

## SUPPORTING INFORMATION

### Synthesis of Annulated $\gamma$ -Carbolines and Heteropolycycles by Palladium-Catalyzed Intramolecular Annulation of Alkynes

Haiming Zhang and Richard C. Larock\*

*Department of Chemistry, Iowa State University, Ames, IA 50011*

*larock@iastate.edu*

#### Table of Contents

General	S2
Preparation of Starting Materials	S2
Preparation of <i>N</i> -Tethered Indoles	S5
General Procedure for Intramolecular Iminoannulation	S10
Preparation of Annulated $\gamma$ -Carbolines	S10
Reference	S12
$^1\text{H}$ and $^{13}\text{C}$ NMR Spectra	S13

**General.**  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz, respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm) and a basic  $\text{KMnO}_4$  solution [3 g of  $\text{KMnO}_4$  + 20 g of  $\text{K}_2\text{CO}_3$  + 5 mL of  $\text{NaOH}$  (5 %) + 300 mL of  $\text{H}_2\text{O}$ ]. All melting points are uncorrected. All reagents were used directly as obtained commercially unless otherwise noted. The following starting materials were prepared as described.

**(E)-7-Chloro-1-phenylhept-1-en-3-yne.** To a 4-dram vial was added (*E*)- $\beta$ -iodostyrene<sup>1</sup> (0.230 g, 1.0 mmol),  $\text{CuI}$  (1 mol %),  $\text{PdCl}_2(\text{PPh}_3)_2$  (2 mol %) and  $\text{Et}_3\text{N}$  (5 mL). The mixture was stirred for 1 min and 5-chloro-1-pentyne (1.2 mmol) was added. The mixture was flushed with Ar and stirred at 60 °C for 3 h. The completion of the reaction was monitored by TLC analysis. The reaction mixture was cooled, diluted with ether and filtered. The solvent was evaporated and the residue was purified on a silica gel column using 50:1 hexanes/EtOAc to afford 70% yield of the indicated compound as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.01 (quintet,  $J = 6.6$  Hz, 2H), 2.56 (dt,  $J = 2.1, 6.6$  Hz, 2H), 3.68 (t,  $J = 6.6$  Hz, 2H), 6.13 (dt,  $J = 16.2, 2.1$  Hz, 1H), 6.88 (d,  $J = 16.2$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.4, 31.8, 44.0, 80.8, 90.2, 108.4, 126.1, 128.4, 128.7, 136.3, 140.6.

**5-Chloro-1-triethylsilyl-1-pentyne.** *n*-BuLi (2.5 M in hexanes, 1.1 equiv) was added dropwise to a stirred solution of 5-chloro-1-pentyne (0.513 g, 5.0 mmol) in dry THF (10 mL) at -78 °C under Ar. After 30 min, a solution of triethylsilyl chloride (0.980, 1.3 equiv) in THF (10 mL) was added dropwise. The mixture was warmed to room temperature for 3 h, quenched with satd aq  $\text{NH}_4\text{Cl}$  and extracted with ether. The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and the solvent was evaporated. The residue was purified using 100:1 hexanes/EtOAc to afford 0.97 g (90%) of the indicated compound as a colorless oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.57 (q,  $J = 8.0$  Hz, 6H), 0.98 (t,  $J = 8.0$  Hz, 9H), 1.98

(quintet,  $J = 6.4$  Hz, 2H), 2.43 (t,  $J = 6.4$  Hz, 2H), 3.66 (t,  $J = 6.4$  Hz, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  4.6, 7.5, 17.3, 31.5, 43.5, 82.8, 106.2.

**4,4'-Bis-(5-chloropent-1-ynyl)biphenyl.** This compound was prepared by the procedure used to synthesize (*E*)-7-chloro-1-phenylhept-1-en-3-yne, but using 4,4'-diiodobiphenyl and 5-chloro-1-pentyne (2.4 equiv). The product was purified using 10:1 hexanes/EtOAc to afford a 99% yield of the indicated compound as a pale yellow solid: mp 112-114 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.07 (quintet,  $J = 6.8$  Hz, 4H), 2.63 (t,  $J = 6.8$  Hz, 4H), 3.72 (t,  $J = 6.8$  Hz, 4H), 7.45 (d,  $J = 8.0$  Hz, 4H), 7.51 (d,  $J = 8.0$  Hz, 4H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.0, 31.5, 43.8, 81.4, 89.1, 122.9, 126.8, 132.1, 139.7.

**4-Phenylbut-3-yn-1-ol.** This compound was prepared by the procedure used to synthesize (*E*)-7-chloro-1-phenylhept-1-en-3-yne, but using iodobenzene and 3-butyne-1-ol. The product was purified using 2:1 hexanes/EtOAc to afford a 93% yield of the indicated compound as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.36 (t,  $J = 6.4$  Hz, 1H), 2.67 (t,  $J = 6.4$  Hz, 2H), 3.79 (m, 2H), 7.28 (m, 3H), 7.40 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  23.8, 61.2, 82.4, 86.5, 123.4, 128.0, 128.3, 131.7.

**11-Phenylundec-10-yn-1-ol.** This compound was prepared by the procedure used to synthesize (*E*)-7-chloro-1-phenylhept-1-en-3-yne, but using iodobenzene and 10-undecyn-1-ol. The product was purified using 3:1 hexanes/EtOAc to afford a 95% yield of the indicated compound as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.30-1.50 (m, 10H), 1.50-1.65 (m, 5H), 2.41 (t,  $J = 7.2$  Hz, 2H), 3.63 (t,  $J = 7.2$  Hz, 2H), 7.25-7.30 (m, 3H), 7.35-7.42 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.6, 26.0, 29.0, 29.1, 29.3, 29.6, 29.7, 33.0, 63.2, 80.8, 90.7, 124.3, 127.7, 128.4, 131.8.

**2-(Phenylethynyl)benzyl chloride.** This compound was prepared by the procedure used to synthesize (*E*)-7-chloro-1-phenylhept-1-en-3-yne, but using 2-iodobenzyl chloride and phenylacetylene. The product was purified using 50:1 hexanes/EtOAc to afford a 100% yield of the indicated compound as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  4.88 (s, 2H), 7.30-7.45 (m, 5H), 7.50-7.62 (m, 4H);  $^{13}\text{C}$  NMR

(CDCl<sub>3</sub>)  $\delta$  44.8, 86.5, 94.9, 123.0, 123.1, 128.5, 128.7, 128.8, 129.4, 131.7, 132.4, 132.6, 138.9.

**2-(Hex-1-ynyl)benzyl alcohol.** This compound was prepared by the procedure used to synthesize (*E*)-7-chloro-1-phenylhept-1-en-3-yne, but using 2-iodobenzyl alcohol and 1-hexyne. The product was purified using 5:1 hexanes/EtOAc to afford a 73% yield of the indicated compound as a yellow oil: <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  13.7, 19.3, 22.1, 30.9, 64.2, 78.2, 95.5, 122.2, 127.2, 127.4, 128.0, 132.2, 142.4. All other spectral properties are identical to those already in the literature.<sup>2</sup>

**(Z)-1-Bromo-5-phenylpent-2-en-4-yne.** To a solution of (*Z*)-5-phenylpent-2-en-4-yn-1-ol<sup>3</sup> (2.2 mmol, 0.348 g) and CBr<sub>4</sub> (0.948 g, 1.3 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0 °C was added PPh<sub>3</sub> (1.5 equiv, 0.866 g) portionwise. The mixture was stirred at room temperature for 2 h. The reaction mixture was flushed through a short silica gel column to remove the triphenylphosphine oxide. The solvent was evaporated and the residue was purified using 25:1 hexanes/EtOAc to afford 0.462 g (95%) of the indicated compound as a yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  4.27 (d, *J* = 8.1 Hz, 2H), 5.85 (d, *J* = 10.5 Hz, 1H), 6.20 (m, 1H), 7.35 (m, 3H), 7.47 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  28.7, 84.3, 97.6, 113.6, 123.0, 128.7, 129.0, 131.9, 137.1.

**Methyl 2-iodo-1-phenylsulfonyl-1*H*-indole-3-carboxylate:** *n*-BuLi (2.0 mmol, 2.5 M in hexanes) was added under Ar to a mixture of diisopropylamine (4.0 mmol) and dry THF (20 mL) at -78 °C and the mixture was stirred for 30 min. Methyl 1-phenylsulfonyl-1*H*-indole-3-carboxylate<sup>4</sup> (0.63 g, 2.0 mmol) in dry THF (8 mL) was added to the mixture and stirring was continued at -78 °C for 30 min. I<sub>2</sub> (1.52 g, 6.0 mmol) in dry THF (10 mL) was added and the mixture was stirred at -78 °C for 2 h. The reaction was quenched by satd aq NH<sub>4</sub>Cl, washed with satd aq Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and extracted with EtOAc. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, and the solvent was evaporated. The residue was purified using 3:1 hexanes/EtOAc to afford 0.756 g (86%) of the indicated compound as a white solid: mp 138-140 °C (lit.<sup>5</sup> mp 142 °C); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  51.8, 85.5, 115.4,

121.1, 121.6, 124.5, 125.7, 127.5, 128.3, 129.4, 134.6, 138.2, 139.2, 164.0. All other spectral properties are identical to those already in the literature.<sup>5</sup>

**Methyl 2-iodo-1*H*-indole-3-carboxylate:** To a mixture of methyl 2-iodo-1-phenylsulfonyl-1*H*-indole-3-carboxylate (0.441 g, 1.0 mmol) in methanol (15 mL) and 1,4-dioxane (5 mL) was added NaOH (0.120 g, 3.0 mmol) and the mixture was heated at 60 °C for 18 h. The solvent was evaporated and the residue was purified using 3:1 hexanes/EtOAc to afford 0.181 g (63%) of the indicated compound as a white solid: mp 159-160 °C (lit.<sup>5</sup> mp 161 °C). All other spectral properties are identical to those already in the literature.<sup>5</sup>

**2-Iodo-1*H*-indole-3-acetonitrile:** To a mixture of 1*H*-indole-3-acetonitrile (0.781 g, 5.0 mmol) and AgOTs (1.535 g, 5.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was added slowly a solution of I<sub>2</sub> (1.396 g, 5.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and the mixture was stirred at room temperature for 15 min. The precipitate was filtered and washed with CH<sub>2</sub>Cl<sub>2</sub>. The solvent was evaporated and the residue was purified using 2:1 hexanes/EtOAc to afford 0.560 g (40%) of the indicated compound as a yellow solid: mp 116-118 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.78 (s, 2H), 7.15-7.22 (m, 2H), 7.34 (dd, *J* = 2.0, 6.4 Hz, 1H), 7.64 (m, 1H), 8.24 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 16.4, 79.6, 110.7, 111.0, 117.5, 117.7, 121.0, 123.3, 126.6, 138.9.

**General Procedure for the Synthesis of *N*-Substituted 2-Bromo-1*H*-indole-3-carboxaldehydes.** Method A: 2-bromo-1*H*-indole-3-carboxaldehyde<sup>4</sup> (0.5 mmol), the alkynyl halide (0.6 mmol), NaI (0.75 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.75 mmol) were placed in a 4-dram vial and acetone (3 mL) was added. The vial was flushed with Ar and heated in an oil bath at 75 °C for 24 h. The mixture was cooled and diluted with ether (5 mL). The precipitate was removed by filtration and the solvent was evaporated. The residue was purified by chromatography on a silica gel column. Method B: to a mixture of 2-bromo-1*H*-indole-3-carboxaldehyde (0.5 mmol), the alkynyl alcohol (0.6 mmol), and PPh<sub>3</sub> (0.75 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) was added diethyl azodicarboxylate (0.75 mmol) at 0 °C.

The resulting mixture was flushed with Ar and stirred at room temperature for 24 h. The mixture was concentrated and the residue was purified by chromatography on a silica gel column.

### ***N*-Substituted 2-Bromo-1*H*-indole-3-carboxaldehydes Prepared**

**2-Bromo-1-[5-(triethylsilyl)pent-4-ynyl]-1*H*-indole-3-carboxaldehyde (3g).** This compound was prepared using 5-chloro-1-triethylsilyl-1-pentyne and (*i*-Pr)<sub>2</sub>NEt as the base using a modification of method A. The product was purified using 5:1 hexanes/EtOAc to afford a 90% yield of the indicated compound as a yellow oil, which solidifies upon cooling and standing: mp 59-61 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.65 (m, 6H), 1.03 (m, 9H), 2.05 (quintet, *J* = 7.2 Hz, 2H), 2.39 (t, *J* = 7.2 Hz, 2H), 4.44 (t, *J* = 7.2 Hz, 2H), 7.27-7.33 (m, 2H), 7.48 (m, 1H), 8.33 (m, 1H), 10.05 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 4.7, 7.8, 17.6, 28.6, 44.4, 57.4, 84.1, 106.2, 110.0, 115.7, 121.5, 123.6, 124.63, 125.6, 125.7, 137.2, 185.6; IR (neat, cm<sup>-1</sup>) 3056, 2954, 2805, 2172, 1653; HRMS calcd for C<sub>22</sub>H<sub>26</sub>BrNOSi: 403.0967. Found: 403.0974.

**2-Bromo-1-(pent-4-ynyl)-1*H*-indole-3-carboxaldehyde (3h).** This compound was prepared using 5-chloro-1-pentyne according to method A. The product was purified using 5:1 hexanes/EtOAc to afford a 96% yield of the indicated compound as a yellow solid: mp 94-96 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.05 (quintet, *J* = 7.2 Hz, 2H), 2.11 (t, *J* = 2.7 Hz, 1H), 2.31 (dt, *J* = 2.7, 7.2 Hz, 2H), 4.40 (t, *J* = 7.2 Hz, 2H), 7.26-7.35 (m, 2H), 7.43 (m, 1H), 8.31 (m, 1H), 10.03 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 16.2, 28.4, 44.3, 70.3, 82.7, 110.0, 115.7, 121.5, 123.6, 124.4, 125.6, 125.8, 137.1, 185.6; IR (neat, cm<sup>-1</sup>) 3223, 2926, 2806, 1648; HRMS calcd for C<sub>14</sub>H<sub>12</sub>BrNO: 289.0102. Found: 289.0106.

**4,4'-Bis-[5-(2-bromo-3-formylindol-1-yl)pent-1-ynyl]biphenyl (3i).** This compound was prepared using 4,4'-bis-(5-chloropent-1-ynyl)biphenyl (178 mg, 0.5 mmol), 2-bromo-1*H*-indole-3-carboxaldehyde<sup>6</sup> (268 mg, 1.2 mmol), K<sub>2</sub>CO<sub>3</sub> (208 mg, 1.5 mmol) and NaI (224 mg, 1.5 mmol) in acetone (6 mL) at 75 °C for 48 h using a modification of method A. The product was purified using 3:2

hexanes/EtOAc to afford 343 mg (94%) of the indicated compound as a yellow solid: mp 135-137 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.17 (m, 4H), 2.56 (t,  $J = 7.2$  Hz, 4H), 4.49 (t,  $J = 7.2$ , 4H), 7.27-7.35 (m, 4H), 7.45-7.50 (m, 6H), 7.51-7.60 (m, 4H), 8.33 (m, 2H), 10.04 (s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.1, 28.5, 44.3, 82.0, 89.0, 109.9, 115.5, 121.4, 122.7, 123.5, 124.2, 125.5, 125.6, 126.9, 132.1, 136.9, 139.9, 185.5; IR (neat,  $\text{cm}^{-1}$ ) 3022, 2922, 2262, 1653; HRMS calcd for  $\text{C}_{40}\text{H}_{30}\text{Br}_2\text{N}_2\text{O}_2$ : 730.0654. Found: 730.0667.

**2-Bromo-1-(11-phenylundec-10-ynyl)indole-3-carboxaldehyde (3m).**

This compound was prepared using 11-phenylundec-10-yn-1-ol according to Method B. The product was purified using 8:1 hexanes/EtOAc to afford a 75% yield of the indicated compound as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.25-1.50 (m, 10H), 1.59 (quintet,  $J = 7.2$  Hz, 2H), 1.82 (quintet,  $J = 7.2$  Hz, 2H), 2.39 (t,  $J = 7.2$  Hz, 2H), 4.24 (t,  $J = 7.2$  Hz, 2H), 7.22-7.40 (m, 8H), 8.32 (m, 1H), 10.03 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.6, 27.0, 28.9, 29.0, 29.2, 29.4, 29.5, 29.7, 45.7, 80.9, 90.6, 110.1, 115.4, 121.5, 123.5, 124.2, 124.3, 125.6, 125.9, 127.7, 128.4, 131.7, 136.9, 185.7; IR (neat,  $\text{cm}^{-1}$ ) 3017, 2930, 2856, 1654; HRMS calcd for  $\text{C}_{26}\text{H}_{28}\text{BrNO}$ : 449.1354. Found: 449.1363.

**2-Bromo-1-[2-(hex-1-ynyl)benzyl]-1*H*-indole-3-carboxaldehyde (3o).**

This compound was prepared using 2-(hex-1-ynyl)benzyl alcohol according to method B for 72 h. The product was purified using 7:1 hexanes/EtOAc to afford a 36% yield of the indicated compound as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.98 (t,  $J = 7.2$  Hz, 2H), 1.54 (sextet,  $J = 7.2$  Hz, 2H), 1.67 (quintet,  $J = 7.2$  Hz, 2H), 2.54 (t,  $J = 7.2$  Hz, 2H), 6.52 (d,  $J = 7.8$  Hz, 1H), 7.10 (t,  $J = 7.8$  Hz, 1H), 7.18-7.32 (m, 4H), 7.48 (d,  $J = 7.8$  Hz, 1H), 8.35 (d,  $J = 7.8$  Hz, 1H), 10.09 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  13.7, 19.4, 22.2, 30.9, 47.3, 77.8, 97.3, 110.4, 115.7, 121.3, 122.2, 123.6, 124.4, 125.3, 125.4, 126.4, 127.7, 128.3, 132.5, 136.4, 137.2, 185.6; IR (neat,  $\text{cm}^{-1}$ ) 3058, 2956, 2930, 2226, 1661; HRMS calcd for  $\text{C}_{22}\text{H}_{20}\text{BrNO}$ : 393.0728. Found: 393.0733.

**2-Bromo-1-[(*Z*)-5-phenylpent-2-en-4-ynyl]-1*H*-indole-3-carboxaldehyde (3p).** This compound was prepared using (*Z*)-1-bromo-5-

phenylpent-2-en-4-yne according to method A for 48 h or (*Z*)-5-phenylpent-2-en-4-yn-1-ol<sup>3</sup> according to method B for 48 h. The product was purified using 5:1 hexanes/EtOAc to afford a 22% yield (method A) or a 31% yield (method B) of the indicated compound as a yellow solid: mp 129-131 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 5.33 (d, *J* = 6.0 Hz, 2H), 5.94 (dd, *J* = 6.0, 8.4 Hz, 1H), 5.99 (d, *J* = 8.4 Hz, 1H), 7.25-7.31 (m, 2H), 7.31-7.40 (m, 3H), 7.45-7.52 (m, 3H), 8.31 (m, 1H), 10.03 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 44.9, 84.5, 97.2, 110.2, 113.8, 115.7, 121.3, 122.6, 123.5, 124.3, 125.4, 125.6, 128.6, 129.0, 131.6, 134.5, 136.9, 185.5; IR (neat, cm<sup>-1</sup>) 3055, 2808, 2196, 1654; HRMS calcd for C<sub>20</sub>H<sub>14</sub>BrNO: 363.0259. Found: 363.0265.

