General Approach for the Synthesis of 12-Methoxy Substituted Sarpagine Indole Alkaloids including (-)-12-Methoxy-N_b-methylvoachalotine, (+)-12-Methoxy-N_a-methylvellosimine, (+)-12-Methoxyaffinisine, and (-)-Fuchsiaefoline

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Supporting Information

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Gerneral. Microanalysis and melting points were performed in house on a commercial microanalyzer using standard protocols. Proton and carbon NMR spectra were recorded on 300 and 500 MHz NMR spectrometers. The analytical TLC plates used were UV-active silica gel on plastic. The TLC plates were visualized under UV light or developed with spray reagents. Alkaloids were visualized with Dragendorf's reagent or a saturated solution of ceric ammonium sulfate in 50% sulfuric acid or an aqueous solution of 2,4-dinitrophenylhydrazine in 30% sulfuric acid. Chromatography refers to flash chromatography using 230-400 mesh 60 A silica gel, grade 60. Methanol was dried by distillation over magnesium metal/I_2, Tetrahydrofuran, benzene, and toluene were dried by distillation from sodium-benzophenone ketyl. Methylene chloride was dried over $MgSO_4$ and then was distilled from P_2O_5.

(6S,10S)-Methyl-4-methoxy-5-methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[b]indole-8-carboxylate (9). Sodium hydride (1.5 g of 60% NaH in mineral oil, 36.85 mmol) was added to a solution of *trans* diester **8a** (5.2 g, 11.2 mmol) in dry toluene (140 mL) in a dry ice bath under argon. Dry methanol (3.0 mL) was then added carefully to the above mixture (a large amount of H_2 was evolved at this point). The mixture which resulted was stirred at rt for 0.5 h, and then heated to reflux for an additional 5 h. The reaction mixture was then allowed to cool to rt, and treated with a saturated aq solution of $NaHCO_3$ (10 mL). The organic layer was separated, washed with brine, and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the residue was used in the next step without further purification. The residue obtained above was dissolved in 1,4-dioxane (35 mL). The 40% aq KOH (35 mL) was then added to the above solution. The reaction mixture which resulted was heated to reflux for 3 d. The

solution was then allowed to cool to rt and the 1,4-dioxane was removed under reduced pressure. The mixture which remained was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was separated, washed with brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (hexane/ ethyl acetate, 3/1) to afford **9** (3.2 g, 80%). FTIR: 1714, 1570 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.95-2.18(m, 2H), 2.41-2.51(m, 2H), 2.67 (d, 1H, J = 16.8 Hz), 3.25(dd, 1H, J = 16.8, 6.8 Hz), 3.74(s, 2H), 3.77 (d, 1H, J = 6.9 Hz), 3.90(s, 3H), 3.97(s, 3H), 4.15(bs, 1H), 6.68(d, 1H, J = 7.6 Hz), 7.04(t, 1H, J = 7.8 Hz), 7.13(d, 1H, J = 7.7 Hz), 7.35(m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.5, 29.6, 32.3, 34.3, 48.6, 55.4, 56.1, 64.8, 102.8, 105.9, 111.0, 119.6, 127.2, 128.4, 128.5, 128.6, 133.3, 138.2, 147.6, 210.0; EIMS *m/e* 360 (M^+, 30.0), 304 (33.0), 303 (100.0), 212 (19.2), 197 (19.2); HRMS $C_{23}H_{24}N_2O_2$. Calc. 360.1838; found 360.1825. Anal. Calcd. for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77. Found: C, 76.66; H, 6.68; N, 7.76.

(6S,10S)-4-Methoxy-5-methyl-9-oxo-12-H-6,7,8,9,10,11-hexahydro-6,10-imino-cyclooct[b]indole (10). The tetracyclic ketone **9** (1.34 g, 3.72 mmol) was mixed with dry EtOH (15 mL). A saturated solution of ethanolic HCl (g) (5 mL) was then added dropwise into the above mixture until the solid completely dissolved. The solvent was removed under reduced pressure to furnish an HCl salt. The residue was then dissolved in dry EtOH (20 mL), after which Pd/C (10%, 0.2 g) was added. The mixture which resulted was allowed to stir at rt under an atmosphere of hydrogen for 7 h. After analysis by TLC (silica gel plate was exposed to NH_3 vapors) indicated the absence of starting material **9**, the catalyst was removed by filtration and washed with EtOH (3 × 15 mL). The solvent was removed under reduced pressure and the residue was purified by chromatography to provide N_b-H tetracyclic

ketone **10** (0.92 g, 92%). FTIR: 1708, 1570 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.09-2.22 (m, 3H), 2.36-2.52 (m, 2H), 2.78 (d, 1H, J = 16.5 Hz), 3.10 (dd, 1H, J = 16.5, 6.8 Hz), 3.92 (m, 1H), 3.95 (s, 3H), 3.96 (s, 3H), 4.34 (d, 1H, J = 3.5 Hz), 6.65 (d, 1H, J = 7.7 Hz), 7.00 (t, 1H, J = 7.7 Hz), 7.08 (dd, 1H, J = 7.8, 1.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.9, 31.2, 32.3, 34.9, 44.8, 55.3, 59.6, 102.8, 106.6, 110.9, 119.6, 126.3, 128.5, 135.3, 147.6, 210.6; EIMS *m/e* 270 (M^+). HRMS $C_{16}H_{18}N_2O_2$. Calc. 270.1368; found 270.1361. Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.90; H, 6.80; N, 10.20.

