

**Synthesis of Isoindolo[2,1-a]indoles by the Palladium-Catalyzed
Annulation of Internal Alkynes**

Kevin R. Roesch and Richard C. Larock*

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

Supporting Information

General Procedure for the Palladium-Catalyzed Formation of Isoindolo[2,1-a]indoles. Procedure A: DMF (10 mL), Pd(OAc)₂ (6 mg, 0.027 mmol), LiCl (21 mg, 0.5 mmol), Na₂CO₃ (56 mg, 0.5 mmol), and the alkyne (1.0 mmol) were placed in a 4 dram vial. Procedure B: DMF (5 mL), Pd(OAc)₂ (6 mg, 0.027 mmol), *n*-Bu₄NCl (139 mg, 0.5 mmol), *i*-Pr₂NEt (130 mg, 1.0 mmol), and the alkyne (0.6 mmol) were placed in a 2 dram vial. Procedure C: DMF (10 mL), Pd(OAc)₂ (6 mg, 0.027 mmol), *n*-Bu₄NCl (139 mg, 0.5 mmol), *i*-Pr₂NEt (130 mg, 1.0 mmol), and the alkyne (1.2 mmol) were placed in a 4 dram vial. The chemicals for procedures A-C were mixed and the appropriate imine (0.5 mmol) was added. The vial was flushed with nitrogen and heated in an oil bath at 100 °C for the indicated period of time. The reaction was monitored by TLC to establish completion. The reaction mixture was then cooled to room temperature, diluted with 30 ml of ether, washed with 45 mL (Procedures A and C) or 30 mL (Procedure B) of saturated aqueous NH₄Cl, dried (Na₂SO₄), and filtered. The solvent was evaporated under

reduced pressure, and the product was isolated by chromatography on a silica gel column.

Compounds Prepared

6,11-Diphenylisoindolo[2,1-a]indole (3). The reaction was run using procedure C and chromatographed using 25:1 hexanes/EtOAc to afford 168 mg (94%) of the indicated compound as a white solid: mp 168-169 °C (hexanes/EtOAc); $^1\text{H NMR}$ (CDCl_3) δ 6.20 (s, 1H), 7.02 (dt, $J = 0.6, 8.1$ Hz, 1H), 7.16 (dddd, $J = 1.5, 7.2, 7.2, 22.2$ Hz, 2H), 7.25-7.49 (m, 9H), 7.63 (t, $J = 7.5$ Hz, 2H), 7.87-7.94 (m, 4H); $^{13}\text{C NMR}$ (CDCl_3) δ 64.5, 109.8, 110.3, 120.3, 120.5, 121.1, 122.4, 124.1, 126.5, 127.3, 127.7, 128.4, 128.6, 128.9, 129.3, 129.5, 131.9, 132.0, 133.7, 135.1, 138.9, 139.5, 147.5; IR (CHCl_3 , cm^{-1}) 3065, 3028, 1602, 1450; MS m/z (rel intensity) 358 (28, $\text{M}+1$), 357 (100, M^+), 356 (26), 280 (78). Anal. Calcd for $\text{C}_{27}\text{H}_{19}\text{N}$: C, 90.72; H, 5.36; N, 3.92. Found: C, 90.39; H, 5.61; N, 3.94.

11-Ethyl-6-phenylisoindolo[2,1-a]indole (4). The reaction was run using procedure B and chromatographed using 25:1 hexanes/EtOAc to afford 126 mg (81%) of the indicated compound as a white solid: mp 144-145 °C (hexanes/EtOAc); $^1\text{H NMR}$ (CDCl_3) δ 1.50 (t, $J = 7.5$ Hz, 3H), 3.18 (q, $J = 7.5$ Hz, 2H), 6.14 (s, 1H), 6.97 (dd, $J = 1.8, 7.8$ Hz, 1H), 7.06-7.16 (m, 2H), 7.22-7.26 (m, 4H), 7.35-7.47 (m, 4H), 7.75 (d, $J = 8.1$ Hz, 1H), 7.84 (d, $J = 7.8$ Hz, 1H); $^{13}\text{C NMR}$ (CDCl_3) δ 15.9, 18.1, 64.3, 109.9, 110.1, 119.1, 119.8, 120.9, 121.7, 124.1, 126.8,

127.2, 128.4, 128.5, 129.1, 132.5, 132.8, 133.6, 139.1, 139.4, 147.2; IR (CHCl₃, cm⁻¹) 3057, 2926, 1611, 1451; HRMS Calcd for C₂₃H₁₉N: 309.1518. Found: 309.1516. Anal. Calcd for C₂₃H₁₉N: C, 89.28; H, 6.19; N, 4.53. Found: C, 88.95; H, 6.47; N, 4.66.

11-*n*-Butyl-6-phenylisoindolo[2,1-*a*]indole (5). The reaction was run using procedure B and chromatographed using 25:1 hexanes/EtOAc to afford 137 mg (81%) of the indicated compound as a white solid: mp 135-136 °C (hexanes/EtOAc); ¹H NMR (CDCl₃) δ 1.04 (t, *J* = 7.5 Hz, 3H), 1.56 (sextet, *J* = 7.5 Hz, 2H), 1.86 (quintet, *J* = 7.5 Hz, 2H), 3.14 (t, *J* = 7.5 Hz, 2H), 6.14 (s, 1H), 6.93 (dd, *J* = 0.9, 7.5 Hz, 1H), 7.09 (dddd, *J* = 1.2, 7.2, 7.2, 17.7 Hz, 2H), 7.18-7.24 (m, 4H), 7.33-7.44 (m, 4H), 7.71 (dd, *J* = 0.6, 8.1 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H); ¹³C NMR (CDCl₃) δ 14.3, 22.9, 24.5, 33.5, 64.3, 108.3, 110.0, 119.1, 119.9, 120.9, 121.6, 124.1, 126.8, 127.2, 128.3, 128.4, 129.1, 132.5, 133.1, 133.5, 139.4, 139.5, 147.2; IR (CHCl₃, cm⁻¹) 3046, 2922, 1610, 1450; HRMS Calcd for C₂₅H₂₃N: 337.1831. Found: 337.1831. Anal. Calcd for C₂₅H₂₃N: C, 88.98; H, 6.87; N, 4.15. Found: C, 88.72; H, 7.00; N, 4.26.

Ethyl 6-phenylisoindolo[2,1-*a*]indole-11-carboxylate (6). The reaction was run using procedure A and chromatographed using 7:1 hexanes/EtOAc to afford 141 mg (80%) of the indicated compound as a white solid: mp 181-182 °C (hexanes/EtOAc); ¹H NMR (CDCl₃) δ 1.57 (t, *J* = 7.2 Hz, 3H), 4.55 (q, *J* = 7.2 Hz, 2H), 6.02 (s, 1H), 6.90 (d, *J* = 8.1 Hz, 1H), 7.06-7.13 (m, 3H), 7.24 (dt, *J* = 0.9, 14.4 Hz, 2H), 7.30-7.37 (m, 4H), 7.49 (dt, *J* = 0.6, 14.7 Hz, 1H), 8.28 (d, *J* =

8.1 Hz, 1H), 8.78 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.9, 60.0, 64.9, 99.9, 110.4, 122.0, 122.9, 123.4, 125.7, 127.2, 128.8, 129.2, 129.3, 130.7, 131.2, 133.1, 137.5, 148.3, 148.6, 165.8 (two sp^2 carbons missing due to overlap); IR (CHCl_3 , cm^{-1}) 3056, 2980, 1688, 1559; HRMS Calcd for $\text{C}_{24}\text{H}_{19}\text{NO}_2$: 353.1416. Found: 353.1416.

11-(4-Hydroxybutyl)-6-phenylisoindolo[2,1-*a*]indole (7). The reaction was run using procedure B and chromatographed using 1:1 hexanes/EtOAc to afford 127 mg (72%) of the indicated compound as a white solid: mp 136-137 °C (hexanes/EtOAc); ^1H NMR (CDCl_3) δ 1.61 (br s, 1H), 1.73-1.82 (m, 2H), 1.89-1.99 (m, 2H), 3.16 (t, $J = 7.2$ Hz, 2H), 3.71 (t, $J = 6.6$ Hz, 2H), 6.13 (s, 1H), 6.93 (dd, $J = 1.2, 7.2$ Hz, 1H), 7.08 (dddd, $J = 1.2, 7.2, 7.2, 15.9$ Hz, 2H), 7.17-7.26 (m, 4H), 7.31-7.43, (m, 4H), 7.68 (dd, $J = 1.2, 6.9$ Hz, 1H), 7.80 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 24.4, 27.3, 32.7, 63.1, 64.2, 107.6, 110.1, 119.2, 119.8, 120.8, 121.7, 124.1, 126.9, 127.2, 128.3, 128.4, 129.1, 132.4, 133.0, 133.5, 139.3, 139.6, 147.1; IR (CHCl_3 , cm^{-1}) 3046, 2922, 1610, 1450; IR (CHCl_3 , cm^{-1}) 3365, 3049, 2935, 1610, 1450; HRMS Calcd for $\text{C}_{25}\text{H}_{23}\text{NO}$: 353.1780. Found: 353.1787.

