**Supporting Information**

# *Enantioselective Synthesis of (+)-Peganumine A*

**Cyril Piemontesi, Qian Wang, and Jieping Zhu***

**Laboratory of Synthesis and Natural Products, Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne, EPFL-SB-ISIC-LSPN, BCH5304, CH-1015 Lausanne, Switzerland**

# 1. General Information

Reagents and solvents were purchased from commercial sources (Aldrich, Acros, Merck, Fluka and VWR international) and preserved under argon. More sensitive compounds were stored in a desiccator or glove-box if required. Reagents were used without further purification unless otherwise noted.

All reactions were performed under argon (or nitrogen) unless otherwise noted. When needed, glassware was dried overnight in an oven (T > 100 °C) or *in vacuo* with a heat gun (T > 200 °C).

When solvents are indicated as dry they were either purchased as such, distilled prior to use or were dried by a passage through a column of anhydrous alumina or copper using a Puresolv MD 5 from Innovative Technology Inc., based on the Grubb's design.

Flash column chromatography was performed using Silicycle P60 silica: 230-400 mesh (40-63 µm) silica.

Reactions were monitored using Merck Kieselgel $60F_{254}$ aluminum or glass backed plates. TLC's were visualized by UV fluorescence (254 nm) then one of the According to: $KMnO_4$, phosphomolybdic acid, ninhydrin, pancaldi, *p*-anisaldehyde or vanillin.

NMR spectra were recorded on a Brüker Avance III-400 or Brüker Avance III HD-600 spectrometer at room temperature, $^{1}H$ frequency is at 400.13 MHz, $^{13}C$ frequency is at 100.62 MHz. Chemical shifts (δ) were reported in parts per million (ppm) relative to residual solvent peaks rounded to the nearest 0.01 ppm for proton and 0.1 ppm for carbon (ref : $CHCl_3$ [$^{1}H$: 7.26 ppm, $^{13}C$: 77.2 ppm], MeOH [$^{1}H$: 3.31 ppm, $^{13}C$: 49.0 ppm], DMSO [$^{1}H$: 2.50 ppm, $^{13}C$: 39.5 ppm]). Coupling constants (J) were reported in Hz to the nearest 0.1 Hz. Peak multiplicity was indicated as follows s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Attribution of peaks was done using the multiplicities and integrals of the peaks. When needed, the COSY, HSQC and HMBC experiments were carried out to confirm the attribution.

IR spectra were recorded in a Jasco FT/IR-4100 spectrometer outfitted with a PIKE technology MIRacleTM ATR accessory as neat films compressed onto a Zinc Selenide window. The spectra are reported in $cm^{-1}$. Abbreviations used are: w (weak), m (medium), s (strong) and br (broad).

Mass spectra were obtained by using a Waters ACQUITY H-class UPLC/MS ACQ-SQD by electron ionization (EI positive and negative) or a Finnigan TSQ7000 by electrospray ionization (ESI+). The accurate masses were measured by the mass spectrometry service of the EPFL by ESI-TOF using a QTOF Ultima from Waters.

Specific optical rotations $[\alpha]_D$ were obtained with a Jasco P-2000 polarimeter (589 nm).

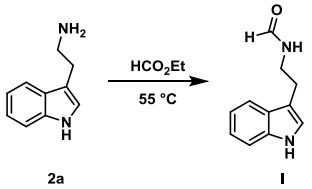
Melting points are uncorrected and were recorded on a Stuart SMP30 melting point apparatus.

For all general procedures the order of addition of reagents has to be respected.

CuDPP was prepared according to the literature.[1]

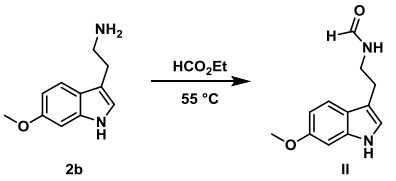
The thiourea catalyst **(*S*)-18** was prepared according to the literature.[2]

## 2. Experimental procedures and characterization data




**N-(2-(1H-indol-3-yl)ethyl)formamide (I):** According to a reported procedure,[3] a solution of tryptamine (**2a**) (16.0 g, 100 mmol, 1 equiv) in dry ethyl formate (60 mL, 1.67 M) was refluxed for 5 h. The reaction mixture was cooled to room temperature and evaporated *in vacuo* to obtain the formamide **I** (18.8 g) which was used directly in the next step without further purification. For analysis, the crude product can be purified by flash column chromatography ($SiO_2$, 95:5 DCM/MeOH) to yield the pure product **I** as a yellowish oil.

The spectral data were in accordance with those reported in the literature.[4]



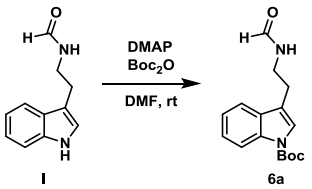

**N-(2-(6-methoxy-1H-indol-3-yl)ethyl)formamide (II):** According to a reported procedure,[5] a solution of 6-methoxytryptamine (**2b**) (3100 mg, 16.3 mmol, 1 equiv) in dry ethyl formate (50 mL, 0.33 M) was refluxed for 12 h. The reaction mixture was cooled to room temperature and evaporated *in vacuo* to obtain the formamide **II** (3.45 g) which was used directly in the next step without further purification. For analysis, the crude product can be purified by flash column chromatography ($SiO_2$, 95:5 DCM/MeOH) to yield the pure product **II** as a yellowish oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 8.34 (br s, 0.2H), 8.30 (br s, 0.8H), 8.06 (s, 0.8H), 7.85 (d, *J* = 12.2 Hz, 0.2H), 7.43 (d, *J* = 8.6 Hz, 0.8H), 7.39 (d, *J* = 8.4 Hz, 0.2H), 6.89 (s, 0.8 H), 6.83 (s, 1.2 H), 6.78 (d, *J* = 8.6 Hz, 1H), 5.79 (s, 1H), 3.82 (s, 3H), 3.60 (q, *J* = 6.5 Hz, 1.6H), 3.46 (q, *J* = 6.3 Hz, 0.4H), 2.98 – 2.85 (m, 2H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ Major rotamer: 161.4, 156.7, 137.3, 121.7, 121.1, 119.3, 112.4, 109.6, 94.9, 55.8, 38.4, 25.3. Minor rotamer: 164.8, 156.7, 137.4, 121.6, 121.3, 119.0, 111.4, 109.7, 95.0, 55.8, 42.1, 27.5.

**HRMS:** (ESI) *m/z* calcd for $C_{12}H_{15}N_2O_2$ ($[M+H]^+$): 219.1128; found: 219.1131.

**IR:** ν ($cm^{-1}$) 3297 (w), 2937 (w), 2818 (w), 1660 (s), 1626 (m), 1552 (w), 1504 (m), 1457 (m), 1385 (w), 1342 (w), 1306 (w), 1259 (m), 1199 (m), 1160 (s), 1093 (w), 1027 (m), 943 (w), 804 (m).



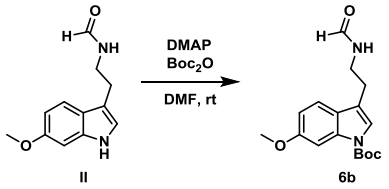

**tert-butyl 3-(2-formamidoethyl)-1H-indole-1-carboxylate (6a):** According to a reported procedure,[3] the above-obtained formamide **I** (18.8 g, 1 equiv) and DMAP (305 mg, 2.5 mmol, 0.025 equiv) were dissolved in dry DMF (333 mL, 0.3 M). $Boc_2O$ (21.8 g, 100 mmol, 1 equiv) in DMF (60 mL) was added dropwise and the reaction mixture was stirred at room temperature for 24 h. The mixture was quenched with water and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over $Na_2SO_4$ and evaporated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, 98:2 DCM/MeOH) to yield the pure product **6a** (20.8 g, 72% over 2 steps) as a yellowish oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 8.12 (br s, 1.7H), 7.96 –7.93 (m, 0.3H), 7.53 (dt, *J* = 7.8, 0.9 Hz, 0.85H), 7.47 (dt, *J* = 7.8, 1.0 Hz, 0.15H), 7.42 (br s, 1H), 7.36 – 7.28 (m, 1H), 7.29 – 7.19 (m, 1H), 5.92 (s, 1H), 3.62 (q, *J* = 6.6 Hz, 1.7H), 3.53 (q, *J* = 6.7 Hz, 0.3H), 2.96 – 2.87 (m, 2H), 1.66 (s, 9H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ Major rotamer: 161.4, 149.7, 135.6, 130.3, 124.7, 123.4, 122.7, 118.9, 117.4, 115.4, 83.8, 37.8, 28.3, 25.1. Minor rotamer: 164.5, 149.6, 135.7, 129.9, 124.8, 123.7, 122.7, 118.6, 116.4, 115.6, 83.9, 41.4, 28.3, 27.3.

**HRMS:** (ESI) *m/z* calcd for $C_{16}H_{21}N_2O_3$ ($[M+H]^+$): 289.1547; found: 289.1550.

**IR:** ν ($cm^{-1}$) 3282 (w), 3052 (w), 2978 (w), 2934 (w), 2865 (w), 1735 (m), 1728 (s), 1662 (s), 1537 (w), 1453 (m), 1375 (s), 1308 (w), 1254 (m), 1224 (w), 1156 (s), 1090 (s), 1050 (w), 1019 (w), 857 (w), 766 (m), 746 (s).



II 6b

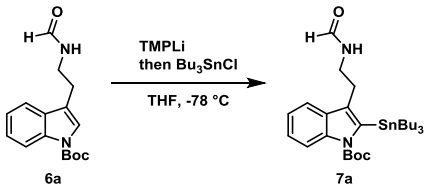
**tert-butyl 3-(2-formamidoethyl)-6-methoxy-1H-indole-1-carboxylate (6b):** According to a reported procedure,[5] the above-obtained formamide **II** (3450 mg, 1 equiv) and DMAP (50 mg, 0.41 mmol, 0.025 equiv) were dissolved in dry DMF (50 mL, 0.3 M). $Boc_2O$ (3557 mg, 16.30 mmol, 1 equiv) in DMF (10 mL) was added dropwise and the reaction mixture was stirred at room temperature for 24 h. The mixture was quenched with water and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over $Na_2SO_4$ and evaporated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, 98:2 DCM/MeOH) to yield the pure product **6b** (4.52 g, 87% over 2 steps) as a yellowish oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 8.10 (d, *J* = 1.6 Hz, 0.85H), 7.92 (d, *J* = 11.9 Hz, 0.15H), 7.71 (s, 1H), 7.36 (d, *J* = 8.6 Hz, 0.85H), 7.33 – 7.27 (m, 1.15H), 6.87 – 6.84 (m, 1H), 5.99 (s, 1H), 3.85 (s, 0.45 H), 3.80 (s, 2.55 H), 3.59 (q, *J* = 6.6 Hz, 1.70H), 3.50 (q, *J* = 6.6 Hz, 0.3H), 2.92 – 2.80 (m, 2H), 1.65 (s, 9H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ Major rotamer: 161.3, 158.0, 149.8, 136.6, 124.0, 121.9, 119.4, 117.4, 111.9, 99.6, 83.6, 55.7, 37.7, 28.2, 25.2. Minor rotamer: 164.5, 158.1, 149.7, 136.6, 123.6, 122.3, 119.1, 116.4, 112.1, 99.6, 83.7, 55.7, 41.4, 28.2, 27.3.

**HRMS:** (ESI) *m/z* calcd for $C_{17}H_{23}N_2O_4$ ($[M+H]^+$): 319.1652; found: 319.1657.

**IR:** ν ($cm^{-1}$) 3291 (w), 2977 (w), 2936 (w), 1726 (s), 1663 (m), 1619 (w), 1572 (w), 1533 (w), 1487 (m), 1442 (m), 1380 (s), 1325 (w), 1253 (m), 1226 (s), 1156 (s), 1091 (s), 1037 (m), 905 (m), 851 (w), 808 (w), 767 (w), 732 (m).



6a 7a

**tert-butyl 3-(2-formamidoethyl)-2-(tributylstannyl)-1H-indole-1-carboxylate (7a):** According to a reported procedure,[5] to a solution of tetramethylpiperidine (19.6 mL, 115 mmol, 2.3 equiv) in dry THF (170 mL) was added *n*-BuLi (2.35 M, 53.2 mL, 125 mmol, 2.5 equiv) dropwise at -78 °C. After stirring at -78 °C for 10 minutes, the formamide **6a** (14.4 g, 50 mmol, 1 equiv) in THF (80 mL) was added dropwise at -78 °C. After stirring at -78 °C for 40 minutes, $Bu_3SnCl$ (40.7 mL, 150 mmol, 3 equiv) was added and the reaction mixture was stirred at -78 °C for another 20 min. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $Na_2SO_4$ and evaporated *in vacuo*. The crude product was purified by flash column

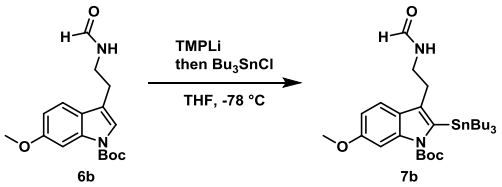
chromatography ($SiO_2$, PE/EA 95:5 + 3% $NEt_3$ to PE/EA 2:1 + 3% $NEt_3$) to yield the pure product **7a** (23.1 g, 80%) as a yellowish solid.

**$^1$H NMR (400 MHz, $CD_3OD$):** δ 8.04 (s, 1H), 7.97 – 7.91 (m, 1H), 7.63 – 7.57 (m, 1H), 7.26 – 7.18 (m, 2H), 3.48 – 3.38 (m, 2H), 3.00 – 2.92 (m, 2H), 1.70 (s, 9H), 1.62 – 1.49 (m, 6H), 1.42 – 1.29 (m, 6H), 1.18 – 1.07 (m, 6H), 0.88 (t, *J* = 7.3 Hz, 9H).

**$^{13}$C NMR (101 MHz, $CD_3OD$):** δ 163.6, 153.8, 140.1, 138.8, 133.5, 130.6, 124.9, 123.4, 119.4, 116.4, 85.4, 40.4, 30.4, 28.5, 28.4, 27.2, 14.1, 14.0.

**HRMS:** (ESI) *m/z* calcd for $C_{28}H_{47}N_2O_3Sn$ ($[M+H]^+$): 579.2603; found: 579.2607.

**IR:** ν ($cm^{-1}$) 3475 (w), 2950 (w), 2922 (w), 2851 (w), 1713 (s), 1660 (m), 1613 (w), 1488 (w), 1441 (w), 1369 (s), 1333 (m), 1292 (w), 1218 (m), 1158 (s), 1103 (m), 1065 (w), 1038 (w), 960 (w), 915 (w), 812 (w), 769 (w).



6b 7b

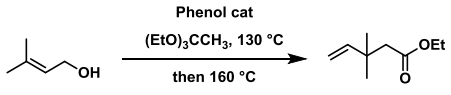
**tert-butyl 3-(2-formamidoethyl)-6-methoxy-2-(tributylstannyl)-1H-indole-1-carboxylate (7b):** According to a reported procedure,[5] to a solution of tetramethylpiperidine (5.61 mL, 32.93 mmol, 2.3 equiv) in dry THF (47 mL) was added *n*-BuLi (2.35 M, 15.23 mL, 35.79 mmol, 2.5 equiv) dropwise at -78 °C. After stirring at -78 °C for 10 minutes, the formamide **6b** (4558 mg, 14.32 mmol, 1 equiv) in THF (24 mL) was added dropwise at -78 °C. After stirring at -78 °C for 40 min, $Bu_3SnCl$ (11.65 mL, 42.95 mmol, 3 equiv) was added and the reaction mixture was stirred at -78 °C for another 20 min. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $Na_2SO_4$ and evaporated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, PE/EA 95:5 + 3% $NEt_3$ to PE/EA 2:1 + 3% $NEt_3$) to yield the pure product **7b** (6.79 g, 78%) as a yellowish solid.

**$^1$H NMR (400 MHz, $CD_3OD$):** δ 8.04 (s, 0.9H), 7.77 (s, 0.1H), 7.52 (d, *J* = 2.2 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 0.9H), 7.35 (d, *J* = 8.6 Hz, 0.1H), 6.83 (dd, *J* = 8.6, 2.3 Hz, 1H), 3.80 (s, 3H), 3.44 – 3.34 (m, 2H), 2.96 – 2.85 (m, 2H), 1.68 (s, 9H), 1.64 – 1.42 (m, 6H), 1.39 – 1.25 (m, 6H), 1.20 – 0.98 (m, 6H), 0.87 (t, *J* = 7.3 Hz, 9H).

**$^{13}$C NMR (101 MHz, $CD_3OD$):** δ 163.6, 159.0, 153.7, 139.7, 138.1, 130.6, 127.5, 119.8, 112.1, 101.1, 85.1, 55.9, 40.4, 30.4, 28.5, 28.4, 27.2, 14.1, 14.0.

**HRMS:** (ESI) *m/z* calcd for $C_{29}H_{49}N_2O_4Sn$ ($[M+H]^+$): 609.2709; found: 609.2712.

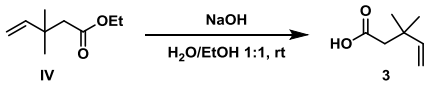
**IR:** ν ($cm^{-1}$) 3476 (w), 2954 (w), 2923 (w), 2852 (w), 1709 (s), 1660 (m), 1613 (w), 1485 (w), 1438 (w), 1369 (s), 1327 (m), 1291 (w), 1240 (w), 1218 (m), 1158 (s), 1103 (m), 1065 (w), 1038 (w), 960 (w), 915 (w), 855 (w), 812 (w), 769 (w).



III IV

**ethyl 3,3-dimethylpent-4-enoate (IV):** According to a reported procedure,[6] a solution of prenol **III** (10.0 g, 116 mmol, 1 equiv) and phenol (1.00 g, 12 mmol, 0.1 equiv) in trimethyl orthoacetate (45 mL, 244 mmol, 2.1 equiv) was heated to 130 °C for 12 h with continuous distillation of the ethanol produced then to 160 °C for 4 h. The reaction mixture was cooled to room temperature, partitioned between $Et_2O$ and 4 M HCl and extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over $Na_2SO_4$ and evaporated *in vacuo* to obtain the pure ester **IV** (18.1 g, quantitative) which was used directly in the next step without further purification.

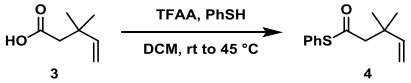
The spectral data were in accordance with those reported in the literature.[7]



IV 3

**3,3-dimethylpent-4-enoic acid (3):** According to a reported procedure,[7] to a solution of 50 % NaOH (1024 mg in 1 mL $H_2O$, 25.6 mmol, 2 equiv) in EtOH/$H_2O$ (1:1, 6.4/6.4 mL, 1 M) at 0 °C was added dropwise ester **IV** (2000 mg, 12.8 mmol, 1 equiv) over 1 h. After the addition was complete, the reaction mixture was warmed to room temperature, stirred for 5 h, and partitioned between $Et_2O$ and $H_2O$. The organic phase was extracted with 5% KOH, and the combined aqueous phases were cooled in an ice bath, acidified with concentrated HCl, and extracted with DCM. The combined organic extracts were dried over $Na_2SO_4$ and evaporated *in vacuo*. The residue was distilled at reduced pressure through a Vigreux column (bp 87 °C at 4 mm Hg) to afford **3** (1214 mg, 74%) as a colorless liquid.

The spectral data were in accordance with those reported in the literature.[7]



3 4

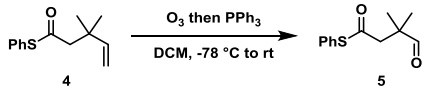
**S-phenyl 3,3-dimethylpent-4-enethioate (4):** According to a reported procedure,[8] to a solution of the acid **3** (2.91 g, 22.7 mmol, 1 equiv) in dry DCM (76 mL, 0.3 M) was added dropwise TFAA (3.16 mL, 22.7 mmol, 1 equiv) at room temperature. The mixture was stirred for 10 minutes and thiophenol (2.32 mL, 22.7 mmol, 1 equiv) was added. The mixture was stirred at 45 °C overnight, quenched with an aqueous saturated $NaHCO_3$ solution and extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over $Na_2SO_4$ and evaporated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, pure PE to PE/$Et_2O$ 9:1) to yield the pure product **4** (4.25 g, 85%) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.48 – 7.32 (m, 5H), 5.93 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.00 (dd, *J* = 17.4, 1.1 Hz, 1H), 4.98 (dd, *J* = 10.7, 1.1 Hz, 1H), 2.65 (s, 2H), 1.18 (s, 6H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 195.5, 146.6, 134.5, 129.5, 129.3, 128.3, 111.4, 55.1, 37.3, 27.0.

**HRMS:** (ESI) *m/z* calcd for $C_{13}H_{17}OS$ ($[M+H]^+$): 221.0995; found: 221.0998

**IR:** ν ($cm^{-1}$) 3082 (w), 2963 (m), 2874 (w), 1708 (s), 1642 (w), 1586 (w), 1476 (w), 1441 (w), 1417 (w), 1328 (w), 1192 (w), 1111 (w), 1001 (s), 915 (m), 746 (s), 714 (m), 690 (m).



4 5

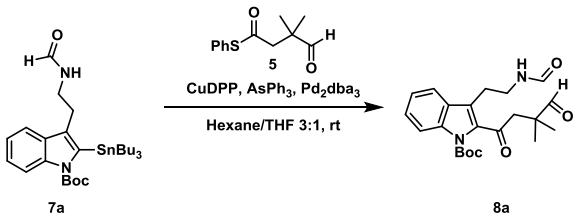
**S-phenyl 3,3-dimethyl-4-oxobutanethioate (5):** According to a reported procedure,[9] the thioester **4** (4.00 g, 18.2 mmol, 1 equiv) was dissolved in dry DCM (180 mL, 0.1 M) and cooled to -78 °C. Ozone was bubbled through the reaction mixture until a blue color persisted. $N_2$ was then bubbled through the reaction mixture until the blue color disappeared. $PPh_3$ (9.52 g, 36.3 mmol, 1.05 equiv) was added and the reaction mixture was warmed to room temperature and stirred for 5 hours. The reaction mixture was evaporated *in vacuo.* The residue was purified by flash column chromatography ($SiO_2$, PE/$Et_2O$ 9:1 to 8:1) to yield the pure product **5** (3.35 g, 83%) as a yellowish oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 9.55 (s, 1H), 7.65 – 7.26 (m, 5H), 2.91 (s, 2H), 1.19 (s, 6H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 203.6, 195.4, 134.5, 129.7, 129.4, 127.4, 50.6, 45.3, 21.9.

**HRMS:** (ESI) *m/z* calcd for $C_{12}H1_5O_2S$ ($[M+H]^+$): 223.0787; found: 223.0790.

**IR:** ν ($cm^{-1}$) 2967 (w), 2928 (w), 2711 (w), 1725 (s), 1700 (s), 1583 (w), 1474 (w), 1442 (w), 1397 (w), 1327 (w), 1194 (w), 1004 (s), 908 (m), 878 (w), 785 (w), 745 (s), 689 (m).



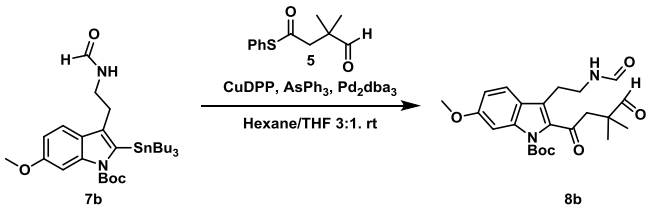

**tert-butyl 2-(3,3-dimethyl-4-oxobutanoyl)-3-(2-formamidoethyl)-1H-indole-1-carboxylate (8a):** The aldehyde **5** (321 mg, 1.44 mmol, 1 equiv), compound **7a** (600 mg, 1.59 mmol, 1.1 equiv), $Pd_2dba_3$ (132 mg, 0.14 mmol, 0.1 equiv), $AsPh_3$ (44 mg, 0.14 mmol, 0.1 equiv), and CuDPP (500 mg, 1.73 mmol, 1.2 equiv) were dissolved in dry degassed THF/Hexane (1:3, 5.4/16.2 mL, 0.067 M). After being stirred at room temperature for 6 h, the reaction mixture was filtered through Celite. The filtrate was washed with 1 M HCl, 10% $NH_4OH$ and brine, dried over $Na_2SO_4$ and evaporated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, PE/EA 1:2) to yield the pure product **8a** (544 mg, 94%) as a yellow amorphous solid.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 9.63 (s, 1H), 8.09 (s, 1H), 7.95 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.64 – 7.56 (m, 1H), 7.43 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.30 (ddd, *J* = 8.1, 7.2, 1.0 Hz, 1H), 6.97 (br s, 1H), 3.58 – 3.50 (m, 2H), 3.07 (s, 2H), 2.94 – 2.83 (m, 2H), 1.69 (s, 9H), 1.14 (s, 6H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 204.7, 195.8, 161.9, 150.2, 136.2, 136.1, 128.9, 127.6, 123.9, 123.6, 120.7, 115.8, 85.8, 51.0, 45.3, 38.3, 28.2, 23.1, 22.1.

