SUPPORTING INFORMATION

Structure−Functional−Selectivity Relationship Studies of Novel Apomorphine Analogs to Develop D1R/D2R Biased Ligands

Hyejin Park,[+§] Aarti N. Urs,[‡§] Joseph Zimmerman,[‡] Chuan Liu,[+] Qiu Wang[+]* and Nikhil M. Urs[‡]*

[+]Department of Chemistry, Duke University, Durham, NC 27708

[‡]Department of Pharmacology and Therapeutics, University of Florida, Gainesville FL 32610

[§]Contributed equally to this work.

*Corresponding Author: nikhilurs@ufl.edu, qiu.wang@duke.edu

Table of Contents

I. Synthesis of Apomorphine Analogs

I. a. General Procedure.

General Information and Instrumentation.

Unless otherwise noted, reactions were performed without exclusion of air or moisture. All commercially available reagents and solvents were of analytical grade (>95%) and used without further purification. All reactions were run in round-bottom flasks or microwave tubes. Reactions were stirred with Teflon-coated magnetic stir bars. Analytical thin-layer chromatography (TLC) was performed using aluminum plates pre-coated with 0.25 mm of 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light and/or vanillin and/or $KMNO_4$ stains. Organic solutions were concentrated *in vacuo* using a rotary evaporator. Column chromatography was performed with silica gel (60 Å, standard grade) and HPLC-grade solvents.

Nuclear magnetic resonance (NMR) spectra were recorded at ambient temperature on Varian iNova 400 MHz or Bruker 500 MHz spectrometers. Chemical shifts are reported as parts per million (ppm, δ) referenced to the residual internal $CHCl_3$ (δ 7.26) and CHD_2OD (δ 3.31) for ^1H NMR. Chemical shifts for ^{13}C are reported in reference to the residual internal $CHCl_3$ (δ 77.36) and CHD_2OD (δ 49.77). Values for ^1H NMR are reported in the following order: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet), coupling constants (*Hz*) and integration. Data for ^{13}C NMR are reported as δ values.

High resolution mass spectra (HRMS) were recorded by the Mass Spectrometry Facility at the Department of Chemistry at Duke University using an Agilent 6224 TOF LC/MS instrument (denoted by LC/ESI). High resolution *m*/*z* values are reported in Daltons, calculated to 4 decimal points from the molecular formula. All found values are within 5 ppm tolerance.

Infrared (IR) spectra were recorded on a ThermoScientific Nicolet 6700 FTIR equipped with a diamond ATR. Only selected peaks are reported and are quoted in wavenumbers (cm^{-1}).

High-pressure liquid chromatography (HPLC) analysis was performed on a Shimadzu HPLC fitted with a C8 normal-phase column (Lux 5 μm Celluclose-1, 250 × 4.6 mm) with a flow rate of 1.0 mL/min using an isocratic eluent of hexanes and *i*-PrOH with 0.1% diethylamine.

Compound purity and Stereochemistry Determination.

All the compounds in biological tests have been confirmed >90.0% pure by ^1H NMR and HPLC.

For the enantiomers obtained from the derivation of commercially available (*R*)-apomorphine or (*R*)-*N*-Propylnorapomorphine all were assigned as (*R*)-enantiomer, including compounds **7–15**, and **18–19**.

For the enantiomers resulting from the separation of the racemic form, including compounds **3–6**, and **16**, the assignment was based on the HPLC retention time and the optical rotation sign (+ or –) of isolated enantiomers: the (*R*) isomer has a shorter retention time and a (–) sign while the (*S*) isomer has a longer retention time and a (+) sign. Note that optical rotation values are not provided due to the large error range resulting from inadequate amount of samples.

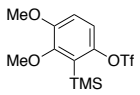
The enantiomeric excess (ee) was determined by HPLC.

Standard protocol for Negishi cross-coupling reactions.

A flame-dried microwave tube was charged with aryl halide (1.0 equiv) and Pd catalyst (2 mol% or 5 mol%). The tube was placed under N_2 via sequential vacuum purge and nitrogen backfill (× 3). Anhydrous 1,4-Dioxane (0.5 mL) was added and the reaction mixture was heated to 70 °C. To the stirred solution was added dropwise alkyl zinc (2.0 equiv) and the resulting reaction mixture was allowed to stir at 70 °C for 20 to 24 h. The reaction was quenched by the addition of DI H_2O (10 mL) and extracted with CH_2Cl_2 (10 mL × 4). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and the filtrate was concentrated *in vacuo*. Purification of the alkylated product was performed by silica column chromatography.

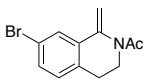
I. b. Total Synthesis of Apomorphine Analogs 3–6.

3,4-Dimethoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (I).



Synthesized following to a reported procedure[1] to afford **I** as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.01 (d, *J* = 9.0 Hz, 1H), 6.90 (d, *J* = 9.0 Hz, 1H), 3.85 (s, 3H), 3.85 (s, 3H), 0.37 (s, 9H); Matches with the reported spectra.[1]

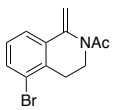
1-(5-Bromo-1-methylene-3,4-dihydroisoquinolin-2(1*H*)-yl)ethan-1-one (II-A).



N-(4-Bromophenethyl)acetamide was synthesized following a reported procedure.[2] To a 100-mL round-bottom flask were added *N*-(4-Bromophenethyl)acetamide (1.69 g, 7.0 mmol, 1.0 equiv) and CH_2Cl_2 (21 mL). The mixture was cooled to 0 °C and oxalyl chloride (1.08 mL, 12.6 mmol, 1.8 equiv) was added dropwise resulting in a milky orange mixture. The mixture was allowed to warm up to room temperature and stirred for 4.5 h under nitrogen. The reaction was then cooled to 0 °C and ferric chloride (1.36 g, 8.4 mmol, 1.2 equiv) was added. The reaction was warmed up to room temperature and stirred overnight. Then, the reaction was quenched with 2 M HCl (15 mL), and the organic layer was separated and concentrated *in vacuo* in a 100-mL round-bottom flask to form a brown solid. The crude was dissolved in MeOH (27 mL) and concentrated sulfuric acid (1.4 mL) was added dropwise at room temp. The mixture stirred at 100 ºC for 5 mins, cooled to 60 °C and stirred overnight. The reaction was then cooled to 0 °C and quenched with saturated aqueous solution of NH_4OH until pH 8. The solvent was removed *in vacuo*, water (30 mL) was added and extracted with CH_2Cl_2 (30 mL × 6). The combined organic layers were dried over Na_2SO_4, filtered, and filtrate concentrated *in vacuo*. The crude was used for the next step without further purification.

To a 50-mL round-bottom flask were added the crude mixture, acetic anhydride (3.5 mL) and pyridine (3.5 mL). The mixture was heated to 60 ºC and stirred for 1.5 h. The reaction was then cooled to room temperature and diluted with CH_2Cl_2 (50 mL). The organic layer was washed with water (20 mL), saturated aqueous solution of $NaHCO_3$ (20 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and subjected to silica gel column chromatography using 25% EtOAc/hexanes as an eluent to afford **II-A** as an orange solid (0.609 g, 33%, over two steps). $\mathbf{R_f}$ = 0.74 (100% EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 7.61 (d, *J* = 7.8 Hz, 1H), *δ* 7.53 (d, *J* = 7.8 Hz, 1H), *δ* 7.12 (t, *J* = 7.8 Hz, 1H), 5.79 (s, 1H), 5.11 (s, 1H), 3.99 (t, *J* = 6.0 Hz, 2H), 2.91 (t, *J* = 6.0 Hz, 2H), 2.20 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.9, 168.9, 134.4, 133.9, 132.6, 127.5, 125.5, 123.2, 107.4, 53.5, 29.7, 22.1; **HRMS-ESI** (m/z) calcd. for $C_{12}H_{13}BrNO$ ($[M+H]^+$): 266.0175; found: 266.0182; **FTIR** (thin film): 1650, 1389, 789 cm^{-1}

1-(7-Bromo-1-methylene-3,4-dihydroisoquinolin-2(1*H*)-yl)ethan-1-one (II-B).

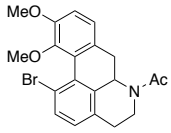


N-(2-Bromophenethyl)acetamide was synthesized following a reported procedure.[2] To a 100-mL round-bottom flask were added *N*-(2-Bromophenethyl)acetamide (1.69 g, 7.0 mmol, 1.0 equiv) and CH_2Cl_2 (21 mL). The mixture was cooled to 0 °C and oxalyl chloride (1.08 mL, 12.6 mmol, 1.8 equiv) was added dropwise resulting in a milky

orange mixture. The mixture was allowed to warm up to room temperature and stirred for 4.5 h under nitrogen. The reaction was then cooled to 0 °C and ferric chloride (1.36 g, 8.4 mmol, 1.2 equiv) was added. The reaction was warmed up to room temperature and stirred overnight. Then, reaction was quenched with 2 M HCl (15 mL), the organic layer was separated and concentrated *in vacuo* in a 100-mL round-bottom flask to form a brown solid. The crude was dissolved in MeOH (27 mL) and concentrated sulfuric acid (1.4 mL) was added dropwise at room temp. The mixture stirred at 100 ºC for 5 min, cooled to 60 °C and stirred for 3 h. The reaction was then cooled to 0 °C and quenched with saturated aqueous solution of NH_4OH until pH 8. The solvent was removed *in vacuo*, water (30 mL) was added and extracted with CH_2Cl_2 (30 mL×6). The combined organic layers were dried over Na_2SO_4, filtered, and filtrate was concentrated. The crude was used for the next step without further purification.

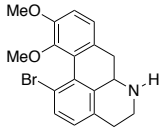
To a 50-mL round-bottom flask were added the crude mixture, acetic anhydride (3.5 mL) and pyridine (3.5 mL). The mixture was heated to 60 ºC and stirred for 1.5 h. The reaction was then cooled to room temperature and diluted with CH_2Cl_2 (50 mL). The organic layer was washed with water (20 mL), saturated aqueous solution of $NaHCO_3$ (20 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and subjected to silica gel column chromatography using 25% EtOAc/hexanes as an eluent to afford **II-B** as an orange solid (0.197 g, 11%, over two steps). $\mathbf{R}_f$ = 0.62 (5% NEt_3, 1:1 EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.75 (d, J = 2.0 Hz, 1H), 7.35 (dd, J = 8.1, 2.0 Hz, 1H), 7.01 (d, J = 8.1 Hz, 1H), 5.73 (s, 1H), 5.10 (s, 1H), 3.95 (t, J = 6.0 Hz, 2H), 2.83 (t, J = 6.0 Hz, 2H), 2.20 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.4, 133.9, 133.6, 131.7, 131.0, 127.0, 120.2, 107.5, 41.5, 41.3, 28.4, 22.4; **HRMS-ESI** (m/z) calcd. for $C_{12}H_{13}BrNO$ ($[M+H]^+$): 266.0175; found: 266.0181; **FTIR** (thin film): 2933, 1651, 1381, 899 cm^{-1}

1-(1-Bromo-10,11-dimethoxy-4,5,6a,7-tetrahydro-6*H*-dibenzo[*de*,*g*]quinolin-6-yl)ethan-1-one (III-A).



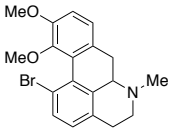
To a 50-mL round-bottom flask were added heterocyclic compound **II-A** (166 mg, 0.62 mmol, 1.0 equiv), 2-(trimethylsylil)phenyl trifluoromethanesufonate (**I**) (335 mg, 0.94 mmol, 1.5 equiv), and MeCN (10 mL). CsF (284 mg, 1.87 mmol, 3.0 equiv) was added and the flask was capped with a rubber septum and stirred at 80 ºC for 24 h. Afterwards, brine (20 mL) was added to the mixture, which was extracted with EtOAc (20 mL × 3). The organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo.* The residue was purified by silica gel column chromatography gel using 5% NEt_3 2:5 EtOAc/hexanes as an eluent, affording **III-A** as a brown solid (127 mg, 51%). $\mathbf{R}_f$ = 0.59 (5% NEt_3 in EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.55 (d, J = 8.2 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 5.02 (d, J = 12.5 Hz, 1H), 4.03 (d, J = 12.5 Hz, 1H), 3.90 (s, 3H), 3.51 (s, 3H), 3.22 (t, J = 12.3 Hz, 1H), 2.90–2.86 (m, 1H), 2.77 (d, J = 15.0 Hz, 1H), 2.59 (t, J = 13.0 Hz, 1H), 2.22 (s, 3H), 2.16–2.15 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.4, 152.1, 147.6, 137.4, 132.9, 132.5, 131.6, 130.8, 128.7, 126.3, 122.8, 121.6, 112.4, 61.4, 56.3, 51.5, 42.0, 34.3, 30.2, 22.6; **HRMS-ESI** (m/z) calcd. for $C_{20}H_{21}BrNO_3$ ($[M+H]^+$): 402.0699; found: 402.0699; **FTIR** (thin film): 2936, 1639, 1422, 729 cm^{-1}

1-Bromo-10,11-dimethoxy-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (IV-A).



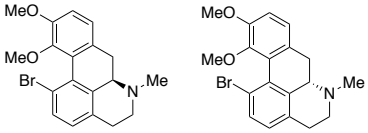
Synthesized following to a reported procedure using **III-A** (108 mg, 0.27 mmol).[1] The residue was purified by column chromatography on silica gel using 5% NEt_3 in EtOAc as an eluent, affording **IV-A** as a yellow oil (57.4 mg, 59%). $\mathbf{R}_f$ = 0.35 (5% NEt_3 in EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.45 (d, J = 8.2 Hz, 1H), 6.92 (d, J = 8.1Hz, 1H), 6.90 (d, J = 8.2 Hz, 1H), 6.82 (d, J = 8.1 Hz, 1H), 3.84 (s, 3H), 3.67–3.64 (m, 1H), 3.46 (s, 3H), 3.33–3.28 (m, 1H), 2.95–2.87 (m, 2H), 2.74–2.65 (m, 2H), 2.47–2.41 (t, J = 12.9 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 151.9, 147.1, 140.1, 132.2, 131.9, 131.9, 130.3, 129.3, 126.7, 121.8, 120.2, 111.9, 61.1, 56.1, 55.3, 42.5, 37.5, 28.4; **HRMS-ESI** (m/z) calcd. for $C_{18}H_{19}BrNO_2$ ($[M+H]^+$): 360.0594; found: 360.0595. **FTIR** (thin film): 3306, 2933, 1710, 1254 cm^{-1}

1-Bromo-10,11-dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (3).



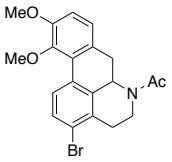
Synthesized following to a reported procedure using **IV-A** (47 mg, 0.13 mmol).[1] The residue was purified by column chromatography on silica gel using 5% NEt_3 in 1:1 EtOAc/hexanes as eluent, affording **3** as a yellow oil (20.9 mg, 43%). $\mathbf{R}_f$ = 0.52 (5% NEt_3 in EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.50 (d, J = 8.2 Hz, 1H), 6.99 (d, J = 8.1 Hz, 1H), 6.95 (d, J = 8.2 Hz, 1H), 6.88 (d, J = 8.1 Hz, 1H), 3.90 (s, 3H), 3.52 (s, 3H), 3.11 (ddd, J = 16.3, 12.3, 5.9 Hz, 1H), 3.02 (dd, J = 13.3, 3.8 Hz, 2H), 2.92–2.89 (m, 1H), 2.71 (dd, J = 16.3, 2.5 Hz , 1H), 2.53 (s, 3H), 2.49 (dd, J = 11.9, 3.8 Hz, 1H), 2.38 (t, J = 13.3 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 151.9, 147.1, 139.0, 132.3, 131.8, 131.6, 130.7, 128.7, 126.7, 121.8, 120.4, 111.9, 64.1, 61.1, 56.2, 52.5, 44.1, 35.2, 28.6; **HRMS-ESI** (m/z) calcd. for $C_{19}H_{21}BrNO_2$ ($[M+H]^+$): 374.0750; found: 374.0751; **FTIR** (thin film): 2952, 1710, 1199 cm^{-1}

Resolution of 3 to (*R*)-3 and (*S*)-3.



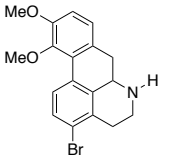
The (*R*) and (*S*) enantiomers were separated by chiral HPLC using Lux 5 μm Cellulose-1 column (250 × 4.6 mm) with an isocratic gradient of 99:1 (vol/vol) of 0.1% DEA in hexanes: 0.1% DEA in *i*-PrOH. **(*R*)-(–)-3**: **HPLC** retention time: 8.121 min, 98% ee; **(*S*)-(+)-3**: **HPLC** retention time: 9.263 min, 98% ee.

1-(3-Bromo-10,11-dimethoxy-4,5,6a,7-tetrahydro-6*H*-dibenzo[*de*,*g*]quinolin-6-yl)ethan-1-one (III-B).



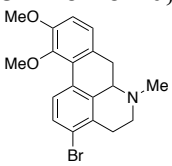
To a 50-mL round-bottom flask were added heterocyclic compound **II-B** (175 mg, 0.66 mmol, 1.0 equiv), 2-(trimethylsylil)phenyl trifluoromethanesufonate (**I**) (354 mg, 0.99 mmol, 1.5 equiv), and MeCN (10 mL). CsF (300 mg, 1.97 mmol, 3.0 equiv) was added and the flask was capped with a rubber septum and stirred at 80 °C for 24 h. Afterwards, brine (20 mL) was added to the mixture, which was extracted with EtOAc (20 mL × 3). The organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo.* The residue was purified by silica gel column chromatography using 5% NEt_3 1:3 EtOAc/hexanes as an eluent, affording **III-B** as a brown solid (61.4 mg, 23%). $\mathbf{R}_f$ = 0.73 (5% NEt_3 in EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.19 (d, J = 8.3 Hz, 1H), 7.49 (d, J = 8.3 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 5.21 (d, J = 12.2 Hz, 1H), 4.02 (d, J = 11.3 Hz, 1H), 3.88 (s, 3H), 3.67 (s, 3H), 3.26 (t, J = 12.2 Hz, 1H), 3.12–2.93 (m, 3H), 2.76–2.67 (m, 2H), 2.21 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 169.0, 152.3, 147.1, 135.9, 132.5, 132.0, 131.0, 130.5, 129.4, 128.1, 126.5, 124.1, 123.4, 60.5, 560, 50.3, 41.4, 33.0, 31.0, 22.3; **HRMS-ESI** (m/z) calcd. for $C_{20}H_{21}BrNO_3$ ($[M+H]^+$): 402.0699; found: 402.0699. **FTIR** (thin film): 2936, 1641, 1427, 1257 cm^{-1}

3-Bromo-10,11-dimethoxy-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (IV-B).



Synthesized following to a reported procedure using **III-B** (217 mg, 0.54 mmol).[1] The residue was purified by silica gel column chromatography using 5% NEt_3 in EtOAc as an eluent, affording **IV-B** as a yellow oil (161 mg, 83%). $\mathbf{R}_f$ = 0.45 (5% NEt_3 in EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.11 (d, J = 8.6 Hz, 1H), 7.50 (d, J = 8.6Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 3.88 (s, 3H), 3.90–3.86 (m, 1H), 3.68 (s, 3H), 3.44–3.39 (m, 1H), 3.02–2.95 (m, 1H) 2.85–2.80 (m, 3H), 2.58 (t, J = 13.8 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 152.4, 146.9, 139.0, 133.0, 130.5, 130.4, 129.1, 127.5, 127.2, 124.8, 123.2, 111.4, 60.3, 56.0, 54.1, 42.9, 36.8, 30.7; **HRMS-ESI** (m/z) calcd. for $C_{18}H_{19}BrNO_2$ ($[M+H]^+$): 360.0594; found: 360.0596; **FTIR** (thin film): 2929, 1260, 804 cm^{-1}

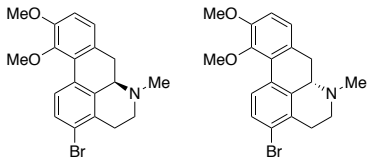
3-Bromo-10,11-dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (4).



Synthesized following to a reported procedure using **IV-B** (107 mg, 0.29 mmol).[1] The residue was purified by silica gel column chromatography using 5% NEt_3 in 1:1 EtOAc/hexanes as an eluent, affording **4** as a yellow oil (60 mg, 55%). $\mathbf{R}_f$ = 0.55 (5% NEt_3, 1:1 EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.10 (d, J = 8.5 Hz, 1H),

7.50 (d, J = 8.5 Hz, 1H), 6.98 (d, J = 8.2 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 3.89 (s, 3H), 3.68 (s, 3H), 3.12–3.05 (m, 3H), 3.03–2.96 (m, 1H), 2.86 (dd, J = 16.5, 2.7 Hz, 1H), 2.55 (s, 3H), 2.53–2.46 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 152.4, 146.8, 137.6, 132.7, 130.7, 130.4, 129.3, 127.6, 127.0, 124.3, 123.3, 111.5, 62.6, 60.4, 56.1, 52.8, 43.9, 34.33, 30.5; **HRMS-ESI** (m/z) calcd. for $C_{19}H_{21}BrNO_2$ ($[M+H]^+$): 374.0750; found: 374.0757; **FTIR** (thin film): 2958, 1653, 1261, 1048 cm^{-1}

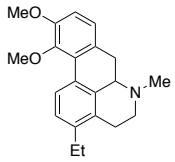
Resolution of 4 to (*R*)-4 and (*S*)-4.



To a 10-mL round-bottom flask was added racemic **4** (90 mg, 0.24 mmol, 1.0 equiv) and (+)-dibenzoyl tartaric acid (86 mg, 0.24 mmol, 1.0 equiv). EtOAc (1 mL) was added and then stirred at room temperature for 5 min, which caused yellow precipitates to form. The mixture was then heated to 80 ºC and stirred for 15 min. After, isopropanol (0.5 mL) was added and refluxed for 1.5 h, causing the mixture to become a clear solution. The mixture was then cooled to room temperature and left to stand overnight. The crystals were separated from the mother liquid and white solid was dissolved in water (10 mL), neutralized with potassium carbonate and extracted with EtOAc (10 mL × 3). Organic layers were combined, dried over Na_2SO_4, filtered and filtrate was concentrated *in vacuo* to produce **(*R*)-(−)-4**: **HPLC** retention time: 8.487 min, 96% ee.

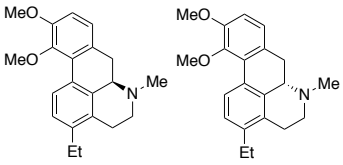
To the mother liquid from the above resolution was added water (10 mL), neutralized with potassium carbonate and extracted with EtOAc (10 mL × 3). Organic layers were combined, dried over Na_2SO_4, filtered and filtrate was concentrated *in vacuo* to produce **(*S*)-(+)-4**: **HPLC** retention time: 10.075 min, 96% ee.

3-Ethyl-10,11-dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (5).



