

Continuous-Flow Synthesis of Monoarylated Acetaldehydes Using Aryldiazonium Salts

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General information:*General Reagent Information*

All anilines were purchased from Aldrich Chemical Co., Alfa Aesar, Acros Organics, or TCI America in 98% or higher commercial quality and were used as received without further purification. Ferrocene was purchased in 98.8% purity from Aldrich Chemical Co. and was used as received. Acetone was purchased in 98% purity from Mallinckrodt Chemicals.

General Analytical Information

Reactions were analyzed by gas chromatography. Thin-layer chromatography (TLC) was carried out on 0.25 mm E. Merck silica gel plates (60F-254) using KMnO_4 or UV light as the visualizing agent. Flash chromatography was performed using Silicycle SiliaFlashP60 (230-400 mesh) silica gel. NMR spectra were recorded on either a Bruker AMX 400 or on a Varian XL 300 MHz NMR spectrometer that were calibrated using residual solvent as an internal reference (CDCl_3 : 7.26 ppm for ^1H NMR and 77.16 ppm for ^{13}C NMR). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, at = apparent triplet, ad = apparent doublet. IR spectra were recorded on a Perkin-Elmer 2000 FTIR spectrometer using KBr plates (thin film). Melting points (m.p.) were obtained on a Mel-Temp capillary melting point apparatus. Gas chromatographic analyses were performed on an Agilent 6890 gas chromatograph with an FID detector using a J & W DB-200 column (30 m, 0.25 mm ID) or a DB-1 column (10 m, 0.1 mm I.D.). Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA.

General Experiment Information

For the continuous-flow experiments, reagents were weighed into 10.0 mL volumetric flasks. The flasks were filled to 10.0 mL with acetone, water, or acetone/water combinations. Each solutions were then loaded into a syringe, and all of them were injected into a 5 mL sample loop. Yields refer to chromatographically and spectroscopically homogeneous materials, unless otherwise stated. All yields stated are the average of at least two experiments.

Optimization of the reaction conditions

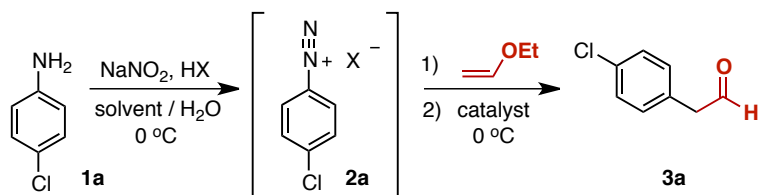
Optimization of the reaction conditions was performed on 60 μmol scale by mixing stock solutions of reagents. All stock solutions were prepared in 10.0 mL volumetric flasks. The 0.3 M acidic stock solution of *p*-chloroaniline was prepared by dissolving a mixture of 3.0 mmol of *p*-chloroaniline (**1a**) and 0.6 mL of 12 M aqueous HCl (2.4 mmol) or 0.128 mL of concentrated H₂SO₄ (2.4 mmol) in organic solvent. The NaNO₂ stock solution was prepared by dissolving 225 mg of NaNO₂ in water. The catalyst solution was prepared by dissolving 0.03 mmol of catalyst in 10.0 mL of organic solvent. The 3.0 M alkene solution was prepared by dissolving 2.9 mL of ethyl vinyl ether (30.0 mmol) in organic solvent.

General procedure for optimization of the reaction conditions:

Warning! Diazonium salts are unstable and dangerously explosive intermediates.

All diazonium salts, used for optimizations of the reaction conditions in batch, were generated in situ at 0 °C on 60 μmol scale. Upon completion, every batch experiment was neutralized at low temperature with excess of aqueous solution of NaHCO₃ to quench potential leftovers of generated diazonium salt.

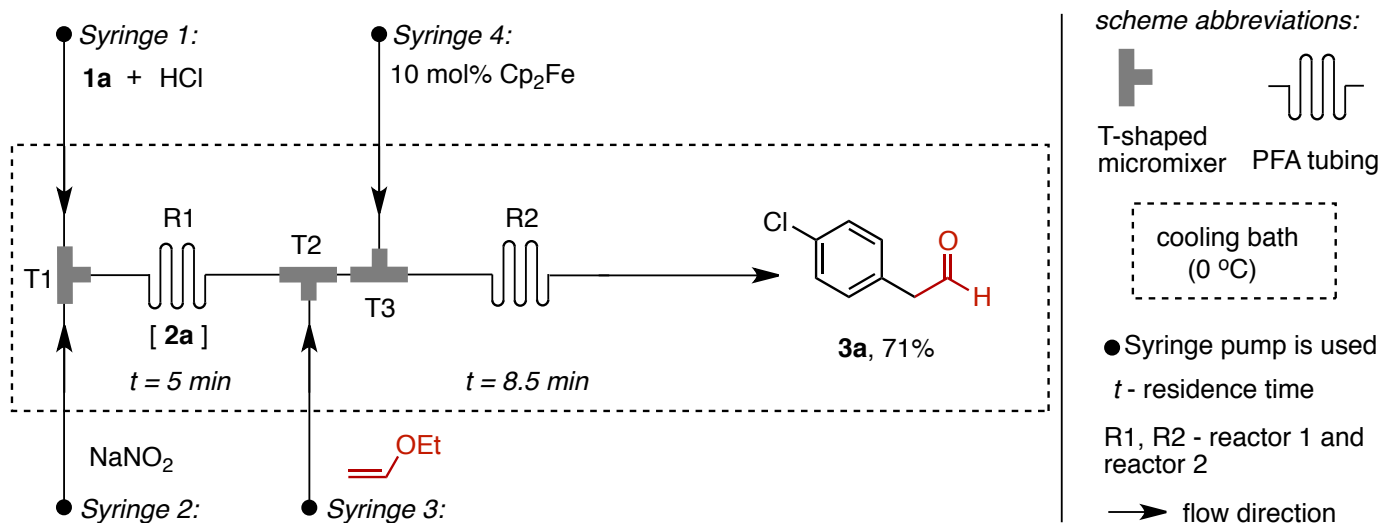
A test tube equipped with a stirring bar was charged with 200 μL of acidic aniline solution. The content was cooled to 0 °C (water/ice bath). A 200 μL aliquot of the NaNO₂ stock solution was slowly added at 0 °C and the reaction mixture was further stirred for 5.0 min. At the same temperature, a 200 μL portion of the solution of alkene was added next, followed by the addition of a 200 μL aliquot of the catalyst solution. The reaction mixture was allowed to stir at 0 °C until the evolution of N₂ had ceased (approximately 10 min). The reaction mixture was layered with saturated aqueous NaHCO₃ and diethyl ether, and the organic phase was analyzed by GC and GC/MS analyses. The yields of product were determined versus *n*-decane as calibrated internal standard.

Table S1. Optimization of the reaction conditions

#	catalyst [mol%]	HX	solvent/ H_2O	yield (%)
1	CuCl [5]	HCl	MeCN/ H_2O	32
2	CuCl [100]	HCl	MeCN/ H_2O	52
3	CuCl [100]	H_2SO_4	MeCN/ H_2O	60
4	$\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ [10]	H_2SO_4	DMSO/ H_2O	71
5	$\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ [10]	HCl	DMSO/ H_2O	43
6	$\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ [10]	HCl	acetone/ H_2O	32
7	Cp_2Fe [10]	H_2SO_4	acetone/ H_2O	65
8	Cp_2Fe [10]	H_2SO_4	DMSO/ H_2O	63
9	Cp_2Fe [10]	HCl	acetone/ H_2O	80
10	Cp_2Fe [10]	HCl	MeCN/ H_2O	79

Experimental procedures

Figure S1. Experimental setup for the continuous-flow synthesis of *p*-chlorophenylacetaldehyde (3a**) from *p*-chloroaniline (**1a**) via diazotization/Meerwein arylation sequence.**



The equipment configuration that was used for the continuous synthesis of monoarylated acetaldehydes from anilines via diazotization/Meerwein arylation sequence is depicted in Figure S1. Two Harvard Apparatus PHD2000 syringe pumps were used to continuously deliver reagents from Normject plastic syringes to the reactors. The first syringe pump was equipped with Syringe 1, containing an acetone-water solution of *p*-chloroaniline (**1a**) and 12 M aqueous HCl mixture, and Syringe 2, containing a NaNO₂ solution in water or acetone : water – 1:1 (v:v). The second syringe pump was equipped with Syringe 3, containing an acetone solution of ethyl vinyl ether, and Syringe 4, containing an acetone solution of ferrocene. Both reactors for the aniline diazotization and subsequent Meerwein arylation reaction, as well as the connecting mixing loop between mixing tees T2 and T3 were made out of PFA capillary tubing (1/16" OD x 0.04 ID). The diazotization reactor (reactor 1, R1) had a volume of 500 μL, and the Meerwein arylation reactor (reactor 2, R2) had a volume of 2.5 mL (1/16" OD x 0.04 ID). The tubing from the syringes to the reactors was also composed of PFA capillary tubing (1/16" OD x 500 μm ID) and all fluidic connections were made using either 1/4-28 flat-bottomed flangeless fittings or 10-32 coned fittings (IDEX Health and Science). The mixing tees used in this work were made out of TEFZEL® (ETFE) (500 μm ID) and purchased from IDEX Health and Science.

Unless noted otherwise, first mixing tee T1, reactor 1, second mixing tee T2, the mixing loop, third mixing tee T3, and reactor 2 were submerged in a sonication bath filled with an ice/water mixture (0 °C) and were sonicated. The bath temperature was monitored via a thermocouple Waage immersion heater controlled by a J-KEM Scientific Gemini PID controller, and constant temperature was maintained manually by addition of ice into the sonication bath. The stream exiting Reactor 2 was collected in an argon-flushed, dry, precooled round-bottom flask equipped with a stir bar.

General procedure for the continuous-flow synthesis of monoarylated acetaldehydes from anilines via diazotization/Meerwein arylation sequence:

I. Preparation of stock solutions:

Syringe 1:

A dry 10.0 mL volumetric flask was charged with 3.0 mmol of aniline (1.0 equiv), followed by 2.0 mL of acetone. To this solution was then added 0.6 mL of 12 M aqueous HCl. The resulting homogeneous acidic solution was further diluted to 10.0 mL total volume with acetone. If a precipitate formed, distilled water was added until all solids were dissolved, and the solution was subsequently diluted with acetone to a volume of 10.0 mL. The resulting homogeneous solutions were loaded into 10.0 mL plastic syringes. After removing bubbles, the total volume of the liquid in the syringe was set to 9.0 mL.

Syringe 2:

A dry 10.0 mL volumetric flask was charged with 225 mg of NaNO₂ (3.26 mmol, 1.09 equiv) and 5.0 mL of water. The solids were completely dissolved upon sonication. The resulting homogeneous solution was further diluted with acetone or water to 10.0 mL total volume. The solution was then further sonicated for 3 minutes to remove most of the air bubbles (*if a decrease in a volume occurred after the sonication, the amount of acetone necessary to make total volume equal to 10.0 mL was added*). Next, the prepared homogeneous NaNO₂ solution was loaded into a 10 mL plastic syringe. Total volume of liquid in the syringe was adjusted to 9.0 mL.

Syringe 3:

A dry 10.0 mL volumetric flask was charged with 2.9 mL of ethyl vinyl ether (30 mmol, 10 equiv). The content was diluted with acetone to a 10.0 mL total volume. The prepared homogeneous solution was loaded into a 10.0 mL plastic syringe. After removing bubbles, the total volume of the liquid in the syringe was adjusted to 9.0 mL.

Syringe 4:

A dry 10.0 mL volumetric flask was charged with 55 mg of ferrocene (0.3 mmol, 0.1 equiv), which was subsequently dissolved in 2 mL of acetone. The resulting solution was further diluted with acetone

to a total volume of 10.0 mL. This homogeneous solution was loaded into the 10.0 mL plastic syringe, and the total volume of the liquid in the syringe was adjusted to 9.0 mL.

II. Continuous-flow experiment and work-up:

The feeding rates were adjusted to 50 $\mu\text{L}/\text{min}$. Once the reaction mixture passed the T3, the sonication was turned on, and the system was left to equilibrate for the next 30-35 minutes. After system has reached a steady state, the receiver flask was changed to a pre-cooled round-bottom flask flushed with argon and equipped with a stir bar (stirring improved solution cooling), and the flowed reaction mixture was collected for an additional 2.5 h. The collected cold solution was next transferred into the graduated cylinder to measure the exact volume, which was further used for yield calculations. Next, water was added to the cold solution, and the mixture was extracted with equal amount of EtOAc (approximately 200 mL of total volume). After phase separation, the aqueous phase was further extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with a cold saturated solution of NaHCO_3 and then dried over anhydrous Na_2SO_4 . After removal of the solvent, the residue was purified by flash chromatography on silica gel to provide the final monoarylacetaldehyde product.

Synthesis of monoarylated acetaldehydes:

Monoarylacetaldehydes were prepared following the above general procedure and the experimental setup depicted in Figure S2.

Figure S2. Experimental setup for the continuous-flow synthesis of arylacetaldehydes **3 from anilines **1** via diazotization/Meerwein arylation sequence.**

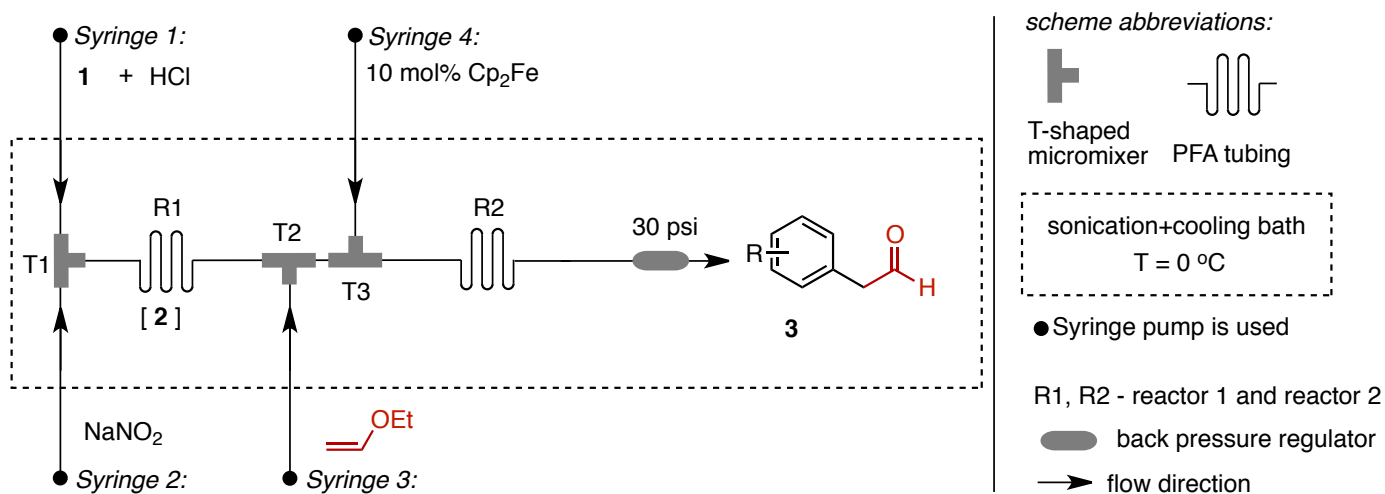


Table S1. Diazotization conditions in reactor 1

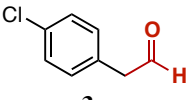
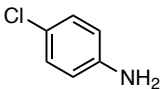
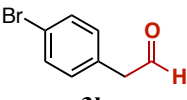
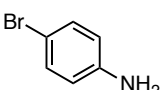
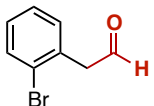
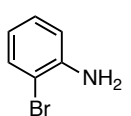
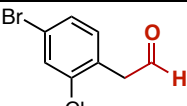
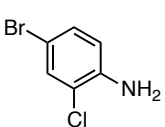
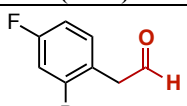
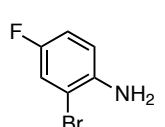
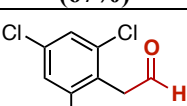
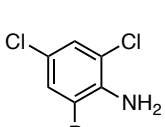
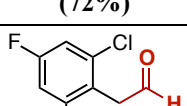
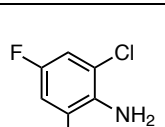
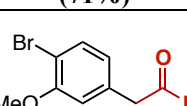
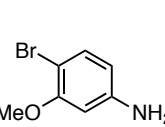
#	Product	Aniline used	<i>Syringe 1</i>	<i>Syringe 2</i>	Diazotization reactor 1 (internal diameter PFA tubing 0.04')
			Aniline/HCl solution (all diluted with acetone to total volume of 10.0 mL)	NaNO ₂ solution (total volume 10.0 mL)	
1	 3a (71%)		m (aniline) = 383 mg + V (HCl conc) = 0.625 mL	225 mg of NaNO ₂ dissolved in water	V = 0.250 mL
2	 3b (69%)		m (aniline) = 550 mg + V (HCl conc) = 0.625 mL + 2.0 mL of water	225 mg of NaNO ₂ dissolved in 1:1 (v:v) acetone-water mixture	V = 0.130 mL
3	 3c (70%)		m (aniline) = 550 mg + V (HCl conc) = 0.625 mL + 2.0 mL of water	225 mg of NaNO ₂ dissolved in 1:1 (v:v) acetone-water mixture	V = 0.130 mL
4	 3d (69%)		m (aniline) = 619 mg + V (HCl conc) = 0.700 mL + 2.0 mL of water	225 mg of NaNO ₂ dissolved in 1:1 (v:v) acetone-water mixture	V = 0.130 mL
5	 3e (67%)		m (aniline) = 570 mg + V (HCl conc) = 0.700 mL + 2.0 mL of water	225 mg of NaNO ₂ dissolved in 1:1 (v:v) acetone-water mixture	V = 0.130 mL
6	 3f (72%)		m (aniline) = 723 mg + V (HCl conc) = 0.700 mL + 2.0 mL of water	225 mg of NaNO ₂ dissolved in 1:1 (v:v) acetone-water mixture	V = 0.200 mL
7	 3g (71%)		m (aniline) = 673 mg + V (HCl conc) = 0.700 mL + 3.0 mL of water	225 mg of NaNO ₂ dissolved in 1:1 (v:v) acetone-water mixture	V = 0.2 mL
8	 3h (64%)		m (aniline) = 606 mg + V (HCl conc) = 0.700 mL + 2.0 mL of water	225 mg of NaNO ₂ dissolved in 1:1 (v:v) acetone-water mixture	V = 0.125 mL

Table S1. Diazotization conditions in reactor 1 (continued)

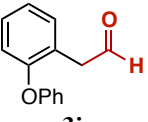
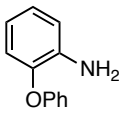
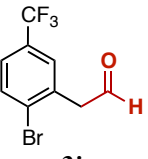
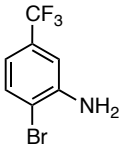
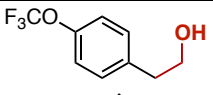
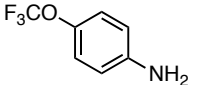
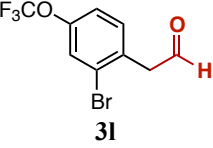
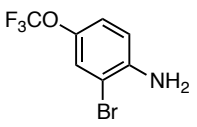
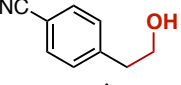
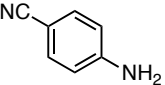
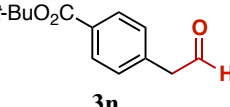
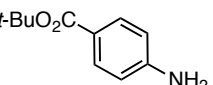
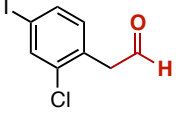
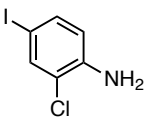
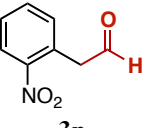
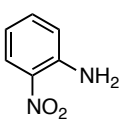
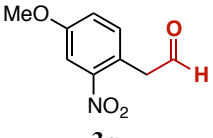
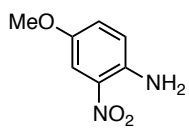
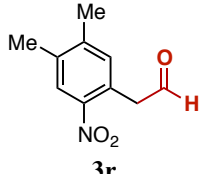
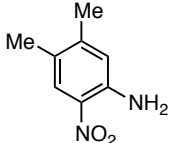
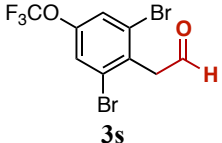
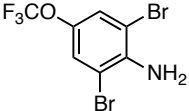
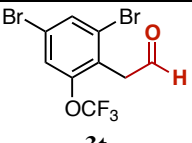
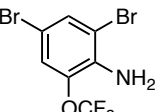
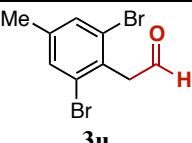
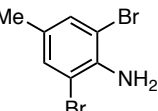
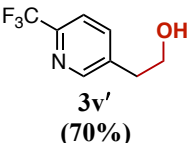
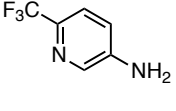
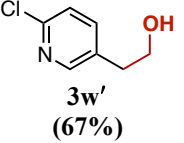
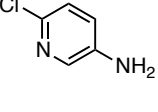
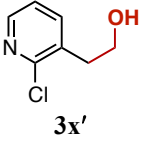
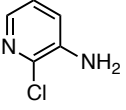
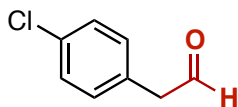
#	Product	Aniline used	Syringe 1	Syringe 2	Diazotization reactor I (internal diameter PFA tubing 0.04')
			Aniline/HCl solution (all diluted with acetone to total volume 10.0 mL)	NaNO ₂ solution (total volume 10.0 mL)	
9	 3i (73%)		m (aniline) = 556 mg + V (HCl conc) = 0.625 mL	225 mg of NaNO ₂ dissolved in 1:1 (v:v) acetone-water mixture	V = 0.200 mL
10	 3j (67%)		m (aniline) = 720 mg + V (HCl conc) = 1.0 mL + 2.0 mL of water	225 mg of NaNO ₂ dissolved in 1:1 (v:v) acetone-water mixture	V = 0.130 mL
11	 3k' (68%)		m (aniline) = 531 mg + V (HCl conc) = 1.0 mL	225 mg of NaNO ₂ dissolved in 1:1 (v:v) acetone-water mixture	V = 0.130 mL
12	 3l (65%)		m (aniline) = 768 mg + V (HCl conc) = 1.0 mL	225 mg of NaNO ₂ dissolved in 1:1 (v:v) acetone-water mixture	V = 0.130 mL
13	 3m' (72%)		m (aniline) = 354 mg + V (HCl conc) = 1.0 mL + 2.0 mL of water	225 mg of NaNO ₂ dissolved in 1:1 (v:v) acetone-water mixture	V = 0.300 mL
14	 3n (70%)		m (aniline) = 580 mg + V (HCl conc) = 0.7 mL + 1.0 mL of water	225 mg of NaNO ₂ dissolved in water	V = 0.130 mL
15	 3o (59%)		m (aniline) = 760 mg + V (HCl conc) = 0.7 mL + 1.0 mL of water	225 mg of NaNO ₂ dissolved in 1:1 (v:v) acetone-water mixture	V = 0.130 mL
16	 3p (72%)		m (aniline) = 414 mg + V (HCl conc) = 0.7 mL + 2.0 mL of water	225 mg of NaNO ₂ dissolved in 1:1 (v:v) acetone-water mixture	V = 0.3 mL
17	 3q (73%)		m (aniline) = 505 mg + V (HCl conc) = 0.7 mL + 3.0 mL of water	225 mg of NaNO ₂ dissolved in 1:1 (v:v) acetone-water mixture	V = 0.3 mL

Table S1. Diazotization conditions in reactor 1 (*continued*)

#	Product	Aniline used	Syringe 1	Syringe 2	Diazotization reactor I (internal diameter PFA tubing 0.04')
			Aniline/HCl solution (all diluted with acetone to total volume 10.0 mL)	NaNO ₂ solution (total volume 10.0 mL)	
18	 3r (76%)		m (aniline) = 499 mg + V (HCl conc) = 0.7 mL + 3.0 mL of water	225 mg of NaNO ₂ dissolved in 1:1 (v:v) acetone-water mixture	V = 0.3 mL
19	 3s (69%)		m (aniline) = 1.0 g + V (HCl conc) = 0.8 mL	225 mg of NaNO ₂ dissolved in water	V = 0.130 mL
20	 3t (64%)		m (aniline) = 1.0 g + V (HCl conc) = 0.8 mL	225 mg of NaNO ₂ dissolved in water	V = 0.130 mL
21	 3u (74%)		m (aniline) = 795 mg + V (HCl conc) = 0.8 mL	225 mg of NaNO ₂ dissolved in 1:1 (v:v) acetone-water mixture	V = 0.250 mL
22	 3v' (70%)		m (aniline) = 486 mg + V (HCl conc) = 0.8 mL + 1.0 mL of water	225 mg of NaNO ₂ dissolved in 1:1 (v:v) acetone-water mixture	V = 0.063 mL
23	 3w' (67%)		m (aniline) = 386 mg + V (HCl conc) = 0.8 mL + 1.0 mL of water	225 mg of NaNO ₂ dissolved in 1:1 (v:v) acetone-water mixture	V = 0.063 mL
24	 3x' (65%)		m (aniline) = 386 mg + V (HCl conc) = 0.8 mL + 1.0 mL of water	225 mg of NaNO ₂ dissolved in water	V = 0.063 mL

Characterization and analytical data for products in Table 2



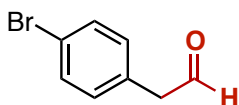
2-(4-chlorophenyl)acetaldehyde (3a).¹ Obtained following the general procedure and using diazotization conditions from [Table S1, entry 1](#). Collected volume of the crude reaction mixture: $V = 20$ mL (1.5 mmol scale). The crude material was purified by column chromatography on silica gel (eluent hexanes : Et₂O – 10:1 (v:v)) to yield 165 mg (71%) of the title aldehyde **3a** as a yellowish oil.

¹H-NMR (400 MHz; CDCl₃): δ 9.76 (t, $J = 2.1$ Hz, 1H), 7.38-7.35 (m, 2H), 7.18-7.16 (m, 2H), 3.70 (d, $J = 2.1$ Hz, 2H).

¹³C-NMR (101 MHz; CDCl₃): δ 198.6, 133.5, 130.9, 130.3, 129.1, 49.8.

FTIR (neat): cm⁻¹ 1916, 1793, 1701, 1597, 1491, 1403, 1317, 1179.

Anal. Calcd. for C₈H₇ClO C, 62.15; H, 4.56. Found: C, 62.19; H, 4.60



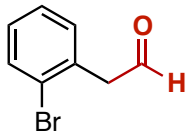
2-(4-bromophenyl)acetaldehyde (3b). Obtained following the general procedure and using diazotization conditions from [Table S1, entry 2](#). Collected volume of the crude reaction mixture: $V = 20$ mL (1.5 mmol scale). The crude material was purified by column chromatography on silica gel (hexanes : Et₂O – 9:1 (v:v)) to yield 206 mg (69 %) of the title aldehyde **3b** as a yellowish oil.

¹H-NMR (400 MHz; CDCl₃): δ 9.76 (t, $J = 2.1$ Hz, 1H), 7.52 (d, $J = 8.3$ Hz, 2H), 7.11 (d, $J = 8.2$ Hz, 2H), 3.69 (d, $J = 1.9$ Hz, 2H).

¹³C-NMR (101 MHz; CDCl₃): δ 198.5, 132.1, 131.3, 130.8, 121.5, 49.8.

FTIR (neat): cm⁻¹ 3422, 2937, 1723, 1375, 1313, 1187, 1137, 1052, 1011.

Anal. Calcd. for C₈H₇BrO C, C, 48.27; H, 3.54. Found: C, 48.28; H, 3.55.



2-(2-bromophenyl)acetaldehyde (3c).² Obtained following the general procedure and using diazotization conditions from [Table S1, entry 3](#). Collected volume of the crude reaction mixture: V

(1) Chen, G.-Q.; Xu, Z.-J.; Zhou C.-Y.; Che, C.-M. *Chem. Commun.* **2011**, *47*, 10963.

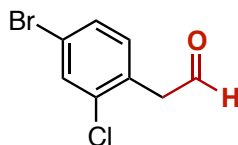
(2) (1) Chang, C.-F.; Huang, C.-Y.; Huang, Y.-C.; Lin, K.-Y.; Lee, Y.-J.; Wang, C.-J. *Synth. Commun.* **2010**, *40*, 3452.

= 25 mL (1.875 mmol scale). The crude material was purified by column chromatography on silica gel (hexanes : Et₂O – 9:1 (v:v)) to yield 263 mg (70 %) of the title aldehyde **3c** as a yellow oil.

¹H-NMR (400 MHz; CDCl₃): δ 9.78 (t, *J* = 1.8 Hz, 1H), 7.64 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.33 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.27-7.18 (m, 2H), 3.89 (d, *J* = 1.8 Hz, 2H).

¹³C-NMR (101 MHz; CDCl₃): δ 198.3, 133.0, 132.6, 131.8, 129.3, 127.9, 125.0, 50.5.

FTIR (neat): cm⁻¹ 3500, 2974, 2864, 1725, 1471, 1439, 1381, 1073.

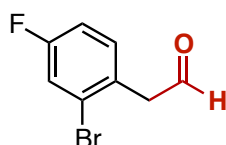


2-(4-bromo-2-chlorophenyl)acetaldehyde (3d). Obtained following the general procedure and using diazotization conditions from [Table S1, entry 4](#). Collected volume of the crude reaction mixture: *V* = 20 mL (1.5 mmol scale). The crude material was purified by column chromatography on silica gel (hexanes : EtOAc – 10:1 (v:v)) to yield 242 mg (69 %) of the title aldehyde **3e** as a light yellow oil.

¹H-NMR (400 MHz; CDCl₃): δ 9.76 (t, *J* = 1.4 Hz, 1H), 7.62 (d, *J* = 1.9 Hz, 1H), 7.42 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 3.84 (d, *J* = 1.2 Hz, 2H).

¹³C-NMR (101 MHz; CDCl₃): δ 197.2, 135.5, 132.8, 132.3, 130.4, 129.8, 121.9, 47.7.

FTIR (neat): cm⁻¹ 3405, 2898, 2843, 2740, 2106, 2085, 1793, 1912, 1793, 1701, 1590, 1485, 1402, 1315.



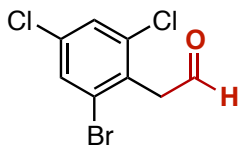
2-(2-bromo-4-fluorophenyl)acetaldehyde (3e). Obtained following the general procedure and using diazotization conditions from [Table S1, entry 5](#). Collected volume of the crude reaction mixture: *V* = 20 mL (1.5 mmol scale). The crude material was purified by column chromatography on silica gel (hexanes : EtOAc – 10:1 (v:v)) to yield 220 mg (67 %) of the title aldehyde **3e** as a light yellow oil.

¹H-NMR (400 MHz; CDCl₃): δ 9.76 (t, *J* = 1.4 Hz, 1H), 7.62 (d, *J* = 1.9 Hz, 1H), 7.42 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 3.84 (d, *J* = 1.2 Hz, 2H).

¹³C-NMR (101 MHz; CDCl₃): δ 197.2, 135.5, 132.8, 132.3, 130.4, 129.8, 121.9, 47.7.

FTIR (neat): cm⁻¹ 3405, 2898, 2843, 2740, 2106, 2085, 1793, 1912, 1991, 1991, 1912, 1793, 1701, 1590, 1485, 1402, 1315, 1106, 1068, 1011, 932, 844, 787, 737, 677.

Anal. Calcd. for C₈H₆BrFO C, C, 44.27; H, 2.79. Found: C, 48.18; H, 2.80.



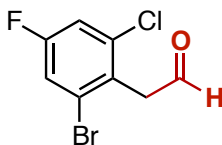
2-(2-bromo-4,6-dichlorophenyl)acetaldehyde (3f). The compound was obtained following the general procedure and using diazotization conditions from [Table S1, entry 6](#). Collected volume of the crude reaction mixture: $V = 18$ mL (1.35 mmol scale). The crude material was purified by column chromatography on silica gel (hexanes : Et₂O – 18:1 (v:v)) to yield 260 mg (72%) of the title aldehyde **3f** as a white solid.

¹H-NMR (400 MHz; CDCl₃): δ 7.60 (d, $J = 2.3$ Hz, 1H), 7.14-7.11 (m, 1H), 7.03 (dd, $J = 9.4, 2.1$ Hz, 1H), 6.80-6.80 (m, 1H).

¹³C-NMR (101 MHz; CDCl₃): δ 161.6, 159.2, 154.79, 154.65, 145.99, 145.95, 126.32, 126.19, 123.4, 111.9, 111.7, 105.1, 98.2, 98.0.

FTIR (neat): cm⁻¹ 2869, 1705, 1576, 1539, 1442, 1378, 1303, 1164, 1129, 1062.

Anal. Calcd. for C₈H₅BrCl₂O C, C, 35.86; H, 1.88. Found: C, 36.12; H, 2.50.



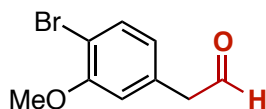
2-(2-bromo-6-chloro-4-fluorophenyl)acetaldehyde (3g). The compound was obtained following the general procedure and using diazotization conditions from [Table S1, entry 7](#). Collected volume of the crude reaction mixture: $V = 20$ mL (1.5 mmol scale). The crude material was purified by column chromatography on silica gel (hexanes : Et₂O – 10:1 (v:v)) to yield 268 mg (71%) of the title aldehyde **3g** as a light yellow solid.

¹H-NMR (400 MHz; CDCl₃): δ 9.75 (t, $J = 1.0$ Hz, 1H), 7.34 (dd, $J = 7.7, 2.6$ Hz, 1H), 7.21 (dd, $J = 8.0, 2.6$ Hz, 1H), 4.15 (d, $J = 0.3$ Hz, 2H).

¹³C-NMR (101 MHz; CDCl₃): δ 196.1, 162.3, 159.8, 136.24, 136.13, 127.70, 127.66, 126.11, 126.01, 119.4, 119.1, 116.7, 116.5, 47.8.

FTIR (neat): cm⁻¹ 3050, 2938, 2880, 2002, 1895, 1569, 1418, 1236, 1147, 1056.

Anal. Calcd. for C₈H₅BrClFO C, C, 38.21; H, 2.00. Found: C, 37.83; H, 2.50.

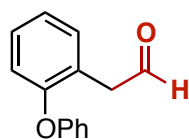


2-(4-bromo-3-methoxyphenyl)acetaldehyde (3h). The compound was obtained following the general procedure and using diazotization conditions from [Table S1, entry 8](#). Collected volume of the crude reaction mixture: $V = 18$ mL (1.35 mmol scale). The crude material was purified by column chromatography on silica gel (hexanes : Et₂O – 10:1 (v:v)) to yield 198 mg (64%) of the title aldehyde **3h** as a yellow oil.

¹H-NMR (400 MHz; CDCl₃): δ 9.74 (t, $J = 2.2$ Hz, 1H), 7.52 (d, $J = 7.9$ Hz, 1H), 6.74-6.70 (m, 2H), 3.90 (s, 4H), 3.67 (d, $J = 2.2$ Hz, 2H).

¹³C-NMR (101 MHz; CDCl₃): δ 198.6, 156.2, 133.7, 132.5, 122.9, 113.2, 110.8, 56.2, 50.3.

FTIR (CH₂Cl₂ film): cm^{-1} 3422, 2938, 1720, 1590, 1578, 1463, 1484, 1408, 1280, 1255, 1171.

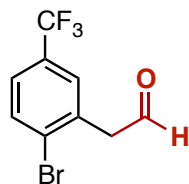


2-(2-phenoxyphenyl)acetaldehyde (3i). The compound was obtained following the general procedure and using diazotization conditions from [Table S1, entry 9](#). Collected volume of the crude reaction mixture: $V = 16$ mL (1.2 mmol scale). The crude material was purified by column chromatography on silica gel (hexanes : Et₂O – 10:1 (v:v)) to yield 185 mg (73%) of the title aldehyde **3i** as a yellow oil.

¹H-NMR (400 MHz; CDCl₃): δ 9.79 (td, $J = 2.0, 0.5$ Hz, 1H), 7.38-7.32 (m, 2H), 7.30-7.28 (m, 2H), 7.17-7.12 (m, 2H), 7.00-6.98 (m, 2H), 6.96-6.93 (m, 1H), 3.77 (d, $J = 1.9$ Hz, 2H).

¹³C-NMR (101 MHz; CDCl₃): δ 199.2, 156.9, 155.3, 131.8, 129.9, 129.1, 123.92, 123.88, 123.4, 118.8, 118.5, 45.3.

FTIR (neat): cm^{-1} 3109, 2871, 1706, 1591, 1568, 2873, 2800, 1460, 1380, 1311, 1246, 1158.

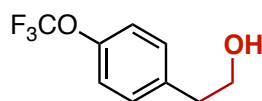


2-(2-bromo-5-(trifluoromethyl)phenyl)acetaldehyde (3j). The compound was obtained following the general procedure and using diazotization conditions from [Table S1, entry 10](#). Collected volume of the crude reaction mixture: $V = 20$ mL (1.5 mmol scale). The crude material was purified by column

chromatography on silica gel (hexanes : Et₂O – 10:1 (v:v)) to yield 257 mg (67%) of the title aldehyde **3j** as a light yellow oil.

¹H-NMR (400 MHz; CDCl₃): δ 9.80 (t, *J* = 1.5 Hz, 1H), 7.53 (dd, *J* = 2.3, 0.7 Hz, 1H), 7.29 (s, 1H), 7.22 (ddd, *J* = 8.4, 2.4, 1.0 Hz, 1H), 3.92 (d, *J* = 1.5 Hz, 2H).

¹³C-NMR (101 MHz; CDCl₃): δ 197.3, 148.70, 148.68, 132.4, 131.5, 125.5, 125.1, 121.6, 120.3, 119.0, 49.8.



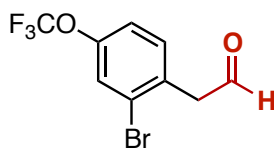
2-(4-(trifluoromethoxy)phenyl)ethanol (3k'). The corresponding aldehyde **3k** was prepared following the general procedure and using diazotization conditions from [Table S1, entry 11](#). Collected volume of the crude reaction mixture: *V* = 16 mL (1.2 mmol scale). The obtained crude material was dissolved in 20 mL of DCM/EtOH 4:1 (v:v) mixture, and 50 mg of NaBH₄ (1.5 mmol) was added in one portion at room temperature. The reaction was vigorously stirred for 1 h (a complete reduction of aldehyde was confirmed by both GC and TLC analysis). The reaction mixture was cooled to 0 °C, and 30 mL of saturated solution of NH₄Cl in water was carefully added followed by 30 mL of EtOAc. The phases were separated, and aqueous layer was extracted with EtOAc (2 X 20mL). The combined organic fractions were washed with saturated aqueous solution of NaHCO₃ and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure, and the crude mixture was further purified by flash column chromatography on silica gel (hexanes/EtOAc, gradually from 4:1(v:v) to 2:1(v:v)) to yield 167 mg (68%) of the 2-(4-(trifluoromethoxy)phenyl)ethanol (**3k'**) as a yellowish oil.