**HRMS:** (ESI) *m/z* calcd for $C_{22}H_{29}N_2O_5$ ($[M+H]^+$): 401.2071; found: 401.2070.

**IR:** ν ($cm^{-1}$) 3335 (w), 2979 (w), 2935 (w), 2362 (w), 2338 (w), 1726 (s), 1673 (s), 1617 (w), 1560 (w), 1492 (w), 1440 (w), 1370 (s), 1324 (m), 1291 (m), 1213 (m), 1149 (s), 1084 (w), 1035 (m), 922 (w), 841 (w), 811 (w), 717 (w).



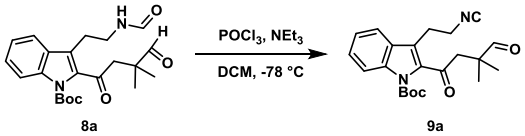

**tert-butyl 2-(3,3-dimethyl-4-oxobutanoyl)-3-(2-formamidoethyl)-6-methoxy-1H-indole-1-carboxylate (8b):** The aldehyde **5** (1.44 g, 6.49 mmol, 1 equiv), compound **7b** (4.34 g, 7.14 mmol, 1.1 equiv), $Pd_2dba_3$ (594 mg, 0.65 mmol, 0.1 equiv), $AsPh_3$ (199 mg, 0.65 mmol, 0.1 equiv), and CuDPP (2.19 g, 7.79 mmol, 1.2 equiv) were dissolved in dry degassed THF/Hexane (1:3, 24/96 mL, 0.067 M). After being stirred at room temperature for 6 h, the reaction mixture was filtered through Celite. The filtrate was washed with 1 M HCl, 10% $NH_4OH$ and brine, dried over $Na_2SO_4$ and evaporated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, PE/EA 1:2) to yield the pure product **8b** (2.65 g, 95%) as a yellow amorphous solid.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 9.63 (s, 1H), 8.11 (s, 1H), 7.52 (d, *J* = 2.3 Hz, 1H), 7.48 (d, *J* = 8.7 Hz, 1H), 7.00 (s, 1H), 6.93 (dd, *J* = 8.7, 2.3 Hz, 1H), 3.88 (s, 3H), 3.59 – 3.49 (m, 2H), 3.05 (s, 2H), 2.88 – 2.85 (m, 2H), 1.70 (s, 9H), 1.13 (s, 6H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 204.6, 195.1, 161.8, 160.5, 150.3, 137.9, 135.5, 125.1, 122.6, 121.5, 113.2, 100.0, 85.7, 55.7, 50.9, 45.5, 38.4, 28.3, 23.2, 22.1.

**HRMS:** (ESI) *m/z* calcd for $C_{23}H_{31}N_2O_6$ ($[M+H]^+$): 431.2177; found: 431.2178.

**IR:** ν ($cm^{-1}$) 3330 (w), 2976 (w), 2936 (w), 2361 (w), 2338 (w), 1726 (s), 1673 (s), 1616 (w), 1554 (w), 1490 (w), 1441 (w), 1368 (s), 1322 (m), 1289 (w), 1213 (m), 1149 (s), 1084 (w), 1035 (m), 922 (w), 841 (w), 811 (w), 766 (w), 717 (w).



8a 9a

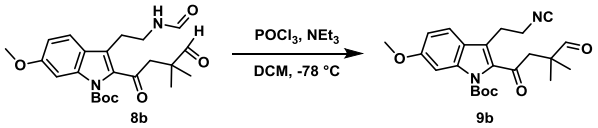
**tert-butyl 2-(3,3-dimethyl-4-oxobutanoyl)-3-(2-isocyanoethyl)-1H-indole-1-carboxylate (9a):** To a solution of the formamide **8a** (204 mg, 0.51 mmol, 1 equiv) and $NEt_3$ (354 µL, 2.55 mmol, 5 equiv) in dry DCM (1.7 mL, 0.3 M) was added $POCl_3$ (71 µL, 0.76 mmol, 1.5 equiv) dropwise at -78 °C over 30 min. The reaction mixture was stirred at this temperature for 3 h. The mixture was poured into cold aqueous saturated $Na_2CO_3$ solution and extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over $Na_2SO_4$ and evaporated *in vacuo*. The crude product was purified by flash column chromatography ($Al_2O_3$, PE/$Et_2O$ 2:1 + 3% $NEt_3$ to PE/$Et_2O$ 1:1 + 3% $NEt_3$) to yield the pure product **9a** (174 mg, 89%) as a yellowish solid.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 9.65 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.45 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 3.73 (t, *J* = 7.1 Hz, 2H), 3.13 – 3.02 (m, 4H), 1.70 (s, 9H), 1.16 (s, 6H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 204.7, 194.7, 157.1, 150.1, 136.4, 136.0, 129.1, 127.6, 123.9, 121.9, 120.6, 115.8, 86.0, 51.2, 45.2, 42.5, 28.3, 24.9, 22.3.

**HRMS:** (ESI) *m/z* calcd for $C_{22}H_{27}N_2O_4$ ($[M+H]^+$): 383.1965; found: 383.1968.

**IR:** ν ($cm^{-1}$) 2976 (w), 2934 (w), 2148 (w), 1728 (s), 1676 (w), 1617 (w), 1557 (w), 1499 (w), 1371 (m), 1323 (m), 1287 (w), 1239 (w), 1211 (m), 1153 (s), 1079 (w), 1031 (w), 839 (w).



8b 9b

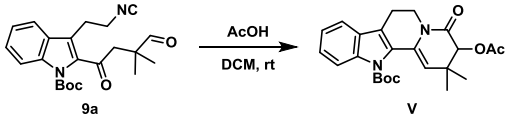
**tert-butyl 2-(3,3-dimethyl-4-oxobutanoyl)-3-(2-isocyanoethyl)-6-methoxy-1H-indole-1-carboxylate (9b):** To a solution of the formamide **8b** (1.96 g, 4.56 mmol, 1 equiv) and $NEt_3$ (3.17 mL, 22.81 mmol, 5 equiv) in dry DCM (15 mL, 0.3 M) was added $POCl_3$ (638 µL, 6.84 mmol, 1.5 equiv) dropwise at -78 °C over 30 min. The reaction mixture was stirred at this temperature for 3 h. The mixture was poured into cold aqueous saturated $Na_2CO_3$ solution and extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over $Na_2SO_4$ and evaporated *in vacuo*. The crude product was purified by flash column chromatography ($Al_2O_3$, PE/$Et_2O$ 2:1 + 3% $NEt_3$ to PE/$Et_2O$ 1:1 + 3% $NEt_3$) to yield the pure product **9b** (1.73 g, 92%) as a yellowish solid.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 9.64 (s, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.54 (d, *J* = 2.3 Hz, 1H), 6.96 (dd, *J* = 8.8, 2.3 Hz, 1H), 3.89 (s, 3H), 3.73 (t, *J* = 7.0 Hz, 2H), 3.05 (s, 2H), 3.02 (t, *J* = 7.0 Hz, 2H), 1.70 (s, 9H), 1.13 (s, 6H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 204.6, 193.9, 160.4, 157.0, 150.2, 137.7, 135.4, 123.6, 122.8, 121.5, 113.3, 99.8, 85.8, 55.8, 51.0, 45.3, 42.7, 28.3, 25.1, 22.2.

**HRMS:** (ESI) *m/z* calcd for $C_{23}H_{29}N_2O_5$ ($[M+H]^+$): 413.2071; found: 413.2075.

**IR:** ν ($cm^{-1}$) 2974 (w), 2934 (w), 2148 (w), 1728 (s), 1676 (w), 1617 (w), 1555 (w), 1494 (w), 1368 (m), 1322 (m), 1290 (w), 1238 (m), 1211 (m), 1150 (s), 1076 (w), 1032 (w), 840 (w).



9a V

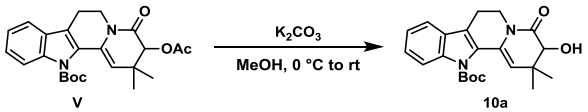
**tert-butyl 3-acetoxy-2,2-dimethyl-4-oxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (V):** To a solution of the isonitrile **9a** (20 mg, 0.052 mmol, 1 equiv) in dry DCM (5.3 mL, 0.01 M) was added acetic acid (3 µL, 0.052 mmol, 1 equiv) and the reaction mixture was stirred at room temperature for 1.5 days. The mixture was quenched with an aqueous saturated $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $Na_2SO_4$ and evaporated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, PE/EA 4:1) to yield the pure product **V** (19 mg, 85%) as a yellowish solid.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.99 (d, *J* = 8.4 Hz, 1H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.30 – 7.22 (m, 1H), 5.37 (s, 1H), 5.30 (s, 1H), 4.36 (dt, *J* = 12.9, 5.2 Hz, 1H), 3.79 (ddd, *J* = 12.9, 8.1, 4.8 Hz, 1H), 2.97 – 2.78 (m, 2H), 2.25 (s, 3H), 1.66 (s, 9H), 1.20 (s, 3H), 1.15 (s, 3H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 170.8, 166.3, 150.6, 139.5, 129.1, 127.6, 127.3, 126.2, 123.4, 122.4, 119.2, 115.0, 114.0, 84.5, 75.9, 38.9, 34.5, 28.2, 26.4, 21.4, 21.0.

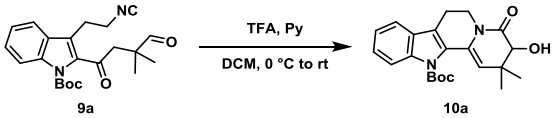
**HRMS:** (ESI) *m/z* calcd for $C_{24}H_{29}N_2O_5$ ($[M+H]^+$): 425.2071; found: 425.2075.

**IR:** ν ($cm^{-1}$) 3469 (w), 2982 (m), 1736 (m), 1665 (m), 1610 (w), 1568 (w), 1497 (w), 1461 (w), 1428 (w), 1354 (m), 1312 (m), 1276 (m), 1250 (m), 1207 (m), 1150 (s), 1049 (m), 917 (m), 851 (m), 808 (w), 731 (s).



V 10a

**tert-butyl 3-hydroxy-2,2-dimethyl-4-oxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (10a):** $K_2CO_3$ (5.2 mg, 0.038 mmol, 1.5 equiv) was added to a solution of the ester **V** (8 mg, 0.019 mmol, 1 equiv) in dry MeOH (0.19 mL, 0.1 M) at 0 °C and the reaction was warmed to room temperature and stirred for 2 hours. The mixture was quenched with an aqueous saturated $NH_4Cl$ solution and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $Na_2SO_4$ and evaporated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, PE/EA 4:1) to yield the pure product **10a** (7 mg, 98%) as a yellowish solid.



9a 10a

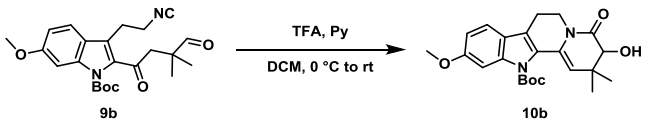
**tert-butyl 3-hydroxy-2,2-dimethyl-4-oxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (10a):** According to a reported procedure,[10] to a solution of the isonitrile **9a** (1.50 g, 3.85 mmol, 1 equiv) and pyridine (1.87 mL, 23.1 mmol, 6 equiv) in dry DCM (385 mL, 0.01 M) at 0 °C was added TFA (857 µL, 11.5 mmol, 3 equiv) and the reaction mixture was stirred at 0 °C for 2 hours and then at room temperature for 7 days. The mixture was evaporated *in vacuo*. The residue was dissolved in ethyl acetate and stirred with aqueous saturated $NaHCO_3$ for 1h. The organic phase was separated and washed with 1 M HCl, aqueous saturated $NaHCO_3$ and brine, dried over $Na_2SO_4$ and evaporated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, PE/EA 4:1) to yield the pure product **10a** (1.25 g, 85%) as a yellowish solid.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.99 (dt, *J* = 8.3, 0.8 Hz, 1H), 7.50 – 7.40 (m, 1H), 7.35 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.25 (td, *J* = 7.5, 1.0 Hz, 1H), 5.40 (s, 1H), 4.35 (dt, *J* = 12.8, 5.3 Hz, 1H), 4.04 (d, *J* = 1.9 Hz, 1H), 3.85 (ddd, *J* = 12.8, 7.9, 4.9 Hz, 1H), 3.81 (d, *J* = 2.0 Hz, 1H), 2.99 – 2.79 (m, 2H), 1.66 (s, 9H), 1.31 (s, 3H), 1.02 (s, 3H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 171.5, 150.6, 139.4, 129.1, 127.5, 126.5, 126.1, 123.3, 121.7, 119.1, 116.3, 115.0, 84.6, 74.7, 39.4, 35.4, 28.2, 26.5, 21.3, 19.4.

**HRMS:** (ESI) *m/z* calcd for $C_{22}H_{27}N_2O_4$ ($[M+H]^+$): 383.1965; found: 383.1970.

**IR:** ν ($cm^{-1}$) 3467 (w), 2975 (w), 1736 (m), 1660 (m), 1610 (w), 1568 (w), 1497 (w), 1465 (w), 1422 (w), 1351 (m), 1313 (m), 1281 (m), 1246 (m), 1207 (m), 1150 (s), 1110 (s), 1049 (m), 913 (m), 851 (m), 808 (w), 731 (s).




9b 10b

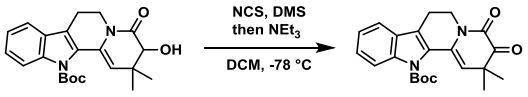
**tert-butyl 3-hydroxy-10-methoxy-2,2-dimethyl-4-oxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (10b):** According to a reported procedure,[10] to a solution of the isonitrile **9b** (1.25 g, 3.04 mmol, 1 equiv) and pyridine (984 µL, 12.2 mmol, 6 equiv) in dry DCM (304 mL, 0.01 M) at 0 °C was added TFA (452 µL, 6.08 mmol, 3 equiv) and the reaction mixture was stirred at 0 °C for 2 hours and then at room temperature for 5 days. The mixture was evaporated *in vacuo*. The residue was dissolved in ethyl acetate and stirred with aqueous saturated $NaHCO_3$ for 1h. The organic phase was separated and washed with 1 M HCl, aqueous saturated $NaHCO_3$ and brine, dried over $Na_2SO_4$ and evaporated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, PE/EA 4:1) to yield the pure product **10b** (1.07 g, 85%) as a yellowish solid.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.58 (d, *J* = 2.2 Hz, 1H), 7.31 (dd, *J* = 8.5, 0.5 Hz, 1H), 6.87 (dd, *J* = 8.6, 2.2 Hz, 1H), 5.30 (s, 1H), 4.34 (dt, *J* = 12.8, 5.3 Hz, 1H), 4.02 (s, 1H), 3.87 (s, 3H), 3.86 – 3.77 (m, 2H), 2.93 – 2.73 (m, 2H), 1.65 (s, 9H), 1.30 (s, 3H), 1.01 (s, 3H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 171.4, 159.2, 150.6, 140.7, 127.8, 126.6, 121.9, 121.4, 119.6, 114.9, 112.2, 99.5, 84.4, 74.7, 55.7, 39.3, 35.2, 28.1, 26.6, 21.3, 19.5.

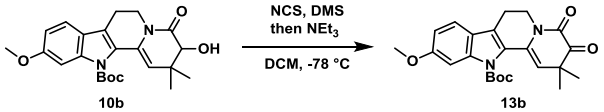
**HRMS:** (ESI) *m/z* calcd for $C_{23}H_{29}N_2O_5$ ($[M+H]^+$): 413.2071; found: 413.2073.

**IR:** ν ($cm^{-1}$) 3459 (w), 2974 (w), 1731 (m), 1665 (m), 1613 (w), 1560 (w), 1493 (w), 1464 (w), 1420 (w), 1352 (m), 1311 (m), 1278 (m), 1244 (m), 1206 (m), 1152 (s), 1113 (s), 1047 (m), 911 (m), 852 (m), 805 (w), 730 (s), 683 (w).



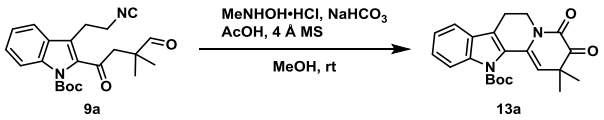

10a 13a

**tert-butyl 2,2-dimethyl-3,4-dioxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (13a):** According to a reported procedure,[11] to a solution of NCS (1.49 g, 11.1 mmol, 5 equiv) in dry DCM (56 mL) at 0 °C was added dropwise DMS (4.12 mL, 55.7 mmol, 25 equiv) and the reaction mixture was stirred at -78 °C for 1 h. The alcohol **10a** (852 mg, 2.23 mmol, 1 equiv) in DCM (10 mL) was added dropwise and then the mixture was stirred at -78 °C for two hours. Triethylamine (5.17 mL, 37.2 mmol, 17 equiv) in DCM (4 mL) was added and the mixture was stirred at -78 °C for 2 hours. The mixture was quenched with an aqueous saturated $NH_4Cl$ solution and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $Na_2SO_4$ and evaporated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, PE/EA 3:1) to yield the pure product **13a** (805 mg, 95%) as a yellow solid.




10b 13b

**tert-butyl 10-methoxy-2,2-dimethyl-3,4-dioxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (13b):** According to a reported procedure,[11] to a solution of NCS (1.16 g, 8.69 mmol, 5 equiv) in dry DCM (44 mL) at 0 °C was added dropwise DMS (3.21 mL, 43.4 mmol, 25 equiv) and the reaction mixture was stirred at -78 °C for 1 h. The alcohol **10b** (716 mg, 1.74 mmol, 1 equiv) in DCM (9 mL) was added dropwise and the mixture was stirred at -78 °C for two hours. Triethylamine (4.03 mL, 29.0 mmol, 17 equiv) in DCM (2.3 mL) was added and the mixture was stirred at -78 °C for 2 hours. The mixture was quenched with an aqueous saturated $NH_4Cl$ solution and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $Na_2SO_4$ and evaporated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, PE/EA 3:1) to yield the pure product **13b** (685 mg, 96%) as a yellow solid.



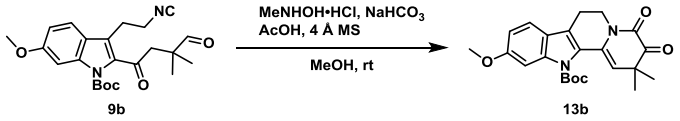

**tert-butyl 2,2-dimethyl-3,4-dioxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (13a):** According to a reported procedure,[12] a mixture of the isonitrile **9a** (200 mg, 0.52 mmol, 1 equiv), MeNHOH·HCl (48.2 mg, 0.58 mmol, 3 equiv), $NaHCO_3$ (9.21 mg, 1.05 mmol, 6 equiv) and 4 Å molecular sieves (750 mg/mmol isonitrile) in MeOH (5.3 mL, 0.01 M) was stirred for 30 min. AcOH (274 µL, 4.71 mmol, 27 equiv) was added and the reaction mixture was stirred at room temperature for 5 days. The reaction mixture was then filtered, and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, PE/EA 3:1) to yield the pure product **13a** (150 mg, 75%) as a yellow solid.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.98 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.49 (ddd, *J* = 7.6, 1.4, 0.8 Hz, 1H), 7.37 (ddd, *J* = 8.5, 7.2, 1.4 Hz, 1H), 7.32 – 7.25 (m, 1H), 5.34 (s, 1H), 4.21 (t, *J* = 5.8 Hz, 2H), 2.95 (t, *J* = 5.8 Hz, 2H), 1.65 (s, 9H), 1.39 (s, 6H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 195.7, 156.6, 150.5, 139.6, 129.1, 127.4, 126.5, 125.6, 123.6, 122.8, 119.3, 115.2, 113.0, 84.8, 45.3, 39.7, 28.2, 25.1, 21.2.

**HRMS:** (ESI) *m/z* calcd for $C_{22}H_{25}N_2O_4$ ($[M+H]^+$): 381.1809; found: 381.1812.

**IR:** ν ($cm^{-1}$) 2979 (w), 2938 (w), 2932 (w), 1731 (s), 1681 (s), 1612 (w), 1567 (w), 1491 (w), 1465 (w), 1421 (w), 1395 (w), 1355 (m), 1307 (m), 1283 (m), 1256 (m), 1166 (m), 1157 (s), 1138 (s), 1036 (m), 911 (w), 843 (w), 728 (s).



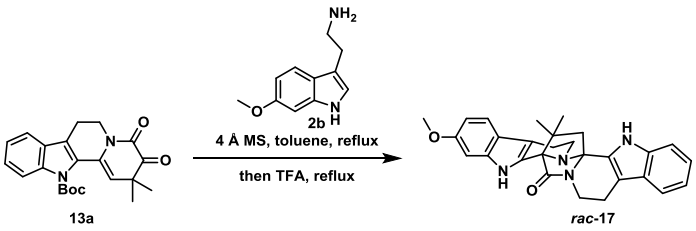

**tert-butyl 10-methoxy-2,2-dimethyl-3,4-dioxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (13b):** According to a reported procedure,[12] a mixture of the isonitrile **9b** (2.00 g, 4.85 mmol, 1 equiv), MeNHOH·HCl (1.22 g, 14.6 mmol, 3 equiv), $NaHCO_3$ (2.44 g, 29.1 mmol, 6 equiv) and 4 Å molecular sieves (750 mg/mmol isonitrile) in MeOH (485 mL, 0.01 M) was stirred for 30 min. AcOH (7.50 mL, 131 mmol, 27 equiv) was added and the reaction mixture was stirred at room temperature for 5 days. The reaction mixture was then filtered, and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, PE/EA 3:1) to yield the pure product **13b** (1.49 g, 75%) as a yellow solid.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.54 (d, *J* = 2.4 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 6.86 (dd, *J* = 8.6, 2.3 Hz, 1H), 5.23 (s, 1H), 4.15 (t, *J* = 5.8 Hz, 2H), 3.84 (s, 3H), 2.87 (t, *J* = 5.8 Hz, 2H), 1.63 (s, 9H), 1.35 (s, 6H).

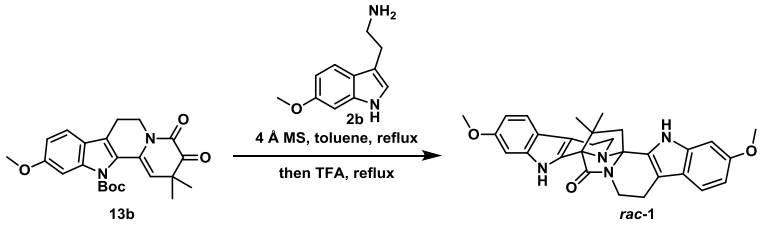
**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 195.7, 159.3, 156.5, 150.4, 140.8, 127.7, 125.6, 122.9, 121.1, 119.8, 112.3, 111.5, 99.6, 84.5, 55.6, 45.1, 39.4, 28.1, 25.0, 21.1.

**HRMS:** (ESI) *m/z* calcd for $C_{23}H_{27}N_2O_5$ ($[M+H]^+$): 411.1914; found: 411.1910.

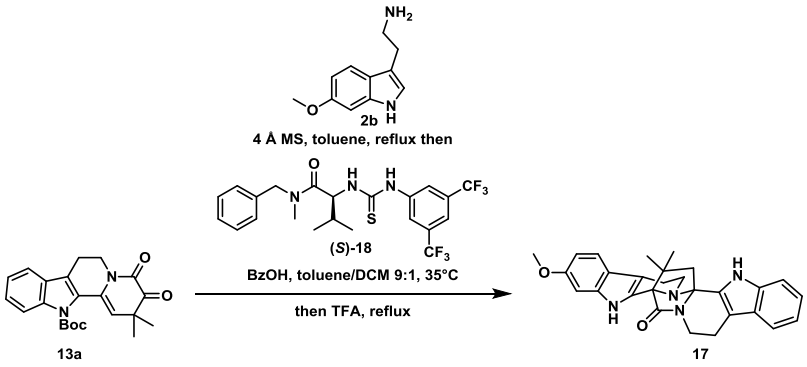
**IR:** ν ($cm^{-1}$) 2977 (w), 2936 (w), 2930 (w), 1732 (s), 1678 (s), 1614 (w), 1565 (w), 1493 (w), 1462 (w), 1421 (w), 1391 (w), 1353 (m), 1304 (m), 1280 (m), 1252 (m), 1168 (m), 1156 (s), 1133 (s), 1040 (m), 909 (m), 843 (m), 729 (s).



***rac*-17:** A mixture of ketoamide **13a** (185 mg, 0.487 mmol, 1 equiv), 6-methoxytryptamine (**2b**) (102 mg, 0.536 mmol 1.1 equiv) and 4 Å molecular sieves (750 mg/mmol ketoamide) in toluene (4.9 mL, 0.1 M) was heated to reflux for 24 h. The reaction mixture was cooled to room temperature and toluene (4.9 mL) and TFA (7.2 µL, 0.097 mmol, 0.2 equiv) were added. The mixture was heated to reflux for 6 days. The solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, DCM/Acetone 98:2) to yield the pure product ***rac*-17** (201 mg, 91%) as a white solid. **(*rac*)-17** is poorly soluble in most of the common organic solvents including methanol and DMSO.




