

## **Supporting Information**

### **Synthesis of 1,3-Diynes Via Cadiot-Chodkiewicz Coupling of Volatile, in Situ-Generated**

#### **Bromoalkynes**

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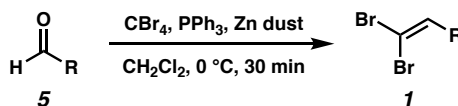
## Materials and Methods

Reactions were performed under an argon atmosphere unless otherwise noted. Tetrahydrofuran, dichloromethane, *N,N*-dimethylformamide, and toluene were purified by passing through activated alumina columns. CH<sub>3</sub>CN was distilled from CaH<sub>2</sub>. 1,1,1,3,3,3-Hexamethyldisilazane was distilled from CaH<sub>2</sub>. Deionized water was used for the coupling reactions. All other solvents and reagents were used as received unless otherwise noted. Commercially available chemicals and reagents were purchased from Alfa Aesar (Ward Hill, MA), MilliporeSigma (St. Louis, MO), Oakwood Products (West Columbia, SC), Acros Organics (Geel, Belgium), and TCI America (Portland, OR). Qualitative TLC analysis was performed on 250 mm thick, 60 Å, glass backed, F254 silica (SiliCycle, Quebec City, Canada). Visualization was accomplished with UV light, exposure to *p*-anisaldehyde solution followed by heating, or exposure to KMnO<sub>4</sub> solution followed by heating. Flash chromatography was performed using SiliCycle silica gel (230-400 mesh). <sup>1</sup>H NMR spectra were acquired on a Varian Mercury Plus NMR (at 400 MHz) and are reported relative to SiMe<sub>4</sub> (δ 0.00). <sup>13</sup>C NMR spectra were acquired on a Varian Mercury Plus NMR (at 100 MHz) and are reported relative to SiMe<sub>4</sub> (δ 0.0). <sup>19</sup>F NMR spectra were acquired on a Varian Mercury Plus NMR (at 376 MHz) and are reported relative to CFCl<sub>3</sub> (δ 0.0). All IR spectra were obtained on an ATR-ZnSe as thin films with a Nicolet iS-50 FT-IR or Shimadzu IRPrestige-21 FT-IR spectrometer and are reported in wavenumbers (ν). High resolution mass spectrometry (HRMS) data were acquired by the Proteomics and Mass Spectrometry Facility at the University of Georgia on a Thermo Orbitrap Elite.

## Experimental Section

### Dibromoolefin Syntheses

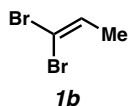
**General Procedure 1 (GP1):** *Synthesis of dibromoolefins.*



To a mixture of  $\text{CBr}_4$  (2.00 equiv) and Zn dust (8.00 equiv) in anhydrous  $\text{CH}_2\text{Cl}_2$  (0.25 M, in reference to aldehyde) under argon at 0 °C was added a solution of  $\text{PPh}_3$  (2.00 equiv) in  $\text{CH}_2\text{Cl}_2$  (1.0 M, in reference to aldehyde). After 30 min, aldehyde (1.00 equiv) was added and the reaction mixture was stirred at 0 °C for 30 min. Upon completion, the mixture was filtered through a plug of silica ( $\text{CH}_2\text{Cl}_2$  eluent), and the filtrate was concentrated under reduced pressure. (Caution! 1,1-dibromopropene and 1,1-dibromobutene are volatile, and care should be taken during concentration.) The excess  $\text{PPh}_3\text{O}$  and  $\text{PPh}_3$  was removed by washing with cold  $\text{Et}_2\text{O}$  and filtering off the white solid. The filtrate was concentrated in vacuo. No further purification was necessary.

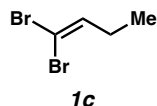
*Note:* It should be noted that in the synthesis of the dibromoalkenes, bromoform was a possible byproduct (singlet at 6.83 ppm in  $\text{CDCl}_3$ ), and if taken on to the coupling, would inhibit reactivity. We concluded that the presence of bromoform correlated with two experimental factors: 1) when there was residual  $\text{EtOH}$  in our  $\text{CBr}_4$  ( $\text{CBr}_4$  is frequently purified by recrystallizing from  $\text{EtOH}$ ) and 2) when the reaction was not maintained at 0 °C throughout. (Warming to room temperature is common in previously reported experimental protocols.)  $\text{CBr}_4$  procured from MilliporeSigma was found to be free of  $\text{EtOH}$ . Keeping the reaction cold were important in reducing the amount of byproduct in the reaction. Attempts at separating the product from bromoform were unsuccessful.

#### 1,1-Dibromoprop-1-ene (**1b**)



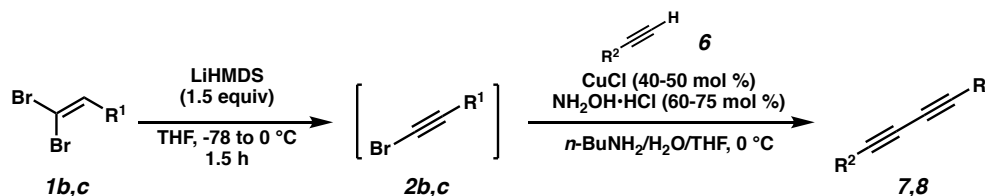
According to GP1, 1,1-dibromopropene (**1b**) was prepared as a light-yellow liquid (810 mg, 80% yield). The product was used in the subsequent reaction without further purification. The spectroscopic data for alkene **1b** matched the reported data.<sup>1</sup>

#### 1,1-Dibromobut-1-ene (**1c**)



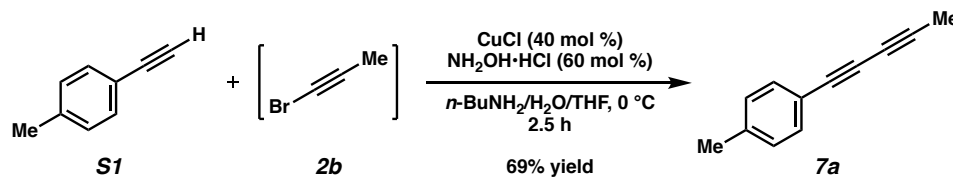
According to GP1, 1,1-dibromobutene (**1c**) was prepared as a colorless oil (3.88 g, 33% yield). The product was used in the subsequent reaction without further purification. The spectroscopic data for alkene **1c** matched the reported data.<sup>2</sup>

## Cadiot-Chodkiewicz Couplings from In Situ Generated 1-Bromoalkynes

**General procedure 2 (GP2):** Synthesis of diynes.

To a solution of freshly distilled HMDS (1.56 equiv) in anhydrous THF (1.45 M) under argon at -78 °C, *n*-BuLi (2.5 M in hexanes, 1.50 equiv) was added dropwise. The LiHMDS was generated over 30 min stirring at -78 °C. In a separate flask, dibromoalkene **1** (1.50 equiv in relation to the terminal alkyne) was dissolved in anhydrous THF (1.45 M) under argon, and the solution was cooled to -78 °C. To this solution, the LiHMDS solution was added dropwise. The reaction mixture was stirred for 30 min at -78 °C, and then it was warmed to 0 °C and stirred for an additional 1 h to ensure complete elimination. The resulting solution of 1-bromoalkyne was carried on immediately to the next reaction. *Note: Although we have experienced no issues, the literature does repeatedly report 1-bromo-1-propyne as a highly flammable, volatile, and potentially explosive compound. Appropriate safety and handling measures should be taken.*

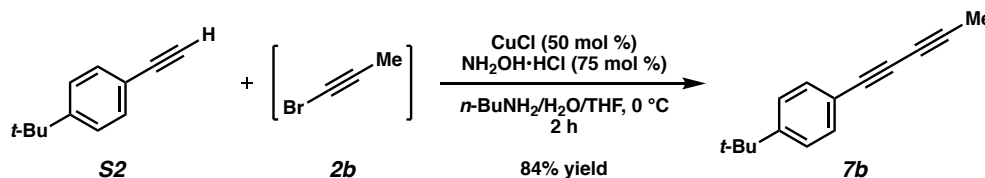
While this elimination was ongoing, in a separate flask, CuCl (0.400-0.500 equiv) was added to a stirred solution of *n*-BuNH<sub>2</sub> (20.0 equiv) and H<sub>2</sub>O (0.30 M) under argon at 0 °C, resulting in a deep blue solution. NH<sub>2</sub>OH·HCl (0.600-0.750 equiv) was added, returning the mixture to colorless. A solution of the terminal alkyne (1.00 equiv) in THF (0.5 M) was added to the reaction mixture, resulting in a bright yellow solution. Quickly following, the solution of freshly generated 1-bromoalkyne (held at 0 °C) was then added to the reaction mixture via syringe, and the resulting mixture was allowed to stir at 0 °C until the reaction went to completion. The dark brown mixture was then poured into EtOAc, the phases were separated, and the aqueous layer was extracted with EtOAc (2x). The organic layers were combined, washed with brine, dried over MgSO<sub>4</sub>, and concentrated in vacuo. The crude material was purified by flash chromatography to afford the diyne product.

**1-Methyl-4-(penta-1,3-diyn-1-yl)benzene (7a)**

According to GP2, alkyne **S1** (58.1 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromopropyne (assume 0.750 mmol) using CuCl (19.8 mg, 0.200 mmol), NH<sub>2</sub>OH·HCl (20.8 mg, 0.300 mmol), *n*-BuNH<sub>2</sub> (990 μL, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 2.5 h. The crude material was purified by flash chromatography (hexanes eluent) to afford diyne **7a** (53.2 mg, 69% yield) as a yellow solid. The spectroscopic data for diyne **7a** was in agreement with literature data.<sup>3</sup> **R<sub>f</sub>**: 0.68 (hexanes, KMnO<sub>4</sub>).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 7.37 (d, *J* = 7.8 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 2.34 (s, 3H), 2.02 (s, 3H).

**1-(*tert*-Butyl)-4-(penta-1,3-diyn-1-yl)benzene (7b)**



According to GP2, alkyne **S2** (79.1 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromopropyne (assume 0.750 mmol) using CuCl (24.8 mg, 0.250 mmol), NH<sub>2</sub>OH·HCl (26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990 μL, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 2 h. The crude material was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to afford diyne **7b** (82.4 mg, 84% yield) as a yellow oil.

**R<sub>f</sub>**: 0.71 (4:1 hexanes/EtOAc, KMnO<sub>4</sub>).

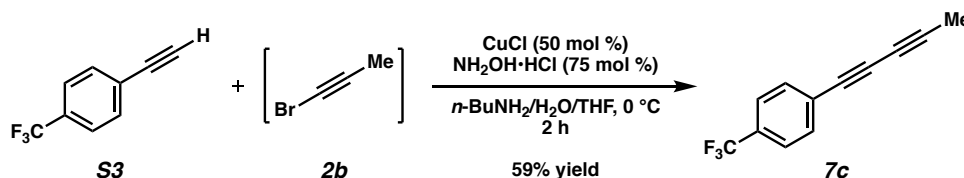
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 7.41 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 2.02 (s, 3H), 1.30 (s, 9H).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ 152.3, 132.4, 125.5, 119.1, 80.0, 74.5, 73.8, 64.6, 35.0, 31.2, 4.8.

**IR** (film): 2963, 2868, 2253, 1501, 1363 cm<sup>-1</sup>.

**HRMS** (ESI<sup>+</sup>): *m/z* calc. for (M + H)<sup>+</sup> [C<sub>15</sub>H<sub>16</sub> + H]<sup>+</sup>: 197.1330, found 197.1325.

**1-(Penta-1,3-diyn-1-yl)-4-(trifluoromethyl)benzene (7c)**



According to GP2, alkyne **S3** (85.1 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromopropyne (assume 0.750 mmol) using CuCl (24.8 mg, 0.250 mmol), NH<sub>2</sub>OH·HCl (26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990 μL, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 2 h. The crude material was purified by flash chromatography (hexanes eluent) to afford diyne **7c** (61.8 mg, 59% yield) as an off-white solid.

**R<sub>f</sub>**: 0.62 (hexanes, KMnO<sub>4</sub>).

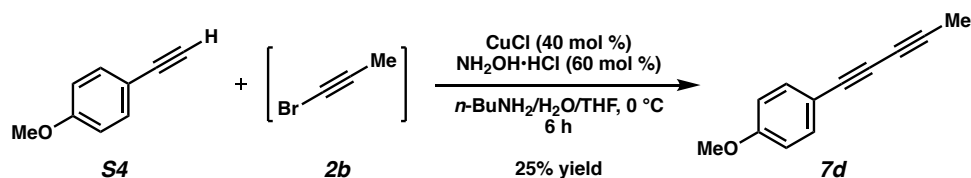
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 7.67-7.52 (comp. m, 4H), 2.04 (s, 3H).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ 132.9, 130.6 (q, *J* = 32.8 Hz), 126.1, 125.4 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 272.3 Hz), 82.0, 76.9, 72.6, 64.1, 4.8.

**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>): δ -66.02.

**IR** (film): 2934, 2854, 2245, 2142, 1325 cm<sup>-1</sup>.

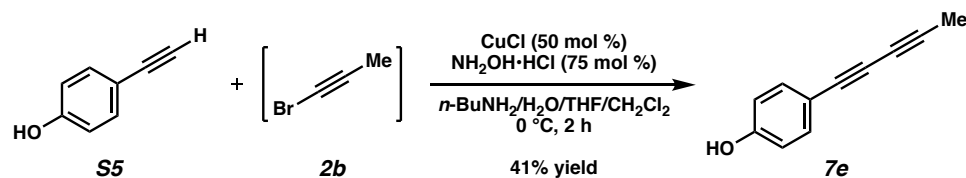
**HRMS** (ESI<sup>+</sup>) *m/z* calc. for (M + H)<sup>+</sup> [C<sub>12</sub>H<sub>7</sub>F<sub>3</sub> + H]<sup>+</sup>: 209.0578, found 209.0573.

**1-Methoxy-4-(penta-1,3-diyn-1-yl)benzene (7d)**

According to GP2, alkyne **S4** (66.1 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromopropyne (assume 0.750 mmol) using CuCl (19.8 mg, 0.200 mmol), NH<sub>2</sub>OH·HCl (20.8 mg, 0.300 mmol), *n*-BuNH<sub>2</sub> (990  $\mu$ L, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 6 h. The crude material was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford diyne **7d** (21.3 mg, 25% yield) as a pale yellow solid. The spectroscopic data for diyne **7d** was in agreement with literature data.<sup>4</sup>

**R<sub>f</sub>**: 0.55 (9:1 hexanes/EtOAc, KMnO<sub>4</sub>).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.41 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 3.81 (s, 3H), 2.01 (s, 3H).

**4-(Penta-1,3-diyn-1-yl)phenol (7e)**

According to GP2, alkyne **S5** (59.1 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromopropyne (assume 0.750 mmol) using CuCl (24.8 mg, 0.250 mmol), NH<sub>2</sub>OH·HCl (26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990  $\mu$ L, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 2 h. (*Note: In order to help solubilize the terminal alkyne in the reaction mixture, 2.00 mL of CH<sub>2</sub>Cl<sub>2</sub> was added.*) The crude material was purified by flash chromatography (2:1 hexanes/EtOAc eluent) to afford diyne **7e** (31.9 mg, 41% yield) as a light brown solid.

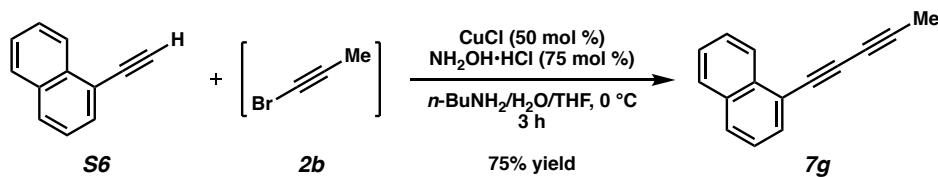
**R<sub>f</sub>**: 0.44 (2:1 hexanes/EtOAc, KMnO<sub>4</sub>).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.37 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 2H), 5.15 (s, 1H), 2.01 (s, 3H).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>):  $\delta$  156.2, 134.4, 115.7, 114.3, 79.9, 74.3, 73.2, 64.5, 4.7.

**IR** (film): 3304 (br), 2911, 2168, 1509, 832 cm<sup>-1</sup>.

**HRMS** (ESI<sup>+</sup>) *m/z* calc. for (M<sup>+</sup>) [C<sub>11</sub>H<sub>8</sub>O]<sup>+</sup>: 156.0575, found 156.0571.

**1-(Penta-1,3-diyn-1-yl)naphthalene (7g)**

According to GP2, alkyne **S6** (76.1 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromopropyne (assume 0.750 mmol) using CuCl (24.8 mg, 0.250 mmol), NH<sub>2</sub>OH•HCl (26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990 μL, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 3 h. The crude material was purified by flash chromatography (hexanes eluent) to afford diyne **7g** (71.2 mg, 75% yield) as a yellow oil.

**R<sub>f</sub>**: 0.39 (hexanes, KMnO<sub>4</sub>).

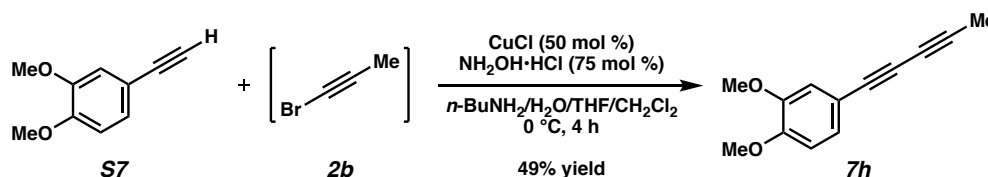
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 8.32 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.73 (d, *J* = 7.3 Hz, 1H), 7.58 (app. t, *J* = 7.3 Hz, 1H), 7.52 (app. t, *J* = 7.3 Hz, 1H), 7.41 (app. t, *J* = 7.3 Hz, 1H), 2.08 (s, 3H).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ 134.1, 133.2, 132.0, 129.4, 128.5, 127.2, 126.7, 126.2, 125.3, 119.8, 81.6, 79.2, 72.5, 64.7, 4.9.

**IR** (film): 3058, 2912, 2240, 1399, 799 cm<sup>-1</sup>.

**HRMS** (ESI+) *m/z* calc. for (M)<sup>+</sup> [C<sub>15</sub>H<sub>10</sub>]<sup>+</sup>: 190.0783, found 190.0778.

### 1,2-Dimethoxy-4-(penta-1,3-diyn-1-yl)benzene (7h)



According to GP2, alkyne **S7** (81.1 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromopropyne (assume 0.750 mmol) using CuCl (24.8 mg, 0.250 mmol), NH<sub>2</sub>OH•HCl (26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990 μL, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 4 h. (*Note: In order to help solubilize the terminal alkyne in the reaction mixture, 2.00 mL of CH<sub>2</sub>Cl<sub>2</sub> was added.*) The crude material was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford diyne **7h** (49.3 mg, 49% yield) as a yellow oil.

**R<sub>f</sub>**: 0.36 (9:1 hexanes/EtOAc, KMnO<sub>4</sub>).

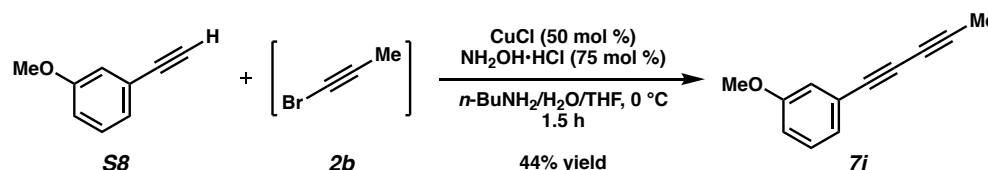
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 7.10 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.97 (d, *J* = 1.9 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 2.02 (s, 3H).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ 150.1, 148.6, 126.2, 114.9, 114.1, 111.0, 79.9, 74.4, 73.1, 64.5, 55.97, 55.95, 4.7.

**IR** (film): 2935, 2837, 2151, 1138, 1024 cm<sup>-1</sup>.

**HRMS** (ESI+) *m/z* calc. for (M + H)<sup>+</sup> [C<sub>13</sub>H<sub>12</sub>O<sub>2</sub> + H]<sup>+</sup>: 201.0916, found 201.0911.

### 1-Methoxy-3-(penta-1,3-diyn-1-yl)benzene (7i)



According to GP2, alkyne **S8** (66.1 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromopropyne (assume 0.750 mmol) using CuCl (24.8 mg, 0.250 mmol), NH<sub>2</sub>OH•HCl (26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990 μL, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 1.5 h. The crude



material was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford diyne **7i** (37.6 mg, 44% yield) as a yellow oil.

**R<sub>f</sub>**: 0.56 (9:1 hexanes/EtOAc, KMnO<sub>4</sub>).

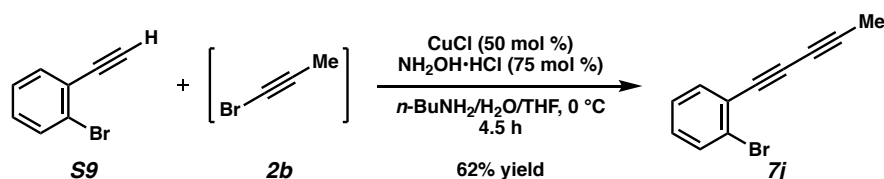
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 7.21 (app. t, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.99 (s, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 3.79 (s, 3H), 2.02 (s, 3H).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ 159.3, 129.6, 125.2, 123.1, 117.2, 115.8, 80.5, 74.3, 74.2, 64.4, 55.4, 4.8.

**IR** (film): 3002, 2913, 2836, 2246, 1602, 1221 cm<sup>-1</sup>.

**HRMS** (ESI+) *m/z* calc. for (M + H)<sup>+</sup> [C<sub>12</sub>H<sub>10</sub>O + H]<sup>+</sup>: 171.0810, found 171.0805.

### 1-Bromo-2-(penta-1,3-diyne-1-yl)benzene (**7j**)



According to GP2, alkyne **S9** (90.5 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromopropyne (assume 0.750 mmol) using CuCl (24.8 mg, 0.250 mmol), NH<sub>2</sub>OH·HCl (26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990 μL, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 4.5 h. The crude material was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to afford diyne **7j** (67.9 mg, 62% yield) as a yellow oil.

**R<sub>f</sub>**: 0.41 (hexanes, KMnO<sub>4</sub>).

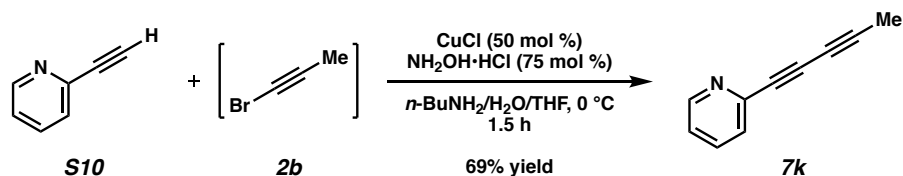
**<sup>1</sup>H NMR** (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ 7.58 (dd, *J* = 7.7, 0.3 Hz, 1H), 7.50 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.27 (app. td, *J* = 7.7, 0.3 Hz, 1H), 7.22 (app. td, *J* = 7.7, 1.2 Hz, 1H), 2.03 (s, 3H).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ 134.5, 132.6, 130.0, 127.1, 126.3, 124.5, 82.3, 78.8, 72.4, 64.3, 4.9.

**IR** (film): 2911, 2359, 2341, 1470, 1432 cm<sup>-1</sup>.

**HRMS** (ESI+) *m/z* calc. for (M\*) [C<sub>11</sub>H<sub>7</sub>Br\*]: 217.9731, found 217.9725.

### 2-(Penta-1,3-diyne-1-yl)pyridine (**7k**)



According to GP2, alkyne **S10** (51.6 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromopropyne (assume 0.750 mmol) using CuCl (24.8 mg, 0.250 mmol), NH<sub>2</sub>OH·HCl (26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990 μL, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 1.5 h. The crude material was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to afford diyne **7k** (47.2 mg, 69% yield) as a clear oil.

**R<sub>f</sub>**: 0.35 (4:1 hexanes/EtOAc, KMnO<sub>4</sub>).

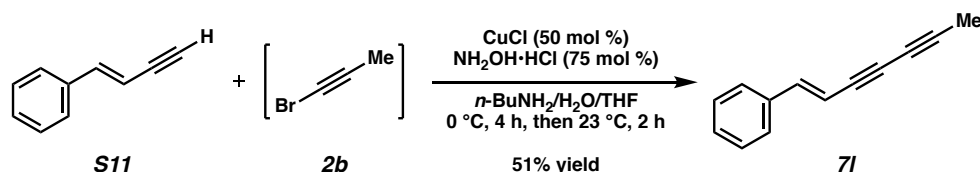
**<sup>1</sup>H NMR** (400 MHz, C<sub>6</sub>D<sub>6</sub>): δ 8.30 (d, *J* = 4.6 Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 6.76-6.69 (m, 1H), 6.41-6.38 (m, 1H), 1.27 (s, 3H).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ 150.3, 142.6, 136.2, 128.1, 123.3, 81.7, 74.5, 73.0, 64.1, 4.8.

**IR** (film): 2914, 2360, 2341, 2264, 2236, 1579 cm<sup>-1</sup>.

**HRMS** (ESI+)  $m/z$  calc. for  $(M + H)^+ [C_{10}H_7N + H]^+$ : 142.0657, found 142.0653.

**(E)-Hepta-1-en-3,5-diyn-1-ylbenzene (7l)**



According to GP2, alkyne **S11** (64.1 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromopropyne (assume 0.750 mmol) using CuCl (24.8 mg, 0.250 mmol), NH<sub>2</sub>OH·HCl (26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990 μL, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 4 h at 0 °C and 2 h at room temperature. The crude material was purified by flash chromatography (hexanes eluent) to afford diyne **7l** (42.4 mg, 51% yield) as a yellow oil.

**R<sub>f</sub>**: 0.76 (hexanes, KMnO<sub>4</sub>).

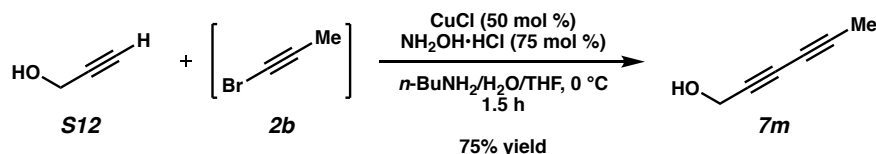
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 7.40-7.28 (comp. m, 5H), 7.05 (d, *J* = 16.3 Hz, 1H), 6.16 (d, *J* = 16.3 Hz, 1H), 2.01 (s, 3H).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ 144.2, 136.0, 129.2, 128.9, 126.5, 107.2, 81.2, 76.8, 74.0, 64.7, 4.9.

**IR** (film): 3029, 2911, 2233, 2140, 1597 cm<sup>-1</sup>.

**HRMS** (ESI+)  $m/z$  calc. for  $(M + H)^+ [C_{13}H_{10} + H]^+$ : 167.0861, found 167.0855.

**Hexa-2,4-diyn-1-ol (7m)**

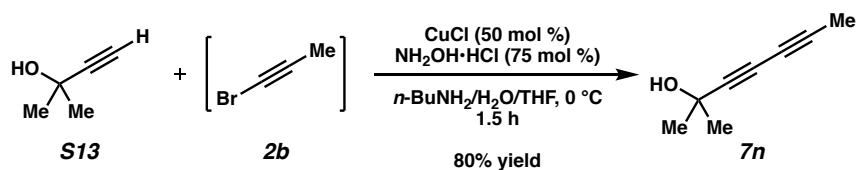


According to GP2, alkyne **S12** (73.1 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromopropyne (assume 0.750 mmol) using CuCl (24.8 mg, 0.250 mmol), NH<sub>2</sub>OH·HCl (26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990 μL, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 1.5 h. The crude material was purified by flash chromatography (2:1 hexanes/EtOAc eluent) to afford diyne **7m** (35.3 mg, 75% yield) as a yellow solid. The spectroscopic data for diyne **7m** was in agreement with literature data.<sup>5</sup>

**R<sub>f</sub>**: 0.46 (2:1 hexanes/EtOAc, KMnO<sub>4</sub>).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 4.31 (d, *J* = 6.2 Hz, 2H), 1.94 (s, 3H), 1.54 (br. t, *J* = 6.2 Hz, 1H).

**2-Methylhepta-3,5-diyn-2-ol (7n)**



According to GP2, alkyne **S13** (42.1 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromopropyne (assume 0.750 mmol) using CuCl (24.8 mg, 0.250 mmol), NH<sub>2</sub>OH·HCl

(26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990  $\mu$ L, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 1.5 h. The crude material was purified by flash chromatography (2:1 hexanes/EtOAc eluent) to afford diyne **7n** (33.6 mg, 80% yield) as a yellow solid.

**R<sub>f</sub>**: 0.52 (2:1 hexanes/EtOAc, KMnO<sub>4</sub>).

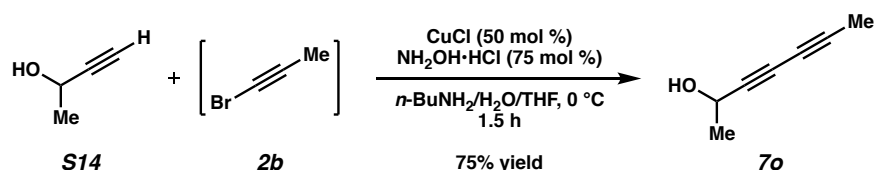
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  1.94 (s, 3H), 1.55 (br. s, 1H), 1.52 (s, 6H).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>):  $\delta$  79.4, 77.6, 67.5, 65.6, 63.5, 31.3, 4.4.

**IR** (film): 3358 (br), 2982, 2255, 1156, 959 cm<sup>-1</sup>.

**HRMS** (ESI+) *m/z* calc. for (M + H)<sup>+</sup> [C<sub>8</sub>H<sub>10</sub>O + H]<sup>+</sup>: 123.0810, found 123.0804.

### Hepta-3,5-diyn-2-ol (**7o**)

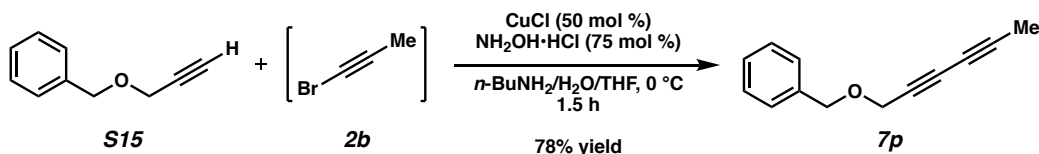


According to GP2, alkyne **S14** (35.0 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromopropyne (assume .750 mmol) using CuCl (24.8 mg, 0.250 mmol), NH<sub>2</sub>OH·HCl (26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990  $\mu$ L, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 1.5 h. The crude material was purified by flash chromatography (2:1 hexanes/EtOAc eluent) to afford diyne **7o** (40.5 mg, 75% yield) as a yellow oil. The spectroscopic data for diyne **7o** was in agreement with literature data.<sup>6</sup>

**R<sub>f</sub>**: 0.50 (2:1 hexanes/EtOAc, KMnO<sub>4</sub>).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  4.55 (q, *J* = 6.6 Hz, 1H), 1.94 (s, 3H), 1.71 (s, 1H), 1.25 (d, *J* = 6.6 Hz, 3H).

### ((Hexa-2,4-diyn-1-yloxy)methyl)benzene (**7p**)



According to GP2, alkyne **S15** (73.1 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromopropyne (assume 0.750 mmol) using CuCl (24.8 mg, 0.250 mmol), NH<sub>2</sub>OH·HCl (26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990  $\mu$ L, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 1.5 h. The crude material was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford diyne **7p** (71.8 mg, 78% yield) as a clear oil.

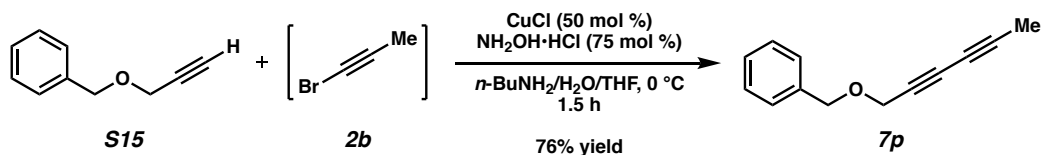
**R<sub>f</sub>**: 0.60 (9:1 hexanes/EtOAc, KMnO<sub>4</sub>).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.37-7.27 (comp. m, 5H), 4.60 (s, 2H), 4.22 (s, 2H), 1.95 (s, 3H).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>):  $\delta$  137.3, 128.6, 128.3, 128.1, 77.0, 71.70, 71.68, 71.2, 63.9, 57.7, 4.4.

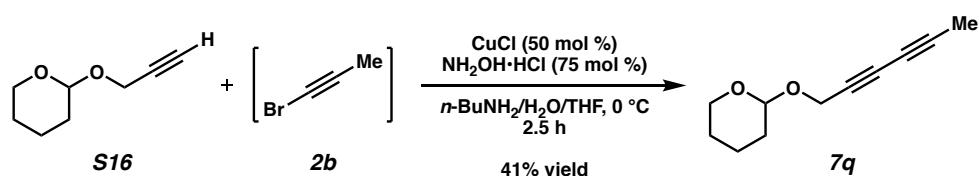
**IR** (film): 3031, 2847, 2257, 1350, 1073 cm<sup>-1</sup>.

**HRMS** (ESI+) *m/z* calc. for (M + H)<sup>+</sup> [C<sub>13</sub>H<sub>12</sub>O + H]<sup>+</sup>: 185.0966, found 185.0961.



(Gram scale experiment) According to GP2, alkyne **S15** (1.10 g, 7.52 mmol) was subjected to the coupling with in situ generated 1-bromopropyne (assume 11.3 mmol) using CuCl (372 mg, 3.76 mmol), NH<sub>2</sub>OH·HCl (392 mg, 5.64 mmol), *n*-BuNH<sub>2</sub> (14.9 mL, 150 mmol), and H<sub>2</sub>O (25.1 mL) for 1.5 h. The crude material was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford diyne **7p** (1.05 g, 76% yield) as a clear oil.

### 2-(Hexa-2,4-diyn-1-yloxy)tetrahydro-2H-pyran (**7q**)



According to GP2, alkyne **S16** (70.1 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromopropyne (assume 0.750 mmol) using CuCl (24.8 mg, 0.250 mmol), NH<sub>2</sub>OH·HCl (26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990 μL, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 2.5 h. The crude material was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to afford diyne **7q** (26.3 mg, 41% yield) as a yellow oil.

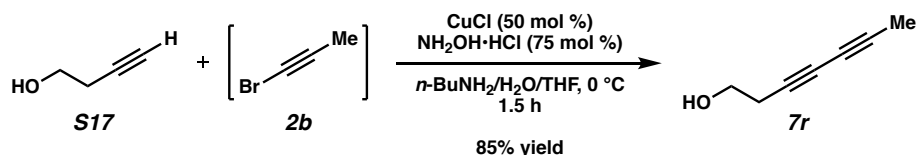
**R<sub>f</sub>**: 0.69 (4:1 hexanes/EtOAc, KMnO<sub>4</sub>).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 4.81 (br. t, *J* = 3.3 Hz, 1H), 4.31 (s, 2H), 3.82 (ddd, *J* = 11.6, 8.8, 3.3 Hz, 1H), 3.56-3.50 (m, 1H), 1.93 (s, 3H), 1.90-1.69 (comp. m, 2H), 1.70-1.47 (comp. m, 4H). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ 96.9, 76.7, 71.2, 71.0, 63.9, 62.1, 54.6, 30.3, 25.4, 19.1, 4.4.

**IR** (film): 2943, 2851, 2259, 1440, 1343 cm<sup>-1</sup>.

**HRMS** (ESI+) *m/z* calc. for (M + Na)<sup>+</sup> [C<sub>11</sub>H<sub>14</sub>O<sub>2</sub> + Na]<sup>+</sup>: 201.0891, found 201.0886.

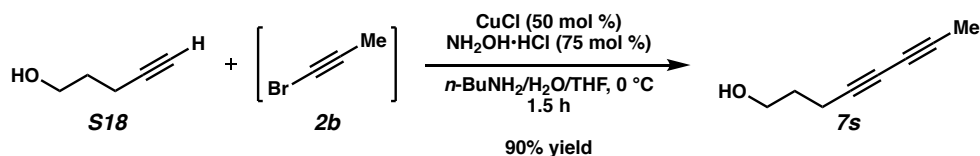
### Hepta-3,5-diyn-1-ol (**7r**)



According to GP2, alkyne **S17** (35.0 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromopropyne (assume 0.750 mmol) using CuCl (24.8 mg, 0.250 mmol), NH<sub>2</sub>OH·HCl (26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990 μL, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 1.5 h. The crude material was purified by flash chromatography (2:1 hexanes/EtOAc eluent) to afford diyne **7r** (46.2 mg, 85% yield) as a yellow oil. The spectroscopic data for diyne **7r** was in agreement with literature data.<sup>7</sup>

**R<sub>f</sub>**: 0.35 (2:1 hexanes/EtOAc, KMnO<sub>4</sub>).

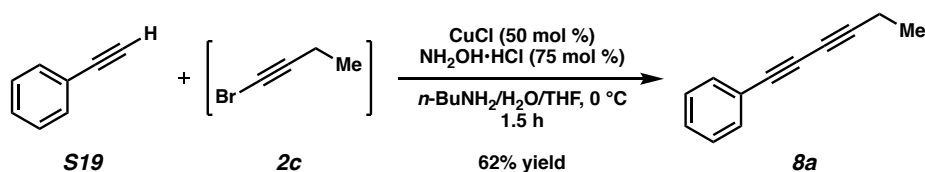
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 3.74 (app. q, *J* = 5.8 Hz, 2H), 2.53 (t, *J* = 5.8 Hz, 2H), 1.91 (s, 3H), 1.72 (t, *J* = 5.8 Hz, 1H).

