Supporting Information for

Enantioselective Pictet-Spengler Reactions of Isatins for the Synthesis of Spiroindolones

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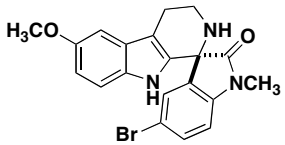
Experimental Section

General Information: All reactions were performed in oven-dried and argon-purged glassware. Na_2SO_4 was activated in a vacuum chamber by heating them with a heat gun for ~15 min. All ^1H and ^{13}C spectra were recorded at ambient temperature at 400 (or 300, 600) and 100 (or 75, 150) MHz, respectively. The ^1H spectral data are reported as follows: chemical shift in parts per million downfield from tetramethylsilane on the δ scale, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; s, septet; m, multiplet; dd, doublet of doublets, dt doublets of triplets, td triplet of doublets, and bs, broad singlet), coupling constant (Hz), and integration. Carbon NMR chemical shifts are reported in ppm from tetramethylsilane with the solvent reference employed as the internal standard (deuterochloroform ($CDCl_3$) at 77.0 ppm).

All HPLC analyses were performed on a Shimadzu LC-20AB system with a Daicel CHIRALPAK® AD-H column (4.6 x 250 mm, 5 μm) or CHIRALPAK® OD-H column (4.6 x 250 mm, 5 μm) with a flow rate of 0.8 mL/min, unless otherwise indicated, (isopropanol/hexanes isocratic system) using Shimadzu SPD-M20A photodiode array detector and 25-40 °C column oven temperature. Compounds were analyzed for HRMS on a Thermo Fisher Orbitrap (San Jose, CA) using electrospray in the positive ion mode at >60,000 resolution and using typical ESI source values. These settings result in mass accuracies <5ppm. Compounds analyzed for MS (ESI) by an Applied Biosystems Qtrap (Foster City, CA) in the positive ion mode. Source parameters were 5kV spray voltage, with a curtain plate temperature of 275 ˚C and sheath gas setting of 15. Samples were analyzed via flow injection analysis by injecting 20 mL samples into a stream of 50% MeOH/20% aqueous formic acid (0.1%) flowing at 200 mL/min. When indicated, the progress of reactions was monitored by analytical thin layer chromatography using glass or aluminum backed plates pre-coated with EMD silica gel 60 F254 and visualized with UV light. Flash chromatography was performed either on Acros silica gel 60 Å (0.035-0.070 mm), Aldrich silica gel 150 Å grade 62 (60-200 mesh), or using a CombiFlash Companion system (Teledyne ISCO, Inc.) with pre-packed FLASH silica columns (RediSep, Rf® and RediSep, Rf® GOLD). Reactions at –15 °C were run in a low-temp freezer. Infrared spectra were recorded on a FTIR spectrophotometer Mattson Genesis II or Bruker Tensor 27. Optical rotations were obtained on a Rudolph AUTOPOL IV polarimeter at a wavelength of 589 nm (sodium D line) using a 1.0 dm cell. Specific rotations are reported in degrees per decimeter at 23-24 °C and the concentrations are given in grams per 100 mL of solvent. Solvents used for optical rotation was $CHCl_3$ (stabilized with 0.5% - 1% EtOH, and filtered through basic alumina).

General Procedures for Chiral-Acid Catalyzed Spirocyclization of Tryptamines with Isatins, Method A. A solution of isatin (0.035 mmol, 1.2 equiv), tryptamine (0.03 mmol, 1.0 equiv) and (*R*)-3,3′-bis(9-anthracenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (0.006 mmol, 0.2 equiv) was prepared in dry CH_2Cl_2 (0.06 M) at 25 °C in an oven-dried and Ar-purged 4 mL vial fitted with a magnetic stir bar. The reaction was stirred until it was complete as judged by TLC (80% EtOAc/hexanes). The reaction was then concentrated and loaded onto a flash silica gel column (gradient of EtOAc/hexanes ending in 80% EtOAc/hexanes) to afford the spiroindolone product.

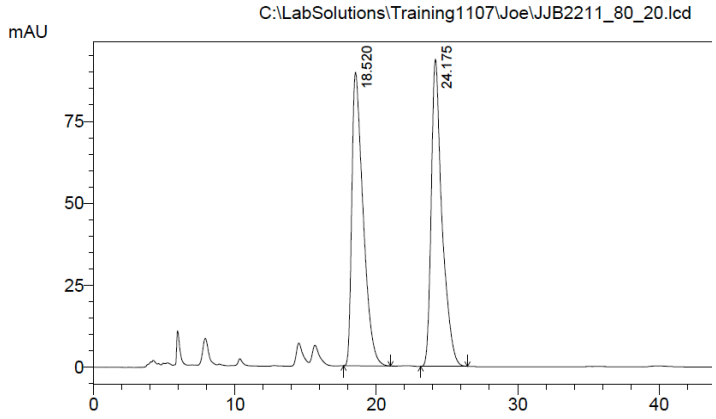
Method B. A solution of isatin (0.05 mmol, 1.0 equiv), tryptamine (0.05 mmol, 1.0 equiv) and *(S)*-3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (0.005 mmol, 0.1 equiv) was prepared in dry DMF (0.2 M) at 40 °C in a 4 mL vial fitted with a magnetic stir bar. The reaction was stirred until it was complete as judged by TLC (10% EtOAc/DCM). The reaction was then diluted with ether (10 mL), washed with 10% K_2CO_3 (2 x 5 mL), brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The resulting residue was purified by flash chromatography (gradient of EtOAc/hexanes ending in 80%EtOAc/hexanes) to afford the spiroindolone. NOTE: depending on substitution, additional useful column conditions include, gradient 100% DCM to 10-20% EtOAc/DCM, and 25% acetone/hexanes to 50% acetone/hexanes.



(*S*)-5-bromo-6'-methoxy-1-methyl-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (4aa): The compound was prepared using both Method A and B, yielding a pink foamy solid; Method A (99%), Method B (70%). Enantiomeric ratio was determined by HPLC with a Daicel CHIRALPAK® AD-H column (20% IPA/hexanes), 0.8 mL/min. t_R (major) = 24.0 min, t_R (minor) = 18.7 min. Method A 92:8 er, $[\alpha]_D^{24}$ -74.5 (c = 0.48, $CHCl_3$). Method B 82:18 er. IR (neat, selected peaks): ν_{max} 3293, 3074, 2929, 1633, 1466, 1088 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 8.3, 2.0, 1H), 7.32 (d, *J* = 2.0, 1H), 7.18 (s, 1H), 7.07 (d, *J* = 8.7, 1H), 7.01 (d, *J* = 2.4, 1H), 6.81 (m, 2H), 3.86 (s, 3H), 3.81 (m, 1H), 3.32 (dt, *J* = 13.3, 5.4, 1H), 3.25 (s, 3H), 2.93 (t, *J* = 5.7, 2H), 2.05 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 154.5, 142.7, 133.7, 132.9, 131.5, 130.2, 128.2, 127.7, 116.3, 112.9, 112.0, 110.4, 100.9, 61.8, 56.2, 40.3, 26.9, 22.3. Exact mass calculated for $C_{20}H_{19}BrN_3O_2$ $[M + H]^+$, 412.0655, Found 412.0656. Recrystallization from DCM layered with hexanes and EtOAc afforded single crystals. The

absolute stereochemistry and structure was confirmed by X-ray analysis.

Racemic standard for (**4aa**)



1 PDA Multi 1/254nm 4nm

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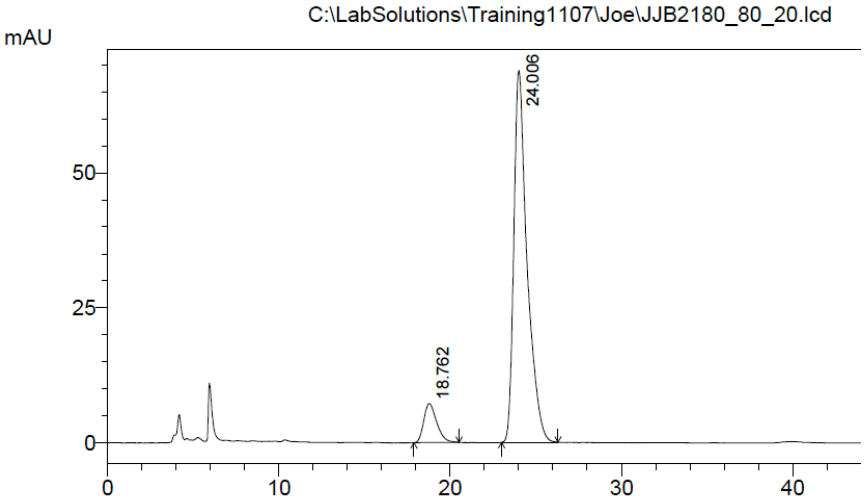
Peak#	Ret. Time	Area	Height	Area %	Height %
1	18.520	4961772	89517	49.994	48.852
2	24.175	4962917	93724	50.006	51.148
Total		9924689	183242	100.000	100.000

Enantiomerically enriched (**4aa**) (Method A, 91:9 er)



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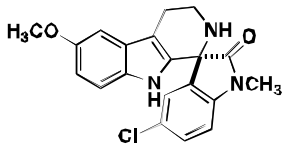
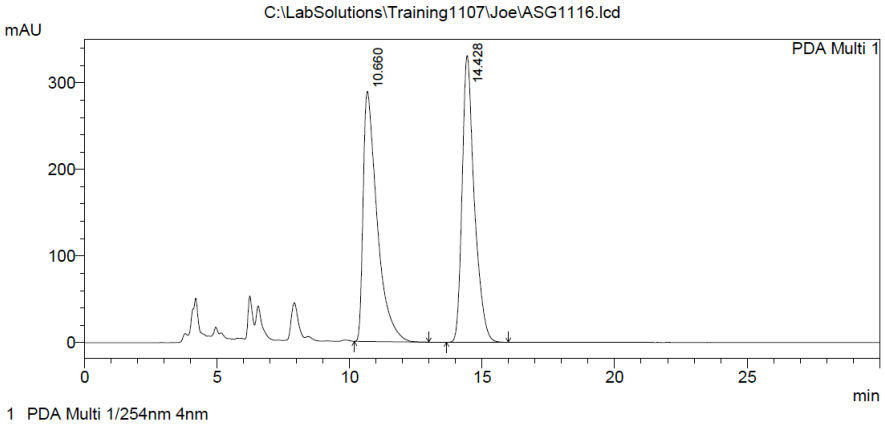
Peak#	Ret. Time	Area	Height	Area %	Height %
1	18.762	379432	7239	9.271	9.506
2	24.006	3713244	68913	90.729	90.494
Total		4092676	76152	100.000	100.000



(*S*)-5-chloro-6'-methoxy-1-methyl-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (4ba): The compound was prepared using both Method A and B, yielding a pink foamy solid; Method A (99%), Method B (90%). Enantiomeric ratio was determined by HPLC with a Daicel CHIRALPAK® AD-H column (30% IPA/hexanes), 0.8 mL/min. t_R (major) = 14.5 min, t_R (minor) = 11.4 min. Method A 98:2 er, $[\alpha]D^{24}$ -66.1° (*c* = 0.3, $CHCl_3$). Method B 88:12 er. IR (neat, selected peaks): ν_{max} 3267, 2922, 2853, 1609, 1455, 1210, 813 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 8.3, 2.1, 1H), 7.18 (d, *J* = 2.1, 1H), 7.06 – 6.98 (m, 2H), 6.86 – 6.76 (m, 2H), 3.85 (s, 3H), 3.80 (ddd, *J* = 13.2, 6.8, 5.0, 1H), 3.31 (dt, *J* = 13.2, 5.4, 1H), 3.22 (s, 3H), 2.92 (t, *J* = 5.7, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 154.2, 142.0, 133.1, 131.3, 129.7, 128.8, 127.5, 125.2, 112.7, 112.6, 111.7, 109.6, 100.7, 61.6, 56.0, 40.0, 26.7, 22.1. Exact mass calculated for $C_{20}H_{19}ClN_3O_2$ $[M + H]^+$, 368.1166, Found 368.1164.

Racemic standard (**4ba**)



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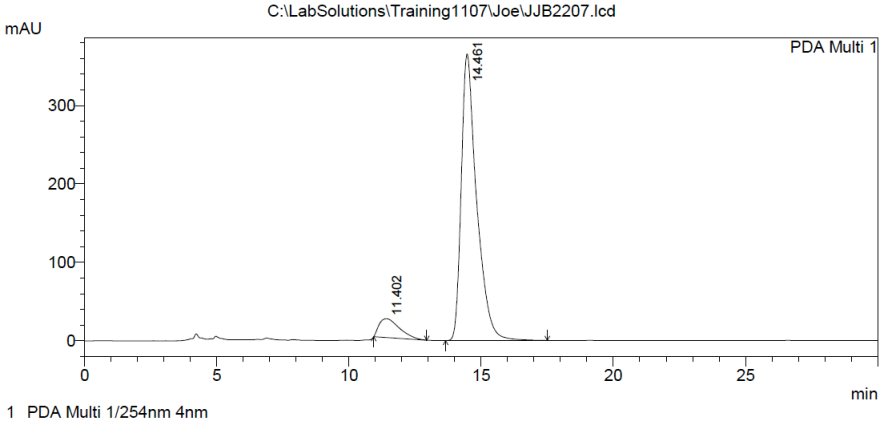
PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.660	10575193	288833	49.927	46.601
2	14.428	10606269	330961	50.073	53.399
Total		21181461	619794	100.000	100.000

Enantiomerically enriched (**4ba**) (Method A, 92:8 er)



1 PDA Multi 1/254nm 4nm

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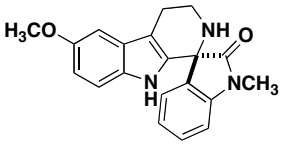
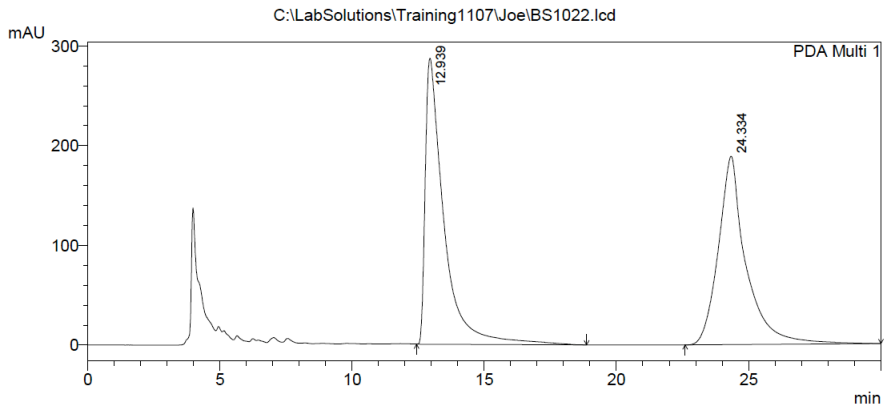
PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.402	1296557	24083	8.072	6.187
2	14.461	14766764	365143	91.928	93.813
Total		16063321	389226	100.000	100.000



***(S)*-6'-methoxy-1-methyl-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (4ca):** The compound was prepared using both Method A and B, yielding a while foamy solid; Method A (99%), Method B (99%). Enantiomeric ratio was determined by HPLC with a Daicel CHIRALPAK® AD-H column (30% IPA/hexanes), 0.8 mL/min. t_R (major) = 24.5 min, t_R (minor) = 13.4 min. Method A 88:12 er. Method B 95:5 er, $[\alpha]_D^{23}$ -17.2° (*c* = 0.27, $CHCl_3$). IR (neat, selected peaks): ν_{max} 3298, 3269, 2898, 1681, 1610, 1468, 1376, 1211, 1102 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (td, *J* = 7.8, 1.2, 1H), 7.20 (d, *J* = 7.4, 1H), 7.17 (s, 1H), 7.07 – 7.03 (m, 2H), 7.01 (d, *J* = 2.4, 1H), 6.93 (d, *J* = 7.8, 1H), 6.79 (dd, *J* = 8.7, 2.5, 1H), 3.90 – 3.81 (m, 4H), 3.35 (dt, *J* = 12.8, 5.4, 1H), 3.27 (s, 3H), 2.94 (t, *J* = 5.7, 2H), 1.70 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 154.4, 143.7, 131.6, 131.4, 131.1, 130.1, 127.8, 124.9, 123.6, 112.6, 111.9, 108.9, 100.9, 61.7, 56.2, 40.2, 26.8, 22.4. Exact mass calculated for $C_{20}H_{20}N_3O_2$ $[M + H]^+$, 334.1556, Found 334.1548.

