SUPPLEMENTARY MATERIAL

Synthetic Studies Toward Diazonamide A. A Novel Approach for Polyoxazole Synthesis

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Experimental parts. ^{1}H and ^{13}C NMR spectra.

General: All reactions were performed in flame-dried or oven-dried glassware under a dry nitrogen atmosphere. THF and ether were distilled over Na/benzophenone, while toluene, CH_2CH_2, and *i*-Pr_2NH were distilled over CaH_2. Hexanes and EtOAc were distilled prior to use. All other reagents and solvents were used as received unless otherwise noted. NMR spectra were recorded in $CDCl_3$ (unless otherwise noted) at either 300 MHz (^{1}H NMR) or 75 MHz (^{13}C NMR) using Bruker Avance 300 with XWIN-NMR software. IR spectra were obtained neat unless otherwise noted.

(5-Phenyl-oxazol-2-ylmethyl)-carbamic acid benzyl ester (12). A suspension of Cbz-Gly[1] (5.01 g, 24.0 mmol) in 100 mL of CH_2Cl_2 was treated with *i*-Pr_2NEt (12.5 mL, 71.8 mmol) and cooled to -20 °C. Diethyl cyanophosphonate (5.00 mL, 33.0 mmol) was added and the mixture was stirred for 30 min. After the addition of a solution of α-aminoacetophenone hydrochloride (3.75 g, 21.8 mmol) in 20 mL of CH_2Cl_2, the reaction mixture was stirred for 2 h at –20 °C, and for 14 h at room temperature. The solution was diluted with CH_2Cl_2, washed with 10% HCl and saturated $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated. Chromatography on SiO_2 (EtOAc/hexanes, 1:1) provided 6.19 g (87%) of the desired ketoamide as a foam: ^{1}H NMR (DMSO-d_6) δ 8.20 (t, 1 H, *J* = 5.2 Hz), 7.99 (d, 2 H, *J* = 7.6 Hz), 7.67 (t, 1 H, *J* = 7.3 Hz), 7.57-7.52 (m, 3 H), 7.37-7.30 (m, 5 H), 5.04 (s, 2 H), 4.64 (d, 2 H, *J* = 5.4 Hz), 3.72 (d, 2 H, *J* = 6.2 Hz).

A solution of this ketoamide (6.19 g, 19.0 mmol) in 200 mL of CH_2Cl_2 was treated with PPh_3 (10.0 g, 3.81 mmol) and NEt_3 (10.6 mL, 7.61 mmol). At 0 °C, a solution of Cl_3CCCl_3 (9.00 g, 3.80 mmol) in 50 mL of CH_2Cl_2 was added dropwise. The reaction mixture was stirred for 1 h, then warmed to room temperature and stirred for another 1 h. The black solution was washed with 10% HCl and saturated $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated. Chromatography on SiO_2 (EtOAc/hexanes, 1:4) provided 3.31 g (56%) of oily oxazole **12**: R_f 0.50 (EtOAc/hexanes, 1:1); IR 1724 cm^{-1}; ^{1}H NMR δ 7.59 (d, 2 H, *J* = 7.4 Hz), 7.5-7.3 (m, 9 H), 7.24 (s, 1 H), 5.85 (br m, 1 H), 5.17 (s, 2 H), 4.58 (d, 2 H, *J* = 5.8 Hz); ^{13}C NMR δ 160.5, 156.5, 152.1, 136.4, 129.1, 128.7, 128.4, 127.8, 124.4, 122.0, 67.4, 38.7; MS (EI) *m/z* (rel. intensity) 308 (M^+, 13), 217 (15), 203 (7), 173 (95), 91 (100); HRMS (EI) *m/z* calculated for $C_{18}H_{16}N_2O_3$ 308.1161, found 308.1147.

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[1] Hayashi, T.; Asai, T.; Ogoshi, H. *Tetrahedron Lett.* **1997**, *38*, 3039-3042.

(2,2-Dimethyl-propionyl)-(5-phenyl-oxazol-2-ylmethyl)-carbamic *tert*-butyl ester (13). A solution of oxazole **12** (854 mg, 2.77 mmol) in 20 mL of EtOH was treated with 10% Pd/C (150 mg, ca. 0.05 eq). After repeated degassing under vacuum/H_2, the suspension was stirred vigorously for 2 h under 1 atm of H_2, filtered and concentrated. The residue was dissolved in 50 mL of CH_2Cl_2, then treated with NEt_3 (1.00 mL, 7.17 mmol) and PivCl (0.500 mL, 4.05 mmol). The reaction mixture was stirred for 1 h, diluted with CH_2Cl_2, washed with 10% HCl and saturated $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated. Chromatography on SiO_2 (EtOAc/hexanes, 3:7) gave 513 mg (72%) of the desired oily pivaloyl amide: R_f 0.24 (EtOAc/hexanes, 1:1); ^{1}H NMR δ 7.59 (2 d, 2 H, J = 8.2, 7.2 Hz), 7.40 (t, 2 H, J = 7.1 Hz), 7.32 (d, 1 H, J = 7.1 Hz), 7.24 (s, 1 H), 6.49 (br, 1 H), 4.61 (d, 2 H, J = 5.1 Hz), 1.26 (s, 9 H); ^{13}C NMR δ 178.6, 160.4, 151.9, 128.9, 128.6, 127.7, 124.2, 121.7, 38.8, 37.2, 27.6.

A solution of this pivaloyl amide (96 mg, 0.38 mmol) in 2 mL of THF was treated at -78 °C with a 1.6 M solution of BuLi in hexane (0.250 mL, 0.400 mmol), Boc_2O (166 mg, 0.806 mmol), and DMAP (5.0 mg, 0.041 mmol). The reaction mixture was stirred overnight at room temperature, diluted with CH_2Cl_2, washed with 10% HCl and 2 N NaOH, dried ($MgSO_4$), filtered, and concentrated. Chromatography on SiO_2 (EtOAc/hexanes, 1:9) gave 36 mg (38%) of recovered starting material, and 58 mg (43%) of the desired oily imide **13**: R_f 0.60 (EtOAc/hexanes, 3:7); IR 1747, 1741, 1688 cm^{-1}; ^{1}H NMR δ 7.58 (d, 1 H, J = 8.5 Hz), 7.57 (d, 1 H, J = 7.2 Hz); 7.39 (t, 2 H, J = 7.2 Hz); 7.31 (d, 1 H, J = 5.2 Hz), 7.25 (s, 1 H), 4.90 (s, 2 H), 1.46 (s, 9 H), 1.38 (s, 9 H); ^{13}C NMR δ 184.9, 160.2, 153.1, 151.3, 128.9, 128.4, 127.9, 124.1, 122.1, 83.4, 44.1, 43.5, 28.1, 27.9; MS (EI) *m/z* (rel. intensity) 358 (M^+, 15), 287 (10), 258 (65), 201 (77), 173 (45), 153 (30), 136 (22), 107 (26); HRMS (EI) *m/z* calculated for $C_{20}H_{26}N_2O_4$, 358.1893, found 358.1896.

[3,3-Dimethyl-2-oxo-1-(5-phenyl-oxazol-2-yl)-butyl]-carbamic acid *tert*-butyl ester (14). A solution of *i*-Pr_2NH (0.100 mL, 0.715 mmol) in 1 mL of THF was treated with a 1.6 M solution of BuLi in hexane (0.500 mL, 0.800 mmol) and cooled to -78 °C. A solution of **13** (58 mg, 0.162 mmol) in 1 mL of THF was added and the mixture was stirred for 30 min, quenched with saturated NH_4Cl, and extracted into EtOAc. The EtOAc layer was washed with 10% HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated. Chromatography on SiO_2

(EtOAc/hexanes, 1:9 to 3:7) provided the rearranged product as an oil (51.5 mg; 89%): R_f 0.60 (EtOAc/hexanes, 3:7); IR 1713 cm^{-1}; 7.62 (d, 2 H, *J* = 7.2 Hz), 7.42 (t, 2 H, *J* = 7.0 Hz), 7.36 (d, 1 H, *J* = 7.1 Hz), 7.30 (s, 1 H), 6.06 (d, 1 H, *J* = 8.4 Hz), 5.85 (d, 1 H, *J* = 7.7 Hz), 1.45 (s, 9 H), 1.20 (s, 9 H); ^{13}C NMR δ 207.7, 158.5, 154.7, 152.2, 129.0, 128.9, 127.4, 124.4, 122.4, 80.6, 52.7, 44.3, 28.3, 26.4; MS (EI) *m/z* (rel. intensity) 358 (M^+, 1), 285 (5), 273 (8), 217 (24), 200 (22), 173 (100); HRMS (EI) *m/z* calculated for $C_{20}H_{26}N_2O_4$ 358.1893, found 358.1902.

***N*-(5'-*tert*-Butyl-5-phenyl-[2,4']bioxazolyl-2'-ylmethyl)-benzamide (15).** A solution of **14** (73 mg, 0.20 mmol) in 3 mL of ether pre-saturated with HCl was stirred for 1 h and concentrated to dryness. In a separate flask, *N*-benzoyl-glycine[2] (50 mg, 0.28 mmol) was dissolved in 2 mL of DMF and treated with *N*-methylmorpholine (0.100 mL, 0.91 mmol). To this solution was added at -30 °C, isobutylchloroformate (0.040 mL, 0.30 mmol). The mixture was stirred for 10 min, treated with a solution of the deprotected amine in 1 mL of DMF, stirred at -20 °C for 2 h, diluted with EtOAc, washed with 10% HCl and saturated $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated. Chromatography on SiO_2 (EtOAc/hexanes, 1:1) gave 59 mg (70%) of the desired Bz-Gly adduct as an oil: R_f 0.06 (EtOAc/hexanes, 1:1); ^1H NMR δ 7.89 (d, 1 H, *J* = 7.9 Hz), 7.82 (d, 2 H, *J* = 7.2 Hz), 7.57-7.54 (m, 2 H), 7.47-7.28 (m, 7 H), 7.25 (s, 1 H), 6.37 (d, 1 H, *J* = 7.6 Hz), 4.29 (d, 2 H, *J* = 5.1 Hz), 1.19 (s, 9 H).

A solution of the Bz-Gly adduct (59 mg, 0.14 mmol) in 1 mL of toluene was treated with *p*-TsOH (10 mg, 0.053 mmol) and stirred for 2 d at 90 °C. The reaction mixture was cooled, diluted with EtOAc, washed with 10% HCl and saturated $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated. Chromatography on SiO_2 (EtOAc/hexanes, 1:4 to 1:1) gave 32 mg (57%) of bisoxazole **15** as an oil: R_f 0.25 (EtOAc/hexanes, 1:1); IR 1651 cm^{-1}; ^1H NMR δ 7.84-7.81 (m, 3 H), 7.62 (2 d, 2 H, *J* = 8.4, 7.1 Hz), 7.44-7.32 (m, 7 H), 4.80 (d, 2 H, *J* = 5.4 Hz), 1.50 (s, 9 H); ^{13}C NMR δ 167.7, 160.9, 158.7, 155.4, 151.6, 133.6, 131.8, 129.1, 128.7, 128.6, 127.8, 127.4, 124.4, 123.4, 123.3, 37.2, 33.2, 28.6; MS (EI) *m/z* (rel. intensity) 401 (M^+, 80), 296 (100), 105 (95), 77 (44); HRMS (EI) calculated for $C_{24}H_{23}N_3O_3$, 401.1739, found 401.1741.

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[2] Glase, S. A.; Akunne, H. G.; Georgic, L. M.; Heffner, T. G.; MacKenzie, R. G. *J. Med. Chem.* **1997**, *40*, 1771-1772.

[1-(5'-*tert*-Butyl-5-phenyl-[2,4']bioxazolyl-2'-yl)-2-oxo-2-phenyl-ethyl]-carbamic acid *tert*-butyl ester (16). A solution of bisoxazole **15** (32 mg, 0.080 mmol) in 1 mL of THF was treated with DMAP (10 mg, 0.089 mmol) and Boc_2O (35 mg, 0.16 mmol). The reaction mixture was stirred for 19 h, diluted with EtOAc, washed with 10% HCl and saturated $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated. Chromatography on SiO_2 (EtOAc/hexanes, 1:19 to 1:9) gave 37 mg (92%) of the desired imide as an oil: R_f 0.64 (EtOAc/hexanes, 1:1); ^{1}H NMR δ 7.76-7.71 (m, 4 H), 7.55-7.30 (m, 7 H), 5.20 (s, 2 H), 1.52 (s, 9 H), 1.22 (s, 9 H); ^{13}C NMR δ 173.0, 160.5, 157.3, 155.7, 152.9, 151.3, 137.4, 131.6, 129.1, 128.6, 128.3, 128.1, 124.5, 123.8, 123.3, 84.0, 42.3, 33.2, 28.6, 27.6.

A solution of *i*-Pr_2NH (0.050 mL, 0.36 mmol) in 1 mL of THF was treated with a 1.6 M solution of BuLi in hexane (0.200 mL, 0.32 mmol) and cooled to –78 °C. A solution of the imide (35 mg, 0.070 mmol) in 1 mL of THF was added and the reaction mixture was stirred for 30 min, diluted with EtOAc, washed with 10% HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. Chromatography on SiO_2 (EtOAc/hexanes, 1:9 to 3:7) gave 30 mg (86%) of oily **16**: R_f 0.64 (EtOAc/hexanes, 1:1); IR 1716, 1697 cm^{-1}; ^{1}H NMR δ 8.17 (d, 2 H, *J* = 7.5 Hz), 7.70 (d, 2 H, *J* = 7.3 Hz), 7.63 (d, 1 H, *J* = 7.3 Hz), 7.55-7.30 (m, 6 H), 6.58 (d, 1 H, *J* = 8.2 Hz), 6.18 (d, 1 H, *J* = 8.1 Hz), 1.50 (s, 9 H), 1.43 (s, 9 H); ^{13}C NMR δ 191.8, 161.2, 156.3, 155.2, 151.7, 134.5, 134.1, 129.5, 129.1, 129.0, 128.8, 127.9, 124.5, 124.1, 123.3, 80.9, 54.3, 33.3, 28.6, 28.5; MS (EI) *m/z* (rel. intensity) 501 (M^+, 5), 428 (5), 401 (6), 340 (6), 323 (25), 296 (60), 105 (70); HRMS (EI) *m/z* calculated for $C_{29}H_{31}N_3O_5$ 501.2264, found 501.2256.

(5'-*tert*-Butyl-5,5''-diphenyl-[2,4';2',4'']teroxazol-2''-ylmethyl)-carbamic acid benzyl ester (17). A solution of **16** (30 mg, 0.060 mmol) in 1 mL of ether pre-saturated with HCl was stirred for 30 min and concentrated to dryness. In a separate flask, a solution of Cbz-Gly[1] (50 mg, 0.24 mmol) and *i*-Pr_2NEt (0.200 mL, 1.15 mmol) in 1 mL of CH_2Cl_2 was treated at –20 °C with isobutylchloroformate (0.030 mL, 0.24 mmol) and stirred for 20 min. This reaction mixture was treated with a solution of the deprotected amine in 1 mL of CH_2Cl_2, stirred for 2 h, diluted with EtOAc and washed with 10% HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. Chromatography on SiO_2 (EtOAc/hexanes, 1:4) gave 22.3 mg (63%) of the oily Cbz-glycine adduct: ^{1}H NMR δ 8.11 (d, 2 H, *J* = 7.4 Hz), 7.72 (t, 1 H, *J* = 7.1 Hz), 7.67-7.60 (m, 3 H), 7.55-7.25 (m, 10 H), 7.23 (s, 1 H), 6.82 (d, 1

H, *J* = 7.6 Hz), 5.64 (t, 1 H, *J* = 5.2 Hz), 5.15 (s, 2 H), 4.09 (d, 2 H, *J* = 5.3 Hz), 1.40 (s, 9 H).

A solution of this ketoamide (19.5 mg, 0.033 mmol) in 1 mL of toluene was treated with *p*-TsOH (10 mg, 0.0051 mmol) and stirred at 65 °C for 18 h. The reaction mixture was diluted with EtOAc and washed with saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. Chromatography on SiO_2 (EtOAc/hexanes, 1:1) provided 12.7 mg (67%) of **17**: R_f 0.25 (EtOAc/hexanes, 1:1); IR 1722, 1651, 1635 cm^{-1}; ^1H NMR δ 8.18 (d, 1 H, *J* = 8.0 Hz), 8.17 (d, 1 H, *J* = 7.5 Hz), 7.79 (2 d, 2 H, *J* = 8.6, 7.2 Hz), 7.53-7.36 (m, 12 H), 5.60 (br m, 1 H), 5.22 (s, 2 H), 4.71 (d, 2 H, *J* = 5.7 Hz), 1.56 (s, 9 H); ^{13}C NMR δ 160.7, 160.1, 155.4, 153.0, 151.6, 136.3, 130.2, 129.1, 128.8, 128.7, 128.5, 128.4, 128.1, 127.8, 127.1, 124.8, 124.6, 124.2, 123.3, 67.5, 38.7, 33.5, 28.7; MS (EI) *m/z* (rel. intensity) 574 (M^+, 100), 559 (11), 517 (16), 466 (10), 439 (50); HRMS (EI) *m/z* calculated for $C_{34}H_{30}N_4O_5$ 574.2216, found 574.2213.

3-[2-(Benzyloxycarbonylamino-methyl)-oxazol-5-yl]-indole-1-carboxylic acid ethyl ester (19). A solution of Cbz-Gly[1] (2.40 g, 11.5 mmol) and *N*-methylmorpholine (5.00 mL, 45.4 mmol) in 50 mL of DMF was treated at –30 °C with isobutylchloroformate (1.50 mL, 11.6 mmol), stirred for 25 min, and treated with α-aminoketone monoacetic acid salt **18**[3] (2.69 g, 11.5 mmol) was added. The mixture mixture was stirred at –20 °C for 2 h, diluted with 200 mL of CH_2Cl_2 and washed with 10% HCl. The suspension was filtered and the filtrate was concentrated and filtered. The combined precipitates were dried by azeotropic distillation with toluene to give 2.77 g (66%) of the desired ketoamide as a solid: mp 213.1-214.9 °C; IR (KBr) 1708, 1662, 1634 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.05 (s, 1 H), 8.45 (d, 1 H, *J* = 3.1 Hz), 8.20-8.15 (m, 2 H), 7.59 (t, 1 H, *J* = 5.9 Hz), 7.51-7.48 (m, 1 H), 7.38-7.29 (m, 5 H), 7.26-7.18 (m, 2 H), 5.07 (s, 2 H), 4.52 (d, 2 H, *J* = 5.5 Hz), 3.75 (d, 2 H, *J* = 6.2 Hz); ^{13}C NMR δ 190.6, 170.0, 157.2, 137.7, 137.1, 134.4, 129.0, 128.4 (d), 126.0, 123.5, 122.5, 121.8, 114.6, 112.8, 66.1, 46.3, 44.2; MS (EI) *m/z* (rel. intensity) 365 (M^+, 4), 257 (4), 144 (100); HRMS (EI) *m/z* calculated for $C_{20}H_{19}N_3O_4$ 365.1376, found 365.1391.

A suspension of this ketoamide (283 mg, 0.775 mmol), PPh_3 (350 mg, 1.55 mmol), and NEt_3 (0.500 mL, 3.59 mmol) in 30 mL of CH_2Cl_2 was treated portionwise with Cl_3CCCl_3 (370 mg, 1.57 mmol) over a 30 min period and stirred

[3] Prepared according to Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.*, **2000**, *2*, 2121-2123, and triturated with EtOH to a colorless solid.

for 1 h. The black solution was washed with 10% HCl and 2 N NaOH, dried (Na_2SO_4), filtered and concentrated. The residue was dissolved in 10 mL of CH_2Cl_2 and treated with $ClCO_2Et$ (0.120 mL, 1.26 mmol), DMAP (10 mg, 0.082 mmol), and NEt_3 (0.200 mL, 1.44 mmol). The reaction mixture was stirred for 30 min, diluted with CH_2Cl_2, washed with 10% HCl and 2 N NaOH, dried (Na_2SO_4), filtered and concentrated. Chromatography on SiO_2 (EtOAc/hexanes, 1:4 to 1:1) gave 171 mg (53%) of indolyloxazole **19** as a solid: R_f 0.26 (EtOAc/hexanes, 1:1); mp 134.0-135.5 °C; IR (KBr) 1744, 1724 cm^{-1}; ^1H NMR δ 8.24 (d, 1 H, *J* = 8.1 Hz), 7.88 (s, 1 H), 7.73 (d, 1 H, *J* = 7.7 Hz), 7.45-7.30 (m, 7 H), 7.29 (s, 1 H), 5.84 (br m, 1 H), 5.20 (s, 2 H), 4.62 (d, 2 H, *J* = 5.7 Hz), 4.53 (q, 2 H, *J* = 7.1 Hz), 1.51 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 159.6, 156.4, 150.7, 146.6, 136.3, 135.6, 128.6, 128.2, 126.5, 125.5, 123.7, 122.4, 120.1, 115.6, 109.7, 67.3, 63.7, 38.6, 14.5; MS (EI) *m/z* (rel. intensity) 419 (M^+, 30), 311 (40), 284 (100); HRMS (EI) *m/z* calculated for $C_{23}H_{21}N_3O_5$ 419.1481, found 419.1492.