**Octa-4,6-diyn-1-ol (7s)**

According to GP2, alkyne **S18** (42.1 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromopropyne (assume 0.750 mmol) using CuCl (24.8 mg, 0.250 mmol), NH<sub>2</sub>OH·HCl (26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990 μL, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 1.5 h. The crude material was purified by flash chromatography (2:1 hexanes/EtOAc eluent) to afford diyne **7s** (54.9 mg, 90% yield) as a yellow oil. The spectroscopic data for diyne **7s** was in agreement with literature data.<sup>8</sup>

**R<sub>f</sub>**: 0.27 (2:1 hexanes/EtOAc, KMnO<sub>4</sub>).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 3.75 (app. q, *J* = 5.5 Hz, 2H), 2.38 (t, *J* = 6.9 Hz, 2H), 1.90 (s, 3H), 1.78 (app. quintet, *J* = 6.5 Hz, 2H), 1.36 (br. t, *J* = 4.4 Hz, 1H).

**Hexa-1,3-diyn-1-ylbenzene (8a)**

According to GP2, alkyne **S19** (51.1 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromobut-1-yne (assume 0.750 mmol) using CuCl (24.8 mg, 0.250 mmol), NH<sub>2</sub>OH·HCl (26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990 μL, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 1.5 h. The crude material was purified by flash chromatography (hexanes eluent) to afford diyne **8a** (48.1 mg, 62% yield) as a pale yellow oil.

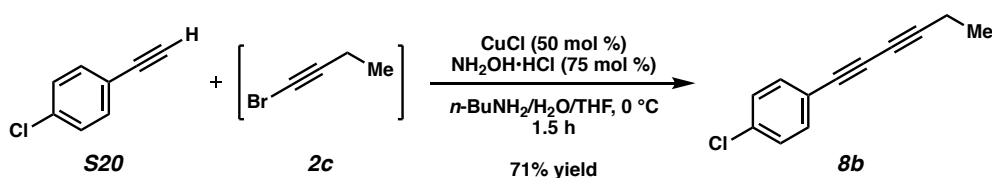
**R<sub>f</sub>**: 0.59 (100% hexanes, KMnO<sub>4</sub>).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 7.47 (dd, *J* = 7.5, 1.4 Hz, 2H), 7.36-7.27 (comp. m, 3H), 2.38 (q, *J* = 7.5 Hz, 2H), 1.21 (t, *J* = 7.5 Hz, 3H).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ 132.6, 128.9, 128.5, 122.2, 86.0, 74.9, 74.4, 64.6, 13.44, 13.43.

**IR** (film): 2979, 2938, 2243, 1489, 688 cm<sup>-1</sup>.

**HRMS** (ESI+) *m/z* calc. for (M + H)<sup>+</sup> [C<sub>12</sub>H<sub>10</sub> + H]<sup>+</sup>: 155.0861, found 155.0855.

**1-Chloro-4-(hexa-1,3-diyn-1-yl)benzene (8b)**

According to GP2, alkyne **S20** (68.3 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromobut-1-yne (assume 0.750 mmol) using CuCl (24.8 mg, 0.250 mmol), NH<sub>2</sub>OH·HCl

(26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990  $\mu$ L, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 1.5 h. The crude material was purified by flash chromatography (hexanes eluent) to afford diyne **8b** (67.1 mg, 71% yield) as a white solid.

**R<sub>f</sub>**: 0.59 (100% hexanes, KMnO<sub>4</sub>).

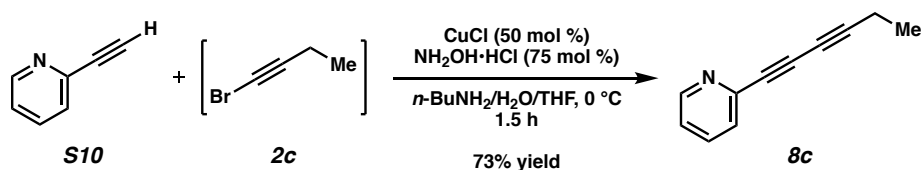
**<sup>1</sup>H NMR** (400 MHz, C<sub>6</sub>D<sub>6</sub>):  $\delta$  6.97 (d, *J* = 8.5 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 1.85 (q, *J* = 7.5 Hz, 2H), 0.78 (t, *J* = 7.5 Hz, 3H).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>):  $\delta$  135.0, 133.8, 128.9, 120.7, 85.7, 75.4, 73.7, 64.4, 13.5, 13.4.

**IR** (film): 2981, 2938, 2242, 1488, 549 cm<sup>-1</sup>.

**HRMS** (ESI+) *m/z* calc. for (M + H)<sup>+</sup> [C<sub>12</sub>H<sub>9</sub>Cl + H]<sup>+</sup>: 189.0471, found 189.0468.

## 2-(Hexa-1,3-diyn-1-yl)pyridine (**8c**)



According to GP2, alkyne **S10** (51.6 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromobut-1-yne (assume 0.750 mmol) using CuCl (24.8 mg, 0.250 mmol), NH<sub>2</sub>OH·HCl (26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990  $\mu$ L, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 1.5 h. The crude material was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to afford diyne **8c** (55.3 mg, 73% yield) as a yellow oil.

**R<sub>f</sub>**: 0.41 (4:1 hexanes/EtOAc, KMnO<sub>4</sub>).

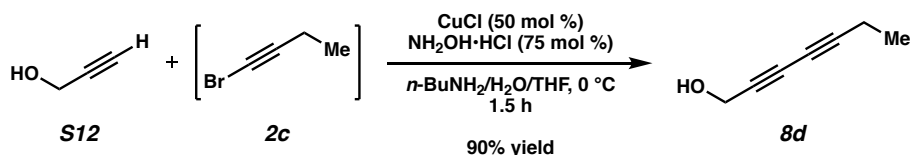
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.56 (d, *J* = 5.1 Hz, 1H), 7.63 (app. t, *J* = 7.7 Hz, 1H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.24 (dd, *J* = 7.7, 5.1 Hz, 2H), 2.38 (q, *J* = 7.5 Hz, 2H), 1.21 (t, *J* = 7.5 Hz, 3H).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>):  $\delta$  150.2, 142.5, 136.2, 128.0, 123.3, 87.2, 74.4, 73.7, 64.3, 13.4, 13.2.

**IR** (film): 3051, 2980, 2938, 2233, 1464 cm<sup>-1</sup>.

**HRMS** (ESI+) *m/z* calc. for (M + H)<sup>+</sup> [C<sub>11</sub>H<sub>9</sub>N + H]<sup>+</sup>: 156.0813, found 156.0807.

## Hepta-2,4-diyn-1-ol (**8d**)



According to GP2, alkyne **S12** (28.0 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromobut-1-yne (assume 0.750 mmol) using CuCl (24.8 mg, 0.250 mmol), NH<sub>2</sub>OH·HCl (26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990  $\mu$ L, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 1.5 h. The crude material was purified by flash chromatography (2:1 hexanes/EtOAc eluent) to afford diyne **8d** (48.7 mg, 90% yield) as a yellow oil.

**R<sub>f</sub>**: 0.44 (2:1 hexanes/EtOAc, KMnO<sub>4</sub>).

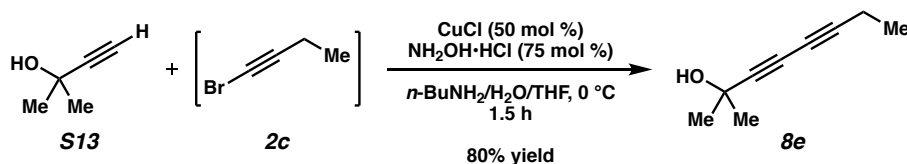
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  4.32 (d, *J* = 5.6 Hz, 2H), 2.30 (q, *J* = 7.5 Hz, 2H), 1.55 (br. t, *J* = 5.6 Hz, 1H), 1.77 (t, *J* = 7.5 Hz, 3H).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>):  $\delta$  83.0, 73.8, 70.9, 63.9, 51.6, 13.3, 13.1.

**IR** (film): 3330 (br), 2939, 2257, 1023, 776 cm<sup>-1</sup>.

Attempts to acquire mass data for diyne **8d** were unsuccessful, including ESI (positive or negative), EESI, MALDI, as well as two attempts at elemental analysis.

## 2-Methylocta-3,5-diyne-2-ol (**8e**)



According to GP2, alkyne **S13** (42.1 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromobut-1-yne (assume 0.750 mmol) using CuCl (24.8 mg, 0.250 mmol), NH<sub>2</sub>OH·HCl (26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990  $\mu$ L, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 1.5 h. The crude material was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to afford diyne **8e** (54.6 mg, 80% yield) as a yellow oil.

**R<sub>f</sub>**: 0.47 (4:1 hexanes/EtOAc, KMnO<sub>4</sub>).

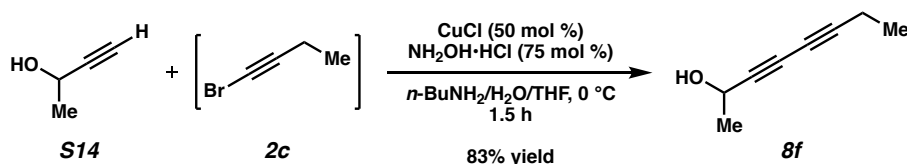
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  2.29 (q,  $J$  = 7.5 Hz, 2H), 1.90 (s, 1H), 1.52 (s, 6H), 1.16 (t,  $J$  = 7.5 Hz, 3H).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>):  $\delta$  83.1, 80.1, 67.4, 65.7, 63.8, 31.3, 13.3, 13.1.

**IR** (film): 3358 (br), 2982, 2938, 2255, 1155 cm<sup>-1</sup>.

**HRMS** (ESI+)  $m/z$  calc. for (M<sup>+</sup>) [C<sub>9</sub>H<sub>12</sub>O<sup>+</sup>]: 136.0888, found 136.0885.

## Octa-3,5-diyne-2-ol (**8f**)



According to GP2, alkyne **S14** (35.0 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromobut-1-yne (assume 0.750 mmol) using CuCl (24.8 mg, 0.250 mmol), NH<sub>2</sub>OH·HCl (26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990  $\mu$ L, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 1.5 h. The crude material was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to afford diyne **8f** (50.4 mg, 83% yield) as a yellow oil.

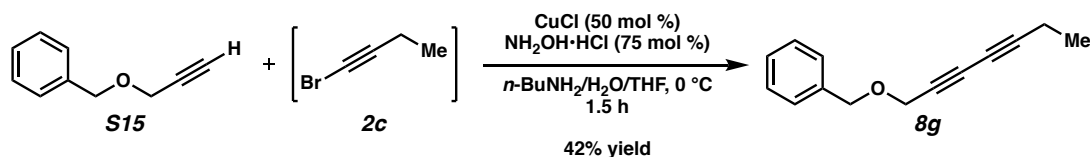
**R<sub>f</sub>**: 0.42 (4:1 hexanes/EtOAc, KMnO<sub>4</sub>).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  4.56 (app. quintet,  $J$  = 6.3 Hz, 1H), 2.29 (q,  $J$  = 7.5 Hz, 2H), 1.79 (d,  $J$  = 5.4 Hz, 1H), 1.46 (d,  $J$  = 6.3 Hz, 3H), 1.17 (t,  $J$  = 7.5 Hz, 3H).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>):  $\delta$  83.1, 77.4, 69.2, 63.8, 58.9, 24.2, 13.3, 13.1.

**IR** (film): 3342 (br), 2981, 2938, 2255, 1100 cm<sup>-1</sup>.

**HRMS** (ESI+)  $m/z$  calc. for (M + H)<sup>+</sup> [C<sub>8</sub>H<sub>10</sub>O + H]<sup>+</sup>: 123.0810, found 123.0804.

**((Hepta-2,4-diyn-1-yloxy)methyl)benzene (8g)**

According to GP2, alkyne **S15** (73.1 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromobutyne (assume 0.750 mmol) using CuCl (24.8 mg, 0.250 mmol), NH<sub>2</sub>OH·HCl (26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990 μL, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 1.5 h. The crude material was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford diyne **8g** (41.8 mg, 42% yield) as a clear oil.

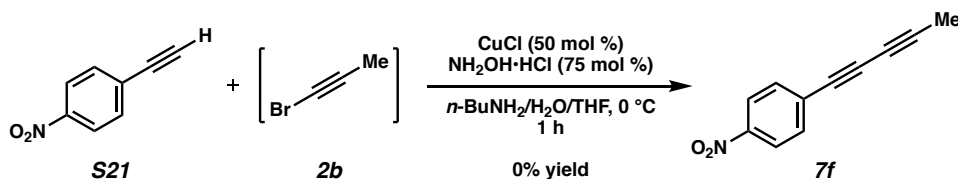
**R<sub>f</sub>**: 0.39 (9:1 hexanes/EtOAc, KMnO<sub>4</sub>).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 7.37-7.27 (comp. m, 5H), 4.60 (s, 2H), 4.23 (s, 2H), 2.31 (q, *J* = 7.5 Hz, 2H), 1.18 (t, *J* = 7.5 Hz, 3H).

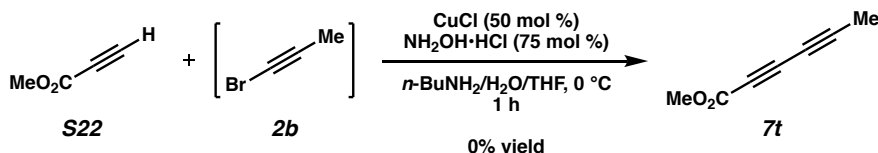
**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ 137.3, 128.6, 128.3, 128.1, 82.5, 71.9, 71.7, 71.6, 64.1, 57.8, 13.3, 13.1.

**IR** (film): 3031, 2979, 2256, 1073, 698 cm<sup>-1</sup>.

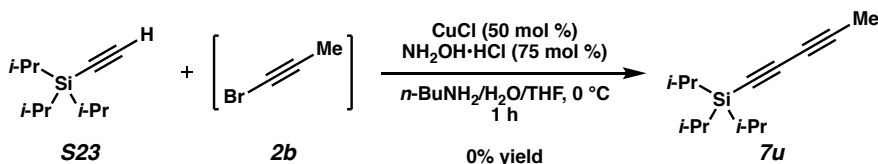
**HRMS** (ESI<sup>+</sup>) *m/z* calc. for (M + H)<sup>+</sup> [C<sub>14</sub>H<sub>14</sub>O + H]<sup>+</sup>: 199.1123, found 199.1118.

*Unsuccessful couplings*

According to GP2, alkyne **S21** (73.6 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromopropyne (assume 0.750 mmol) using CuCl (24.8 mg, 0.250 mmol), NH<sub>2</sub>OH·HCl (26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990 μL, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 1 h. No product was observed by crude <sup>1</sup>H NMR.



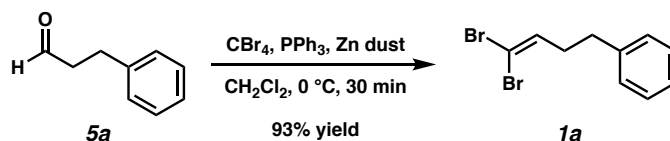
According to GP2, alkyne **S22** (42.0 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromopropyne (assume 0.750 mmol) using CuCl (24.8 mg, 0.250 mmol), NH<sub>2</sub>OH·HCl (26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990 μL, 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 1 h. No product was observed by crude <sup>1</sup>H NMR.





According to GP2, alkyne **S23** (91.2 mg, 0.500 mmol) was subjected to the coupling with in situ generated 1-bromopropyne (assume 0.750 mmol) using CuCl (24.8 mg, 0.250 mmol),  $\text{NH}_2\text{OH}\cdot\text{HCl}$  (26.1 mg, 0.375 mmol), *n*-BuNH<sub>2</sub> (990  $\mu\text{L}$ , 10.0 mmol), and H<sub>2</sub>O (1.70 mL) for 1 h. No product was observed by crude <sup>1</sup>H NMR.

## Coupling Optimization

(4,4-Dibromobut-3-en-1-yl)benzene (**1a**)

According to GP1, 1,1-dibromoalkene **1a** was prepared. After the plug, the dibromoolefin was purified via column chromatography (hexanes eluent) to afford **1a** as a yellow oil (2.05 g, 93% yield). The spectroscopic data for alkene **1a** matched the reported data.<sup>9</sup>

<sup>1</sup>H NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.33–7.28 (comp. m, 2H), 7.24–7.17 (comp. m, 2H), 6.42 (t,  $J = 7.2$  Hz, 1H), 2.74 (t,  $J = 7.7$  Hz, 2H), 2.42 (app. q,  $J = 7.7$  Hz, 2H).

Table 1 (reproduced).

Reaction scheme showing the synthesis of **4a,b** from **1a,b**. **1a,b** (1,1-dibromoalkene) undergoes base-mediated elimination to form **2a,b** (alkyne). **2a,b** then reacts with **3** (an enyne derivative) in the presence of  $\text{CuCl}$ ,  $\text{NH}_2\text{OH}\cdot\text{HCl}$ , and  $n\text{-BuNH}_2$  in a solvent at  $0$  to  $23^\circ\text{C}$  to yield **4a,b**.

entry	equiv <b>1</b>	Base (equiv)	catalyst (mol %)	mol % $\text{NH}_2\text{OH}\cdot\text{HCl}$	equiv $n\text{-BuNH}_2$	solvent	time (h)	isolated yield (%)
<b>R = <math>-\text{CH}_2\text{CH}_2\text{Ph}</math> (a)</b>								
1	—	NaH (2)	—	—	—	—	—	— <sup>b</sup>
2	2.0	TBAF·3H <sub>2</sub> O (10)	CuCl (20)	30	30	DMF	24	0
3	2.0	LiHMDS (2.0)	CuCl (20)	30	2	DMF	24	21
4	2.0	LiHMDS (2.0)	CuI (2) Pd(dba) <sub>3</sub> (4)	0	2 <sup>c</sup>	DMF	24	0
5	2.0	LiHMDS (2.0)	CuCl (20) Pd(dba) <sub>3</sub> (4)	30	2	THF	18	14
6	2.0	LiHMDS (2.0)	CuCl (50)	150	10	THF	18	28
7	2.0	LiHMDS (2.0)	CuCl (20)	30	10	H <sub>2</sub> O/THF	18	49
8	2.0	LiHMDS (2.0)	CuCl (20)	30	20	H <sub>2</sub> O/THF	3	80
<b>R = <math>-\text{CH}_3</math> (b)</b>								
9	2.0	LiHMDS (2.0)	CuCl (20)	30	20	H <sub>2</sub> O/THF	18	44
10	2.5	LiHMDS (2.5)	CuCl (20)	30	20	H <sub>2</sub> O/THF	1	27
11	1.0	LiHMDS (1.0)	CuCl (20)	30	20	H <sub>2</sub> O/THF	1	57
12	1.5	LiHMDS (1.5)	CuCl (20)	30	20	H <sub>2</sub> O/THF	1	69
13	1.5	LiHMDS (1.5)	CuCl (40)	60	20	H <sub>2</sub> O/THF	1	72

<sup>a</sup> Elimination conditions: NaH: THF,  $0$  to  $23^\circ\text{C}$ , 24 h; TBAF·3H<sub>2</sub>O: DMF,  $60^\circ\text{C}$ , 3 h; LiHMDS: THF,  $-78$  to  $0^\circ\text{C}$ , 1.5 h. <sup>b</sup> Bromoalkyne intermediate **2a** was not observed; coupling was not attempted. <sup>c</sup> Et<sub>3</sub>N used as base instead of  $n\text{-BuNH}_2$ .

## General optimization procedures:

## Using NaH (entry 1):

To a solution of 1,1-dibromoalkene **1a** (1.00 equiv) in anhydrous THF (0.1 M) under argon at  $0^\circ\text{C}$ , NaH (60% dispersion in mineral oil, 1.05 equiv in relation to the terminal alkyne) was added in two portions. After stirring at  $0^\circ\text{C}$  for 30 min, the reaction was allowed to warm to room temperature and was stirred for 24 h. The reaction was quenched with H<sub>2</sub>O and the aqueous layer was extracted

with EtOAc (3x). The organic layers were combined, washed with brine, dried over  $\text{MgSO}_4$ , and concentrated in vacuo. No bromoalkyne was observed under these conditions by crude  $^1\text{H}$  NMR.

*Using TBAF•3H<sub>2</sub>O (entry 2):*

To a solution of 1,1-dibromoalkene **1a** (2.00 equiv in relation to the terminal alkyne) in anhydrous DMF (0.4 M) under argon at room temperature, TBAF•3H<sub>2</sub>O (5.00 equiv in relation to dibromoalkene **1a**) was added. The reaction was heated to 60 °C and allowed to stir for 3 h, at which point it was allowed to cool to room temperature. The resulting solution of 1-bromoalkyne was carried on immediately to the next reaction.

*Using LiHMDS (entries 3-13):*

To a mixture of freshly distilled HMDS (1.05-2.08 equiv) in anhydrous THF (1.45 M) under argon at -78 °C, *n*-BuLi (2.5 M in hexanes, 1.00-2.00 equiv) was added dropwise. The LiHMDS was generated over 30 min stirring at -78 °C. In a separate flask, dibromoalkene **1a** or **1b** (1.00-2.00 equiv in relation to the terminal alkyne, equal amount to LiHMDS) was dissolved in anhydrous THF (1.45 M) under argon, and the solution was cooled to -78 °C. To this solution, the LiHMDS solution was added dropwise. The reaction mixture was stirred for 30 min at -78 °C, and then it was warmed to 0 °C and stirred for an additional 1 h to ensure complete elimination. The resulting solution of 1-bromoalkyne was carried on immediately to the next reaction.

*Coupling Reaction using CuCl, NH<sub>2</sub>OH•HCl, and Pd(dba)<sub>2</sub> (entries 4,5):*

While the elimination was ongoing, in a separate flask, Cu halide (2 or 20 mol %), Pd(dba)<sub>2</sub> (4 mol %), and NH<sub>2</sub>OH•HCl (0 or 0.300 equiv) were added to a stirred solution of Et<sub>3</sub>N (2.00 equiv) in DMF (0.60 M, in relation to terminal alkyne) or *n*-BuNH<sub>2</sub> (2.00 equiv) in THF (1.0 M, in relation to terminal alkyne) under argon at 0 °C. A solution of the terminal alkyne (1.00 equiv) in THF or DMF (0.50 M) was added. Quickly following, the solution of freshly generated 1-bromoalkyne (held at 0 °C) was then added to the reaction mixture via syringe, and the resulting mixture was allowed to stir at 0 °C until the reaction went to completion. The dark brown mixture was then poured into EtOAc, the phases were separated, and the aqueous layer was extracted with EtOAc (2x). The organic layers were combined, washed with brine, dried over  $\text{MgSO}_4$ , and concentrated in vacuo. The crude material was purified by flash chromatography to afford the diyne product.

*Coupling Reaction using CuCl and NH<sub>2</sub>OH•HCl - non-aqueous (entries 3,6):*

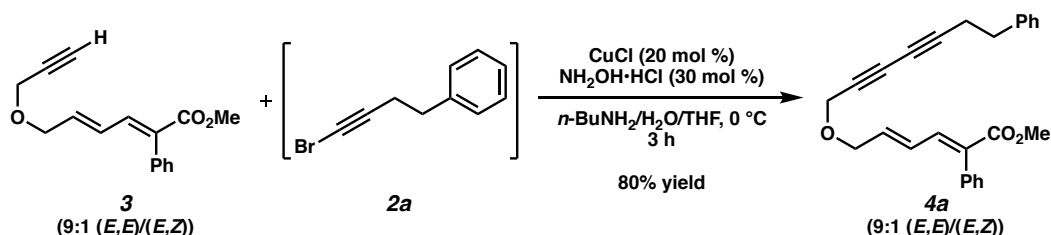
While the elimination was ongoing, in a separate flask, CuCl (0.200 to 0.500 equiv) was added to a stirred solution of *n*-BuNH<sub>2</sub> (2.00 to 20.0 equiv) and DMF (0.60 M, in relation to terminal alkyne) or THF (1.0 M, in relation to terminal alkyne) under argon at 0 °C, resulting in a deep blue solution. NH<sub>2</sub>OH•HCl (0.300 to 0.600 equiv) was added, returning the mixture to colorless. A solution of the terminal alkyne (1.00 equiv) in DMF or THF (0.5 M) was added to the reaction mixture, resulting in a bright yellow solution. Quickly following, the solution of freshly generated 1-bromoalkyne (held at 0 °C) was then added to the reaction mixture via syringe, and the resulting mixture was allowed to stir at 0 °C until the reaction went to completion. The dark brown mixture was then poured into EtOAc, the phases were separated, and the aqueous layer was extracted with EtOAc (2x). The organic layers were combined, washed with brine, dried over  $\text{MgSO}_4$ , and concentrated in vacuo. The crude material was purified by flash chromatography to afford the diyne product.

*Coupling Reaction using CuCl and NH<sub>2</sub>OH•HCl - aqueous (entries 7-13):*

While the elimination was ongoing, in a separate flask, CuCl (0.200 to 0.500 equiv) was added to a stirred solution of *n*-BuNH<sub>2</sub> (2.00 to 20.0 equiv) and H<sub>2</sub>O (0.30 M) under argon at 0 °C, resulting

in a deep blue solution.  $\text{NH}_2\text{OH}\cdot\text{HCl}$  (0.300 to 0.600 equiv) was added, returning the mixture to colorless. A solution of the terminal alkyne (1.00 equiv) in THF (0.5 M) was added to the reaction mixture, resulting in a bright yellow solution. Quickly following, the solution of freshly generated 1-bromoalkyne (held at 0 °C) was then added to the reaction mixture via syringe, and the resulting mixture was allowed to stir at 0 °C until the reaction went to completion. The dark brown mixture was then poured into EtOAc, the phases were separated, and the aqueous layer was extracted with EtOAc (2x). The organic layers were combined, washed with brine, dried over  $\text{MgSO}_4$ , and concentrated in vacuo. The crude material was purified by flash chromatography to afford the diyne product.

### Methyl (4*E*)-2-phenyl-6-((7-phenylhepta-2,4-diyn-1-yl)oxy)hexa-2,4-dienoate (4a)



**Table 1, Entry 8.** Alkyne **3** (40.0 mg, 0.156 mmol, 9:1 (*E,E*)/(*E,Z*) mixture) was subjected to the coupling with in situ generated bromoalkyne **2a** (assume 0.312 mmol) using  $\text{CuCl}$  (3.1 mg, 0.0312 mmol),  $\text{NH}_2\text{OH}\cdot\text{HCl}$  (3.3 mg, 0.0468 mmol),  $n\text{-BuNH}_2$  (308  $\mu\text{L}$ , 3.12 mmol), and  $\text{H}_2\text{O}$  (520  $\mu\text{L}$ ) for 3 h. The crude mixture of isomers was purified via column chromatography (9:1 hexanes/EtOAc eluent) to afford diyne **4a** (48.1 mg, 80% yield, 9:1 (*E,E*)/(*E,Z*)) as a pale yellow oil. *Note: The two alkene isomers were inseparable by column chromatography. Characterization data for the major isomer is presented.*

#### Major product (*E,E*):

**R<sub>f</sub>**: 0.68 (4:1 hexanes/EtOAc,  $\text{KMnO}_4$ ).

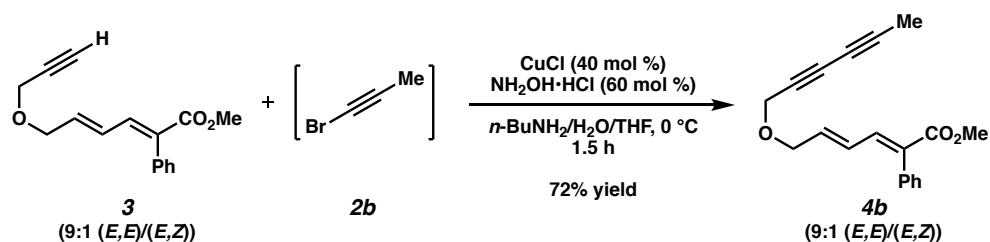
**<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.46 (d,  $J$  = 11.1 Hz, 1H), 7.42-7.27 (comp. m, 6H), 7.25-7.18 (comp. m, 5H), 6.31 (dd,  $J$  = 15.4, 11.1 Hz), 6.19 (dt,  $J$  = 15.4, 5.5 Hz, 1H), 4.16 (s, 2H), 4.09 (d,  $J$  = 5.5 Hz, 2H), 3.77 (s, 1H), 2.84 (d,  $J$  = 7.4 Hz, 2H), 2.57 (d,  $J$  = 7.4 Hz, 2H).

**<sup>13</sup>C NMR** (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  168.0, 140.1, 139.7, 138.0, 134.9, 133.1, 130.3, 128.8, 128.6, 128.5, 128.2, 127.9, 126.6, 80.5, 71.8, 69.7, 65.2, 59.2, 58.2, 52.4, 34.6, 21.6.

**IR** (film): 2949, 2254, 2188, 1711, 1434  $\text{cm}^{-1}$ .

**HRMS** (ESI<sup>+</sup>):  $m/z$  calc. for  $(\text{M} + \text{Na})^+ [\text{C}_{26}\text{H}_{24}\text{Na}]^+$ : 407.1623, found 407.1618.

### Methyl (4*E*)-6-(hexa-2,4-diyn-1-yloxy)-2-phenylhexa-2,4-dienoate (XX)

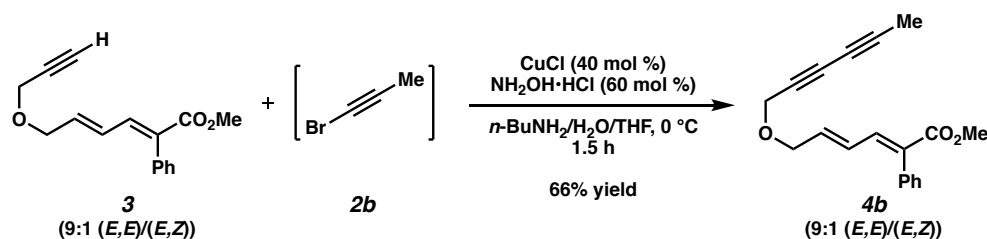


**Table 1, Entry 13.** According to GP2, alkyne **3** (50.0 mg, 0.195 mmol, 9:1 (*E,E*)/(*E,Z*) mixture) was subjected to the coupling with in situ generated 1-bromopropyne (assume 0.293 mmol) using  $\text{CuCl}$

(7.7 mg, 0.0780 mmol),  $\text{NH}_2\text{OH}\cdot\text{HCl}$  (8.1 mg, 0.117 mmol),  $n\text{-BuNH}_2$  (385  $\mu\text{L}$ , 3.90 mmol), and  $\text{H}_2\text{O}$  (650  $\mu\text{L}$ ) for 1.5 h. The crude mixture of isomers was purified via column chromatography (9:1 hexanes/EtOAc eluent) to afford diyne **4b** as a mixture of (*E,E*)- and (*E,Z*)-isomers (41.5 mg, 72% yield, 9:1 (*E,E*)/(*E,Z*)) as a pale yellow oil. *Note: The two alkene isomers were not separated by column chromatography. Characterization data for the major isomer is presented. The full spectroscopic data for diyne 4b have been previously reported.*<sup>10</sup>

**R<sub>f</sub>**: 0.44 (9:1 hexanes/EtOAc, anisaldehyde).

**<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.45 (d,  $J$  = 11.0 Hz, 1H), 7.39–7.34 (comp. m, 3H), 7.21 (d,  $J$  = 7.2 Hz, 2H), 6.30 (dd,  $J$  = 15.3, 11.0 Hz, 1H), 6.19 (dt,  $J$  = 15.3, 5.5 Hz, 1H), 4.15 (s, 2H), 4.08 (d,  $J$  = 5.5 Hz, 2H), 3.76 (s, 3H), 1.93 (s, 3H).

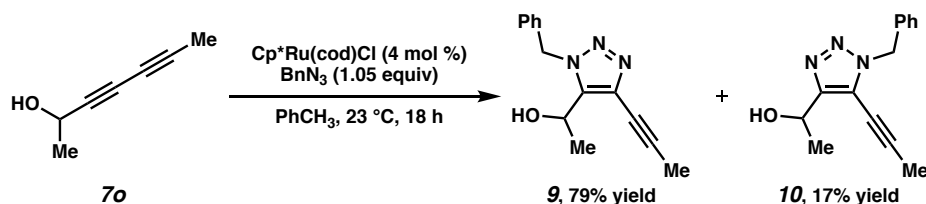


(*Multigram scale experiment*) According to GP2, alkyne **3** (15.4 g, 60.1 mmol, 9:1 (*E,E*)/(*E,Z*) mixture) was subjected to the coupling with in situ generated 1-bromopropyne (assume 90.2 mmol) using  $\text{CuCl}$  (23.8 g, 24.0 mmol),  $\text{NH}_2\text{OH}\cdot\text{HCl}$  (25.1 g, 36.1 mmol),  $n\text{-BuNH}_2$  (119 mL, 1200 mmol), and  $\text{H}_2\text{O}$  (200 mL) for 1.5 h. The crude mixture of isomers was purified via column chromatography (9:1 hexanes/EtOAc eluent) to afford diyne **4b** as a mixture of (*E,E*)- and (*E,Z*)-isomers (11.5 g, 66% yield, 9:1 (*E,E*)/(*E,Z*)) as a pale yellow oil.

## Azide-Alkyne Cycloadditions

### *Ru-catalyzed azide-alkyne cycloadditions*

#### 1-(1-benzyl-4-(prop-1-yn-1-yl)-1H-1,2,3-triazol-5-yl)ethan-1-ol (**9**) and 1-(1-benzyl-5-(prop-1-yn-1-yl)-1H-1,2,3-triazol-4-yl)ethan-1-ol (**10**)



In a glove box,  $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$  (5.6 mg, 0.0148 mmol) was weighed into a flame-dried vial equipped with a stirbar. The vial was sealed with a septa and removed from the box. Degassed toluene (2.47 mL) was added to the vial containing the catalyst. At room temperature, a degassed solution of the diyne (40.1 mg, 0.370 mmol) and benzyl azide (48.6  $\mu\text{L}$ , 0.389 mmol) in toluene (1.23 mL) in a flame-dried vial was added dropwise to the vial containing the catalyst in degassed toluene. The mixture stirred at room temperature until the reaction went to completion, at which time it was passed through a short plug of silica. The filtrate was concentrated in vacuo, and the crude residue was purified via flash chromatography (2:1 hexanes/EtOAc eluent) to give triazole **9** (70.5 mg, 79% yield) as a yellow oil and triazole **10** (15.2 mg, 17% yield) as a pale yellow oil.

#### Triazole **9**

**R<sub>f</sub>**: 0.30 (2:1 hexanes/EtOAc).

**<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.34-7.27 (m, 3H), 7.20-7.16 (m, 2H), 5.65 (ABq,  $J = 15.3$  Hz,  $\Delta\nu = 30.5$  Hz, 2H), 5.03 (app. quintet,  $J = 6.2$  Hz, 1H), 3.09 (d,  $J = 6.2$  Hz, 1H), 2.05 (s, 3H), 1.40 (d,  $J = 6.2$  Hz, 3H).

**<sup>13</sup>C NMR** (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  140.6, 135.3, 129.1, 129.0, 128.4, 127.5, 91.9, 69.1, 61.3, 52.9, 22.3, 4.6.

**IR** (film): 3311 (br), 3069, 3033, 2980, 2249, 1456  $\text{cm}^{-1}$ .

**HRMS** (ESI+)  $m/z$  calc. for  $(\text{M} + \text{H})^+$  [ $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O} + \text{H}$ ] $^+$ : 242.1293, found 242.1289.

#### Triazole **10**

**R<sub>f</sub>**: 0.15 (2:1 hexanes/EtOAc).

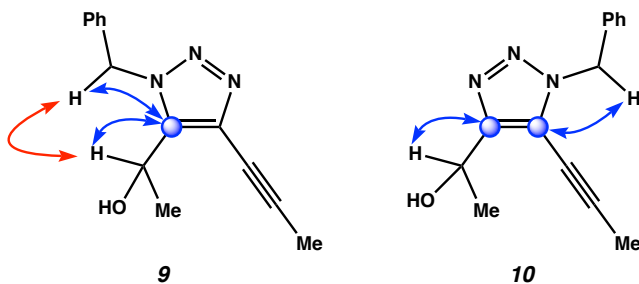
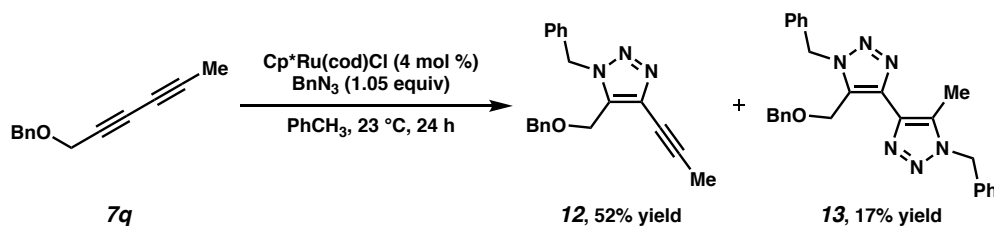
**<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.38-7.28 (m, 5H), 5.51 (s, 2H), 5.05 (app. quintet,  $J = 6.5$  Hz, 1H), 2.40 (d,  $J = 6.5$  Hz, 1H), 2.13 (s, 3H), 1.62 (d,  $J = 6.6$  Hz, 3H).

**<sup>13</sup>C NMR** (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  134.9, 128.9, 128.6, 128.2, 100.1, 65.0, 63.3, 52.7, 22.7, 4.9.

**IR** (film): 3365 (br), 3069, 3034, 2244, 1497, 1456  $\text{cm}^{-1}$ .

**HRMS** (ESI+)  $m/z$  calc. for  $(\text{M} + \text{H})^+$  [ $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O} + \text{H}$ ] $^+$ : 242.1293, found 242.1288.