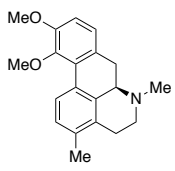
Synthesized following general procedure A with **4** (21 mg, 0.059 mmol), $Pd(dppf)Cl_2$ (0.9 mg, 2 mol%) and $Zn(Et)_2$ (1.0 M in hexane, 0.12 mL, 2.0 equiv). Isolated by silica gel column chromatography using 5% NEt_3, 1:1 EtOAc/hexanes as an eluent to yield racemic **5** as a yellow/orange solid (7.4 mg, 39%); $\mathbf{R}_f$ = 0.42 (5% NEt_3 in 1:1 EtOAc/hexanes); **^{1}H NMR** (500MHz, $CDCl_3$): δ 8.12 (d, J = 8.1 Hz, 1H), 7.08 (d, J = 8.1 Hz, 1H), 6.90 (d, J = 8.1 Hz, 1H), 6.73 (d, J = 8.1 Hz, 1H), 3.82 (s, 3H), 3.63 (s, 3H), 3.06–2.94 (m, 4H), 2.71–2.68 (m, 1H), 2.56 (q, J = 7.5 Hz, 2H), 2.54 (s, 3H), 2.44–2.39 (m, 2H), 1.18 (t, J = 7.5 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 152.5, 146.9, 141.4, 135.2, 130.7, 129.7, 129.1, 128.2, 126.4, 126.0, 123.2, 110.9, 63.2, 60.4, 56.2, 53.1, 44.3, 34.8, 26.7, 25.5, 14.1; **HRMS-ESI** (m/z) calcd. for $C_{21}H_{26}NO_2$ ($[M+H]^+$): 324.1958; found: 324.1965; **FTIR** (thin film): 2959, 1486, 1261, 1081, 802 cm^{-1}

Resolution of (*R*)-5 and (*S*)-5.



The (*R*) and (*S*) enantiomers were separated by chiral HPLC using Lux 5 μm Cellulose-1 column (250×4.6 mm) with an isocratic gradient of 99:1 (vol/vol) of 0.1% DEA in hexanes: 0.1% DEA in *i*-PrOH. **(*R*)-(–)-5**: **HPLC** retention time: 8.851 min, 98% ee; **(*S*)-(+)-5**: **HPLC** retention time: 13.526 min, 98% ee.

(*R*)-10,11-Dimethoxy-3,6-dimethyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (6).

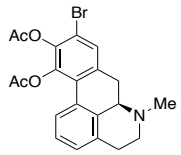


Synthesized following general procedure A with (*R*)-**4** (16.4 mg, 0.044 mmol), $Pd(dppf)Cl_2$ (0.7 mg, 2 mol%) and $Zn(Me)_2$ (0.5 M in THF, 0.19 mL, 2.2 equiv). Isolated by silica gel column chromatography using 5% NEt_3, 1:4 EtOAc/hexanes as an eluent to yield **6** as a yellow oil (3.8 mg, 29%). $\mathbf{R}_f$ = 0.52 (5% NEt_3, 1:1 EtOAc/hexanes); **^{1}H NMR** (500MHz, $CDCl_3$): δ 8.15 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 6.98 (d, J = 8.1 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 3.89 (s, 3H), 3.69 (s, 3H), 3.44–3.39 (m, 1H), 3.15–3.13 (m, 1H), 3.08 (dd, J = 13.8, 4.0 Hz, 1H), 3.01–2.95 (m, 1H), 2.69 (dd, J = 16.8, 3.4 Hz, 1H), 2.57 (s, 3H), 2.55–2.48 (m, 2H), 2.27 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ

152.3, 146.6, 135.5, 134.7, 131.1, 129.3, 128.9, 125.9, 123.0, 110.7, 62.7, 60.1, 55.9, 52.7, 43.8, 34.4, 26.9, 19.1**;** **HRMS-ESI** (m/z) calcd. for $C_{20}H_{24}NO_2$ ($[M+H]^+$): 310.1802; found: 310.1804; **FTIR** (thin film): 2953, 1486, 1261, 1081 cm^{-1}; **HPLC** retention time: 10.355 min.

I. c. Functionalization of C-9 of the Catechol Ring.

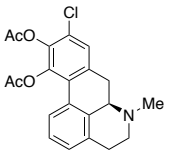
(*R*)-9-Bromo-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline-10,11-diyl diacetate (7).



To (*R*)-(−)-apomorphine hydrochloride hemihydrate (0.43 g, 1.60 mmol, 1.0 equiv) in a 50-mL round bottom flask was added TFA (10 mL) and the mixture was cooled to 0° C using an ice bath. *N*-bromosuccinimide (0.284 g, 1.60 mmol, 1.0 equiv) was added and was stirred in dark for 2 h. The reaction mixture was quenched by removal of TFA *in vacuo,* providing a crude mixture that was taken to the protection step without further purification

The crude mixture was transferred to a 15-mL round-bottom flask and acetic anhydride (3.3 mL) and pyridine (0.55 mL) were added at room temp. The reaction was allowed to stir at room temperature for 2 h, then was diluted with DI H_2O (20 mL). The resulting mixture was extracted with CH_2Cl_2 (20 mL × 3). Organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and subjected to silica gel column chromatography using 5% NEt_3, 1:3 EtOAc/hexanes as an eluent to afford **7** as a yellow solid (0.350 g, 51%). $\mathbf{R_f}$ = 0.33 (5% NEt_3, 1:2 EtOAc/hexanes); **^{1}H NMR** (400MHz, $CDCl_3$): δ 7.70 (d, *J* = 7.7 Hz, 1H), 7.38 (s, 1H), 7.20 (t, *J* = 7.7 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 3.66 (dd, *J* = 15.0, 4.1 Hz, 1H), 3.16–3.19 (m, 2H), 3.07 (dd, *J* = 10.9, 5.9 Hz, 1H), 2.76 (dd, *J* = 15.2, 3.0 Hz, 1H), 2.60 (s, 3H), 2.55 (dd, *J* = 12.6, 3.8 Hz, 1H), 2.35–2.39 (m, 1H), 2.31 (s, 3H), 2.25 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 168.2, 167.8, 142.2, 138.7, 135.3, 135.1, 133.6, 133.5, 130.9, 129.9, 129.3, 126.5, 126.4, 125.9, 125.0, 120.5, 61.4, 52.9, 44.2, 34.3, 29.1, 20.9, 20.8; **HRMS-ESI** (m/z) calcd. for $C_{21}H_{21}BrNO_4$ ($[M+H]^+$): 432.0628; found: 432.0620; **FTIR** (thin film): 2789, 1773, 1190 cm^{-1}; **HPLC** retention time: 13.598 min.

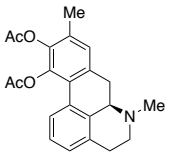
(*R*)-9-Chloro-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline-10,11-diyl diacetate (8).



To (*R*)-(−)-apomorphine hydrochloride hemihydrate (59.8 mg, 0.191 mmol, 1.0 equiv) in a 15-mL round bottom flask was added TFA (1.2 mL) and the mixture was cooled to 0° C using an ice bath. *N*-chlorosuccinimide (25.5 mg, 0.191 mmol, 1.0 equiv) was added and was stirred in dark for 2 h. The reaction mixture was quenched by removal of TFA *in vacuo,* providing a crude mixture that was taken to the protection step without further purification.

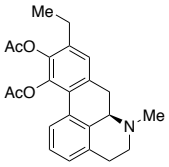
To a 1.5-mL glass vial was added crude mixture, acetic anhydride (0.5 mL) and pyridine (60 µL) at room temperature. The reaction was allowed to stir at room temperature for 2 h, then was diluted with DI H_2O (10 mL). The resulting mixture was extracted with CH_2Cl_2 (10 mL × 3). Organic layers were combined, washed with brine (10 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and subjected to silica gel column chromatography using 5% NEt_3, 1:3 EtOAc/hexanes as an eluent to afford **8** as a yellow solid (36 mg, 49%). $\mathbf{R_f}$ = 0.33 (5% NEt_3, 1:2 EtOAc/hexanes); **^{1}H NMR** (400MHz, $CDCl_3$): δ 7.71 (d, *J* = 7.7 Hz, 1H), 7.21 (t, *J* = 7.7 Hz, 1H), 7.21 (s, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 3.67 (dd, *J* = 15.0, 4.1 Hz, 1H), 3.18–3.14 (m, 3H), 3.06 (ddd, *J* = 11.5, 5.8, 0.8 Hz, 1H), 2.73 (ddd, *J* = 16.5, 2.6, 1.2 Hz, 1H), 2.58 (s, 3H), 2.53 (dd *J* = 11.7, 3.8 Hz, 1H), 2.31 (s, 3H), 2.25 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.1, 167.7, 142.0, 138.0, 135.2, 133.5, 133.2, 130.6, 130.4, 129.8, 129.2, 126.4, 124.9, 122.8, 61.2, 52.8, 44.1, 31.1, 29.0, 20.8, 20.7.; **HRMS-ESI** (m/z) calcd. for $C_{21}H_{21}ClNO_4$ ($[M+H]^+$): 386.1154; found: 386.1153. **FTIR** (thin film): 2790, 1773, 1189, 726 cm^{-1}; **HPLC** retention time: 14.077 min.

(*R*)-6,9-Dimethyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline-10,11-diyl diacetate (9).



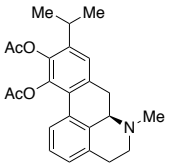
Synthesized following general procedure A with **7** (29 mg, 0.070 mmol), $Pd(dppf)Cl_2$ (1.5 mg, 3 mol%) and $Zn(Me)_2$ (0.44 M in THF, 0.35 mL, 2.2 equiv). Isolated by silica gel column chromatography using 5% NEt_3, 1:3 EtOAc/hexanes as an eluent to yield **9** (14.7 mg, 57%). $\mathbf{R_f}$ = 0.21 (5% NEt_3, 1:2 EtOAc/hexanes); **^{1}H NMR** (400MHz, $CDCl_3$): δ 7.71 (d, *J* = 7.7 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 7.08 (d, *J* = 7.7 Hz, 1H), 6.96 (s, 1H), 3.30 (dd, *J* = 14.5, 3.9 Hz, 1H), 3.22–3.07 (m, 3H), 3.05 (ddd, *J* = 11.6, 5.7, 1.5 Hz, 1H), 2.76–2.72 (m, 1H), 2.60 (s, 3H), 2.53 (dd, *J* = 12.1, 3.8 Hz, 1H), 2.36 (s, 3H), 2.30 (s, 3H), 2.24 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 168.8, 168.2, 141.2, 137.3, 135.1, 133.9, 133.74, 133.1, 130.6, 128.9, 128.5, 126.3, 125.9, 123.6, 61.6, 52.9, 44.1, 30.5, 29.0, 20.9, 20.8, 20.0; **HRMS-ESI** (m/z) calcd. for $C_{22}H_{24}NO_4$ ($[M+H]^+$): 366.1699; found: 366.1696; **FTIR** (thin film): 2951, 1767, 1190 cm^{-1}; **HPLC** retention time: 17.276 min.

(*R*)-9-Ethyl-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline-10,11-diyl diacetate (10).



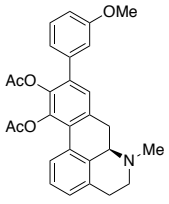
Synthesized following general procedure A with **7** (30 mg, 0.070 mmol), $Pd(dppf)Cl_2$ (1.02 mg, 2 mol%) and $Zn(Et)_2$ (1.0M in hexane, 0.14 mL, 2.0 equiv). Isolated by silica gel column chromatography using 5% NEt_3, 1:4 EtOAc/hexanes as an eluent to yield **10** (8.9 mg, 35%). $\mathbf{R_f}$ = 0.36 (5% NEt_3, 1:2 EtOAc/hexanes); **^{1}H NMR** (400MHz, $CDCl_3$): δ 7.70 (d, *J* = 7.7 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 7.08 (d, *J* = 7.7 Hz, 1H), 6.97 (s, 1H), 3.34 (dd, *J* = 14.5, 3.9 Hz, 1H), 3.22–3.10 (m, 2H), 3.05 (dd, *J* = 11.6, 5.7, 1H), 2.77–2.69 (m, 2H), 2.72 (q, *J* = 7.5 Hz, 2H), 2.57 (s, 3H), 2.53 (dd *J* = 12.1, 3.8 Hz, 1H), 2.31 (s, 3H), 2.24 (s, 3H), 1.23 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 168.8, 168.2, 141.5, 139.7, 137.3, 135.4, 133.4, 133.1, 130.7, 129.1, 128.4, 126.3, 125.0, 122.1, 61.8, 53.0, 44.2, 30.2, 29.1, 26.7, 21.0, 20.9, 14.6; **HRMS-ESI** (m/z) calcd. for $C_{23}H_{26}NO_4$ ($[M+H]^+$): 380.1856; found: 380.1848; **FTIR** (thin film): 2963, 1768, 1201 cm^{-1}; **HPLC** retention time: 15.797 min.

(*R*)-9-Isopropyl-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline-10,11-diyl diacetate (11).



Synthesized following general procedure A with **7** (30 mg, 0.070 mmol), $Pd(dppf)Cl_2$ (1.02 mg, 2 mol%) and $Zn(iPr)_2$ (1.0 M in toluene, 0.15 mL, 2.2 equiv). Isolated by silica gel column chromatography using 5% NEt_3, 1:4 EtOAc/hexanes as an eluent to yield **11** as a yellow oil (5 mg, 19%). $\mathbf{R_f}$ = 0.28 (5% NEt_3, 1:1 EtOAc/hexanes); **^{1}H NMR** (400MHz, $CDCl_3$): δ 7.70 (d, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.03 (s, 1H), 3.45 (dd, *J* = 14.5, 3.7 Hz, 1H), 3.06–3.31 (m, 4H), 3.24 (sex, *J* = 6.9 Hz, 1H), 4.15 (dd, *J* = 16.0, 3.8 Hz, 1H), 2.60 (s, 3H), 2.31 (s, 3H), 2.23 (s, 3H), 1.32 (d, *J* = 6.9 Hz, 3H), 1.21 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 168.7, 168.2, 144.1, 141.8, 137.2, 135.1, 132.9, 132.8, 130.9, 129.0, 128.4, 126.4, 125.1, 119.1, 61.9, 52.9, 45.9, 29.7, 28.9, 23.2, 23.2, 21.0, 20.9, 8.8; **HRMS-ESI** (m/z) calcd. for $C_{24}H_{28}NO_4$ ($[M+H]^+$): 394.2013; found: 394.2006; **FTIR** (thin film): 2960, 1770, 1203 cm^{-1}; **HPLC** retention time: 11.801 min.

(*R*)-9-(3-Methoxyphenyl)-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline-10,11-diyl diacetate (12).

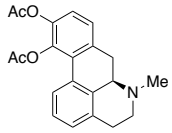


A flame-dried 15-mL round bottom flask was charged with **7** (50 mg, 0.124 mmol, 1.0 equiv), $Pd(OAc)_2$ (1 mol%), RuPhos (1 mol%), 3-methoxyphenylboronic acid (28 mg, 0.186 mmol, 1.5 equiv), and K_3PO_4 (53 mg, 0.249 mmol, 2.0 equiv). The flask was placed under N_2 via sequential vacuum purge and N_2 backfill (× 3). THF (0.25 mL) and H_2O (2 μL) were added and the mixture was stirred at room temperature for 10 min. Aryl halide (50 mg, 0.124 mmol, 1.0 equiv) was added and the reaction was allowed to stir at room temperature overnight. The reaction was then diluted with Et_2O, filtered through a silica plug, washed with Et_2O (20 mL) and the filtrate was concentrated under reduced pressure. The crude mixture was subjected to silica gel column chromatography

using 5% NEt_3, 1:4 EtOAc/hexanes as an eluent to yield **12** (9.6 mg, 17%). $\mathbf{R_f}$ = 0.34 (5% NEt_3, 1:2 EtOAc/hexanes); **^{1}H NMR** (400MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.9 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.22 (t, *J* = 7.7 Hz, 1H), 7.12 (d, *J* = 6.9 Hz, 2H), 6.93–6.88 (m, 3H), 3.82 (s, 3H), 3.24–3.00 (m, 5H), 2.74–2.72 (m, 1H), 2.76–2.72 (m, 1H), 2.34 (s, 3H), 2.32 (s, 3H), 2.28 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 168.6, 168.2, 159.5, 141.4, 141.2, 139.5, 138.5, 135.3, 133.1, 133.1, 130.6, 129.6, 129.4, 128.7, 126.4, 125.1, 123.4, 121.9, 114.7, 113.7, 61.9, 55.4, 52.8, 44.0, 32.4, 29.0, 21.0, 20.8; **HRMS-ESI** (m/z) calcd. for $C_{28}H_{28}NO_5$ ($[M+H]^+$): 458.1962; found: 458.1958; **FTIR** (thin film): 2926, 1772, 1204, 726 cm^{-1}; **HPLC** retention time: 21.824 min.

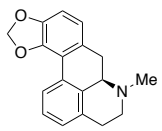
I. d. Catechol Protection of Apomorphine.

(*R*)-6-Methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline-10,11-diyl diacetate (13).



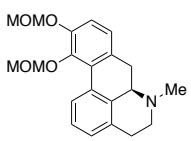
(*R*)-(–)-apomorphine hydrochloride (22.4 mg, 0.072 mmol), acetic anhydride (0.15 mL) and pyridine (25 µL) were mixed in a 1.5-mL glass vile. The reaction stirred at room temperature for 5 hours, then was diluted with DI H_2O (1 mL). The resulting mixture was extracted with CH_2Cl_2 (1 mL × 3). Combined organic layers were washed with brine (1 mL) and dried over Na_2SO_4. The dried solution was filtered and concentrated under reduced pressure, affording a yellow oil. The crude mixture was subjected silica gel column chromatography using 10% MeOH/CH_2Cl_2 as an eluent to afford **13** as a yellow solid. (25 mg, 99%). $\mathbf{R_f}$ = 0.23 (5% NEt_3, 1:2 EtOAC/hexanes); **^{1}H NMR** (400MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.8 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 8.1 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 3.40–3.24 (m, 2H), 3.19 (dd, *J* =14.1, 4.1 Hz, 1H), 3.12–3.15 (m, 1H), 2.78 (dd, *J* = 16.5, 3.7 Hz, 1H), 2.81–2.69 (m, 2H), 2.62 (s, 3H), 2.31 (s, 3H), 2.27 (s, 3H). Matches with the reported spectra[4]; **HRMS-ESI** (m/z) calcd. for $C_{21}H_{22}NO_4$ ($[M+H]^+$): 352.1543; found: 352.1552; **HPLC** retention time: 15.119 min.

(*R*)-7-Methyl-6a,7,8,9-tetrahydro-6*H*-[1,3]dioxolo[4',5':5,6]benzo[1,2-*g*]benzo[*de*]quinoline (14).



To a solution of (*R*)-(–)-apomorphine hydrochloride (0.502 g, 1.61 mmol, 1.0 equiv) and DMSO (16 mL) in a 50-mL round-bottom flask was added finely ground NaOH (193 mg, 4.83 mmol, 3.0 equiv). The reaction mixture turned dark blue/black within 10 minutes upon the addition of NaOH. The reaction was stirred under N_2 at room temperature for 1 hour and methylene dibromide (170 µL, 2.4 mmol, 1.5 equiv) was added dropwise. The mixture was heated to 80 °C for 4.5 hours and then cooled to room temperature. The mixture was poured to ice water (50 mL) and extracted with EtOAc (30 mL × 4). The combined organic layers were washed with DI H_2O (30 mL × 3) to remove DMSO, and then the organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated to afford a brown oil. The crude mixture was subjected to silica gel chromatography using 5% MeOH/CH_2Cl_2 as an eluent to afford **14** as a brown oil (0.276 g, 61%). $\mathbf{R_f}$ = 0.74 (10% MeOH/CH_2Cl_2, neutral pH TLC); **^{1}H NMR** (400MHz, $CDCl_3$): δ 7.91 (d, *J* = 7.7 Hz, 1H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.06 (d, *J* = 7.7 Hz, 1H), 6.74 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.69 (d, *J* = 7.8 Hz, 1H), 6.10 (d, 1.5 Hz, 1H), 5.96 (d, 1.5 Hz, 1H), 3.25–3.13 (m, 3H), 3.07 (ddd, *J* = 11.7, 5.3, 1.3, Hz 1H), 2.76 (dd, *J* = 16.4, 3.3 Hz, 1H), 2.61 (td, *J* = 13.0, 3.8 Hz, 2H), 2.56 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.0, 144.1, 133.9, 133.4, 130.3, 129.5, 128.2, 126.7, 124.9, 120.8, 117.7, 107.2, 101.0, 62.5, 53.5, 44.2, 34.1, 29.3. **HRMS-ESI** (m/z) calcd. for $C_{18}H_{18}NO_2$ ($[M+H]^+$): 280.1332; found: 280.1340; **FTIR** (thin film): 2787, 1244 cm^{-1}; **HPLC** retention time: 7.784 min.

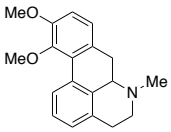
(*R*)-10,11-Bis(methoxymethoxy)-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (15).



(*R*)-(−)-Apomorphine hydrochloride hemihydrate (0.32 mmol, 1.0 equiv, 100 mg) was neutralized using saturated aqueous solution of $NaHCO_3$ (5 mL), extracted with CH_2Cl_2 (10 mL × 3) and the organic layers were concentrated *in vacuo*. To the neutralized (*R*)-(−)-Apomorphine in a 15-mL round-bottom flask was added

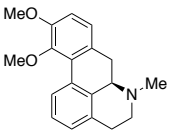
CH_2Cl_2 (1 mL) and aqueous NaOH (10 M, 1.66 mmol, 5.2 equiv, 0.17 mL). The mixture was cooled to 0 °C using ice/water bath for 20 mins. MOMCl (1.6 mmol, 0.122 mL, 5.0 equiv) was added dropwise and the reaction was allowed to warm up to room temp, resulting in a dark brown/purple solution. The reaction was stirred overnight and was diluted with DI H_2O (10 mL) and extracted with CH_2Cl_2 (10 mL × 3). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude mixture was subjected to silica gel column chromatography using 5% NEt_3, 1:4 EtOAc/hexanes as an eluent to yield **15** (6.0 mg, 5.3%). $\mathbf{R}_f$ = 0.4 (5% NEt_3, 1:2 EtOAc/hexanes). **^{1}H NMR** (400MHz, $CDCl_3$): δ 8.14 (d, *J* = 7.8 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 5.24 (d, *J* = 6.6 Hz, 1H), 5.20 (d, *J* = 6.6 Hz, 1H), 4.97 (d, *J* = 5.8 Hz, 1H), 4.92 (d, *J* = 5.8 Hz, 1H), 3.52 (s, 3H), 3.36 (s, 3H), 3.23–3.13 (m, 2H), 3.09 (s, 1H), 3.06–3.01 (m, 2H), 2.74 (dd, *J* = 16.4, 2.7 Hz, 1H), 2.54 (s, 3H), 2.51–2.45 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 149.9, 144.4, 132.7, 131.5, 128.7, 128.0, 126.6, 126.4, 124.0, 115.8, 99.2, 95.7, 62.4, 57.7, 56.4, 53.0, 44.2, 34.7, 29.3; **HRMS-ESI** (m/z) calcd. for $C_{21}H_{26}NO_4$ ($[M+H]^+$): 356.1856; found: 356.1853; **FTIR** (thin film): 2953, 1257, 1154 cm^{-1}; **HPLC** retention time: 10.111 min.

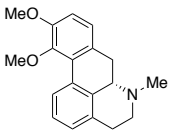
10,11-Dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (16).



