

**THE APPLICATION OF NEW METHODS TO THE SYNTHESIS OF CONSTRAINED
PROLINE DERIVATIVES, (+)-SERRATEZOMINE A, AND HAPALINDOLES A, G, I,
AND K
(CHAPTER II. EXPERIMENTAL PROCEDURE AND CHARACTERIZATION DATA)**

By

Aroop Chandra

Dissertation

Submitted to the Faculty of the
Graduate School of Vanderbilt University
in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

in

Chemistry

May, 2011

Nashville, TN

Approved

Professor Jeffrey N. Johnston

Professor Gary A. Sulikowski

Professor Ned A. Porter

Professor Lawrence J. Marnett

Experimental Section

Unless otherwise noted, all reactions were carried out under argon or nitrogen using flame or oven dried glassware. Tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were dried by passage through a column of activated alumina as described by Grubbs.¹ Molecular sieves (spheres, 4Å) were activated at 400 °C and then stored at room temperature in an air-tight container.

Flash column chromatography was performed using Sorbent Technologies 40-63 mm, pore size 60 Å silica gel with solvent systems indicated. Analytical thin layer column chromatography was performed using Sorbent Technologies 250 mm glass-backed UV254 silica gel plates that were visualized by fluorescence upon 250 nm radiation and/or the by use of ceric ammonium molybdate or potassium permanganate. Solvent removal was effected by rotary evaporation under vacuum (~ 25-40 mmHg).

IR spectra were recorded on a Nicolet Avatar 360 spectrophotometer and are reported in wavenumbers (cm^{-1}). Liquids and oils were analyzed as neat films on a NaCl plate (transmission), whereas solids were applied to a diamond plate (ATR). Proton nuclear magnetic resonance spectra were recorded on either a Varian INOVA-400 (400 MHz), VXR-400 (400 MHz) or Bruker DRX-500 (500 MHz) spectrometers and are recorded in parts per million from residual undeuterated chloroform and are reported as follows: chemical shift (multiplicity [s=singlet, d=doublet, t=triplet, q=quartet, qu=quintet, m=multiplet], coupling constant(s), integration). ¹³C NMR data were recorded on a Bruker DRX-500 spectrometer. Ratios of diastereomers and isomeric products were

¹ Pangborn, A. B.; Giardello, M.A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.

measured directly from integration of ^1H NMR absorptions of protons common to the components.

Characterization data for few compounds included here have been reported earlier.²

Optimized reaction conditions and yields for these compounds are included here in this section.

² Viswanathan, R. Ph. D. Dissertation, Indiana University Bloomington, IN, **2005** and Pigza, J. A. Ph. D. Dissertation, Indiana University Bloomington, IN, **2008**

Experimental procedures

<i>Compound Name</i>	<i>Page</i>
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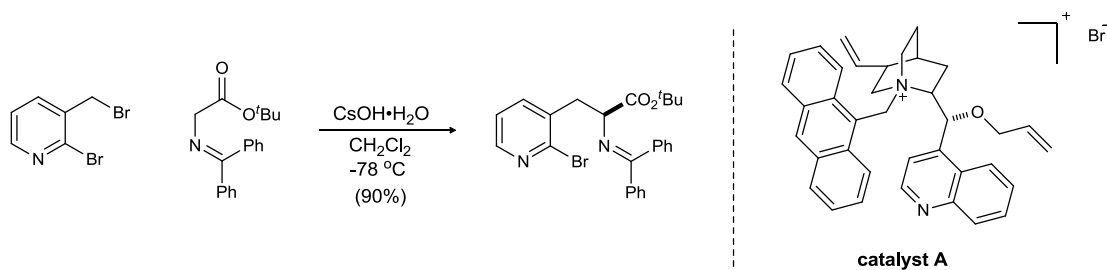
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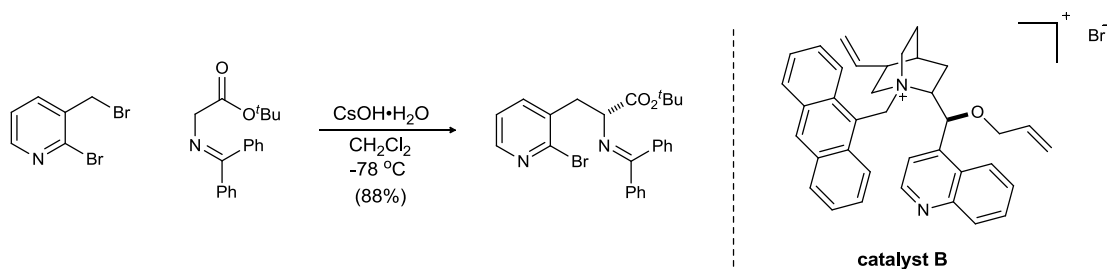
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Figure 183. ^1H NMR Spectrum (500 MHz, CDCl_3) of 612.....	333



**(S)-tert-Butyl-3-(2-bromopyridin-3-yl)-2-(diphenylmethyleneamino)propanoate
(18a).**

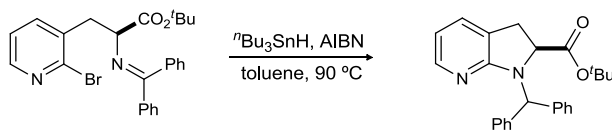
To a 500 mL round bottom flask equipped with a mechanical stirrer was added the Schiff base (17.0 g, 57.5 mmol), the cinchonidine derived catalyst A (2.32 g, 3.87 mmol) and dichloromethane (100 mL). The dibromo pyridine (9.63 g, 38.4 mmol) was added, cooled to -78 °C and the mixture was stirred for 15 minutes. Hand pulverized CsOH·H₂O was added (9.66 g, 57.5 mmol), the reaction was cooled in a dewar to -60 °C using a cold finger and stirred for 3 d. The reaction was diluted with Et₂O, the organic layer was washed with water, dried (Na₂SO₄), and concentrated to an oil. The crude oil was purified by flash chromatography (Al₂O₃, 5-50% diethyl ether in hexanes) to afford the Schiff base as a white solid (18.3 g, 90% yield). HPLC (Chiralcel AD, 2% *i*-PrOH/Hexanes, 1 mL/min) t_R (R) = 7.3 m, t_R (S) = 8.5 m. (S) = 89% ee.³



³ The alkylation product can be triturated with hexanes to provide the material >99%

(R)-tert-Butyl 3-(2-bromopyridin-3-yl)-2-((diphenylmethylene)amino)propanoate (18b).

To a 500 mL round bottom flask equipped with a mechanical stirrer was added the Schiff base (31.9 g, 108 mmol), the cinchonine derived catalyst A (4.36 g, 7.20 mmol) and dichloromethane (180 mL). The dibromo pyridine (18.1 g, 72.0 mmol) was added, cooled to -78 °C and the mixture was stirred for 15 minutes. Hand pulverized CsOH•H₂O was added (18.1 g, 72.0 mmol), the reaction was cooled in a dewar to -60 °C using a cold finger and stirred for 3 d. The reaction was diluted with Et₂O, the organic layer was washed with water, dried (Na₂SO₄), and concentrated to an oil. The crude oil was purified by flash chromatography (Al₂O₃, 5-50% diethyl ether in hexanes) to afford the Schiff base as a white solid (28.9 g, 88% yield). HPLC (Chiralcel AD, 2% *i*-PrOH/Hexanes, 1 mL/min) t_R (*R*) = 7.3 m, t_R (*S*) = 8.5 m. (*S*) = 88% ee.¹

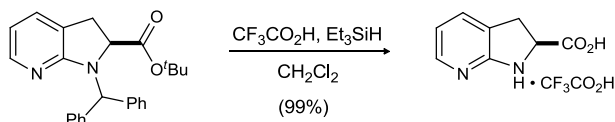


tert-Butyl-1-benzhydryl-2,3-dihydro-1H-pyrrolo[2,3-*b*]pyridine-2-carboxylate (19a and 19b).

A flame dried 5 L round bottom flask was charged with benzene (4.1 L). The solution was degassed by freeze-pump-thaw cycles, and then Schiff base (19.0 g, 40.9 mmol). The solution was warmed to 80 °C and a benzene solution (25 mL) of $n\text{Bu}_3\text{SnH}$ (11.6 mL, 43.8 mmol) and AIBN (2.87 g, 17.5 mmol) was added over 4 h. The reaction was then allowed to stir at 82 °C for 12 h. The reaction was cooled to rt, and toluene was removed by vacuum. The oily residue was diluted with Et₂O (100 mL) and a saturated KF solution

(ca 20 equiv) was added. The mixture was stirred for 3 hours, during which a precipitate formed at the interface. The organic layer was separated, dried, and concentrated to an oil. The crude mixture was purified via flash chromatography (SiO₂, 0-40% ethyl acetate in hexanes) and subsequent trituration with hexanes afforded the indoline as a white solid (8.70 g, 55%). HPLC (Chiralcel AD, 10% *i*-PrOH-Hexanes, 1 mL/min) t_R (*S*) = 5.9 min, t_R (*R*) = 11.8 min (*S*) = >99% ee. Analytical data was identical to that in the literature.

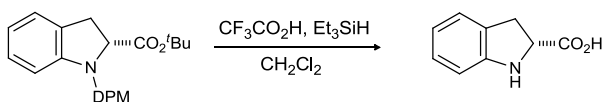
When the enantiomeric Schiff base was substituted into the procedure above, (*R*)-indoline (**19b**) was isolated as a white solid (9.9 g, >99% ee, 48% yield).



2-Carboxy-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine-1-ium-2,2,2-trifluoroacetate (**20a** and **20b**).

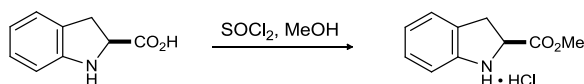
Protected (*S*)-azaindoline (5.52 g, 14.3 mmol) was treated with trifluoroacetic acid (14.5 mL, 186 mmol) and triethylsilane (2.95 mL, 35.8 mmol) in CH₂Cl₂ (29.0 mL). The reaction was stirred overnight and then concentrated under vacuum. Et₂O (20.0 mL) was added to the oily residue to precipitate a white solid that was filtered, trituated with Et₂O and dried to afford the product as the trifluoroacetate salt (3.90 g, 99% yield). Analytical data was identical to that in the literature.

Substitution of (*R*)-azaindoline (**19b**, 1.75 g, 4.54 mmol) into the procedure above provided **20b** as a white solid (5.81 g, 98%).



(R)-2,3-Dihydro-1H-indole-2-carboxylic acid (21b).

To a solution of trifluoroacetic acid (1.25 mL, 16.2 mmol) and triethylsilane (0.26 mL, 3.12 mmol) in CH₂Cl₂ (2.5 mL) was added the indoline (0.48 g, 1.25 mmol). The reaction was stirred for 8 h at rt and solvent was removed in vacuo. Et₂O (5 mL) was added to the oily residue to precipitate a white solid that was filtered, triturated with Et₂O, and dried to afford the product as a white solid. (134 mg, 66%).⁴



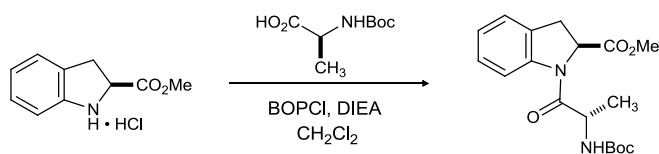
Methyl indoline-2-carboxylate hydrochloride (22a and 22b).

To a 0 °C solution of the amino acid (1.01 g, 6.13 mmol) in methanol (10.2 mL) was added thionyl chloride (670 μL, 9.19 mmol) over 5 minutes. The solution was slowly warmed to room temperature and stirred for 4 h. The solvent was removed *in vacuo* and the residue obtained was treated with diethyl ether. The resulting oil was dried under vacuum for 24 h to afford the title compound as a brown viscous oil (1.29 g, 100%). *R_f* = 0.43 (50% EtOAc/hexanes); [α]_D²⁴ -15.7 (*c* 3.05, CHCl₃); IR (film) 3388, 2468, 1747, 1486, 1440, 1033 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 9.23 (s, 2H), 7.16 (d, *J* = 7.0 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.84 (m, 2H), 4.60 (dd, *J* = 10.0, 6.5 Hz, 1H), 3.71 (s, 3H) 3.38 (dd, *J* = 16.0, 10.0 Hz, 1H), 3.18 (dd, *J* = 16.0, 6.5 Hz, 1H); ¹³C NMR (125 MHz, DMSO-d₆) ppm 172.7, 146.5, 129.1, 128.0, 125.0, 121.7, 112.5, 59.4, 52.7, 33.3; HRMS (EI): Exact mass calcd for C₁₀H₁₁NO₂ [M-HCl]⁺ 177.0790, found 177.0789.

Substitution of (*R*)-indoline amino acid (500 mg, 3.06 mmol) into the above procedure furnished the enantiomeric product (620 mg, 100%). *R_f* = 0.43 (50%

⁴ Commercially available

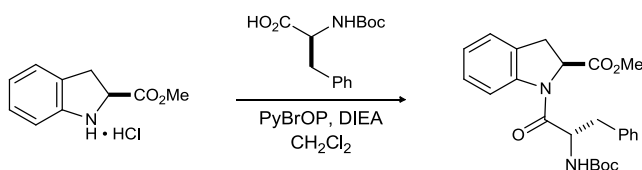
EtOAc/hexanes); $[\alpha]_D^{24} +14.8$ (c 1.6, CHCl_3); IR (film) 3390, 2474, 1748, 1440, 1248 cm^{-1} ; ^1H NMR (400 MHz, MeOD-d_4) δ 7.55-7.44 (m, 4H), 5.16-5.11(m, 2H), 5.08 (dd, $J = 9.6, 7.2$ Hz, 1H), 3.90 (s, 3H) 3.72 (dd, $J = 16.4, 9.6$ Hz, 1H), 3.53 (dd, $J = 16.4, 7.2$ Hz, 1H); ^{13}C NMR (100 MHz, MeOD-d_4) ppm 169.8, 136.7, 134.9, 131.3, 130.0, 127.3, 120.4, 61.2, 54.2, 33.9; HRMS (EI): Exact mass calcd for $\text{C}_{10}\text{H}_{12}\text{ClNO}_2$ $[\text{M-HCl}]^+$ 177.0790, found 177.0798.



(S)-Methyl-1-((S)-2-(tert-butoxycarbonylamino)propanoyl)indoline-2-carboxylate (23a).

To a 0 °C solution of the carboxylic acid (22.0 mg, 117 μmol), the methyl ester (25.0 mg, 117 μmol) and diisopropyl ethylamine (80.0 μL , 469 μmol) in CH_2Cl_2 (1 mL) was added BOP-Cl (213 μL , 1.64 mmol). The reaction was slowly warmed to rt and stirred for 12 h. The reaction was diluted with CH_2Cl_2 and washed with water, 1 N HCl, and brine. The organic layer was dried, filtered, and concentrated to a brown oil. Column chromatography (SiO_2 , 0-10-20% ethyl acetate in hexanes) afforded the desired dipeptide as a 1:1 mixture of *cis-trans* rotamers (14 mg, 35%). $R_f = 0.19$ (20% EtOAc/hexanes); $[\alpha]_D^{24} -133.8$ (c 1.80, CHCl_3); IR (film) 3330, 2979, 1742, 1665, 1511, 1478 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.24 (d, $J = 8.0$ Hz, 1H), 7.26-7.12 (m, 5H), 7.09-7.05 (m, 2H), 5.46-5.43 (m, 2H), 5.25 (dd, $J = 11.2, 3.5$ Hz, 1H), 5.04 (t, $J = 7.1$ Hz, 1H), 4.95 (d, $J = 10.3$ Hz, 1H), 4.45 (t, $J = 7.0$ Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.61 (dd, $J = 16.8, 10.7$ Hz, 1H), 3.49 (dd, $J = 16.5, 11.1$ Hz, 1H), 3.34 (d, $J = 16.6$ Hz, 1H), 3.12 (dd, $J =$

16.5, 3.3 Hz, 1H), 1.54 (d, $J = 7.0$ Hz, 3H), 1.44 (s, 18H), 1.39 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) ppm 171.9, 171.6, 155.3, 154.9, 142.5, 140.1, 131.2, 128.8, 128.4, 128.2, 126.0, 124.8, 124.6, 124.2, 117.7, 114.3, 79.9, 79.8, 60.5, 60.4, 53.4, 52.7, 48.8, 48.5, 33.7, 31.4, 28.5, 20.0, 18.9; HRMS (ESI): Exact mass calcd for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_5$ $[\text{M}]^+$ 349.1758, found 349.1763.

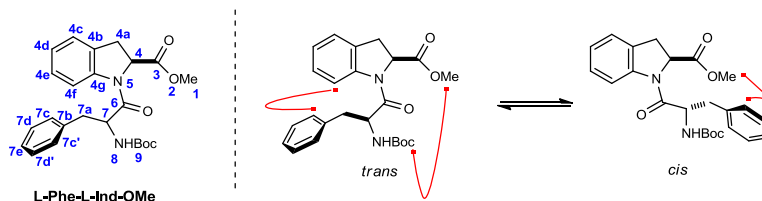


(S)-Methyl-1-(S)-((2-(tert-butoxycarbonylamino)-3-phenylpropanoyl)indoline-2-carboxylate (23b).

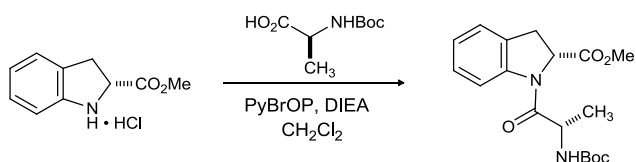
To a 0 °C solution of the carboxylic acid (560 mg, 2.10 mmol), the methyl ester (300 mg, 1.40 mmol), and diisopropyl ethylamine (910 μL , 5.18 mmol) in CH_2Cl_2 (3 mL) was added PyBrOP (980 mg, 2.10 mmol). The reaction was slowly warmed to room temperature and stirred for 2 days. The reaction was diluted with CH_2Cl_2 and washed with satd aq NH_4Cl , satd aq NaHCO_3 and brine. The organic layer was dried, filtered, and concentrated to a brown oil. Column chromatography (SiO_2 , 20% ethyl acetate in hexanes) afforded the dipeptide as a mixture of 5:1 *cis/trans* rotamers (480 mg, 81%). $R_f = 0.23$ (20% EtOAc/hexanes); $[\alpha]_D^{24} -25.5$ (c 1.30, CHCl_3); IR (film) 3345, 2975, 2929, 1742, 1710, 1658, 1481, 1169 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3 , *cis*- rotamer) δ 8.24 (d, $J = 8.4$ Hz, 1H), 7.32 (d, $J = 4.2$ Hz, 1H), 7.26-7.21 (m, 5H), 7.07-7.02 (m, 2H), 5.53 (d, $J = 8.4$ Hz, 1H), 4.59 (ddd, $J = 9.3, 9.3, 5.4$ Hz, 1H), 4.10 (dd, $J = 10.8, 1.8$ Hz, 1H), 3.67 (s, 3H), 3.12 (dd, $J = 13.2, 5.4$ Hz, 1H), 3.05-2.99 (m, 2H), 2.80 (dd, $J = 16.2, 10.8$ Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3 , *cis* and *trans*) ppm 171.1, 170.8, 154.7,

141.5, 136.2, 129.7, 129.4, 129.1, 128.7, 128.4, 128.3, 127.8, 127.1, 126.9, 125.9, 124.6, 124.3, 124.2, 117.6, 114.1 79.7, 60.5, 60.3, 54.6, 53.1, 52.5, 41.6, 38.2, 32.7, 31.3, 28.3, 28.2; HRMS (ESI): Exact mass calcd for C₂₄H₂₈N₂NaO₅ [M+Na]⁺ 447.1896, found 447.1897.

Conformational analysis of Boc-L-Phe-L-Ind-OMe



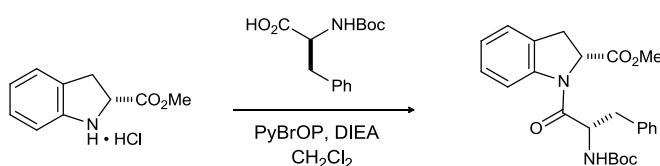
NOESY was performed to confirm the absolute conformation of *trans* and *cis* rotamers. H7c/H4a and H9/H1 correlations confirmed the presence of *trans* rotamer. In the *trans*-amide isomer, the 6-keto group lies close to the H4f resulting in the downfield shift (δ 8.24 ppm) of this aromatic hydrogen. A strong H7c/H1 correlation is consistent with the prolyl *cis*-amide bond.



(R)-Methyl 1-((S)-2-(tert-butoxycarbonylamino)propanoyl)indoline-2-carboxylate (23c).

To a 0 °C solution of the carboxylic acid (39.7 mg, 210 μ mol), the methyl ester (30.0 mg, 140 μ mol), and diisopropyl ethylamine (90.2 μ L, 518 μ mol) in CH₂Cl₂ (0.6 mL) was added PyBrOP (98.0 mg, 210 μ mol). The reaction was slowly warmed to room temperature and stirred for 2 days. The reaction was diluted with CH₂Cl₂ and washed

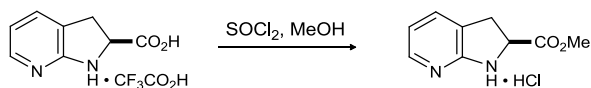
with satd aq NH₄Cl, satd aq NaHCO₃ and brine. The organic layer was dried, filtered, and concentrated to a brown oil. Column chromatography (SiO₂, 20% ethyl acetate in hexanes) afforded the dipeptide as a mixture of 4:1 *cis/trans* rotamers (36.7 mg, 75%). *R_f* = 0.20 (20% EtOAc/hexanes); [α]_D²⁴ +115.2 (*c* 0.61, CHCl₃); IR (film) 3330, 2978, 2933, 1747, 1701, 1659, 1482, 1249, 1168 cm⁻¹; ¹H NMR (600 MHz, CDCl₃, *cis*- rotamer) δ 8.19 (d, *J* = 7.8 Hz, 1H), 7.26-7.14 (m, 2H), 7.05 (t, *J* = 7.2 Hz, 1H), 5.66 (br d, *J* = 10.2 Hz, 1H), 5.15 (br d, *J* = 7.2 Hz, 1H), 4.40 (dt, *J* = 7.2, 7.2 Hz, 1H), 3.76 (s, 3H), 3.63 (dd, *J* = 15.6, 10.8 Hz, 1H), 3.32 (d, *J* = 16.2 Hz, 1H), 1.45-1.42 (m, 12H); ¹³C NMR (150 MHz, CDCl₃, *cis*- rotamer) ppm 172.2, 172.0, 155.3, 142.2, 129.5, 127.7, 124.5, 124.3, 117.8, 80.0, 61.0, 52.9, 48.1, 33.2, 28.3, 18.2; HRMS (ESI): Exact mass calcd for C₁₈H₂₅N₂O₅ [M+H]⁺ 349.1763, found 349.1764.



(R)-Methyl 1-((S)-2-(tert-butoxycarbonylamino)-3-phenylpropanoyl)indoline-2-carboxylate (23d).

To a 0 °C solution of the carboxylic acid (560 mg, 2.10 mmol), the methyl ester (300 mg, 1.40 mmol), and diisopropyl ethylamine (910 μ L, 5.18 mmol) in CH₂Cl₂ (3 mL) was added PyBrOP (980 mg, 2.10 mmol). The reaction was slowly warmed to room temperature and stirred for 2 days. The reaction was diluted with CH₂Cl₂ and washed with satd aq NH₄Cl, satd aq NaHCO₃ and brine. The organic layer was dried, filtered, and concentrated to a brown oil. Column chromatography (SiO₂, 20% ethyl acetate in hexanes) afforded the dipeptide as a mixture of 2.5:1 *cis/trans* rotamers (480 mg, 81%).

$R_f = 0.23$ (20% EtOAC/hexanes); $[\alpha]_D^{24} +62.5$ (c 0.80, CHCl_3); IR (film) 3314, 2977, 2967, 1746, 1702, 1655, 1482, 1250, 1169 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 8.21 (d, $J = 8.4$ Hz, 1H), 7.48 (d, $J = 8.8$ Hz, 1H), 7.40-7.01 (m, 18 H), 5.66 (d, $J = 10.8$ Hz, 1H), 5.50 (br s, 1H), 5.01 (br d, $J = 9.0$ Hz, 1H), 4.93 (br d, $J = 10.2$ Hz, 1H), 4.60 (ddd, $J = 9.6, 9.6, 4.2$ Hz, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 3.62 (dd, $J = 16.8, 10.8$ Hz, 1H), 3.33 (br d, $J = 16.2$ Hz, 1H), 3.24 (dd, $J = 14.4, 4.2$ Hz, 1H), 3.13 (dd, $J = 15.6, 10.8$ Hz, 1H), 2.99-2.92 (m, 3H), 1.45 (s, 9H), 1.32 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3 , *cis* and *trans*) ppm 172.0, 171.4, 171.2, 170.2, 155.4, 155.1, 142.2, 140.0, 137.0, 135.7, 129.6, 129.3, 129.2, 128.4, 128.1, 127.8, 126.7 (2C), 125.5, 124.9, 124.6, 124.4, 124.2, 80.0, 79.9, 61.1, 60.5, 53.8, 53.1, 52.9, 52.5, 39.7, 38.2, 33.2, 31.5, 28.3, 28.2; HRMS (ESI): Exact mass calcd for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ 425.2076, found 425.2067.

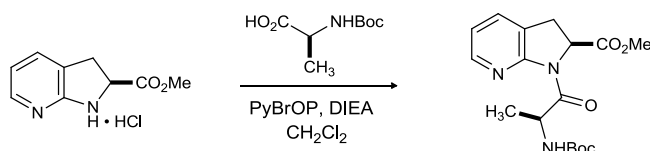


Methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-2-carboxylate hydrochloride (24a and 24b).

To a solution of the amine salt (100 mg, 360 μmol) in methanol (0.6 mL) at 0 $^\circ\text{C}$ was added thionyl chloride (40.1 μL , 546 μmol) over 2 minutes. The solution was slowly warmed to room temperature and stirred for 4 h. The solvent was removed *in vacuo* and the residue obtained was treated with diethyl ether. The resulting oil was dried under vacuum for 24 h to afford the title compound as a brown viscous oil (76 mg, 99%). $R_f = 0.47$ (10% $\text{MeOH}/\text{CH}_2\text{Cl}_2$); $[\alpha]_D^{24} -13.5$ (c 1.55, CHCl_3); IR (film) 3281, 3083, 2948, 2868, 1736, 1647, 1548, 1200, 1021 cm^{-1} ; ^1H NMR (500 MHz, MeOD) δ 7.23 (d, $J = 7.0$

Hz, 1H), 7.64 (d, $J = 6.5$ Hz, 1H), 6.85 (t, $J = 7.0$ Hz, 2H), 4.82 (dd, $J = 11.0, 5.0$ Hz, 1H), 3.83 (s, 2H), 3.62 (dd, $J = 18.0, 11.0$ Hz, 1H), 3.41 (dd, $J = 18.0, 5.0$ Hz, 1H), 3.33 (s, 3H); ^{13}C NMR (125 MHz, MeOD) ppm 169.7, 154.8, 135.1, 129.9, 127.1, 111.6, 57.1, 50.6, 28.8, 33.3; HRMS (EI): Exact mass calcd for $\text{C}_9\text{H}_{11}\text{N}_2\text{O}_2$ $[\text{M}-\text{Cl}]^+$ 179.0821, found 179.0820.

Substitution of **20b** (500 mg) into the above procedure furnished the enantiomeric product as a colorless oil (391 mg, 100%); $[\alpha]_D^{24} +7.9$ (c 1.9, CHCl_3).⁵

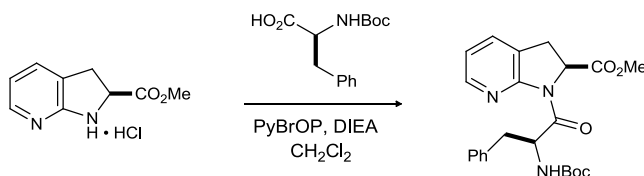


(S)-Methyl-1-((S)-2-(tert-butoxycarbonylamino)propanoyl)-2,3-dihydro-1H-pyrrolo[2,3-*b*]pyridine-2-carboxylate (25a).

To a 0 °C solution of the carboxylic acid (530 mg, 2.80 mmol), the methyl ester (400 mg, 1.87 mmol), and diisopropyl ethylamine (1.22 mL, 6.91 mmol) in CH_2Cl_2 (3 mL) was added PyBrOP (1.31 g, 2.80 mmol). The reaction was slowly warmed to room temperature and stirred for 2 days. The reaction was diluted with CH_2Cl_2 and washed with satd aq NH_4Cl , satd aq NaHCO_3 and brine. The organic layer was dried, filtered, and concentrated to a brown oil. Column chromatography (SiO_2 , 30% ethyl acetate in hexanes) afforded the dipeptide as $\geq 99\%$ *trans*-rotamer (470 mg, 71%). $R_f = 0.37$ (50% EtOAc/hexanes); $[\alpha]_D^{24} -26.7$ (c 2.25, CHCl_3); IR (film) 3395, 2921, 1654, 1422 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 8.18 (d, $J = 4.9$ Hz, 1H), 7.44 (d, $J = 7.2$ Hz, 1H), 6.91 (t, $J =$

⁵ The difference in the optical rotation values might have been caused by the residual thionyl chloride from the reaction.

12.5, 5.5 Hz, 1H), 6.00-5.93 (m, 1H), 5.33 (d, $J = 8.0$ Hz, 1H), 5.13 (dd, $J = 10.4, 4.3$ Hz, 1H), 3.75 (s, 3H), 3.46 (dd, $J = 16.8, 11.5$ Hz, 1H), 3.07 (dd, $J = 17.0, 3.9$ Hz, 1H), 1.47 (d, $J = 6.9$ Hz, 3H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) ppm 173.6, 171.5, 155.6, 154.9, 147.3, 133.6, 123.2, 118.7, 79.6, 57.9, 52.7, 49.4, 29.3, 28.5, 18.9; HRMS (ESI): Exact mass calcd for $\text{C}_{17}\text{H}_{23}\text{N}_3\text{NaO}_5$ $[\text{M}+\text{Na}]^+$ 372.1535, found 372.1535.

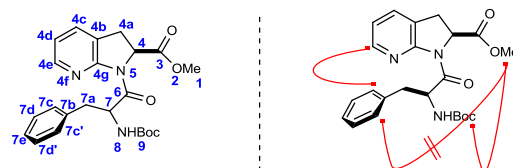


(S)-Methyl-1-(S)-((2-(*tert*-butoxycarbonylamino)-3-phenylpropanoyl)-2,3-dihydro-1H-pyrrolo[2,3-*b*]pyridine-2-carboxylate (25b).

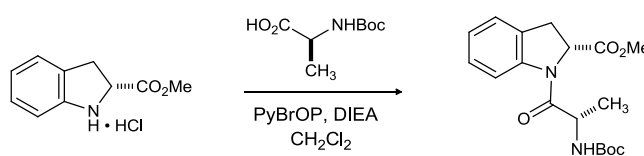
To a 0 °C solution of the carboxylic acid (480 mg, 1.82 mmol), the methyl ester (260 mg, 1.21 mmol), and diisopropyl ethylamine (780 μL , 4.48 mmol) in CH_2Cl_2 (2.5 mL) was added PyBrOP (850 mg, 1.82 mmol). The reaction was slowly warmed to room temperature and stirred for 2 days. The reaction was diluted with CH_2Cl_2 and washed with satd aq NH_4Cl , satd aq NaHCO_3 and brine. The organic layer was dried, filtered, and concentrated to a brown oil. Column chromatography (SiO_2 , 30% ethyl acetate in hexanes) afforded the title product as $\geq 99\%$ *trans*-rotamer (430 mg, 84%). $R_f = 0.45$ (50% EtOAc/hexanes); $[\alpha]_D^{24} -19.1$ (c 1.10, CHCl_3); IR (film) 3332, 2975, 1750, 1712, 1663, 1595, 1425, 1170 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.27 (d, $J = 4.5$ Hz, 1H), 7.46 (d, $J = 7.0$ Hz, 1H), 7.41 (d, $J = 7.5$ Hz, 2H), 7.31 (t, $J = 7.5$ Hz, 2H), 7.22 (t, $J = 7.5$ Hz, 1H), 6.96 (m, 1H), 6.24 (dt, $J = 10.0, 3.5$ Hz, 1H), 5.16 (m, 2H), 3.77 (s, 3H), 3.49 (m, 2H), 3.11 (dd, $J = 17.0, 3.5$ Hz, 1H), 2.75 (dd, $J = 14.0, 10.0$ Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) ppm 172.2, 171.3, 155.5, 154.8, 147.0, 137.2, 133.5,

129.6, 128.1, 126.4, 123.2, 118.7, 79.3, 57.8, 54.2, 52.6, 38.1, 29.2, 28.2; HRMS (ESI):
 Exact mass calcd for C₂₃H₂₇N₃NaO₅ [M+Na]⁺ 448.1848, found 448.1838.

Conformational analysis of Boc-L-Phe-L-N⁷Ind-OMe



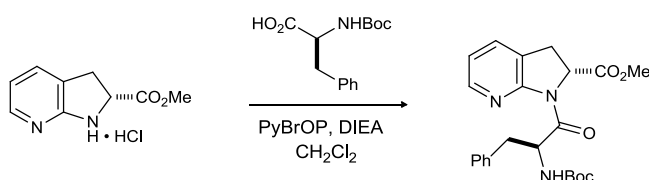
A NOESY correlation for H4e/H7c and H9/H1 is consistent with the prolyl *trans*-amide bond. No H7c'/H1 correlation was observed, supporting the assignment exclusively as *trans*-amide rotamer.



(R)-Methyl-1-((S)-2-(tert-butoxycarbonylamino)propanoyl)-2,3-dihydro-1H-pyrrolo[2,3-*b*]pyridine-2-carboxylate (25c).

To a 0 °C solution of the carboxylic acid (530 mg, 2.80 mmol), the methyl ester (400 mg, 1.87 mmol) and diisopropyl ethylamine (1.22 mL, 6.91 mmol) in CH₂Cl₂ (3.6 mL) was added PyBrOP (1.31 g, 2.80 mmol). The reaction was slowly warmed to room temperature and stirred for 2 days. The reaction was diluted with CH₂Cl₂ and washed with satd aq NH₄Cl, satd aq NaHCO₃ and brine. The organic layer was dried, filtered, and concentrated to a brown oil. Column chromatography (SiO₂, 20% ethyl acetate in hexanes) afforded the title product as ≥99% *trans*-rotamer (430 mg, 70%). R_f = 0.38 (50% EtOAc/hexanes); [α]_D²⁴ +56.7 (c 1.85, CHCl₃); IR (film) 3357, 2977, 1750, 1712,

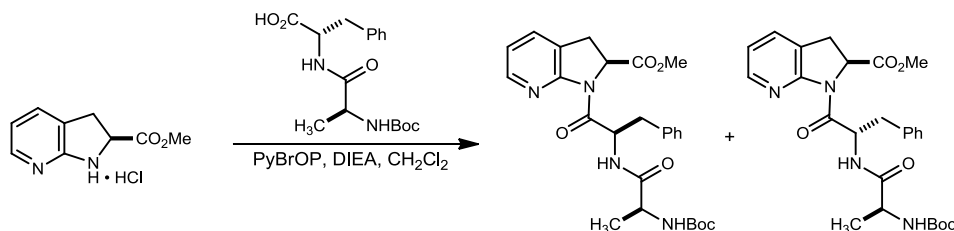
1426, 1301, 1024 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.12 (d, $J = 4.4$ Hz, 1H), 7.42 (d, $J = 7.2$ Hz, 1H), 6.87 (m, 1H), 6.03 (s, 1H), 5.55 (d, $J = 7.6$ Hz, 1H), 4.94 (dd, $J = 11.2, 3.6$ Hz, 1H), 3.67 (s, 3H), 3.39 (dd, $J = 16.8, 11.2$ Hz, 1H), 3.02 (dd, $J = 17.2, 3.2$ Hz, 1H), 1.45 (s, 9H), 1.30 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) ppm 172.9, 171.1, 154.8, 154.4, 147.0, 133.5, 123.1, 118.6, 79.1, 58.3, 52.4, 49.4, 29.5, 29.1, 28.3, 19.3. HRMS (ESI): Exact mass calcd for $\text{C}_{17}\text{H}_{23}\text{N}_3\text{NaO}_5$ $[\text{M}+\text{Na}]^+$ 372.1535, found 372.1530.



(R)-Methyl-1-(S)-((2-(tert-butoxycarbonylamino)-3-phenylpropanoyl)-2,3-dihydro-1H-pyrrolo[2,3-b] pyridine-2-carboxylate (25d).

To a 0 °C solution of the carboxylic acid (810 mg, 3.03 mmol), the methyl ester (430 mg, 2.02 mmol) and diisopropyl ethylamine (1.32 mL, 7.48 mmol) in CH_2Cl_2 (4.0 mL) was added PyBrOP (1.41 g, 3.03 mmol). The reaction was slowly warmed to room temperature and stirred for 2 days. The reaction was diluted with CH_2Cl_2 and washed with satd aq NH_4Cl , satd aq NaHCO_3 and brine. The organic layer was dried, filtered, and concentrated to a brown oil. Column chromatography (SiO_2 , 20% ethyl acetate in hexanes) afforded the title product as $\geq 99\%$ *trans*-rotamer (690 mg, 81%). $R_f = 0.42$ (50% EtOAc/hexanes); $[\alpha]_D^{24} +68.5$ (c 3.65, CHCl_3); IR (film) 3331, 2977, 1748, 1713, 1666, 1204 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.25 (d, $J = 5.2$ Hz, 1H), 7.43 (d, $J = 7.2$ Hz, 1H), 7.41-7.22 (m, 5H), 6.94 (m, 1H), 6.49 (d, $J = 5.6$ Hz, 1H), 5.41 (d, $J = 8.4$ Hz, 1H), 4.94 (dd, $J = 11.2, 3.6$ Hz, 1H), 3.78 (s, 3H), 3.37 (dd, $J = 17.2, 11.2$ Hz, 1H), 3.14 (dd, $J = 12.8, 5.2$ Hz, 1H), 3.05 (dd, $J = 17.2, 3.6$ Hz, 1H), 2.87 (dd, $J = 13.6, 8.0$ Hz,

1H), 1.38 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) ppm 171.5, 171.0, 154.8, 154.5, 146.9, 136.6, 133.5, 129.5, 127.9, 126.5, 123.2, 118.7, 79.1, 58.3, 54.0, 52.5, 39.9, 29.2, 28.2; HRMS (ESI): Exact mass calcd for C₂₃H₂₇N₃NaO₅ [M+Na]⁺ 448.1848, found 448.1852.



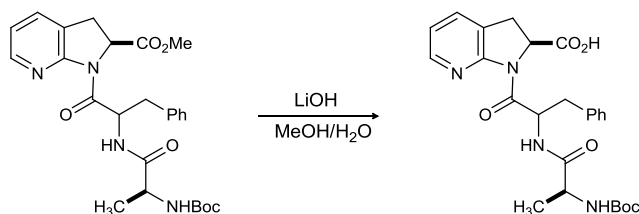
Methyl-1-(2-((S)-2-(tert-butoxycarbonylamino)propanamido)-3-phenylpropanoyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (28aa, and 28ab).

To a 0 °C solution of the amine salt (750 mg, 3.50 mmol) and the carboxylic acid (1.77 g, 5.25 mmol) in CH₂Cl₂ (8 mL) was added diisopropylethylamine (2.26 mL, 12.96 mmol) and PyBrOP (2.45 g, 5.26 mmol). The reaction was slowly warmed to the room temperature and stirred for 2 days. The reaction was diluted with CH₂Cl₂ and washed with satd aq NH₄Cl, satd aq NaHCO₃, and brine. The organic layer was dried, filtered, and concentrated to a brown oil. Column chromatography (SiO₂, 0-20-40% ethyl acetate in hexanes) afforded the tetrapeptide as an inseparable mixture of diastereomers (1.22 g, 70%), which was characterized as a 3:1 ratio of diastereomers. *R_f* = 0.66 (10% MeOH/CH₂Cl₂); IR (film) 3330, 3063, 2101, 2933, 1660, 1167, 1120 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.26 (d, *J* = 5.0 Hz, 1H), 8.24 (d, *J* = 5.0 Hz, 1H), 7.46 (d, *J* = 7.0 Hz, 1H), 7.42 (d, *J* = 7.0 Hz, 1H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.26 (d, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 5.2 Hz, 1H), 7.19 (d, *J* = 5.6 Hz, 1H), 7.16-7.08 (m, 6H), 6.96-6.91 (m, 2H), 6.86 (s, 1H), 6.67 (d, *J* = 6.0 Hz, 1H), 6.55 (d, *J* = 6.0 Hz, 1H), 6.45 (m, 1H), 5.11 (dd, *J* = 11.5, 4.0 Hz, 1H), 5.03 (s, 1H), 4.89 (dd, *J* = 11.5, 4.2 Hz, 1H), 4.81 (s, 1H), 4.15-4.04 (m,

2H), 3.75 (s, 3H), 3.68 (s, 3H), 3.52-3.45 (m, 2H), 3.34 (dd, $J = 16.5, 11.0$ Hz, 1H), 3.15 (dd, $J = 13.5, 5.5$ Hz, 1H), 3.09 (dd, $J = 17.0, 4.0$ Hz, 1H), 3.02 (dd, $J = 17.0, 3.5$ Hz, 1H), 2.93 (dd, $J = 13.5, 7.0$ Hz, 1H), 2.85 (dd, $J = 14.0, 9.0$ Hz, 1H), 1.40 (s, 9H), 1.39 (s, 9H), 1.23 (d, $J = 7.0$ Hz, 3H), 1.13 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) ppm 172.0, 170.9, 170.8, 170.7, 154.9, 154.8, 154.2, 154.0, 146.4, 146.3, 136.6, 136.1, 133.5 (2C), 129.3, 129.0, 127.7, 127.6, 126.2, 126.1, 123.1, 123.0, 118.7, 118.5, 79.0, 64.2, 60.0, 58.0, 57.5, 52.9, 52.6, 52.1 (2C), 49.6, 37.7, 37.3, 33.1, 28.7, 27.9, 20.1, 18.6, 18.3, 14.1, 13.8; HRMS (EI): Exact mass calcd for $\text{C}_{26}\text{H}_{33}\text{N}_4\text{O}_6$ $[\text{M}+\text{H}]^+$ 497.2400, found 497.2400.

Substitution of **24b** (0.89 mg, 4.16 mmol) into the above procedure afforded the product as an inseparable mixture of diastereomers (**28ba**, and **28bb**, 1.41 g, 69%), which was characterized as a 10:9 ratio of diastereomers. $R_f = 0.64$ (10% MeOH/ CH_2Cl_2); IR (film) 3300, 2977, 2931, 1745, 1710, 1650, 1482, 1169 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.31 (d, $J = 4.8$ Hz, 1H), 8.26 (d, $J = 4.8$ Hz, 1H), 7.49 (d, $J = 7.6$ Hz, 1H), 7.43 (d, $J = 7.6$ Hz, 1H), 7.36 (d, $J = 7.2$ Hz, 2H), 7.30-7.26 (m, 2H), 7.23-7.11 (m, 6H), 6.98 (dd, $J = 7.6, 5.2$ Hz, 1H), 6.94 (dd, $J = 7.6, 5.2$ Hz, 1H), 6.85 (s, 1H), 6.66 (br s, 2H), 6.48 (m, 1H), 5.14 (dd, $J = 11.2, 4.4$ Hz, 1H), 4.99 (br s, 2H), 4.92 (dd, $J = 11.2, 4.4$ Hz, 1H), 4.14-4.06 (m, 2H), 3.77 (s, 3H), 3.70 (s, 3H), 3.56-3.46 (m, 2H), 3.35 (dd, $J = 17.2, 11.2$ Hz, 1H), 3.18 (dd, $J = 13.2, 5.6$ Hz, 1H), 3.11 (dd, $J = 11.2, 4.0$ Hz, 1H), 3.03 (dd, $J = 17.2, 4.0$ Hz, 1H), 2.97 (dd, $J = 13.6, 7.2$ Hz, 1H), 2.85 (dd, $J = 14.0, 9.2$ Hz, 1H), 1.43 (s, 9H), 1.39 (s, 9H), 1.26 (d, $J = 7.2$ Hz, 3H), 1.14 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) ppm 172.2, 171.7, 171.4, 171.2, 171.0, 170.6, 155.2, 154.6, 154.4, 147.1, 147.1, 147.0, 136.8, 136.3, 133.7, 133.6, 129.6, 129.5, 128.2, 128.0,

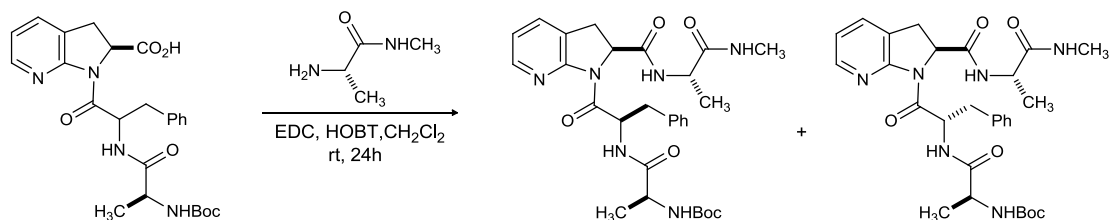
126.7, 123.3, 123.2, 118.9, 79.7, 60.3, 58.4, 57.9, 53.4, 53.1, 52.8, 52.6 (2C), 50.1, 49.9, 38.5, 37.8, 29.3 (2C), 28.3, 21.0, 18.8, 18.7, 14.2; HRMS (EI): Exact mass calcd for $C_{26}H_{33}N_4O_6$ $[M+H]^+$ 497.2400, found 497.2411.



1-(2-((S)-2-(tert-butoxycarbonylamino)propanamido)-3-phenylpropanoyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (31aa and 31ab).

To a solution of the methyl ester (760 mg, 1.53 mmol) in MeOH-H₂O (30 mL, 4:1) was added an aqueous solution (2.0 mL) of LiOH (66.0 mg, 2.75 mmol) and the reaction was stirred for 2 h at rt. The solvent was removed *in vacuo* and the resulting residue acidified to pH = 2 with 1M HCl. The acidic solution was extracted with CH₂Cl₂ and the combined organic layers were washed with brine, dried, and filtered. The filtrate was evaporated to afford the desired product as a white solid (628 mg, 85%); IR (film) 3360, 3314, 2936, 2852, 1652, 1428 cm⁻¹; ¹H NMR experiment analysis revealed poorly resolved, broad peaks.

Substitution of **28ba** and **28bb** (1.41 g, 2.83 mmol) into the above procedure afforded the product as a white solid (**31ba** and **31bb**, 1.12 g, 83%). ¹H NMR experiment analysis revealed in poorly resolved, broad peaks. HRMS (EI): Exact mass calcd for $C_{25}H_{31}N_4O_6$ $[M+H]^+$ 483.2244, found 483.2243.

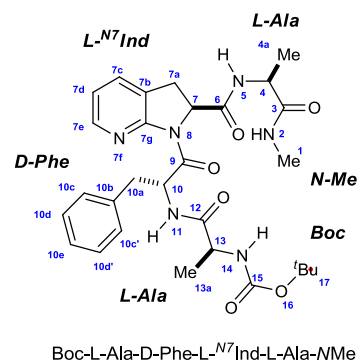


***tert*-Butyl(2*S*)-1-(1-(2-(*S*)-1-(methylamino)-1-oxopropan-2-ylcarbamoyl)-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine-1-yl)-1-oxo-3-phenylpropan-2-ylamino)-1-oxopropan-2-ylcarbamate (33aa and 33ab).**

To a solution of the carboxylic acid (630 mg, 1.30 mmol), EDC (240 mg, 1.56 mmol) and HOBT (210 mg, 1.56 mmol) in CH₂Cl₂ (10 mL) was added the amine (130 mg, 1.30 mmol). The reaction was stirred for 24 h at rt and quenched with satd aq NaHCO₃. The mixture was extracted with CH₂Cl₂ and washed with satd aq NH₄Cl, satd aq NaHCO₃ and brine. The organic layers were combined, dried, filtered, and concentrated to a brown oil. Column chromatography (SiO₂, 1-3-5% MeOH in CH₂Cl₂) afforded the diastereomers as colorless oils (480 mg, 66%).

More polar diastereomer 33aa

(160 mg, 22%). $R_f = 0.36$ (10% MeOH/CH₂Cl₂); $[\alpha]_D^{24} -7.8$ (c 1.90, CHCl₃); IR (film) 3411 (br), 1662, 1428, 1026 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.28 (d, $J = 4.5$ Hz, 1H, 7e), 7.51 (d, $J = 7.5$ Hz, 1H, 7c), 7.38 (s, 1H, 5), 7.33-7.24 (m, 5H, 10c, 10c', 10d, 10d', 11), 7.17 (t, $J = 7.5$ Hz, 1H, 10e), 7.00 (dd, $J = 7.5, 4.5$ Hz, 1H, 7d), 6.51 (br s, 1H, 10), 6.32 (d, $J = 4.0$ Hz, 1H, 2), 5.10 (br s, 1H, 14), 5.01 (dd, $J =$

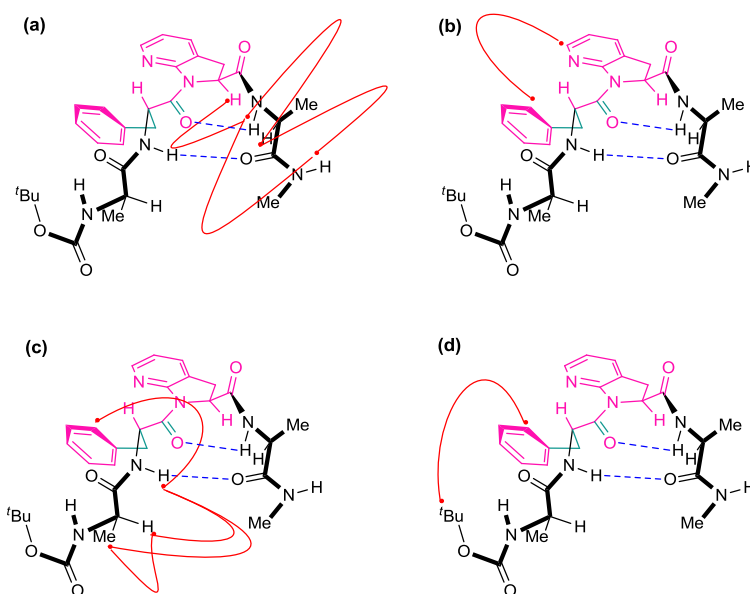


10.5, 3.0 Hz, 1H, 7), 4.43 (dq, $J = 7.5, 7.5$ Hz, 1H, 4), 4.28 (br s, 1H, 13), 3.44-3.34 (m, 2H, 7a, 10a), 3.22 (dd, $J = 17.0, 3.0$ Hz, 1H, 7a), 2.93 (dd, $J = 12.5, 8.5$ Hz, 1H, 10a), 2.76 (d, $J = 4.5$ Hz, 3H, 1), 1.42 (s, 9H, 17), 1.27 (d, $J = 7.0$ Hz, 3H, 4a), 1.22 (d, $J = 7.0$ Hz, 3H, 13a); ^{13}C NMR (125 MHz, CDCl_3) ppm 172.4, 172.2, 172.1, 170.4, 154.7, 146.8, 136.6, 133.8, 129.7, 128.3, 126.7, 124.4, 119.3, 79.9, 59.1, 52.5, 49.8, 49.0, 38.1, 29.2, 28.3, 26.3, 19.3, 17.7; HRMS (ESI): Exact mass calcd for $\text{C}_{29}\text{H}_{38}\text{N}_6\text{NaO}_6$ $[\text{M}+\text{Na}]^+$ 589.2750, found 589.2747.

Conformational Analysis of Boc-L-Ala-D-Phe-L- N7 Ind-L-Ala-NMe (33aa)

The crosspeaks could be separated into three local regions and a long range correlation. Beginning from the C-terminal methyl amide, crosspeaks for H2/H4 and H2/H5 defined the *s-trans* conformation of the methyl amide. However a weaker NOESY correlation for H2/H4 suggests that the peptide chain C-terminal to N7 Ind does not fold back upon itself by 180° . A similar *s-trans* assignment for the alanine amide could be made by observation of a H5/H7 cross peak.

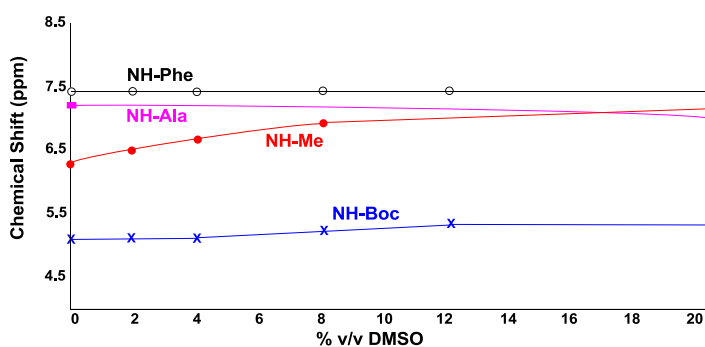
Observed Regional (a-c) and Long Range (d) NOESY Correlation (33aa)



The *s-trans* conformation of the azaindoline amide bond was determined by observation of crosspeaks between H10/H10c and H10c/H7e. Complementary to these are crosspeaks for H10/H11 and H11/H10c', although crosspeaks could not be observed to definitively assign the local conformation of the alanine amide bond as *trans*. Long range crosspeak H17/H10c is consistent with *syn* conformation of the *tert*-butyl group such that it is positioned at the exterior of the turn. Absence of crosspeak H10/H5 confirms the configuration of phenylalanine as (*R*). Absence of H17/H1, H17/H2, H13a/H2 or H13a/H1 crosspeaks are also indicative of the fact that the peptide chain does not fold back on itself by 180°.

Identification of Intramolecular Hydrogen Bonding in (33aa)

The experiment clearly showed the presence of three NH signals (NH11, NH5, NH14) that were affected minimally by the increasing addition of DMSO-*d*₆. This study indicated the presence of a hydrogen bond between NH11 and O3 to form an 11-membered ring and a hydrogen bond between NH5 and O9 to form a 7-



membered ring (δ -turn). In contrast, NH2 shifted appreciably with increasing amounts of DMSO-*d*₆ indicating that this hydrogen was solvent exposed and not involved in hydrogen bonding.

Less polar diastereomer: 33ab.

(320 mg, 44%). $R_f = 0.40$ (10% MeOH/CH₂Cl₂); $[\alpha]_D^{24} -45.4$ (c 1.85, CHCl₃); IR (film)

3327, 2957, 2921, 2846, 1653 cm⁻¹; ¹H NMR (500

MHz, CDCl₃) δ 8.24 (d, $J = 4.5$ Hz, 1H, 7e), 7.48 (d,

$J = 7.5$ Hz, 1H, 7c), 7.41 (d, $J = 8.0$ Hz, 1H, 5), 7.31-

7.18 (m, 6H, 10c, 10c', 10d, 10d', 10e, 11), 6.99 (dd,

$J = 7.5, 4.5$ Hz, 1H, 7d), 6.67 (br s, 1H, 2), 6.55 (br

s, 1H, 10), 5.11 (s, 1H, 14), 5.04 (dd, $J = 11.5, 5.0$

Hz, 1H, 7), 4.45 (dq, $J = 8.0, 8.0$ Hz, 1H, 4), 4.13 (t, $J = 8.0$ Hz, 1H, 13), 3.43 (dd, $J =$

17.5, 2.8 Hz, 1H, 7a), 3.22-3.18 (m, 2H, 7a, 10a), 2.86 (dd, $J = 13.5, 10.0$ Hz, 1H, 10a),

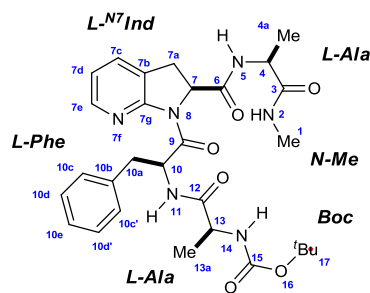
2.80 (d, $J = 4.5$ Hz, 3H, 1), 1.45 (s, 9H, 17), 1.39 (d, $J = 7.5$ Hz, 3H, 4a), 1.22 (d, $J = 7.0$

Hz, 3H, 13a); ¹³C NMR (125 MHz, CDCl₃) ppm 173.7, 173.3, 172.8, 170.6, 154.5,

146.6, 136.0, 134.0, 129.2, 128.5, 127.1, 124.1, 119.3, 80.4, 60.0, 53.9, 49.3 (2C), 36.4,

29.6, 28.4, 26.4, 16.7, 16.3; HRMS (EI): Exact mass calcd for C₂₉H₃₈N₆O₆ [M]⁺

566.2853, found 566.2853.



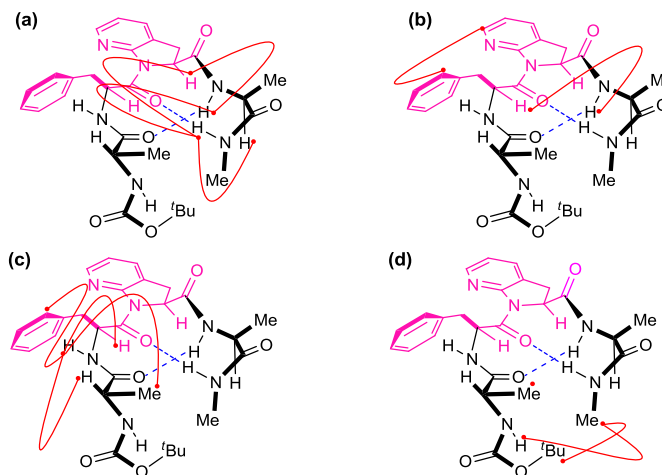
Boc-L-Ala-L-Phe-L-N⁷Ind-L-Ala-NMe

Conformational Analysis of Boc-L-Ala-L-Phe-L-N⁷Ind-L-Ala-NMe (33ab)

Assignment of both phenyl alanine configuration (as L-Phe) and tetrapeptide conformation was made using NOESY data and molecular models. The crosspeaks could again be separated into three local regions and long range correlations. Beginning from the C-terminal methyl amide, crosspeaks for H2/H4 and H2/H5 defined the *s-trans* conformation of the methyl amide. A long range weak correlation between H7/H2 suggests the folding of C-terminal peptide chain (L-Ala) such that a 10-membered hydrogen bond exists between H2/O9. A similar *s-trans* assignment for the alanine amide could be made by observation of an H5/H7 cross peak.

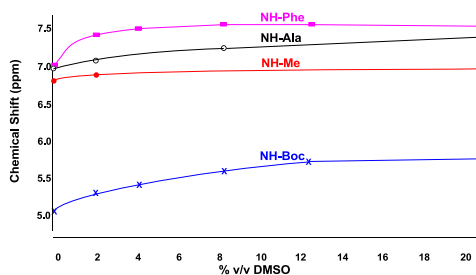
The *s-trans* conformation of the azaindoline amide bond was determined by observation of crosspeaks between H10/H10c and H10c/H7e. Complementary to these are crosspeaks for H10/H11 and H11/H10c', although crosspeaks could not be observed to definitively assign the local conformation of the alanine amide bond as *trans*. This assignment is supported, however, by a long range crosspeak H1/H13a for which such a geometry would be necessary. Additional long range crosspeaks H14/H1 and H1/H17 are consistent with *anti*-conformation of the *tert*-butyl group such that it is positioned at the interior of the turn. The presence of crosspeak H10/H5 confirms the configuration of phenylalanine as (*S*).

Observed Regional (a-c) and Long Range (d) NOESY Correlation (33ab)

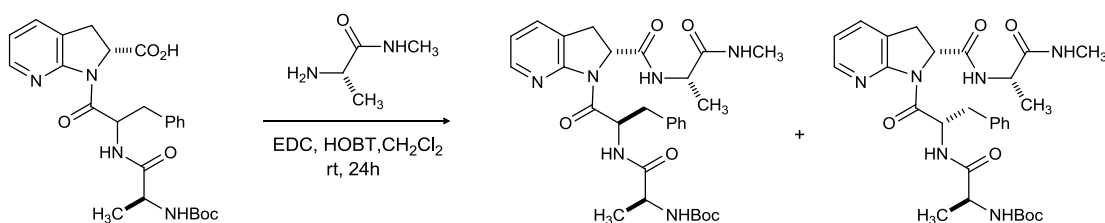


Identification of Intramolecular Hydrogen Bonding in (33ab)

The experiment suggested the presence of a hydrogen bond between NH5 and O12 to form a 10-membered ring (β -turn) and another hydrogen bond between NH2 and O9 to form a 10-



membered ring (β -turn). The experiment showed the presence of two NH signals (NH5 and NH2) that were affected minimally by the increasing addition of DMSO- d_6 . In contrast, NH11 and NH14 shifted appreciably with increasing amounts of DMSO- d_6 indicating that these hydrogens were solvent exposed, also consistent with the β -turn conformation.



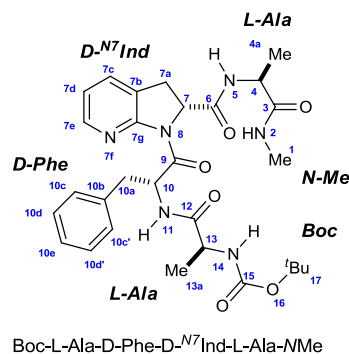
***tert*-Butyl(2*S*)-1-(1-(2-(*S*)-1-(methylamino)-1-oxopropan-2-ylcarbamoyl)-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine-1-yl)-1-oxo-3-phenylpropan-2-ylamino)-1-oxopropan-2-ylcarbamate (33ba and 33bb).**

To a solution of the carboxylic acid (1.12 g, 2.32 mmol), EDC (430 mg, 2.78 mmol) and HOBT (380 mg, 2.78 mmol) in CH_2Cl_2 (18 mL) was added the amine (240 mg, 2.33 mmol). The reaction was stirred for 24 h at rt and quenched with satd aq $NaHCO_3$. The mixture was extracted with CH_2Cl_2 and washed with satd aq NH_4Cl , satd aq $NaHCO_3$ and brine. The organic layers were combined, dried, filtered, and concentrated to a brown oil. Column chromatography (SiO_2 , 1-5% MeOH in CH_2Cl_2) afforded the individual diastereomers as colorless oils (751 mg, 57%).

More polar diastereomer: 33ba

(291 mg, 22%). $R_f = 0.36$ (10% MeOH/ CH_2Cl_2); $[\alpha]_D^{24} +37.6$ (c 1.25, $CHCl_3$); IR (film) 3341, 2963, 2952, 1641, 1115 cm^{-1} ; 1H NMR (600 MHz, $CDCl_3$) δ 8.24 (d, $J = 4.8$ Hz, 1H, 7e), 7.44 (d, $J = 6.6$ Hz, 1H, 7c), 7.25-7.22 (m, 4H, 10c, 10c', 10d, 10d'), 7.18 (t, $J =$

7.2 Hz, 1H, 10e), 7.11 (br s, 1H, 5), 6.97 (dd, $J = 7.2, 4.8$ Hz, 1H, 7d), 6.73 (br s, 1H, 11), 6.72 (br s, 1H, 2), 6.41 (d, $J = 4.8$ Hz, 1H, 10), 5.10 (d, $J = 6.6$ Hz, 1H, 14), 4.92 (dd, $J = 15.6, 8.4$ Hz, 1H, 7), 4.49 (dq, $J = 7.8, 7.8$ Hz, 1H, 4), 4.12 (br s, 1H, 13), 3.39 (dd, $J = 13.8, 4.2$ Hz, 1H, 10a), 3.24 (m, 2H, 7a), 2.93 (dd, $J = 14.4, 7.8$ Hz, 1H, 10a), 2.58 (d, $J = 4.8$ Hz, 3H, 1), 1.42 (d, $J = 7.2$ Hz, 3H, 4a), 1.40 (s, 9H, 17), 1.18 (d, $J = 7.2$ Hz, 3H, 13a);

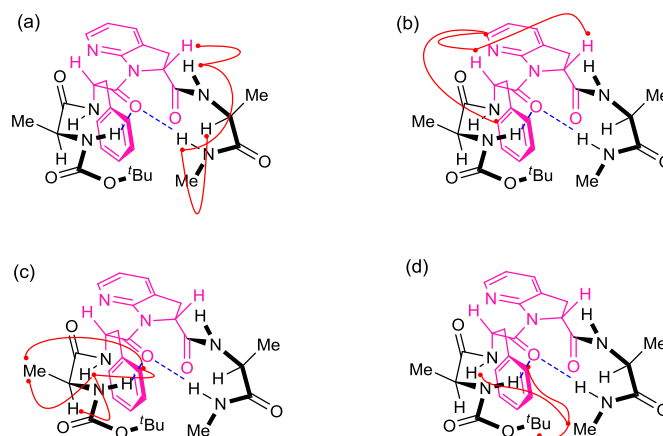


¹³C NMR (150 MHz, CDCl₃) ppm 172.4, 172.2, 172.1, 170.4, 155.2, 154.6, 146.8, 136.1, 133.8, 129.8, 129.5, 128.4, 126.8, 124.2, 119.2, 79.9, 59.7, 52.8, 50.0, 49.1, 37.6, 29.0, 28.3, 26.3, 18.7, 17.7; HRMS (EI): Exact mass calcd for C₂₉H₃₈N₆O₆ [M]⁺ 566.2853, found 566.2849.

Conformational Analysis of Boc-L-Ala-D-Phe-D-^{N7}Ind-L-Ala-NMe (33ba)

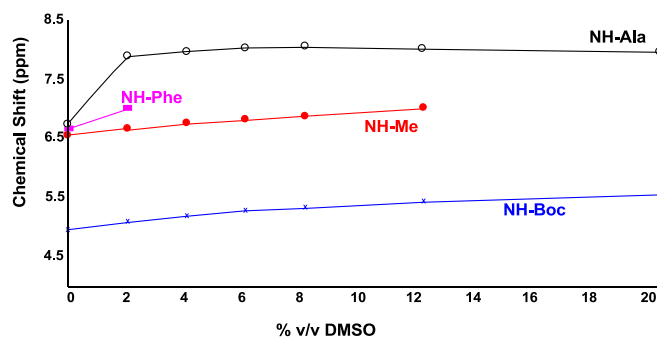
The *s-trans* conformation of the azaindoline amide bond was determined by observation of crosspeaks between H7/H10, H10/H10c and H10c/H7e. Complementary to these are crosspeaks for H10/H11 and H11/H10c', although crosspeaks could not be observed to definitively assign the local conformation of the alanine amide bond as *trans*. This assignment is supported, however, by a long range crosspeak H1/H17 for which such a geometry would be necessary. Additional long range crosspeaks H1/H11 and H1/H10c' are consistent with (*Z*)-*O*-carbamate geometry and an *anti* conformation of the *tert*-butyl group such that it is positioned at the interior of the turn. Since the Ala-NH residue is oriented by the azaindoline ring, crosspeak H1/H10c' between the methyl and phenyl can be used to assign the configuration of phenylalanine as (*R*).

Observed Regional (a-c) and Long Range (d) NOESY Correlation (33ba)



Identification of Intramolecular Hydrogen Bonding in 33ba

The experiment suggested the presence of a hydrogen bond between NH2 and O9 to form a 10-membered ring (β turn) and another hydrogen bond between NH14 and O9 to form an eight membered ring (δ turn). The experiment clearly showed the presence of two NH signals

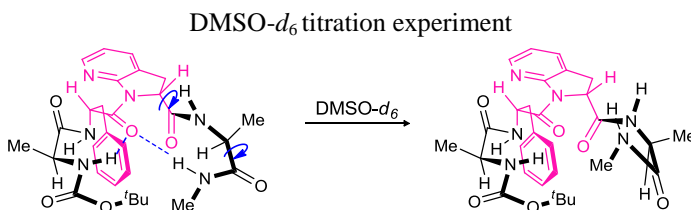


(NH14 and NH2) that were affected minimally by the increasing addition of DMSO- d_6 . In contrast, NH11 and NH5 shifted appreciably with increasing amounts of DMSO- d_6 indicating that these hydrogens were solvent exposed, also consistent with the β -turn conformation.

DMSO-Denatured Conformational Analysis of Boc-L-Ala-D-Phe-D-^{N7}Ind-L-Ala-NMe

(33ba)

To ascertain the extent to which intramolecular hydrogen bonding dictates the conformation of the tetrapeptide, the conformational analysis was repeated with the

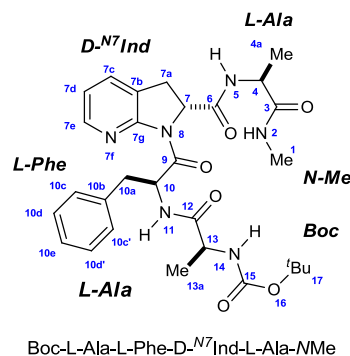


tetrapeptide as a solution in DMSO-*d*₆. Most peaks in the ¹H NMR spectrum could be assigned on the basis of coupling patterns and chemical shift relative to the sample in CDCl₃. NOESY was used to assign the amide protons that shifted appreciably by the change of solvent. Crosspeaks observed for Boc-L-Ala-D-Phe-D-^{N7}Ind-L-Ala-NMe in DMSO-*d*₆ were generally similar to those in CDCl₃ with the following exception—correlations between H1/H17 and H1/H10c were not present. Since all remaining crosspeaks were conserved, and disruption of the H2 intramolecular hydrogen bond by solvation follows from the DMSO-*d*₆ titration experiment, a conformational change, perhaps by rotation about C6-C7 has occurred. The observation of H4a/H2 crosspeak also supports rotation about the C3-C4 bond.

Less polar diastereomer: 33bb

(460 mg, 35%). $R_f = 0.38$ (10% MeOH/CH₂Cl₂); $[\alpha]_D^{24} +67.1$ (*c* 1.55, CHCl₃); IR (film) 3411 (br), 1657, 1152 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 8.22 (d, $J = 4.8$ Hz, 1H, 7e), 7.46 (d, $J = 7.2$ Hz, 1H, 7c), 7.19-7.13 (m, 6H, 10c, 10c', 10d, 10d', 10e, 5), 6.98 (dd, $J = 7.6, 5.2$ Hz, 1H, 7d), 6.82 (br s, 1H, 11), 6.61 (dd, $J = 13.6, 6.4$ Hz, 1H, 10), 6.48 (br s, 1H, 2), 5.00 (dd, $J = 10.8, 3.2$ Hz, 1H, 7), 4.88 (br s, 1H, 14), 4.36 (dq, $J = 7.2, 7.2$ Hz,

1H, 4), 4.18 (s, 1H, 13), 3.38 (dd, $J = 12.8, 2.8$ Hz, 1H, 7a), 3.15(m, 2H, 7a, 10a), 2.94 (dd, $J = 13.6, 5.2$ Hz, 1H, 10a), 2.71 (d, $J = 4.8$ Hz, 3H, 1), 1.42 (s, 9H, 17), 1.40 (d, $J = 7.2$ Hz, 3H, 4a), 1.28 (d, $J = 6.8$ Hz, 3H, 13a); ^{13}C NMR (600 MHz, CDCl_3) ppm 172.9, 172.3 (2C), 170.1, 155.4, 154.2, 146.5, 135.8, 134.0, 129.2 (2C), 128.3, 127.0, 124.7, 119.5, 80.1, 59.8, 53.5, 50.0, 49.6, 37.2, 28.6, 28.3, 26.3, 18.1, 17.6; HRMS (ESI): Exact mass calcd for $\text{C}_{29}\text{H}_{38}\text{N}_6\text{NaO}_6$ $[\text{M}+\text{Na}]^+$ 589.2750, found 589.2748.



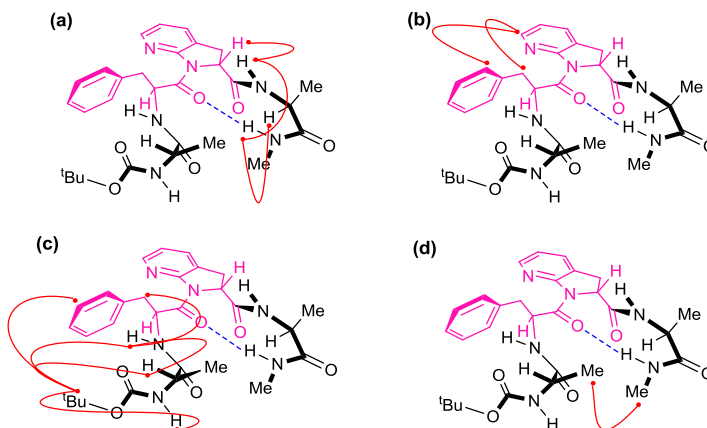
Conformational Analysis of Boc-L-Ala-L-Phe-D- N^7 Ind-L-Ala-NMe (33bb)

Assignment of both phenylalanine configurations (as L-Phe) and tetrapeptide conformation was made using NOESY data and molecular models. Definitive assignments were possible. The crosspeaks could be separated into three local regions (*a-c*) and a long range correlation (*d*). Beginning from the C-terminal methyl amide, crosspeaks for H2/H4 and H2/H5 defined the *s-trans* conformation of the methyl amide. A similar *s-trans* assignment for the alanine amide could be made by observation of a H5/H7 cross peak.

The *s-trans* conformation of the azaindoline amide bond was determined by observation of crosspeaks between H10/H10c and H10c/H7e. Complementary to these are crosspeaks for H10/H11 and H11/H10c', although crosspeaks could not be observed to definitively assign the local conformation of the alanine amide bond as *trans*. This assignment is supported, however, by a long range crosspeak H1/H13a for which such a geometry would be necessary. Additional long range crosspeaks H13/H17 and H10c/H17 are

consistent with *syn* conformation of the *tert*-butyl group such that it is positioned at the exterior of the turn. Assignment of phenylalanine as (*S*) configuration was made by exclusion: whereas a positive definite crosspeak (H7/H10) was observed for its epimer, the only crosspeak observed here between Phe and D-^{N7}Ind was H7e/H10c.

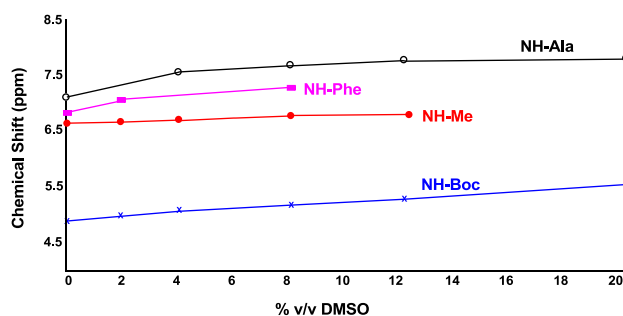
Observed Regional (a-c) and Long Range (d) NOESY Correlation (**33bb**)



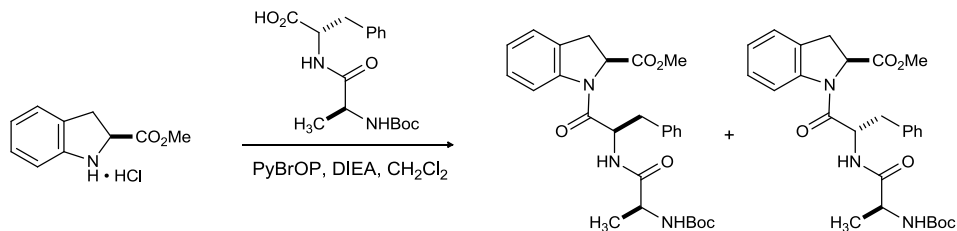
Identification of Intramolecular Hydrogen Bonding in 33bb

The experiment suggested the presence of a hydrogen bond between NH2 and O9 to form a 10-membered ring (β turn).

The experiment showed the presence of one NH signal (NH2) that was affected minimally by the increasing addition of DMSO-*d*₆. In



contrast, NH11 and NH14, and NH5 shifted appreciably with increasing amounts of DMSO-*d*₆ indicating that these hydrogens were solvent exposed.



Methyl-1-(2-((S)-2-(tert-butoxycarbonylamino)propanamido)-3-phenylpropanoyl)indoline-2-carboxylate (34aa, 34ab, 34ba, and 34bb).

To a 0 °C solution of the amine salt (1.00 g, 4.69 mmol) and the carboxylic acid (2.37 g, 7.04 mmol) in CH₂Cl₂ (9.5 mL) was added diisopropylethylamine (3.03 mL, 17.36 mmol) and PyBrOP (3.28 g, 7.04 mmol). The reaction was slowly warmed to the room temperature and stirred for 2 days. The reaction was diluted with CH₂Cl₂ and washed with satd aq NH₄Cl, satd aq NaHCO₃ and brine. The organic layer was dried, filtered, and concentrated to a brown oil. Column chromatography (SiO₂, 0-20-40% ethyl acetate in hexanes) furnished each diastereomer as a colorless oil (1.69 g, 73%).

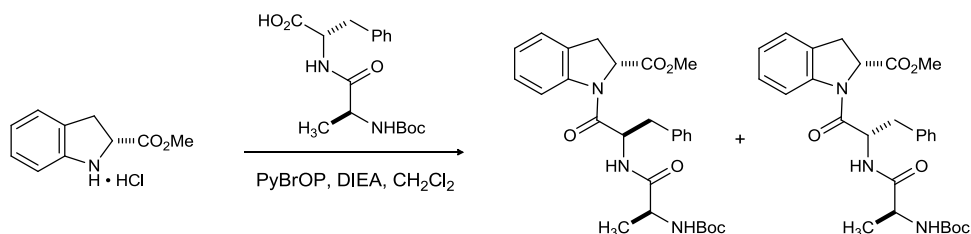
Less polar diastereomer: 34aa

(798 mg, 34%). $R_f = 0.55$ (50% EtOAc/hexanes); $[\alpha]_D^{24} -35.7$ (c 1.45, CHCl₃); IR (film) 3317, 3299, 2976, 2933, 1746, 1649, 1512, 1498, 1463 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.19 (d, $J = 8.1$ Hz, 1H), 7.29-7.17 (m, 5H), 7.12-7.04 (m, 3H), 6.69 (d, $J = 6.4$ Hz, 1H), 5.74 (d, $J = 10.0$ Hz, 1H), 4.94-4.77 (m, 2H), 4.11-4.04 (m, 1H), 3.78-3.60 (m, 5H), 3.38-3.28 (m, 1H), 3.06-2.98 (m, 1H), 1.45 (d, $J = 4.4$ Hz, 3H), 1.40 (s, 9H); HRMS (ESI): Exact mass calcd for C₂₇H₃₃N₃NaO₆ [M+Na]⁺ 518.2267, found 518.2264.

More polar diastereomer: 34ab

(896 mg, 39%). $R_f = 0.37$ (50% EtOAc/hexanes); $[\alpha]_D^{24} -51.1$ (c 0.90, CHCl₃); IR (film) 3329, 3316, 2976, 1744, 1649, 1511, 1498, 1481 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ

8.27 (d, $J = 8.1$ Hz, 1H), 7.32-7.26 (m, 5H), 7.10-7.08 (m, 3H), 7.02 (d, $J = 8.0$ Hz, 1H), 5.05 (br s, 1H), 4.93-4.86 (m, 1H), 4.22-4.18 (m, 2H), 3.71 (s, 3H), 3.20-3.00 (m, 3H), 2.82 (dd, $J = 16.4, 10.6$ Hz, 1H), 1.51 (s, 9H), 1.41 (d, $J = 7.2$ Hz, 3H); HRMS (ESI): Exact mass calcd for $C_{27}H_{33}N_3NaO_6$ $[M+Na]^+$ 518.2267, found 518.2248.



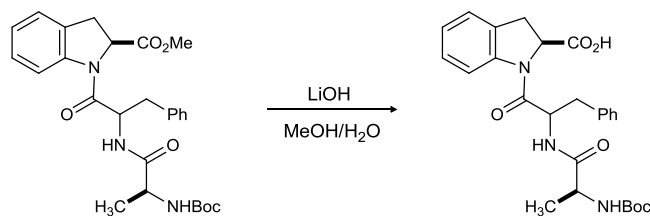
Substitution of the enantiomeric amine salt (450 mg, 2.11 mmol) into the above procedure furnished the corresponding diastereomers as colorless oils.

Less polar diastereomer: 34ba

(264 mg, 25%). $R_f = 0.49$ (50% EtOAC/hexanes); 1H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, $J = 8.0$ Hz, 1H), 7.28-7.16 (m, 5H), 7.11-7.06 (m, 3H), 6.67 (d, $J = 8.4$ Hz, 1H), 5.69 (br, 1H), 4.86-4.79 (m, 1H), 4.65 (br s, 1H), 4.16-4.04 (m, 1H), 3.72-3.59 (m, 5H), 3.37-3.28 (m, 1H), 3.06-2.98 (m, 1H), 1.46 (d, $J = 2.6$ Hz, 3H), 1.40 (s, 9H).

More polar diastereomer: 34bb

(517 mg, 49%). $R_f = 0.44$ (50% EtOAC/hexanes); 1H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, $J = 8.2$ Hz, 1H), 7.28-7.22 (m, 5H), 7.10-7.04 (m, 3H), 6.96 (d, $J = 7.4$ Hz, 1H), 4.94 (br s, 1H), 4.91-4.83 (m, 1H), 4.22-4.04 (m, 2H), 3.66 (s, 3H), 3.15-2.96 (m, 3H), 2.81 (dd, $J = 16.2, 10.6$ Hz, 1H), 1.47 (s, 9H), 1.36 (d, $J = 7.1$ Hz, 3H).

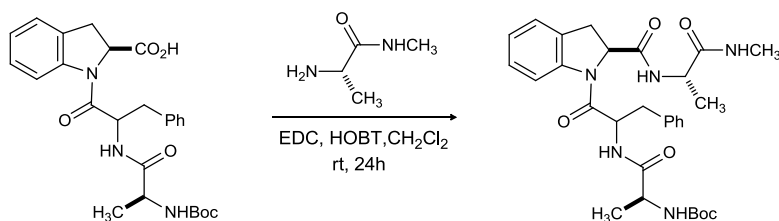


1-[2-(2-*tert*-Butoxycarbonylamino-propionylamino)-3-phenyl-propionyl]-2,3-dihydro-1*H*-indole-2-carboxylic acid (35aa**, **35ab**, **35ba** and **35bb**).**

To the methyl ester (**580** mg, 1.18 mmol) in MeOH-H₂O (25 mL, 4:1) at rt was added LiOH (51 mg, 2.1 mmol) and the reaction was stirred for 2 h. The solvent was removed *in vacuo* and the resulting residue acidified to pH = 2 with 1M HCl. The acidic solution was extracted with CH₂Cl₂ and the combined organic layers were washed with brine, dried, and filtered. The filtrate was evaporated to afford the desired product as a white solid (540 mg, 96%). ¹H NMR experiment analysis revealed poorly resolved, broad peaks.

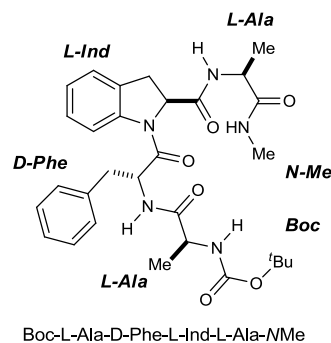
Substitution of **34ab** (560 mg, 1.13 mmol), **34ba** (190 mg, 0.38 mmol), and **34bb** (511 mg, 1.03 mmol) into the above procedure resulted in **35ab** (515 mg, 93%), **35ba** (165 mg, 90%), and **35bb** (493 mg, 99%), respectively.

HRMS (EI): Exact mass calcd for C₂₆H₃₂N₃O₆ [M+H]⁺ 482.2291, found 482.2291.



***tert*-Butyl-(2(*S*))-1-(1-(2)-((*S*)-1-(methylamino)-1-oxopropan-2-ylcarbamoyl)indolin-1-yl)-1-oxo-3-phenylpropan-2-ylamino)-1-oxopropan-2-ylcarbamate (36aa, 36ab).**

To a solution of the carboxylic acid (515 mg, 1.07 mmol), EDC (199 mg, 1.28 mmol) and HOBT (173 mg, 1.28 mmol) in CH₂Cl₂ (9 mL) was added the amine (109 mg, 1.07 mmol). The reaction was stirred for 24 h and quenched with satd aq NaHCO₃. The mixture was extracted with CH₂Cl₂ and washed with satd aq NH₄Cl, satd aq NaHCO₃, and brine. The organic layers were combined, dried, filtered, and concentrated to a brown oil. Flash chromatography (SiO₂, 1-2-3% MeOH in CH₂Cl₂) furnished the

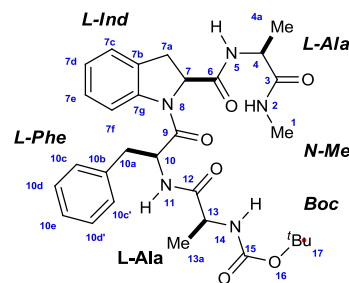


tetrapeptide as a colorless oil (498 mg, 82%). $R_f = 0.72$ (5% MeOH/CH₂Cl₂); $[\alpha]_D^{24} -146.5$ (c 1.6, CHCl₃); IR (film) 3299, 3062, 2978, 2934, 1650, 1542, 1483, 1415, 1167 cm⁻¹. ¹H NMR experiment resulted in poorly resolved, broad peaks and the 2D NMR experiments failed to provide well-resolved cross peaks, indicating that the tetrapeptide might have been aggregated in solution. As a result, the compound could not be fully characterized. HRMS (EI): Exact mass calcd for C₃₀H₃₉N₅NaO₆ [M+Na]⁺ 588.2798, found 588.2800.

Substitution of 35ab

(540 mg, 1.12 mmol) into the above procedure furnished the product (501 mg, 79%) as \geq 9:1 *cis/trans* rotamers. $R_f = 0.63$ (5% MeOH/CH₂Cl₂); $[\alpha]_D^{24} -70.8$ (c 1.3, CHCl₃); IR (film) 3307, 2959, 2922, 2847, 1653, 1536, 1410 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 8.09 (d, $J = 7.8$ Hz, 1H, 7f), 7.31-7.18 (m, 7H, 10c, 10c', 10d, 10d', 10e, 7d, 7e), 7.08 (s,

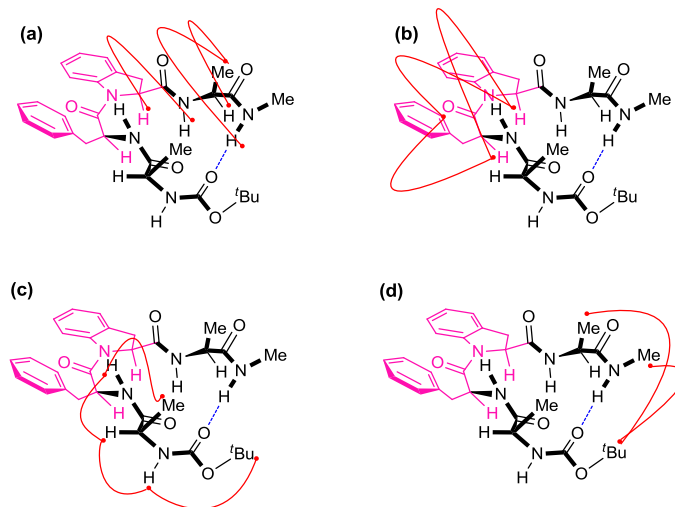
1H, 7c), 6.97 (s, 1H, 11), 6.86 (br s, $J = 6.6$ Hz, 1H, 5), 6.65 (s, 1H, 2), 5.01 (s, 1H, 14), 4.69 (dd, $J = 9.0, 6.0$ Hz, 1H, 10), 4.24-4.15 (m, 3H, 4, 13, 7), 3.12-3.02 (m, 3H, 10a, 10a, 7a), 2.77 (d, $J = 4.8$ Hz, 3H, 1), 2.75 (dd, $J = 15.6, 9.6$ Hz, 1H, 7a), 1.46 (s, 9H, 17), 1.37 (d, $J = 7.2$ Hz, 3H, 13a), 1.21 (d, $J = 7.2$ Hz, 3H, 4a); ^{13}C NMR (125 MHz, CDCl_3) ppm 173.0, 172.3, 170.5, 169.8, 140.8, 135.0, 130.1, 129.3.0, 129.0, 127.6 (2C), 125.2, 124.5, 118.4, 80.1, 61.9, 53.5, 50.2, 39.4, 34.0, 28.3, 26.2, 17.6; HRMS (EI): Exact mass calcd for $\text{C}_{30}\text{H}_{40}\text{N}_5\text{O}_6$ $[\text{M}+\text{H}]^+$ 566.2976, found 566.3001.



Conformational analysis of Boc-L-Ala-L-Phe-L-Ind-L-Ala-NMe (36ab)

Assignment of both phenylalanine configuration (as L-Phe) and tetrapeptide conformation was made using NOESY data and molecular models. Definitive assignments were possible.

Observed Regional (a-c) and Long Range (d) NOESY Correlation (36ab)



The crosspeaks could be separated into three local regions and a long range correlation. Beginning from the C-terminal methyl amide, crosspeaks for H2/H4 and H2/H3 defined the *s-trans* conformation of the methyl amide. A similar *s-trans* assignment for the alanine amide could be made by observation of a H5/H7 cross peak. The *s-cis* conformation of the indoline amide bond was determined by observation of crosspeaks between H10/H10c, H7/H10 and H10c/H7. Complementary to these are crosspeaks for H10/H11 and H11/H10c', although crosspeaks could not be observed to definitively assign the local conformation of the alanine amide bond as *trans*. This assignment is supported, however, by a long range crosspeak H17/H1 and H17/H14a for which such geometry would be necessary. Additional long range crosspeaks H11/H13, H13/H15, H15/H17 are consistent with *syn* conformation of the *tert*-butyl group such that it is positioned at the exterior of the turn. Assignment of phenyl alanine as (*S*) configuration was made by the observation of H7/H10 crosspeak.

Identification of Intramolecular Hydrogen Bonding in 36ab

The experiment suggested the presence of a hydrogen bond between NH2 and O15 to form a 16-membered ring and

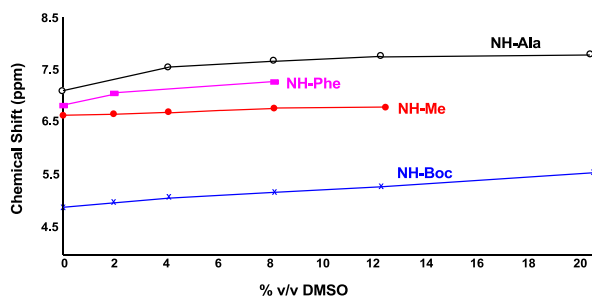
another weak hydrogen bond

between NH5 and O12 to form

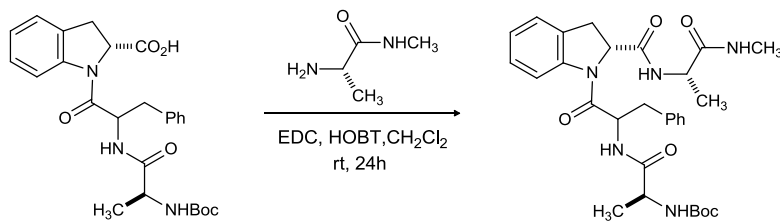
a ten membered ring (β turn)

where *L-Ind* is present as *i*+2

residue. The experiment clearly showed the presence of one NH signal (NH2) that was affected minimally by the increasing addition of DMSO-*d*₆ and the other NH signal (NH5) which was affected less than the other two NH signal (NH11 and NH14). In



contrast, NH11 and NH14 shifted appreciably with increasing amounts of DMSO-*d*₆ indicating that these hydrogens were solvent exposed.

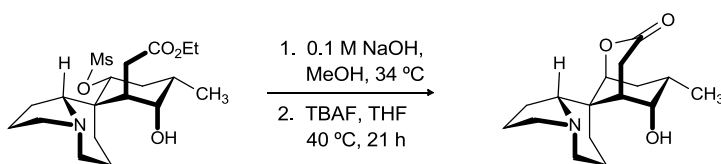


***tert*-Butyl-(2(*S*))-1-(1-(2)-((*R*)-1-(methylamino)-1-oxopropan-2-ylcarbamoyl)indolin-1-yl)-1-oxo-3-phenylpropan-2-ylamino)-1-oxopropan-2-ylcarbamate (**36ba**, **36bb**).**

To a solution of the carboxylic acid (104 mg, 216 μ mol), EDC (40.2 mg, 259 μ mol) and HOBT (35.1 mg, 259 μ mol) in CH₂Cl₂ (2 mL) was added the amine (22.1 mg, 216 μ mol). The reaction was stirred for 24 h at rt and was quenched with satd aq NaHCO₃. The mixture was extracted with CH₂Cl₂ and washed with satd aq NH₄Cl, satd aq NaHCO₃ and brine. The organic layers were combined, dried (Na₂SO₄), filtered, and concentrated to a brown oil. Flash chromatography (SiO₂, 1-2-3% MeOH in CH₂Cl₂) yielded the desired tetrapeptide as a colorless oil (92 mg, 75%). R_f = 0.68 (5% MeOH/CH₂Cl₂). IR (film) 3299, 2965, 2933, 1656, 1548, 1483, 1417 cm⁻¹. ¹H NMR experiment analysis revealed poorly resolved, broad peaks and the 2D NMR experiments failed to provide well-resolved cross peaks, indicating that the tetrapeptide might have been aggregated in solution. As a result, the compound could not be further characterized.

Substitution of **35bb** (420 mg, 870 μ mol) into the above procedure resulted in the tetrapeptide (410 mg, 83%) as a 4:1 *cis/trans* rotamer mixture. R_f = 0.63 (5% MeOH/CH₂Cl₂); $[\alpha]_D^{24}$ +75.0 (*c* 1.32, CHCl₃); IR (film) 3297 (br), 3057, 2975, 2976, 2929, 1653, 1533, 1481 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, *cis*-rotamer) δ 8.13 (d, *J* = 8.0

Hz, 1H), 7.61 (br s, 1H), 7.45 (br s, 1H), 7.29-7.04 (m, 8H), 6.24 (br s, 1H), 5.29 (d, $J = 7.1$ Hz, 1H), 4.69-4.67 (m, 1H), 4.39-4.21 (m, 3H), 3.15-3.06 (m, 3H), 2.80 (dd, $J = 15.5, 10.8$ Hz, 1H), 2.66 (d, $J = 4.1$ Hz, 3H), 1.50 (s, 9H), 1.34-1.29 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) ppm 173.0, 172.7, 170.8, 170.0, 155.9, 141.6, 135.8, 130.0, 129.5, 129.1, 127.8, 127.6, 125.2, 124.6, 118.4, 80.6, 61.8, 54.5, 50.1, 49.7, 39.7, 34.1, 28.5, 26.4, 18.1, 17.6; HRMS (EI): Exact mass calcd for $\text{C}_{30}\text{H}_{40}\text{N}_5\text{O}_6$ $[\text{M}+\text{H}]^+$ 566.2976, found 566.2957.



(+)-Serratezomine A ((+)-37).

To a solution of the ester (13.2 mg, 25.5 μmol) in MeOH (600 μL) at 0 $^\circ\text{C}$ was added sodium hydroxide (220 μL , 0.1 M in H_2O). The reaction was stirred for 30 min before being warmed to 34 $^\circ\text{C}$ and stirred for another 10 h. The solvent was removed *in vacuo* and the resulting residue was dissolved in CH_2Cl_2 . The organic layer was washed once with H_2O and then satd aq NH_4Cl and dried, filtered, and concentrated to a yellow oil. To the crude oil in THF (300 μL) was added TBAF (63.8 μL , 1.0 M in THF). The reaction was stirred for 15 min before being warmed to 40 $^\circ\text{C}$ and stirred for another 20 h. The solvent was evaporated and the resulting crude oil was subjected to mass directed LC purification (15% $\text{CH}_3\text{CN}/0.1\%$ TFA) to afford (+)-serratezomine A as a white solid (2.4 mg, 33%). $R_f = 0.22$ (10% MeOH/ CH_2Cl_2); $[\alpha]_D^{24} +9.5$ (c 0.3, MeOH); IR (film) 3423, 2920, 2850, 1720, 1463, 1200, 1134 cm^{-1} ; ^1H NMR (400 MHz, MeOD) δ 4.32 (dd, $J = 5.6, 2.8$ Hz, 1H), 3.81 (dd, $J = 11.2, 6.4$ Hz, 1H), 3.77 (dd, $J = 3.6, 3.6$ Hz, 1H), 3.54 (ddd, $J = 9.6, 9.6, 9.6$ Hz, 1H), 3.36-3.34 (m, 1H), 3.28-3.25 (m, 1H), 3.14 (dd, $J = 20.0,$

8.0 Hz, 1H), 2.98 (ddd, $J = 13.2, 13.2, 3.6$ Hz, 1H), 2.83 (br d, $J = 13.6$ Hz, 1H), 2.62-2.61 (m, 1H), 2.46 (d, $J = 20.0$ Hz, 1H), 2.29-2.13 (m, 4H), 2.05-1.99 (m, 1H), 1.85-1.74 (m, 4H), 1.40 (ddd, $J = 13.6, 13.6, 3.2$ Hz, 1H), 1.01 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (125 MHz, MeOD) ppm 173.2, 83.5, 76.2, 66.7, 56.0, 48.7, 37.3, 37.1, 34.3, 34.2, 27.0, 23.6, 22.0, 20.6, 19.7, 17.3.

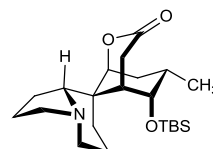
The intermediate TBS protected lactone was also isolated.

Data for latone 277:

$R_f = 0.35$ (10% MeOH/ CH_2Cl_2); $[\alpha]_D^{24} +3.5$ (c 0.5, MeOH); IR

(film) 2927, 2855, 1738, 1672, 1196, 1039 cm^{-1} ; ^1H NMR (600

MHz, CDCl_3) δ 4.18 (s, 1H), 3.75 (s, 1H), 3.57 (br d, $J = 9.0,$



1H), 3.48 (br d, $J = 9.6,$ 1H), 3.37 (dd, $J = 20.4, 7.8$ Hz, 1H), 3.17 (br s, 1H), 2.87 (d, $J =$

13.8 Hz, 1H), 2.79 (br s, 1H), 2.72 (d, $J = 14.4$ Hz, 1H), 2.63 (d, $J = 10.8$ Hz, 1H), 2.37

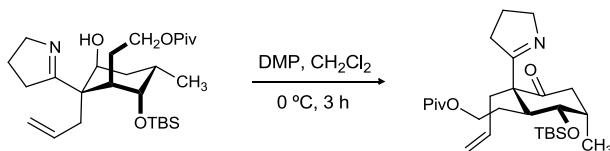
(d, $J = 20.4$ Hz, 1H), 2.28-2.25 (m, 1H), 2.16-2.04 (m, 4H), 1.85-1.82 (m, 2H), 1.79-1.74

(m, 2H), 1.63-1.60 (m, 1H), 0.94 (d, $J = 6.6$ Hz, 3H), 0.89 (s, 9H), 0.14 (s, 3H), 0.07 (s,

3H); ^{13}C NMR (150 MHz, CDCl_3) ppm 170.0, 81.3, 75.9, 64.0, 53.9, 46.6, 45.8, 35.7,

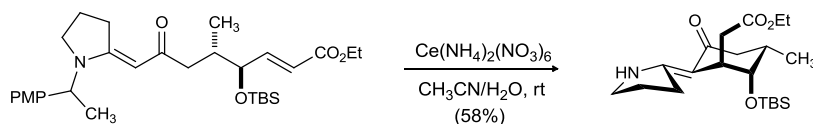
35.4, 33.4, 30.7, 26.0, 22.4, 21.0, 19.5, 18.0, 16.9, 14.1, -4.3, -5.2; HRMS (EI): Exact

mass calcd for $\text{C}_{22}\text{H}_{39}\text{NO}_3\text{Si}$ $[\text{M}]^+$ 393.2699, found 393.2774.



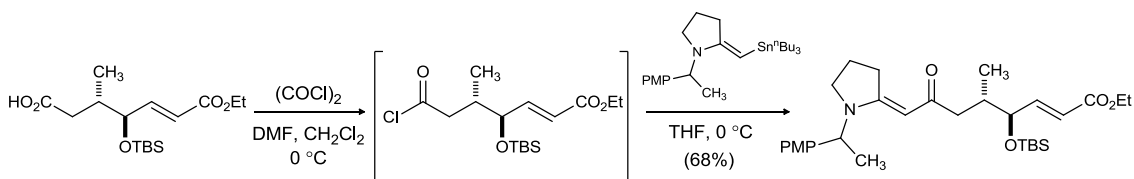
2-((1R,2S,5S)-2-Allyl-6-(*tert*-butyldimethylsilyloxy)-2-(3,4-dihydro-2H-pyrrol-5-yl)-3-hydroxy-5-methylcyclohexyl)ethyl pivalate (221).

Dess-Martin periodinane (342 mg, 805 μmol) was added to the alcohol (200 mg, 366 μmol) in CH_2Cl_2 (4 mL) at rt and stirred for 3 h. The reaction was quenched by the addition of an aqueous solution containing 2:1 satd aq $\text{Na}_2\text{S}_2\text{O}_3:\text{NaHCO}_3$ and was stirred until both layers became clear (~20 min). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried, filtered, and concentrated to a cloudy oil. Column chromatography (SiO_2 , 10-15% ethyl acetate in hexanes) provided the desired product as thick colorless oil (199 mg, 100%). $R_f = 0.47$ (25% EtOAc/hexanes); $[\alpha]_D^{24} -85.9$ (c 1.5, CHCl_3); IR (film) 2956, 2928, 2858, 1744, 1709 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.73 (dddd, $J = 16.7, 10.5, 8.3, 6.3$ Hz, 1H), 5.09 (d, $J = 17.3$ Hz, 1H), 5.08 (d, $J = 10.1$ Hz, 1H), 4.53 (dd, $J = 9.2, 3.8$ Hz, 1H), 4.11 (dq, $J = 10.8, 7.2$ Hz, 1H), 4.04 (dq, $J = 10.8, 7.2$ Hz, 1H), 3.88-3.77 (m, 2H), 2.99 (dd, $J = 13.9, 6.1$ Hz, 1H), 2.91-2.85 (m, 1H), 2.75 (dd, $J = 14.1, 5.2$ Hz, 1H), 2.54 (dd, $J = 17.0, 7.4$ Hz, 1H), 2.49-2.32 (m, 3H), 2.32-2.20 (m, 2H), 2.29 (dd, $J = 16.9, 3.2$ Hz, 1H), 1.83-1.67 (m, 2H), 1.22 (t, $J = 7.2$ Hz, 3H), 0.94 (d, $J = 6.8$ Hz, 3H), 0.87 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) ppm 209.1, 176.9, 173.1, 133.7, 119.3, 73.5, 61.8, 61.2, 60.4, 44.3, 40.8, 38.0, 36.6, 35.3, 35.1, 26.1, 22.3, 18.3, 14.3, 14.0, -4.2, -4.4; HRMS (CI): Exact mass calcd for $\text{C}_{24}\text{H}_{41}\text{NO}_4\text{Si}$ $[\text{M}]^+$ 435.2799, found 435.2800.



Ethyl 2-((1*S*,2*R*,3*S*,*Z*)-2-(*tert*-butyldimethylsilyloxy)-3-methyl-5-oxo-6-(pyrrolidin-2-ylidene)cyclohexyl)acetate (222).

Ceric ammonium nitrate (16.8 g, 30.6 mmol) was added in one portion to the substrate (8.10 g, 15.3 mmol) in CH₃CN/H₂O (5:1, 765 mL) at rt. After 5 min, the reaction was quenched with satd aq NaHCO₃ and extracted with EtOAc. The combined organic layers were washed once with brine, and dried, filtered, and concentrated to an orange/brown oil. The crude oil was subsequently chromatographed (SiO₂, 10-32-38% ethyl acetate in hexanes) to provide the product as a yellow/brown oil (2.8 g, 46%). Analytical data was identical to that in the literature.

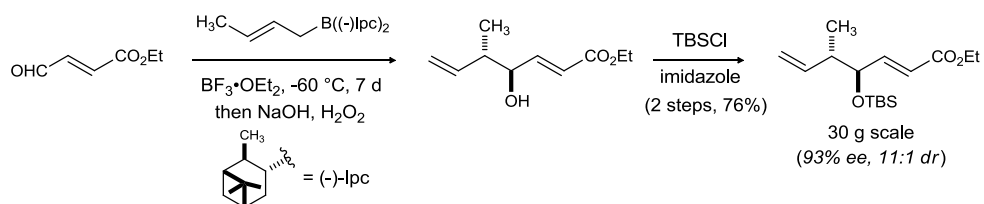


(2*E*,4*S*,5*S*,8*E*)-Ethyl 4-(*tert*-butyldimethylsilyloxy)-8-(1-(1-(4-methoxyphenyl)ethyl)-pyrrolidin-2-ylidene)-5-methyl-7-oxooct-2-enoate (223).

Preparation of the β-stannyleneamine: To a flame-dried 1L round bottom flask fitted with a reflux condenser was added the alkynyl imine (5.8 g, 27 mmol) and the flask was evacuated and refilled with nitrogen three times. Benzene (660 mL) was added via cannula to the flask, along with ^tBu₃SnH (1.6 mL, 10% of total 59.6 mmol) and the contents were heated in an oil bath to 90-95 °C. In a separate flask, AIBN (4.4 g, 27 mmol) was added and the flask was evacuated and refilled with nitrogen three times. Then benzene (110 mL, 1.5 mL benzene/60 mg AIBN) and ^tBu₃SnH (14.4 mL, 90% of total 59.6 mmol) was added and the solution was added dropwise to the reaction vessel over 5-7 hours. After the addition is complete, the reaction is stirred an additional 1 h and

then cooled to ~ 40 °C. The solvent was removed *in vacuo* and the crude oil was redissolved in THF (192 mL, 0.14M) and cooled to 0 °C.

Preparation of the acid chloride: When the above reaction is cooled and ready for solvent removal, the preparation of the acid chloride is then initiated. To the carboxylic acid (5.0 g, 15 mmol) in CH₂Cl₂ (150 mL) at 0 °C was added oxalyl chloride (6.6 mL, 75 mmol). After several minutes, catalytic DMF was added (20 μL). The reaction was stirred for 30 min at 0 °C and 15 min at rt. The solvent is removed *in vacuo* and the crude orange oil is placed under high vacuum for at least 30 min. The crude acid chloride is then dissolved in THF (108 mL), cooled to 0 °C, and then cannulated, quick dropwise, to the β-stannyl enamine solution in THF. After the addition was complete, the reaction is allowed to stir an additional 5 min at 0 °C and then warmed to rt and stirred overnight. The solvent is removed *in vacuo* and the crude dark orange oil is loaded directly for column chromatography (SiO₂, 10-20-25-30-35-40% ethyl acetate in hexanes) to provide the desired vinylogous amide 4.95 g (68%). Analytical data was identical to that in the literature.



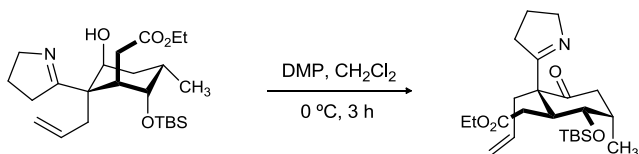
(4R,5S,E)-Ethyl 4-(tert-butyldimethylsilyloxy)-5-methylhepta-2,6-dienoate (232).

Crotylation, step 1: A 3 L three necked, round bottom flask, fitted with a mechanical stirrer and pressure addition funnel, was charged with KO^tBu (52.6 g, 468 mmol), trans-2-butene (63.8 mL, 710 mmol), and THF (425 mL) and cooled to -78 °C (CO₂, ⁱPrOH). ⁿBuLi (188 mL, 2.5 M in hexanes) was added dropwise via the addition funnel and the

reaction becomes yellow. After the addition was complete, the bath was changed to a -60 °C bath (CO₂, 80/20 EtOH/H₂O) for 45 min, at which time the reaction mixture turned orange in color. The bath was then changed back to the -78 °C bath, this time using a large insulated container. To the round bottom was cannulated a solution of the (-)-Ipc₂BOMe (150 g, 474 mmol) in ether (474 mL) and the reaction was stirred an additional one hour, at which time the reaction becomes colorless. Then BF₃·OEt₂ (105 mL, 829 mmol) was added via addition funnel and the reaction stirred an additional hour. The aldehyde (50.6 g, 395 mmol) in ether (10 mL) was added slowly via cannula and the reaction was stirred for 3 d before the addition of more aldehyde (22 g) and then stirred for 4 d more, maintaining the temperature at a constant -60 °C. The reaction was quenched using 3N NaOH (780 mL) and then 30% H₂O₂ (378 mL), both via addition funnel, and the cold bath was removed and the reaction warmed to rt and stirred for 12 h. To the crude reaction was added satd aq Na₂S₂O₃ and it was extracted with ether. The combined organic layers were washed with brine, dried, filtered, and concentrated to a yellow oil. Subsequent distillation was utilized to remove a main portion of the (-)-IpcOH byproduct (full vacuum ~ 300 mTorr, 60-65 °C) which cools to a white solid. The remaining yellow oil contained a ~ 1.6:1 ratio of the (-)-IpcOH to homoallylic OH, crude oil weight (80.8 g, ~80% crude yield of the desired alcohol). The crude alcohols were then protected as their TBS ethers to allow for easier separation via chromatography.

TBS protection, step 2: The crude alcohols (80.8 g, 487 mmol) and imidazole (49.7 g, 730 mmol) were dissolved in DMF (1000 mL) and cooled to 0 °C. TBSCl (110 g, 730 mmol) was added and the reaction was stirred for 10 min at 0 °C and at least 4 h at rt. Water was added and the reaction was extracted with EtOAc and the combined organic layers were

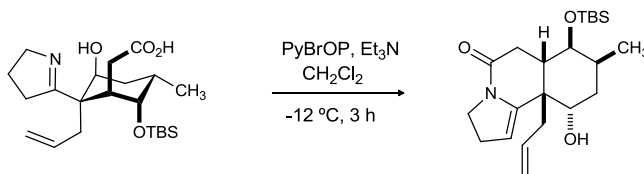
washed with brine and then dried, filtered, and concentrated to a yellow oil. The oil was dissolved in CH₂Cl₂ and then extracted with H₂O several times to remove the DMF and then placed under high vacuum for several hours. Column chromatography (SiO₂, 1.5-3% ethyl acetate in hexanes) provided the desired TBS-protected product (53.1 g, 76% over two steps, dr 11:1, ee 92.3%). Analytical data was identical to that in the literature



Ethyl 2-((1*S*,2*S*,5*S*,6*S*)-2-allyl-6-(*tert*-butyldimethylsilyloxy)-2-(3,4-dihydro-2*H*-pyrrol-5-yl)-5-methyl-3-oxocyclohexyl)acetate (250).

