Supporting Information

Non-racemic Antifolates Stereo-selectively Recruit Alternate Cofactors and Overcome Resistance in S. *aureus*

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LIST OF ABBREVIATIONS

TMP-SMX	Trimethoprim-Sulfamethoxazole
PLAs	Propargyl-linked antifolates
NADPH	Nicotinamide adenine dinucleotide phosphate
MRSA	Methicillin-resistant Staphylococcus aureus
Sa	Staphylococcus aureus
DHFR	Dihydrofolate reductase
DHPS	Dihydropteroate synthase
DHF	Dihydrofolate
WT	Wild-type
EDTA	Ethylenediaminetetraacetic acid
TES	N-[Tris(hydroxymethyl)methyl]-2-aminoethanesulfonic acid
BSA	Bovine serum albumin
MES	4-Morpholineethanesulfonic acid hemisodium salt
MTBE	tert-Butyl methyl ether
MIC	Minimum Inhibitory concentration

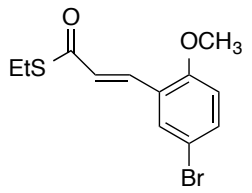
General Experimental. All reactions, unless specified, were conducted under an atmosphere of Argon in glassware that had been flame dried. Methylene chloride (CH_2Cl_2) was used from Baker Cycle-Tainers, anhydrous toluene, *tert*-butyl methyl ether (MTBE), dioxane, triethylamine and dimethylformamide (DMF) were purchased from Sigma-Aldrich. Josiphos was purchased from STREM, pyridine boronic acid from Frontier Scientific, MeMgBr (3.0 M in diethyl ether); $CuBr{\cdot}Me_2S$ from Sigma-Aldrich and was recrystallized from Me_2S prior to use. 2-Methoxy-5-bromocinnamic acid was purchased from Fischer Scientific. Where appropriate, control of temperature was achieved with a Neslab Cryocool CC-100 II immersion cooler, ice-bath or a heated oil bath. ^{1}H NMR spectra were recorded at 400 MHz, and/or at 500 MHz and calibrated to the $CDCl_3$ peak at 7.28 ppm. ^{13}C NMR spectra were recorded at 100MHz, and/or at 125 MHz and calibrated to the $CDCl_3$ peak at 77.23 ppm. Chemical shifts are reported in units of parts per million (ppm). High-resolution mass spectra were obtained on the JMS-AX505HA instruments and/or on an AccuTOF instrument at the University of Connecticut. IR spectra were obtained on the Bruker FT-IR instrument at the University of Connecticut. Flash chromatography was performed on Silica Gel, 40 microns, 32-63 flash silica and/or -NH_2 capped spherical silica gel. Thin layer chromatography was performed on silica gel (Silica Gel 60 F_{254}) glass plates and the compounds were visualized by UV and/or potassium permanganate stain. Racemic conjugate addition products were prepared for HPLC analysis using MeMgBr, copper iodide and dimethylsulfide.[1]

[1] Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 14200-14201.

Synthetic Procedures

Procedure A

Synthesis of 3-(5-Bromo-2-methoxy-phenyl)-thioacrylic acid S-ethyl ester (6)



To 2-methoxy-4-bromo benzaldehyde (2.00 g, 9.30 mmol) in toluene (0.25 M) was added the thioester ylide[2] (4.07 g, 11.2 mmol) followed by DMAP (0.34 g, 2.79 mmol) and stirred the mixture at 90 ^{o}C for 14 h. Reaction mixture concentrated and purified by flash chromatography on silica gel (petroleum ether/EtOAc 80:20) to yield **6** (2.49 g, 89% yield) as pale yellow solid; mp 68-69 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 16 Hz, 1H), 7.60 (d, *J* = 2.4 Hz, 1H), 7.42 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 1H), 6.75 (d, *J* = 16 Hz, 1H); 3.87 (s, 3H), 3.02 (q, *J* = 7.4 Hz, 2H), 1.33 (t, *J* = 7.43 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.2, 157.8, 134.1, 131.3, 126.8, 125.3, 113.2, 113.1, 56.0, 23.6, 15.0; IR (neat cm^{-1}) 2965, 2930, 1652, 1608, 1482, 1250; HRMS (DART, M^{+}+H) *m/z* 300.9890 (calculated for $C_{12}H_{14}BrO_2S$, 300.9898).

[2] Keck, G. E.; Boden, E. P.; Mabury, S. A. *Journal of Organic Chemistry* **1985**, *50*, 709-710.

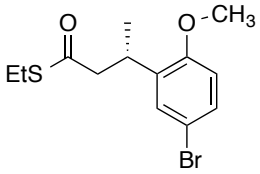
Alternative Procedure

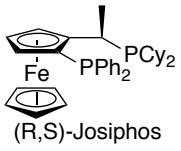
***Synthesis of* 3-(5-Bromo-2-methoxy-phenyl)-thioacrylic acid S-ethyl ester (6)**

To 2-methoxy-4-bromo cinnamic acid (5.00 g, 19.4 mmol) in CH_2Cl_2 (125 mL) was added EtSH (1.82 mL, 25.3 mmol) and DMAP (0.240 g, 1.94 mmol) followed by DCC (4.22 g, 20.4 mmol) at rt and stirred the mixture for 16 h. The reaction mixture was filtered through celite and washed with CH_2Cl_2 (150 mL). The organic washes were concentrated and purified by flash chromatography on silica gel petroleum ether/EtOAc 80:20) to yield **6** as pale yellow solid (4.5 g, 77% yield).

Procedure B

***Synthesis of* 3*S*-(5-Bromo-2-methoxy-phenyl)-thiobutyric acid S-ethyl ester (11)**





(R,S)-Josiphos

L1

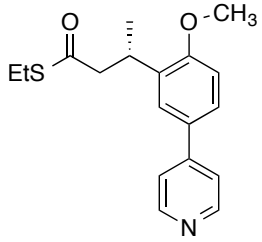
To R_{Fe},S-Josiphos **L1**[3] (0.220 g, 0.330 mmol) and CuBr·Me_2S (61.7 mg, 0.300 mmol) was added MTBE (36 mL) and stirred at rt for 1 h. The solution was cooled to -78 ^oC and 3.0 M MeMgBr in diethyl ether (3.32 ml, 9.96 mmol) was added dropwise for 10 min with good stirring. The yellow reaction mixture was stirred at -78 ^oC for 15 min. Later unsaturated thioester **6** (1.00 g, 3.32 mmol) was dissolved in MTBE (16 mL) and added dropwise to the yellow reaction

[3] **L1 and *ent*-L1** were purchased from STREM with ≥97% purity. Therefore amount of ligand used was adjusted to 100%.

mixture for 1h at -78 ^{o}C and stirred at -55 ^{o}C for 18 h. Reaction mixture was quenched with sat. ammonium chloride (6 mL) followed by water (30 mL) and extracted with diethylether (3 X 20 mL). The combined organic extracts were washed with brine (30 mL) and dried (Na_2SO_4) and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 92:8) provided 3*S*-(5-Bromo-2-methoxy-phenyl)-thiobutyric acid S-ethyl ester **11** as colorless oil (740 mg, 70% yield); $[\alpha]^{27}_{D}$ +20.6 (c 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.26 (d, *J* = 2.3 Hz, 1H), 6.74 (d, *J* = 8.7 Hz, 1H), 3.83 (s, 3H), 3.67 (sextet, 6.9 Hz, 1H), 2.87 (m, 3H), 2.70 (dd, *J* = 14.7, 8.9 Hz, 1H), 1.27 (d, *J* = 6.9 Hz, 3H), 1.23 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.4, 156.2, 135.9, 130.2, 130.1, 113.0, 112.4, 55.7, 50.5, 30.9, 23.5, 19.6, 14.9; IR (neat cm^{-1}) 2966, 2931, 1682, 1486,1241; HRMS (DART, M^{+}+H) *m/z* 317.0238 (calculated for $C_{13}H_{18}BrO_2S$, 317.0211); *er* determination by LC CHIRALPAK AY-3 column (4.6 mm x 250 mm) with particle size 3 μm, mobile phase: 0.5% IPA / 99.5% Hexane with flow rate of 0.6 mL/min, retention time: 14.79 min (*S* isomer).

Procedure C

***Synthesis of* 3*S*-(2-Methoxy-5-pyridin-4-yl-phenyl)-thiobutyric acid S-ethyl ester**

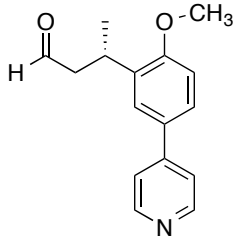


To pyridine boronic acid (814 mg, 6.62 mmol), $Pd(PPh_3)_4$ (509 mg, 0.440 mmol), and Cs_2CO_3 (2.16 g, 6.62 mmol) was added followed by 3*S*-(5-Bromo-2-methoxy-phenyl)-thiobutyric acid S-ethyl ester **11** (700 mg, 2.21 mmol) dissolved in dioxane (18 mL). To the reaction mixture was added water (5 mL) and stirred at 89 ^oC for 14 h. Later the reaction mixture was quenched with water (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 70:30) provided 3*S*-(2-Methoxy-5-pyridin-4-yl-phenyl)-thiobutyric acid S-ethyl ester as a yellow solid (420 mg, 60% yield); mp 90 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 8.63 (br s, 2H), 7.48 (m, 4H), 6.96 (d, *J* = 8.4 Hz, 1H), 3.91 (s, 3H), 3.76 (sextet, *J* = 7.0 Hz, 1H), 2.99 (dd, *J* = 14.7, 5.9 Hz, 1H), 2.86 (q, *J* = 7.3 Hz, 2H), 2.79 (dd, *J* = 14.6, 8.6 Hz, 1H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.21 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.6, 158.1, 150.3, 148.2, 134.3, 130.3, 126.2, 126.0, 121.3, 111.2, 55.7, 50.5, 31.4, 23.5, 19.9, 14.9; IR (neat cm^{-1}) 3001, 2964, 2928, 1674, 1594, 1489, 1249; HRMS (DART, M^++H) *m/z* 316.1354 (calculated for $C_{18}H_{22}NO_2S$, 316.1371).

Procedure D

***Synthesis of* 3*S*-(2-Methoxy-5-pyridin-4-yl-phenyl)-butyraldehyde**

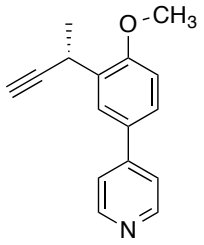
(16)

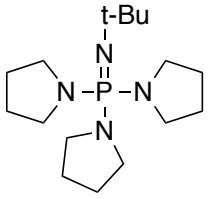


To 3*S*-(2-Methoxy-5-pyridin-4-yl-phenyl)-thiobutyric acid S-ethyl ester (400 mg, 1.26 mmol) dissolved in CH_2Cl_2 (10 mL) was added 10% Pd/C (134 mg, 0.130 mmol Pd) followed by Et_3SiH (0.600 mL, 3.78 mmol) and stirred vigorously at rt for 30-40 min. The reaction monitored by TLC and filtered through the celite and washed with CH_2Cl_2 (30 mL). The solution was concentrated and purified by flash chromatography on silica gel (petroleum ether/EtOAc 60:40) to yield **16** as pale yellow oil (276 mg, 86% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (t, *J* = 2.1 Hz, 1H), 8.63 (d, *J* = 4.8 Hz, 2H), 7.49 (m, 4H), 6.97 (d, *J* = 8.5 Hz, 1H), 3.90 (s, 3H), 3.81 (sextet, *J* = 7.0 Hz, 1H), 2.79 (ddd, *J* = 16.4, 6.4, 2.0 Hz, 1H), 2.68 (ddd, *J* = 16.4, 7.8, 2.3 Hz, 1H), 1.37 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.3, 157.9, 150.3, 148.2, 134.3, 130.6, 126.3, 125.9, 121.3, 111.2, 55.7, 50.7, 28.2, 20.4; IR (neat cm^{-1}) 3157, 3015, 1672, 1581; HRMS (DART, M^++H) *m/z* 256.1309 (calculated for $C_{16}H_{18}NO_2$, 256.1338).

Procedure E

***Synthesis of* 4-[4-Methoxy-3-(1*S*-methyl-prop-2-ynyl)-phenyl]-pyridine (21)**

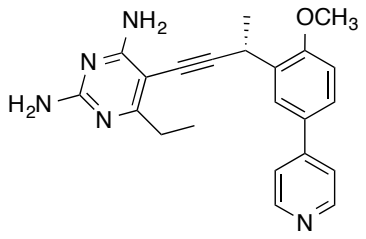




P_1- base

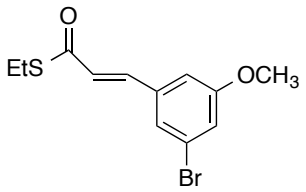
To (S)-aldehyde **16** (0.28 g, 1.1 mmol) dissolved in DMF (7 mL) was added NfF (0.65 mL, 3.4 mmol) at -15 ^{o}C followed by the phosphazene base (1.6 mL, 5.4 mmol) and stirred vigorously at rt for 18 h. The reaction mixture was quenched with water (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 60:40) provided (S)-alkyne **21** as pale yellow oil (0.22 g, 86 % yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (d, *J* = 4.6 Hz, 2H), 7.91 (d, *J* = 2.3 Hz, 1H), 7.52 (m, 3H), 6.96 (d, *J* = 8.5 Hz, 1H), 4.25 (dq, *J* = 7.0, 2.3 Hz, 1H), 3.91 (s, 3H), 2.29 (d, *J* = 2.3 Hz, 1H), 1.50 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.2, 150.1, 148.3, 131.9, 130.4, 126.7, 126.6, 121.3, 111.1, 87.2, 70.2, 55.8, 25.7, 22.8; IR (neat cm^{-1}) 3292, 2975, 2934, 1597, 1545, 1510, 1252; HRMS (DART, M^{+}+H) *m/z* 238.1239 (calculated for $C_{16}H_{16}NO$, 238.1232); *er* determination by LC CHIRALCEL OJ column (0.46 cm x 25 cm), mobile phase: 2.5% IPA / 97.5% Hexane with flow rate of 1.5 mL/min, retention time: 20.12 min (*S* isomer).

Synthesis of 6-Ethyl-5-[3*S*-(2-methoxy-5-pyridin-4-yl-phenyl)-but-1-ynyl]-pyrimidine-2,4-diamine (26)



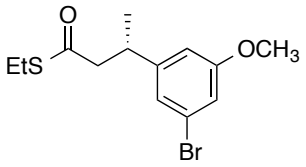
To (S)-alkyne **21** (0.22 g, 0.92 mmol), iodo-ethyl pyrimidine (0.24 g, 0.92 mmol), CuI (35 mg, 0.18 mmol), and $PdCl_2(PPh_3)_2$ (65 mg, 0.092 mmol) was added followed by DMF (3.0 mL) and NEt_3 (3.0 mL) and stirred at 70 ^{0}C for 18 h. The reaction mixture was concentrated by azeotroping with toluene (3 x 10 mL) and purified by gradient flash chromatography (EtOAc followed by 2% to 10% MeOH in CH_2Cl_2) to yield coupled pyrimidine **26** as pale yellow solid (230 mg, 67%); mp 153-155 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (s, 2H), 7.89 (d, *J* = 2.4 Hz, 1H), 7.55 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.49 (dd, *J* = 4.5, 1.6 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 1H), 5.34 (br s, 2H), 5.11 (br s, 2H), 4.48 (q, *J* = 7.0 Hz, 1H), 3.94 (s, 3H), 2.73 (q, *J* = 7.6 Hz, 2H), 1.58 (d, *J* = 7.0 Hz, 3H), 1.24 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 164.6, 160.9, 157.2, 150.4, 147.9, 132.5, 130.6, 126.7, 126.5, 121.2, 111.2, 101.8, 90.8, 75.1, 55.8, 29.8, 27.3, 23.1, 12.7; IR (neat cm^{-1}) 3466, 3311, 3174, 2974, 2931, 1599, 1571, 1547, 1440, 1288, 1251; HRMS (DART, M^++H) *m/z* 374.1972 (calculated for $C_{22}H_{24}N_5O$, 374.1981); A small amount of sample was further purified using NH_2-capped spherical silica gel followed by gradient separation on normal phase flash silica gel for biological studies.

Synthesis of 3-(5-Bromo-3-methoxy-phenyl)-thioacrylic acid S-ethyl ester (7)



3-(5-Bromo-3-methoxy-phenyl)-thioacrylic acid S-ethyl ester **7** was obtained from 3-methoxy-5-bromo benzaldehyde (2.00 g, 9.26 mmol) following the general procedure A as pale yellow solid (2.70 g, 97% yield); mp 56-57 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 15.8 Hz, 1H), 7.25 (s, 1H), 7.05 (s, 1H), 6.94 (s, 1H), 6.65 (d, *J* = 15.8 Hz, 1H), 3.80 (s, 3H), 3.01 (q, *J* = 7.4 Hz, 2H), 1.32 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.7, 160.7, 138.6, 137.2, 126.7, 123.6, 123.5, 119.2, 113.1, 55.9, 23.8, 15.0; IR (neat cm^{-1}) 2971, 2934, 2870, 2836, 1654, 1598, 1564, 1425; HRMS (DART, M^{+}+H) *m/z* 300.9844 (calculated for $C_{12}H_{14}BrO_2S$, 300.9898).

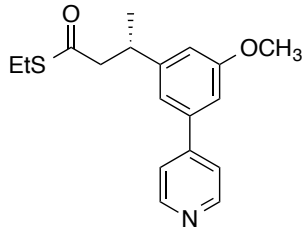
Synthesis of 3*S*-(5-Bromo-3-methoxy-phenyl)-thiobutyric acid S-ethyl ester (12)



3*S*-(5-Bromo-3-methoxy-phenyl)-thiobutyric acid S-ethyl ester **12** was obtained from unsaturated thioester **7** (200 mg, 0.660 mmol) following the general procedure B as colorless oil (170 mg, 81% yield); $[\alpha]^{27}_{D}$ +25.7 (c 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.90 (s, 1H), 6.69 (s, 1H), 3.78 (s, 3H),

3.28 (sextet, *J* = 6.9 Hz, 1H), 2.86 (q, *J* = 7.4 Hz, 2H), 2.81 (dd, *J* = 14.9, 6.6 Hz, 1H), 2.73 (dd, *J* = 14.9, 8.2 Hz, 1H), 1.28 (d, *J* = 6.9 Hz, 3H), 1.22 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.9, 160.6, 148.8, 122.9, 122.5, 115.1, 112.3, 55.6, 51.9, 36.9, 23.5, 21.4, 14.9; IR (neat cm^{-1}) 2965, 2930, 2871, 2835, 1680, 1596, 1566, 1455, 1427, 1264; HRMS (DART, M^++H) *m/z* 317.0185 (calculated for $C_{13}H_{18}BrO_2S$, 317.0211).

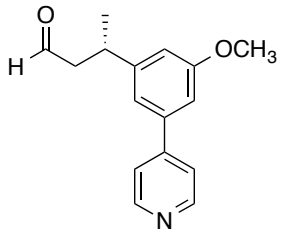
Synthesis of 3*S*-(3-Methoxy-5-pyridin-4-yl-phenyl)-thiobutyric acid S-ethyl ester



3*S*-(3-Methoxy-5-pyridin-4-yl-phenyl)-thiobutyric acid S-ethyl ester was obtained from 3*S*-(5-Bromo-3-methoxy-phenyl)-thiobutyric acid S-ethyl ester **12** (170 mg, 0.540 mmol) following the general procedure C as yellow oil (127 mg, 74% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (br s, 2H), 7.48 (d, *J* = 4.0 Hz, 2H), 7.06 (s, 1H), 6.99 (s, 1H), 6.84 (s, 1H), 3.86 (s, 3H), 3.40 (sextet, *J* = 7.1 Hz, 1H), 2.84 (m, 4H), 1.34 (d, *J* = 6.9 Hz, 3H), 1.19 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.1, 160.5, 150.3, 148.4, 148.1, 121.9, 118.3, 113.4, 110.8, 55.5, 52.1, 37.3, 23.5, 21.6, 14.9; IR (neat cm-1) 3157, 3016, 2975, 1691, 1594, 1501; HRMS (DART, M^++H) *m/z* 316.1362 (calculated for $C_{18}H_{22}NO_2S$, 316.1371).

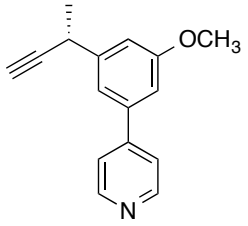
Synthesis of 3*S*-(3-Methoxy-5-pyridin-4-yl-phenyl)-butyraldehyde

(17)



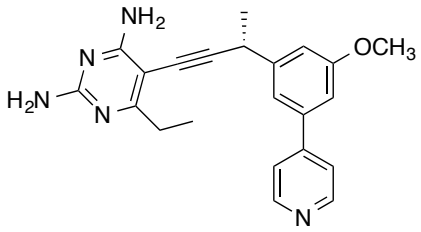
(S)-Aldehyde **17** was obtained from 3*S*-(3-Methoxy-5-pyridin-4-yl-phenyl)-thiobutyric acid S-ethyl ester (110 mg, 0.350 mmol) following the general procedure D as pale yellow oil (70 mg, 79% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (s, 1H), 8.65 (s, 2H), 7.48 (d, *J* = 4.7 Hz, 2H), 7.07 (s, 1H), 6.99 (s, 1H), 6.85 (s, 1H), 3.87 (s, 3H), 3.42 (sextet, *J* = 7.0 Hz, 1H), 2.80 (dd, *J* = 16.9, 6.9 Hz, 1H), 2.71 (dd, *J* = 16.9, 7.5 Hz, 1H), 1.36 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.4, 160.6, 150.4, 148.3, 140.1, 121.9, 118.2, 113.5, 110.7, 55.6, 51.8, 34.5, 22.3; IR (neat cm^{-1}) 2960, 2827, 1719, 1593; HRMS (DART, M^++H) *m/z* 256.1344 (calculated for $C_{16}H_{18}NO_2$, 256.1338).

Synthesis of 4-[3-Methoxy-5-(1*R*-methyl-prop-2-ynyl)-phenyl]-pyridine (22)



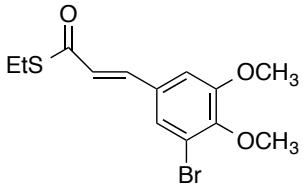
To (S)-aldehyde **17** (60 mg, 0.24 mmol) dissolved in DMF (2 mL) was added NfF (0.27 mL, 1.6 mmol) at -15 ^{o}C followed by the phosphazene base (0.37 mL, 1.2 mmol) and stirred vigorously at rt for 18 h. The reaction mixture was quenched with water (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 60:30) provided (R)-alkyne **22** as pale yellow oil (40 mg, 70 % yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, *J* = 5.3 Hz, 2H), 7.52 (d, *J* = 5.8 Hz, 2H), 7.27 (s, 1H), 7.05 (s, 2H), 3.91 (s, 3H), 3.84 (dq, *J* = 7.0, 2.3 Hz, 1H), 2.33 (d, *J* = 2.3 Hz, 1H), 1.58 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6, 150.3, 148.5, 145.4, 140.0, 121.9, 118.3, 113.4, 111.3, 86.7, 70.8, 55.6, 31.9, 24.4; IR (neat cm^{-1}) 3291, 2976, 2934, 1686, 1594, 1550, 1216; HRMS (DART, M^{+}+H) *m/z* 238.1243 (calculated for $C_{16}H_{16}NO$, 238.1232); *er* determination by LC CHIRALCEL OJ column (0.46 cm x 25 cm), mobile phase: 0.25% IPA / 99.75% Hexane with flow rate of 1.5 mL/min, retention time: 79.13 min (*R* isomer).

Synthesis of 6-Ethyl-5-[3*R*-(3-methoxy-5-pyridin-4-yl-phenyl)-but-1-ynyl]-pyrimidine-2,4-diamine (27)



To (R)-alkyne **22** (65 mg, 0.27 mmol), iodo-ethyl pyrimidine (72 mg, 0.27 mmol), CuI (10 mg, 0.054 mmol), and $PdCl_2(PPh_3)_2$ (19 mg, 0.027 mmol) was added followed by DMF (1.0 mL) and NEt_3 (1.0 mL) and stirred at 70 ^{0}C for 12 h. The reaction mixture was concentrated by azeotroping with toluene (3 x 5 mL) and purified by gradient flash chromatography (EtOAc followed by 2% to 10% MeOH in CH_2Cl_2) to yield coupled pyrimidine **27** as pale yellow solid (80 mg, 79%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, *J* = 5.6 Hz, 2H), 7.50 (d, *J* = 5.1 Hz, 2H), 7.29 (s, 1H), 7.08 (s, 1H), 7.06 (s, 1H), 5.22 (br s, 2H), 5.00 (br s, 2H), 4.11 (q, *J* = 7.1 Hz, 1H), 3.90 (s, 3H), 2.72 (q, *J* = 7.8 Hz, 2H), 1.65 (d, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 164.5, 160.9, 160.7, 150.4, 148.3, 146.1, 140.1, 121.9, 118.2, 113.3, 111.2, 101.3, 90.5, 75.9, 55.6, 33.3, 29.8, 24.9, 12.7; IR (neat cm^{-1}) 3319, 3174, 2975, 1594, 1571, 1547, 1440, 1217; HRMS (DART, M^++H) *m/z* 374.1971 (calculated for $C_{22}H_{24}N_5O$, 374.1981); A small amount of sample was further purified using NH_2-capped spherical silica gel followed by gradient separation (2% to 8% MeOH in CH_2Cl_2) on normal phase flash silica gel for biological studies.

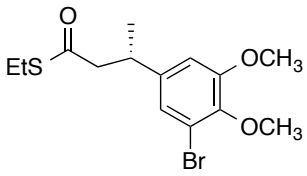
Synthesis of 3-(5-Bromo-3,4-dimethoxy-phenyl)-thioacrylic acid S-ethyl ester (8)



Unsaturated thioester **8** was obtained from 3,4-dimethoxy-5-bromo benzaldehyde (1.07 g, 4.37 mmol) following the general procedure A as pale yellow solid (1.25 g, 86% yield); mp 79-80 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 15.7 Hz, 1H), 7.37 (d, *J* = 1.8 Hz, 1H), 7.02 (s, 1H), 6.63 (d, *J* = 15.7 Hz, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.04 (q, *J* = 7.4 Hz, 2H), 1.35 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.7, 153.4, 148.5, 138.6, 131.4, 125.6, 125.4, 118.3, 111.1, 60.9, 56.3, 23.6, 14.9; IR (neat cm^{-1}) 2967, 2933, 1660, 1613, 1590, 1555, 1487; HRMS (DART, M^{+}+H) *m/z* 331.0011 (calculated for $C_{13}H_{16}BrO_3S$, 331.0004).

Synthesis of 3*S*-(5-Bromo-3,4-dimethoxy-phenyl)-thiobutyric acid S-ethyl ester

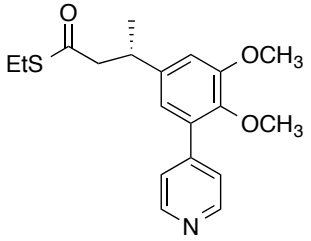
(13)



3*S*-(5-Bromo-3,4-dimethoxy-phenyl)-thiobutyric acid S-ethyl ester **13** was obtained from unsaturated thioester **8** (240 mg, 0.720 mmol) following the general procedure B as colorless oil (200 mg, 80% yield); $[\alpha]^{27}_{D}$ +36.9 (c 0.46, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (s, 1H), 6.69 (s, 1H), 3.86 (s, 3H),

3.82 (s, 3H), 3.27 (sextet, *J* = 7.0 Hz, 1H), 2.85 (qd, *J* = 7.4, 1.0 Hz, 2H), 2.79 (dd, *J* = 14.8, 6.7 Hz, 1H), 2.73 (dd, *J* = 14.8, 8.1 Hz, 1H), 1.28 (d, *J* = 6.9 Hz, 3H), 1.21 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.1, 153.7, 145.1, 142.7, 122.8, 117.7, 110.9, 60.7, 56.3, 52.2, 36.8, 23.5, 21.5, 14.9; IR (neat cm^{-1}) 2963, 2931, 1685, 1592, 1415; HRMS (DART, M^++H) *m/z* 347.0322 (calculated for $C_{14}H_{20}BrO_3S$, 347.0317).

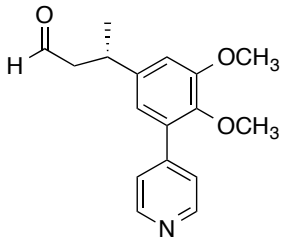
Synthesis of 3*S*-(3,4-dimethoxy-5-pyridin-4-yl-phenyl)-thiobutyric acid S-ethyl ester



3-(3,4-dimethoxy-5-pyridin-4-yl-phenyl)-thiobutyric acid S-ethyl ester was obtained from 3*S*-(5-Bromo-3,4-dimethoxy-phenyl)-thiobutyric acid S-ethyl ester **13** (0.17 g, 0.49 mmol) following the general procedure C ($PdCl_2(PPh_3)_2$ for 8h) as yellow oil (107 mg, 61% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, *J* = 6.1 Hz, 2H), 7.49 (d, *J* = 6.1 Hz, 2H), 6.84 (d, *J* = 2.0 Hz, 1H), 6.80 (d, *J* = 2.0 Hz, 1H), 3.94 (s, 3H), 3.62 (s, 3H), 3.37 (sextet, *J* = 7.0 Hz, 1H), 2.87 (q, *J* = 7.05 Hz, 2H), 2.87 (dd, *J* = 14.7, 8.1 Hz, 1H), 2.78 (dd, *J* = 14.7, 8.1 Hz, 1H), 1.34 (d, *J* = 7.0 Hz, 3H), 1.22 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.3, 153.2, 149.8, 146.3, 145.3, 141.9, 132.9, 124.2, 120.1, 111.8, 60.9, 56.2, 52.4, 37.1, 23.6, 21.7, 14.9; IR (neat cm^{-1}) 2964, 2929, 2875, 1681, 1585, 1546, 1262; HRMS (DART, M^++H) *m/z* 346.1476 (calculated for $C_{19}H_{24}NO_3S$, 346.1477).

Synthesis of 3*S*-(3,4-dimethoxy-5-pyridin-4-yl-phenyl)-butyraldehyde

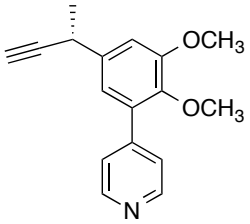
(18)



(S)-Aldehyde **18** was obtained from 3-(3,4-dimethoxy-5-pyridin-4-yl-phenyl)-thiobutyric acid S-ethyl ester (75 mg, 0.22 mmol) following the general procedure D as pale yellow oil (45 mg, 73% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.67 (br s, 2H), 7.51 (d, *J* = 4.0 Hz, 2H), 6.85 (s, 1H), 6.81 (s, 1H), 3.93 (s, 3H), 3.62 (s, 3H), 3.39 (sextet, *J* = 6.9 Hz, 1H), 2.79 (dd, *J* = 16.8, 6.9 Hz, 1H), 2.70 (dd, *J* = 16.8, 7.4 Hz, 1H), 1.36 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.5, 153.4, 149.5, 146.6, 145.4, 142.1, 132.9, 124.4, 119.9, 111.8, 60.9, 56.2, 51.9, 34.3, 22.4; IR (neat cm^{-1}) 2961, 2932, 2827, 2720, 1720, 1593, 1584; HRMS (DART, M^{+}+H) *m/z* 286.1460 (calculated for $C_{17}H_{20}NO_3$, 286.1443).

Synthesis of 4-[2,3-dimethoxy-5-(1*R*-methyl-prop-2-ynyl)-phenyl]-pyridine

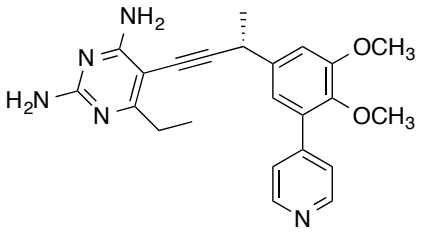
(23)



To (S)-aldehyde **18** (45 mg, 0.16 mmol) dissolved in DMF (2 mL) was added NfF (0.16 mL, 0.95 mmol) at -15 ^{o}C followed by the phosphazene base (0.4 mL, 1.3 mmol) and stirred vigorously at rt for 18 h. The reaction mixture was quenched

with water (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 60:30) provided (R)-alkyne **23** as pale yellow oil (40 mg, 70 % yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, *J* = 4.9 Hz, 2H), 7.61 (d, *J* = 4.9 Hz, 2H), 7.08 (s, 1H), 6.99 (s, 1H), 3.97 (s, 3H), 3.82 (q, *J* = 7.0 Hz, 1H), 3.65 (s, 3H), 2.33 (s, 1H), 1.57 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 153.3, 148.8, 147.1, 145.6, 139.2, 132.6, 124.5, 120.1, 111.9, 86.8, 70.8, 61.0, 56.2, 31.7, 24.4; IR (neat cm^{-1}) 3291, 2974, 2934, 2938, 1712, 1680, 1586, 1406, 1138, 1001; HRMS (DART, M^++H) *m/z* 268.1338 (calculated for $C_{17}H_{18}NO_2$, 268.1338); *er* determination by LC CHIRALPAK AY-3 column (4.6 mm x 250 mm), mobile phase: 5% IPA / 95% Hexane with flow rate of 1.5 mL/min, retention time: 17.81 min (*R* isomer).

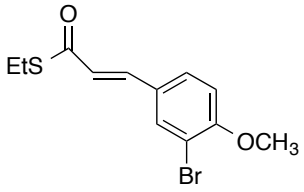
Synthesis of 6-Ethyl-5-[3*R*-(3,4-dimethoxy-5-pyridin-4-yl-phenyl)-but-1-ynyl]-pyrimidine-2,4-diamine (28)



To (R)-alkyne **23** (0.030 g, 0.11 mmol), iodo-ethyl pyrimidine (0.030 g, 0.11 mmol), CuI (4.3 mg, 0.02 mmol), and $PdCl_2(PPh_3)_2$ (7.9 mg, 0.011 mmol) was added followed by DMF (0.5 mL) and NEt_3 (0.4 mL) and stirred at 70 ^{0}C for 12h. The reaction mixture was concentrated by azeotroping with toluene and purified by gradient flash chromatography (EtOAc followed by 2% to 10% MeOH in CH_2Cl_2) to yield coupled pyrimidine **28** as pale yellow solid (31 mg, 66%). An

analytical sample was purified using NH_2-capped spherical silica gel followed by normal phase silica gel for biological studies; mp 159-161 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, *J* = 5.9 Hz, 2H), 7.51 (d, *J* = 6.1 Hz, 2H), 7.09 (d, *J* = 2.0 Hz, 1H), 7.01 (d, *J* = 1.9 Hz, 1H), 5.29 (s, 2H), 5.22 (s, 2H), 4.08 (q, *J* = 7.1 Hz, 1H), 3.96 (s, 3H), 3.65 (s, 3H), 2.75 (q, *J* = 7.6 Hz, 2H), 1.65 (d, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 164.4, 159.9, 153.5, 149.9, 146.1, 145.7, 139.6, 133.1, 124.2, 120.2, 111.5, 101.9, 90.9, 75.2, 61.0, 56.2, 33.1, 29.2, 24.9, 12.6; IR (neat cm^{-1}) 3309, 3147, 2975, 2931, 1641, 1546, 1461, 1139, 1000; HRMS (DART, M^++H) *m/z* 404.2058 (calculated for $C_{23}H_{26}N_5O_2$, 404.2087).

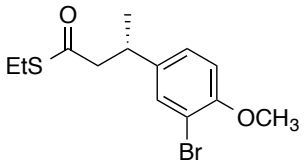
Synthesis of 3-(5-Bromo-4-methoxy-phenyl)-thioacrylic acid S-ethyl ester (9)



Unsaturated thioester **9** was obtained from 4-methoxy-3-bromo benzaldehyde (2.00 g, 9.26 mmol) following the general procedure A as pale yellow solid (2.16 g, 77% yield); mp 85-86 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.50 (d, *J* = 15.8 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 6.60 (d, *J* = 15.7 Hz, 1H), 3.95 (s, 3H), 3.03 (q, *J* = 7.4 Hz, 2H), 1.34 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.8, 157.7, 138.5, 132.9, 129.5, 128.4, 124.2, 112.6, 112.0, 56.6, 23.6, 15.0; IR (neat cm^{-1}) 2959, 2922, 1663, 1643, 1609, 1257,

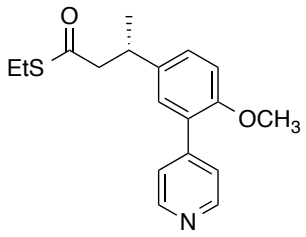
1128; HRMS (DART, M^++H) *m/z* 300.9866 (calculated for $C_{12}H_{14}BrO_2S$, 300.9898).

Synthesis of 3*S*-(5-Bromo-4-methoxy-phenyl)-thiobutyric acid S-ethyl ester (14)



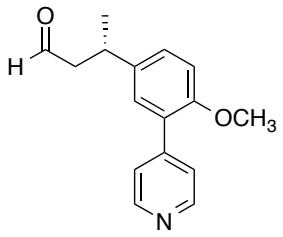
3*S*-(5-Bromo-4-methoxy-phenyl)-thiobutyric acid S-ethyl ester **14** was obtained from unsaturated thioester **9** (500 mg, 1.66 mmol) following the general procedure B as colorless oil (270 mg, 52% yield); $[\alpha]^{27}_D$ +45.8 (c 0.35, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 3.87 (s, 3H), 3.28 (sextet, *J* = 6.9 Hz, 1H), 2.84 (q, *J* = 7.4 Hz, 2H), 2.79 (dd, *J* = 14.8, 6.9 Hz, 1H), 2.73 (dd, *J* = 14.8, 7.9 Hz, 1H), 1.27 (d, *J* = 6.9 Hz, 3H), 1.21 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.1, 154.6, 139.2, 131.8, 126.9, 112.1, 111.7, 56.4, 52.4, 36.1, 23.5, 21.7, 14.9; IR (neat cm^{-1}) 2963, 2928, 1681, 1603, 1497, 1256, 1182; HRMS (DART, M^++H) *m/z* 317.0167 (calculated for $C_{13}H_{18}BrO_2S$, 317.0211).

Synthesis of 3*S*-(4-Methoxy-5-pyridin-4-yl-phenyl)-thiobutyric acid S-ethyl ester



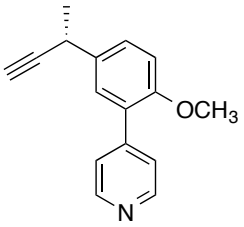
3*S*-(4-Methoxy-5-pyridin-4-yl-phenyl)-thiobutyric acid S-ethyl ester was obtained from 3*S*-(5-Bromo-4-methoxy-phenyl)-thiobutyric acid S-ethyl ester **14** (0.16 g, 0.50 mmol) following the general procedure C ($PdCl_2(PPh_3)_2$ for 8h) as yellow oil (98 mg, 62% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, *J* = 4.1 Hz, 2H), 7.47 (d, *J* = 4.1 Hz, 2H), 7.24 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.19 (d, *J* = 2.3 Hz, 1H), 6.95 (d, *J* = 8.5 Hz, 1H), 3.81 (s, 3H), 3.37 (sextet, *J* = 7.1 Hz, 1H), 2.86 (q, *J* = 7.4 Hz, 2H), 2.83 (m, 2H), 1.32 (d, *J* = 6.9 Hz, 3H), 1.20 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.3, 155.3, 149.7, 146.5, 138.1, 129.1, 128.4, 127.8, 124.4, 111.7, 55.8, 52.2, 36.4, 23.5, 21.9, 14.9; IR (neat cm^{-1}) 2965, 2930, 1686, 1609, 1270, 1243; HRMS (DART, M^++H) *m/z* 316.1364 (calculated for $C_{18}H_{22}NO_2S$, 316.1371).

Synthesis of 3*S*-(4-Methoxy-5-pyridin-4-yl-phenyl)-butyraldehyde (19)



(S)-Aldehyde **19** was obtained from 3*S*-(4-Methoxy-5-pyridin-4-yl-phenyl)-thiobutyric acid S-ethyl ester (90 mg, 0.28 mmol) following the general procedure D as pale yellow oil (55 mg, 76% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.3 Hz, 1H), 8.64 (d, *J* = 5.4 Hz, 2H), 7.47 (d, J = 5.8 Hz, 2H), 7.25 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.20 (d, *J* = 2.1 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 1H), 3.82 (s, 3H), 3.39 (sextet, *J* = 7.0 Hz, 1H), 2.77 (ddd, *J* = 16.7, 7.1, 1.3 Hz, 1H), 2.69 (ddd, *J* = 16.7, 7.3, 1.8 Hz, 1H), 1.34 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.7, 155.3, 149.6, 146.4, 138.2, 129.1, 128.4, 127.9, 124.4, 111.8, 55.8, 52.0, 33.6, 22.5; IR (neat cm^{-1}) 2958, 2927, 1715, 1582, 1261, 1003; HRMS (DART, M^{+}+H) *m/z* 256.1342 (calculated for $C_{16}H_{18}NO_2$, 256.1338).

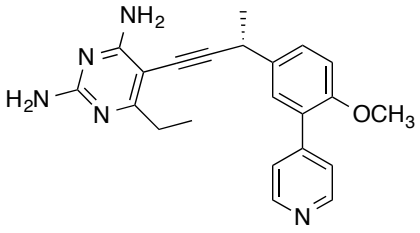
Synthesis of 4-[2-Methoxy-5-(1*R*-methyl-prop-2-ynyl)-phenyl]-pyridine (24)



To (S)-aldehyde **19** (55 mg, 0.21 mmol) dissolved in DMF (2 mL) was added NfF (0.14 mL, 0.81 mmol) at -15 ^{o}C followed by the phosphazene base (0.36 mL, 1.2 mmol) and stirred vigorously at rt for 18 h. The reaction mixture was quenched

with water (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 60:30) provided (R)-alkyne **24** as pale yellow oil (42 mg, 85 % yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, *J* = 4.4 Hz, 2H), 7.50 (d, *J* = 5.1 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.38 (s, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 3.84 (s, 3H), 3.80 (q, *J* = 7.2 Hz, 1H), 2.30 (d, *J* = 1.9 Hz, 1H), 1.55 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 149.7, 146.4, 135.5, 129.1, 128.5, 127.9, 124.5, 111.8, 87.2, 70.5, 55.9, 30.9, 24.5; IR (neat cm^{-1}) 3291, 2966, 2929, 2849, 1713, 1676, 1597, 1404, 1269, 1021; HRMS (DART, M^++H) *m/z* 238.1234 (calculated for $C_{16}H_{16}NO$, 238.1232); *er* determination by LC CHIRALPAK AY-3 column (4.6 mm x 250 mm), mobile phase: 0.5% IPA / 99.5% Hexane with flow rate of 1.5 mL/min, retention time: 44.96 min (*R* isomer).

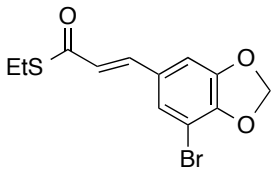
Synthesis of 6-Ethyl-5-[3*R*-(4-methoxy-5-pyridin-4-yl-phenyl)-but-1-ynyl]-pyrimidine-2,4-diamine (29)



To (R)-alkyne **24** (35 mg, 0.15 mmol), iodo-ethyl pyrimidine (43 mg, 0.16 mmol), CuI (5.6 mg, 0.030 mmol), and $PdCl_2(PPh_3)_2$ (10 mg, 0.015 mmol) was added followed by DMF (1.0 mL) and NEt_3 (1.0 mL) and stirred at 70 ^{0}C for 12 h. The reaction mixture was concentrated by azeotroping with toluene (3 x 5 mL) and purified by gradient flash chromatography (EtOAc followed by 2% to 10% MeOH

in CH_2Cl_2) to yield coupled pyrimidine **29** as pale yellow solid (47 mg, 84%); mp 148-149 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 8.65 (br s, 2H), 7.49 (d, *J* = 4.3 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.40 (s, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 5.17 (br s, 2H), 4.93 (br s, 2H), 4.06 (q, *J* = 6.9 Hz, 1H), 3.85 (s, 3H), 2.70 (q, *J* = 7.5 Hz, 2H), 1.62 (d, *J* = 6.9 Hz, 3H), 1.23 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 164.5, 160.9, 155.6, 149.8, 146.4, 136.2, 129.1, 128.4, 128.0, 124.5, 111.9, 101.8, 90.7, 75.7, 55.9, 32.4, 29.9, 25.1, 12.3; IR (neat cm^{-1}) 3467, 3312, 3166, 2971, 2932, 1598, 1570, 1546, 1440, 1271, 1240; HRMS (DART, M^++H) *m/z* 374.1973 (calculated for $C_{22}H_{24}N_5O$, 374.1981); A small amount of sample was further purified using NH_2-capped spherical silica gel followed by gradient separation (2% to 8% MeOH in CH_2Cl_2) on normal phase flash silica gel for biological studies.

