General Approach to the Total Synthesis of 9-Methoxy Substituted Indole Alkaloids: Synthesis of Mitragynine, as well as 9-Methoxygeissoschizol and 9-Methoxy-N_b-methylgeissoschizol

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General Experimental Methods. All samples submitted for CHN analyses were first dried under high vacuum for a minimum of six hours using a drying pistol with methylene chloride or isopropyl alcohol as the solvent with phosphorus pentoxide in the drying bulb. ^{1}H NMR and ^{13}C NMR were obtained on a 300 MHz in $CDCl_3$ unless otherwise indicated. Infrared spectra were recorded on a FTIR spectrometer. Analytical thin layer chromatography plates were UV-active silica gel (Kieselgel 60 F254) on plastic. Silica gel 60A, grade 60 was used for flash chromatography. Alkaloids were visualized with a saturated solution of ceric ammonium sulfate in 50% sulfuric acid. Methanol (MeOH) was dried by distillation over magnesium metal and iodine. Tetrahydrofuran (THF), benzene, toluene and diethyl ether were dried by distillation from sodium-benzophenone ketyl. Methylene chloride, triethylamine, and diisopropylamine were dried over $MgSO_4$ and then distilled over CaH_2.

***tert*-Butyl 4-Methoxy-3-methyl-1H-indole-1-carboxylate (11).** Carbamate **10b** (48.2 g, 0.138 mol) in DMF (890 mL) was cooled with an ice bath and stirred at 0 °C for 10 min. To this cold solution was added NaH (60% dispersion in mineral oil, 6.90 g, 0.172 mol) and the mixture stirred at 0 °C for 30 min. Allyl bromide (12.7 mL, 0.147 mol) was injected via a syringe, and the mixture was allowed to warm to rt and was stirred for 5 h. To this solution was added palladium(II) acetate (754 mg, 3.367 mmol), potassium carbonate (47.6 g, 0.344 mol), and triphenylphosphine (1.748 g, 6.664 mmol). The reaction mixture was degassed under vacuum and stirred at 90 °C under a slow stream of argon for 24 h. The reaction mixture was poured into EtOAc (1 L), which was then filtered through Celite to remove the Pd black and inorganic salts. The solution which resulted was diluted with another portion of EtOAc (2 L), and was then washed with

water, brine and dried (Na_2SO_4). The solvent was removed under reduced pressure. The residue contained a mixture of N-Boc-4-methoxy-3-methylindole (**11**) and N-Boc-4-methoxy-3-methyleneindoline (**12**). The residue was dissolved in THF (500 mL), and aq 2 N HCl (100 mL) was added. This solution was stirred for 8 h until examination by TLC indicated all of the indoline **12** had been isomerized to the indole **11**. The reaction mixture was then poured into EtOAc (1 L) and solution of 10% aq ammonium hydroxide (100 mL) and ice. The aq layer was extracted with EtOAc. The organic layers were combined, washed with water, brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (gradient elution from hexane to 60% EtOAc in hexane) to afford the desired 4-methoxyindole **11** (33.6 g) in 92% yield. IR (film), 2977, 2837, 1730, 1605, 1571, 1494, 1434.5, 1380.0, 1348.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.68 (9H, s), 2.44 (3H, d, *J* = 1.3 Hz), 3.92 (3H, s), 6.66 (1H, d, *J* = 8.0 Hz), 7.23 (1H, s), 7.23 (1H, t, *J* = 8.2 Hz), 7.78 (1H, d, *J* = 8.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.4, 28.1, 55.2, 83.0, 103.0, 108.2, 116.7, 120.5, 121.4, 125.0, 137.1, 149.7, 154.6; EIMS (*m/e*, relative intensity): 261 (M^+, 93), 205 (100), 188 (12), 161 (68), 146 (64). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36; Found: C, 69.32; H, 7.05; N, 5.23.

(R)-*tert*-Butyl 3-(2-Amino-3-ethoxy-3-oxopropyl)-4-methoxy-1H-indole-1-carboxylate (19). To a solution of the bislactim **18** (5.35 g, 11.3 mmol) in THF (50 mL) was added an aq 2 N HCl (45 mL) solution at 0 °C. The solution was warmed to rt and stirred for 6 h until the disappearance of the bislactim **18** by TLC (silica gel). Ice (~20 g) was added to the mixture and the pH of the solution was adjusted to 7 with 10% aq NH_4OH. EtOAc (150 mL) was added to the mixture and the aq layer was extracted with EtOAc.

The organic layers were combined, washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure. The residue was purified by flash chromatography (100% hexane gradient to 50% EtOAc in hexane) to afford the N_a-Boc-4-methoxytryptophan ethyl ester (**19**) (3.70 g) in 90% yield. IR (film), 3367, 2978, 2937, 2838, 1732, 1601, 1567, 1435, 1368 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (3H, t**,** *J* = 7.1 Hz), 1.59 (9H, s), 1.84 (1H, t, *J* = 3.2 Hz), 2.82 (1H, dd, *J* = 8.8, 13.9 Hz), 3.35 (1H, ddd, *J* = 1.0, 4.8, 13.8 Hz), 3.73 (1H, t, *J* = 3.2 Hz), 3.86 (1H, m), 3.86 (3H, s), 4.12 (2H, q, *J* = 7.1 Hz), 6.59 (1H, d, *J* = 8.2 Hz), 7.15 (1H, t, *J* = 8.1 Hz), 7.28 (1H, s), 7.70 (1H, d, *J* = 8.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 28.0, 32.8, 54.9, 60.6, 67.8, 83.4, 103.1, 108.3, 116.5, 119.5, 123.0, 125.2, 137.2, 149.5, 154.0, 175.2; EIMS (*m/e*, relative intensity): 362 (M^+, 7), 204 (32), 160 (100). HRMS m/z: $C_{19}H_{27}N_2O_5$ $(M+H)^+$ cacld: 363.1920, found: 363.1909.

***tert*-Butyl 3-(((2*S*,5*R*)-3,6-Diethoxy-5-isopropyl-2,5-dihydropyrazin-2-yl)methyl)-4-methoxy-2-(tri-methylsilyl)-1H-indole-1-carboxylate (22c).** To carbamate **10b** (3.928 g, 11.25 mmol) was added the internal alkyne **21a** (4.344 g, 13.47 mmol), palladium (II) acetate (62 mg, 0.277 mmol), potassium carbonate (3.881 g, 28.1 mmol), lithium chloride (0.490 g, 11.56 mmol) and DMF (25 mL). The reaction mixture was degassed under vacuum, purged with argon and then heated at 100 °C under a slow stream of argon for 6 h. The mixture was cooled to rt and poured into EtOAc (200 mL) and then filtered through a pad of Celite to remove the Pd black and the inorganic salts. The solution which resulted was diluted with another portion of EtOAc (200 mL) and washed with water, brine and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified on silica gel (gradient elution from hexane to 4% EtOAc in

hexane) to give the desired 4-methoxy indole **22c** as a yellow oil (4.893 g, 80%). IR (film) 2974, 1727, 1691, 1588 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.39 (9H, s), 0.72 (3H, d, *J* = 6.7 Hz), 1.08 (3H, d, *J* = 6.8 Hz), 1.17 (3H, t, *J* = 7.1 Hz), 1.25 (3H, t, *J* = 7.1 Hz), 1.70 (9H, s), 2.29-2.31 (1H, m), 3.12 (1H, t, *J* = 11.2 Hz), 3.63 (1H, d, *J* = 13.0), 3.90 (3H, s), 3.89-4.02 (3H, m), 4.05-4.19 (1H, m), 4.21-4.28 (1H, m), 4.30-4.38 (1H, m), 6.59 (1H, d, *J* = 7.9 Hz), 7.17 (1H, t, *J* = 8.2 Hz), 7.61 (1H, d, *J* = 8.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 2.9, 14.2, 16.6, 19.2, 28.2, 31.1, 31.9, 54.8, 58.0, 60.2, 60.4, 83.3, 102.4, 108.2, 121.4, 124.9, 130.0, 135.7, 139.0, 151.4, 154.2, 162.8, 164.6; EIMS (*m/e*, relative intensity): 543 (M^+, 27), 472 (22), 332 (35), 276 (100), 232 (64), 169 (38). Anal. Calcd for $C_{29}H_{45}N_3O_5Si$: C, 64.05; H, 8.34; N, 7.73. Found: C, 64.54; H, 8.48; N, 7.63.

3-(((2*R*,5*S*)-3,6-Diethoxy-5-isopropyl-2,5-dihydropyrazin-2-yl)methyl)-4-methoxy-2-(triethylsilyl)-1H-indole (22a). The TES substituted 4-methoxytryptophan derivative **22a** was prepared analogous to the TMS derivative **22b** in 70% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72 (3H, d, *J* = 6.8 Hz), 0.91 (6H, t, *J* = 8.2 Hz), 0.96-1.06 (9H, m), 1.10 (3H, d, *J* = 7.0 Hz), 1.17 (6H, dt, *J* = 2.9, 7.1 Hz), 2.28-2.46 (1H, m), 3.00 (1H, dd, *J* = 10.0, 13.5 Hz), 3.50 (1H, dd, *J* = 5.1, 13.5 Hz), 3.87 (3H, s), 3.89-3.96 (2H, m), 4.10-4.23 (1H, m), 4.36-4.45 (1H, m), 6.41 (1H, d, *J* = 7.7 Hz), 6.95 (1H, dd, *J* = 0.7, 8.0 Hz), 7.05 (1H, t, *J* = 8.0 Hz), 7.88 (1H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 3.8 (3 carbons), 7.4 (3 carbons), 14.16, 14.24, 16.5, 19.3, 30.9, 32.8, 54.6, 58.8, 60.0, 60.2, 60.3, 98.5, 103.9, 119.4, 122.6, 123.4, 130.0, 140.2, 154.6, 162.8, 164.9. EIMS (*m/e*, relative intensity): 485 (M^+, 19.8), 276 (15.2), 275 (39.1), 274 (100), 246 (8.3), 212 (15.5), 169 (14.3). HRMS m/z: $C_{27}H_{44}N_3O_3Si$ $(M+H)^+$ cacld: 486.3152, found: 486.3164.

4-Methoxy-(D)-tryptophan ethyl ester (20). To a solution of 4-methoxytryptophan derivative **22b** (25.5 g, 57.5 mmol) in THF (500 mL) was added 2 N aq HCl (400 mL) at 0 °C. The solution was stirred at rt for 3 h, ice (100g) was added and the pH of the reaction mixture was adjusted to 8 (pH paper) with aq NH_4OH (conc) at 0 °C. The mixture was extracted with EtOAc and the organic layers were combined and washed with water, brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was subjected to Kugelrohr distillation at 80 °C (0.3 mm Hg) to remove L-valine ethyl ester while pure 4-methoxy-D-tryptophan ethyl ester (13.72 g, 91%) remained. This material was used directly in the next step. An analytical sample was obtained by flash chromatography (gradient elution from hexane to 80% EtOAc in hexane) to afford the desired 4-methoxyindole **20** as a light yellow solid. $[\alpha]_D^{25}$ -9.7° (*c* 1.01, CH_3CH_2OH), IR (film) 3362, 3156, 2956, 1732, 1586, 1511, 1463, 1434, 1361 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (3 H, t, *J* = 7.1 Hz), 1.75 (2H, s, b), 2.95 (1H, dd, *J* = 8.5, 13.9 Hz), 3.50 (1H, dd, *J* = 4.4, 13.9 Hz), 3.91 (1H, m), 3.94 (3H, s), 4.20 (2H, q, *J* = 7.1 Hz), 6.50 (1H, d, *J* = 7.7 Hz), 6.88 (1H, s), 6.96 (1H, d, *J* = 8.0 Hz), 7.09 (1H, t, *J* = 7.9 Hz), 8.37 (1H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 29.6, 54.9, 55.7, 60.5, 99.3, 104.5, 111.9, 117.2, 121.8, 122.8, 138.1, 154.5, 175.6; EIMS (*m/e*, relative intensity): 262 (M^+, 7.3), 189 (7.4), 160 (100), 130 (27.0). HRMS m/z: $C_{14}H_{19}N_2O_3$ $(M+H)^+$ cacld: 263.1396, found: 263.1392.

(*R*)-Ethyl 2-(*tert*-Butoxycarbonylamino)-3-(4-methoxy-1H-indol-3-yl)propanoate (26). To the solution of 4-methoxytyptophan ethyl ester (**20**) (40 mg, 0.152 mmol) in THF (2 mL) was added $(Boc)_2O$ (66 mg, 0.304 mmol). The solution was heated to reflux for 4 h until the disappearance of the starting material by TLC (silica gel). The solvent

was removed under reduced pressure and the residue was purified by flash column chromatography (gradient elution from hexane to 50% EtOAc in hexane) to provide the N_b-Boc derivative **26** in 90% yield (49 mg). IR (film) 3290, 1729, 1682, 1514, 1366 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (3H, t, *J* = 7.2 Hz), 1.31 (9H, s), 3.12-3.46 (2H, m), 3.94 (3H, s), 4.14 (2H, q, *J* = 7.3 Hz), 4.38-4.52 (1H, m), 5.69 (1H, d, *J* = 6.8 Hz), 6.49 (1H, d, *J* = 7.7 Hz), 6.88 (1H, s), 6.94 (1H, d, *J* = 8.0 Hz), 7.07 (1H, t, *J* = 8.0 Hz), 8.12 (1H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 28.1, 29.1, 54.9, 55.7, 60.8, 79.1, 99.5, 104.7, 111.0, 117.4, 121.8, 122.8, 137.8, 154.0, 155.5, 172.8; EIMS (*m/e*, relative intensity): 362 (M^+, 32.2), 289 (11.5), 245 (14.6), 160 (100). HRMS m/z: $C_{19}H_{27}N_2O_5$ $(M+H)^+$ cacld: 363.1920, found: 363.1913.

4-Methoxy-D-tryptophan benzyl ester (27). To the solution 4-methoxy-(D)-tryptophan ethyl ester **20** (1.8 g, 6.87 mmol) in ethanol (35 mL) was added aq 1 N NaOH (22 mL, 22 mmol). The solution was heated to 45 ºC for 3 h until complete consumption of starting material (by TLC). Aqueous 2 N HCl (~ 11 mL) was added to this solution to bring the pH to 7 and the resulting mixture was cooled to 0 ºC after which a white precipitate formed. The precipitate was collected by vacuum filtration to afford a white solid (0.851 g after drying) and the filtrate was concentrated under reduced pressure. The yellow residue which resulted was extracted with 20% MeOH in CH_2Cl_2. The combined organic solution was concentrated under vacuum to give an additional amount of a light yellow solid (0.740 g after drying). IR (film) 3383, 1619, 1457, 1356 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ 2.87 (1 H, dd, *J* = 7.1, 13.9 Hz), 3.41-3.57 (2H, m), 3.83 (3H, s), 6.44 (1H, dd, *J* = 2.4, 6.0 Hz), 6.90-6.97 (2H, m), 7.03 (1H, s), 10.90 (1H, s); ^{13}C NMR (75.5 MHz, DMSO) δ 29.8, 55.3, 56.0, 99.1, 105.3, 111.0, 117.3, 122.0, 122.9, 138.5, 154.5.

Solid triphosgene (769 mg, 2.59 mol, 0.38 eq) was added in one portion at 45 °C to a suspension of 4-methoxy-D-tryptophan (1.6 g, 6.83 mmol) in dry THF (15 mL), after which the slurry was kept at 45-48 °C for 3 h. The solution was allowed to cool to rt, after which a saturated ethereal solution of anhydrous HCl (30 mL) was added to the reaction mixture. This was followed by addition of anhydrous benzyl alcohol (3.9 mL). After stirring carefully at rt for 2 d the solvent was removed under reduced pressure. At this point, anhydrous ethyl ether (30 mL) was added into the residue, after which a large amount of solid precipitated out of the solution. The solid was collected by vacuum filtration and washed with cold ethyl ether to afford the HCl salt of 4-methoxy-D-tryptophan benzyl ester **27**. The filtrate was concentrated under reduced pressure and a saturated ethereal solution of anhydrous HCl (25 mL) was added to this residue. Additional solid was collected from this solution following the same procedure as above. Both solids were combined and washed with cold ether to provide the HCl salt of the benzyl ester **27**. The free base, benzyl ester **27**, was obtained by a neutralization process as described below. The HCl salt of the benzyl ester **27** was added in portions to a mixture of ethyl acetate (100 mL) and cold dilute aq NH_4OH (30 mL) with stirring, after which the organic layer was separated from the aq layer. The aq layer was extracted with ethyl acetate. The organic layers were combined and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was loaded onto a short wash column. The column was eluted with ethyl acetate (20%)/hexane to remove benzyl alcohol. The 4-methoxy-(D)-tryptophan benzyl ester **27** was eluted with MeOH (8%)/CH_2Cl_2. After removal of the solvent under reduced pressure the ester **27** was obtained. $[\alpha]_D^{25}$ - 26.81° (*c* 0.94, CH_3CH_2OH), IR (film), 3366, 1731, 1586, 1510, 1361 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$) δ 1.73 (2H, s, b), 2.99 (1H, dd, *J* = 8.6, 13.7 Hz), 3.52 (1H, dd, *J* = 4.8, 13.7), 3.86 (3H, s), 4.00 (1H, dd, *J* = 4.8, 8.6 Hz), 5.16 (2H, s), 6.48 (1H, d, *J* = 7.9 Hz), 6.78 (1H, d, *J* = 1.5 Hz), 6.94 (1H, d, *J* = 8.2 Hz), 7.08 (1H, t, *J* = 8.0 Hz), 7.28-7.48 (5H, m), 7.94 (1H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 32.7, 54.9, 55.7, 66.3, 99.3, 104.6, 111.4, 117.2, 122.0, 122.7, 128.0 (3 carbons), 128.4 (2 carbons), 135.8, 138.1, 154.4, 175.2. Anal. Calcd for the HCl salt $C_{19}H_{21}ClN_2O_3 \bullet H_2O$: C, 60.24; H, 6.12; N, 7.39, found: C, 60.60; H, 5.76; N, 7.73. HRMS m/z: $C_{19}H_{21}N_2O_3$ $(M+H)^+$ cacld: 325.1552, found: 325.1538.

(*R*,*Z*)-Benzyl 2-(2-Iodobut-2-enylamino)-3-(4-methoxy-1H-indol-3-yl)propanoate (7)

To a mixture of benzyl ester **27** (2.8 g, 8.64 mmol) , allylic bromide **28** (2.37 g, 9.08 mmol), cesium carbonate (2.850 g, 8.74 mmol) and 4 Å molecular sieves (2 g) was added dry THF (10 mL) and DMF (10 mL). The suspension which resulted was stirred at rt for 18 h, after which it was poured into EtOAc (250 mL) and water (50 mL). This mixture was filtered through Celite to remove the molecular sieves. The aq layer was extracted with EtOAc and the organic layer was washed with water, brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to give a yellow oil, which was purified by flash column chromatography (gradient elution from hexane to 50% EtOAc in hexane) to give the desired secondary amine **7** (3.70 g, 86%) as a white powder. IR (film) 3397, 2932, 2835, 1731 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (3 H, d, *J* = 6.4 Hz), 2.04 (1 H, b), 3.20 (1 H, dd, *J* = 13.7, 7.9 Hz), 3.55 (1 H, dd, *J* = 13.5, 6.4 Hz), 3.44 (2 H, q, *J* = 14.0 Hz), 3.83 (1 H, dd, *J* = 7.7, 6.4 Hz), 3.89 (3 H, s), 5.11 (2 H, s), 5.57 (1 H, q, *J* = 6.4 Hz), 6.49 (1 H, d, *J* = 8.05 Hz), 6.84 (1 H, d, *J* = 2.2 Hz), 6.95 (1 H, d, *J* = 8.0 Hz), 7.10 (1 H, t, *J* = 8.0 Hz), 7.16-7.24 (2 H, m), 7.29-7.35 (3 H, m), 8.02 (1 H, s); ^{13}C NMR (75.5

MHz, $CDCl_3$) δ 14.1, 21.5, 30.9, 54.9, 59.5, 60.2, 99.4, 104.4, 109.6, 111.6, 117.3, 121.9, 122.8, 128.0 (3 carbons), 128.4 (2 carbons), 131.6, 135.9, 138.0, 154.6, 174.7; EIMS (*m/e*, relative intensity) 504 (M^+, 30.5), 369 (29.5), 344 (12.2), 188 (32.2), 160 (100). Anal. Calcd for $C_{23}H_{25}IN_2O_3$: C, 54.77; H, 5.00; N, 5.55, found: C, 54.62; H, 4.98; N, 5.48.

(1*S*,3*R*,*Z*)-Benzyl 2-(2-iodobut-2-enyl)-5-methoxy-1-(4-methoxy-4-oxo-3,3-bis(phenyl thio)butyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (29). To a solution of secondary amine **7** (2.50 g, 4.96 mmol) and aldehyde **8** (1.71 g, 4.94 mmol) in CH_2Cl_2 (25 mL) was added acetic acid (1.3 mL, 5.0 eq) at 0 °C. The mixture was warmed to rt and stirred for 5 d. Alternatively, the *cis* and *trans* mixture (obtained after stirring **7** and **8** with acetic acid in CH_2Cl_2 for 1 day) could be stirred in dilute TFA/CH_2Cl_2 solution for 30 min, The mixture was poured into water, brought to pH = 9 with cold aq NH_4OH and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was chromatographed using gradient elution (gradient elution from hexane to 15% EtOAc in hexane) to afford the desired indole **29** (3.70 g, 90%) as a foam. IR (film) 3389, 3120, 2950, 1729, 1621, 1571, 1510, 1436cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71 (3H, d, *J* = 6.4 Hz), 1.76-1.93 (1H, m), 1.94-2.10 (2H, m), 2.17-2.36 (1H, m), 3.12 (1H, dd, *J* = 5.1, 10.8 Hz), 3.28-3.46 (2H, m), 3.47-3.59 (1H, m), 3.57 (3H, s), 3.80 (1H, t, *J* = 5.5 Hz), 3.89 (3H, s), 4.12 (1H, t, *J* = 4.2 Hz), 5.05 (2H, s), 5.74 (1H, q, *J* = 6.6 Hz), 6.48 (1H, d, *J* = 7.9 Hz), 6.83 (1H, d, *J* = 8.0 Hz), 7.03 (1H, t, *J* = 8.0 Hz), 7.11-7.59 (16H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.7, 25.0, 28.9, 31.4, 52.6, 54.5, 55.1, 56.2, 61.2, 65.7, 69.18, 99.6, 104.4, 107.4, 108.7, 116.9, 122.1, 127.5, 127.8, 128.2, 128.6,

128.7, 129.3, 130.8, 131.2, 131.9, 132.0, 135.8, 136.0, 137.4, 154.1, 169.9, 172.7; EIMS (*m/e*, relative intensity): 832 (M^+, 14.8), 697 (7.5), 651 (16.0), 515 (100), 379 (23.5), 199 (22.5).

(1*S*,3*R*)-Benzyl 2-((*Z*)-2-iodobut-2-enyl)-5-methoxy-1-((*E*)-4-methoxy-4-oxobut-2-enyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (6). To a solution of the thioketal **29** (3.50 g, 4.20 mmol) in freshly distilled THF (25 mL; DME works as well), thiophenol (0.47 mL 1.1 eq) was added at rt and this was followed by addition of a 60% dispersion of NaH (32 mg) in mineral oil. The mixture was stirred at rt for 12 h, it was poured into water (50 mL) and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography using gradient elution (gradient elution from hexane to 30% ethyl acetate in hexane) to afford the sulfide **30** (2.80 g) in 92% yield as a mixture of diastereomers (1:1) at the thiophenyl position. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72-1.98 (6H, m), 2.05-2.30 (1H, m), 3.12-3.28 (1H, m), 3.48-3.56 (2H, m), 3.56-3.77 (5H, m), 3.91 (3H, s), 3.92-4.01 (1H, m), 4.12-4.30 (1H, m), 5.05-5.13 (2H, m), 5.75-5.88 (1H, m), 6.52 (1H, d, *J* = 7.8 Hz), 6.91 (1H, d, *J* = 8.0 Hz), 7.07 (1H, d, *J* = 8.0 Hz), 7.20-7.58 (10H, m), 7.75 (0.5H, s), 7.86 (0.5H). This material was employed directly to the next step without further characterization.

To a solution of the 1:1 mixture of sulfides **30** (2.80 g) in CH_2Cl_2 (30 mL) was added a solution of m-CPBA (77%, 860 mg) in CH_2Cl_2 (8 mL) at –78 °C. The mixture was stirred at -78°C for 2h and then warmed slowly to rt. The reaction mixture was poured into a mixture of EtOAc (150 mL) and 10% aq NaOH (30 mL). The aq layer was extracted with EtOAc. The organic layers were combined and washed with 10% NaOH,

brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford the desired sulfoxide (2.54 g) in 89% yield as an oil. This material was used directly in the next step.

The combined sulfoxides were dissolved in toluene (50 mL) and K_2CO_3 (697 mg, 5.04 mmol) was added. The mixture was degassed and heated to reflux under argon for 3 h until the disappearance of starting material (TLC). After cooling, the reaction mixture was poured into EtOAc (250 mL) and water (40 mL). The aq layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was subjected to gradient flash chromatography (gradient elution from hexane to 20% EtOAc in hexanes) to provide the unsaturated ester **6** (1.94 g, 72% over 3 steps) as a light yellow solid. IR (film) 3384, 2948, 2834, 1723, 1654, 1508, 1435, 1353 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.78 (3 H, d, *J* = 6.3 Hz), 2.69-2.75 (2 H, m), 3.28 (1H, dd, *J* = 16.0, 5.2 Hz), 3.50 (1H, dd, *J* = 16.0, 5.8 Hz), 3.54 (1H, d, *J* = 15.4 Hz), 3.68 (1H, d, *J* = 16.9 Hz), 3.66-3.78 (1H, m), 3.71 (3H, s), 3.90 (3H, s), 3.98 (1H, t, *J* = 5.5 Hz), 4.3 (1H, t, *J* = 5.5 Hz), 5.11 (2H, s), 5.88 (2H, m), 6.51 (1H, d, *J* = 7.8 Hz), 6.91 (1H, d, *J* = 8.1 Hz), 7.07 (1H, t, *J* = 7.9 Hz), 7.23-7.30 (5H, m), 7.84 (1H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.6, 25.9, 37.0, 51.4, 55.1, 57.0, 63.5, 66.0, 99.7, 104.2, 107.4, 108.6, 116.8, 122.5, 123.1, 127.6, 127.8, 128.3, 131.6, 132.1, 135.9, 137.5, 145.8, 154.3, 166.6, 172.7; EIMS (*m/e*, relative intensity): 614 (M^+, 2.0), 515 (100), 379 (40.5), 199 (32.0), 184 (22.5). Anal. Calcd for $C_{29}H_{31}IN_2O_5$: C, 56.68; H, 5.09; N, 4.56, found: C, 56.62; H, 5.06; N, 4.42.

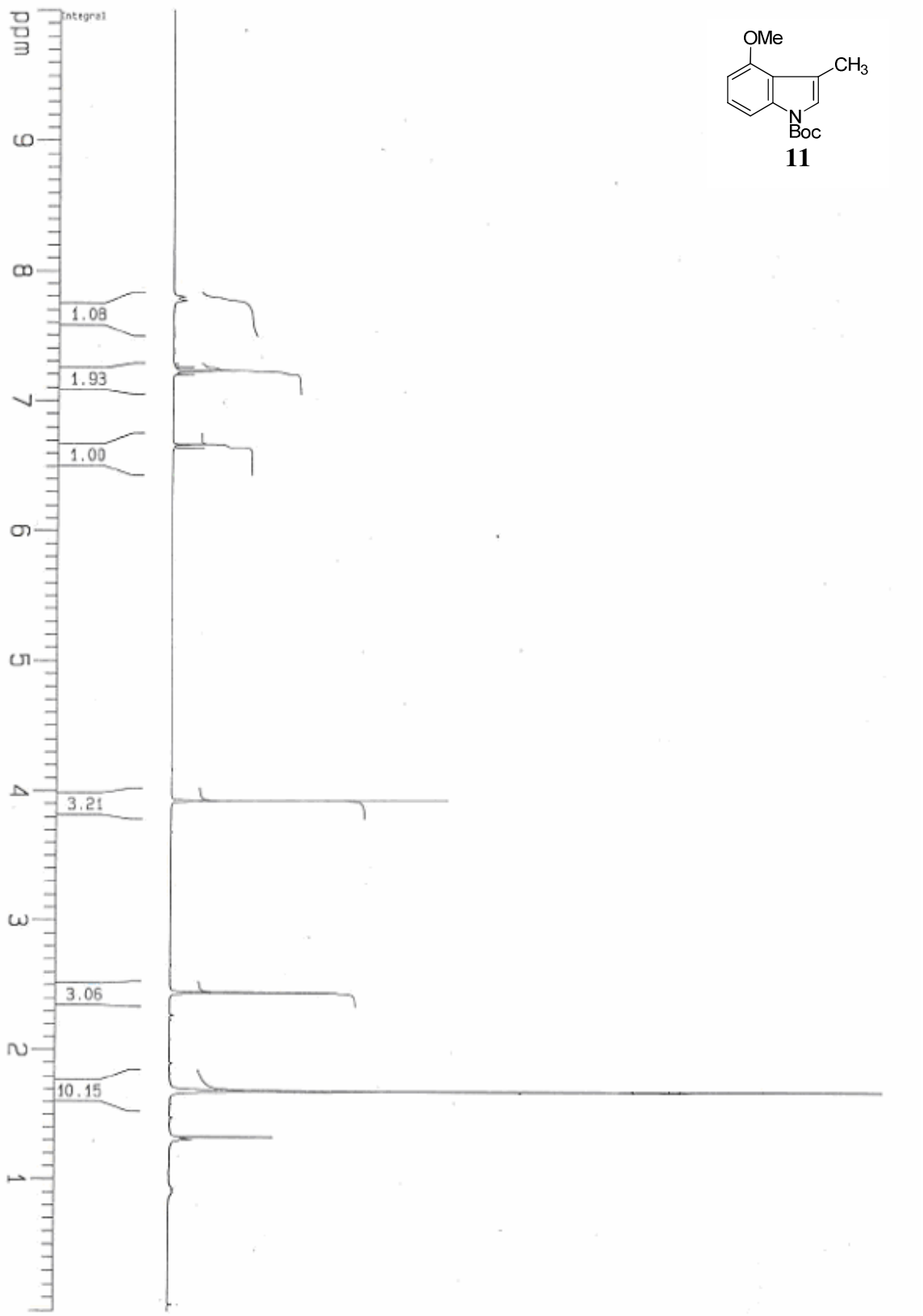
Methyl 2-((2*R*,12b*S*,*E*)-3-Ethylidene-8-methoxy-1,2,3,4,6,7,12,12b-octahydroindolo [2, 3-a]quino-lizin-2-yl)acetate (5). A mixture of the benzyl ester **31** (156 mg , 0.32

mmol), Et_3N (0.1 mL) and $PdCl_2$ (14 mg , 0.08 mmol) in Et_3SiH (3 mL) and freshly distilled toluene (5 mL) was stirred at rt for 6 h, at which time the starting material had disappeared (TLC). The solvent was removed under reduced pressure and the residue was subjected to flash chromatography (15% CH_3OH in CH_2Cl_2) to give the desired carboxylic acid (103 mg) in 91% yield. This carboxylic acid was employed directly in the next step.