Dess-Martin periodinane (737 mg, 1.74 mmol) was added to the alcohol (380 mg, 869 μ mol) in CH₂Cl₂ (10 mL) at rt and stirred for 3 h. The reaction was quenched by the addition of an aqueous solution containing 2:1 satd aq Na₂S₂O₃:NaHCO₃ and was stirred until both layers became clear (~20 min). The two layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried, filtered, and concentrated to a cloudy oil. Column chromatography (SiO₂, 10-15% ethyl acetate in hexanes) provided the desired product as pale yellow oil (361 mg, 96%). $R_f = 0.47$ (25% EtOAc/hexanes); $[\alpha]_D^{24} -7.1$ (c 0.3, CHCl₃); IR (film) 2956, 2928, 2858, 1744, 1709 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.73 (dddd, $J = 16.7, 10.5, 8.3, 6.3$ Hz, 1H), 5.09 (d, $J = 17.3$ Hz, 1H), 5.08 (d, $J = 10.1$ Hz, 1H), 4.53 (dd, $J = 9.2, 3.8$ Hz, 1H), 4.11 (dq, $J = 10.8, 7.2$ Hz, 1H), 4.04 (dq, $J = 10.8, 7.2$ Hz, 1H), 3.88-3.77 (m, 2H), 2.99 (dd, $J = 13.9, 6.1$ Hz, 1H), 2.91-2.85 (m, 1H), 2.75 (dd, $J = 14.1, 5.2$ Hz, 1H), 2.54 (dd, $J = 17.0, 7.4$ Hz, 1H), 2.49-2.32 (m, 3H), 2.32-2.20 (m, 2H), 2.29 (dd, $J = 16.9, 3.2$ Hz,

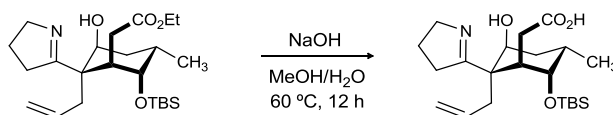
1H), 1.83-1.67 (m, 2H), 1.22 (t, $J = 7.2$ Hz, 3H), 0.94 (d, $J = 6.8$ Hz, 3H), 0.87 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) ppm 209.1, 176.9, 173.1, 133.7, 119.3, 73.5, 61.8, 61.2, 60.4, 44.3, 40.8, 38.0, 36.6, 35.3, 35.1, 26.1, 22.3, 18.3, 14.3, 14.0, -4.2, -4.4; HRMS (CI): Exact mass calcd for $\text{C}_{24}\text{H}_{41}\text{NO}_4\text{Si}$ $[\text{M}]^+$ 435.2799, found 435.2800.



(6a*S*,7*S*,8*S*,10*S*,10a*S*)-10a-Allyl-7-(*tert*-butyldimethylsilyloxy)-10-hydroxy-8-methyl-2,3,6a,7,8,9,10,10a-octahydropyrrolo[2,1-*a*]isoquinolin-5(6*H*)-one (250).

To a -12 °C solution of the carboxylic acid (14.6 mg, 35.7 μmol) and diisopropyl ethylamine (12.4 μL , 71.4 mmol) in CH_2Cl_2 (0.6 mL) was added PyBrOP (33.3 mg, 71.4 μmol) and the reaction was stirred for 3 h. The reaction was diluted with CH_2Cl_2 and washed with satd aq NH_4Cl , satd aq NaHCO_3 and brine. The organic layer was dried, filtered, and concentrated to a brown oil. Column chromatography (SiO_2 , 30-50% ethyl acetate in hexanes) afforded the cyclic enamide (13.9 mg, 100%). $R_f = 0.16$ (50% EtOAc/hexanes); $[\alpha]_D^{24} -7.1$ (c 0.3, CHCl_3); mp 55.5-57.5 °C; IR (film) 3396 (br), 2956, 2928, 2858, 1628 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.90-5.75 (m, 1H), 5.54 (br s, 1H), 5.19-5.13 (m, 2H), 3.99 (br s, 1H), 3.81-3.72 (m, 2H), 3.38-3.37 (m, 1H), 2.66-2.41 (m, 6H), 2.24 (dd, $J = 14.1, 7.9$ Hz, 1H), 2.04 (br s, 2H), 1.80 (br s, 1H), 1.68-1.65 (m, 1H), 0.93 (d, $J = 7.1$ Hz, 3H), 0.86 (s, 9H), 0.00 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) ppm 165.2, 141.0, 132.5, 119.2, 108.7, 71.4, 67.5, 44.2, 43.8, 39.3, 36.5, 34.8,

34.2, 29.2, 27.1, 25.8, 18.0, 12.1, -4.5, -5.2; HRMS (EI): Exact mass calcd for $C_{22}H_{37}NO_3Si$ $[M]^+$ 391.2537, found 391.2539.



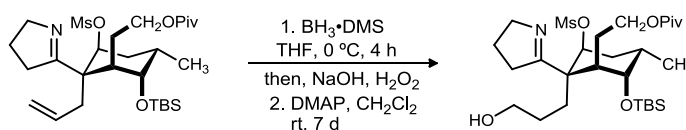
2-((1R,2S,5S)-2-Allyl-6-(*tert*-butyldimethylsilyloxy)-2-(3,4-dihydro-2H-pyrrol-5-yl)-3-hydroxy-5-methylcyclohexyl)acetic acid (251).

To a solution of the ester (28.0 mg, 64.1 μ mol) in MeOH (660 μ L) at 0 °C was added sodium hydroxide (220 μ L, 0.05 M in H₂O). The reaction was stirred for 30 min before being warmed to 60 °C and stirred for 12 h. The solvent was removed *in vacuo* and the resulting residue acidified to pH = 2 with 1M HCl. The acidic solution was extracted with CH₂Cl₂ and the combined organic layers were washed with brine, dried, and filtered. Column chromatography (SiO₂, 5-10% methanol in dichloromethane) provided the title compound as a pale yellow oil (20.6 mg, 79%). R_f = 0.40 (10% MeOH/CH₂Cl₂); $[\alpha]_D^{24}$ -40.5 (*c* 1.05, CHCl₃); IR (film) 3396 (br), 2956, 2928, 2858, 1628 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 5.53-5.46 (m, 1H), 4.98-4.94 (m, 2H), 4.19 (s, 1H), 3.89 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H), 3.80 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H), 3.66-3.64 (m, 1H), 2.99 (br s, 1H), 2.64-2.58 (m, 1H), 2.51-2.48 (m, 2H), 2.38 (br d, *J* = 9.6 Hz, 1H), 2.32-2.29 (m, 1H), 2.22-2.20 (m, 1H), 2.04-2.00 (m, 1H), 1.92-1.77 (m, 3H), 1.63-1.60 (m, 1H), 1.48 (br d, *J* = 13.8 Hz, 1H), 0.93-0.92 (m, 12H), 0.15 (s, 3H), 0.06 (s, 3H), -COOH proton not observed; ¹³C NMR (150 MHz, CDCl₃) ppm 176.7, 174.6, 134.2, 116.9, 75.0, 59.1, 48.6, 43.2, 40.9, 34.1, 30.8, 26.0, 24.8, 22.7, 21.7, 18.2, 18.1, 14.1, -4.0, -5.2; HRMS (EI): Exact mass calcd for $C_{22}H_{40}NO_4Si$ $[M+H]^+$ 410.2727, found 410.2728.



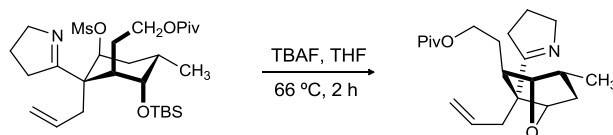
2-((1*R*,2*S*,5*S*)-2-Allyl-6-(*tert*-butyldimethylsilyloxy)-2-(3,4-dihydro-2*H*-pyrrol-5-yl)-5-methyl-3-(methylsulfonyloxy)cyclohexyl)ethyl pivalate (263).

To a solution of the alcohol (400 mg, 834 μmol) and triethylamine (255 μL , 1.83 mmol) in CH_2Cl_2 (8 mL) at 0 $^\circ\text{C}$ was added methanesulfonyl chloride (124 μL , 1.08 mmol). The reaction was stirred for 30 min before it was warmed to rt and stirred for 15 min. The reaction was quenched with satd aq NH_4Cl and extracted with CH_2Cl_2 . The combined organic layers were dried, filtered, and concentrated to a pale yellow oil. Column chromatography (SiO_2 , 10-20% ethyl acetate in hexanes) provided the title compound as a pale yellow oil (464 mg, 100%). $R_f = 0.70$ (50% EtOAc/hexanes); $[\alpha]_D^{24} +18.0$ (c 1.0, CHCl_3); IR (film) 3396 (br), 2956, 2928, 2858, 1628 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.48-5.38 (m, 1H), 5.20 (br s, 1H), 4.98-4.90 (m, 2H), 4.10-3.98 (m, 2H), 3.89-3.80 (m, 1H), 3.78 (br s, 1H), 3.78-3.71 (m, 1H), 3.34 (dd, $J = 15.0, 9.0$ Hz, 1H), 3.07 (s, 3H), 2.71-2.62 (m, 1H), 2.41 (ddd, $J = 8.0, 8.0, 8.0$ Hz, 1H), 2.30 (br s, 1H), 2.17 (dd, $J = 15.0, 4.0$ Hz, 1H), 1.98 (br d, $J = 11.5$ Hz, 1H), 1.93-1.82 (m, 3H), 1.81-1.64 (m, 2H), 1.50-1.40 (m, 1H), 1.20 (s, 9H), 0.96 (d, $J = 7.0$ Hz, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) ppm 178.4, 177.0, 133.2, 117.6, 83.3, 73.1, 63.3, 59.7, 49.0, 44.5, 41.4, 38.8, 38.7, 33.7, 30.3, 30.0, 27.2, 25.9, 25.7, 22.4, 18.0 (2C), -3.9, -4.9; HRMS (ESI): Exact mass calcd for $\text{C}_{28}\text{H}_{52}\text{NO}_6\text{SSi}$ $[\text{M}+\text{H}]^+$ 558.3285, found 558.3278.



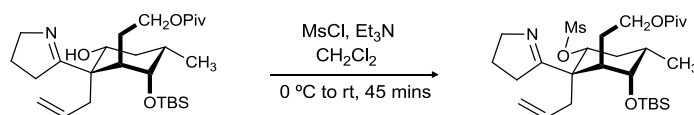
2-((1*R*,2*S*,5*S*)-6-(*tert*-Butyldimethylsilyloxy)-2-(3,4-dihydro-2*H*-pyrrol-5-yl)-2-(3-hydroxypropyl)-5-methyl-3-(methylsulfonyloxy)cyclohexyl)ethyl pivalate (264).

BH₃·DMS (34.1 μL, 353 μmol) was added to the alkene (93.0 mg, 168 μmol) in THF (1.7 mL) at 0 °C. The reaction was stirred for 2 h before being warmed to rt and stirred for another 1 h. The reaction was stirred for 2 h before being warmed to rt and stirred for another 1 h. The reaction was cooled to 0 °C, quenched by the addition of 3 N NaOH (650 μmol) and 30% H₂O₂ (500 μmol) and was allowed to stir at rt overnight. The reaction was extracted with EtOAc and the combined organic layers were dried, filtered, and concentrated to an oily solid. The residue was redissolved in CH₂Cl₂ (1 mL) and treated with 4-dimethyl aminopyridine (205 mg, 1.68 mmol) at rt for 7 d before it was filtered, concentrated, and purified via flash column chromatography (SiO₂, 20-35%-50% ethyl acetate in hexanes) to afford the product as a colorless oily solid (48 mg, 50%) in addition to mg of the alkene (22 mg, 23%). *R*_f = 0.30 (50% EtOAc/hexanes); [α]_D²⁴ -20.0 (*c* 0.6, CHCl₃); IR (film) 2956, 2928, 2858, 1744, 1709 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.27 (br s, 1H), 3.96 (br s, 1H), 3.85-3.81 (m, 2H), 3.68-3.63 (m, 2H), 3.48 (br s, 1H), 3.08 (s, 1H), 3.07 (br s, 1H), 2.81 (br s, 1H), 2.55-2.50 (m, 2H), 2.50-2.45 (m, 1H), 2.07-2.84 (m, 7H), 1.87-1.84 (m, 1H), 1.40-1.36 (m, 1H), 1.19-1.16 (m, 10H), 0.95-0.91 (m, 15H), 0.06 (s, 3H), 0.04 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) ppm 178.4 (2C), 83.6, 72.5, 63.5, 63.0, 59.8, 48.5, 39.3, 38.7, 34.2, 32.9, 32.0, 31.3, 30.3, 28.1, 27.2, 26.0, 22.3, 18.0, 17.9, 14.2, -3.8, -4.9; HRMS (ESI): Exact mass calcd for C₂₈H₅₄NO₇SSi [M+H]⁺ 576.3390, found 576.3378.



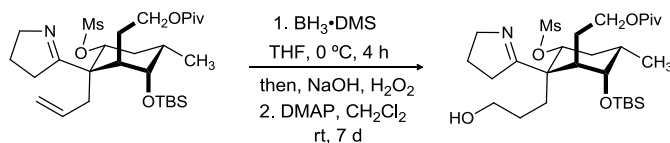
2-((1*R*,2*S*,3*S*,6*S*)-3-Allyl-3-(3,4-dihydro-2*H*-pyrrol-5-yl)-6-methyl-7-oxabicyclo[2.2.1]heptan-2-yl)ethyl pivalate (266).

TBAF (80.0 μL , 80.0 μmol) was added to the silyl ether (15.0 mg, 26.8 μmol) in THF (0.5 mL) and the reaction was refluxed for 2 h, quenched with satd aq. NaHCO_3 , and extracted with ether. The combined organic layers were dried, filtered, and concentrated to a crude oil that was purified via column chromatography (SiO_2 , 12-25-50% ethyl acetate in hexanes) to furnish the cyclic ether as a yellow oil (7.5 mg, 81%) in addition to the alkene (1.5 mg, 10%). $R_f = 0.60$ (50% EtOAc/hexanes); $[\alpha]_D^{24} -12.6$ (c 1.5, CHCl_3); IR (film) 2956, 2928, 2858, 1744, 1709 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 5.56 (dddd, $J = 16.8, 10.2, 7.8, 6.6$ Hz, 1H), 5.04 (d, $J = 16.8$ Hz, 1H), 5.01 (d, $J = 10.2$ Hz, 1H), 4.28 (d, $J = 5.4$ Hz, 1H), 4.07 (d, $J = 4.8$ Hz, 1H), 4.04-3.95 (m, 2H), 3.84-3.74 (m, 2H), 2.55-2.49 (m, 2H), 2.33-2.25 (m, 3H), 2.13 (dddd, $J = 9.0, 6.6, 6.6, 3.6$ Hz, 1H), 2.06 (ddd, $J = 5.4, 5.4, 5.4$ Hz, 1H), 1.95 (dd, $J = 12.0, 8.4$ Hz, 1H), 1.81-1.70 (m, 3H), 1.20 (s, 9H), 1.16 (ddd, $J = 12.6, 5.4, 4.2$ Hz, 1H), 0.97 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) ppm 178.7, 177.7, 133.8, 117.8, 86.8, 84.2, 64.3, 60.5, 53.6, 47.2, 45.4, 38.7, 37.5, 35.5, 29.7, 27.4, 27.2, 22.2, 21.2; HRMS (ESI): Exact mass calcd for $\text{C}_{21}\text{H}_{34}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 348.2539, found 348.2533.



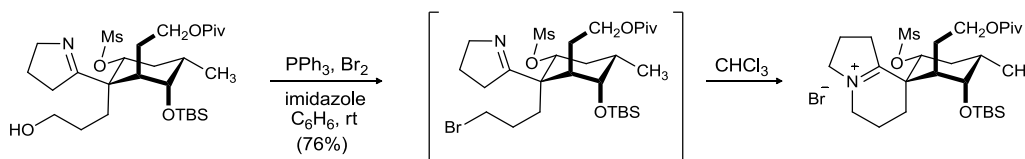
2-((1R,2S,5S)-2-Allyl-6-(*tert*-butyldimethylsilyloxy)-2-(3,4-dihydro-2H-pyrrol-5-yl)-5-methyl-3-(methylsulfonyloxy)cyclohexyl)ethyl pivalate (269).

To a solution of the alcohol (283 mg, 590 μmol) and triethylamine (181 μL , 1.30 mmol) in CH_2Cl_2 (7.0 mL) at 0 $^\circ\text{C}$ was added methanesulfonyl chloride (60.1 μL , 767 μmol). The reaction was stirred for 30 min before it was warmed to rt and stirred for 15 min. The reaction was quenched with satd aq NH_4Cl and extracted with CH_2Cl_2 . The combined organic layers were dried, filtered, and concentrated to a pale yellow oil. Column chromatography (SiO_2 , 10-20% ethyl acetate in hexanes) provided the title product as a thick colorless oil (291 mg, 89%). $R_f = 0.68$ (50% EtOAc/hexanes); $[\alpha]_D^{24} -44.8$ (c 1.45, CHCl_3); IR (film) 3396 (br), 2956, 2928, 2858, 1628 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.73 (dddd, $J = 17.0, 10.0, 8.0, 6.0$ Hz, 1H), 5.31 (dd, $J = 12.0, 5.0$ Hz, 1H), 4.94 (d, $J = 16.5$, Hz, 1H), 4.87 (d, $J = 10.0$ Hz, 1H), 3.98-3.95 (m, 2H), 3.84-3.70 (m, 2H), 3.65 (br s, 1H), 3.48 (br s, 1H), 3.07 (s, 3H), 2.55 (ddd, $J = 8.5, 8.5, 8.5$ Hz, 1H), 2.40 (ddd, $J = 8.5, 8.5, 8.5$ Hz, 1H), 2.33 (dd, $J = 8.5, 8.0$ Hz, 1H), 2.10-1.88 (m, 3H), 1.84-1.78 (m, 2H), 1.65 (br s, 1H), 1.50-1.38 (m, 2H), 1.19 (s, 9H), 0.96 (d, $J = 6.5$ Hz, 3H), 0.93 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) ppm 178.4 (2C), 136.9, 115.5, 83.1, 72.5, 62.1, 59.6, 49.6, 47.9, 40.4, 39.3, 38.7, 34.6, 32.7, 31.1, 27.9, 27.2, 26.0, 22.4, 18.0 (2C), -3.8, -4.9; HRMS (ESI): Exact mass calcd for $\text{C}_{28}\text{H}_{52}\text{NO}_6\text{SSi}$ $[\text{M}+\text{H}]^+$ 558.3285, found 558.3287.



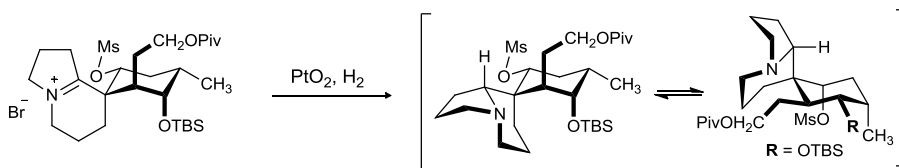
2-((1R,2S,5S)-6-(*tert*-Butyldimethylsilyloxy)-2-(3,4-dihydro-2H-pyrrol-5-yl)-2-(3-hydroxypropyl)-5-methyl-3-(methylsulfonyloxy)cyclohexyl)ethyl pivalate (270).

BH₃·DMS (102 μL, 1.06 mmol) was added to the alkene (279 mg, 504 μmol) in THF (5.0 mL) at 0 °C. The reaction was stirred for 2 h before being warmed to rt and stirred for another 1 h. The reaction was cooled to 0 °C, quenched by the addition of 3 N NaOH (2.0 mL) and 30% H₂O₂ (1.5 mL) and was allowed to stir at rt overnight. The reaction was extracted with EtOAc and the combined organic layers were dried, filtered, and concentrated to an oily solid. The residue was redissolved in CH₂Cl₂ (3 mL) and treated with 4-dimethyl aminopyridine (610 mg, 5.01 mmol) at rt for 7 d before it was filtered, concentrated, and purified via flash column chromatography (SiO₂, 20-40-60% ethyl acetate in hexanes) to yield a colorless oily solid (228 mg, 79%). R_f = 0.24 (50% EtOAc/hexanes); [α]_D²⁴ -18.2 (c 0.55, CHCl₃); IR (film) 2956, 2928, 2858, 1744, 1709 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.29 (br s, 1H), 3.96 (br s, 1H), 3.85-3.81 (m, 2H), 3.68-3.63 (m, 2H), 3.48 (br s, 1H), 3.08 (s, 1H), 3.07 (br s, 1H), 2.81 (br s, 1H), 2.55-2.50 (m, 2H), 2.50-2.45 (m, 1H), 2.07-2.84 (m, 7H), 1.87-1.84 (m, 1H), 1.40-1.36 (m, 1H), 1.19-1.16 (m, 10H), 0.95-0.91 (m, 15H), 0.06 (s, 3H), 0.04 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) ppm 178.4 (2C), 83.6, 72.5, 63.5, 63.0, 59.8, 48.5, 39.3, 38.7, 34.2, 32.9, 32.0, 31.3, 30.3, 28.1, 27.2, 26.0, 22.3, 18.0, 17.9, 14.2, -3.8, -4.9; HRMS (ESI): Exact mass calcd for C₂₈H₅₄NO₇SSi [M+H]⁺ 576.3390, found 576.3395.



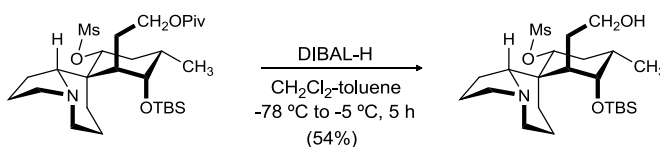
(1*S*,2*R*,4*S*)-3-(*tert*-Butyldimethylsilyloxy)-4-methyl-6-(methylsulfonyloxy)-2-(2-(pivaloyloxy)ethyl)-1',2',3',5',6',7'-hexahydrospiro[cyclohexane-1,8'-indolizin]-4'-ium bromide (272).

Bromine (25.2 μ L, 493 μ mol) was added to a solution of the alcohol (142 mg, 247 μ mol), PPh₃ (67 mg, 249 μ mol), and imidazole (33.5 mg, 493 μ mol) in benzene (8 mL) at rt. After 10 min, the reaction was quenched with satd aq Na₂S₂O₃ and extracted with EtOAc. The combined organic layers were dried, filtered, and concentrated *in vacuo* to provide a pale yellow oily solid. The crude was dissolved in CHCl₃ (5 mL) and allowed to sit for 1 d (until TLC revealed the disappearance of the primary bromide). The solvent was removed and the resulting crude oil was purified by column chromatography (SiO₂, 80% ethyl acetate in hexanes then 5-12% methanol in dichloromethane) to afford the title compound as a colorless oil (120 mg, 76%). R_f = 0.12 (10% MeOH/CH₂Cl₂); $[\alpha]_D^{24}$ -21.4 (c 1.05, CHCl₃); IR (film) 2956, 2928, 2858, 1744, 1709 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.22 (dd, J = 9.0, 4.0 Hz, 1H), 5.85 (dd, J = 21.5, 9.0 Hz, 1H), 4.34-4.20 (m, 2H), 4.18 (ddd, J = 6.0, 6.0, 6.0 Hz, 1H), 4.09 (ddd, J = 6.0, 6.0, 6.0 Hz, 1H), 3.98 (dd, J = 16.0, 7.0 Hz, 1H), 3.75 (br s, 1H), 3.75-3.62 (m, 1H), 3.39 (s, 3H), 3.35-3.22 (m, 1H), 3.01 (br d, J = 13.5 Hz, 1H), 2.52-2.40 (m, 2H), 2.35-2.26 (m, 1H), 2.22 (ddd, J = 12.5, 9.0, 9.0 Hz, 1H), 2.18-2.11 (m, 2H), 2.07 (ddd, J = 13.5, 3.0, 3.0 Hz, 1H), 2.03-1.90 (m, 2H), 1.82-1.73 (m, 1H), 1.71-1.63 (m, 1H), 1.75-1.64 (m, 1H), 1.19 (s, 9H), 0.99 (d, J = 6.0 Hz, 3H), 0.98 (s, 9H), 0.13 (s, 3H), 0.07 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) ppm 193.0, 178.3, 78.2, 72.2, 62.9, 62.3, 49.6, 47.4, 45.8, 40.9, 39.1, 38.7, 31.0, 30.4, 29.7, 28.7, 27.1, 25.7, 19.9, 19.0, 17.9, 16.8, -3.7, -5.0; HRMS (ESI): Exact mass calcd for C₂₈H₅₃NO₆SSi [M-Br]⁺ 558.3285, found 558.3292.



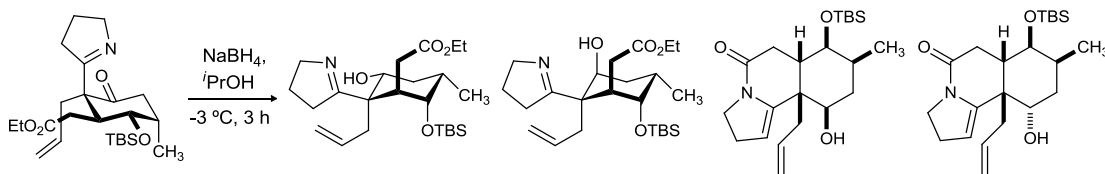
2-((1*S*,4*S*,6*R*)-5-(*tert*-Butyldimethylsilyloxy)-4-methyl-2-(methylsulfonyloxy)hexahydro-1'*H*-spiro[cyclohexane-1,8'-indolizine]-6-yl)ethyl pivalate (273).

PtO₂ (71.0 mg, 313 μmol) was added to the iminium salt (91.1 mg, 143 μmol) in MeOH (4.0 mL) and a balloon atmosphere of hydrogen was administered. After 5 h, the reaction was complete by TLC and was filtered through Celite with MeOH and then concentrated. The crude oil was chromatographed (SiO₂, 5-10% methanol in dichloromethane) to provide the amine as a colorless oil (45.3 mg, 57%). *R_f* = 0.30 (10% MeOH/CH₂Cl₂); [α]_D²⁴ -11.4 (*c* 1.4, CHCl₃); IR (film) 3396 (br), 2956, 2928, 2858, 1628 cm⁻¹; ¹H NMR (600 MHz, MeOD) δ 5.24 (br s, 1H), 4.14-4.06 (m, 2H), 3.88 (dd, *J* = 7.8, 3.6 Hz, 1H), 3.09 (s, 3H), 3.05 (br s, 1H), 2.15-2.14 (m, 1H), 2.12-2.06 (m, 1H), 2.02 (ddd, *J* = 14.4, 4.2, 4.2 Hz, 1H), 1.95 (ddd, *J* = 6.6, 6.6, 6.6 Hz, 1H), 1.91-1.70 (m, 12H), 1.59 (br s, 1H), 1.49 (dddd, *J* = 13.8, 7.2, 7.2, 4.8 Hz, 1H), 1.19 (s, 9H), 1.09 (d, *J* = 6.6 Hz, 3H), 0.93 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ¹³C NMR (150 MHz, MeOD) ppm 178.6, 82.0, 71.6, 64.8, 63.6, 53.1, 46.7, 42.0, 40.9, 39.2, 31.3, 30.2, 29.7, 27.2, 25.9, 25.8, 25.7, 23.7, 18.9 (2C), 18.5, 17.9, -3.6, -4.9; HRMS (ESI): Exact mass calcd for C₂₈H₅₄NO₆SSi [M+H]⁺ 560.3434, found 560.3441.



(1*S*,2*R*,4*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-(2-hydroxyethyl)-4-methylhexahydro-1'*H*-spiro[cyclohexane-1,8'-indolizine]-6-yl methanesulfonate (274).

To a solution of the ester (42.2 mg, 75.0 μmol) in CH_2Cl_2 -toluene (1:1, 4.0 mL) at 78 $^\circ\text{C}$ was added DIBAL (375 μL , 375 μmol , 1.0 M solution in toluene). The reaction was stirred for 30 min before being warmed to -5 $^\circ\text{C}$ and stirred for 5 h. The reaction was quenched with satd aq NH_4Cl and extracted with CH_2Cl_2 . The combined organic layers were dried, filtered, and concentrated to a pale yellow oil. Column chromatography (SiO_2 , 10-15% methanol in dichloromethane) provided the alcohol as a yellow oil (18.0 mg, 54%). $R_f = 0.11$ (10% MeOH/ CH_2Cl_2); $[\alpha]_D^{24} -32.1$ (c 0.95, CHCl_3); IR (film) 3396 (br), 2956, 2928, 2858, 1628 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 4.72 (br d, $J = 6.0$ Hz 1H), 3.82 (br d, $J = 10.8$ Hz 1H), 3.70 (s, 1H), 3.65 (dd, $J = 7.8, 2.4$ Hz, 1H), 3.40 (br s, 1H), 3.35-3.31 (m, 1H), 3.06 (s, 3H), 2.79 (br d, $J = 18.0$ Hz, 1H), 2.71 (br s, 1H), 2.60 (br t, $J = 10.8$ Hz, 1H), 2.35-2.28 (m, 2H), 2.22-1.85 (m, 7H), 1.72-1.60 (m, 5H), 0.94 (d, $J = 6.0$ Hz, 3H), 0.91 (s, 9H), 0.88-0.81 (m, 1H), 0.28 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) ppm 82.2, 73.4, 65.2, 60.6, 53.0, 46.8, 42.0, 41.4, 40.8, 31.9, 31.3, 31.2, 30.4, 26.0, 22.7, 19.1, 18.0 (2C), 14.1, -3.9, -5.0; HRMS (EI): Exact mass calcd for $\text{C}_{23}\text{H}_{46}\text{NO}_5\text{SSi}$ $[\text{M}+\text{H}]^+$ 476.2866, found 476.2863.



Ethyl 2-((1*S*,2*S*,5*S*,6*S*)-2-allyl-6-(*tert*-butyldimethylsilyloxy)-2-(3,4-dihydro-2*H*-pyrrol-5-yl)-3-hydroxy-5-methylcyclohexyl)acetate (279).

To the ketone (61.0 mg, 140 μmol) in isopropanol (2.5 mL) at $-3\text{ }^{\circ}\text{C}$ was added NaBH_4 (7.40 mg, 196 μmol) and the reaction was stirred for 3 h. The reaction was quenched with butyraldehyde (20.6 μL , 240 μmol), and allowed to warm to rt for 20 min. The reaction mixture was extracted with EtOAc and the combined organic layers were dried, filtered, and concentrated to a pale yellow oil. Column chromatography (SiO_2 , 10-15-20-25-30-50-70% ethyl acetate in hexanes) provided the desired alcohol (38.3 mg, 63%), epimeric alcohol (12.8 mg, 21%), tricyclic enamide (3.0 mg, 5%), and the epimeric tricyclic enamide (2.1 mg, 3%).

Data for α -alcohol **279**

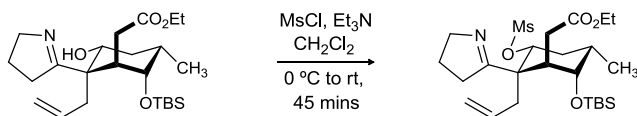
$R_f = 0.50$ (50% EtOAc/hexanes); $[\alpha]_D^{24} -11.4$ (c 1.85, CHCl_3); IR (film) 3358 (br), 2955, 2927, 2855, 1728 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.99-5.91 (dddd, $J = 18.0, 10.8, 10.8, 6.0$ Hz, 1H), 4.83 (d, $J = 17.0$ Hz, 1H), 4.76 (d, $J = 10.0$ Hz, 1H), 4.17-4.06 (m, 3H), 3.77-3.71 (m, 2H), 3.57 (br s, 1H), 3.35 (dd, $J = 15.0, 6.0$ Hz, 1H), 2.48-2.43 (m, 3H), 2.21 (dd, $J = 15.5, 9.0$ Hz, 1H), 2.15 (dd, $J = 16.5, 11.5$ Hz, 1H), 1.88 (dd, $J = 16.5, 1.0$ Hz, 1H), 1.86-1.65 (m, 4H), 1.57 (ddd, $J = 13.5, 3.0, 3.0$ Hz, 1H), 1.26 (t, $J = 7.0$ Hz, 3H), 0.93 (d, $J = 7.0$ Hz, 3H), 0.90 (s, 9H), 0.16 (s, 3H), 0.01 (s, 3H), -OH proton not observed; ^{13}C NMR (125 MHz, CDCl_3) ppm 183.4, 172.6, 137.9, 114.3, 73.9, 71.6, 60.7, 59.4, 50.5, 45.5, 39.4, 34.7, 34.1, 31.8, 31.3, 26.0, 22.1, 18.1, 18.0, 14.2, -4.0, -5.4; HRMS (ESI): Exact mass calcd for $\text{C}_{24}\text{H}_{44}\text{NO}_4\text{Si}$ $[\text{M}+\text{H}]^+$ 438.3040, found 438.3028.

Data for β -alcohol **249**: $R_f = 0.62$ (50% EtOAc/hexanes); $[\alpha]_D^{24} +65.3$ (c 1.0, CHCl_3); IR (film) 3385 (br), 2949, 2932, 2862, 1730 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.66 (br s,

1H), 5.49-5.36 (m, 1H), 4.98 (d, $J = 17.2$ Hz, 1H), 4.94 (d, $J = 10.9$ Hz, 1H), 4.20 (br s, 1H), 4.14 (dq, $J = 10.8, 7.1$ Hz, 1H), 4.09 (dq, $J = 10.8, 7.1$ Hz, 1H), 3.95-3.86 (m, 1H), 3.82-3.72 (m, 1H), 3.67 (br s, 1H), 3.33 (dd, $J = 15.2, 8.2$ Hz, 1H), 2.63 (dd, $J = 16.9, 11.4$ Hz, 1H), 2.57-2.45 (m, 2H), 2.34 (br d, $J = 11.4$ Hz, 1H), 2.26-2.19 (m, 1H), 2.18 (dd, $J = 16.1, 6.0$ Hz, 1H), 1.97 (br d, $J = 17.0$ Hz, 1H), 1.90-1.70 (m, 3H), 1.50 (ddd, $J = 14.0, 3.0, 3.0$ Hz, 1H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.01-0.88 (m, 12H), 0.19 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) ppm 183.6, 173.4, 134.4, 116.9, 74.6, 69.4, 60.4, 59.6, 48.0, 44.1, 41.8, 36.3, 33.9, 30.1, 26.0, 25.1, 21.9, 18.3, 18.1, 14.2, -3.9, -5.3; HRMS (EI): Exact mass calcd for $\text{C}_{24}\text{H}_{43}\text{NO}_4\text{Si}$ $[\text{M}]^+$ 437.2956, found 437.2949.

Data for cyclic enamide **282**: See **250** for characterization data

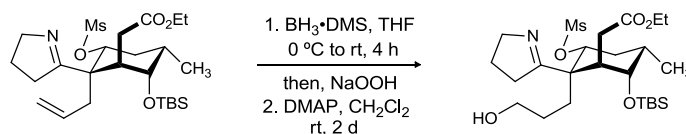
Data for epimeric cyclic enamide . See **283** for characterization data.



Ethyl 2-((1*S*,2*S*,5*S*)-2-allyl-6-(*tert*-butyldimethylsilyloxy)-2-(3,4-dihydro-2*H*-pyrrol-5-yl)-5-methyl-3-(methanesulfonyloxy)cyclohexyl) acetate (280**).**

To a solution of the alcohol (283 mg, 647 μmol) and triethylamine (198 μL , 1.42 mmol) in CH_2Cl_2 (15 mL) at 0 $^\circ\text{C}$ was added methanesulfonyl chloride (65.1 μL , 842 μmol). The reaction was stirred for 30 min before it was warmed to rt and stirred for 15 min. The reaction was quenched with satd aq NH_4Cl and extracted with CH_2Cl_2 . The combined organic layers were dried, filtered, and concentrated to a pale yellow oil. Column chromatography (SiO_2 , 10-20% ethyl acetate in hexanes) provided the title compound as a pale yellow oil (328 mg, 98%). $R_f = 0.64$ (50% EtOAc/hexanes); $[\alpha]_D^{24} -26.2$ (c 1.45,

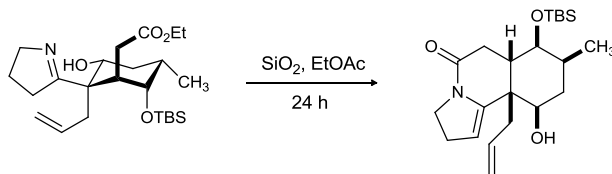
CHCl₃); IR (film) 2956, 2930, 1731, 1343, 1173 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 5.74-5.68 (dddd, *J* = 16.8, 9.9, 7.8, 6.0 Hz, 1H), 5.23 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.92 (d, *J* = 17.2 Hz, 1H), 4.84 (d, *J* = 10.2 Hz, 1H), 4.14-4.01 (m, 2H), 3.77-3.70 (m, 2H), 3.52 (br s, 1H), 3.44 (br d, *J* = 12.6, 1H), 3.03 (s, 3H), 2.54-2.50 (m, 2H), 2.36 (dd, *J* = 16.2, 7.8 Hz, 1H), 2.31 (dd, *J* = 16.8, 8.4 Hz, 1H), 2.08-1.98 (m, 3H), 1.94 (ddd, *J* = 13.2, 4.2, 4.2 Hz, 1H), 1.90-1.82 (m, 1H), 1.80-1.70 (m, 2H), 1.21 (t, *J* = 7.2 Hz, 3H), 0.98-0.93 (m, 12H), 0.15 (s, 3H), 0.00 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) ppm 178.2, 172.2, 136.8, 115.5, 82.8, 73.4, 60.7, 59.5, 48.9, 46.5, 39.9, 39.1, 34.5, 34.3, 32.5, 31.1, 25.9, 22.3, 17.9, 17.6, 14.1, -4.1, -5.4; HRMS (ESI): Exact mass calcd for C₂₅H₄₆NO₆SSi [M+H]⁺ 516.2815, found 516.2811.



Ethyl 2-((1*S*,2*S*,5*S*)-6-(*tert*-butyldimethylsilyloxy)-2-(3,4-dihydro-2*H*-pyrrol-5-yl)-2-(3-hydroxypropyl)-5-methyl-3-(methylsulfonyloxy)cyclohexyl) acetate (281).

BH₃·DMS (119 μL, 1.26 mmol) was added to the alkene (309 mg, 601 μmol) in THF (6.0 mL) at 0 °C. The reaction was stirred for 2 h before it was warmed to rt and stirred for another 1 h. The reaction was cooled to 0 °C, quenched by the addition of 3 N NaOH (2.4 mL) and 30% H₂O₂ (1.8 mL) and was allowed to stir at rt overnight. The reaction was extracted with EtOAc and the combined organic layers were dried, filtered, and concentrated to an oily solid. The residue was redissolved in CH₂Cl₂ (3 mL) and treated with 4-dimethyl aminopyridine (732 mg, 6.01 mmol) at rt for 2 d before it was filtered, concentrated, and purified via flash column chromatography (SiO₂, 20-40-60% ethyl acetate in hexanes) to yield a colorless oily solid (141 mg, 44%) in addition to the alkene

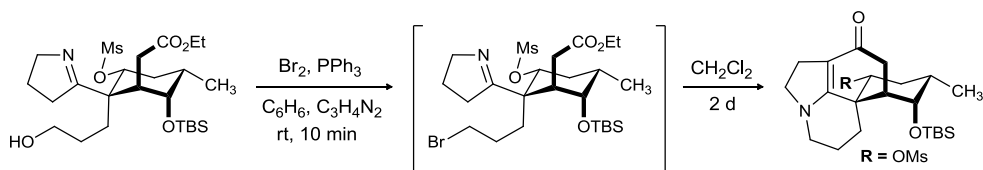
(44.7 mg, 14%). $R_f = 0.20$ (50% EtOAc/hexanes); $[\alpha]_D^{24} -41.1$ (c 0.9, CHCl_3); IR (film) 2955, 2930, 2856, 1730, 1633, 1336, 1292, 1172 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.23 (br d, $J = 8.0$ Hz, 1H), 4.12 (dq, $J = 11.0, 7.0$ Hz, 1H), 4.08 (dq, $J = 10.8, 7.2$ Hz, 1H), 3.81 (br t, $J = 6.0$, 2H), 3.61 (ddd, $J = 9.5, 7.0, 7.0$ Hz, 1H), 3.53 (br s, 1H), 3.47 (ddd, $J = 9.5, 7.0, 7.0$ Hz, 1H), 3.07 (s, 3H), 2.83 (br s, 1H), 2.58-2.48 (m, 2H), 2.45-2.34 (m, 1H), 2.10-2.02 (m, 3H), 1.99 (br s, 1H), 1.94-1.78 (m, 4H), 1.72-1.50 (m, 2H), 1.22 (t, $J = 7.0$ Hz, 3H), 1.19-1.09 (m, 1H), 0.95-0.93 (m, 12H), 0.16 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) ppm 178.6, 172.4, 83.4, 73.6, 63.4, 60.8, 59.8, 47.6, 39.2, 34.6, 34.2, 32.8, 31.6, 31.4, 30.3, 29.7, 26.0, 22.3, 18.0, 17.7, 14.2, -4.0, -5.3; HRMS (ESI): Exact mass calcd for $\text{C}_{25}\text{H}_{48}\text{NO}_7\text{SSi}$ $[\text{M}+\text{H}]^+$ 534.2921, found 534.2910.



(6a*S*,7*S*,8*S*,10*R*,10a*S*)-10a-Allyl-7-(*tert*-butyldimethylsilyloxy)-10-hydroxy-8-methyl-2,3,6a,7,8,9,10,10a-octahydropyrrolo[2,1-*a*]isoquinolin-5-(6*H*)-one (283).

SiO_2 (500 mg) was added to the alcohol (20.0 mg, 45.8 μmol) in EtOAc (1.0 mL) at rt and the reaction was stirred for 24 h. The reaction was concentrated *in vacuo* and the residual solid was purified via flash column chromatography (SiO_2 , 40-70% ethyl acetate in hexanes) to afford the desired product as a colorless oil (17 mg, 91%). : $R_f = 0.12$ (50% EtOAc/hexanes); $[\alpha]_D^{24} -19.0$ (c 1.0, CHCl_3); IR (film) 3396 (br), 2956, 2928, 2858, 1628 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 5.85-5.73 (m, 1H), 5.13-5.03 (m, 2H), 4.84 (br s, 1H), 3.96 (br s, 1H), 3.88-3.85 (m, 2H), 3.43 (br s, 1H), 2.82-2.12 (m, 7H), 2.12-1.75 (m, 3H), 1.70 (dd, $J = 13.8, 5.4$ Hz, 1H), 1.09 (br s, 3H), 0.90 (s, 9H), 0.45 (s, 3H), 0.02 (s,

3H); ^{13}C NMR (150 MHz, CDCl_3) ppm 165.7, 142.2, 134.1, 118.1, 106.8, 72.8, 68.7, 47.0, 44.4, 43.1, 39.8, 32.9, 29.7, 27.2, 27.0, 26.0, 18.1, 14.1, -4.5, -5.0; HRMS (EI): Exact mass calcd for $\text{C}_{22}\text{H}_{38}\text{NO}_3\text{Si}$ $[\text{M}+\text{H}]^+$ 392.2621, found 392.2621.

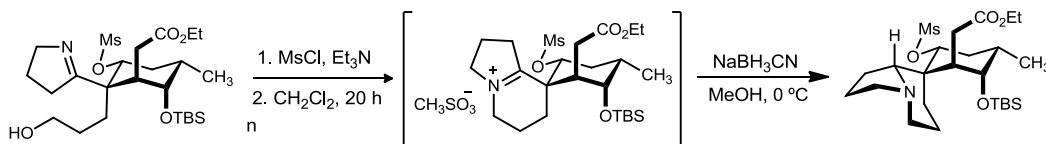
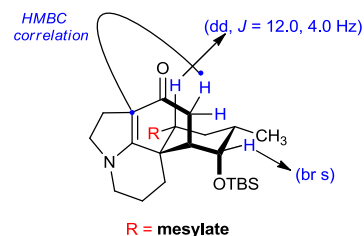


(8a*R*,9*R*,10*S*,12*S*)-9-(*tert*-Butyldimethylsilyloxy)-10-methyl-7-oxo-1,2,3,5,6,7,8,8a,9,10,11,12-dodecahydrobenzo[*e*]pyrrolo[3,2,1-*ij*]quinolin-12-ylmethanesulfonate (286).

Bromine (12.8 μL , 249 μmol) was added to a solution of the alcohol (66.0 mg, 124 μmol), PPh_3 (67 mg, 249 μmol), and imidazole (16.9 mg, 249 μmol) in benzene (4 mL) at rt. After 10 min, the reaction was quenched with satd aq $\text{Na}_2\text{S}_2\text{O}_3$ and extracted with EtOAc. The combined organic layers were dried, filtered, and concentrated *in vacuo* to provide a pale yellow oily solid. The crude was dissolved in CH_2Cl_2 (5 mL) and allowed to sit for 2 d (until TLC revealed the disappearance of the primary bromide). SiO_2 (500 mg) was added to the reaction and stirred for 24 h. The solvent was removed and the resulting crude solid was purified by column chromatography (SiO_2 , 80% ethyl acetate in hexanes then 5-12% methanol in dichloromethane) to afford the vinylogous amide as a pale yellow oil (36 mg, 62%). $R_f = 0.43$ (10% MeOH/ CH_2Cl_2); $[\alpha]_D^{24} -45.3$ (c 0.75, CHCl_3); IR (film) 2956, 2928, 2858, 1744, 1709 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.23 (dd, $J = 12.0, 4.0$ Hz, 1H), 3.64 (ddd, $J = 11.5, 11.5, 4.0$ Hz, 1H), 3.50 (br s, 1H), 3.36-3.25 (m, 2H), 2.93-2.82 (m, 5H), 2.58 (ddd, $J = 14.5, 11.5, 11.5$ Hz, 1H), 2.42-2.30

(m, 2H), 2.30-2.22 (m, 2H), 2.15-2.09 (m, 1H), 2.06 (ddd, $J = 12.0, 12.0, 12.0$ Hz, 1H), 1.86 (ddd, $J = 12.0, 3.5, 3.5$ Hz, 1H), 1.75-1.64 (m, 1H), 1.42 (ddd, $J = 9.5, 9.5, 4.5$ Hz, 1H), 0.98 (d, $J = 6.5$ Hz, 3H), 0.91 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) ppm 187.2, 170.6, 180.9, 85.8, 73.3, 54.8, 50.6, 46.8, 39.4, 38.3, 37.3, 32.1, 32.0, 29.6, 28.6, 26.0, 23.5, 20.0, 18.1, 17.6, -4.1, -5.1; HRMS (ESI): Exact mass calcd for $\text{C}_{23}\text{H}_{40}\text{NO}_5\text{SSi}$ $[\text{M}+\text{H}]^+$ 470.2397, found 470.2392.

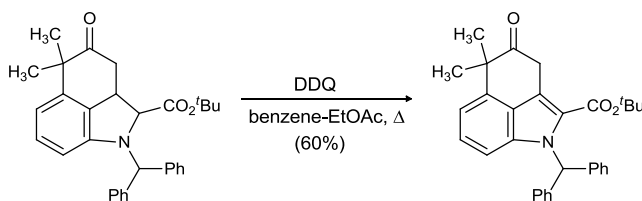
A HMBC correlation was observed between the geminal quaternary carbon and geminal methylene protons to the vinylogous amide ketone. Other coupling constants, including the hydrogen adjacent to the TBS and mesylate, establish the chair conformation of the cyclohexane ring.



Ethyl 2-((1S,4S,5R,6R)-5-(*tert*-butyldimethylsilyloxy)-4-methyl-2-(methylsulfonyloxy) hexahydro-1'*H*-spiro[cyclohexane-1,8'-indolizine]-6-yl)acetate(291).

To a solution of the alcohol (50.0 mg, 93.6 μmol) and triethylamine (26.0 μL , 186 μmol) in CH_2Cl_2 (1 mL) at 0 $^\circ\text{C}$ was added methanesulfonyl chloride (12.4 μL , 159 μmol). The reaction was stirred for 40 min and quenched with satd aq NH_4Cl . This reaction mixture was stirred for 24 h and then extracted with CH_2Cl_2 . The combined organic layers were dried, filtered, and concentrated *in vacuo* to provide a white solid. The crude iminium salt was dissolved in MeOH (2 mL) and the solution was cooled to 0 $^\circ\text{C}$. NaBH_3CN (17.3

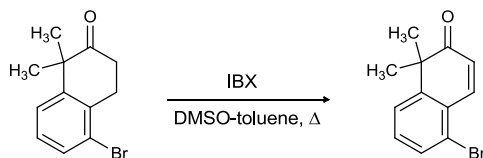
mg, 275 μmol) was added to the solution and the reaction was stirred for 30 minutes. The reaction was poured into H_2O (10 mL) and extracted with CH_2Cl_2 . The combined organic layers were washed with satd aq NaHCO_3 , and then dried, filtered, and concentrated *in vacuo* to provide a yellow oil. Column chromatography (SiO_2 , 80% ethyl acetate in hexanes then 5-12% methanol in dichloromethane) furnished the tertiary amine as a yellow oil (47.9 mg, 97%). $R_f = 0.29$ (10% $\text{MeOH}/\text{CH}_2\text{Cl}_2$); $[\alpha]_D^{24} -6.8$ (c 2.35, CHCl_3); IR (film) 2954, 2927, 2855, 1733, 1252 cm^{-1} ; The ^1H NMR experiment resulted in poorly resolved, broad peaks, and as a result the amine could not be characterized; HRMS (ESI): Exact mass calcd for $\text{C}_{25}\text{H}_{48}\text{NO}_6\text{SSi}$ $[\text{M}+\text{H}]^+$ 518.2972, found 518.2991.



***tert*-Butyl 2-benzhydryl-6,6-dimethyl-7-oxo-2,6,7,8-tetrahydrobenzo[*cd*]indole-1-carboxylate (448).**

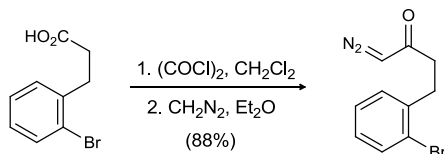
A solution of indoline (100 mg, 214 μmol) and DDQ (51.0 mg, 225 μmol) in EtOAc-benzene (1:2, 2 mL) was stirred for 8 hours at 60 $^\circ\text{C}$. The reaction mixture was then cooled to room temperature, diluted with EtOAc, and washed with satd aq NaHCO_3 , dried, filtered, and concentrated. The resulting yellow residue was purified by flash column chromatography (SiO_2 , 5-15% ether in hexanes) to afford the desired product as a viscous oil (59.8 mg, 60%) in addition to *ca.* 19.6 mg of the indoline (*ca.* 20%). $R_f = 0.44$ (20% $\text{Et}_2\text{O}/\text{hexanes}$); IR (film) 2973, 2925, 1696, 1655, 1604, 1450, 1396, 1368, 1324, 1211, 1171, 1132 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.29 (s, 1H), 7.33-7.28 (m, 6H),

7.23-7.21 (m, 4H), 7.02 (dd, $J = 12.0, 6.5$ Hz, 1H), 6.94 (d, $J = 6.0$ Hz, 1H), 6.50 (d, $J = 7.0$ Hz, 1H), 4.06 (s, 2H), 1.57 (s, 9H), 1.45 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) ppm 211.1, 161.6, 139.9, 139.8, 136.7, 128.4 (2C), 127.4, 126.3, 123.8, 123.6, 118.5, 114.3, 112.2, 81.9, 62.4, 48.1, 38.2, 28.5, 26.3; HRMS (EI): Exact mass calcd for $\text{C}_{31}\text{H}_{30}\text{BrNO}_3$ $[\text{M}]^+$ 465.2304, found 465.2298.



5-Bromo-1,1-dimethylnaphthalen-2(1H)-one (463).

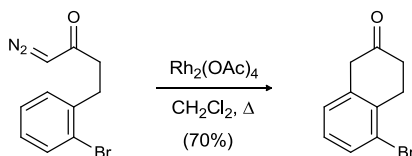
To a solution of 5-bromo-1,1-dimethyl-3,4-dihydronaphthalen-2(1H)-one (2.62 g, 10.3 mmol) in toluene/DMSO (2:1, 140 mL) was added IBX (11.56 g, 41.30 mmol) and the mixture was stirred at 85 °C for 16 h. The reaction mixture was then cooled to room temperature, diluted with Et_2O , and washed with 5% aq NaHCO_3 , H_2O , and brine, and then dried, filtered, and concentrated. The resulting yellow residue was purified by flash column chromatography (SiO_2 , 5-10% ethyl acetate in hexanes) to afford the desired product as a yellow oil (1.92 g, 65%). $R_f = 0.32$ (10% EtOAc /hexanes); IR (film) 2973, 2928, 2867, 1664, 1613, 1583, 1551, 1458, 1438, 1385, 1291, 1216, 1197 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.91 (d, $J = 10.0$ Hz, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.36 (d, $J = 8.0$ Hz, 1H), 7.19 (t, $J = 8.0$ Hz, 1H), 6.18 (d, $J = 10.0$ Hz, 1H), 1.41 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) ppm 203.3, 149.8, 141.9, 131.0, 130.7, 127.6, 125.5 (2C), 124.6, 47.3, 27.6; HRMS (EI): Exact mass calcd for $\text{C}_{12}\text{H}_{11}\text{BrO}$ $[\text{M}]^+$ 249.9993, found 249.9998.



4-(2-Bromophenyl)-1-diazobutan-2-one (464).

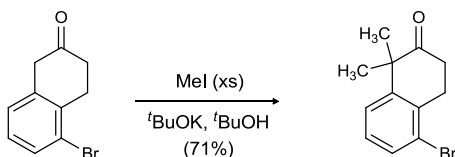
To a 0 °C solution of 3-(2-bromophenyl)propanoic acid (8.00 g, 34.9 mmol) in dichloromethane (0.5 M), was added oxalyl chloride (5.90 mL, 69.8 mmol) over 5 minutes. The solution was slowly warmed to room temperature and stirred until complete conversion was achieved, as evidenced by ¹H NMR. The solvent was removed *in vacuo* to give the title compound, which was used without further purification.

The acid chloride (8.50 g, 34.6 mmol) in diethyl ether (80 mL) was added dropwise over 20 min to an ethereal diazomethane solution [prepared from *N*-methyl-*N*-nitrosourea (14.24 g, 138.2 mmol)], at -40 °C while stirring under nitrogen. The solution was allowed to warm to room temperature, and it was then stirred for an additional 6 h. The ether and residual diazomethane were evaporated under reduced pressure at room temperature, using a rotary evaporator fitted with an acetic acid trap. The resulting yellow residue was purified by flash column chromatography (SiO₂, 15% ethyl acetate in hexanes) to afford the desired product as a yellow oil (7.76 g, 88%). *R_f* = 0.27 (20% EtOAc/hexanes); IR (film) 3087, 2101, 1641 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.51 (d, *J* = 8.0 Hz, 1H), 7.22 (m, 2H), 7.06 (m, 1H), 5.27 (s, 1H), 3.05 (t, *J* = 4.5 Hz, 2H), 2.62 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) ppm 193.5, 139.8, 132.8, 130.6, 128.0, 127.61, 124.2, 54.5, 40.5, 31.4; HRMS (EI): Exact mass calcd for C₁₀H₉BrO [M]⁺ 223.9837, found 223.9839.



5-Bromo-3,4-dihydronaphthalen-2(1H)-one (466).

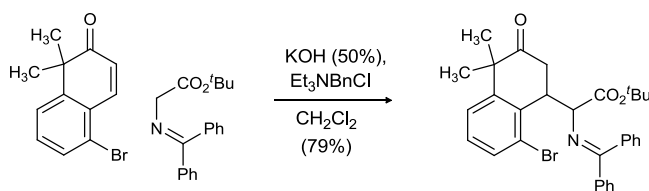
The α -diazo ketone (7.70 g, 30.4 mmol) in CH_2Cl_2 (200 mL) was added dropwise over 1 h to a refluxing solution of rhodium(II) acetate (80 mg, 180 μmol) in CH_2Cl_2 (2 L). The reaction was monitored by TLC and was complete once the diazoketone had been added. The solution was cooled, washed with water and satd aq NaHCO_3 , dried, and concentrated to 500 mL solution. This solution was treated with trifluoroacetic acid (3 mL) and the solution was stirred for 4 h at room temperature, washed with water and satd aq NaHCO_3 , and dried. After solvent removal, the red residue was purified by flash column chromatography (SiO_2 , 5-10% ethyl acetate in hexanes) to afford the desired product as a viscous oil (4.80 g, 70%). $R_f = 0.30$ (10% EtOAc/hexanes); IR (film) 2960, 2923, 1705, 1393, 1301 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.45 (dd, $J = 6.0, 3.0$ Hz, 1H), 7.04 (m, 2H), 3.57 (s, 2H), 3.20 (t, $J = 6.5$ Hz, 2H), 2.53 (t, $J = 6.5$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) ppm 211.1, 136.1, 135.3, 130.9, 128.1, 127.5, 123.7, 45.0, 37.6, 28.0; HRMS (EI): Exact mass calcd for $\text{C}_{10}\text{H}_9\text{BrO}$ $[\text{M}]^+$ 223.9837, found 223.9840.



5-Bromo-1,1-dimethyl-3,4-dihydronaphthalen-2(1H)-one (472).

To a 0 $^\circ\text{C}$ solution of β -tetralone (800 mg, 4.36 mmol) in *tert*-butanol (7 mL), was added potassium *tert*-butoxide (480 mg, 4.28 mmol) in small portions over 10 minutes. The

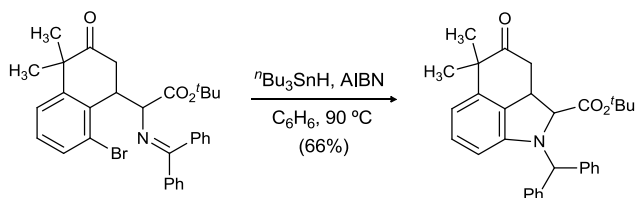
reaction was stirred for 10 minutes at 0 °C, and methyl iodide (357 μ L, 7.14 mmol) in THF (1 mL) was added to the solution. The reaction was allowed to warm to room temperature and the reaction stirred for 2 h at room temperature. MeI (268 μ L, 5.36 mmol) in THF (1mL) was added to the solution and the reaction stirred for another 6 h at room temperature. The reaction was quenched with satd aq NH_4Cl , the layers were separated, and the aqueous layer was extracted with Et_2O . The combined organic layers were washed with water, dried, filtered, and concentrated. The resulting red residue was purified by flash column chromatography (SiO_2 , 5-10% ethyl acetate in hexanes) to afford the dimethylated product as a colorless oil (634 mg, 71% yield). $R_f = 0.34$ (10% EtOAc/hexanes); IR (film) 2971, 2929, 2867, 1716, 1560, 1461, 1301 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.45 (dd, $J = 8.0, 0.5$ Hz, 1H), 7.31 (d, $J = 8.0$ Hz, 1H), 7.13 (t, $J = 8.0$ Hz, 1H), 3.22 (t, $J = 7.0$ Hz, 2H), 2.70 (t, $J = 7.0$ Hz, 2H), 1.43 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) ppm 213.7, 146.1, 134.6, 130.7, 128.3, 125.6, 124.4, 47.7, 36.5, 28.7, 27.2; HRMS (EI): Exact mass calcd for $\text{C}_{12}\text{H}_{13}\text{BrO}$ $[\text{M}]^+$ 252.0150, found 252.0144.



***tert*-Butyl 2-(8-bromo-4,4-dimethyl-3-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)-2-(diphenylmethyleneamino)acetate (473).**

The enone (50.0 mg, 199 μ mol), Schiff base (88.0 mg, 119 μ mol), and benzyl triethyl ammonium chloride (13.6 mg, 59.6 μ mol) were dissolved in CH_2Cl_2 (1 mL). 50% KOH (140 μ L) was then added and the mixture was stirred vigorously for 8 h. The reaction

mixture was diluted with CH₂Cl₂, and the organic layer was separated, washed with water, dried (NaSO₄), filtered, and concentrated. Flash column chromatography (SiO₂, 5-15% ether in hexanes) of the resulting oil furnished the desired Michael adduct as a white solid (85.4 mg, 79%) in addition to *ca.* 6.1 mg of the enone (*ca.* 12%). A single diastereomer was detected by ¹H NMR. mp 172-174 °C; R_f = 0.20 (20% Et₂O/hexanes); IR (film) 3059, 2976, 2918, 2849, 1719, 1623, 1447, 1368, 1266, 1152 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.47 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 7.0 Hz, 2H), 7.32 (m, 2H), 7.28-7.21 (m, 5H), 7.15 (t, *J* = 8.0 Hz, 1H), 6.36 (d, *J* = 5.0 Hz, 2H), 4.50 (d, *J* = 2.0 Hz, 1H), 4.41 (m, 1H), 2.95 (m, 2H), 1.43 (s, 9H), 1.33 (s, 3H), 1.12 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) ppm 210.9, 172.5, 169.1, 148.5, 138.8, 136.2, 133.6, 130.9, 130.4, 130.1, 129.5, 128.7, 128.2 (2C), 127.7, 127.1, 126.9, 124.8, 81.7, 67.8, 47.0, 44.1, 38.2, 33.5, 29.7, 28.1, 25.7; HRMS (ESI): Exact mass calcd for C₃₁H₃₂BrNO₃Na [M+Na]⁺ 568.1463, found 568.1440.

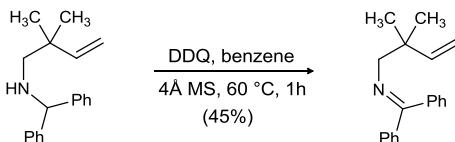


***tert*-Butyl 1-benzhydryl-5,5-dimethyl-4-oxo-1,2,2a,3,4,5-hexahydrobenzo[*cd*]indole-2-carboxylate (474).**

To a refluxing (90 °C) benzene (12 mL) solution of the ketimine (65.0 mg, 119 μmol) and ⁿBu₃SnH (34.1 μL, 125 μmol) was added AIBN (23.6 mg, 143 μmol) and ⁿBu₃SnH (34.1 μL, 125 μmol) dissolved separately in benzene (1 mL) via a syringe pump over 4 h. The solution was stirred for an additional 6 h at 90 °C and the solvent was removed in

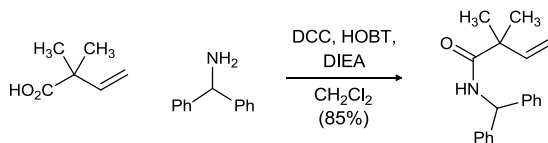
vacuo. The residue was treated with a 1:1 (v/v) solution of Et₂O (5 mL) and satd aq KF,⁶ and the mixture was stirred vigorously until a white solid precipitated. The organic layer was washed with water, dried (NaSO₄), filtered, and concentrated. The resulting white residue was purified by flash column chromatography (SiO₂, 15% ether in hexanes) to afford the product as a viscous oil (36 mg, 66%) in addition to *ca.* 8.5 mg of the aryl bromide (*ca.* 13%). The indoline was characterized as a 5:3 ratio of diastereomers (¹H NMR). R_f = 0.33 (20% Et₂O/hexanes); IR (film) 2975, 2927, 2855, 1730, 1711, 1596, 1454, 1367, 1276, 1238, 1217, 1150 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.55 (d, *J* = 7.5 Hz, 2H), 7.50 (d, *J* = 7.5 Hz, 2H), 7.40-7.36 (m, 4H), 7.32-7.20 (m, 12H), 6.96-6.90 (m, 2H), 6.63 (d, *J* = 7.5 Hz, 1H), 6.59 (d, *J* = 7.5 Hz, 1H), 5.96 (d, *J* = 7.5 Hz, 1H), 5.78 (d, *J* = 7.5 Hz, 1H), 5.59 (s, 1H), 5.55 (s, 1H), 4.20 (d, *J* = 9.5 Hz, 1H), 3.94 (d, *J* = 9.5 Hz, 1H), 3.89 (ddd, *J* = 11.0, 11.0, 5.5 Hz, 1H), 3.61 (ddd, *J* = 11.0, 11.0, 5.5 Hz, 1H), 2.91 (dd, *J* = 15.5, 5.5 Hz, 1H), 2.75 (dd, *J* = 15.5, 5.5 Hz, 1H), 2.52 (dd, *J* = 16.0, 12.0 Hz, 1H), 2.43 (dd, *J* = 16.0, 12.0 Hz, 1H), 1.45 (s, 3H), 1.39 (s, 3H), 1.38 (s, 9H), 1.36 (s, 3H), 1.32 (s, 3H), 1.27 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) ppm 214.2, 213.5, 171.6, 169.3, 149.7, 149.6, 142.6, 140.5 (2C), 139.8, 139.5, 139.0, 130.4, 129.5, 129.4, 129.1, 128.8, 128.7, 128.4, 128.3, 127.6 (2C), 127.4, 127.0, 126.7, 126.4, 125.9, 114.8, 114.7, 107.7, 107.6, 81.8, 81.6, 74.3, 70.7, 67.9, 67.1, 46.9, 46.5, 42.9, 40.9, 40.0, 38.5, 28.0 (2C), 27.3, 26.9, 26.3, 24.6; HRMS (ESI): Exact mass calcd for C₃₁H₃₃NO₃Na [M+Na]⁺ 490.2358, found 490.2376.

⁶ Complete saturation by KF is necessary.



***N*-(Diphenylmethylene)-2,2-dimethylbut-3-en-1-amine (478).**

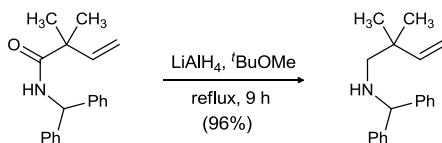
To an anhydrous solution of benzene (18 mL) and crushed 4Å molecular sieves were added the amine (501 mg, 1.88 mmol) and DDQ (430 mg, 1.88 mmol). The reaction mixture was stirred at 60 °C for 1 h. The deep red solution became light orange over the course of the reaction. The solution was cooled to room temperature and quickly filtered through a pad of neutral alumina. The filtrate was concentrated and the resulting red residue was column chromatographed (Al₂O₃, 0-5% diethyl ether in hexanes) to afford the desired product as a pale yellow oil (230 mg, 45%). *R_f* = 0.52 (10% Et₂O/hexanes); IR (film) 3080, 3059, 3023, 2996, 2958, 2925, 2854, 1626, 1463, 1445, 1376, 1313, 1287 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.66 (dd, *J* = 7.5, 1.0 Hz, 2H), 7.65-7.43 (m, 3H), 7.40-7.18 (m, 3H), 7.15 (dd, *J* = 7.5, 1.0 Hz, 2H), 5.97 (dd, *J* = 17.5, 11.0 Hz, 1H), 4.93 (dd, *J* = 17.5, 1.5 Hz, 1H), 4.89 (dd, *J* = 11.0, 1.5 Hz, 1H), 3.17 (s, 2H), 1.04 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) ppm 167.7, 147.5, 140.2, 137.0, 129.7, 128.4 (2C), 128.2, 128.0 (2C), 110.8, 64.3, 38.8, 25.2; HRMS (EI) Exact mass calcd for C₁₉H₂₁N [M]⁺ 263.1674, found 263.1669.



***N*-Benzhydryl-2,2-dimethylbut-3-enamide (483).**

The acid (3.00 g, 17.5 mmol), 1,3-dicyclohexylcarbodiimide (DCC) (3.98 g, 19.3 mmol), and 1-hydroxybenzotriazole (HOBT) (2.61 g, 19.3 mmol) were dissolved in

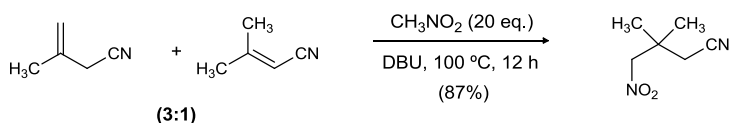
dichloromethane (1 M). Benzhydrylamine (3.02 mL, 17.5 mmol) was added to the solution, and the mixture was stirred at room temperature for 36 h. The reaction was diluted with CH₂Cl₂ (20 mL) and filtered off through a pad of celite. The organic layer was washed with 1 M HCl, brine, and 1 M sodium bicarbonate, then dried (Na₂SO₄), filtered, and concentrated. The crude material was purified by flash column chromatography (SiO₂, 0-15% ethyl acetate in hexanes) to give the product as a colorless oil (4.15 g, 85%). R_f = 0.32 (20% EtOAc/hexanes); IR (film) 3307, 3025, 2978, 1646, 1635, 1523, 1494, 1450 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.33 (t, *J* = 7.5 Hz, 4H), 7.27 (t, *J* = 7.5 Hz, 2H), 7.19 (d, *J* = 7.5 Hz, 4H), 6.32 (d, *J* = 8.0 Hz, 1H), 6.19 (d, *J* = 8.0 Hz, 1H), 6.07 (dd, *J* = 17.5, 10.5 Hz, 1H), 5.29-5.23 (m, 2H), 1.34 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) ppm 174.9, 143.2, 141.6, 128.6, 127.4, 127.2, 114.9, 56.8, 45.4, 24.6; HRMS (EI) Exact mass calcd for C₁₉H₂₁NO [M]⁺ 279.1623, found 279.1616.



***N*-Benzhydryl-2,2-dimethylbut-3-en-1-amine (484).**

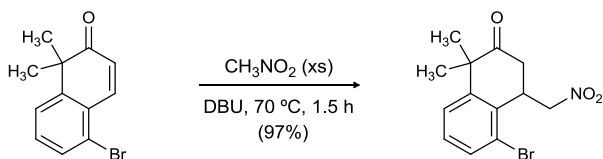
To a 0 °C solution of LiAlH₄ (1.73 g, 45.1 mmol) in *tert*-butyl methyl ether (150 mL) was added the amide (3.15 g, 11.3 mmol) in *tert*-butyl methyl ether (50 mL) dropwise over 20 minutes. The solution was stirred for 9 h at 55 °C. The reaction was quenched with sequential addition of NaF (7.58 g, 180.5 mmol) and water (2.44 mL, 135.4 mmol) at 0 °C, and stirring was continued for an additional 1 h. The resulting gray precipitate was filtered off through a pad of Celite, and the filtrate was concentrated. The resulting oil was column chromatographed (SiO₂, 0-5% ethyl acetate in hexanes) to afford the title

compound as a colorless oil (2.86 g, 96%). $R_f = 0.52$ (10% EtOAc/hexanes); IR (film) 3082, 3061, 3025, 2958, 2928, 2902, 2868, 2810, 1492, 1452 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.44 (d, $J = 7.5$ Hz, 4H), 7.33 (t, $J = 7.5$ Hz, 4H), 7.24 (t, $J = 7.5$ Hz, 2H), 5.84 (dd, $J = 17.5, 11.0$ Hz, 1H), 5.07-5.03 (m, 2H), 4.80 (s, 1H), 2.46 (s, 2H), 1.49 (s, 1H), 1.10 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) ppm 146.9, 144.6, 128.4, 127.2, 126.8, 112.0, 67.9, 58.7, 37.8, 25.2; HRMS (EI) Exact mass calcd for $\text{C}_{19}\text{H}_{23}\text{N}$ $[\text{M}]^+$ 265.1830, found 265.1825.



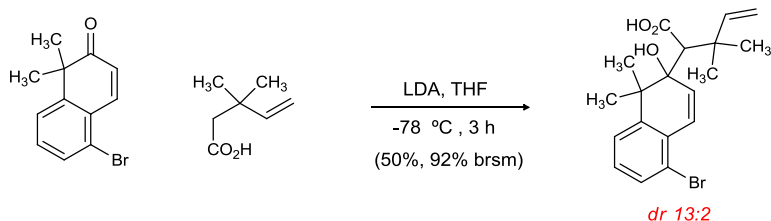
3,3-Dimethyl-4-nitrobutanenitrile (485).

To a solution of isomeric nitriles (3.70 g, 45.6 mmol) in nitromethane (55.7 g, 912 mmol) was added DBU (1.39 g, 9.10 mmol) and the reaction was stirred at 103 °C for 12 h. The reaction mixture was cooled concentrated in *vacuo*. To the resulting residue, dichloromethane (30 mL) and 5% sulfuric acid (30 mL) were added and the solution was stirred for 30 minutes. The reaction was extracted with CH_2Cl_2 and the combined organic layers were dried, filtered, and concentrated. Column chromatography (SiO_2 , 20% ethyl acetate in hexanes) furnished the title product as a colorless oil (6.1 g, 87%). $R_f = 0.22$ (20% EtOAc/hexanes); IR (film) 2974, 2940, 2246, 1553, 1472, 1379 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.36 (s, 2H), 2.55 (s, 2H), 1.21 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) ppm 116.7, 83.4, 34.5, 28.3, 24.8; HRMS (EI): Exact mass calcd for $\text{C}_6\text{H}_{11}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 143.0742, found 143.0815.



5-Bromo-1,1-dimethyl-4-(nitromethyl)-3,4-dihydronaphthalen-2(1H)-one (489).

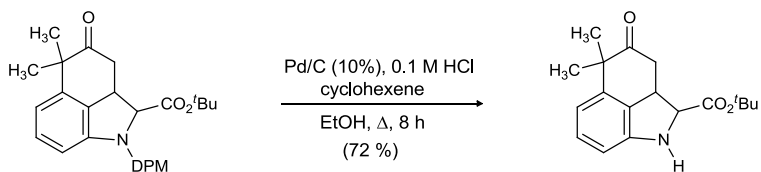
To a solution of enone (38.0 mg, 152 μmol) in nitromethane (164 μL , 3.04 mmol) was added DBU (22.7 μL , 152 μmol) and the reaction was stirred at 70 $^{\circ}\text{C}$ for 1.5 h. The reaction was quenched with satd aq NH_4Cl and extracted with CH_2Cl_2 . The combined organic layers were dried, filtered, and concentrated. Column chromatography (SiO_2 , 20% ethyl acetate in hexanes) furnished the ketone as a yellow solid (46.5 mg, 97%). $R_f = 0.33$ (20% EtOAc/hexanes); mp 112-114 $^{\circ}\text{C}$; IR (film) 2972, 2929, 1717, 1552, 1461, 1280 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.54 (dd, $J = 8.0, 0.8$ Hz, 1H), 7.36 (dd, $J = 8.0, 0.8$ Hz, 1H), 7.24 (dd, 8.0, 8.0 Hz, 1H), 4.61 (ddd, $J = 13.2, 3.2, 1.2$ Hz, 1H), 4.50 (dddd, $J = 11.2, 5.6, 2.8, 2.8$ Hz, 1H), 4.09 (dd, $J = 13.6, 11.2$ Hz, 1H), 3.10 (ddd, $J = 14.0, 6.0, 1.2$ Hz, 1H), 2.72 (dd, $J = 14.0, 2.4$ Hz, 1H), 1.49 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) ppm 211.2, 147.6, 131.7, 130.9, 130.1, 127.2, 124.4, 76.1, 47.5, 39.3, 38.9, 30.3, 29.7; HRMS (EI): Exact mass calcd for $\text{C}_{13}\text{H}_{14}\text{BrNO}_3$ $[\text{M}+\text{H}]^+$ 312.0235, found 312.0220.



2-(5-Bromo-2-hydroxy-1,1-dimethyl-1,2-dihydronaphthalen-2-yl)-3,3-dimethylpent-4-enoic acid (491).

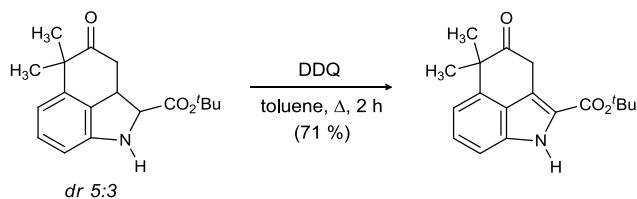
To a -78 °C solution of diisopropylamine (137 μ L, 0.98 mol) in THF (500 μ L) was added n BuLi (391 μ L, 2.5 M solution in THF, 0.98 mol,) dropwise over 3 mins and the mixture was stirred at -78 °C for 30 mins and at 0 °C for additional 20 mins. After return of the reaction to -78 °C, enone (50.0 mg, 0.39 mmol) in THF (150 μ L) was added dropwise over 5 mins. The solution was stirred at -78 °C for 30 mins and at 0 °C for additional 20 mins. The reaction was quenched with satd aq NH_4Cl , the layers were separated, and the aqueous layer was extracted with Et_2O . The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO_2 , 20-40-60-80% ethyl acetate in hexanes) to afford the acid as a pale yellow oil (37.0 mg, 50%) in addition to the enone (21.0 mg, 42%). The acid was characterized as a 6.5:1 ratio of diastereomers by ^1H NMR. $R_f = 0.15$ (80% EtOAc /hexanes); IR (film) 3418, 2966, 2926, 2853, 1714, 1454 cm^{-1} .

Data for major diastereomer: ^1H NMR (600 MHz, CDCl_3) δ 7.41 (dd, $J = 7.8, 1.2$ Hz, 1H), 7.20 (d, $J = 7.8$ Hz, 1H), 7.05 (dd, $J = 7.8, 7.8$ Hz, 1H), 6.68 (d, $J = 10.2$ Hz, 1H), 5.92 (d, $J = 10.2$ Hz, 1H), 5.76 (dd, $J = 18.0, 10.8$ Hz, 1H), 4.90 (d, $J = 17.2$ Hz, 1H), 4.85 (d, $J = 11.4$ Hz, 1H), 1.38 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) ppm 180.7, 149.0, 146.2, 138.1, 131.4, 130.9, 129.0, 127.1, 123.5, 122.4, 110.1, 79.3, 53.0, 46.7, 39.9, 29.7, 25.1, 24.5, 19.7; Exact mass calcd for $\text{C}_{19}\text{H}_{23}\text{BrO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 401.0728, found 401.0718.



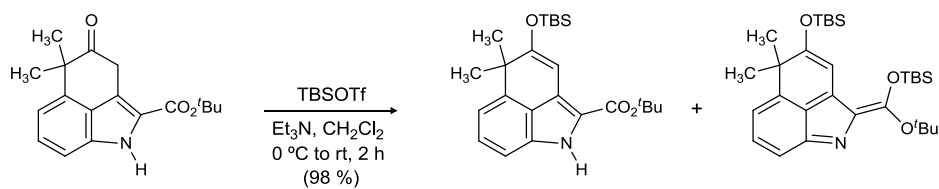
***tert*-Butyl 5,5-dimethyl-4-oxo-1,2,2a,3,4,5-hexahydrobenzo[*cd*]indole-2-carboxylate (493).**

To a solution of indoline (320 mg, 653 μmol) in cyclohexene (7 mL) and ethanol (7 mL) was added aq 1 N HCl (0.65 mL) and 10% Pd/C (320 mg). The reaction was stirred at 80 $^{\circ}\text{C}$ for 8 h and quenched with triethylamine (5 mL). The reaction was filtered through a pad of SiO_2 and the solution was concentrated. Flash column chromatography (SiO_2 , 10-15% ethyl acetate in hexanes) of the resulting oil furnished the disubstituted amine as a light yellow oil (152 mg, 72%). The product was characterized as 5:3 ratio of diastereomers. $R_f = 0.28$ (20% EtOAc/hexanes); IR (film) 3328, 2957, 2924, 2853, 1707 (br), 1457, 1368, 1253, 1155 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.13-7.09 (m, 2H), 6.72-6.69 (m, 2H), 6.62 (d, $J = 7.6$ Hz, 1H), 6.58 (d, $J = 7.6$ Hz, 1H), 4.39 (d, $J = 10.0$ Hz, 1H), 4.38 (br s, 1H), 4.29 (br s, 1H), 4.17 (d, $J = 10.8$ Hz, 1H), 3.95-3.88 (m, 1H), 3.66 (ddd, $J = 11.2, 11.2, 6.0$ Hz, 1H), 3.06 (dd, $J = 16.0, 5.6$ Hz, 1H), 2.96 (dd, $J = 14.4, 5.2$ Hz, 1H), 2.54 (dd, $J = 16.0, 12.0$ Hz, 1H), 2.39 (dd, $J = 14.0, 14.0$ Hz, 1H), 1.53 (s, 9H), 1.46 (s, 3H), 1.45 (s, 9H), 1.42 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) ppm 214.2, 213.6, 171.6, 170.8, 149.1, 147.6, 140.5, 140.3, 129.5, 126.5, 125.2, 115.7, 115.6, 107.8, 107.6, 82.6, 82.2, 70.5, 65.0, 46.8, 46.7, 43.1, 41.4, 39.9, 39.1, 28.2, 28.1, 26.9, 26.8, 25.9, 24.5; HRMS (ESI): Exact mass calcd for $\text{C}_{14}\text{H}_{16}\text{NO}_3$ [$\text{M}-\text{C}_4\text{H}_7$] $^+$ 246.1130, found 246.0760.



***tert*-Butyl 6,6-dimethyl-7-oxo-2,6,7,8-tetrahydrobenzo[*cd*]indole-2-carboxylate (494).**

A solution of indoline (152 mg, 469 μmol) and DDQ (117 mg, 515 μmol) in toluene (7.5 mL) was stirred for 2 h at 80 $^{\circ}\text{C}$. The reaction mixture was filtered through a pad of SiO_2 and the solution was concentrated. The resulting yellow residue was purified by flash column chromatography (SiO_2 , 5-15% ether in hexanes) to afford the desired indole as a viscous oil (107 mg, 71%). $R_f = 0.36$ (20% EtOAc/hexanes); IR (film) 3332, 2962, 2926, 2854, 1702 (br), 1455, 1159 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.98 (br s, 1H), 7.34 (dd, $J = 7.6, 7.6$ Hz, 1H), 7.24 (d, $J = 8.4$ Hz, 1H), 7.02 (d, $J = 7.6$ Hz, 1H), 4.05 (s, 2H), 1.64 (s, 9H), 1.53 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) ppm 210.7, 161.6, 139.9, 133.9, 127.2, 124.6, 122.7, 115.6, 114.5, 109.4, 82.0, 62.4, 48.1, 36.9, 28.4, 26.2; HRMS (EI): Exact mass calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_3$ $[\text{M}]^+$ 299.1521, found 299.1432.



***tert*-Butyl 4-(*tert*-butyldimethylsilyloxy)-5,5-dimethyl-1,5-dihydrobenzo[*cd*]indole-2-carboxylate (495).**

To a 0 $^{\circ}\text{C}$ solution of indole (16.0 mg, 49.7 μmol) and Et_3N (20.7 μL , 149 μmol) in CH_2Cl_2 (0.8 mL) was added TBSOTf (12.5 μL , 54.7 μmol) dropwise over 2 minutes. The reaction was allowed to warm to room temperature and the reaction stirred for 2 h at rt. The reaction was quenched with satd aq NH_4Cl , the layers were separated, and the

aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting orange residue was purified by flash column chromatography (SiO₂, 5-10% ethyl acetate in hexanes) to afford the monosilylated product as a colorless oil (17.6 mg, 81%) in addition to (4.7 mg, 17%) of disilylated product

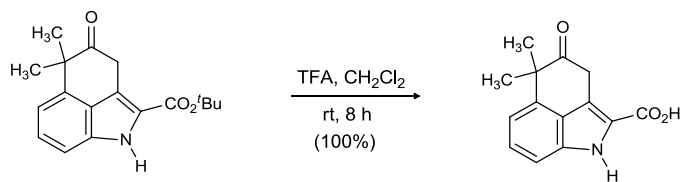
Data for monosilylated product (495):

R_f = 0.54 (20% EtOAc/hexanes); IR (film) 3333, 2925, 2855, 1733, 1456, 1136 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.20 (br s, 1H), 7.28 (dd, *J* = 8.0, 7.6 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.18 (s, 1H), 1.64 (s, 9H), 1.51 (s, 6H), 1.03 (s, 9H), 0.33(s, 6H); ¹³C NMR (150 MHz, CDCl₃) ppm 163.5, 162.4, 142.2, 134.5, 127.3, 123.4, 119.3, 118.9, 114.8, 108.0, 97.1, 80.9, 41.9, 29.7, 28.6, 25.8, 18.3, -4.5; HRMS (EI): Exact mass calcd for C₂₄H₃₅NO₃Si [M]⁺ 413.2386, found 413.2373.

Data for disilylated product (496)

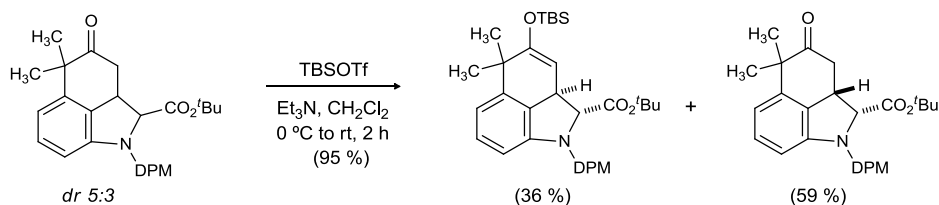
R_f = 0.70 (20% EtOAc/hexanes); IR (film) 2955, 2929, 2857, 1701, 1135 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.21 (d, *J* = 5.2 Hz, 1H), 7.20 (d, *J* = 2.8 Hz, 1H), 6.96 (dd, *J* = 5.2, 2.8 Hz, 1H), 6.16 (s, 1H), 1.63 (s, 9H), 1.50 (s, 6H), 1.15 (s, 9H), 1.02(s, 9H), 0.43 (s, 6H), 0.33(s, 6H); ¹³C NMR (150 MHz, CDCl₃) ppm 163.0, 162.6, 141.9, 141.6, 126.0, 125.9, 125.4, 122.8, 115.1, 112.5, 97.4, 80.4, 41.7, 29.8, 28.7, 27.9, 25.8, 20.1, 18.3, -0.41, -4.5; HRMS (EI): Exact mass calcd for C₃₀H₄₉NO₃Si₂ [M]⁺ 527.3251.⁷

⁷ Highly unstable compound. HRMS could not be obtained



6,6-Dimethyl-7-oxo-2,6,7,8-tetrahydrobenzo[*cd*]indole-2-carboxylic acid (498).

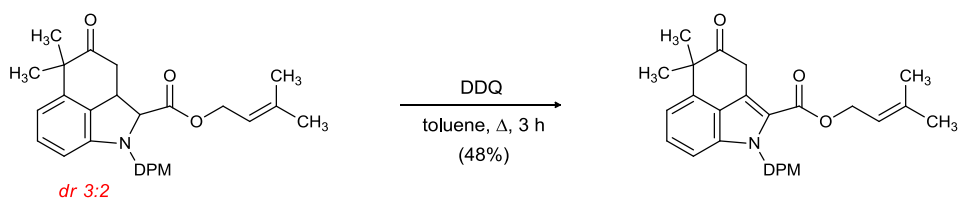
To a solution of trifluoroacetic acid (244 μL , 3.17 mmol) in CH_2Cl_2 (1.0 mL) was added the indoline (51.0 mg, 158 μmol) and the reaction was stirred for 8 h at rt. The reaction was quenched with satd aq NH_4Cl , the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried, filtered, and concentrated to afford the carboxylic acid as a red oil (41.9 mg, 100%). $R_f = 0.42$ (50% EtOAc/hexanes); IR (film) 3306 (br), 2973, 2929, 1691, 1461, 1124 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.31-7.24 (m, 2H), 6.98 (d, $J = 7.0$ Hz, 1H), 4.05 (s, 2H), 1.48 (s, 6H), -NH and -COOH peaks not observed; ^{13}C NMR (125 MHz, CDCl_3) ppm 212.8, 164.9, 140.7, 136.2, 128.1, 125.4, 123.0, 117.3, 115.0, 110.9, 49.3, 37.9, 26.6; HRMS (EI): Exact mass calcd for $\text{C}_{14}\text{H}_{14}\text{ClNO}_3$ $[\text{M}+\text{HCl}]^+$ 279.0662, found 279.0612.



(2*R*, 2*aR*)-tert-Butyl 1-benzhydryl-4-(tert-butyldimethylsilyloxy)-5,5-dimethyl,1,2,2*a*,5-tetrahydrobenzo[*cd*]indole-2-carboxylate (S1).

To a 0 $^\circ\text{C}$ solution of indoline (48.0 mg, 98.1 μmol) and Et_3N (41.0 μL , 294 μmol) in CH_2Cl_2 (1.0 mL) was added TBSOTf (49.5 μL , 216 μmol) dropwise over 2 minutes. The reaction was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with satd aq NH_4Cl , the layers were separated, and the aqueous layer was

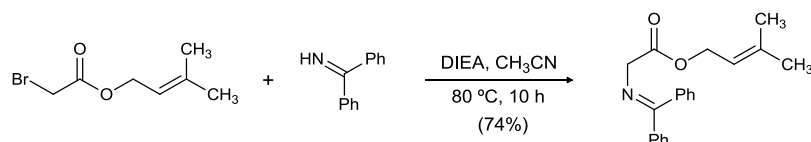
extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 5-10% ethyl acetate in hexanes) to afford the title product as a light yellow oil (20.5 mg, 36%) in addition to the indoline (28.1 mg, 59%). Single diastereomers of the silylated product and recovered indoline were detected respectively by ¹H NMR. R_f = 0.60 (20% EtOAc/hexanes); IR (film) 2954, 2929, 2857, 1742, 1646, 1456, 1216 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.60 (d, *J* = 7.2 Hz, 2H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.30-7.23 (m, 6H), 6.89 (ddd, *J* = 7.8, 7.8, 0.6 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 5.90 (d, *J* = 7.8 Hz, 1H), 5.47 (s, 1H), 4.98 (d, *J* = 1.8 Hz, 1H), 3.88 (d, *J* = 12.0 Hz, 1H), 3.83 (dd, *J* = 12.0, 1.2 Hz, 1H), 1.42 (s, 3H), 1.36 (s, 9H), 1.29 (s, 3H), 0.97 (s, 9H), 0.20 (s, 3H), 0.18 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) ppm 172.3, 159.2, 149.4, 141.3, 141.0, 139.1, 130.9, 128.5 (2C), 128.4, 128.2, 128.1, 127.9, 127.4, 127.1, 114.5, 106.7, 98.9, 80.8, 74.3, 68.2, 42.5, 40.2, 28.5, 28.1, 25.7, 24.1, 18.3, -4.3, -4.9; HRMS (EI): Exact mass calcd for C₃₇H₄₇NO₃Si [M]⁺ 581.3325, found 581.3280.



3-Methylbut-2-en-1-yl 1-benzhydryl-5,5-dimethyl-4-oxo-1,3,4,5-tetrahydrobenzo[cd]indole-2-carboxylate (505).

A solution of indoline (100 mg, 209 μmol) and DDQ (66.0 mg, 292 μmol) in toluene (5.0 mL) was stirred for 3 h at 80 °C. The reaction mixture was filtered through a pad of SiO₂ and the solution was concentrated. The resulting yellow residue was purified by flash column chromatography (SiO₂, 5-15% ether in hexanes) to afford the desired product as a

viscous oil (48.0 mg, 48%). $R_f = 0.54$ (20% EtOAc/hexanes); IR (film) 3061, 3029, 2976, 2928, 1707, 1659, 1448, 1278, 1176 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 8.27 (br s, 1H), 7.32-7.27 (m, 6H), 7.20-7.18 (m, 4H), 7.02 (dd, $J = 8.4, 7.2$ Hz, 1H), 6.94 (d, $J = 7.2$ Hz, 1H), 6.47 (d, $J = 8.4$ Hz, 1H), 5.45 (ddq, $J = 7.2, 7.2, 1.2$ Hz, 1H), 4.79 (d, $J = 7.2$ Hz, 2H), 4.09 (s, 2H), 1.79 (s, 3H), 1.75 (s, 3H), 1.52 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) ppm 211.0, 162.4, 140.0, 139.8, 139.2, 137.6, 137.0, 132.4, 130.1, 128.5, 128.4, 128.3, 127.5, 126.7, 123.6, 122.5, 119.5, 118.4, 114.4, 112.2, 62.7, 61.6, 48.2, 38.1, 29.7, 26.3, 25.8, 18.2; Exact mass calcd for $\text{C}_{32}\text{H}_{31}\text{NO}_3$ $[\text{M}]^+$ 477.2332, found 477.2305.

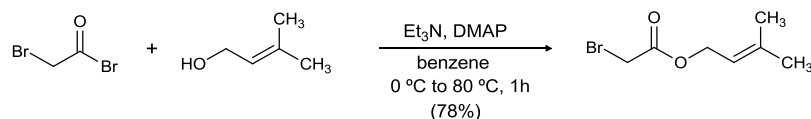


3-Methylbut-2-enyl 2-(diphenylmethyleneamino)acetate (506).

To a solution of bromo acetate (2.40 g, 11.6 mmol), imine (2.21g, 12.2 mmol) in acetonitrile (15 mL) was added diisopropyl ethylamine (2.03 mL, 11.6 mmol) and the mixture was stirred at $80\text{ }^\circ\text{C}$ for 10 h. The reaction mixture was then cooled to room temperature and diluted with H_2O and Et_2O . The layers were separated and the aqueous layer was extracted with Et_2O . The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (basic alumina, 5-10% ethyl acetate in hexanes) to afford the Schiff base as a colorless oil (2.65 g, 74%). $R_f = 0.22$ (basic alumina, 10% EtOAc/hexanes); IR (film) 3057, 3024, 2972, 2933, 1742, 1626, 1174 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.67-7.66 (m, 2H), 7.47-7.43 (m, 3H), 7.40 (dddd, $J = 7.2, 7.2, 1.2, 1.2$ Hz, 1H), 7.35-7.32 (m, 2H), 7.19-7.17 (m, 2H), 5.35 (tq, $J = 7.2, 1.2$ Hz, 1H), 4.64 (d, $J = 7.2$ Hz, 2H), 4.21 (s, 2H), 1.75 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) ppm 171.8, 170.6,

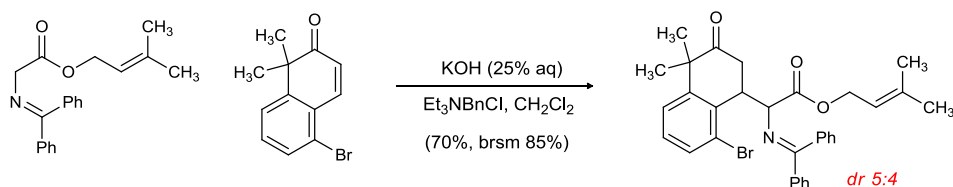
139.3, 139.2, 136.0, 130.4, 128.7, 128.6, 128.0, 127.6, 118.4, 62.0, 55.6, 25.7, 18.0;

HRMS (EI): Exact mass calcd for C₂₀H₂₁NO₂Na [M+Na]⁺ 330.1470, found 333.1466.



3-Methylbut-2-enyl 2-bromoacetate (507).

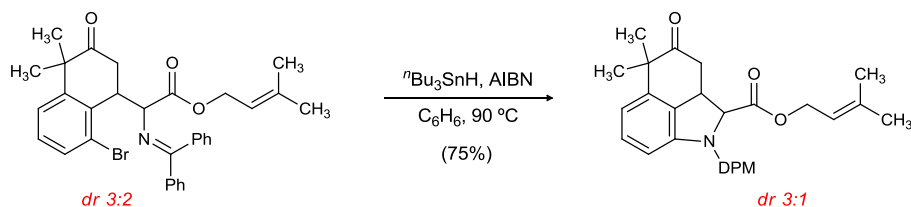
To a solution of alcohol (3.02 mL, 29.7 mmol), triethylamine (3.73 mL, 26.7 mmol) and 4-dimethyl aminopyridine (363 mg, 2.97 mmol) in benzene (40 mL) was added acyl bromide (0.65 mL) and the mixture was stirred at 80 °C for 1 h. The reaction mixture was then cooled to room temperature, filtered through a pad of SiO₂, and the solution was concentrated. Flash column chromatography (SiO₂, 0-5% ethyl acetate in hexanes) of the resulting oil furnished the ester as a light colorless oil (6.0 g, 78%). Analytical data was identical to that in the literature.



3-Methylbut-2-enyl 2-(8-bromo-4,4-dimethyl-3-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)-2-(diphenylmethyleneamino)acetate (508).

The enone (382 mg, 1.53 mmol), Schiff base (940 mg, 3.06 mmol), and benzyl triethyl ammonium chloride (87.0 mg, 0.38 mmol) were dissolved in CH₂Cl₂ (5.0 mL). 25% aq KOH (2.5 mL) was then added and the mixture was stirred vigorously for 14 h. The reaction mixture was diluted with CH₂Cl₂, and the organic layer was separated, washed with water, dried, filtered, and concentrated. Flash column chromatography (SiO₂, 5-15%

ethyl acetate in hexanes) of the resulting oil furnished the Michael adduct as a colorless oil (596 mg, 70%) in addition to the enone (68.0 mg, 17.1%). The Michael adduct was characterized as a 5:4 ratio of diastereomers by ^1H NMR. $R_f = 0.38$ (20% EtOAc/hexanes); IR (film) 2974, 2931, 2911, 1734, 1717, 1180 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.65-7.64 (m, 2H), 7.48-7.46 (m, 1H), 7.45-7.43 (m, 2H), 7.41 (dd, $J = 7.8, 1.2$ Hz, 1H), 7.37-7.34 (m, 2H), 7.34-7.32 (m, 1H), 7.31-7.27 (m, 4H), 7.26-7.23 (m, 5H), 7.21-7.16 (m, 3H), 7.11 (dd, $J = 7.8, 7.8$ Hz, 1H), 6.67 (br d, $J = 6.6$ Hz, 2H), 6.33 (br s, 2H), 5.35 (ddq, $J = 7.2, 7.2, 1.2$ Hz, 1H), 5.33 (ddq, $J = 7.2, 7.2, 1.2$ Hz, 1H), 4.68 (dd, $J = 12.0, 6.6$ Hz, 1H), 4.63-4.61 (m, 3H), 4.56 (dd, $J = 12.0, 6.6$ Hz, 1H), 4.49 (ddd, $J = 6.6, 1.8, 1.8$ Hz, 1H), 4.42 (ddd, $J = 5.4, 5.4, 3.0$ Hz, 1H), 4.17 (d, $J = 8.4$ Hz, 1H), 3.04-2.95 (m, 4H), 1.76 (s, 6H), 1.70 (s, 6H), 1.36 (s, 3H), 1.30 (s, 3H), 1.15 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) ppm 212.2, 211.1, 173.0, 170.2, 170.0, 169.9, 148.4, 147.4, 139.1 (2C), 139.0, 138.5, 135.9, 135.6, 134.1, 133.3, 130.9, 130.5, 130.3, 129.6, 129.3, 128.8, 128.7, 128.6 (2C), 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.1, 126.9, 126.8, 125.1, 124.9, 118.4 (2C), 69.7, 67.3, 62.2, 62.1, 47.3, 47.0, 43.8, 43.2, 39.2, 38.2, 33.5, 32.2, 25.7 (2C), 25.6, 25.0, 18.1 (2C); HRMS (ESI): Exact mass calcd for $\text{C}_{32}\text{H}_{33}\text{BrNO}_3$ $[\text{M}+\text{H}]^+$ 558.1638, found 558.1627.

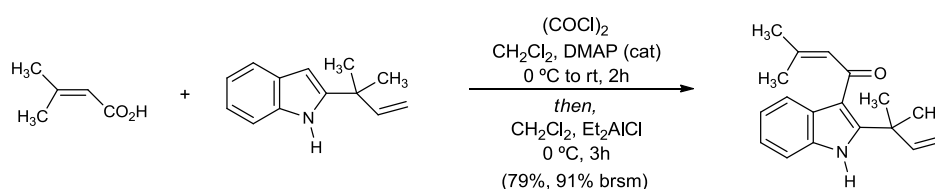


3-Methylbut-2-enyl 1-benzhydryl-5,5-dimethyl-4-oxo-1,2,2a,3,4,5-hexahydrobenzo[cd] indole-2-carboxylate (509).

To a refluxing (90 °C) benzene (167 mL) solution of the ketimine (930 mg, 1.67 mmol) and ⁿBu₃SnH (108 μL, 0.41 mmol) was added AIBN (219 mg, 1.36 mmol) and ⁿBu₃SnH (972 μL, 3.69 mmol) dissolved separately in benzene (10 mL) via a syringe pump over 4 h. The solution was stirred for an additional 6 h at 90 °C and the solvent was removed in *vacuo*. The residue was treated with a 1:1 (v/v) solution of Et₂O (75 mL) and satd aq KF,⁸ and the mixture was stirred vigorously until a white solid precipitated. The organic layer was washed with water, dried (NaSO₄), filtered, and concentrated. The resulting white residue was purified by flash column chromatography (SiO₂, 10% ethyl acetate in hexanes) to afford the product as a viscous oil (568 mg, 75%). The indoline was characterized as a 3:1 ratio of diastereomers by ¹H NMR. R_f = 0.48 (20% EtOAc/hexanes); IR (film) 3060, 3027, 2970, 2931, 2870, 1741, 1710, 1622, 1595, 1493, 1454, 1277, 1187 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.59 (d, *J* = 7.2 Hz, 2H), 7.50 (d, *J* = 7.8 Hz, 2H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.35-7.26 (m, 10 H), 7.24-7.22 (m, 4H), 6.96 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.92 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.66 (d, *J* = 7.8 Hz, 1H), 6.60 (d, *J* = 7.8 Hz, 1H), 5.98 (d, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 5.57 (s, 1H), 5.50 (s, 1H), 5.21 (ddq, *J* = 7.2, 7.2, 1.2 Hz, 1H), 5.12 (ddq, *J* = 7.2, 7.2, 1.2 Hz, 1H), 4.48 (dd, *J* = 12.0, 7.2 Hz, 1H), 4.37 (dd, *J* = 12.0, 7.2 Hz, 1H), 4.34 (dd, *J* = 12.0, 7.2 Hz, 1H), 4.31 (dd, *J* = 12.0, 7.2 Hz, 1H), 4.28 (d, *J* = 9.0 Hz, 1H), 4.00 (d, *J* = 10.2 Hz, 1H), 3.91 (ddd, *J* = 9.6, 9.6, 5.4 Hz, 1H), 3.66 (ddd, *J* = 11.4, 11.4, 5.4 Hz, 1H), 2.89 (dd, *J* = 15.6, 5.4 Hz, 1H), 2.71 (dd, *J* = 14.4, 5.4 Hz, 1H), 2.52 (dd, *J* = 15.6, 12.0 Hz, 1H), 2.26 (dd, *J* = 14.4, 14.4 Hz, 1H), 1.75 (s, 3H), 1.71 (s, 3H), 1.67 (s, 3H), 1.60 (s, 3H), 1.45 (s, 3H),

⁸ Complete saturation by KF is necessary.

1.39 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) ppm 213.9, 213.2, 172.7, 170.0, 149.8, 149.5, 142.3, 140.8, 140.2, 139.8 (2C), 139.5, 139.4, 138.6, 130.7, 129.6, 129.4, 129.1, 128.7, 128.6, 128.5, 128.2, 128.1, 127.9, 127.7, 127.4, 127.1, 126.8, 126.3, 125.9, 118.0 (2C), 115.0, 114.9, 107.7, 107.6, 74.1, 70.4, 68.4, 67.2, 62.0, 61.1, 46.9, 46.5, 42.5, 40.9, 39.7, 38.2, 26.8, 26.7, 26.5, 25.7, 25.6, 24.7, 18.1, 18.0; HRMS (ESI): Exact mass calcd for $\text{C}_{32}\text{H}_{33}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 502.2358, found 502.2338.

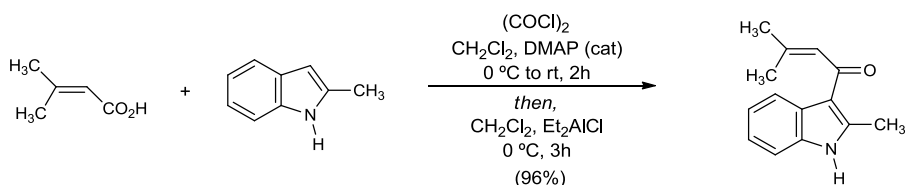


2,3-Dimethyl-1-(2-methyl-1H-indol-3-yl)but-2-en-1-one (520).

To a $0\text{ }^\circ\text{C}$ solution of the acid (550 mg, 5.00 mmol) in dichloromethane (0.5 M), was added oxalyl chloride (866 μL , 10.00 mmol) over 5 minutes. Dimethyl aminopyridine (6.40 mg, 0.05 mmol) was added and the solution was slowly warmed to room temperature and stirred until complete conversion was achieved, as evidenced by ^1H NMR. The solvent was removed *in vacuo* to give the acyl chloride, which was used without further purification.

To a $0\text{ }^\circ\text{C}$ solution of indole (150 mg, 810 μmol) in CH_2Cl_2 (3.5 mL) was added Et_2AlCl (540 μL , 972 μmol , 1.8 M in toluene) dropwise. The reaction was stirred for 30 minutes at $0\text{ }^\circ\text{C}$, and acyl chloride (115 mg, 972 μmol) in CH_2Cl_2 (3.5 mL) was added dropwise to the solution. The reaction was stirred for 3 h at $0\text{ }^\circ\text{C}$, with the last 30 min having minimal ice within the ice/water bath. The reaction was quenched by slow dropwise addition of pH=7 buffer solution and then addition of satd aq NaHCO_3 in the same fashion. The

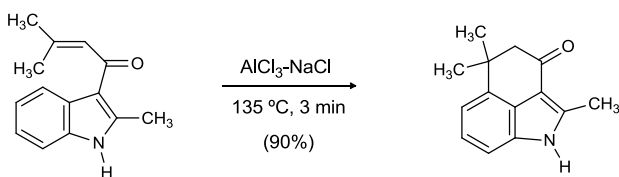
layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 10-20% ethyl acetate in hexanes) to afford the title product as a yellow oil (172 mg, 79%) in addition to the indole (19 mg, 13%). R_f = 0.37 (SiO₂, 20% EtOAc/hexanes); IR (film) 3313, 2964, 2927, 2854, 1647, 1601, 1421, cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.94 (br s, 1H), 7.82-7.76 (m, 1H), 7.41-7.35 (m, 1H), 7.22-7.17 (m, 2H), 6.69 (s, 1H), 6.30 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.24 (d, *J* = 18.0 Hz, 1H), 5.22 (d, *J* = 10.4 Hz, 1H), 2.21 (s, 3H), 2.04 (s, 3H), 1.69 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) ppm 190.8, 151.8, 148.9, 145.1, 133.3, 127.8, 127.7, 121.9, 120.9, 120.3, 115.4, 113.2, 111.1, 39.5, 27.3, 26.4, 20.6; HRMS (EI): Exact mass calcd for C₁₈H₂₂NO [M+H]⁺ 268.1701, found 268.1696.



2,3-Dimethyl-1-(2-methyl-1H-indol-3-yl)but-2-en-1-one (521).

To a 0 °C solution of the acid (338 mg, 3.38 mmol) in dichloromethane (0.5 M), was added oxalyl chloride (586 μL, 6.76 mmol) over 5 minutes. Dimethyl aminopyridine (6.40 mg, 0.05 mmol) was added and the solution was slowly warmed to room temperature and stirred until complete conversion was achieved, as evidenced by ¹H NMR. The solvent was removed *in vacuo* to give the acyl chloride, which was used without further purification.

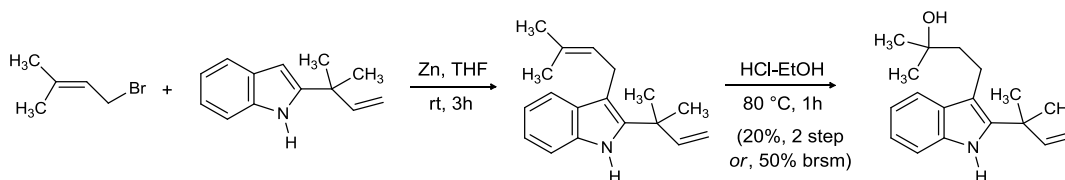
To a 0 °C solution of 2-methylindole (294 mg, 2.24 mmol) in CH₂Cl₂ (10 mL) was added Et₂AlCl (1.91 mL, 3.44 mmol, 1.8 M in toluene) dropwise. The reaction was stirred for 30 minutes at 0 °C, and acyl chloride (400 mg, 3.37 mmol) in CH₂Cl₂ (6.0 mL) was added dropwise to the solution. The reaction was stirred for 3 h at 0 °C, with the last 30 min having minimal ice within the ice/water bath. The reaction was quenched by slow dropwise addition of pH=7 buffer solution and then addition of satd aq NaHCO₃ in the same fashion. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 10-20% ethyl acetate in hexanes) to afford the title product as a yellow solid (460 mg, 96%). R_f = 0.42 (SiO₂, 50% EtOAc/hexanes); mp = 188 °C; IR (film) 3158 (br), 2967, 2937, 1653, 1564, 1456, 1378 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 8.62 (br s, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.20 (ddd, *J* = 7.2, 7.2, 1.2 Hz, 1H), 7.18 (ddd, *J* = 7.2, 7.2, 1.2 Hz, 1H), 6.64 (s, 1H), 2.73 (s, 3H), 2.17 (s, 3H), 2.02 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) ppm 189.7, 151.0, 143.0, 134.6, 126.9, 126.4, 122.3, 121.7, 120.9, 116.0, 110.7, 27.3, 20.7, 14.9; HRMS (EI): Exact mass calcd for C₁₄H₁₆NO [M+H]⁺ 214.1232. found 214.1237.



1,6,6-Trimethyl-6,7-dihydrobenzo[cd]indol-8(2H)-one (522).

The substrate (40.0 mg, 188 μmol) was added in one portion to a melt of AlCl₃ (362 mg, 1.88 mmol) and NaCl (99.0 mg, 1.69 mmol) at 135 °C. After 3 min, the reaction was

poured into ice cold water and the solution was made basic by the addition of satd aq NaHCO_3 . The solution was extracted with CH_2Cl_2 and the combined organic layers were dried, filtered, and concentrated to a brown oil. Column chromatography (SiO_2 , 20-30% ethyl acetate in hexanes) provided the tricyclic indole as a pale yellow solid (36.0 mg, 90%). $R_f = 0.34$ (SiO_2 , 50% EtOAc/hexanes); mp = 138-140 °C; IR (film) 3241, 2957, 2867, 1640, 1606, 1552, 1452 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 9.43 (br s, 1H), 7.23-7.18 (m, 2H), 7.12 (dd, $J = 6.0, 2.4$ Hz, 1H), 2.77 (s, 3H), 2.73 (s, 2H), 1.42 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) ppm 194.8, 138.9, 137.9, 132.8, 128, 5, 123.5, 115.6, 110.5, 108.6, 55.8, 38.9, 29.2, 13.3; Exact mass calcd for $\text{C}_{14}\text{H}_{16}\text{NO}$ $[\text{M}+\text{H}]^+$ 214.1232, found 214.1231.

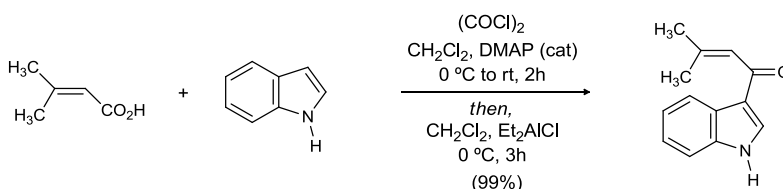


2-Methyl-4-(2-(2-methylbut-3-en-2-yl)-1H-indol-3-yl)butan-2-ol (524).

To a 0 °C solution of 2-prenyl indole (100 mg, 540 μmol) in THF (1.0 mL), was added zinc powder (79.5 μL , mg, 1.22 mmol). The solution was slowly warmed to room temperature and stirred for 12 h. The reaction was quenched with satd aq NH_4Cl , the layers were separated, and the aqueous layer was extracted with Et_2O . The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting crude oil was used in the next step without any further purification.