To a 10-mL round-bottom flask were added **4** (12.5 mg, 0.033 mmol, 1.0 equiv), $RuCl_2$(p-cymene)$_2$ (1.02 mg, 0.0017 mmol, 0.05 equiv), and K_2CO_3 (5.5 mg, 0.040 mmol, 1.2 equiv). Flask was vacuum purged and N_2-refilled three times. *i*-PrOH (0.5 mL) was added and the mixture was heated to 100 ºC resulting in a dark-red reaction. The reaction was allowed to stir for 24 hours, then filtered through a silica plug, washed with 5% NEt_3 in EtOAc (10 mL). The filtrate was concentrated *in vacuo.* The crude was subjected to silica gel column chromatography using 5% NEt_3, 1:10 EtOAc/hexanes as an eluent to afford **16** as a yellow oil (9.0 mg, 92%). $\mathbf{R}_f$ = 0.45 (5% NEt_3, 1:1 EtOAc/hexanes); **^{1}H NMR** (500MHz, $CDCl_3$): δ 8.23 (d, *J* = 7.7 Hz, 1H), 7.25 (t, *J* = 7.7 Hz, 1H), 7.09 (d, *J* = 7.7 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 3.90 (s, 3H), 3.70 (s, 3H), 3.26–3.19 (m, 1H), 3.16–3.14 (m, 1H), 3.11–3.06 (m, 2H), 2.77 (dd, *J* = 16.3, 2.2 Hz, 1H), 2.57 (s, 3H), 2.54–2.51 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 152.5, 147.1, 132.7, 131.6, 129.8, 129.7, 128.1, 127.8, 126.6, 126.3, 123.4, 111.3, 62.6, 60.5, 56.2, 53.1, 34.7, 29.8, 29.3. **HRMS-ESI** (m/z) calcd. for $C_{19}H_{22}NO_2$ ($[M+H]^+$): 296.1647; found: 296.1647; **FTIR** (thin film): 2925, 1490, 1261 cm^{-1};

Resolution of 16 to (*R*)-16 and (*S*)-16.

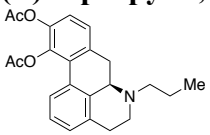




The **(*R*)-16** and **(*S*)-16** enantiomers were separated by chiral HPLC using Lux 5 μm Cellulose-1 column (250 × 4.6 mm) with an isocratic gradient of 99:1 (vol/vol) of 0.1% DEA in hexanes: 0.1% DEA in *i*-PrOH. **(*R*)-(–)-16**: **HPLC** retention time: 8.649 min, 98% ee; **(*S*)-(+)-16**: **HPLC** retention time: 16.831 min, 98% ee.

I. e. Synthesis of *N*-propyl apomorphine analog.

(*R*)-6-propyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline-10,11-diyl diacetate (18).



To a 1.5-mL glass vile were added (*R*)-(–)-*N*-propylnorapomorphine (8.5 mg, 0.023 mmol), acetic anhydride (80 μL) and pyridine (12 μL) at room temperature. The reaction was allowed to stir at room temperature for 2 h, then was diluted with DI H_2O (1 mL). The resulting mixture was extracted with CH_2Cl_2 (1 mL × 3). Organic layers were combined, washed with brine (1 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford **18** as a yellow oil (9.0 mg, quant). $\mathbf{R}_f$ = 0.58 (5% NEt_3, 1:1 EtOAc/hexanes); **^{1}H NMR** (400MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.7 Hz, 1H), 7.21 (t, *J* = 7.7 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 1H), 7.10 (d, *J* = 7.7 Hz, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 3.58–3.54 (m, 1H), 3.29–3.25 (m, 1H), 3.16 (dd, *J* = 14.1, 3.9 Hz, 1H), 2.99–2.92 (m, 1H), 2.79 –2.74 (m, 1H), 2.70–2.55 (m, 4 H), 2.31 (s, 3H), 2.27 (s, 3H), 1.68–1.58 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR**

(126 MHz, $CDCl_3$): δ 168.7, 168.0, 142.2, 139.3, 135.5, 133.7, 133.5, 130.6, 128.9, 128.8, 126.6, 126.2, 125.0, 121.9, 59.0, 56.0, 48.6, 34.2, 29.8, 28.6, 21.0, 18.8, 12.1. **HRMS-ESI** (m/z) calcd. for $C_{23}H_{26}NO_4$ ($[M+H]^+$): 380.1856; found: 380.1866; **FTIR** (thin film): 2961, 1768, 1201 cm^{-1}; **HPLC** retention time: 11.691 min.

II. Biological Evaluations of Apomorphine Analogs

cAMP GloSensor assay.
To measure dopamine receptor mediated regulation of cAMP levels, HEK293T cells were co-transfected in a 1:1 ratio with either human D1 or $D2_{Long}$ receptor and a split-luciferase based cAMP biosensor (GloSensor, Promega, Durham NC). The next day, transfected cells were transferred to clear MEM media with 2% Fetal Bovine Serum (FBS) and 1X Glutamax, and plated in poly-D-lysine (Sigma Aldrich) coated 96-well white clear-bottom cell culture plates, at a density of 50,000 cells per 100 µL per well and incubated overnight. Next day, in a separate drug plate, serial drug dilutions ranging from 10^{-3} M (1 mM) to 10^{-12} M (1 pM) were prepared in fresh assay buffer (1X HBSS, 0.03% ascorbic acid, pH 7.4) such that the final concentrations would range from 10^{-4} to 10^{-13}. Before adding drugs, 25 µl/well GloSensor reagent (4 mM D-Luciferin, Cayman Chemicals) in assay buffer was added to each well. Plates were allowed to incubate for 2 h in the dark at room temperature, and immediately afterwards, 10-20 µL assay buffer (to bring final volume to 50 µL) and 5 µL of drugs or dopamine with concentrations corresponding to dose-response curves were added and allowed to incubate for an additional 5 minutes. To stimulate endogenous cAMP production (for D2R mediated inhibition) 5 µL of Forskolin (Sigma Aldrich) (1 µM final concentration) was added after addition of drugs and incubated for an additional 5 minutes. Luminescence intensity was quantified 15 minutes later using a Cytation 5 (BioTek) plate reader. For antagonist assays 10 µM dopamine was used as competition for apomorphine analogs, and SCH23390 (D1R) and raclopride (D2R) were used as reference antagonists.

β-Arrestin Bioluminiscence resonance energy transfer (BRET) assay.
To measure D1R- or D2R-mediated βarr2 recruitment, HEK293T cells were co-transfected in a 1:20 ratio with D1 or $D2_{Long}$ receptor fused to C-terminal *renilla* luciferase (*R*Luc8 or 2), and a *N*-terminal Venus-tagged β-arrestin2. The next day, transfected cells were plated in poly-D-lysine coated 96-well white clear-bottom cell culture plates with clear MEM media + 2% FBS and 1X Glutamax at a density of 100,000 cells in 100 µL per well, and incubated overnight. Buffers used for the BRET assay and to dilute drugs were exactly the same as for the cAMP inhibition assay. Next day, media was decanted and cells were washed twice with assay buffer and 80 µL of assay buffer was added/well. The *R*Luc substrate, coelenterazine h (Cayman Chemicals, 5 µM final concentration), was added per well, and exactly 5 minutes later drugs were added at concentrations corresponding to the dose-response curves and allowed to incubate for 5 minutes. Luminescence at 485 nm and fluorescent eYFP emission at 530 nm were measured for 1 second per well using a Cytation 5 plate Reader (BioTek). For antagonist assays, EC80 of dopamine was added to each well and allowed to incubate for 5 minutes before adding drugs. The ratio of eYFP/*R*Luc was calculated per well and data are presented as percent of dopamine response. The percent response was plotted as a function of drug concentration using Graphpad Prism 7 (Graphpad Software Inc., San Diego, CA).

III. References

(1) Raminelli, C., Muraca, A., Perecim, G., Rodrigues, A. (2017) Convergent Total Synthesis of (±)-Apomorphine via Benzyne Chemistry: Insights into the Mechanisms Involved in the Key Step, *Synthesis,* 49, 3546–3557.

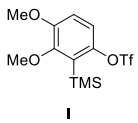
(2) Kubo, T., Katoh, C., Yamada, K., Okano, K., Tokuyama, H., Fukuyama, T. (2008) A mild inter- and intramolecular amination of aryl halides with a combination of CuI and CsOAc, *Tetrahedron,* 64, 11230–11236.

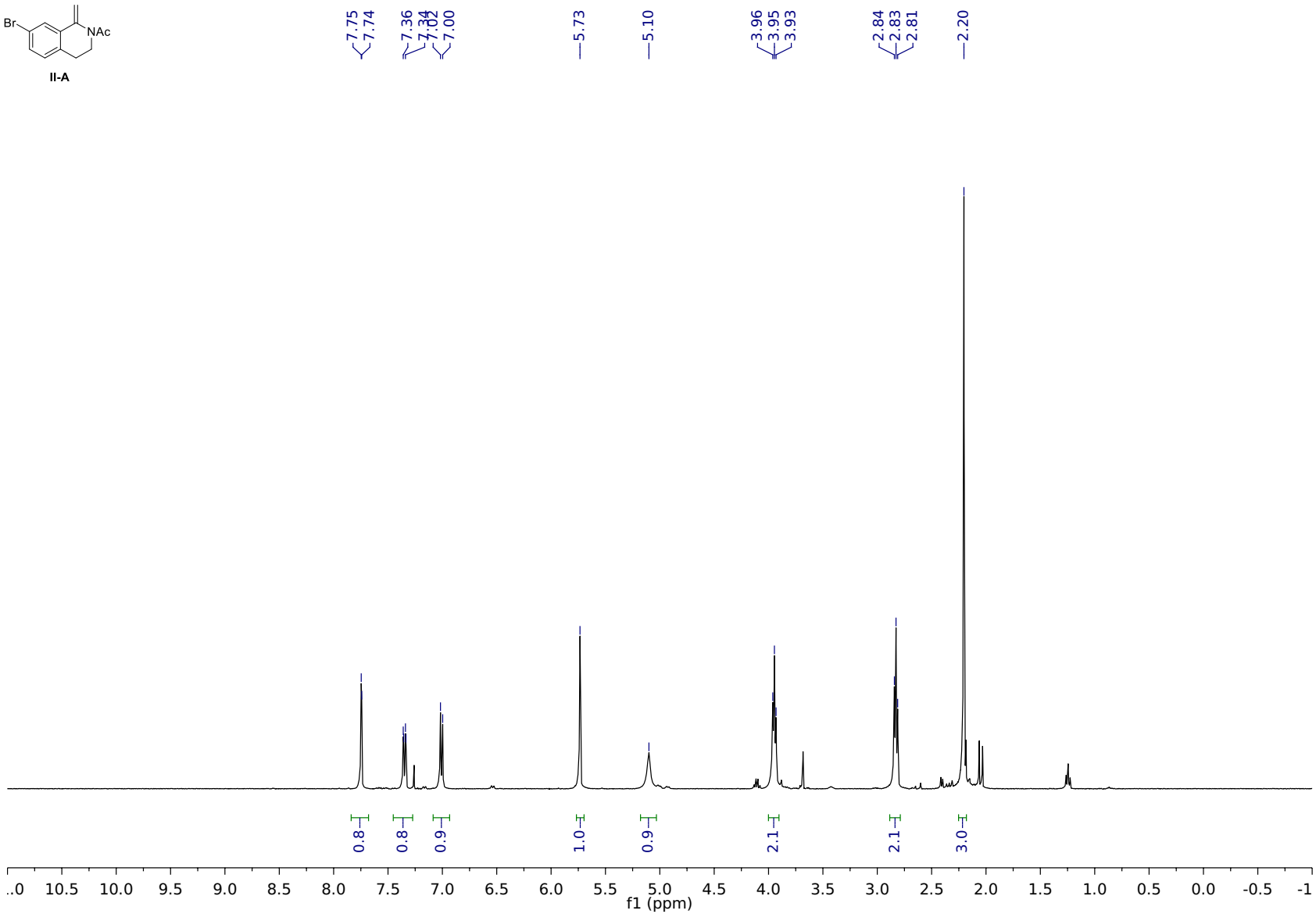
(3) Akhter, S., Lund, B. A., Ismael, A., Langer, M., Isaksson, J., Christopeit, T., Leiros, H.-K. S., Bayer, A. (2018) A focused fragment library targeting the antibiotic resistance enzyme - Oxacillinase-48: Synthesis, structural evaluation and inhibitor design, *Eur. J. Med. Chem.* 145, 634–648.

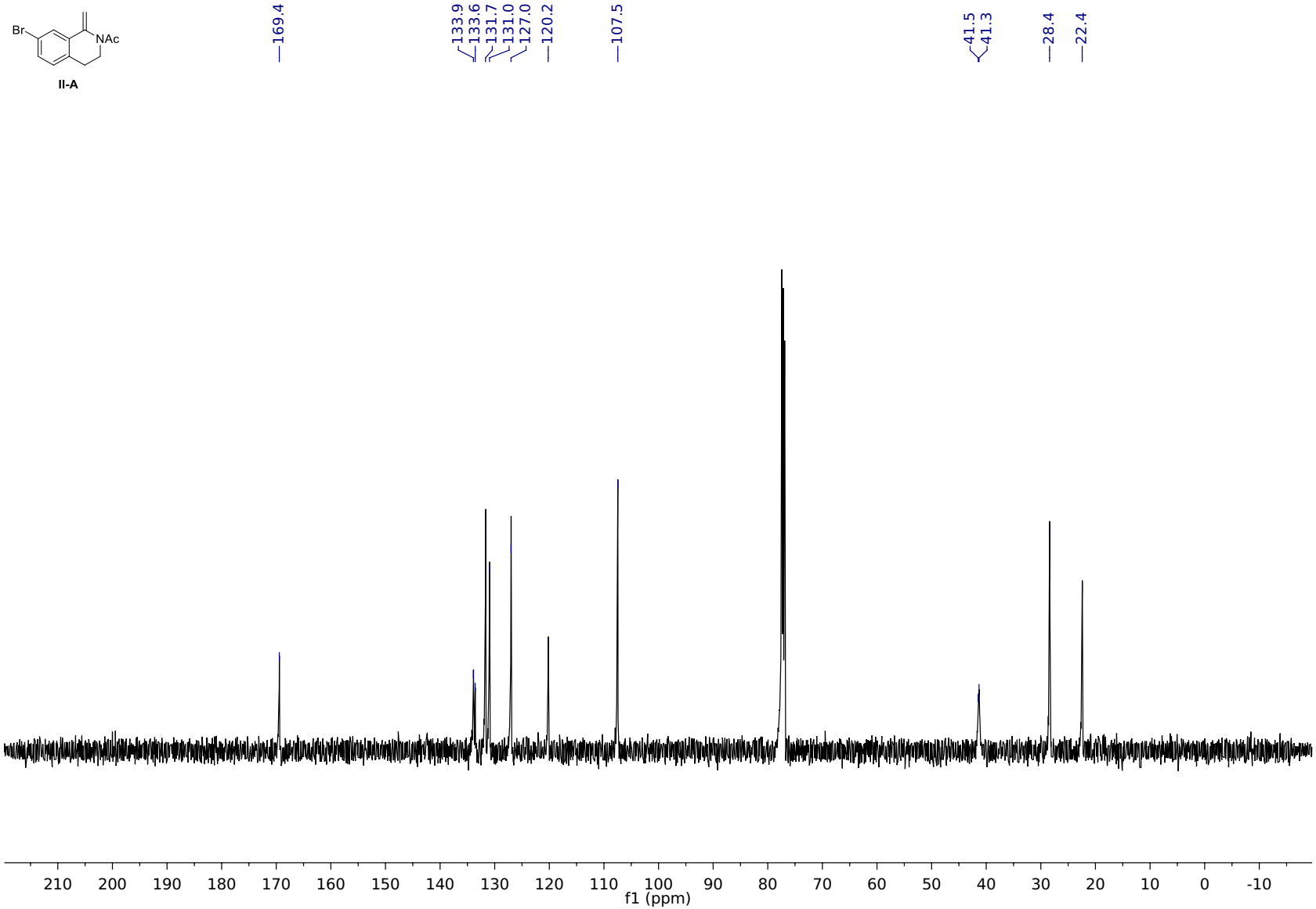
(4) Shi, X.-X., Ni, F., Shang, H.-X., Yan, M.-L., Su, J.-Q. (2006) Racemization of (S)-(+)-10,11-dimethoxyaporphine and (S)-(+)-aporphine: efficient preparations of (R)-(−)-apomorphine and (R)-(−)-aporphine via a recycle process of resolution, *Tetrahedron: Asymmetry,* 17, 2210–2215.

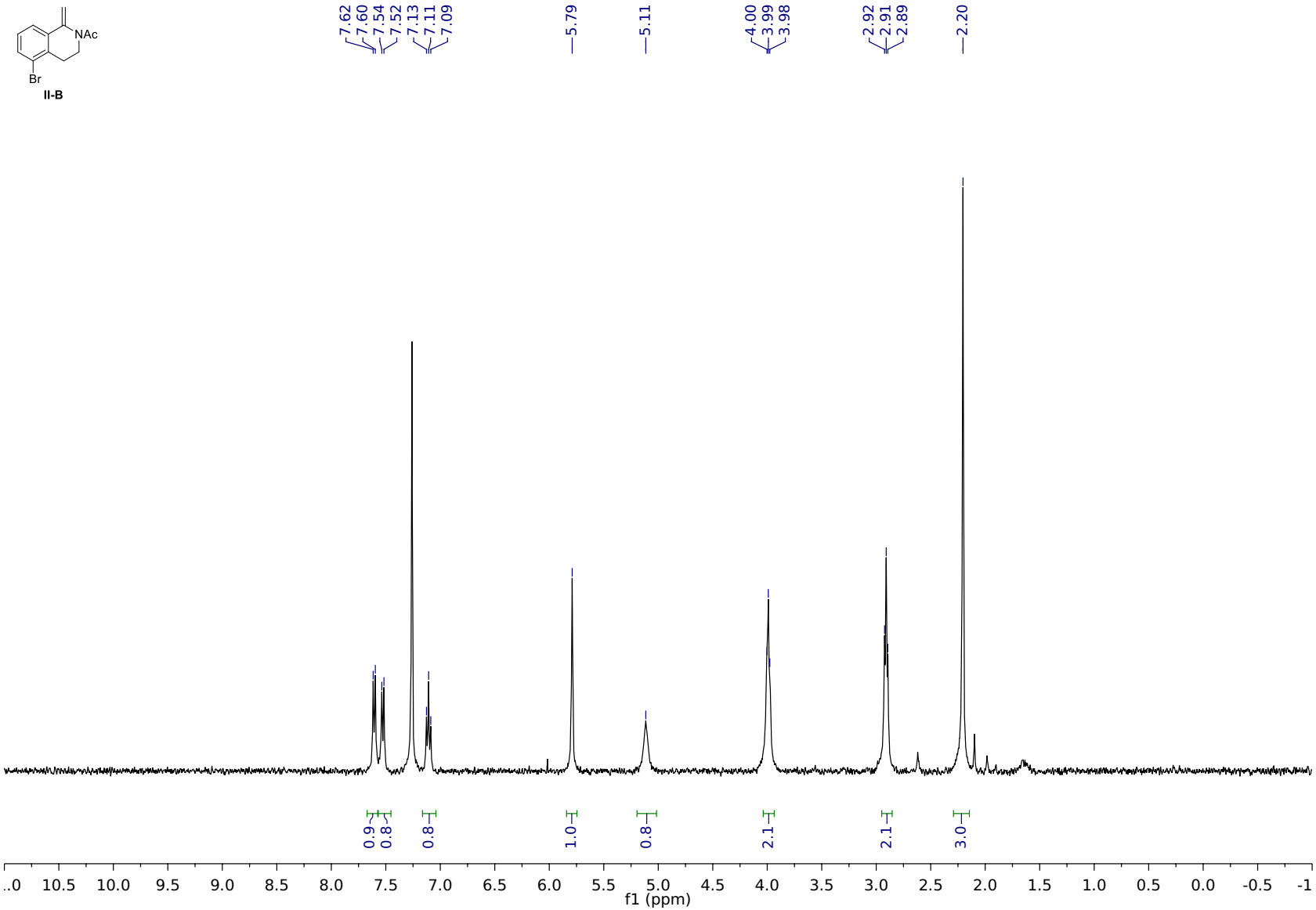
(5) Kenakin, T., Watson, C., Muniz-Medina, V., Christopoulos, A., Novick, S. (2012) A Simple Method for Quantifying Functional Selectivity and Agonist Bias. *ACS Chem. Neurosci.* 3, 193–203.