To a solution of the acid (103 mg, 0.26 mmol) in anhydrous THF (10 mL) was added *iso*-butyl chloroformate (42 uL, 0.33 mmol) and NMM (0.32 uL, 0.30 mmol) at rt. The mixture was stirred at rt for 1 h at which time it was observed that all the starting material had disappeared (TLC). To the above solution was added C_6H_5SeLi [0.30 mmol, freshly prepared from C_6H_5SeH (52 mg) and of *n*-BuLi (0.12 mL, 2.5 M in hexanes; The C_6H_5SeH had been prepared from PhSeSePh (52 mg) and aq 50% H_3PO_2 (0.2 mL) in refluxing THF (2 mL)]. The mixture was stirred at rt for 1 h until examination by TLC indicated the disappearance of the mixed anhydride and the formation of the selenoester. The mixture was poured into water (10 mL) and ethyl acetate (50 mL). The aq layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was dissolved in anhydrous benzene (5 mL) and the solution was heated at reflux with Bu_3SnH (0.10 mL, 0.37 mmol) and AIBN (3 mg) for 4 h. At this time the selenoester was observed to have completely disappeared (TLC). The solvent was removed under reduced pressure and the residue was subjected to flash chromatography (2% methanol in ethyl acetate) to afford the tetracycle **5** (64 mg) 65% yield. IR (film) 3248, 2854, 1730, 1672, 1620, 1591, 1566, 1510, 1435, 1353 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.65 (3 H,

d, *J* = 5.7 Hz), 2.08-2.31 (4 H, m), 2.84-2.99 (2H, m), 3.08-3.30 (4H, m), 3.62 (1 H, d, *J* = 12.4 Hz), 3.67 (3 H, s), 4.10 (3 H, s), 4.34 (1 H, s), 5.49 (1 H, q, *J* = 6.7 Hz), 6.49 (1 H, d, *J* = 7.5 Hz), 6.98 (1 H, d, *J* = 7.9 Hz), 7.05 (1 H, t, *J* = 9.1 Hz), 8.70 (1 H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.6, 19.6, 30.2, 30.7, 37.7, 51.4, 51.7, 52.1, 53.0, 55.5, 99.6, 104.5, 107.1, 117.5, 121.4, 122.1, 130.9, 135.1, 137.3, 154.2, 173.8; EIMS (*m/e*, relative intensity) 354 (M^+, 100), 281 (70.2), 199 (71.3), 155 (52.0), 96 (97.1). HRMS m/z: $C_{29}H_{32}N_2O_5$ $(M+H)^+$ cacld: 355.2022, found: 355.2004.

(2*R*,3*S*,12bS)-*tert*-Butyl 3-Ethyl-8-methoxy-2-(2-methoxy-2-oxoethyl)-1,2,3,4,6,7-hexahydroindo-lo[2,3-a]quinolizine-12(12bH)-carboxylate (36). To a tetracyclic ester **35** (25 mg, 0.0701 mmol) solution in THF (2 mL) was added $(Boc)_2O$ (30 mg, 0.138 mmol). The solution was heated to reflux for 4 h until the disappearance of the starting material by TLC (silica gel). The solvent was removed under reduced pressure and the residue was purified by a flash column (gradient elution from hexane to 50% EtOAc in hexane)to provide the N_a-Boc derivative **36** in 91% yield (29 mg). IR (film) 2955, 2800, 1730, 1606, 1579, 1494, 1443, 1370 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 6.8 Hz), 1.18-1.39 (2H, m), 1.39-1.69 (2H, m), 1.65 (9H, s), 1.94-2.06 (1H, m), 2.09-2.32 (3H, m), 2.64-2.75 (2H, m), 2.76-2.94 (2H, m), 2.99 (2H, d, *J* = 10.8 Hz), 3.66 (3H, s), 3.62-3.69 (1H, m), 3.84 (3H, s), 6.60 (1H, d, *J* = 8.0 Hz), 7.12 (1H, t, *J* = 8.2 Hz), 7.68 (1H, d, *J* = 8.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.4, 18.3, 25.2, 28.0 (3 carbons), 32.9, 37.1, 38.2, 39.4, 51.2, 51.4, 55.3, 57.3, 61.2, 83.6, 103.4, 108.2, 117.0, 118.7, 124.3, 134.8, 138.5, 150.5, 153.9, 173.2; EIMS (*m/e*, relative intensity): 456 (M^+, 37.8), 399 (100), 355 (38.0), 327 (20.2), 299 (20.6), 281 (18.5), 258 (18.8), 244 (23.5), 199 (21.8).



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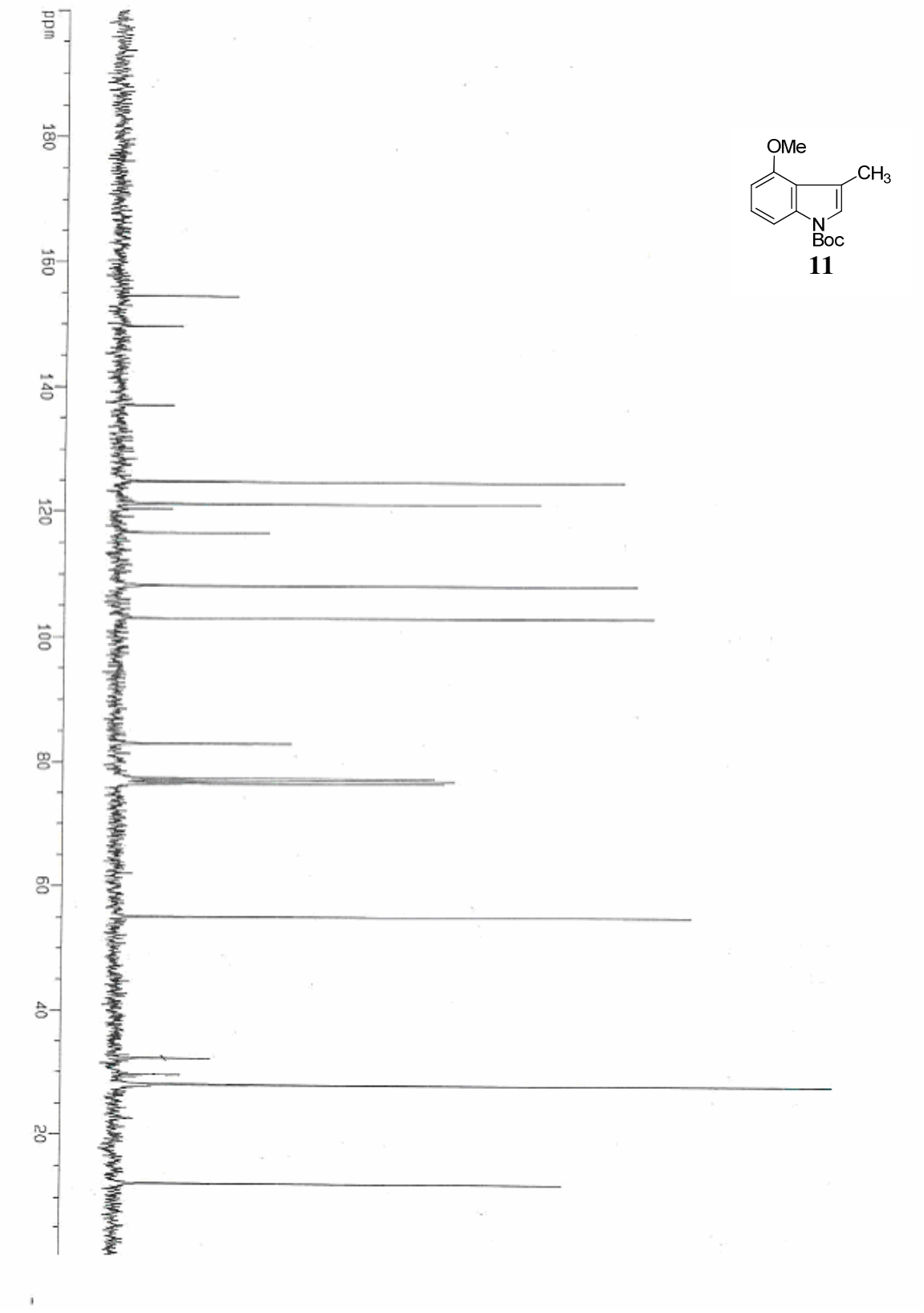

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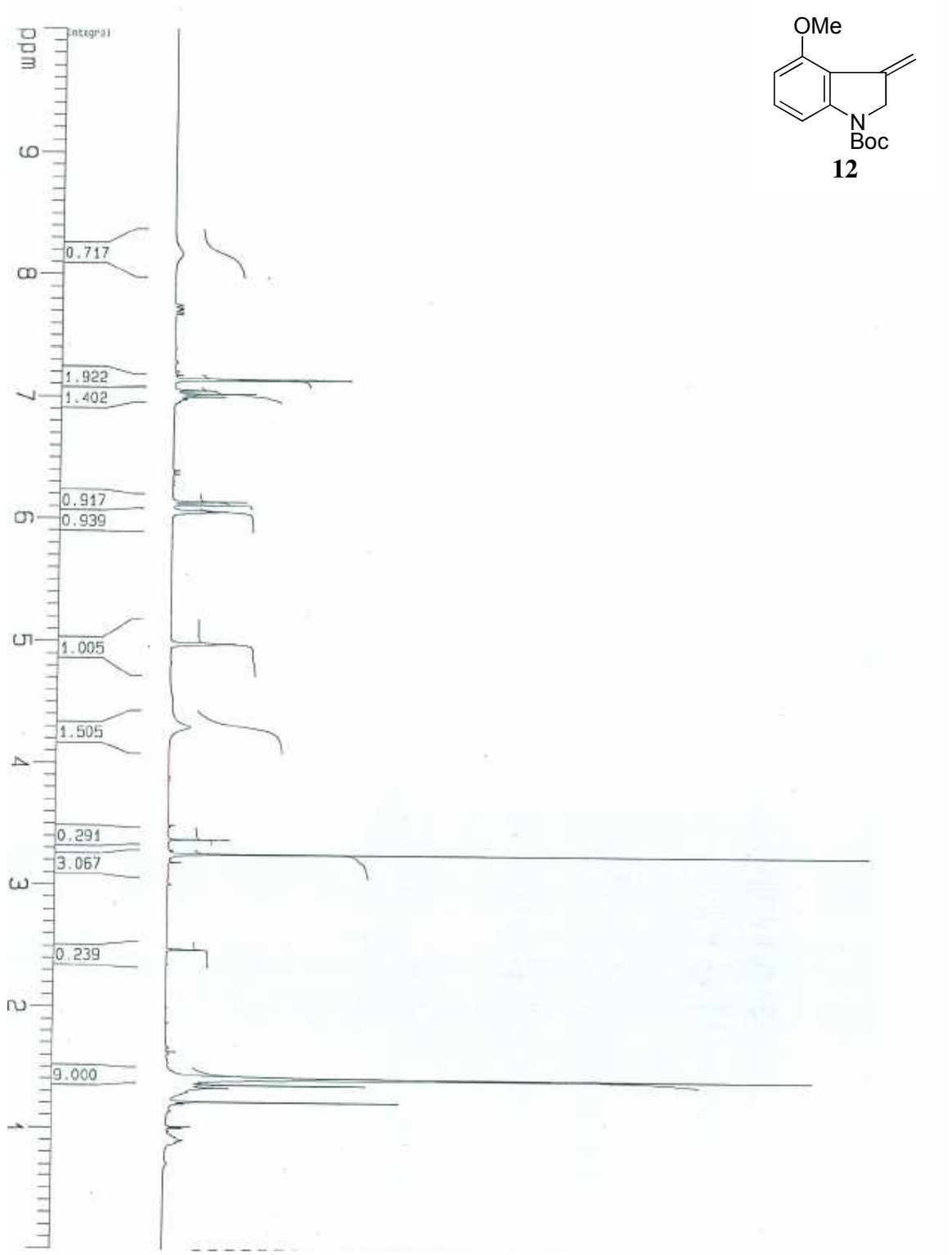
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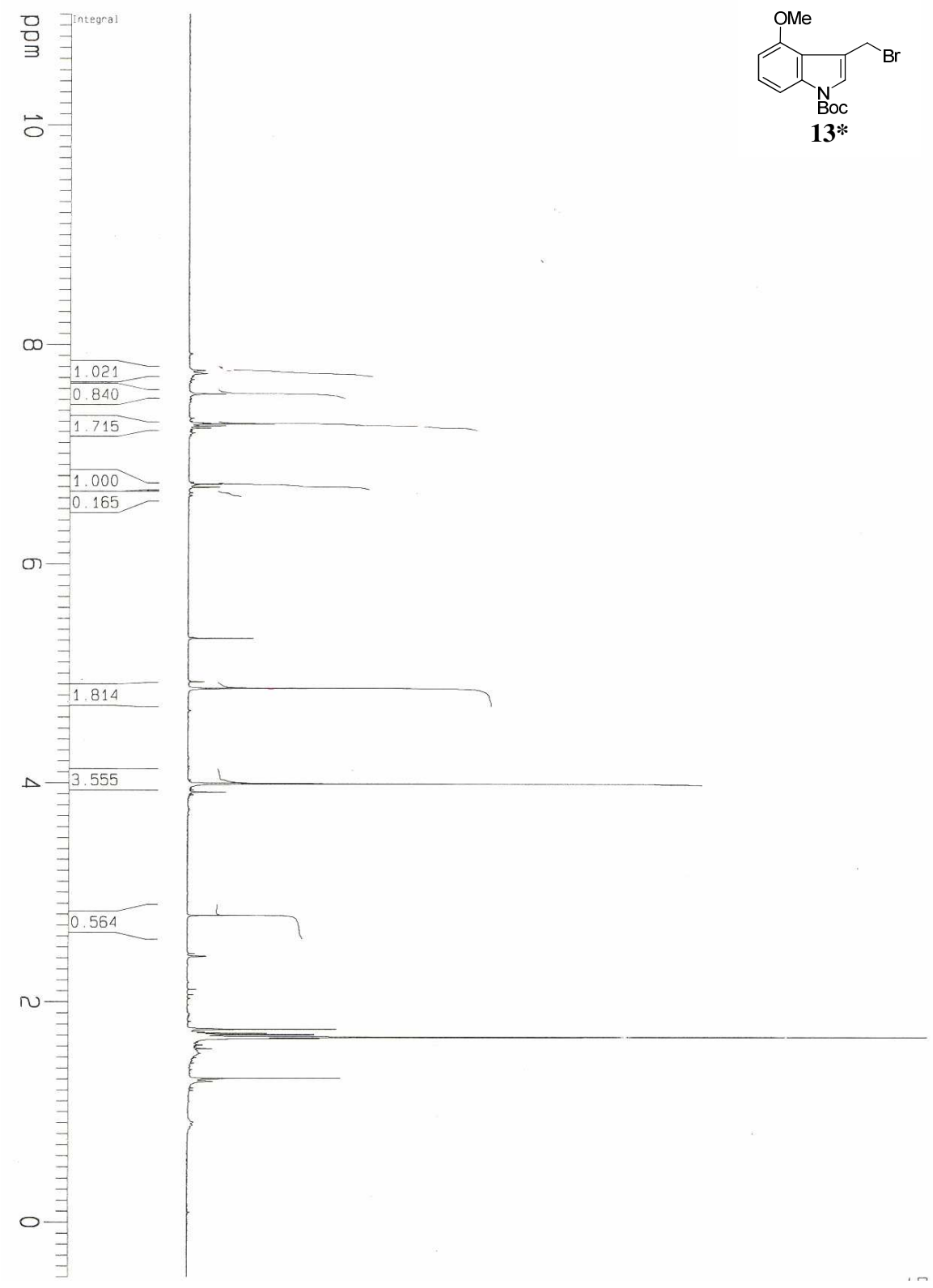
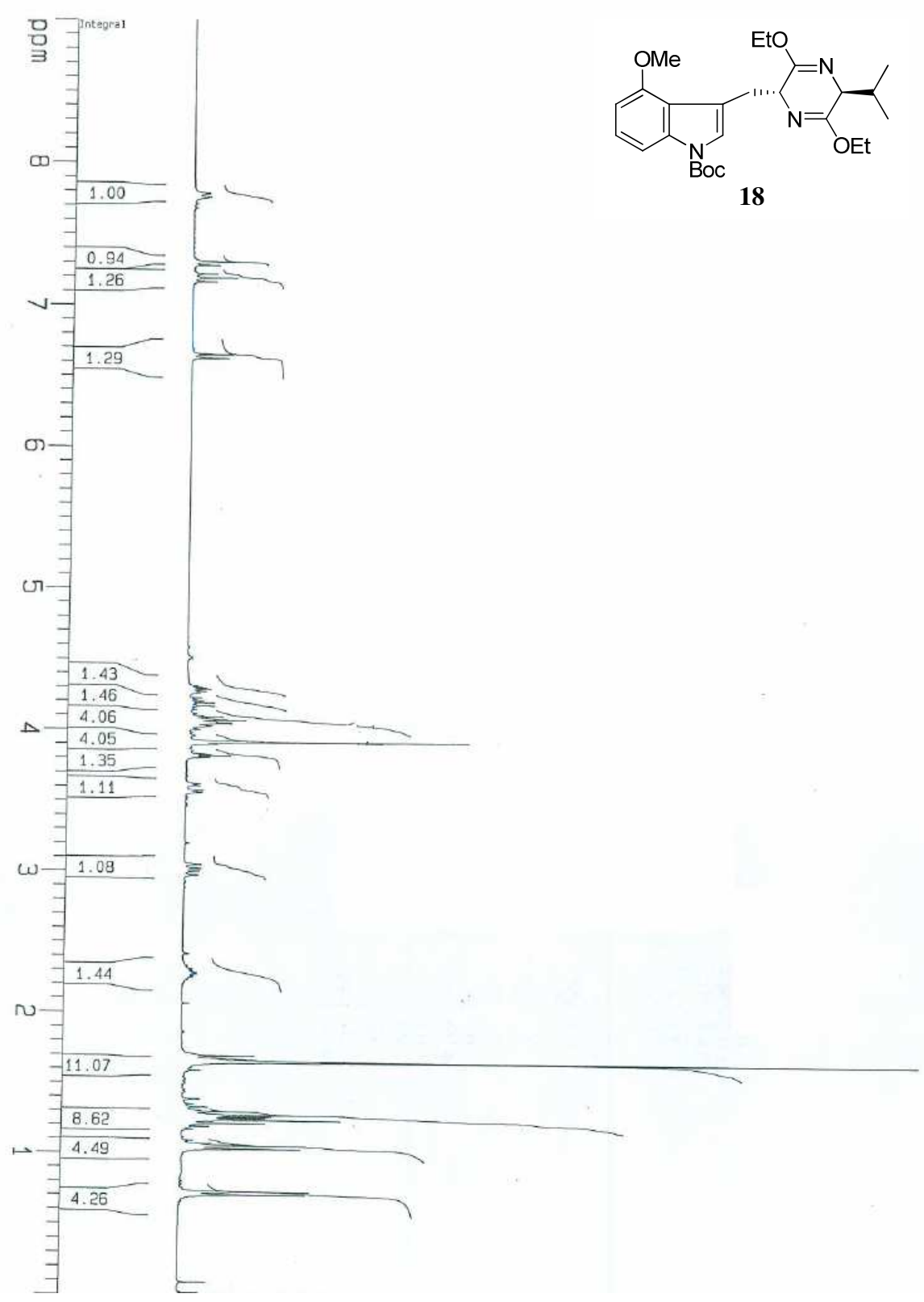


*: Compound **13** is not stable upon removal of the solvent. NMR was obtained by dissolving the crude CCl_4 solution of Compound **13** in $CDCl_3$.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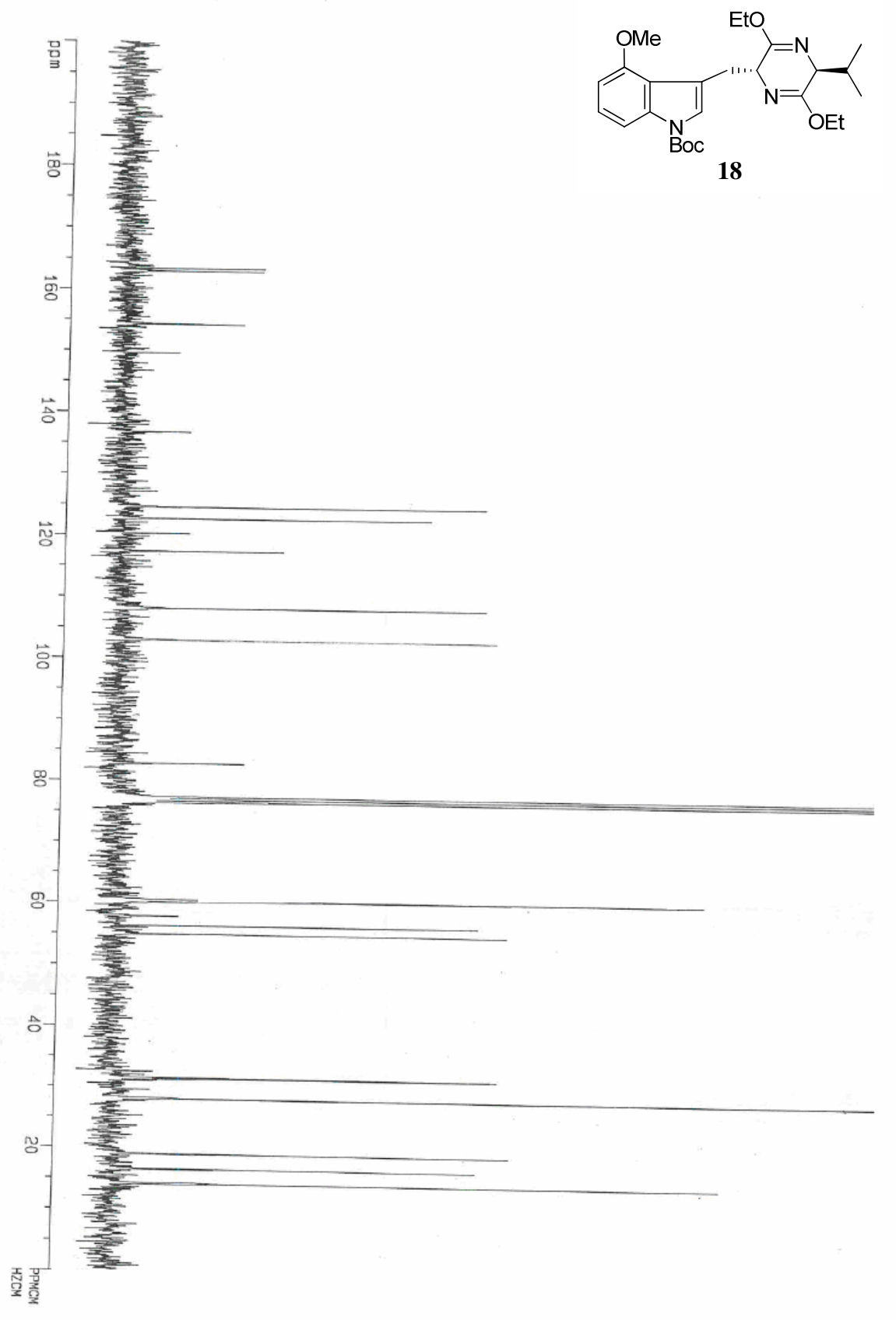
Boc

18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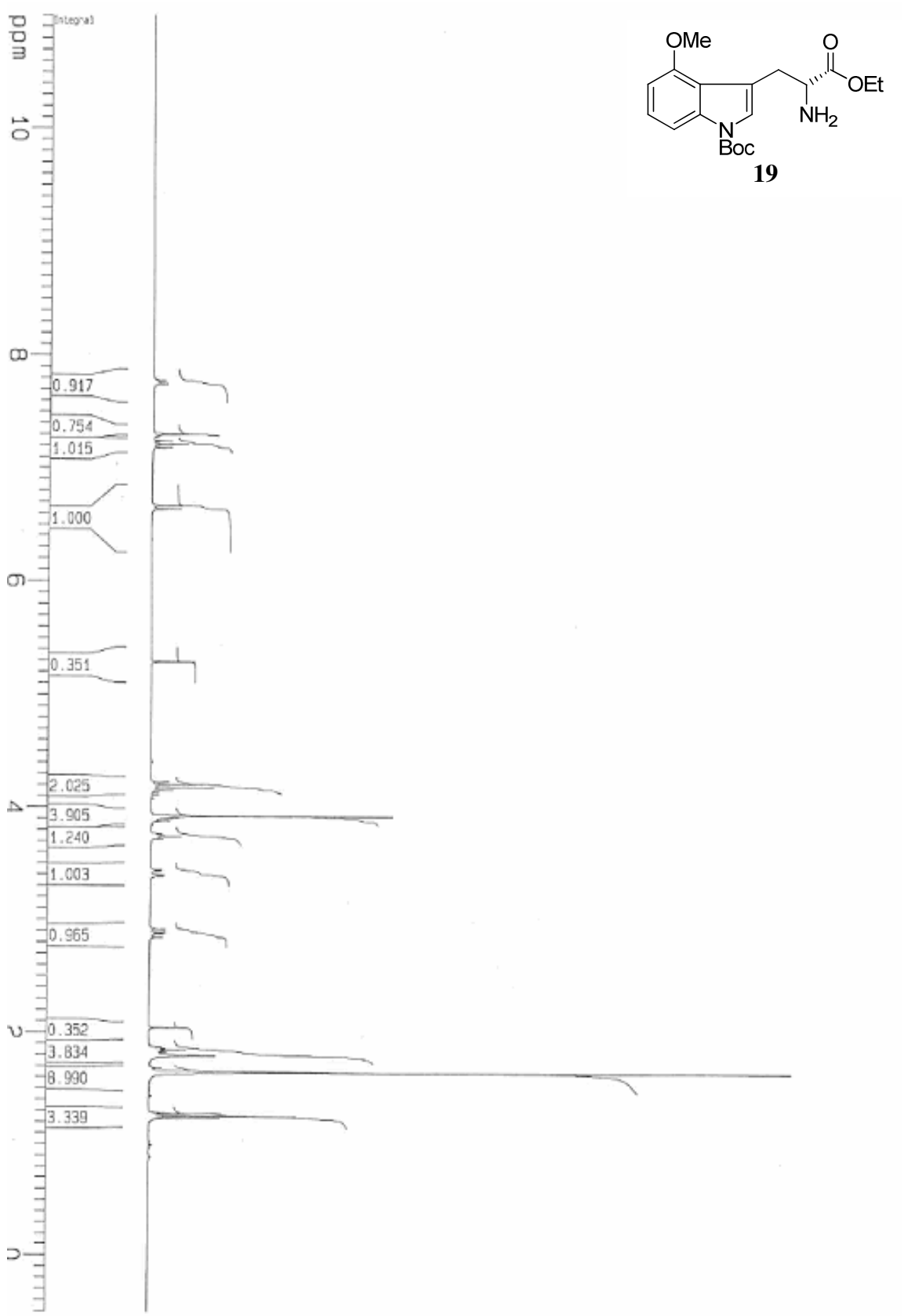
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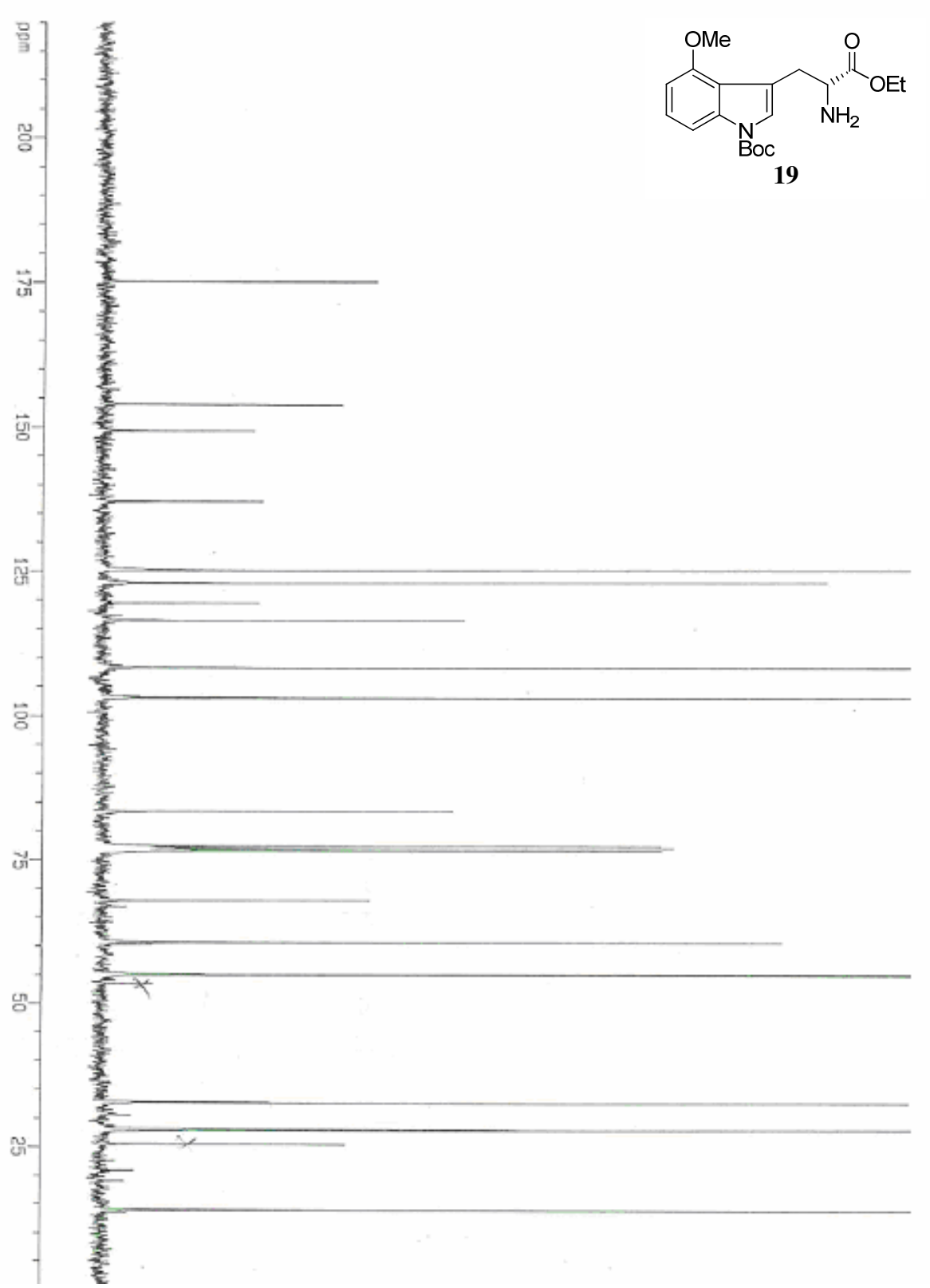
Boc