To a solution of the crude allylation product (120 mg) in EtOH (1.0 mL) was added HCl (3 M, 1.0 mL) and the reaction stirred at 80 °C for 1 h. The reaction was quenched with satd aq NaOH (1.0 M), the layers were separated, and the aqueous layer was extracted

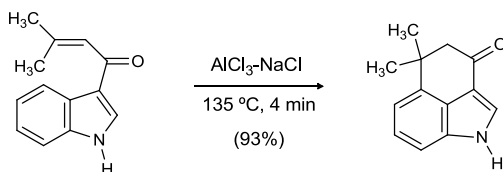
with Et₂O. The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 20-25-30% ethyl acetate in hexanes) to afford the title product as a pale yellow oil (29.2 mg, 20%) in addition to the indole (60 mg, 60%). R_f = 0.15 (SiO₂, 20% EtOAc/hexanes); IR (film) 3356, (br), 2970, 2926 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.81 (br s, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.12 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 7.07 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.14 (dd, *J* = 17.5, 10.5 Hz, 1H), 5.17 (d, *J* = 17.5 Hz, 1H), 5.15 (d, *J* = 10.5 Hz, 1H), 2.90 (dt, *J* = 8.5, 4.5 Hz, 2H), 1.81 (dt, *J* = 8.5, 4.5 Hz, 2H), 1.54 (s, 6H), 1.34 (s, 6H), -OH proton not observed; ¹³C NMR (150 MHz, CDCl₃) ppm 145.0, 137.6, 133.2, 128.5, 120.2, 118.1, 117.1, 110.8, 110.2, 109.4, 70.1, 43.9, 37.9, 28.1, 26.6, 18.8; HRMS (EI): Exact mass calcd for C₁₈H₂₅NO [M]⁺ 271.1931, found 271.1938.



1-(1*H*-Indol-3-yl)-3-methylbut-2-en-1-one (527).

To a 0 °C solution of the acid (1.50 g, 15.0 mmol) in dichloromethane (0.5 M), was added oxalyl chloride (2.60 mL, 30.0 mmol) over 5 minutes. Dimethyl aminopyridine (6.40 mg, 0.05 mmol) was added and the solution was slowly warmed to room temperature and stirred until complete conversion was achieved, as evidenced by ¹H NMR. The solvent was removed *in vacuo* to give the acyl chloride, which was used without further purification.

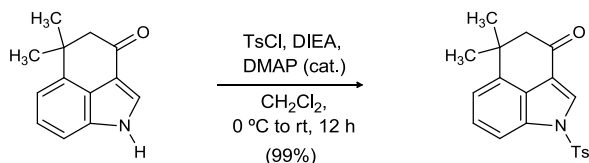
To a 0 °C solution of indole (1.17 g, 10.0 mmol) in CH₂Cl₂ (50 mL) was added Et₂AlCl (8.33 mL, 15.0 mmol, 1.8 M in toluene) dropwise. The reaction was stirred for 30 minutes at 0 °C, and acyl chloride (1.77 g, 15.0 mmol) in CH₂Cl₂ (32.4 mL) was added dropwise to the solution. The reaction was stirred for 3 h at 0 °C, with the last 30 min having minimal ice within the ice/water bath. The reaction was quenched by slow dropwise addition of pH=7 buffer solution followed by the addition of satd aq NaHCO₃ in the same fashion. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 10-20% ethyl acetate in hexanes) to afford the title product as a yellow solid (1.97 g, 99%). R_f = 0.72 (SiO₂, 50% EtOAc/hexanes); mp = 114-115 °C. IR (film) 3252, 2971, 2932, 1645, 1589, 1520, 1434 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.57 (br s, 1H), 8.51 (m, 1H), 7.85 (d, *J* = 3.2 Hz, 1H), 7.42 (m, 1H), 7.31-7.28 (m, 2H), 6.65 (m, 1H), 2.28 (d, *J* = 0.8 Hz, 3H), 2.01 (d, *J* = 0.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) ppm 188.1, 152.7, 136.6, 131.4, 125.9, 123.5, 122.7, 122.4, 122.3, 119.5, 111.6, 27.7, 20.5; HRMS (EI): Exact mass calcd for C₁₃H₁₃NO [M]⁺ 199.0992, found 199.0986.



6,6-Dimethyl-6,7-dihydrobenzo[cd]indol-8(2H)-one (528).

The substrate (1.40 g, 7.03 mmol) was added in one portion to a melt of AlCl₃ (14.2 g, 73.8 mmol) and NaCl (3.7 g, 63.3 mmol) at 135 °C and the solution was stirred vigorously for 4 minutes. The reaction was poured into ice cold water and the solution

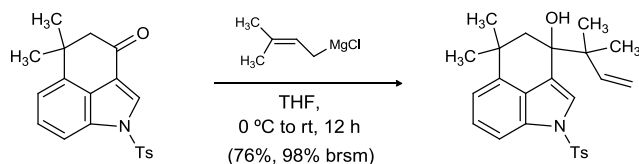
was made basic by the addition of satd aq NaHCO₃. The solution was extracted with CH₂Cl₂ and the combined organic layers were dried, filtered, and concentrated to a brown oil. Column chromatography (SiO₂, 20-30% ethyl acetate in hexanes) provided the indole as a pale yellow solid (1.31 g, 93%). R_f = 0.50 (SiO₂, 50% EtOAc/hexanes); mp = 145 °C; IR (film) 3239 (br), 2958, 2868, 1651, 1527, 1439, 1338 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 9.21 (br s, 1H), 7.73 (d, *J* = 2.4 Hz, 1H), 7.32-7.28 (m, 2H), 7.18 (dd, *J* = 6.0, 1.8 Hz, 1H), 2.77 (s, 2H), 1.44 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) ppm 194.4, 138.9, 133.8, 127.7, 124.5, 123.5, 116.0, 114.5, 109.4, 55.7, 39.1, 29.3; HRMS (EI): Exact mass calcd for C₁₃H₁₄NO [M+H]⁺ 200.1075, found 200.1068.



6-Dimethyl-2-tosyl-6,7-dihydrobenzo[*cd*]indol-8(2*H*)-one (530).

To a solution of the indole (420 mg, 2.11 mmol) and diisopropyl ethylamine (551 μL, 3.17 mmol) in CH₂Cl₂ (10 mL) at 0 °C was added *p*-toluenesulfonyl chloride (523 mg, 2.75 mmol) and dimethyl aminopyridine (9.8 mg, 80 μmol). The reaction was stirred for 30 min before being warmed to rt and stirred for 15 h. The reaction was quenched with satd aq NH₄Cl and extracted with CH₂Cl₂. The combined organic layers were dried, filtered, and concentrated to a yellow oil. Column chromatography (SiO₂, 10-20% ethyl acetate in hexanes) provided the title product as a pale yellow oil (737 mg, 99%). R_f = 0.62 (SiO₂, 50% EtOAc/hexanes); mp = 119-121 °C; IR (film) 3126, 2961, 2871, 1686, 1544, 1379, 1190 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 8.04 (s, 1H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.39 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 2H),

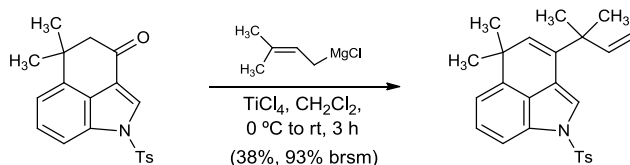
7.25 (d, $J = 7.2$ Hz, 1H), 2.70 (s, 2H), 2.38 (s, 3H), 1.37 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) ppm 194.1, 145.9, 139.7, 134.8, 133.2, 130.2, 128.7, 127.2, 126.5, 124.0, 118.5, 117.8, 111.5, 55.7, 39.2, 29.4, 21.7; HRMS (EI): Exact mass calcd for $\text{C}_{20}\text{H}_{20}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$ 354.1164, found 354.1152.



6,6-Dimethyl-8-(2-methylbut-3-en-2-yl)-2-tosyl-2,6,7,8-tetrahydrobenzo[*cd*]indol-8-ol (532).

To a 0 °C solution of indole (80.0 mg, 226 μmol) in THF (2.0 mL) was added 3,3-dimethylallyl magnesium chloride (847 μL , 678 μmol , 0.75 M in THF) dropwise over 2 minutes. The reaction was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched with satd aq NH_4Cl , the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO_2 , 10-20% ethyl acetate in hexanes) to afford the title product as a colorless oil (73.0 mg, 76%) in addition to indole (18 mg, 23%). $R_f = 0.65$ (SiO_2 , 50% EtOAc/hexanes); IR (film) 3356, 2962, 2926, 2879, 1371, 1187, 1179, 1131 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.78 (d, $J = 8.5$ Hz, 2H), 7.71 (d, $J = 8.5$ Hz, 1H), 7.65 (s, 1H), 7.29 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.23 (d, $J = 8.0$ Hz, 2H), 7.16 (d, $J = 7.0$ Hz, 1H), 6.39 (dd, $J = 17.0, 11.0$ Hz, 1H), 5.24 (d, $J = 11.5$ Hz, 1H), 5.23 (d, $J = 16.5$ Hz, 1H), 2.34 (s, 3H), 1.97 (d, $J = 14.0$ Hz, 1H), 1.93 (d, $J = 14.0$ Hz, 1H), 1.82 (br s, 1H), 1.43 (s, 3H), 1.38 (s, 3H), 1.25 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) ppm 145.4,

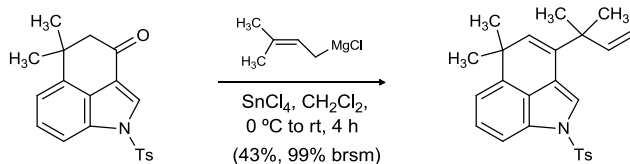
144.8, 141.1, 135.4, 133.0, 129.9, 128.1, 126.8, 125.5, 122.8, 120.8, 117.6, 114.1, 110.4, 74.2, 45.6, 45.3, 34.8, 32.3, 29.8, 23.1, 22.9, 21.5; HRMS (EI): Exact mass calcd for $C_{25}H_{29}NO_3SNa$ $[M+Na]^+$ 446.1766, found 446.1770.



5-Dimethyl-3-(2-methylbut-3-en-2-yl)-1-tosyl-1,5-dihydrobenzo[cd]indole (534).

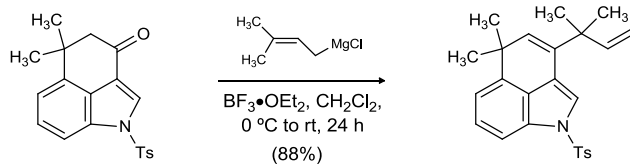
To a $0\text{ }^\circ C$ solution of indole (40.0 mg, 113 μmol) in CH_2Cl_2 (1.5 mL) was added $TiCl_4$ (18.7 μL , 170 μmol) dropwise and the reaction was stirred for 10 minutes. Grignard reagent (756 μL , 454 μmol , 0.8 M in THF) was then added and the mixture was stirred vigorously for 2h at $0\text{ }^\circ C$ and an additional 2h at rt. The reaction was quenched with satd aq $NaHCO_3$, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO_2 , 5-10% ethyl acetate in hexanes) to afford the title product as a white solid (17.4 mg, 38%) in addition to the the indole (23.1 mg, 58%). $R_f = 0.68$ (SiO_2 , 50% EtOAc/hexanes); mp = 139-140 $^\circ C$; IR (film) 2961, 2925, 2855, 1123 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, $J = 8.4$ Hz, 2H), 7.65 (d, $J = 8.0$ Hz, 1H), 7.29 (dd, $J = 7.6, 7.6$ Hz, 1H), 7.27 (d, $J = 6.4$ Hz, 1H), 7.21 (d, $J = 8.0$ Hz, 2H), 7.11 (d, $J = 7.6$ Hz, 1H), 5.97 (dd, $J = 17.6, 10.8$ Hz, 1H), 5.59 (s, 1H), 5.11 (dd, $J = 17.6, 1.2$ Hz, 1H), 5.08 (dd, $J = 10.8, 1.2$ Hz, 1H), 2.34 (s, 3H), 1.36 (s, 6H), 1.33 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 147.0, 144.5, 139.3, 135.5, 135.3, 133.7, 133.0, 129.7, 128.5, 126.8, 125.9, 119.5, 118.5, 117.3, 112.0, 110.6, 40.9,

38.1, 31.9, 27.1, 21.5; HRMS (EI): Exact mass calcd for C₂₅H₂₈NO₂S [M+H]⁺ 406.1835, found 406.1817.



5,5-Dimethyl-3-(2-methylbut-3-en-2-yl)-1-tosyl-1,5-dihydrobenzo[cd]indole (534).

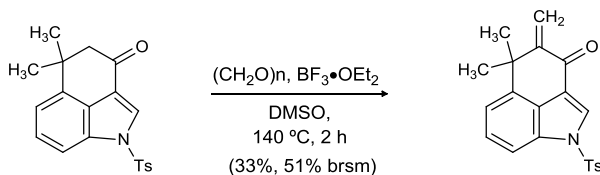
To a 0 °C solution of indole (40.0 mg, 113 μmol) in CH₂Cl₂ (1.5 mL) was added SnCl₄ (19.9 μL, 170 μmol) dropwise and the reaction was stirred for 10 minutes. Grignard reagent (756 μL, 454 μmol, 0.8 M in THF) was then added and the mixture was stirred vigorously for 2h at 0 °C and at rt for additional 2 h. The reaction was quenched with satd aq NaHCO₃, the layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 5-10% ethyl acetate in hexanes) to afford the title product as a white solid (19.7 mg, 43%) in addition to the the indole (22.3 mg, 57%). See above for the analytical data.



5,5-Dimethyl-3-(2-methylbut-3-en-2-yl)-1-tosyl-1,5-dihydrobenzo[cd]indole (534).

To a 0 °C solution of indole (40.0 mg, 113 μmol) in CH₂Cl₂ (1.5 mL) was added BF₃•OEt₂ (21.5 μL, 170 μmol) dropwise and the reaction was stirred for 10 minutes. Grignard reagent (756 μL, 454 μmol, 0.8 M in THF) was then added and the mixture was stirred vigorously for 2h at 0 °C and at rt for additional 22 h. The reaction was quenched

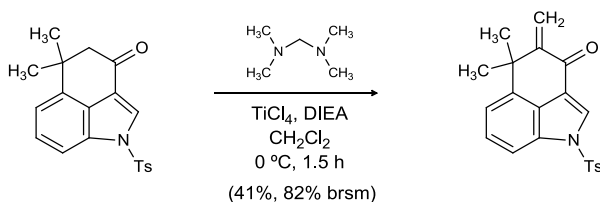
with satd aq NaHCO₃, the layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 5-10% ethyl acetate in hexanes) to afford the title product as a white solid (40.4 mg, 88%). See above for the analytical data.



6,6-Dimethyl-7-methylene-2-tosyl-6,7-dihydrobenzo[cd]indol-8(2H)-one (535).

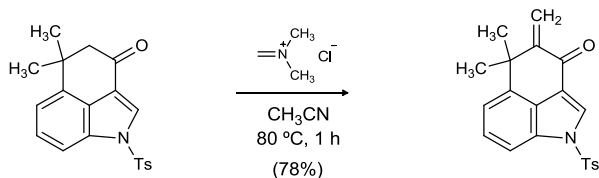
To a 0 °C solution of indole (90.0 mg, 255 μmol) and paraformaldehyde (91.8 mg, 3.06 mmol) in DMSO (2.1 mL) was added BF₃•OEt₂ (84.0 μL, 637 μmol) dropwise over 2 minutes. The reaction was heated in microwave oven for 2 h at 140 °C. The reaction was quenched with H₂O, the layers were separated, and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 5-10-15% ethyl acetate in hexanes) to afford the title product as pale yellow oil (33.0 mg, 35%) in addition to indole (30.0 mg, 33%). R_f = 0.29 (SiO₂, 20% EtOAc/hexanes); IR (film) 2961, 2924, 2853, 1675, 1599, 1543, 1382, 1190 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.19 (s, 1H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.40 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.29 (dd, *J* = 8.0, 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 1H), 6.32 (s, 1H), 5.67 (s, 1H), 2.37 (s, 3H), 1.53 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) ppm 184.1, 154.4, 145.9, 138.4, 134.7, 133.1, 130.2, 127.5, 127.2, 126.6, 125.9, 121.4, 118.7, 117.2, 111.4,

42.3, 30.6, 21.6; HRMS (EI): Exact mass calcd for C₂₁H₂₀NO₃S [M]⁺ 366.1158, found 366.1148.



6,6-Dimethyl-7-methylene-2-tosyl-6,7-dihydrobenzo[cd]indol-8(2H)-one (535).

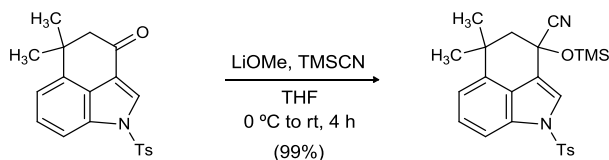
To a 0 °C solution of indole (70.0 mg, 198 μmol) in CH₂Cl₂ (1.3 mL) was added TiCl₄ (43.6 μL, 396 μmol). The reaction was stirred for 5 minutes at 0 °C and, diisopropyl ethylamine (51.7 μL, 297 μmol) was added dropwise to the solution. To the resulting orange solution was added tetramethyl methylamine (41.0 μL, 297 μmol) and the mixture was stirred for 1h at 0 °C. The reaction was quenched with satd aq NH₄Cl, the layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 5-10-15% ethyl acetate in hexanes) to afford the title product as a pale yellow oil (29.8 mg, 41%) in addition to indole (35.0 mg, 50%). See above for the analytical data.



6,6-Dimethyl-7-methylene-2-tosyl-6,7-dihydrobenzo[cd]indol-8(2H)-one (535).

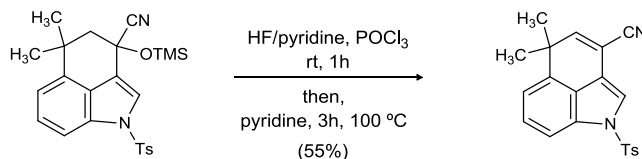
To a solution of indole (23.3 mg, 66.0 μmol) in CH₃CN (0.5 mL) was added Eschenmoser's salt (24.5 μL, 264 μmol) and the reaction stirred at 80 °C for 1 h. The reaction was quenched with H₂O, the layers were separated, and the aqueous layer was

extracted with Et₂O. The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 5-10-15% ethyl acetate in hexanes) to afford the title compound as a pale yellow compound (18.9 mg, 78%). See above for the analytical data.



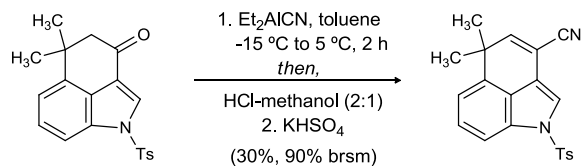
5,5-Dimethyl-1-tosyl-3-((trimethylsilyloxy)-1,3,4,5-tetrahydrobenzo[cd]indole-3-carbonitrile (539).

To a 0 °C solution of LiOMe (21.5 mg, 566 μmol) in THF (15.0 mL) was added TMSCN (604 μL, 4.53 mmol) and the reaction was allowed to warm to room temperature and stirred for 10 minutes. Ketone (1.00 g, 2.83 mmol) in THF (4.0 mL) was added and the reaction was stirred for an additional 4 h at rt. The reaction was quenched with satd aq KH₂PO₄, the layers were separated, and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with satd aq KH₂PO₄, dried, filtered, and concentrated. The resulting cyanohydrin was pure for analytical purpose (1.28 g, 99%). R_f = 0.40 (SiO₂, 20% EtOAc/hexanes); IR (film) 2962, 2934, 1431, 1378, 1189 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.85 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.67 (s, 1H), 7.35 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 7.6 Hz, 1H), 2.37 (s, 3H), 2.36 (d, *J* = 14.0 Hz, 1H), 2.21 (d, *J* = 14.0 Hz, 1H), 1.42 (s, 3H), 1.40 (s, 3H), 0.11 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) ppm 145.4, 139.6, 135.3, 133.0, 130.1, 127.0, 126.3, 125.2, 122.2, 121.1, 119.2, 118.1, 111.06, 64.3, 51.8, 35.3, 30.9, 29.7, 21.6, 1.0; HRMS (EI): Exact mass calcd for C₂₄H₂₈N₂O₃SSi [M]⁺ 452.1584, found 452.1564.



5,5-Dimethyl-1-tosyl-1,5-dihydrobenzo[*cd*]indole-3-carbonitrile (540).

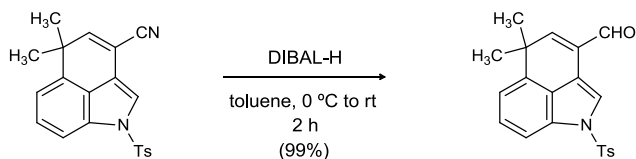
To a 0 °C solution of cyanohydrin (200 mg, 450 μmol) in POCl₃ (209 μL, 2.25 mmol) was added HF-pyridine (17.5 μL, 650 μmol) dropwise. The reaction was stirred for 60 minutes at 0 °C and pyridine (563 μL, 7.00 mmol) was added. The reaction was stirred at 80 °C for 2 h and then cooled to 0 °C. The reaction was quenched with 1.0 M HCl and the solution was stirred for 10 minutes. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with satd aq NaHCO₃, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 10-15-20% ethyl acetate in hexanes) to afford the title product as a white solid (29.2 mg, 20%). *R*_f = 0.61 (SiO₂, 50% EtOAc/hexanes); mp = 118-120 °C; IR (film) 2965, 2924, 2229, 1596, 1437, 1369 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.48 (s, 1H), 7.38 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 2H), 7.13 (d, *J* = 7.6 Hz, 1H), 6.46 (s, 1H), 2.37 (s, 3H), 1.42 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) ppm 152.6, 145.3, 136.8, 135.1, 133.3, 130.1, 127.4, 127.0, 125.3, 119.0, 118.9, 116.1, 114.1, 111.6, 104.0, 39.4, 31.1, 21.6; HRMS (EI): Exact mass calcd for C₂₁H₁₉N₂O₂S [M+H]⁺ 363.1162, found 363.1151.



5,5-Dimethyl-1-tosyl-1,5-dihydrobenzo[*cd*]indole-3-carbonitrile (540).

To a -15 °C solution of ketone (40.0 mg, 109 μmol) in toluene (0.7 mL) was added Et₂AlCN (152 μL, 152 μmol, 1.0 M in toluene). The reaction was stirred for 1 h at -15 °C and 1 h at 5 °C. HCl-MeOH mixture (1.05 mL, 2:1) was added to the reaction at 5 °C and the reaction was stirred for an additional hour. The reaction was allowed to warm to rt and the layers were separated. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried, filtered, and concentrated. The crude cyanohydrin was immediately subjected to the dehydration reaction.

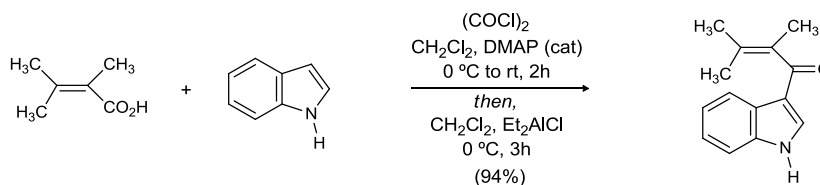
To a solution of the crude cyanohydrin (47 mg) in DME (150 μL) was added KHSO₄ (52.0 mg, 382 μmol) and the reaction stirred at 90 °C for 1 h. The reaction was quenched with satd aq NaHCO₃ and the resulting solution was stirred for 5 minutes. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 10-15-20% ethyl acetate in hexanes) to afford the nitrile as a white solid (12.1 mg, 30%) in addition to the starting ketone (27.1 mg, 67%).



5,5-Dimethyl-1-tosyl-1,5-dihydrobenzo[*cd*]indole-3-carbaldehyde (542).

To a 0 °C solution of nitrile (6.6 mg, 18 μmol) in toluene (200 mL) was added DIBAL-H (17.8 μL, 26.6 μmol, 1.0 M in toluene) and stirred for 1 h at 0 °C. The reaction was quenched by the stepwise addition of H₂O (200 μL) and 6M HCl (400 μL). The reaction

was allowed to warm to room temperature and stirred until the layers became clear (~6 h). The layers were separated, and the aqueous layer was extracted with Et₂O. The combined organic layers were dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 20% ethyl acetate in hexanes) to afford the enal as a brown solid (6.6 mg, 99%). *R_f* = 0.23 (SiO₂, 20% EtOAc/hexanes); mp = 180-182 °C; IR (film) 2961, 2922, 2850, 1688, 1370, 1188, 1176, 1164, 1116 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.67 (s, 1H), 7.98 (s, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.36 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 7.6 Hz, 1H), 6.62 (s, 1H), 2.34 (s, 3H), 1.48 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) ppm 191.6, 158.1, 144.9, 137.1, 135.5, 133.0, 131.1, 130.6, 129.9, 126.9, 126.7, 121.1, 118.7, 111.9, 111.4; 39.4, 31.0, 21.6 HRMS (ED): Exact mass calcd for C₂₁H₁₉NNaO₃S [M+Na]⁺ 388.0983, found 388.0983.



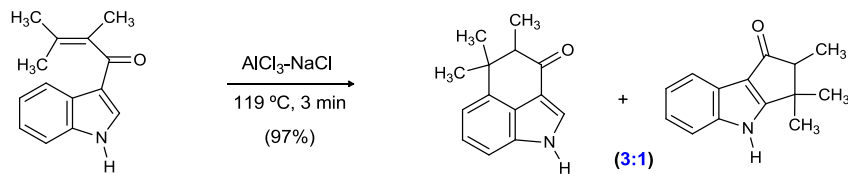
1-(1*H*-Indol-3-yl)-2,3-dimethylbut-2-en-1-one (545).

To a 0 °C solution of the acid (12.3 g, 112 mmol) in dichloromethane (240 mL), was added oxalyl chloride (19.6 mL, 224 mmol) over 5 minutes. Dimethyl aminopyridine (12.8 mg, 0.10 mmol) was added and the solution was slowly warmed to room temperature and stirred until complete conversion was achieved, as evidenced by ¹H

NMR. The solvent was removed *in vacuo* to give the acyl chloride (13.5 g, 91%), which was used without further purification.⁹

To a 0 °C solution of indole (9.24 g, 78.7 mmol) in CH₂Cl₂ (300 mL) was added Et₂AlCl (56.8 mL, 102 mmol, 1.8 M in toluene) dropwise. The reaction was stirred for 30 minutes at 0 °C, and acyl chloride (13.5 g, 102 mmol) in CH₂Cl₂ (50 mL) was added dropwise to the solution. The reaction was stirred for 3 h at 0 °C, with the last 30 min having minimal ice within the ice/water bath. The reaction was quenched by slow dropwise addition of pH=7 buffer solution followed by the addition of satd aq NaHCO₃ in the same fashion. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 10-20% ethyl acetate in hexanes) to afford the title product as a yellow solid (15.8 g, 94%). R_f = 0.65 (SiO₂, 50% EtOAc/hexanes); mp = 118-120 °C; IR (film) 3184 (br s), 2983, 2926, 1597 (br s), 1517, 1436, 1376 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 10.11 (br s, 1H), 8.39 (ddd, *J* = 10.0, 4.0, 3.2 Hz, 1H), 7.73 (d, *J* = 3.2 Hz, 1H), 7.45 (ddd, *J* = 10.0, 4.0, 3.2 Hz, 1H), 7.33-7.26 (m, 2H), 1.96 (br d, *J* = 1.2 Hz, 3H), 1.81 (s, 3H) 1.68 (br d, *J* = 1.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) ppm 198.0, 137.0, 134.6, 131.5, 130.5, 125.5, 123.6, 122.6, 121.9, 117.0, 111.9, 22.4, 19.8, 17.0; HRMS (EI): Exact mass calcd for C₁₄H₁₆NO [M+H]⁺ 214.1226, found 214.1220.

⁹ Due to the low boiling point (~145 °C), the acyl chloride should be put under high vacuum for longer duration of time (~2 minutes).

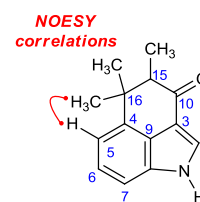


4,5,5-Trimethyl-4,5-dihydrobenzo[*cd*]indol-3(1H)-one (**514**).

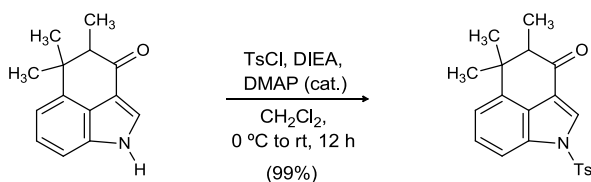
The indole (3.00 g, 14.1 mmol) was added in one portion to a melt of AlCl₃ (27.1 g, 141 mmol) and NaCl (4.11 g, 70.4 mmol) at 119 °C. After 3 min, the reaction was poured into ice cold water and the solution was made basic by the addition of satd aq NaHCO₃. The solution was extracted with CH₂Cl₂ and the combined organic layers were dried, filtered, and concentrated to a brown oil. Column chromatography (SiO₂, 15-20-25-30-35% ethyl acetate in hexanes) provided the desired tricyclic indole as a pale yellow oil (2.17 g, 73%) and its regioisomer as a white solid (710 mg, 23%).

Data for (**514**): R_f = 0.42 (SiO₂, 50% EtOAc/hexanes); IR (film) 3238 (br), 2967, 2870, 1651, 1607, 1525, 1451, 1338 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 8.87 (br s, 1H), 7.72 (dd, *J* = 6.6, 3.6 Hz, 1H), 7.30 (s, 1H), 7.29 (dd, *J* = 10.1, 8.2 Hz, 1H), 7.16 (ddd, *J* = 7.8, 4.8, 4.8 Hz, 1H), 2.64 (q, *J* = 7.2 Hz, 1H), 1.38 (s, 6H), 1.14 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) ppm 198.3, 138.7, 133.5, 127.0, 124.6, 123.7, 116.7, 113.5, 109.3, 56.8, 41.7, 29.9, 23.8, 13.1; Exact mass calcd for C₁₄H₁₆NO [M+H]⁺ 214.1226. found 214.1225.

A NOESY crosspeak was observed between the methyl protons and C5 aromatic proton. Other key observations, including HMBC correlation between C16 and H5, confirmed the assigned structure of the desired tricyclic indole.



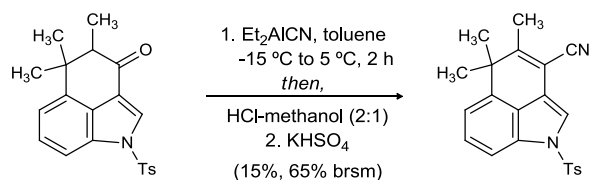
Data for (**546**): $R_f = 0.38$ (SiO_2 , 50% EtOAc/hexanes); mp = 235-237 °C; IR (film) 3212 (br), 2960, 2834, 1661, 1471, 1450 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 10.16 (br s, 1H), 7.87 (d, $J = 7.6$ Hz, 1H), 7.44 (d, $J = 8.0$ Hz, 1H), 7.27-7.19 (m, 2H), 2.87 (q, $J = 7.6$ Hz, 1H), 1.53 (s, 3H), 1.37 (s, 3H), 1.29 (d, $J = 7.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) ppm 198.1, 173.8, 142.1, 123.6, 122.3, 121.5, 121.0, 117.1, 112.3, 59.1, 38.8, 27.5, 24.2, 11.3; Exact mass calcd for $\text{C}_{14}\text{H}_{16}\text{NO}$ $[\text{M}+\text{H}]^+$ 214.1226, found 214.1224.



6,6-Dimethyl-2-tosyl-6,7-dihydrobenzo[*cd*]indol-8(2*H*)-one (**547**).

To a solution of the indole (3.05 g, 14.3 mmol) and diisopropyl ethylamine (4.0 mL, 22.9 mmol) in CH_2Cl_2 (90 mL) at 0 °C was added *p*-toluenesulfonyl chloride (3.54 mg, 18.6 mmol) and dimethyl aminopyridine (39.2 mg, 320 μmol). The reaction was stirred for 30 min before being warmed to rt and stirred for 15 h. The reaction was quenched with satd aq NH_4Cl and extracted with CH_2Cl_2 . The combined organic layers were dried, filtered, and concentrated to a yellow oil. Column chromatography (SiO_2 , 10-20% ethyl acetate in hexanes) provided the *N*-tosylated indole as a white solid (5.2 g, 99%). $R_f = 0.29$ (SiO_2 , 20% EtOAc/hexanes); mp = 142-144 °C; IR (film) 3127, 2969, 2925, 2870, 1690, 1544, 1434, 1379, 1366 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.02 (s, 1H), 7.86 (d, $J = 8.0$ Hz, 2H), 7.76 (d, $J = 8.0$ Hz, 1H), 7.38 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.29 (d, $J = 8.0$ Hz, 2H), 7.23 (d, $J = 7.2$ Hz, 1H), 2.64 (q, $J = 7.2$ Hz, 1H), 2.38 (s, 3H), 1.33 (s, 3H), 1.28 (s, 3H), 1.09 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) ppm 197.7, 145.8, 139.6, 134.8,

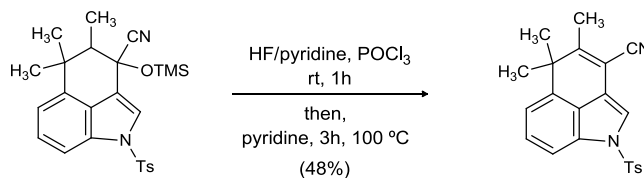
133.0, 130.2, 128.2, 127.2, 126.6, 124.3, 119.1, 117.0, 111.4, 56.7, 41.8, 29.3, 24.3, 21.7, 12.0; HRMS (EI): Exact mass calcd for C₂₁H₂₂NO₃S [M+H]⁺ 368.1315, found 368.1311.



4,5,5-Trimethyl-1-tosyl-1,5-dihydrobenzo[cd]indole-3-carbonitrile (549).

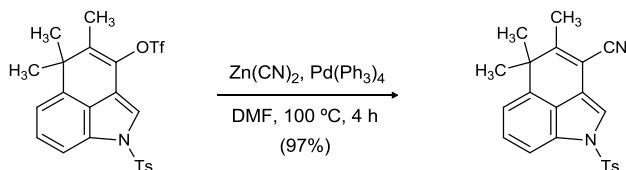
To a -15 °C solution of ketone (136 mg, 371 μmol) in toluene (1.8 mL) was added Et₂AlCN (1.6 mL, 1.67 mmol, 1.0 M in toluene). The reaction was stirred for 1 h at -15 °C and 1 h at 5 °C. HCl-MeOH mixture (1.05 mL, 2:1) was added to the reaction at 5 °C and the reaction was stirred for an additional hour. The reaction was allowed to warm to rt and the layers were separated. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried, filtered, and concentrated. The crude cyanohydrin was immediately subjected to the dehydration reaction.

To a solution of the crude cyanohydrin (150 mg) in DME (600 μL) was added KHSO₄ (260 mg, 1.91 mmol) and the reaction stirred at 90 °C for 1 h. The reaction was quenched with satd aq NaHCO₃ and the solution was stirred for 5 minutes. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 10-15-20% ethyl acetate in hexanes) to afford the nitrile as a white solid (21.0 mg, 20%) in addition to the starting ketone (104 mg, 76%). See below for the characterization data.



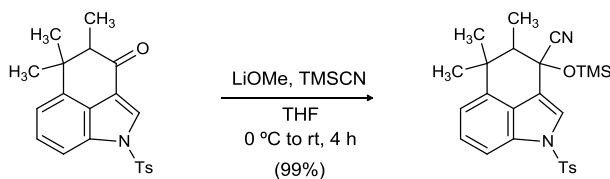
4,5,5-Trimethyl-1-tosyl-1,5-dihydrobenzo[cd]indole-3-carbonitrile (549).

To a 0 °C solution of cyanohydrin (3.05 g, 6.54 mmol) in POCl₃ (15.0 mL, 164 mmol) was added HF-pyridine (700 μL, 26.1 mmol) dropwise. The reaction was stirred for 60 minutes at 0 °C and pyridine (33.0 mL, 410 mmol) was added. The reaction was stirred at 80 °C for 2 h and then cooled to 0 °C. The reaction was quenched with 1.0 M HCl and the solution was stirred for 10 minutes. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with satd aq NaHCO₃, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 10-15-20% ethyl acetate in hexanes) to afford the nitrile as a white solid (1.18 g, 48%). *R*_f = 0.29 (SiO₂, 20% EtOAc/hexanes); mp = 192 °C; IR (film) 2973, 2927, 2222, 1439, 1369, 1090 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.81 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.39 (s, 1H), 7.36 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 7.6 Hz, 1H), 2.36 (s, 3H), 2.30 (s, 3H), 1.48 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) ppm 160.2, 145.1, 137.6, 135.2, 133.1, 130.0, 127.3, 126.9, 125.0, 119.1, 117.7, 116.0, 115.0, 111.4, 102.0, 42.3, 29.9, 21.6, 18.7; HRMS (EI): Exact mass calcd for C₂₂H₂₁N₂O₂S [M+H]⁺ 377.1318, found 377.1309.



4,5,5-Trimethyl-1-tosyl-1,5-dihydrobenzo[*cd*]indole-3-carbonitrile (549).

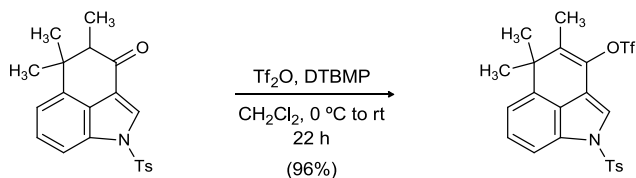
To a degassed solution of enol triflate (3.90 g, 7.82 mmol) and zinc cyanide (1.10 g, 9.38 mmol) in DMF (20 mL) was added Pd(Ph₃)₄ (451 mg, 0.39 mmol) and the reaction stirred at 100 °C for 4 h. The reaction was cooled to rt and quenched with H₂O. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 10-20% ethyl acetate in hexanes) to afford the nitrile as a white solid (2.79 g, 97%). The data matched with the earlier reported data for the cyanide. See above for the characterization data.



4,5,5-Trimethyl-1-tosyl-3-((trimethylsilyl)oxy)-1,3,4,5-tetrahydrobenzo[*cd*]indole-3-carbonitrile (550).

To a 0 °C solution of LiOMe (1.0 mg, 27 μmol) in THF (1.1 mL) was added TMSCN (26.2 μL, 196 μmol) and the reaction was allowed to warm to room temperature and stirred for 10 minutes. Ketone (40.0 mg, 109 μmol) was added and the reaction was stirred for an additional 4 h at rt. The reaction was quenched with satd aq KH₂PO₄, the layers were separated, and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with satd aq KH₂PO₄, dried, filtered, and concentrated. The resulting cyanohydrin was sufficiently pure for analytical purposes (50.0 mg, 99%). The

cyanohydrin was isolated as a 1:1 mixture of diastereomers.¹⁰ $R_f = 0.49$ (SiO₂, 20% EtOAc/hexanes); IR (film) 2971, 2926, 1376, 1253, 1189, 1175, 1124 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, data for both diastereomers) δ 7.85 (d, $J = 8.0$ Hz, 2H), 7.83 (d, $J = 8.0$ Hz, 2H), 7.77 (d, $J = 8.0$ Hz, 1H), 7.75 (d, $J = 8.0$ Hz, 1H), 7.68 (s, 1H), 7.63 (s, 1H), 7.37 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.35 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.26 (d, $J = 8.0$ Hz, 2H), 7.26 (d, $J = 8.0$ Hz, 2H), 7.20 (d, $J = 7.2$ Hz, 1H), 7.15 (d, $J = 7.6$ Hz, 1H), 2.36 (s, 3H), 2.36 (s, 3H), 2.19 (q, $J = 6.8$ Hz, 1H), 2.03 (q, $J = 6.8$ Hz, 1H), 1.44-1.42 (m, 6H), 1.39 (s, 3H), 1.35 (s, 3H), 1.21 (s, 3H), 1.12 (br s, 3H), 0.15 (s, 9H), 0.11 (s, 9H); ¹³C NMR (100 MHz, CDCl₃, data for both diastereomers) ppm 145.3, 140.9, 135.3 (2C), 133.1, 133.0, 130.1 (2C), 127.0, 126.9, 125.5, 126.4, 124.9, 124.6, 122.3, 120.8, 119.6, 118.6, 111.1, 110.9, 77.2, 68.3, 50.9, 49.1, 38.9, 37.9, 29.7, 29.6, 27.8, 27.7, 25.8, 21.6, 10.5 (2C), 1.3, 0.7; HRMS (EI): Exact mass calcd for C₂₄H₂₈N₂O₃SSi [M]⁺ 489.1644, found 489.1642.

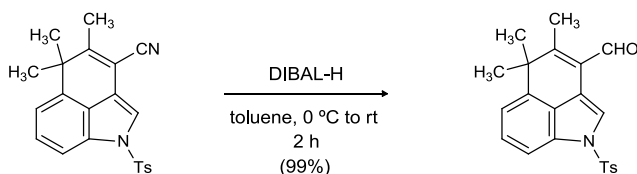


4,5,5-Trimethyl-1-tosyl-1,5-dihydrobenzo[*cd*]indol-3-yl trifluoromethanesulfonate (551).

To a 0 °C solution of ketone (1.05 g, 2.86 mmol) and 4-methyl-2,6-di-*t*-butylpyridine (1.06 g, 5.15 mmol) in CH₂Cl₂ (5.0 mL) was added trifluoromethanesulfonyl anhydride (0.77 mL, 4.58 mmol) dropwise. The reaction was allowed to warm to room temperature and stirred for 22 h. The reaction was quenched by slow dropwise addition of satd aq

¹⁰ The cyanohydrin was found to hydrolyze upon exposure to SiO₂ or upon storage for a longer duration of time (>7 days). As a result the crude cyanohydrin was subjected to the subsequent (elimination) reaction immediately after isolation.

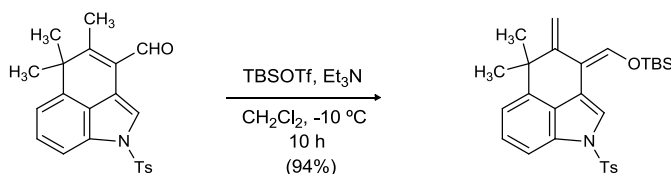
NaHCO₃ at 0 °C and the solution was stirred for 5 minutes at rt. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 5-10% ethyl acetate in hexanes) to afford the enol triflate as a white solid (1.32 g, 53%). R_f = 0.42 (SiO₂, 20% EtOAc/hexanes); mp = 101-103 °C; IR (film) 2969, 2926, 2855, 1428, 1378, 1246, 1190, 1008 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.37 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.32 (s, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 7.6 Hz, 1H), 2.35 (s, 3H), 2.03 (s, 3H), 1.49 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) ppm 145.1, 138.2, 137.4, 135.4, 135.0, 133.2, 130.0, 127.1, 126.9, 126.6, 119.3, 118.5 (q, ¹J_{CF} = 320 Hz), 116.7, 113.7, 111.4, 44.4, 29.9, 21.6, 12.4; HRMS (EI): Exact mass calcd for C₂₂H₂₁F₃NO₅S₂ [M+H]⁺ 500.0808, found 500.0815.



4,5,5-Trimethyl-1-tosyl-1,5-dihydrobenzo[cd]indole-3-carbaldehyde (552).

To a 0 °C solution of nitrile (2.45 g, 6.51 mmol) in toluene (30 mL) was added DIBAL-H (4.99 mL, 7.49 mmol, 1.5 M in toluene) and stirred for 1 h at 0 °C. The reaction was quenched by the stepwise addition of H₂O (30 mL) and 6M HCl (100 mL). The reaction was allowed to warm to room temperature and stirred until the layers became clear (~6 h). The layers were separated, and the aqueous layer was extracted with Et₂O. The combined organic layers were dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 20% ethyl acetate in hexanes) to afford

the enal as a white solid (2.45 g, 99%). $R_f = 0.16$ (SiO₂, 20% EtOAc/hexanes); mp = 188 °C; IR (film) 2972, 2925, 2871, 1672, 1438, 1370 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 10.42 (s, 1H), 8.05 (s, 1H), 7.82 (d, $J = 8.4$ Hz, 2H), 7.73 (d, $J = 7.8$ Hz, 1H), 7.33 (dd, $J = 8.4, 8.4$ Hz, 1H), 7.21 (d, $J = 8.4$ Hz, 2H), 7.14 (d, $J = 7.8$ Hz, 1H), 2.44 (s, 3H), 2.33 (s, 3H), 1.52 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) ppm 190.2, 161.9, 144.6, 137.8, 135.6, 132.6, 129.8, 126.9, 126.4, 126.3, 126.1, 120.8, 118.7, 113.0, 111.1, 42.9, 29.7, 21.6, 13.9; HRMS (EI): Exact mass calcd for C₂₂H₂₂NO₃S [M+H]⁺ 380.1320, found 380.1332.

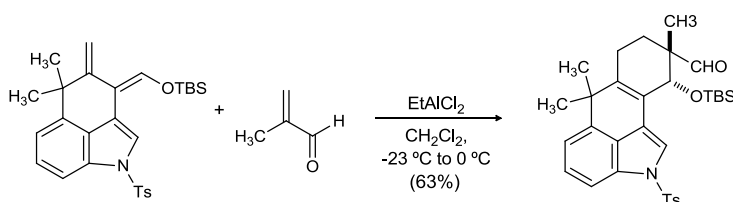
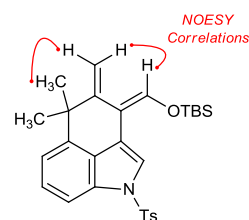


(Z)-3-(((*tert*-Butyldimethylsilyl)oxy)methylene)-5,5-dimethyl-4-methylene-1-tosyl-1,3,4,5-tetrahydrobenzo[*cd*]indole (553).

To a -10 °C solution of enal (1.03 g, 2.72 mmol) and triethylamine (833 μ L, 5.98 mmol) in CH₂Cl₂ (13 mL) was added TBSOTf (808 μ L, 4.62 mmol) dropwise and the reaction was stirred for 10 h at -10 °C. The reaction was quenched by slow dropwise addition satd aq NH₄Cl and the solution was warmed to rt. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 5-10% ethyl acetate in hexanes) to afford the diene as a colorless oil (1.26 g, 94%). $R_f = 0.57$ (SiO₂, 20% EtOAc/hexanes); IR (film) 2955, 2927, 2856, 1637, 1375, 1174 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.76 (d, $J = 10.5$ Hz, 2H), 7.74 (d, $J = 10.5$ Hz, 1H), 7.66 (s, 1H), 7.28 (dd, $J = 10.0, 10.0$ Hz, 1H), 7.18 (d, $J = 10.5$ Hz,

2H), 7.15 (d, $J = 9.5$ Hz, 1H), 6.83 (s, 1H), 5.06 (d, $J = 0.5$ Hz, 1H), 4.90 (d, $J = 0.5$ Hz, 1H), 2.33 (s, 3H), 1.40 (s, 6H), 1.01 (s, 9H), 0.30 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) ppm 151.2, 144.5, 140.3, 137.9, 135.7, 132.9, 129.8, 127.1, 126.8, 125.6, 119.6, 116.8, 116.3, 114.7, 111.1, 106.5, 40.2, 29.7, 28.4, 25.7, 21.5, 18.3, -5.2; HRMS (EI): Exact mass calcd for $\text{C}_{22}\text{H}_{21}\text{NO}_3\text{S}$ $[\text{M}-\text{C}_6\text{H}_{14}\text{Si}]^+$ 379.1278, found 379.1278.¹¹

A NOESY crosspeak was observed between the methylene proton of the exocyclic alkene and the methine proton, thus confirming the formation of requisite diene with the desired diene geometry.



(9*S*,10*R*)-10-((*tert*-Butyldimethylsilyl)oxy)-6,6,9-trimethyl-2-tosyl-2,6,7,8,9,10-hexahydronaphtho[1,2,3-*cd*]indole-9-carbaldehyde (558).

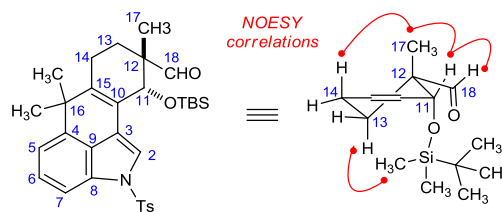
To a -23 °C solution of diene (100 mg, 203 μmol) and methacrolein (335 μL , 4.06 mmol) in CH_2Cl_2 (850 μL) was added EtAlCl_2 (112 μL , 203 μmol , 1.8 M in toluene) dropwise over 5 minutes.¹² The reaction was stirred for 30 minutes at -23 °C and 1.5 h at 0 °C. The reaction was quenched by slow dropwise addition of satd aq NaHCO_3 and the solution was warmed to rt. The layers were separated, and the aqueous layer was

¹¹ TBS group was lost

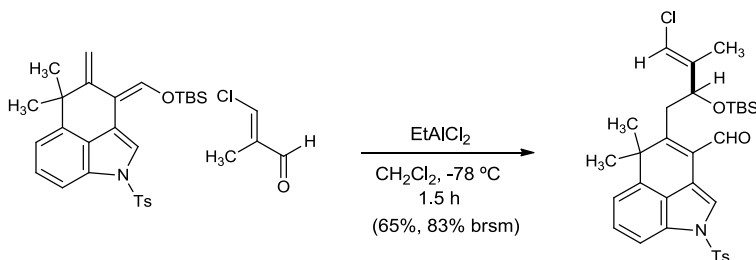
¹² Rapid addition leads to lower yields.

extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 5-10% ethyl acetate in hexanes) to afford the Diels Alder adduct as a viscous oil (72 mg, 63%). The adduct was isolated as a single diastereomer as indicated by the NMR analysis. R_f = 0.40 (SiO₂, 20% EtOAc/hexanes); IR (film) 2956, 2928, 2856, 1729, 1368, 1172, 1118, 1100 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.70 (s, 1H), 7.82 (d, *J* = 8.3 Hz, 2H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.36 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.25 (s, 1H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.15 (d, *J* = 7.5 Hz, 1H), 4.67 (s, 1H), 2.55 (ddd, 11.5, 11.5, 2.5 Hz, 1H), 2.37-2.34 (m, 1H), 2.35 (s, 3H), 1.73-1.59 (m, 2H), 1.44 (s, 3H), 1.41 (s, 3H), 0.92 (s, 3H), 0.74 (s, 9H), 0.00 (s, 3H), -0.29 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) ppm 205.2, 144.8, 144.7, 140.2, 135.7, 133.5, 129.9, 126.9, 126.7, 126.5, 121.4, 119.8, 118.8, 115.7, 110.8, 70.8, 49.8, 49.3, 40.9, 31.0, 29.0, 25.7, 22.1, 21.9, 21.5, 18.3, 16.0, -3.5, -4.1; HRMS (EI): Exact mass calcd for C₃₂H₄₁NNaO₄SSi [M+Na]⁺ 586.2423, found 586.2426.

A complete 2D NMR analysis was carried out to elucidate the structure of Diels-Alder adduct. HSQC was effective in identifying peaks in the overlapping regions and allowed for NOESY correlations to these regions to be readily distinguishable. NOESY correlations from both H11 to H17 and H11 to aldehyde proton, and the absence of the NOESY correlations between H11 to either H13 and H14, strongly suggested that the H11 proton is equatorial. Additionally, a NOESY correlation between TBS-methyl protons and H13 α indicated that the -OTBS is in the axial position, thus confirming the



stereochemistry at C11. The stereochemistry at C12, which has an axial methyl group, could be relayed to both H14 β and H18. These analyses confirmed the structure of the desired Diels-Alder adduct.



(8*S*,10*R*)-10-((*tert*-Butyldimethylsilyl)oxy)-8-((*E*)-1-chloroprop-1-en-2-yl)-6,6-dimethyl-2-tosyl-6,7,8,10-tetrahydro-2*H*-isochromeno[8,7,6-*cd*]indole (559).

To a $-78\text{ }^\circ\text{C}$ solution of diene (25.0 mg, 50.7 μmol) and β -chloro methacrolein (52.5 μL , 507 μmol) in CH_2Cl_2 (220 μL) was added EtAlCl_2 (28 μL , 50.8 μmol , 1.8 M in toluene) dropwise over 5 minutes.¹³ The reaction was stirred for 30 minutes at $-78\text{ }^\circ\text{C}$ and 3.0 h at $-23\text{ }^\circ\text{C}$. The reaction was quenched by slow dropwise addition of satd aq NaHCO_3 and the solution was warmed to rt. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO_2 , 5-10% ethyl acetate in hexanes) to afford the Mukaiyama aldol product as a yellow oil (19.5 mg, 63%) in addition to the hydrolyzed enal (**552**, 5.3 mg, 21%). $R_f = 0.31$ (SiO_2 , 20% EtOAc/hexanes); IR (film) 2956, 2928, 2886, 2857, 1675, 1367, 1170, 1118, 1117, 1095 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 10.25 (s, 1H), 8.13 (s, 1H), 7.78 (d, $J = 8.4$ Hz, 2H), 7.74 (d, $J = 8.0$ Hz, 1H), 7.34 (dd, $J = 7.6, 7.6$ Hz, 1H), 7.19 (d, $J = 8.0$ Hz, 2H), 7.14 (d, $J = 7.6$ Hz, 1H), 6.13 (d, $J = 0.6$ Hz, 1H), 4.22 (dd, $J =$

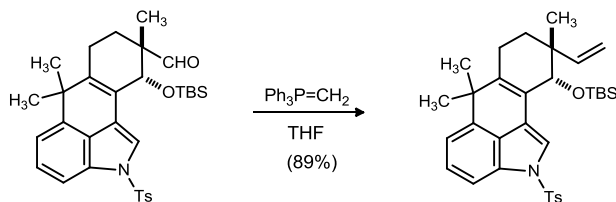
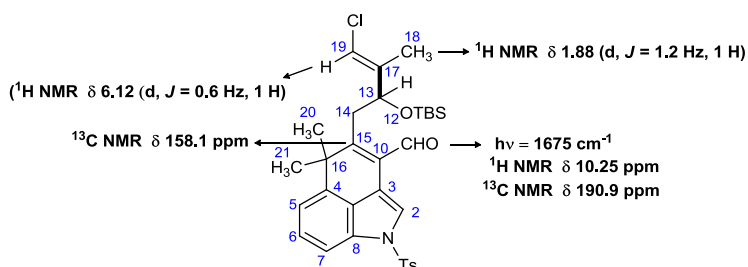
¹³ Rapid addition leads to lower yields.

10.0, 2.4 Hz, 1H), 3.40 (dd, $J = 14.0, 10.0$ Hz, 1H), 2.59 (dd, $J = 14.4, 2.4$ Hz, 1H), 2.32 (s, 3H), 1.88 (d, $J = 1.2$ Hz, 3H), 1.57 (s, 3H), 1.42 (s, 3H), 0.70 (s, 9H), -0.16 (s, 3H), -0.32 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) ppm 190.9, 158.1, 144.5, 141.0, 137.5, 135.5, 132.6, 129.7, 129.1, 126.8, 126.4, 126.3, 121.7, 118.5, 115.5, 113.3, 111.3, 75.3, 43.1, 34.4, 32.6, 27.6, 25.6, 21.5, 18.0, 12.1; HRMS (EI): Exact mass calcd for $\text{C}_{26}\text{H}_{25}\text{ClNO}_3\text{S}$ $[\text{M}-\text{C}_6\text{H}_{15}\text{O}]^+$ 466.12, found 466.12.¹⁴

The appearance of a proton as doublet at 6.13 ppm, and the carbon connected to it at 115.5 ppm as shown by HSQC analysis, indicated that this carbon is most probably sp^2 hybridized (C19). The ^1H

NMR showed three well resolved dd patterns at 4.22, 3.40 and 2.59, which are the methine (C13) and

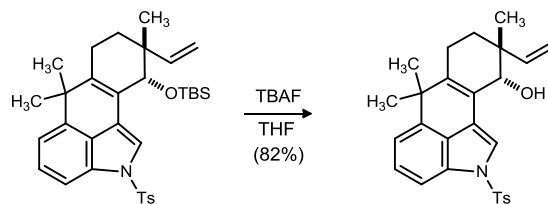
methylene (C14) protons adjacent to each other. A weak IR stretch at 1675 cm^{-1} , and the presence of ^1H NMR and ^{13}C NMR peaks at 10.25 and 190.9 ppm indicated the presence of an α,β -unsaturated aldehyde. The presence of the enal was confirmed by a downfield shift of the C17 in the ^{13}C NMR spectrum (158.1 ppm).



¹⁴ Loss of TBSOH was observed, due to elimination, resulting in a highly conjugated system.

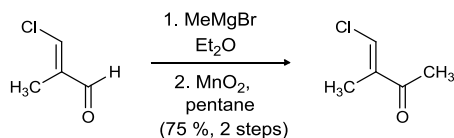
(9R,10S)-10-((*tert*-Butyldimethylsilyl)oxy)-6,6,9-trimethyl-2-tosyl-9-vinyl-2,6,7,8,9,10-hexahydronaphtho[1,2,3-*cd*]indole (560).

To a -78 °C solution of methyl triphenylphosphonium bromide (60.9 mg, 170 μmol) in THF (600 μL) was added ⁿBuLi (63.1 μL, 157 μmol) dropwise. The reaction was stirred for 10 minutes at -78 °C before being warmed to 0 °C and stirred for another 30 min. The reaction was cooled to -78 °C and a solution of aldehyde (24.0 mg, 42.6 μmol) in THF (400 μL) was added dropwise over 5 minutes. The reaction was stirred for 1 h at -78 °C before being warmed to rt and stirred for 10 h. The reaction was quenched with H₂O and the layers were separated. The aqueous layer was extracted with Et₂O and the combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 8% ethyl acetate in hexanes) to afford the alkene as a yellow oil (21.4 mg, 89%). *R*_f = 0.55 (SiO₂, 20% EtOAc/hexanes); IR (film) 2956, 2927, 2855, 1369, 1187, 1171, 1099, 1088 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.81 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.33 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.18 (s, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 6.07 (dd, *J* = 17.5, 10.5 Hz, 1H), 5.04 (d, *J* = 12.0 Hz, 1H), 5.04 (d, *J* = 17.0 Hz, 1H), 4.13 (s, 1H), 2.48 (dd, *J* = 19.0, 6.5 Hz, 1H), 2.38-2.27 (m, 1H), 2.34 (s, 3H), 2.20 (ddd, *J* = 12.0, 10.5, 7.0 Hz, 1H), 1.48-1.45 (m, 1H), 1.44 (s, 3H), 1.40 (s, 3H), 0.89 (s, 3H), 0.74 (s, 9H), 0.00 (s, 3H), -0.25 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) ppm 147.1, 144.6, 142.5, 140.6, 135.7, 133.4, 129.7, 126.9, 126.8, 126.3, 123.1, 120.2, 118.6, 115.5, 111.4, 110.6, 73.4, 40.6, 39.6, 31.1, 28.7, 26.4, 25.9, 22.6, 21.5, 20.0, 18.4, -3.6, -3.8; HRMS (ED): Exact mass calcd for C₃₃H₄₃NNaO₃SSi [M+Na]⁺ 584.2631, found 584.2646.



(9*R*,10*S*)-6,6,9-Trimethyl-2-tosyl-9-vinyl-2,6,7,8,9,10-hexahydronaphtho[1,2,3-*cd*]indol-10-ol (561).

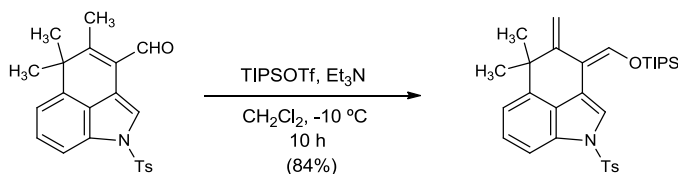
To a 0 °C solution of the TBS ether (30.5 mg, 54.4 μ mol) in THF (1.0 mL) was added TBAF (136 μ L, 136 μ mol, 1.0 M in THF). The reaction was warmed to rt and stirred for 1 h. The reaction was quenched with satd aq NaHCO₃ and the layers were separated. The aqueous layer was extracted with Et₂O and the combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 15% ethyl acetate in hexanes) to afford the alcohol as a white foam (22.9 mg, 95%). R_f = 0.28 (SiO₂, 20% EtOAc/hexanes); IR (film) 3551, 2969, 2926, 2870, 1436, 1362, 1188, 1170, 1116, 1098 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.80 (d, J = 8.5 Hz, 2H), 7.68 (d, J = 8.5 Hz, 1H), 7.42 (s, 1H), 7.31 (dd, J = 8.0, 8.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 1H), 6.04 (dd, J = 17.5, 11.0 Hz, 1H), 5.26 (d, J = 11.0 Hz, 1H), 5.22 (d, J = 17.5 Hz, 1H), 4.16 (s, 1H), 2.49 (ddd, J = 19.0, 5.0, 5.0 Hz, 1H), 2.39-2.35 (m, 1H), 2.35 (s, 3H), 1.94 (ddd, J = 12.5, 9.0, 6.0 Hz, 1H), 1.75 (s, 1H), 1.58 (ddd, J = 13.0, 5.0, 5.0 Hz, 1H), 1.44 (s, 3H), 1.42 (s, 3H), 1.08 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) ppm 144.5, 143.3, 142.8, 139.9, 135.7, 133.2, 129.8, 127.2, 126.9 (2C), 126.2, 122.5, 118.8, 118.5, 117.2 (2C), 115.2, 110.7, 72.9, 40.8, 39.6, 30.7, 29.7, 28.4, 22.4, 21.9, 21.5; HRMS (EI): Exact mass calcd for C₂₇H₂₉NNaO₃S [M+Na]⁺ 470.1776, found 470.1776.



4-Chloro-3-methyl-but-3-en-2-one (231).

A solution of methyl magnesium bromide (240 mL, 3.0 M in ether, 721 mmol), in ether (600 mL) was cooled to 0 °C and treated with a solution of β -chloro- α -methyl acrolein (68.5 g, 655 mmol) as a pre-dissolved solution in ether (80 mL). The mixture was warmed to room temperature and quenched with an ether-ice mixture, followed by an aqueous work-up to give the alcohol in sufficient purity for oxidation.

The alcohol (55.5 g, 95.7 mmol) was added to a slurry of MnO₂ (476 g, 5.48 mol) in pentane (1.5 L) and stirred vigorously for 36 hours. Additional MnO₂ (119 g, 1.12 mol) was added and the mixture was stirred for an additional 12 h. The mixture was filtered over Celite and concentrated to a yellow oil that was purified by flash chromatography (SiO, 8% ether in hexanes) to furnish the ketone as a yellow oil (54 g, 74%). Analytical data was identical to that in the literature.

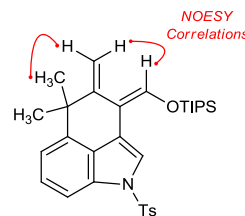


(Z)-5,5-Dimethyl-4-methylene-1-tosyl-3-(((triisopropylsilyl)oxy)methylene)-1,3,4,5-tetrahydrobenzo[cd]indole (563).

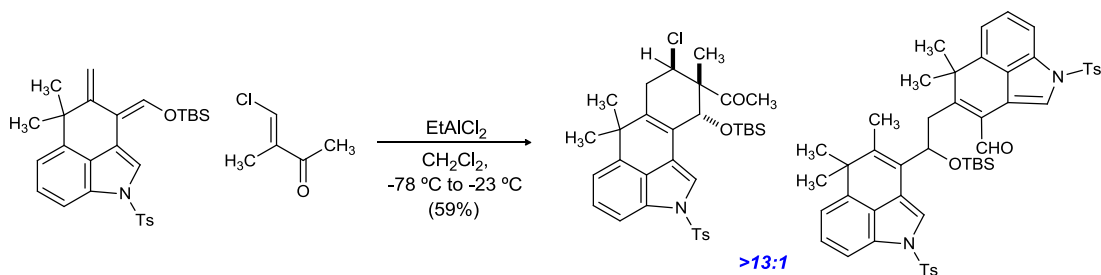
To a -10 °C solution of enal (11.0 mg, 29.0 μ mol) and triethylamine (12.0 μ L, 87.0 μ mol) in CH₂Cl₂ (400 μ L) was added TIPSOTf (23.4 μ L, 87.0 μ mol) dropwise and the

reaction was stirred for 10 h at -10 °C. The reaction was quenched by slow dropwise addition of satd aq NH₄Cl and the solution was warmed to rt. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 5% ethyl acetate in hexanes) to afford the diene as a colorless oil (13.0 mg, 84%). R_f = 0.56 (SiO₂, 20% EtOAc/hexanes); IR (film) 2944, 2925, 2866, 1375, 1174, 1096 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.70 (s, 1H), 7.28 (dd, *J* = 8.4, 8.4 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.15 (d, *J* = 7.2 Hz, 1H), 6.89 (s, 1H), 5.05 (d, *J* = 0.6 Hz, 1H), 4.90 (d, *J* = 0.6 Hz, 1H), 2.33 (s, 3H), 1.40 (s, 6H), 1.32 (sept, *J* = 7.8 Hz, 3H), 1.16 (d, *J* = 7.2 Hz, 18H); ¹³C NMR (125 MHz, CDCl₃) ppm 151.3, 144.5, 140.3, 138.5, 135.7, 132.9, 129.7, 127.1, 126.8, 125.6, 119.7, 116.8, 116.3, 114.4, 111.1, 106.3, 40.2, 28.4, 21.5, 17.7, 11.8; HRMS (EI): Exact mass calcd for C₂₂H₂₂NO₃S [M-C₉H₁₈Si]⁺ 380.1320, found 380.1295.¹⁵

A NOESY crosspeak was observed between the methylene proton of the exocyclic alkene and the methine proton, thus confirming the formation of requisite diene with the desired diene geometry.



¹⁵ TIPS group was lost



1-((8*R*,9*S*,10*R*)-10-((*tert*-Butyldimethylsilyl)oxy)-8-chloro-6,6,9-trimethyl-2-tosyl-2,6,7,8,9,10-hexahydronaphtho[1,2,3-*cd*]indol-9-yl)ethanone (564).

EtAlCl₂ (1.79 mL, 3.22 mmol, 1.8 M in toluene) was added dropwise to a -78 °C solution of the diene (1.59 g, 3.22 mmol) and the dienophile (2.66 g, 22.6 mmol) in CH₂Cl₂ (13.0 mL).¹⁶ The reaction was stirred for 30 minutes at -78 °C and 2.5 h at -23 °C. The reaction was quenched by slow dropwise addition of satd aq NaHCO₃ and the solution was warmed to rt. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 5-10% ethyl acetate in hexanes) to afford the Diels-Alder adduct (1.16 g, 59%) in addition to the Mukaiyama aldol product (96 mg, 7%).

Diels-Alder adduct (564)

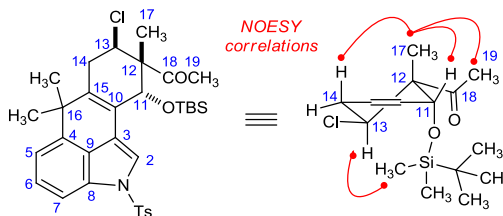
The adduct was isolated as a single diastereomer (¹H NMR). R_f = 0.36 (SiO₂, 20% EtOAc/hexanes); mp 240-241 °C (decomp); IR (film) 2928, 2887, 2856, 1716, 1367, 1186, 1170, 1117, 1091 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.37 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.25 (s, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 7.8 Hz, 1H), 5.10 (dd, *J* = 9.6, 7.2 Hz, 1H), 4.76 (s, 1H), 3.15 (dd, *J* =

¹⁶ Rapid addition leads to lower yields.

19.2, 7.2 Hz, 1H), 2.61 (dd, $J = 18.6, 9.6$ Hz, 1H), 2.35 (s, 3H), 2.33 (s, 3H), 1.48 (s, 3H), 1.42 (s, 3H), 1.11 (s, 3H), 0.71 (s, 9H), -0.08 (s, 3H), -0.31 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) ppm 207.3, 144.9, 142.7, 139.7, 135.8, 133.6, 129.9 (2C), 126.9, 126.4, 121.7, 119.2, 118.9, 116.3, 111.1, 74.5, 56.7, 56.1, 40.8, 34.9, 31.2, 28.8, 26.5, 25.6, 21.5, 18.2, 13.8, -3.7, -4.2; HRMS (EI): Exact mass calcd for $\text{C}_{33}\text{H}_{42}\text{ClNO}_4\text{SSi}$ $[\text{M}]^+$ 611.2287, found 611.2306.

A complete 2D NMR analysis was carried out to elucidate the structure of Diels-Alder adduct. NOESY correlations from both

H11 to H17¹⁷ and H11 to C19, and the absence of NOESY correlations between H11 to either H13 and H14, suggested that



the H11 proton is equatorial. Additionally, a NOESY correlation between TBS-methyl protons and H13 α indicated that the -OTBS is in the axial position, thus confirming the stereochemistry at C11. The stereochemistry at C12, which has an axial methyl group, could be relayed to both H14 β and H19. These observations support the assignment of the Diels-Alder adduct as depicted.

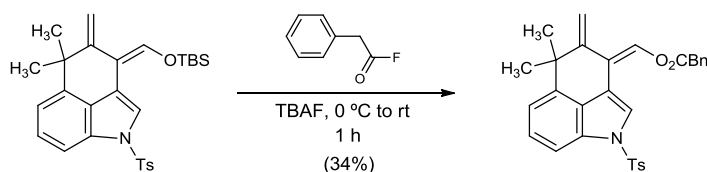
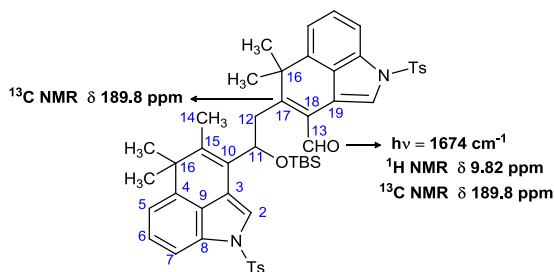
Mukaiyama aldol product (576)

$R_f = 0.23$ (SiO_2 , 20% EtOAc/hexanes); mp 200-202 °C; IR (film) 2962, 2928, 2857, 1674, 1437, 1367, 1187, 1169, 1095 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.83 (s, 1H), 8.07 (s, 1H), 7.82 (d, $J = 8.5$ Hz, 2H), 7.77 (d, $J = 8.5$ Hz, 2H), 7.76 (d, $J = 8.5$ Hz, 1H), 7.75 (d, $J = 8.0$ Hz, 1H), 7.57 (s, 1H), 7.36 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.25 (s, 1H), 7.22 (d, $J = 8.5$ Hz, 2H), 7.20 (d, $J = 8.0$ Hz, 2H), 7.17 (d, $J = 7.5$ Hz, 1H), 7.14 (d, $J = 7.5$ Hz,

¹⁷ Heterocycle numbering used here throughout instead of IUPAC/CAS numbering.

1H), 4.99 (dd, $J = 6.5, 6.5$ Hz, 1H), 3.28 (br s, 2H), 2.33 (s, 6H), 1.65 (s, 3H), 1.64 (s, 3H), 1.50 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H), 0.77 (s, 9H), -0.08 (s, 3H), -0.25 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) ppm 189.7, 159.0, 144.4, 144.3, 139.3, 137.4, 135.5, 135.3, 132.8, 132.4, 129.6, 129.5, 128.4, 126.8, 126.5 (2C), 126.1, 126.0, 121.3, 118.6, 118.3, 115.2, 113.1, 111.0, 110.4, 71.9, 43.1, 41.2, 34.5, 30.7, 27.4, 25.5, 21.3, 17.8, 15.0, -5.0, -5.3; HRMS (EI): Exact mass calcd for $\text{C}_{50}\text{H}_{56}\text{N}_2\text{Na O}_6\text{S}_2\text{Si}$ $[\text{M}]^+$ 895.3247, found 895.3283.

The ^1H NMR analysis showed one well resolved dd pattern at 4.95 in addition to two poorly resolved patterns at 3.30 and 2.25, which are the methine (C11) and methylene (C12) adjacent to each other. A weak IR stretch at 1675 cm^{-1} , and the presence of ^1H NMR and ^{13}C NMR peaks at 9.82 and 189.8 ppm indicated the presence of an α,β -unsaturated aldehyde. The presence of enal was confirmed by the downfield shift of C17 in ^{13}C NMR spectrum (159.0 ppm).



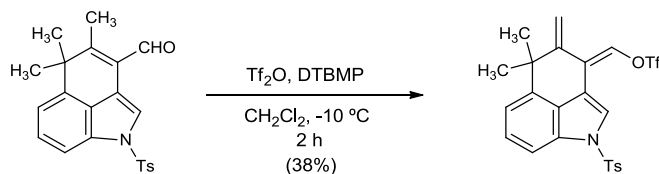
(Z)-(5,5-Dimethyl-4-methylene-1-tosyl-4,5-dihydrobenzo[cd]indol-3(1H)-ylidene)methyl 2-phenylacetate (566).

To a $0\text{ }^\circ\text{C}$ solution of phenylacetic acid (500 mg, 3.67 mmol) in CH_2Cl_2 (18.0 mL) was added (diethylamino)sulfur trifluoride (824 μL , 6.24 mmol) dropwise. The reaction was

stirred for 10 minutes before being warmed to rt and stirred for another 30 min. The organic layer was washed once with H₂O and then brine and dried, filtered, and concentrated to a pale yellow oil. The crude acyl fluoride was used in the next reaction without any further purification.

To a 0 °C solution of acyl fluoride (210 mg, 152 μmol) in THF (1.0 mL) was added diene (30.0 mg, 60.8 μmol) and TBAF (5.00 μL, 4.87 μmol, 1.0 M in THF). The reaction was stirred for 10 minutes at 0 °C before being warmed to rt and stirred for another 30 min. The reaction was quenched by slow dropwise addition of satd aq NaHCO₃. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 10-20% ethyl acetate in hexanes) to afford the diene as a pale yellow oil (10.0 g, 34%). *R_f* = 0.41 (SiO₂, 20% EtOAc/hexanes); IR (film) 3030, 2968, 2925, 1752, 1373, 1232, 1189, 1122 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.74 (d, *J* = 8.5 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.70 (s, 1H), 7.56 (s, 1H), 7.49-7.45 (m, 4H), 7.37 (ddd, *J* = 9.0, 5.5, 2.0 Hz, 1H), 7.29 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 7.0 Hz, 1H), 5.22 (s, 1H), 5.03 (s, 1H), 3.94 (s, 2H), 2.34 (s, 3H), 1.40 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) ppm 168.0, 150.0, 144.9, 139.9, 139.8, 132.8, 131.2, 129.9, 129.4, 129.1, 127.6, 126.8, 126.6, 126.0, 121.0, 118.2, 117.4, 117.1, 114.8, 111.2, 109.5, 41.6, 40.2, 28.2, 21.6; HRMS (EI): Exact mass calcd for C₂₂H₂₁NO₃S [M-C₈H₆O]⁺ 379.1242, found 379.1220.¹⁸

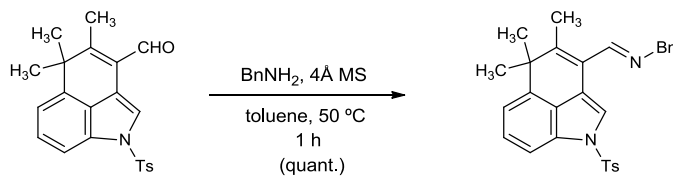
¹⁸ Benzyl group was lost



(Z)-5,5-Dimethyl-4-methylene-1-tosyl-4,5-dihydrobenzo[cd]indol-3(1H)-ylidene)methyl trifluoromethanesulfonate (569).

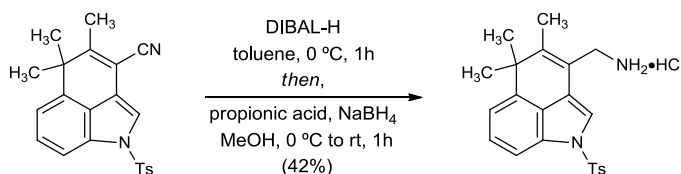
To a $-10\text{ }^\circ\text{C}$ solution of enal (42.0 mg, 111 μmol) and 4-methyl-2,6-di-*t*-butylpyridine (68.3 mg, 333 μmol) in CH_2Cl_2 (700 μL) was added trifluoromethanesulfonyl anhydride (46.7 μL , 277 μmol) dropwise and the reaction was stirred for 2 h. The reaction was quenched with satd aq NaHCO_3 at $-10\text{ }^\circ\text{C}$ and the solution was stirred for 5 minutes at rt. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO_2 , 5-10% ethyl acetate in hexanes) to afford the diene as a pale yellow oil (21.0 mg, 38%). The enol triflate was isolated as a 10:1 inseparable mixture of *E* and *Z* isomers.¹⁹ $R_f = 0.44$ (SiO_2 , 20% EtOAc/hexanes); IR (film) 2969, 2926, 2855, 1428, 1378, 1246, 1213, 1190, 1175, 1139 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3 , data for the major isomer) δ 7.83 (d, $J = 8.4$ Hz, 2H), 7.77 (d, $J = 8.0$ Hz, 1H), 7.38 (s, 1H), 7.35 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.25 (d, $J = 8.0$ Hz, 2H), 7.19 (d, $J = 7.2$ Hz, 1H), 7.07 (s, 1H), 5.27 (s, 1H), 5.14 (s, 1H), 2.36 (s, 3H), 1.43 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3 , data for the major isomer) ppm 148.4, 145.2, 139.3, 135.1, 132.7, 130.7, 130.0, 127.0, 126.4, 126.0, 124.2, 122.0, 117.3, 112.4, 111.5, 111.3, 40.2, 27.9, 27.3, 21.5, $-\text{CF}_3$ carbon peaks not observed; HRMS (EI): Exact mass calcd for $\text{C}_{23}\text{H}_{21}\text{F}_3\text{NO}_5\text{S}_2$ $[\text{M}+\text{H}]^+$ 512.0808, found 512.0808.

¹⁹ 2D NMR analysis to determine the regioselectivity was not carried out.



(E)-1-Phenyl-N-((4,5,5-trimethyl-1-tosyl-1,5-dihydrobenzo[cd]indol-3-yl)methylene)methanamine (570).

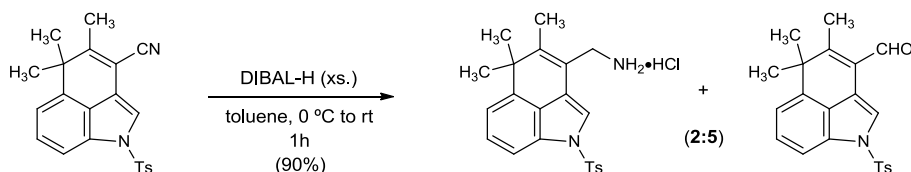
The benzylamine (25.0 mg, 65.9 μmol) was added to the flask containing the aldehyde (25.0 mg, 65.9 μmol) and 4 Å molecular sieves in toluene (300 μL) and the reaction was stirred for 1 h at 50 °C. The solution filtered through a pad of celite and concentrated to a pale yellow oil. The crude imine was sufficiently pure for all analytical purposes (31.3 mg, 100%)²⁰. $R_f = 0.41$ (SiO₂, 20% EtOAc/hexanes); IR (film) 3028, 2971, 2925, 1637, 1437, 1369, 1168, 1094 cm^{-1} ; ¹H NMR (600 MHz, CDCl₃) δ 8.70 (s, 1H), 8.14 (s, 1H), 7.77 (d, $J = 8.4$ Hz, 2H), 7.71 (d, $J = 8.4$ Hz, 1H), 7.43-7.39 (m, 4H), 7.32-7.29 (m, 2H), 7.17 (d, $J = 7.8$ Hz, 2H), 7.13 (d, $J = 7.8$ Hz, 1H), 4.87 (s, 2H), 2.32 (s, 3H), 2.20 (s, 3H), 1.46 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) ppm 159.2, 151.2, 144.3, 139.9, 138.7, 135.7, 132.7, 129.7, 128.5, 127.8, 127.1, 126.8 (2C), 125.8, 123.1, 121.3, 118.6, 115.6, 110.8, 65.8, 42.1, 29.8, 21.5, 14.6; HRMS (EI): Exact mass calcd for C₂₉H₂₉N₂O₂S [M+H]⁺ 469.1944, found 469.1934.



²⁰ The imine was found to hydrolyze on silica and upon storage for longer duration of time (>7 days).

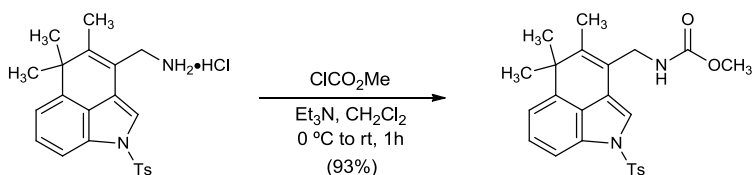
(4,5,5-Trimethyl-1-tosyl-1,5-dihydrobenzo[*cd*]indol-3-yl)methanaminehydrochloride (572).

To a 0 °C solution of nitrile (260 mg, 691 μmol) in toluene (5.0 mL) was added DIBAL-H (1.05 mL, 725 μmol, 1.5 M in toluene). The reaction was stirred for 30 min at 0 °C and an additional 30 min at rt. The reaction was cooled to 0 °C and propionic acid (55.2 μL, 725 μmol) was added. The reaction was stirred for a minute and NaBH₄ (104 mg, 2.76 mmol) in MeOH (5.0) was added to the reaction. The reaction was stirred for 30 min at 0 °C and an additional 30 min at rt. The reaction was quenched by slow dropwise addition of NH₄OH. The layers were separated, and the aqueous layer was extracted with Et₂O. The combined organic layers were washed once with NH₄Cl and then brine and dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 10% MeOH in CH₂Cl₂) to afford the ammonium salt as a brown oil (116 mg, 42%). *R_f* = 0.14 (SiO₂, 10% MeOH/CH₂Cl₂); IR (film) 3000 (br), 2970, 2927, 1369, 1170, 1119 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.88 (d, *J* = 8.0 Hz, 2H), 7.77 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.25 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.06 (br s, 3H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 7.6 Hz, 1H), 4.06 (br s, 2H), 2.12 (s, 3H), 1.90 (s, 3H), 1.26 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) ppm 146.8, 144.6, 139.8, 135.1, 133.2, 129.8, 127.2, 126.5, 126.4, 118.9, 118.1, 117.8, 117.2, 110.5, 41.7, 38.1, 29.8, 21.3, 14.6; HRMS (EI): Exact mass calcd for C₂₂H₂₄N₂OS [M]⁺ 380.1553, found 380.1560.



4,5,5-Trimethyl-1-tosyl-1,5-dihydrobenzo[*cd*]indole-3-carbaldehyde (572).

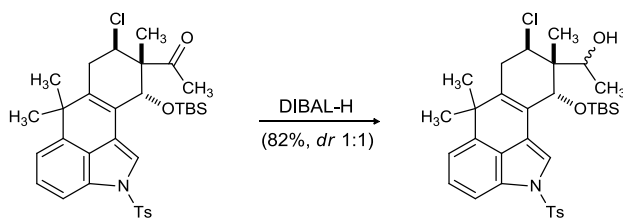
To a 0 °C solution of nitrile (20.0 mg, 53.2 μmol) in toluene (250 μL) was added DIBAL-H (159 μL, 157 μmol, 1.0 M in toluene). The reaction was warmed to rt and stirred for 2 h. The reaction was cooled to 0 °C and more DIBAL-H was added (106 μL, 105 μmol, 1.0 M in toluene). The reaction was warmed to rt and stirred for an additional 4 h. The reaction was quenched by the stepwise addition of H₂O (1.0 mL) and 6M HCl (3 mL). The reaction was stirred vigorously until the layers became clear (~6 h). The layers were separated, and the aqueous layer was extracted with Et₂O. The combined organic layers were dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 2%-5%-10% MeOH in CH₂Cl₂) to afford the amine (5.0 mg, 25%) in addition to the enal (13.0 mg, 65%). See above for the characterization data.



Methyl ((4,5,5-trimethyl-1-tosyl-1,5-dihydrobenzo[*cd*]indol-3-yl)methyl)carbamate (573).

To a 0 °C solution of the amine salt (22.0 mg, 52.8 μmol) and triethyl amine (22.1 μL, 158 μmol) in CH₂Cl₂ (700 μL) was added methyl chloroformate (5.30 μL, 68.6 μmol). The reaction was warmed to rt and stirred for 2 h. The reaction was quenched with satd aq NH₄Cl and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ and the combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 30% ethyl acetate in hexanes) to afford the carbamate as a pale yellow foam (21.5 mg,

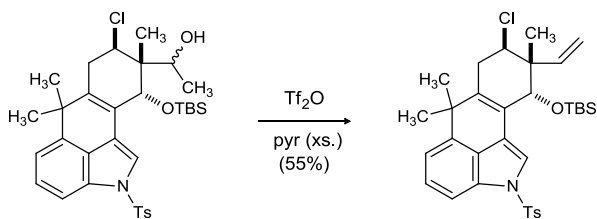
93%). $R_f = 0.08$ (SiO₂, 20% EtOAc/hexanes); IR (film) 3396, 2969, 2928, 1704, 1524, 1438, 1364, 1254, 1186, 1170, 1101 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, $J = 8.4$ Hz, 2H), 7.67 (d, $J = 8.0$ Hz, 1H), 7.32 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.25 (s, 1H), 7.20 (d, $J = 8.4$ Hz, 2H), 7.12 (d, $J = 7.6$ Hz, 1H), 4.70 (s, 1H), 4.21 (br d, $J = 5.2$ Hz, 1H), 3.72 (s, 3H), 2.33 (s, 3H), 1.99 (s, 3H), 1.40 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) ppm 157.0, 144.6, 143.7, 139.9, 135.5, 133.5, 129.8, 126.8, 126.6, 126.5, 120.6, 119.3, 118.9, 116.2, 110.8, 52.3, 41.5, 39.9, 29.9, 21.5, 14.2; HRMS (EI): Exact mass calcd for C₂₄H₂₆N₂O₄S [M]⁺ 438.1608, found 438.1406.



1-((8*R*,9*R*,10*R*)-10-((*tert*-Butyldimethylsilyl)oxy)-8-chloro-6,6,9-trimethyl-2-tosyl-2,6,7,8,9,10-hexahydronaphtho[1,2,3-*cd*]indol-9-yl)ethanol (577).

DIBAL-H (1.70 mL, 2.54 mmol, 1.5 M in toluene) was added to a 0 °C solution of ketone (1.25 g, 2.05 mmol) in toluene (24 mL). The reaction was warmed to rt and stirred for 1 h. After return of the solution to 0 °C, additional DIBAL-H was added (1.70 mL, 2.54 mmol, 1.5 M in toluene). The solution was warmed to rt and stirred for an additional 1 h. The reaction was quenched by the stepwise addition of H₂O (1.0 mL) and 1 M HCl. The layers were separated, and the aqueous layer was extracted with Et₂O. The combined organic layers were dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 10-20% ethyl acetate in hexanes) to afford the alcohol as a viscous oil (1.04 g, 82%). The alcohol was isolated as an inseparable 1:1

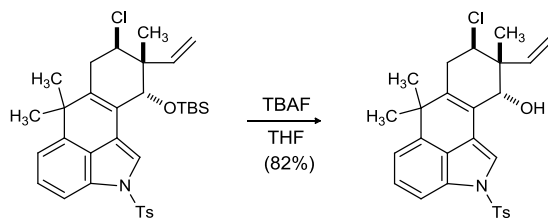
mixture of diastereomers.²¹ $R_f = 0.31$ (SiO₂, 20% EtOAc/hexanes); IR (film) 3568, 2928, 2855, 1460, 1437, 1369, 1171, 1095 cm⁻¹; ¹H NMR (600 MHz, CDCl₃, data for both diastereomers) δ 7.81 (d, $J = 8.4$ Hz, 2H), 7.80 (d, $J = 7.8$ Hz, 2H), 7.73 (d, $J = 8.4$ Hz, 1H), 7.72 (d, $J = 7.8$ Hz, 1H), 7.38 (dd, $J = 7.8, 7.8$ Hz, 1H), 7.37 (dd, $J = 7.8, 7.8$ Hz, 1H), 7.24 (s, 1H), 7.23 (d, $J = 8.4$ Hz, 2H), 7.22 (d, $J = 7.8$ Hz, 2H), 7.22 (s, 1H), 5.07 (dd, $J = 10.2, 7.2$ Hz, 1H), 4.94 (dd, $J = 9.6, 6.6$ Hz, 1H), 4.76 (s, 1H), 4.47 (s, 1H), 4.22 (dd, $J = 12.6, 6.0$ Hz, 1H), 3.96 (ddd, $J = 16.8, 6.0, 6.0$ Hz, 1H), 3.14 (dd, $J = 18.6, 7.2$ Hz, 1H), 3.04 (s, 1H), 3.03 (s, 1H), 3.14 (dd, $J = 18.6, 7.2$ Hz, 1H), 3.14 (dd, $J = 16.2, 6.0$ Hz, 1H), 2.66 (ddd, $J = 18.6, 9.6, 5.4$ Hz, 1H), 2.35 (s, 3H), 2.35 (s, 3H), 1.47 (s, 3H), 1.45 (s, 3H), 1.44 (s, 3H), 1.42 (d, $J = 6.6$ Hz, 3H), 1.41 (s, 3H), 1.34 (d, $J = 7.2$ Hz, 3H), 0.86 (s, 3H), 0.80 (s, 9H), 0.80 (s, 9H), 0.73 (s, 3H), 0.25 (s, 3H), -0.02 (s, 3H), -0.33 (s, 3H), -0.42 (s, 3H), -OH protons (2) not observed; ¹³C NMR (150 MHz, CDCl₃) ppm 145.0, 144.9, 143.6, 142.4, 139.7, 135.7, 135.6, 133.5, 129.9, 126.9, 126.8, 126.4, 126.3, 123.1, 122.5, 119.7, 119.4, 119.0, 118.9, 116.1 (2C), 111.0, 75.1, 74.1, 73.3, 71.8, 64.1, 58.9, 45.7, 44.3, 40.8, 40.5, 36.0, 35.0, 30.8, 29.7, 29.3, 28.9, 25.9, 25.7, 21.5, 18.4, 18.3, 17.2, 14.1, 14.0, 9.6, -3.3, -3.6, -3.8, -4.3; HRMS (EI): Exact mass calcd for C₃₃H₄₄ClNO₄SSi [M]⁺ 611.2443, found 611.2441.



²¹ The alcohol is highly sensitive to the base, and should not be stored for an extended period of time.

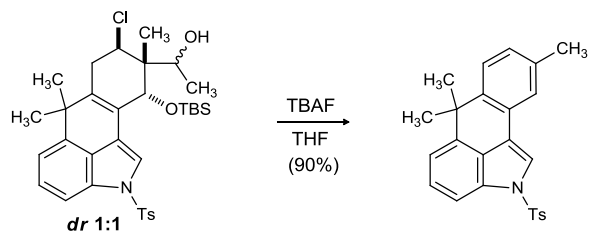
(8*R*,9*R*,10*R*)-10-((*tert*-Butyldimethylsilyl)oxy)-8-chloro-6,6,9-trimethyl-2-tosyl-9-vinyl-2,6,7,8,9,10-hexahydronaphtho[1,2,3-*cd*]indole (578).

To a 0 °C solution of the alcohols (116 mg, 189 μmol) in CH₂Cl₂ (3.0 mL) was added Tf₂O (63.7 μL, 378 μmol) and pyridine (40.8 μL, 567 μmol) and the reaction was stirred for 30 minutes at 0 °C. The solution was warmed to rt and more pyridine (183 μL, 2.27 mmol) was added. The reaction was stirred for 12 h and quenched by slow dropwise addition of satd aq NaHCO₃ at 0 °C. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 5-10% ethyl acetate in hexanes) to afford the desired alkene as a viscous oil (61.6 mg, 55%). *R*_f = 0.52 (SiO₂, 20% EtOAc/hexanes); IR (film) 2956, 2926, 2855, 1371, 1171, 1120, 1099 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.35 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.17 (s, 1H), 7.15 (d, *J* = 7.2 Hz, 1H), 6.17 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.25 (dd, *J* = 10.8, 1.2 Hz, 1H), 5.22 (d, *J* = 18.0 Hz, 1H), 4.77 (dd, *J* = 10.2, 6.6 Hz, 1H), 4.27 (s, 1H), 3.06 (dd, *J* = 18.6, 6.6 Hz, 1H), 2.60 (dd, *J* = 18.6, 10.8 Hz, 1H), 2.35 (s, 3H), 1.47 (s, 3H), 1.40 (s, 3H), 1.01 (s, 3H), 0.73 (s, 9H), -0.08 (s, 3H), -0.21 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) ppm 144.8, 144.1, 141.3, 139.9, 135.7, 133.4, 129.9, 126.9, 126.6 (2C), 123.6, 119.1, 118.7, 116.0, 114.3, 110.9, 76.5, 61.4, 45.6, 40.7, 34.6, 31.6, 28.3, 25.9, 21.5, 18.4, 13.3, -3.82, -3.92 ; HRMS (EI): Exact mass calcd for C₃₃H₄₂ClNO₃SSi [M]⁺ 595.2338, found 595.2310.



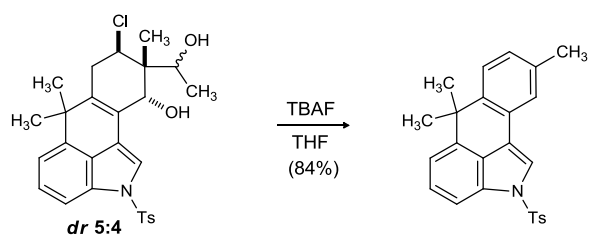
(8*R*,9*R*,10*R*)-8-Chloro-6,6,9-trimethyl-2-tosyl-9-vinyl-2,6,7,8,9,10-hexahydronaphtho[1,2,3-*cd*]indol-10-ol (579).

To a 0 °C solution silyl ether (16.0 mg, 26.9 μmol) in THF (1.0 mL) was added TBAF (80.8 μL , 80.8 μmol , 1.0 M in THF). The solution was warmed to rt and stirred for 1 h. The reaction was quenched with satd aq NaHCO_3 and the layers were separated. The aqueous layer was extracted with Et_2O and the combined organic layers were dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO_2 , 20% ethyl acetate in hexanes) to afford the alcohol as a yellow solid (10.5 mg, 82%). $R_f = 0.27$ (SiO_2 , 20% EtOAc/hexanes); mp 138-140 °C (decomp); IR (film) 3546, 2973, 2925, 1363, 1169, 1117, 1098 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.80 (d, $J = 8.4$ Hz, 2H), 7.68 (d, $J = 8.4$ Hz, 1H), 7.37 (s, 1H), 7.33 (dd, $J = 8.4, 8.4$ Hz, 1H), 7.22 (d, $J = 8.4$ Hz, 2H), 7.13 (d, $J = 7.8$ Hz, 1H), 6.11 (dd, $J = 18.0, 10.8$ Hz, 1H), 5.43 (d, $J = 10.8$ Hz, 1H), 5.37 (d, $J = 18.0$ Hz, 1H), 4.52 (dd, $J = 9.0, 5.4$ Hz, 1H), 4.39 (d, $J = 4.8$ Hz, 1H), 3.02 (dd, $J = 18.6, 5.4$ Hz, 1H), 2.66 (dd, $J = 18.6, 9.0$ Hz, 1H), 2.35 (s, 3H), 1.98 (d, $J = 4.8$ Hz, 1H), 1.46 (s, 3H), 1.44 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) ppm 144.7, 141.2, 140.8, 139.3, 135.6, 133.2, 126.9 (2C), 126.8, 126.5, 122.2, 118.7, 118.0, 117.3, 117.2, 110.8, 74.5, 61.3, 45.3, 40.7, 33.6, 30.6, 29.4, 21.6, 15.8; HRMS (EI): Exact mass calcd for $\text{C}_{27}\text{H}_{28}\text{ClNO}_3\text{S}$ $[\text{M}]^+$ 481.1473, found 481.1471.



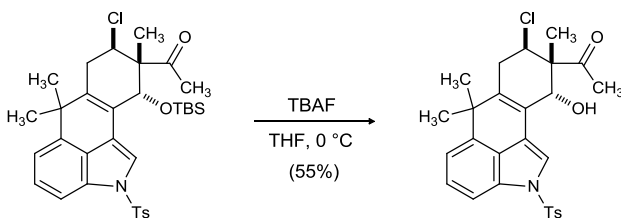
6,6,9-Trimethyl-2-tosyl-2,6-dihydronaphtho[1,2,3-*cd*]indole (580).

To a 0 °C solution of alcohol (10.0 mg, 19.3 μmol) in THF (600 μL) was added TBAF (38.6 μL , 38.6 μmol , 1.0 M in THF). The reaction was warmed to rt and stirred for 1 h. The reaction was quenched with satd aq NaHCO_3 and the layers were separated. The aqueous layer was extracted with Et_2O and the combined organic layers were dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO_2 , 10% ethyl acetate in hexanes) to afford the elimination product as a colorless oil (5.9 mg, 90%). $R_f = 0.44$ (SiO_2 , 20% EtOAc /hexanes); IR (film) 2966, 2924, 2859, 1369, 1186, 1173, 1123, 1091, 1061 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) 7.81 (d, $J = 7.8$ Hz, 2H), 7.74 (d, $J = 8.4$ Hz, 1H), 7.70 (s, 1H), 7.51 (s, 1H), 7.46 (d, $J = 8.4$ Hz, 1H), 7.37 (dd, $J = 7.8, 7.8$ Hz, 1H), 7.24 (d, $J = 7.2$ Hz, 1H), 7.21 (d, $J = 7.8$ Hz, 2H), 7.12 (dd, $J = 8.4, 1.2$ Hz, 1H), 2.38 (s, 3H), 2.33 (s, 3H), 1.62 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) ppm 144.7, 142.4, 139.8, 135.9, 135.5, 133.7, 129.9, 129.0, 127.7, 126.8, 126.6, 126.4, 126.1, 124.1, 119.1, 118.6, 116.8, 110.8, 39.1, 33.8, 21.6, 20.9; HRMS (EI): Exact mass calcd for $\text{C}_{25}\text{H}_{24}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$ 402.1522, found 402.1516.



6,6,9-Trimethyl-2-tosyl-2,6-dihydronaphtho[1,2,3-*cd*]indole (580).

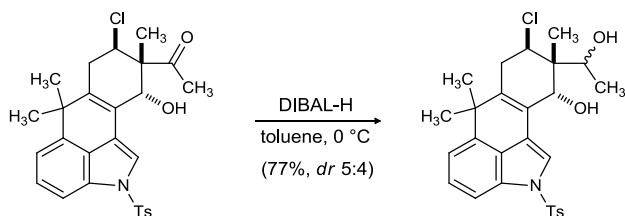
To a 0 °C solution of alcohol (6.0 mg, 12.0 μmol) in THF (500 μL) was added TBAF (24.0 μL, 24.0 μmol, 1.0 M in THF). The reaction was warmed to rt and stirred for 1 h. The reaction was quenched with satd aq NaHCO₃ and the layers were separated. The aqueous layer was extracted with Et₂O and the combined organic layers were dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 10% ethyl acetate in hexanes) to afford the elimination product as a colorless oil (4.3 mg, 84%). R_f= 0.44 (SiO₂, 20% EtOAc/hexanes). Please see above for characterization data.



1-((8*R*,9*S*,10*R*)-8-Chloro-10-hydroxy-6,6,9-trimethyl-2-tosyl-2,6,7,8,9,10-hexahydronaphtho [1,2,3-*cd*]indol-9-yl)ethanone (582).

To a 0 °C solution of silyl ether (18.6 mg, 30.4 μmol) in THF (1.5 mL) was added TBAF (60.8 μL, 60.8 μmol, 1.0 M in THF) and the reaction stirred for 40 minutes at 0 °C. The reaction was quenched with satd aq NaHCO₃ and the layers were separated. The aqueous layer was extracted with Et₂O and the combined organic layers were dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 20-30% ethyl acetate in hexanes) to afford the alcohol as a yellow oil (8.3 mg, 55%). R_f= 0.11 (SiO₂, 20% EtOAc/hexanes); IR (film) 3503, 2970, 2924, 1704, 1366, 1187, 1170,

1119, 1094 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) 7.81 (d, $J = 8.4$ Hz, 2H), 7.69 (d, $J = 8.4$ Hz, 1H), 7.38 (s, 1H), 7.34 (dd, $J = 7.8, 7.8$ Hz, 1H), 7.22 (d, $J = 8.4$ Hz, 2H), 7.13 (d, $J = 7.2$ Hz, 1H), 4.90 (dd, $J = 9.6, 5.4$ Hz, 1H), 3.00 (dd, $J = 18.6, 5.4$ Hz, 1H), 2.67 (s, 1H), 2.60 (dd, $J = 18.6, 9.6$ Hz, 1H), 2.41 (s, 3H), 2.34 (s, 3H), 1.45 (s, 3H), 1.43 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) ppm 144.8, 140.5, 139.1, 135.5, 133.2, 129.9, 126.9, 126.7, 126.6, 122.0, 118.7, 117.5, 117.0, 111.0, 73.5, 57.7, 55.5, 40.7, 33.6, 30.8, 29.1, 28.0, 21.6, 14.5; HRMS (EI): Exact mass calcd for $\text{C}_{27}\text{H}_{26}\text{ClNO}_3\text{S}$ $[\text{M-OH}]^+$ 480.13, found 480.13.²²

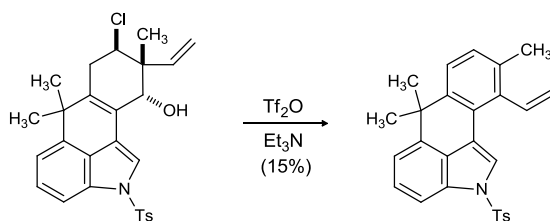


(8*R*,9*R*,10*R*)-8-Chloro-9-(1-hydroxyethyl)-6,6,9-trimethyl-2-tosyl-2,6,7,8,9,10-hexahydro naphtho[1,2,3-*cd*]indol-10-ol (583).

To a 0 °C solution of ketone (15.0 mg, 30.2 μmol) in toluene (200 μL) was added DIBAL-H (20.1 μL , 30.2 μmol , 1.5 M in toluene). The reaction was warmed to rt and stirred for 1 h. The reaction was cooled to 0 °C and more DIBAL-H was added (20.1 μL , 30.2 μmol , 1.5 M in toluene). The reaction was warmed to rt and stirred for an additional 1 h and quenched by the stepwise addition of H_2O (20 μL) and 1M HCl. The layers were separated, and the aqueous layer was extracted with Et_2O . The combined organic layers were dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO_2 , 20-30% ethyl acetate in hexanes) to afford the alcohol as a

²² Loss of a H_2O molecule due to elimination was observed.

colorless oil (11.6 mg, 77%). The alcohol was isolated as a 5:4 mixture of diastereomers.²³ $R_f = 0.50$ (SiO₂, 50% EtOAc/hexanes); IR (film) 3418, 2972, 2927, 1437, 1367, 1187, 1169, 1118, 1095 cm⁻¹; ¹H NMR (600 MHz, CDCl₃, data for both diastereomers) δ 7.82 (d, $J = 8.0$ Hz, 2H), 7.81 (d, $J = 8.4$ Hz, 2H), 7.68 (d, $J = 8.0$ Hz, 1H), 7.67 (d, $J = 8.0$ Hz, 1H), 7.36 (s, 1H), 7.35 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.34 (s, 1H), 7.34 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.25 (d, $J = 8.4$ Hz, 2H), 7.24 (d, $J = 8.4$ Hz, 2H), 7.13 (d, $J = 7.6$ Hz, 2H), 5.94 (dd, $J = 11.2, 6.0$ Hz, 1H), 4.66 (dd, $J = 10.8, 5.6$ Hz, 1H), 4.64 (s, 1H), 4.54 (s, 1H), 4.12-4.09 (m, 2H), 3.10 (s, 1H), 3.07 (dd, $J = 18.4, 6.0$ Hz, 1H), 3.00 (s, 1H), 2.95 (dd, $J = 18.0, 5.6$ Hz, 1H), 2.66 (dd, $J = 10.4, 10.4$ Hz, 1H), 2.62 (dd, $J = 10.4, 10.4$ Hz, 1H), 2.69-2.62 (m, 1H), 2.43-2.42 (m, 1H), 2.35 (s, 3H), 2.35 (s, 3H), 1.54 (d, $J = 6.8$ Hz, 3H), 1.52 (d, $J = 6.4$ Hz, 3H), 1.46 (s, 3H), 1.45 (s, 3H), 1.44 (s, 3H), 1.43 (s, 3H), 0.99 (s, 3H), 0.83 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) ppm 144.8, 141.7, 141.5, 139.4, 139.3, 135.5, 133.3, 129.9, 126.9, 126.7, 126.6, 122.4, 122.3, 118.7, 118.0, 117.9, 116.5, 116.3, 110.9, 75.0, 74.2, 73.2, 72.0, 60.5, 59.1, 44.4, 43.7, 40.8, 40.7, 34.4, 34.0, 31.0, 29.1, 18.9, 21.6, 19.4, 17.8, 14.2, 13.9; HRMS (EI): Exact mass calcd for C₂₅H₂₄NO₂S [M-C₂H₂ClO]⁺ 402.1522, found 402.1.²⁴

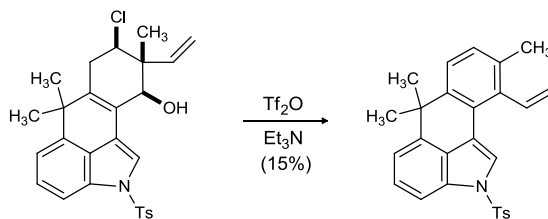


²³ The alcohol is highly sensitive to the base, and should not be stored for an extended period of time.

²⁴ The HRMS indicated that the product has gone a tandem Grob fragmentation/elimination sequence to give compound **580**.

6,6,9-Trimethyl-2-tosyl-10-vinyl-2,6-dihydronaphtho[1,2,3-*cd*]indole (586).

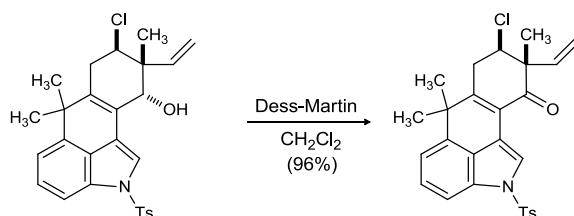
To a 0 °C solution of alcohol (10.0 mg, 20.9 μmol) in CH₂Cl₂ (300 μL) was added Tf₂O (10.6 μL, 62.7 μmol) and Et₃N (14.5 μL, 105 μmol). The reaction was stirred for 30 minutes at 0 °C and at rt for 1 h. The reaction was quenched by slow dropwise addition of satd aq NaHCO₃ and the layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 5-10% ethyl acetate in hexanes) to afford the rearranged tetracyclic product as a white foam (1.4 mg, 15%). R_f = 0.52 (SiO₂, 20% EtOAc/hexanes); IR (film) 2959, 2924, 2853, 1457, 1431, 1371, 1187, 1175, 1133, 1094 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) 7.90 (s, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.37 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 7.8 Hz, 2H), 6.92 (dd, *J* = 27.0, 18.0 Hz, 1H), 5.81 (dd, *J* = 16.8, 3.0 Hz, 1H), 5.42 (dd, *J* = 27.0, 3.0 Hz, 1H), 2.35 (s, 3H), 2.32 (s, 3H), 1.63 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) ppm 144.7, 143.4, 139.5, 137.2, 136.7, 135.4, 133.9, 132.9, 129.8, 129.5, 127.2, 126.7, 126.5, 126.2, 124.9, 121.7, 120.7, 118.9, 117.8, 110.5, 39.4, 34.4, 21.5, 20.7; HRMS (EI): Exact mass calcd for C₂₇H₂₆NO₂S [M+H]⁺ 428.1684, found 428.1688.



6,6,9-Trimethyl-2-tosyl-10-vinyl-2,6-dihydronaphtho[1,2,3-*cd*]indole (586).

To a 0 °C solution of alcohol (25.0 mg, 52.8 μmol) in CH₂Cl₂ (800 μL) was added Tf₂O (21.2 μL, 126 μmol) and Et₃N (29.0 μL, 210 μmol). The reaction was stirred for 30

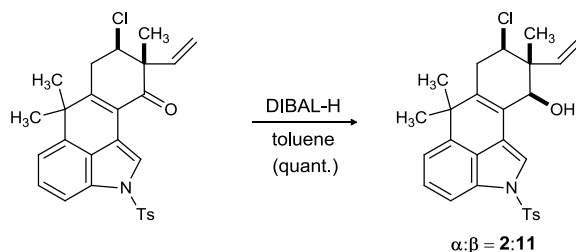
minutes at 0 °C and at rt for 1 h. The reaction was quenched by slow dropwise addition of satd aq NaHCO₃ and the layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 5-10% ethyl acetate in hexanes) to afford the rearranged tetracyclic product as a white foam (1.0 mg, 4%). Please see above for the characterization data.



(8*R*,9*R*)-8-Chloro-6,6,9-trimethyl-2-tosyl-9-vinyl-6,7,8,9-tetrahydronaphtho[1,2,3-*cd*]indol-10(2H)-one (587).

To a 0 °C solution of alcohol (6.0 mg, 12.0 μmol) in CH₂Cl₂ (500 μL) was added Dess-Martin periodinane (12.6 mg, 30.0 μmol). The reaction was warmed to rt and stirred for 1 h. The reaction was quenched by the addition of an aqueous solution containing 2:1 satd aq Na₂S₂O₃:NaHCO₃ and was stirred until both layers became clear (~20 min). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ and the combined organic layers were dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 15% ethyl acetate in hexanes) to afford the enone as a pale yellow foam (5.8 mg, 96%). R_f = 0.27 (SiO₂, 20% EtOAc/hexanes); IR (film) 2974, 2928, 2359, 2342, 1677, 1369, 1187, 1171, 1116, 1096 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.13 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.34 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 7.6 Hz, 1H), 5.86 (dd, *J* = 17.6, 10.4 Hz, 1H), 5.23 (d, *J* = 10.8 Hz, 1H), 5.12 (d, *J* = 17.2 Hz, 1H), 4.49 (dd, *J* = 4.8, 4.0

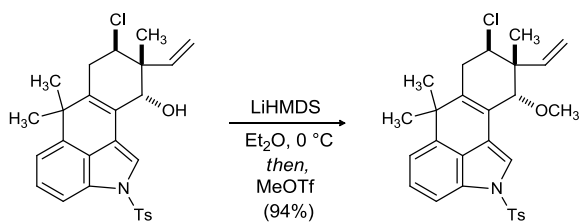
Hz, 1H), 3.20 (dd, $J = 18.4, 4.0$ Hz, 1H), 3.04 (dd, $J = 18.6, 5.2$ Hz, 1H), 2.34 (s, 3H), 1.51 (s, 3H), 1.49 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) ppm 157, 144.7, 137.9, 137.4, 135.7, 132.6, 129.9, 127.0, 126.7, 126.3, 124.0, 121.8, 118.5, 117.2, 112.7, 111.2, 64.1, 54.0, 41.8, 33.5, 30.3, 28.9, 21.6, 19.5; HRMS (EI): Exact mass calcd for $\text{C}_{27}\text{H}_{27}\text{ClNO}_3\text{S}$ $[\text{M}+\text{H}]^+$ 480.1400, found 480.1415.