Synthesis of 3-(7-Bromo-benzo[1,3]dioxol-5-yl)-thioacrylic acid S-ethyl ester (10)



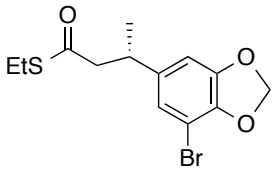
Unsaturated thioester **10** was obtained from dioxolane-3-bromo benzaldehyde[4] (0.56 g, 2.5 mmol) following the general procedure A as pale yellow solid (0.75 g, 96% yield); mp 113 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 16 Hz, 1H), 7.14 (s, 1H), 6.93 (s, 1H), 6.52 (d, *J* = 16 Hz, 1H), 6.07 (s, 2H), 3.00 (q, *J* = 7.4 Hz, 2H), 1.31 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.6, 148.8,

[4] Wielens, J.; Headey, S. J.; Deadman, J. J.; Rhodes, D. I.; Parker, M. W.; Chalmers, D. K.; Scanlon, M. J. *ChemMedChem* **2011**, *6*, 258-261.

148.0, 138.6, 130.2, 127.5, 124.7, 106.1, 102.3, 101.2, 23.7, 15.1; IR (neat cm^{-1}) 3063, 2963, 1652, 1590, 1486, 1031; HRMS (DART, M^++H) *m/z* 314.9700 (calculated for $C_{12}H_{12}BrO_3S$, 314.9691).

Synthesis of 3*S*-(7-Bromo-benzo[1,3]dioxol-5-yl)-thiobutyric acid S-ethyl ester

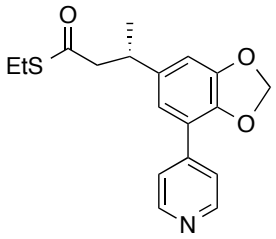
(15)



3*S*-(7-Bromo-benzo[1,3]dioxol-5-yl)-thiobutyric acid S-ethyl ester **15** was obtained from unsaturated thioester **10** (0.31 g, 0.99 mmol) following the general procedure B[5] of as colorless oil (0.26 g, 80% yield); $[\alpha]^{27}_D$ +55.3 (c 0.2, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (s, 1H), 6.64 (s, 1H), 6.00 (s, 2H), 3.25 (sextet, *J* = 7.1 Hz, 1H), 2.86 (q, *J* = 7.4 Hz, 2H), 2.76 (dd, *J* = 14.8, 6.9 Hz, 1H), 2.72 (dd, *J* = 14.8, 6.9 Hz, 1H), 1.25 (d, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.0, 148.3, 144.5, 141.0, 123.2, 106.6, 101.5, 100.6, 52.3, 36.8, 23.5, 21.7, 14.9; IR (neat cm^{-1}) 2965, 2929, 2903, 1682, 1609, 1501, 1253, 1047; HRMS (DART, M^++H) *m/z* 331.0005 (calculated for $C_{13}H_{16}BrO_3S$, 331.0004); *er* determination by LC CHIRALPAK AY-3 column (4.6 mm x 250 mm) with particle size 3 μm, mobile phase: 1.5% IPA / 98.5% Hexane with flow rate of 0.6 mL/min, retention time: 17.99 min (*S* isomer).

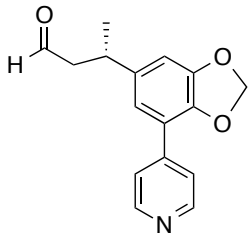
[5] Dry methylene chloride (2.5 mL) was added as a co-solvent to help dissolve unsaturated thioester **10** in MTBE.

Synthesis of 3*S*-(7-Pyridin-4-yl-benzo[1,3]dioxol-5-yl)-thiobutyric acid S-ethyl ester



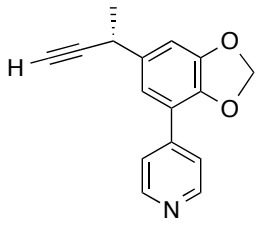
3*S*-(7-Pyridin-4-yl-benzo[1,3]dioxol-5-yl)-thiobutyric acid S-ethyl ester was obtained from 3*S*-(7-Bromo-benzo[1,3]dioxol-5-yl)-thiobutyric acid S-ethyl ester **15** (0.26 g, 0.79 mmol) following the general procedure C using $PdCl_2(PPh_3)_2$ as yellow solid (0.17 g, 66% yield); mp 104 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, *J* = 5.0 Hz, 2H), 7.62 (d, *J* = 5.0 Hz, 2H), 6.93 (s, 1H), 6.75 (s, 1H), 6.01 (s, 2H), 3.32 (sextet, *J* = 7.1 Hz, 1H), 2.82 (q, *J* = 7.1 Hz, 2H), 2.80 (dd, *J* = 15.0, 6.9 Hz, 1H), 2.74 (dd, *J* = 15.0, 6.9 Hz, 1H), 1.28 (d, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.1, 150.3, 148.7, 144.1, 143.4, 140.2, 122.2, 119.3, 118.8, 107.9, 101.4, 52.4, 37.1, 23.5, 21.9, 14.9; IR (neat cm^{-1}) 3028, 2965, 2929, 2903, 1681, 1596, 1403, 1197, 1049, 824; HRMS (DART, M^++H) *m/z* 330.1163 (calculated for $C_{18}H_{20}NO_3S$, 330.1164).

Synthesis of 3*S*-(7-Pyridin-4-yl-benzo[1,3]dioxol-5-yl)-butyraldehyde (20)



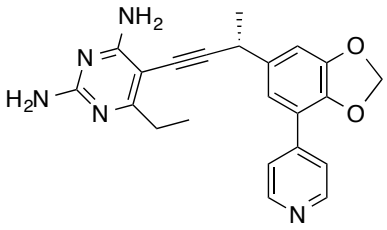
(S)-Aldehyde **20** was obtained from 3*S*-(7-Pyridin-4-yl-benzo[1,3]dioxol-5-yl)-thiobutyric acid S-ethyl ester (0.17 g, 0.52 mmol) following the general procedure D as yellow oil (0.11 g, 80% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (t, *J* = 1.9 Hz, 1H), 8.68 (br s, 2H), 7.65 (d, *J* = 5.1 Hz, 2H), 6.97 (d, *J* = 1.7 Hz, 1H), 6.80 (d, *J* = 1.7 Hz, 1H), 6.07 (s, 2H), 3.40 (sextet, *J* = 7.0 Hz, 1H), 2.78 (ddd, *J* = 16.8, 7.2, 1.8 Hz, 1H), 2.69 (ddd, *J* = 16.8, 7.1, 1.8 Hz, 1H), 1.35 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.4, 150.3, 148.9, 144.2, 143.4, 140.4, 122.2, 119.6, 118.8, 107.8, 101.5, 52.0, 34.4, 22.5; IR (neat cm^{-1}) 3028, 2962, 2894, 2825, 2721, 1719, 1595, 1402, 1195, 824; HRMS (DART, M^{+}+H) *m/z* 270.1122 (calculated for $C_{16}H_{16}NO_3$, 270.1130).

Synthesis of 4-[6-(1*R*-Methyl-prop-2-ynyl)-benzo[1,3]dioxol-4-yl]-pyridine (25)



To (S)-Aldehyde **20** (72 mg, 0.27 mmol) dissolved in DMF (2 mL) was added NfF (0.18 mL, 1.0 mmol) at -15 ^{o}C followed by the phosphazene base (0.45 mL, 1.5 mmol) and stirred vigorously at rt for 18 h. The reaction mixture was quenched with water (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 60:30) provided (R)-alkyne **25** as yellow solid (55 mg, 81 % yield); mp 63 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, *J* = 5.0 Hz, 2H), 7.67 (d, *J* = 5. 0 Hz, 2H); 7.16 (s, 1H), 6.98 (s, 1H), 6.08 (s, 2H), 3.78 (dq, *J* = 7.5, 2.4 Hz, 1H), 2.33 (d, *J* = 2.4 Hz, 1H), 1.55 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.3, 148.8, 144.5, 143.4, 137.6, 122.3, 119.4, 118.8, 108.2, 101.6, 86.9, 70.8, 31.7, 24.5; IR (neat cm^{-1}) 3294, 2976, 2897, 1675, 1597, 1403, 1197, 1044, 825; HRMS (DART, M^{+}+H) *m/z* 252.1020 (calculated for $C_{16}H_{14}NO_2$, 252.1025); *er* determination by LC CHIRALCEL OJ column (0.46 cm x 25 cm), mobile phase: 2.5% IPA / 98.5% Hexane with flow rate of 1.5 mL/min, retention time: 45.98 min (*R* isomer).

Synthesis of 6-Ethyl-5-[3*R*-(7-pyridin-4-yl-benzo[1,3]dioxol-5-yl)-but-1-ynyl]-pyrimidine-2,4-diamine (30)



To (R)-alkyne **25** (51 mg, 0.20 mmol), iodo-ethyl pyrimidine (59 mg, 0.22 mmol), CuI (7.7 mg, 0.040 mmol), and $PdCl_2(PPh_3)_2$ (14 mg, 0.020 mmol) was added followed by DMF (1.5 mL) and NEt_3 (1.5 mL) and stirred at 70 ^{0}C for 12h. The reaction mixture was concentrated by azeotroping with toluene and purified by gradient flash chromatography (EtOAc followed 2% to 10% MeOH in CH_2Cl_2) to yield coupled pyrimidine **30** as pale yellow solid (54 mg, 70%). An analytical sample was purified using NH_2-capped spherical silica gel followed by normal phase silica gel for biological studies; mp 148-150 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, *J* = 5.0 Hz, 2H), 7.67 (d, *J* = 5.0 Hz, 2H), 7.19 (s, 1H), 7.00 (s, 1H), 6.09 (s, 2H), 5.21 (br s, 2H), 4.99 (br s, 2H), 4.05 (q, *J* = 7.0 Hz, 1H), 2.72 (q, *J* = 7.5 Hz, 2H), 1.62 (d, *J* = 7.0 Hz, 3H), 1.25 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 164.4, 160.9, 150.4, 148.9, 144.5, 143.3, 138.3, 122.2, 119.5, 118.7, 108.1, 101.6, 101.4, 90.5, 75.9, 33.1, 29.9, 25.1, 12.7; IR (neat cm^{-1}) 3469, 3310, 3165, 2975, 1598, 1570, 1545, 1438, 1044; HRMS (DART, M^++H) *m/z* 388.1761 (calculated for $C_{22}H_{22}N_5O_2$, 388.1773).

==== Shimadzu LCsolution Analysis Report ====

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Sample ID	: skk-nb1-162
Tray#	: 1
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Batch File Name	:
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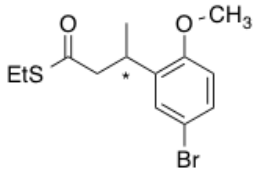
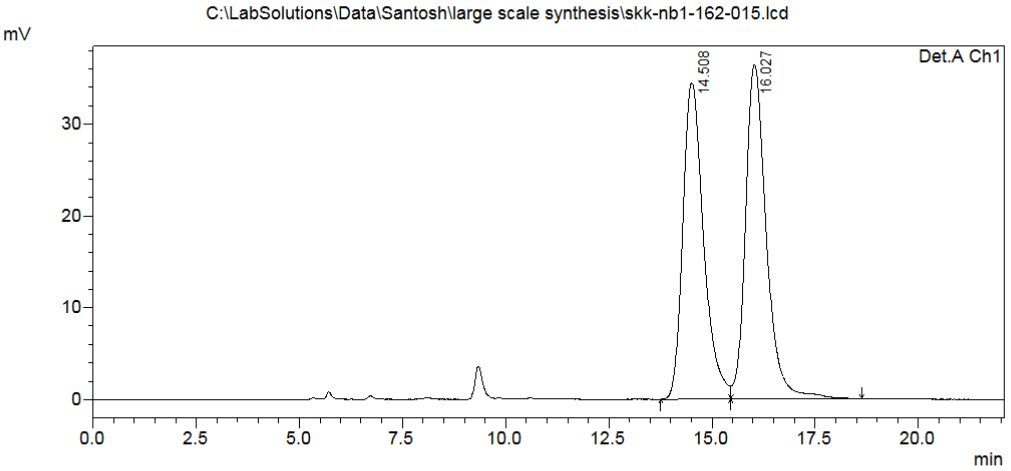


rac-11



1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

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2	16.027	1277364	36403	51.401	51.389
Total		2485092	70837	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

Sample Information

Acquired by	: Admin
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Sample ID	: skk-nb2-119
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Vail#	: 22
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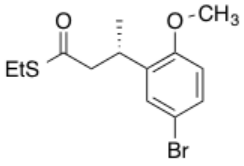

(S)-11

Chromatogram

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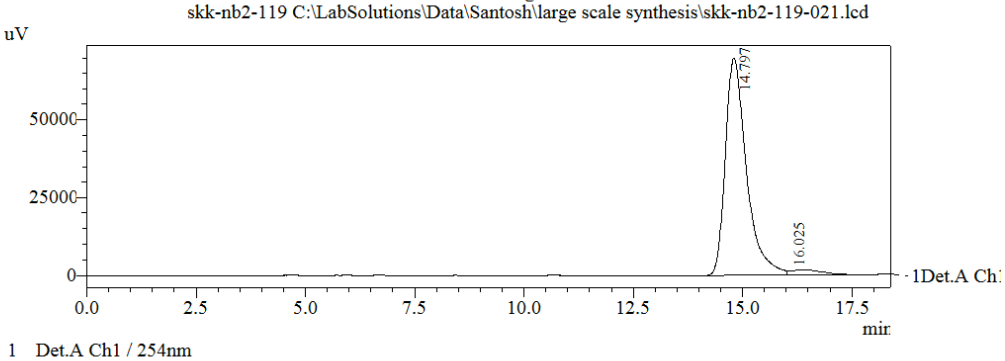

1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
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2	16.025	61855	1315	2.565	1.845
Total		2411781	71261	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Santosh\dioxolane thioester racemic\dioxolane racemic thioester-007.lcd

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Sample ID	: skk-dioxolane thioester racemic
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Vail #	: 53
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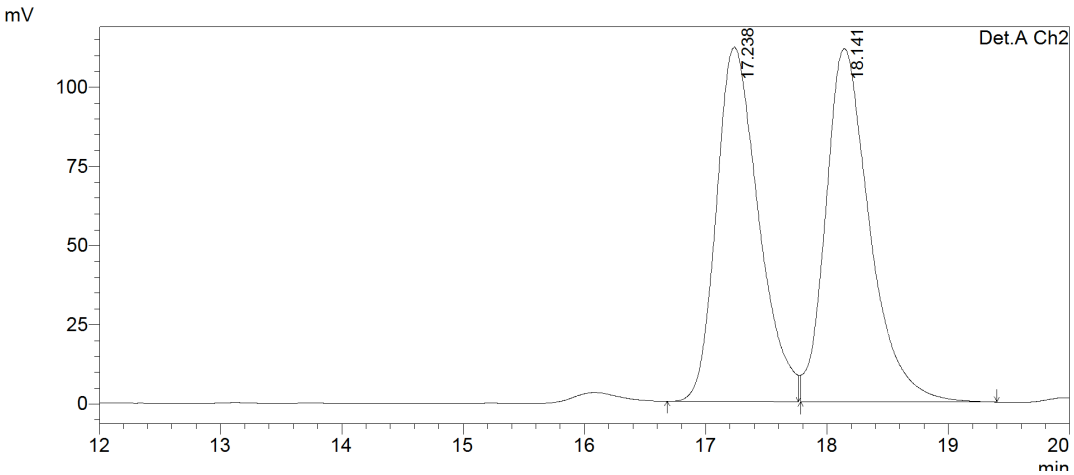

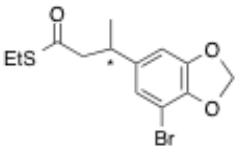

rac-15

PeakTable

Detector A Ch2 240nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	17.238	2706046	111786	49.070	50.064
2	18.141	2808584	111498	50.930	49.936
Total		5514630	223284	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Santosh\dioxolane thioester racemic\skk-b3-003-s,r-josiphos-011.lcd

Acquired by	: Admin
Sample Name	: skk-dioxolane thioester chiral
Sample ID	: skk-nb3-016
Tray#	: 1
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Injection Volume	: 5 uL
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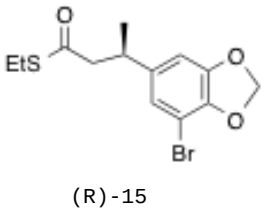
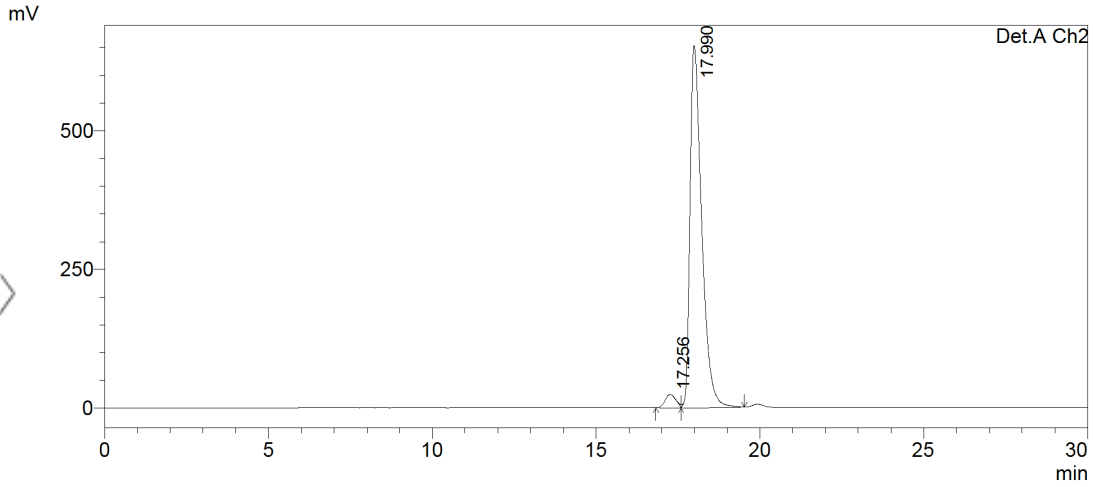


(R)-15



PeakTable

Detector A Ch2 240nm

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2	17.990	16087066	653037	96.679	96.363
Total		16639710	677685	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Santosh\alkyne files\chiral HPLC files 1040 and 1006\racemic nb2-036.lcd

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Sample Name	: skk-nb2-35-racemic
Sample ID	: racemic nb2-35
Tray#	: 1
Vail #	: 64
Injection Volume	: 4 uL
Data File Name	: racemic nb2-036.lcd
Method File Name	: Test.lcm
Batch File Name	:
Report File Name	: Default.lcr
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Data Processed	: 3/15/2013 2:14:00 PM

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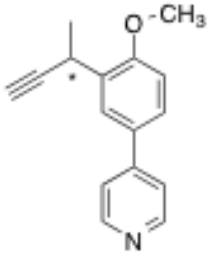
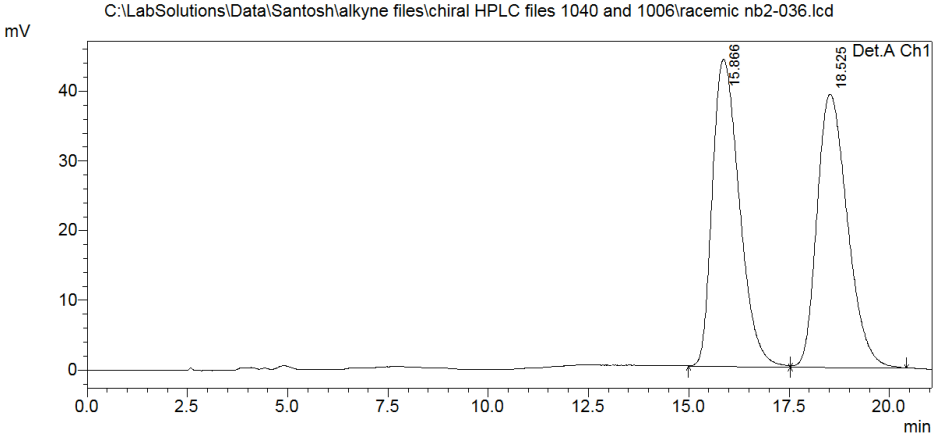


rac-21



Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.866	2066802	44043	49.993	52.922
2	18.525	2067345	39180	50.007	47.078
Total		4134147	83223	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Santosh\alkyne files\chiral 169.lcd

Acquired by	: Admin
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Sample ID	: chiral alkyne 169
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Vail #	: 62
Injection Volume	: 1 uL
Data File Name	: chiral 169.lcd
Method File Name	: Test.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 12/13/2012 7:00:52 PM
Data Processed	: 12/13/2012 7:29:20 PM

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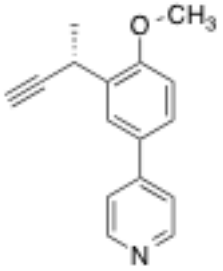
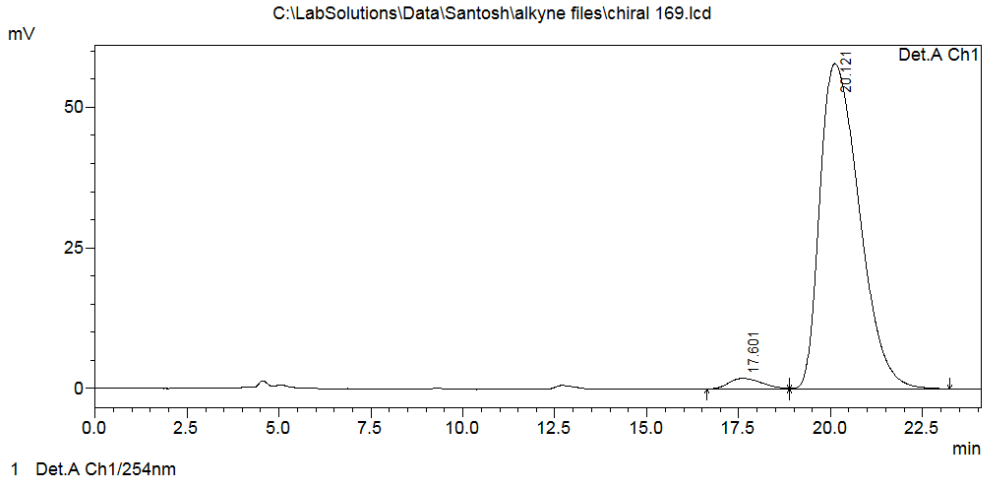


(S)-21



1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	17.601	117211	1908	2.642	3.193
2	20.121	4318732	57856	97.358	96.807
Total		4435943	59765	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Santosh\skk-nb2-94 with S,R josiphos-004.lcd

Acquired by	: Admin
Sample Name	: skk-nb2-94
Sample ID	: chiral 1040 with S,R -josiphos
Tray#	: 1
Vail #	: 43
Injection Volume	: 3 uL
Data File Name	: skk-nb2-94 with S,R josiphos-004.lcd
Method File Name	: Test.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 7/21/2013 1:42:36 PM
Data Processed	: 8/5/2013 4:16:02 PM

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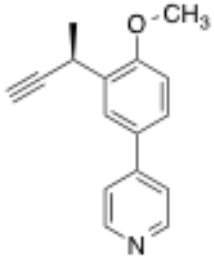
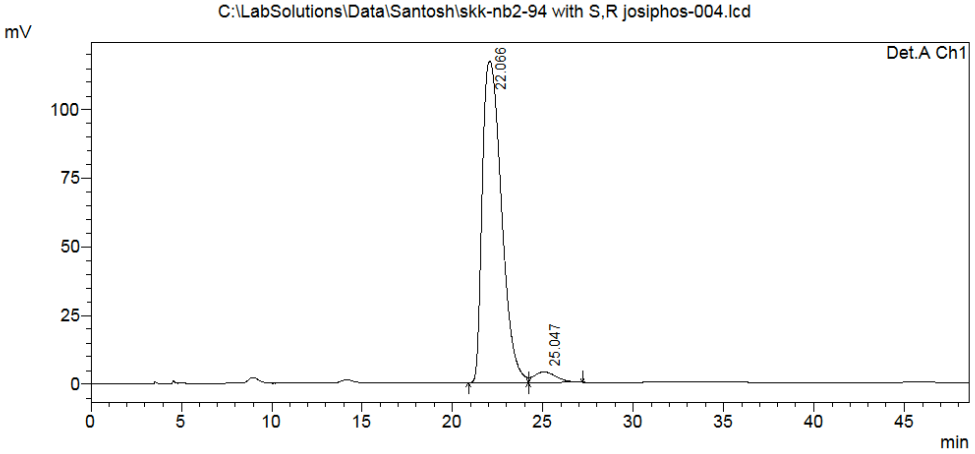


(R)-21



1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	22.066	8568919	117159	96.248	96.745
2	25.047	334026	3942	3.752	3.255
Total		8902945	121101	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Santosh\alkyne files\chiral HPLC files 1040 and 1006\racemic nb2-44-SR josiphos002.lcd

Acquired by	: Admin
Sample Name	: racemic 1006
Sample ID	: racemic 1006
Tray#	: 1
Vail #	: 66
Injection Volume	: 5 uL
Data File Name	: racemic nb2-44-SR josiphos002.lcd
Method File Name	: Test.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 4/1/2013 4:21:52 PM
Data Processed	: 6/26/2013 2:56:22 PM

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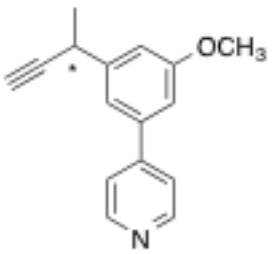
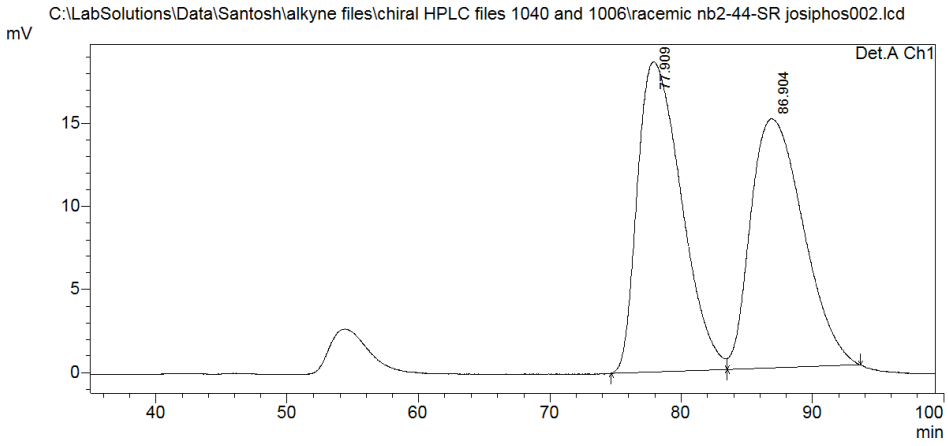


rac-22



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	77.909	4341179	18652	50.887	55.482
2	86.904	4189867	14966	49.113	44.518
Total		8531046	33619	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Santosh\alkyne files\chiral HPLC files 1040 and 1006\chiral nb2-44-SR josiphos001.lcd

Acquired by	: Admin
Sample Name	: skk-nb2-44
Sample ID	: skk-nb2-44
Tray#	: 1
Vail #	: 65
Injection Volume	: 2 uL
Data File Name	: chiral nb2-44-SR josiphos001.lcd
Method File Name	: Test.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 4/1/2013 12:38:28 PM
Data Processed	: 6/26/2013 2:59:46 PM

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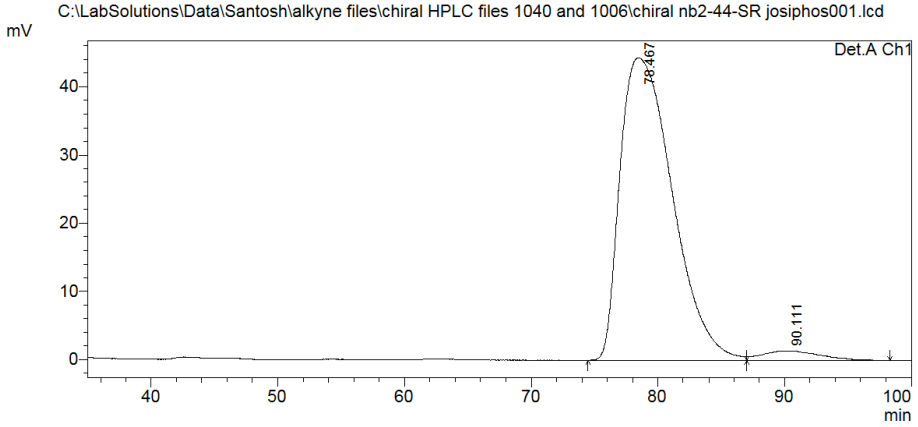
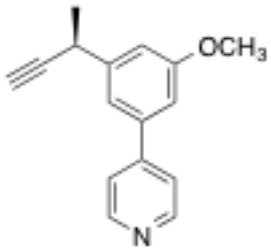
C:\LabSolutions\Data\Santosh\alkyne files\chiral HPLC files 1040 and 1006\chiral nb2-44-SR josiphos001.lcd





(S)-22

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	78.467	12756133	44334	96.642	96.992
2	90.111	443234	1375	3.358	3.008
Total		13199367	45709	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Santosh\alkyne files\chiral HPLC files 1040 and 1006\chiral skk nb2-46 r,s josiphos001.lcd

Acquired by	: Admin
Sample Name	: skk-nb2-46
Sample ID	: skk-nb2-46
Tray#	: 1
Vail #	: 67
Injection Volume	: 5 uL
Data File Name	: chiral skk nb2-46 r,s josiphos001.lcd
Method File Name	: Test.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 4/4/2013 3:01:50 PM
Data Processed	: 6/26/2013 3:16:41 PM

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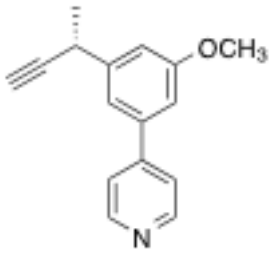
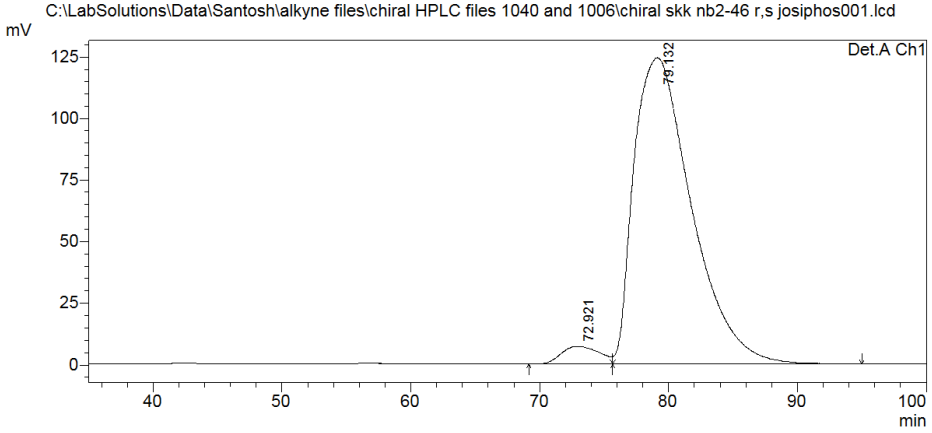


(R)-22



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	72.921	1506707	7227	3.746	5.495
2	79.132	38716406	124298	96.254	94.505
Total		40223113	131525	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Santosh\racemic dimethoxy naren 001.lcd

Acquired by	: Admin
Sample Name	: racemic dimethoxy naren
Sample ID	: racemic dimethoxy naren
Tray#	: 1
Vail #	: 31
Injection Volume	: 3 uL
Data File Name	: racemic dimethoxy naren 001.lcd
Method File Name	: Test.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 9/9/2013 4:19:23 PM
Data Processed	: 9/9/2013 4:48:52 PM

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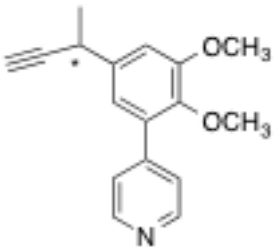
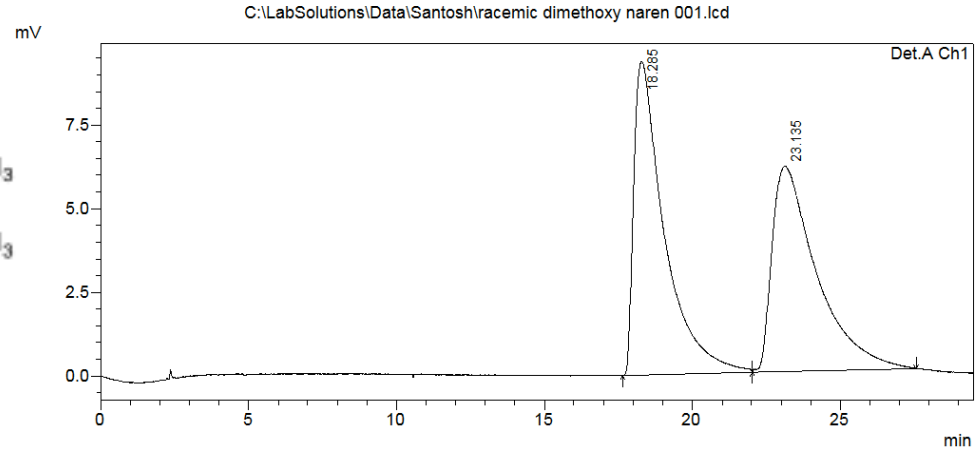


rac-23



1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	18.285	671523	9365	51.013	60.416
2	23.135	644862	6136	48.987	39.584
Total		1316385	15502	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Santosh\skk-nb2-83-chiral-002.lcd

Acquired by	: Admin
Sample Name	: chiral nb2-83
Sample ID	: chiral nb2-83
Tray#	: 1
Vail #	: 33
Injection Volume	: 40 uL
Data File Name	: skk-nb2-83-chiral-002.lcd
Method File Name	: Test.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 9/9/2013 6:24:07 PM
Data Processed	: 9/10/2013 1:27:07 PM

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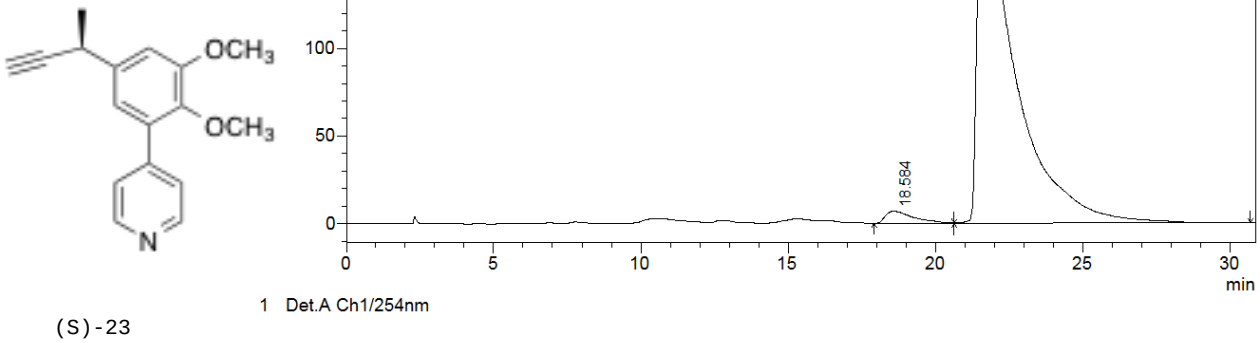

1 Det.A Ch1/254nm

(S)-23

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	18.584	448539	6839	2.550	3.476
2	21.666	17139704	189878	97.450	96.524
Total		17588243	196717	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Santosh\skk-nb2-81-chiral-003.lcd

Acquired by	: Admin
Sample Name	: chiral nb2-81
Sample ID	: chiral nb2-81
Tray#	: 1
Vail #	: 32
Injection Volume	: 3 uL
Data File Name	: skk-nb2-81-chiral-003.lcd
Method File Name	: Test.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 9/9/2013 6:56:03 PM
Data Processed	: 9/10/2013 1:15:11 PM

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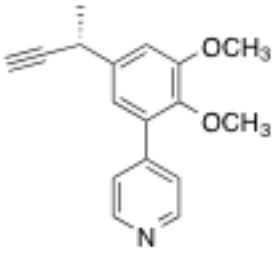
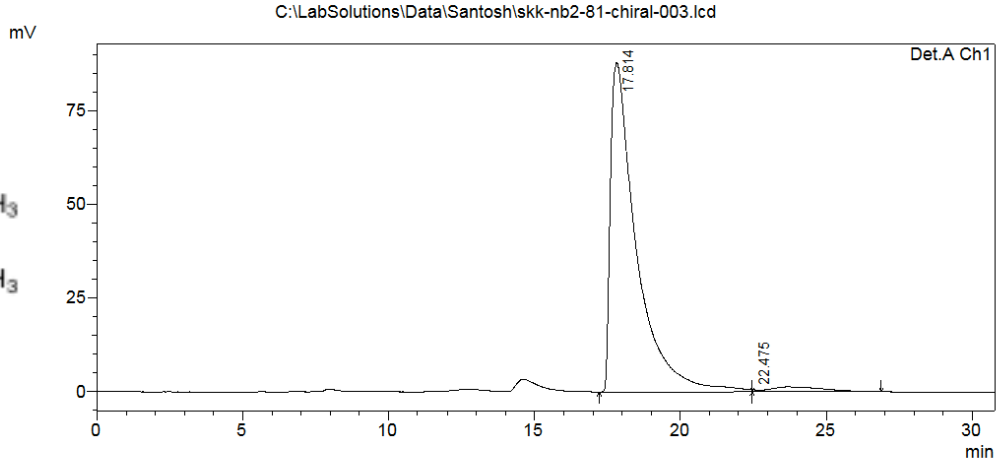


(R)-23



1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	17.814	5444015	88075	98.777	99.360
2	22.475	67409	567	1.223	0.640
Total		5511424	88642	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Santosh\alkyne files\racemic dioxolane alkyne.lcd

Acquired by	: Admin
Sample Name	: skk-nb1-racemic dioxolane-1038
Sample ID	: skk-nb1-racemic dioxolane-1038
Tray#	: 1
Vail #	: 51
Injection Volume	: 2 uL
Data File Name	: racemic dioxolane alkyne.lcd
Method File Name	: Test.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 1/15/2013 2:56:31 PM
Data Processed	: 1/15/2013 4:04:23 PM

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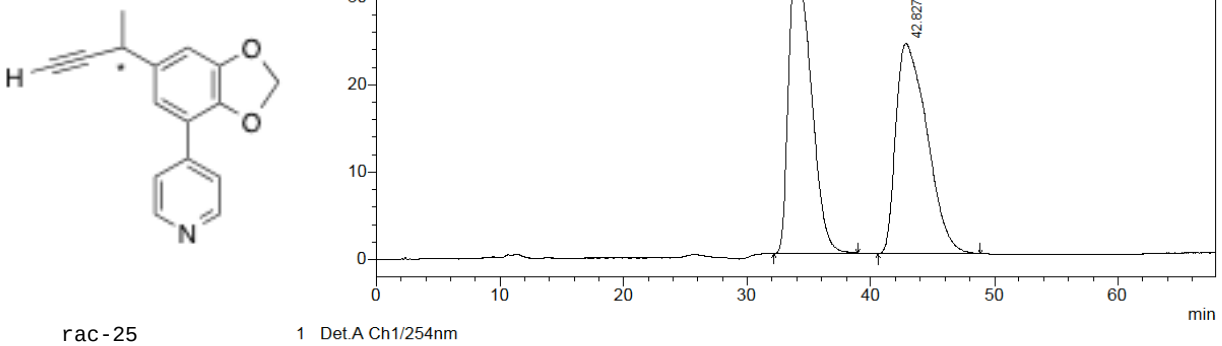
C:\LabSolutions\Data\Santosh\alkyne files\racemic dioxolane alkyne.lcd



rac-25

1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	33.966	4258346	34553	50.206	58.940
2	42.827	4223420	24071	49.794	41.060
Total		8481766	58625	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Santosh\skk-nb3-005-001.lcd

Acquired by	: Admin
Sample Name	: skk-nb3-005
Sample ID	: skk-nb3-005
Tray#	: 1
Vail #	: 27
Injection Volume	: 2 uL
Data File Name	: skk-nb3-005-001.lcd
Method File Name	: Test.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 12/11/2013 6:49:10 PM
Data Processed	: 12/11/2013 7:46:13 PM

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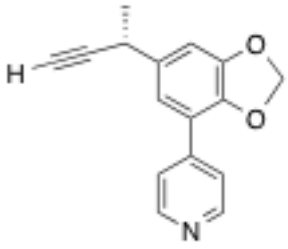
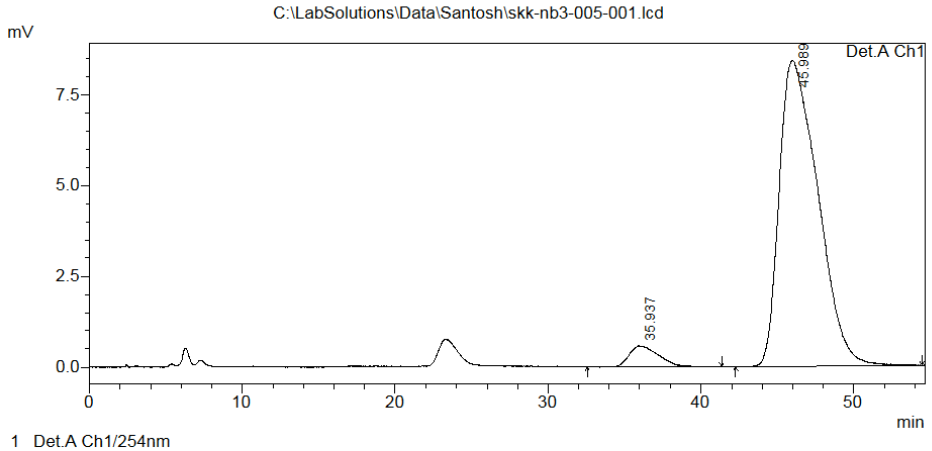


(R)-25



1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	35.937	76924	579	4.926	6.424
2	45.989	1484570	8433	95.074	93.576
Total		1561494	9012	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Santosh\dioxolane files\skk-nb3-19-002.lcd

Acquired by	: Admin
Sample Name	: skk-nb3-19
Sample ID	: skk-nb3-19
Tray#	: 1
Vail #	: 45
Injection Volume	: 5 uL
Data File Name	: skk-nb3-19-002.lcd
Method File Name	: Test.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 12/27/2013 2:10:43 PM
Data Processed	: 1/8/2014 2:15:47 PM