3-(2-{[*tert*-Butoxycarbonyl-(2,2-diphenyl-propionyl)-amino]-methyl}-oxazol-5-yl-indole-1-carboxylic acid ethyl ester (20). A solution of **19** (340 mg, 0.690 mmol) in 5 mL of EtOH was treated with 10% Pd/C (73 mg, 0.069 mmol) and degassed by repeated vacuum/H_2 exchange. The suspension was stirred vigorously for 4 h at room temperature under 1 atm of hydrogen, filtered and concentrated. A solution of the oily residue in 5 mL of DMF was treated with 2,2-diphenylpropionic acid (230 mg, 1.02 mmol), *i*-Pr_2NEt (0.250 mL, 1.44 mmol), and benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate ("PyBOP", 520 mg, 1.00 mmol). The mixture was stirred at room temperature for 18 h, diluted with EtOAc, washed with 10% HCl and 2 N NaOH, dried (Na_2SO_4), filtered and concentrated. Chromatography on SiO_2 (EtOAc/CH_2Cl_2, 1:9) provided 253 mg (74%) of the desired coupling product as colorless foam: R_f 0.18 (EtOAc/hexanes, 1:1); IR 1748, 1660 cm^{-1}; ^1H NMR δ 8.30 (d, 1 H, *J* = 8.2 Hz), 7.94 (s, 1 H), 7.80-7.77 (m, 1 H), 7.5-7.3 (m, 13 H), 6.21 (t, 1 H, *J* = 5.4 Hz), 4.72 (d, 2 H, *J* = 5.6 Hz), 4.58 (q, 2 H, *J* = 7.1 Hz), 2.10 (s, 3 H), 1.55 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 175.4, 150.7, 144.7, 135.6, 129.1, 128.6, 128.3, 128.2, 127.2, 126.5, 125.5, 123.8, 122.4, 122.3, 120.1, 115.6, 109.9, 63.8, 57.1, 37.4, 27.2, 14.5; MS (EI) *m/z* (rel. intensity) 493 (M^+, 75), 284 (45), 269 (41), 181 (100); HRMS (EI) *m/z* calculated for $C_{30}H_{27}N_3O_4$ 493.2002, found 493.2014.

A solution of this coupling product (193 mg, 0.391 mmol) in 5 mL of THF was treated at –78 °C with a 1.6 M solution of BuLi in hexane (0.250 mL, 0.400

mmol), Boc_2O (170 mg, 0.787 mmol), and DMAP (44 mg, 0.39 mmol). The reaction mixture was stirred at room temperature for 18 h, diluted with EtOAc, washed with 10% HCl and water, dried (Na_2SO_4), filtered and concentrated. Chromatography on SiO_2 (EtOAc/hexanes, 1:9 to 1:1) gave 69 mg (36%) of recovered starting material and 97 mg (42%) of oily imide **20**: R_f 0.55 (EtOAc/hexanes, 1:1); IR 1744 cm^{-1}; ^1H NMR δ 8.29 (d, 1 H, *J* = 8.0 Hz), 7.95 (s, 1 H), 7.83 (d, 1 H, *J* = 7.5 Hz), 7.45-7.18 (m, 13 H), 5.15 (s, 2 H), 4.55 (q, 2 H, *J* = 7.1 Hz), 2.12 (s, 3 H), 1.50 (t, 3 H, *J* = 7.1 Hz), 1.08 (s, 9 H); ^{13}C NMR δ 180.0, 159.3, 151.0, 150.7, 146.0, 144.3, 135.7, 128.7, 128.5, 128.2, 127.9, 126.6, 126.3, 125.5, 123.8, 122.8, 122.1, 120.3, 115.6, 110.1, 83.6, 63.7, 60.6, 43.8, 31.2, 27.4, 14.5; MS (EI) *m/z* (rel. intensity) 593 (M^+, 3), 493 (35), 361 (22), 345 (15), 312 (24), 269 (47), 181 (100); HRMS (EI) *m/z* calculated for $C_{35}H_{35}N_3O_6$ 593.2526, found 593.2535.

3-[2-(1-*tert*-Butoxycarbonylamino-2-oxo-3,3-diphenyl-butyl)-oxazol-5-yl]-indole-1-carboxylic acid ethyl ester (21). A solution of *i*-Pr_2NH (0.200 mL, 1.43 mmol) in 1 mL of THF was treated with a 1.6 M solution of BuLi in hexane (0.600 mL, 0.960 mmol) and cooled to –78 °C. A solution of **20** (121 mg, 0.204 mmol) in 1 mL of THF was added and the reaction mixture was stirred for 30 min, quenched with saturated NH_4Cl and extracted into EtOAc. The EtOAc layer was washed with 10% HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. Chromatography on SiO_2 (EtOAc/hexanes, 1:4) gave 94 mg (78%) of oily **21**: R_f 0.51 (EtOAc/hexanes, 1:1); IR 1743, 1714 cm^{-1}; ^1H NMR δ 8.29 (d, 1 H, *J* = 8.0 Hz), 7.75 (s, 1 H), 7.70 (d, 1 H, *J* = 7.6 Hz), 7.46-7.14 (m, 13 H), 6.05 (d, 1 H, *J* = 8.7 Hz), 5.95 (d, 1 H, *J* = 8.1 Hz), 4.59 (q, 2 H, *J* = 7.1 Hz), 2.10 (s, 3 H), 1.57 (t, 3 H, *J* = 7.1 Hz), 1.48 (s, 9 H); ^{13}C NMR δ 204.1, 157.1, 154.7, 150.8, 146.7, 142.5, 142.3, 135.7, 128.9, 128.6, 128.5, 128.3, 127.2, 126.5, 125.6, 123.9, 123.0, 120.3, 115.7, 109.7, 80.8, 63.9, 61.7, 54.5, 28.4, 27.9, 26.3, 14.6; MS (EI) *m/z* (rel. intensity) 401 (M^+, 80), 296 (100), 105 (95); HRMS (EI) *m/z* calculated for $C_{35}H_{35}N_3O_6$ 593.2526, found 593.2518.

3-[2'-(1-Benzyloxycarbonylamino-2-methyl-propyl)-5'-(1,1-diphenyl-ethyl)-[2,4']bioxazolyl-5-yl]-indole-1-carboxylic acid ethyl ester (22). A solution of **21** (137 mg, 0.231 mmol) in 2 mL of Et_2O pre-saturated with HCl gas was stirred for 2 h. The reaction mixture was concentrated and the residue kept

under vacuum overnight. A solution of Cbz-*L*-valine[4] (90 mg, 0.359 mmol) in 1 mL of CH_2Cl_2 was treated with *i*-Pr_2NEt (0.150 mL, 1.36 mmol), and at –30 °C, isobutylchloroformate (0.045 mL, 0.347 mmol). The reaction mixture was stirred for 20 min. at –20 °C, and treated with a solution of the deprotected amine in 1 mL of CH_2Cl_2. The reaction mixture was slowly warmed to 0 °C over 4 h, diluted with EtOAc, washed with 10% HCl and 1 N NaOH, dried (Na_2SO_4), filtered and concentrated. Chromatography on SiO_2 (EtOAc/hexanes, 1:4) gave 119 mg (71%) of the valine adduct as an oily 1:1 mixture of diastereomers: R_f 0.15 (EtOAc/hexanes, 3:7); ^{1}H NMR δ 8.29 (d, 1 H, *J* = 8.1 Hz), 7.75 (s, 1 H), 7.68 (d, 1 H, *J* = 7.5 Hz), 7.5-7.1 (m, 19 H), 6.28, 6.27 (2 d, 1 H, *J* = 8.1, 7.8 Hz), 5.38, 5.32 (2 d, 1 H, *J* = 8.8, 10.9 Hz), 5.16-5.10 (m, 2 H), 4.62-4.55 (m, 2 H), 4.22-4.15 (m, 1 H), 2.25-2.05 (m, 1 H), 2.08-2.07 (m, 3 H), 1.59-1.54 (m, 3 H), 1.02-0.87 (m, 6 H).

A solution of this ketoamide (25 mg, 0.034 mmol) in 2 mL of toluene was stirred at 65 °C in the presence of 4 Å MS (200 mg) and TsOH (1.0 mg, 0.0051 mmol) for 4 d. The reaction mixture was diluted with EtOAc and washed with saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. Chromatography on SiO_2 (EtOAc/hexanes, 1:4) gave 14 mg (58%) of the desired oily bisoxazole **22**[5]: R_f 0.20 (EtOAc/hexanes, 3:7); $[\alpha]_D$ -13 (*c* 0.93, CH_2Cl_2); IR 1740, 1643 cm^{-1}; ^{1}H NMR 8.25 (d, 1 H, *J* = 8.3 Hz), 7.62 (d, 1 H, *J* = 7.8 Hz), 7.59 (s, 1 H), 7.45-7.16 (m, 18 H), 5.66 (d, 1 H, *J* = 8.9 Hz), 5.16, 5.15 (AB, 2 H, *J* = 12.2 Hz), 4.91 (dd, 1 H, *J* = 8.8, 5.6 Hz), 4.57 (q, 2 H, *J* = 7.1 Hz), 2.3-2.1 (m, 1 H), 2.24 (s, 3 H), 1.53 (t, 3 H, *J* = 7.1 Hz), 0.95 (d, 6 H, *J* = 6.7 Hz); ^{13}C NMR δ 162.2, 157.3, 156.1, 153.8, 150.7, 146.3, 144.7, 136.3, 135.5, 128.6, 128.2 (2C), 128.1, 127.8 (2C), 127.0, 126.5, 125.7, 125.4, 123.7, 123.4, 122.7, 120.2. 115.5, 109.6, 67.1, 63.7, 54.8, 49.8, 33.2, 28.7, 18.5, 18.1, 14.5; MS (EI) *m/z* (rel. intensity) 708 (M^+, 70), 690 (8), 621 (10), 600 (35); HRMS (EI) *m/z* calculated for $C_{43}H_{40}N_4O_6$ 708.2948, found 708.2957.

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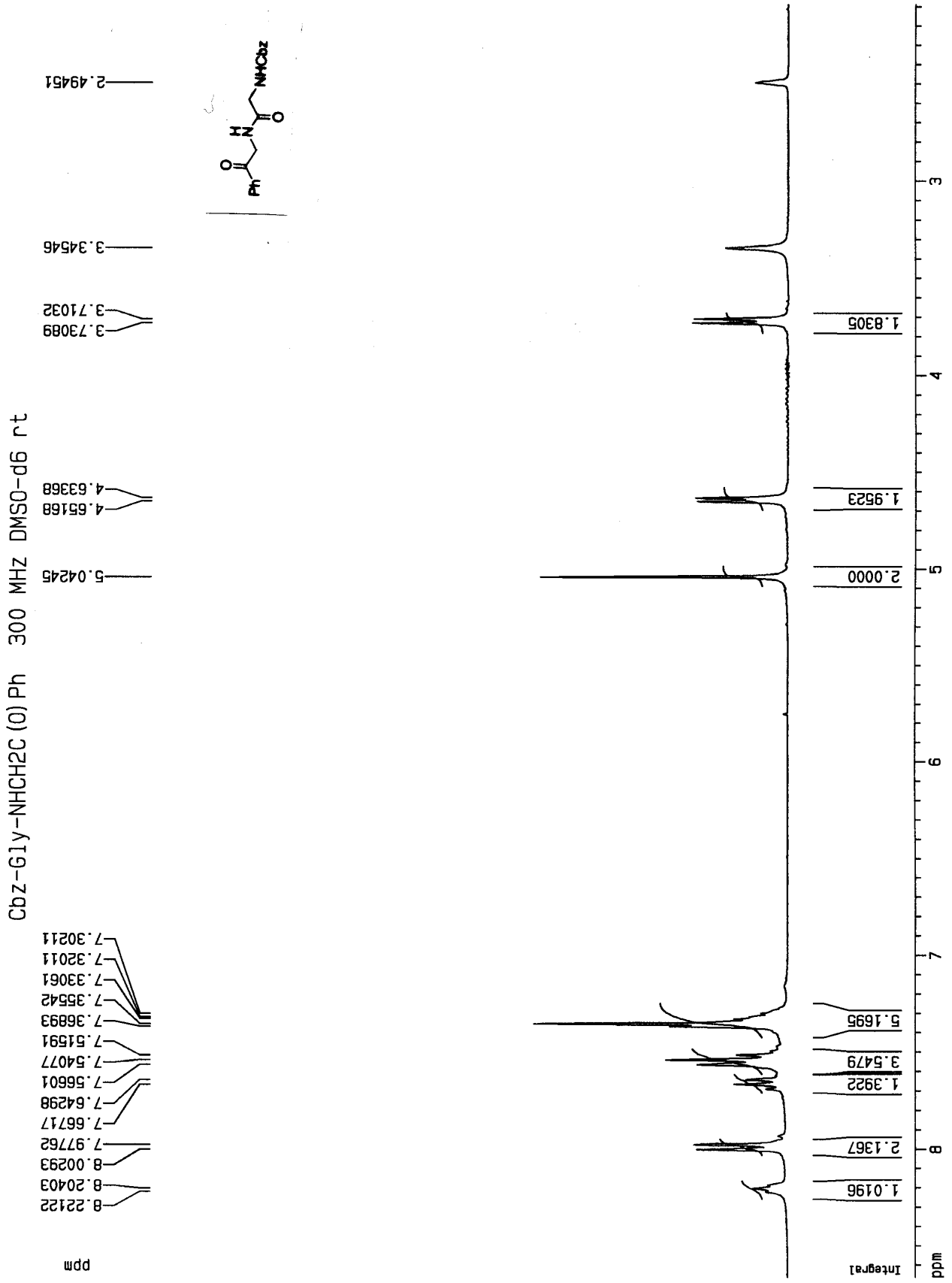
[4] Faessler, A.; Bold, G.; Capraro, H.-G.; Cozens, R.; Mestan, J. *J. Med. Chem.*, **1996**, *39*, 3203-3216.

[5] Mosher amide analysis with both (*R*)-MTPA and (*S*)-MTPA indicated >95:5 enantiomeric purity. For a procedure, see Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.*, **1969**, *34*, 2543-2549.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8.00293
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7.56601
7.54077
7.51591
7.36893
7.35542
7.33061
7.32011
7.30211
5.04245
4.65168
4.63368
3.73089
3.71032
3.45446
2.49451
Integral
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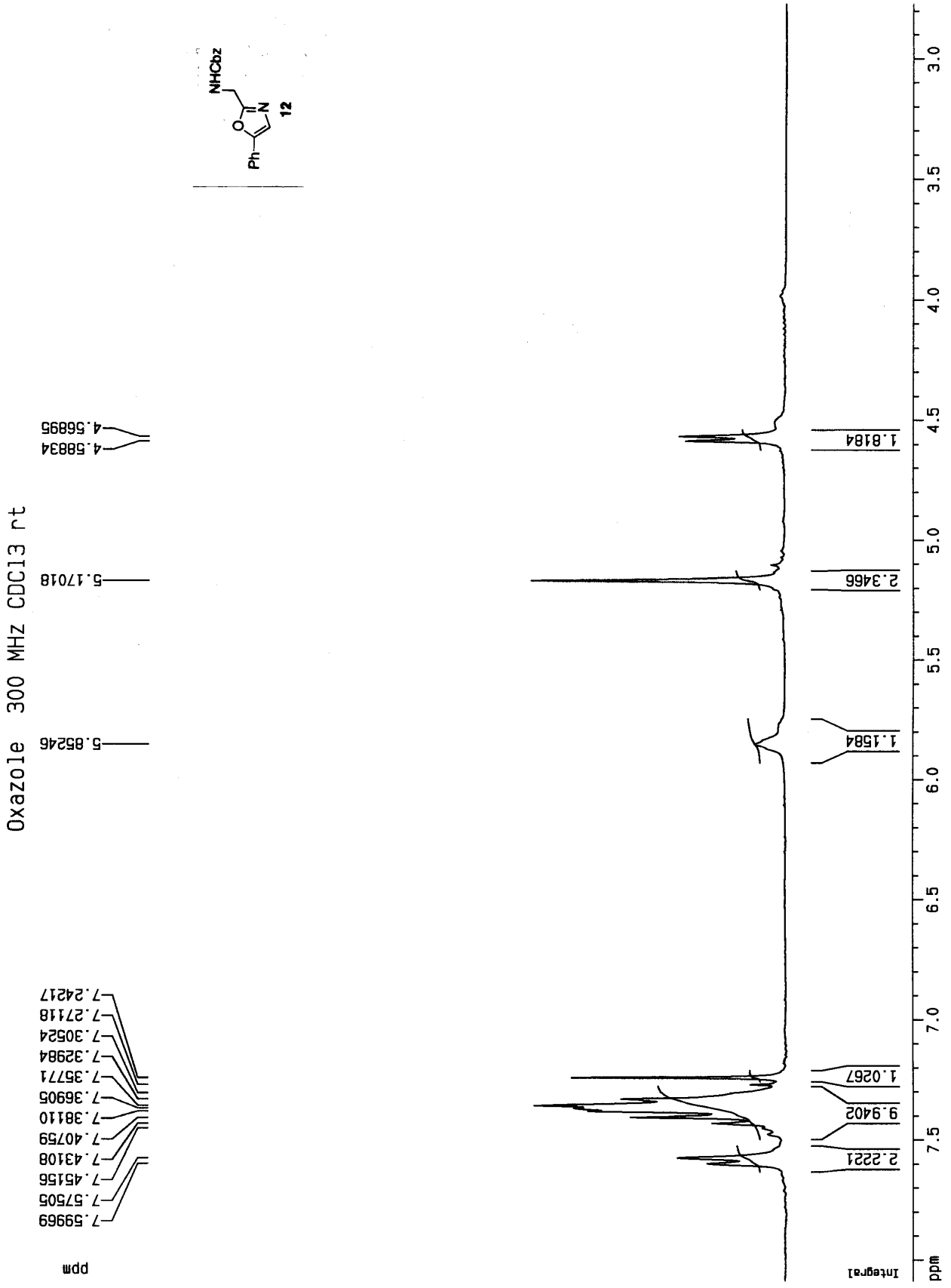
2.0000
1.9523
1.8305
ppm
NHCbz
Ph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NHCbz
O
N
Ph
12
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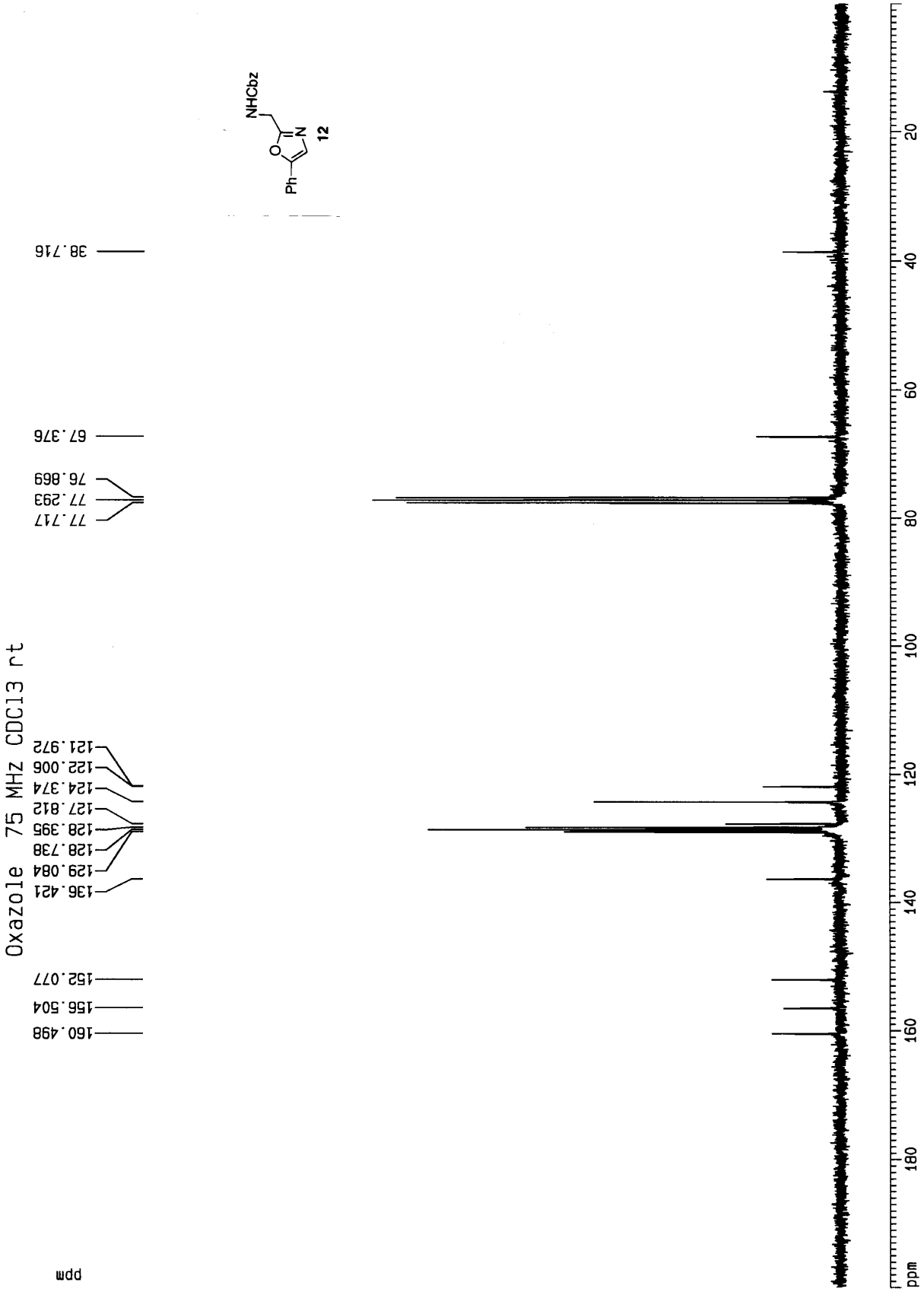
4.58834
5.17018
5.85246
7.24217
7.27118
7.30524
7.32984
7.35771
7.36905
7.38110
7.40759
7.43108
7.45156
7.57505
7.59969
ppm
1.8184
2.3466
1.1584
1.0267
9.9402
2.2221
Integral
ppm
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5