(6S,10S)-4-Methoxy-5-methyl-9-oxo-12-(Z-2′-iodo-2′-butenyl)-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct[b]indole (11). Azabicyclononane **10** (0.85 g, 3.15 mmol) and *Z*-1-bromo-2-iodo-2-butene (0.99 g, 3.78 mmol) were dissolved in THF (15 mL) and anhydrous K_2CO_3 (2.83 g, 20.46 mmol) was added. The reaction mixture which resulted was heated to 60 °C for 24 h until analysis by TLC (silica gel, $CHCl_3$: C_2H_5OH = 4 : 1) indicated the absence of tetracyclic ketone **10**. The K_2CO_3 was then removed by filtration and was washed with EtOAc (3 × 10 mL). After removal of the solvent under reduced pressure, the crude product was purified by flash chromatography (silica gel, EtOAc : hexane = 1 : 9) to provide *N*b-Z-2′-iodo-2′-butenyl tetracyclic ketone **11** (1.27 g, 90%). $[\alpha]^{25}_{D}$ = -129.6° (c 0.25, $CHCl_3$); FTIR: 1714, 1571 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83(d, 3H, J = 6.4 Hz), 2.02-2.17(m, 2H), 2.45-2.50(m, 2H), 2.68 (d, 1H, J = 16.9 Hz), 3.12 (dd, 1H, J = 16.9, 6.8 Hz), 3.35 (brs, 2H), 3.71 (d, 1H, J = 6.7 Hz), 3.94 (s, 3H), 3.95 (s, 3H), 4.07 (brs, 1H), 5.83 (brq, 1H, J = 6.4 Hz), 6.66 (d, 1H, J = 7.2 Hz), 7.01 (t, 1H, J = 7.7 Hz), 7.08 (d, 1H, J = 7.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.6, 21.7, 29.6, 32.4, 34.2, 48.6, 55.3, 63.5, 63.9, 102.8, 105.9, 108.4, 110.9, 126.5, 128.4, 132.9, 133.4, 147.6, 210.0; EIMS *m/e* 450 (M^+); Anal. Calcd. for $C_{20}H_{23}N_2O_2I$: C, 53.34; H, 5.15; N, 6.22. Found: C, 53.16; H, 5.08; N, 6.05.

Palladium catalyzed cyclization of (6S,10S)-4-methoxy-9-oxo-12-(Z-2′-iodo-2′-butenyl)-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct[b]indole (11) to provide pentacyclic ketone (12). A mixture of N_b-Z-2′-iodo-2′-butenyl tetracyclic ketone **11** (1.03 g, 2.36 mmol), $Pd(OAc)_2$ (19 mg, 0.085 mmol), Bu_4NBr (0.762 g, 2.36 mmol), PPh_3 (0.186 g, 0.709 mmol) and K_2CO_3 (1.3 g, 9.45 mmol) in a solution of DMF-H_2O (9 : 1, 8 mL) was degassed under reduced pressure (Ar). The mixture was then heated to 70 °C (oil bath temperature) under an atmosphere of argon for 12 h. Analysis by TLC (silica gel, EtOAc : hexane = 4 : 1) indicated the absence of N_b-Z-2′-iodo-2′-butenyl tetracyclic ketone **11** and the presence of a new indole component of lower *Rf* value. The mixture was cooled to rt, diluted with EtOAc (220 mL), washed with H_2O (5 × 50 mL), and dried (K_2CO_3). The solvent was removed under reduced pressure and the oil which resulted was chromatographed (silica gel, EtOAc : hexane = 3 : 7) to provide pentacyclic ketone **12** (0.59 g, 80%). FTIR: 1725, 1572 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.68 (dt, 3H, J = 7.8, 1.8 Hz), 2.16 (dt, 1H, J = 12.6, 3.7 Hz), 2.53 (td, 1H, J = 11.1, 1.9 Hz), 2.98 (dd, 1H, J = 15.5, 6.3 Hz), 3.28 (dd, 1H, J = 15.5, 1.4 Hz), 3.40 (dd, 1H, J = 3.9, 1.8 Hz), 3.59 (dd, 1H, J = 5.8 Hz), 3.84 (m, 2H), 3.90 (s, 3H), 3.93 (s, 3H), 4.33 (dd, 1H, J = 9.4, 2.3 Hz), 5.54 (brq, 1H, J = 6.9 Hz), 6.63 (d, 1H, J = 7.7 Hz), 6.98 (t, 1H, J = 7.8 Hz), 7.10 (d, 1H, J = 7.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.6, 22.6, 32.3, 35.8, 44.3, 49.5, 55.3, 55.5, 64.0, 102.7, 104.7, 111.4, 119.4, 120.8, 126.7, 128.6, 132.4, 138.0, 147.4, 217.4. EIMS *m/e* 322 (M^+). HRMS $C_{20}H_{22}N_2O_2$. Calc. 322.1681; found 322.1680. This material was used directly in the next step.

12-Methoxy-N_a-methylvellosimine (13). A mixture of anhydrous potassium t-butoxide (1.05 g, 8.88 mmol) and methoxylmethyl triphenylphosphonium chloride (2.85 g, 8.08 mmol) in dry benzene (55 mL) was allowed to stir at rt for 1 h. The pentacyclic ketone **12**