(8*R*,9*R*,10*R*)-8-Chloro-6,6,9-trimethyl-2-tosyl-9-vinyl-2,6,7,8,9,10-hexahydrophtho[1,2,3-*cd*]indol-10-ol (588).

To a 0 °C solution of ketone (29.3 mg, 62.1 μmol) in toluene (900 μL) was added DIBAL-H (80.8 μL , 124 μmol , 1.5 M in toluene). The reaction was warmed to rt and stirred for 1 h. The reaction was cooled to 0 °C and more DIBAL-H was added (40.4 μL , 62.0 μmol , 1.5 M in toluene). The reaction was warmed to rt and stirred for an additional 1 h and quenched by the stepwise addition of H_2O (50 μL) and 1M HCl. The layers were separated, and the aqueous layer was extracted with Et_2O . The combined organic layers were dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO_2 , 10-20% ethyl acetate in hexanes) to afford the alcohol as a viscous oil (29.1 g, 99%). The alcohol was isolated as an inseparable 11:2 ($\beta:\alpha$) mixture of diastereomers. $R_f = 0.27$ (SiO_2 , 20% EtOAc/hexanes); IR (film) 3547, 2926, 2925, 1437, 1363, 1187, 1169, 1118, 1092 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3 , data for both isomers) δ 8.10 (d, $J = 8.4$ Hz, 2H), 8.09 (d, $J = 8.4$ Hz, 2H), 7.69 (d, $J = 8.4$ Hz, 1H),

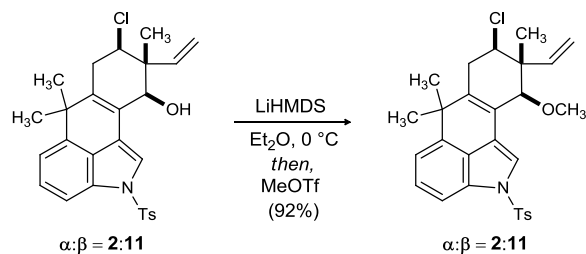
7.68 (d, $J = 8.0$ Hz, 1H), 7.59 (s, 1H), 7.37 (s, 1H), 7.33 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.32 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.20 (d, $J = 8.4$ Hz, 2H), 7.19 (d, $J = 8.4$ Hz, 2H), 7.13 (d, $J = 7.2$ Hz, 1H), 7.12 (d, $J = 7.6$ Hz, 1H), 6.11 (dd, $J = 17.6, 11.2$ Hz, 1H), 5.80 (dd, $J = 17.2, 10.8$ Hz, 1H), 5.43 (d, $J = 10.8$ Hz, 1H), 5.37 (d, $J = 17.6$ Hz, 1H), 5.32 (d, $J = 10.8$ Hz, 1H), 5.27 (d, $J = 17.6$ Hz, 1H), 4.52 (dd, $J = 9.2, 5.2$ Hz, 1H), 4.44 (d, $J = 6.0$ Hz, 1H), 4.39 (br s, 1H), 4.17 (dd, $J = 9.2, 5.2$ Hz, 1H), 3.02 (dd, $J = 18.6, 5.4$ Hz, 1H), 2.89 (ddd, $J = 18.0, 5.2, 1.2$ Hz, 1H), 2.73 (ddd, $J = 18.0, 8.8, 2.4$ Hz, 1H), 2.66 (dd, $J = 18.4, 9.2$ Hz, 1H), 2.35 (s, 3H), 2.33 (s, 3H), 2.06 (br d, $J = 6.8$ Hz, 2H), 1.46 (s, 3H), 1.44 (s, 3H), 1.42 (s, 3H), 1.26 (s, 3H), 1.24 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3 , data for both isomers) ppm 144.5, 142.6, 141.2, 139.1, 138.4, 135.6, 133.1, 132.8, 129.8 (2C), 129.0, 128.2, 127.0, 126.8, 126.4, 126.1, 123.0, 119.4, 118.6, 118.5, 118.0, 117.2, 117.1, 116.7, 116.4, 110.8, 110.7, 74.4, 73.5, 63.1, 61.3, 46.3, 45.3, 40.7, 40.6, 33.5, 33.2, 30.5, 30.0, 29.6, 29.3, 21.5, 15.7, 12.4; HRMS (EI): Exact mass calcd for $\text{C}_{27}\text{H}_{28}\text{ClNNaO}_3\text{S}$ $[\text{M}+\text{Na}]^+$ 504.1376, found 504.1387.



(8R,9R,10R)-8-Chloro-10-methoxy-6,6,9-trimethyl-2-tosyl-9-vinyl-2,6,7,8,9,10-hexahydro naphtho[1,2,3-*cd*]indole (596).

To a 0 °C solution of alcohols (24.0 mg, 50.4 μmol) in THF (750 μL) was added LiHMDS (202 μL , 202 μmol , 1.0 M in toluene) dropwise. The reaction was stirred for 1 h at 0 °C, and MeOTf (34.0 μL , 302 μmol) was added dropwise to the solution. The reaction was stirred for 30 min at 0 °C and 30 min at rt. The reaction was quenched with

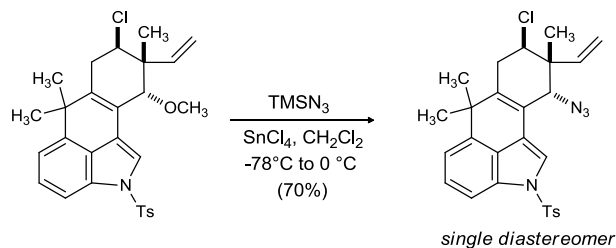
saturated aqueous NH_4Cl and the layers were separated. The aqueous layer was extracted with Et_2O and the combined organic layers were dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO_2 , 10% ethyl acetate in hexanes) to afford the methyl ether as a yellow oil (23.2 mg, 94%). $R_f = 0.46$ (SiO_2 , 20% EtOAc /hexanes); IR (film) 2973, 2929, 1437, 1368, 1187, 1170, 1120, 1097 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.78 (d, $J = 8.0$ Hz, 2H), 7.68 (d, $J = 8.5$ Hz, 1H), 7.33 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.23 (s, 1H), 7.20 (d, $J = 8.0$ Hz, 2H), 7.13 (d, $J = 7.5$ Hz, 1H), 6.17 (dd, $J = 17.5, 11.0$ Hz, 1H), 5.33 (d, $J = 11.0$ Hz, 1H), 5.28 (d, $J = 17.5$ Hz, 1H), 4.56 (dd, $J = 10.5, 6.0$ Hz, 1H), 3.79 (s, 1H), 3.57 (s, 3H), 3.01 (dd, $J = 18.5, 6.0$ Hz, 1H), 2.58 (dd, $J = 18.5, 10.5$ Hz, 1H), 2.35 (s, 3H), 1.45 (s, 3H), 1.44 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) ppm 144.8, 142.6, 141.5, 139.6, 135.5, 133.3, 129.9, 126.8 (2C), 126.6, 121.8, 119.5, 118.7, 116.1, 115.1, 110.9, 85.1, 61.3, 61.2, 45.2, 40.7, 33.8, 30.9, 29.3, 21.6, 13.9; HRMS (EI): Exact mass calcd for $\text{C}_{28}\text{H}_{30}\text{ClNNaO}_3\text{S}$ $[\text{M}+\text{Na}]^+$ 518.1533, found 518.1520.



(8*R*,9*R*,10*S*)-8-Chloro-10-methoxy-6,6,9-trimethyl-2-tosyl-9-vinyl-2,6,7,8,9,10-hexahydro naphtho[1,2,3-*cd*]indole (597).

To a 0 °C solution of alcohols (20.4 mg, 42.7 μmol , $\alpha:\beta = 2:11$) in THF (500 μL) was added LiHMDS (138 μL , 138 μmol , 1.0 M in toluene) dropwise. The reaction was stirred for 1 h at 0 °C, and MeOTf (19.3 μL , 171 μmol) was added dropwise to the solution. The

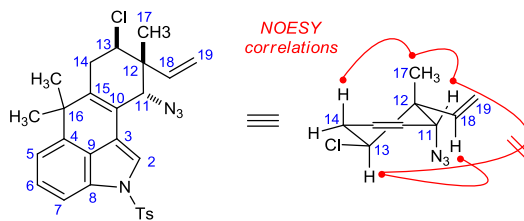
reaction was stirred for 30 min at 0 °C and 30 min at rt. The reaction was quenched with satd aq NH₄Cl and the layers were separated. The aqueous layer was extracted with Et₂O and the combined organic layers were dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 10% ethyl acetate in hexanes) to afford the methyl ether as a yellow oil (19.3 mg, 92%). The alcohol was isolated as an inseparable 11:2 (β:α) mixture of diastereomers. R_f = 0.46 (SiO₂, 20% EtOAc/hexanes); IR (film) 2969, 2925, 2852, 1367, 1187, 1170, 1120, 1100 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, data for both isomers) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.32 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.30 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.25-7.19 (m, 6 H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 6.16 (dd, *J* = 18.0, 11.2 Hz, 1H), 5.90 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.35 (d, *J* = 10.4 Hz, 1H), 5.33 (d, *J* = 10.8 Hz, 1H), 5.32 (d, *J* = 16.8 Hz, 1H), 5.28 (d, *J* = 17.6 Hz, 1H), 4.58 (dd, *J* = 10.4, 5.6 Hz, 1H), 4.14 (br d, *J* = 1.6 Hz, 1H), 4.06 (dd, *J* = 10.4, 5.6 Hz, 1H), 3.79 (s, 1H), 3.69 (s, 3H), 3.57 (s, 3H), 3.01 (dd, *J* = 18.4, 6.0 Hz, 1H), 2.89 (ddd, *J* = 18.0, 5.2, 0.8 Hz, 1H), 2.66 (ddd, *J* = 17.6, 10.8, 3.2 Hz, 1H), 2.57 (dd, *J* = 18.4, 10.8 Hz, 1H), 2.35 (s, 6H), 1.45 (s, 3H), 1.44 (s, 3H), 1.43 (s, 3H), 1.42 (s, 3H), 1.22 (s, 3H), 1.08 (s, 3H); ¹³C NMR (100 MHz, CDCl₃, data for β-isomer) ppm 144.6, 144.4, 139.4, 139.2, 135.7, 132.7, 129.9, 127.2, 126.9, 126.8, 126.1, 123.6, 118.6, 118.4, 116.4, 116.1, 85.2, 62.5, 61.3, 47.0, 40.8, 33.2, 30.6, 29.7, 21.6, 10.5; HRMS (EI): Exact mass calcd for C₂₈H₃₀CINNaO₃S [M+Na]⁺ 518.1533, found 518.1533.



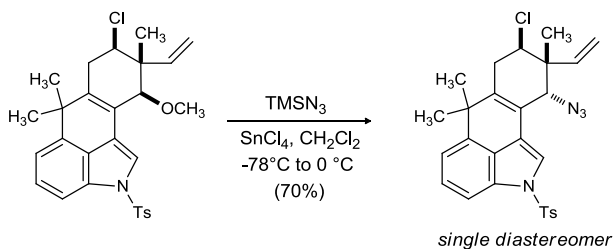
(8*R*,9*R*,10*R*)-10-Azido-8-chloro-6,6,9-trimethyl-2-tosyl-9-vinyl-2,6,7,8,9,10-hexahydro naphtho[1,2,3-*cd*]indole (598).

To a -78 °C solution of methyl ether (9.9 mg, 20 μmol) in CH₂Cl₂ (700 μL) was added SnCl₄ (5.0 μL, 61 μmol) and stirred for 5 min. The reaction was allowed to warm to 0 °C and stirred for 30 min and an additional 30 min at rt. The reaction was quenched with satd aq NaHCO₃ and the layers were separated. The aqueous layer was extracted with Et₂O and the combined organic layers were dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 10% ethyl acetate in hexanes) to afford the azide as a yellow oil (7.1 mg, 70%). Only one diastereomer could be detected by NMR analysis. *R_f* = 0.49 (SiO₂, 20% EtOAc/hexanes); IR (film) 2970, 2923, 2851, 2096, 1369, 1171, 1120 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.35 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.28 (s, 1H), 7.23 (d, *J* = 7.8 Hz, 2H), 7.14 (d, *J* = 7.2 Hz, 1H), 6.13 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.38 (d, *J* = 10.8 Hz, 1H), 5.33 (d, *J* = 17.4 Hz, 1H), 4.39 (dd, *J* = 10.2, 5.4 Hz, 1H), 4.10 (s, 1H), 3.04 (dd, *J* = 18.6, 5.4 Hz, 1H), 2.63 (dd, *J* = 18.6, 10.2 Hz, 1H), 2.35 (s, 3H), 1.48 (s, 3H), 1.46 (s, 3H), 1.19 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) ppm 144.9, 142.5, 141.4, 139.1, 135.3, 133.4, 129.9, 126.9, 126.8, 126.3, 119.4, 118.8, 118.2, 116.7, 116.3, 111.1, 67.7, 60.4, 44.6, 41.1, 33.7, 31.6, 28.9, 21.6, 15.0; HRMS (EI): Exact mass calcd for C₂₇H₂₇ClN₄NaO₂S [M+Na]⁺ 529.1441, found 529.1451.

A complete 2D NMR analysis was carried out to determine the stereochemistry at C11. NOESY correlations from both H11 to H17 and

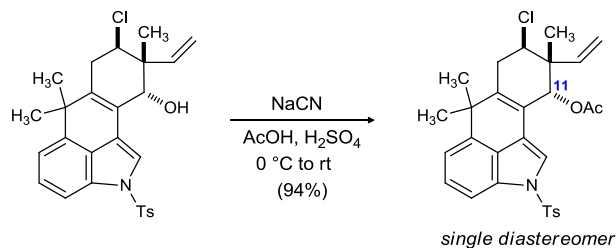


H11 to H19, and the absence of the NOESY correlations between H11 to either H13 and H14, strongly suggested that the H11 proton is equatorial.



(8*R*,9*R*,10*R*)-10-Azido-8-chloro-6,6,9-trimethyl-2-tosyl-9-vinyl-2,6,7,8,9,10-hexahydro naphtho[1,2,3-*cd*]indole (598).

To a -78 °C solution of methyl ether (4.9 mg, 9.9 μmol) in CH₂Cl₂ (300 μL) was added SnCl₄ (2.5 μL, 3.0 μmol) and stirred for 5 min. The reaction was allowed to warm to 0 °C and stirred for 30 min and an additional 30 min at rt. The reaction was quenched with satd aq NaHCO₃ and the layers were separated. The aqueous layer was extracted with Et₂O and the combined organic layers were dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 10% ethyl acetate in hexanes) to afford the azide as a yellow oil (2.0 mg, 40%). Only one diastereomer could be detected by NMR analysis. Please see above for the characterization data.



(8*R*,9*R*,10*R*)-8-Chloro-6,6,9-trimethyl-2-tosyl-9-vinyl-2,6,7,8,9,10-hexahydronaphtho[1,2,3-*cd*]indol-10-yl acetate (600).

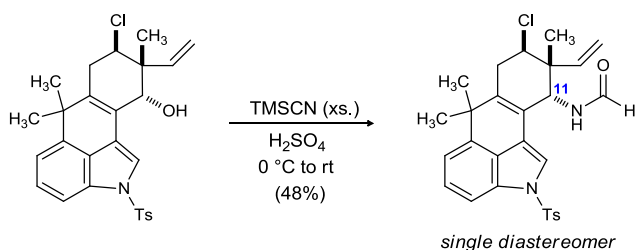
H₂SO₄ (8.0 μL, 0.15 mmol)²⁵ was added dropwise to a 0 °C solution of alcohol (8.0 mg, 17 μmol) in AcOH (170 μL). The reaction was stirred for 30 min at 0 °C and 30 min at rt. The reaction was cooled to 0 °C and quenched by the sequential addition of satd aq Na₂CO₃ followed by 1.0 M NaOH. The solution was warmed to rt and stirred for 10 min. The layers were separated, the aqueous layer was extracted with CH₂Cl₂, and the combined organic layers were dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 10% ethyl acetate in hexanes) to afford the acetate as a pale yellow foam (7.7 mg, 94%). The acetate was isolated as a 7:1 ratio of diastereomers (¹H NMR). R_f = 0.35 (SiO₂, 20% EtOAc/hexanes); IR (film) 2971, 2927, 1734, 1558, 1506, 1457, 1369 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.33 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.23 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 7.6 Hz, 1H), 5.83 (dd, *J* = 17.2, 11.2 Hz, 1H), 5.76 (s, 1H), 5.30 (d, *J* = 10.8 Hz, 1H), 5.29 (d, *J* = 18.0 Hz, 1H), 4.55 (dd, *J* = 10.4, 5.6 Hz, 1H), 3.06 (dd, *J* = 18.4, 6.0 Hz, 1H), 2.58 (dd, *J* = 18.0, 10.8 Hz, 1H), 2.35 (s, 3H), 2.03 (s, 3H), 1.47 (s, 3H), 1.46 (s, 3H), 1.17 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) ppm 170.1, 144.7, 143.0, 140.0, 139.0, 135.6, 133.4, 129.8, 127.0, 126.6, 126.5, 119.9, 118.6, 117.7, 117.4, 116.7,

²⁵ 95-98% EMD

111.0, 74.1, 60.3, 44.0, 40.9, 33.6, 30.8, 29.3, 21.6, 21.0, 14.5; HRMS (EI): Exact mass calcd for C₂₇H₂₇ClNO₂S [M-C₂H₃O₂]⁺ 464.1451, found 464.1465.²⁶

The stereochemistry at C11 was determined by comparing the NMR of **16a** with the acetylated product of the α -alcohol (**15**). The consistency between coupling constants of these two compounds in ¹H NMR analysis suggested similar configuration.

Procedure for alcohol acylation: To a 0 °C solution of α -alcohol (4.0 mg, 8.4 μ mol) in THF (200 μ L) was added LHMDS (37 μ L, 37 μ mol, 1.0 M in toluene) dropwise. The reaction was stirred for 1 h at 0 °C, and acetyl bromide (2.5 μ L, 34 μ mol) was added to the solution. The reaction was stirred for 30 min at 0 °C and 30 min at rt. The reaction was quenched with satd aq NH₄Cl and the layers were separated. The aqueous layer was extracted with Et₂O and the combined organic layers were dried, filtered, and concentrated. The resulting acetate was pure for analytical purposes.



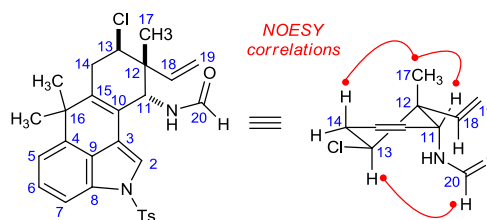
***N*-((8*R*,9*R*,10*R*)-8-Chloro-6,6,9-trimethyl-2-tosyl-9-vinyl-2,6,7,8,9,10-hexahydronaphtha [1,2,3-*cd*]indol-10-yl)formamide (**601**).**

H₂SO₄ (225 μ L, 4.20 mmol) was added dropwise to a 0 °C solution of alcohol (100 mg, 210 μ mol) in TMSCN (420 μ L, 3.15 mmol). The reaction was stirred for 30 min at 0 °C and 30 min at rt. The solution was cooled to 0 °C and quenched by the sequential

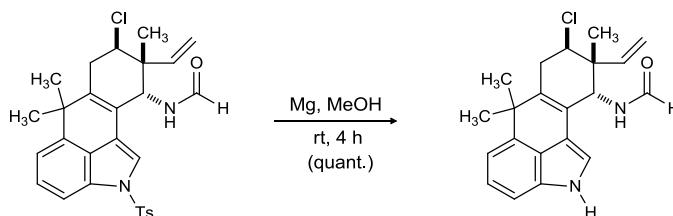
²⁶ Elimination of AcOH observed.

addition of satd aq Na_2CO_3 followed by 1.0 M NaOH. The solution was warmed to rt and stirred for 10 min. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 , and the combined organic layers were dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO_2 , 20-30-40% ethyl acetate in hexanes) to afford the formamide as a yellow oil (52 mg, 48%). Only one diastereomer could be detected by NMR analysis. $R_f = 0.39$ (SiO_2 , 50% EtOAc/hexanes); IR (film) 3276, 2962, 2924, 2853, 1663, 1368, 1170, 1119 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.26 (s, 1H), 7.81 (d, $J = 8.4$ Hz, 2H), 7.71 (d, $J = 8.0$ Hz, 1H), 7.33 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.24 (d, $J = 7.6$ Hz, 2H), 7.23 (s, 1H), 7.14 (d, $J = 7.6$ Hz, 1H), 5.90 (dd, $J = 17.6, 10.8$ Hz, 1H), 5.44 (br d, $J = 8.8$ Hz, 1H), 5.34 (d, $J = 16.8$ Hz, 1H), 5.33 (d, $J = 11.6$ Hz, 1H), 5.09 (d, $J = 10.4$ Hz, 1H), 4.23 (dd, $J = 9.6, 5.6$ Hz, 1H), 3.04 (dd, $J = 18.4, 5.2$ Hz, 1H), 2.68 (dd, $J = 18.4, 9.2$ Hz, 1H), 2.35 (s, 3H), 1.45 (s, 3H), 1.44 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) ppm 160.5, 144.7, 140.6, 139.9, 138.9, 135.5, 129.9, 129.8, 126.9 (2C), 126.4, 121.1, 118.5, 117.2, 117.1, 116.9, 110.9, 70.5, 61.2, 52.2, 44.0, 40.8, 33.3, 30.6, 29.4, 21.5; HRMS (EI): Exact mass calcd for $\text{C}_{28}\text{H}_{30}\text{ClN}_2\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$ 509.1666 found 509.1664.

A NOESY experiment was carried out to determine the stereochemistry at C11. NOESY correlations from both H11¹⁷ to H17 and H11 to H19, and the absence of crosspeaks between H11 to either H13 and H14, suggested that the H11 proton is



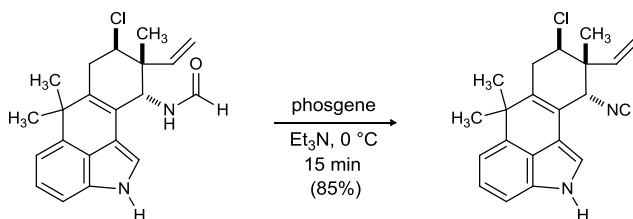
equatorial. Additionally, a NOESY crosspeak between H13 and H20 was observed which indicated the axial orientation of the formamide functionality. These two observations are consistent with the formation of the α -formamide.



***N*-((8*R*,9*R*,10*R*)-8-Chloro-6,6,9-trimethyl-9-vinyl-2,6,7,8,9,10-hexahydronaphtho[1,2,3-*cd* indol-10-yl]formamide (605).**

To a solution of formamide (13.0 mg, 25.6 μmol) in MeOH (3.6 mL) was added Mg turnings (56.0 mg, 2.30 mmol) and the reaction and stirred for 4 h at rt. The reaction was quenched with satd aq NH_4Cl and the solution was stirred for 30 min at rt. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 , and the combined organic layers were dried, filtered, and concentrated. The resulting desosylated product was isolated as a mixture of *cis*- and *trans*-rotamers and found to be pure for all analytical purposes (9.0 mg, 100%). $R_f = 0.24$ (SiO_2 , 50% EtOAc/hexanes); IR (film) 3357, 3278, 2962, 2924, 2850, 1684, 1679, 1669, 1653 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3 , data for the major diastereomer) δ 8.21 (s, 1H), 7.91 (br s, 1H), 7.23 (dd, $J = 7.8, 7.8$ Hz, 1H), 7.11 (d, $J = 8.0$ Hz, 1H), 7.00 (d, $J = 7.2$ Hz, 1H), 6.95 (d, $J = 2.1$ Hz, 1H), 5.93 (dd, $J = 17.6, 11.0$ Hz, 1H), 5.62 (br d, $J = 10.4$ Hz, 1H), 5.34 (d, $J = 17.5$ Hz, 1H), 5.33 (d, $J = 11.0$ Hz, 1H), 5.09 (d, $J = 10.4$ Hz, 1H), 4.30 (dd, $J = 10.2, 5.4$ Hz, 1H), 3.06 (dd, $J = 18.1, 5.5$ Hz, 1H), 2.71 (dd, $J = 18.1, 10.1$ Hz, 1H), 1.51 (s, 3H), 1.48 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3 , data for both isomers) ppm 164.9, 160.8, 140.7, 140.6, 140.4,

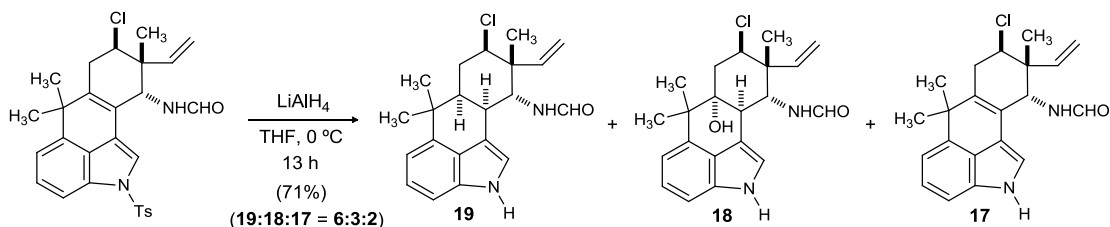
138.8, 138.7, 136.9, 136.1, 133.9, 133.7, 124.7, 124.5, 124.4, 122.3, 118.0, 116.6, 116.4, 114.9 (2C), 114.8, 112.2, 112.1, 111.9, 108.0, 107.9, 62.5, 61.7, 58.4, 53.0, 44.7, 44.0, 41.1, 40.9, 33.3, 31.9, 31.1, 30.7, 30.0, 29.6, 17.2, 15.8; HRMS (EI): Exact mass calcd for C₂₁H₂₄ClN₂O [M+H]⁺ 355.1577, found 355.1572.



(±)-Hapalindole K (602).

To a 0 °C solution of formamide (1.9 mg, 5.4 μmol) and Et₃N (14.4 μL, 107 μmol) in CH₂Cl₂ (0.4 mL) was added phosgene (9.3 μL, 19 μmol, 20% in toluene). The reaction was stirred for 15 min at 0 °C and quenched with satd aq NaHCO₃. The solution was warmed to rt and stirred for 10 min. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ and the combined organic layers were dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 20-30% ethyl acetate in hexanes) to afford hapalindole A (1.6 mg, 85%). R_f = 0.70 (SiO₂, 50% EtOAc/hexanes); IR(film) 3411, 2958, 2920, 2850, 2134 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.93 (br s, 1H), 7.25 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.17 (d, *J* = 1.8 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.16 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.43 (d, *J* = 10.8 Hz, 1H), 5.38 (d, *J* = 17.4 Hz, 1H), 4.50 (s, 1H), 4.43 (dd, *J* = 7.8, 5.4 Hz, 1H), 3.08 (ddd, *J* = 18.0, 4.8, 0.6 Hz, 1H), 2.68 (br dd, *J* = 18.4, 9.2 Hz, 1H), 1.50 (s, 3H), 1.49 (s, 3H), 1.33 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) ppm 158.5, 139.9, 138.6, 136.6, 133.8,

124.7, 124.4, 118.8, 117.6, 116.3, 114.9, 111.5, 108.0, 61.4, 60.3, 43.3, 41.1, 32.9, 30.5, 30.1, 16.7; LRMS (EI): Exact mass calcd for C₂₁H₂₂ClN₂ [M+H]⁺ 357.15, found 357.20.



***N*-((6*aS*,8*R*,9*R*,10*R*,10*aR*)-8-Chloro-6,6,9-trimethyl-9-vinyl-2,6,6*a*,7,8,9,10,10*a*-octahydrophtho[1,2,3-*cd*]indol-10-yl)formamide (603).**

LiAlH₄ (452 μL, 678 μmol, 1.5 M in THF) was added to a 0 °C solution of formamide (17.0 mg, 33.9 μmol) in THF (3.0 mL) and the reaction was stirred for 13 h at 0 °C. The reaction was quenched with sequential addition of H₂O (100 μL) and 0.5 M NaOH and the solution was stirred for 5 min at rt. The layers were separated and the aqueous layer was extracted with Et₂O and the combined organic layers were dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 30-40-50-60-70% ethyl acetate in hexanes) to afford the formamide as a yellow oil in addition to the side products **604** and **605**.

Formamide 603

(isolated as a mixture of *cis*- and *trans*-rotamers):²⁷ yellow oil (4.6 mg, 39%). R_f = 0.15 (SiO₂, 50% EtOAc/hexanes); IR (film) 3396, 3287, 2961, 2923, 2853, 1679 (br s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃, data for the both isomer) δ 8.23 (s, 1H), 8.16 (s, 1H), 8.13 (br s, 1H), 8.08 (br s, 1H), 7.23-7.18 (m, 4H), 7.08 (dd, *J* = 2.0, 2.0 Hz, 1H), 6.97-6.95 (m, 2H), 6.94 (dd, *J* = 6.8, 0.8 Hz, 1H), 6.39 (dd, *J* = 8.8, 8.8 Hz, 1H), 5.91 (br d, *J* = 8.8

²⁷ The assigned structure was confirmed after the compound was converted to (±)-hapalindole A

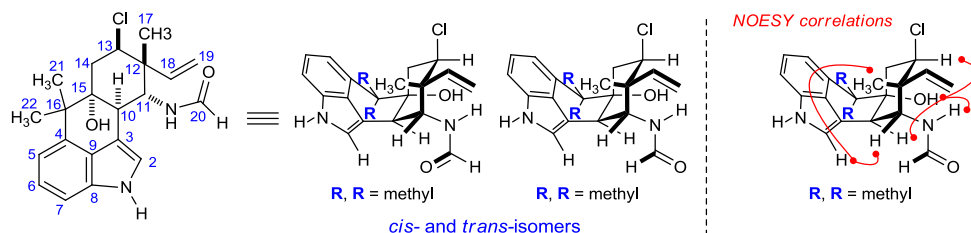
Hz, 1H), 5.83 (dd, $J = 16.6, 11.2$ Hz, 1H), 5.84 (dd, $J = 16.6, 11.2$ Hz, 1H), 5.30 (d, $J = 17.0, 10.8$ Hz, 1H), 5.30 (d, $J = 10.8$ Hz, 1H), 5.22 (d, $J = 16.8$ Hz, 1H), 5.21 (d, $J = 11.6$ Hz, 1H), 5.17 (d, $J = 17.6$ Hz, 1H), 4.94 (dd, $J = 9.2, 1.2$ Hz, 1H), 4.19 (dd, $J = 12.4, 4.4$ Hz, 1H), 4.16 (dd, $J = 10.4, 3.6$ Hz, 1H), 3.64 (br s, 1H), 3.63 (br s, 1H), 2.14 (ddd, $J = 12.8, 7.6, 7.6$ Hz, 1H), 2.00-1.96 (m, 2H), 1.94 (ddd, $J = 13.2, 4.0, 4.0$ Hz, 1H), 1.55 (s, 3H), 1.55-1.52 (m, 1H), 1.54 (s, 3H), 1.51 (dd, $J = 7.6, 4.0$ Hz, 1H), 1.17 (s, 3H), 1.15 (s, 3H), 1.00 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3 , data for both rotamers) ppm 165.1, 160.1, 144.7, 143.1, 137.7 (2C), 133.6, 133.5, 124.3, 124.0, 123.5, 123.1, 119.5, 118.9, 115.8, 114.8, 113.9, 113.6, 112.0, 111.7, 108.6, 108.5, 64.4, 64.0, 60.9, 55.3, 46.2, 45.8, 45.7, 45.4, 38.1, 38.0, 37.7, 36.4, 32.1, 31.5, 31.1, 24.6 (2C), 22.7, 21.3, 20.0; HRMS (EI): Exact mass calcd for $\text{C}_{21}\text{H}_{25}\text{ClN}_2\text{NaO}$ $[\text{M}+\text{Na}]^+$ 379.1553, found 379.1557.

Alcohol 604

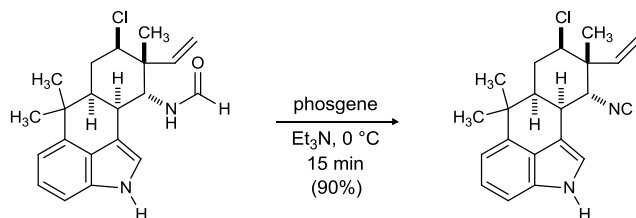
(isolated as a mixture of *cis*- and *trans*- rotamers): pale yellow oil (1.7 mg, 14%). $R_f = 0.07$ (SiO_2 , 50% EtOAc/hexanes); IR (film) 3356 (br s), 2961, 2923, 2852, 1669 (br s) cm^{-1} ; ^1H NMR (600 MHz, CDCl_3 , data for the both isomer) δ 8.12 (s, 1H), 8.16 (br s, 1H), 8.02 (s, 1H), 8.00 (s, 1H), 7.42 (br d, $J = 9.6$ Hz, 1H), 7.37 (br d, $J = 9.6$ Hz, 1H), 7.23 (d, $J = 8.4$ Hz, 1H), 7.22 (d, $J = 7.8$ Hz, 1H), 7.20 (dd, $J = 7.8, 7.8$ Hz, 1H), 7.18 (dd, $J = 8.4, 8.4$ Hz, 1H), 7.09 (dd, $J = 1.8, 1.8$ Hz, 1H), 6.98 (d, $J = 7.8$ Hz, 1H), 6.97 (dd, $J = 1.8, 1.8$ Hz, 1H), 6.96 (d, $J = 7.2$ Hz, 1H), 5.86 (dd, $J = 16.8, 10.8$ Hz, 2H), 5.30 (d, $J = 11.4$ Hz, 1H), 5.18 (d, $J = 10.8$ Hz, 1H), 5.17 (d, $J = 18.6$ Hz, 1H), 5.02 (d, $J = 9.6$ Hz, 1H), 4.59 (dd, $J = 12.6, 4.2$ Hz, 1H), 4.54 (dd, $J = 12.6, 4.2$ Hz, 1H), 4.15 (br d, $J = 7.2$ Hz, 1H), 3.58 (br s, 1H), 3.44 (br d, $J = 0.8$ Hz, 1H), 2.13 (ddd, $J = 13.8, 3.6, 1.2$ Hz, 1H), 2.13-2.12 (m, 1H), 2.01 (s, 2H), 1.90 (dd, $J = 13.8, 12.6$ Hz, 1H), 1.86 (dd, $J = 13.8,$

12.6 Hz, 1H), 1.52 (s, 3H), 1.51 (s, 3H), 1.14 (s, 6H), 0.82 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3 , data for both isomers) ppm 165.0, 159.9, 145.1, 143.0, 138.4, 138.0, 133.4, 133.3, 123.7, 123.5, 123.4 (2C), 119.9, 119.0, 115.9, 114.8, 113.8, 113.6, 111.9, 111.8, 109.0 (2C), 80.6, 80.2, 62.0, 61.6, 61.1, 55.2, 45.6, 43.5, 42.3, 42.1, 37.2, 36.8, 31.9, 26.7, 26.9 (2C), 22.7, 20.3, 19.7, 18.6; HRMS (EI): Exact mass calcd for $\text{C}_{21}\text{H}_{25}\text{ClN}_2\text{NaO}_2$ $[\text{M}+\text{Na}]^+$ 395.1502, found 395.1503.

The ^1H NMR analysis indicated a 5:1 mixture of *cis*- and *trans*-rotamers and as a result, the NMR peaks in general were broadened. First, HSQC was used to assign the formamide $-\text{NH}$ and $-\text{OH}$ protons and then NOESY correlations were used to assign the stereochemistry of newly formed quaternary center (C15). The alcohol proton shows strong correlations to formamide $-\text{NH}$, H13, and H10. As previously elucidated, the formamide functionality is α which indicates that the newly formed quaternary center has $\alpha\text{-OH}$. Additionally, the formamide $-\text{NH}$ was observed to shift downfield (δ 7.37 ppm) which also suggests the possibility of hydrogen bonding with $\alpha\text{-OH}$. The presence of NOESY correlation between H2, H11 and H2, H17 also supports the assigned chair conformation of the cyclohexane core.

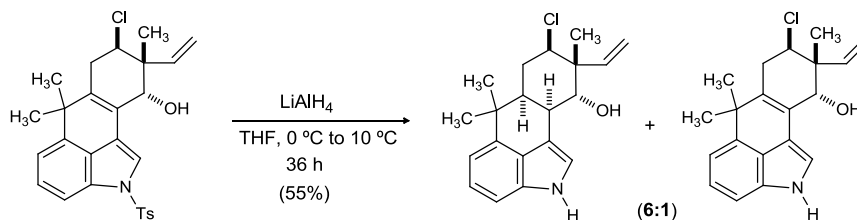


Formamide 605 (isolated as a mixture of *cis*- and *trans*-isomer): Please see above for characterization data.



(±)-Hapalindole A (606).

To a 0 °C solution of the formamide (3.8 mg, 10.7 μmol) and Et₃N (29.8 μL, 214 μmol) in CH₂Cl₂ (0.8 mL) was added phosgene (18.5 μL, 37.5 μmol, 20% in toluene). The reaction was stirred for 15 min at 0 °C and quenched with satd aq NaHCO₃. The solution was warmed to rt and stirred for 10 min. The layers were separated, the aqueous layer was extracted with CH₂Cl₂, and the combined organic layers were dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 20% ethyl acetate in hexanes) to afford hapalindole A (3.4 mg, 90%) as a oil. R_f = 0.60 (SiO₂, 50% EtOAc/hexanes); IR (film) 3417, 2964, 2924, 2853, 2134, 1439 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.07 (br s, 1H), 7.22-7.19 (m, 2H), 6.98 (dd, *J* = 5.4, 2.2 Hz, 1H), 6.89 (dd, *J* = 1.7, 1.7 Hz, 1H), 6.11 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.35 (d, *J* = 11.0 Hz, 1H), 5.24 (d, *J* = 17.5 Hz, 1H), 4.38 (br s, 1H), 4.23 (dd, *J* = 12.5, 4.0 Hz, 1H), 3.88 (br s, 1H), 2.32 (ddd, *J* = 13.4, 4.2, 4.2 Hz, 1H), 2.15 (dddd, *J* = 13.5, 3.5, 3.5, 0.7 Hz, 1H), 1.56 (s, 3H), 1.48 (ddd, *J* = 13.0, 13.0, 13.0 Hz, 1H), 1.20 (s, 3H), 0.89 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) ppm 157.9, 143.3, 138.0, 133.5, 124.0, 123.6, 118.7, 116.2, 114.1, 110.7, 108.6, 63.9, 63.2, 44.7, 44.2, 38.1, 37.1, 32.0, 31.1, 24.4, 18.9; HRMS (EI): Exact mass calcd for C₂₁H₂₄ClN₂ [M+H]⁺ 339.1628, found 339.1617.



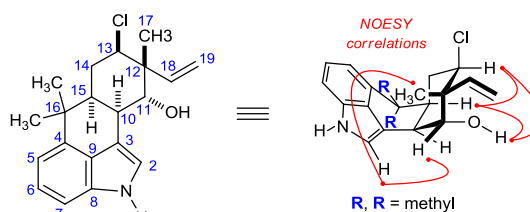
(6a*S*,8*R*,9*R*,10*R*,10a*R*)-8-Chloro-6,6,9-trimethyl-9-vinyl-2,6,6a,7,8,9,10,10a-octahydro naphtho[1,2,3-*cd*]indol-10-ol (607).

To a 0 °C solution of alcohol (45.0 mg, 94.3 μmol) in THF (6.0 mL) was added LiAlH₄ (1.56 mL, 2.37 mmol, 1.5 M in THF) and the reaction was stirred for 36 h at 10 °C. The reaction was quenched with sequential addition of H₂O (500 μL) and 0.5 M NaOH and the solution was stirred for 5 min at rt. The layers were separated and the aqueous layer was extracted with Et₂O and the combined organic layers were dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 10-20-25% ethyl acetate in hexanes) to afford the desired reduced product as a viscous oil (14.3 mg, 47%) in addition to the detosylated side co-product (2.4 mg, 8%). *R_f* = 0.60 (SiO₂, 50% EtOAc/hexanes); IR (film) 3364 (br), 2959, 2923, 2851, 1457, 1441 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.98 (br s, 1H), 7.20-7.16 (m, 2H), 6.95 (dd, *J* = 6.6, 1.2 Hz, 1H), 6.90 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.98 (dd, 18.0, 10.8 Hz, 1H), 5.40 (dd, *J* = 11.4, 0.6 Hz, 1H), 5.33 (d, *J* = 18.0 Hz, 1H), 4.53 (dd, *J* = 12.0, 4.2 Hz, 1H), 4.43 (br s, 1H), 3.74 (br s, 1H), 2.28 (ddd, *J* = 13.2, 4.2, 4.2 Hz, 1H), 2.18 (br d, *J* = 1.2 Hz, 1H), 2.10 (dddd, *J* = 13.2, 3.6, 3.6, 0.6 Hz, 1H), 1.53 (s, 3H), 1.48 (ddd, *J* = 13.2, 13.2, 13.2 Hz, 1H), 1.20 (s, 3H), 0.86 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) ppm 143.9, 138.6, 133.5, 124.5, 123.2, 118.7, 116.3, 113.7, 112.2, 108.3, 64.0, 47.7, 44.5, 37.7, 36.3, 32.1, 31.6, 29.7,

24.6, 20.17; HRMS (ED): Exact mass calcd for C₂₀H₂₅ClNO [M+H]⁺ 330.1619, found 330.1607.

A complete 2D NMR analysis was performed to ascertain the stereochemical outcome of reduction step. First, HSQC was used to assign the –OH proton and also differentiate between H15 and H14 α , H14 β protons, as the latter is connected to a secondary carbon. Then NOESY correlations were used to assign the stereochemistry of newly formed

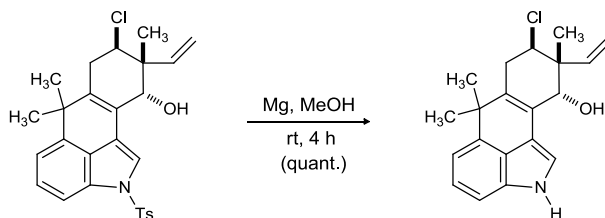
chiral center (C15 and C10). The alcohol proton shows strong NOESY correlations to H13, and H15. As previously elucidated, the alcohol



functionality is α which means that the newly formed chiral centers have α -protons. The presence of NOESY correlations between H2, H11 and H2, H17 also confirms the assigned chair conformation of the cyclohexane core.

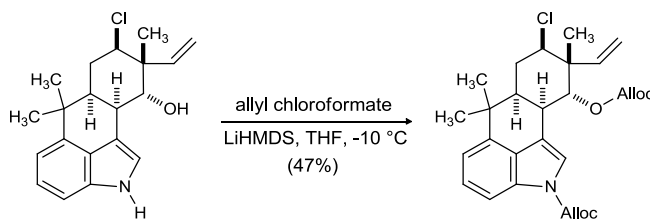
Data for 609:

R_f = 0.06 (SiO₂, 20% EtOAc/hexanes); IR (film) 3401 (br), 2963, 2923, 2851, 1460, 1444 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.86 (br s, 1H), 7.23 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 7.01 (s, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.18 (dd, *J* = 18.0, 11.2 Hz, 1H), 5.40 (d, *J* = 11.2 Hz, 1H), 5.35 (d, *J* = 18.0 Hz, 1H), 4.59 (dd, *J* = 9.6, 5.6 Hz, 1H), 4.42 (s, 1H), 3.05 (dd, *J* = 18.0, 5.6 Hz, 1H), 2.70 (dd, *J* = 18.0, 9.6 Hz, 1H), 1.51 (s, 3H), 1.49 (s, 3H), 1.20 (s, 3H), (-OH proton not observed); ¹³C NMR (100 MHz, CDCl₃) ppm 141.9, 139.1, 136.5, 134.0, 124.6, 123.3, 116.4, 115.8, 114.8, 113.1, 107.8, 77.2, 75.2, 61.8, 45.3, 40.7, 33.6, 31.1, 29.6, 15.3; HRMS (ED): Exact mass calcd for C₂₀H₂₃ClNO [M+H]⁺ 328.1468, found 328.1455.



(8*R*,9*R*,10*R*)-8-Chloro-6,6,9-trimethyl-9-vinyl-2,6,7,8,9,10-hexahydro[1,2,3-*cd*]indol-10-ol (609).

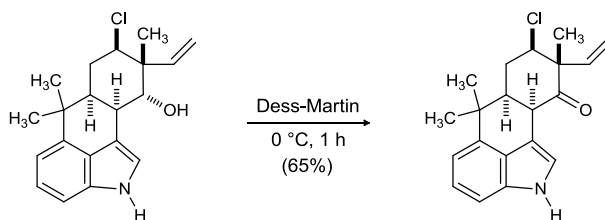
To a solution of alcohol (10.0 mg, 21.0 μmol) in MeOH (3.0 mL) was added Mg turnings (45.8 mg, 1.88 mmol) and the reaction was stirred for 4 h at rt. The reaction was quenched with satd aq NH_4Cl and the solution was stirred for 30 min at rt. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried, filtered, and concentrated. The resulting desotylated product was found to be pure for all analytical purposes (6.8 mg, 99%). See above for the characterization data.



(6*aS*,8*R*,9*R*,10*R*,10*aR*)-Allyl 10-(((allyloxy)carbonyl)oxy)-8-chloro-6,6,9-trimethyl-9-vinyl-6*a*,7,8,9,10,10*a*-hexahydro[1,2,3-*cd*]indole-2(6*H*)-carboxylate (610).

To a $-10\text{ }^\circ\text{C}$ solution of alcohol (4.0 mg, 12.1 μmol) in THF (200 μL) was added LiHMDS (61 μL , 61 μmol , 1.0 M in toluene) dropwise. The reaction was stirred for 1 h at $-10\text{ }^\circ\text{C}$, and allyl chloroformate (5.2 μL , 48 μmol) was added dropwise to the solution. The reaction was stirred for 30 min at $-10\text{ }^\circ\text{C}$ and 30 min at $0\text{ }^\circ\text{C}$. The reaction was

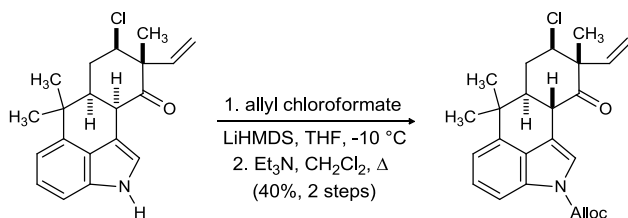
quenched with satd aq NH_4Cl and the layers were separated. The aqueous layer was extracted with Et_2O and the combined organic layers were dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO_2 , 10% ethyl acetate in hexanes) to afford the desired product as a colorless oil (2.8 mg, 47%). $R_f = 0.44$ (SiO_2 , 20% EtOAc/hexanes); IR (film) 2955, 2925, 2853, 1742 (br s), 1439, 1394, 1252 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.85 (br s, 1H), 7.46 (br s, 1H), 7.31 (dd, $J = 7.8, 7.8$ Hz, 1H), 7.10 (d, $J = 7.2$ Hz, 1H), 6.10 (dddd, 17.4, 10.2, 6.0, 6.0 Hz, 1H), 5.96 (dddd, 17.4, 10.8, 6.0, 6.0 Hz, 1H), 5.91 (dd, $J = 17.4, 10.8$ Hz, 1H), 5.47 (d, $J = 17.4$ Hz, 1H), 5.45 (d, $J = 2.4$ Hz, 1H), 5.38 (dd, $J = 17.4, 1.2$ Hz, 1H), 5.37 (dd, $J = 10.2, 1.2$ Hz, 1H), 5.31 (dd, $J = 10.8, 1.2$ Hz, 1H), 5.23 (d, $J = 12.0$ Hz, 1H), 5.21 (d, $J = 18.0$ Hz, 1H), 4.95 (dd, 12.6, 6.0 Hz, 1H), 4.91 (dd, 13.2, 6.0 Hz, 1H), 4.69 (ddd, 12.6, 6.0, 0.6 Hz, 1H), 4.65 (ddd, 13.2, 6.0, 0.6 Hz, 1H), 4.20 (dd, 12.6, 3.6 Hz, 1H), 3.58 (s, 1H), 2.24 (ddd, 13.2, 4.2, 4.2 Hz, 1H), 2.15 (ddd, 13.2, 3.6, 3.6 Hz, 1H), 1.46 (ddd, 13.2, 13.2, 13.2 Hz, 1H), 1.52 (s, 3H), 1.14 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) ppm 165.4, 154.3, 142.3, 138.5, 131.5, 125.9, 120.5, 120.4, 119.5, 119.1, 117.7, 117.6, 116.1, 115.7, 112.9, 82.9, 68.7, 67.6, 63.7, 46.0, 44.4, 37.5, 35.2, 32.2, 31.2, 24.5, 19.1; HRMS (EI): Exact mass calcd for $\text{C}_{28}\text{H}_{32}\text{ClNO}_5$ $[\text{M}]^+$ 497.1969, found.²⁸



²⁸ Decomposition of the compound was observed. The desired mass of the compound or its fragment could not be obtained in HRMS.

(6a*S*,8*R*,9*R*,10a*R*)-8-Chloro-6,6,9-trimethyl-9-vinyl-6,6a,7,8,9,10a-hexahydronaphtho[1,2,3-*cd*]indol-10(2H)-one (611).

To a 0 °C solution of alcohol (5.9 mg, 17.9 μmol) in CH₂Cl₂ (600 μL) was added Dess-Martin periodinane (19.0 mg, 44.8 μmol) and the reaction was stirred for 1 h. The reaction was quenched by the addition of an aqueous solution containing 2:1 satd aq Na₂S₂O₃:NaHCO₃ and was stirred until both layers became clear (~20 min). The layers were separated, the aqueous layer was extracted with CH₂Cl₂, and the combined organic layers were dried, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 15% ethyl acetate in hexanes) to afford the enone as a pale yellow foam (3.8 mg, 65%). R_f = 0.60 (SiO₂, 40% EtOAc/hexanes); IR (film) 3399 (br), 2923, 2953, 1698 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 8.07 (br s, 1H), 7.23-7.19 (m, 2H), 6.99 (dd, *J* = 6.6, 1.2 Hz, 1H), 6.76 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.93 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.38 (d, *J* = 10.8 Hz, 1H), 5.23 (d, *J* = 17.4 Hz, 1H), 4.24 (dd, *J* = 12.6, 3.6 Hz, 1H), 4.23 (br s, 1H), 2.27 (dddd, *J* = 13.8, 3.6, 3.6, 1.8 Hz, 1H), 2.18 (ddd, *J* = 13.2, 3.6, 3.6 Hz, 1H), 1.76 (ddd, *J* = 13.2, 13.2, 13.2 Hz, 1H), 1.58 (s, 3H), 1.20 (s, 3H), 1.11 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) ppm 211.3, 139.7, 137.3, 133.8, 123.6, 123.5, 120.0, 116.5, 113.9, 108.8, 108.4, 64.9, 57.2, 46.5, 45.8, 37.5, 31.6, 30.7, 24.6, 20.1; HRMS (EI): Exact mass calcd for C₂₀H₂₃ClNO [M+H]⁺ 328.1468, found 328.1391.



(6a*S*,8*R*,9*R*,10a*S*) Allyl 8-chloro-6,6,9-trimethyl-10-oxo-9-vinyl-6a,7,8,9,10,10a-hexahydro naphtho[1,2,3-*cd*]indole-2(6*H*)-carboxylate (612).

To a -10 °C solution of indole (4.5 mg, 13.7 μmol) in THF (500 μL) was added LiHMDS (34.2 μL, 34.2 μmol, 1.0 M in toluene). The reaction was stirred for 1 h at -10 °C, and allyl chloroformate (3.6 μL, 34 μmol) was added dropwise to the solution. The solution was stirred for 30 min at -10 °C and 30 min at 0 °C. The reaction was quenched with satd aq NH₄Cl and the layers were separated. The aqueous layer was extracted with Et₂O and the combined organic layers were dried, filtered, and concentrated to provide a yellow oil. The crude Alloc protected indole was carried on to the next step without further purification.

To a solution of the crude indole (2.6 mg) in CH₂Cl₂ (300 μL) was added triethyl amine (30.0 μL, 73.5 μmol) and the reaction was stirred for 4 h at 40 °C. The reaction was concentrated and the resulting residue was purified by flash column chromatography (SiO₂, 10% ethyl acetate in hexanes) to afford the desired product as a colorless oil (2.2 mg, 40%). The NMR data matched that in the literature.²⁹

²⁹ Fukuyama, T.; Chen, X. Q. *J. Am. Chem. Soc.* **1994**, *116*, 3125.