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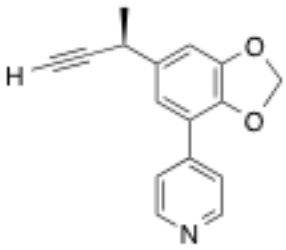
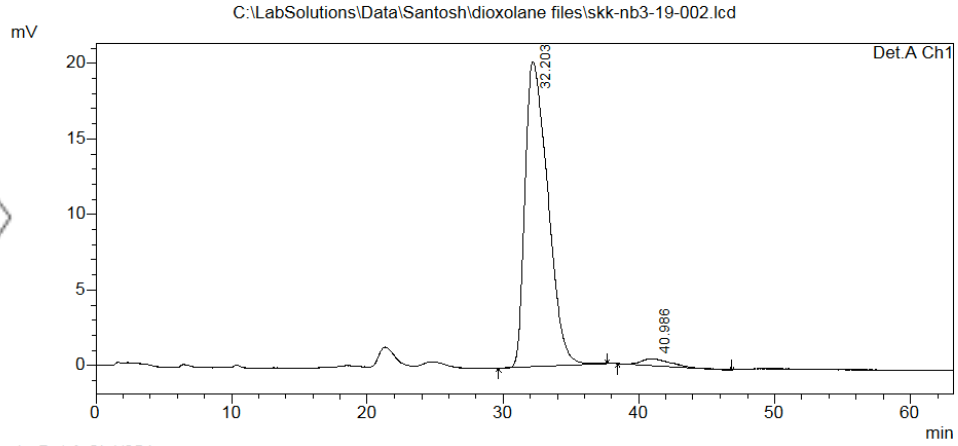


(S)-25



1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	32.203	2354190	20190	96.965	97.759
2	40.986	73697	463	3.035	2.241
Total		2427887	20652	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Santosh\4-methoxy chiral compunds\skk-nb3-11 and 013-013.lcd

Acquired by	: Admin
Sample Name	: skk-nb3-11+13
Sample ID	: skk-nb3-11+13
Tray#	: 1
Vail #	: 41
Injection Volume	: 2 uL
Data File Name	: skk-nb3-11 and 013-013.lcd
Method File Name	: Test.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 12/24/2013 12:38:14 PM
Data Processed	: 12/24/2013 1:45:50 PM

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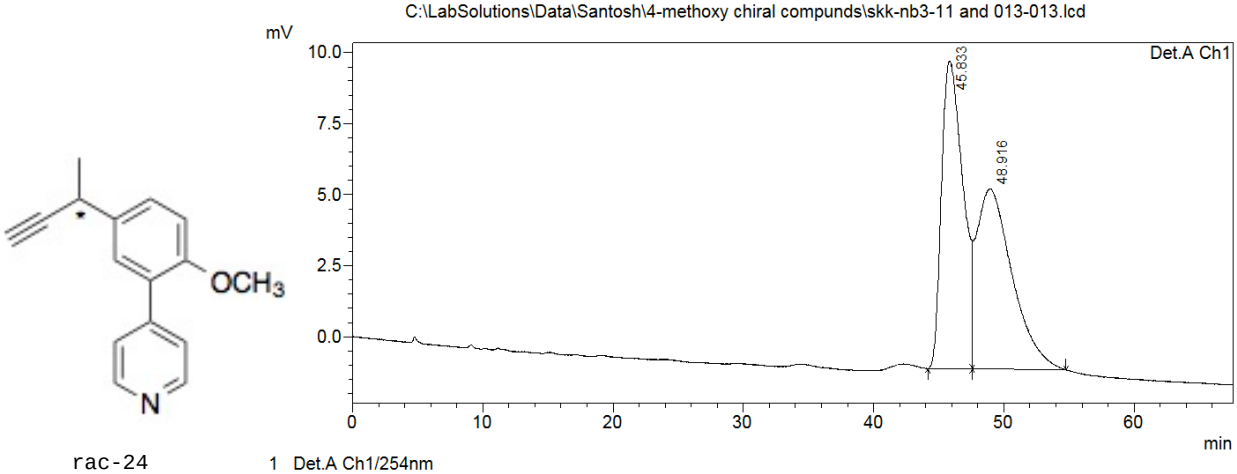
C:\LabSolutions\Data\Santosh\4-methoxy chiral compunds\skk-nb3-11 and 013-013.lcd



rac-24

1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	45.833	1247237	10827	50.783	63.023
2	48.916	1208786	6352	49.217	36.977
Total		2456023	17179	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Santosh\4-methoxy chiral compunds\skk-nb3-13-002.lcd

Acquired by	: Admin
Sample Name	: skk-nb3-13
Sample ID	: skk-nb3-13
Tray#	: 1
Vail #	: 43
Injection Volume	: 2 uL
Data File Name	: skk-nb3-13-002.lcd
Method File Name	: Test.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 12/24/2013 5:39:25 PM
Data Processed	: 12/24/2013 7:09:29 PM

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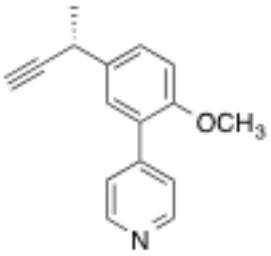
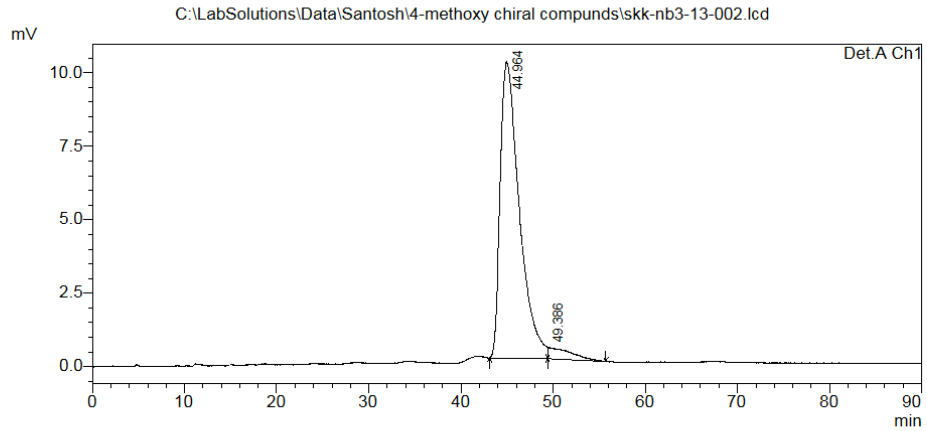


(R)-24



1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	44.964	1451333	10080	95.270	96.163
2	49.386	72052	402	4.730	3.837
Total		1523385	10482	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Santosh\4-methoxy chiral compunds\skk-nb3-11-002.lcd

Acquired by	: Admin
Sample Name	: skk-nb3-11
Sample ID	: skk-nb3-11
Tray#	: 1
Vail #	: 42
Injection Volume	: 2 uL
Data File Name	: skk-nb3-11-002.lcd
Method File Name	: Test.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 12/24/2013 4:14:09 PM
Data Processed	: 12/24/2013 5:38:37 PM

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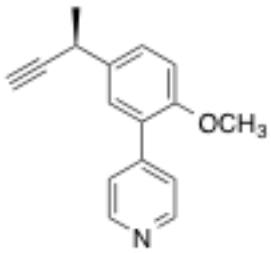
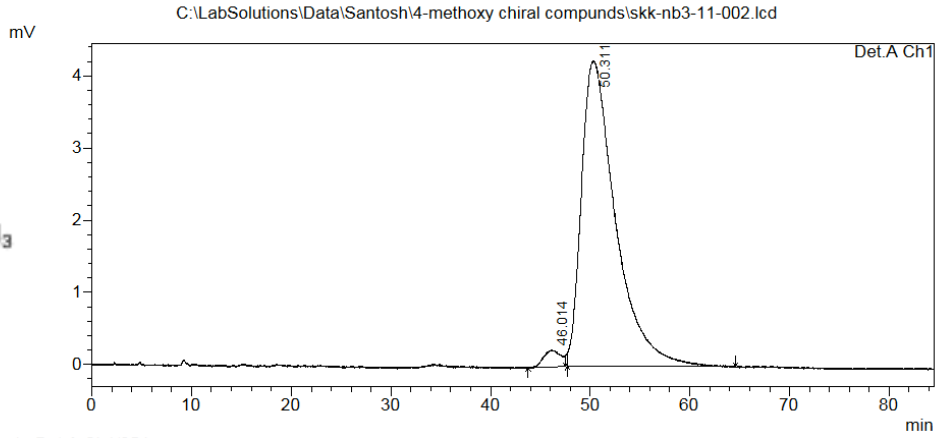


(S)-24

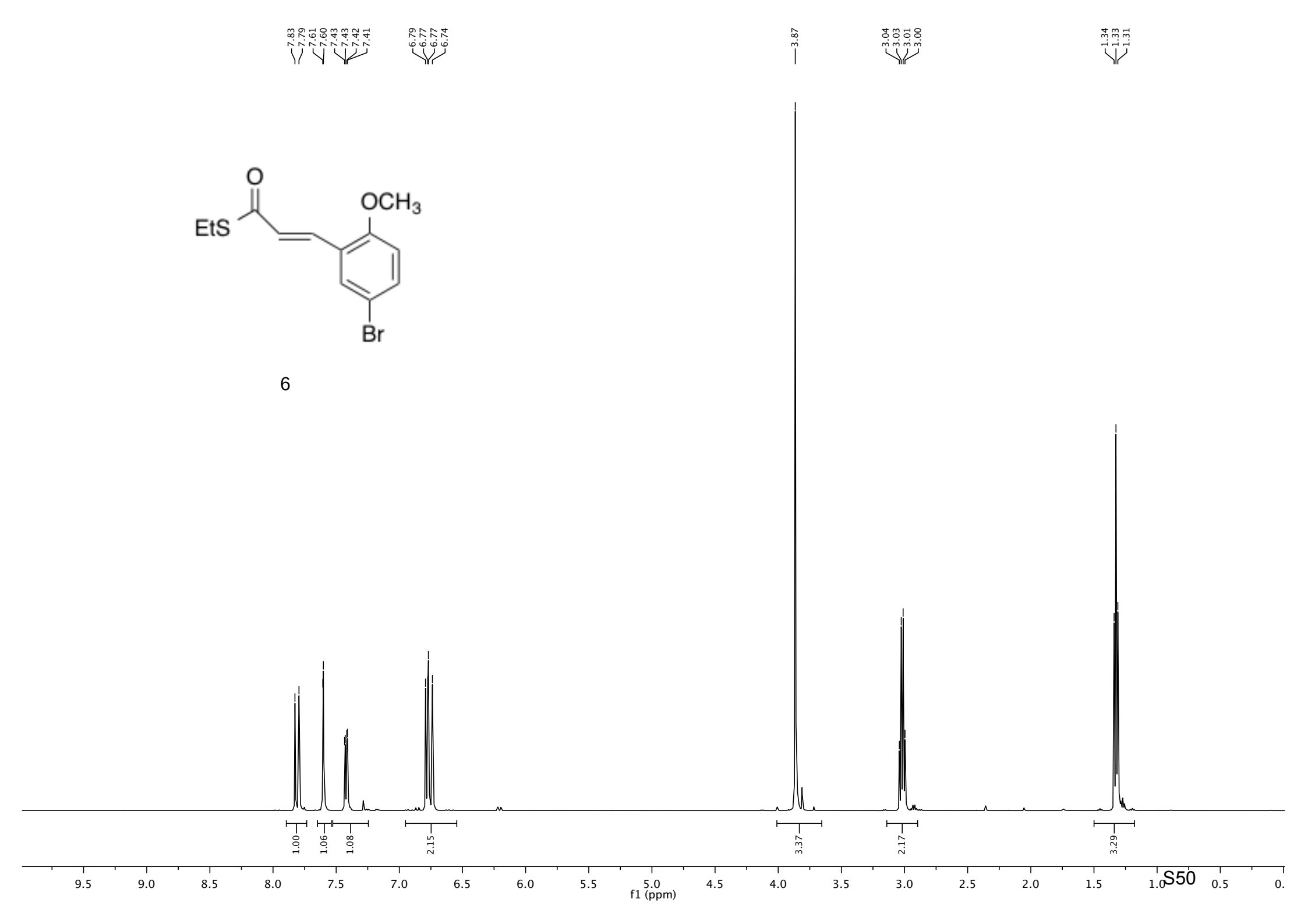


1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	46.014	27436	230	2.659	5.164
2	50.311	1004401	4226	97.341	94.836
Total		1031838	4456	100.000	100.000


7.83
7.79
7.61
7.60
7.43
7.43
7.42
7.41
6.79
6.77
6.77
6.74
3.87
3.04
3.03
3.01
3.00
1.34
1.33
1.31
O
EtS
OCH3
Br
6
1.00
1.06
1.08
2.15
3.37
2.17
3.29
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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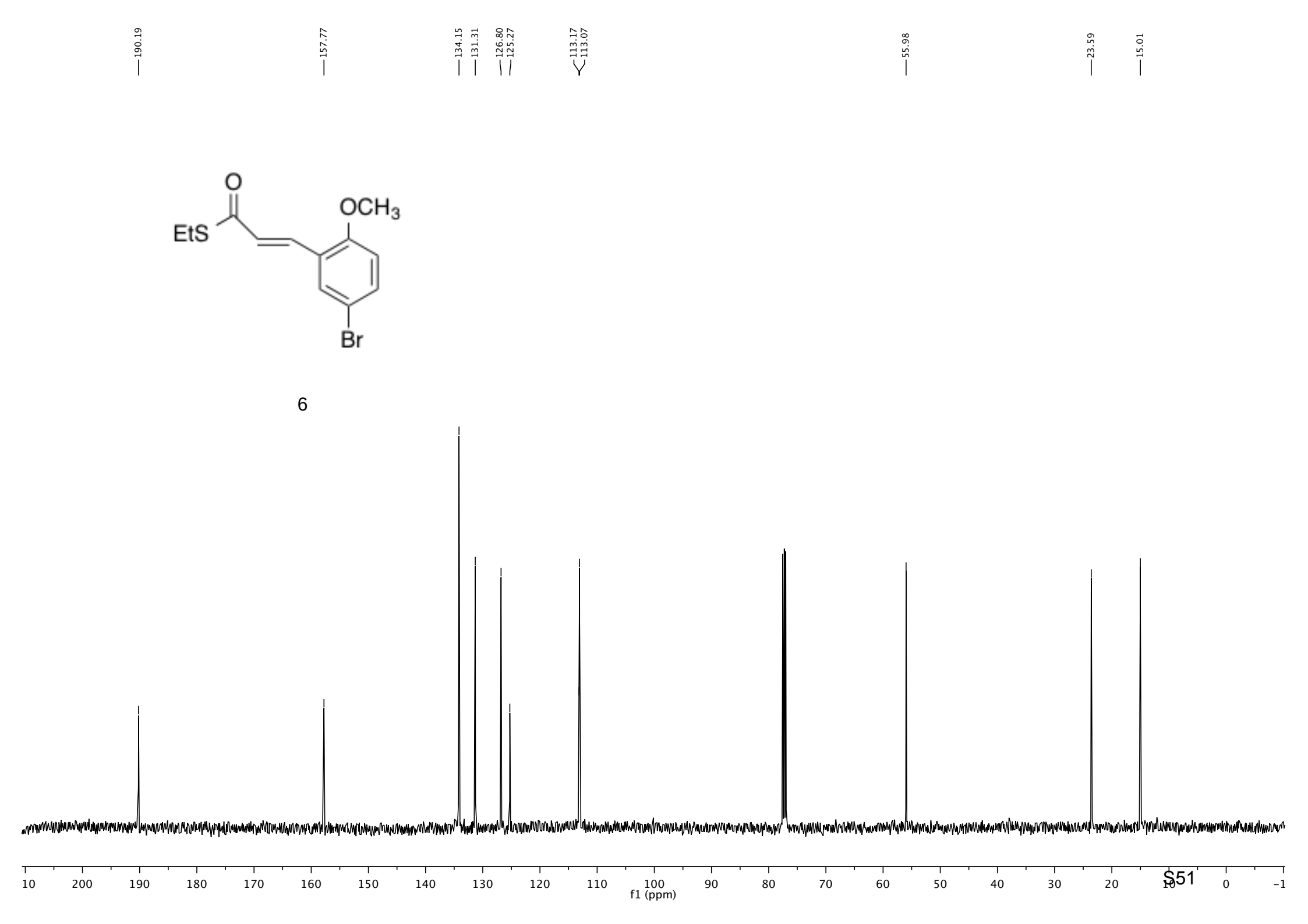
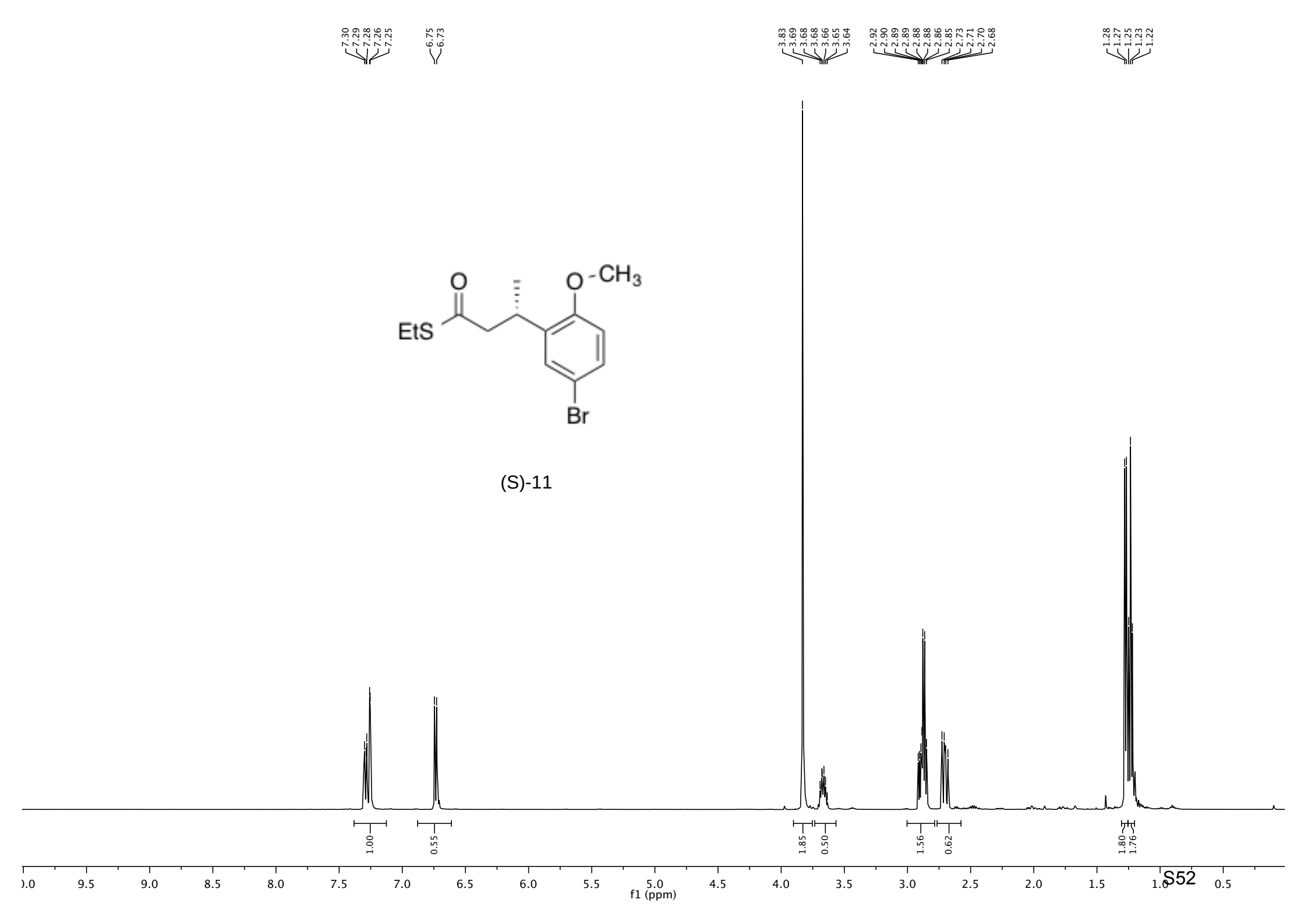
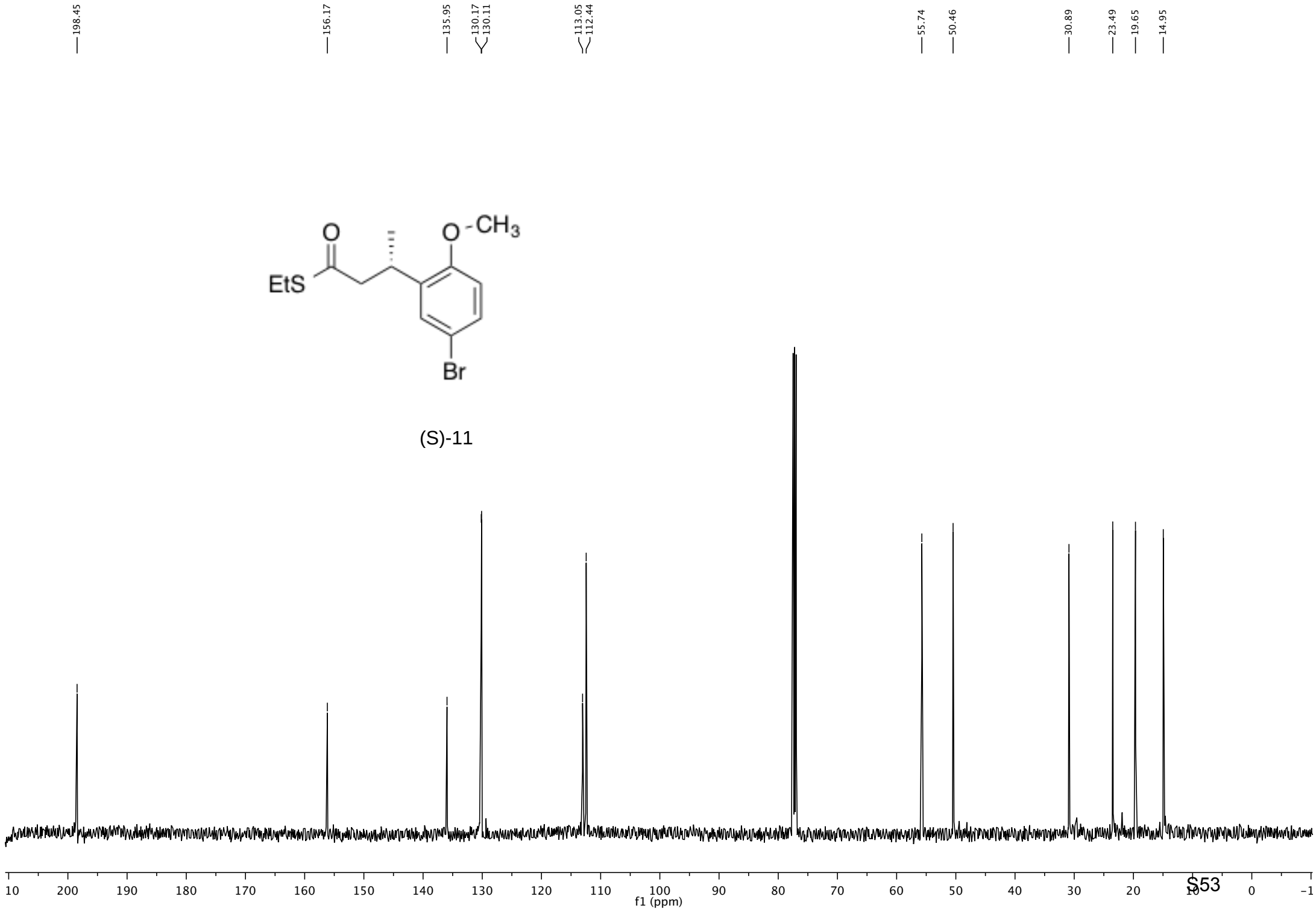
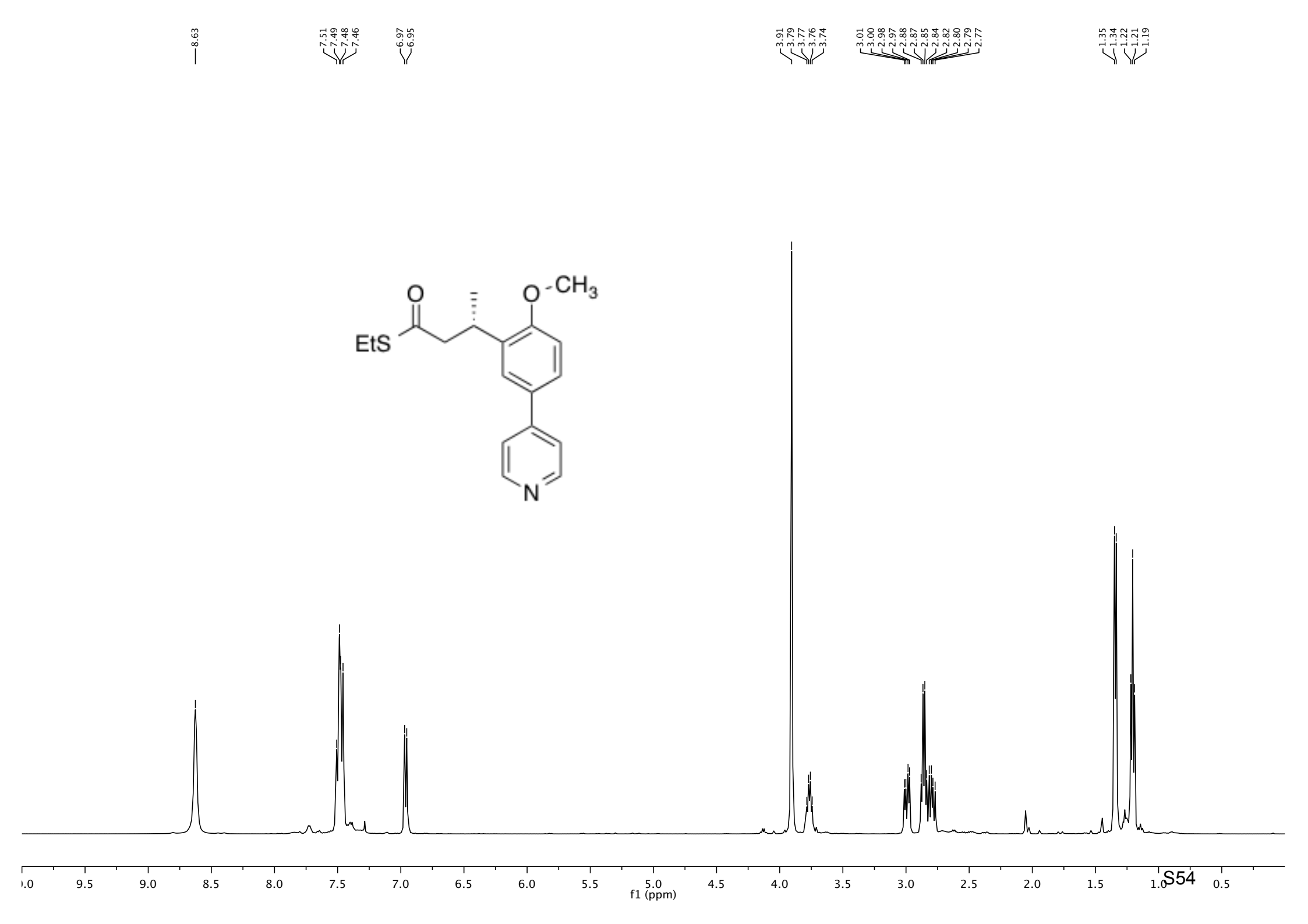
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.
f1 (ppm)

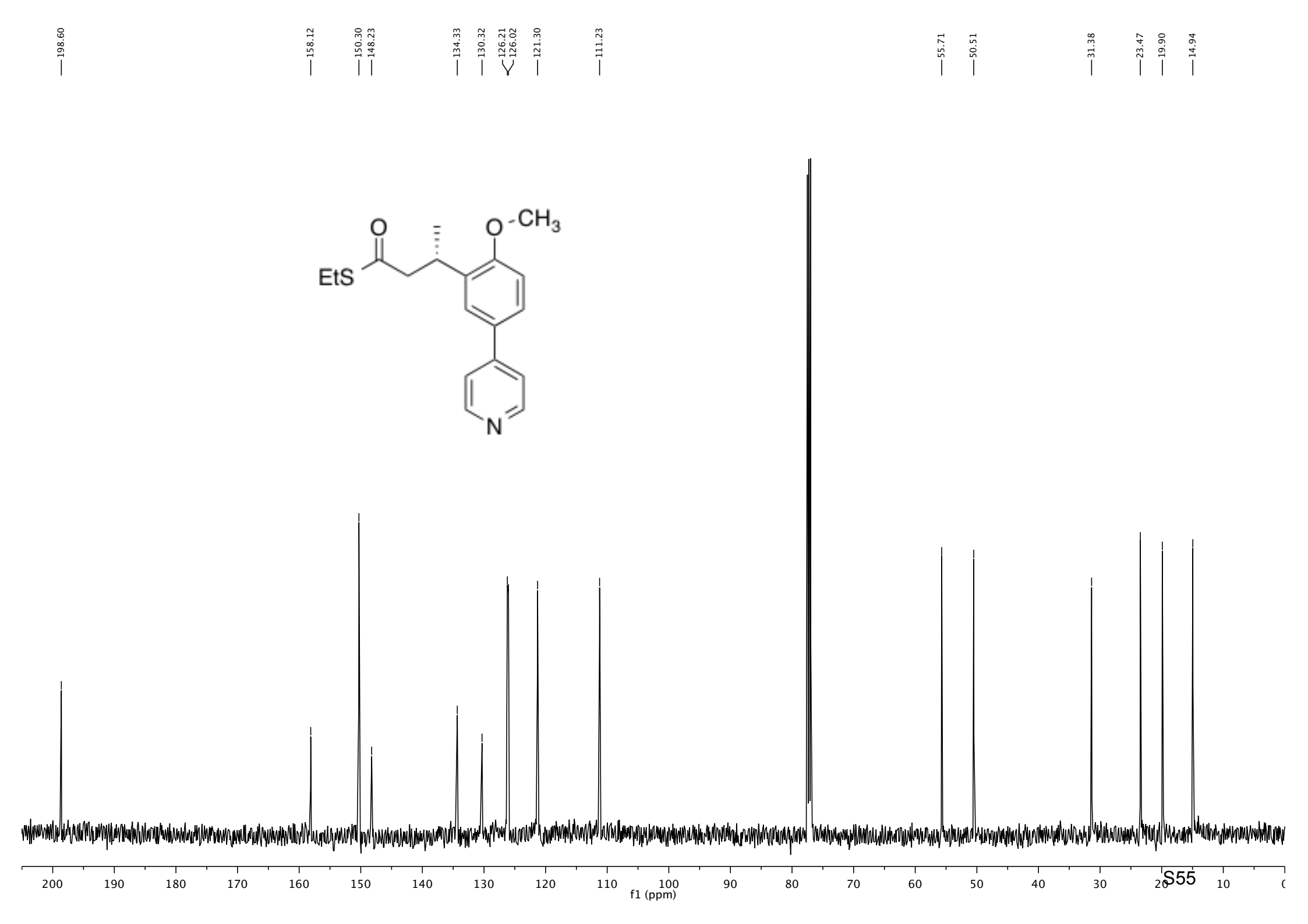

190.19
157.77
134.15
131.31
126.80
125.27
113.17
113.07
55.98
23.59
15.01
O
EtS
OCH3
Br
6
f1 (ppm)

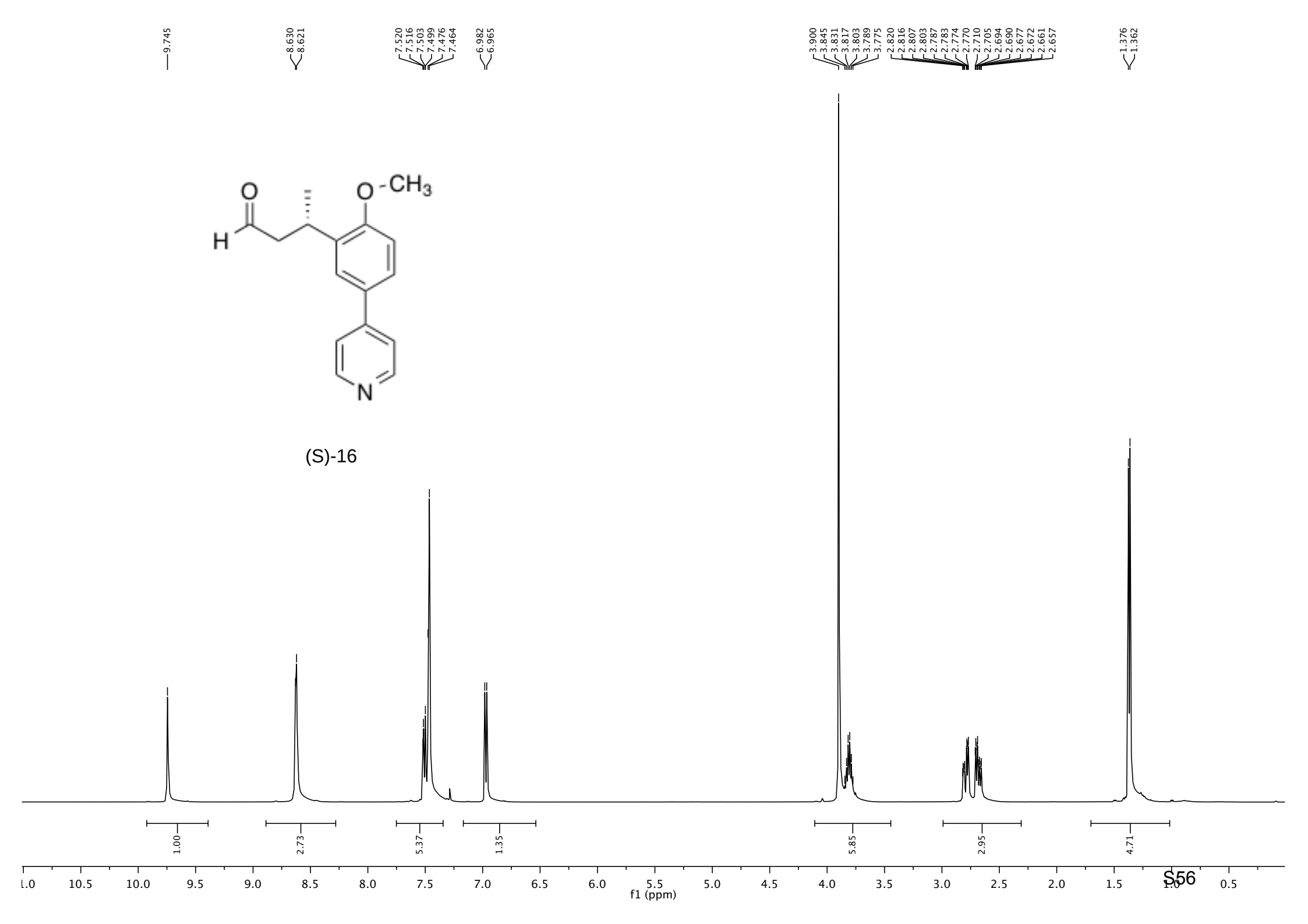

7.30
7.29
7.28
7.26
7.25
6.75
6.73
3.83
3.69
3.68
3.68
3.66
3.65
3.64
2.92
2.90
2.89
2.89
2.88
2.88
2.86
2.85
2.73
2.71
2.70
2.68
1.28
1.27
1.25
1.23
1.22
O
O
CH3
EtS
Br
(S)-11
1.00
0.55
1.85
0.50
1.56
0.62
1.80
1.76
f1 (ppm)

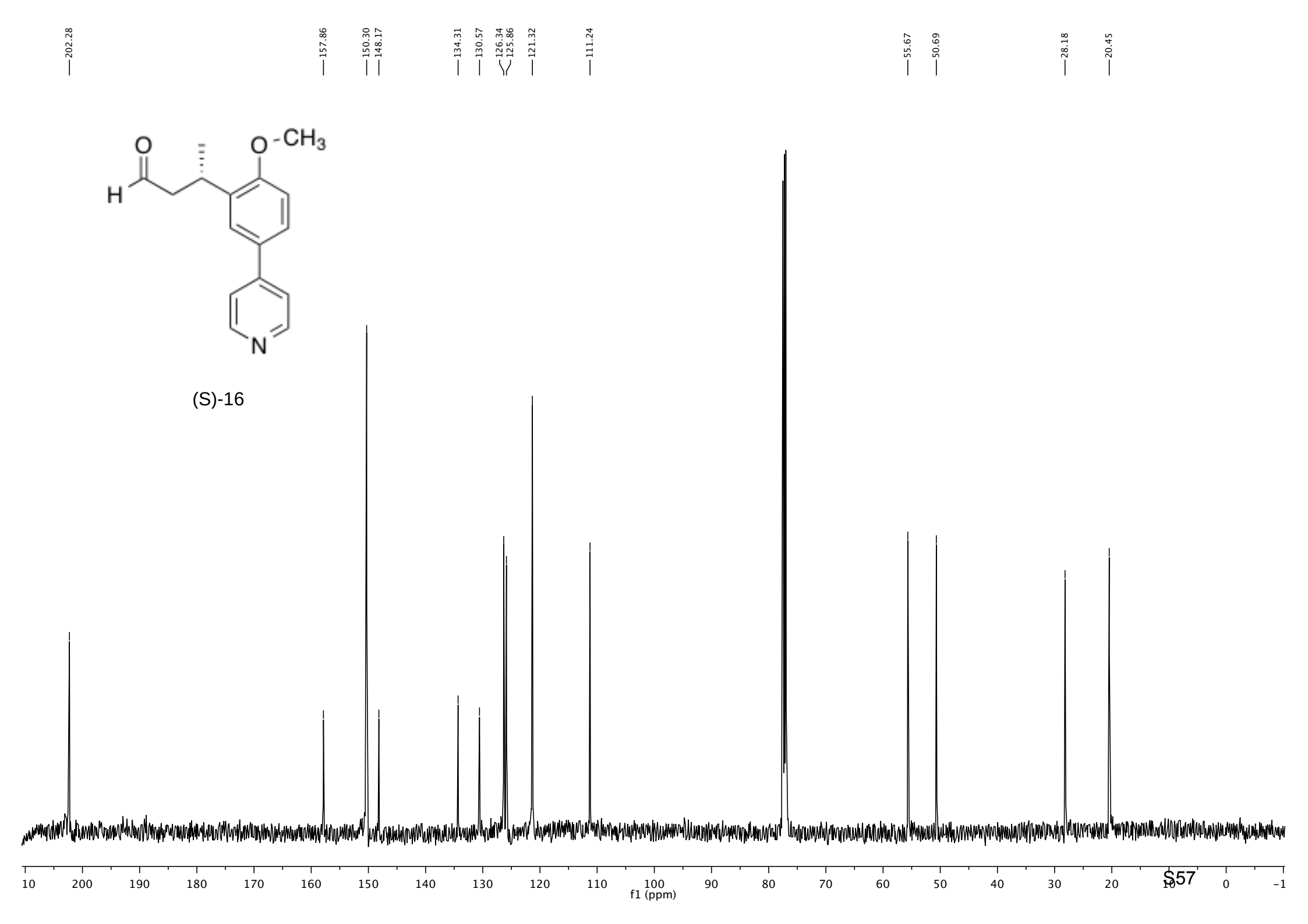

198.45
156.17
135.95
130.17
130.11
113.05
112.44
55.74
50.46
30.89
23.49
19.65
14.95
O
O
CH3
EtS
Br
f1 (ppm)

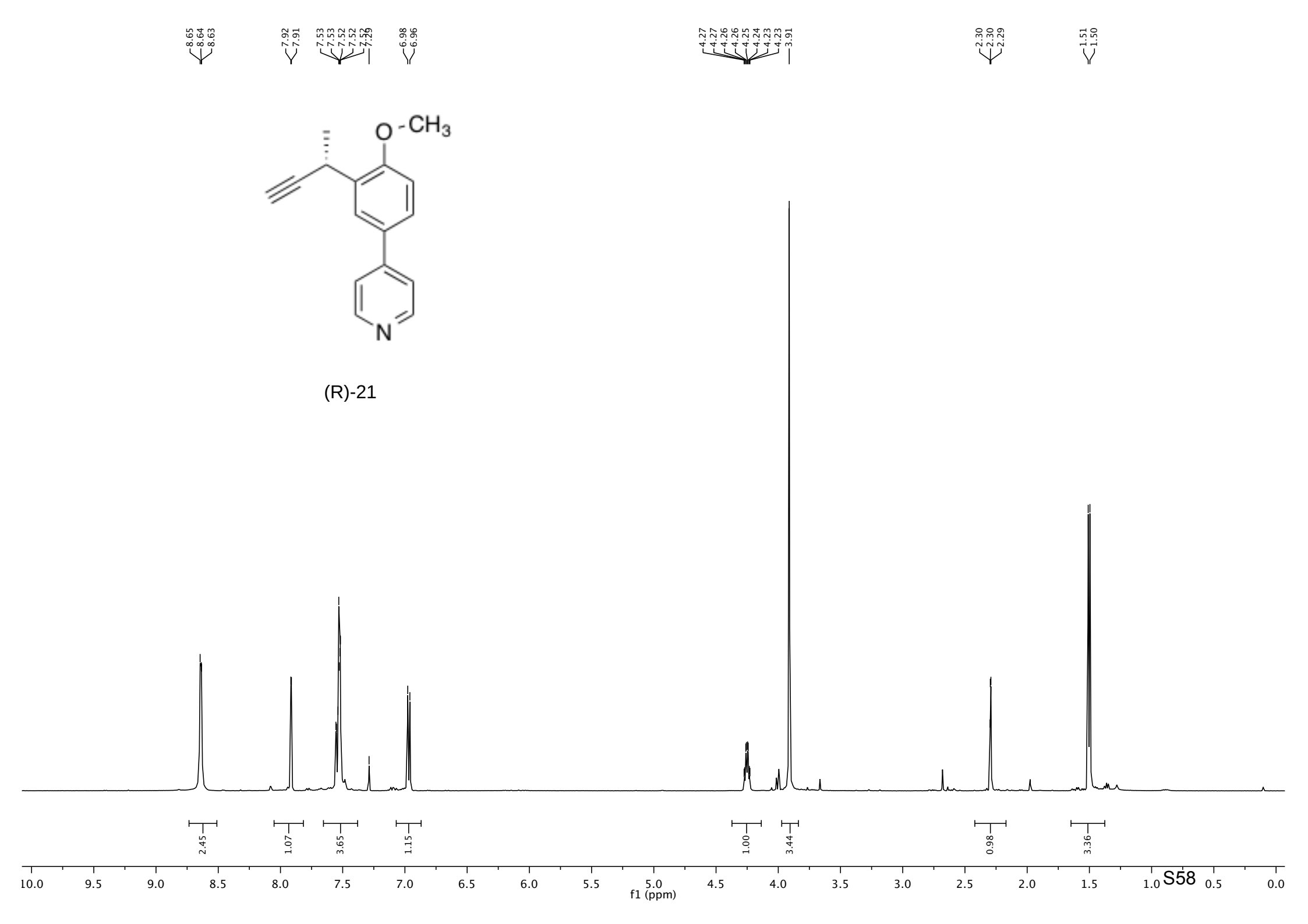
(S)-11


8.63
7.51
7.49
7.48
7.46
6.97
6.95
3.91
3.79
3.77
3.76
3.74
3.01
3.00
2.98
2.97
2.88
2.87
2.85
2.84
2.82
2.80
2.79
2.77
1.35
1.34
1.22
1.21
1.19
O
O
CH3
EtS
N
f1 (ppm)

