Supporting Information

Short Total Syntheses of Arylindolizidine Alkaloids (+)-Ipalbidine and (+)-Antofine

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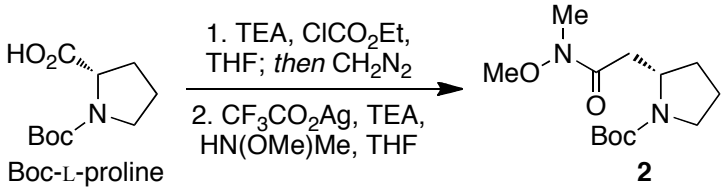
GENERAL EXPERIMENTAL PARAGRAPH

Unless otherwise specified, all starting materials, reagents and solvents are commercially available and were used without further purification. Flash column chromatography was carried out on silica gel. TLC was conducted on silica gel 250 micron, F_{254} plates. ^{1}H NMR spectra were recorded on either a 400 or 500 MHz NMR instrument. Chemical shifts are reported in ppm with TMS or $CHCl_3$ as an internal standard (TMS: 0.00 ppm, $CHCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, b = broad, m = multiplet), integration and coupling constants (Hz). ^{13}C NMR spectra were recorded on either a 100 or 125 MHz NMR spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent as internal standard ($CHCl_3$: 77.2 ppm). IR of solids were obtained by dissolving the sample in $CHCl_3$ and letting the solvent evaporate on a KBr plate.

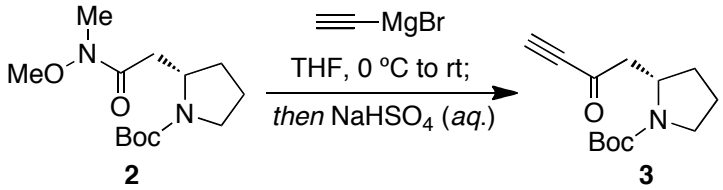
EXPERIMENTAL AND CHARACTERIZATION DATA



(*S*)-*tert*-Butyl 2-(2-(Methoxy(methyl)amino)-2-oxoethyl)pyrrolidine-1-carboxylate (2). *Warning: Large amounts of diazomethane were used for this transformation. Proper care should be taken when handling this highly explosive reagent. All glassware used was free of cracks, scratches or ground-glass joints and a blast shield was used.* Boc-L-proline (10.8 g, 50.0 mmol, 1.00 equiv) was taken into THF (100 mL) with stirring and cooled to 0 ºC with an ice bath. The reaction solution was treated with TEA (7.66 mL, 55.0 mmol, 1.10 equiv) and allowed to react for 15 min to fully deprotonate the carboxylic acid. With the addition of ethyl chloroformate (5.23 mL, 55.0 mmol, 1.10 equiv), a thick white precipitate formed. Stirring was continued for 15 min then stopped. In a separate flask, an ice-cold ethereal solution of diazomethane was prepared and, without stirring, was carefully decanted into the freshly prepared anhydride reaction flask

using a glass funnel. The reaction solution was lightly stirred for 4 seconds then stirring was stopped. The mixture was allowed to warm to room temperature and react overnight. Any additional diazomethane was carefully quenched with 0.5 N acetic acid (100 mL). The drop-wise addition of saturated sodium bicarbonate regulated the solution back to a basic pH 8-9 with gentle stirring. The organic and aqueous layers were separated. The organic phase was washed twice each with saturated sodium bicarbonate and brine then dried over sodium sulfate. The solvent was evaporated under reduced pressure. The diazoketone was purified by chromatography on silica gel (15% EtOAc/hexanes) to provide the title compound (**1**) as a yellow oil (72%). The spectral data matched that in the literature.[1]

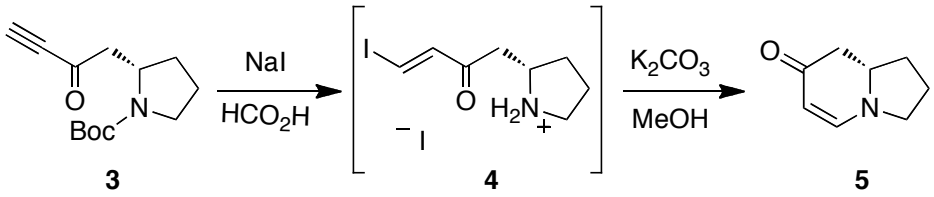
Diazoketone **1** (7.37 g, 30.8 mmol, 1.00 equiv) was taken into THF (130 mL) and cooled to 0 ºC. Foil was used to cover the reaction flask so as to exclude light from the reaction solution. To this was added freshly distilled *N,O*-dimethylhydroxylamine (4.00 g, 92.4 mmol, 3.00 equiv).[2] In a separate foil covered flask, silver(I) trifluoroacetate (1.37 g, 6.20 mmol, 0.20 equiv) was dissolved in TEA (86 mL). This solution was added to the diazoketone mixture over 30 min. The reaction temperature was allowed to slowly warm to room temperature and the solution was stirred overnight. To the reaction mixture was added activated charcoal (~2 g) and the reaction mixture was stirred for 5 min and filtered. The filtrate was concentrated and the residue redissolved in EtOAc. To this was added activated charcoal (~2 g) and the process repeated. When the filtrate had been concentrated a second time the residue was purified via SiO_2 flash chromatography (50% EtOAc/hexanes) affording the pure Weinreb amide as a clear oil (97%). Spectral data of the title compound was identical to that reported in the literature.[3]



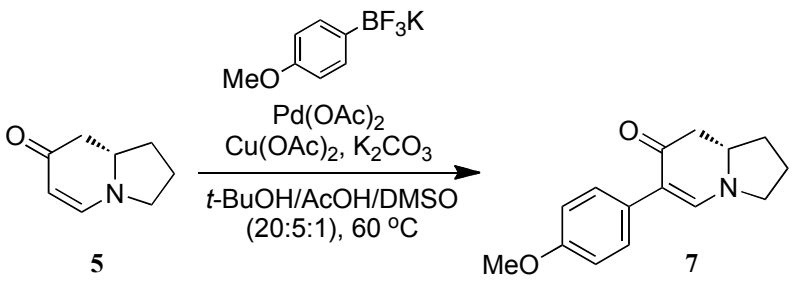
2 **3**

(*S*)-tert-Butyl 2-(2-Oxobut-3-yn-1-yl)pyrrolidine-1-carboxylate (3). Weinreb amide **2** (4.7 g, 17 mmol, 1.0 equiv) was dissolved in anhydrous THF (200 mL) under nitrogen atmosphere and cooled to 0 °C. To this reaction vessel, was added dropwise, a solution of ethynyl magnesium bromide reagent (170 mL, 86 mmol, 5.0 equiv, 0.5 M in THF) and

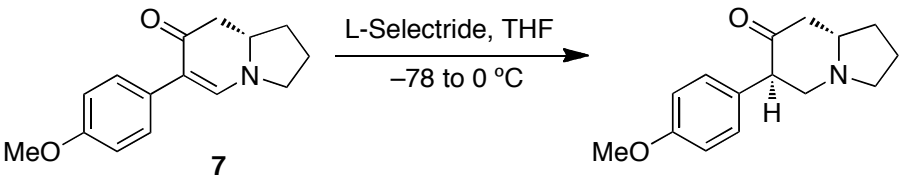
allowed to come to room temperature. After the reaction was judged complete by TLC it was quenched by the addition of an ice cold 10% HCl solution (15 mL) and allowed to stir at this temperature for 5 min. The reaction was diluted with water and extracted with EtOAc (x3). The combined organic layers were washed with saturated $NaHCO_3$ (x1), dried over Na_2SO_4, filtered and concentrated. The title compound was obtained as a clear oil (3.9 g, 97% yield) after SiO_2 flash chromatography (20% EtOAc/hexanes): Spectral data was identical to that reported in the literature.[4]



(*S*)-2,3,8,8a-Tetrahydroindolizin-7(1*H*)-one (5). Ynone **3** (3.74 g, 15.8 mmol, 1.0 equiv) was dissolved in formic acid (50 mL) solution under a N_2 atmosphere and NaI (7.09 g, 47.3 mmol, 3.0 equiv) was added. The reaction was left stirring for 6 h at room temperature. The solvent was removed by passing N_2 over the reaction mixture. The remaining residue was placed under vacuum for 15 minutes and then dissolved in MeOH (100 mL). A separate flask was charged with 700 mL of MeOH and K_2CO_3 (10.9 g, 79.0 mmol, 5.0 equiv). To this flask was added the solution of deprotected ynone over 15 minutes. The reaction was stirred for 1 h and the solvent was evaporated. At this time CH_2Cl_2 was added to redissolve the product (but not the inorganic salts), the slurry was suction filtered, and the filtrate concentrated. To the solid residue was added more CH_2Cl_2 and the precipitates were once again filtered away. This residue after removal of solvent was purified via SiO_2 flash chromatography to provide the title compound as an off-white solid (2.05 g, 95% yield) after SiO_2 flash chromatography (100% acetone). Spectral data of the title compound was identical to that reported in the literature.[4a] Optical rotation. $[\alpha]_D^{22} = -727$ (*c* 1.00, $CHCl_3$).[4b]

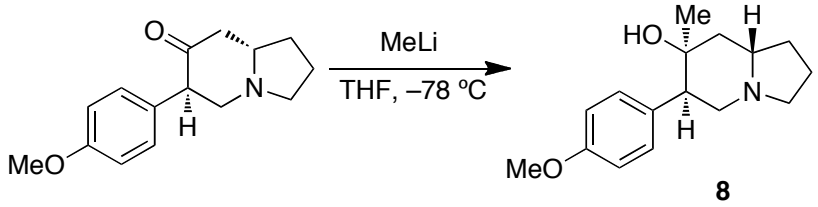


(*S*)-6-(4-Methoxyphenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (7). Freshly purified enaminone (750 mg, 5.5 mmol, 1.0 equiv), $Pd(OAc)_2$ (370 mg, 1.7 mmol, 0.30 equiv), anhydrous $Cu(OAc)_2$ powder (3.0 g, 17 mmol, 3.0 equiv) and granular K_2CO_3 (1.5 g, 11 mmol, 2.0 equiv) were combined in a 20:5:1 mixture of degassed *t*-BuOH/AcOH/DMSO (55 mL) under N_2 and stirred for 5 min (*Note: Solvents were used without purification*). The reaction mixture was heated to 60 °C and the potassium trifluoroborate (3.5 g, 17 mmol, 3.0 equiv) was added slowly over 5 h as a solid. Approximately, 0.20 equivalents of trifluoroborate were added every 30 min. The reaction was stirred for an additional hour and was monitored by TLC using 100% EtOAc as the mobile phase. The reaction mixture was diluted with EtOAc and added to a separatory funnel containing brine. The product was extracted with EtOAc (3x). The combined organic layers were washed brine (2x) and sat. $NaHCO_3$ (*aq.*) (2x), dried over Na_2SO_4 and concentrated *in vacuo*. The title compound was obtained as a pale yellow solid (930 mg, 70% yield) after SiO_2 flash chromatography (80% EtOAc/hexanes). Spectral data of the title compound was identical to that reported in the literature[5] with the exception of optical rotation. $[\alpha]_D^{22}$ = –97.5 (*c* 1.00, $CHCl_3$). Enantiomeric ratio was determined to be 98.5:1.5 via chiral HPLC using a Chiralcel OJ column. Conditions: *i*-PrOH 70% in hexanes, 30 min, 1.0 mL/min, 30 °C. (–)-Enantiomer: R_t = 20.9 min; (+)-Enantiomer: R_t = 11.1 min.



