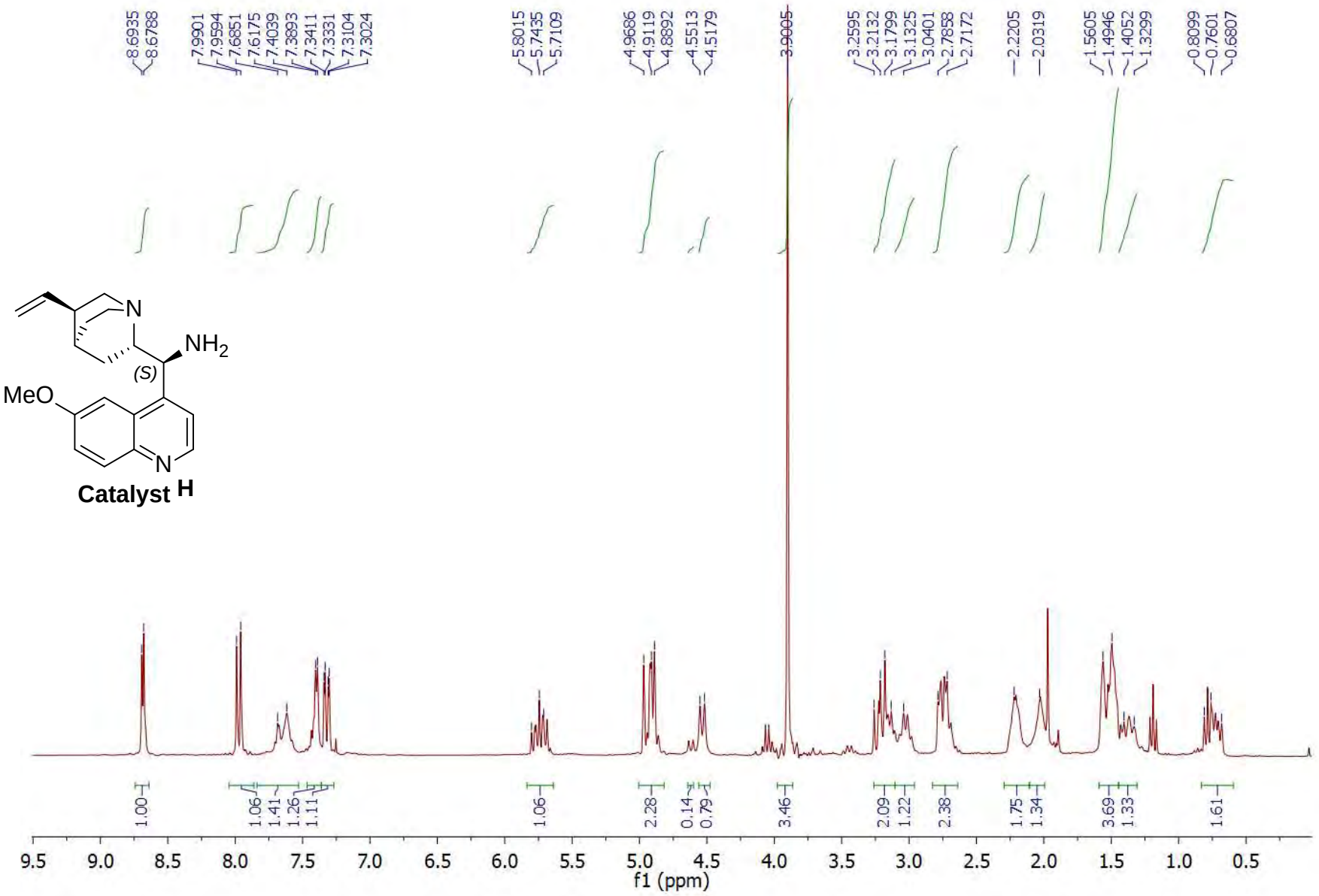
7.5937
7.5784
7.3255
7.3173
7.2862
5.7643
5.7060
5.6478
5.5118
5.5009
4.9538
4.8970
4.8799
4.8412
3.7075
3.6720
3.6202
3.2890
3.1013
3.0567
3.0372
2.7297
2.6704
2.6262
2.3213
1.8778
1.7705
1.5926
1.5633
1.5081
1.4564
1.4026
1.3789
N
OH
(R)
HO
N
Catalyst G
1.00
1.02
1.13
2.08
1.10
1.13
1.65
1.15
3.94
2.13
2.10
1.01
3.27
0.98
0.94
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)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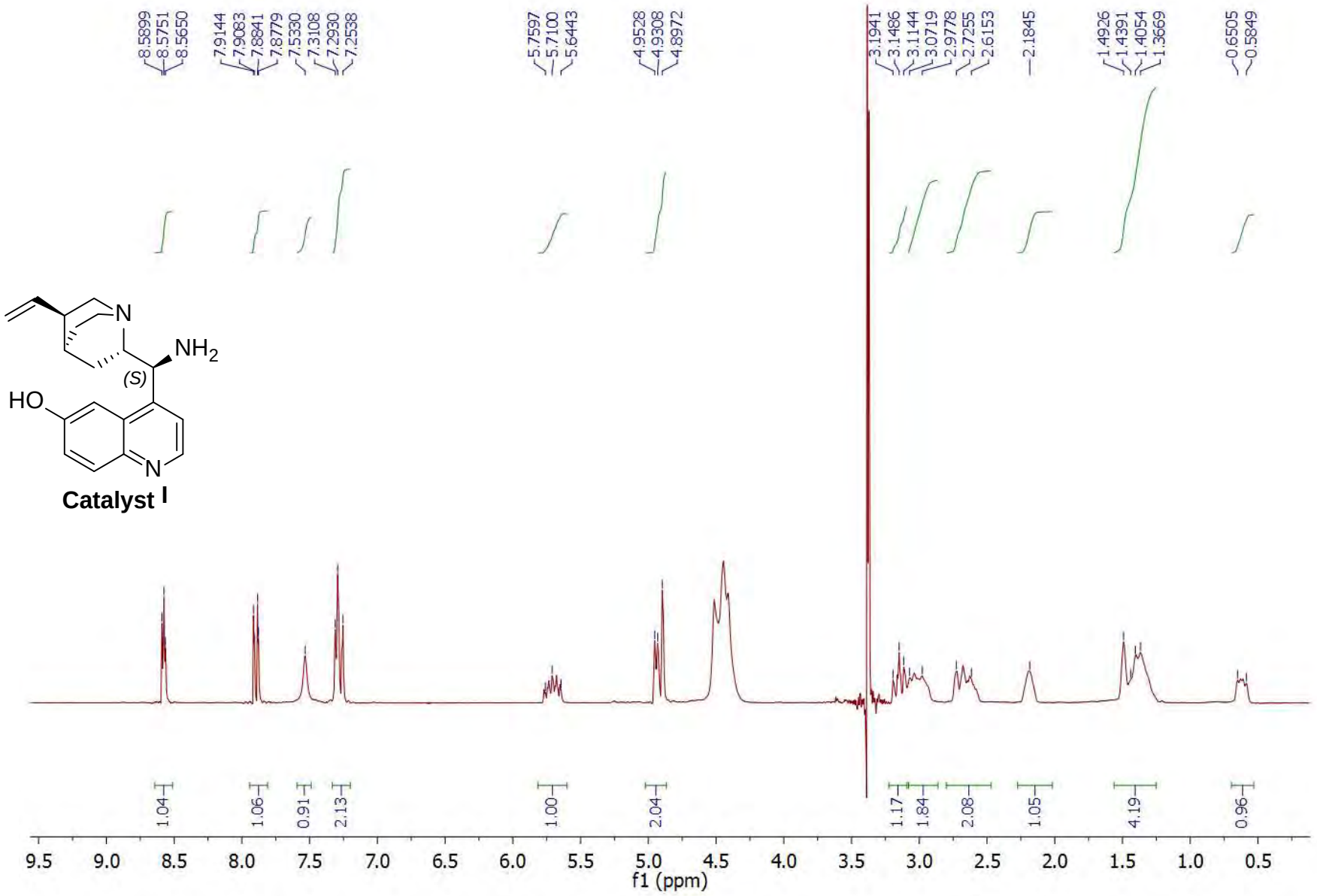
7.6851
7.6175
7.4039
7.3893
7.3411
7.3331
7.3104
7.3024
5.8015
5.7435
5.7109
4.9686
4.9119
4.8892
4.5513
4.5179
3.9005
3.2595
3.2132
3.1799
3.1325
3.0401
2.7858
2.7172
2.2205
2.0319
1.5605
1.4946
1.4052
1.3299
0.8099
0.7601
0.6807
N
NH2
(S)
MeO
N
Catalyst H
1.00
1.06
1.41
1.26
1.11
1.06
2.28
0.14
0.79
3.46
2.09
1.22
2.38
1.75
1.34
3.69
1.33
1.61
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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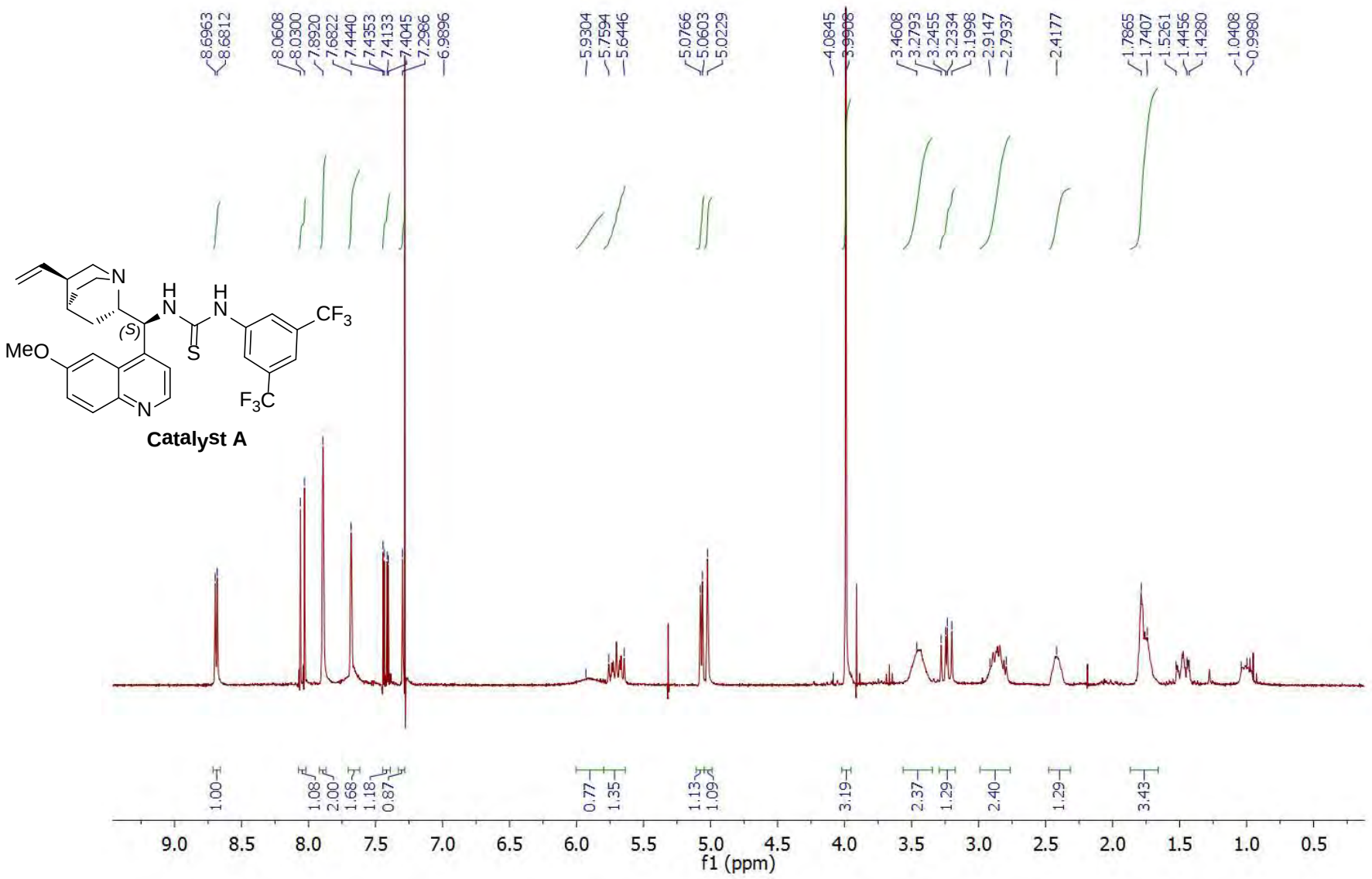
8.5751
8.5650
7.9144
7.9083
7.8841
7.8779
7.5330
7.3108
7.2930
7.2538
5.7597
5.7100
5.6443
4.9528
4.9308
4.8972
3.1941
3.1486
3.1144
3.0719
2.9778
2.7255
2.6153
2.1845
1.4926
1.4391
1.4054
1.3669
0.6505
0.5849
N
NH2
(S)
HO
N
1.04
1.06
0.91
2.13
1.00
2.04
1.17
1.84
2.08
1.05
4.19
0.96
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