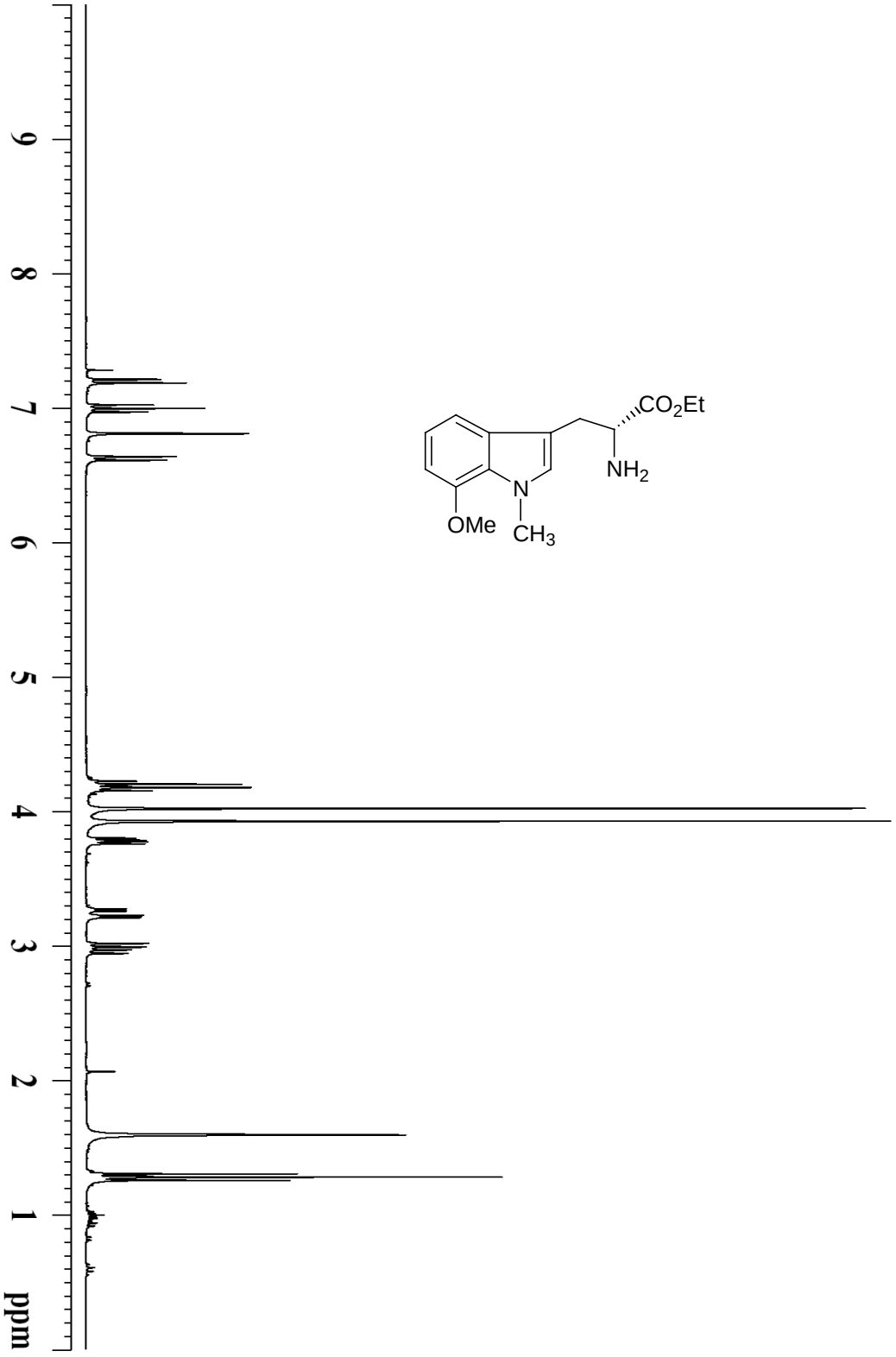
(500 mg, 1.55 mmol) in THF (17.5 mL) was then added into the above orange colored solution dropwise at rt. The mixture which resulted was stirred at rt for 24 h (The reaction progress was monitored by ^{1}H-NMR spectroscopy of a sample from the mixture). The solution was diluted with EtOAc (3 × 75 mL), washed with H_2O (3 × 5 mL), brine (5 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was dissolved (without further purification) in a solution of aq 2N HCl in H_2O/THF (150 mL). The solution which resulted was stirred at 55 °C (oil bath temperature) under an atmosphere of argon for 6 h. The reaction progress was monitored by analysis of the crude mixture by ^{1}H-NMR spectroscopy. After the reaction was complete, the THF was removed under reduced pressure. The acidic reaction mixture was diluted with H_2O (50 mL) and extracted with diethyl ether (6 × 50 mL) to remove PPh_3=O. The aq layer was then brought to pH=8 with an aq solution of 28% NH_4OH. The aq layer which resulted was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were washed with H_2O (3 × 5 mL), brine (5 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford an oil which was chromatographed (silica gel, EtOAc/hexane = 3 : 2) to provide pure (+)-**13** (470 mg, 90%). $[\alpha]^{25}_D$ = 40.6 ° (c=1.3, $CHCl_3$); FTIR: 2923, 1714, 1618 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.61 (dt, 3H, J = 6.8, 2.0 Hz), 1.75 (dt, 1H, J = 10, 2.0 Hz), 2.11 (ddd, 1H, J = 12.0, 4.1, 1.9 Hz), 2.46 (d, 1H, J = 7.1 Hz), 2.56 (dd, 1H, J = 15.7, 2.0 Hz), 3.11 (dd, 1H, J = 15.8, 5.9 Hz), 3.18 (m, 1H), 3.59 (m, 1H), 3.63 (brs, 2H), 3.90 (s, 3H), 3.90 (s, 3H), 4.23 (dd, 1H, J = 10.1, 2.0 Hz), 5.35 (q, 1H, J = 7.2 Hz), 6.61 (d, 1H, J = 7.8 Hz), 6.96 (t, 1H, J = 7.9 Hz), 7.04 (d, 1H, J = 7.8 Hz), 9.61 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.6, 26.5, 27.2, 32.3, 32.4, 49.3, 50.4, 54.8, 55.3, 56.1, 102.5, 103.3, 111.1, 116.9, 119.3, 126.6, 129.1, 134.2, 139.3, 147.5,

202.7. EIMS *m/e* 336 (M^+, 68), 335 (32), 307, (100), 293 (10.3), 213 (65), 212 (67), 197 (67).

Ethyl Ester (15). (+)-12-Methoxy-N_a-methylvellosimine 13 (0.15 g, 0.446mmol) was dissolved in EtOH (6 mL) and cooled to 0 ^oC. The KOH (85%, 0.076 g, 1.161mmol) in EtOH (2mL) and I_2 (0.147g, 0.580 mmol) in EtOH (2 mL) were successively added to the above solution dropwise at 0 ^oC. The reaction mixture was stirred at rt for 3h and then diluted with EtOAc (150 mL). The mixture was then washed with 10 % aq $Na_2S_2O_3$ (30 mL), brine and dried (Na_2SO_4). The solution was then concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (CH_2Cl_2/MeOH: 20/1) to afford ester 15 (0.144 g, 85%). FTIR: 2923, 1728, 1572 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 3H, J = 7.1 Hz), 1.62 (d, 3H, J = 6.8 Hz), 1.74 (m, 1H), 2.08 (td, 1H, J = 11.2, 1.9 Hz), 2.53 (dd, 1H, J = 7.7, 1.3 Hz), 2.66 (d, 1H, J = 15.6 Hz), 3.12 (dd, 1H, J = 15.6, 5.2 Hz), 3.20 (m, 1H), 3.59-3.70 (m, 3H), 3.93 (s, 3H), 3.94 (s, 3H), 4.14 (qd, 2H, J = 7.1, 3.8 Hz), 4.20(bd, 1H, J = 9.3 Hz), 5.35 (q, 1H, J = 6.8 Hz), 6.63(d, 1H, J = 7.6 Hz), 6.98 (t, 1H, J = 7.8 Hz), 7.08 (d, 1H, J = 7.8 Hz); ^{13}C NMR (75.7 MHz, $CDCl_3$) δ 12.8, 14.2, 27.3, 28.4, 32.4, 32.6, 46.8, 48.9, 52.7, 55.3, 56.1, 60.4, 102.4, 103.6, 111.1, 116.6, 119.2, 127.5, 129.3, 134.5, 139.4, 147.5, 173.5. EIMS *m/e* 380 (M^+). HRMS $C_{23}H_{28}N_2O_3$. Calc. 380.2100; found 380.2079. This material was employed directly in the next step.