Oxazole 75 MHz CDCl3 rt
NHCbz
O
N
Ph
12
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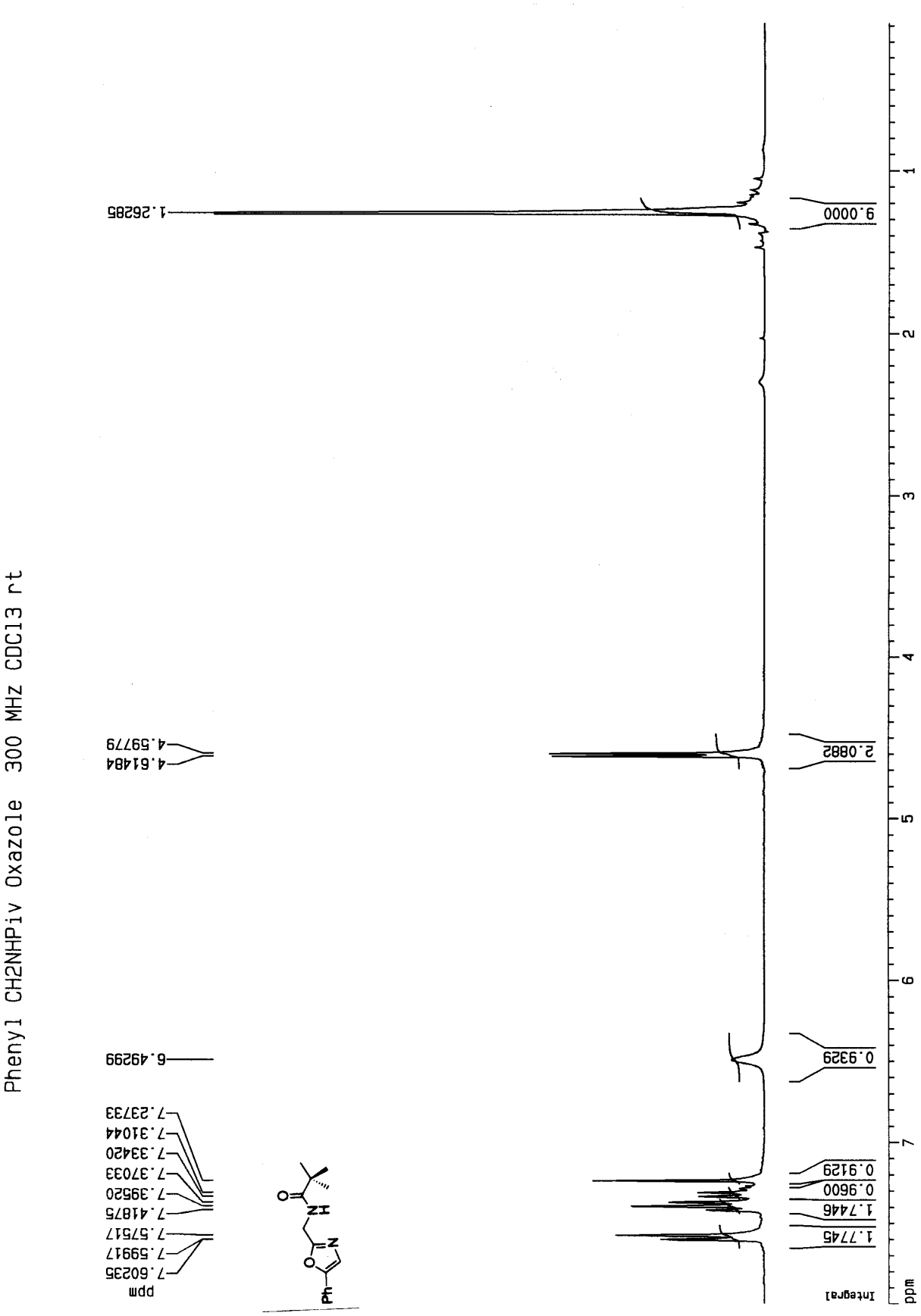
67.376
76.869
77.293
77.717
121.972
122.006
124.374
127.812
128.395
128.738
129.084
136.421
152.077
156.504
160.498
ppm
20
40
60
80
100
120
140
160
180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7.59917
7.57517
7.41875
7.39520
7.37033
7.33420
7.31044
7.23733
6.49299
4.61484
4.59779
1.26285
Integral
1.7745
1.7446
0.9600
0.9129
0.9329
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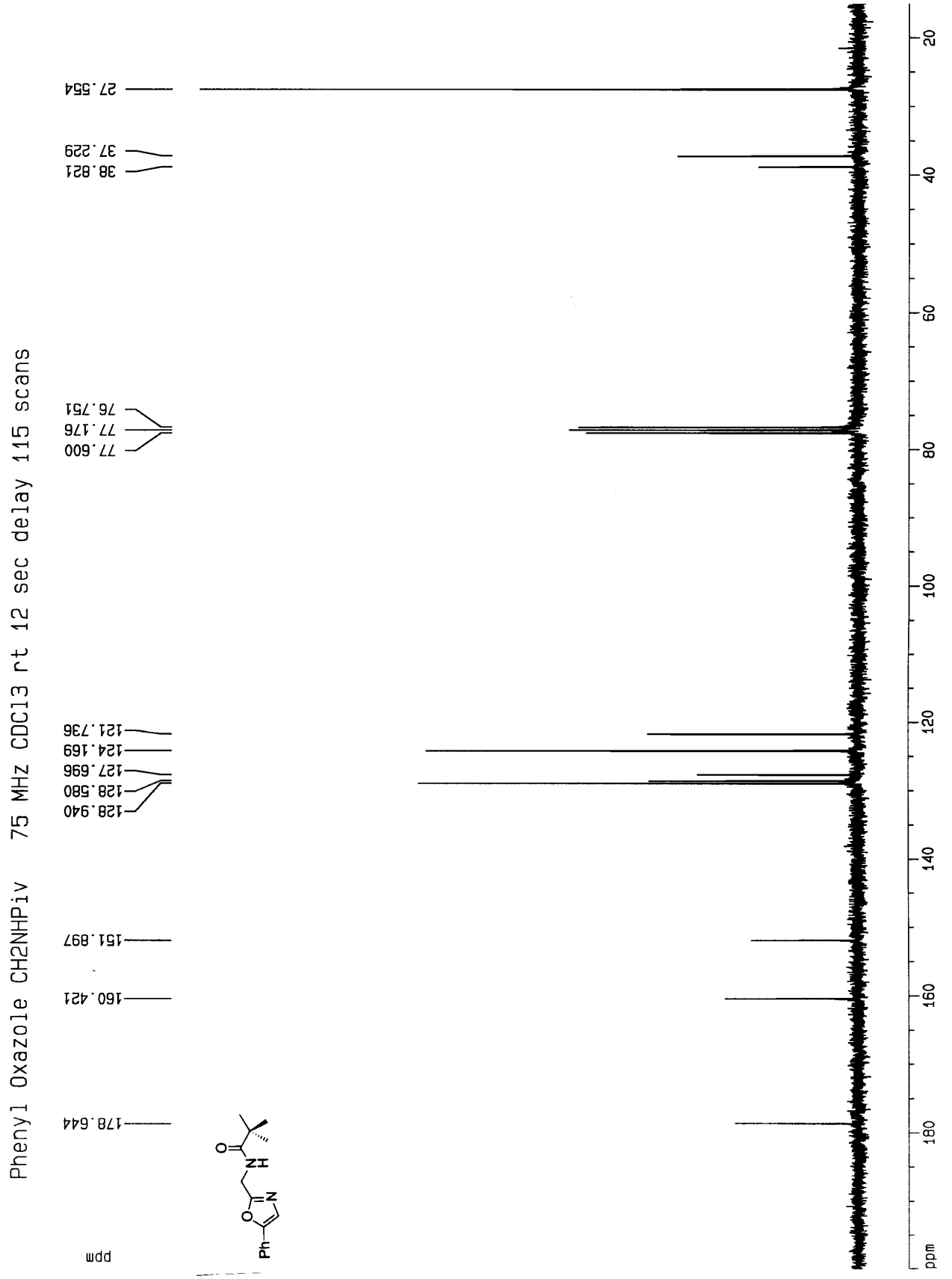
9.0000
ppm