Racemic standard (**4ca**)



1 PDA Multi 1/254nm 4nm

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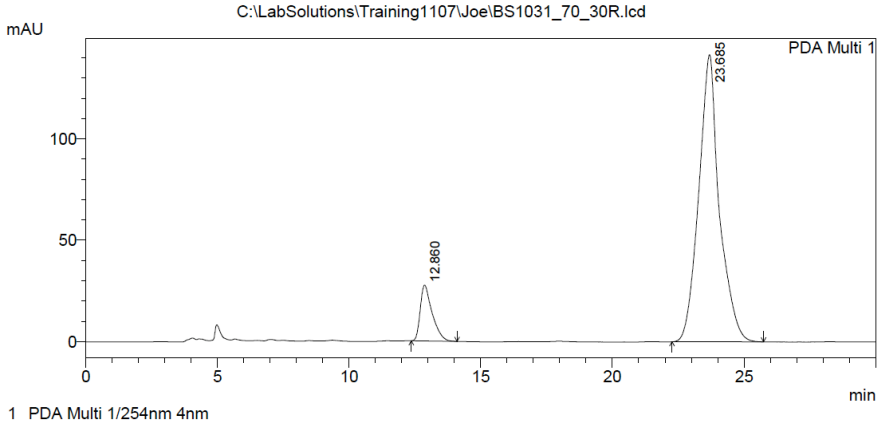
PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.939	14094960	286919	50.584	60.288
2	24.334	13769273	188998	49.416	39.712
Total		27864233	475918	100.000	100.000

Enantiomerically enriched (**4ca**) (Method B 90:10 er)



1 PDA Multi 1/254nm 4nm

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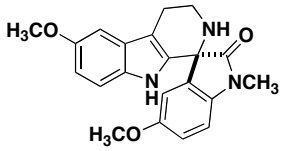
PDA Ch1 254nm 4nm

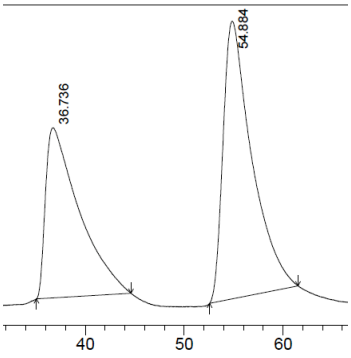
Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.860	861353	27494	10.081	16.281
2	23.685	7682716	141380	89.919	83.719
Total		8544069	168874	100.000	100.000



(*S*)-1-methyl-5-methoxy-6'-methoxy-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (4da). The compound was prepared using both Method A and B, yielding a white solid; Method A (99%), Method B (79%). Enantiomeric excess was determined by HPLC with a Daicel CHIRALPAK® AD-H column (20% IPA/hexanes), 0.8 mL/min. t_R (major) = 54.8 min, t_R (minor) = 36.7 min. Method A 58:42 er. Method B 70:30 er, $[\alpha]_D^{23}$ -63.2° (*c* = 0.44, $CHCl_3$). IR (neat, selected peaks): ν_{max} 3302, 2924, 2841, 1720, 1495, 2114, 1169, 1028, 812 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 1H), 7.01 (dd, *J* = 10.4, 5.5, 2H), 6.83 (s, 1H), 6.87 (dd, *J* = 8.5, 2.4, 1H), 6.84 – 6.75 (m, 1H), 3.91 – 3.81 (m, 4H), 3.69 (s, 3H), 3.35 – 3.27 (m, 1H), 3.21 (s, 3H), 2.92 (t, *J* = 5.7, 2H), 2.00 (bs, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 156.8, 154.3, 137.0, 132.8, 131.5, 131.1, 127.8, 114.9, 112.6, 112.4, 111.9, 111.6, 109.4, 100.9, 62.1, 56.2, 56.1, 40.3, 26.8, 22.3. Exact mass calculated for $C_{21}H_{22}N_3O_3$ $[M + H]^+$, 364.1656, Found 364.1656.

Enantiomerically enriched (**4da**) (Method A, 58:42 er)

ining1107\Joe\JJB2239_mc.lcd



1 PDA Multi 1/254nm 4nm

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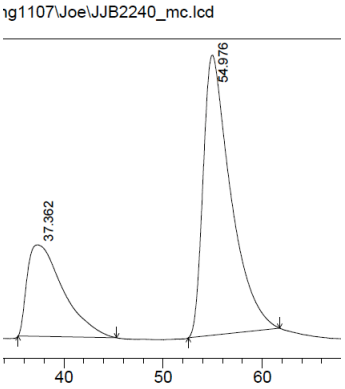
PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	36.736	1912955	8104	41.725	38.009
2	54.884	2671672	13217	58.275	61.991
Total		4584627	21321	100.000	100.000

Enantiomerically enriched (**4da**) (Method B, 70:30 er)



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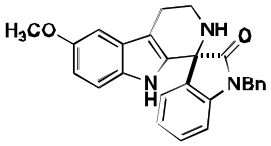
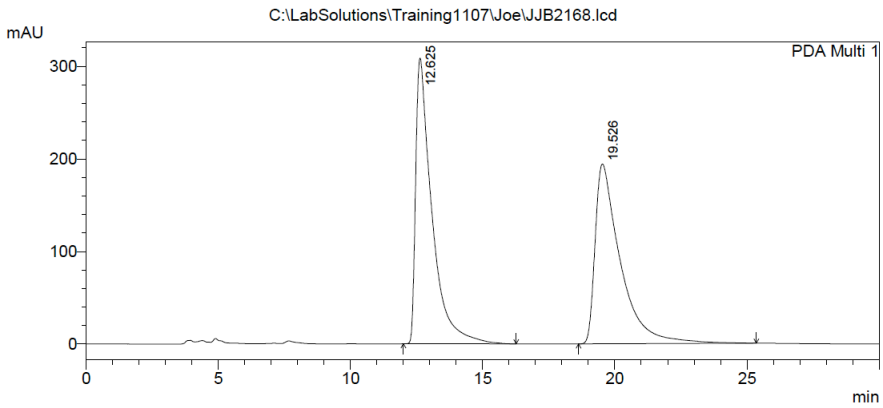
PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	37.362	2167816	8601	29.806	24.634
2	54.976	5105278	26316	70.194	75.366
Total		7273094	34917	100.000	100.000



(*S*)-1-benzyl-6'-methoxy-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (4ea): The compound was prepared using both Method A and B, yielding a pink foamy solid; Method A (99%), Method B (95%). Enantiomeric ratio was determined by HPLC with a Daicel CHIRALPAK® AD-H column (30% IPA/hexanes), 0.8 mL/min. t_R (major) = 12.6 min, t_R (minor) = 19.6 min. Method A 82:18 er. Method B 96:4, $[\alpha]_D^{24}$ -21.3° (*c* = 0.41, $CHCl_3$). IR (neat, selected peaks): ν_{max} 3279, 3342, 1684, 1610, 1454, 1216, 1175, 986 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.13 (m, 8H), 6.99 (m, 3H), 6.82 (d, *J* = 7.8, 1H), 6.77 (dd, *J* = 8.8, 2.4, 1H), 4.94 (d, *J* = 15.5, 1H), 4.85 (d, *J* = 15.5, 1H), 3.90 (dt, *J* = 18.8, 6.0, 1H), 3.85 (s, 3H), 3.34 (dt, *J* = 13.1, 5.2, 1H), 2.94 (t, J = 5.7, 2H), 2.16 (b, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 154.4, 142.8, 136.0, 131.7, 131.6, 131.3, 129.9, 129.2, 128.1, 127.9, 127.8, 125.0, 123.6, 112.6, 112.0, 109.8, 100.9, 61.7, 56.2, 44.2, 40.3, 22.4. Exact mass calculated for $C_{26}H_{24}N_3O_2$ $[M + H]^+$, 410.1869, LRMS Found 410.2.

Racemic standard for (**4ea**)



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PDA Ch1 254nm 4nm

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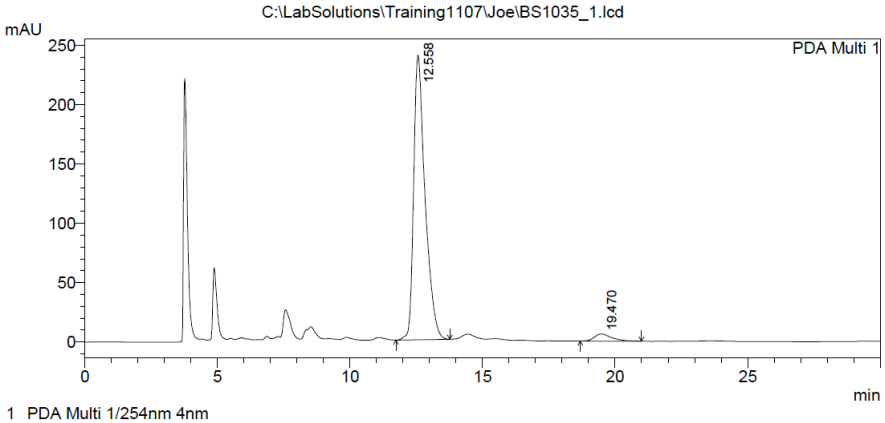
1	12.625	13180963	308706	50.556	61.371
2	19.526	12891254	194309	49.444	38.629
Total		26072217	503014	100.000	100.000

Enantiomerically enriched (**4ea**) (Method B, 96:4 er)



1 PDA Multi 1/254nm 4nm

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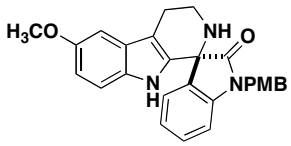
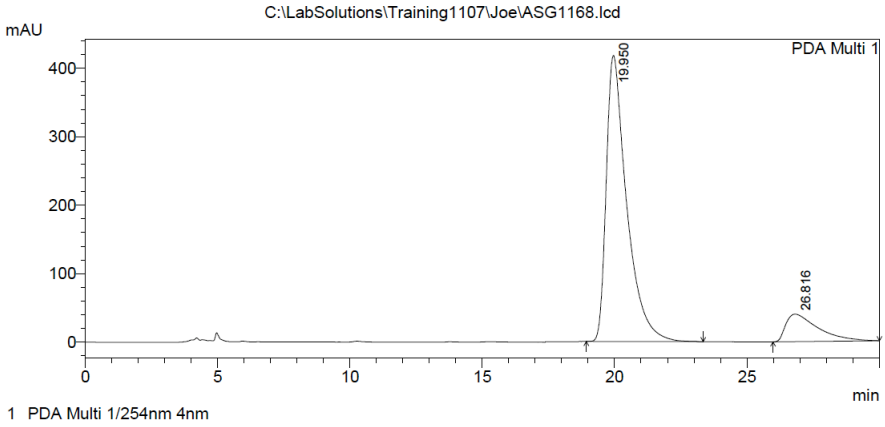
PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.558	7193270	239753	96.252	97.521
2	19.470	280083	6094	3.748	2.479
Total		7473353	245847	100.000	100.000



(*S*)-6'-methoxy-1-(4-methoxyphenyl)-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (4fa): The compound was prepared using both Method A and B, yielding a white solid; Method A (72%), Method B (87%). Enantiomeric ratio was determined by HPLC with a Daicel CHIRALPAK® AD-H column (30% IPA/hexanes), 0.8 mL/min. t_R (major) = 19.7 min, t_R (minor) = 26.5 min. Method A 87:13. Method B 93:7 er, $[\alpha]_D^{24}$ -38.5° (*c* = 0.32, $CHCl_3$). IR (neat, selected peaks): ν_{max} 2924, 1704, 1606, 1459, 1244, 1169, 1027 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 7.6, 4.9, 1H), 7.23 (dd, *J* = 7.7, 1.3, 1H), 7.18 (d, *J* = 7.4, 2H), 7.13 (s, 1H), 7.05 – 6.94 (m, 4H), 6.91 – 6.84 (m, 2H), 6.82 – 6.75 (m, 1H), 4.92 (d, *J* = 15.2, 1H), 4.78 (d, *J* = 15.2, 1H), 3.97 – 3.83 (m, 4H), 3.79 (s, 3H), 3.35 (dt, J = 11.5, 5.2, 1H), 2.94 (t, J = 5.7, 1H), 2.0 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 159.5, 154.4, 142.8, 131.8, 131.5, 131.3, 129.9, 129.2, 128.1, 127.9, 124.9, 123.5, 114.5, 112.6, 112.5, 111.9, 109.9, 100.9, 61.7, 56.2, 55.5, 43.7, 40.4, 22.4. Exact mass calculated for $C_{27}H_{26}N_3O_3$ $[M + H]^+$, 440.1974, LRMS Found 440.2.

Enantiomerically enriched (**4fa**) (Method A, 87:13 er)



1 PDA Multi 1/254nm 4nm

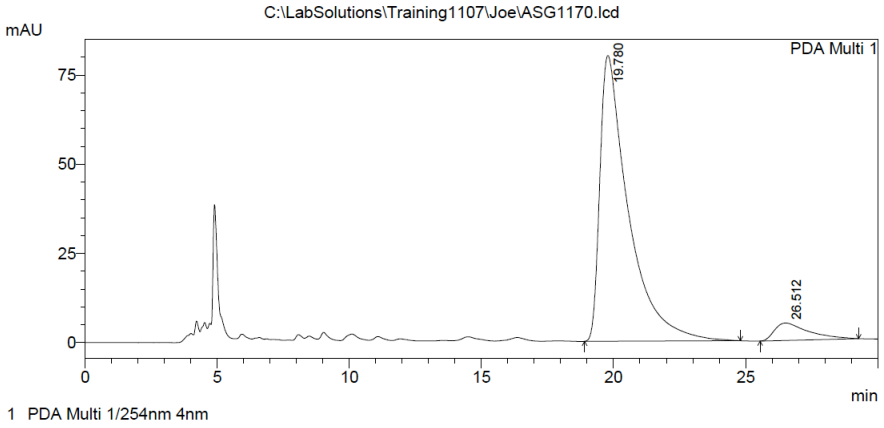
< Peak Table >

PeakTable C:\LabSolutions\Training1107\Joe\ASG1168.lcd

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.950	22458067	417832	86.929	91.267
2	26.816	3376880	39979	13.071	8.733
Total		25834947	457811	100.000	100.000

Enantiomerically enriched (**4fa**) (Method B 93:7 er)



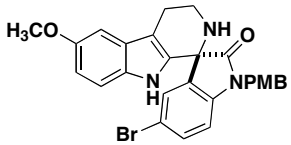
1 PDA Multi 1/254nm 4nm

< Peak Table >

PeakTable C:\LabSolutions\Training1107\Joe\ASG1170.lcd

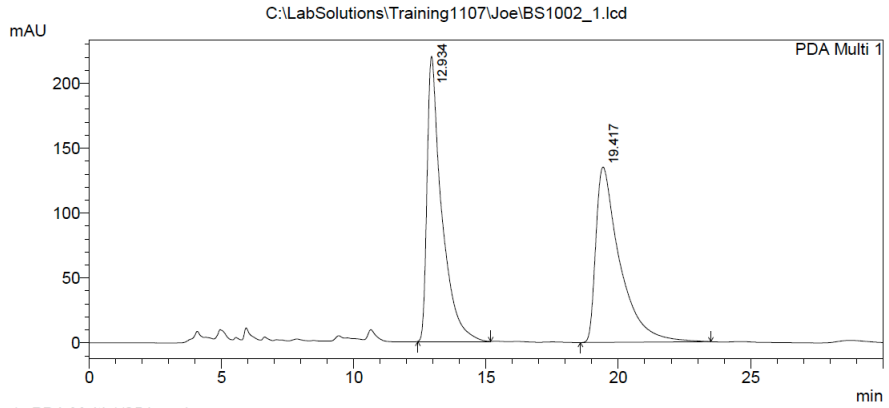
PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.780	6011112	80142	93.280	94.276
2	26.512	433065	4866	6.720	5.724
Total		6444176	85008	100.000	100.000



(*S*)-5-bromo-6'-methoxy-1-(4-methoxyphenyl)-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (4ga): The compound was prepared using both Method A and B, yielding a pink foamy solid; Method A (86%), Method B (81%). Enantiomeric ratio was determined by HPLC with a Daicel CHIRALPAK® AD-H column (30% IPA/hexanes), 0.8 mL/min. t_R (major) = 13.1 min, t_R (minor) = 20.1 min. Method A 87:13 er, $[\alpha]_D^{24}$ -48.7° (*c* = 0.68, $CHCl_3$). Method B 75:25 er. IR (neat, selected peaks): ν_{max} 3347, 2923, 1682, 1476, 1173, 1026, 820 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.3, 1.9, 1H), 7.30 (d, *J* = 1.9, 1H), 7.26 (d, *J* = 8.6, 1H), 7.13 (s, 1H), 7.05 (d, *J* = 8.8, 1H), 7.01 (d, *J* = 2.4, 1H), 6.90 – 6.84 (m, 2H), 6.80 (dd, *J* = 8.8, 2.4, 1H), 6.72 (d, *J* = 8.3, 1H), 4.83 (dd, *J* = 47.0, 15.3, 2H), 3.86 (s, 3H), 3.79 (s, 3H), 3.39 – 3.27 (m, 1H), 2.94 (t, *J* = 5.6, 2H), 1.98 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 159.7, 154.6, 141.8, 132.9, 132.7, 131.5, 129.1, 128.2, 127.7, 127.6, 116.3, 114.6, 113.0, 112.0, 111.4, 106.1, 105.5, 101.0, 61.9, 56.3, 55.5, 44.1, 40.5, 22.4. Exact mass calculated for $C_{27}H_{25}BrN_3O_3$ $[M + H]^+$, 518.1074, Found 518.1069.