(3-Ethylidene-13-hydroxymethyl-11-methoxy-12-methyl-1,3,4,7,12,12b-hexahydro-2H,6H-2,6-methano-indolo[2,3-a]quinolizin-13-yl)-methanol (17). To a solution of aldehyde 13 (300 mg, 0.892mmol) in MeOH (10 mL) were added formaldehyde [(25 equiv, 25 mmol) 1.7 mL of a 37% w / w solution in water] and

85% KOH (10 equiv, 588 mg, 8.92 mmol) in MeOH (10 mL). The reaction mixture was stirred at rt for 10 h, diluted with brine and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue that resulted was purified by flash chromatography (silica gel, $MeOH/CH_2Cl_2$: 1/10) to provide diol 17 (280 mg, 85%). FTIR: 3330, 2937, 1571 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.61 (d, 3H, J = 6.7 Hz), 1.72 (dt, 1H, J = 13.1, 3.3 Hz), 1.85 (td, 1H, J = 10.2, 2.0 Hz), 2.58 (d, 1H, J = 16.0 Hz), 2.67 (d, 1H, J = 6.1 Hz), 2.79 (dd, 1H, J =15.9, 6.1 Hz), 2.87 (t, 1H, J = 2.7 Hz), 3.31-3.57 (m, 8H), 3.87 (s, 3H), 3.94 (s, 3H), 4.01 (dd, 1H, J = 10.1, 3.3 Hz), 5.29 (q, 1H, J = 6.8 Hz), 6.63 (d, 1H, J = 7.8 Hz), 6.95-7.05 (m, 2H); ^{13}C NMR (75.7 MHz, $CDCl_3$) δ 12.7, 22.4, 27.5, 28.3, 32.2, 42.3, 48.5, 55.3, 56.0, 56.2, 64.0, 70.7, 102.3, 105.3, 111.1, 115.9, 119.1, 126.4, 128.1, 137.0, 138.6, 147.4. EIMS *m/e* 368 (M^+). This material was employed directly in the next step.