## HSQC (blue) and NOESY (red) Data

1-benzyl-5-((benzyloxy)methyl)-4-(prop-1-yn-1-yl)-1H-1,2,3-triazole (**12**) and 1,1'-dibenzyl-5-((benzyloxy)methyl)-5'-methyl-1H,1'H-4,4'-bi(1,2,3-triazole) (**13**)

In a glove box,  $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$  (12.4 mg, 0.0326 mmol) was weighed into a flame-dried round-bottom flask equipped with a stirbar. The flask was sealed with a septa and removed from the box. Degassed toluene (5.43 mL) was added to the flask containing the catalyst. At room temperature, a degassed solution of the diyne (**7q**, 150 mg, 0.814 mmol) and benzyl azide (107  $\mu\text{L}$ , 0.855 mmol) in toluene (1.23 mL) in a flame-dried vial was added dropwise to the flask containing the catalyst in degassed toluene. The reaction was stirred at room for 24 h, at which time it was passed through a short plug of silica. The filtrate was concentrated in vacuo, and the crude residue was purified via flash chromatography (4:1 hexanes/EtOAc eluent) to give the starting material diyne (**7q**, 34.4 mg, 23% yield) as a clear oil, triazole **12** (134 mg, 52% yield) as a green-yellow oil, and bistriazole **13** (62.3 mg, 17% yield) as a white solid.

**Triazole 12**

$R_f$ : 0.25 (4:1 hexanes/EtOAc).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.39-7.27 (comp. m, 8H), 7.18-7.12 (comp. m, 2H), 5.56 (s, 2H), 4.45 (s, 2H), 4.42 (s, 2H), 2.06 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  137.0, 134.6, 134.5, 132.3, 129.0, 128.6, 128.5, 128.3, 128.2, 127.8, 91.5, 72.4, 68.7, 59.0, 52.8, 4.6.

IR (film): 3064, 3032, 2916, 2862, 2245, 1454  $\text{cm}^{-1}$ .

HRMS (ESI+)  $m/z$  calc. for  $(\text{M} + \text{H})^+$  [ $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O} + \text{H}$ ] $^+$ : 318.1606 found 318.1601.

**Bistriazole 13**

$R_f$ : 0.10 (4:1 hexanes/EtOAc).

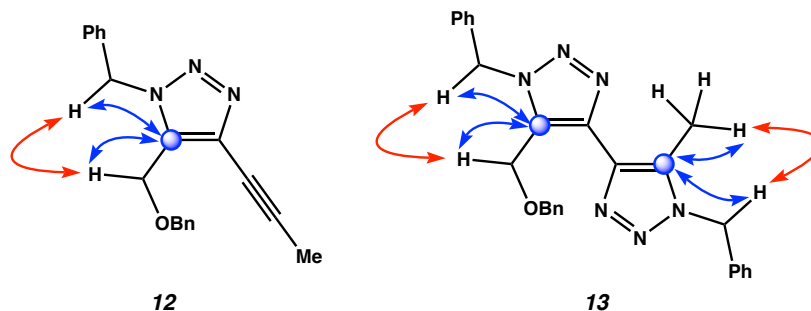
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.38-7.27 (comp. m, 10H), 7.25-7.15 (comp. m, 5H), 5.65 (s, 2H), 5.54 (s, 2H), 5.02 (s, 2H), 4.53 (s, 2H), 2.57 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  139.5, 137.64, 137.61, 134.9, 134.7, 131.8, 130.9, 129.2, 129.0, 128.6, 128.5, 128.4, 128.2, 128.1, 127.8, 127.4, 73.0, 60.1, 52.7, 52.0, 9.3.

**IR** (film): 3063, 2939, 2861, 2360, 1497, 1455  $\text{cm}^{-1}$ .

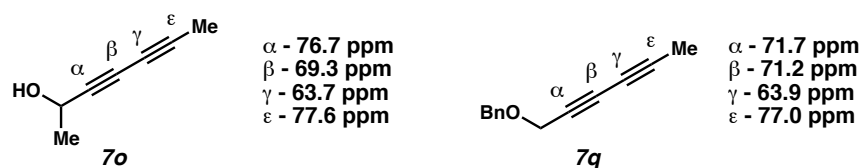
**HRMS** (ESI+)  $m/z$  calc. for  $(M + H)^+$  [ $\text{C}_{27}\text{H}_{26}\text{N}_6\text{O} + \text{H}$ ] $^+$ : 451.2246, found 451.2241.

### HSQC (blue) and NOESY (red) Data

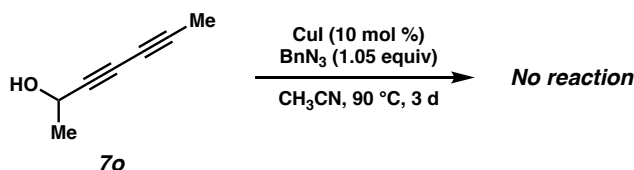


### Analysis of Regioselectivity with Respect to $^{13}\text{C}$ NMR Data

In the ruthenium-catalyzed azide alkyne cycloaddition, it is generally expected that absent other effects (e.g., H-bonding) the more nucleophilic carbon of an alkyne will become C-4 in the triazole, and the more electrophilic carbon will become C-5. In an attempt to ascertain alkyne carbon nucleophilicity in the substrates tested (**7o** and **7q**),  $^{13}\text{C}$  NMR data was analyzed. For both alcohol **7o** and ether **7q**, C( $\gamma$ ) is the most electron rich, but the C( $\alpha$ )-C( $\beta$ ) alkyne is the one that preferentially reacts. Although H-bonding can be invoked to rationalize the regioselectivity for diyne **7o**, ether **7q** cannot be similarly explained. Further, the data suggests similar electronic character at C( $\alpha$ ) and C( $\beta$ ), but the regioselectivity of this process appears to be exclusive. Further investigation will be necessary to elucidate the origins of this selectivity.

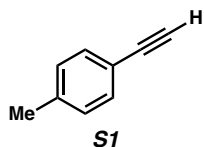


### Cu-catalyzed azide-alkyne cycloaddition attempt

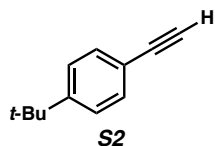


According to the procedure by Kundu and coworkers,<sup>11</sup> to a mixture of diyne **7o** (20.0 mg, 0.185 mmol) in anhydrous  $\text{CH}_3\text{CN}$  (950  $\mu\text{L}$ ) under argon at room temperature, benzyl azide (24.0  $\mu\text{L}$ , 0.194 mmol) and  $\text{CuI}$  (3.5 mg, 0.0185 mmol) were added. This was allowed to stir for roughly 10 min at room temperature and subsequently heated to 90  $^\circ\text{C}$  and allowed to stir for 3 d. The reaction was cooled to room temperature and filtered through a pad of celite. The solvent was removed by rotary evaporation. Only starting material was detected by  $^1\text{H}$  NMR; no product was formed.

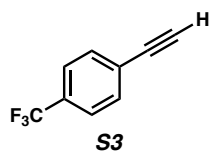


**Starting Material Syntheses**

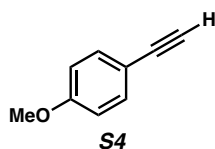
**Alkyne S1.** Prepared according to the procedure reported by Chen and coworkers.<sup>12</sup> The spectroscopic data was in agreement with the reported data.



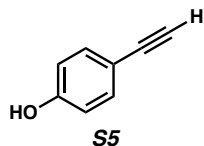
**Alkyne S2.** Prepared according to the procedure reported by Woodward and coworkers.<sup>13</sup> The spectroscopic data was in agreement with the reported data.



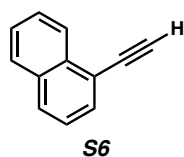
**Alkyne S3.** Prepared according to the procedure reported by Hashmi and coworkers.<sup>14</sup> The spectroscopic data was in agreement with the reported data.



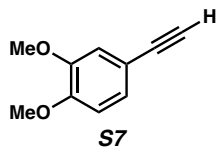
**Alkyne S4.** Prepared according to the procedure reported by Schilde and coworkers.<sup>15</sup> The spectroscopic data was in agreement with the reported data.



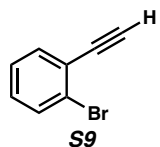
**Alkyne S5.** Prepared according to the procedure reported by Ros and coworkers.<sup>16</sup> The spectroscopic data was in agreement with the reported data.



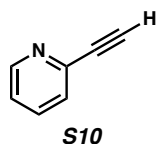
**Alkyne S6.** Prepared according to the procedure reported by Wang and coworkers.<sup>17</sup> The spectroscopic data was in agreement with the reported data.



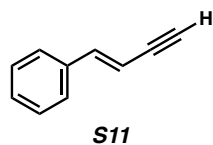
**Alkyne S7.** Prepared according to the procedure reported by Alexis and coworkers.<sup>18</sup> The spectroscopic data was in agreement with the reported data.



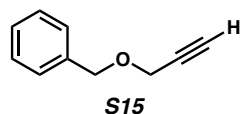
**Alkyne S9.** Prepared according to the procedure reported by Brückner and coworkers.<sup>19</sup> The spectroscopic data was in agreement with the reported data.



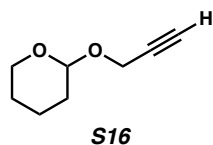
**Alkyne S10.** Prepared according to the procedure reported by Andrew and coworkers.<sup>20</sup> The spectroscopic data was in agreement with the reported data.



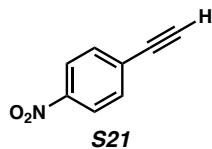
**Alkyne S11.** Prepared according to the procedure reported by Liu and coworkers.<sup>21</sup> The spectroscopic data was in agreement with the reported data.



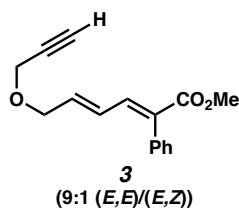
**Alkyne S15.** Prepared according to the procedure reported by Gandon and coworkers.<sup>22</sup> The spectroscopic data was in agreement with the reported data.



**Alkyne S16.** Prepared according our previously reported procedure.<sup>23</sup> The spectroscopic data was in agreement with the reported data.



**Alkyne S21.** Prepared according to the procedure reported by Schilde and coworkers.<sup>15</sup> The spectroscopic data was in agreement with the reported data.

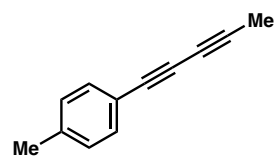


**Alkyne 3.** Prepared according to our previously reported procedure.<sup>10</sup> The spectroscopic data was in agreement with the reported data.

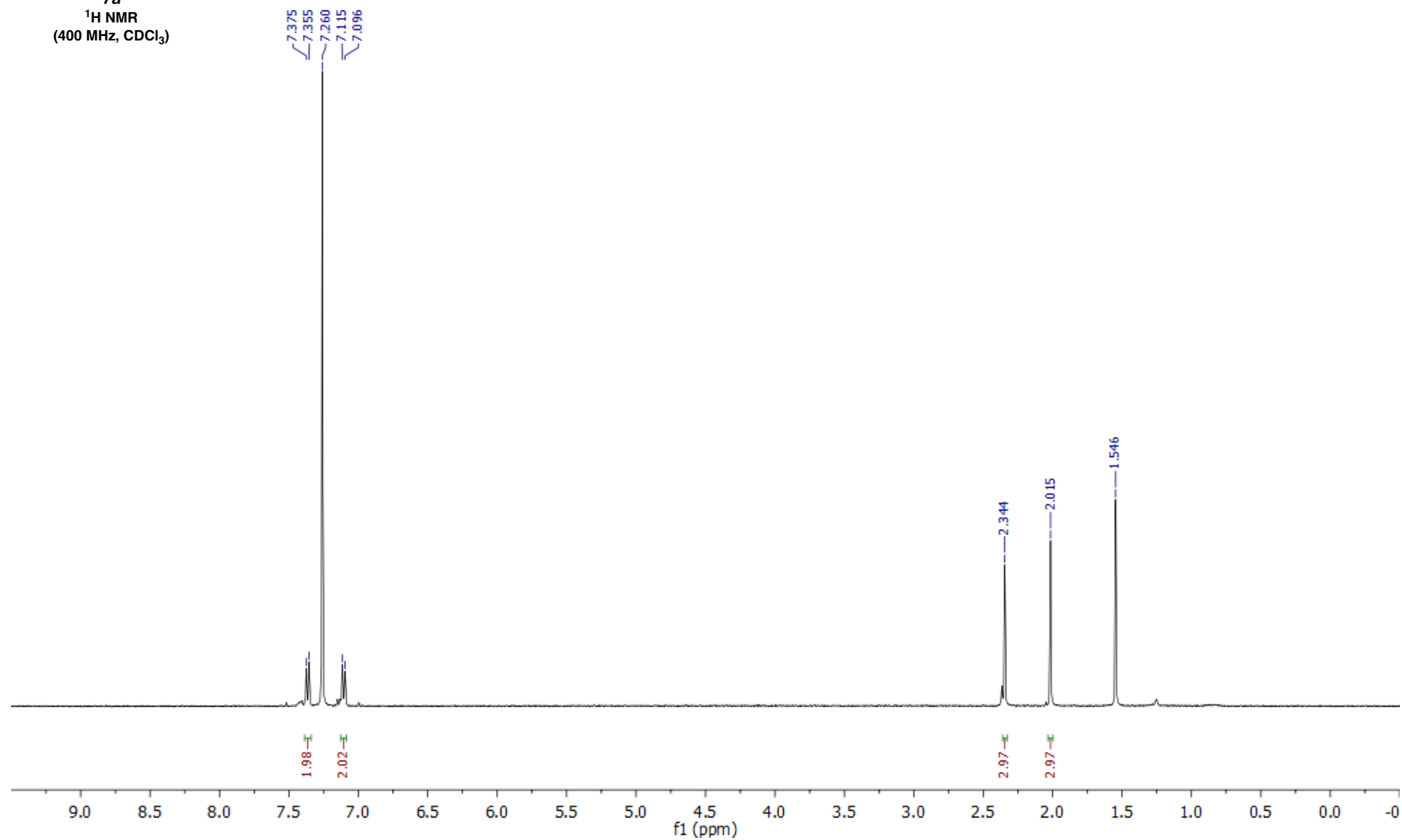
All other starting material alkynes were commercially obtained.

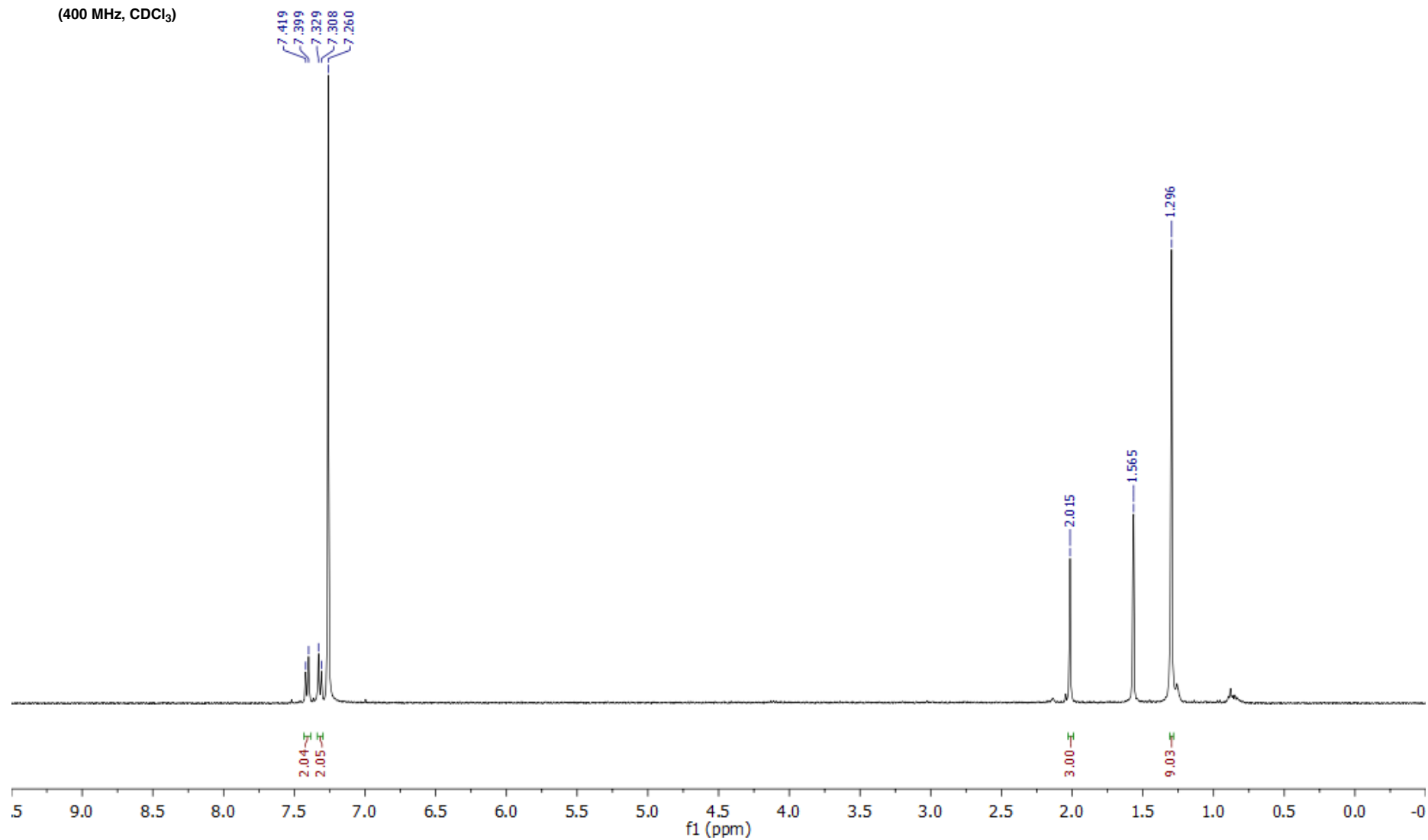
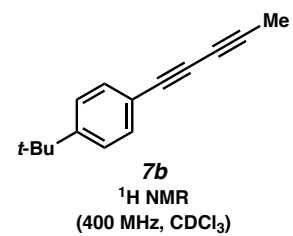
## References

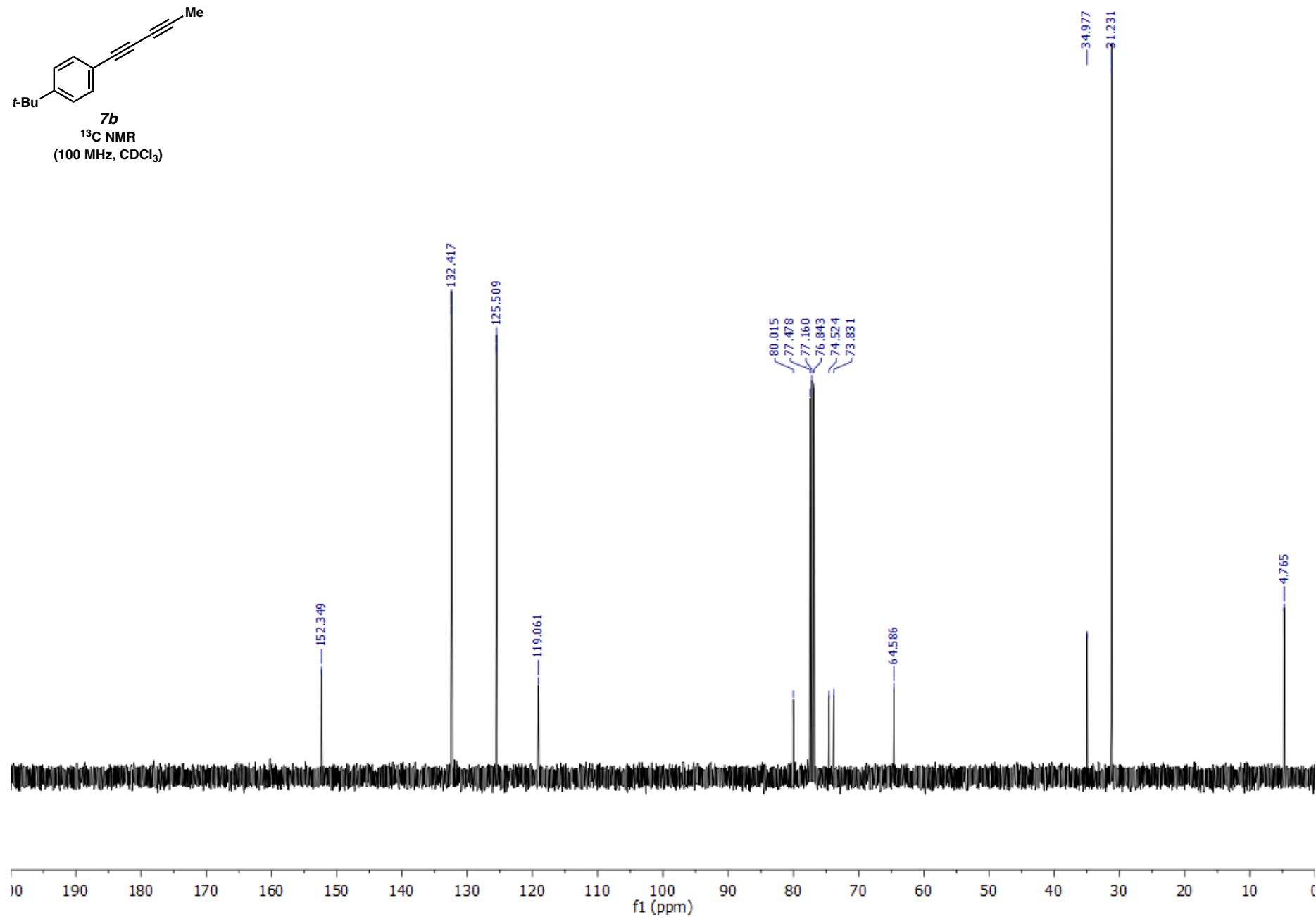
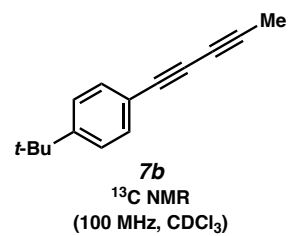
- <sup>1</sup> Perriot, P.; Normant, J. F.; Villieras, J. *C. R. Acad. Sci., Ser. C Chim.* **1979**, 289, 259.
- <sup>2</sup> Tang, S.; Erickson, K. L. *J. Nat. Prod.* **2008**, 71, 898.
- <sup>3</sup> Lysenko, S.; Volbeda, J.; Jones, P. G.; Tamm, M. *Angew. Chem. Int. Ed.* **2012**, 51, 6757.
- <sup>4</sup> Huang, Z.; Shang, R.; Zhang, Z.; Tan, X.; Xiao, X.; Fu, Y. *J. Org. Chem.* **2013**, 78, 4551.
- <sup>5</sup> Myrtle, J. D.; Beekman, A. M.; Barrow, R. A. *Org. Biomol. Chem.* **2016**, 14, 8253.
- <sup>6</sup> Bowling, N. P.; Burrmann, N. J.; Halter, R. J.; Hodges, J. A.; McMahon, R. J. *J. Org. Chem.* **2010**, 75, 6382.
- <sup>7</sup> Zhang, J.; Niu, D.; Brinker, V. A.; Hoyer, T. R. *Org. Lett.* **2016**, 18, 5596–5599.
- <sup>8</sup> Matovic, N. J.; Hayes, P. Y.; Penman, K.; Lehmann, R. P.; De Voss, J. J. *J. Org. Chem.* **2011**, 76, 4467.
- <sup>9</sup> Harada, T.; Katsuhira, T.; Kara, D.; Kotani, Y.; Maejima, K.; Kaji, R.; Oku, A. *J. Org. Chem.* **1993**, 58, 4897.
- <sup>10</sup> Newcomb, E. T.; Knutson, P. C.; Pedersen, B. A.; Ferreira, E. M. *J. Am. Chem. Soc.* **2016**, 138, 108.
- <sup>11</sup> Mandadapu, A. K.; Sharma, S. K.; Gupta, S.; Krishna, D. G. V.; Kundu, B. *Org. Lett.* **2011**, 13, 3162.
- <sup>12</sup> Ji, L.; Zhou, G. -Q.; Qian, C.; Chen, X. -Z. *Eur. J. Org. Chem.* **2014**, 3622.
- <sup>13</sup> Burroughs, L.; Ritchie, J.; Ngwenya, M.; Khan, D.; Lewis, W.; Woodward, S. *Beilstein J. Org. Chem.* **2015**, 11, 273.
- <sup>14</sup> Weingand, V.; Wurm, T.; Vethacke, V.; Dietl, M. C.; Ehjeij, D.; Rudolph, M.; Rominger, F.; Xie, J.; Hashmi, A. S. K. *Chem. Eur. J.* **2018**, 24, 3725.
- <sup>15</sup> Schmidt, B.; Berger, R.; Kelling, A.; Schilde, U. *Chem. Eur. J.* **2011**, 17, 7032.
- <sup>16</sup> Gimeno, N.; Martín-Rapún, R.; Rodríguez-Conde, S.; Serrano, J. L.; Folcia, C. L.; Pericás, M. A.; Ros, M. B. *J. Mater. Chem.* **2012**, 22, 16791.
- <sup>17</sup> Sirivolu, V. R.; Vernekar, S. K. V.; Ilina, T.; Myshakina, N. S.; Parniak, M. A.; Wang, Z. *J. Med. Chem.* **2013**, 56, 8765.
- <sup>18</sup> Koufaki, M.; Theodorou, E.; Galaris, D.; Nousis, L.; Katsanou, E. S.; Alexis, M. N. *J. Med. Chem.* **2006**, 49, 300.
- <sup>19</sup> Arican, D.; Brückner, R. *Org. Lett.* **2013**, 15, 2582.
- <sup>20</sup> Deems, G. S.; Andrew, T. Novel Triazole Compounds II, U.S. Patent 2012115868, May 10, 2012.
- <sup>21</sup> Mokar, B. D.; Liu, R. -S. *Chem. Commun.* **2014**, 50, 8966.
- <sup>22</sup> Li, H. -J.; Guillot, R.; Gandon, V. *J. Org. Chem.* **2010**, 75, 8435.
- <sup>23</sup> Allegretti, P. A.; Ferreira, E. M. *Org. Lett.* **2011**, 13, 5924.

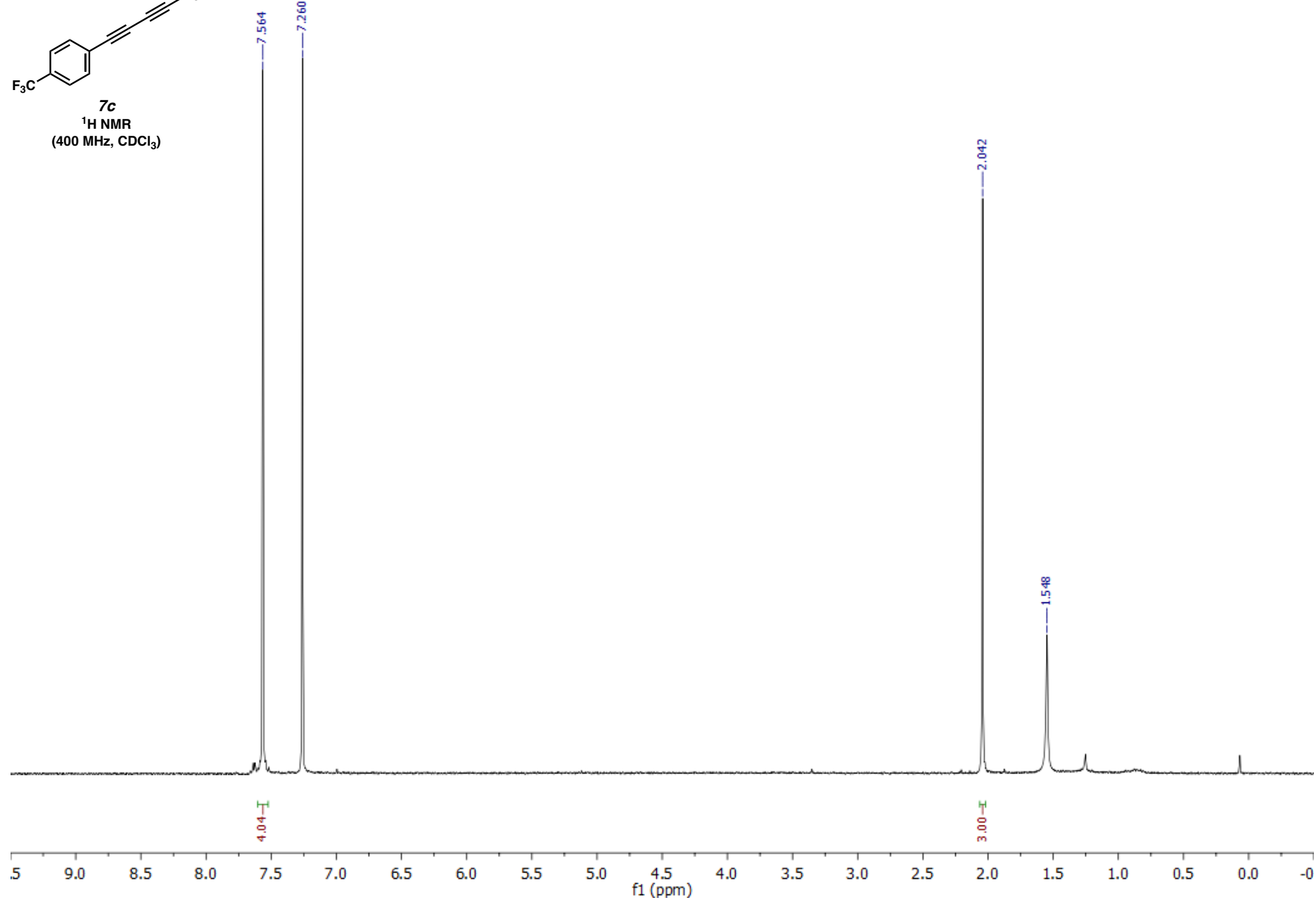
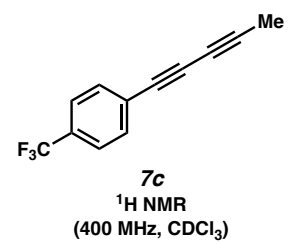


**7a**  
 $^1\text{H}$  NMR  
(400 MHz,  $\text{CDCl}_3$ )

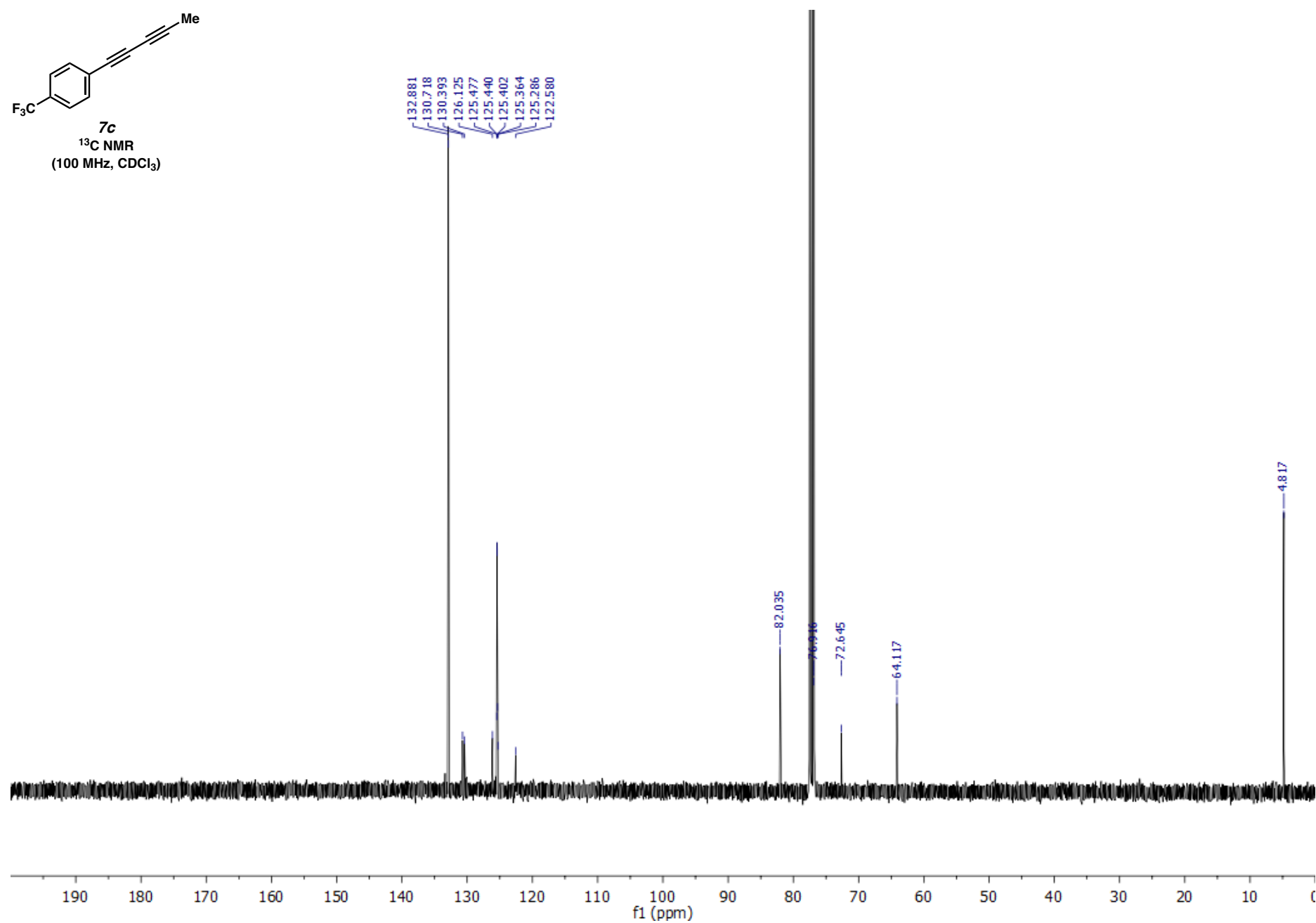
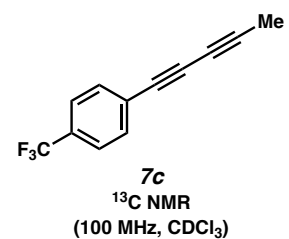