**2-Bromo-1-[2-(phenylethynyl)benzoyl]-1*H*-indole-3-carboxaldehyde (3r).** To a mixture of 2-bromo-1*H*-indole-3-carboxaldehyde<sup>6</sup> (86 mg, 0.38 mmol) and 2-(phenylethynyl)benzoic acid<sup>7</sup> (111 mg, 0.5 mmol) in THF (5 mL) was added DMAP (6 mg) and DCC (105 mg), and the mixture was stirred at room temperature for 28 h. The precipitate was filtered and the solvent was evaporated and the residue was purified using 4:1 hexanes/EtOAc to afford a 50% yield of the indicated compound as a yellow solid: mp 136-138 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.69 (d, *J* = 8.0 Hz, 2H), 7.09 (t, *J* = 7.8 Hz, 2H), 7.20 (m, 1H), 7.32-7.38 (m, 2H), 7.54 (m, 1H), 7.60 (m, 2H), 7.69 (m, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 8.24 (m, 1H), 10.05 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 84.6, 95.6, 113.7, 119.9, 121.1, 121.5, 122.2, 123.5, 125.1, 125.9, 126.1, 128.1, 128.8, 128.9, 130.5, 131.4, 132.9, 133.3, 136.3, 137.1, 168.0, 186.8; IR (neat, cm<sup>-1</sup>) 3061, 2214, 1699, 1669; HRMS calcd for C<sub>24</sub>H<sub>14</sub>BrNO<sub>2</sub>: 427.0208. Found: 427.0213.

### Other Tethered Indoles Prepared

**Methyl 2-iodo-1-(5-phenylpent-4-ynyl)-1*H*-indole-3-carboxylate (3s).** This compound was prepared using methyl 2-iodo-1*H*-indole-3-carboxylate and 5-chloro-1-pentyne at 100 °C using a modification of method A. The product was purified using 4:1 hexanes/EtOAc to afford a 78% yield of the indicated compound as a yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.08 (quintet, *J* = 7.5 Hz, 2H), 2.51

(t,  $J = 7.5$  Hz, 2H), 3.96 (s, 3H), 4.48 (t,  $J = 7.5$  Hz, 2H), 7.18-7.25 (m, 2H), 7.28-7.33 (m, 3H), 7.40-7.50 (m, 3H), 8.12 (m, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.0, 28.6, 47.0, 51.2, 82.1, 88.4, 94.2, 110.2, 111.6, 121.8, 122.0, 123.1, 123.5, 127.5, 128.0, 128.4, 131.6, 138.2, 164.9; IR (neat,  $\text{cm}^{-1}$ ) 3053, 2949, 2228, 1697; HRMS calcd for  $\text{C}_{21}\text{H}_{18}\text{INO}_2$ : 443.0382. Found: 443.0389.

**2-Iodo-3-phenyl-1-(5-phenylpent-4-ynyl)-1H-indole (3t).** This compound was prepared using 2-iodo-3-phenyl-1H-indole,<sup>8</sup> 5-chloro-1-pentyne and  $\text{Cs}_2\text{CO}_3$  as the base at 100 °C for 40 h using a modification of method A. The product was purified using 10:1 hexanes/EtOAc to afford an 86% yield of the indicated compound as a yellow oil, which solidifies upon cooling and standing: mp 68-70 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.13 (quintet,  $J = 7.2$  Hz, 2H), 2.53 (t,  $J = 7.2$  Hz, 2H), 4.45 (t,  $J = 7.2$  Hz, 2H), 7.08 (t,  $J = 7.6$ , 1H), 7.21 (t,  $J = 7.6$ , 1H), 7.28-7.38 (m, 4H), 7.41-7.51 (m, 5H), 7.54-7.61 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.1, 29.1, 46.5, 81.8, 85.8, 88.8, 109.8, 119.2, 120.2, 122.4, 123.4, 123.7, 126.9, 127.9, 128.4, 128.5, 130.1, 131.7, 135.2, 138.1 (one  $\text{sp}^2$  carbon missing due to overlap); IR (neat,  $\text{cm}^{-1}$ ) 3052, 2933, 2223; HRMS calcd for  $\text{C}_{25}\text{H}_{20}\text{IN}$ : 461.0641. Found: 461.0646.

**2-Bromo-1-(5-phenylpent-4-ynyl)-1H-indole-3-acetonitrile (3u).** This compound was prepared using 2-bromo-1H-indole-3-acetonitrile,<sup>9</sup> 5-chloro-1-pentyne and  $\text{Cs}_2\text{CO}_3$  as the base at 75 °C using a modification of method A. The product was purified using 5:1 hexanes/EtOAc to afford a 99% yield of the indicated compound as a yellow oil, which solidifies upon cooling and standing: mp 68-70 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.07 (quintet,  $J = 7.2$  Hz, 2H), 2.46 (t,  $J = 7.2$  Hz, 2H), 3.79 (s, 2H), 4.37 (t,  $J = 7.2$  Hz, 2H), 7.16-7.32 (m, 5H), 7.38-7.48 (m, 3H), 7.62 (d,  $J = 6.6$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.7, 17.2, 29.1, 44.3, 82.1, 88.7, 103.6, 110.1, 114.0, 117.3, 118.1, 121.0, 123.0, 123.8, 126.3, 128.2, 128.6, 131.8, 136.6; IR (neat,  $\text{cm}^{-1}$ ) 3055, 2929, 2231; HRMS calcd for  $\text{C}_{21}\text{H}_{17}\text{BrN}_2$ : 376.0575. Found: 376.0580.

**2-Iodo-1-(5-phenylpent-4-ynyl)-1H-indole-3-acetonitrile (3v).** This compound was prepared using 2-iodo-1H-indole-3-acetonitrile, 5-chloro-1-pentyne and  $\text{Cs}_2\text{CO}_3$  as the base at 100 °C for 40 h using a modification of

method A. The product was purified using 4:1 hexanes/EtOAc to afford a 71% yield of the indicated compound as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.03 (quintet,  $J = 7.2$  Hz, 2H), 2.45 (t,  $J = 7.2$  Hz, 2H), 3.77 (s, 2H), 4.34 (t,  $J = 7.2$  Hz, 2H), 7.14-7.22 (m, 2H), 7.25-7.32 (m, 3H), 7.40-7.45 (m, 3H), 7.62 (d,  $J = 7.2$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  16.9, 17.0, 29.0, 46.6, 82.0, 87.7, 88.6, 109.8, 110.2, 117.3, 117.9, 120.5, 122.8, 123.6, 127.0, 128.0, 128.4, 131.6, 138.1; IR (neat,  $\text{cm}^{-1}$ ) 3057, 2939, 2243; HRMS calcd for  $\text{C}_{21}\text{H}_{17}\text{N}_2$ : 424.0437. Found: 424.0442.

**General Procedure for the Synthesis of Annulated  $\gamma$ -Carbolines by Palladium-Catalyzed Intramolecular Iminoannulation.** The *N*-substituted 2-bromo-1*H*-indole-3-carboxaldehyde (0.25 mmol) was placed in a 2-dram vial and *tert*-butylamine (1 mL) was added. The vial was flushed with Ar and carefully sealed. The mixture was heated at 100 °C for 8 h and cooled, diluted with ether, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and filtered. The solvent was evaporated and the residue was dissolved in DMF (5 mL) and transferred to a 4-dram vial containing  $\text{Pd}(\text{OAc})_2$  (5 mol %),  $\text{PPh}_3$  (10 mol %) and  $\text{Na}_2\text{CO}_3$  (0.25 mmol). The mixture was flushed with Ar and heated at 100 °C for the indicated time. The completion of the reaction was established by the observation of palladium black. The mixture (except for entries 4 and 6-8 in Table 1, which produce reasonably water soluble products) was diluted with EtOAc, washed with satd aq  $\text{NH}_4\text{Cl}$  and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated and the residue was purified by chromatography on a silica gel column. The solvent from the reaction mixtures of entries 4 and 6-8 was directly evaporated and the residue was purified by chromatography on a silica gel column.

### Annulated $\gamma$ -Carbolines Prepared

**5,6-Dihydro-4*H*-indolo[3,2,1-*ij*]-1,6-naphthyridine (4h).** The mixture was chromatographed using 10:1  $\text{CHCl}_3/\text{MeOH}$  to afford 21 mg (40%) of the indicated compound as a yellow solid: mp 268-270 °C (lit.<sup>10a</sup> mp 270 °C). All other spectral properties are identical to those previously reported.<sup>10</sup>

**4,4'-Bis-{5,6-dihydro-4*H*-indolo[3,2,1-*ij*]-1,6-naphthyrid-3-yl}biphenyl (4i).** The aldehyde (**3i**, 146 mg, 0.20 mmol), *tert*-butylamine (3 mL) and CHCl<sub>3</sub> (5 mL) were placed in a 2-dram vial. The vial was flushed with Ar and carefully sealed, and the mixture was heated at 100 °C for 20 h. The mixture was cooled, diluted with ether, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and the solvent was evaporated. The residue was dissolved in 8 mL of DMF and transferred to a 4-dram vial containing 10 mol % Pd(OAc)<sub>2</sub>, 20 mol % PPh<sub>3</sub> and Na<sub>2</sub>CO<sub>3</sub> (0.40 mmol). The mixture was then flushed with Ar and heated at 100 °C for 10 h. The mixture was chromatographed using 8:1 CHCl<sub>3</sub>/MeOH on a short silica gel column to afford 103 mg (91%) of the indicated compound as a yellow solid: mp >300 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.32 (quintet, *J* = 5.6 Hz, 4H), 3.27 (t, *J* = 5.6 Hz, 4H), 4.29 (t, *J* = 5.6 Hz, 4H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.45 (d, *J* = 7.6 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.81 (d, *J* = 8.4 Hz, 4H), 7.86 (d, *J* = 8.4 Hz, 4H), 8.19 (d, *J* = 7.6 Hz, 2H), 9.28 (s, 2H); the <sup>13</sup>C NMR spectrum of compound **4i** was not obtained due to its extremely poor solubility in all the solvents we tried; IR (neat, cm<sup>-1</sup>) 3050, 2929, 2862; HRMS calcd for C<sub>40</sub>H<sub>30</sub>N<sub>4</sub>: 566.2471. Found: 566.2478.

**3-Phenyl-4,5-dihydrobenzo[*b*]pyrido[3,4,5-*gh*]pyrrolizine (4k).** The mixture was chromatographed using 3:2 hexanes/EtOAc to afford 57 mg (84%) of the indicated compound as a yellow solid: mp 171-172 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.06 (t, *J* = 7.2 Hz, 2H), 4.53 (t, *J* = 7.2 Hz, 2H), 7.28 (m, 1H), 7.37 (t, *J* = 8.0 Hz, 2H), 7.42-7.50 (m, 3H), 8.02 (m, 2H), 8.08 (d, *J* = 8.0 Hz, 2H), 9.07 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 35.0, 48.7, 110.5, 112.8, 116.5, 120.2, 123.0, 126.0, 127.6, 128.2, 128.7, 139.4, 140.4, 141.0, 146.8, 158.2; IR (neat, cm<sup>-1</sup>) 3055, 2922, 1559; HRMS calcd for C<sub>19</sub>H<sub>14</sub>N<sub>2</sub>: 270.1157. Found: 270.1161.

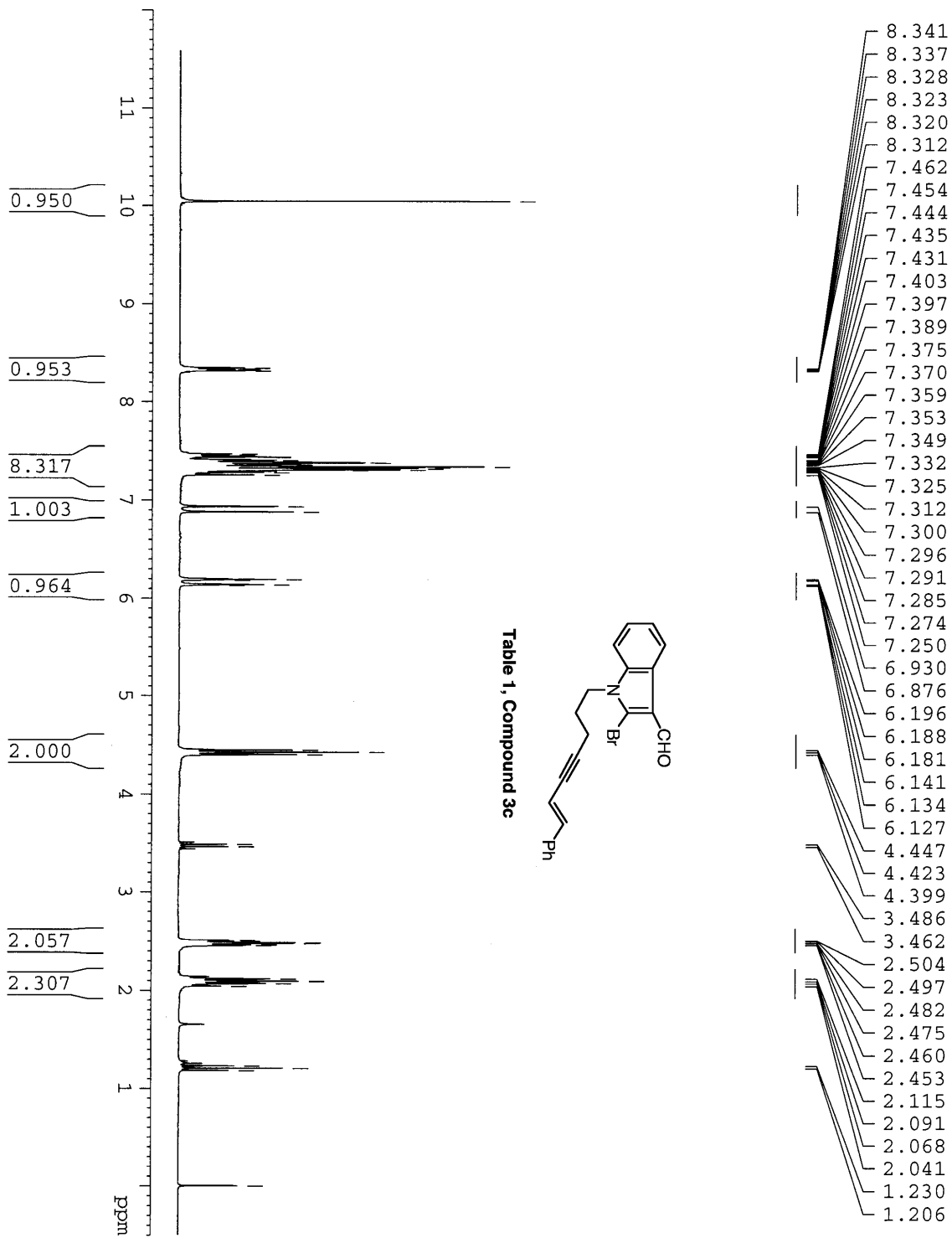
**1-*n*-Butyl-9*H*-benzo[*c*]indolo[3,2,1-*ij*]-1,6-naphthyridine (4o).** The mixture was chromatographed using 2:3 hexanes/EtOAc to afford 58 mg (75%) of the indicated compound as a yellow solid: mp 129-130 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.03 (t, *J* = 7.2 Hz, 3H), 1.58 (m, 2H), 1.90 (m, 2H), 3.29 (t, *J* = 8.0 Hz, 2H), 5.40 (s, 2H), 7.30-7.37 (m, 3H), 7.38-7.45 (m, 2H), 7.50 (dt, *J* = 0.8, 8.0 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 8.99 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ

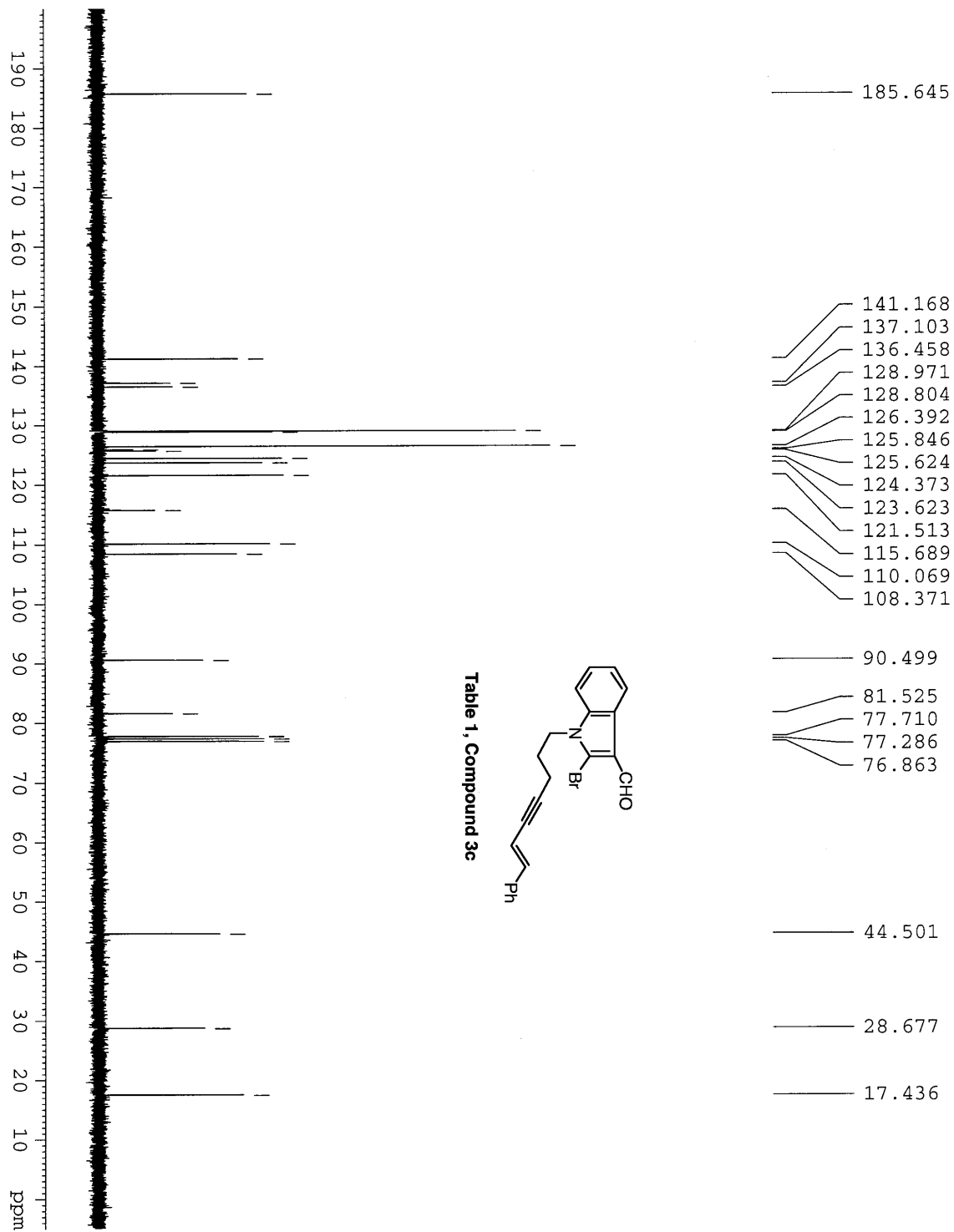
14.1, 23.1, 31.4, 38.1, 45.7, 109.2, 112.2, 116.8, 121.0, 121.2, 122.0, 126.3, 126.7, 127.8, 128.1, 128.2, 129.6, 130.9, 140.3, 140.9, 143.7; IR (neat,  $\text{cm}^{-1}$ ) 3059, 2956, 2870; HRMS calcd for  $\text{C}_{22}\text{H}_{20}\text{N}_2$ : 312.1626. Found: 312.1630.

