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

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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), Na_2CO_3 (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*-Bu_4NCl (139 mg, 0.5 mmol), *i*-Pr_2NEt (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*-Bu_4NCl (139 mg, 0.5 mmol), *i*-Pr_2NEt (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 NH_4Cl, dried (Na_2SO_4), 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}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}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, M+1), 357 (100, M$^+$), 356 (26), 280 (78). Anal. Calcd for $C_{27}H_{19}N$: 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}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}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 ($CHCl_3$, cm^{-1}) 3057, 2926, 1611, 1451; HRMS Calcd for $C_{23}H_{19}N$: 309.1518. Found: 309.1516. Anal. Calcd for $C_{23}H_{19}N$: 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 ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 ($CHCl_3$, cm^{-1}) 3046, 2922, 1610, 1450; HRMS Calcd for $C_{25}H_{23}N$: 337.1831. Found: 337.1831. Anal. Calcd for $C_{25}H_{23}N$: 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 ($CDCl_3$) 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 $C_{24}H_{19}NO_2$: 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); ^{1}H 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 $C_{25}H_{23}NO$: 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); ^{1}H 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 $C_{26}H_{25}N$: 351.1987. Found: 351.1987.

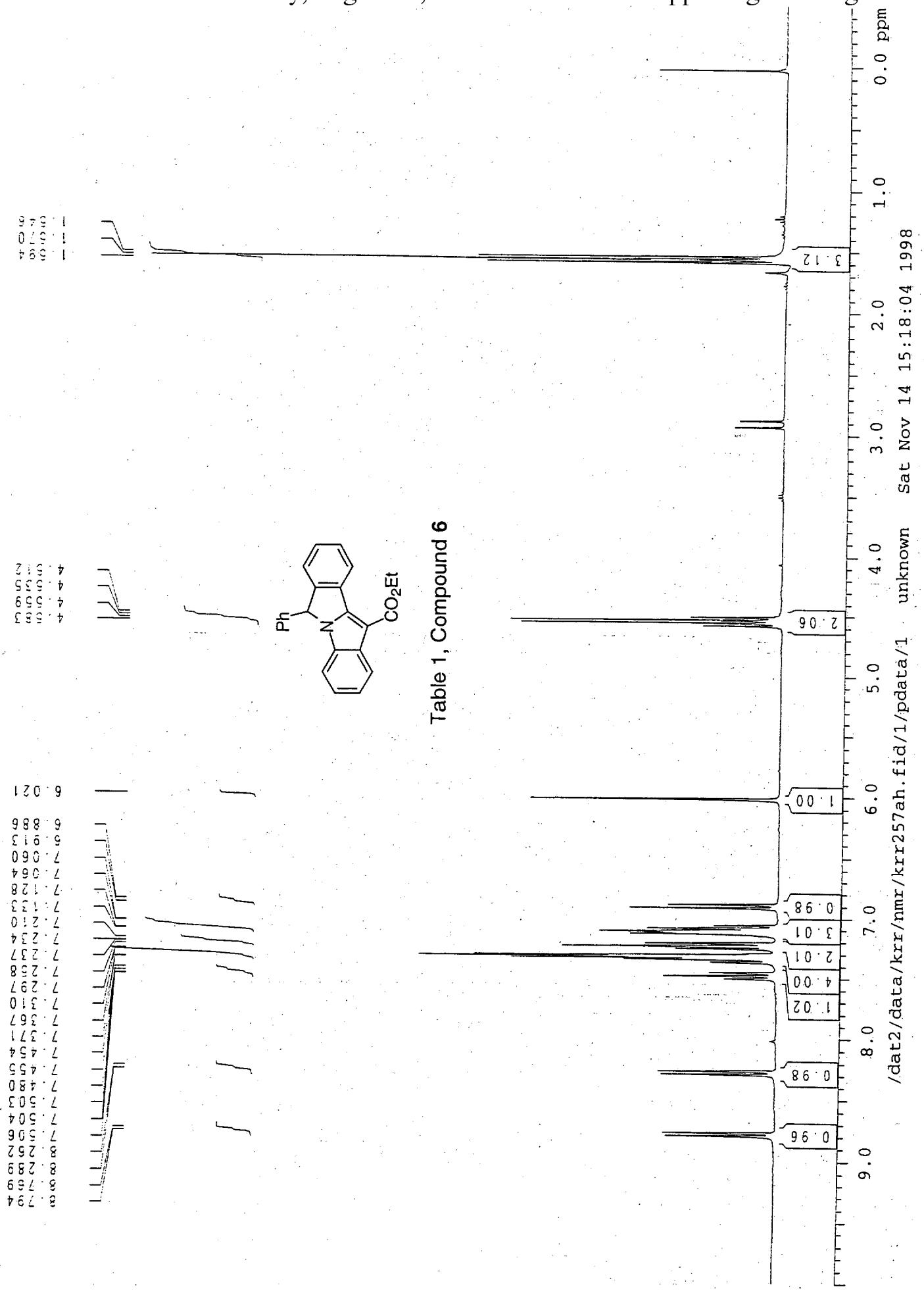
11-*n*-Butyl-7-methoxy-6-phenylisoindolo[2,1-*a*]indole (9). The reaction was run using procedure B and chromatographed using 25:1 hexanes/EtOAc to afford 144 mg (78%) of the indicated compound as a white solid: mp 153-154 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.99 (t, J = 7.5 Hz, 3H), 1.52 (sextet, 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 $C_{26}H_{25}NO$: 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); ^{1}H 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, $^3J_{C\text{-}F}$ = 2.8 Hz), 119.4, 120.3, 122.3, 123.6 (q, $^4J_{C\text{-}F}$ = 2.7 Hz), 124.2 (q, $^1J_{C\text{-}F}$ = 204.1 Hz), 124.4, 127.1, 128.7, 129.3, 130.0 (q, $^2J_{C\text{-}F}$ = 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 $C_{26}H_{22}F_3N$: 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); ^{1}H 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 $C_{26}H_{27}NO_2$: 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); ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 ($CHCl_3$, cm^{-1}) 3028, 2953, 1495, 1456; HRMS Calcd for $C_{23}H_{21}N_3$: 339.1736. Found: 339.1738.