***rac*-Peganumine A:** A mixture of ketoamide **13b** (200 mg, 0.487 mmol, 1 equiv), 6-methoxytryptamine (**2b**) (102 mg, 0.536 mmol 1.1 equiv) and 4 Å molecular sieves (750 mg/mmol ketoamide) in toluene (4.9 mL, 0.1 M) was heated to reflux for 24 h. The reaction mixture was cooled to room temperature and toluene (4.9 mL) and TFA (7.2 µL, 0.097 mmol, 0.2 equiv) were added. The mixture was heated to reflux for 6 days. The solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, DCM/Acetone 98:2) to yield the pure product ***rac*-1** (170 mg, 72%) as a white solid. **(*rac*)-1** is poorly soluble in most of the common organic solvents including methanol and DMSO.




**(*+*)-17:** A mixture of ketoamide **13a** (200 mg, 0.53 mmol, 1 equiv), 6-methoxytryptamine (**2b**) (113 mg, 0.58 mmol 1.1 equiv) and 4 Å molecular sieves (750 mg/mmol ketoamide) in toluene (0.5 mL, 0.1 M) was heated to reflux for 24 h. The reaction mixture was cooled to room temperature and toluene/DCM were added (0.5/0.1 mL, 0.05 M). The thiourea **(*S*)-18** (52 mg, 0.11 mmol, 0.2 equiv) and benzoic acid (13 mg, 0.11 mmol, 0.2 equiv) were added and the reaction mixture was stirred at 35 °C for 5 days. The reaction mixture was cooled to room temperature, TFA (8 µL, 0.11 mmol, 0.2 equiv) was added and the mixture was heated to reflux for 2 days. The solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, DCM/Acetone 98:2) to yield the pure product **(*+*)-17** (161 mg, 67%, er 96:4) as a white solid. **(*+*)-17** is poorly soluble in most of the common organic solvents including methanol and DMSO.

**$^1$H NMR (400 MHz, $CD_3OD$):** δ 7.47 – 7.35 (m, 2H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 2.2 Hz, 1H), 6.73 (dd, *J* = 8.6, 2.2 Hz, 1H), 4.14 (dd, *J* = 13.1, 5.8 Hz, 1H), 3.84 (s, 3H), 3.19 (td, *J* = 12.4, 4.7 Hz, 1H), 2.99 (dd, *J* = 15.3, 4.5 Hz, 1H), 2.89 – 2.81 (m, 2H), 2.79 – 2.70 (m, 1H), 2.61 (dd, *J* = 11.0, 5.3 Hz, 1H), 2.51 – 2.40 (m, 1H), 2.41 (d, *J* = 11.3 Hz, 1H), 1.96 (d, *J* = 11.3 Hz, 1H), 1.46 (s, 3H), 1.24 (s, 3H).

**$^{13}$C NMR (101 MHz, $CD_3OD$):** δ 175.0, 158.4, 139.6, 138.7, 129.1, 127.7, 126.4, 122.4, 122.2, 120.0, 119.8, 118.7, 112.9, 112.4, 112.3, 110.5, 95.7, 81.3, 79.7, 56.0, 51.9, 41.8, 41.6, 37.3, 27.3, 26.3, 22.5, 22.1.

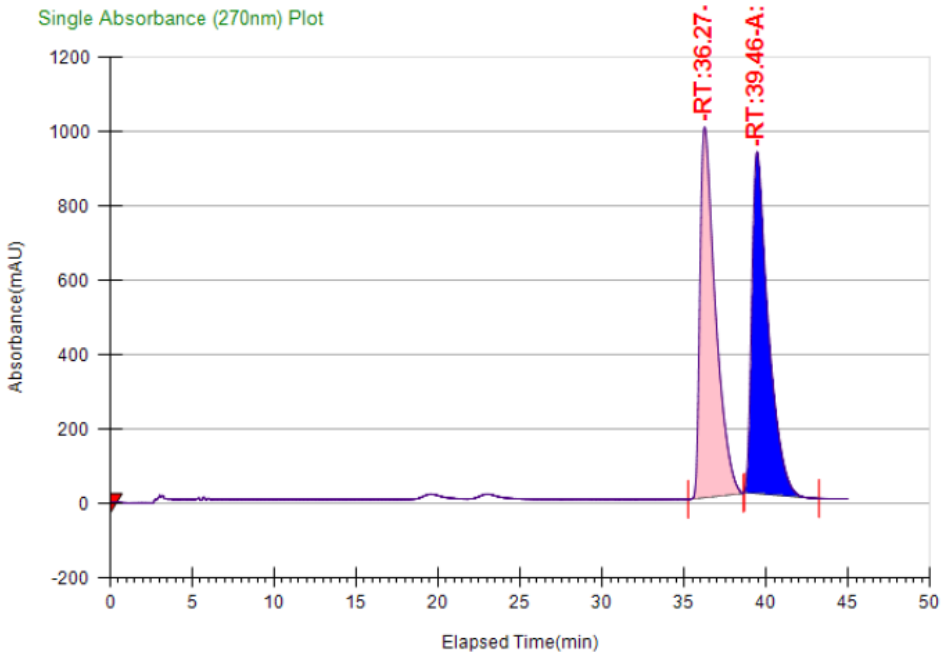
**HRMS:** (ESI) *m/z* calcd for $C_{28}H_{29}N_4O_2$ ($[M+H]^+$): 453.2285; found: 453.2288.

**IR:** ν ($cm^{-1}$) 2979 (w), 2937 (w), 2931 (w), 1734 (s), 1676 (s), 1612 (w), 1498 (w), 1467 (w), 1425 (w), 1387 (w), 1359 (m), 1308 (m), 1254 (m), 1169 (m), 1156 (s), 1133 (s), 1041 (m), 913 (m), 843 (m), 732 (s).

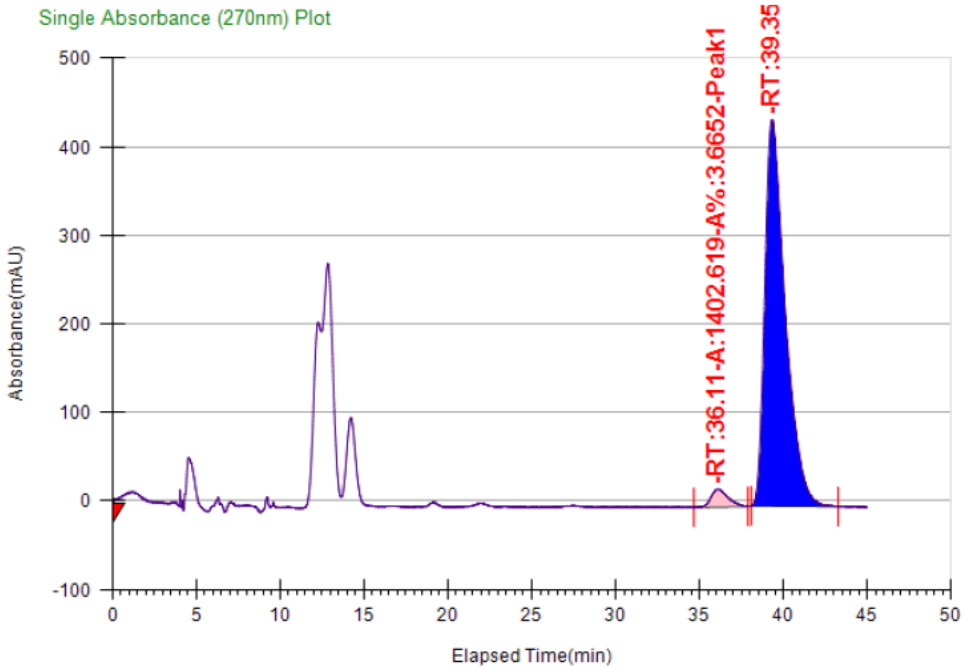
**$[\alpha]_D^{20}$** +9.6 (*c* 0.10, MeOH).

The enantiomeric purity was determined by SFC (Chiralcel, OD-H, 15% MeOH, 270 nm) $t_R$ (minor) = 36 min, $t_R$ (major) = 39 min: er 96.3 : 3.7.

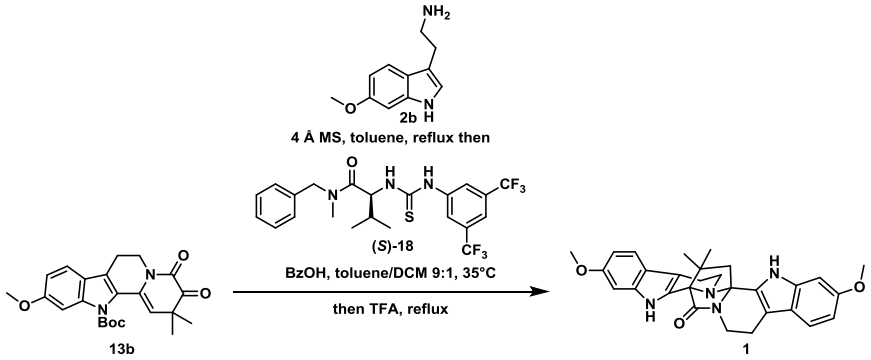
| Co-Solvent % | Total Flow | Column | Co-Solvent | Back Pressure |
|---|---|---|---|---|
| 15 | 4 | OD-H | MeOH | 150 |




| Peak # | Ret. Time | Area | Area % |
|---|---|---|---|
| 1 | 36.27 min | 65125.8981 | 50.3364 |
| 2 | 39.46 min | 64255.2983 | 49.6636 |




| Peak # | Ret. Time | Area | Area % |
|---|---|---|---|
| 1 | 36.11 min | 1402.619 | 3.6652 |
| 2 | 39.35 min | 36866.3008 | 96.3348 |




**(+)-Peganumine A (1):** A mixture of ketoamide **13b** (1.50 g, 3.65 mmol, 1 equiv), 6-methoxytryptamine (**2b**) (765 mg, 4.02 mmol 1.1 equiv) and 4 Å molecular sieves (750 mg/mmol ketoamide) in toluene (38 mL, 0.1 M) was heated to reflux for 24 h. The reaction mixture was cooled to room temperature and toluene/DCM were added (38/9 mL, 0.05 M). The thiourea **(*S*)-18** (359 mg, 0.73 mmol, 0.2 equiv) and benzoic acid (90 mg, 0.73 mmol, 0.2 equiv) were added and the reaction mixture was stirred at 35 °C for 5 days. The reaction mixture was cooled to room temperature, TFA (54 µL, 0.73 mmol, 0.2 equiv) was added and the mixture was heated to reflux for 2 days. The solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, DCM/Acetone 98:2) to yield the pure product **(*+*)-1** (1.22 g, 69%, er 96:4) as a white solid. **(*+*)-1** is poorly soluble in most of the common organic solvents including methanol and DMSO.

**$^1$H NMR (600 MHz, DMSO-$d_6$):** 11.27 (s, 1H), 10.80 (s, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 7.24 (d, *J* = 8.5 Hz, 1H), 6.92 (d, *J* = 2.3 Hz, 1H), 6.87 (d, *J* = 2.3 Hz, 1H), 6.69 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.63 (dd, *J* = 8.5, 2.3 Hz, 1H), 4.00 (dd, *J* = 12.9, 5.9 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.09 (td, *J* = 12.5, 4.4 Hz, 1H), 2.90 (dd, *J* = 15.4, 4.3 Hz, 1H), 2.77 – 2.60 (m, 3H), 2.45 (dd, *J* = 10.6, 4.9 Hz, 1H), 2.34 (dd, *J* = 11.0, 4.8 Hz, 1H), 2.30 (d, *J* = 11.3 Hz, 1H), 1.88 (d, *J* = 11.3 Hz, 1H), 1.38 (s, 3H), 1.14 (s, 3H).

**$^{13}$C NMR (151 MHz, DMSO-$d_6$):** δ 171.4, 156.1, 155.4, 137.6, 137.5, 127.3, 125.7, 120.5, 120.4, 119.1, 118.2, 111.3, 109.5, 109.1, 108.3, 94.9, 94.7, 78.8, 77.4, 55.2, 55.2, 50.4, 40.1, 40.0, 35.6, 26.9, 26.1, 21.1, 21.0.

**$^{1}$H NMR (400 MHz, $CD_3OD$):** δ 7.38 (d, *J* = 8.6 Hz, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 6.99 (d, *J* = 2.3 Hz, 1H), 6.93 (d, *J* = 2.2 Hz, 1H), 6.73 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.67 (dd, *J* = 8.6, 2.3 Hz, 1H), 4.14 (dd, *J* = 13.0, 5.8 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.18 (td, *J* = 12.3, 4.7 Hz, 1H), 2.98 (dd, *J* = 15.4, 4.5 Hz, 1H), 2.90 – 2.74 (m, 2H), 2.69 (dd, *J* = 15.2, 3.8 Hz, 1H), 2.59 (dd, *J* = 10.8, 5.2 Hz, 1H), 2.44 (dd, *J* = 11.2, 4.1 Hz, 1H), 2.39 (d, *J* = 11.6 Hz, 1H), 1.94 (d, *J* = 11.5 Hz, 1H), 1.44 (s, 3H), 1.24 (s, 3H).

**$^{13}$C NMR (101 MHz, $CD_3OD$):** δ 175.2, 158.4, 157.6, 139.5, 139.4, 127.8, 126.5, 122.3, 122.2, 120.0, 119.2, 112.9, 112.2, 110.5, 109.8, 96.0, 95.7, 81.3, 79.7, 56.0, 56.0, 51.9, 41.7, 41.6, 37.3, 27.3, 26.3, 22.5, 22.1.

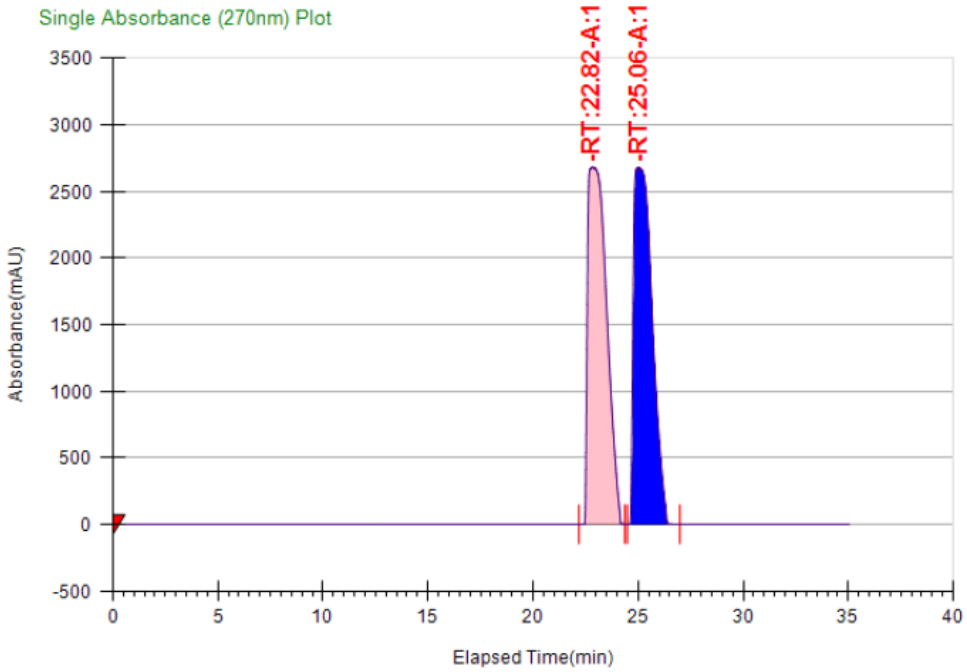
**HRMS:** (ESI) *m/z* calcd for $C_{29}H_{31}N_4O_3$ ($[M+H]^+$): 483.2391; found: 483.2392.

**IR:** ν ($cm^{-1}$) 2981 (w), 2938 (w), 1734 (s), 1676 (s), 1612 (w), 1499 (w), 1467 (w), 1430 (w), 1387 (w), 1359 (m), 1308 (m), 1254 (m), 1168 (m), 1153 (s), 1137 (s), 1040 (m), 914 (m), 842 (m), 731 (s).

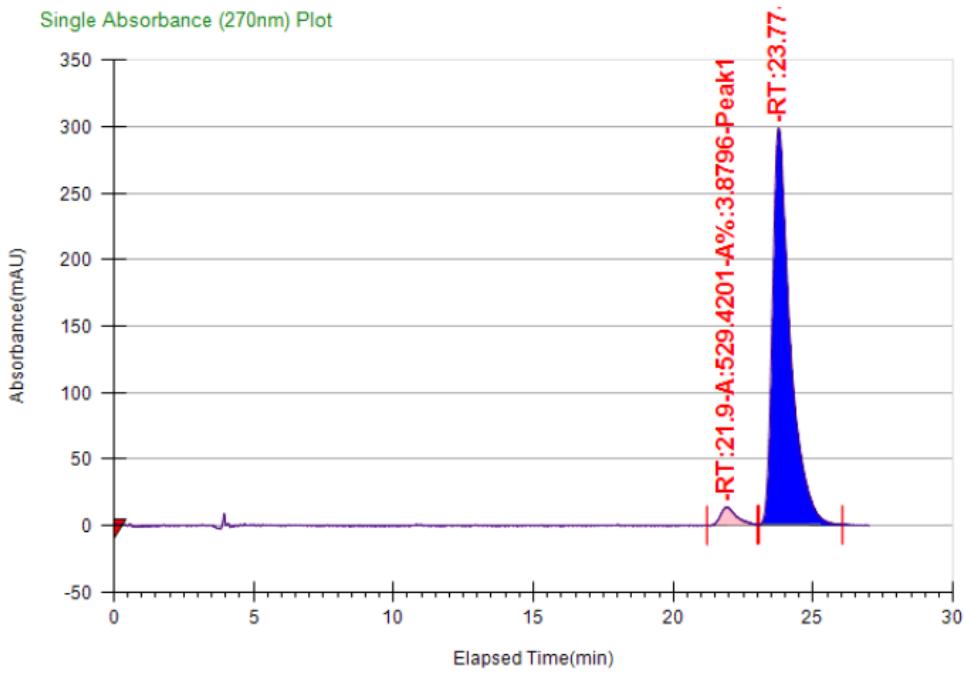
**$[\alpha]_D^{20}$** +6.2 (*c* 0.10, MeOH).

The enantiomeric purity was determined by SFC (Chiralcel, OD-H, 18% MeOH, 270 nm) $t_R$ (minor) = 22 min, $t_R$ (major) = 24 min: er 96.1 : 3.9.

| Co-Solvent % | Total Flow | Column | Co-Solvent | Back Pressure |
|---|---|---|---|---|
| 18 | 4 | OD-H | MeOH | 150 |

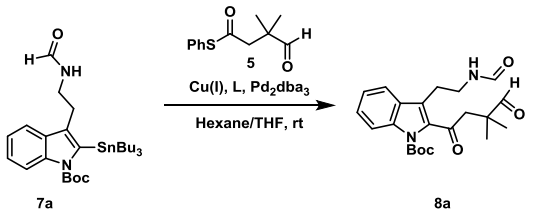



| Peak # | Ret. Time | Area | Area % |
|---|---|---|---|
| 1 | 22.82 min | 167936.5875 | 50.4525 |
| 2 | 25.06 min | 164923.935 | 49.5475 |




| Peak # | Ret. Time | Area | Area % |
|---|---|---|---|
| 1 | 21.9 min | 529.4201 | 3.8796 |
| 2 | 23.77 min | 13116.7061 | 96.1204 |

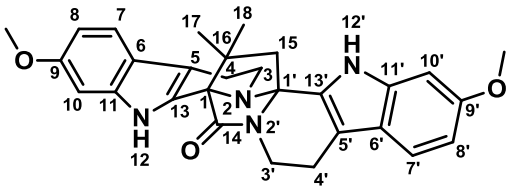
## 3. Optimization of the Liebeskind-Srogl coupling




| Entry | Cu(I) source | L | L/Pd ratio | Hex/THF (v/v) | Yield of **8a** (%) |
|---|---|---|---|---|---|
| 1 | CuTC | $PPh_3$ | 8/1 | 0/1 | 0 |
| 2 | CuTC | $PPh_3$ | 8/1 | 3/1 | 18 |
| 3 | CuDPP | $PPh_3$ | 8/1 | 3/1 | 22 |
| 4 | CuDPP | $AsPh_3$ | 8/1 | 3/1 | 52 |
| 5 | CuDPP | $AsPh_3$ | 4/1 | 3/1 | 78 |
| 6 | CuDPP | $AsPh_3$ | 1/1 | 3/1 | 94 |

**Table 1 – Conditions optimization for the Liebeskind-Srogl coupling of 7a with 5**

## 4. $^{1}H$ and $^{13}C$ NMR chemical shifts of the natural and the synthetic (+)-peganumine A



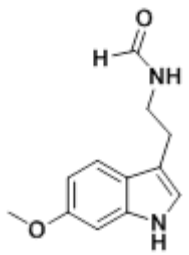
| Natural | | | | Synthesized | | | |
|---|---|---|---|---|---|---|---|
| N° | $^{13}C$ [ppm] (150 MHz) (DMSO-$d_6$) | $^{1}H$ [ppm] (600 MHz) (DMSO-$d_6$) | | N° | $^{13}C$ [ppm] (151 MHz) (DMSO-$d_6$) | $^{1}H$ [ppm] (600 MHz) (DMSO-$d_6$) | |
| 1 | 77.4 | - | - | 1 | 77.4 | - | - |
| 3 | 40.0 | 2.34 | 2.45 | 3 | 40.0 | 2.34 | 2.45 |
| 4 | 21.0 | 2.63 | 2.64 | 4 | 21.1 | 2.63 | 2.65 |
| 5 | 109.5 | - | - | 5 | 109.5 | - | - |
| 6 | 120.5 | - | - | 6 | 120.5 | - | - |
| 7 | 118.2 | 7.24 | - | 7 | 118.2 | 7.24 | - |
| 8 | 108.3 | 6.63 | - | 8 | 108.3 | 6.63 | - |
| 9 | 155.4 | - | - | 9 | 155.4 | - | - |
| 10 | 94.9 | 6.93 | - | 10 | 94.9 | 6.92 | - |
| 11 | 137.6 | - | - | 11 | 137.6 | - | - |
| 13 | 127.3 | - | - | 13 | 127.3 | - | - |
| 14 | 171.4 | - | - | 14 | 171.4 | - | - |
| 15 | 50.4 | 1.88 | 2.30 | 15 | 50.4 | 1.88 | 2.30 |
| 16 | 40.0 | - | - | 16 | 40.0 | - | - |
| 17 | 26.8 | 1.15 | - | 17 | 26.9 | 1.14 | - |
| 18 | 26.0 | 1.38 | - | 18 | 26.1 | 1.38 | - |
| 1’ | 78.8 | - | - | 1’ | 78.8 | - | - |
| 3’ | 35.6 | 4.00 | 3.09 | 3’ | 35.6 | 4.00 | 3.09 |
| 4’ | 20.9 | 2.70 | 2.90 | 4’ | 21.0 | 2.71 | 2.90 |
| 5’ | 111.3 | - | - | 5’ | 111.3 | - | - |
| 6’ | 120.4 | - | - | 6’ | 120.4 | - | - |
| 7’ | 119.0 | 7.38 | - | 7’ | 119.1 | 7.38 | - |
| 8’ | 109.1 | 6.70 | - | 8’ | 109.1 | 6.69 | - |
| 9’ | 156.1 | - | - | 9’ | 156.1 | - | - |
| 10’ | 94.7 | 6.87 | - | 10’ | 94.7 | 6.87 | - |
| 11’ | 137.5 | - | - | 11’ | 137.5 | - | - |
| 13’ | 125.7 | - | - | 13’ | 125.7 | - | - |
| 12-NH | - | 11.25 | - | 12-NH | - | 11.27 | - |
| 12’-NH | - | 10.77 | - | 12’-NH | - | 10.80 | - |
| 9-OMe | 55.2 | 3.78 | - | 9-OMe | 55.2 | 3.77 | - |
| 9’-OMe | 55.2 | 3.77 | - | 9’-OMe | 55.2 | 3.76 | - |

Table 2 – Comparison of NMR data between the natural and the synthesized (+)-peganumine A in DMSO-$d_6$