19



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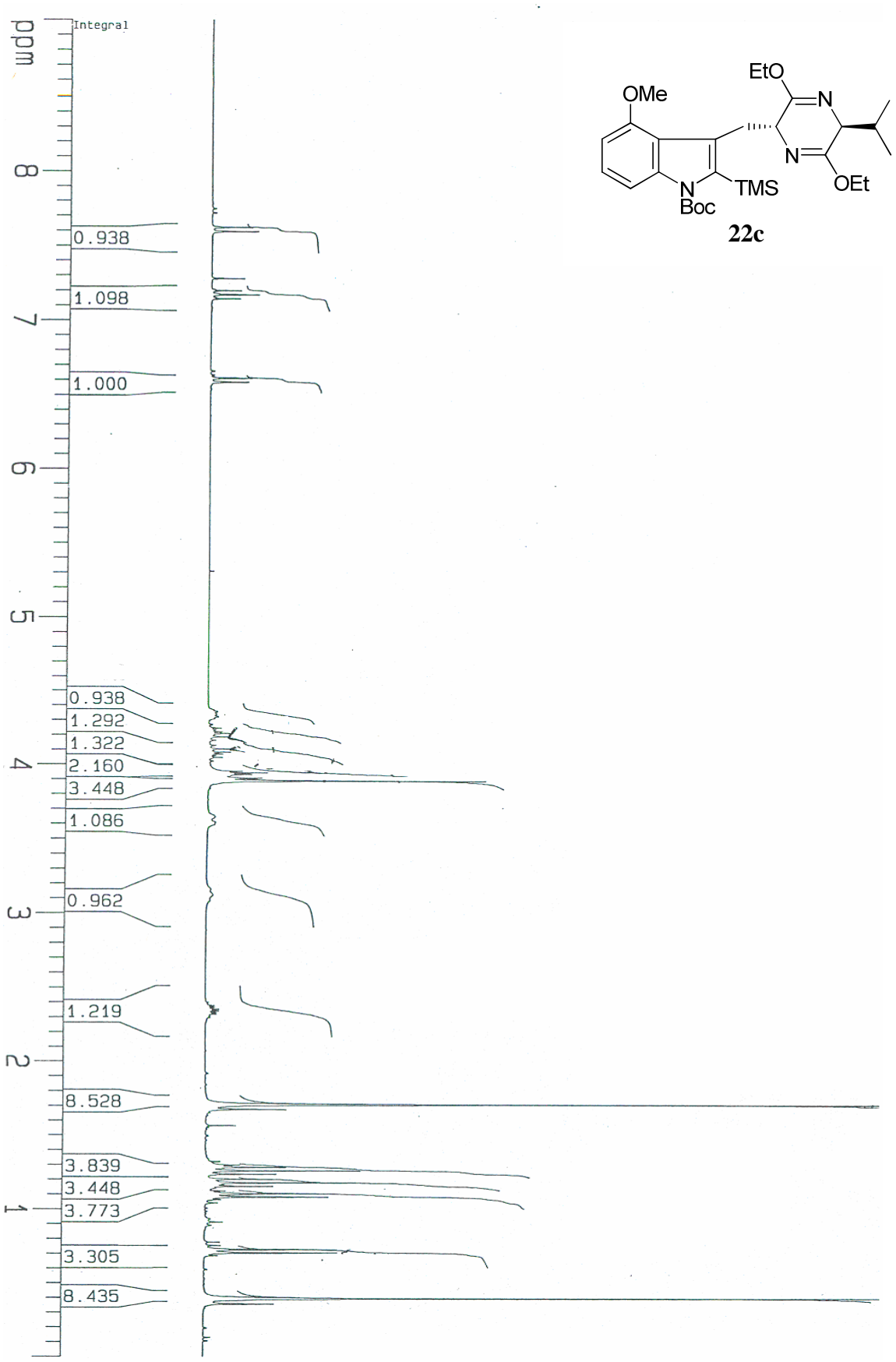
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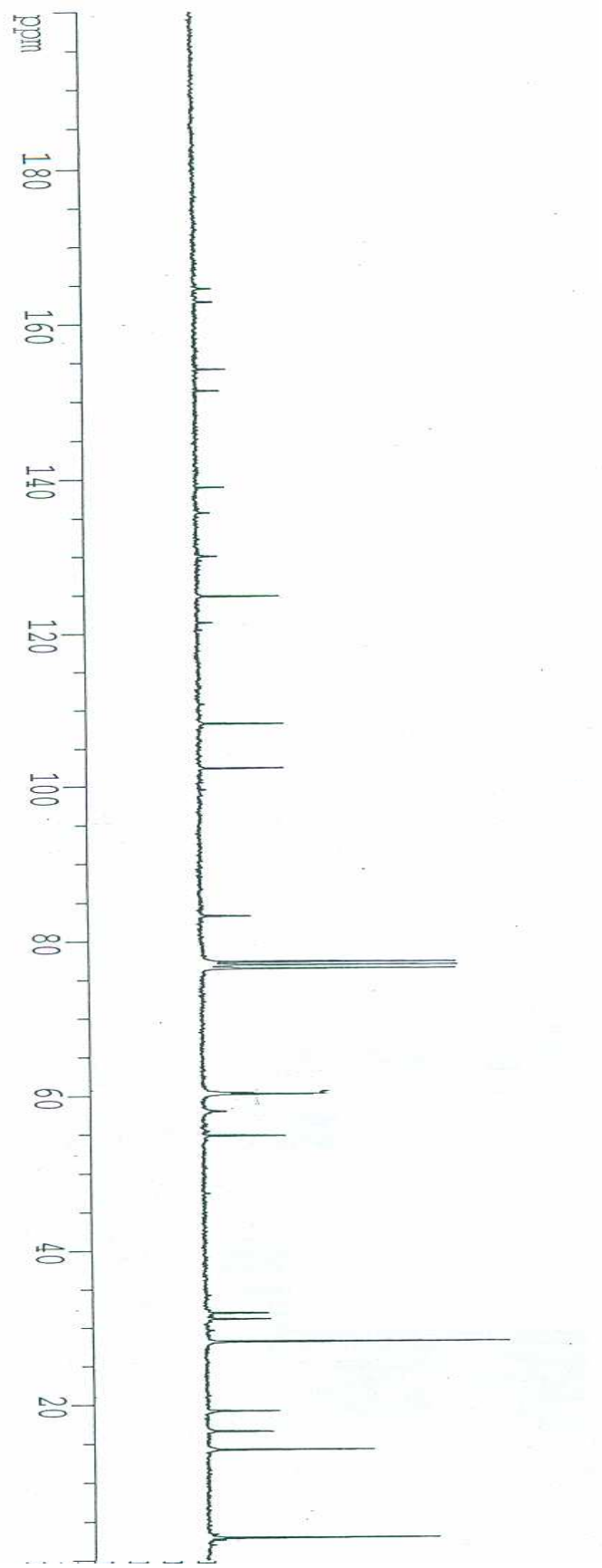
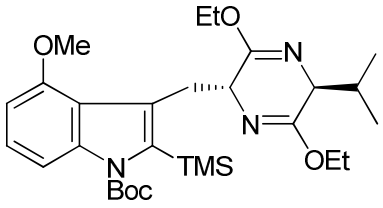
N
Boc
TMS

22c





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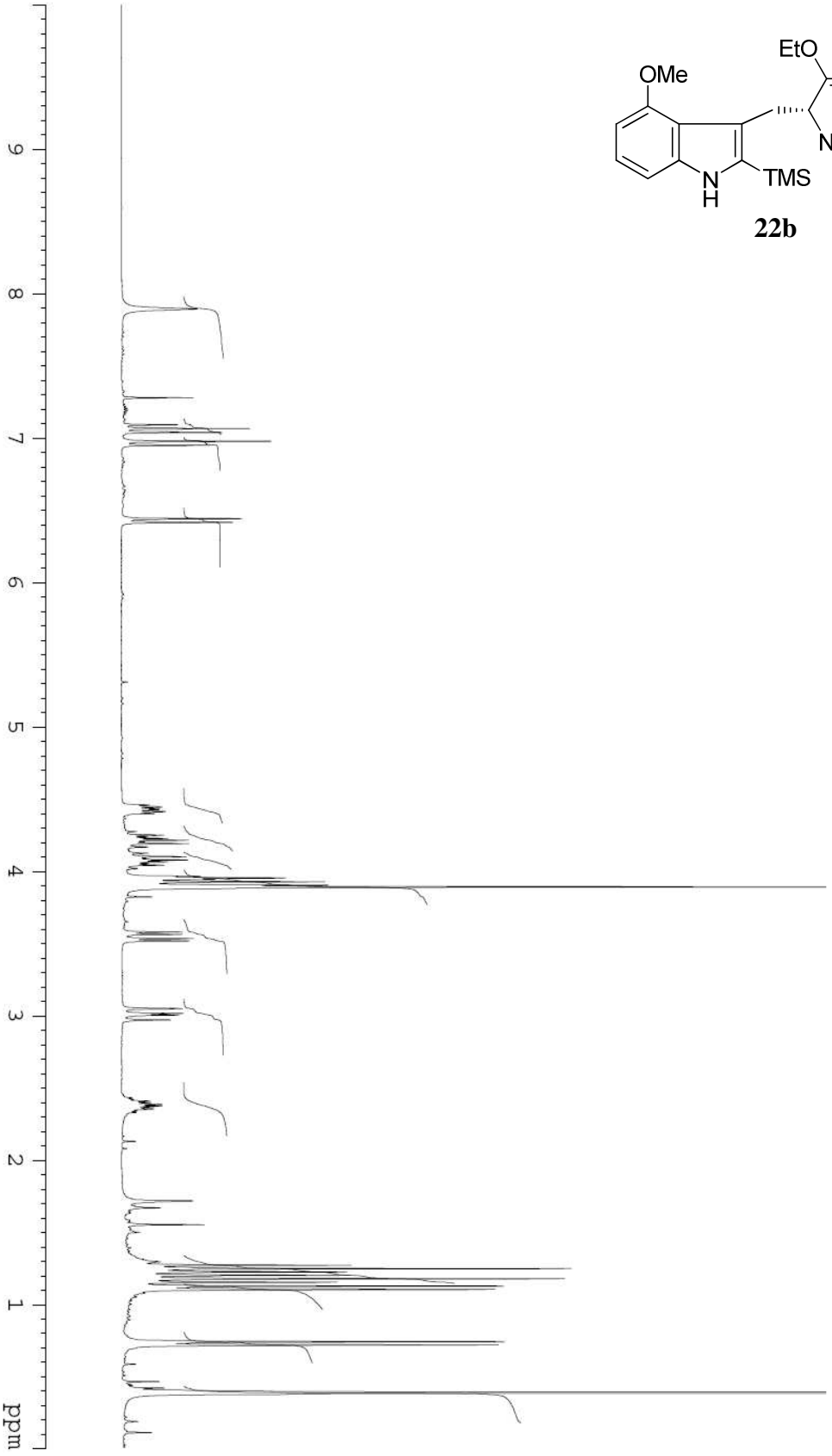

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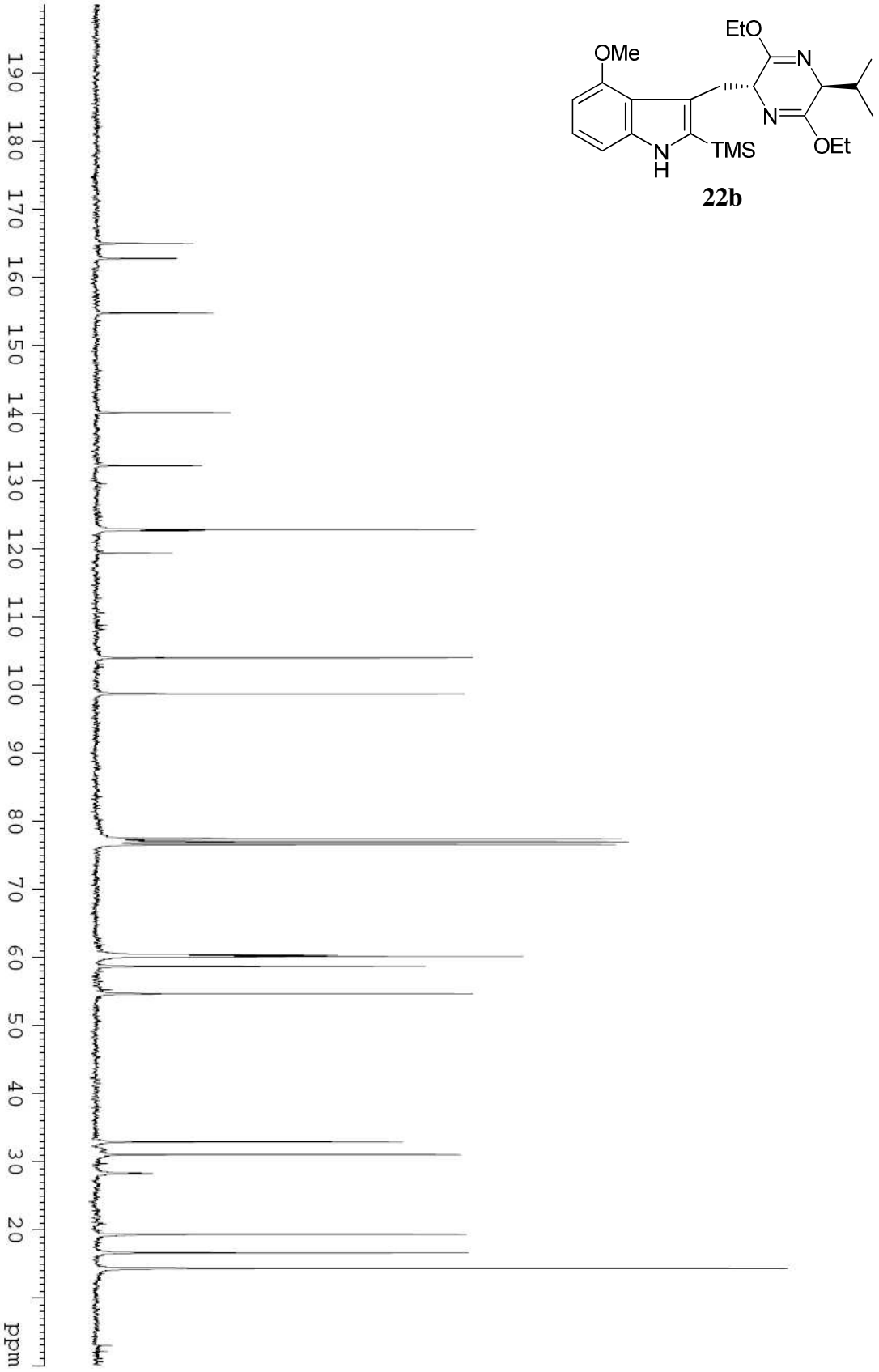
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H
TMS
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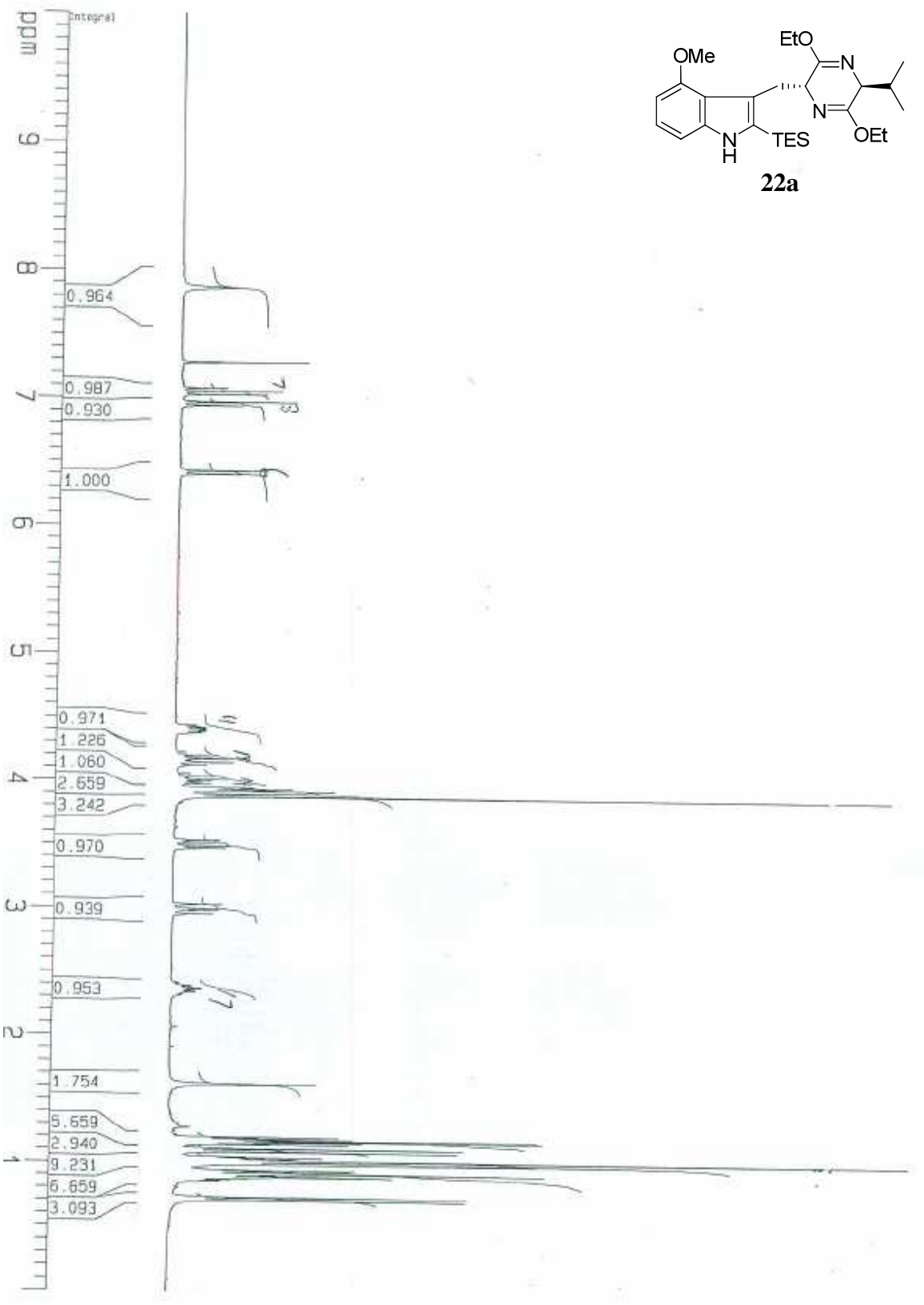
ppm

22b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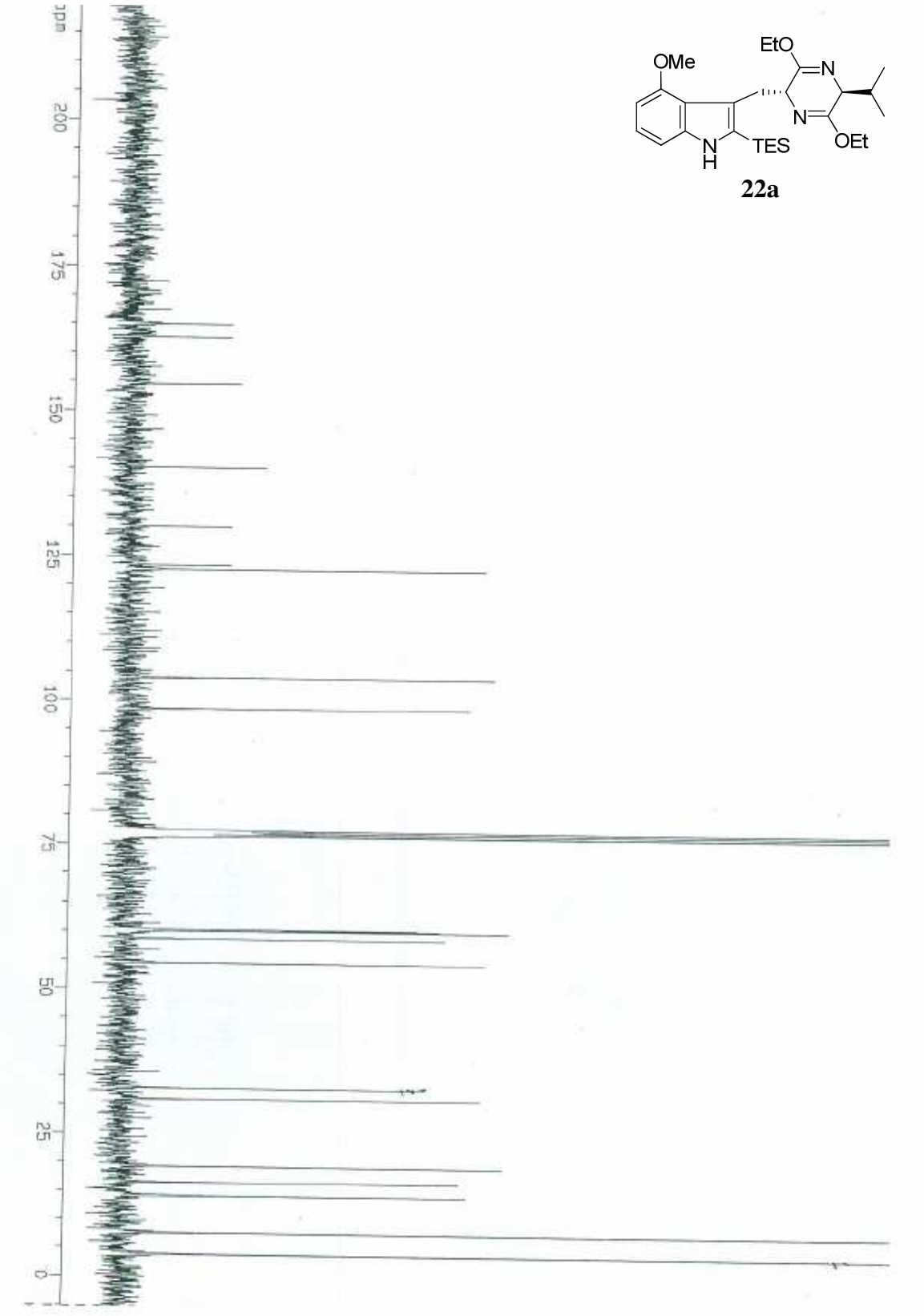
OEt
N
H
TES