Catalyst I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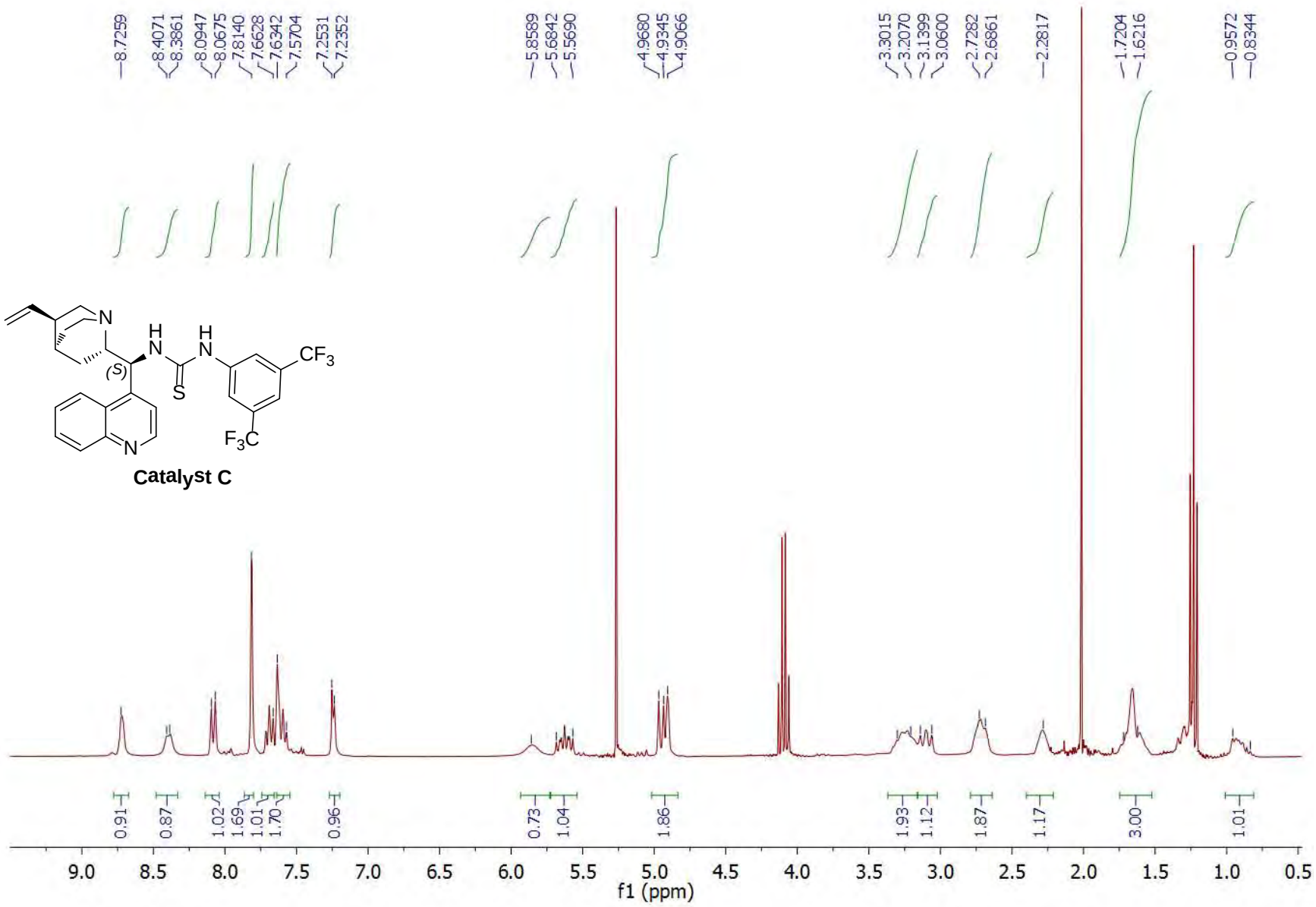
8.0608
8.0300
7.8920
7.6822
7.4440
7.4353
7.4133
7.4045
7.2986
6.9896
5.9304
5.7594
5.6446
5.0766
5.0603
5.0229
4.0845
3.9908
3.4608
3.2793
3.2455
3.2334
3.1998
2.9147
2.7937
2.4177
1.7865
1.7407
1.5261
1.4456
1.4280
1.0408
0.9980
1.00
1.08
2.00
1.68
1.18
0.87
0.77
1.35
1.13
1.09
3.19
2.37
1.29
2.40
1.29
3.43
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
MeO
N
H
N
(S)
H
N
S
CF3
F3C
N

Catalyst A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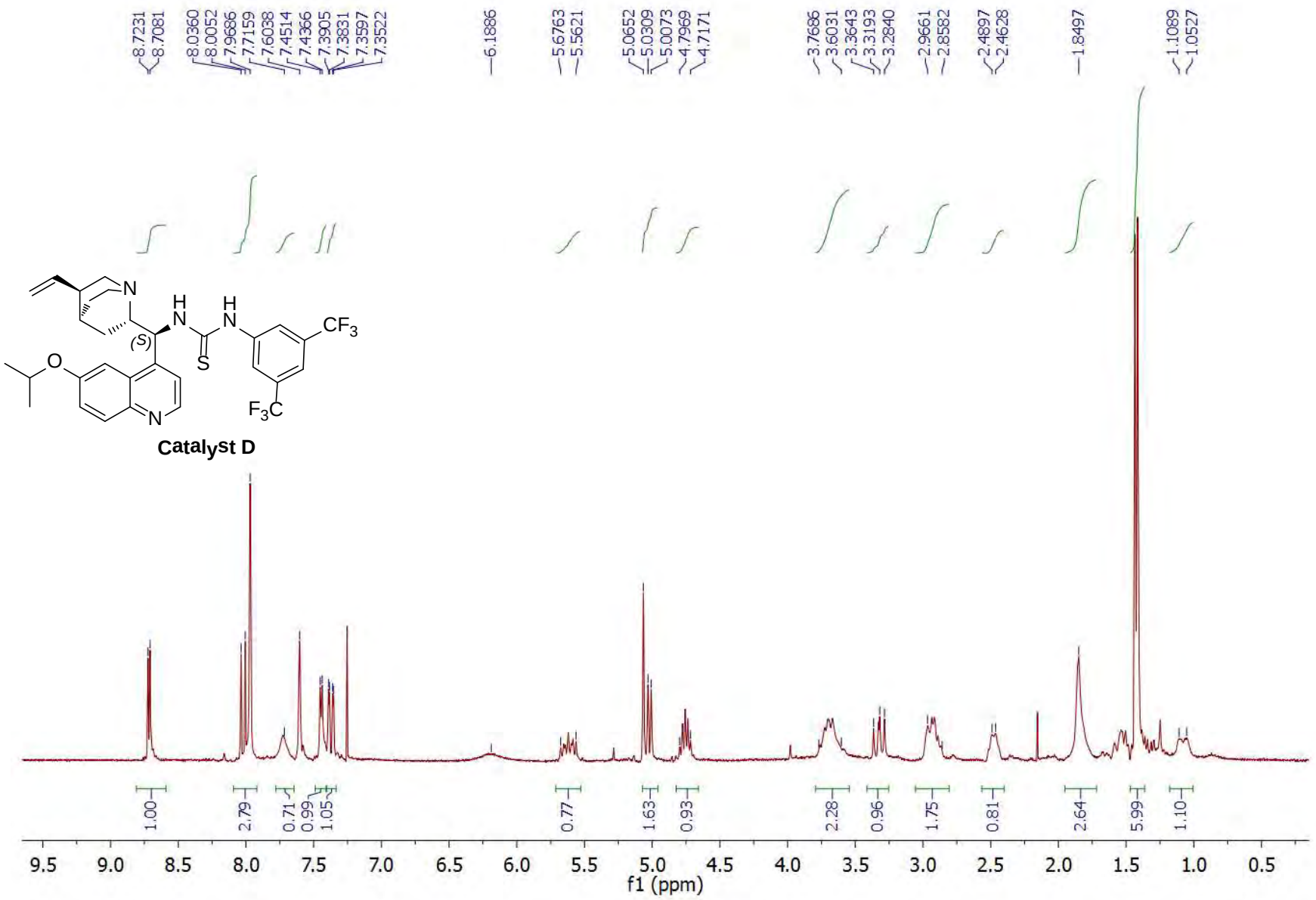
8.4071
8.3861
8.0947
8.0675
7.8140
7.6628
7.6342
7.5704
7.2531
7.2352
5.8589
5.6842
5.5690
4.9680
4.9345
4.9066
3.3015
3.2070
3.1399
3.0600
2.7282
2.6861
2.2817
1.7204
1.6216
0.9572
0.8344
0.91
0.87
1.02
1.69
1.01
1.70
0.96
0.73
1.04
1.86
1.93
1.12
1.87
1.17
3.00
1.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