11-*n*-Butyl-9-methyl-6-phenylisoindolo[2,1-*a*]indole (8). The reaction was run using procedure B and chromatographed using 50:1 hexanes/EtOAc to afford 142 mg (81%) of the indicated compound as a yellow solid: mp 122-124 °C (hexanes/EtOAc); ^1H NMR (CDCl_3) δ 1.08 (t, $J = 7.2$ Hz, 3H), 1.61 (sextet, $J = 7.5$ Hz, 2H), 1.90 (quintet, $J = 7.2$ Hz, 2H), 2.51 (s, 3H), 3.18 (t, $J = 7.5$ Hz, 2H), 6.11 (s, 1H), 6.95 (dd, $J = 1.2, 6.9$ Hz, 1H), 7.05-7.17 (m, 4H), 7.20-7.25

(m, 2H), 7.32-7.40 (m, 3H), 7.65 (s, 1H), 7.74 (dd; $J = 0.6, 7.2$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.4, 21.8, 22.9, 24.5, 33.5, 64.1, 108.2, 110.0, 119.0, 119.9, 121.5, 121.6, 123.8, 127.2, 127.7, 128.3, 129.1, 132.7, 133.2, 133.6, 138.2, 139.6, 139.7, 144.6; IR (CDCl_3 , cm^{-1}) 3058, 2954, 1620, 1452; HRMS Calcd for $\text{C}_{26}\text{H}_{25}\text{N}$: 351.1987. Found: 351.1987.

11-*n*-Butyl-7-methoxy-6-phenylisoindolo[2,1-*a*]indole (9). The reaction was run using procedure B and chromatographed using 25:1 hexanes/EtOAc to afford 144 mg (78%) of the indicated compound as a white solid: mp 153-154 °C (hexanes/EtOAc); ^1H NMR (CDCl_3) δ 0.99 (t, $J = 7.5$ Hz, 3H), 1.52 (sextet, $J = 7.5$ Hz, 2H), 1.81 (quintet, $J = 7.5$ Hz, 2H), 3.08 (t, $J = 7.5$ Hz, 2H), 3.88 (s, 3H), 6.08 (s, 1H), 6.75 (dd, $J = 2.4, 8.4$ Hz, 1H), 6.89 (dddd, $J = 0.9, 0.9, 0.9, 8.1$ Hz, 1H), 7.04 (dddd, $J = 1.2, 6.9, 6.9, 22.2$ Hz, 2H), 7.10 (d, $J = 8.4$ Hz, 1H), 7.14-7.20 (m, 2H), 7.28-7.36 (m, 4H), 7.65 (dddd, $J = 0.9, 0.9, 0.9, 7.8$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.4, 22.9, 24.5, 33.5, 55.7, 63.8, 106.7, 108.5, 110.0, 112.3, 119.1, 120.0, 121.7, 124.7, 127.2, 128.3, 129.1, 133.1, 133.6, 133.8, 139.3, 139.6, 139.8, 160.2; IR (CHCl_3 , cm^{-1}) 3043, 2925, 1626, 1456; HRMS Calcd for $\text{C}_{26}\text{H}_{25}\text{NO}$: 367.1936. Found: 367.1936.

11-*n*-Butyl-9-trifluoromethyl-6-phenylisoindolo[2,1-*a*]indole (10). The reaction was run using procedure B and chromatographed using 25:1 hexanes/EtOAc to afford 193 mg (95%) of the indicated compound as a yellow solid: mp 139-140 °C (hexanes/EtOAc); ^1H NMR (CDCl_3) δ 1.01 (t, $J = 7.2$ Hz, 3H), 1.52 (sextet, $J = 7.5$ Hz, 2H), 1.83 (quintet, $J = 7.5$ Hz, 2H), 3.11 (t, $J = 7.5$ Hz, 2H),

6.23 (s, 1H), 6.90 (dd, $J = 1.2, 6.3$ Hz, 1H), 7.09 (dddd, $J = 1.5, 7.2, 7.2, 14.1$ Hz, 2H), 7.15 (d, $J = 1.8$ Hz, 1H), 7.17 (d, $J = 4.2$ Hz, 1H), 7.29-7.37 (m, 4H), 7.46 (dd, $J = 0.6, 8.1$ Hz, 1H), 7.70 (dd, $J = 1.5, 6.9$ Hz, 1H), 7.96 (s, 1H); ^{13}C NMR (CDCl_3) δ 14.2, 22.8, 24.4, 33.3, 64.1, 109.7, 110.1, 117.4 (q, $^3J_{\text{C-F}} = 2.8$ Hz), 119.4, 120.3, 122.3, 123.6 (q, $^4J_{\text{C-F}} = 2.7$ Hz), 124.2 (q, $^1J_{\text{C-F}} = 204.1$ Hz), 124.4, 127.1, 128.7, 129.3, 130.0 (q, $^2J_{\text{C-F}} = 24.2$ Hz), 133.0, 133.2, 133.5, 137.9, 138.4, 150.3; IR (CHCl_3 , cm^{-1}) 3049, 2926, 1455, 1438; HRMS Calcd for $\text{C}_{26}\text{H}_{22}\text{F}_3\text{N}$: 405.1704. Found: 405.1705.

Ethyl 11-*n*-butyl-6-phenylisoindolo[2,1-*a*]indole-7-carboxylate

(11). The reaction was run using procedure B and chromatographed using 10:1 hexanes/EtOAc to afford 151 mg (74%) of the indicated compound as a yellow solid: mp 120-121 °C (hexanes/EtOAc); ^1H NMR (CDCl_3) δ 1.02 (t, $J = 7.5$ Hz, 3H), 1.44 (t, $J = 7.2$ Hz, 3H), 1.53 (sextet, $J = 7.5$ Hz, 2H), 1.84 (quintet, $J = 7.5$ Hz, 2H), 3.14 (t, $J = 7.5$ Hz, 2H), 4.44 (q, $J = 7.2$ Hz, 2H), 6.15 (s, 1H), 6.90 (ddd, $J = 0.9, 0.9, 8.1$ Hz, 1H), 7.07 (dddd, $J = 1.2, 7.2, 7.2, 14.7$ Hz, 2H), 7.15-7.18 (m, 2H), 7.26 (d, $J = 8.1$ Hz, 1H), 7.31-7.36 (m, 3H), 7.68 (ddd, $J = 1.5, 6.6$ Hz, 1H), 7.90 (dd, $J = 1.5, 8.1$ Hz, 1H), 8.41 (d, $J = 1.2$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.3, 14.5, 22.8, 24.4, 33.4, 61.3, 64.3, 109.3, 110.1, 119.4, 120.2, 121.8, 122.1, 123.9, 127.2, 128.2, 128.6, 129.2, 131.0, 132.9, 133.1, 133.5, 138.4, 138.7, 151.5, 166.4; IR (CDCl_3 , cm^{-1}) 3056, 2967, 1720, 1437; HRMS Calcd for $\text{C}_{26}\text{H}_{27}\text{NO}_2$: 409.2042. Found: 409.2048.

Compound 12 (Table 1, entry 10). The reaction was run using procedure B and chromatographed using 1:1 hexanes/EtOAc to afford 158 mg (93%) of the indicated compound as an off-white solid: mp 200-201 °C (hexanes/EtOAc); ¹H NMR (CDCl₃) δ 0.99 (t, *J* = 7.2 Hz, 3H), 1.49 (sextet, *J* = 7.5 Hz, 2H), 1.82 (quintet, *J* = 7.5 Hz, 2H), 3.08 (t, *J* = 7.5 Hz, 2H), 6.17 (s, 1H), 6.96 (dddd, *J* = 3.6, 3.6, 7.8, 7.8 Hz, 1H), 7.13 (dddd, *J* = 1.2, 1.2, 8.1, 8.1 Hz, 2H), 7.19 (dd, *J* = 3.6, 7.5 Hz, 2H), 7.35-7.38 (m, 3H), 7.71 (dddd, *J* = 3.3, 3.3, 11.1, 11.1 Hz, 1H), 9.00 (s, 1H), 9.04 (s, 1H); ¹³C NMR (CDCl₃) δ 14.2, 22.8, 24.9, 33.2, 64.6, 110.7, 112.4, 120.0, 120.5, 123.2, 125.5, 127.2, 129.0, 129.3, 132.1, 133.5, 134.1, 135.9, 147.8, 156.0, 173.6; IR (CHCl₃, cm⁻¹) 3028, 2953, 1495, 1456; HRMS Calcd for C₂₃H₂₁N₃: 339.1736. Found: 339.1738.