22a



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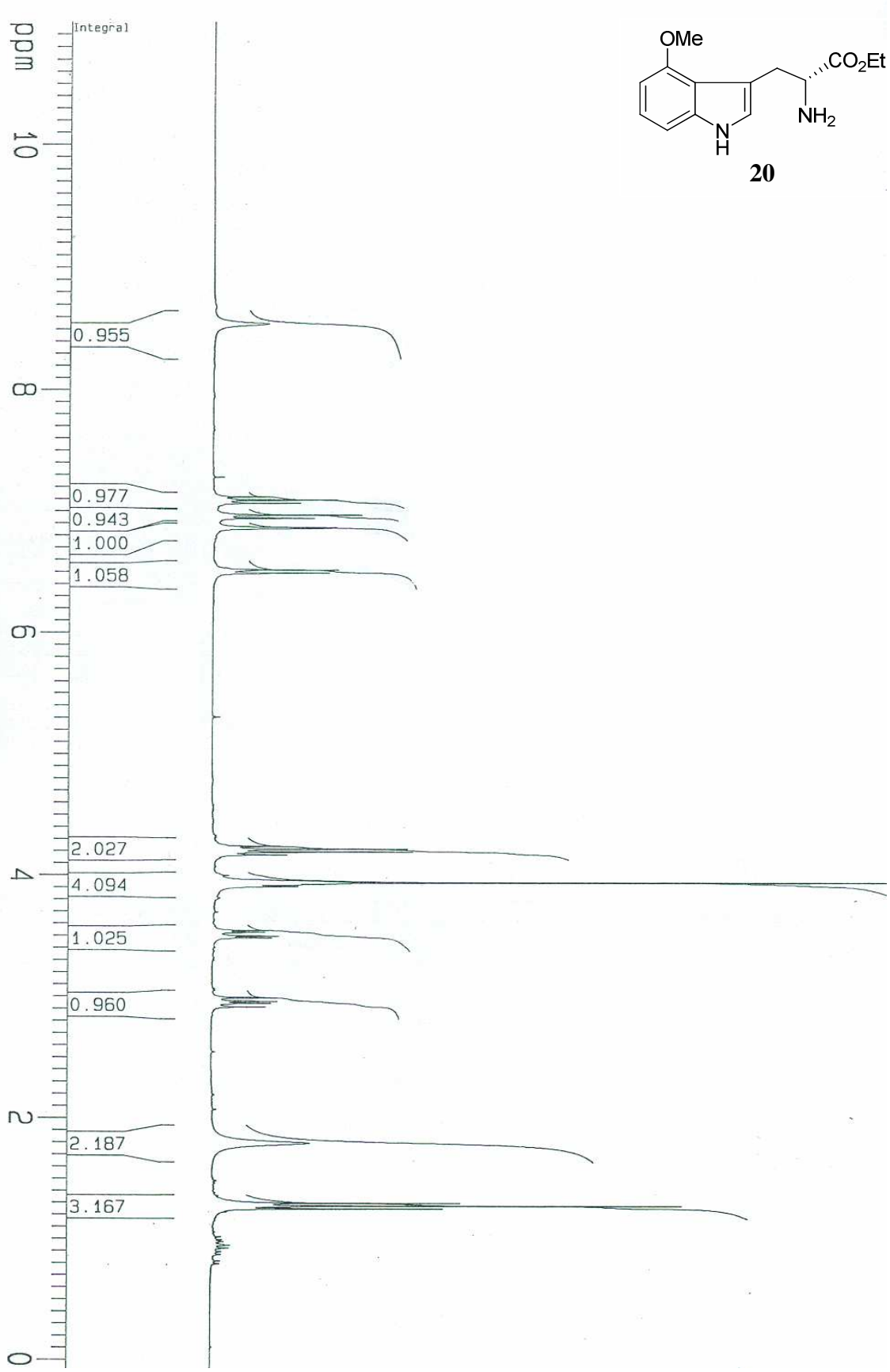
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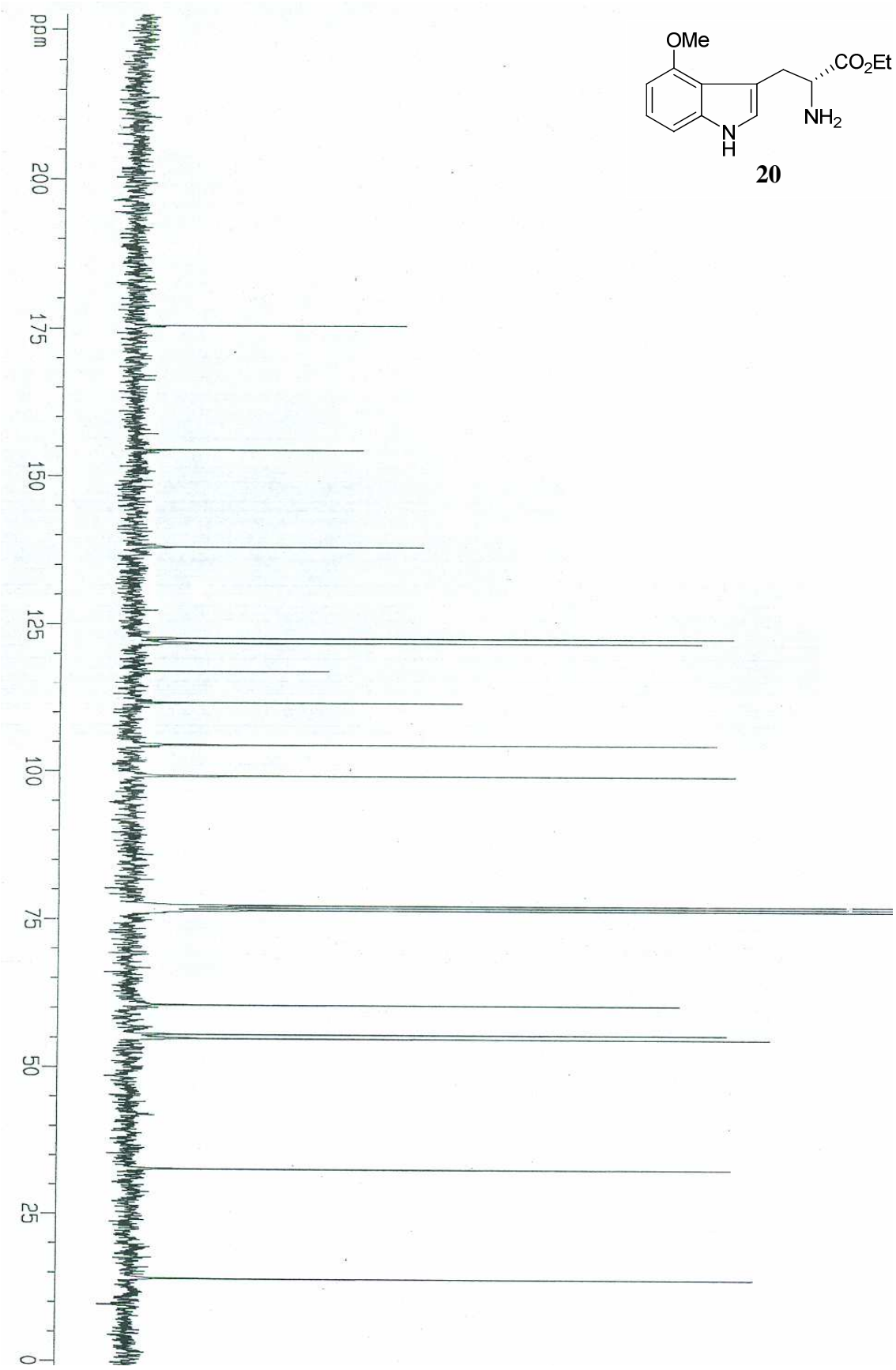
20



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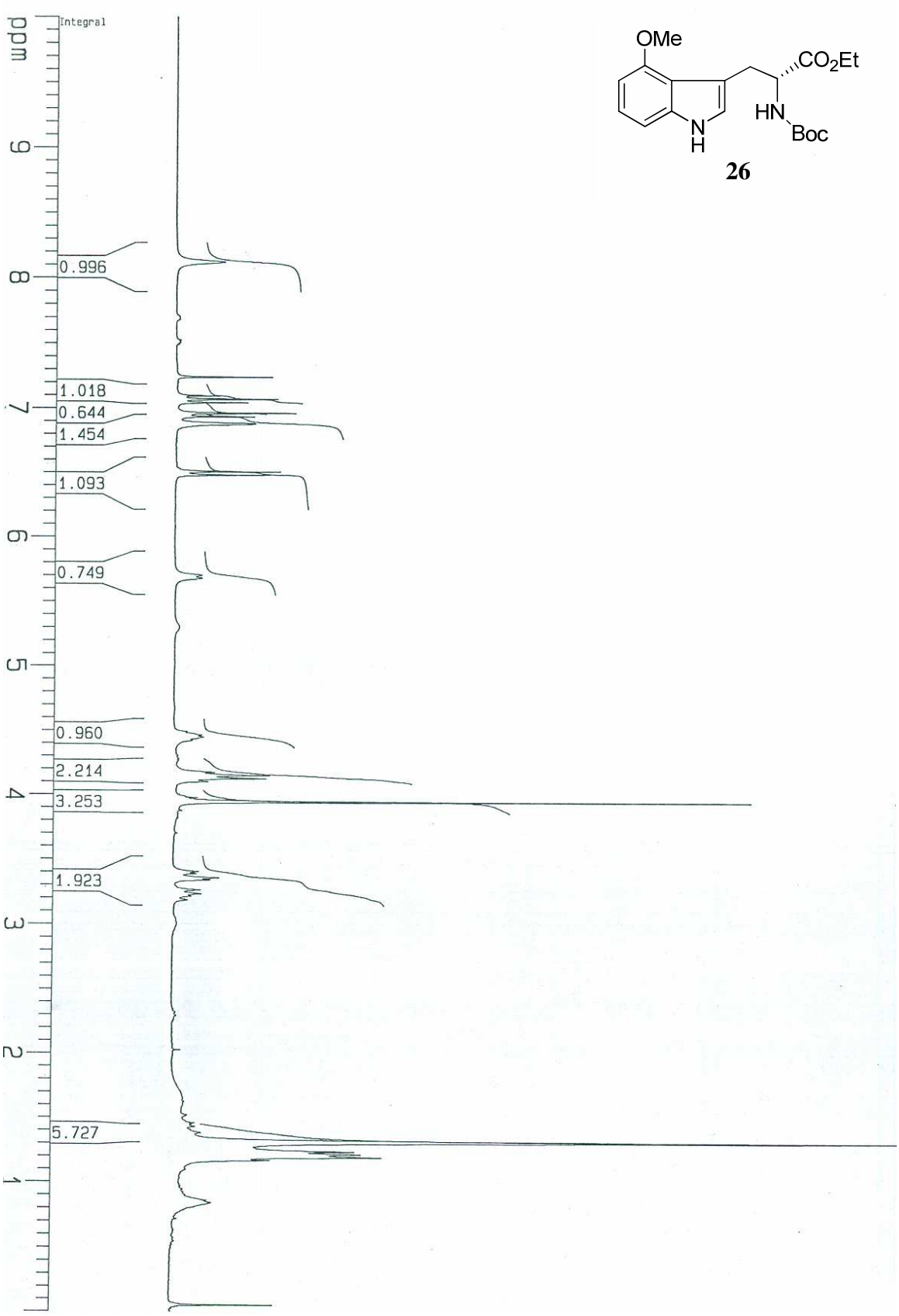
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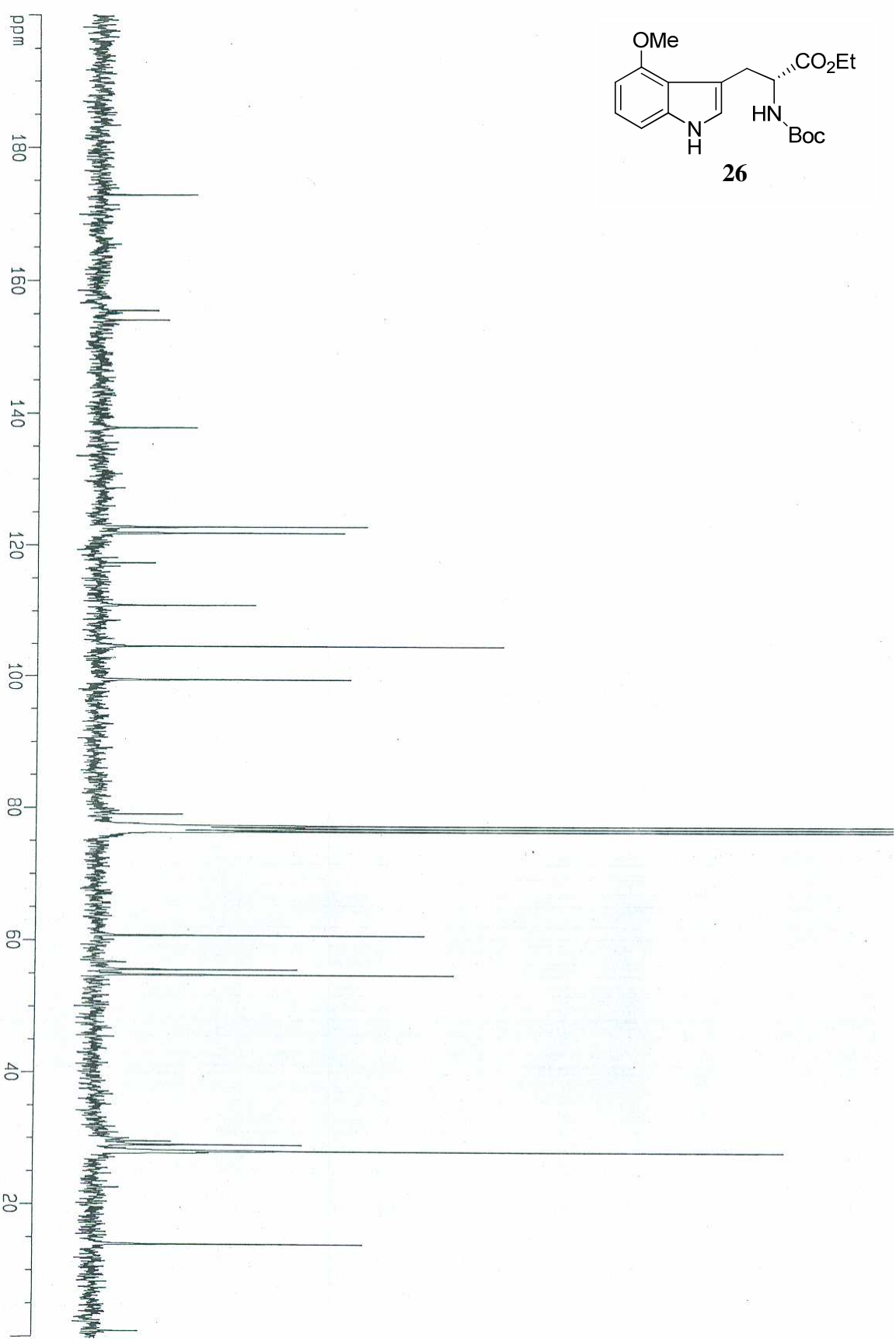
26



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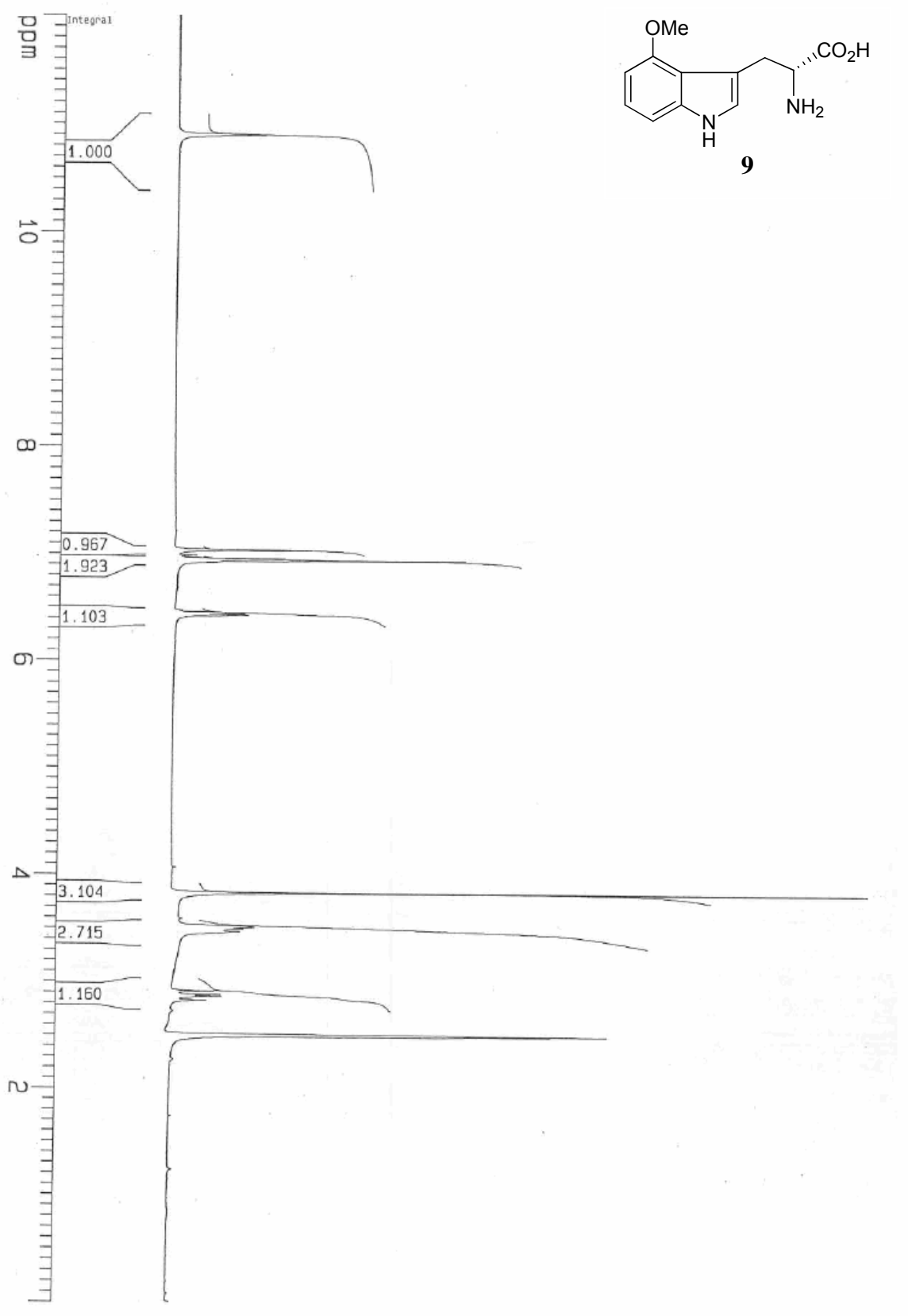
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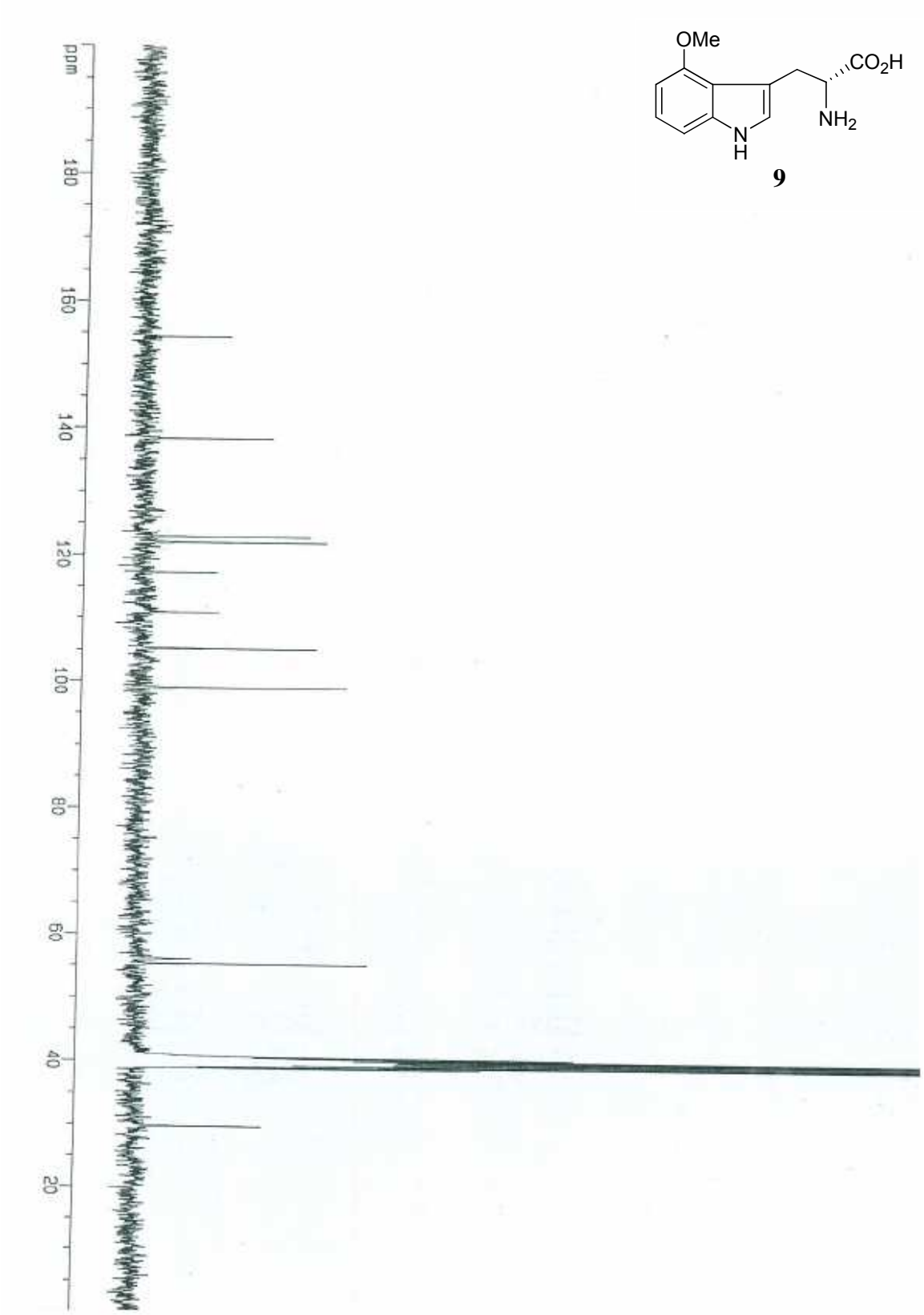
9



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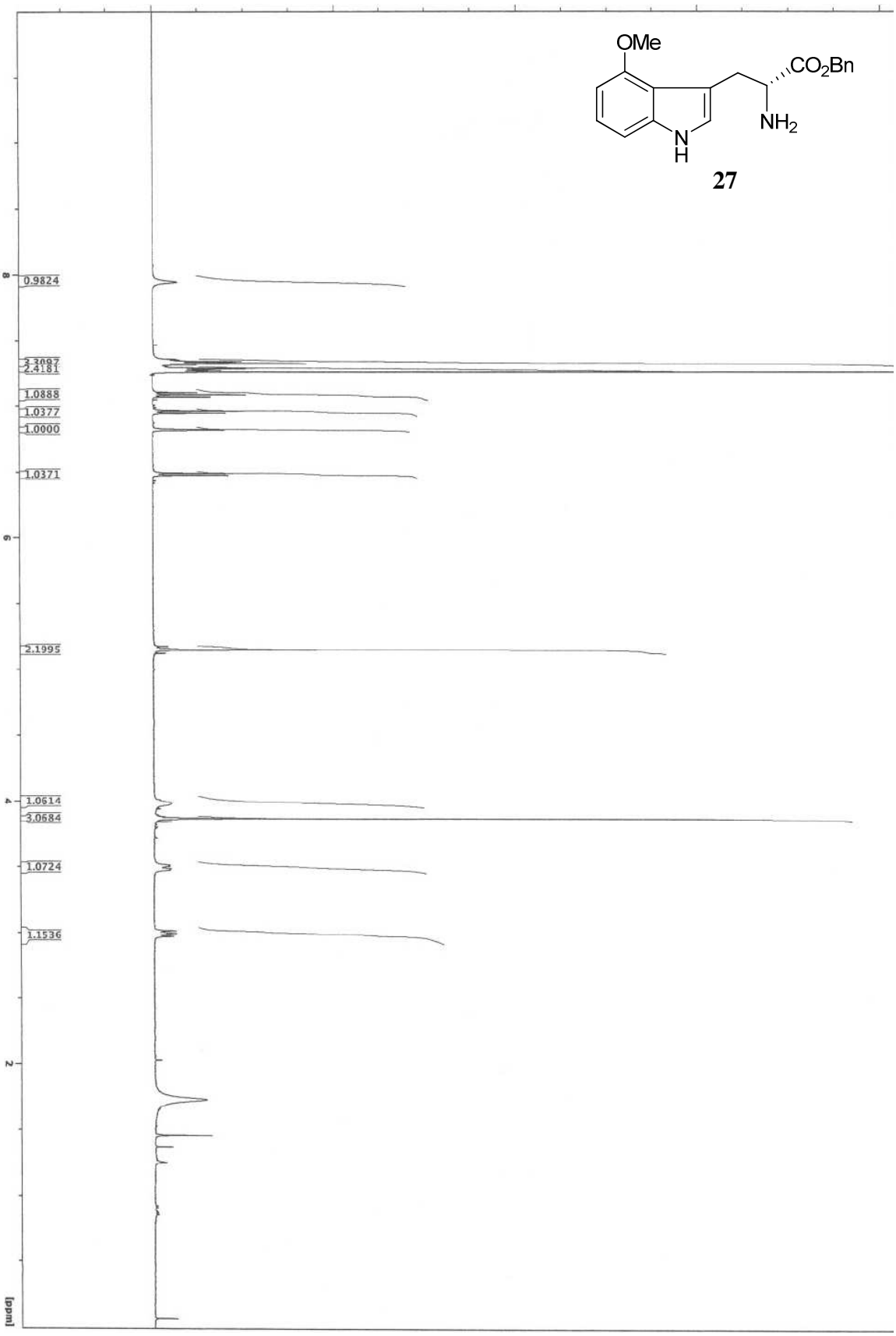
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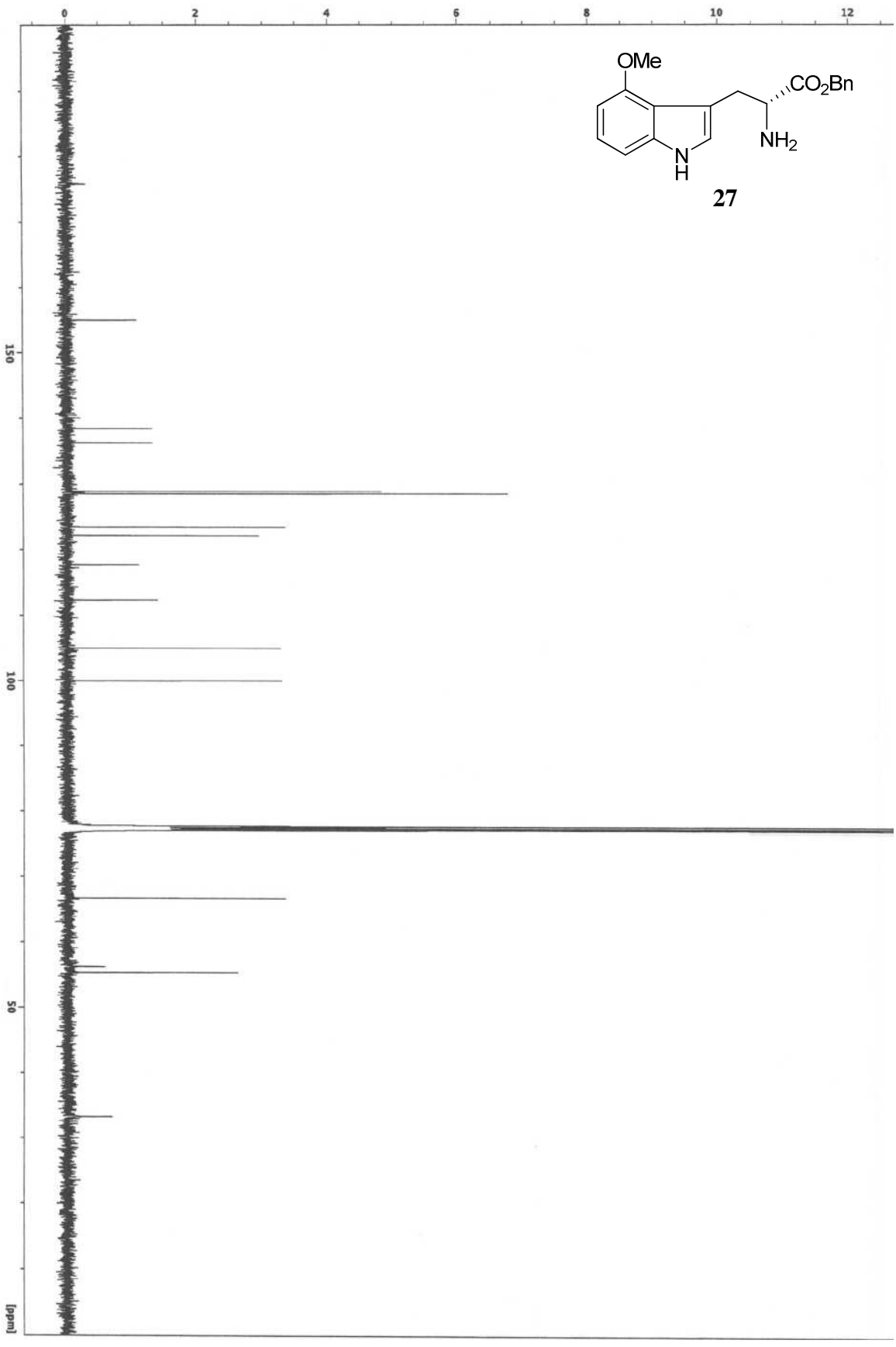
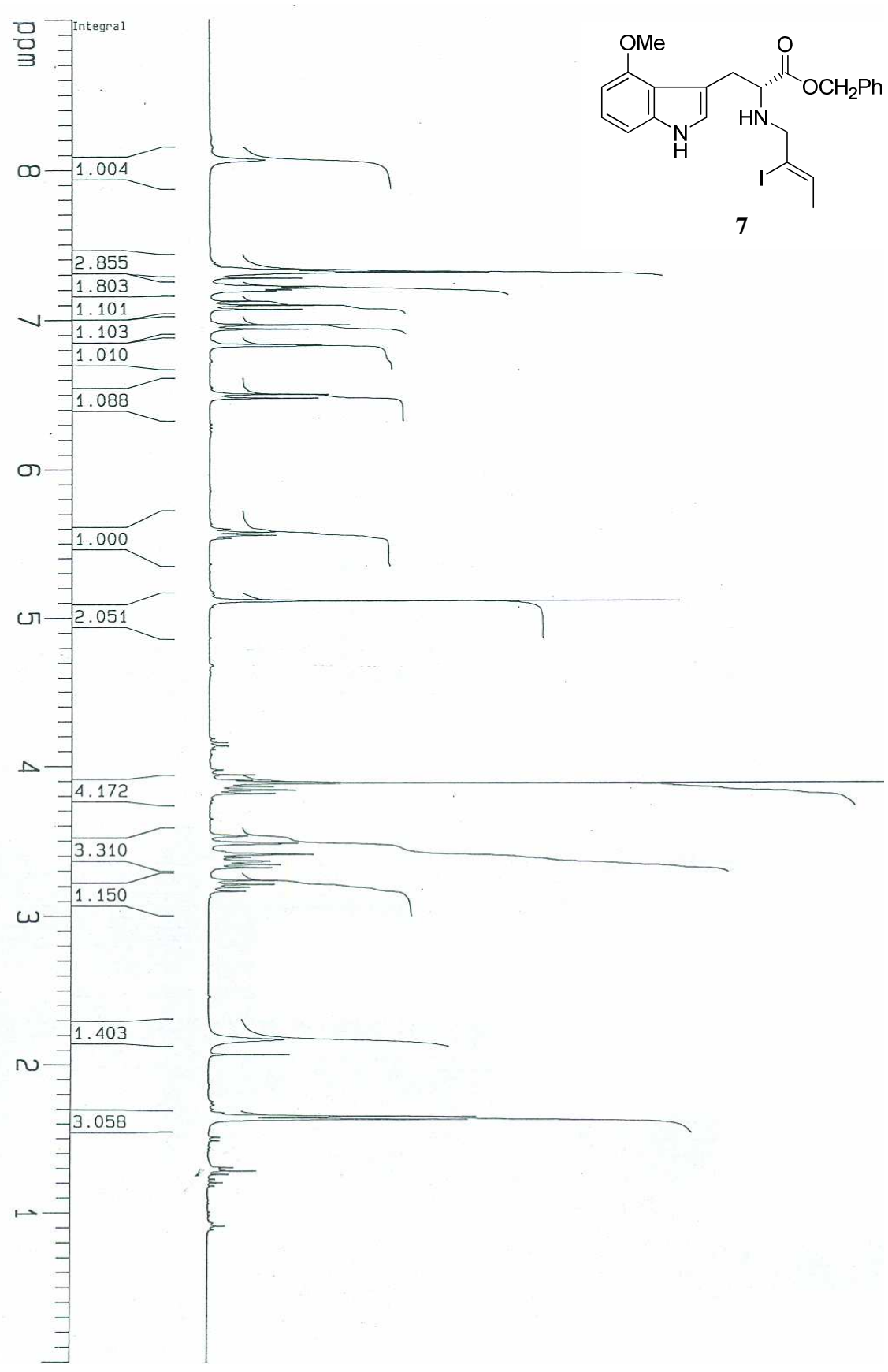