¹H-NMR (400 MHz; CDCl₃): δ 7.47 (dd, *J* = 2.3, 0.6 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.15 (ddd, *J* = 8.4, 2.4, 1.0 Hz, 1H), 3.89 (t, *J* = 6.6 Hz, 2H), 3.04 (t, *J* = 6.6 Hz, 2H), 1.70 (s, 1H).

¹³C-NMR (101 MHz; CDCl₃): δ 147.87, 147.85, 136.8, 131.8, 125.5, 124.6, 124.2, 121.6, 120.0, 119.1, 116.5, 61.7, 38.6.

FTIR (neat): cm⁻¹ 3510, 2323, 2231, 2118, 1942, 1606, 1502, 1474, 1407, 1317, 1255, 1177, 1117, 1071

Anal. Calcd. for C₉H₉F₃O₂ C, 52.43; H, 4.40; Found: C, 52.48; H, 4.39.



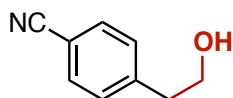
2-(2-bromo-4-(trifluoromethoxy)phenyl)acetaldehyde (3l). The compound was obtained following the general procedure and using diazotization conditions from [Table S1, entry 12](#). Collected volume of the crude reaction mixture: $V = 20$ mL (1.5 mmol scale). The crude material was purified by column chromatography on silica gel (hexanes : Et₂O –10:1 (v:v)) to yield 276 mg (65%) of the title aldehyde **3j** as yellow oil.

¹H-NMR (400 MHz; CDCl₃): δ 9.80 (t, $J = 1.5$ Hz, 1H), 7.53 (dd, $J = 2.3, 0.7$ Hz, 1H), 7.29 (s, 1H), 7.22 (ddd, $J = 8.4, 2.4, 1.0$ Hz, 1H), 3.92 (d, $J = 1.5$ Hz, 2H).

¹³C-NMR (101 MHz; CDCl₃): δ 197.3, 148.70, 148.68, 132.4, 131.5, 125.5, 125.1, 121.6, 120.3, 119.0, 49.8.

FTIR (neat): cm⁻¹ 3747, 3056, 1727, 1487, 1263, 1218, 1172, 941, 735.

Anal. Calcd. for. C₉H₆BrF₃O₂ C, 38.19; H, 2.14. Found: C, 38.3; H, 2.14.



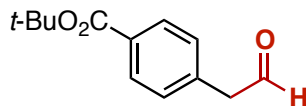
4-(2-hydroxyethyl)benzonitrile (3m'). The corresponding aldehyde **3m** was obtained following the general procedure and using diazotization conditions from [Table S1, entry 13](#). Collected volume of the crude reaction mixture: $V = 20$ mL (1.5 mmol scale). The obtained crude material was subjected to reduction with NaBH₄ following the [reduction procedure for 3k'](#). The crude mixture was further purified by flash column chromatography on silica gel (hexanes/EtOAc, gradually from 4:1(v:v) to 2:1(v:v)) to yield 158 mg (72%) of 4-(2-hydroxyethyl)benzonitrile (**3m'**) as a light yellow oil.

¹H-NMR (400 MHz; CDCl₃): δ 7.59-7.56 (m, 2H), 7.36-7.33 (m, 2H), 3.86 (t, $J = 6.5$ Hz, 2H), 2.91 (t, $J = 6.5$ Hz, 2H), 2.17 (s, 1H).

¹³C-NMR (101 MHz; CDCl₃): δ 144.8, 132.2, 129.9, 119.0, 110.0, 62.8, 39.1.

FTIR (neat): cm⁻¹ 3510, 2873, 2800, 2323, 2231, 1606, 1502, 1474, 1407, 1317, 1255, 1171.

Anal. Calcd. for. C₉H₉NO C, C, 73.45; H, 6.16. Found: C, 74.00; H, 6.63.



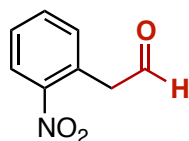
tert-butyl 4-(2-oxoethyl)benzoate (3n). The compound was obtained following the general procedure and using diazotization conditions from [Table S1, entry 14](#). Collected volume of the crude reaction mixture: $V = 20$ mL (1.5 mmol scale). The crude material was purified by column chromatography on

silica gel (eluent Hexanes : MTBE – 4:1 (v:v)) to yield 234 mg (70%) of the title aldehyde **3n** as a light orange oil.

¹H-NMR (400 MHz; CDCl₃): δ 9.78 (t, *J* = 2.2 Hz, 1H), 8.02-8.00 (m, 2H), 7.30-7.28 (m, 2H), 3.78 (d, *J* = 2.2 Hz, 2H), 1.62 (s, 9H).

¹³C-NMR (101 MHz; CDCl₃): δ 198.4, 165.4, 136.4, 131.3, 130.1, 129.5, 81.1, 50.4, 28.2.

FTIR (neat): cm⁻¹ 1502, 1474, 1407, 1317, 1255, 1171, 1071, 1043, 849, 824.

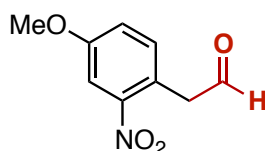


2-(2-nitrophenyl)acetaldehyde (3o).³ The compound was obtained following the general procedure and using diazotization conditions from [Table S1, entry 16](#). Collected volume of the crude reaction mixture: *V* = 25 mL (1.875 mmol scale). The crude material was purified by column chromatography on silica gel (hexanes : EtOAc – 4:1 (v:v)) to yield 223 mg (72%) of the title aldehyde **3p** as a light yellow oil.

¹H-NMR (400 MHz; CDCl₃): δ 9.86 (t, *J* = 0.7 Hz, 1H), 8.15 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.64 (td, *J* = 7.5, 1.3 Hz, 1H), 7.54-7.49 (m, 1H), 7.35 (dd, *J* = 7.6, 1.2 Hz, 1H), 4.14 (s, 2H).

¹³C-NMR (101 MHz; CDCl₃): δ 196.8, 148.8, 133.8, 133.5, 128.8, 128.5, 125.3, 48.5.

FTIR (neat): cm⁻¹ 3400, 2710, 2118, 1942, 1725, 1525, 1350.



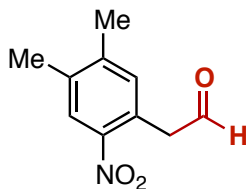
2-(4-methoxy-2-nitrophenyl)acetaldehyde (3q). The compound was obtained following the general procedure and using diazotization conditions from [Table S1, entry 17](#). Collected volume of the crude reaction mixture: *V* = 25 mL (1.875 mmol scale). The crude material was purified by column chromatography on silica gel (hexanes : EtOAc – 4:1 (v:v)) to yield 267 mg (73%) of the title aldehyde **3q** as a light yellow oil.

¹H-NMR (400 MHz; CDCl₃): δ 9.82 (t, *J* = 0.9 Hz, 1H), 7.66 (d, *J* = 2.7 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 7.17 (dd, *J* = 8.5, 2.7 Hz, 1H), 4.05 (s, 2H), 3.89 (s, 3H).

¹³C-NMR (101 MHz; CDCl₃): δ 197.3, 159.5, 149.3, 134.2, 120.38, 120.25, 110.0, 55.9, 47.8.

FTIR (neat): cm⁻¹ 3400, 1606, 1502, 1474, 1407, 1317, 1255, 1171, 1071, 1043.

(3) Noland, W. E.; Sellstedt, J. H. *J. Org. Chem.* **1966**, *31*, 345.



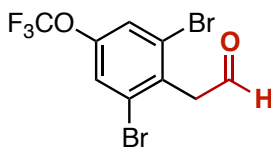
2-(4,5-dimethyl-2-nitrophenyl)acetaldehyde (3r). The compound was obtained following the general procedure and using diazotization conditions from [Table S1, entry 18](#). Collected volume of the crude reaction mixture: $V = 20$ mL (1.5 mmol scale). The crude material was purified by column chromatography on silica gel (hexanes : DCM – 1:2 (v:v)) to yield 220 mg (76%) of the title aldehyde **3r** as yellow oil.

$^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 9.84 (t, $J = 0.9$ Hz, 1H), 7.97 (s, 1H), 7.08 (s, 1H), 4.05 (s, 2H), 2.35 (s, 7H).

$^{13}\text{C-NMR}$ (101 MHz; CDCl_3): δ 197.4, 146.3, 144.0, 137.8, 134.5, 126.3, 125.9, 48.2, 19.8, 19.4.

FTIR (neat): cm^{-1} 3302, 3050, 2938, 2880, 1569, 1418, 1381, 1290, 1147, 1056, 1019.

Anal. Calcd. for. $\text{C}_{10}\text{H}_{11}\text{NO}_3$ C, 62.17; H, 5.74. Found: C, 62.14; H, 5.10.



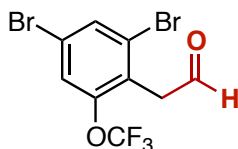
2-(2,6-dibromo-4-(trifluoromethoxy)phenyl)acetaldehyde (3s). The compound was obtained following the general procedure and using diazotization conditions from [Table S1, entry 19](#). Collected volume of the crude reaction mixture: $V = 18$ mL (1.35 mmol scale). The crude material was purified by column chromatography on silica gel (hexanes : DCM – 4:1 (v:v)) to yield 337 mg (69%) of the title aldehyde **3s** as light yellow solid.

$^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 9.78 (s, 1H), 7.51 (s, 2H), 4.25 (s, 2H).

$^{13}\text{C-NMR}$ (101 MHz; CDCl_3): δ 195.8, 148.37, 148.35, 132.1, 125.8, 124.7, 121.5, 118.9, 50.6.

FTIR (neat): cm^{-1}

Anal. Calcd. for. $\text{C}_9\text{H}_5\text{Br}_2\text{F}_3\text{O}_2$ C, 29.87; H, 1.39. Found: C, XXX; H, XXX.



2-(2,4-dibromo-6-(trifluoromethoxy)phenyl)acetaldehyde (3t). The compound was obtained following the general procedure and using diazotization conditions from [Table S1, entry 19](#). Collected

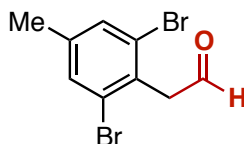
volume of the crude reaction mixture: $V = 18$ mL (1.35 mmol scale). The crude material was purified by column chromatography on silica gel (hexanes : DCM – 4:1 (v:v)) to yield 312 mg (64%) of the title aldehyde **3t** as yellowish solid.

$^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 9.74 (s, 1H), 7.76 (d, $J = 0.7$ Hz, 1H), 7.46 (s, 1H), 4.00 (s, 2H).

$^{13}\text{C-NMR}$ (101 MHz; CDCl_3): δ 195.3, 148.40, 148.38, 133.8, 126.9, 125.9, 123.07, 123.05, 121.9, 121.5, 118.9, 44.5.

FTIR (neat): cm^{-1} 3097, 2846, 1720, 1584, 1562, 1462, 1396, 1379, 1270.

Anal. Calcd. for. $\text{C}_9\text{H}_5\text{Br}_2\text{F}_3\text{O}_2$ C, 29.87; H, 1.39. Found: C, XXX; H, XXX.

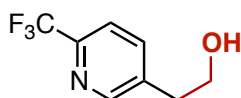


2-(2,6-dibromo-4-methylphenyl)acetaldehyde (3u). The compound was obtained following the general procedure and using diazotization conditions from [Table S1, entry 21](#). Collected volume of the crude reaction mixture: $V = 18$ mL (1.35 mmol scale). The crude material was purified by column chromatography on silica gel (hexanes : Et_2O – 9:1 (v:v)) to yield 292 mg (74%) of the title aldehyde **3u** as white solid.

$^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 9.74 (t, $J = 1.1$ Hz, 1H), 7.42 (s, 2H), 4.18 (d, $J = 0.7$ Hz, 2H), 2.33 (s, 3H).

$^{13}\text{C-NMR}$ (101 MHz; CDCl_3): δ 197.1, 140.7, 132.8, 129.7, 125.5, 50.7, 20.4.

FTIR (neat): cm^{-1} 2923, 2846, 2732, 1711, 1599, 1536, 1460, 1375, 1313, 1279, 1218, 1168, 1054.



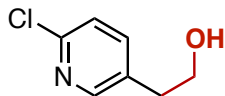
2-(6-(trifluoromethyl)pyridin-3-yl)ethanol (3v'). The corresponding aldehyde **3s** was obtained following the general procedure and using diazotization conditions from [Table S1, entry 19](#). Collected volume of the crude reaction mixture: $V = 20$ mL (1.5 mmol scale). The obtained crude material was subjected to reduction with NaBH_4 following the [reduction procedure for 3k'](#). The crude mixture was further purified by flash column chromatography on silica gel (hexanes/ EtOAc , gradually from 1:1(v:v) to 1:2(v:v)) to yield 200 mg (70%) of 2-(6-(trifluoromethyl)pyridin-3-yl)ethanol (**3v'**) as white solid.

$^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 7.59-7.56 (m, 2H), 7.36-7.33 (m, 1H), 3.86 (t, $J = 6.5$ Hz, 2H), 2.91 (t, $J = 6.5$ Hz, 2H), 2.17 (s, 1H).

$^{13}\text{C-NMR}$ (101 MHz; CDCl_3): δ 144.8, 132.2, 129.9, 119.0, 110.0, 62.8, 39.1.

FTIR (neat): cm^{-1} 3302, 3050, 2938, 2880, 2002, 1895, 1569, 1418, 1381, 1290, 1236, 1147, 1056, 1019, 953, 896, 851, 743, 714, 660.

Anal. Calcd. for. $\text{C}_8\text{H}_8\text{F}_3\text{NO}$ C, 50.27; H, 4.22. Found: C, 50.08; H, 4.33.



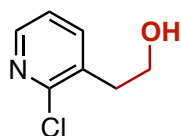
2-(6-chloropyridin-3-yl)ethanol (3w'). The corresponding aldehyde **3s** was obtained following the general procedure and using diazotization conditions from [Table S1, entry 20](#). Collected volume of the crude reaction mixture: $V = 16$ mL (1.2 mmol scale). The obtained crude material was subjected to reduction with NaBH_4 following the [reduction procedure for 3k'](#). The crude mixture was further purified by flash column chromatography on silica gel (hexanes/EtOAc, 4:1 (v:v) to 2:1 (v:v) gradient) to yield 127 mg (67%) of 2-(6-chloropyridin-3-yl)ethanol (**3w'**) as a colorless oil.

$^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 8.19 (d, $J = 2.4$ Hz, 1H), 7.56 (dd, $J = 8.2, 2.5$ Hz, 1H), 7.24 (d, $J = 8.2$ Hz, 1H), 3.87 (q, $J = 5.4$ Hz, 2H), 2.83 (t, $J = 6.3$ Hz, 2H), 2.70 (t, $J = 4.5$ Hz, 1H).

$^{13}\text{C NMR}$ (101 MHz; CDCl_3): δ 149.9, 149.2, 139.6, 133.6, 124.0, 62.6, 35.4.

FTIR (neat): cm^{-1} 3356, 2924, 1406, 1333, 1175, 1127, 1084, 1030.

Anal. Calcd. for. $\text{C}_8\text{H}_8\text{F}_3\text{NO}$ C, 50.27; H, 4.22. Found: C, 50.08; H, 4.33.



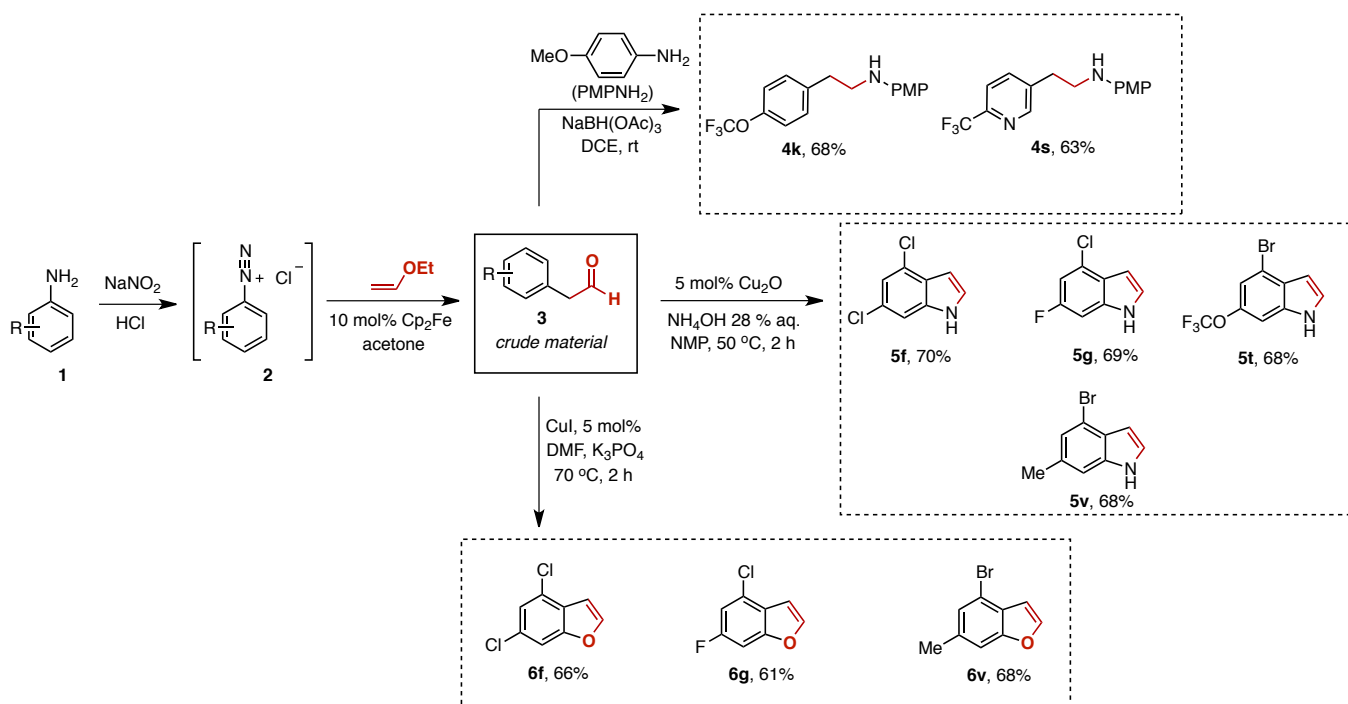
2-(2-chloropyridin-3-yl)ethanol (3x'). The corresponding aldehyde **3v** was obtained following the general procedure and using diazotization conditions from [Table S1, entry 21](#). Collected volume of the crude reaction mixture: $V = 16$ mL (1.2 mmol scale). The obtained crude material was subjected to reduction with NaBH_4 following the [reduction procedure for 3k'](#). The crude mixture was further purified by flash column chromatography on silica gel (hexanes/EtOAc, 4:1 (v:v) to 2:1 (v:v) gradient) to yield 123 mg (65%) of 2-(2-chloropyridin-3-yl)ethanol (**3x'**) as a light yellow oil.

$^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 8.23 (dd, $J = 4.7, 1.8$ Hz, 1H), 7.65 (dd, $J = 7.5, 1.8$ Hz, 1H), 7.19 (dd, $J = 7.5, 4.8$ Hz, 1H), 3.93 (t, $J = 6.5$ Hz, 2H), 3.00 (t, $J = 6.5$ Hz, 2H), 2.39 (s, 1H).

$^{13}\text{C NMR}$ (101 MHz; CDCl_3): δ 151.3, 147.6, 140.0, 133.2, 122.6, 61.0, 36.3.

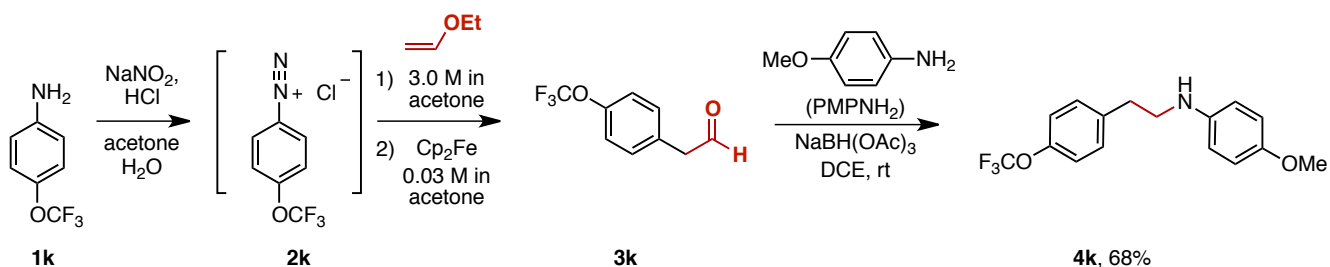
FTIR (neat): cm^{-1} 3324, 2877, 1582, 1564, 1497, 1340, 1181, 1127, 1077, 1047.

Further transformations of arylacetaldehydes **3** obtained via continuous-flow method



Synthesis of arylethylanilines **4k** and **4s**

4-methoxy-*N*-(4-(trifluoromethoxy)phenethyl)aniline (**4k**):



The corresponding aldehyde **3k** was prepared following the general procedure and using diazotization conditions from [Table S1, entry 11](#). Collected volume of the crude reaction mixture: $V = 16 \text{ mL}$ (1.2 mmol scale). The crude material was transferred into a dry 20 mL round bottom flask, which subsequently was charged with 147 mg (1.2 mmol) of *p*-anisidine. The flask was evacuated and backfilled with argon (this cycle was repeated three times), and 20 mL of dry DCM was added via syringe. To this solution 424 mg (2.0 mmol) of solid $\text{NaBH}(\text{OAc})_3$ were added and the resulting suspension was allowed to stir at room temperature for 1 h. The reaction mixture was quenched with 20 mL of saturated solution of NaHCO_3 followed by addition of 30 mL of EtOAc . The phases were

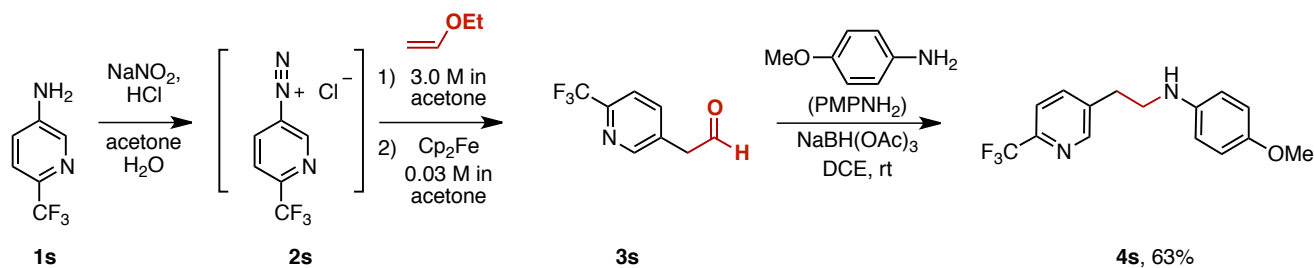
separated, and aqueous layer was extracted with EtOAc (2 X 20mL). The combined organic fractions were dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure and the crude mixture was further purified by flash column chromatography on silica gel (hexanes/EtOAc, 6:1 (v:v) to 4:1 (v:v) gradient) to yield 254 mg (68%) of 4-methoxy-*N*-(4-(trifluoromethoxy)phenethyl)aniline (**4k**) as a colorless liquid.

¹H-NMR (400 MHz; CDCl₃): δ 7.26 (d, *J* = 14.1 Hz, 2H), 7.20 (d, *J* = 0.6 Hz, 2H), 6.82 (d, *J* = 8.9 Hz, 2H), 6.62 (d, *J* = 8.9 Hz, 2H), 3.78 (s, 3H), 3.39 (t, *J* = 7.0 Hz, 3H, overlap with NH), 2.93 (t, *J* = 7.0 Hz, 2H).

¹³C-NMR (101 MHz; CDCl₃): δ 152.3, 147.8, 146.1, 142.0, 138.2, 130.0, 121.8, 121.1, 119.2, 115.0, 114.4, 55.8, 45.9, 34.9.

FTIR (neat): cm⁻¹ 3381, 2932, 2323, 2227, 1509, 1481, 1407, 1231, 1178, 1116, 1034.

4-methoxy-*N*-(2-(6-(trifluoromethyl)pyridin-3-yl)ethyl)aniline (**4s**):



The corresponding aldehyde **3s** was prepared following the general procedure and using diazotization conditions from [Table S1, entry 19](#). Collected volume of the crude reaction mixture: *V* = 16 mL (1.2 mmol scale). The obtained crude material was subjected to the reductive amination with *p*-anisidine in the presence of NaBH(OAc)₃ following the [procedure described for 4k](#). The crude material was purified by flash column chromatography on silica gel (hexanes/EtOAc, 2:1 (v:v) to 1:1 (v:v) gradient) to yield 224 mg (63%) of 4-methoxy-*N*-(2-(6-(trifluoromethyl)pyridin-3-yl)ethyl)aniline (**4k**) as a white solid.

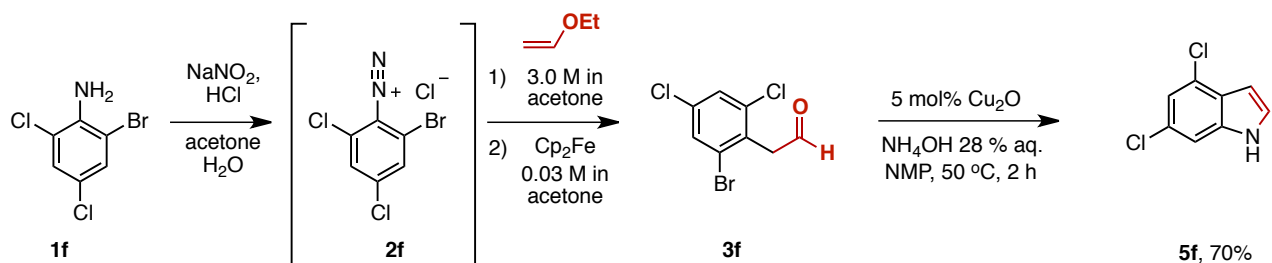
¹H-NMR (400 MHz; CDCl₃): δ 8.61 (d, *J* = 1.8 Hz, 1H), 7.74-7.72 (m, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 6.83-6.81 (m, 2H), 6.62-6.60 (m, 2H), 3.78 (s, 3H), 3.44 (t, *J* = 6.9 Hz, 3H), 3.00 (t, *J* = 6.9 Hz, 2H).

¹³C-NMR (101 MHz; CDCl₃): δ 152.5, 150.4, 146.6, 146.3, 146.0, 141.4, 138.47, 138.46, 137.5, 123.0, 120.29, 120.25, 120.22, 120.20, 115.1, 114.4, 55.8, 45.4, 32.7.

FTIR (neat): cm⁻¹ 3355, 2932, 2227, 1516, 1481, 1293, 1178, 1116, 1034.

Synthesis of indoles **5f**, **5g**, **5s** and **5u**

4,6-dichloro-1*H*-indole (**5f**):

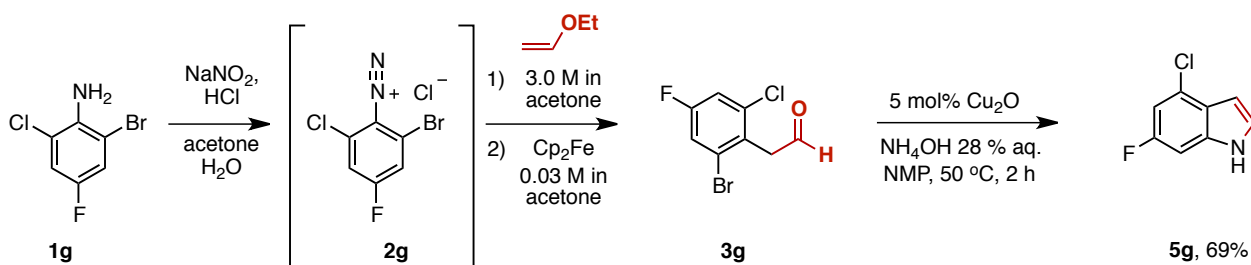


The corresponding aldehyde **3f** was prepared following the general procedure and using diazotization conditions from [Table S1, entry 6](#). Collected volume of the crude reaction mixture: $V = 20$ mL (1.5 mmol scale). After work-up, the obtained crude material was dissolved in 2.0 mL of NMP. The solution was transferred into a dry 30 mL test tube and subsequently charged with 1.0 mL of aqueous NH₄OH (30% in water). To this mixture 10 mg (0.075 mmol, 5 mol%) of Cu₂O were added and the reaction mixture was placed into the 50 °C preheated oil bath and further heated for 2 h. The reaction mixture was quenched with 20 mL of saturated solution of NH₄Cl and extracted of EtOAc (3 X 20 mL). Combined organic fractions were dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure and the crude mixture was further purified by flash column chromatography on silica gel (hexanes/EtOAc, 10:1 (v:v) to 4:1 (v:v) gradient) to yield 193 mg (70%) of 4,6-dichloro-1*H*-indole (**5f**) as a light brown oil.

¹H-NMR (400 MHz; CDCl₃): δ 8.25 (s, 1H), 7.30 (s, 1H), 7.24 (t, $J = 2.7$ Hz, 1H), 7.18 (d, $J = 1.2$ Hz, 1H), 6.66 (d, $J = 0.4$ Hz, 1H).

¹³C-NMR (101 MHz; CDCl₃): δ 136.3, 127.7, 126.5, 125.6, 125.3, 120.2, 109.8, 101.6.

FTIR (neat): cm⁻¹ 3453, 1618, 1581, 1506, 1339, 1319, 1132.

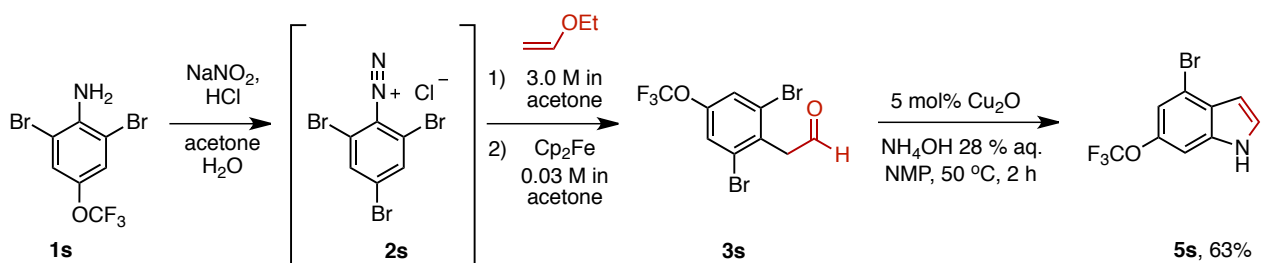
6-methoxy-1*H*-indole (5g):

The corresponding aldehyde **3g** was prepared following the general procedure and using diazotization conditions from [Table S1, entry 7](#). Collected volume of the crude reaction mixture: $V = 20$ mL (1.5 mmol scale). The obtained crude material was reacted with excess of aqueous NH_4OH in the presence of 10 mg (5 mol%) of Cu_2O in NMP at 50 °C following procedure described for **5f**. Crude material was purified by flash column chromatography on silica gel (hexanes/ Et_2O , 4:1 (v:v) to 2:1 (v:v) gradient) to yield 175 mg (69%) of indole (**5g**) as a light yellow oil.

$^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 8.30-8.20 (b. s., 1H), 7.24 (dd, $J = 3.3, 2.4$ Hz, 1H), 7.03 (ddd, $J = 9.1, 2.1, 1.0$ Hz, 1H), 6.99 (dd, $J = 9.5, 2.1$ Hz, 1H), 6.66 (ddd, $J = 3.3, 2.2, 1.0$ Hz, 1H).

$^{13}\text{C-NMR}$ (101 MHz; CDCl_3): δ 160.4, 158.0, 135.75, 135.62, 126.29, 126.15, 124.95, 124.91, 123.6, 109.2, 108.9, 101.4, 96.4, 96.2.

FTIR (neat): cm^{-1} 3452, 1646, 1618, 1581, 1506, 1491, 1426, 1319, 1304, 1132.

4-bromo-6-(trifluoromethoxy)-1*H*-indole (5s):

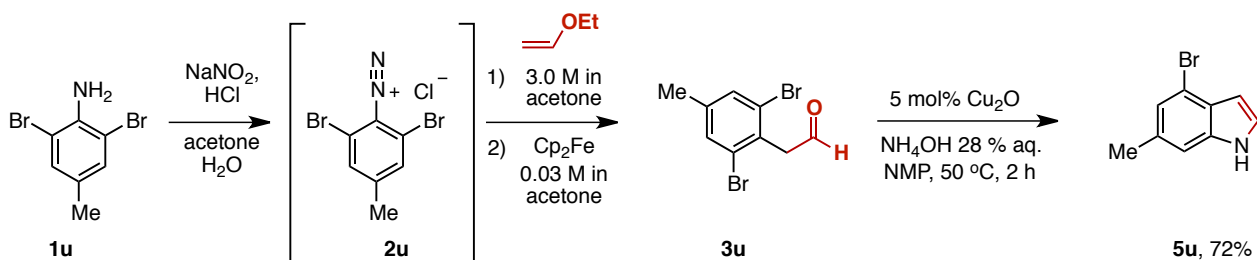
The corresponding aldehyde **3s** was prepared following the general procedure and using diazotization conditions from [Table S1, entry 19](#). Collected volume of the crude reaction mixture: $V = 20$ mL (1.5 mmol scale). The obtained crude material was reacted with excess of aqueous NH_4OH in the presence of 10 mg (5 mol%) of Cu_2O in NMP at 50 °C following procedure described for **5f**. Crude material was purified by flash column chromatography on silica gel (hexanes/ EtOAc , 10:1 (v:v) to 4:1 (v:v) gradient) to yield 264 mg (63%) of indole (**5t**) as red-brown oil.

¹H-NMR (400 MHz; CDCl₃): δ 8.40 (s, 1H), 7.33-7.27 (m, 3H), 6.64 (ddd, J = 3.2, 2.3, 0.9 Hz, 1H).

¹³C-NMR (101 MHz; CDCl₃): δ 144.66, 144.64, 135.0, 127.6, 126.1, 121.9, 119.4, 117.19, 117.18, 114.5, 103.53, 103.52, 103.2.

FTIR (neat): cm⁻¹ 3442, 1712, 1620, 1573, 1428, 1319, 1248, 1218, 1200, 1176, 1154, 802.

4-bromo-6-methyl-1H-indole (5u):



The corresponding aldehyde **3u** was prepared following the general procedure and using diazotization conditions from [Table S1, entry 21](#). Collected volume of the crude reaction mixture: $V = 20$ mL (1.5 mmol scale). The obtained crude material was reacted with excess of aqueous NH₄OH in the presence of 10 mg (5 mol%) of Cu₂O in NMP at 50 °C following procedure described for **5f**. Crude material was purified by flash column chromatography on silica gel (hexanes/EtOAc, 10:1 (v:v) to 4:1 (v:v) gradient) to yield 227 mg (72%) of indole (**5u**) as white solid.

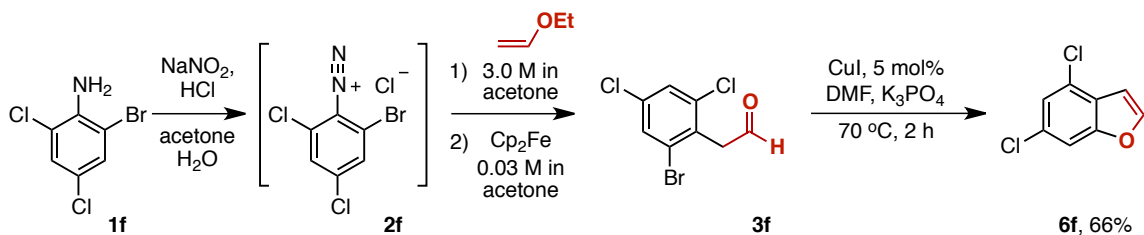
¹H-NMR (400 MHz; CDCl₃): δ 8.14 (s, 1H), 7.20-7.19 (m, 2H), 7.14 (q, J = 0.9 Hz, 1H), 6.58 (ddd, J = 3.2, 2.2, 1.0 Hz, 1H), 2.47 (s, 3H).

¹³C-NMR (101 MHz; CDCl₃): δ 136.4, 133.2, 126.5, 124.4, 124.0, 114.3, 110.2, 102.8, 77.4, 77.1, 76.7, 21.4.

FTIR (neat): cm⁻¹ 3402, 2912, 2856, 1708, 1618, 1577, 1554, 1503, 1422, 1395, 1331, 1090, 1067.

Synthesis of benzofurans **6f**, **6g** and **6u**

4,6-dichlorobenzofuran (**6f**):



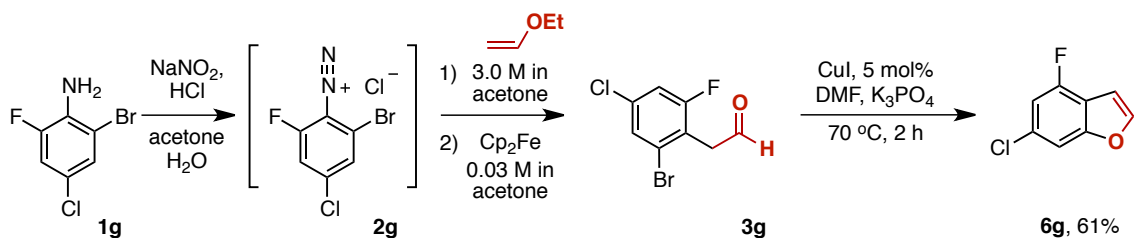
The corresponding aldehyde **3f** was prepared following the general procedure and using diazotization conditions from [Table S1, entry 6](#). Collected volume of the crude reaction mixture: $V = 20\text{ mL}$ (1.5 mmol scale). After work up, the obtained crude material was dissolved in 5.0 mL of dry DMF. The solution was transferred under argon into dry 30 mL test tube containing 14 mg (0.075 mmol) of CuI and 636 mg of K_3PO_4 (2.0 mmol) in 1.0 mL of DMF. The reaction mixture was heated at $70\text{ }^\circ\text{C}$ for 2 h. The reaction mixtures was cooled down to room temperature and then layered between 50 mL of 1:1 mixture of pentane/ Et_2O (v:v) and 50 mL of saturated NH_4Cl solution in water. Phases were separated and aqueous layer was extracted with 1:1 mixture of pentane/ Et_2O (v:v; 3 X 10 mL). The combined organic extracts were dried over Na_2SO_4 . The solvent was concentrated under reduced pressure and the crude material was purified by flash column chromatography on silica gel eluting with pentane to yield 185 mg (66%) of the title compound **6f** as colorless oil:

$^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 7.62 (d, $J = 2.2\text{ Hz}$, 1H), 7.42 (s, 1H), 7.25 (t, $J = 2.4\text{ Hz}$, 1H), 6.82 (d, $J = 2.0\text{ Hz}$, 1H).