7

(6*S*,8a*S*)-6-(4-Methoxyphenyl)hexahydroindolizin-7(1*H*)-one. Enaminone **7** (120 mg, 0.50 mmol, 1.0 equiv.) was dissolved in anhydrous THF (5 mL) under a N_2 atmosphere. The solution was cooled to –78 ºC at which point L-Selectride (0.55 mL, 0.55 mmol, 1.1 equiv, 1.0 M in THF) was added over 15 minutes. After stirring for 1 h, the reaction was slowly warmed to 0 ºC over 1.5 h and stirred at room temperature for an additional 2 h. The reaction was quenched with a saturated solution of $NaHCO_3$ (*aq*.) and added to a separatory funnel. The product was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The title compound (110 mg, 90% yield) was obtained as a white crystalline solid (mp 118–120 ºC) after SiO_2 flash chromatography [60% EtOAc/hexanes (1% TEA)]. Spectral data was identical to that reported.[6] $[\alpha]_D^{22} = +6.05$ (*c* 1.14, $CHCl_3$).



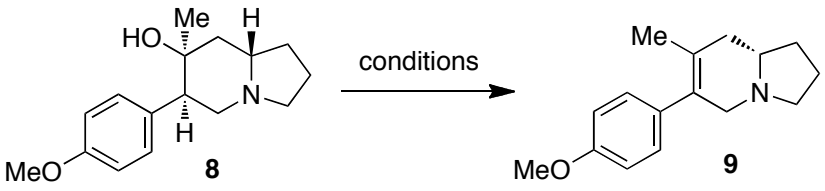
8

(6*S*,7*S*,8a*S*)-6-(4-Methoxyphenyl)-7-methyloctahydroindolizin-7-ol (8). The indolizidinone (105 mg, 0.43 mmol, 1.00 equiv) was taken in anhydrous THF (3.5 mL) in a flame dried RBF and cooled to –78 ºC. Methyl lithium (0.32 mL, 0.52 mmol, 1.2 equiv, 1.6 M in Et_2O) was added dropwise and stirred for 45 min at –78 ºC. The reaction was quenched with MeOH (1 mL) and allowed to warm to room temperature. The quenched reaction mixture was added to a separatory funnel containing 10% NaOH (*aq*.) and the product was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The title compound (85 mg, 75% yield) was obtained as a white crystalline solid (mp 92–96 ºC) after SiO_2 flash chromatography [50% EtOAc/hexanes (1% TEA)]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 3H), 1.37–1.49

(m, 2H), 1.71–1.78 (m, 1H), 1.81–1.91 (m, 2H), 1.97 (dd, J = 13.2, 2.5 Hz, 1H), 2.23 (dd, J = 17.9, 8.9 Hz, 1H), 2.34–2.39 (m, 1H), 2.67 (dd, J = 11.3, 11.3 Hz, 1H), 2.83 (dd, J = 11.9, 3.8 Hz, 1H), 2.94 (dd, J = 10.6, 3.9 Hz, 1H), 3.07 (dd, J = 8.6, 8.6 Hz, 1H), 3.80 (s, 3H), 6.86 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 29.6, 30.1, 44.3, 51.4, 53.7, 53.7, 55.2, 59.4, 70.4, 113.7, 130.3, 131.9, 158.6; IR (neat) 3416, 2961, 1611, 1512, 1246, 1178, 833 cm^{-1}; HRMS (ESI+) *m/e* calc'd for $[M+H]^+$ $C_{16}H_{24}NO_2$: 262.1807, found 262.1790. $[\alpha]_D^{22} = -6.54$ (c 1.10, $CHCl_3$).

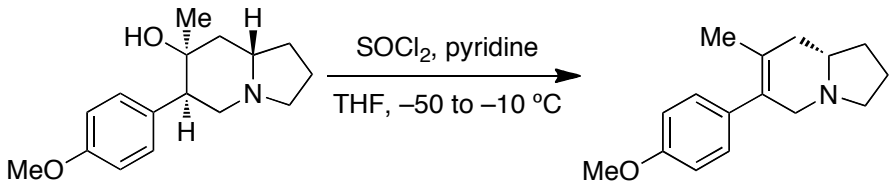
Note: 1D NOE ^{1}H NMR spectrum irradiating at 1.06 ppm shows peaks at 1.49, 1.97, 2.83 and 7.2 ppm. No peaks were seen at 3.07 or 2.67 ppm.

OPTIMIZATION OF DEHYDRATION CONDITIONS.



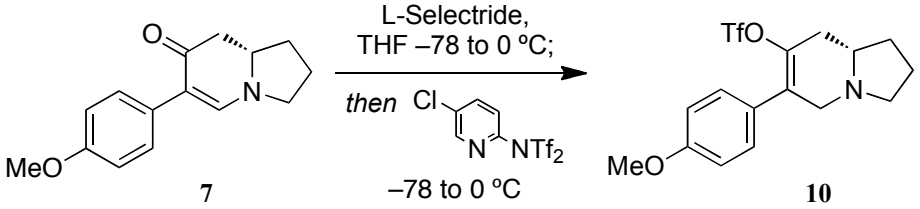
entry	conditions	yield (%)[a]
1	I_2, PPh_3, CH_2Cl_2, 16 h	NR
2	BF_3•OEt_2, CH_2Cl_2, 16 h	NR
3	$POCl_3$, pyridine	30
4	TsOH, AcOH, reflux	NR
5	TsOH, PhMe, reflux	NR
6	$SOCl_2$, pyridine, rt	52
7	$SOCl_2$ (5.0 equiv), pyridine (5.0 equiv), THF, –30 ºC to rt	78
8	$SOCl_2$ (2.5 equiv), pyridine (5.0 equiv), THF, –30 to –10 ºC	88

NR = no reaction (*i.e.* starting material was recovered). [a] Isolated yield.



8 **9**

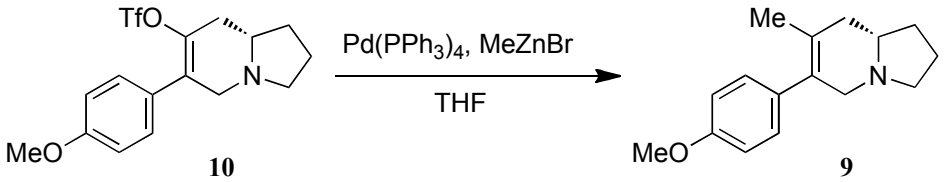
6-(4-Methoxyphenyl)-7-methyl-1,2,3,5,8,8a-hexahydroindolizine (9). Indolizidine **8** (62 mg, 0.24 mmol, 1.0 equiv) was dissolved in anhydrous THF (4.0 mL) and cooled to –50 ºC. Pyridine (0.1 mL) followed by $SOCl_2$ (0.043 mL, 0.59 mmol, 2.5 equiv) in 0.5 mL THF was added dropwise to the reaction mixture. The reaction mixture was kept between –30 and –10 ºC for 1.5 h. The reaction was quenched with 10% NaOH (*aq*.). The quenched reaction mixture was added to a separatory funnel containing 10% NaOH (*aq*.) and the product was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The title compound was obtained as a colorless oil (51 mg, 88% yield) after SiO_2 flash chromatography [20% EtOAc/hexanes (1% TEA)]. See below for spectral data.



7 **10**

(*S*) - 6 - (4-Methoxyphenyl) - 1, 2, 3, 5, 8, 8a – hexahydroindolizin – 7 – yl – trifluoromethanesulfonate (10). Enaminone **7** (590 mg, 2.4 mmol, 1.0 equiv) was dissolved in anhydrous THF (30 mL) under a N_2 atmosphere. The solution was cooled to –78 ºC at which point L-Selectride (0.23 mL, 0.23 mmol, 1.0 equiv, 1.0 M in THF) was added over 15 min. After stirring for 1 h, the reaction was slowly warmed to 0 ºC over 2 h. The reaction mixture was once again cooled to –78 ºC and Comins reagent (1.1 g, 2.7 mmol, 1.1 equiv) was added all at once. The mixture was stirred for another hour at –78 ºC and then slowly warmed to 0 ºC over 2 h. The reaction was quenched with a saturated solution of $NaHCO_3$ (*aq*.) and added to a separatory funnel. The product was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The title compound was obtained as a colorless oil (690 mg,

76% yield) after SiO_2 flash chromatography (10% EtOAc/hexanes (1% TEA): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49-1.57 (m, 1H), 1.76-1.84 (m, 1H), 1.87-1.96 (m, 1H), 2.00-2.07 (m, 1H), 2.22 (dd, J = 18.1, 9.2 Hz, 1H), 2.47-2.62 (m, 3H), 3.06 (d, J = 15.8 Hz, 1H), 3.18 (dt, J = 4.4, 2.1 Hz, 1H), 3.72-3.75 (m, 1H), 3.74 (s, 3H), 6.83 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.2, 30.5, 35.2, 53.4, 55.3, 55.6, 60.5, 113.9, 118.1 (q, J_{CF} = 320 Hz), 126.6, 129.2, 129.5, 142.0, 159.5 ; IR (neat) 2959, 1610, 1512, 1416, 1209, 1146 cm^{-1}; HRMS (ESI+) *m/e* calc'd for $[M+H]^+$ $C_{16}H_{19}F_3NO_4S$: 378.0987, found 378.0974; $[\alpha]_D^{22}$ = + 66.3 (*c* 1.00, $CHCl_3$).