27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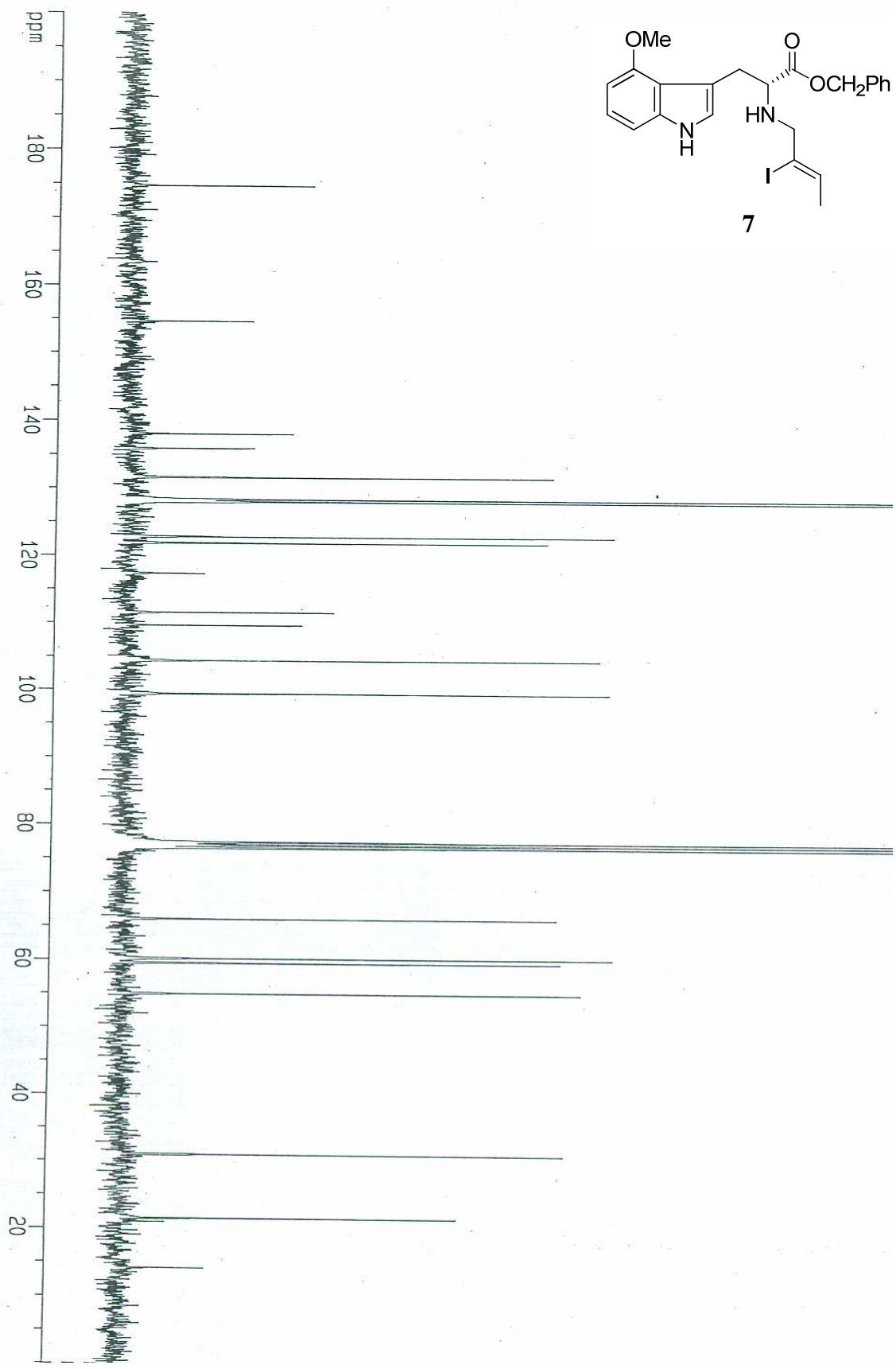
7



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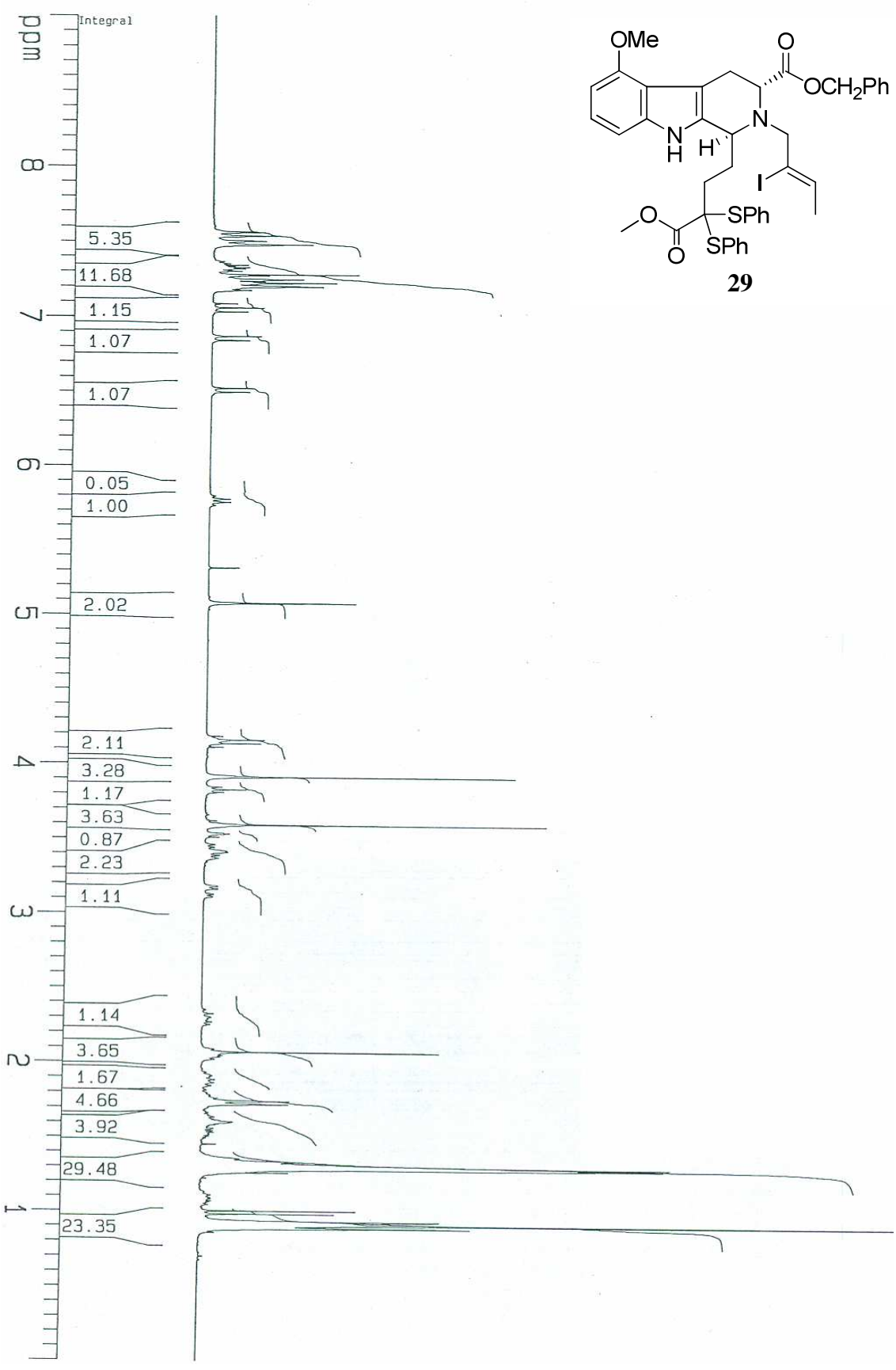
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1.17
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1.11
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4.66
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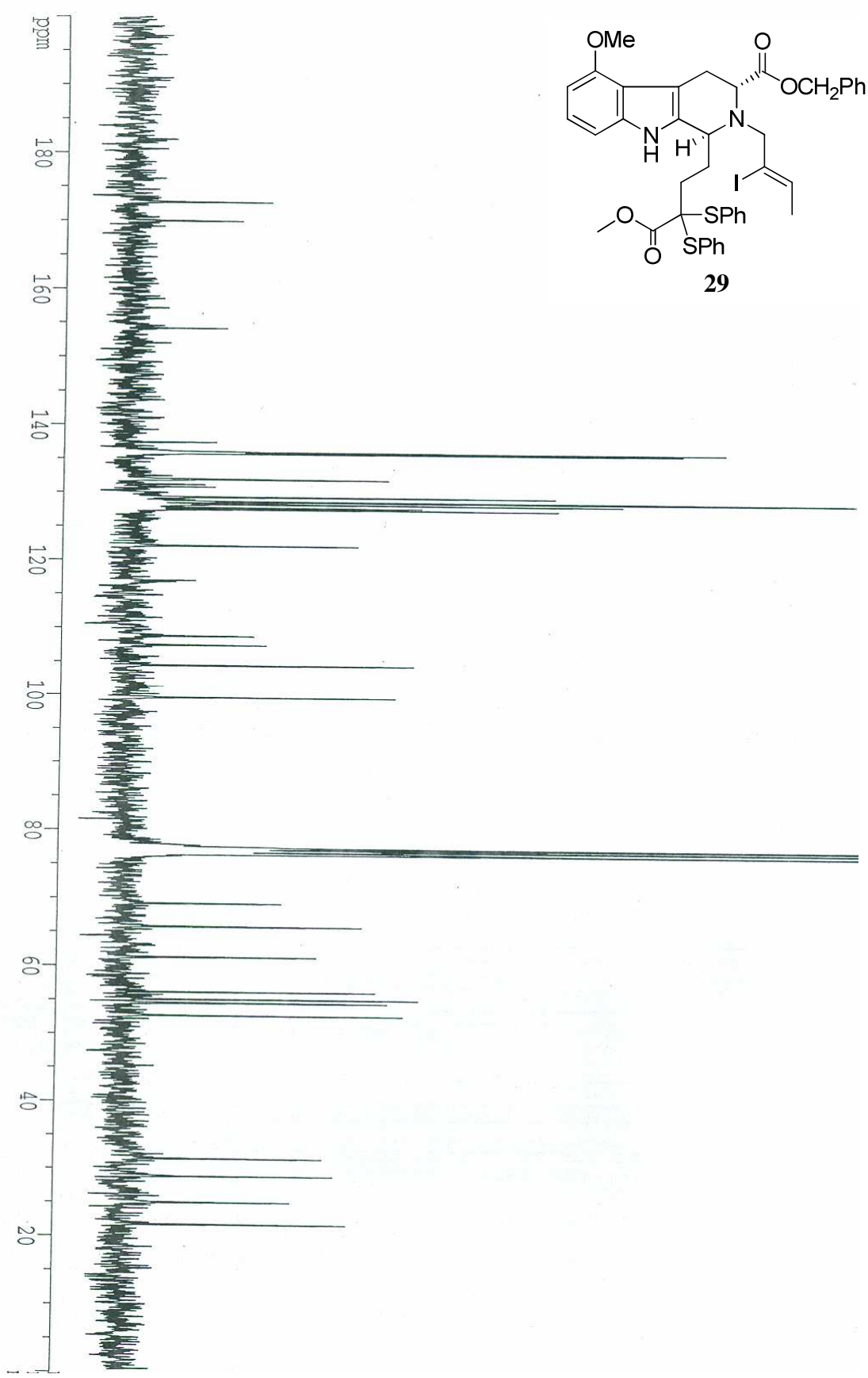
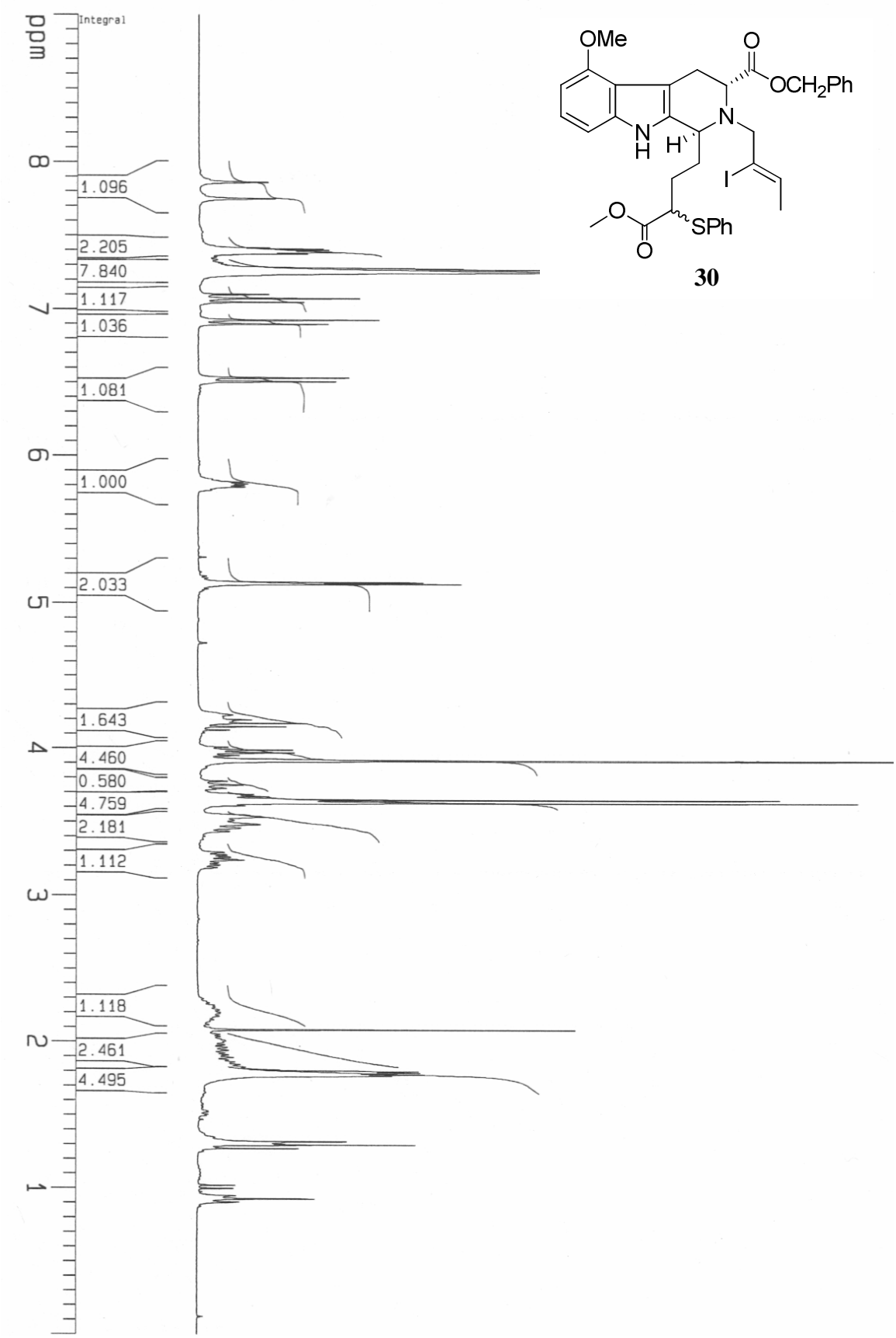
SPh

29



29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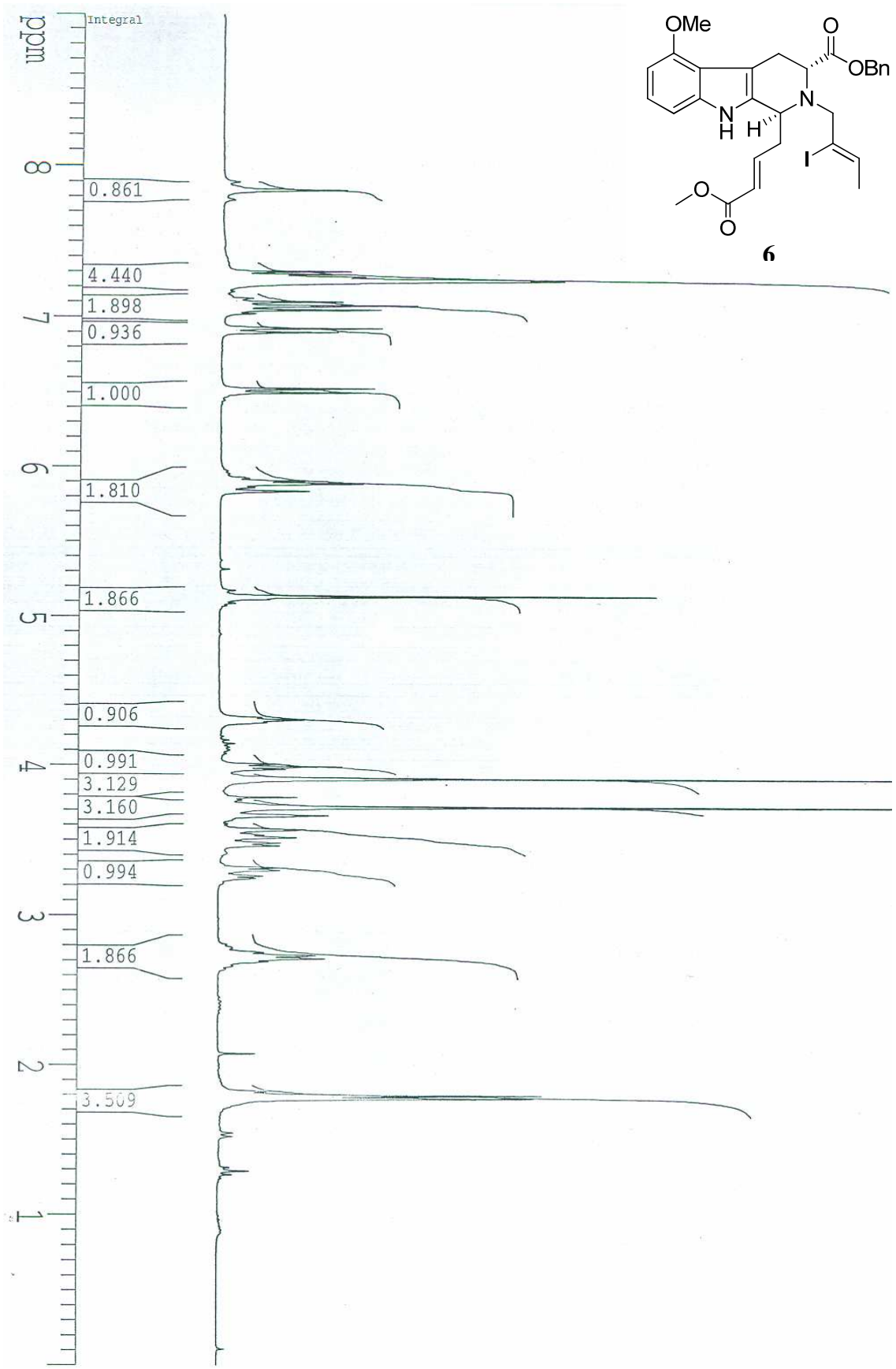
7.840
1.117
1.036
1.081
1.000
2.033
1.643
4.460
0.580
4.759
2.181
1.112
1.118
2.461
4.495
OMe
O
OCH2Ph
N
H
H
N
I
O
SPh
O

30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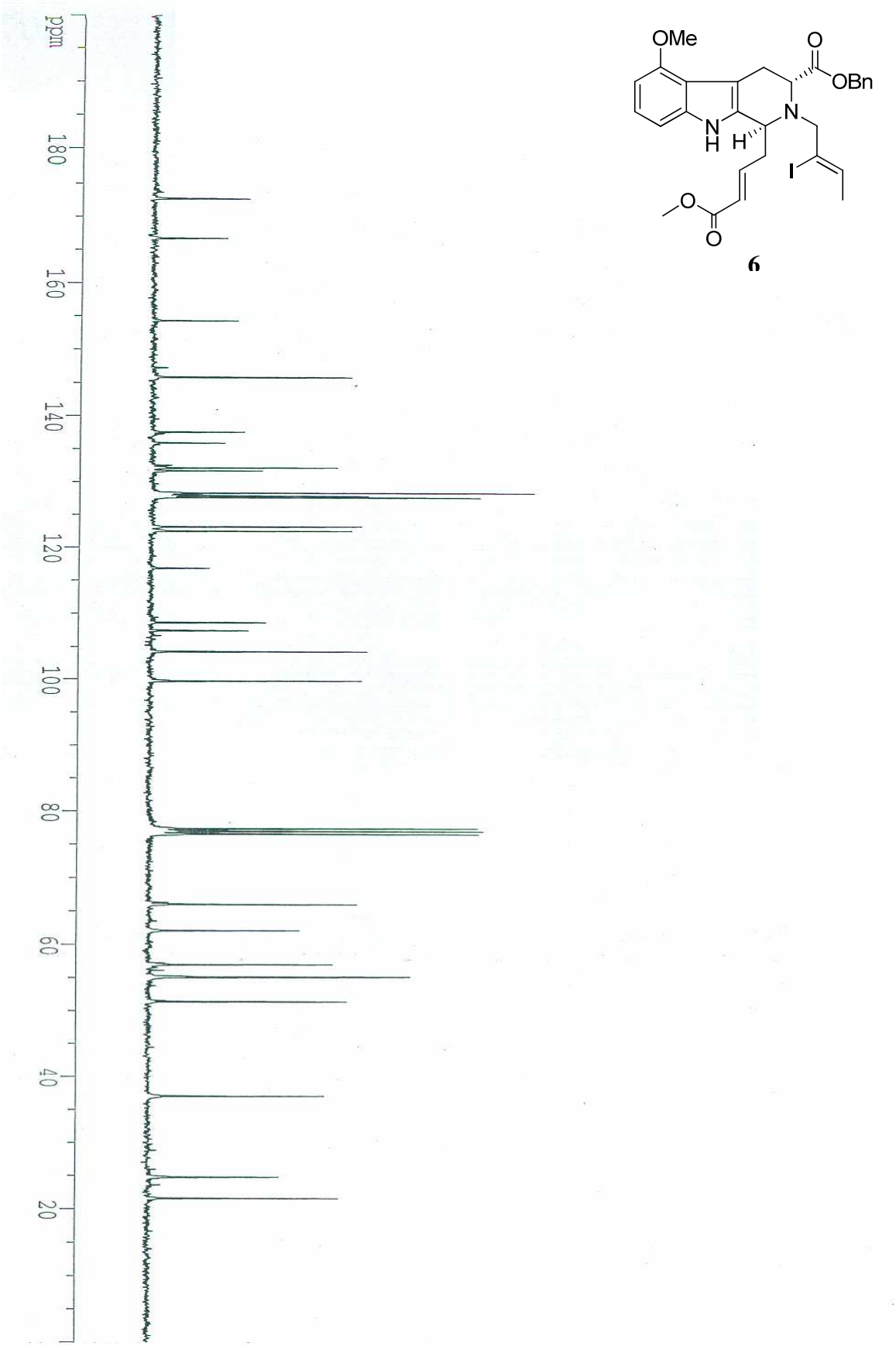
0.936
1.000
1.810
1.866
0.906
0.991
3.129
3.160
1.914
0.994
1.866
3.509
OMe
O
OBn
N
H
H
N
I
O
O