Catalyst C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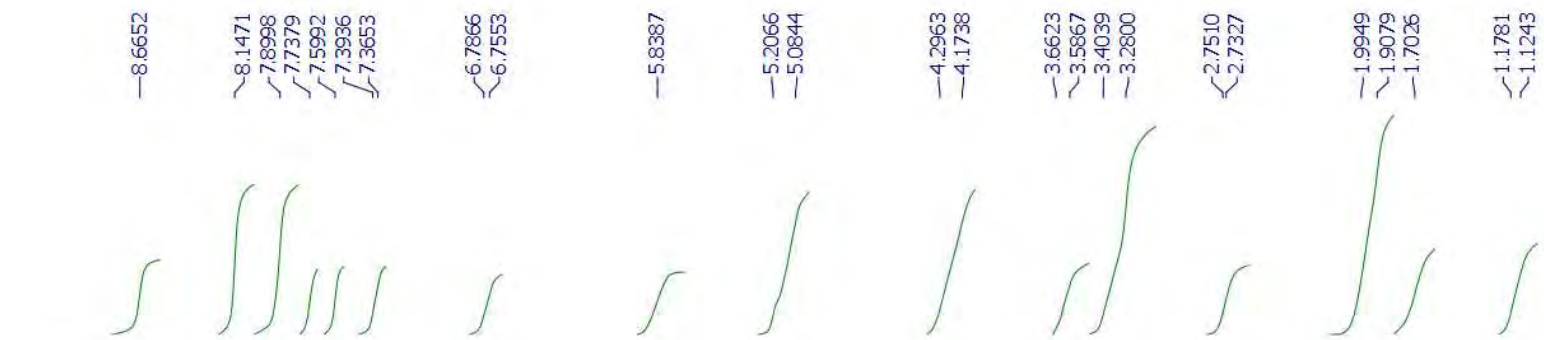
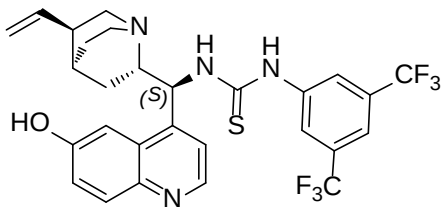
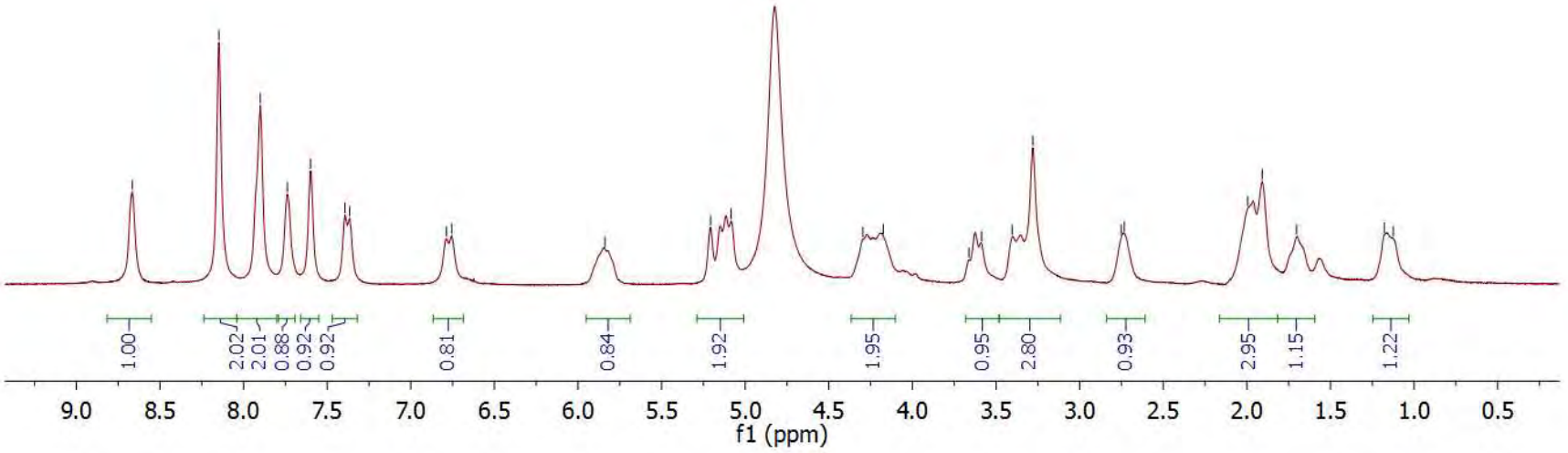
8.7081
8.0360
8.0052
7.9686
7.7159
7.6038
7.4514
7.4366
7.3905
7.3831
7.3597
7.3522
6.1886
5.6763
5.5621
5.0652
5.0309
5.0073
4.7969
4.7171
3.7686
3.6031
3.3643
3.3193
3.2840
2.9661
2.8582
2.4897
2.4628
1.8497
1.1089
1.0527
1.00
2.79
0.71
0.99
1.05
0.77
1.63
0.93
2.28
0.96
1.75
0.81
2.64
5.99
1.10
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

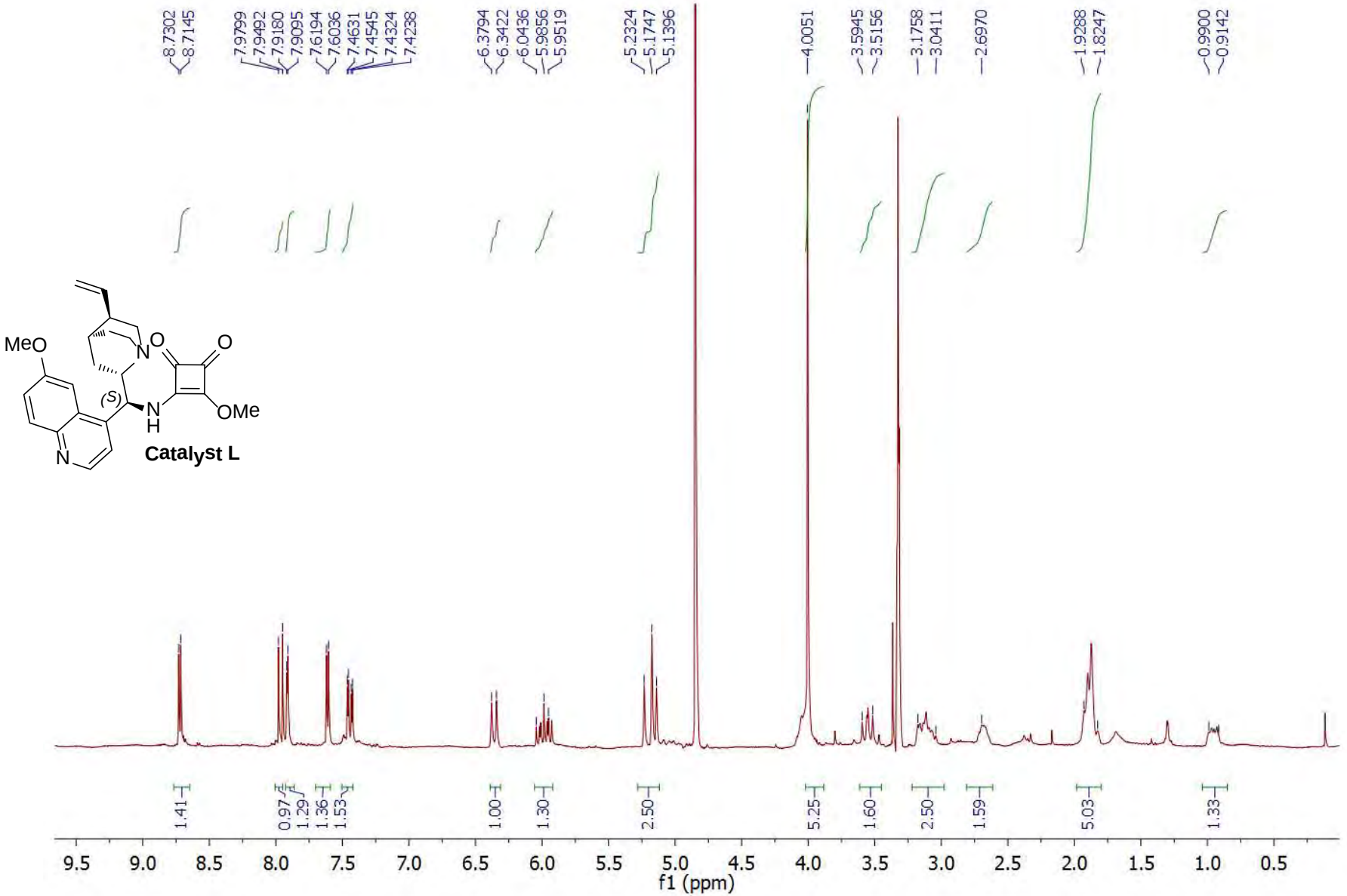
Catalyst D


8.6652
8.1471
7.8998
7.7379
7.5992
7.3936
7.3653
6.7866
6.7553
5.8387
5.2066
5.0844
4.2963
4.1738
3.6623
3.5867
3.4039
3.2800
2.7510
2.7327
1.9949
1.9079
1.7026
1.1781
1.1243