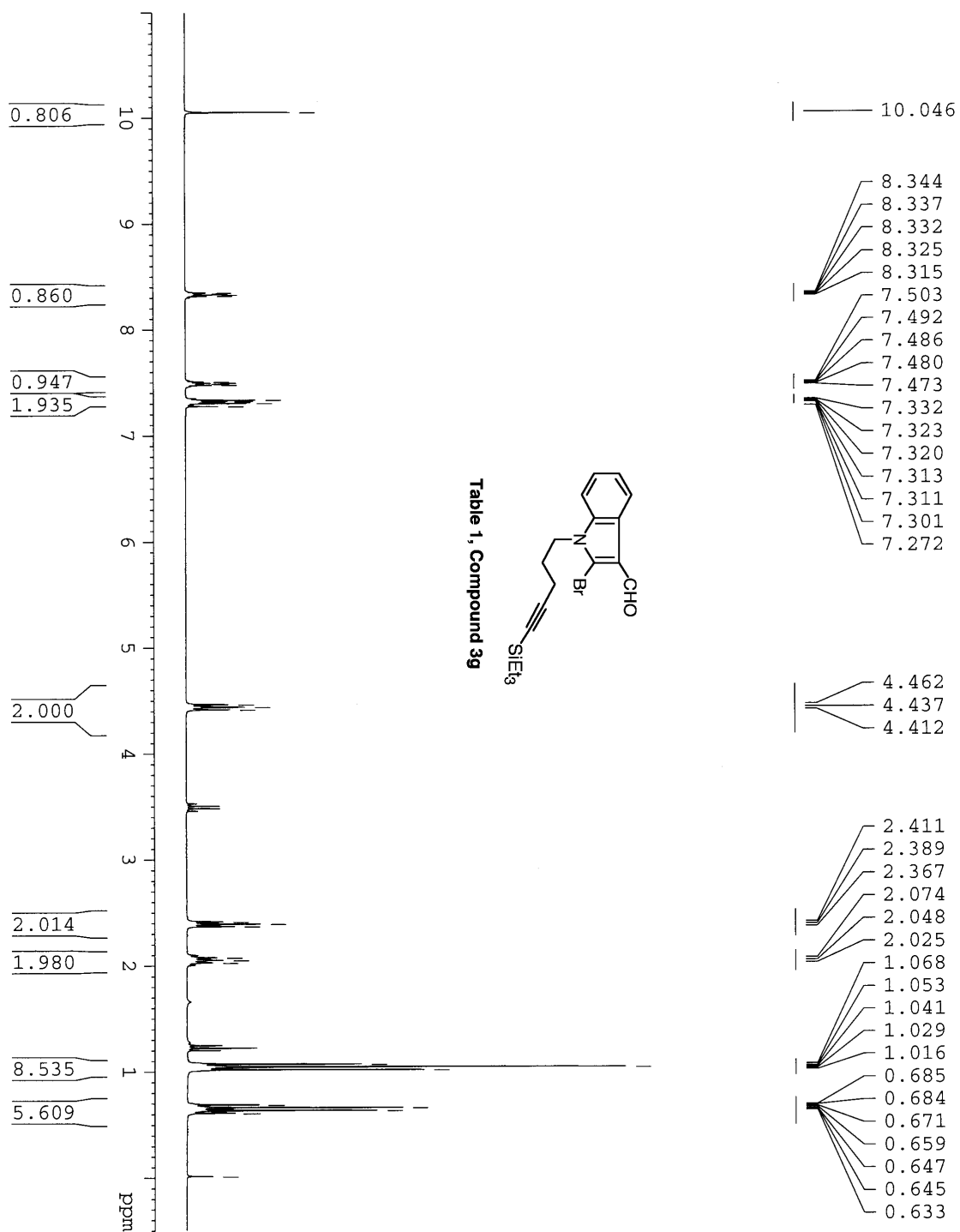
**3-Phenyl-6*H*-indolo[3,2,1-*ij*]-1,6-naphthyridine (4p).** The mixture was chromatographed using 1:2 hexanes/EtOAc to afford 40 mg (57%) of the indicated compound as a yellow solid: mp 160-161 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  5.18 (t,  $J = 2.8$  Hz, 2H), 5.97 (dt,  $J = 10.4, 3.2$  Hz, 1H), 6.88 (dt,  $J = 10.4, 2.0$  Hz, 1H), 7.32-7.44 (m, 3H), 7.46-7.54 (m, 3H), 7.69 (m, 2H), 8.13 (d,  $J = 7.8$  Hz, 1H), 9.10 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  44.0, 109.0, 110.9, 116.0, 121.0, 121.4, 121.7, 122.2, 123.1, 126.2, 128.0, 129.6, 139.1, 140.3, 142.5, 142.6, 148.9; IR (neat,  $\text{cm}^{-1}$ ) 3056, 2927; HRMS calcd for  $\text{C}_{20}\text{H}_{14}\text{N}_2$ : 282.1157. Found: 282.1160.

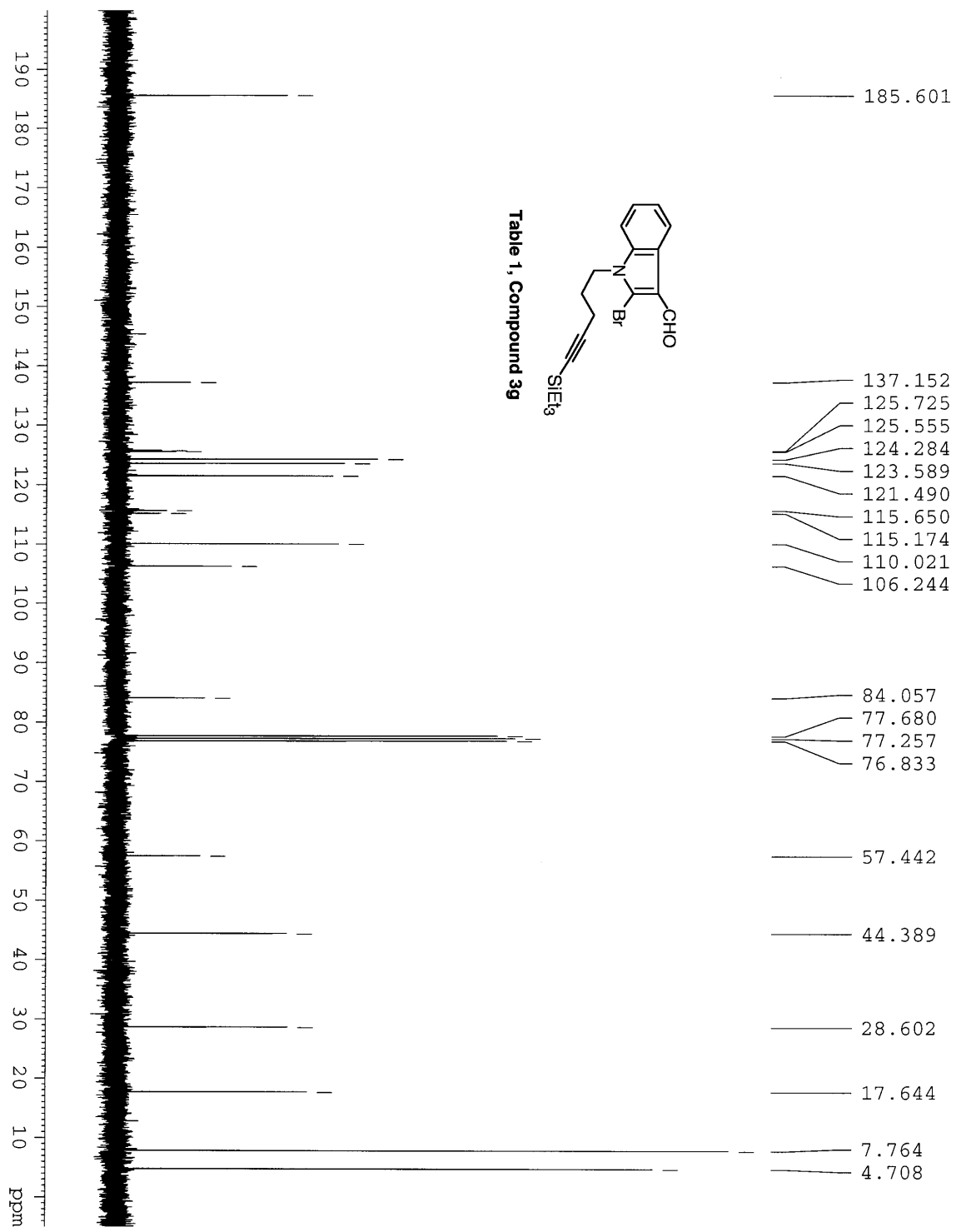
## References

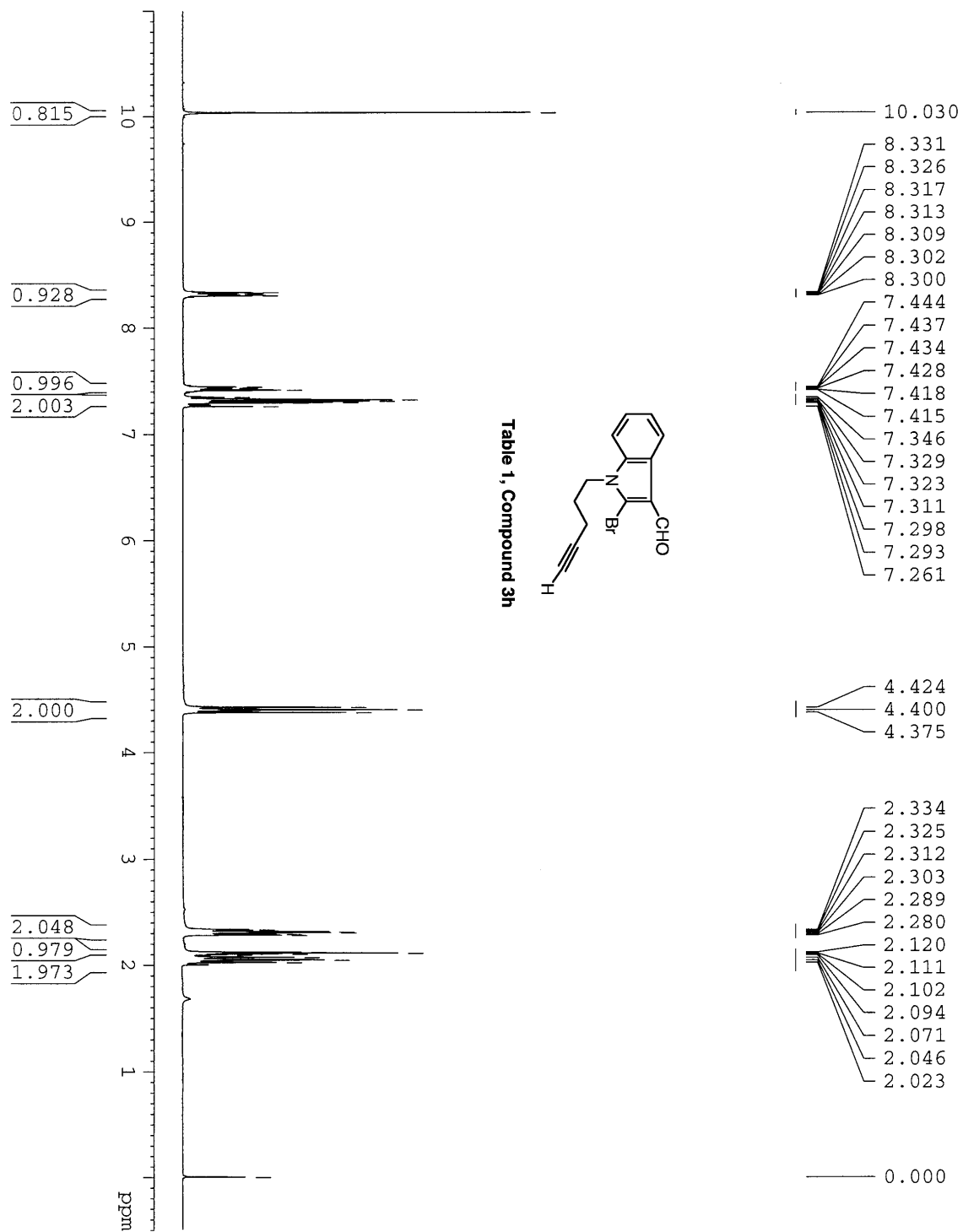
1. Brown, H. C.; Subrahmanyam, C.; Hamaoka, T.; Ravindran, N.; Bowman, D. H.; Misumi, S.; Unni, M. K.; Somayaji, V.; Bhat, N. G. *J. Org. Chem.* **1989**, *54*, 6068.
2. Hiroya, K.; Jouka, R.; Kameda, M.; Yasuhara, A.; Sakamoto, T. *Tetrahedron* **2001**, *57*, 9697.
3. Takeuchi, R.; Tanabe, K.; Tanaka, S. *J. Org. Chem.* **2000**, *65*, 1558.
4. Wenkert, E.; Moeller, P. D.; Piettre, S. R. *J. Am. Chem. Soc.* **1988**, *110*, 7188.
5. Beccalli, E. M.; Brogгинi, G.; Marchesini, A.; Rossi, E. *Tetrahedron* **2002**, *58*, 6673.
6. Zhang, H.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9318.
7. Biagetti, M.; Bellina, F.; Carpita, A.; Stabile, P.; Rossi, R. *Tetrahedron* **2002**, *58*, 5023.
8. Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 5616.
9. Mistry, A. G.; Smith, K.; Bye, M. R. *Tetrahedron Lett.* **1986**, *27*, 1051.
10. (a) Gilchrist, T. L.; Kemmitt, P. D.; Germain, A. L. *Tetrahedron* **1997**, *53*, 4447. (b) Snyder, S. A.; Vosburg, D. A.; Jarvis, M. G.; Markgraf, J. H. *Tetrahedron* **2000**, *56*, 5329.