Phenyl Oxazole CH2NHPiv 75 MHz CDCl3 rt 12 sec delay 115 scans
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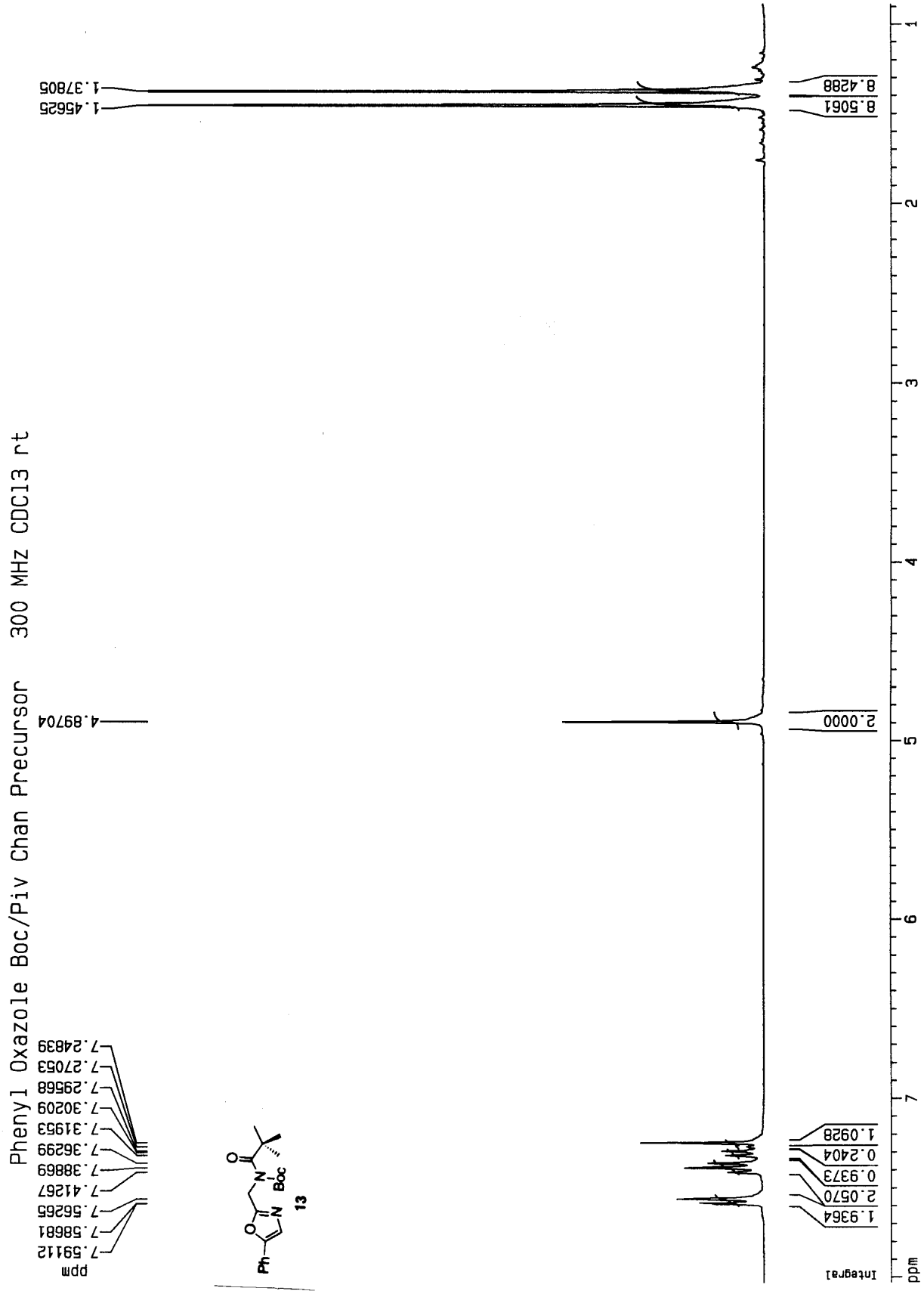
160.421
151.897
128.940
128.580
127.696
124.169
121.736
77.600
77.176
76.751
38.821
37.229
27.554
ppm
20
40
60
80
100
120
140
160
180
O
NH
N
O
Ph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7.27053
7.29568
7.30209
7.31953
7.36299
7.38869
7.41267
7.56265
7.58681
7.59112
ppm
4.89704
1.37805
1.45625
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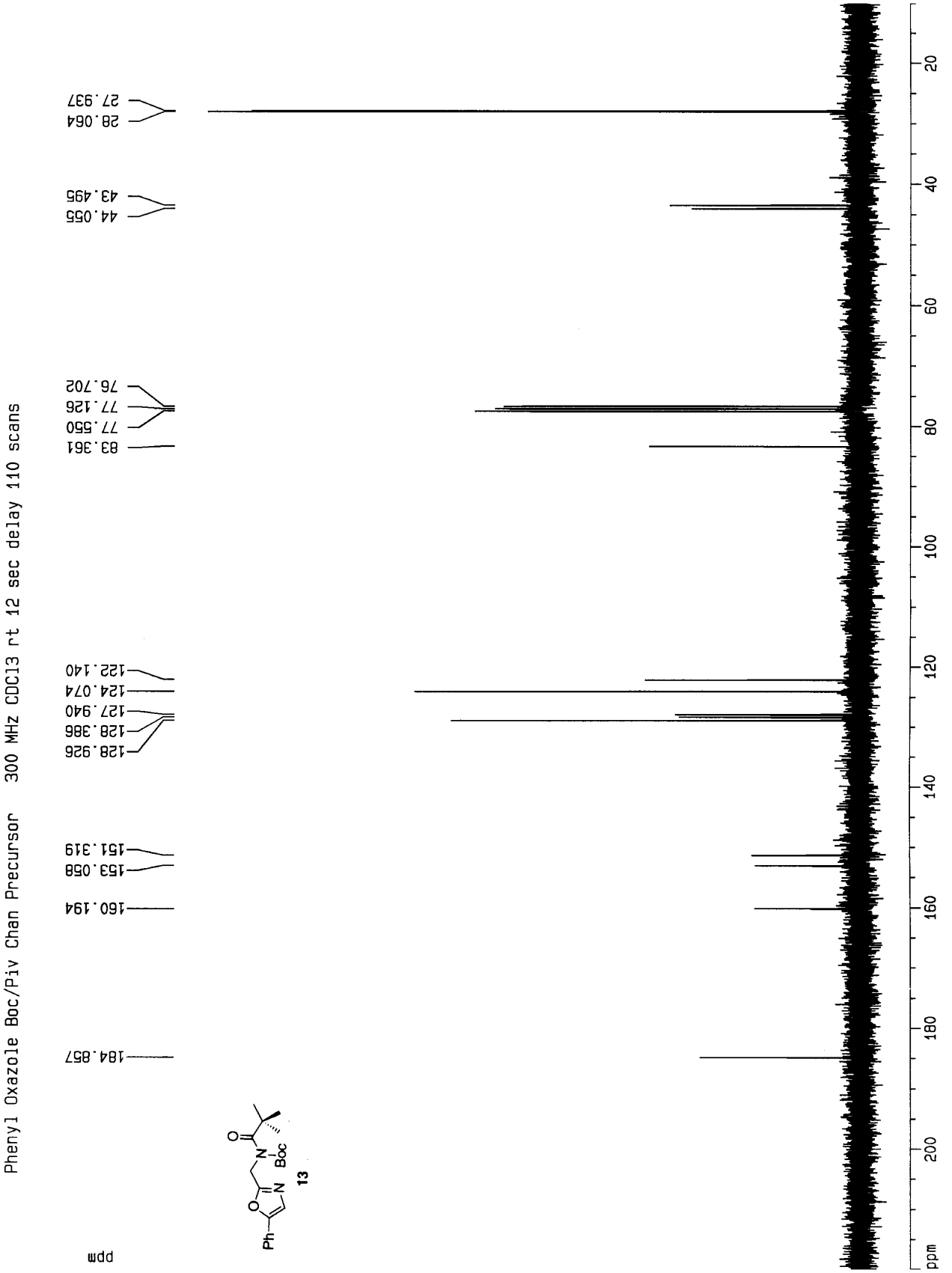
0.2404
0.9373
2.0570
1.9364
Integral
ppm
13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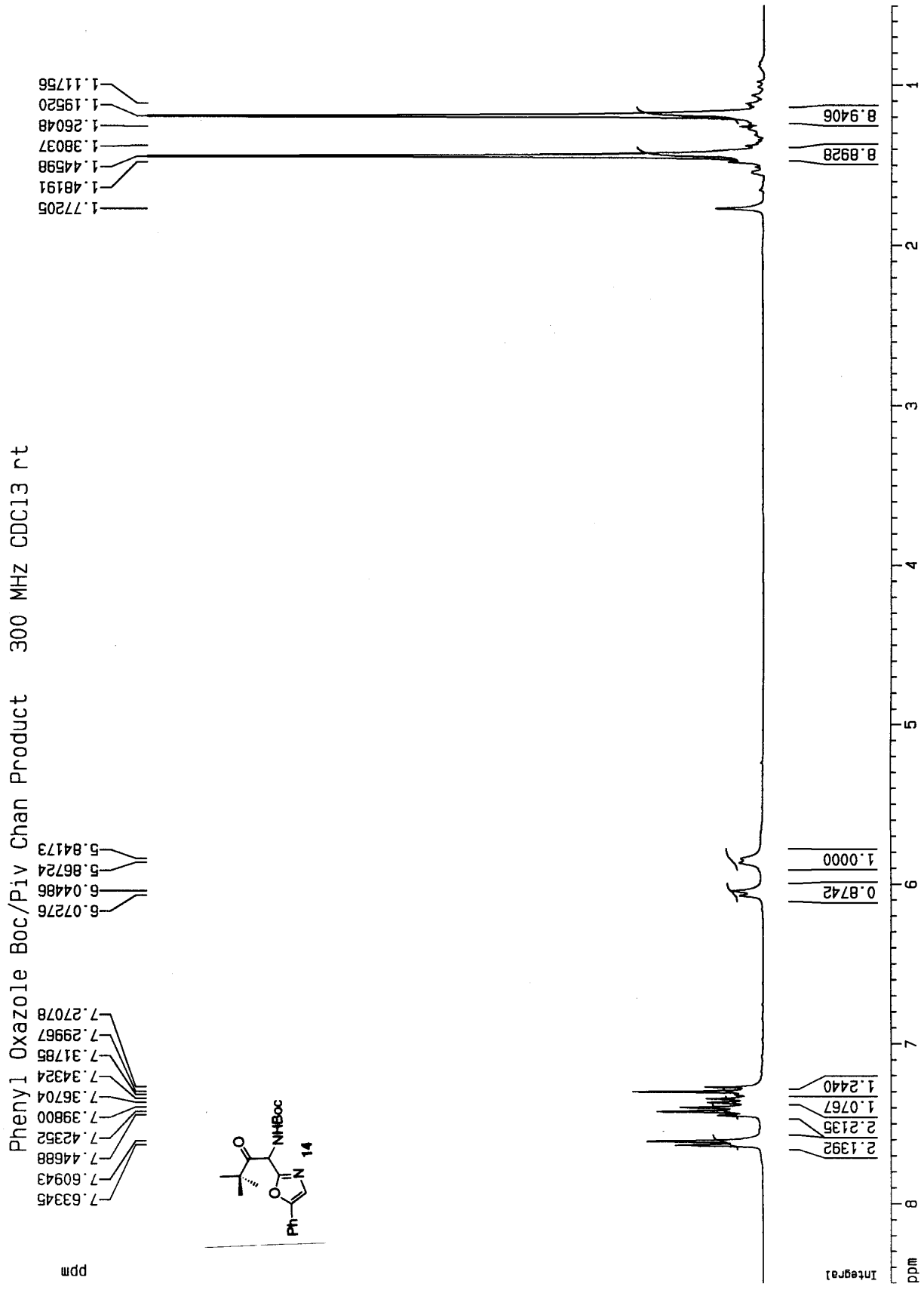
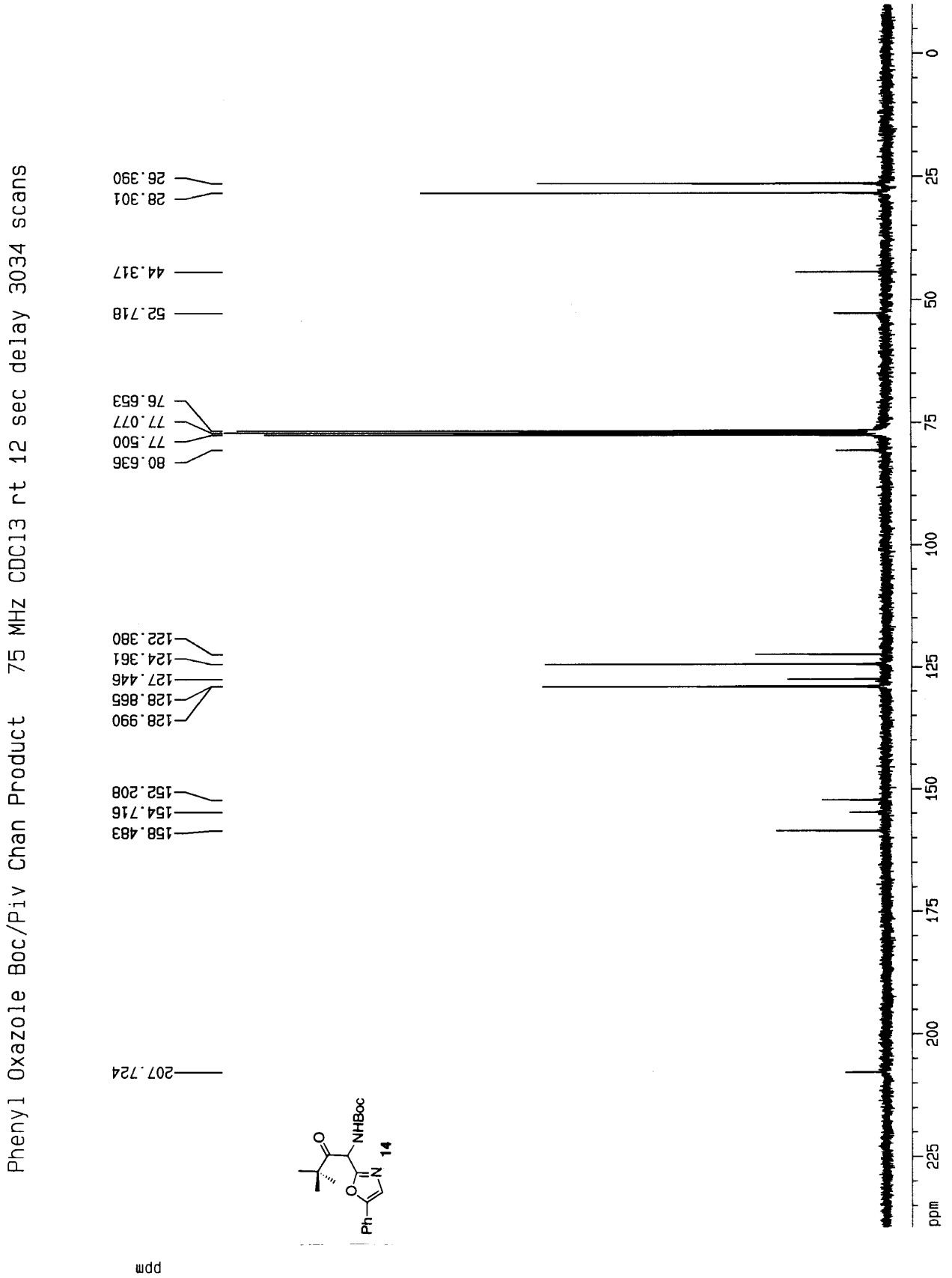
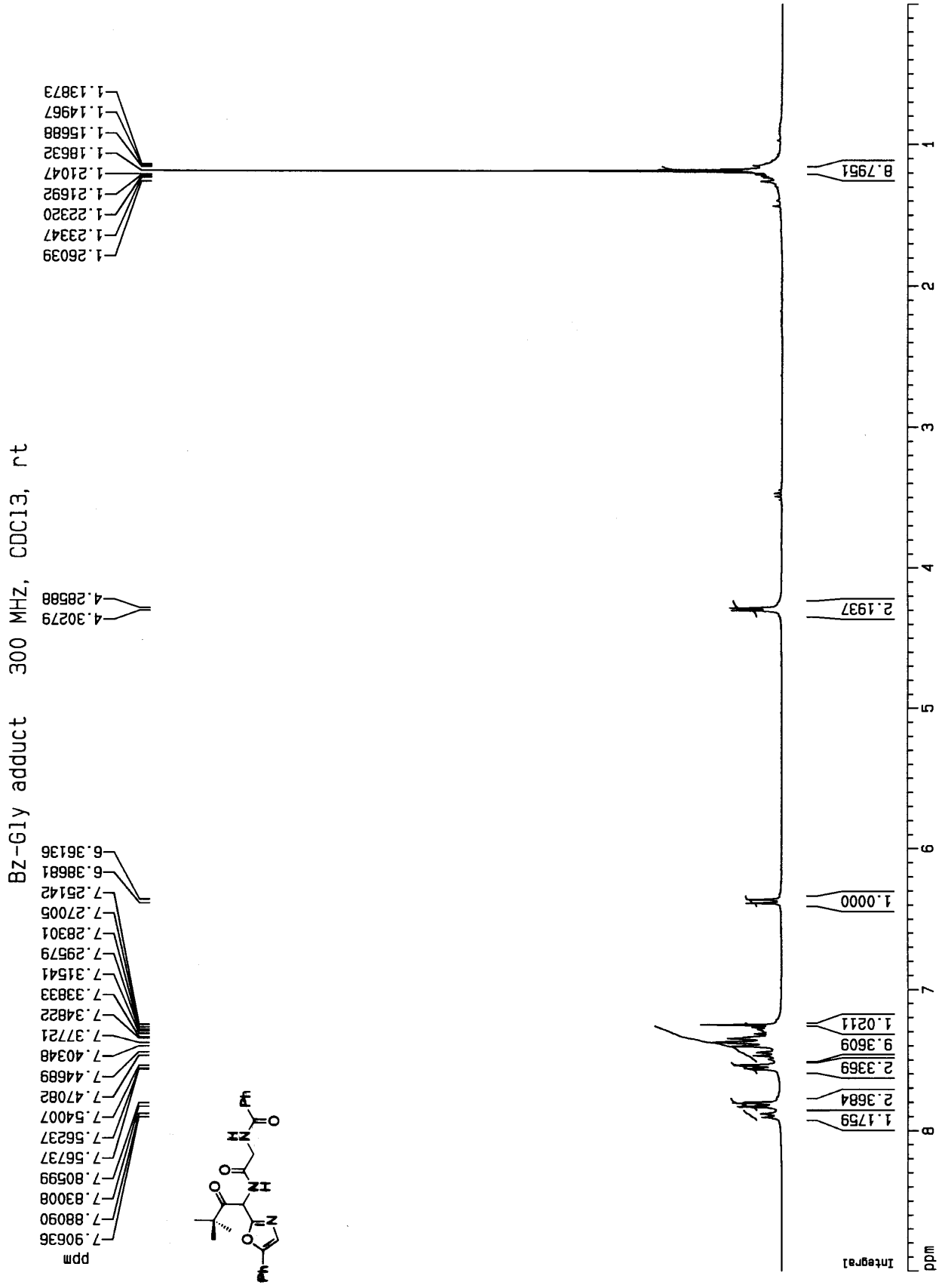
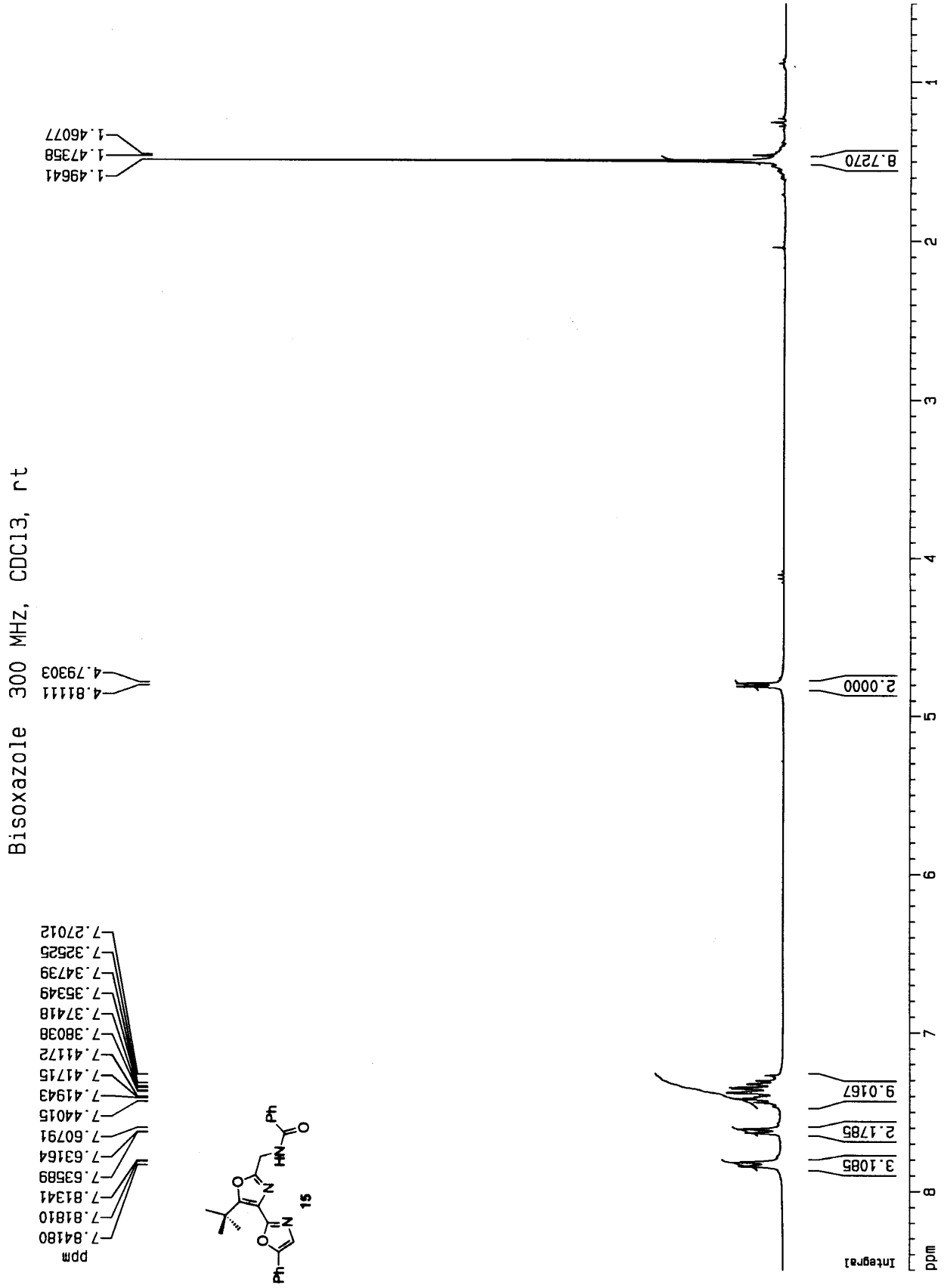
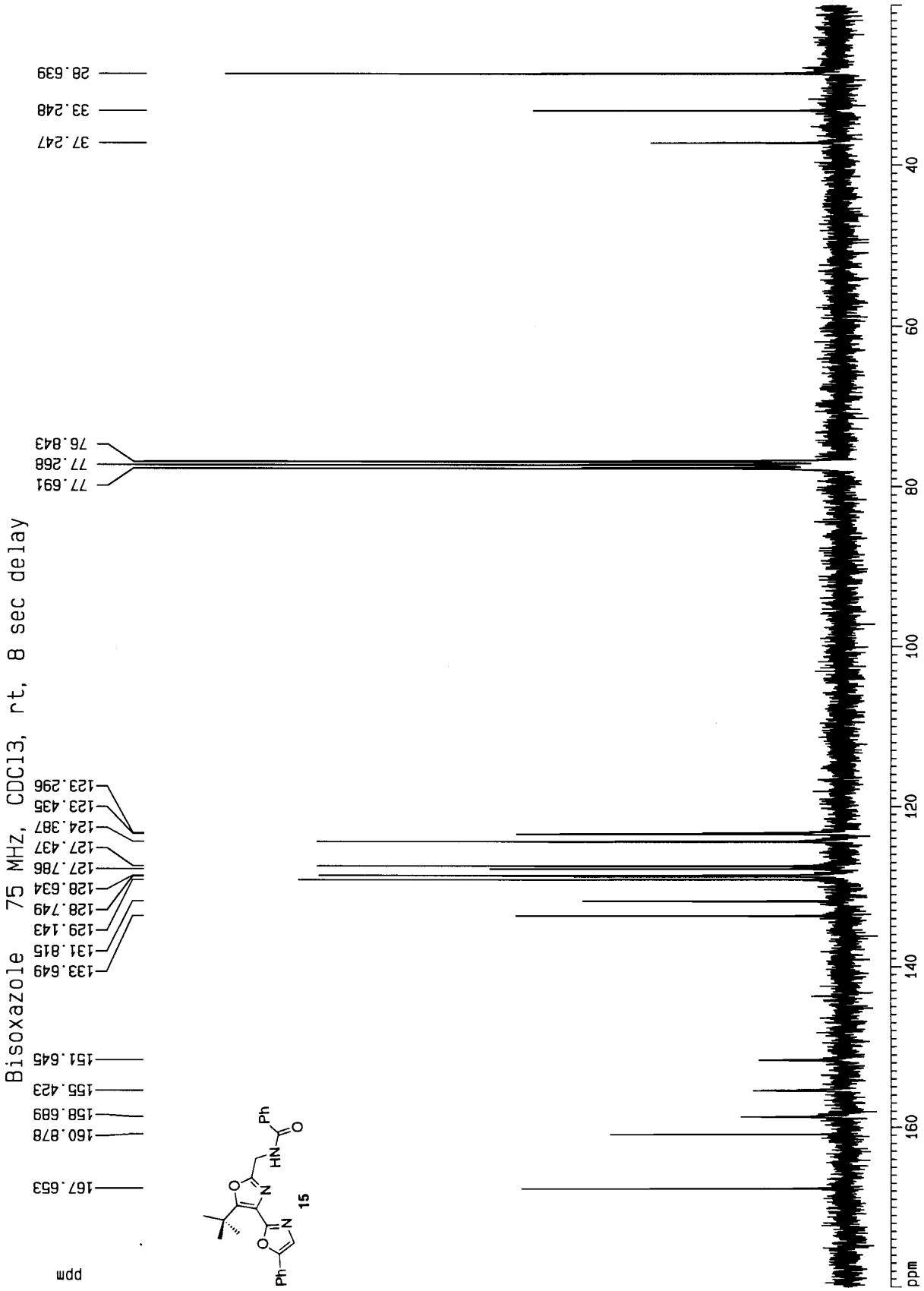
27.937
28.064
43.495
44.055
76.702
77.126
77.550
83.361
122.140
124.074
127.940
128.386
128.926
151.319
153.058
160.194
184.857
13
Ph
N
O
N
Boc
O
ppm

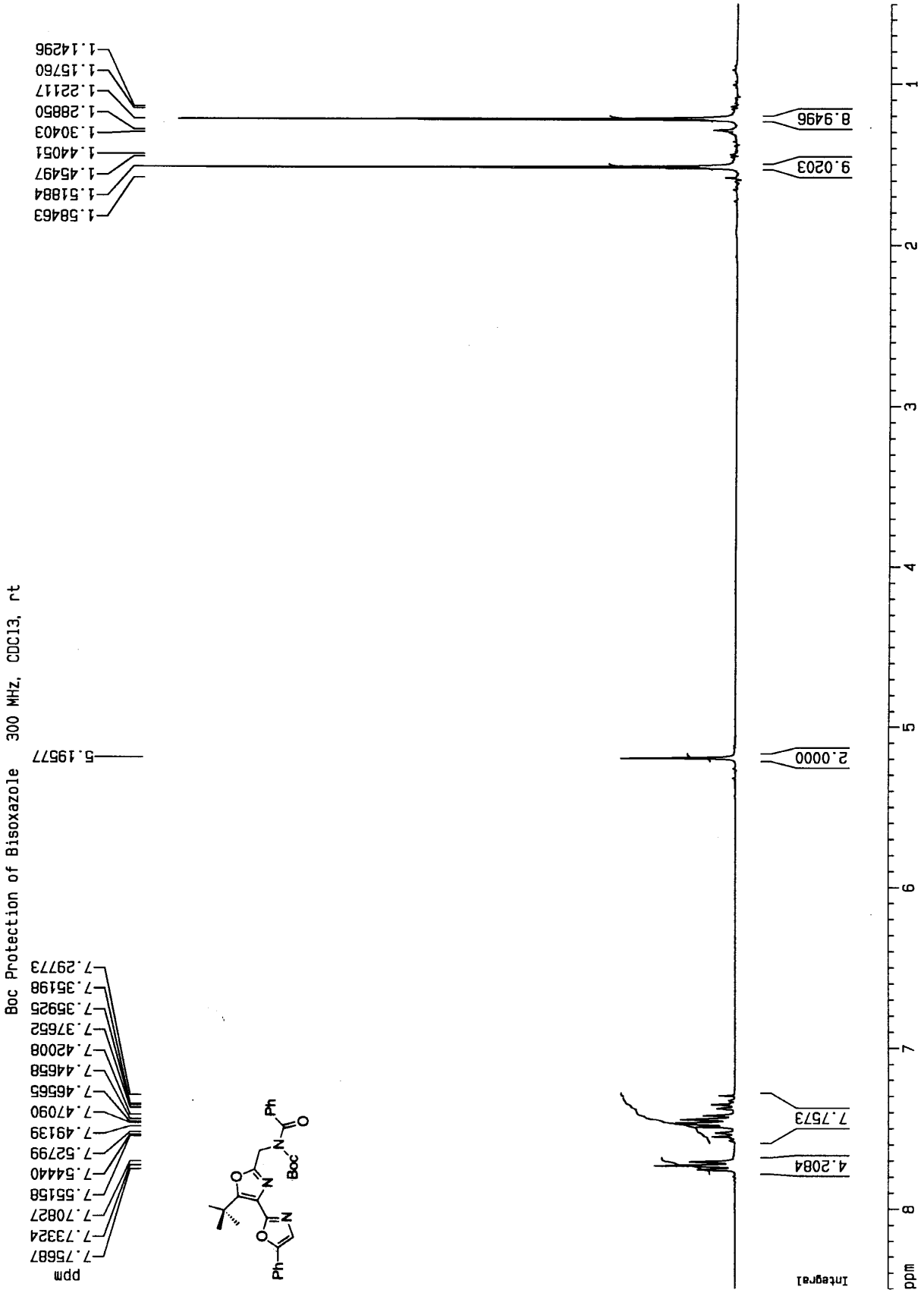

Phenyl Oxazole Boc/Piv Chan Product 300 MHz CDCl3 rt
1.17756
1.19520
1.26048
1.38037
1.45598
1.48191
1.77205
5.84173
5.86724
6.04486
6.07276
7.27078
7.29967
7.31785
7.34324
7.36704
7.39800
7.42352
7.44688
7.60943
7.63345
8.9406
8.8928
1.0000
0.8742
1.2440
1.0767
2.2135
2.1392
NHBoc
Ph
14
ppm
Integral