## 5. References

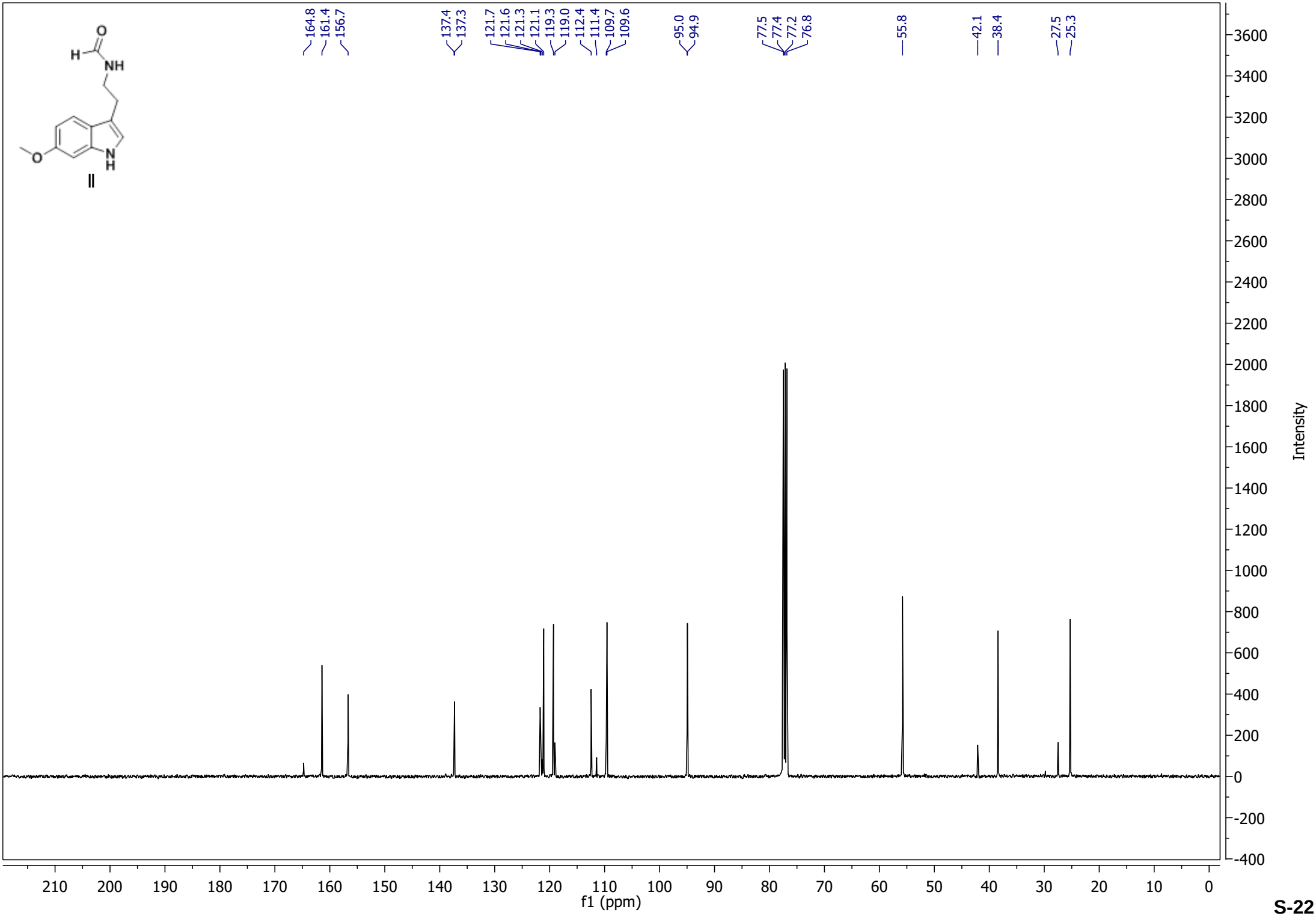

1) Saito, T.; Fuwa, H.; Sasaki, M., *Tetrahedron* **2011**, *67*, 429-445.
2) Klausen, R. S.; Jacobsen, E. N., *Org. Lett.* **2009**, *11*, 887-890.
3) Liu, H.; Dömling, A., *J. Org. Chem.* **2009**, *74*, 6895-6898.
4) Huang, G.; Kling, B.; Darras, F. H.; Heilmann, J.; Decker, M., *Eur. J. Med. Chem.* **2014**, *81*, 15-21.
5) Qi, X.; Bao, H.; Tambar, U. K., *J. Am. Chem. Soc.* **2011**, *133*, 10050-10053.
6) Mirzabekova, N. S.; Kuz'mina, N. E.; Lukashov, O. I.; Sokolova, N. A.; Golosov, S. N.; Kazakov, P. V.; Perlova, T. G.; Potapova, V. V.; Kheinman, V. A.; Ivanova, G. B., Russ. *J. Org. Chem.* **2008**, *44*, 1139-1149.
7) Kleschick, W. A., *J. Org. Chem.* **1986**, *51*, 5429-5433.
8) Best, W. M.; Cook, A. P. F.; Russell, J. J.; Widdowson, D. A., *J. Chem. Soc., Perkin Trans. 1* **1986**, 1139-1143.
9) Keck, G. E.; Welch, D. S.; Vivian, P. K., *Org. Lett.* **2006**, *8*, 3667-3670.
10) Grabowska, U.; Jönsson, D.; KLASSON, B.; Wiktelius, D. *Cysteine protease inhibitors.* WO2012172473 A1, Dec 20, 2012.
11) Yin, W.; Kabir, M. S.; Wang, Z.; Rallapalli, S. K.; Ma, J.; Cook, J. M., *J. Org. Chem.* **2010**, *75*, 3339-3349.
12) Grassot, J.-M.; Masson, G.; Zhu, J., *Angew. Chem. Int. Ed.* **2008**, *47*, 947-950.

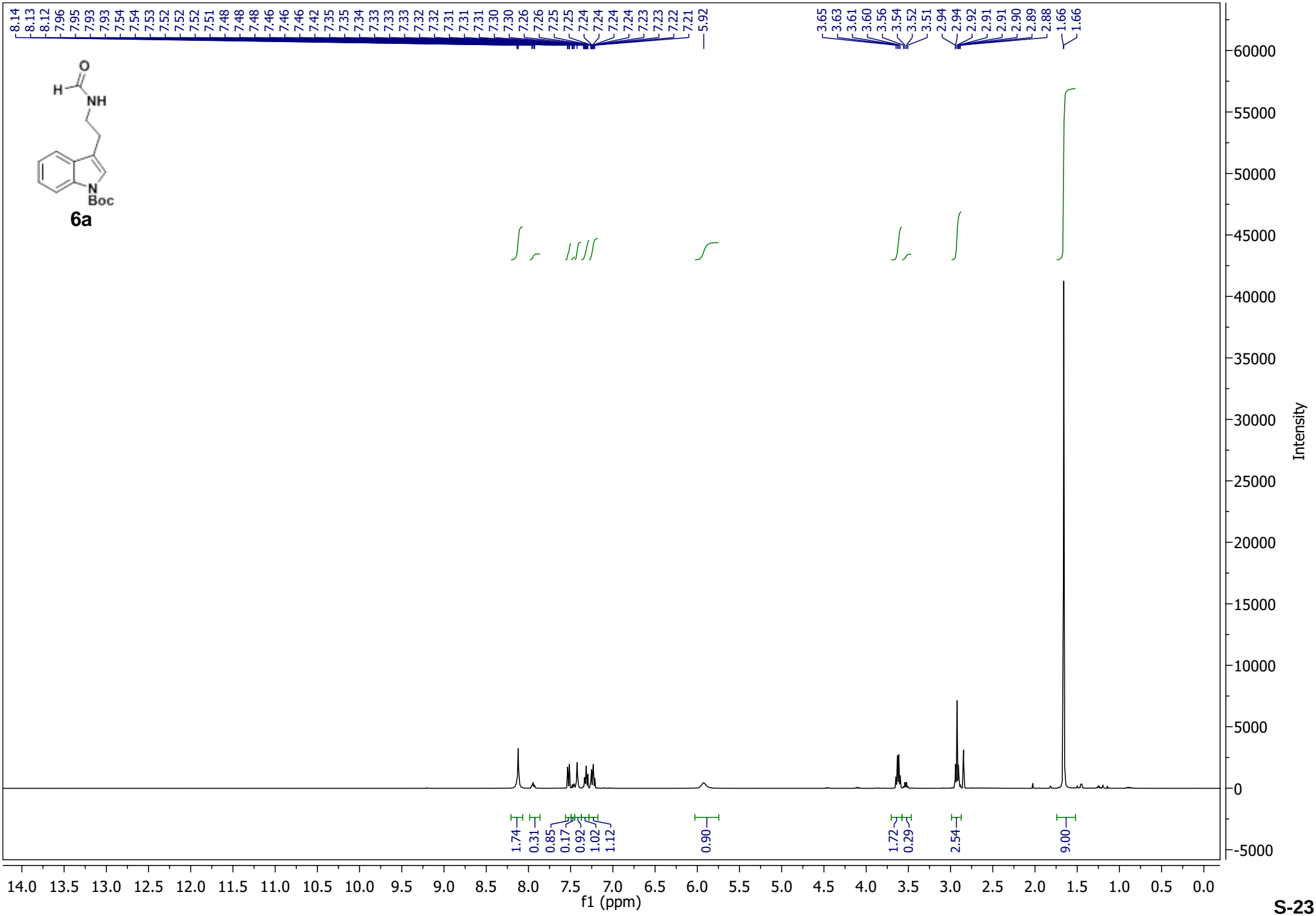
## 6. Copies of the $^{1}H$ and $^{13}C$ NMR spectra

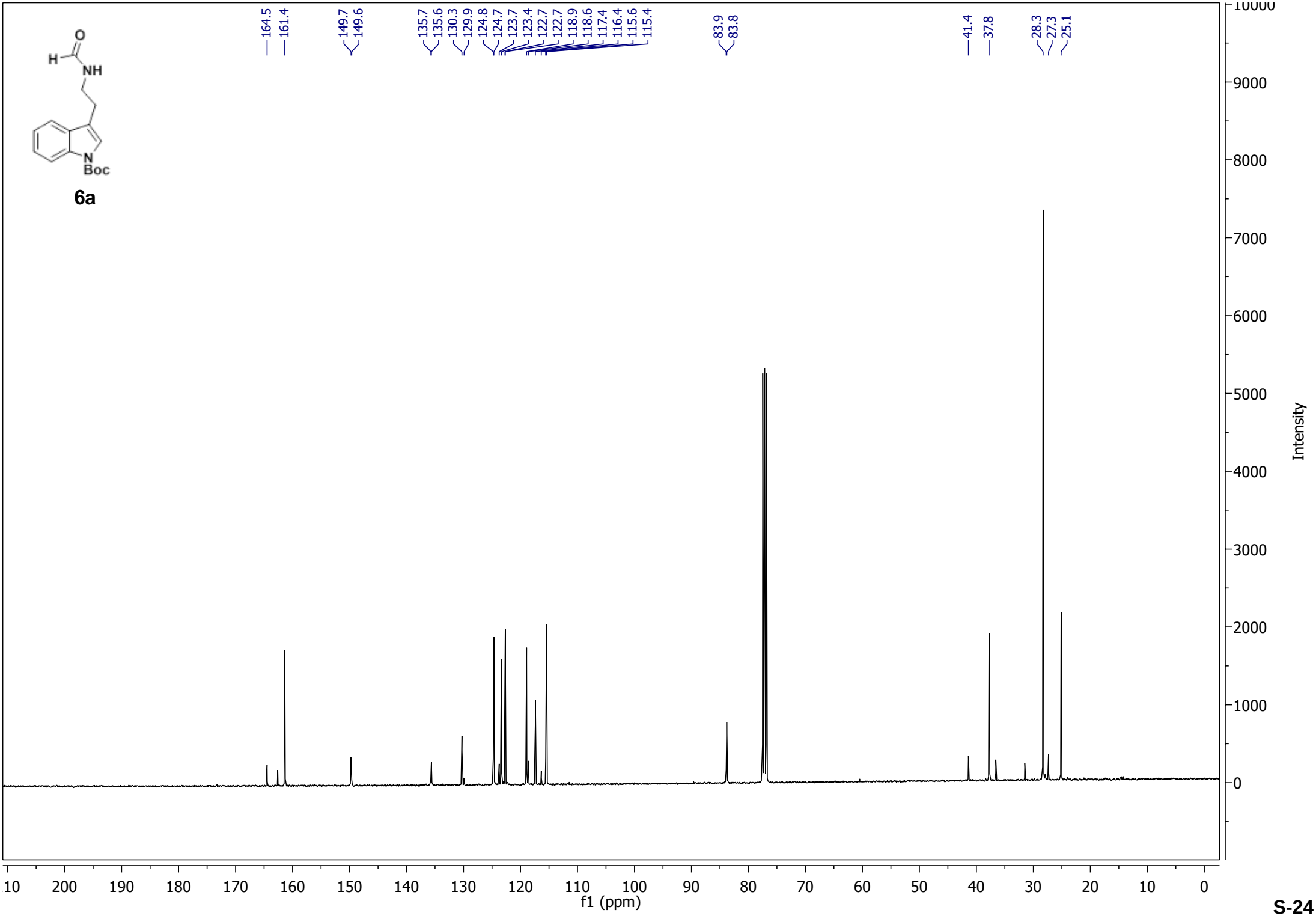


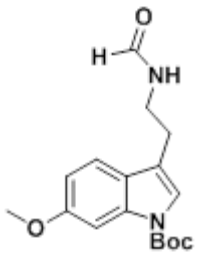
II


8.34
8.30
8.06
7.87
7.84
7.44
7.42
7.40
7.38
7.37
7.26
7.26
7.25
6.89
6.84
6.83
6.80
6.79
6.78
6.77
5.79
3.82
3.82
3.81
3.77
3.63
3.61
3.59
3.58
3.57
3.49
3.48
3.47
3.45
3.44
2.95
2.93
2.91
2.91
2.89
2.87
1.00
0.83
0.20
0.98
0.83
1.17
0.93
0.93
3.03
1.62
0.42
1.98
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
Intensity
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


O
H
NH
O
N
H
II
164.8
161.4
156.7
137.4
137.3
121.7
121.6
121.3
121.1
119.3
119.0
112.4
111.4
109.7
109.6
95.0
94.9
77.5
77.4
77.2
76.8
55.8
42.1
38.4
27.5
25.3
Intensity
f1 (ppm)

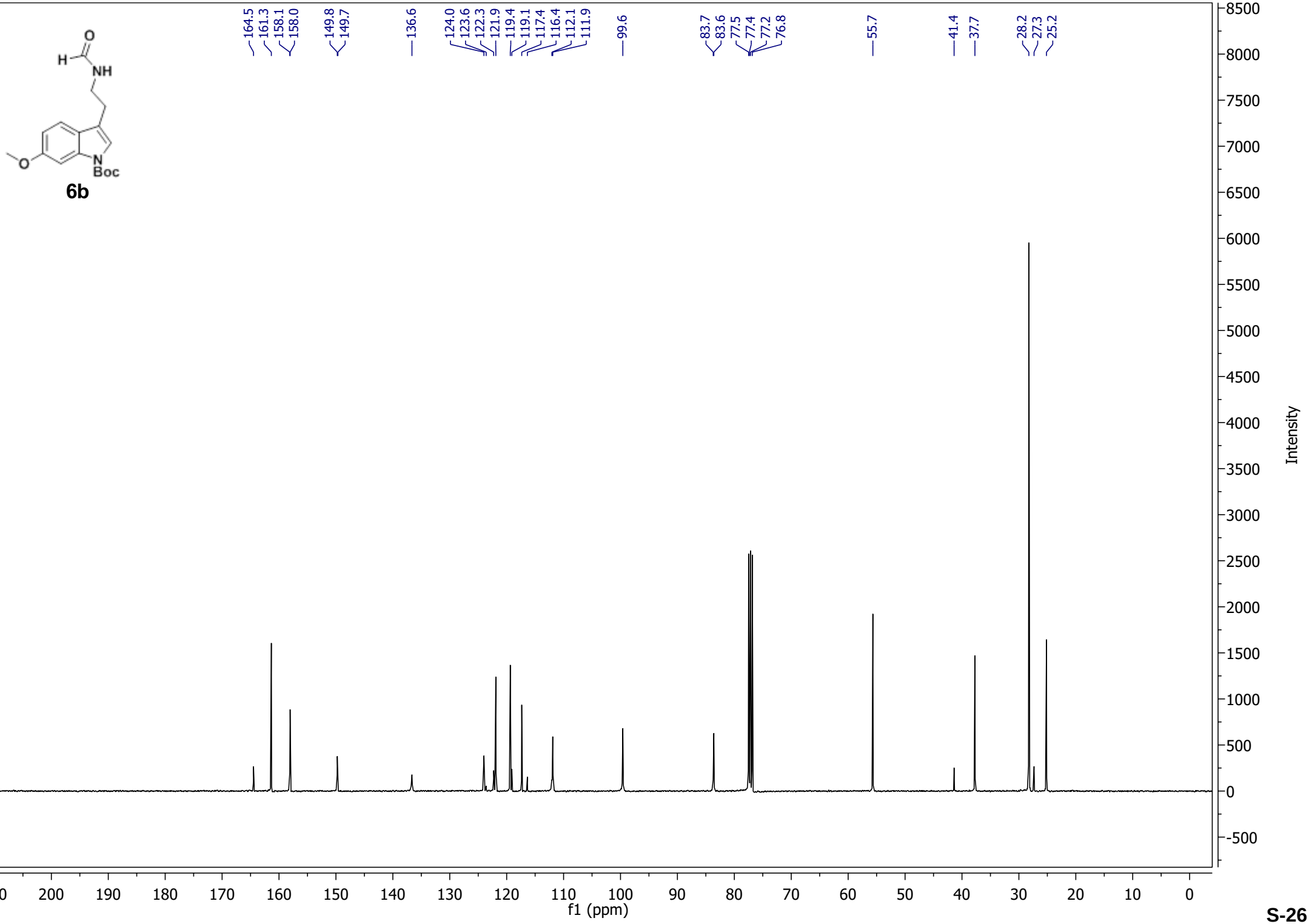

8.14 8.13 8.12 7.96 7.95 7.93 7.93 7.54 7.54 7.53 7.52 7.52 7.52 7.51 7.48 7.48 7.48 7.46 7.46 7.46 7.42 7.35 7.35 7.34 7.33 7.33 7.33 7.32 7.32 7.31 7.31 7.31 7.30 7.30 7.26 7.26 7.25 7.25 7.24 7.24 7.24 7.24 7.23 7.23 7.22 7.21 5.92
3.65 3.63 3.61 3.60 3.56 3.54 3.52 3.51 2.94 2.94 2.92 2.91 2.91 2.90 2.89 2.88 1.66 1.66
O
H
NH
N
Boc
6a
1.74 0.31 0.85 0.17 0.92 1.02 1.12 0.90 1.72 0.29 2.54 9.00
60000 55000 50000 45000 40000 35000 30000 25000 20000 15000 10000 5000 0 -5000
Intensity
14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

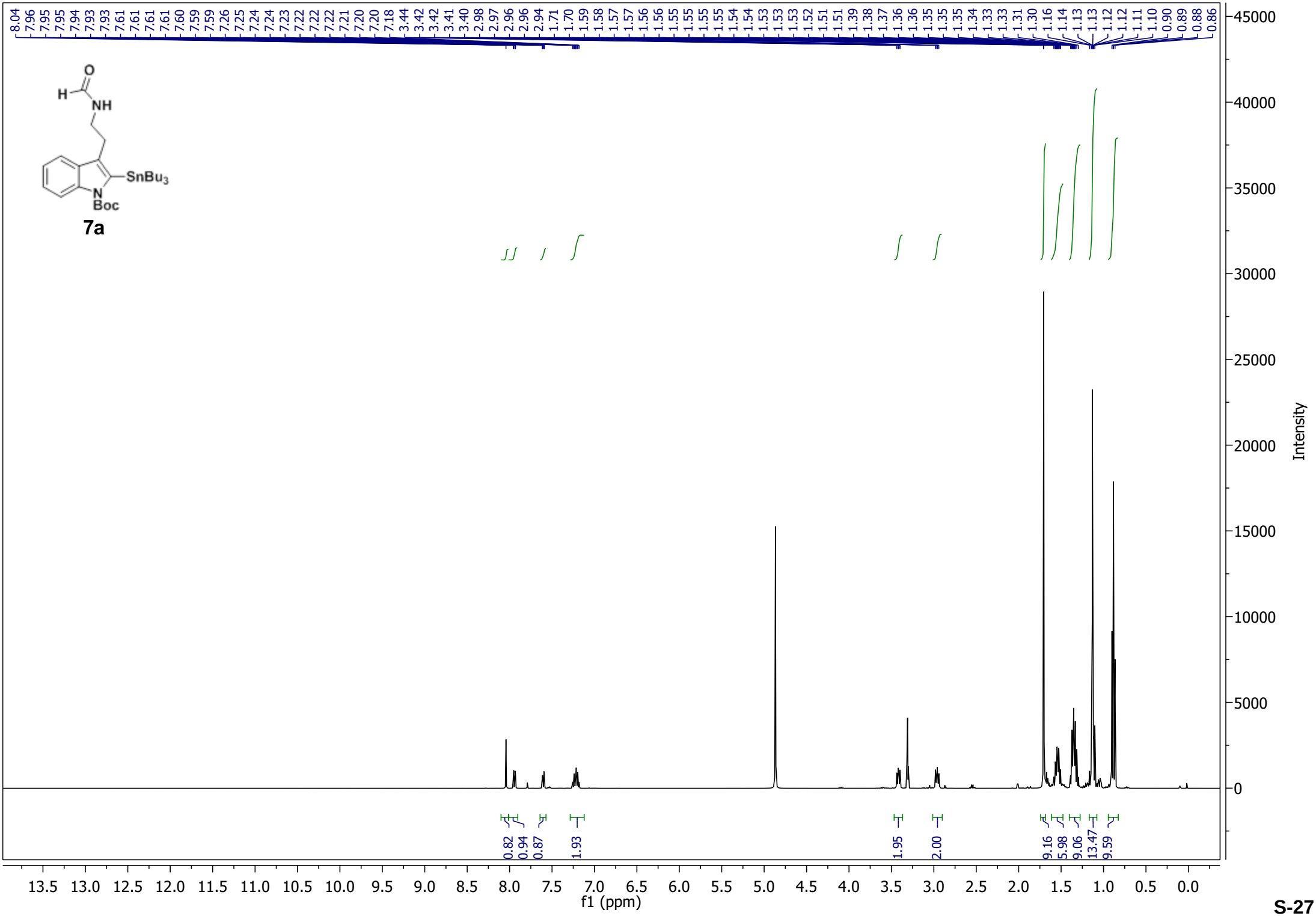

O
H
NH
N
Boc
6a
164.5
161.4
149.7
149.6
135.7
135.6
130.3
129.9
124.8
124.7
123.7
123.4
122.7
122.7
118.9
118.6
117.4
116.4
115.6
115.4
83.9
83.8
41.4
37.8
28.3
27.3
25.1
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
Intensity
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

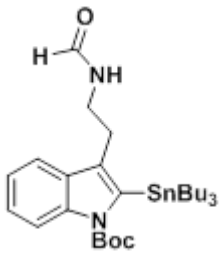

O
H
NH
O
N
Boc

**6b**

8.11 8.10 7.93 7.90 7.71 7.37 7.36 7.35 7.32 7.30 7.29 7.28 7.26 6.87 6.86 6.86 6.85 6.84 6.84 5.99 3.85 3.84 3.61 3.59 3.58 3.56 3.52 3.50 3.49 3.47 2.88 2.88 2.87 2.86 2.85 2.85 2.84 2.83 2.82 1.69 1.68 1.65 1.65 1.63 1.61 1.60
0.86 0.15 0.89 0.89 1.07 1.00 0.96 3.05 1.74 0.31 2.04 9.23
40000 35000 30000 25000 20000 15000 10000 5000 0
Intensity
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0
f1 (ppm)

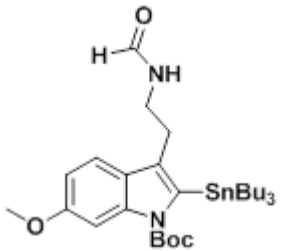

O
H
NH
O
N
Boc
6b
164.5
161.3
158.1
158.0
149.8
149.7
136.6
124.0
123.6
122.3
121.9
119.4
119.1
117.4
116.4
112.1
111.9
99.6
83.7
83.6
77.5
77.4
77.2
76.8
55.7
41.4
37.7
28.2
27.3
25.2
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
Intensity
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
H
NH
SnBu3
N
Boc
7a
Intensity
f1 (ppm)
0.82
0.94
0.87
1.93
1.95
2.00
9.16
5.98
9.06
13.47
9.59

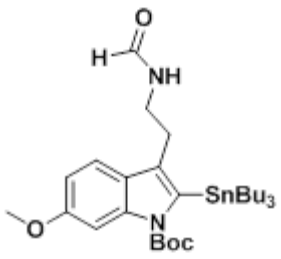

O
H
NH
SnBu3
N
Boc

**7a**


163.6
153.8
140.1
138.8
133.5
130.6
124.9
123.4
119.4
116.4
85.4
51.3
40.4
30.4
28.5
28.4
28.4
27.2
14.1
14.0
Intensity
f1 (ppm)