3.794
 3.759
 3.729
 3.699
 3.671
 3.643
 3.615
 3.587
 3.559
 3.531
 3.503
 3.475
 3.447
 3.419
 3.391
 3.363
 3.335
 3.307
 3.279
 3.251
 3.223
 3.195
 3.167
 3.139
 3.111
 3.083
 3.055
 3.027
 3.000
 2.972
 2.944
 2.916
 2.888
 2.860
 2.832
 2.804
 2.776
 2.748
 2.720
 2.692
 2.664
 2.636
 2.608
 2.580
 2.552
 2.524
 2.496
 2.468
 2.440
 2.412
 2.384
 2.356
 2.328
 2.300
 2.272
 2.244
 2.216
 2.188
 2.160
 2.132
 2.104
 2.076
 2.048
 2.020
 2.000
 1.972
 1.944
 1.916
 1.888
 1.860
 1.832
 1.804
 1.776
 1.748
 1.720
 1.692
 1.664
 1.636
 1.608
 1.580
 1.552
 1.524
 1.496
 1.468
 1.440
 1.412
 1.384
 1.356
 1.328
 1.300
 1.272
 1.244
 1.216
 1.188
 1.160
 1.132
 1.104
 1.076
 1.048
 1.020
 1.000
 0.972
 0.944
 0.916
 0.888
 0.860
 0.832
 0.804
 0.776
 0.748
 0.720
 0.692
 0.664
 0.636
 0.608
 0.580
 0.552
 0.524
 0.496
 0.468
 0.440
 0.412
 0.384
 0.356
 0.328
 0.300
 0.272
 0.244
 0.216
 0.188
 0.160
 0.132
 0.104
 0.076
 0.048
 0.020
 0.000

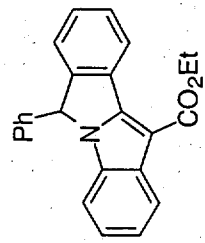
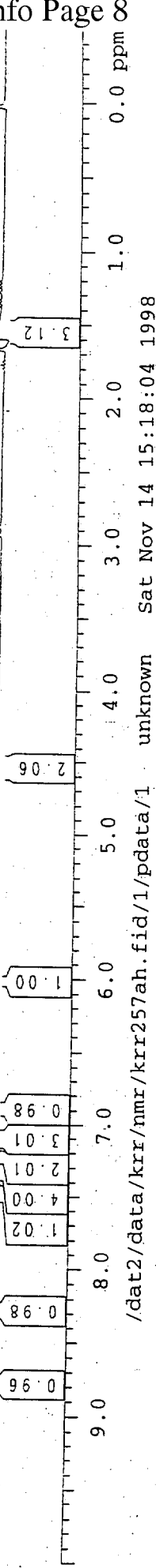
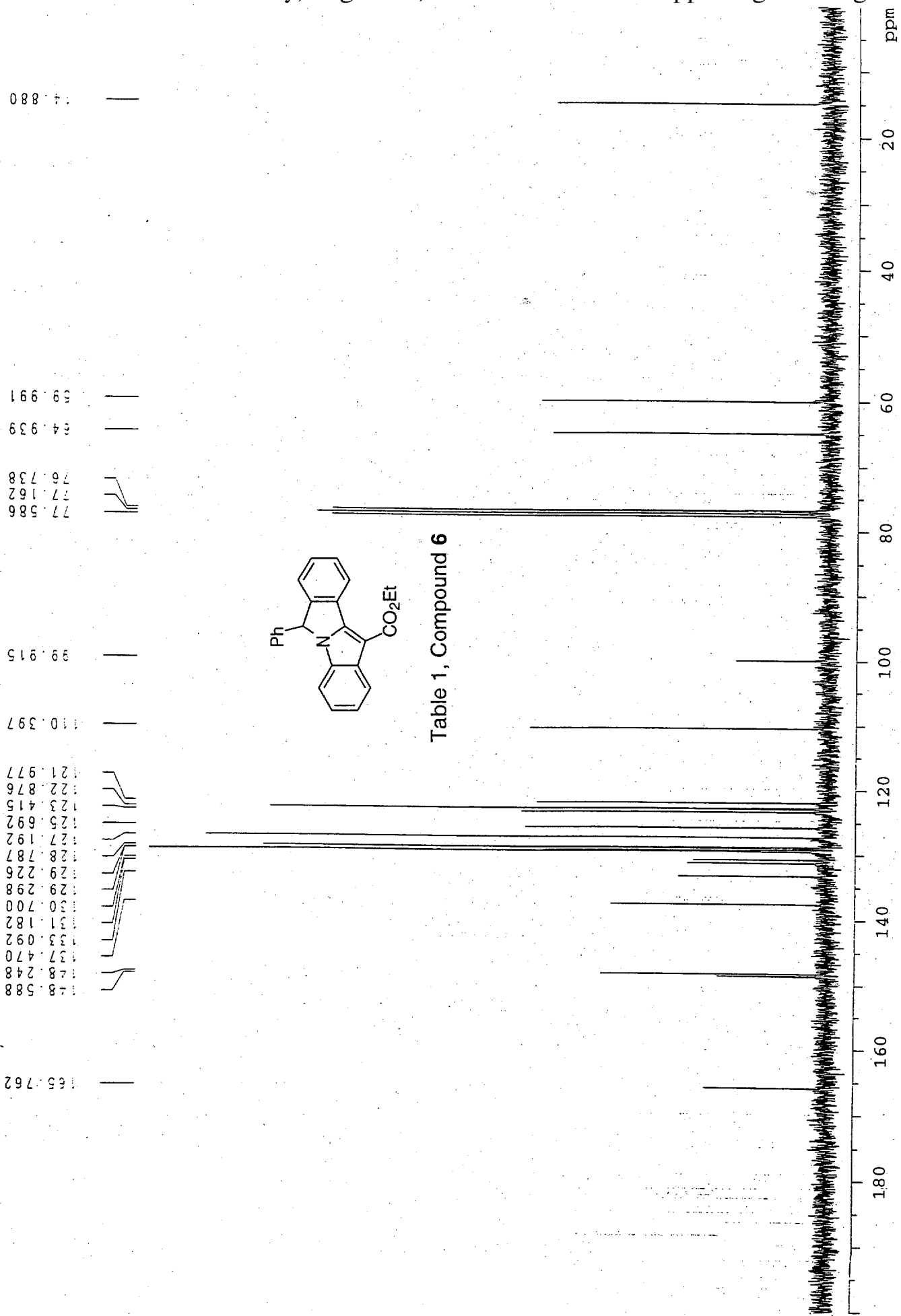
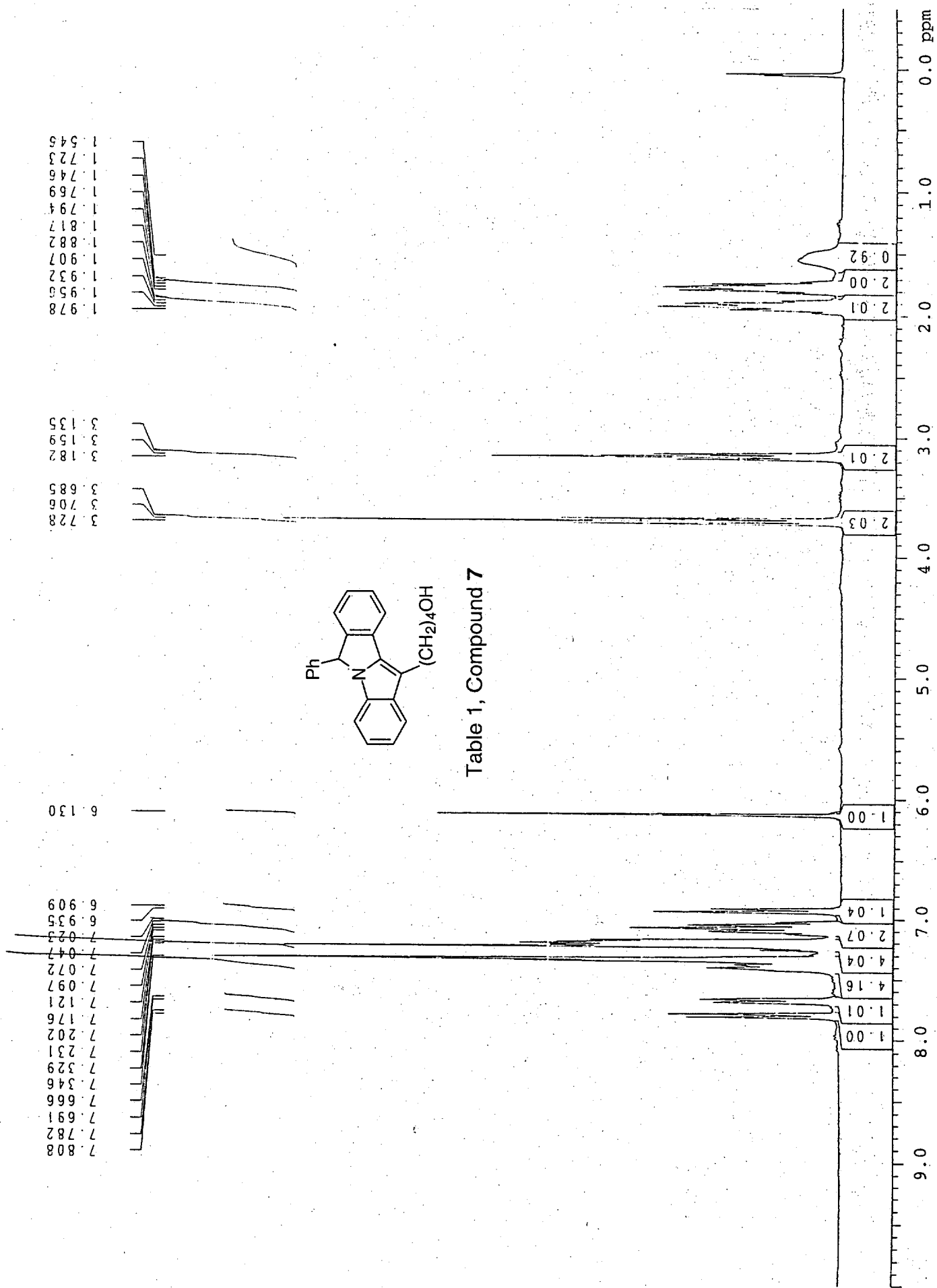