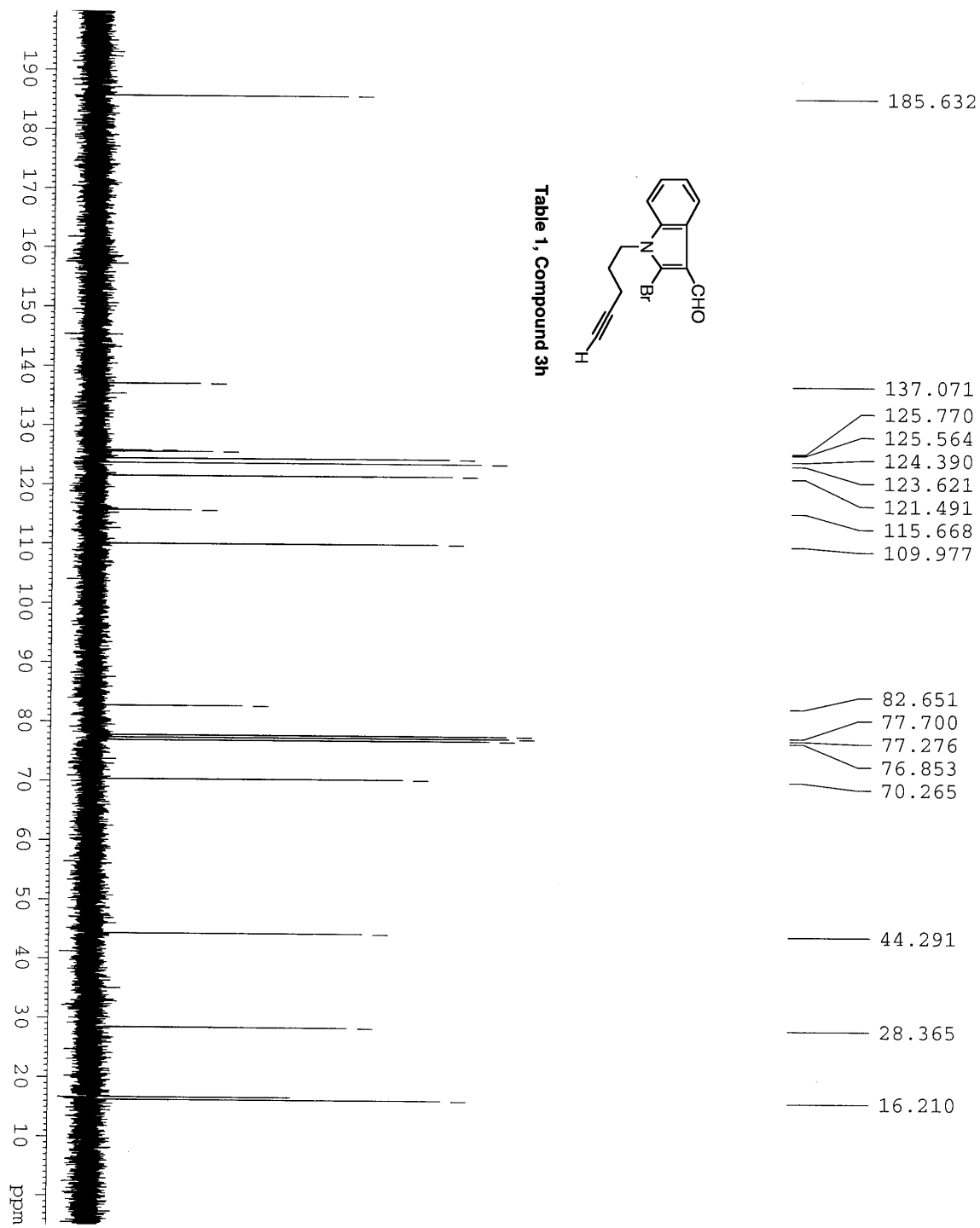


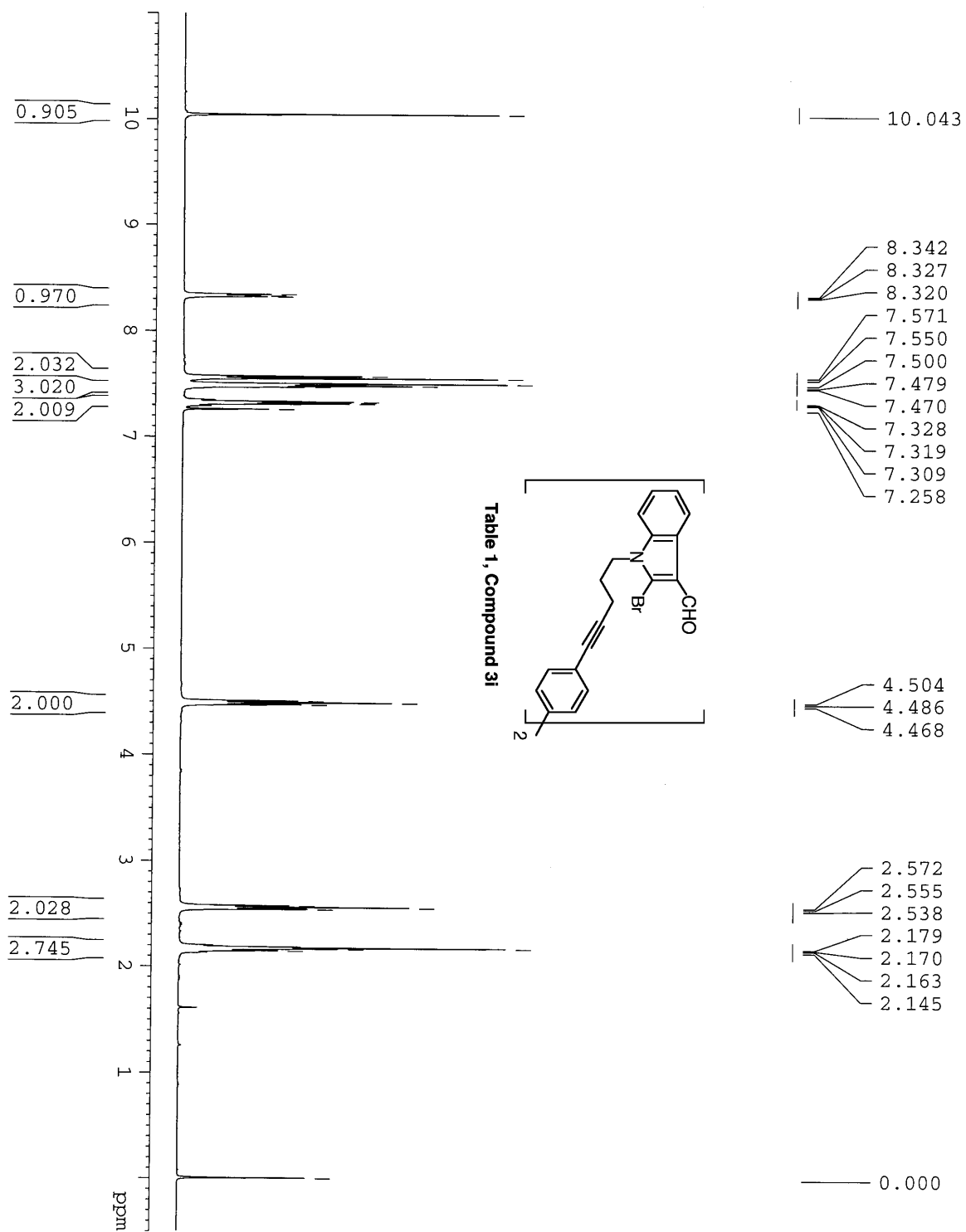


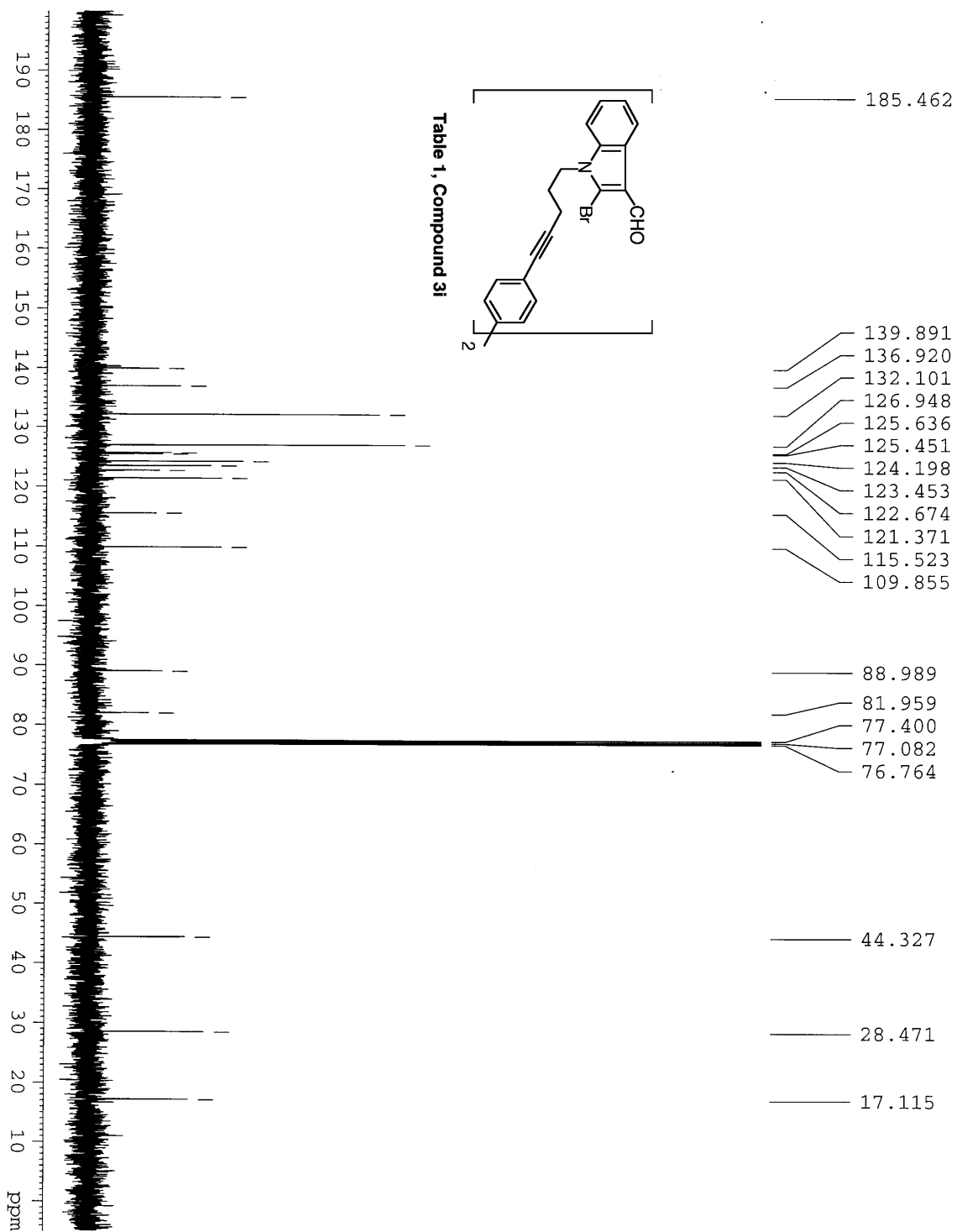


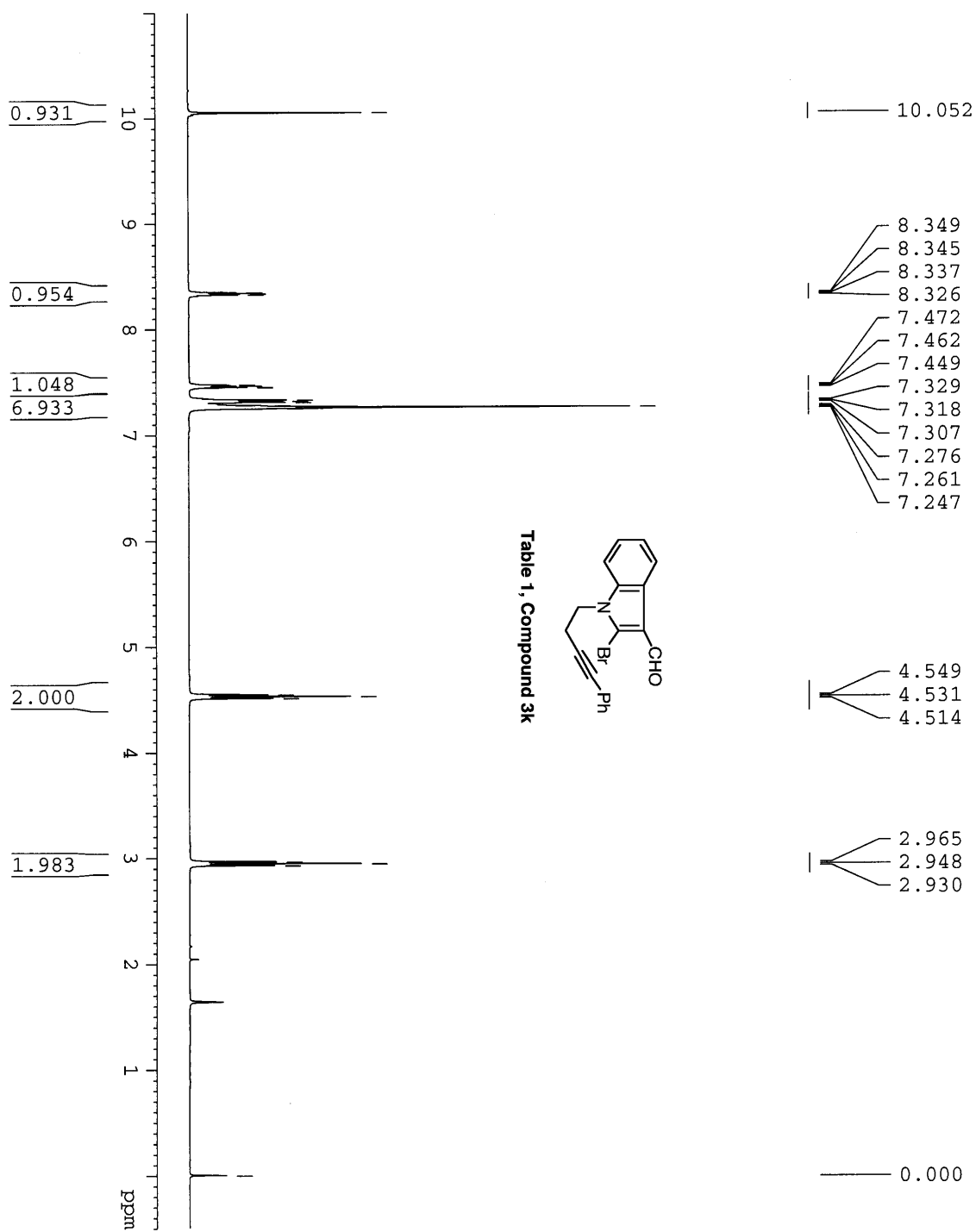


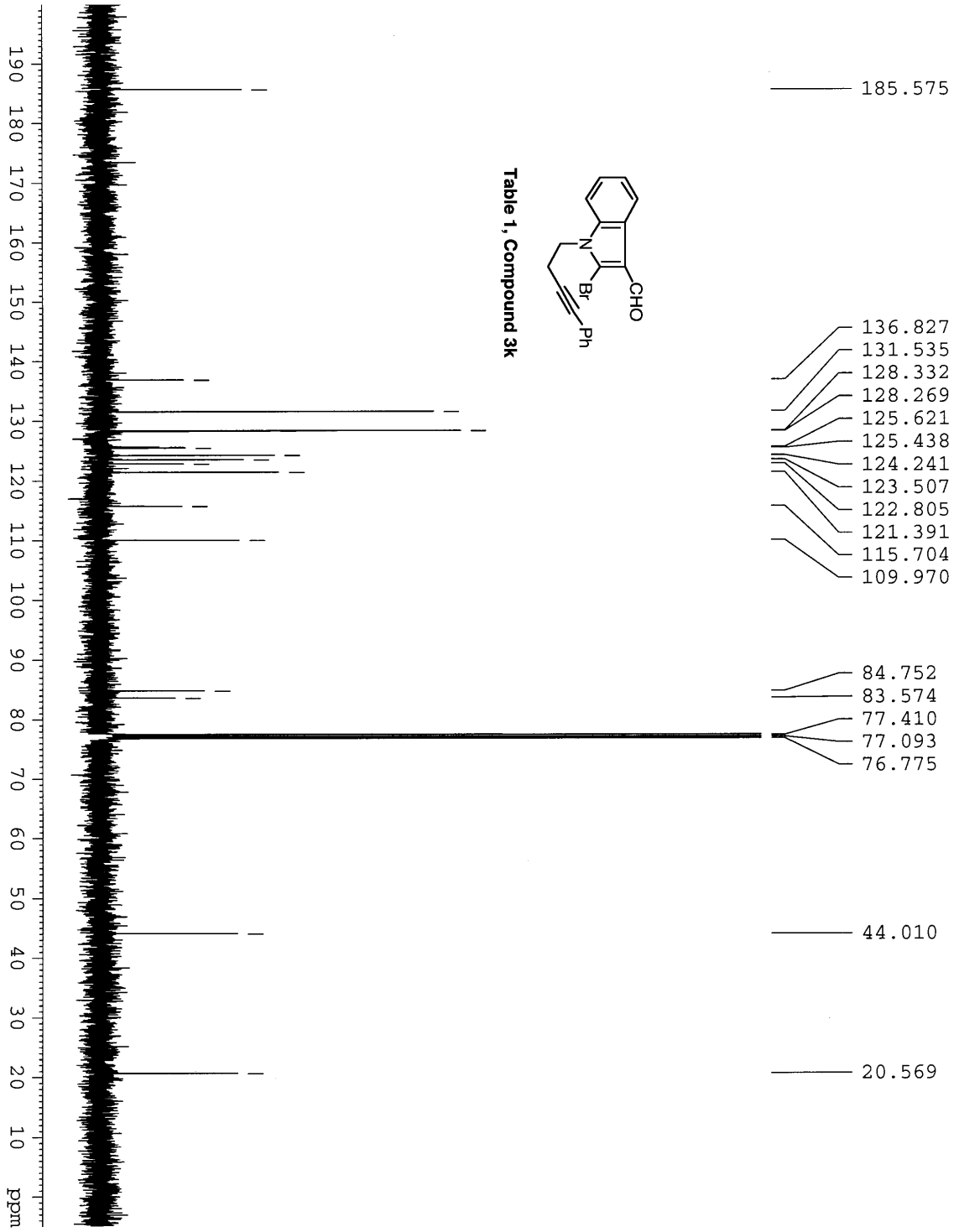












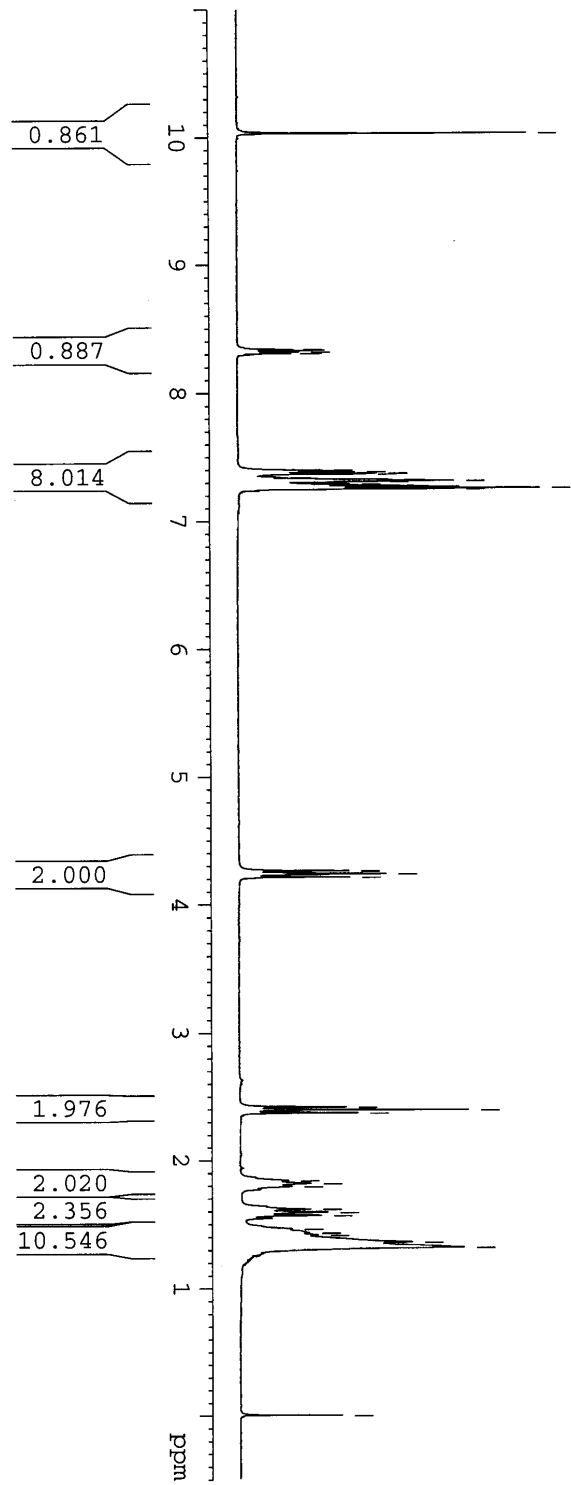
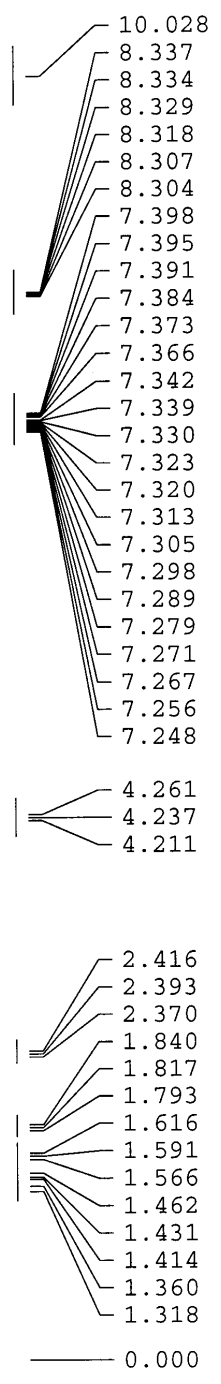
