

# Sonogashira Couplings of Aryl Bromides: Room Temperature, Water Only, No Copper

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## Supporting Information

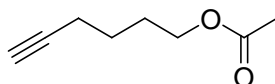
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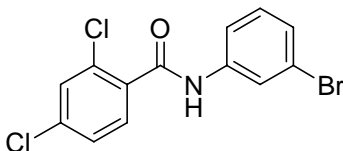
**General Information.** Reactions were performed in oven-dried glassware containing a Teflon coated stir bar and septum. Pd(dtbpf)Cl<sub>2</sub> (CAS# 95408-45-0) was generously supplied by Johnson Matthey, Neolyst™ CX31 (CAS# 884879-23-6) from Umicore AG & Co. KG., phosphine ligands **12-14** from Takasago, and PTS from Zymes, LLC. These and all other commercially available reagents were used without further purification, except for: Et<sub>3</sub>N and CH<sub>2</sub>Cl<sub>2</sub> which were distilled from CaH<sub>2</sub> prior to use. Water (HPLC grade) was purchased from Acros and degassed by sparging with argon prior to use. For TLC analyses Kieselgel 60 F<sub>254</sub> pre-coated silica gel plates (Merck, 0.25 mm thick) were used; and for silica gel chromatography Silia Flash® P60 (SiliCycle, 40-63 μm) was used. GC analyses were performed using Hewlett-Packard HP5890 (with a Restek RTX-1 capillary column) and/or Hewlett-Packard HP6890 (with an Agilent Technologies HP-1 capillary column) gas chromatographs. <sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained using a Varian UNITY INOVA 400 MHz NMR spectrometer. High-resolution mass spectral analyses were obtained using a VG70 double-focusing magnetic sector instrument (VG Analytical) for EI and a PE Sciex QStar Pulsar quadrupole/TOF instrument (API) for ESI. Melting points were measured using a Laboratory Devices, USA MEL-TEMP II melting point apparatus and are uncorrected.

**Preparation of a degassed 3 wt % PTS aqueous solution.** To a 50 mL round-bottom flask was added PTS (4.0 g), degassed on a high-vacuum manifold, and back-flushed with argon. Degassed water (36.0 mL) was added via syringe and the contents of the flask were swirled with periodic heating (via heat gun) until a clear, homogeneous solution was afforded (~5-10 min). This stock solution of 10 wt % PTS (0.3 mL) was diluted with *degassed* water (0.7 mL) to give the 3 wt % aqueous PTS solution (1.0 mL) that was used in each experiment.

**Preparation of a non-degassed 3 wt % PTS aqueous solution.** Same procedure as with the *degassed* PTS solution except the PTS was not degassed and *non-degassed* water was added. The *non-degassed* PTS solution was stored under argon.

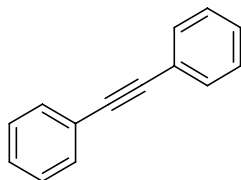


**6-Acetoxy-1-hexyne.** In a 5 mL round-bottom equipped with a stir bar under argon, Ac<sub>2</sub>O (1.0 mL, 10.6 mmol) was added via syringe to a stirring solution of 5-hexyn-1-ol (1.0 mL, 9.07 mmol) and pyridine (860 μL, 10.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5.0 mL) and the reaction was allowed to stir at rt. Reaction progress was monitored by GC. After 26 h the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with water (2x), and the combined aqueous layers were back extracted with CH<sub>2</sub>Cl<sub>2</sub> to afford a crude orange liquid after drying over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentration by rotary evaporation. Kugelrohr distillation (0.1 mm Hg, 90-105 °C) of the crude material provided the titled product (1.01 g, 79%) as a clear colorless liquid; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) matches previously reported spectra data.<sup>1</sup>

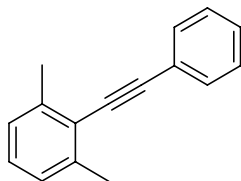


**N-(3'-Bromophenyl)-2,4-dichlorobenzamide (15; Scheme 4).** In a 25 mL round-bottom flask equipped with a stir bar under argon at 0 °C, 3,5-dichlorobenzoyl chloride (520 μL, 3.71 mmol) was

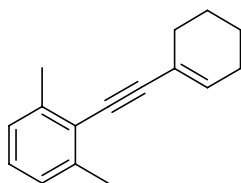
added via syringe to a stirring solution of 3-bromoaniline (400  $\mu\text{L}$ , 3.67 mmol) and  $\text{Et}_3\text{N}$  (1.0 mL, 7.18 mmol) in  $\text{CH}_2\text{Cl}_2$  (7.0 mL) and the reaction was allowed to stir while gradually warming to rt. Reaction progress was monitored by TLC. After 35 min, the mixture was diluted with  $\text{CH}_2\text{Cl}_2$  and washed with water (3x), the organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (eluent: gradient from hexanes to 8% ethyl acetate/hexanes) to afford the titled product (1.16 g, 92%) as a white solid; mp 125-127  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.94 (brs, 1H), 7.90 (s, 1H), 7.73 (d,  $J = 8.4$  Hz, 1H), 7.54 (d,  $J = 8.0$  Hz, 1H), 7.49 (d,  $J = 2.0$  Hz, 1H), 7.38 (dd,  $J = 8.4, 2.0$  Hz, 1H), 7.32 (dt,  $J = 8.4, 1.2$  Hz, 1H), 7.24 (d,  $J = 8.0$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  163.71, 138.71, 137.74, 133.18, 131.66 (2C), 130.65, 130.45, 128.26, 128.02, 123.27, 122.98, 118.80; HRESI-MS  $m/z$  Calcd. for  $\text{C}_{13}\text{H}_8\text{BrCl}_2\text{NO}$  ( $[\text{M}+\text{Na}]^+$ ) 365.9058, found 365.9042.



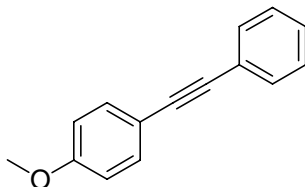
**Standard Procedure A for Sonogashira Coupling: Diphenylacetylene (Scheme 2).** To a 5 mL round-bottom flask equipped with a stir bar was added under argon  $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$  (1.3 mg, 0.005 mmol), X-Phos (5.8 mg, 0.012 mmol), and  $\text{Cs}_2\text{CO}_3$  (543 mg, 1.66 mmol). Under a positive flow of argon were added via syringe first, *degassed* PTS solution (1.0 mL, 3 wt %), then bromobenzene (50.0  $\mu\text{L}$ , 0.48 mmol), and then phenylacetylene (60.0  $\mu\text{L}$ , 0.55 mmol). A milky, tan-colored mixture developed over 3 h while stirring at rt. Reaction progress was monitored by GC. After 4.5 h the mixture was diluted with brine and extracted with ethyl acetate (4x). The combined organic extracts was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated by rotary evaporation to give a crude brown oil. Purification by silica gel chromatography eluting with hexanes afforded the titled product (70 mg, 83%) as a light yellow solid; mp 58-60  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) matches previously reported spectra data.<sup>2</sup>



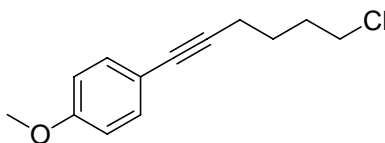
**2,6-Dimethylphenylphenylacetylene (Table 1, entry 1a).** Following standard procedure A, using  $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$  (1.5 mg, 0.006 mmol), X-Phos (6.4 mg, 0.013 mmol),  $\text{Cs}_2\text{CO}_3$  (601 mg, 1.84 mmol), 2-bromo-*m*-xylene (70  $\mu\text{L}$ , 0.52 mmol), phenylacetylene (90  $\mu\text{L}$ , 0.82 mmol), and *degassed* PTS (1.0 mL, 3 wt %) for 20 h, the titled product (107 mg, 99%) was obtained as a colorless oil after silica gel chromatography (eluent: hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) matches previously reported spectra data.<sup>3</sup>



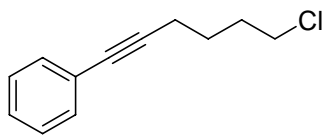
**Standard Procedure B for Sonogashira Coupling: 2-(cyclohex-1-enylethynyl)-1,3-dimethylbenzene (Table 1, entry 1b).** To a 5 mL round-bottom flask equipped with a stir bar was added under argon Pd(CH<sub>3</sub>CN)<sub>2</sub>Cl<sub>2</sub> (1.8 mg, 0.007 mmol) and X-Phos (6.9 mg, 0.014 mmol). Under a positive flow of argon were added via syringe, first *degassed* PTS solution (1.0 mL, 3 wt %), then Et<sub>3</sub>N (150 μL, 1.08 mmol), then 2-bromo-*m*-xylene (70 μL, 0.52 mmol), and finally 1-ethynylcyclohexene (100 μL, 0.85 mmol). A milky brown mixture developed over 20 min while stirring at rt. Reaction progress was monitored by GC. After 23 h the mixture was diluted with brine and extracted with ethyl acetate (4x). The combined organic extracts was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated by rotary evaporation to give a crude brown oil that was purified by silica gel chromatography eluting with hexanes afforded the titled product (110 mg, quant) as a colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) matches previously reported spectra data.<sup>4</sup>



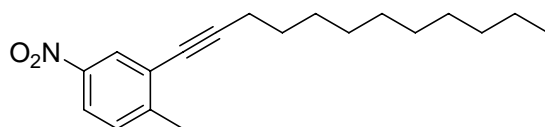
**4-(Phenylethynyl)-anisole (Table 1, entry 2a).** Following standard procedure A, using Pd(CH<sub>3</sub>CN)<sub>2</sub>Cl<sub>2</sub> (1.5 mg, 0.006 mmol), X-Phos (7.0 mg, 0.015 mmol), Cs<sub>2</sub>CO<sub>3</sub> (548 mg, 1.68 mmol), 4-bromoanisole (60 μL, 0.48 mmol), phenylacetylene (70 μL, 0.64 mmol), and *degassed* PTS (1.0 mL, 3 wt %) for 20 h, the titled product (89 mg, 89%) was obtained as a yellow-tan solid after silica gel chromatography (eluent: hexanes); mp 57-59 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) matches previously reported spectra data.<sup>2</sup>



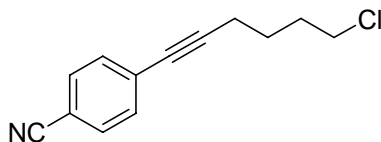
**4-(6-Chlorohex-1-ynyl)-anisole (Table 1, entry 2b).** Following standard procedure B, using Pd(CH<sub>3</sub>CN)<sub>2</sub>Cl<sub>2</sub> (1.3 mg, 0.005 mmol), X-Phos (6.0 mg, 0.012 mmol), Et<sub>3</sub>N (140 μL, 1.00 mmol), 4-bromoanisole (60 μL, 0.48 mmol), 6-chloro-1-hexyne (90 μL, 0.74 mmol), and *degassed* PTS (1.0 mL, 3 wt %) for 25 h, the titled product (59 mg, 55%) was obtained as a yellow oil after silica gel chromatography (eluent: hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.34 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H), 3.62 (t, *J* = 6.6 Hz, 2H), 2.46 (t, *J* = 7.0 Hz, 2H), 2.01-1.94 (m, 2H), 1.80-1.72 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 159.29, 133.08, 116.09, 114.02, 87.84, 81.10, 55.46, 44.86, 31.83, 26.17, 18.92; HREI-MS *m/z* Calcd. for C<sub>13</sub>H<sub>15</sub>ClO (M<sup>+</sup>) 222.0811, found 222.0811.



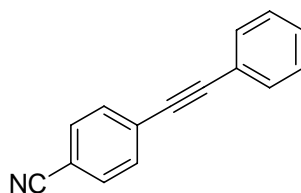
**6-Chloro-1-phenylhex-1-yne (Table 1, entry 3).** Following standard procedure B, using  $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$  (1.3 mg, 0.005 mmol), X-Phos (6.2 mg, 0.013 mmol),  $\text{Et}_3\text{N}$  (140  $\mu\text{L}$ , 1.00 mmol), bromobenzene (50  $\mu\text{L}$ , 0.48 mmol), 6-chloro-1-hexyne (90  $\mu\text{L}$ , 0.74 mmol), and *degassed* PTS (1.0 mL, 3 wt %) for 20 h, the titled product (75 mg, 82%) was obtained as a colorless oil after silica gel chromatography (eluent: hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) matches previously reported spectra data.<sup>5</sup>



**2-(Dodec-1-ynyl)-4-nitrotoluene (Table 1, entry 4).** Following standard procedure B, using  $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$  (1.6 mg, 0.006 mmol), X-Phos (6.4 mg, 0.013 mmol),  $\text{Et}_3\text{N}$  (150  $\mu\text{L}$ , 1.08 mmol), 2-bromo-4-nitrotoluene (109 mg, 0.50 mmol), 1-dodecyne (140  $\mu\text{L}$ , 0.65 mmol), and *degassed* PTS (1.0 mL, 3 wt %) for 18 h, the titled product (150 mg, 99%) was obtained as a yellow oil after silica gel chromatography (eluent: hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.20 (d,  $J = 2.4$  Hz, 1H), 8.00 (dd,  $J = 8.4, 2.4$  Hz, 1H), 7.32 (d,  $J = 8.8$  Hz, 1H), 2.50 (s, 3H), 2.47 (t,  $J = 7.2$  Hz, 2H), 1.67-1.60 (m, 2H), 1.49-1.44 (m, 2H), 1.32-1.28 (m, 12H), 0.88 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  147.75, 146.15, 130.19, 126.82, 125.62, 122.30, 97.60, 77.77, 32.11, 29.79, 29.74, 29.53, 29.34, 29.12, 28.80, 22.90, 21.26, 19.69, 14.33; HREI-MS  $m/z$  Calcd. for  $\text{C}_{19}\text{H}_{27}\text{NO}_2$  ( $\text{M}^+$ ) 301.2042, found 301.2051.

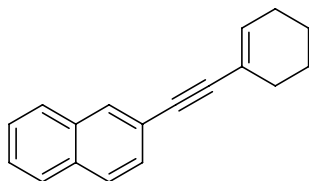


**4-(6-Chlorohex-1-ynyl)benzonitrile (Table 1, entry 5a).** Following standard procedure A, using  $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$  (1.3 mg, 0.005 mmol), X-Phos (6.6 mg, 0.014 mmol),  $\text{Cs}_2\text{CO}_3$  (574 mg, 1.76 mmol), 4-bromobenzonitrile (92 mg, 0.51 mmol), 6-chloro-1-hexyne (90  $\mu\text{L}$ , 0.74 mmol), and *degassed* PTS (1.0 mL, 3 wt %) for 6 h, the titled product (102 mg, 93%) was obtained as a light yellow oil after silica gel chromatography (eluent: hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.58 (d,  $J = 8.4$  Hz, 2H), 7.46 (d,  $J = 8.4$  Hz, 2H), 3.61 (t,  $J = 6.6$  Hz, 2H), 2.50 (t,  $J = 7.0$  Hz, 2H), 1.99-1.92 (m, 2H), 1.82-1.75 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  132.29, 132.14, 128.97, 118.80, 111.16, 94.61, 80.17, 44.63, 31.77, 25.78, 19.03; HREI-MS  $m/z$  Calcd. for  $\text{C}_{13}\text{H}_{12}\text{ClN}$  ( $\text{M}^+$ ) 217.0658, found 217.0668.