Table 1, Compound 6







/dat2/data/krr/nmr/krr31099ah.fid/1/pdata/1 unknown Wed Mar 17 14:11:17 1999

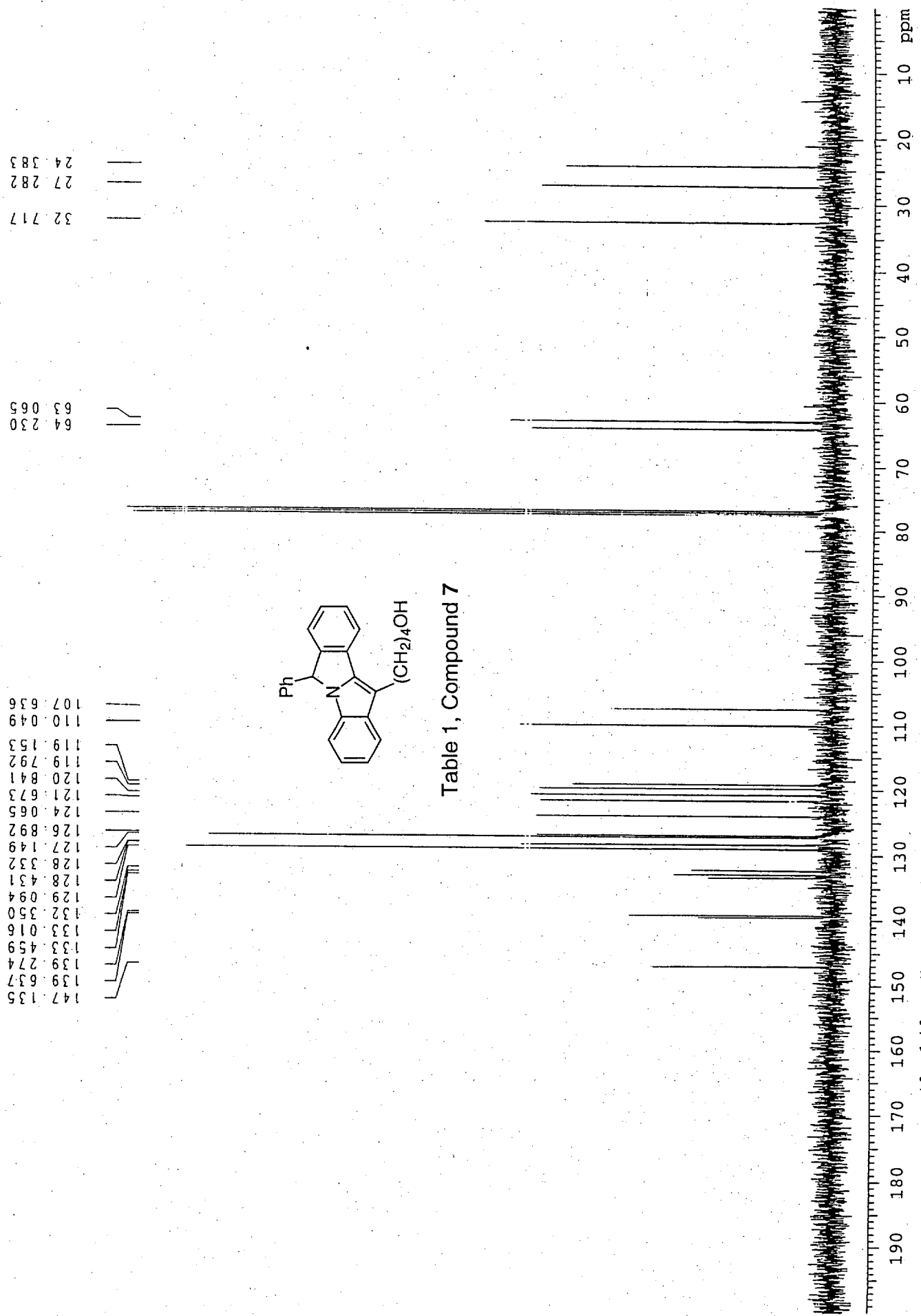


Table 1, Compound 7

7.747
7.721
7.652
7.374
7.368
7.355
7.350
7.231
7.224
7.217
7.206
7.200
7.130
7.121
7.081
6.968
6.964
6.971
6.959
6.106
3.200
3.175
3.151
2.509
1.955
1.931
1.923
1.905
1.898
1.880
1.856
1.649
1.614
1.599
1.588
1.565
1.541
1.106
1.082
1.058