Phenyl Oxazole Boc/Piv Chan Product 75 MHz CDCl3 rt 12 sec delay 3034 scans
26.390
28.301
44.317
52.718
76.653
77.077
77.500
80.636
122.380
124.361
127.446
128.865
128.990
152.208
154.716
158.483
207.724
NHBoc
14
Ph
O
N
O
ppm
0
25
50
75
100
125
150
175
200
225
ppm


Bz-Gly adduct 300 MHz, CDC13, rt
ppm
Integral
8.7951
2.1937
1.0000
1.0211
9.3609
2.3369
2.3684
1.1759
4.30279
4.28588
6.36136
6.38681
7.25142
7.27005
7.28301
7.29579
7.31541
7.33833
7.34822
7.37721
7.40348
7.44689
7.47082
7.54007
7.56237
7.56737
7.80599
7.83008
7.88090
7.90636
1.26039
1.23347
1.22320
1.21692
1.21047
1.18632
1.15688
1.14967
1.13873


Bisoxazole 300 MHz, CDCl3, rt
1.46077
1.47358
1.49641
4.79303
4.81111
7.27012
7.32525
7.34739
7.35349
7.37418
7.38038
7.41172
7.41715
7.41943
7.44015
7.60791
7.63164
7.63589
7.81341
7.81810
7.84180
ppm
Ph
O
HN
N
O
N
O
Ph
15
8.7270
2.0000
9.0167
2.1785
3.1085
Integral
ppm


Bisoxazole 75 MHz, CDCl3, rt, 8 sec delay
28.639
33.248
37.247
76.843
77.268
77.691
123.296
123.435
124.387
127.437
127.786
128.634
128.749
129.143
131.815
133.649
151.645
155.423
158.689
160.878
167.653
15
ppm


Boc Protection of Bisoxazole 300 MHz, CDCl3, rt
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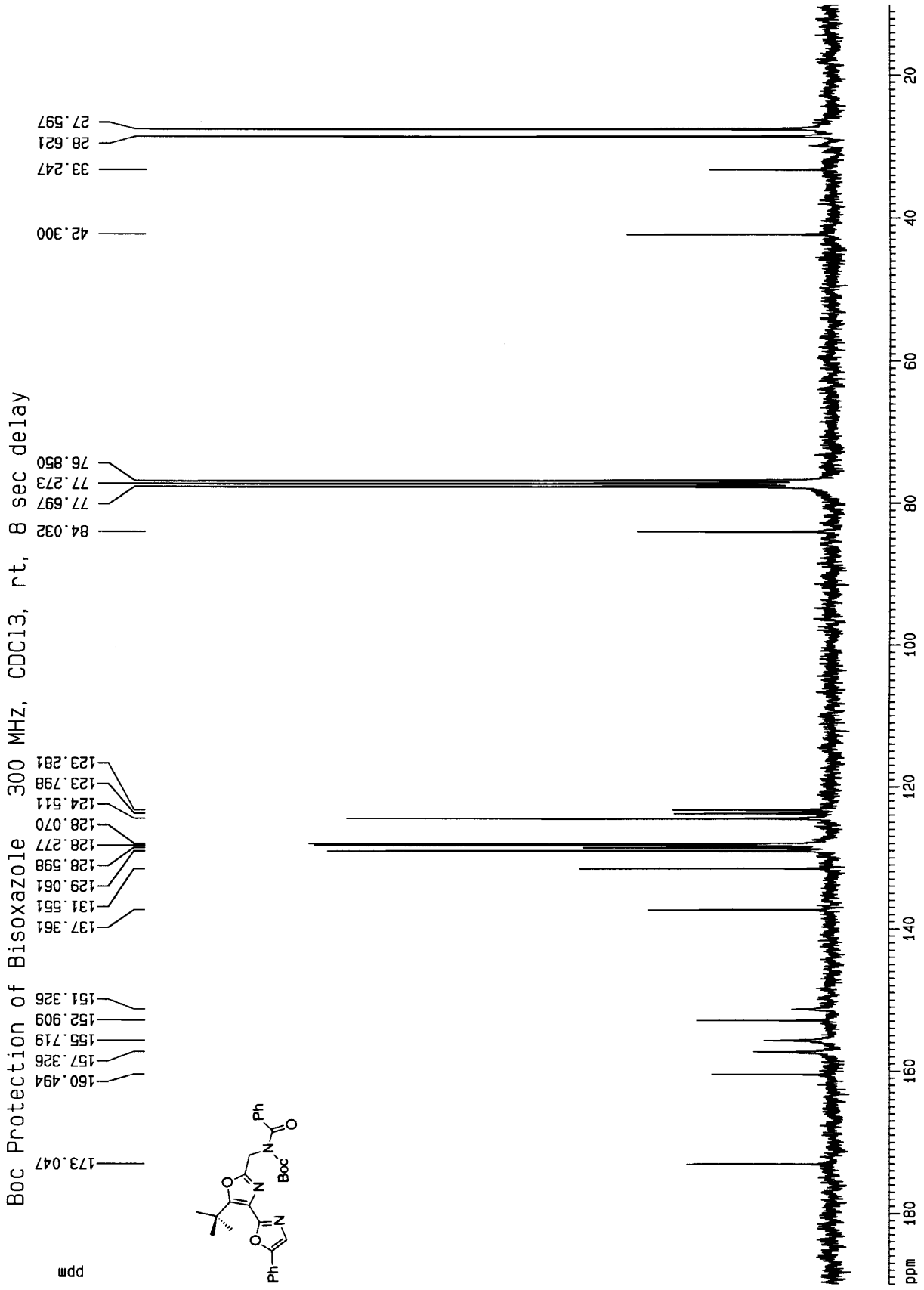
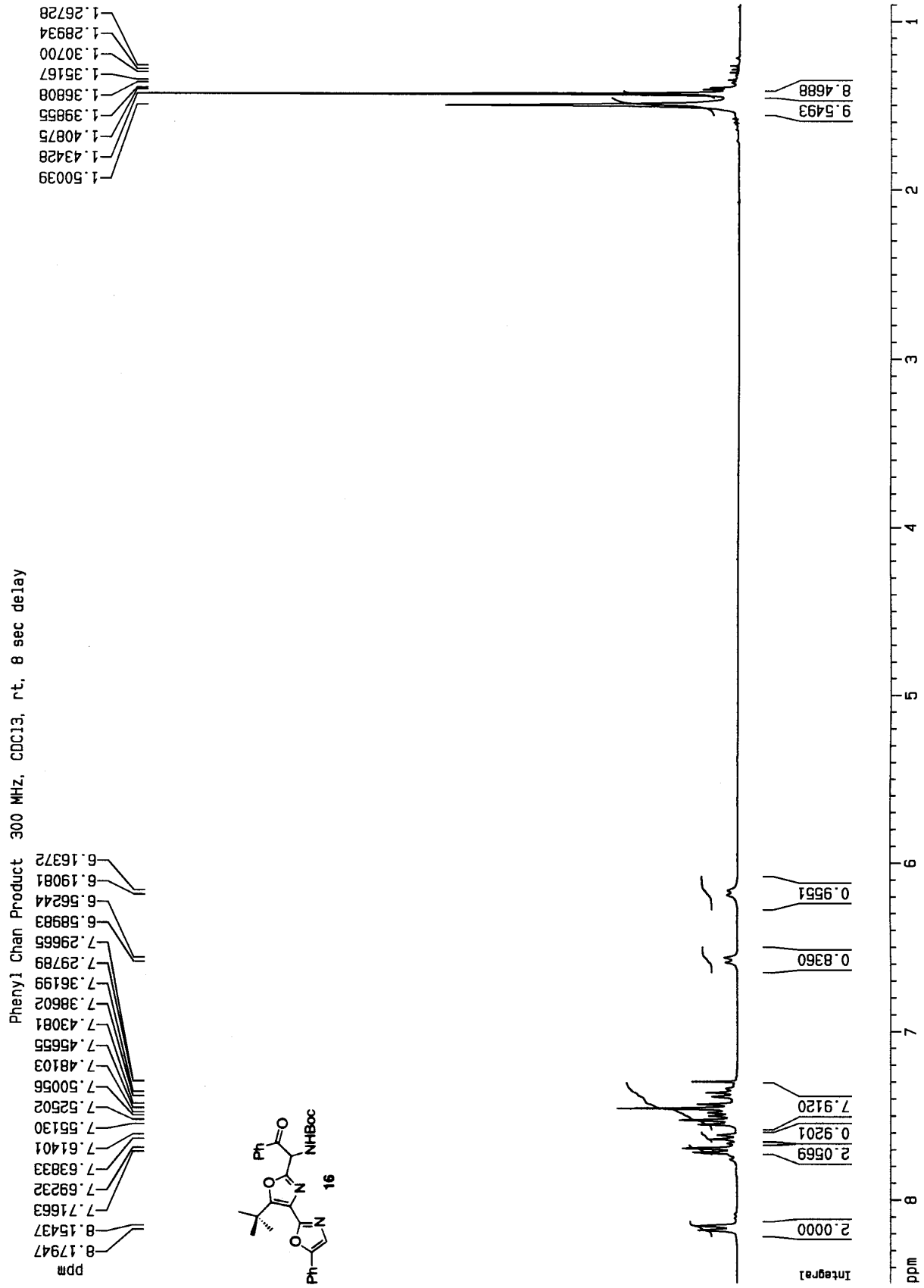
1.15760
1.22117
1.28850
1.30403
1.44051
1.45497
1.51884
1.58463
8.9496
9.0203
5.19577
2.0000
7.29773
7.35198
7.35925
7.37652
7.42008
7.44658
7.46565
7.47090
7.49139
7.52799
7.54440
7.55158
7.70827
7.73324
7.75687
7.7573
4.2084
Integral
ppm
Ph
O
N
Boc
O
N
O
Ph


Boc Protection of Bisoxazole 300 MHz, CDCl3, rt, 8 sec delay
27.597
28.621
33.247
42.300
76.850
77.273
77.697
84.032
123.281
123.798
124.511
128.070
128.277
128.598
129.061
131.551
137.361
151.326
152.909
155.719
157.326
160.494
173.047
Ph
O
N
Boc
O
N
O
N
Ph
ppm
20
40
60
80
100
120
140
160
180
ppm


Phenyl Chan Product 300 MHz, CDCl3, rt, 8 sec delay
ppm
8.17947
8.15437
7.71663
7.69232
7.63833
7.61401
7.55130
7.52502
7.50056
7.48103
7.45655
7.43081
7.38602
7.36199
7.29789
7.29665
6.58983
6.56244
6.19081
6.16372
Integral
2.0000
0.9201
2.0569
7.9120
0.8360
0.9551
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9.5493
ppm
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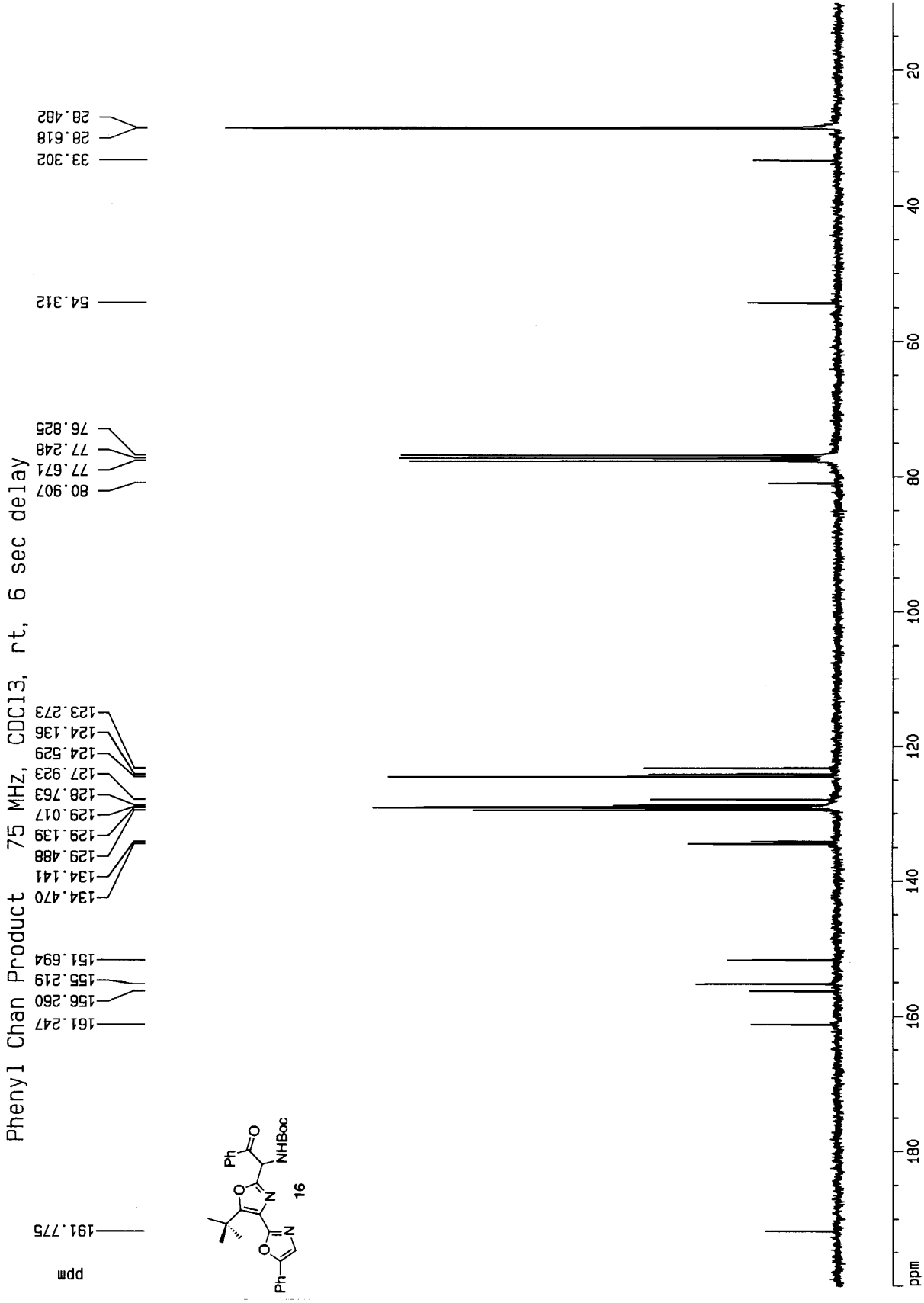
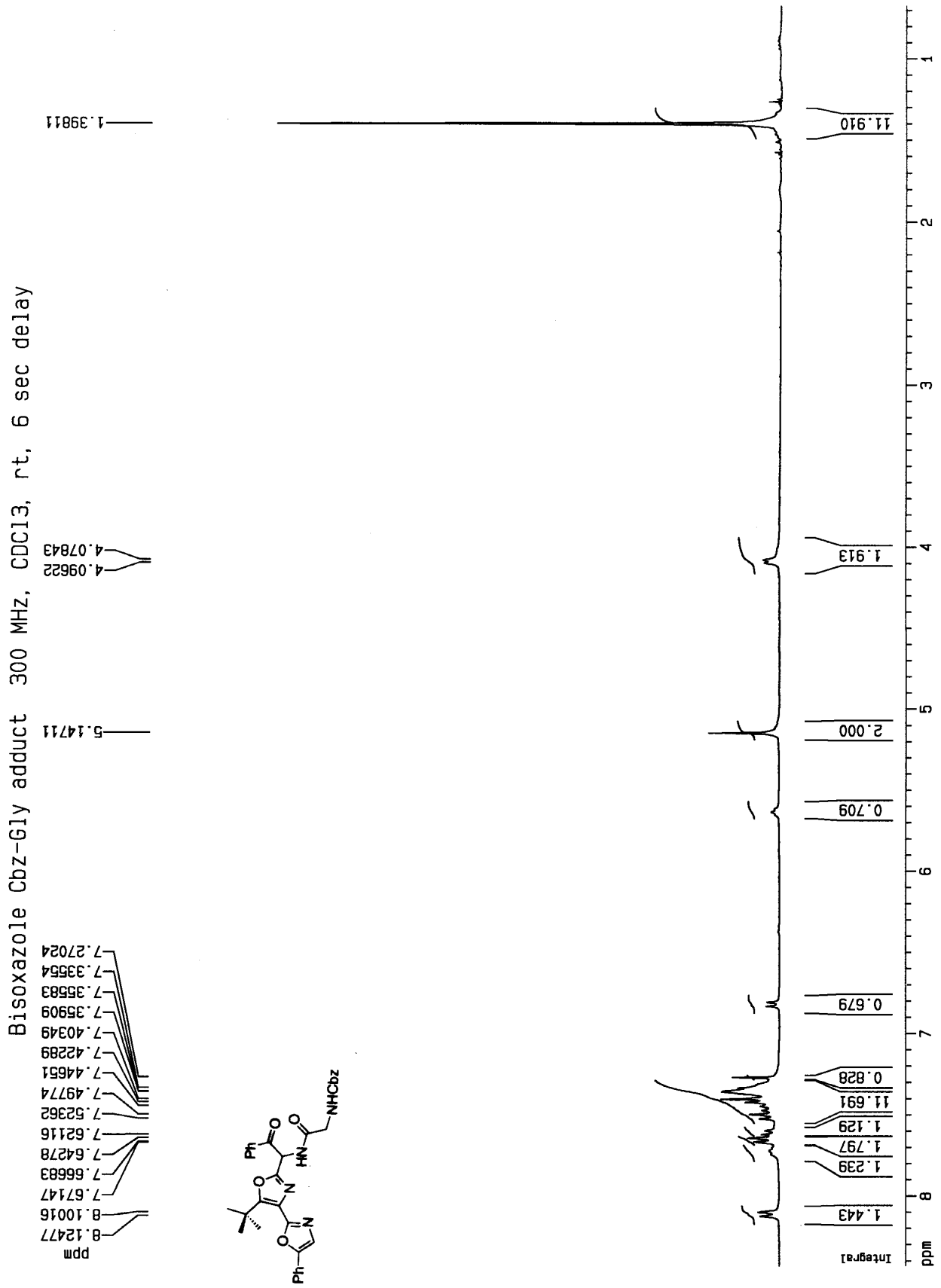
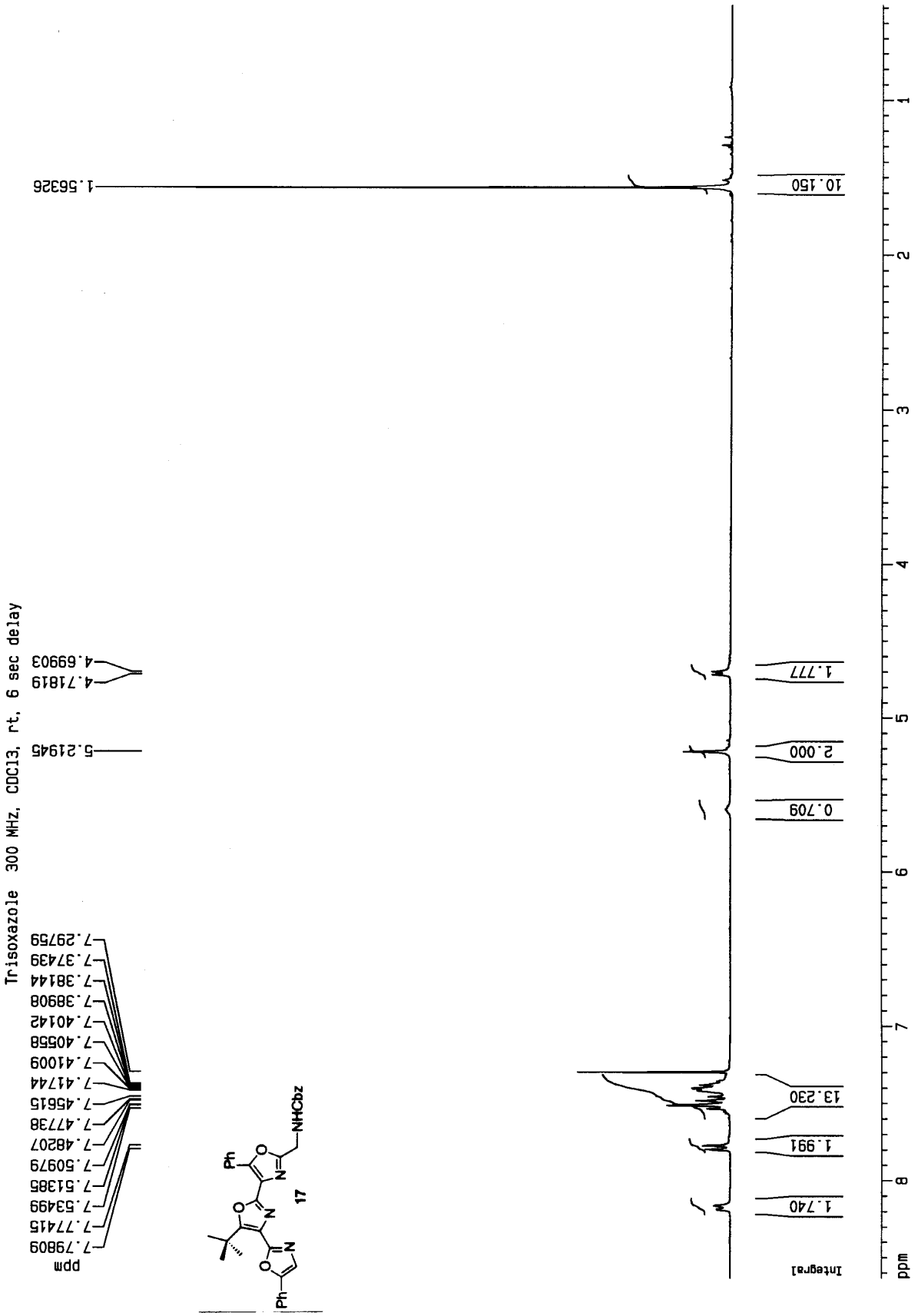
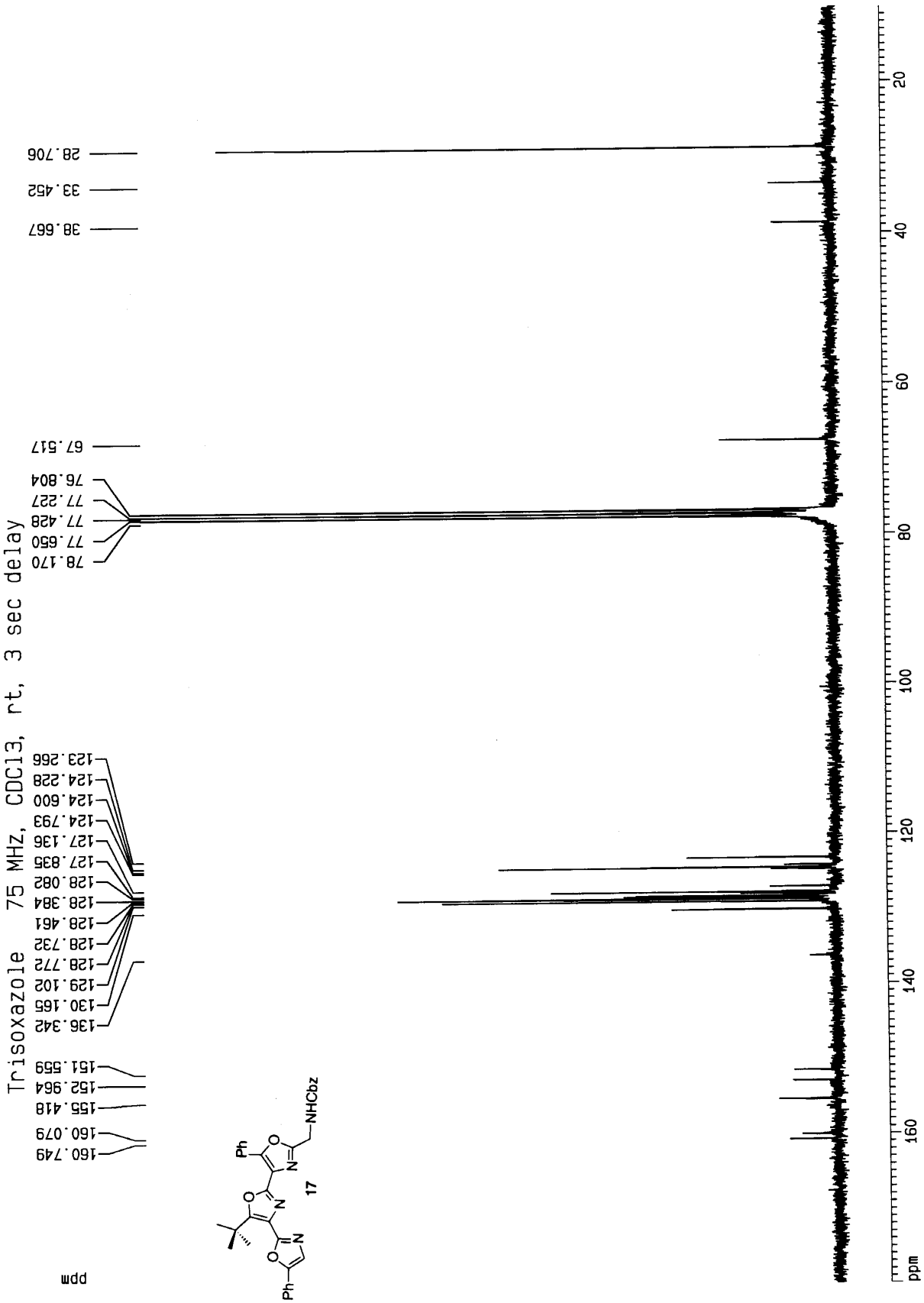
2
3
4
5
6
7
8
Ph
NHBoc
16
Ph