$^{13}\text{C-NMR}$ (101 MHz; CDCl_3): δ 154.9, 146.1, 130.3, 126.5, 125.8, 123.3, 110.8, 105.3.

FTIR (neat): cm^{-1} 3095, 2323, 1609, 1481, 1407, 1216, 1178, 1116, 1033.

6-chloro-4-fluorobenzofuran (**6g**):



The corresponding aldehyde **3g** was prepared following the general procedure and using diazotization conditions from [Table S1, entry 7](#). Collected volume of the crude reaction mixture: $V = 20\text{ mL}$ (1.5 mmol scale). The crude material was subjected to the Cu-catalyzed intramolecular

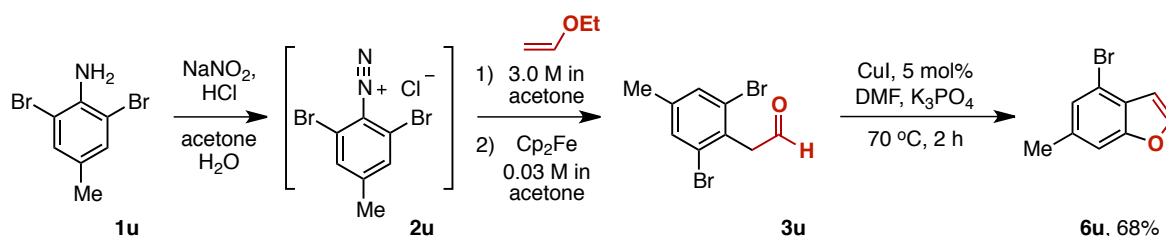
cyclization in the presence of K_3PO_4 in DMF following the procedure described for **6f**. Crude material was purified by flash column chromatography on silica gel eluting with pentane to yield 171 mg (61%) of the title compound **6g** as colorless oil.

1H -NMR (400 MHz; $CDCl_3$): δ 7.60 (d, $J = 2.3$ Hz, 1H), 7.14-7.11 (m, 1H), 7.03 (dd, $J = 9.4, 2.1$ Hz, 1H), 6.80-6.80 (m, 1H).

^{13}C -NMR (101 MHz; $CDCl_3$): δ 161.6, 159.2, 154.79, 154.65, 145.99, 145.95, 126.32, 126.19, 123.4, 111.9, 111.7, 105.1, 98.2, 98.0.

FTIR (neat): cm^{-1} 3097, 2925, 1662, 1617, 1594, 1477, 1408, 1168, 1139, 1109, 1089, 982, 910.

4-bromo-6-methylbenzofuran (**6u**):

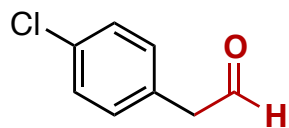
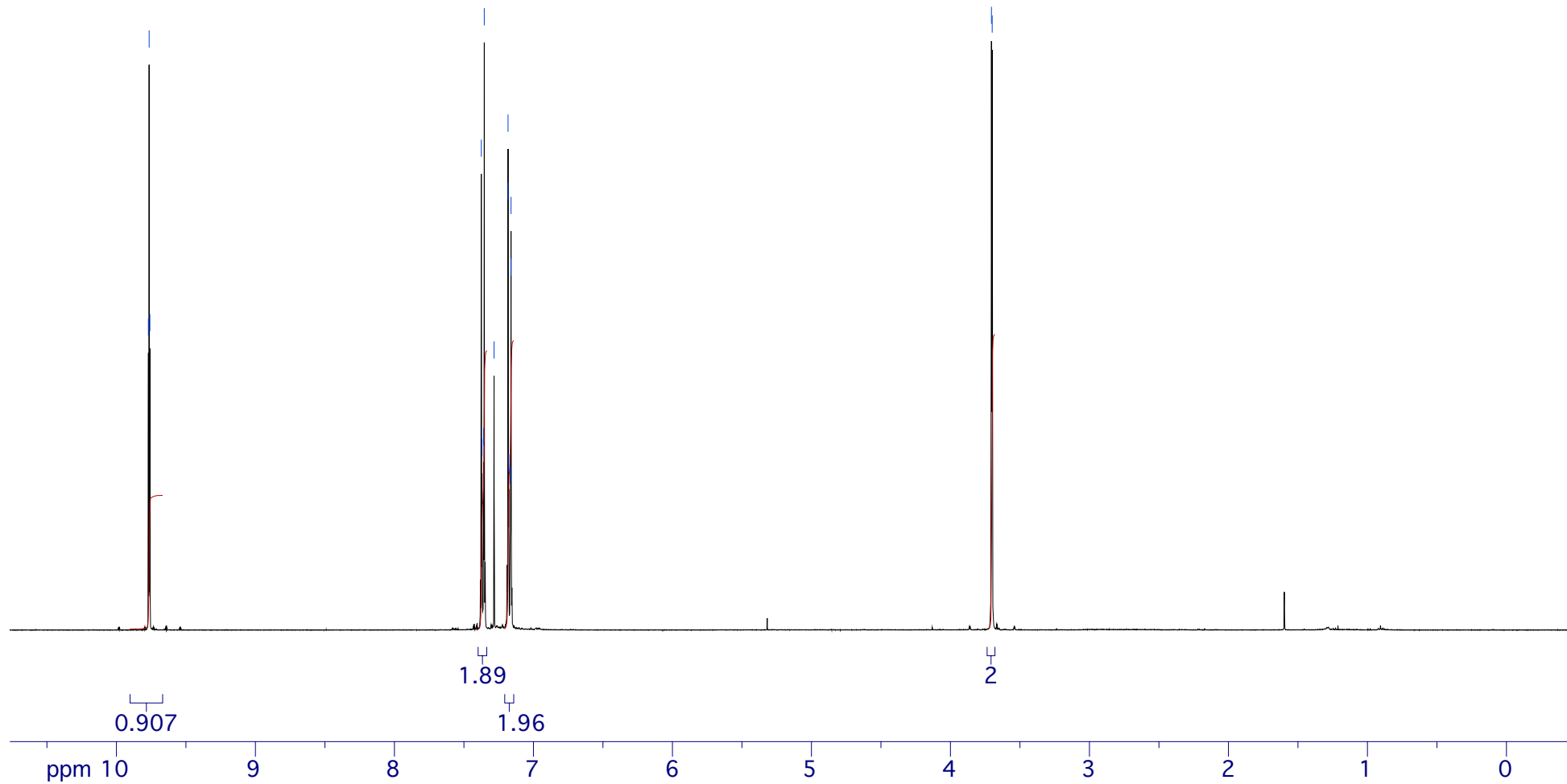


The corresponding aldehyde **3u** was prepared following the general procedure and using diazotization conditions from [Table S1, entry 21](#). Collected volume of the crude reaction mixture: $V = 20$ mL (1.5 mmol scale). The crude material was subjected to the Cu-catalyzed intramolecular cyclization in the presence of K_3PO_4 in DMF following the procedure described for **6f**. Crude material was purified by flash column chromatography on silica gel eluting with pentane to yield 211 mg (68%) of the title compound **6u** as colorless oil.

1H -NMR (400 MHz; $CDCl_3$): δ 7.56 (d, $J = 2.2$ Hz, 1H), 7.22 (s, 2H), 6.72 (d, $J = 2.1$ Hz, 1H), 2.42 (s, 3H).

^{13}C -NMR (101 MHz; $CDCl_3$): δ 155.0, 144.8, 135.9, 127.0, 126.5, 113.6, 110.9, 106.6, 77.4, 77.1, 76.7, 21.4.

FTIR (neat): cm^{-1} 2918, 2359, 1707, 1617, 1570, 1480, 1401, 1342, 1336, 1275, 1213, 1030, 1003.

9.770
9.765
9.7597.375
7.370
7.359
7.354
7.283
7.183
7.182
7.177
7.166
7.162
7.1613.705
3.700Table 1, **3a**

198.569

133.472
130.930
130.271
129.12477.339
77.021
76.704

49.784

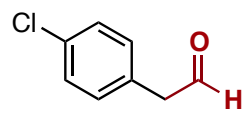
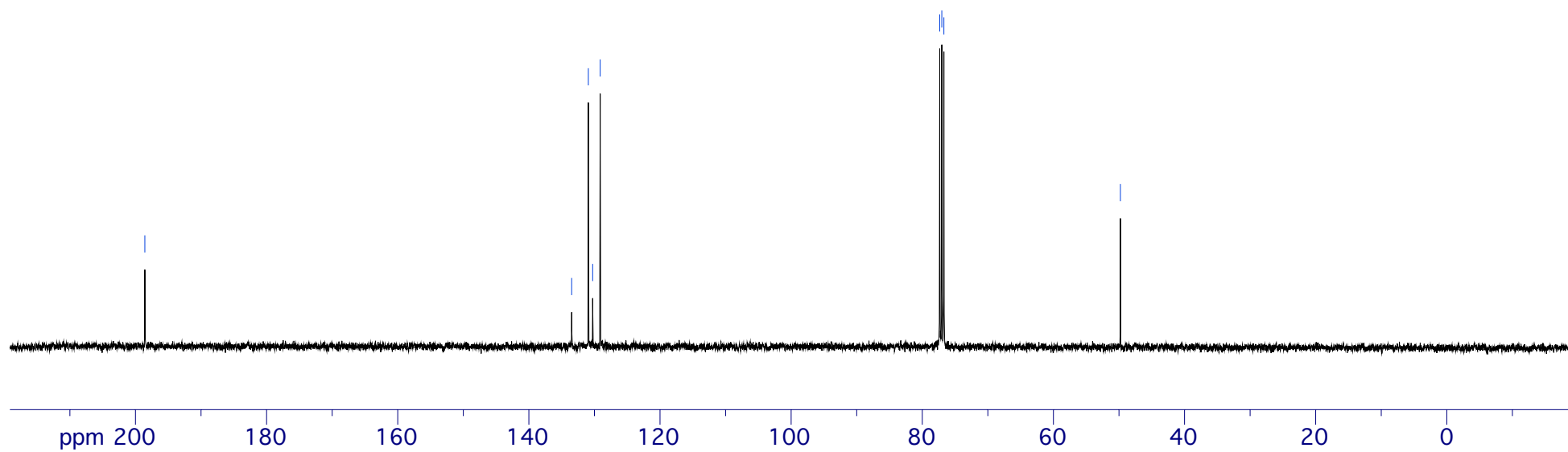
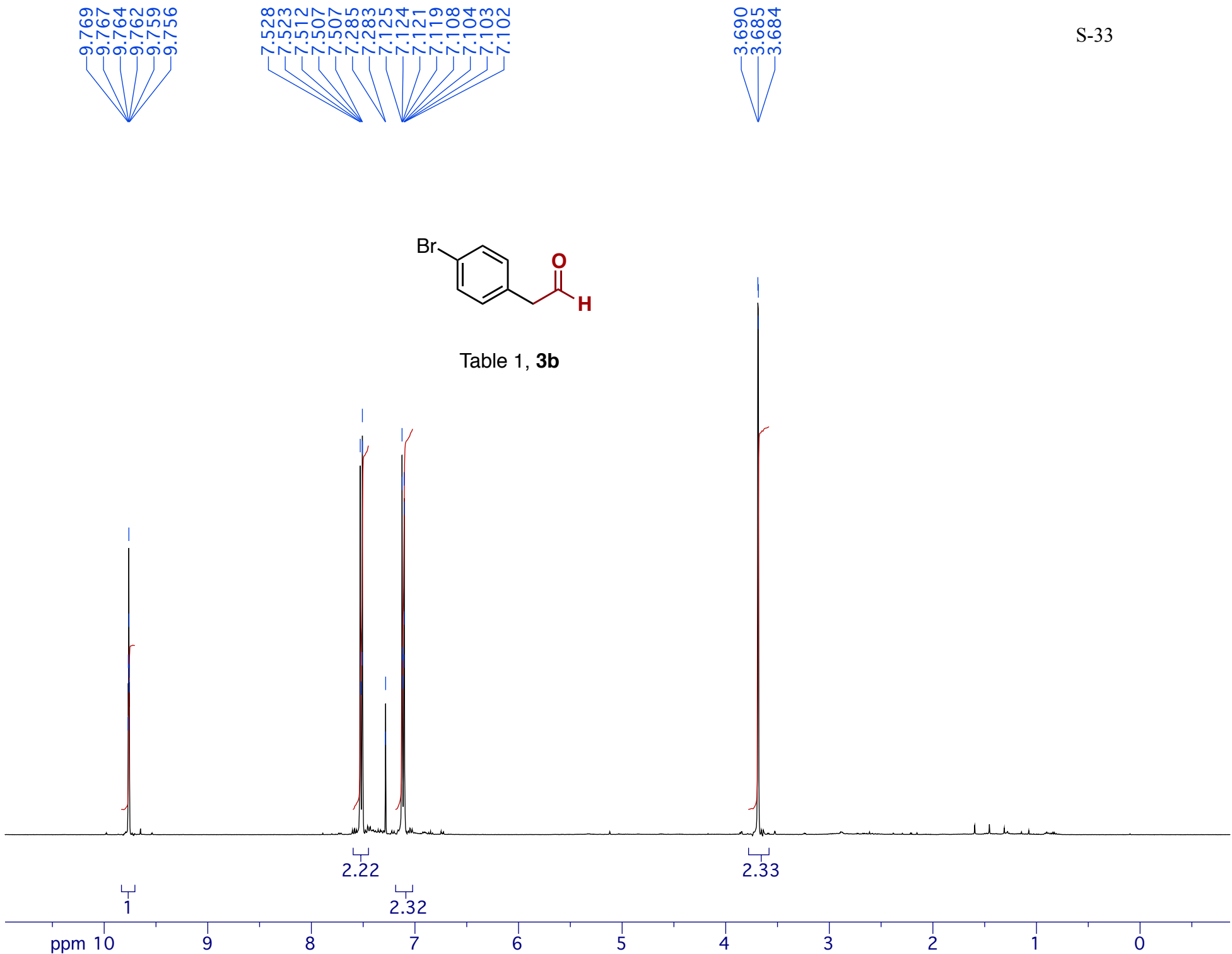


Table 1, entry 3a

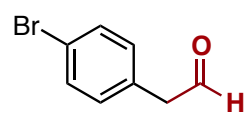
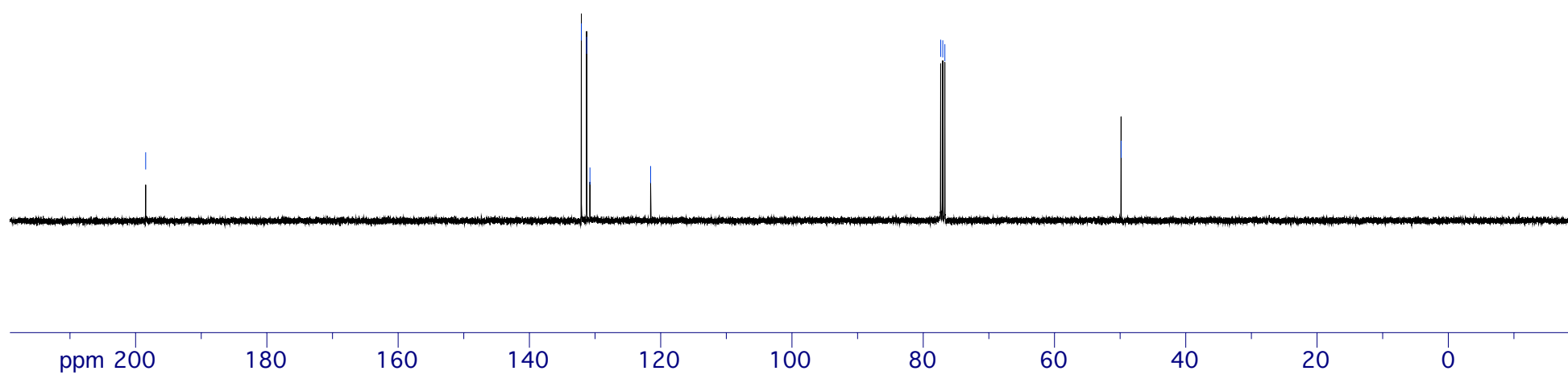




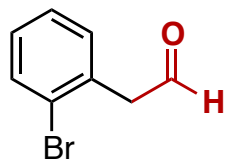
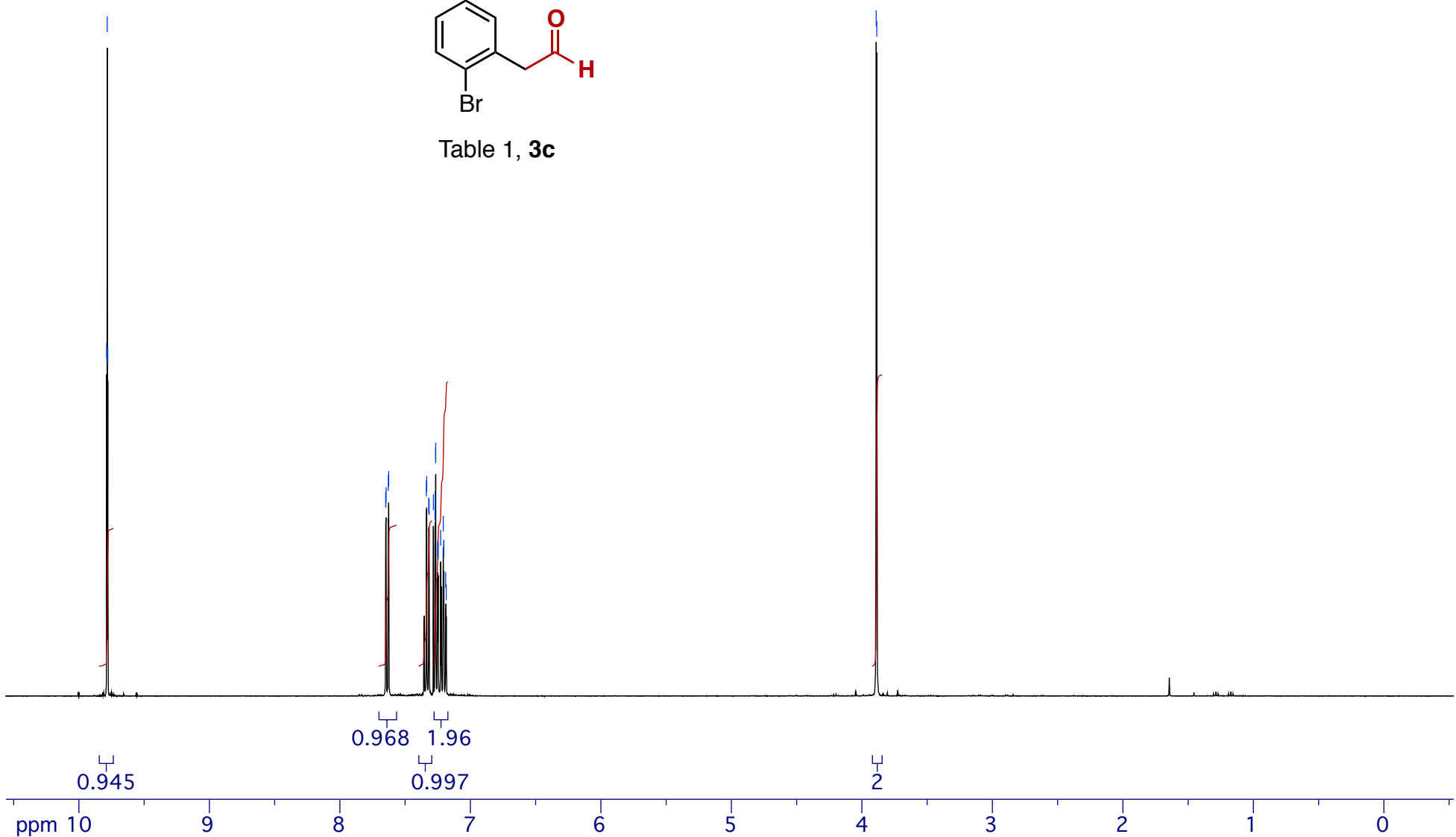
198.465

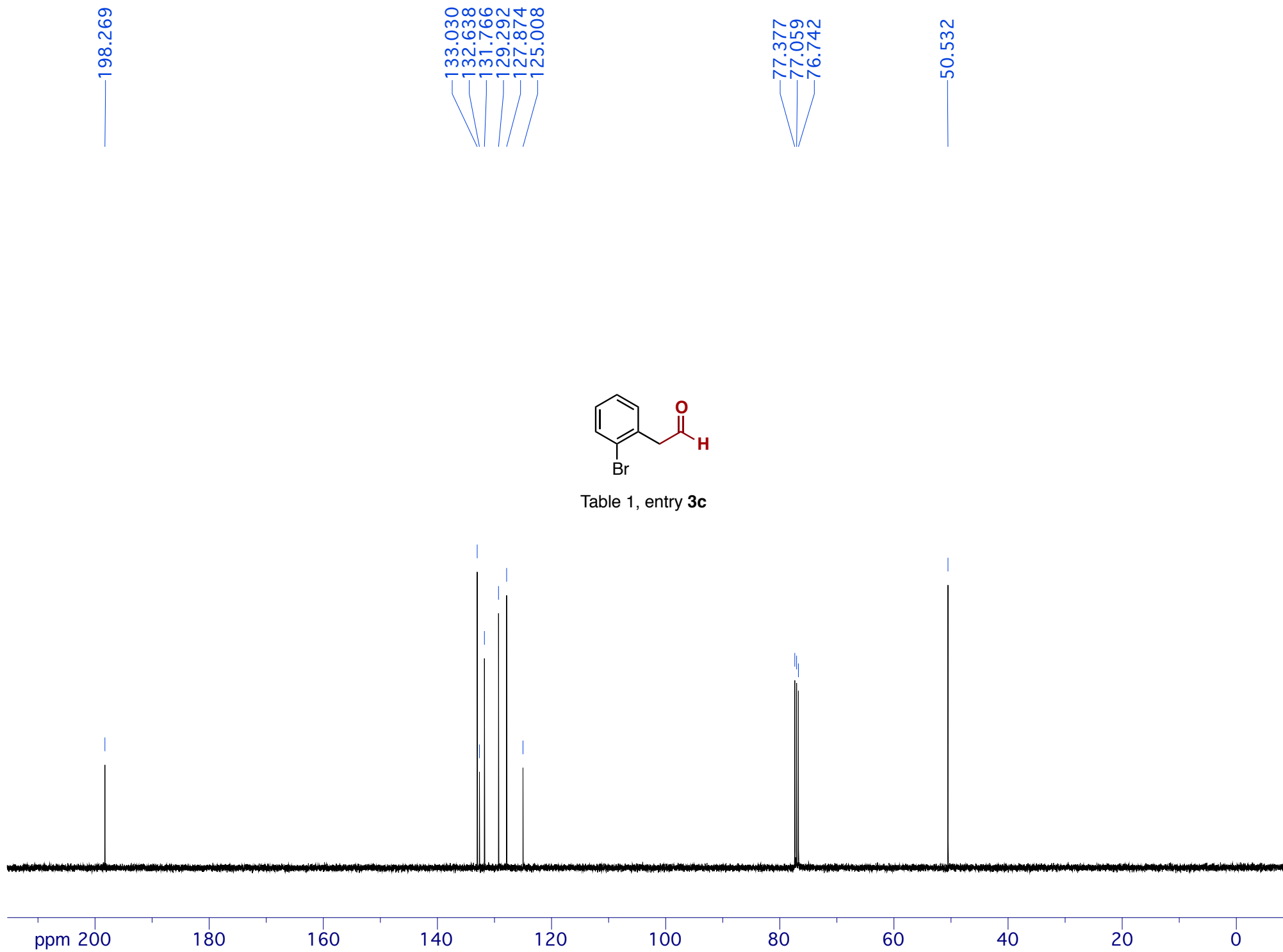
132.083
131.284
130.776
121.53277.338
77.020
76.702

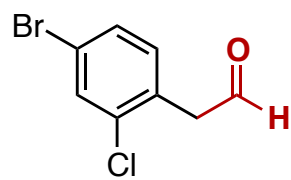
49.849

Table 1, entry **3b**

9.787
9.783
9.779
7.649
7.646
7.629
7.626
7.338
7.335
7.319
7.316
7.283
7.271
7.270
7.267
7.266
7.251
7.247
7.228
7.208
7.204
7.203
7.189
7.185
3.890
3.886

Table 1, **3c**

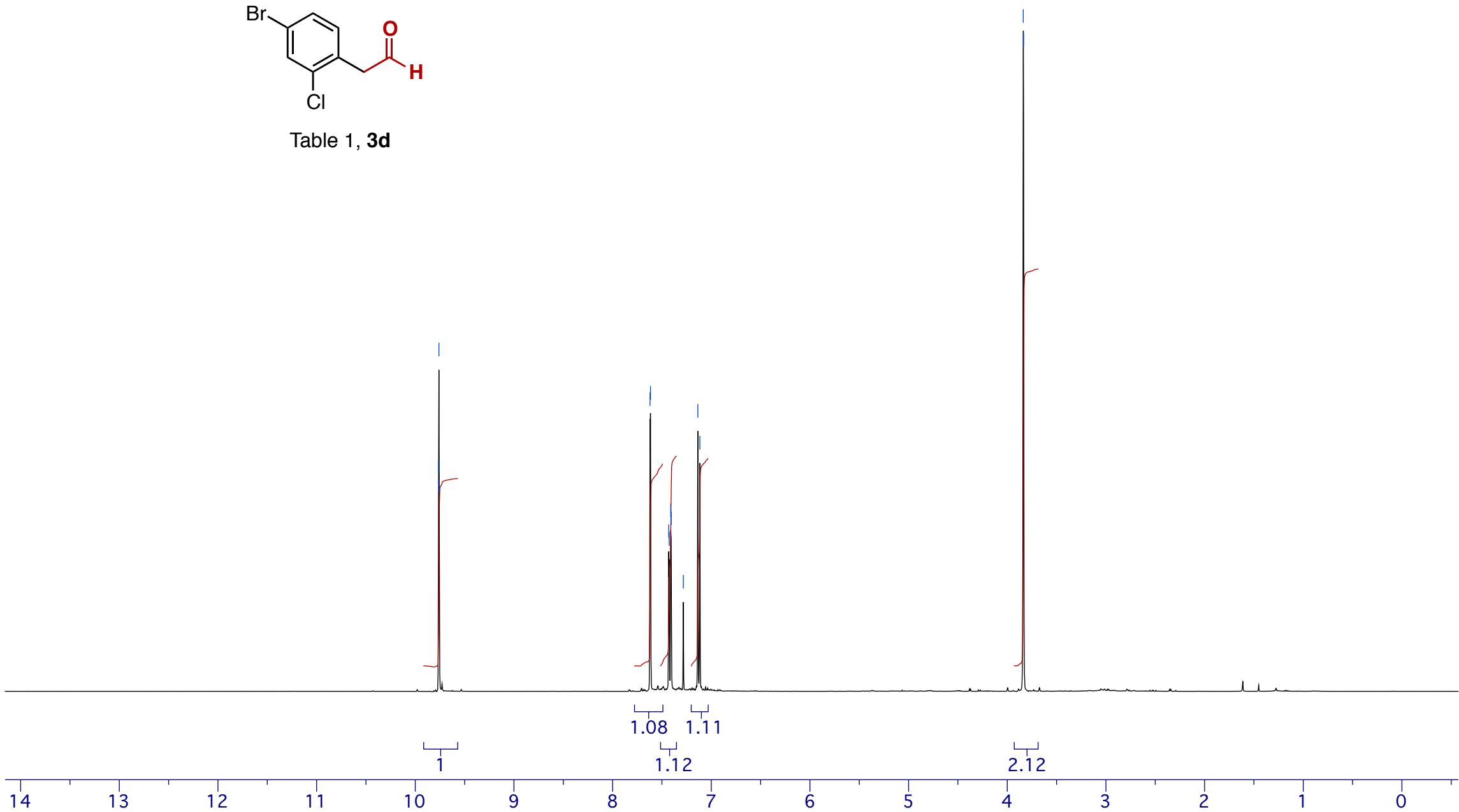


Table 1, **3d**

9.764
9.760
9.757

7.621
7.616
7.431
7.426
7.411
7.406
7.283
7.136
7.116

3.838
3.835



197.238

135.451
132.760
132.314
130.441
129.838
121.889

77.357
77.040
76.722

47.718

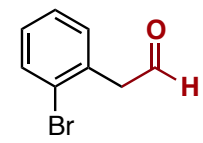
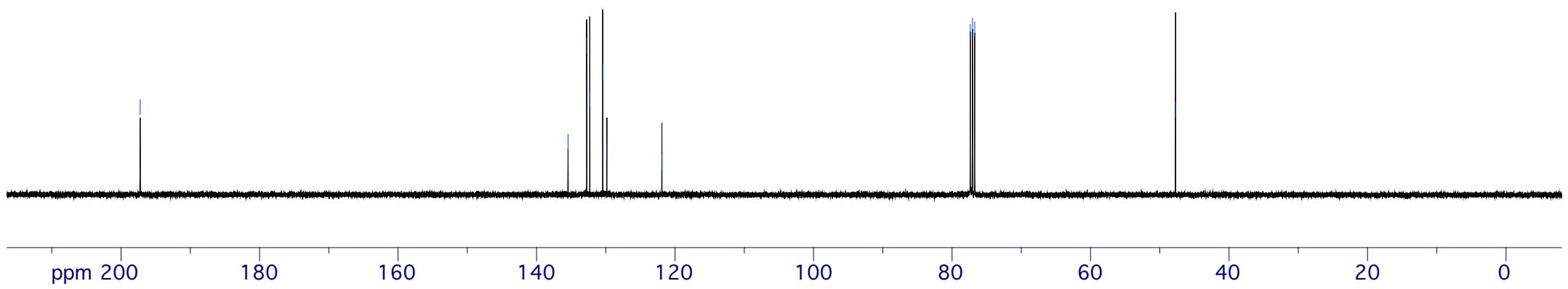
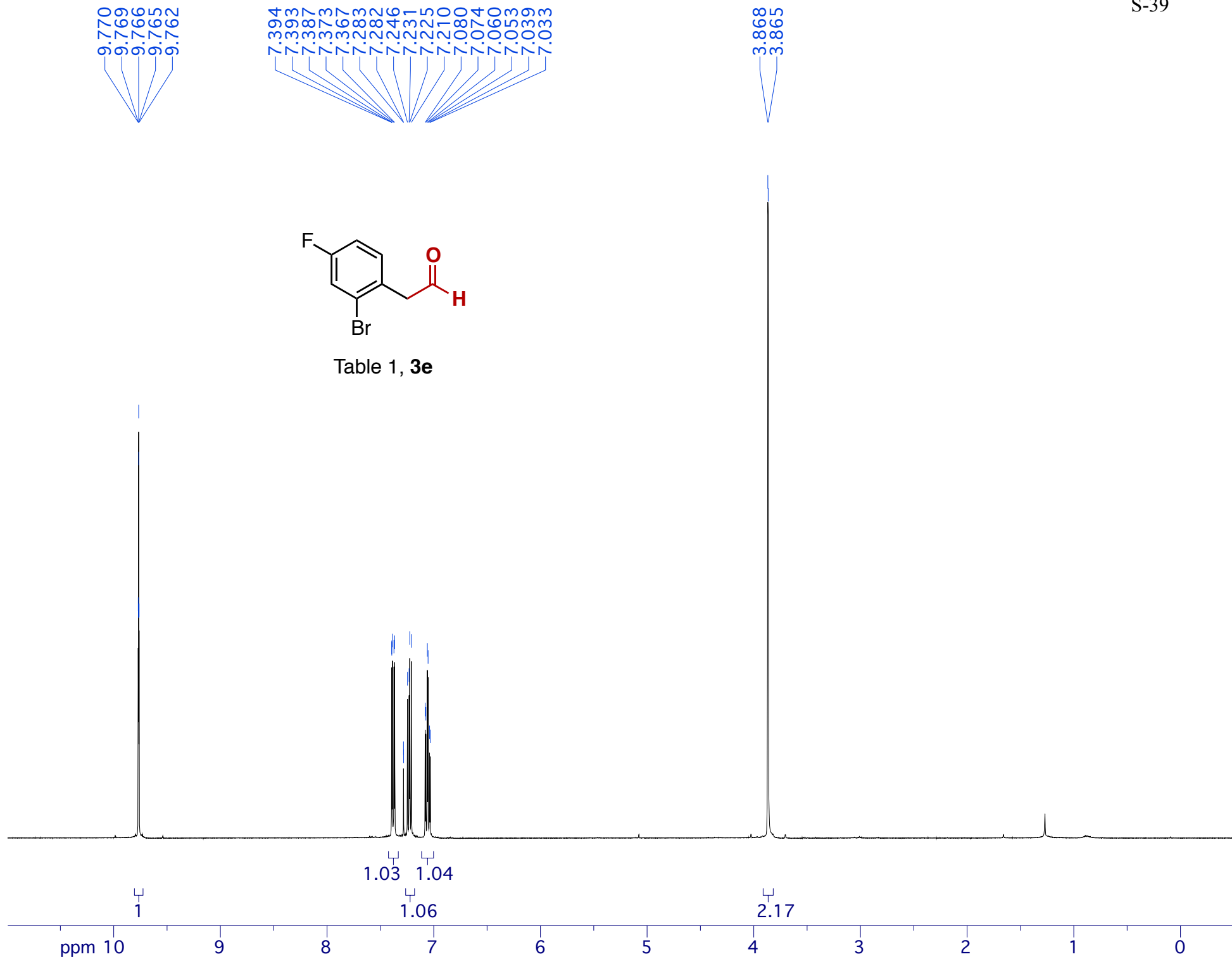
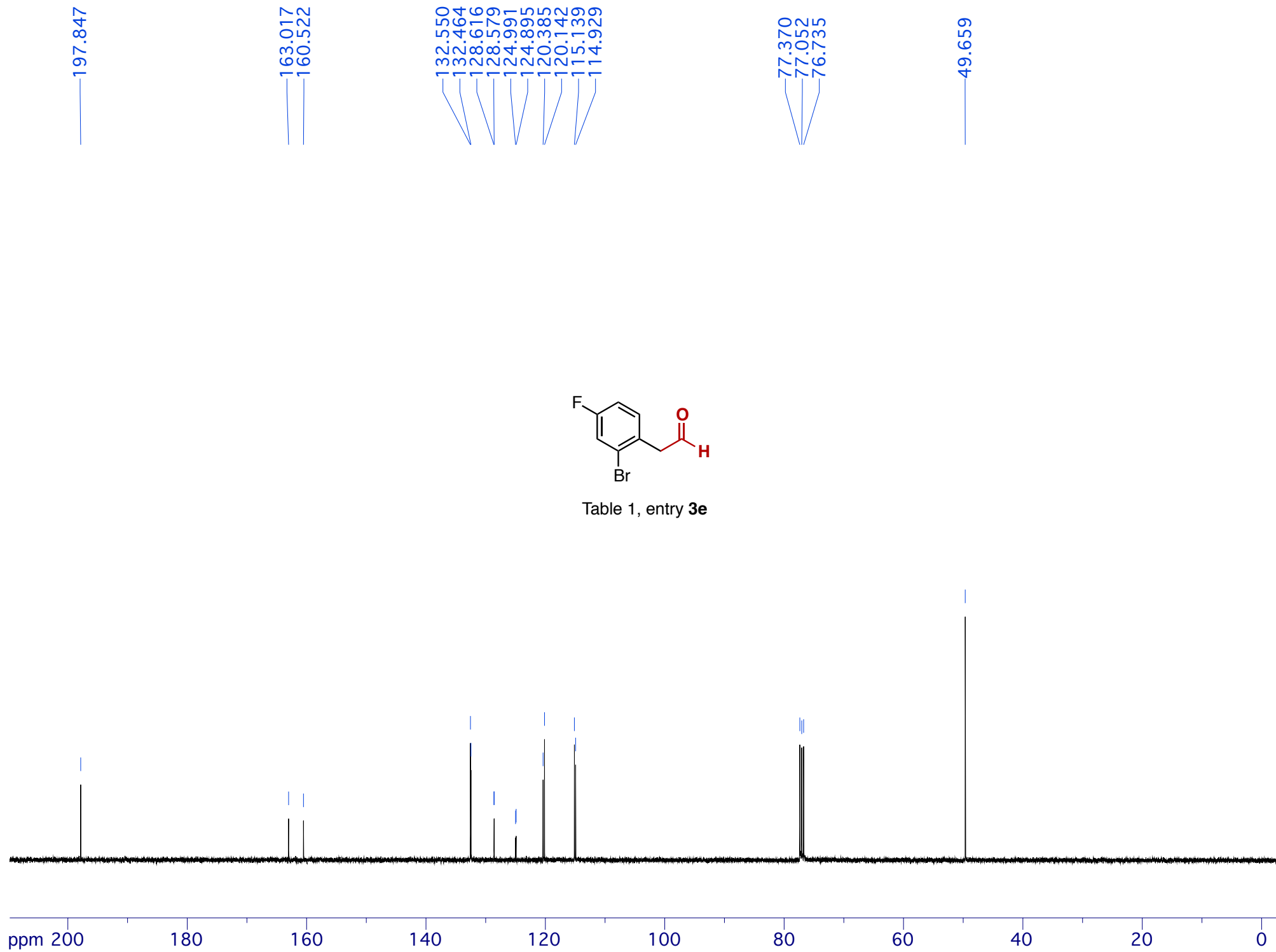
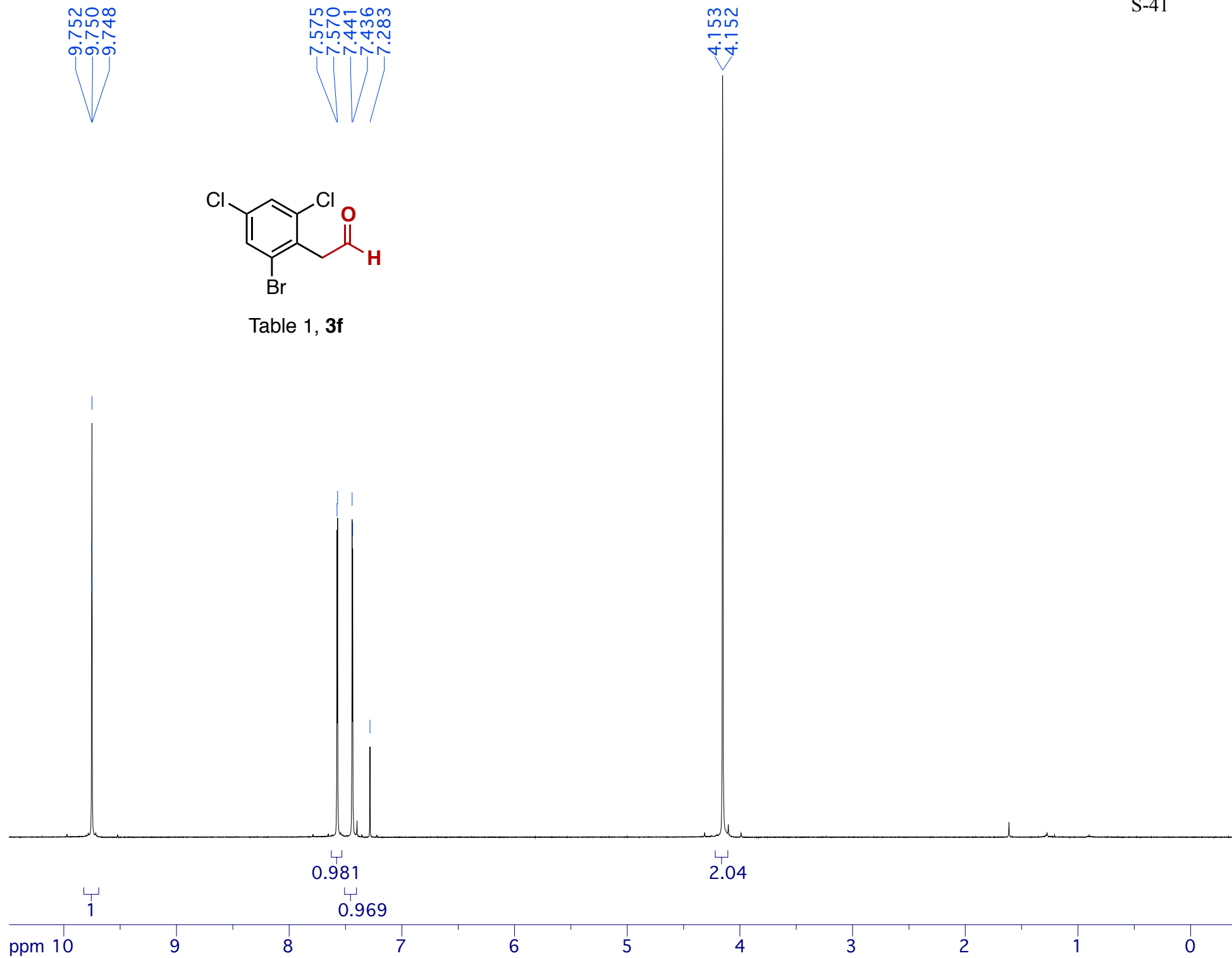