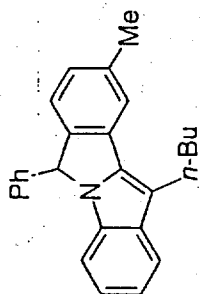
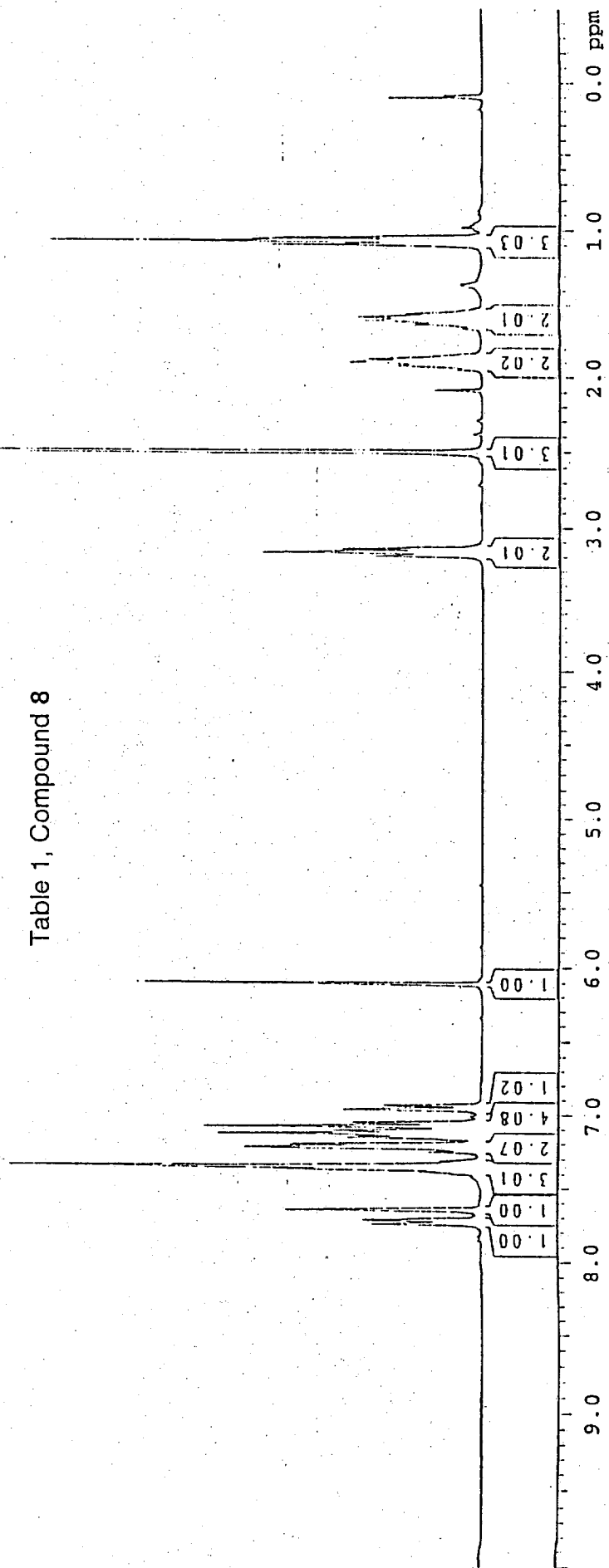


Table 1, Compound 8



144.579	—
139.692	—
139.597	—
138.225	—
133.546	—
133.202	—
132.672	—
129.107	—
128.259	—
127.722	—
127.165	—
123.758	—
121.525	—
119.888	—
119.029	—
110.012	—
108.165	—
64.063	—
33.534	—
24.529	—
22.927	—
21.768	—
14.355	—

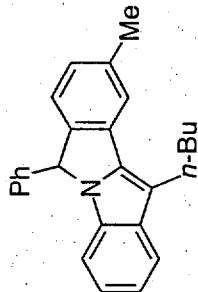
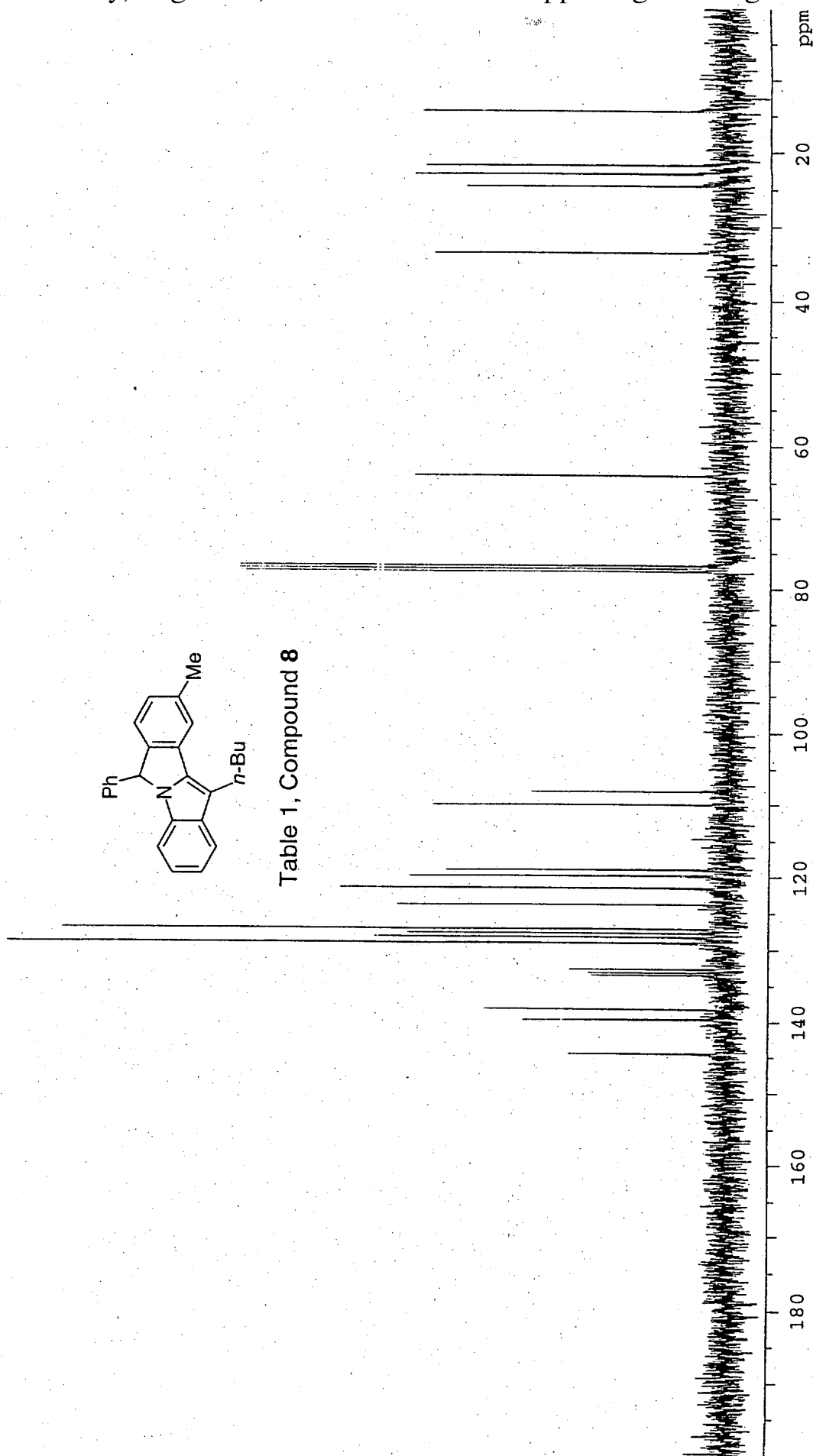