Phenyl Chan Product 75 MHz, CDCl3, rt, 6 sec delay
28.482
28.618
33.302
54.312
76.825
77.248
77.671
80.907
123.273
124.136
124.529
127.923
128.763
129.017
129.139
129.488
134.141
134.470
151.694
155.219
156.260
161.247
191.775
ppm
20
40
60
80
100
120
140
160
180
ppm
Ph
O
NHBoc
N
O
N
Ph
16


Bisoxazole Cbz-Gly adduct 300 MHz, CDCl3, rt, 6 sec delay
ppm
Integral
NHCbz
Ph
Ph


Trisoxazole 300 MHz, CDCl3, rt, 6 sec delay
ppm
7.79809
7.77415
7.53499
7.51385
7.50979
7.48207
7.47738
7.45615
7.41744
7.41009
7.40558
7.40142
7.38908
7.38144
7.37439
7.29759
5.21945
4.71819
4.69903
1.56326
Integral
10.150
1.777
2.000
0.709
13.230
1.991
1.740
ppm
NHCbz
Ph
Ph
17


Trisoxazole 75 MHz, CDCl3, rt, 3 sec delay
28.706
33.452
38.667
67.517
76.804
77.227
77.428
77.650
78.170
123.266
124.228
124.600
124.793
127.136
127.835
128.082
128.384
128.461
128.732
128.772
129.102
130.165
136.342
151.559
152.964
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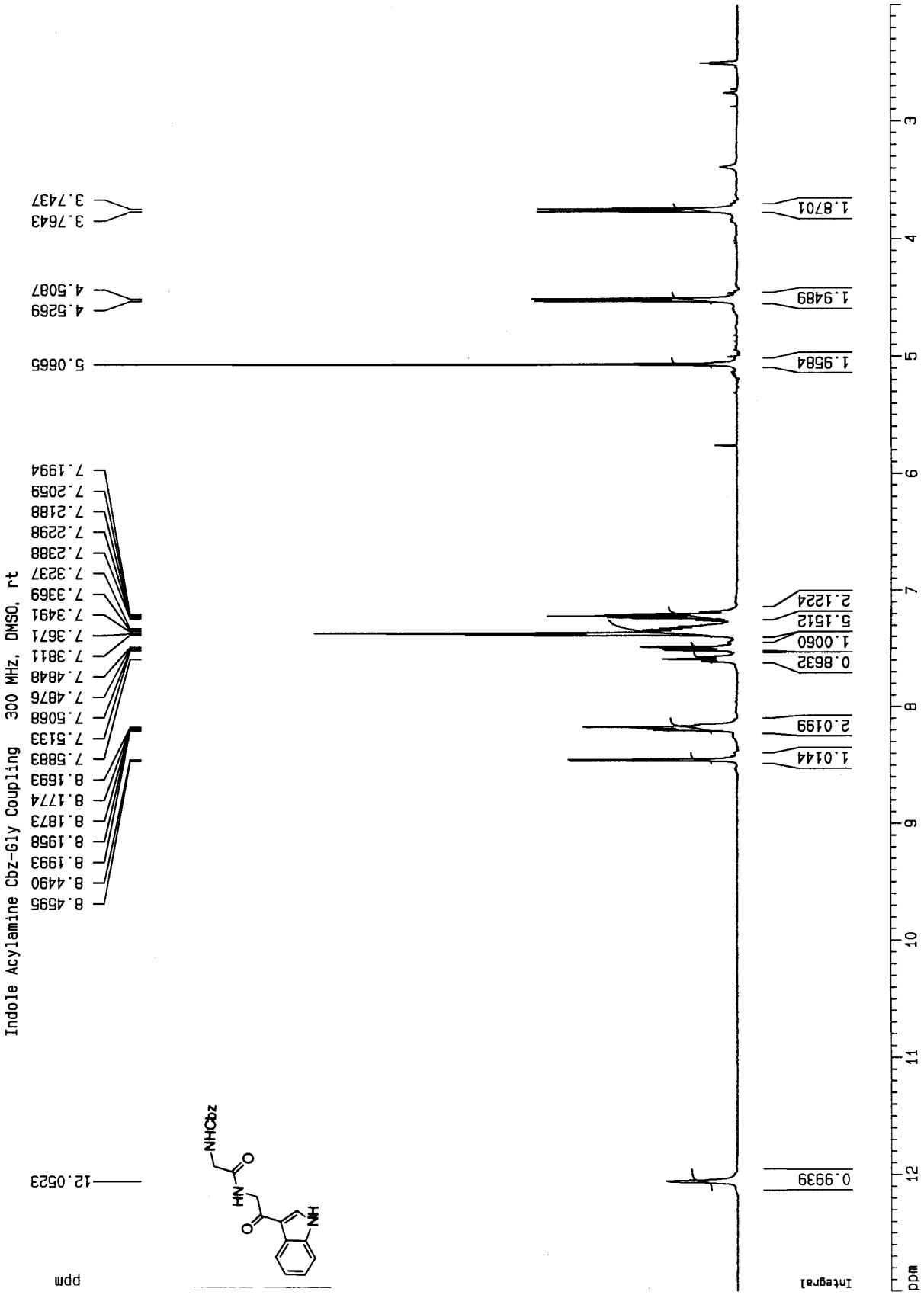
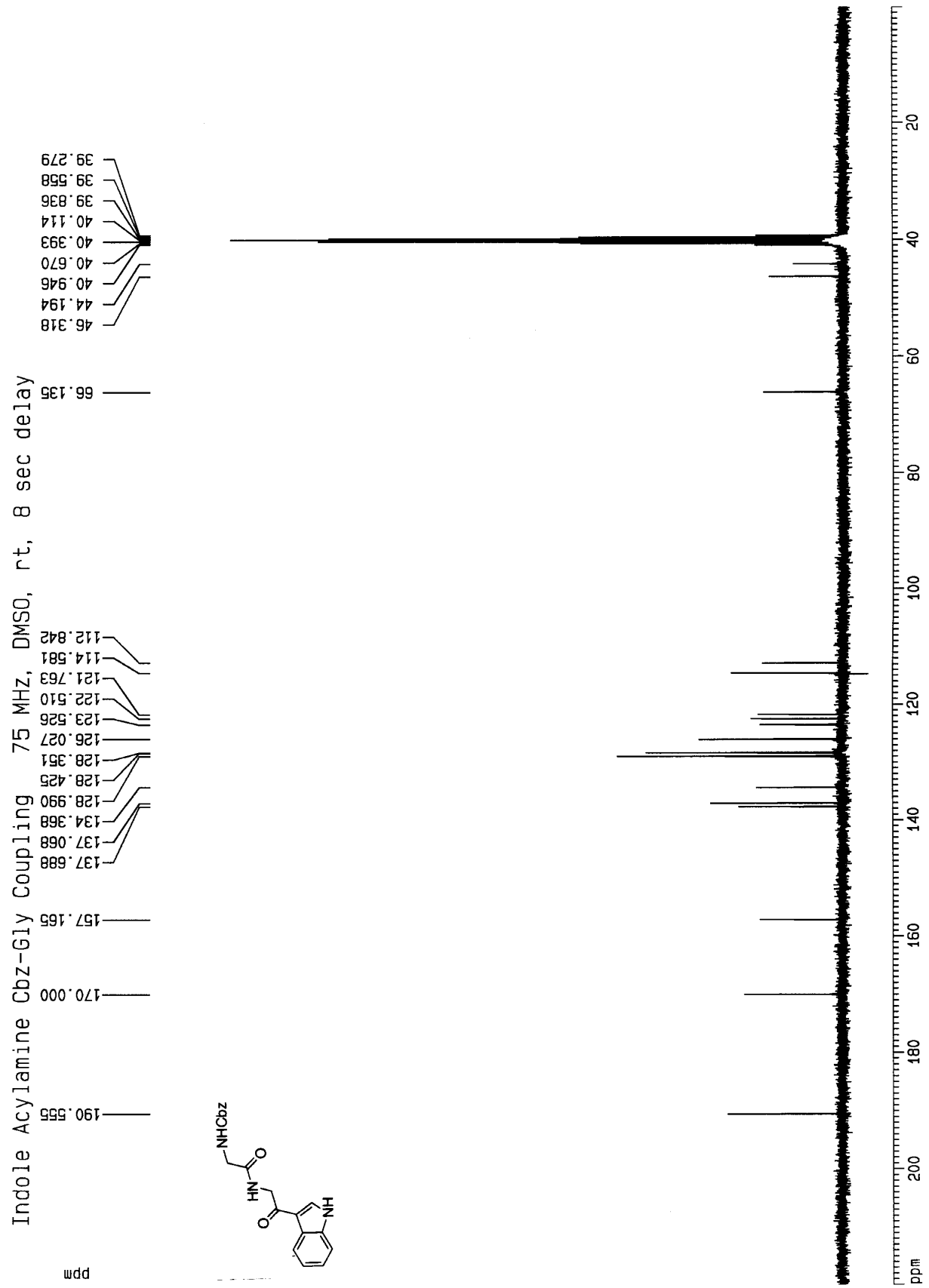
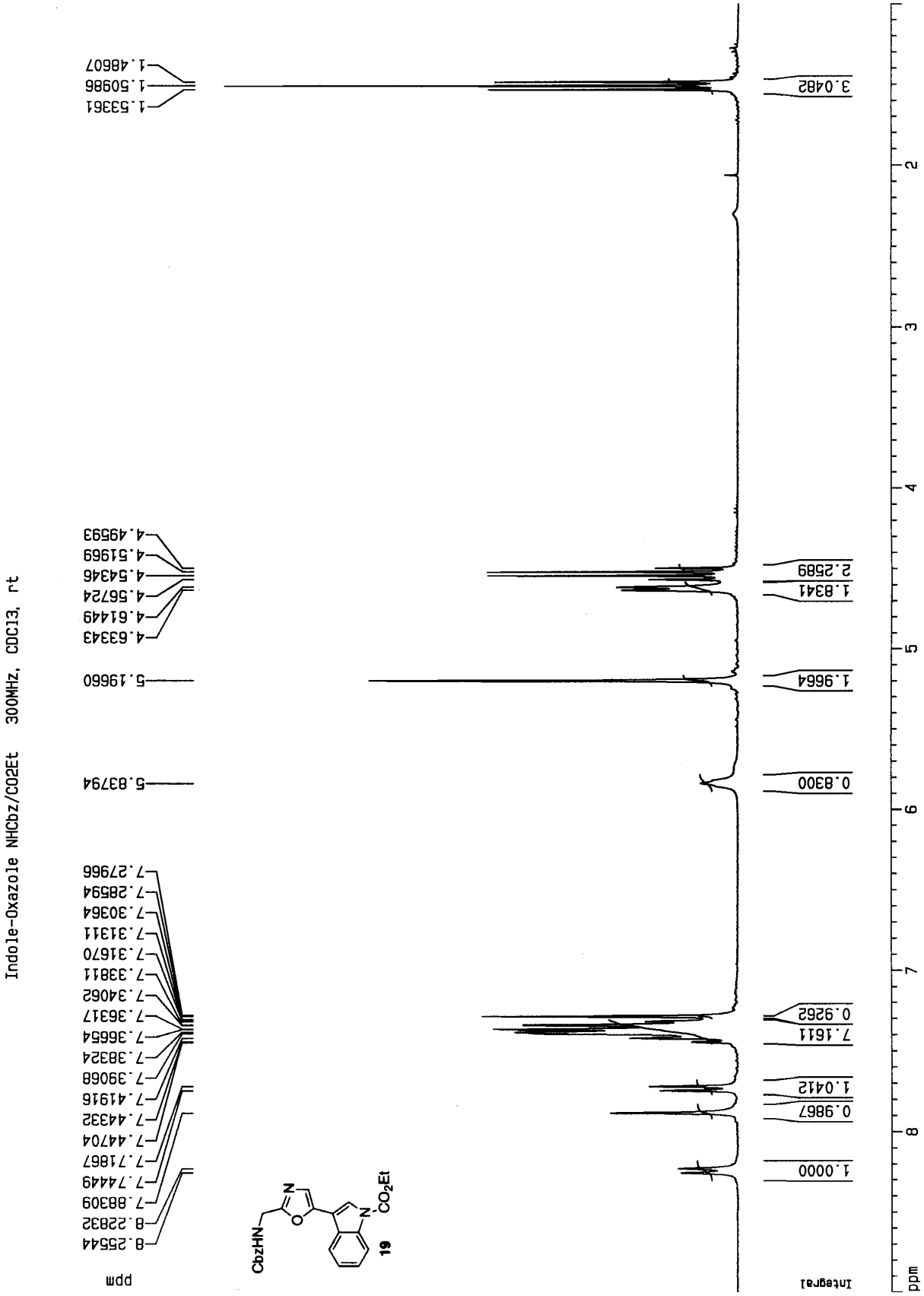
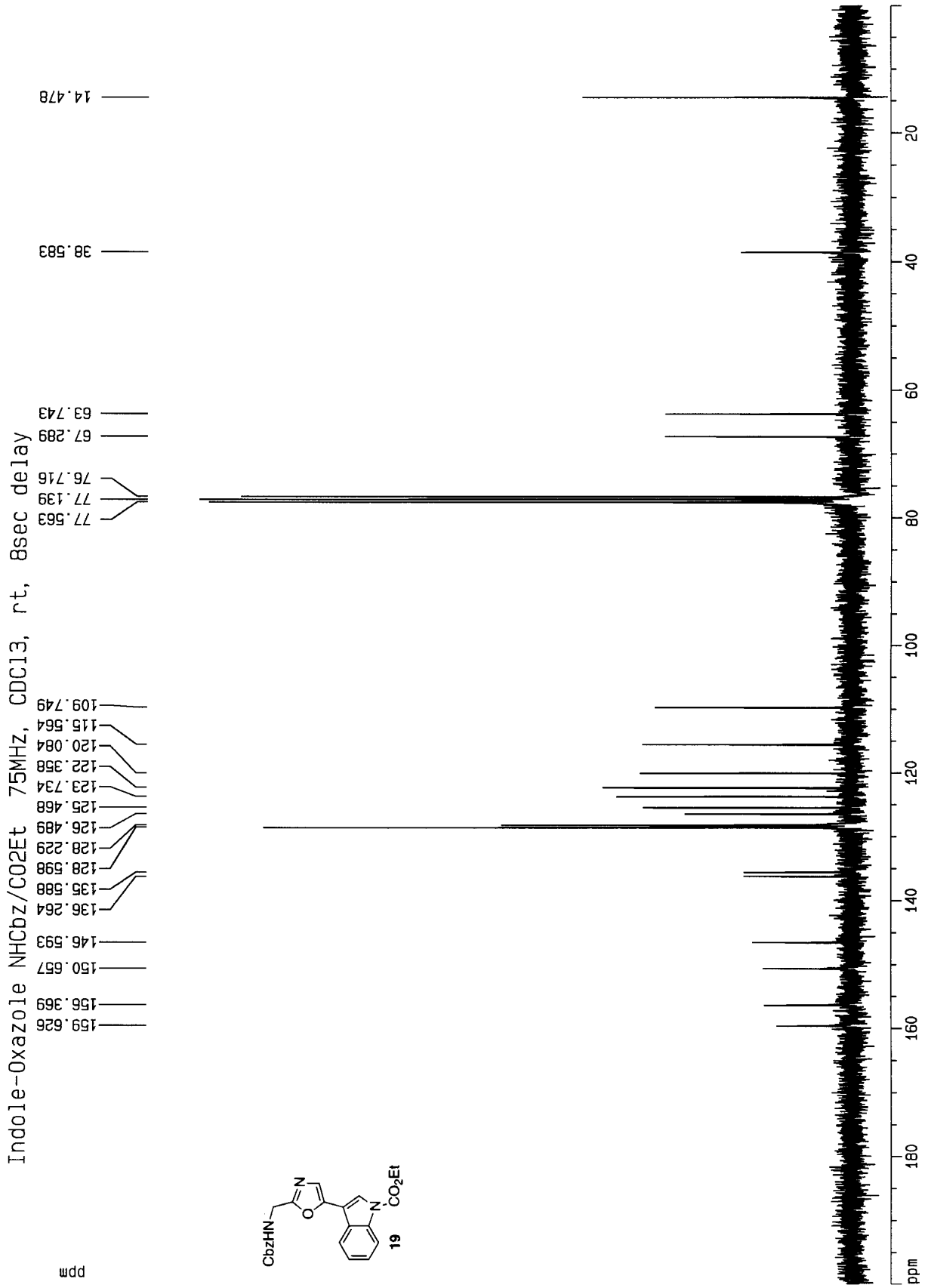
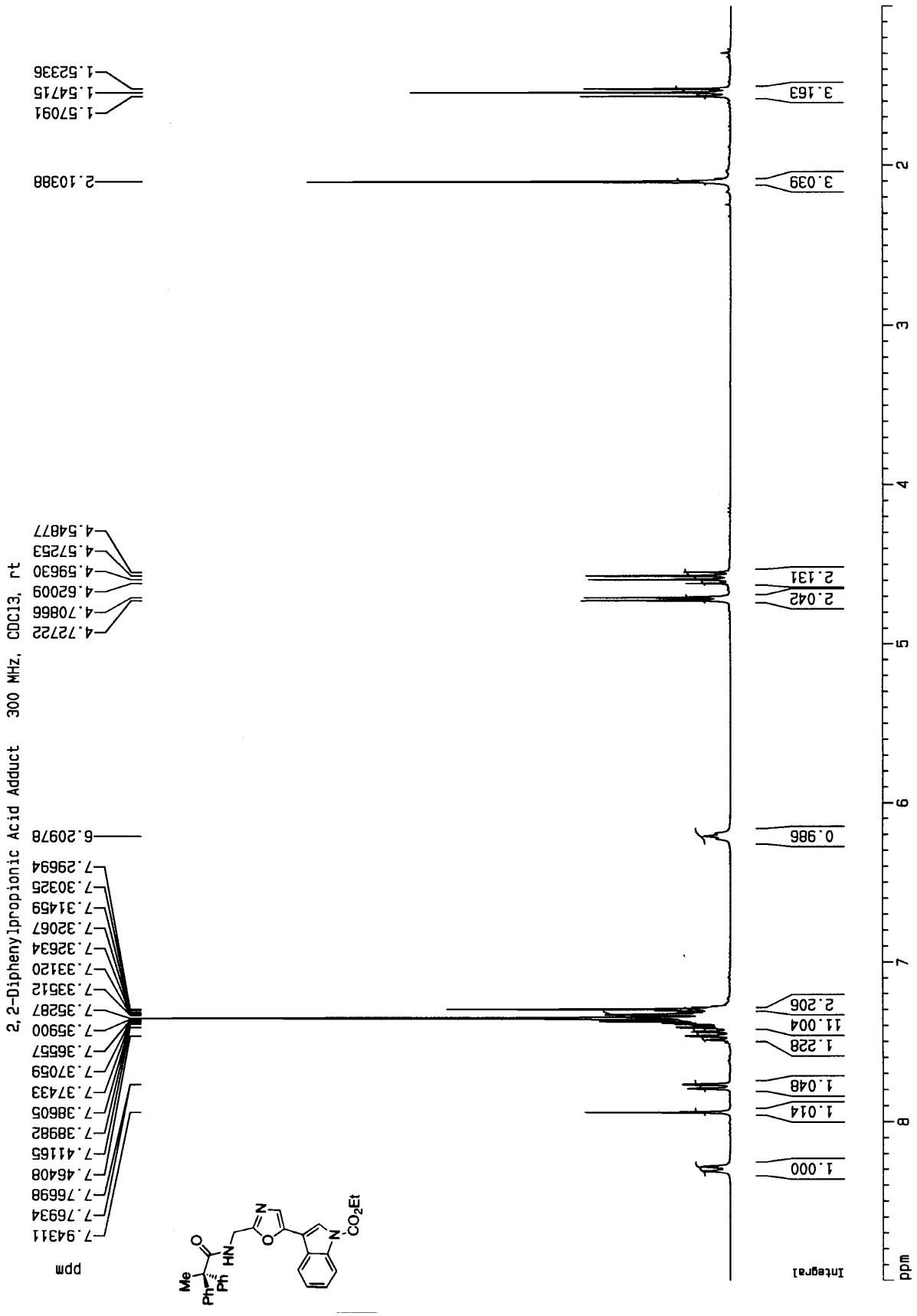
80
100
120
140
160
NHCbz
Ph
17
Ph