Figure 1. ¹H NMR Spectrum (500 MHz, CDCl₃) of 33aa

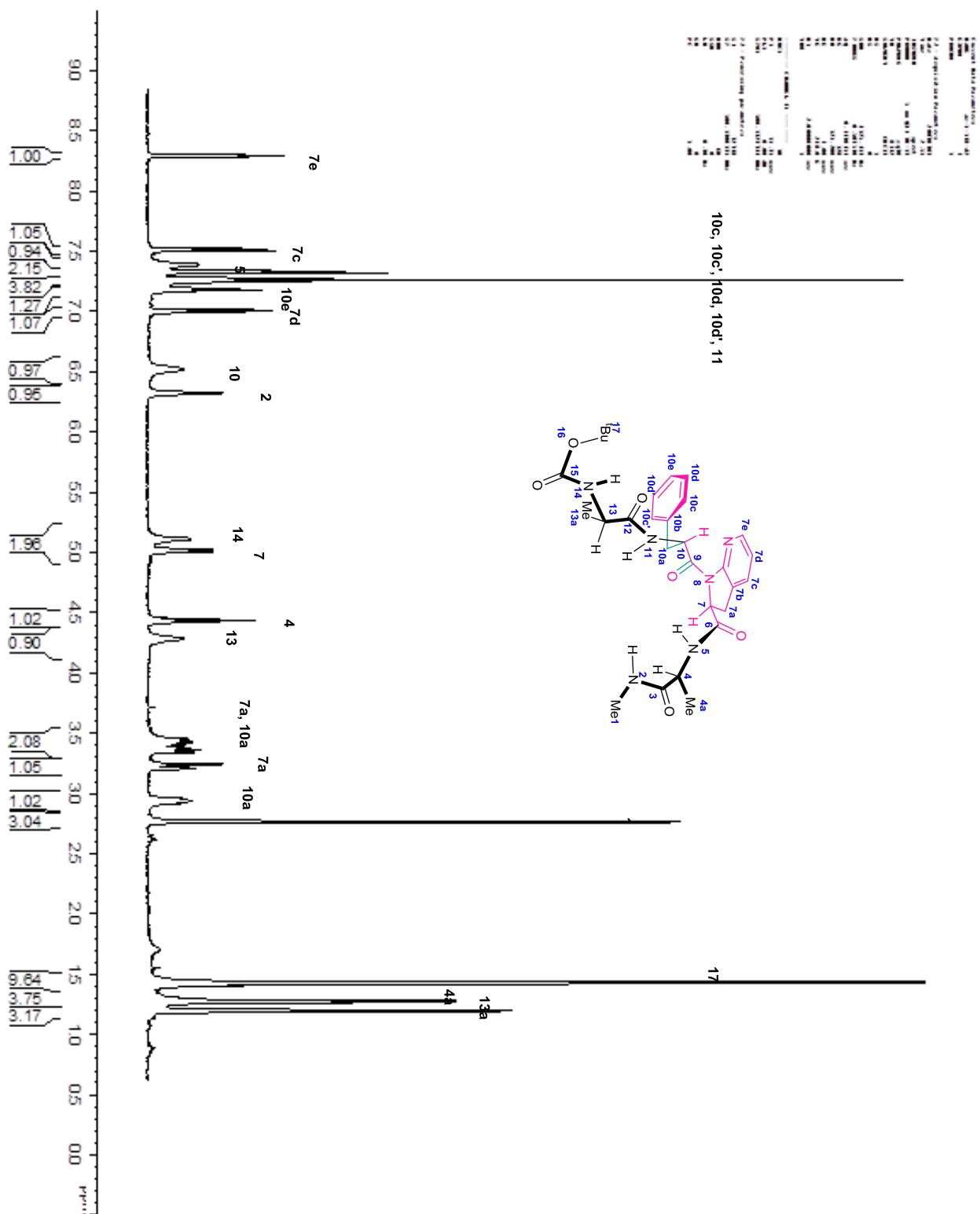


Figure 2. ^{13}C NMR Spectrum (125 MHz, CDCl_3) of 33a

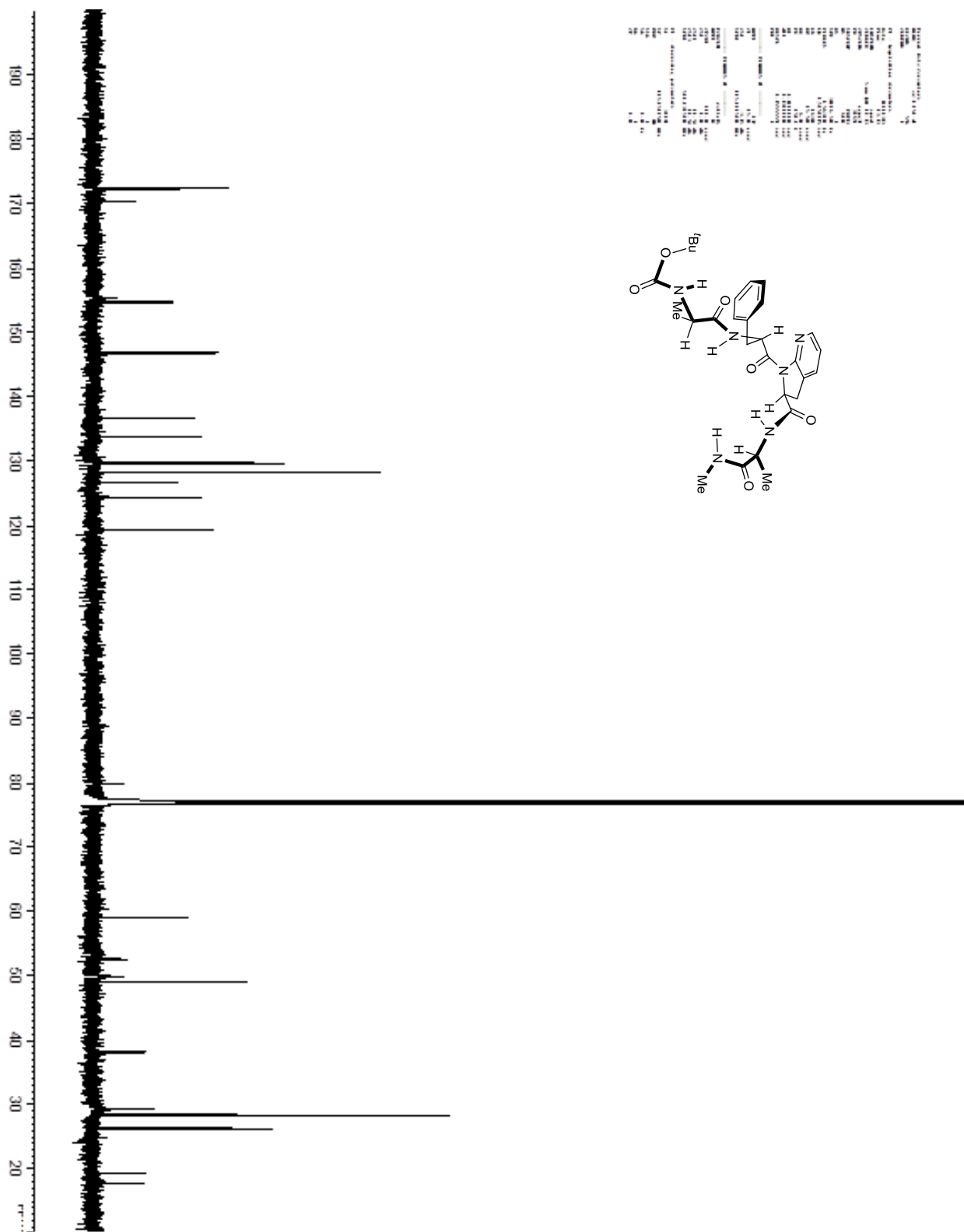


Figure 5. COSY Spectrum (125 MHz, CDCl₃) of 33a

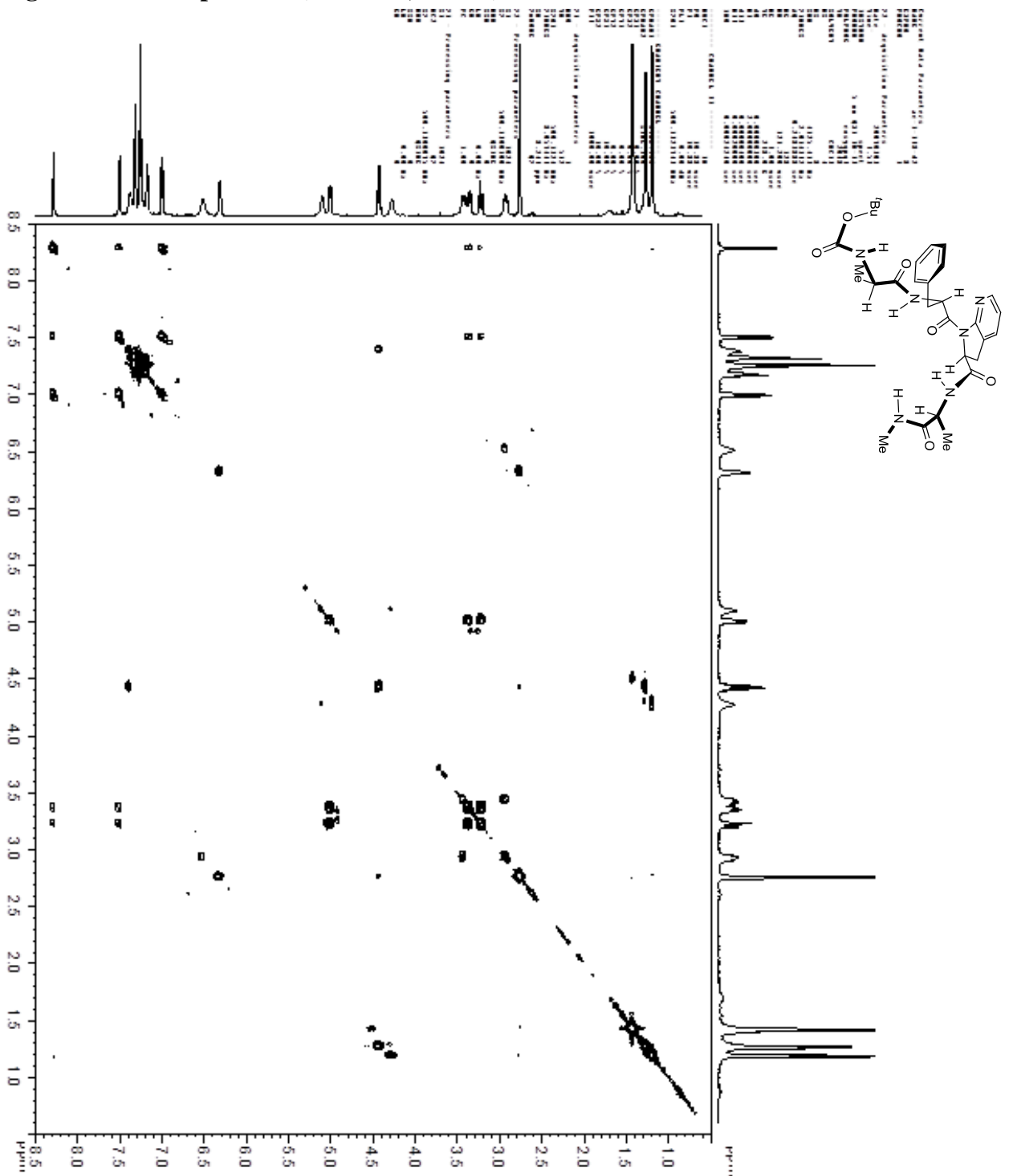


Figure 6. HMBC Spectrum (125 MHz, CDCl₃) of 33a

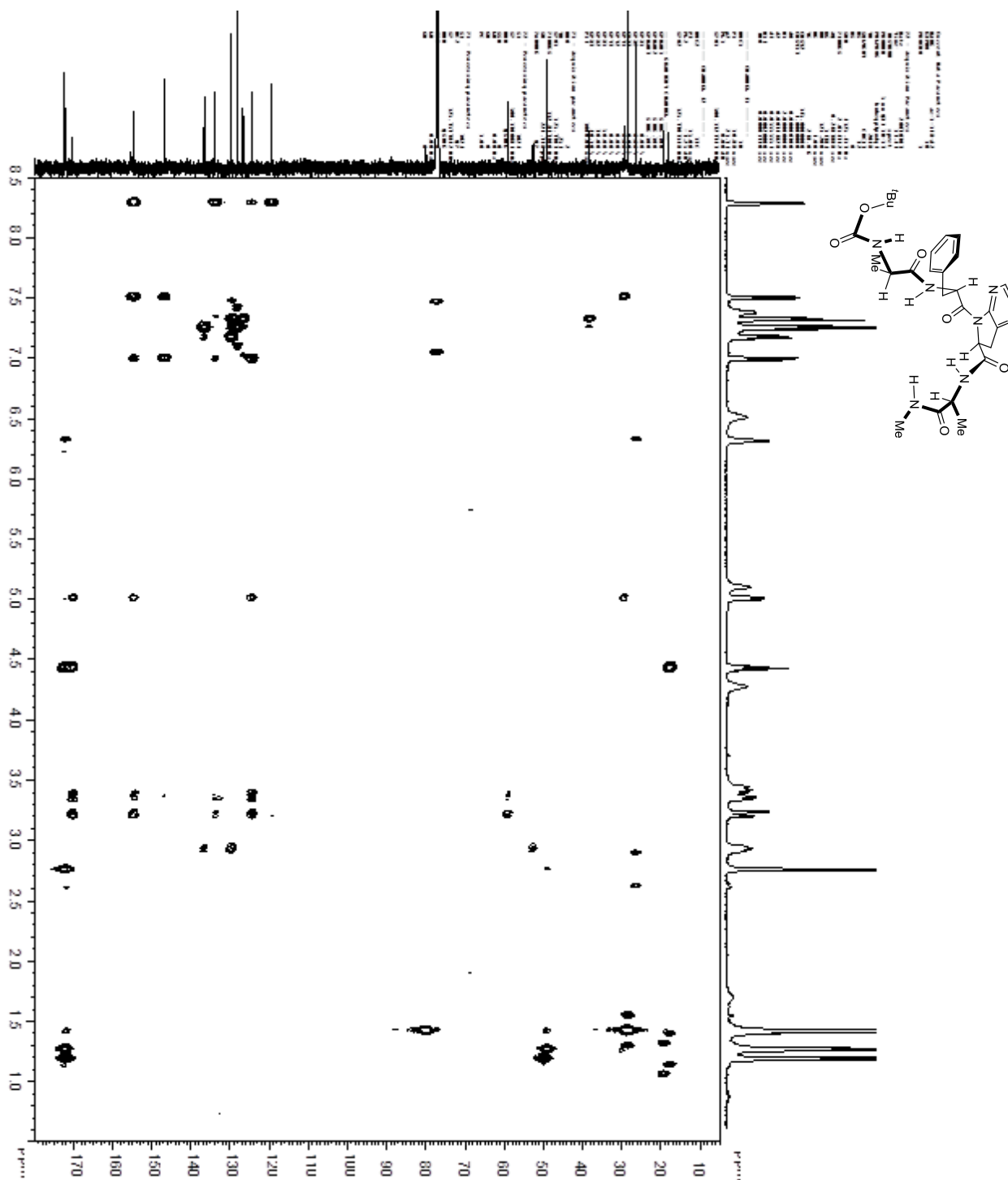


Figure 7. NOESY Spectrum (500 MHz, CDCl₃) of 33a

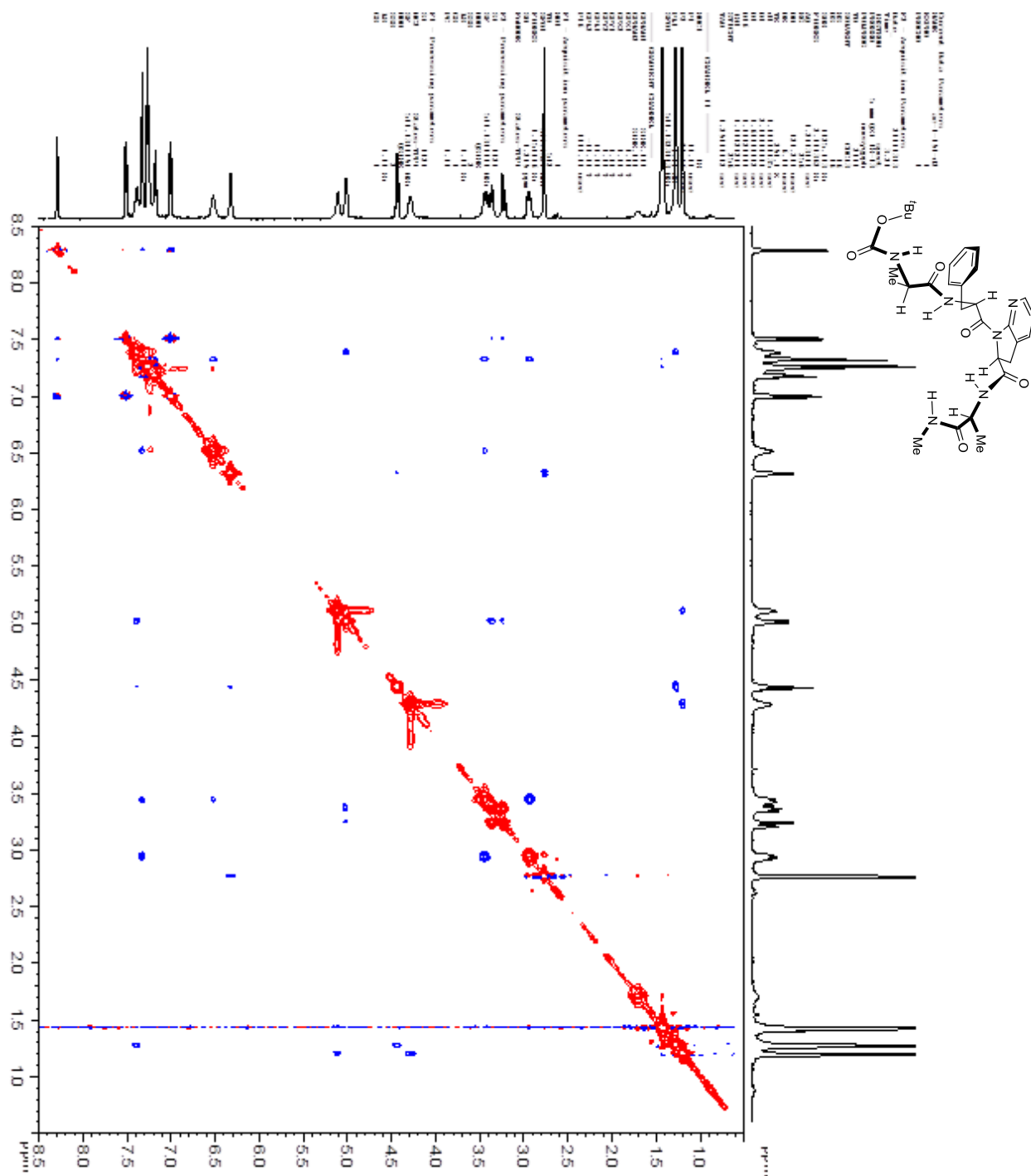


Figure 8. ¹H NMR Spectrum (500 MHz, CDCl₃) of 33ab

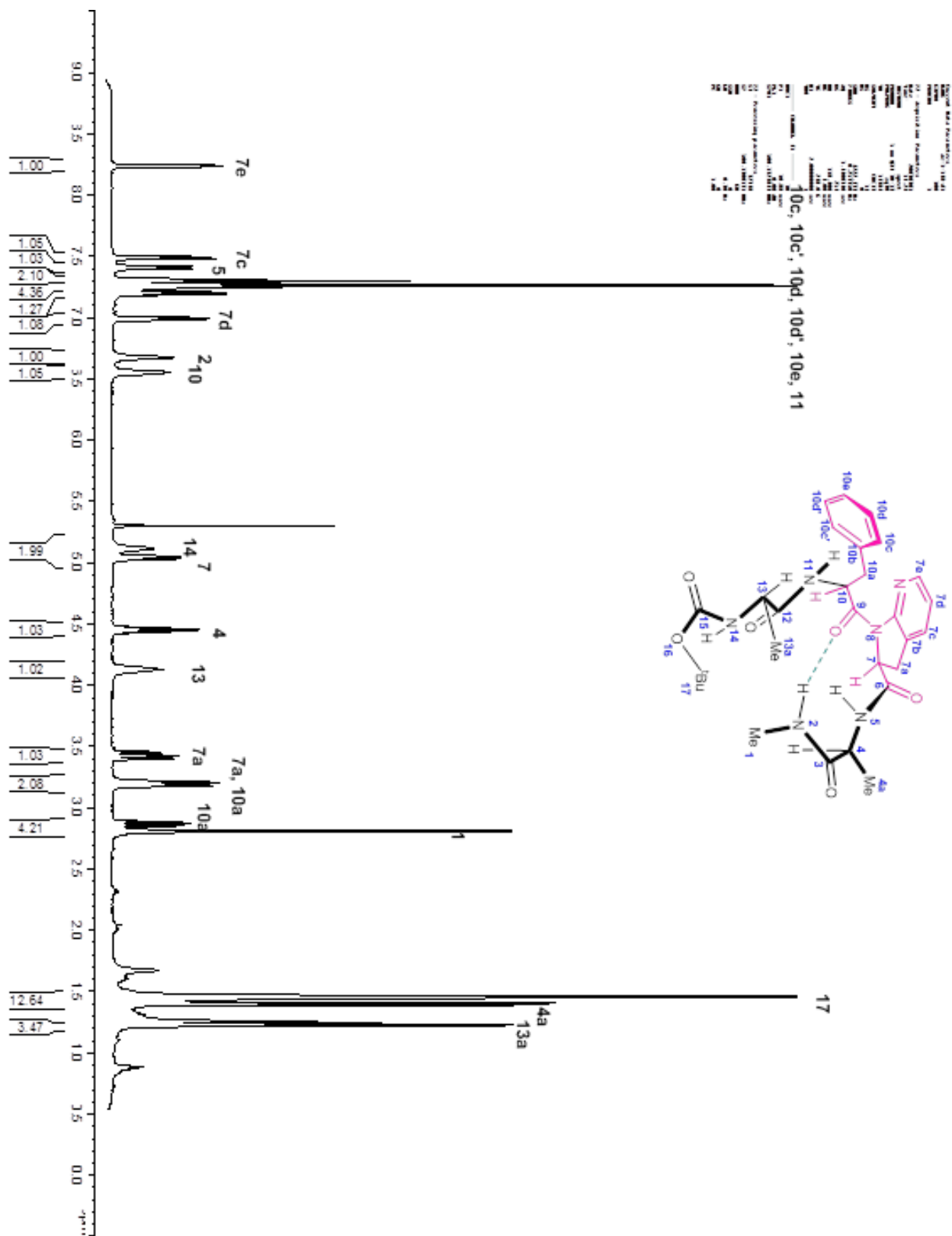


Figure 9. ^{13}C NMR Spectrum (125 MHz, CDCl_3) of 33ab

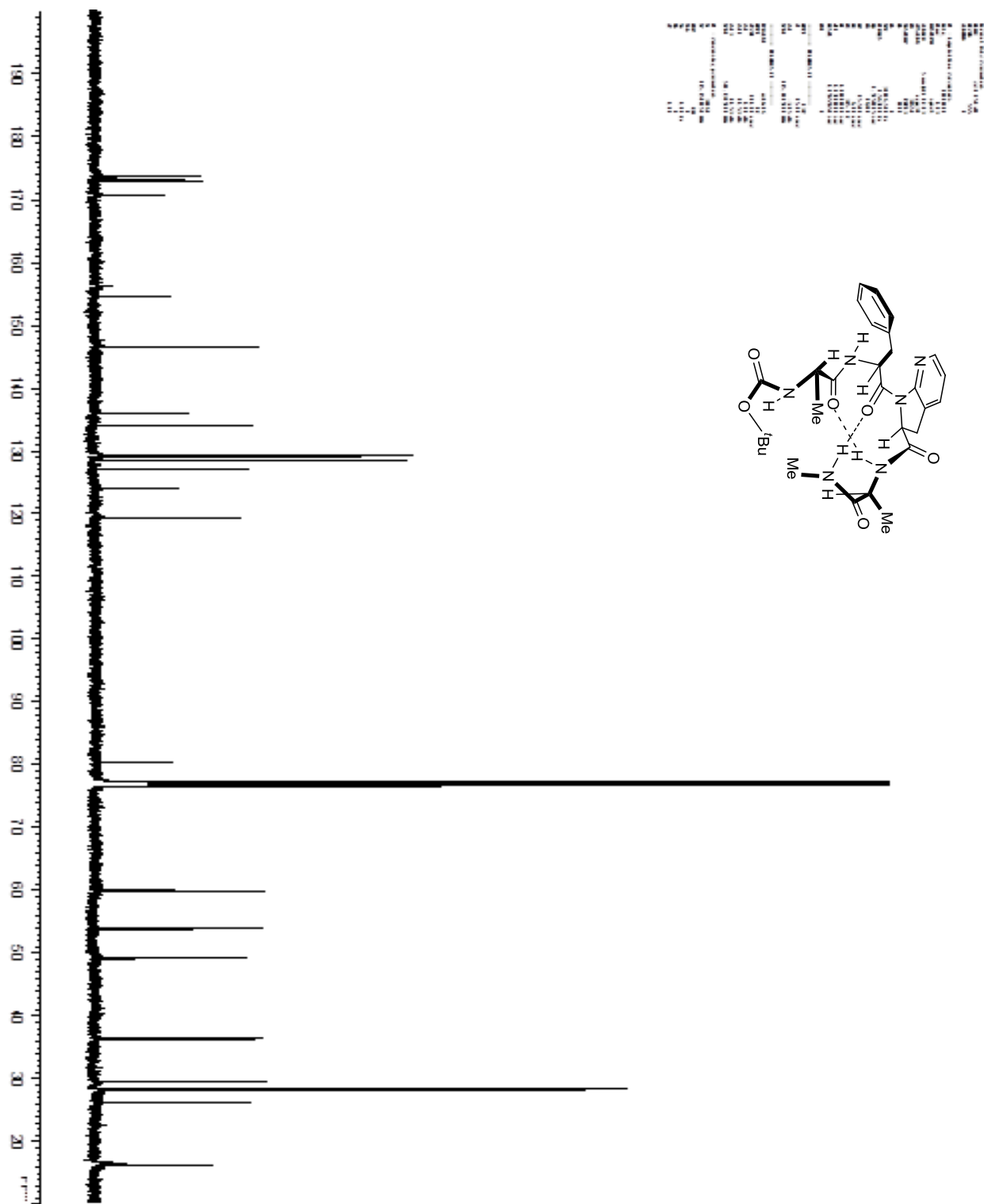


Figure 10. 135 DEPT Spectrum (125 MHz, CDCl₃) of 33ab

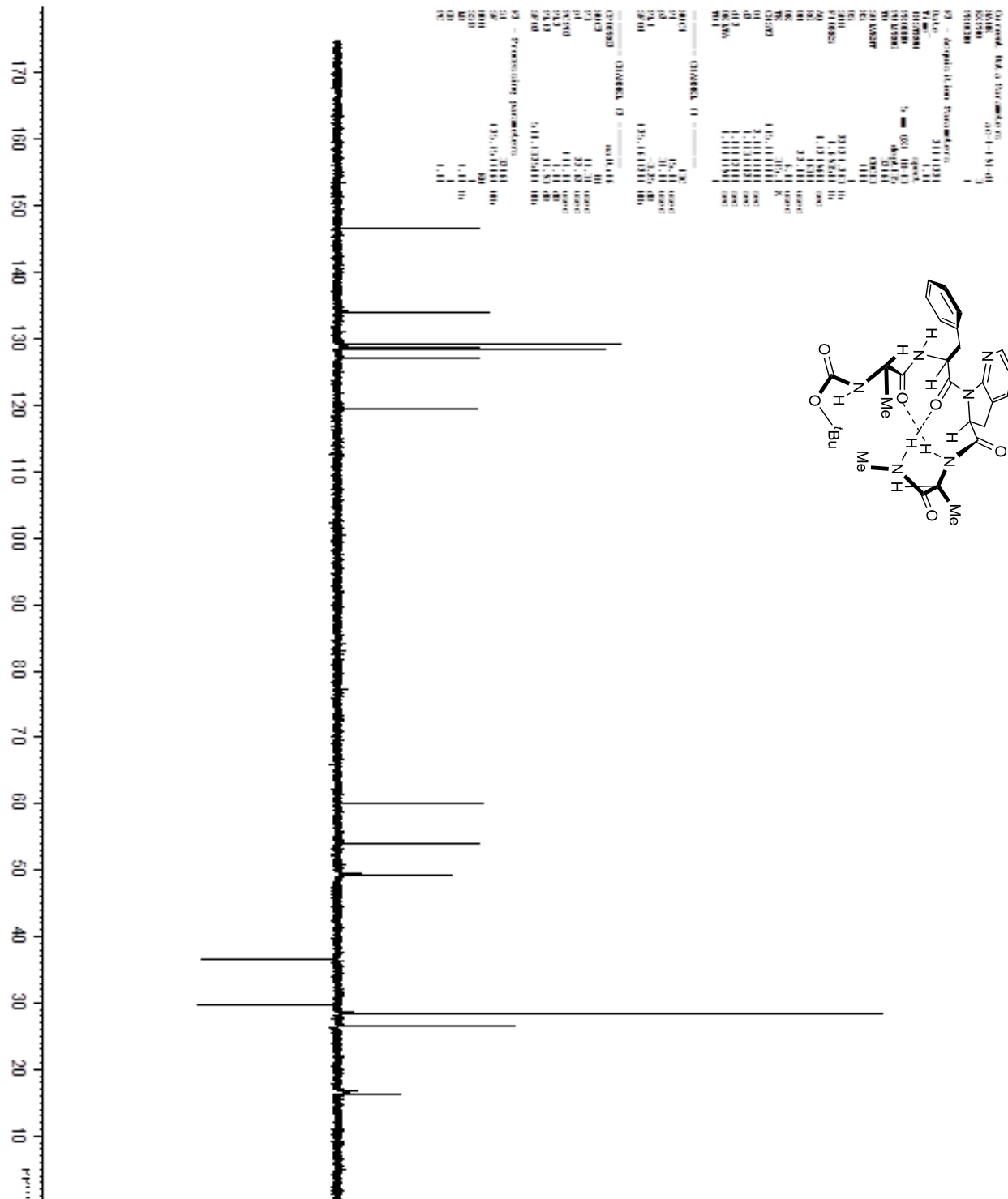


Figure 11. HSQC Spectrum (125 MHz, CDCl₃) of 33ab

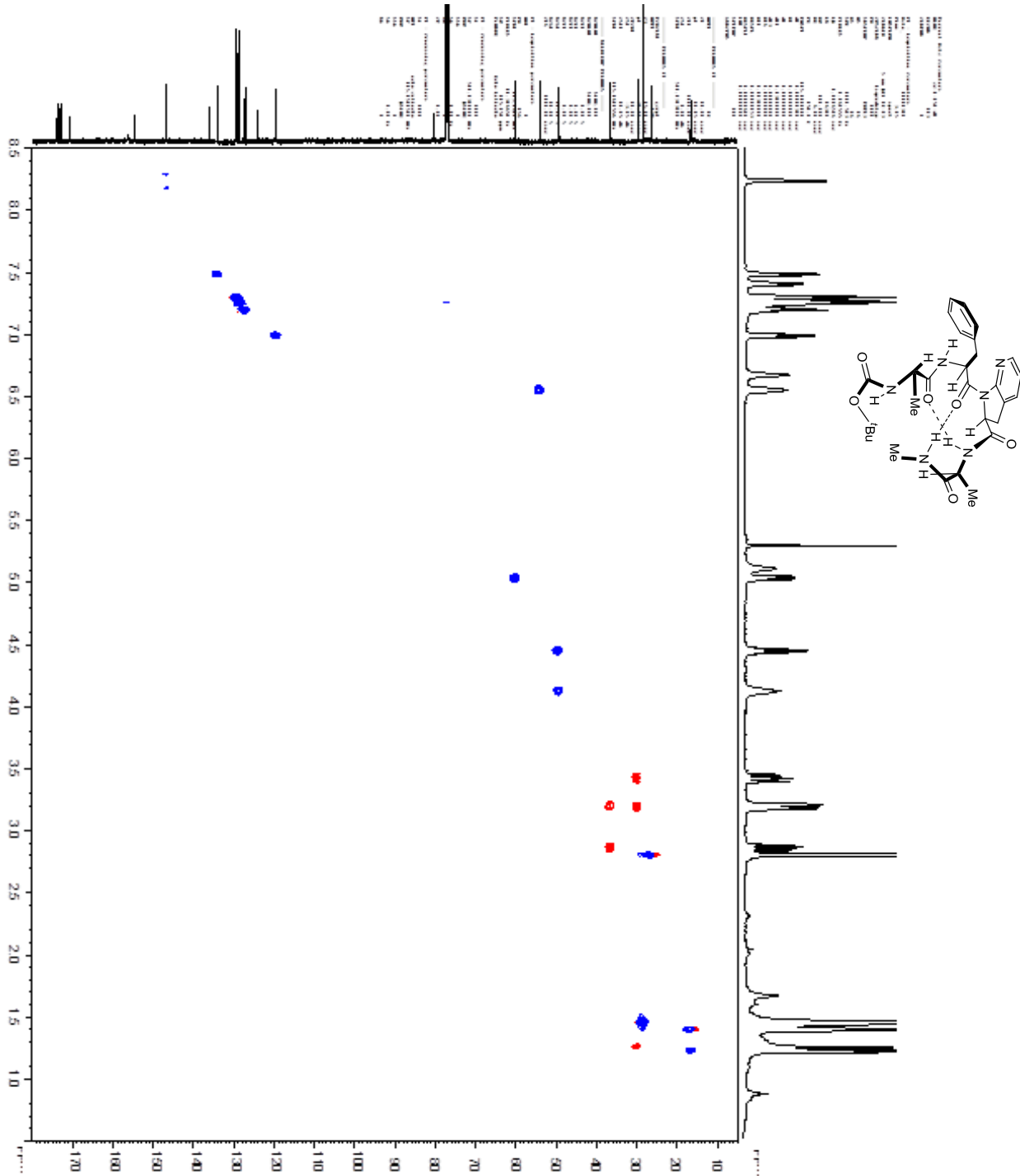


Figure 12. COSY Spectrum (125 MHz, CDCl₃) of 33ab

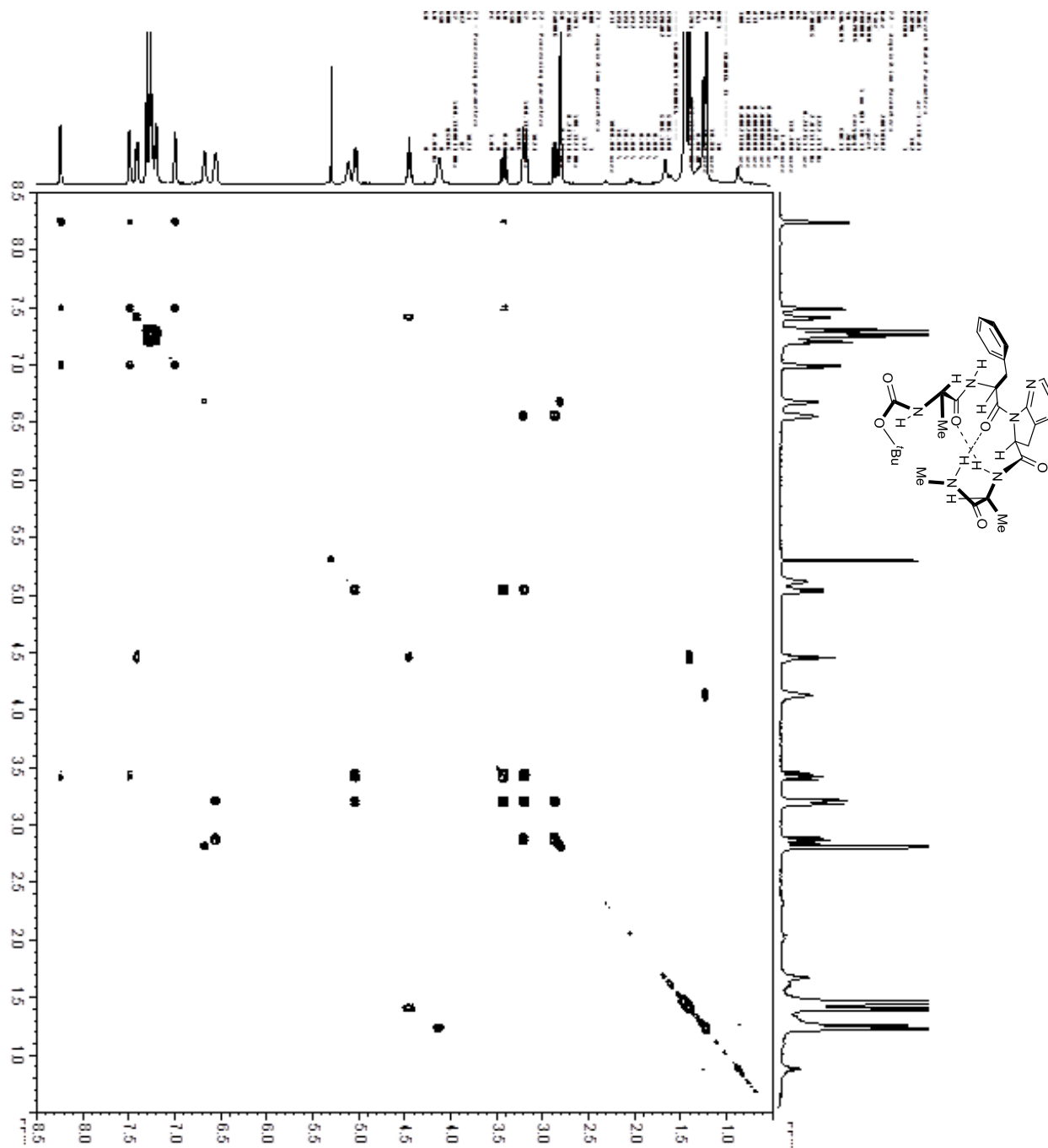


Figure 13. HMBC Spectrum (125 MHz, CDCl₃) of 33ab

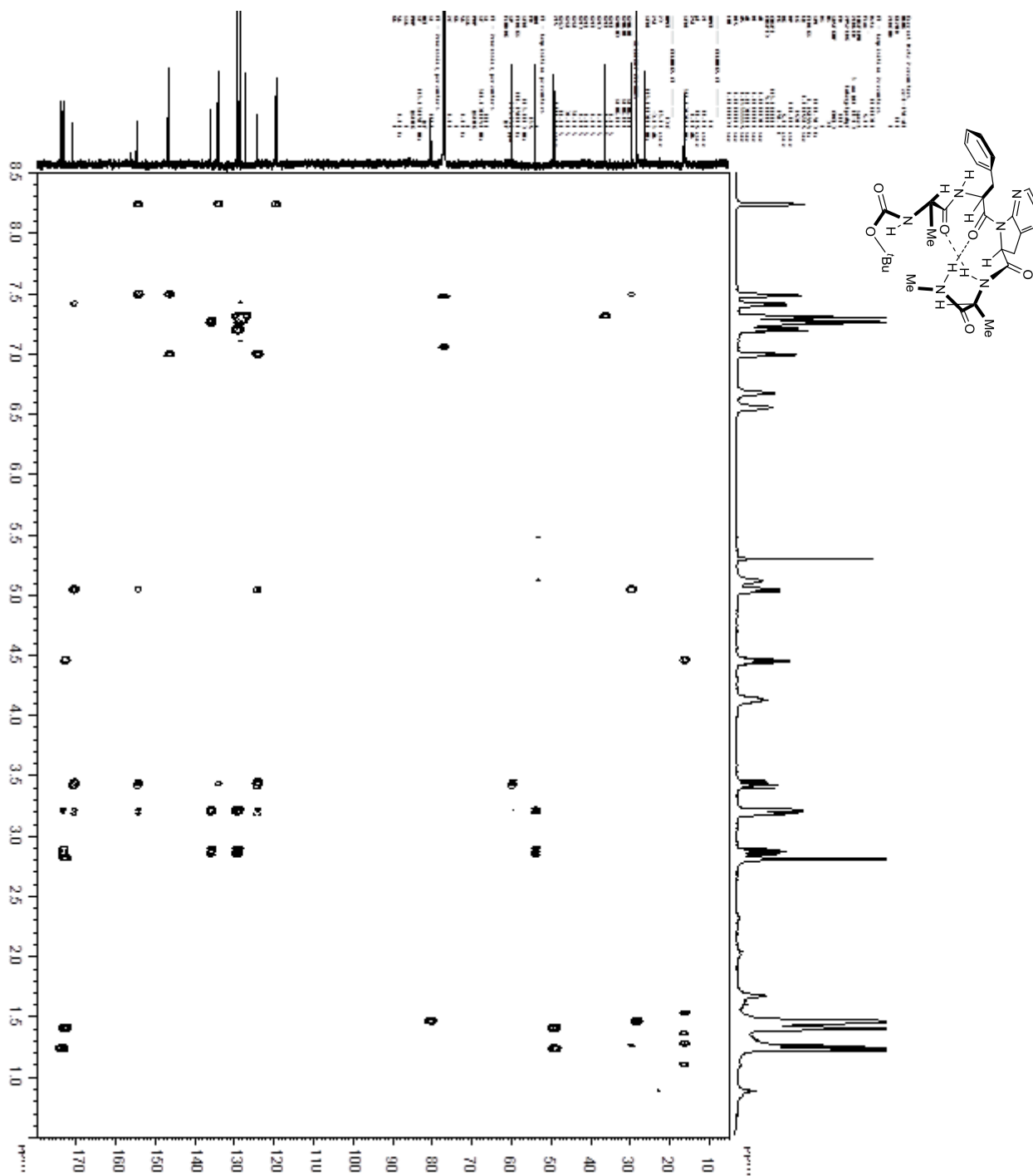


Figure 14. NOESY Spectrum (500 MHz, CDCl₃) of 33ab

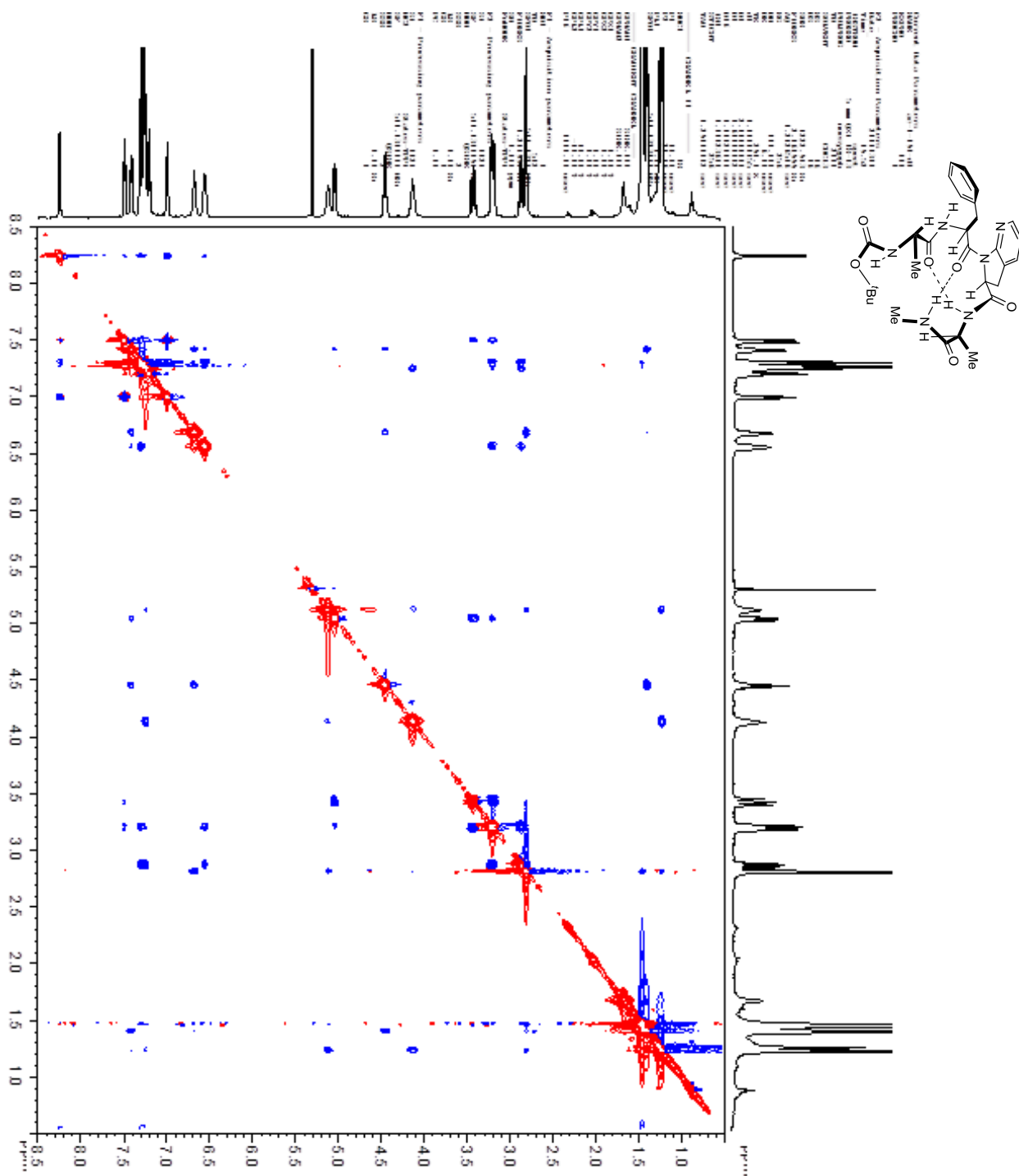


Figure 15. ^1H NMR Spectrum (600 MHz, CDCl_3) of 33ba

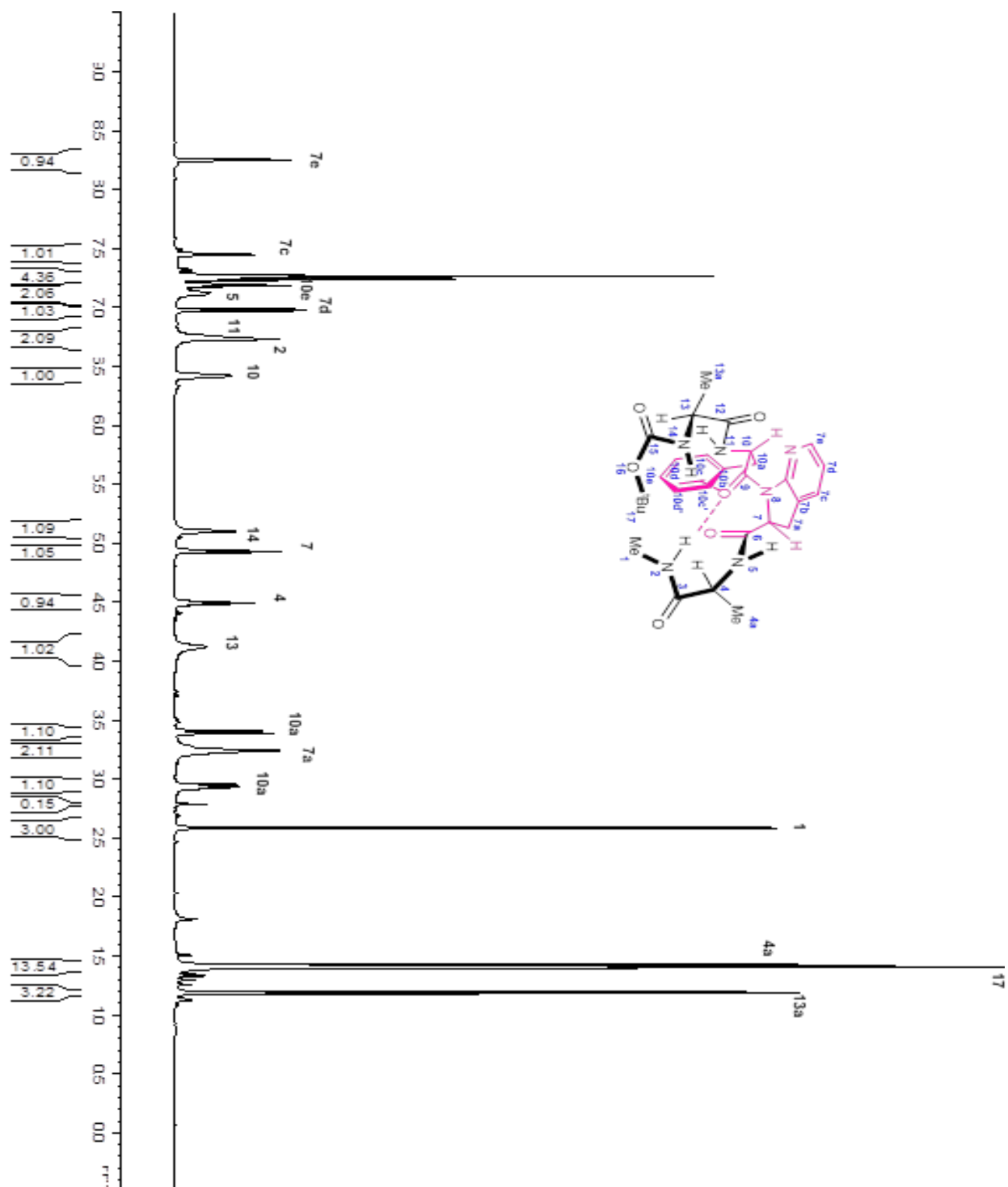


Figure 16. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 33ba

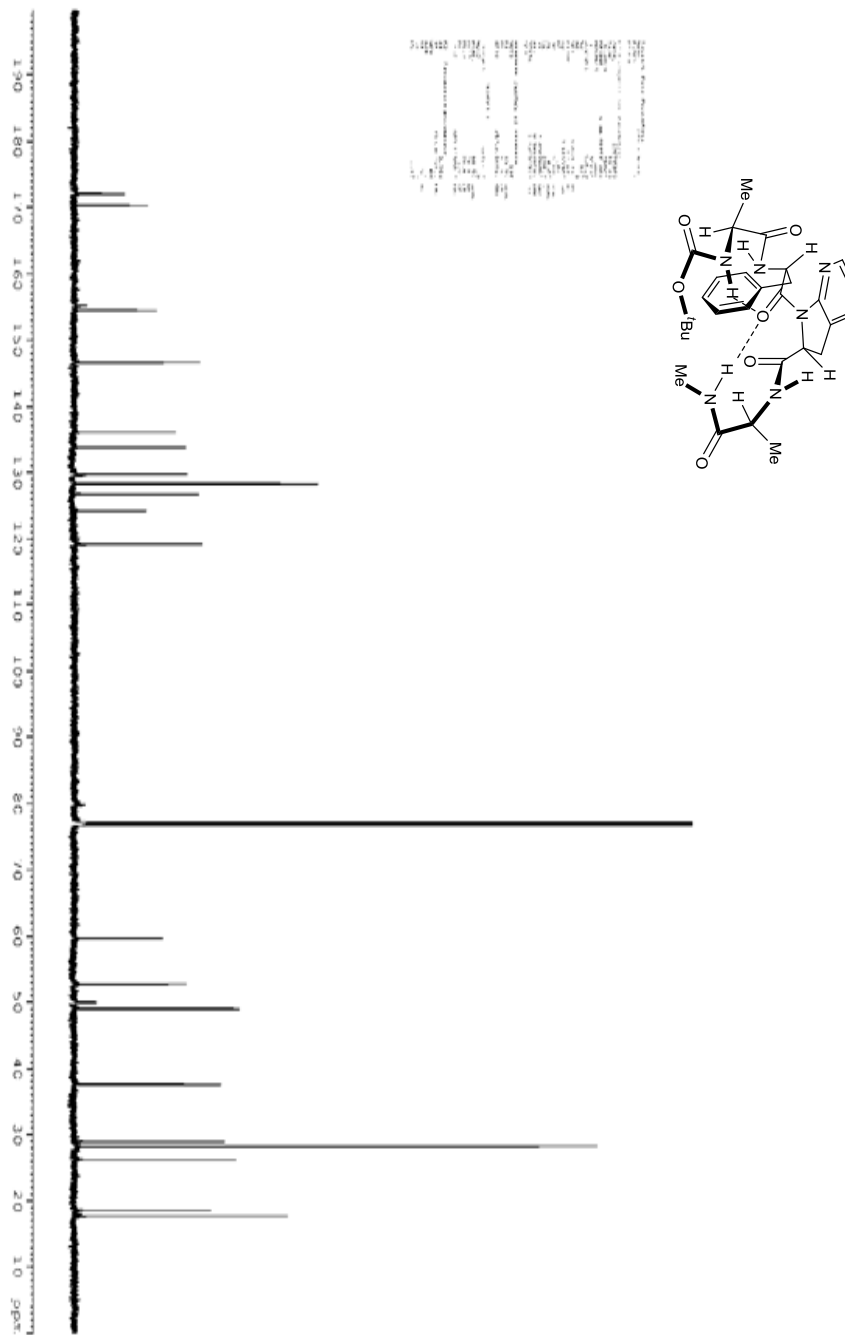


Figure 18. HSQC Spectrum (150 MHz, CDCl₃) of 33ba

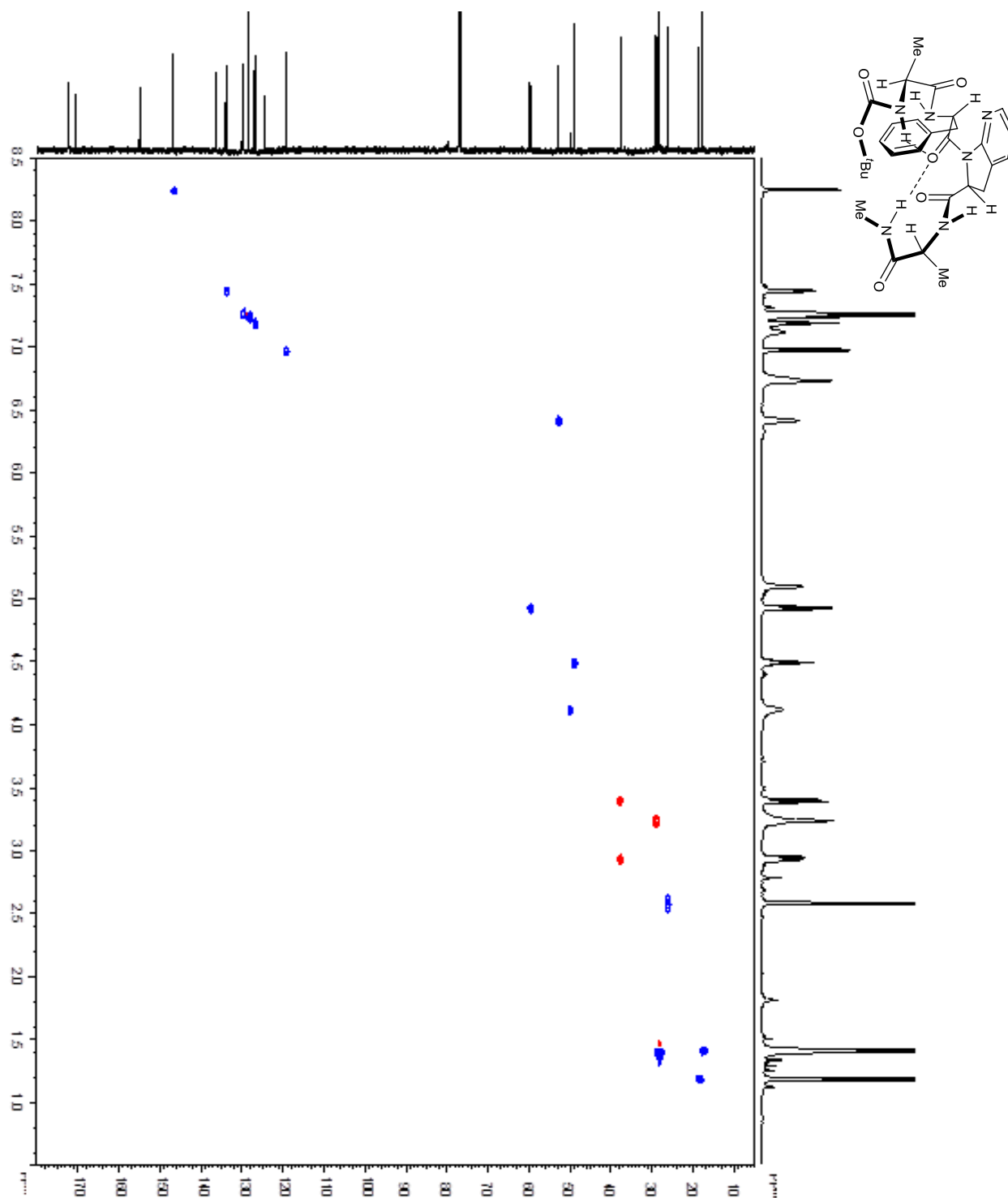


Figure 19. COSY Spectrum (150 MHz, CDCl₃) of 33ba

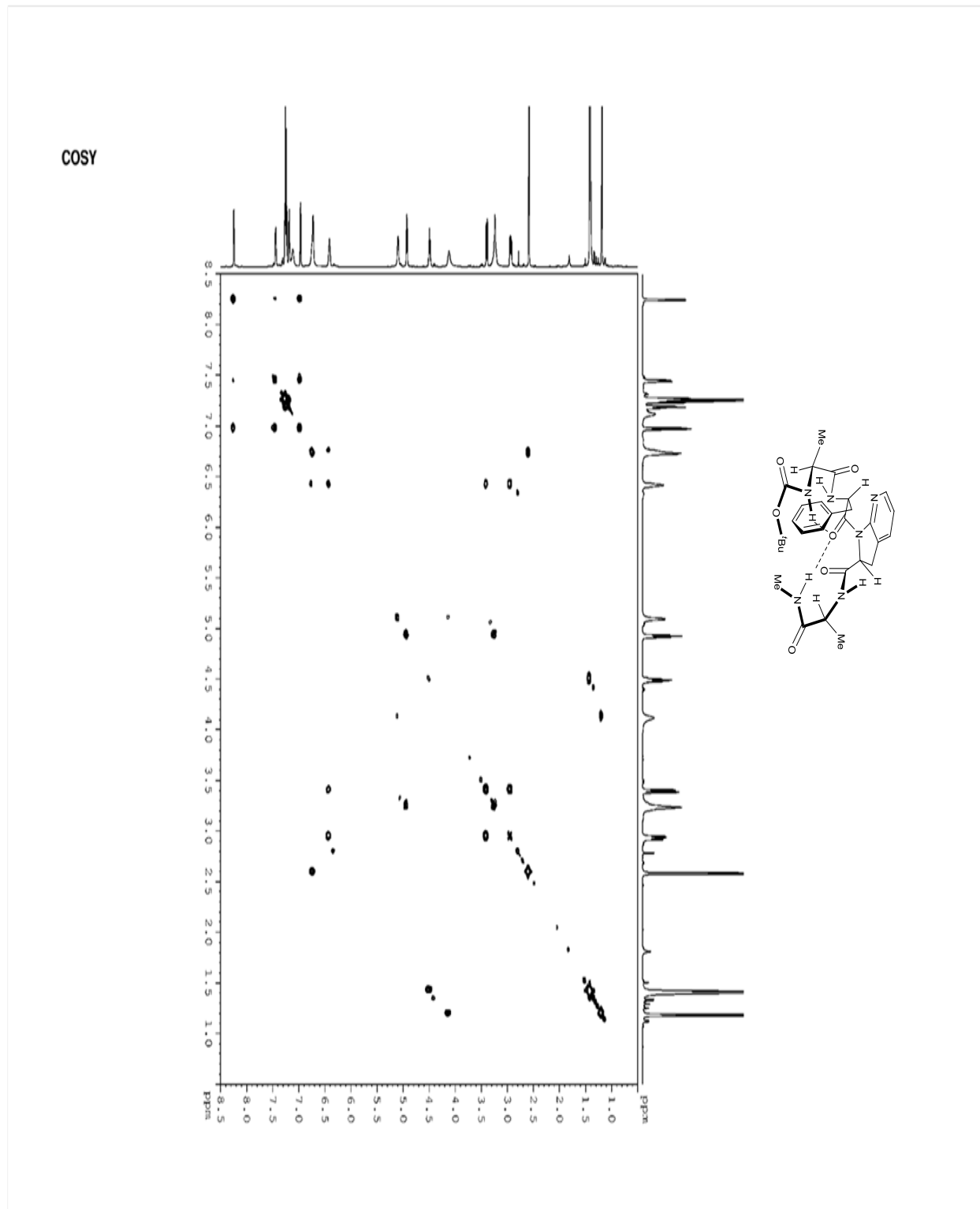


Figure 20. HMBC Spectrum (125 MHz, CDCl₃) of 33ba

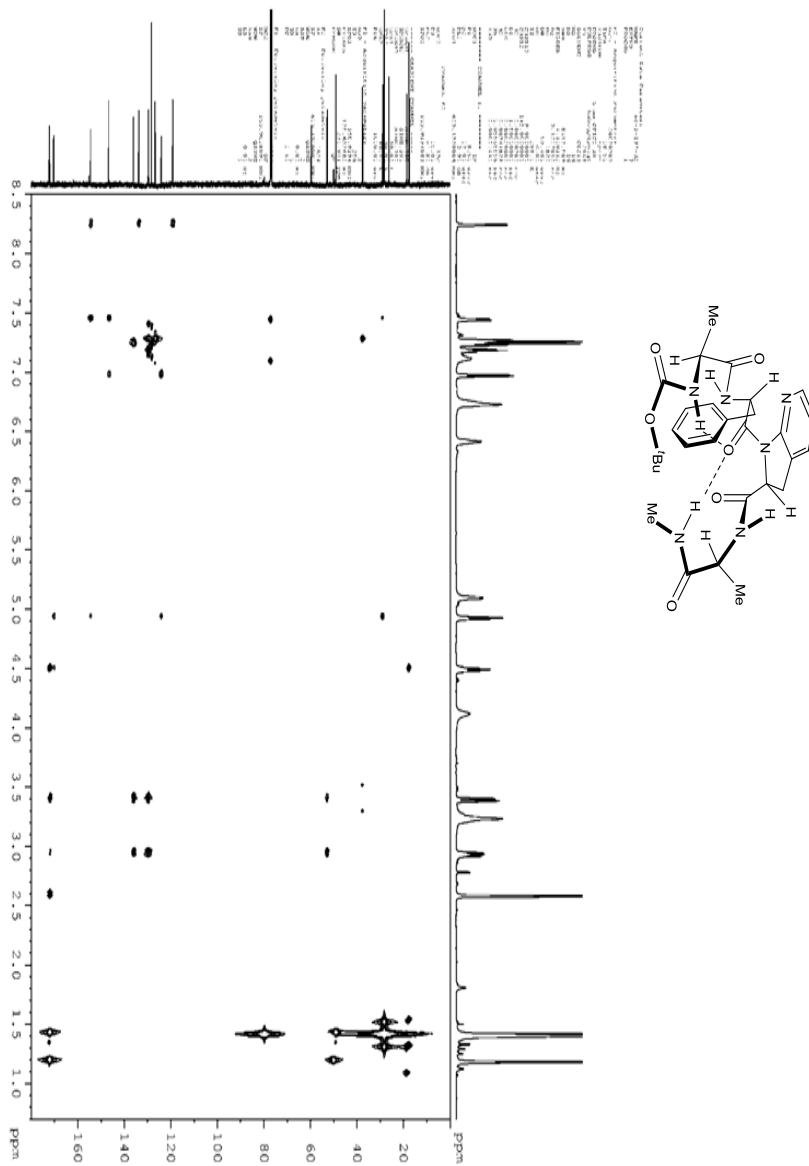


Figure 21. NOESY Spectrum (600 MHz, CDCl₃) of 33ba

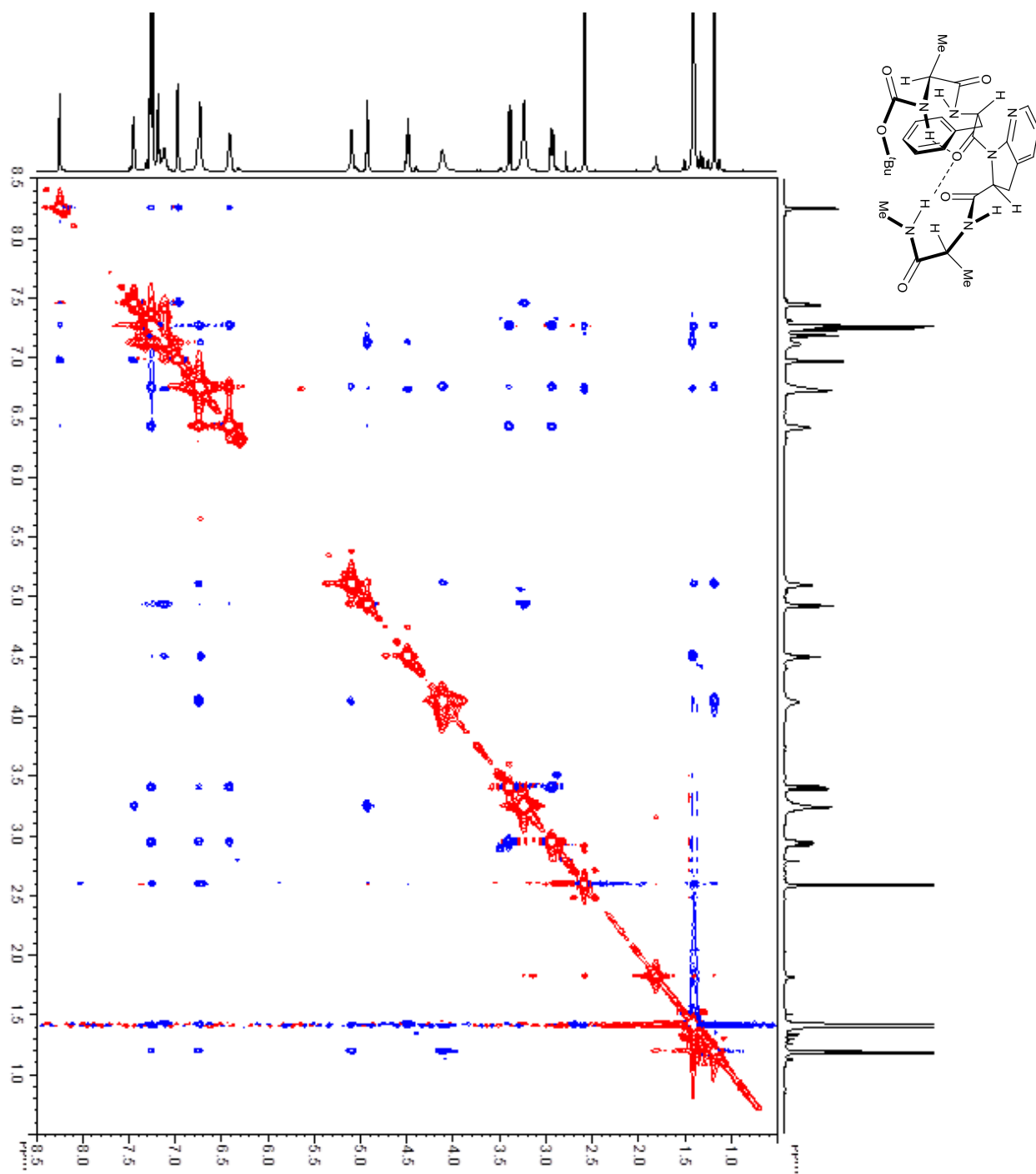


Figure 22. ^1H NMR Spectrum (600 MHz, CDCl_3) of 33bb

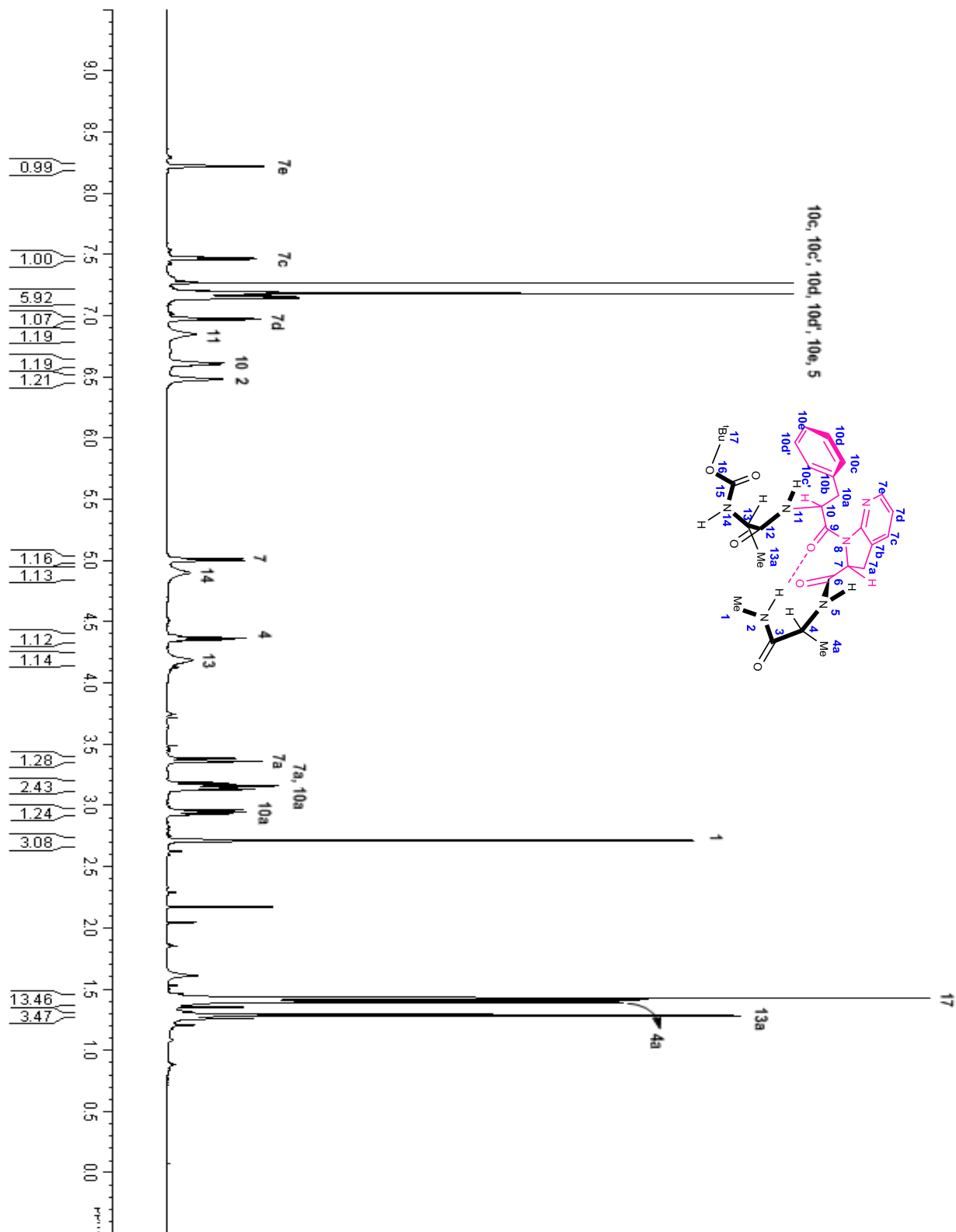


Figure 23. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 33bb

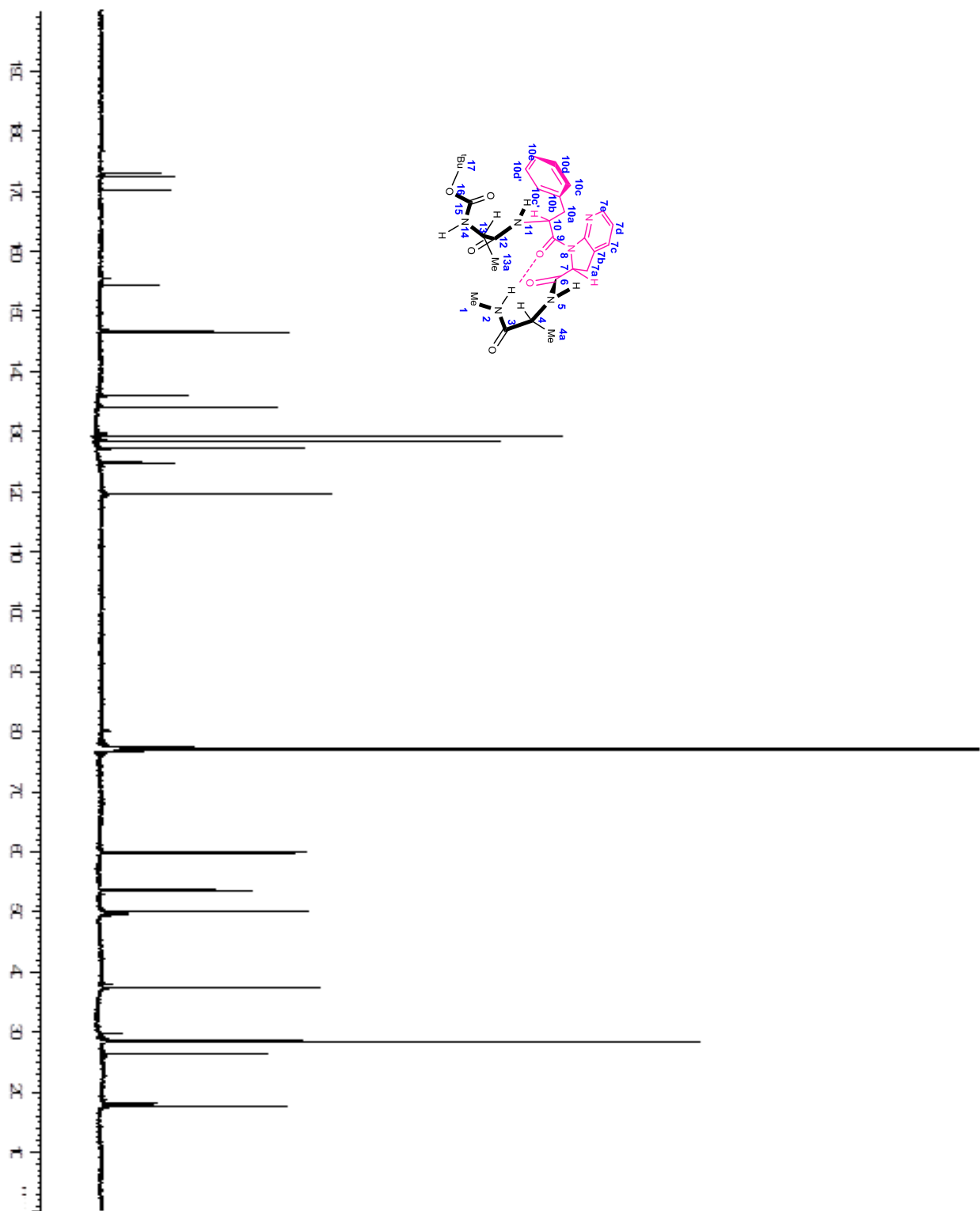


Figure 24. 135 DEPT Spectrum (125 MHz, CDCl₃) of 33bb

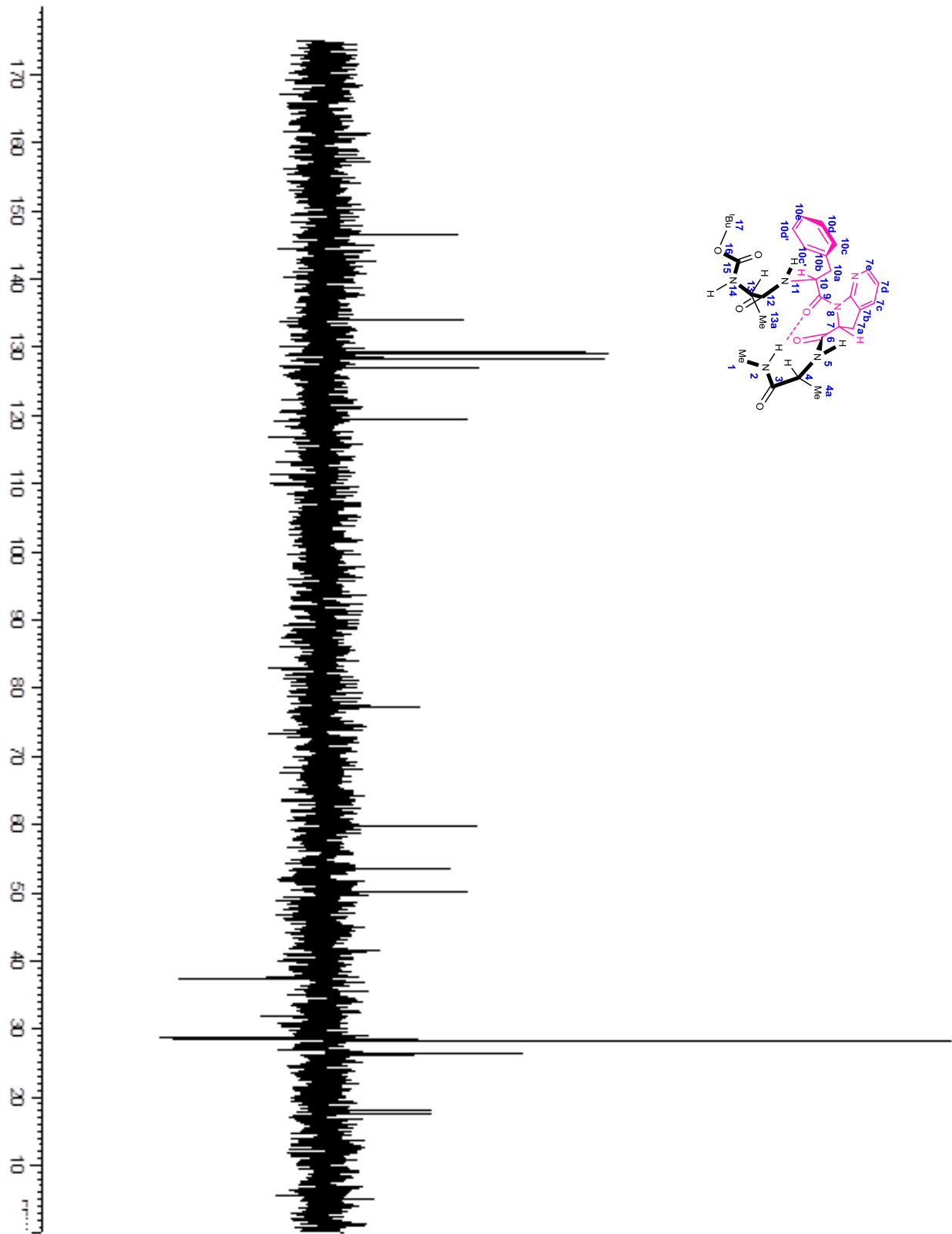


Figure 25. HSQC Spectrum (150 MHz, CDCl₃) of 33bb

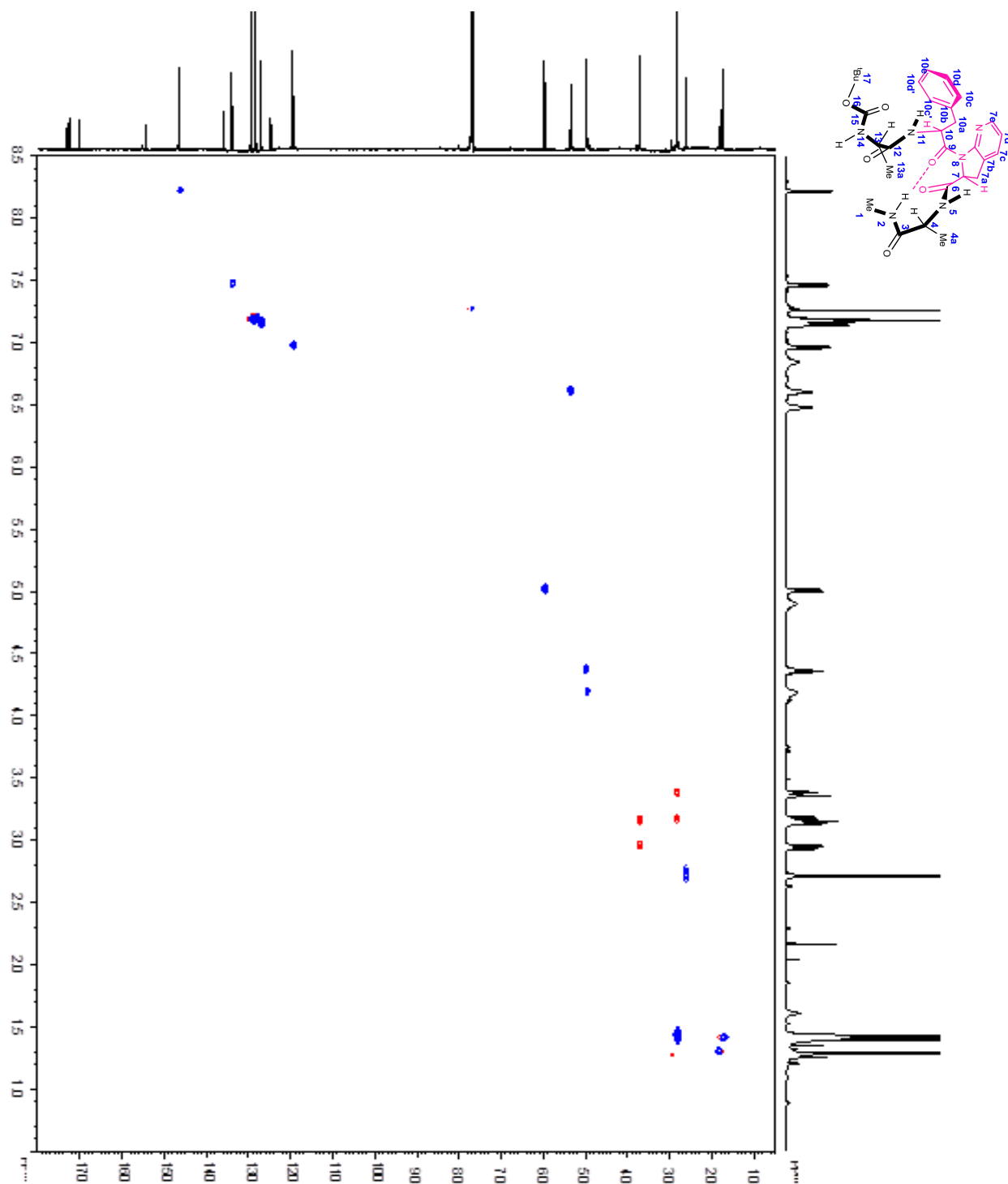


Figure 26. . COSY Spectrum (150 MHz, CDCl₃) of 33bb

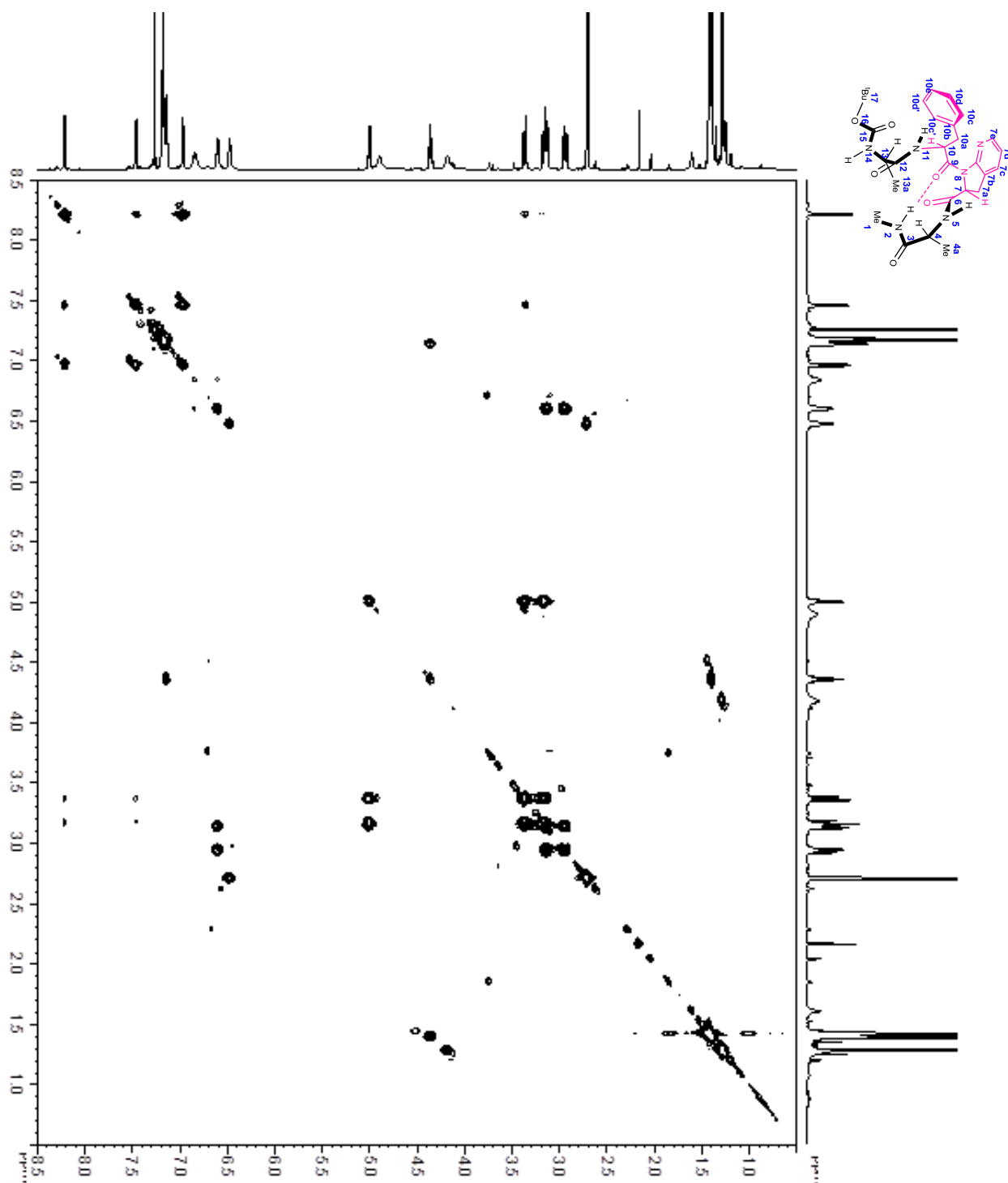


Figure 27. HMBC Spectrum (150 MHz, CDCl₃) of 33bb

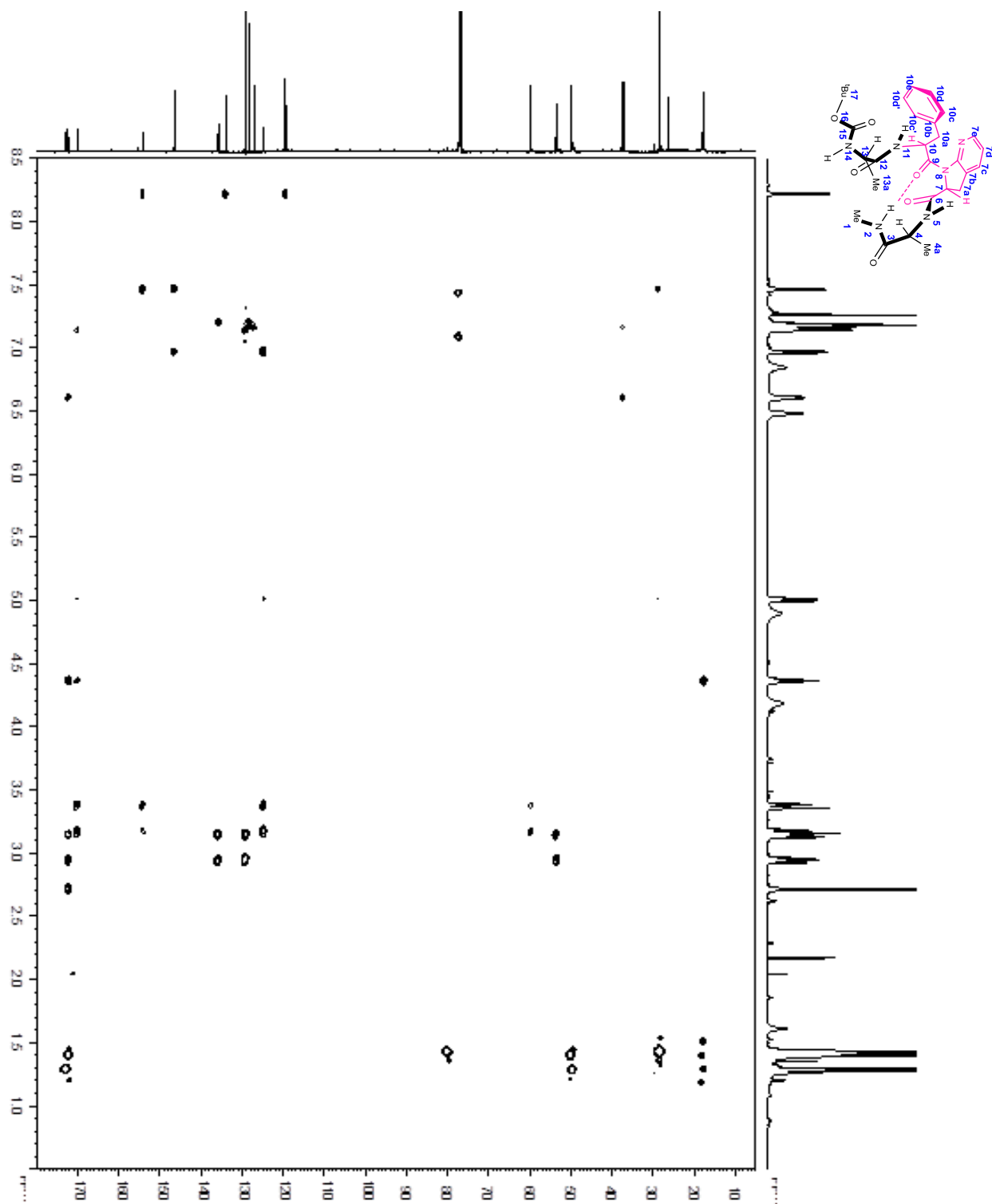


Figure 28. NOESY Spectrum (600 MHz, CDCl₃) of 33bb

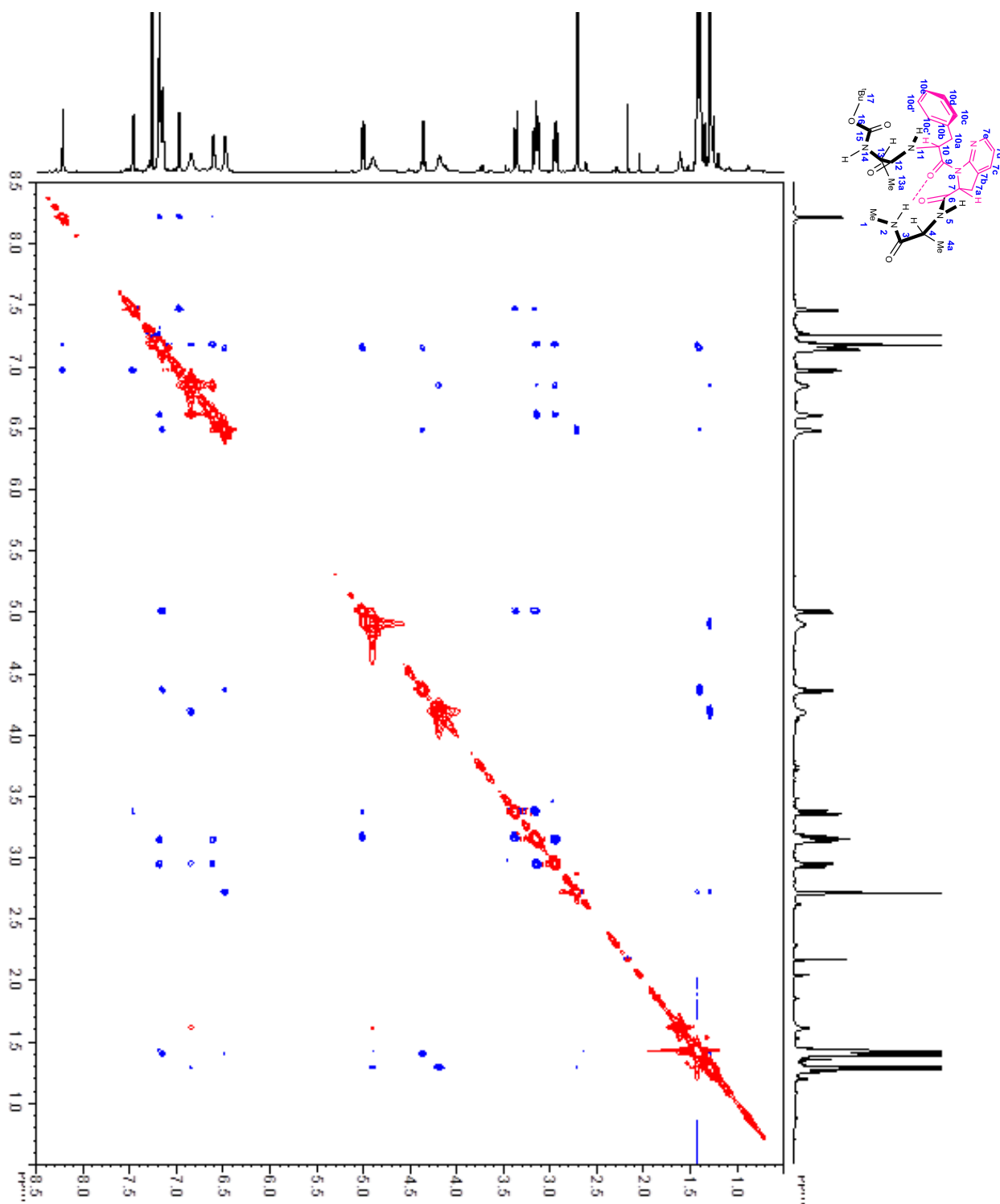


Figure 29. ^1H NMR Spectrum (600 MHz, CDCl_3) of 36ab

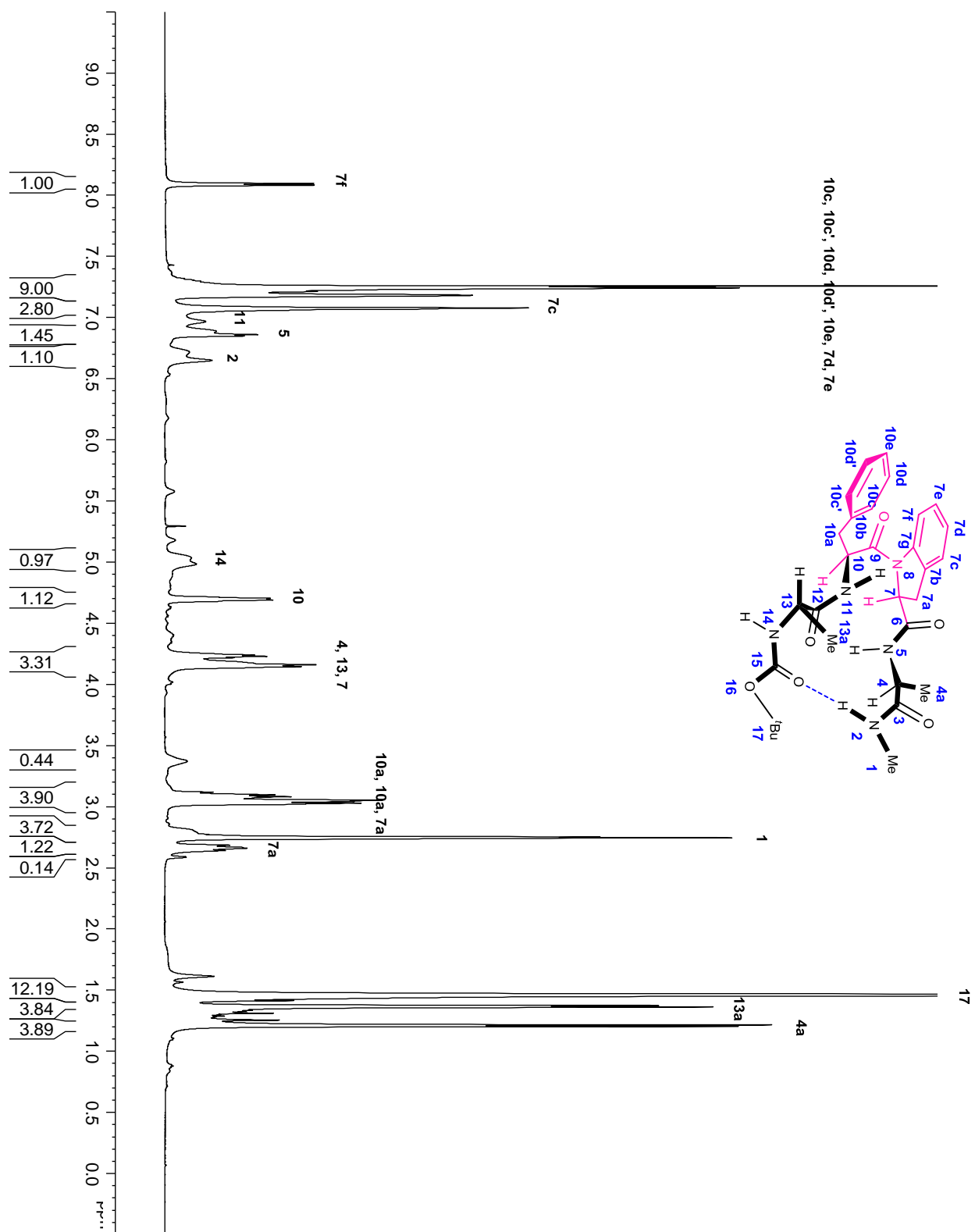


Figure 30. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 36ab

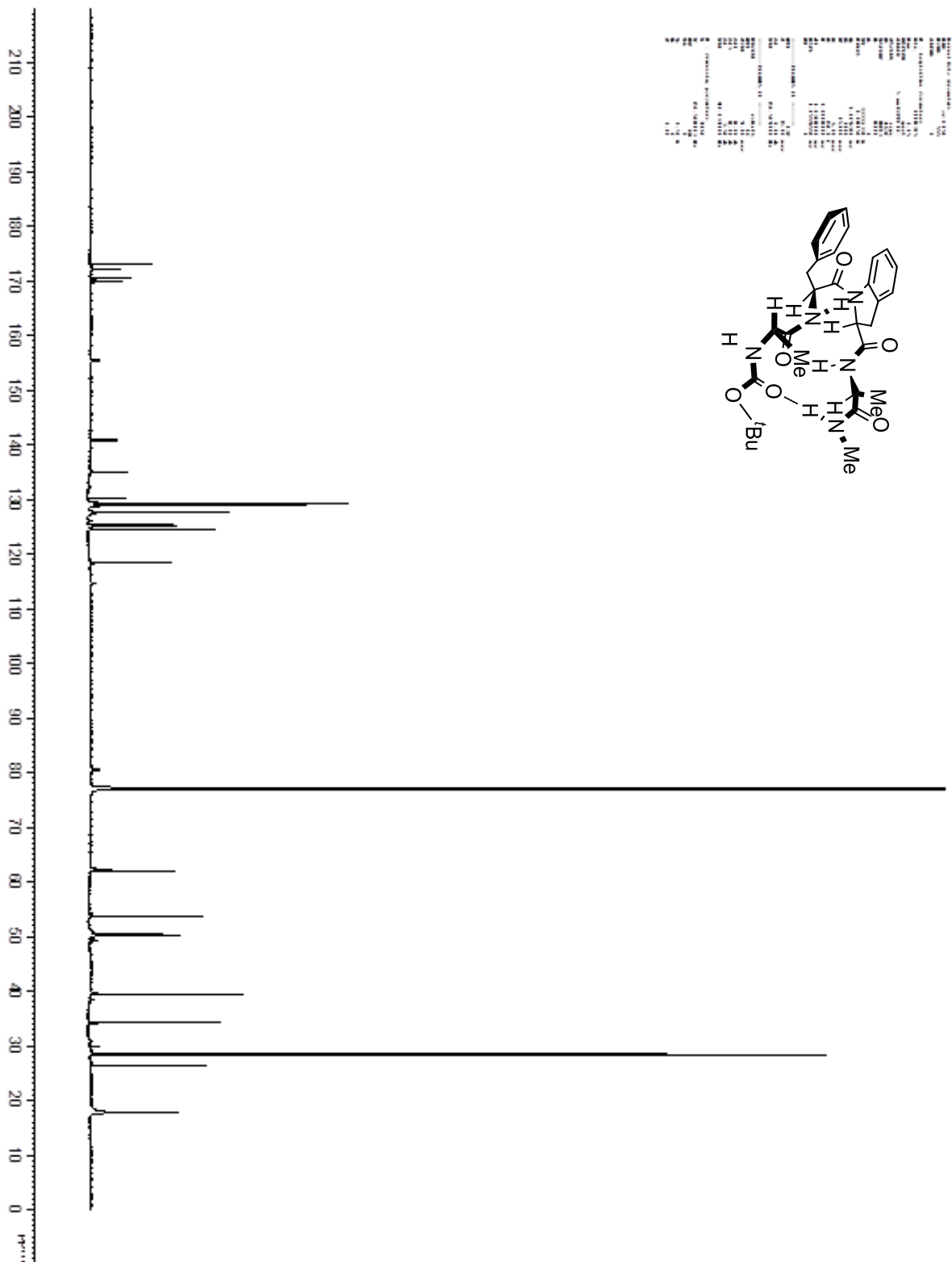


Figure 31. 135 DEPT Spectrum (150 MHz, CDCl₃) of 36ab

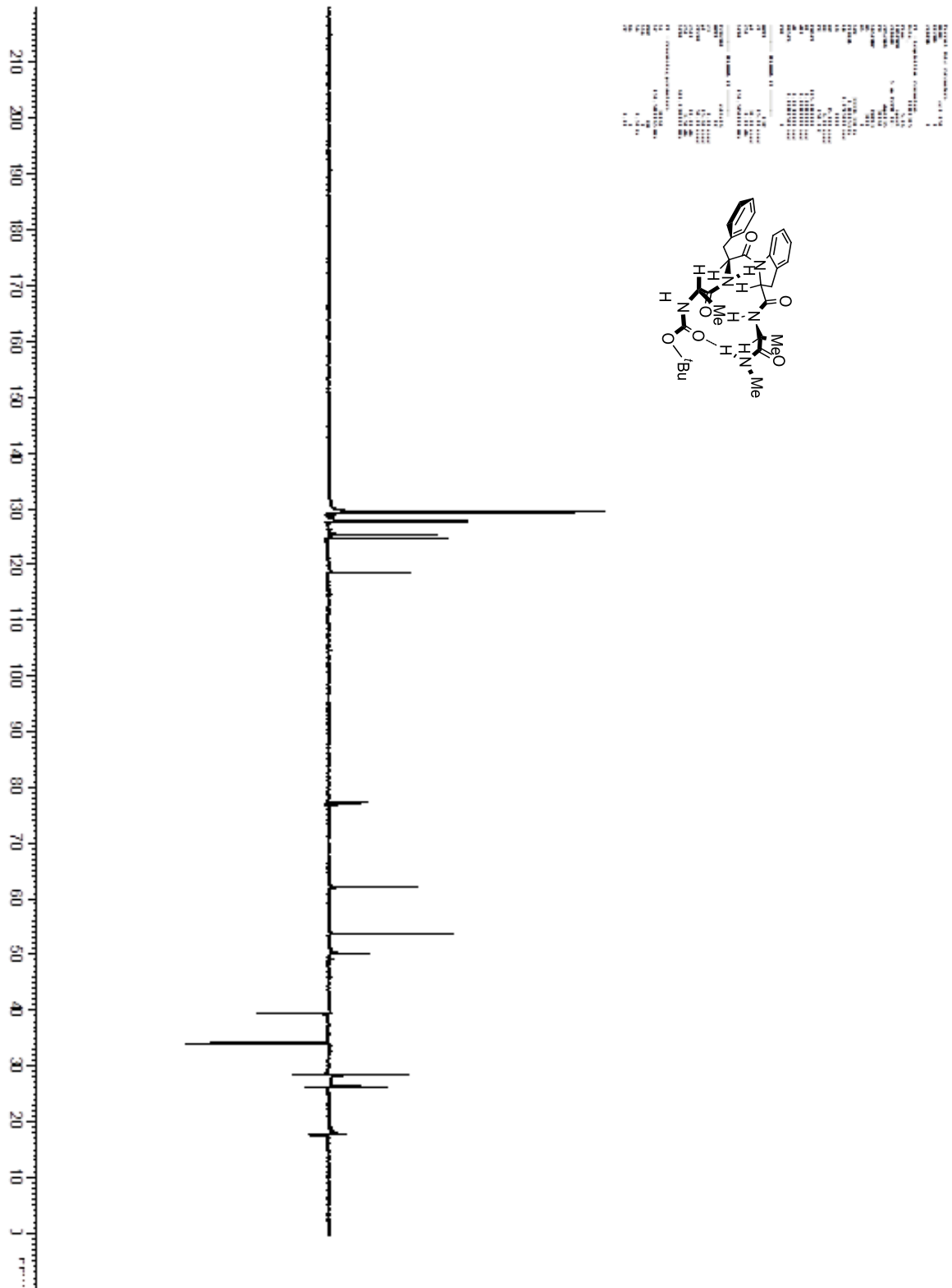


Figure 32. HSQC Spectrum (150 MHz, CDCl₃) of 36ab

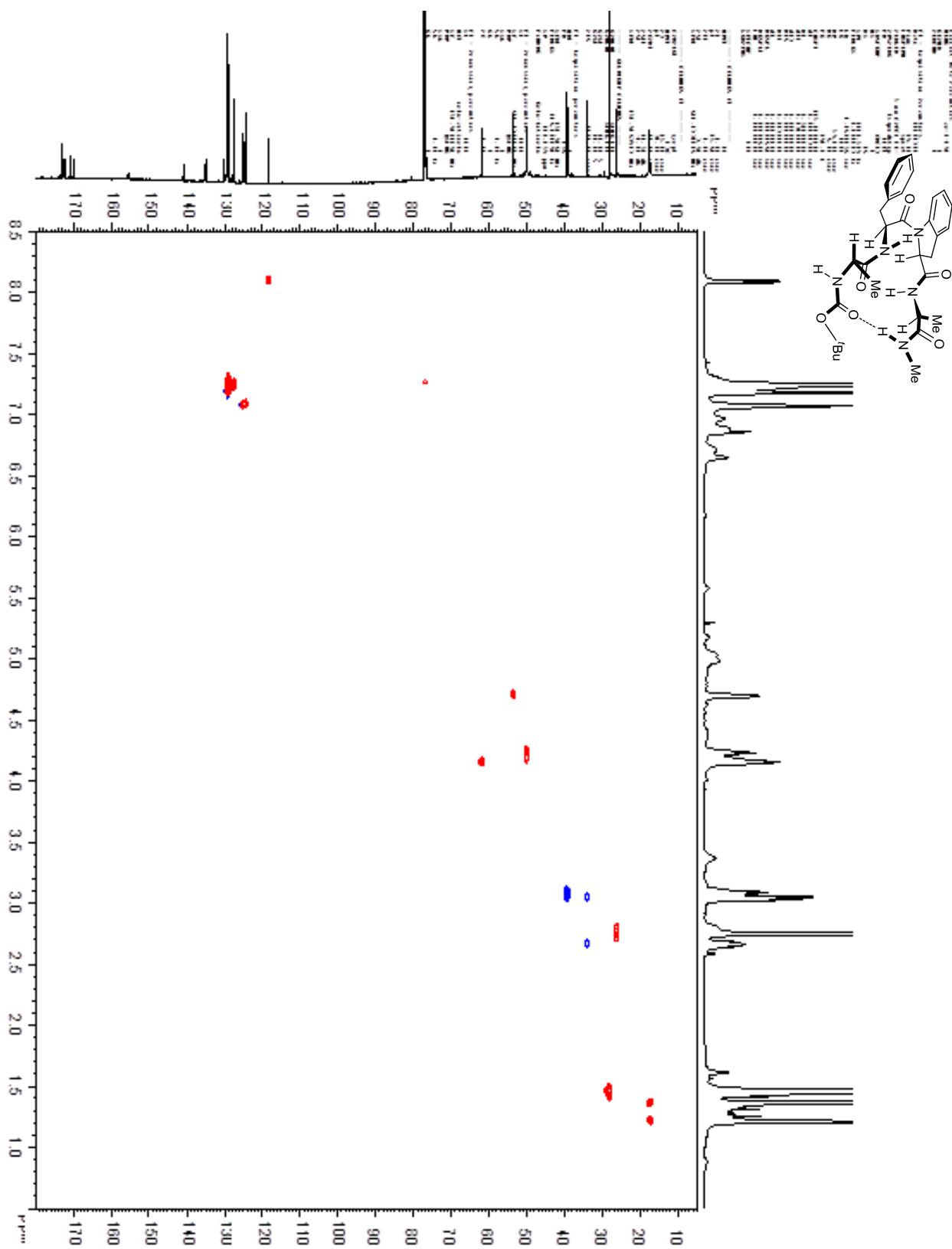


Figure 33. COSY Spectrum (150 MHz, CDCl₃) of 36ab

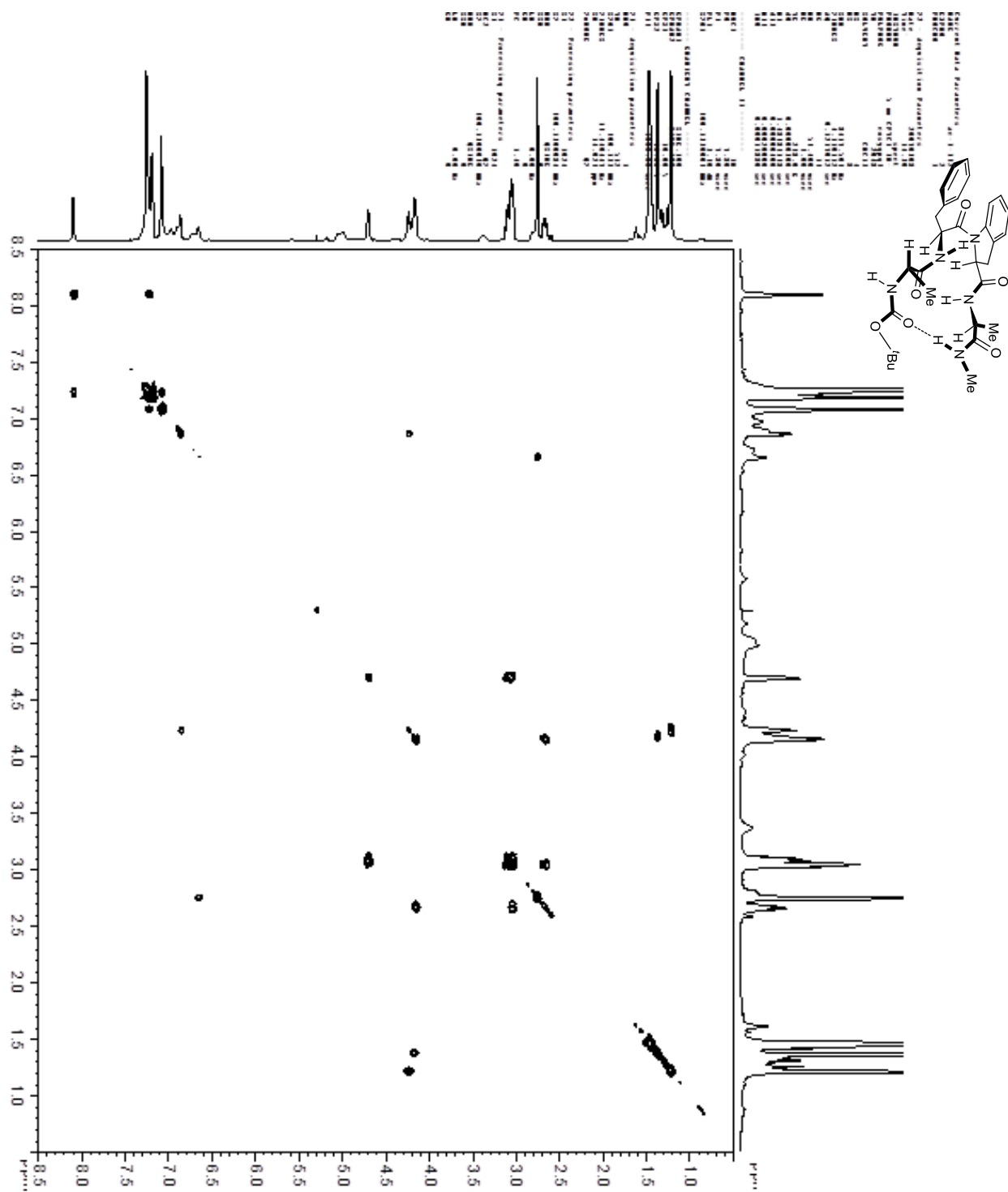


Figure 34. HMBC Spectrum (150 MHz, CDCl₃) of 36ab

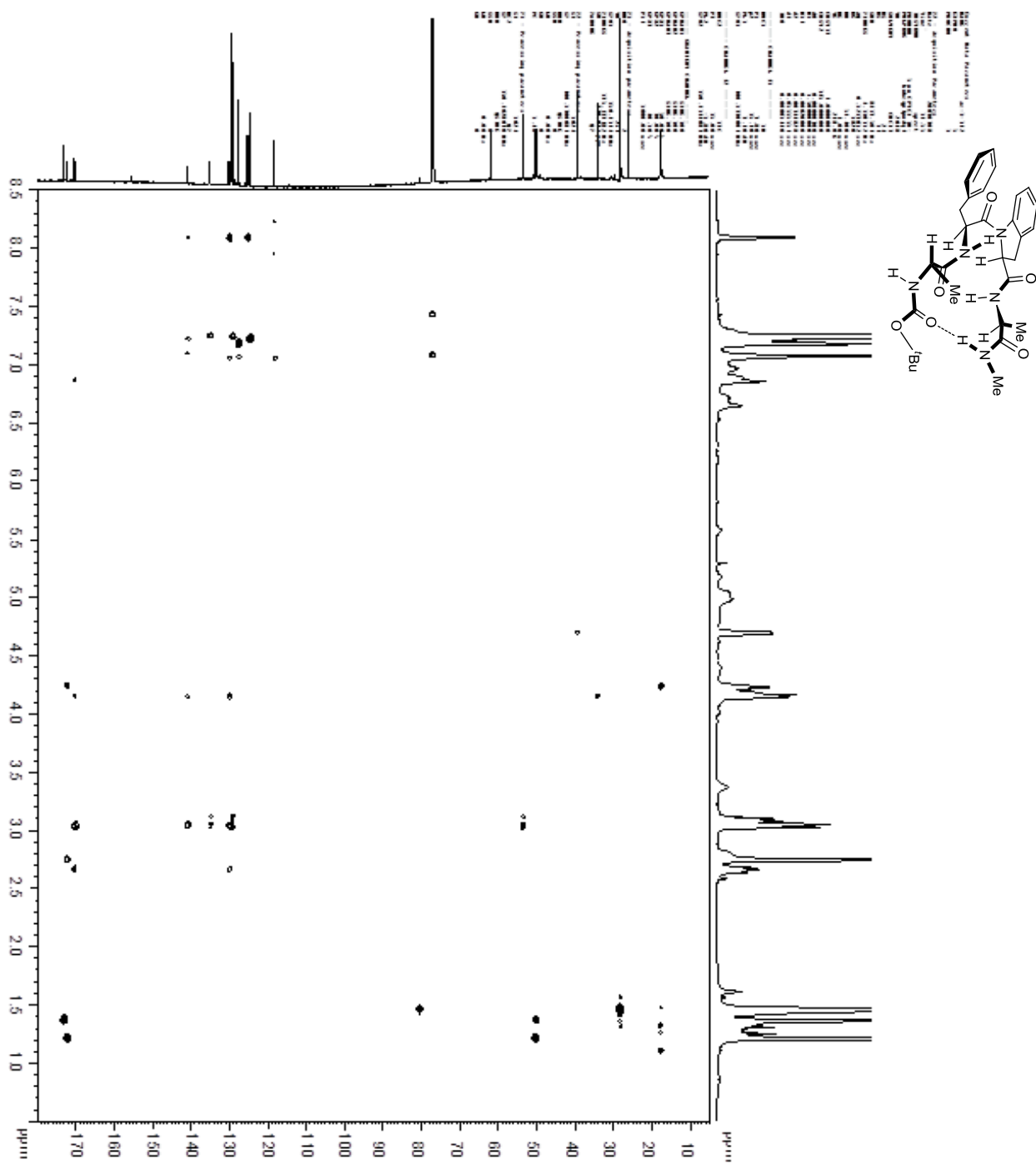


Figure 35. NOESY Spectrum (600 MHz, CDCl₃) of 36ab

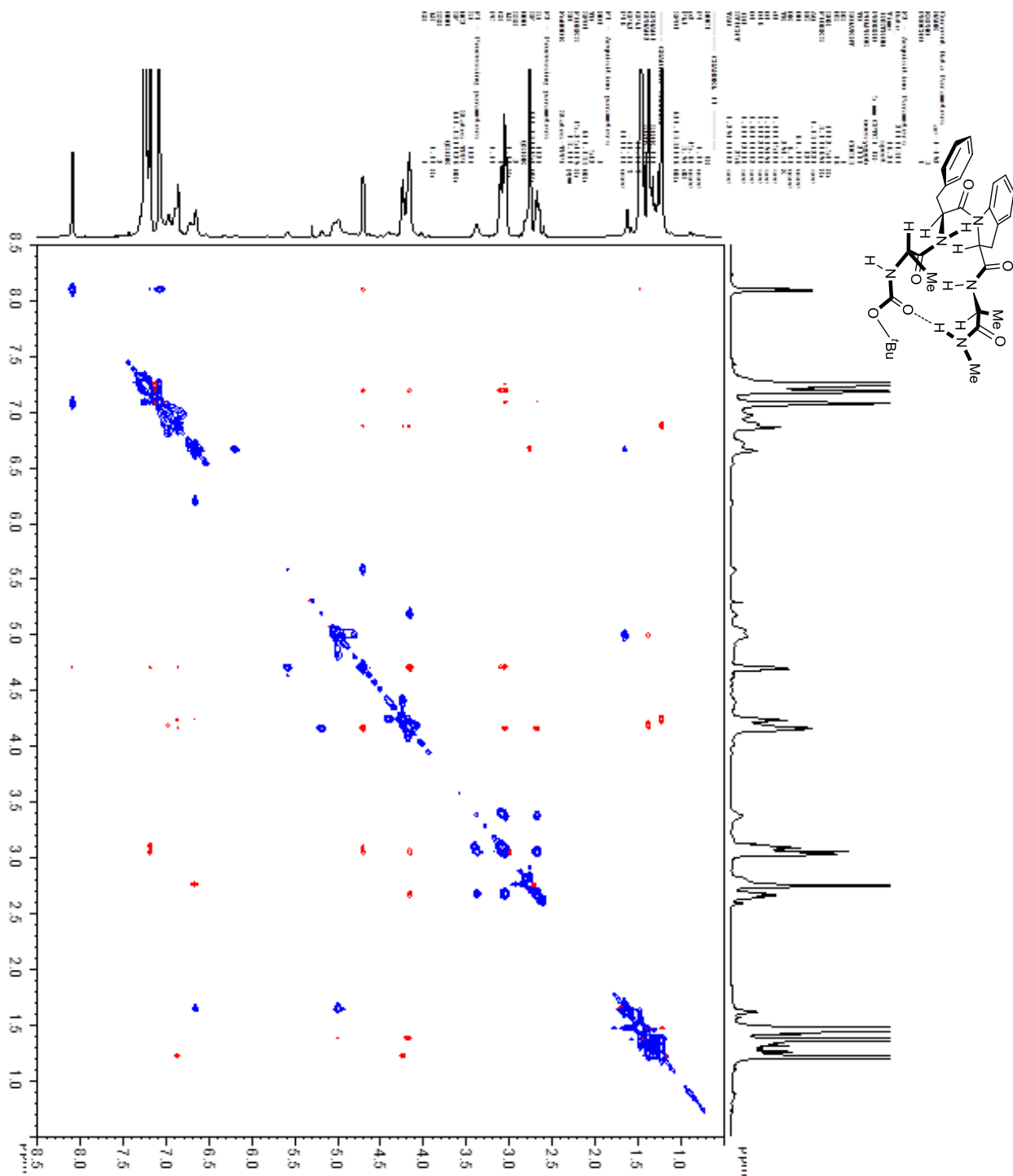


Figure 36. ^1H NMR Spectrum (400 MHz, CD_3OD) of Serratezomine A (37)

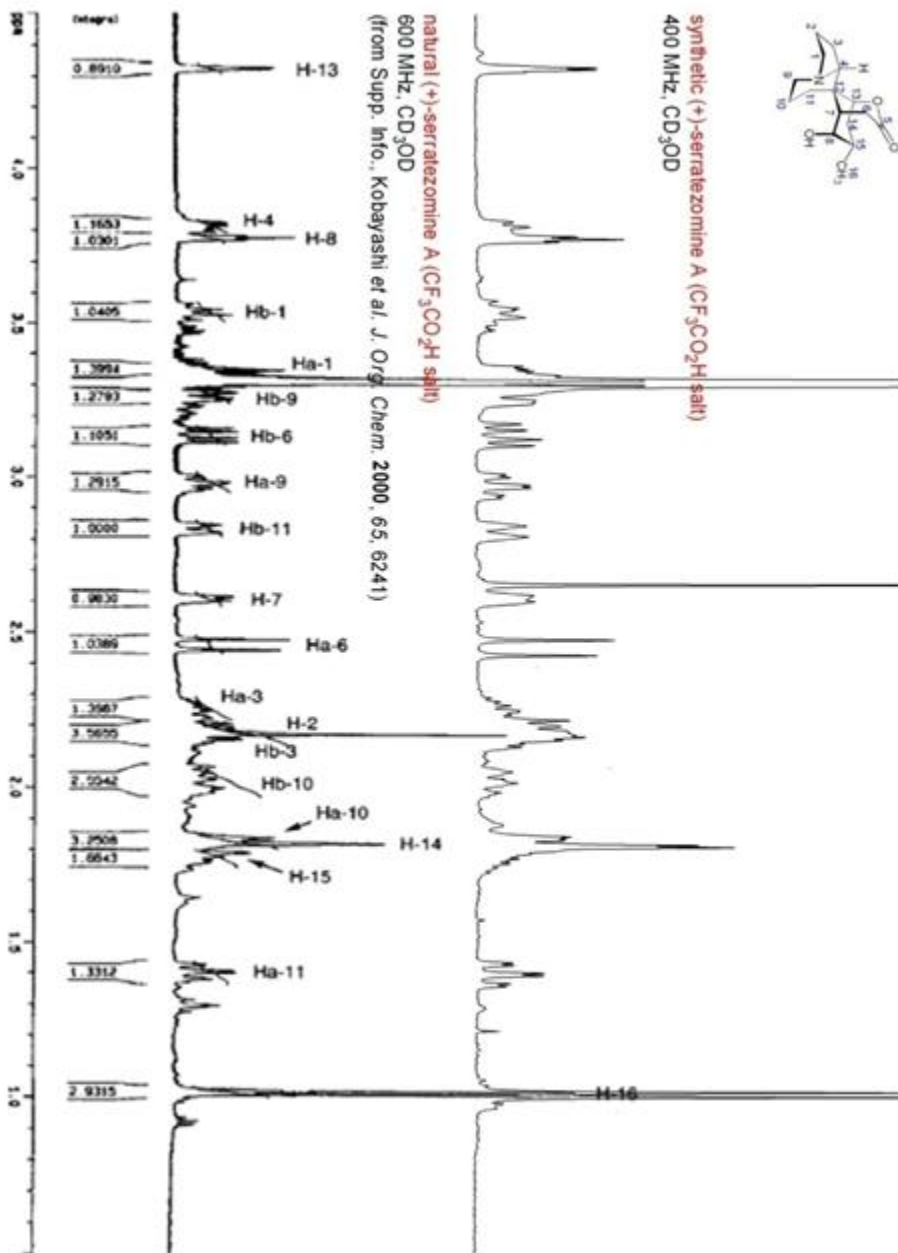


Figure 37. ^{13}C NMR Spectrum (125 MHz, CD_3OD) of Serratezomine A (37)

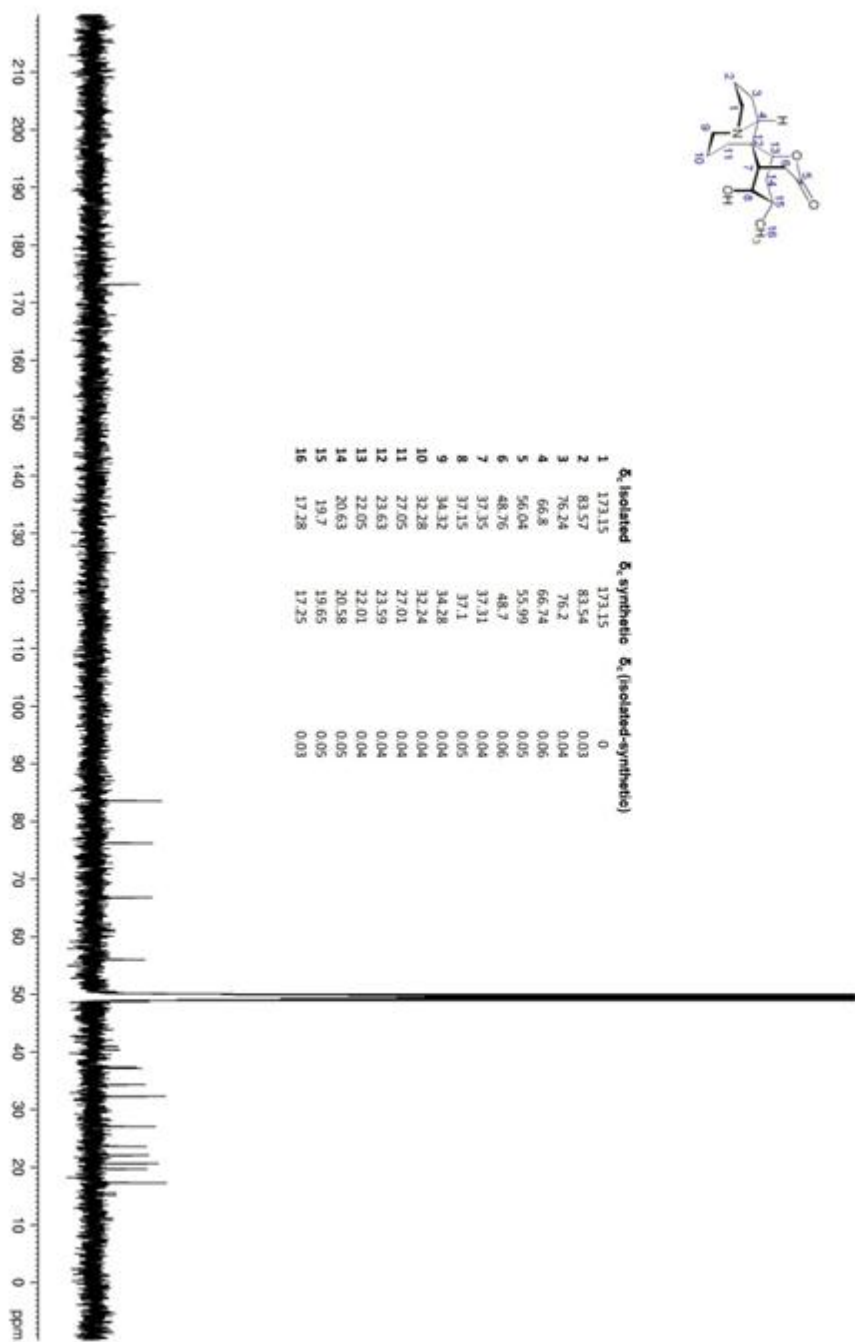


Figure 38. ^1H NMR Spectrum (600 MHz, CDCl_3) of 277

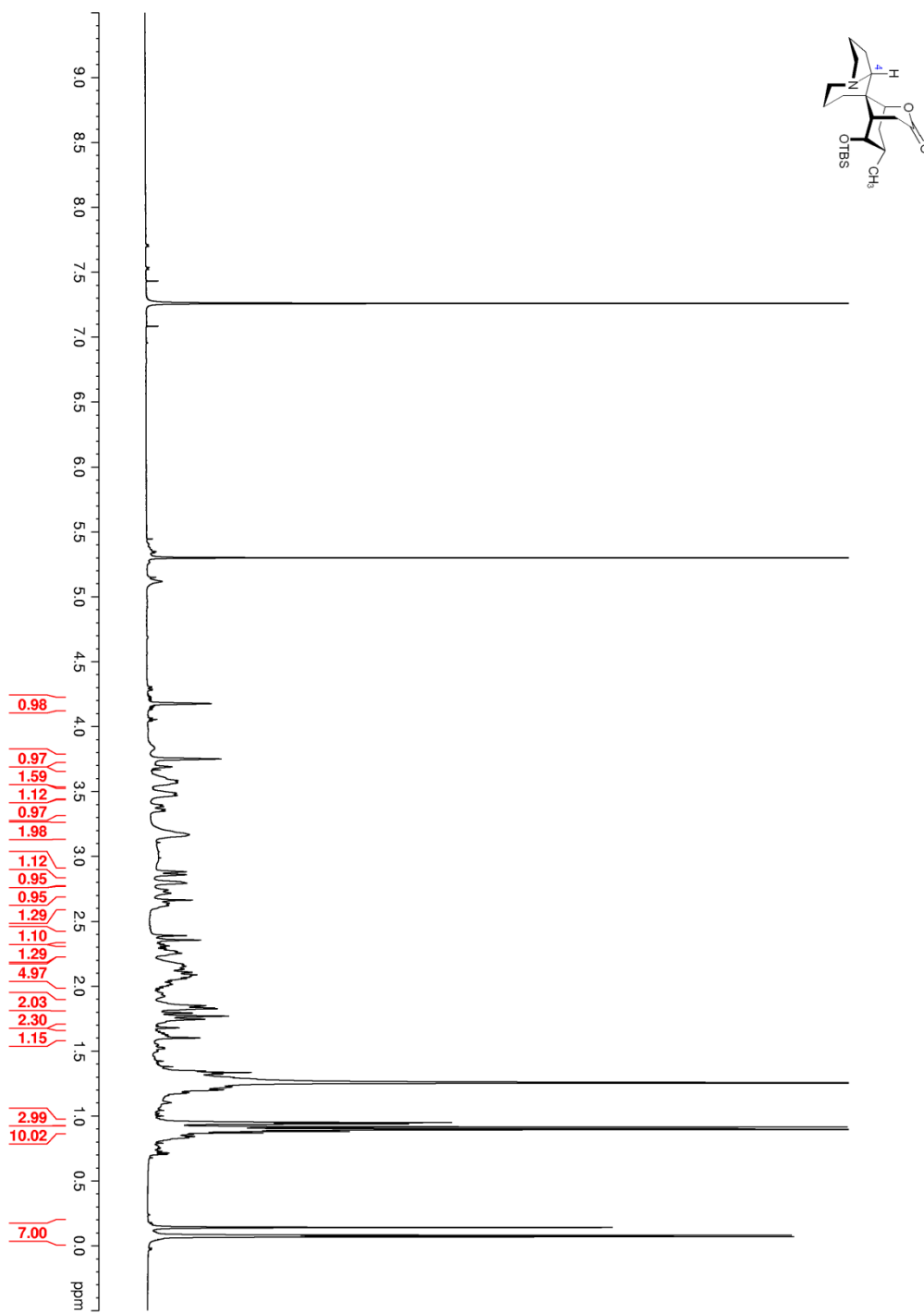


Figure 39. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 277

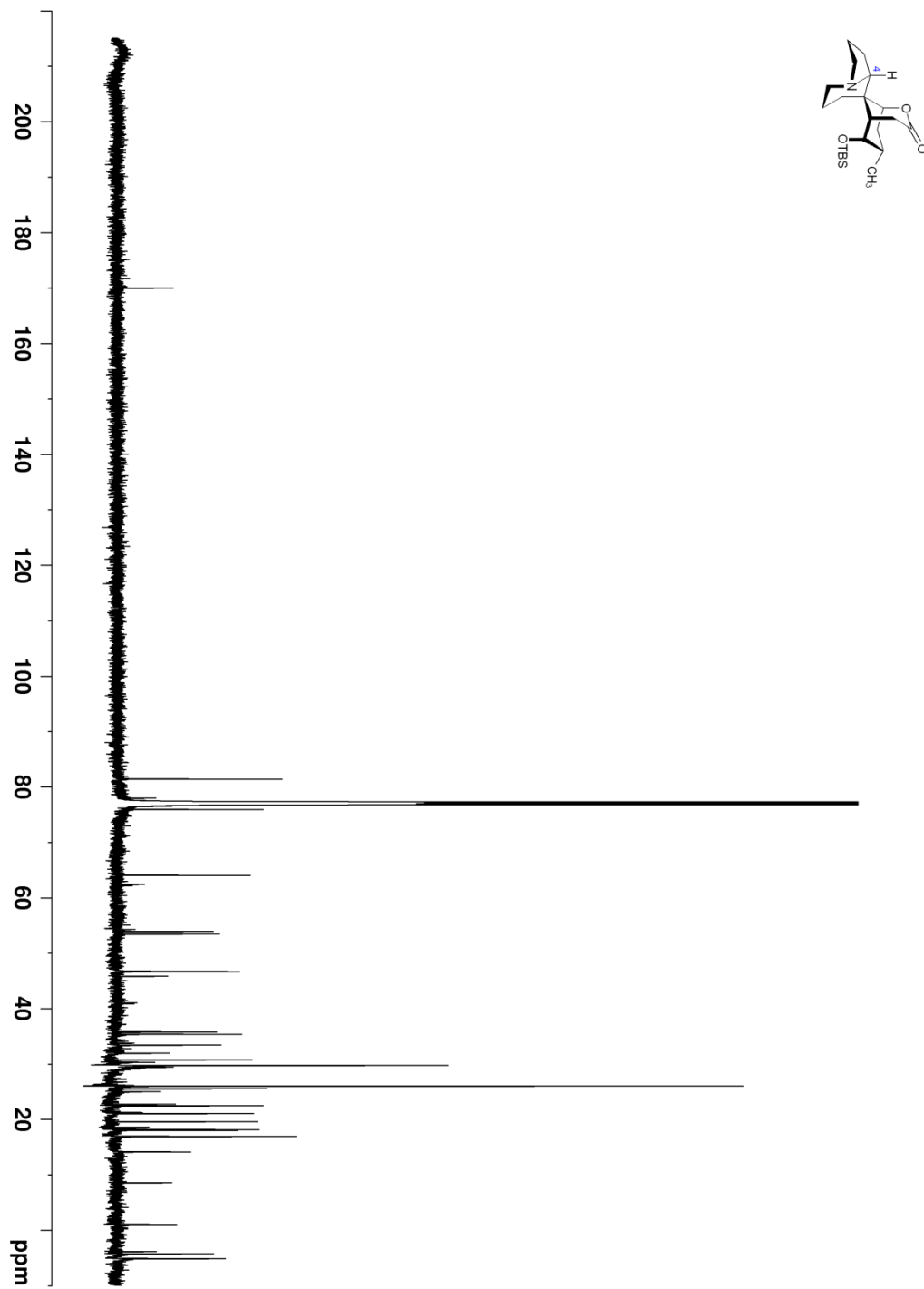


Figure 40. ^1H NMR Spectrum (600 MHz, CDCl_3) of 251

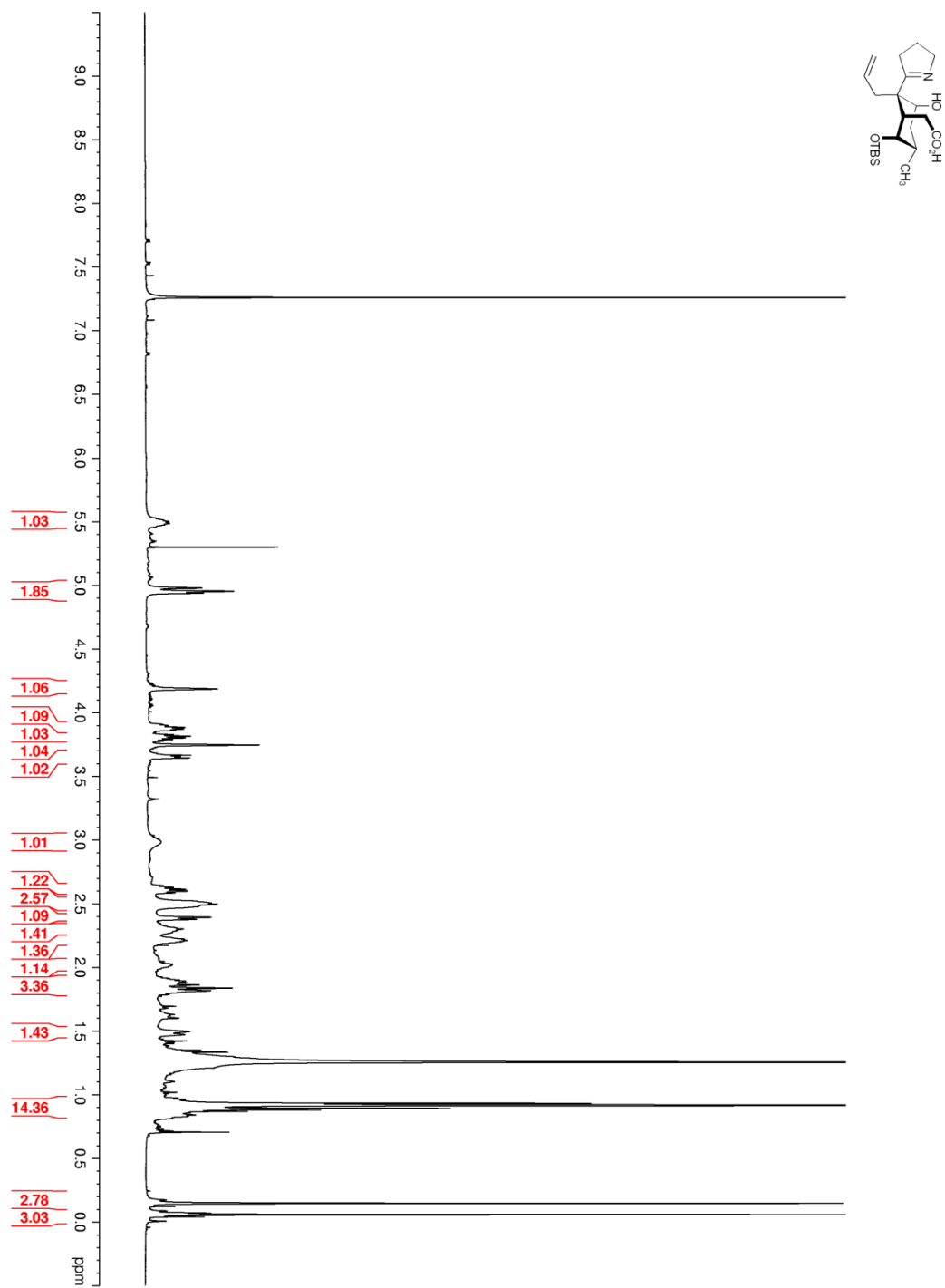


Figure 41. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 251

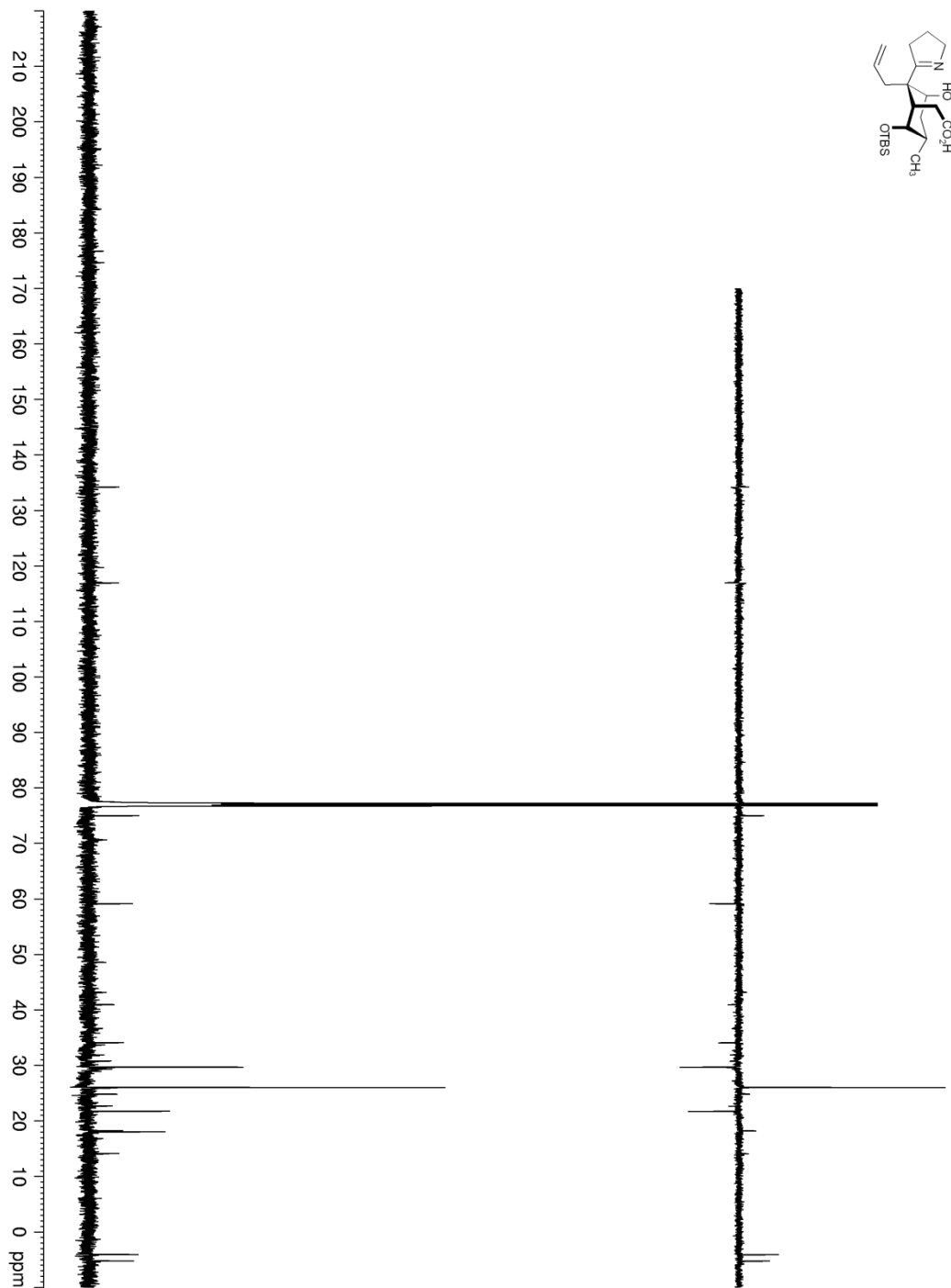


Figure 42. ^1H NMR Spectrum (500 MHz, CDCl_3) of 263

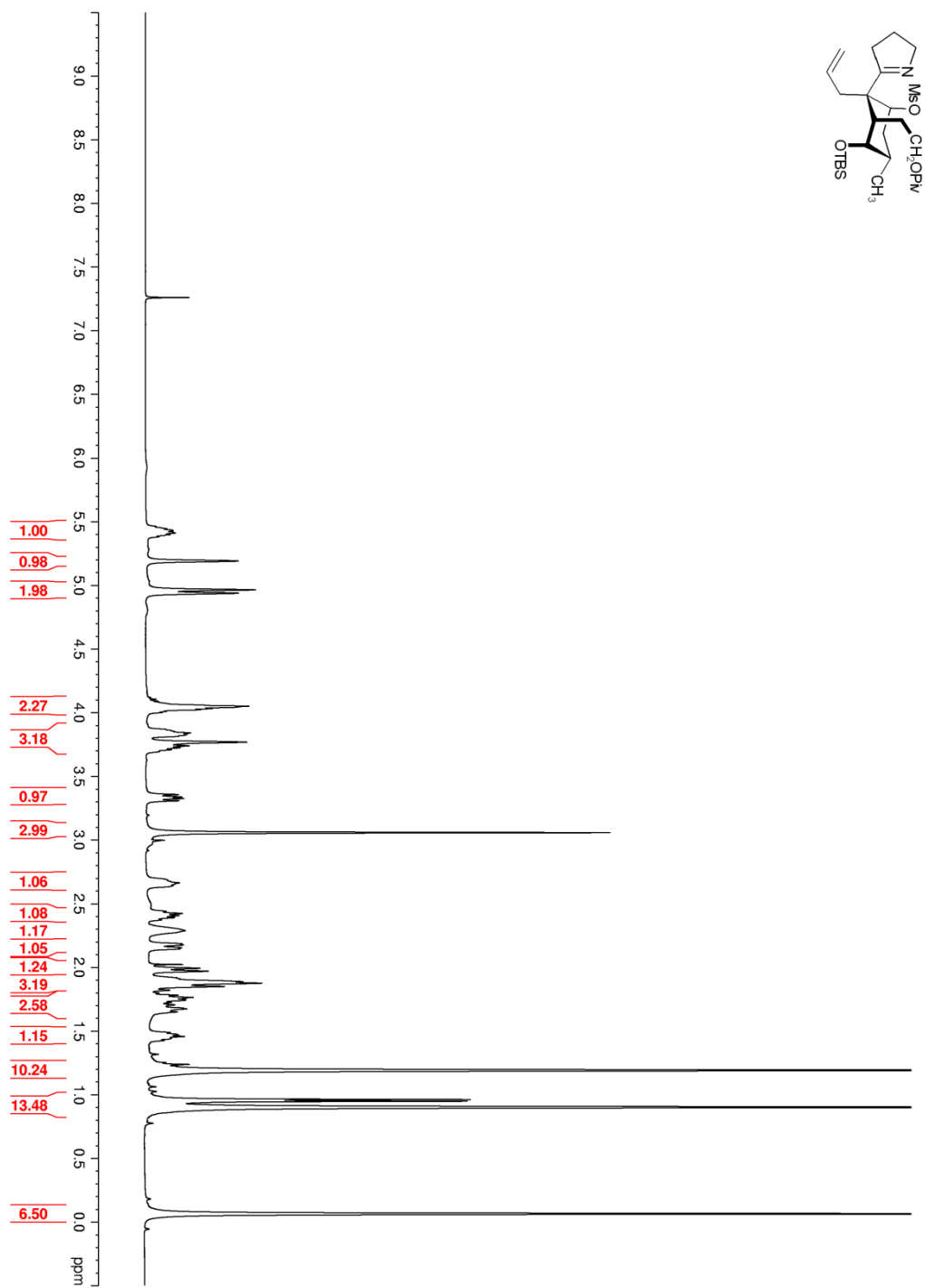


Figure 43. ^{13}C NMR Spectrum (125 MHz, CDCl_3) of 263

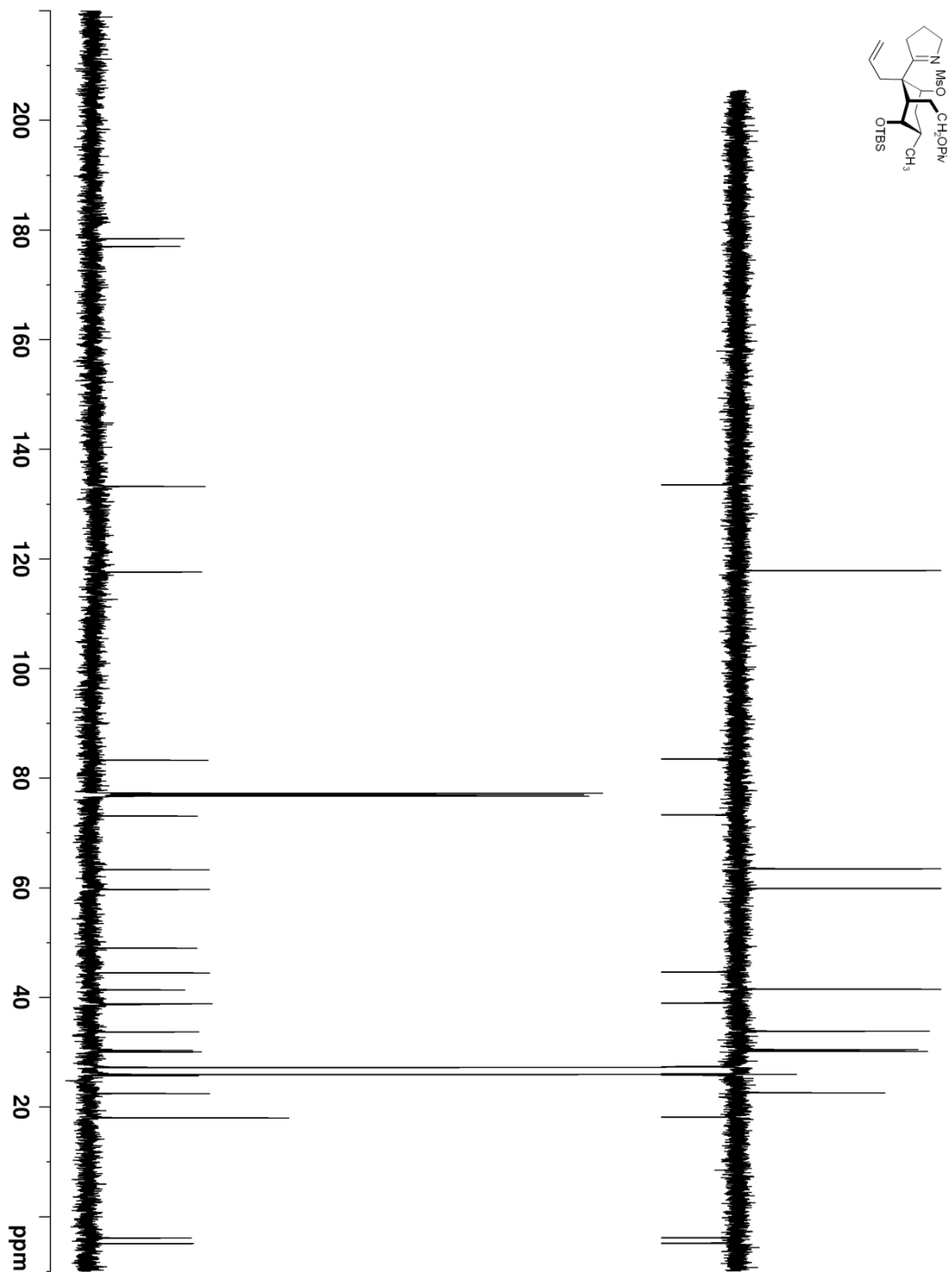


Figure 44. ^1H NMR Spectrum (600 MHz, CDCl_3) of 264

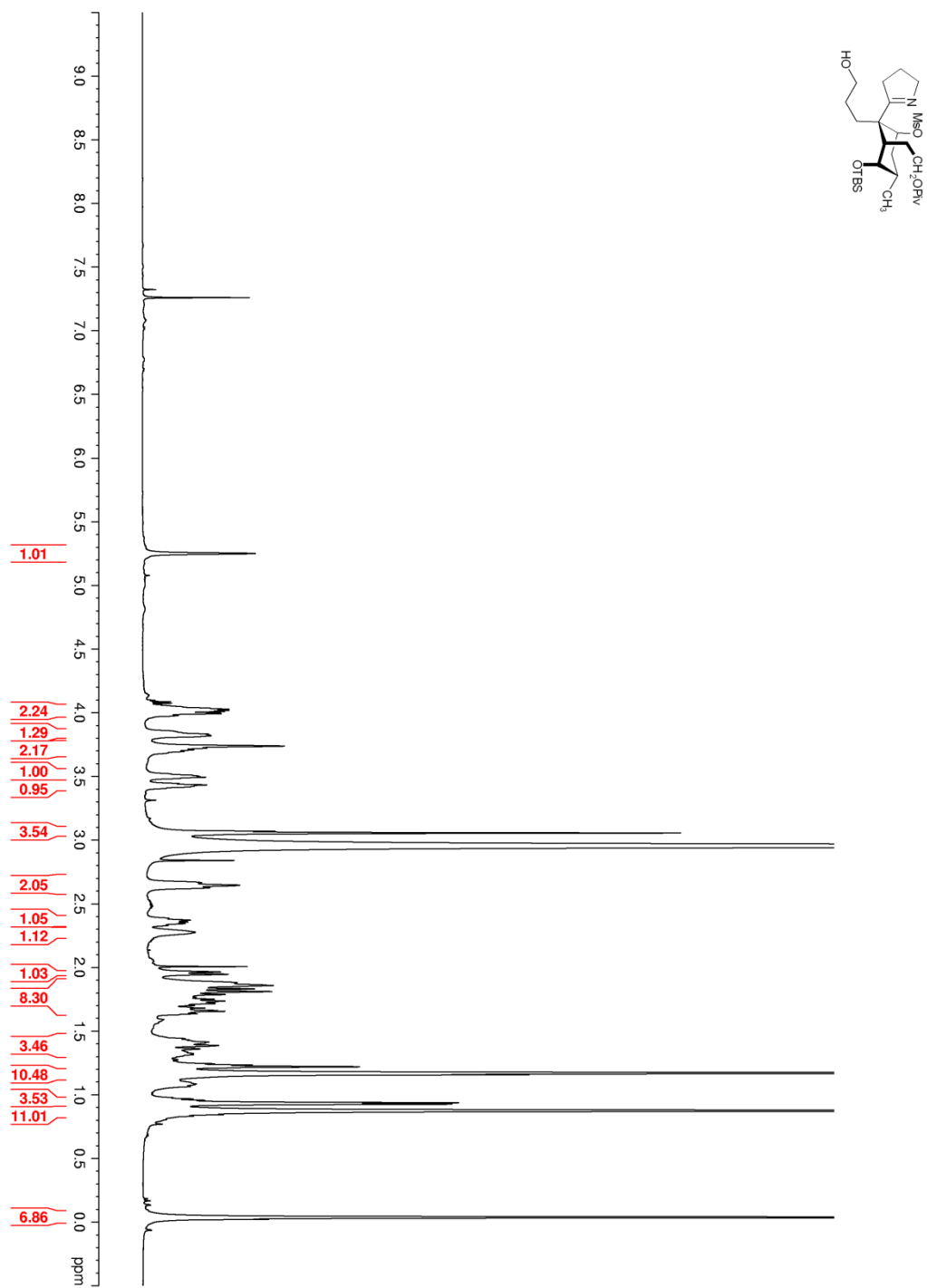


Figure 45. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 264

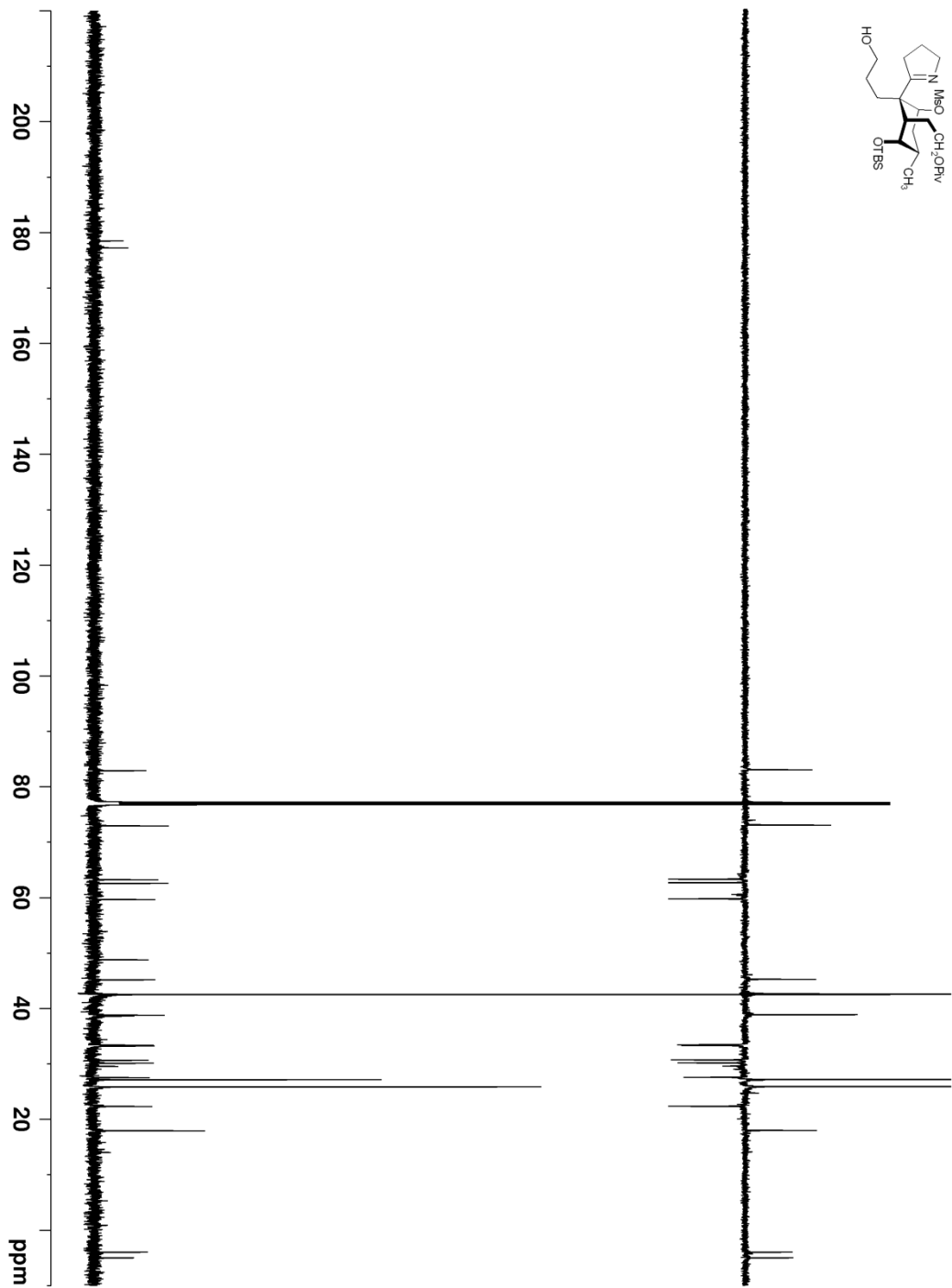


Figure 46. ^1H NMR Spectrum (600 MHz, CDCl_3) of 266

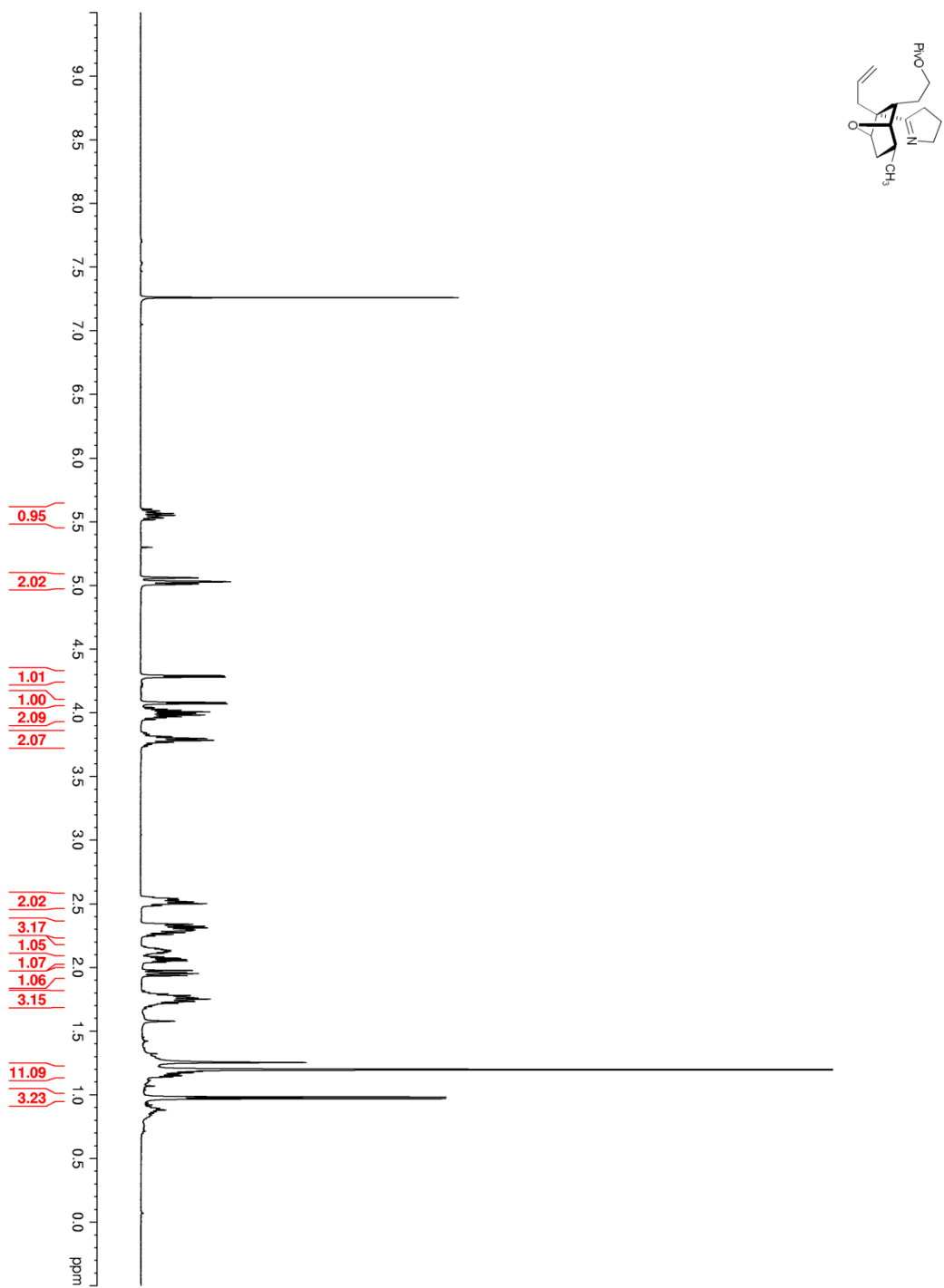


Figure 47. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 266

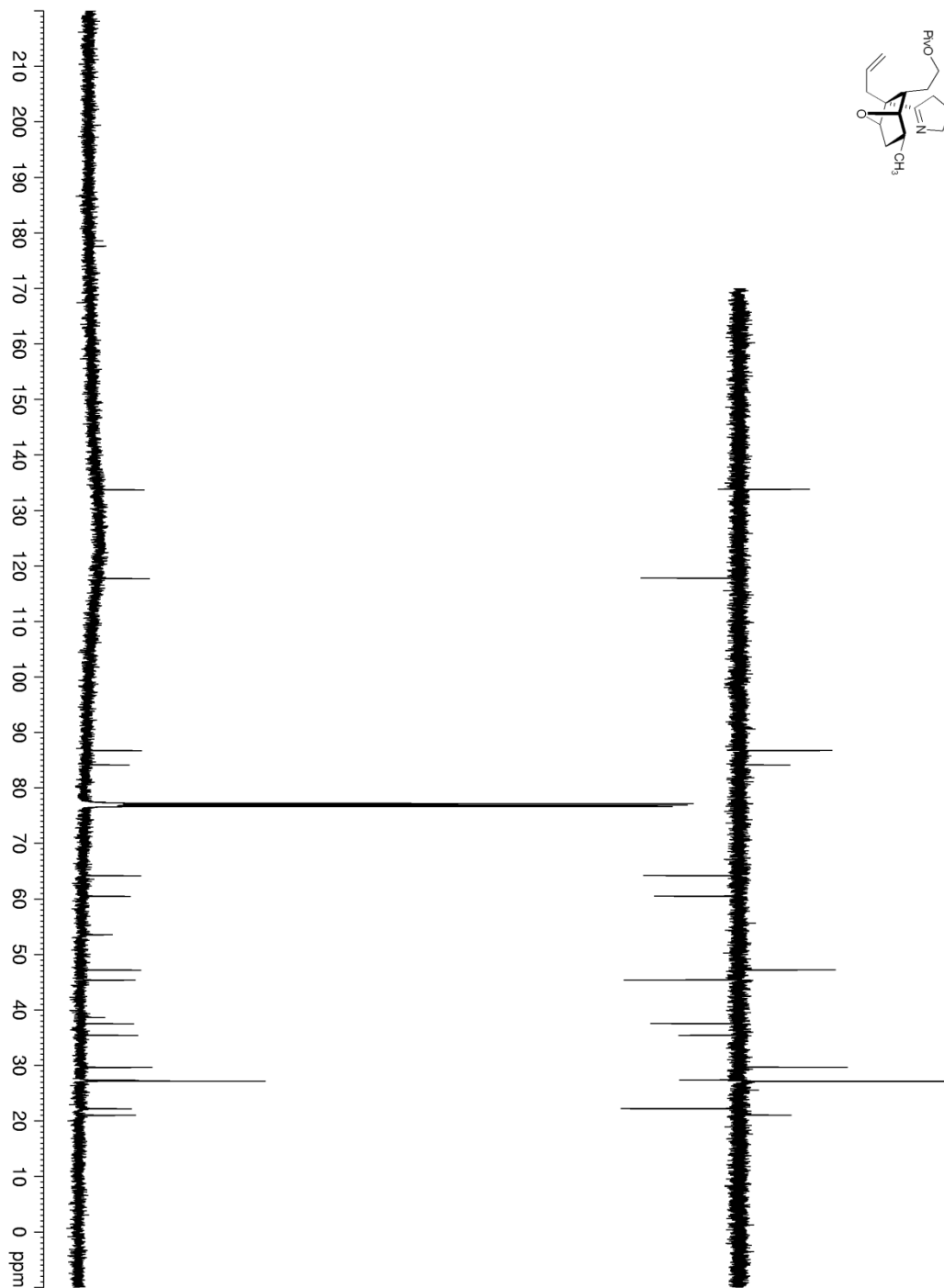


Figure 48. HSQC Spectrum (150 MHz, CDCl₃) of 266

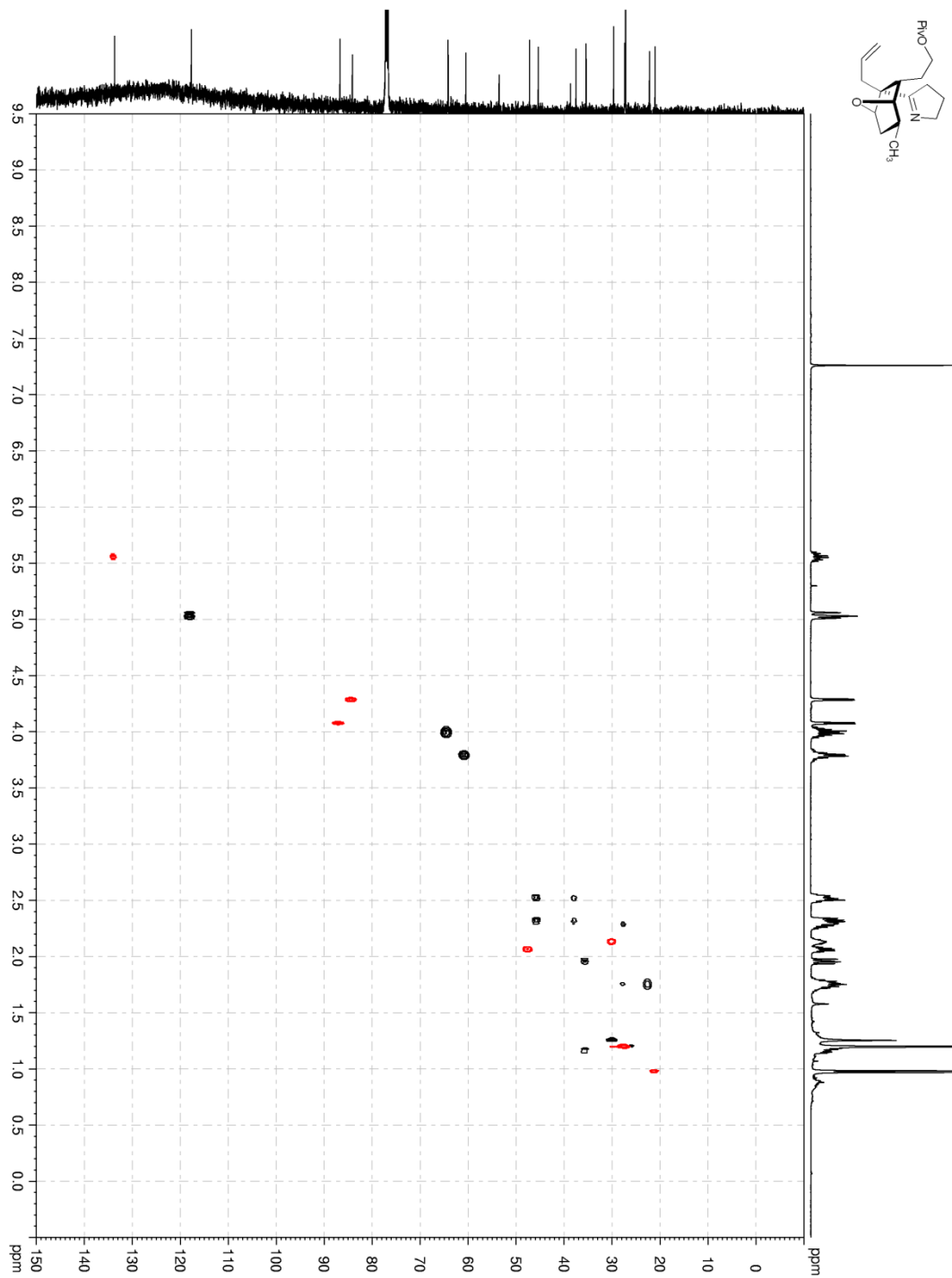


Figure 49. COSY Spectrum (600 MHz, CDCl₃) of 266

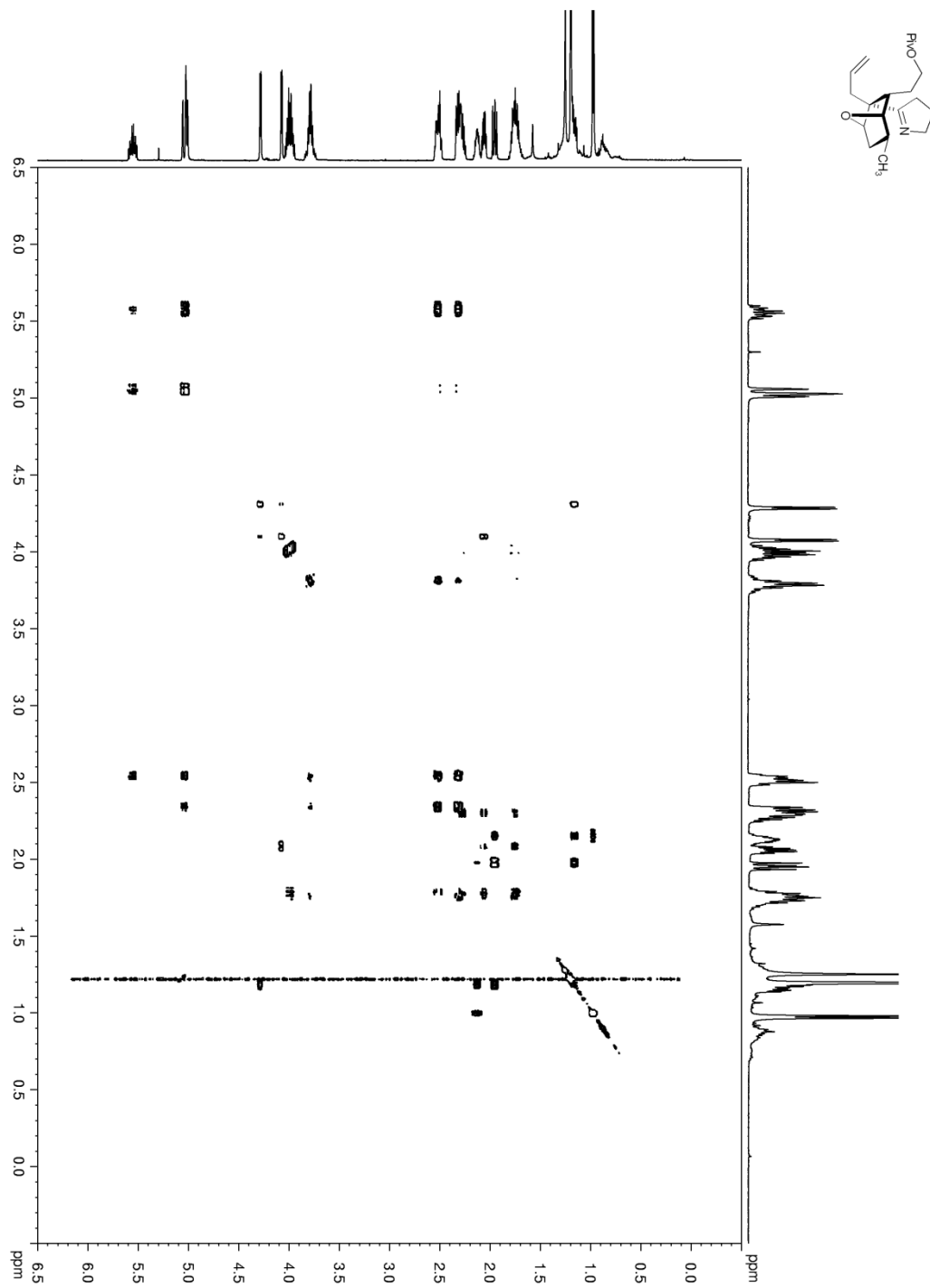


Figure 50. NOESY Spectrum (600 MHz, CDCl₃) of 266

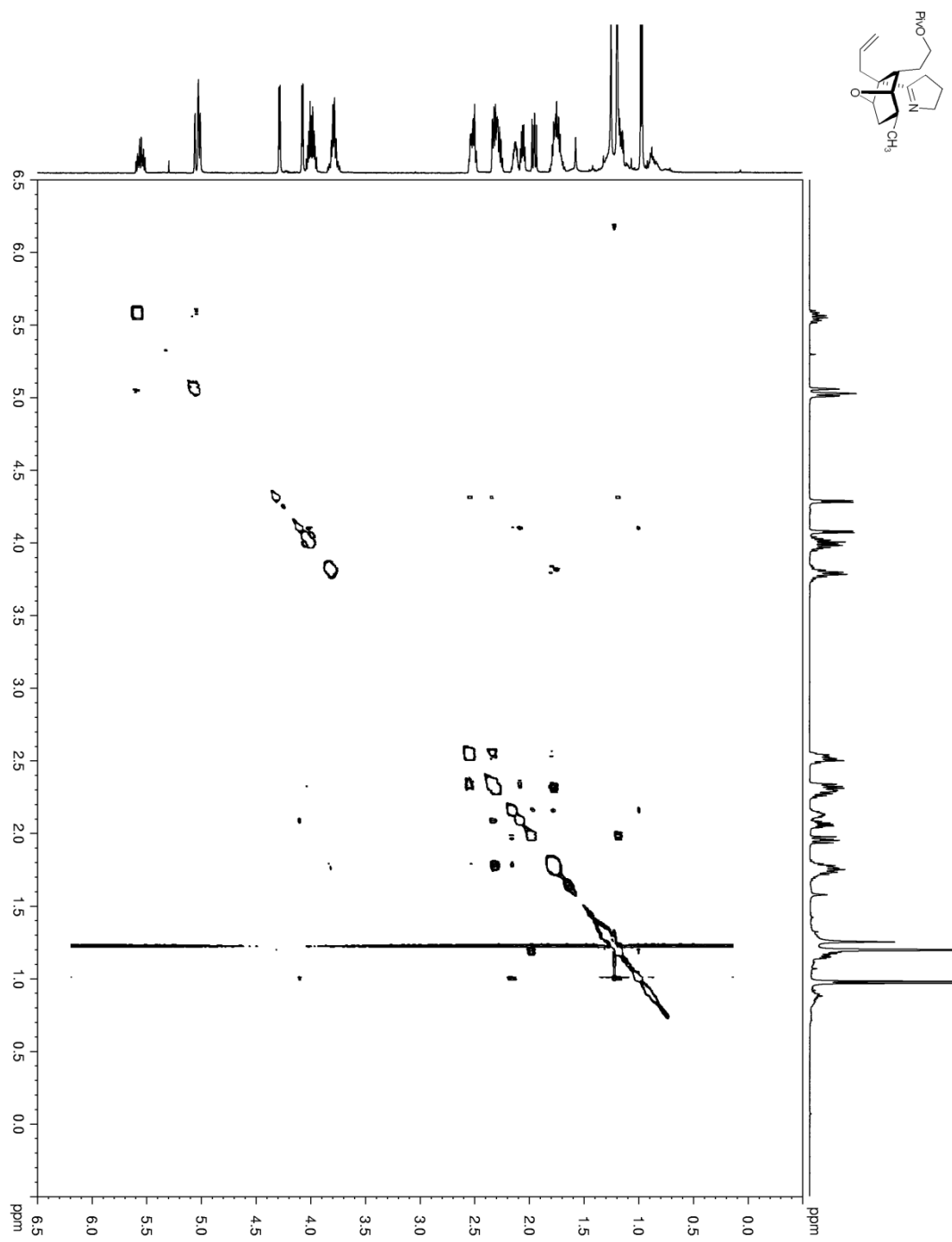


Figure 51. ^1H NMR Spectrum (500 MHz, CDCl_3) of 269

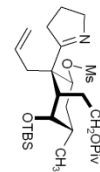
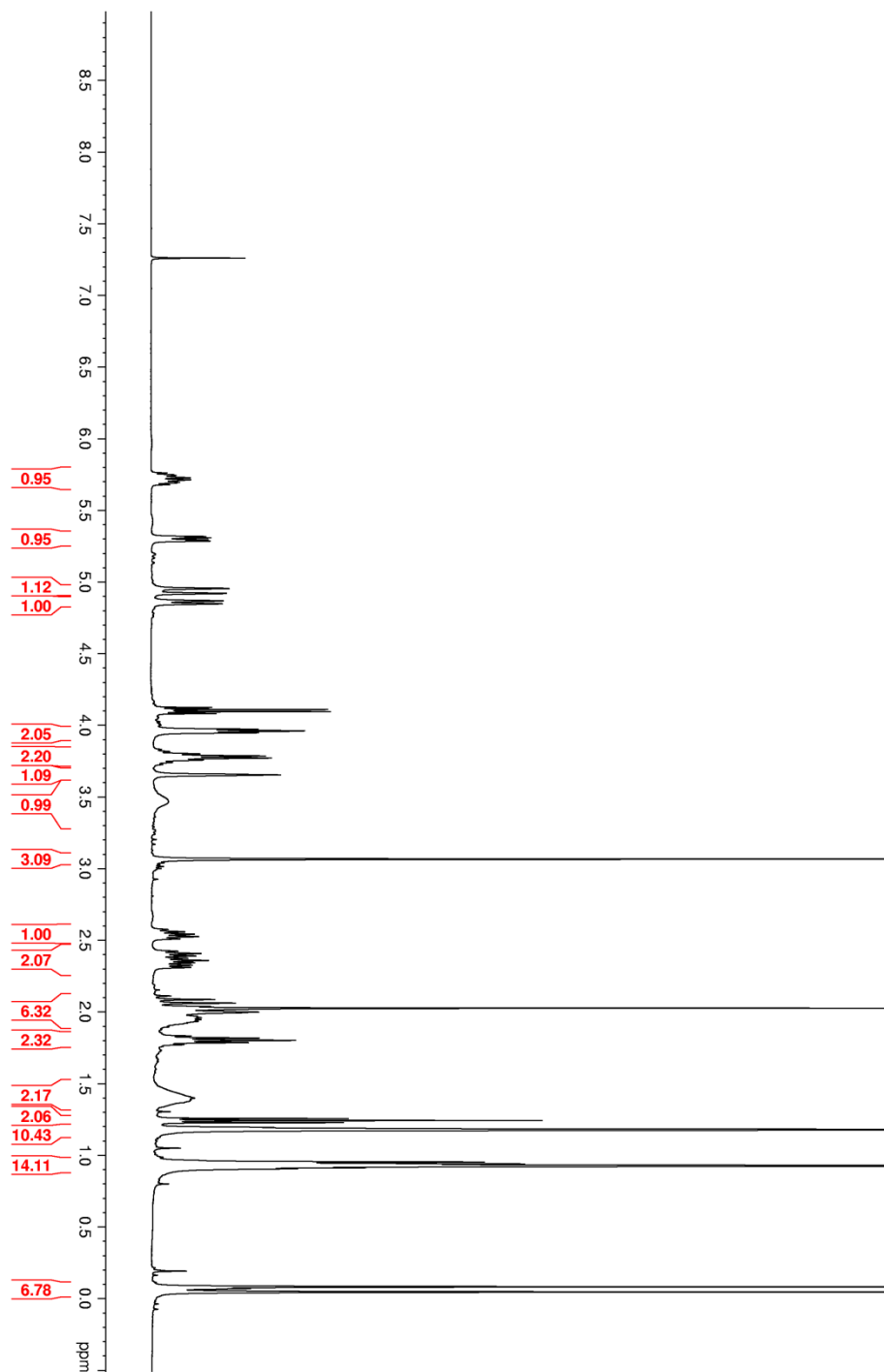