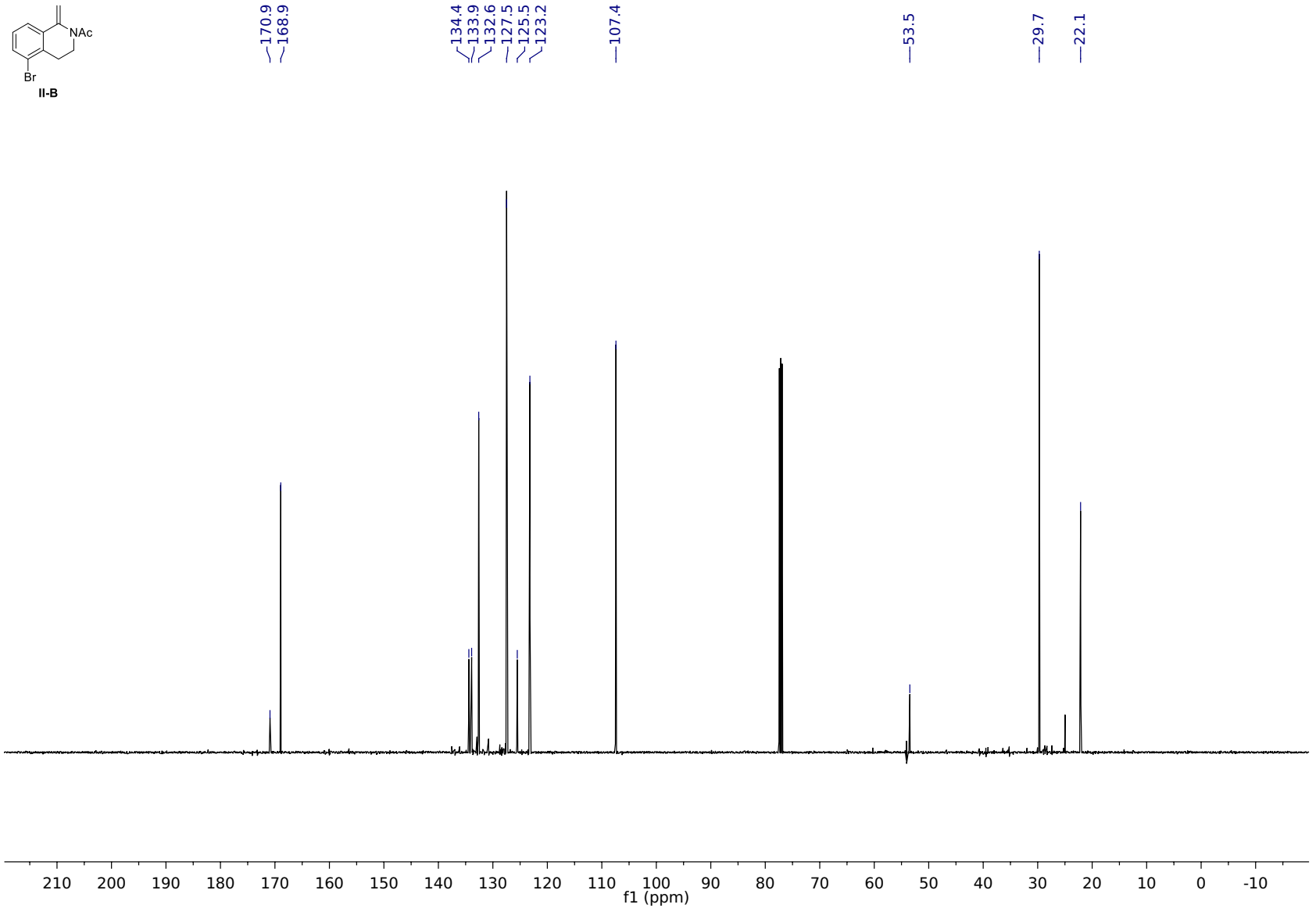
IV. ^{1}H and ^{13}C Spectra

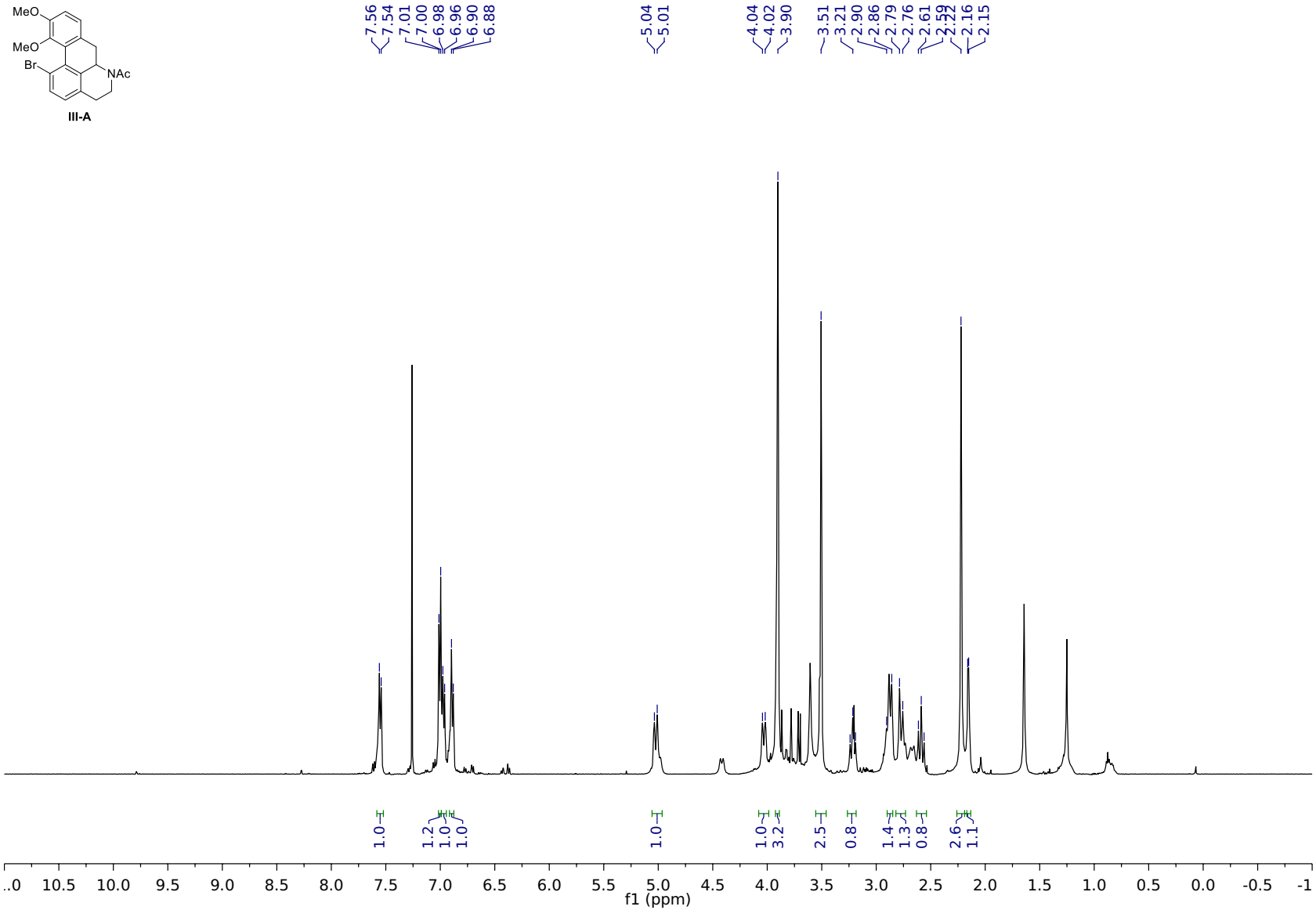


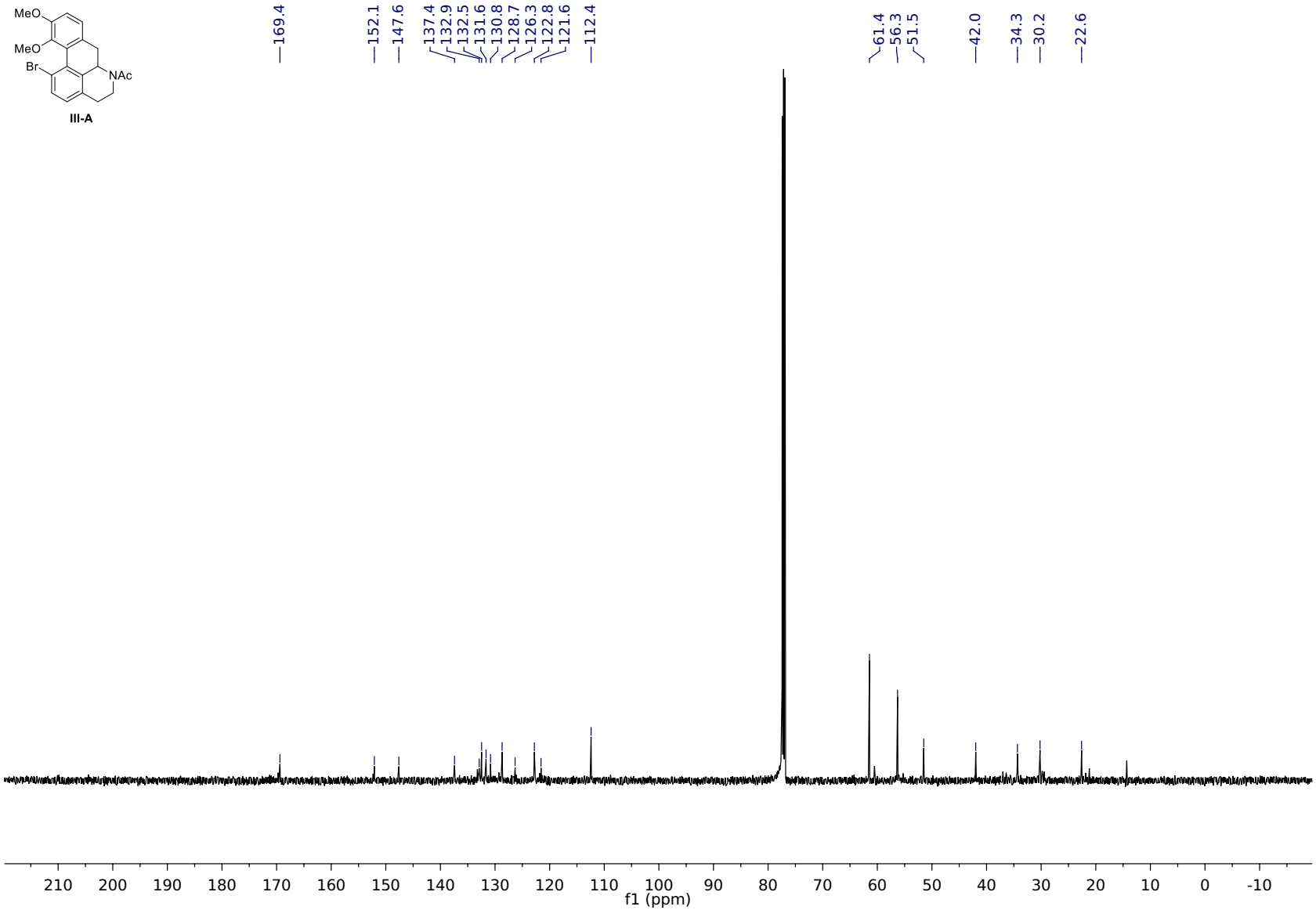

Br
NAc
II-A
7.75
7.74
7.36
7.34
7.02
7.00
5.73
5.10
3.96
3.95
3.93
2.84
2.83
2.81
2.20
0.8
0.8
0.9
1.0
0.9
2.1
2.1
3.0
f1 (ppm)

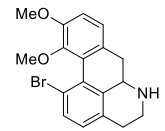

Br
NAc
II-A
169.4
133.9
133.6
131.7
131.0
127.0
120.2
107.5
41.5
41.3
28.4
22.4
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


NAc
Br
II-B
7.62
7.60
7.54
7.52
7.13
7.11
7.09
5.79
5.11
4.00
3.99
3.98
2.92
2.91
2.89
2.20
0.9
0.8
0.8
1.0
0.8
2.1
2.1
3.0
f1 (ppm)


NAc
Br
II-B
170.9
168.9
134.4
133.9
132.6
127.5
125.5
123.2
107.4
53.5
29.7
22.1
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

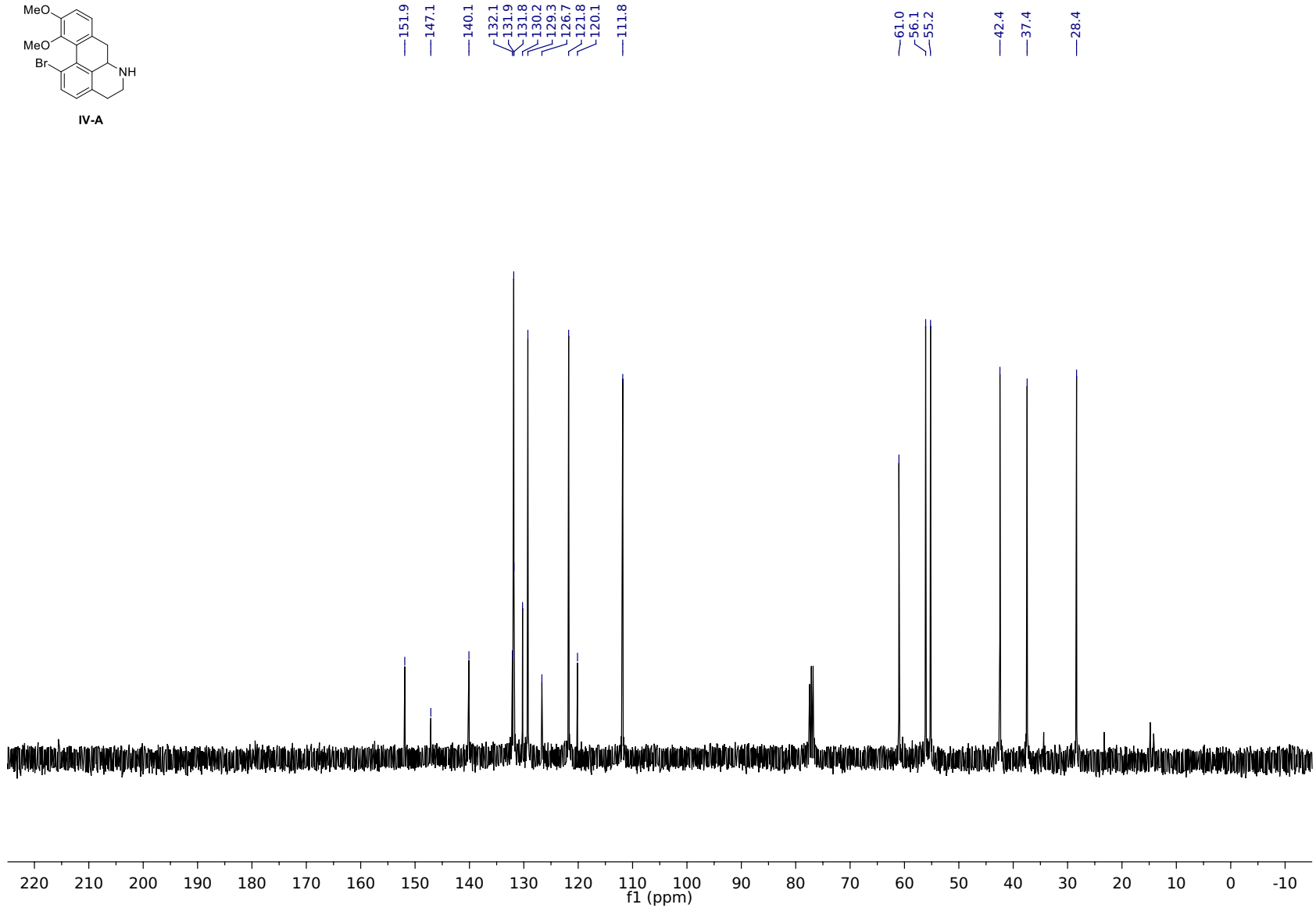

MeO
MeO
Br
NAc
III-A
7.56
7.54
7.01
7.00
6.98
6.96
6.90
6.88
5.04
5.01
4.04
4.02
3.90
3.51
3.21
2.90
2.86
2.79
2.76
2.61
2.59
2.22
2.16
2.15
1.0
1.2
1.0
1.0
1.0
1.0
3.2
2.5
0.8
1.4
1.3
0.8
2.6
1.1
f1 (ppm)

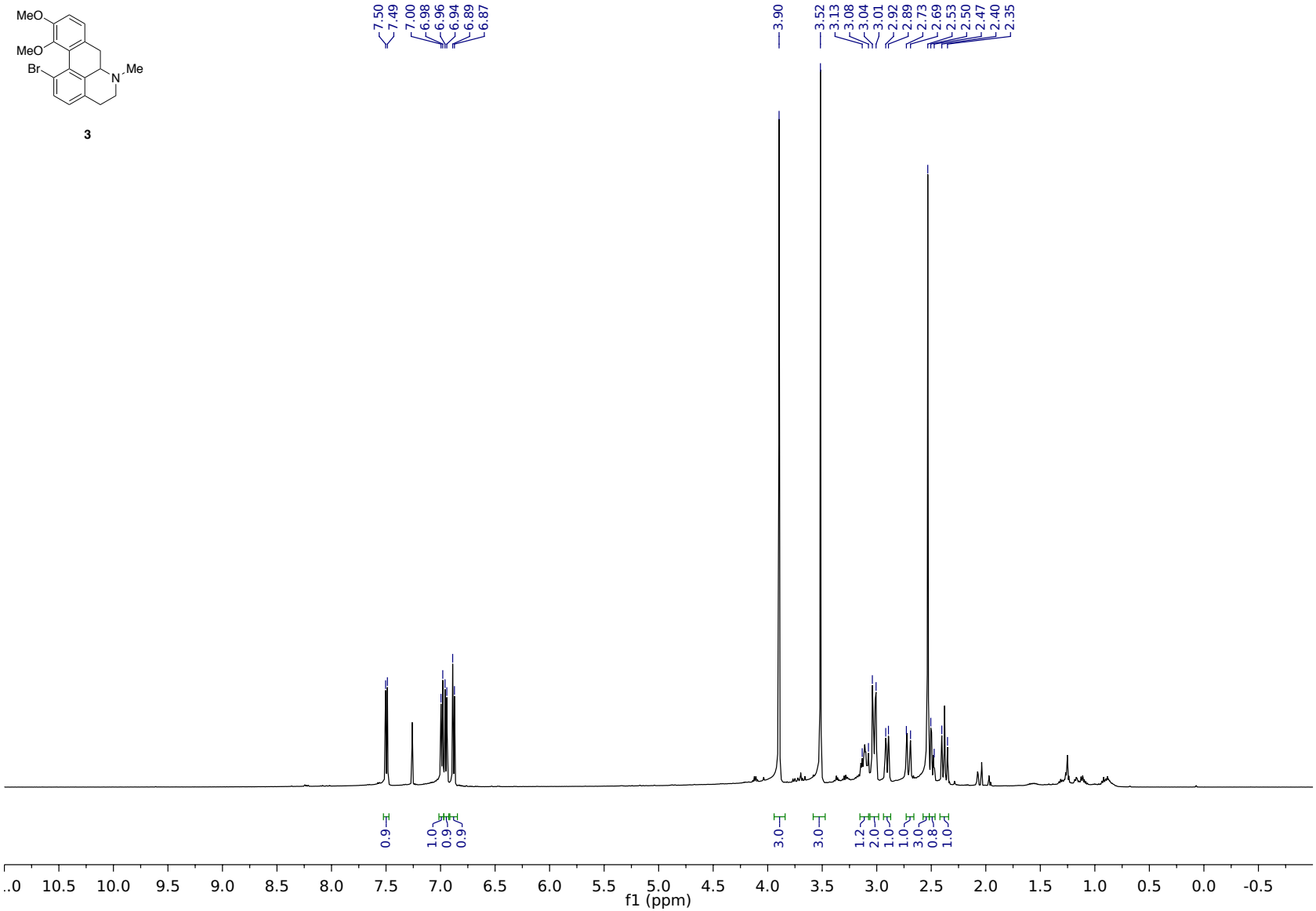

MeO
MeO
Br
NAc
III-A
169.4
152.1
147.6
137.4
132.9
132.5
131.6
130.8
128.7
126.3
122.8
121.6
112.4
61.4
56.3
51.5
42.0
34.3
30.2
22.6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