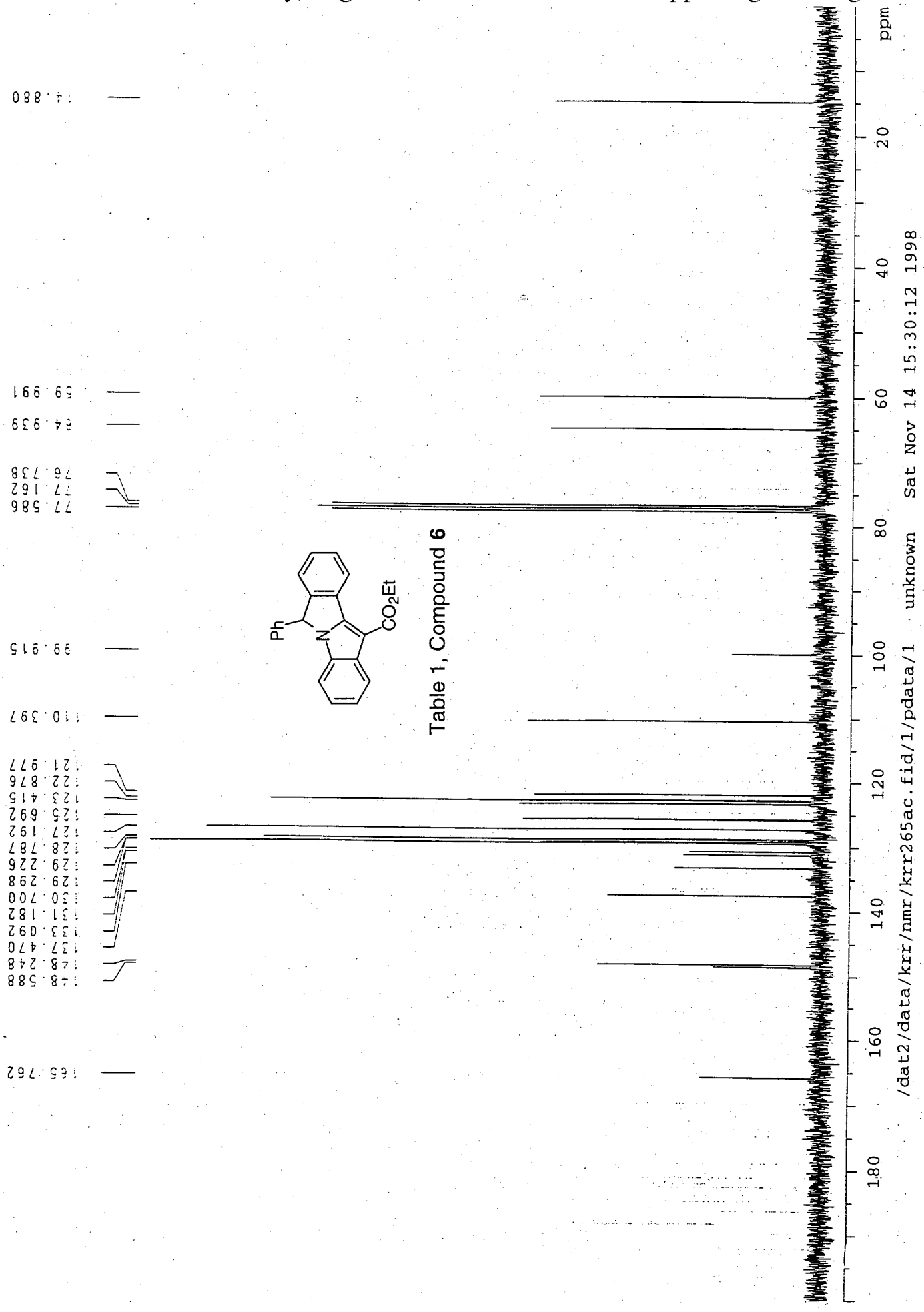
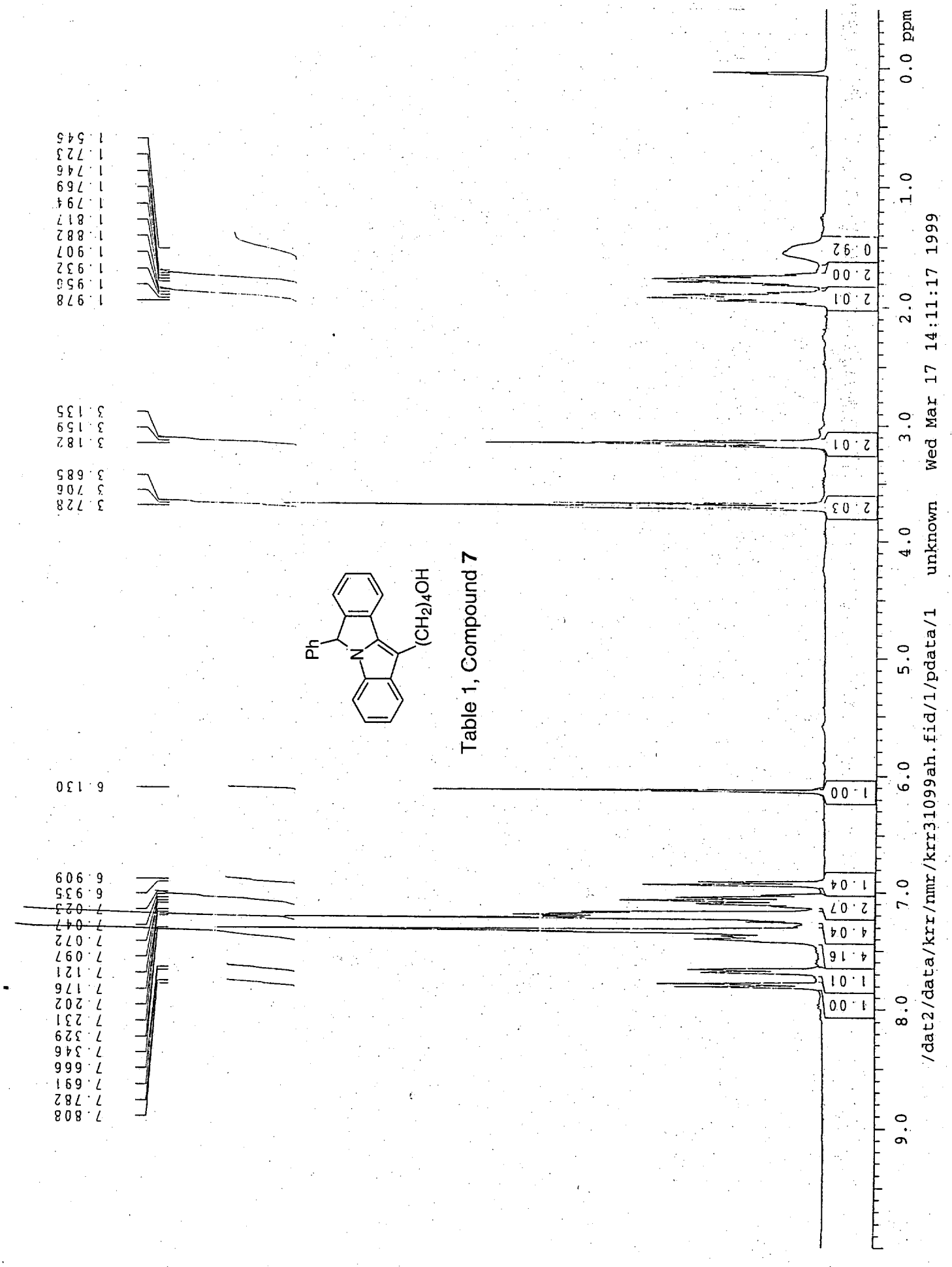