**7b**

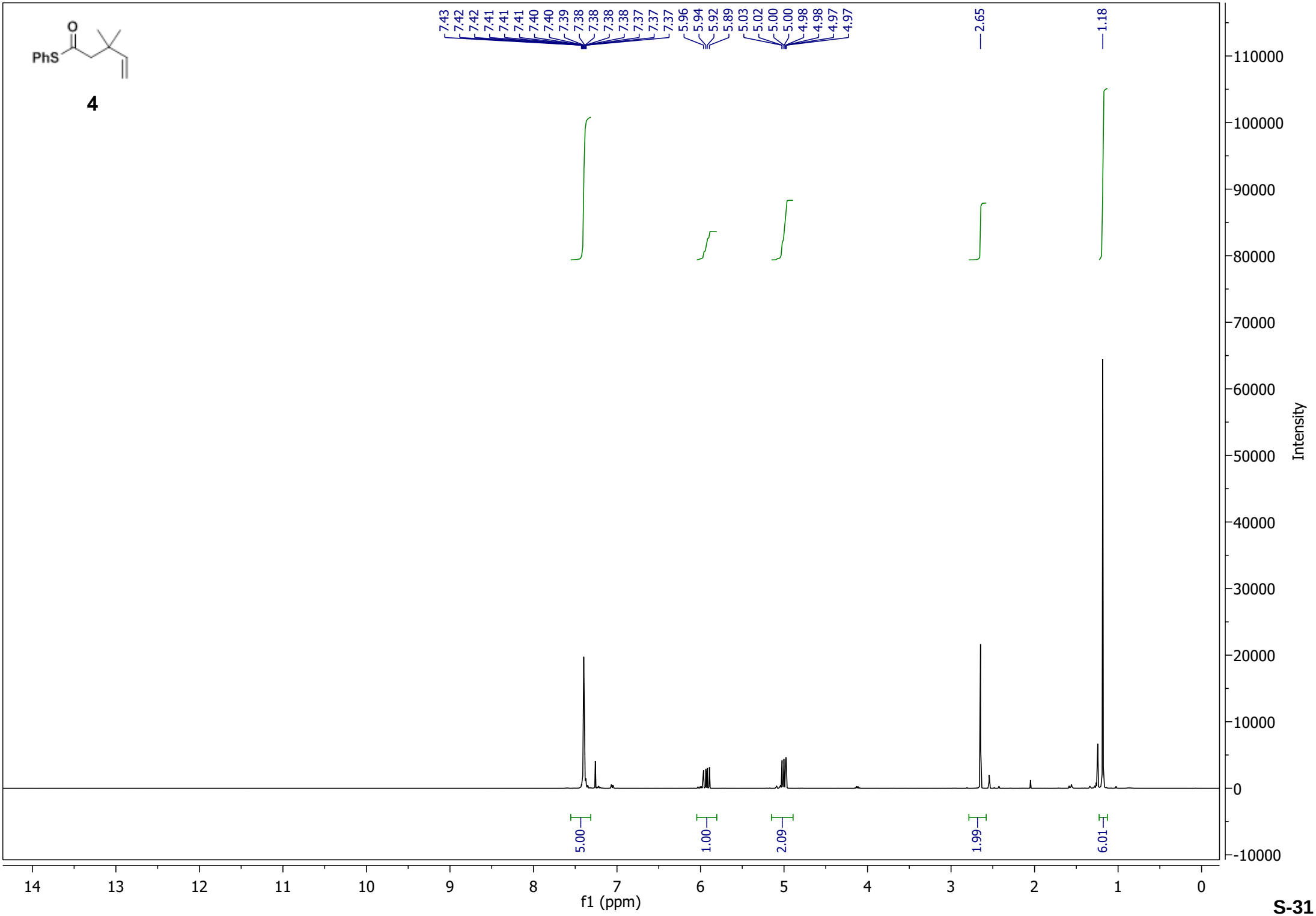


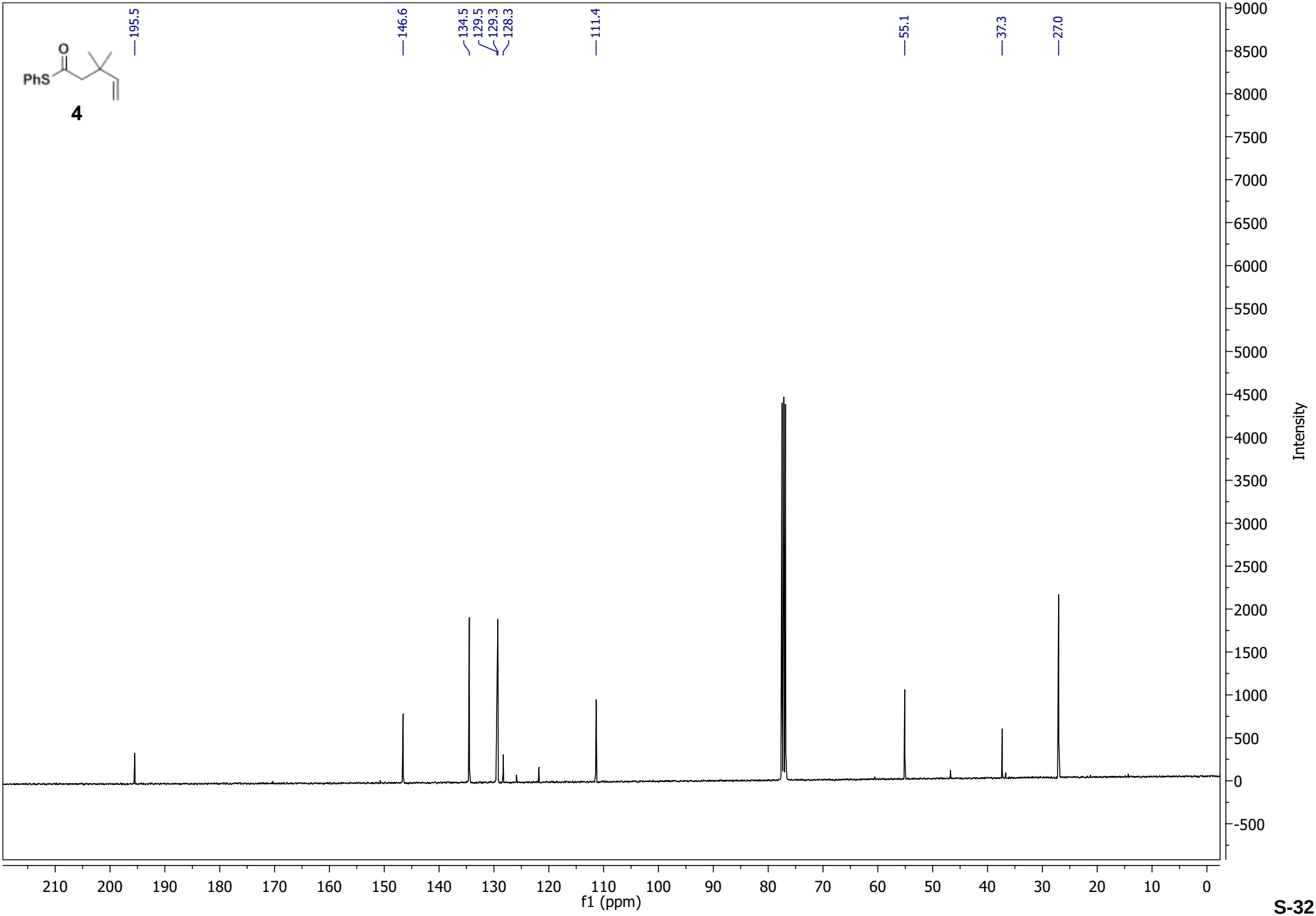

**7b**

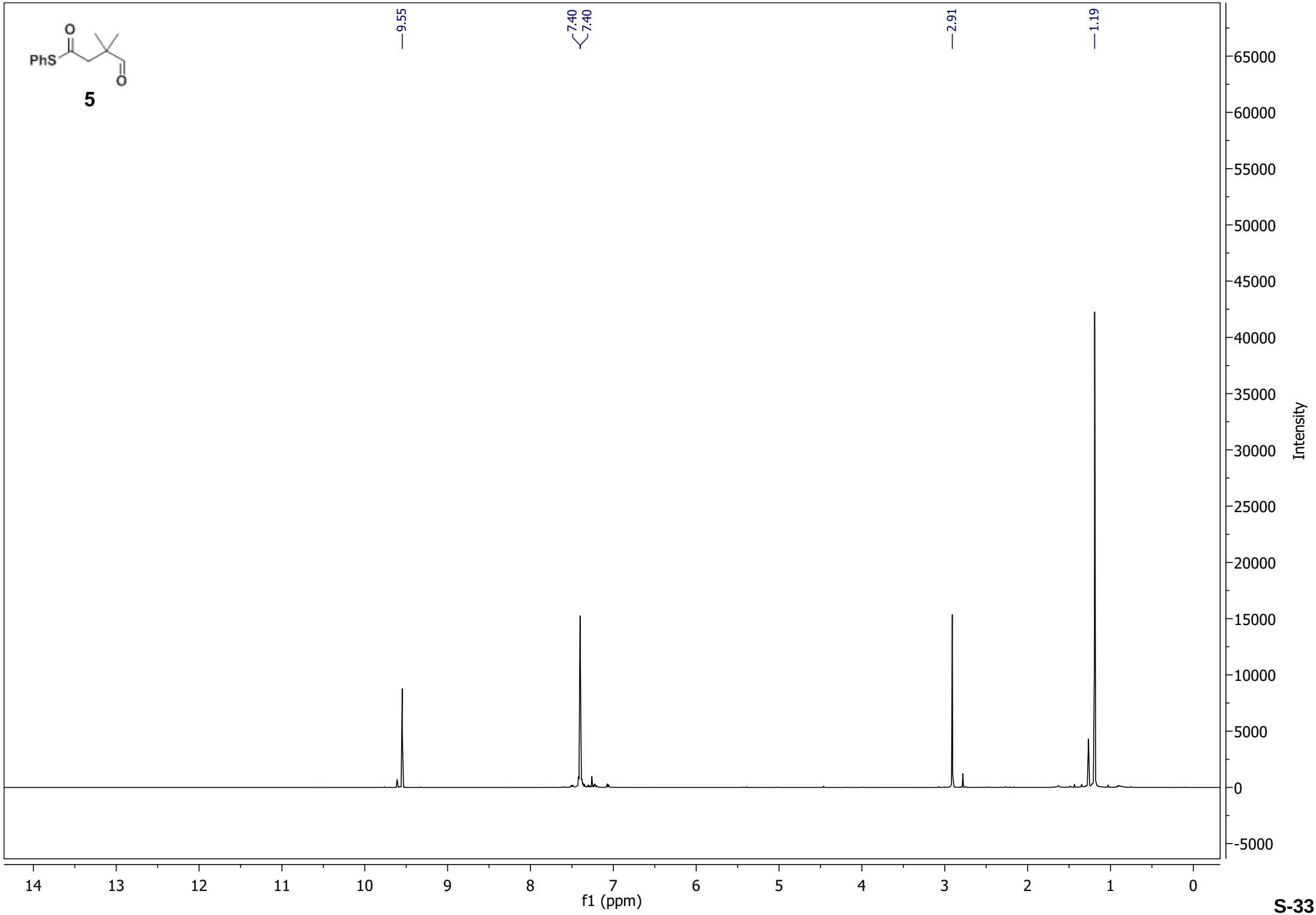
166.6
163.6
159.0
153.7
139.7
138.1
130.6
130.0
127.5
119.8
112.3
112.1
101.1
85.2
85.1
55.9
44.4
40.4
30.4
28.5
28.4
27.2
14.1
14.0

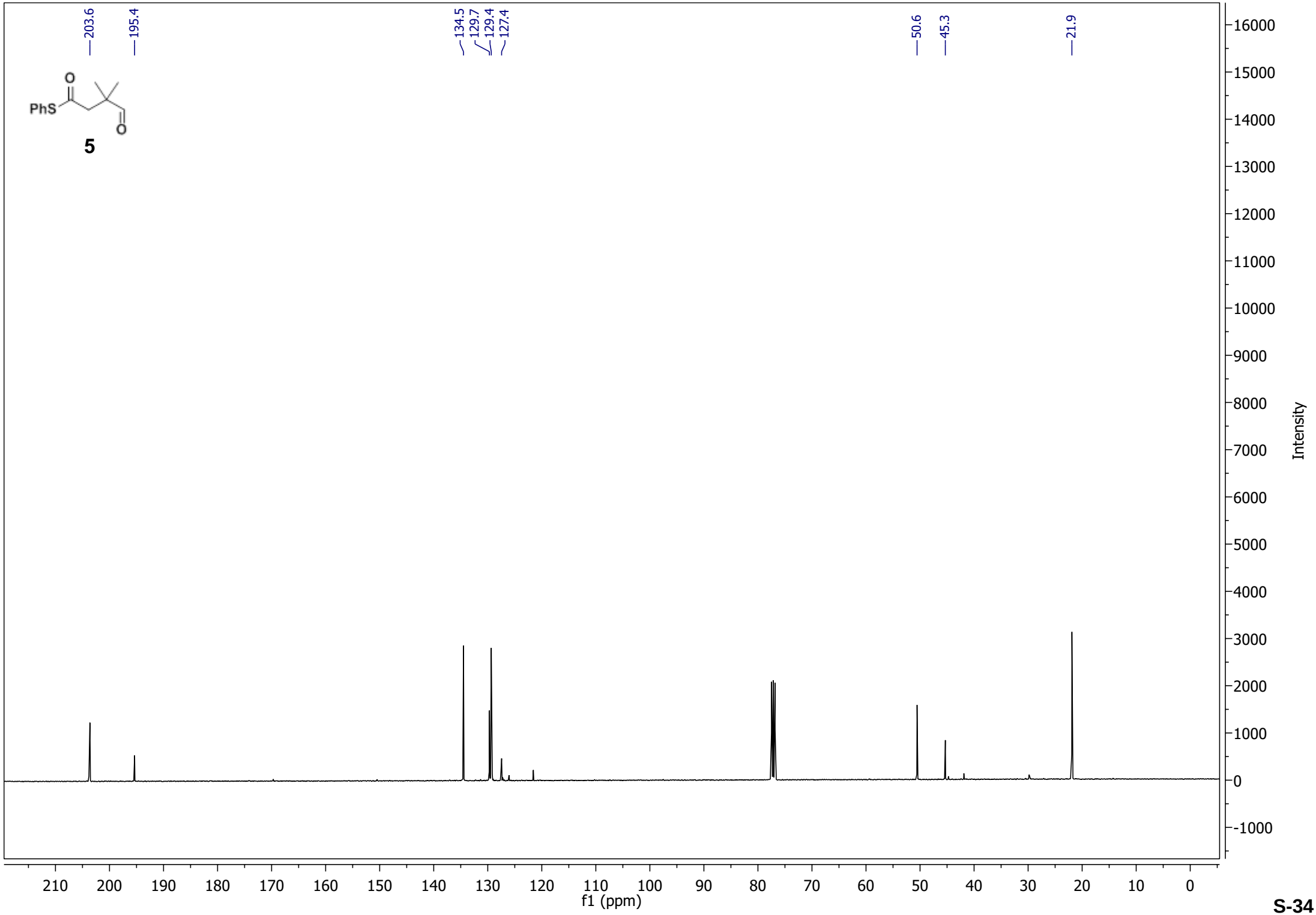
Intensity

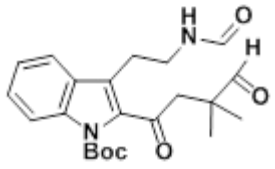
f1 (ppm)


PhS
O
4
7.43
7.42
7.42
7.41
7.41
7.41
7.40
7.40
7.39
7.38
7.38
7.38
7.38
7.37
7.37
7.37
5.96
5.94
5.92
5.89
5.03
5.02
5.00
5.00
4.98
4.98
4.97
4.97
2.65
1.18
5.00
1.00
2.09
1.99
6.01
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
Intensity
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


195.5
146.6
134.5
129.5
129.3
128.3
111.4
55.1
37.3
27.0
PhS
O
4
Intensity
f1 (ppm)

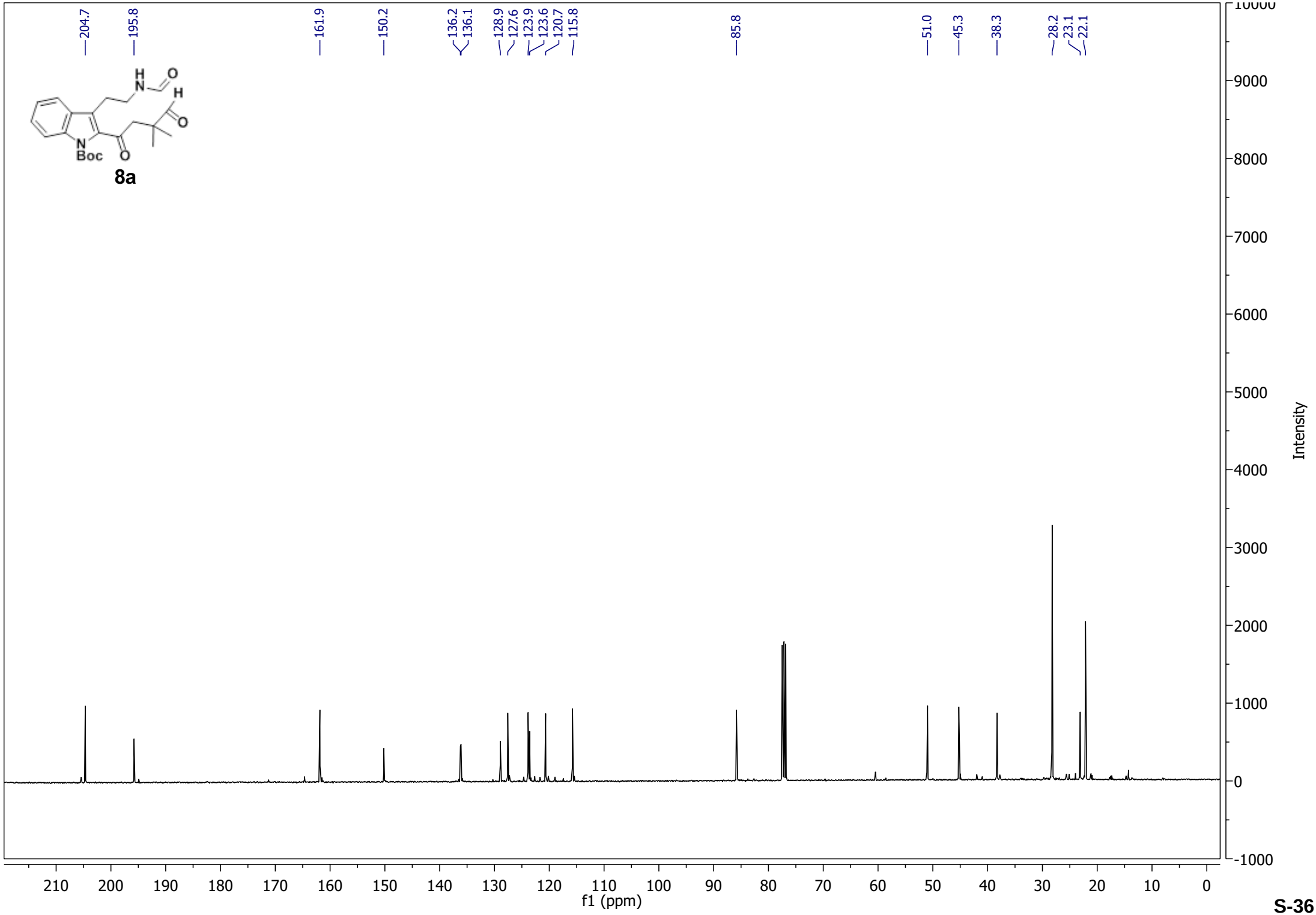

PhS
O
O
5
9.55
7.40
7.40
2.91
1.19
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
Intensity
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

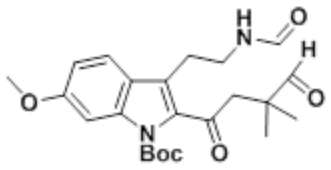

203.6
195.4
134.5
129.7
129.4
127.4
50.6
45.3
21.9
PhS
O
O
5
Intensity
f1 (ppm)


H
N
O
H
O
N
Boc
O

**8a**

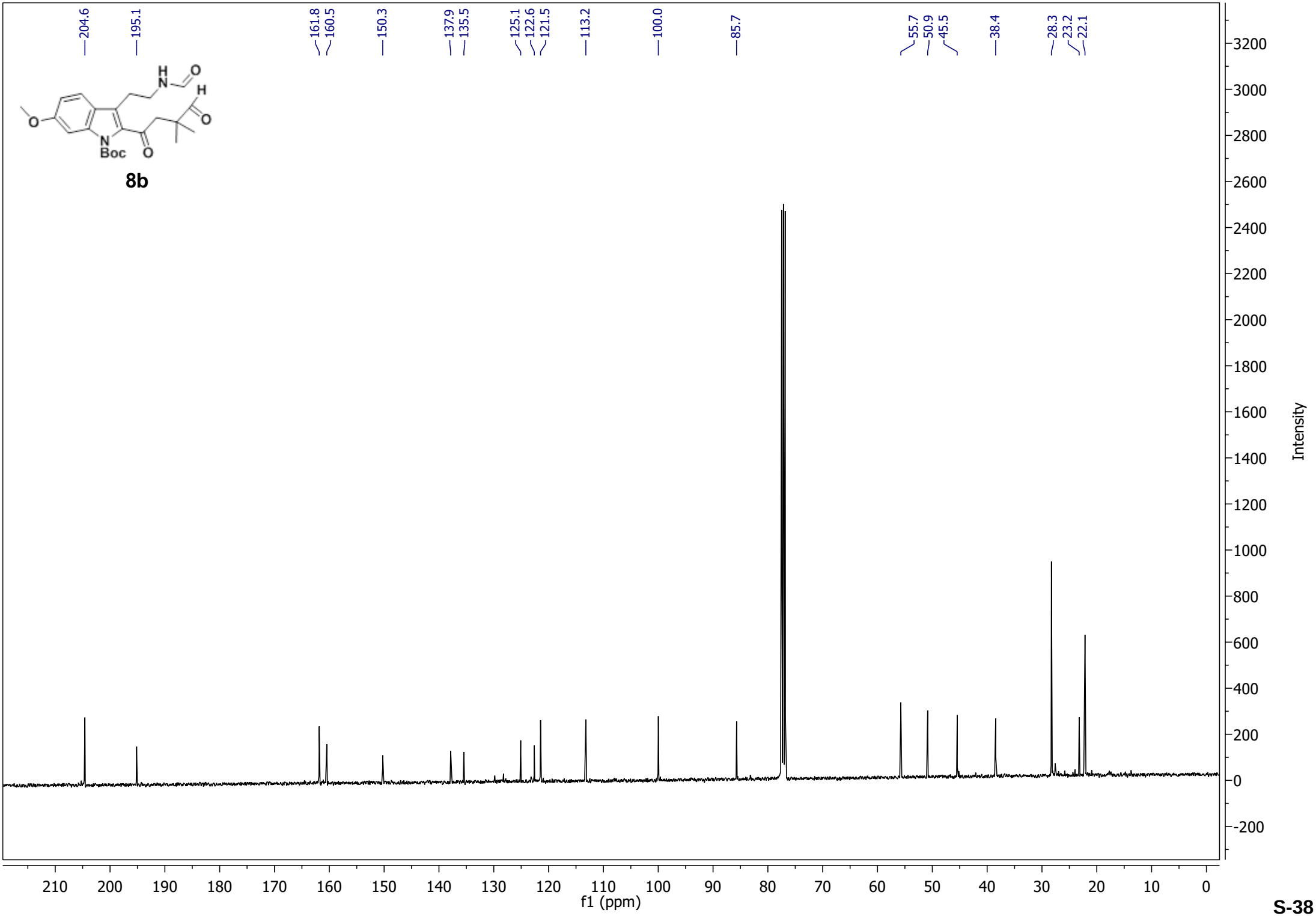

9.63
8.10
8.09
8.09
7.96
7.96
7.96
7.94
7.94
7.94
7.62
7.61
7.61
7.60
7.60
7.59
7.45
7.45
7.43
7.43
7.43
7.41
7.41
7.32
7.31
7.30
7.30
7.29
7.28
7.28
6.97
3.57
3.56
3.56
3.55
3.55
3.54
3.53
3.53
3.52
3.52
3.52
3.07
2.90
2.89
2.88
2.88
2.87
1.69
1.14
1.00
1.04
1.11
1.03
1.23
1.24
0.95
2.28
2.28
2.27
9.61
6.20
Intensity
f1 (ppm)

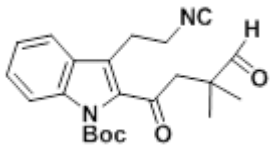

204.7
195.8
161.9
150.2
136.2
136.1
128.9
127.6
123.9
123.6
120.7
115.8
85.8
51.0
45.3
38.3
28.2
23.1
22.1
Boc
8a
Intensity
f1 (ppm)