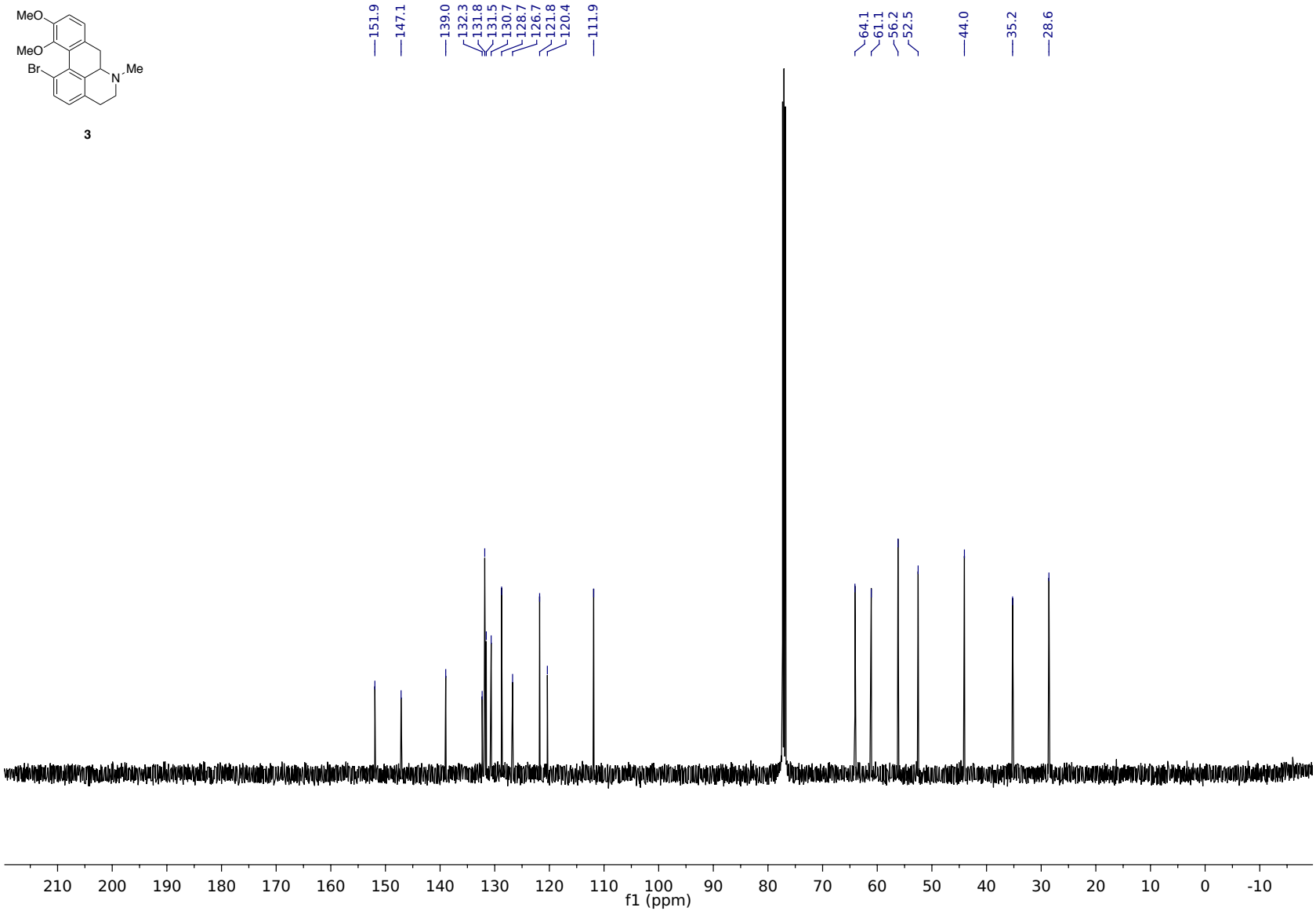

MeO
MeO
Br
NH

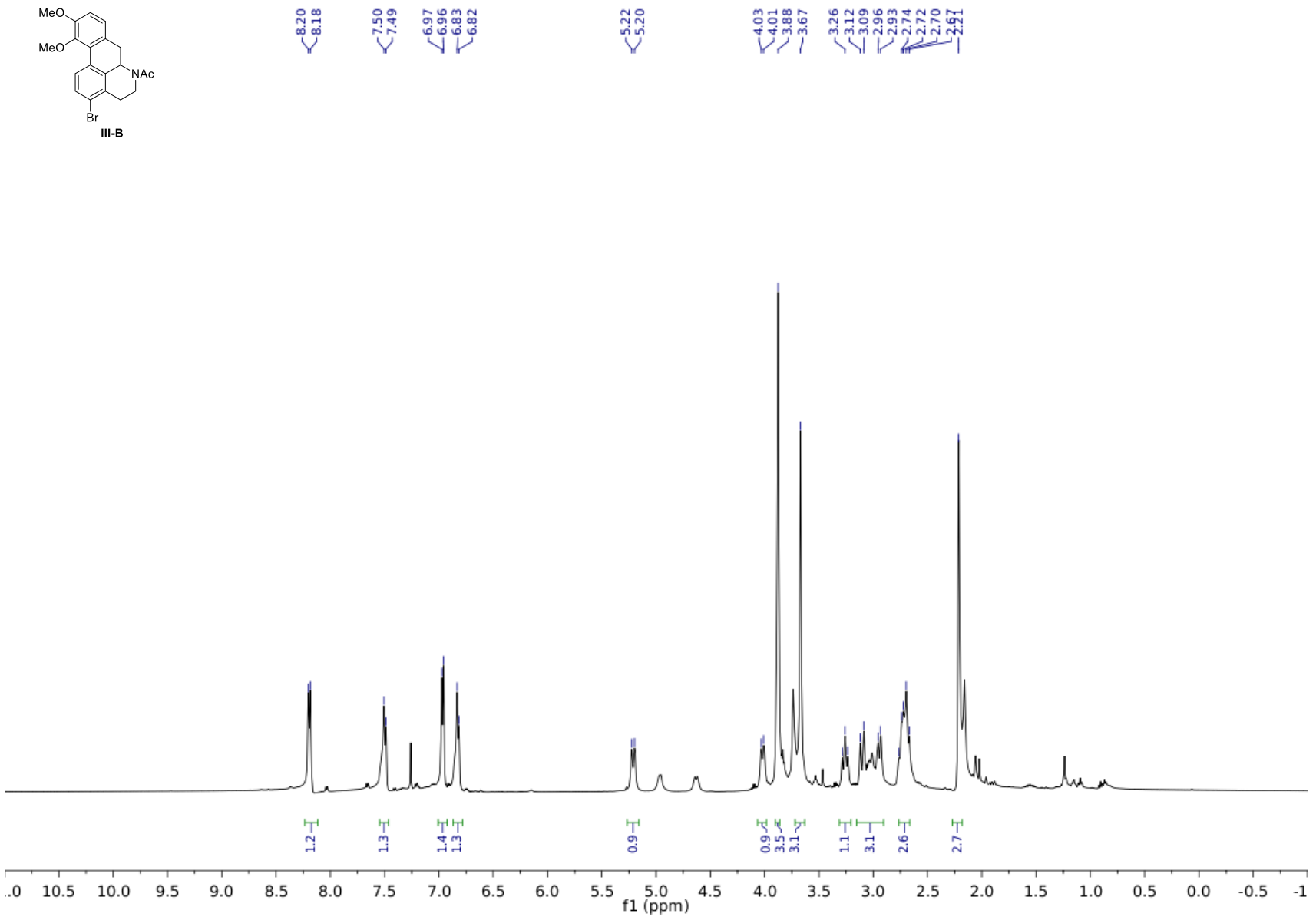
IV-A

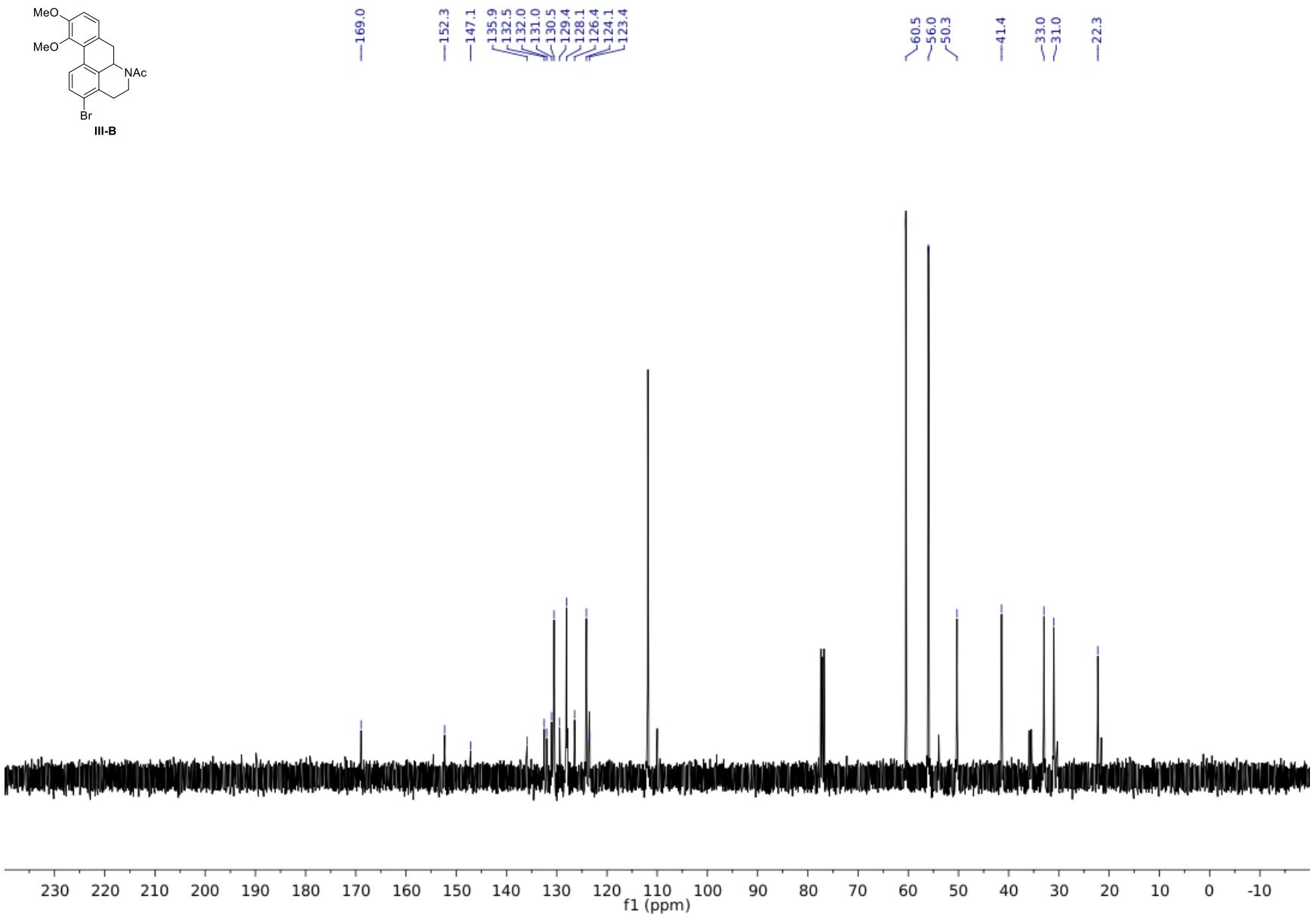
7.46
7.44
6.93
6.91
6.83
6.81
3.84
3.67
3.64
3.46
3.32
3.28
2.95
2.85
2.74
2.65
2.47
2.44
2.41
0.9
2.0
0.9
3.1
1.0
2.8
1.1
2.0
2.1
2.0
f1 (ppm)

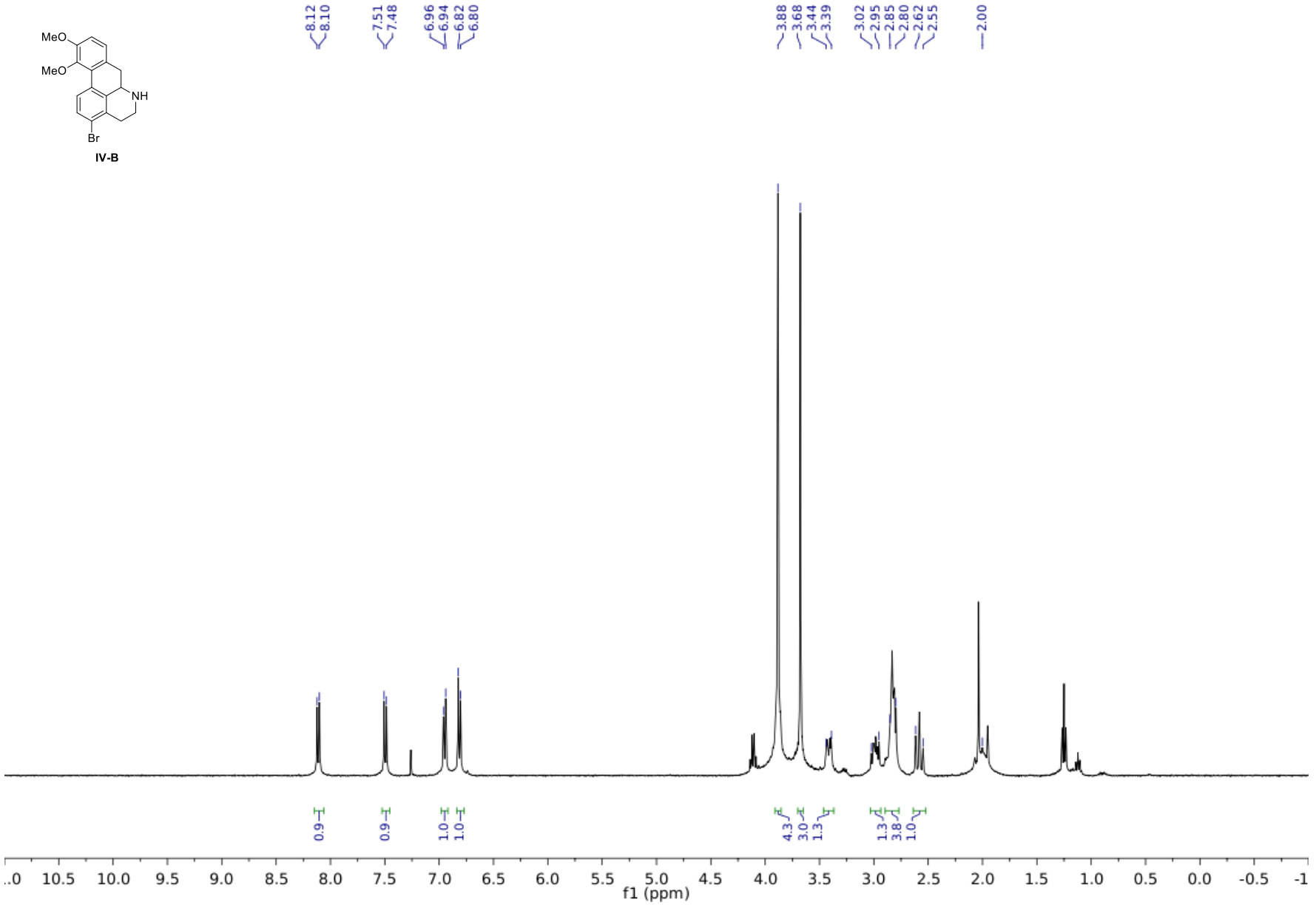

MeO
MeO
Br
NH
IV-A
151.9
147.1
140.1
132.1
131.9
131.8
130.2
129.3
126.7
121.8
120.1
111.8
61.0
56.1
55.2
42.4
37.4
28.4
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

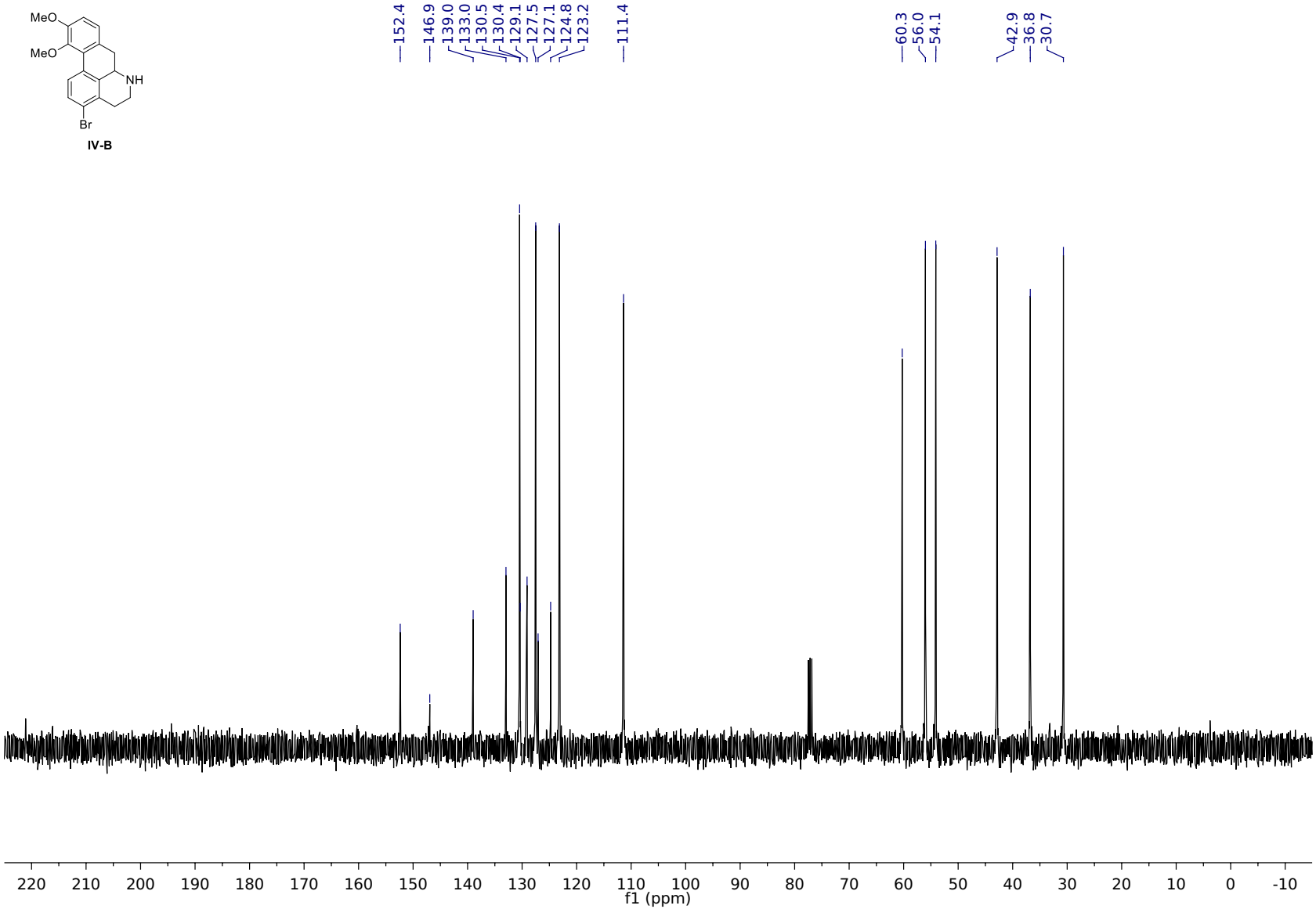

MeO
MeO
Br
N
Me
3
7.50
7.49
7.00
6.98
6.96
6.94
6.89
6.87
3.90
3.52
3.13
3.08
3.04
3.01
2.92
2.89
2.73
2.69
2.53
2.50
2.47
2.40
2.35
0.9
1.0
0.9
0.9
3.0
3.0
1.2
2.0
1.0
1.0
3.0
0.8
1.0
f1 (ppm)

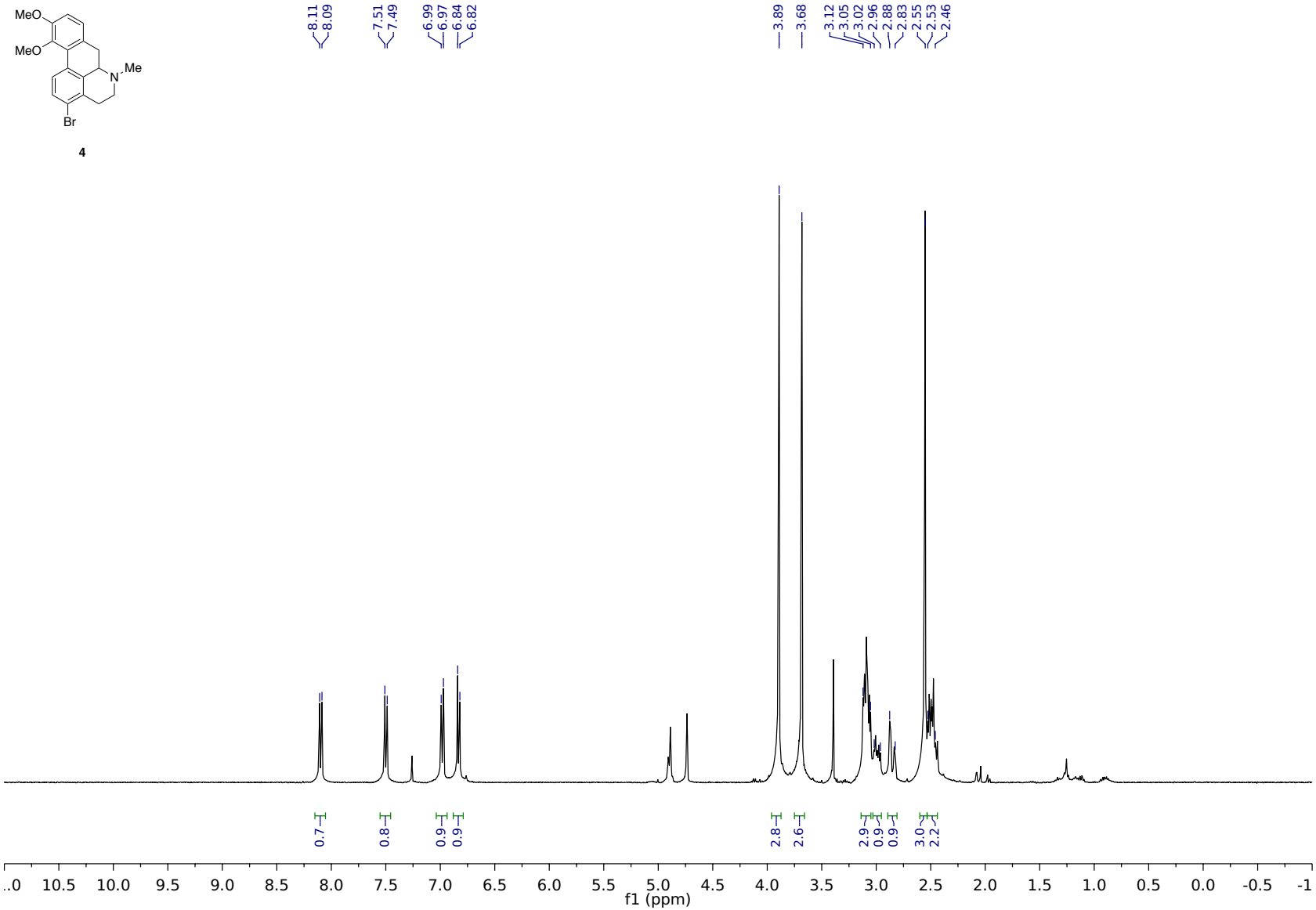

MeO
MeO
Br
N
Me
3
151.9
147.1
139.0
132.3
131.8
131.5
130.7
128.7
126.7
121.8
120.4
111.9
64.1
61.1
56.2
52.5
44.0
35.2
28.6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

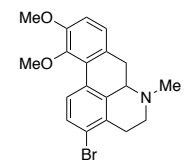

MeO
MeO
NAc
Br
III-B
8.20
8.18
7.50
7.49
6.97
6.96
6.83
6.82
5.22
5.20
4.03
4.01
3.88
3.67
3.26
3.12
3.09
2.96
2.93
2.74
2.72
2.70
2.67
2.21
1.2
1.3
1.4
1.3
0.9
0.9
3.5
3.1
1.1
3.1
2.6
2.7
f1 (ppm)


MeO
MeO
NAc
Br
III-B
169.0
152.3
147.1
135.9
132.5
132.0
131.0
130.5
129.4
128.1
126.4
124.1
123.4
60.5
56.0
50.3
41.4
33.0
31.0
22.3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


MeO
MeO
NH
Br
IV-B
8.12
8.10
7.51
7.48
6.96
6.94
6.82
6.80
3.88
3.68
3.44
3.39
3.02
2.95
2.85
2.80
2.62
2.55
2.00
0.9
0.9
1.0
1.0
4.3
3.0
1.3
1.3
3.8
1.0
f1 (ppm)

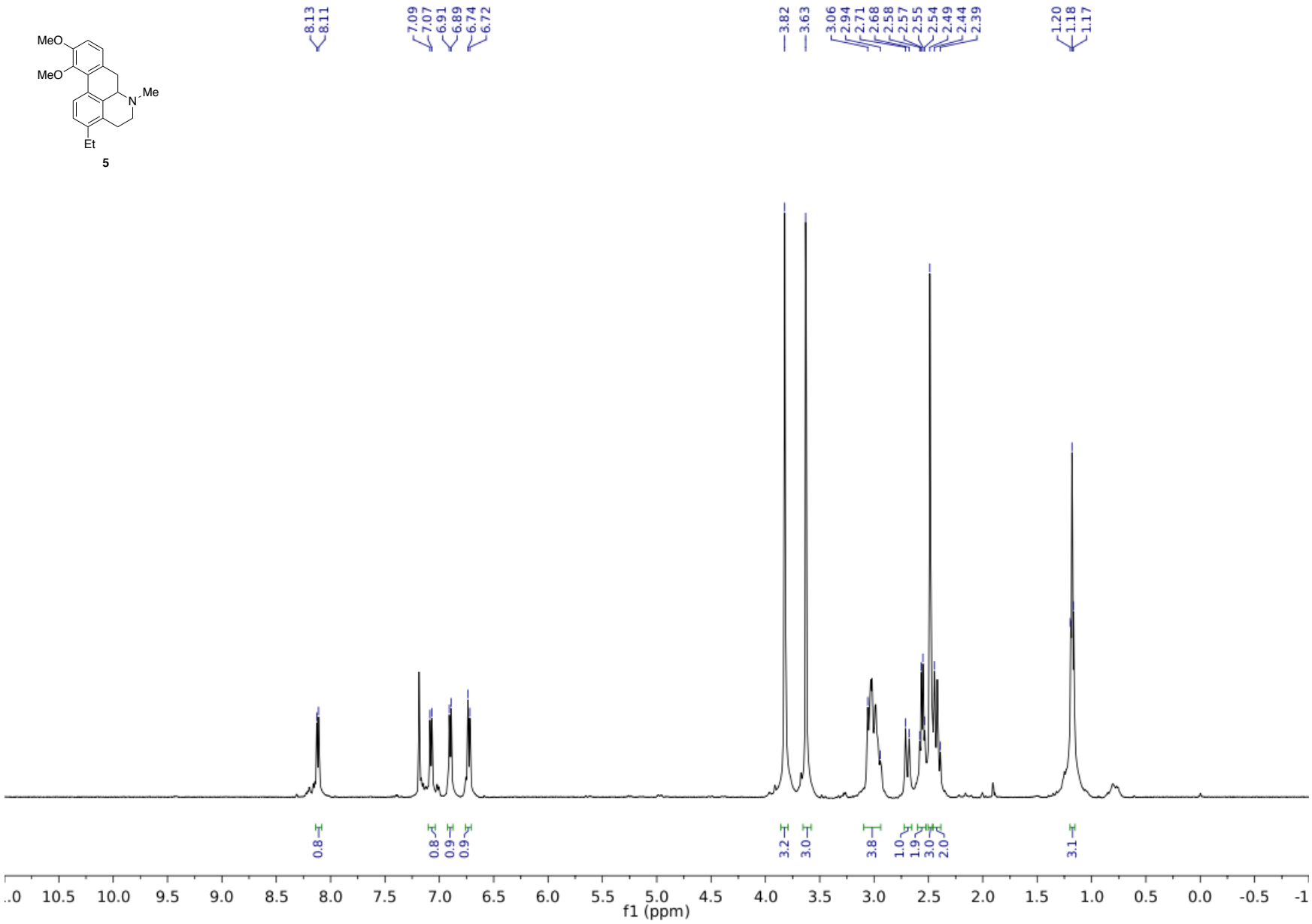

MeO
MeO
NH
Br
IV-B
152.4
146.9
139.0
133.0
130.5
130.4
129.1
127.5
127.1
124.8
123.2
111.4
60.3
56.0
54.1
42.9
36.8
30.7
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