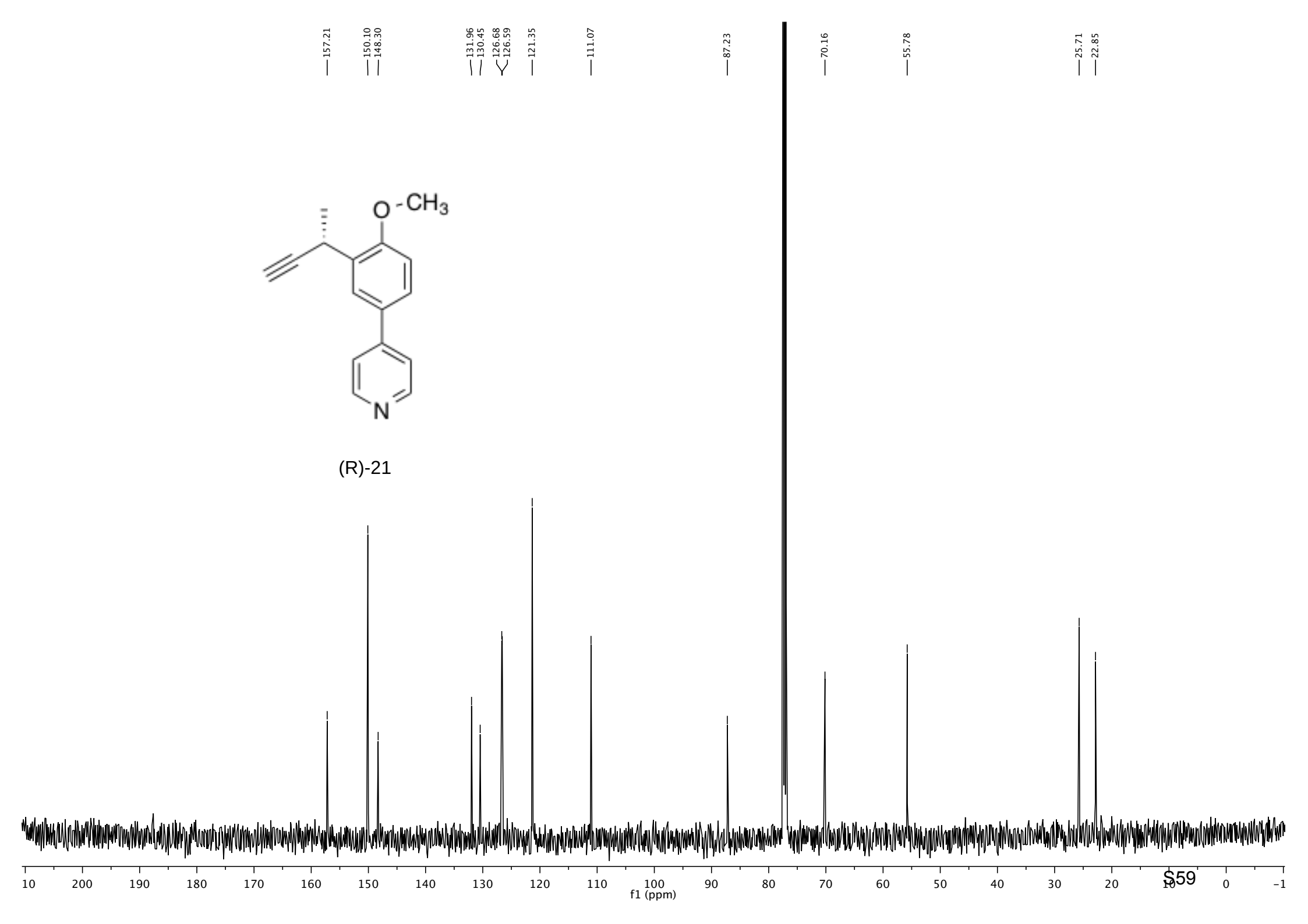

198.60
158.12
150.30
148.23
134.33
130.32
126.21
126.02
121.30
111.23
55.71
50.51
31.38
23.47
19.90
14.94
O
O
CH3
EtS
N
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

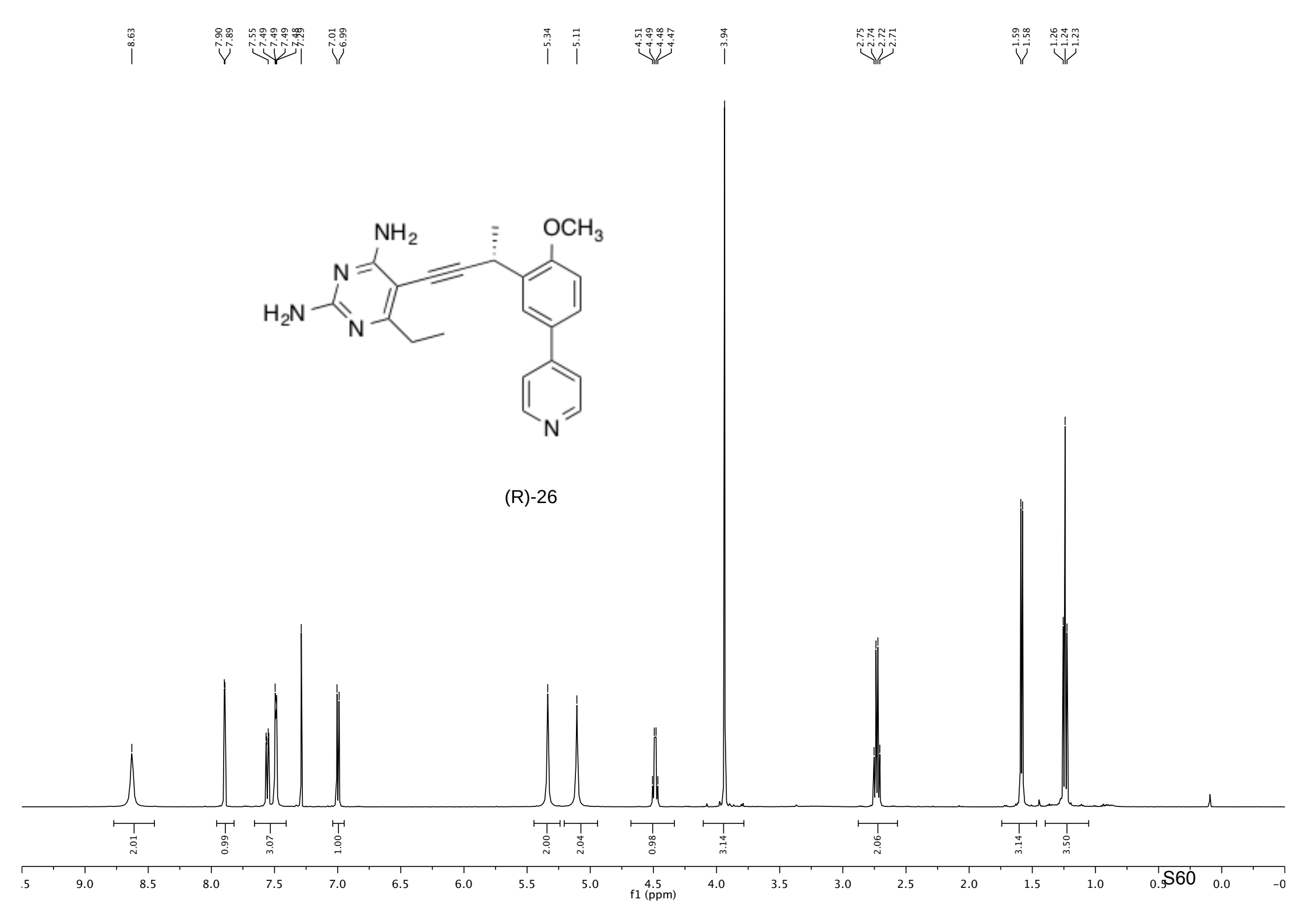

9.745
8.630
8.621
7.520
7.516
7.503
7.499
7.476
7.464
6.982
6.965
3.900
3.845
3.831
3.817
3.803
3.789
3.775
2.820
2.816
2.807
2.803
2.787
2.783
2.774
2.770
2.710
2.705
2.694
2.690
2.677
2.672
2.661
2.657
1.376
1.362
O
O
-CH3
H
N
(S)-16
1.00
2.73
5.37
1.35
5.85
2.95
4.71
f1 (ppm)

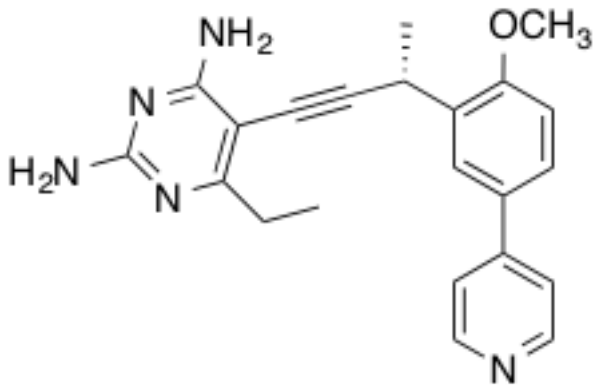

202.28
157.86
150.30
148.17
134.31
130.57
126.34
125.86
121.32
111.24
55.67
50.69
28.18
20.45
O
O
-CH3
H
N
(S)-16
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)


8.65
8.64
8.63
7.92
7.91
7.53
7.53
7.52
7.52
7.52
7.52
7.29
6.98
6.96
4.27
4.27
4.26
4.26
4.25
4.24
4.24
4.23
4.23
3.91
2.30
2.30
2.29
1.51
1.50
O
-CH3
N
2.45
1.07
3.65
1.15
1.00
3.44
0.98
3.36
10.0
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
0.0
f1 (ppm)

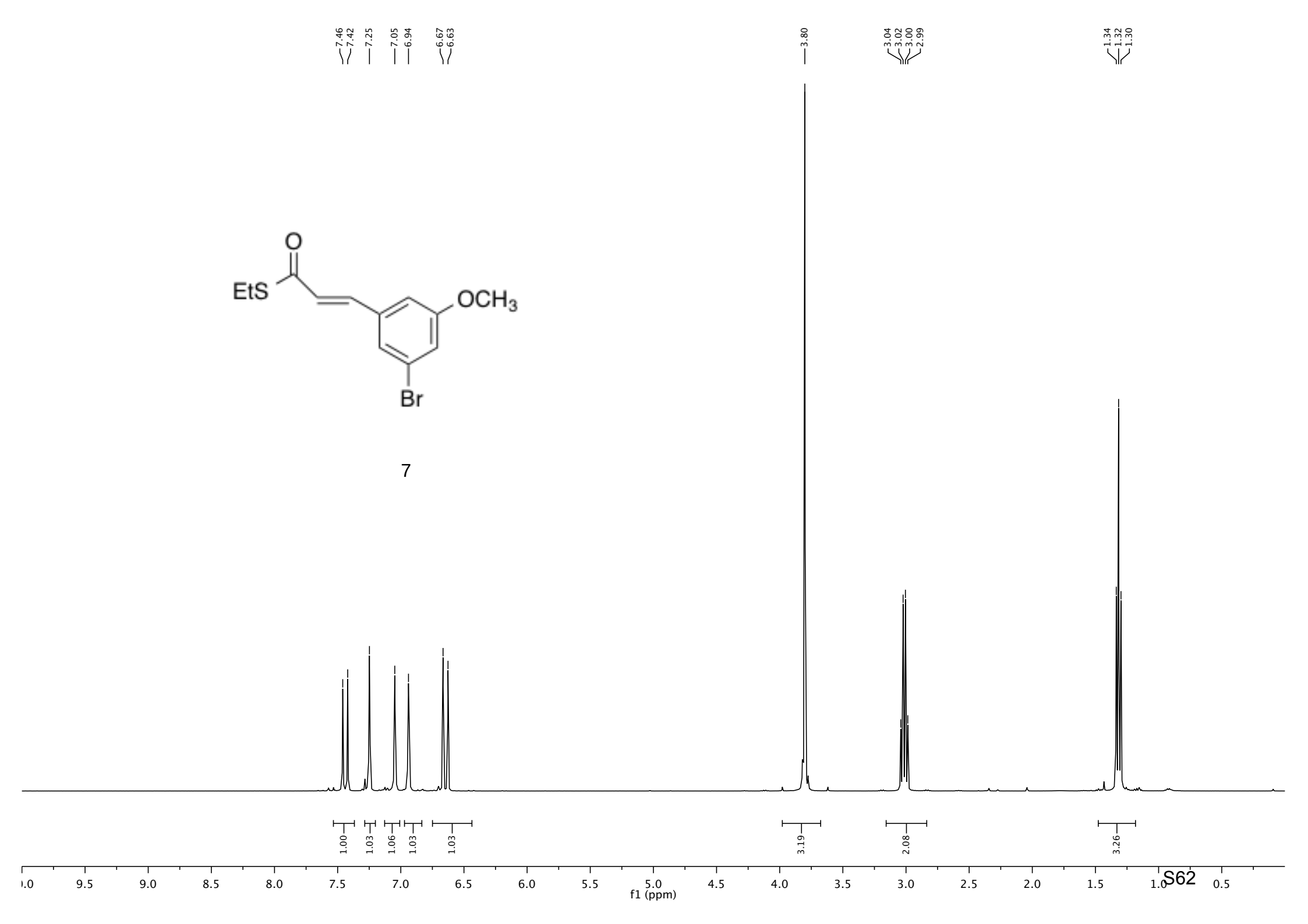
(R)-21


157.21
150.10
148.30
131.96
130.45
126.68
126.59
121.35
111.07
87.23
70.16
55.78
25.71
22.85
O
CH3
N
(R)-21
f1 (ppm)

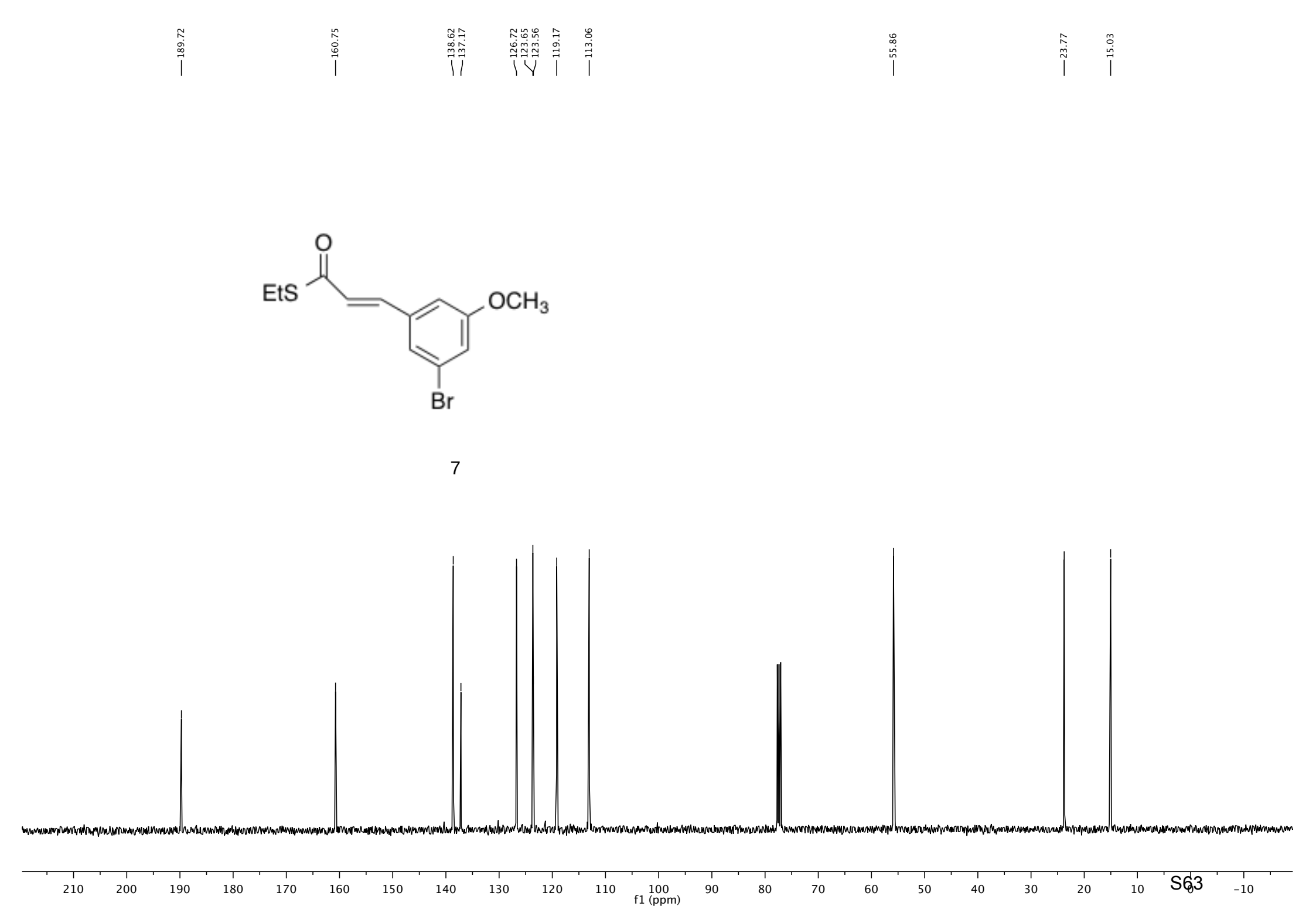

8.63
7.90
7.89
7.55
7.49
7.49
7.49
7.48
7.48
7.01
6.99
5.34
5.11
4.51
4.49
4.48
4.47
3.94
2.75
2.74
2.72
2.71
1.59
1.58
1.26
1.24
1.23
NH2
OCH3
N
H2N
N
N
(R)-26
2.01
0.99
3.07
1.00
2.00
2.04
0.98
3.14
2.06
3.14
3.50
f1 (ppm)

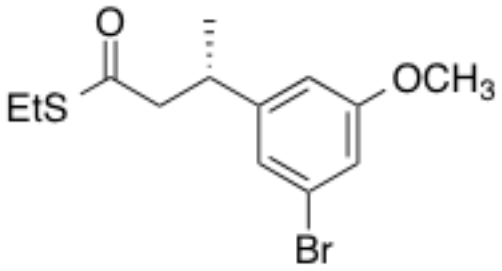


(R)-26

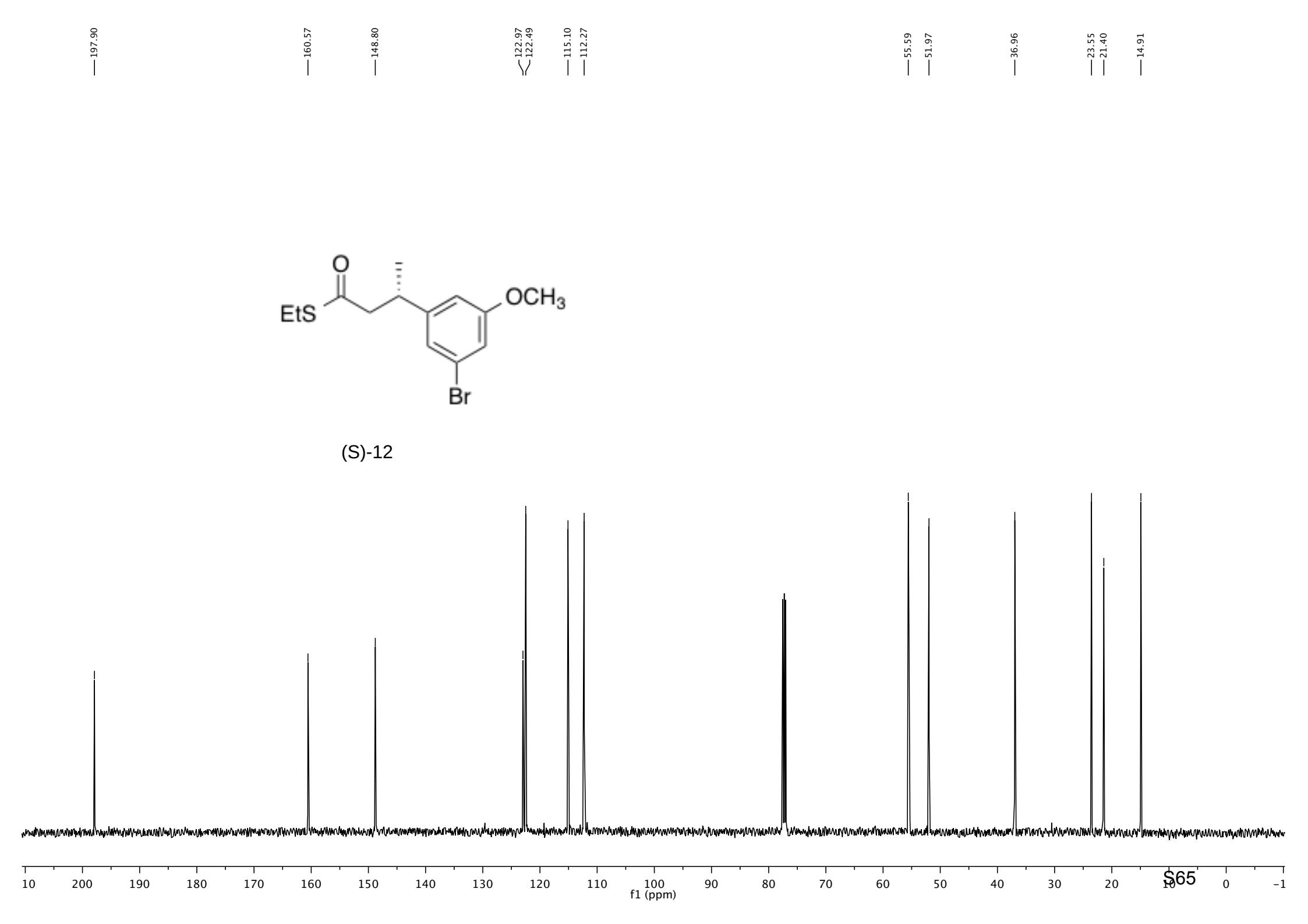

7.46
7.42
7.25
7.05
6.94
6.67
6.63
3.80
3.04
3.02
3.00
2.99
1.34
1.32
1.30
O
EtS
OCH3
Br
1.00
1.03
1.06
1.03
1.03
3.19
2.08
3.26
f1 (ppm)

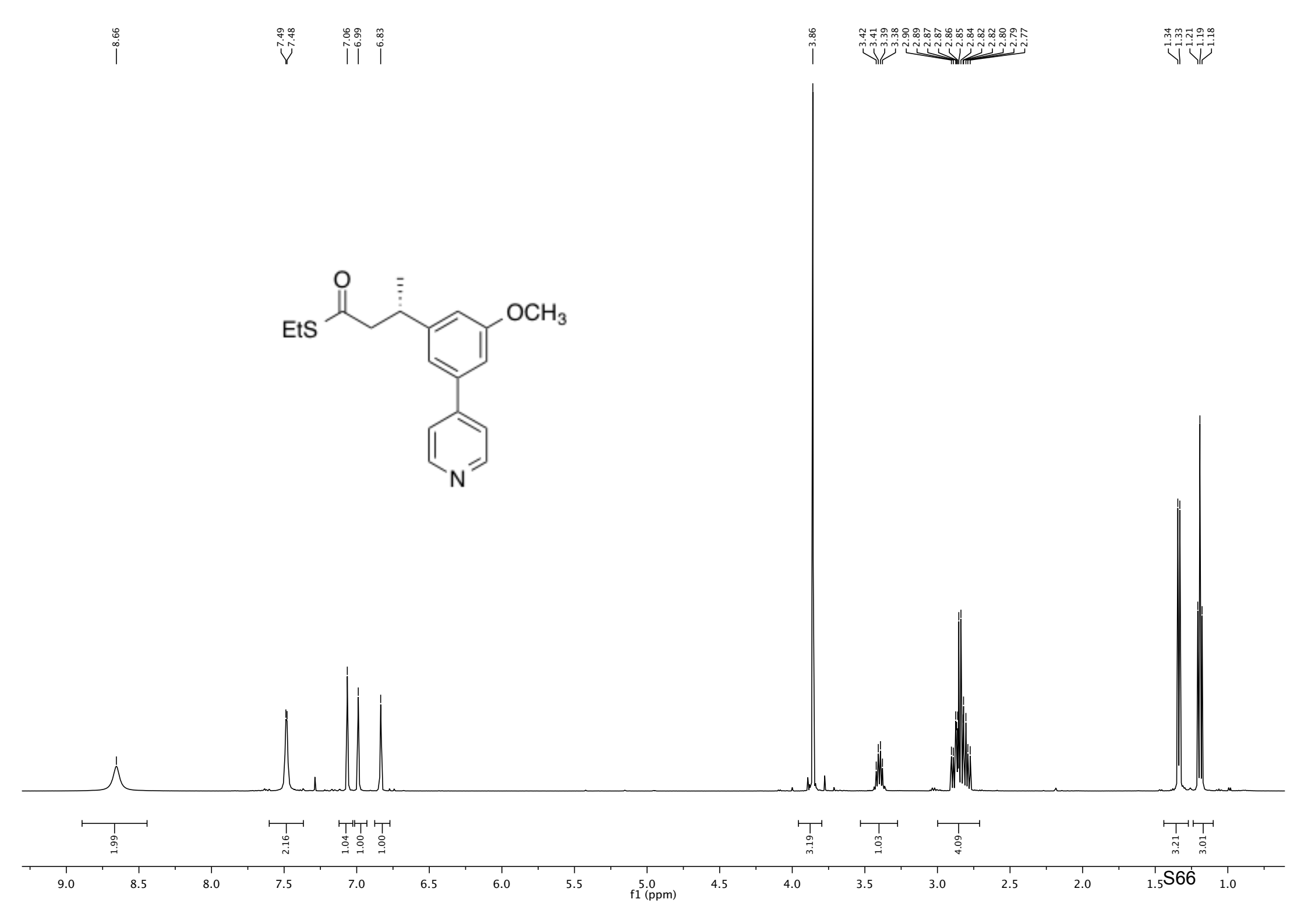
7

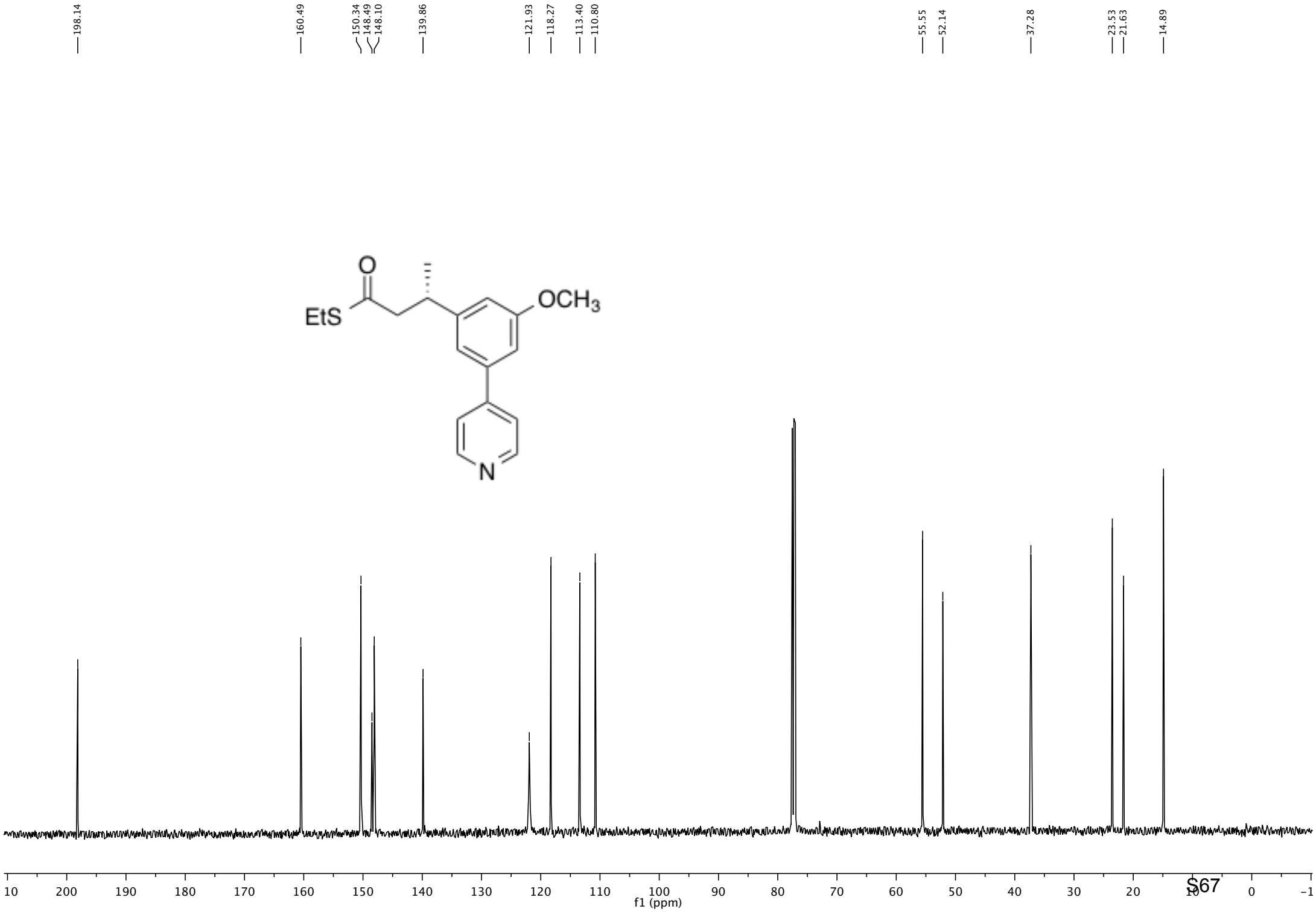

189.72
160.75
138.62
137.17
126.72
123.65
123.56
119.17
113.06
55.86
23.77
15.03
O
EtS
OCH3
Br
7
f1 (ppm)

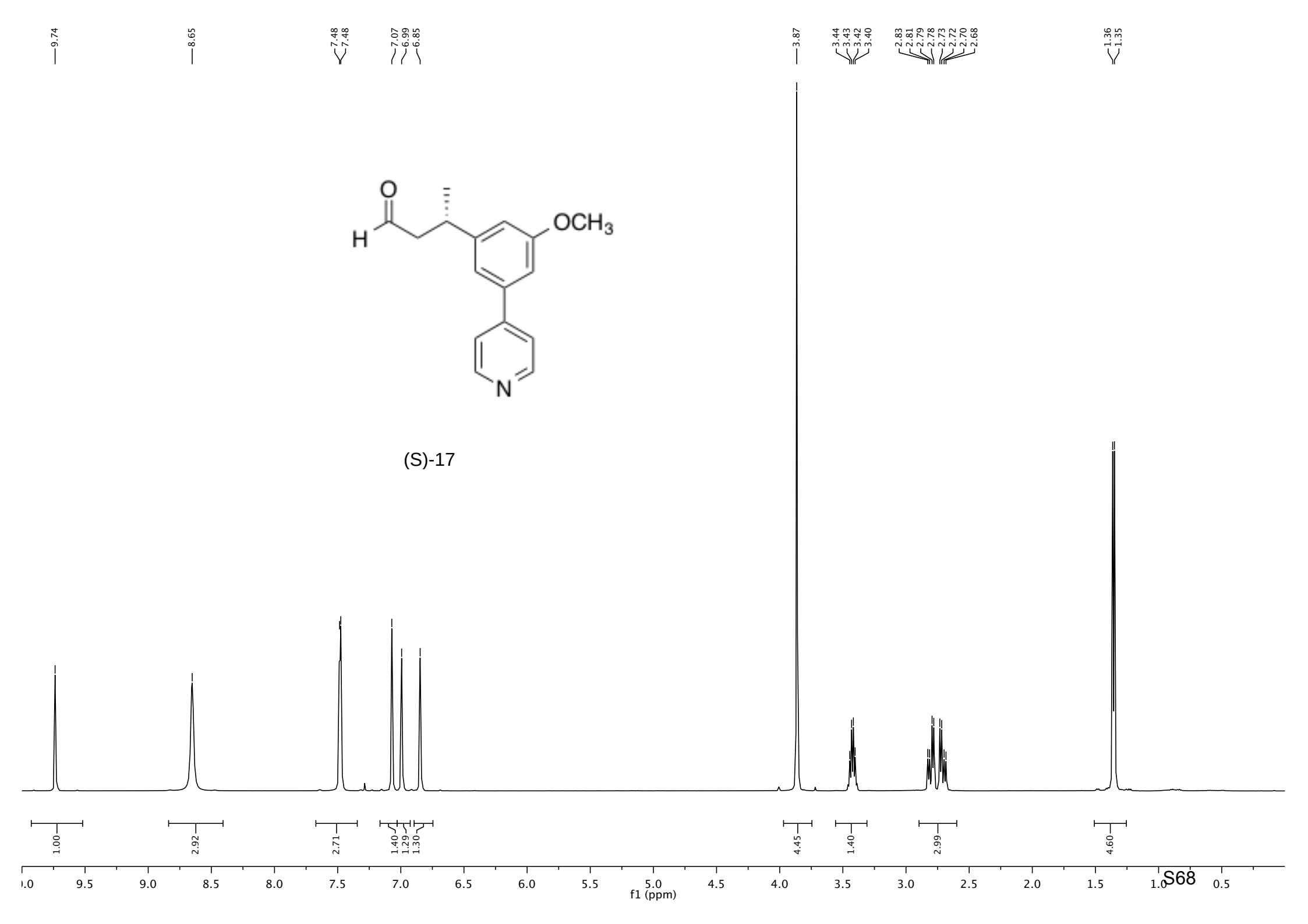


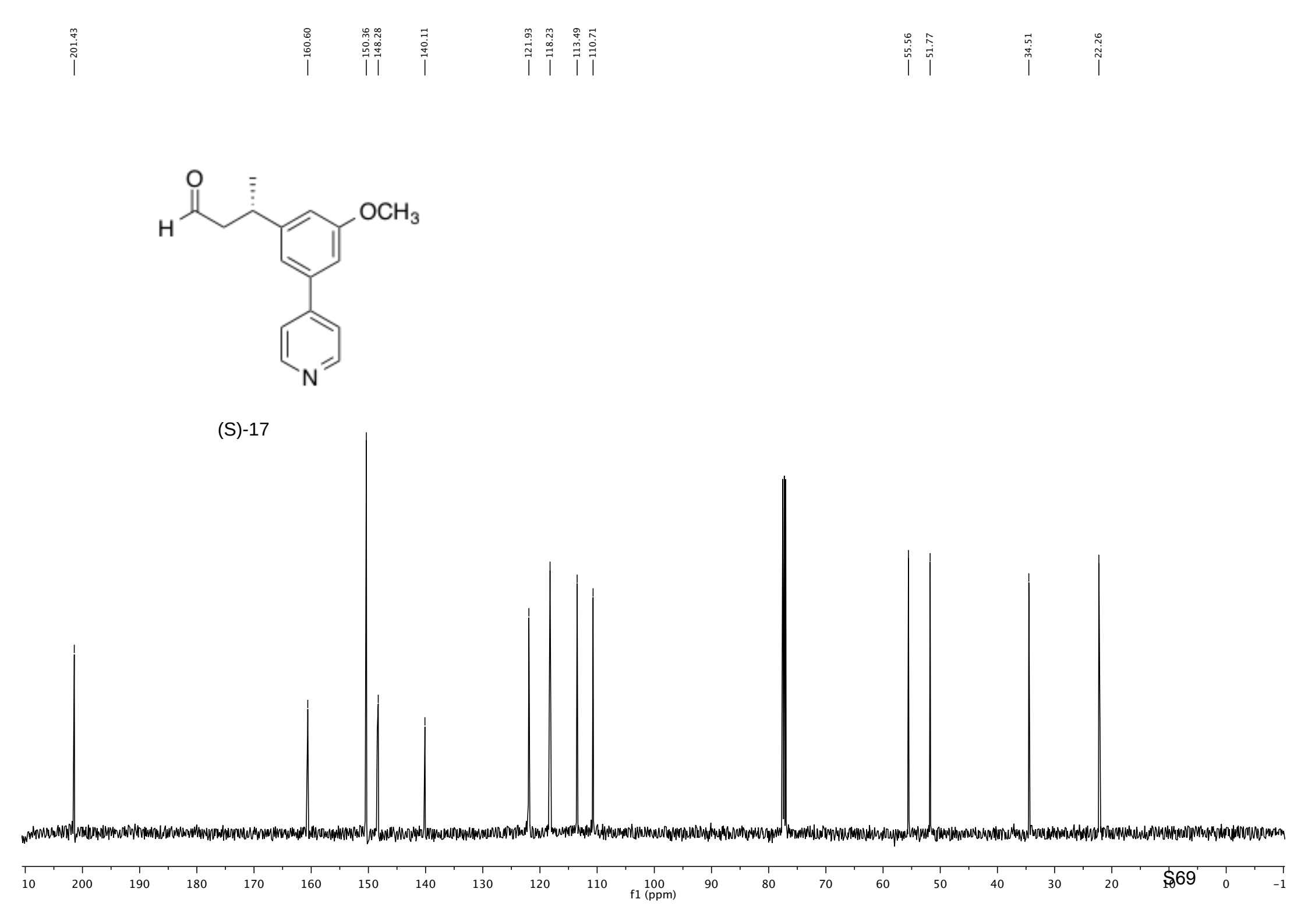
(S)-12

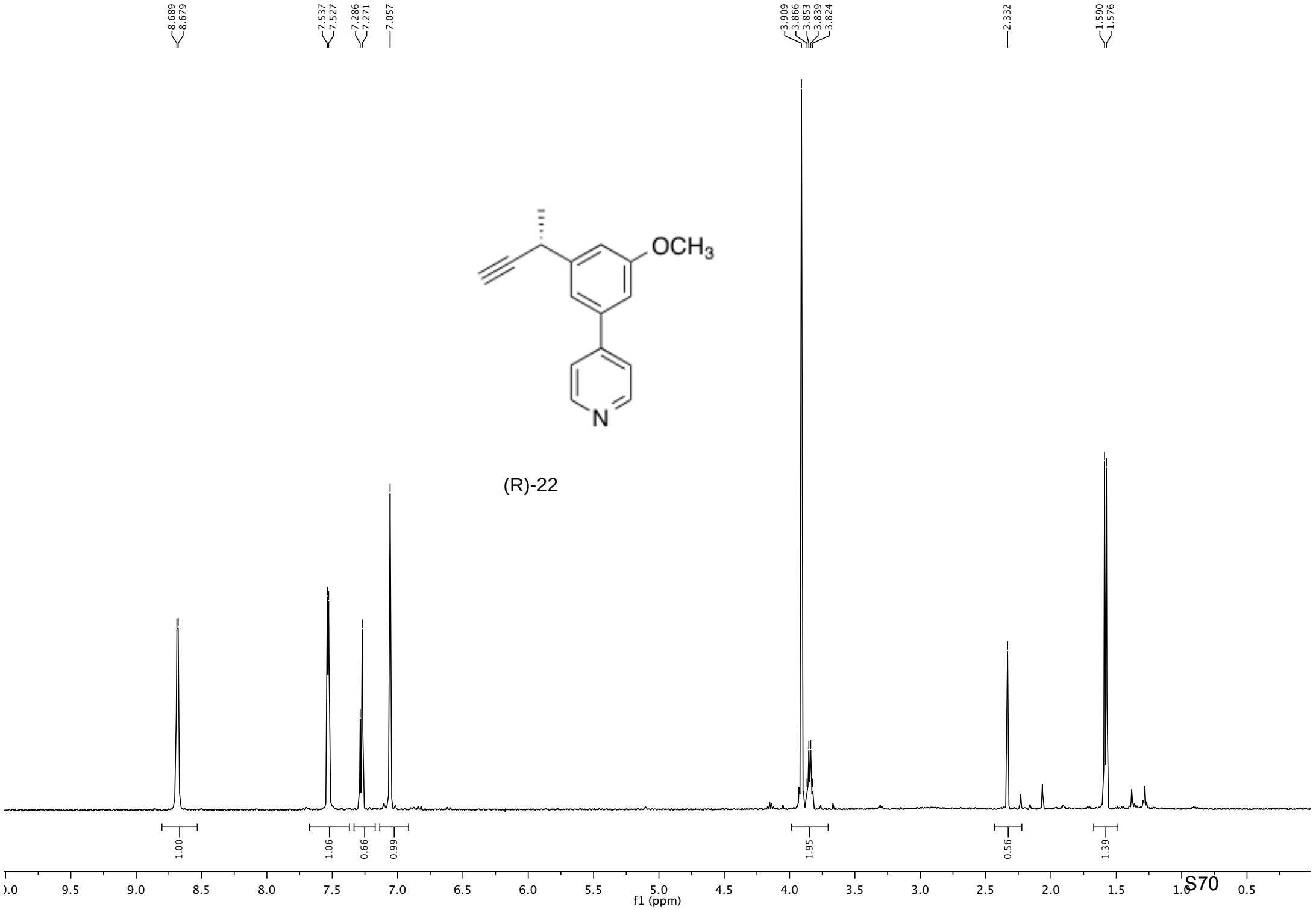

197.90
160.57
148.80
122.97
122.49
115.10
112.27
55.59
51.97
36.96
23.55
21.40
14.91
O
EtS
OCH3
Br
(S)-12
f1 (ppm)

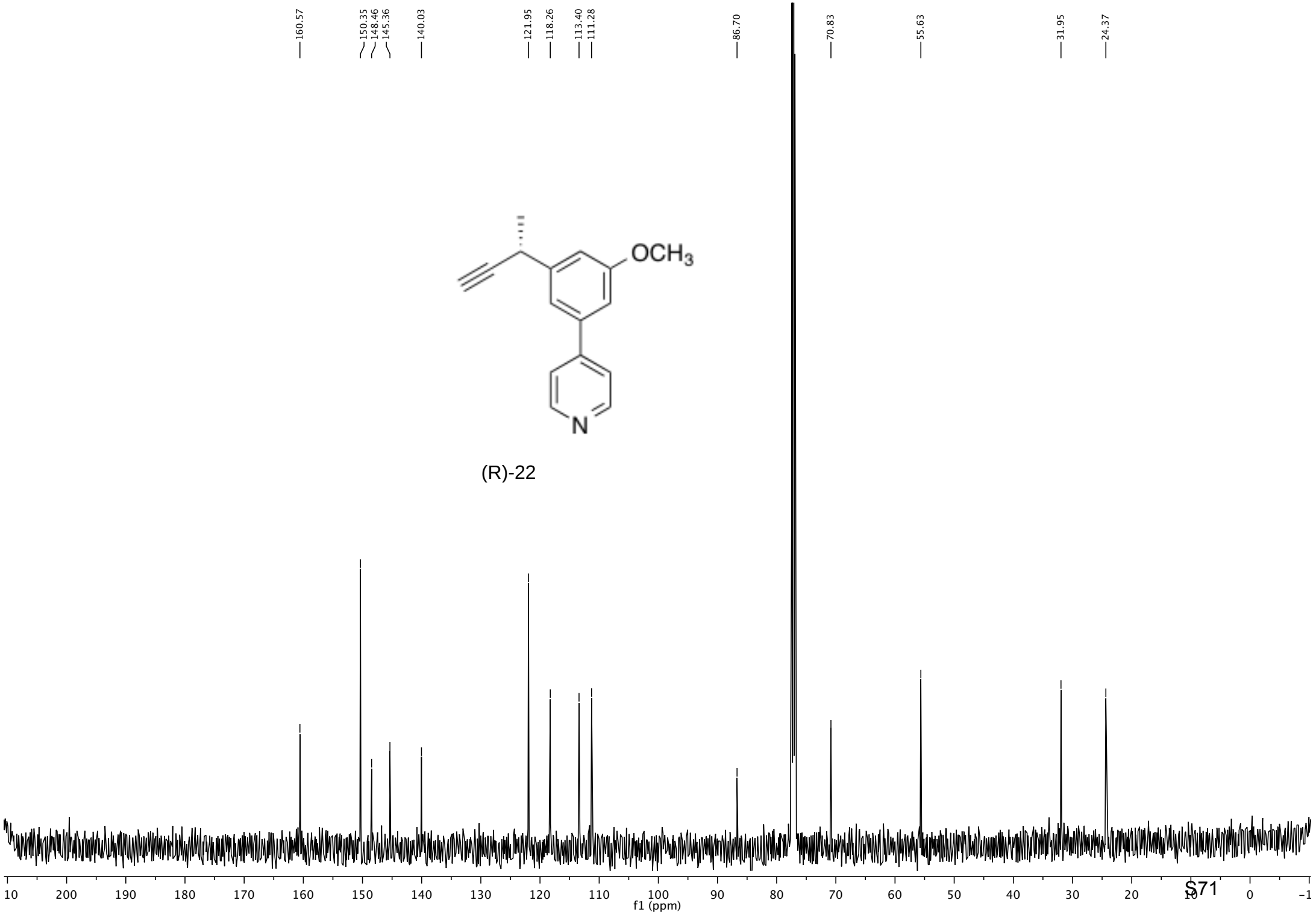

8.66
7.49
7.48
7.06
6.99
6.83
3.86
3.42
3.41
3.39
3.38
2.90
2.89
2.87
2.87
2.86
2.85
2.84
2.82
2.82
2.80
2.79
2.77
1.34
1.33
1.21
1.19
1.18
O
EtS
OCH3
N
1.99
2.16
1.04
1.00
1.00
3.19
1.03
4.09
3.21
3.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