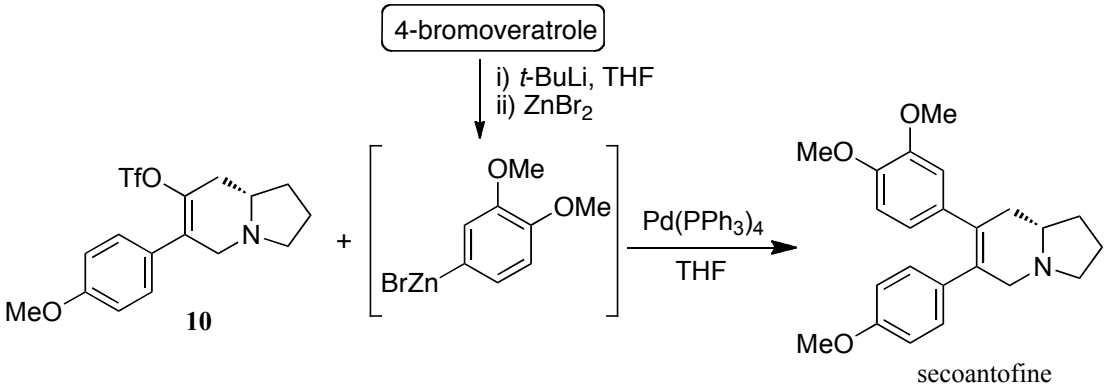


10 **9**

(*S*)-6-(4-Methoxyphenyl)-7-methyl-1,2,3,5,8,8a-hexahydroindolizine (9). *Preparation of organo zinc reagent.* A flame dried RBF under N_2 was charged with anhydrous THF (10.0 mL) and cooled to –78 ºC. Methyl lithium (1.6 mL, 2.5 mmol, 5.0 equiv, 1.6M in Et_2O) was added and the solution was allowed to sit. A separate RBF was charged with anhydrous $ZnBr_2$ (590 mg, 2.6 mmol, 5.2 equiv). The $ZnBr_2$ was dried by heating the RBF under a vacuum with a heat gun for 5 min. When the $ZnBr_2$ had cooled to room temperature it was dissolved in anhydrous THF (6.0 mL) under N_2. This $ZnBr_2$ solution was slowly cannulated into the methyl lithium solution and the resulting solution was stirred at -78 ºC for 5 min and then allowed to warm to room temperature.

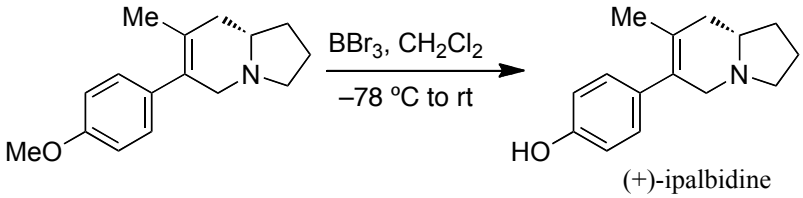
Triflate **10** (190 mg, 0.50 mmol, 1.0 equiv), dissolved in a minimal amount of THF, and $Pd(PPh_3)_4$ (29 mg, 0.025 mmol, 5.0 mol%) were added sequentially to the zinc reagent. If the reaction had not gone to completion after 1 h at room temperature, the reaction mixture was heated to 50 ºC. Upon consumption of the triflate starting material (as judged by TLC) SiO_2 was added to the reaction mixture and the solvent was evaporated to leave a free flowing powder. Following flash chromatography (80% EtOAc/hexanes (1% TEA)) 110 mg (91%) of the title compound was obtained as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46-1.54 (m, 1H), 1.60 (s, 3H), 1.73-1.81 (m, 1H), 1.85-1.94 (m, 1H), 2.00-2.32 (m, 5H), 2.91 (d, J = 15.4 Hz, 1H), 3.22 (dd, J = 3.2, 3.2 Hz, 1H),

3.62 (d, J = 15.4 Hz, 1H), 3.82 (s, 3H), 6.86 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 21.4, 30.8, 38.5, 54.2, 55.2, 57.8, 60.2, 113.5, 127.9, 130.0, 130.3, 133.8, 158.1; IR (neat) 2907, 1609, 1510, 1244, 1175, 831 cm^{-1}; HRMS (ESI+) *m/e* calc'd for $[M+H]^+$ $C_{16}H_{22}NO$: 244.1701, found 244.1688; $[\alpha]_D^{22}$ = + 142 (*c* 1.00, $CHCl_3$).



(+)-Secoantofine. *Preparation of organo zinc reagent.* A flame dried RBF under N_2 was charged with anhydrous THF (15.0 mL) and cooled to –78 ºC. *tert*-Butyllithium (6.6 mL, 11 mmol, 11 equiv, 1.7 M in pentane) was added carefully and the solution was allowed to sit for 5 min at –78 ºC. 4-Bromoveratrole (1.2 g, 5.4 mmol, 5.0 equiv) was then added dropwise and the resulting reaction mixture was stirred for 2 h and –78 ºC. A different RBF was charged with anhydrous $ZnBr_2$ (1.3 g, 5.6 mmol, 5.2 equiv). The $ZnBr_2$ was dried by heating the RBF under a vacuum with a heat gun for 5 min. When the $ZnBr_2$ had cooled to room temperature it dissolved in anhydrous THF (12.0 mL) under N_2. This $ZnBr_2$ solution was slowly cannulated into the yellow aryllithium reagent solution. The resulting cloudy white solution was stirred at –78 ºC for 5 min and then allowed to warm to room temperature. Upon warming the solution became clear. Triflate **10** (400 mg, 1.1 mmol, 1.0 equiv) (dissolved in a minimal amount of THF) and $Pd(PPh_3)_4$ (62 mg, 0.054 mmol, 5.0 mol%) were added sequentially to the zinc reagent. If the reaction had not gone to completion after 1 h at room temperature, the reaction mixture was heated to 50 ºC. Upon consumption of the triflate starting material (as judged by TLC) SiO_2 was added to the reaction mixture and the solvent was evaporated to leave a free flowing powder. Following flash chromatography [40% EtOAc/hexanes (1% TEA)] 380 mg

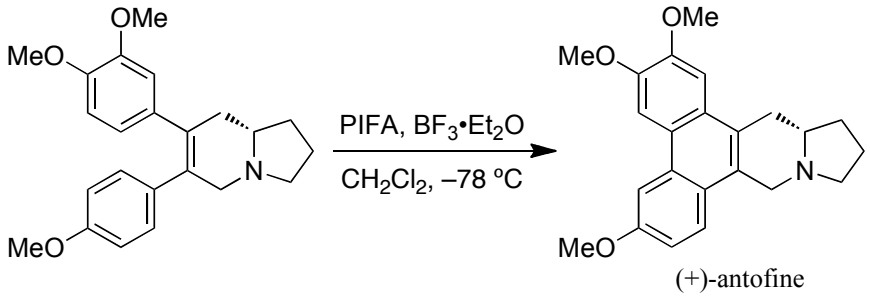
(96%) of the title compound was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51-1.63 (m, 1H), 1.78-2.01 (m, 2H), 2.06-2.14 (m, 1H), 2.25 (dd, *J* = 9.0, 9.0 Hz, 1H), 2.36-2.45 (m, 2H), 2.69-2.77 (m, 1H), 3.07 (dt, *J* = 16.0, 3.1 Hz, 1H), 3.29 (dt, *J* = 4.3, 2.0 Hz, 1H), 3.54 (s, 3H), 3.72 (s, 3H), 3.81 (s, 3H), 3.86 (d, *J* = 15.8 Hz, 1H), 6.47 (d, *J* = 1.1 Hz, 1H), 6.66-6.69 (m, 4H), 6.97 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 30.8, 38.6, 54.3, 55.1, 55.5, 55.7, 57.9, 60.4, 110.4, 113.1, 113.4, 120.7, 130.2, 132.6, 132.7, 133.6, 135.1, 147.1, 147.9, 158.0; IR (neat) 2955, 1607, 1511, 1245, 1030, 755 cm^{-1}; HRMS (ESI+) *m/e* calc'd for $[M+H]^+$ $C_{23}H_{28}NO_3$: 366.2064, found 366.2068; $[\alpha]_D^{22} = +169$ (*c* 1.00, $CHCl_3$).