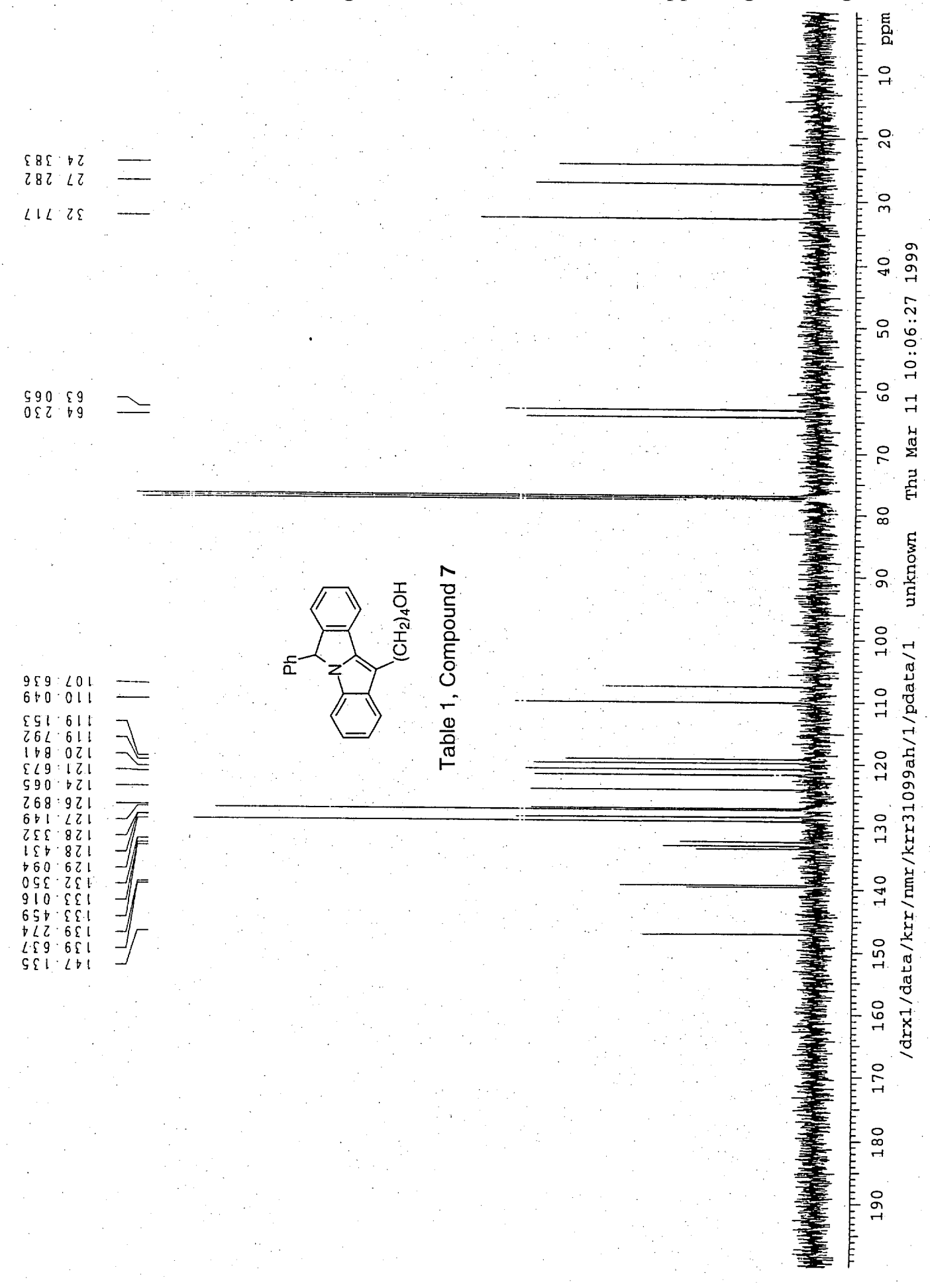