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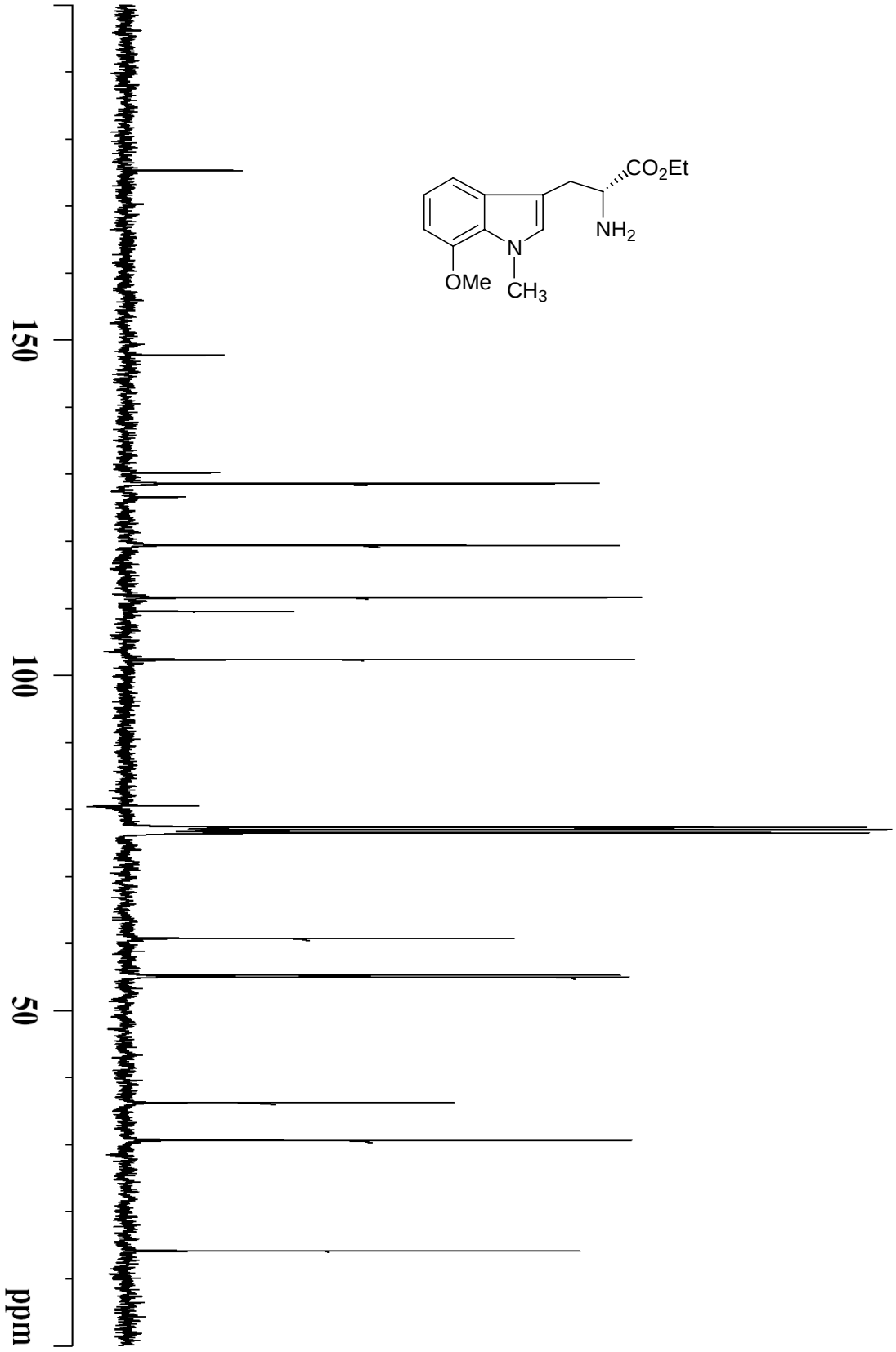
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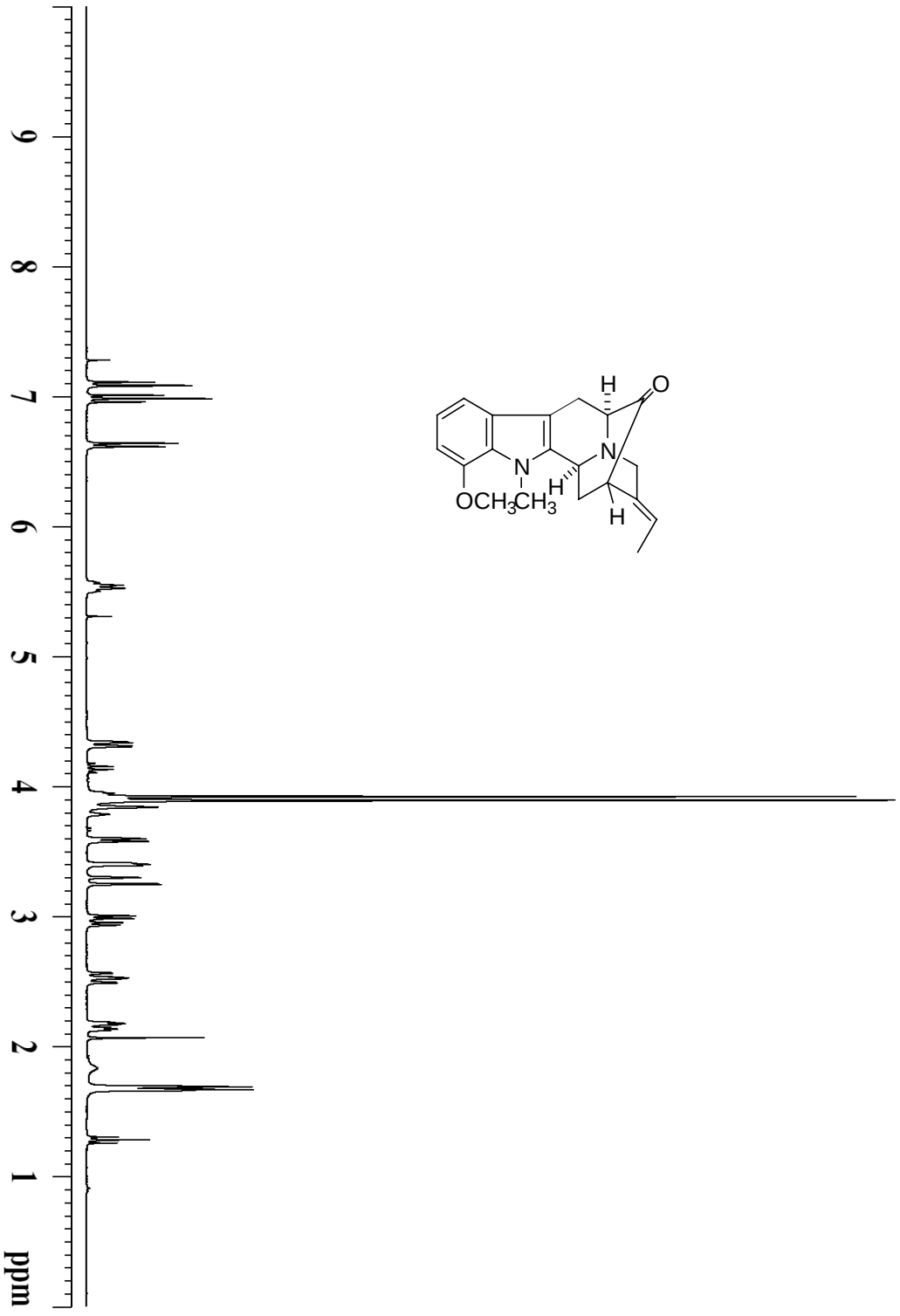
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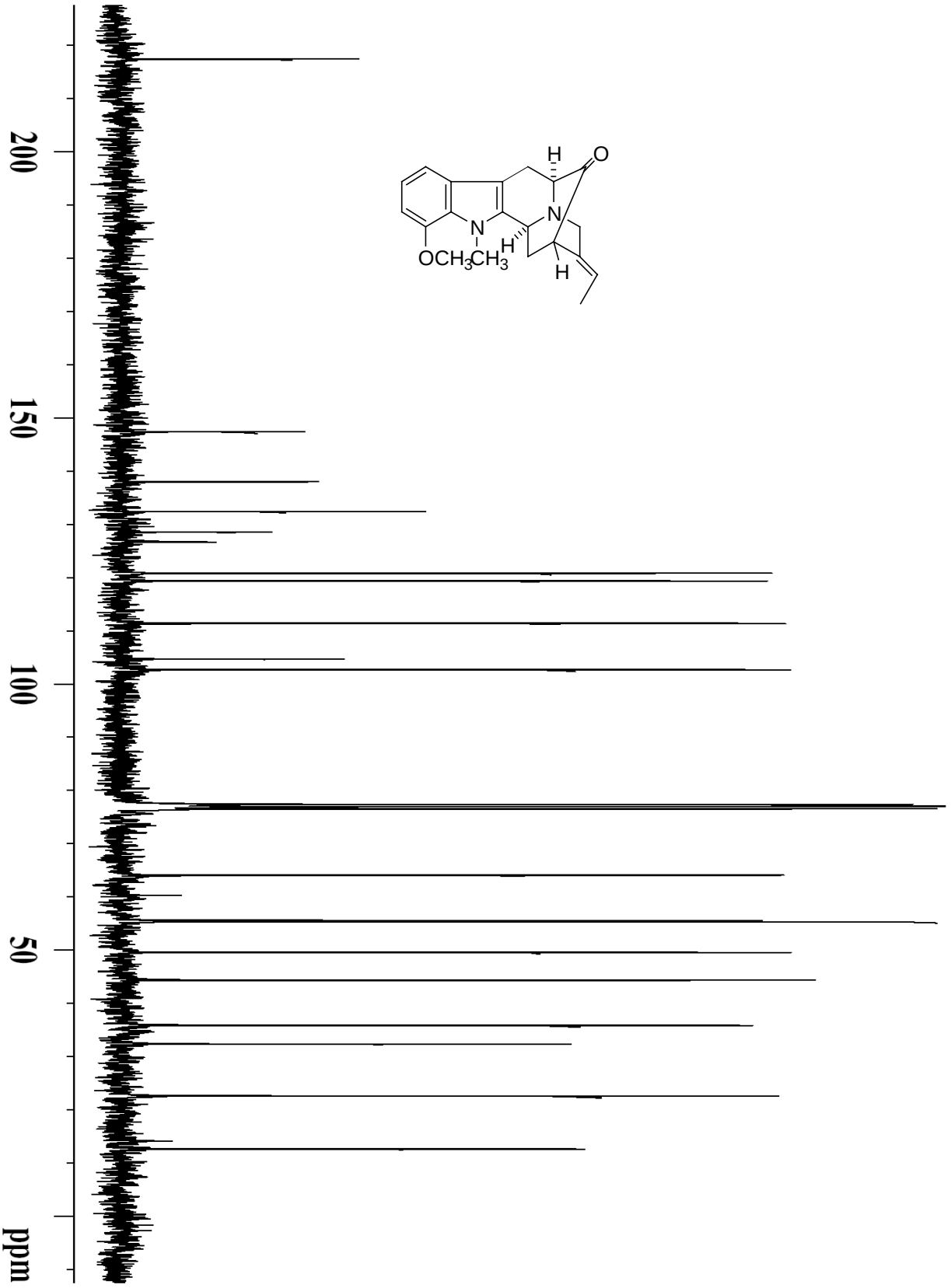
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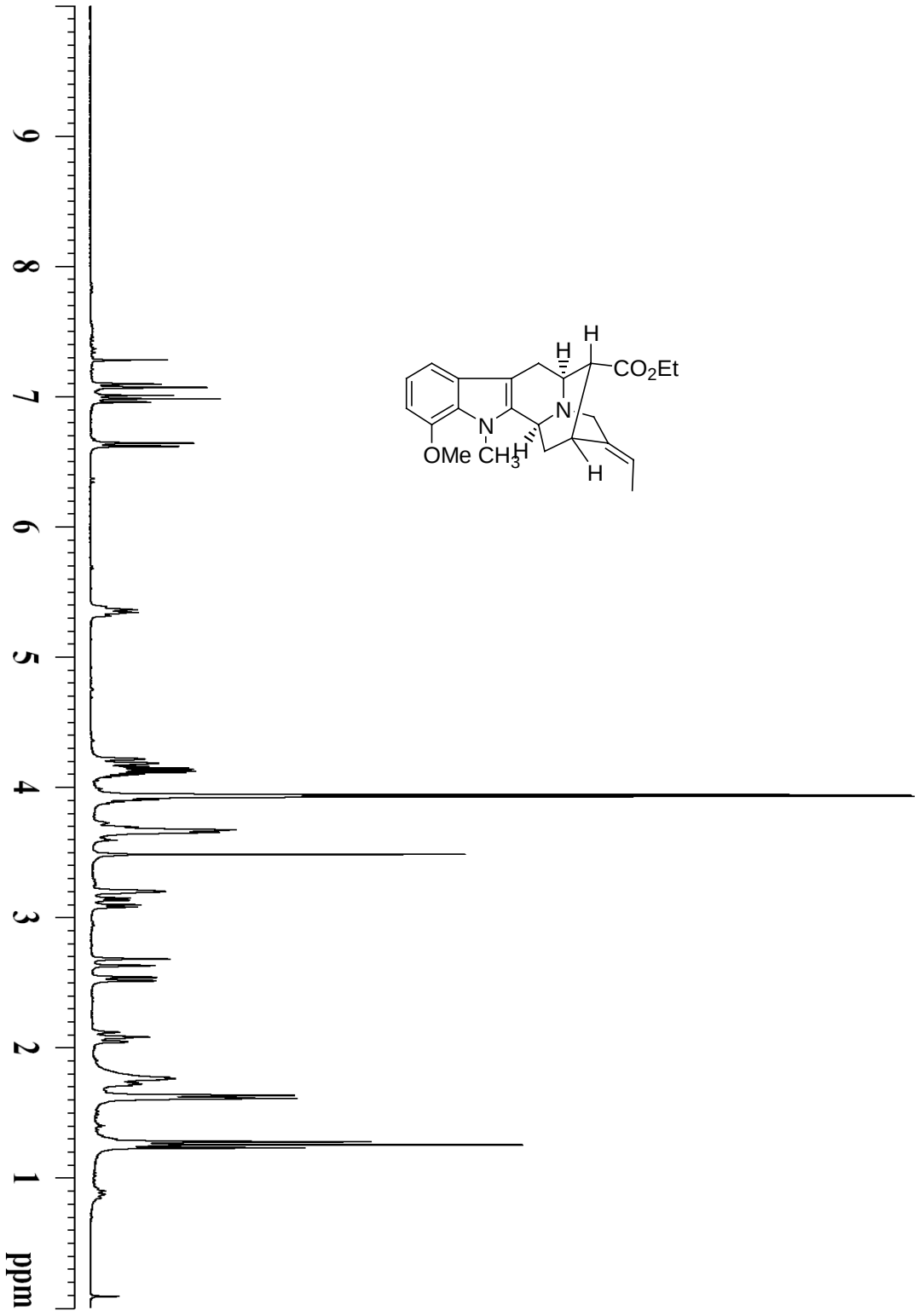