Racemic standard (**4ga**)



1 PDA Multi 1/254nm 4nm

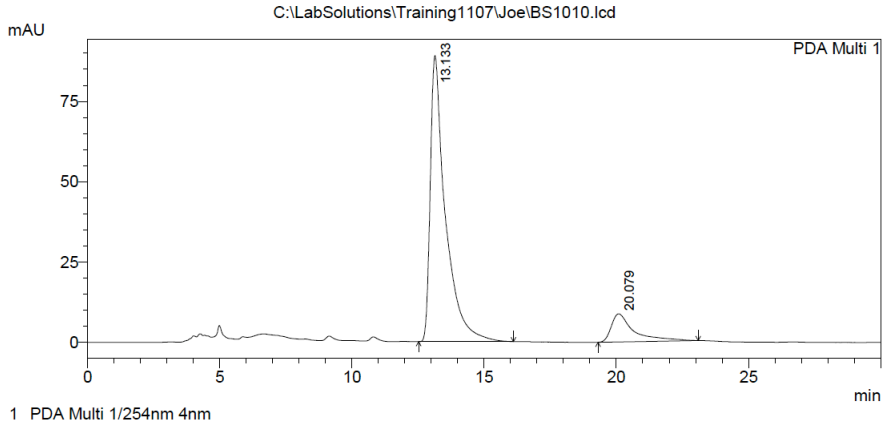
< Peak Table >

PeakTable C:\LabSolutions\Training1107\Joe\BS1002_1.lcd

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.934	8458493	219878	49.801	61.924
2	19.417	8526020	135200	50.199	38.076
Total		16984513	355078	100.000	100.000

Enantiomerically enriched **4ga** (Method A, 87:13 er)



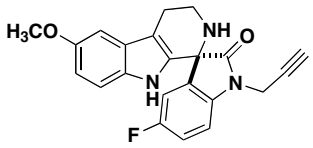
1 PDA Multi 1/254nm 4nm

< Peak Table >

PeakTable C:\LabSolutions\Training1107\Joe\BS1010.lcd

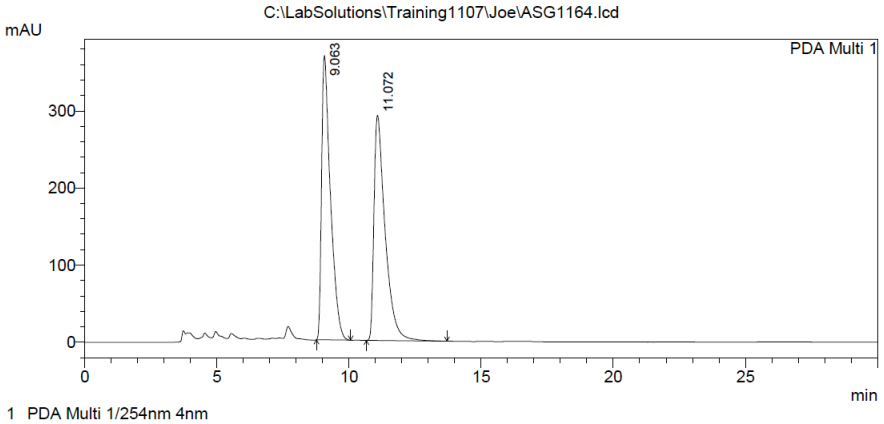
PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.133	3548848	89133	87.190	91.065
2	20.079	521386	8745	12.810	8.935
Total		4070235	97878	100.000	100.000



(*S*)-5-fluoro-1-propargyl-6'-methoxy-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (4ha). The compound was prepared using both Method A and B, yielding a white foamy solid; Method A (60%), Method B (86%). Enantiomeric ratio was determined by HPLC with a Daicel CHIRALPAK® AD-H column (30% IPA/hexanes), 0.8 mL/min. t_R (major) = 9.0 min, t_R (minor) = 11.1 min. Method A 92:8 er. Method B 92:8 er, $[\alpha]_D^{24}$ -12.2° (*c* = 0.27, $CHCl_3$). IR (neat, selected peaks): ν_{max} 3296, 3193, 1977, 1696, 1485, 1173, 1028 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (s, 1H), 7.12 – 6.93 (m, 6H), 6.78 (dd, *J* = 8.8, 1.8, 1H), 4.57 (dd, *J* = 17.7, 2.3, 1H), 4.45 (dd, *J* = 17.7, 2.5, 1H), 3.90 – 3.78 (m, 4H), 3.30 (dt, *J* = 10.8, 5.2, 1H), 2.92 (t, *J* = 6.7, 2H), 2.31 (t, *J* = 2.4, 1H). ^{13}C NMR (100 MHz, CDCl3) δ 175.8, 160.0 (d, J_{FC} = 243.3 Hz), 154.4, 137.6, 133.1 (d, J_{FCCC} = 7.5 Hz), 131.5, 130.1, 127.7, 116.4 (d, J_{FCC} = 23.7 Hz), 113.2 (d, J_{FCC} = 25.0 Hz), 112.9, 112.8, 112.0, 110.7 (d, J_{FCCC} = 7.9 Hz) ,100.9, 76.7, 73.3, 62.0, 56.2, 40.2, 29.9, 22.2. Exact mass calculated for $C_{22}H_{19}FN_3O_2$ $[M + H]^+$, 376.1461, LRMS Found 376.2. Recrystallization from DCM layered with hexanes and EtOAc afforded single crystals. The absolute stereochemistry and structure was confirmed by X-ray analysis.

Racemic standard (**4ha**)



1 PDA Multi 1/254nm 4nm

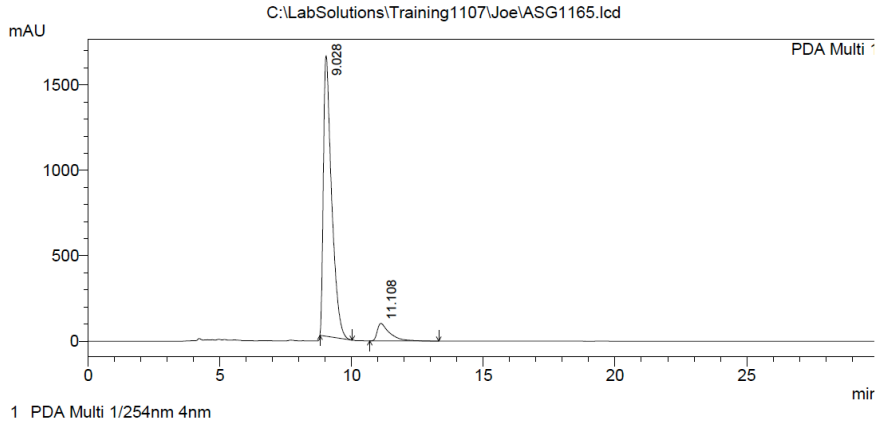
< Peak Table >

PeakTable C:\LabSolutions\Training1107\Joe\ASG1164.lcd

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.063	8555398	368613	49.966	55.805
2	11.072	8566928	291925	50.034	44.195
Total		17122326	660538	100.000	100.000

Enantiomerically enriched (**4ha**) (Method A, 92:8 er)

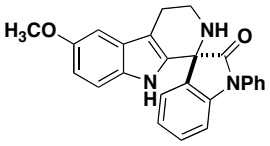


< Peak Table >

PeakTable C:\LabSolutions\Training1107\Joe\ASG1165.lcd

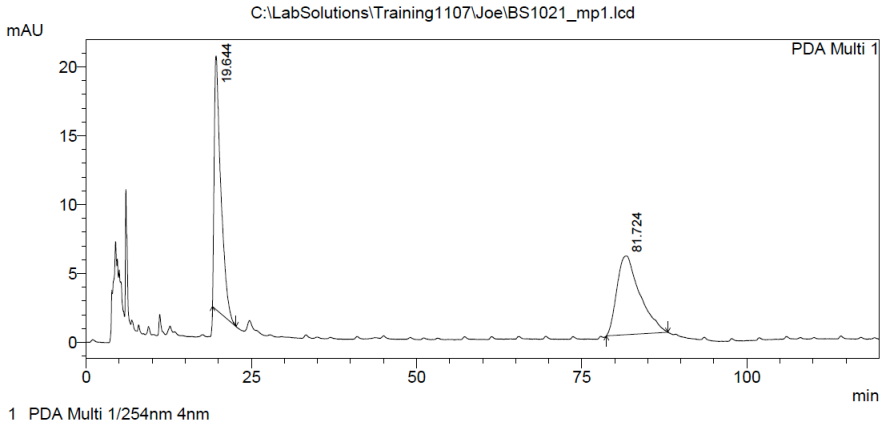
PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.028	35654086	1642103	91.522	94.150
2	11.108	3302569	102040	8.478	5.850
Total		38956655	1744142	100.000	100.000



(*S*)-1-phenyl-6'-methoxy-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (4ia). The compound was prepared using both Method A and B, yielding a white solid; Method A (99%), Method B (44%). Enantiomeric ratio was determined by HPLC with a Daicel CHIRALPAK® AD-H column (20% IPA/hexanes), 0.8 mL/min. t_R (major) = 19.7 min, t_R (minor) = 81.7 min. Method A 85:15 er. Method B 97:3 er, $[\alpha]_D^{24}$ 21.8° (*c* = 0.53, $CHCl_3$). IR (neat, selected peaks): ν_{max} 3297, 2177, 1702, 1605, 1456, 1203, 1113 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.45 (m, 4H), 7.45 – 7.39 (m, 1H), 7.32 – 7.27 (m, 3H), 7.12 – 7.05 (m, 2H), 7.03 (d, *J* = 2.4, 1H), 6.95 (d, *J* = 7.9, 1H), 6.81 (dd, *J* = 8.8, 2.5, 1H), 3.93 (dt, *J* = 12.7, 6.2, 1H), 3.87 (s, 3H), 3.38 (dt, *J* = 13.1, 5.2, 1H), 2.99 – 2.94 (m, 1H), 1.61 (bs, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 154.4, 143.6, 134.3, 131.6, 131.4, 131.2, 129.9, 129.9, 128.4, 127.9, 126.6, 125.3, 124.0, 112.7, 112.0, 110.2, 100.9, 61.8, 56.2, 40.2, 22.4. Exact mass calculated for $C_{25}H_{22}N_3O_2$ $[M + H]^+$, 396.1712, Found 396.1707.

Racemic standard (**4ia**)



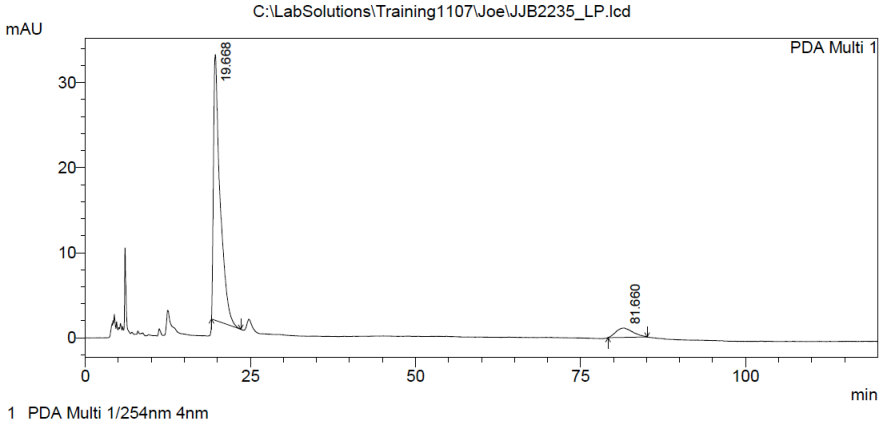
< Peak Table >

PeakTable C:\LabSolutions\Training1107\Joe\BS1021_mp1.lcd

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.644	1288924	18444	48.211	76.314
2	81.724	1384565	5724	51.789	23.686
Total		2673490	24168	100.000	100.000

Enantiomerically enriched (**4ia**) (Method A, 97:3 er)

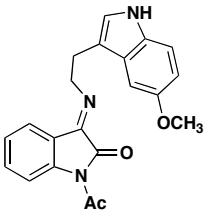


< Peak Table >

PeakTable C:\LabSolutions\Training1107\Joe\JJB2235_LP.lcd

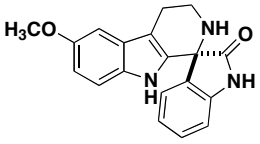
PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.668	2186310	31226	91.907	96.595
2	81.660	192526	1101	8.093	3.405
Total		2378835	32327	100.000	100.000



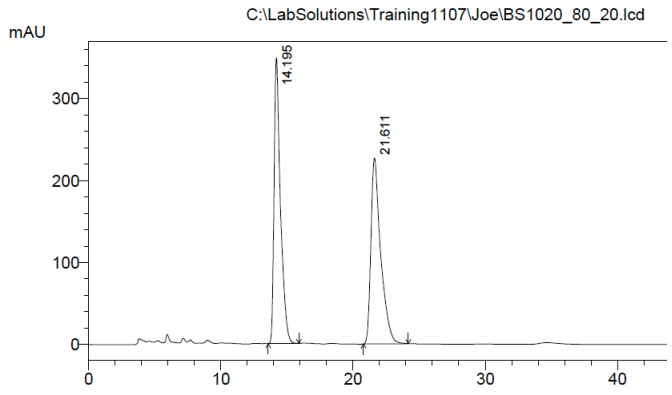
(*E*)-1-acetyl-3-(2-(5-methoxy-1*H*-indol-3-yl)ethylimino)indolin-2-one (4j):

The compound was prepared using both Method A (87%) and Method B (53%). IR (neat, selected peaks): ν_{max} 3402, 2925, 2852, 1701, 1645, 1512, 1222 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 10.92 (s, 1H), 8.66 (d, *J* = 8.5, 1H), 8.32 (d, *J* = 8.0, 1H), 7.99 (s, 1H), 7.60 (t, *J* = 7.9, 1H), 7.28 (d, *J* = 8.8, 1H), 7.15 – 7.03 (m, 3H), 6.89 (dd, *J* = 8.8, 2.3, 1H), 6.86 (s, 1H), 3.86 (s, 3H), 3.76 (q, *J* = 6.5, 2H), 3.07 (t, *J* = 6.6, 2H), 2.21 (s, 3H). Exact mass calculated $C_{21}H_{20}N_3O_3$ $[M + H_2O + H]^+$, 380.1605, LRMS Found 380.0.



(*S*)-6'-methoxy-1-H-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (**4ka**) white solid Method A (66%), Method A (99%). Spectra matches known compound.[27] Enantiomeric excess was determined by HPLC with a Daicel CHIRALPAK® AD-H column (20% IPA/hexanes), 0.8 mL/min. tR (major) = 21.6 min, tR (minor) = 14.2 min. Method A 94:6 er. Method B 94:6 er, $[\alpha]_D^{24}$ -4.51° (*c* = 0.24, $CHCl_3$).

Racemic standard (**4ka**)



1 PDA Multi 1/254nm 4nm

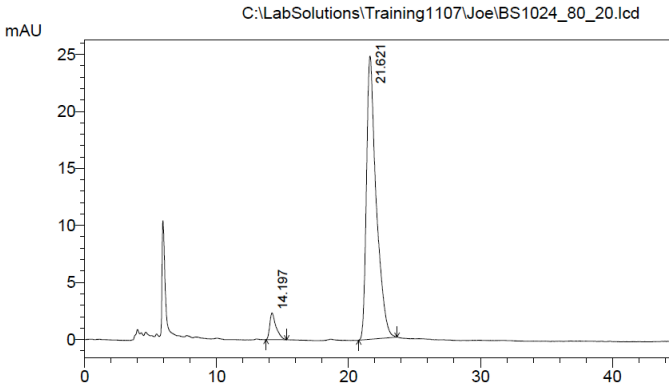
< Peak Table >

PeakTable C:\LabSolutions\Training1107\Joe\BS1020_80_20.lcd

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.195	11623045	348685	49.938	60.600
2	21.611	11651754	226699	50.062	39.400
Total		23274800	575384	100.000	100.000

Enantiomerically enriched (**4ka**) (Method B 94:6 er)



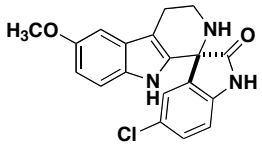
1 PDA Multi 1/254nm 4nm

< Peak Table >

PeakTable C:\LabSolutions\Training1107\Joe\BS1024_80_20.lcd

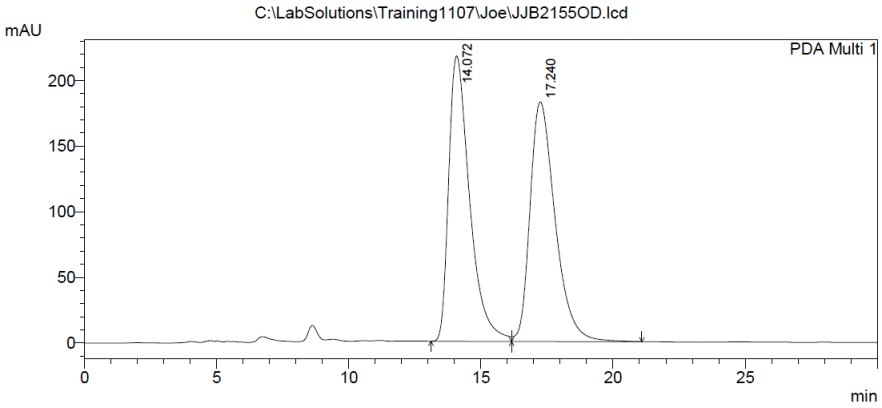
PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.197	76817	2327	5.668	8.568
2	21.621	1278492	24836	94.332	91.432
Total		1355309	27163	100.000	100.000



(*S*)-5-chloro-6'-methoxy-1-H-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (4la): The compound was prepared using both Method A and B, yielding a white foamy solid; Method A (99%), Method B (88%). Enantiomeric excess was determined by HPLC with a Daicel CHIRALPAK® AD-H column (10% IPA/hexanes), 0.8 mL/min. t_R (major) = 14.0 min, t_R (minor) = 17.2 min. Method A 84:16 er, $[\alpha]_D^{24}$ -32.5° (*c* = 0.28, $CHCl_3$). Method B 80:20 er. IR (neat, selected peaks): ν_{max} 3375, 3219, 2922, 1714, 1459, 1174, 823 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.09 (s, 1H), 7.10 (d, *J* = 2.0, 1H), 6.96 (d, *J* = 2.3, 2H), 6.81 (d, *J* = 8.7, 1H), 6.71 (dd, *J* = 8.7, 2.2, 1H), 6.44 (d, *J* = 8.1, 1H), 3.84 (s, 3H), 3.58 – 3.51 (m, 1H), 3.27 – 3.19 (m, 1H), 2.91 – 2.78 (m, 3H), 1.93 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 154.5, 142.7, 133.7, 132.9, 131.5, 130.2, 128.2, 127.7, 116.3, 112.9, 112.0, 110.4, 100.9, 61.8, 56.2, 40.3, 26.9, 22.3. Exact mass calculated for $C_{19}H_{17}ClN_3O_2$ $[M + H]^+$, 354.1009, Found 354.1005.

Racemic standard **4la**



1 PDA Multi 1/254nm 4nm

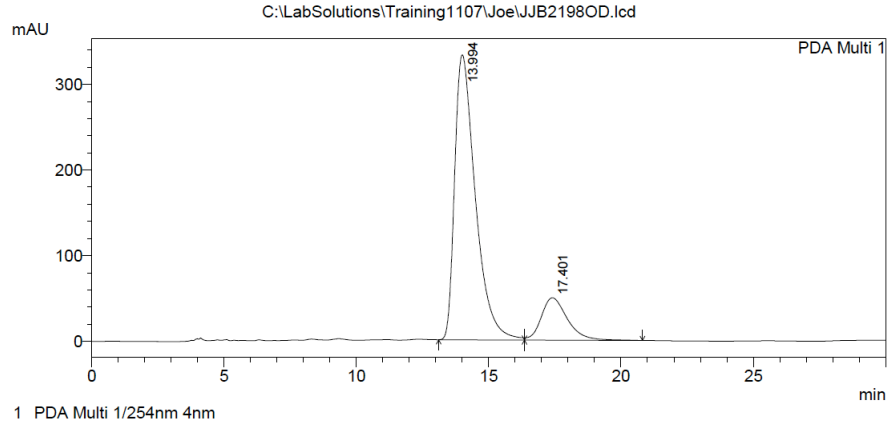
< Peak Table >

PeakTable C:\LabSolutions\Training1107\Joe\JJB2155OD.lcd

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.072	11993912	217499	49.817	54.351
2	17.240	12081928	182676	50.183	45.649
Total		24075839	400175	100.000	100.000

Enantiomerically enriched (**4la**) (Method A, 84:16 er)



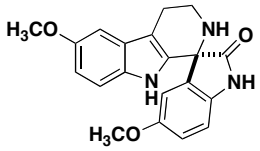
1 PDA Multi 1/254nm 4nm

< Peak Table >

PeakTable C:\LabSolutions\Training1107\Joe\JJB2198OD.lcd

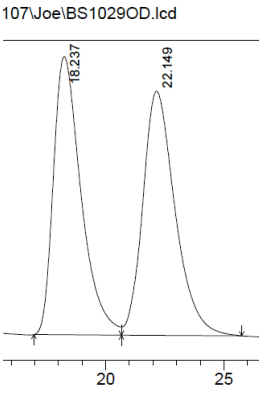
PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.994	18124272	332894	84.171	87.063
2	17.401	3408447	49468	15.829	12.937
Total		21532719	382361	100.000	100.000



(*S*)-5-methoxy-6'-methoxy-1-H-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (4ma): off white foam Method A (84%), Method B (92%). Enantiomeric excess was determined by HPLC with a Daicel CHIRALPAK® OD-H column (20% IPA/hexanes), 0.8 mL/min. t_R (major) = 18.0 min, t_R (minor) = 22.3 min. Method A 93:7 er. Method B 96:4 er, $[\alpha]_D^{24}$ -29.8° (*c* = 0.21, $CHCl_3$). IR (neat, selected peaks): ν_{max} 3181, 2944, 2327, 1688, 1548, 1474, 1218, 781 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.33 (s, 1H), 7.06 (d, *J* = 8.8, 1H), 7.01 (d, *J* = 2.3, 1H), 6.81 (d, *J* = 2.5, 2H), 6.79 (d, *J* = 2.5, 1H), 6.77 (s, 1H), 3.86 (s, 4H), 3.70 (s, 3H), 3.33 (m, 1H), 2.94 (m, 2H). ^{13}C NMR (75 MHz, CD_2Cl_2, CD_3OD, 1:1) δ 179.0, 156.4, 153.9, 134.5, 133.3, 131.5, 130.8, 127.4, 114.9, 112.2, 111.9, 111.4, 111.2, 100.5, 62.3, 55.9, 55.9, 40.0, 22.0. Exact mass calculated for $C_{20}H_{20}N_3O_3$ $[M + H]^+$, 350.1505, Found 350.1499.