(+)-ipalbidine

(+)-Ipalbidine. *O*-Methylipalbidine (56 mg, 0.23 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (1.0 mL) and cooled to -78 ºC under N_2. To this solution was added BBr_3 (0.23 mL, 0.23 mmol, 1.0 M in CH_2Cl_2). The reaction was allowed to warm to room temperature over night. The reaction was quenched with water (1.0 mL) and then 5.0 mL of a saturated solution of $NaHCO_3$ (*aq.*). The product was extracted from the aqueous layer with CH_2Cl_2 (3x). The combined organic layers were dried with Na_2SO_4, concentrated and purified *via* flash chromatography [80% EtOAc/hexane (1% TEA)] to provide 42 mg (80%) of (+)-ipalbidine as a white crystalline solid (mp 122.2-124.6 ºC). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 3H), 1.55-1.68 (m, 1H), 1.74-1.88 (m, 1H), 1.91-2.11 (m, 2H), 2.14-2.32 (m, 3H), 2.35-2.45 (m, 1H), 3.00 (dd, J = 15.6, 2.2 Hz, 1H), 3.26 (ddd, J = 9.1, 9.1, 2.1 Hz, 1H), 3.69 (d, J = 15.6 Hz, 1H), 6.78 (d, J = 8.6 Hz, 2H), 7.00 (d, J = 8.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.0, 21.1, 30.2, 37.6, 54.1, 57.7, 60.6, 115.5, 128.3, 129.7, 129.9, 132.0, 155.9; IR (neat) 2913, 1609, 1513, 1445, 1269, 1169 cm^{-1}; HRMS (ESI+) *m/e* calc'd for $[M+H]^+$ $C_{15}H_{20}NO$: 230.1545, found 230.1531; $[\alpha]_D^{22} = +202$ (*c* 1.00, $CHCl_3$). [Lit. *S-enantiomer:* +233.5 (*c* 1, $CHCl_3$); *R*-

enantiomer: –237 (*c* 1, $CHCl_3$), –190.5 (*c* 1, CH_3OH)].[7] The enantiomeric ratio of (+)-ipalbidine was determined to be 98.5:1.5 via chiral HPLC using a Chiralcel OJ column. Conditions: *i*-PrOH 2–20% in hexanes, 30 min, 1.0 mL/min, 30 °C. (–)-Enantiomer: R_t = 18.5 min; (+)-Enantiomer: R_t = 21.5 min.



(+)-antofine

(+)-Antofine. Secoantofine (48 mg, 0.13 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (2.0 mL) and cooled to –78 ºC. To this solution was added PIFA (62 mg, 0.14 mmol, 1.1 equiv) and BF_3•Et_2O (16 mg, 0.14 mmol, 1.1 equiv) sequentially. The solution was stirred for 4 h while being monitored by TLC. A solution of PIFA (62 mg in 2.0 mL CH_2Cl_2) was added dropwise to the reaction mixture until the reaction had gone to completion. Upon consumption of starting material the reaction was quenched with 10% NaOH (*aq*.) and the mixture was vigorously stirred for 1 h. The product was extracted from the aqueous layer with CH_2Cl_2 (3x). The combined organic layers were dried with Na_2SO_4, concentrated and purified *via* flash chromatography [70% EtOAc/hexane (1% TEA)] to provide 34 mg (70%) of (+)-antofine as a white crystalline solid: mp 226-227 °C (decomp.) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65-1.75 (m, 1H), 1.80-2.02 (m, 2H), 2.13-2.22 (m, 1H), 2.35-2.46 (m, 2H), 2.79-2.86 (m, 1H), 3.28 (ddd, *J* = 15.8, 3.7, 1.5 Hz, 1H), 3.38 (dt, *J* = 4.3, 2.1 Hz, 1H), 3.63 (d, *J* = 14.9 Hz, 1H), 3.95 (s, 3H), 3.99 (s, 3H), 4.04 (s, 3H), 4.63 (d, *J* = 14.9 Hz, 1H), 7.13 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.25 (s, 1H), 7.75 (d, *J* = 9.0 Hz, 1H), 7.83 (d, *J* = 2.5 Hz, 1H), 7.85 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 31.3, 33.7, 53.8, 55.0, 55.5, 55.9, 56.0, 60.3, 104.0, 104.7, 114.9, 123.5, 124.1, 124.2, 125.5, 126.7, 127.0, 130.2, 148.4, 149.4, 157.5; HRMS (ESI+) *m/e* calc'd for $[M+H]^+$ $C_{23}H_{26}NO_3$: 364.1913, found 364.1909; $[\alpha]_D^{22}$ = + 111 (*c* 1.00, $CHCl_3$). [Lit. *R-enantiomer*: – 113.4 (*c* 1.23, $CHCl_3$),[8] −125.2 (*c* 1.27, $CHCl_3$),[9] – 108.2 (*c* 0.71, $CHCl_3$);[10] *S-enantiomer*: + 66 ($CHCl_3$)[11]].

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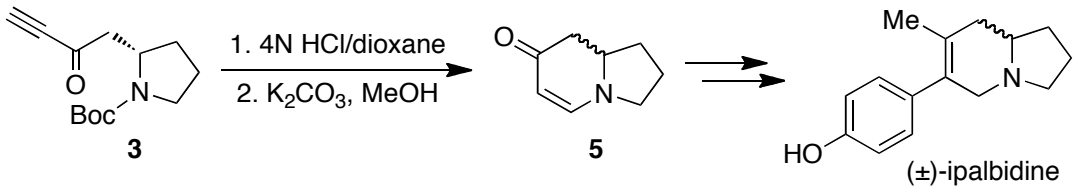
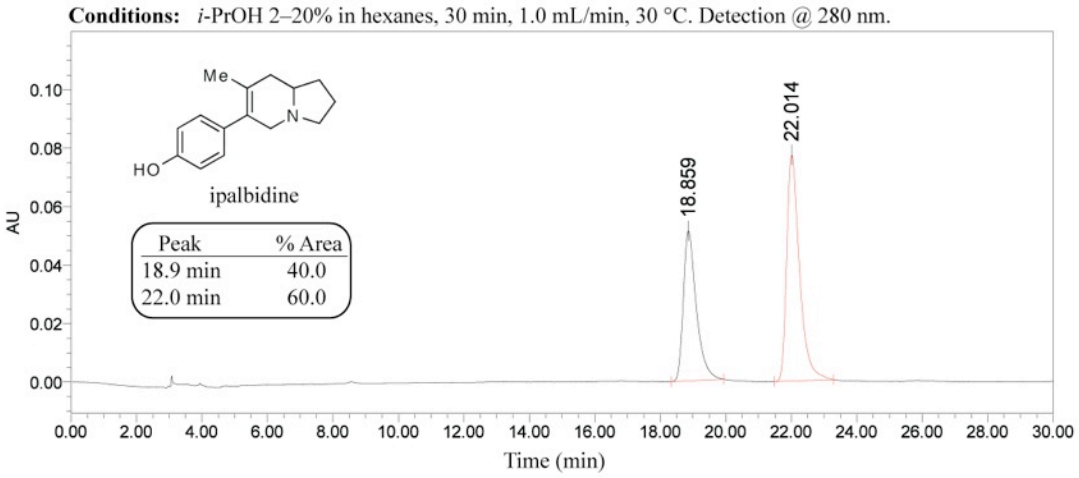
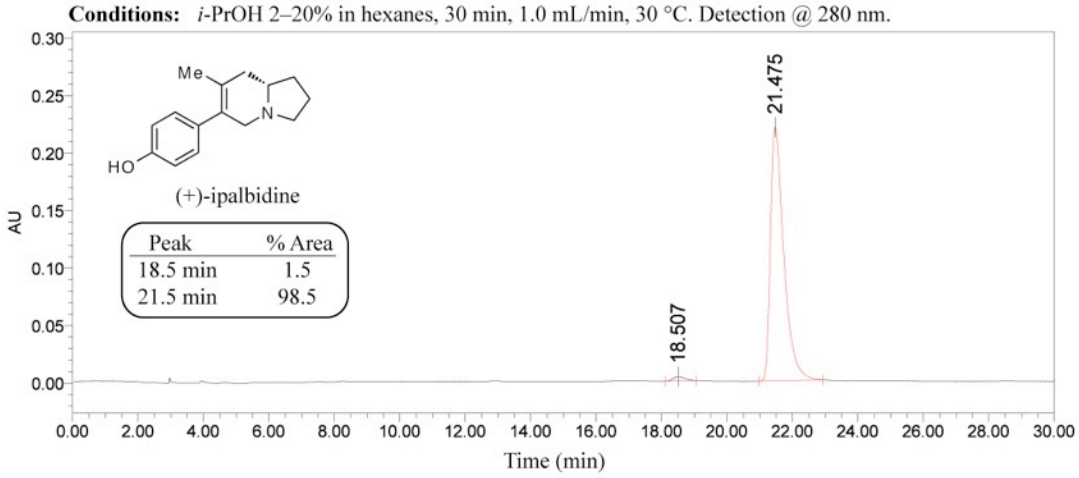
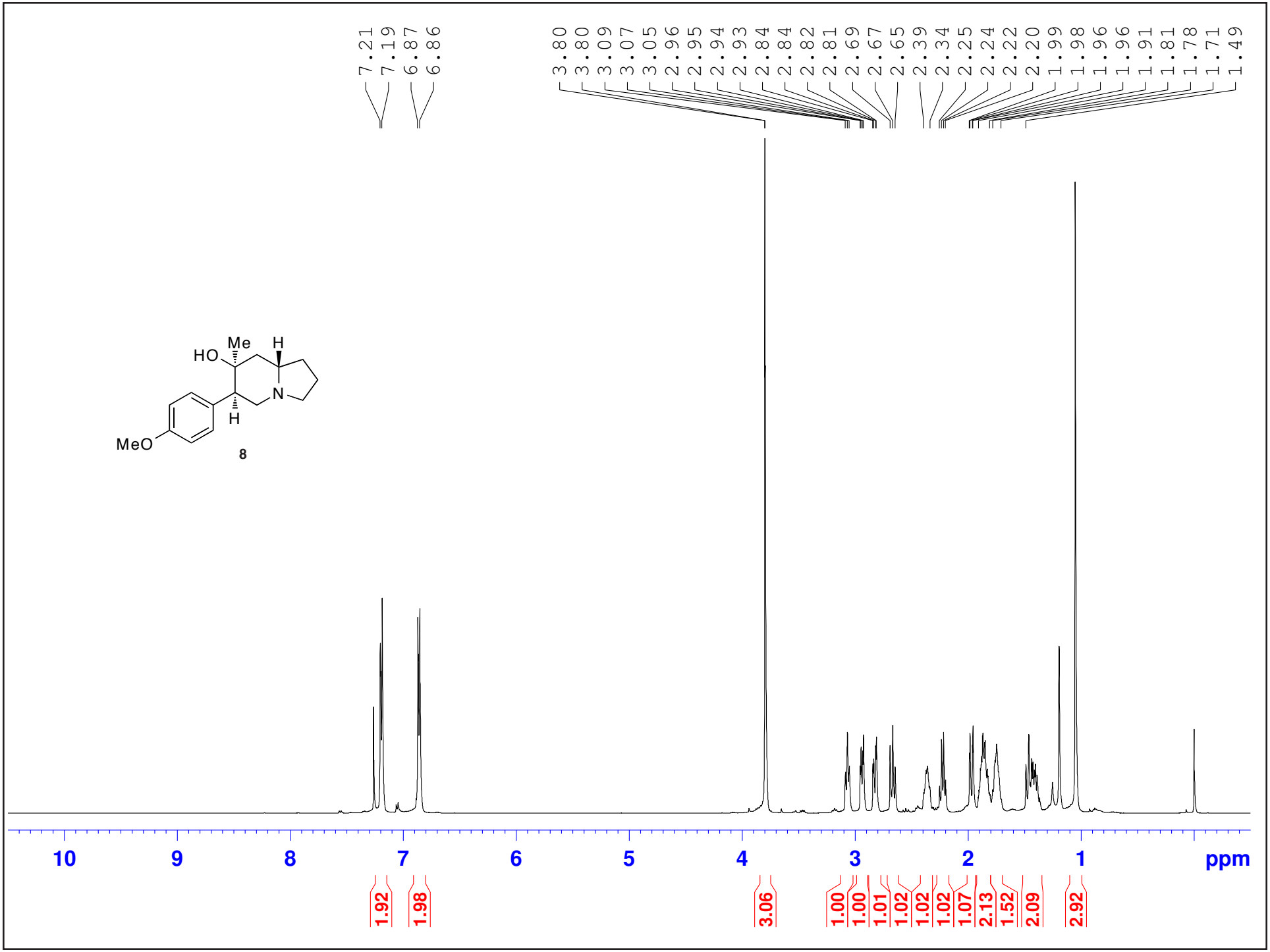
HPLC DATA