Table 1, Compound **6**





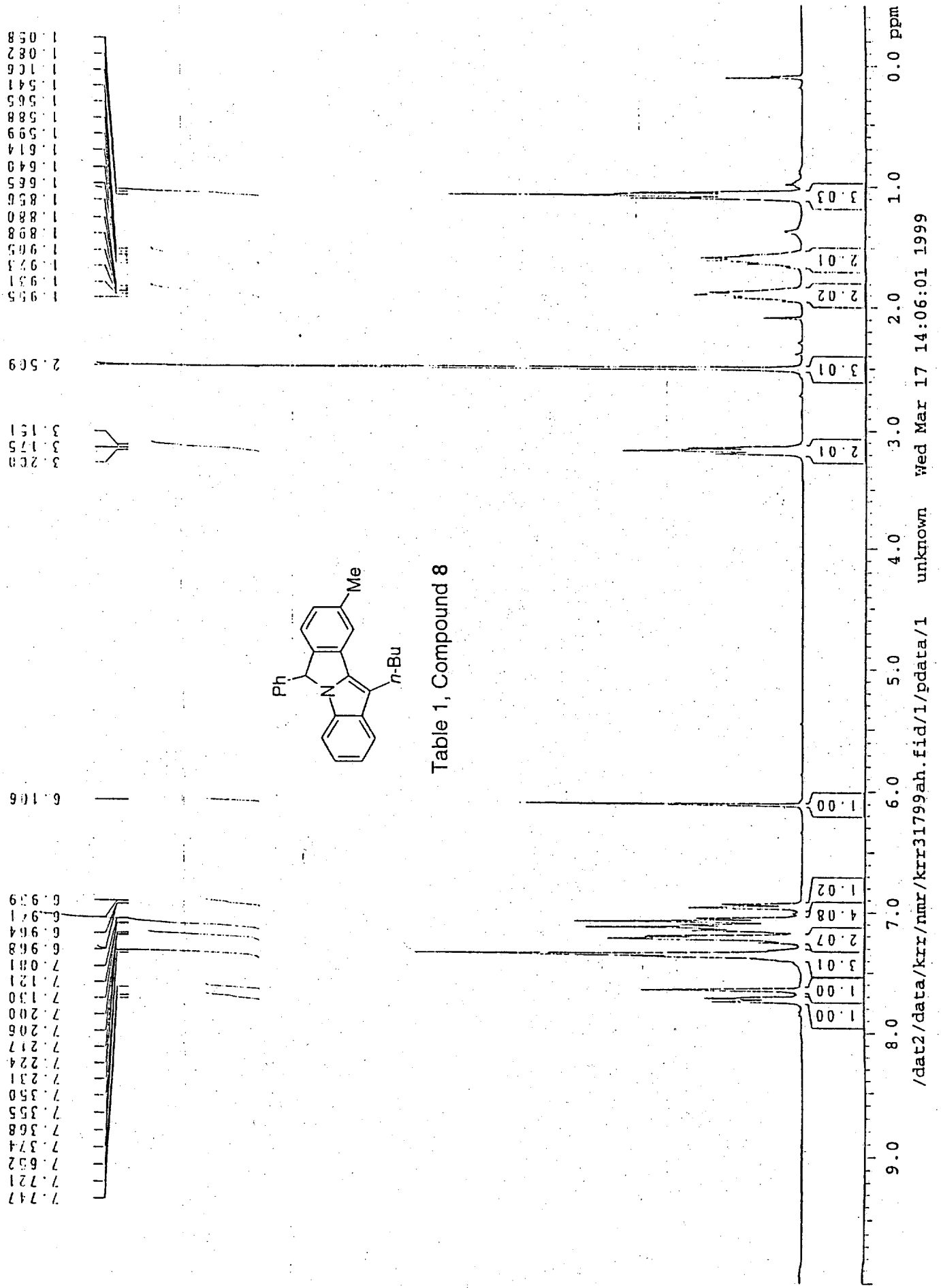
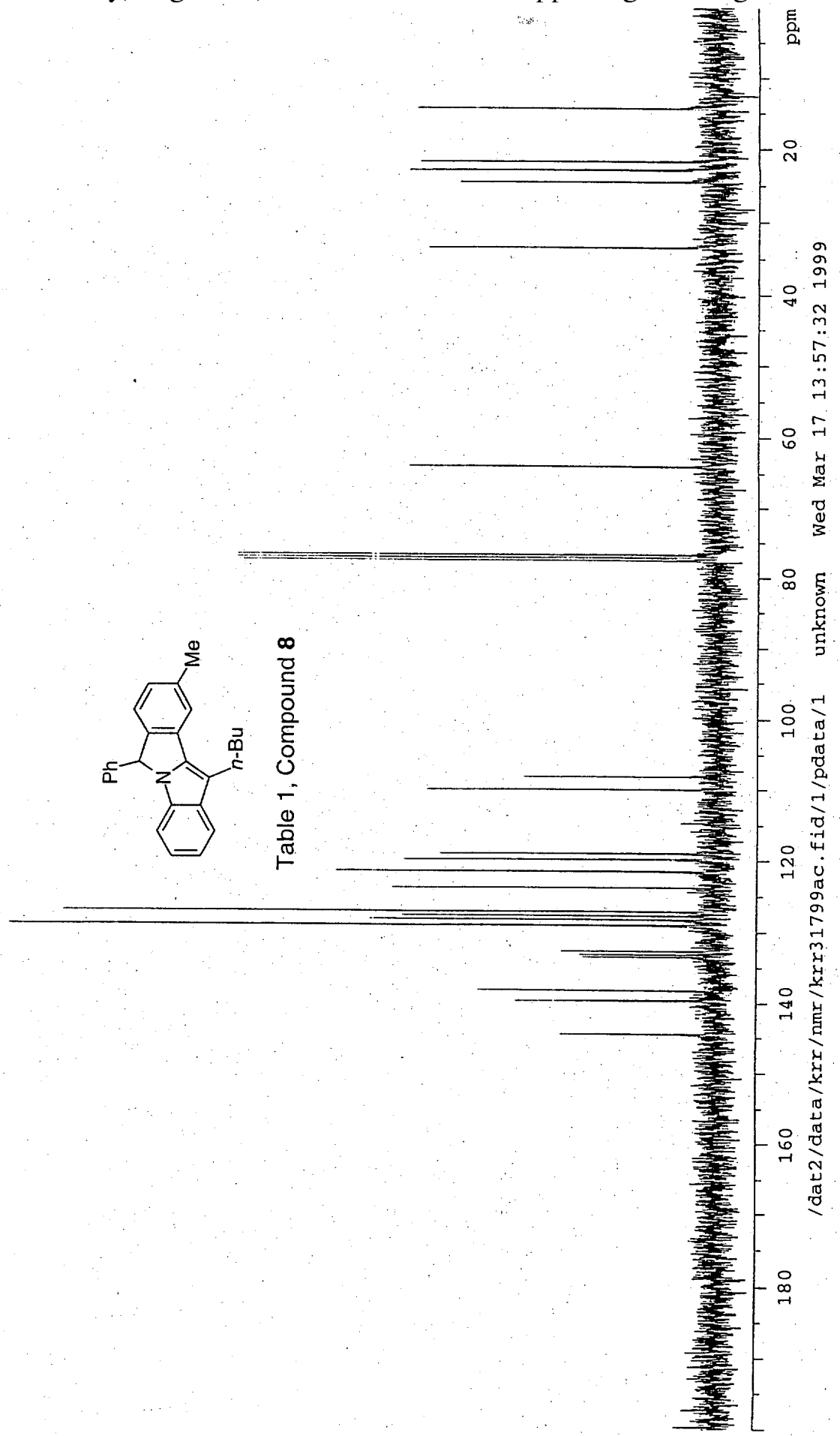