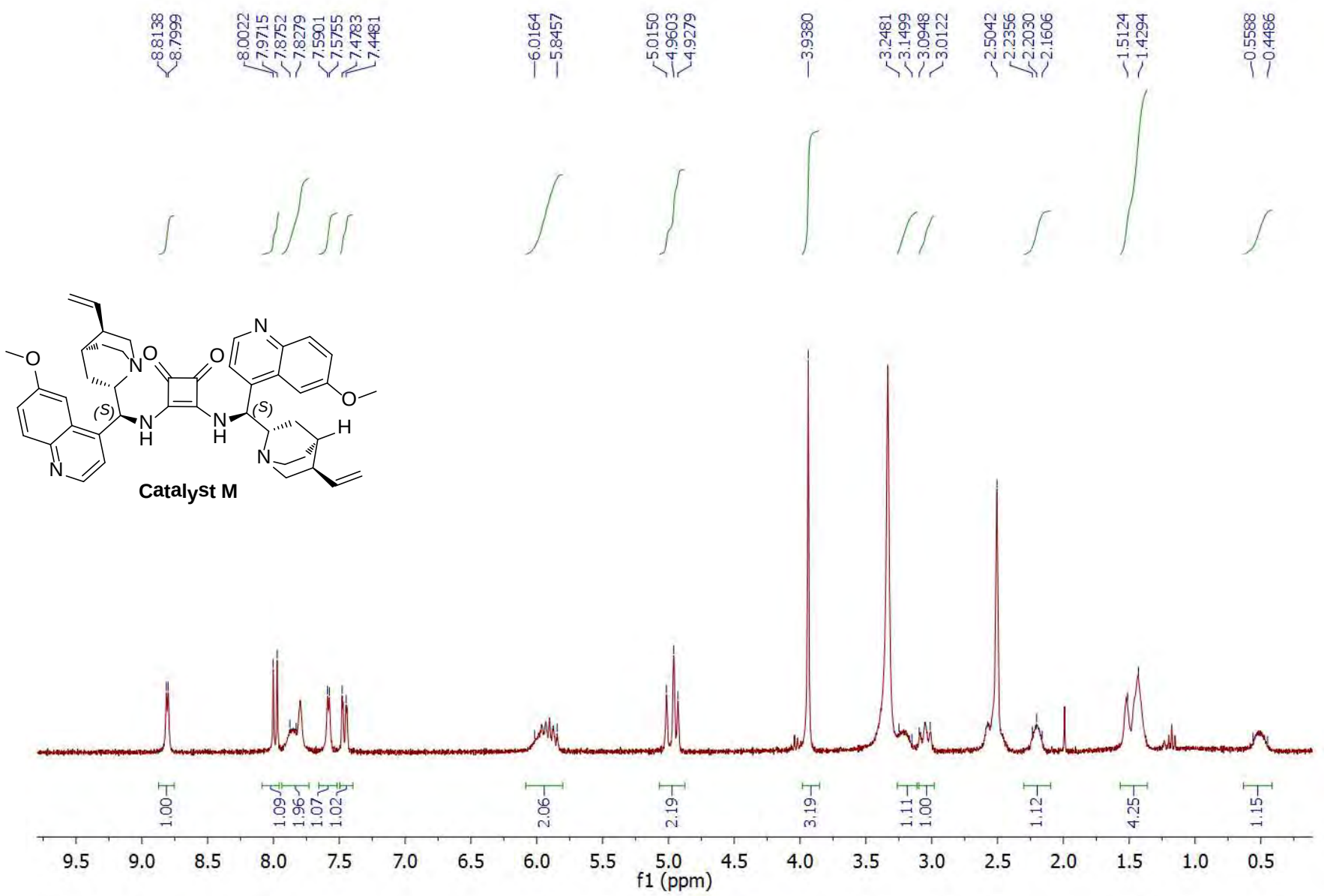

N
H
N
H
N
(S)
S
CF3
HO
F3C
N

Catalyst E

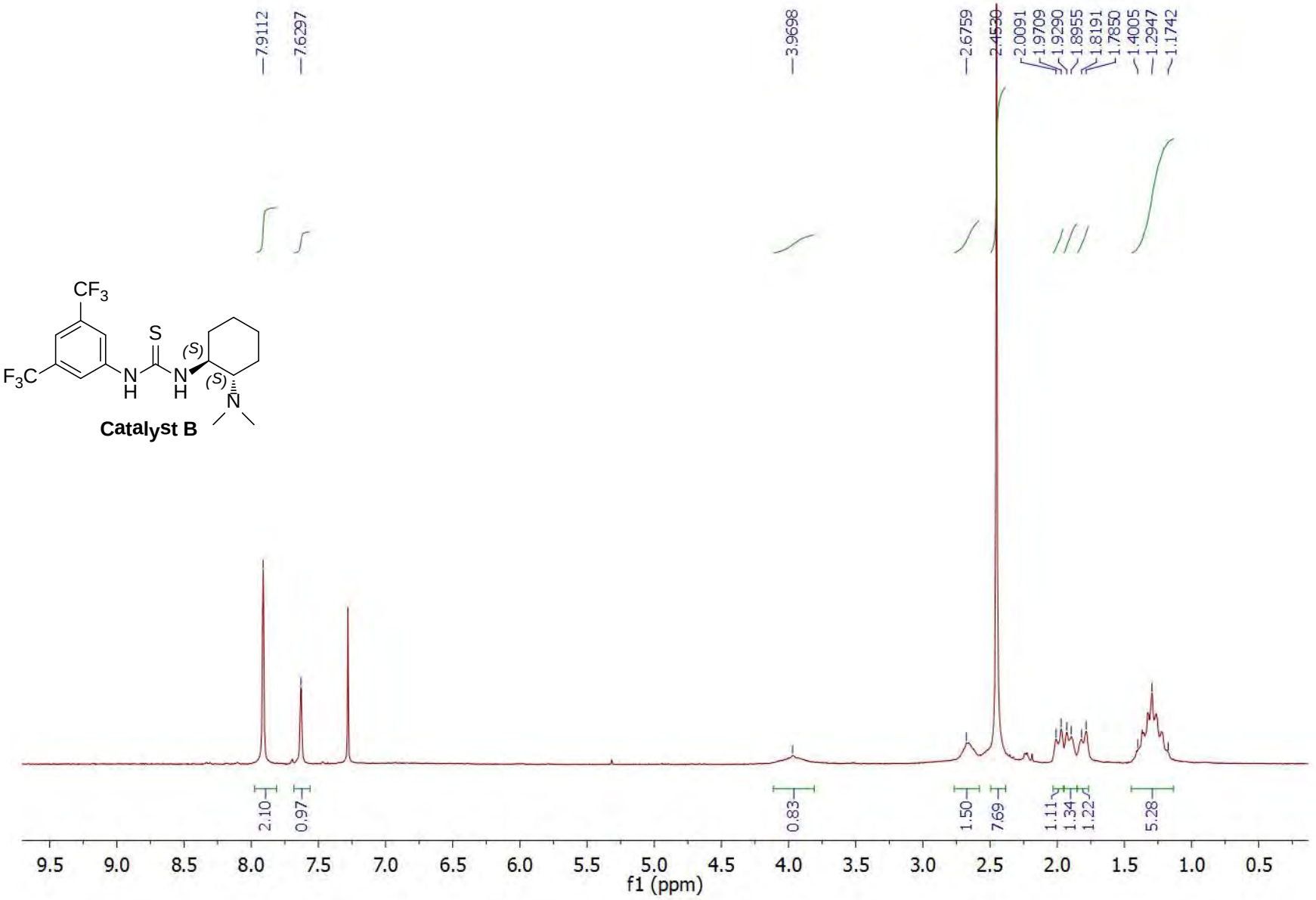

1.00
2.02
2.01
0.88
0.92
0.92
0.81
0.84
1.92
1.95
0.95
2.80
0.93
2.95
1.15
1.22
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

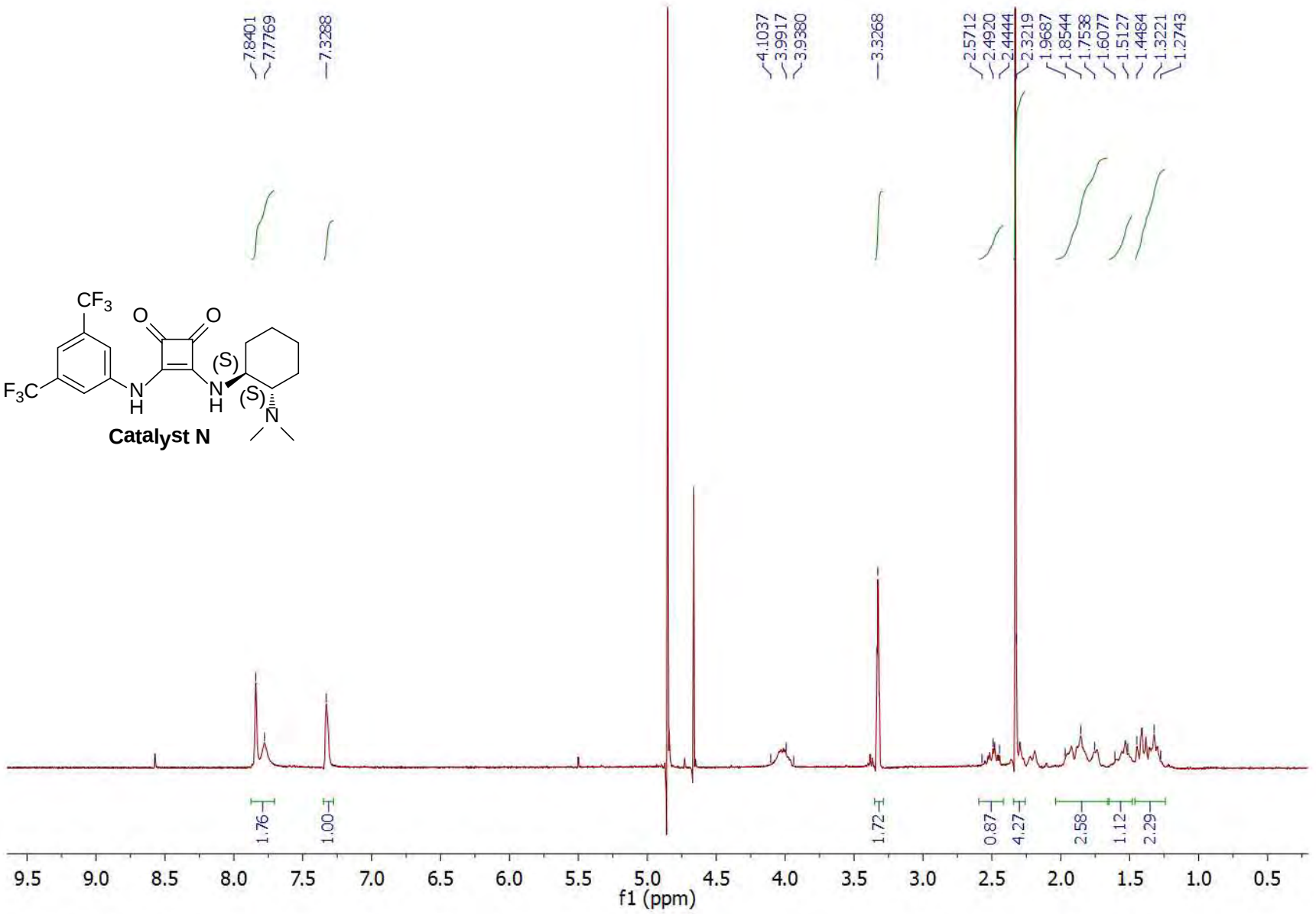

8.7302
8.7145
7.9799
7.9492
7.9180
7.9095
7.6194
7.6036
7.4631
7.4545
7.4324
7.4238
6.3794
6.3422
6.0436
5.9856
5.9519
5.2324
5.1747
5.1396
4.0051
3.5945
3.5156
3.1758
3.0411
2.6970
1.9288
1.8247
0.9900
0.9142
MeO
N
O
O
(S)
N
H
OMe
N
1.41
0.97
1.29
1.36
1.53
1.00
1.30
2.50
5.25
1.60
2.50
1.59
5.03
1.33
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