Table 1, entry 3c





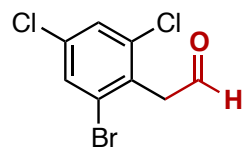
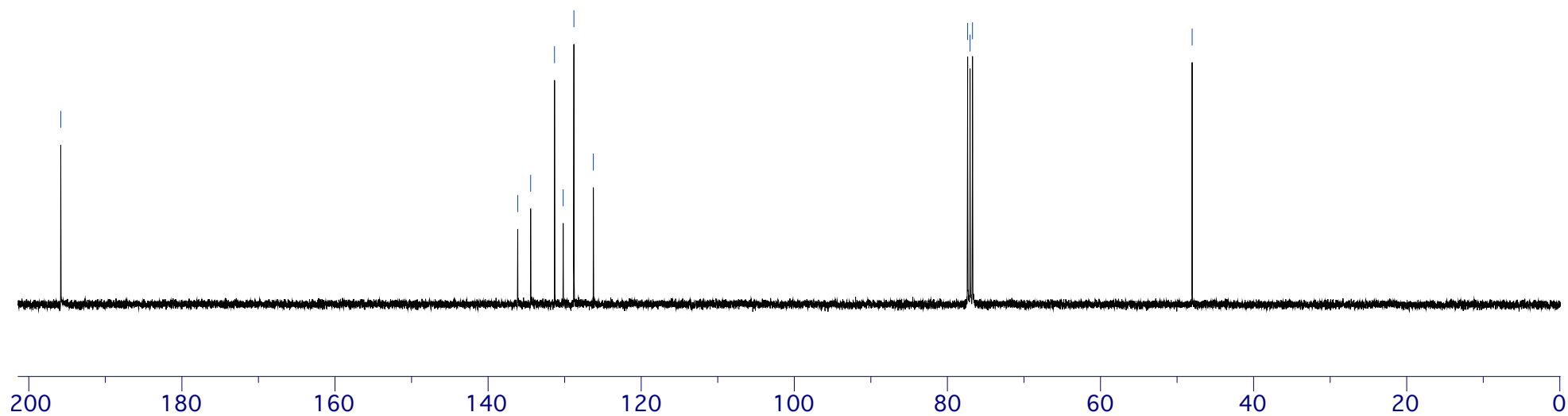


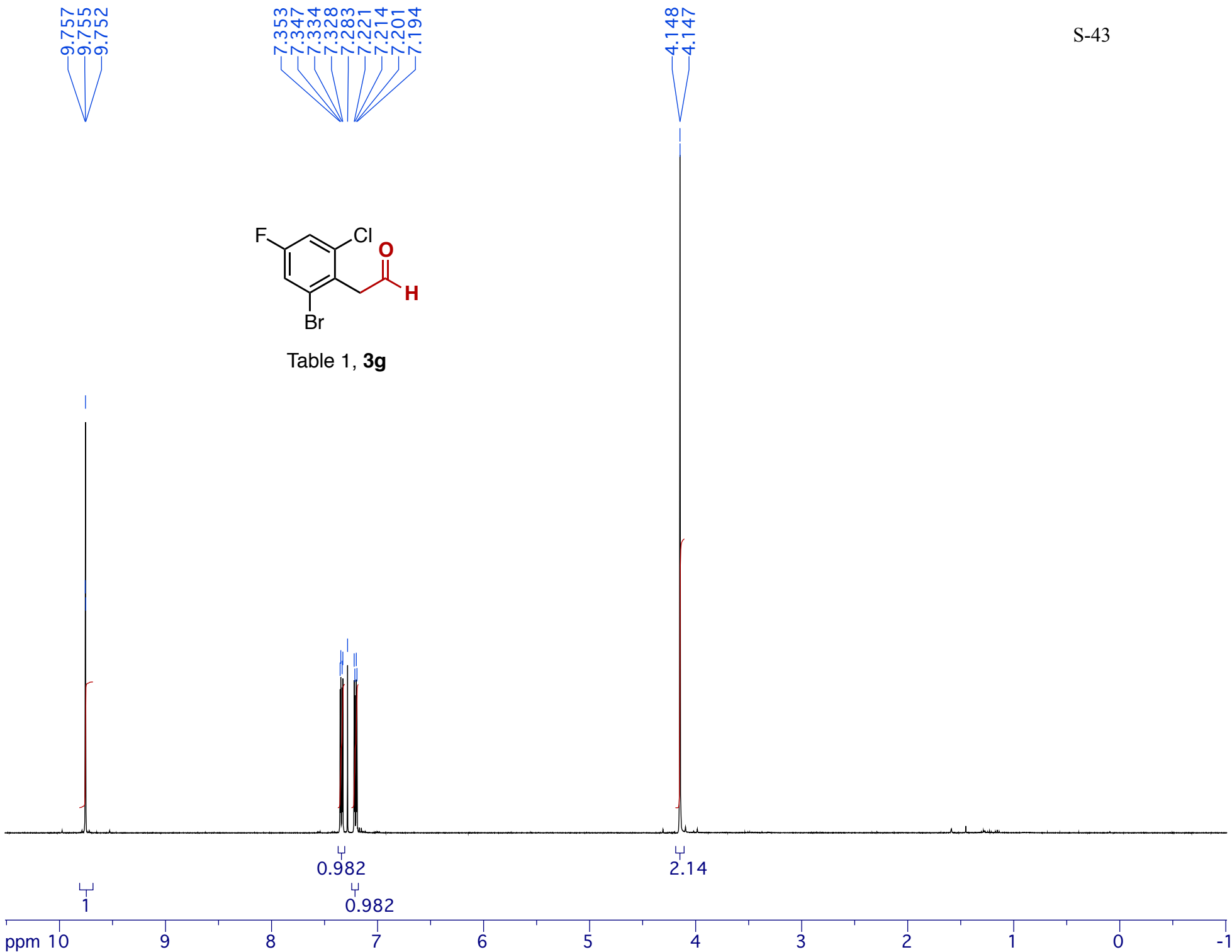


195.826

136.129
134.441
131.323
130.195
128.789
126.25277.356
77.039
76.721

48.031

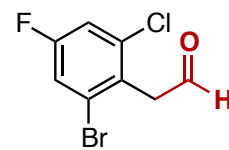
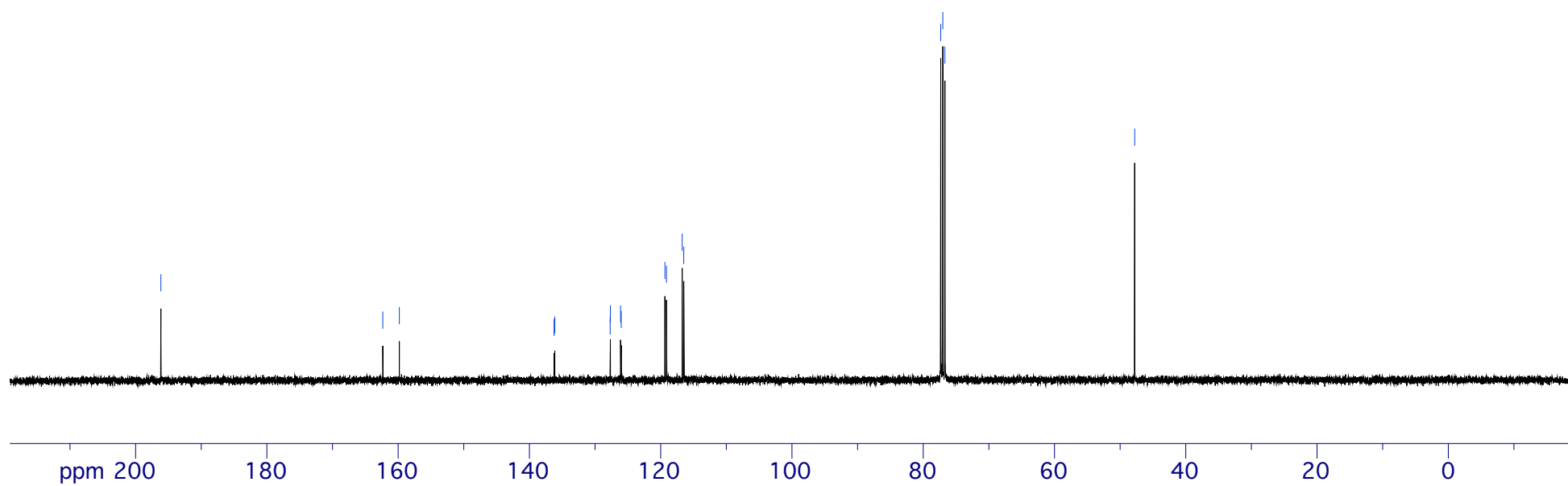
Table 1, entry **3f**

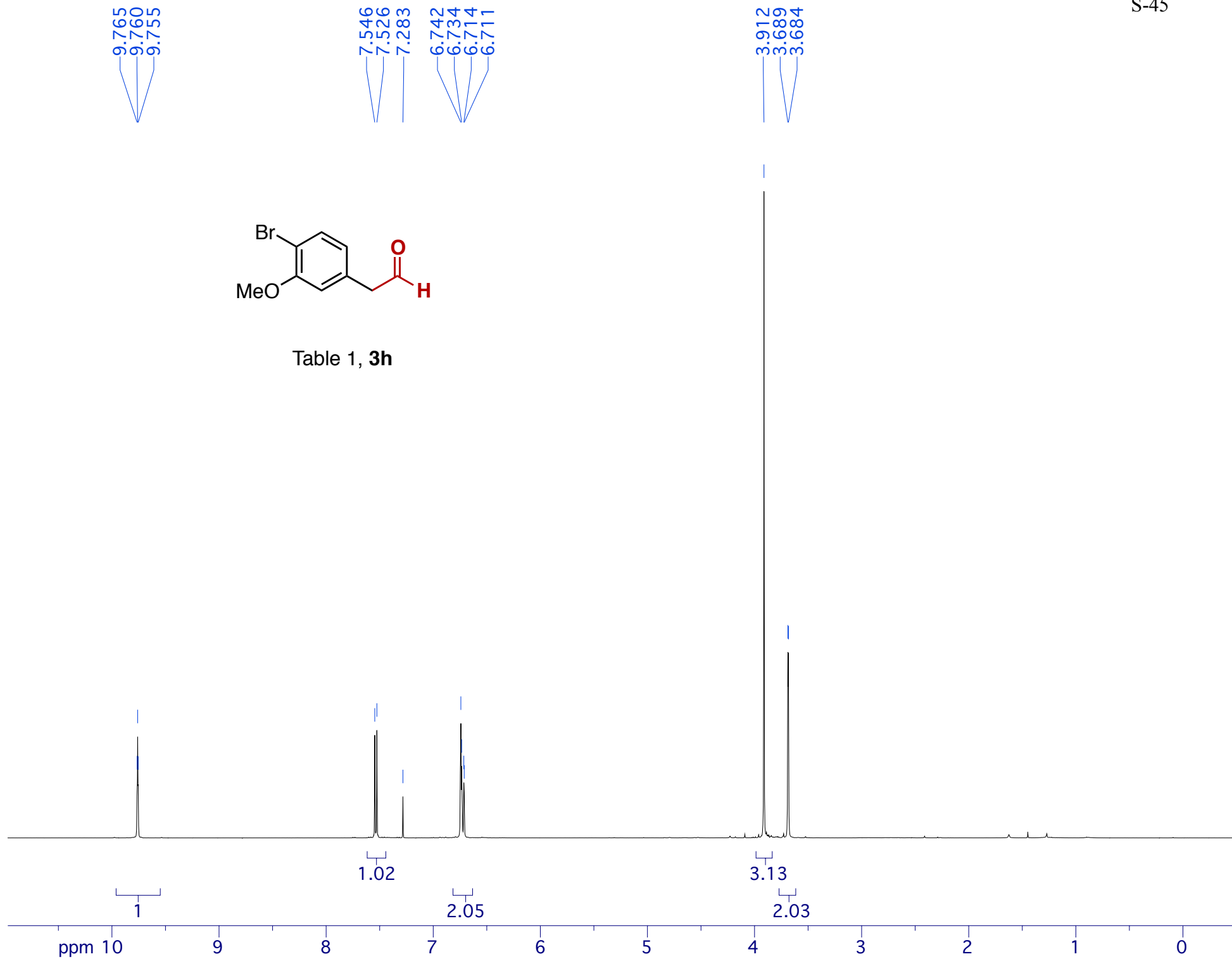


196.147

162.340
159.817136.237
136.128
127.700
127.663
126.114
126.011
119.355
119.115
116.724
116.48477.332
77.014
76.697

47.782

Table 1, entry **3g**



—198.55

—156.19

133.68
132.52

122.95
122.94

—110.82

77.38
77.06
76.74

—56.25

S-46

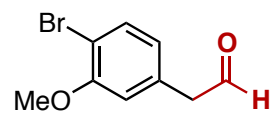
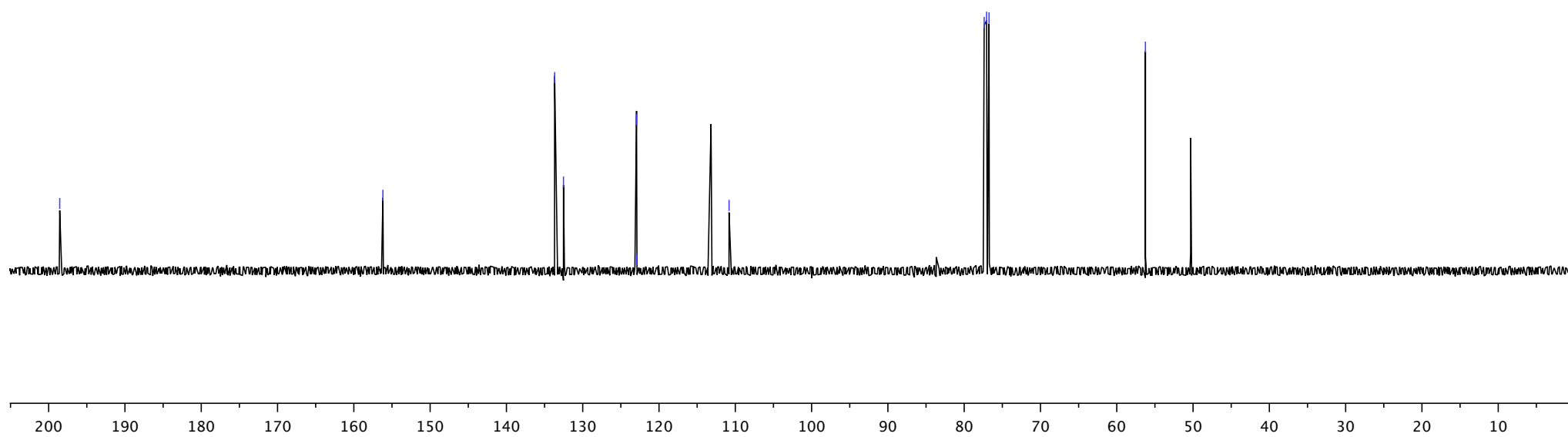
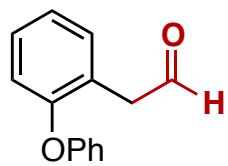
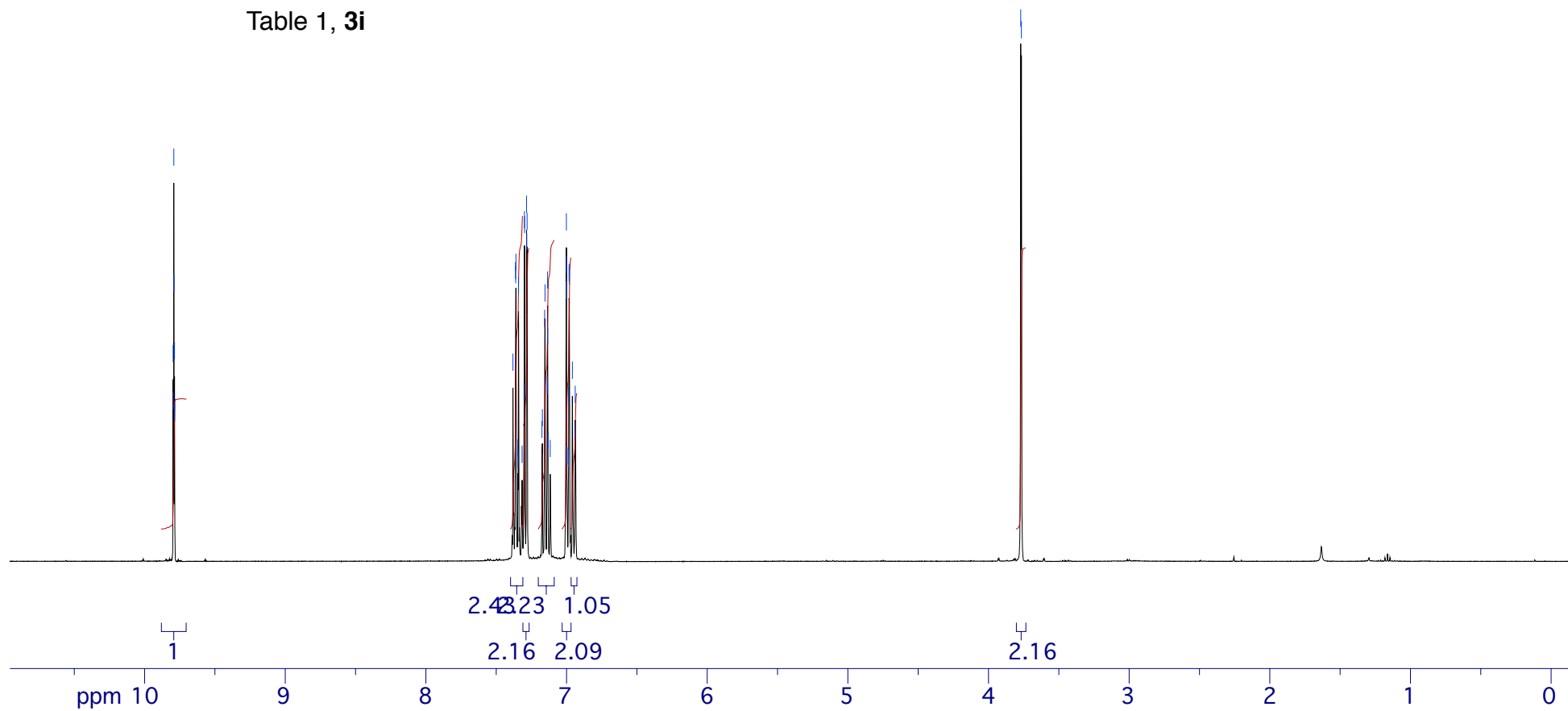
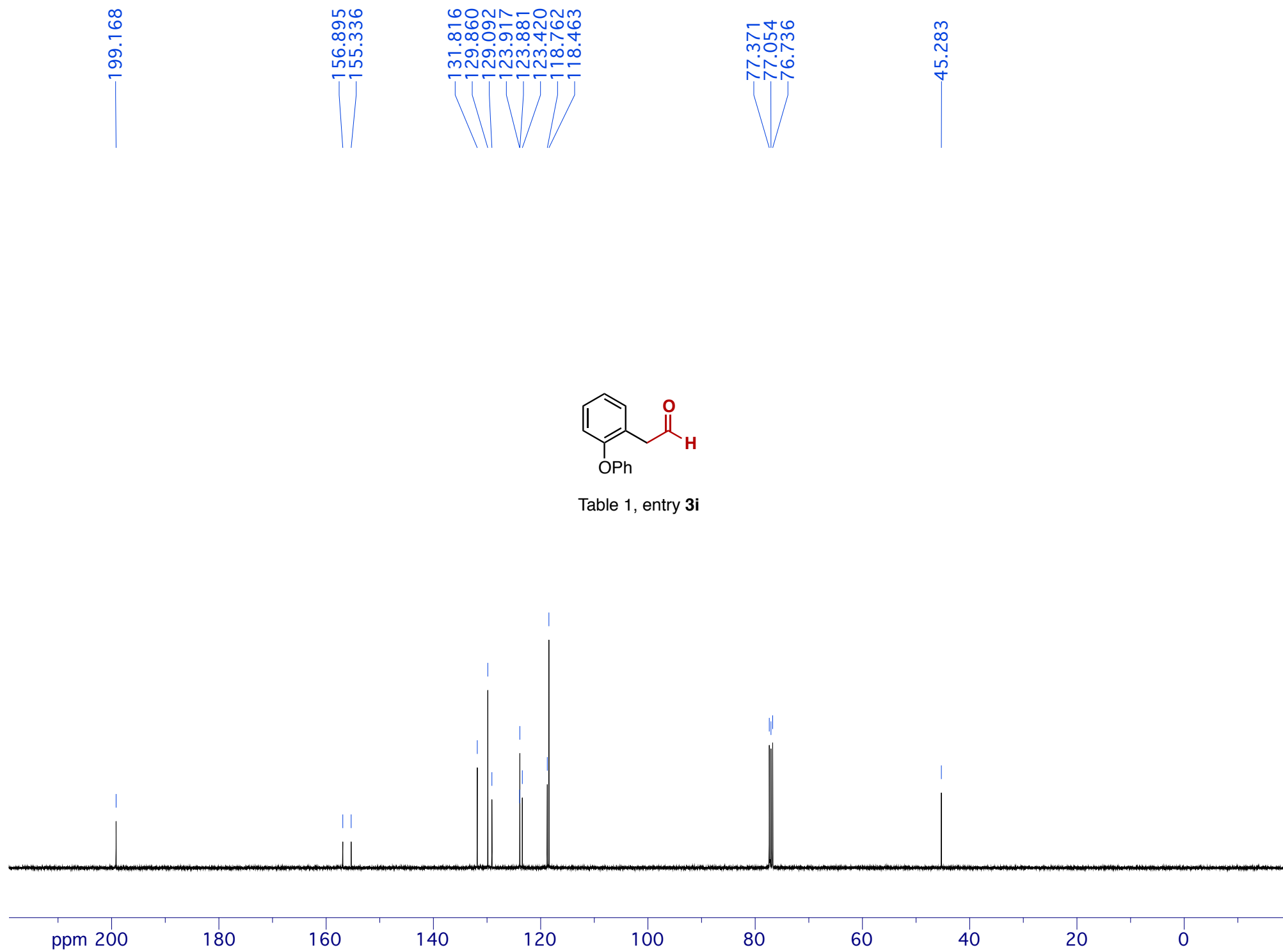


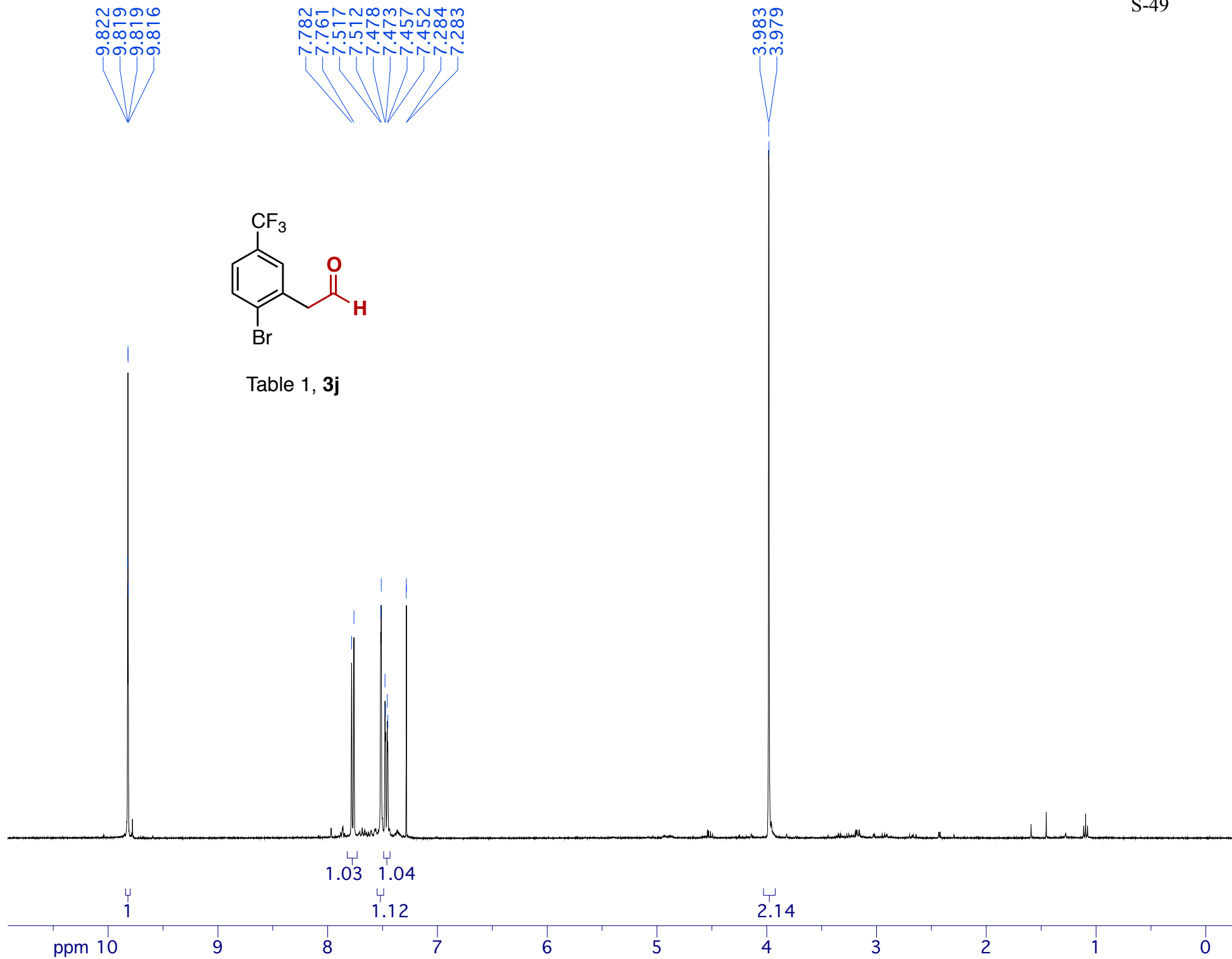
Table 1, entry 3h



9.797
9.796
9.792
9.791
9.787
9.786
7.381
7.363
7.361
7.360
7.346
7.345
7.341
7.316
7.303
7.299
7.298
7.284
7.283
7.280
7.175
7.172
7.156
7.153
7.137
7.135
7.133
7.131
7.116
7.004
7.000
6.996
6.987
6.985
6.982
6.980
6.958
6.938
6.935
3.771
3.766

Table 1, **3i**





—196.99

134.06
133.77
130.70
130.37
129.09
128.65
128.61
126.19
126.15
125.10
122.39

77.52
77.41
77.20
76.89

—50.59

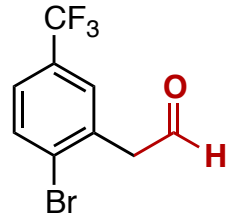
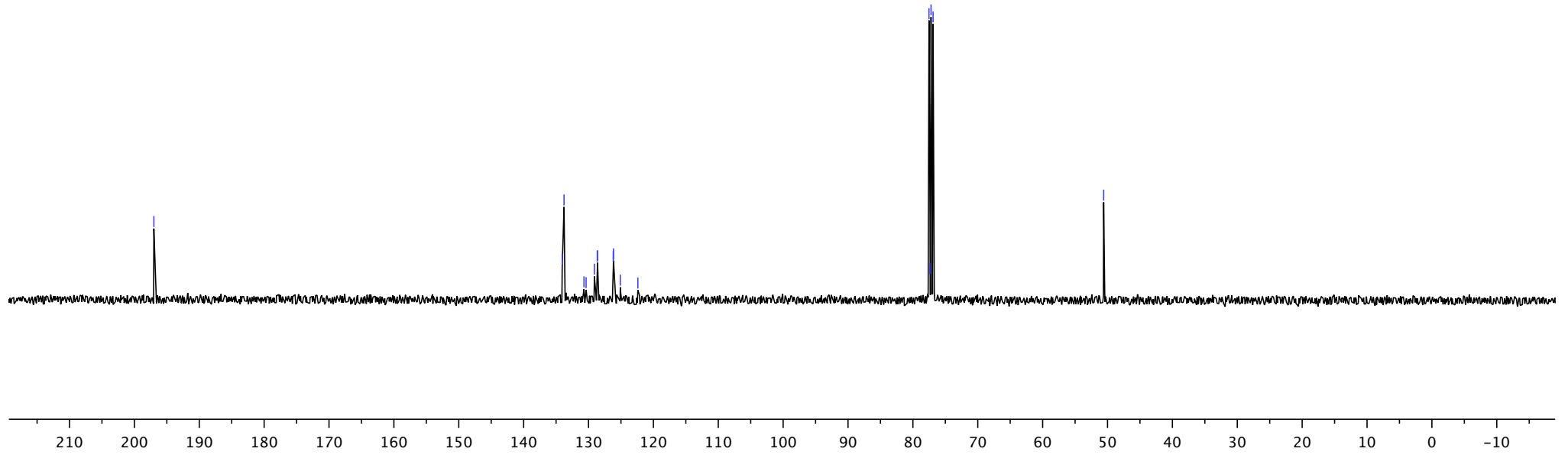
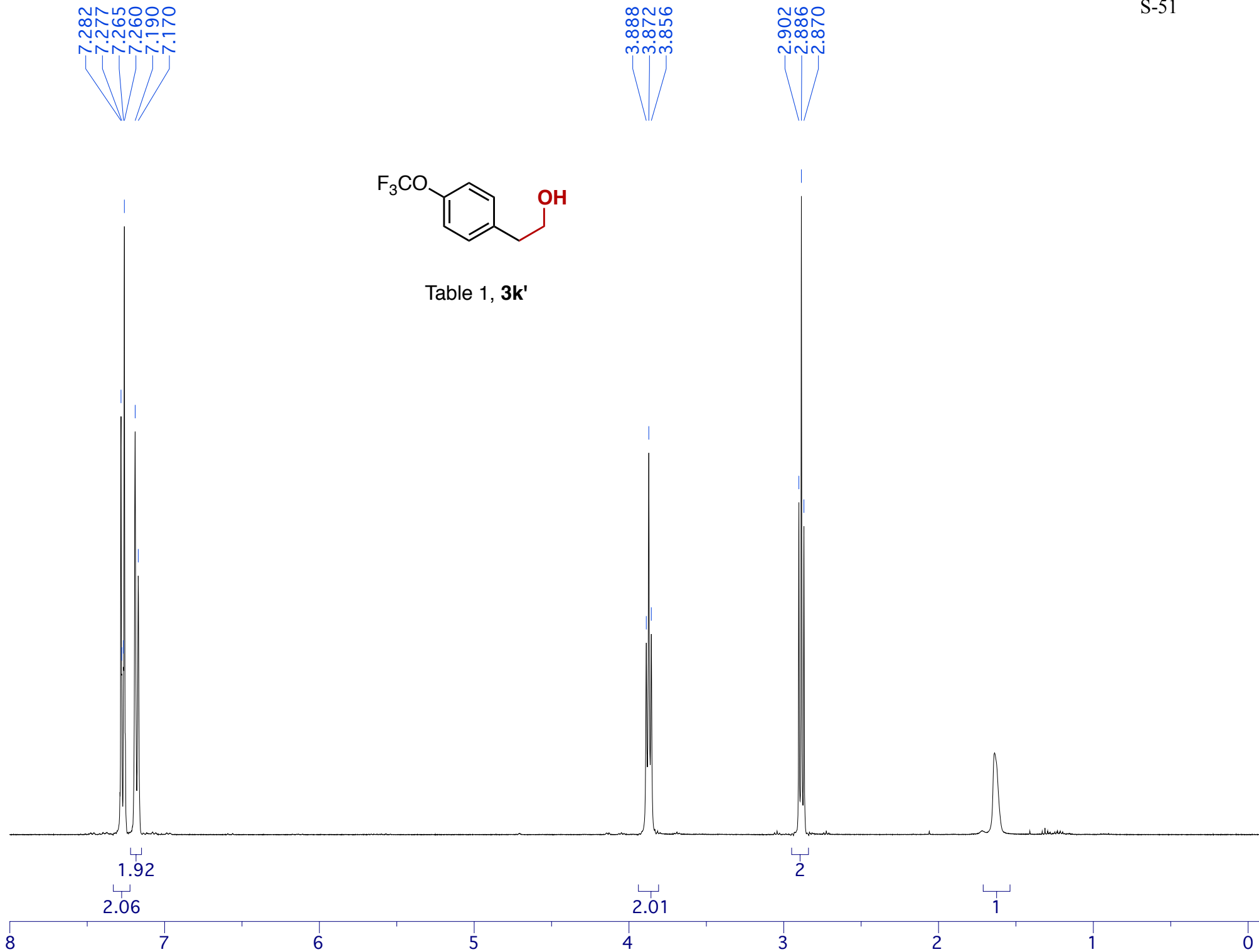