Table 1, Compound **8**



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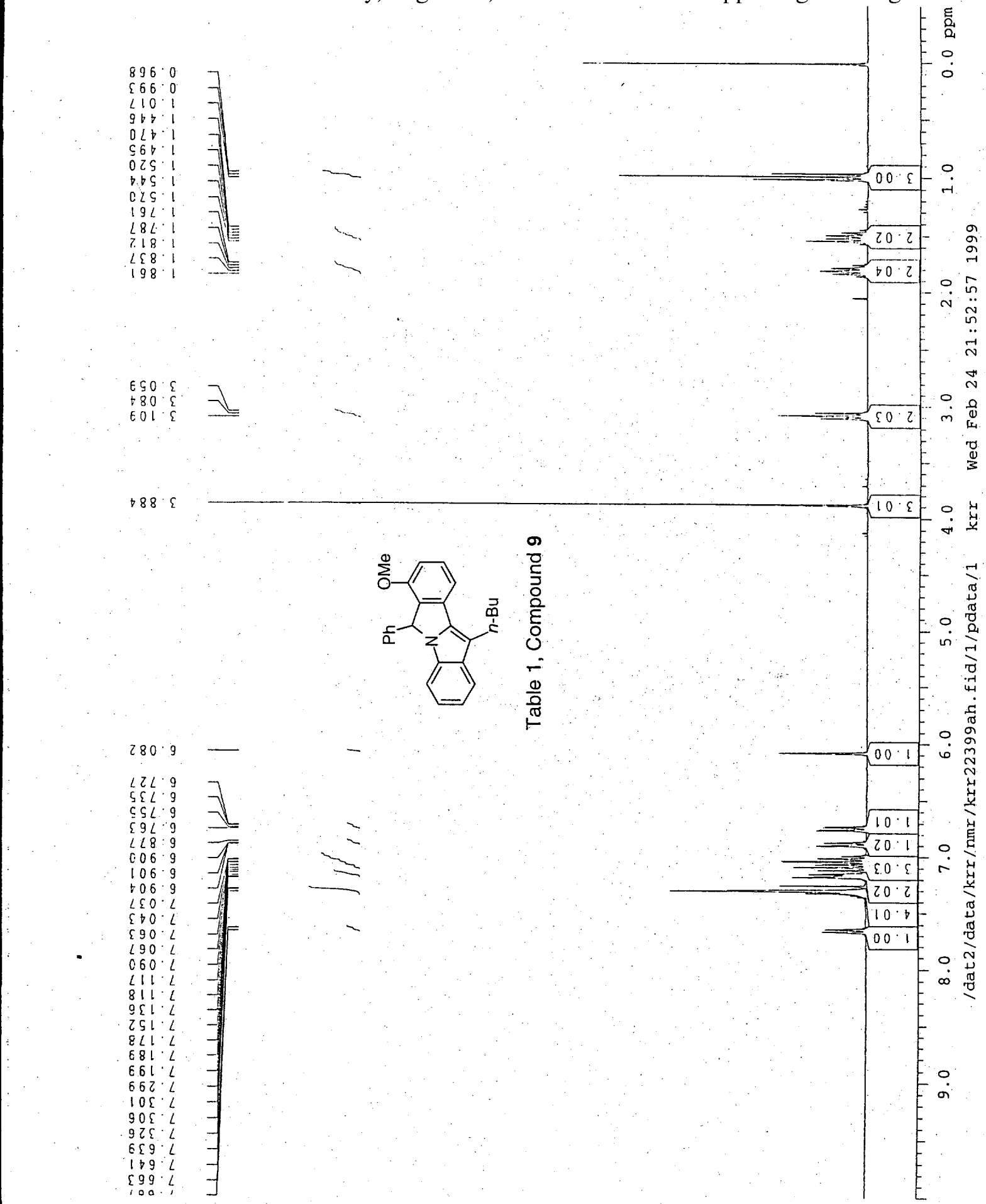

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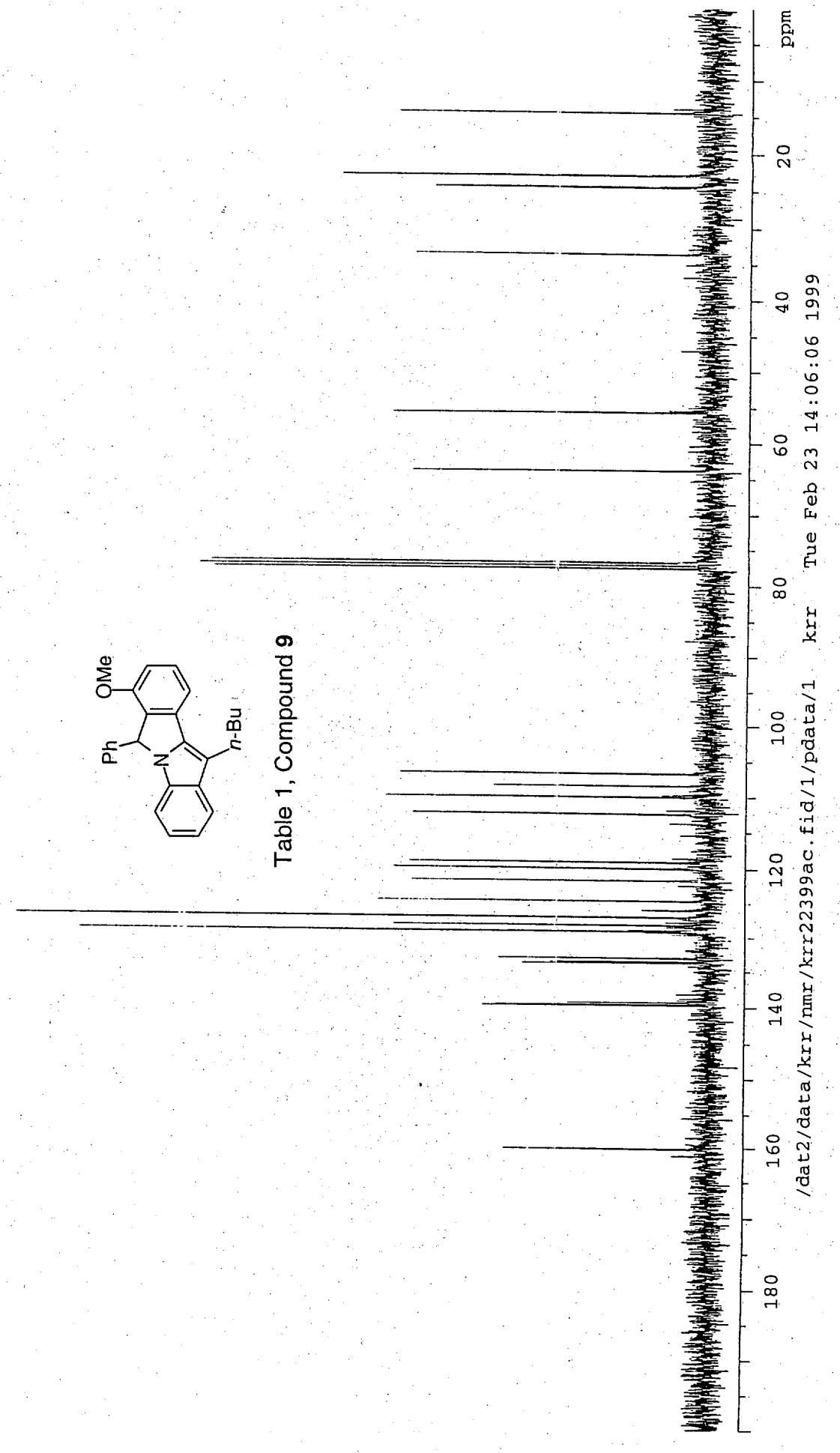