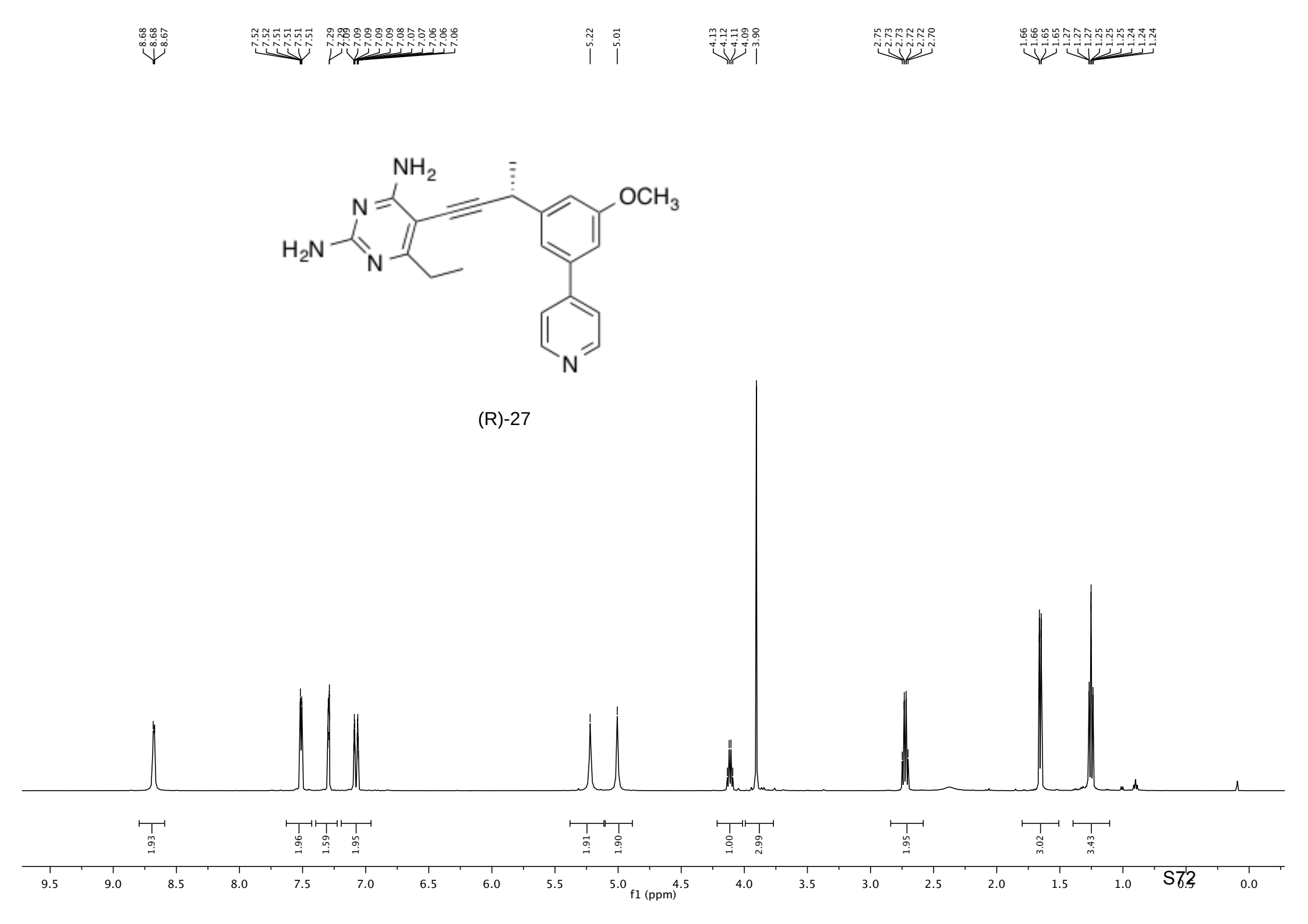

198.14
160.49
150.34
148.49
148.10
139.86
121.93
118.27
113.40
110.80
55.55
52.14
37.28
23.53
21.63
14.89
O
EtS
OCH3
N
f1 (ppm)

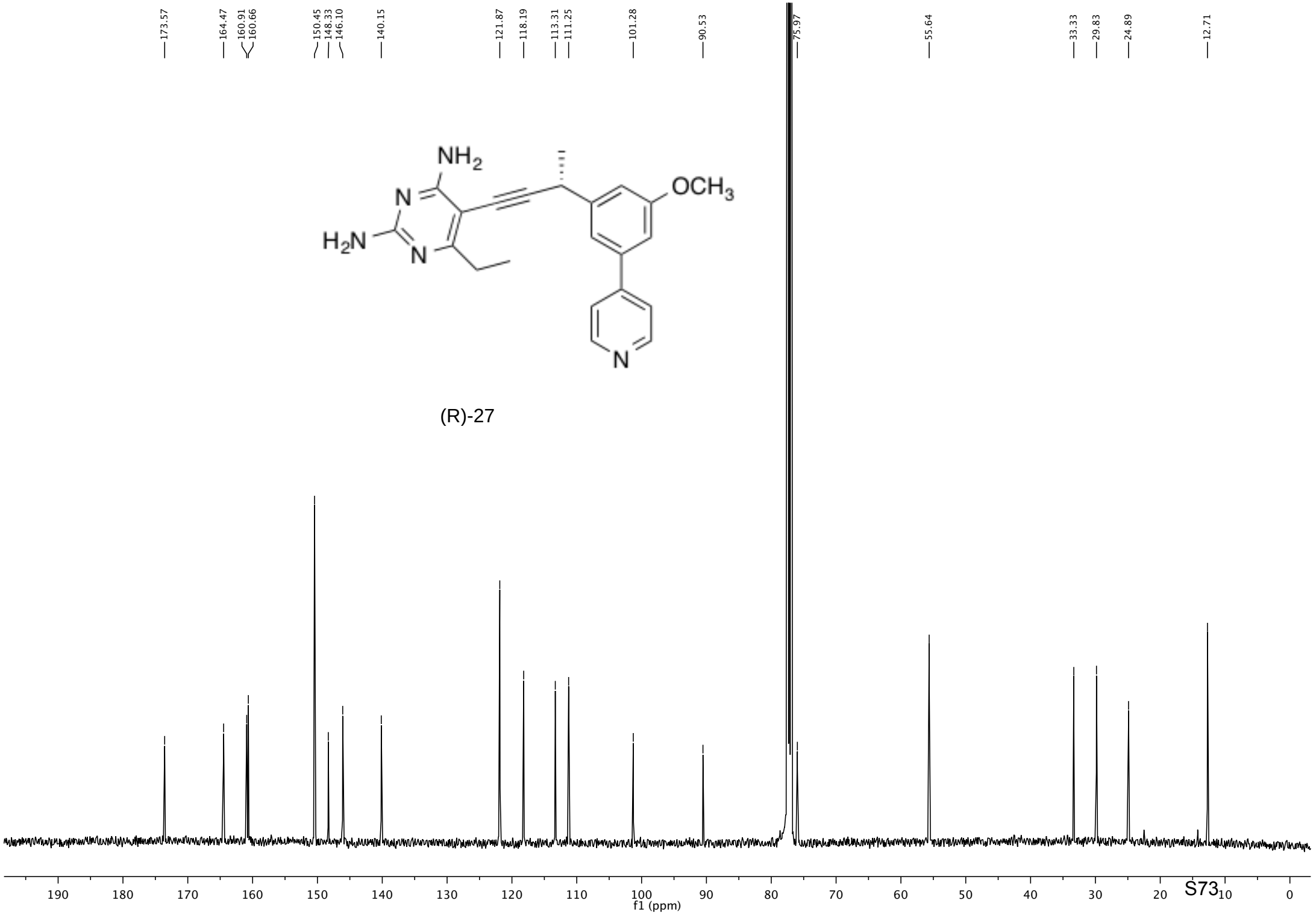

9.74
8.65
7.48
7.48
7.07
6.99
6.85
3.87
3.44
3.43
3.42
3.40
2.83
2.81
2.79
2.78
2.73
2.72
2.70
2.68
1.36
1.35
O
H
OCH3
N
(S)-17
1.00
2.92
2.71
1.40
1.29
1.30
4.45
1.40
2.99
4.60
f1 (ppm)

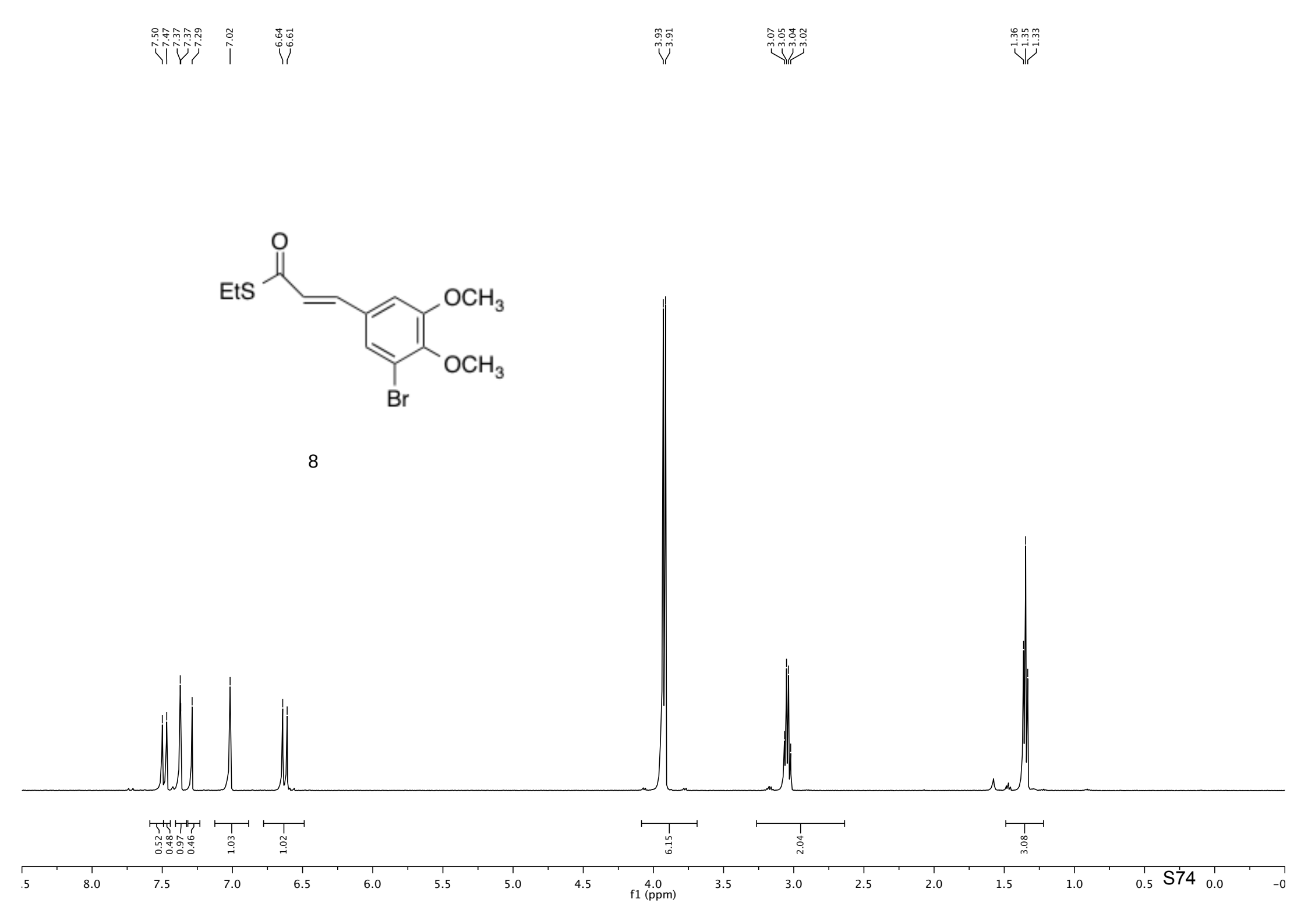

201.43
160.60
150.36
148.28
140.11
121.93
118.23
113.49
110.71
55.56
51.77
34.51
22.26
O
H
OCH3
N
(S)-17
f1 (ppm)

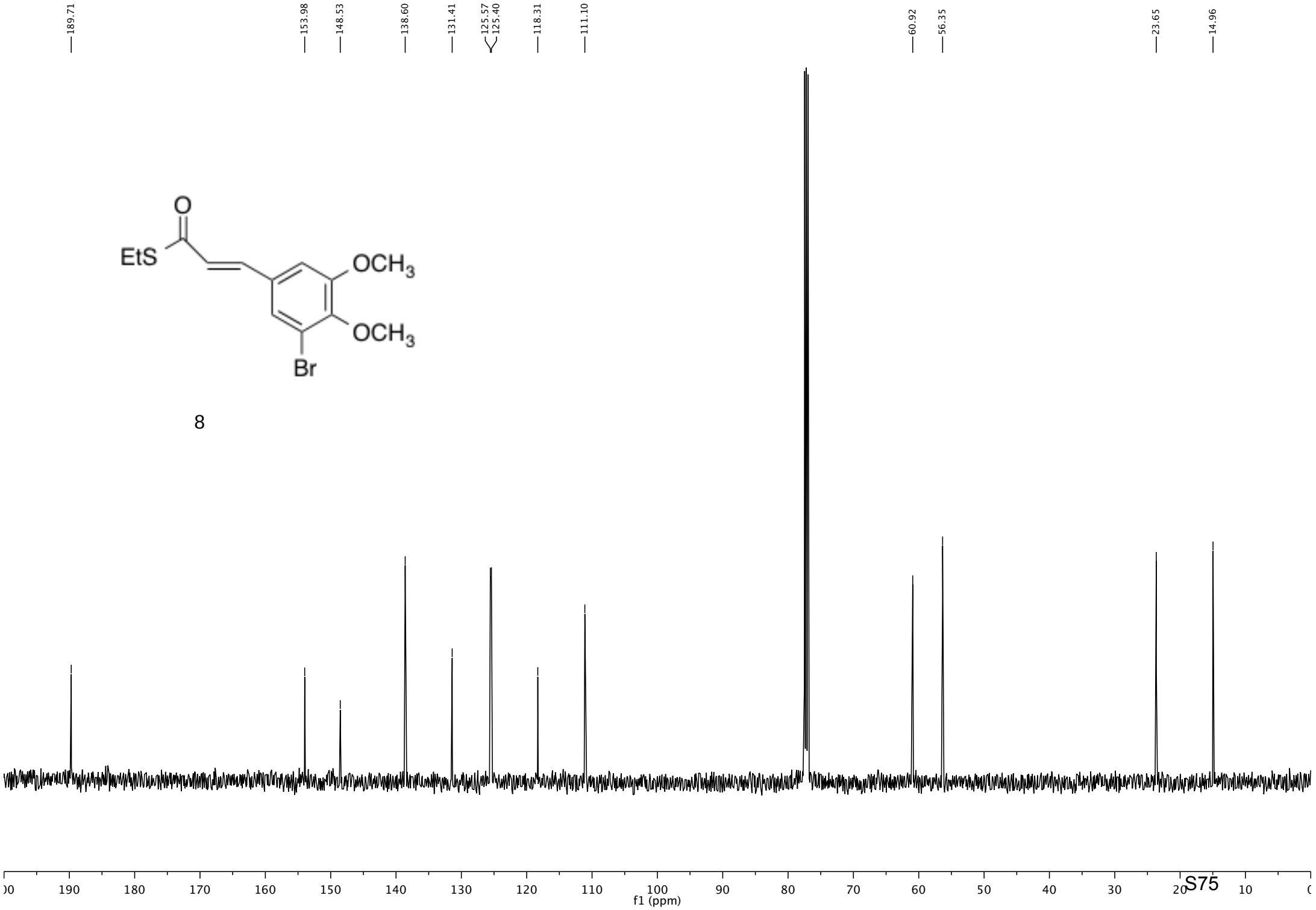

8.689
8.679
7.537
7.527
7.286
7.271
7.057
3.909
3.866
3.853
3.839
3.824
2.332
1.590
1.576
OCH3
N
(R)-22
1.00
1.06
0.66
0.99
1.95
0.56
1.39
f1 (ppm)

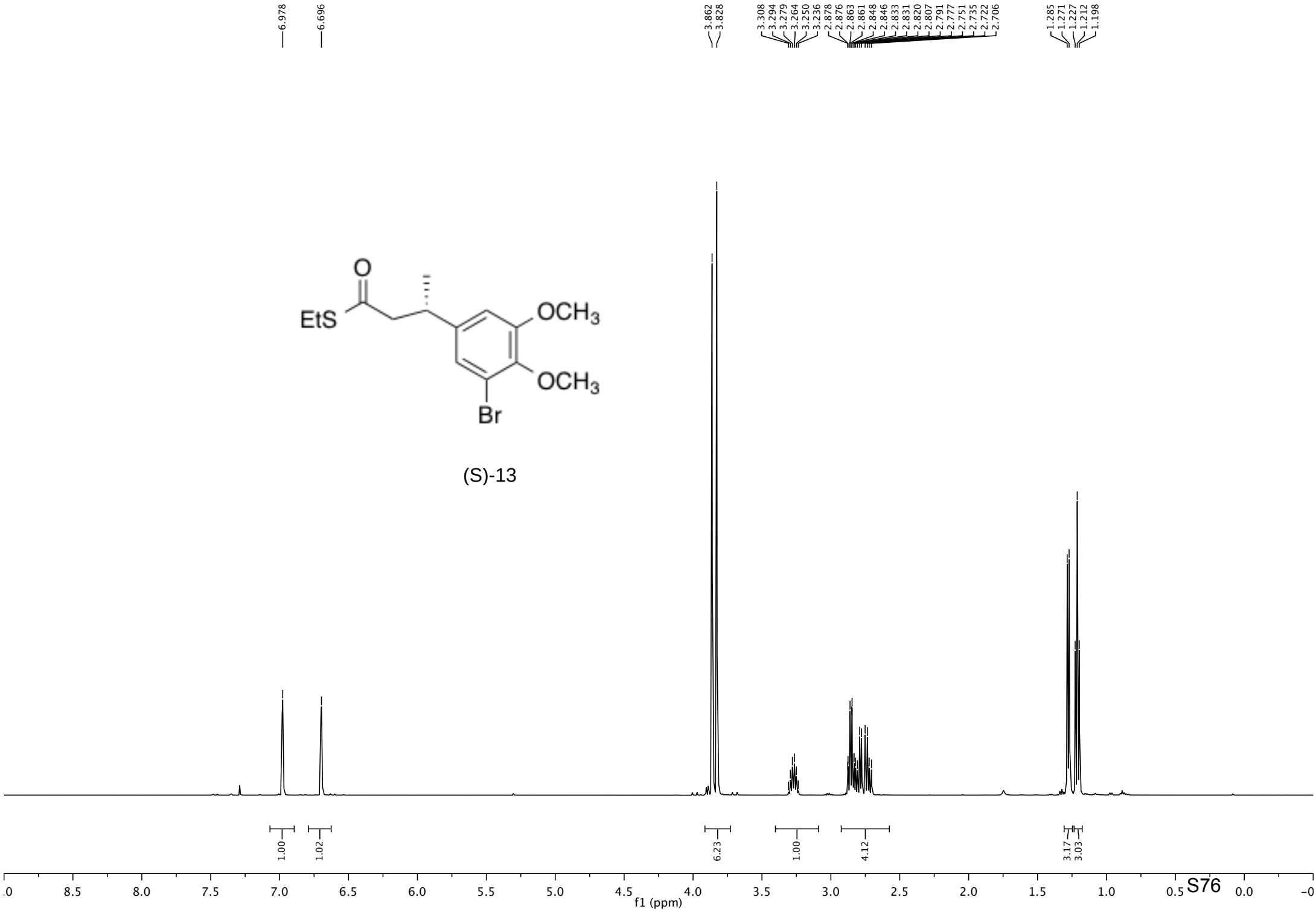

160.57
150.35
148.46
145.36
140.03
121.95
118.26
113.40
111.28
86.70
70.83
55.63
31.95
24.37
OCH3
N
(R)-22
f1 (ppm)


8.68
8.68
8.67
7.52
7.52
7.51
7.51
7.51
7.51
7.29
7.09
7.09
7.09
7.09
7.08
7.07
7.07
7.06
7.06
7.06
5.22
5.01
4.13
4.12
4.11
4.09
3.90
2.75
2.73
2.73
2.72
2.72
2.70
1.66
1.66
1.65
1.65
1.27
1.27
1.27
1.25
1.25
1.25
1.24
1.24
1.24
NH2
N
H2N
N
OCH3
N
(R)-27
1.93
1.96
1.59
1.95
1.91
1.90
1.00
2.99
1.95
3.02
3.43
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
0.0
f1 (ppm)


173.57
164.47
160.91
160.66
150.45
148.33
146.10
140.15
121.87
118.19
113.31
111.25
101.28
90.53
75.97
55.64
33.33
29.83
24.89
12.71
NH2
N
H2N
N
OCH3
N
(R)-27
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

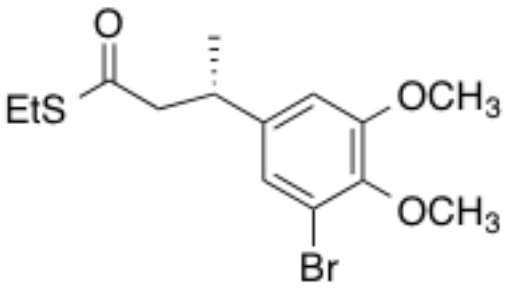

7.50
7.47
7.37
7.37
7.29
7.02
6.64
6.61
3.93
3.91
3.07
3.05
3.04
3.02
1.36
1.35
1.33
O
EtS
OCH3
OCH3
Br
8
0.52
0.48
0.97
0.46
1.03
1.02
6.15
2.04
3.08
f1 (ppm)


189.71
153.98
148.53
138.60
131.41
125.57
125.40
118.31
111.10
60.92
56.35
23.65
14.96
O
EtS
OCH3
OCH3
Br
8
f1 (ppm)

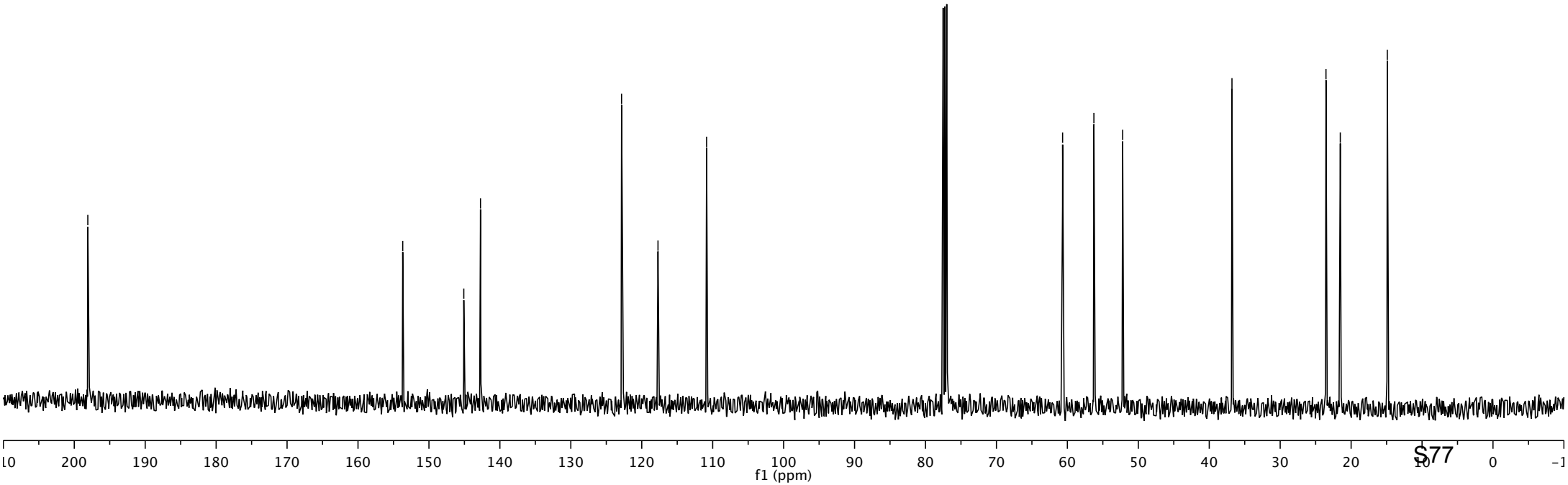

6.978
6.696
3.862
3.828
3.308
3.294
3.279
3.264
3.250
3.236
2.878
2.876
2.863
2.861
2.848
2.846
2.833
2.831
2.820
2.807
2.791
2.777
2.751
2.735
2.722
2.706
1.285
1.271
1.227
1.212
1.198
O
EtS
OCH3
OCH3
Br
1.00
1.02
6.23
1.00
4.12
3.17
3.03
f1 (ppm)

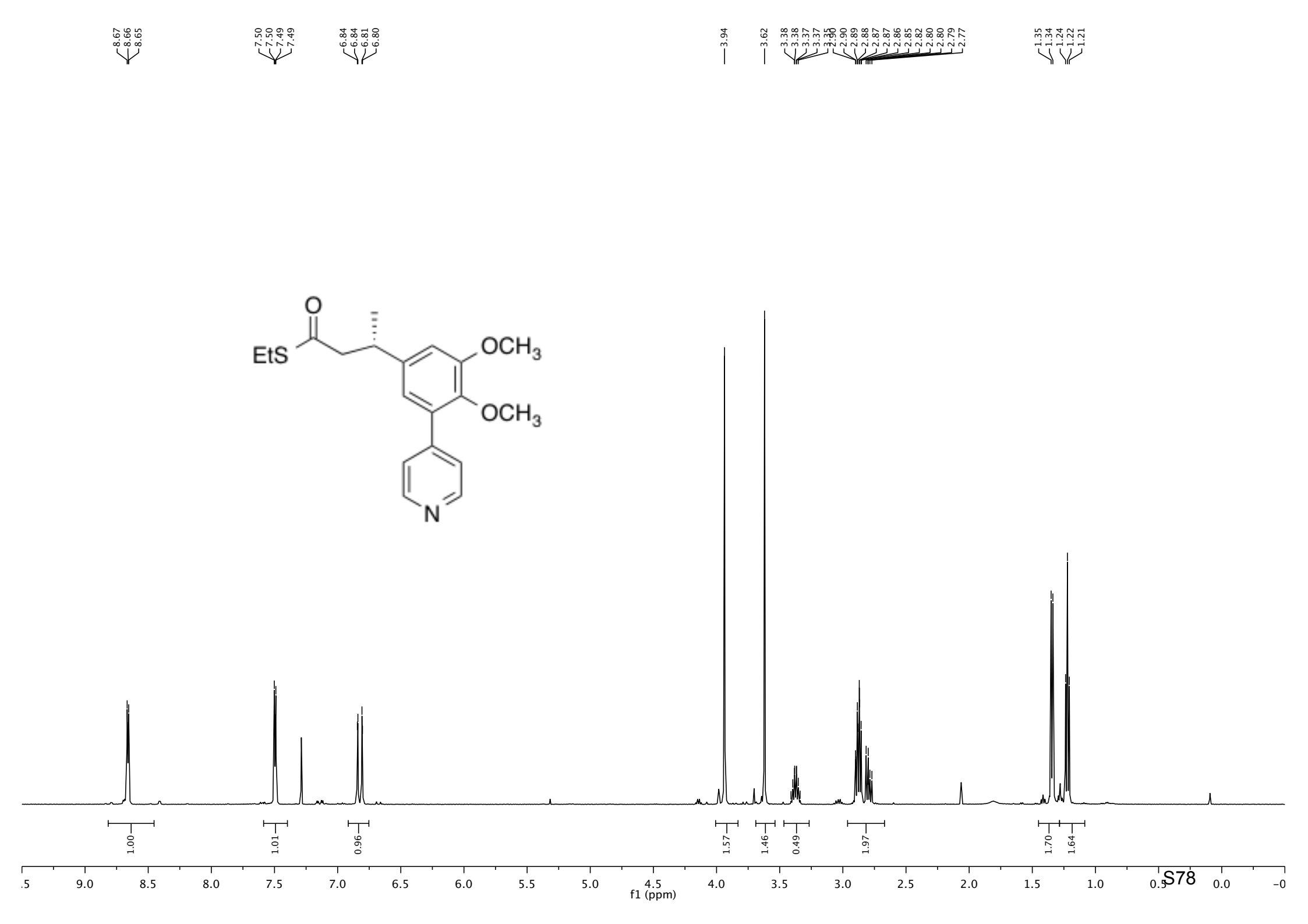
(S)-13

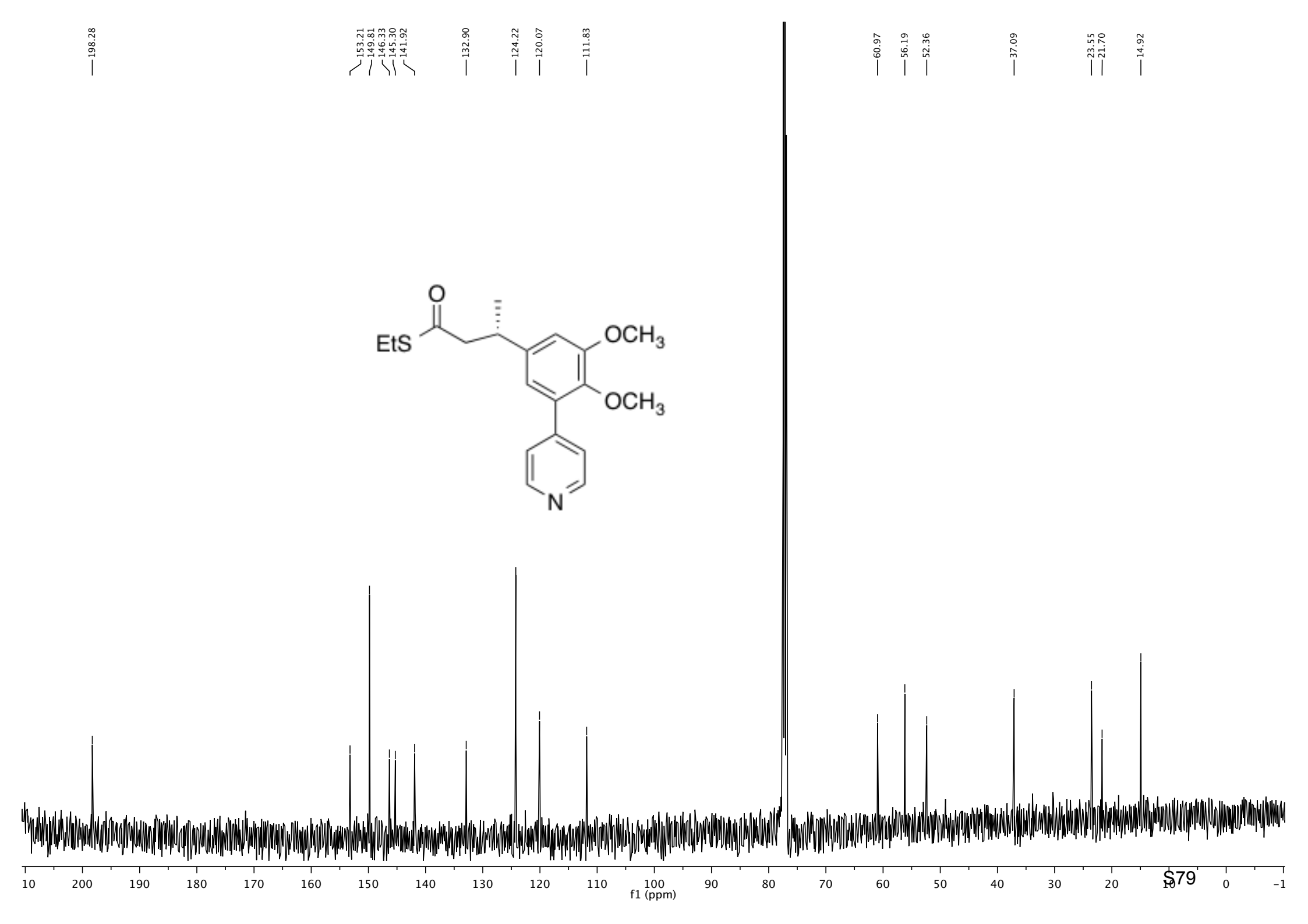
198.09
153.70
145.09
142.73
122.85
117.71
110.86
60.67
56.26
52.20
36.80
23.54
21.53
14.90

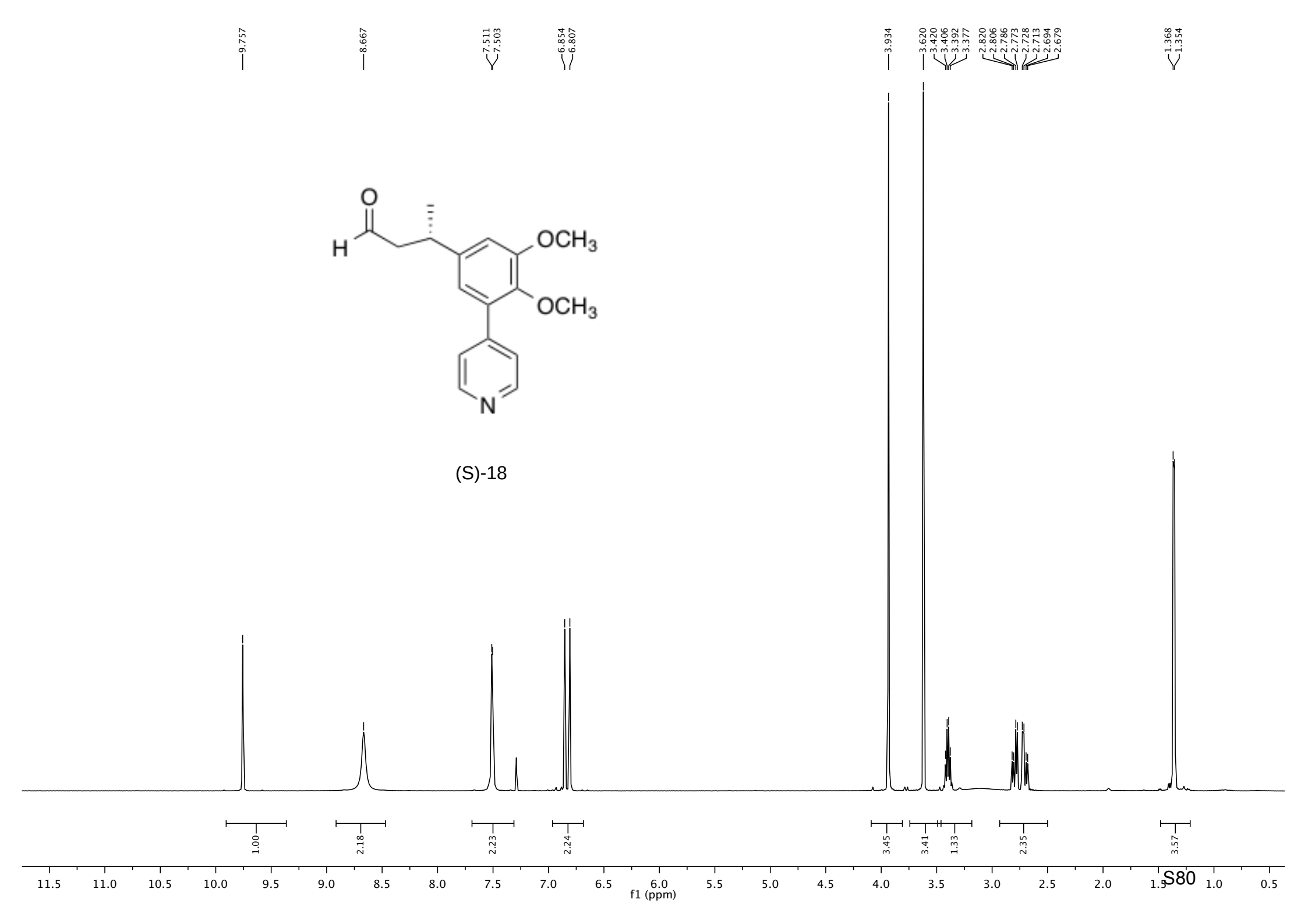


(S)-13

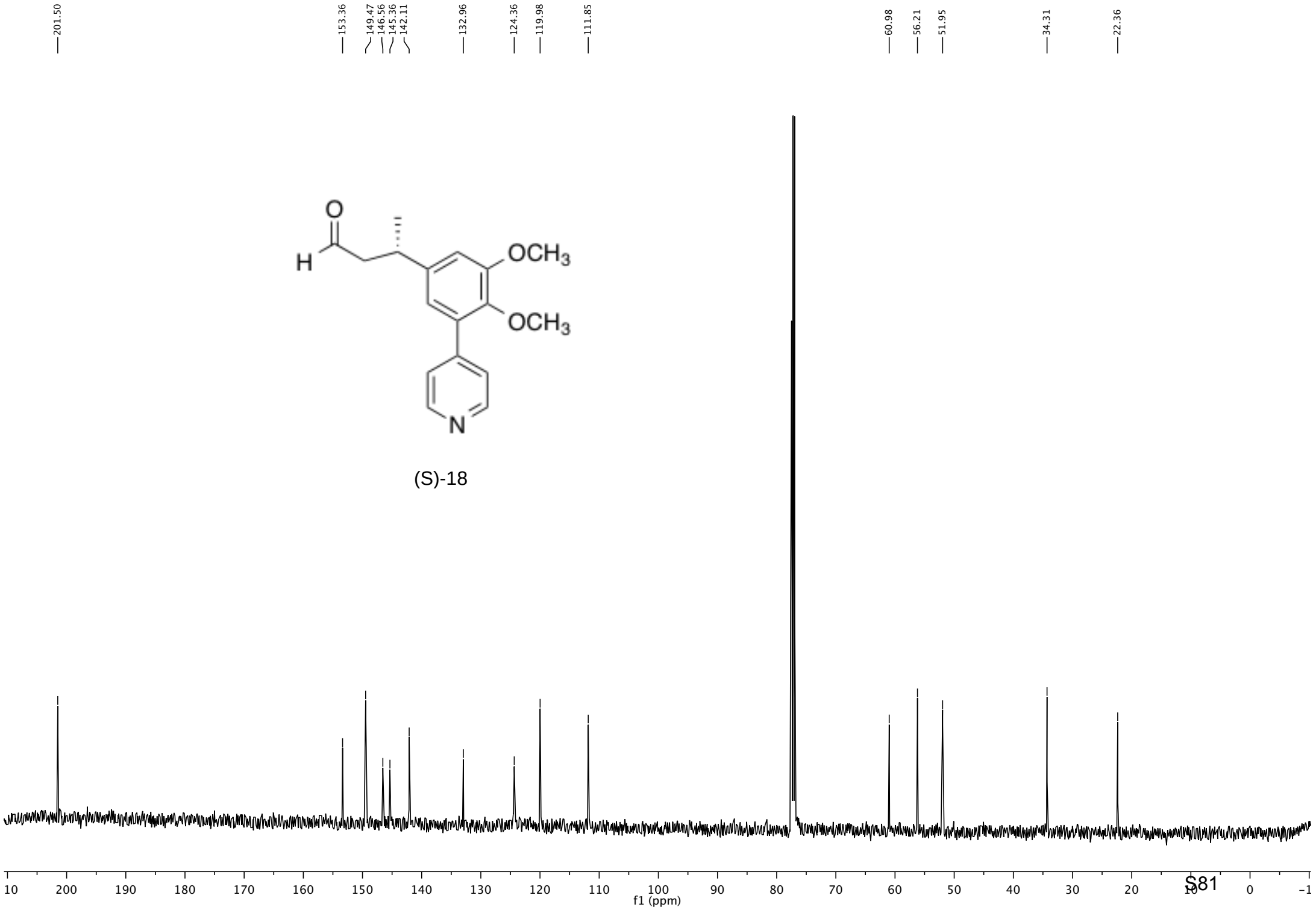



8.67
8.66
8.65
7.50
7.50
7.49
7.49
6.84
6.84
6.81
6.80
3.94
3.62
3.38
3.38
3.37
3.37
2.90
2.89
2.88
2.87
2.87
2.86
2.85
2.82
2.80
2.80
2.79
2.77
1.35
1.34
1.24
1.22
1.21
O
EtS
OCH3
OCH3
N
1.00
1.01
0.96
1.57
1.46
0.49
1.97
1.70
1.64
f1 (ppm)

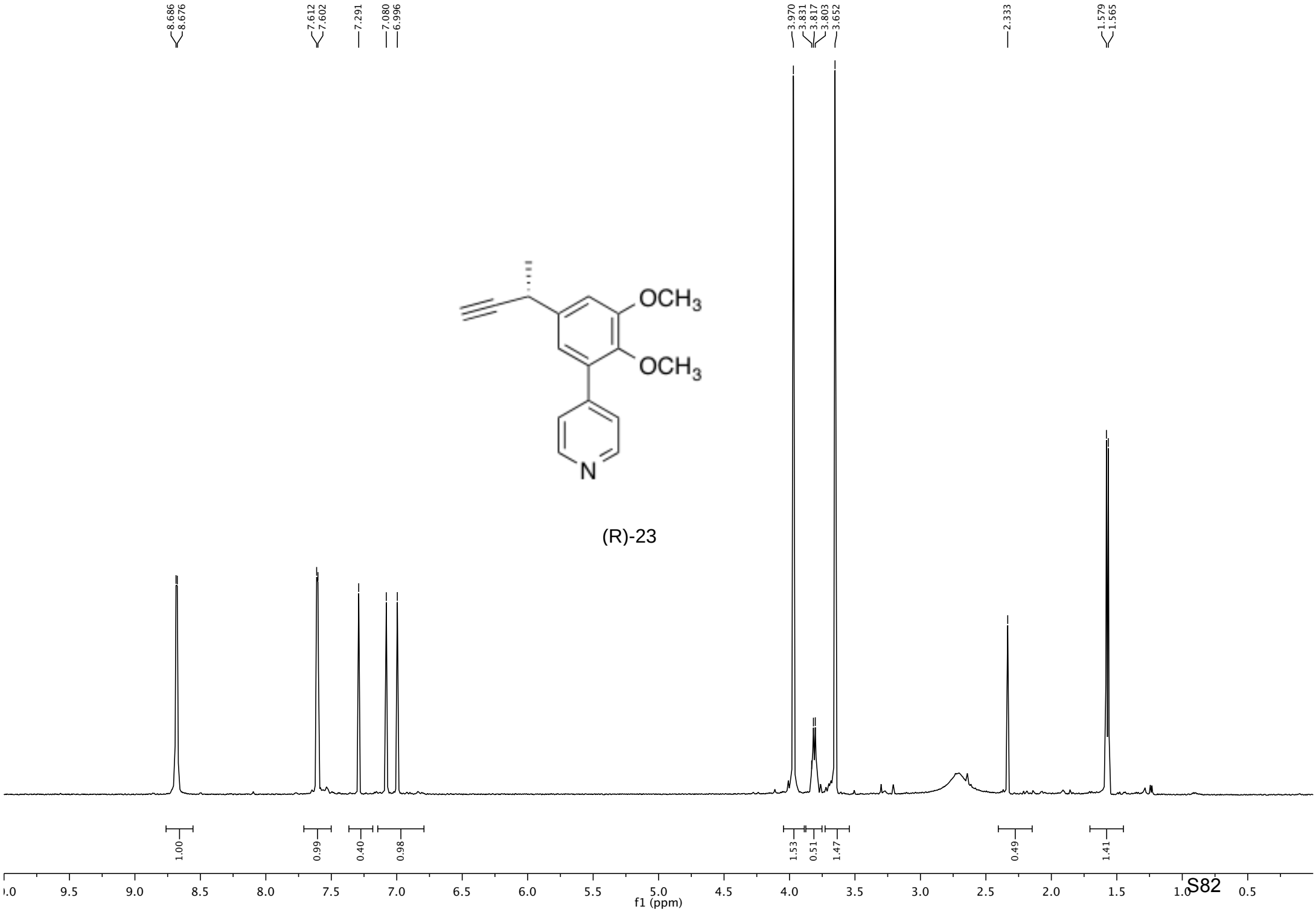

198.28
153.21
149.81
146.33
145.30
141.92
132.90
124.22
120.07
111.83
60.97
56.19
52.36
37.09
23.55
21.70
14.92
O
EtS
OCH3
OCH3
N
f1 (ppm)