Catalyst L

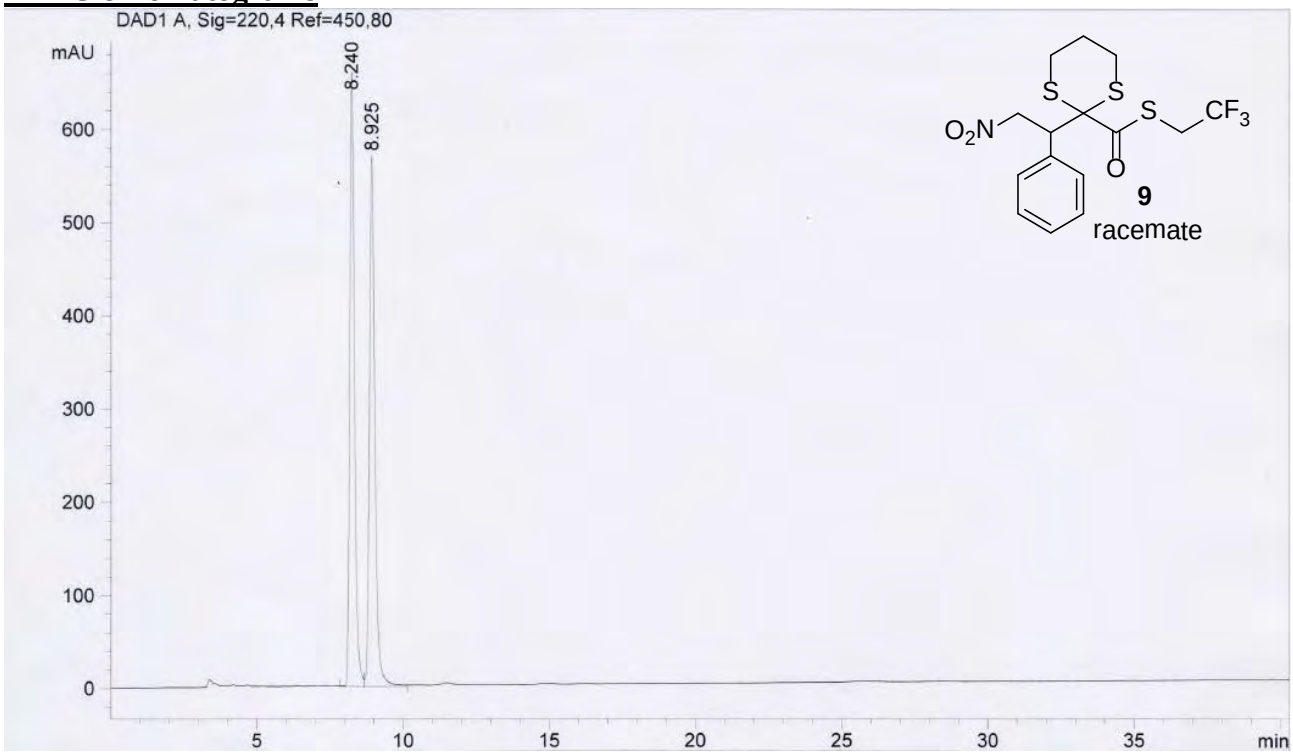

8.8138
8.7999
8.0022
7.9715
7.8752
7.8279
7.5901
7.5755
7.4783
7.4481
6.0164
5.8457
5.0150
4.9603
4.9279
3.9380
3.2481
3.1499
3.0948
3.0122
2.5042
2.2356
2.2030
2.1606
1.5124
1.4294
0.5588
0.4486
1.00
1.09
1.96
1.07
1.02
2.06
2.19
3.19
1.11
1.00
1.12
4.25
1.15
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

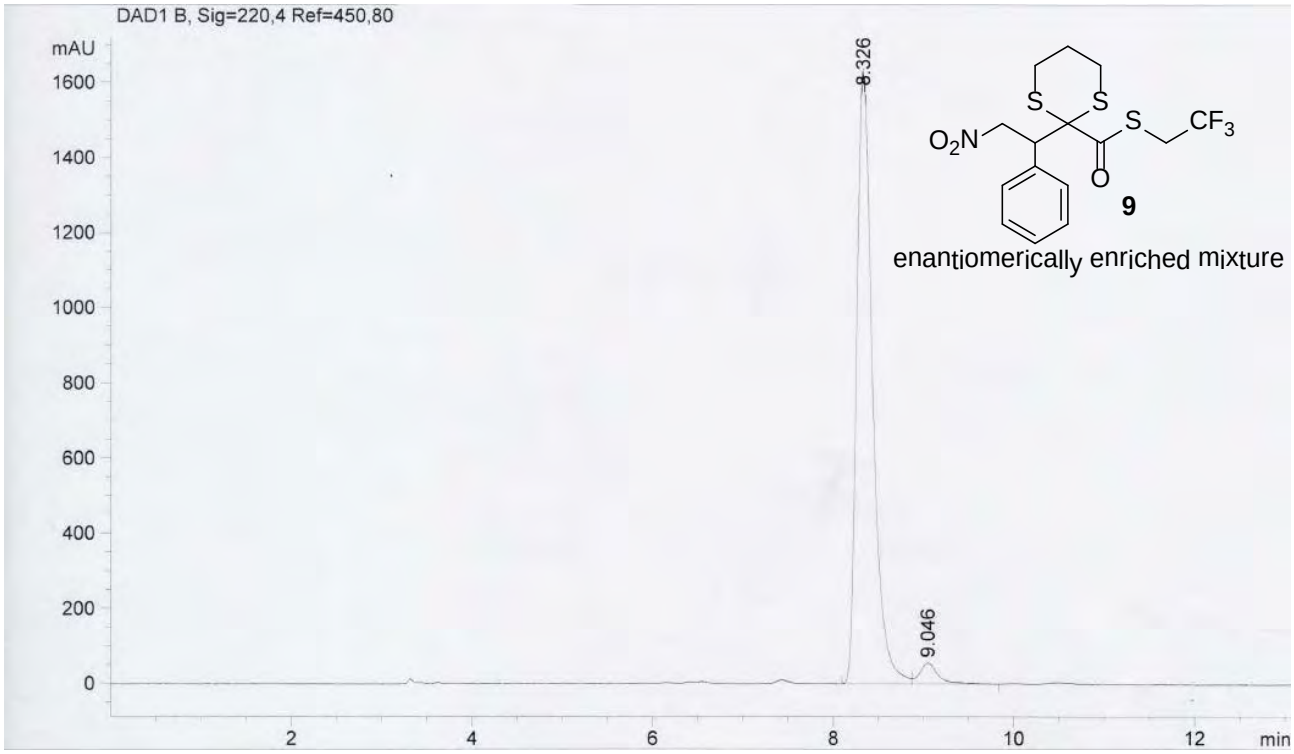
Catalyst M

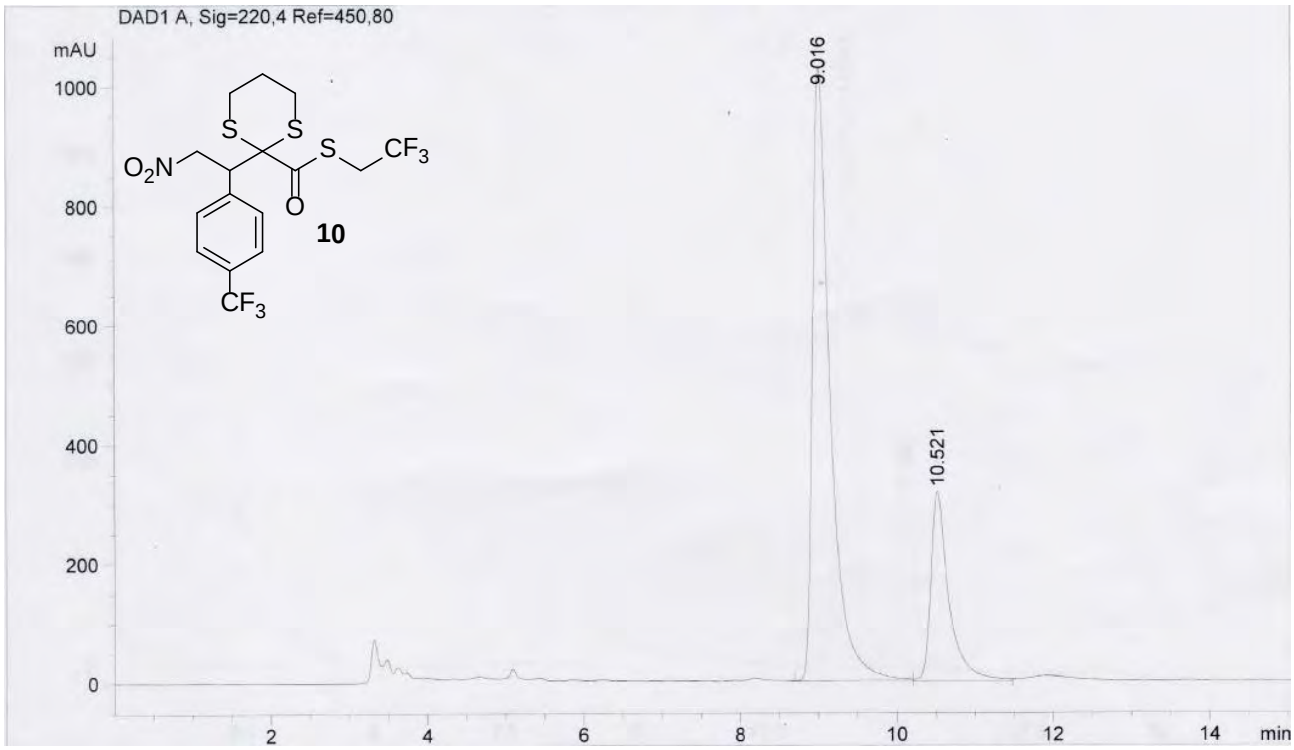

7.9112
7.6297
3.9698
2.6759
2.4530
2.0091
1.9709
1.9290
1.8955
1.8191
1.7850
1.4005
1.2947
1.1742
CF3
F3C
S
N
H
N
H
(S)
(S)
N
Catalyst B
2.10
0.97
0.83
1.50
7.69
1.11
1.34
1.22
5.28
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