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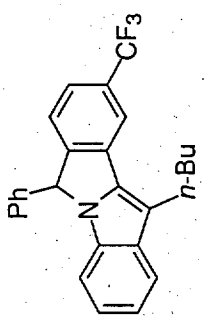

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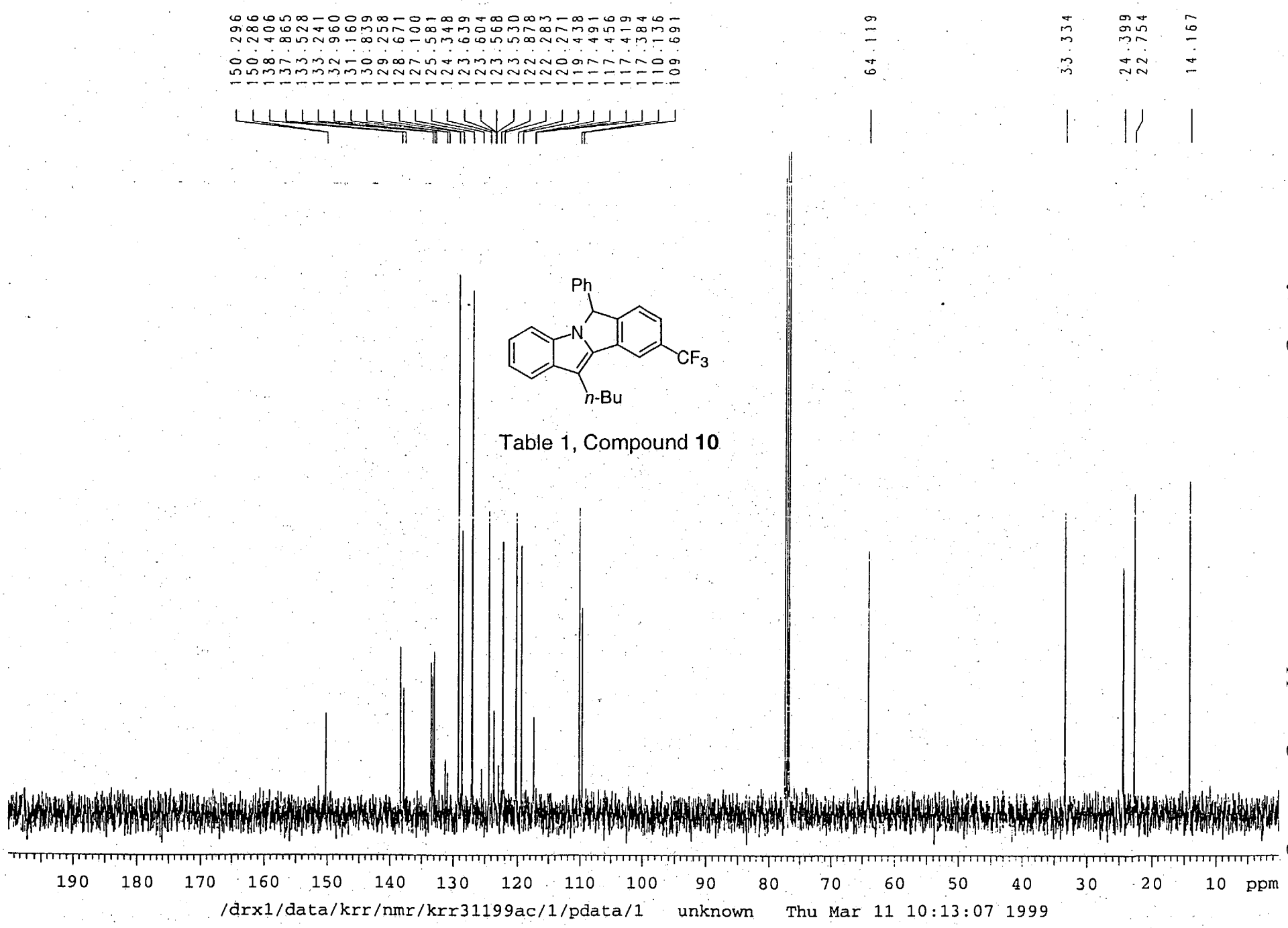