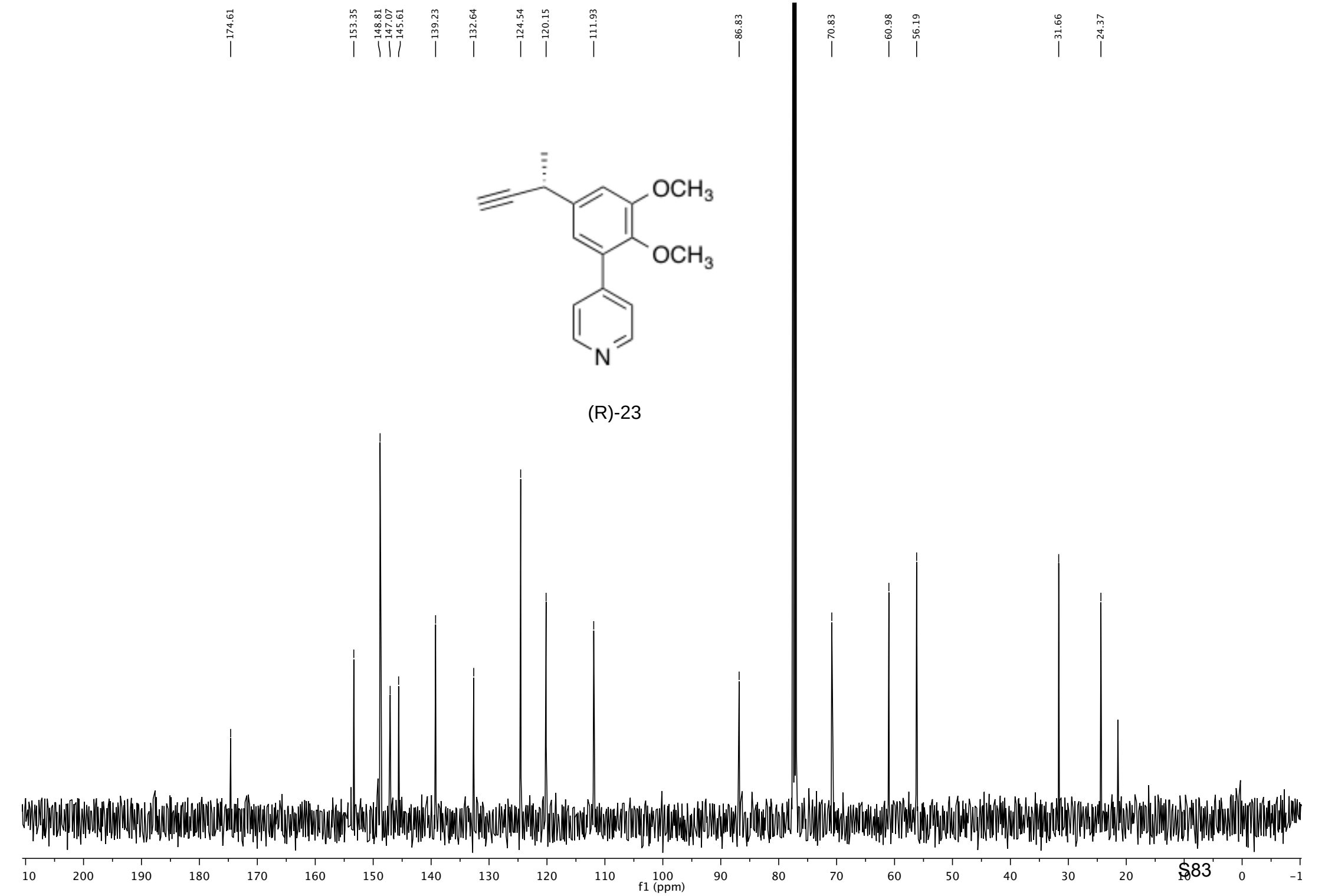

9.757
8.667
7.511
7.503
6.854
6.807
3.934
3.620
3.420
3.406
3.392
3.377
2.820
2.806
2.786
2.773
2.728
2.713
2.694
2.679
1.368
1.354
O
H
OCH3
OCH3
N
1.00
2.18
2.23
2.24
3.45
3.41
1.33
2.35
3.57
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

(S)-18

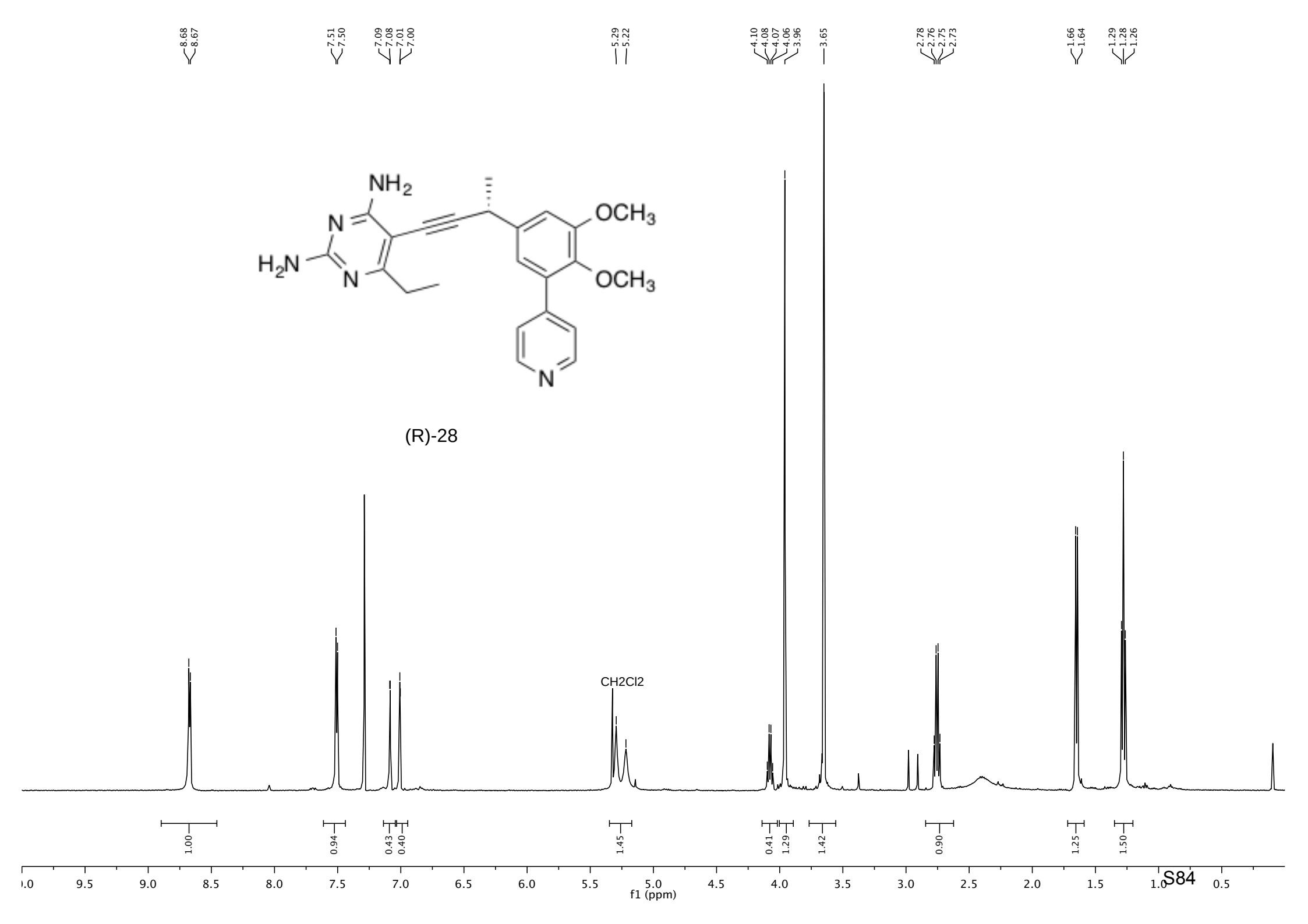

201.50
153.36
149.47
146.56
145.36
142.11
132.96
124.36
119.98
111.85
60.98
56.21
51.95
34.31
22.36
O
H
OCH3
OCH3
N
f1 (ppm)

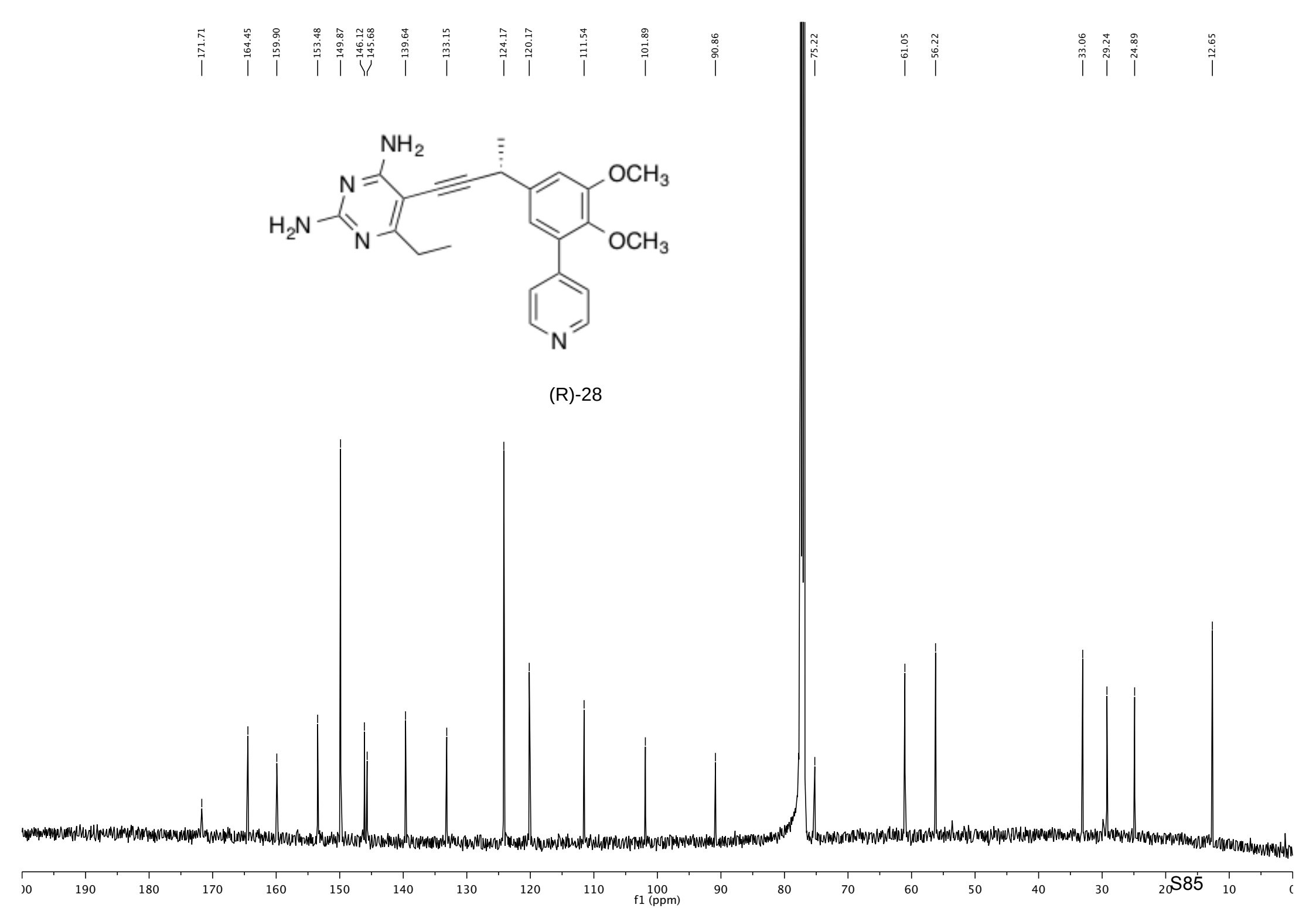
(S)-18


8.686
8.676
7.612
7.602
7.291
7.080
6.996
3.970
3.831
3.817
3.803
3.652
2.333
1.579
1.565
OCH3
OCH3
N
(R)-23
1.00
0.99
0.40
0.98
1.53
0.51
1.47
0.49
1.41
f1 (ppm)

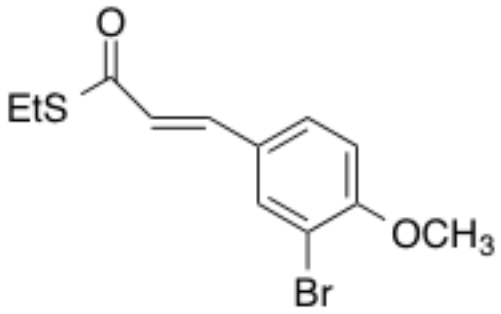

174.61
153.35
148.81
147.07
145.61
139.23
132.64
124.54
120.15
111.93
86.83
70.83
60.98
56.19
31.66
24.37
OCH3
OCH3
N
f1 (ppm)

(R)-23

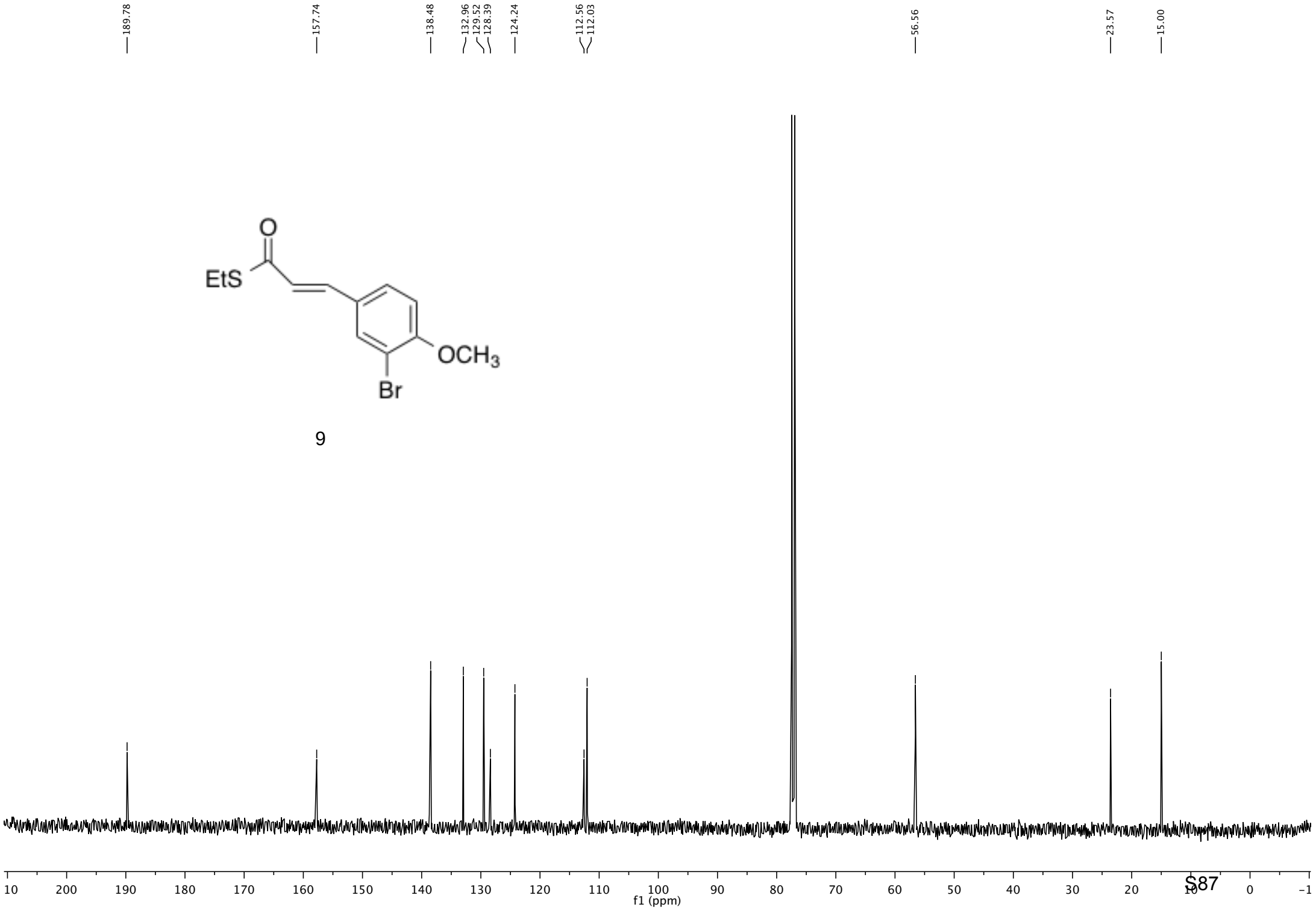

8.68
8.67
7.51
7.50
7.09
7.08
7.01
7.00
5.29
5.22
4.10
4.08
4.07
4.06
3.96
3.65
2.78
2.76
2.75
2.73
1.66
1.64
1.29
1.28
1.26
NH2
N
H2N
N
OCH3
OCH3
N
(R)-28
CH2Cl2
1.00
0.94
0.43
0.40
1.45
0.41
1.29
1.42
0.90
1.25
1.50
f1 (ppm)

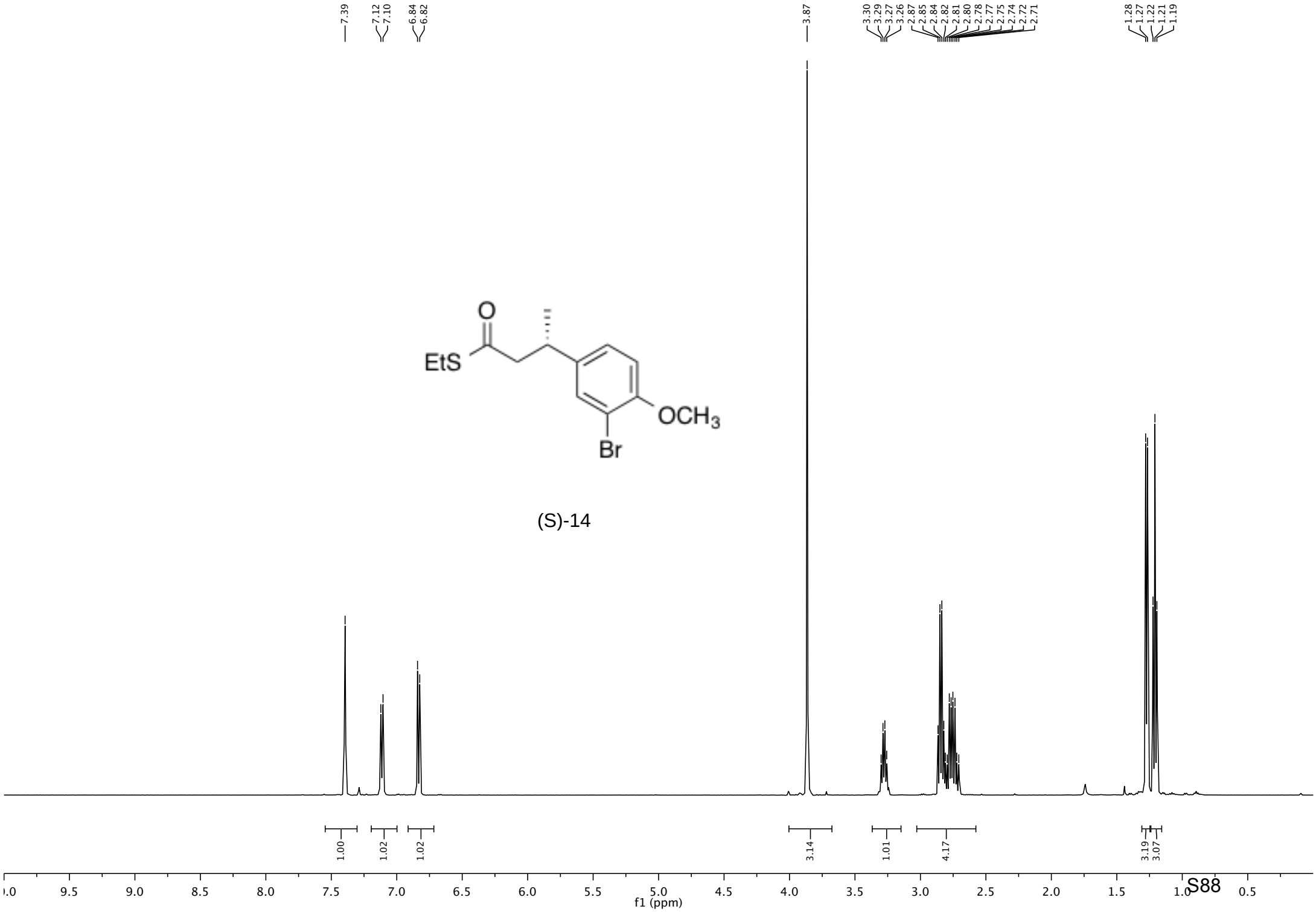

171.71
164.45
159.90
153.48
149.87
146.12
145.68
139.64
133.15
124.17
120.17
111.54
101.89
90.86
75.22
61.05
56.22
33.06
29.24
24.89
12.65
NH2
N
H2N
N
OCH3
OCH3
N
f1 (ppm)

(R)-28

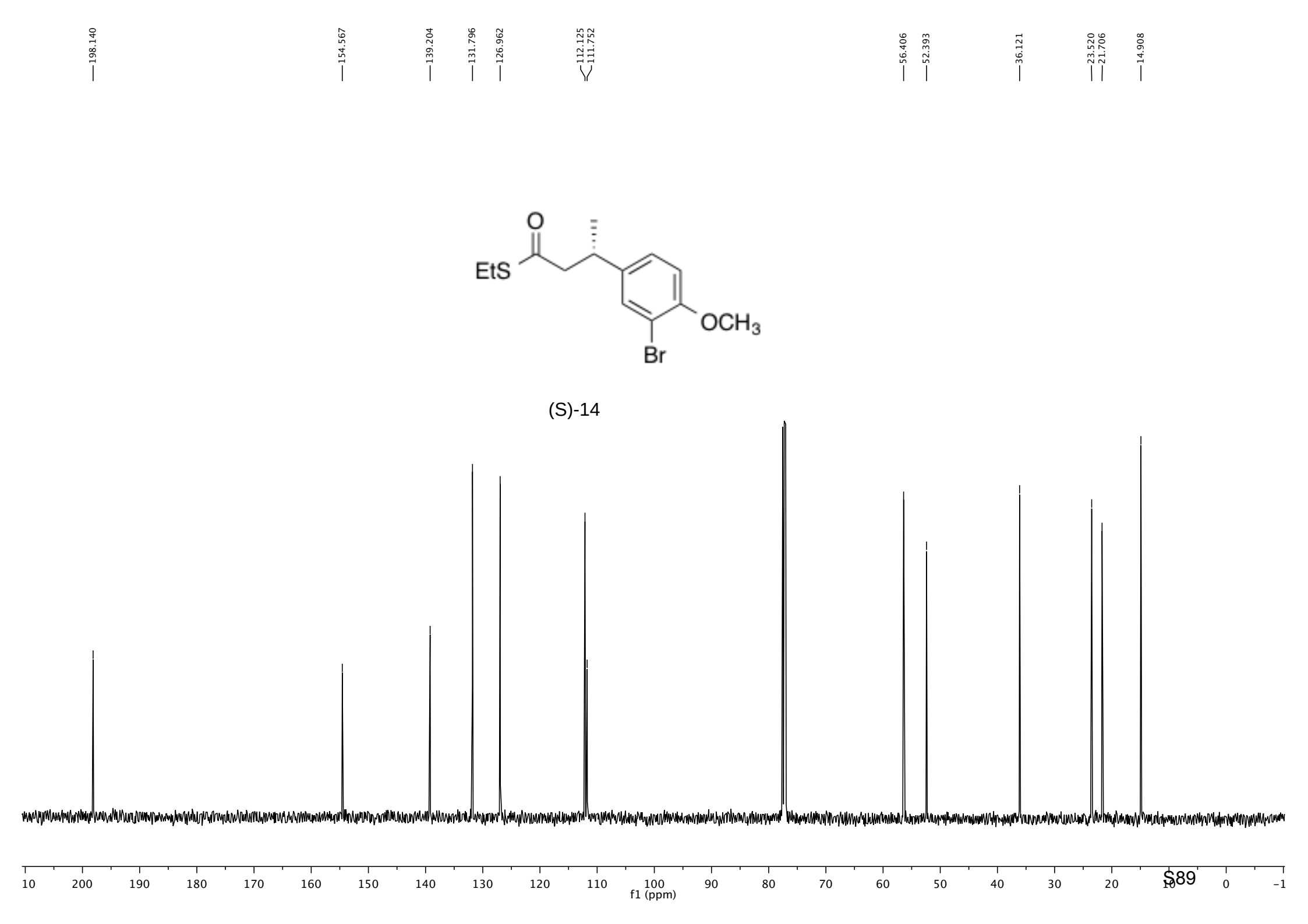


9

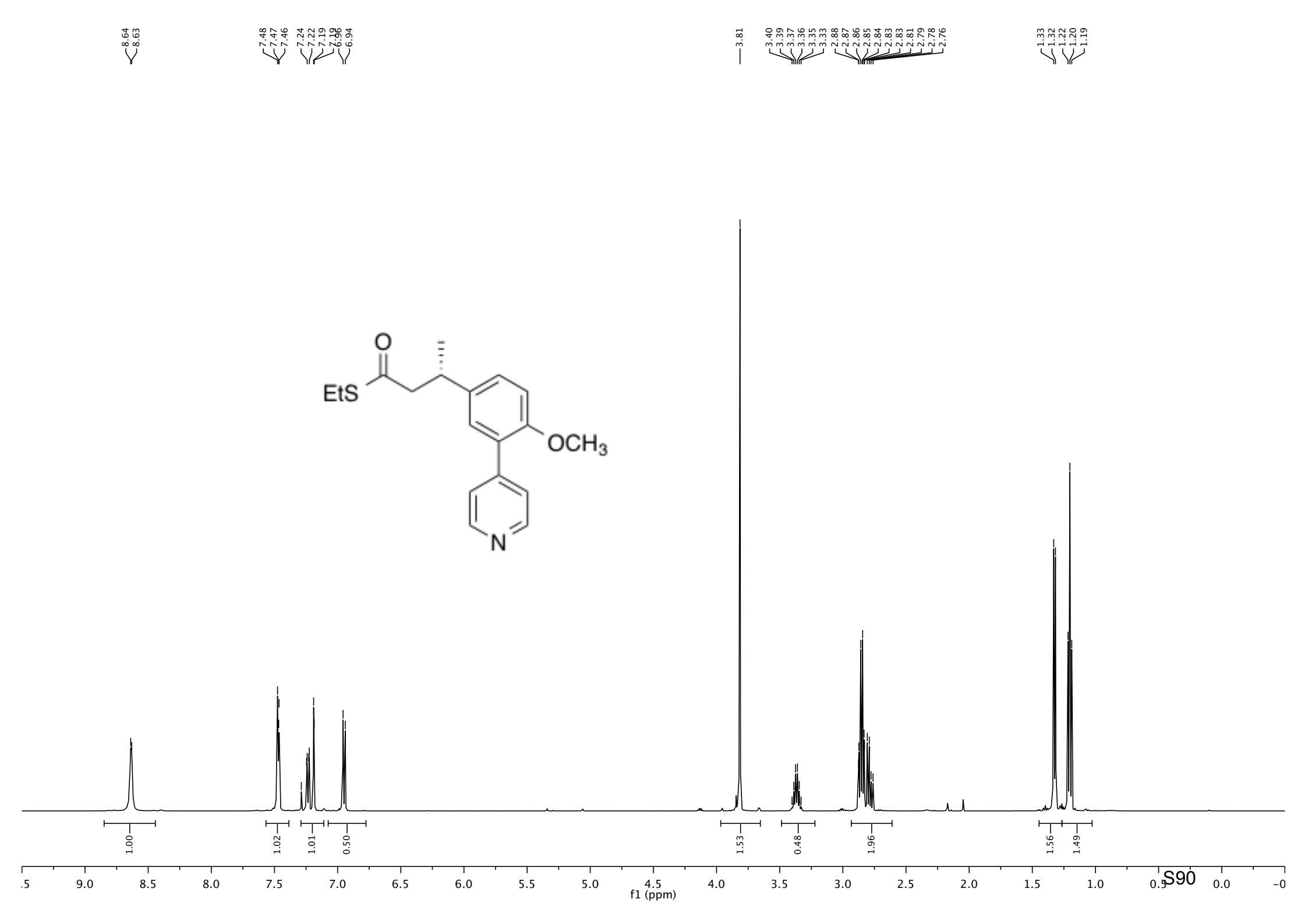

189.78
157.74
138.48
132.96
129.52
128.39
124.24
112.56
112.03
56.56
23.57
15.00
O
EtS
OCH3
Br
9
f1 (ppm)

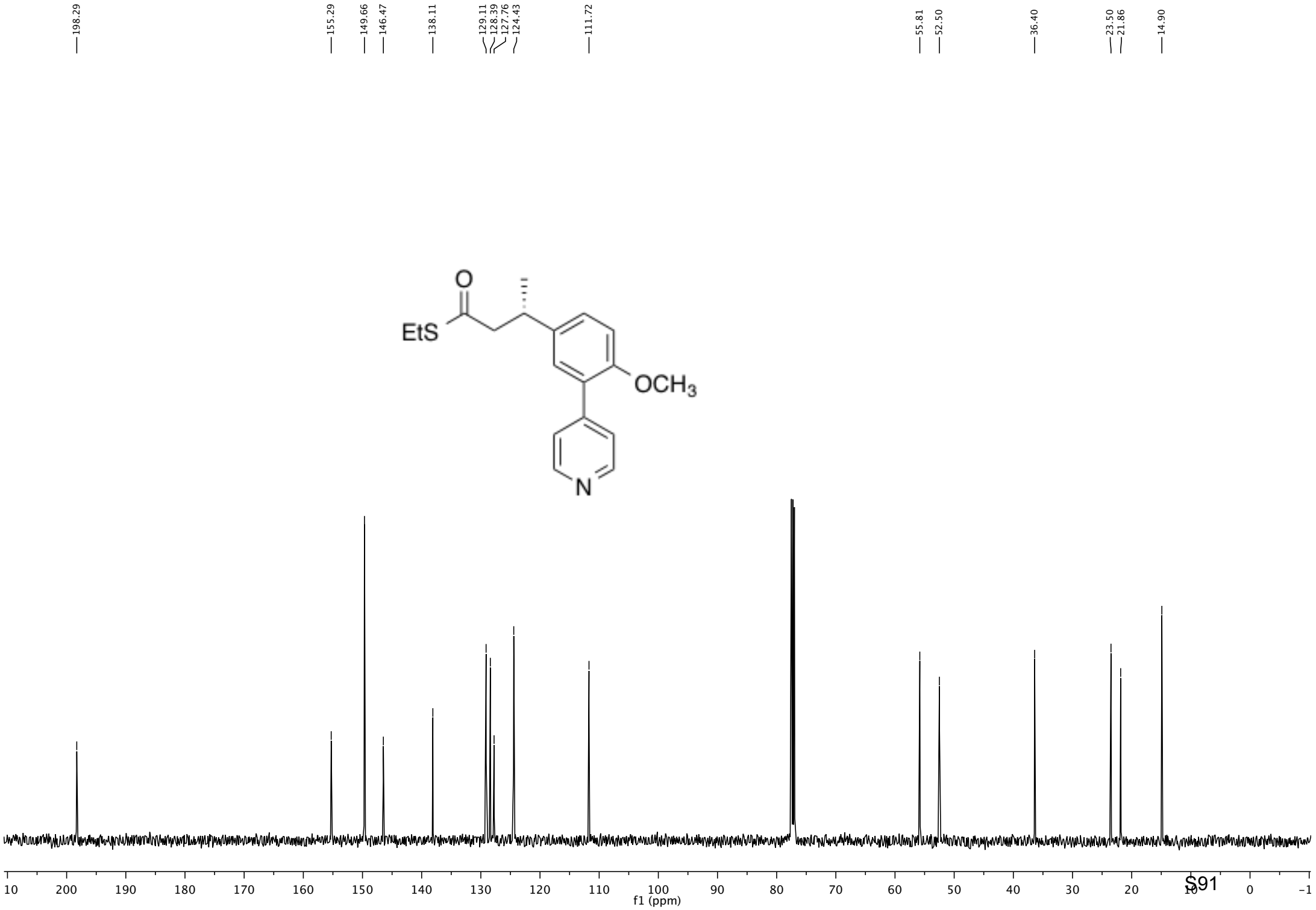

7.39
7.12
7.10
6.84
6.82
3.87
3.30
3.29
3.27
3.26
2.87
2.85
2.84
2.82
2.81
2.80
2.78
2.77
2.75
2.74
2.72
2.71
1.28
1.27
1.22
1.21
1.19
O
EtS
OCH3
Br
1.00
1.02
1.02
3.14
1.01
4.17
3.19
3.07
f1 (ppm)

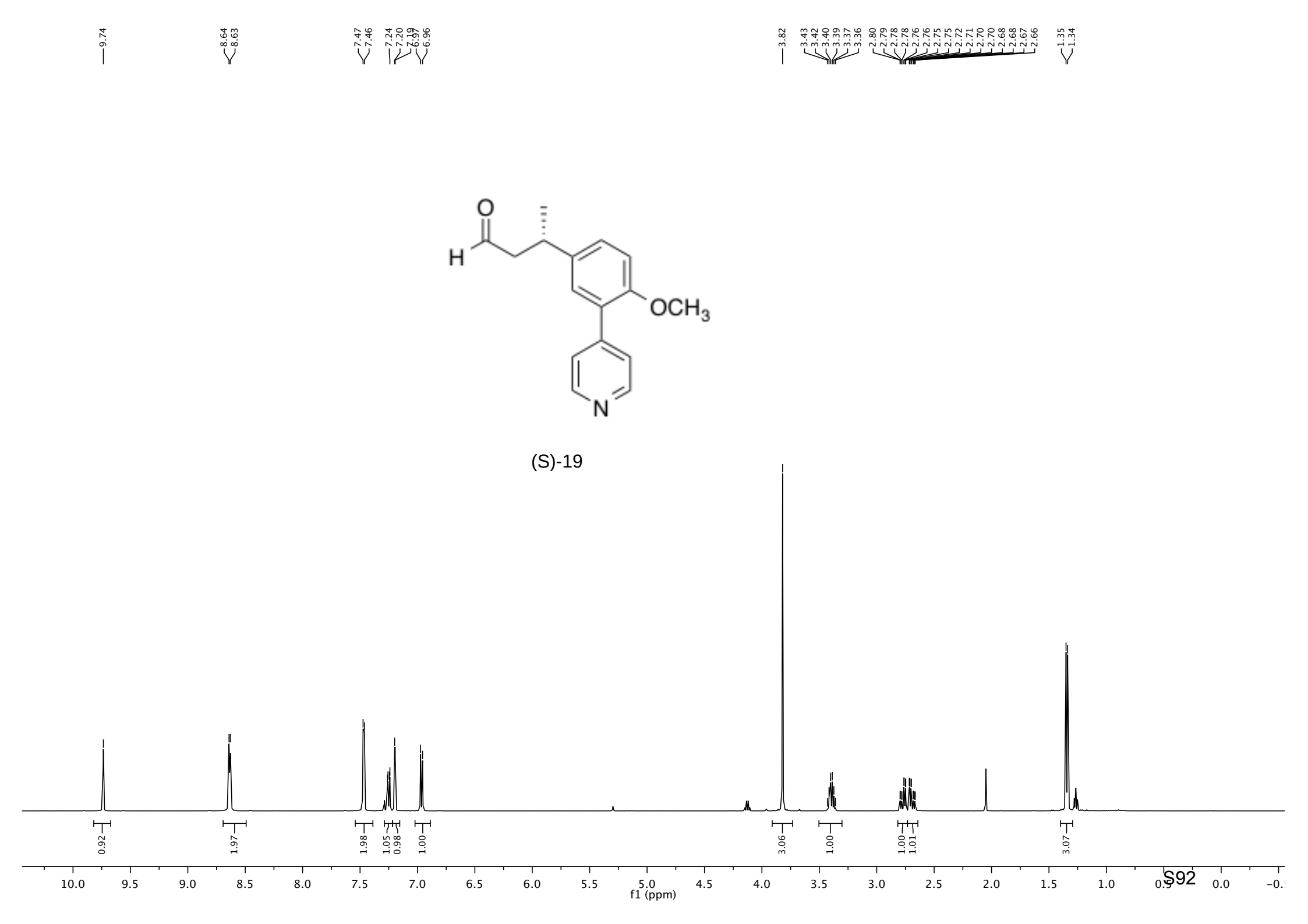
(S)-14

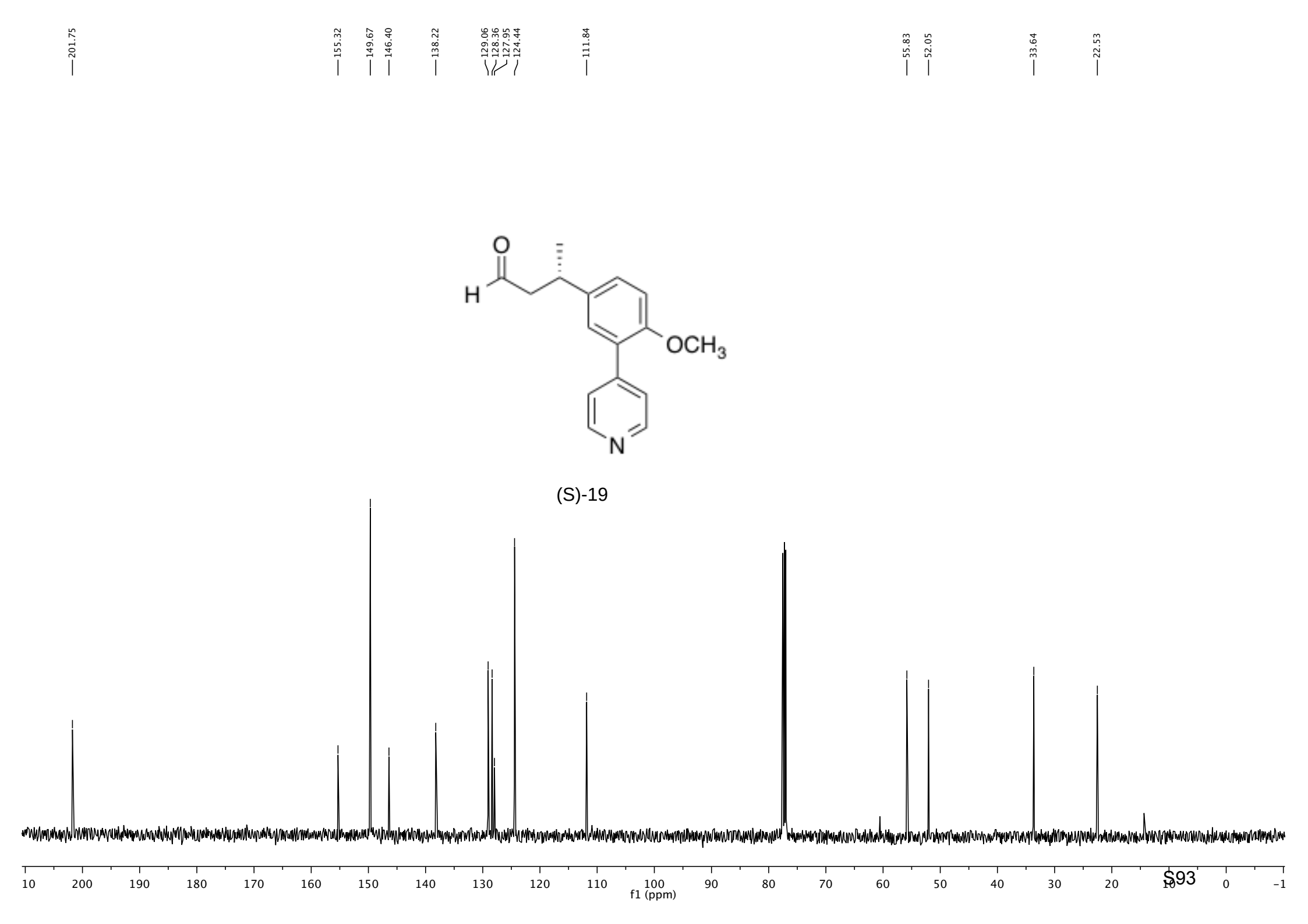

198.140
154.567
139.204
131.796
126.962
112.125
111.752
56.406
52.393
36.121
23.520
21.706
14.908
O
EtS
OCH3
Br
f1 (ppm)

(S)-14

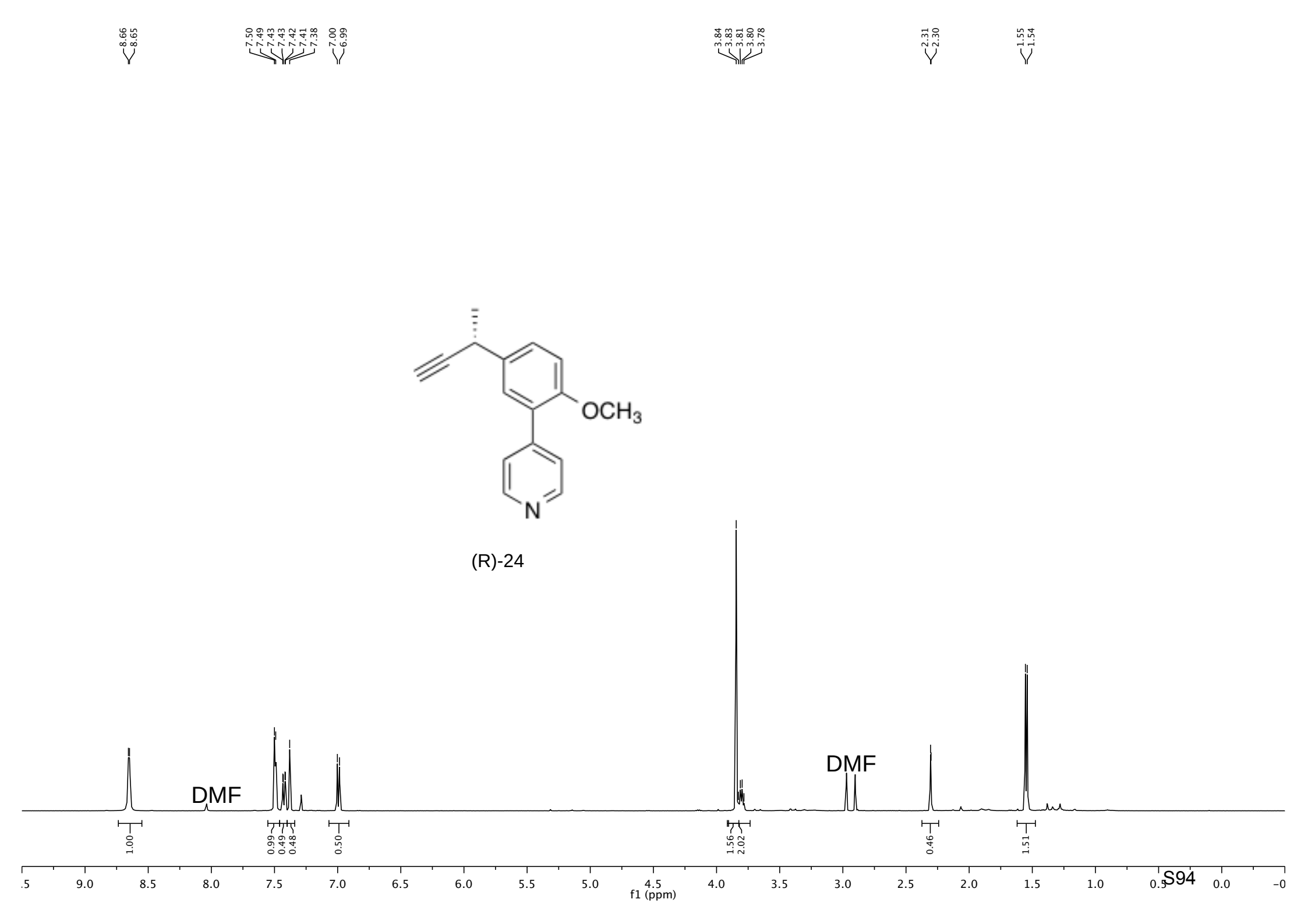

8.64
8.63
7.48
7.47
7.46
7.24
7.22
7.19
6.96
6.94
3.81
3.40
3.39
3.37
3.36
3.35
3.33
2.88
2.87
2.86
2.85
2.84
2.83
2.83
2.81
2.79
2.78
2.76
1.33
1.32
1.22
1.20
1.19
O
EtS
OCH3
N
1.00
1.02
1.01
0.50
1.53
0.48
1.96
1.56
1.49
f1 (ppm)