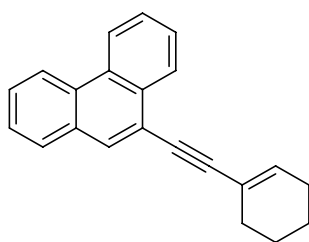


**4-(Phenylethynyl)benzonitrile (Table 1, entry 5b).** Following standard procedure A, using  $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$  (1.5 mg, 0.006 mmol), X-Phos (6.6 mg, 0.014 mmol),  $\text{Cs}_2\text{CO}_3$  (574 mg, 1.76 mmol), 4-

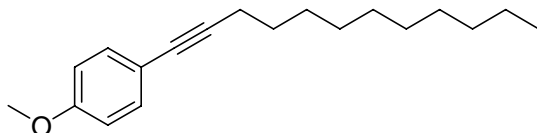
bromobenzonitrile (92 mg, 0.51 mmol), phenylacetylene (80  $\mu$ L, 0.73 mmol), and *degassed* PTS (1.0 mL, 3 wt %) for 4 h, the titled product (100 mg, 97%) was obtained as a light yellow solid after silica gel chromatography (eluent: gradient from hexanes to 1% diethyl ether/hexanes); mp 102-104  $^{\circ}$ C;  $^1$ H NMR (400 MHz,  $\text{CDCl}_3$ ) matches previously reported spectra data.<sup>3</sup>



**2-(Cyclohex-1-enylethynyl)naphthalene (Table 1, entry 6).** Following standard procedure B, using  $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$  (1.3 mg, 0.005 mmol), X-Phos (6.9 mg, 0.014 mmol),  $\text{Et}_3\text{N}$  (150  $\mu$ L, 1.08 mmol), 2-bromonaphthalene (103 mg, 0.50 mmol), 1-ethynylcyclohexene (100  $\mu$ L, 0.85 mmol), and *degassed* PTS (1.0 mL, 3 wt %) for 21 h, the titled product (97 mg, 84%) was obtained as an off-white solid after silica gel chromatography (eluent: hexanes); mp 45-47  $^{\circ}$ C;  $^1$ H NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.95 (s, 1H), 7.82-7.76 (m, 3H), 7.50-7.45 (m, 3H), 6.28 (m, 1H), 2.30-2.26 (m, 2H), 2.21-2.16 (m, 2H), 1.75-1.62 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  135.65, 133.24, 132.74, 131.22, 128.73, 128.04, 127.92, 127.89, 126.62, 126.58, 121.27, 120.95, 91.86, 87.38, 29.46, 26.03, 22.56, 21.73; HREI-MS  $m/z$  Calcd. for  $\text{C}_{18}\text{H}_{16}$  ( $\text{M}^+$ ) 232.1252, found 232.1252.

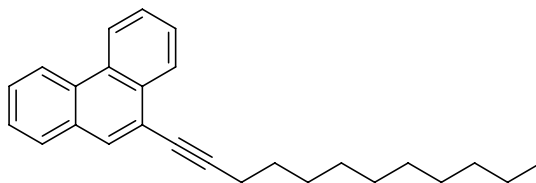


**9-(Cyclohex-1-enylethynyl)phenanthrene (Table 1, entry 7).** Following standard procedure B, using  $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$  (2.0 mg, 0.008 mmol), X-Phos (10.0 mg, 0.021 mmol),  $\text{Et}_3\text{N}$  (150  $\mu$ L, 1.08 mmol), 9-bromophenanthrene (129 mg, 0.50 mmol), 1-ethynylcyclohexene (100  $\mu$ L, 0.85 mmol), and *degassed* PTS (1.0 mL, 3 wt %) for 21 h, the titled product (133 mg, 98%) was obtained as a bright yellow solid after silica gel chromatography (eluent: hexanes); mp 105-107  $^{\circ}$ C;  $^1$ H NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.70-8.65 (m, 2H), 8.47-8.44 (m, 1H), 7.98 (s, 1H), 7.85 (d,  $J = 7.2$  Hz, 1H), 7.72-7.58 (m, 4H), 6.39 (m, 1H), 2.39 (m, 2H), 2.23 (m, 2H), 1.80-1.68 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  135.79, 131.56, 131.41, 130.26, 128.64, 127.36, 127.20, 127.14, 127.07, 122.90, 122.77, 121.10, 120.31, 96.20, 85.25, 29.59, 26.07, 22.59, 21.76; HREI-MS  $m/z$  Calcd. for  $\text{C}_{22}\text{H}_{18}$  ( $\text{M}^+$ ) 282.1408, found 282.1417.

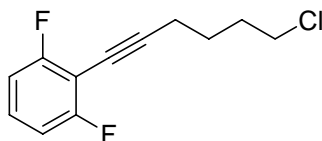


**Standard Procedure C for Sonogashira Coupling: 4-(dodec-1-ynyl)anisole (Table 2).** To a 5 mL round-bottom flask equipped with a stir bar was added under argon  $\text{Pd}(\text{OAc})_2$  (1.4 mg, 0.006 mmol) and **14** (4.1 mg, 0.012 mmol). Under a positive flow of argon were each added via syringe first *non-degassed* PTS solution (1.0 mL, 3 wt %), then  $\text{Et}_3\text{N}$  (200  $\mu$ L, 1.44 mmol), 4-bromoanisole (60  $\mu$ L, 0.48 mmol), and 1-dodecyne (160  $\mu$ L, 0.74 mmol). A milky, tan-colored mixture developed over 30 min

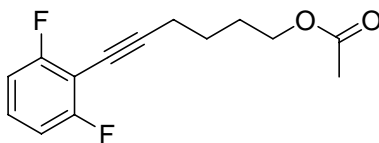
while stirring at rt. Reaction progress was monitored by GC. After 10 h the mixture was diluted with brine and extracted with ethyl acetate (4x). The combined organic extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated by rotary evaporation to give a crude brown oil that was purified by silica gel chromatography eluting with hexanes afforded the titled product (125 mg, 96%) as a light yellow oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34 (d,  $J = 8.8$  Hz, 2H), 6.82 (d,  $J = 8.8$  Hz, 2H), 3.81 (s, 3H), 2.39 (t,  $J = 7.0$  Hz, 2H), 1.64-1.57 (m, 2H), 1.45 (m, 2H), 1.29 (brs, 12H), 0.90 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  159.14, 133.04, 116.45, 113.96, 89.03, 80.40, 55.43, 32.14, 29.81, 29.78, 29.56, 29.40, 29.16, 29.09, 22.91, 19.62, 14.35; HREI-MS  $m/z$  Calcd. for  $\text{C}_{19}\text{H}_{28}\text{O}$  ( $\text{M}^+$ ) 272.2140, found 272.2138.



**9-(Dodec-1-ynyl)phenanthrene (Scheme 3).** Following standard procedure C, using  $\text{Pd}(\text{OAc})_2$  (1.7 mg, 0.008 mmol), **14** (7.2 mg, 0.020 mmol),  $\text{Et}_3\text{N}$  (200  $\mu\text{L}$ , 1.44 mmol), 9-bromophenanthrene (128 mg, 0.50 mmol), 1-dodecyne (160  $\mu\text{L}$ , 0.74 mmol), and *degassed* PTS (1.0 mL, 3 wt %) for 4 h, the titled product (140 mg, 82%) was obtained as a light yellow solid after silica gel chromatography (eluent: hexanes); mp 40-42  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.70-8.65 (m, 2H), 8.49-8.46 (m, 1H), 7.95 (s, 1H), 7.84 (dd,  $J = 8.0, 1.2$  Hz, 1H), 7.72-7.57 (m, 4H), 2.61 (t,  $J = 7.2$  Hz, 2H), 1.79-1.72 (m, 2H), 1.61-1.54 (m, 2H), 1.39-1.30 (m, 12H), 0.90 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  131.74, 131.59, 131.38, 130.28, 130.13, 128.51, 127.22 (2C), 127.07, 127.03, 122.89, 122.76, 120.66, 95.49, 78.91, 32.14, 29.81 (2C), 29.58, 29.43, 29.29, 29.13, 22.92, 19.98, 14.35; HREI-MS  $m/z$  Calcd. for  $\text{C}_{26}\text{H}_{30}$  ( $\text{M}^+$ ) 342.2348, found 342.2354.

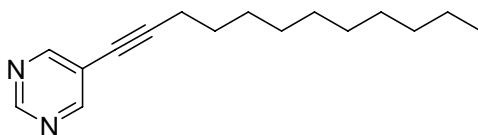


**2-(6-Chlorohex-1-ynyl)-1,3-difluorobenzene (Scheme 3).** Following standard procedure C, using  $\text{Pd}(\text{OAc})_2$  (1.2 mg, 0.005 mmol), **14** (4.2 mg, 0.012 mmol),  $\text{Et}_3\text{N}$  (220  $\mu\text{L}$ , 1.58 mmol), 1-bromo-2,6-difluorobenzene (60  $\mu\text{L}$ , 0.53 mmol), 6-chloro-1-hexyne (110  $\mu\text{L}$ , 0.91 mmol), and *degassed* PTS (1.0 mL, 3 wt %) for 4 h, the titled product (100 mg, 82%) was isolated as a colorless oil after silica gel chromatography (eluent: hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25-7.18 (m, 1H), 6.92-6.86 (m, 2H), 3.63 (t,  $J = 6.6$  Hz, 2H), 2.56 (t,  $J = 6.8$  Hz), 2.04-1.96 (m, 2H), 1.85-1.78 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  164.73, 162.22, 129.11 (t,  $J = 9.9$  Hz), 111.26 (dd,  $J = 19.0, 5.3$  Hz), 100.14, 68.33, 44.76, 31.62, 25.73, 19.25; HREI-MS  $m/z$  Calcd. for  $\text{C}_{12}\text{H}_{11}\text{ClF}_2$  ( $\text{M}^+$ ) 228.0517, found 228.0517.

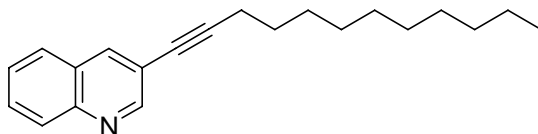


**2-(6-Acetoxyhex-1-ynyl)-1,3-difluorobenzene (Scheme 3).** Following standard procedure C, using  $\text{Pd}(\text{OAc})_2$  (1.2 mg, 0.005 mmol), **14** (4.2 mg, 0.012 mmol),  $\text{Et}_3\text{N}$  (220  $\mu\text{L}$ , 1.58 mmol), 1-bromo-2,6-

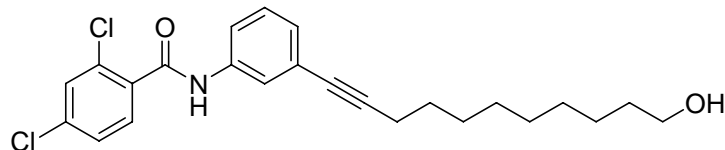
difluorobenzene (60  $\mu\text{L}$ , 0.53 mmol), 6-acetoxy-1-hexyne (130  $\mu\text{L}$ , 0.88 mmol), and *degassed* PTS (1.0 mL, 3 wt %) for 5 h, the titled product (132 mg, 98%) was obtained as a colorless oil after silica gel chromatography (eluent: gradient from hexanes to 3% ethyl acetate/hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25-7.17 (m, 1H), 6.92-6.85 (m, 2H), 4.13 (t,  $J = 6.4$  Hz, 2H), 2.55 (t,  $J = 6.8$  Hz, 2H), 2.07 (s, 3H), 1.88-1.81 (m, 2H), 1.76-1.69 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.43, 164.73, 162.17, 129.05 (t,  $J = 9.9$  Hz), 111.25 (dd,  $J = 18.6, 5.7$  Hz), 100.35, 68.18, 64.19, 27.89, 25.14, 21.21, 19.65; HREI-MS  $m/z$  Calcd. for  $\text{C}_{14}\text{H}_{14}\text{F}_2\text{O}_2$  ( $\text{M}^+$ ) 252.0962, found 252.0961.



**5-(Dodec-1-ynyl)pyrimidine (Scheme 3).** Following standard procedure C, using  $\text{Pd}(\text{OAc})_2$  (1.2 mg, 0.005 mmol), **14** (4.0 mg, 0.011 mmol),  $\text{Et}_3\text{N}$  (210  $\mu\text{L}$ , 1.51 mmol), 5-bromopyrimidine (81 mg, 0.51 mmol), 1-dodecyne (170  $\mu\text{L}$ , 0.79 mmol), and *non-degassed* PTS (1.0 mL, 3 wt %) for 6 h, the titled product (100 mg, 81%) was obtained as a golden oil after silica gel chromatography (eluent: gradient from hexanes to 2% ethyl acetate/hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.08 (s, 1H), 8.72 (s, 2H), 2.45 (t,  $J = 7.2$  Hz, 2H), 1.66-1.59 (m, 2H), 1.46-1.41 (m, 2H), 1.38-1.27 (m, 12H), 0.88 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  158.94, 156.38, 120.78, 98.52, 74.16, 32.10, 29.78, 29.72, 29.52, 29.31, 29.12, 28.54, 22.90, 19.72, 14.34; HREI-MS  $m/z$  Calcd. for  $\text{C}_{16}\text{H}_{24}\text{N}_2$  ( $\text{M}^+$ ) 244.1939, found 244.1937.



**3-(Dodec-1-ynyl)quinoline (Scheme 3).** Following standard procedure C, using  $\text{Pd}(\text{OAc})_2$  (1.2 mg, 0.005 mmol), **14** (4.2 mg, 0.012 mmol),  $\text{Et}_3\text{N}$  (220  $\mu\text{L}$ , 1.58 mmol), 3-bromoquinoline (70  $\mu\text{L}$ , 0.52 mmol), 1-dodecyne (180  $\mu\text{L}$ , 0.83 mmol), and *non-degassed* PTS (1.0 mL, 3 wt %) for 4 h, the titled product (148 mg, 98%) was isolated as a yellow oil after silica gel chromatography (eluent: gradient from hexanes to 1% ethyl acetate/hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.88 (d,  $J = 2.0$  Hz, 1H), 8.16 (d,  $J = 1.6$  Hz, 1H), 8.07 (d,  $J = 8.4$  Hz, 1H), 7.75 (d,  $J = 8.4$  Hz, 1H), 7.69 (td,  $J = 8.4, 1.6$  Hz, 1H), 7.54 (td,  $J = 8.4, 1.2$  Hz, 1H), 2.48 (t,  $J = 7.2$  Hz, 2H), 1.69-1.62 (m, 2H), 1.50-1.44 (m, 2H), 1.40-1.19 (m, 12H), 0.88 (t,  $J = 6.6$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  152.72, 146.66, 138.12, 129.80, 129.47, 127.59, 127.53, 127.27, 118.43, 94.38, 78.09, 32.10, 29.79, 29.74, 29.53, 29.36, 29.17, 28.80, 22.89, 19.75, 14.32; HREI-MS  $m/z$  Calcd. for  $\text{C}_{21}\text{H}_{27}\text{N}$  ( $\text{M}^+$ ) 293.2144, found 293.2136.