Partially racemized ipalbidine was prepared by carrying through enaminone **5** which had been prepared according to the HCl conditions reported in the first disclosure of this reaction.[4]





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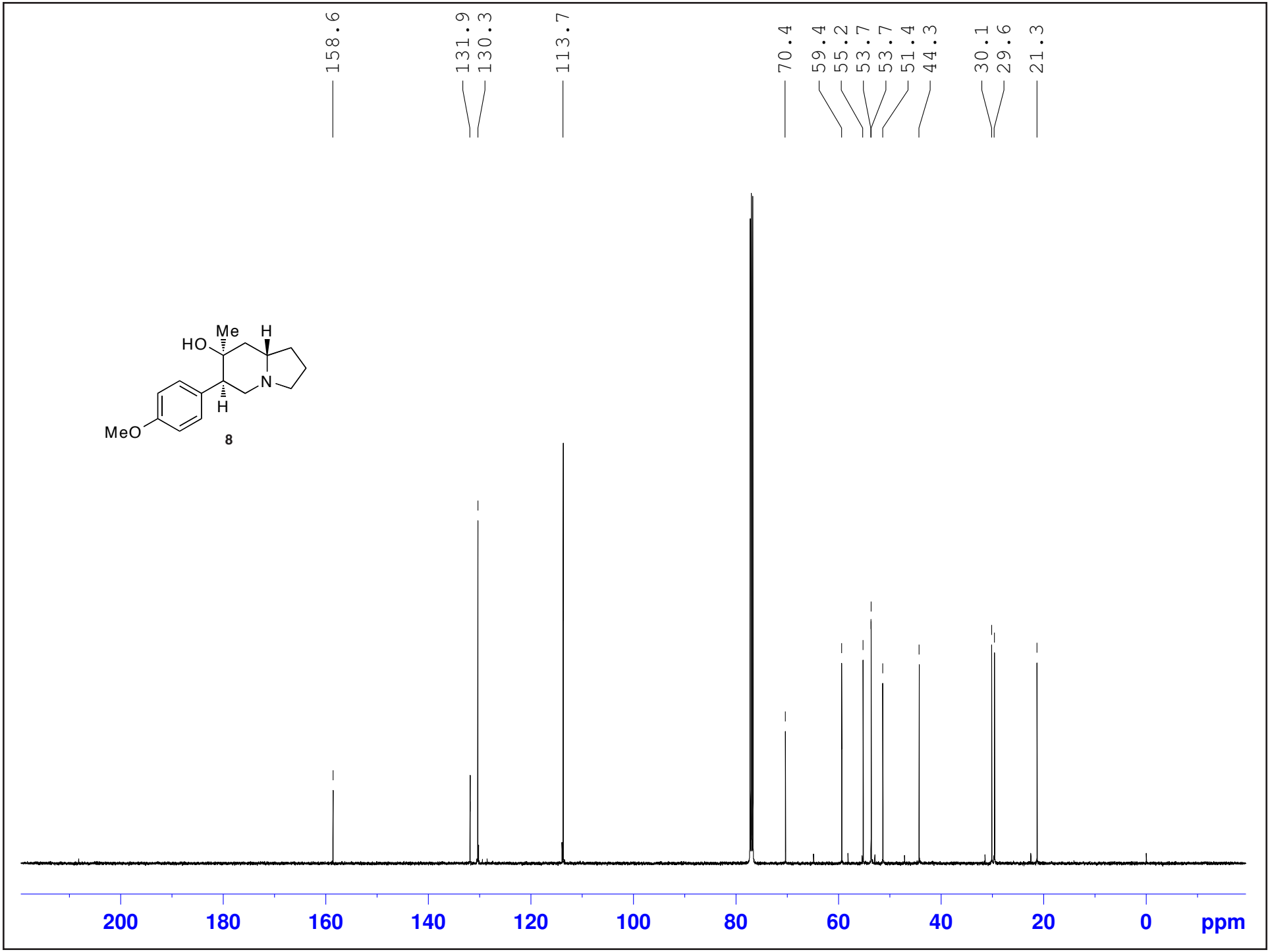