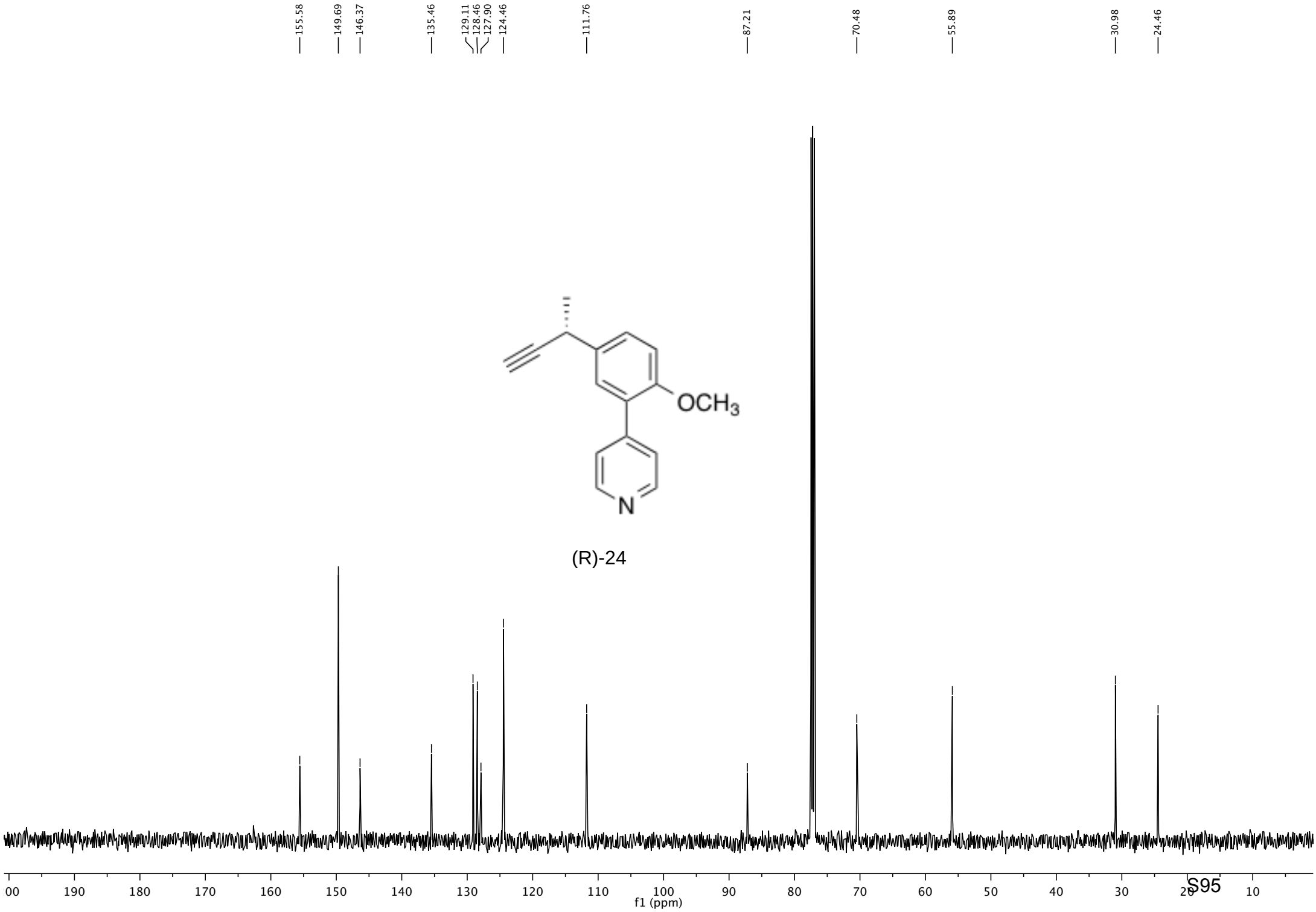

198.29
155.29
149.66
146.47
138.11
129.11
128.39
127.76
124.43
111.72
55.81
52.50
36.40
23.50
21.86
14.90
O
EtS
OCH3
N
f1 (ppm)

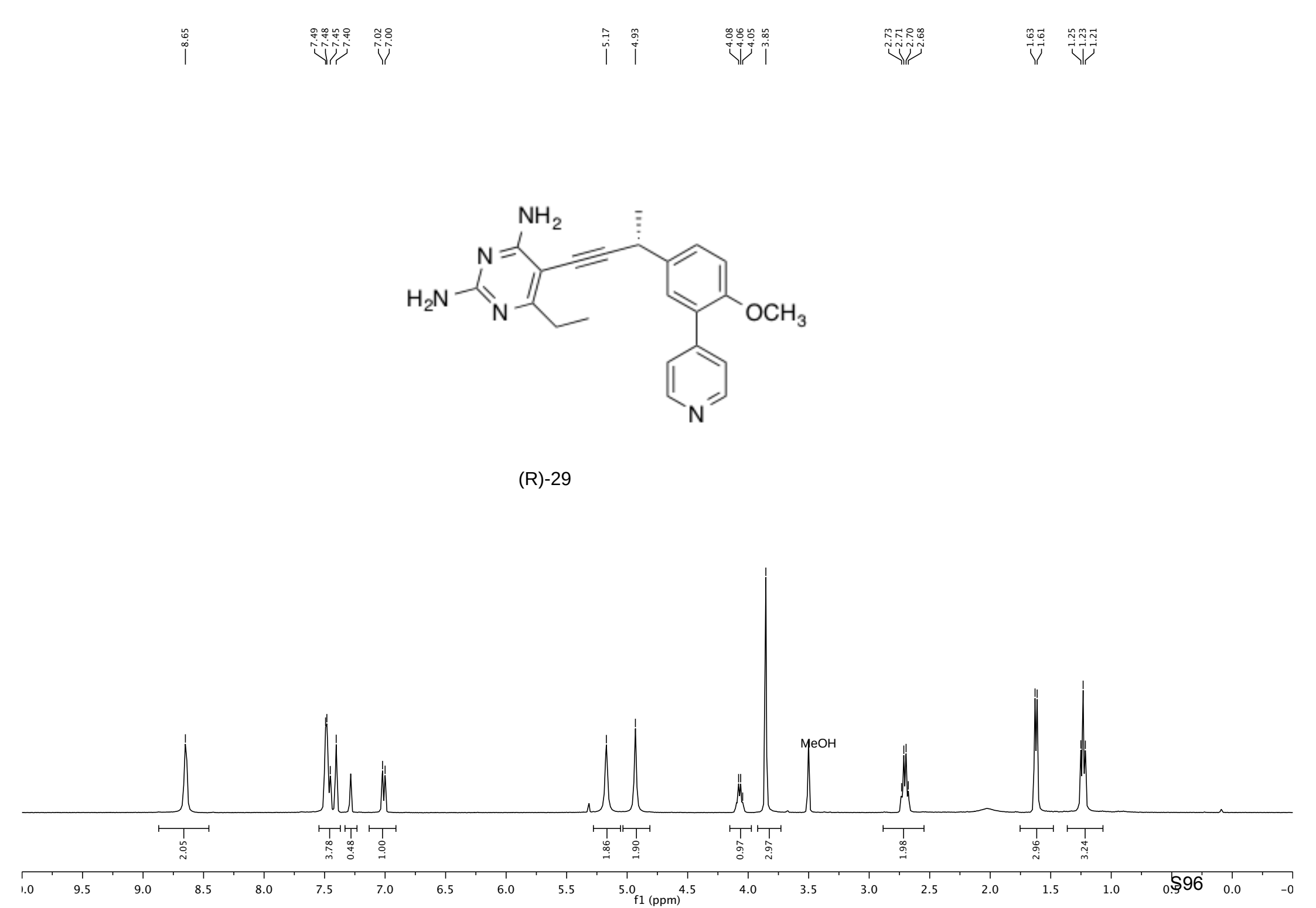

9.74
8.64
8.63
7.47
7.46
7.24
7.20
7.19
6.97
6.96
3.82
3.43
3.42
3.40
3.39
3.37
3.36
2.80
2.79
2.78
2.78
2.76
2.76
2.75
2.75
2.72
2.71
2.70
2.70
2.68
2.68
2.67
2.66
1.35
1.34
O
H
OCH3
N
(S)-19
0.92
1.97
1.98
1.05
0.98
1.00
3.06
1.00
1.00
1.01
3.07
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


201.75
155.32
149.67
146.40
138.22
129.06
128.36
127.95
124.44
111.84
55.83
52.05
33.64
22.53
O
H
OCH3
N
f1 (ppm)

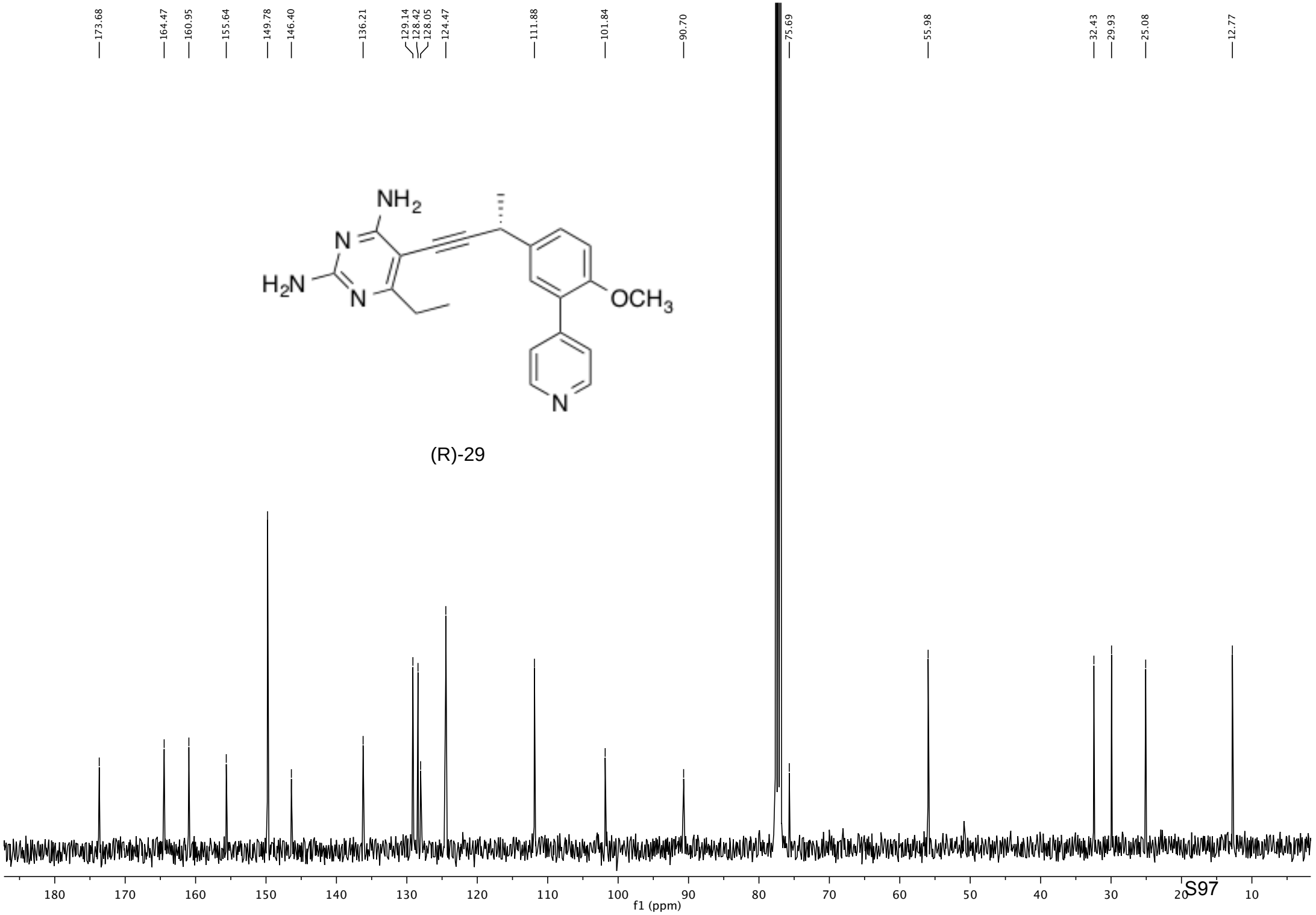
(S)-19

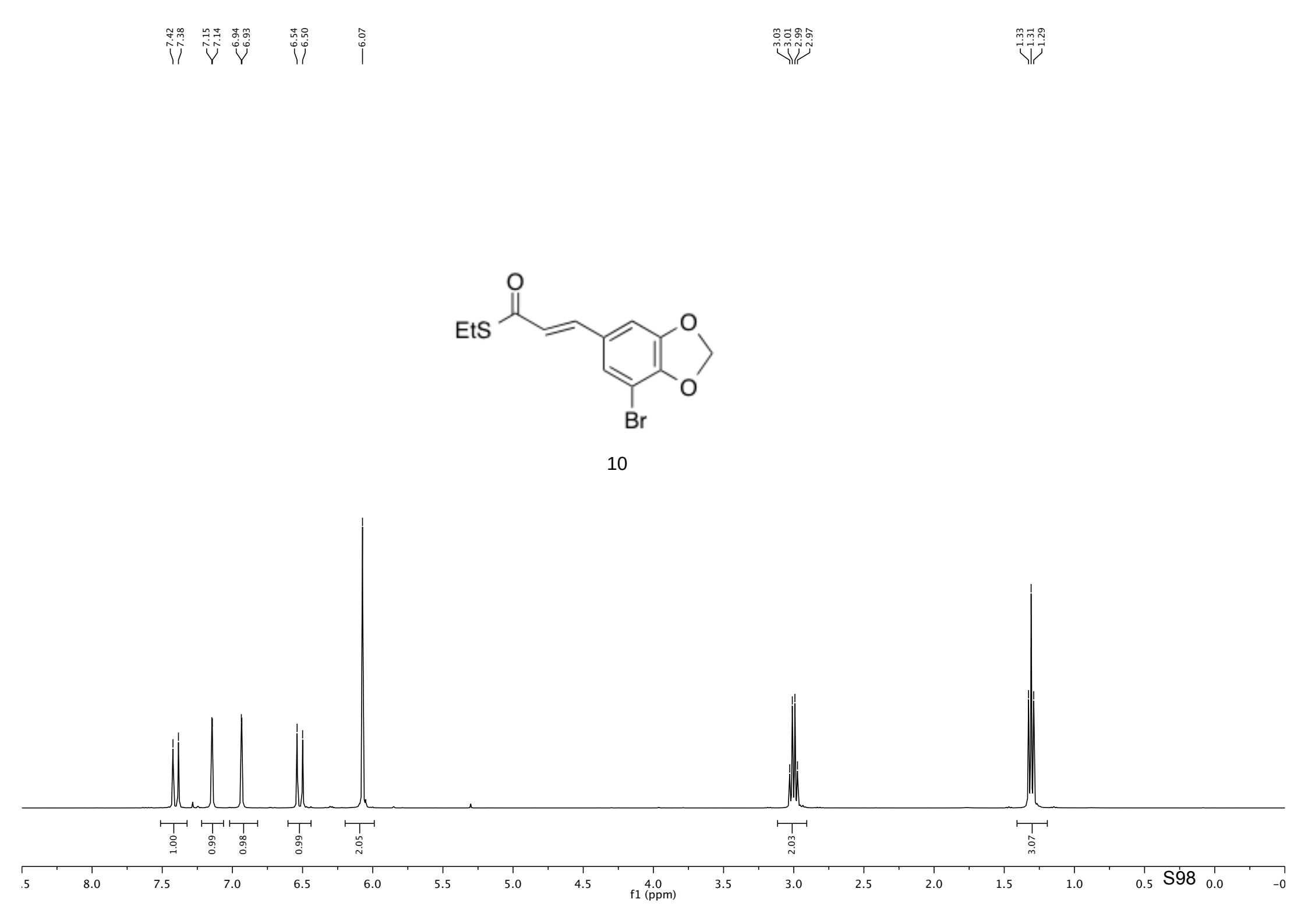

8.66
8.65
7.50
7.49
7.43
7.43
7.42
7.41
7.38
7.00
6.99
3.84
3.83
3.81
3.80
3.78
2.31
2.30
1.55
1.54
OCH3
N
(R)-24
DMF
DMF
1.00
0.99
0.49
0.48
0.50
1.56
2.02
0.46
1.51
f1 (ppm)


155.58
149.69
146.37
135.46
129.11
128.46
127.90
124.46
111.76
87.21
70.48
55.89
30.98
24.46
OCH3
N
(R)-24
f1 (ppm)

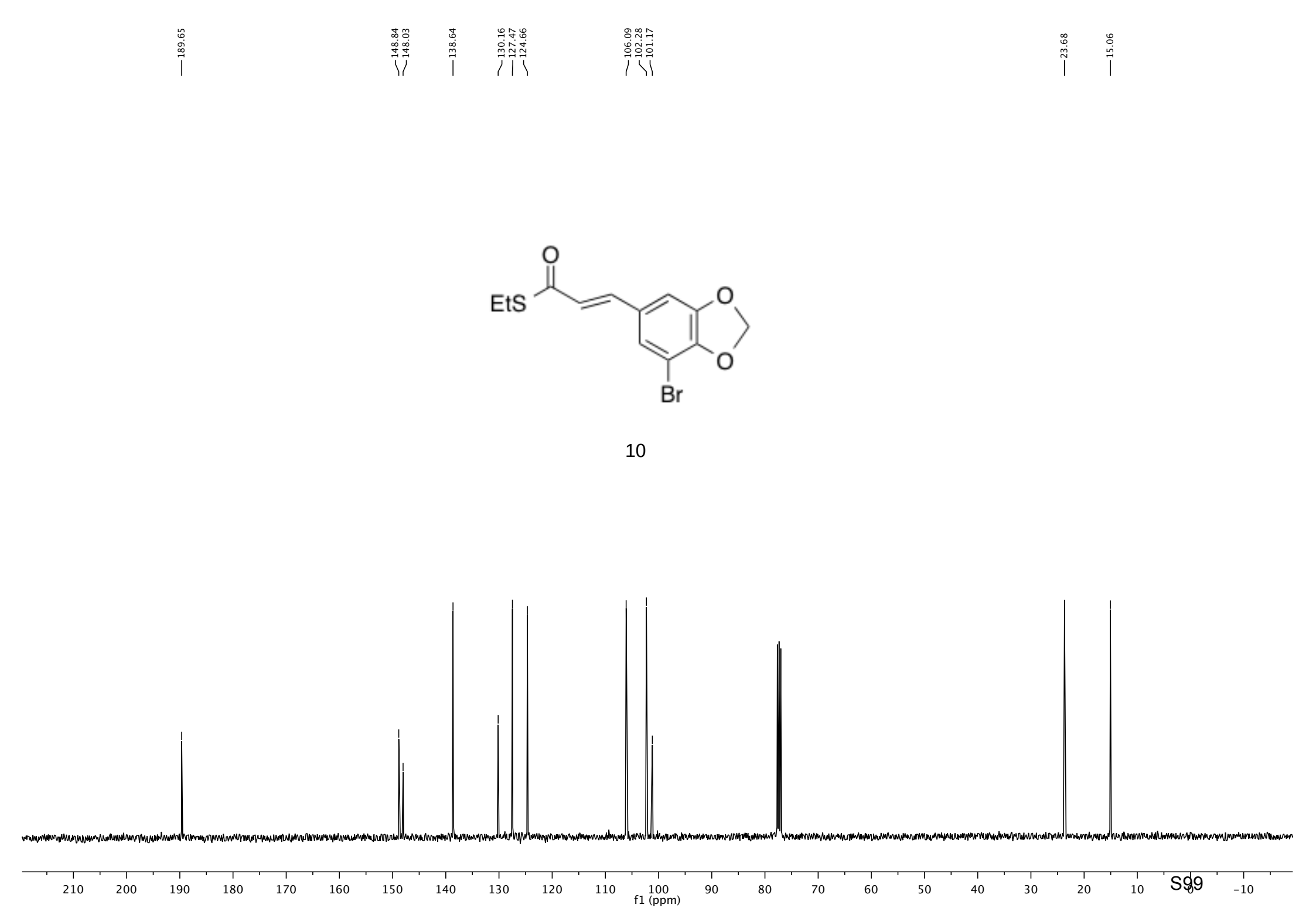

8.65
7.49
7.48
7.45
7.40
7.02
7.00
5.17
4.93
4.08
4.06
4.05
3.85
2.73
2.71
2.70
2.68
1.63
1.61
1.25
1.23
1.21
NH2
N
H2N
N
OCH3
N
MeOH
2.05
3.78
0.48
1.00
1.86
1.90
0.97
2.97
1.98
2.96
3.24
f1 (ppm)

(R)-29

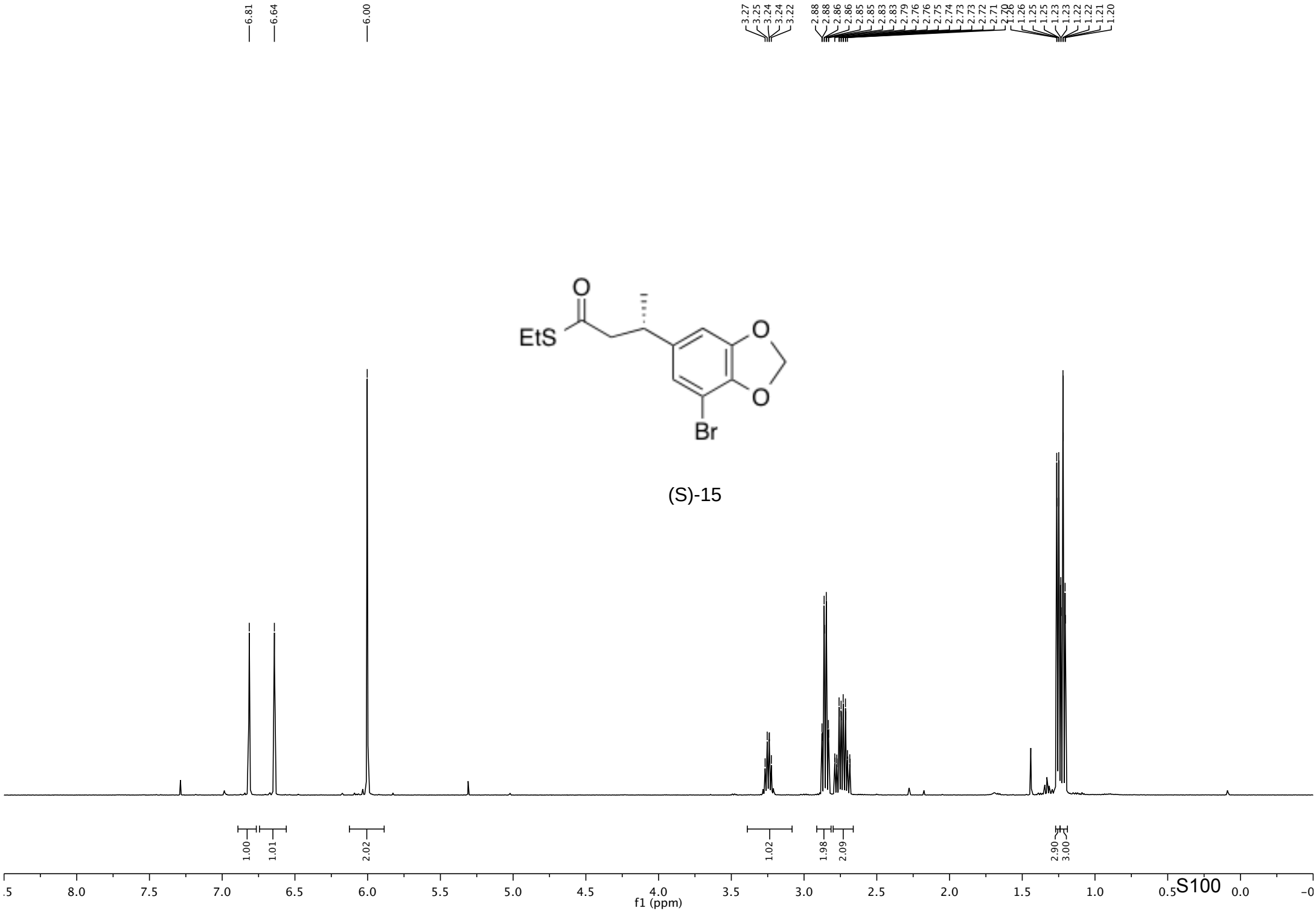

173.68
164.47
160.95
155.64
149.78
146.40
136.21
129.14
128.42
128.05
124.47
111.88
101.84
90.70
75.69
55.98
32.43
29.93
25.08
12.77
NH2
N
H2N
N
OCH3
N
(R)-29
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


7.42
7.38
7.15
7.14
6.94
6.93
6.54
6.50
6.07
3.03
3.01
2.99
2.97
1.33
1.31
1.29
O
EtS
O
O
Br
1.00
0.99
0.98
0.99
2.05
2.03
3.07
f1 (ppm)

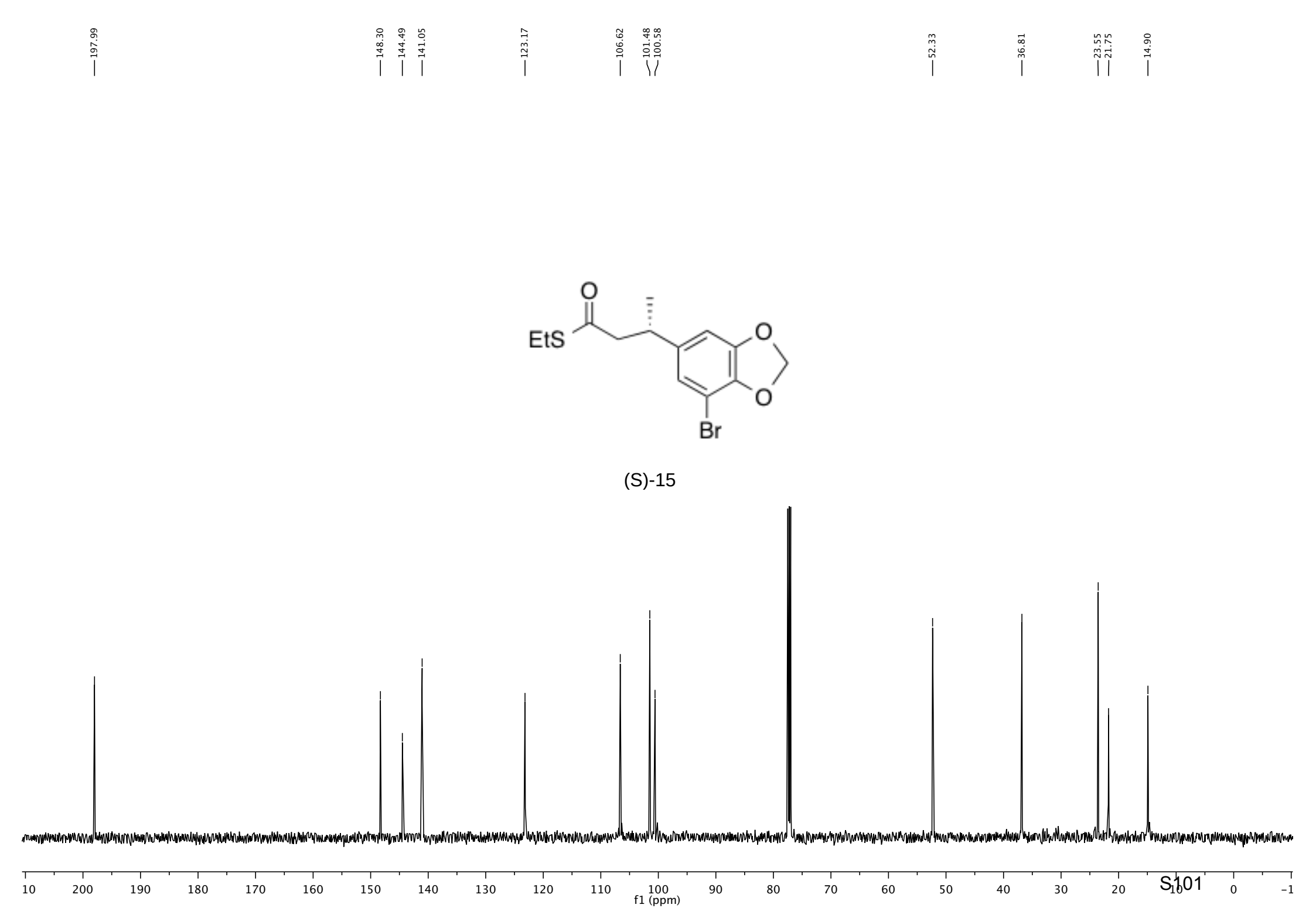
10


189.65
148.84
148.03
138.64
130.16
127.47
124.66
106.09
102.28
101.17
23.68
15.06
O
EtS
O
O
Br
f1 (ppm)

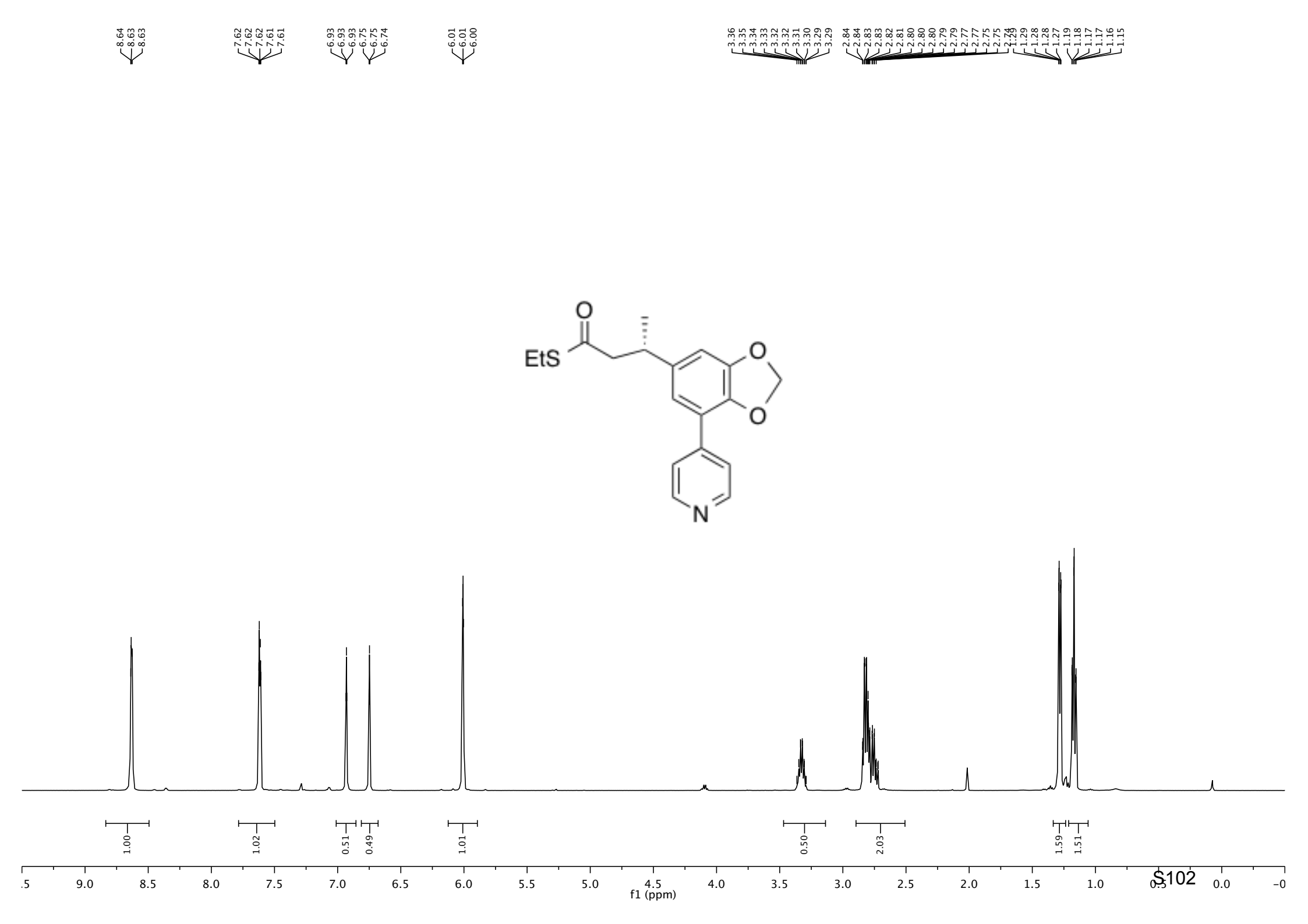
10

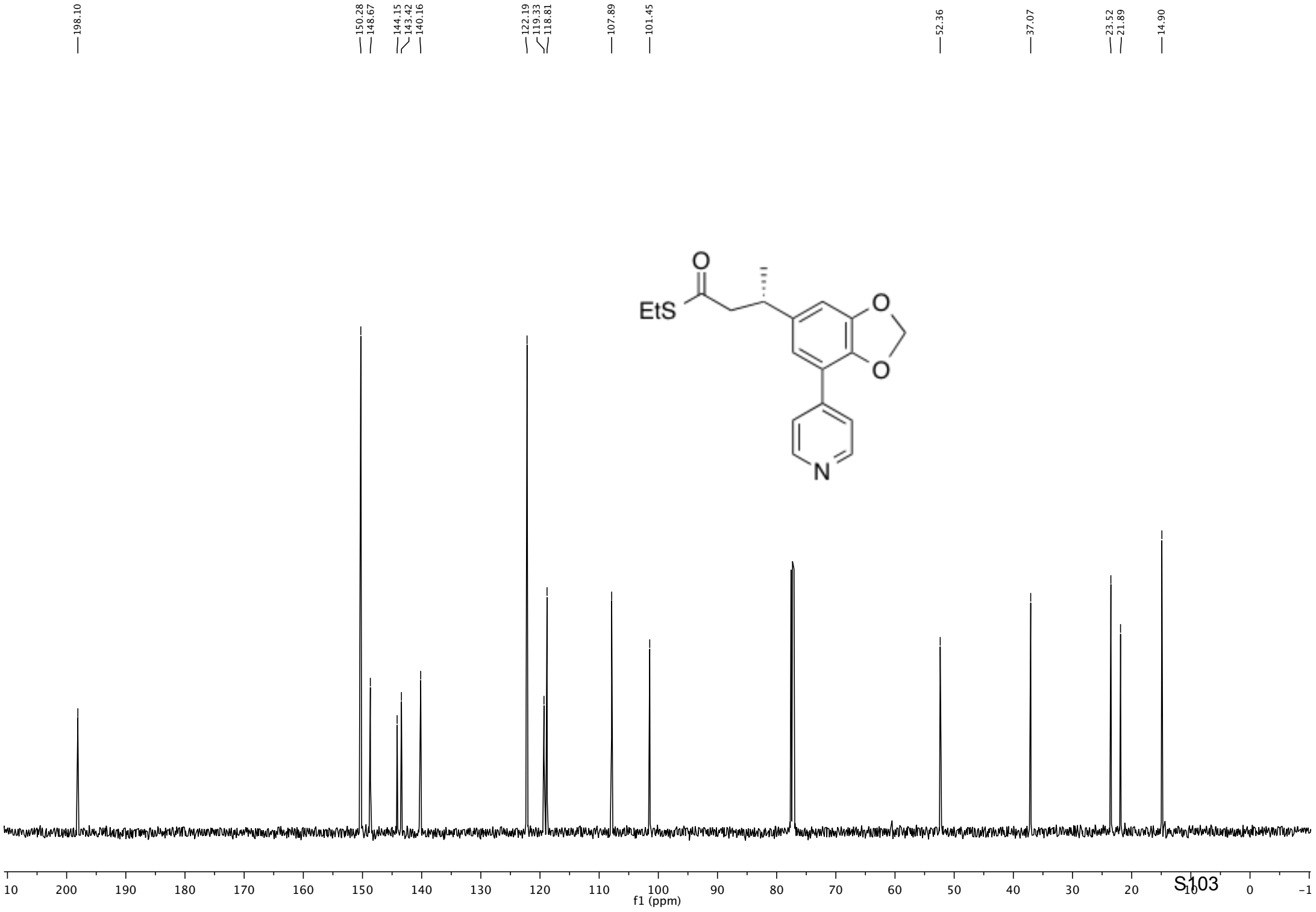

6.81
6.64
6.00
3.27
3.25
3.24
3.24
3.22
2.88
2.88
2.86
2.86
2.85
2.85
2.83
2.83
2.79
2.76
2.76
2.75
2.74
2.73
2.73
2.72
2.71
1.26
1.26
1.25
1.25
1.23
1.23
1.22
1.22
1.21
1.20
O
EtS
O
O
Br
1.00
1.01
2.02
1.02
1.98
2.09
2.90
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

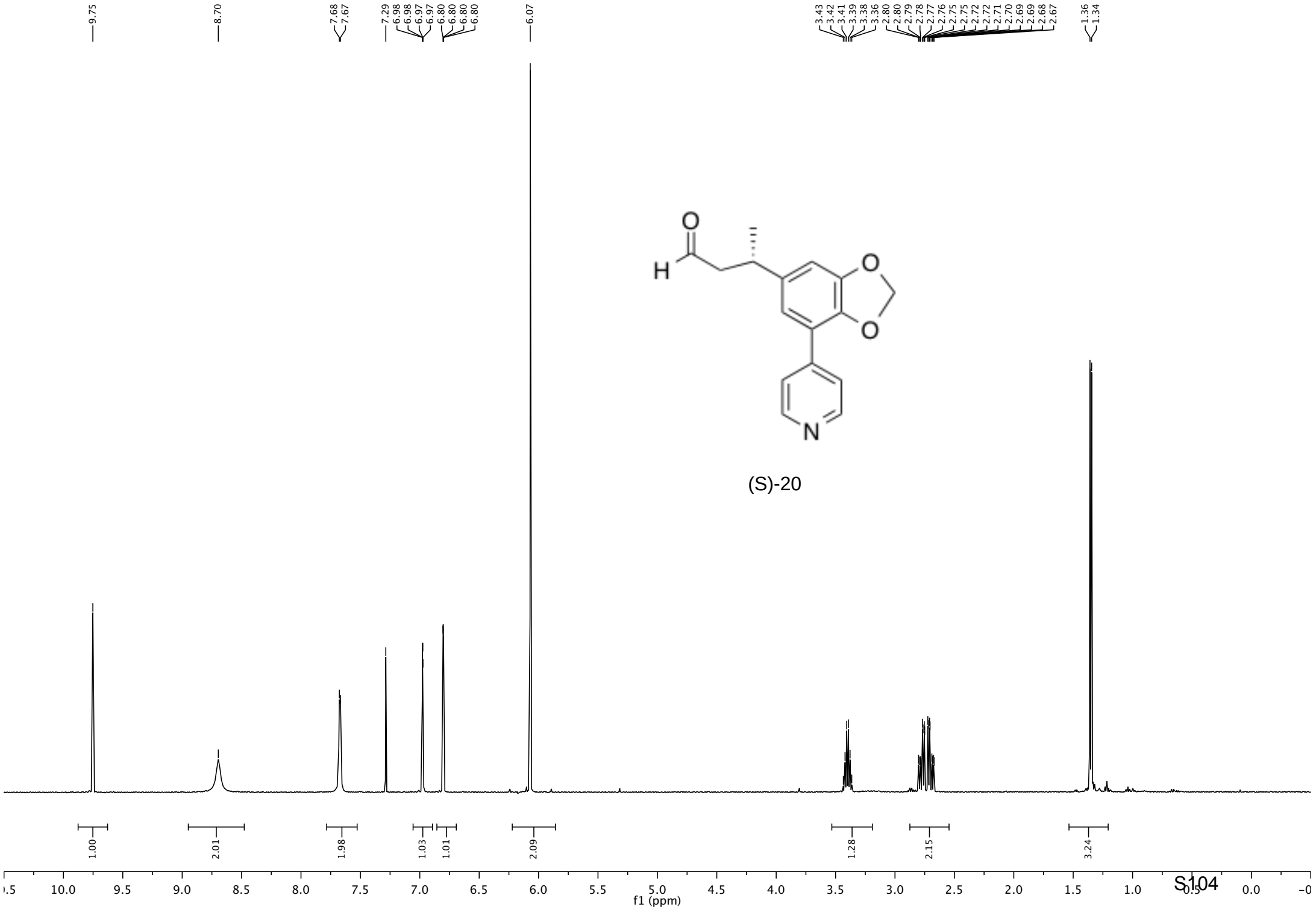
(S)-15


197.99
148.30
144.49
141.05
123.17
106.62
101.48
100.58
52.33
36.81
23.55
21.75
14.90
O
EtS
O
O
Br
f1 (ppm)