**2,4-Dichloro-N-(3'-(11-hydroxyundec-1-ynyl)phenyl)benzamide (16; Scheme 4).** Following standard procedure C (monitored by TLC) using  $\text{Pd}(\text{OAc})_2$  (3.6 mg, 0.016 mmol), **14** (11.3 mg, 0.032 mmol),  $\text{Et}_3\text{N}$  (210  $\mu\text{L}$ , 1.51 mmol), **15** (173 mg, 0.50 mmol), (160  $\mu\text{L}$ , 0.84 mmol), and *non-degassed* PTS (1.0 mL, 3 wt %) for 6 h, the titled product (169 mg, 78%) was obtained as a colorless oil that crystallizes to a white solid upon standing at rt after silica gel chromatography (eluent: gradient from



hexanes to 20% ethyl acetate/hexanes); mp 65-67 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.06 (brs, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.61 (brd, *J* = 9.2 Hz, 2H), 7.47-7.44 (m, 1H), 7.36 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 3.62 (t, *J* = 6.6 Hz, 2H), 2.41 (t, *J* = 7.0 Hz, 2H), 1.64-1.54 (m, 4H), 1.47-1.44 (m, 2H), 1.33 (brs, 8H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 163.75, 137.48, 133.62, 131.66, 131.60, 130.38, 129.24, 128.36, 127.95, 125.24, 123.21, 119.61, 91.38, 80.23, 63.26, 32.95, 29.57, 29.46, 29.14, 28.97, 28.75, 25.87, 19.56; HREI-MS *m/z* calcd. for C<sub>24</sub>H<sub>27</sub>Cl<sub>2</sub>NO<sub>2</sub> (M<sup>+</sup>) 431.1419, found 431.1411.

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<sup>1</sup> Sharma, S.; Oehlschlager, A. C. *J. Org. Chem.* **1989**, *54*, 5064–5073.

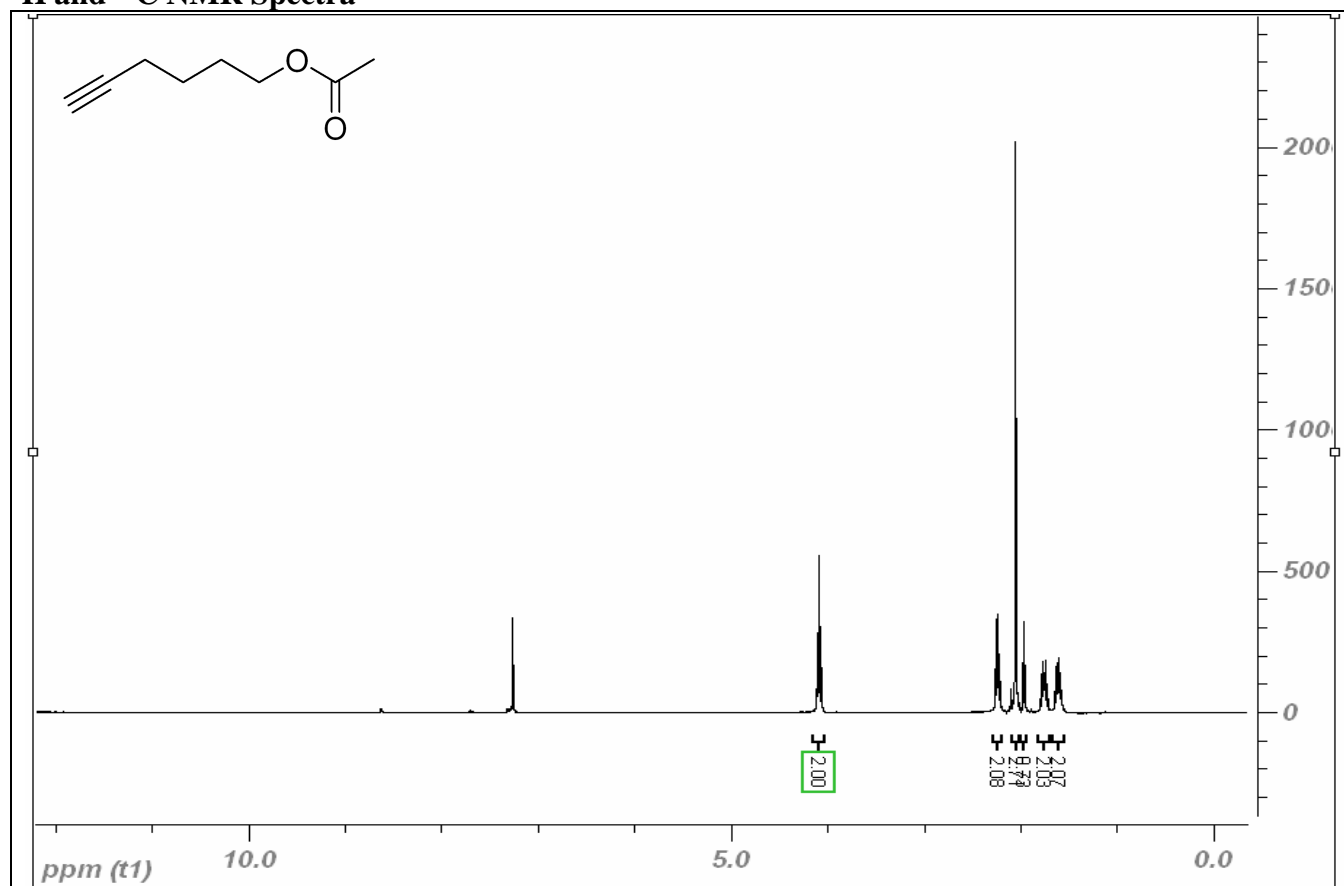
<sup>2</sup> Ma, Y.; Song, C.; Jian, W.; Wu, Q.; Wang, Y.; Liu, X.; Andrus, M. B. *Org. Lett.* **2003**, *5*, 3317–3319.

<sup>3</sup> Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729–1731.

<sup>4</sup> Gelman, D.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2003**, *42*, 5993–5996 and references cited therein.

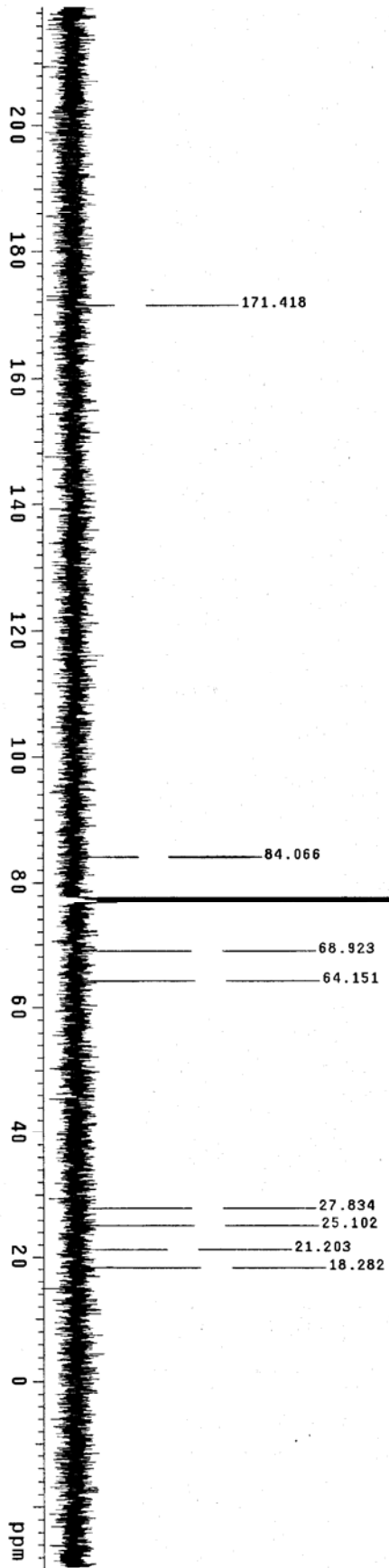
<sup>5</sup> Yus, M.; Ortiz, R.; Huerta, F. F. *Tetrahedron* **2003**, *59*, 8525–8542.

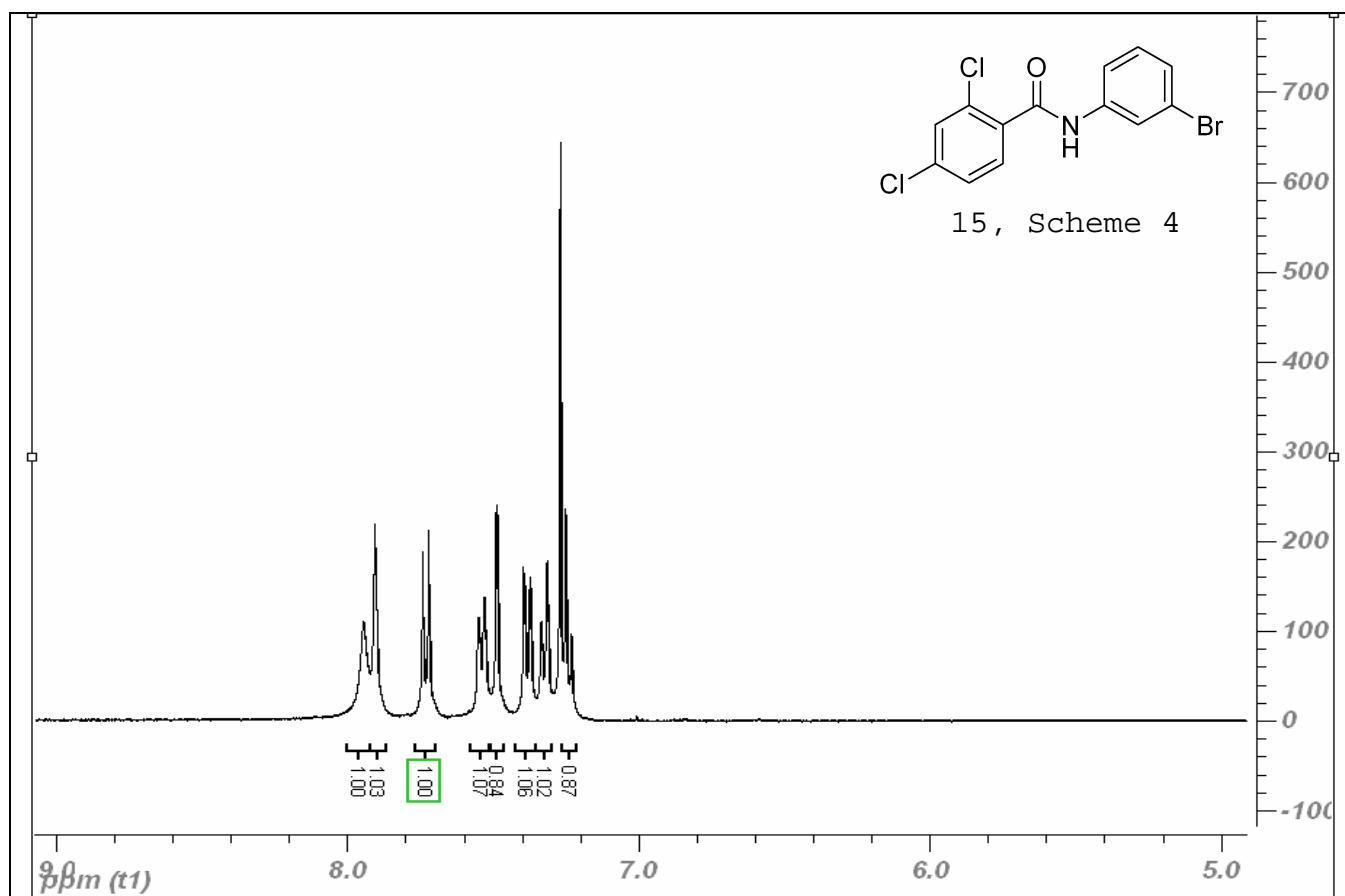
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exp8 std13c

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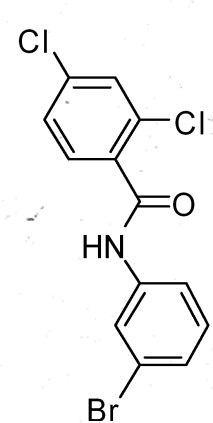
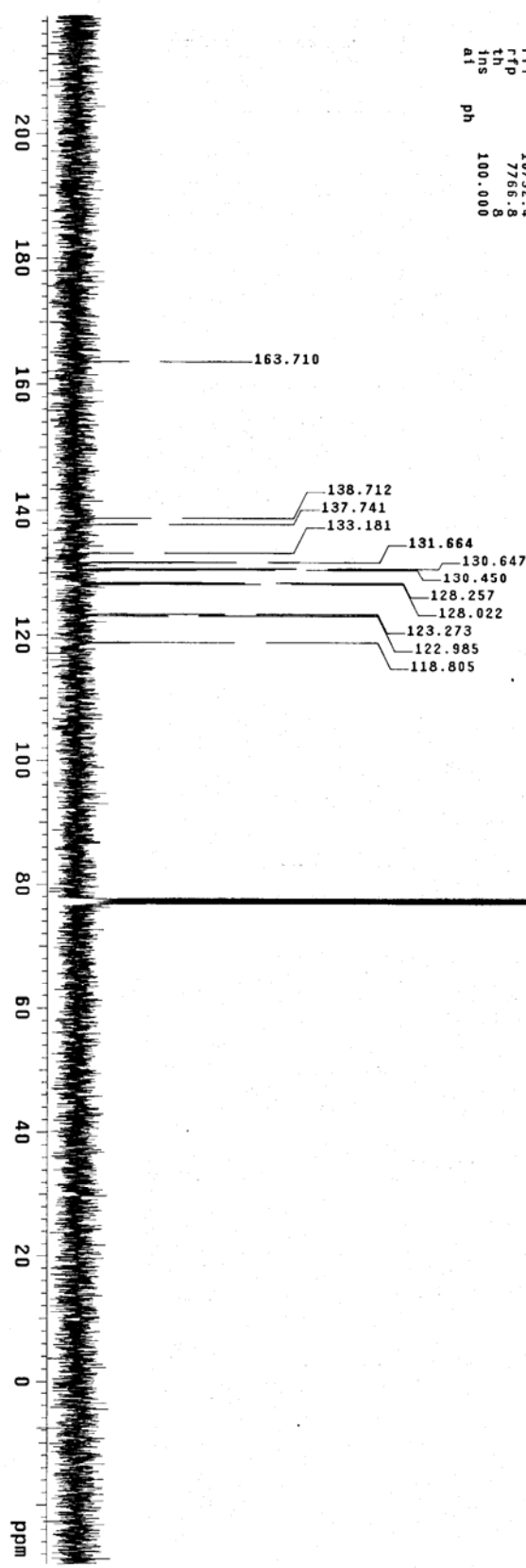