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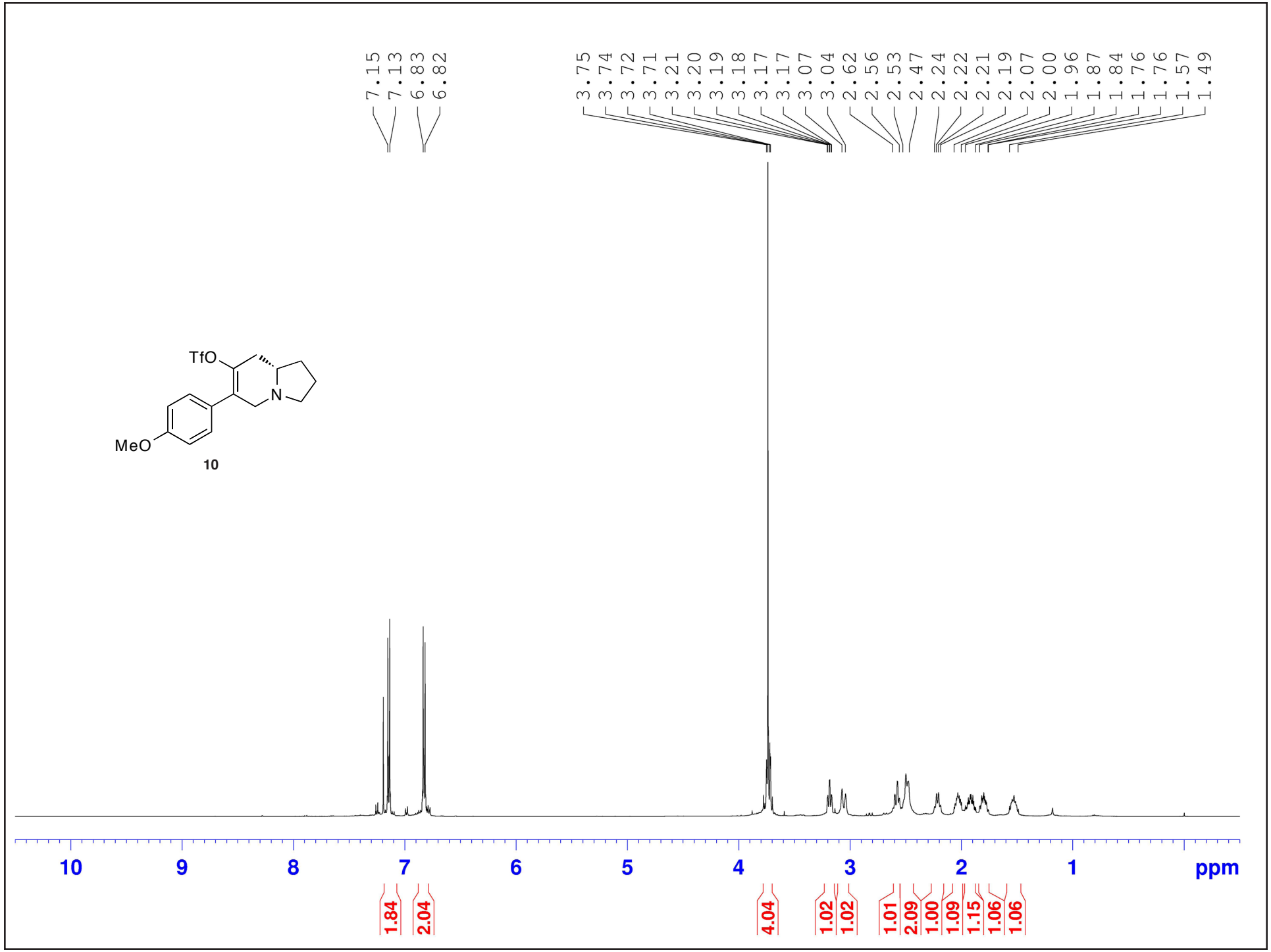
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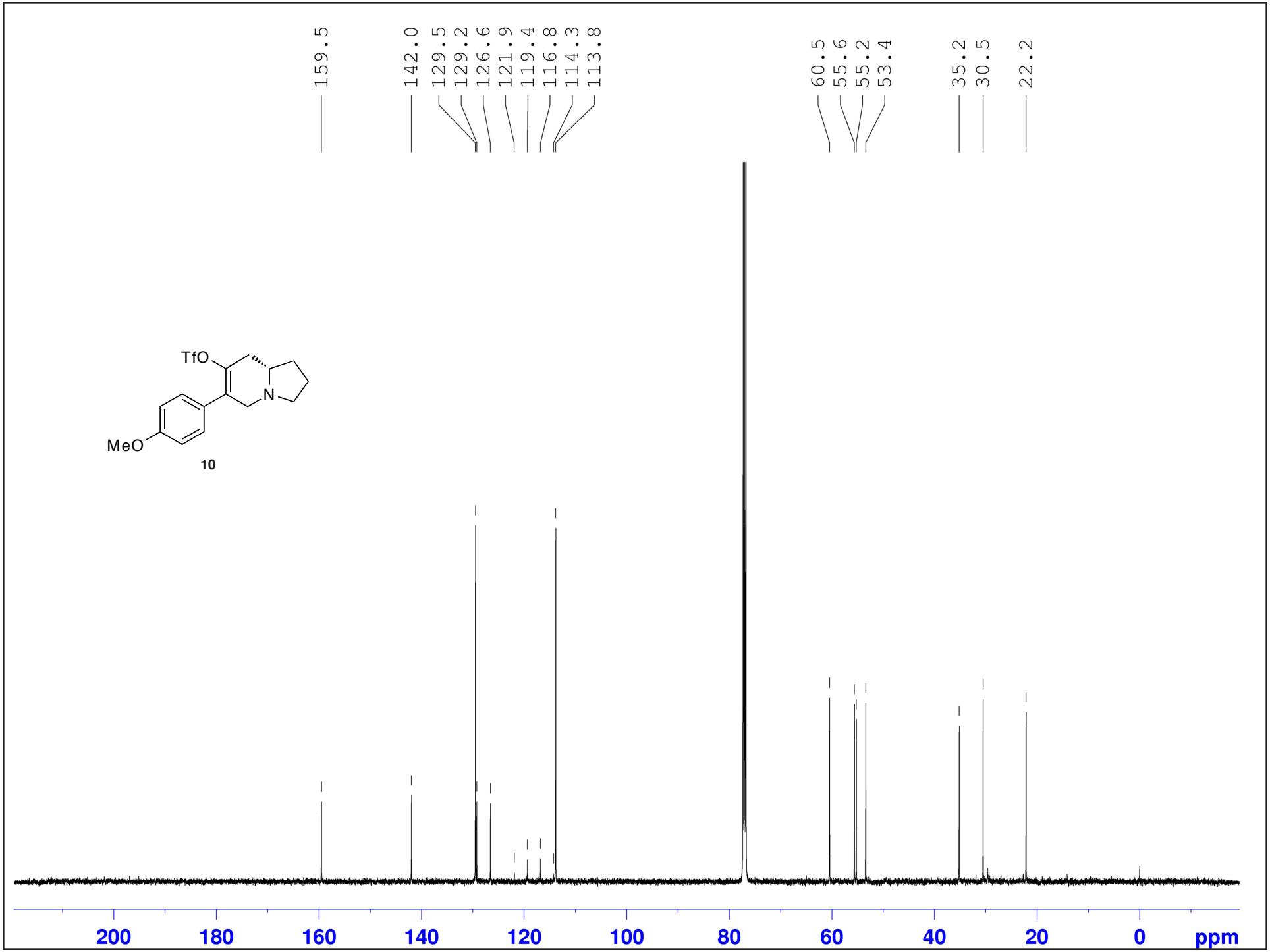
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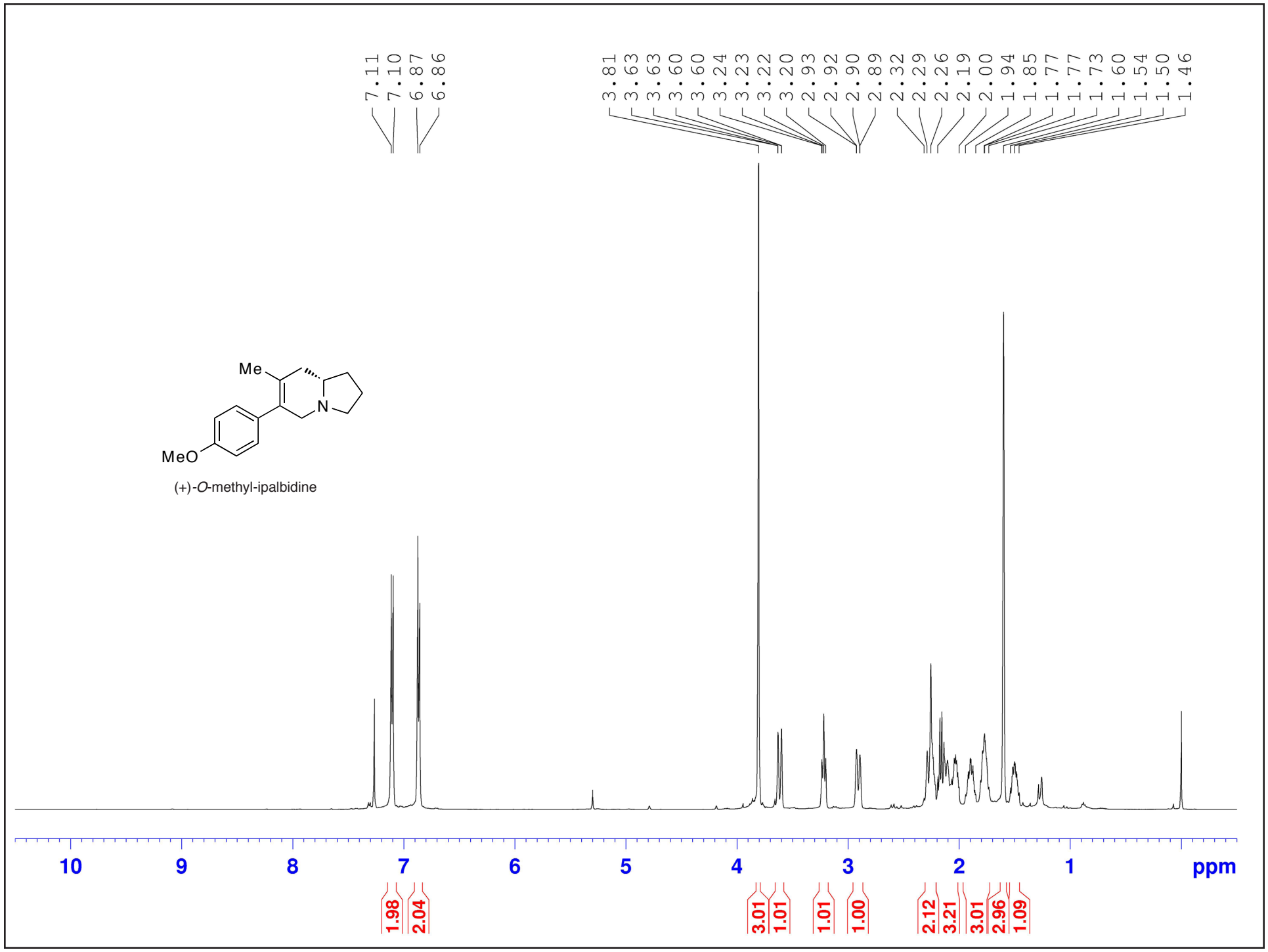