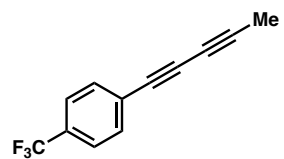




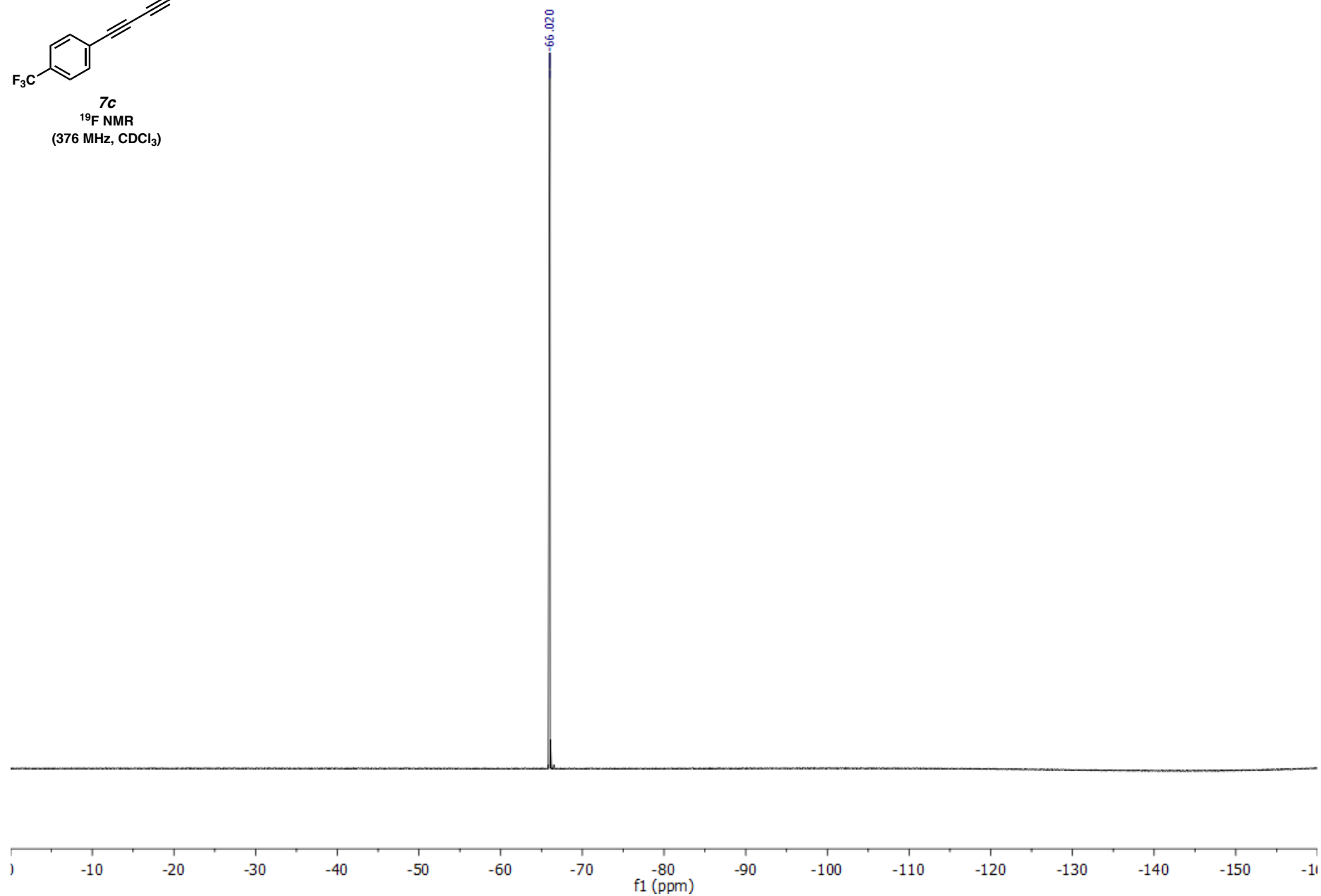


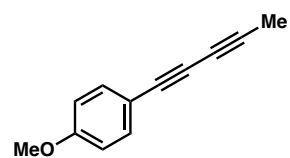




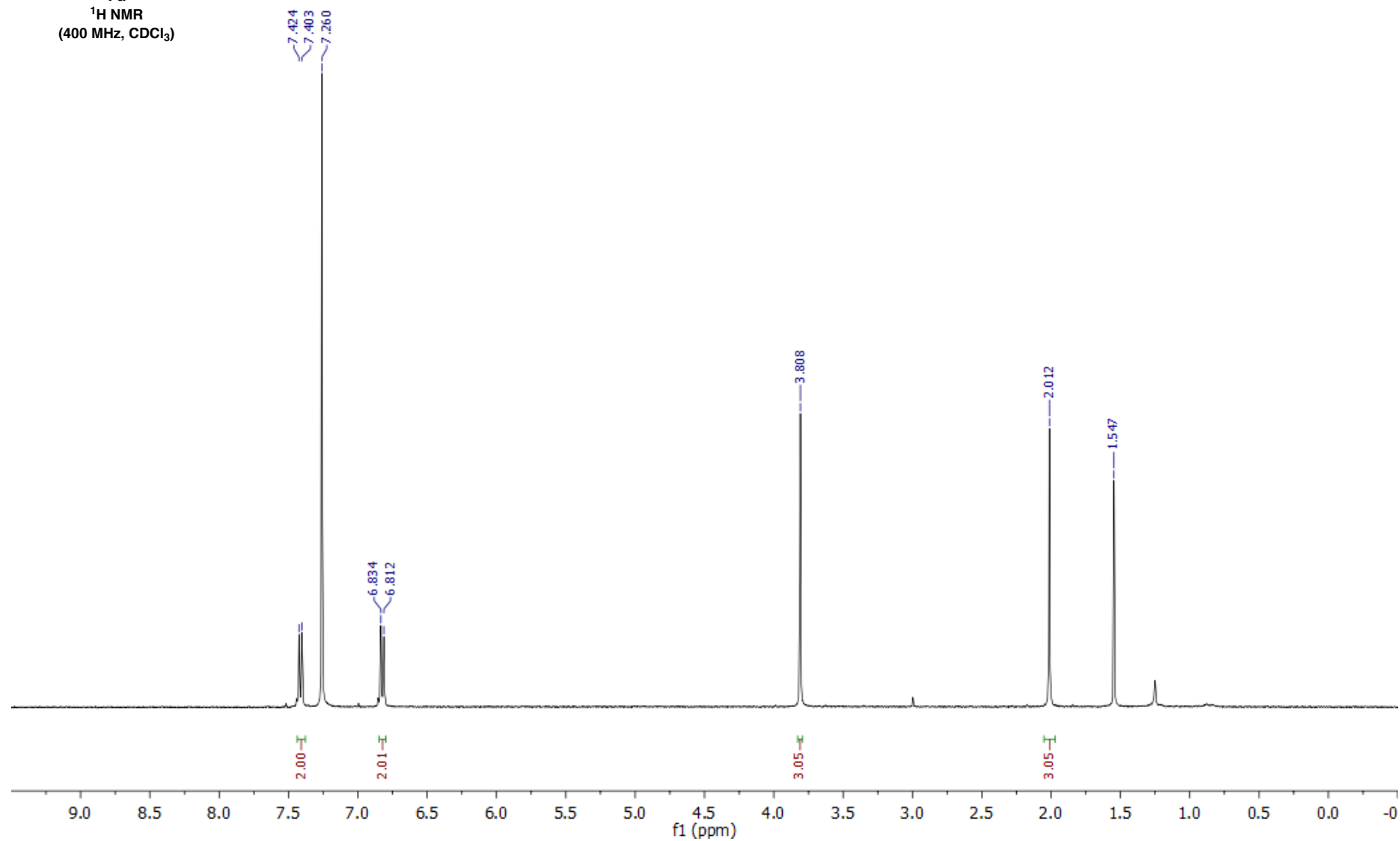


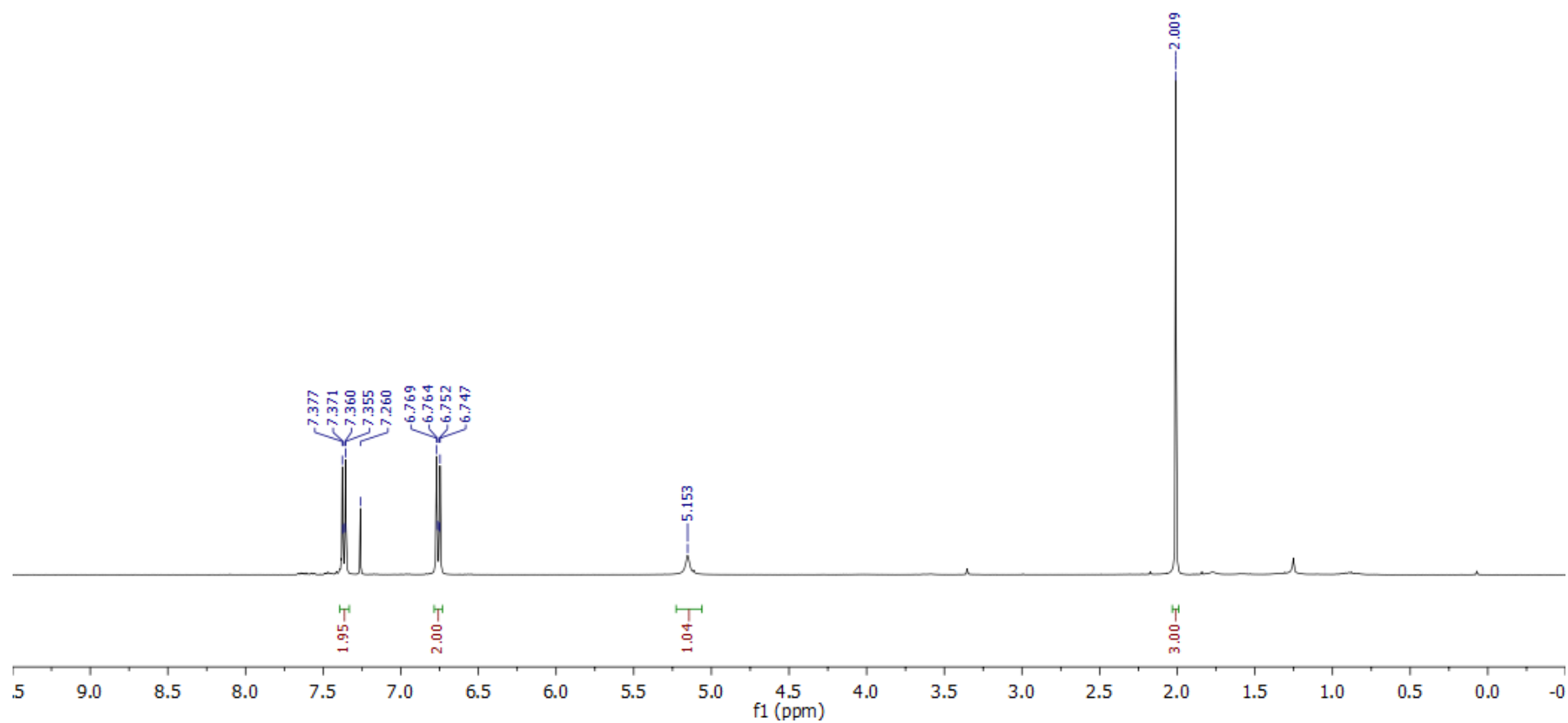
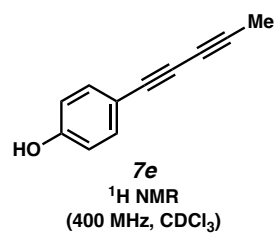
**7c**  
<sup>19</sup>F NMR  
(376 MHz, CDCl<sub>3</sub>)

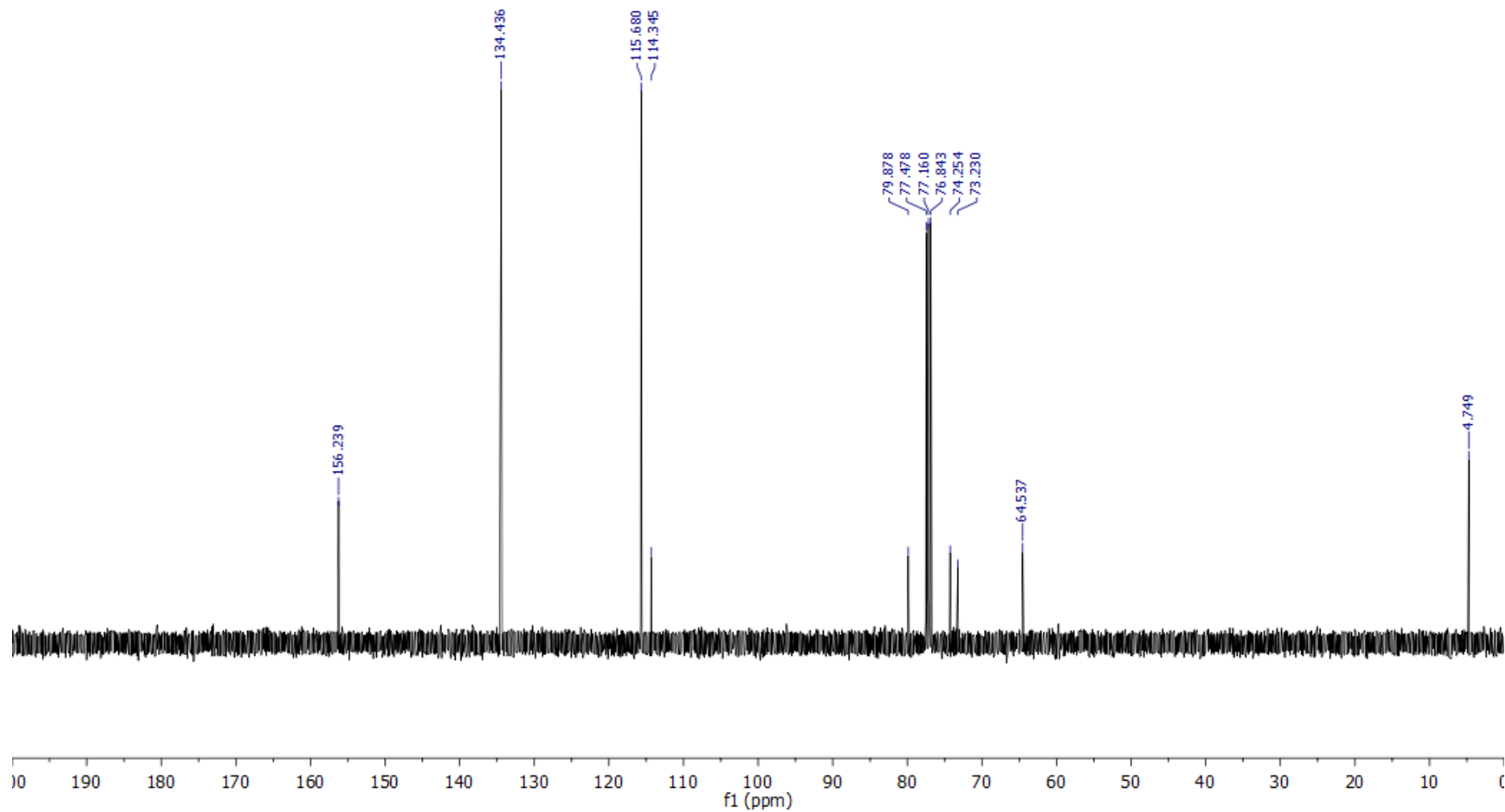
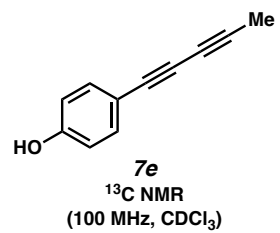


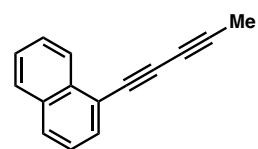
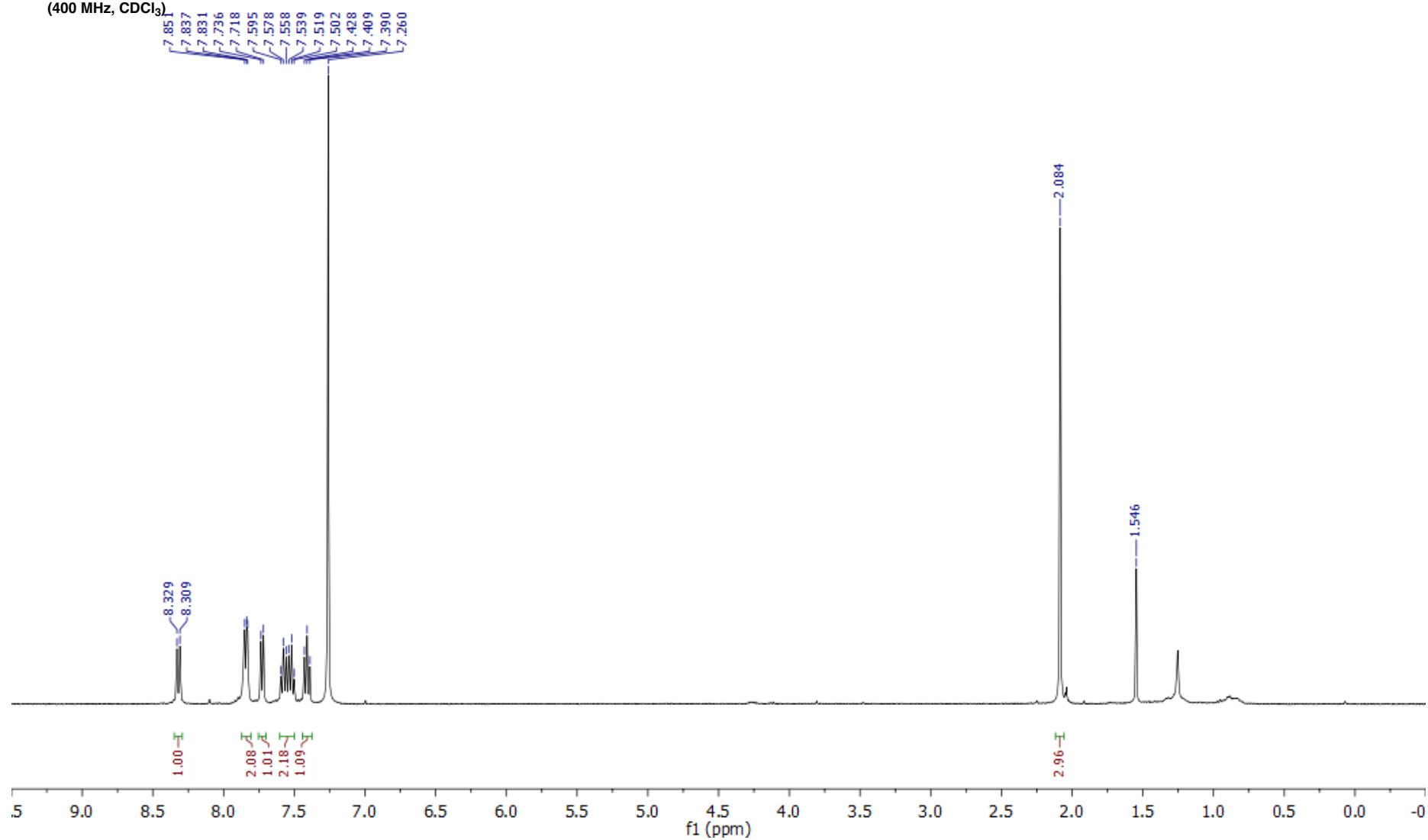


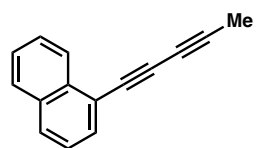
**7d**  
<sup>1</sup>H NMR  
(400 MHz, CDCl<sub>3</sub>)



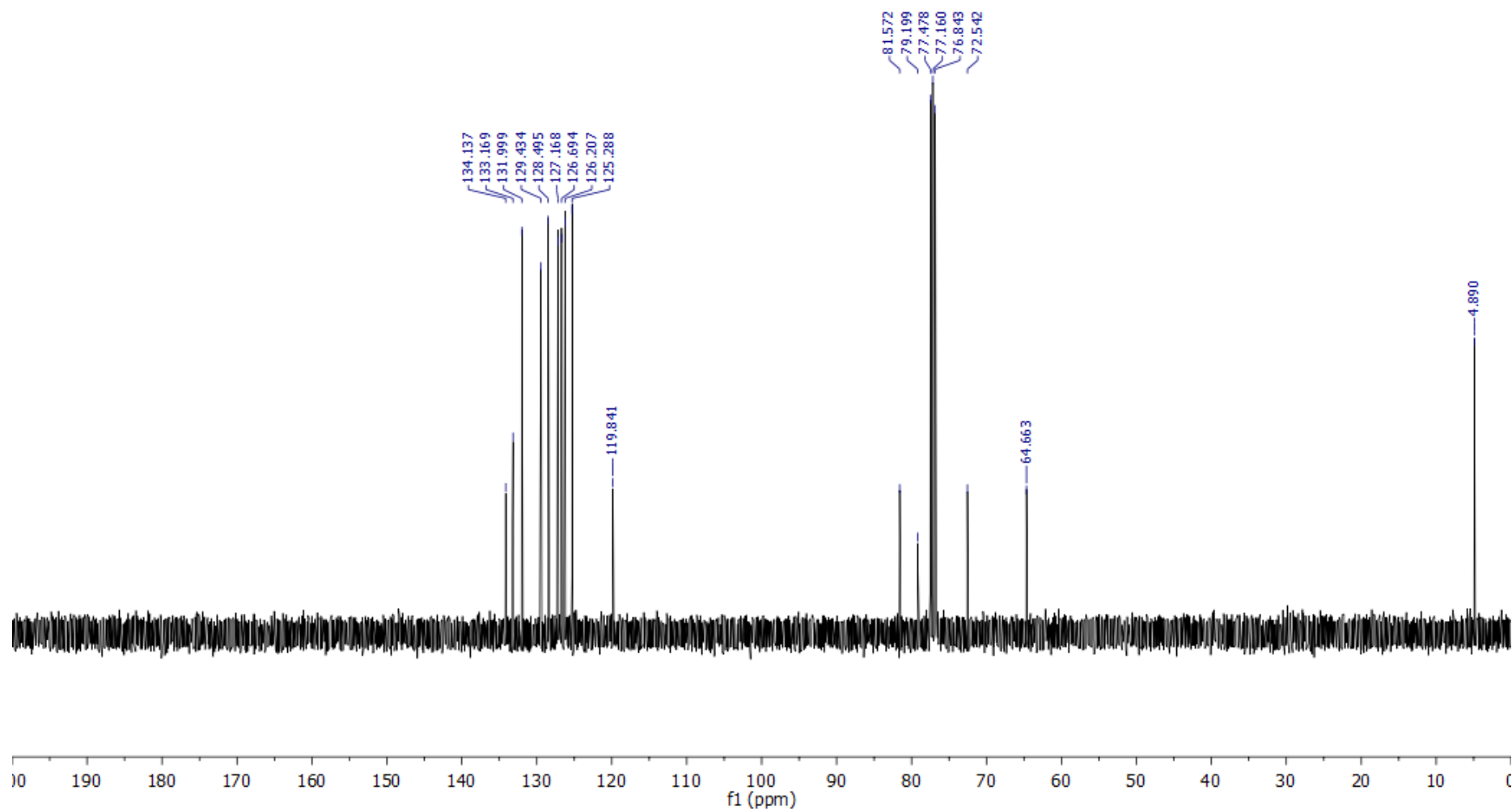


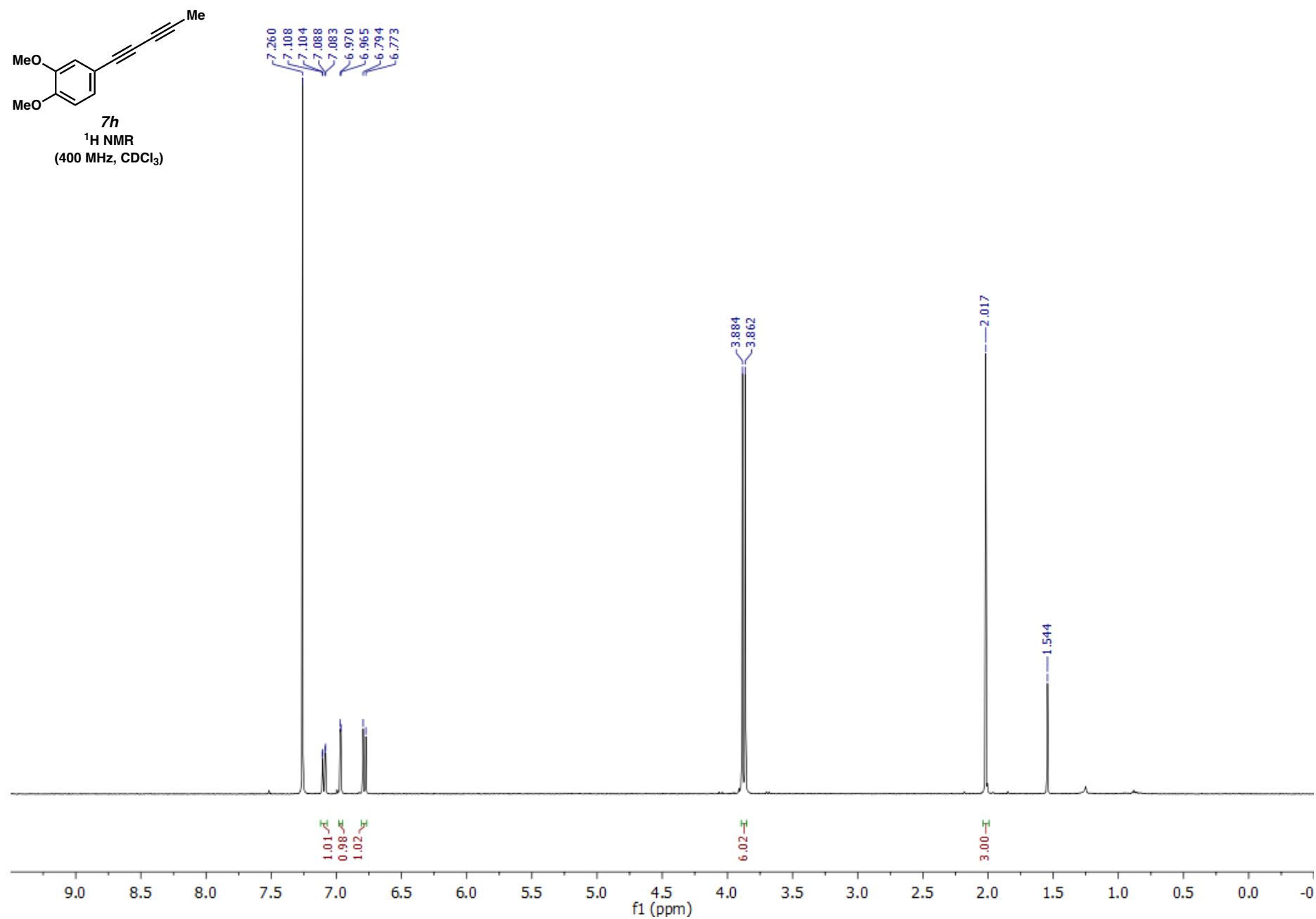


**7g**<sup>1</sup>H NMR  
(400 MHz, CDCl<sub>3</sub>)

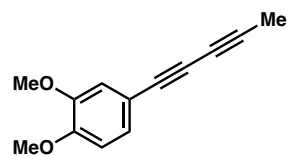


**7g**  
 $^{13}\text{C}$  NMR  
(100 MHz,  $\text{CDCl}_3$ )

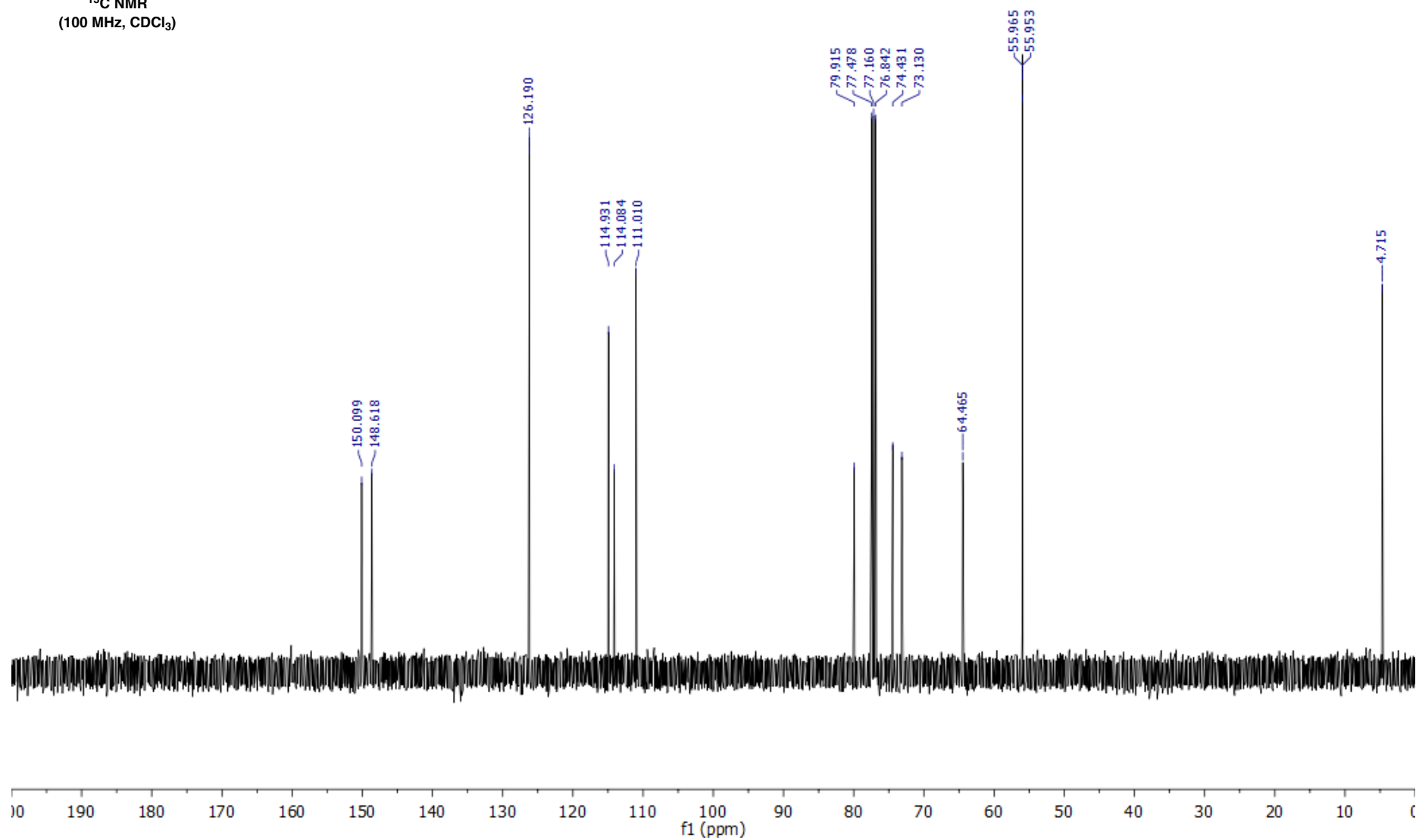


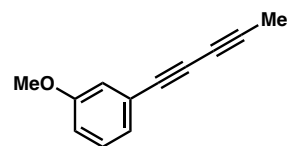




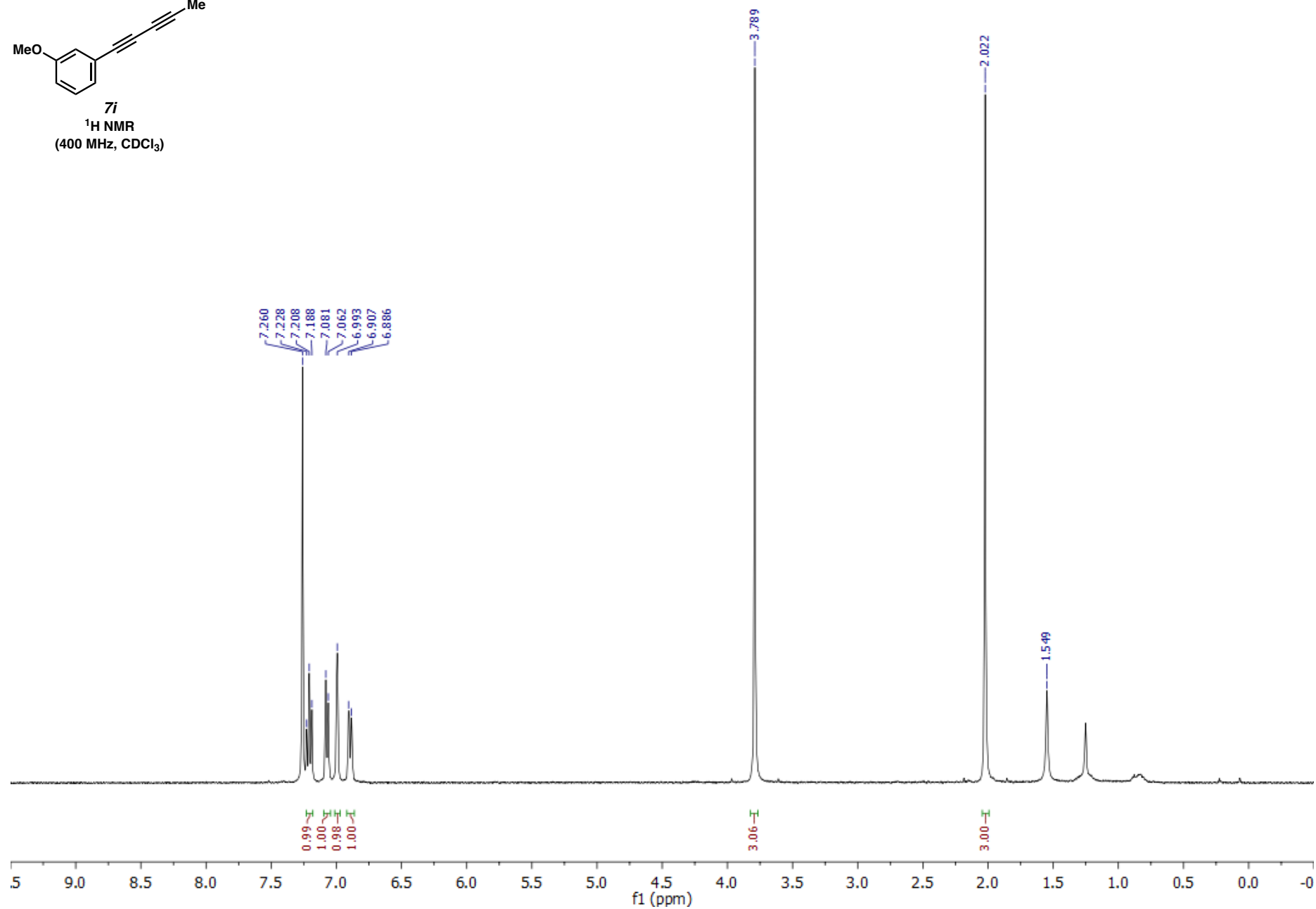


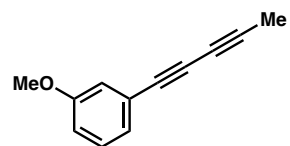
**7h**  
 $^{13}\text{C}$  NMR  
(100 MHz,  $\text{CDCl}_3$ )



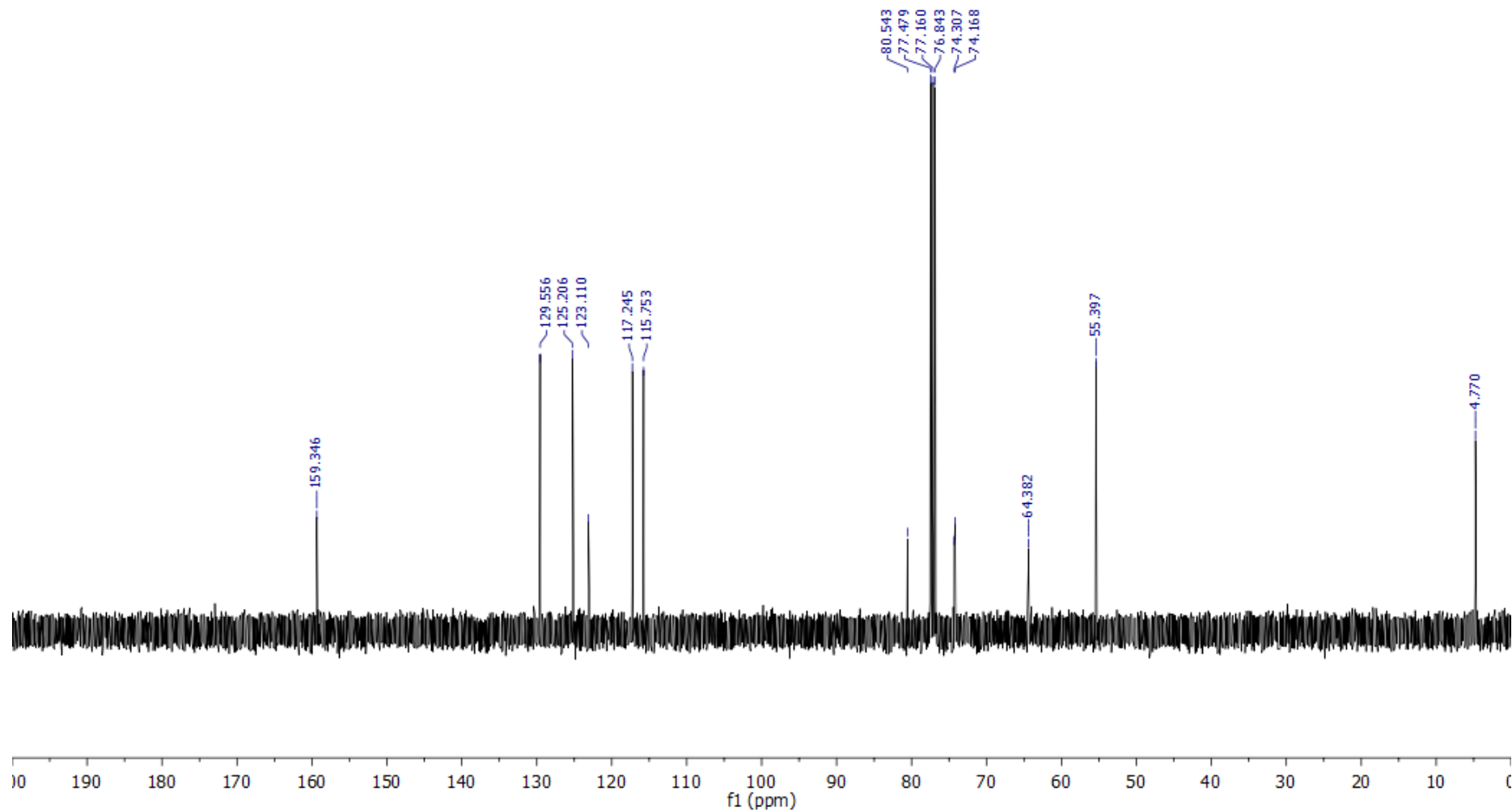


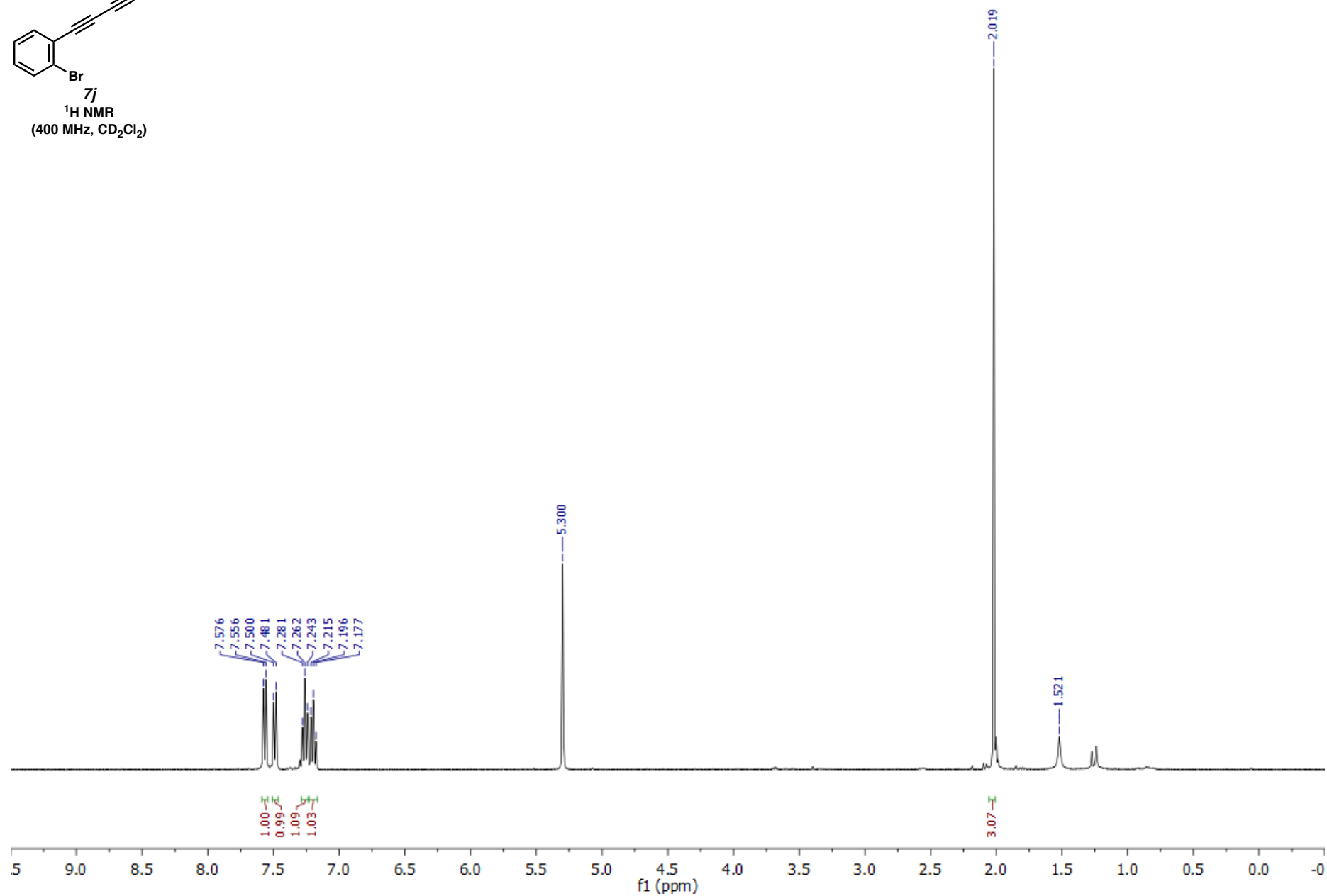
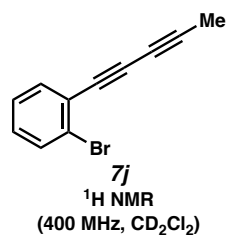
**7i**  
**<sup>1</sup>H NMR**  
**(400 MHz, CDCl<sub>3</sub>)**