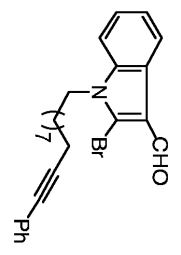
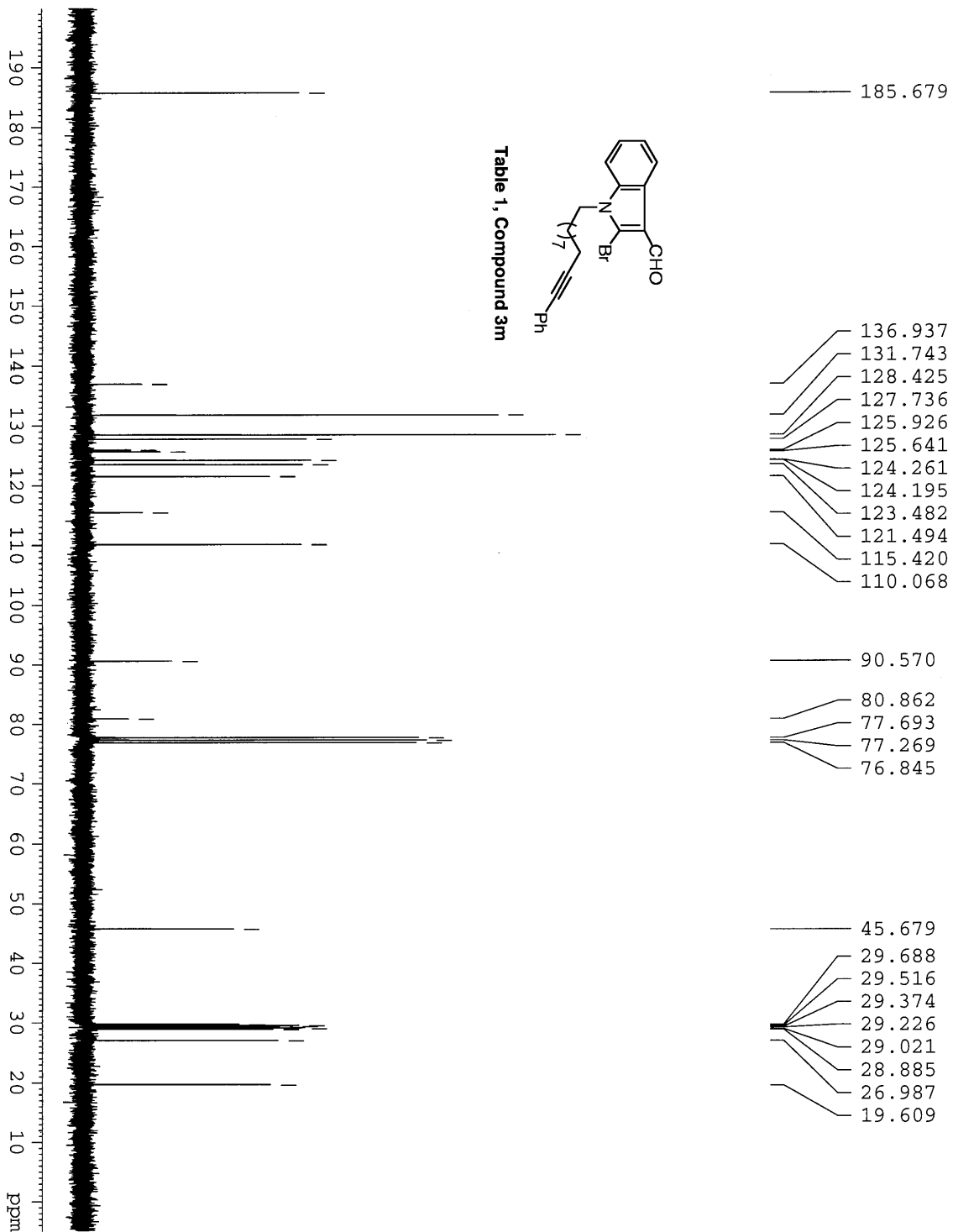
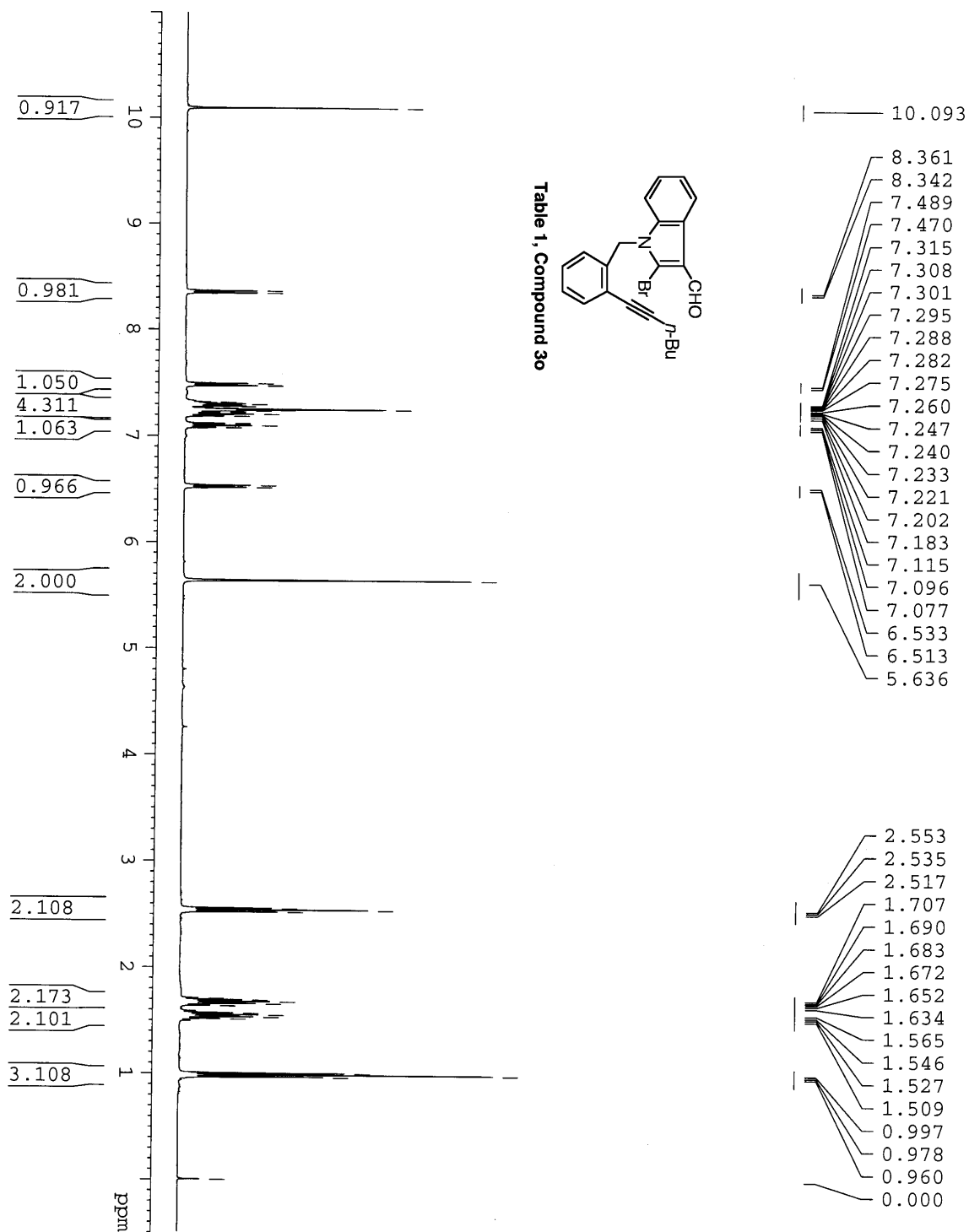
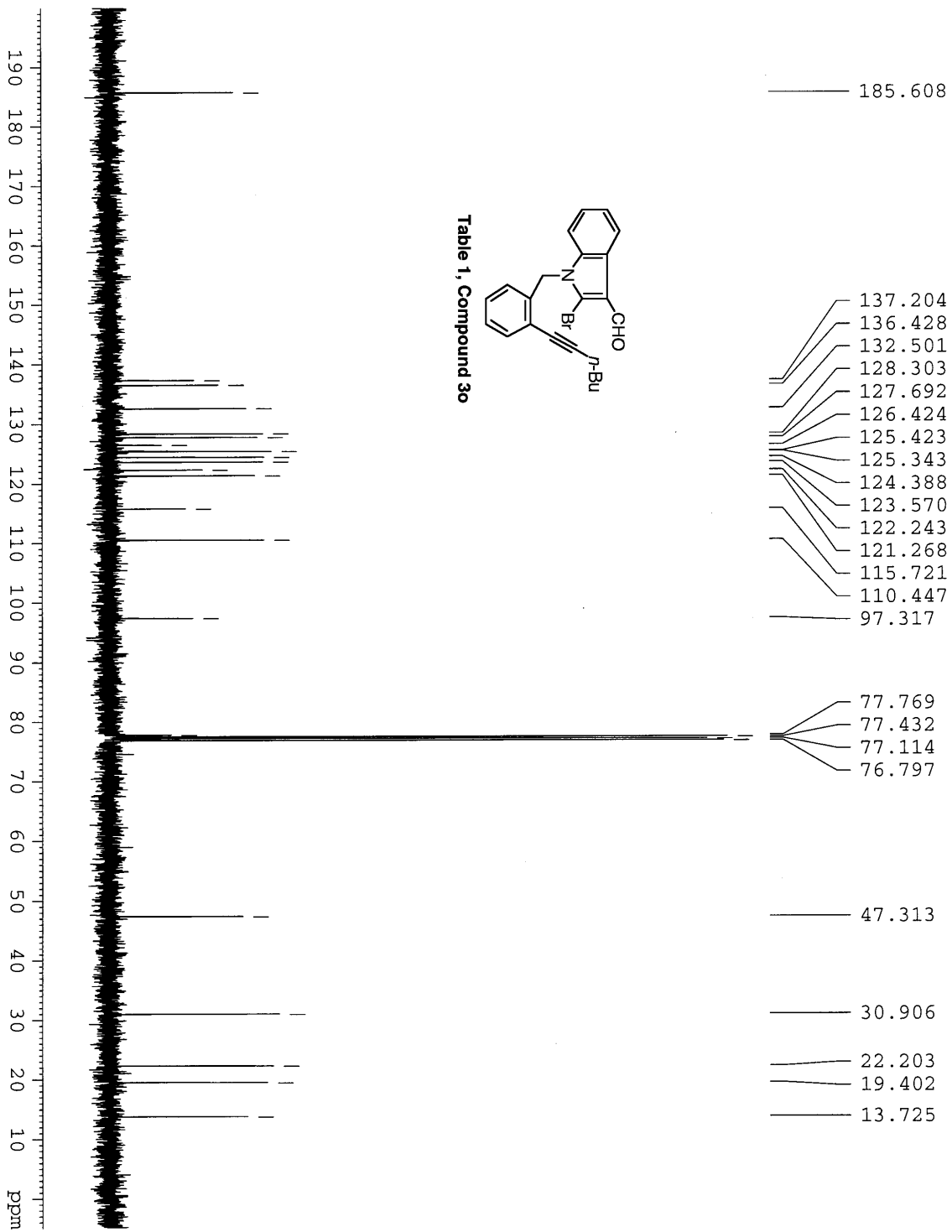


Table 1, Compound 3m









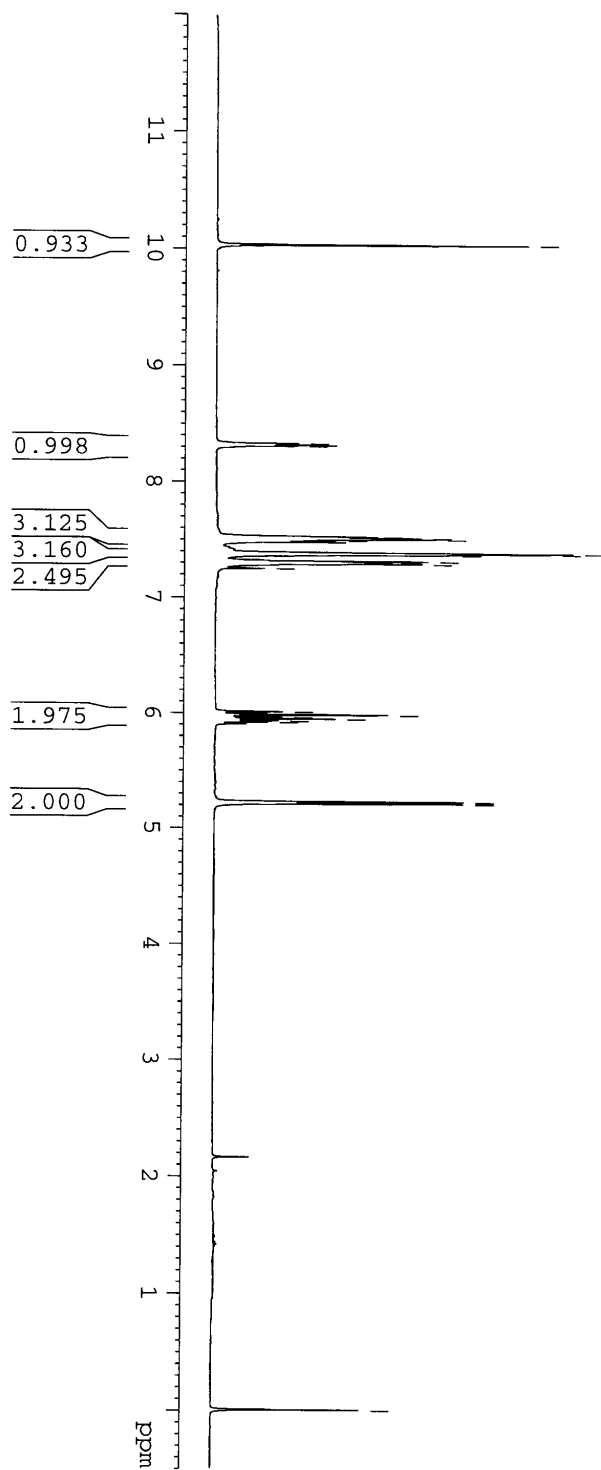
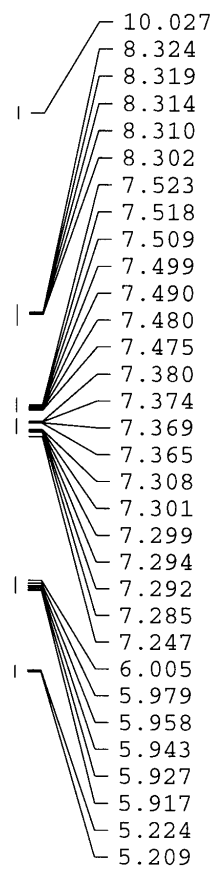
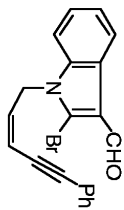