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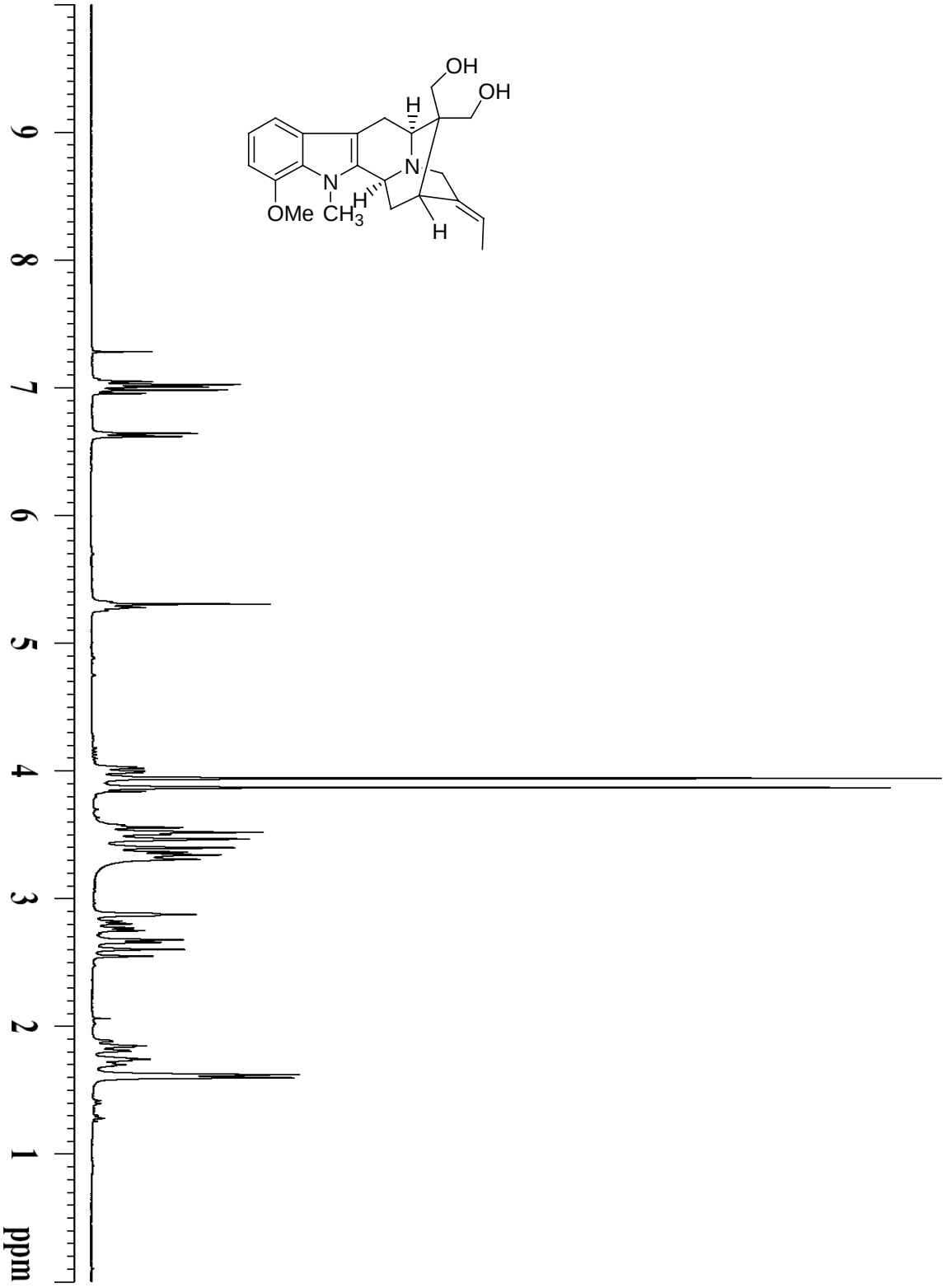
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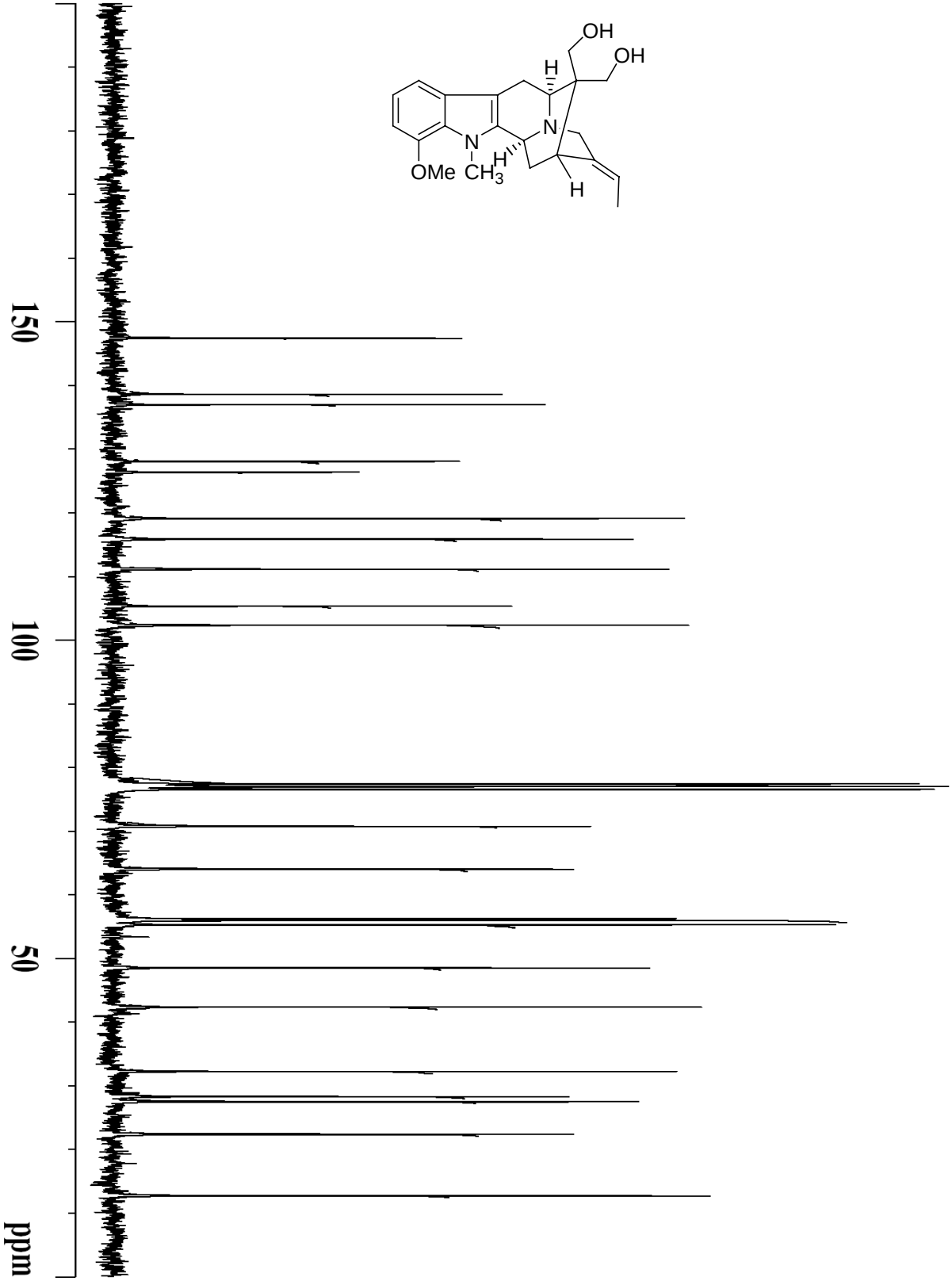
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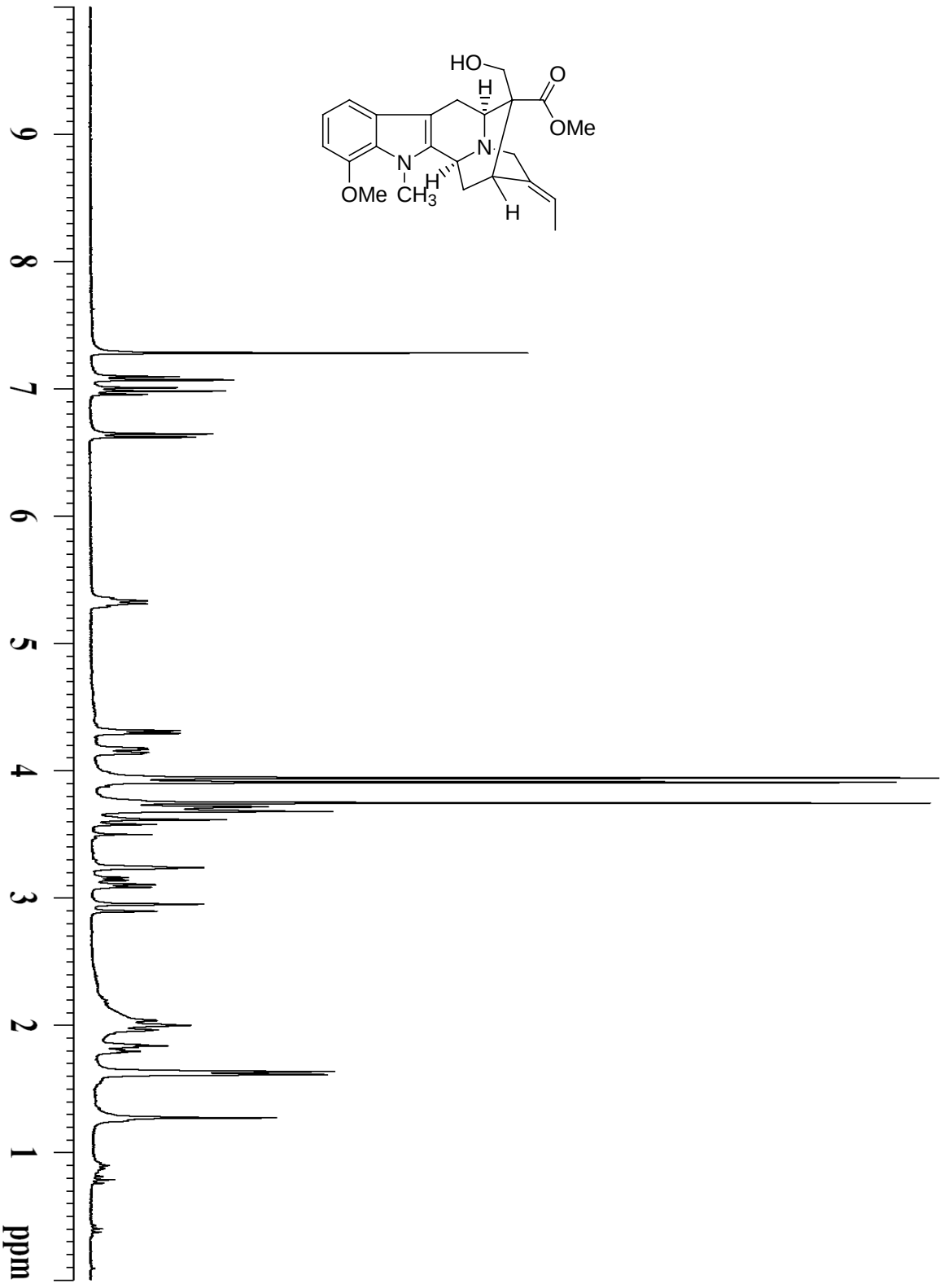
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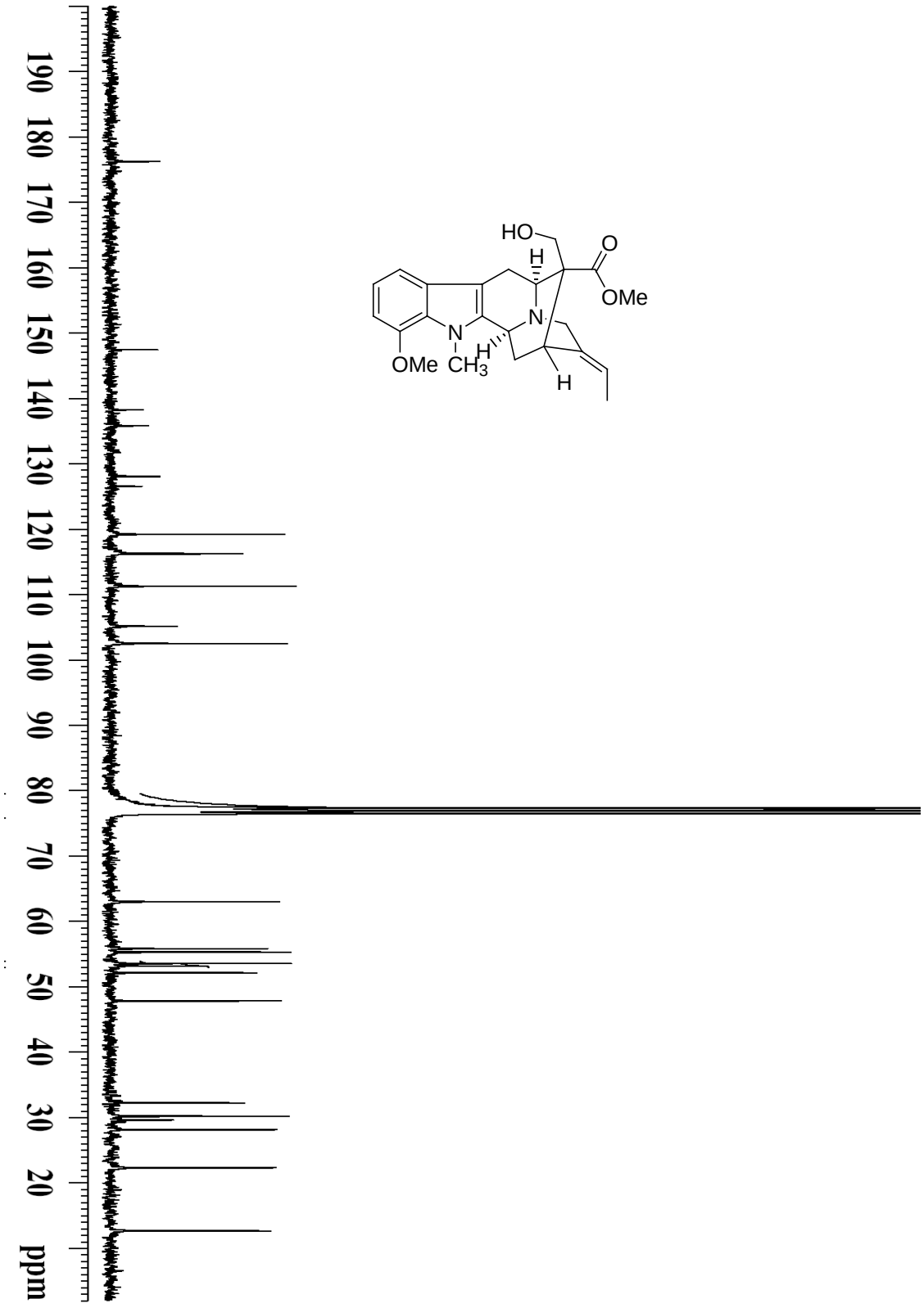
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