Racemic standard **(4ma)**



1 PDA Multi 1/254nm 4nm

< Peak Table >

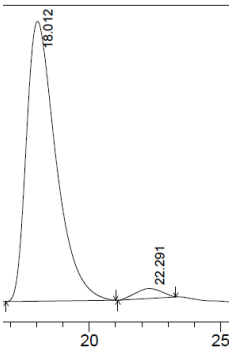
PeakTable C:\LabSolutions\Training1107\Joe\BS1029OD.lcd

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	18.237	3191413	39221	49.371	53.261
2	22.149	3272674	34418	50.629	46.739
Total		6464087	73639	100.000	100.000

Enantiomerically enriched **(4ma)** (Method A, 97:3 er)

S1027OD.lcd



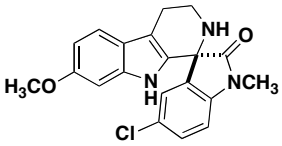
1 PDA Multi 1/254nm 4nm

< Peak Table >

PeakTable C:\LabSolutions\Training1107\Joe\BS1027OD.lcd

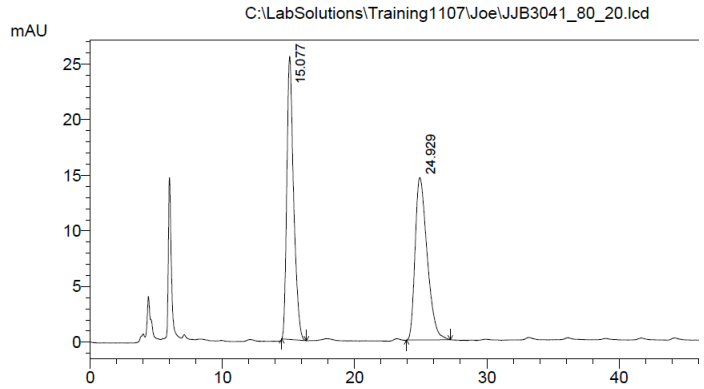
PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	18.012	6453490	82267	96.925	96.597
2	22.291	204769	2898	3.075	3.403
Total		6658259	85166	100.000	100.000



(*S*)-5-chloro-1-methyl-7'-methoxy-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (4bb): The compound was prepared using both Method A and B, yielding an off white foam; Method A (93%), Method B (89%). Enantiomeric excess was determined by HPLC with a Daicel CHIRALPAK® AD-H column (20% IPA/hexanes), 0.8 mL/min. t_R (major) = 15.0 min, t_R (minor) = 24.6 min. Method A 60:40 er. Method B 80:20 er, $[\alpha]_D^{24}$ -76.5° (*c* = 0.17, $CHCl_3$). IR (neat, selected peaks): ν_{max} 3400, 3197, 2928, 1698, 1608, 1458, 1114 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.6, 1H), 7.39 (s, 1H), 7.31 (dd, *J* = 8.3, 2.1, 1H), 7.18 (d, *J* = 2.1, 1H), 6.81 (d, *J* = 8.3, 1H), 6.77 (dd, *J* = 8.6, 2.3, 1H), 6.64 (d, *J* = 2.1, 1H), 3.80 – 3.71 (m, 4H), 3.28 (dt, *J* = 13.3, 5.5, 1H), 3.20 (s, 3H), 2.91 (t, *J* = 5.7, 2H), 1.90 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 157.1, 142.2, 137.3, 133.4, 129.9, 129.0, 128.1, 125.4, 121.7, 119.4, 112.9, 109.9, 109.5, 95.1, 61.8, 55.9, 40.3, 26.9, 22.3. Exact mass calculated for $C_{20}H_{19}ClN_3O_2$ $[M + H]^+$, 368.1166, LRMS Found 368.0.

Racemic Standard (**4bb**)



1 PDA Multi 1/254nm 4nm

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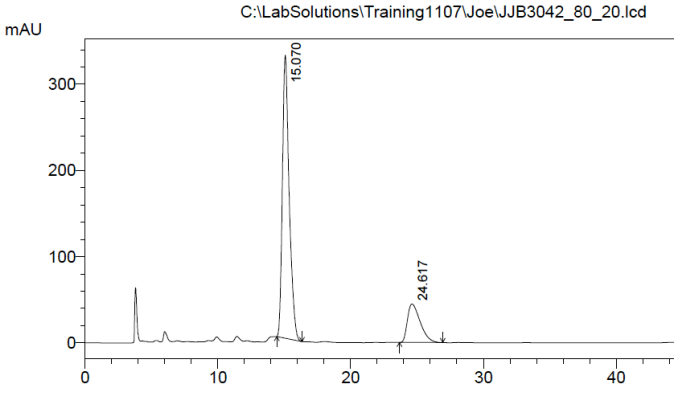
PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.077	912201	25449	49.705	63.538
2	24.929	923027	14605	50.295	36.462
Total		1835227	40054	100.000	100.000

Enantiomerically enriched (**4bb**) (Method B, 80:20 er)



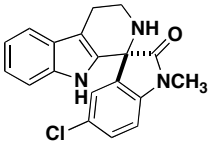
1 PDA Multi 1/254nm 4nm

< Peak Table >

PeakTable C:\LabSolutions\Training1107\Joe\JJB3042_80_20.lcd

PDA Ch1 254nm 4nm

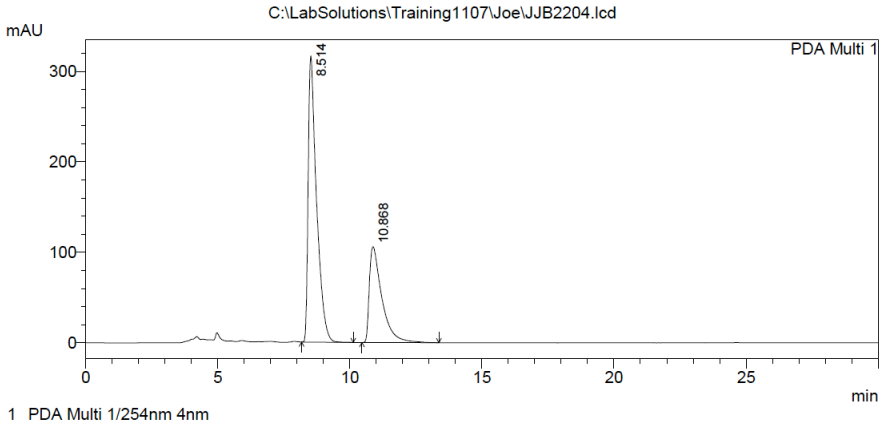
Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.070	11674366	328288	79.706	88.044
2	24.617	2972471	44582	20.294	11.956
Total		14646837	372870	100.000	100.000



(*S*)-5-chloro-1-methyl-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one

(3bc): The compound was prepared using both Method A and B, yielding a off-white foamy solid; Method A (93%). Method B (89%). Enantiomeric excess was determined by HPLC with a Daicel CHIRALPAK® AD-H column (30% IPA/hexanes), 0.8 mL/min. t_R (major) = 8.5 min, t_R (minor) = 10.9 min. Method A 67:33 er. Method B 65:35 er. IR (neat, selected peaks): ν_{max} 3266, 2926, 1697, 1610, 1100, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.2, 1H), 7.34 (dd, *J* = 8.3, 2.1, 2H), 7.21 – 7.08 (m, 5H), 6.86 (d, *J* = 8.3, 1H), 3.82 (dt, *J* = 13.2, 5.9, 1H), 3.32 (dt, *J* = 13.3, 5.5, 1H), 3.25 (s, 3H), 2.96 (t, *J* = 5.7, 2H), 1.79 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 142.2, 136.4, 133.3, 129.9, 129.4, 129.0, 127.3, 125.5, 123.0, 120.0, 118.9, 113.1, 111.2, 109.9, 61.8, 40.3, 26.9, 22.3. Exact mass calculated for $C_{19}H_{17}ClN_3O$ $[M + H]^+$, 338.1060, Found 338.1054.

Enantiomerically enriched (**3bc**) (67:33 er)



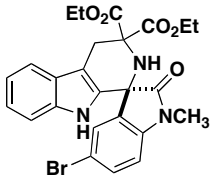
1 PDA Multi 1/254nm 4nm

< Peak Table >

PeakTable C:\LabSolutions\Training1107\Joe\JJB2204.lcd

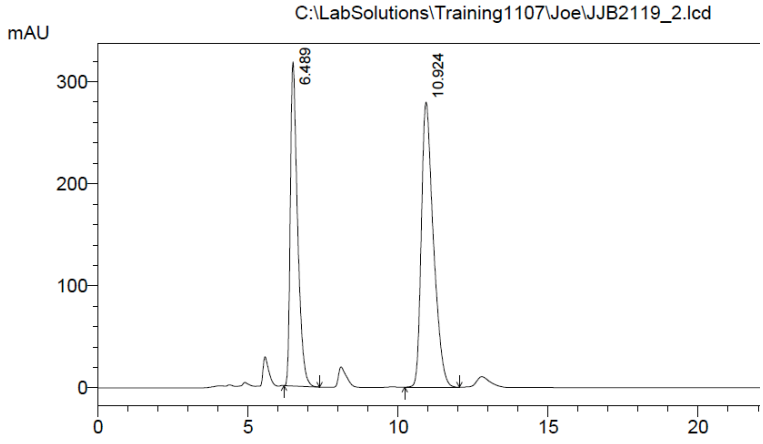
PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.514	6959061	316299	66.632	74.921
2	10.868	3484919	105877	33.368	25.079
Total		10443980	422176	100.000	100.000



(*S*)-diethyl 5-bromo-1-methyl-2-oxo-4',9'-dihydrospiro[indoline-3,1'-pyrido[3,4-*b*]indole]-3',3'(2'*H*)-dicarboxylate (4ad): Method A using catalyst *(S)*-**8e** (92%). Method B with catalyst *(S)*-**8d** (21%). Enantiomeric excess was determined by HPLC with a Daicel CHIRALPAK® AD-H column (30% IPA/hexanes), 0.8 mL/min. t_R (major) = 10.9 min, t_R (minor) = 6.4 min. Method A 59:40 er. Method B 52:48 er. IR (neat, selected peaks): ν_{max} 3394, 3318, 2930, 1709, 1606, 1453, 1247 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 6.6, 1H), 7.50 (dd, *J* = 8.3, 2.0, 1H), 7.38 (d, *J* = 1.9, 1H), 7.25 (s, 1H), 7.19 – 7.09 (m, 3H), 6.80 (d, *J* = 8.3, 1H), 4.33 – 4.16 (m, 4H), 3.68 (d, *J* = 15.4, 1H), 3.50 (d, *J* = 15.4, 1H), 3.32 (s, 1H), 3.20 (d, *J* = 4.6, 3H), 1.30 – 1.19 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 171.1, 169.5, 143.1, 136.8, 133.3, 132.7, 129.2, 128.5, 126.9, 123.1, 120.2, 119.0, 116.3, 111.3, 110.4, 110.3, 65.2, 62.5, 62.3, 61.7, 27.0, 26.9, 14.2. Exact mass calculated for $C_{25}H_{25}BrN_3O_5$ $[M + H]^+$, 526.0972, Found 528.0968.

Enantiomerically enriched (**4ad**) (59:41 er)



1 PDA Multi 1/254nm 4nm

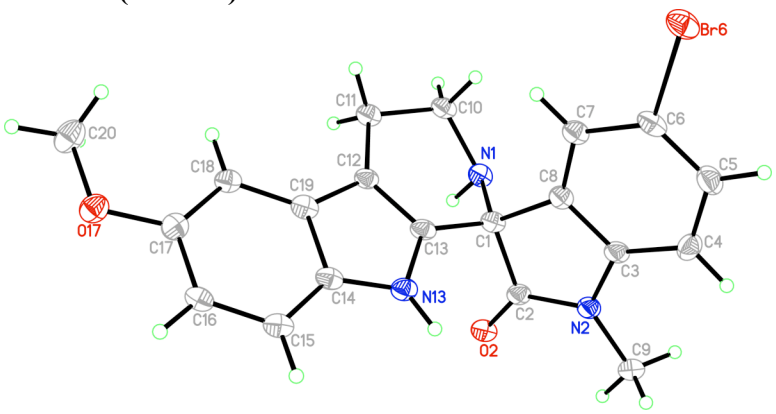
< Peak Table >

PeakTable C:\LabSolutions\Training1107\Joe\JJB2119_2.lcd

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.489	5341806	317531	40.683	53.204
2	10.924	7788512	279288	59.317	46.796
Total		13130319	596820	100.000	100.000

X-ray Structure Analysis of Spiroindolone 4aa (JF2008)



A colorless plate with approximate orthogonal dimensions 0.25 x 0.07 x 0.05mm^3 was placed and optically centered on the Bruker APEX DUO[1] CCD system at –183°C(90K). Indexing of the unit cell was attempted using a random set of reflections collected from three series of 0.5° wide ω-scans, 10 seconds per frame, and 30 frames per series that were well distributed in reciprocal space. Data were collected [CuKα] with 0.5° wide scans at varying ϕ and omega angles for 20, 30 or 40 seconds per frame dependent upon detector 2theta angle such that nearly all unique reflections were collected at least once; overall 96.5% were collected. The crystal to detector distance was 4.96cm, thus providing a nearly complete sphere of data to θ_{max}=72.03°.

Structural determination and Refinement:

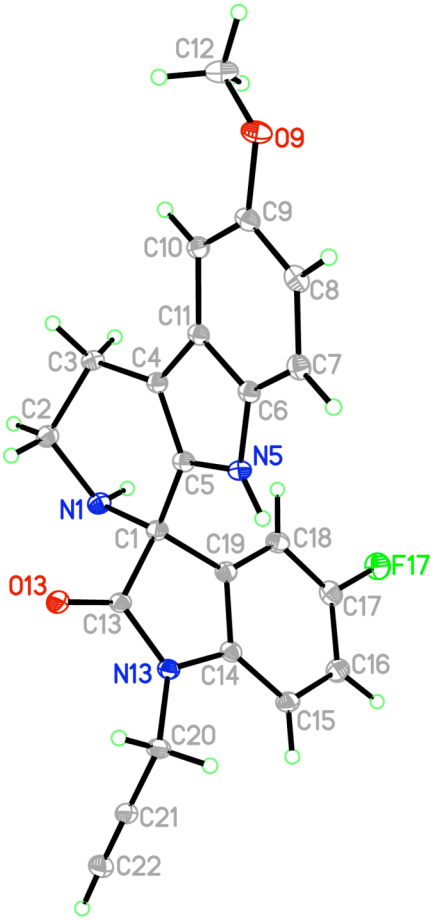
All crystallographic calculations were performed on a Personal computer (PC) with a Pentium 3.20GHz processor and 4GB of extended memory. Data collected were corrected for Lorentz and polarization effects and absorption using Blessing's method and merged as incorporated into the program Twinabs[2,6]. The SHELXTL[3] program package was now implemented to determine, based upon intensity statistics and systematic absences, the non-centrosymmetric monoclinic space group $P2_1$ (no.4). The structure was determined by direct methods with a majority of the non-hydrogen atoms being located directly using the program XS[4]. Refinement of the structure was achieved using the program XL[4]. Difference-Fourier refinement cycles were required to locate the remaining non-hydrogen atoms. Refinement converged to approximately R_F=7% for those data observed. It was evident from the outset that the structure possessed more than a single domain when examining the individual frames so reflections were thresholded in APEX[1] and these reflections were input into Cellnow[5] that determined the twin relationship between the two components and generated the orientation matrices for the components and output a useable multiple matrice input file for the integration program SAINT[1]. Saint was run six times using the output optimized merged matrix file from the previous run. Data collected were now corrected for absorption using TWINABS[2,6] and Blessing's method and merged generating both HKLF4 and HKLF5 files. Convergence of the structure proceeded quickly using both the HKLF5 and HKLF4 files. All of the non-hydrogen atoms were refined anisotropically with the two domains being present as follows: major component 81.6% and minor 18.4%. Since the HKLF5 format file yielded the best results, it was chosen for structure completion. The structure also contains a ehtylacetate molecule at 50% occupancy as it overlays itself throughout the lattice. All of the hydrogen atoms were placed in calculated positions throughout the final convergence cycles but their thermal parameters were allowed to refine freely. The final structure was refined to convergence with R(F)=5.85%, wR(F^2)=15.33%, GOF=1.102 for all 3664 reflections [R(F)=5.81%, wR(F^2)=15.27% for those 3608 data with Fo > 4σ(Fo)]. A final difference-Fourier map was featureless but for the two largest peaks being within 1A of the Bromine atom indicating that the structure is therefore both correct and complete.