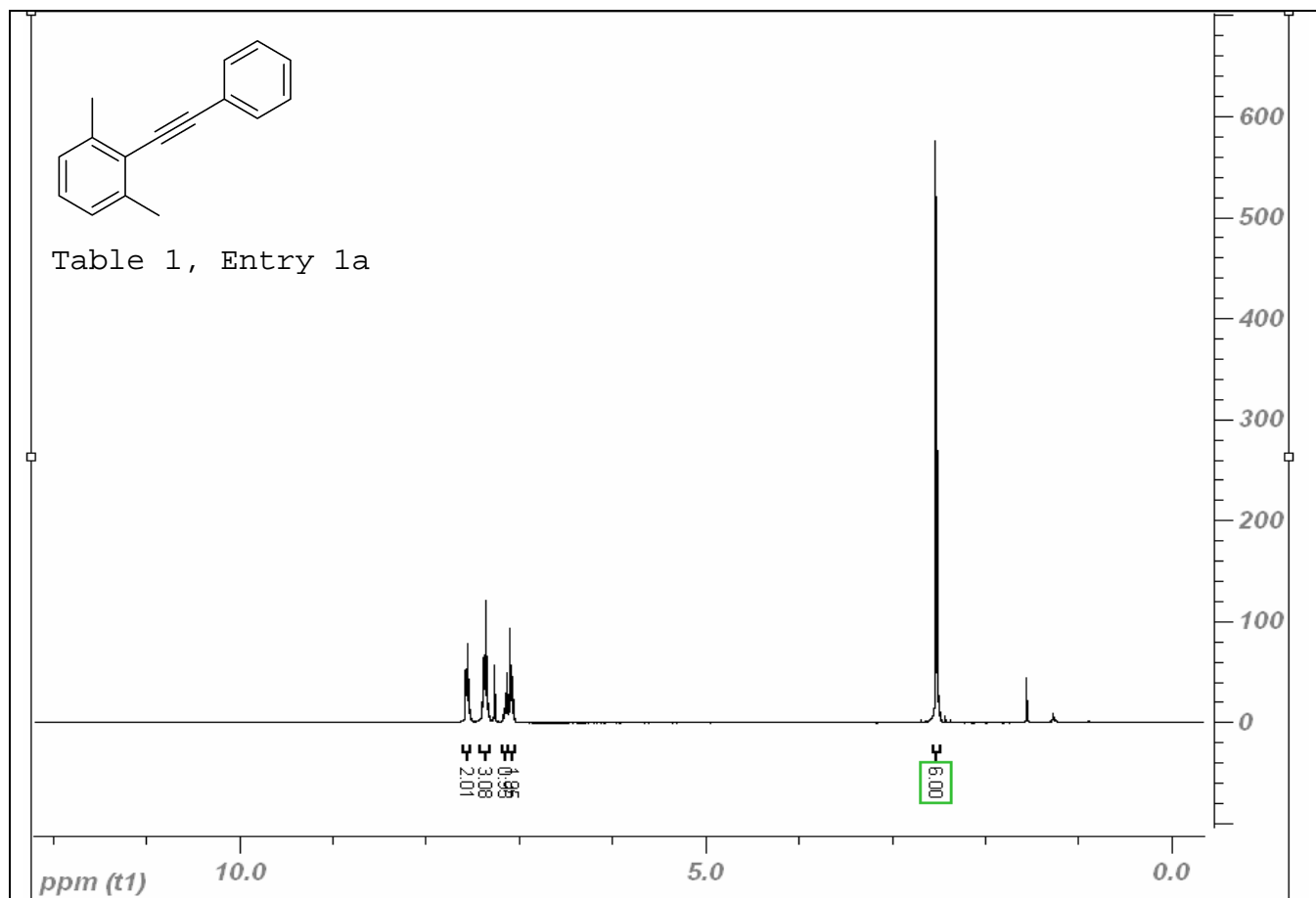
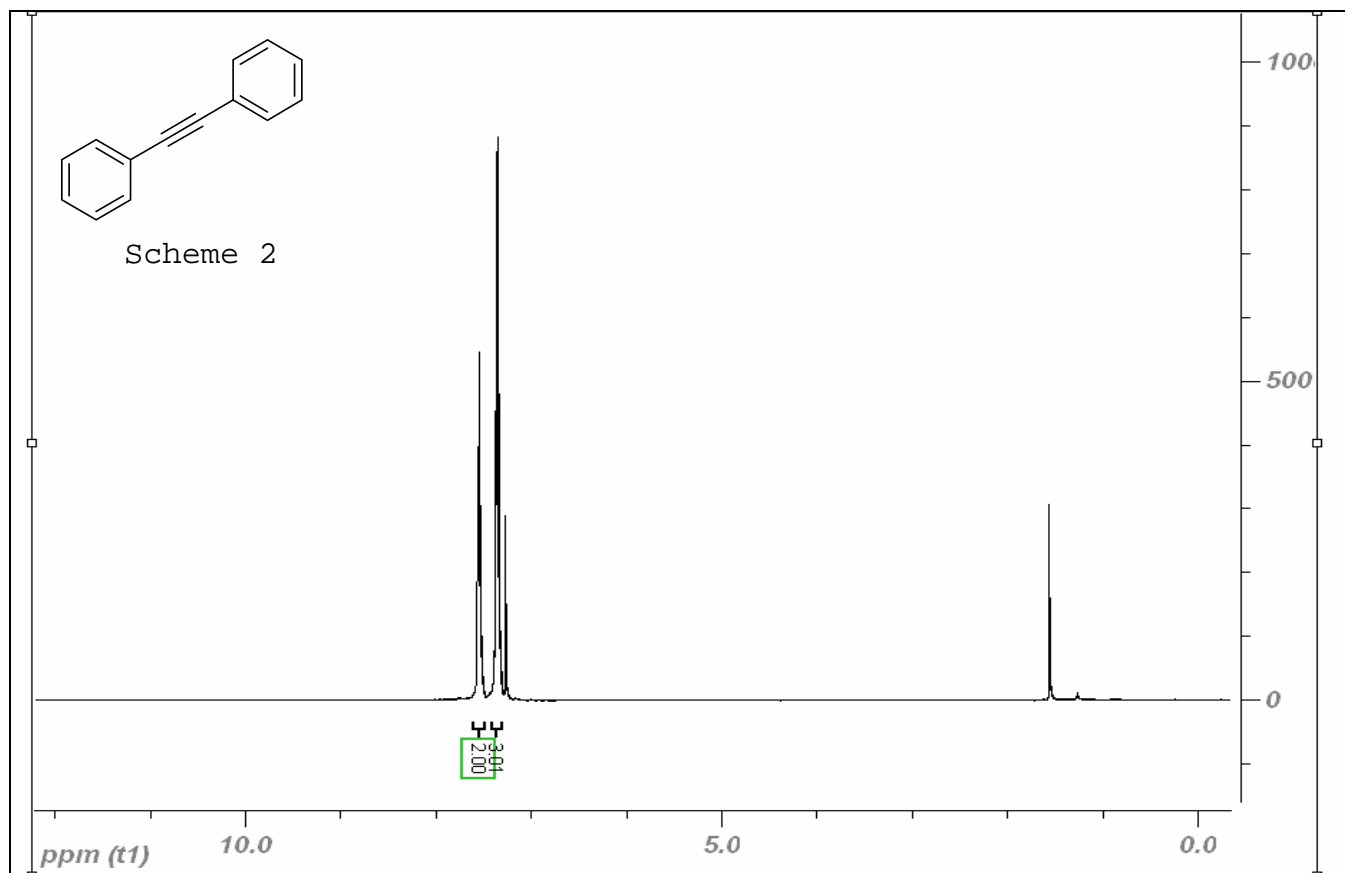