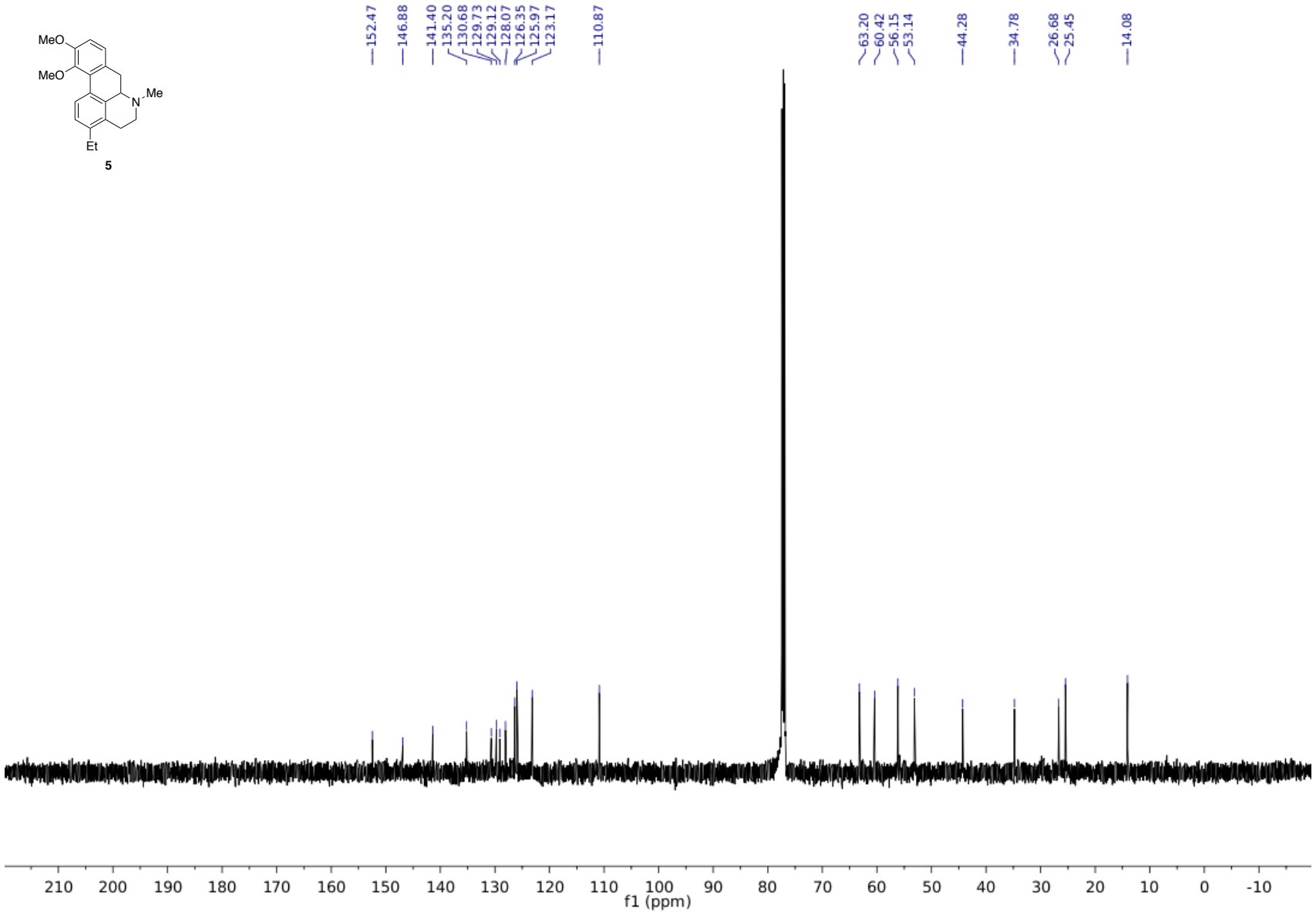

MeO
MeO
N
Me
Br
4
8.11
8.09
7.51
7.49
6.99
6.97
6.84
6.82
3.89
3.68
3.12
3.05
3.02
2.96
2.88
2.83
2.55
2.53
2.46
0.7
0.8
0.9
0.9
2.8
2.6
2.9
0.9
0.9
3.0
2.2
f1 (ppm)

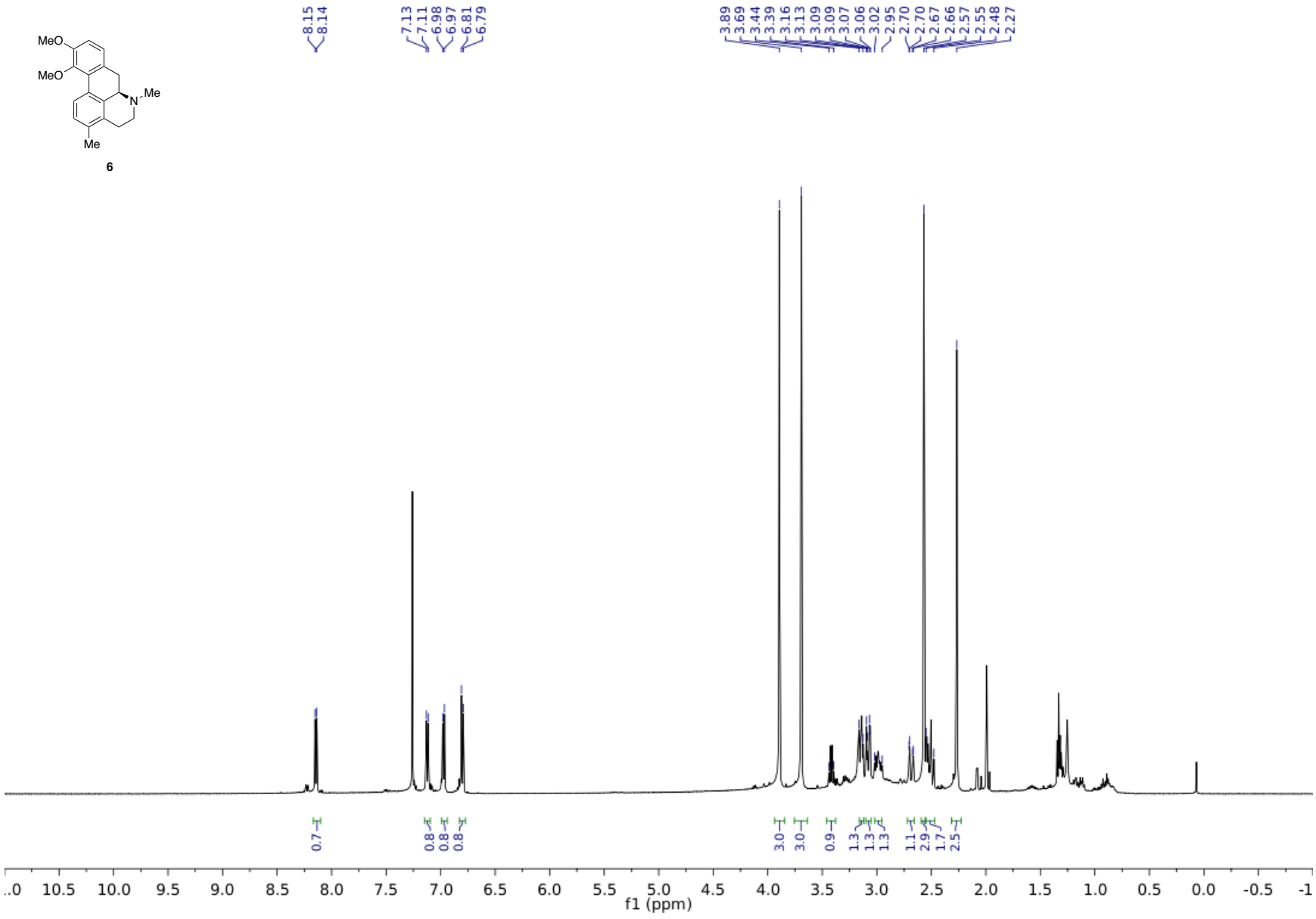

MeO
MeO
N
Me
Br

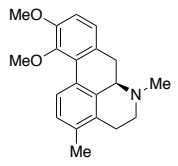
4

152.4
146.7
137.5
132.6
130.7
130.3
129.2
127.5
127.0
124.2
123.2
111.4
62.6
60.3
56.0
52.7
43.9
34.3
30.5
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


MeO
MeO
N
Me
Et
5
8.13
8.11
7.09
7.07
6.91
6.89
6.74
6.72
3.82
3.63
3.06
2.94
2.71
2.68
2.58
2.57
2.55
2.54
2.49
2.44
2.39
1.20
1.18
1.17
0.8
0.8
0.9
0.9
3.2
3.0
3.8
1.0
1.9
3.0
2.0
3.1
f1 (ppm)

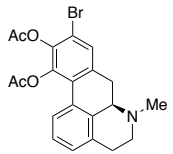

MeO
MeO
N
Me
Et
5
152.47
146.88
141.40
135.20
130.68
129.73
129.12
128.07
126.35
125.97
123.17
110.87
63.20
60.42
56.15
53.14
44.28
34.78
26.68
25.45
14.08
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


MeO
MeO
N
Me
Me
6
8.15
8.14
7.13
7.11
6.98
6.97
6.81
6.79
3.89
3.69
3.44
3.39
3.16
3.13
3.09
3.09
3.07
3.06
3.02
2.95
2.70
2.70
2.67
2.66
2.57
2.55
2.48
2.27
0.7
0.8
0.8
0.8
3.0
3.0
0.9
1.3
1.3
1.3
1.1
2.9
1.7
2.5
f1 (ppm)


MeO
MeO
N
Me
Me

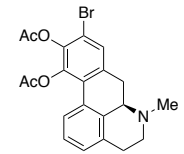
6

152.26
146.62
135.54
134.66
131.06
129.28
128.95
125.91
122.99
110.66
62.68
60.12
55.92
52.70
43.77
34.38
26.91
19.11
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Br
AcO
AcO
N
Me

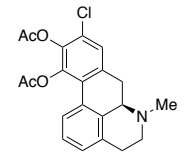
7

7.71
7.70
7.38
7.22
7.21
7.20
7.18
7.13
7.11
3.68
3.67
3.64
3.63
3.19
3.16
2.78
2.74
2.73
2.60
2.57
2.56
2.54
2.53
2.40
2.35
2.31
2.25
0.8
0.5
1.3
1.1
1.0
2.1
1.3
1.3
3.0
1.3
1.3
2.9
3.0
f1 (ppm)


Br
AcO
AcO
N
Me

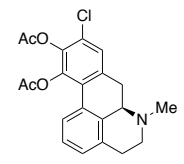
7

168.2
167.7
142.2
138.7
135.3
135.1
133.5
130.8
129.9
129.3
126.4
125.9
125.0
120.5
61.4
52.9
44.2
34.3
29.1
20.9
20.8
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Cl
AcO
AcO
N
Me

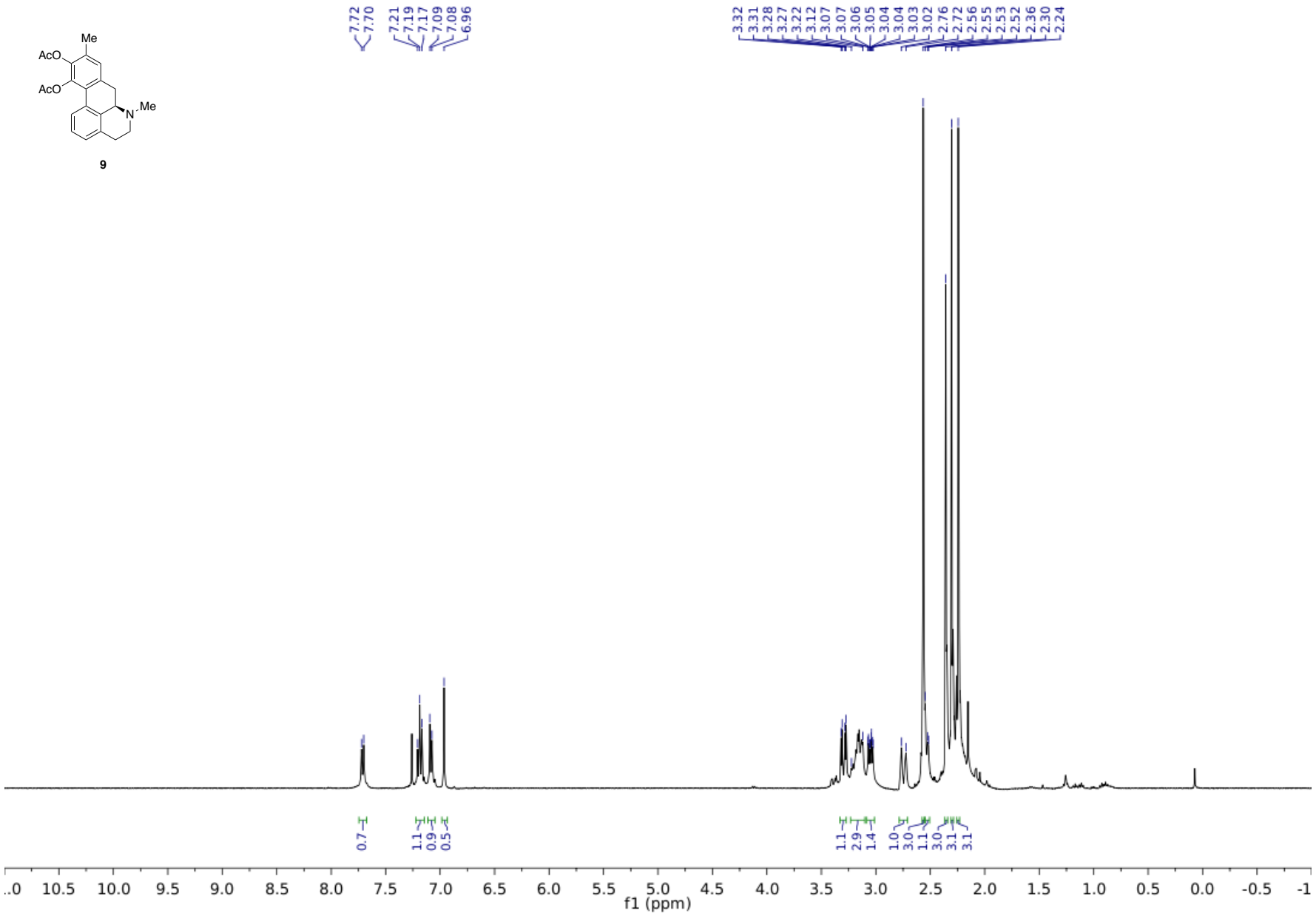
8

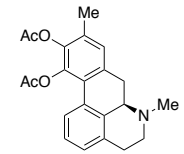
7.72
7.70
7.22
7.21
7.21
7.20
7.18
7.13
7.13
7.11
3.70
3.69
3.66
3.65
3.18
3.17
3.16
3.14
3.07
3.07
3.06
3.06
3.04
3.04
3.03
2.78
2.77
2.73
2.73
2.72
2.58
2.55
2.54
2.52
2.51
2.31
2.25
1.0
1.9
1.1
1.3
2.9
1.2
1.3
3.1
1.2
3.2
3.2
f1 (ppm)


Cl
AcO
AcO
N
Me

8

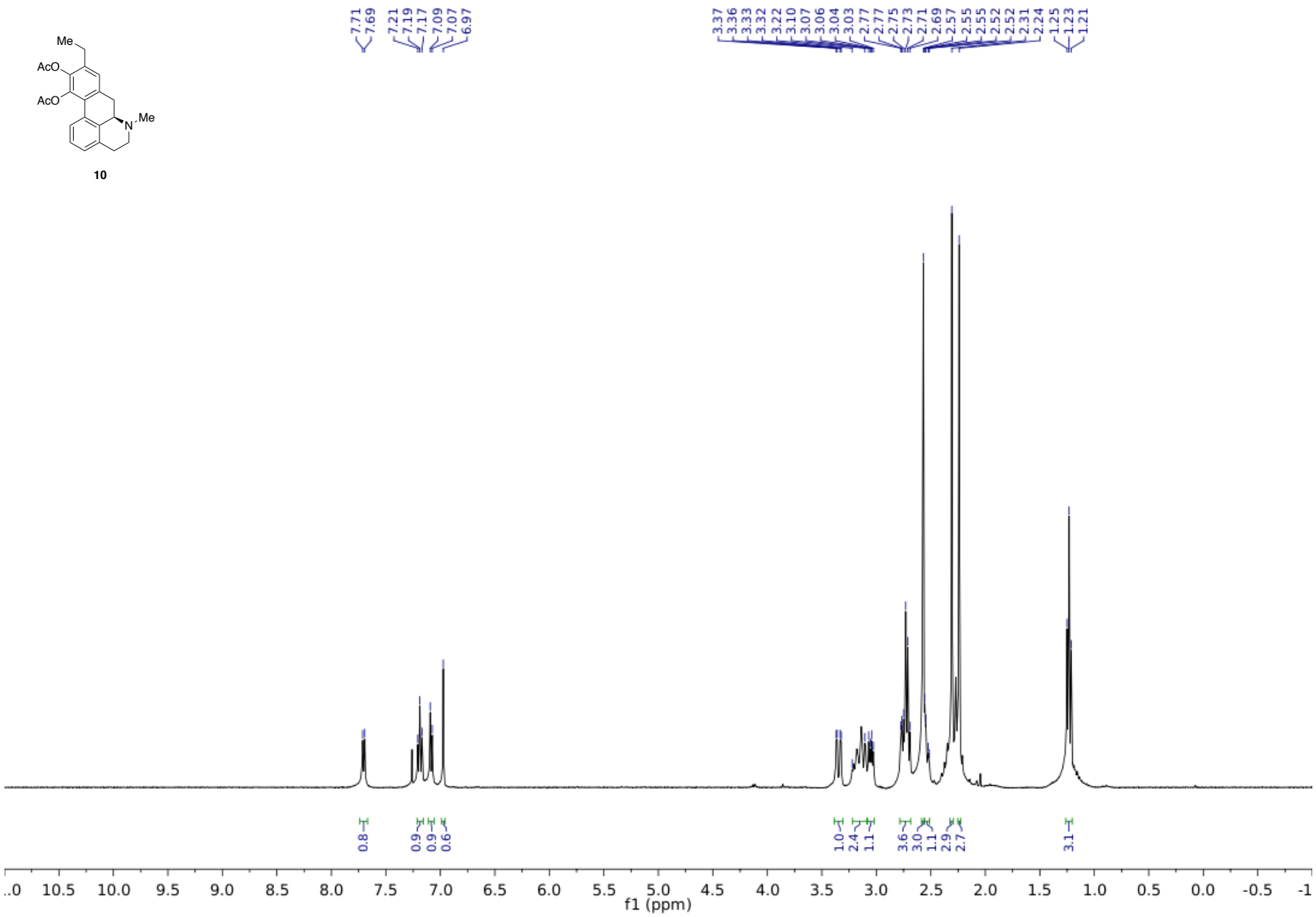
168.1
167.7
142.0
138.0
135.2
133.5
133.2
130.6
130.4
129.8
129.2
126.4
124.9
122.8
61.2
52.8
44.1
31.1
29.0
20.8
20.7
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

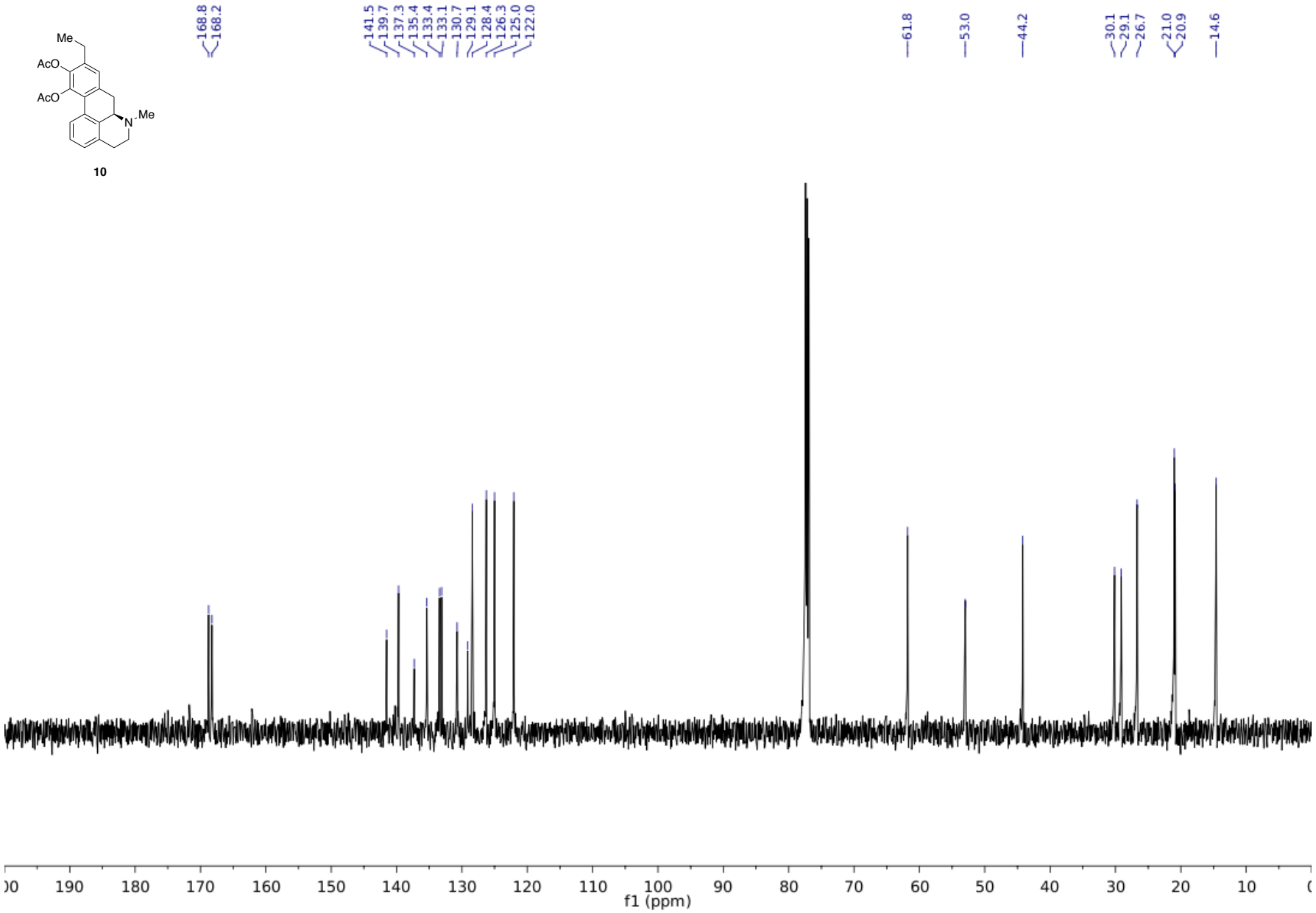

Me
AcO
AcO
N
Me
9
7.72
7.70
7.21
7.19
7.17
7.09
7.08
6.96
3.32
3.31
3.28
3.27
3.22
3.12
3.07
3.07
3.06
3.05
3.04
3.04
3.03
3.02
2.76
2.72
2.56
2.55
2.53
2.52
2.36
2.30
2.24
0.7
1.1
0.9
0.5
1.1
2.9
1.4
1.0
3.0
1.1
3.0
3.1
3.1
f1 (ppm)