Table 1. Crystal data and structure refinement for spiroindolone **4aa** (JF2008).

Identification code	tw51 (2-Comp Twin)	
Empirical formula	C22 H22 Br N3 O3	
Formula weight	456.34	
Temperature	90(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P 2_1$	
Unit cell dimensions	a = 11.3749(10) Å	α= 90°.
	b = 6.6273(6) Å	β= 93.086(5)°.
	c = 13.6225(12) Å	γ = 90°.
Volume	1025.44(16) $Å^3$	
Z	2	
Density (calculated)	1.478 Mg/m^3	
Absorption coefficient	2.969 mm^{-1}	
F(000)	468	
Crystal size	0.25 x 0.07 x 0.05 mm^3	
Crystal color and habit	Colorless Plate	
Diffractometer	Bruker APEX-II Duo CCD	
Theta range for data collection	3.25 to 72.03°.	
Index ranges	-14<=h<=14, -7<=k<=8, -16<=l<=16	
Reflections collected	3664	
Independent reflections	3664 [R(int) = 0.0000]	
Observed reflections (I > 2sigma(I))	3608	
Completeness to theta = 72.03°	96.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8682 and 0.5287	
Solution method	SHELXS-97 (Sheldrick, 2008)	
Refinement method	SHELXL-97 (Sheldrick, 2008)	
Data / restraints / parameters	3664 / 12 / 310	
Goodness-of-fit on F^2	1.102	
Final R indices [I>2sigma(I)]	R1 = 0.0581, wR2 = 0.1527	
R indices (all data)	R1 = 0.0585, wR2 = 0.1533	
Absolute structure parameter	0.00(3)	
Largest diff. peak and hole	1.788 and -0.482 $e.Å^{-3}$	

X-ray Structure Analysis for Spiroindolone 4ah (JF2018)

A colorless plate with approximate orthogonal dimensions 0.05 x 0.14 x 0.48mm^3 was placed and optically centered on the Bruker APEX II Duo[1] CCD system at 90(2)K. The initial unit cell was indexed using a least-squares analysis of a random set of reflections collected from three series of 0.5° wide ω-scans, 10 seconds per frame, and 30 frames per series that were well distributed in reciprocal space. Sixteen Data frame series were collected [CuKα] with 0.5° wide ω-scans, variable scan times dependent upon detector position, and varying φ, ω, and 2θangles. The crystal to detector distance was 5.02cm, thus providing a nearly complete sphere of data with processing to $2\theta_{max}$=136.54°.



Structural determination and Refinement:

All crystallographic calculations were performed on an iMac with 2.80GHz quad core processor and 8GB of extended memory. A total of 16563 reflections were collected and corrected for Lorentz and polarization effects in Saint[1] and absorption using Blessing's method as incorporated into the program SADABS[2,3,4] with 3498 unique based upon point group mm2. The SHELXTL[5] program package was implemented to determine the probable space group and set up the initial files. System symmetry, systematic absences, and intensity statistics indicated the non-centrosymmetric orthorhombic space group $Pca2_1$ (no. 29). The structure was determined by direct methods using XS[6] with a majority of the non-hydrogen atoms comprising the molecule. The structure was refined with XL[6]. The remaining atoms were located from a subsequent difference-Fourier map. The data collected were merged in least-squares refinement to 3237 unique data [R(int)=0.0314]. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were initially placed in calculated idealized positions and later their position and thermal parameters were allowed to refine freely (xyzU). The final structure was refined to convergence with R(F)=2.75%, wR(F^2)=7.37%, GOF=1.037 for all 3237 unique reflections [R(F)=2.74%, wR(F^2)=7.37% for those 3218 data with Fo > 4σ(Fo)]. The final difference-Fourier map was featureless indicating that the structure is both correct and complete. An empirical correction for extinction was also attempted and found to be less than three sigma and therefore not applied. The absolute structure parameters, Flack(x)[6], and Hooft[7] were determined to be -0.02(11) and -0.01(3), respectively, clearly indicating that the correct structure has been determined and 35 reflections were missed during data collection.

Table 2. Crystal data and structure refinement for spiroindolone **4ah** (JF2018).

Identification code	jf2018ff	
Empirical formula	C22 H18 F N3 O2	
Formula weight	375.39	
Temperature	90(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P c a 2_1	
Unit cell dimensions	a = 15.4938(9) Å	α= 90°.
	b = 14.6273(8) Å	β= 90°.
	c = 8.1904(5) Å	γ = 90°.
Volume	1856.21(19) $Å^3$	
Z	4	
Density (calculated)	1.343 Mg/m^3	
Absorption coefficient	0.779 mm^{-1}	
F(000)	784	
Crystal size	0.48 x 0.14 x 0.05 mm^3	
Crystal color and habit	Colourless Plate	
Diffractometer	Bruker APEX-II Duo CCD	
Theta range for data collection	3.02 to 68.35°.	
Index ranges	-16<=h<=17, -17<=k<=17, -9<=l<=9	
Reflections collected	15936	
Independent reflections	3237 [R(int) = 0.0314]	
Observed reflections (I > 2sigma(I))	3218	
Completeness to theta = 68.35°	97.3 %	
Absorption correction	Empirical, SADABS (multi-scan)	
Max. and min. transmission	0.9591 and 0.7062	
Solution method	SHELXS-97 (Sheldrick, 2008)	
Refinement method	SHELXL-97 (Sheldrick, 2008)	
Data / restraints / parameters	3237 / 1 / 325	
Goodness-of-fit on F^2	1.037	
Final R indices [I>2sigma(I)]	R1 = 0.0274, wR2 = 0.0737	
R indices (all data)	R1 = 0.0275, wR2 = 0.0737	
Absolute structure parameter	-0.02(11)	
Largest diff. peak and hole	0.189 and -0.176 $e.Å^{-3}$	

References:

1. Bruker (2010) SMART APEX (2010.9-1) and (2009) SAINT (Version 7.68a). Bruker AXS Inc., Madison, Wisconsin, USA.

2. An Empirical Correction for Absorption Anisotropy, Blessing, R. H. (1995). Acta Cryst., A51, 33-38.

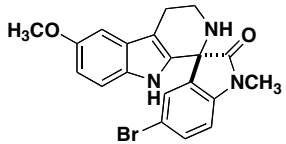
3. Sheldrick, G.M., (2002). SHELXTL. Version 6.1. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

4. Sheldrick, G. M., (1997). SHELXS97 and SHELXL97. Universität Göttingen: Göttingen, Germany.

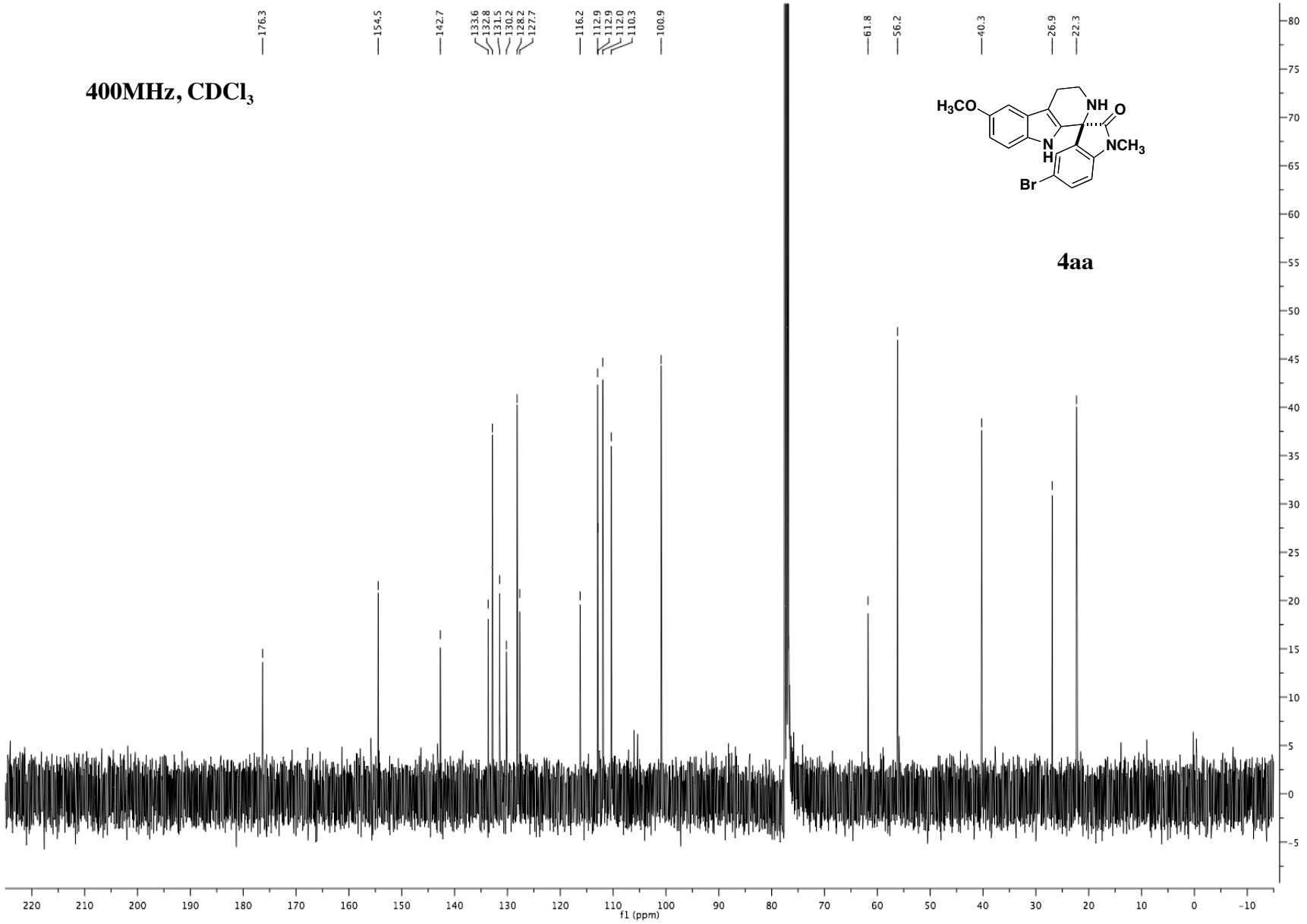
5. Sheldrick, G.M., CELLNOW, Twin matrix determination program, Universität Göttingen: Göttingen, Germany, Version 2008/3.

6. Sheldrick, G.M., TWINABS Version 2008/4 'An Empirical Correction for Absorption Anisotropy applied to Twinned crystals'. Universität Göttingen: Göttingen, Germany, 2003.

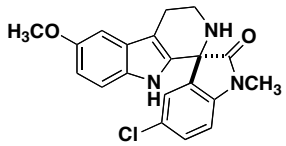
400MHz, $CDCl_3$



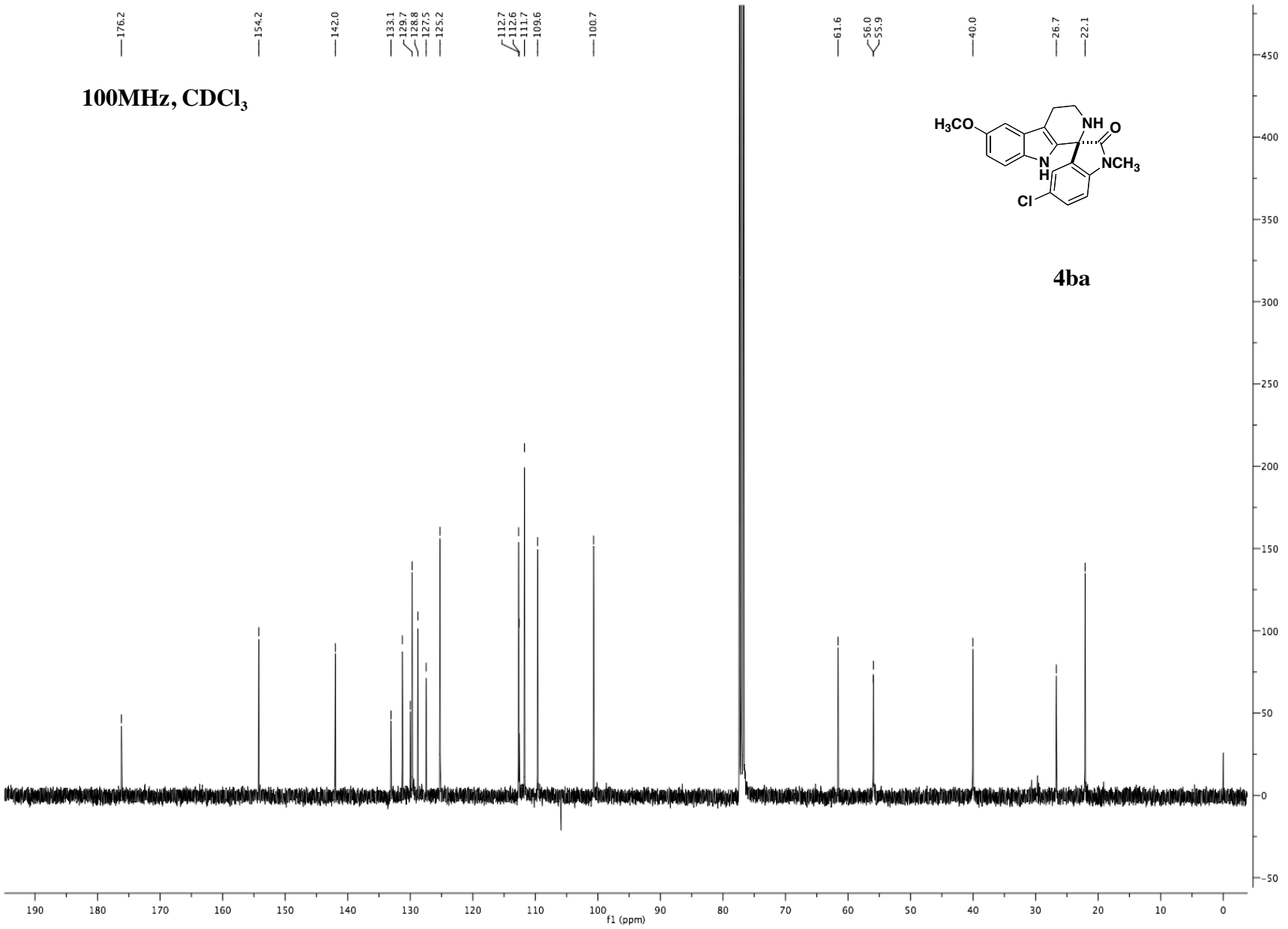
4aa


400MHz, CDCl3
176.3
154.5
142.7
133.6
132.8
131.5
130.2
128.2
127.7
116.2
112.9
112.9
112.0
110.3
100.9
61.8
56.2
40.3
26.9
22.3
H3CO
NH
O
N
H
NCH3
Br
4aa
f1 (ppm)

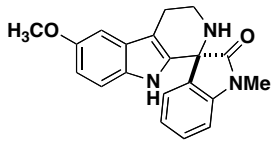
400MHz, $CDCl_3$



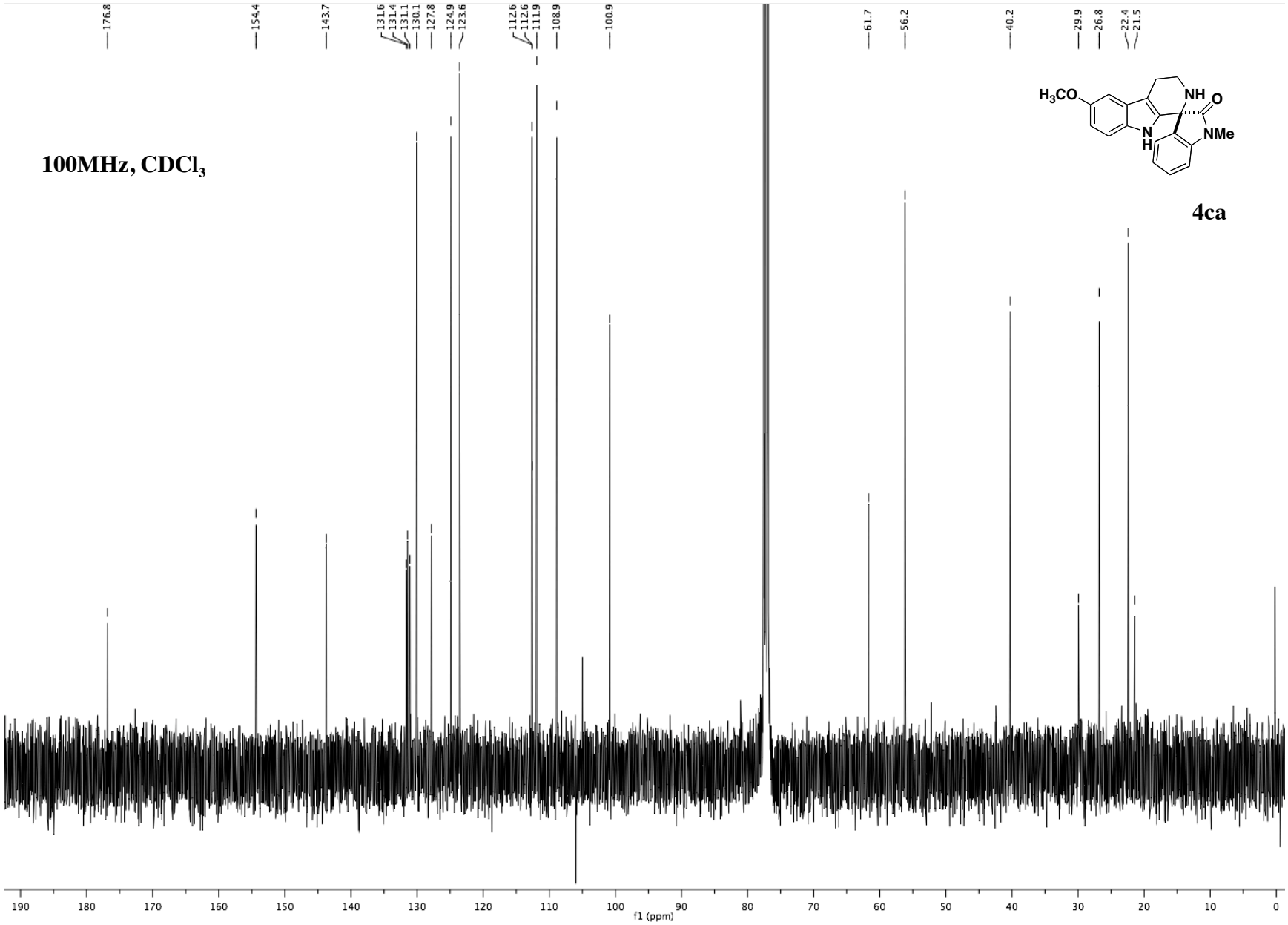
4ba


100MHz, CDCl3
176.2
154.2
142.0
133.1
129.7
128.8
127.5
125.2
112.7
112.6
111.7
109.6
100.7
61.6
56.0
55.9
40.0
26.7
22.1
H3CO
NH
O
N
H
NCH3
Cl
4ba
f1 (ppm)