Table 1, entry 3j





147.882
147.863

137.401

130.268

124.317
121.765
121.081
119.21477.332
77.014
76.697

63.384

38.402

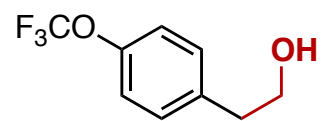
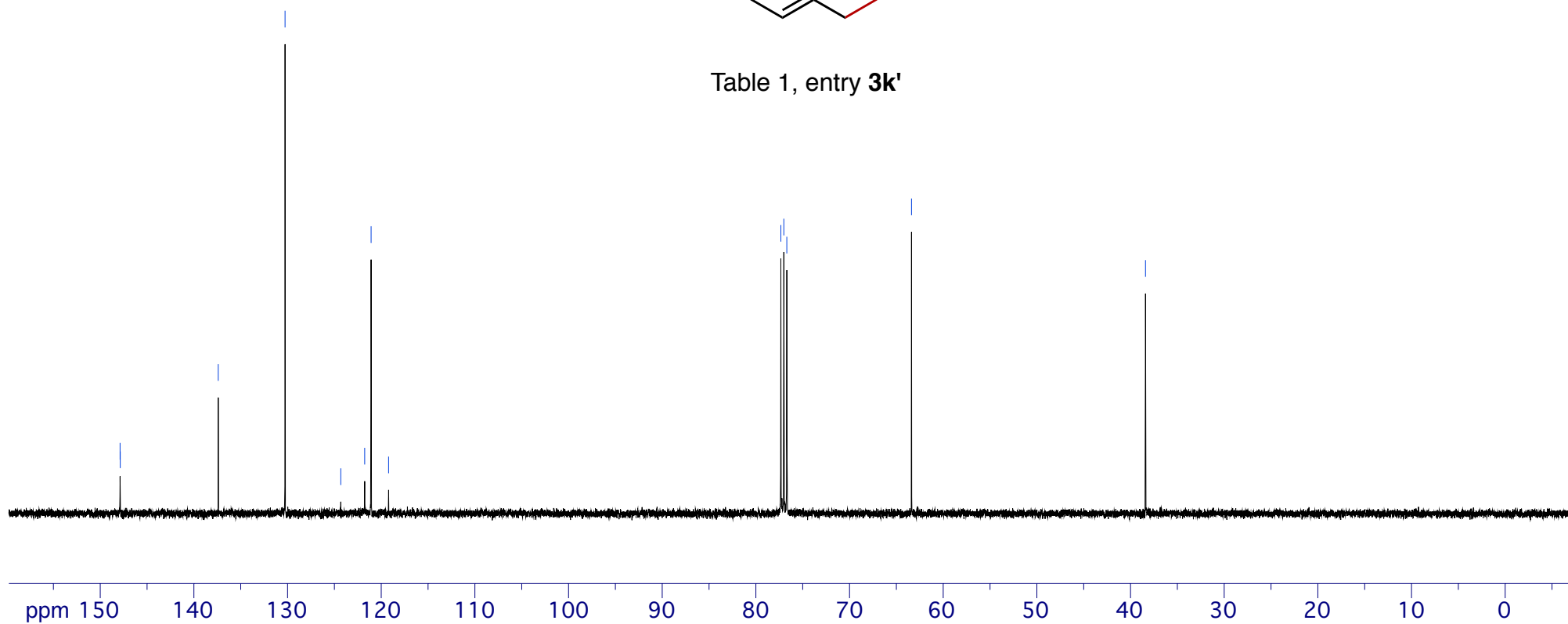
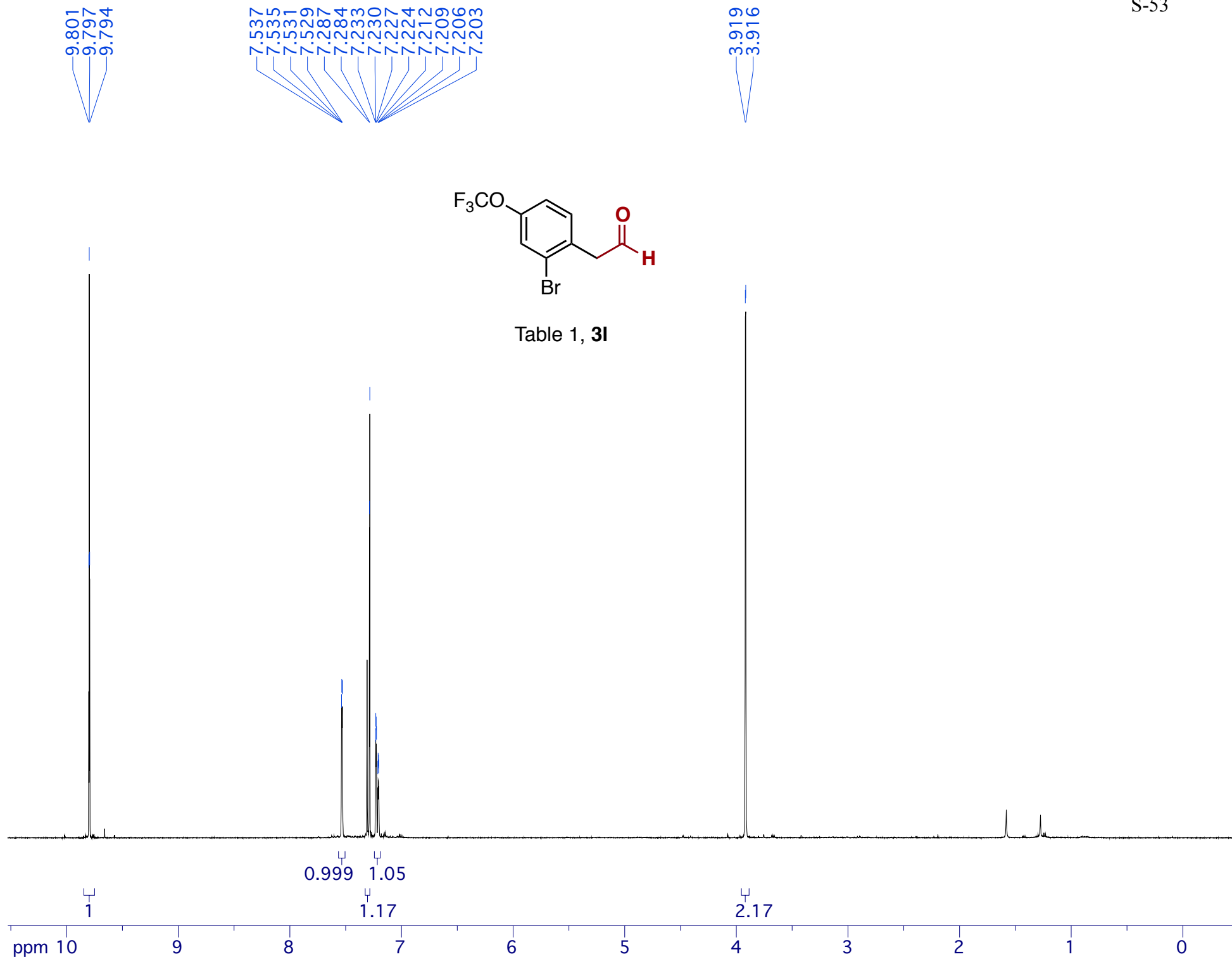


Table 1, entry 3k'





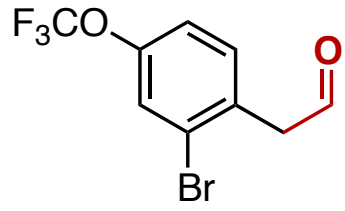
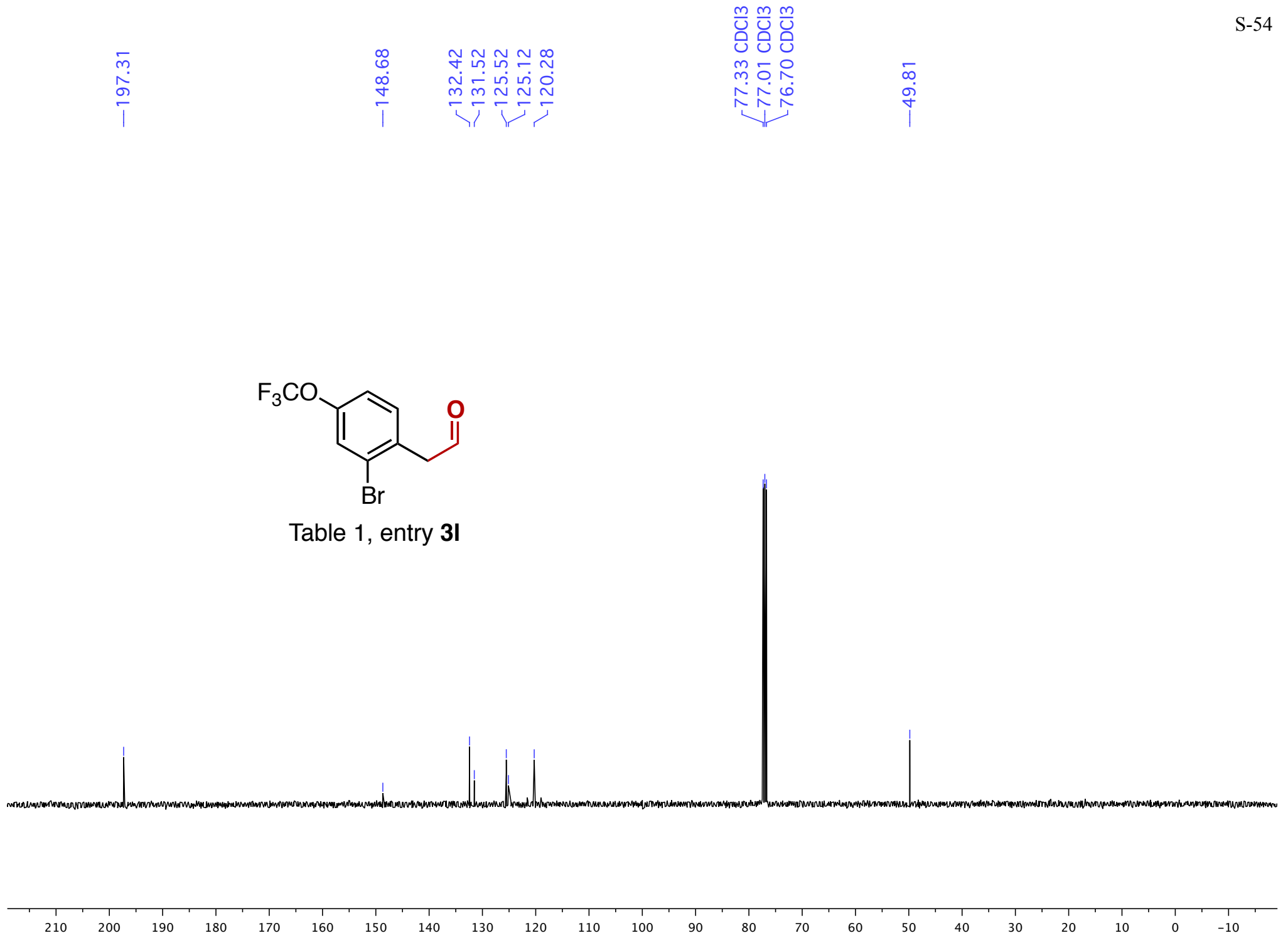


Table 1, entry **31**

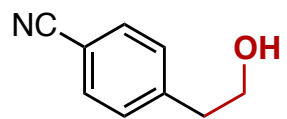
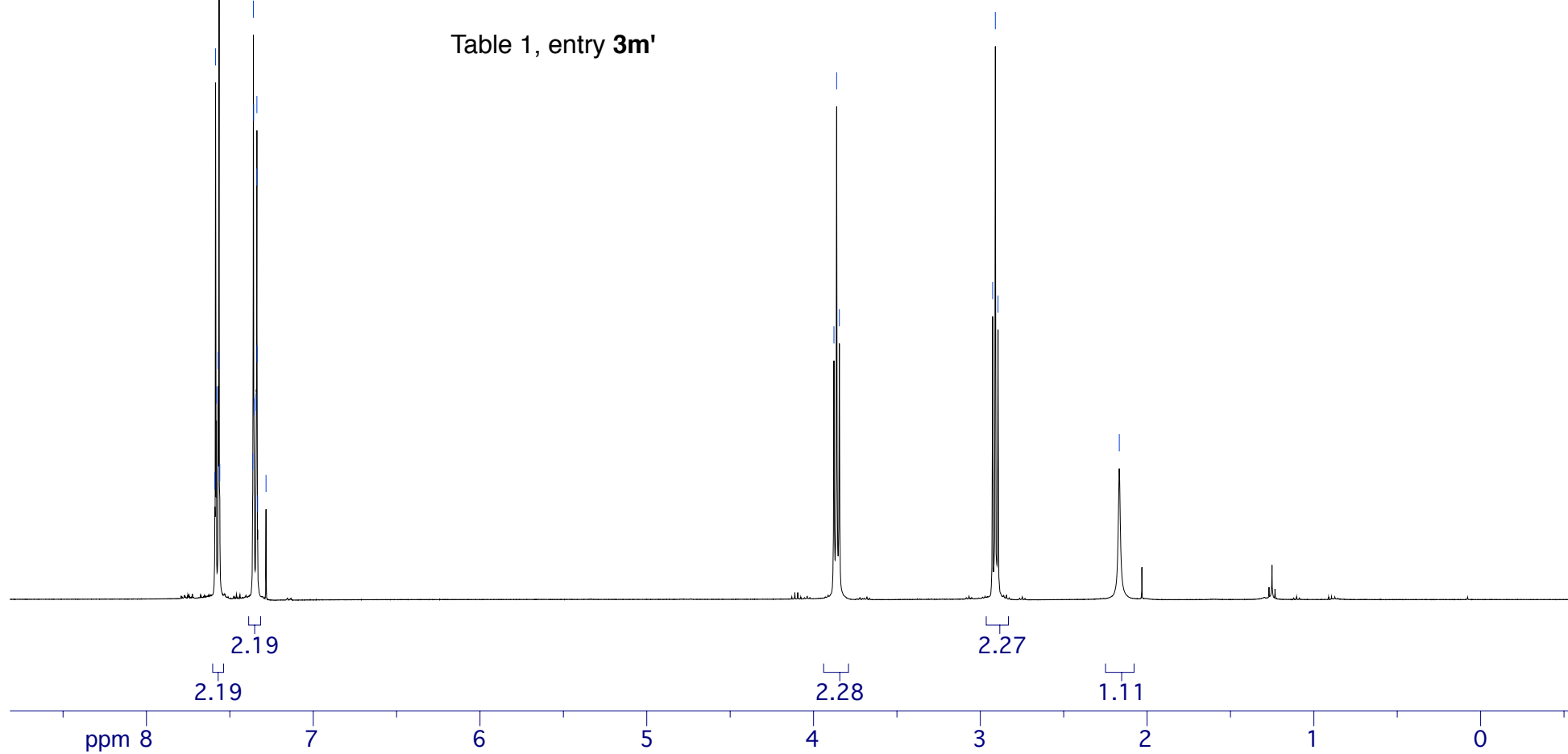


7.590
7.586
7.581
7.569
7.564
7.560
7.363
7.359
7.357
7.354
7.342
7.339
7.338
7.336
7.333
7.283

3.878
3.861
3.845

2.926
2.910
2.894

2.167

Table 1, entry **3m'**

144.83
144.82
132.21
132.20
129.91
129.91
129.88
129.87
129.84
118.98

110.04

77.46
77.14
76.82

62.79
62.75
62.74

39.16
39.14
39.13
39.12
39.12

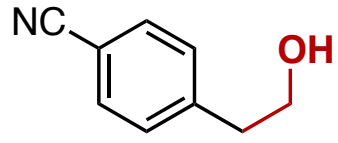
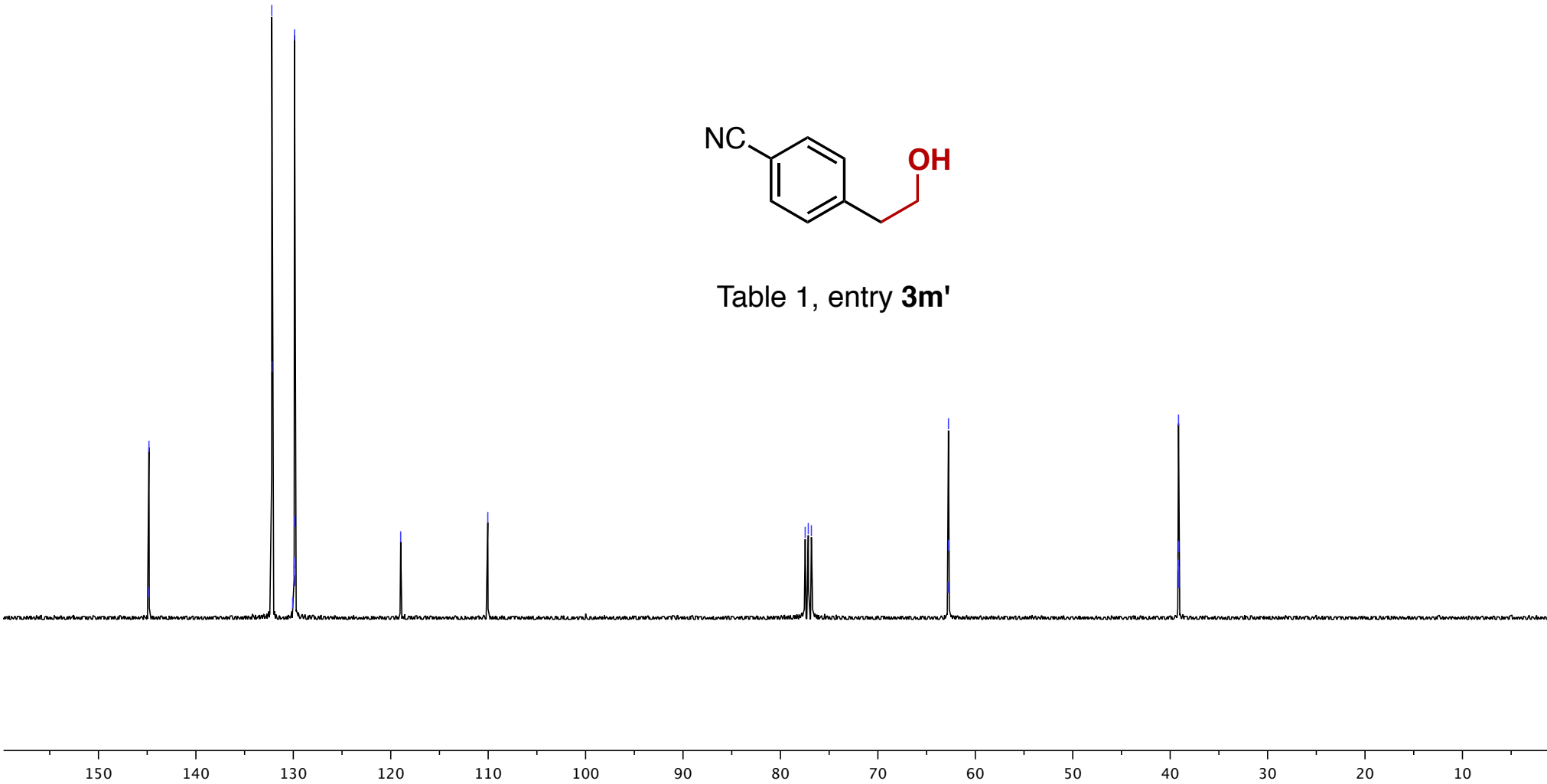
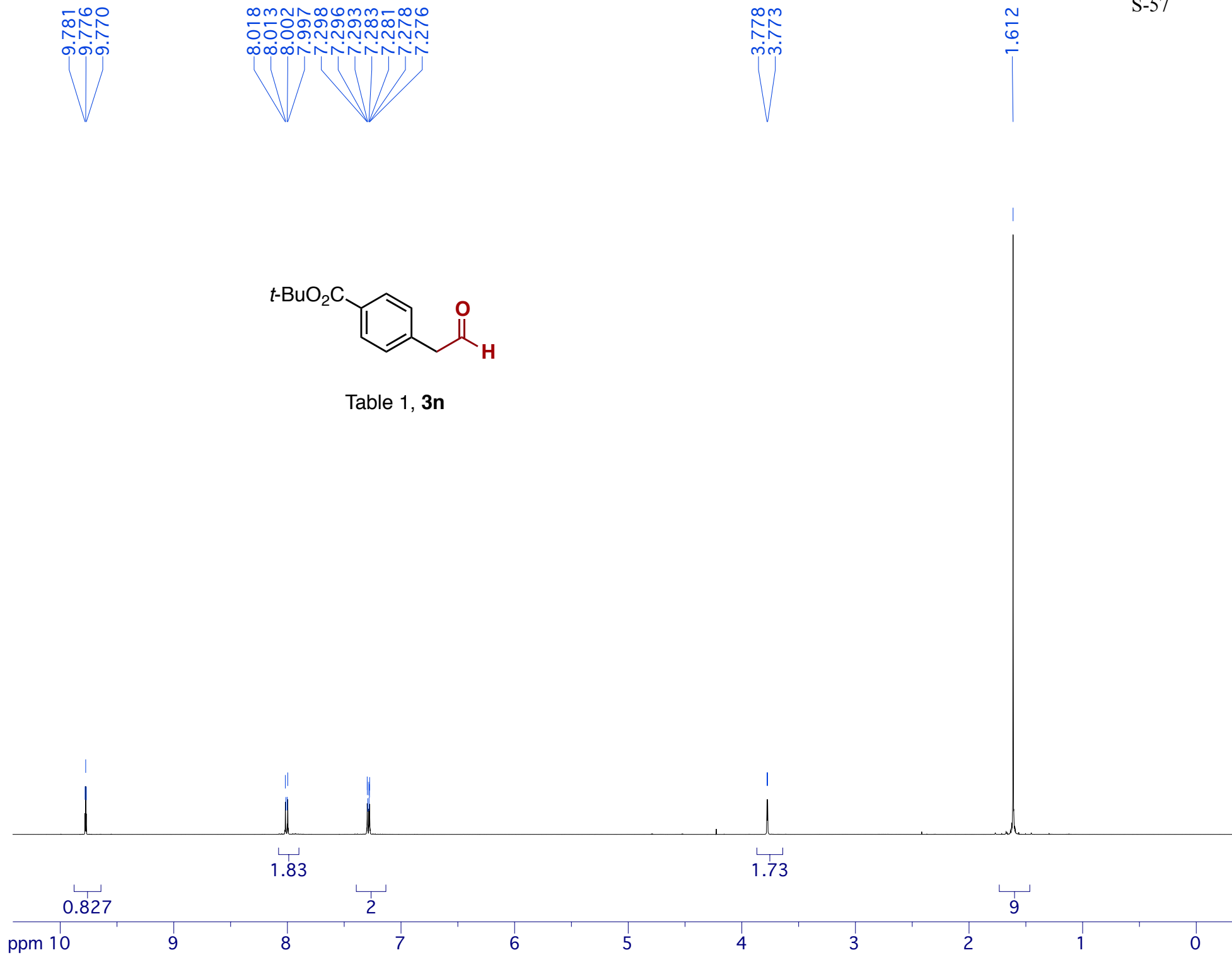


Table 1, entry 3m'



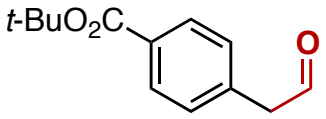
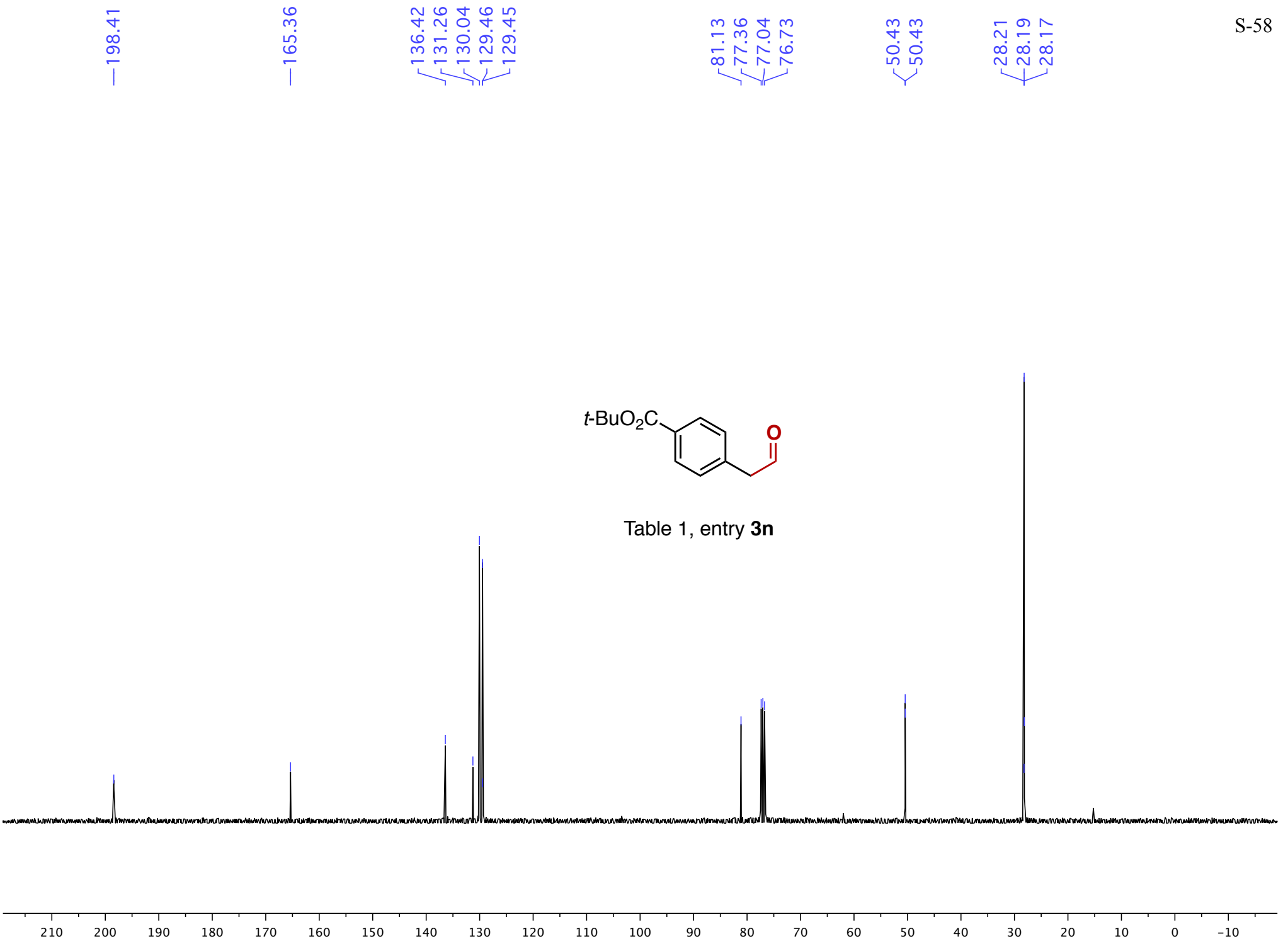
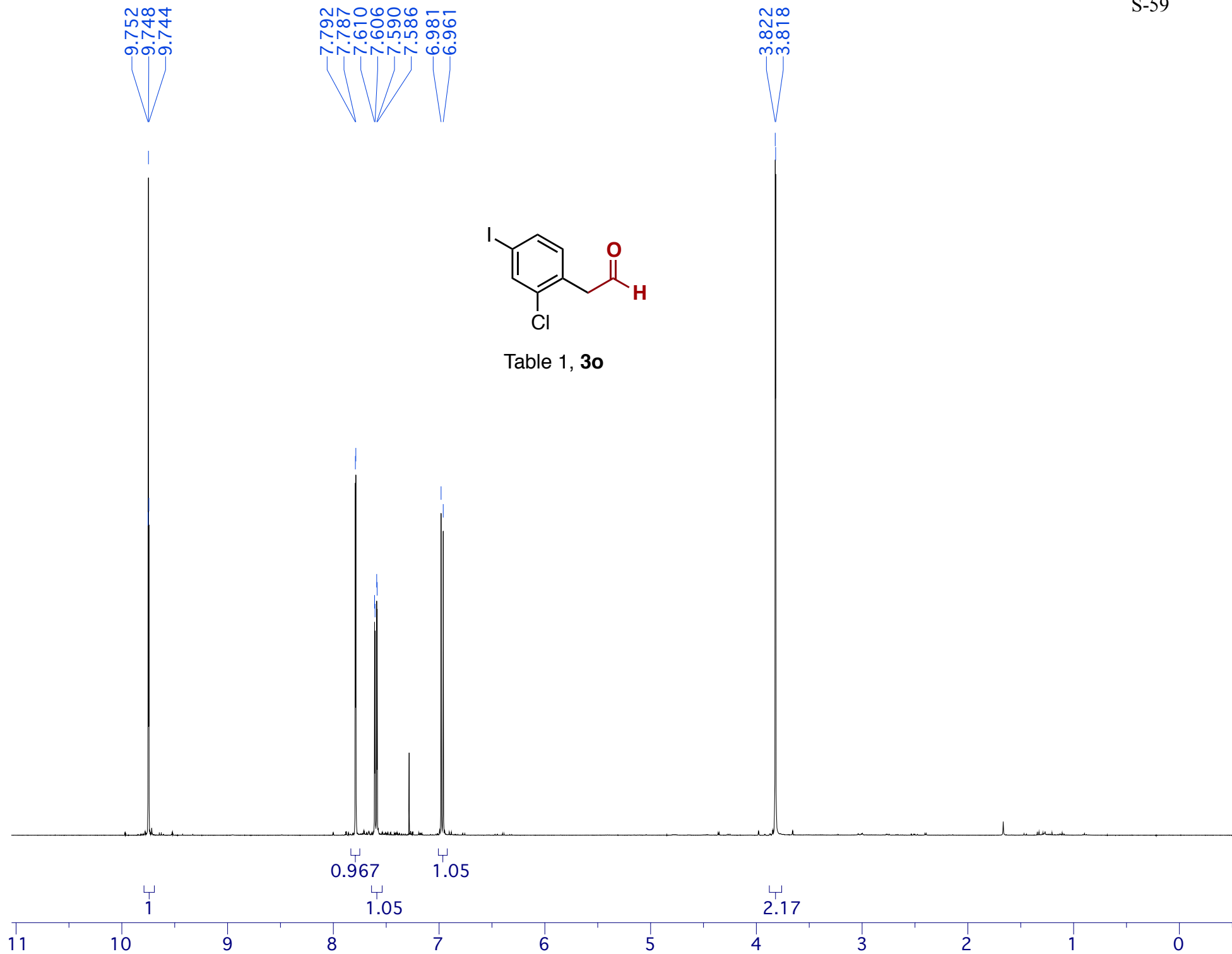


Table 1, entry **3n**





—197.26

137.93
137.93
136.35
135.44
133.02
133.01
130.54

92.97
92.96

77.41
77.09
76.77

47.85
47.83

S-60

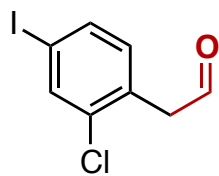
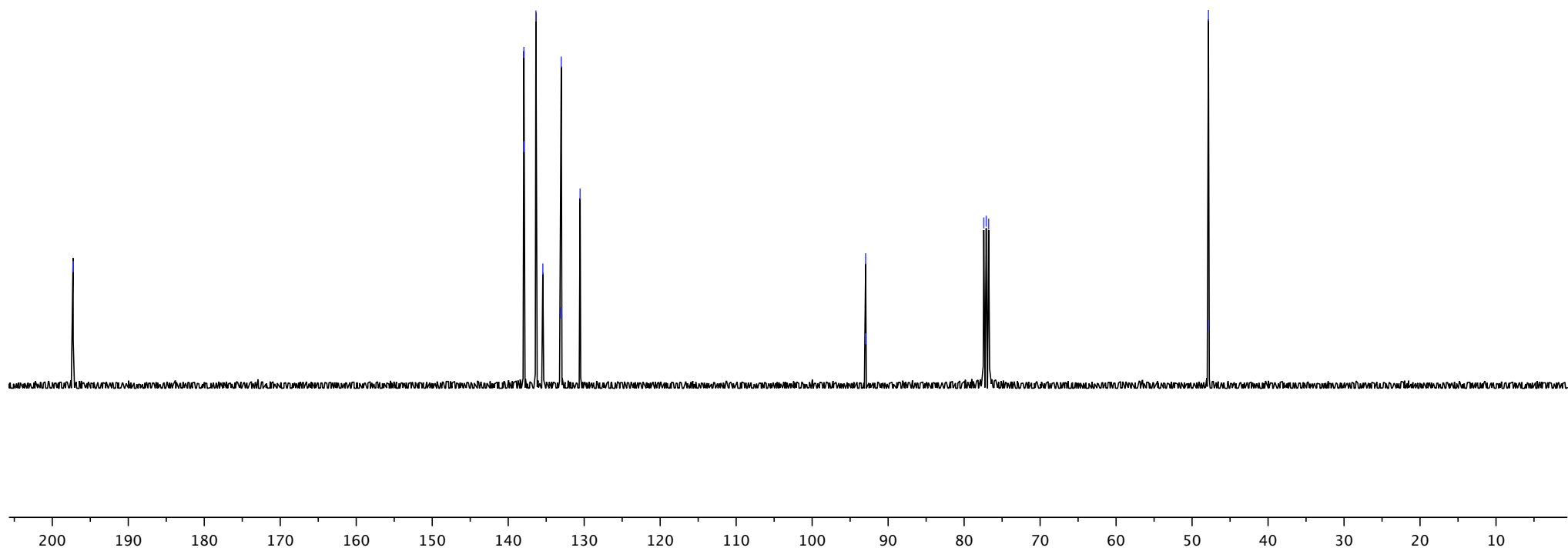
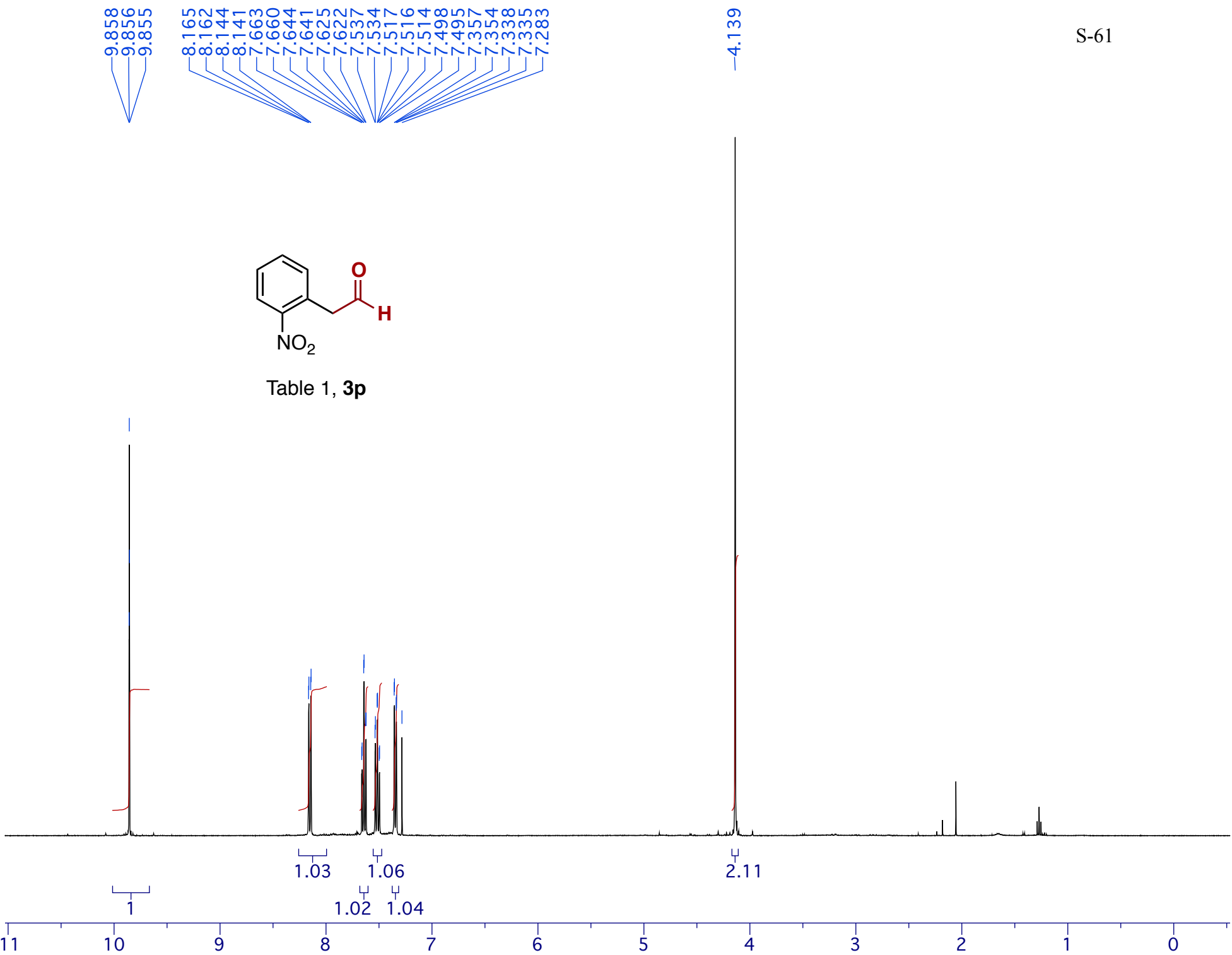