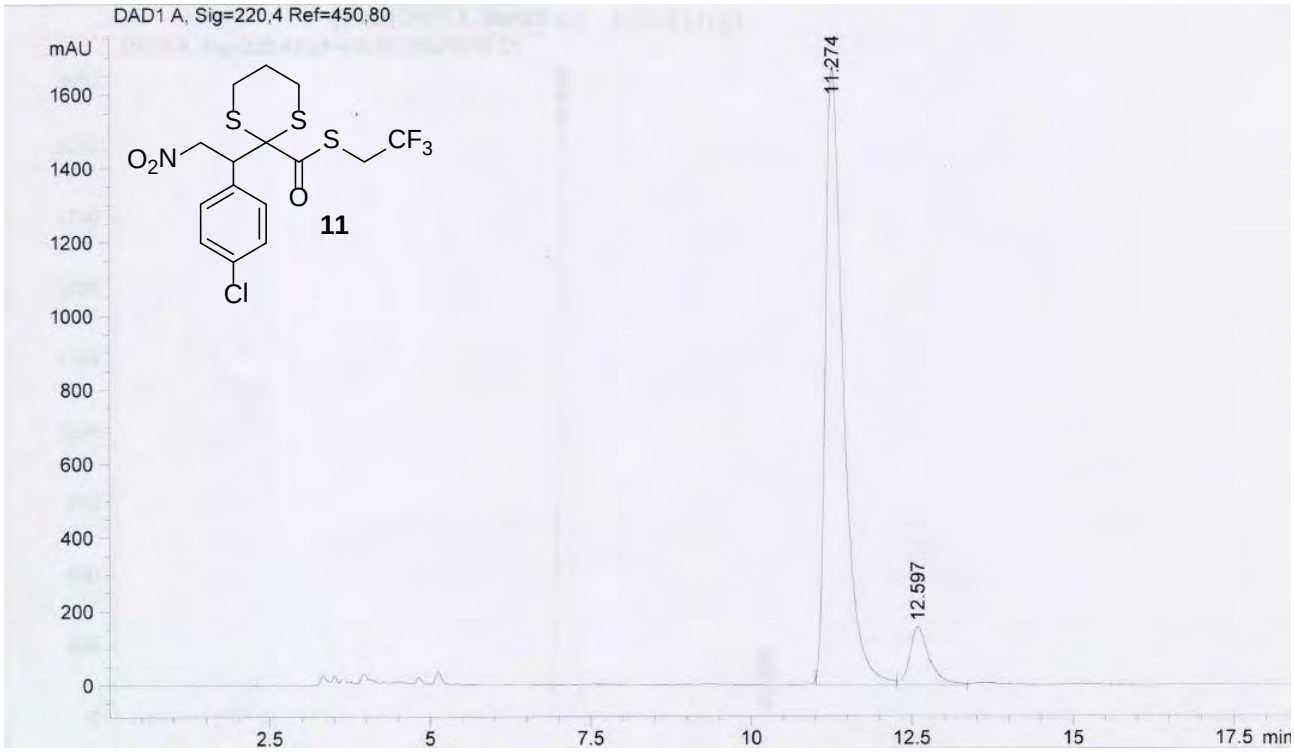

7.8401
7.7769
7.3288
4.1037
3.9917
3.9380
3.3268
2.5712
2.4920
2.4444
2.3219
1.9687
1.8544
1.7538
1.6077
1.5127
1.4484
1.3221
1.2743
CF3
F3C
O
O
N
H
(S)
N
H
(S)
N
Catalyst N
1.76
1.00
1.72
0.87
4.27
2.58
1.12
2.29
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

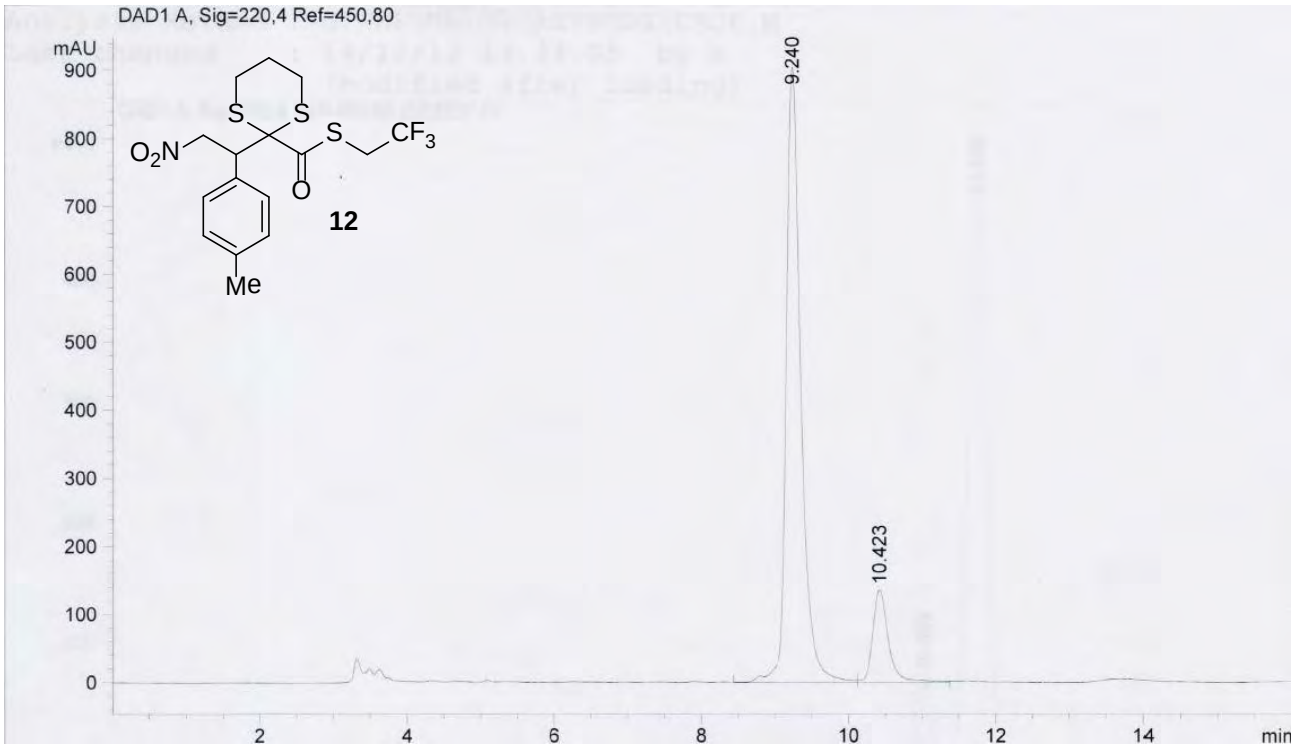
HPLC chromatograms

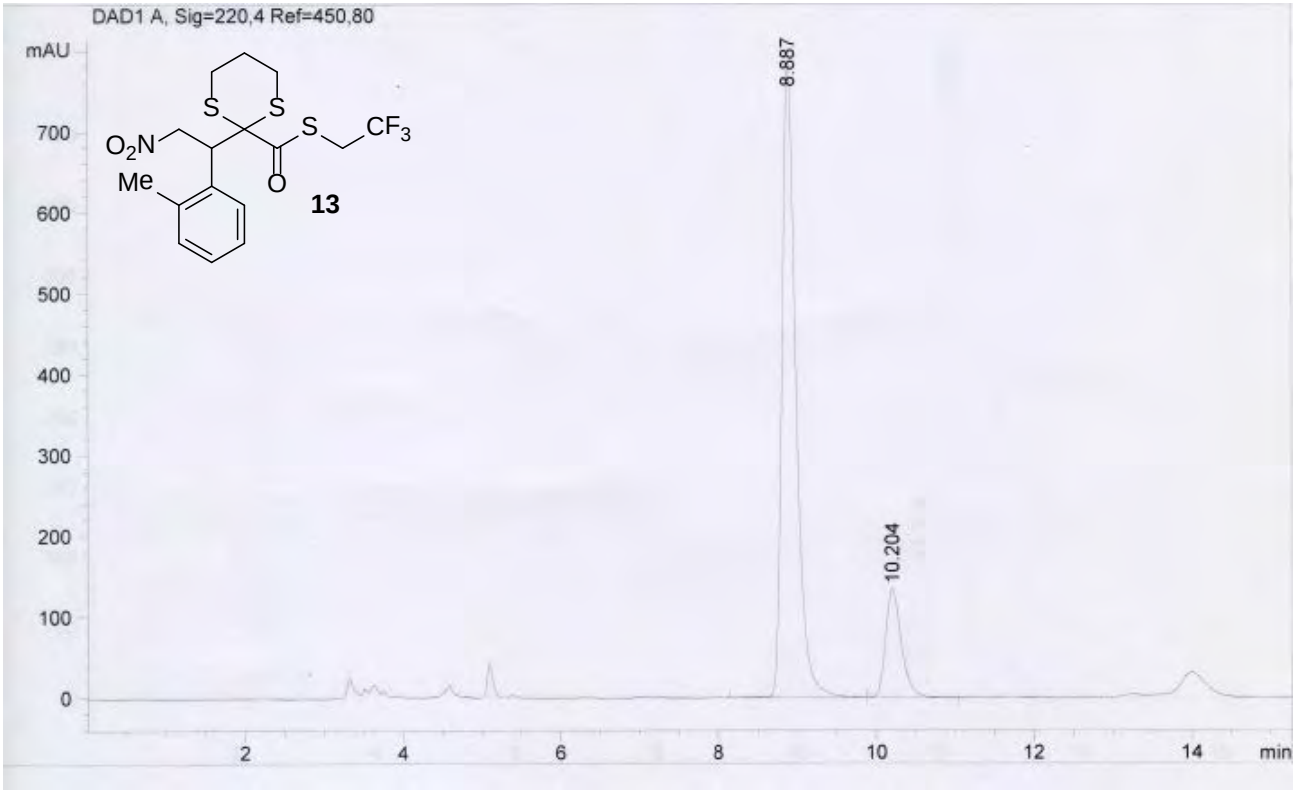





DAD1 A, Sig=220,4 Ref=450,80
mAU
1000
800
600
400
200
0
9.016
10.521
2
4
6
8
10
12
14
min
10