H
N
O
H
O
O
N
Boc
O

**8b**

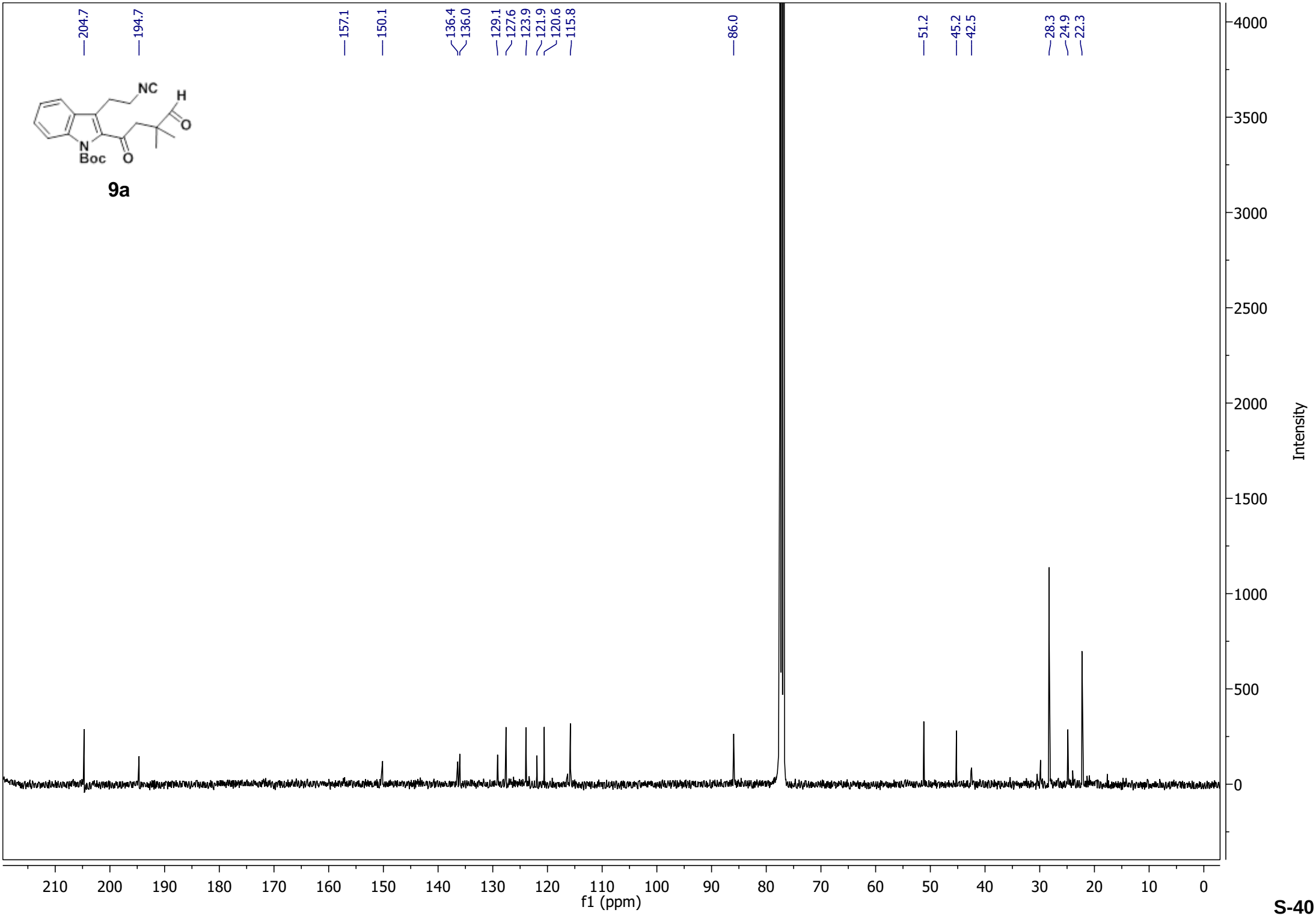

9.63
8.11
7.52
7.52
7.49
7.47
7.00
6.94
6.94
6.92
6.92
3.88
3.57
3.56
3.54
3.54
3.53
3.05
2.88
2.87
2.86
2.85
1.70
1.69
1.13
0.95
0.93
0.93
0.95
0.87
1.04
3.27
2.00
1.97
2.04
9.52
6.16
Intensity
f1 (ppm)

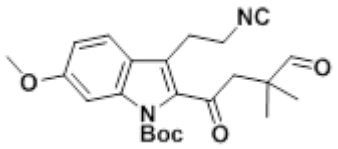

204.6
195.1
161.8
160.5
150.3
137.9
135.5
125.1
122.6
121.5
113.2
100.0
85.7
55.7
50.9
45.5
38.4
28.3
23.2
22.1
8b
Intensity
f1 (ppm)


NC
H
O
N
Boc
O

**9a**


9.65
7.99
7.97
7.67
7.65
7.47
7.47
7.45
7.45
7.45
7.43
7.43
7.35
7.33
7.32
3.75
3.73
3.71
3.08
3.06
3.05
1.70
1.16
1.00
1.11
1.01
1.32
1.32
2.01
3.85
8.26
6.34
Intensity
f1 (ppm)


204.7
194.7
157.1
150.1
136.4
136.0
129.1
127.6
123.9
121.9
120.6
115.8
86.0
51.2
45.2
42.5
28.3
24.9
22.3
NC
H
O
N
Boc
O
9a
4000
3500
3000
2500
2000
1500
1000
500
0
Intensity
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



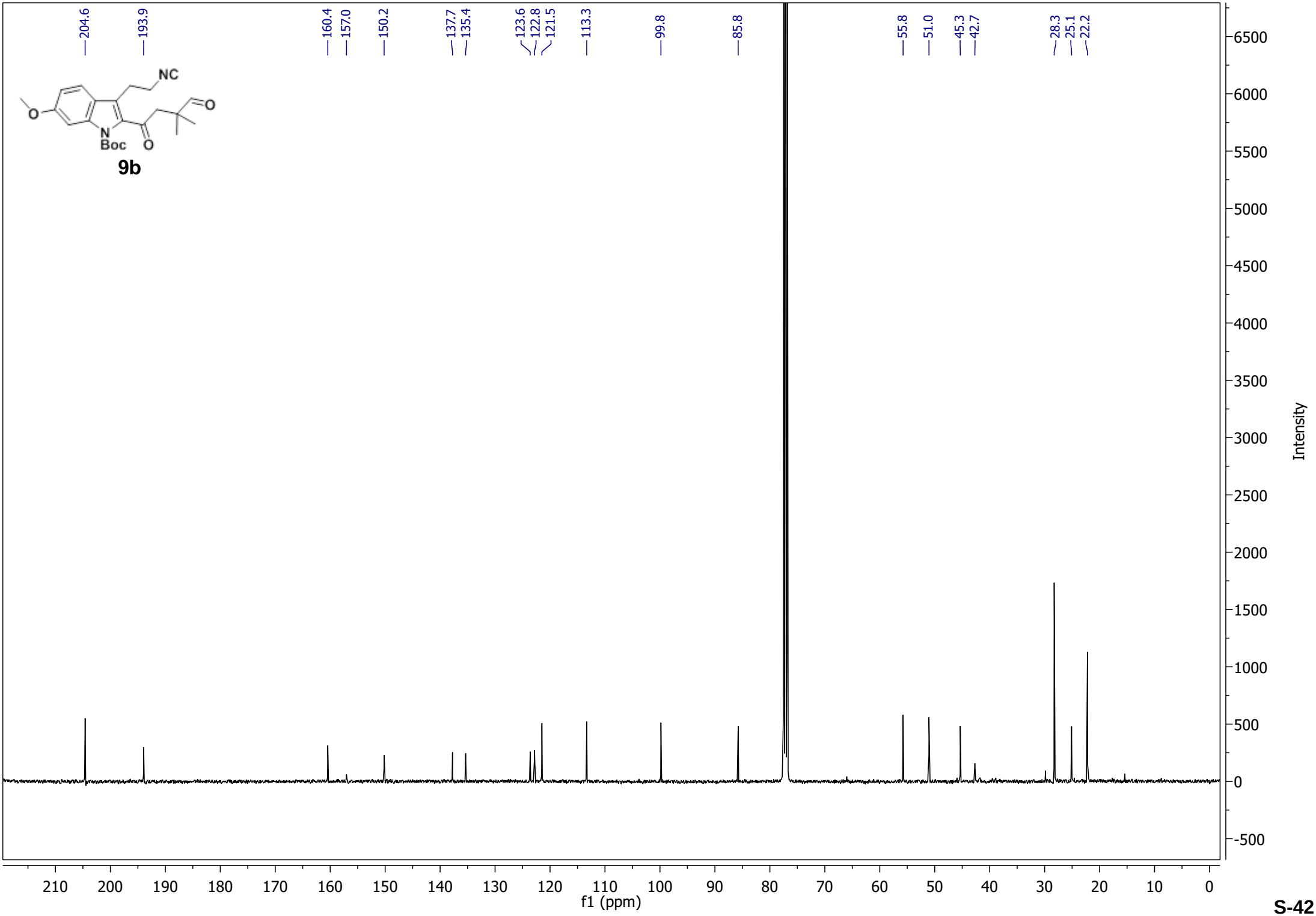

**9b**

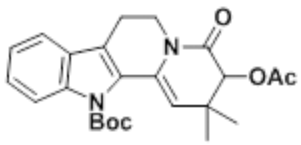
9.64
7.55
7.54
7.54
7.53
7.26
6.97
6.97
6.95
6.94
3.89
3.74
3.73
3.71
3.70
3.05
3.04
3.04
3.02
3.01
1.70
1.13

0.91
1.94
1.01
3.10
2.05
4.00
8.54
5.86

30000
25000
20000
15000
10000
5000
0
Intensity

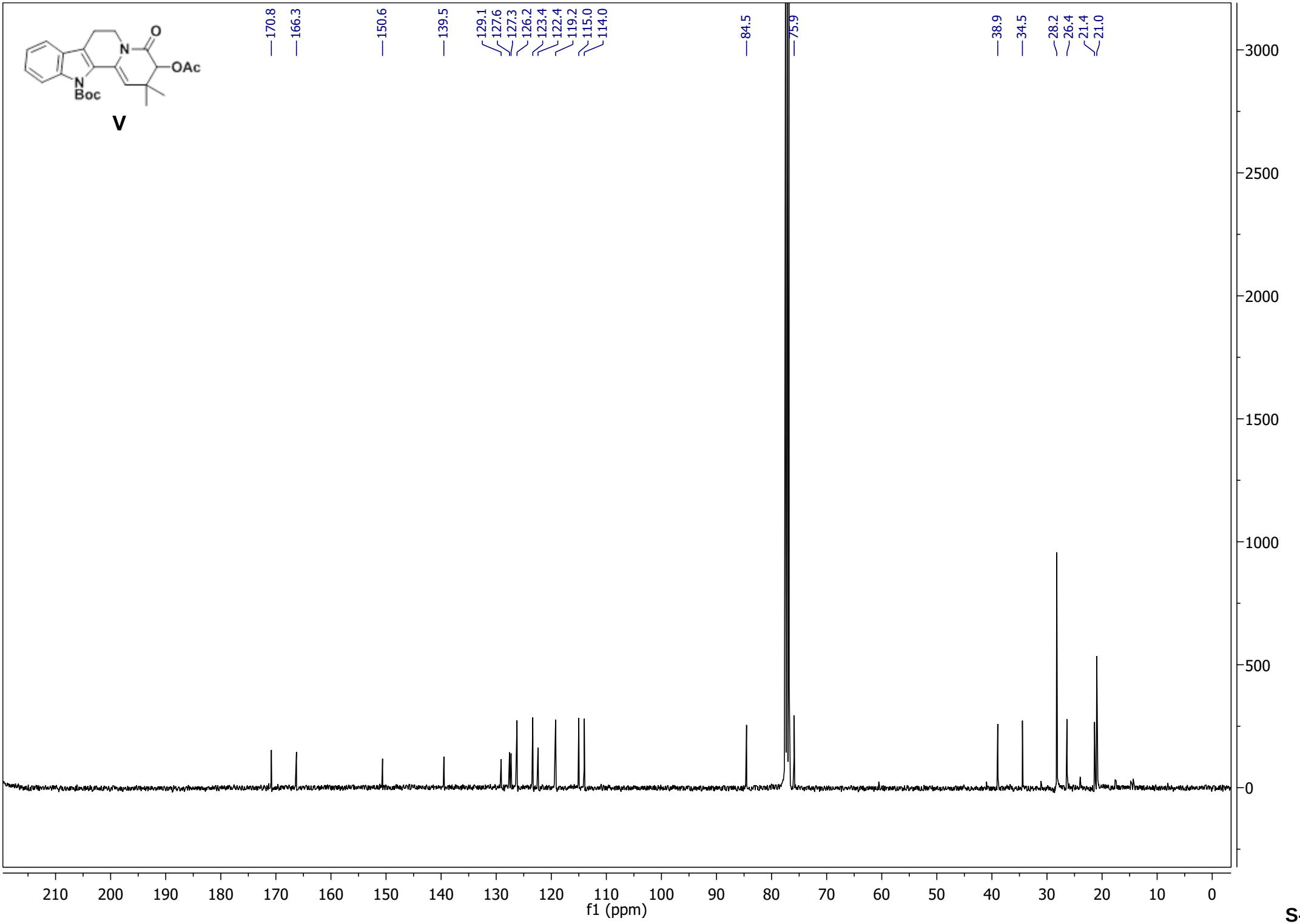
14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

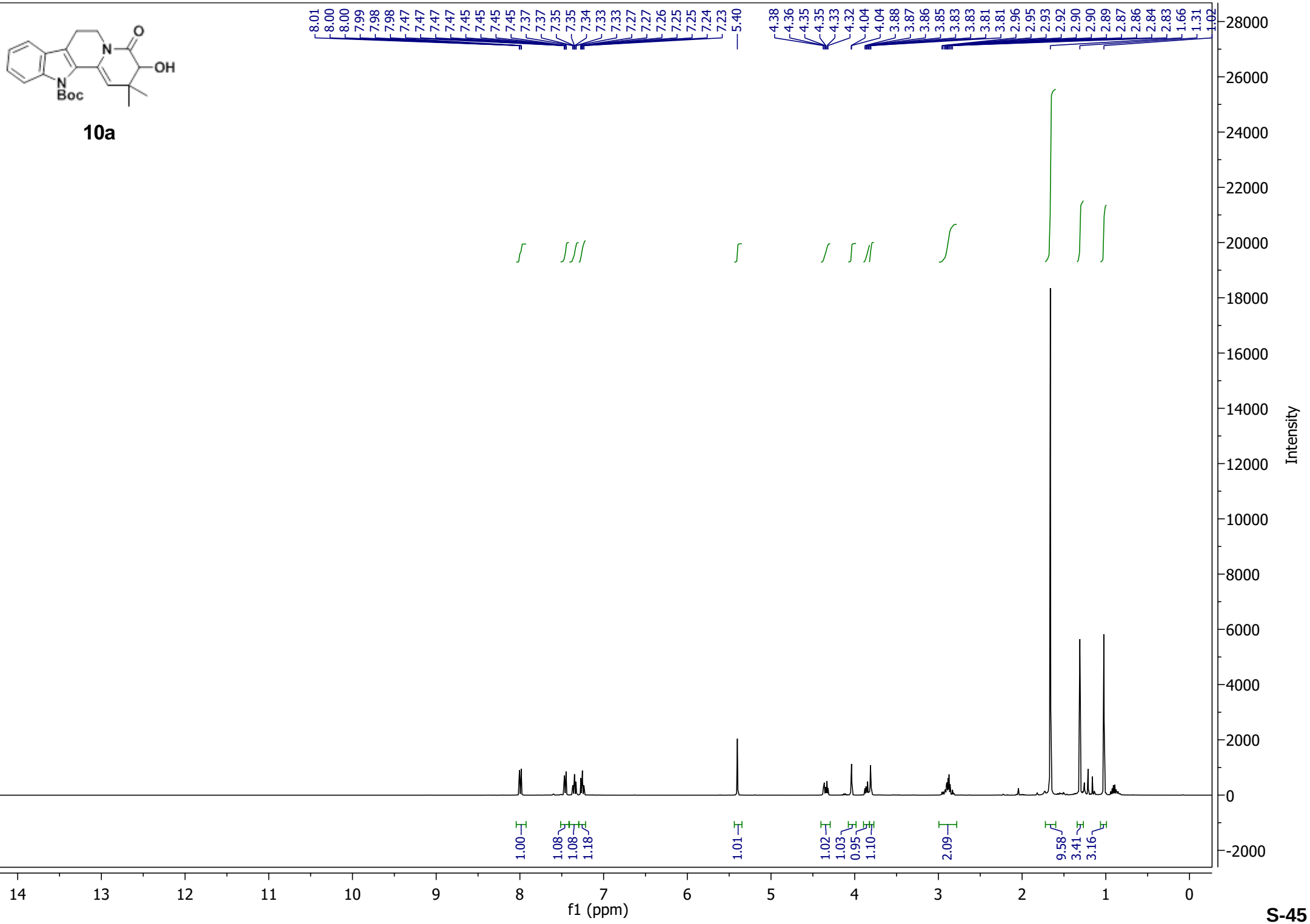

204.6
193.9
160.4
157.0
150.2
137.7
135.4
123.6
122.8
121.5
113.3
99.8
85.8
55.8
51.0
45.3
42.7
28.3
25.1
22.2
NC
O
O
N
Boc
O
9b
Intensity
f1 (ppm)

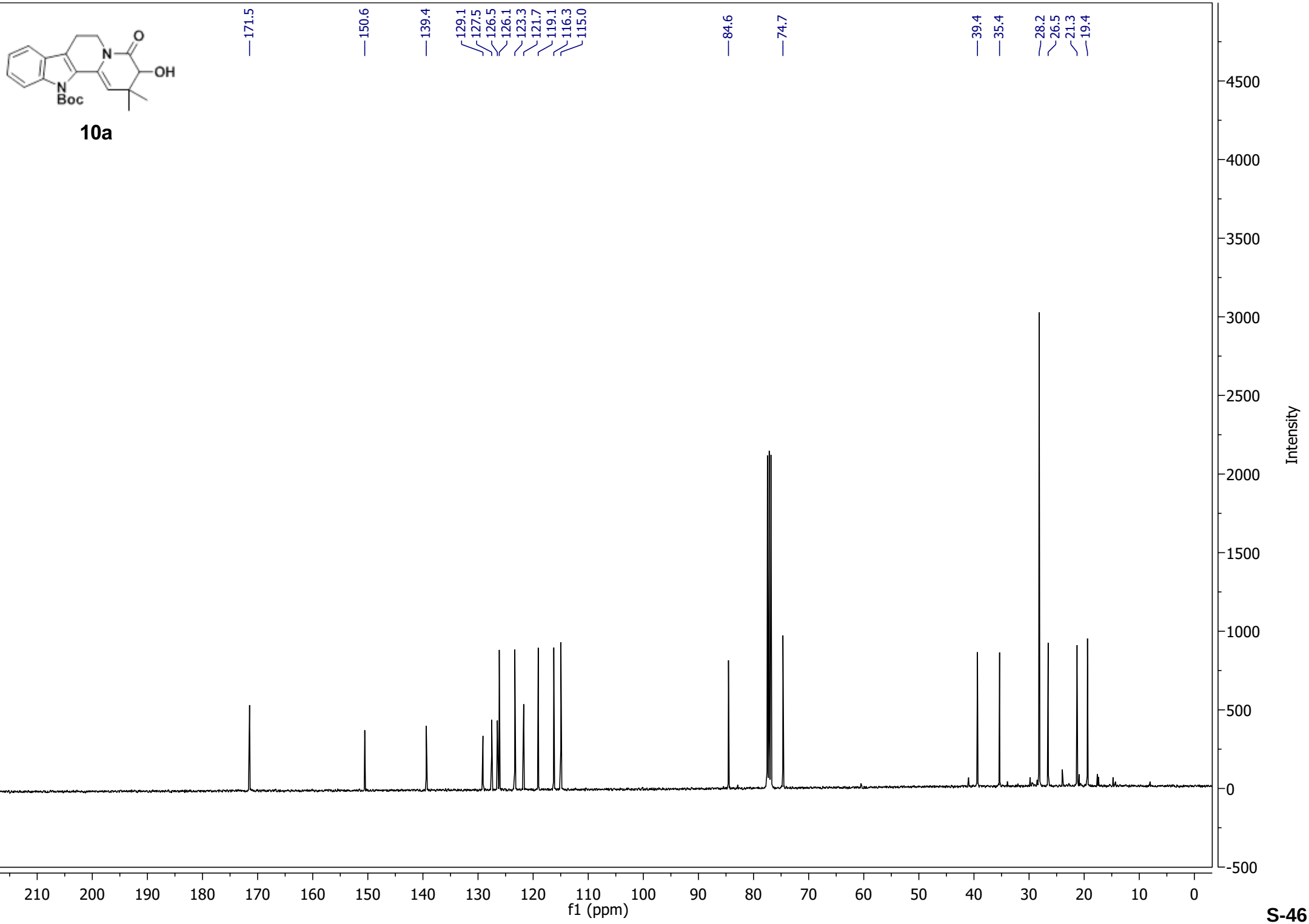

O
N
OAc
N
Boc

**V**

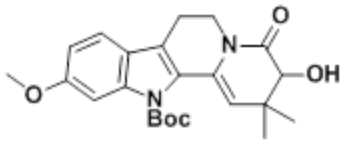

8.00
7.97
7.47
7.45
7.37
7.35
7.35
7.35
7.33
7.28
7.26
7.26
7.26
7.24
5.37
5.30
4.39
4.38
4.36
4.36
4.35
4.33
3.82
3.81
3.80
3.79
3.78
3.77
3.76
2.94
2.92
2.91
2.90
2.89
2.88
2.87
2.85
2.84
2.81
2.25
2.25
1.66
1.66
1.21
1.20
1.15
0.92
1.02
1.03
1.55
0.96
0.97
0.92
0.96
2.00
2.91
9.42
3.65
3.24
f1 (ppm)
Intensity


170.8
166.3
150.6
139.5
129.1
127.6
127.3
126.2
123.4
122.4
119.2
115.0
114.0
84.5
75.9
38.9
34.5
28.2
26.4
21.4
21.0
O
N
OAc
N
Boc
V
3000
2500
2000
1500
1000
500
0
Intensity
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


10a
8.01 8.00 8.00 7.99 7.98 7.98 7.47 7.47 7.47 7.47 7.45 7.45 7.45 7.45 7.37 7.37 7.35 7.35 7.34 7.33 7.33 7.27 7.27 7.26 7.25 7.25 7.24 7.23 5.40
4.38 4.36 4.35 4.35 4.33 4.32 4.04 4.04 3.88 3.87 3.86 3.85 3.83 3.83 3.81 3.81 2.96 2.95 2.93 2.92 2.90 2.90 2.89 2.87 2.86 2.84 2.83 1.66 1.31 1.02
1.00 1.08 1.08 1.18 1.01 1.02 1.03 0.95 1.10 2.09 9.58 3.41 3.16
f1 (ppm)
Intensity

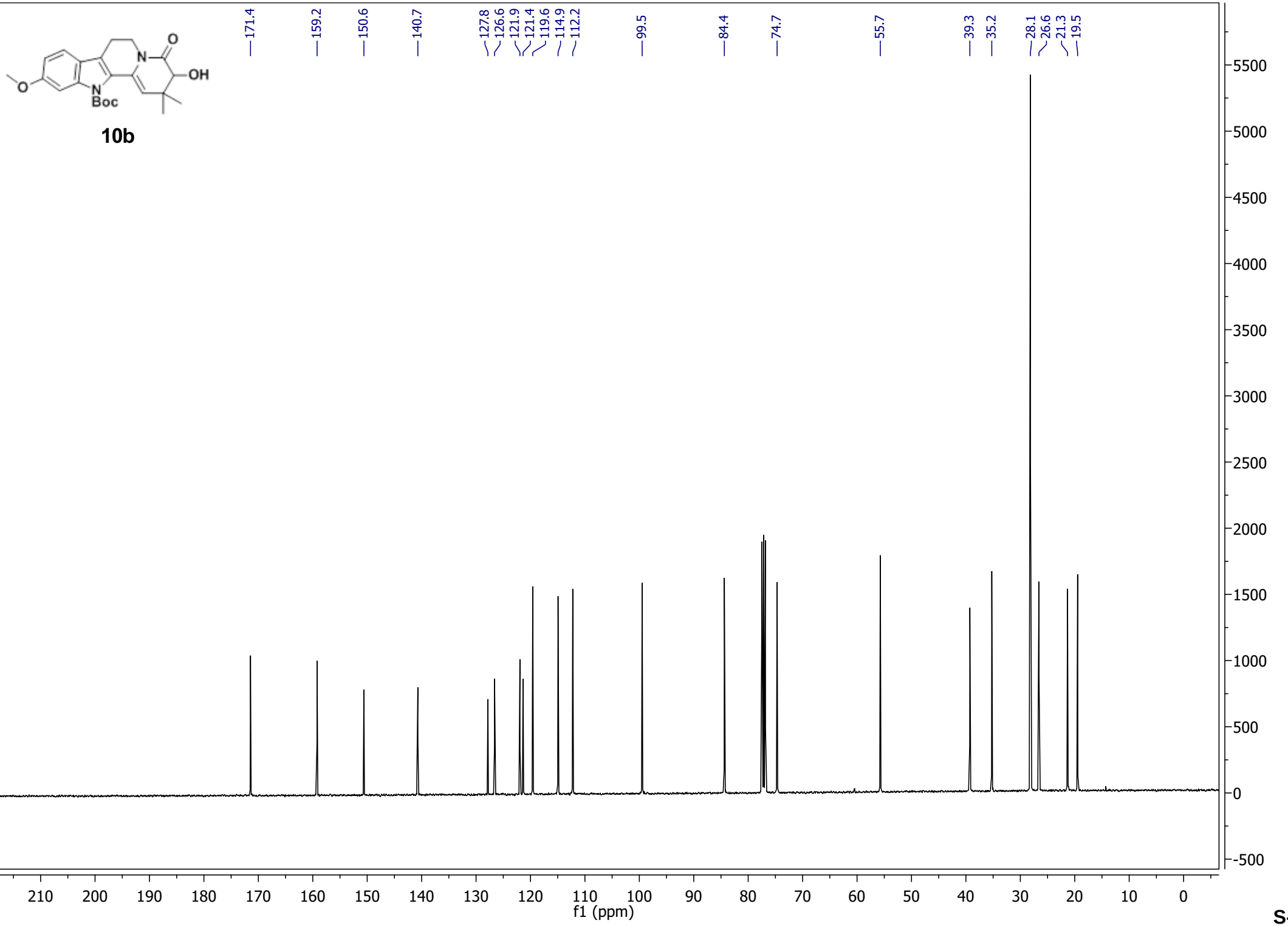

171.5
150.6
139.4
129.1
127.5
126.5
126.1
123.3
121.7
119.1
116.3
115.0
84.6
74.7
39.4
35.4
28.2
26.5
21.3
19.4
O
N
OH
N
Boc
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
Intensity
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