Table 1, entry **3o**





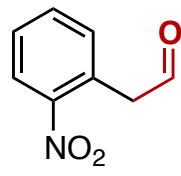
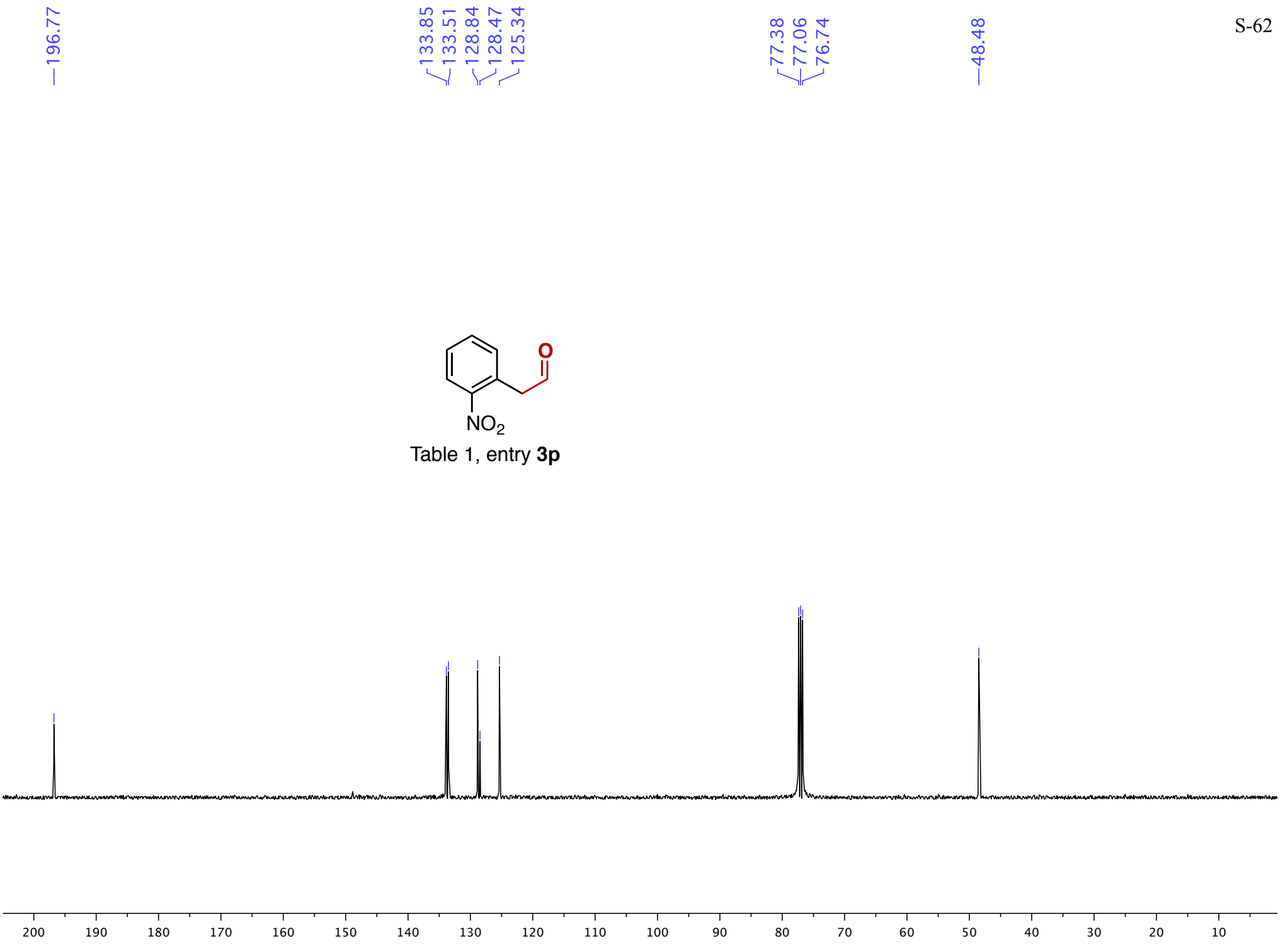
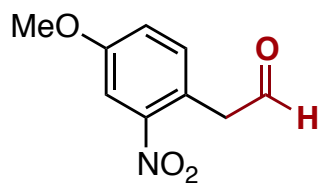
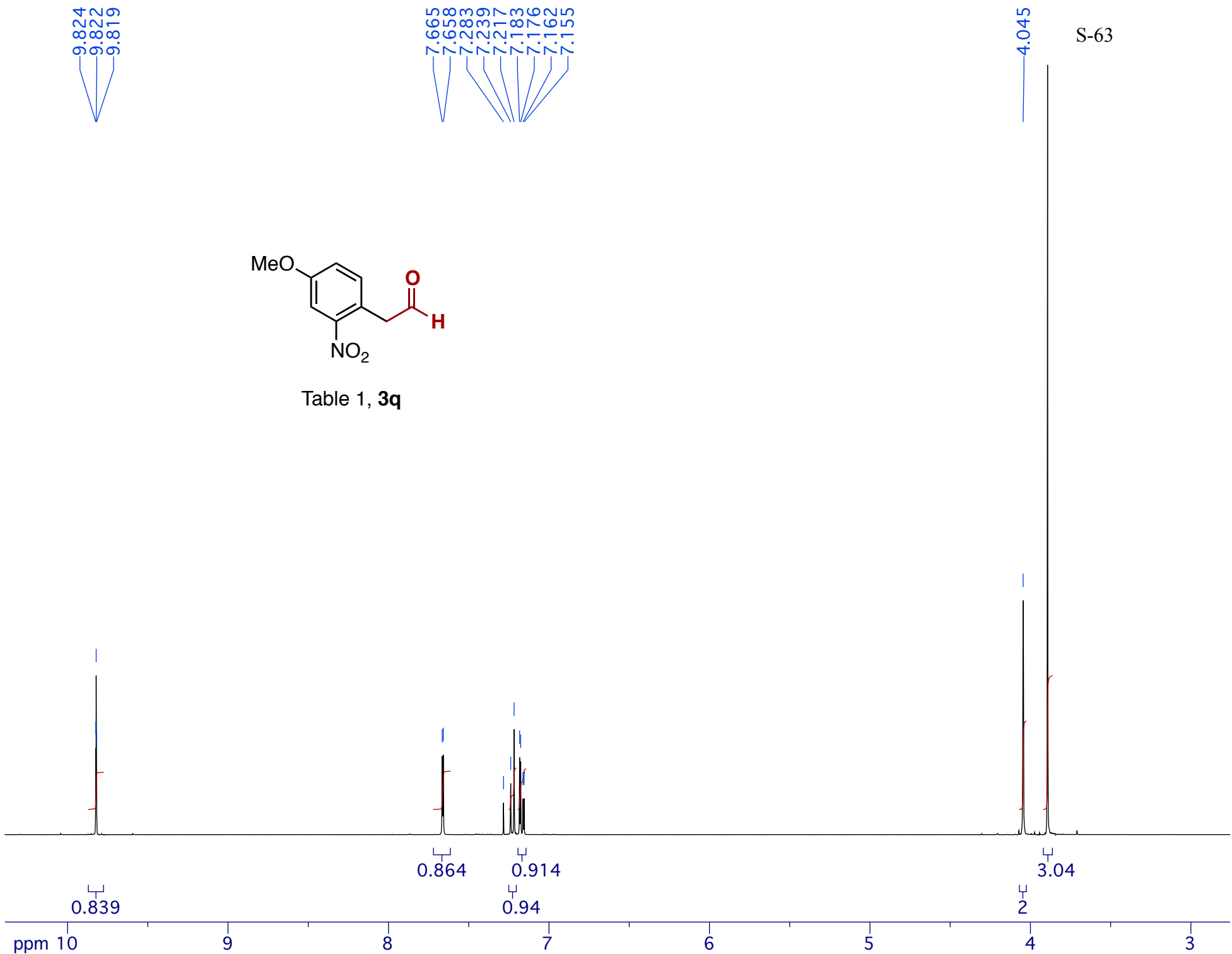
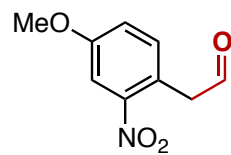
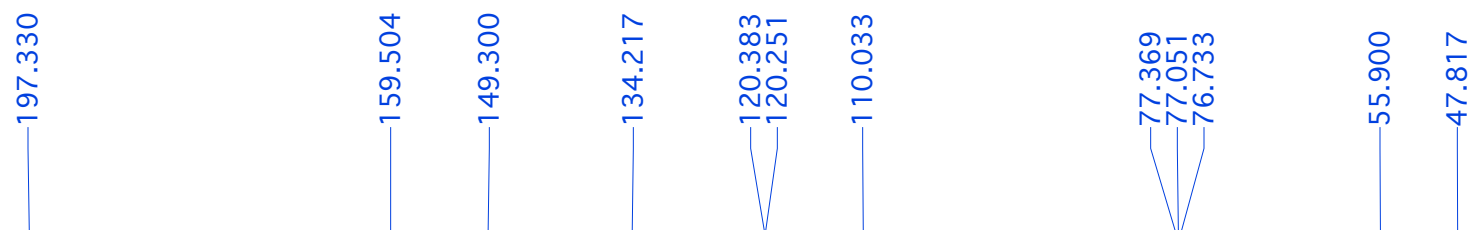
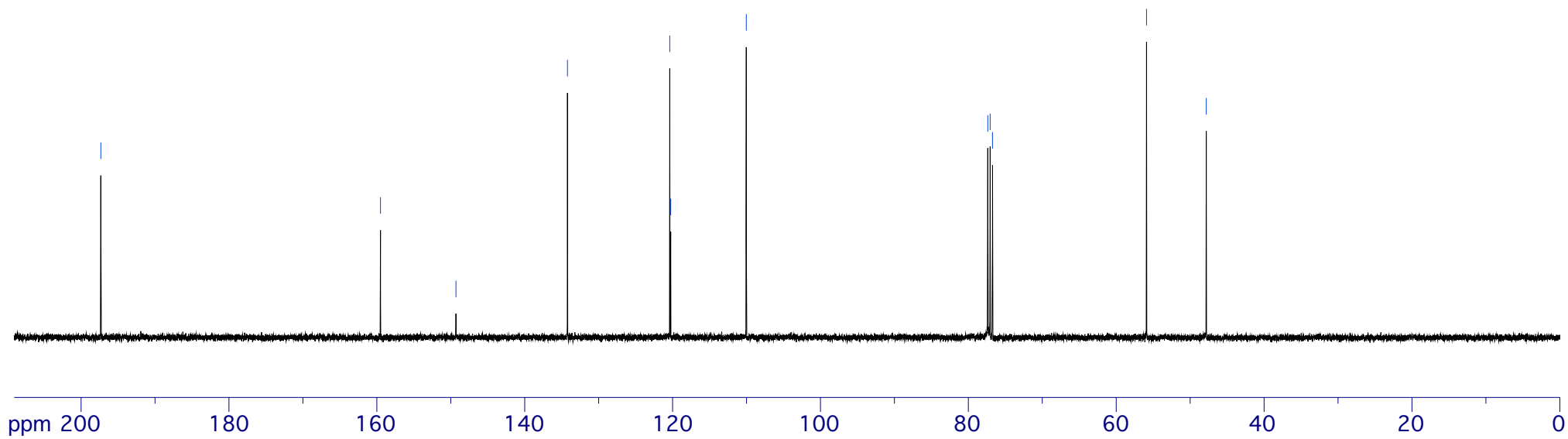
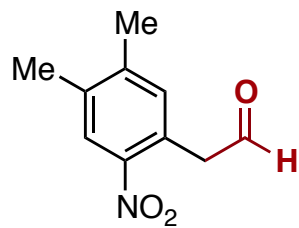
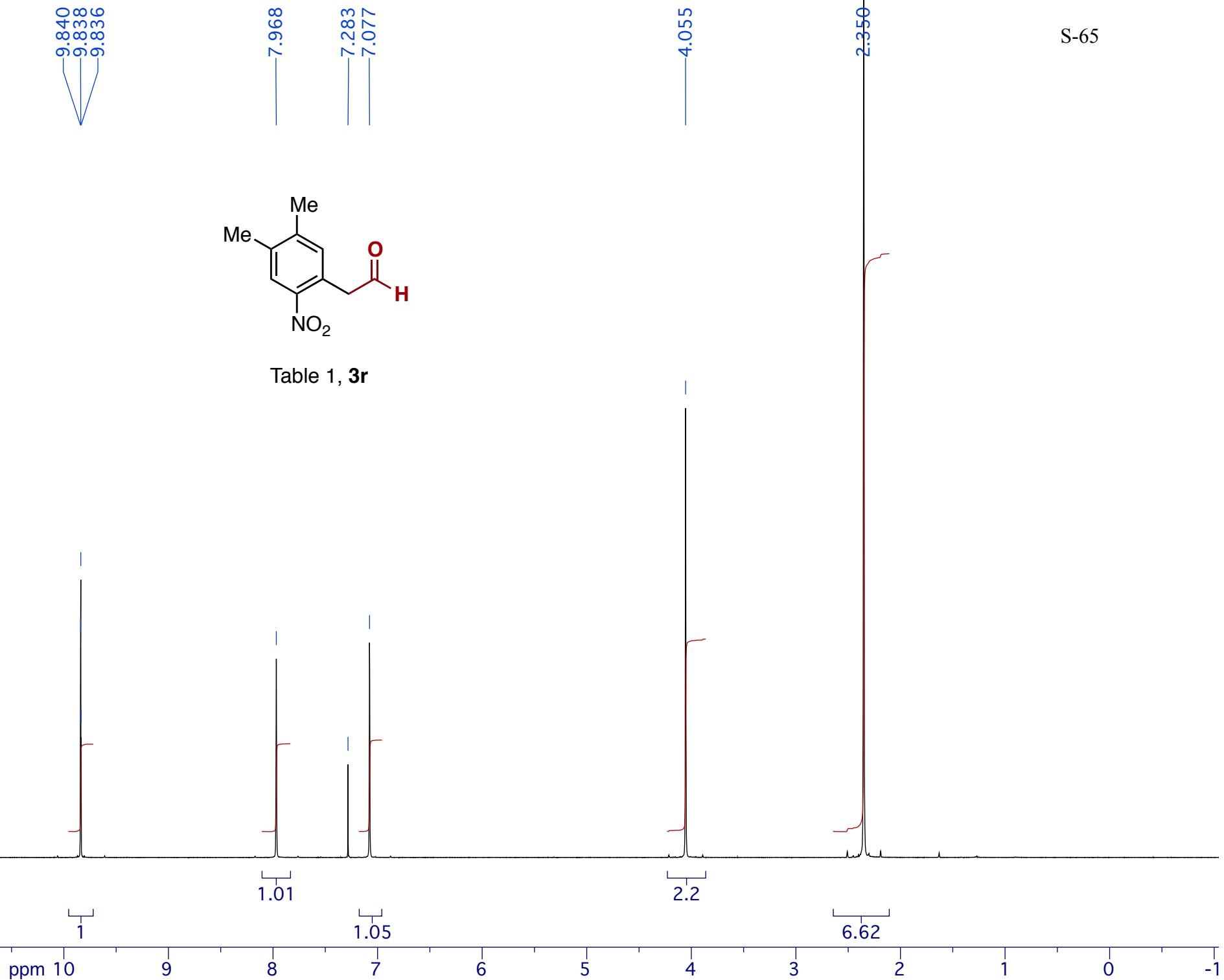


Table 1, entry 3p



Table 1, **3q**

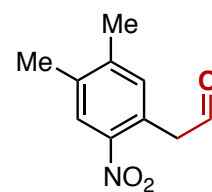
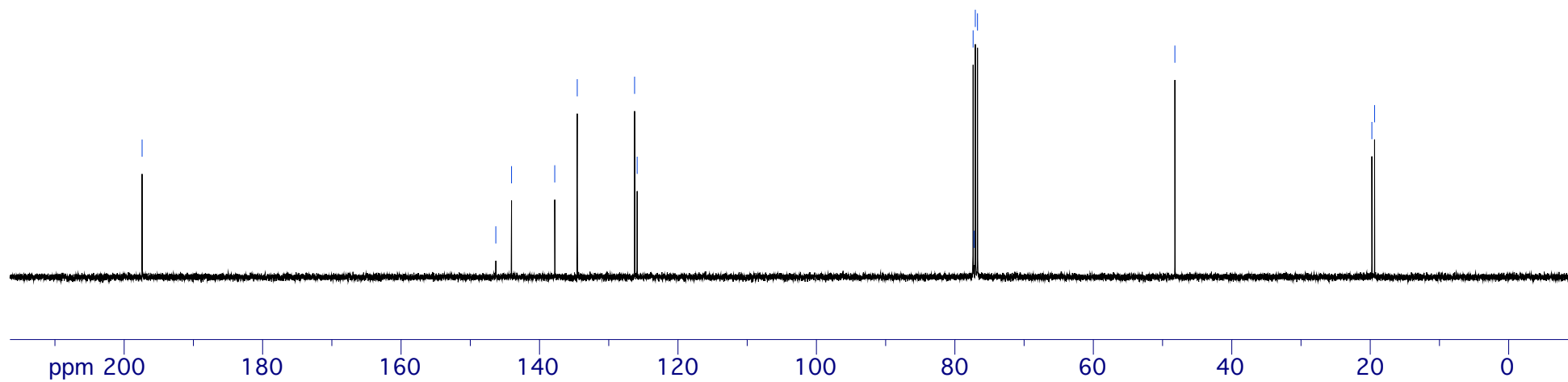
Table 1, entry **3q**

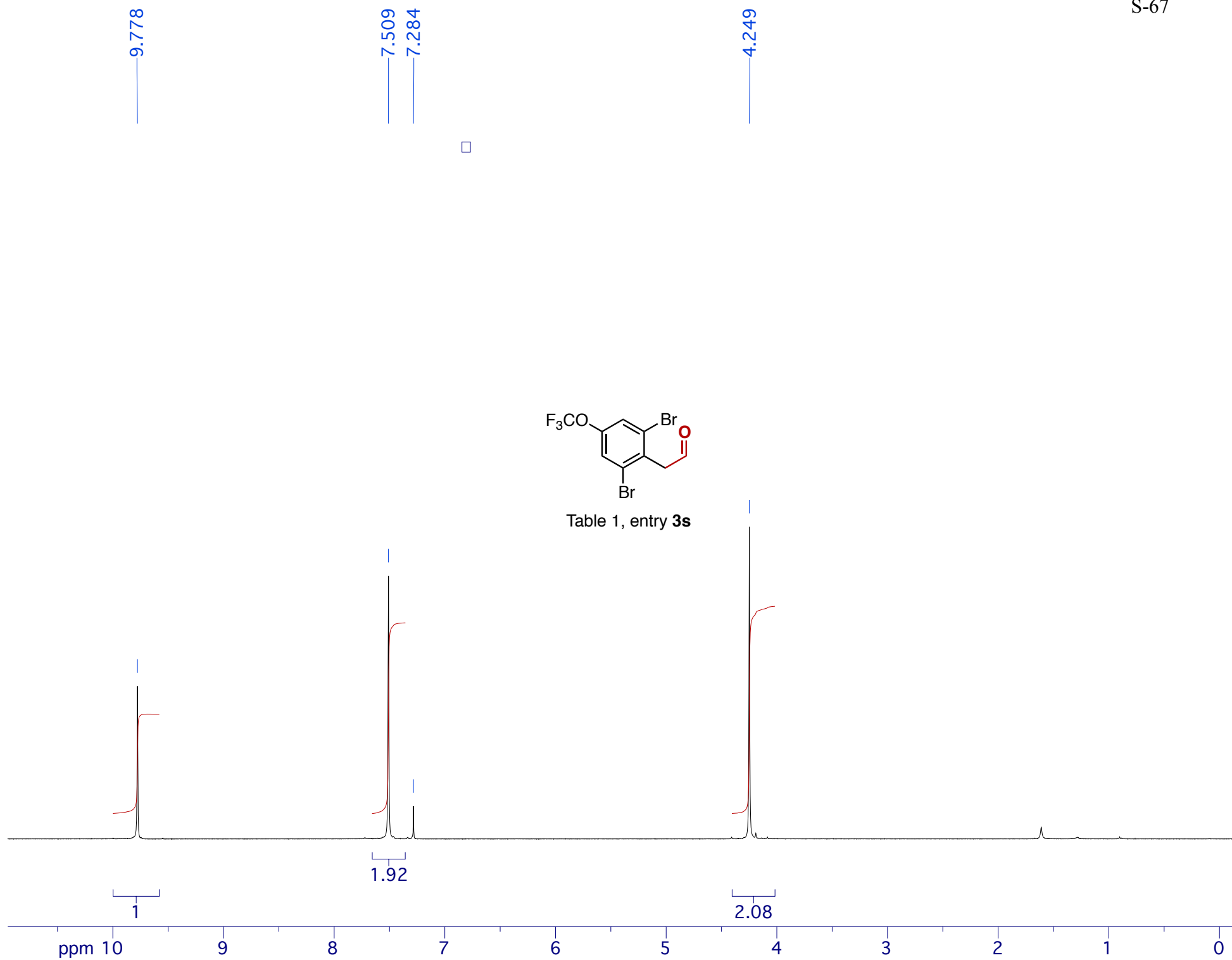
Table 1, **3r**

197.408

146.313
144.042137.801
134.549126.267
125.89577.366
77.249
77.048
76.730

48.219

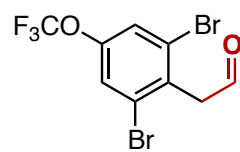
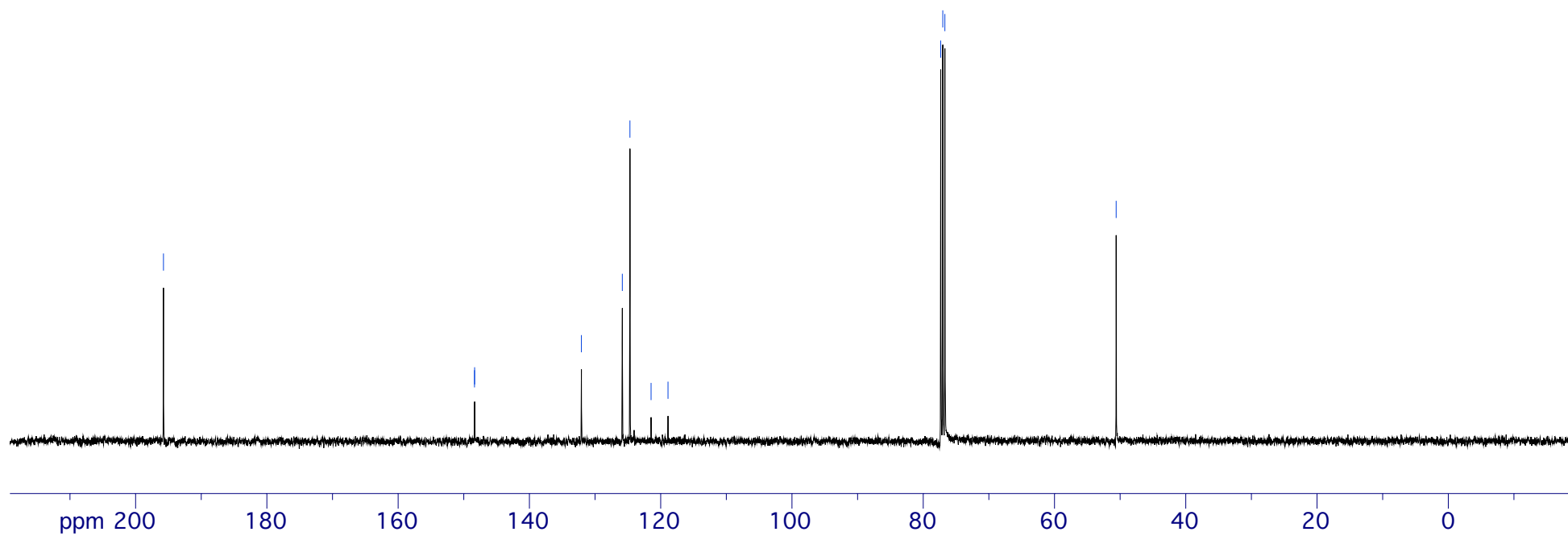
19.764
19.373Table 1, entry **3r**

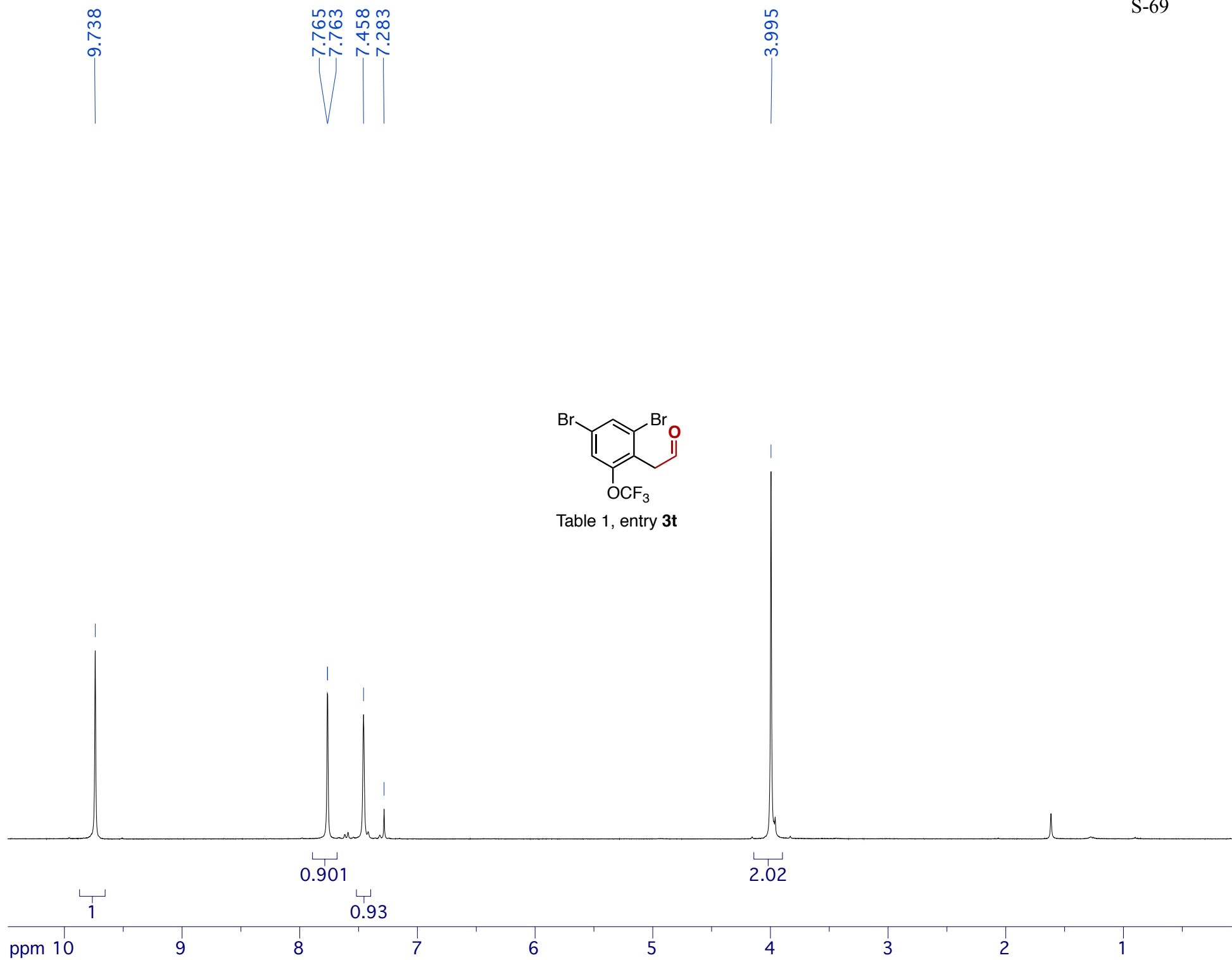


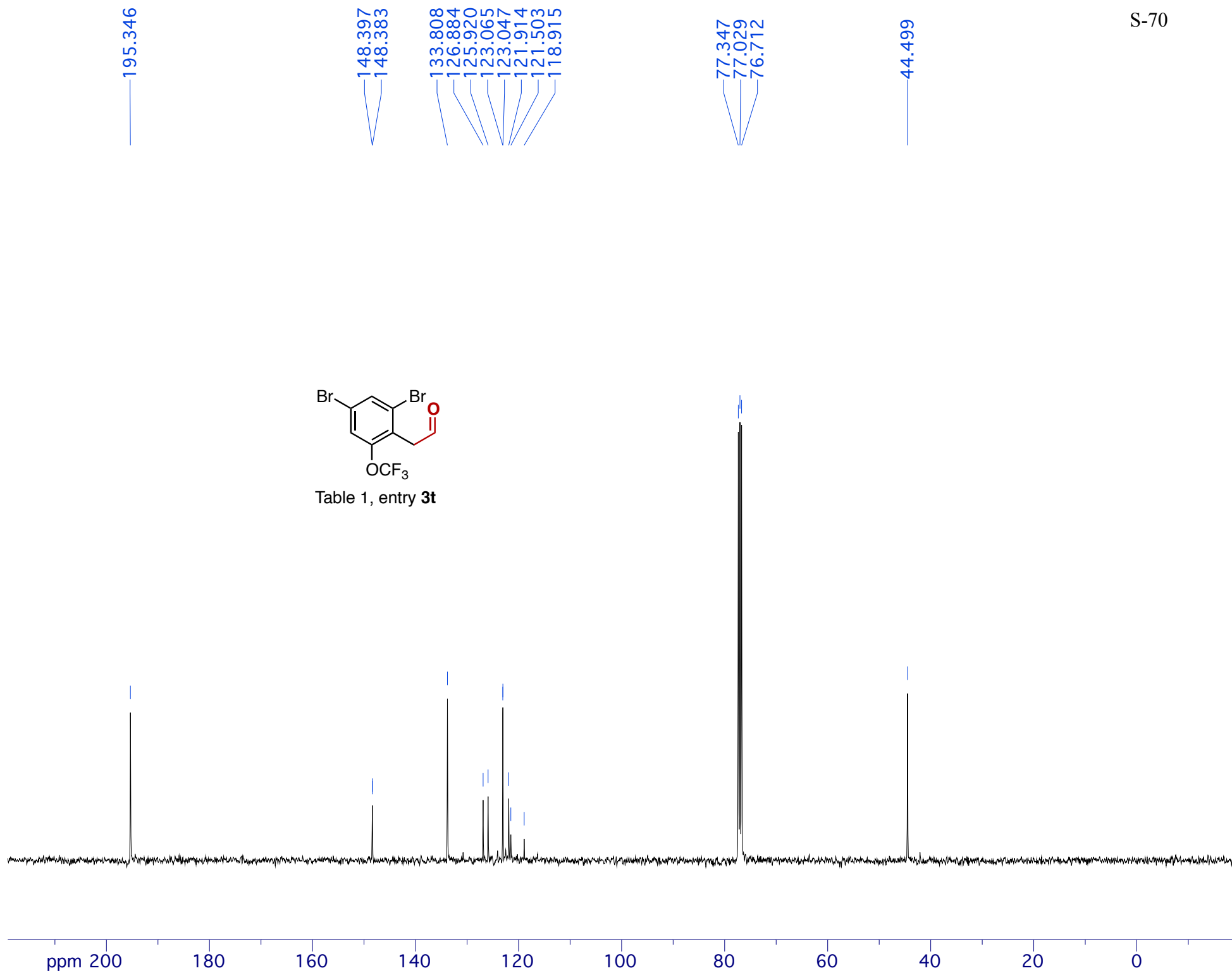
195.755

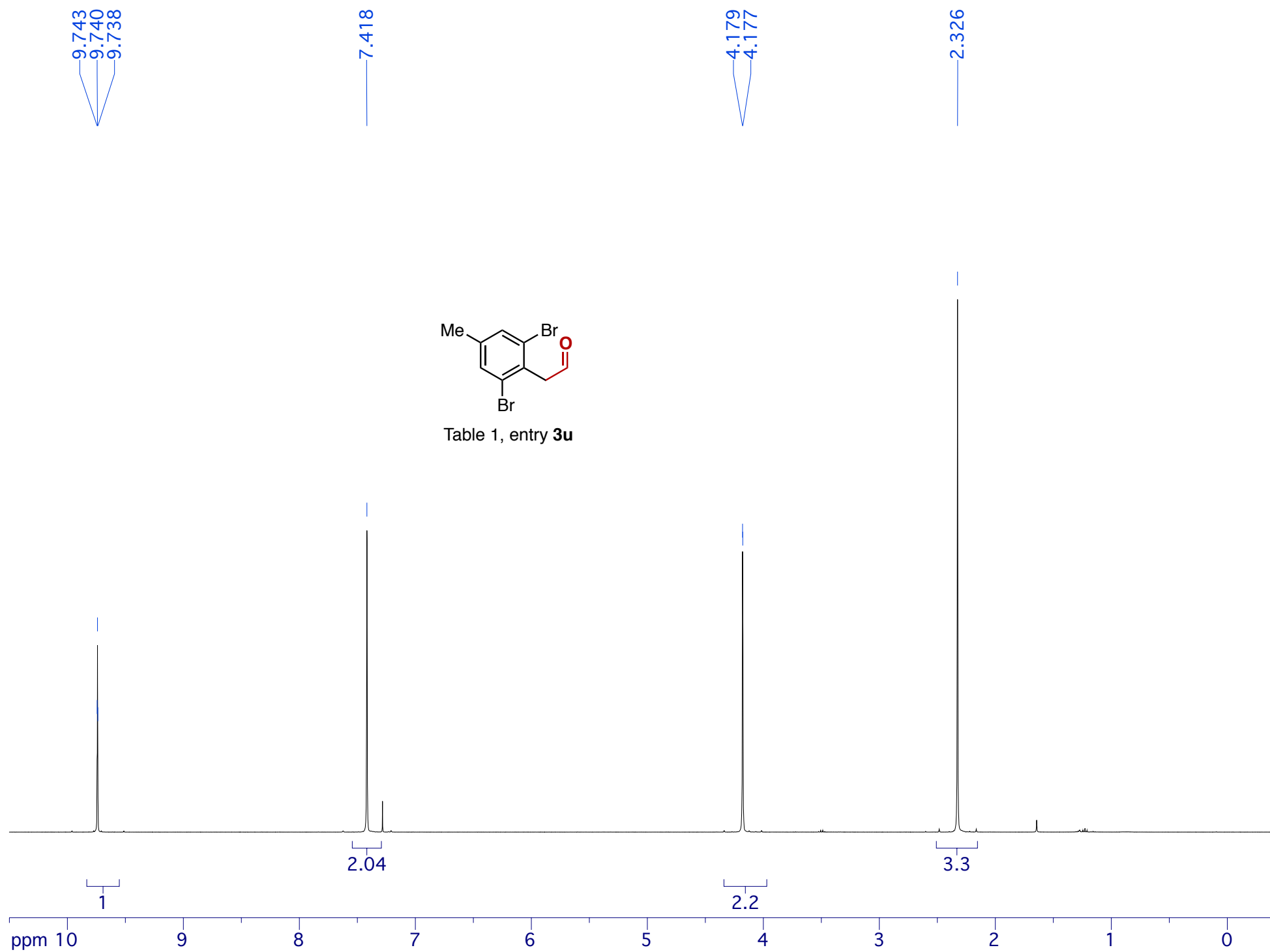
148.368
148.348132.080
125.847
124.685
121.466
118.88577.337
77.020
76.701

50.605

Table 1, entry **3s**







197.057

140.687

132.821

129.710

125.497

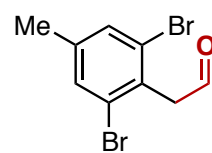
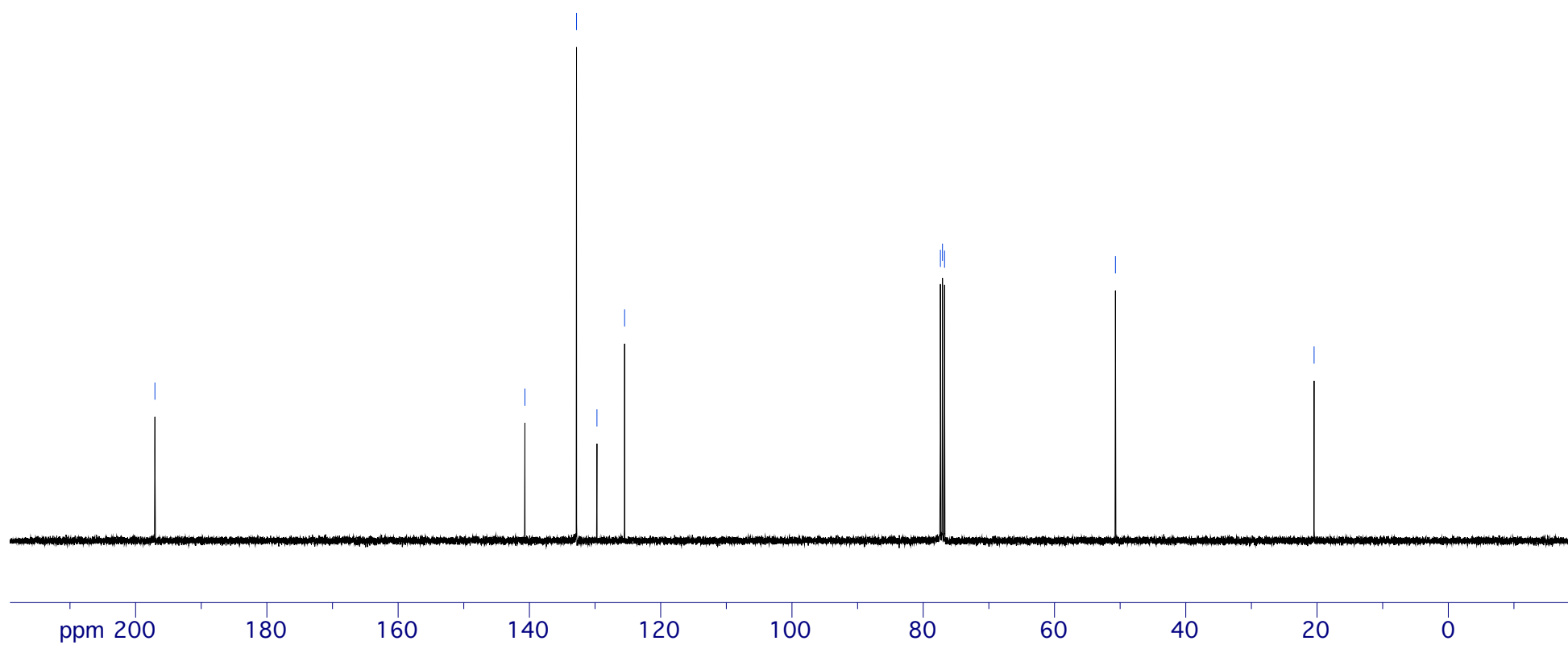
77.384

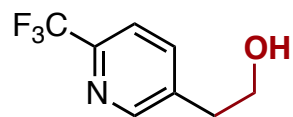
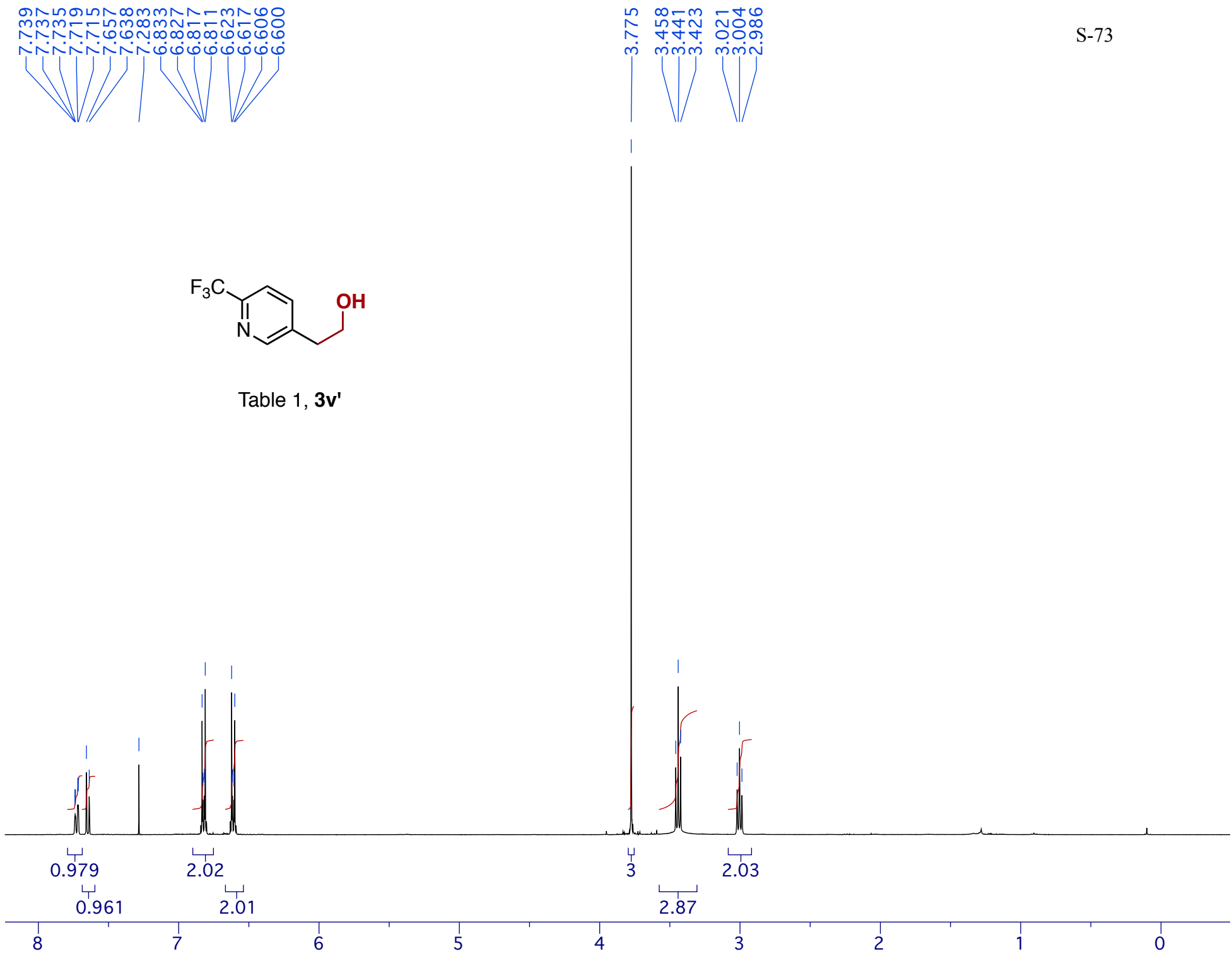
77.066