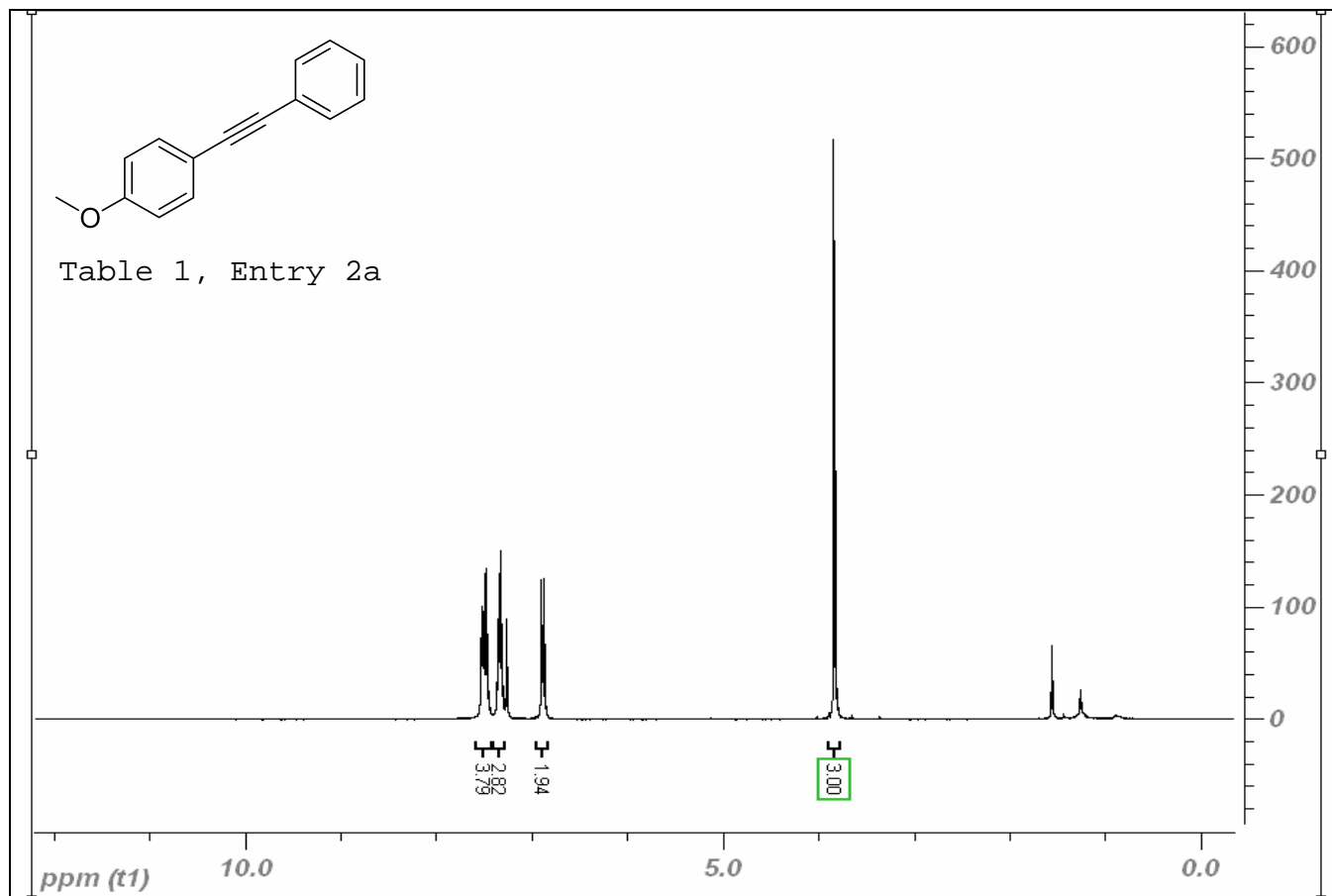
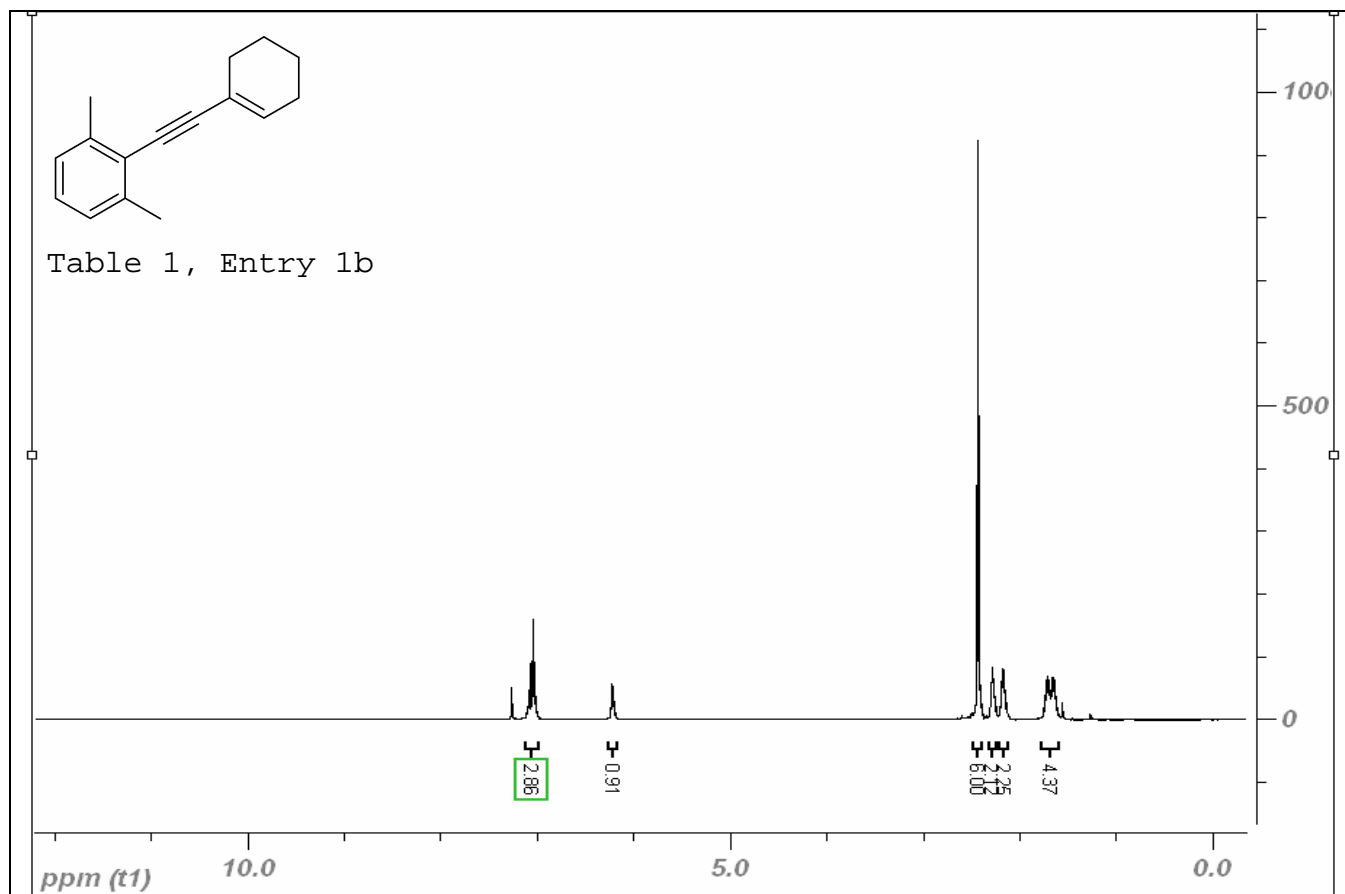
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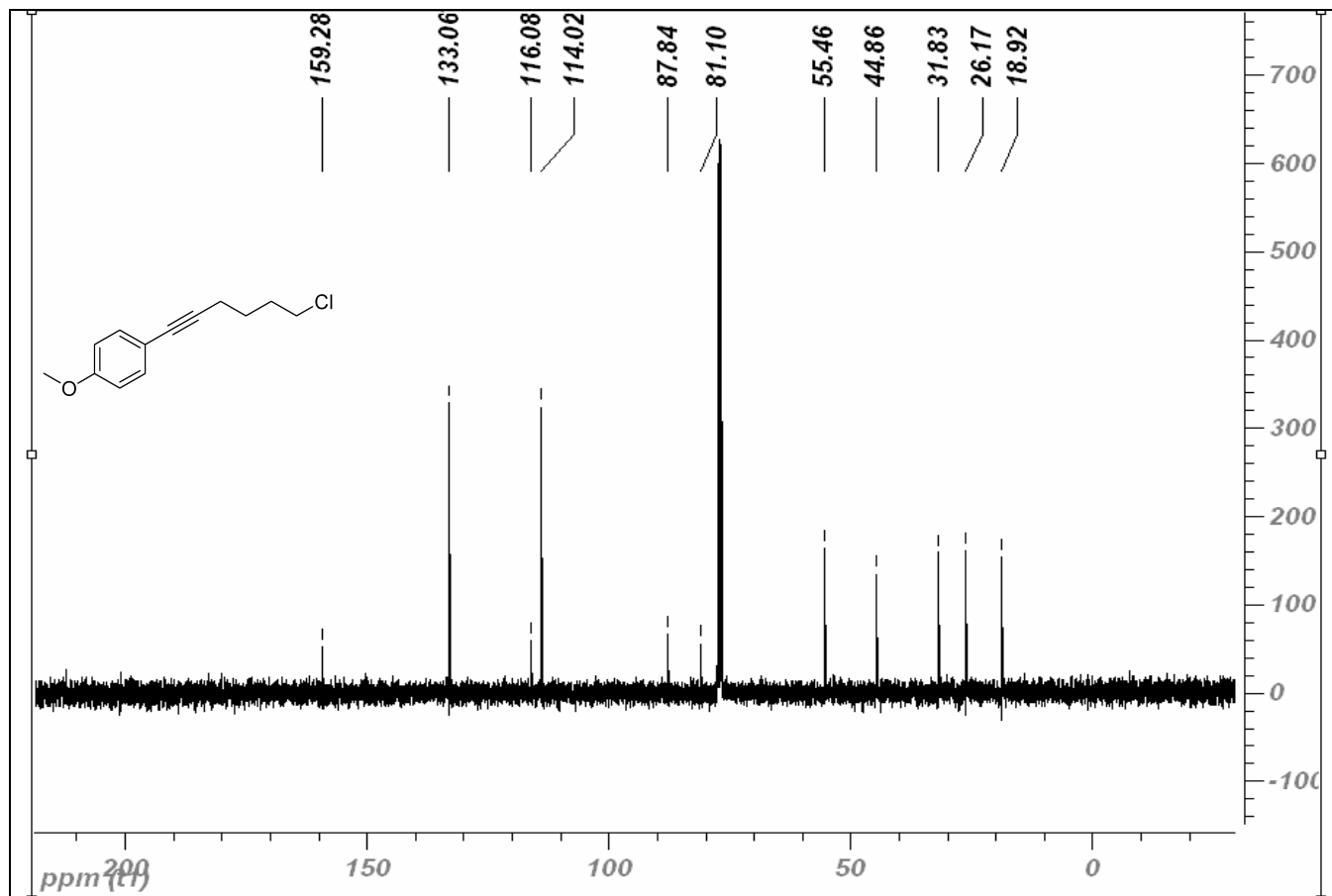
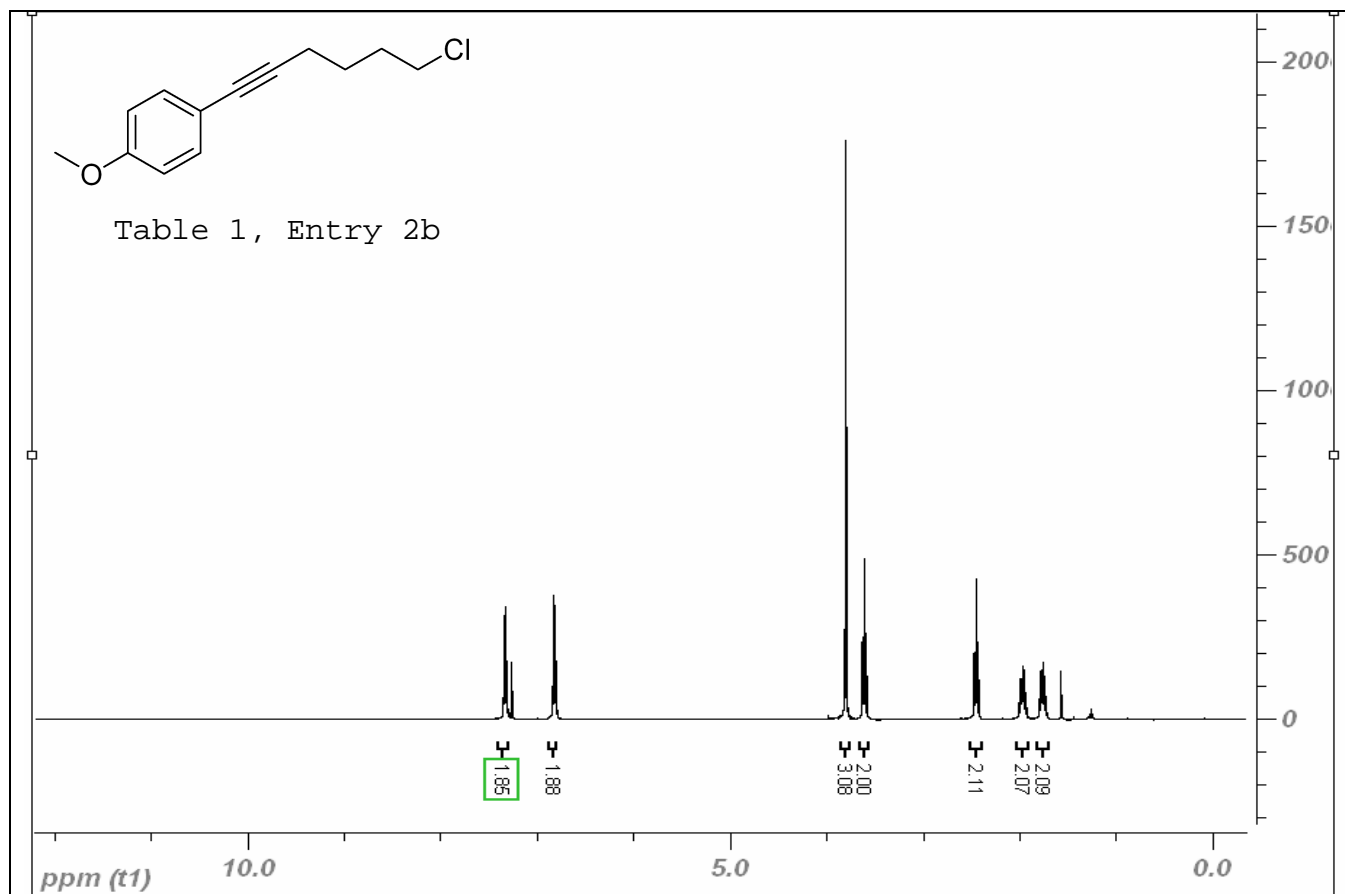
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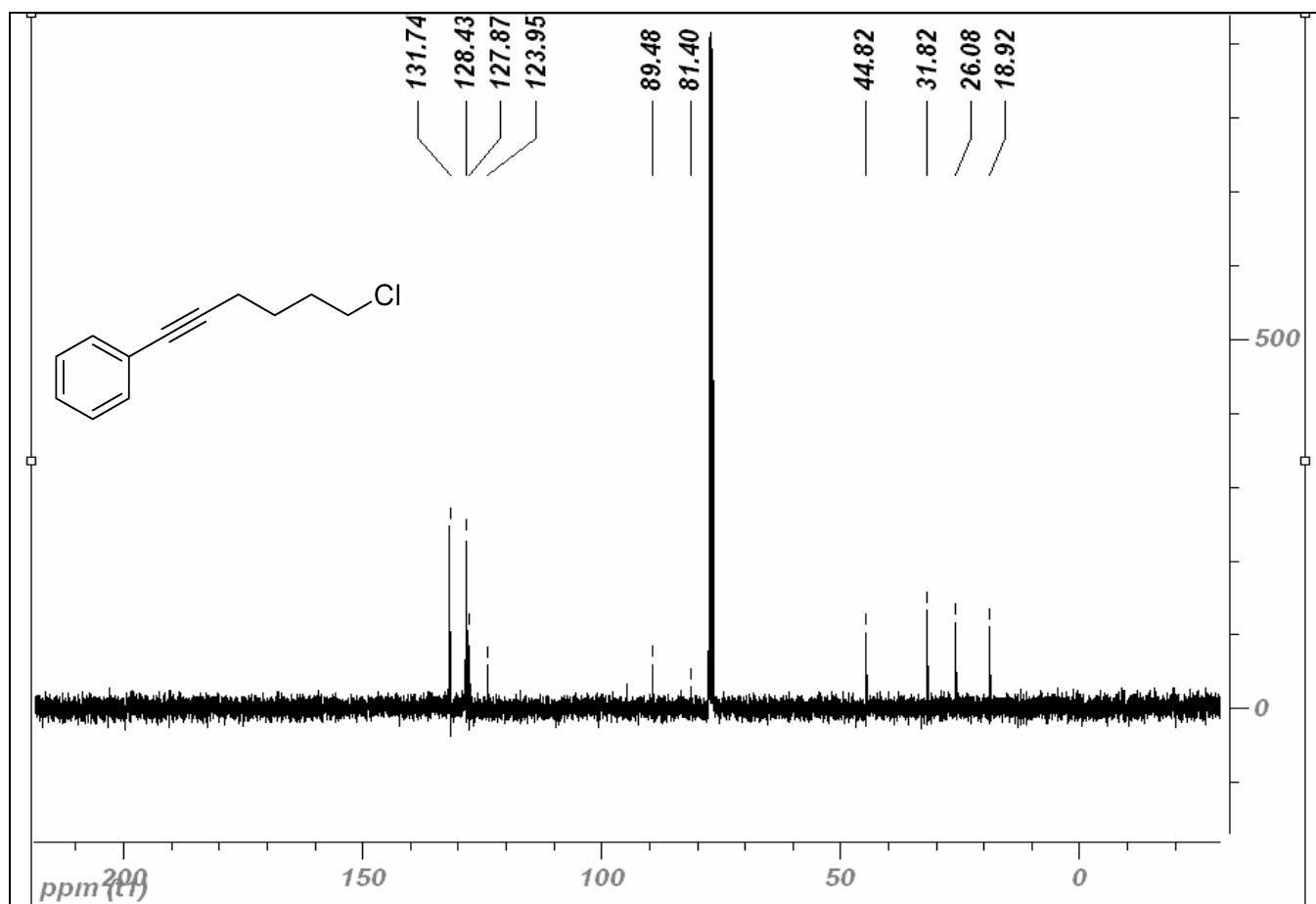
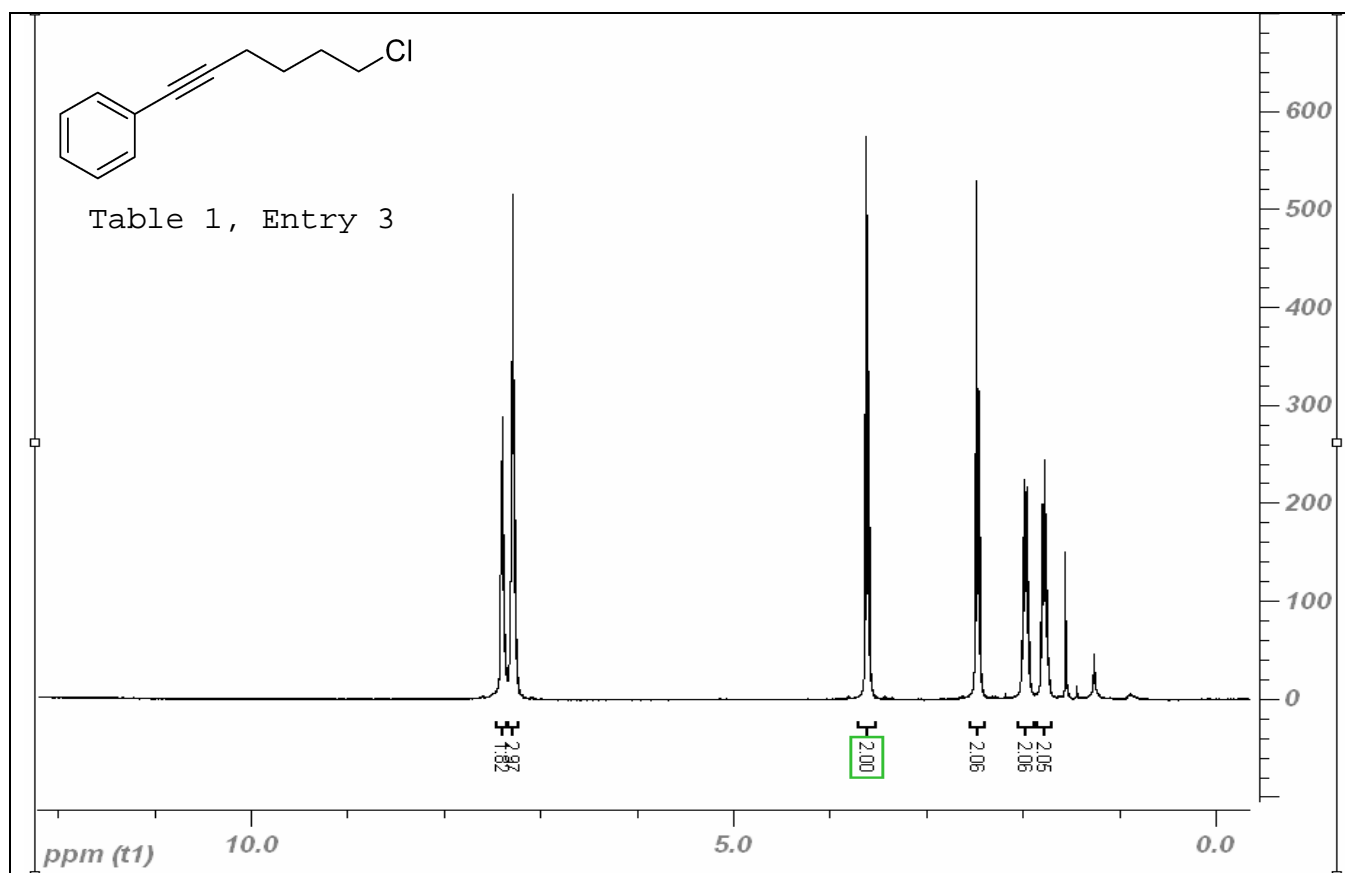