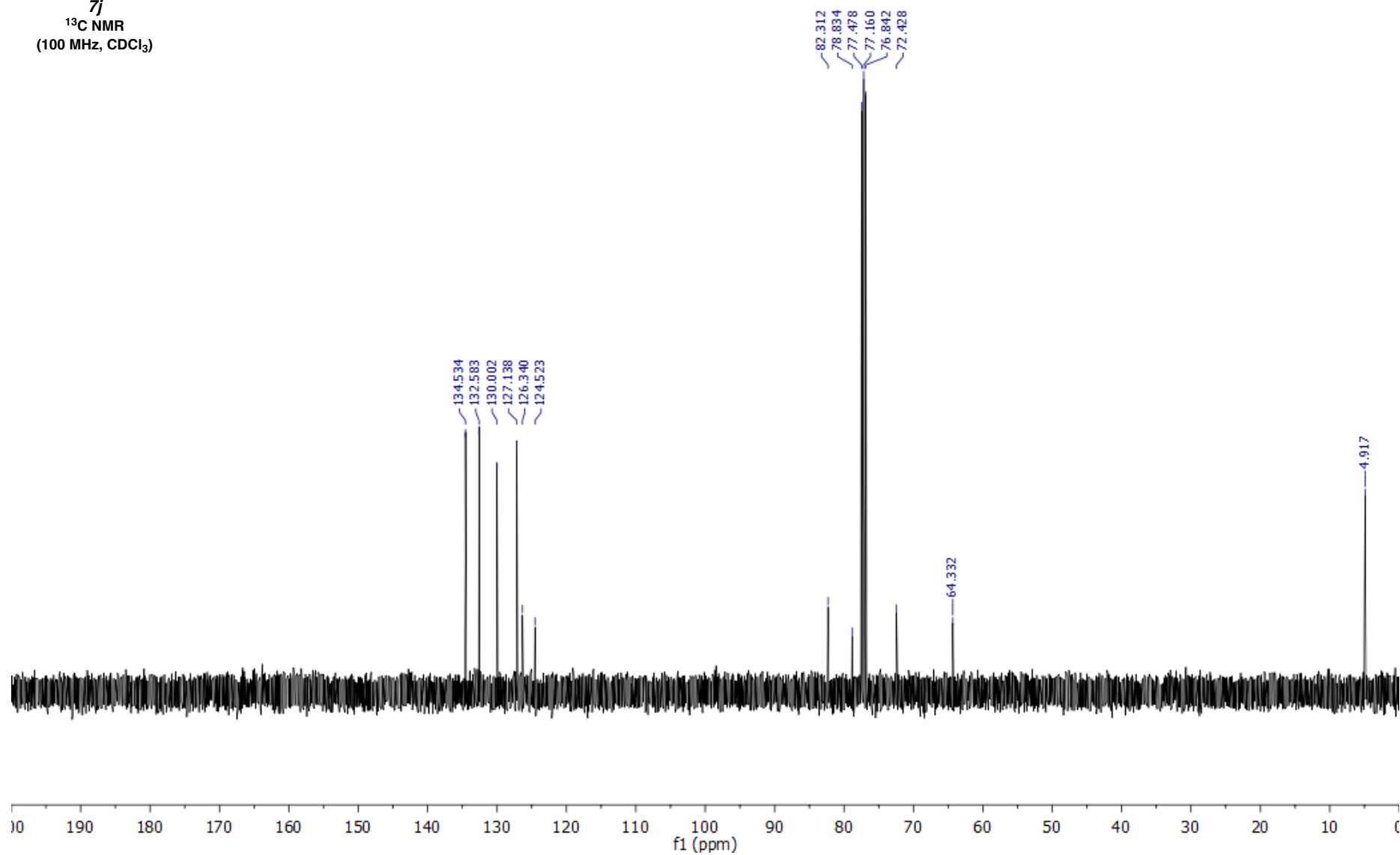
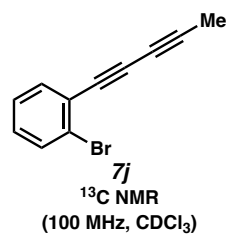


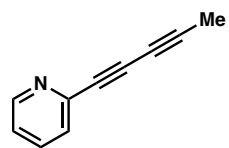


**7i**  
 **$^{13}\text{C}$  NMR**  
**(100 MHz,  $\text{CDCl}_3$ )**

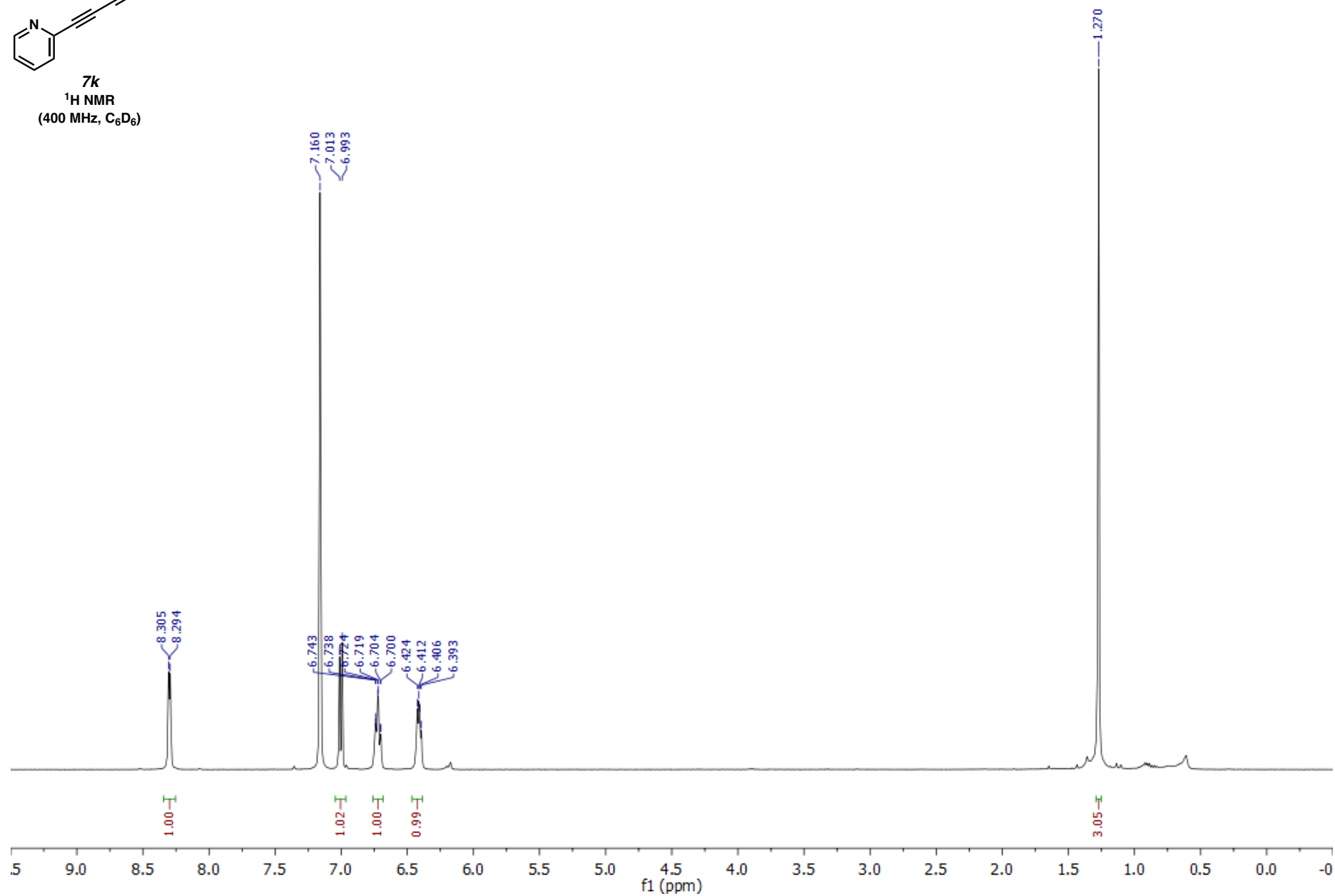


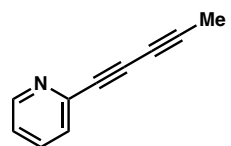




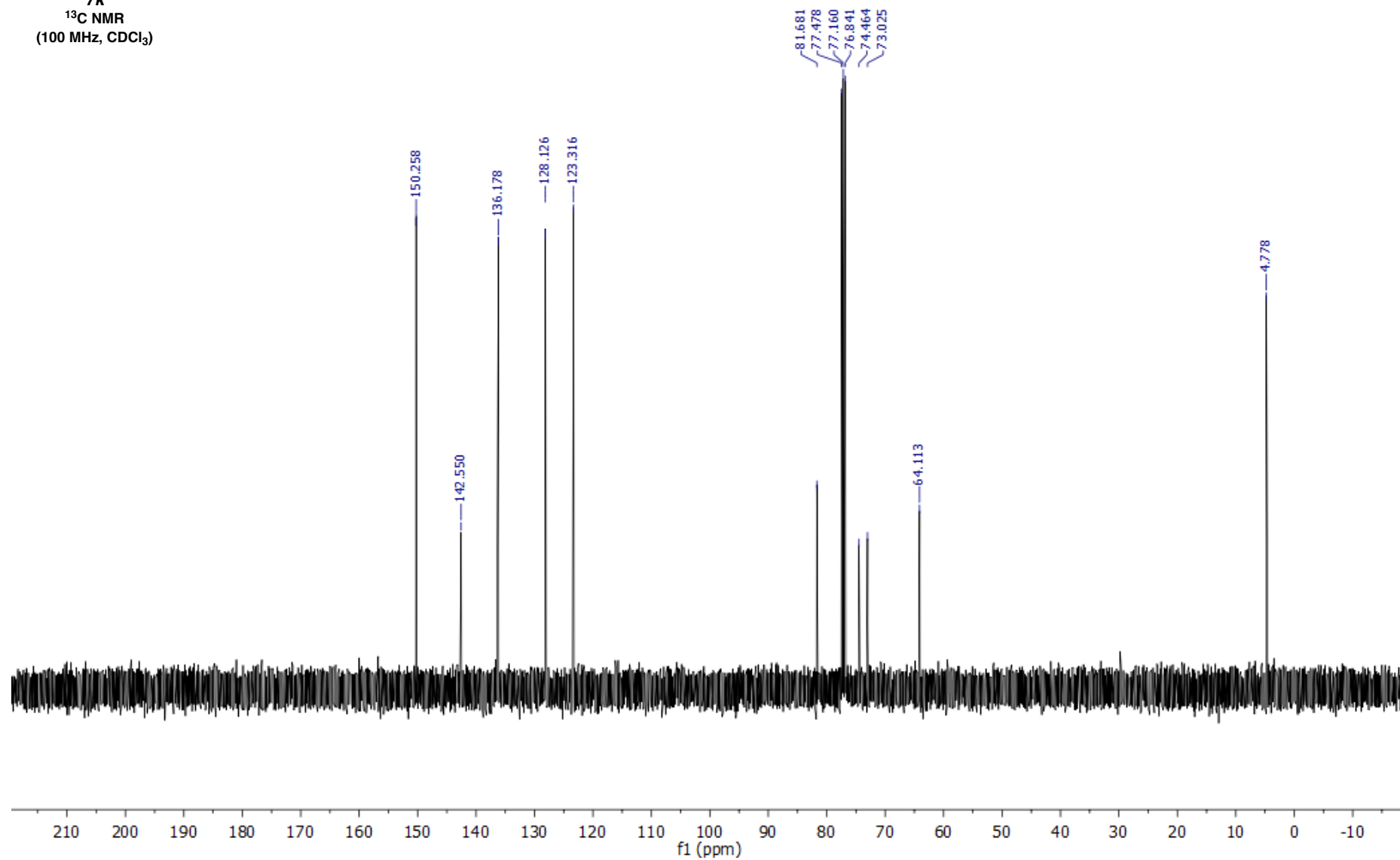


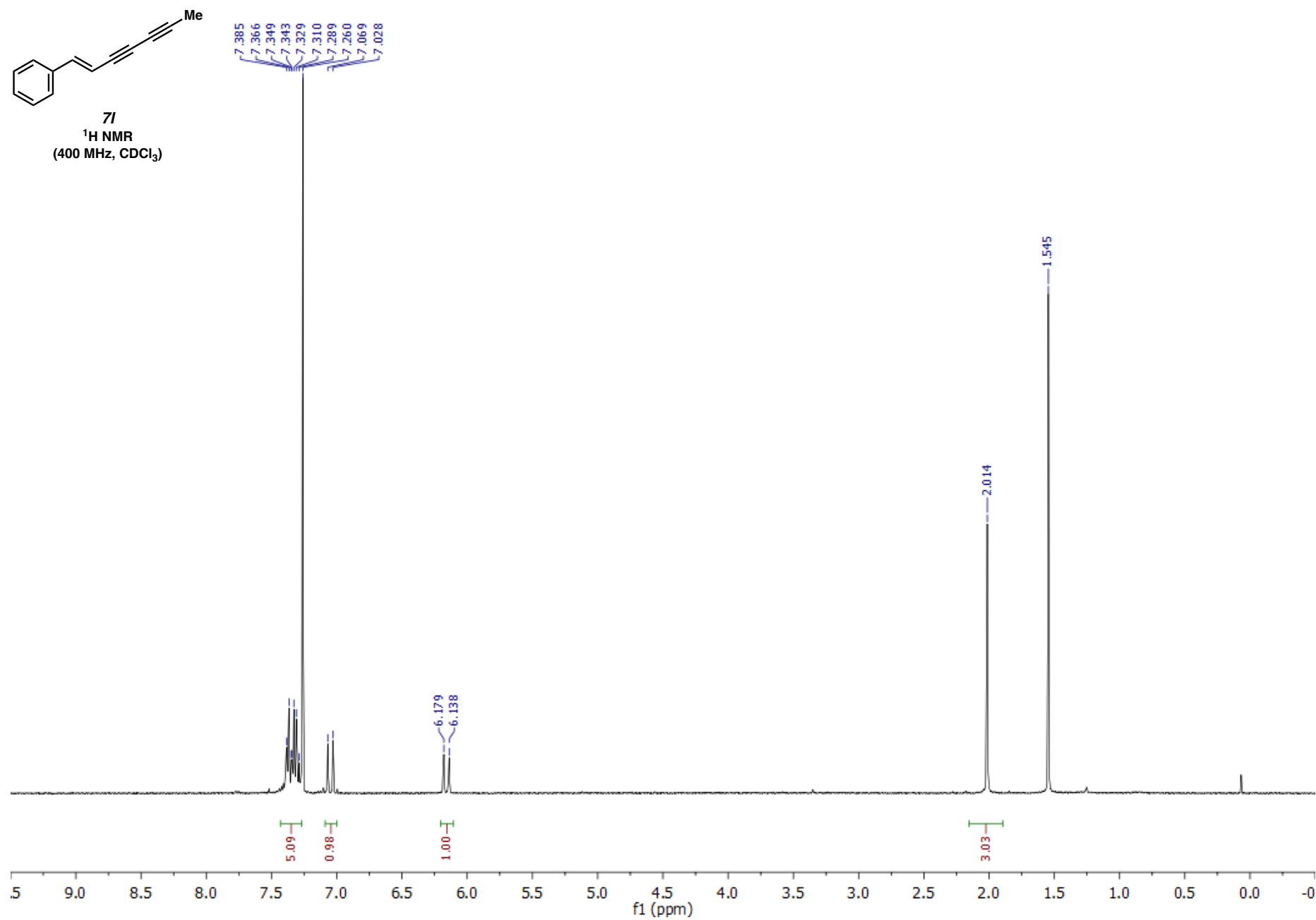
**7k**  
**<sup>1</sup>H NMR**  
(400 MHz, C<sub>6</sub>D<sub>6</sub>)



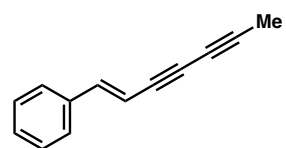


**7k**  
 $^{13}\text{C}$  NMR  
(100 MHz,  $\text{CDCl}_3$ )

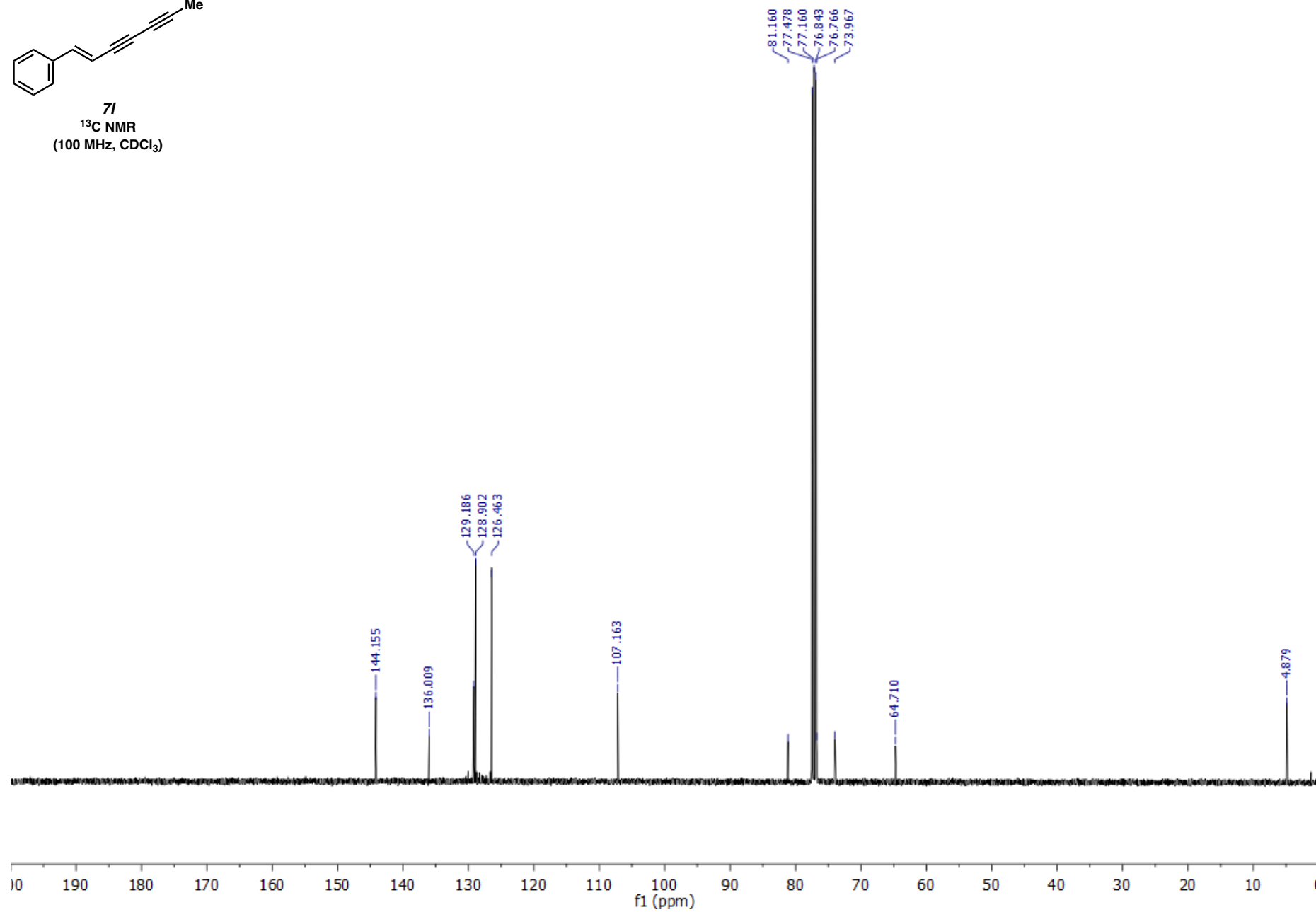


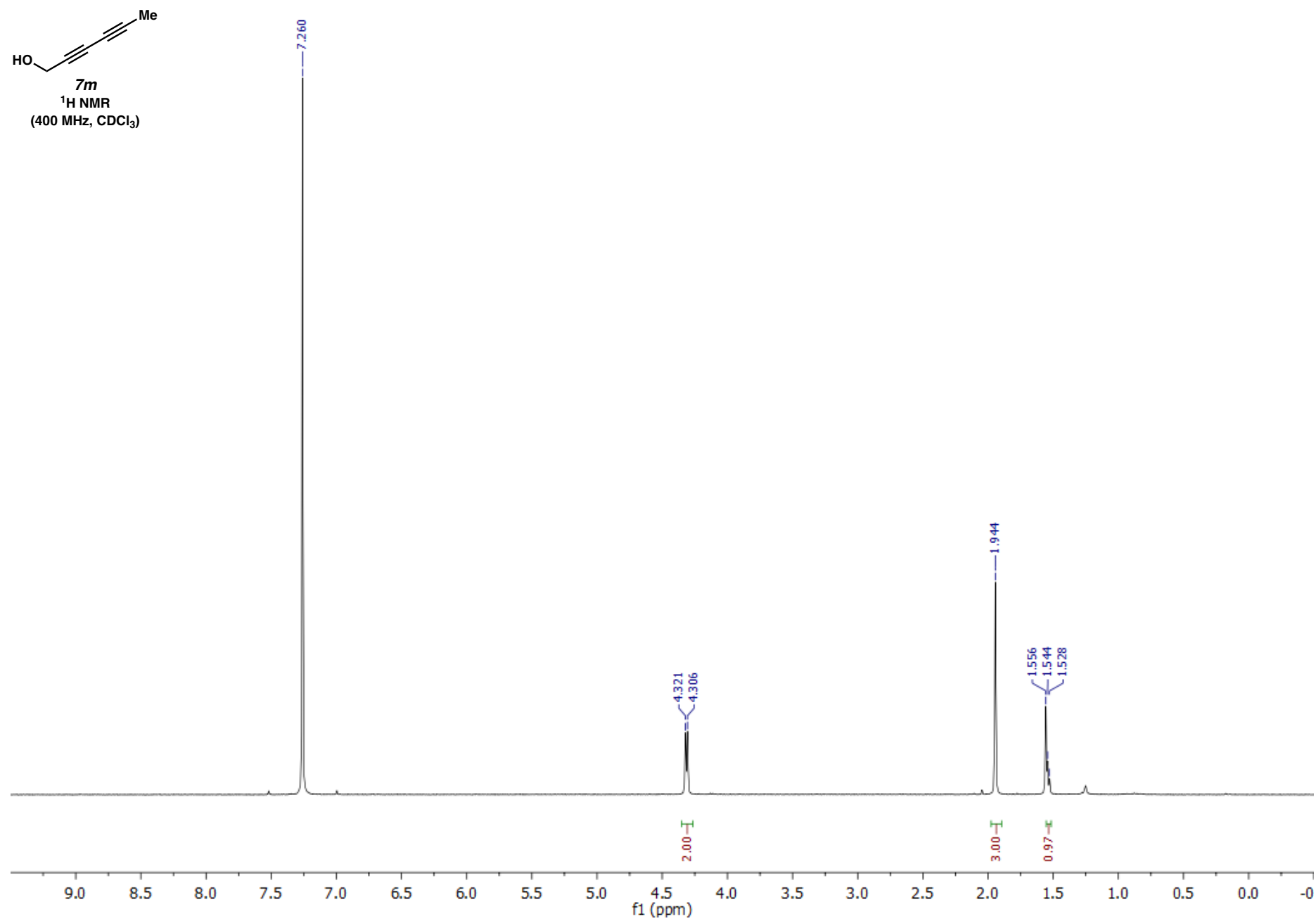


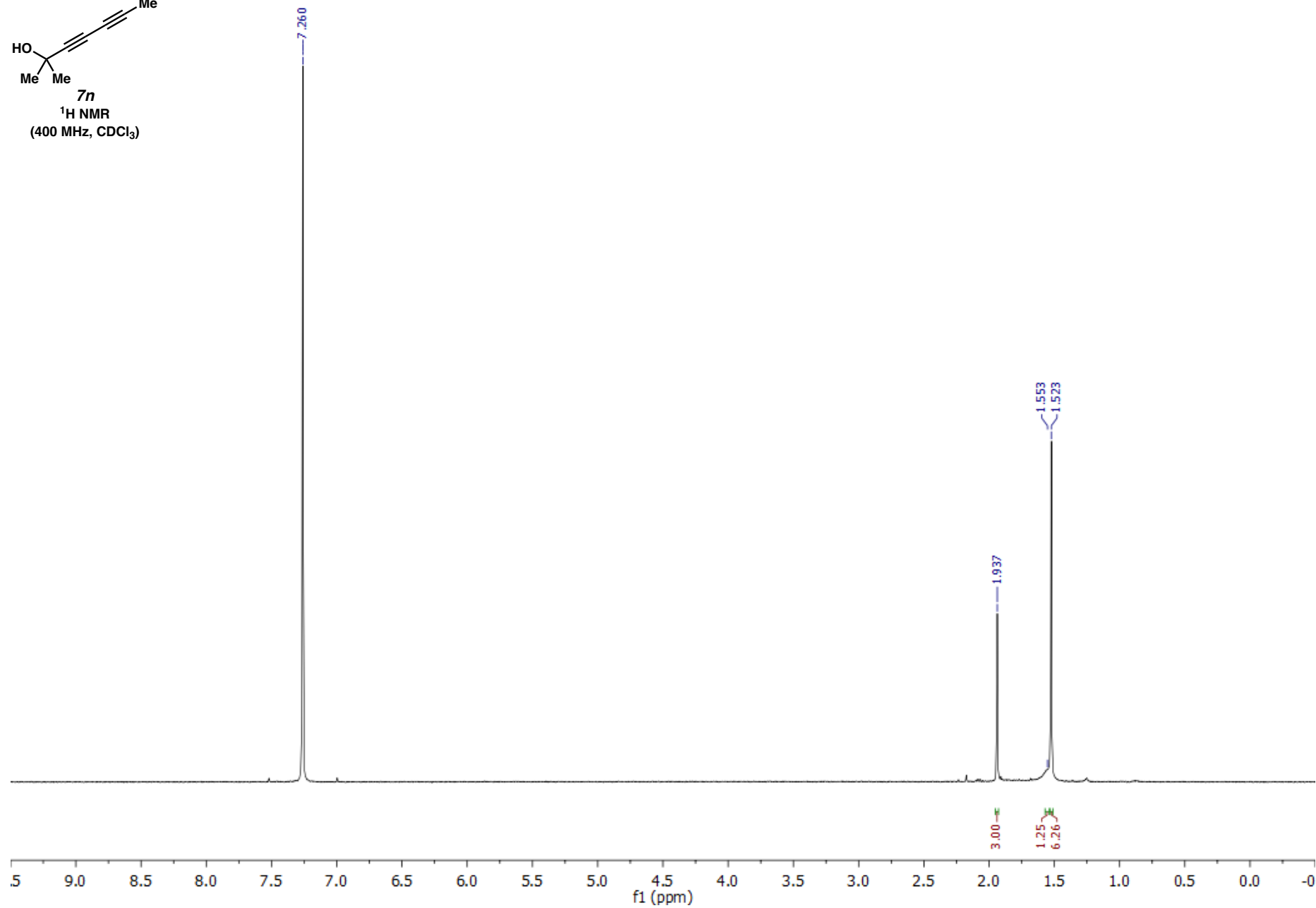
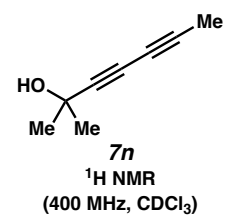


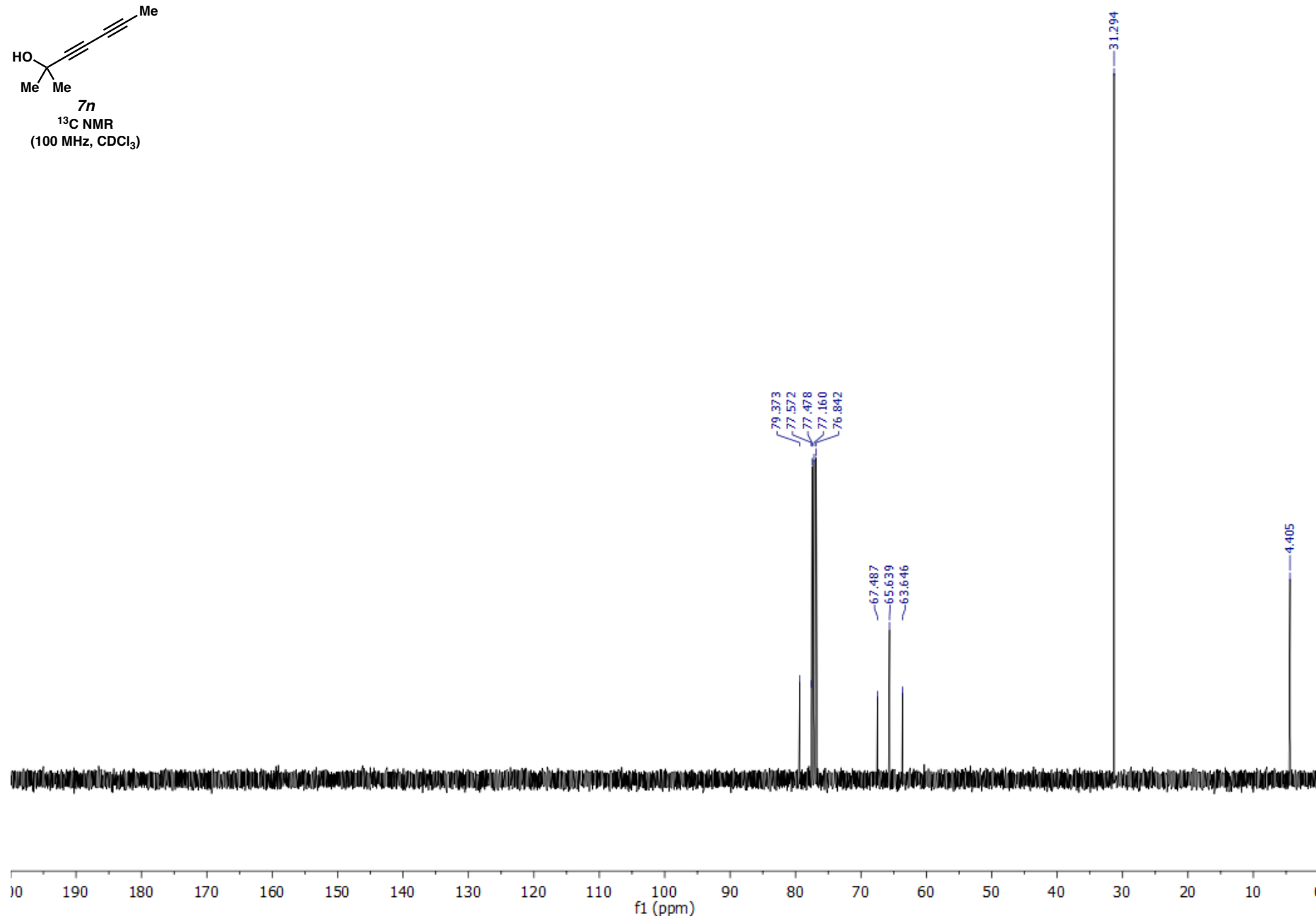
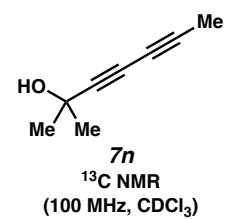


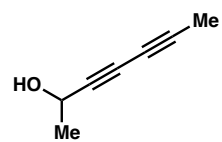
**7I**  
 **$^{13}\text{C}$  NMR**  
**(100 MHz,  $\text{CDCl}_3$ )**