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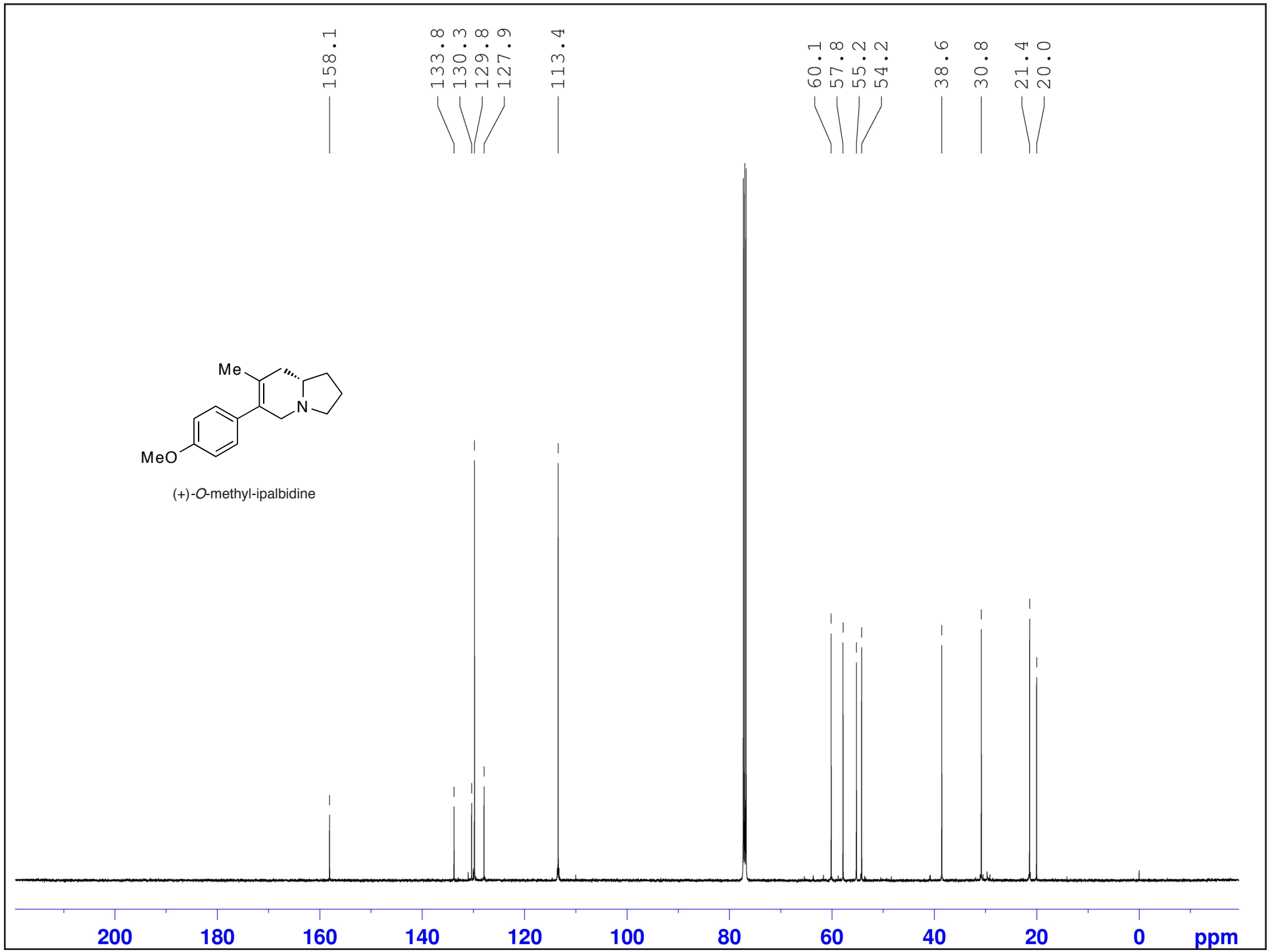
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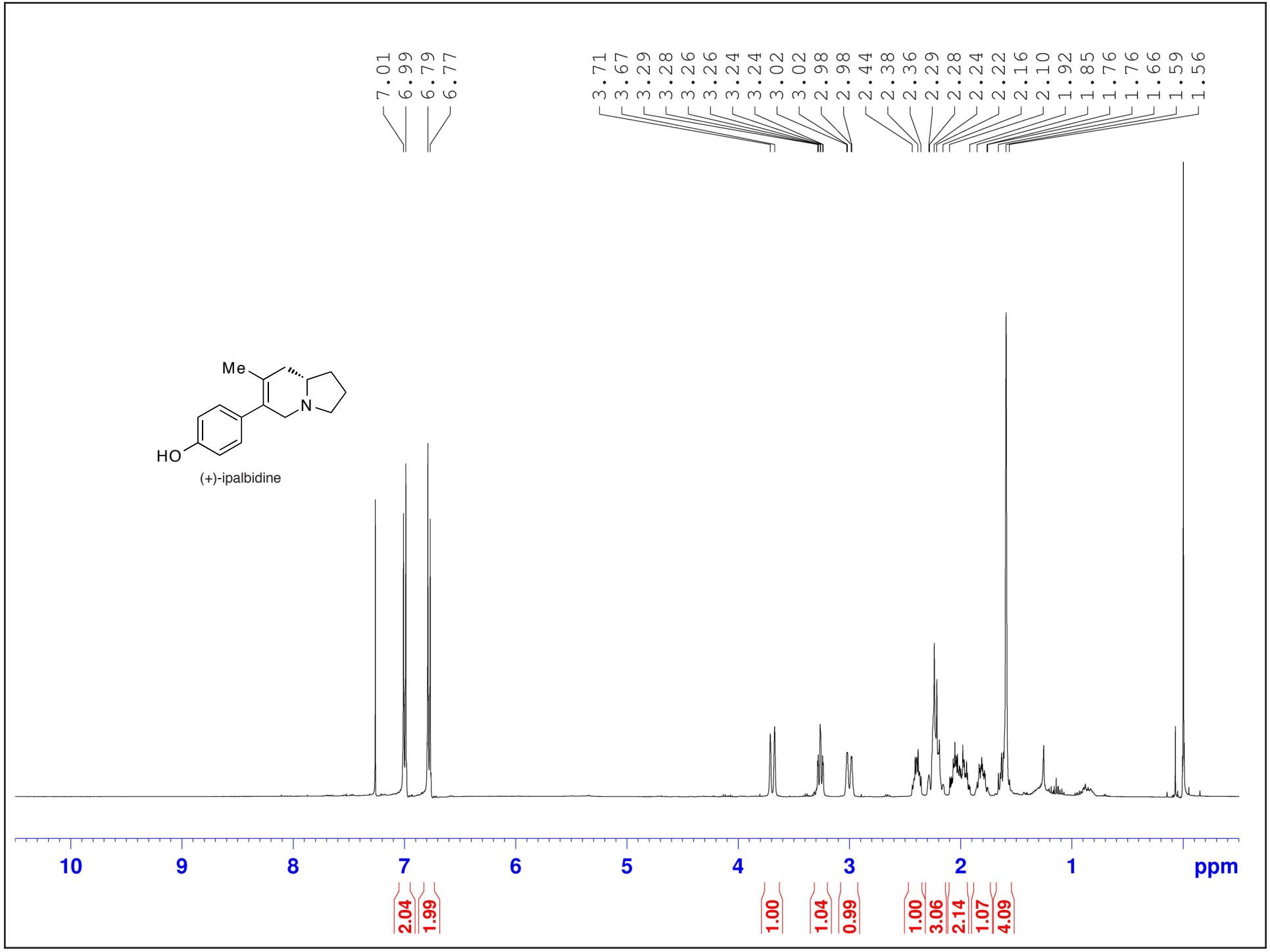
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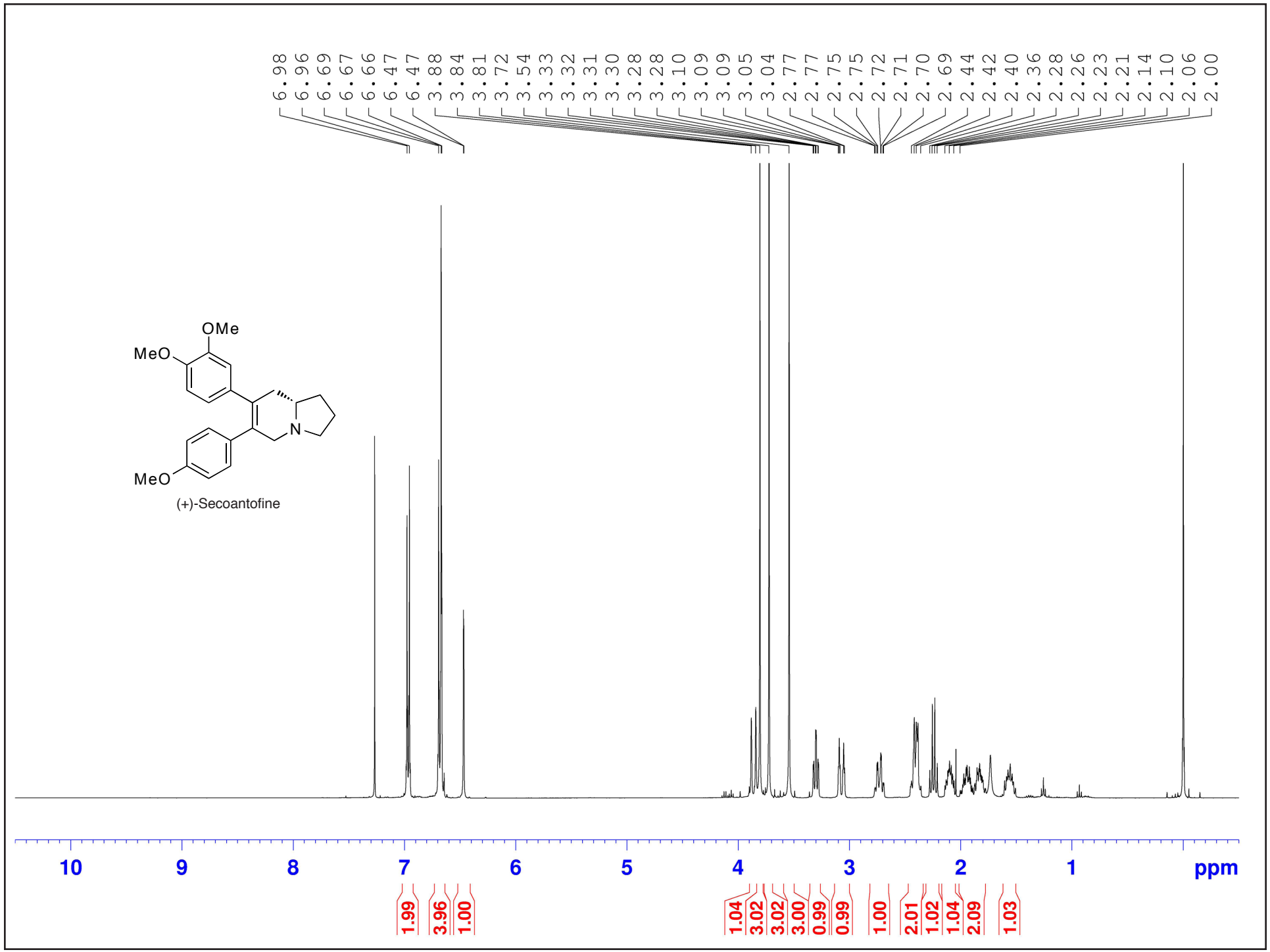