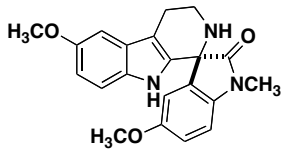
400MHz, $CDCl_3$



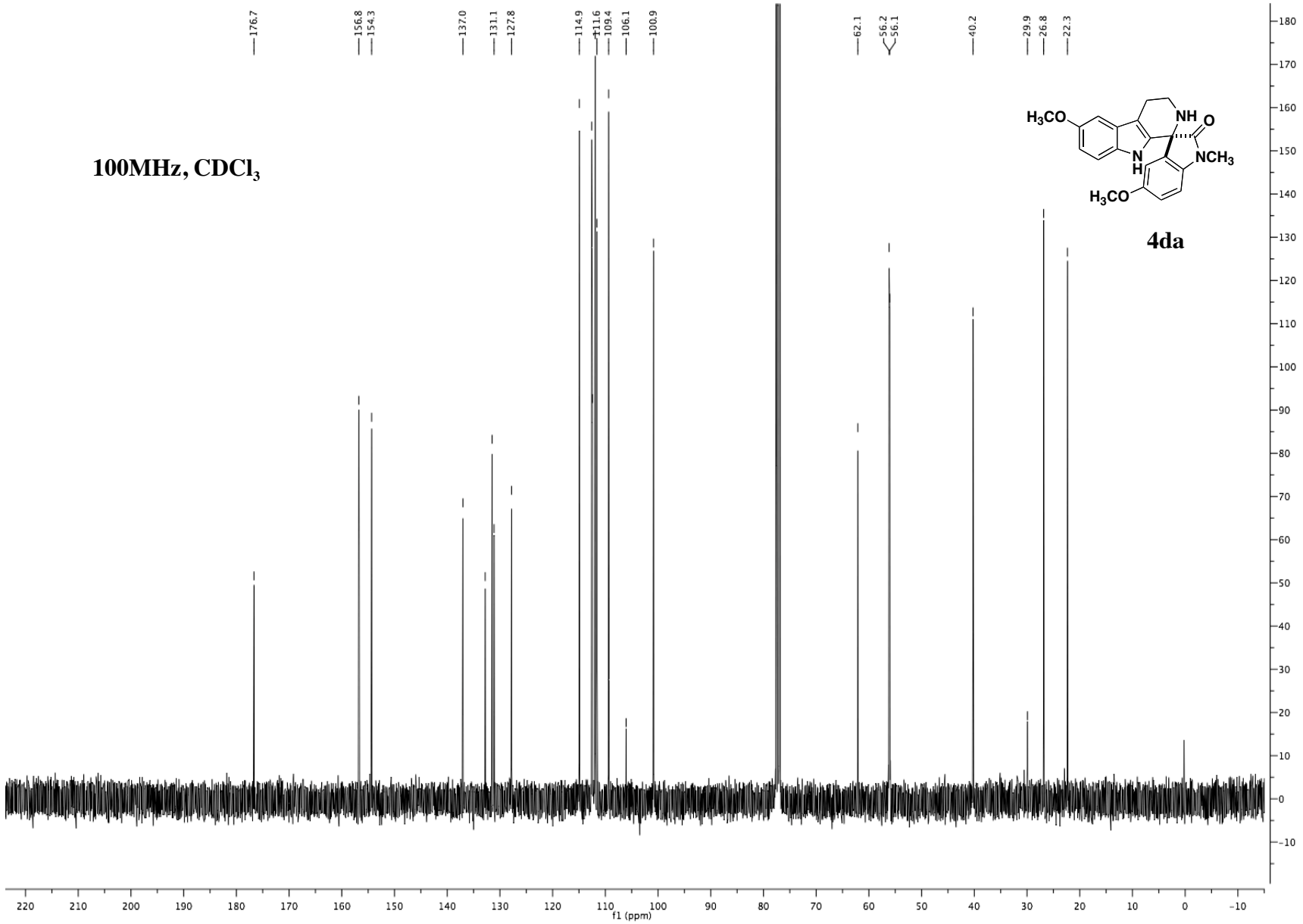
4ca


176.8
154.4
143.7
131.6
131.4
131.1
130.1
127.8
124.9
123.6
112.6
112.6
111.9
108.9
100.9
61.7
56.2
40.2
29.9
26.8
22.4
21.5
100MHz, CDCl3
H3CO
NH
O
N
H
NMe
4ca
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

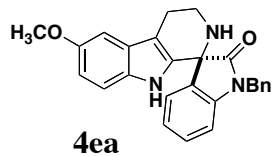
400MHz, $CDCl_3$



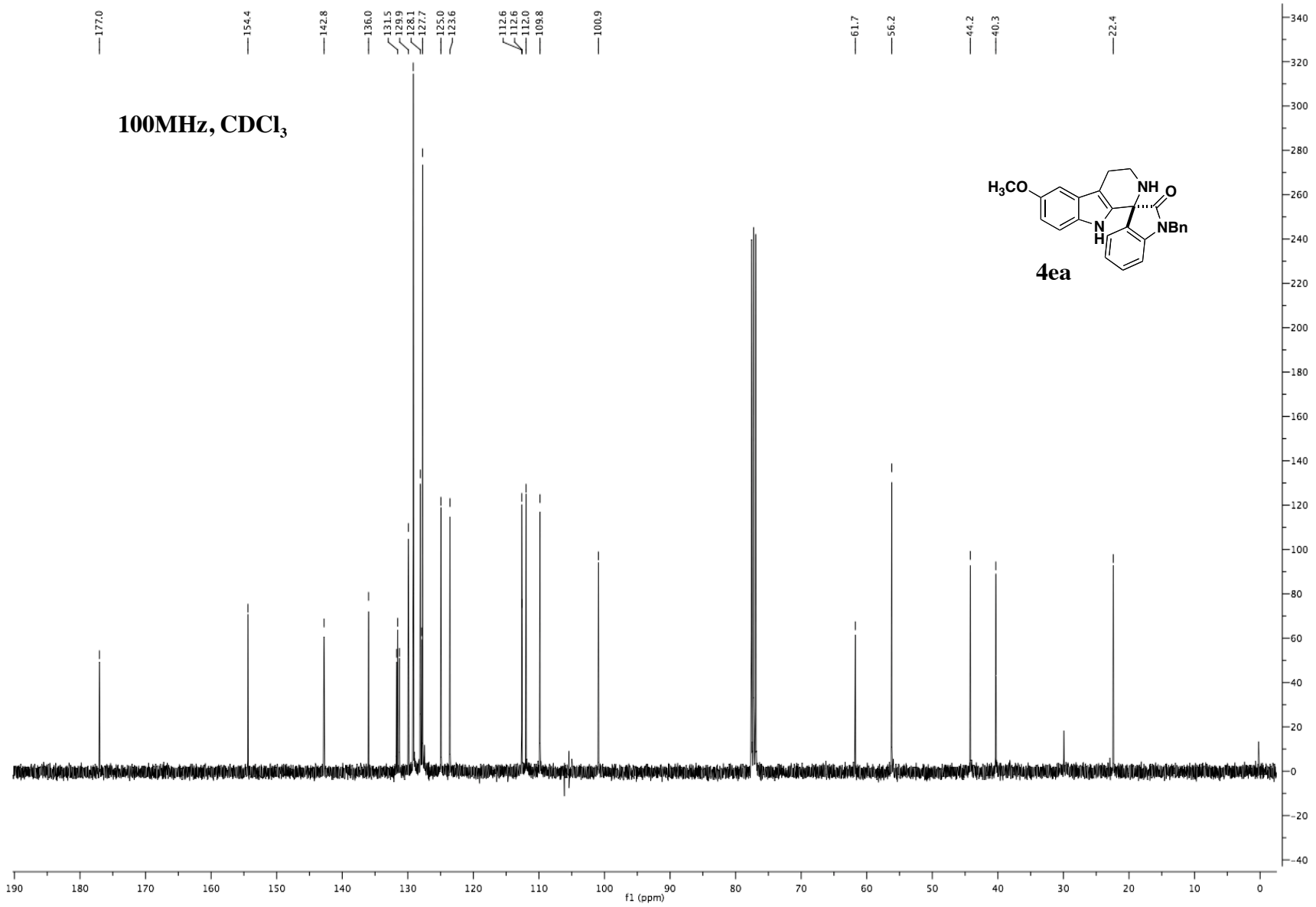
4da


176.7
156.8
154.3
137.0
131.1
127.8
114.9
111.6
109.4
106.1
100.9
62.1
56.2
56.1
40.2
29.9
26.8
22.3
100MHz, CDCl3
H3CO
NH
O
N
H
NCH3
H3CO
4da
f1 (ppm)

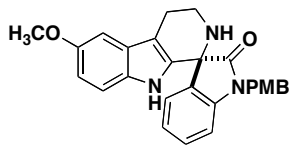
400MHz, $CDCl_3$



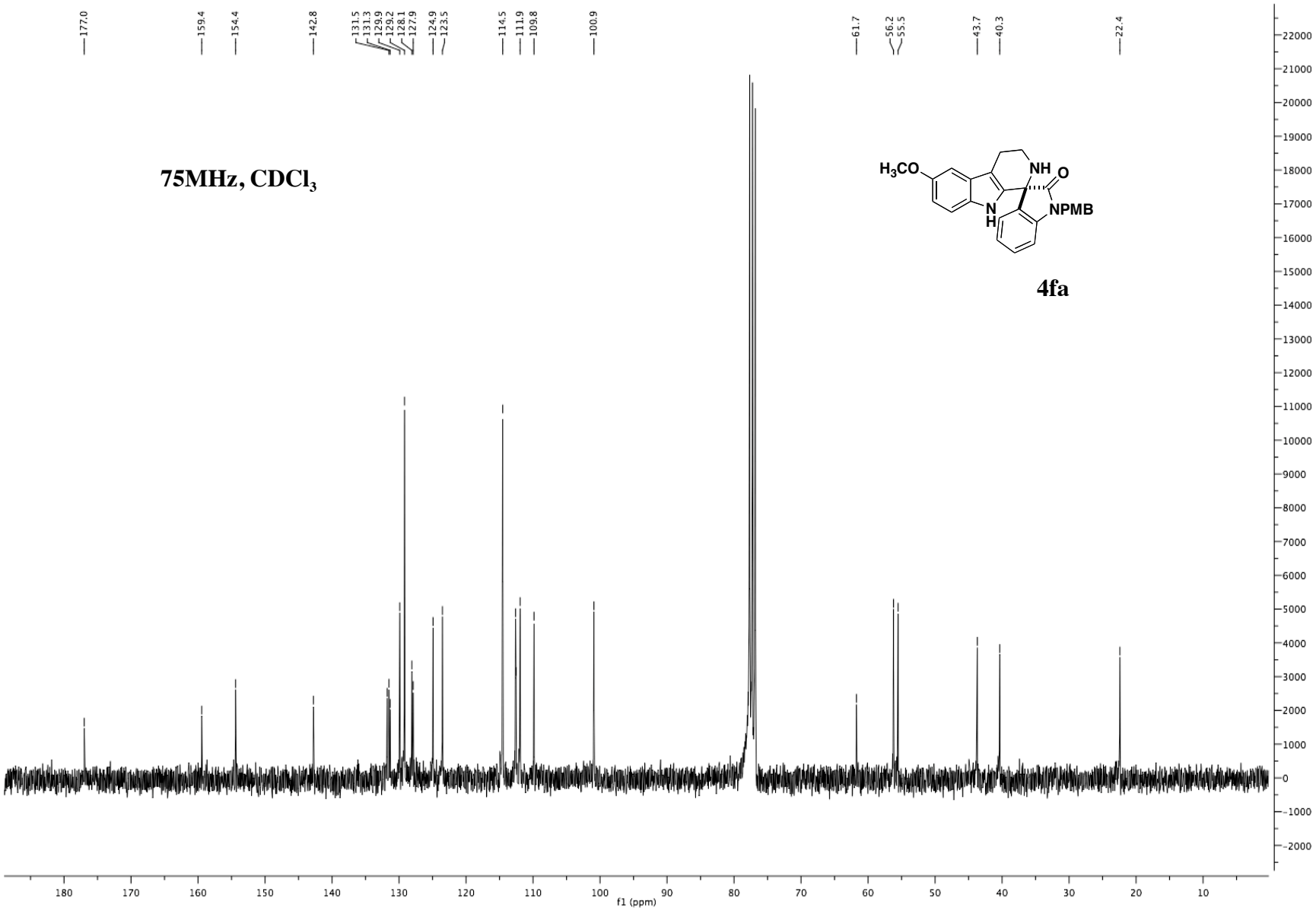
4ea

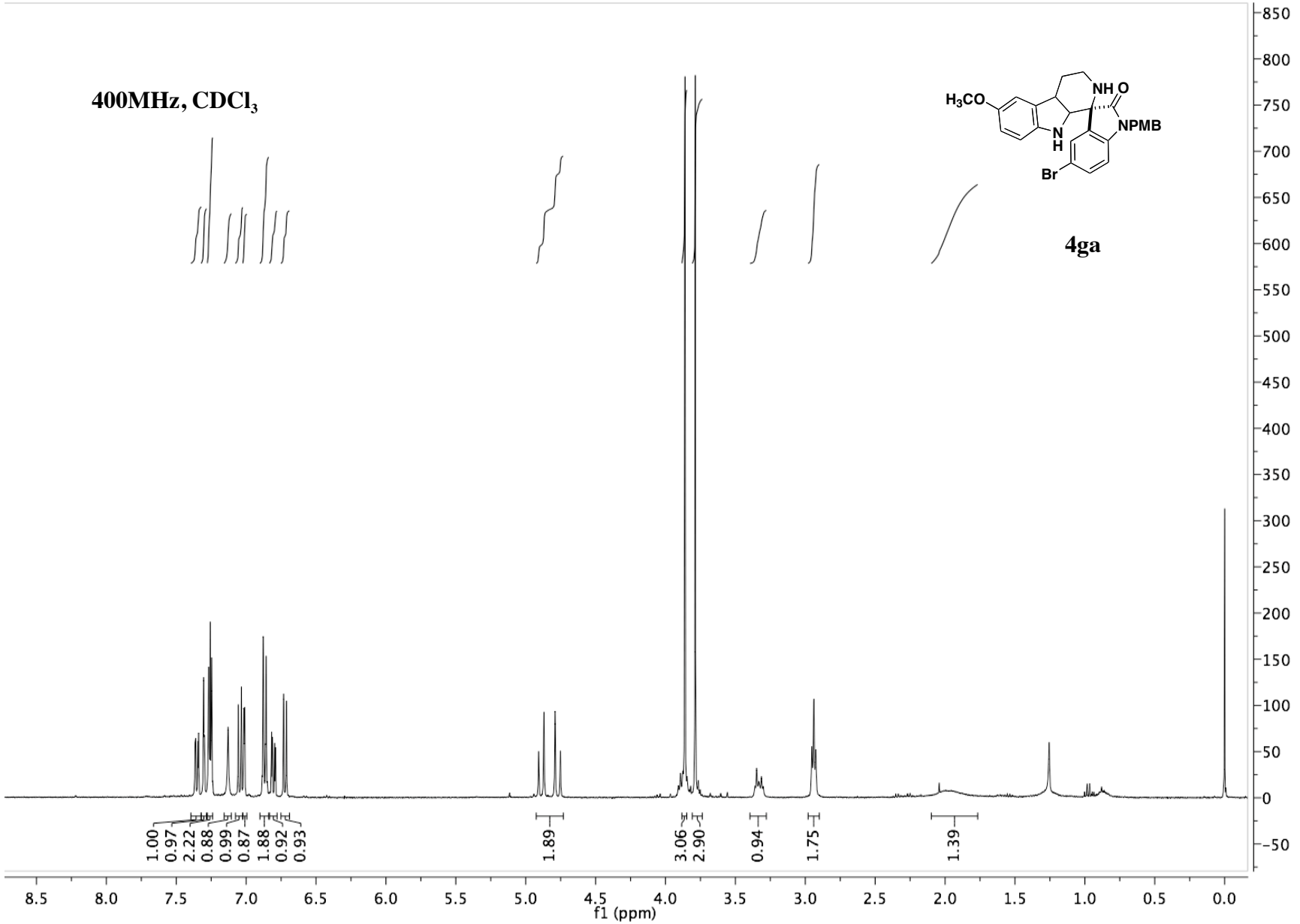

177.0
154.4
142.8
136.0
131.5
129.9
128.1
127.7
125.0
123.6
112.6
112.6
112.0
109.8
100.9
61.7
56.2
44.2
40.3
22.4
100MHz, CDCl3
H3CO
NH
O
N
H
NBn
4ea
f1 (ppm)