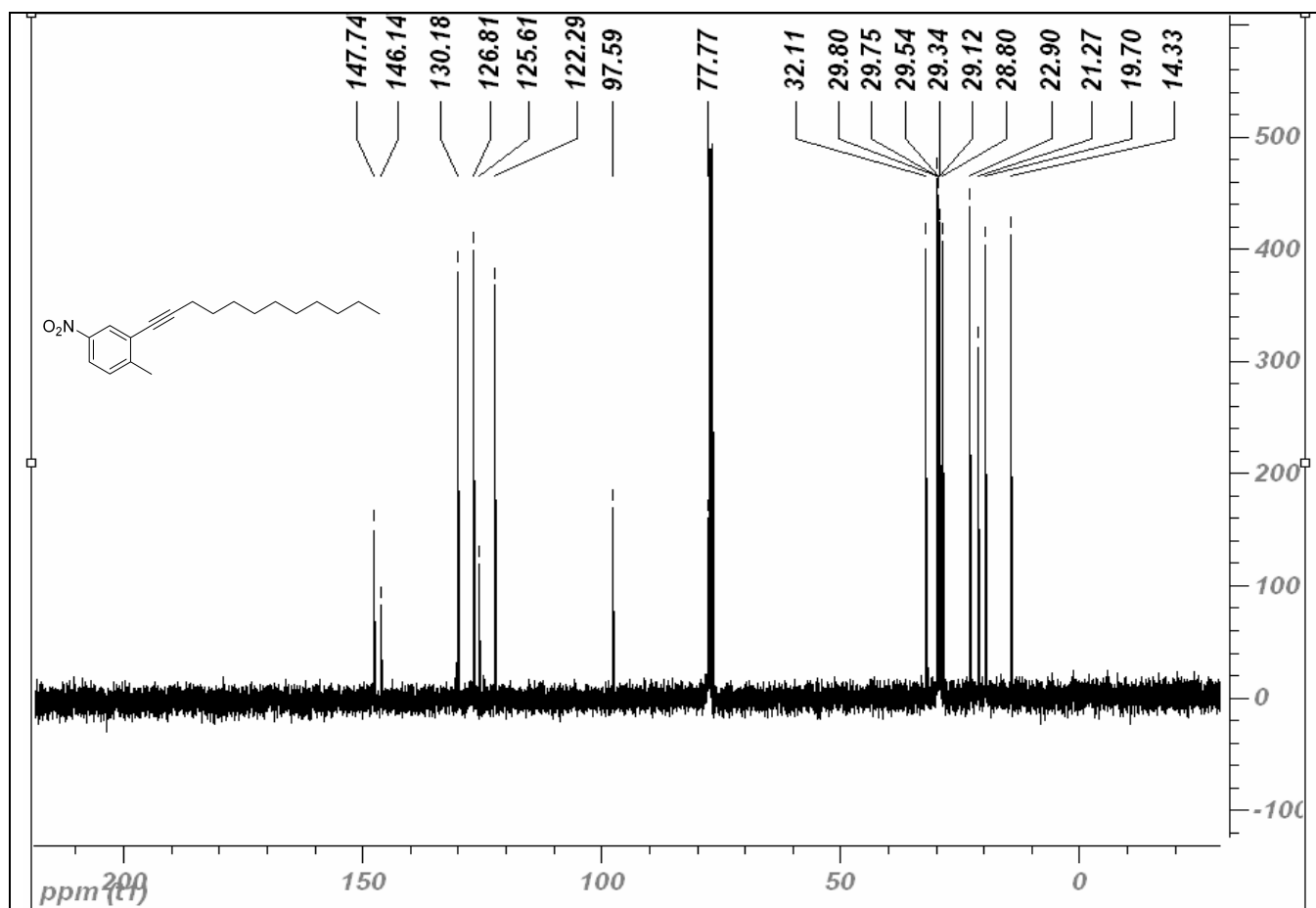
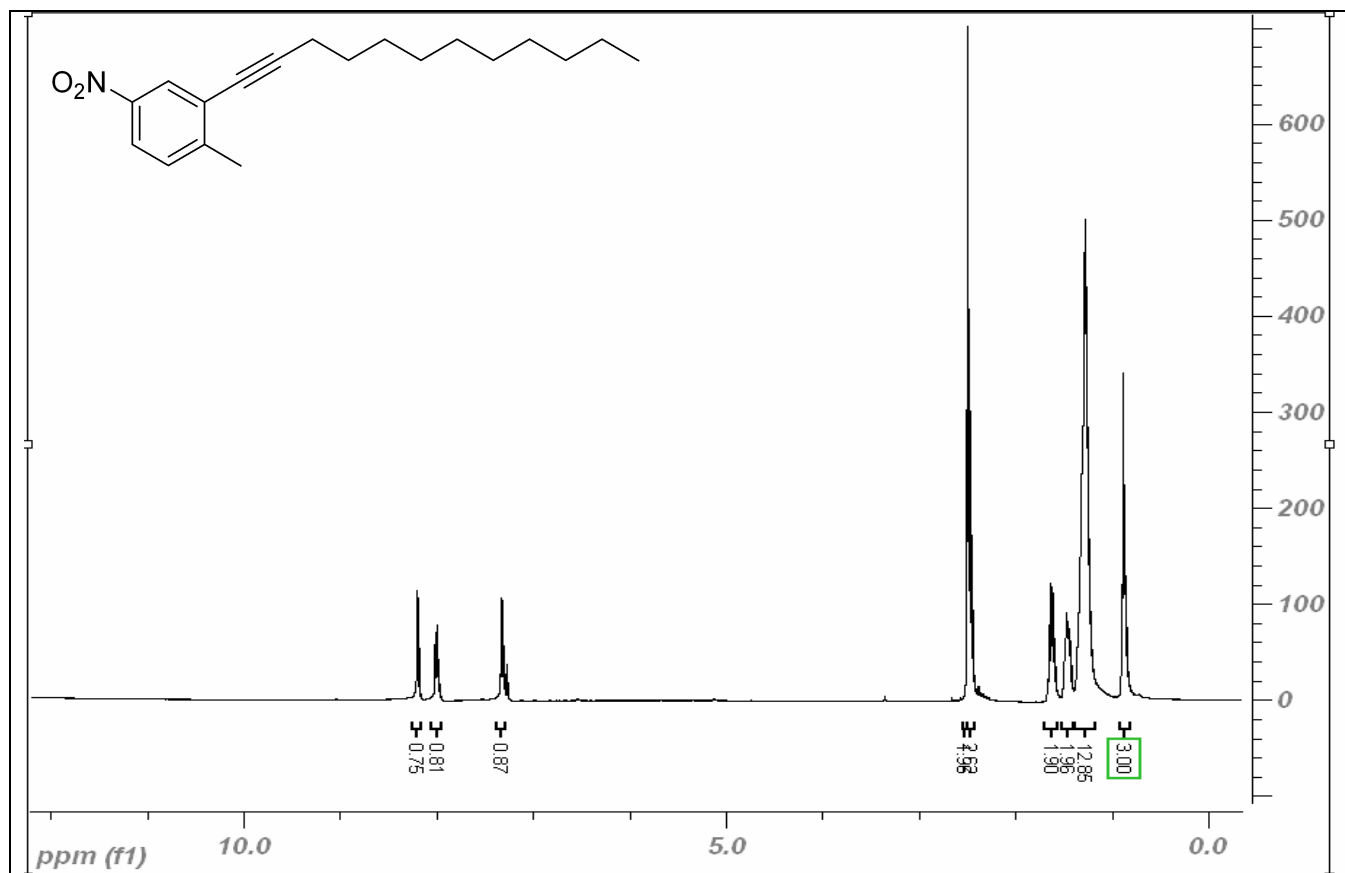


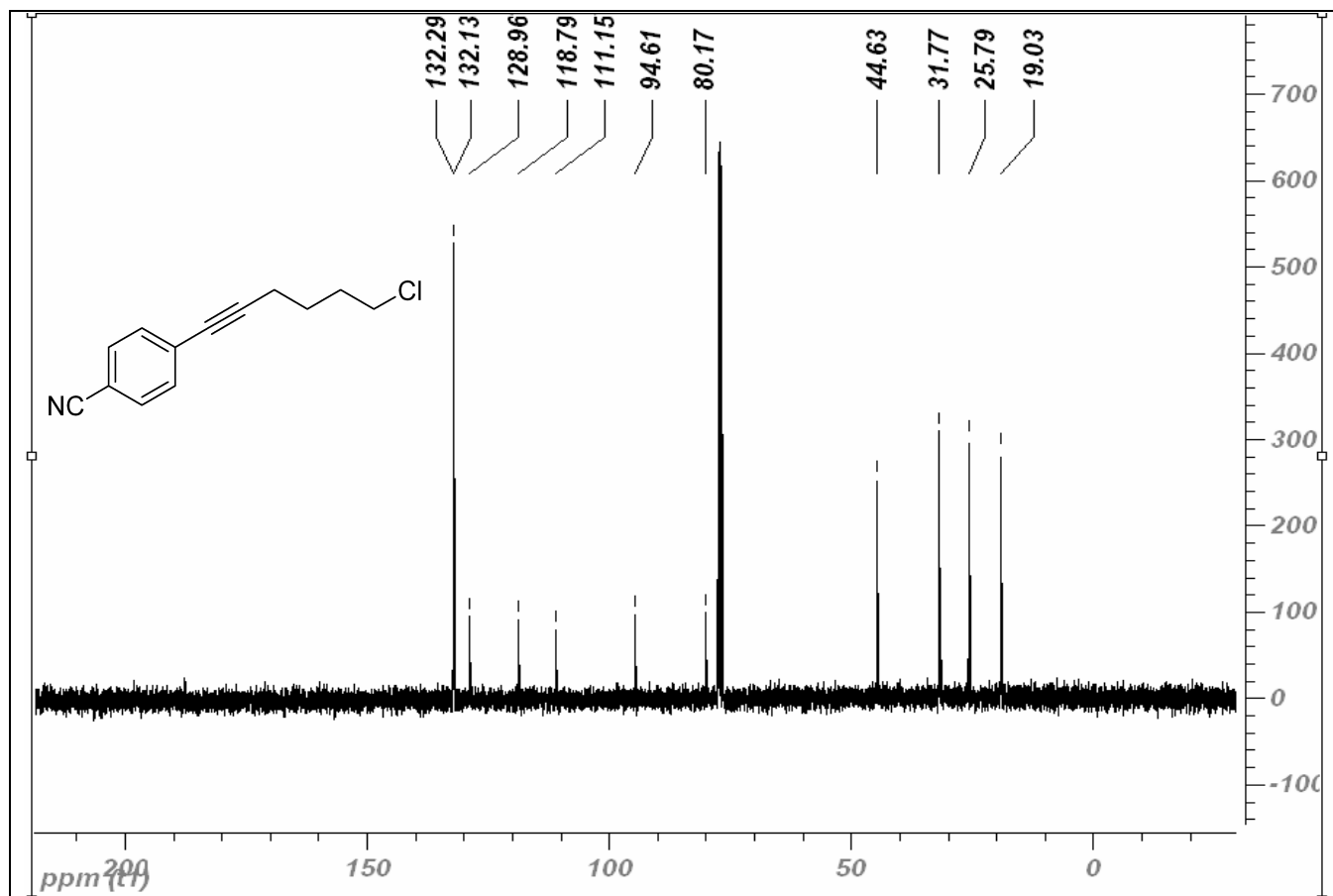
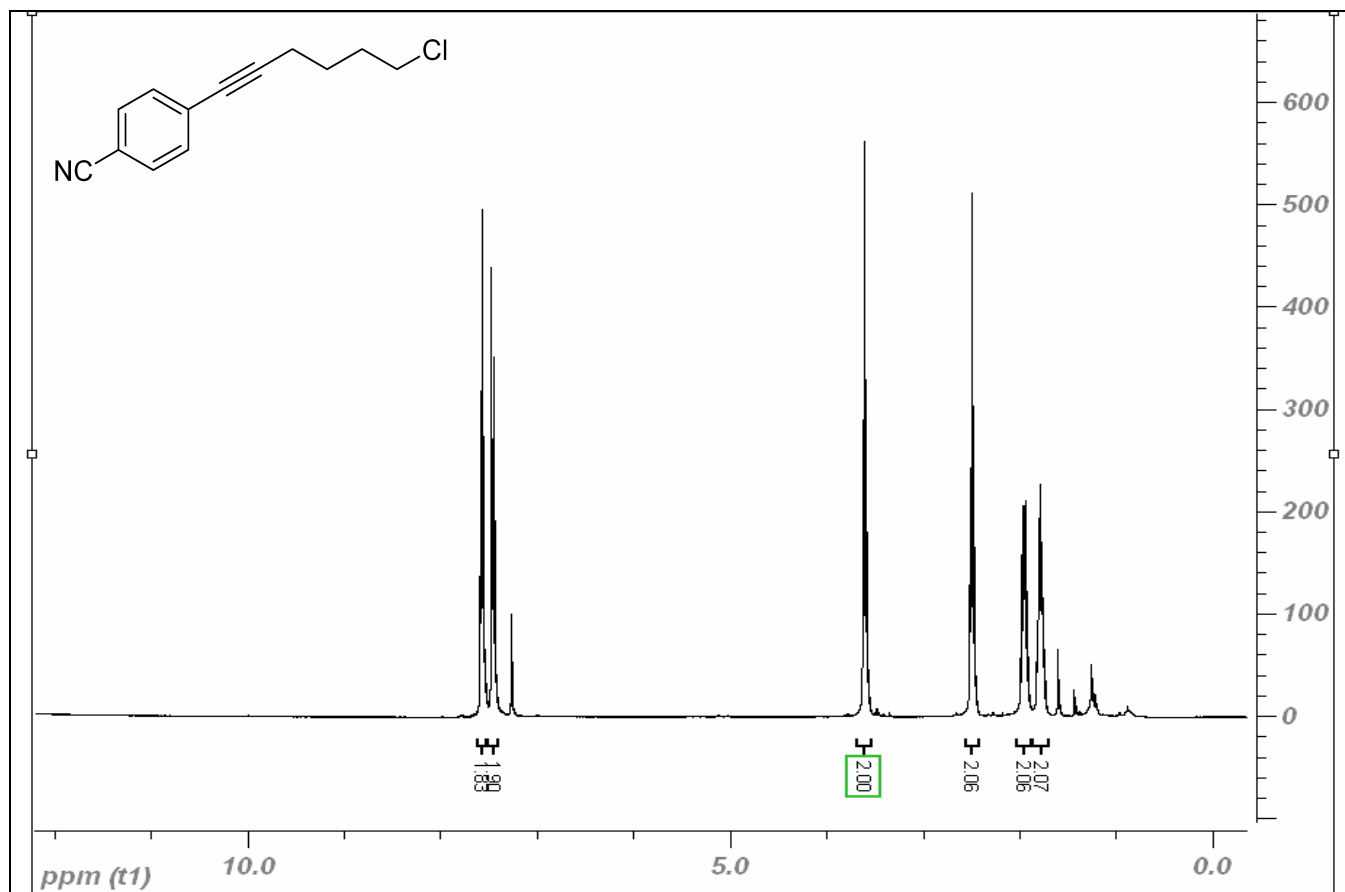