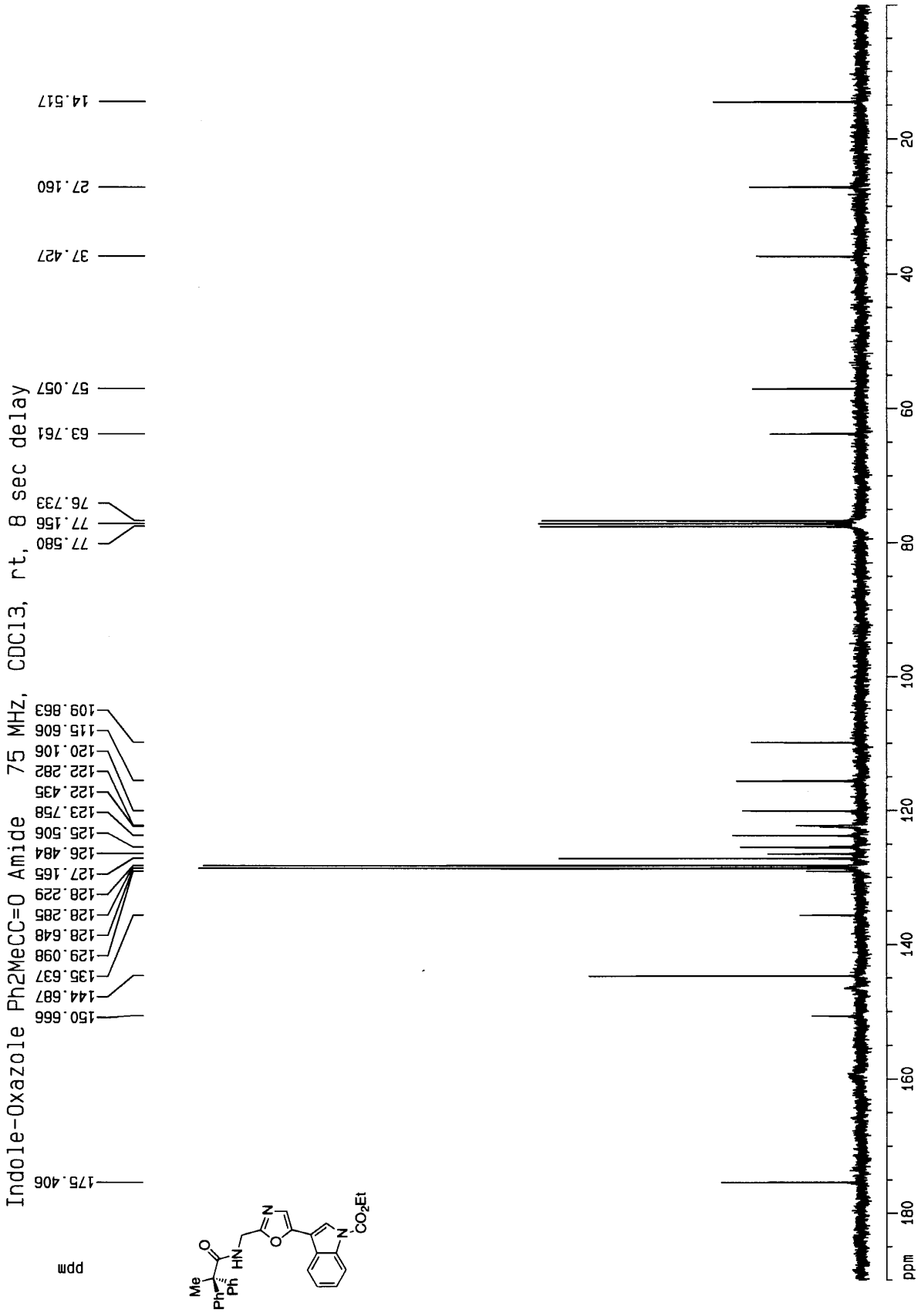

Indole Acylamine Cbz-Gly Coupling 300 MHz, DMSO, rt
12.0523
8.4595
8.4490
8.1993
8.1958
8.1873
8.1774
8.1693
7.5883
7.5133
7.5068
7.4876
7.4848
7.3811
7.3671
7.3491
7.3369
7.3237
7.2388
7.2298
7.2188
7.2059
7.1994
5.0665
4.5269
4.5087
3.7643
3.7437
NHCbz
HN
O
O
NH
ppm
0.9939
2.0199
1.0144
0.8632
1.0060
5.1512
2.1224
1.9584
1.9489
1.8701
Integral
ppm

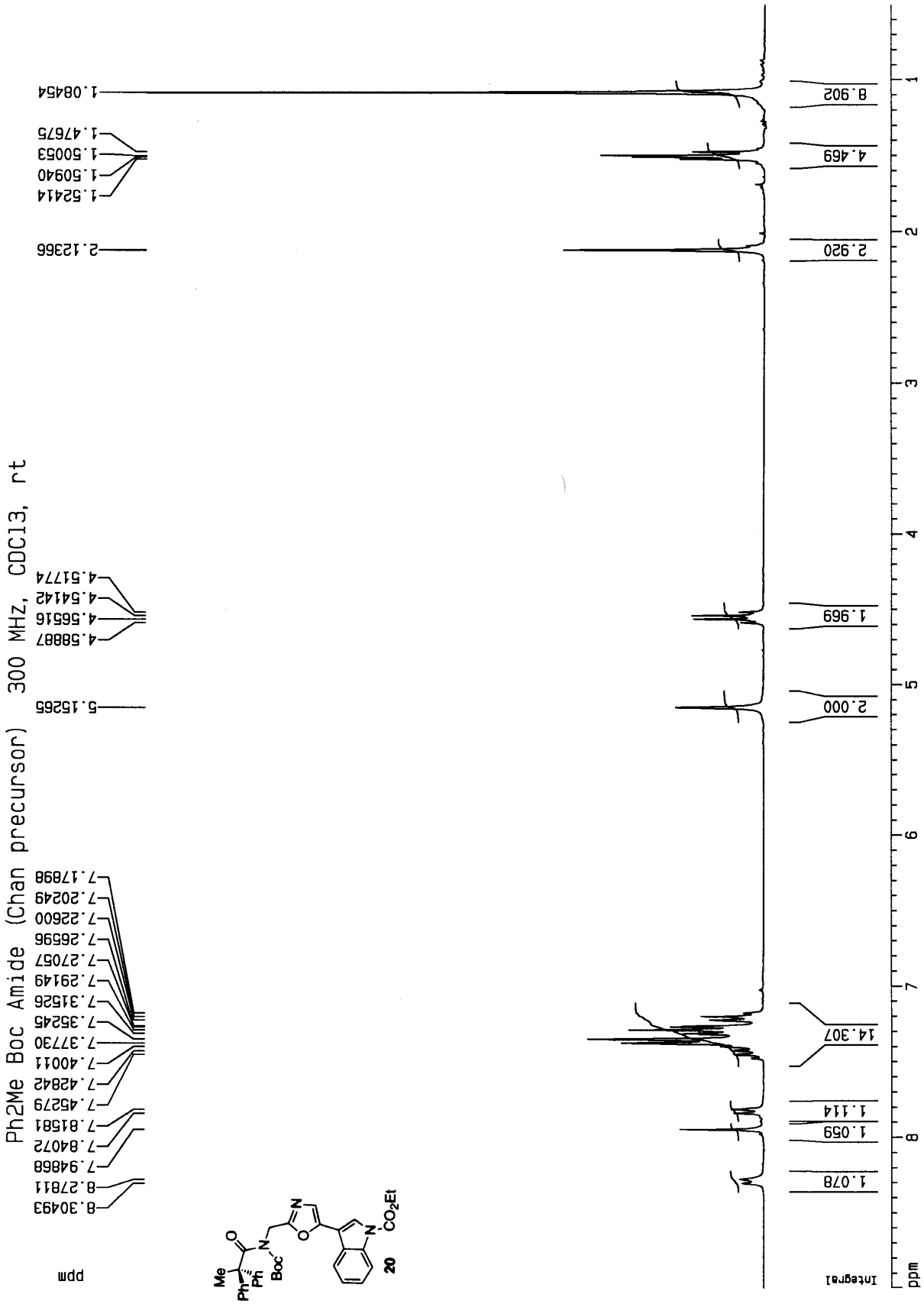

Indole Acylamine Cbz-Gly Coupling 75 MHz, DMSO, rt, 8 sec delay
190.555
170.000
157.165
137.688
137.068
134.368
128.990
128.425
128.351
126.027
123.526
122.510
121.763
114.581
112.842
66.135
46.318
44.194
40.946
40.670
40.393
40.114
39.836
39.558
39.279
NHCbz
HN
O
O
NH
ppm
20
40
60
80
100
120
140
160
180
200
ppm

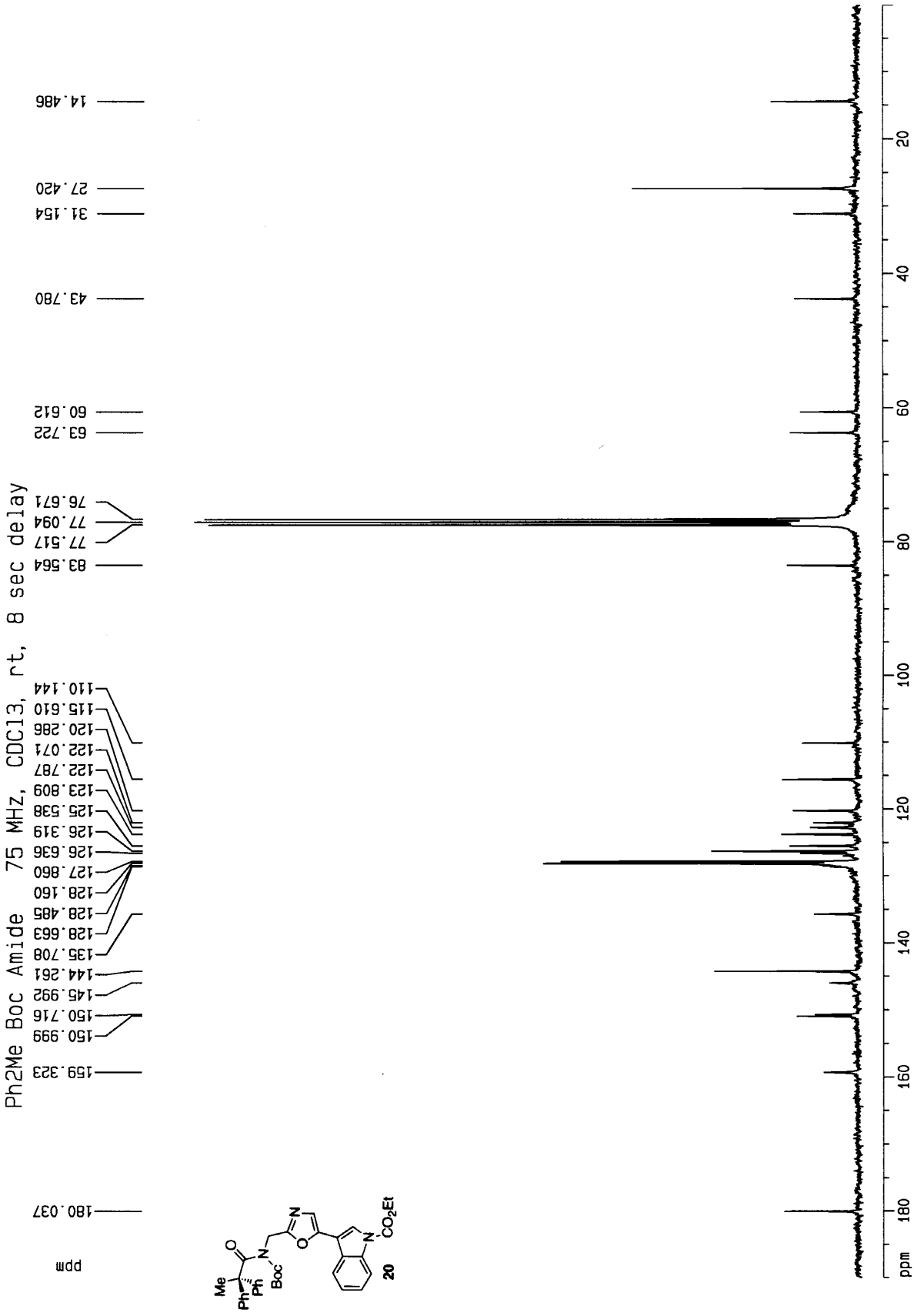

Indole-Oxazole NHCbz/CO2Et 300MHz, CDCl3, rt
1.48607
1.50986
1.53361
4.49593
4.51969
4.54346
4.56724
4.61449
4.63343
5.19660
5.83794
7.27966
7.28594
7.30364
7.31311
7.31670
7.33811
7.34062
7.36317
7.36654
7.38324
7.39068
7.41916
7.44332
7.44704
7.71867
7.74449
7.88309
8.22832
8.25544
ppm
3.0482
2.2589
1.8341
1.9664
0.8300
0.9262
7.1611
1.0412
0.9867
1.0000
Integral
CbzHN
CO2Et
19
1
2
3
4
5
6
7
8
ppm

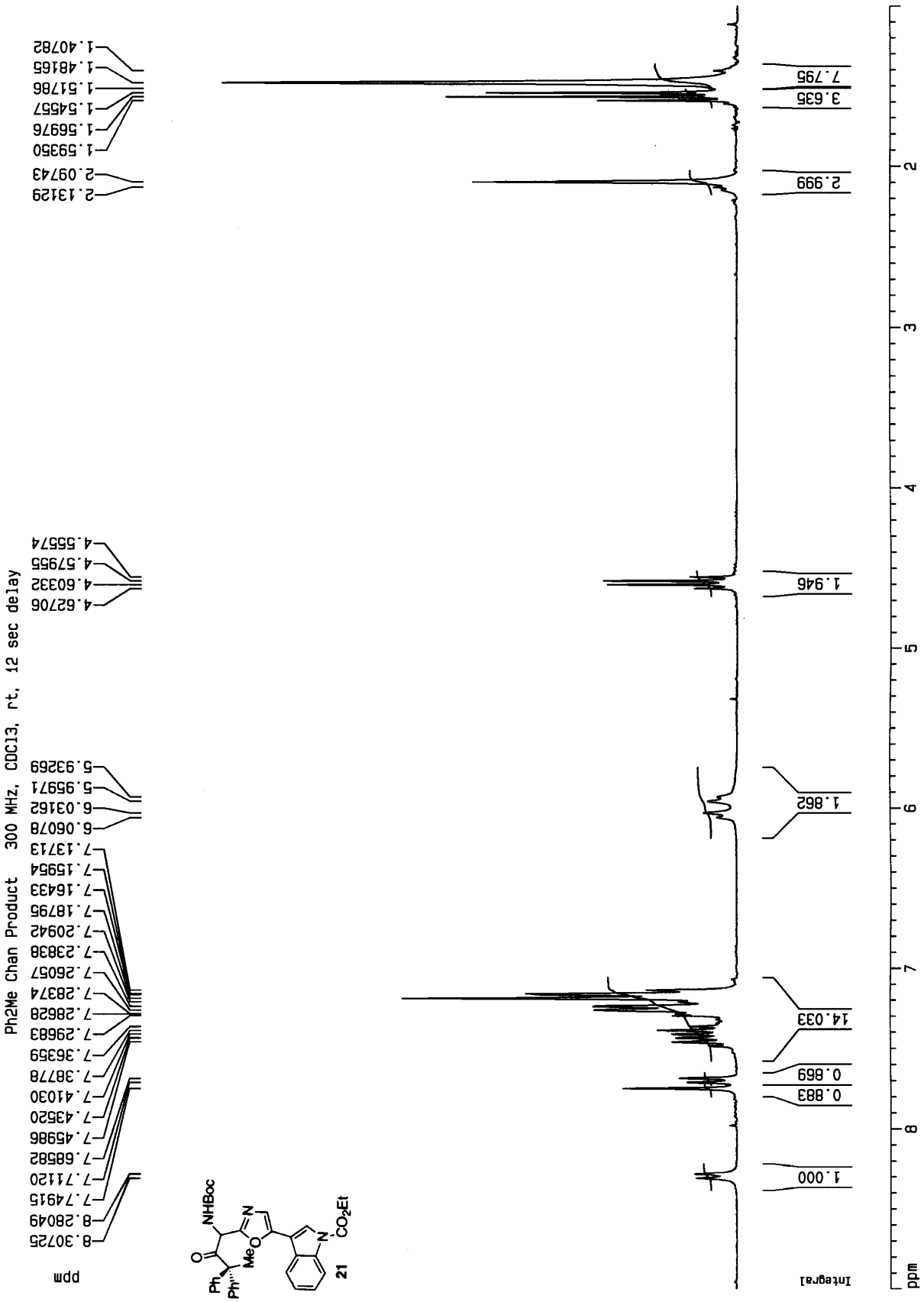

Indole-Oxazole NHCbz/CO2Et 75MHz, CDCl3, rt, 8sec delay
14.478
38.583
63.743
67.289
76.716
77.139
77.563
109.749
115.564
120.084
122.358
123.734
125.468
126.489
128.229
128.598
135.588
136.264
146.593
150.657
156.369
159.626
ppm
20
40
60
80
100
120
140
160
180
ppm
CbzHN
CO2Et
19