Table 1, Compound 8



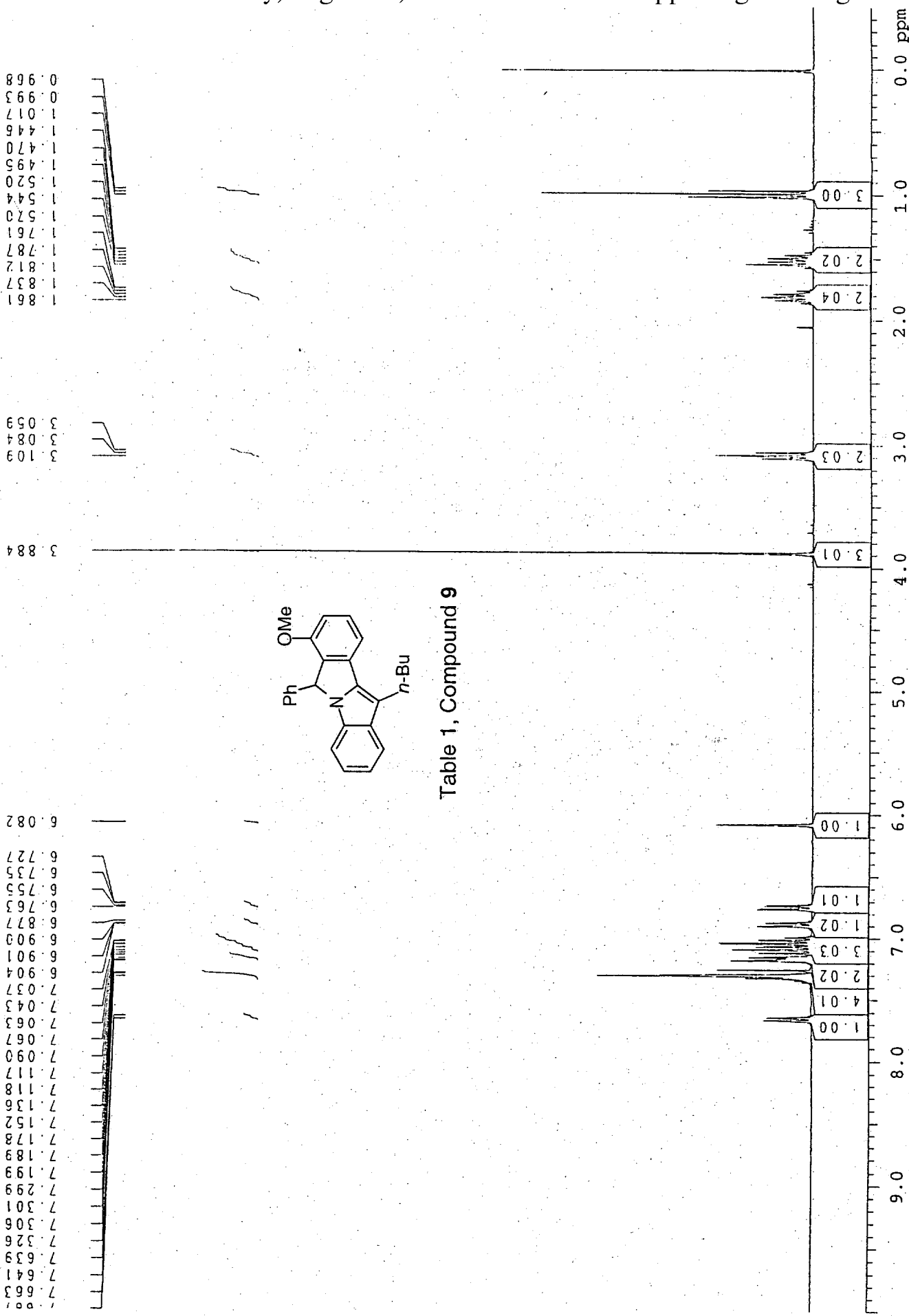
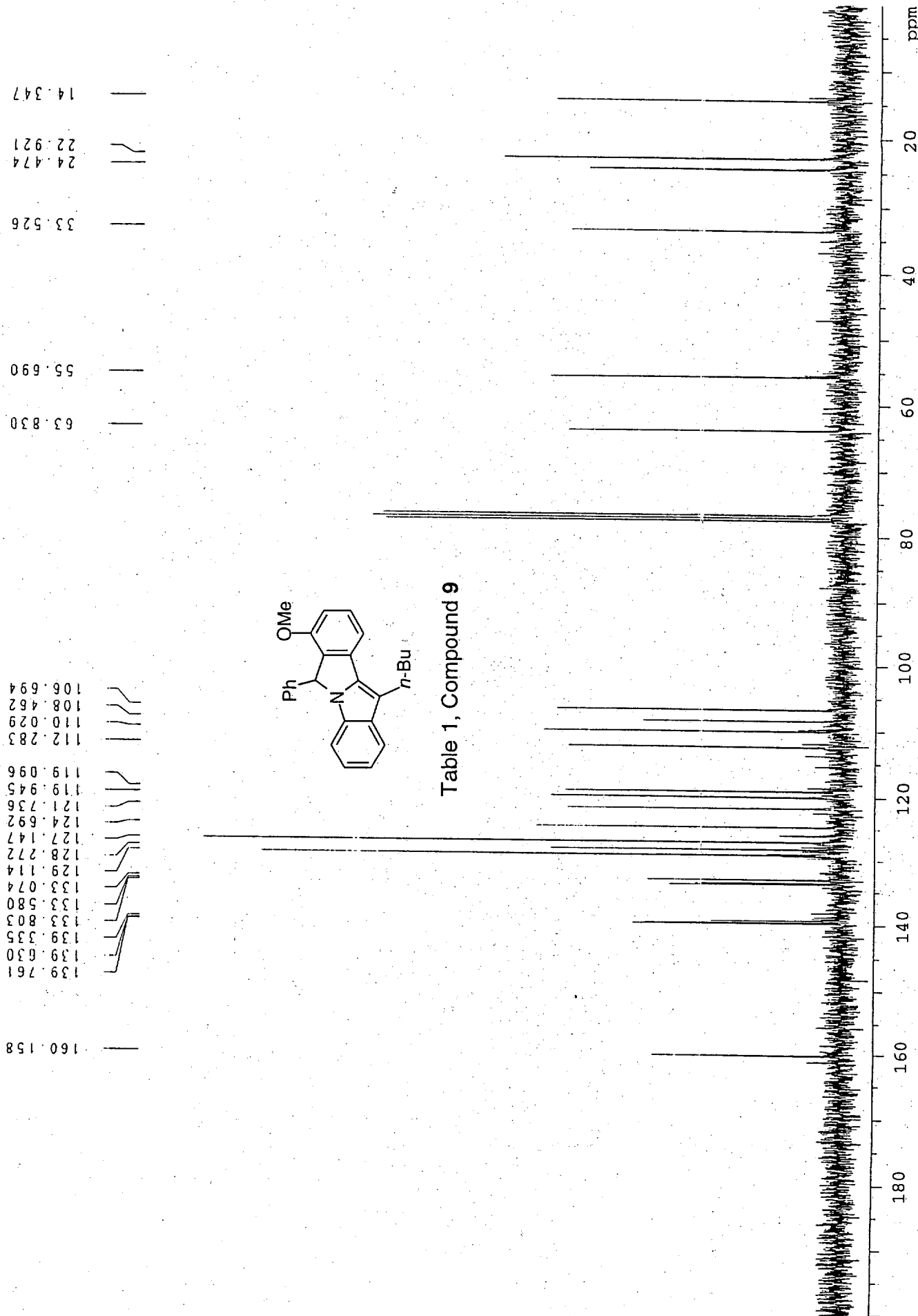


Table 1, Compound 9



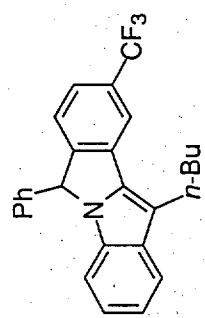
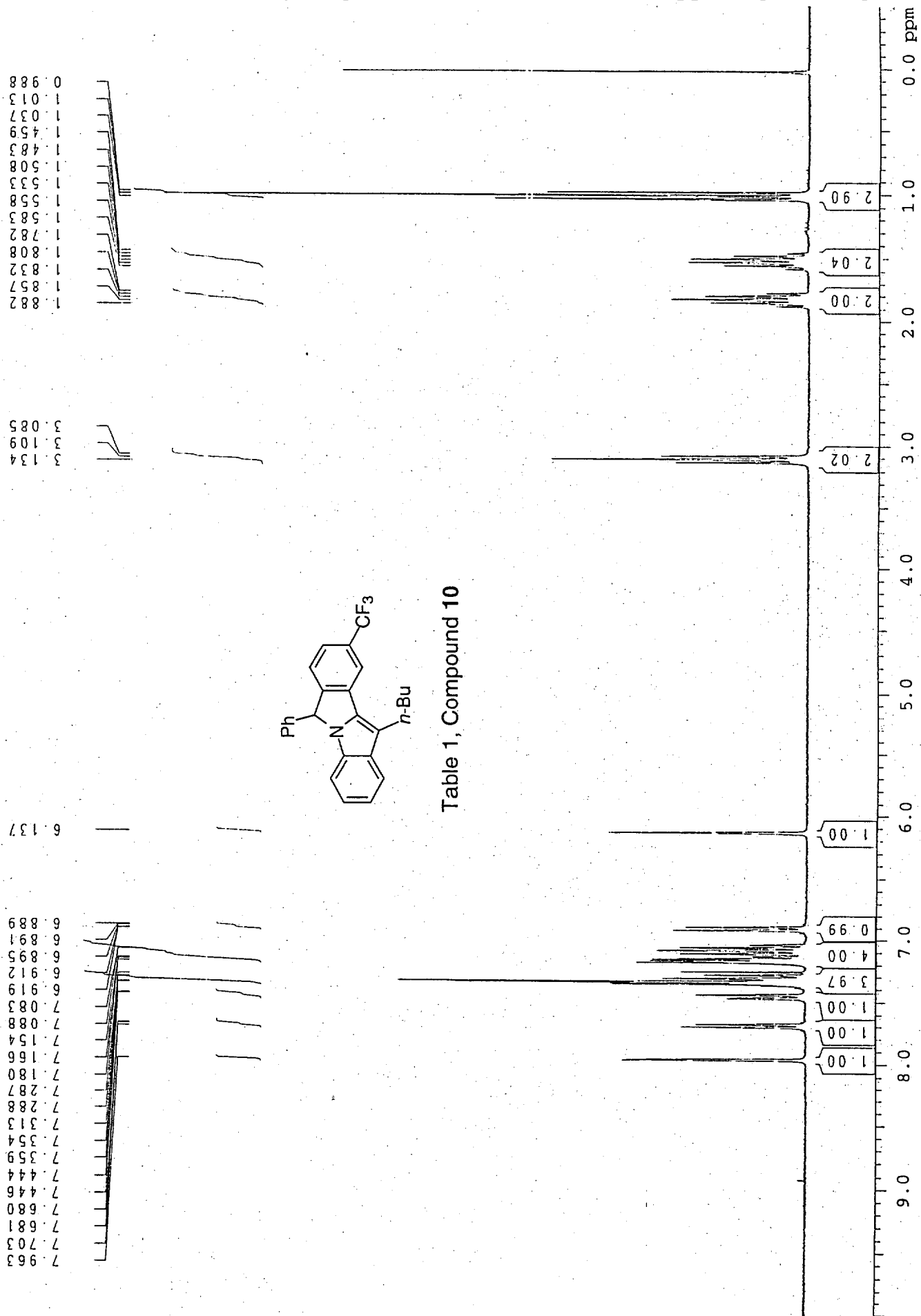