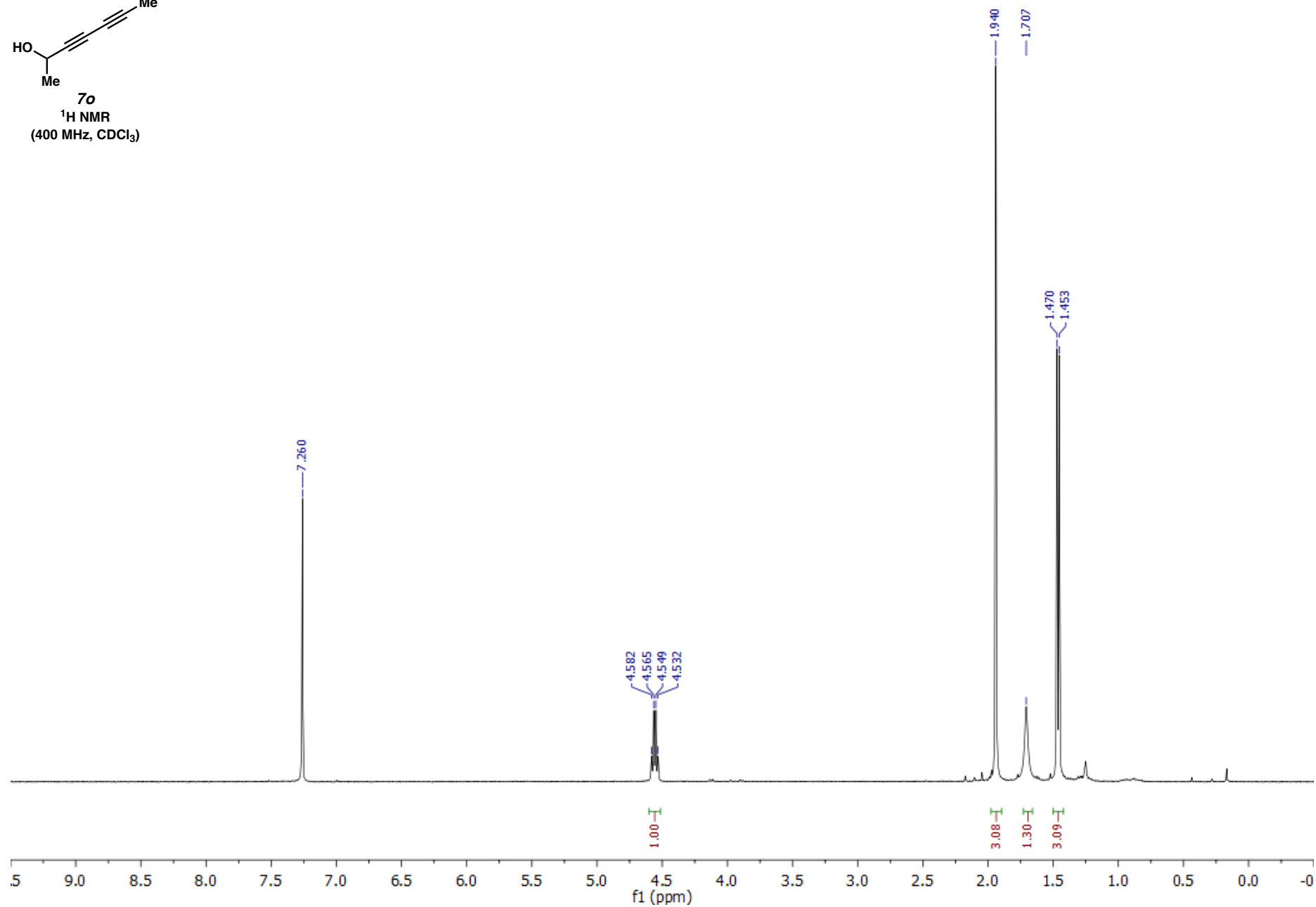


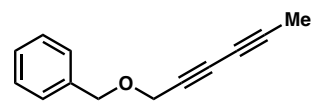




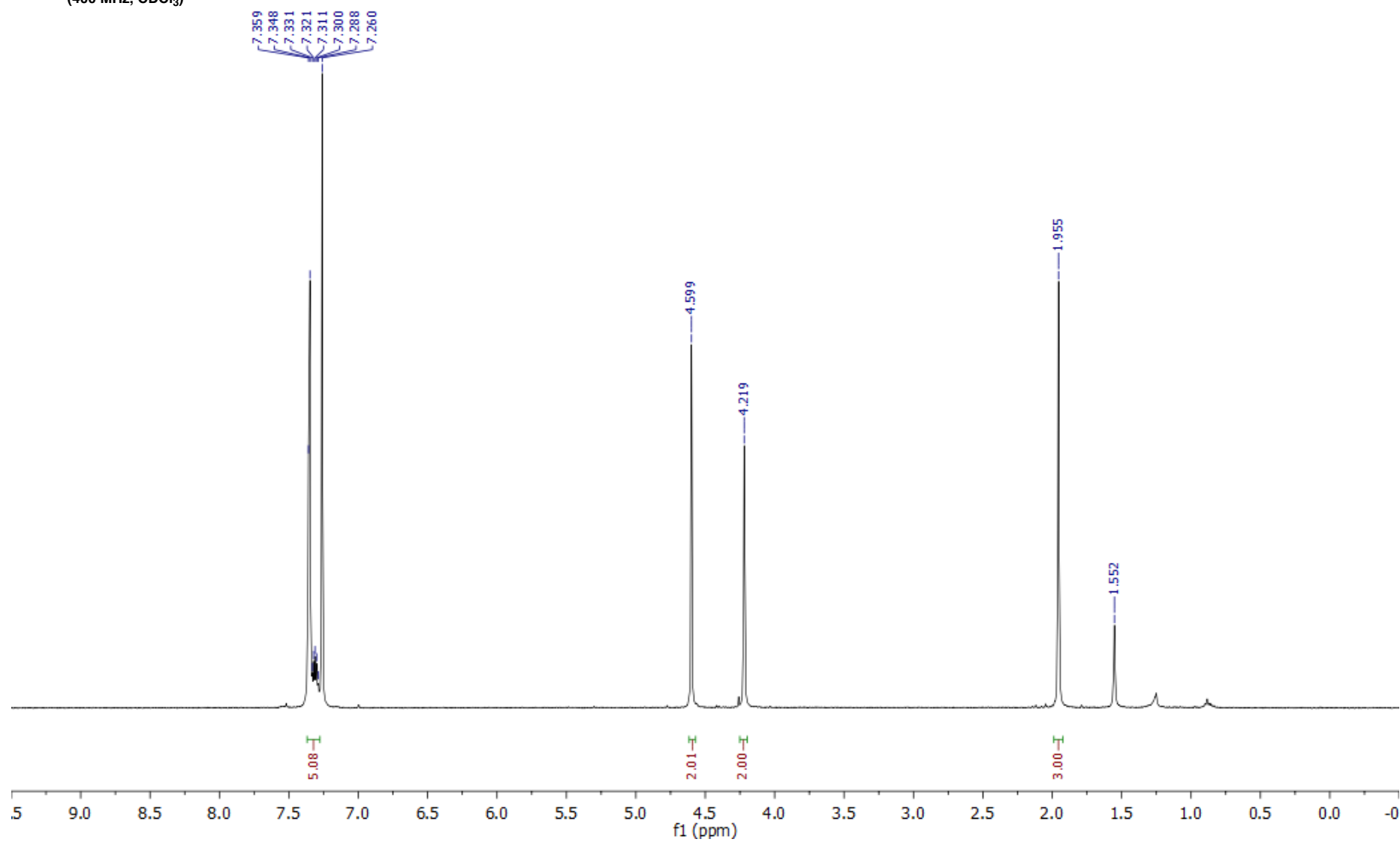


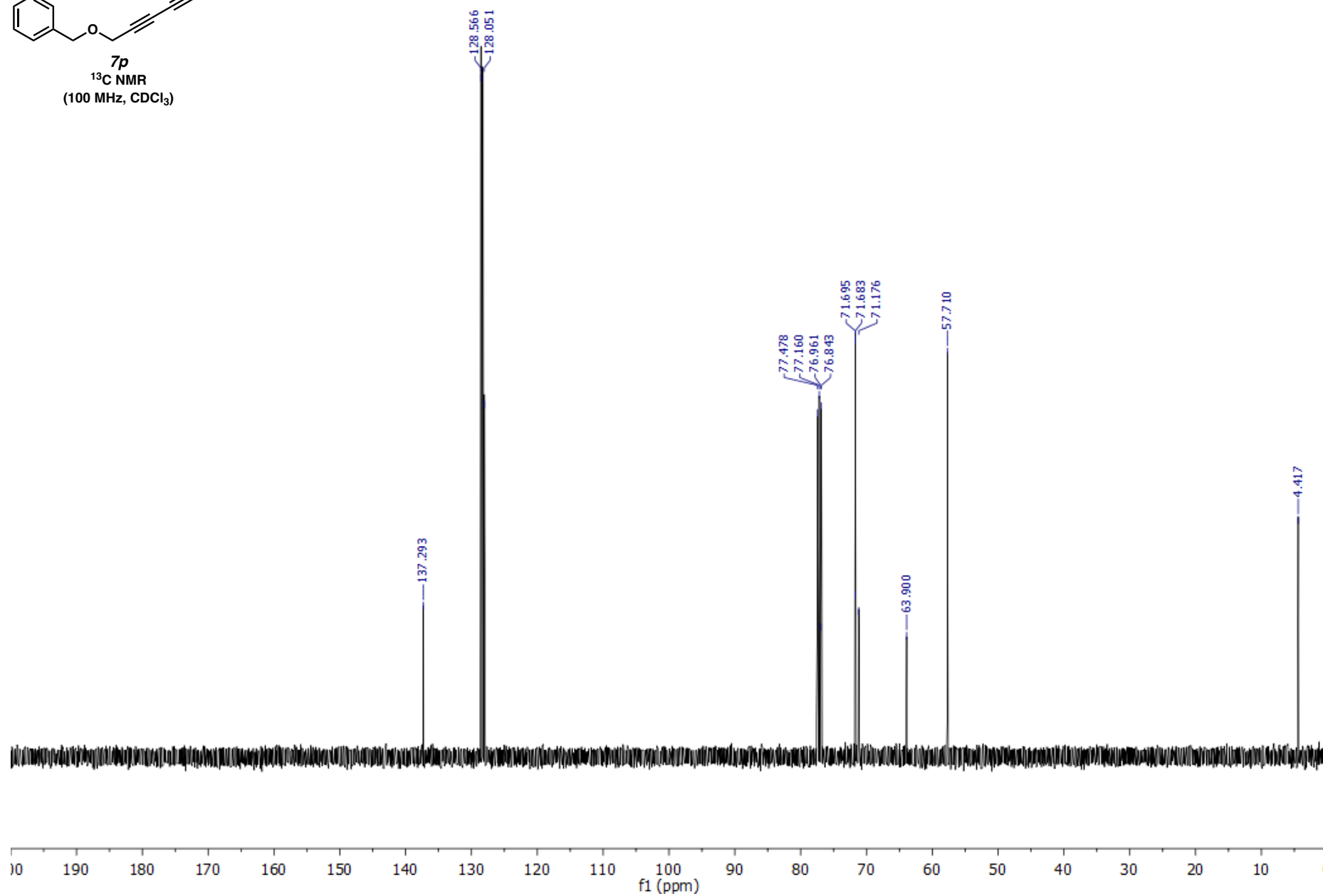
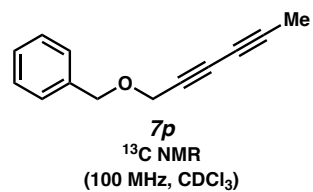
**7o**  
**<sup>1</sup>H NMR**  
(400 MHz, CDCl<sub>3</sub>)

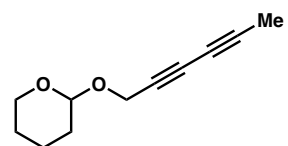




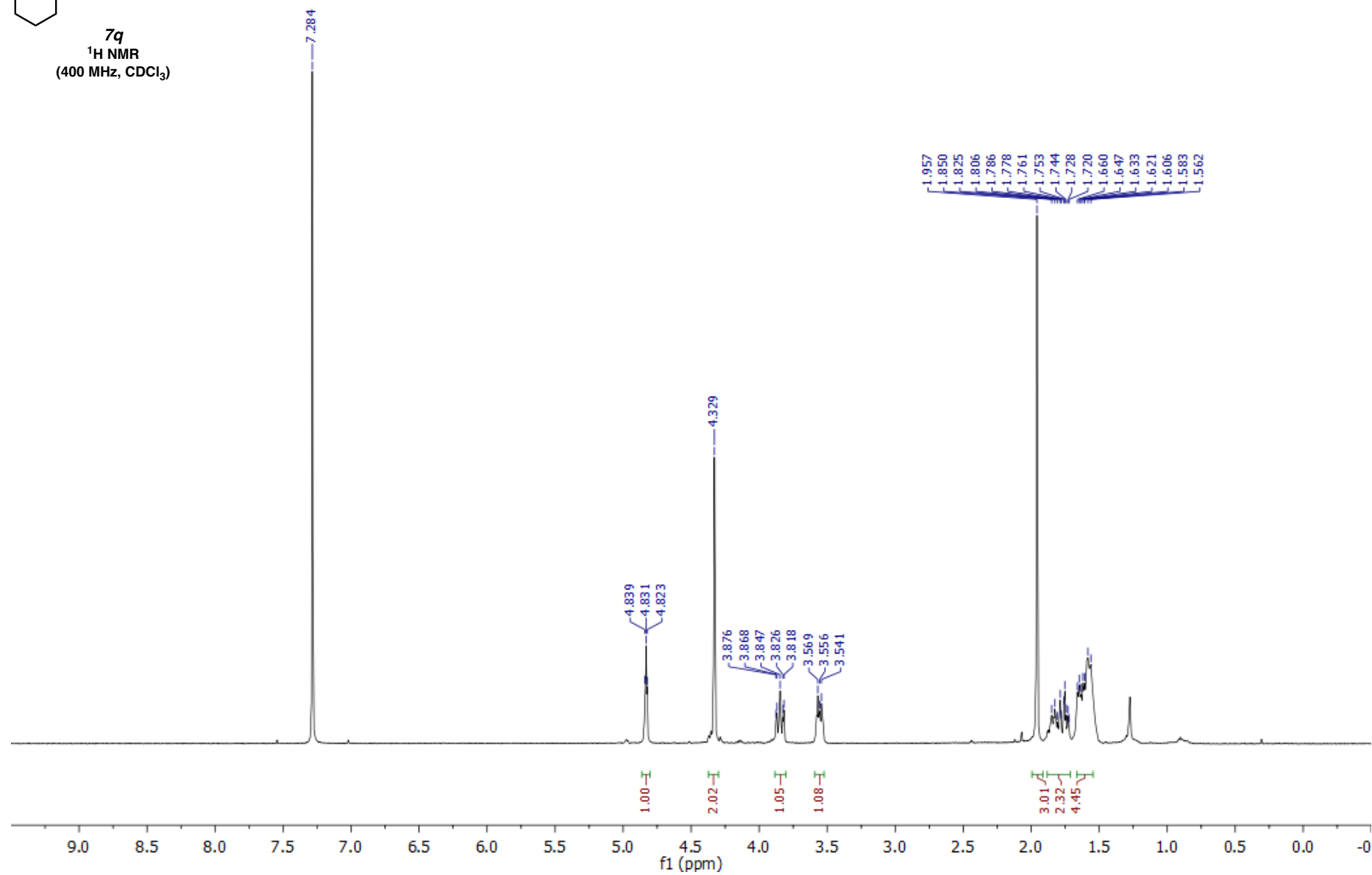
**7p**  
**<sup>1</sup>H NMR**  
(400 MHz, CDCl<sub>3</sub>)



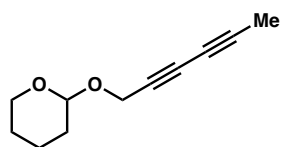




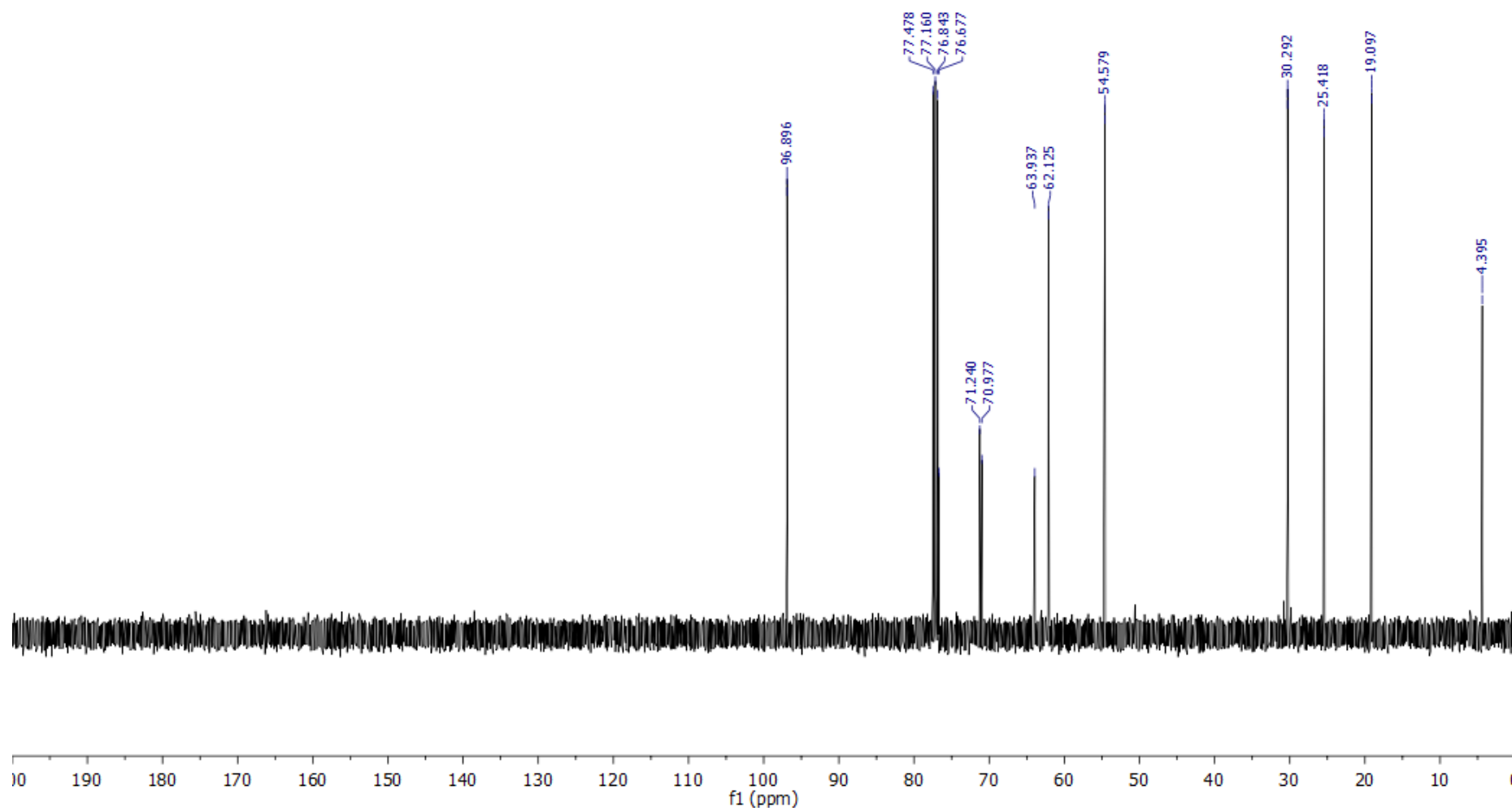
**7q**  
**<sup>1</sup>H NMR**  
(400 MHz, CDCl<sub>3</sub>)

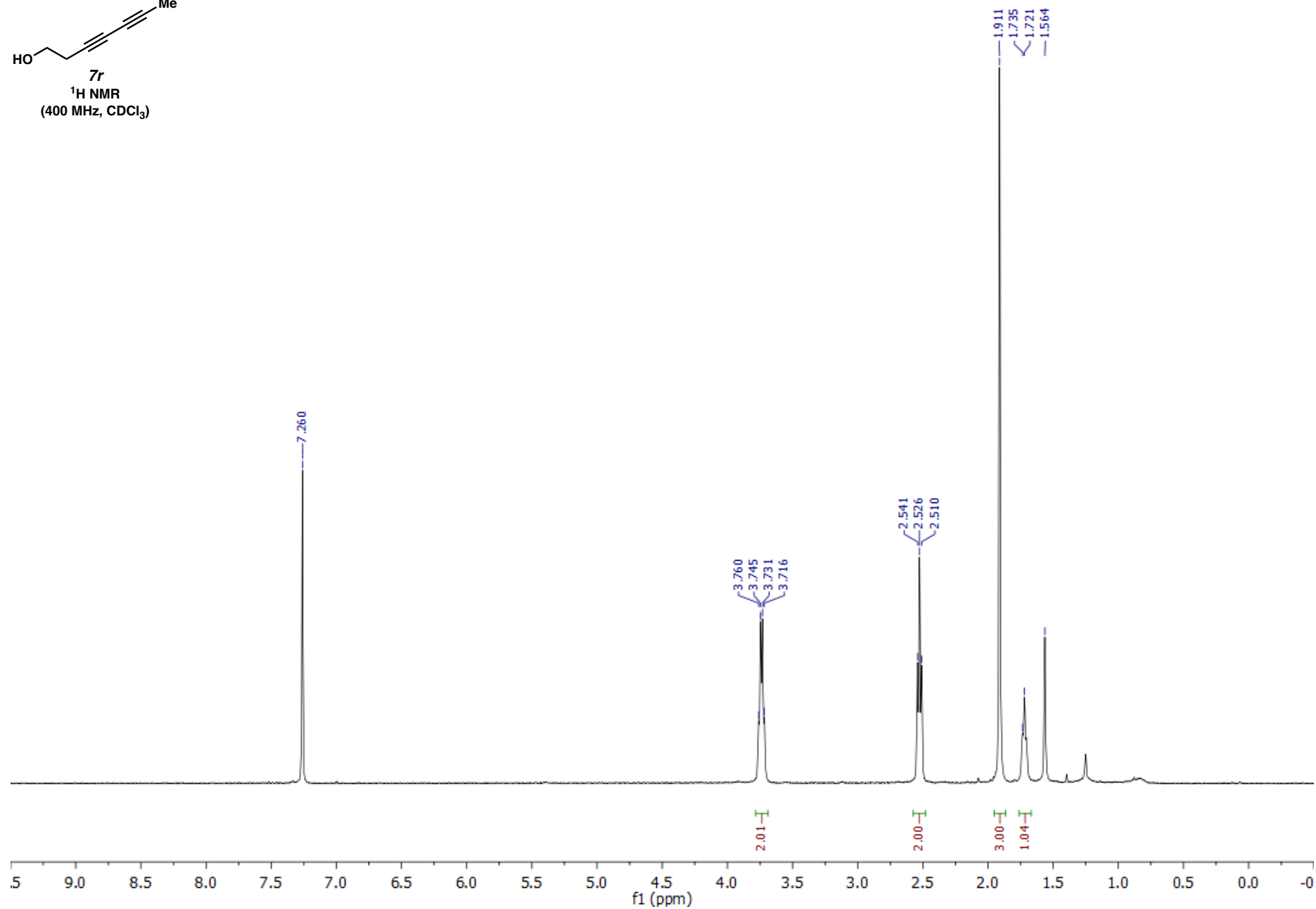
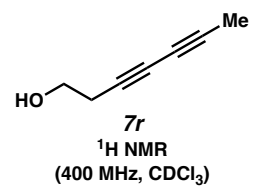


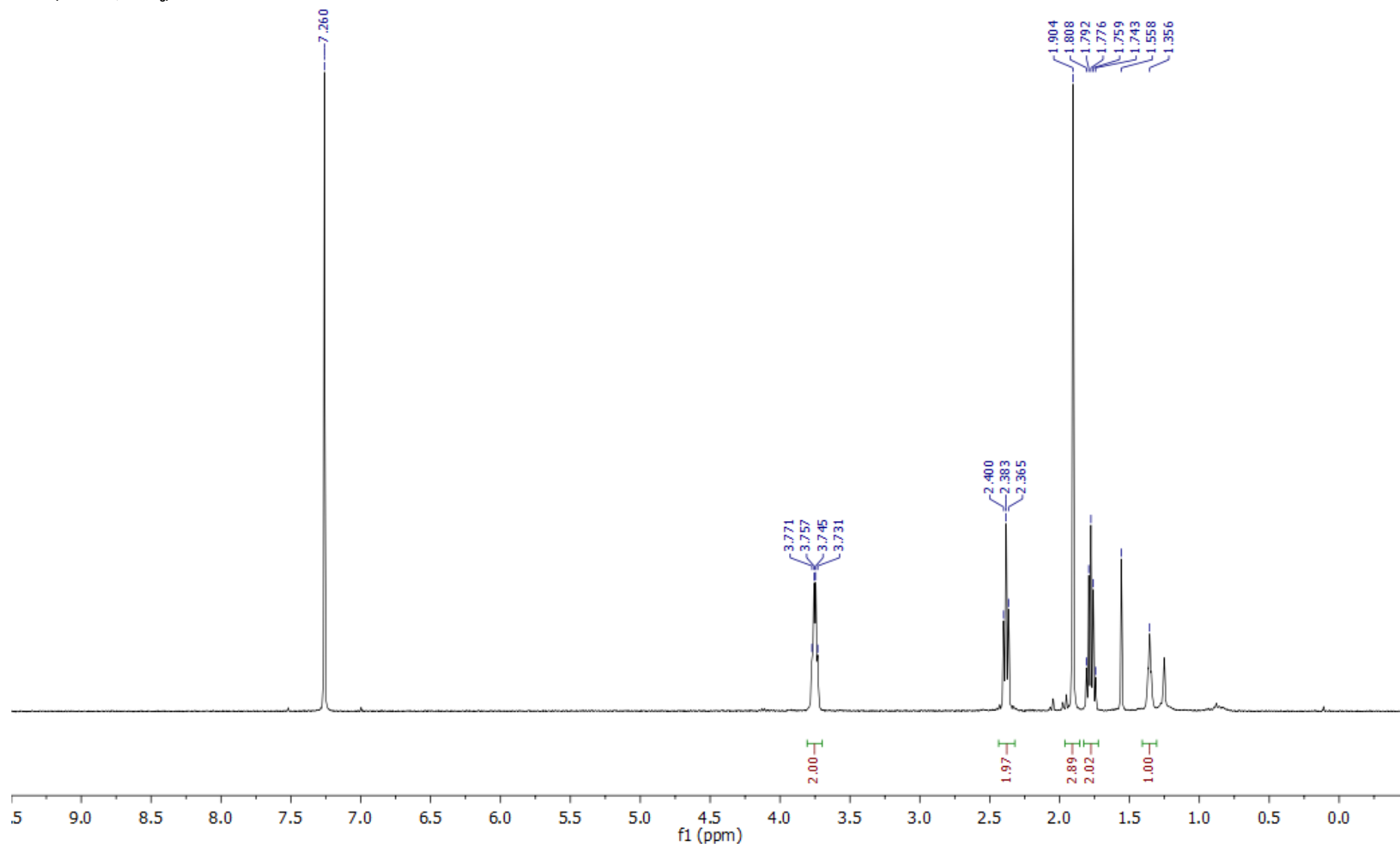
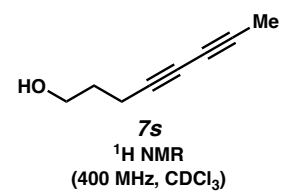


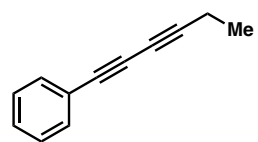
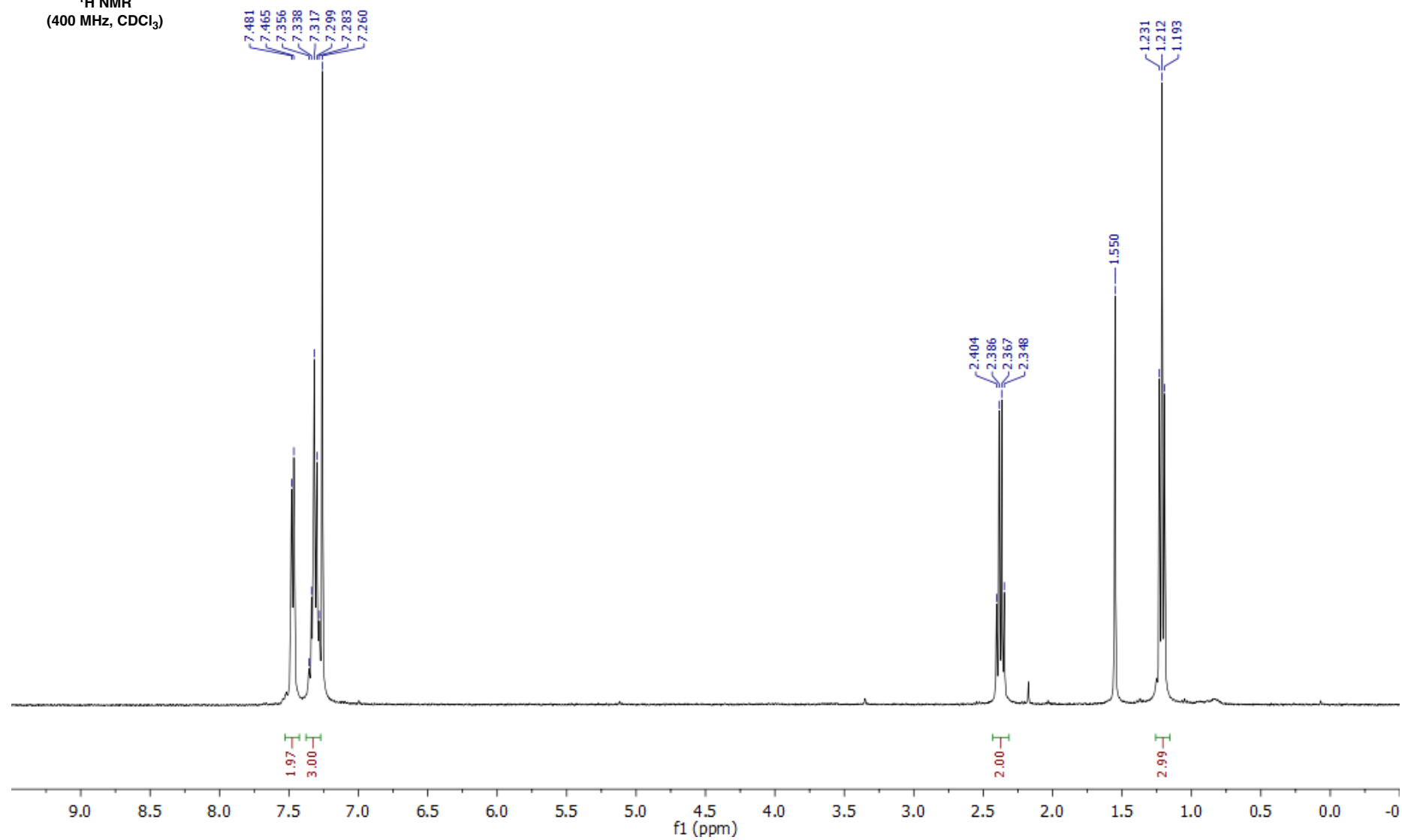


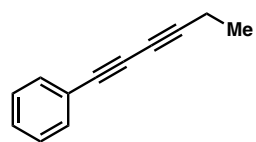
**7q**  
 $^{13}\text{C}$  NMR  
(100 MHz,  $\text{CDCl}_3$ )



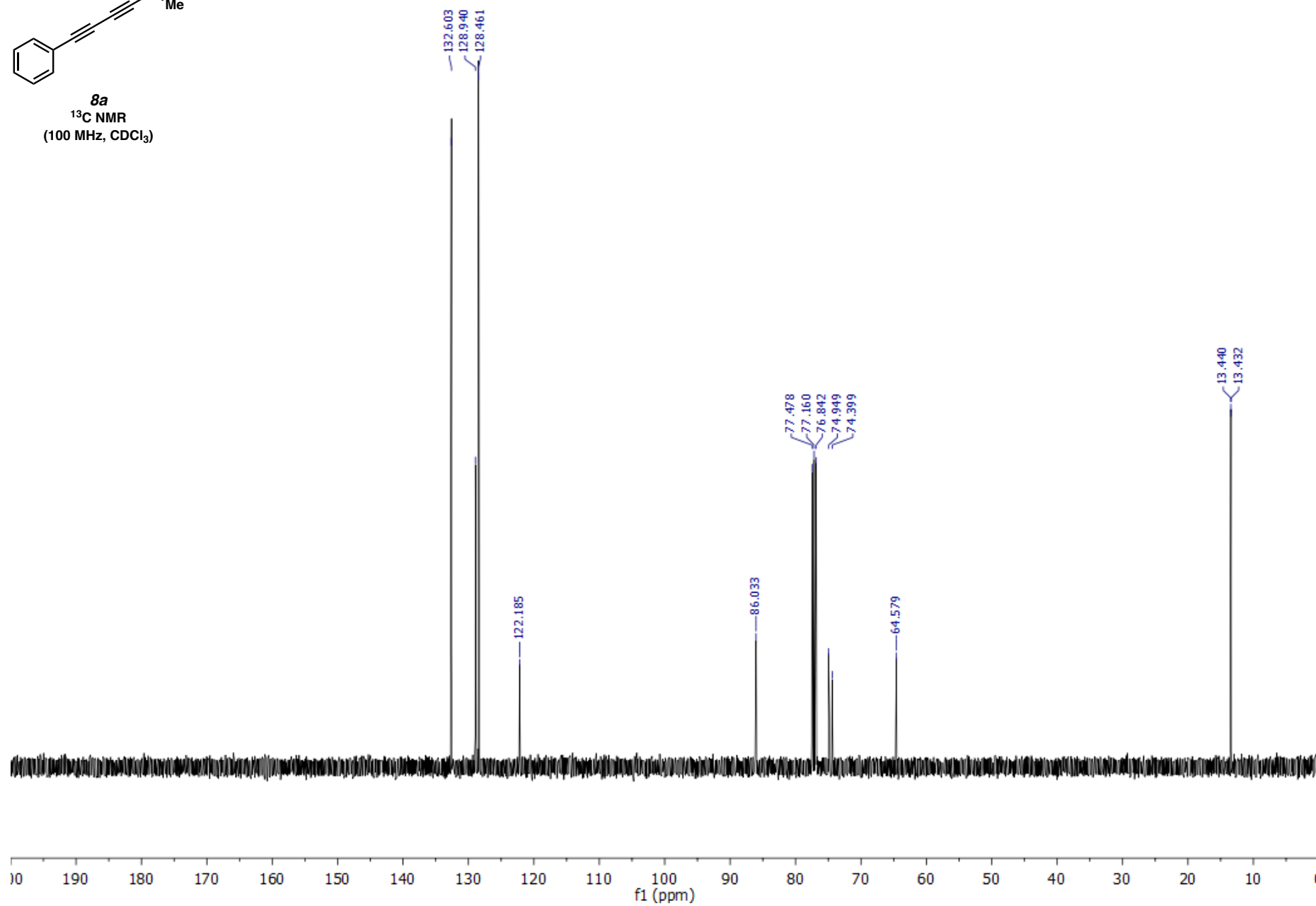


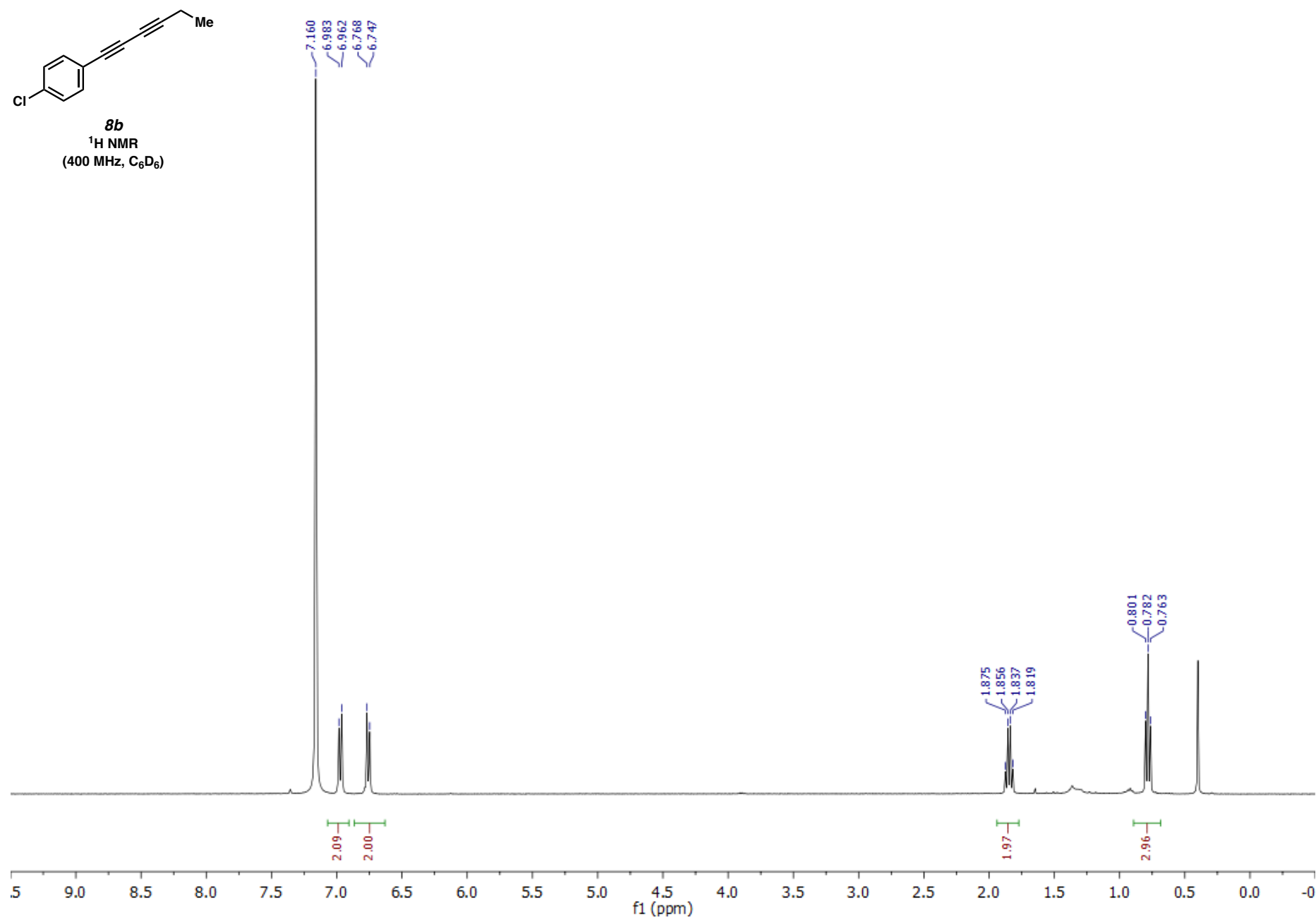


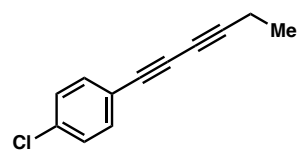
**8a**<sup>1</sup>H NMR  
(400 MHz, CDCl<sub>3</sub>)



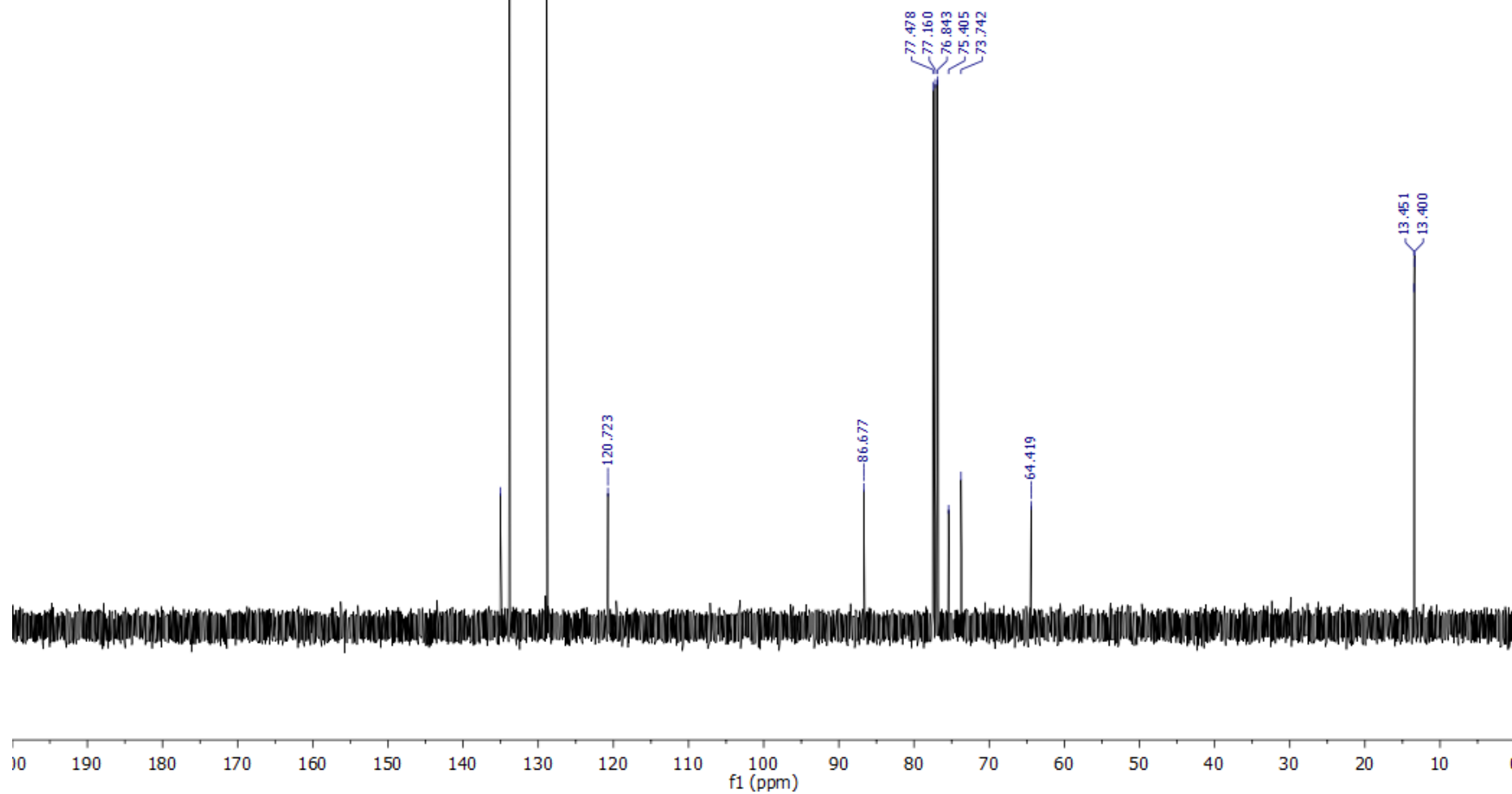
**8a**  
 $^{13}\text{C}$  NMR  
(100 MHz,  $\text{CDCl}_3$ )