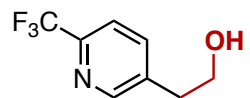
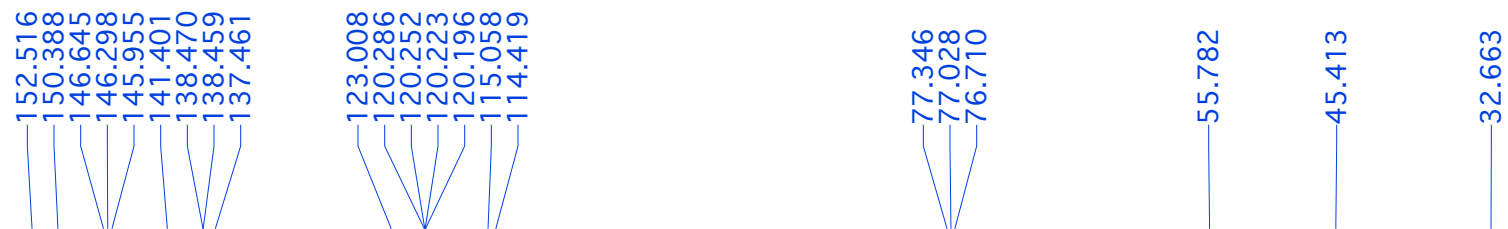
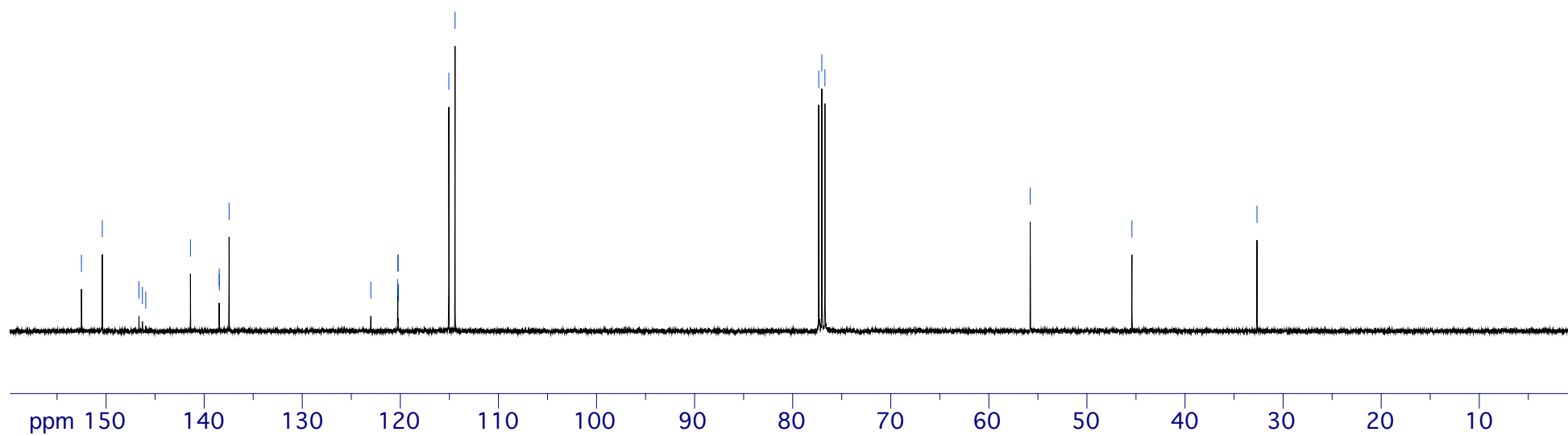
76.748

50.717

20.449

Table 1, entry **3u**

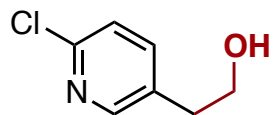
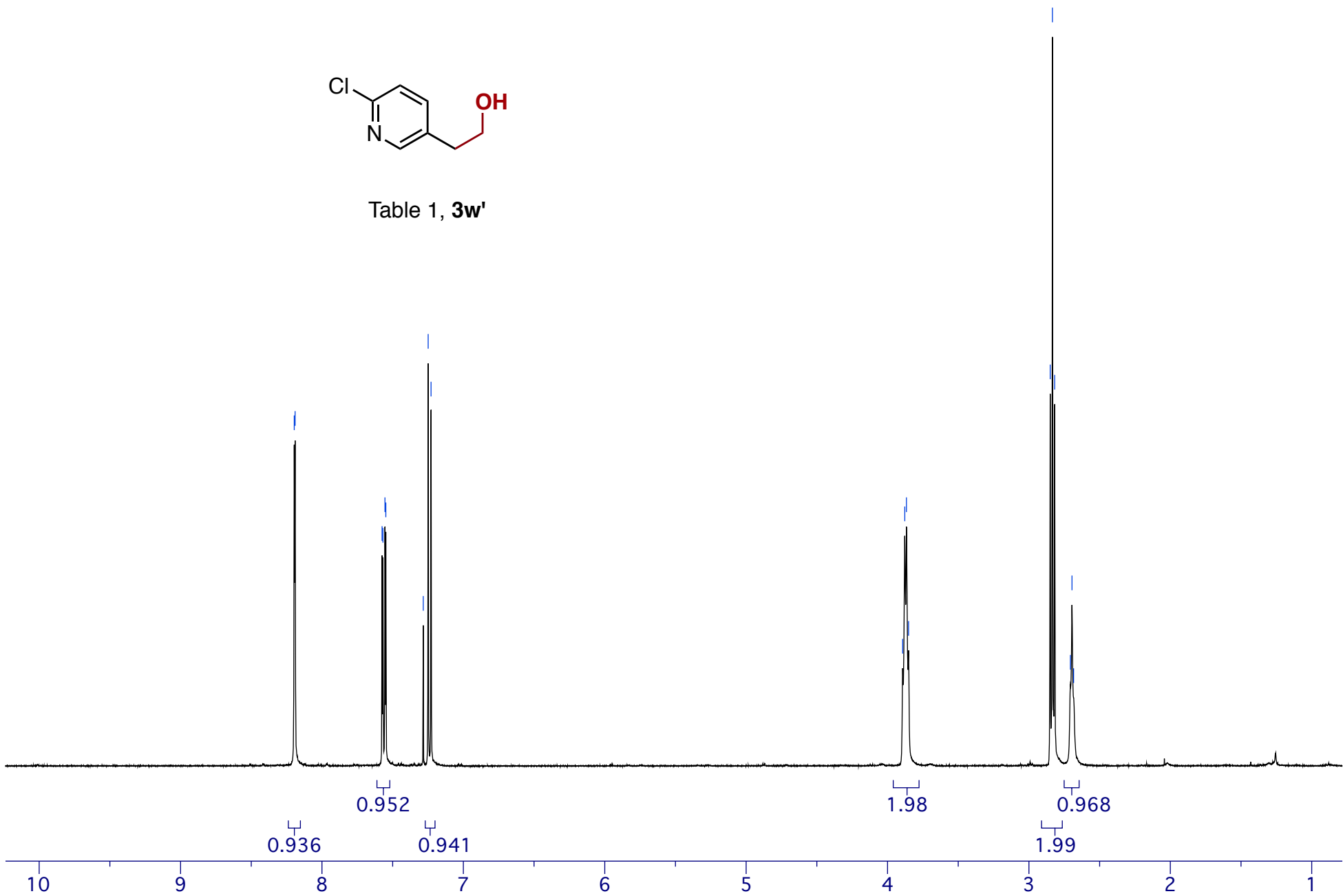
Table 1, **3v'**

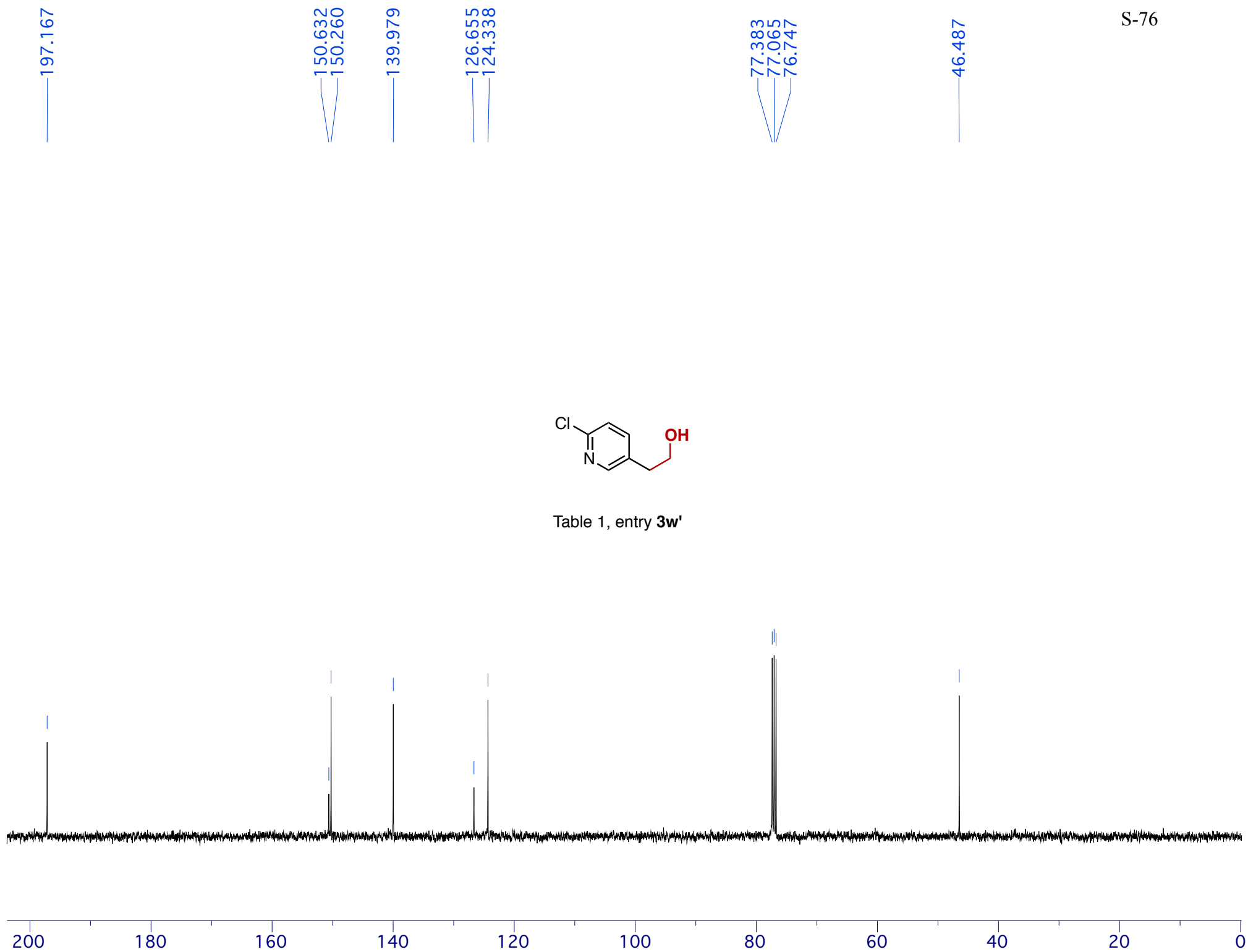
Table 1, entry **3v'**

8.196
8.190
7.575
7.569
7.554
7.548
7.284
7.249
7.228

3.893
3.878
3.866
3.851

2.850
2.834
2.818
2.707
2.695
2.684

Table 1, **3w'**

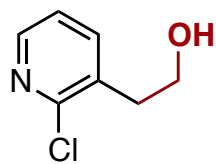
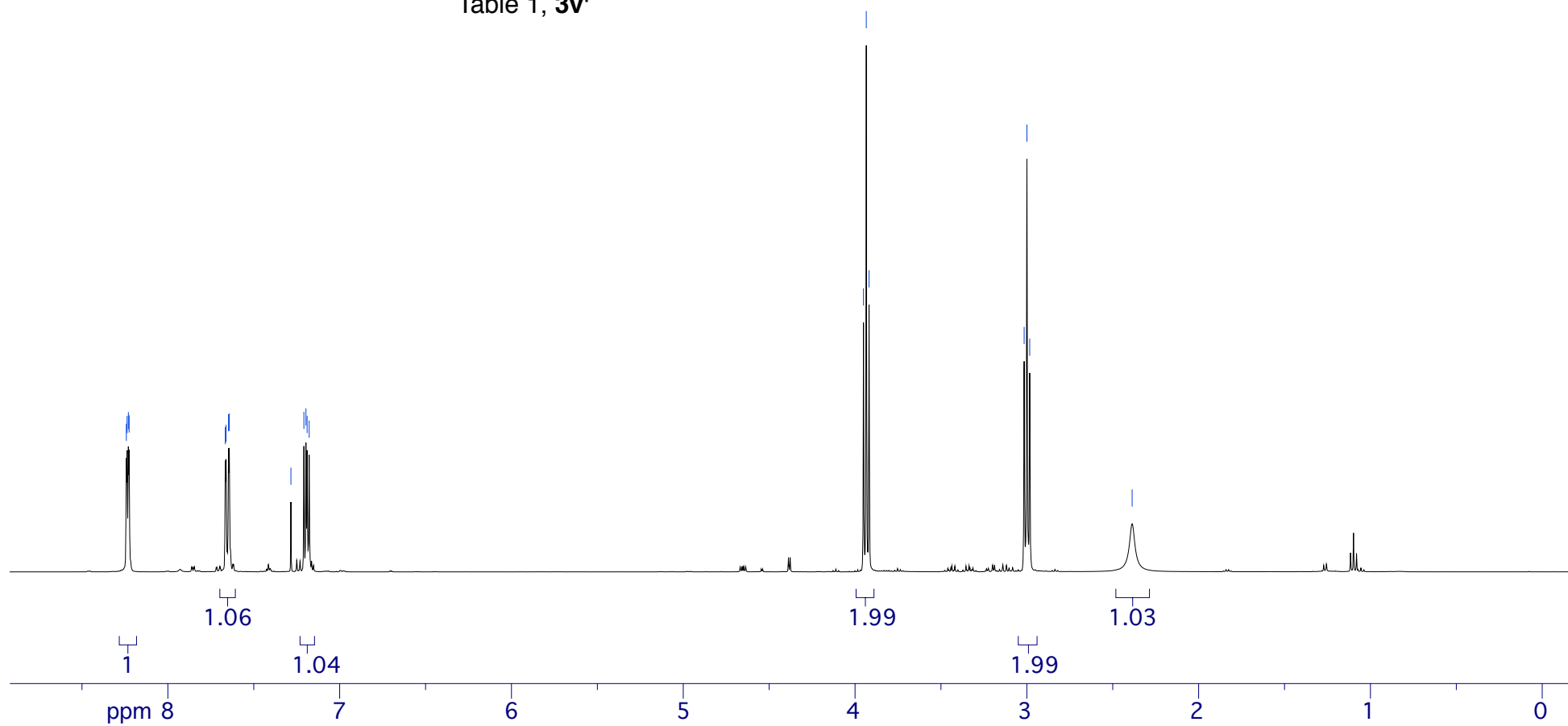


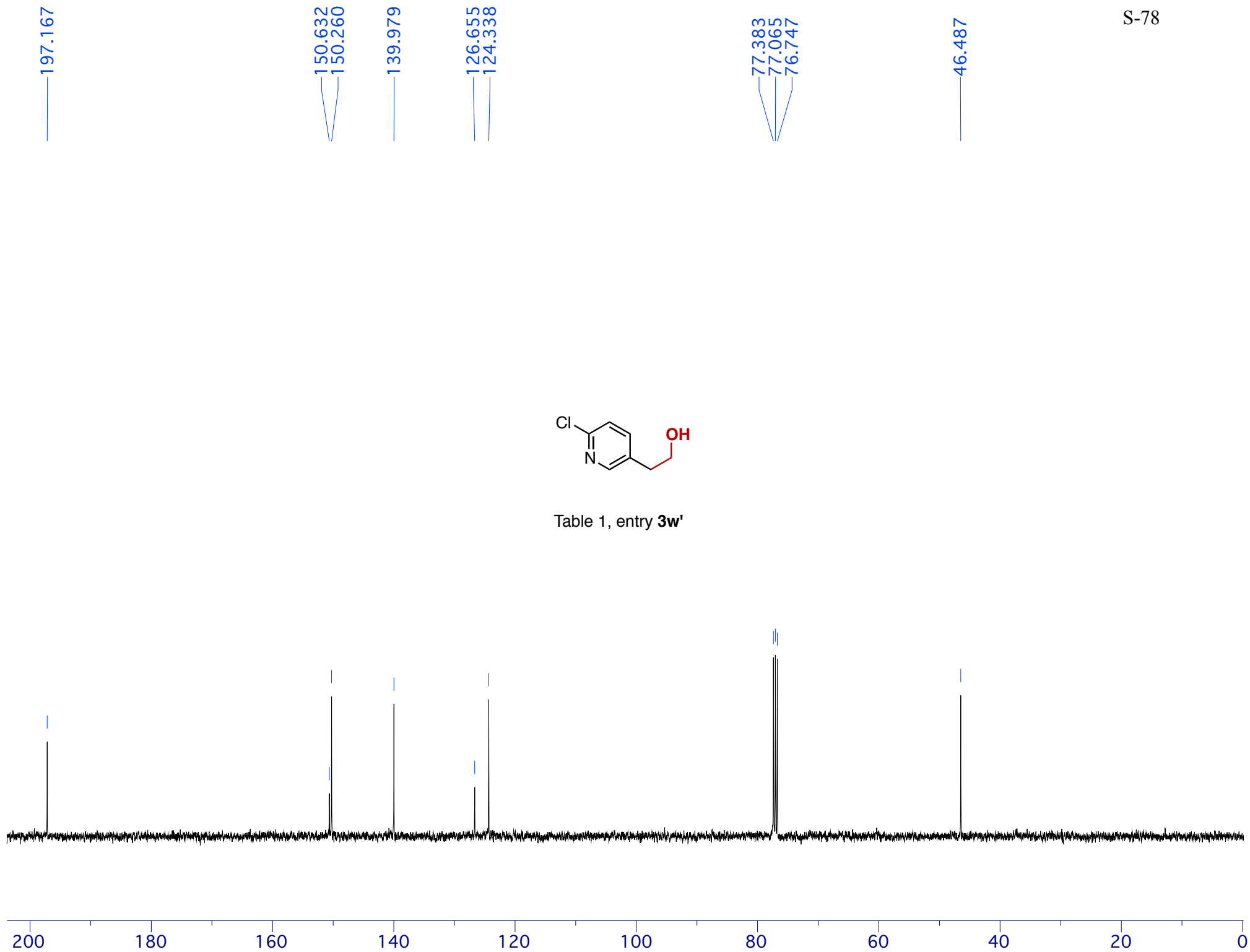
8.242
8.237
8.230
8.225
7.666
7.661
7.647
7.642
7.284
7.208
7.196
7.189
7.178

3.951
3.935
3.918

3.016
2.999
2.983

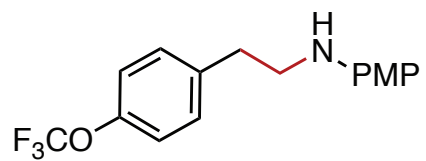
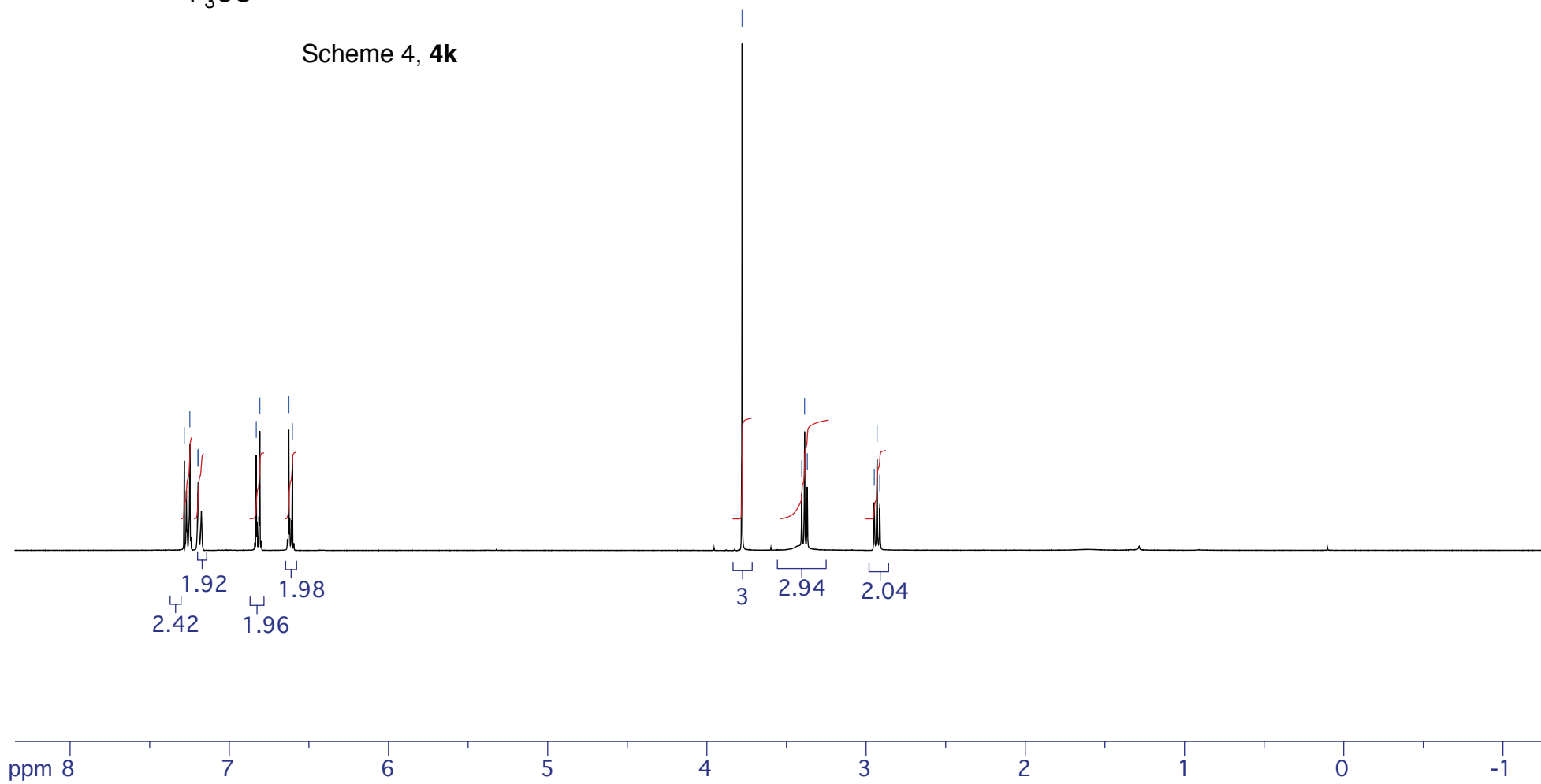
2.387

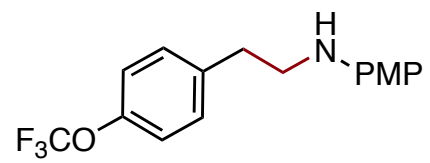
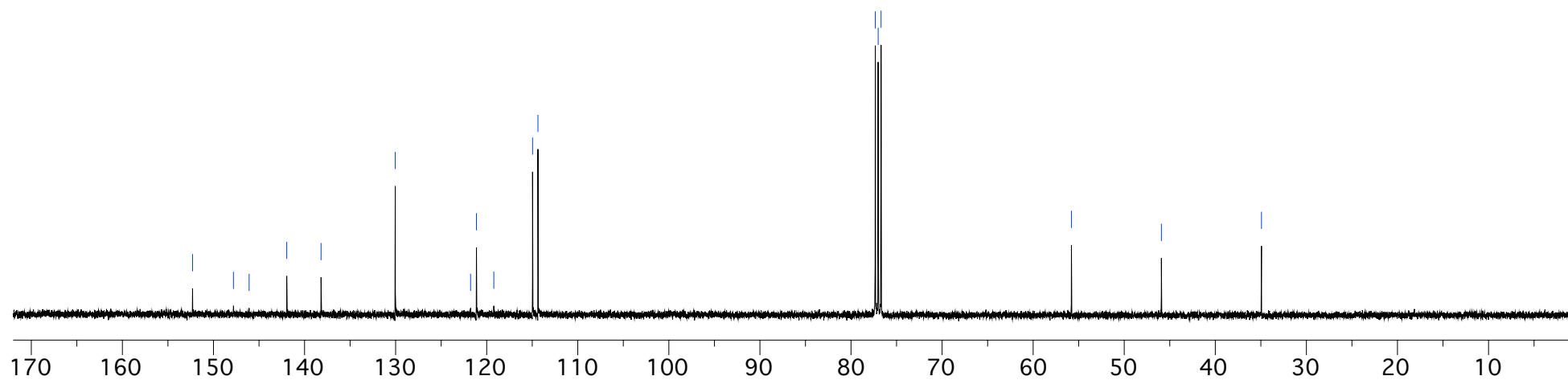
Table 1, **3v'**

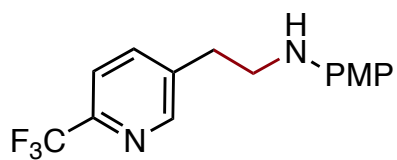
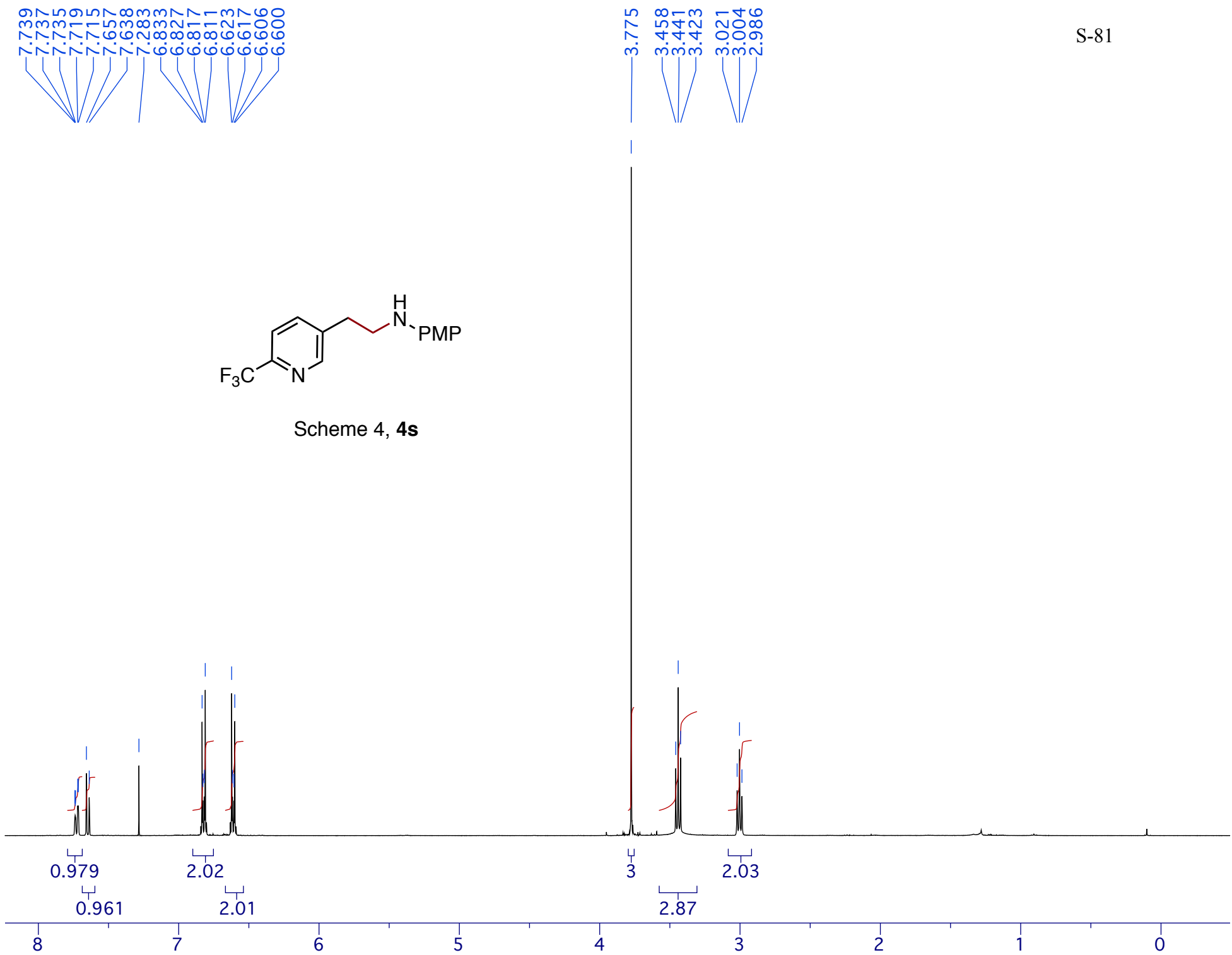


7.283
7.248
7.197
7.195
6.830
6.808
6.626
6.604

3.779
3.404
3.387
3.369
2.949
2.931
2.914

Scheme 4, **4k**

Scheme 4, **4k**

Scheme 4, **4s**

152.516
150.388
146.645
146.298
145.955
141.401
138.470
138.459
137.461

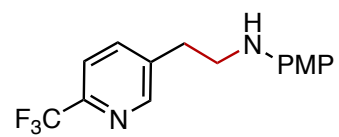
123.008
120.286
120.252
120.223
120.196
115.058
114.419

77.346
77.028
76.710

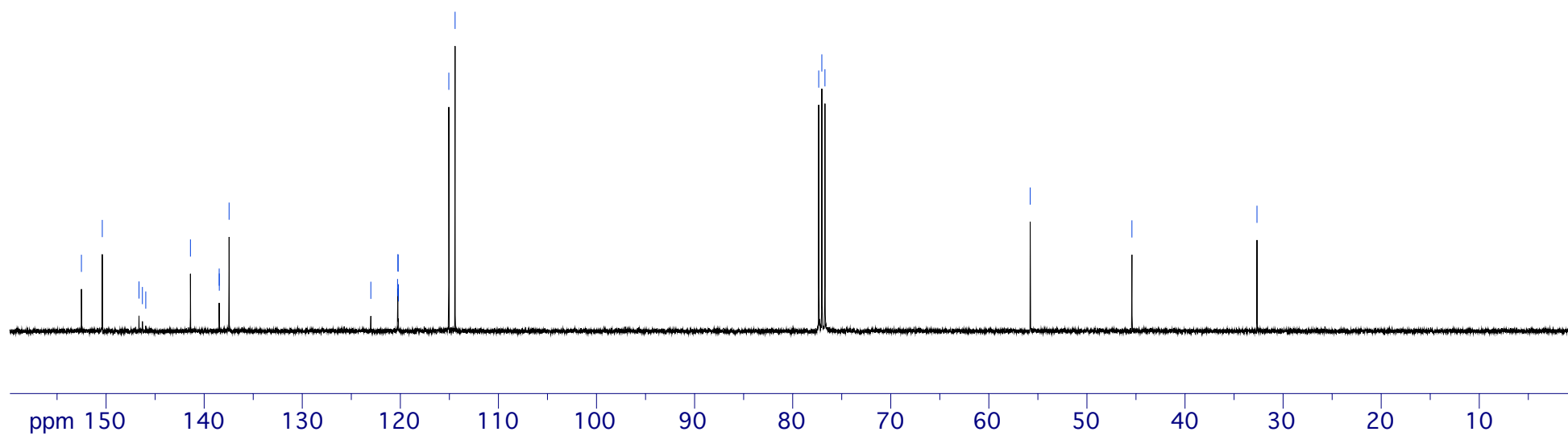
55.782

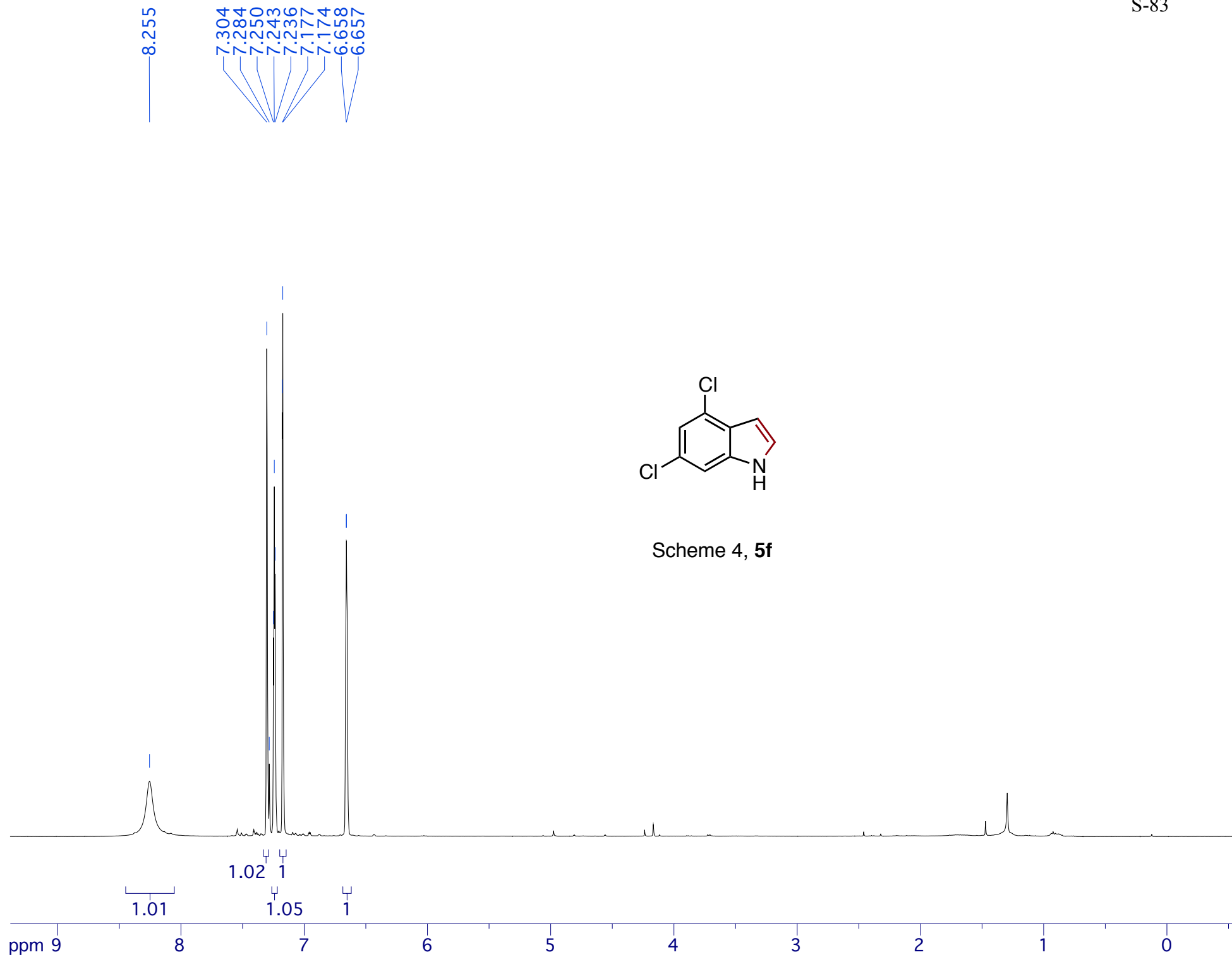
45.413

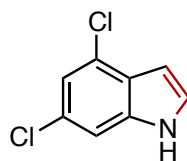
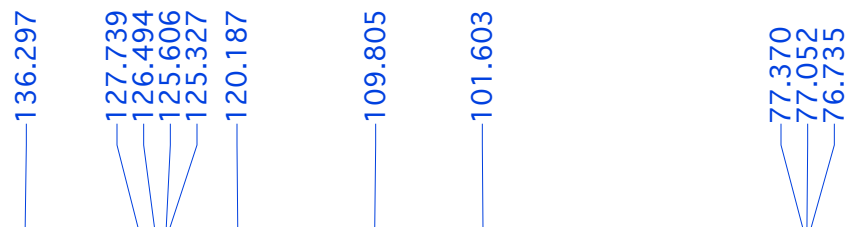
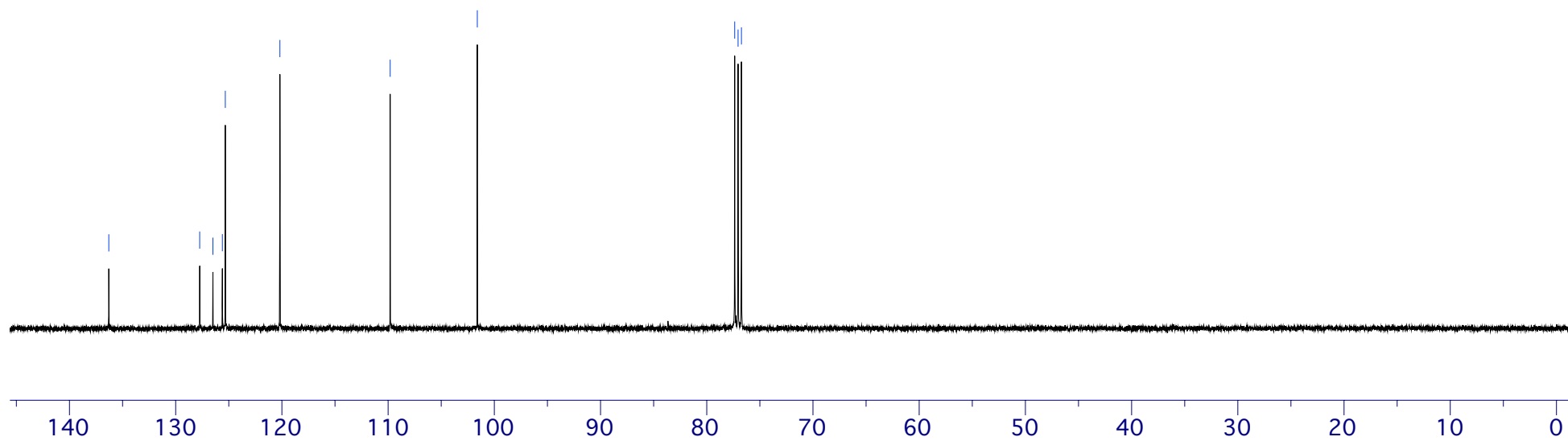
32.663