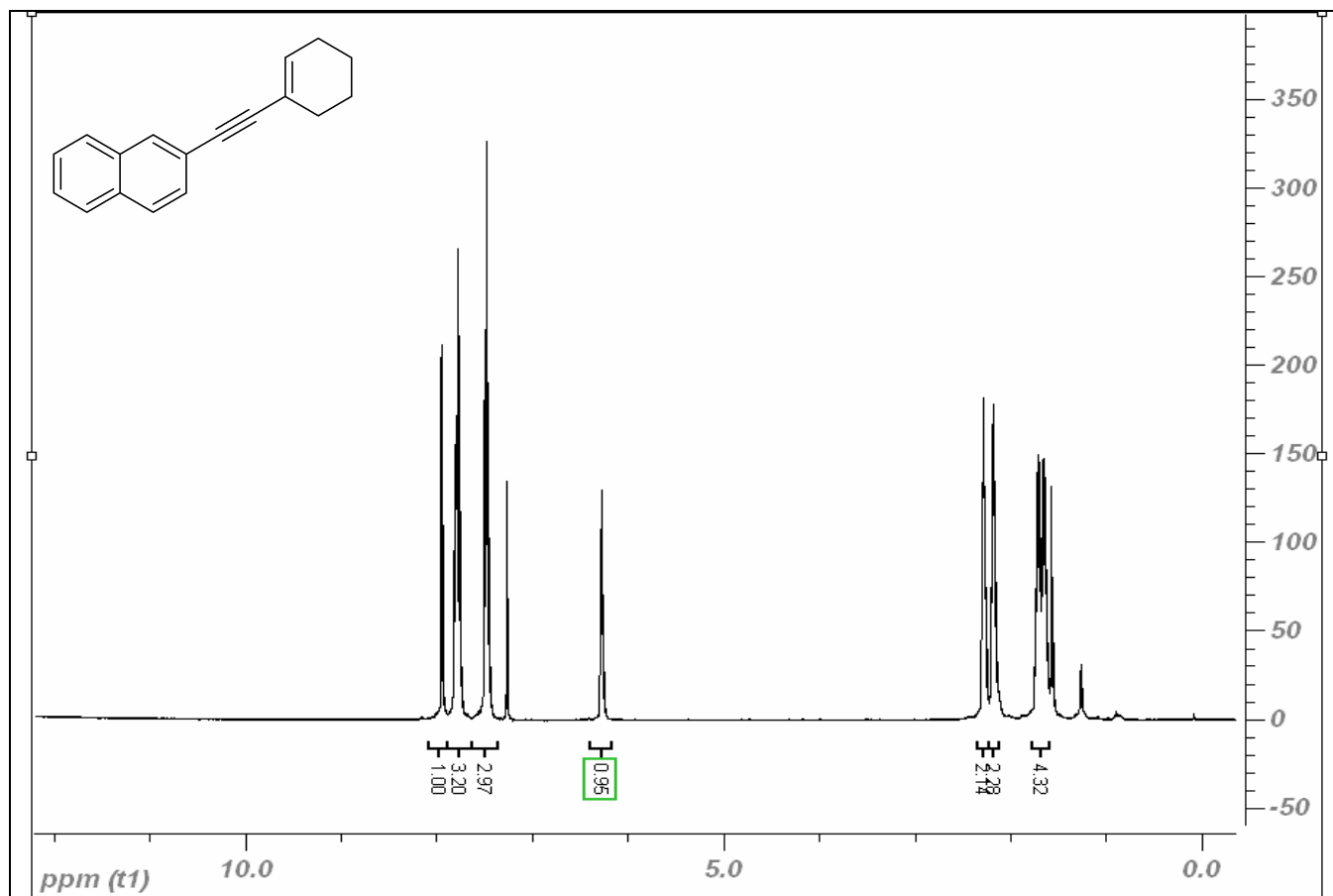
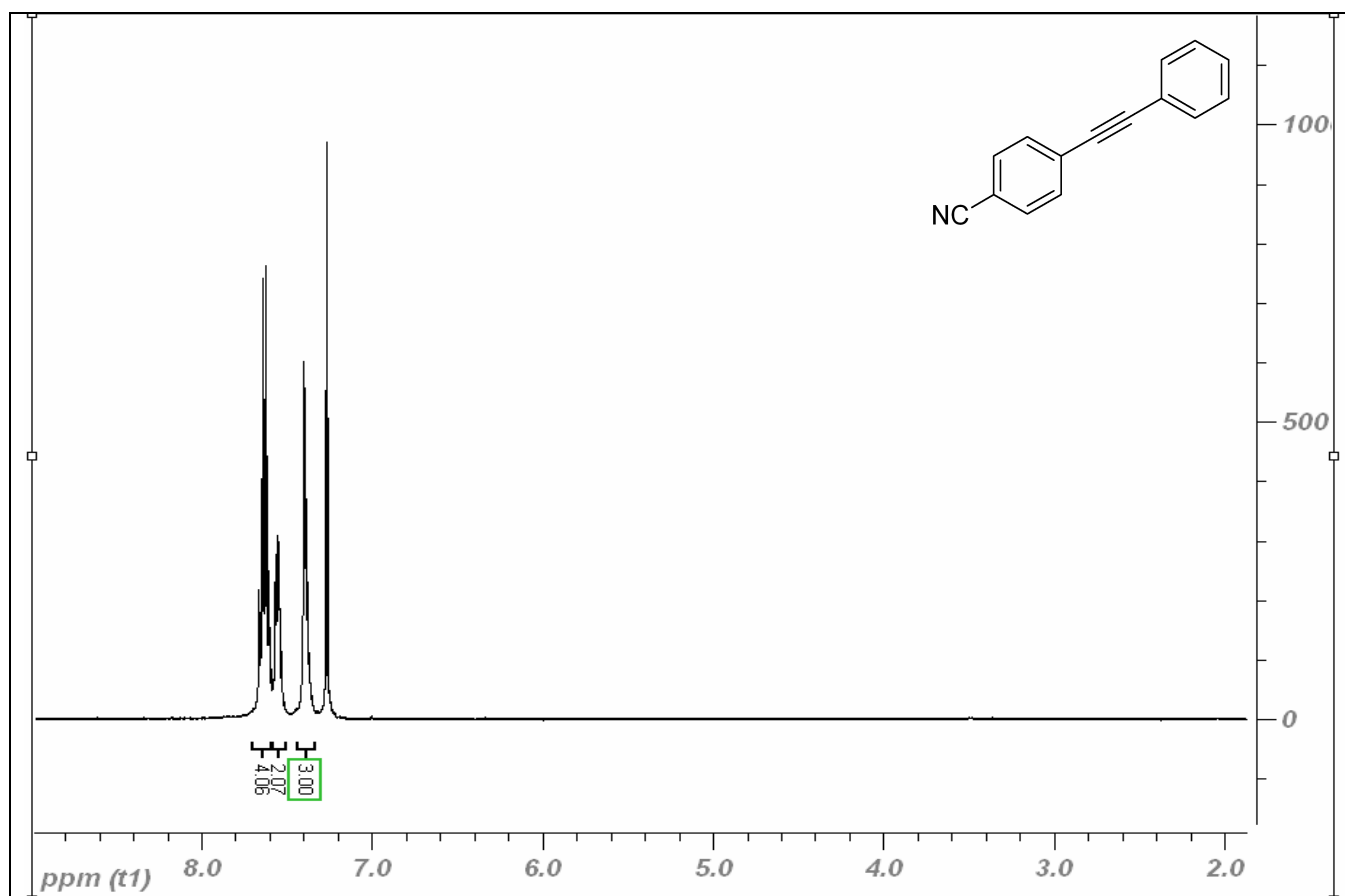


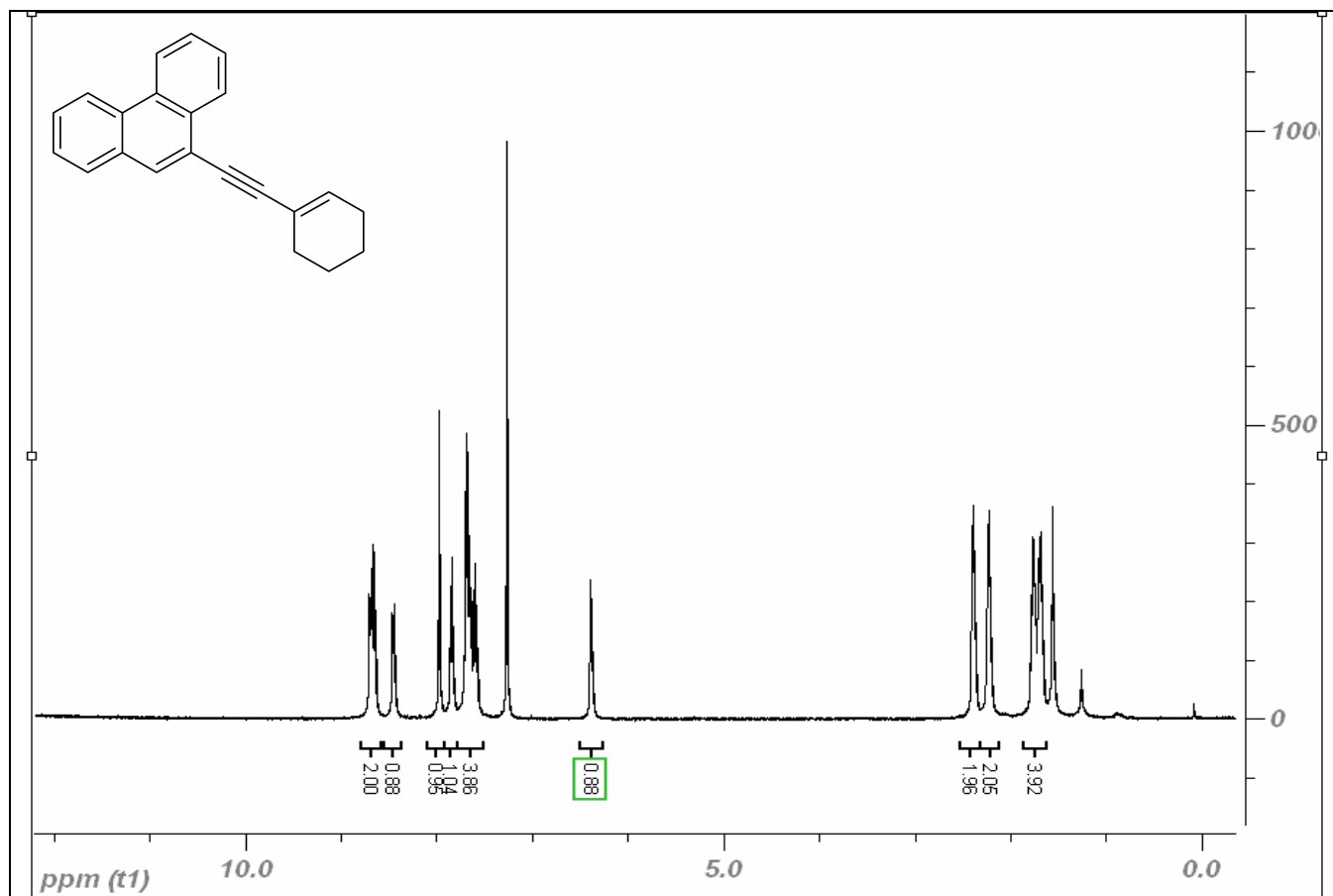
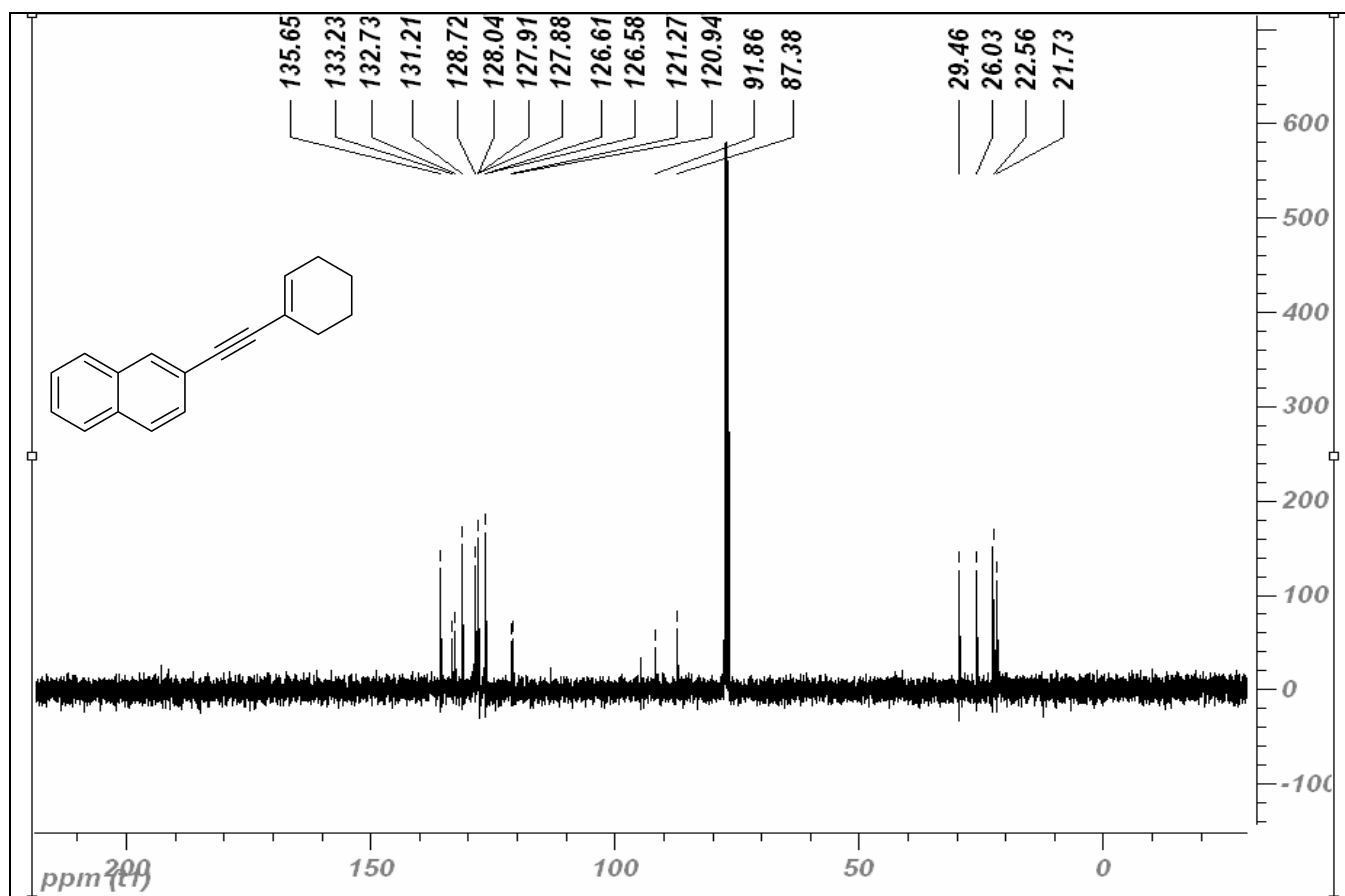