6



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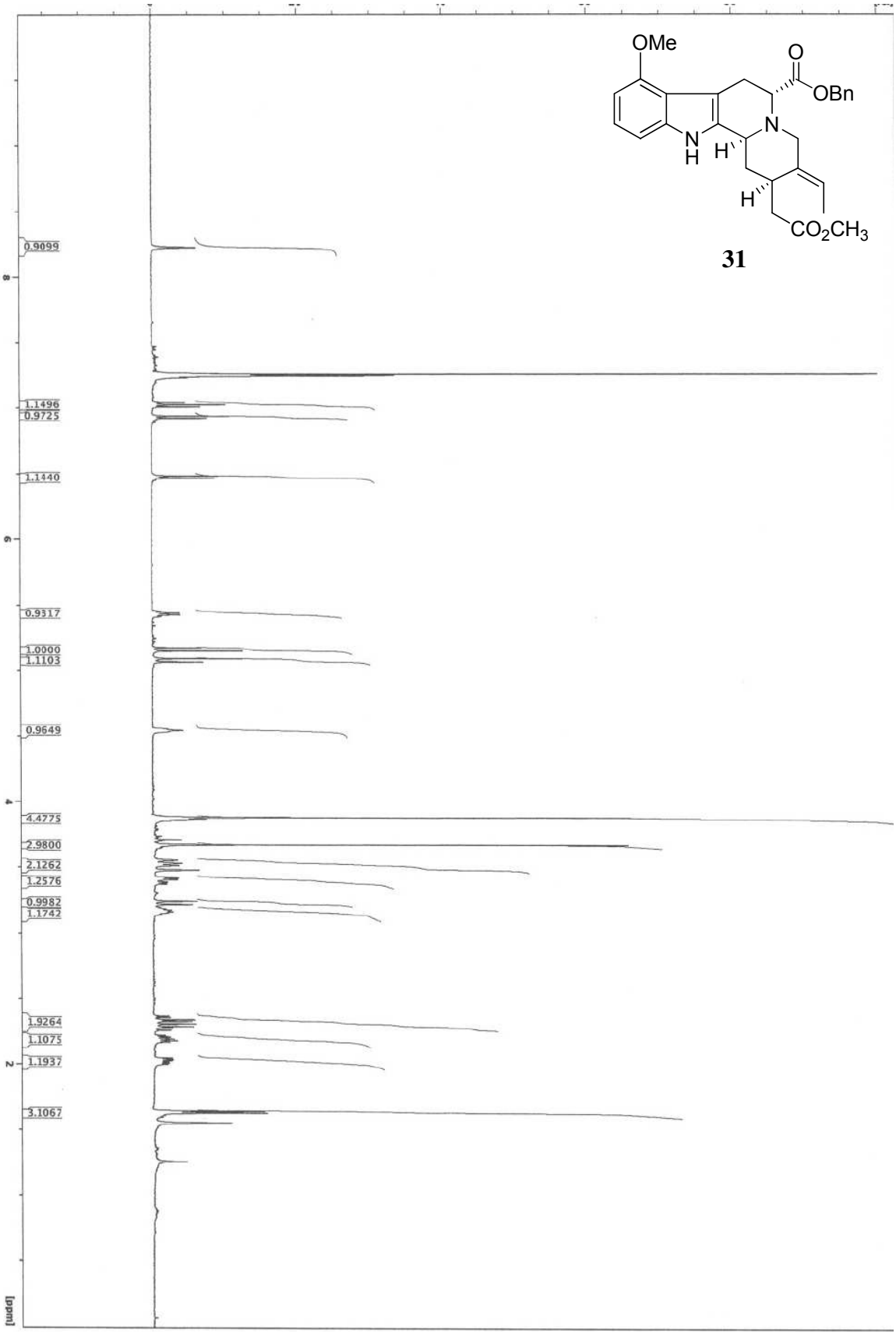
OMe
O
OBn
N
H
H
N
H
CO2CH3
31
0.9099
1.1496
0.9725
1.1440
0.9317
1.0000
1.1103
0.9649
4.4775
2.9800
2.1262
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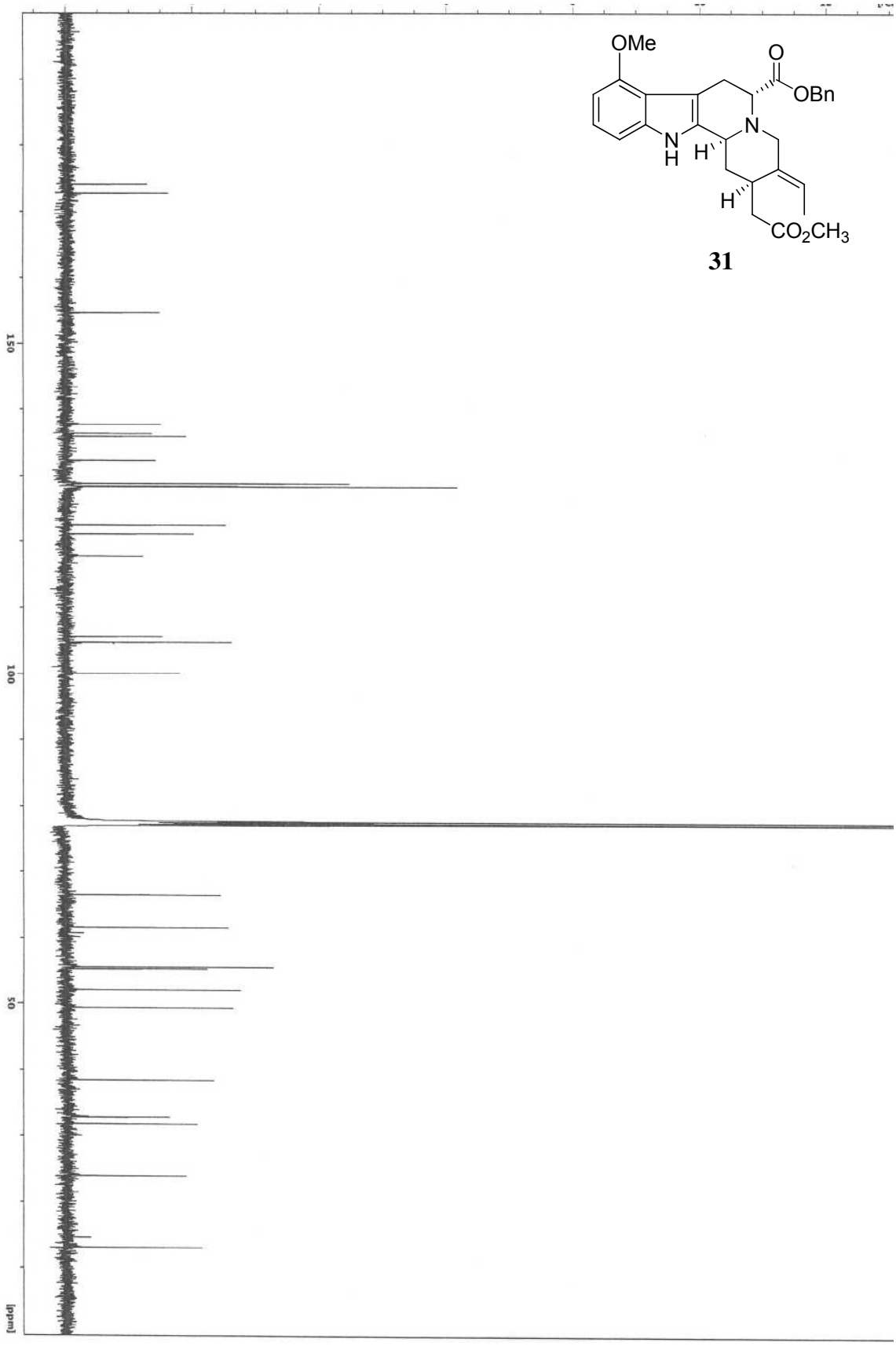
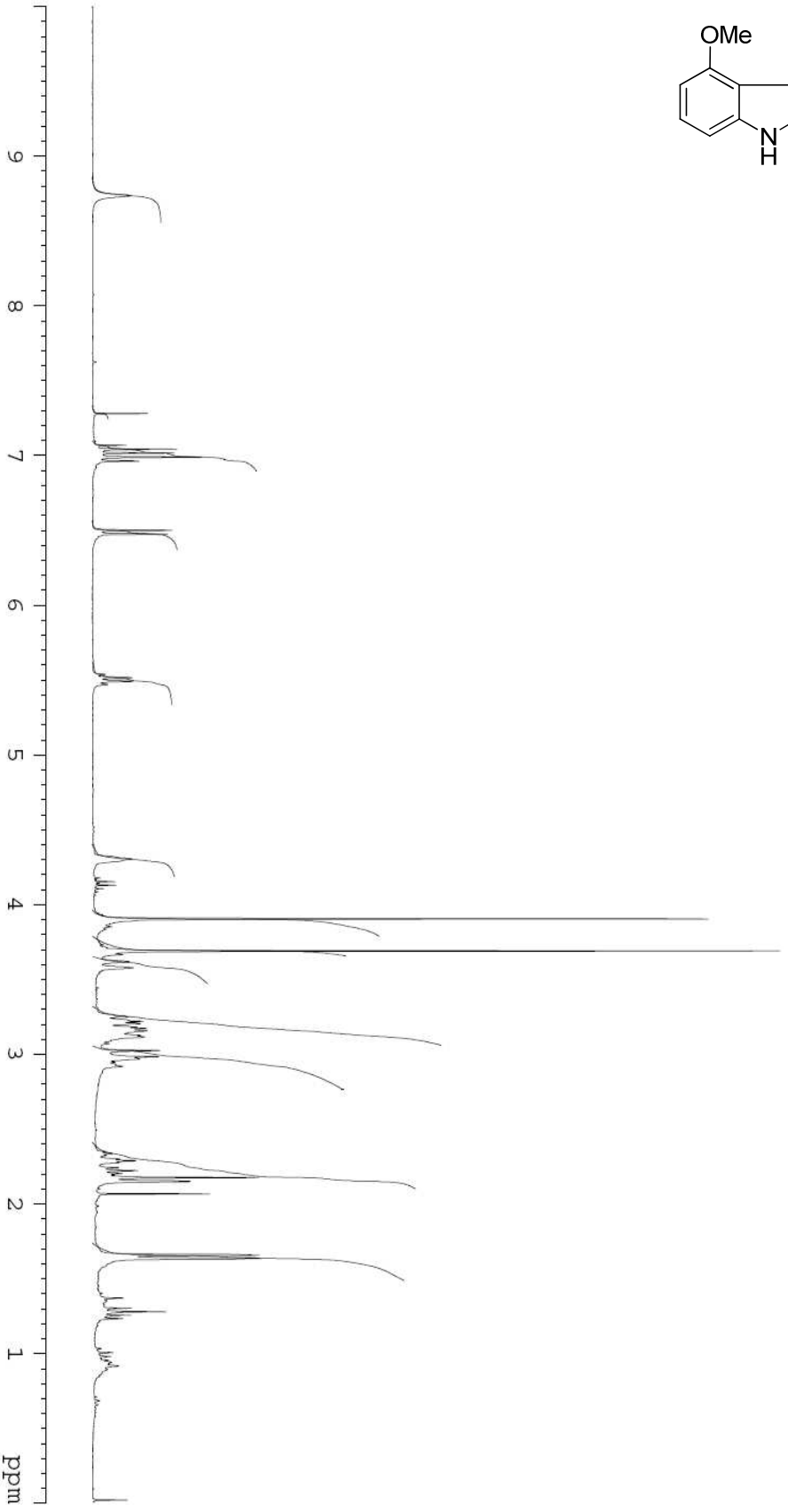
0.9982
1.1742
1.9264
1.1075
1.1937
3.1067
8
6
4
2
[ppm]



31



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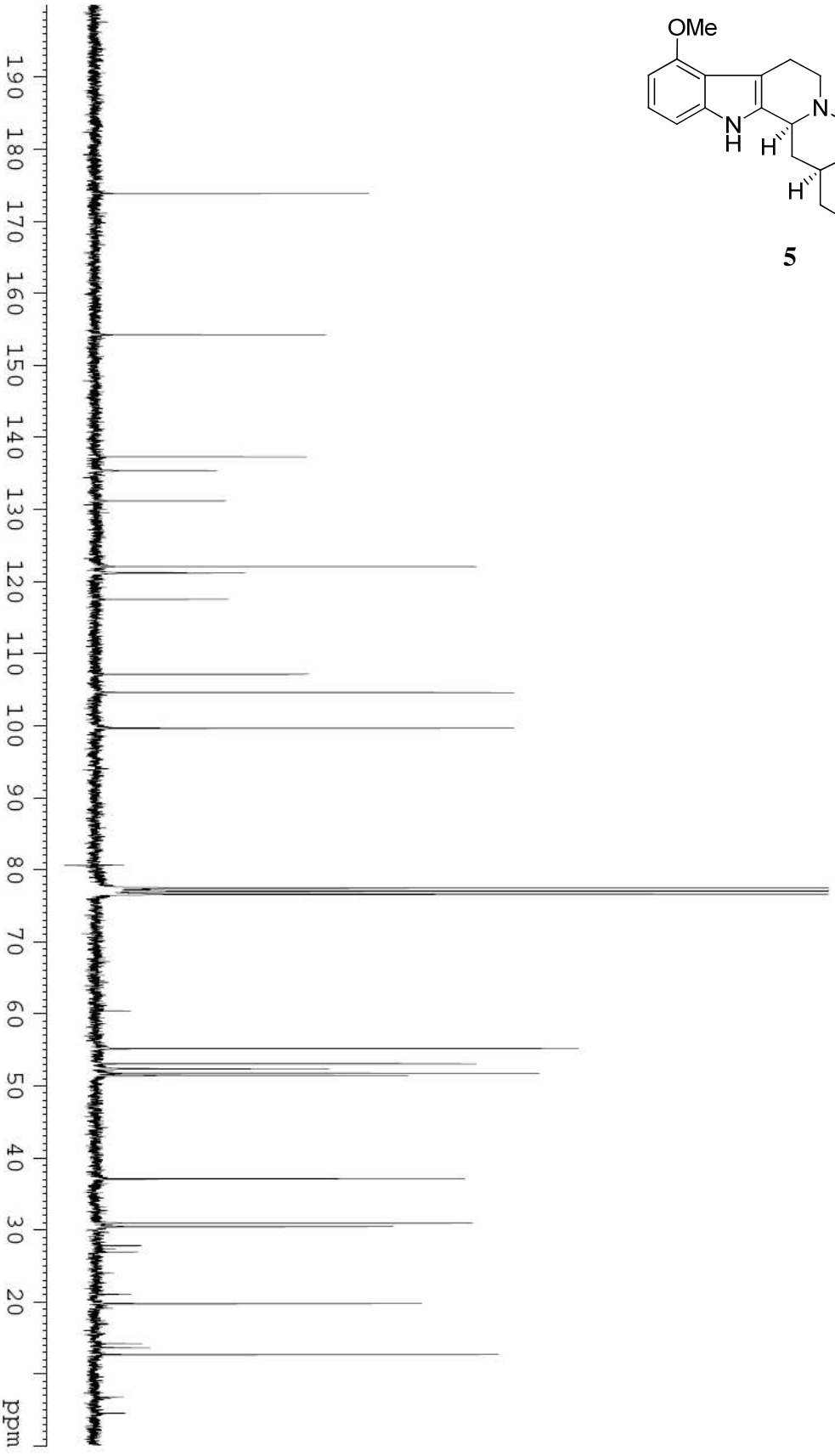
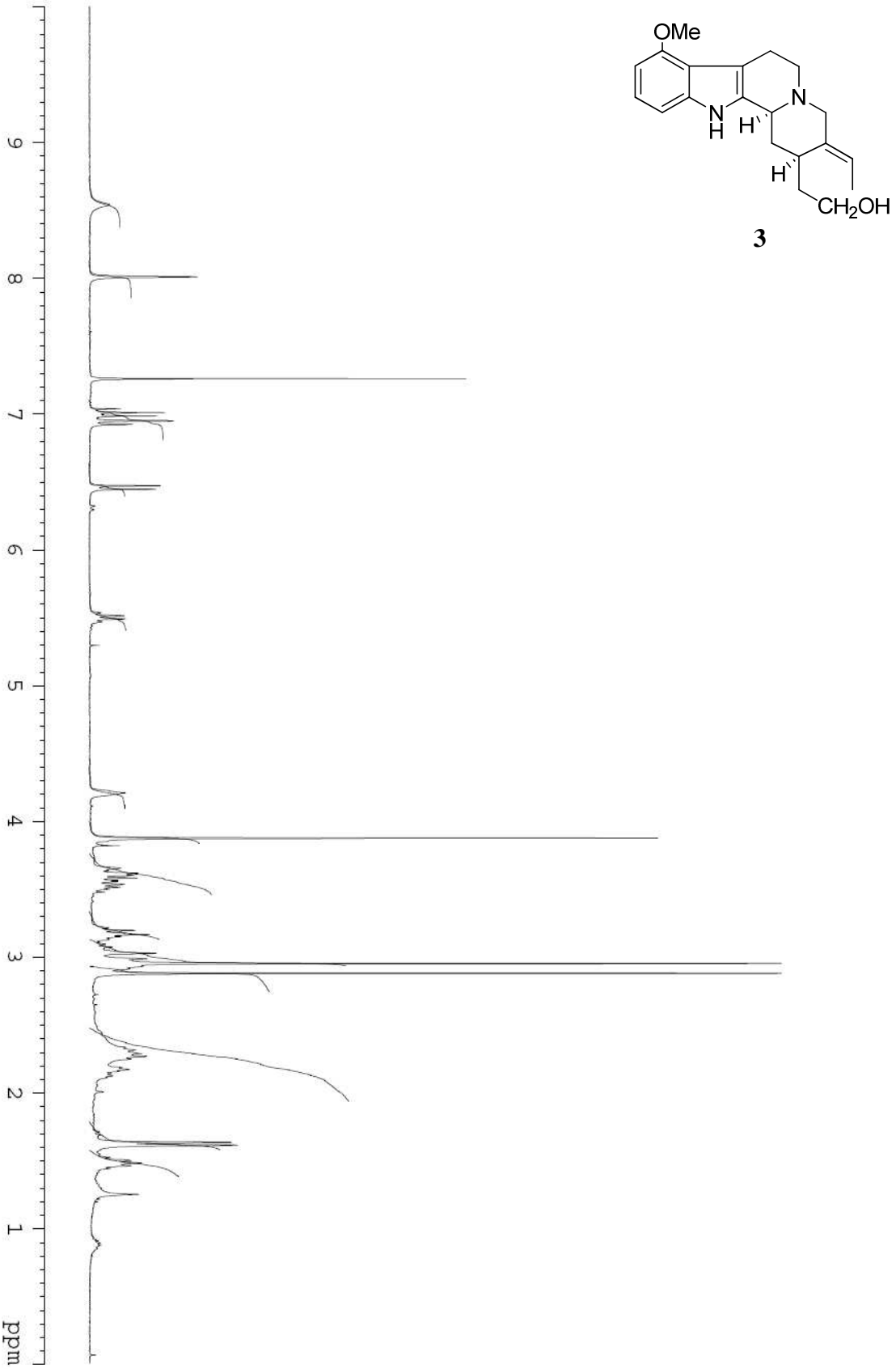

OMe
N
H
N
H
H
CO2CH3
5
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm



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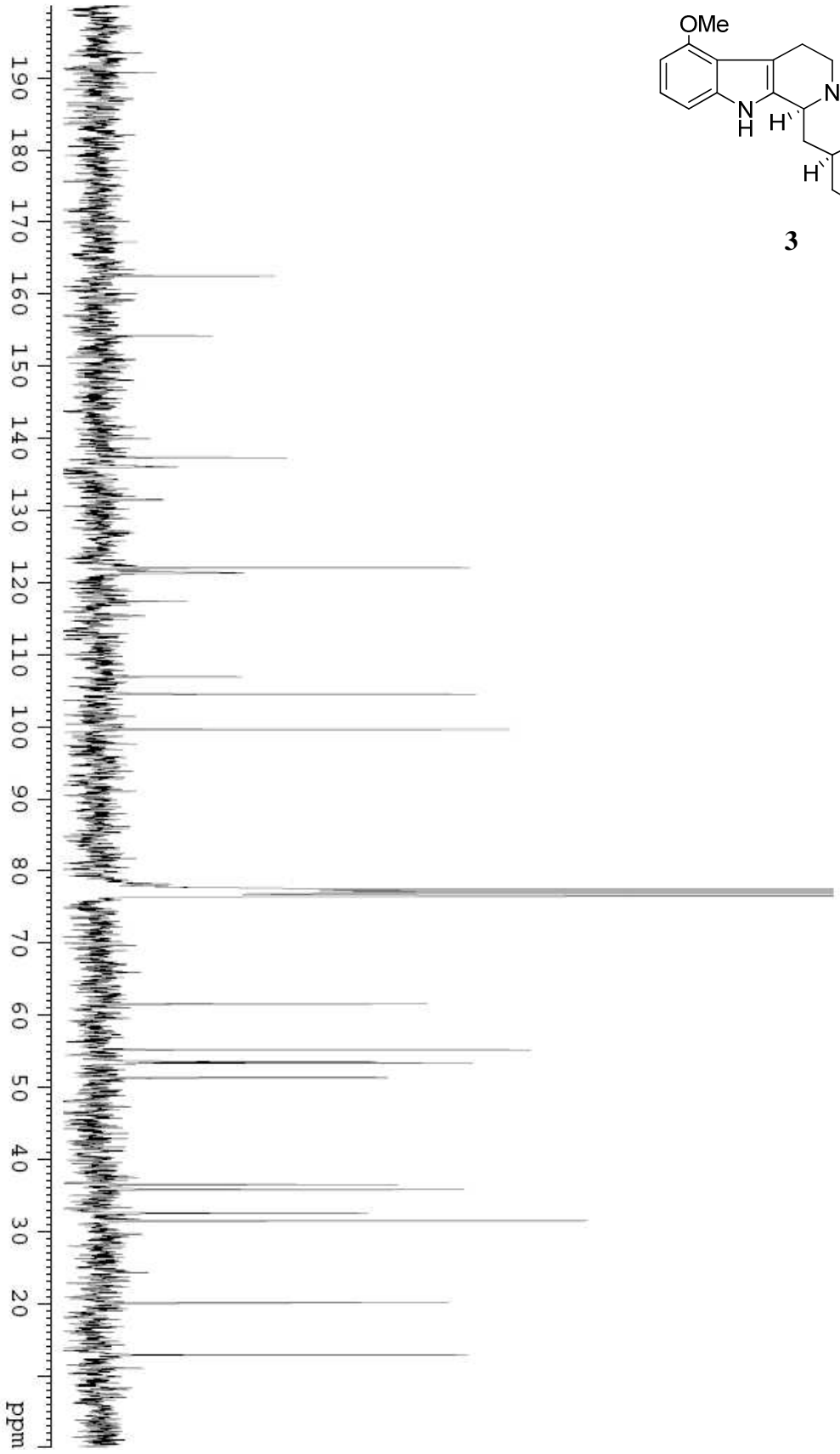
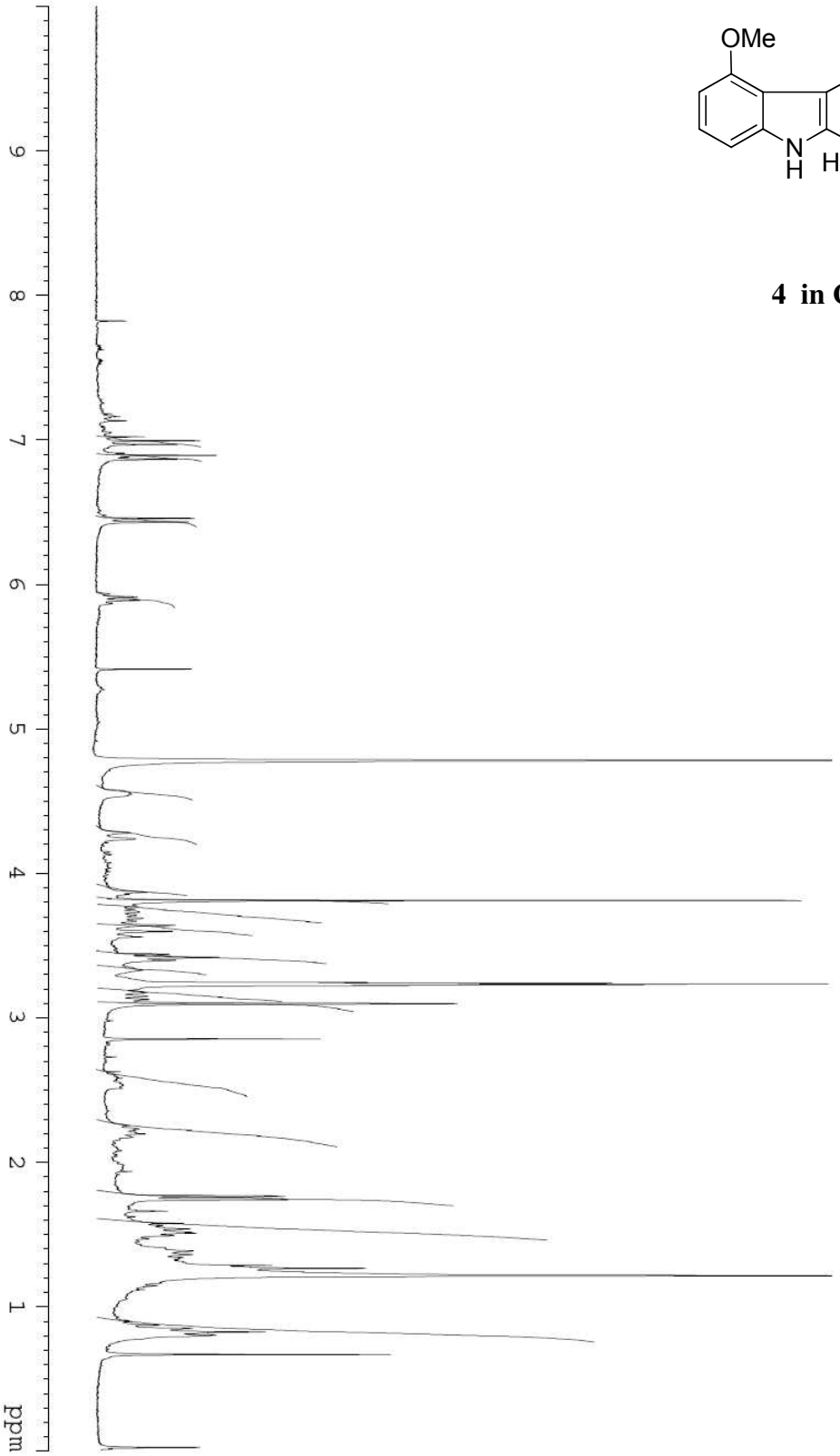
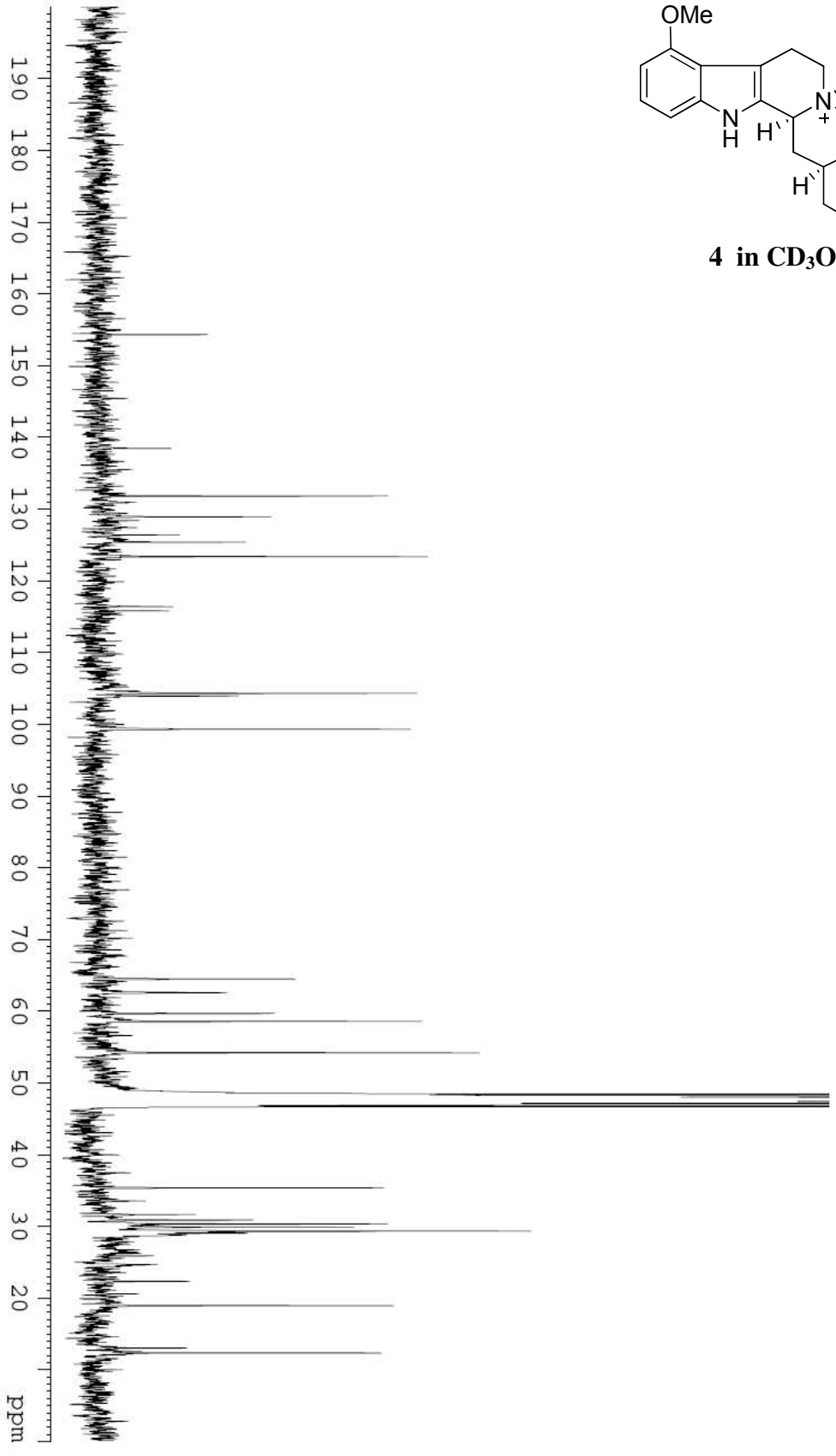