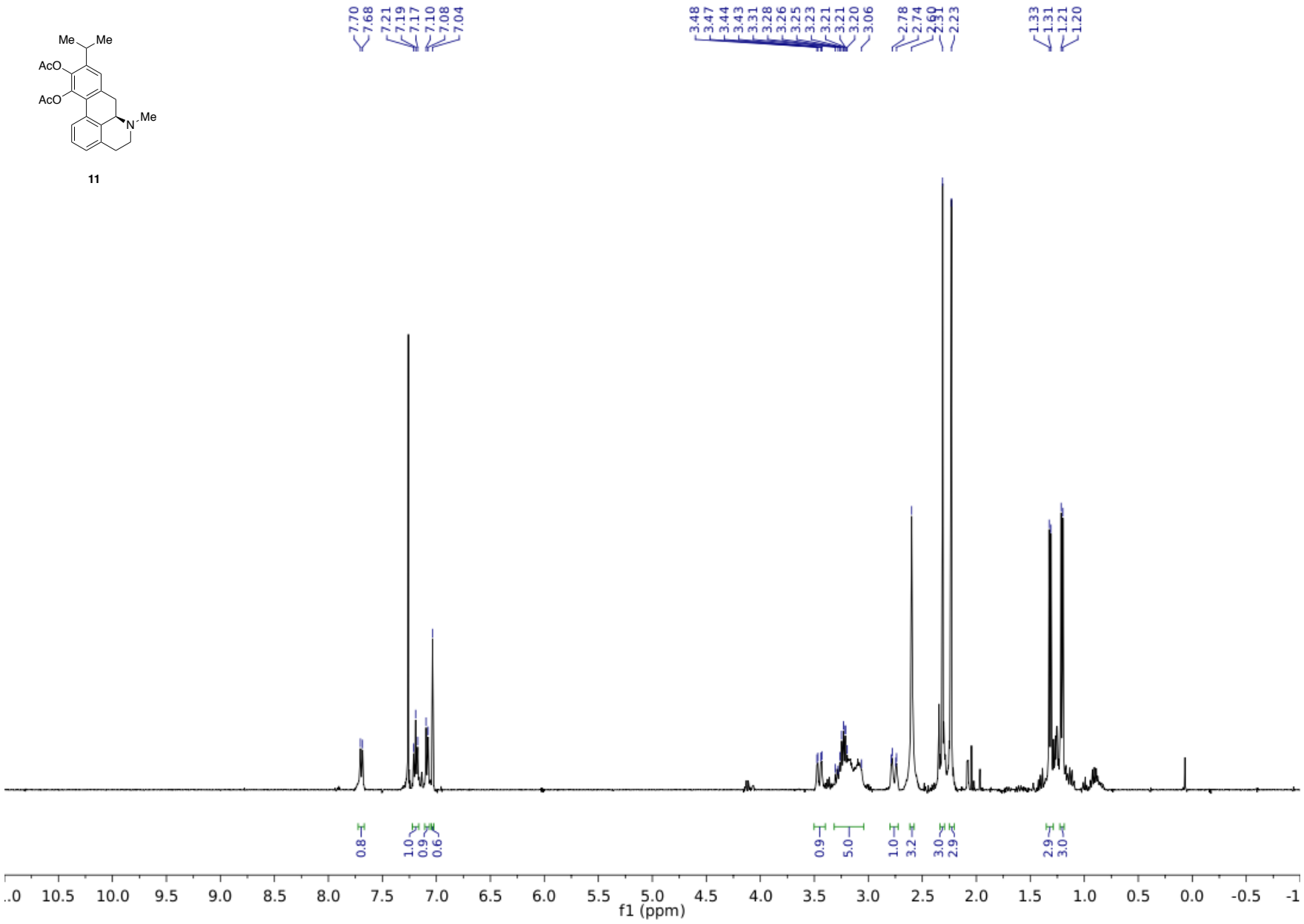

Me
AcO
AcO
N
Me

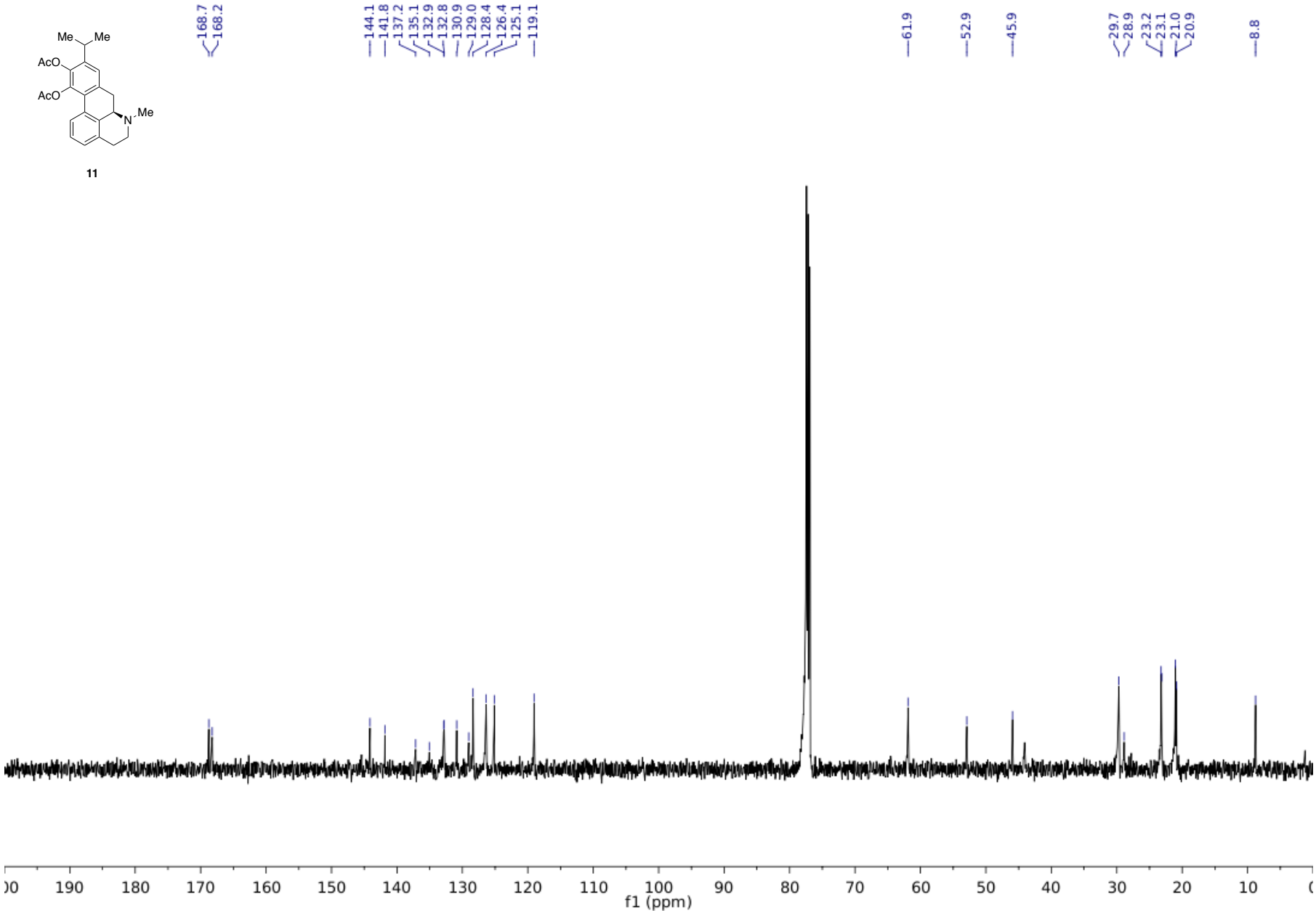
9

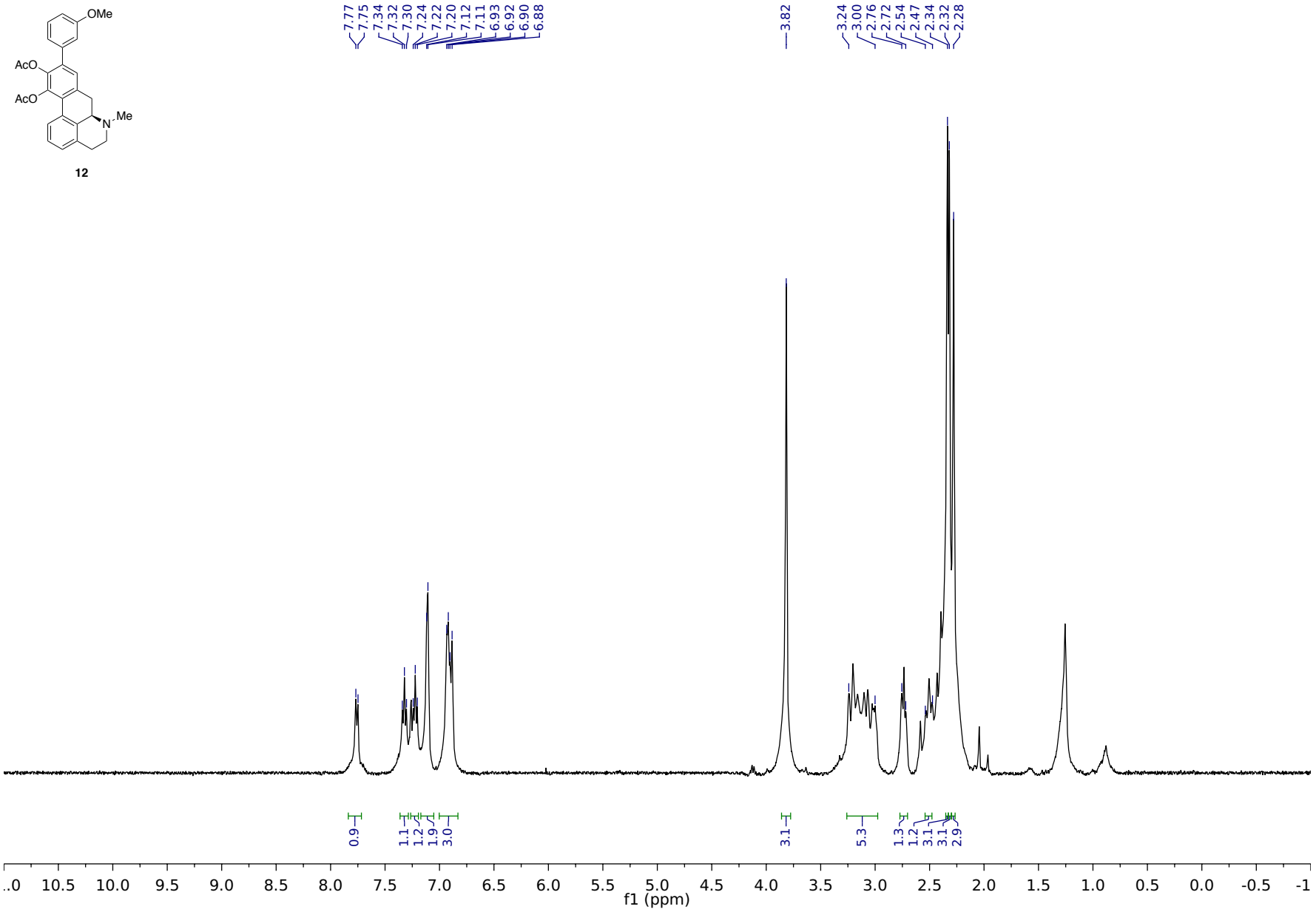
168.8
168.2
141.2
137.3
135.1
133.9
133.7
133.1
130.6
128.9
128.5
126.3
125.0
123.6
61.6
52.9
44.1
30.5
29.0
20.9
20.8
20.0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

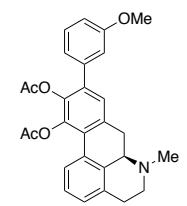

Me
AcO
AcO
N
Me
10
7.71
7.69
7.21
7.19
7.17
7.09
7.07
6.97
3.37
3.36
3.33
3.32
3.22
3.10
3.07
3.06
3.04
3.03
2.77
2.77
2.75
2.73
2.71
2.69
2.57
2.55
2.55
2.52
2.52
2.31
2.24
1.25
1.23
1.21
0.8
0.9
0.9
0.6
1.0
2.4
1.1
3.6
3.0
1.1
2.9
2.7
3.1
f1 (ppm)


Me
AcO
AcO
N
Me
10
168.8
168.2
141.5
139.7
137.3
135.4
133.4
133.1
130.7
129.1
128.4
126.3
125.0
122.0
61.8
53.0
44.2
30.1
29.1
26.7
21.0
20.9
14.6
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


Me
Me
AcO
AcO
N
Me
11
7.70
7.68
7.21
7.19
7.17
7.10
7.08
7.04
3.48
3.47
3.44
3.43
3.31
3.28
3.26
3.25
3.23
3.21
3.21
3.20
3.06
2.78
2.74
2.60
2.51
2.23
1.33
1.31
1.21
1.20
0.8
1.0
0.9
0.6
0.9
5.0
1.0
3.2
3.0
2.9
2.9
3.0
f1 (ppm)

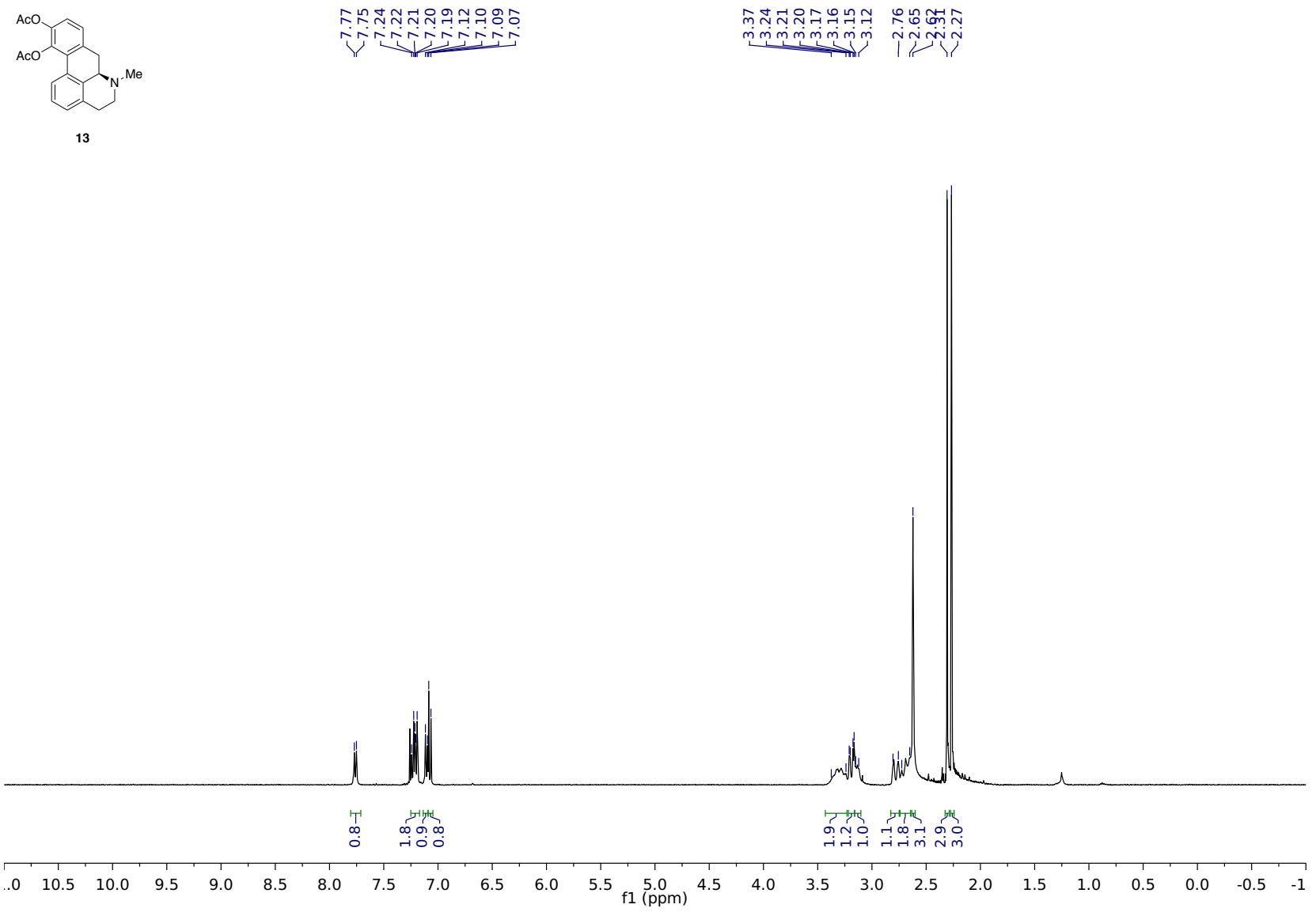

Me
Me
AcO
AcO
N
Me
11
168.7
168.2
144.1
141.8
137.2
135.1
132.9
132.8
130.9
129.0
128.4
126.4
125.1
119.1
61.9
52.9
45.9
29.7
28.9
23.2
23.1
21.0
20.9
8.8
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

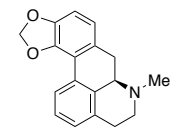

OMe
AcO
AcO
N
Me
12
7.77
7.75
7.34
7.32
7.30
7.24
7.22
7.20
7.12
7.11
6.93
6.92
6.90
6.88
3.82
3.24
3.00
2.76
2.72
2.54
2.47
2.34
2.32
2.28
0.9
1.1
1.2
1.9
3.0
3.1
5.3
1.3
1.2
3.1
2.9
f1 (ppm)


OMe
AcO
AcO
N
Me

12

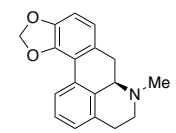
168.6
168.2
159.5
141.2
139.5
133.2
133.1
130.6
129.6
129.4
128.7
126.4
125.1
123.4
114.7
113.7
61.9
55.4
52.8
44.0
32.4
29.0
21.0
20.8
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


AcO
AcO
N
Me
13
7.77
7.75
7.24
7.22
7.21
7.20
7.19
7.12
7.10
7.09
7.07
3.37
3.24
3.21
3.20
3.17
3.16
3.15
3.12
2.76
2.65
2.62
2.31
2.27
0.8
1.8
0.9
0.8
1.9
1.2
1.0
1.1
1.8
3.1
2.9
3.0
f1 (ppm)


O
O
N
Me

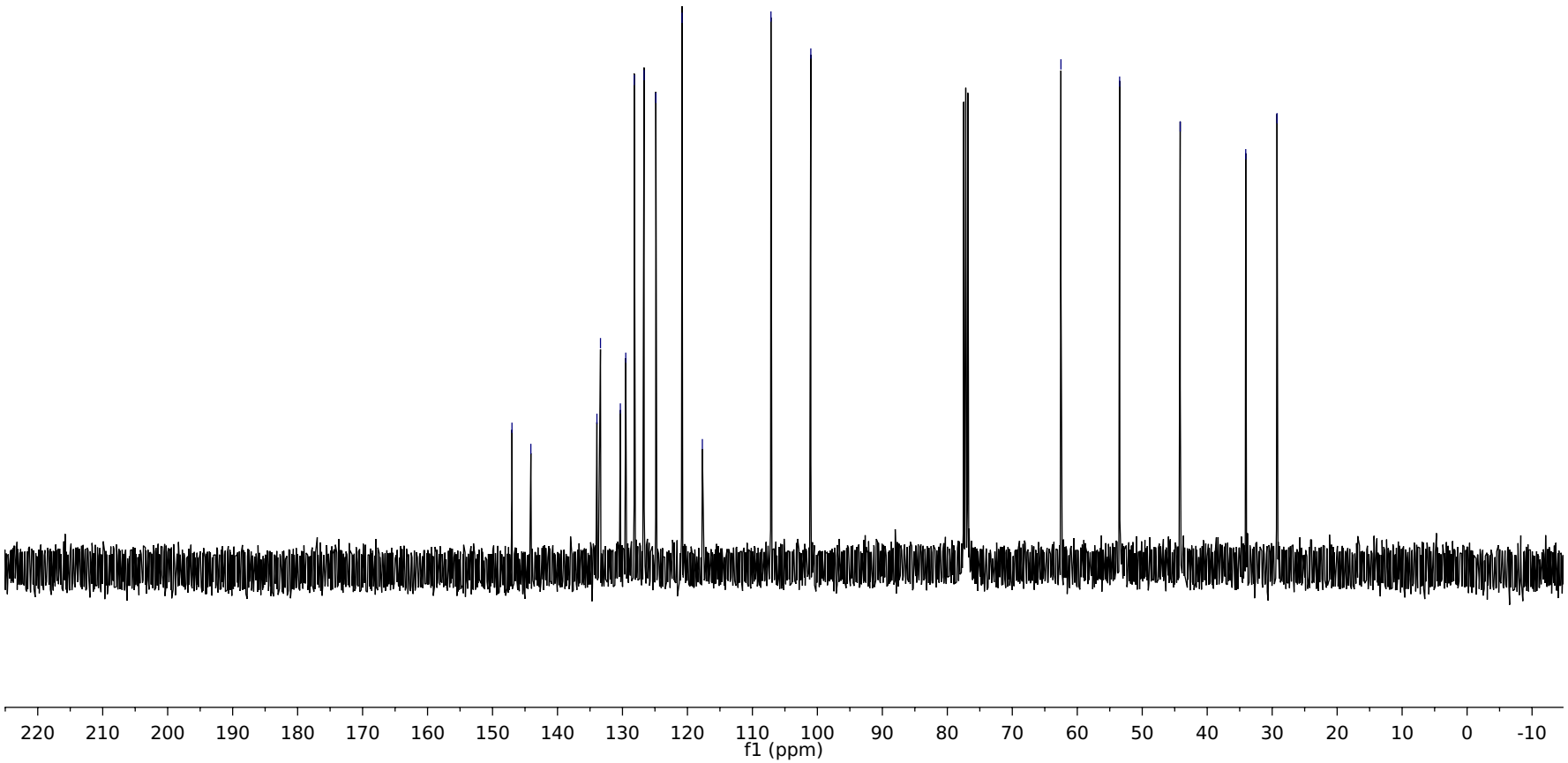
14

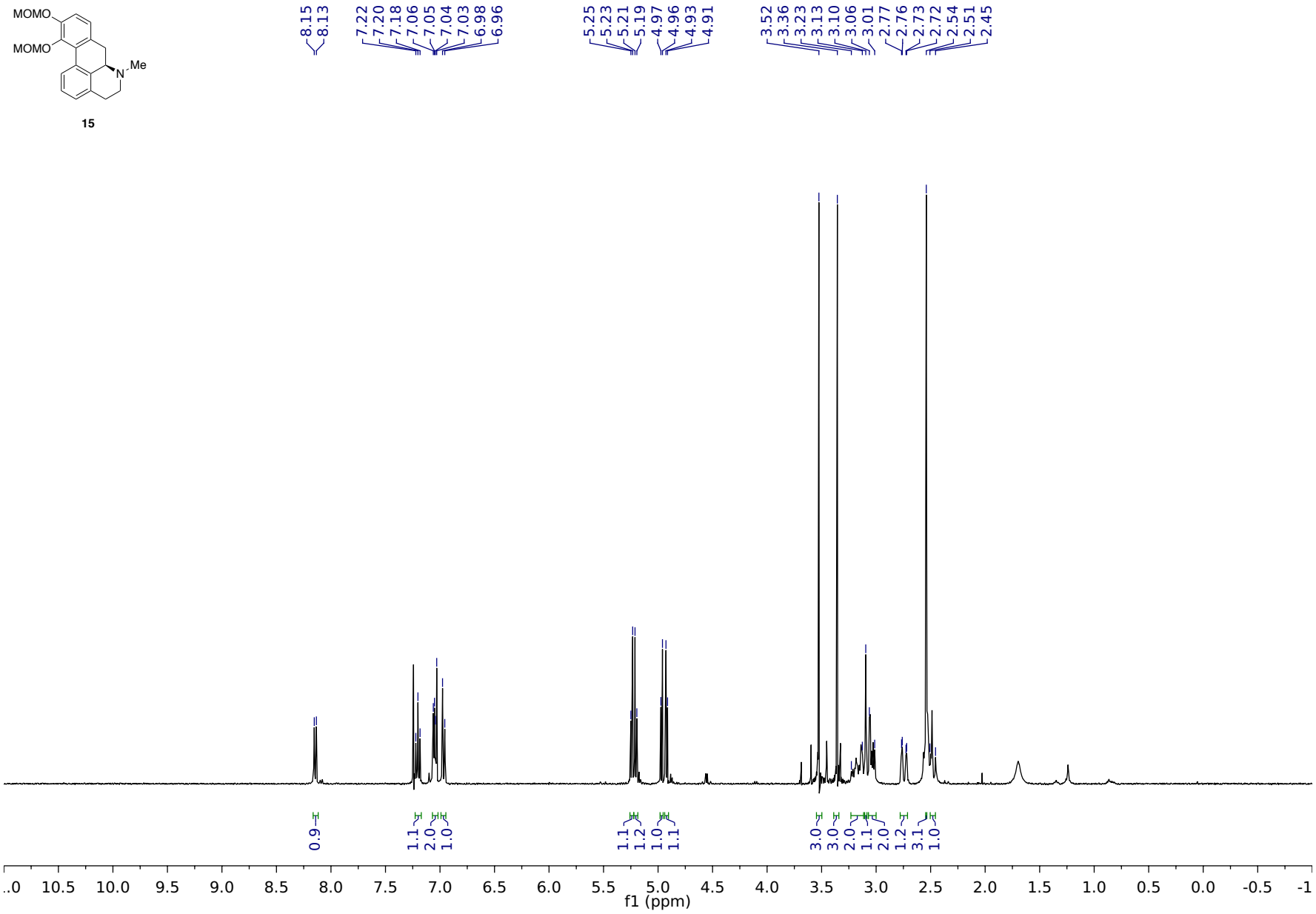
7.94
7.92
7.26
7.25
7.23
7.08
7.07
6.76
6.74
6.72
6.70
6.12
5.98
3.25
3.16
3.14
3.13
3.10
3.05
2.79
2.78
2.74
2.74
2.65
2.58
2.56
0.9
0.9
1.0
1.0
0.9
1.0
1.0
2.9
0.9
1.2
1.1
1.2
3.1
f1 (ppm)