Figure 52. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 269

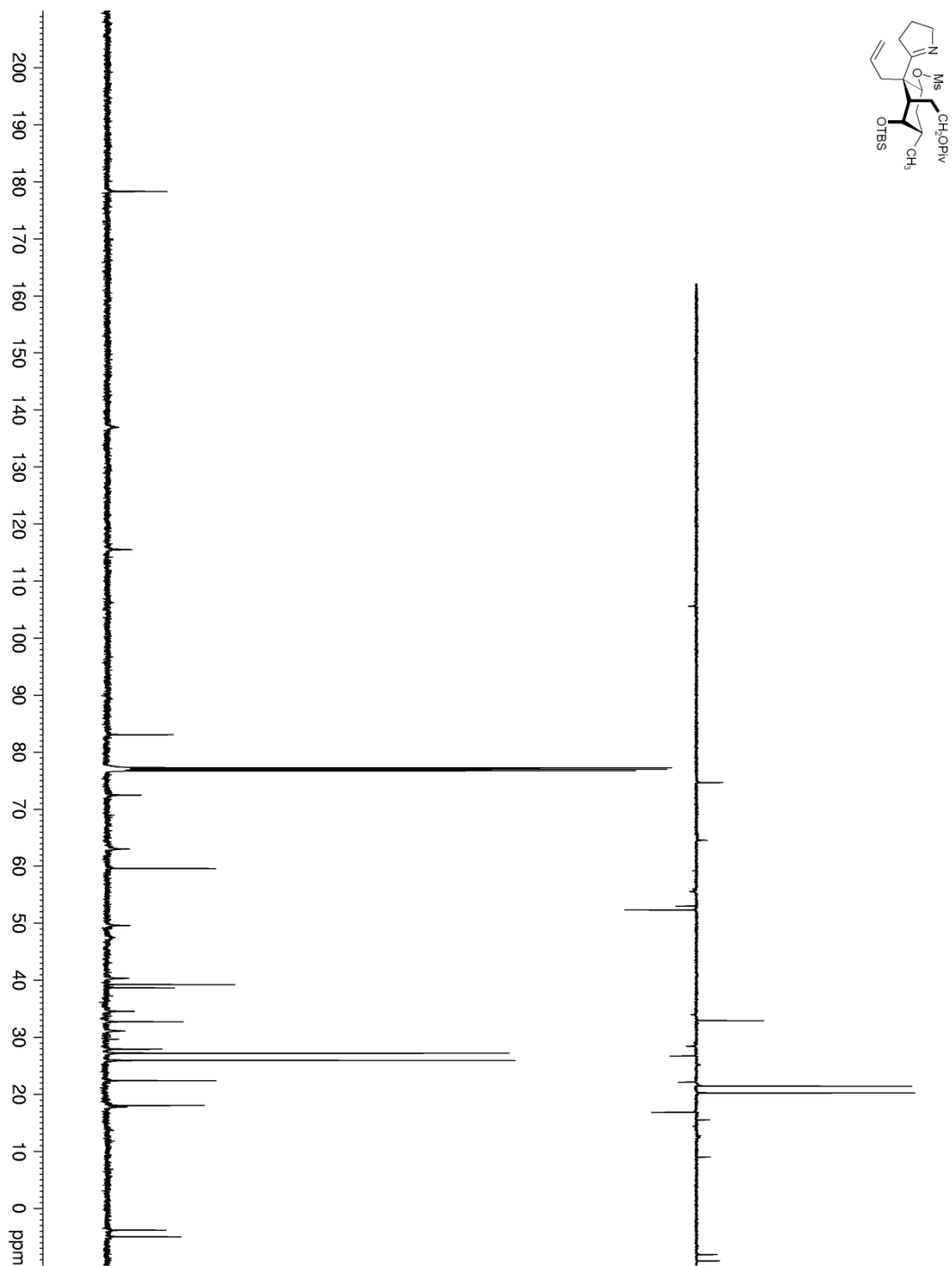


Figure 53. ^1H NMR Spectrum (600 MHz, CDCl_3) of 270

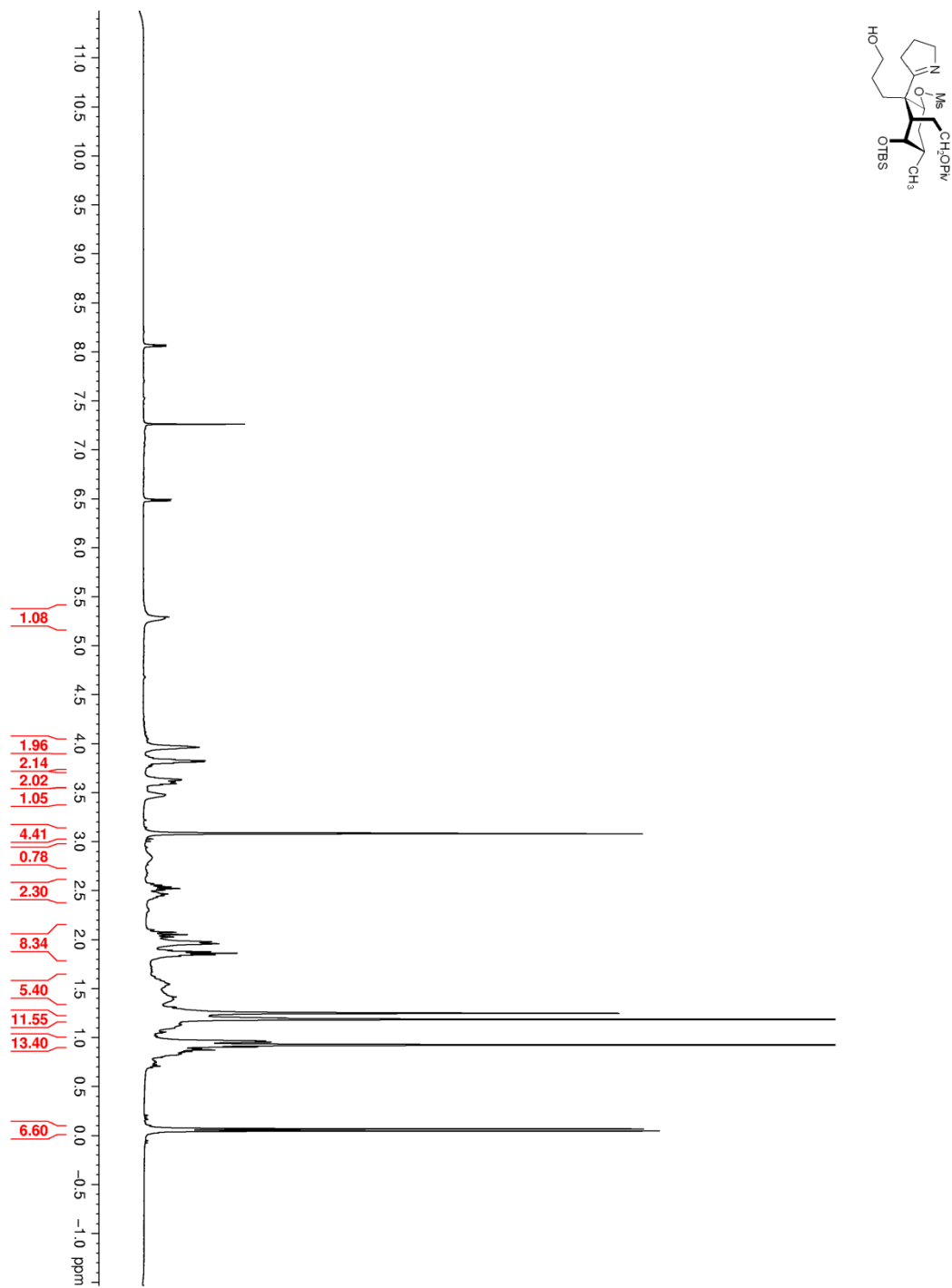


Figure 54. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 270

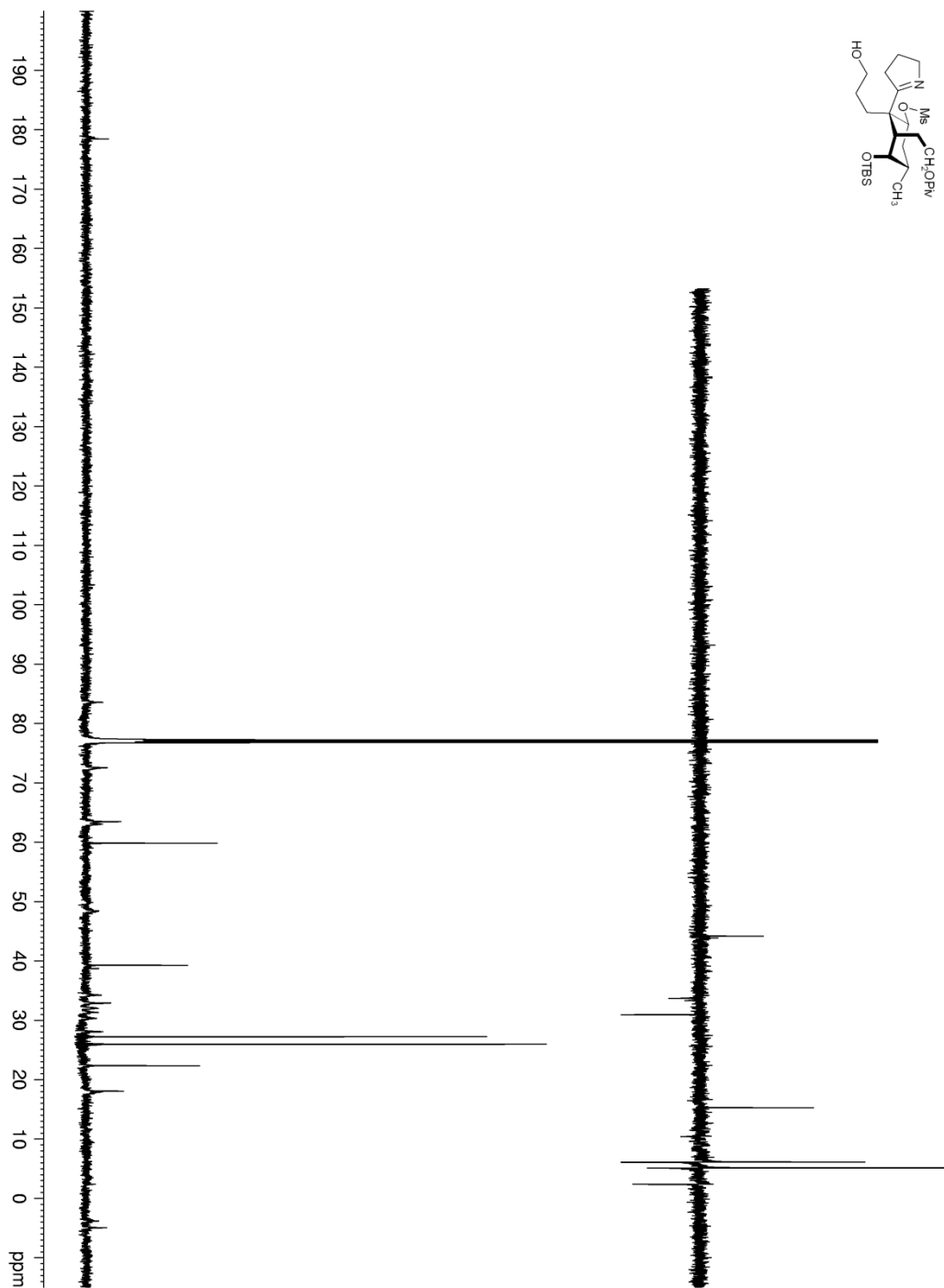


Figure 55. ^1H NMR Spectrum (600 MHz, CDCl_3) of 279

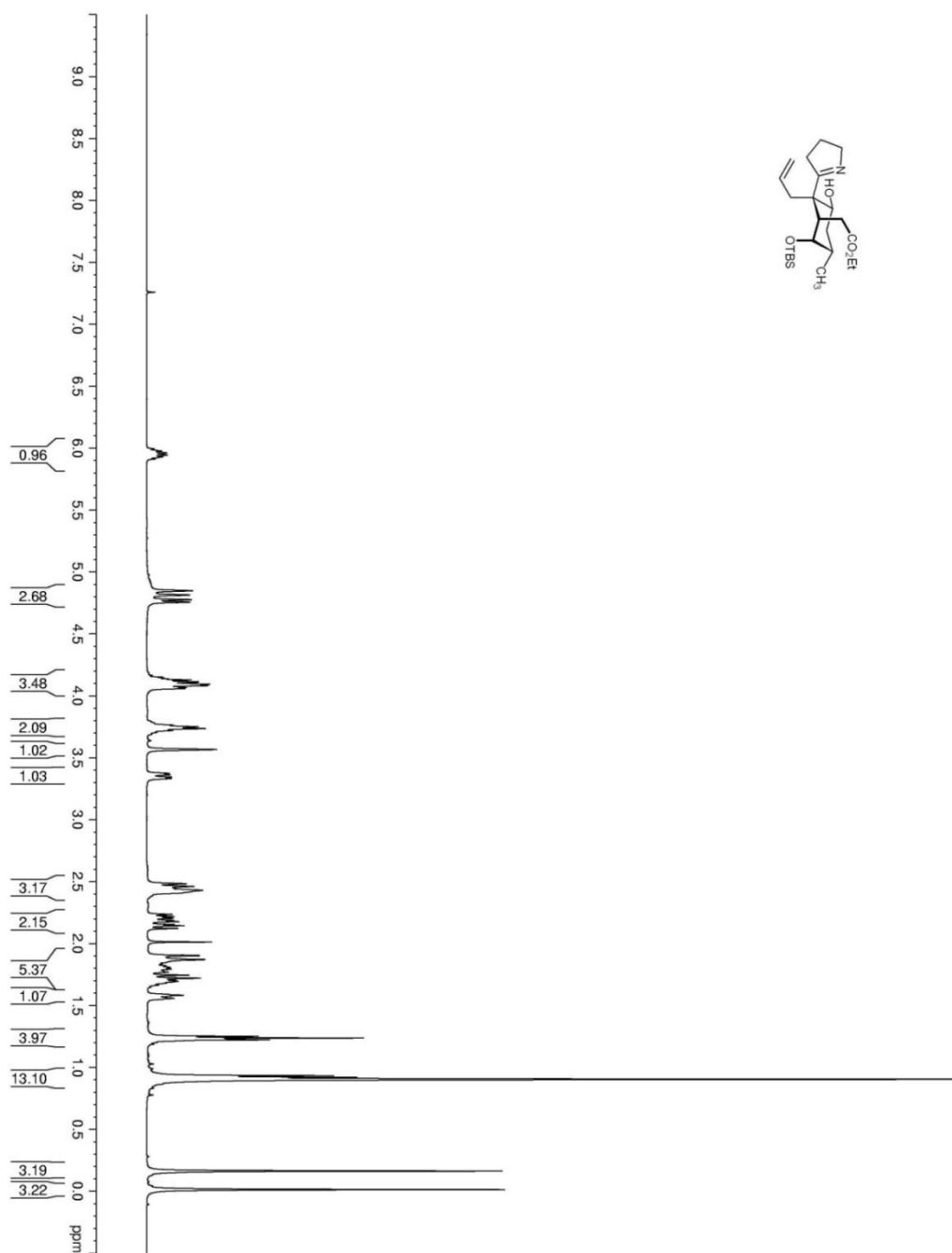


Figure 56. ^{13}C NMR Spectrum (125 MHz, CDCl_3) of 279

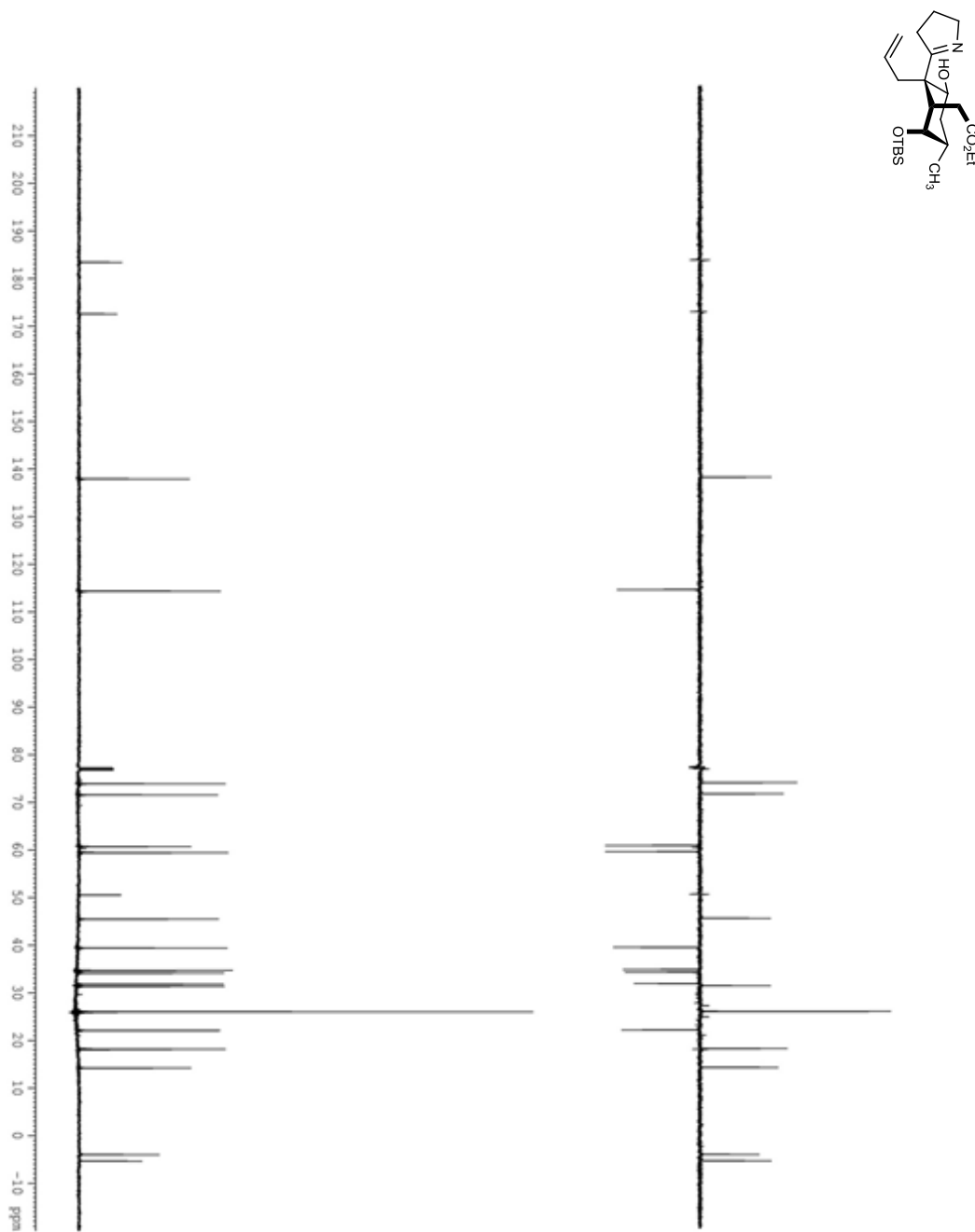


Figure 57. ^1H NMR Spectrum (500 MHz, CDCl_3) of 249

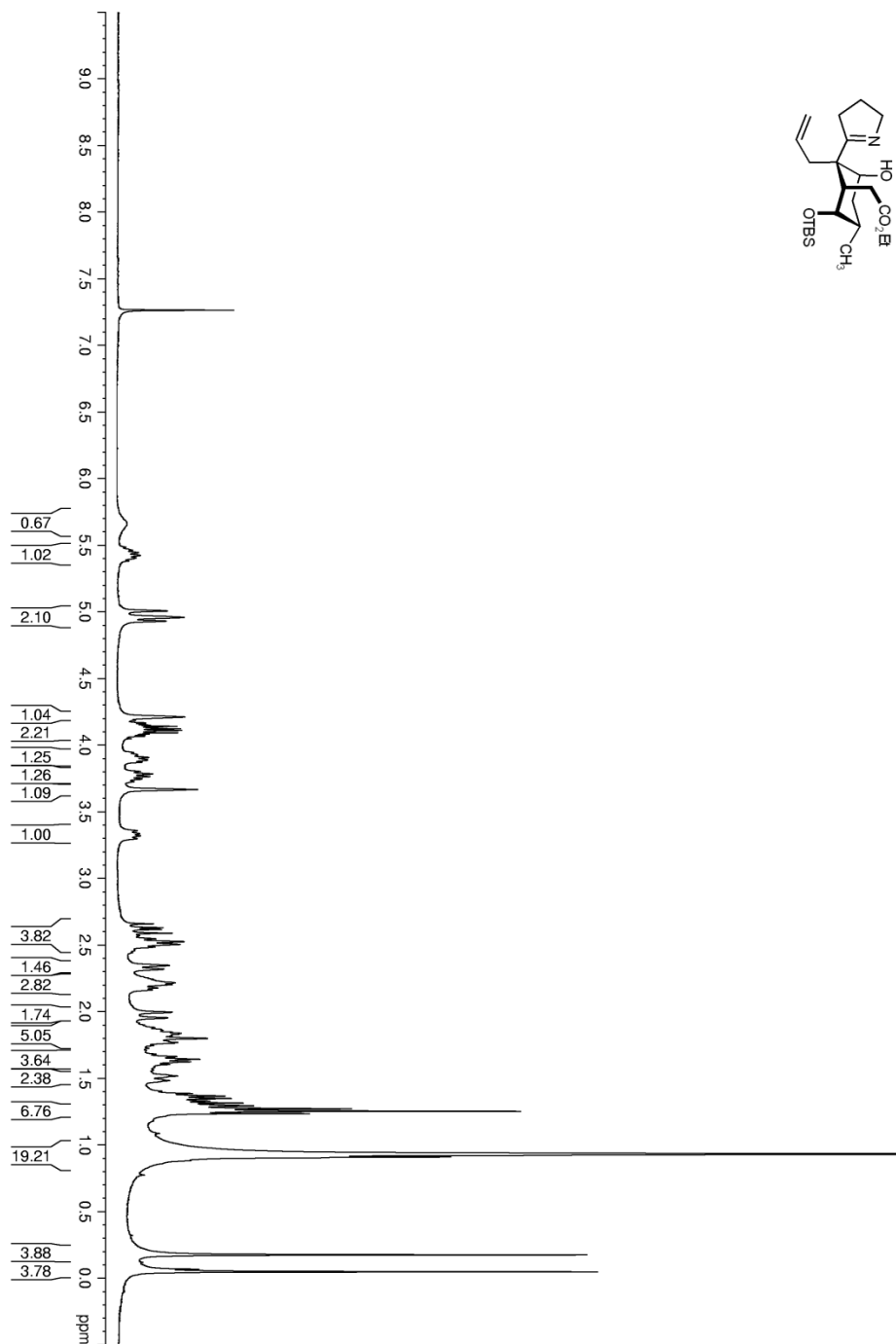


Figure 58. ^{13}C NMR Spectrum (125 MHz, CDCl_3) of 249

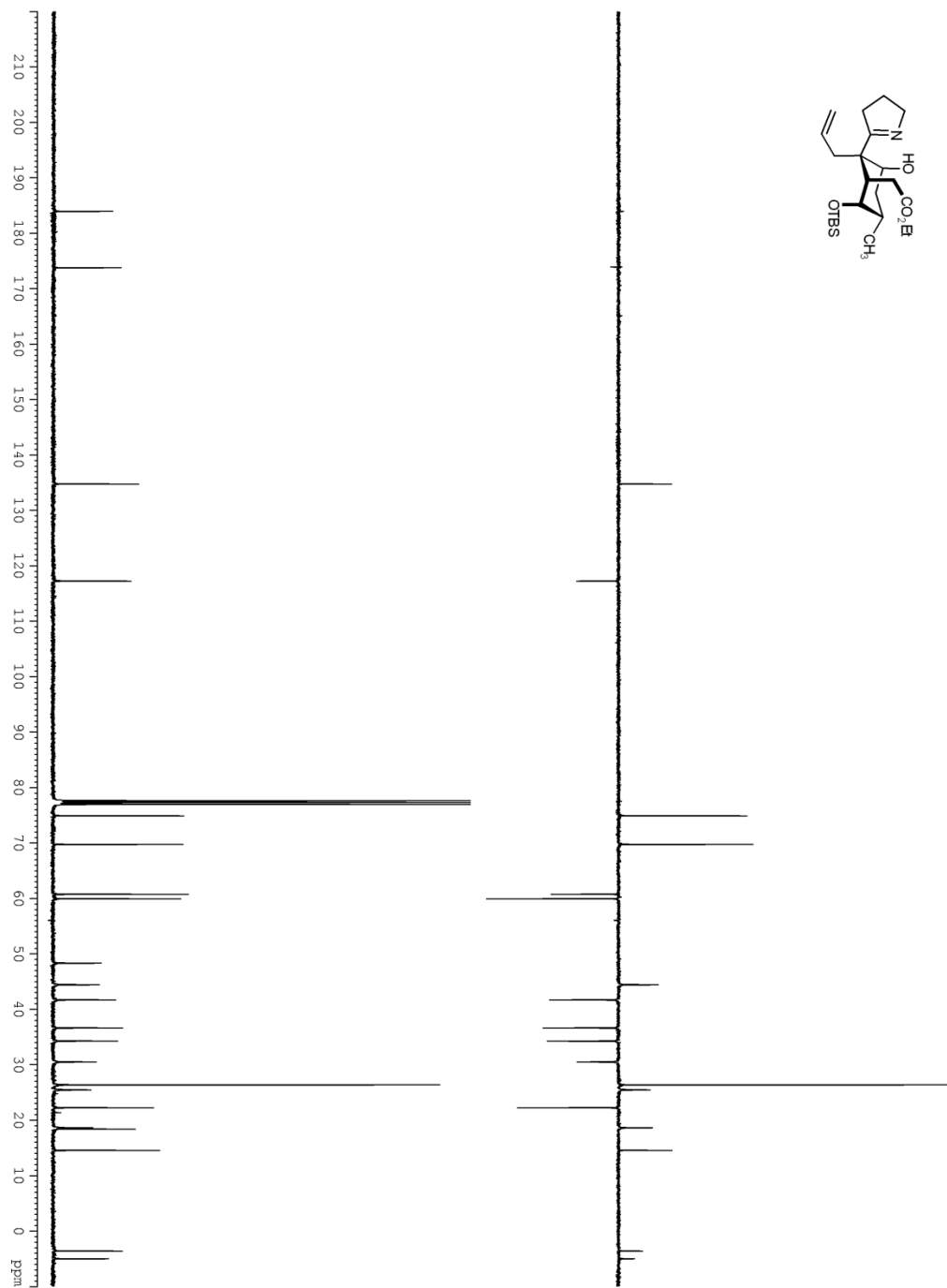


Figure 59. ^1H NMR Spectrum (600 MHz, CDCl_3) of 280

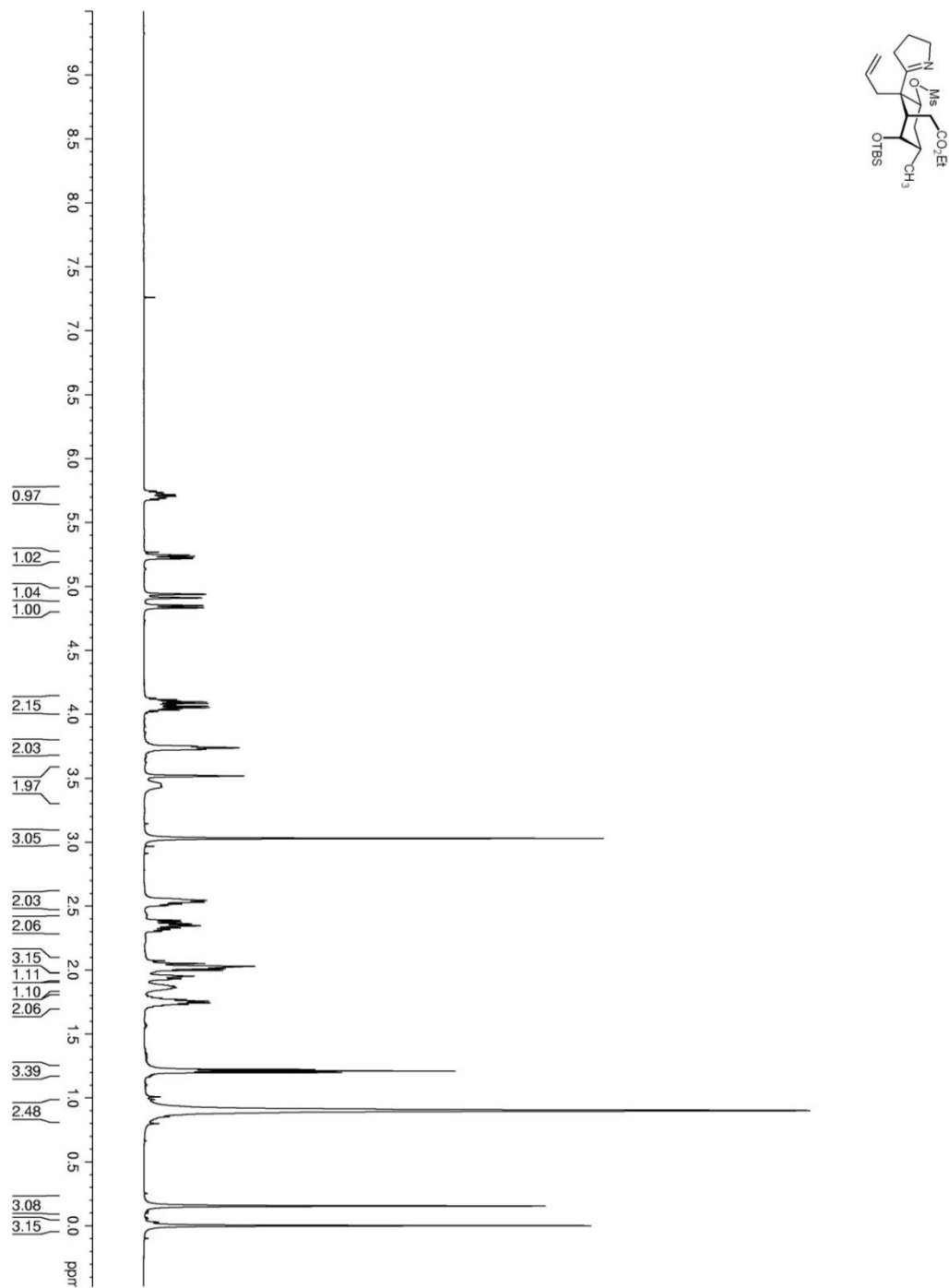


Figure 60. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 280

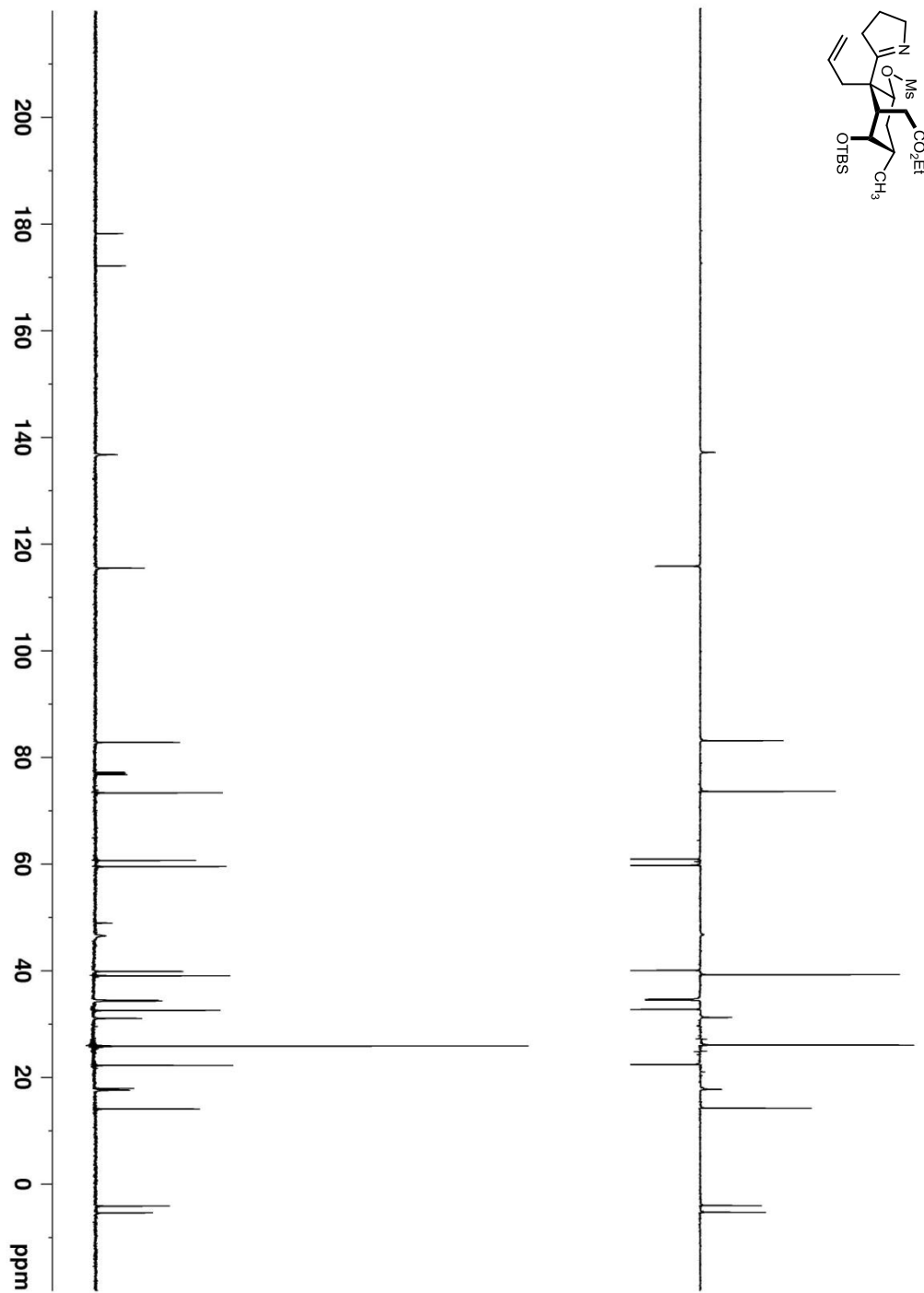


Figure 61. ^1H NMR Spectrum (600 MHz, CDCl_3) of 281

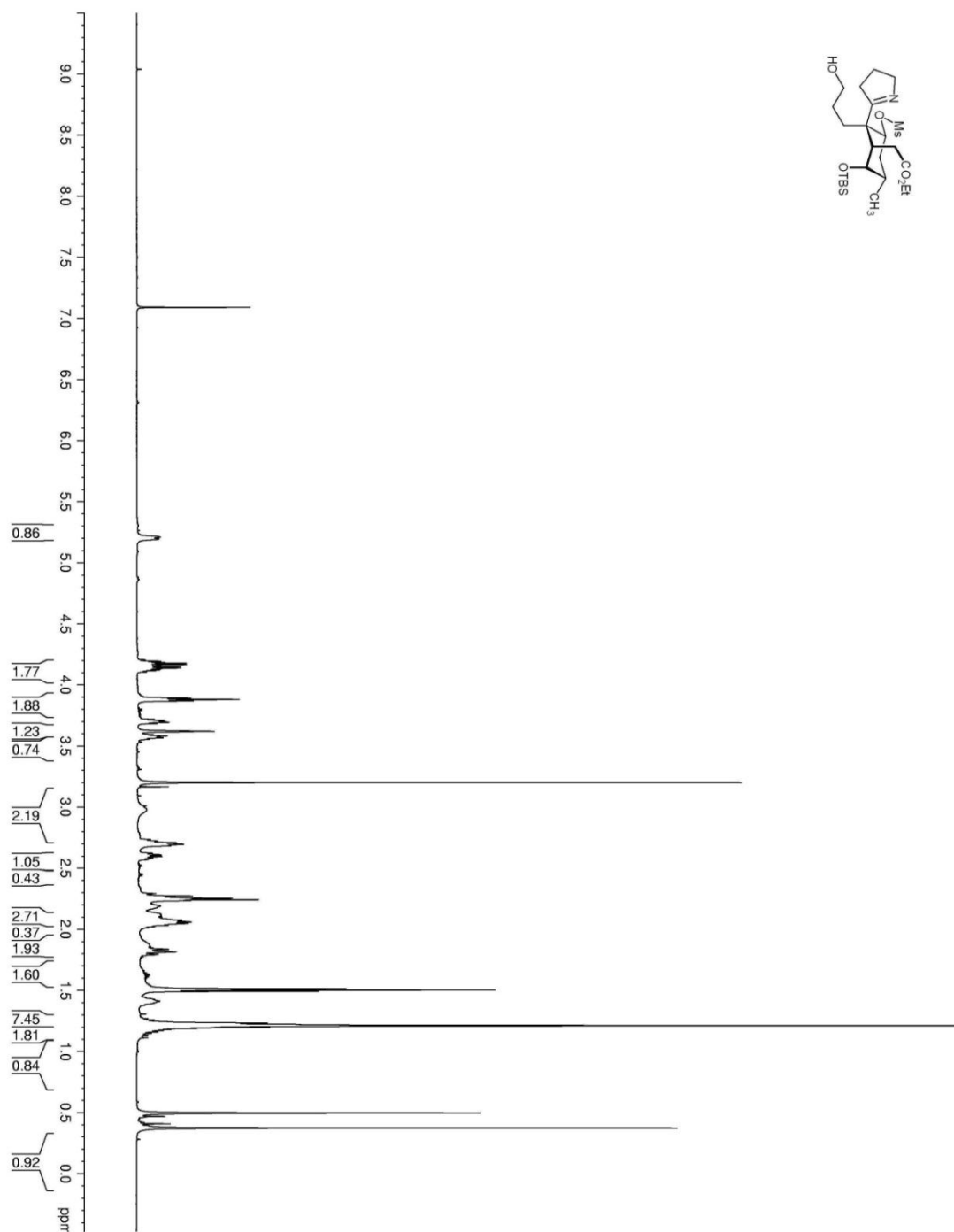


Figure 62. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 281

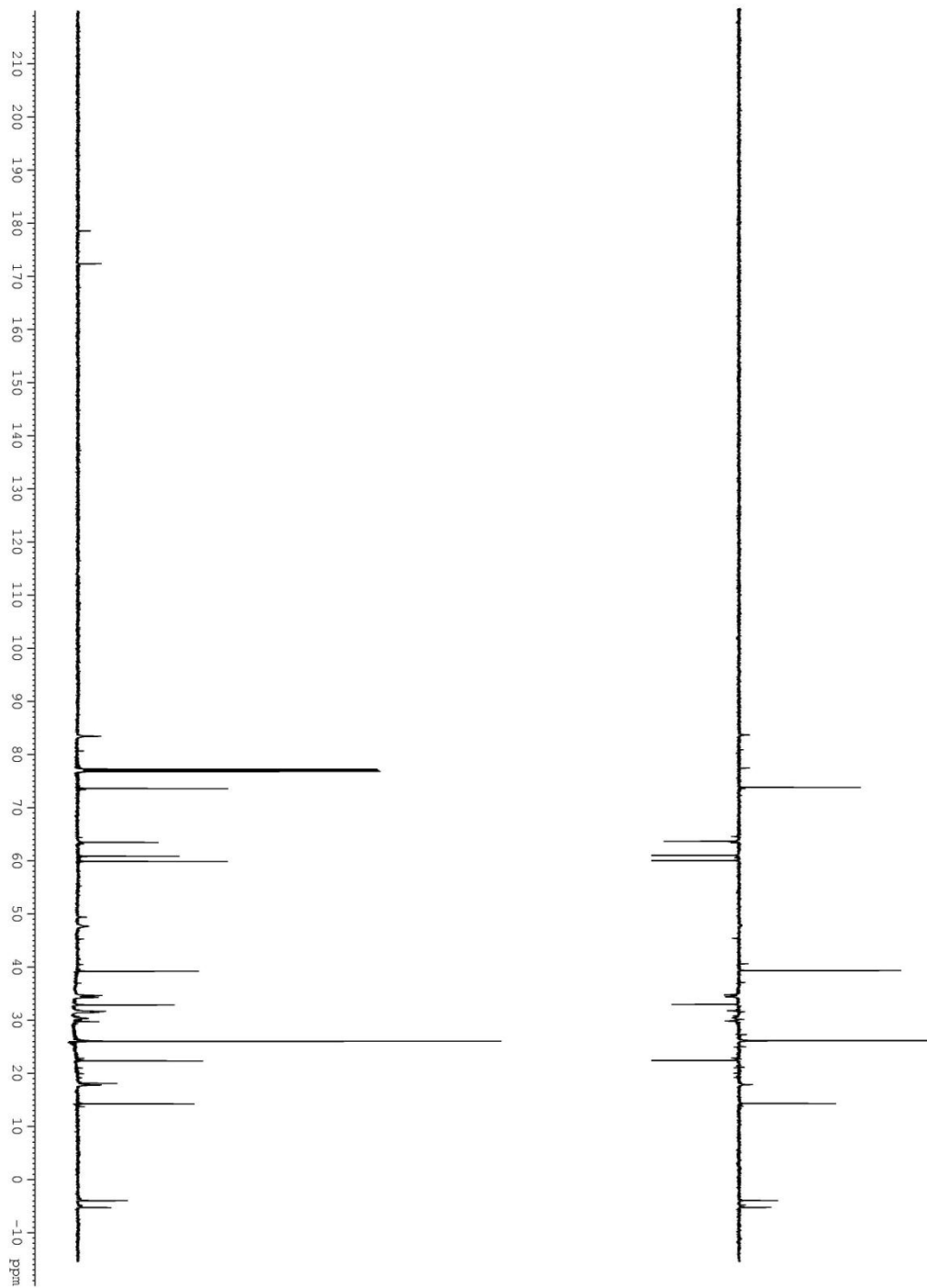


Figure 63. ^1H NMR Spectrum (600 MHz, CDCl_3) of 286

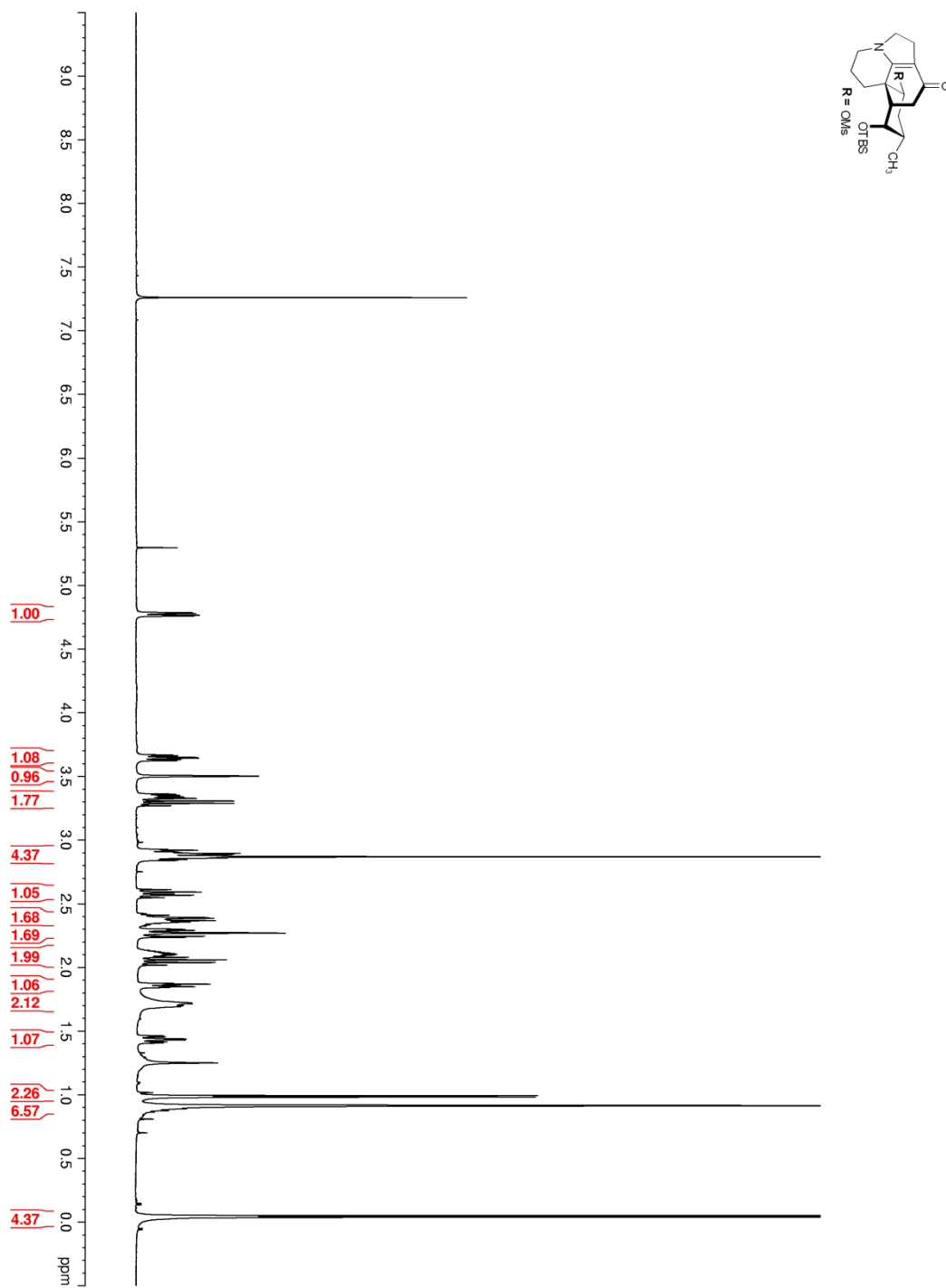


Figure 64. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 286

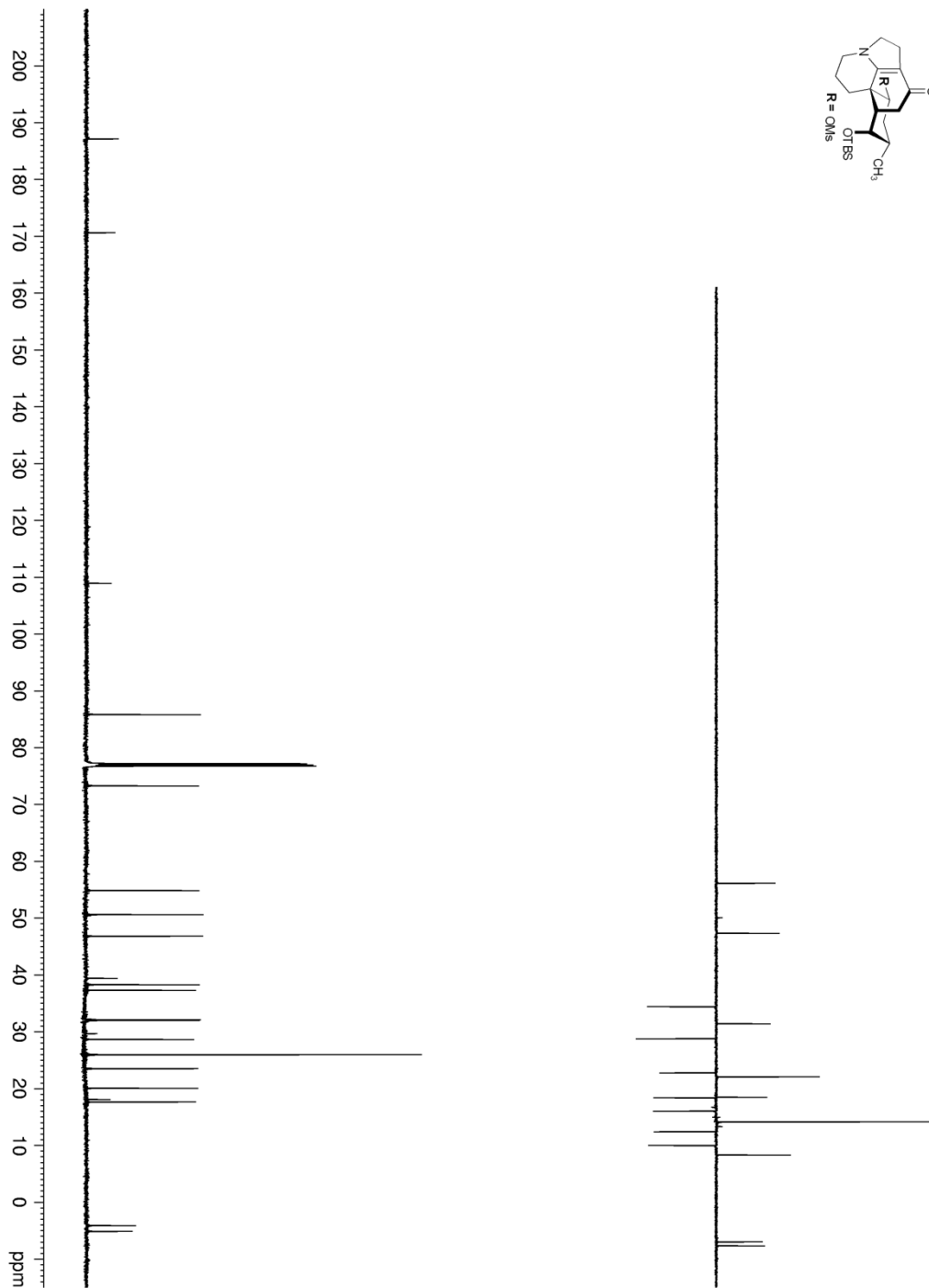


Figure 65. HSQC Spectra (150 MHz, CDCl₃) of 286

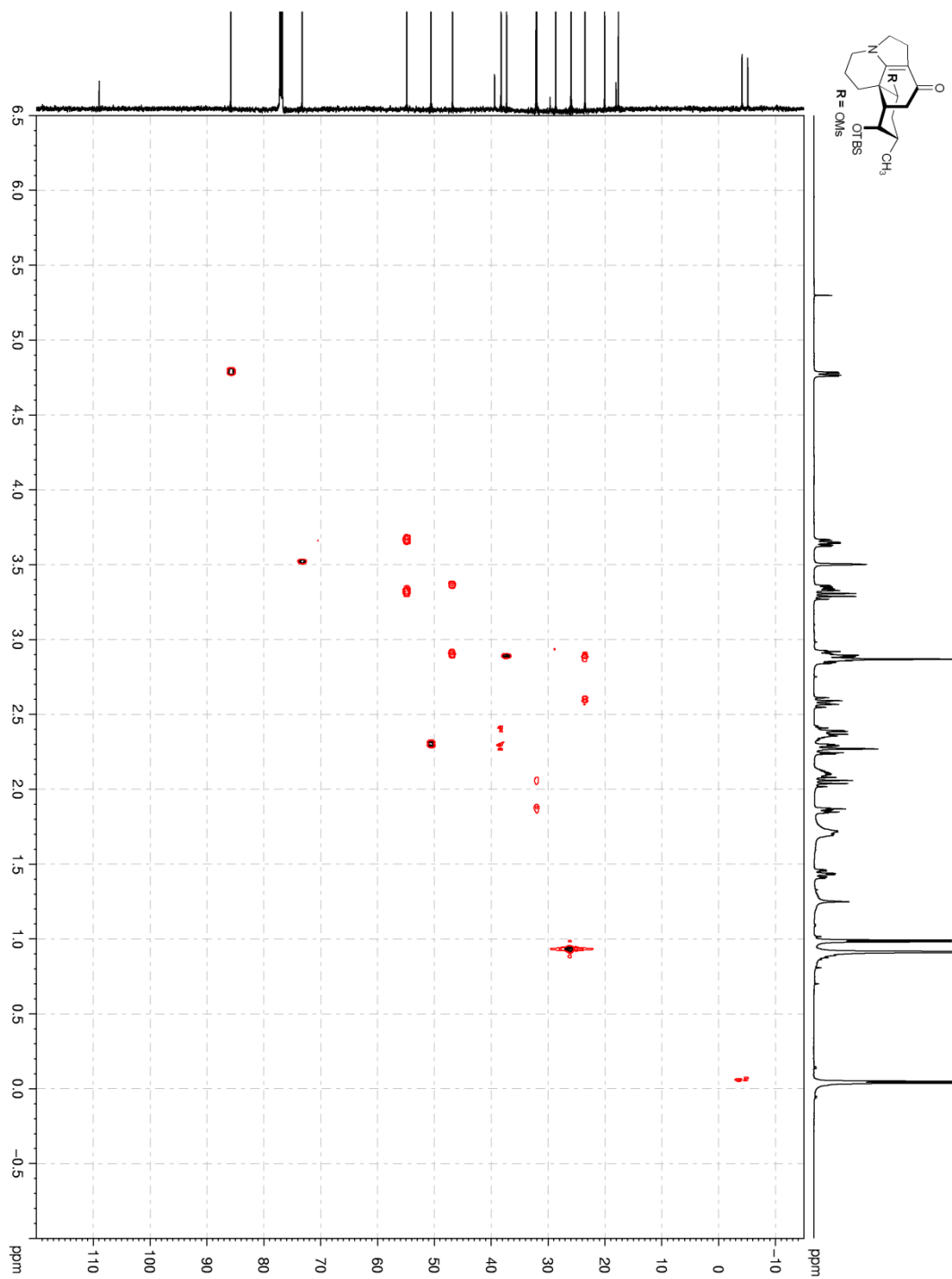


Figure 66. HMBC Spectra (150 MHz, CDCl₃) of 286

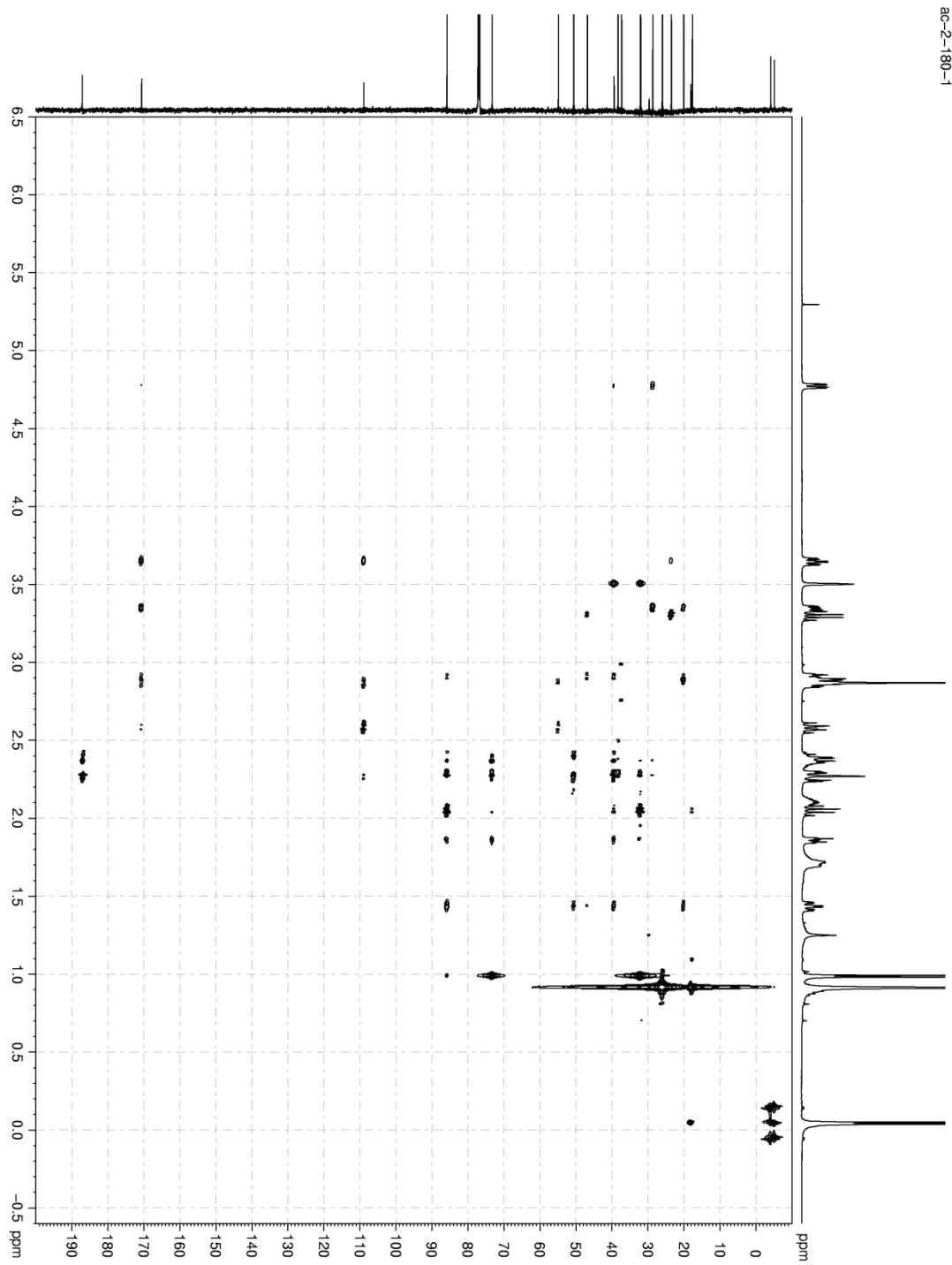


Figure 67. COSY Spectrum (600 MHz, CDCl₃) of 286

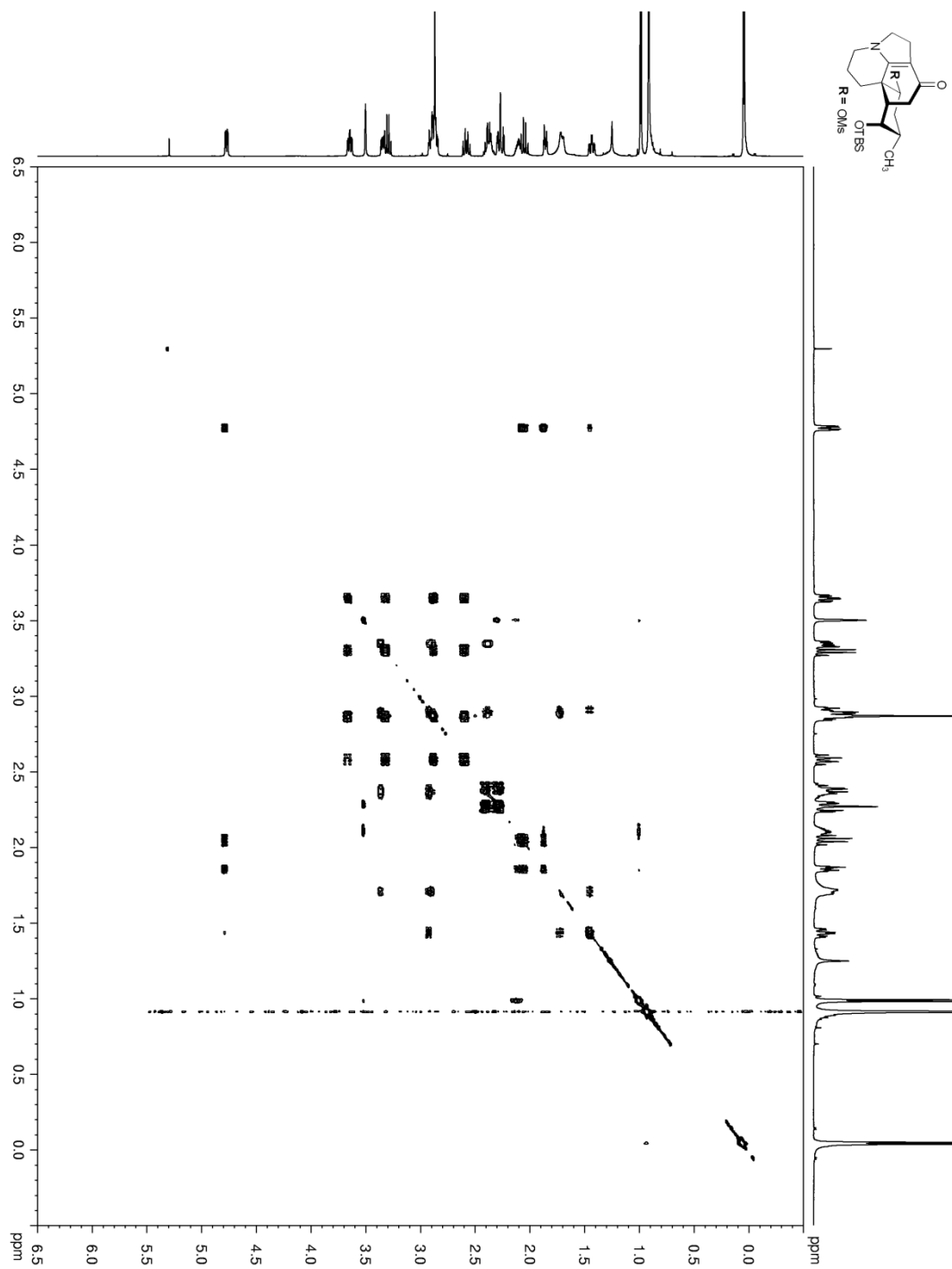


Figure 68. NOESY Spectra (600 MHz, CDCl₃) of 286

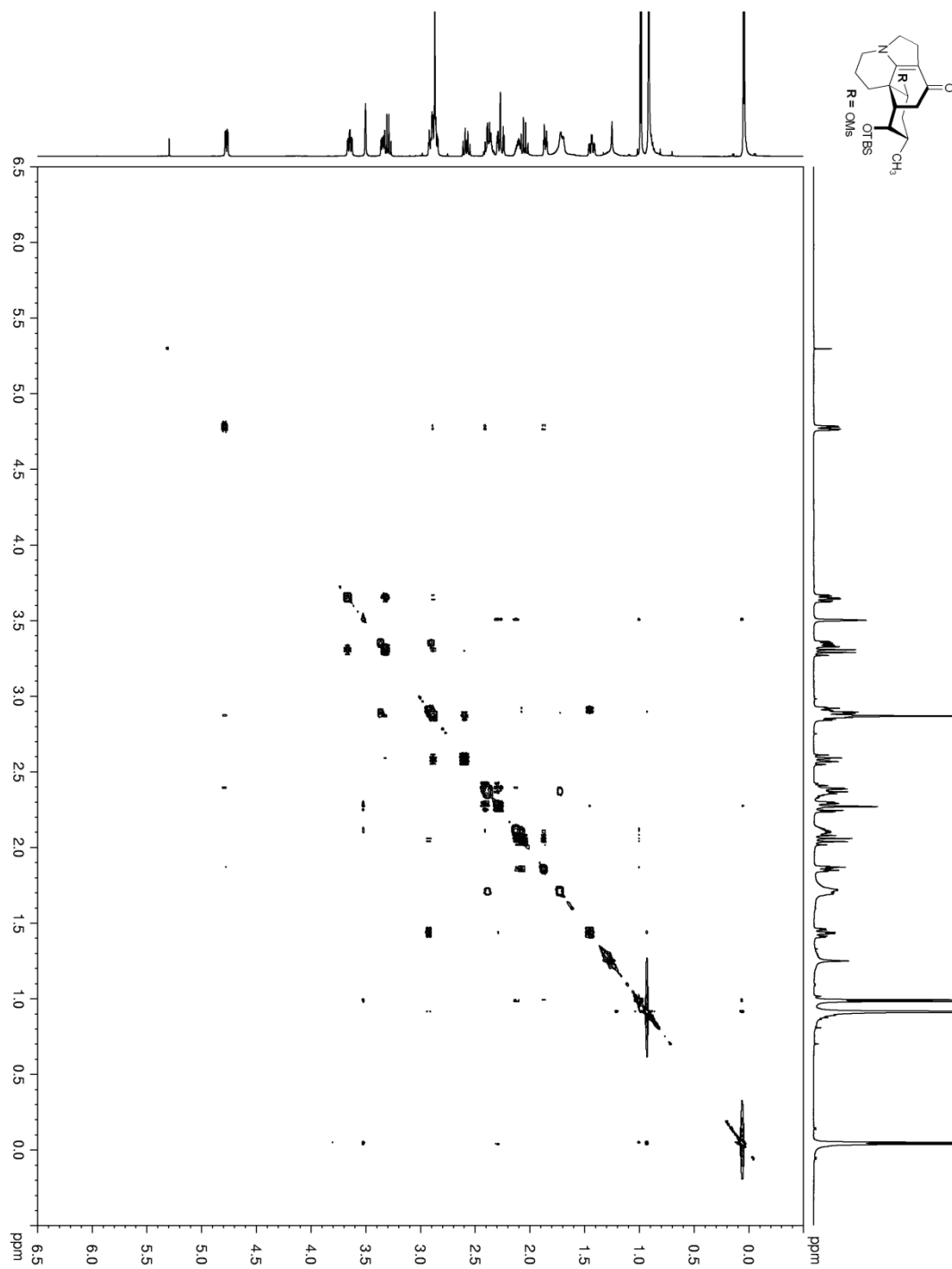


Figure 69. ^1H NMR Spectrum (500 MHz, CDCl_3) of 448

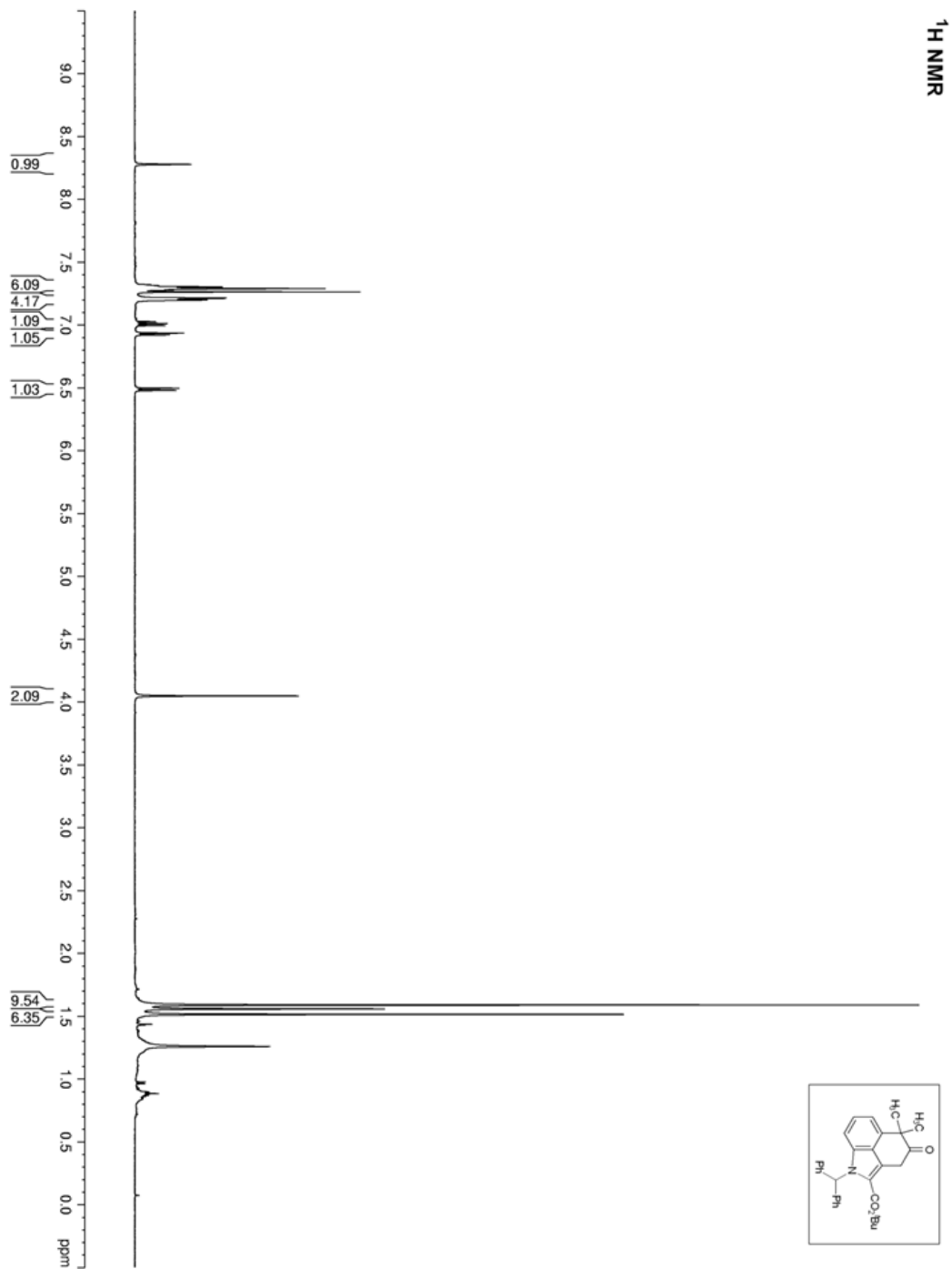


Figure 70. ^{13}C NMR Spectrum (125 MHz, CDCl_3) of 448

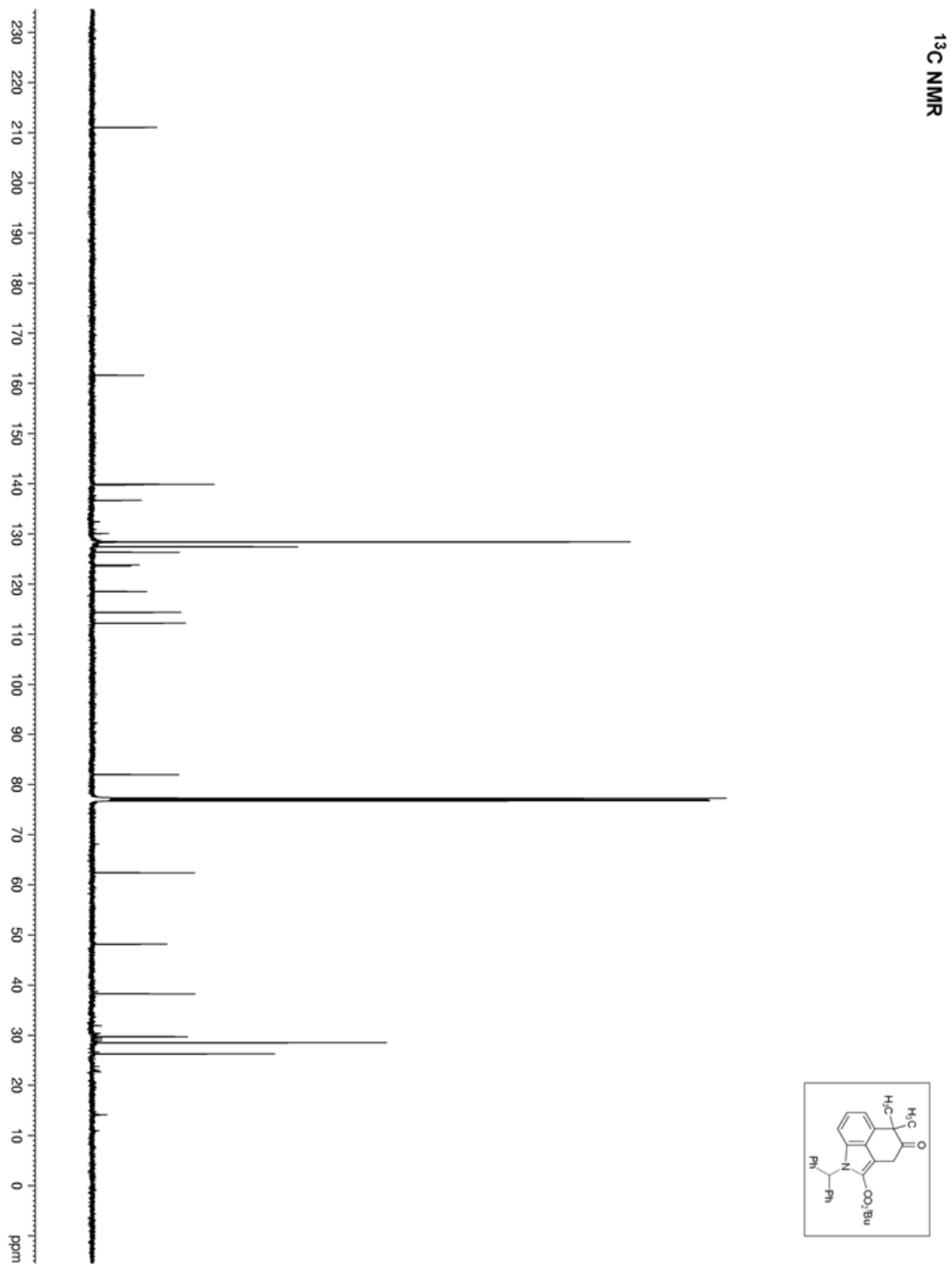


Figure 71. ^1H NMR Spectrum (500 MHz, CDCl_3) of 463

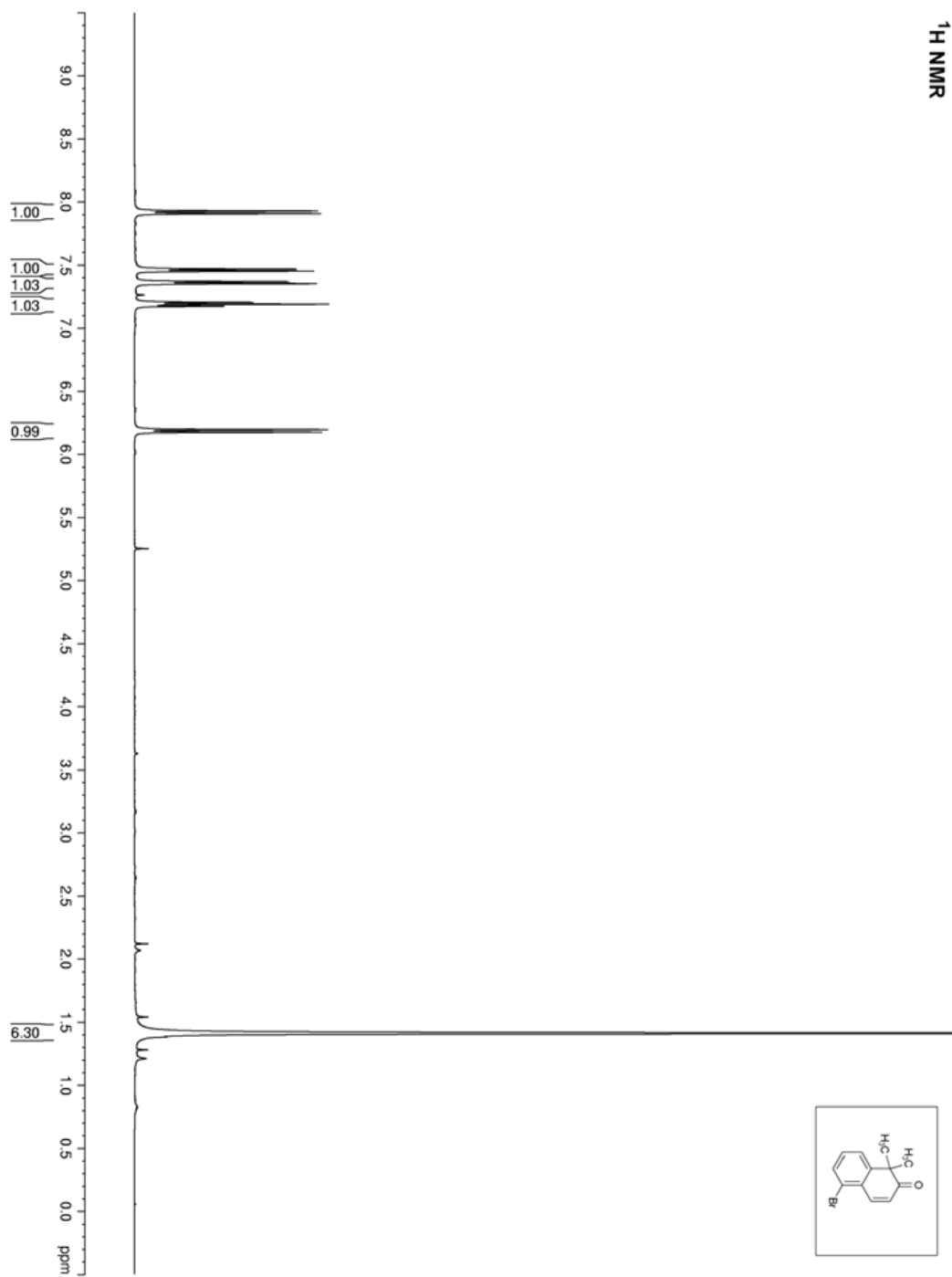


Figure 72. ^{13}C NMR Spectrum (125 MHz, CDCl_3) of 463

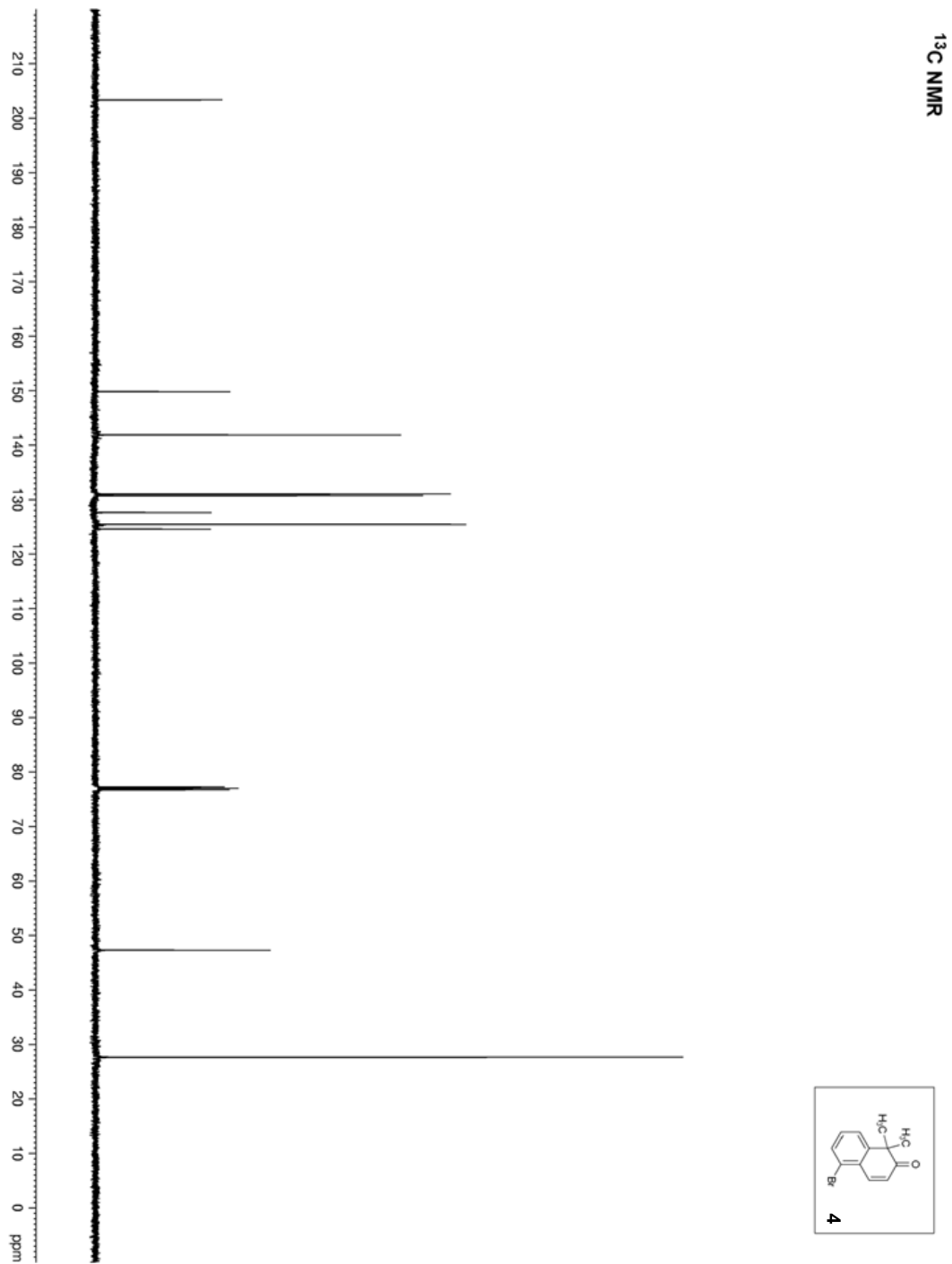


Figure 73. ^1H NMR Spectra (500 Hz, CDCl_3) of 464

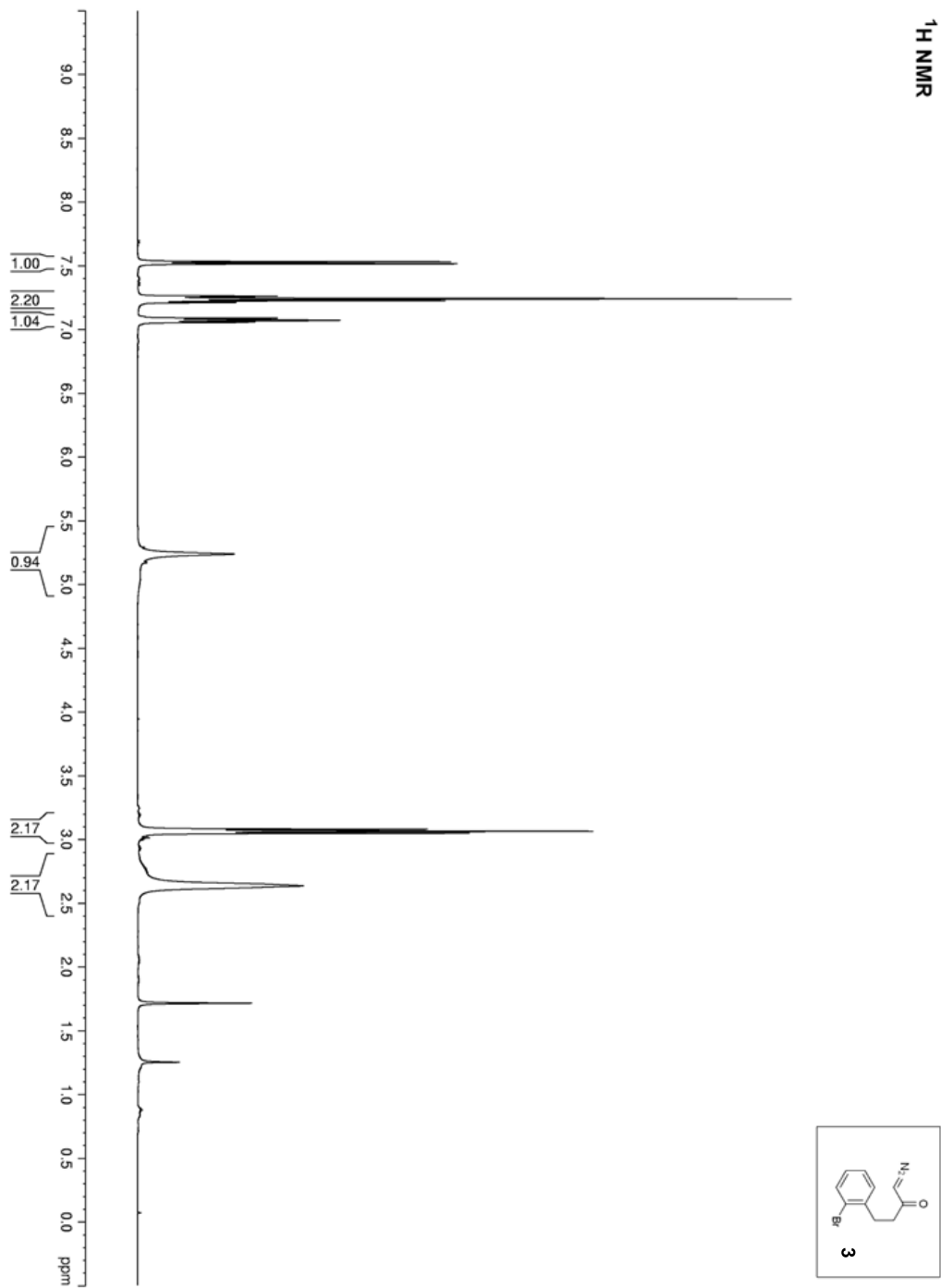
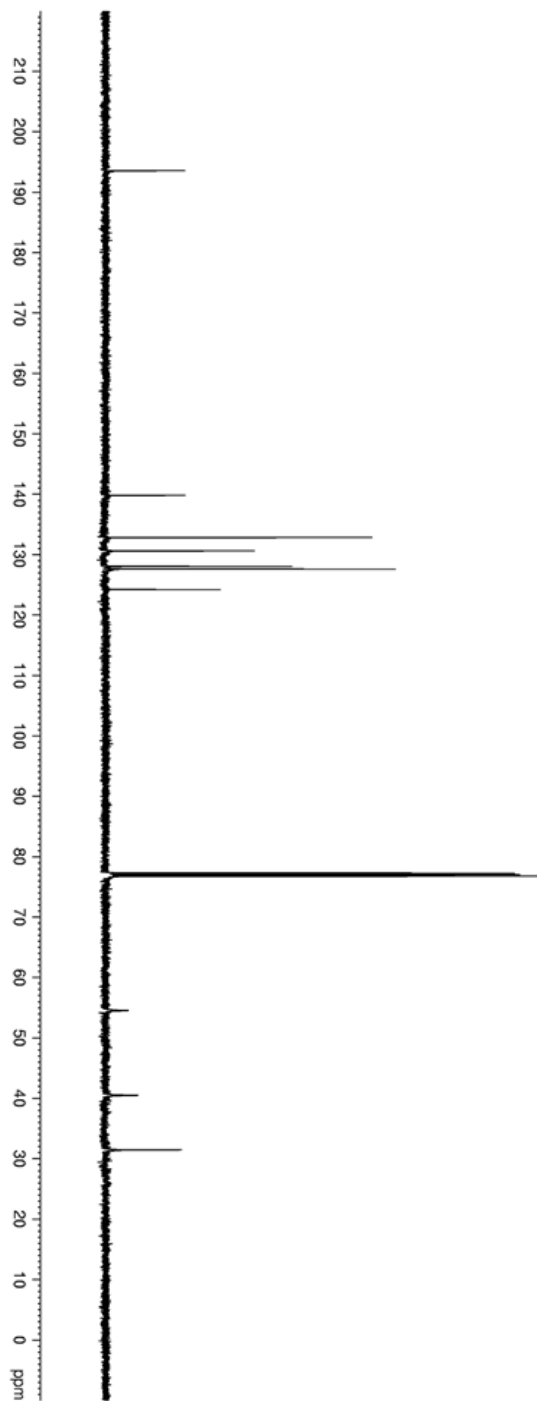


Figure 74. ^{13}C NMR Spectrum (125 MHz, CDCl_3) of 464



^{13}C NMR

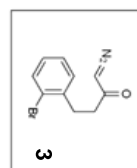
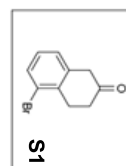
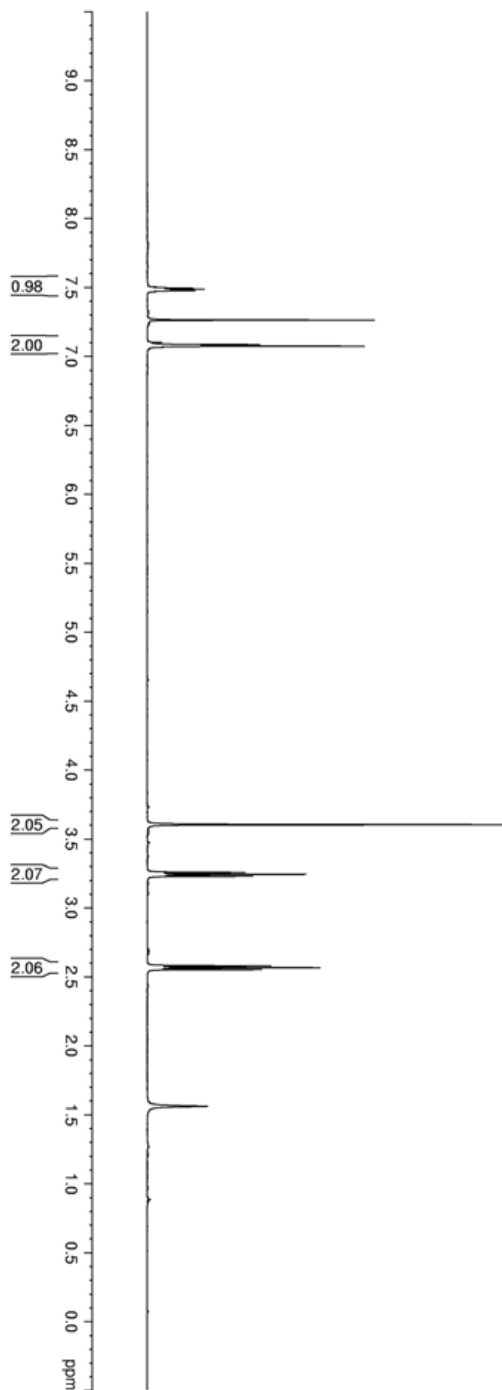