Table 1, Compound 3p



0.000

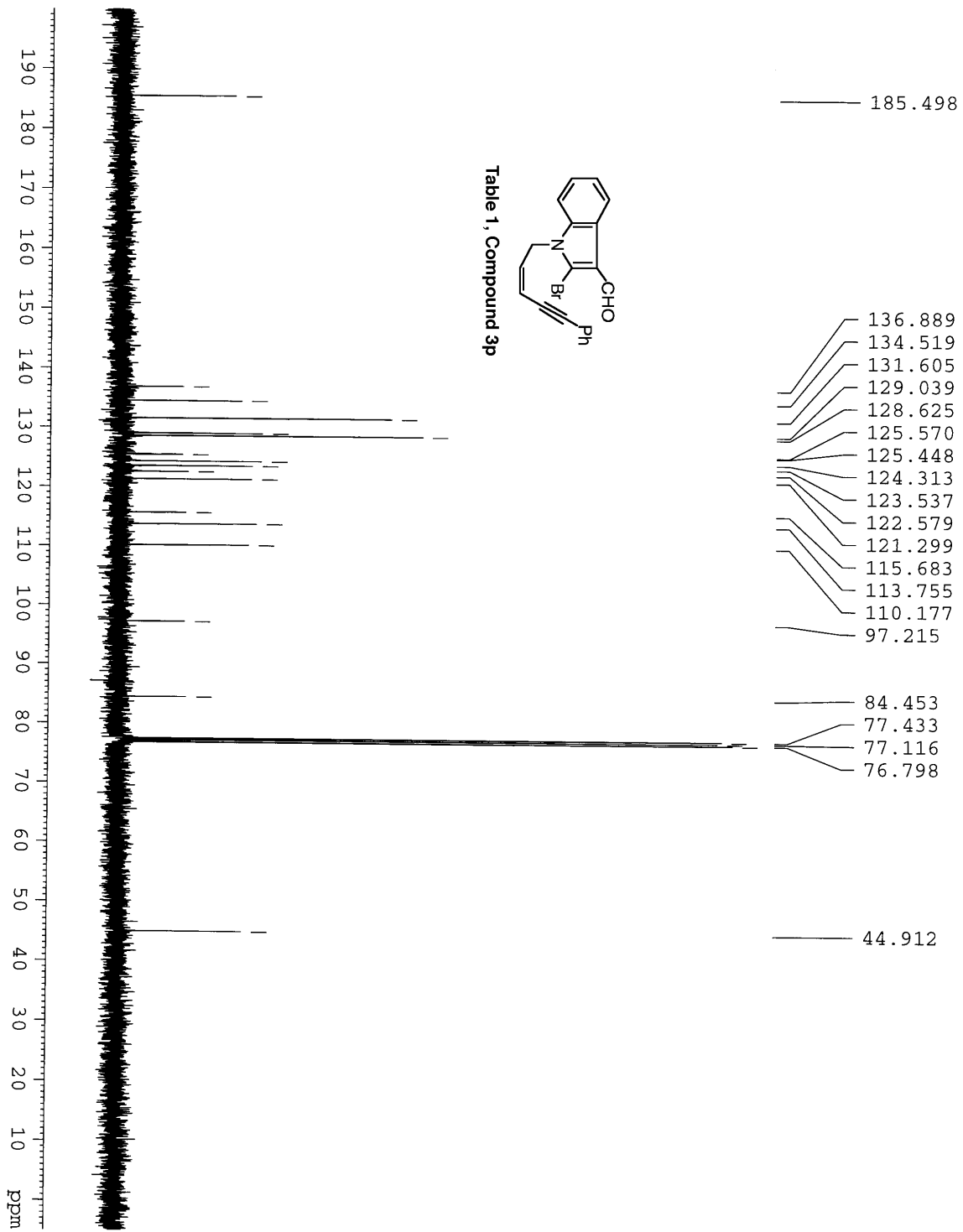
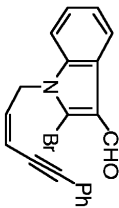
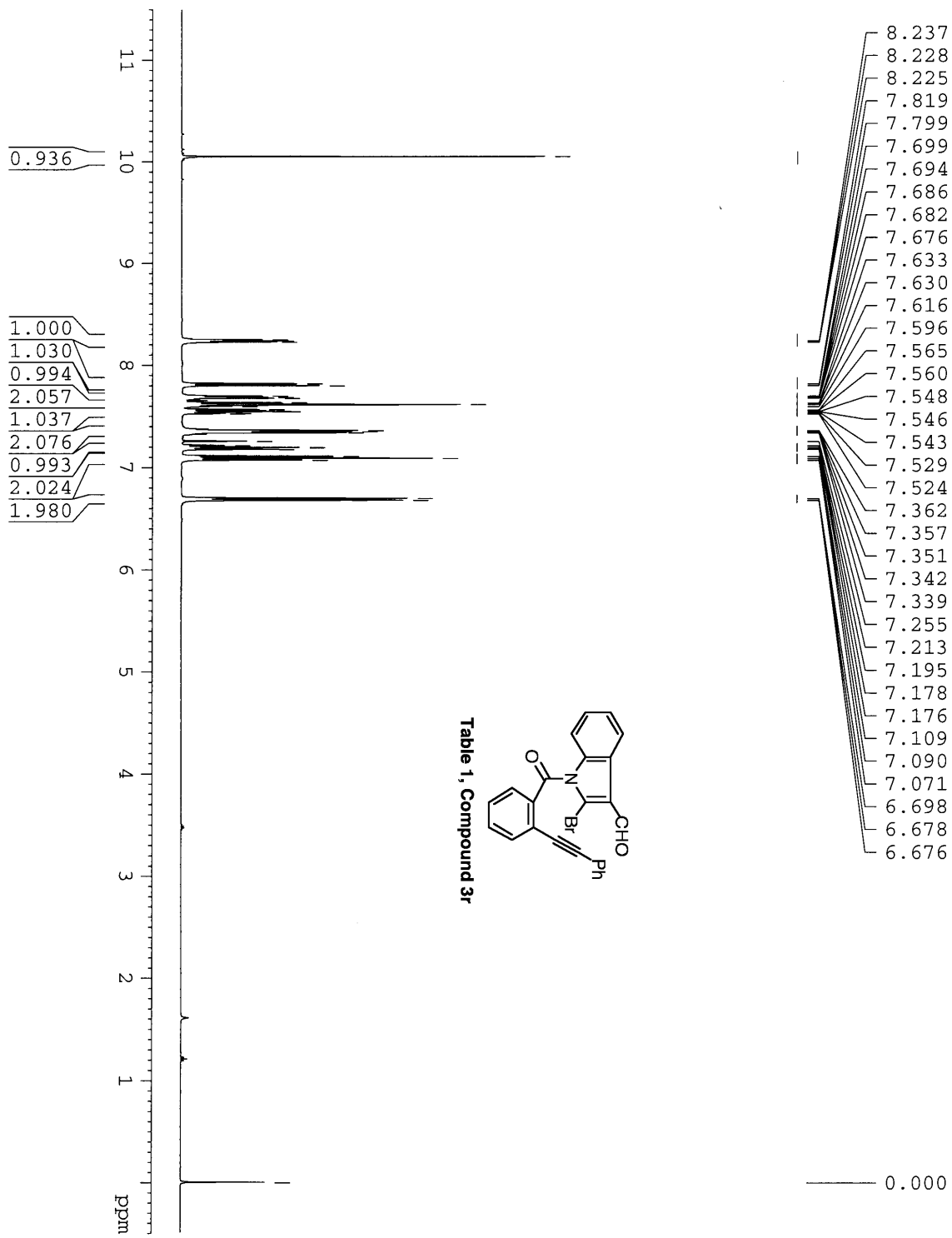
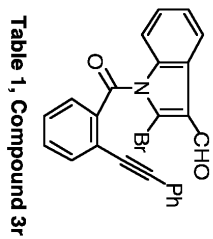
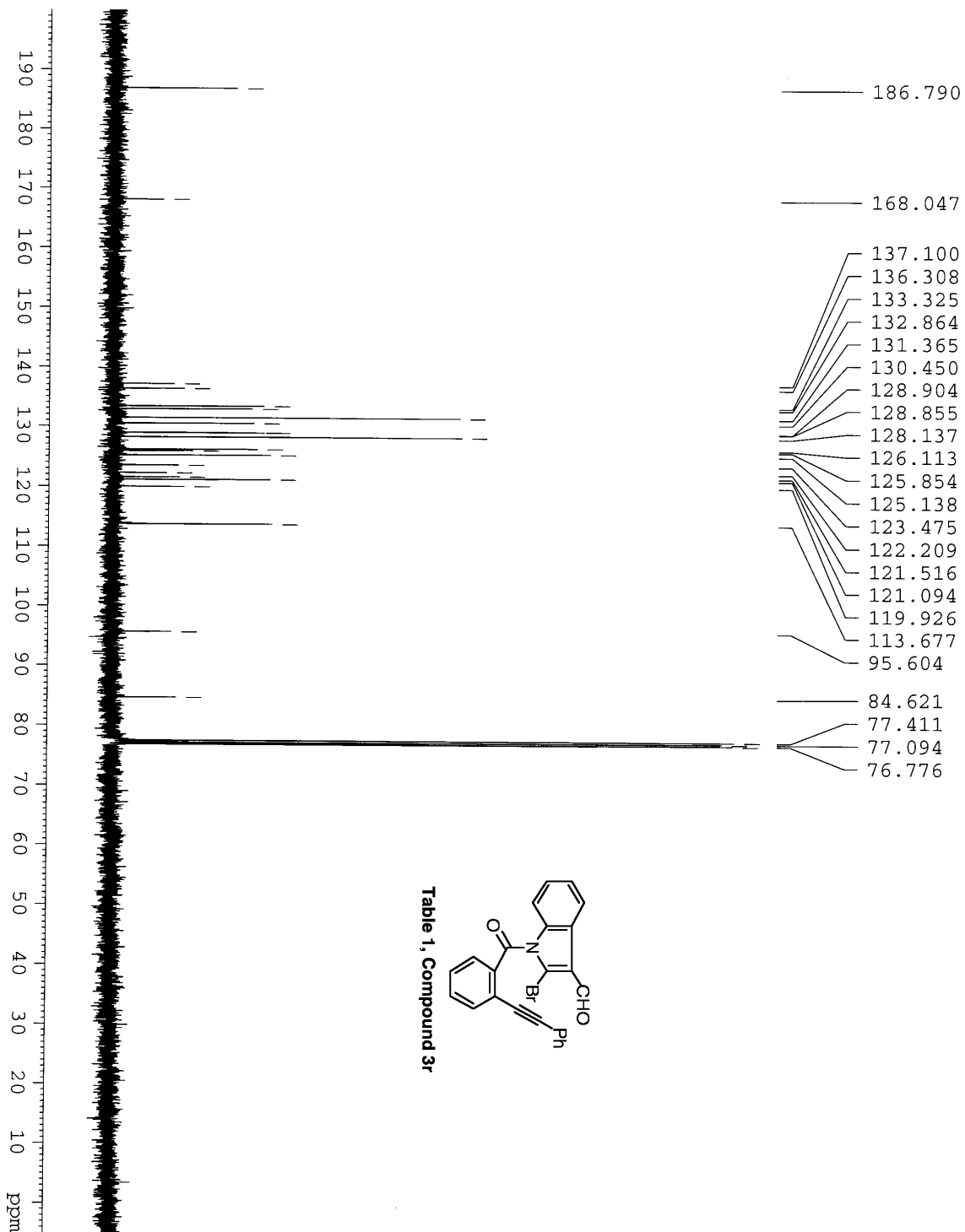
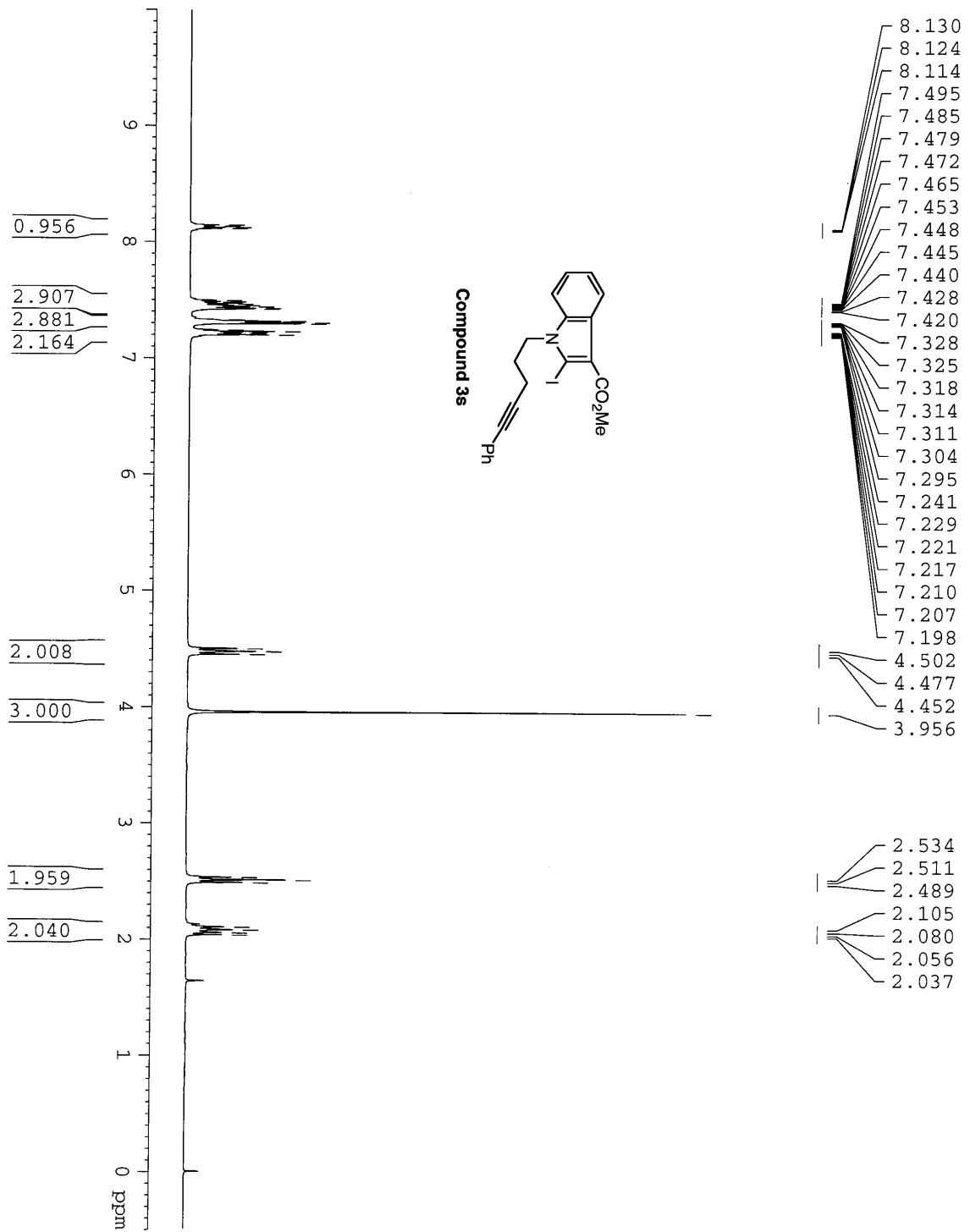