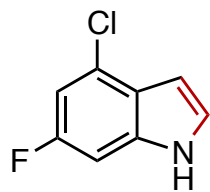
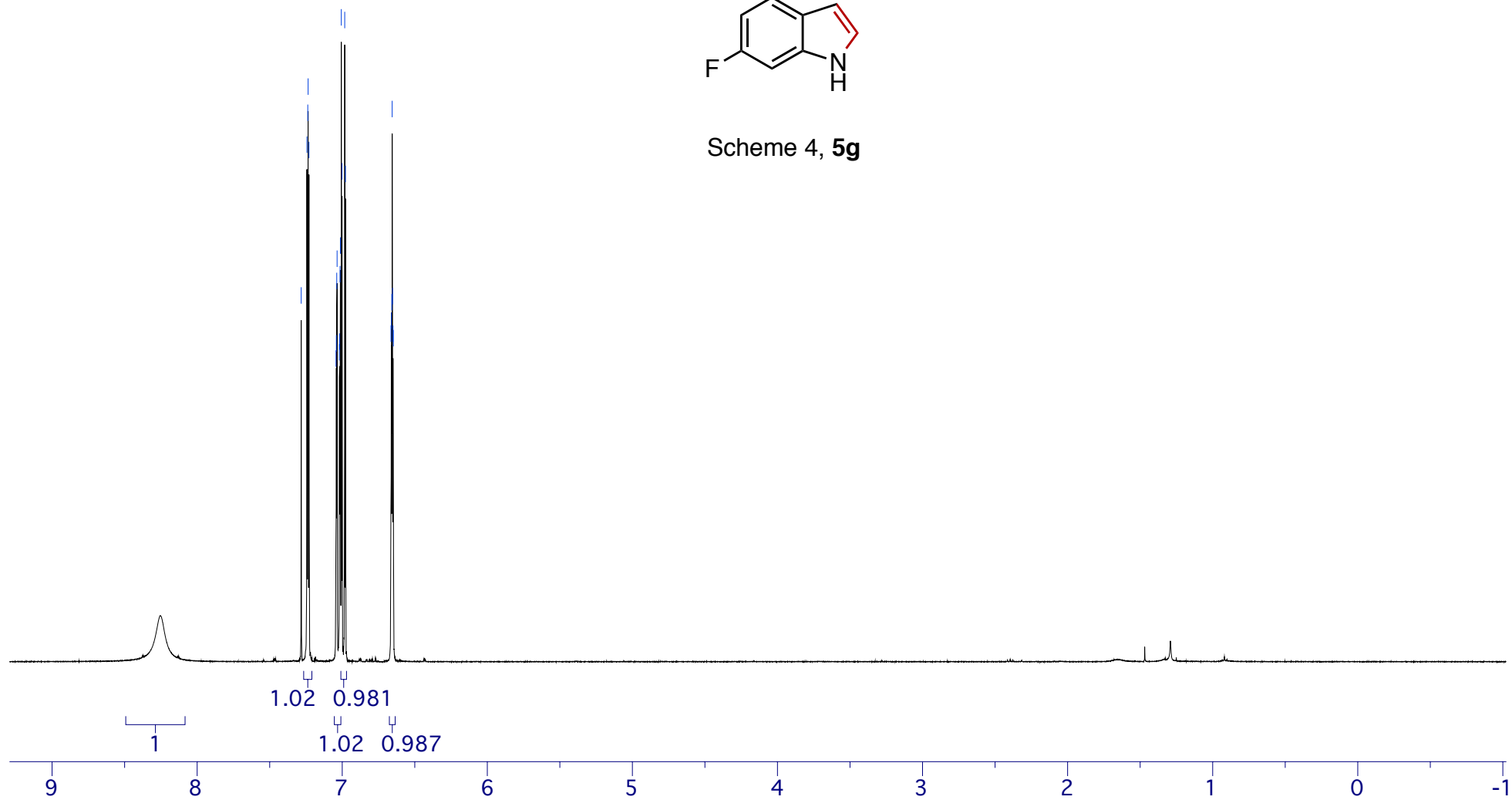
Scheme 4, **4s**





Scheme 4, **5f**

7.283
7.243
7.238
7.235
7.229
7.043
7.041
7.038
7.035
7.020
7.018
7.015
7.013
7.007
7.001
6.983
6.978
6.664
6.662
6.658
6.656
6.653
6.650
6.648

Scheme 4, **5g**

160.400
158.019

135.753
135.619

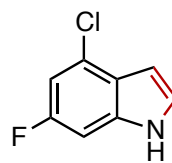
126.286
126.152
124.946
124.913
123.566

109.198
108.920

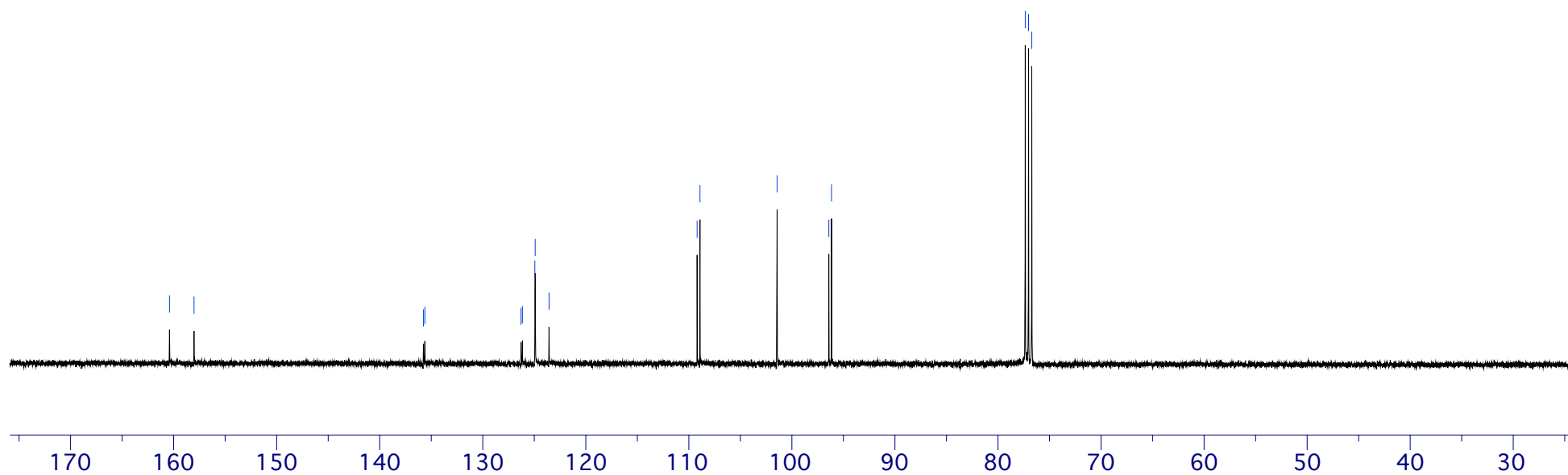
101.438

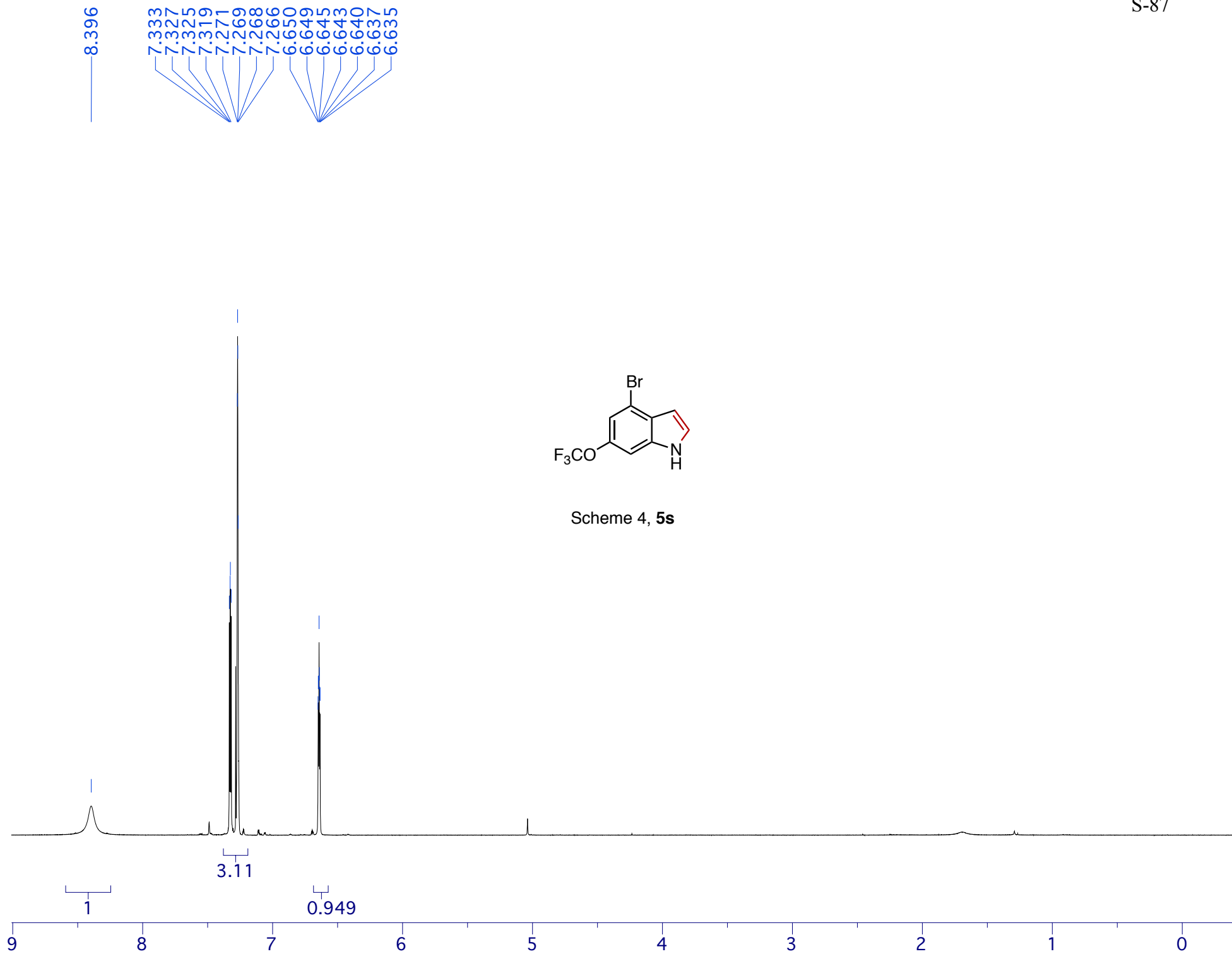
96.417
96.156

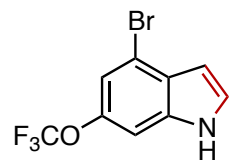
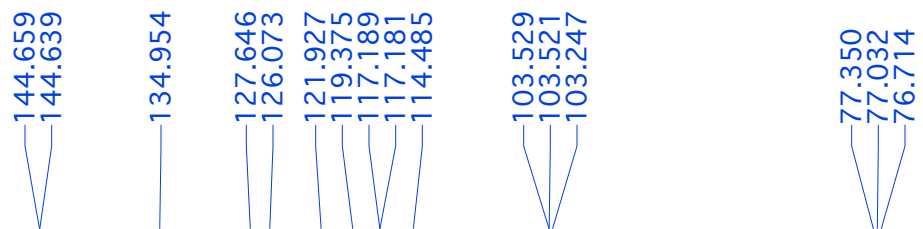
77.355
77.037
76.720



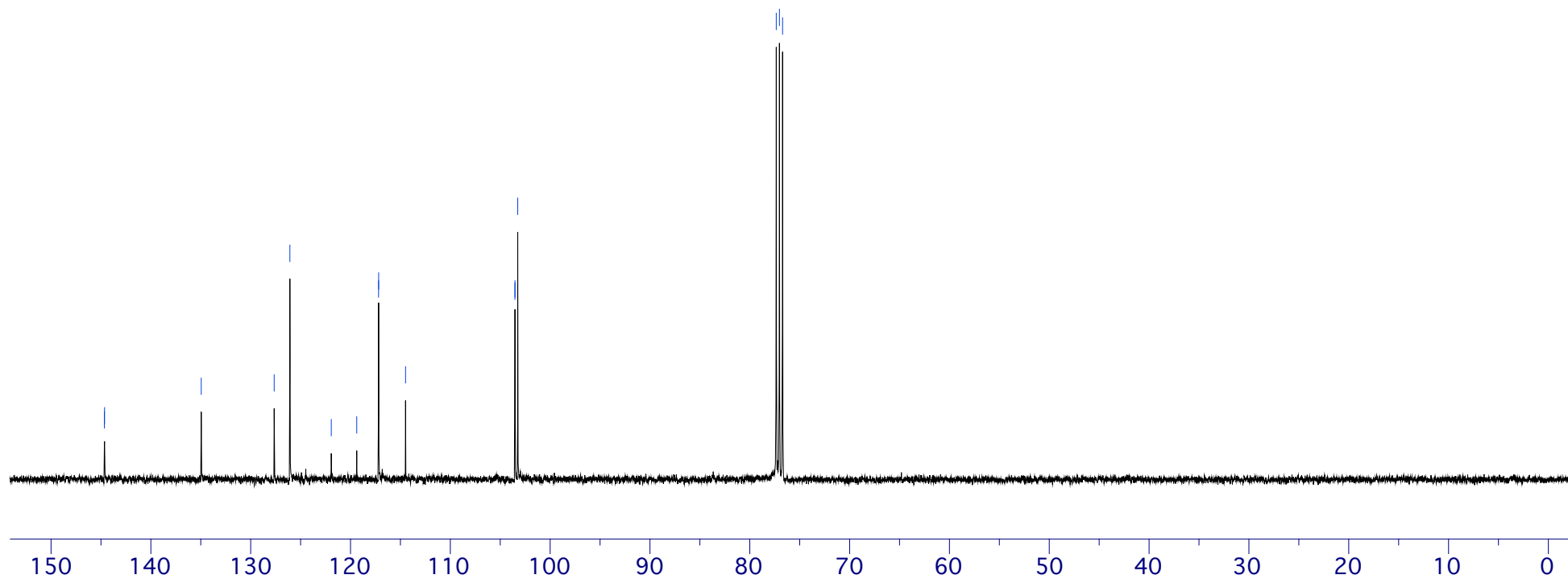
Scheme 4, **5g**

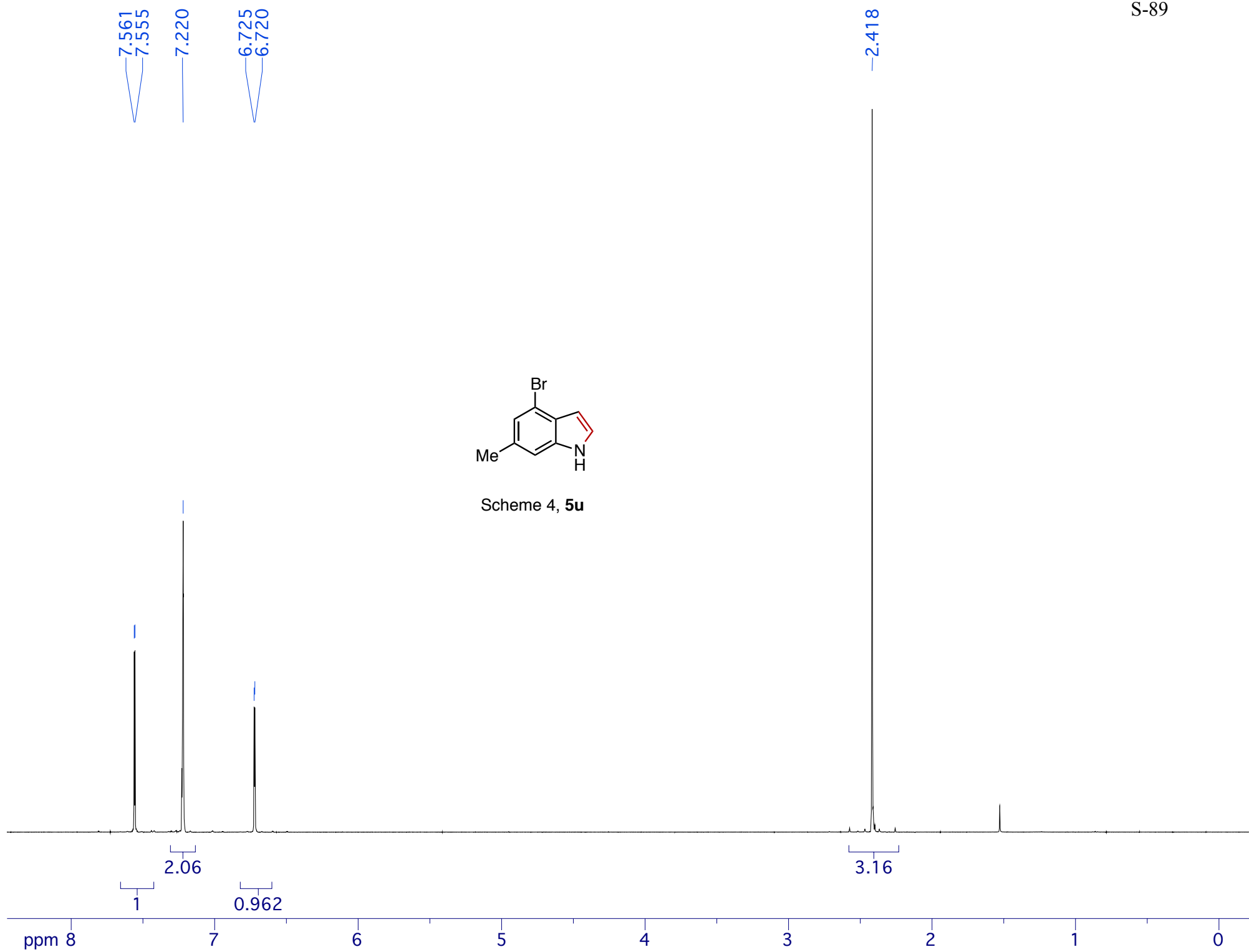


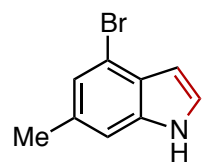
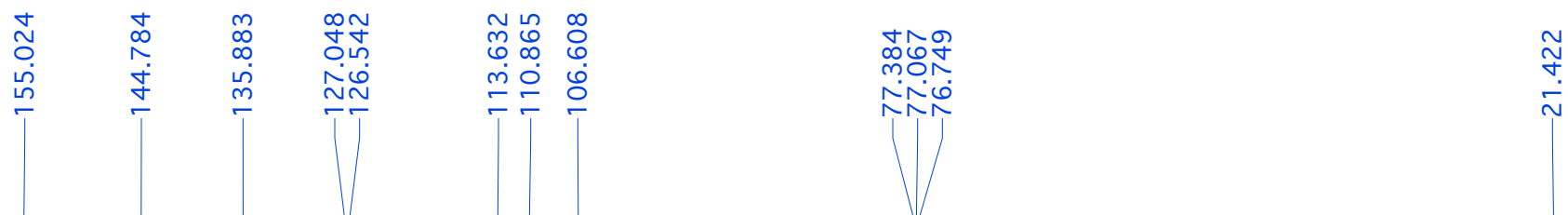
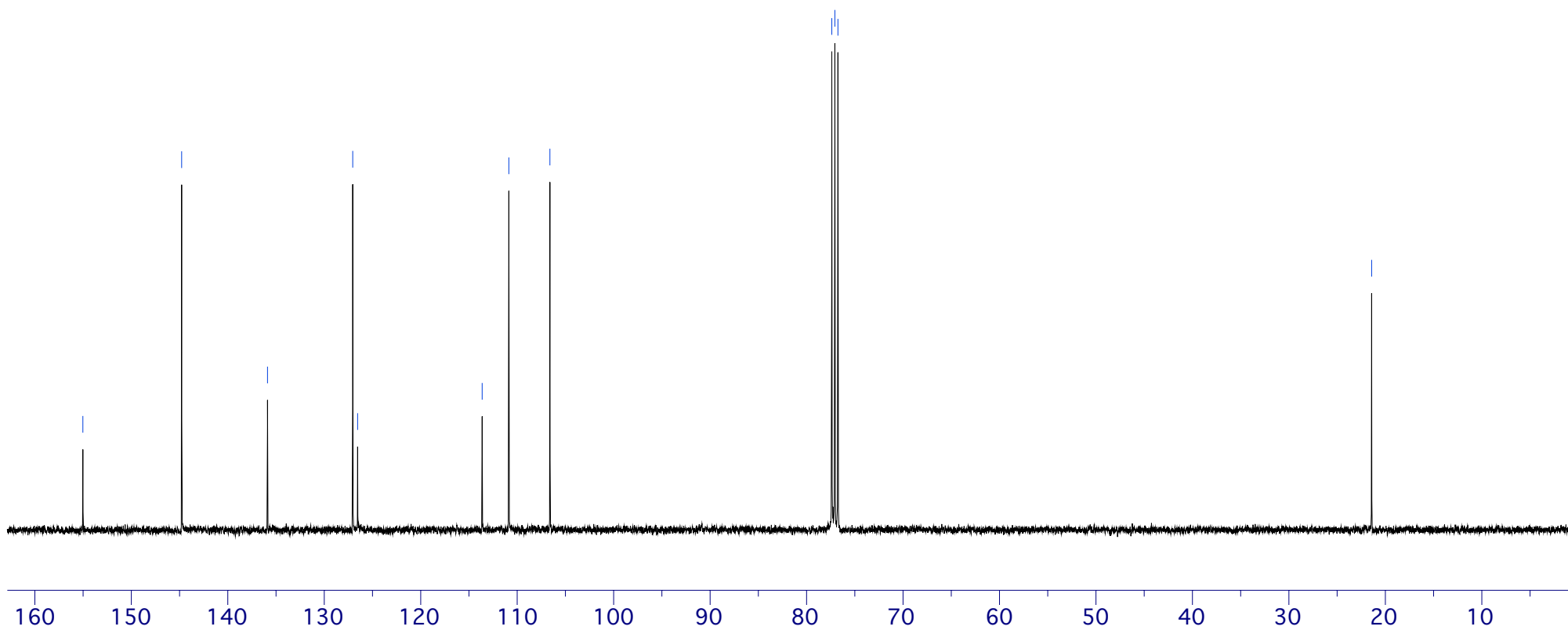




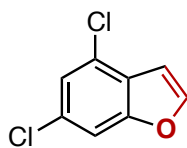
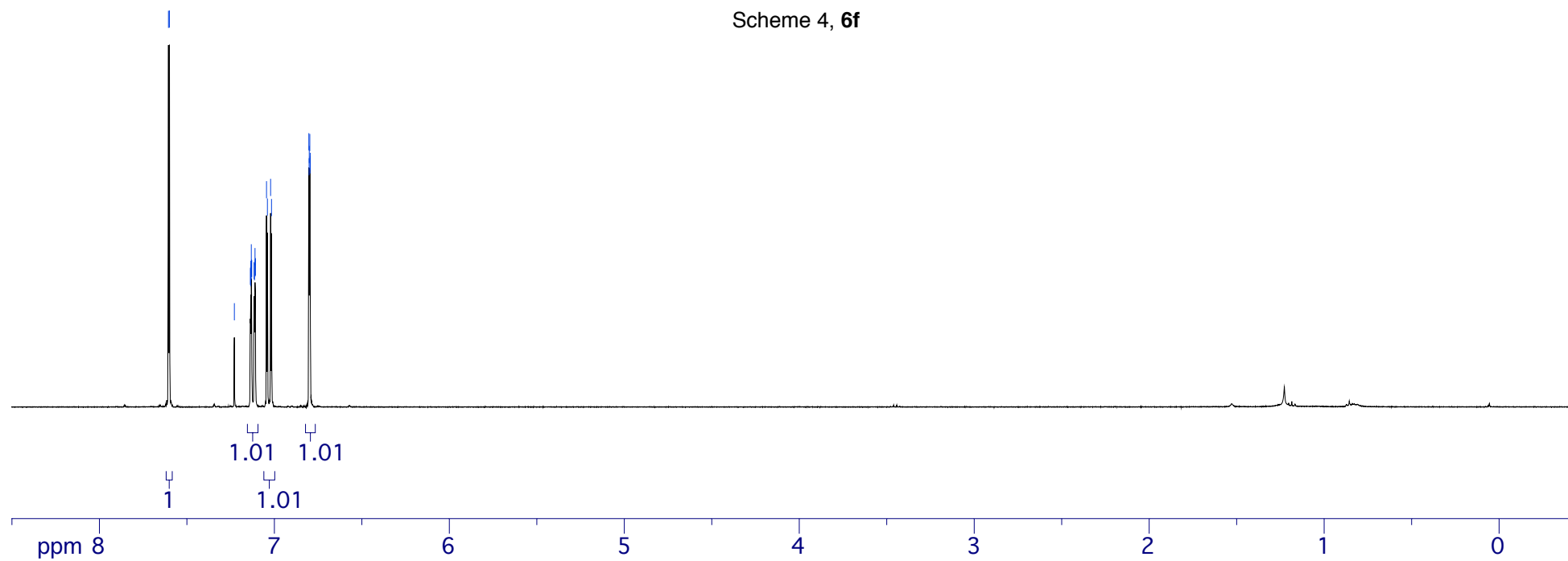
Scheme 4, 5s

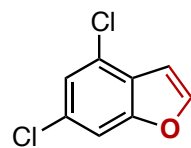
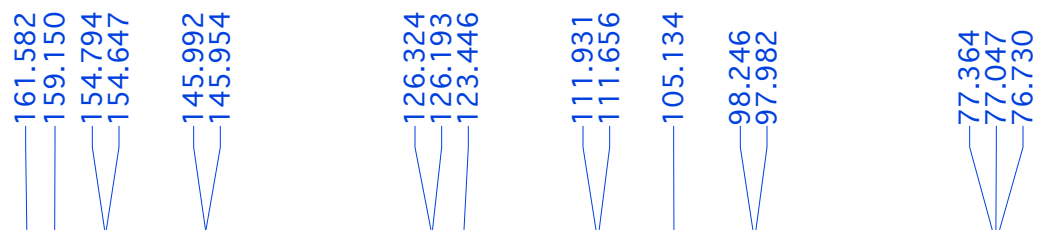
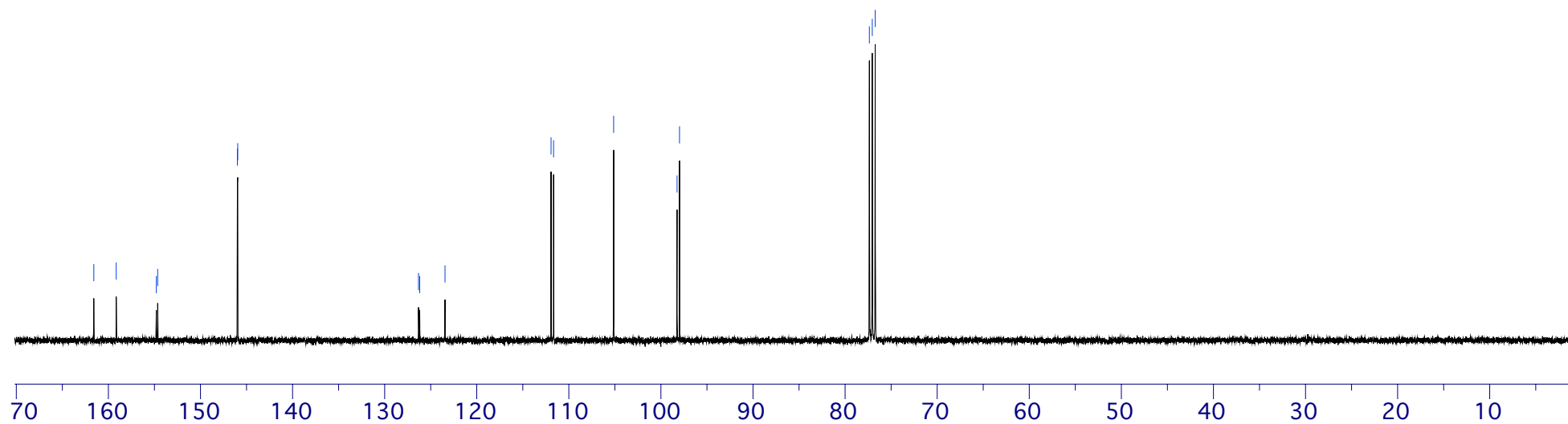




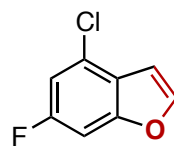
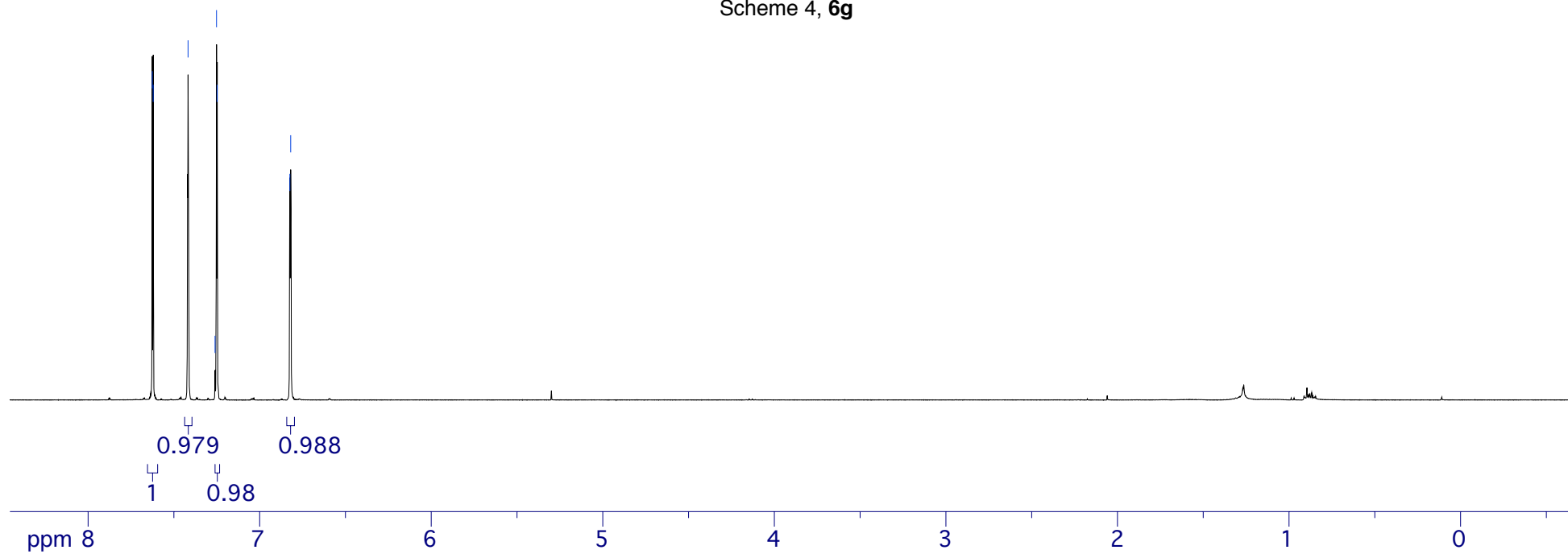
Scheme 4, **5u**

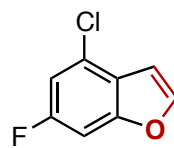
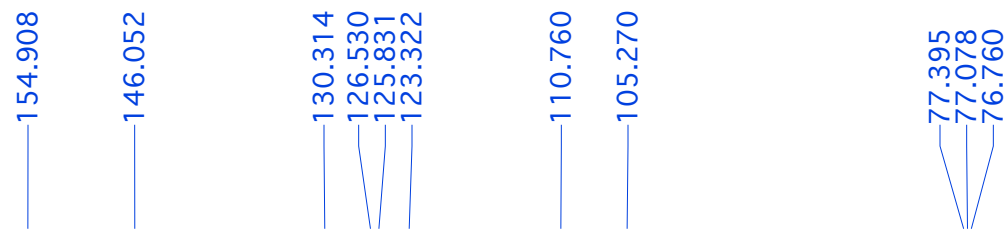
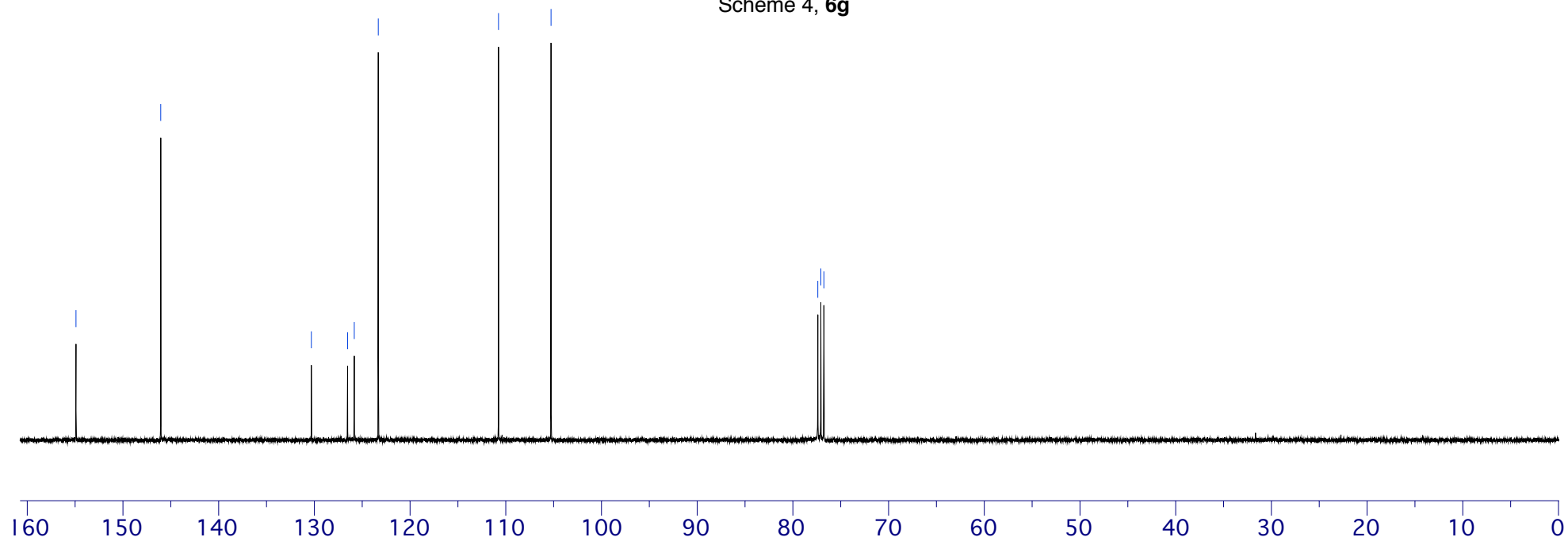
7.606
7.600
7.229
7.137
7.136
7.135
7.133
7.132
7.130
7.129
7.116
7.113
7.111
7.109
7.108
7.045
7.040
7.022
7.016
6.803
6.802
6.801
6.797
6.796
6.795

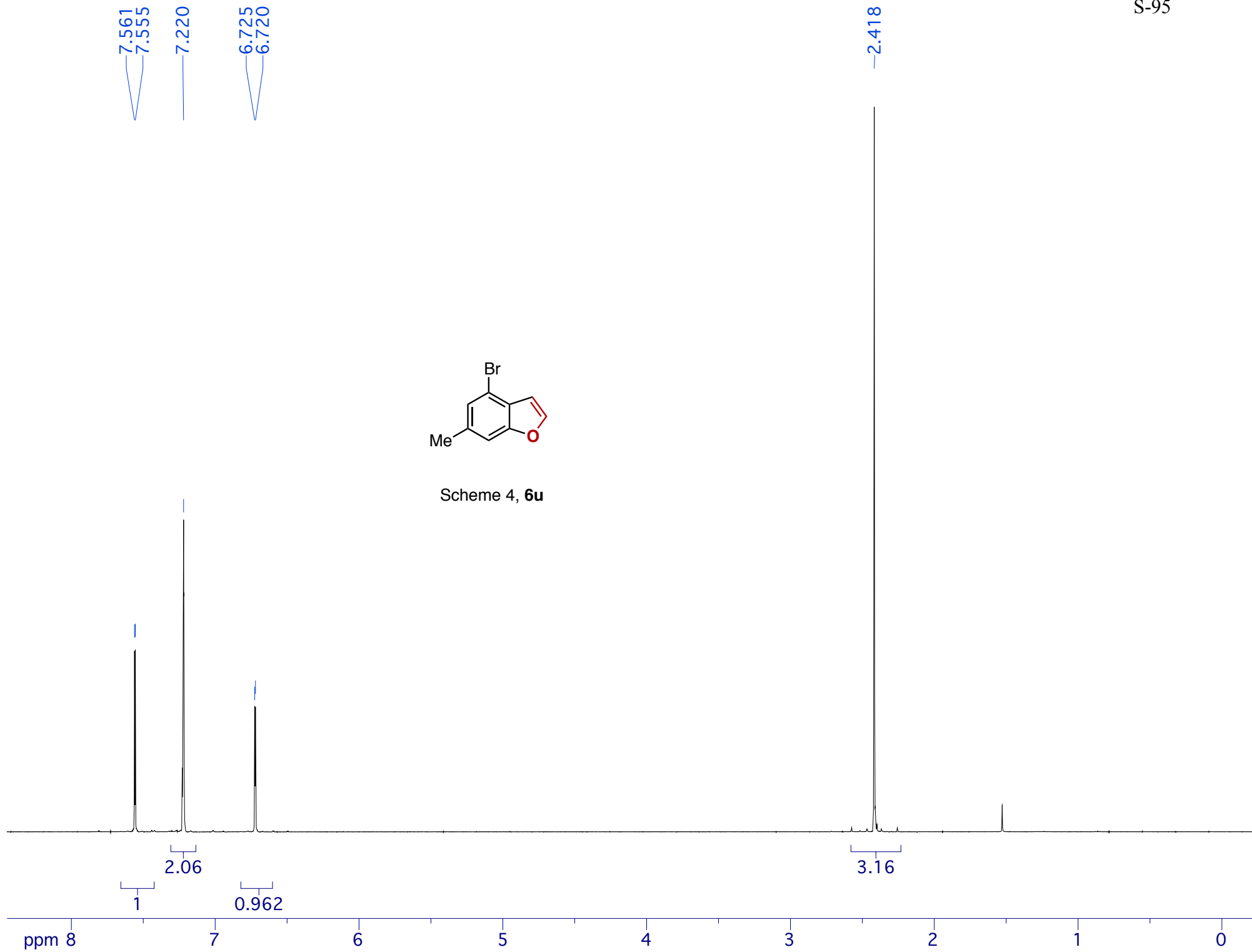
Scheme 4, **6f**

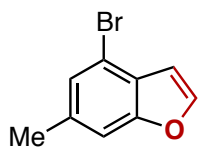
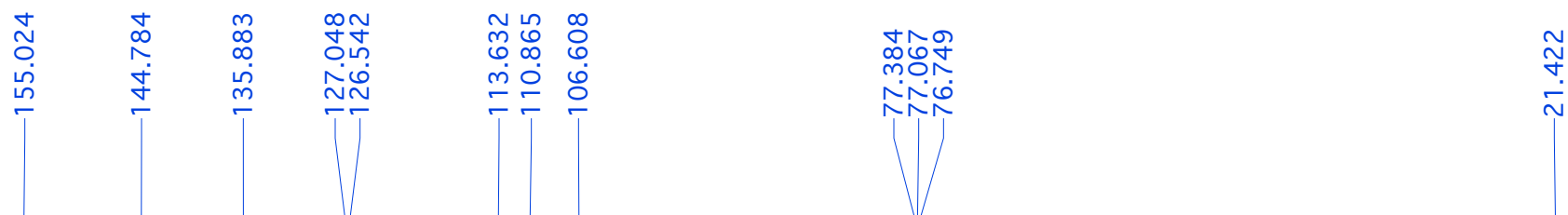
Scheme 4, **6f**

7.626
7.621
7.417
7.260
7.252
7.248
6.824
6.819

Scheme 4, **6g**

Scheme 4, **6g**



Scheme 4, **6u**