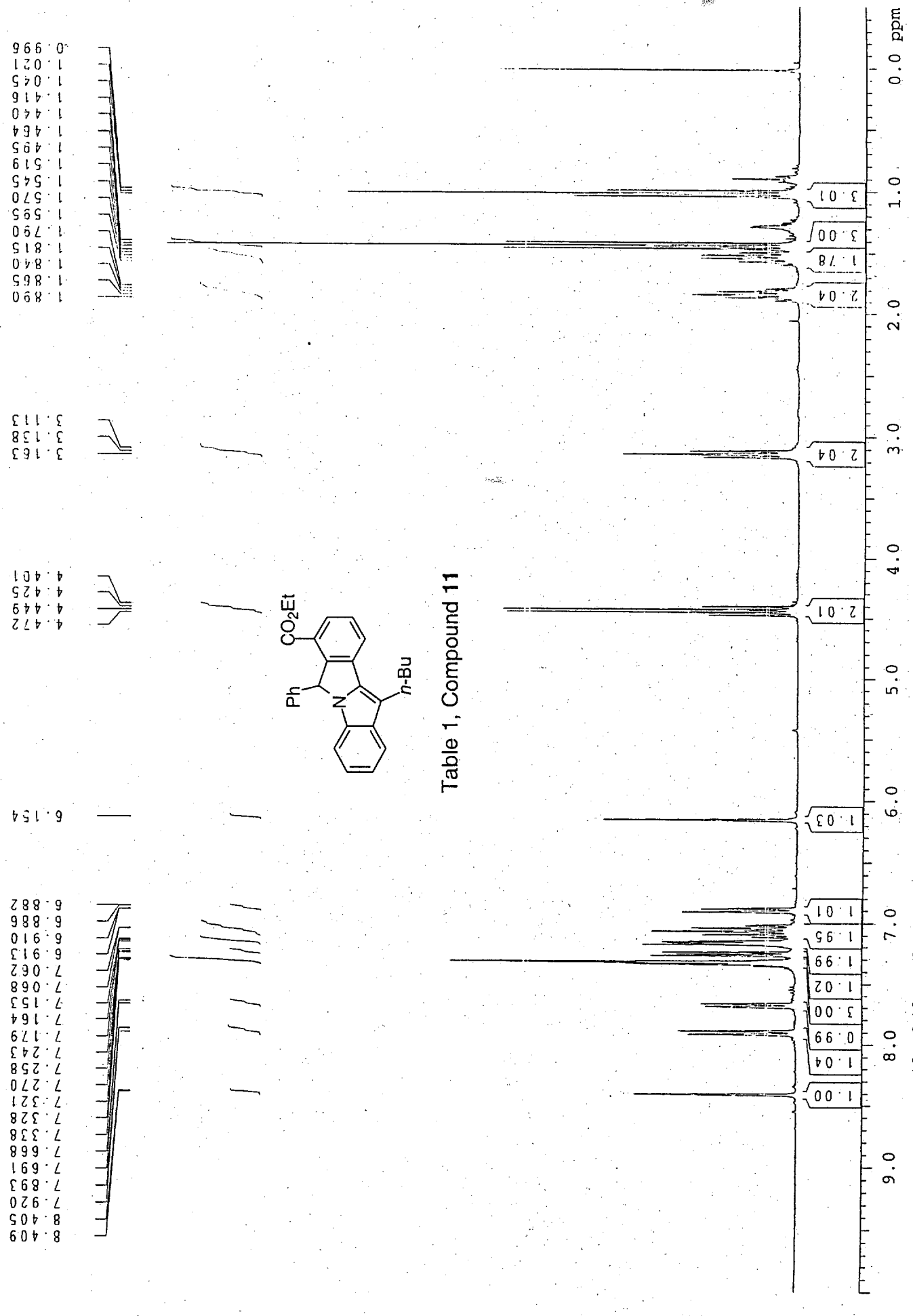

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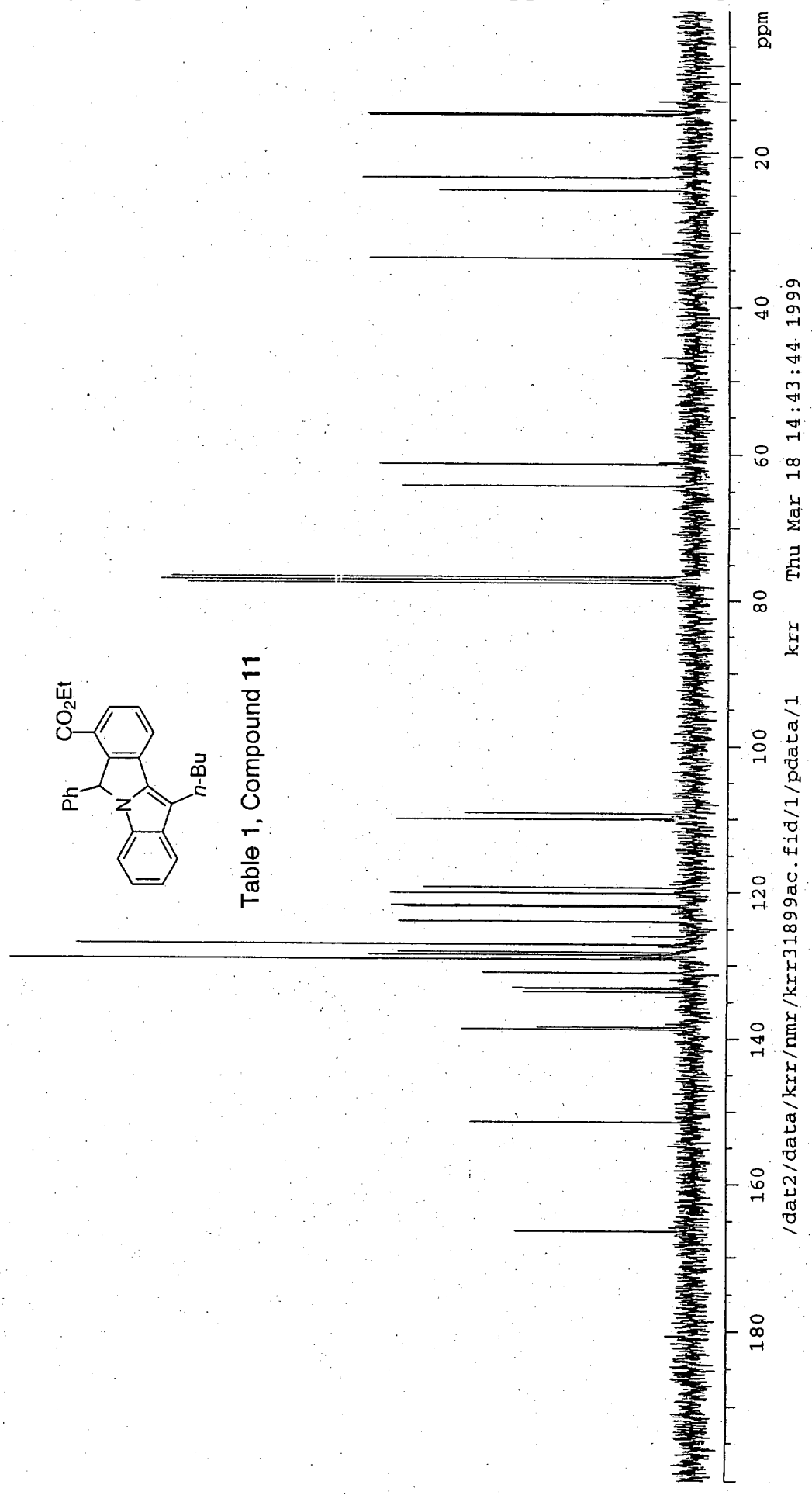