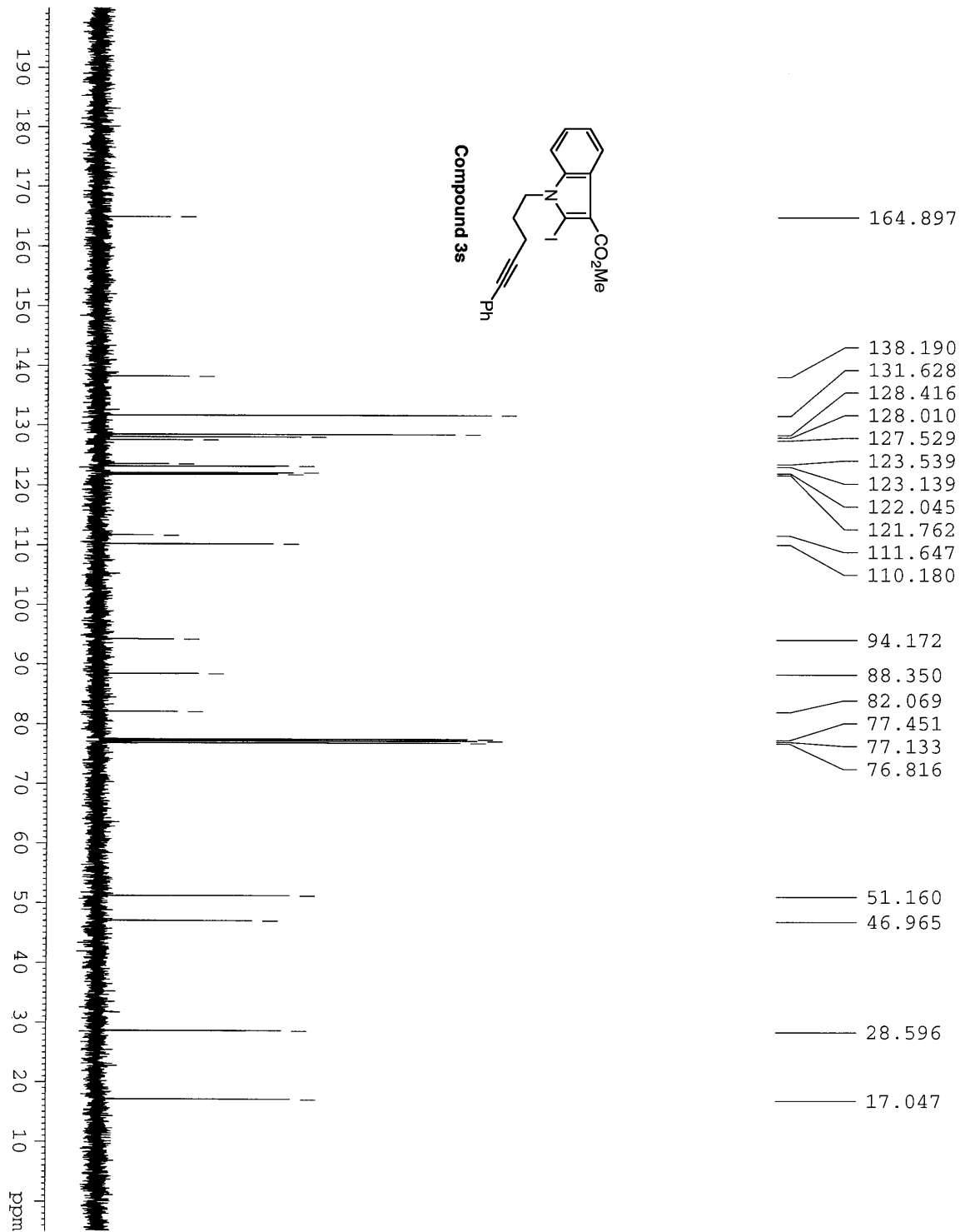
Table 1, Compound 3p

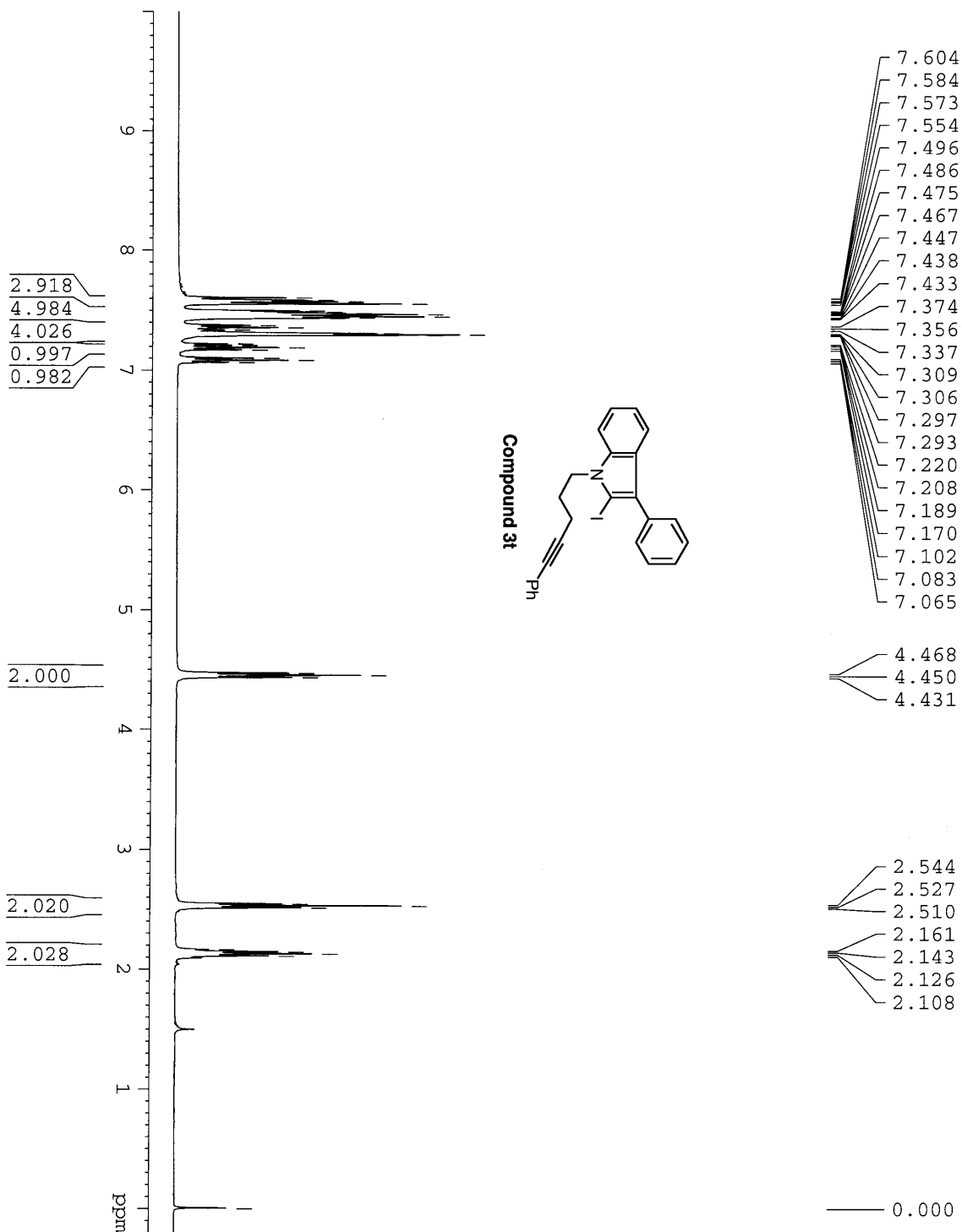


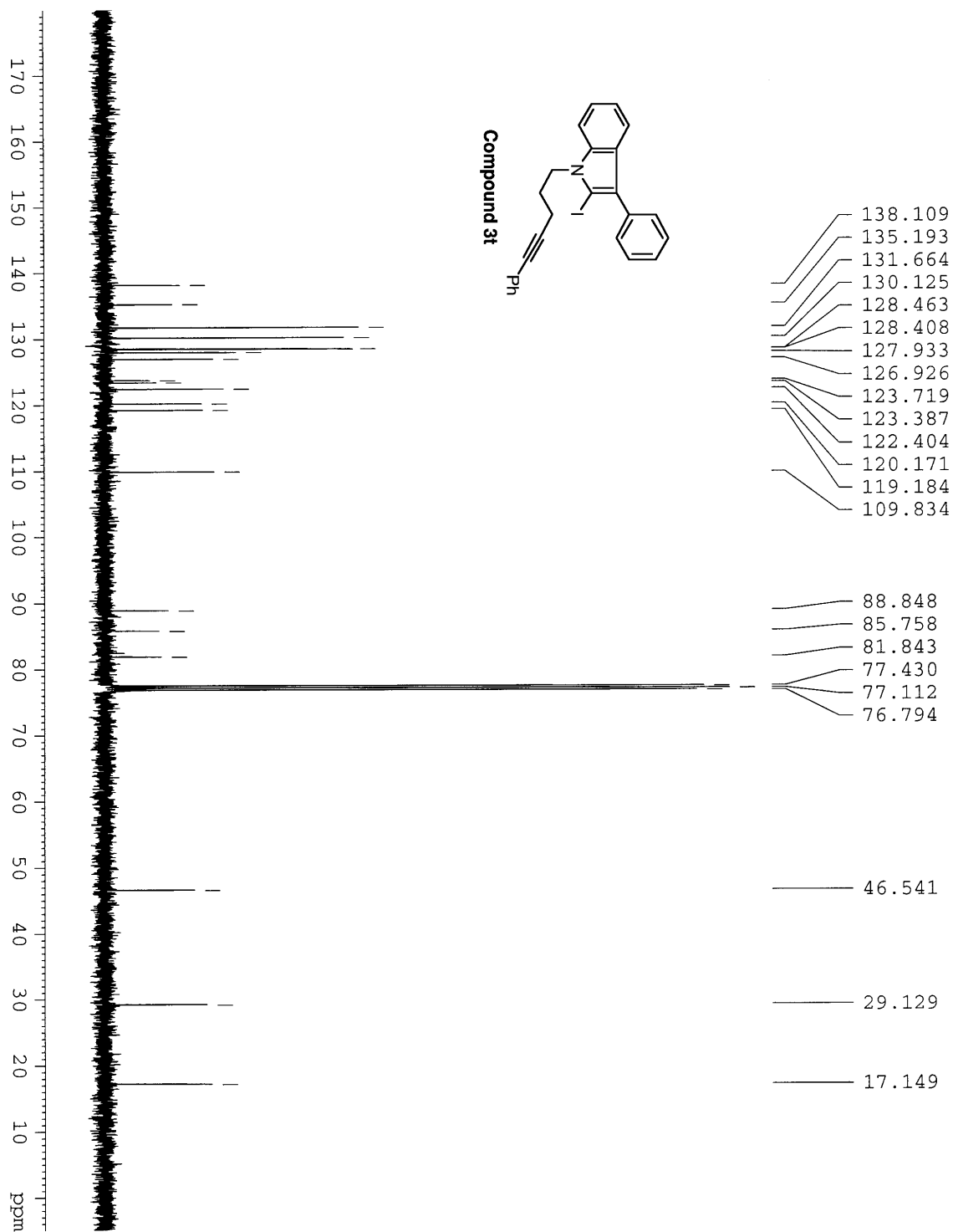


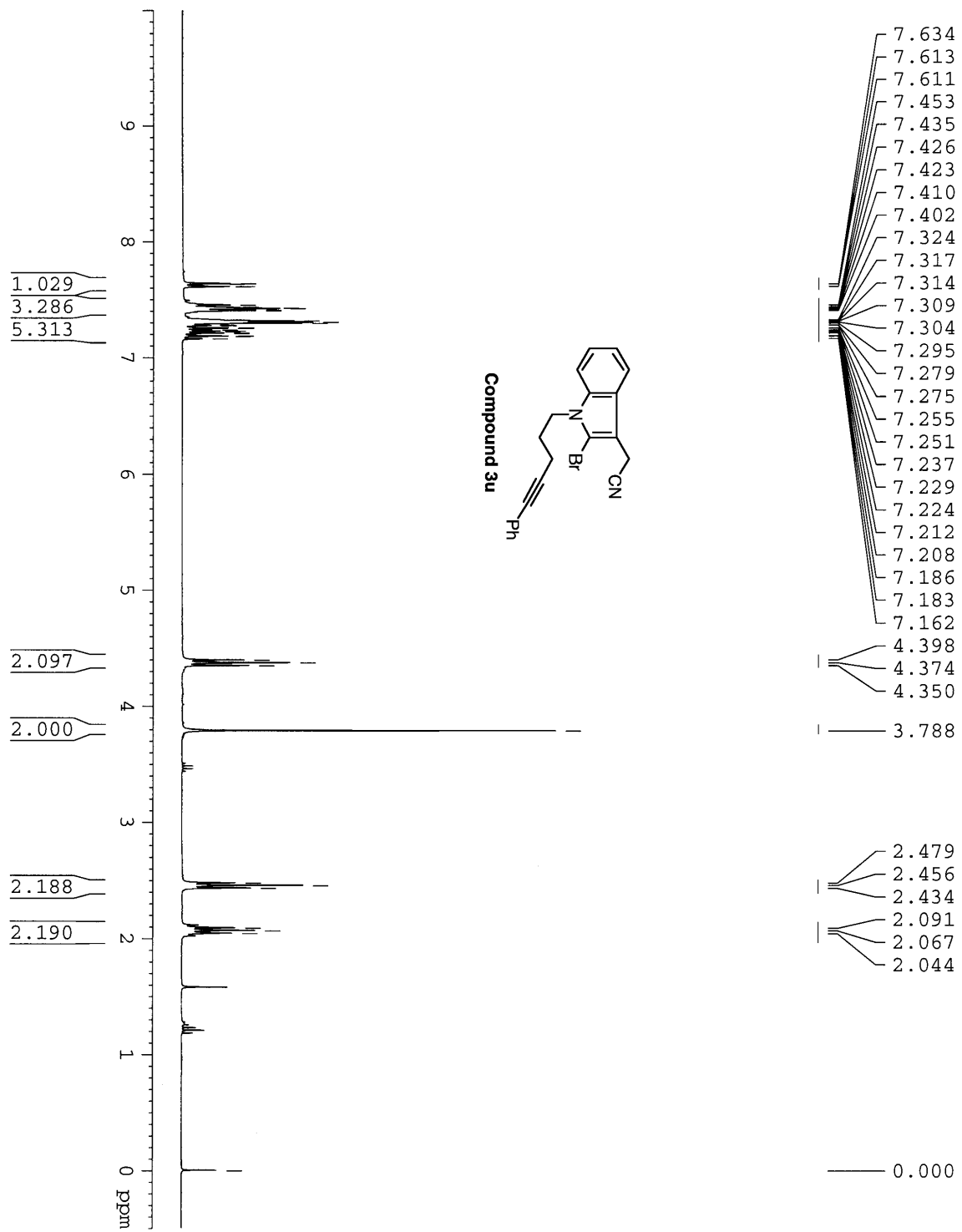


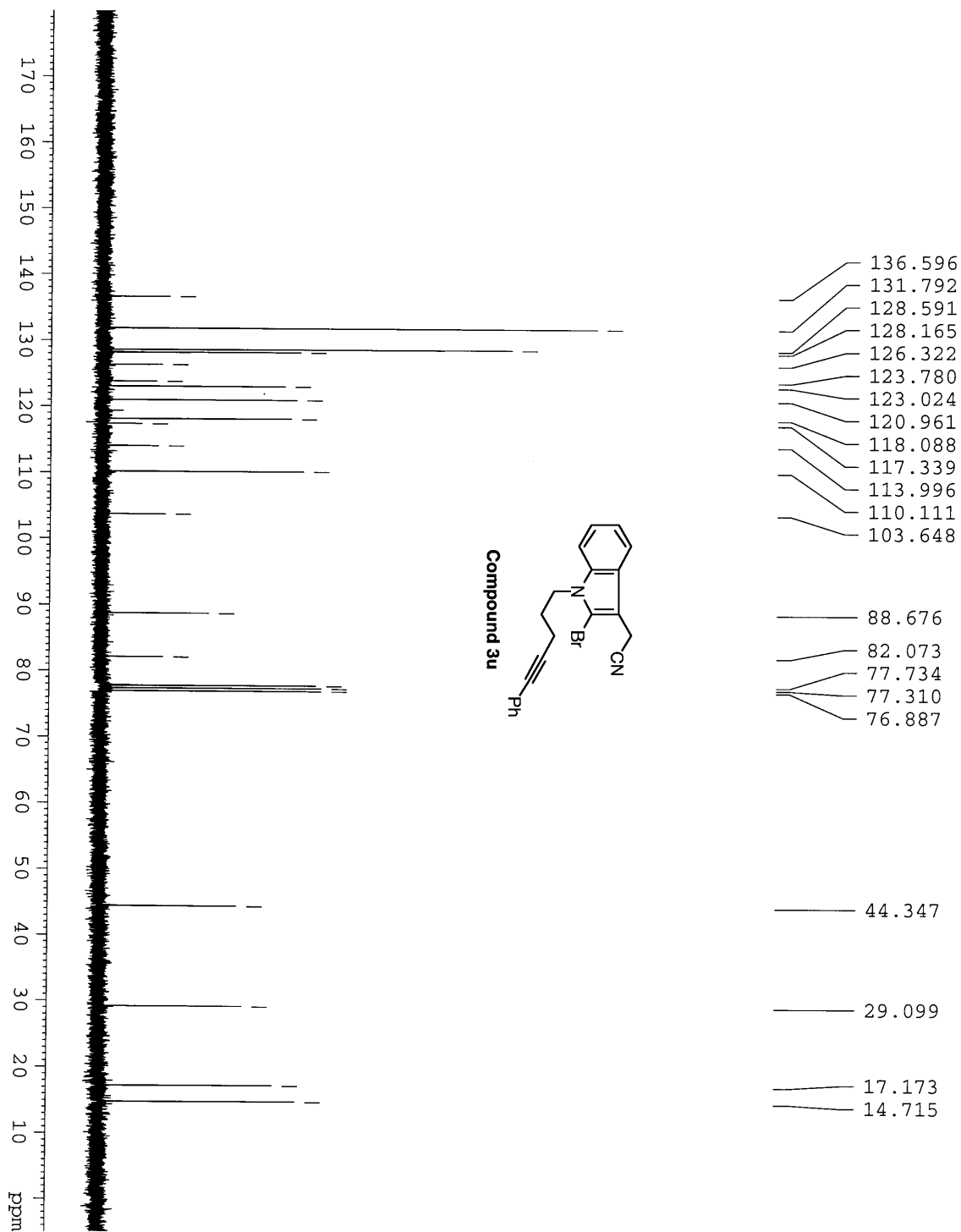


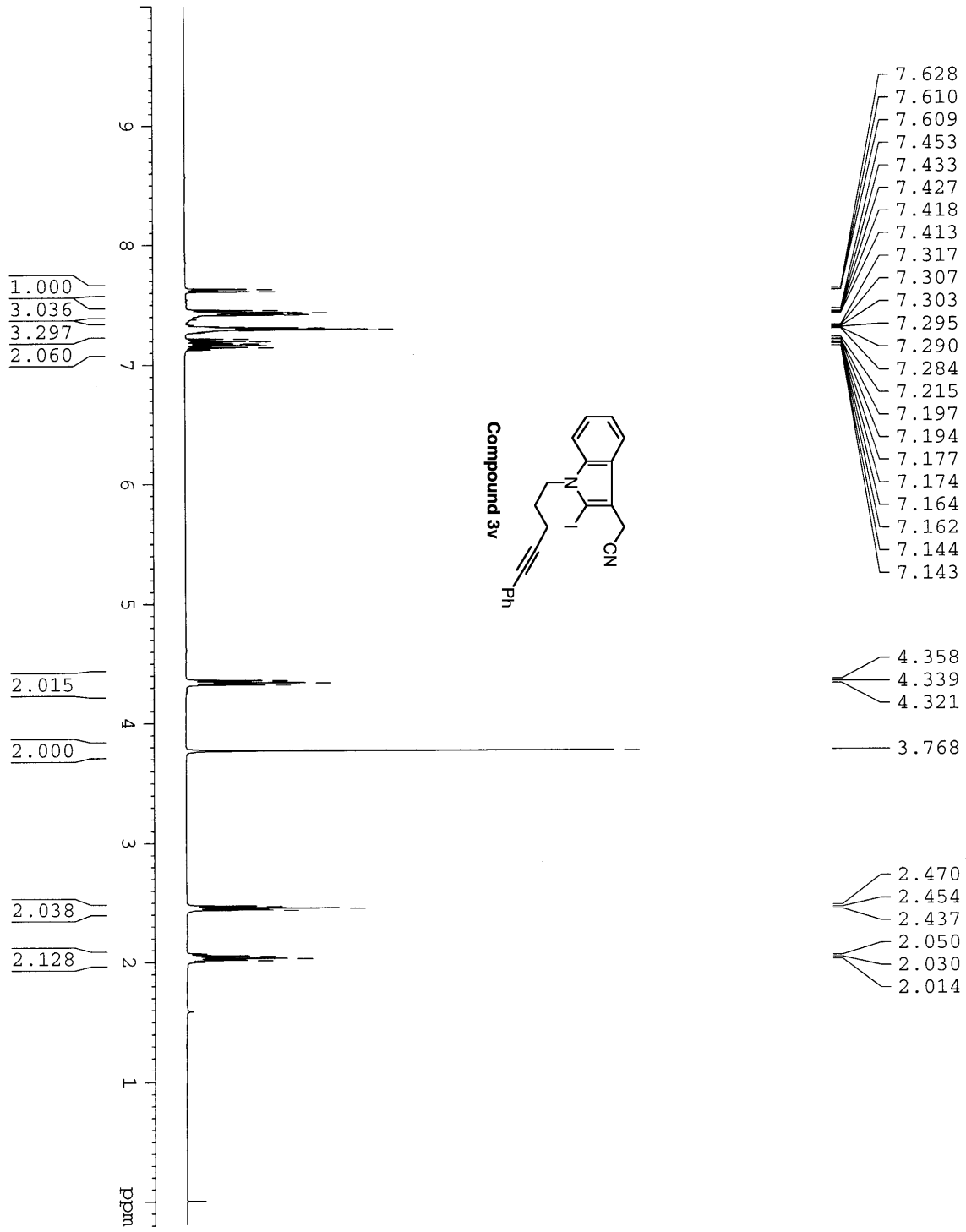


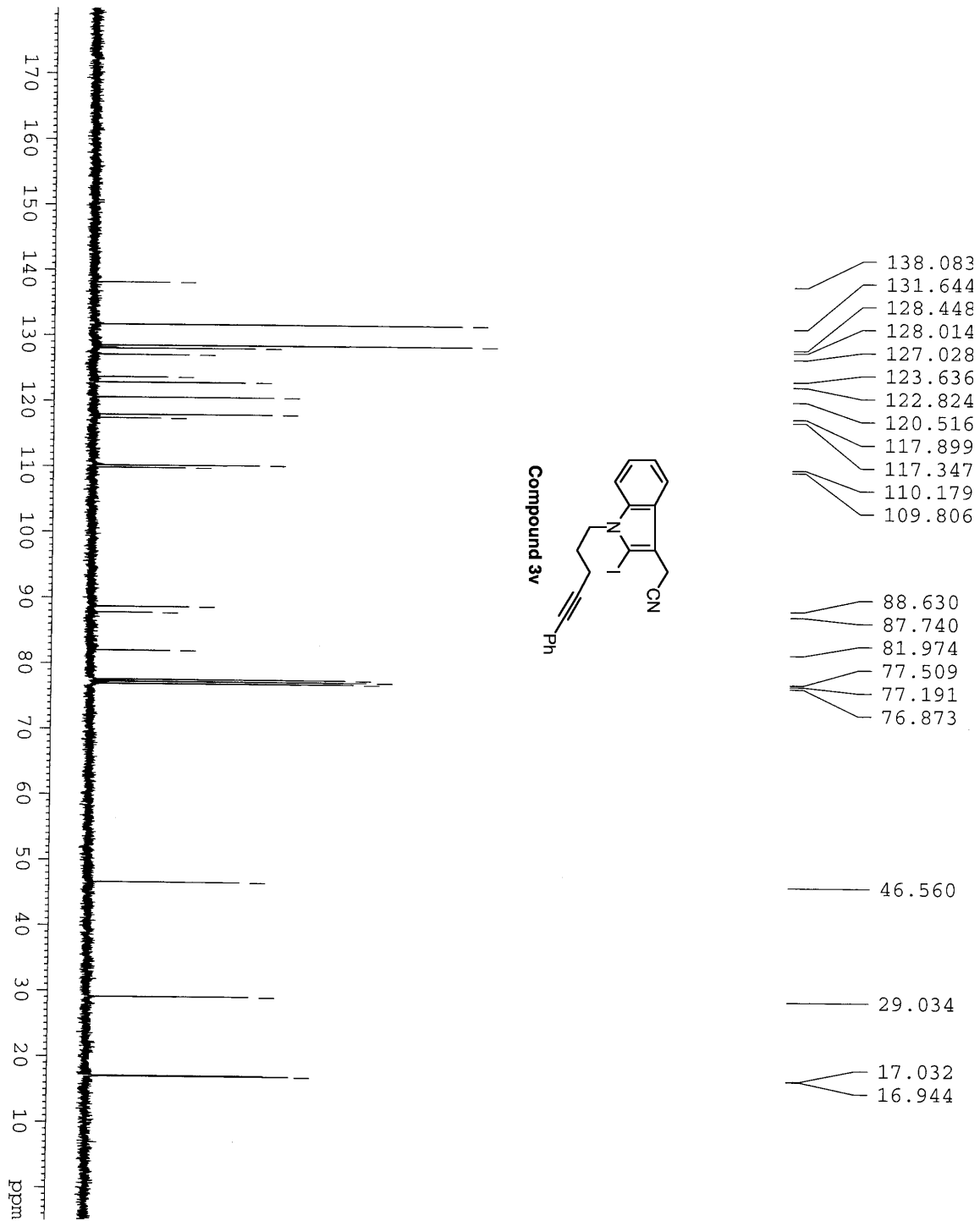












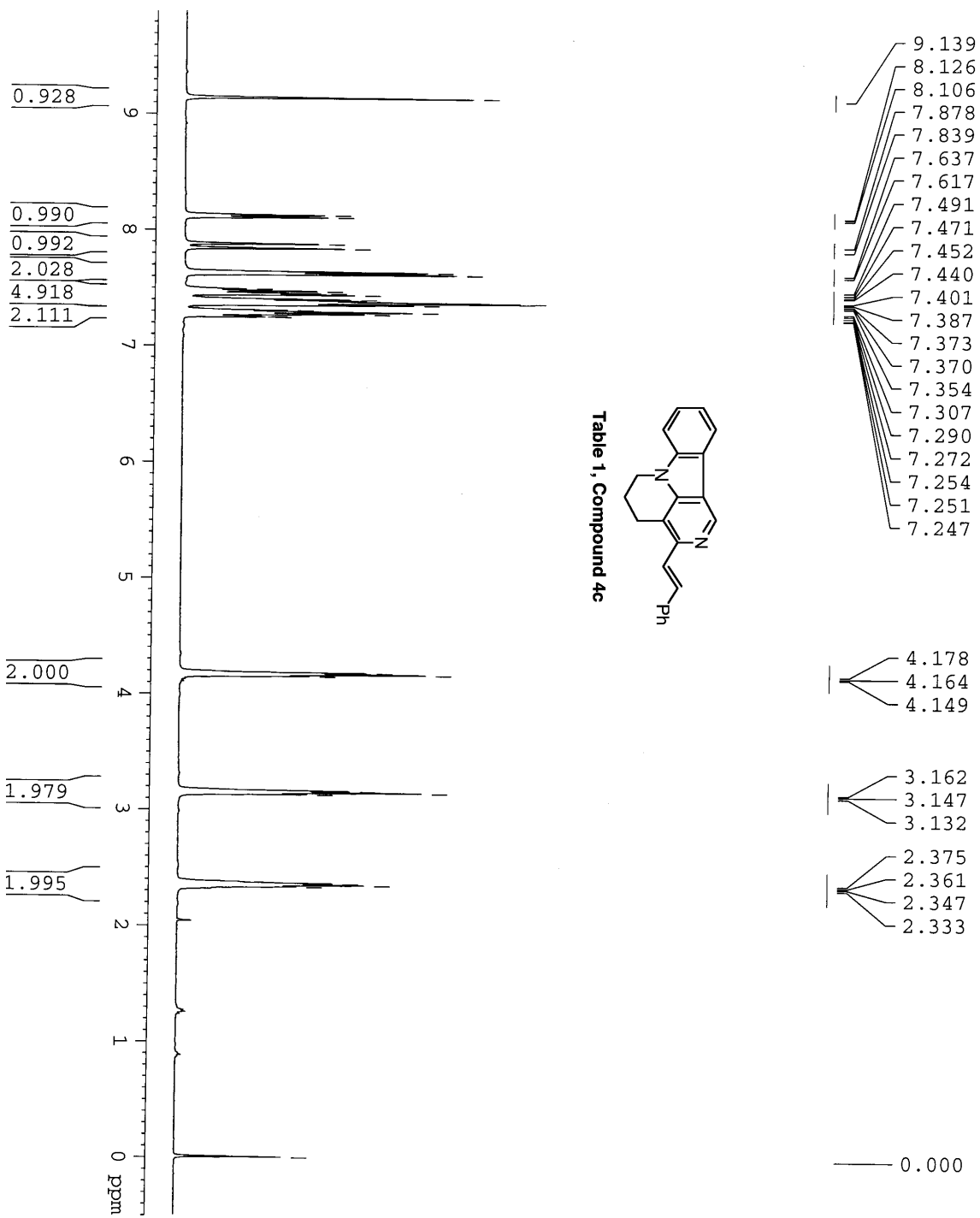
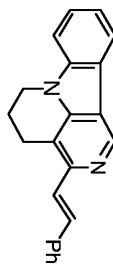
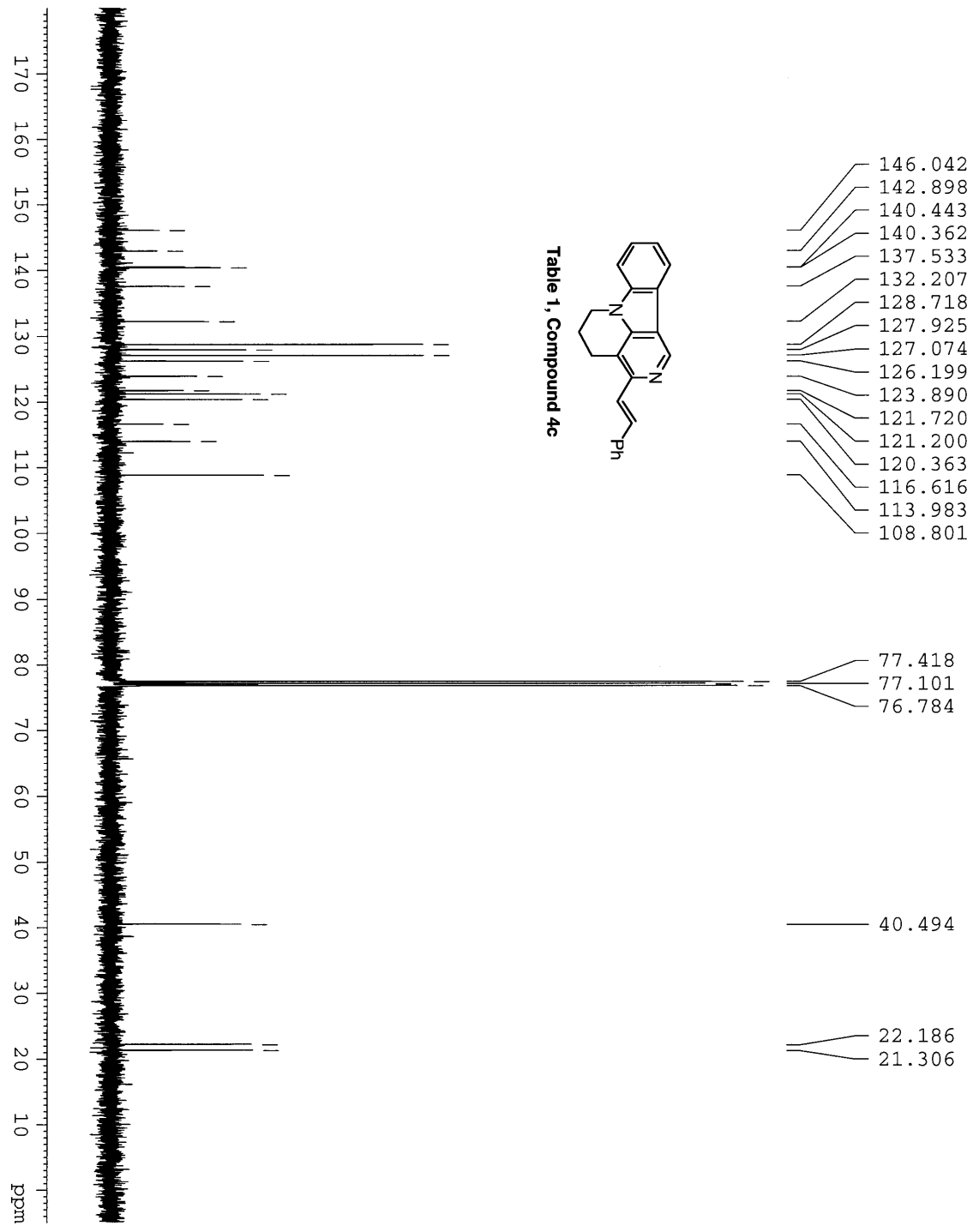
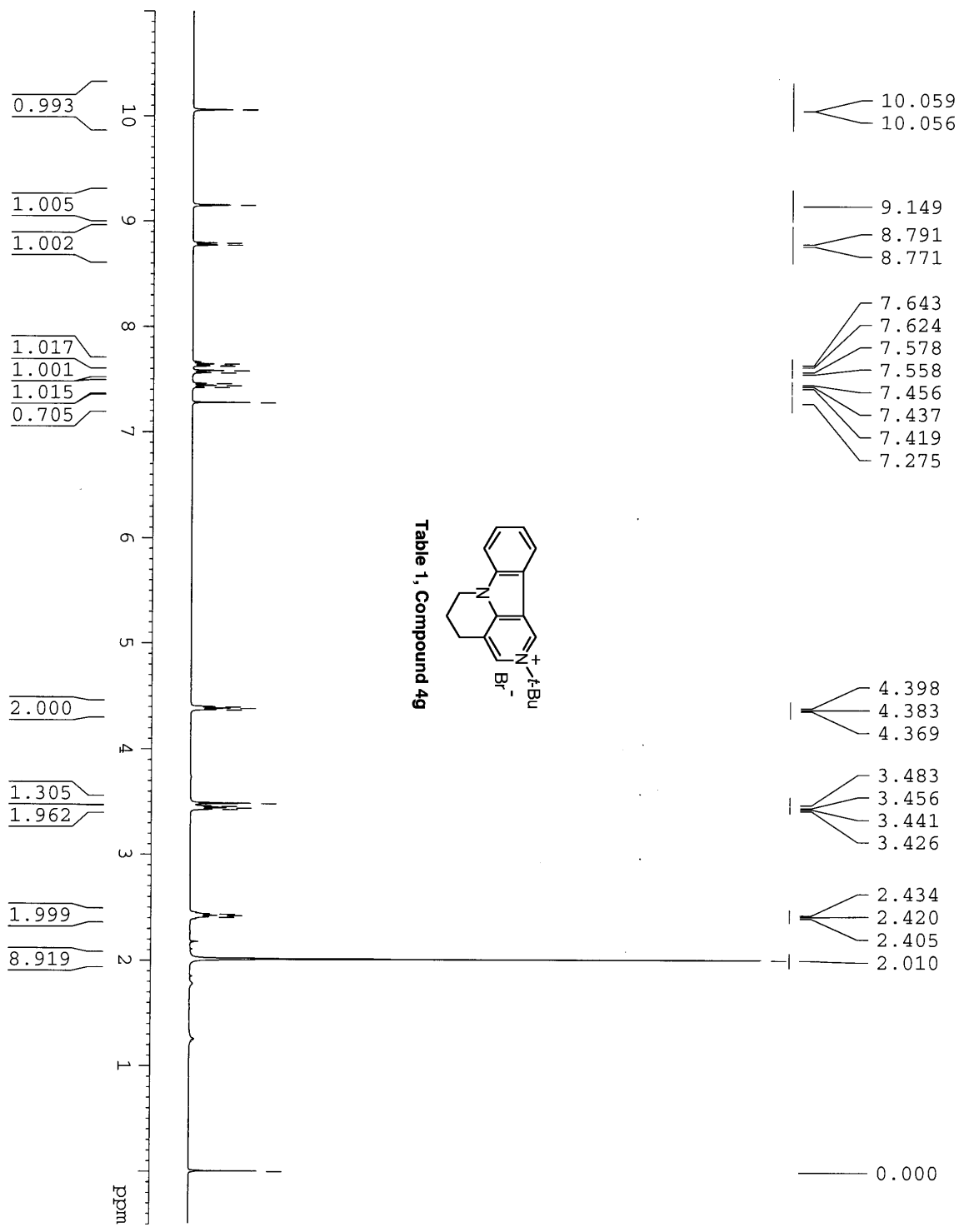