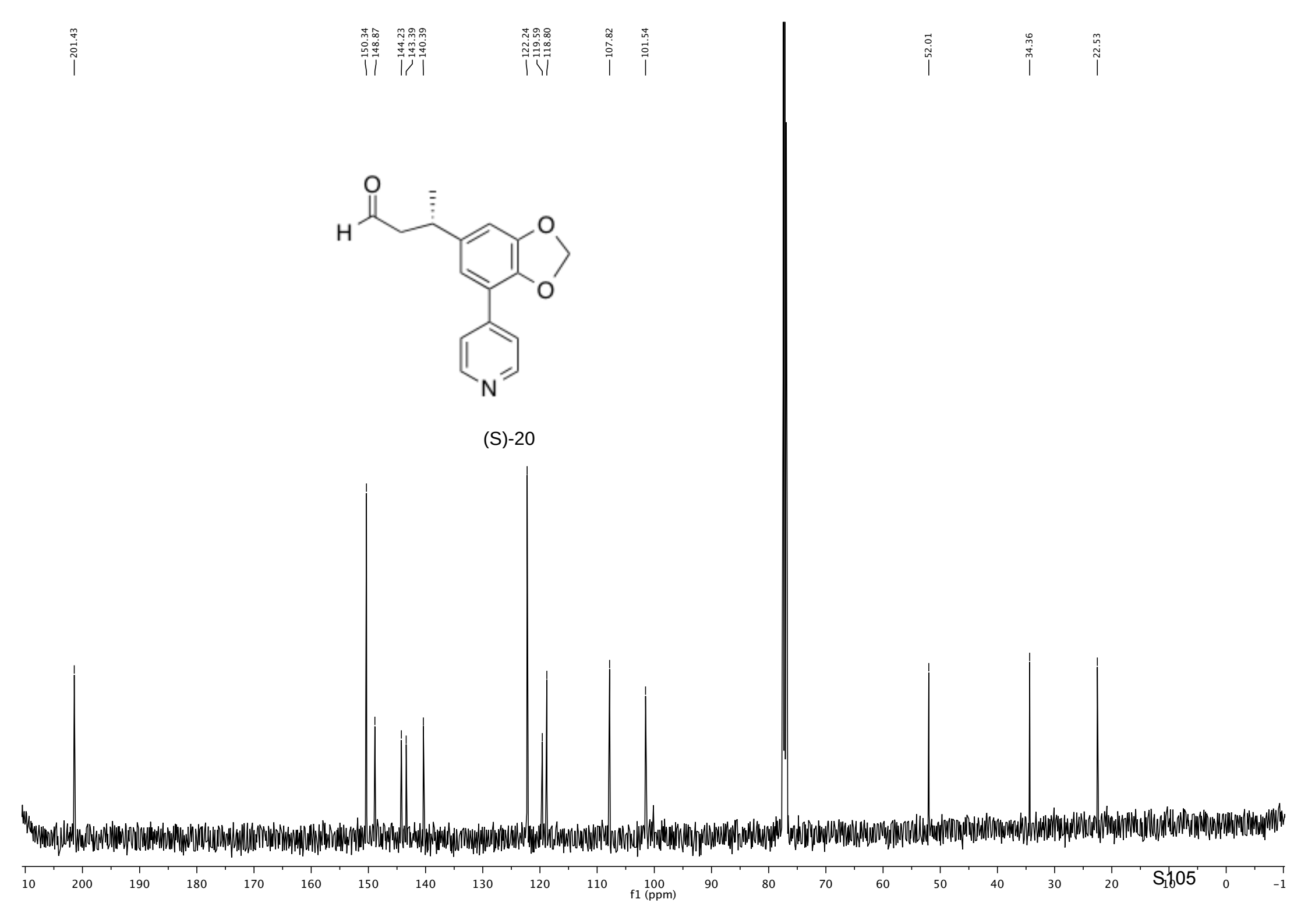
(S)-15

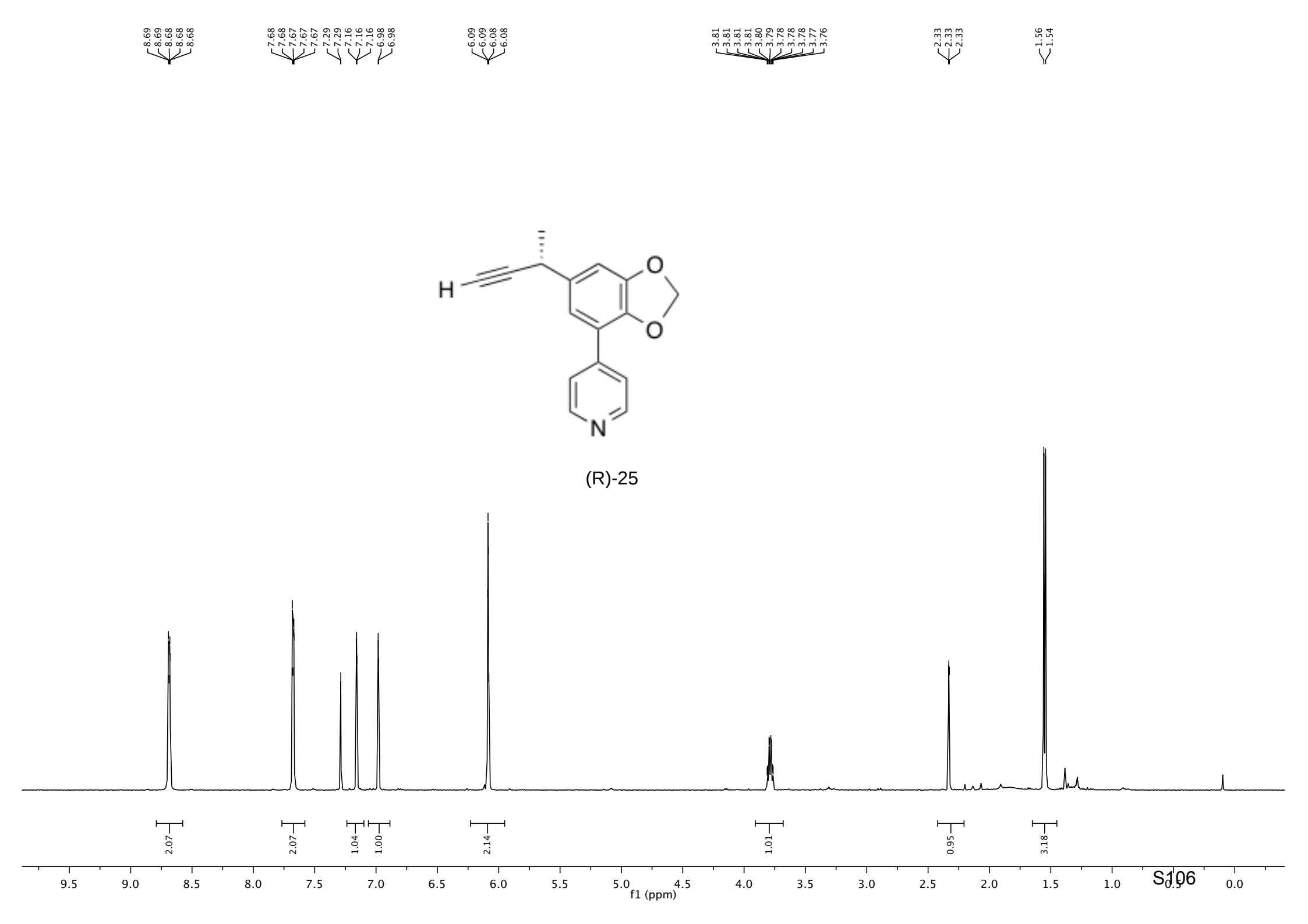

8.64
8.63
8.63
7.62
7.62
7.62
7.61
7.61
6.93
6.93
6.93
6.75
6.75
6.74
6.01
6.01
6.00
3.36
3.35
3.34
3.33
3.32
3.31
3.30
3.29
3.29
2.84
2.84
2.83
2.83
2.82
2.81
2.80
2.80
2.80
2.79
2.79
2.77
2.77
2.75
2.75
1.29
1.28
1.28
1.27
1.19
1.18
1.17
1.17
1.16
1.15
O
EtS
O
O
N
1.00
1.02
0.51
0.49
1.01
0.50
2.03
1.59
1.51
f1 (ppm)

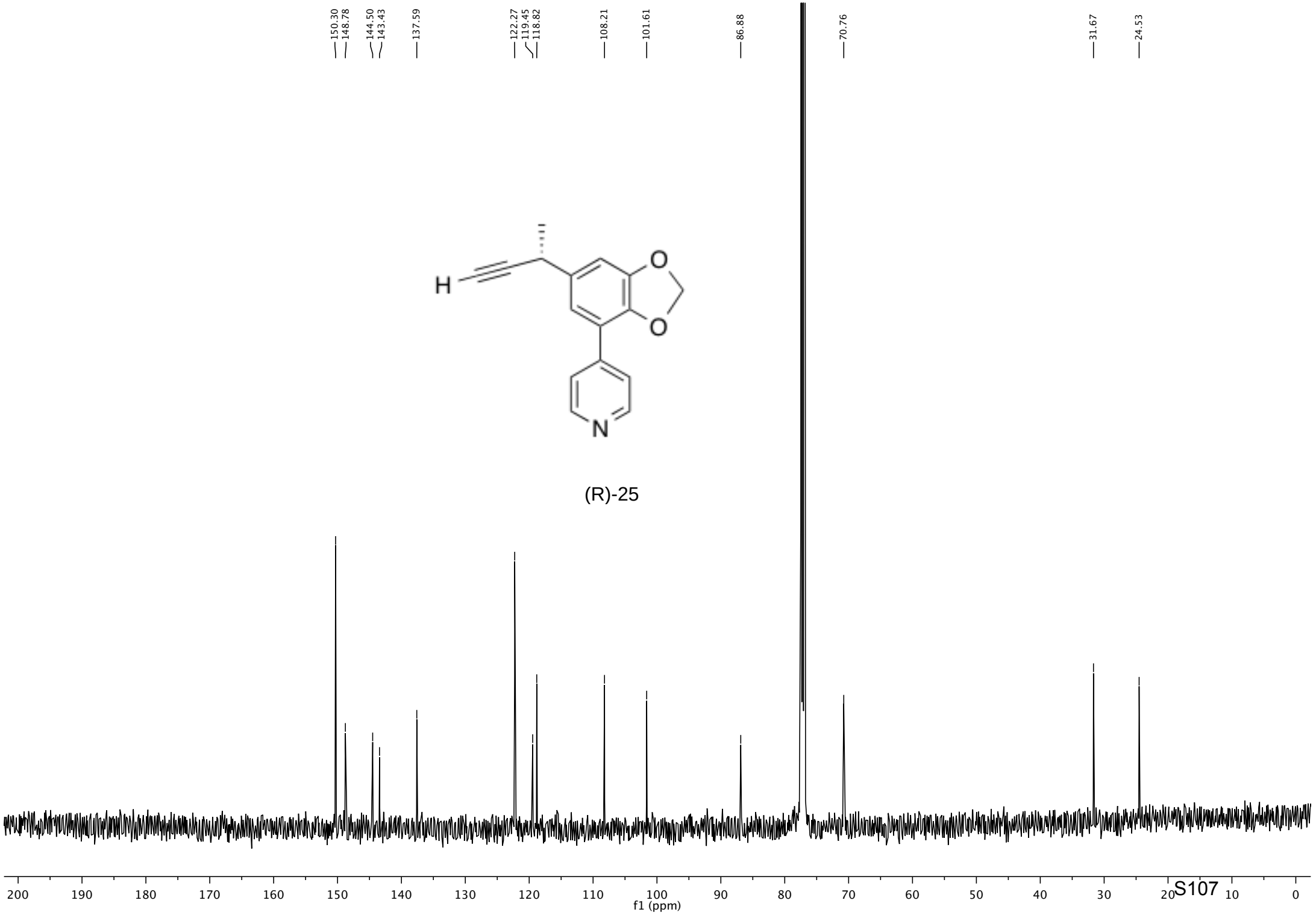

198.10
150.28
148.67
144.15
143.42
140.16
122.19
119.33
118.81
107.89
101.45
52.36
37.07
23.52
21.89
14.90
O
EtS
O
O
N
f1 (ppm)


9.75
8.70
7.68
7.67
7.29
6.98
6.98
6.97
6.97
6.80
6.80
6.80
6.80
6.07
3.43
3.42
3.41
3.39
3.38
3.36
2.80
2.80
2.79
2.78
2.77
2.76
2.75
2.75
2.72
2.72
2.71
2.70
2.69
2.69
2.68
2.67
1.36
1.34
O
H
O
O
N
1.00
2.01
1.98
1.03
1.01
2.09
1.28
2.15
3.24
f1 (ppm)

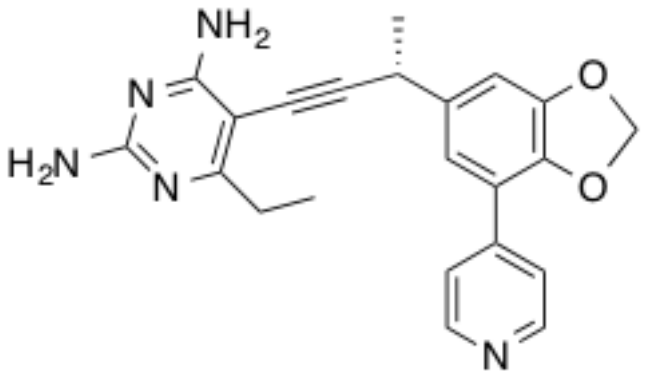
(S)-20


201.43
150.34
148.87
144.23
143.39
140.39
122.24
119.59
118.80
107.82
101.54
52.01
34.36
22.53
O
H
O
O
N
(S)-20
f1 (ppm)

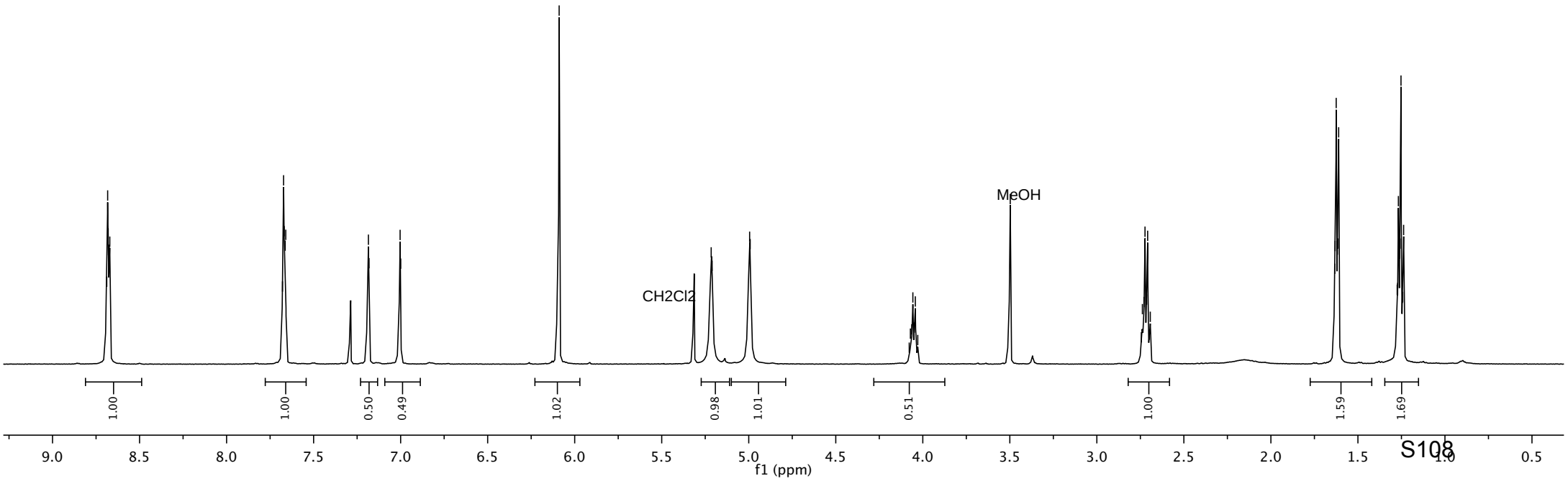

8.69
8.69
8.68
8.68
8.68
7.68
7.68
7.67
7.67
7.67
7.29
7.29
7.16
7.16
7.16
6.98
6.98
6.09
6.09
6.08
6.08
3.81
3.81
3.81
3.81
3.80
3.79
3.78
3.78
3.78
3.77
3.76
2.33
2.33
2.33
1.56
1.54
H
O
O
N
(R)-25
2.07
2.07
1.04
1.00
2.14
1.01
0.95
3.18
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

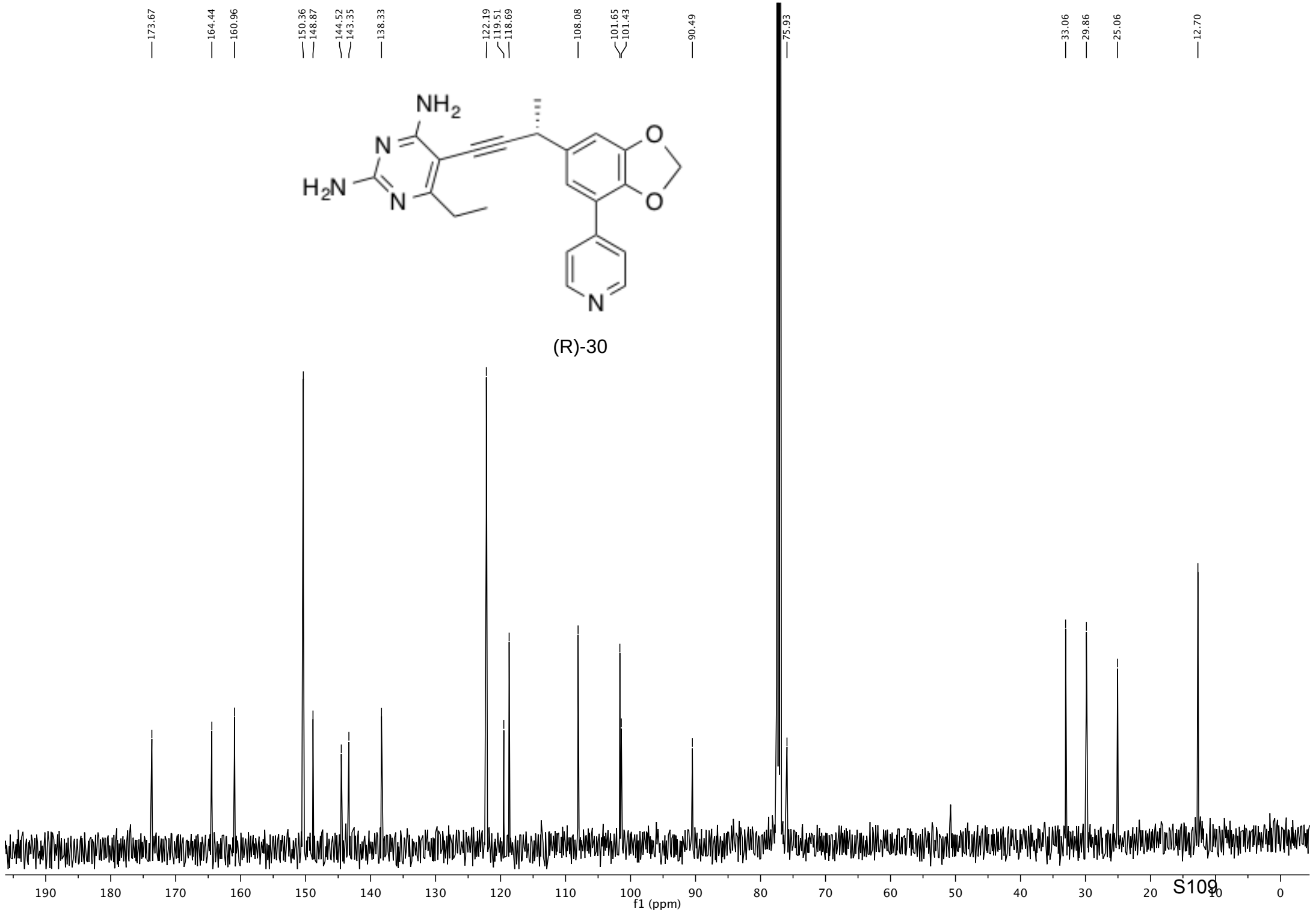

150.30
148.78
144.50
143.43
137.59
122.27
119.45
118.82
108.21
101.61
86.88
70.76
31.67
24.53
H
O
O
N
(R)-25
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.69
8.68
8.68
8.68
8.67
8.67
7.68
7.67
7.67
7.66
7.66
7.19
7.18
7.00
7.00
6.09
5.22
5.21
4.99
4.99
4.08
4.07
4.06
4.06
4.05
4.04
4.03
3.50
2.74
2.74
2.73
2.72
2.71
2.71
2.70
2.69
1.63
1.63
1.62
1.62
1.62
1.61
1.27
1.27
1.27
1.26
1.26
1.25
1.24
1.24
1.24


NH2
N
H2N
N
O
O
N

(R)-30


MeOH
CH2Cl2
1.00
1.00
0.50
0.49
1.02
0.98
1.01
0.51
1.00
1.59
1.69
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)


173.67
164.44
160.96
150.36
148.87
144.52
143.35
138.33
122.19
119.51
118.69
108.08
101.65
101.43
90.49
75.93
33.06
29.86
25.06
12.70
NH2
N
H2N
N
O
O
N
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

(R)-30

Table S1. Crystallographic data collection and refinement statistics

	Sa(WT):NADPH:**R-27**	Sa(WT):NADPH:**S-27**
PDB ID	4XEC	4TU5
Space group	$P6_122$	$P6_122$
No. monomers in asymmetric unit	1	1
Unit cell (*a, b, c* in Å)	78.90, 78.90, 108.12	79.14, 79.14, 108.99
Resolution (Å)	31.89-2.69	58.02-2.16
Completeness % (last shell, %)	99.97 (98.6)	99.8 (100)
Unique reflections	5,929	11,493
Redundancy (last shell)	18.2 (17.4)	12.94 (13.26)
Rsym, (last shell)	0.160 (0.428)	0.154 (0.437)
$\langle I/\sigma \rangle$ (last shell)	38.6 (9.0)	8.8 (3.6)
R-factor/Rfree	0.1564, 0.2327	0.1990, 0.2495
No. of atoms (protein, ligands, solvent)	1,398	1,496
Rms deviation bond lengths (Å), angles (deg)	0.008, 1.343	0.008, 1.248
Average B factor for protein ($Å^2$)	30.22	30.75
Average B factor for ligand ($Å^2$)	26.89 (NADPH) 33.49 (DRG)	25.64 (NADPH) 35.86 (DRG)
Average B factor for solvent molecules ($Å^2$)	28.17	39.06
Residues in most favored regions (%)	96.79	97.44
Residues in additional allowed regions (%)	3.21	2.56
Residues in disallowed regions (%)	0	0
Collection Location	Brookhaven National Lab NSLS X25 Beamline	Rigaku HighFlux HomeLab

Table S2: Reduction (Fold-Change) in Antibacterial Activity in the Presence of Efflux Inhibitors

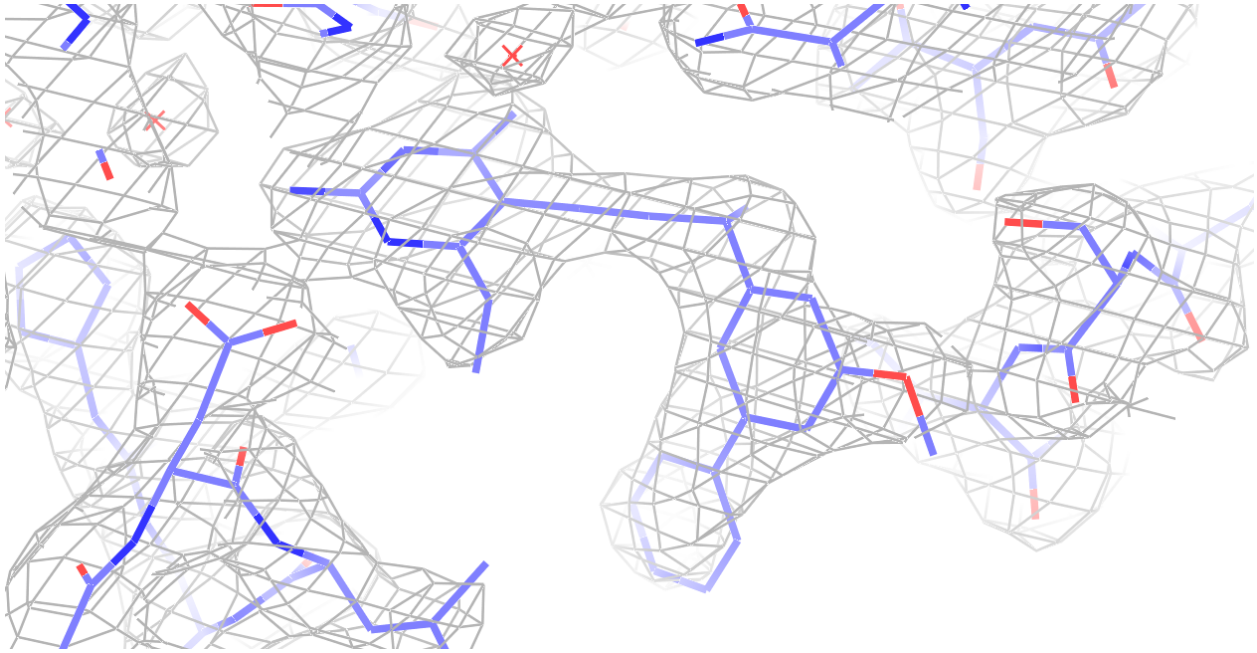
Compounds	Reserpine	Verapamil	Thioridazine[a]
R-26	2	2	8
S-26	2	2	8
R-27	2	2	8
S-27	2	2	8
R-28	No change	2	No change
S-28	2	2	No change
R-29	2	No change	4
S-29	No change	No change	4
R-30	2	2	4
S-30	2	2	4

[a]MIC values in the presence of thioridazine are also affected by the antibacterial effects of the compound, which has an MIC value of 25 μg/mL, in addition to efflux inhibitory properties.

Table S3: MIC Values in the Presence of Thymidine Rescue

Compounds	Isosensitest (μg/mL)	Isosensitest+Thymidine (μg/mL)
R-26	1.25	10
S-26	0.0781	5
R-27	0.3125	5
S-27	0.0391	5
R-28	1.25	10
S-28	2.5	≥20
R-29	1.25	10
S-29	0.3125	10
R-30	0.3125	5
S-30	0.0781	10

Figure S1. Electron Density for Structure of SaDHFR:NADPH:**R-27**



NADPH

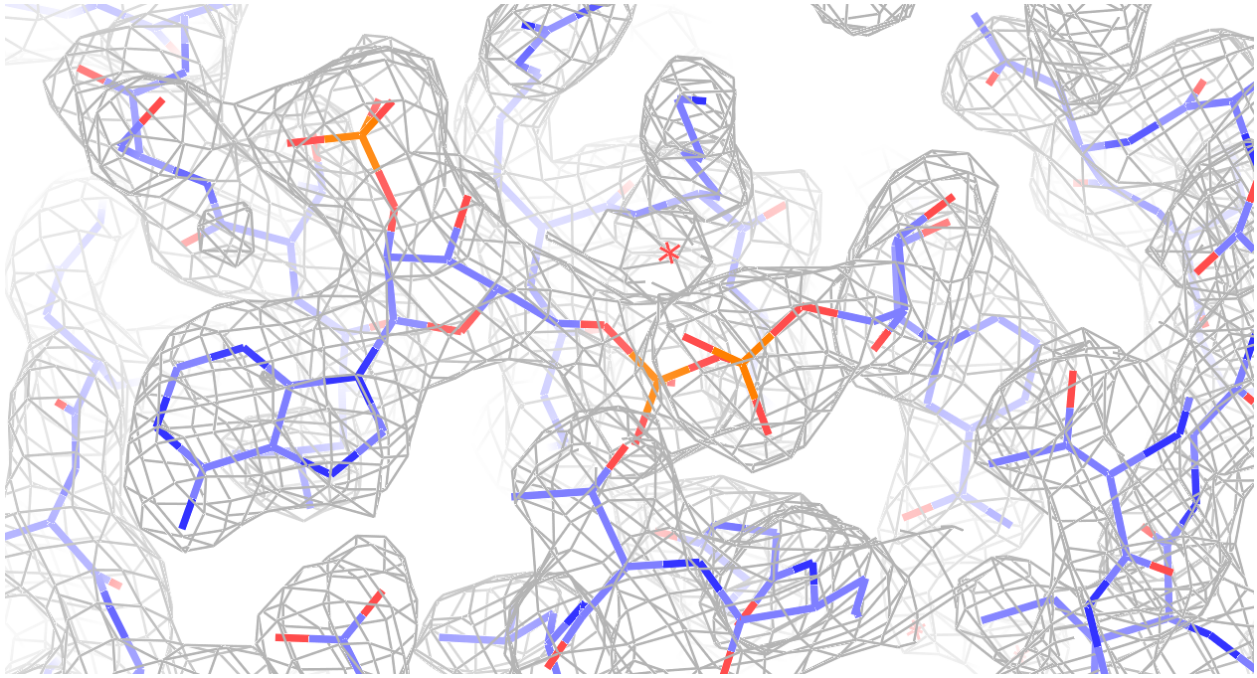
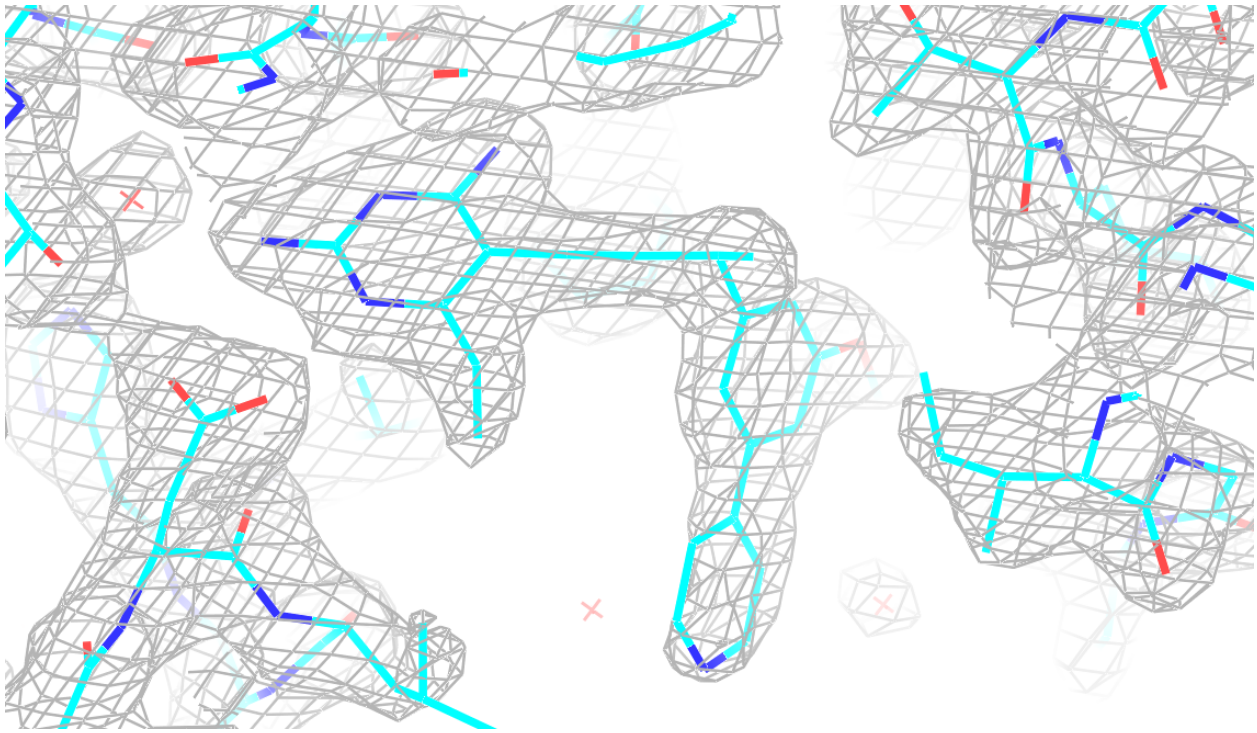


Figure S2. Electron Density for Structure of SaDHFR:NADPH:**S-27**



NADPH

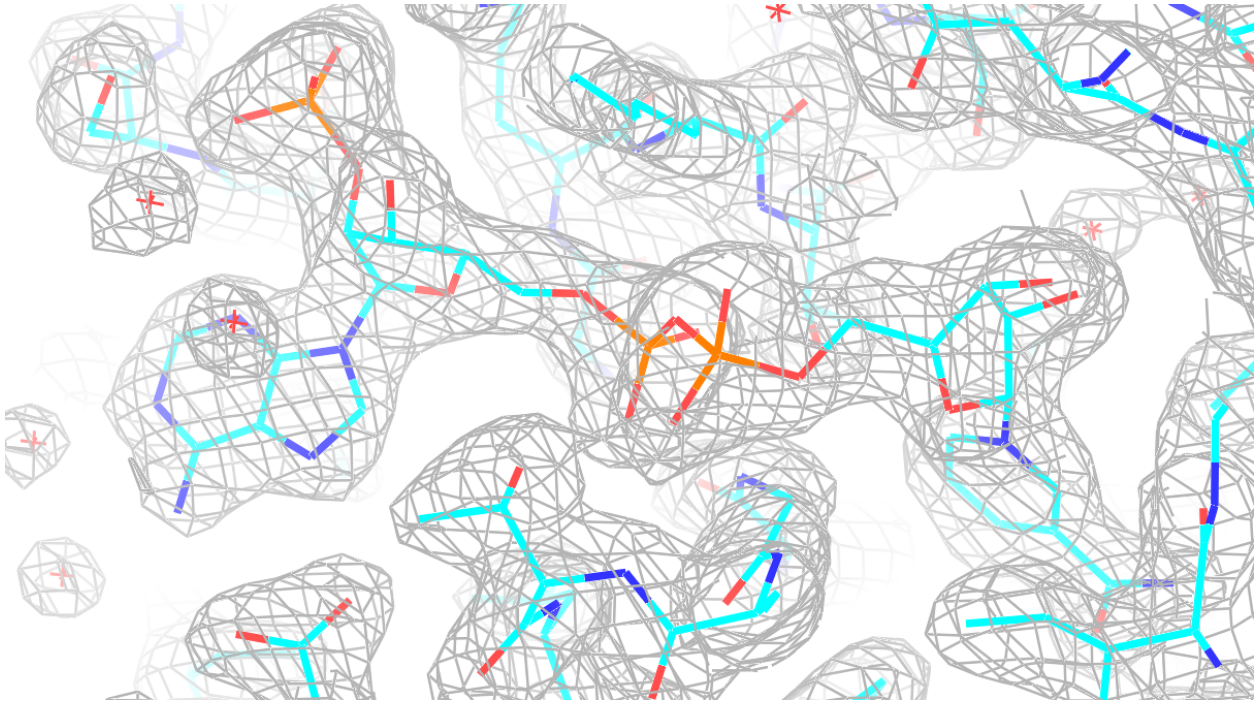


Figure S3. Overlay of **R-27** with **UCP 115A**

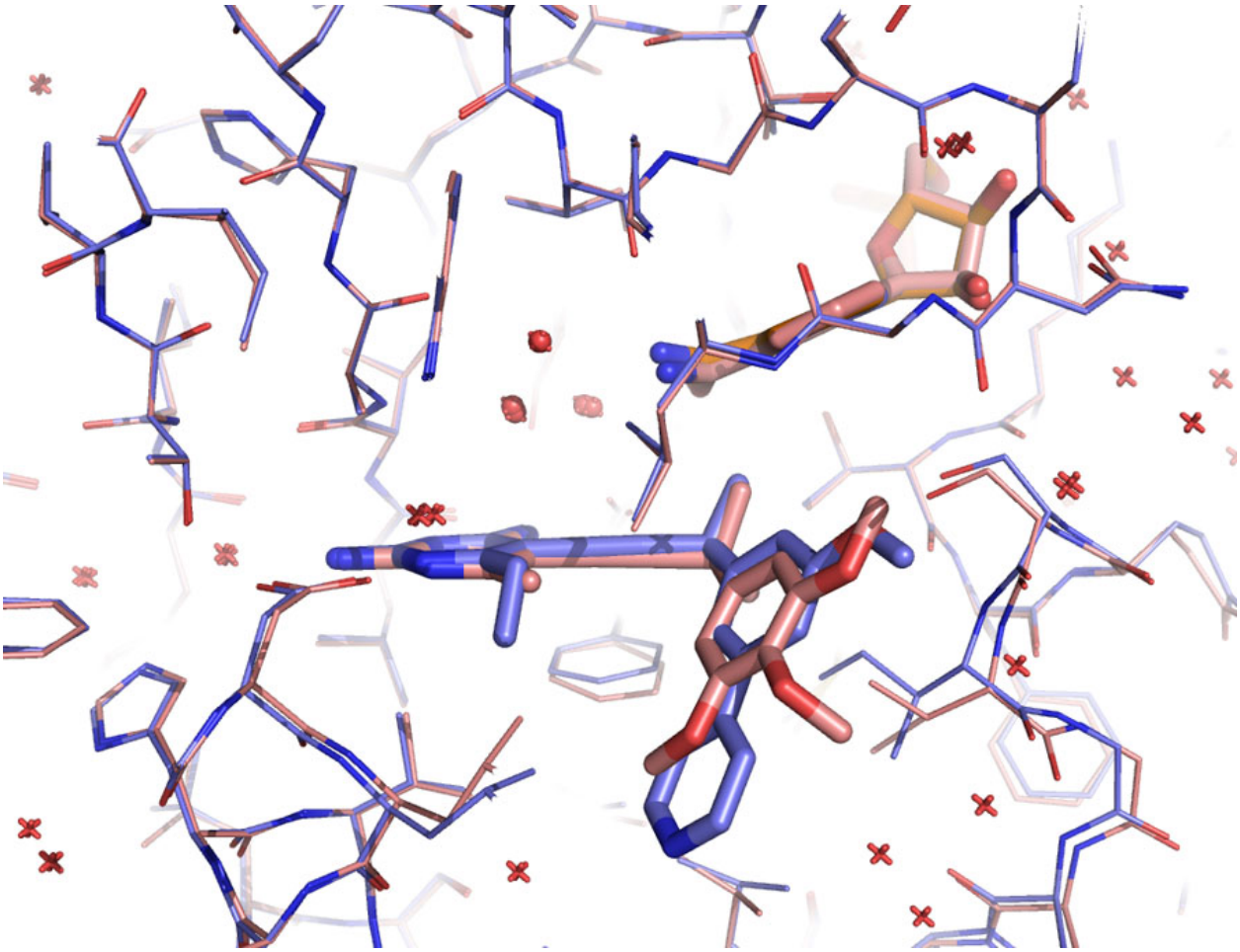
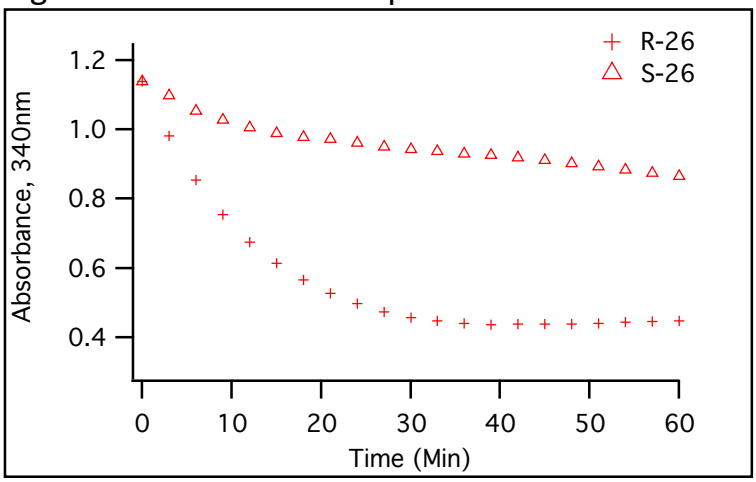
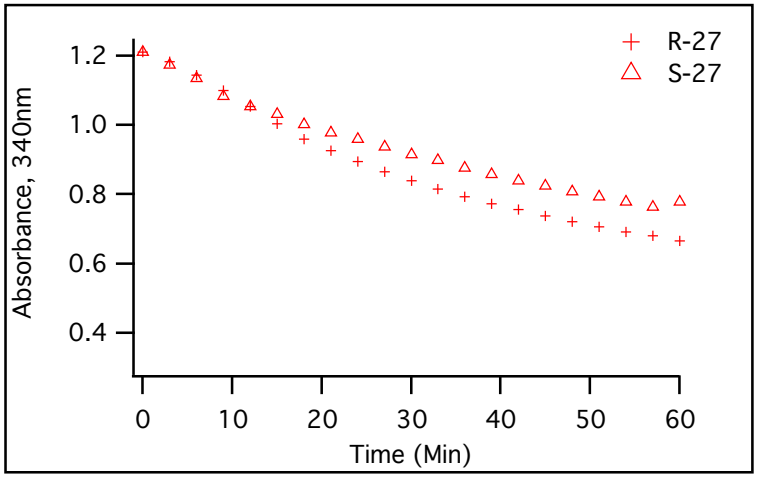
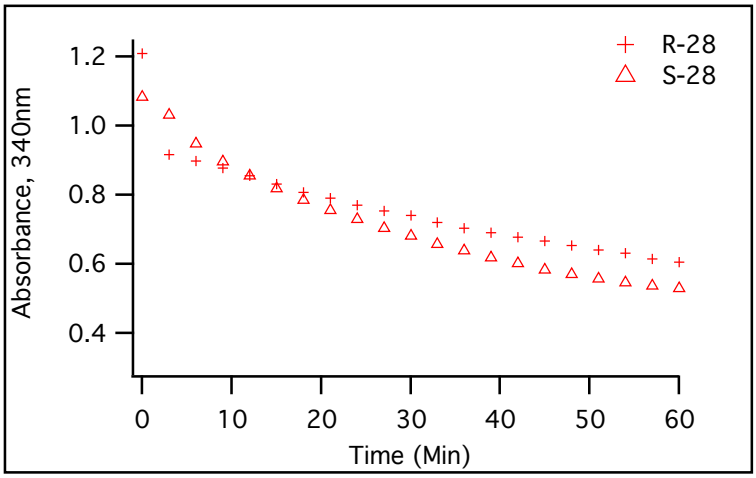
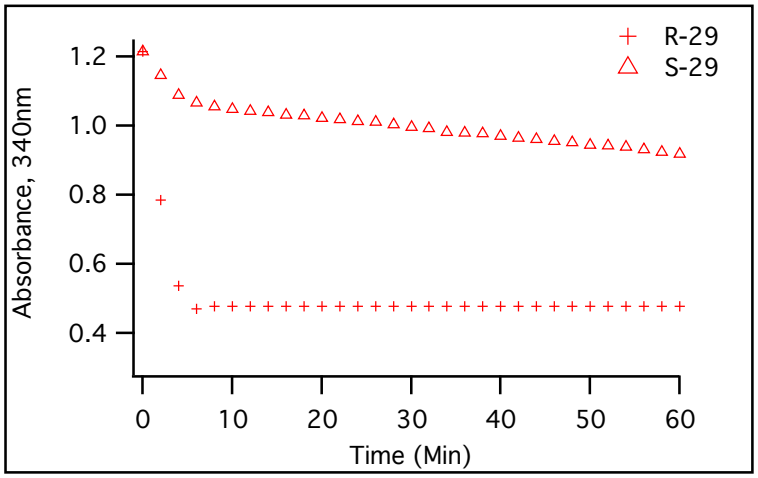


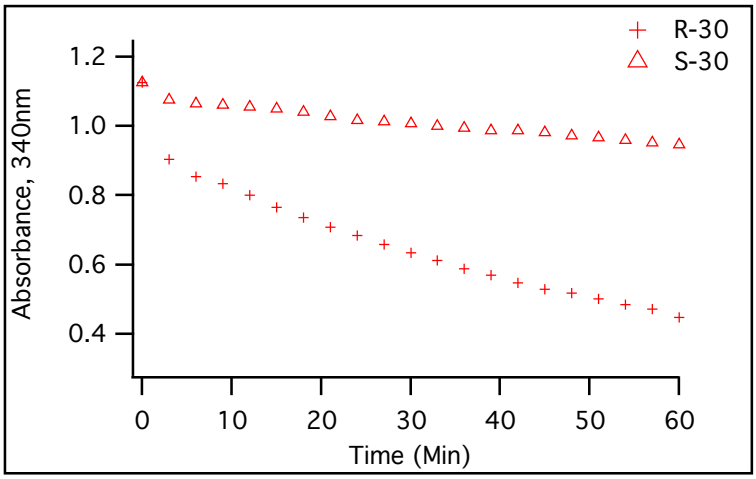
Figure S4. Dissociation experiments with SaDHFR











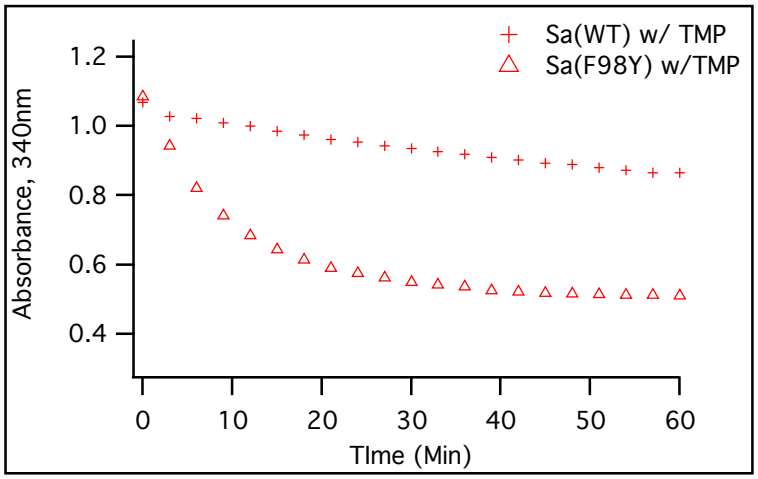


Figure S5. Dissociation experiments with Sa(F98Y)DHFR