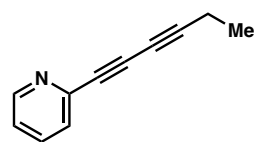




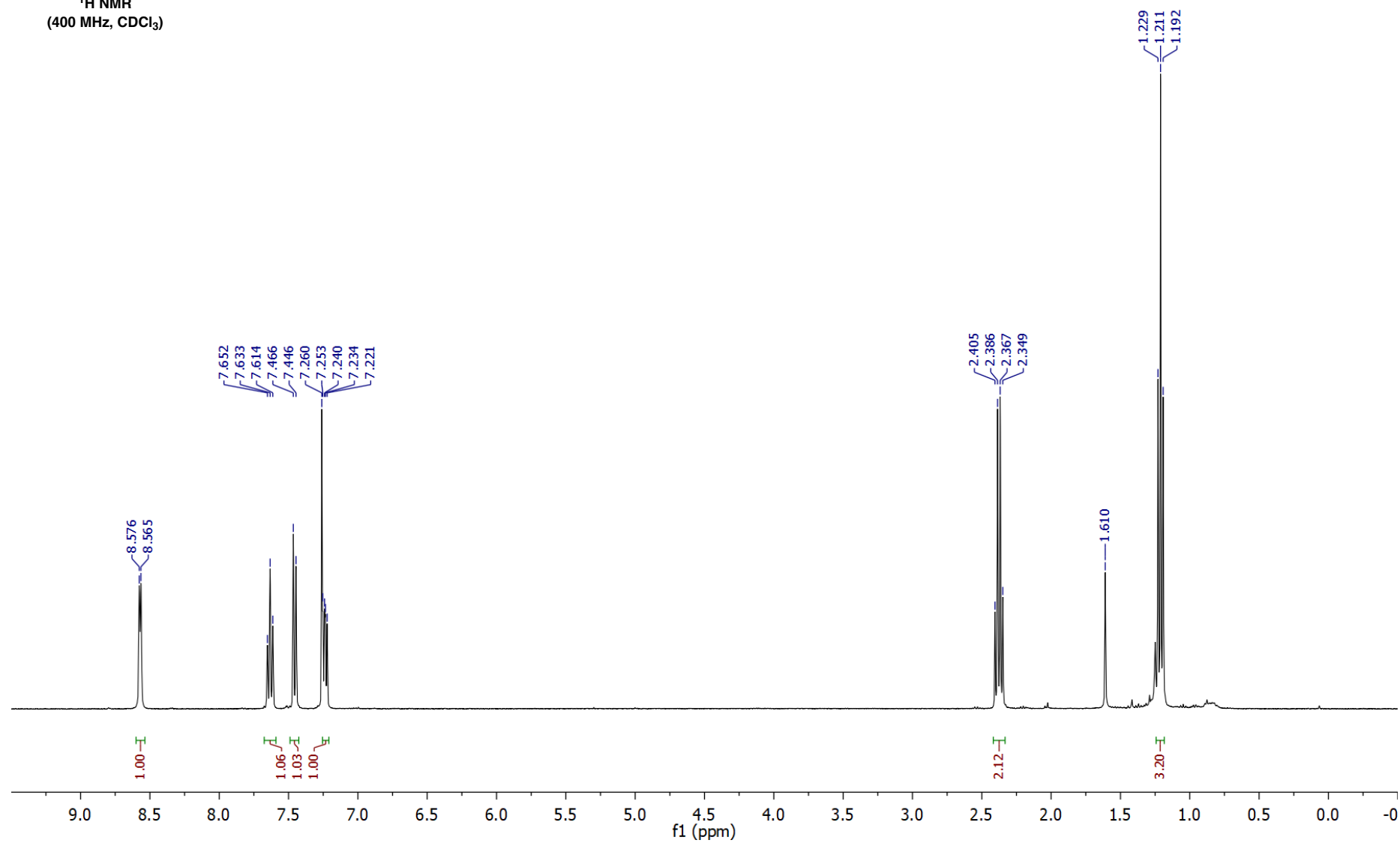


**8b**  
 $^{13}\text{C}$  NMR  
(100 MHz,  $\text{CDCl}_3$ )

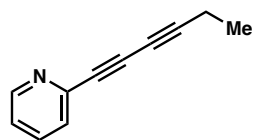




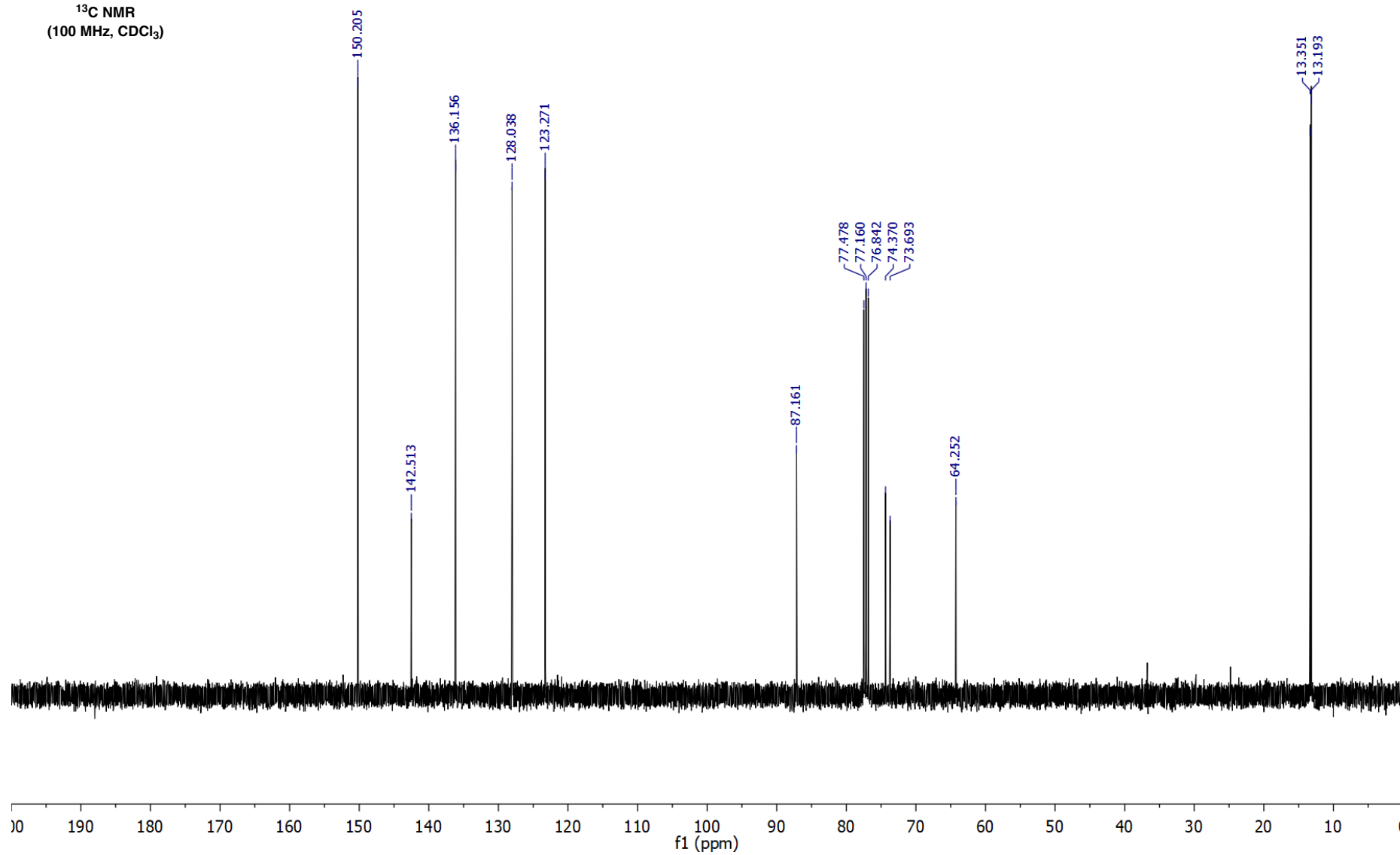
**8c**  
 $^1\text{H}$  NMR  
(400 MHz,  $\text{CDCl}_3$ )

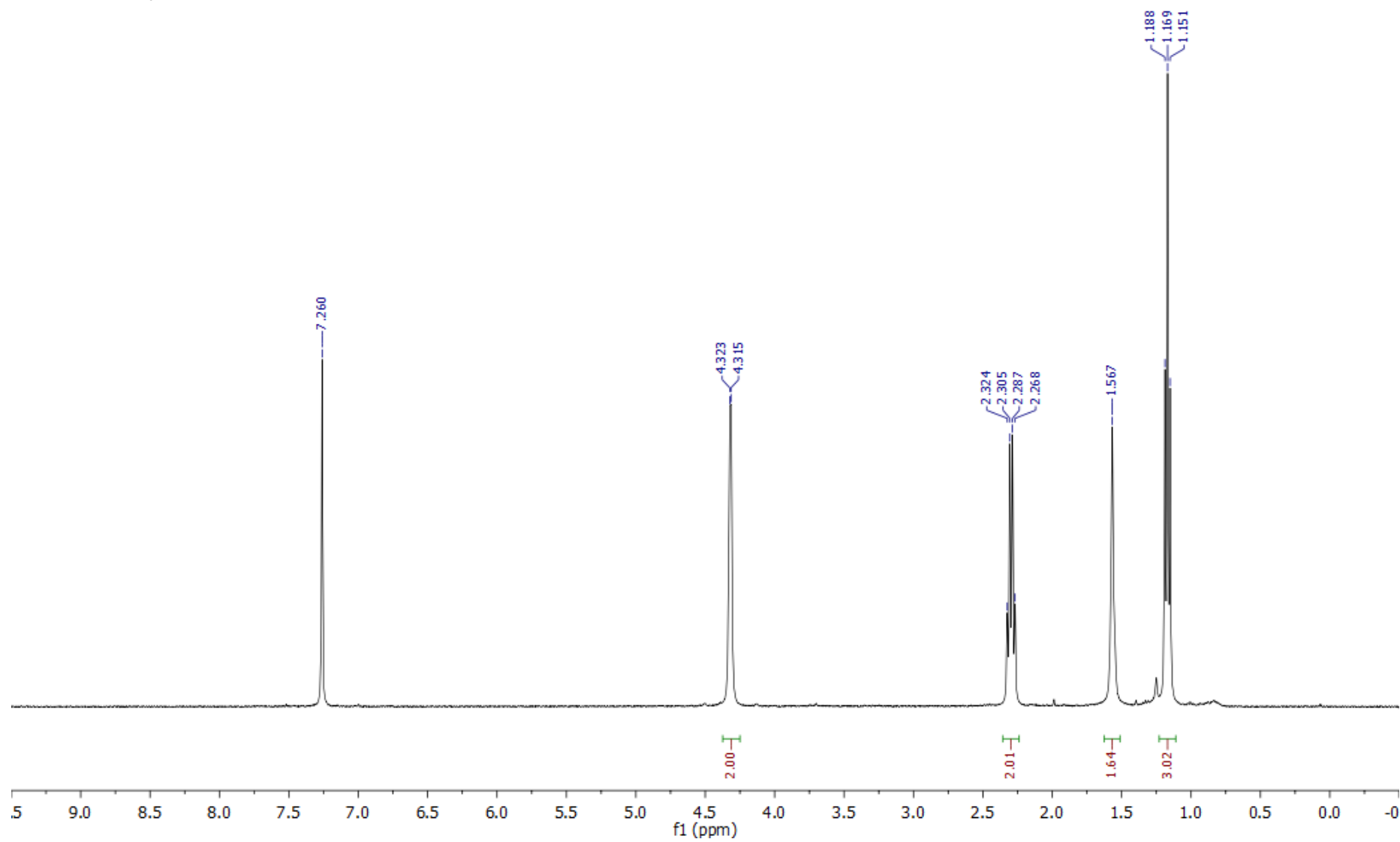
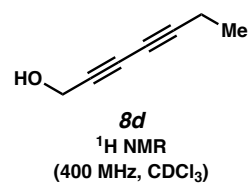


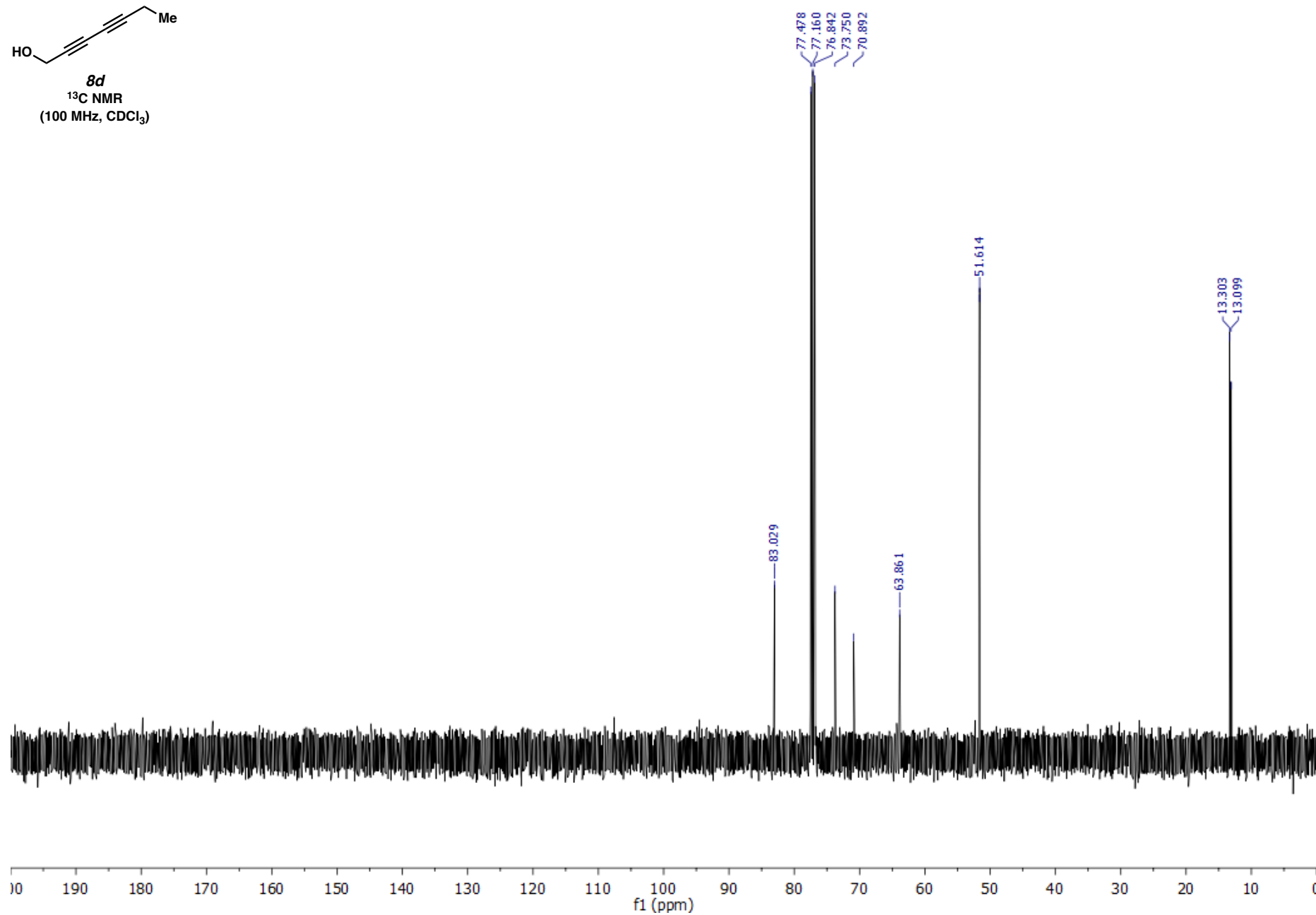
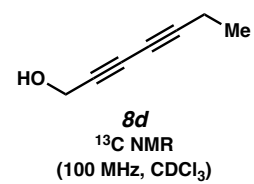


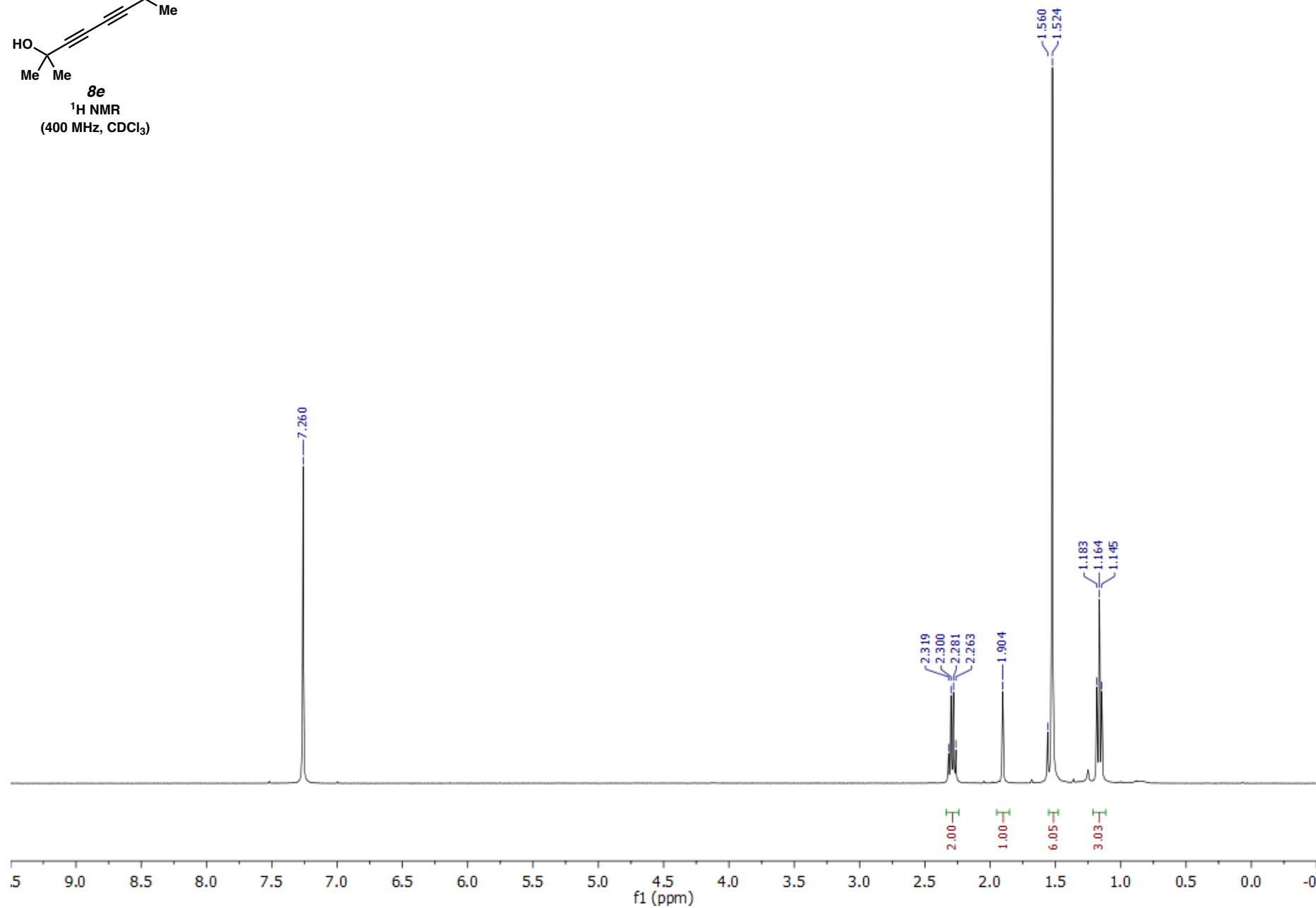
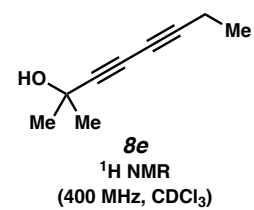


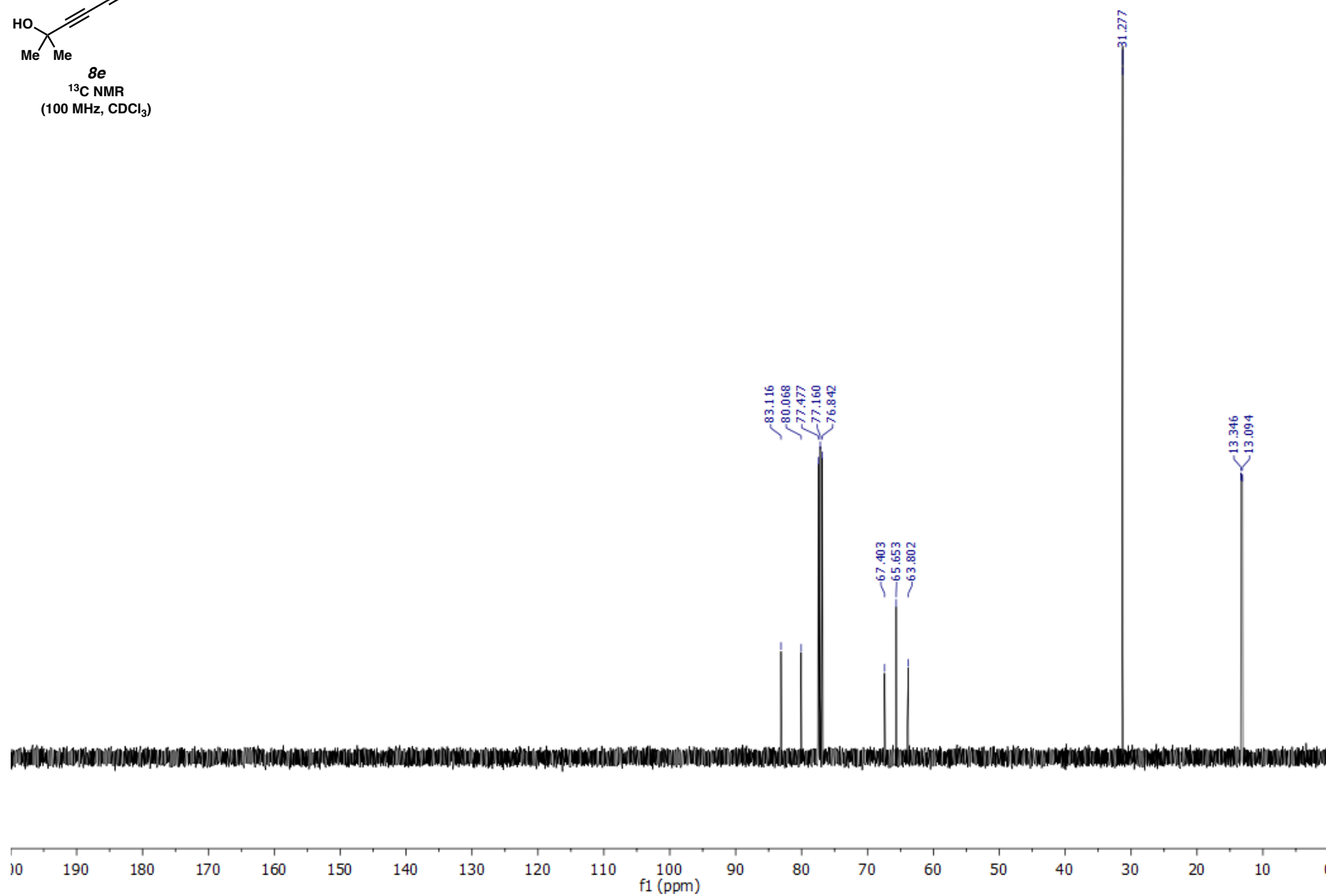
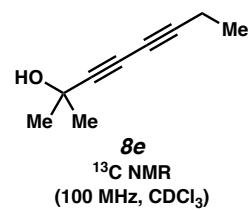
**8c**  
 $^{13}\text{C}$  NMR  
(100 MHz,  $\text{CDCl}_3$ )

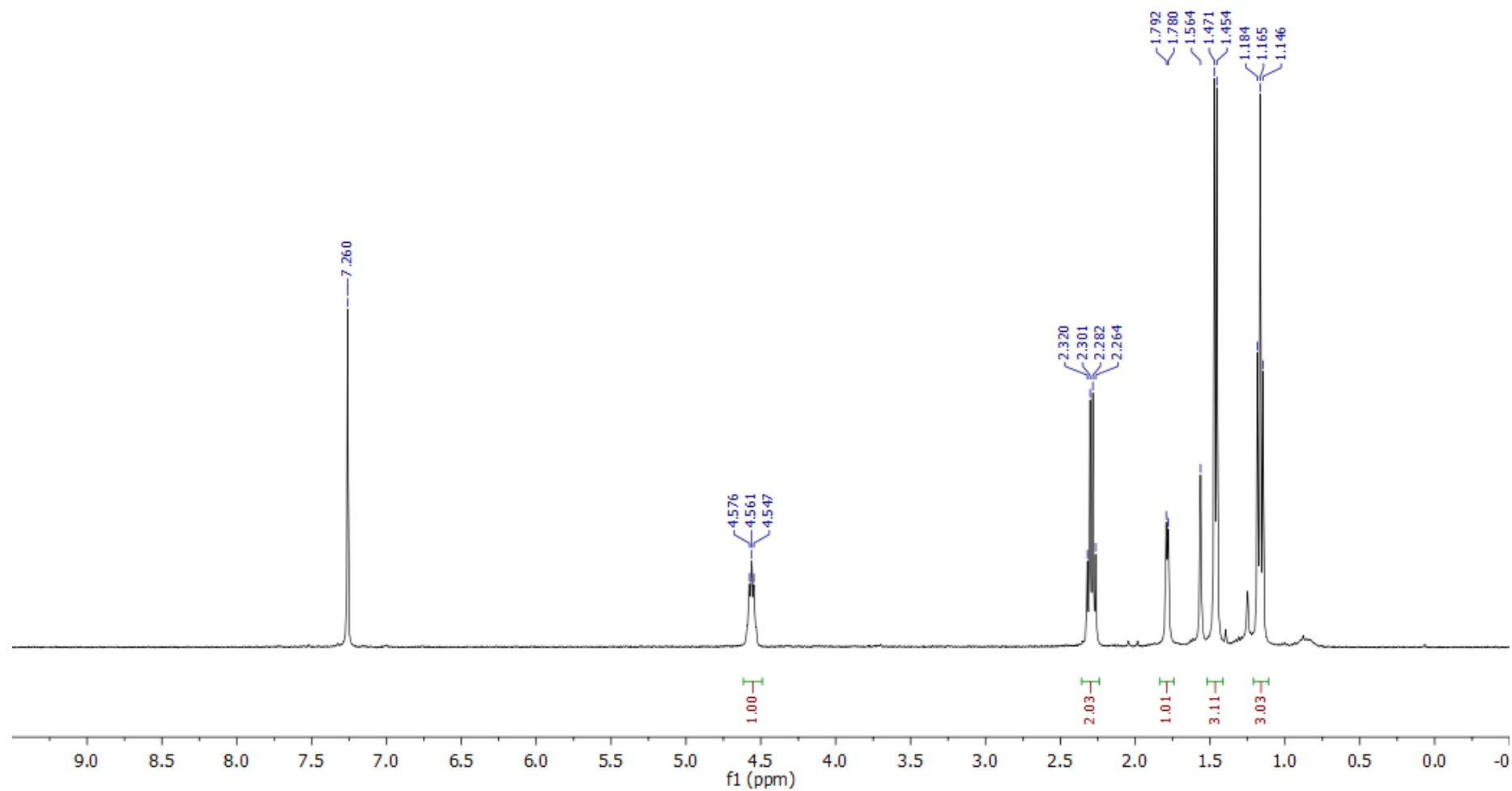
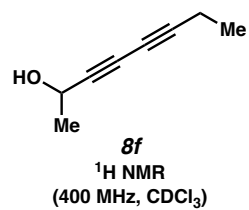


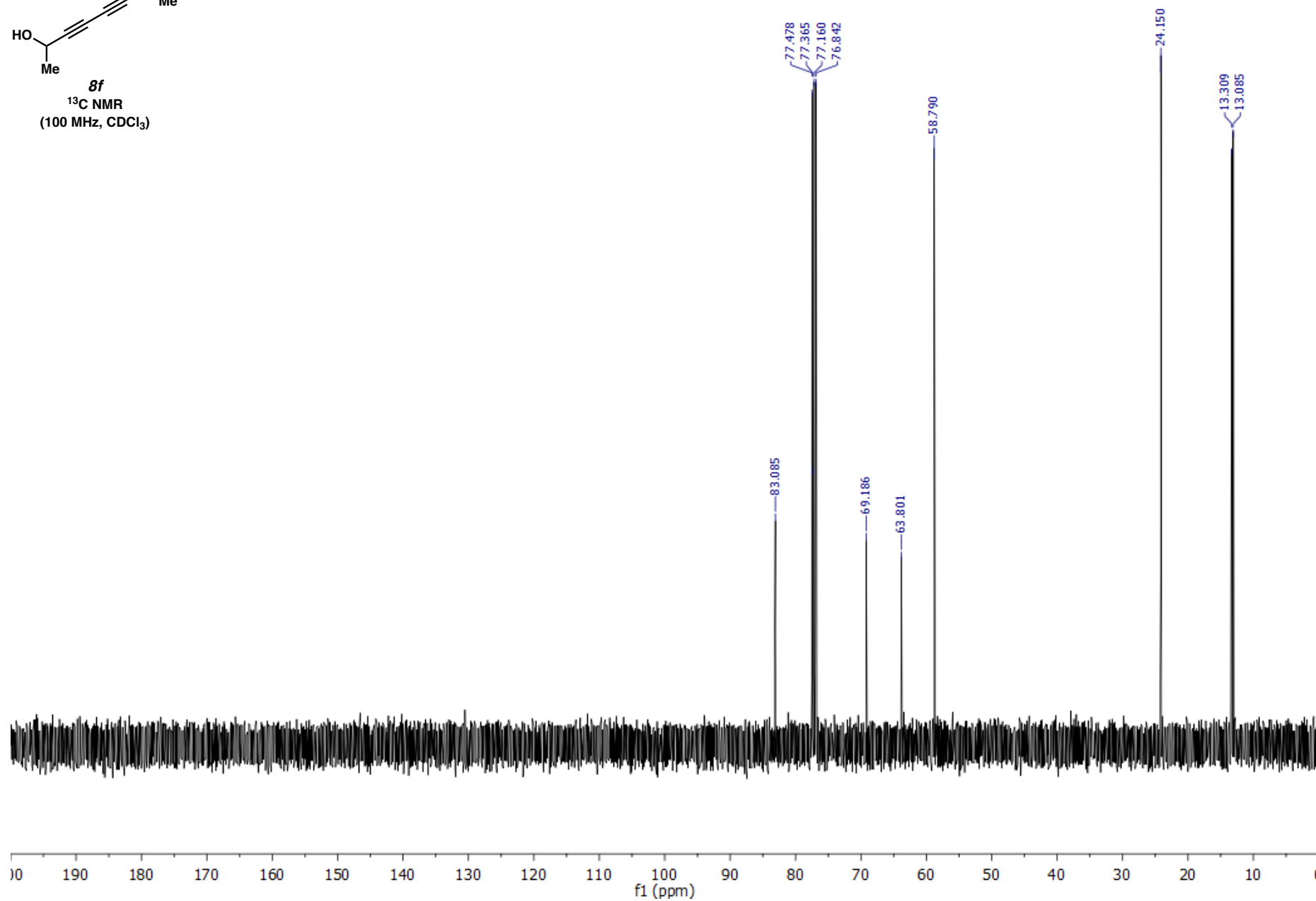
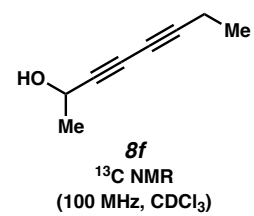


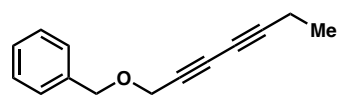




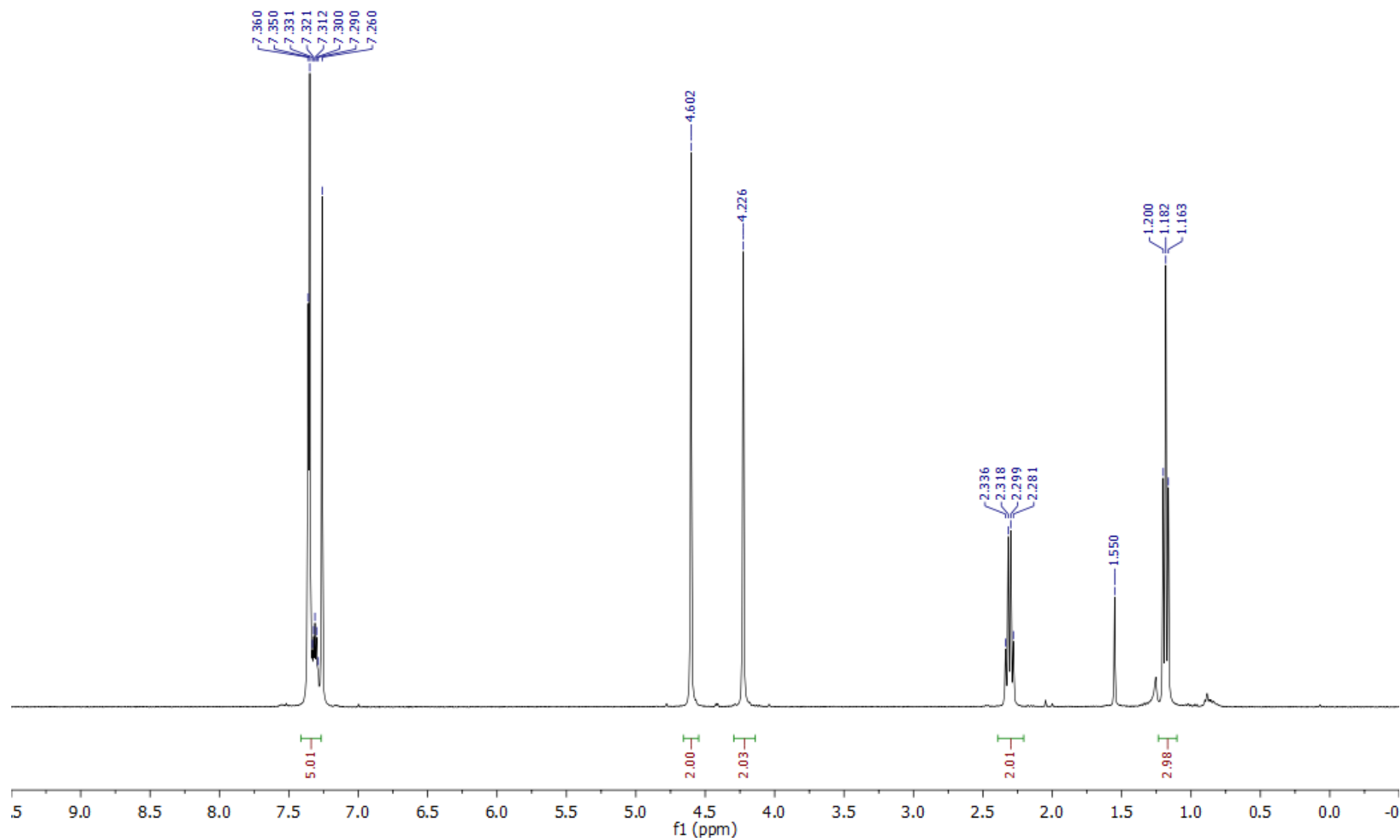




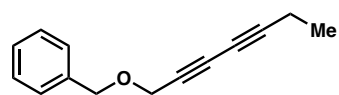




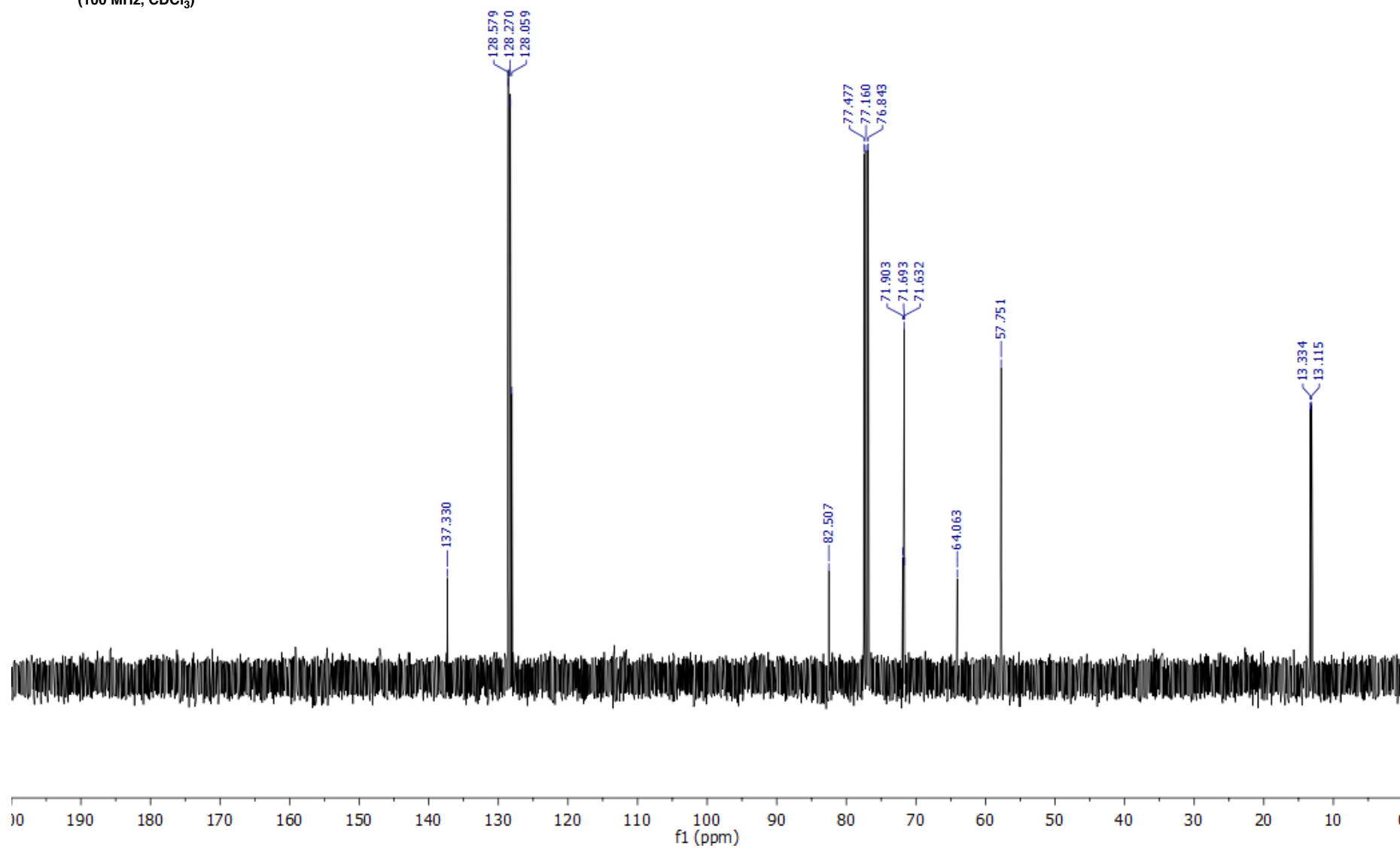
**8g**  
 $^1\text{H}$  NMR  
(400 MHz,  $\text{CDCl}_3$ )