Table 1, Compound 4c







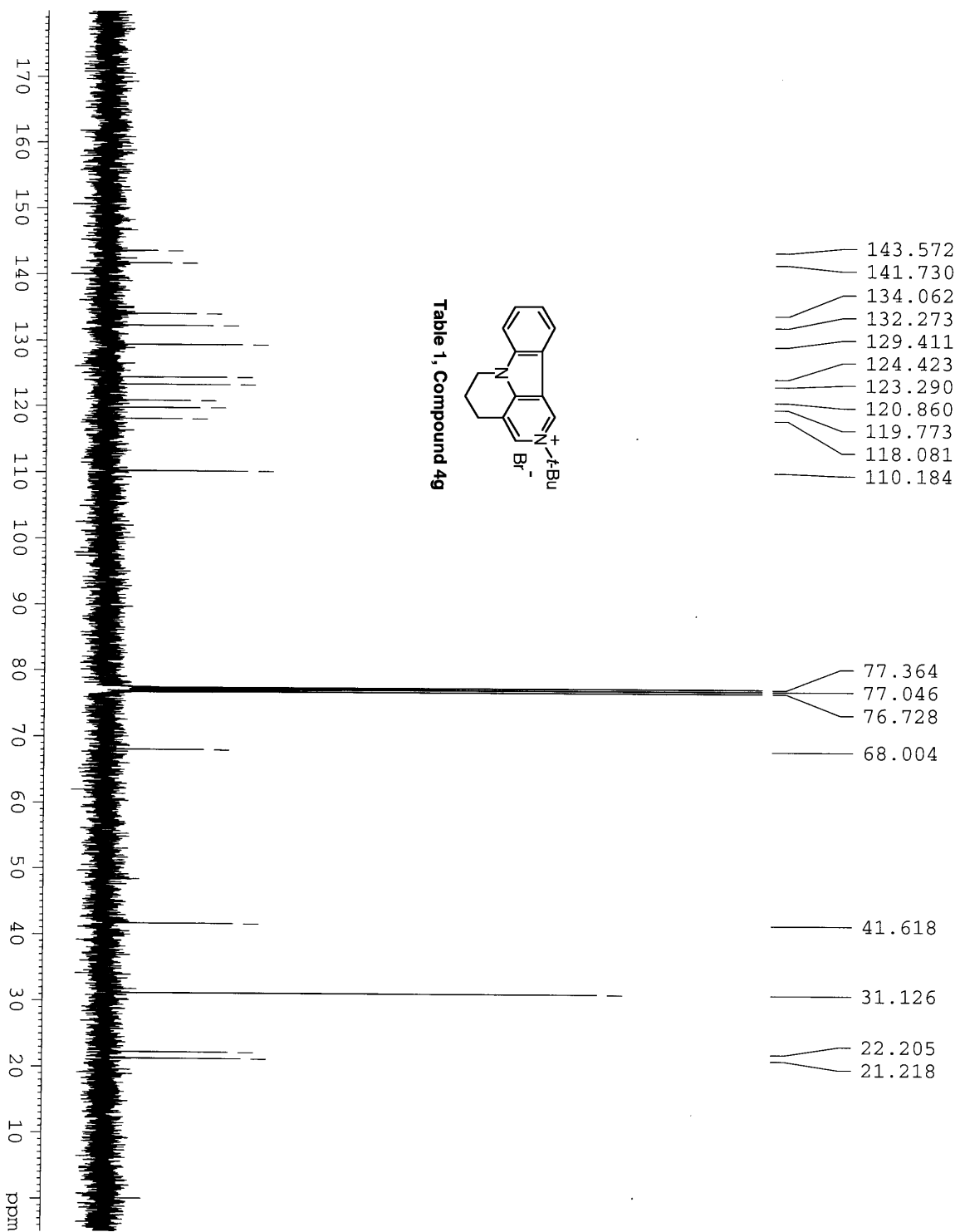
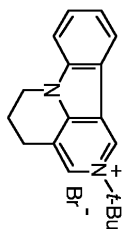
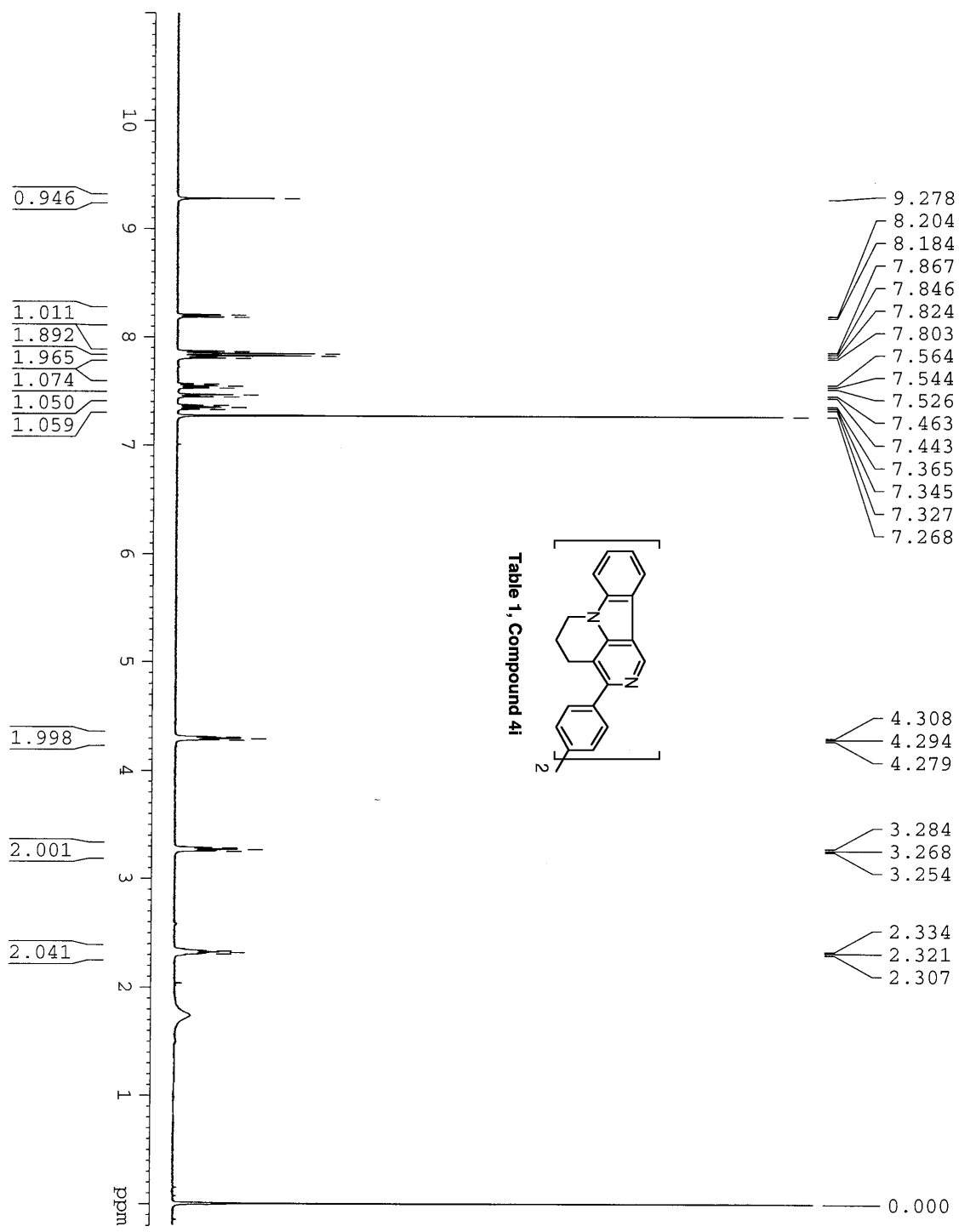


Table 1, Compound 4g





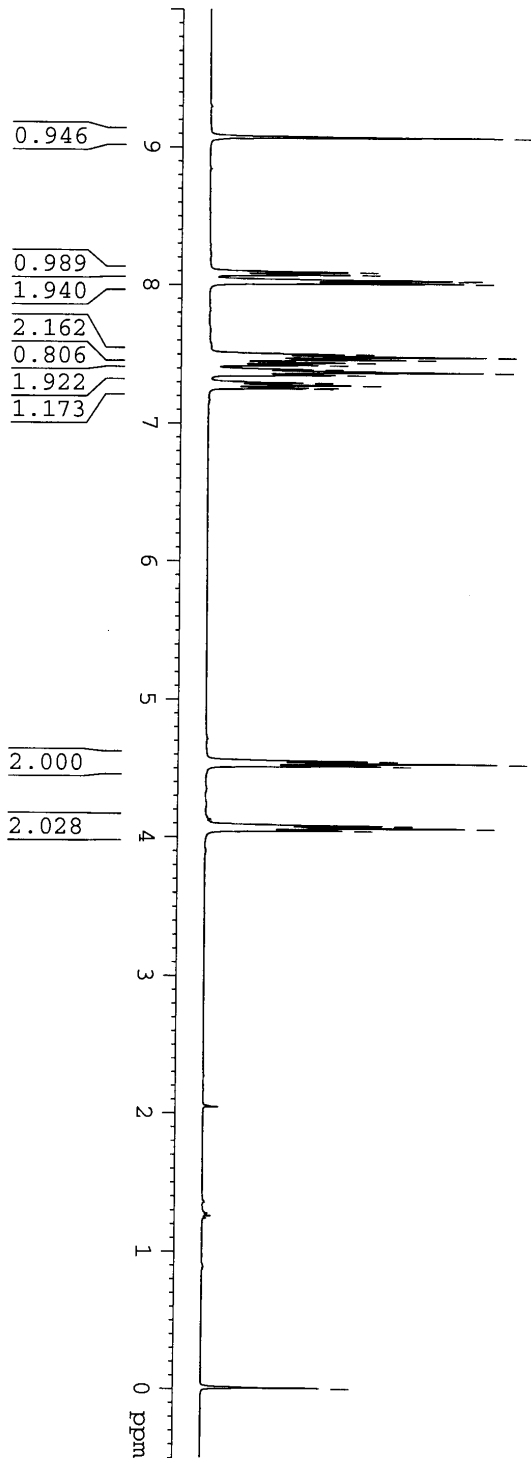
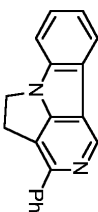


Table 1, Compound 4k



- 9.070
- 8.090
- 8.070
- 8.031
- 8.028
- 8.010
- 7.499
- 7.494
- 7.481
- 7.461
- 7.438
- 7.420
- 7.389
- 7.370
- 7.349
- 7.294
- 7.275
- 7.256
- 7.253
- 7.251

- 4.548
- 4.530
- 4.512
- 4.079
- 4.061
- 4.042

0.000