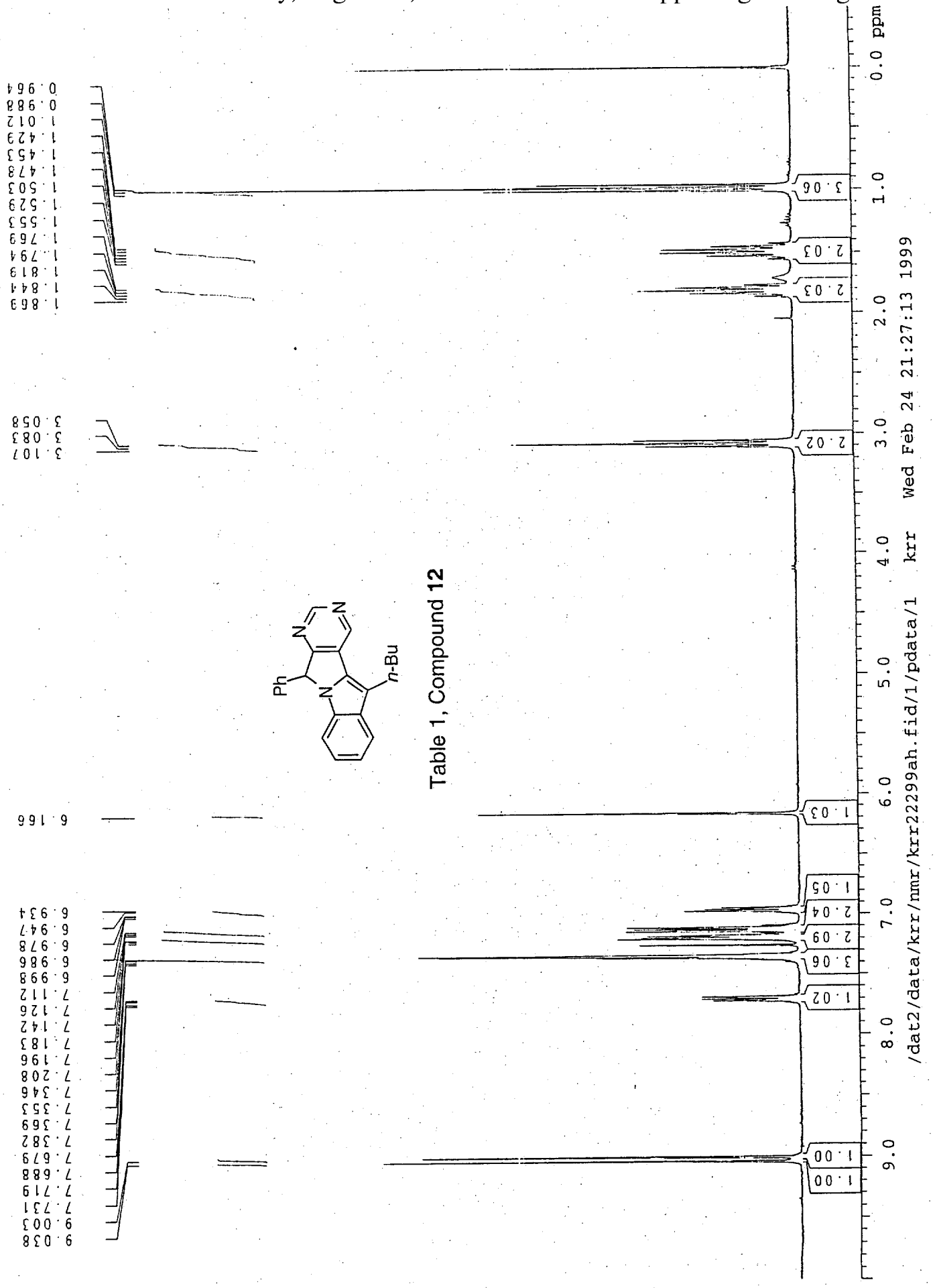

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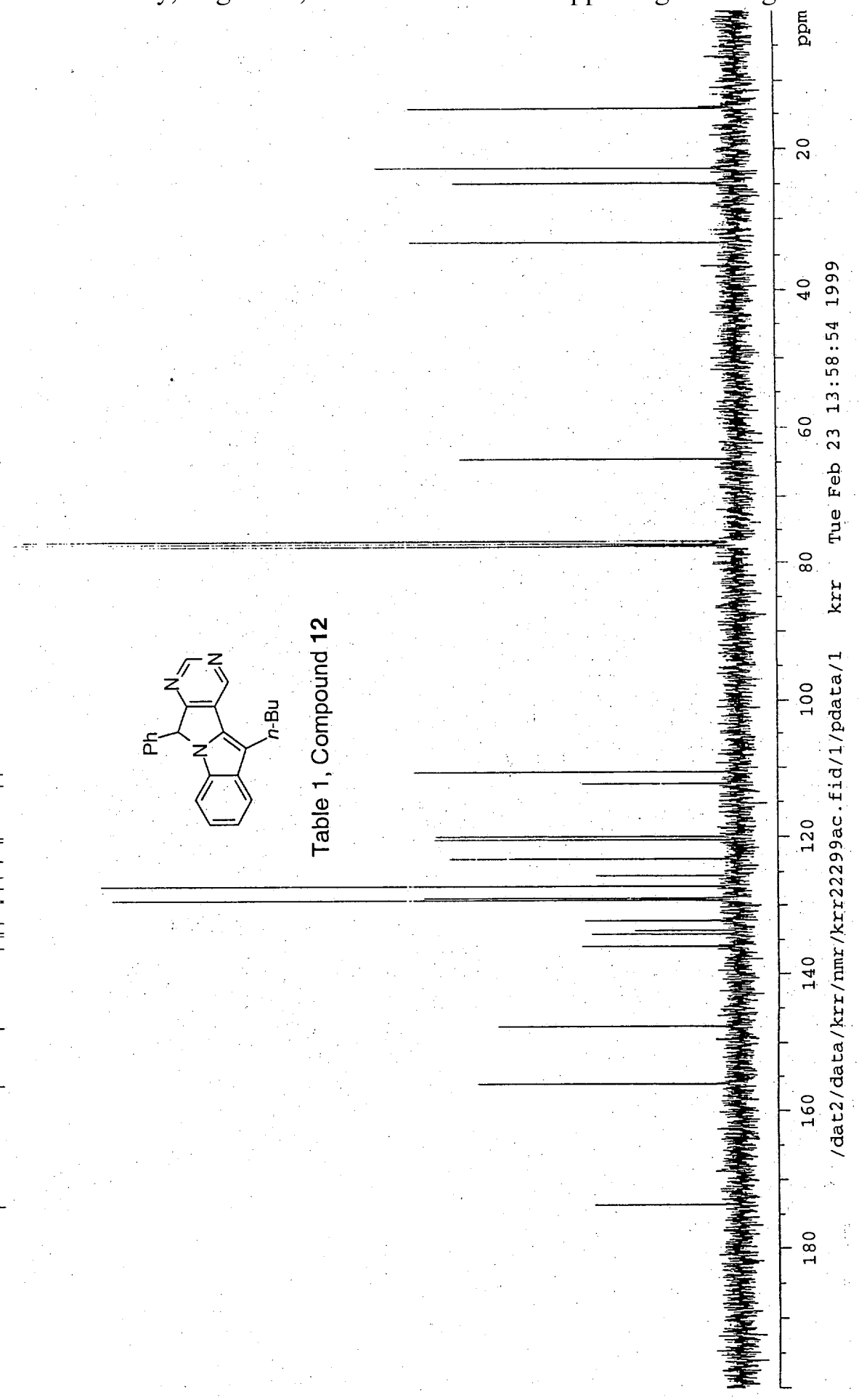

Table 1, Compound **12**