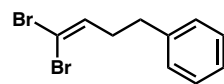




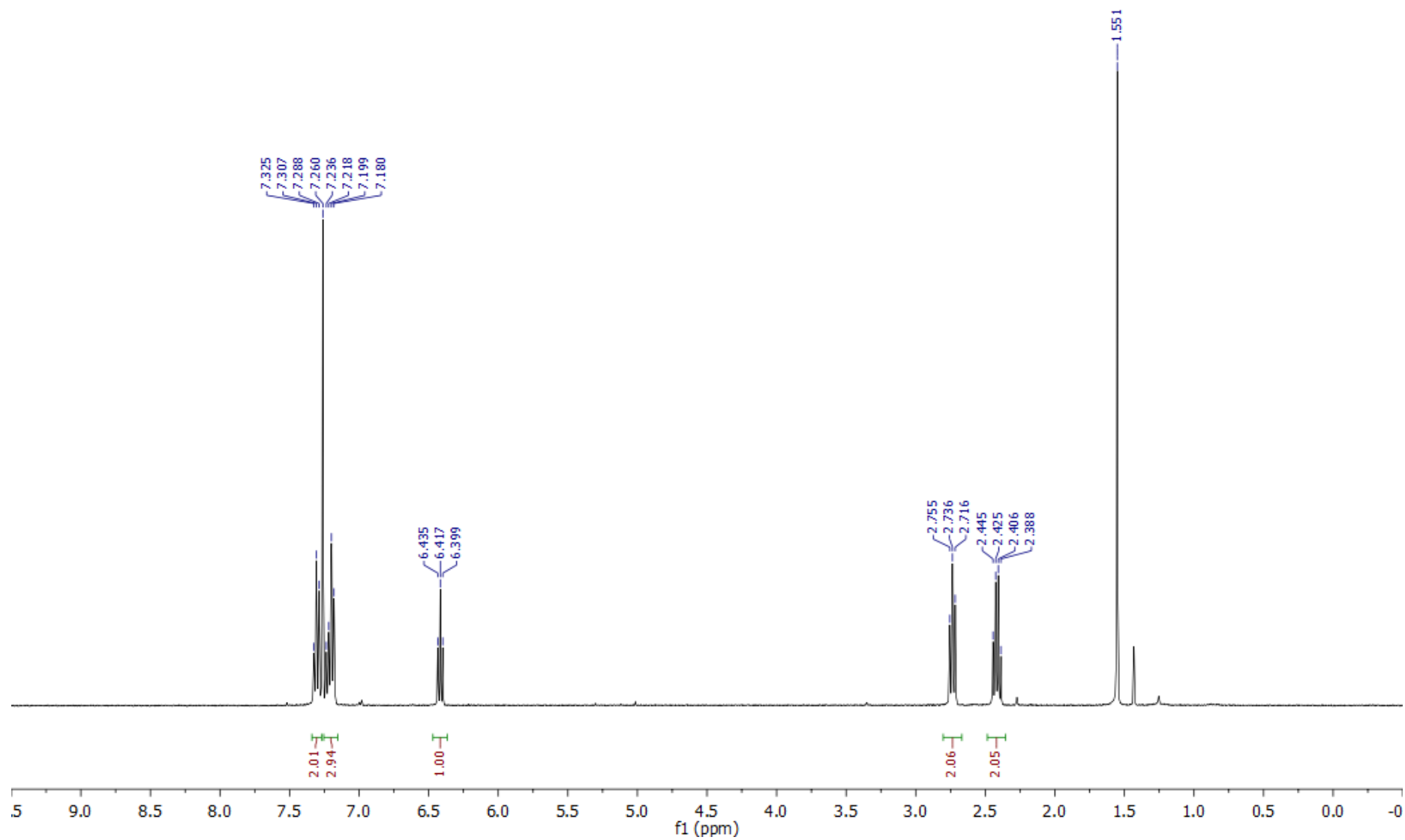


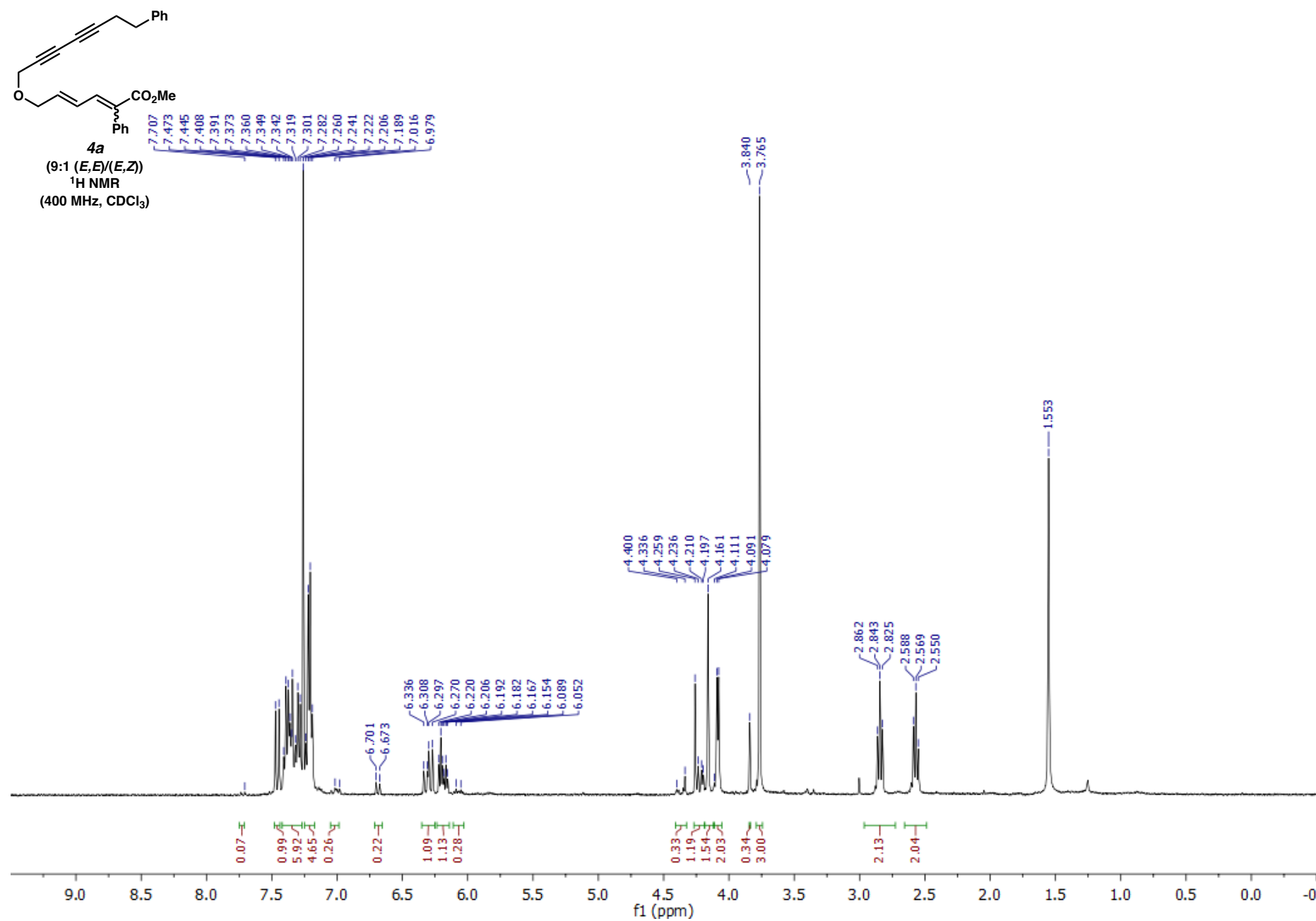
**8g**  
<sup>13</sup>C NMR  
(100 MHz, CDCl<sub>3</sub>)

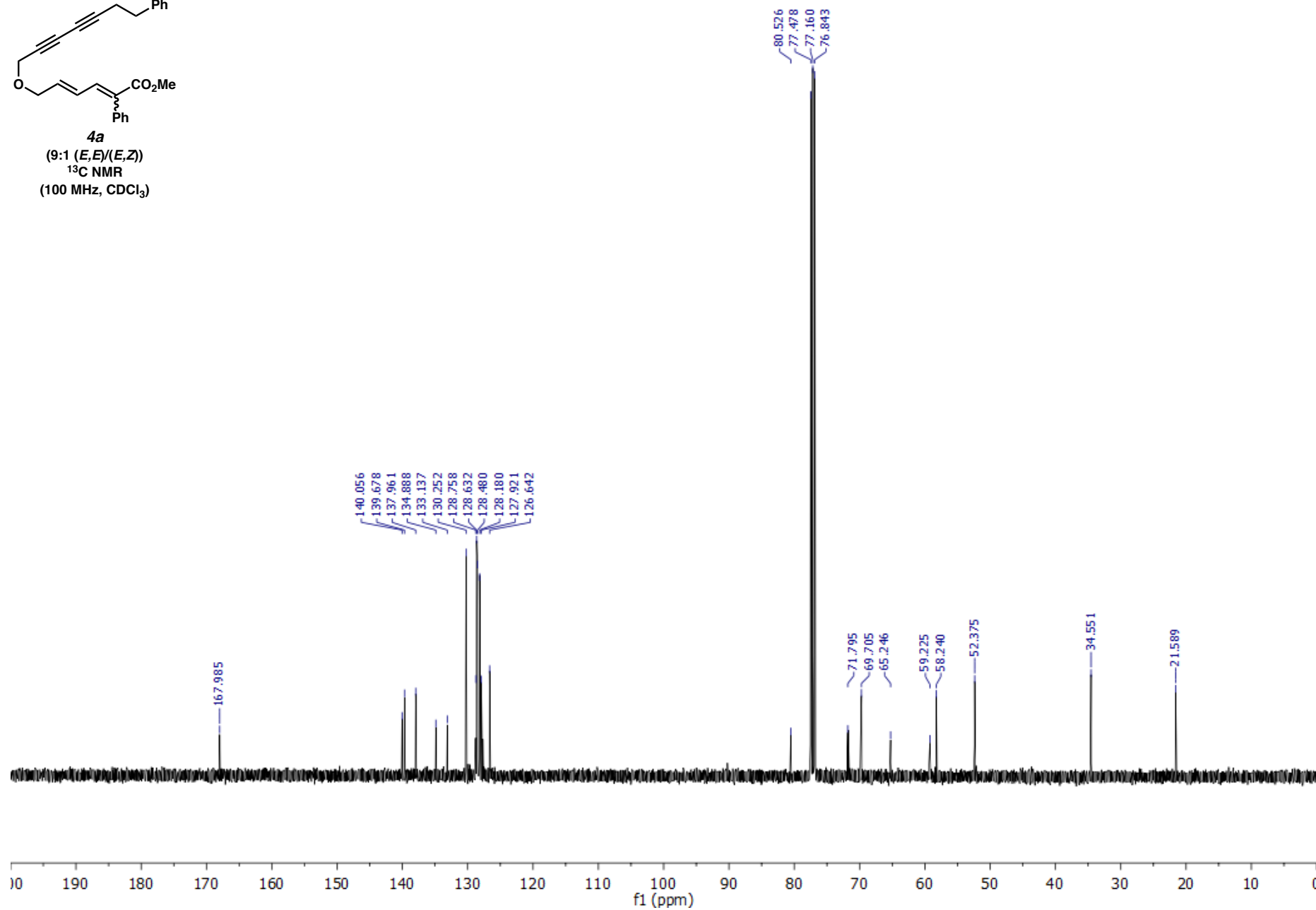
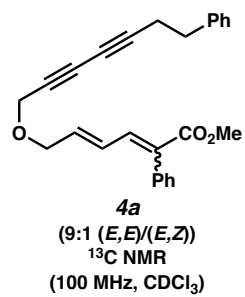


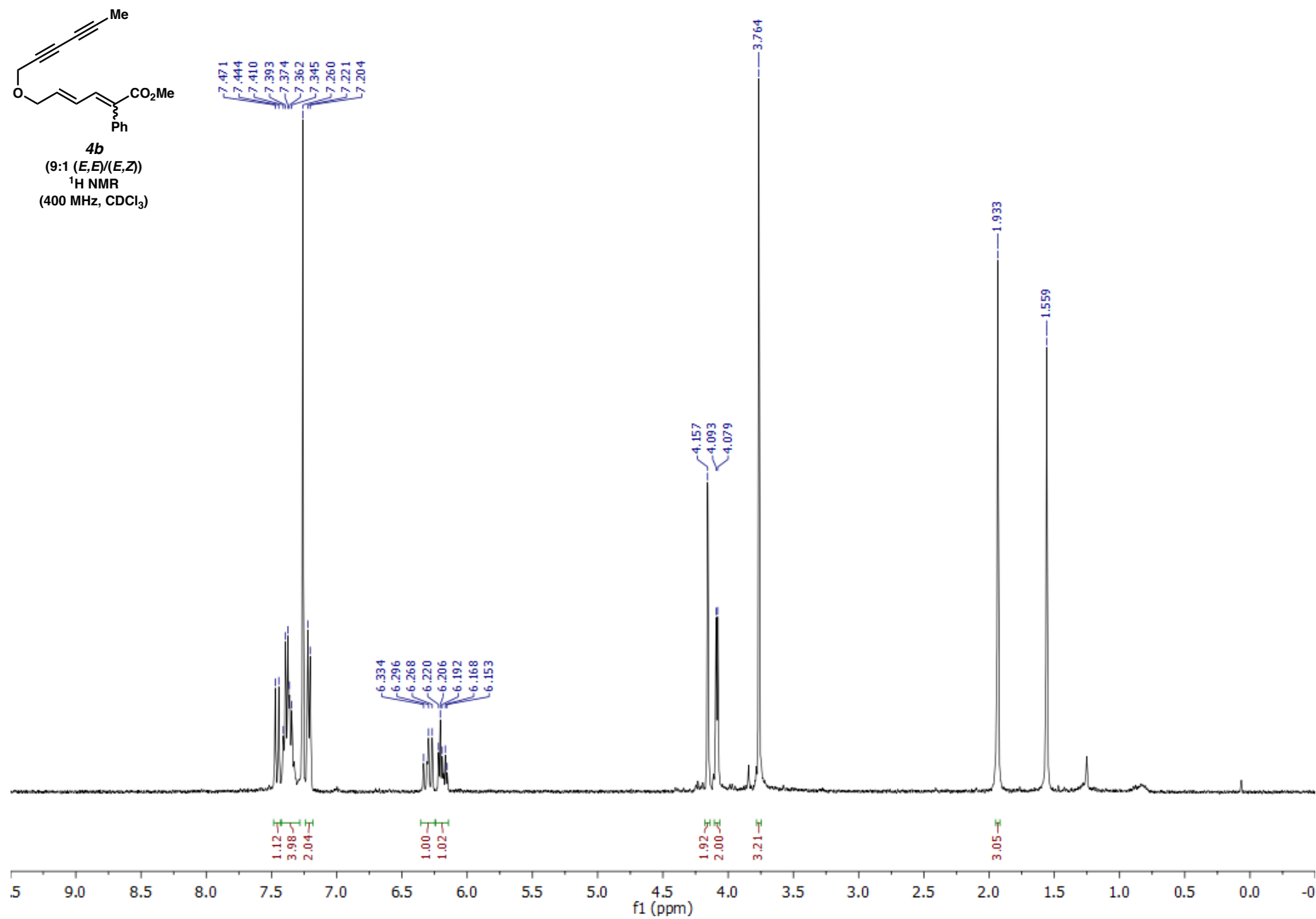


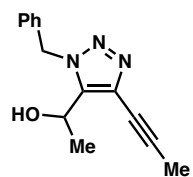
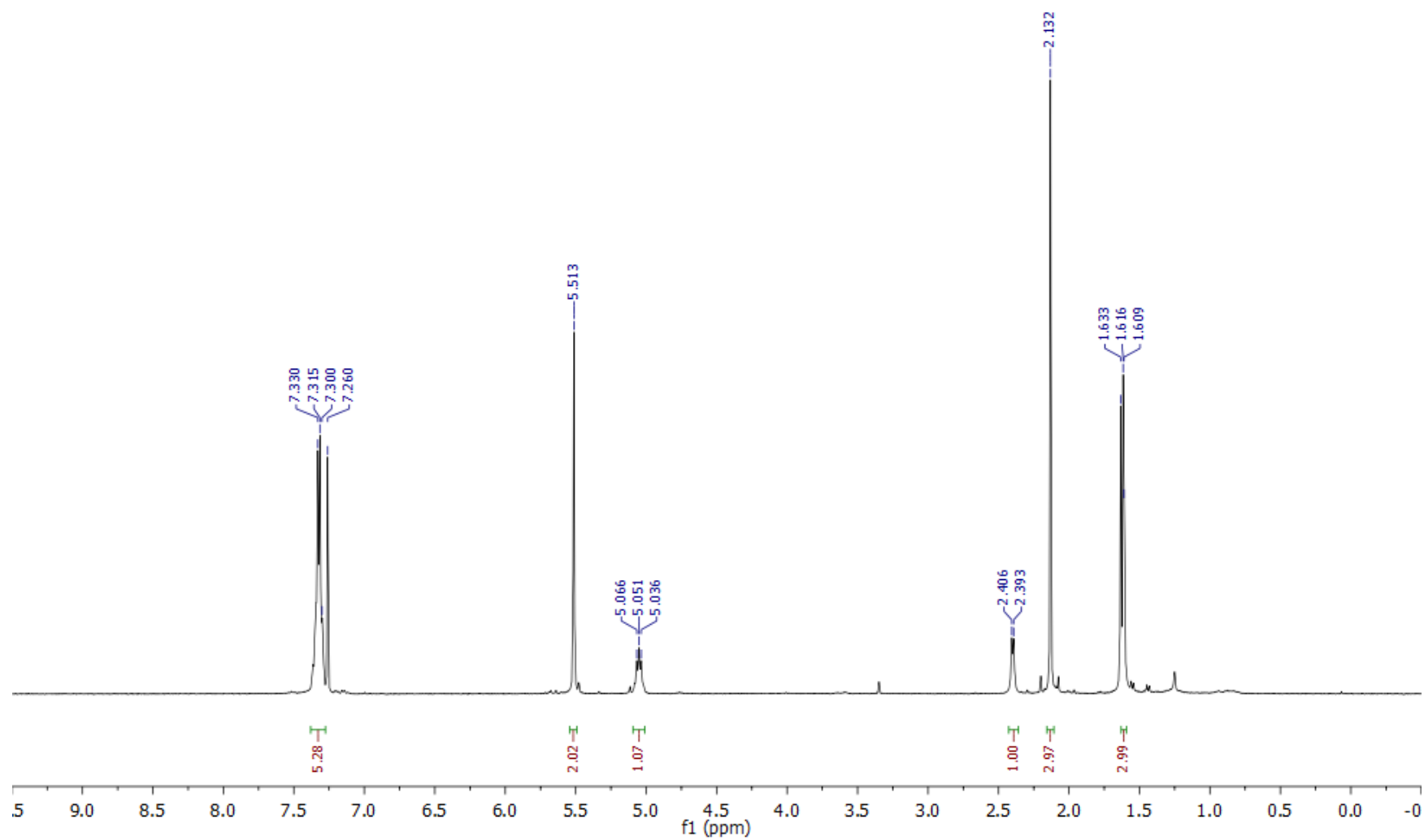
XX  
 $^1\text{H}$  NMR  
(400 MHz,  $\text{CDCl}_3$ )

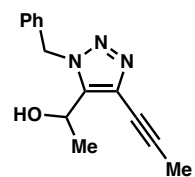




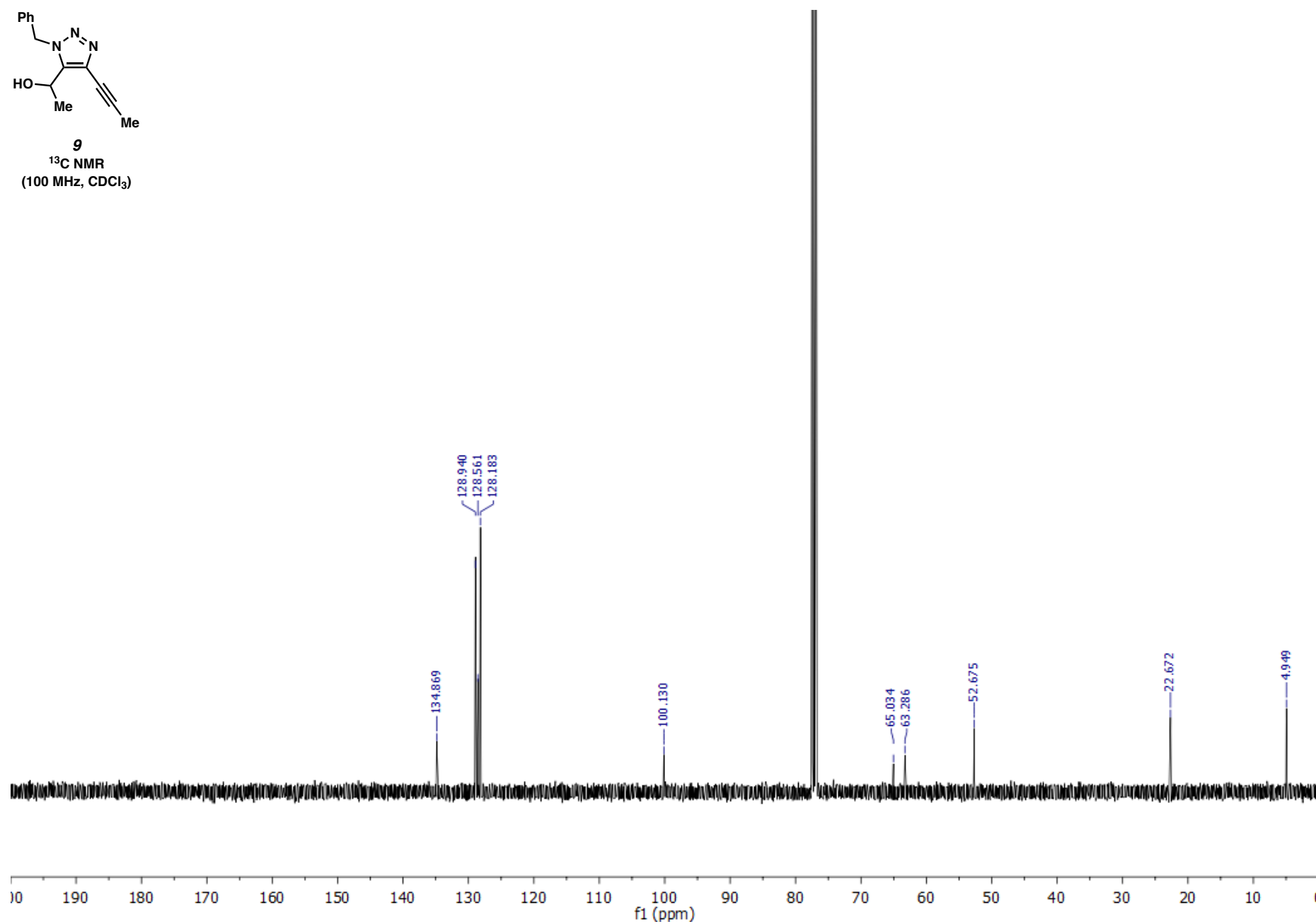


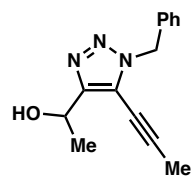


**9**<sup>1</sup>H NMR  
(400 MHz, CDCl<sub>3</sub>)

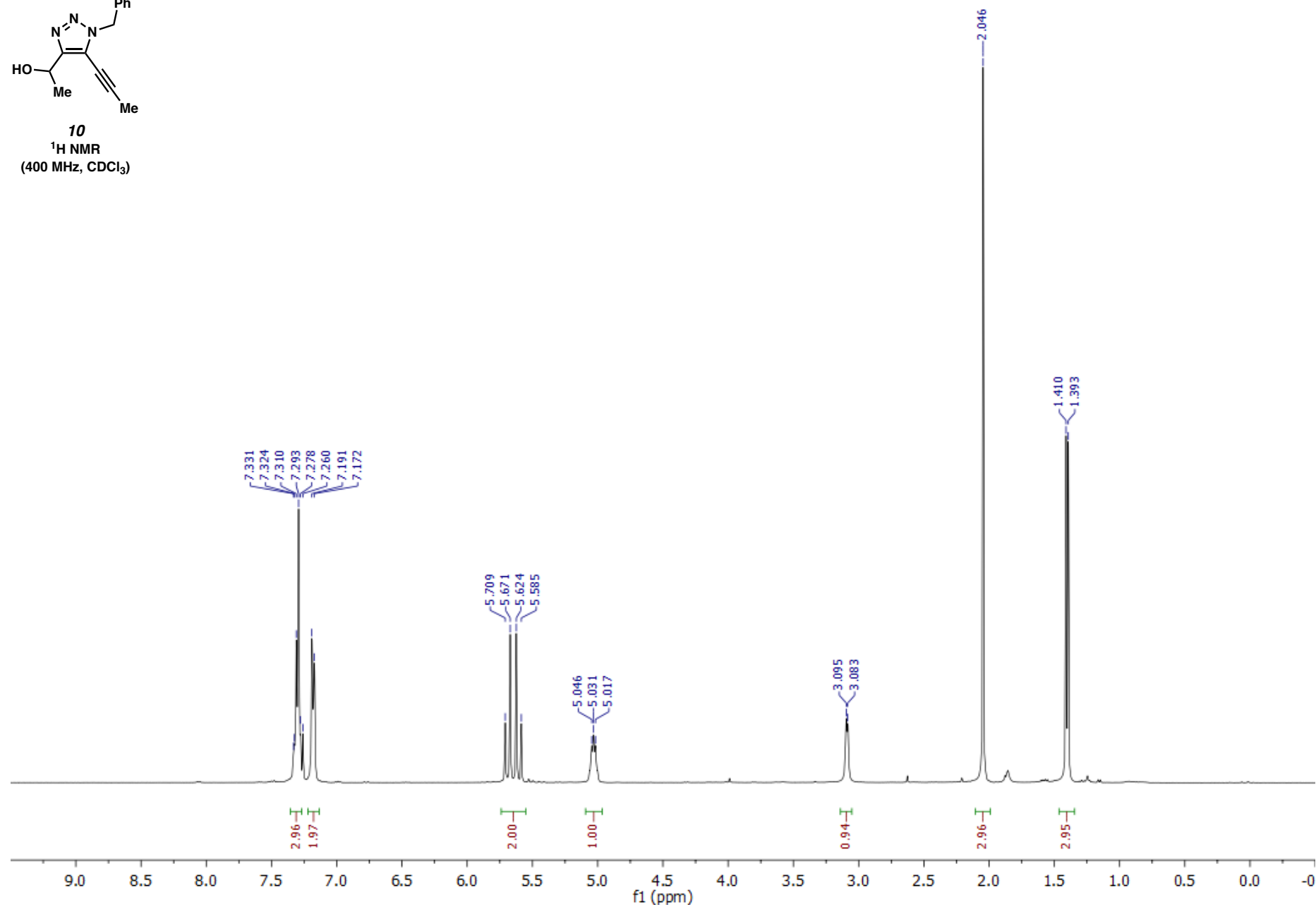


**9**  
 $^{13}\text{C}$  NMR  
(100 MHz,  $\text{CDCl}_3$ )

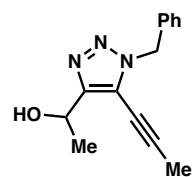




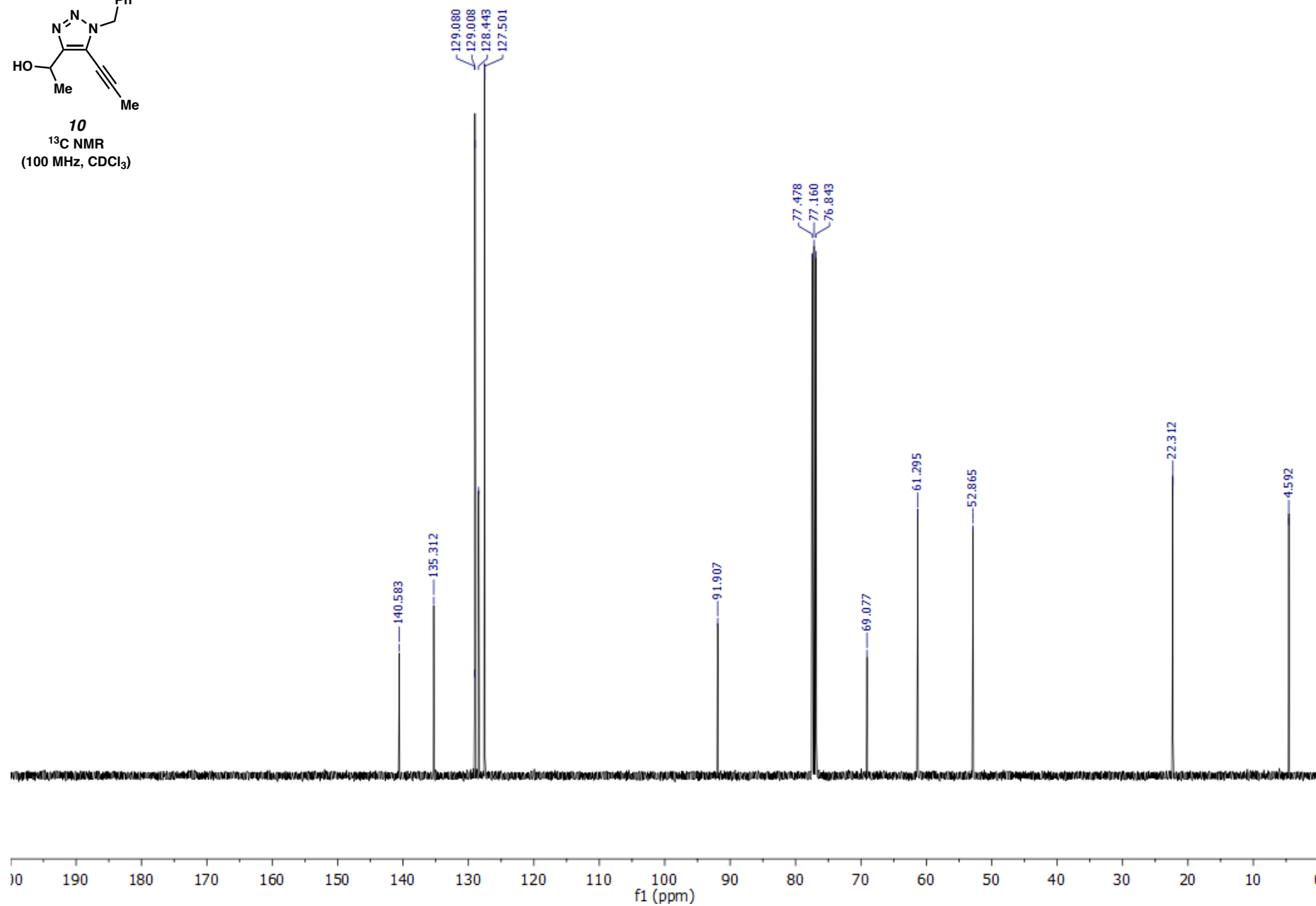
**10**  
 $^1\text{H}$  NMR  
(400 MHz,  $\text{CDCl}_3$ )

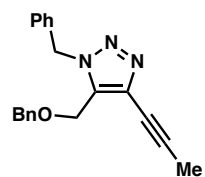




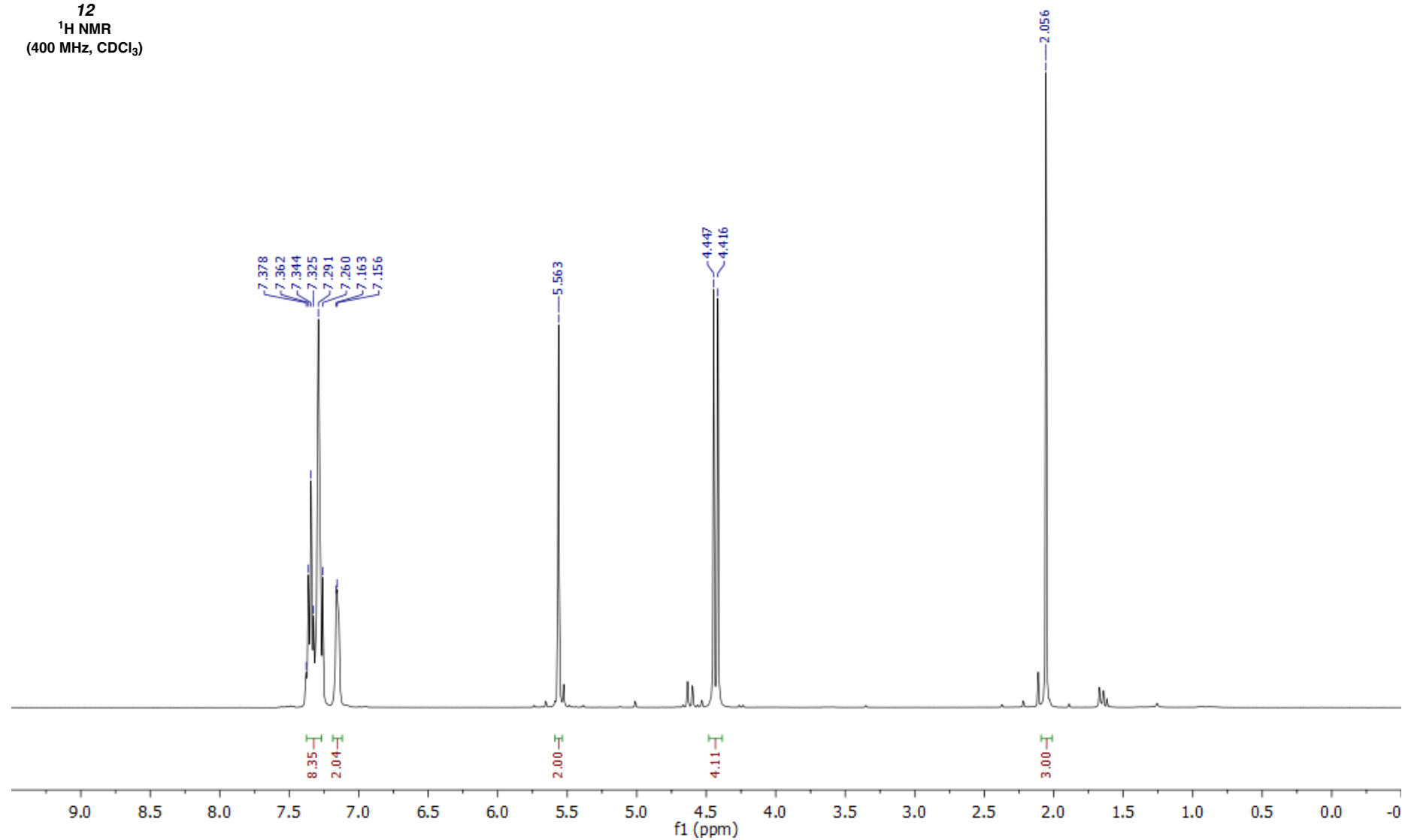


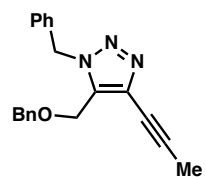
**10**  
 $^{13}\text{C}$  NMR  
(100 MHz,  $\text{CDCl}_3$ )





**12**  
 $^1\text{H}$  NMR  
(400 MHz,  $\text{CDCl}_3$ )





**12**  
 $^{13}\text{C}$  NMR  
(100 MHz,  $\text{CDCl}_3$ )