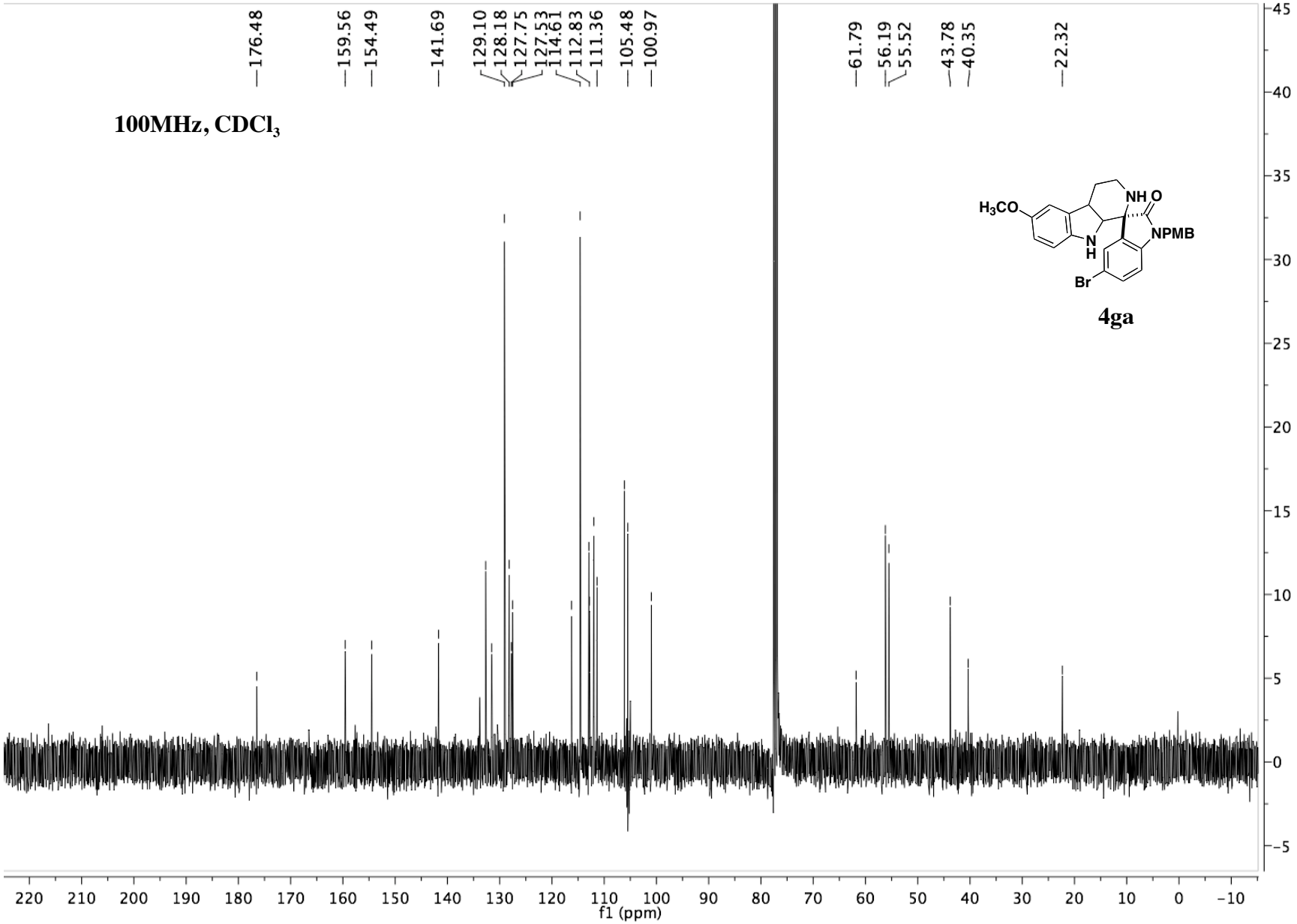
300MHz, $CDCl_3$



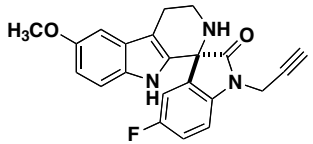
4fa


177.0
159.4
154.4
142.8
131.5
131.3
129.9
129.2
128.1
127.9
124.9
123.5
114.5
111.9
109.8
100.9
61.7
56.2
55.5
43.7
40.3
22.4
75MHz, CDCl3
H3CO
NH
O
N
H
NPMB
4fa
f1 (ppm)

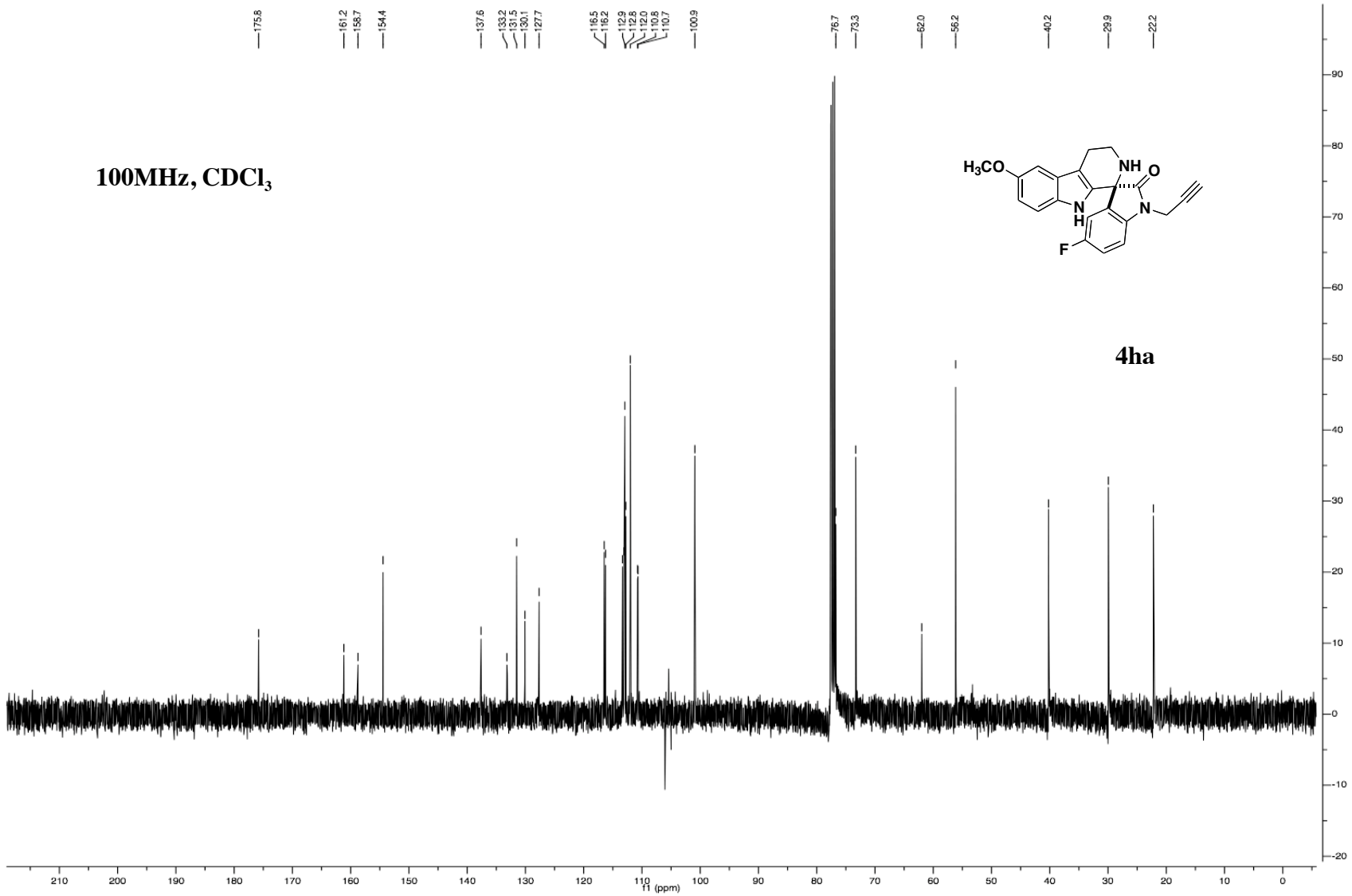

400MHz, CDCl3
H3CO
NH
O
N
H
NPMB
Br
4ga
1.00
0.97
2.22
0.88
0.99
0.87
1.88
0.92
0.93
1.89
3.06
2.90
0.94
1.75
1.39
f1 (ppm)


176.48
159.56
154.49
141.69
129.10
128.18
127.75
127.53
114.61
112.83
111.36
105.48
100.97
61.79
56.19
55.52
43.78
40.35
22.32
100MHz, CDCl3
H3CO
NH O
NPMB
N
H
Br
4ga
f1 (ppm)

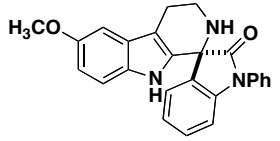
400MHz, $CDCl_3$



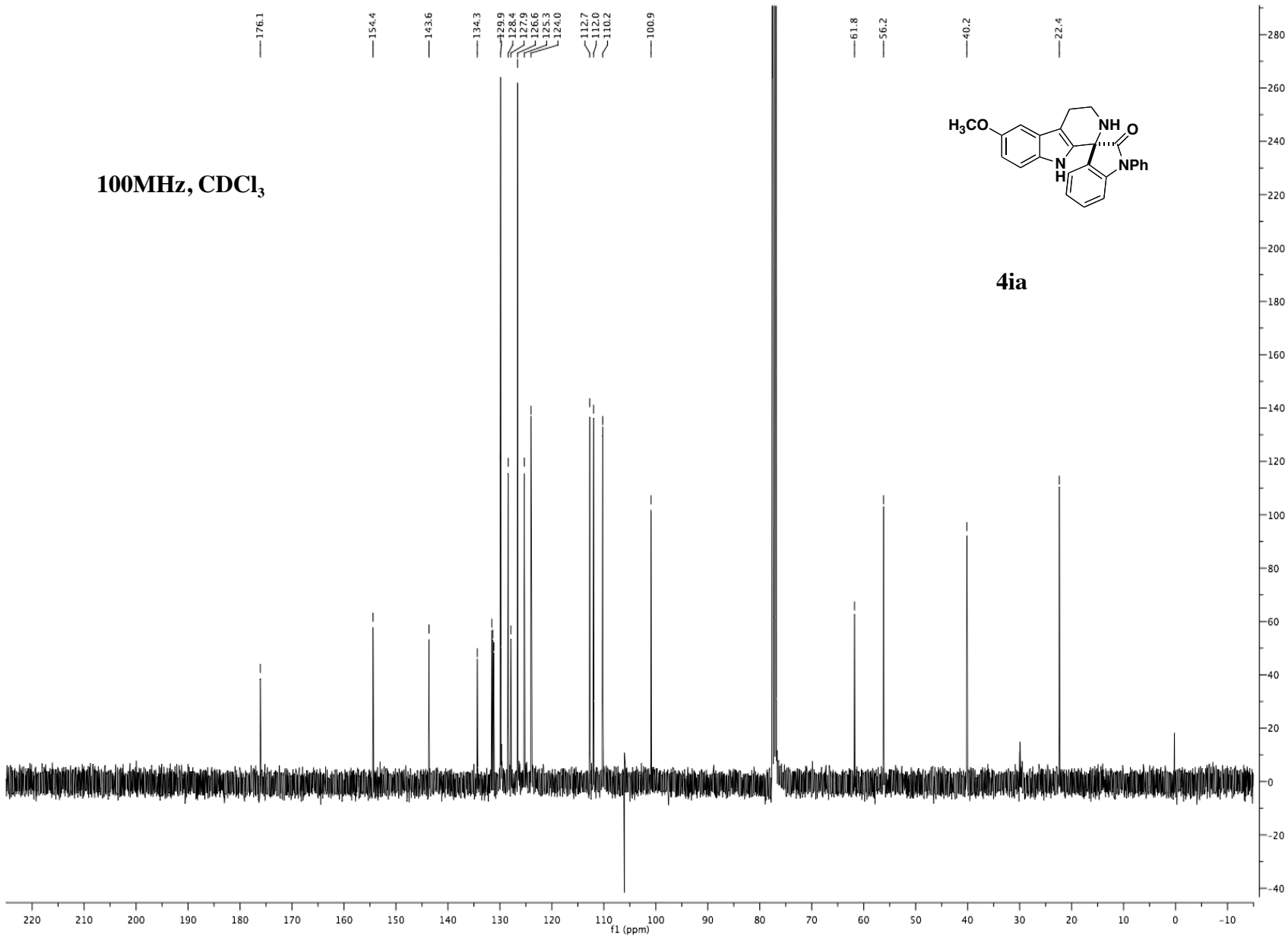
4ha


175.8
161.2
158.7
154.4
137.6
133.2
131.5
130.1
127.7
116.5
116.2
112.9
112.8
112.0
110.8
110.7
100.9
76.7
73.3
62.0
56.2
40.2
29.9
22.2
100MHz, CDCl3
H3CO
NH
O
N
H
N
F
4ha
f1 (ppm)

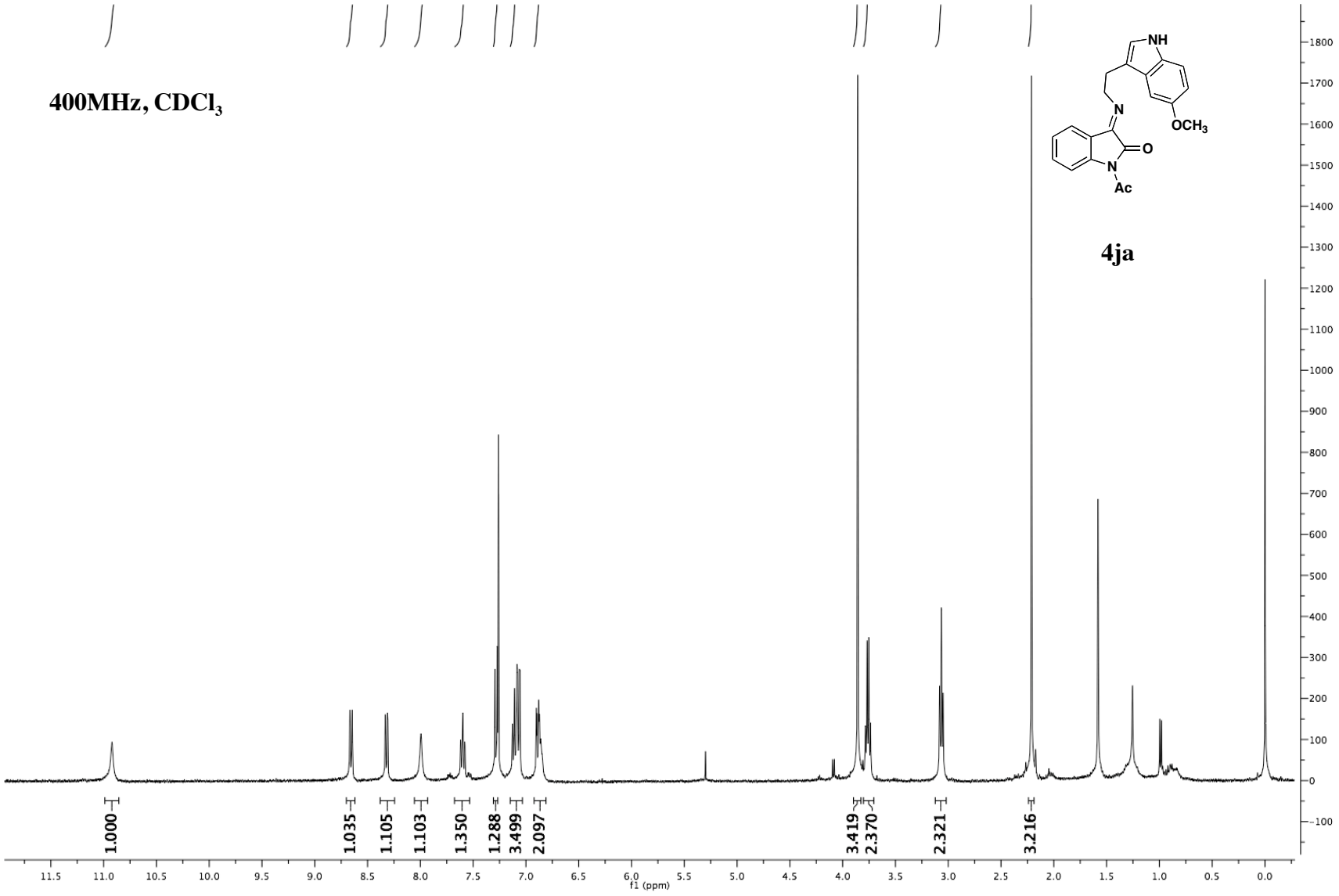
400MHz, $CDCl_3$



4ia

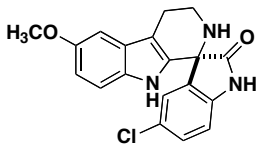

176.1
154.4
143.6
134.3
129.9
128.4
127.9
126.6
125.3
124.0
112.7
112.0
110.2
100.9
61.8
56.2
40.2
22.4
100MHz, CDCl3
H3CO
NH
O
N
H
NPh
4ia
f1 (ppm)