OMe
N
H
H
N
H
CH2OH
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

3

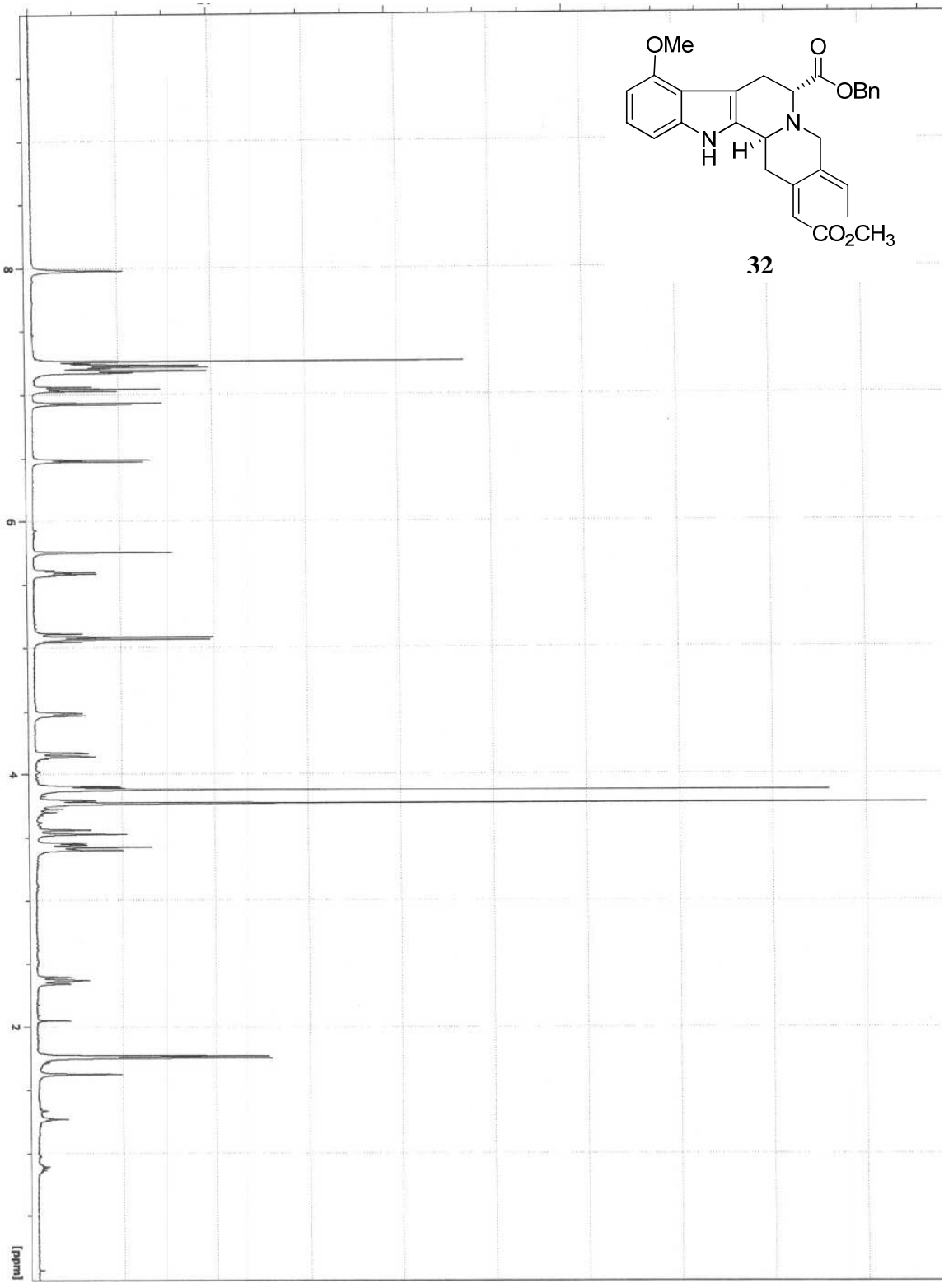


4 in CD_3OD

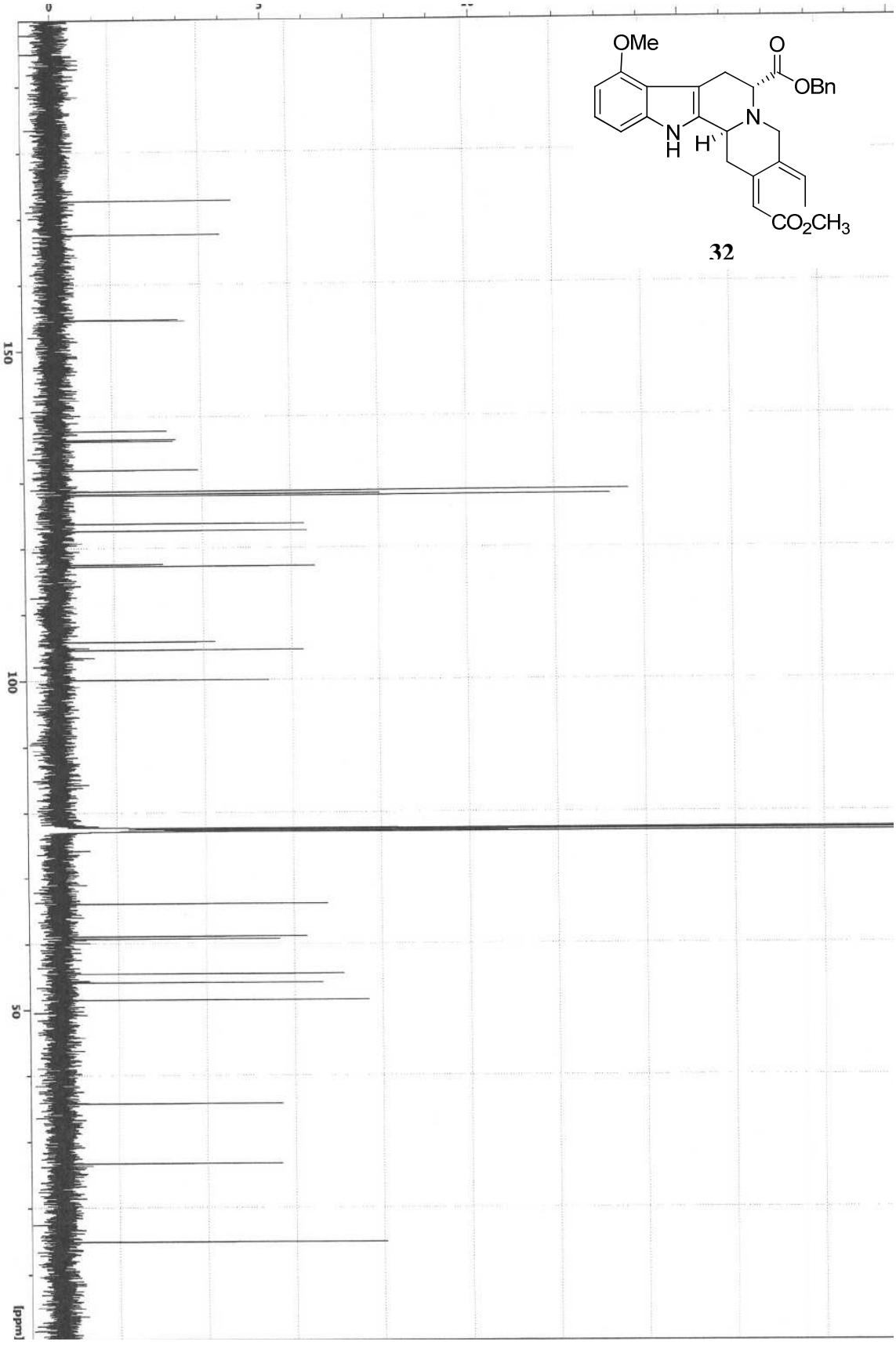

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

OMe
CH3
N
Cl-
N
H
H
H
CH2OH

4 in CD_3OD



32



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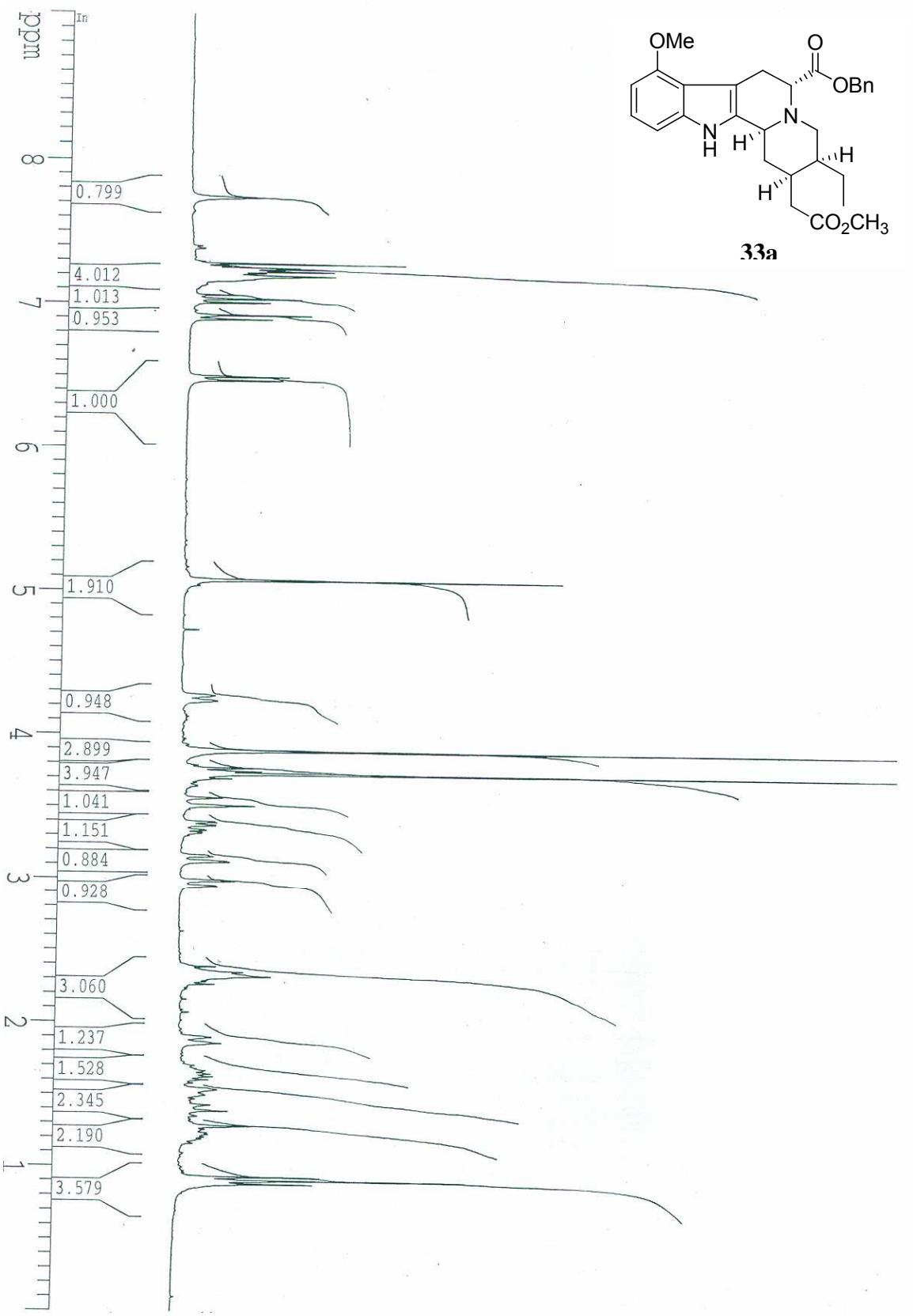
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1.000
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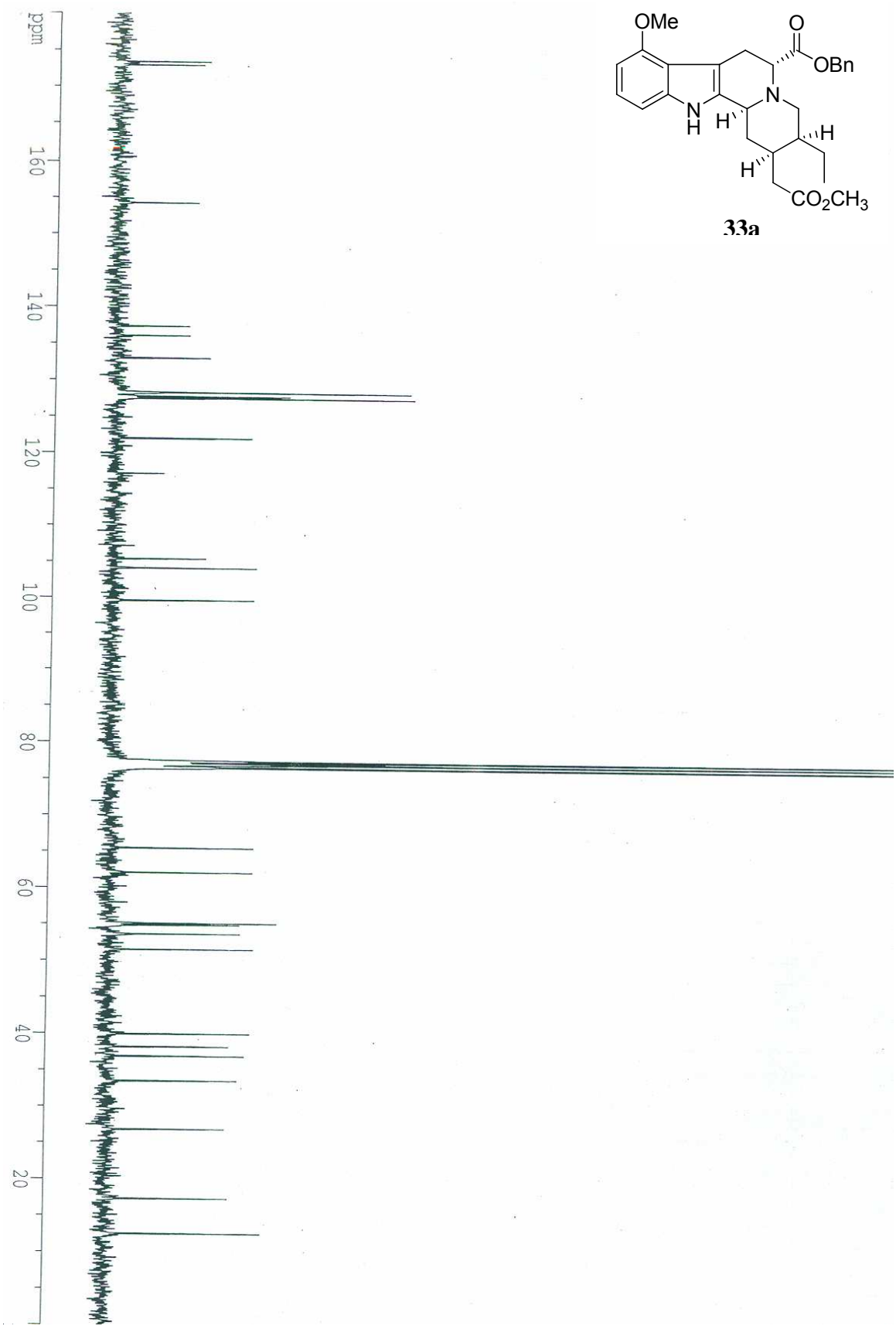
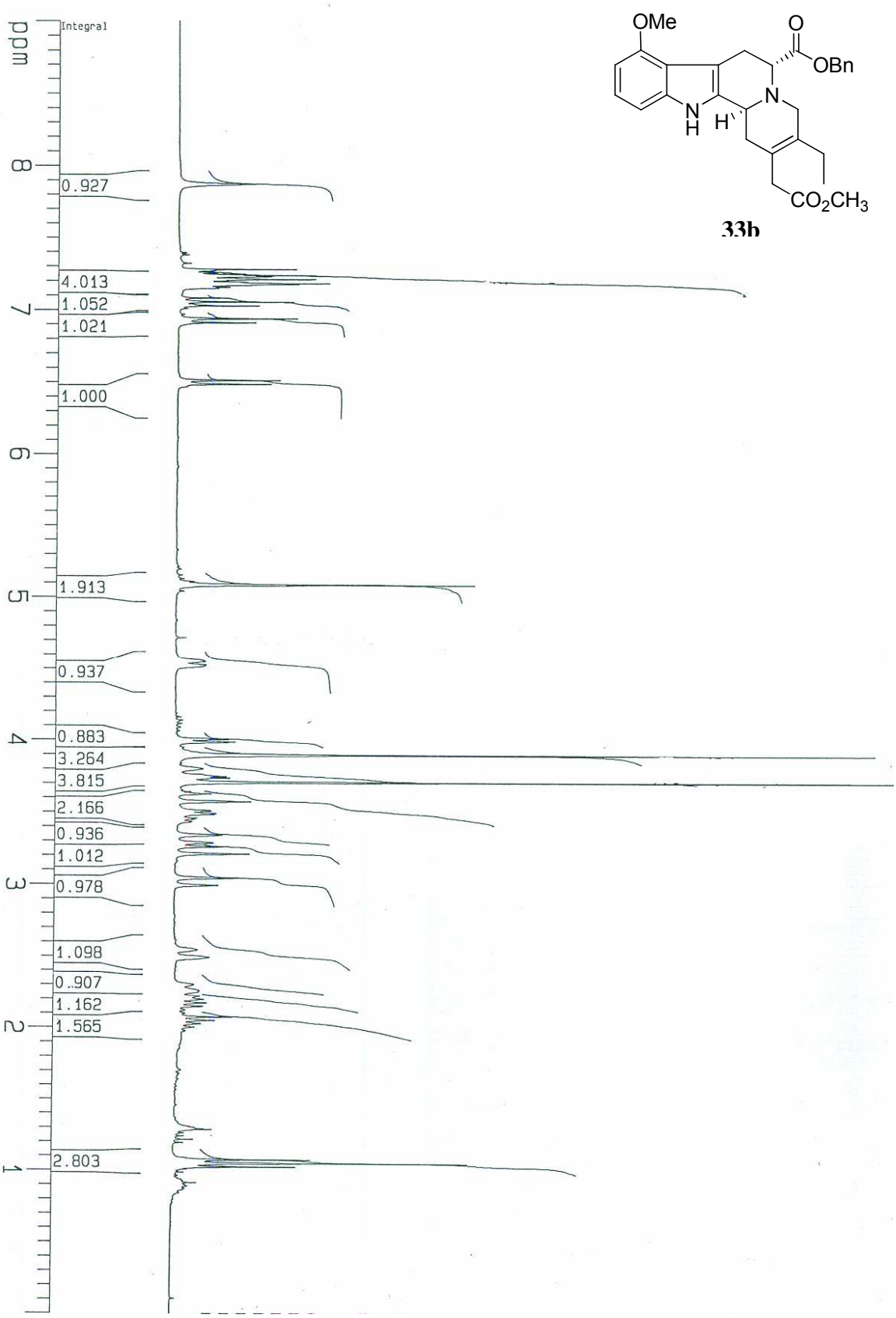
1.151
0.884
0.928
3.060
1.237
1.528
2.345
2.190
3.579
OMe
O
OBn
N
H
N
H
H
H
CO2CH3

33a



33a


Integral
ppm
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7
6
5
4
3
2
1
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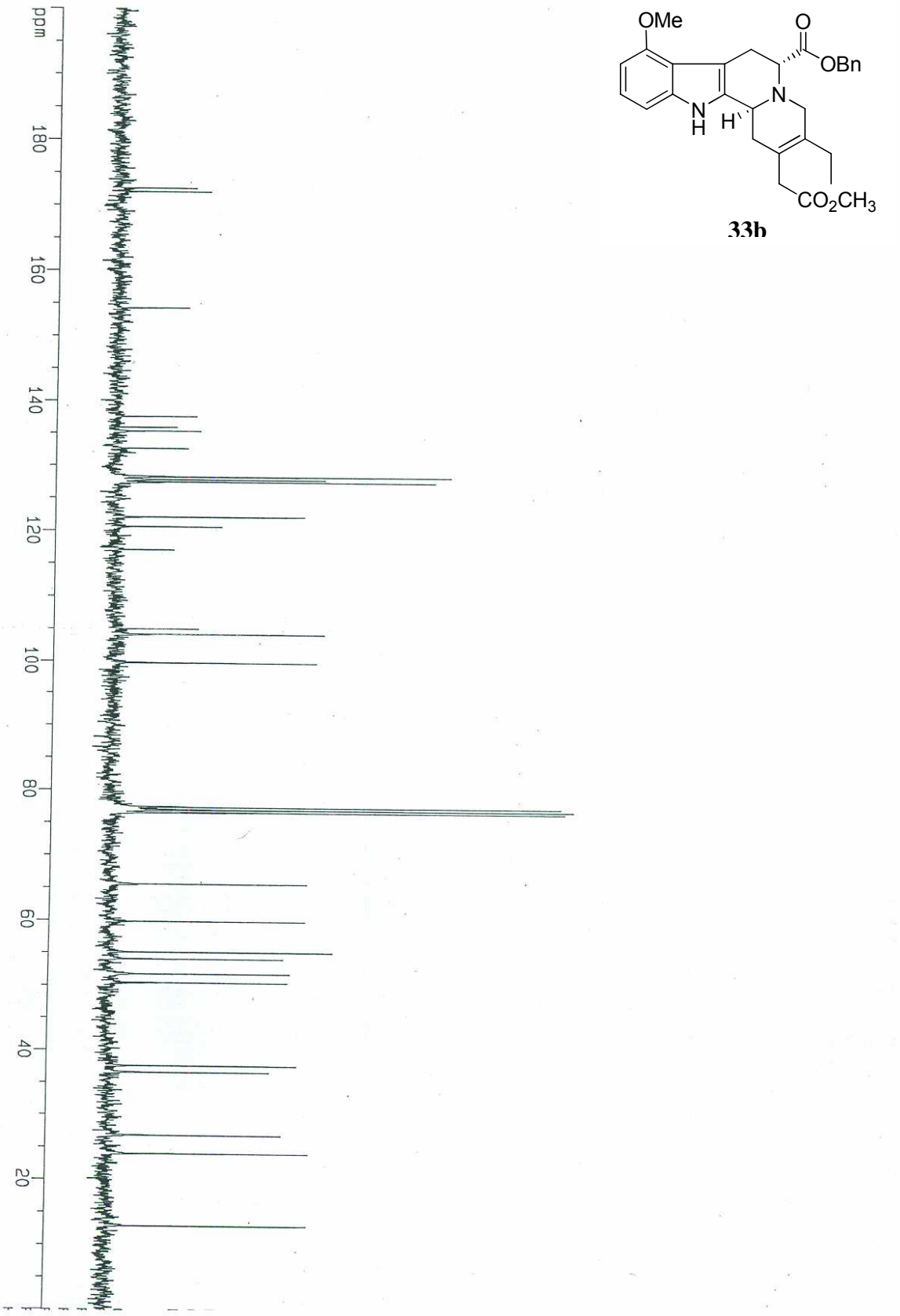
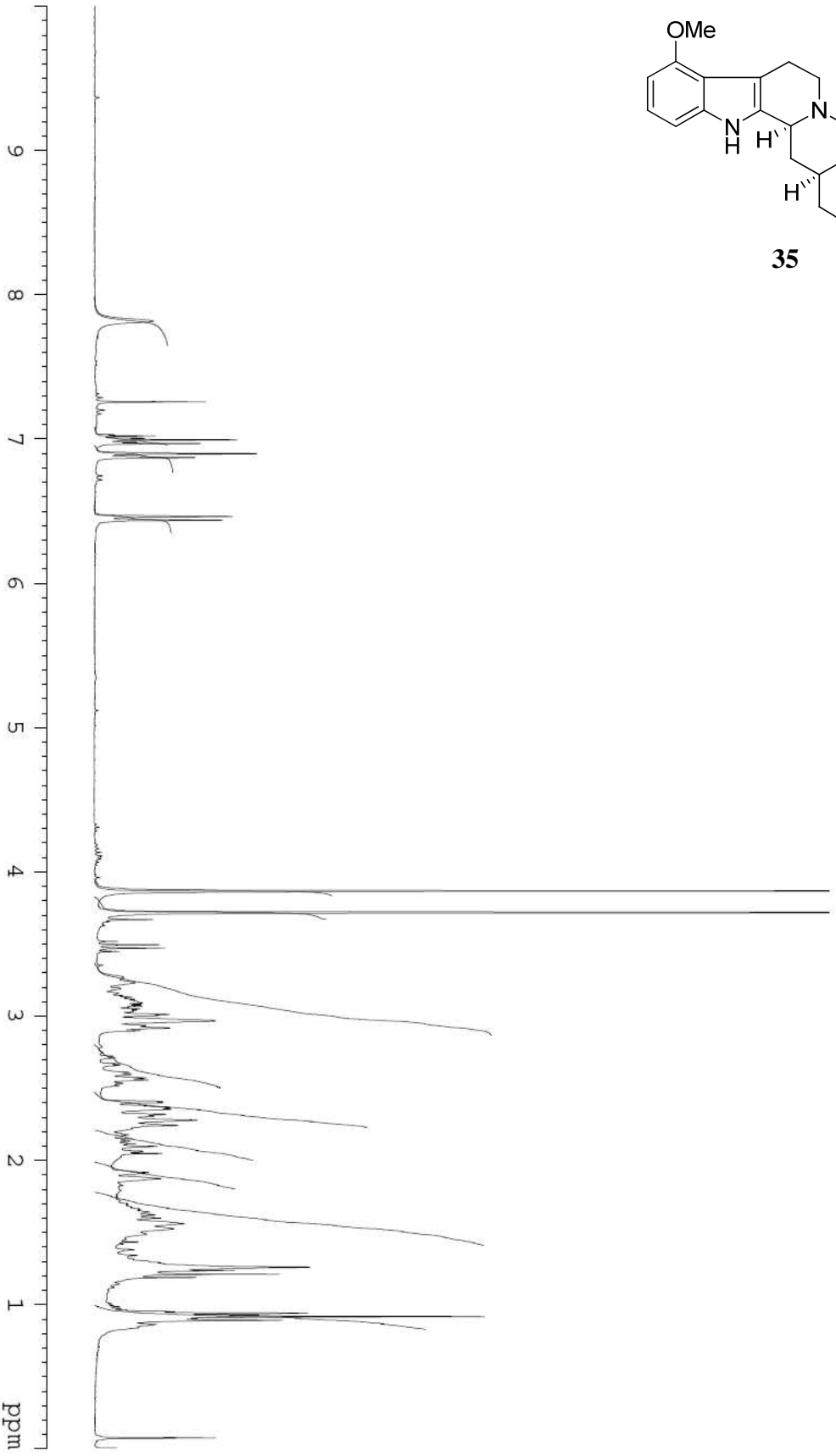
4.013
1.052
1.021
1.000
1.913
0.937
0.883
3.264
3.815
2.166
0.936
1.012
0.978
1.098
0..907
1.162
1.565
2.803
OMe
O
OBn
N
H
H
N
CO2CH3