DAD1 A, Sig=220,4 Ref=450,80
mAU
1600
1400
1200
1000
800
600
400
200
0
11.274
12.597
2.5
5
7.5
10
12.5
15
17.5 min
11


DAD1 A, Sig=220,4 Ref=450,80
mAU
900
800
700
600
500
400
300
200
100
0
9.240
10.423
2
4
6
8
10
12
14
min
S
S
S
CF3
O2N
O
Me
12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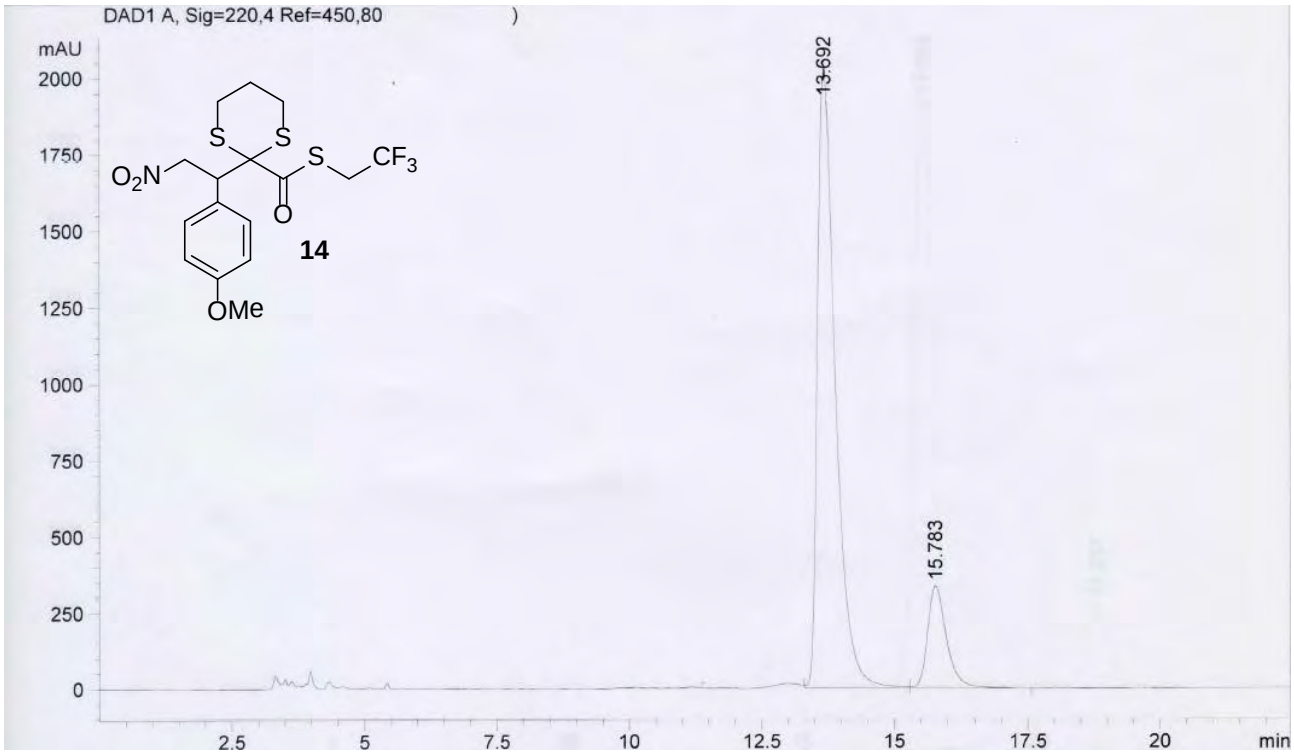
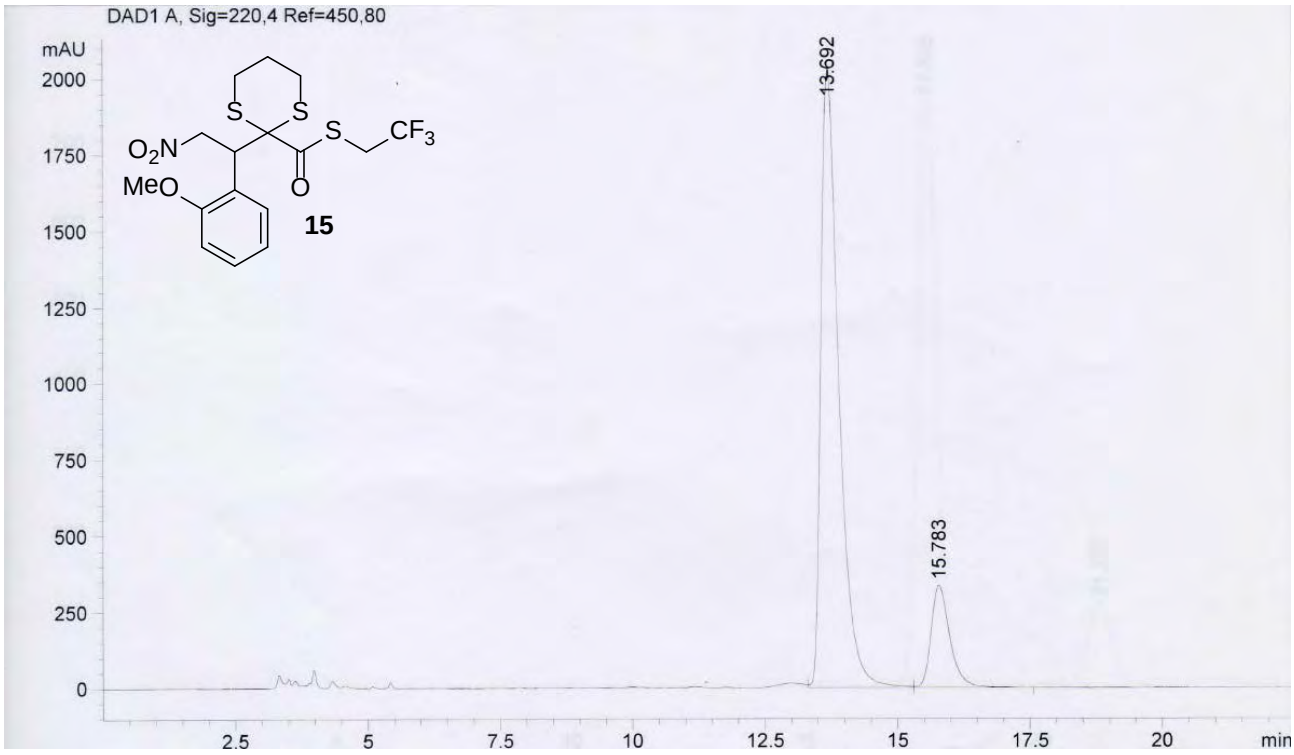
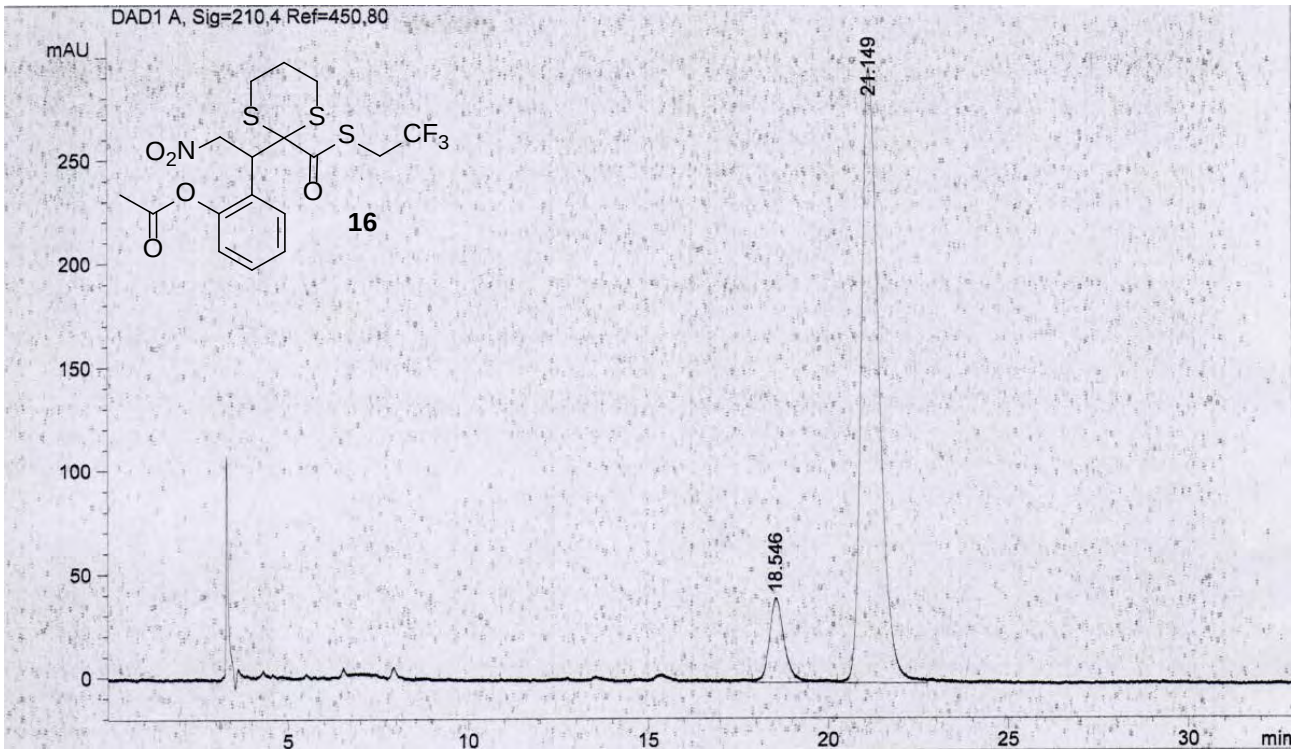
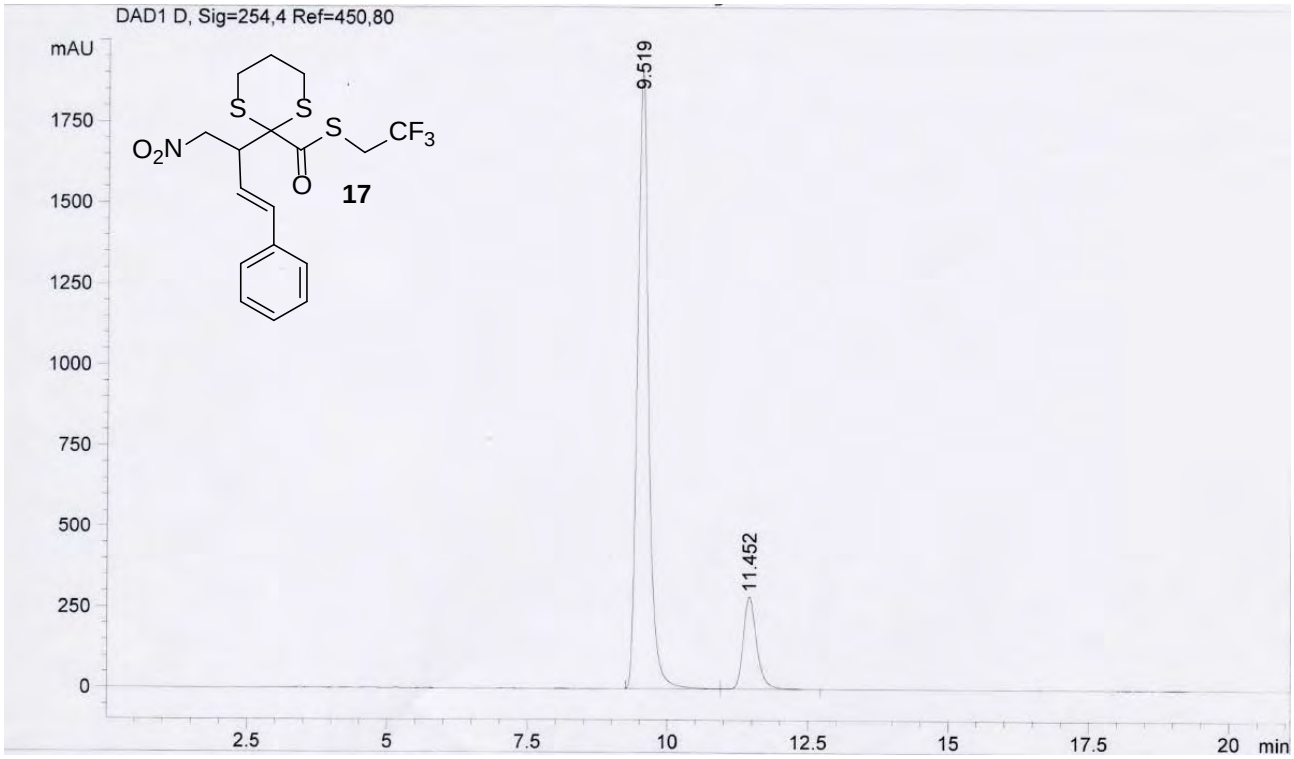
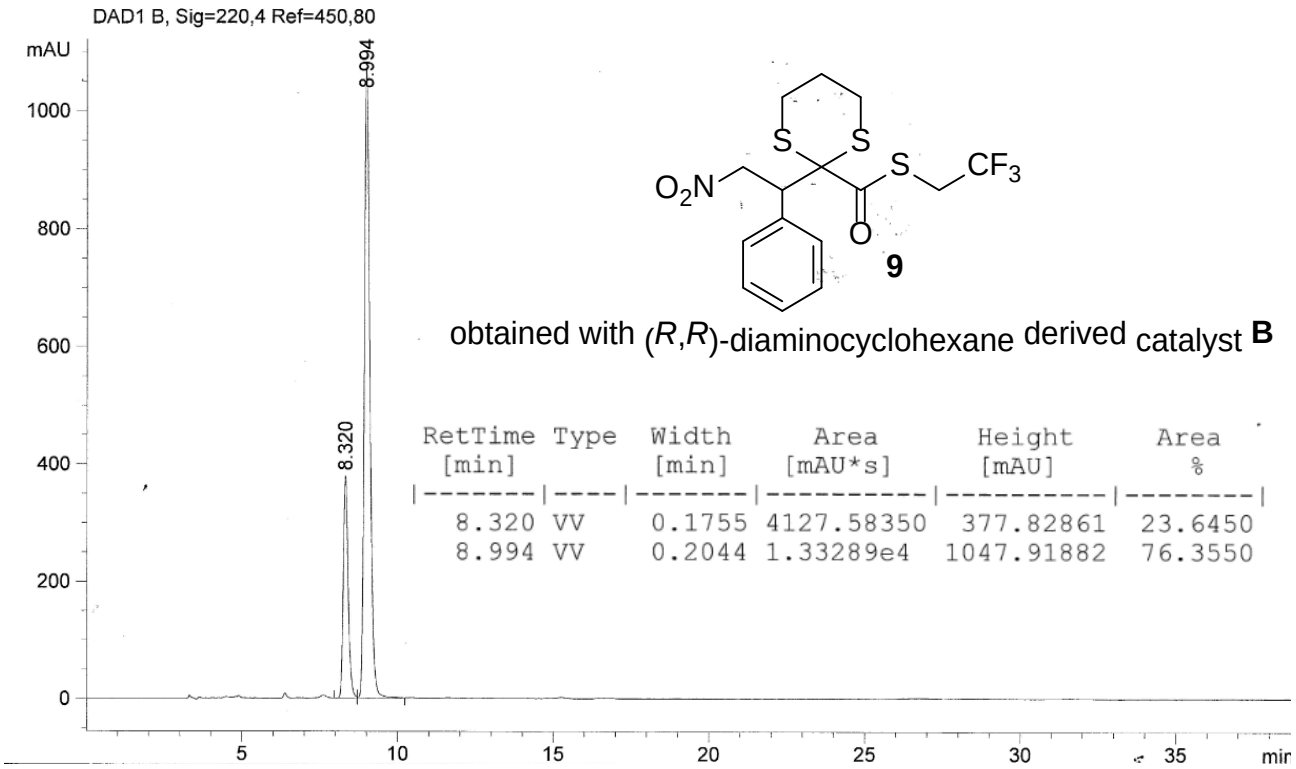
mAU
700
600
500
400
300
200
100
0
8.887
10.204
2
4
6
8
10
12
14
min
S
S
S
CF3
O2N
Me
O
13