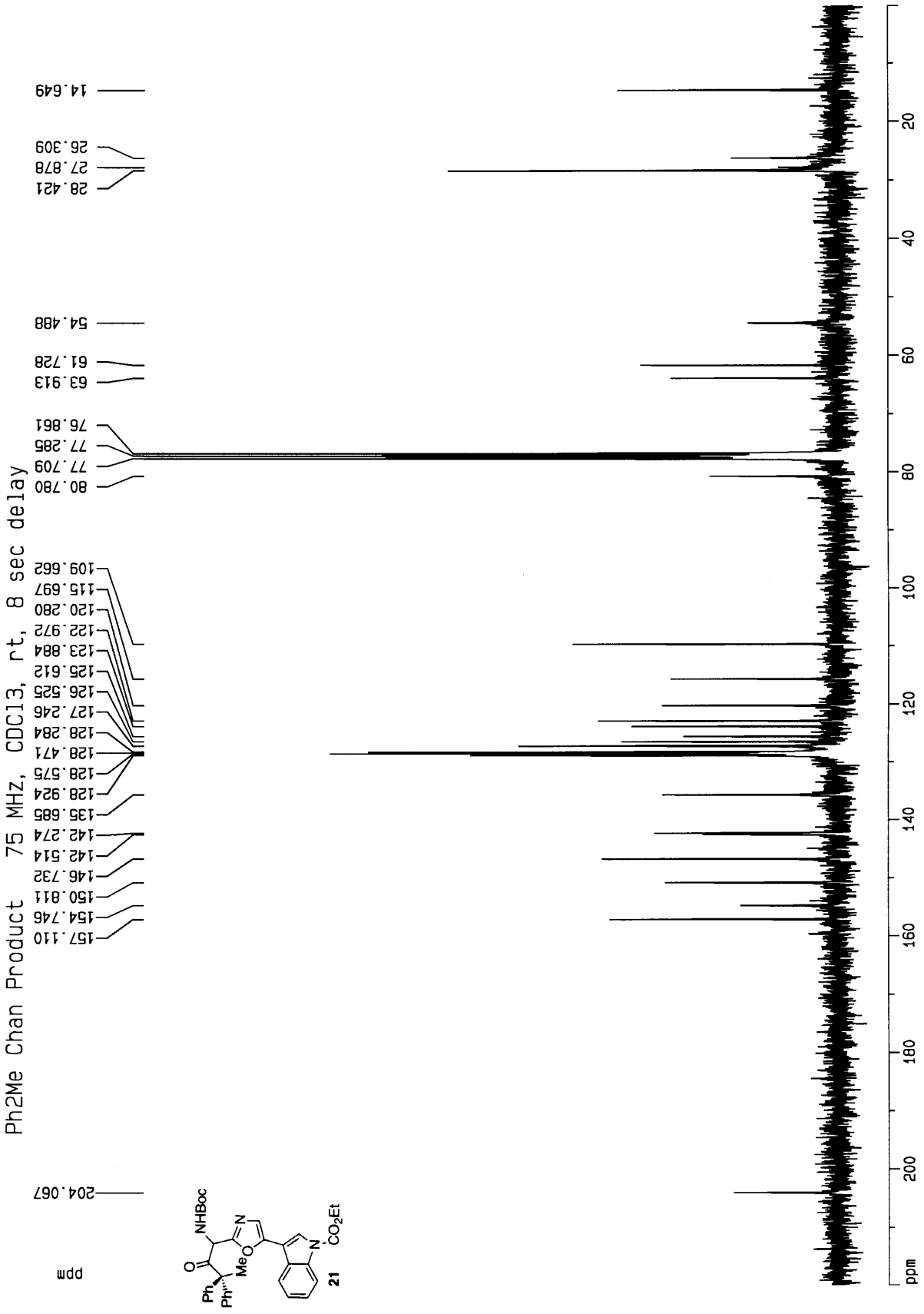

2,2-Diphenylpropionic Acid Adduct 300 MHz, CDCl3, rt
ppm
Integral
1.52336
1.54715
1.57091
2.10388
4.54877
4.57253
4.59630
4.62009
4.70866
4.72722
6.20978
7.29694
7.30325
7.31459
7.32067
7.32634
7.33120
7.33512
7.35287
7.35900
7.36557
7.37059
7.37433
7.38605
7.38982
7.41165
7.46408
7.76698
7.76934
7.94311
3.163
3.039
2.131
2.042
0.986
2.206
11.004
1.228
1.048
1.014
1.000
Me
Ph
Ph
HN
O
N
O
N
CO2Et

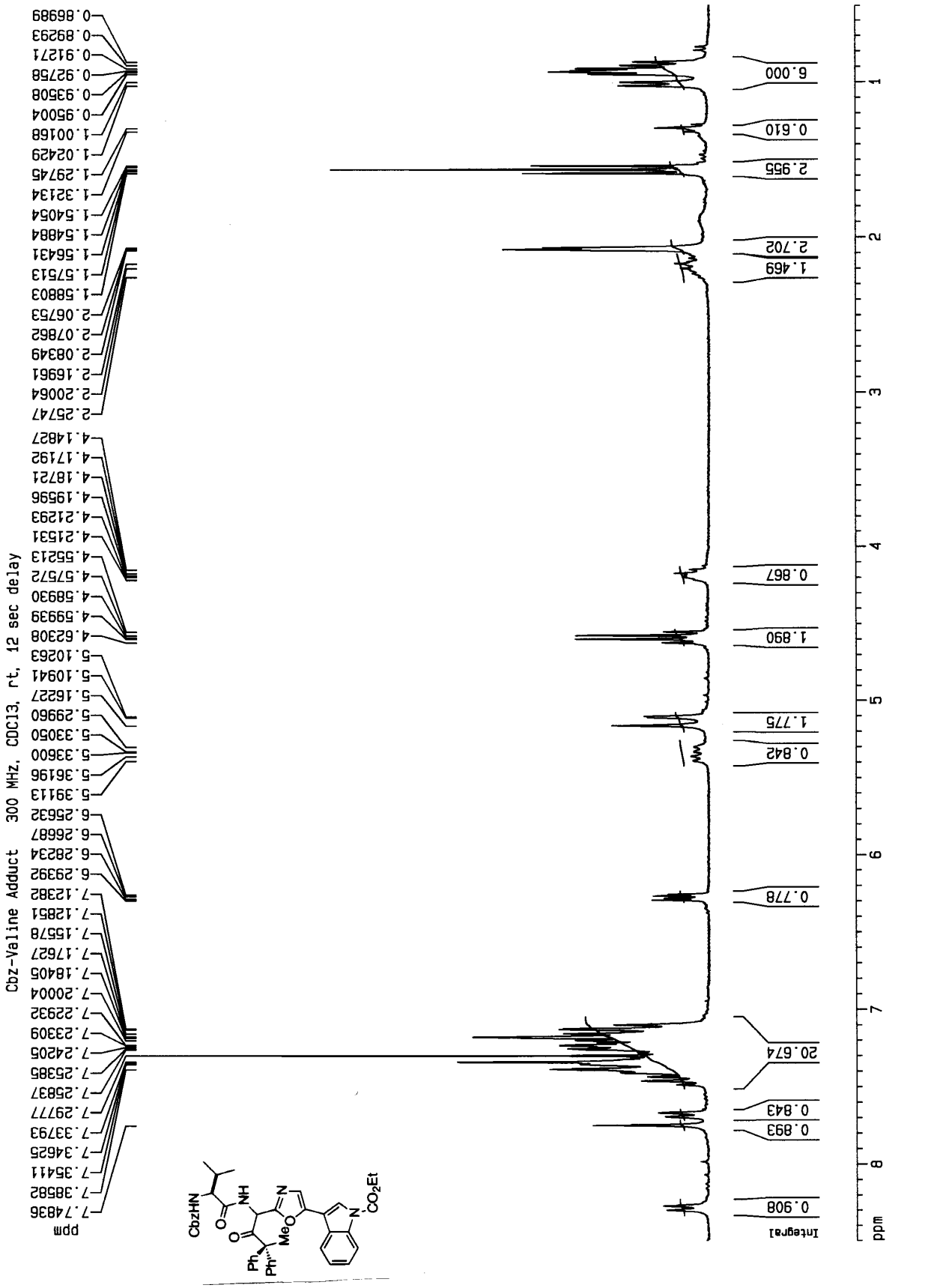

Indole-Oxazole Ph2MeCC=O Amide 75 MHz, CDCl3, rt, 8 sec delay
14.517
27.160
37.427
57.057
63.761
76.733
77.156
77.580
109.863
115.606
120.106
122.282
122.435
123.758
125.506
126.484
127.165
128.229
128.285
128.648
129.098
135.637
144.687
150.666
175.406
ppm
20
40
60
80
100
120
140
160
180
ppm
Me
Ph
Ph
HN
O
N
O
N
CO2Et

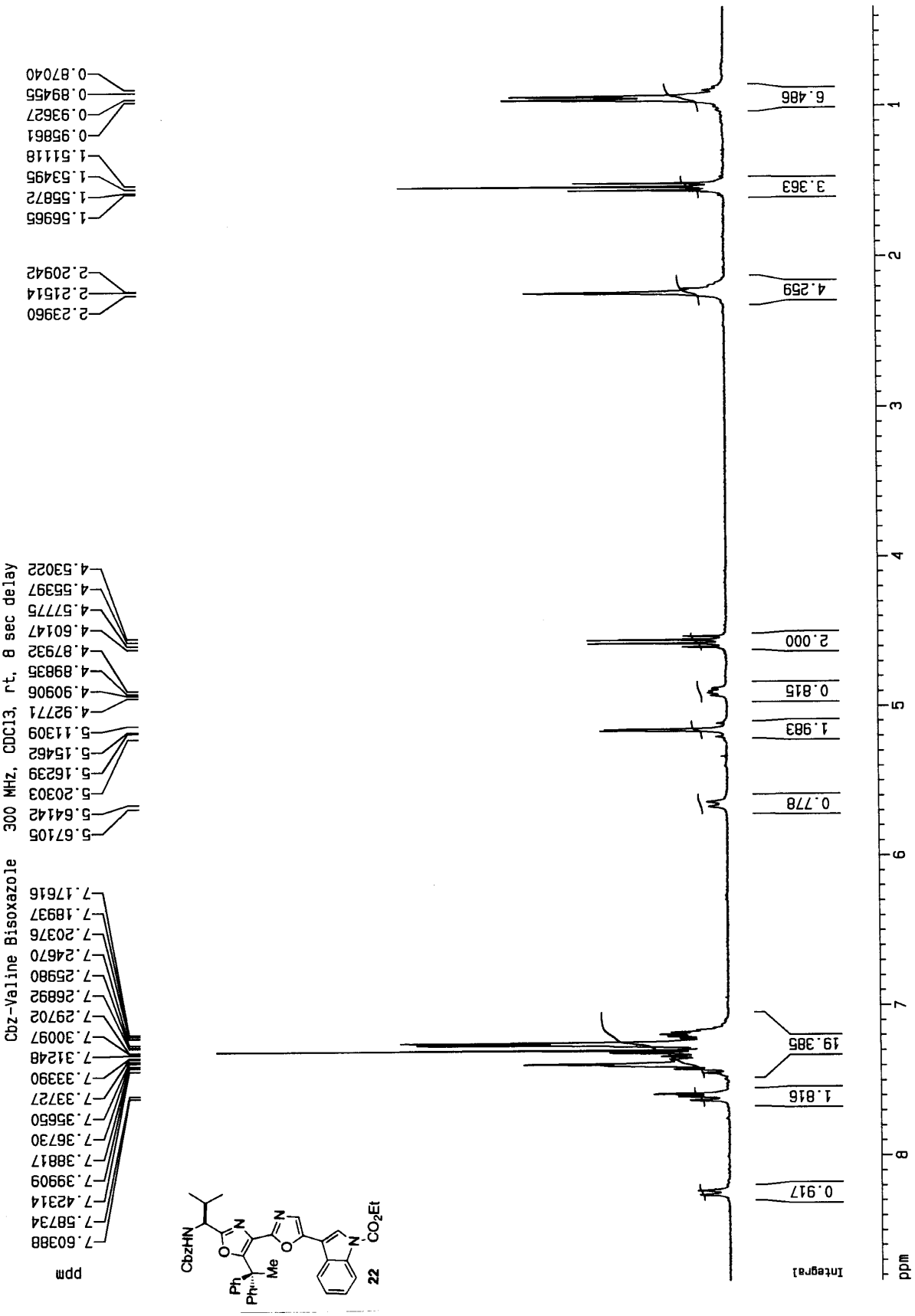

Ph2Me Boc Amide (Chan precursor) 300 MHz, CDCl3, rt
8.30493
8.27811
7.94868
7.84072
7.81581
7.45279
7.42842
7.40011
7.37730
7.35245
7.31526
7.29149
7.27057
7.26596
7.22600
7.20249
7.17898
5.15265
4.58887
4.56516
4.54142
4.51774
2.12366
1.52414
1.50940
1.50053
1.47675
1.08454
Me
Ph
Ph
Boc
N
O
N
O
N
CO2Et
20
ppm
Integral
1.078
1.059
1.114
14.307
2.000
1.969
2.920
4.469
8.902
1
2
3
4
5
6
7
8
ppm

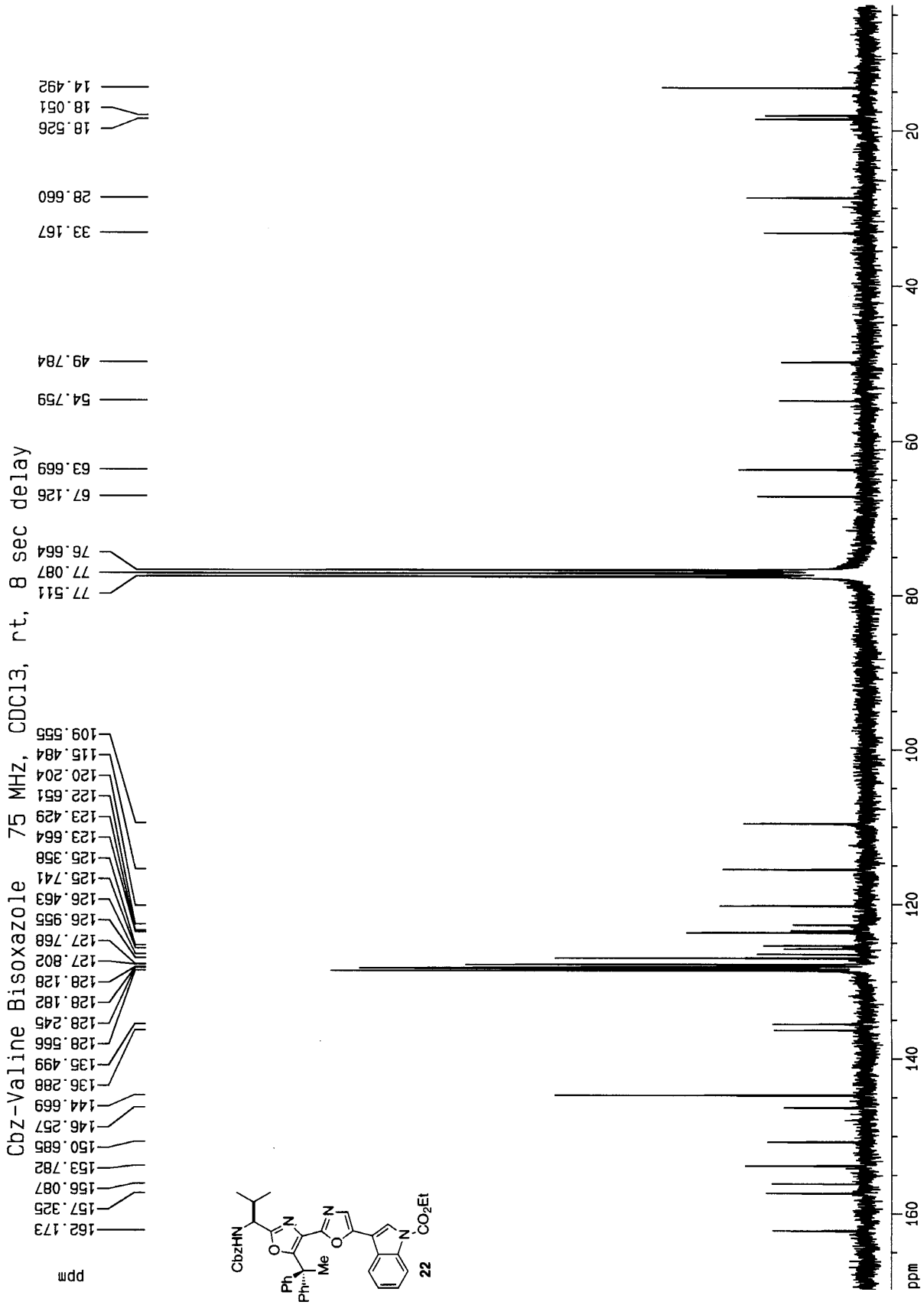

Ph2Me Boc Amide 75 MHz, CDCl3, rt, 8 sec delay
14.486
27.420
31.154
43.780
60.612
63.722
76.671
77.094
77.517
83.564
110.144
115.610
120.286
122.071
122.787
123.809
125.538
126.319
126.636
127.860
128.160
128.485
128.663
135.708
144.261
145.992
150.716
150.999
159.323
180.037
ppm
20
Me
Ph
Ph
Boc
N
O
N
O
N
CO2Et


Ph2Me Chan Product 300 MHz, CDCl3, rt, 12 sec delay
1.40782
1.48165
1.51786
1.54557
1.56976
1.59350
2.09743
2.13129
4.55574
4.57955
4.60332
4.62706
5.93269
5.95971
6.03162
6.06078
7.13713
7.15954
7.16433
7.18795
7.20942
7.23838
7.26057
7.28374
7.28628
7.29683
7.36359
7.38778
7.41030
7.43520
7.45986
7.68582
7.71120
7.74915
8.28049
8.30725
ppm
NHBoc
Me
Ph
Ph
CO2Et
21
Integral
1.000
0.883
0.869
14.033
1.862
1.946
2.999
3.635
7.795
ppm


Ph2Me Chan Product 75 MHz, CDCl3, rt, 8 sec delay
14.649
26.309
27.878
28.421
54.488
61.728
63.913
76.861
77.285
77.709
80.780
109.662
115.697
120.280
122.972
123.884
125.612
126.525
127.246
128.284
128.471
128.575
128.924
135.685
142.274
142.514
146.732
150.811
154.746
157.110
204.067
ppm
NHBoc
Ph
Ph
Me
O
N
O
N
CO2Et
21
20
40
60
80
100
120
140
160
180
200
ppm


Cbz-Valine Adduct 300 MHz, CDCl3, rt, 12 sec delay
ppm
Integral
6.000
0.610
2.955
2.702
1.469
0.867
1.890
1.775
0.842
0.778
20.674
0.843
0.893
0.908
CbzHN
NH
O
O
Ph
Ph
Me
O
N
N
CO2Et


Cbz-Valine Bisoxazole 300 MHz, CDCl3, rt, 8 sec delay
ppm
Integral
6.486
3.363
4.259
2.000
0.815
1.983
0.778
19.385
1.816
0.917
CbzHN
Ph
Me
CO2Et
22


Cbz-Valine Bisoxazole 75 MHz, CDCl3, rt, 8 sec delay
14.492
18.051
18.526
28.660
33.167
49.784
54.759
63.669
67.126
76.664
77.087
77.511
109.555
115.484
120.204
122.651
123.429
123.664
125.358
125.741
126.463
126.955
127.768
127.802
128.128
128.182
128.245
128.566
135.499
136.288
144.669
146.257
150.685
153.782
156.087
157.325
162.173
ppm
CbzHN
Me
Ph
Ph
N
O
CO2Et
22