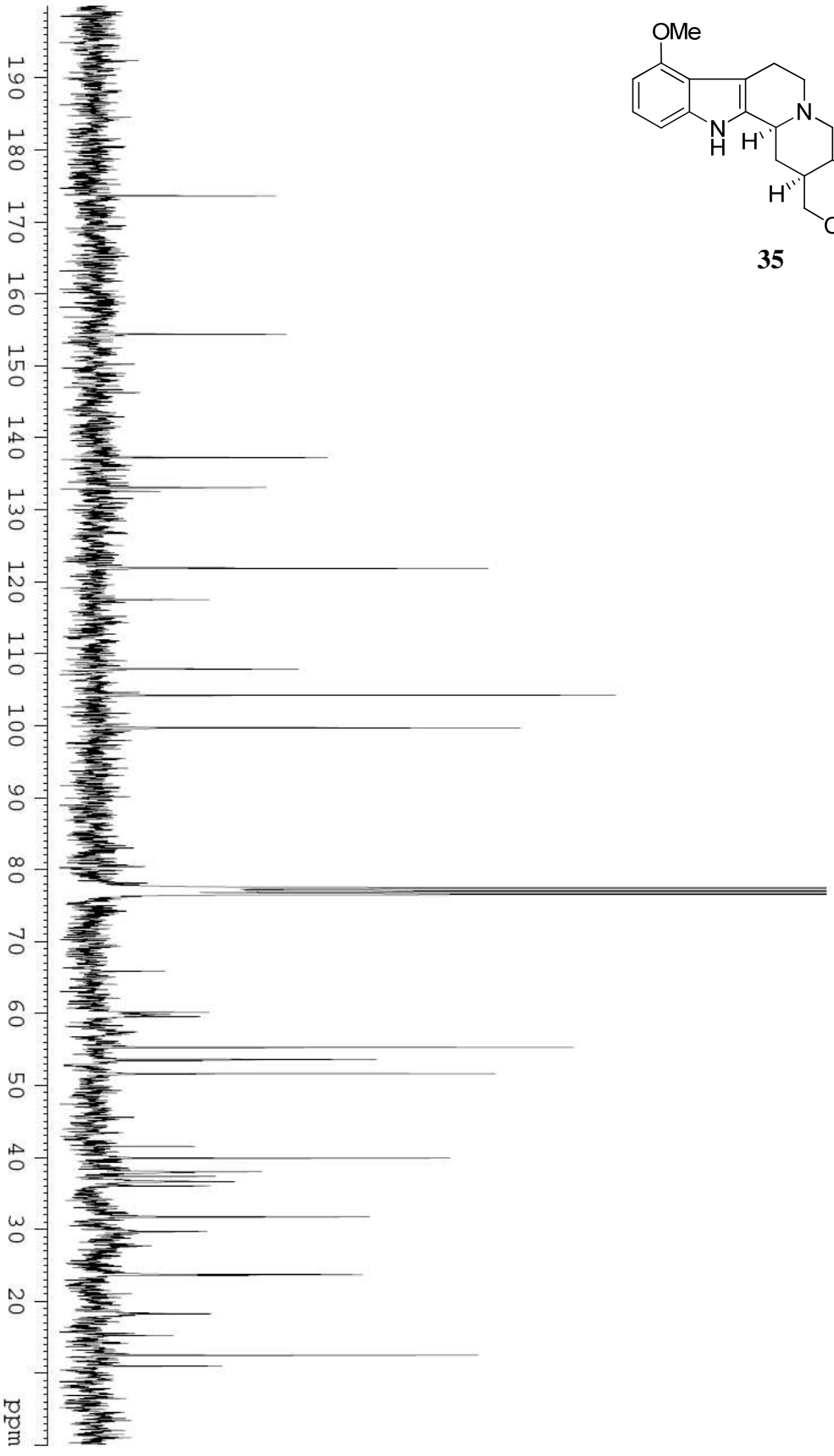
33b



33h

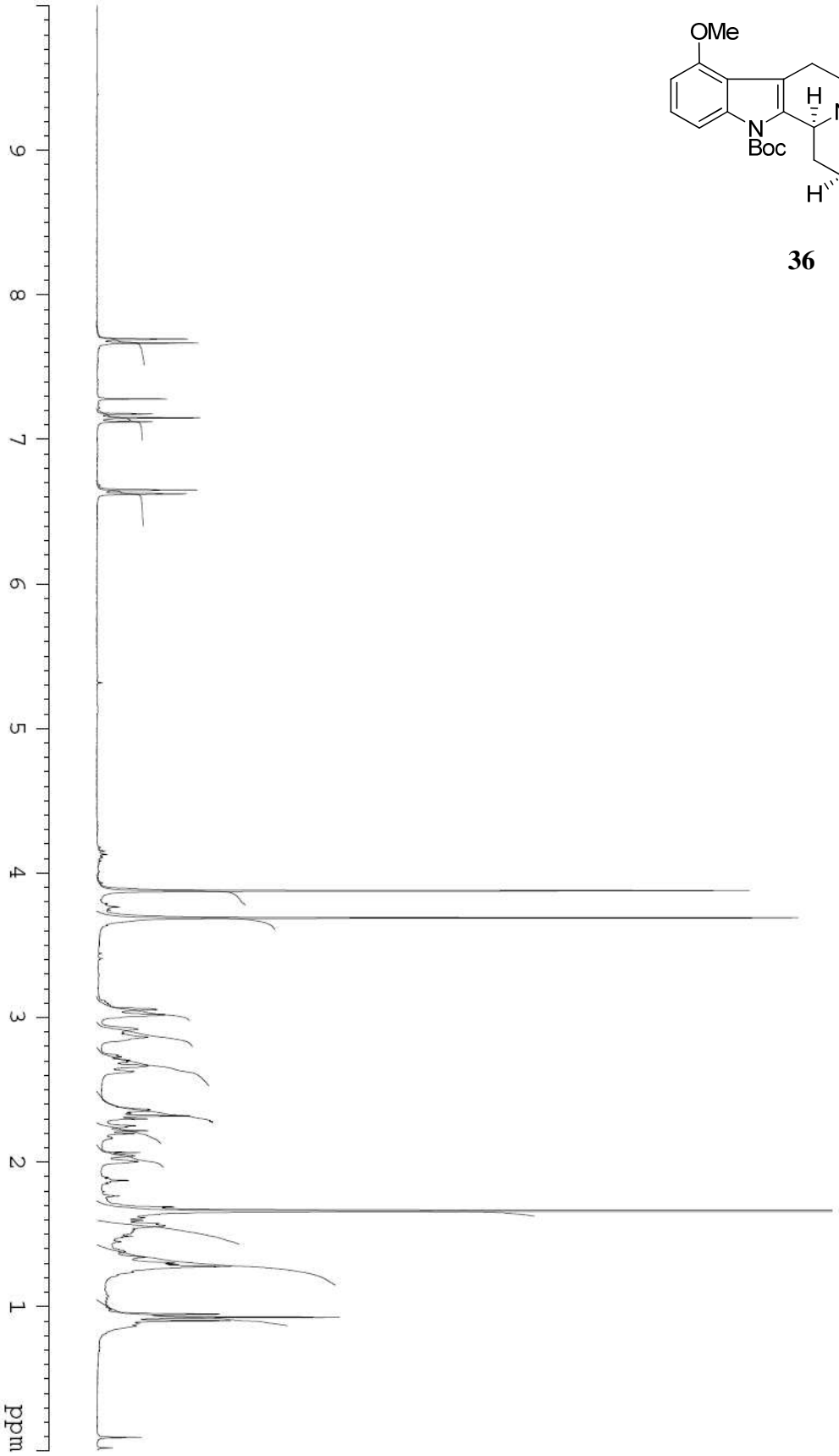


35


190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

OMe
N
H
H
N
H
H
CO2CH3

35



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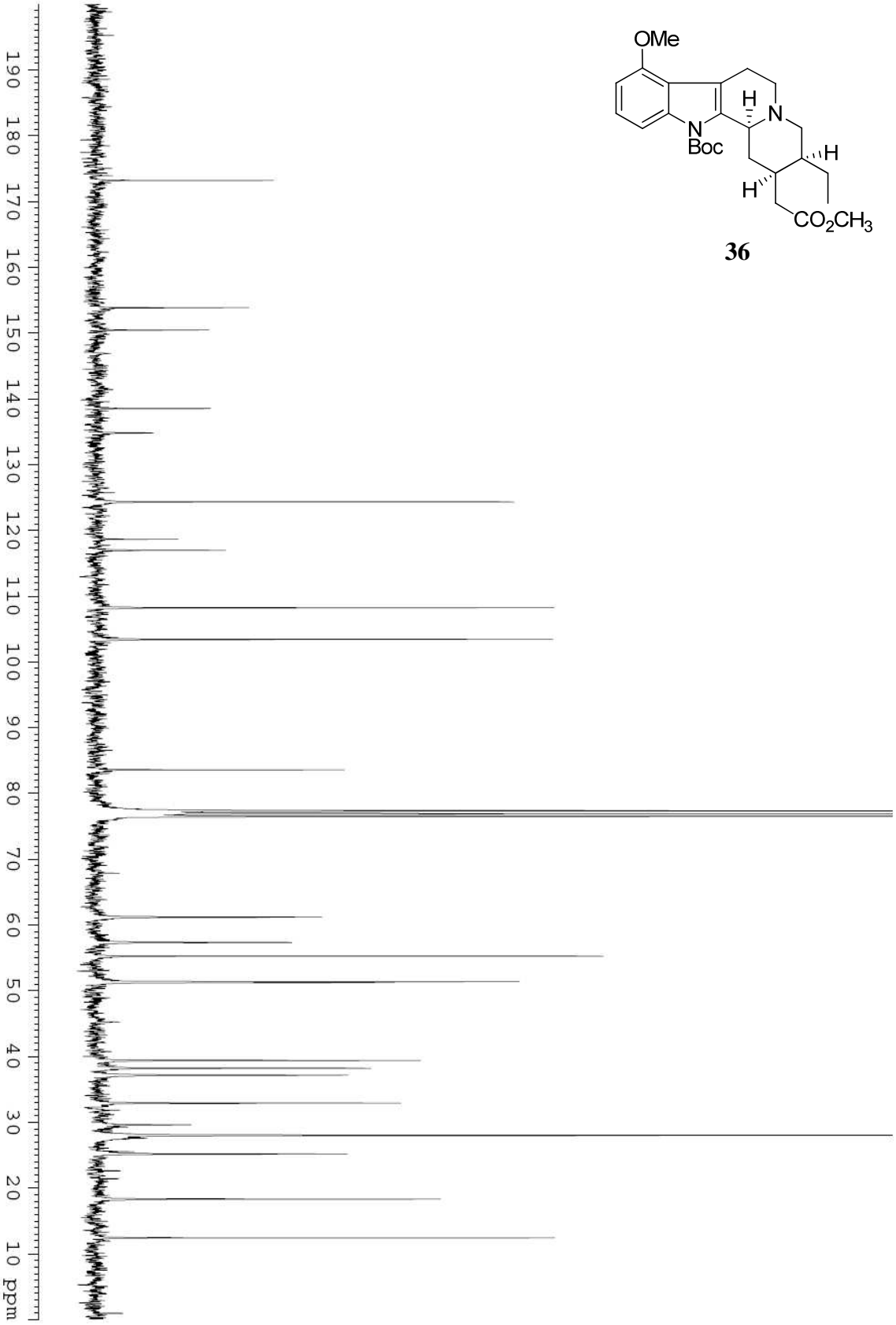
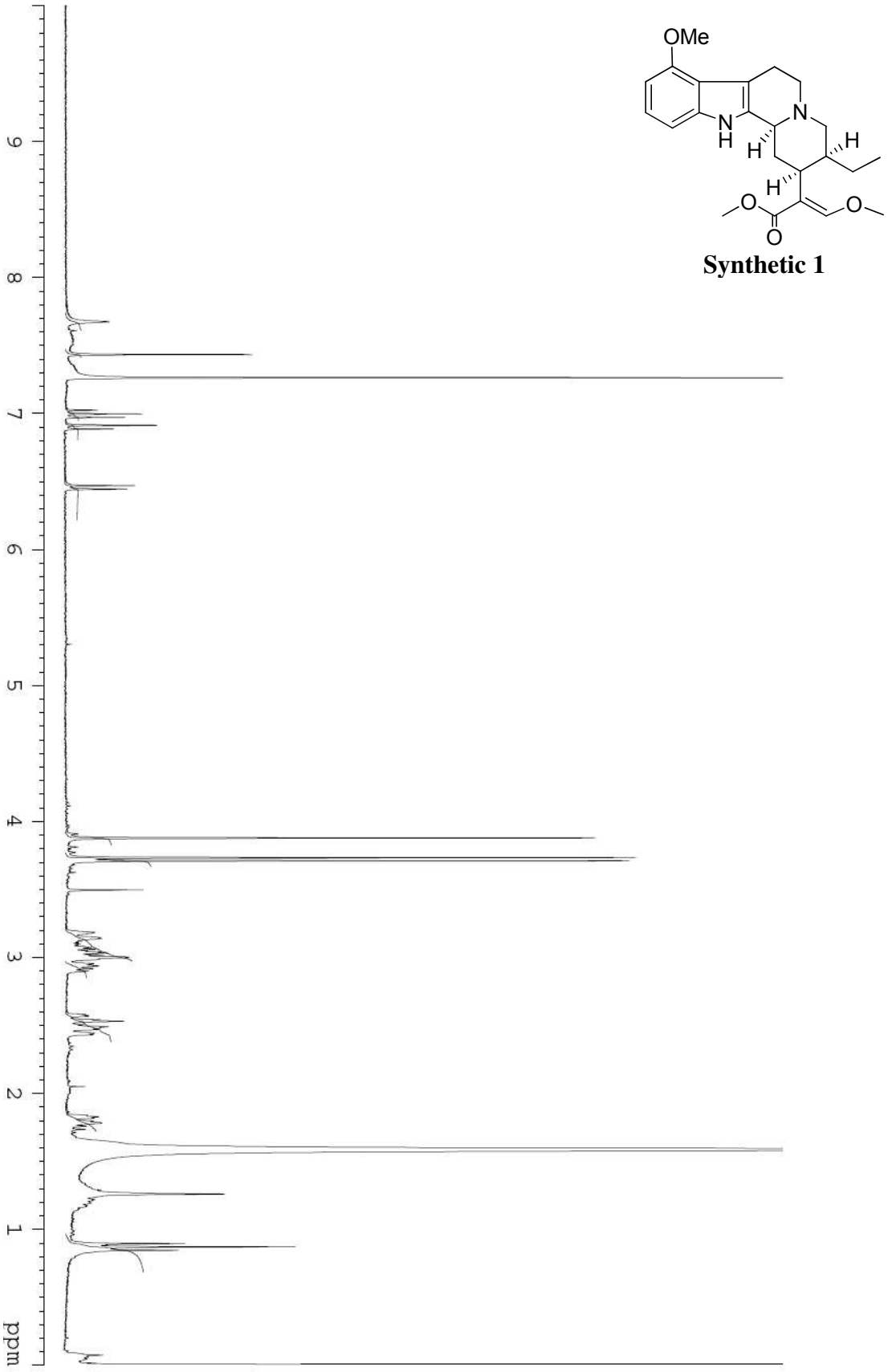
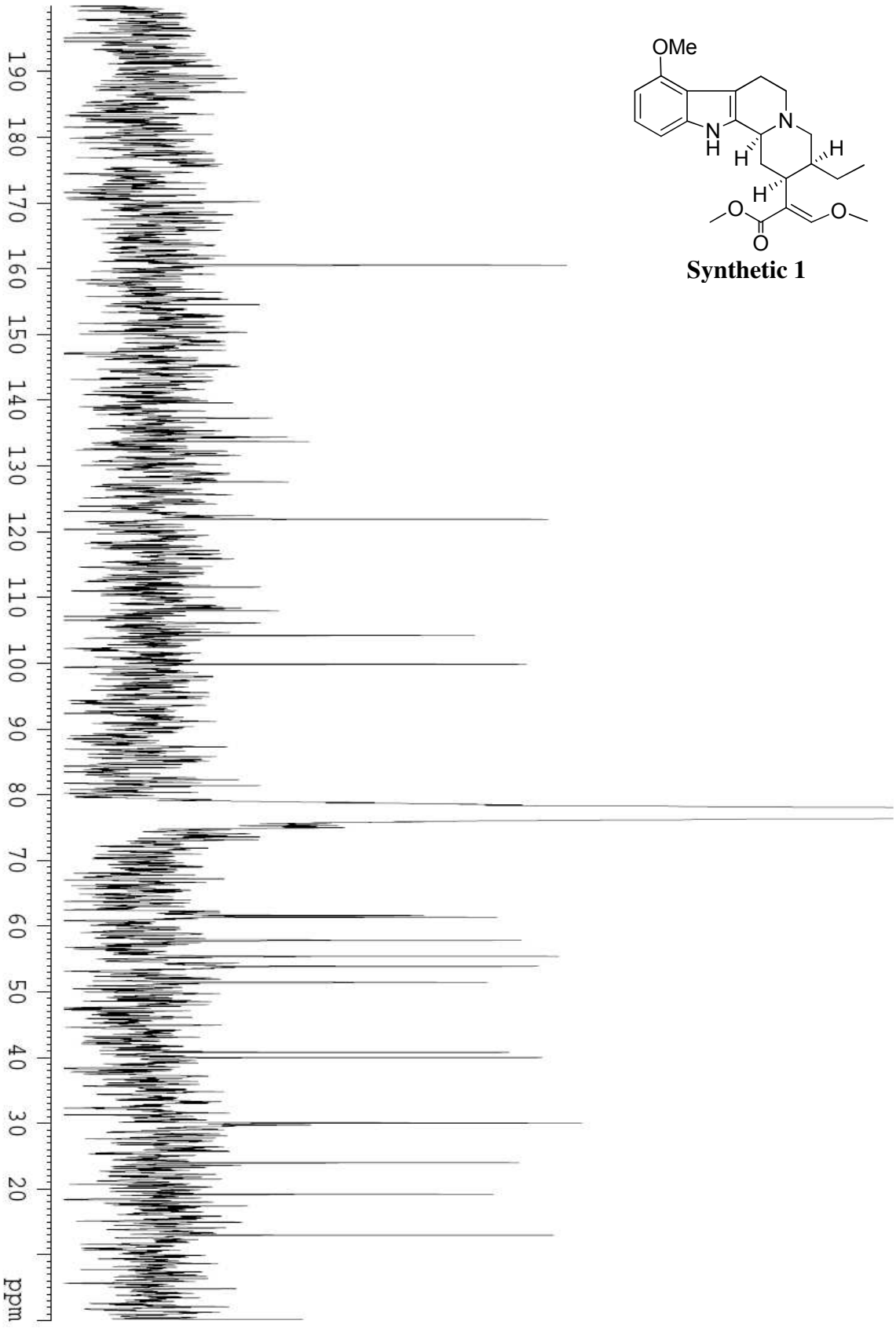

OMe
H
N
N
Boc
H
H
CO2CH3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

36

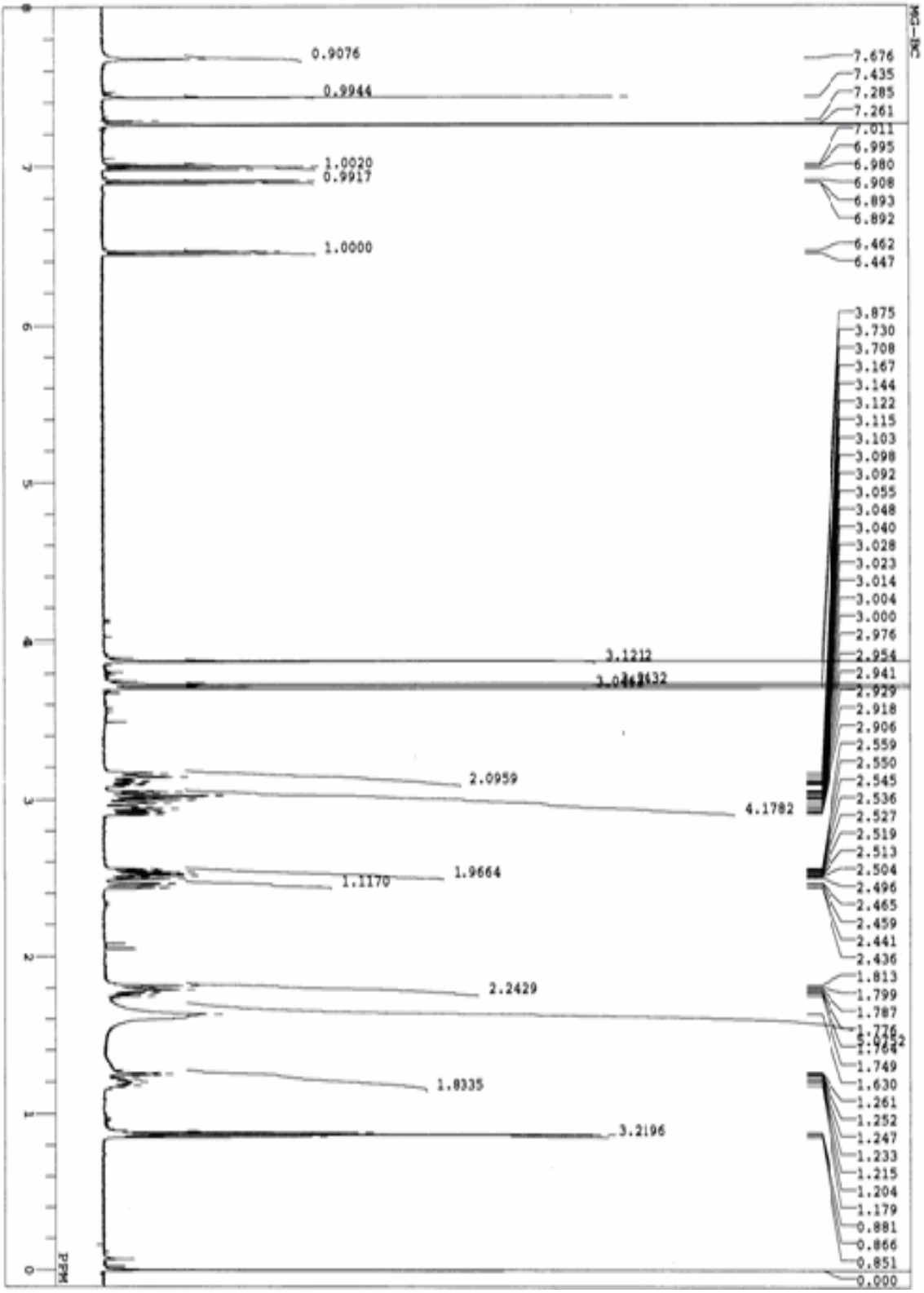


Synthetic 1


OMe
N
H
N
H
H
H
O
O
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

Synthetic 1

Copy of ^{1}H NMR of Natural Mitragynine 1 (Kindly Supplied by Professor Hiromitsu Takayama at Chiba University, Japan. 400 MHz, in $CDCl_3$)



Copy of ^{13}C NMR of Natural Mitragynine 1 (Kindly Supplied by Professor Hiromitsu Takayama at Chiba University, Japan. 100 MHz, in $CDCl_3$)

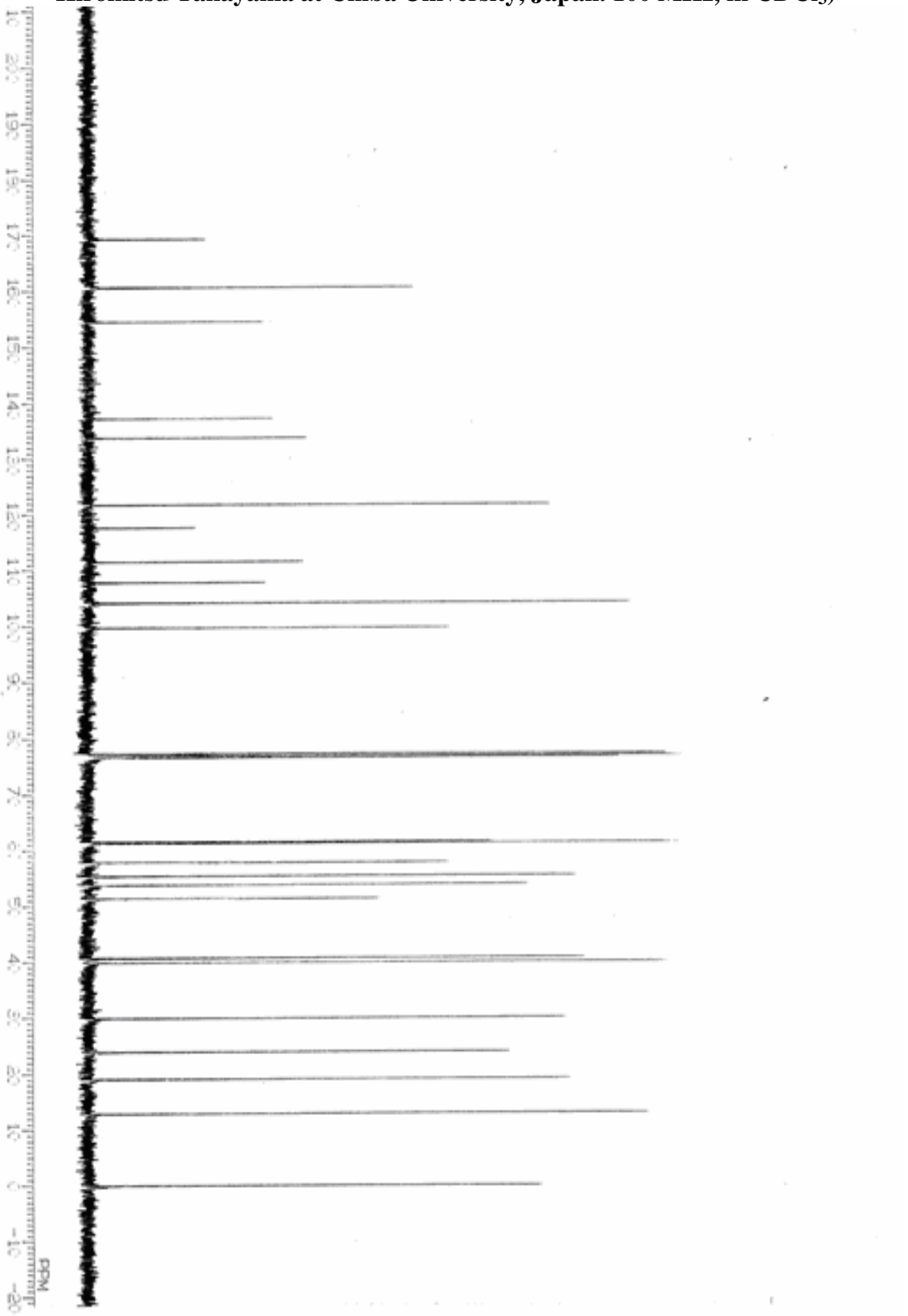
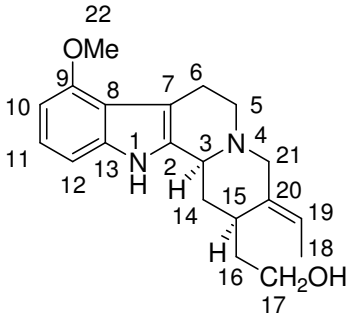


Table I. Comparison of the ^{13}C NMR Spectral Data for Synthetic 9-Methoxygeissoschizol (3) to the Reported Data of the Natural Product Obtained from *Strychnos Guianensis* [6]

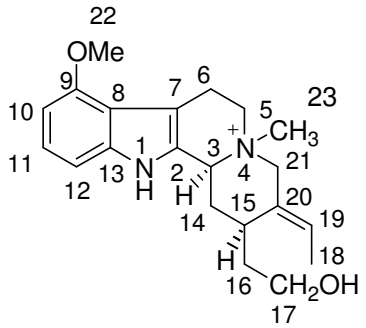


42 9-methoxygeissoschizol

Carbon atom	Natural **3** (δppm)	Synthetic **3** (δppm)	Carbon atom	Natural **3** (δppm)	Synthetic **3** (δppm)
2	131.5	131.8	**13**	137.5	137.3
3	53.5	53.3	**14**	32.4	32.4
5	51.1	51.2	**15**	31.5	31.4
6	20.1	20.0	**16**	35.8	35.7
7	106.9	106.9	**17**	61.4	61.5
8	117.4	117.3	**18**	12.9	12.8
9	154.3	154.2	**19**	121.6	121.3
10	99.6	99.6	**20**	135.9	136.0
11	122.2	122.0	**21**	53.8	53.5
12	104.6	104.5	**22**	55.2	55.1

Table II. Comparison of the ^{13}C NMR Spectral Data for Synthetic 9-methoxy-N_b-methylgeissoschizol (4) to the Reported Data of the Natural Product Obtained from *Strychnos Guianensis* [8]

9-methoxy-N_b-methylgeissoschizol

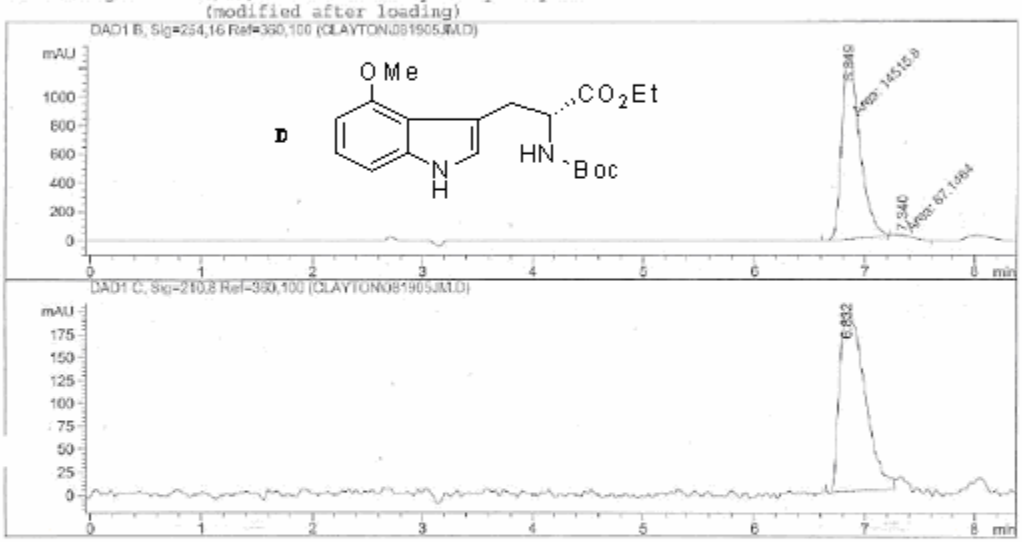


Carbon atom	Natural **4** (δppm)	Synthetic **4** (δppm)	Carbon atom	Natural **4** (δppm)	Synthetic **4** (δppm)
2	126.0	126.3	**13**	139.0	138.4
3	64.9	64.4	**14**	30.3	29.8
5	60.1	59.6	**15**	30.8	30.8
6	19.4	18.8	**16**	35.8	35.3
7	104.4	103.9	**17**	59.0	58.5
8	116.3	116.4	**18**	12.7	12.6
9	155.0	154.3	**19**	132.2	131.8
10	99.7	99.2	**20**	129.4	128.8
11	123.8	123.3	**21**	63.0	62.5
12	104.8	104.3	**22**	54.6	54.1
			23	48.9	48.3

HPLC analysis of the ee% of D-N_b-Boc-4-methoxytryptophan ethyl ester

```
Jun Ma, 50% mixture of 4.8mg D and 4.5 mg L Nb-Boc 4-Me
thoxytryptophan.

------------------------------------------------------------------------
 njection Date  : 8/19/05 2:05:26 AM
Sample Name     : D,L -methoxytry1                    Vial :   3
Acq. Operator   : terry clayton
                                                  Inj Volume : 5 µl
Method          : C:\HPCHEM\1\METHODS\080504.M
Last changed    : 8/19/05 1:50:05 AM by terry clayton
                  (modified after loading)
```




```
------------------------------------------------------------------------
                        Area Percent Report
------------------------------------------------------------------------

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount         :      8.00000  [ng/ul]   (not used in calc.)

Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]      [min]    [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.849 MM    0.1879 1.45158e4  1287.36255  99.4032
   2   7.340 MM    0.1506   87.14835    9.64517   0.5968

Totals :                  1.46029e4  1297.00772

 Results obtained with enhanced integrator!
```

HPLC analysis of D-N_b-Boc-4-methoxytryptophan ethyl ester sample spiked with 10% the L-enantimer

Jun Ma, D Nb-Boc 4-Methoxytryptophan.

```
Injection Date   : 8/19/05 2:33:13 AM
Sample Name      : D,L -Methoxytryl                    Vial :   3
Acq. Operator    : terry clayton
                                                  Inj Volume : 5 µl
Method           : C:\HPCHEM\1\METHODS\080504.M
Last changed     : 8/19/05 1:50:05 AM by terry clayton
                   (modified after loading)
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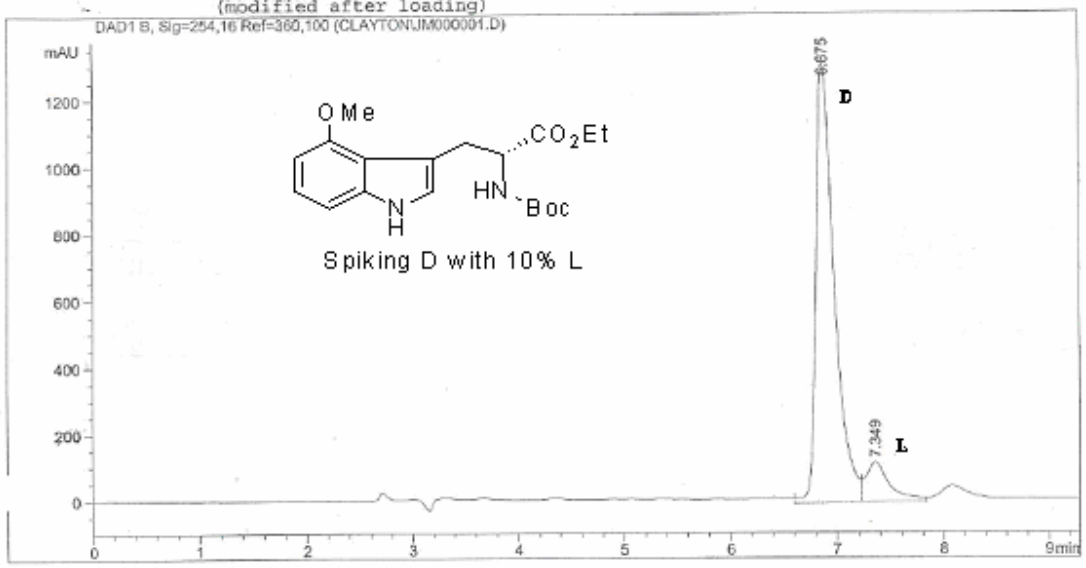


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                        Area Percent Report

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount         :      8.00000  [ng/ul]    (not used in calc.)

Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]     [mAU]      %
----|-------|----|-------|----------|----------|--------|
   1   6.875 VV    0.1832 1.56985e4  1315.51868  89.4709
   2   7.349 VV    0.2251 1847.42908  119.04462  10.5291

Totals :                  1.75459e4  1434.56330

 Results obtained with enhanced integrator!

                        *** End of Report ***
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