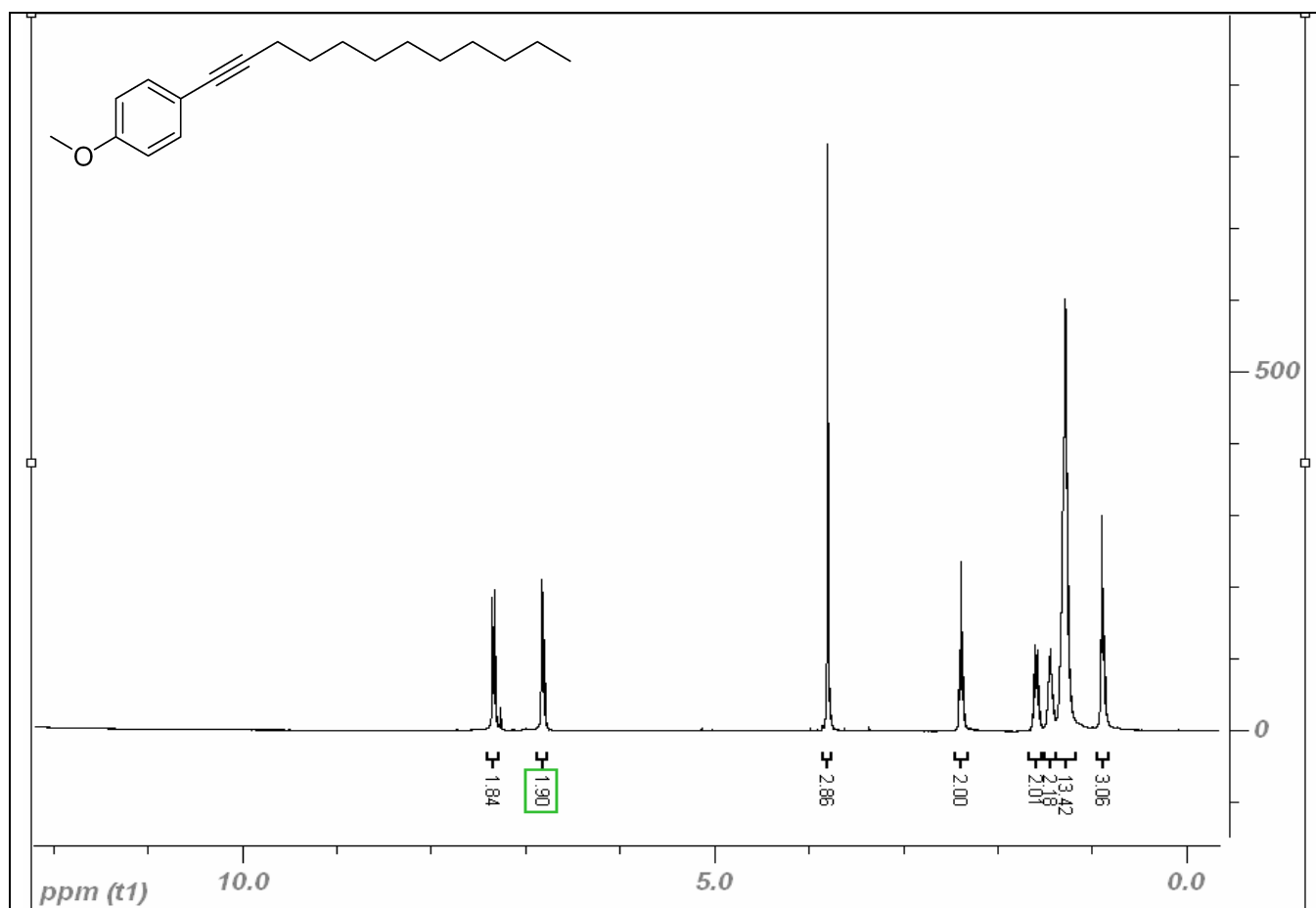
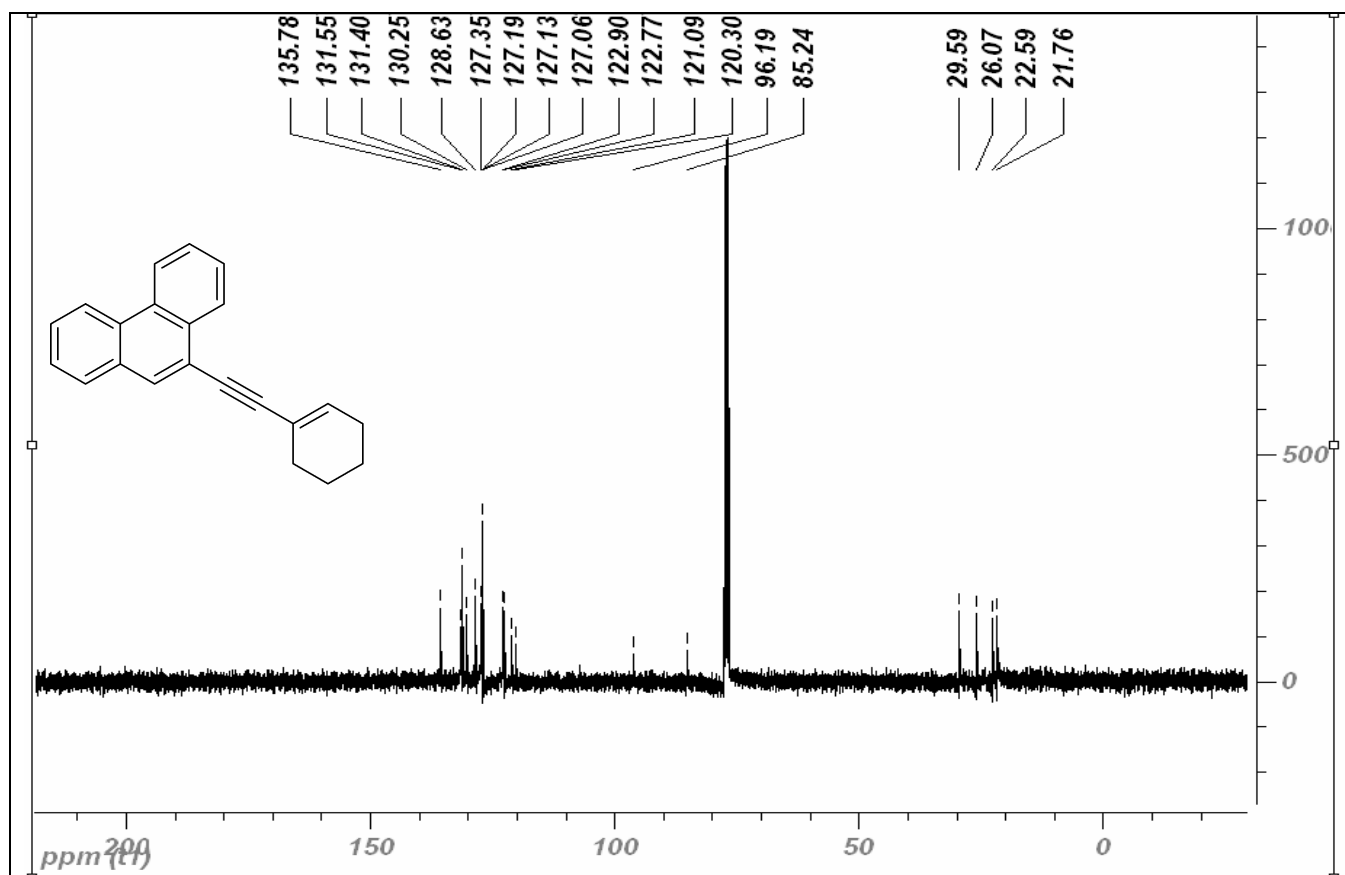


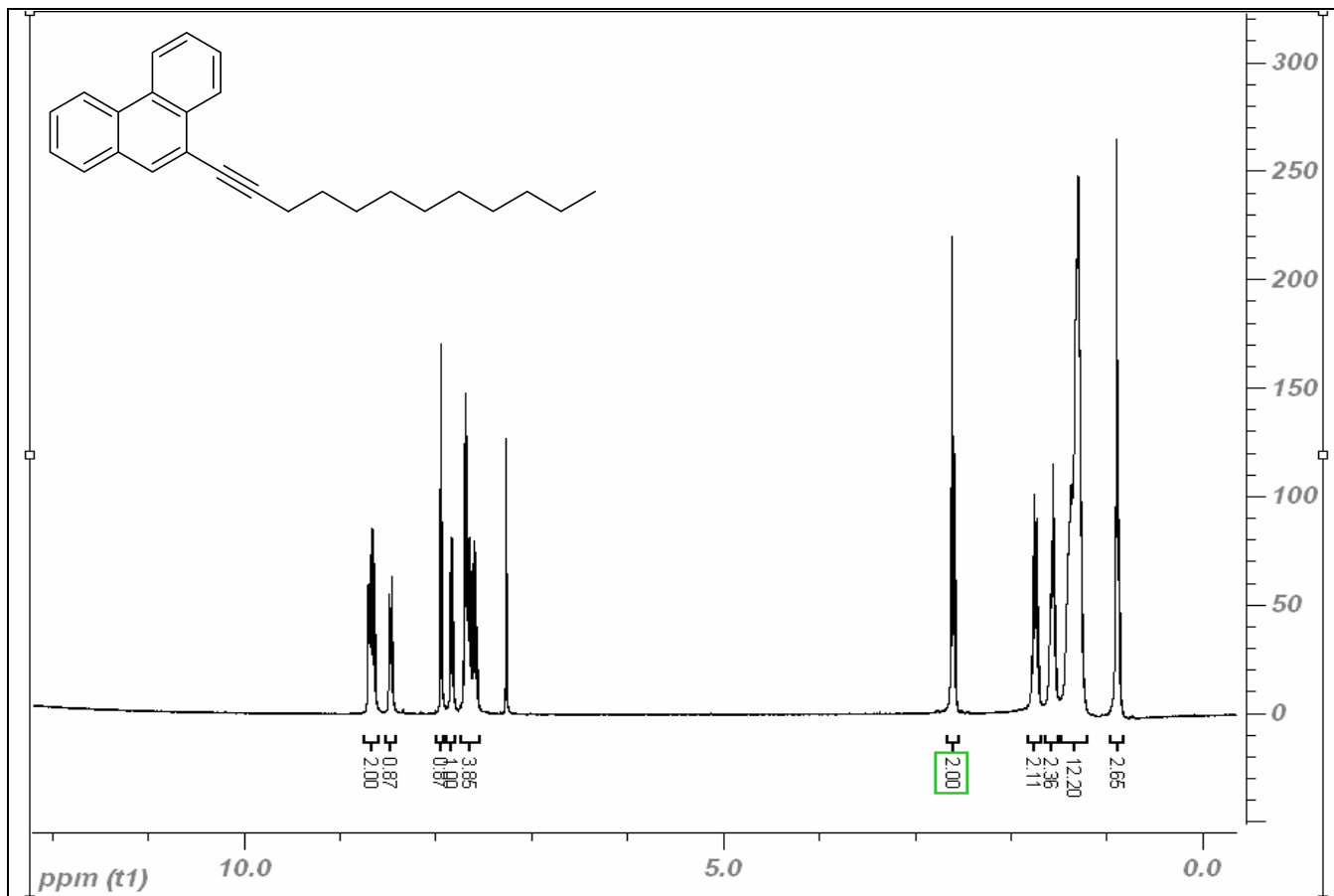
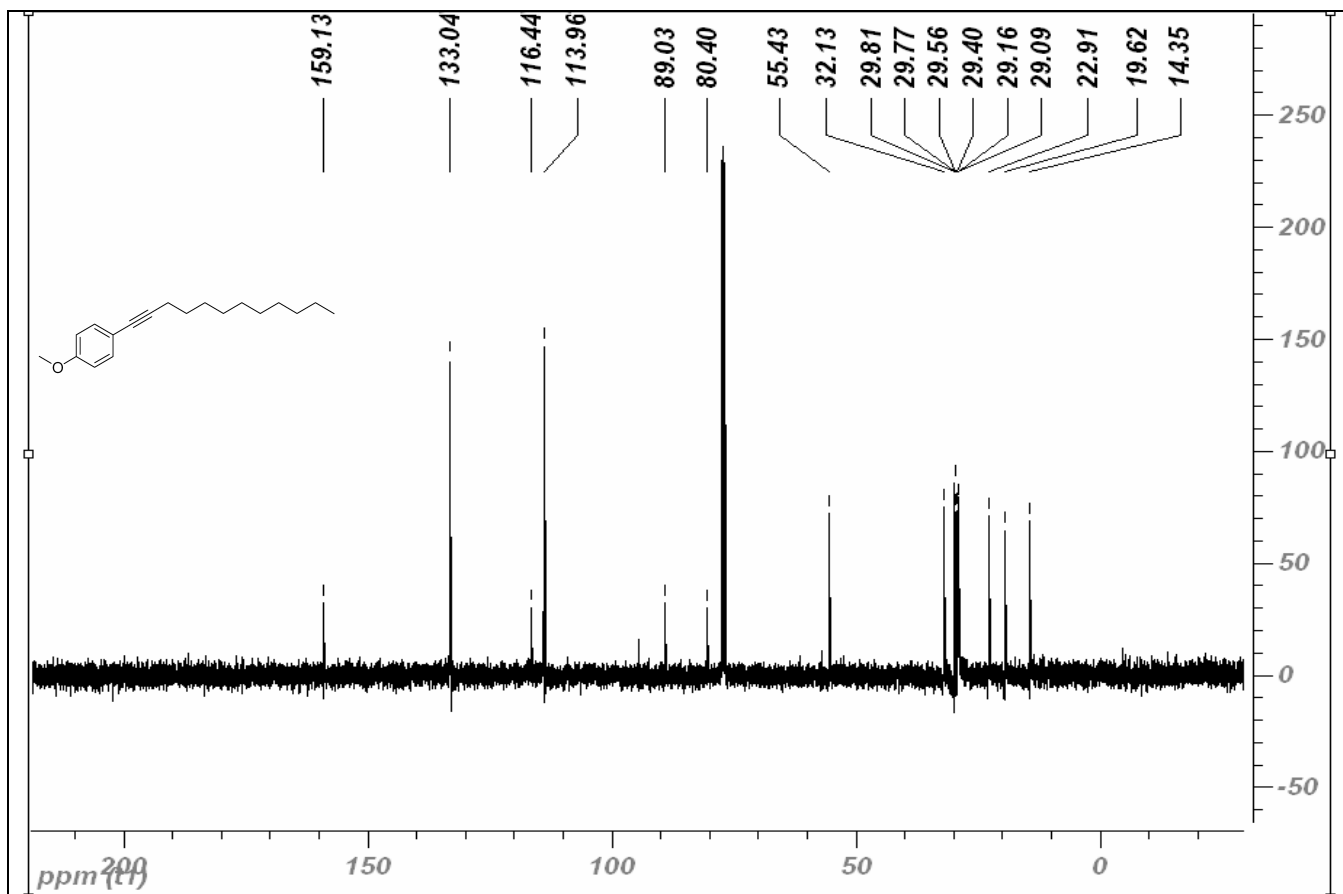












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