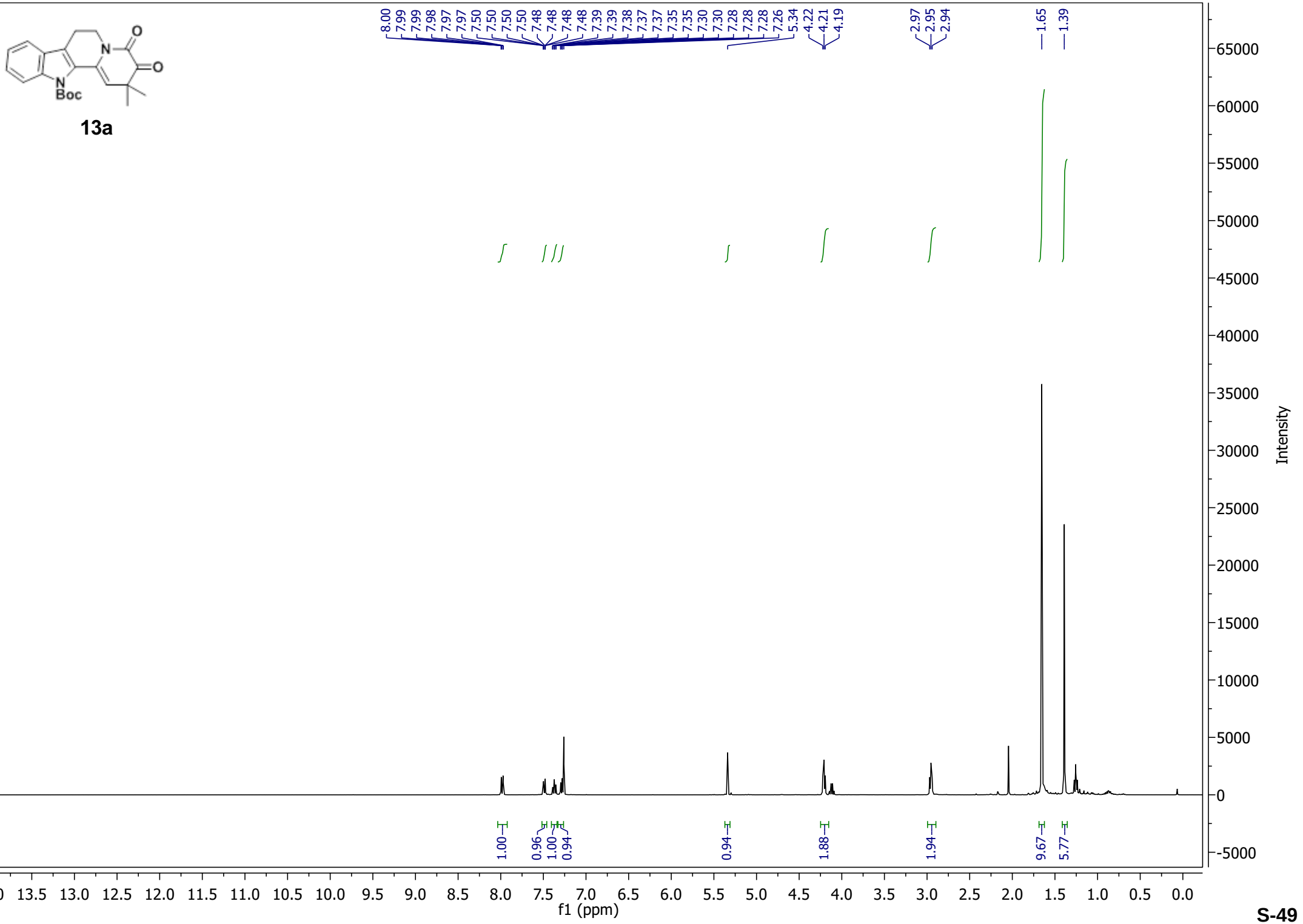
**10a**

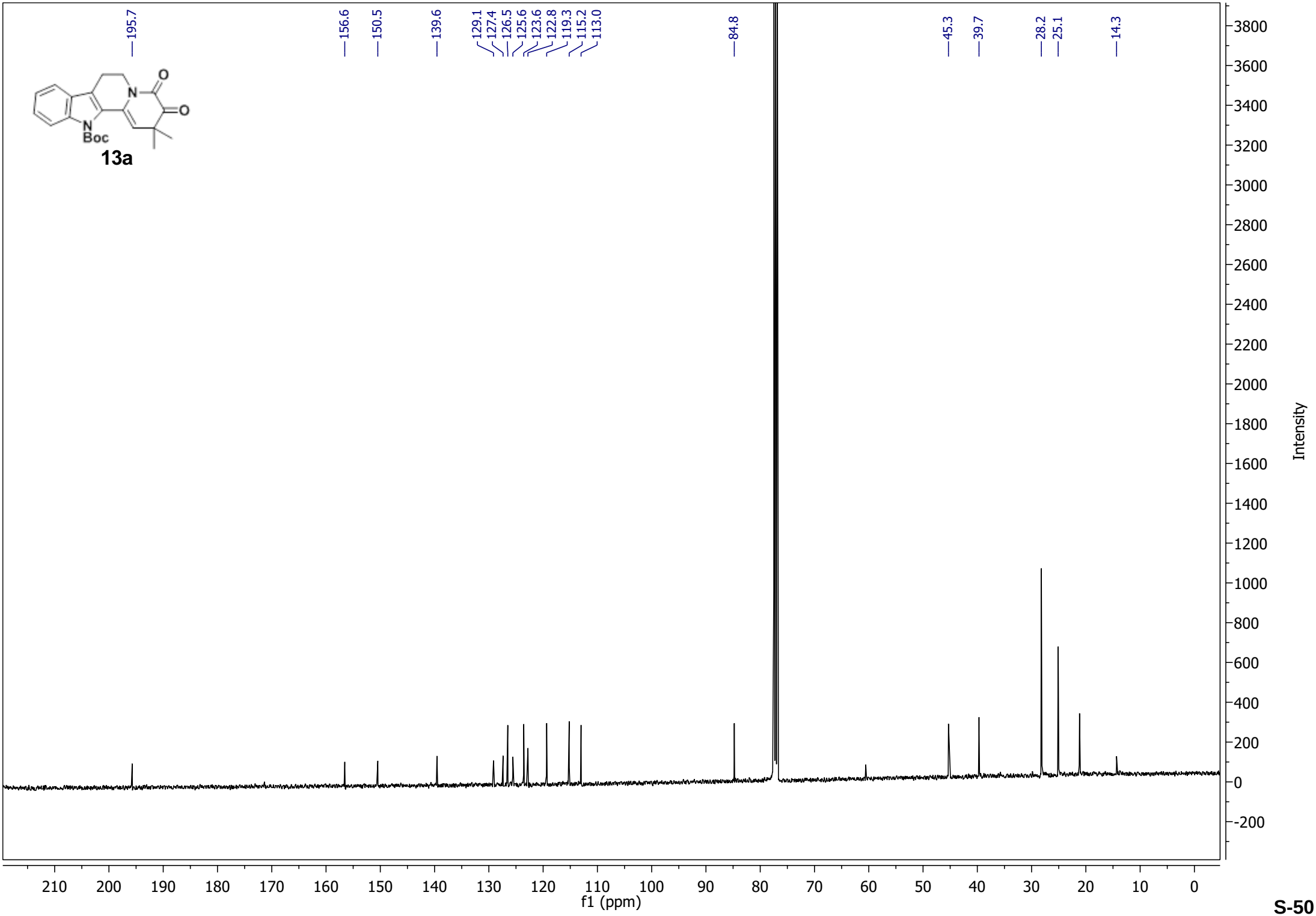

O
N
OH
O
N
Boc

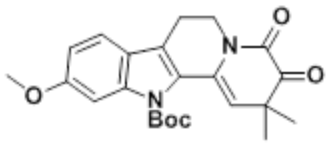
**10b**


7.59 7.58 7.32 7.32 7.30 7.30 6.88 6.88 6.86 6.85 5.30 4.36 4.35 4.34 4.33 4.32 4.31 4.02 3.87 3.84 3.83 3.83 3.82 3.81 3.80 3.79 3.79 3.79 3.78 2.90 2.89 2.89 2.88 2.87 2.86 2.85 2.84 2.83 2.83 2.82 2.80 2.79 2.78 2.76 1.65 1.30 1.01
1.00 1.01 1.00 1.00 1.01 1.03 3.09 1.92 2.04 9.31 3.04 3.07
45000 40000 35000 30000 25000 20000 15000 10000 5000 0
Intensity
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0
f1 (ppm)


171.4
159.2
150.6
140.7
127.8
126.6
121.9
121.4
119.6
114.9
112.2
99.5
84.4
74.7
55.7
39.3
35.2
28.1
26.6
21.3
19.5
O
N
OH
O
N
Boc
10b
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
Intensity
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


13a
8.00
7.99
7.99
7.98
7.97
7.97
7.50
7.50
7.50
7.50
7.48
7.48
7.48
7.48
7.39
7.39
7.38
7.37
7.37
7.35
7.35
7.30
7.28
7.28
7.28
7.26
5.34
4.22
4.21
4.19
2.97
2.95
2.94
1.65
1.39
1.00
0.96
1.00
0.94
0.94
1.88
1.94
9.67
5.77
Intensity
f1 (ppm)


195.7
156.6
150.5
139.6
129.1
127.4
126.5
125.6
123.6
122.8
119.3
115.2
113.0
84.8
45.3
39.7
28.2
25.1
14.3
O
N
O
N
Boc
13a
Intensity
f1 (ppm)



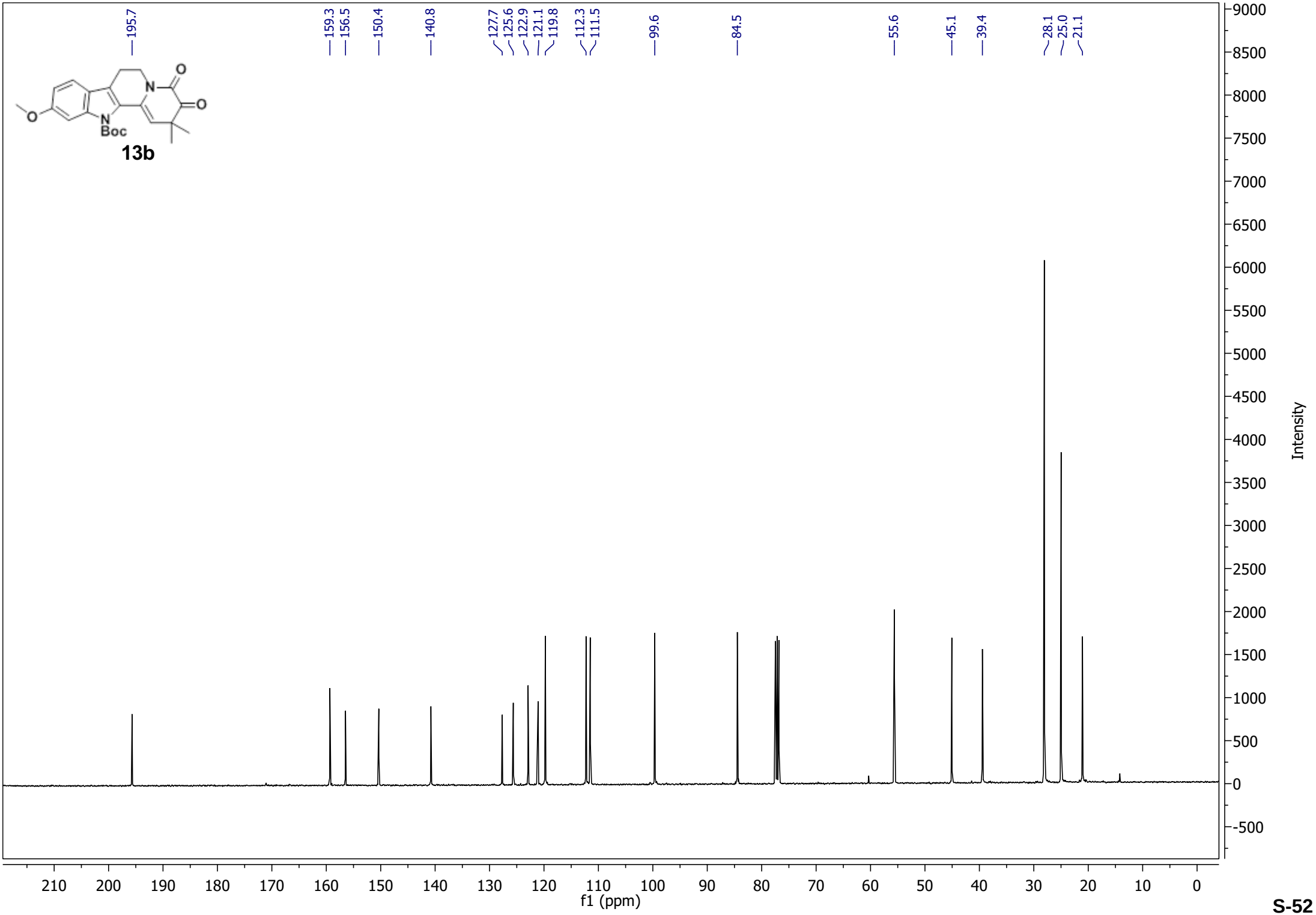

**13b**

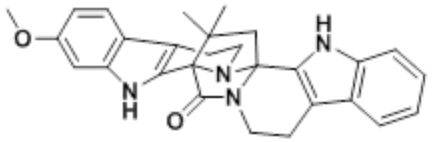
7.55
7.54
7.32
7.30
6.87
6.86
6.85
6.84
5.23
4.17
4.15
4.14
3.84
2.88
2.87
2.85
1.63
1.35

0.95
0.98
0.92
0.89
2.00
3.05
1.93
9.15
6.22

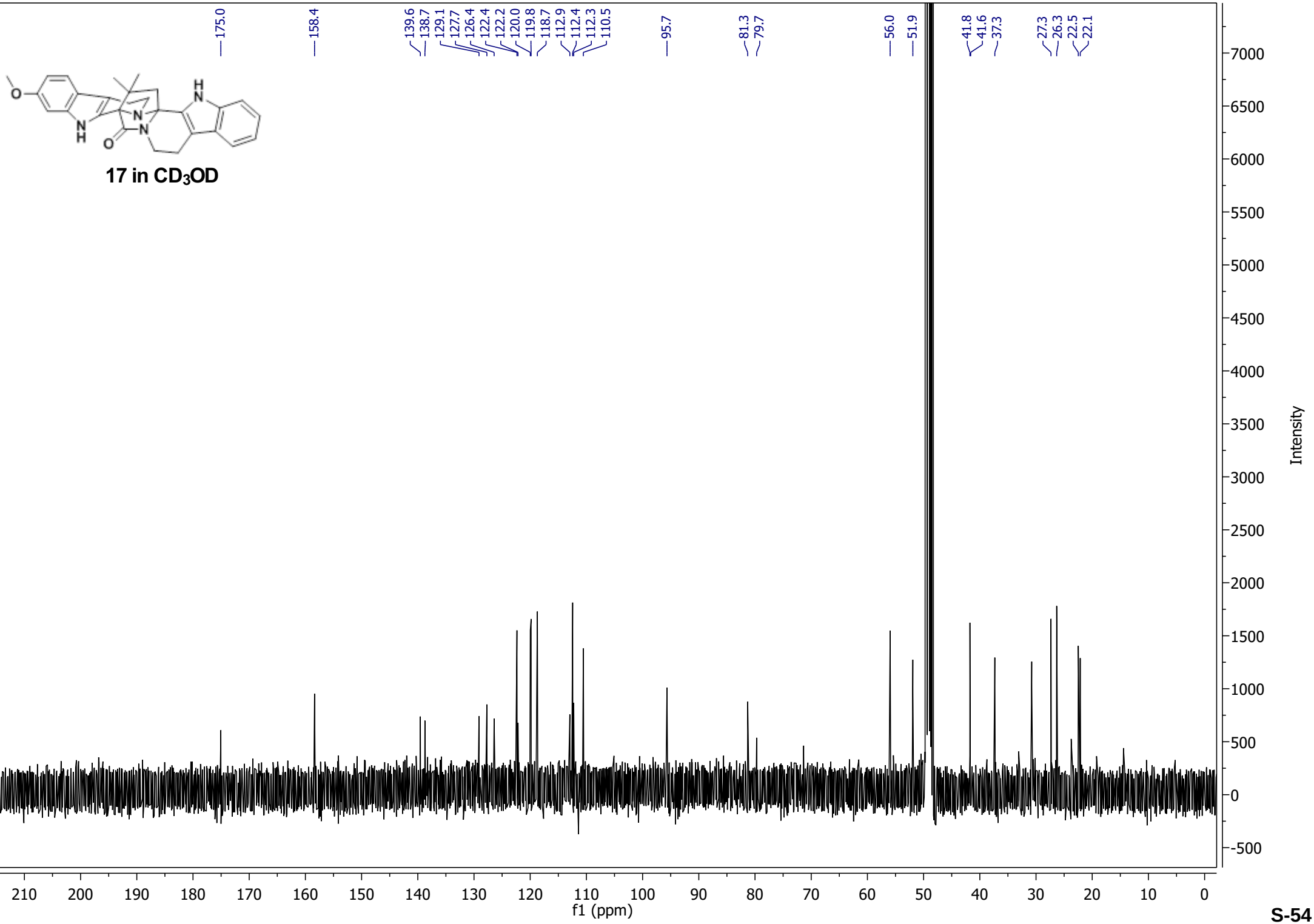
f1 (ppm)

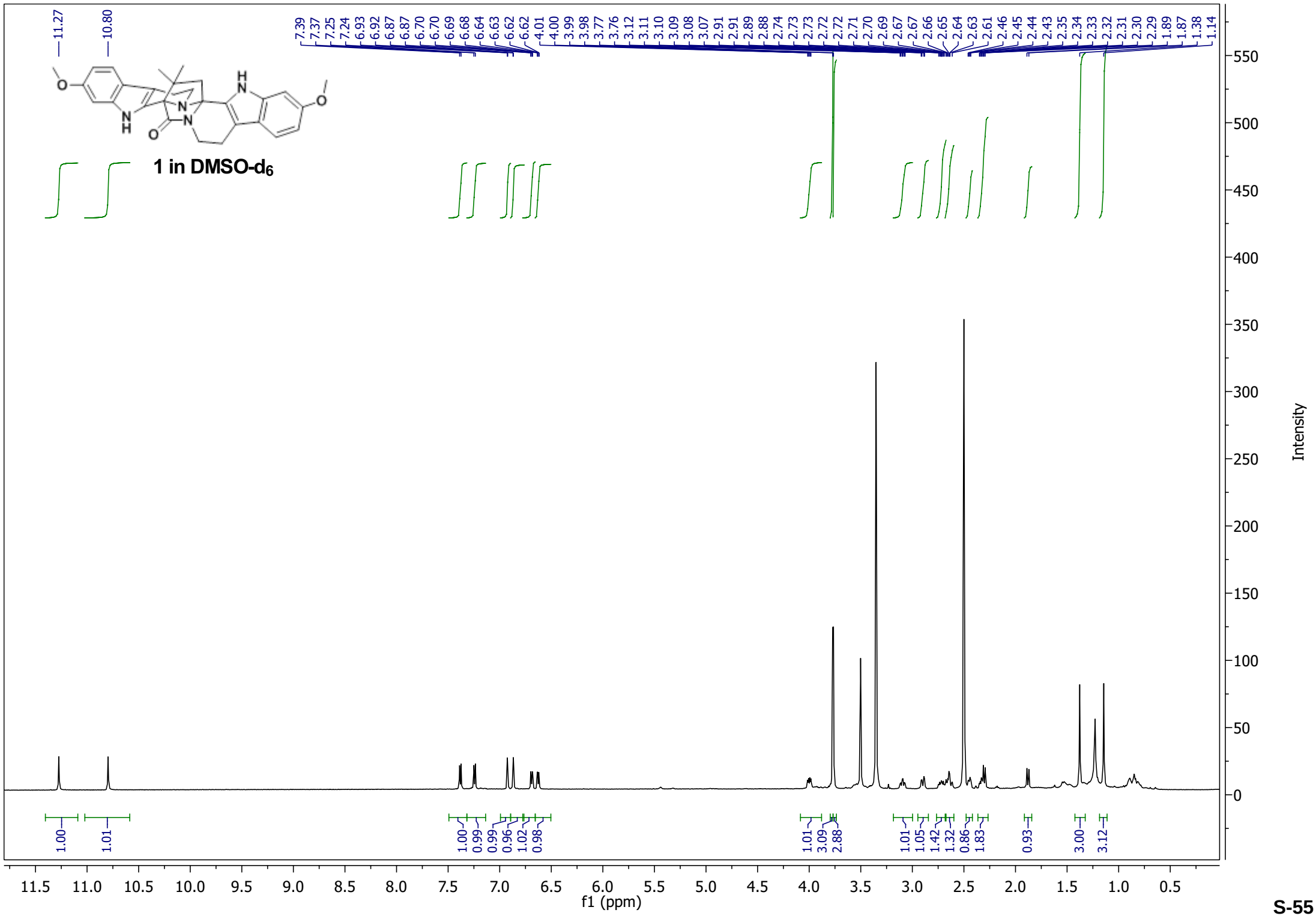
Intensity

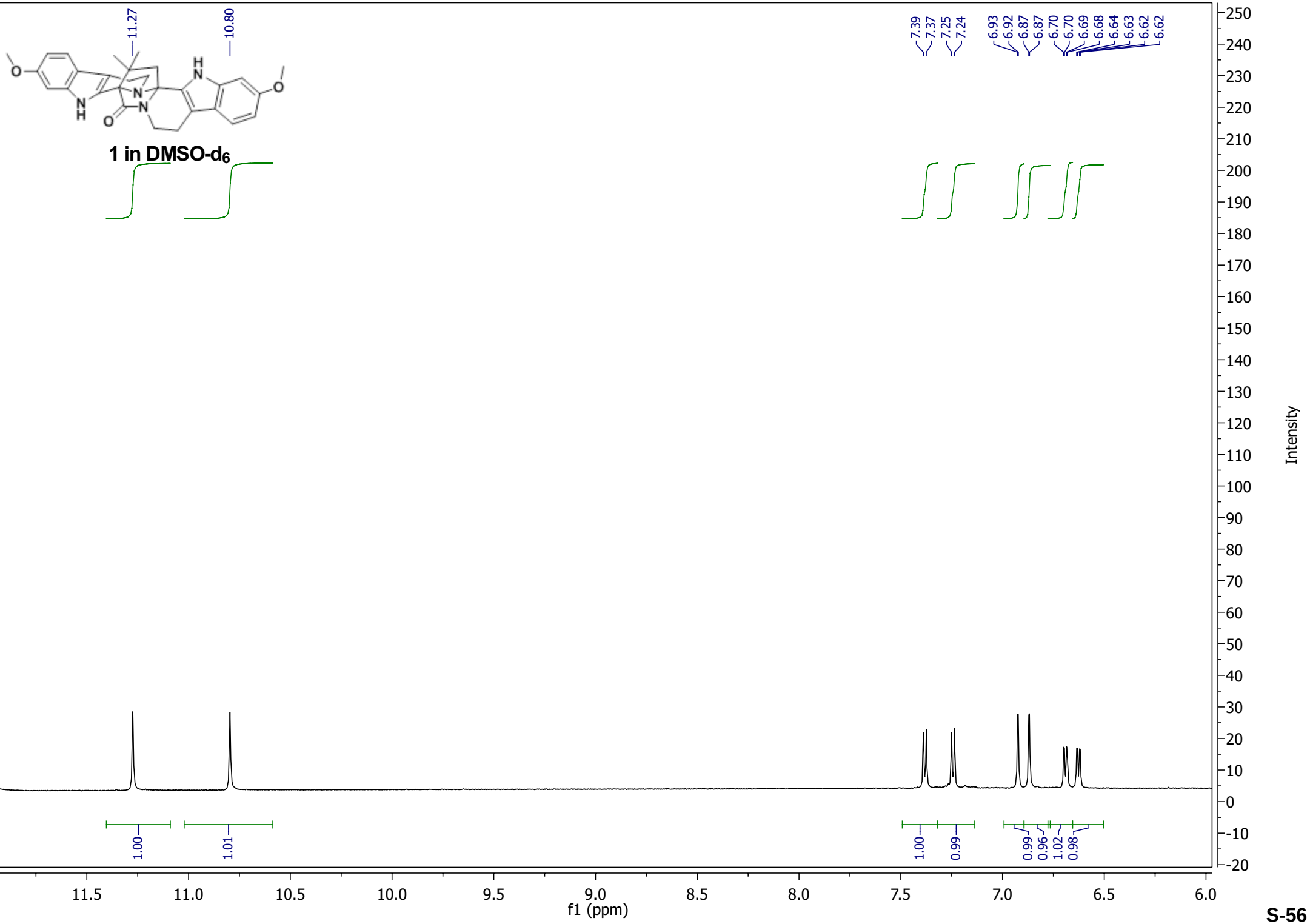

195.7
159.3
156.5
150.4
140.8
127.7
125.6
122.9
121.1
119.8
112.3
111.5
99.6
84.5
55.6
45.1
39.4
28.1
25.0
21.1
O
N
O
O
N
Boc
13b
Intensity
f1 (ppm)