Figure 75. ^1H NMR Spectrum (500 MHz, CDCl_3) of 466



^1H NMR

Figure 76. ^{13}C NMR Spectrum (125 MHz, CDCl_3) of 466

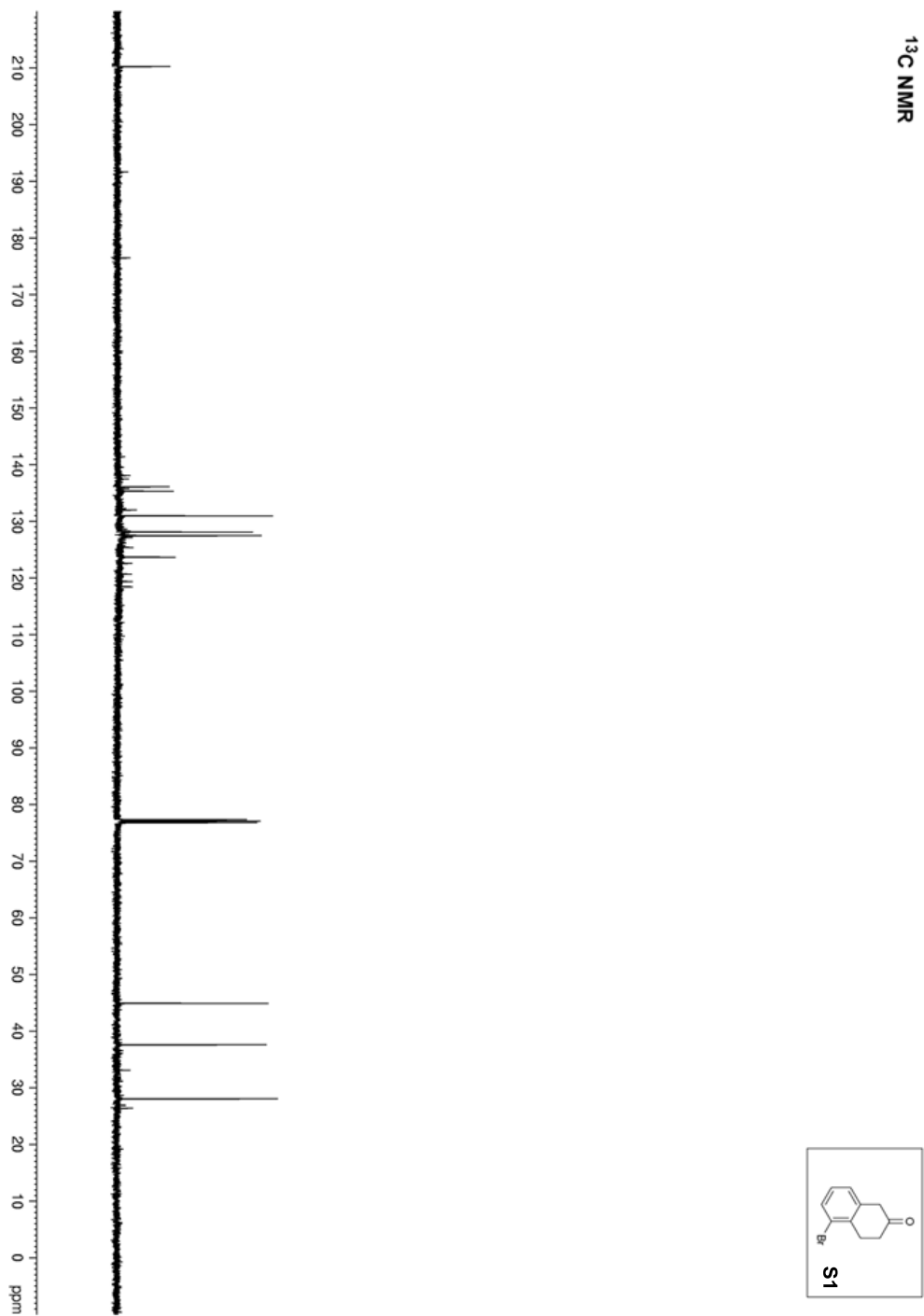


Figure 77. ^1H NMR Spectrum (500 MHz, CDCl_3) of 472

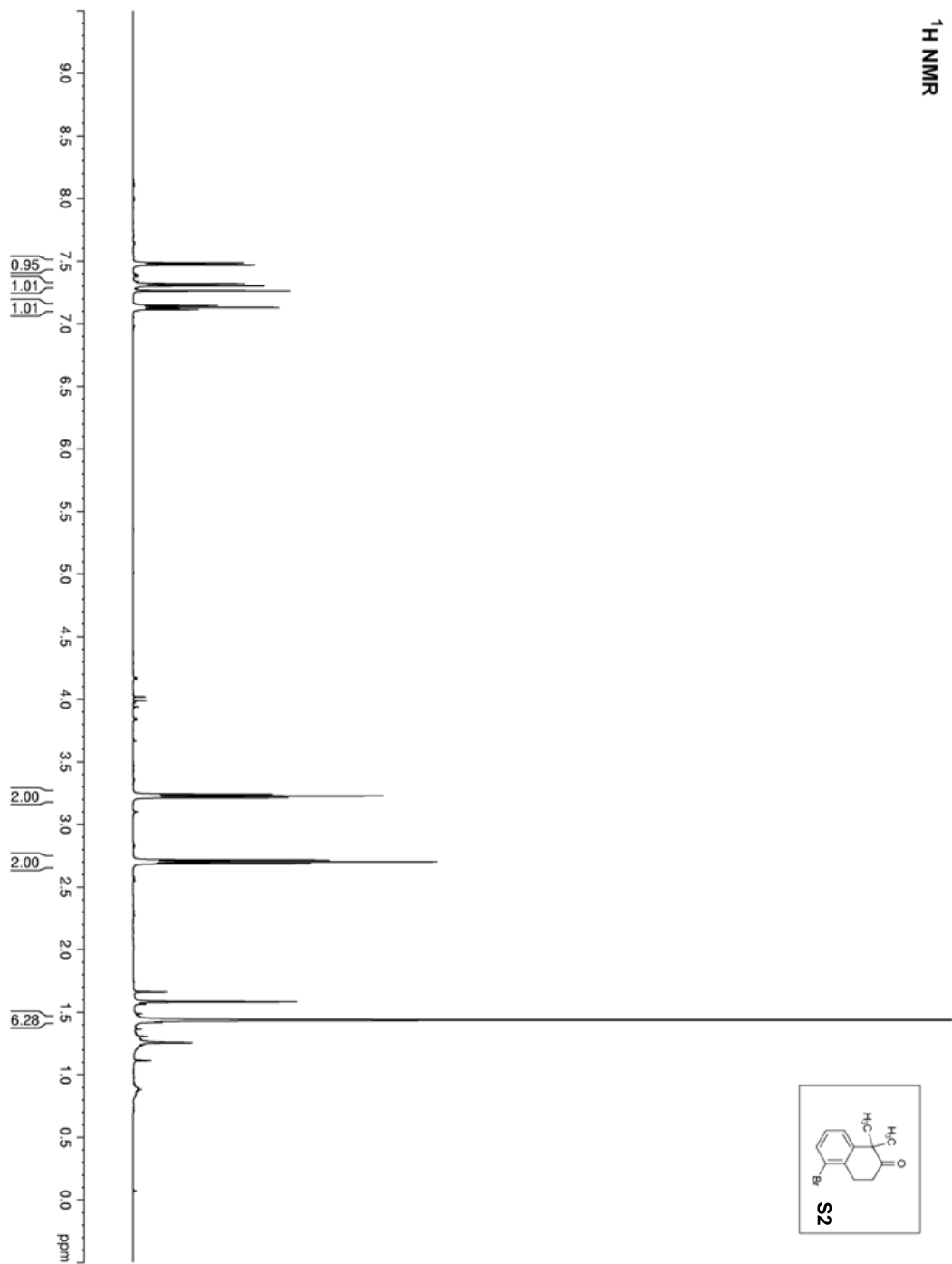


Figure 78. ^{13}C NMR Spectrum (125 MHz, CDCl_3) of 472

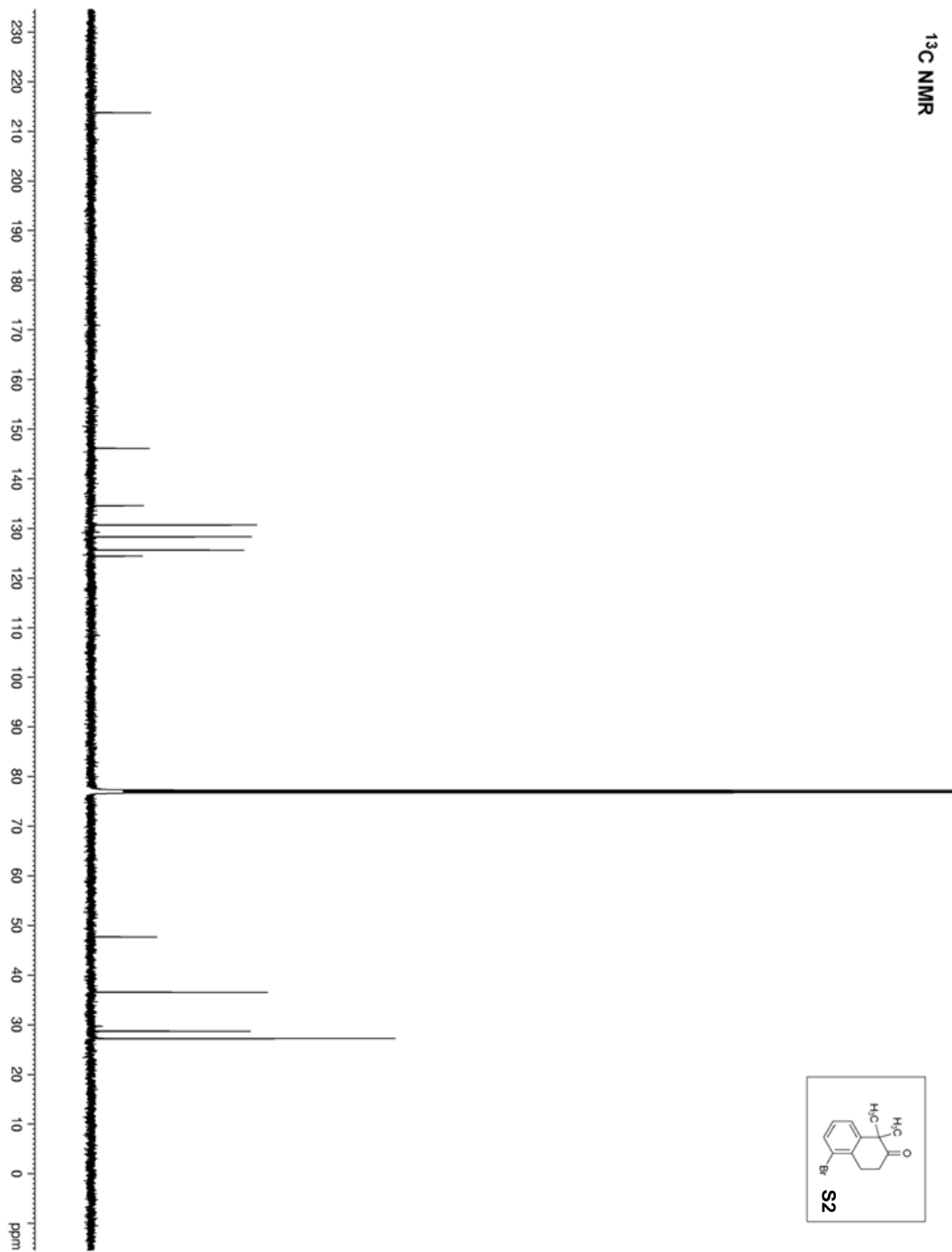


Figure 79. ^1H NMR Spectrum (500 MHz, CDCl_3) of 473

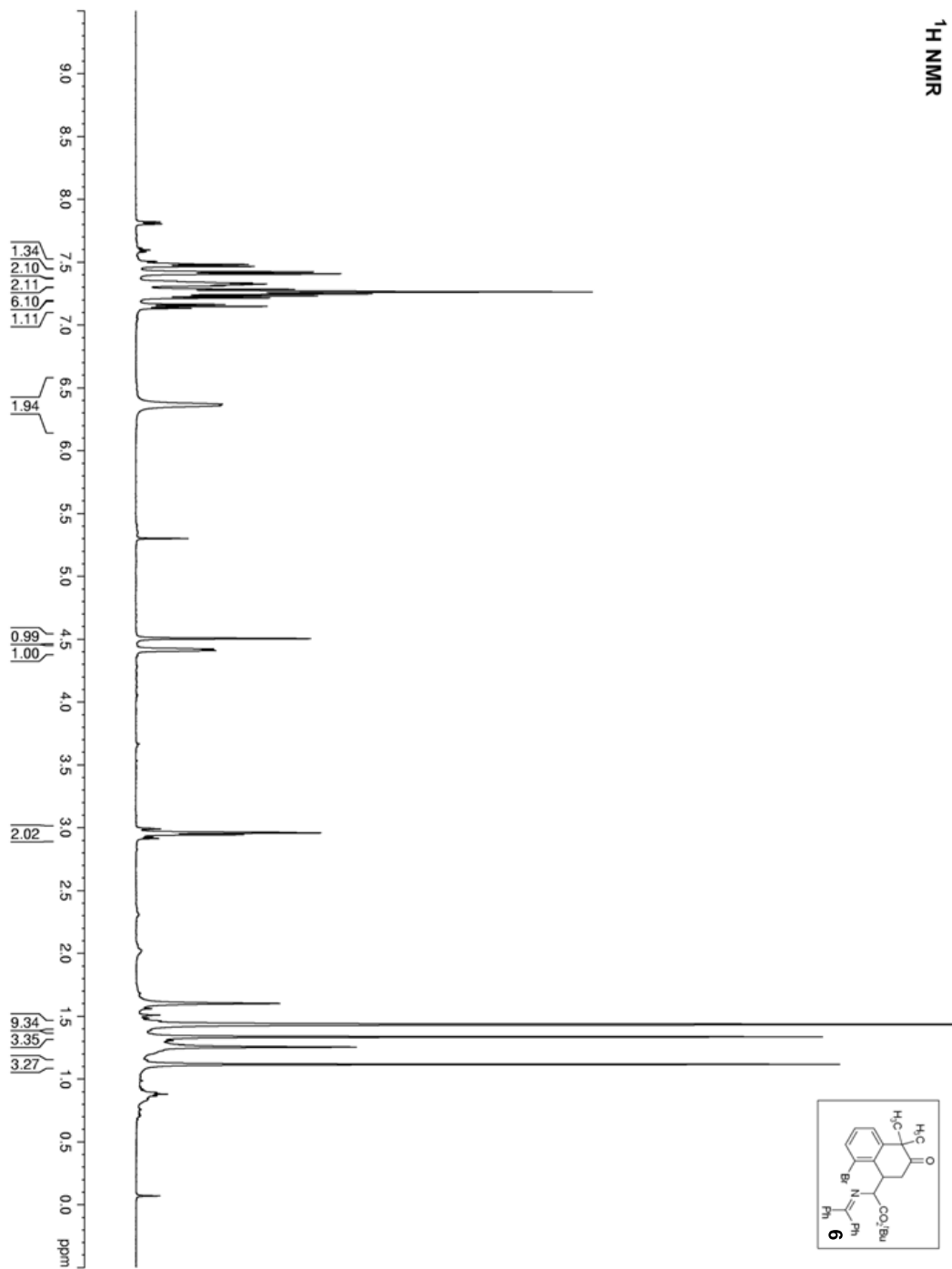


Figure 80. ^{13}C NMR Spectrum (125 MHz, CDCl_3) of 473

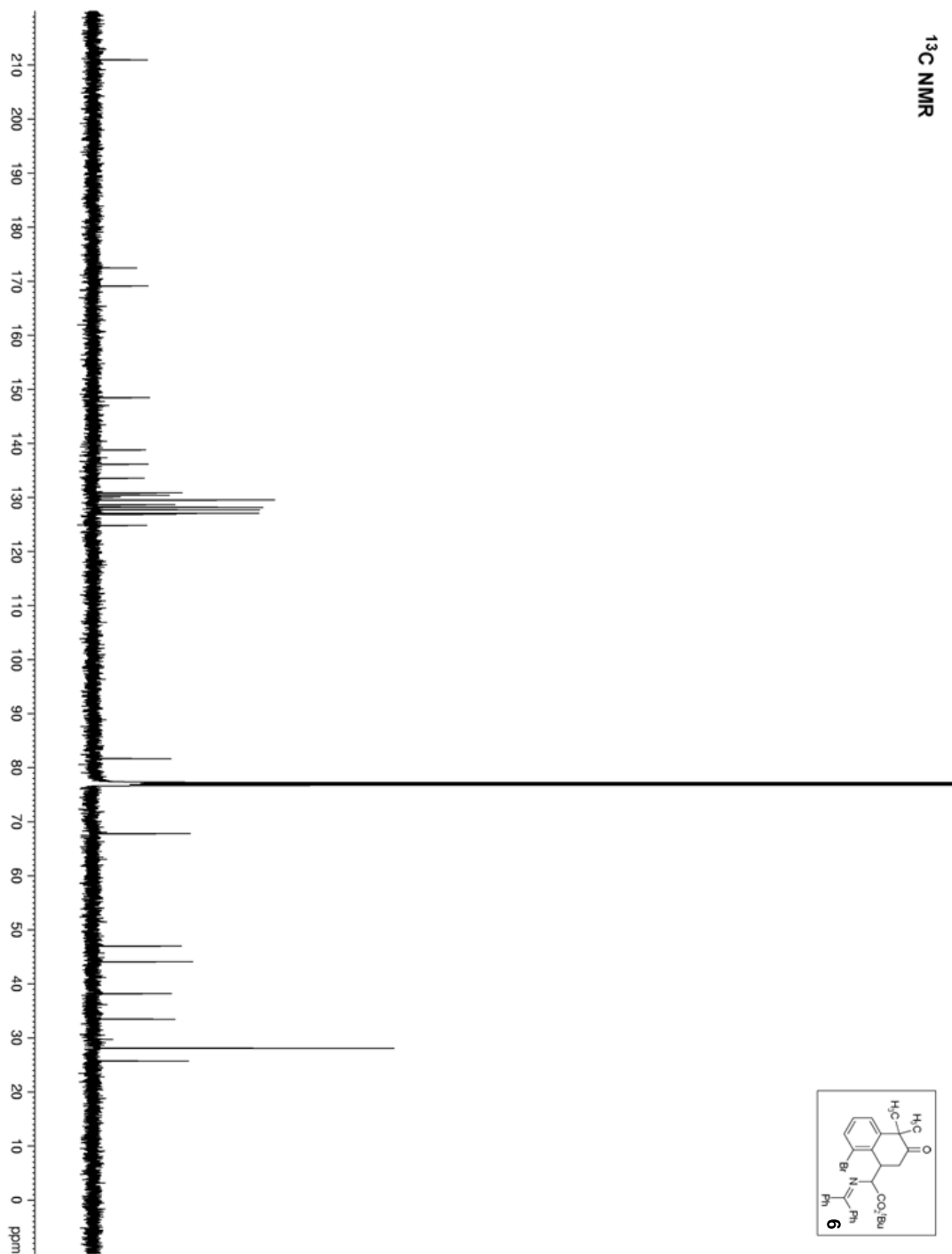


Figure 81. ^1H NMR Spectrum (500 MHz, CDCl_3) of 474

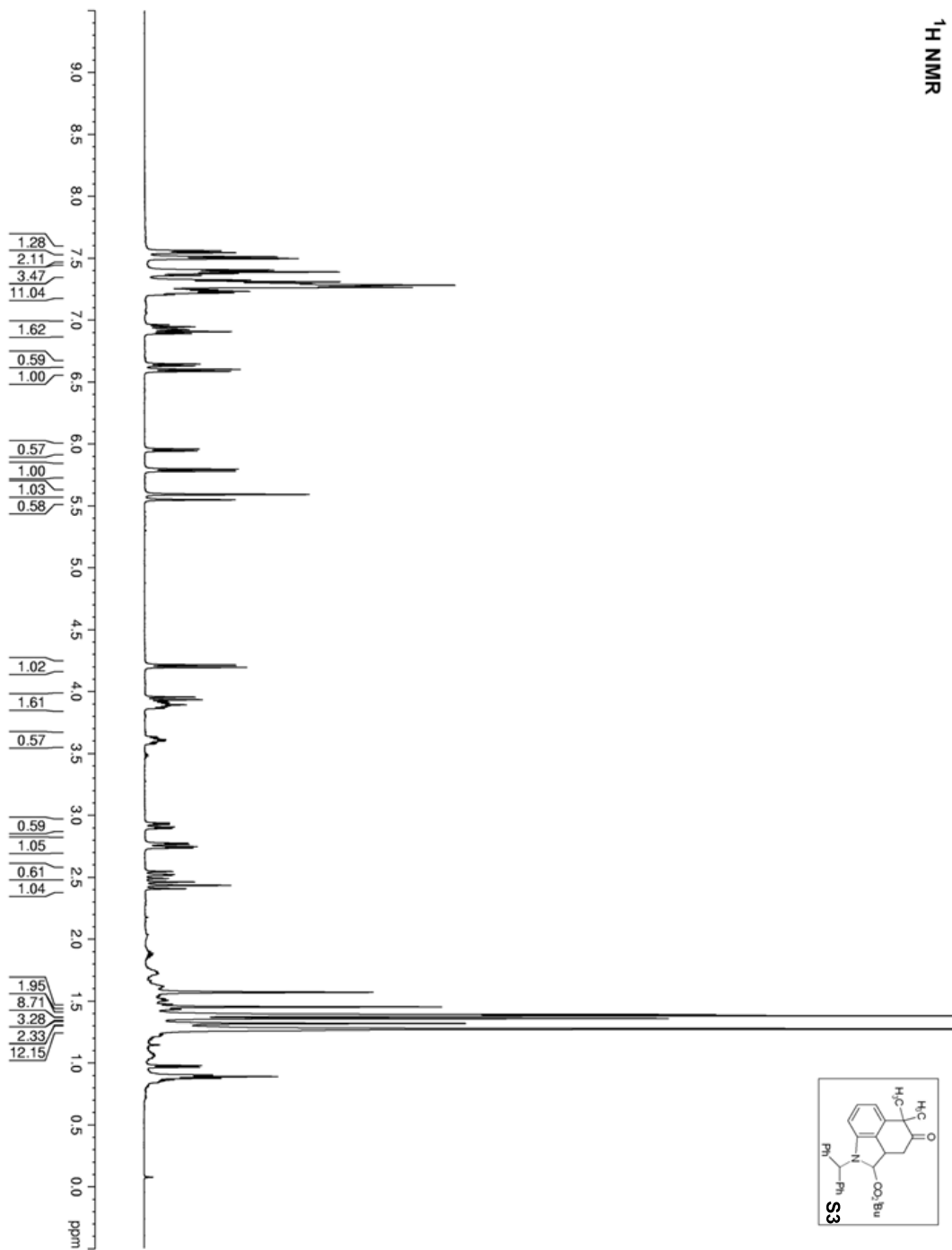


Figure 82. ^{13}C NMR Spectrum (125 MHz, CDCl_3) of 474

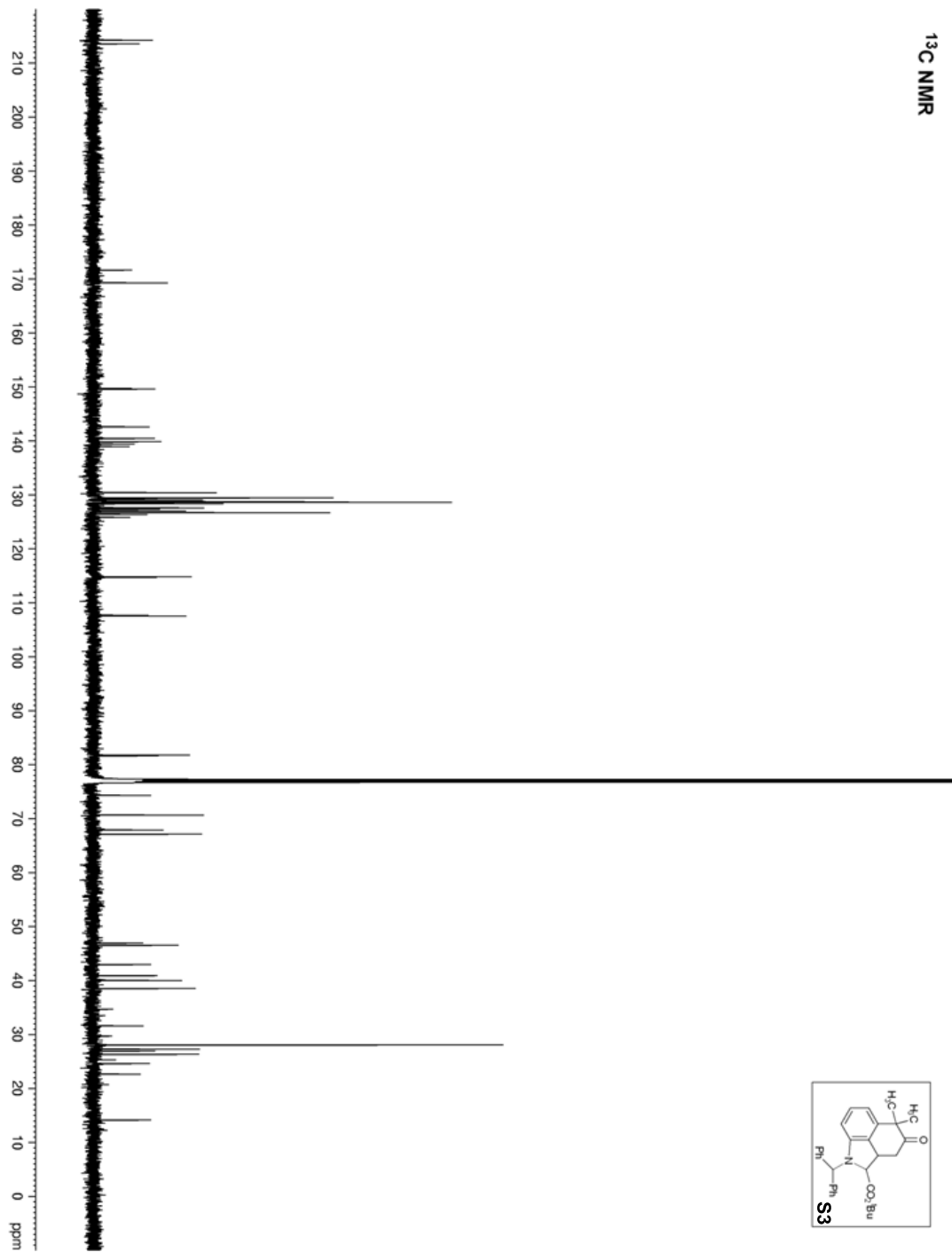


Figure 83. ^1H NMR Spectrum (400 MHz, CDCl_3) of 489

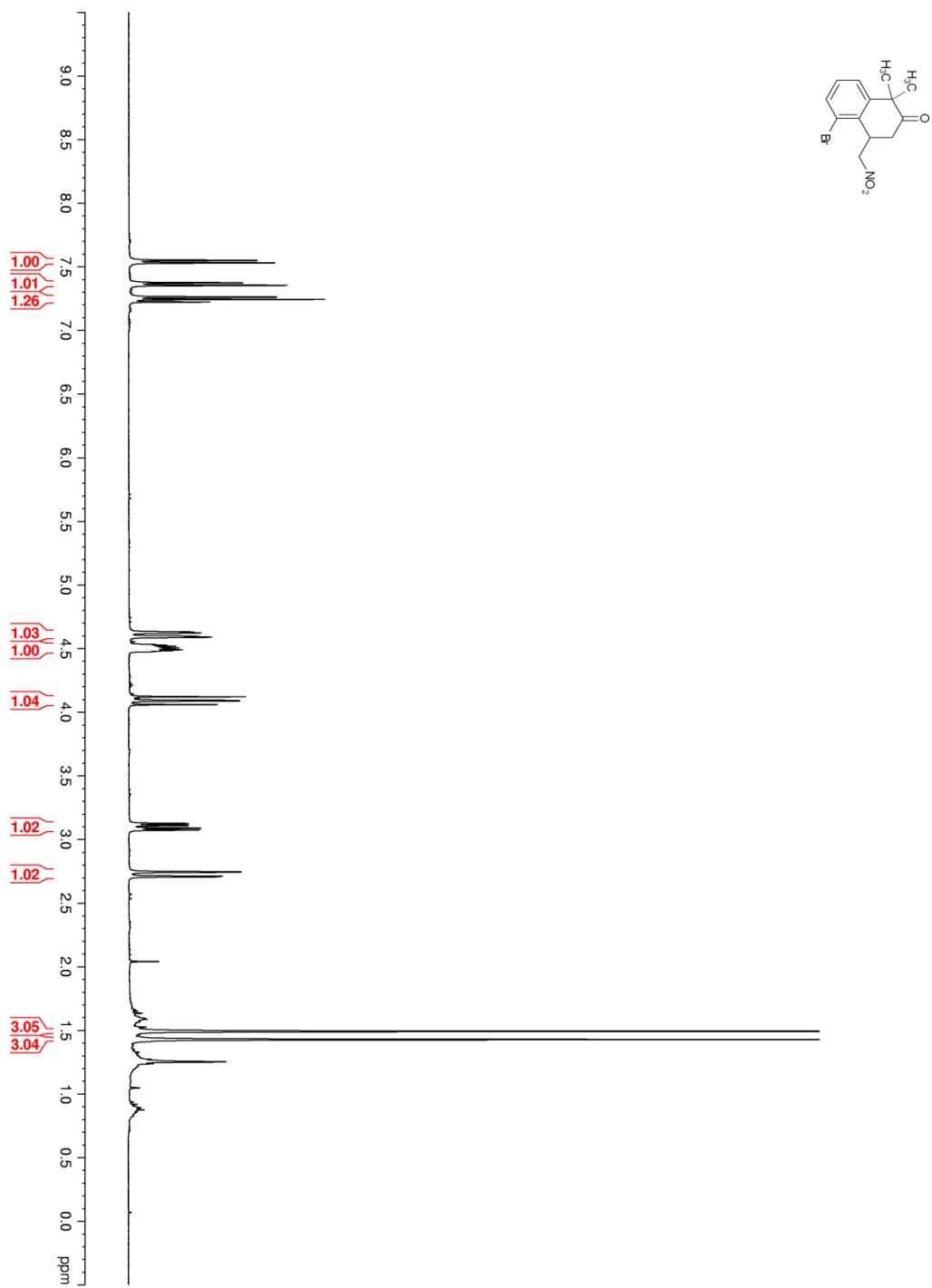


Figure 84. ^{13}C NMR Spectrum (100 MHz, CDCl_3) of 489

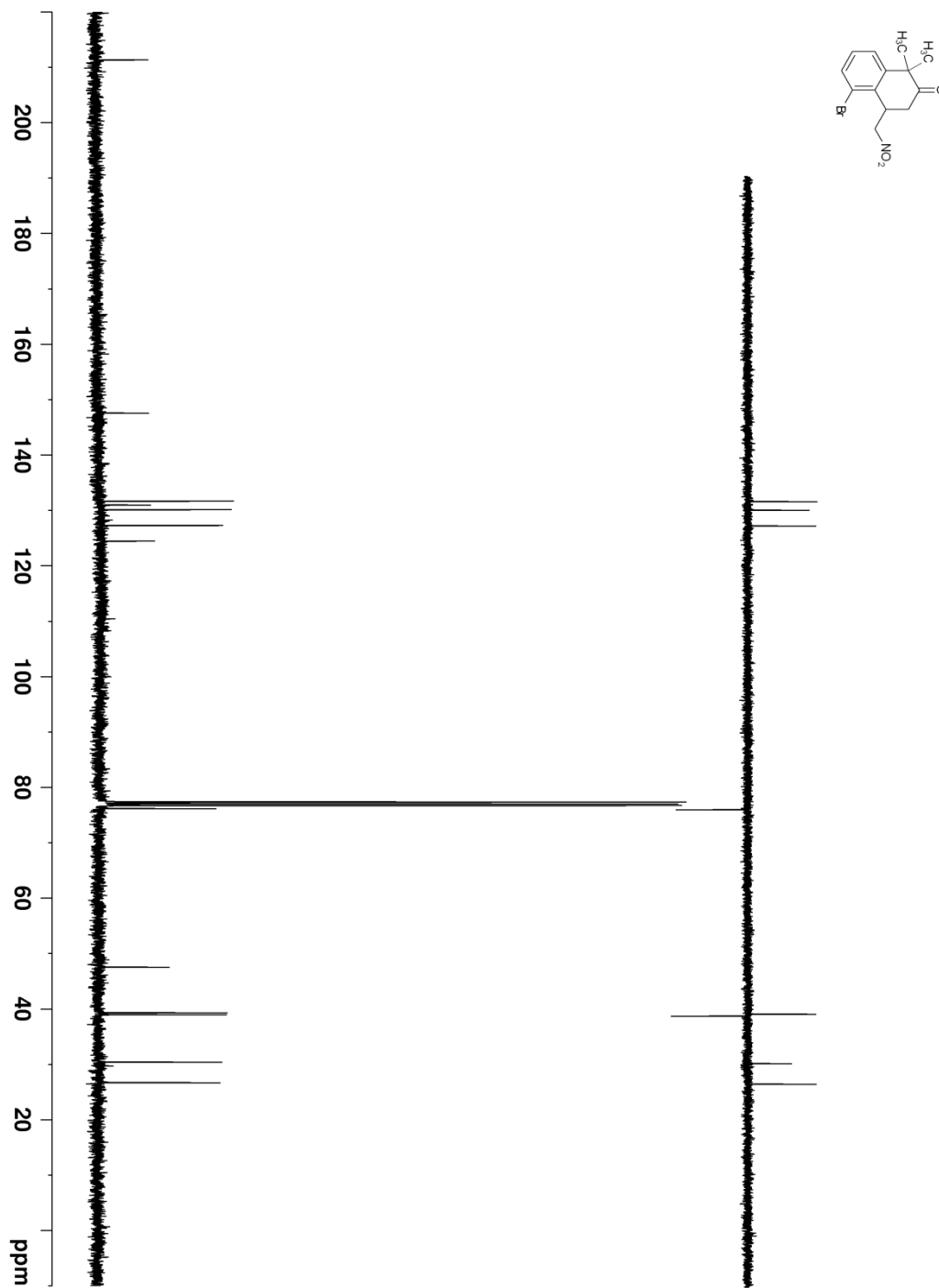


Figure 85. ^1H NMR Spectrum (600 MHz, CDCl_3) of 491

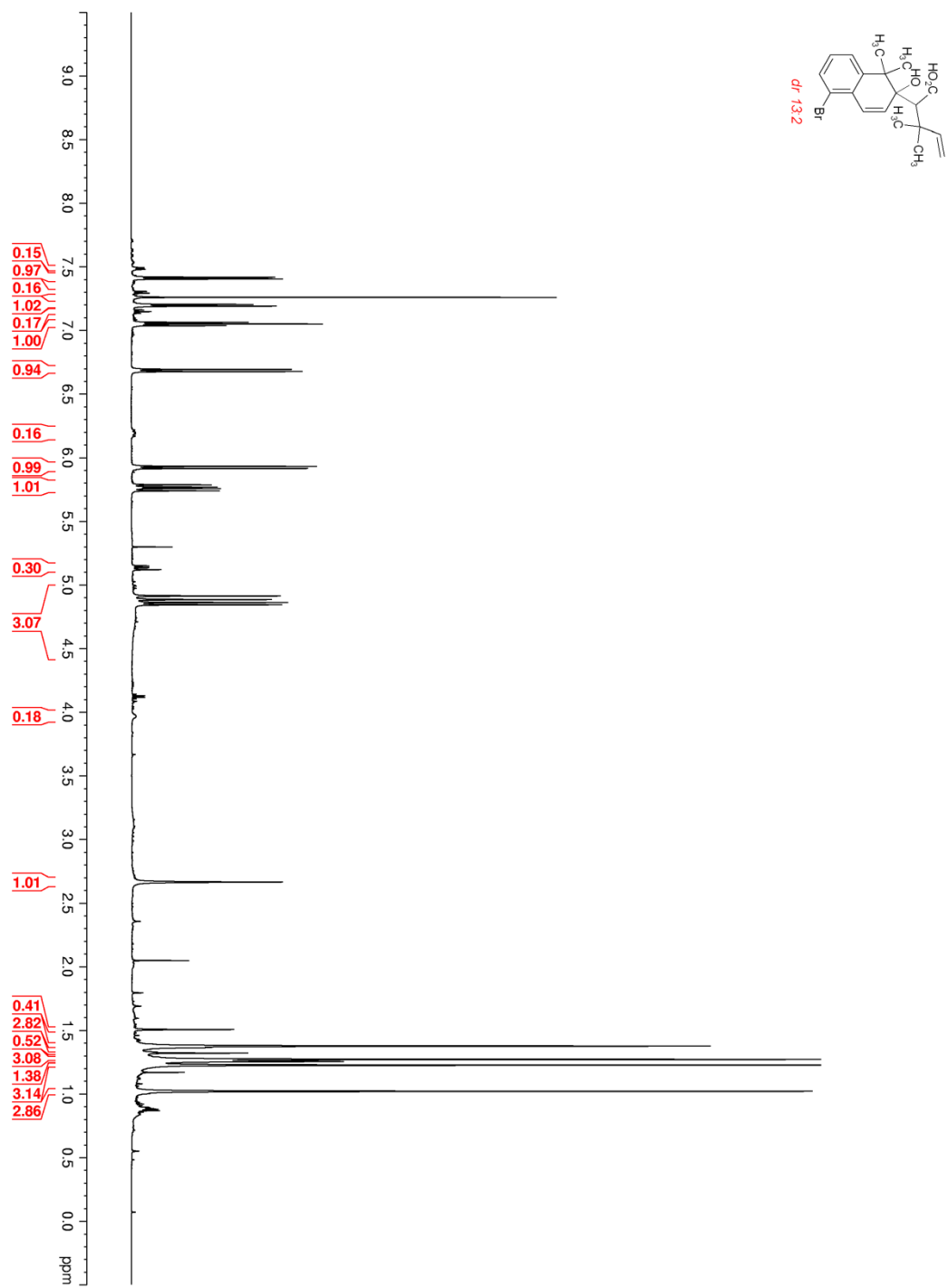


Figure 86. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 491

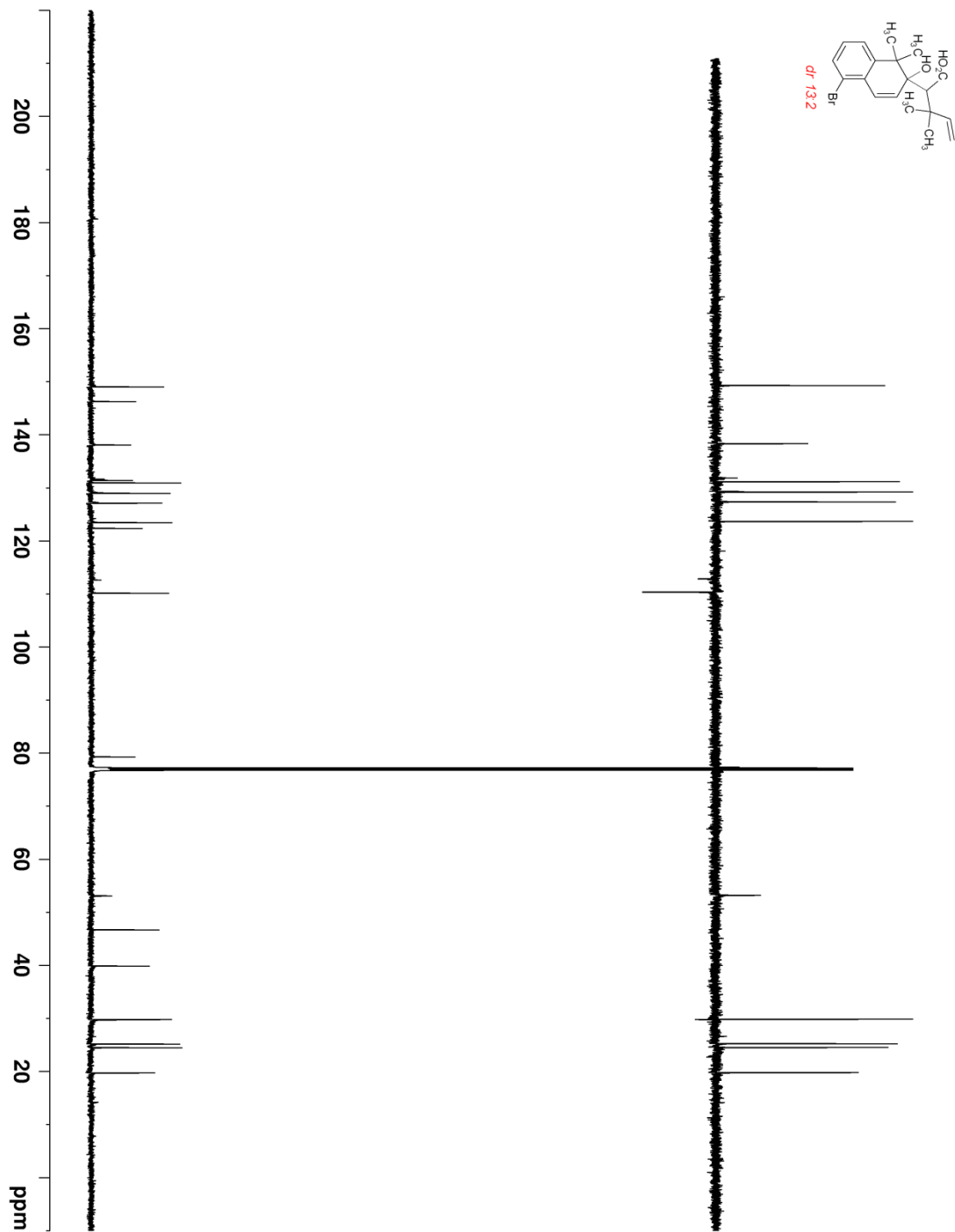


Figure 87. ^1H NMR Spectrum (600 MHz, CDCl_3) of 505

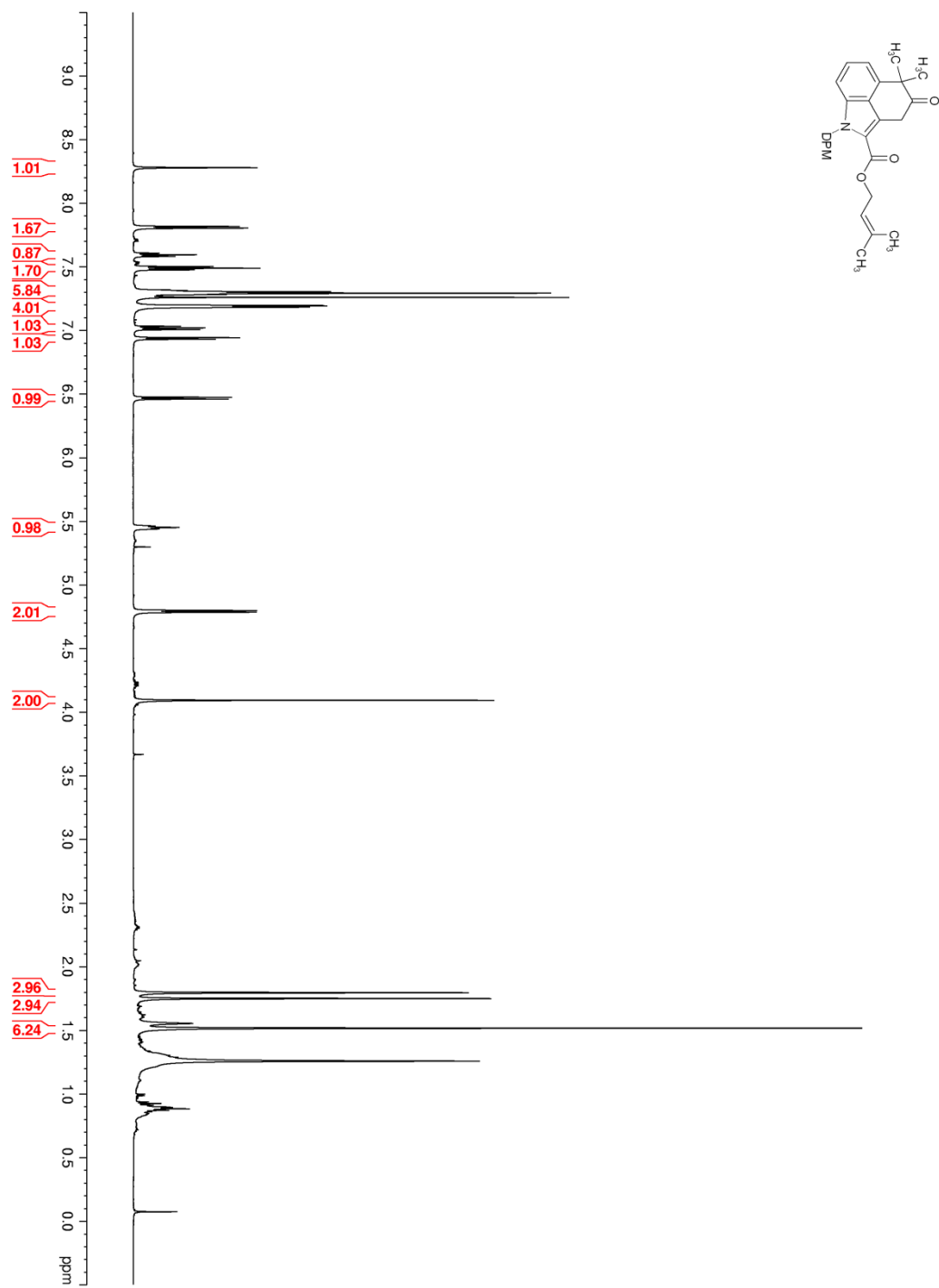


Figure 88. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 505

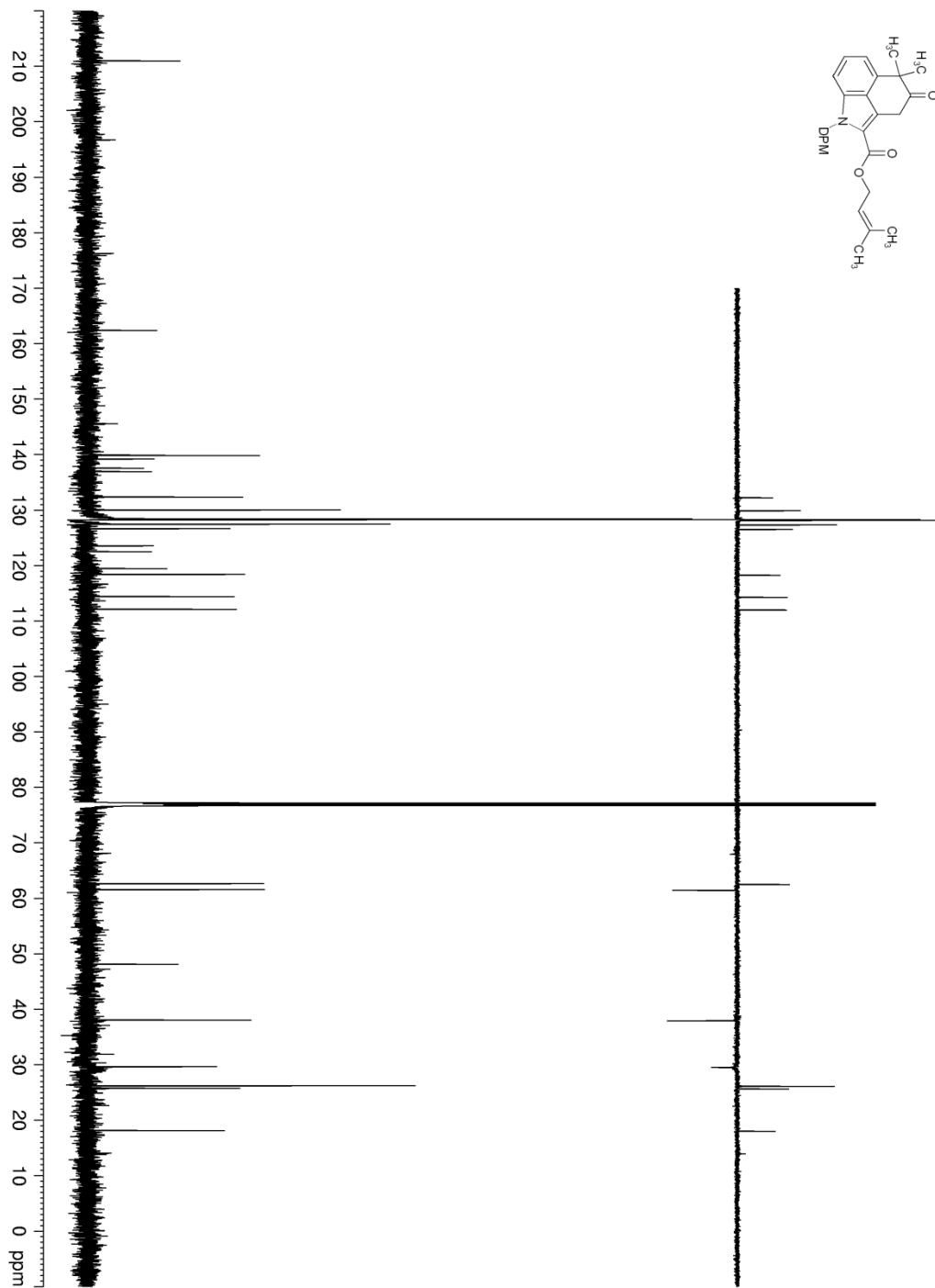


Figure 89. ¹H NMR Spectrum (600 MHz, CDCl₃) of 508

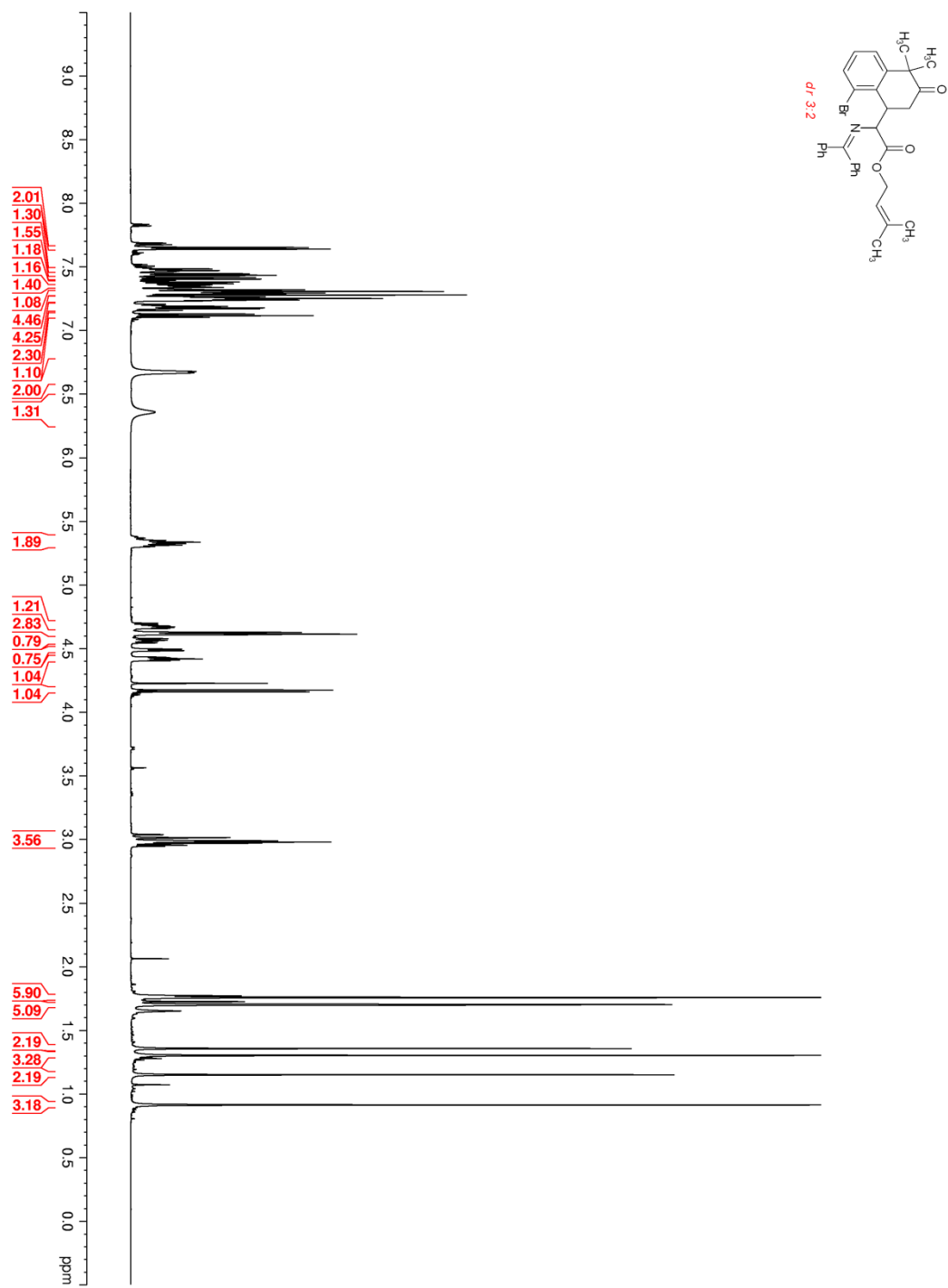


Figure 90. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 508

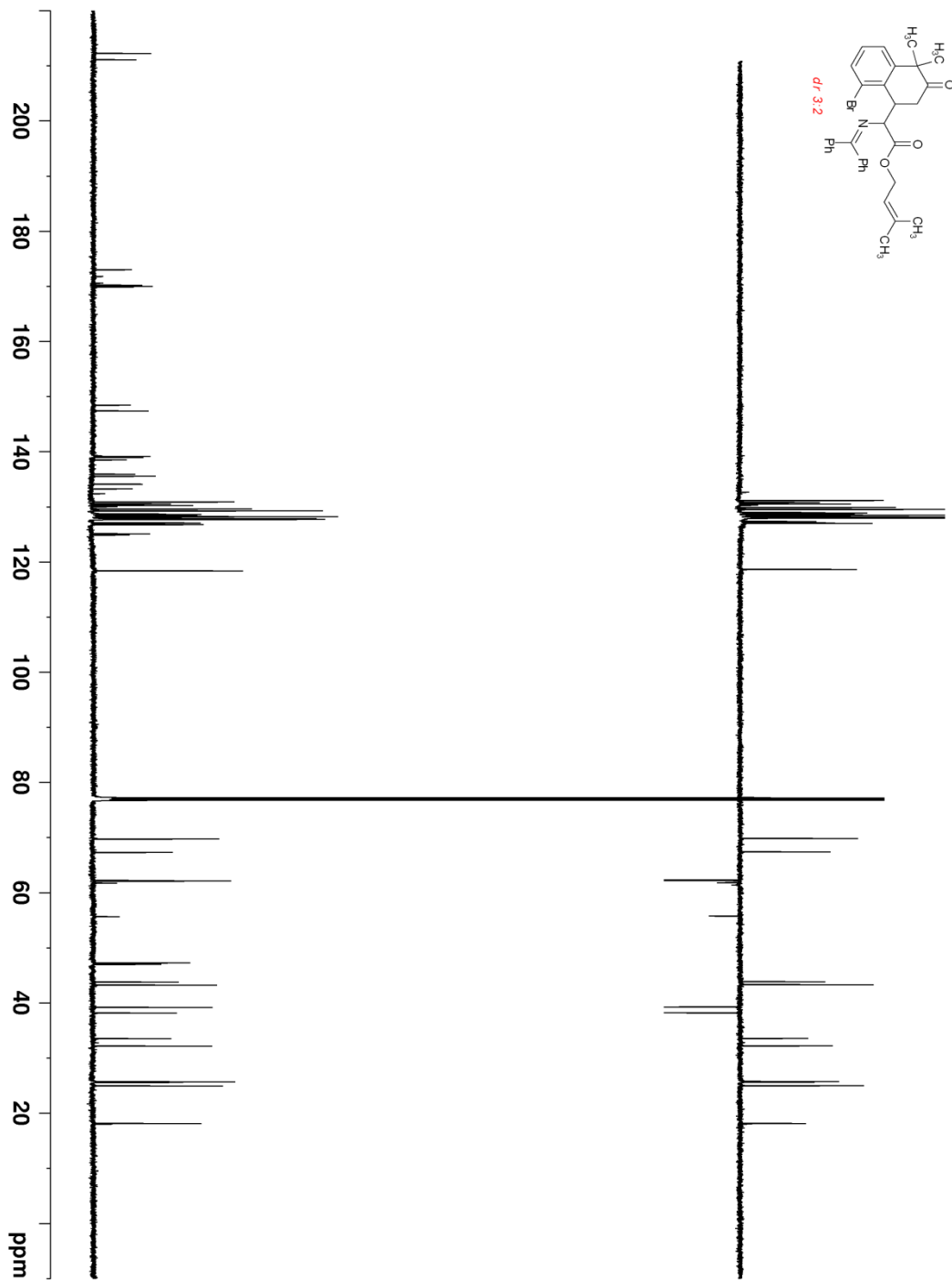


Figure 91. ¹H NMR Spectrum (600 MHz, CDCl₃) of 509

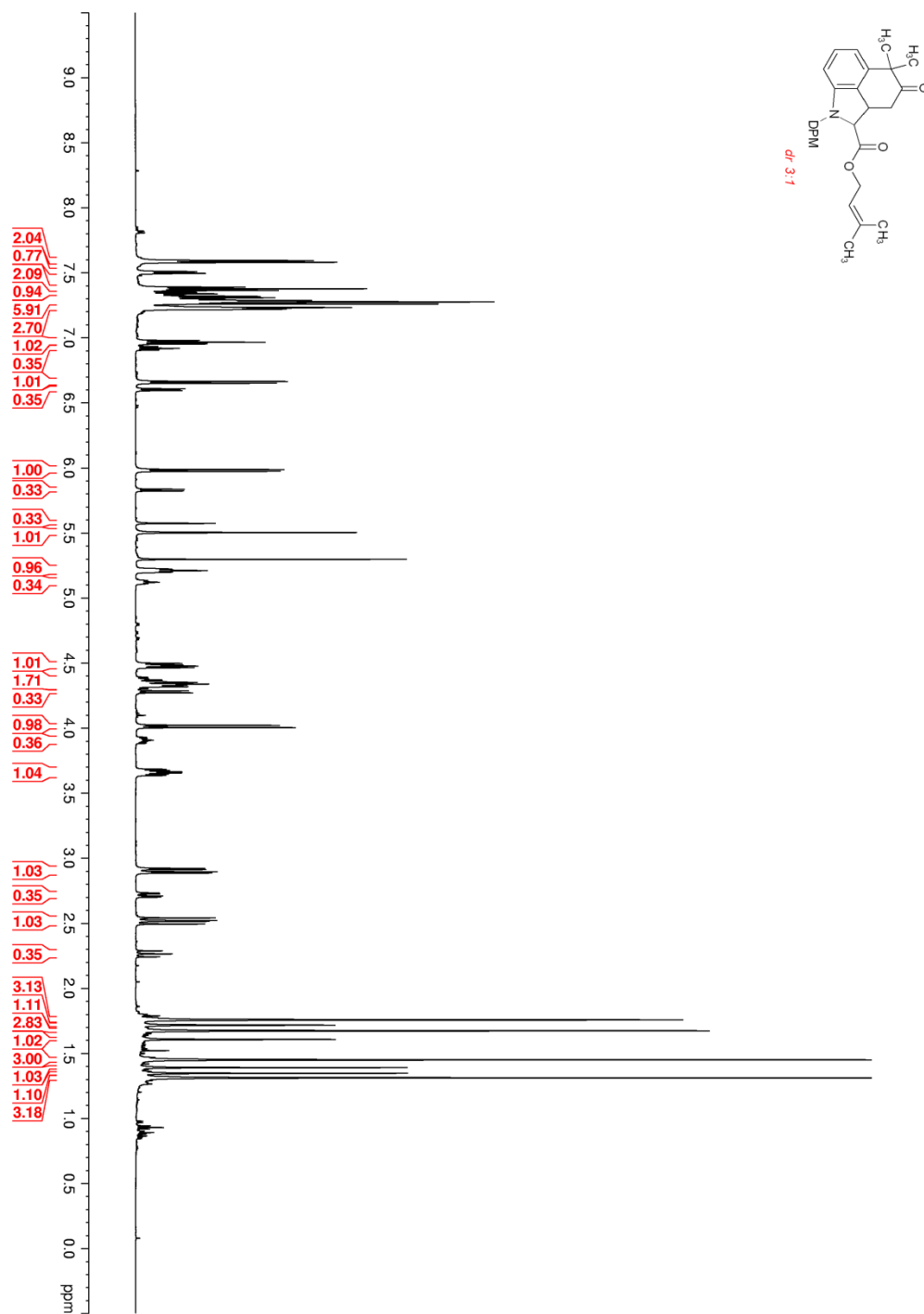


Figure 92. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 509

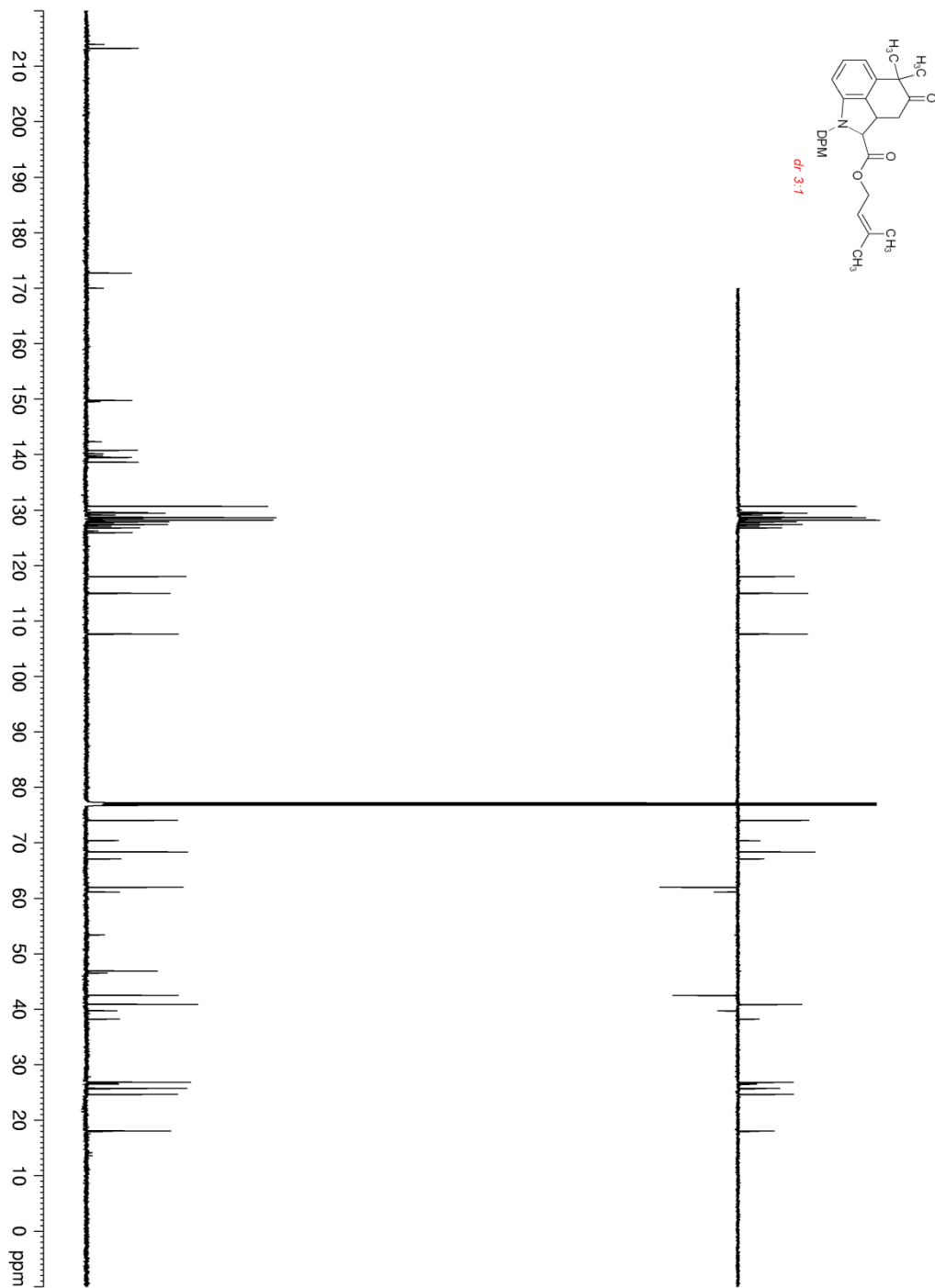


Figure 93. ^1H NMR Spectrum (400 MHz, CDCl_3) of 520

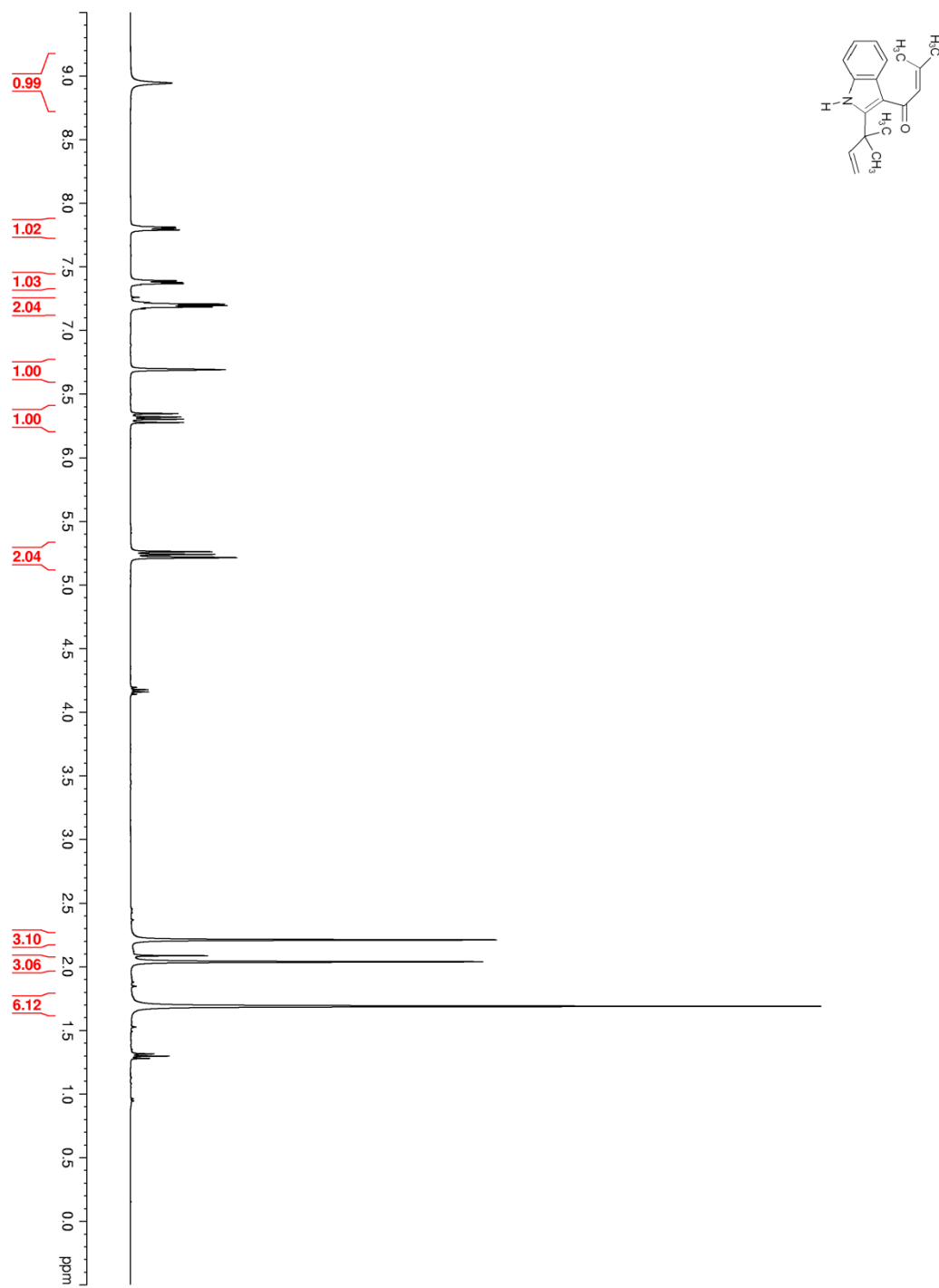


Figure 94. ^{13}C NMR Spectrum (100 MHz, CDCl_3) of 520

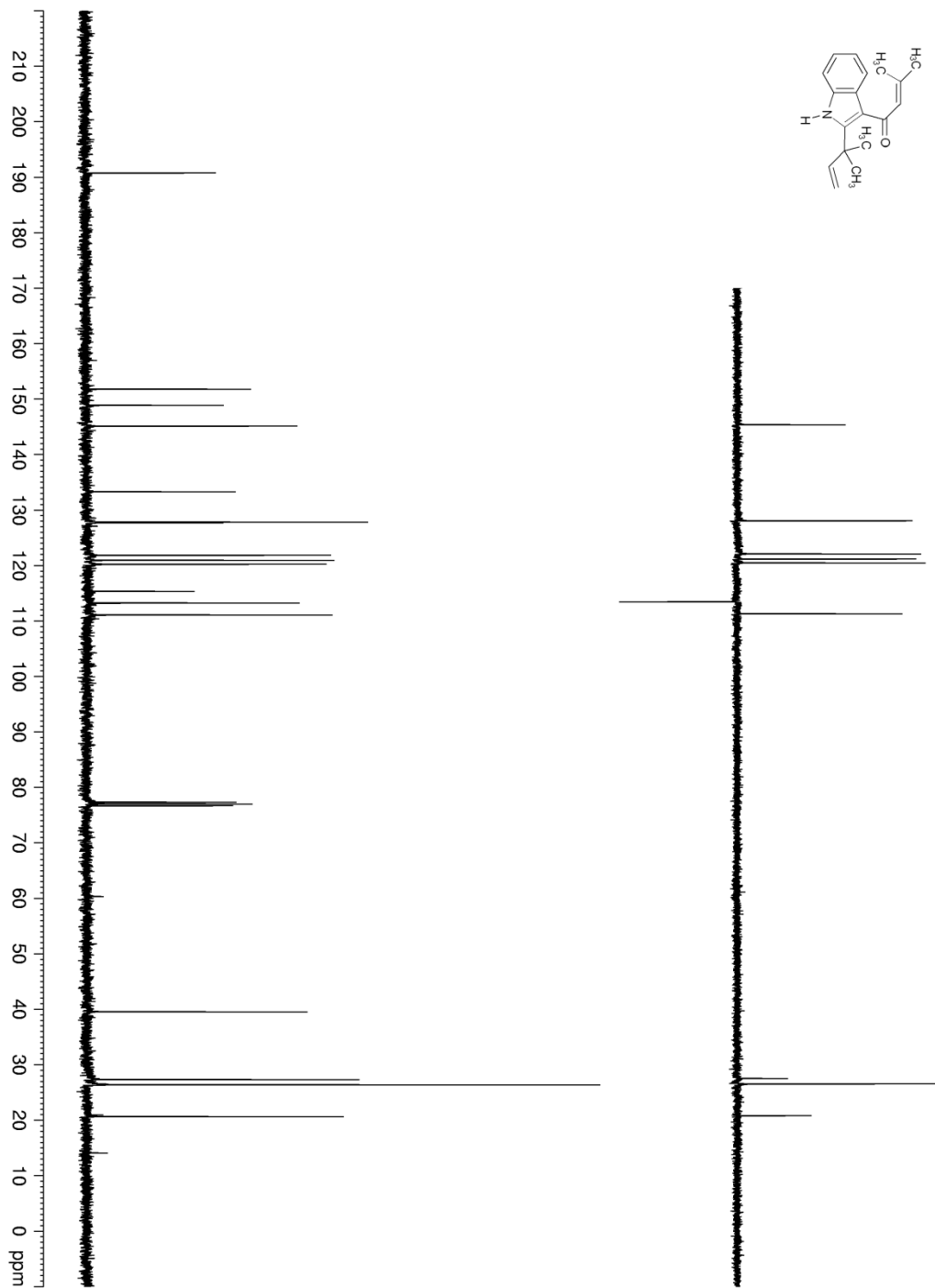


Figure 95. ^1H NMR Spectrum (600 MHz, CDCl_3) of 530

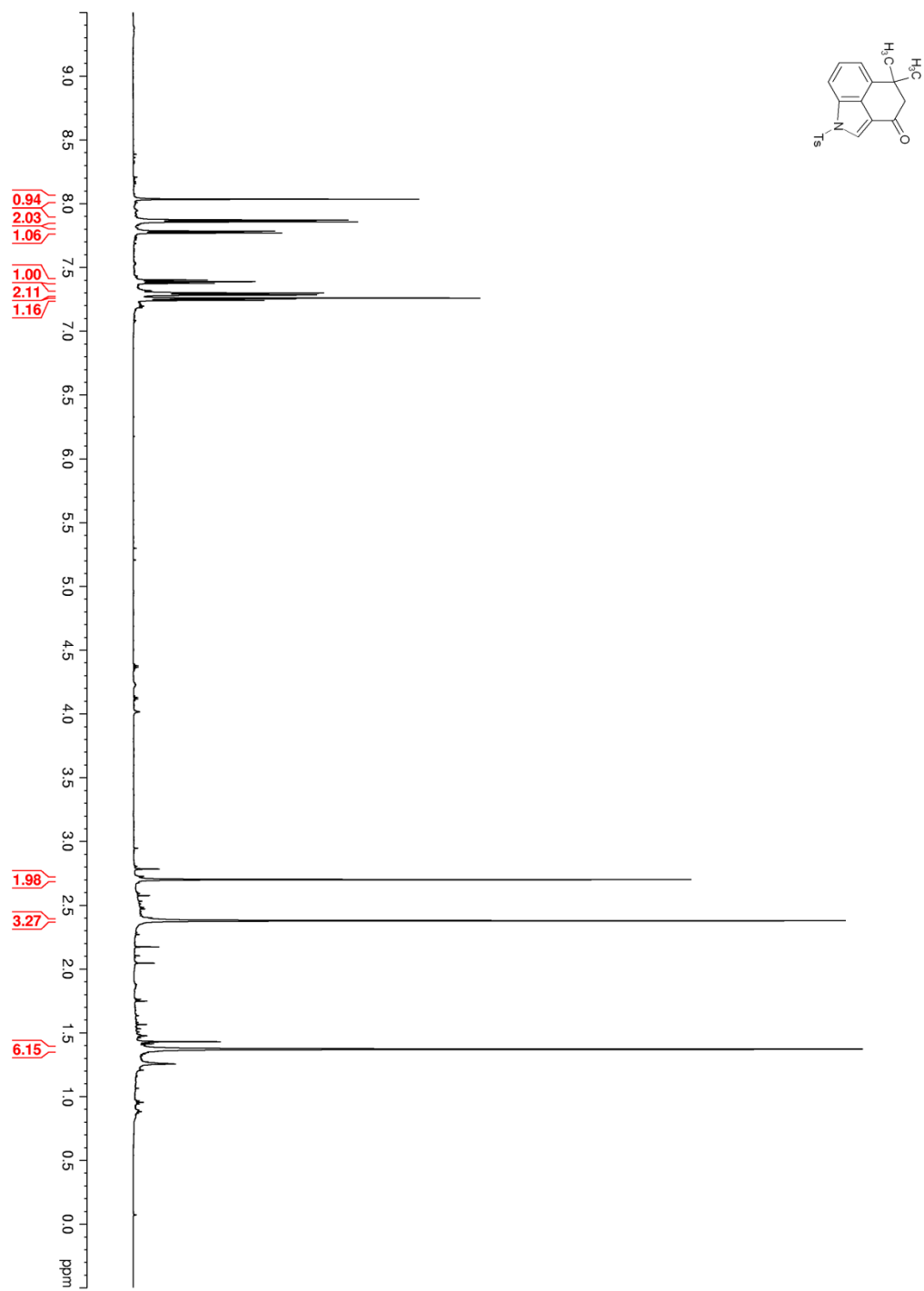


Figure 96. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 530

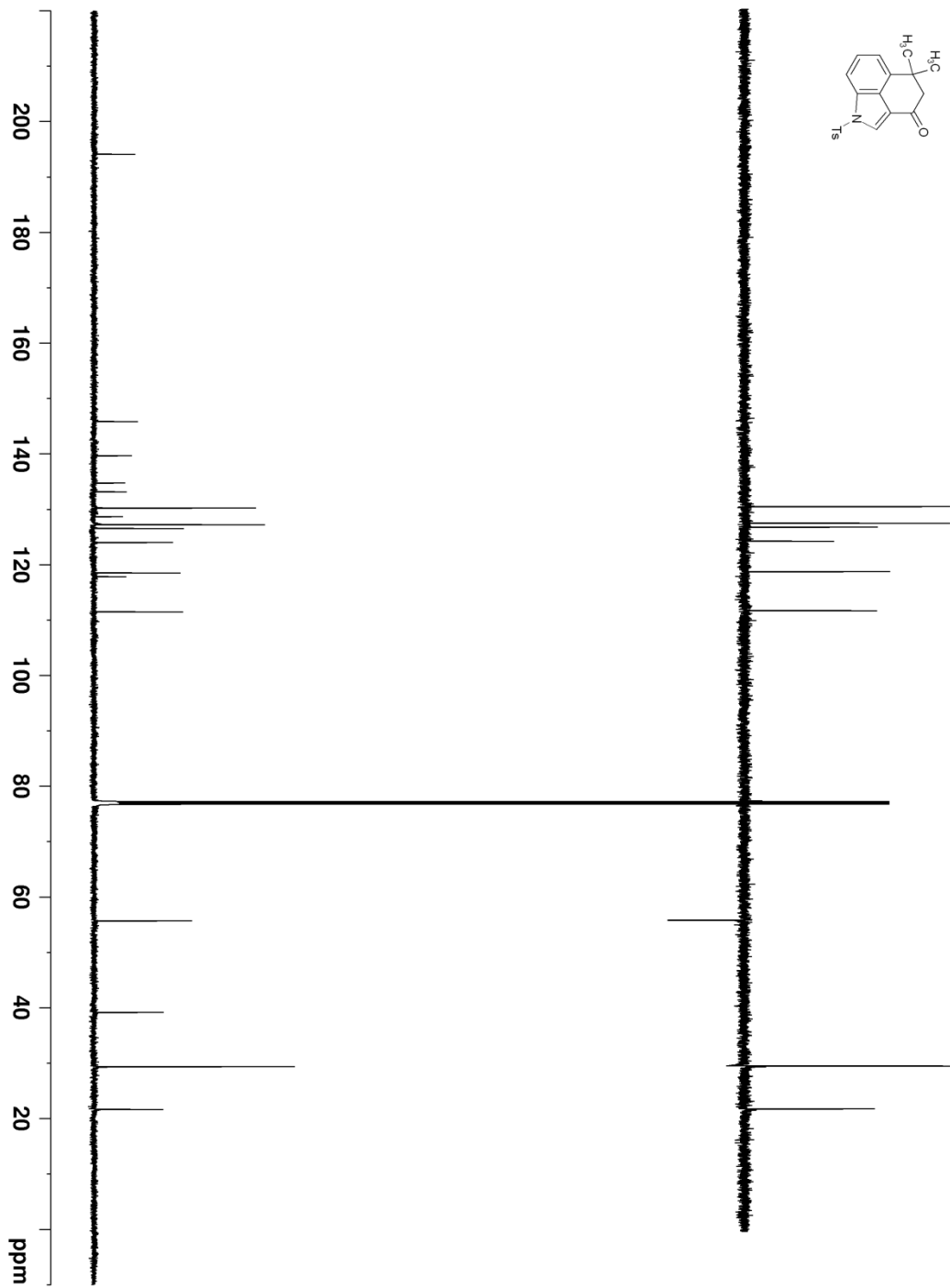


Figure 97. ^1H NMR Spectrum (500 MHz, CDCl_3) of 532

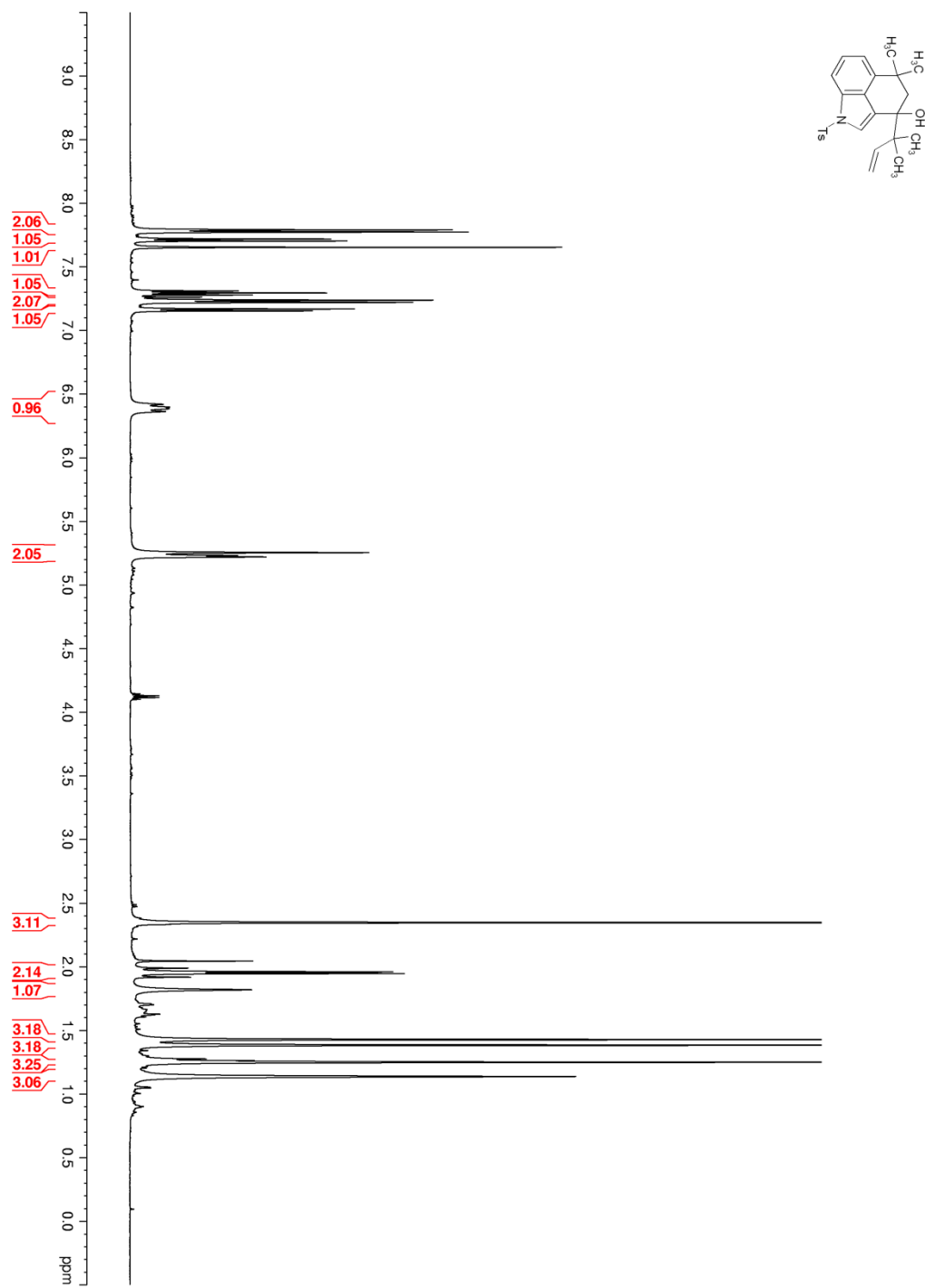


Figure 98. ^{13}C NMR Spectrum (125 MHz, CDCl_3) of 532

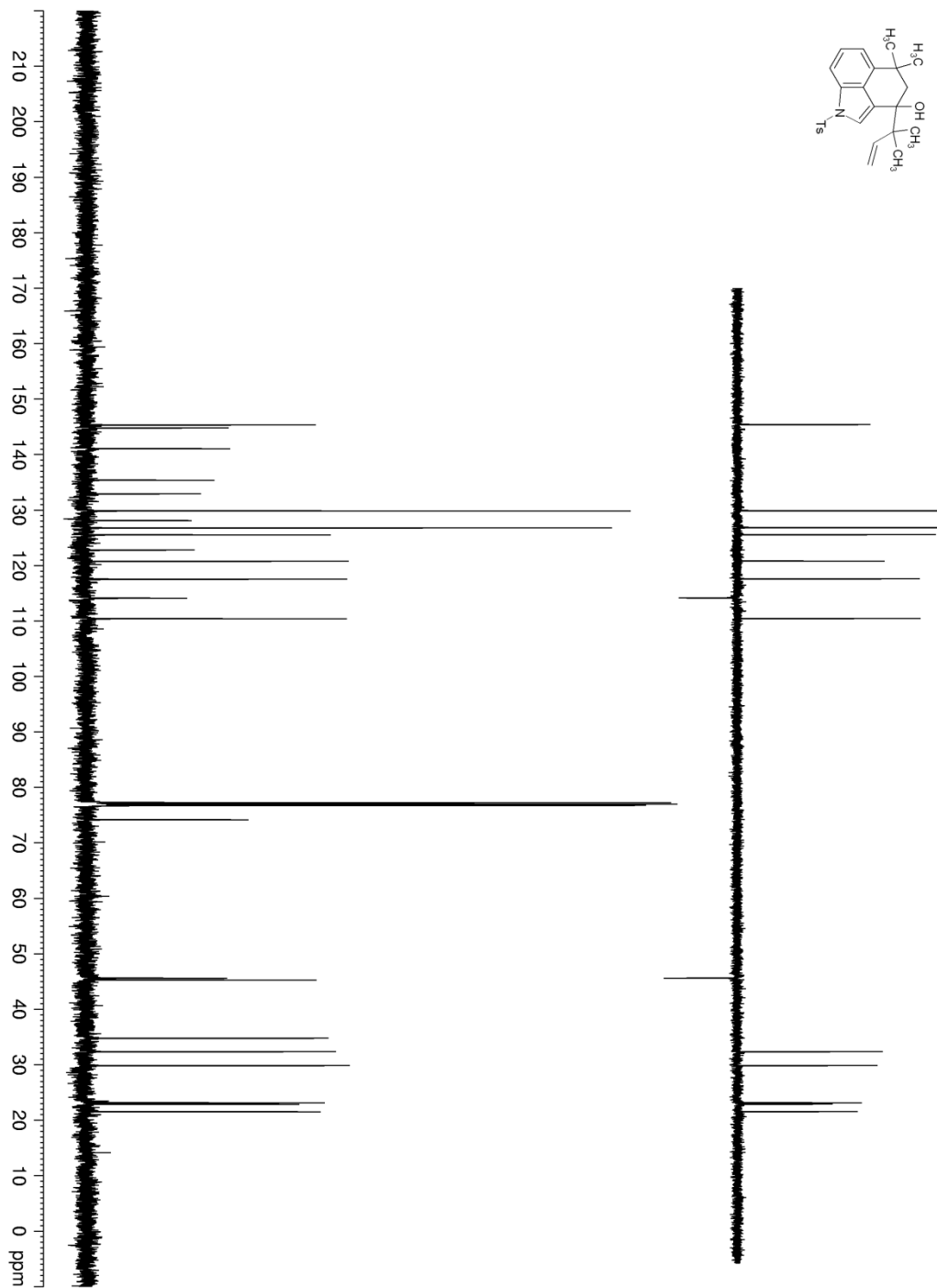


Figure 99. ¹H NMR Spectrum (500 MHz, CDCl₃) of 534

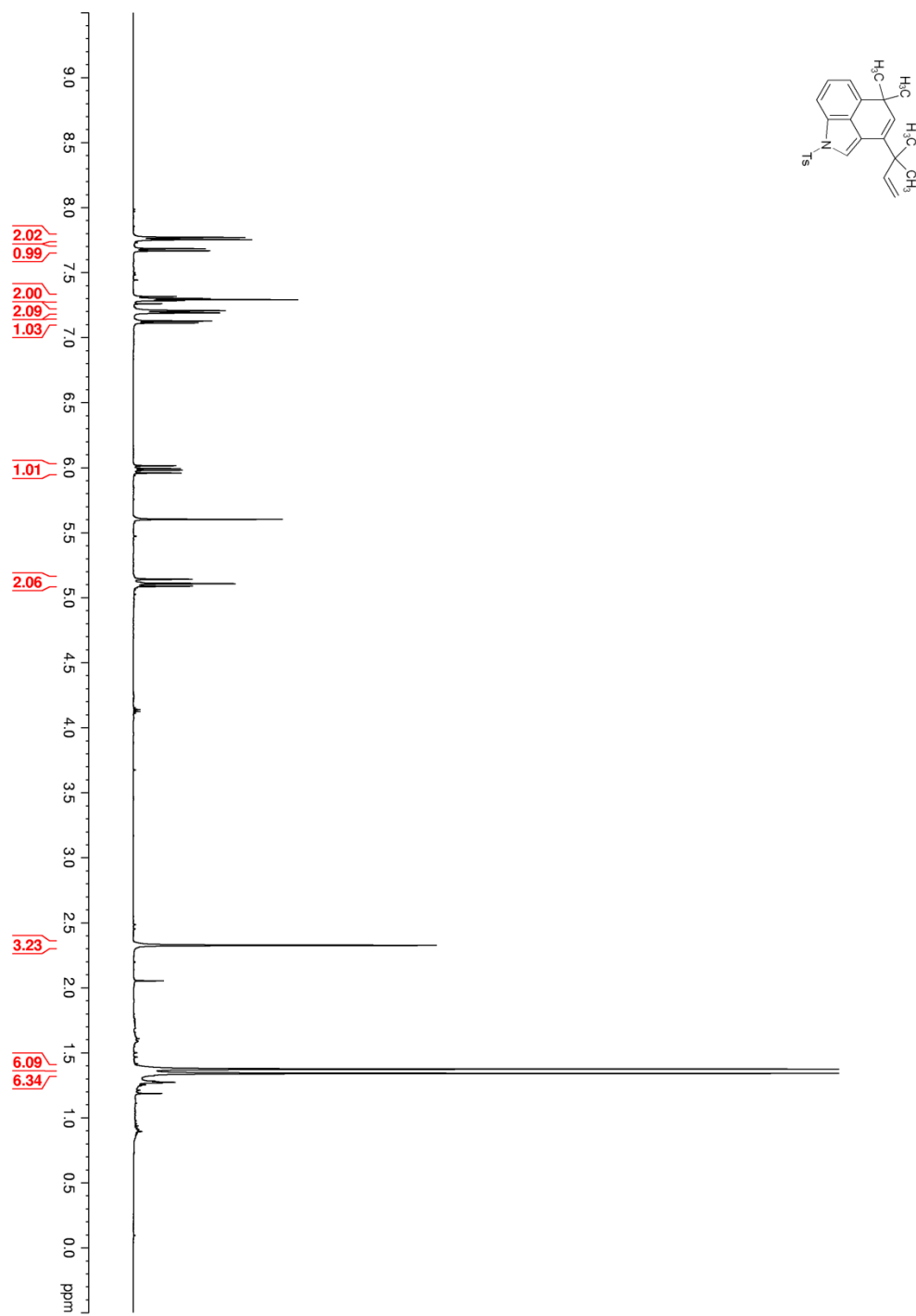


Figure 100. ^{13}C NMR Spectrum (125 MHz, CDCl_3) of 534

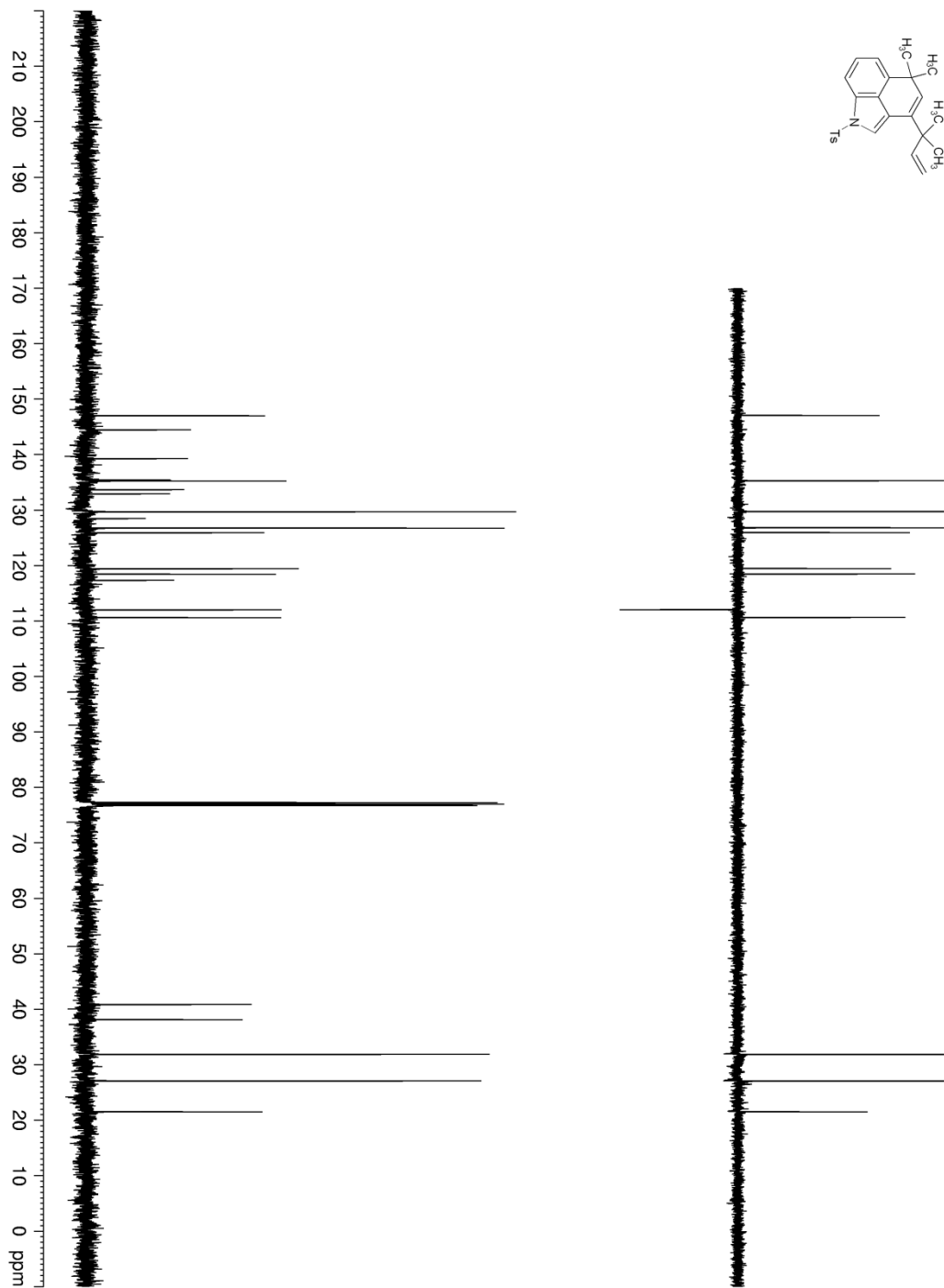


Figure 101. ^1H NMR Spectrum (400 MHz, CDCl_3) of 535

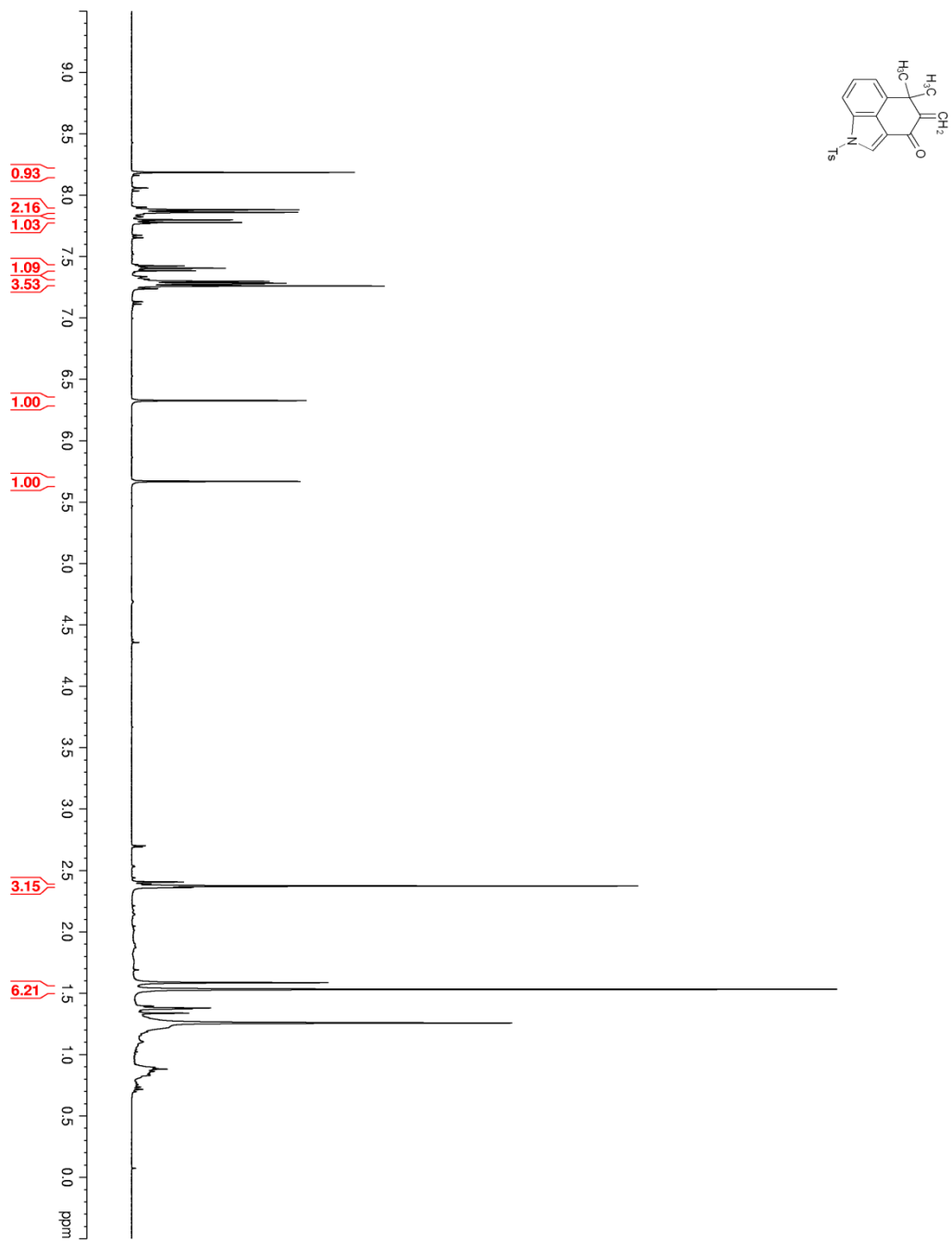


Figure 102. ^{13}C NMR Spectrum (125 MHz, CDCl_3) of 534

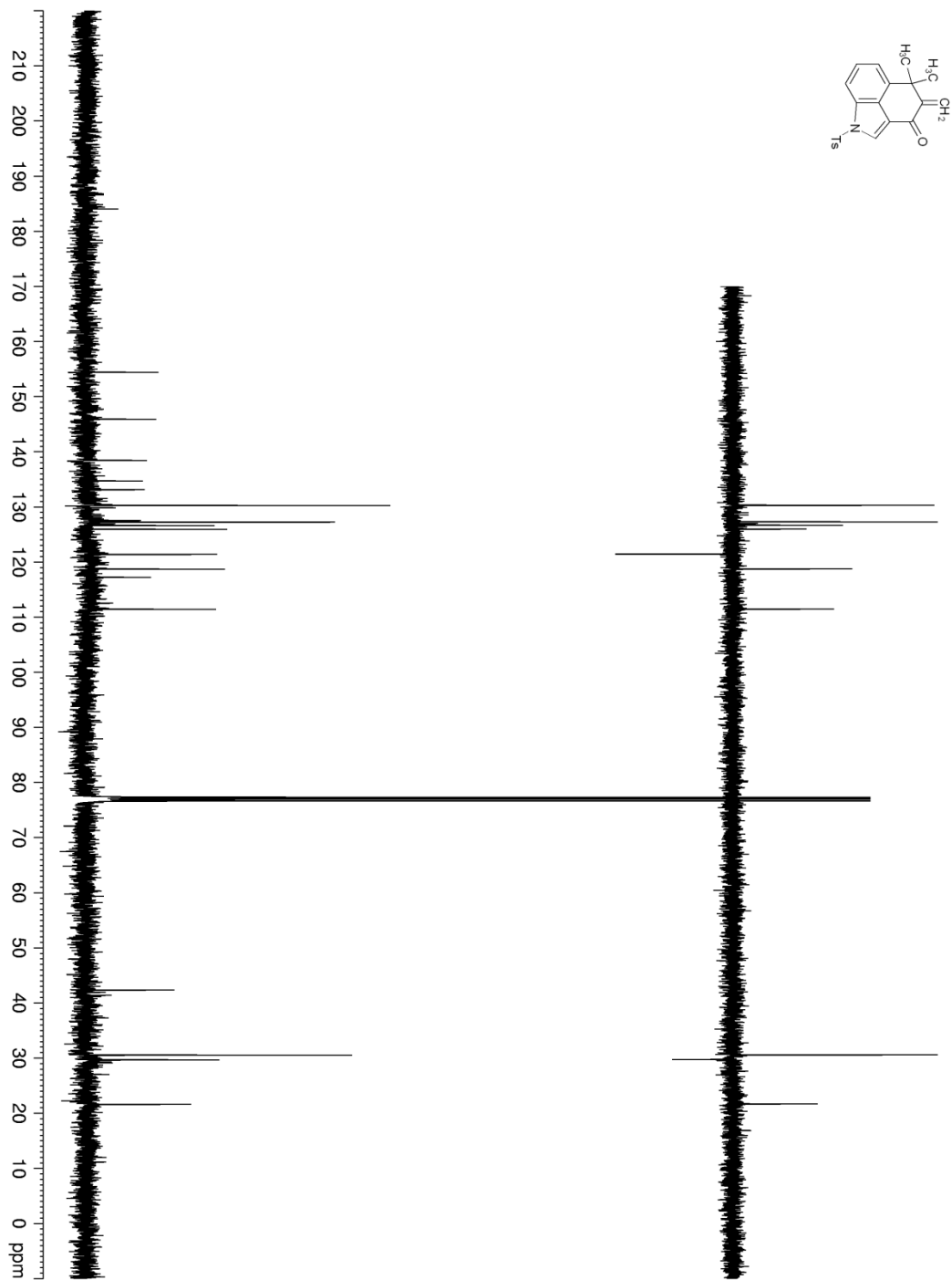


Figure 103. ^1H NMR Spectrum (500 MHz, CDCl_3) of 539

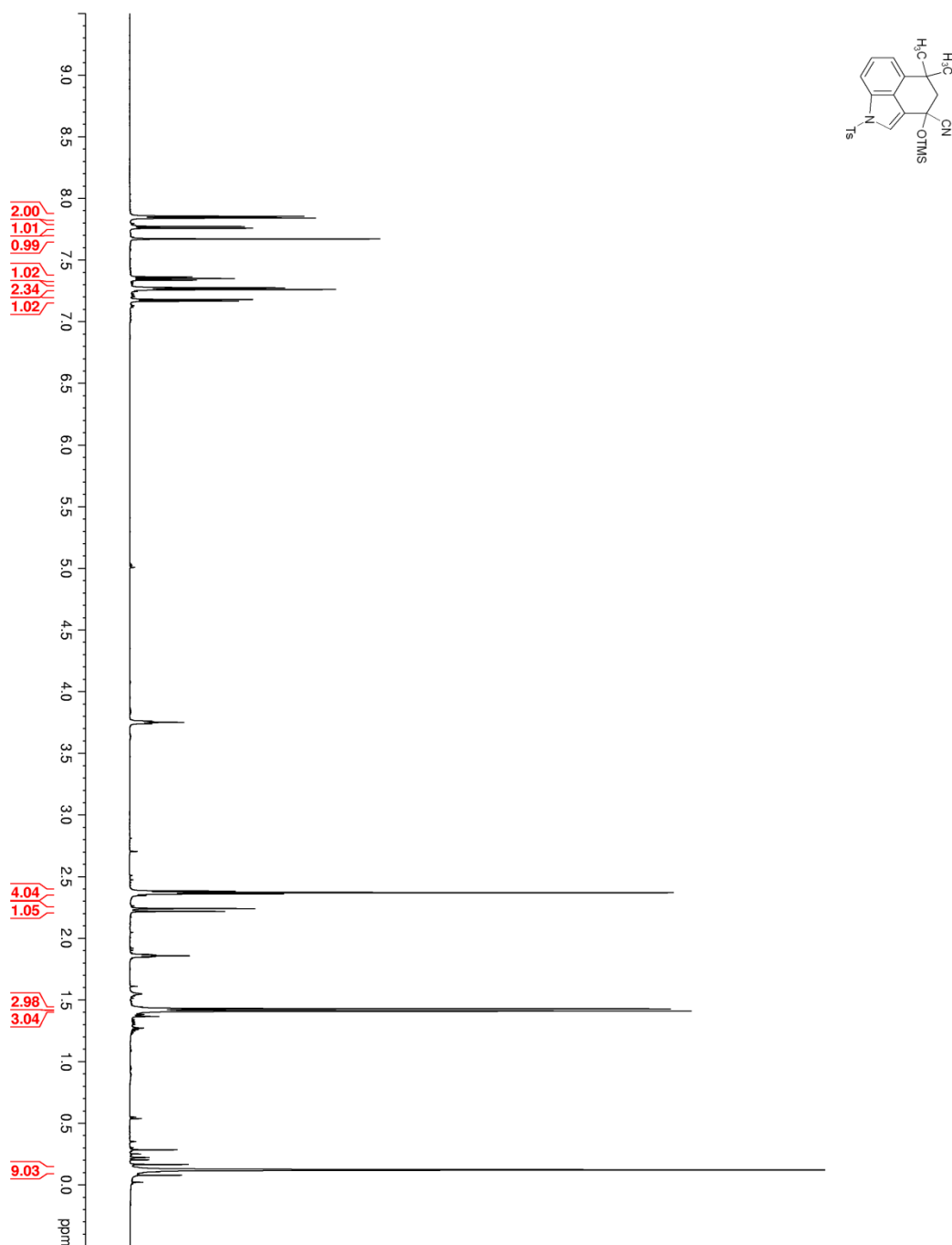


Figure 42. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 21

Figure 104. ^{13}C NMR Spectrum (100 MHz, CDCl_3) of 539

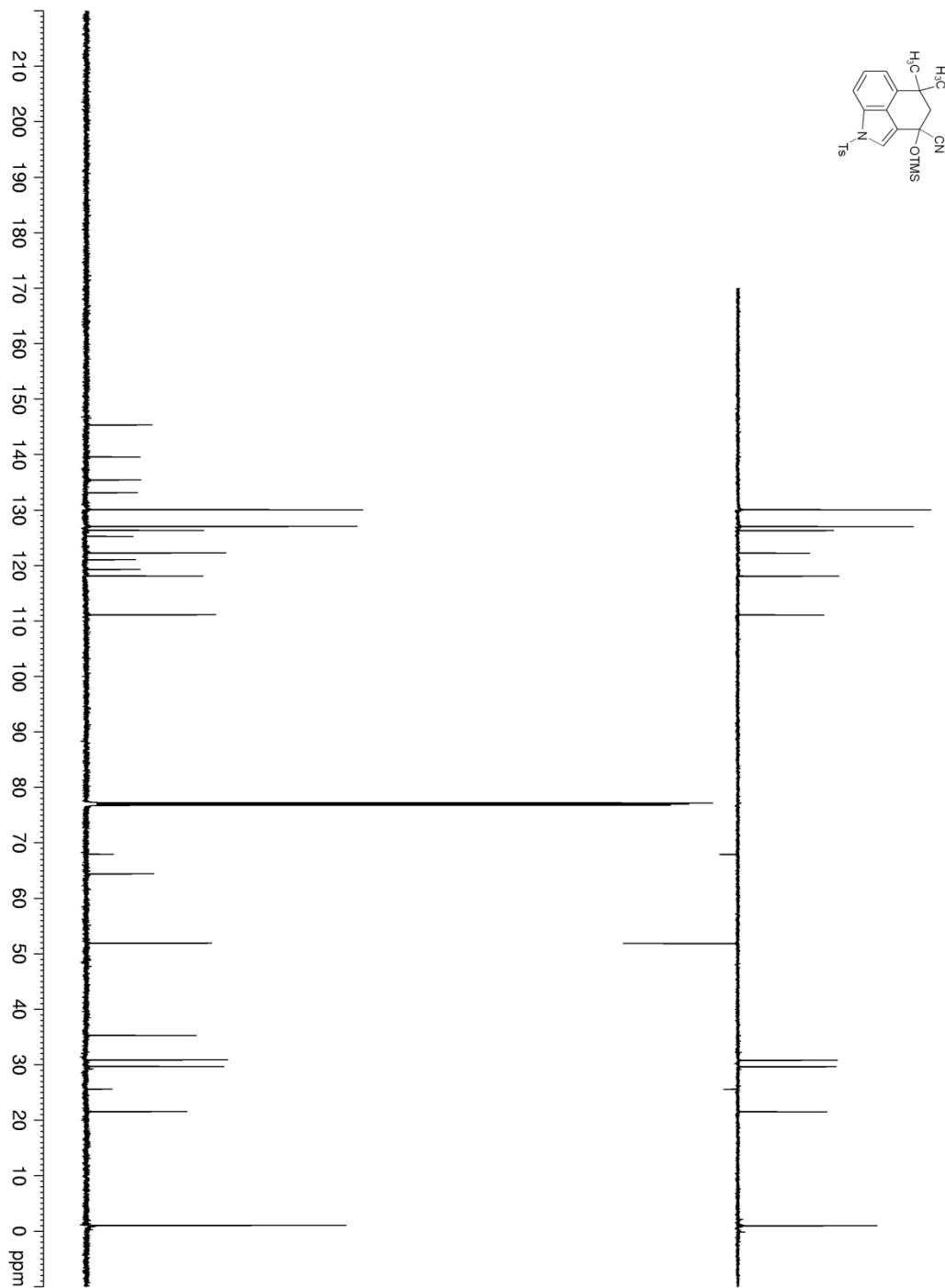


Figure 105. ^1H NMR Spectrum (400 MHz, CDCl_3) of 540

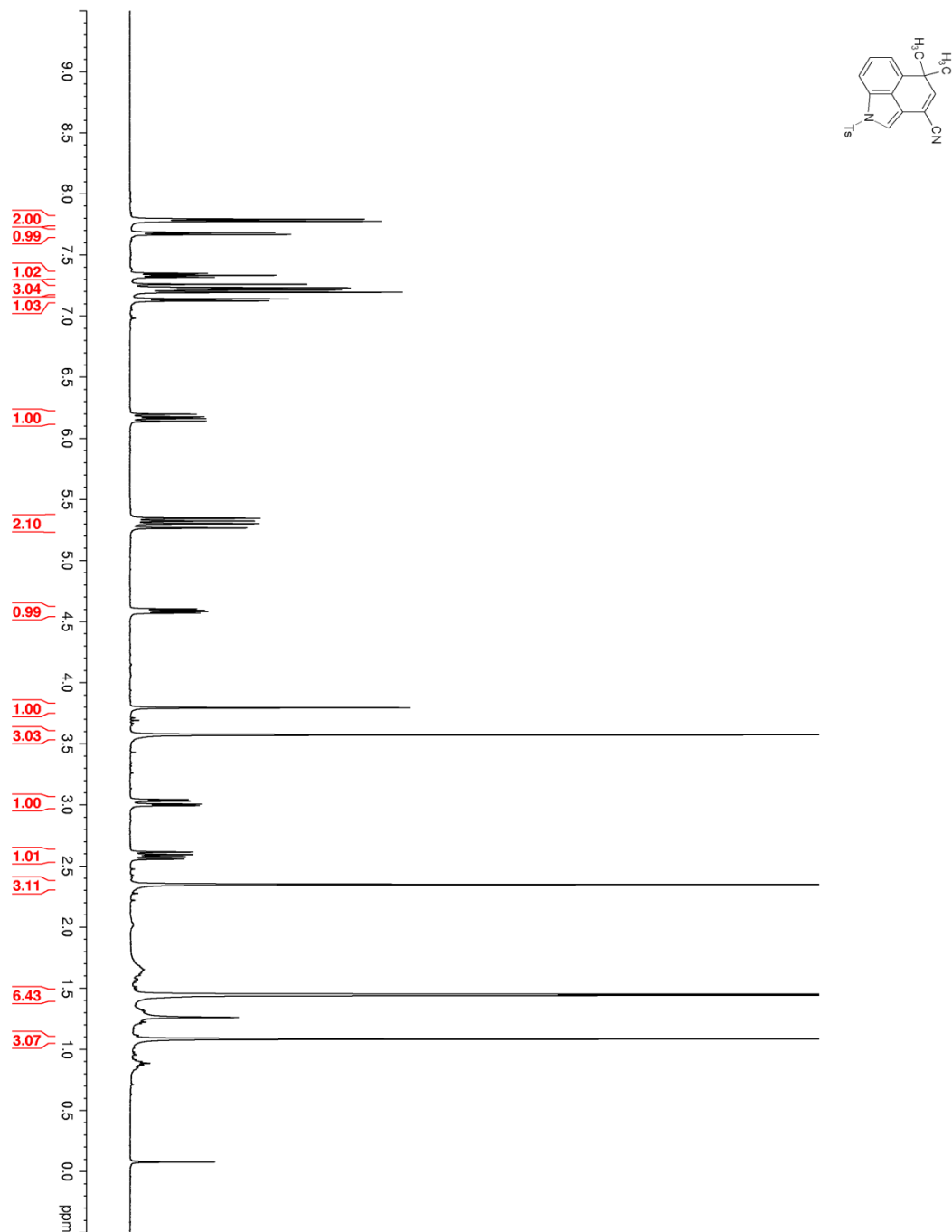