Table 1, Compound 10

150.296
150.286
138.406
137.865
133.528
133.241
132.960
131.160
130.839
129.258
128.671
127.100
125.581
124.348
123.639
123.604
123.568
123.530
122.878
122.283
120.271
119.438
117.491
117.456
117.419
117.384
110.136
109.691

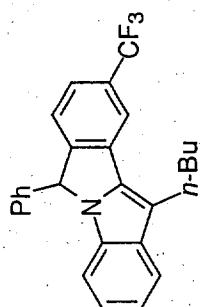
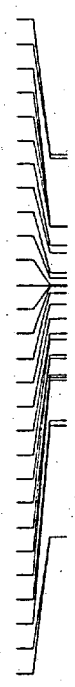
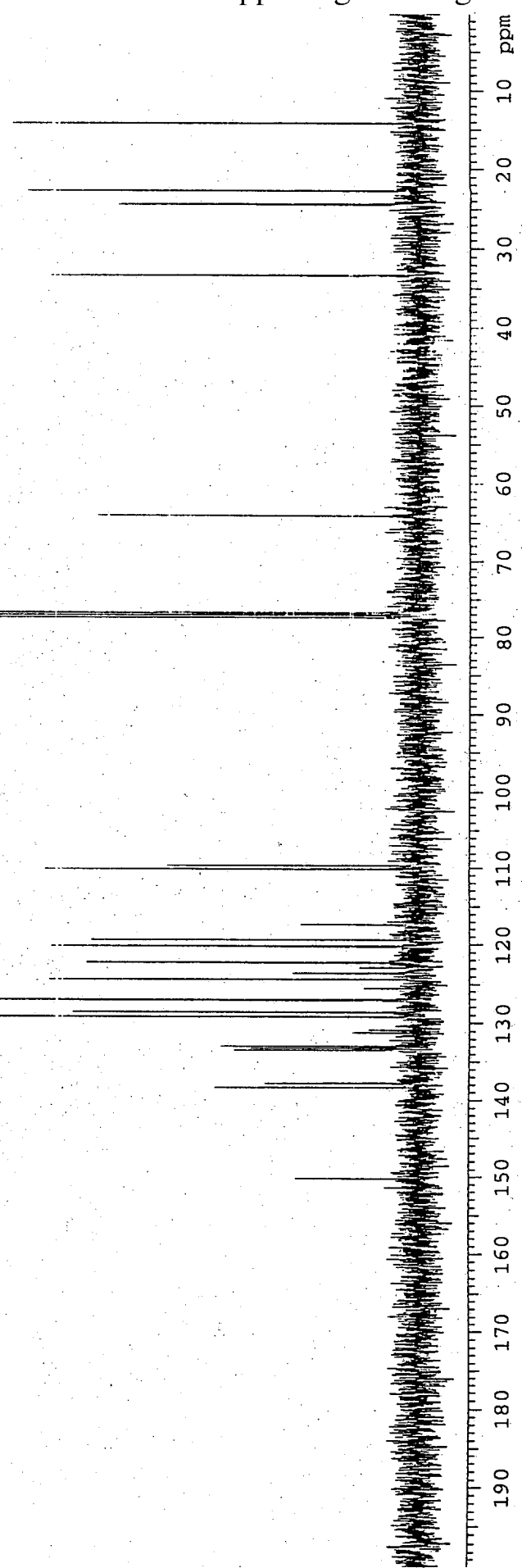
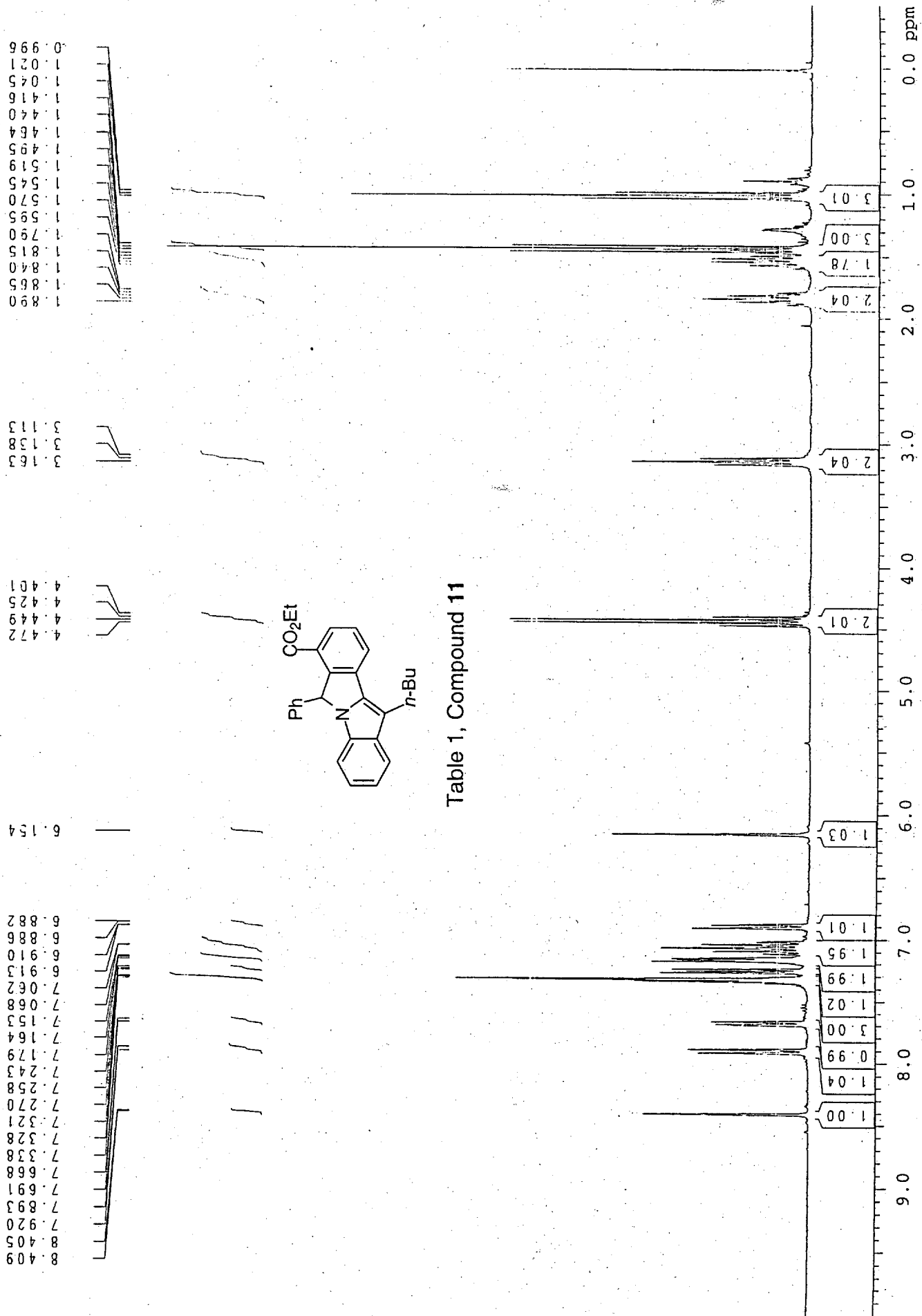


Table 1, Compound 10

64.119
33.334
24.399
22.754
14.167





166.427	—
151.471	—
138.700	—
138.429	—
133.520	—
133.076	—
132.913	—
130.991	—
129.242	—
128.597	—
128.220	—
127.185	—
123.932	—
122.047	—
121.838	—
120.154	—
119.346	—
110.104	—
109.262	—
64.264	—
61.333	—
33.416	—
24.379	—
22.818	—
14.480	—
14.255	—