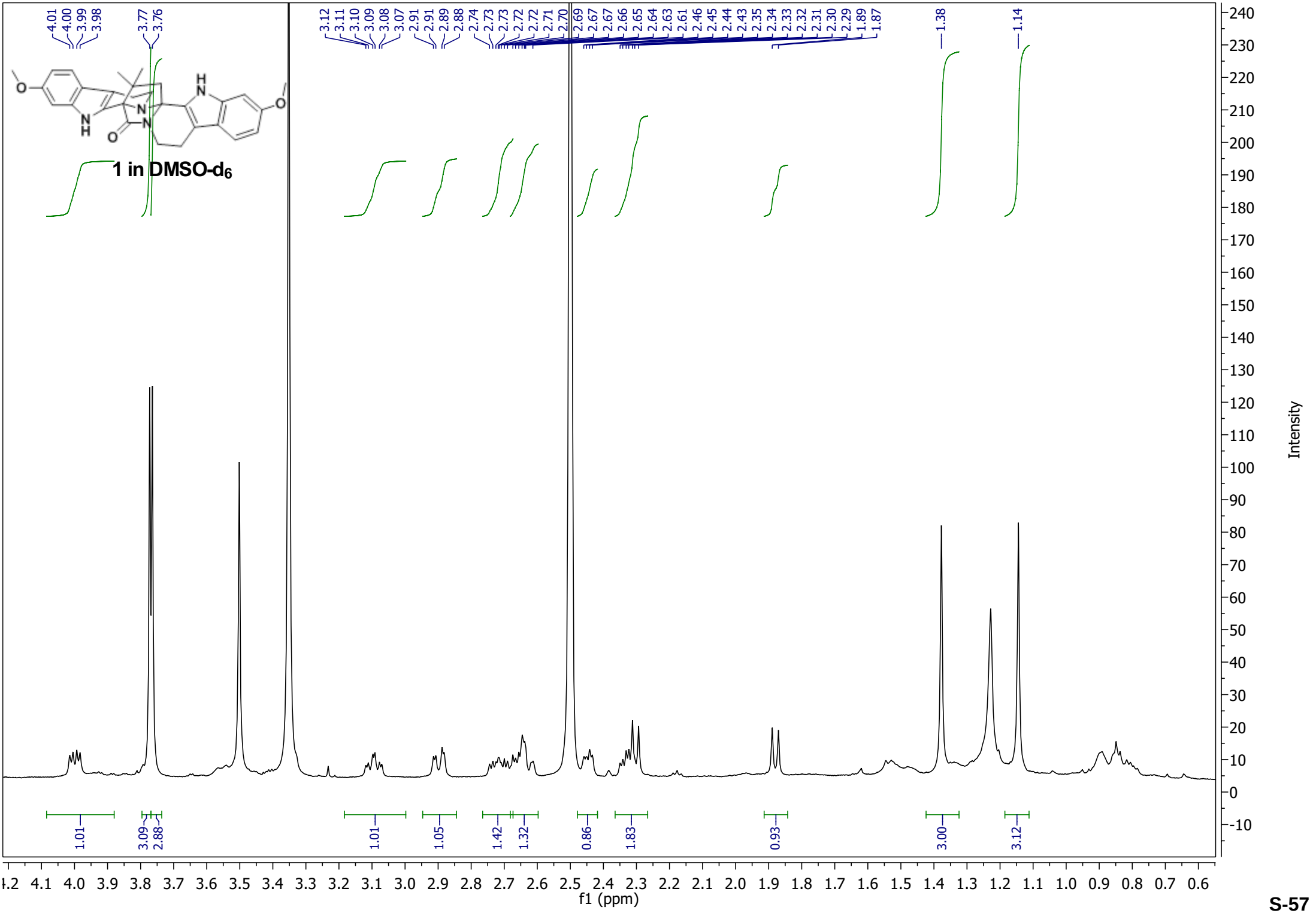


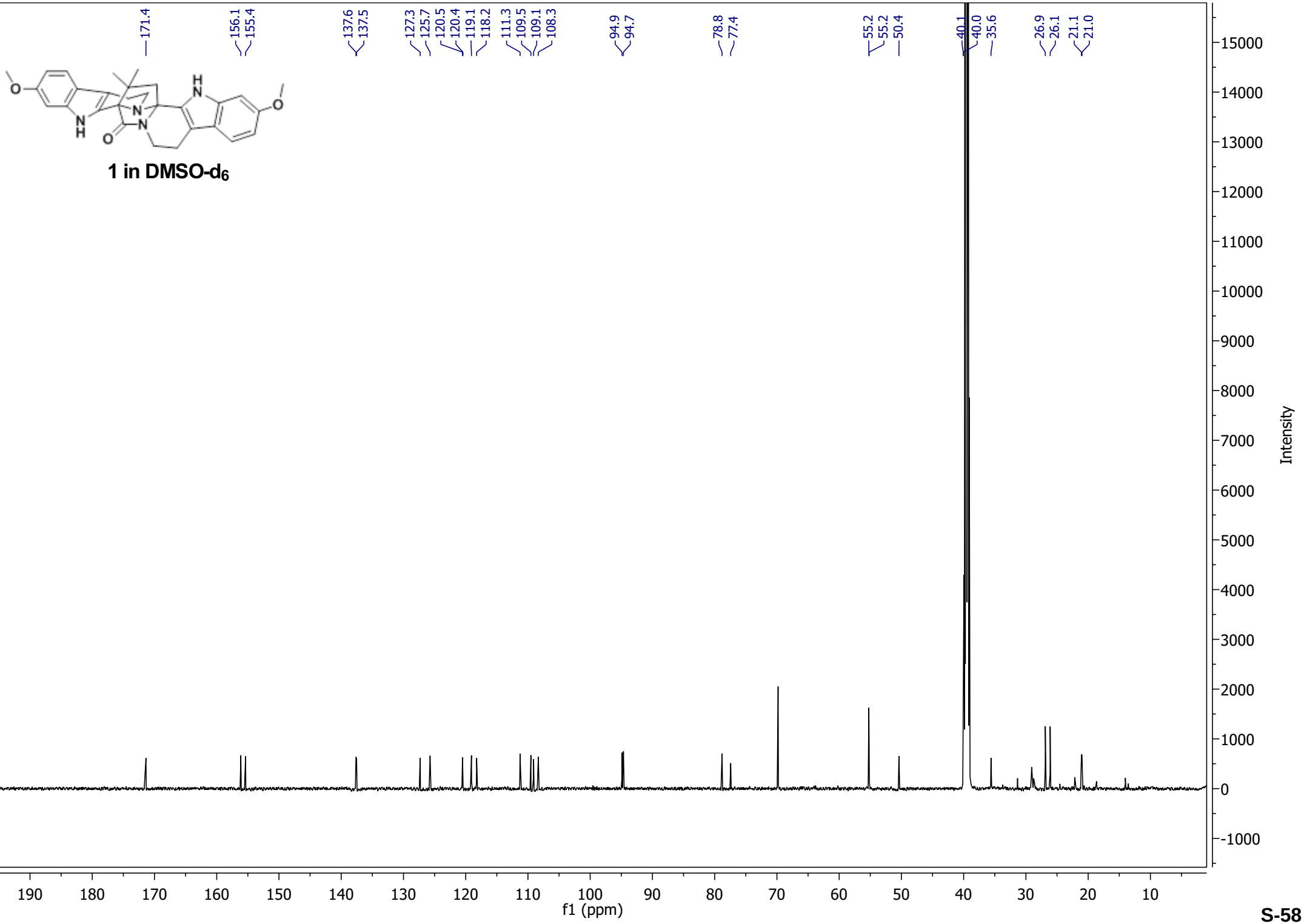
**17 in $CD_3OD$**

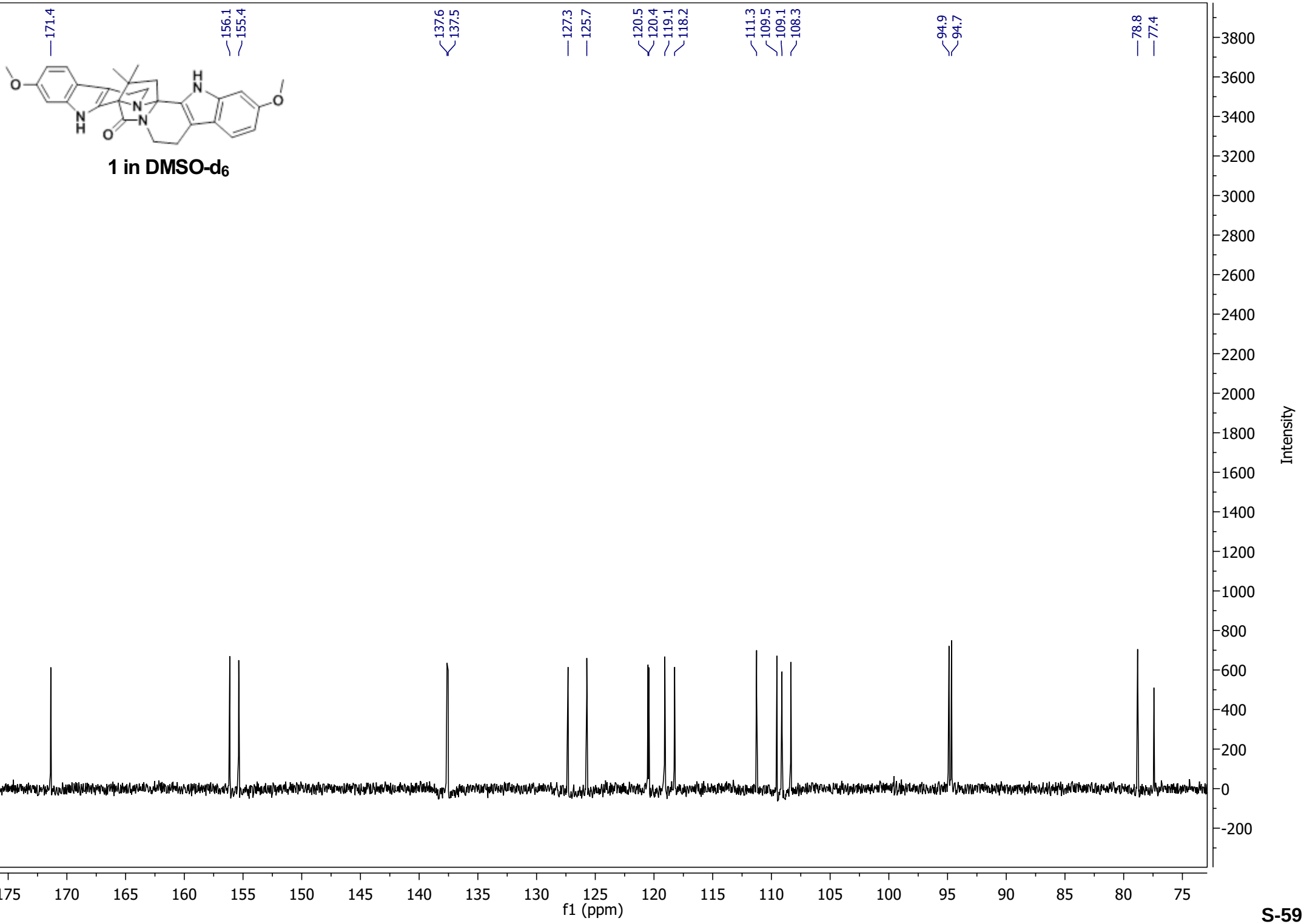

175.0
158.4
139.6
138.7
129.1
127.7
126.4
122.4
122.2
120.0
119.8
118.7
112.9
112.4
112.3
110.5
95.7
81.3
79.7
56.0
51.9
41.8
41.6
37.3
27.3
26.3
22.5
22.1
17 in CD3OD
Intensity
f1 (ppm)

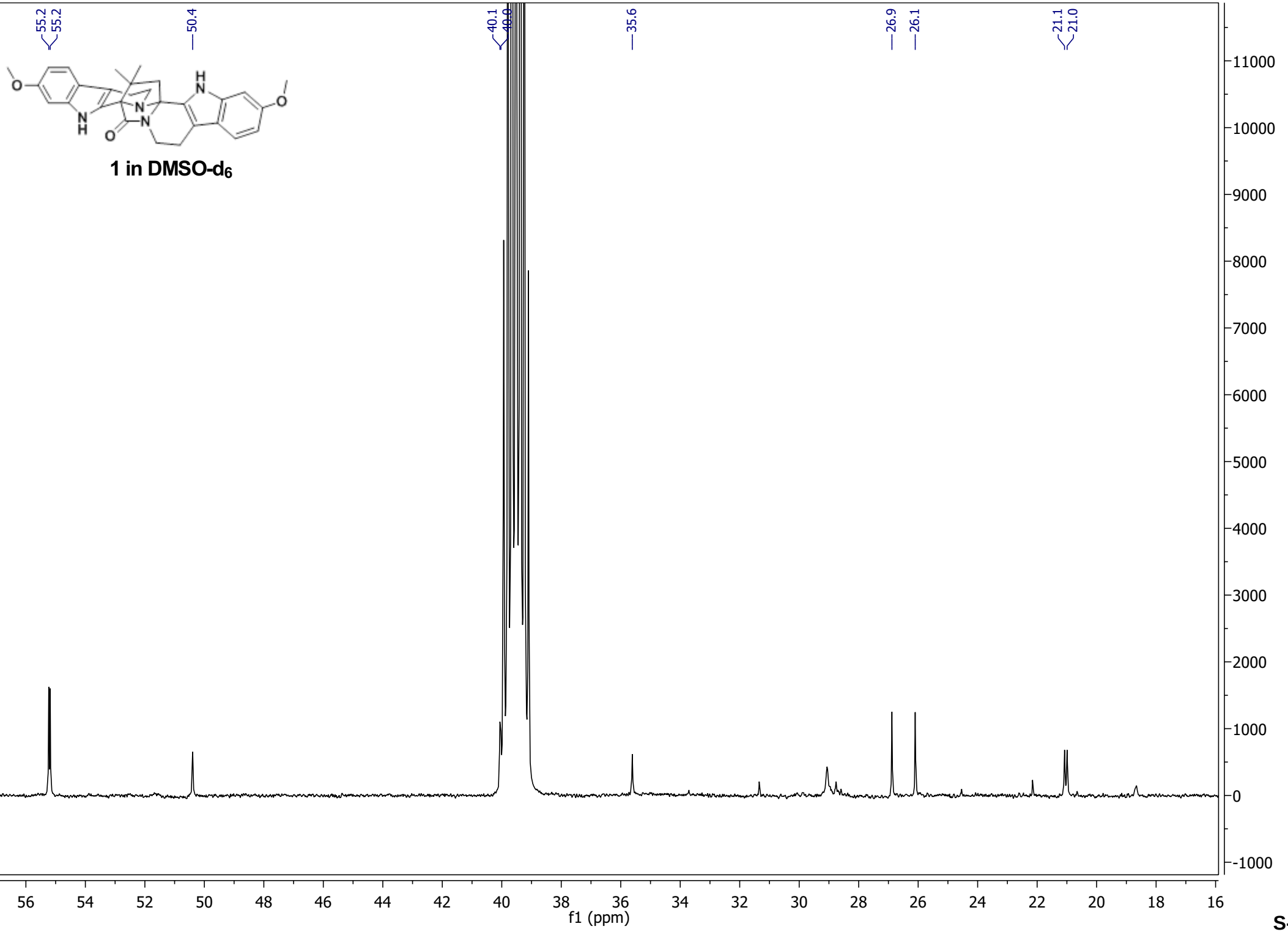

11.27
10.80
7.39 7.37 7.25 7.24 6.93 6.92 6.87 6.87 6.70 6.70 6.69 6.68 6.64 6.63 6.62 6.62 4.01 4.00 3.99 3.98 3.77 3.76 3.12 3.11 3.10 3.09 3.08 3.07 2.91 2.91 2.89 2.88 2.74 2.73 2.73 2.72 2.72 2.71 2.70 2.69 2.67 2.67 2.66 2.65 2.64 2.63 2.61 2.46 2.45 2.44 2.43 2.35 2.34 2.33 2.32 2.31 2.30 2.29 1.89 1.87 1.38 1.14
1 in DMSO-d6
1.00 1.01 1.00 0.99 0.99 0.96 1.02 0.98 1.01 3.09 2.88 1.01 1.05 1.42 1.32 0.86 1.83 0.93 3.00 3.12
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)
550 500 450 400 350 300 250 200 150 100 50 0
Intensity


11.27
10.80
7.39
7.37
7.25
7.24
6.93
6.92
6.87
6.87
6.70
6.70
6.69
6.68
6.64
6.63
6.62
6.62
1 in DMSO-d6
1.00
1.01
1.00
0.99
0.99
0.96
1.02
0.98
f1 (ppm)
Intensity

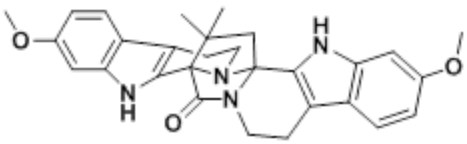

4.01
4.00
3.99
3.98
3.77
3.76
3.12
3.11
3.10
3.09
3.08
3.07
2.91
2.91
2.89
2.88
2.74
2.73
2.73
2.72
2.72
2.71
2.70
2.69
2.67
2.67
2.66
2.65
2.64
2.63
2.61
2.46
2.45
2.44
2.43
2.35
2.34
2.33
2.32
2.31
2.30
2.29
1.89
1.87
1.38
1.14
1 in DMSO-d6
1.01
3.09
2.88
1.01
1.05
1.42
1.32
0.86
1.83
0.93
3.00
3.12
f1 (ppm)
Intensity


171.4
156.1
155.4
137.6
137.5
127.3
125.7
120.5
120.4
119.1
118.2
111.3
109.5
109.1
108.3
94.9
94.7
78.8
77.4
55.2
55.2
50.4
40.1
40.0
35.6
26.9
26.1
21.1
21.0
O
N
H
N
H
N
O
O
1 in DMSO-d6
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
Intensity
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

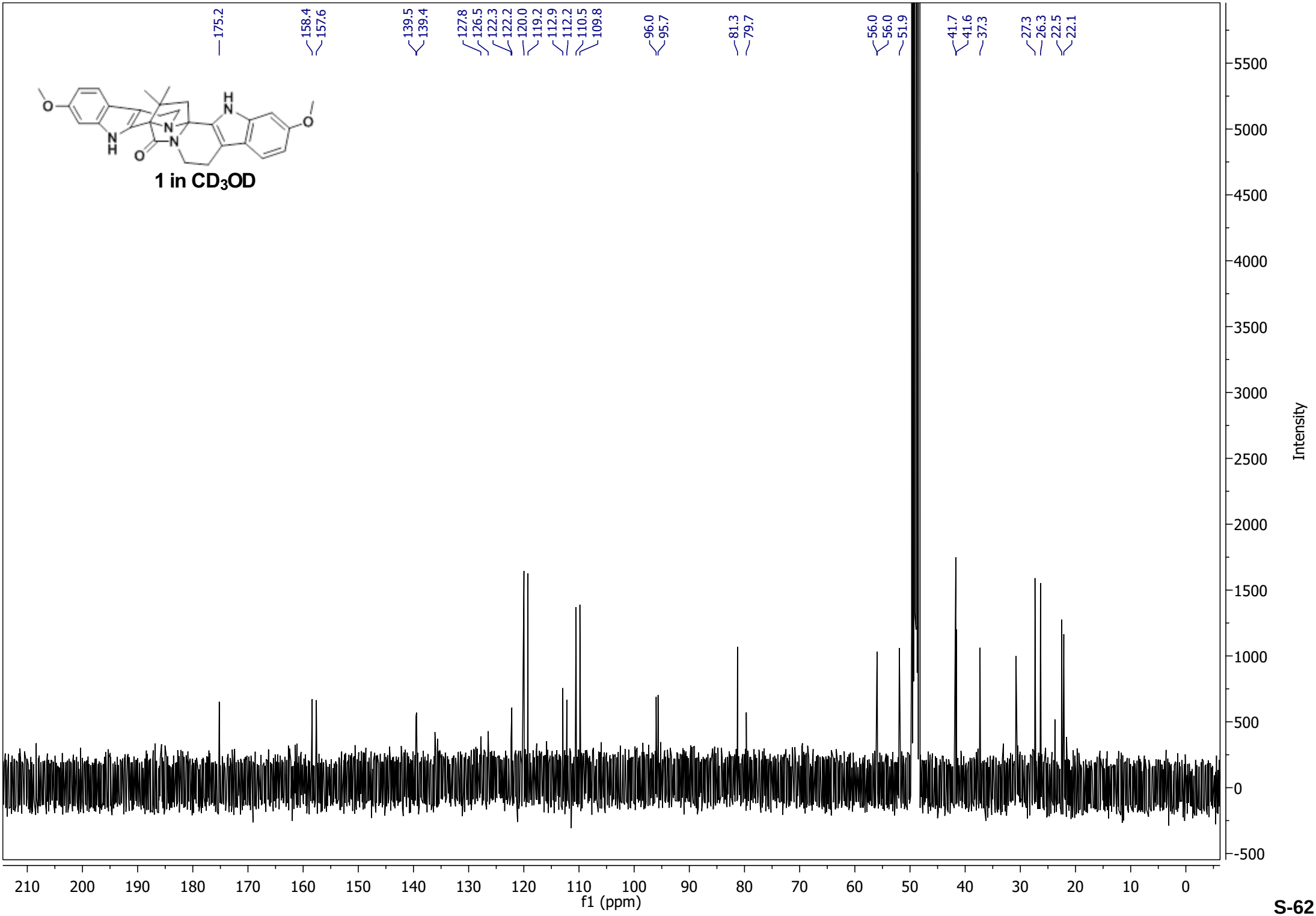

171.4
156.1
155.4
137.6
137.5
127.3
125.7
120.5
120.4
119.1
118.2
111.3
109.5
109.1
108.3
94.9
94.7
78.8
77.4
O
N
H
N
O
N
H
O
1 in DMSO-d6
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
Intensity
175
170
165
160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
f1 (ppm)

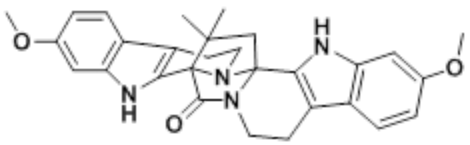

55.2
55.2
50.4
40.1
40.0
35.6
26.9
26.1
21.1
21.0
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
Intensity
56
54
52
50
48
46
44
42
40
38
36
34
32
30
28
26
24
22
20
18
16
f1 (ppm)

**1 in DMSO-$d_6$**

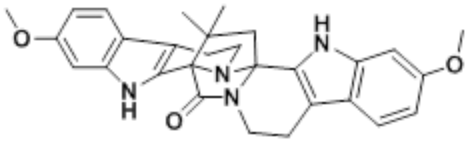


**1 in $CD_3OD$**


175.2
158.4
157.6
139.5
139.4
127.8
126.5
122.3
122.2
120.0
119.2
112.9
112.2
110.5
109.8
96.0
95.7
81.3
79.7
56.0
56.0
51.9
41.7
41.6
37.3
27.3
26.3
22.5
22.1
1 in CD3OD
Intensity
f1 (ppm)



**Racemic 1**



**Enantioenriched 1**
**er 96:4**

2

1

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0

f1 (ppm)