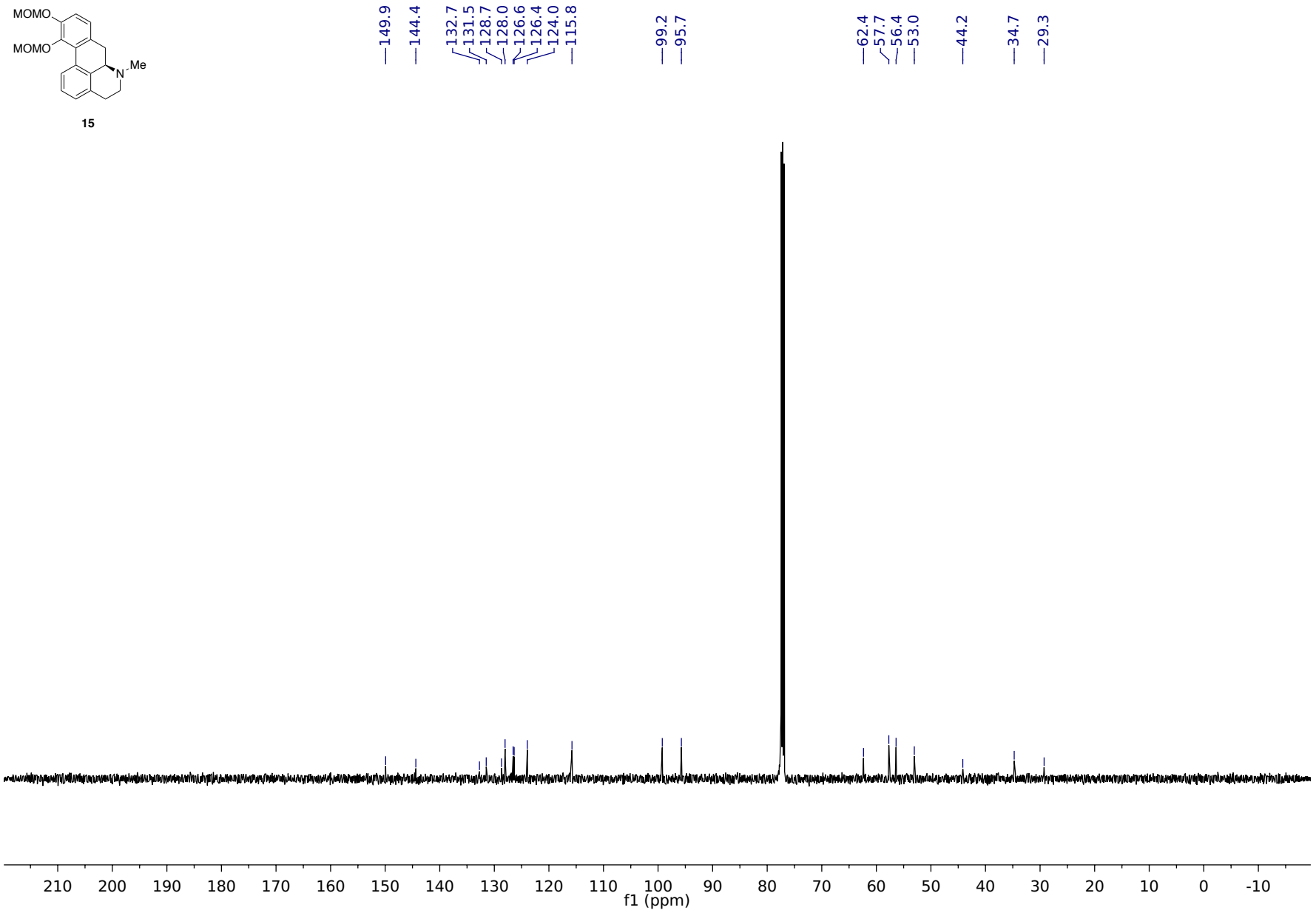


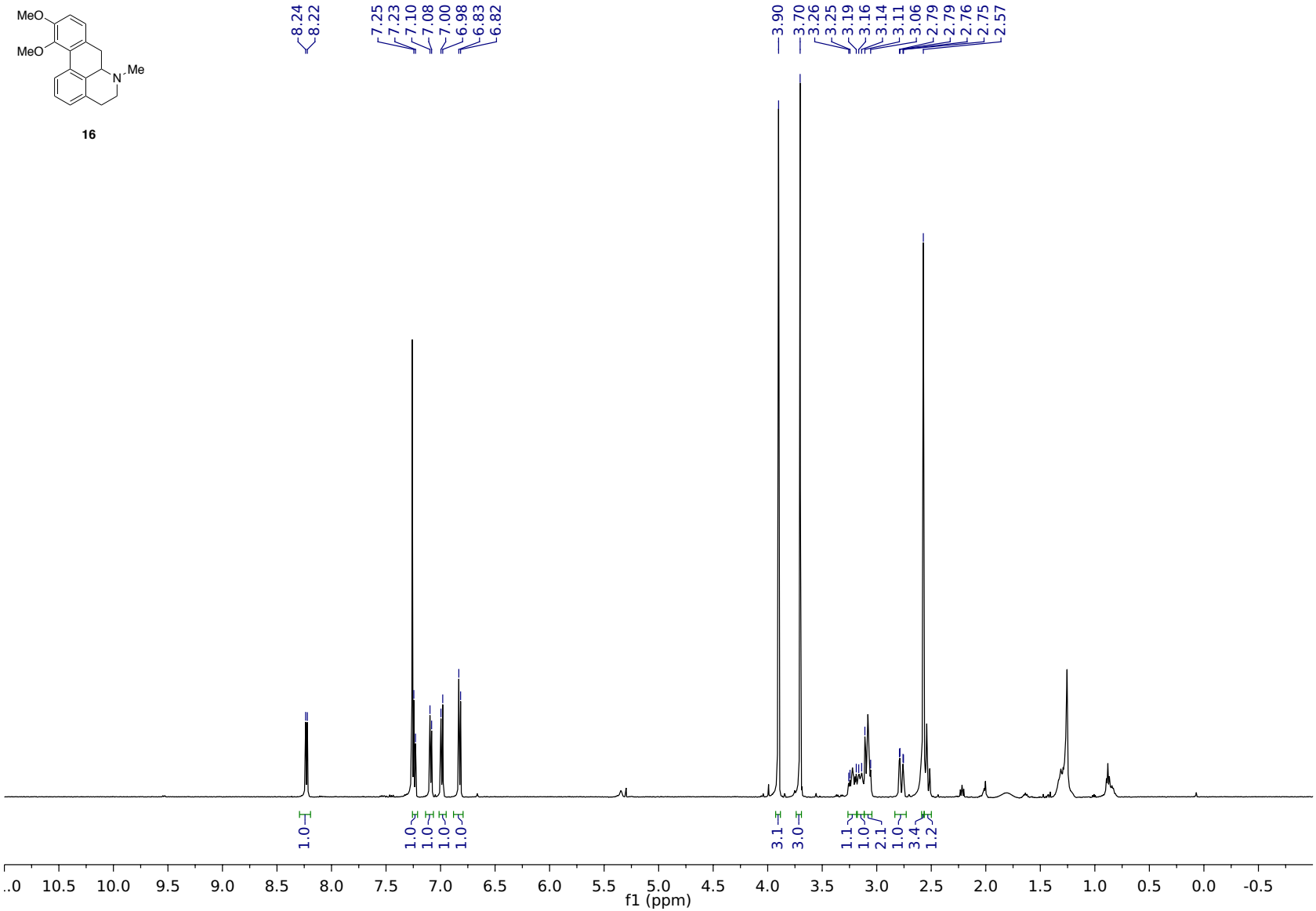
14

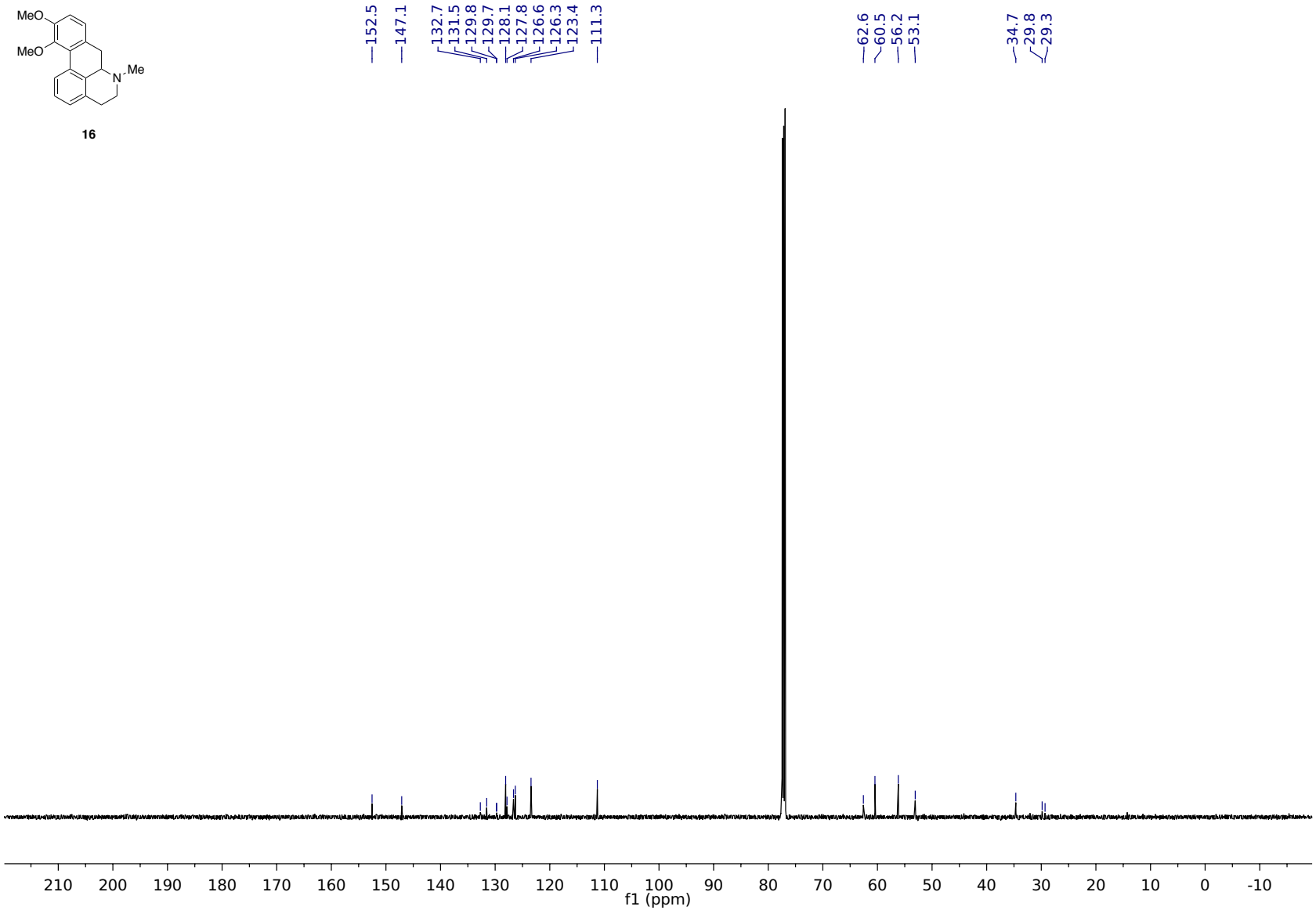
147.0
144.1
133.9
133.4
130.3
129.5
128.2
126.7
124.9
120.8
117.7
107.1
101.0
62.5
53.5
44.2
34.1
29.3

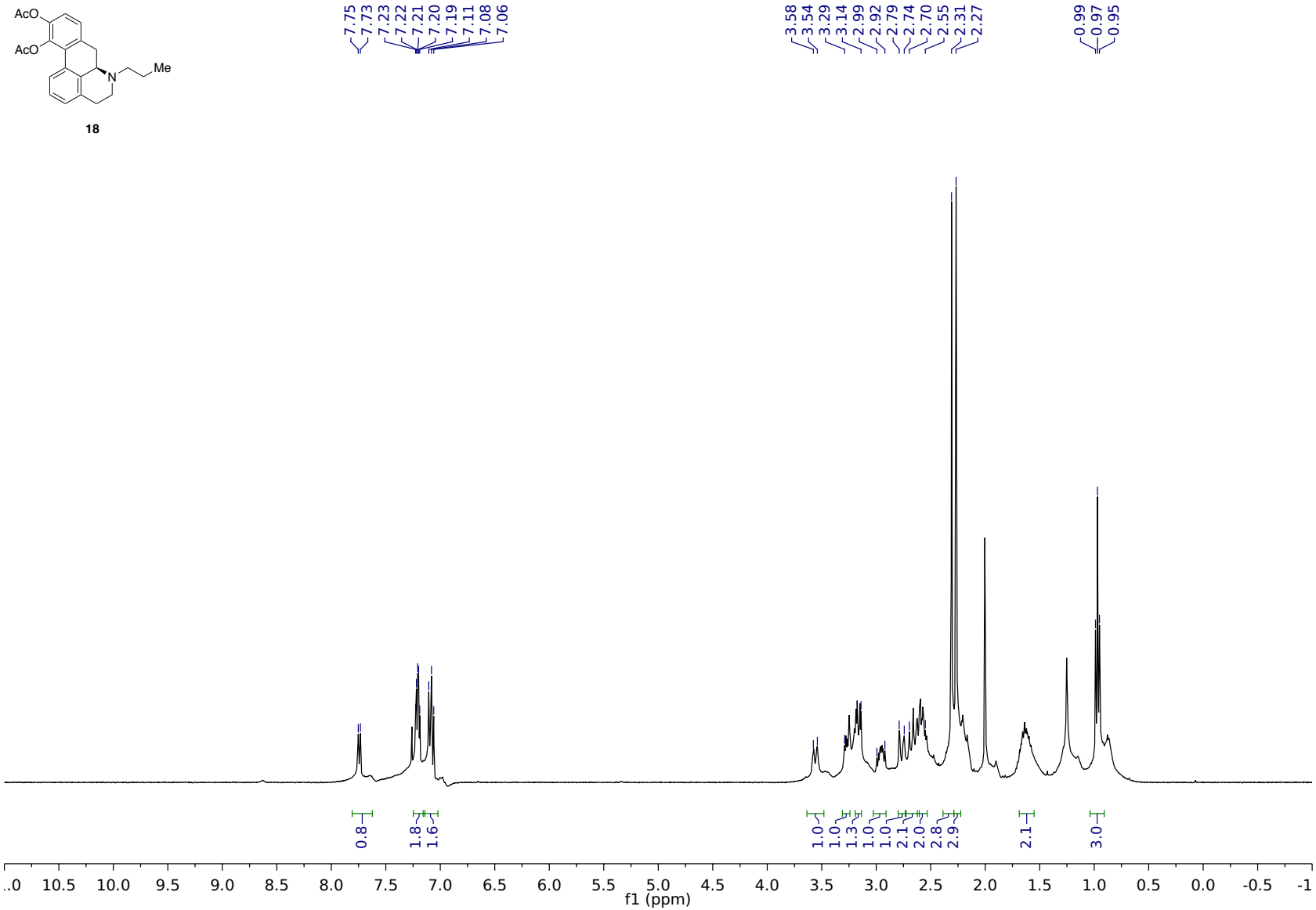


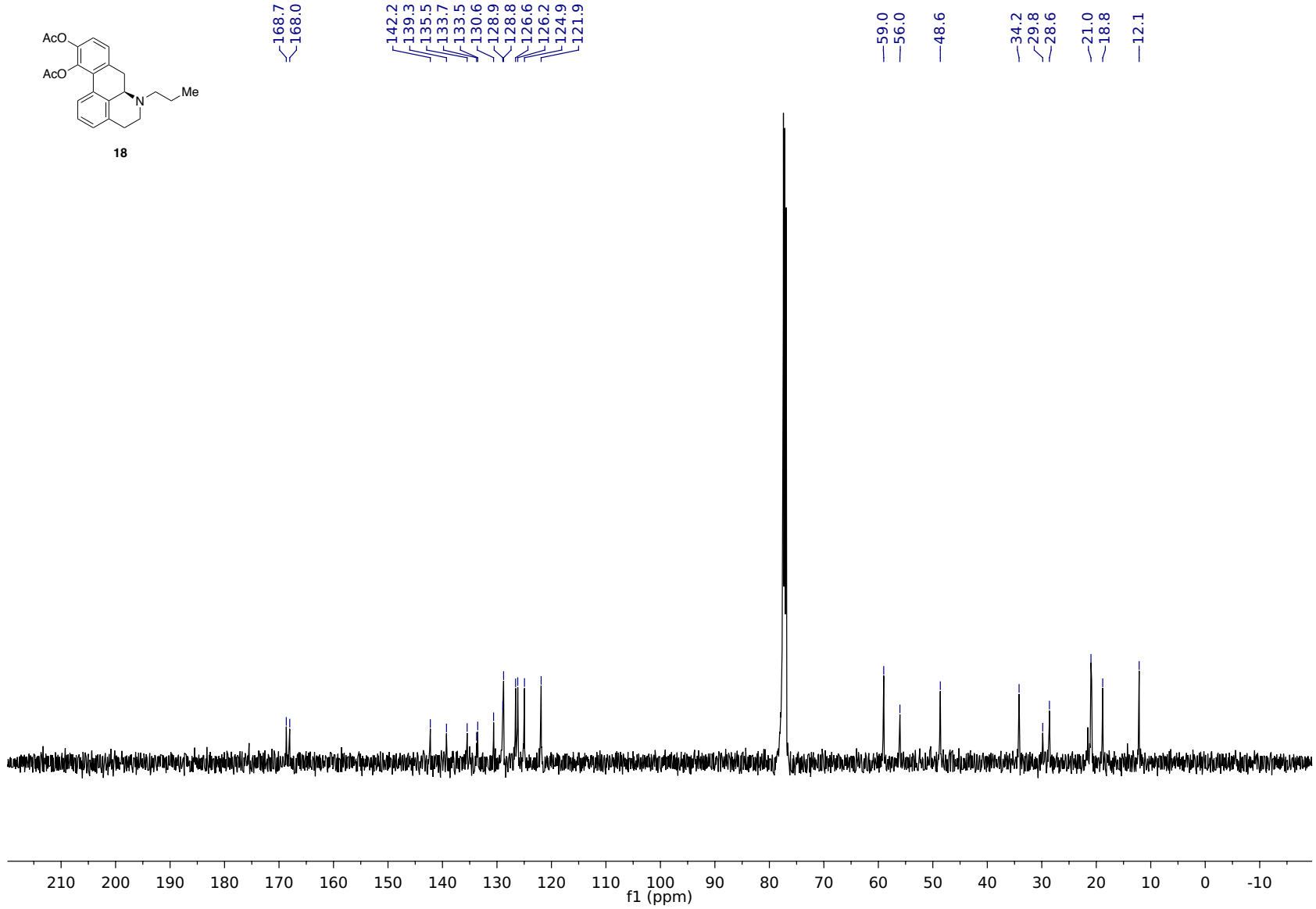

MOMO
MOMO
N
Me
15
8.15
8.13
7.22
7.20
7.18
7.06
7.05
7.04
7.03
6.98
6.96
5.25
5.23
5.21
5.19
4.97
4.96
4.93
4.91
3.52
3.36
3.23
3.13
3.10
3.06
3.01
2.77
2.76
2.73
2.72
2.54
2.51
2.45
0.9
1.1
2.0
1.0
1.1
1.2
1.0
1.1
3.0
3.0
2.0
1.1
2.0
1.2
3.1
1.0
f1 (ppm)


MOMO
MOMO
N
Me
15
149.9
144.4
132.7
131.5
128.7
128.0
126.6
126.4
124.0
115.8
99.2
95.7
62.4
57.7
56.4
53.0
44.2
34.7
29.3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


MeO
MeO
N
Me
16
8.24
8.22
7.25
7.23
7.10
7.08
7.00
6.98
6.83
6.82
3.90
3.70
3.26
3.25
3.19
3.16
3.14
3.11
3.06
2.79
2.79
2.76
2.75
2.57
1.0
1.0
1.0
1.0
1.0
3.1
3.0
1.1
1.0
2.1
1.0
3.4
1.2
f1 (ppm)


MeO
MeO
N
Me
16
152.5
147.1
132.7
131.5
129.8
129.7
128.1
127.8
126.6
126.3
123.4
111.3
62.6
60.5
56.2
53.1
34.7
29.8
29.3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


AcO
AcO
N
Me
18
7.75
7.73
7.23
7.22
7.21
7.20
7.19
7.11
7.08
7.06
3.58
3.54
3.29
3.14
2.99
2.92
2.79
2.74
2.70
2.55
2.31
2.27
0.99
0.97
0.95
0.8
1.8
1.6
1.0
1.0
1.3
1.0
1.0
2.1
2.0
2.8
2.9
2.1
3.0
f1 (ppm)


AcO
AcO
N
Me
18
168.7
168.0
142.2
139.3
135.5
133.7
133.5
130.6
128.9
128.8
126.6
126.2
124.9
121.9
59.0
56.0
48.6
34.2
29.8
28.6
21.0
18.8
12.1
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)