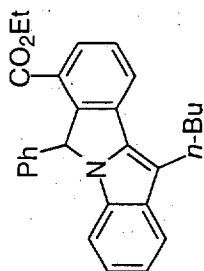
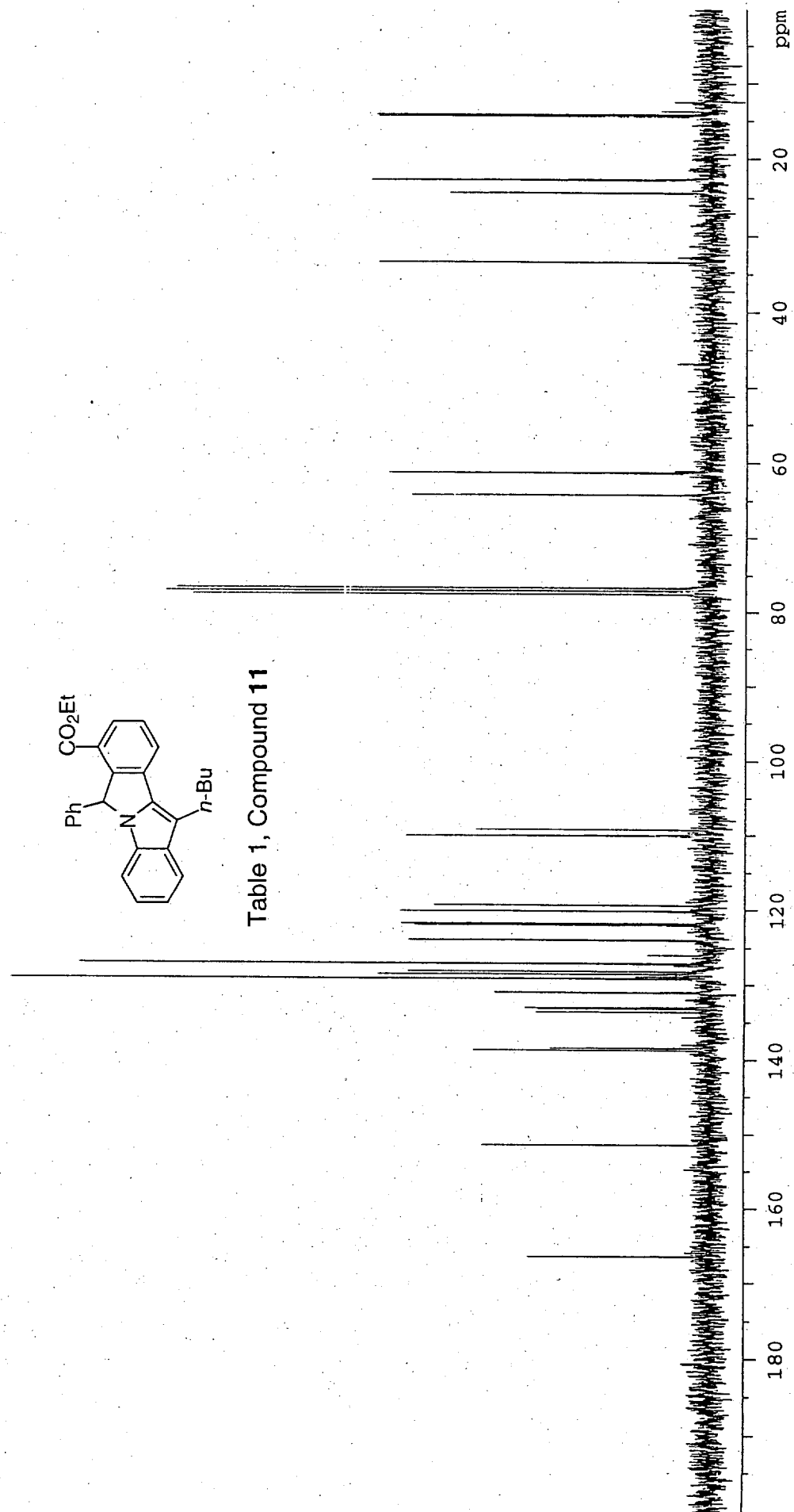


Table 1, Compound 11



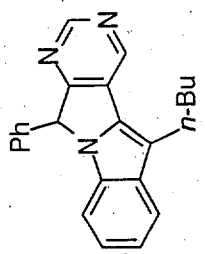
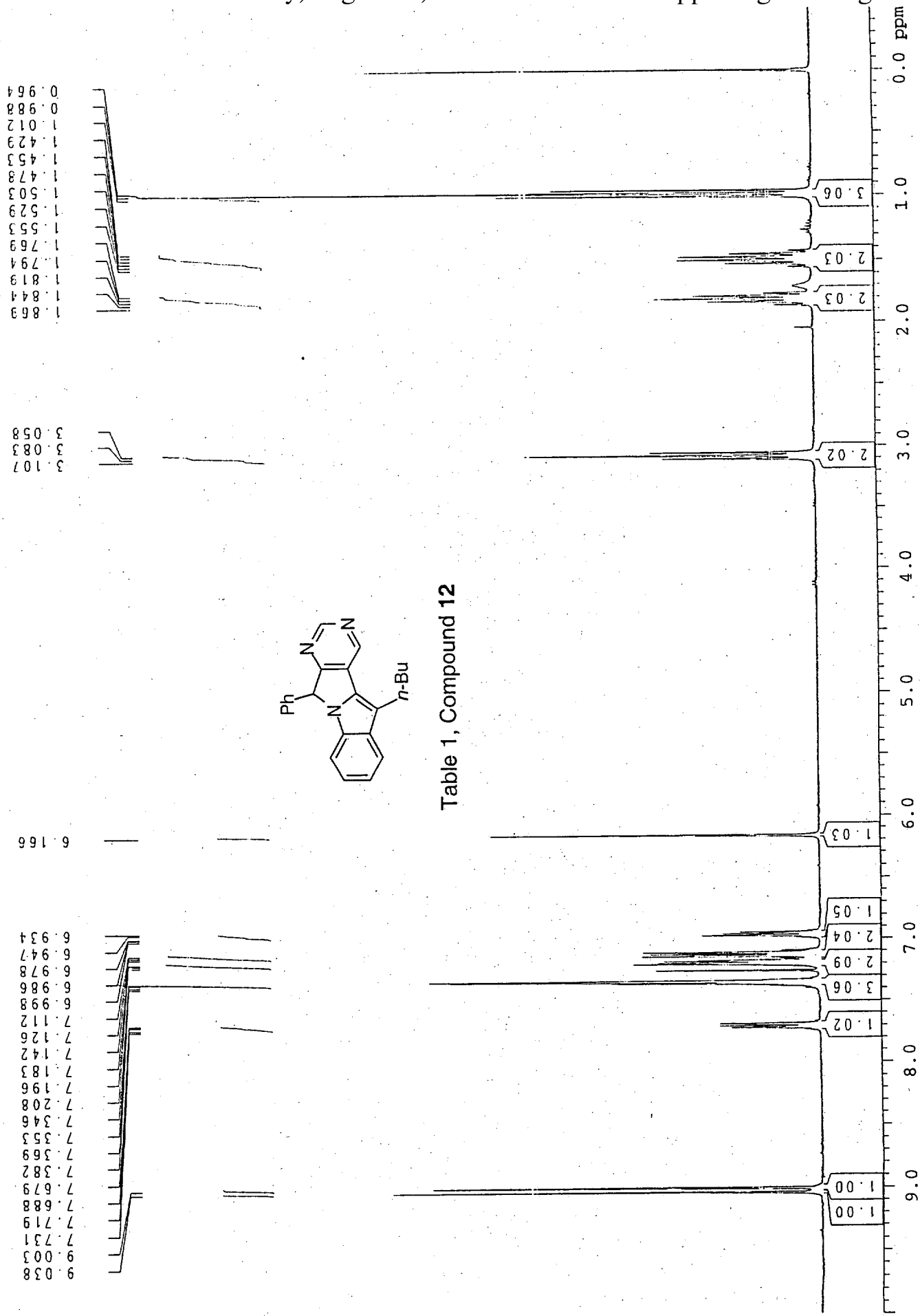


Table 1, Compound 12

/dat2/data/krr/nmr/krr22299ah.fid/1/pdata/1 krr Wed Feb 24 21:27:13 1999