400MHz, $CDCl_3$



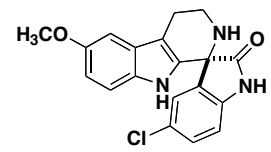
4ja

400MHz, $CDCl_3$



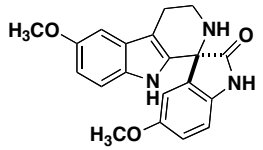
4la

100MHz, $CDCl_3$

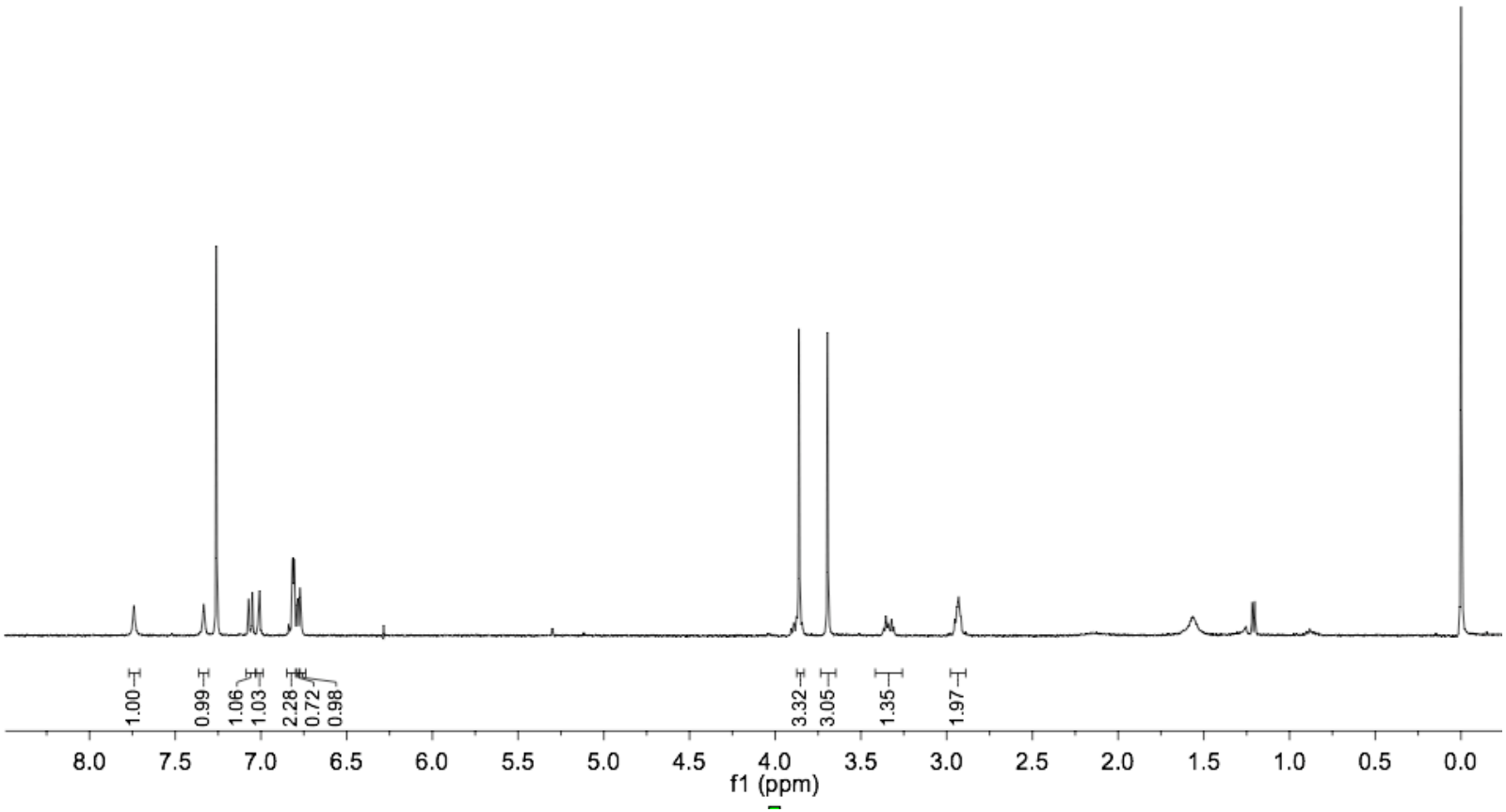


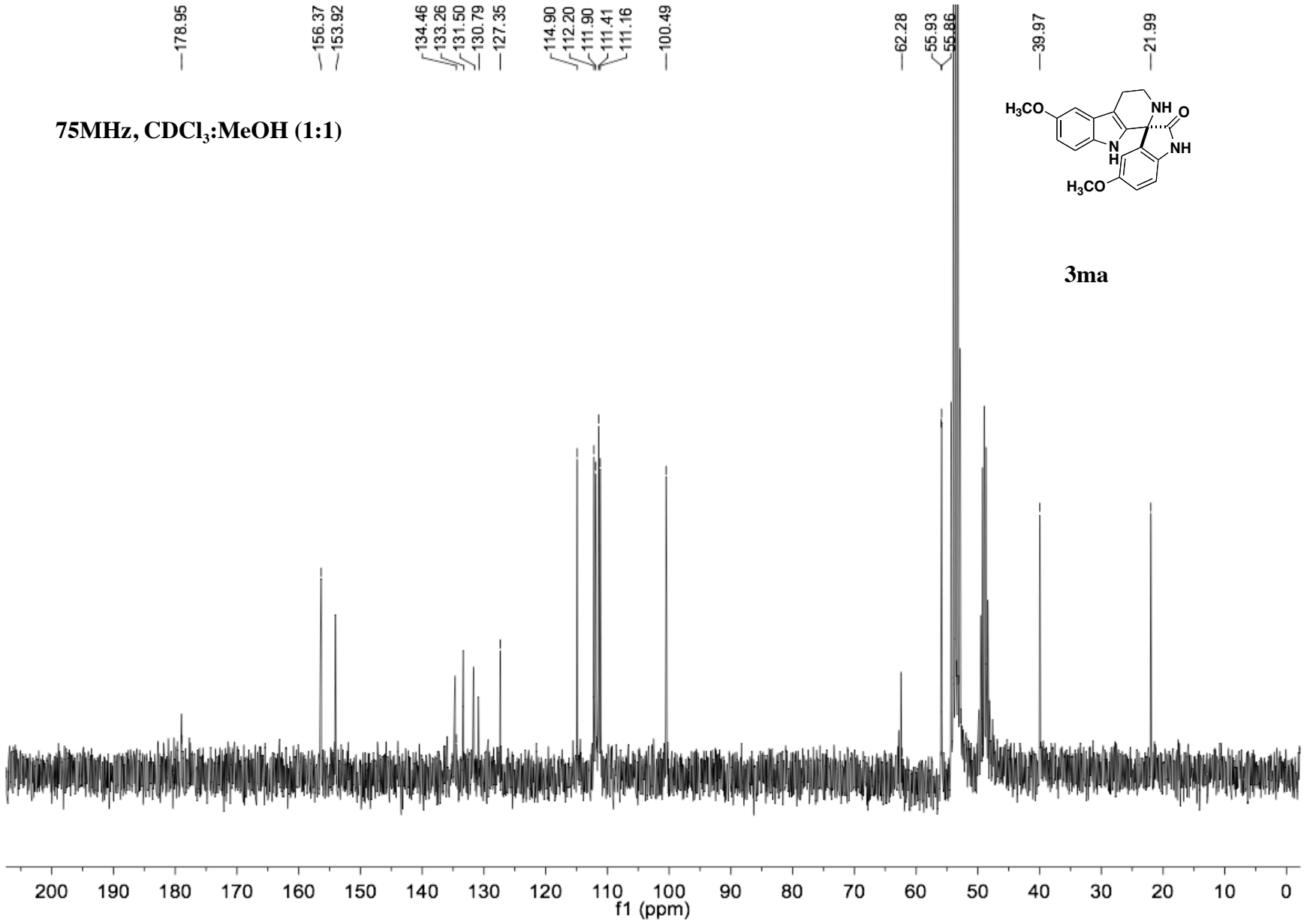
4la

400MHz, $CDCl_3$

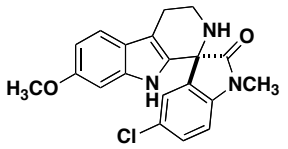


3ma



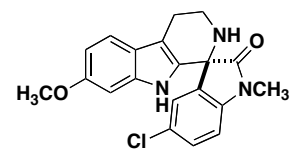

178.95
156.37
153.92
134.46
133.26
131.50
130.79
127.35
114.90
112.20
111.90
111.41
111.16
100.49
62.28
55.93
55.86
39.97
21.99
75MHz, CDCl3:MeOH (1:1)
H3CO
NH
O
N
H
NH
H3CO
3ma
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

400MHz, $CDCl_3$



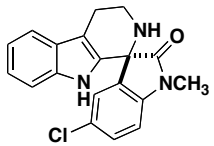
4bb

150MHz, $CDCl_3$



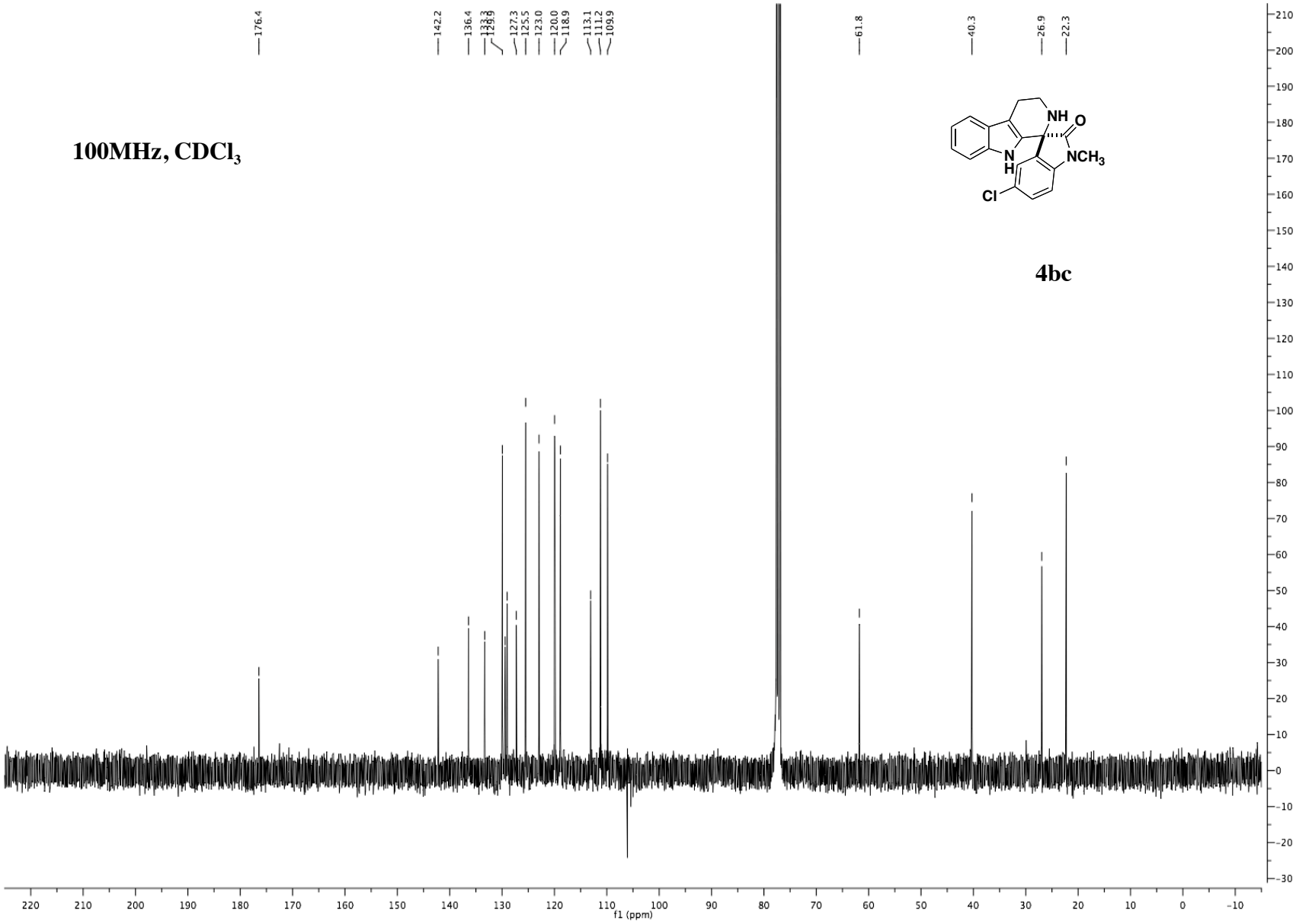
4bb

400MHz, $CDCl_3$



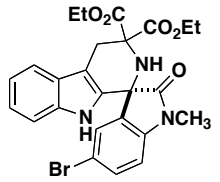
4bc

100MHz, $CDCl_3$

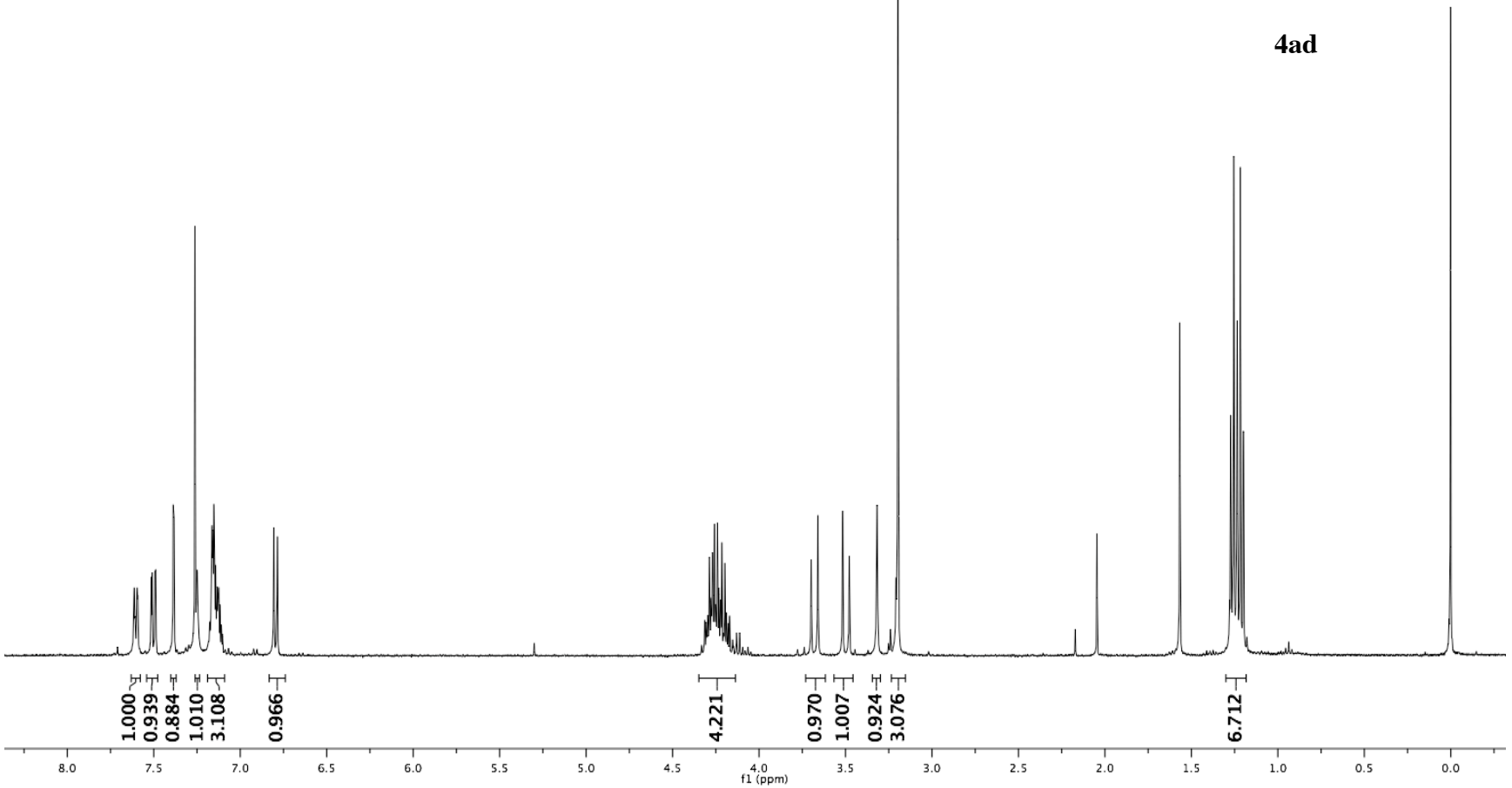


4bc

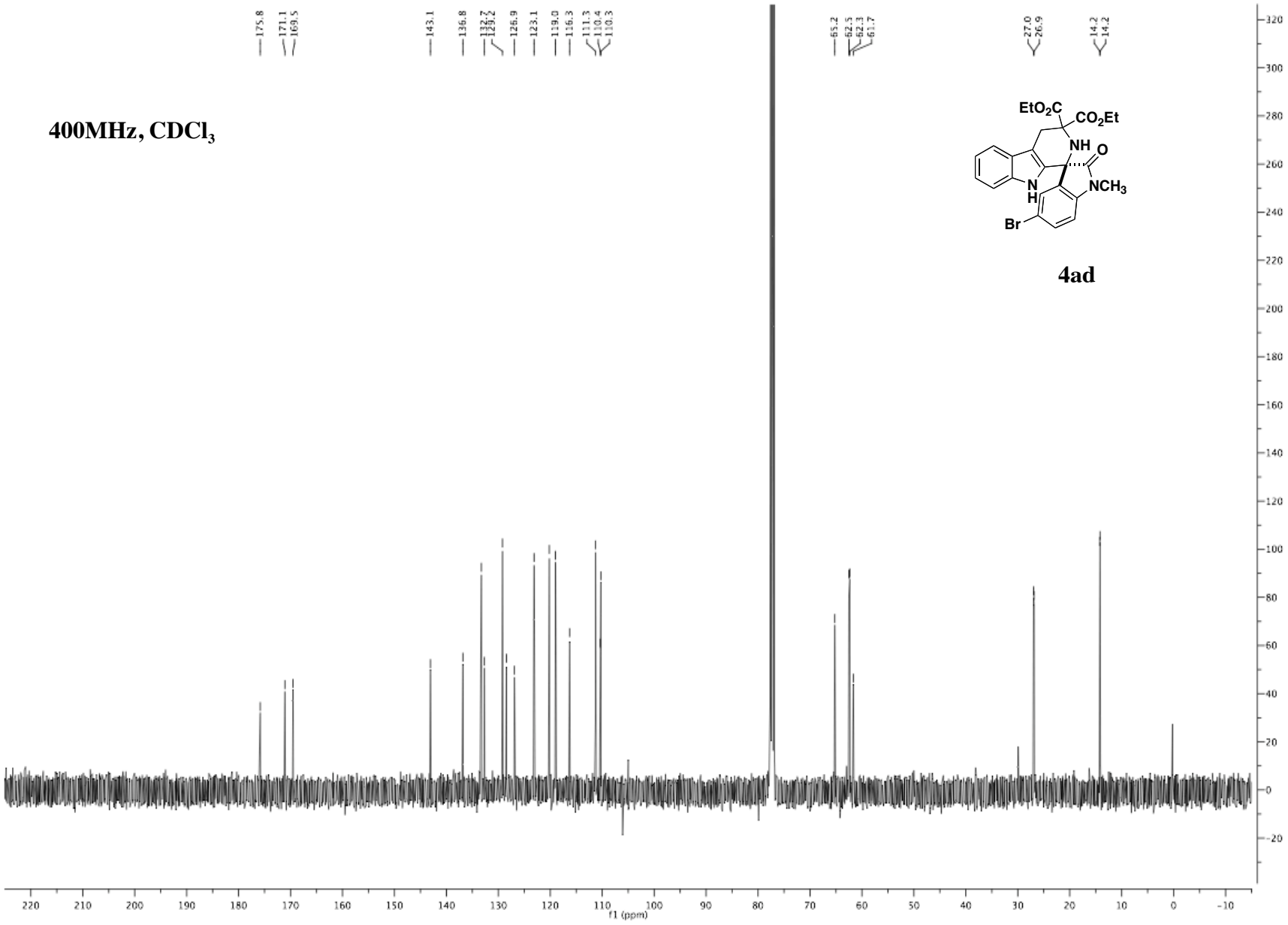
400MHz, $CDCl_3$



4ad



400MHz, $CDCl_3$



4ad