DAD1 A, Sig=220,4 Ref=450,80
mAU
2000
1750
1500
1250
1000
750
500
250
0
13.692
15.783
2.5
5
7.5
10
12.5
15
17.5
20
min
S
S
S
CF3
O2N
O
OMe
14


DAD1 A, Sig=220,4 Ref=450,80
mAU
2000
1750
1500
1250
1000
750
500
250
0
13.692
15.783
2.5
5
7.5
10
12.5
15
17.5
20
min
S
S
S
CF3
O2N
MeO
O
15


DAD1 A, Sig=210,4 Ref=450,80
mAU
250
200
150
100
50
0
5
10
15
20
25
30
min
21.149
18.546
16


DAD1 D, Sig=254,4 Ref=450,80
mAU
1750
1500
1250
1000
750
500
250
0
2.5
5
7.5
10
12.5
15
17.5
20
min
9.519
11.452
17



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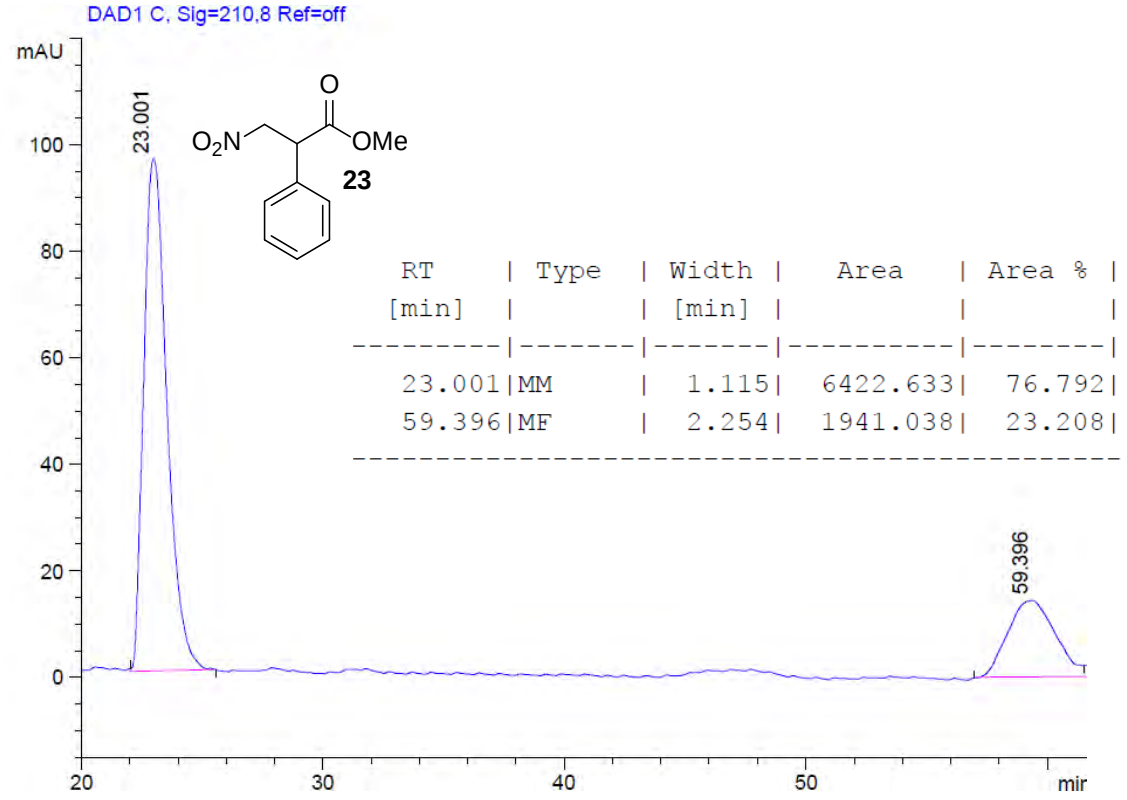
obtained with (*R*,*R*)-diaminocyclohexane derived catalyst **B**

RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
8.320	VV	0.1755	4127.58350	377.82861	23.6450
8.994	VV	0.2044	1.33289e4	1047.91882	76.3550



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RT [min]	Type	Width [min]	Area	Area %
23.001	MM	1.115	6422.633	76.792
59.396	MF	2.254	1941.038	23.208

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