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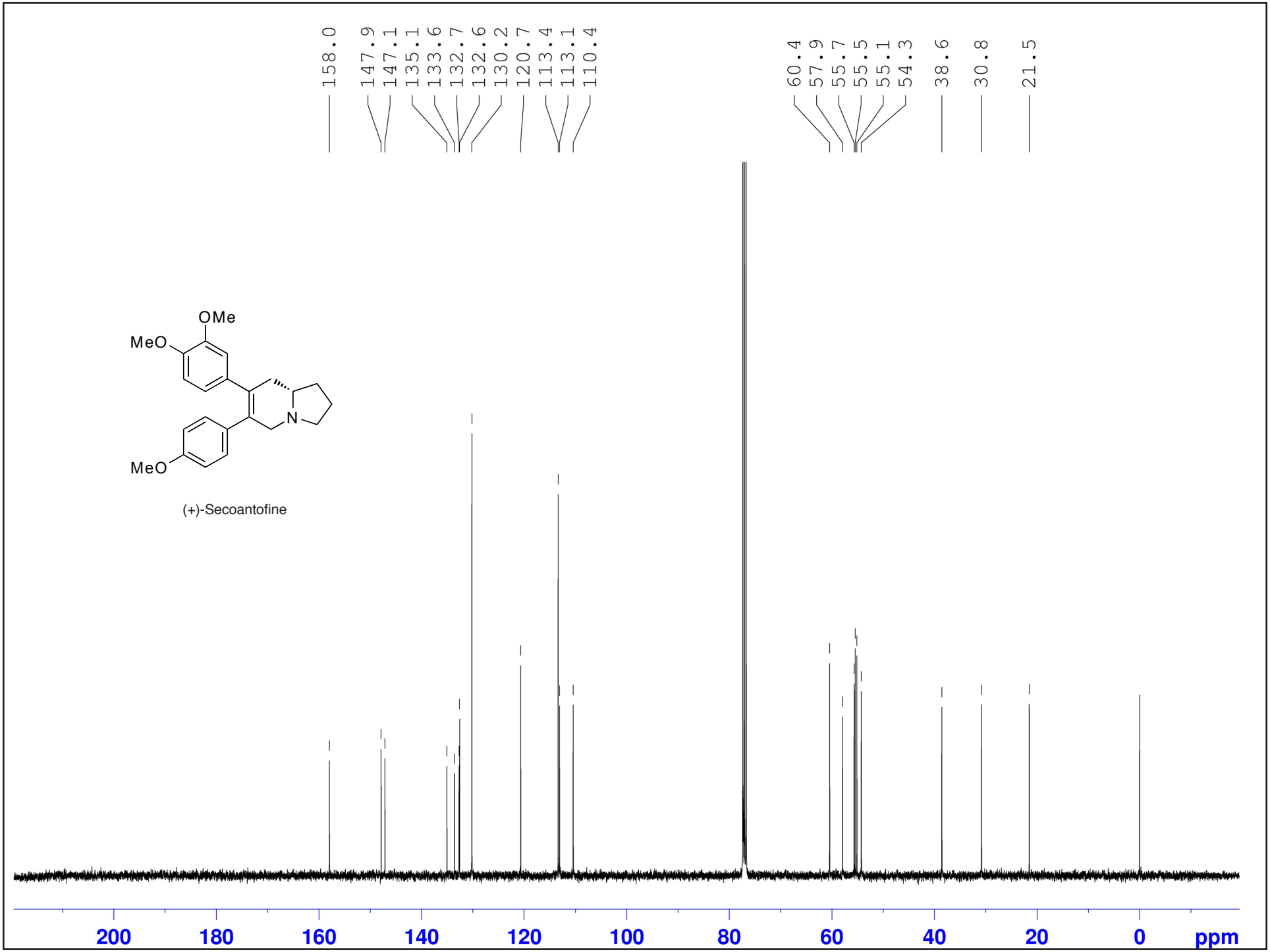
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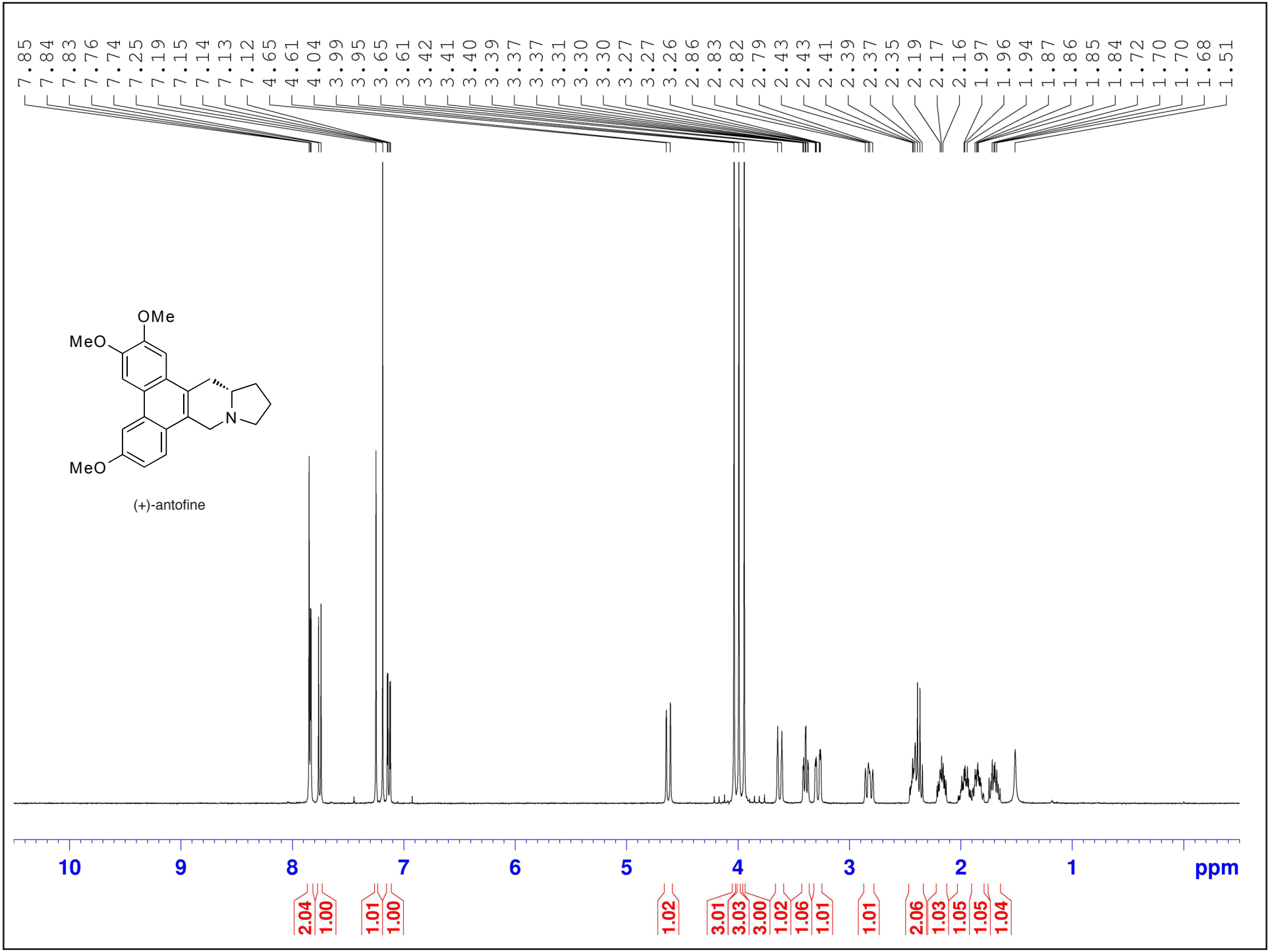
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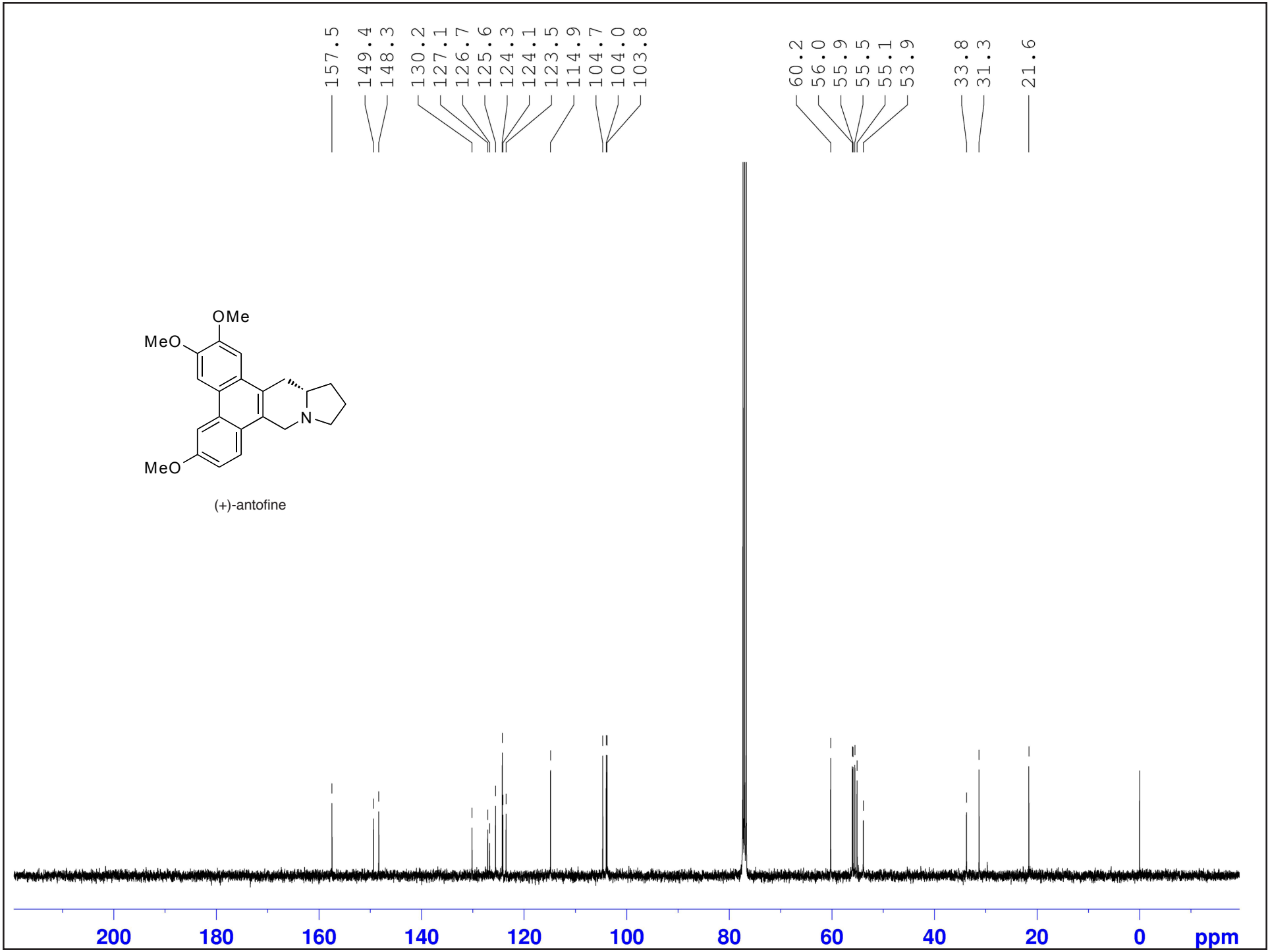
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