Figure 106. ^{13}C NMR Spectrum (100 MHz, CDCl_3) of 540

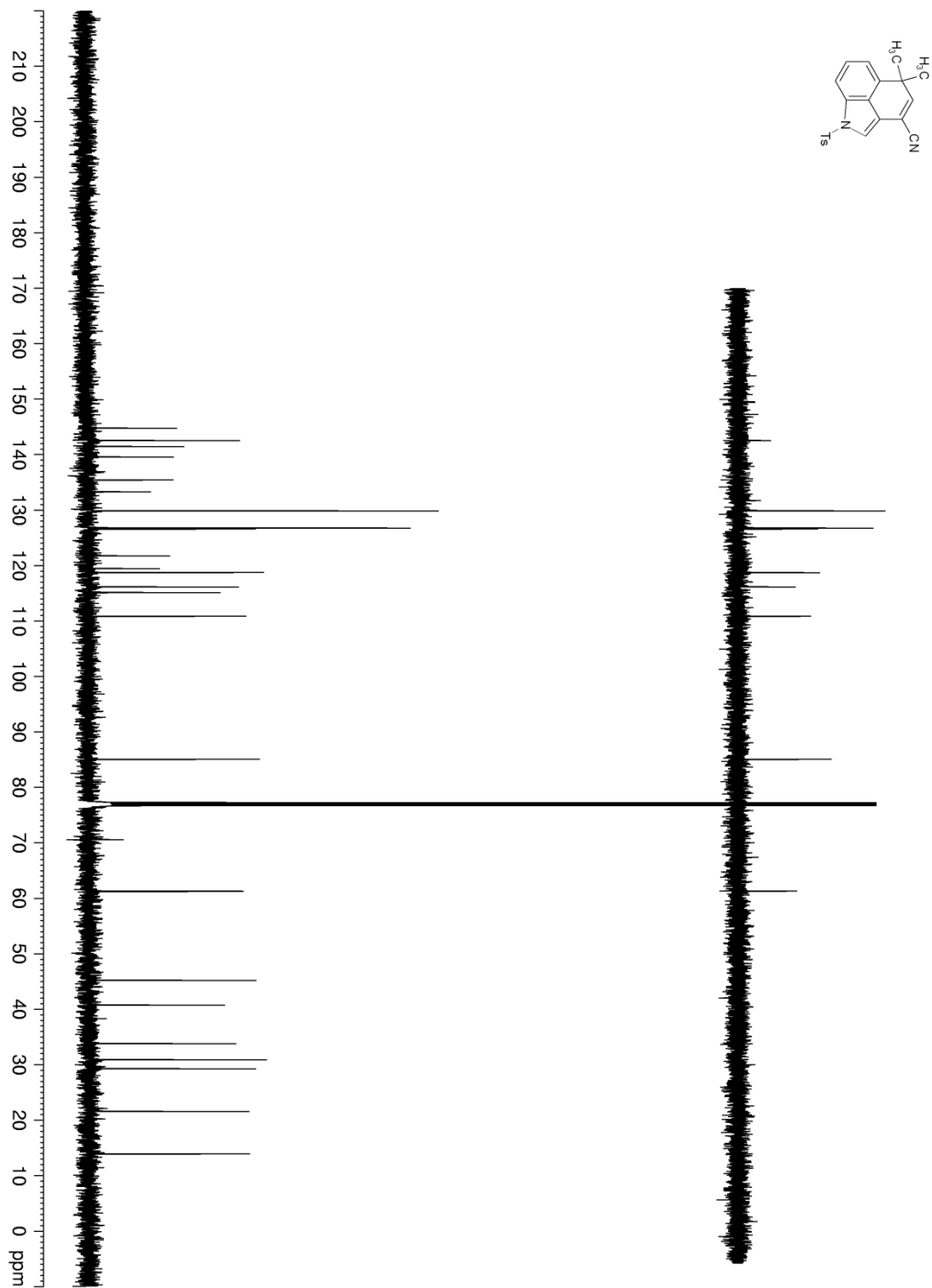


Figure 107. ^1H NMR Spectrum (500 MHz, CDCl_3) of 514

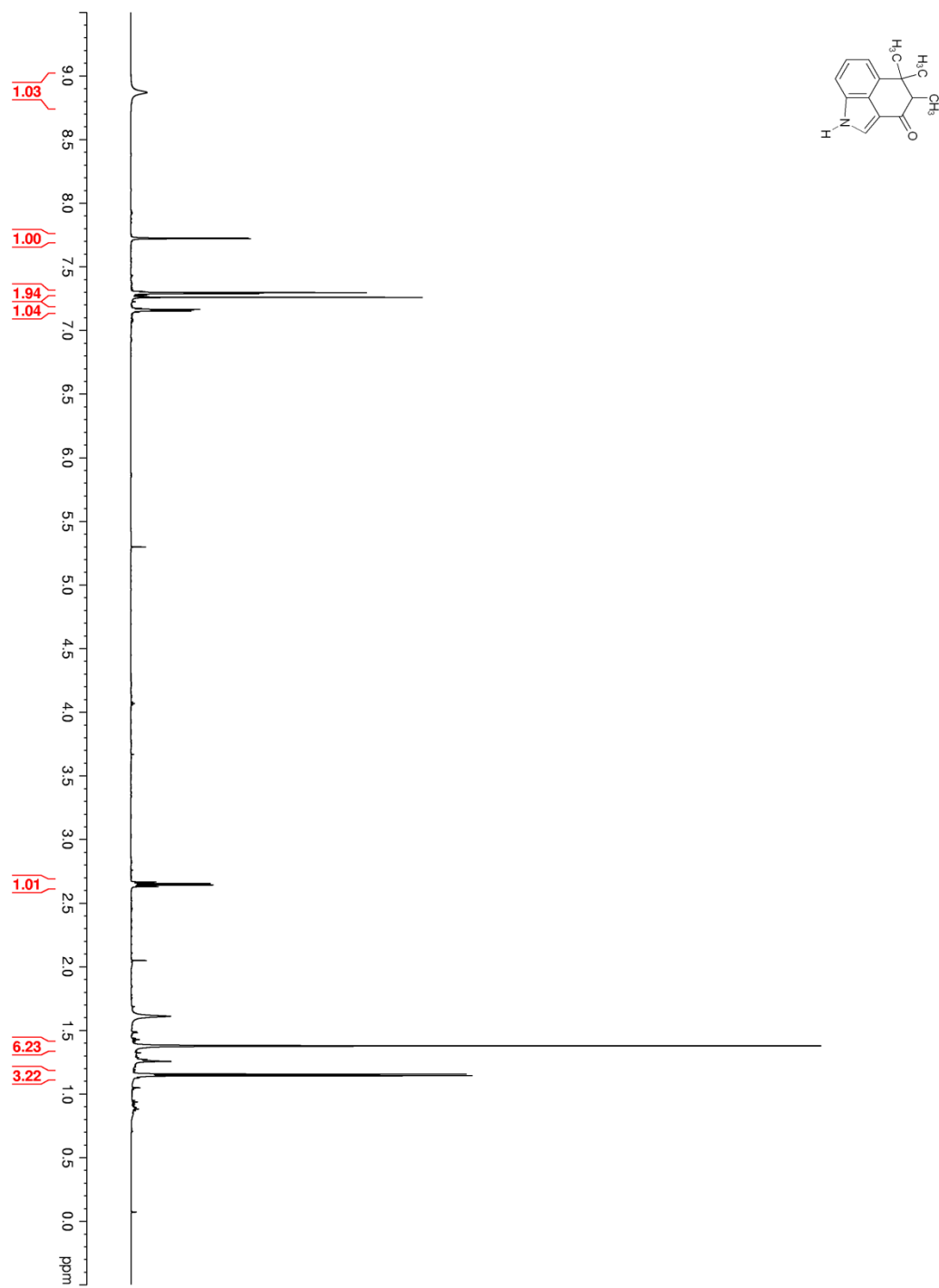


Figure 108. ^{13}C NMR Spectrum (125 MHz, CDCl_3) of 514

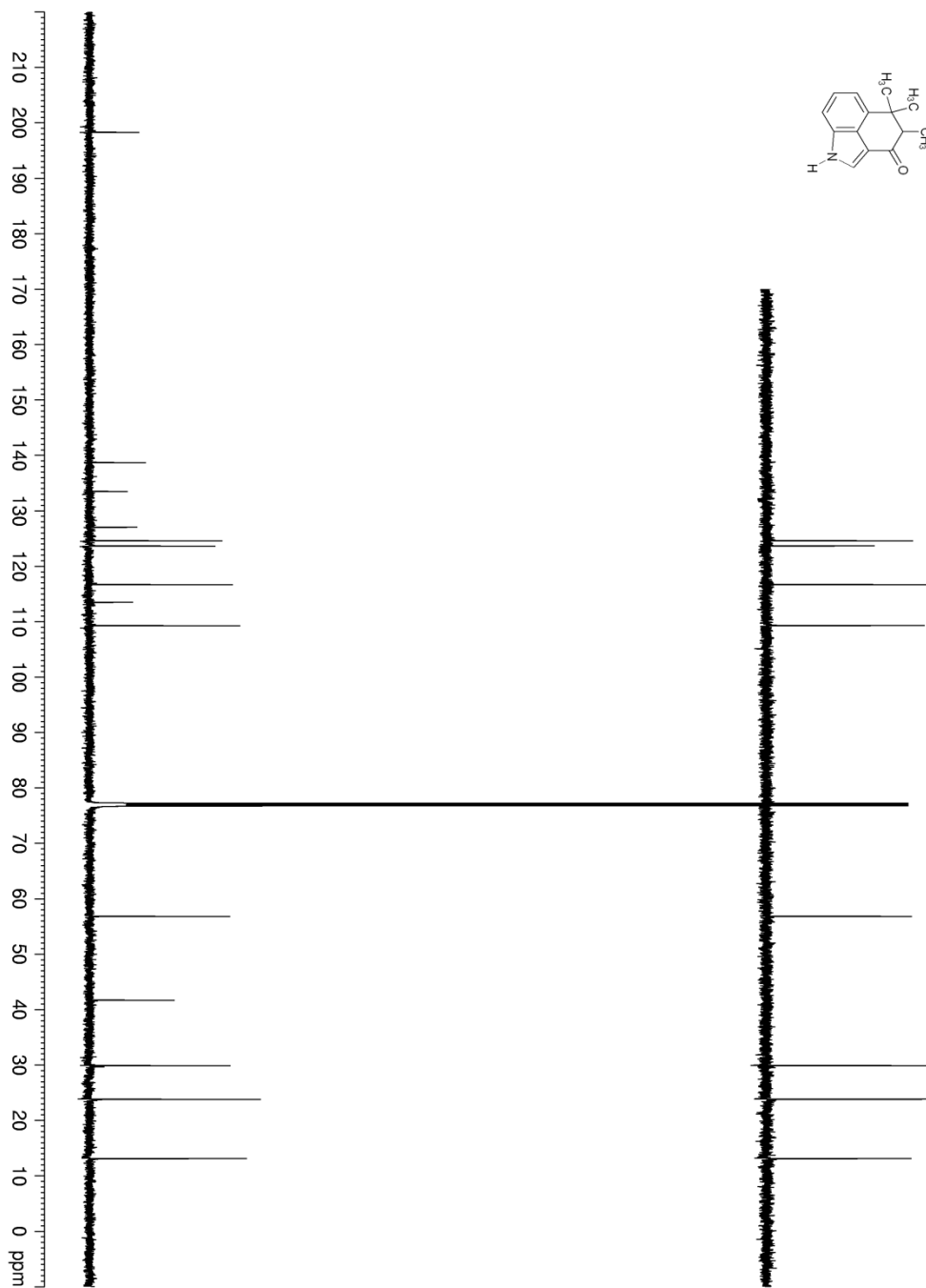


Figure 109. ¹H NMR Spectrum (400 MHz, CDCl₃) of 546

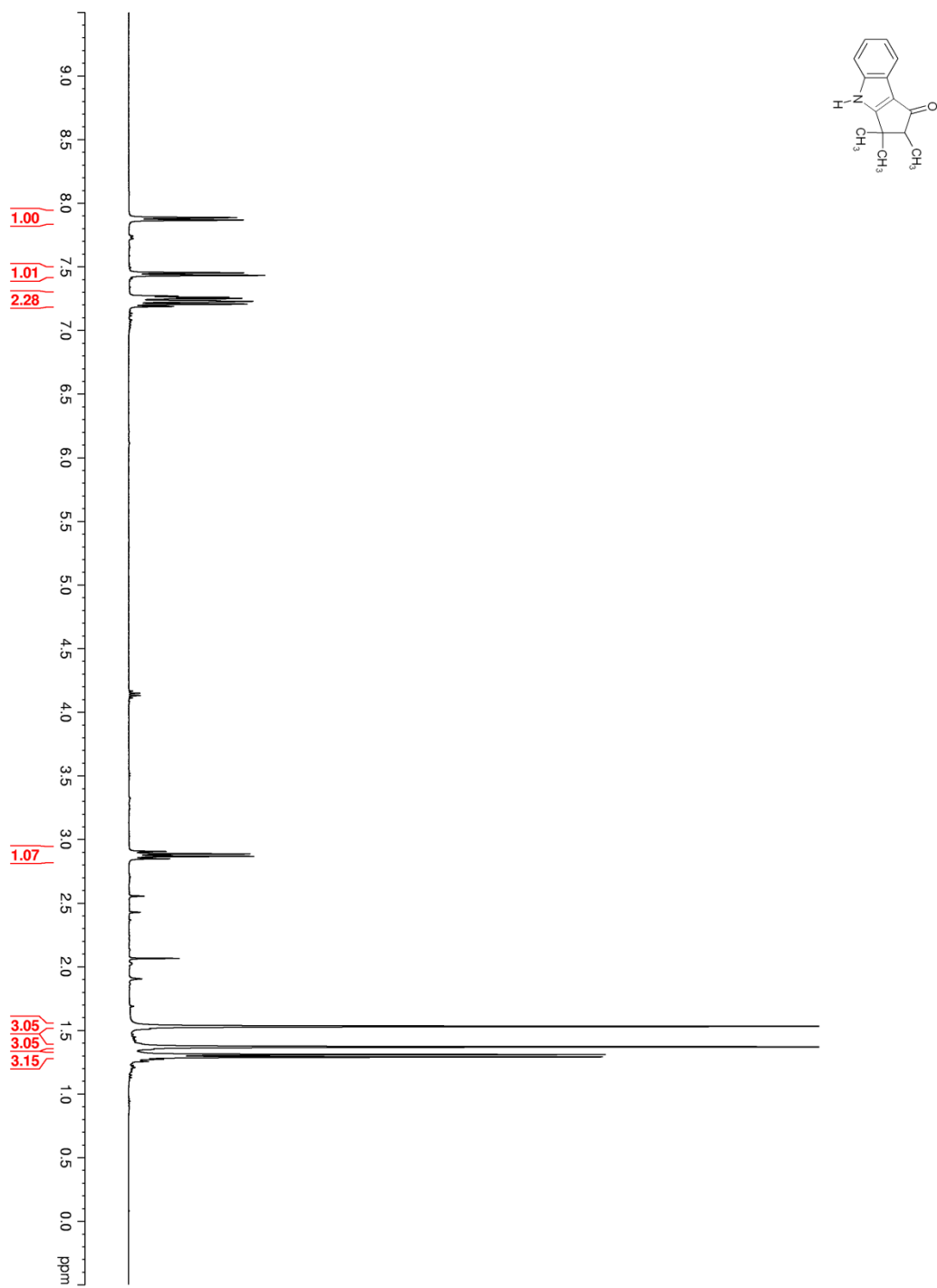


Figure 110. ^{13}C NMR Spectrum (100 MHz, CDCl_3) of 546

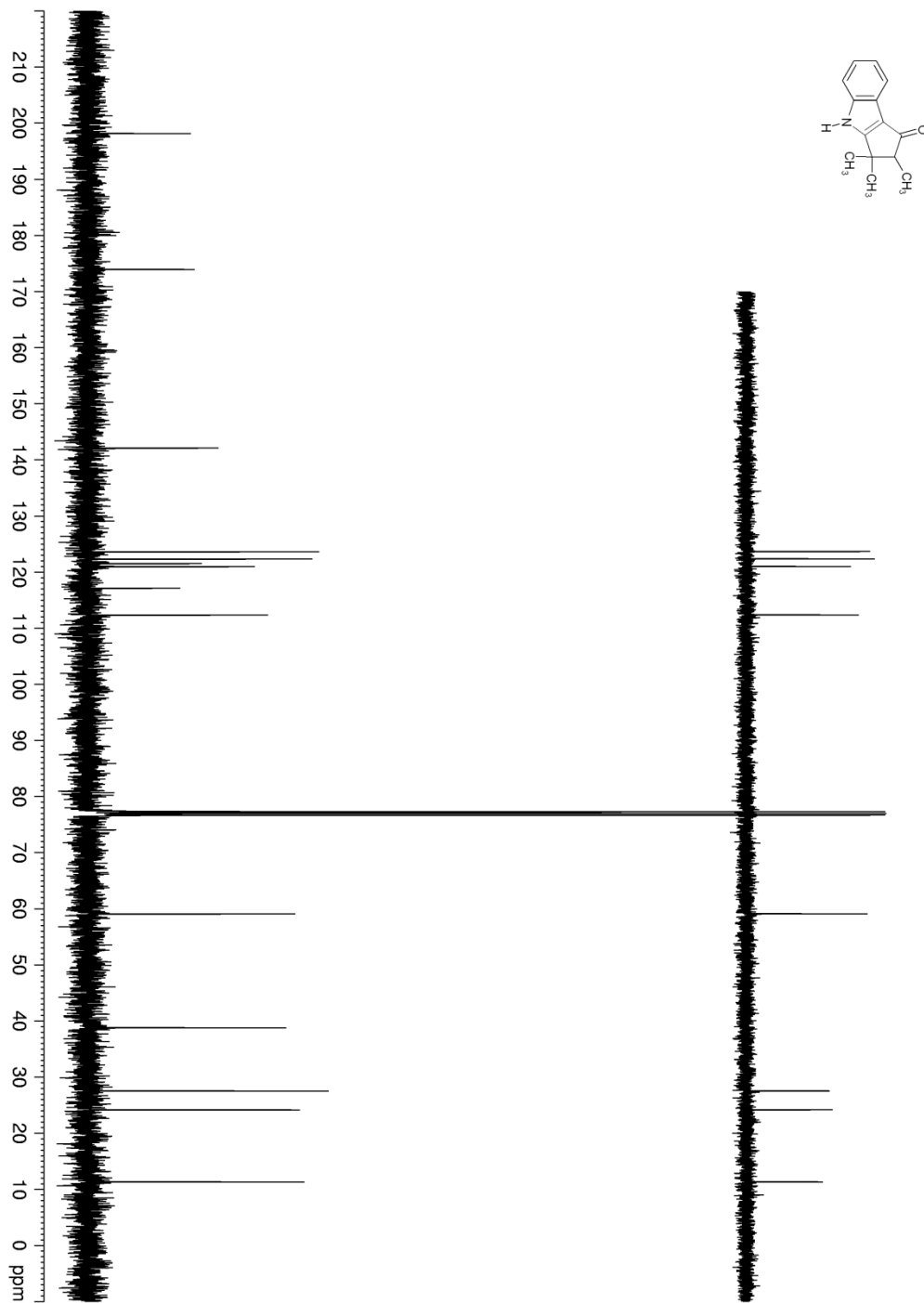


Figure 111. ¹H NMR Spectrum (400 MHz, CDCl₃) of 547

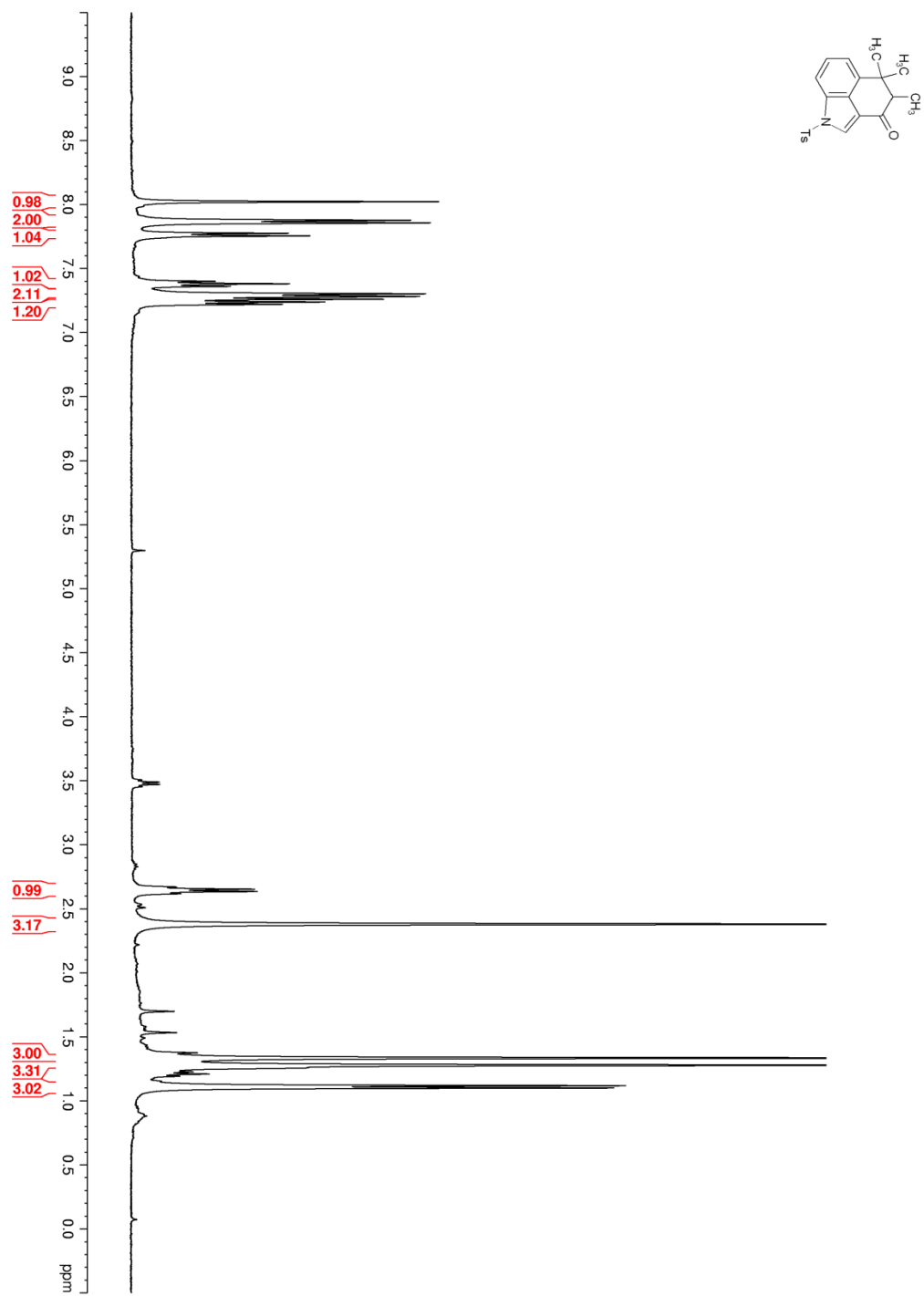


Figure 112. ^{13}C NMR Spectrum (100 MHz, CDCl_3) of 547

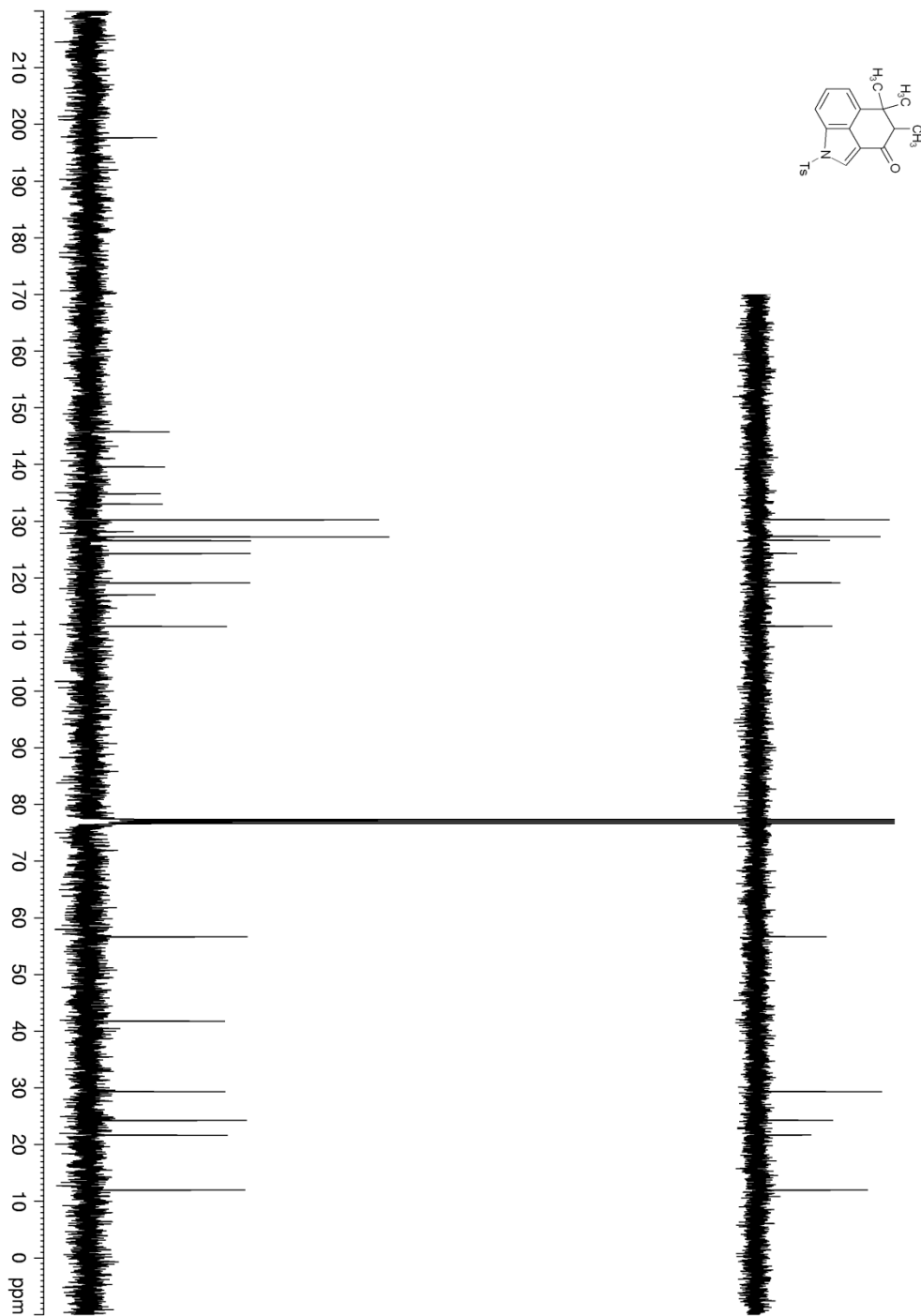


Figure 113. ^1H NMR Spectrum (600 MHz, CDCl_3) of 552

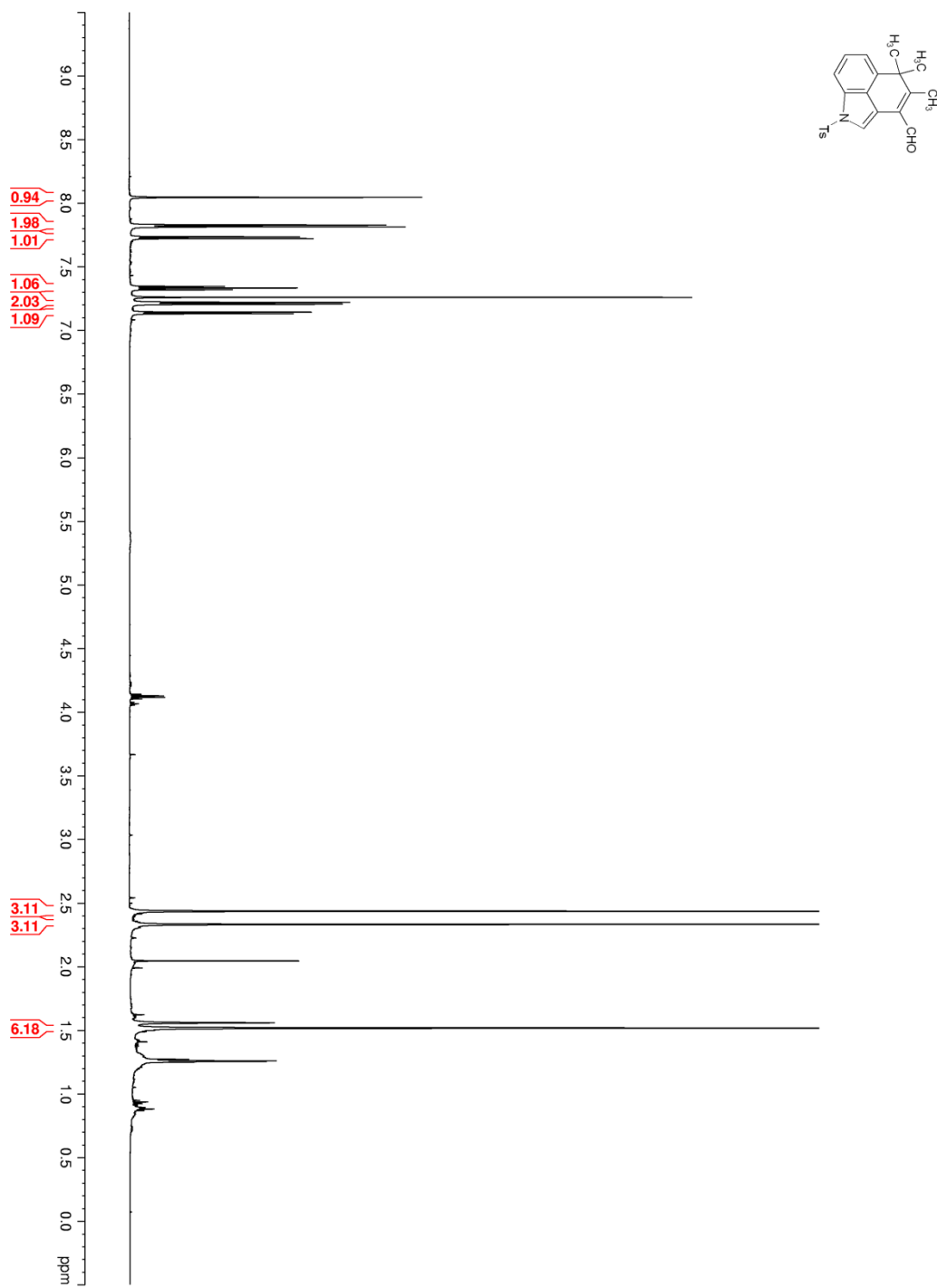


Figure 114. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 552

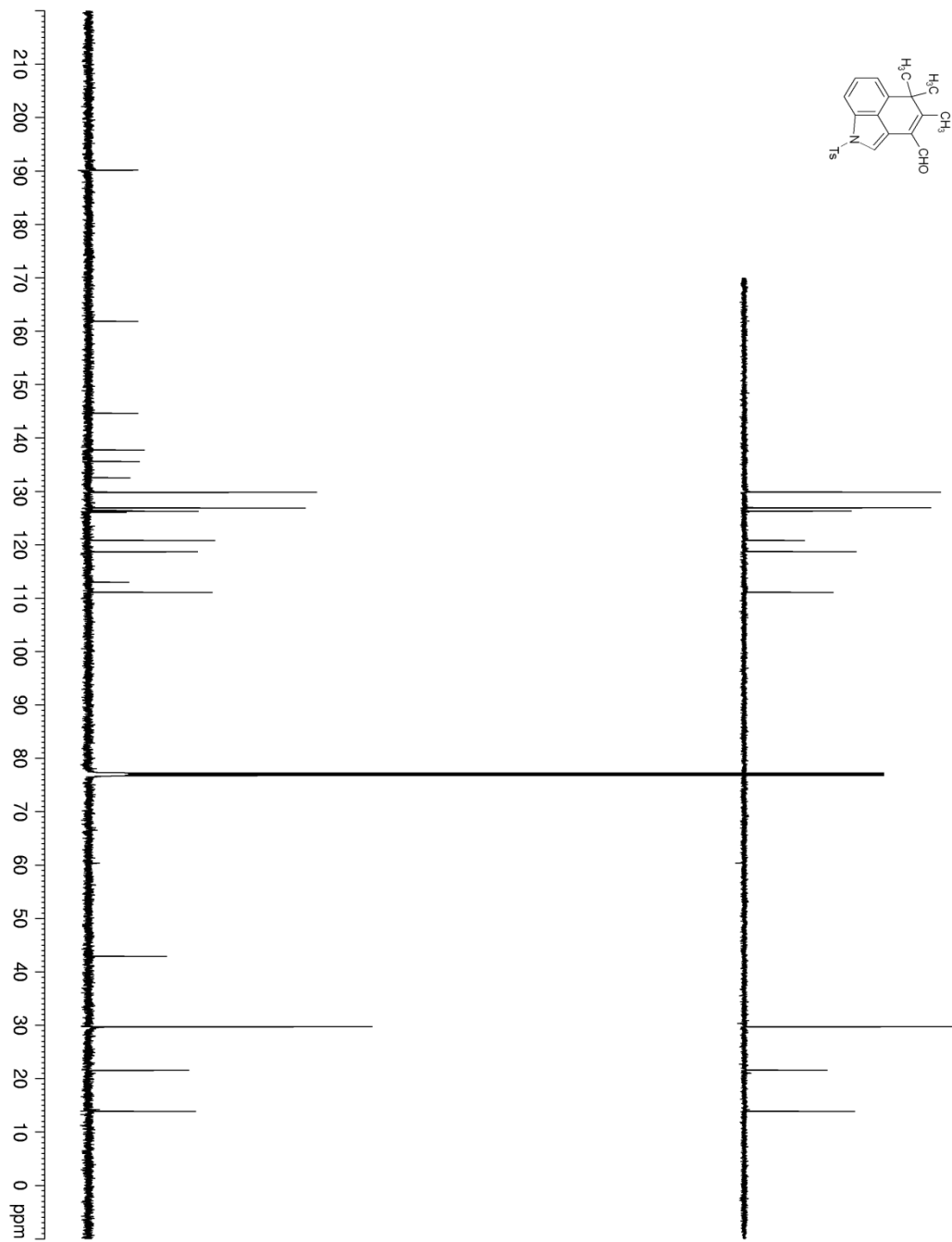


Figure 115. ¹H NMR Spectrum (500 MHz, CDCl₃) of 553

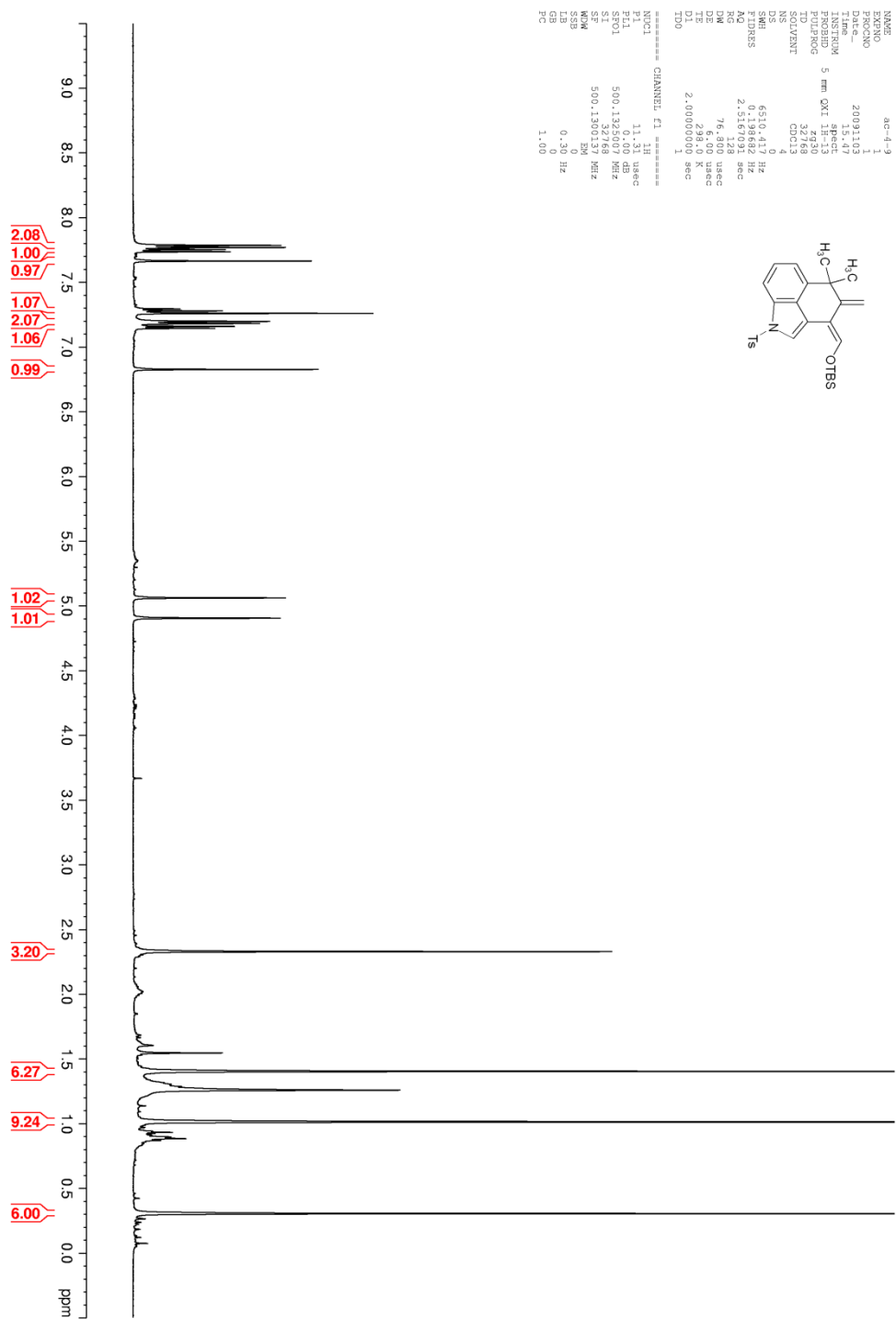


Figure 116. ^{13}C NMR Spectrum (125 MHz, CDCl_3) of 533

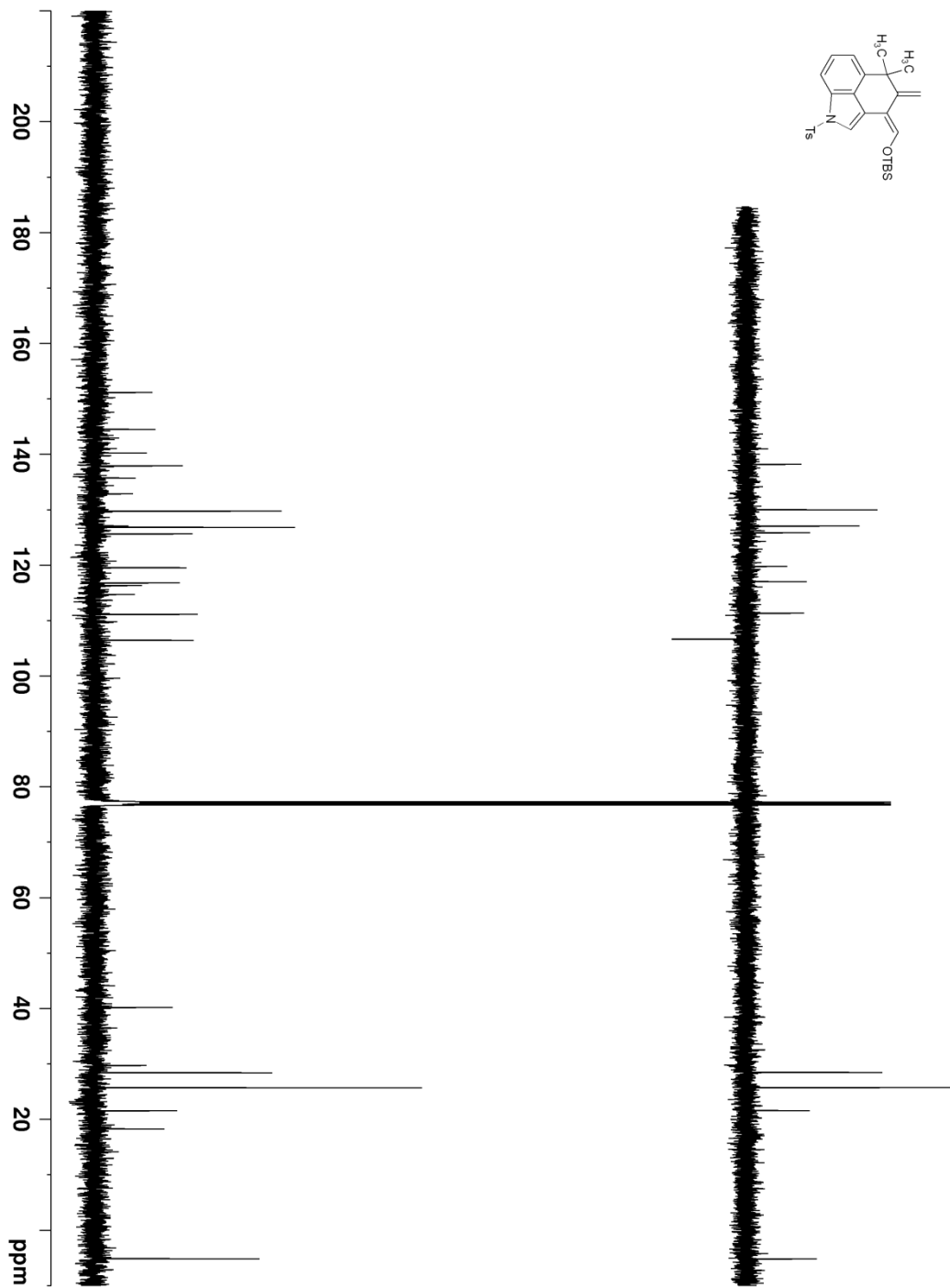


Figure 117. ^1H NMR Spectrum (500 MHz, CDCl_3) of 558

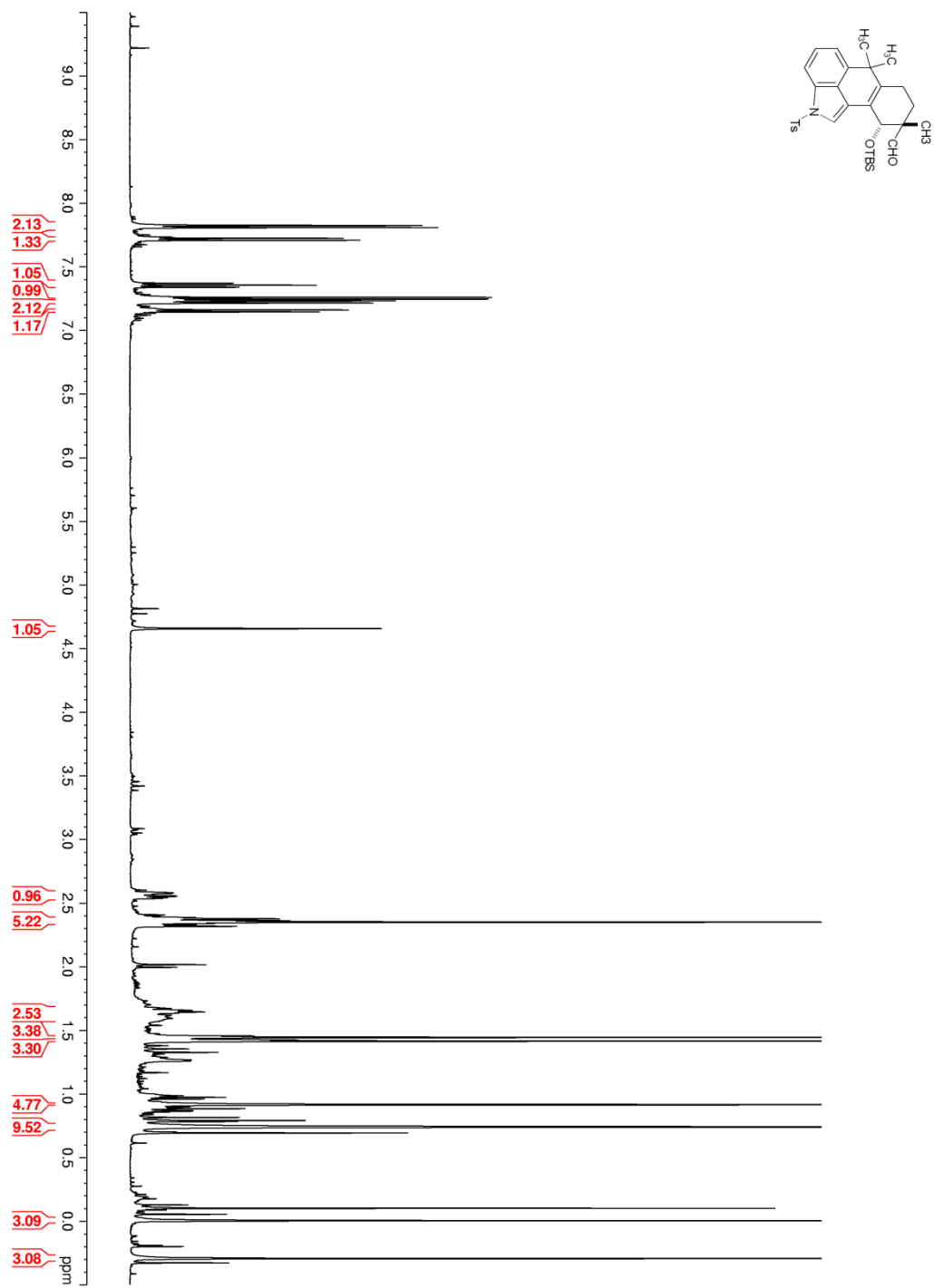


Figure 118. ^{13}C NMR Spectrum (125 MHz, CDCl_3) of 534

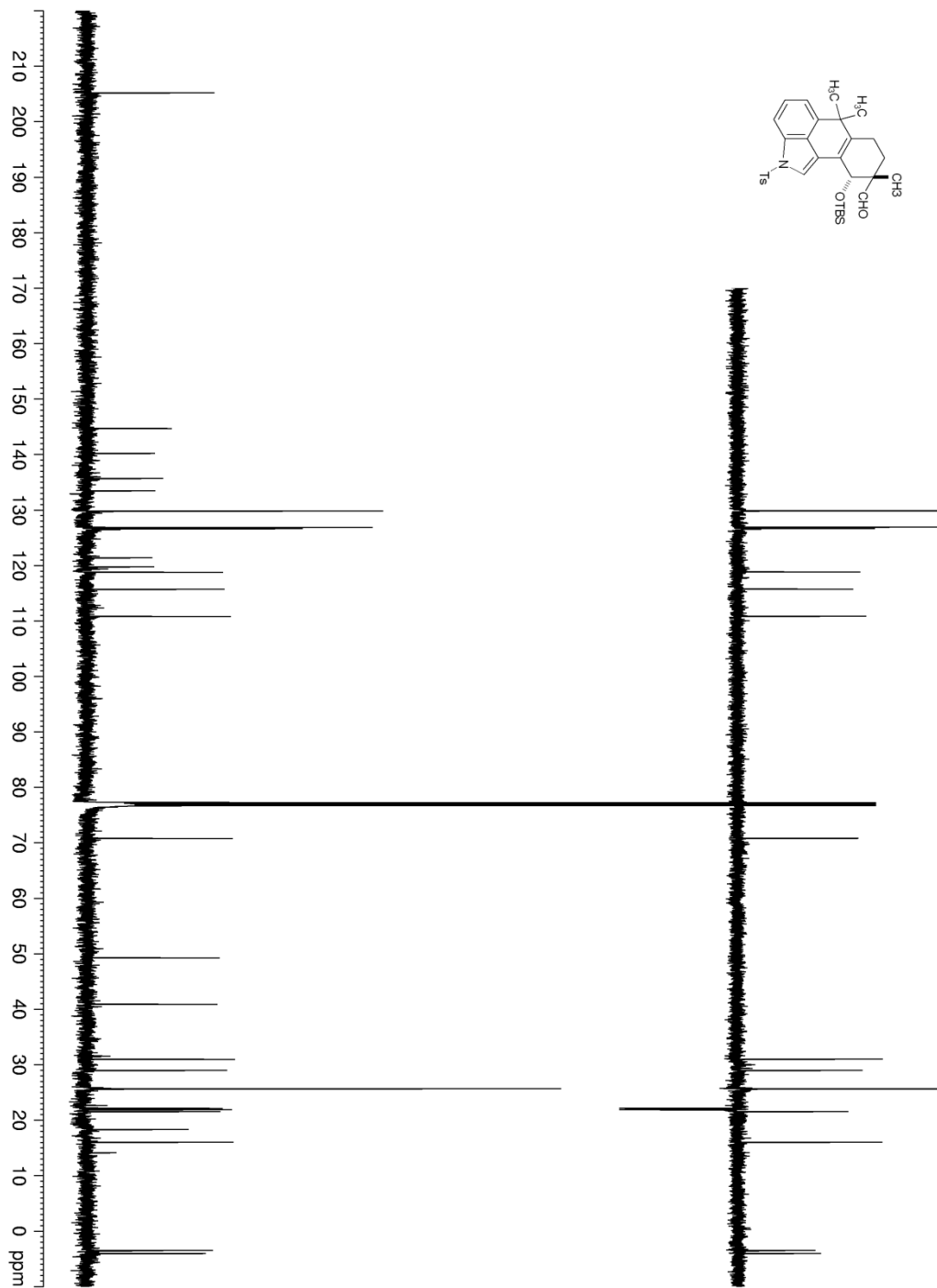


Figure 119. HSQC Spectrum (125 MHz, CDCl₃) of 558

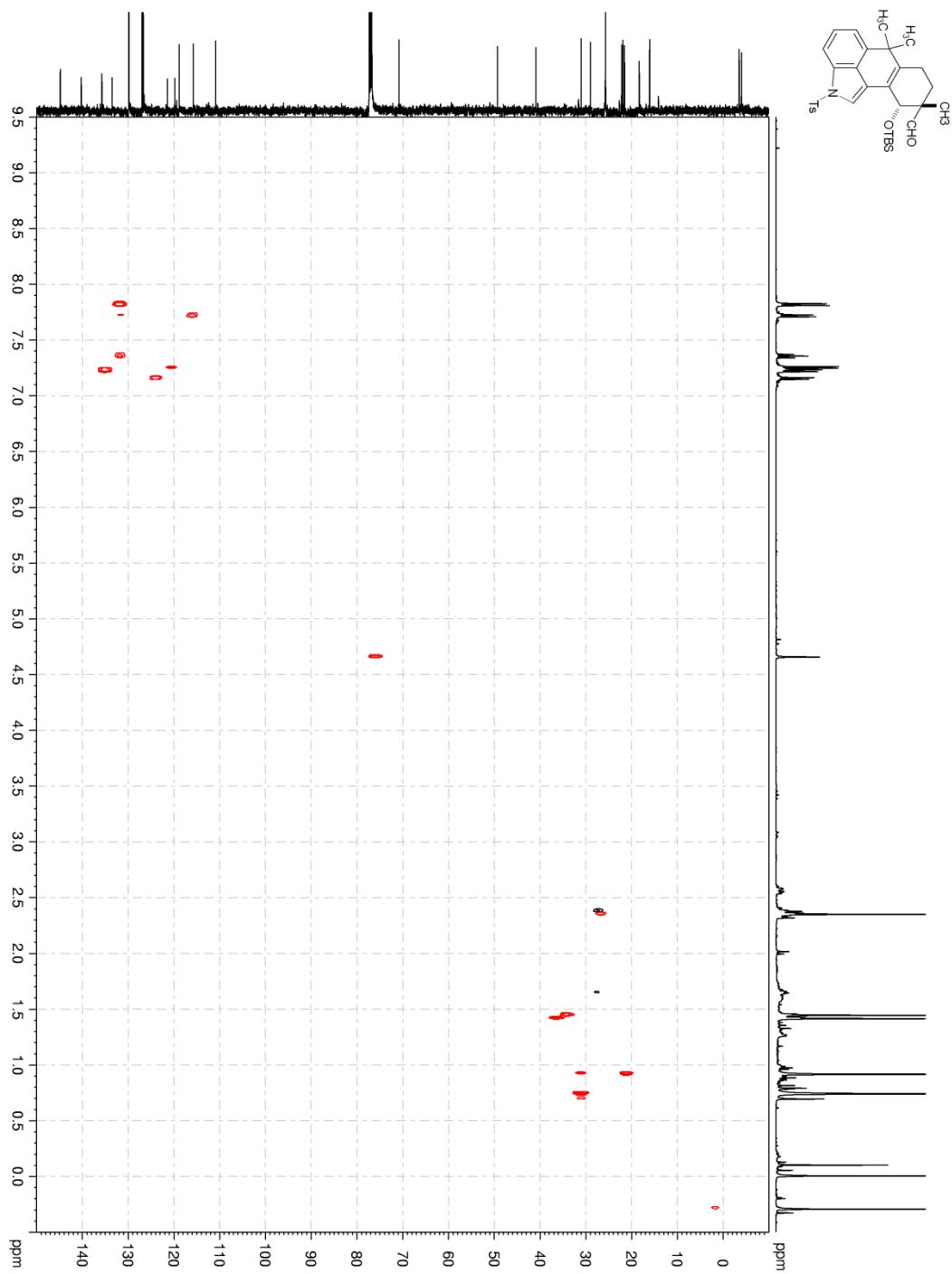


Figure 120. NOESY (500 MHz, CDCl₃) of 558

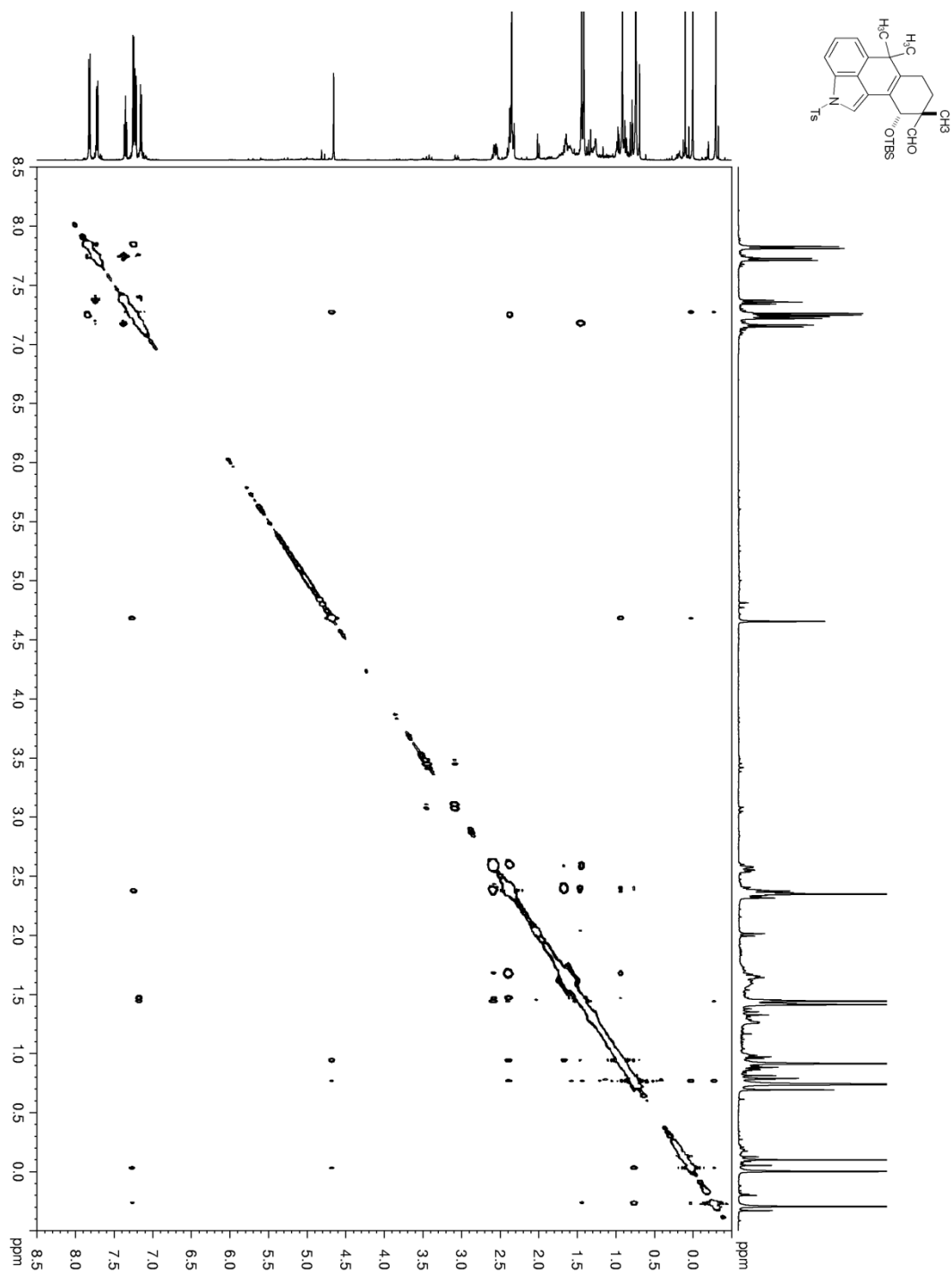


Figure 121. ^1H NMR Spectrum (600 MHz, CDCl_3) of 559

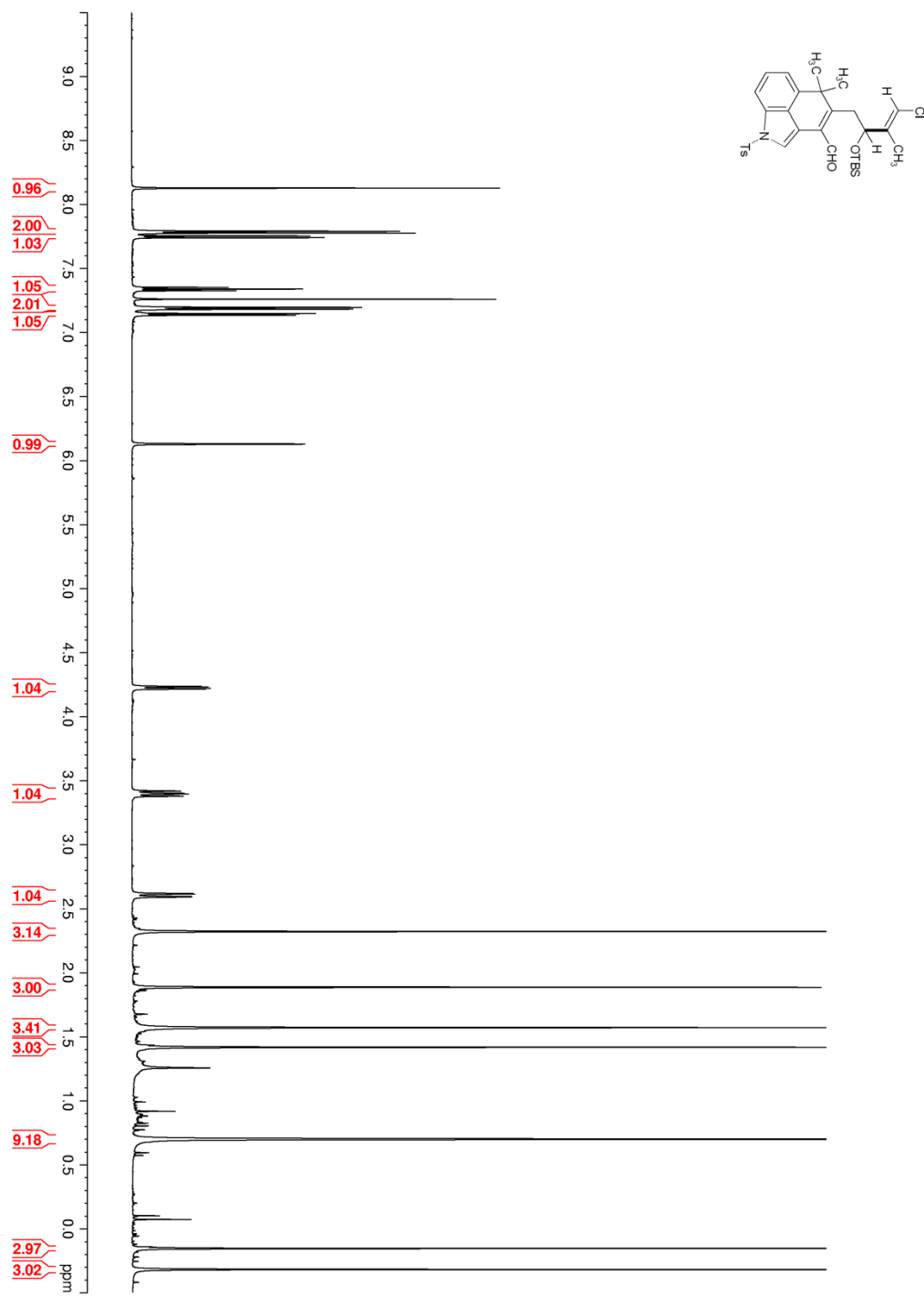


Figure 122. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 559

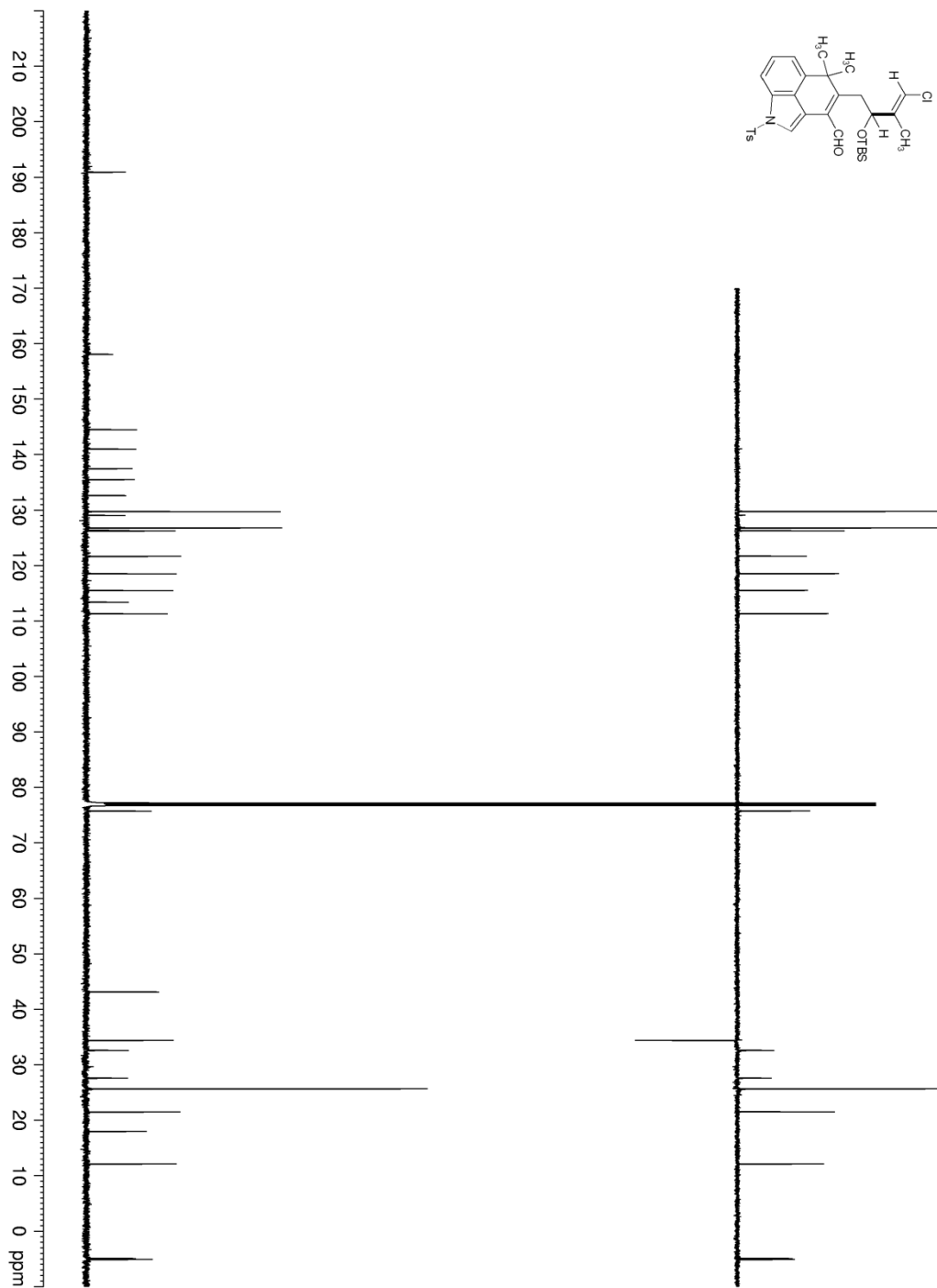


Figure 123. HSQC Spectrum (150 MHz, CDCl₃) of 559

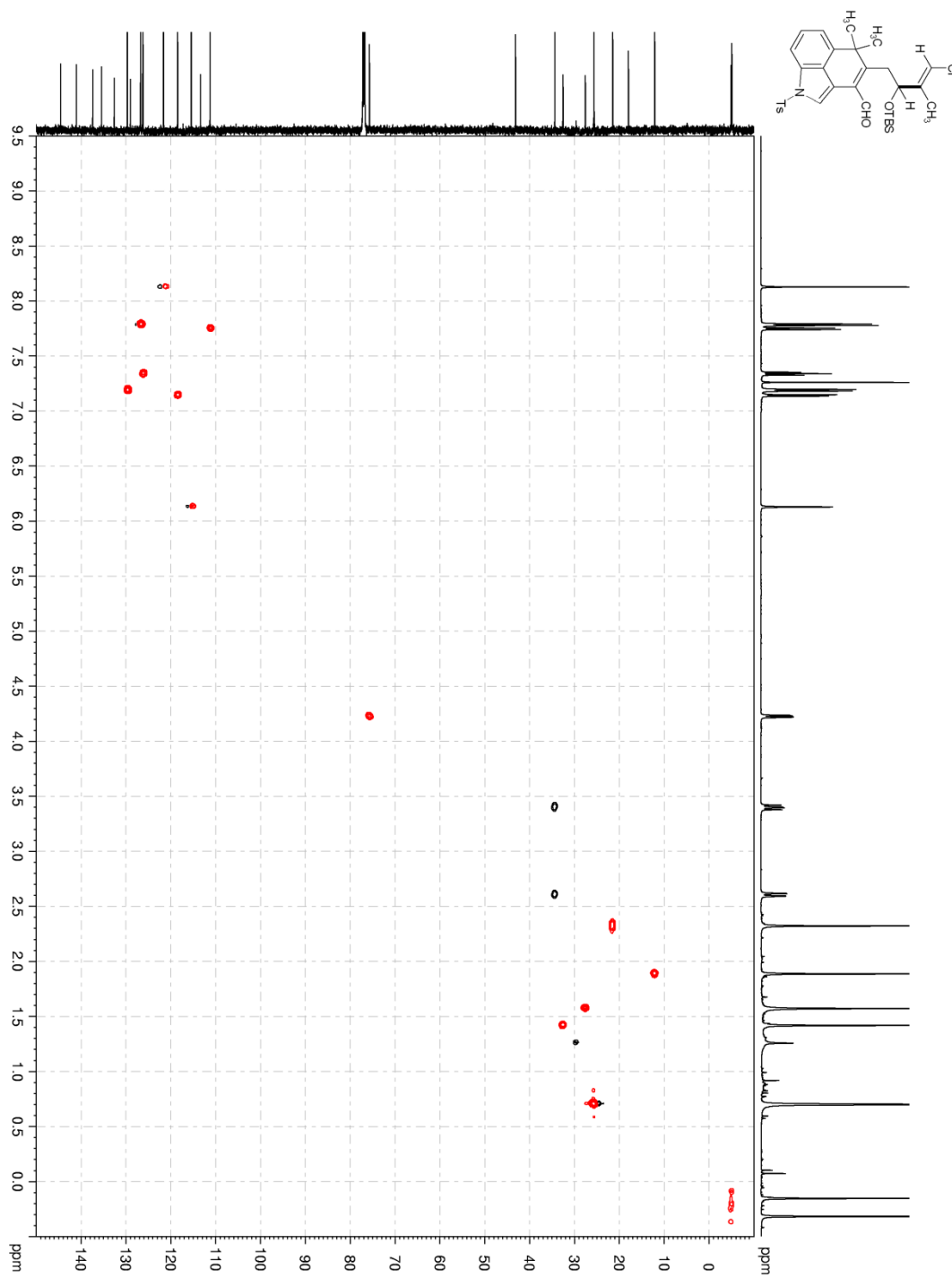


Figure 124. HMBC Spectrum (150 MHz, CDCl₃) of 559

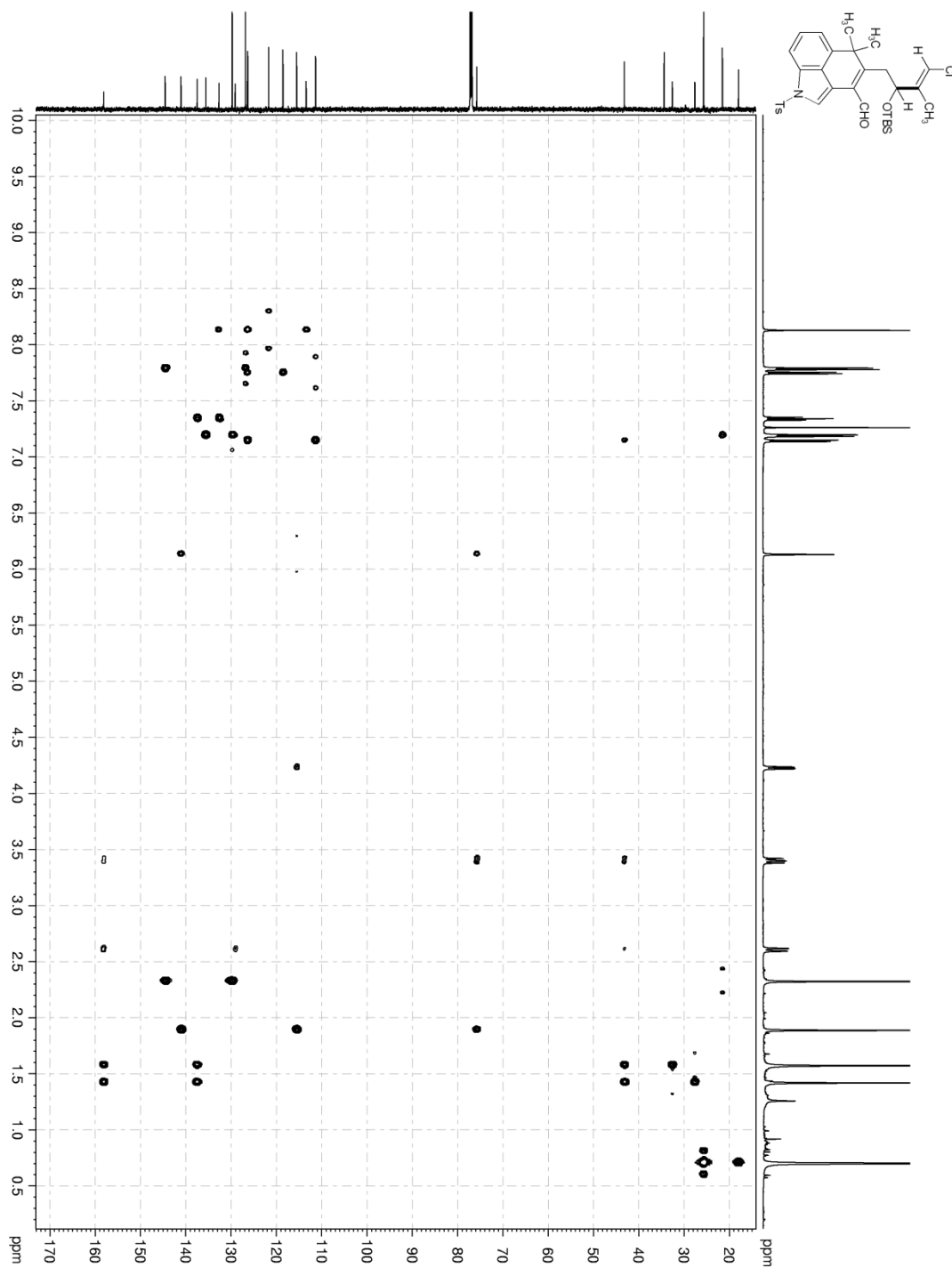


Figure 125. NOESY Spectrum (600 MHz, CDCl₃) of 559

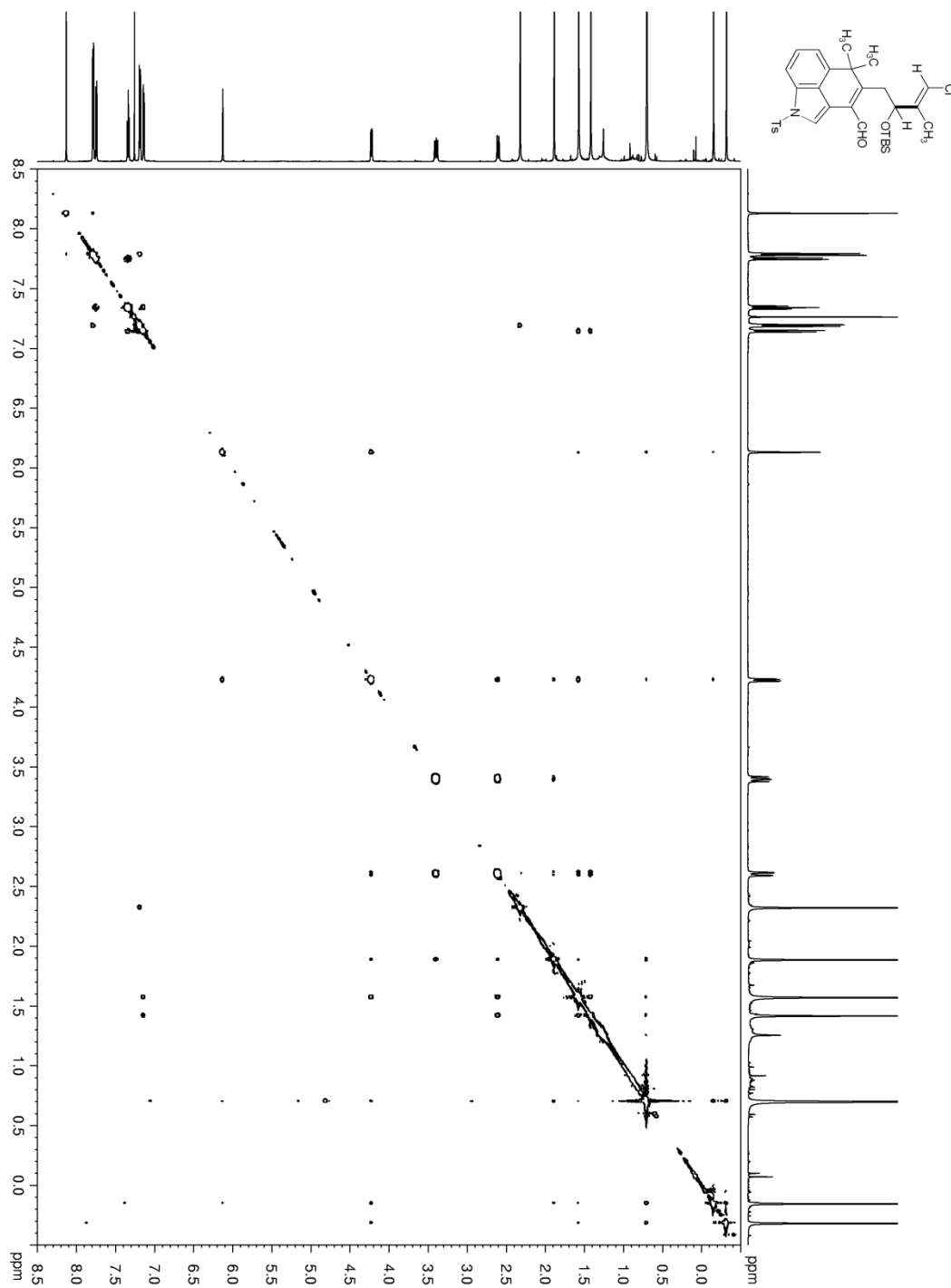


Figure 126. ^1H NMR Spectrum (400 MHz, CDCl_3) of 560

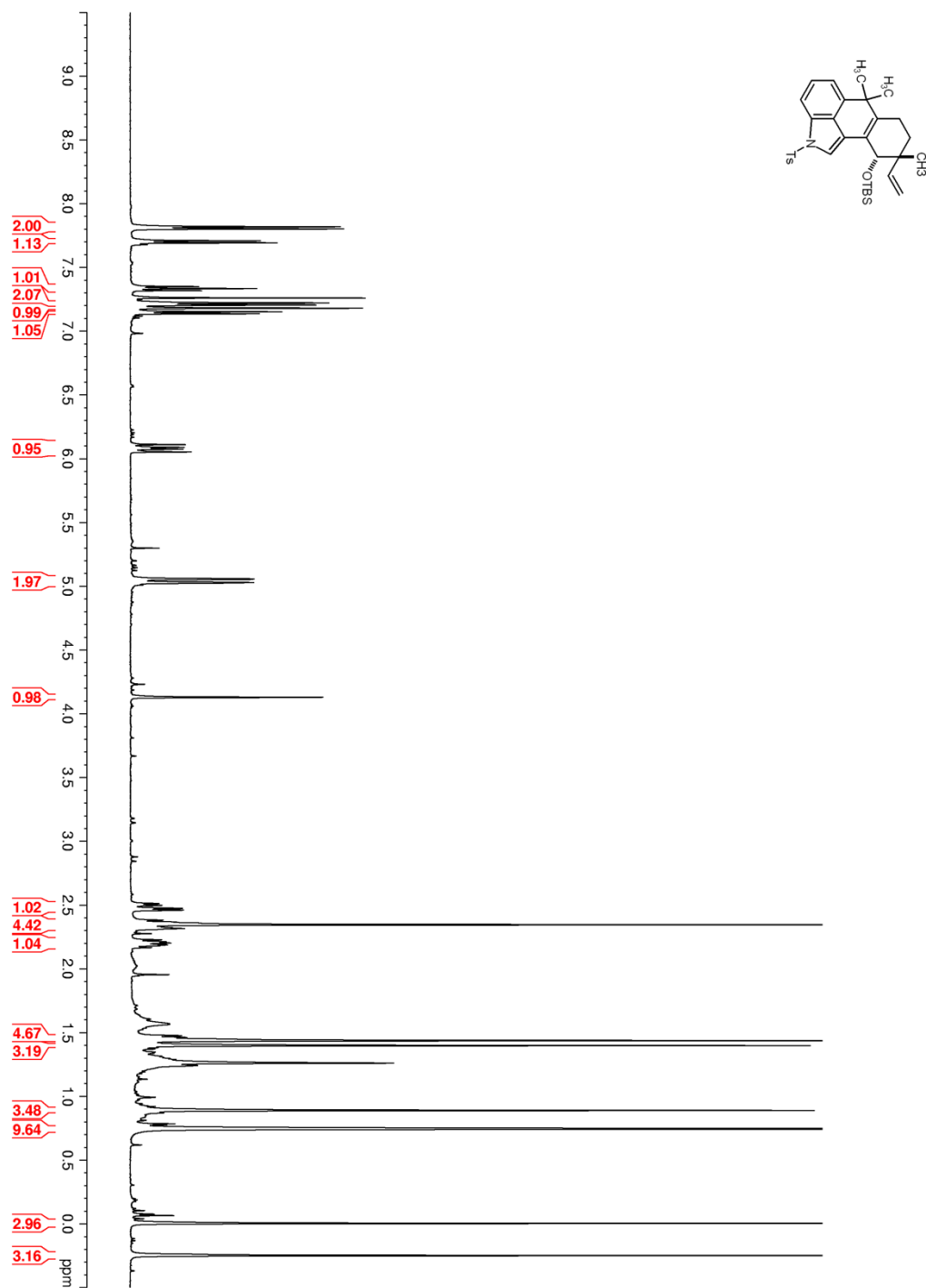


Figure 127. ^{13}C NMR Spectrum (125 MHz, CDCl_3) of 534

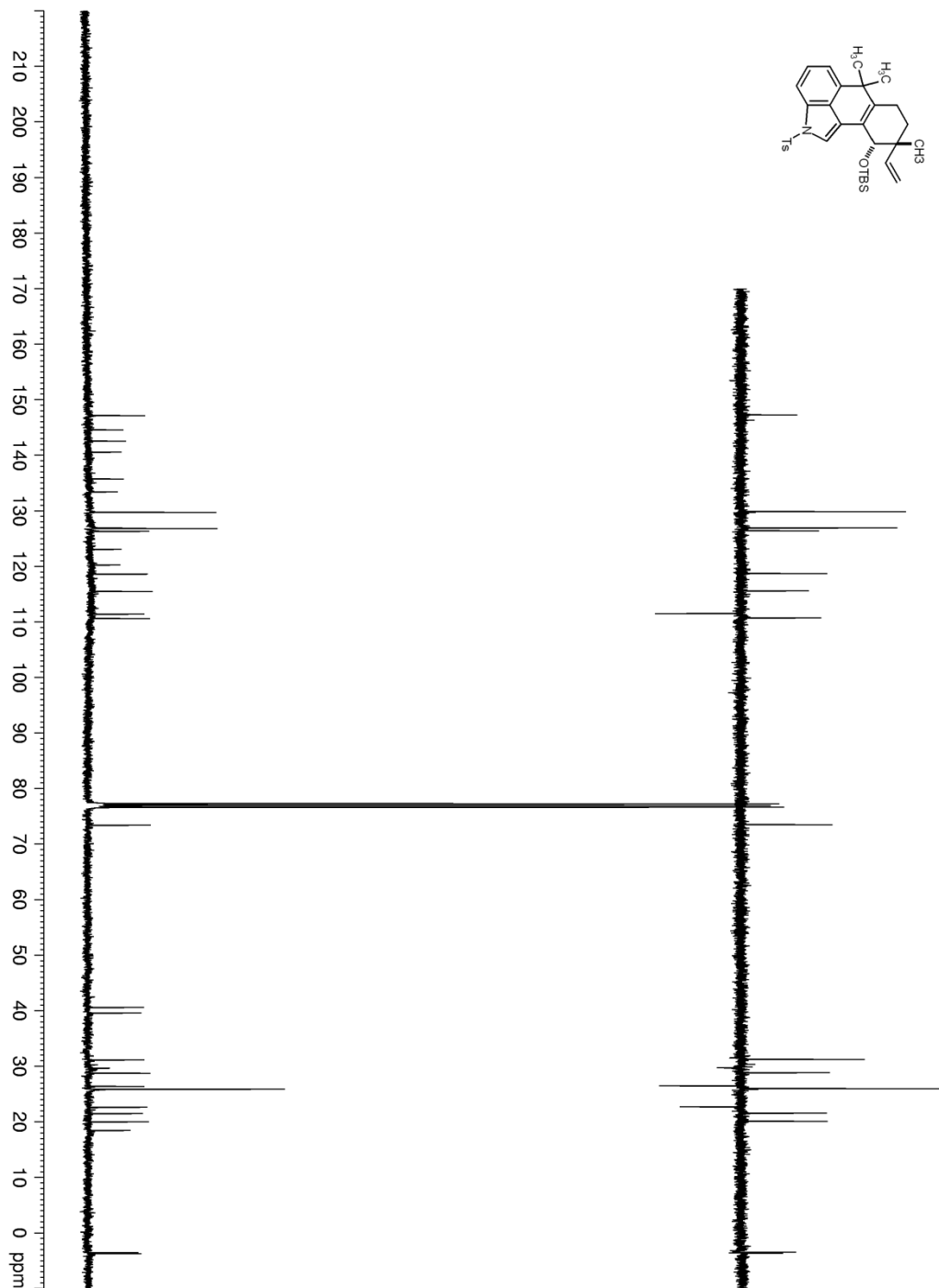


Figure 128. ^1H NMR Spectrum (500 MHz, CDCl_3) of 561

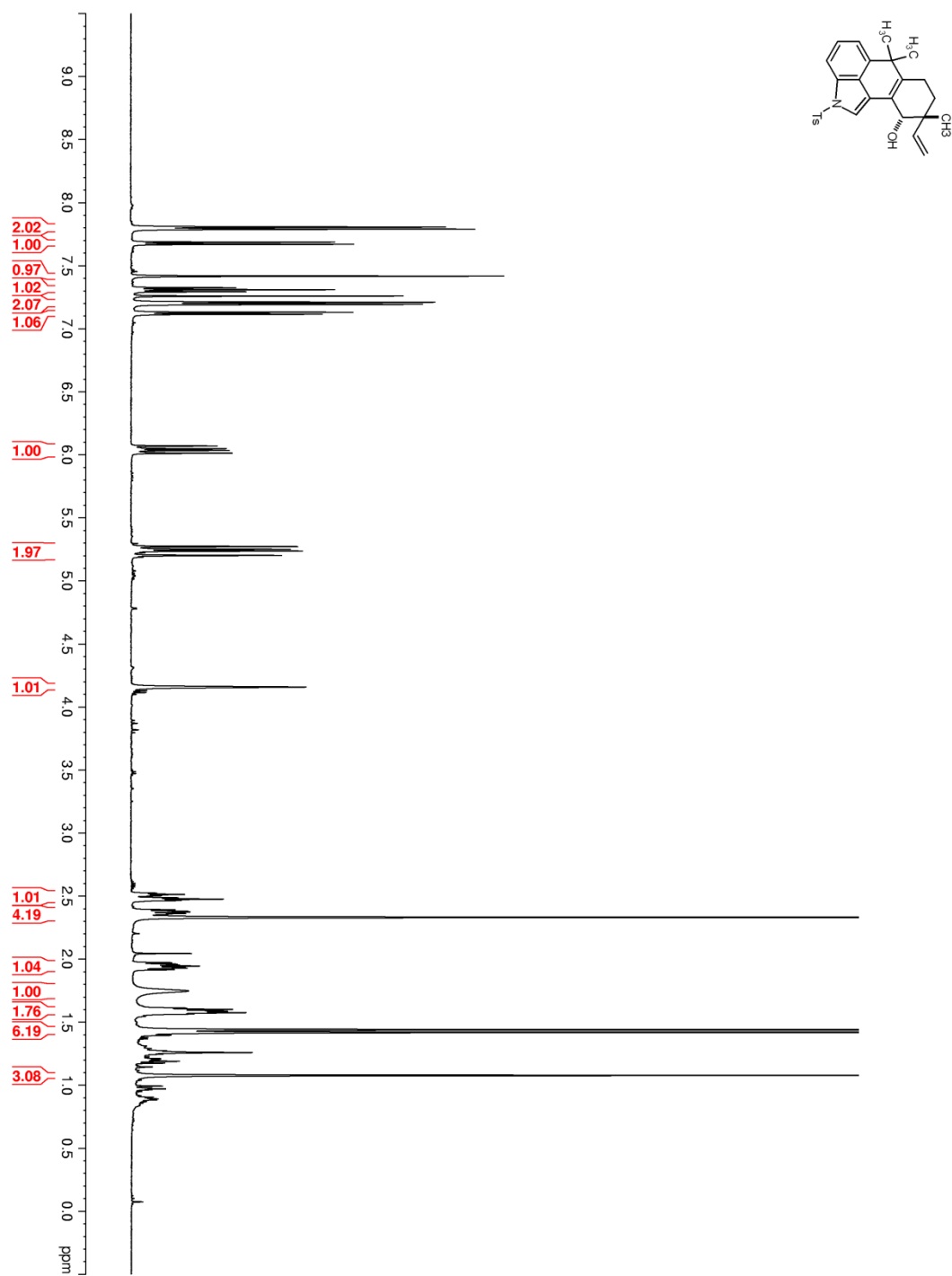


Figure 129. ^{13}C NMR Spectrum (125 MHz, CDCl_3) of 561

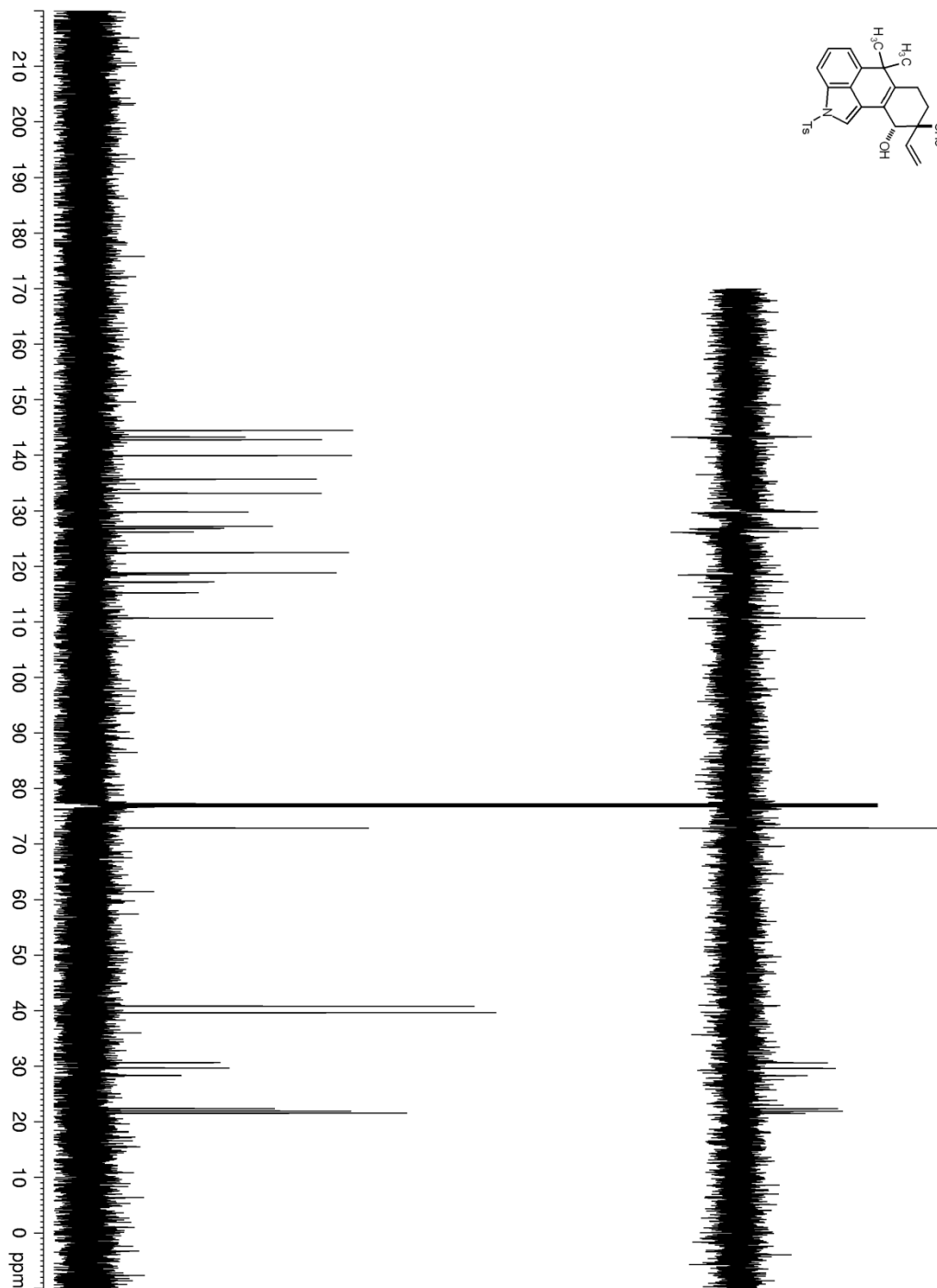


Figure 130. ^1H NMR Spectrum (600 MHz, CDCl_3) of 564

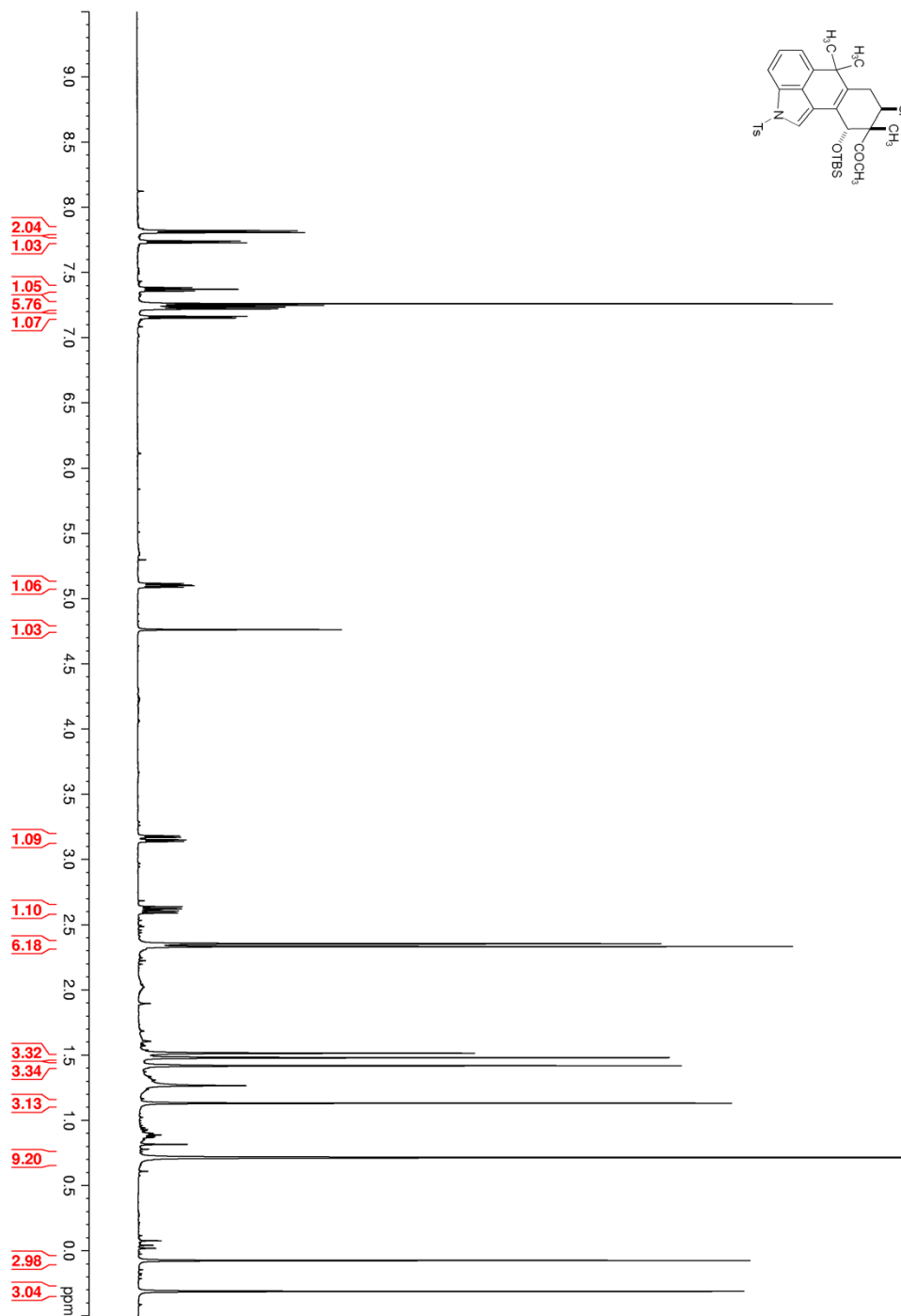


Figure 131. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 564

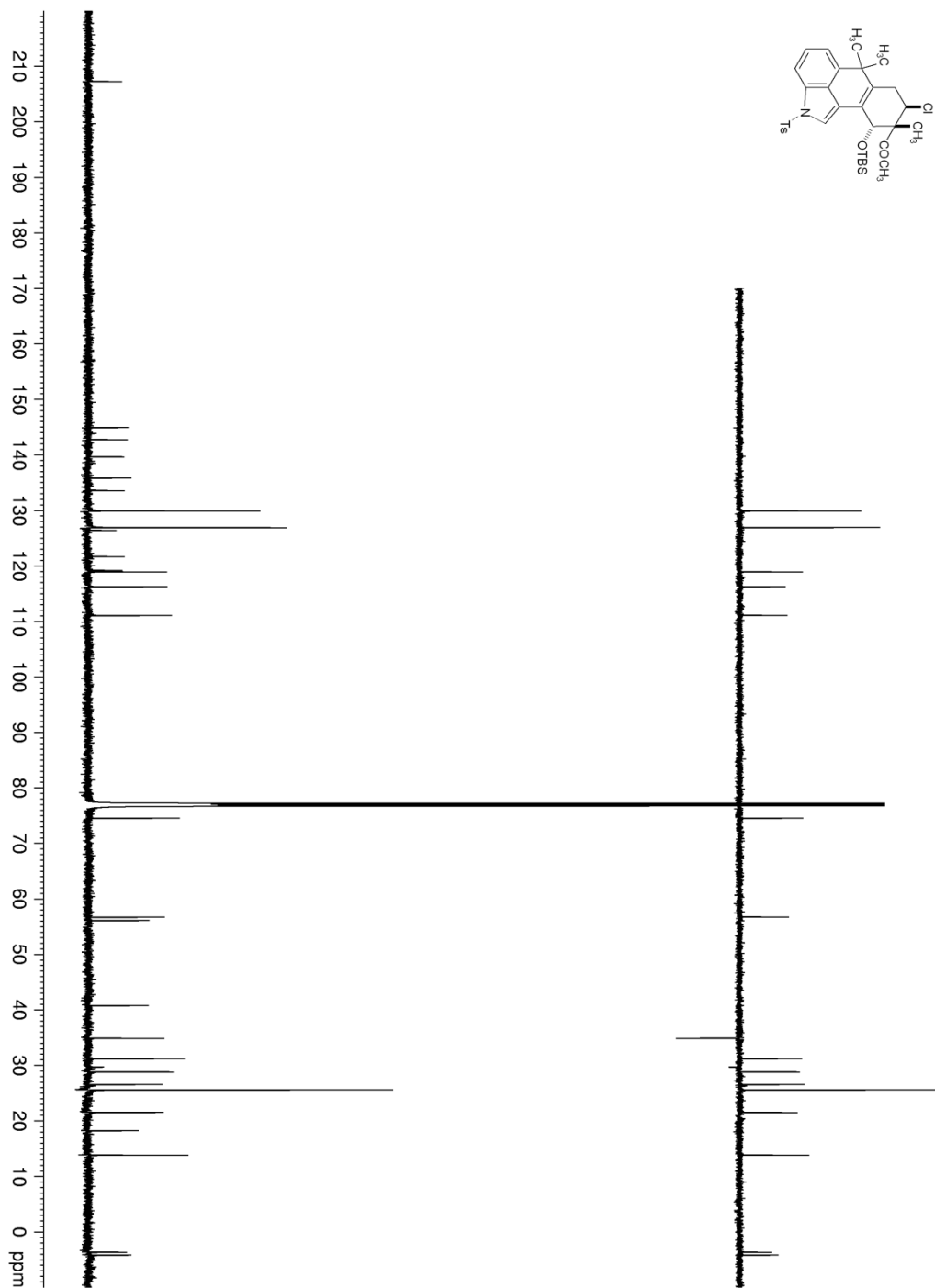


Figure 132. NOESY Spectrum (600 MHz, CDCl₃) of 564

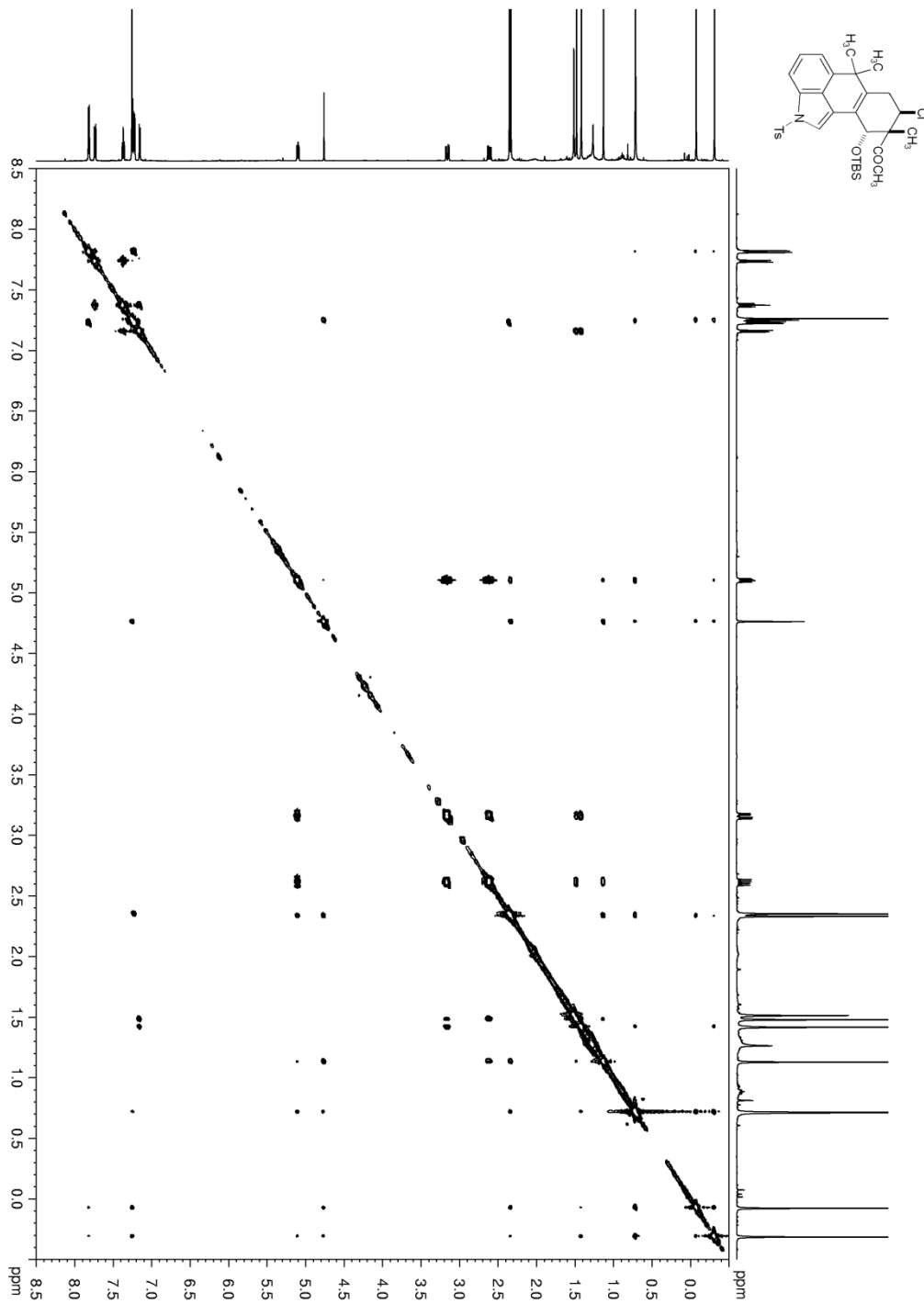


Figure 133. ^1H NMR Spectrum (600 MHz, CDCl_3) of 576

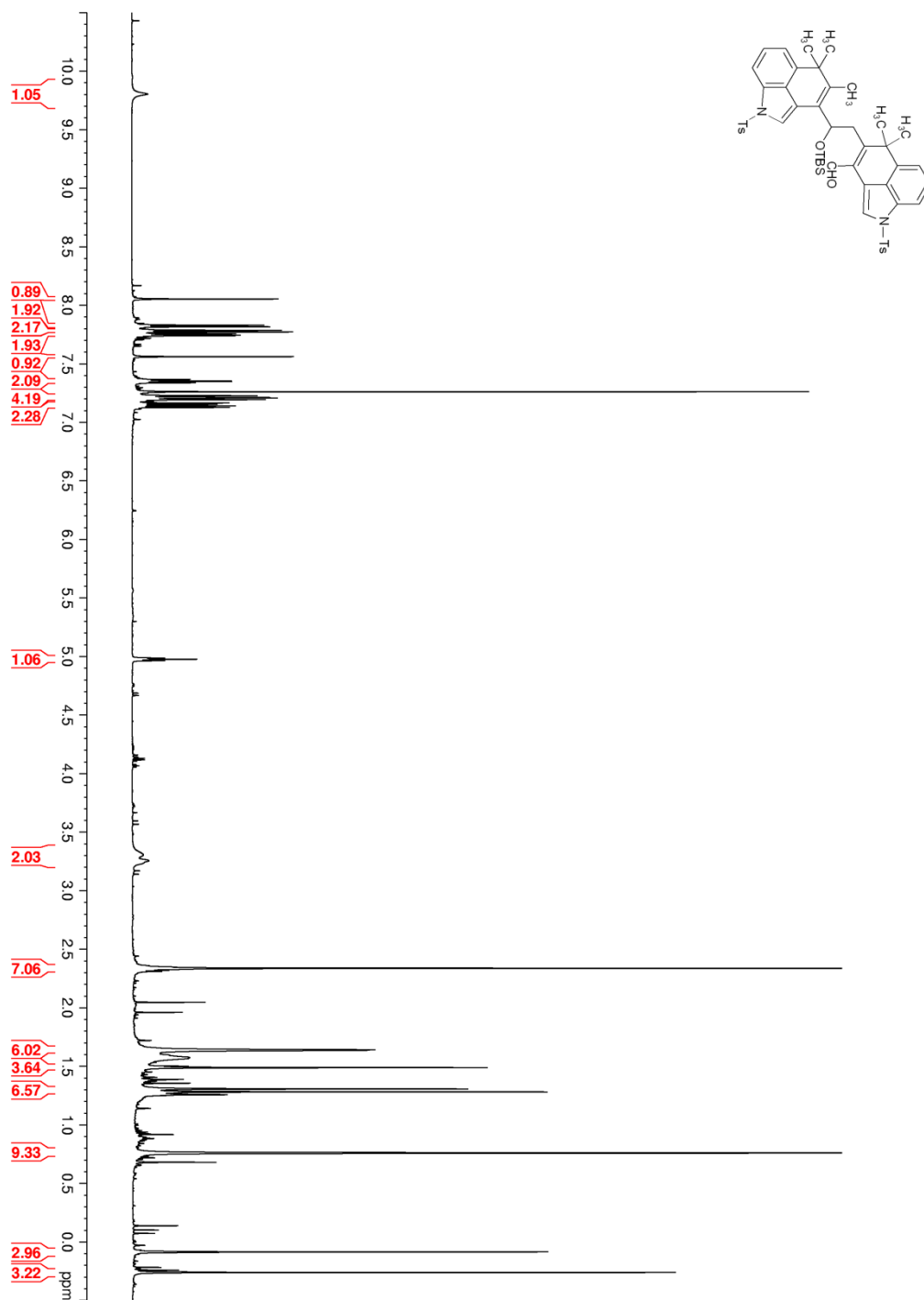


Figure 134. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 576

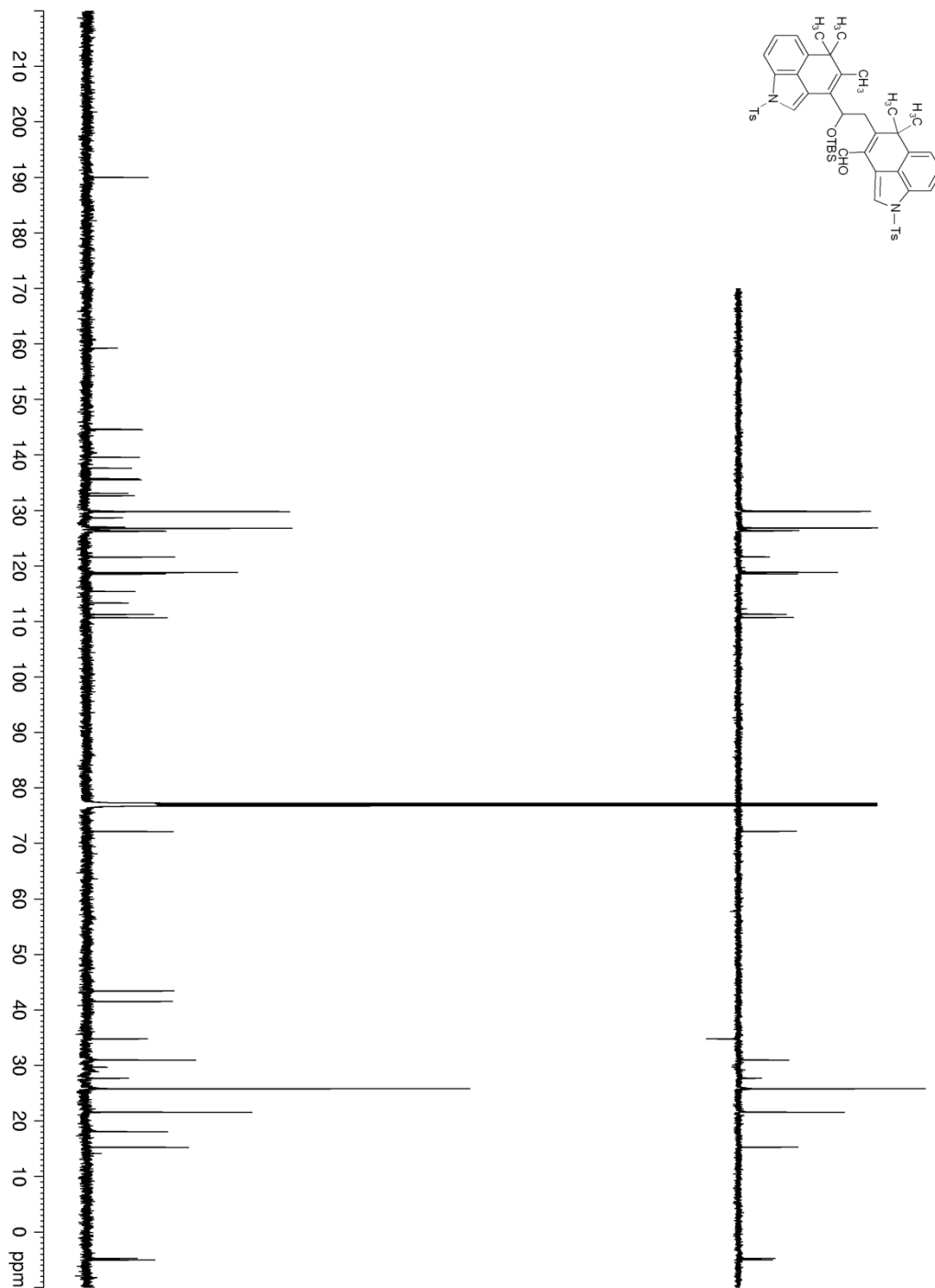


Figure 135. HSQC Spectrum (150 MHz, CDCl₃) of 576

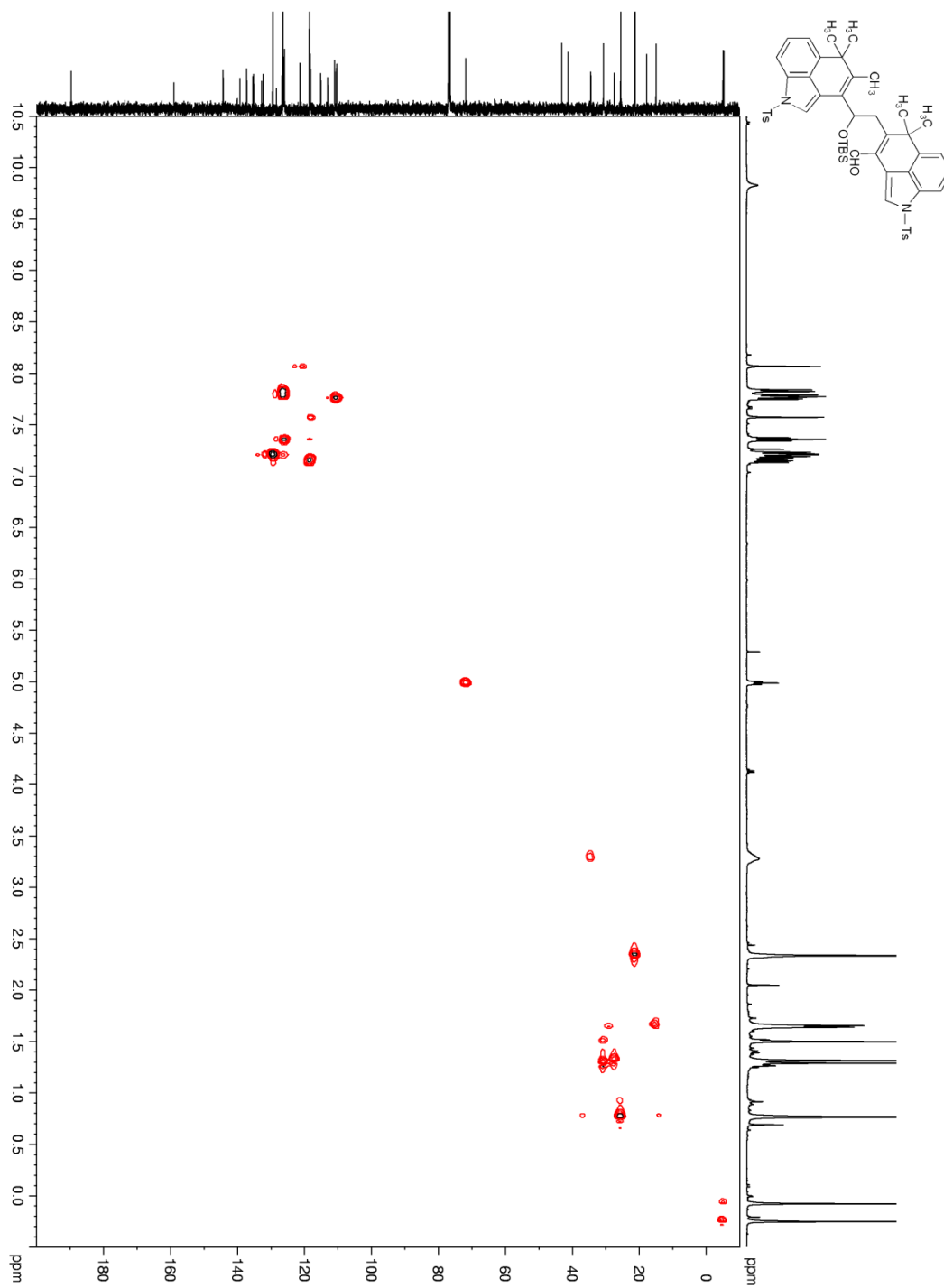


Figure 136. HMBC Spectrum (150 MHz, CDCl₃) of 576

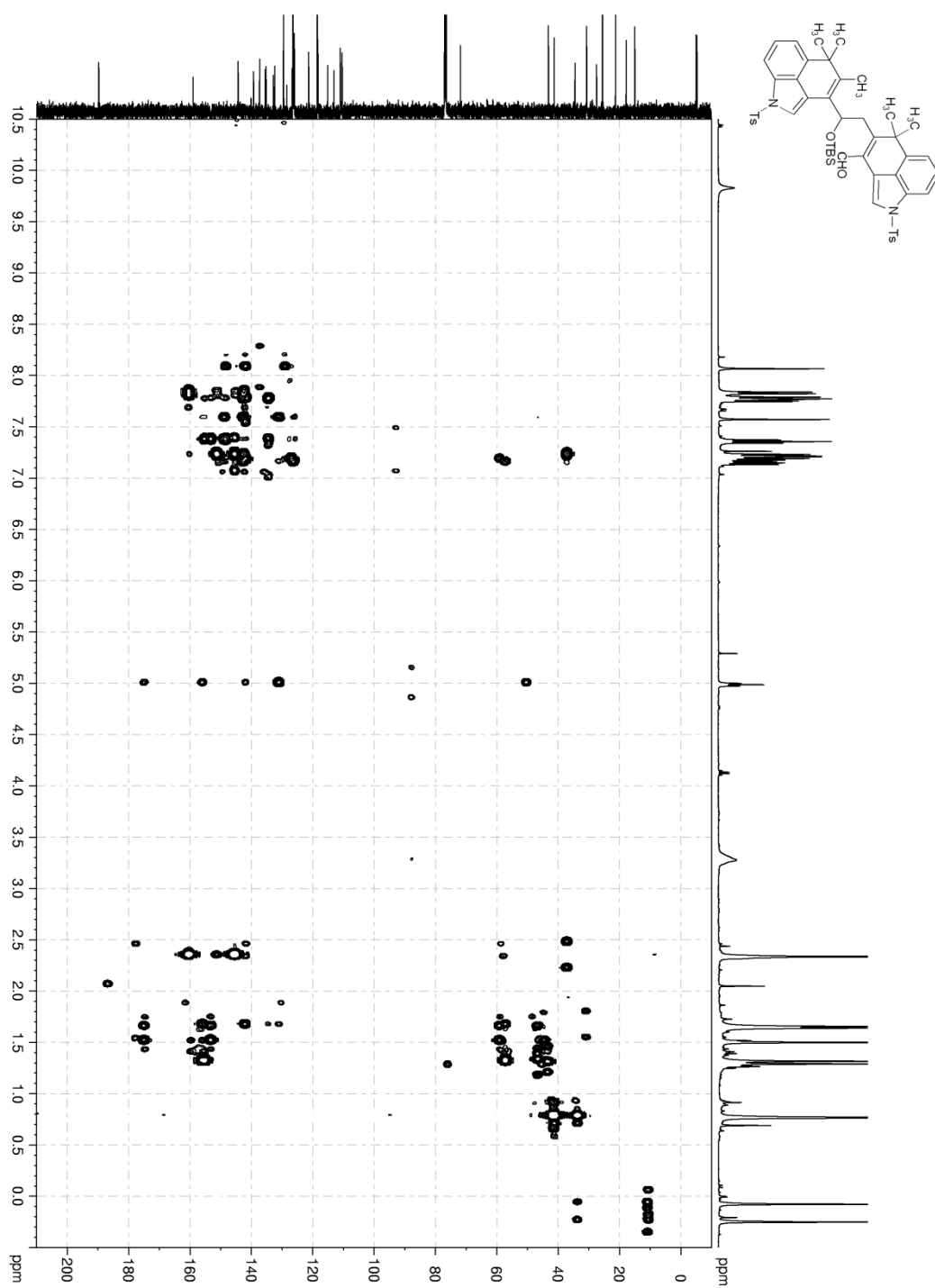


Figure 137. NOESY Spectrum (600 MHz, CDCl₃) of 576

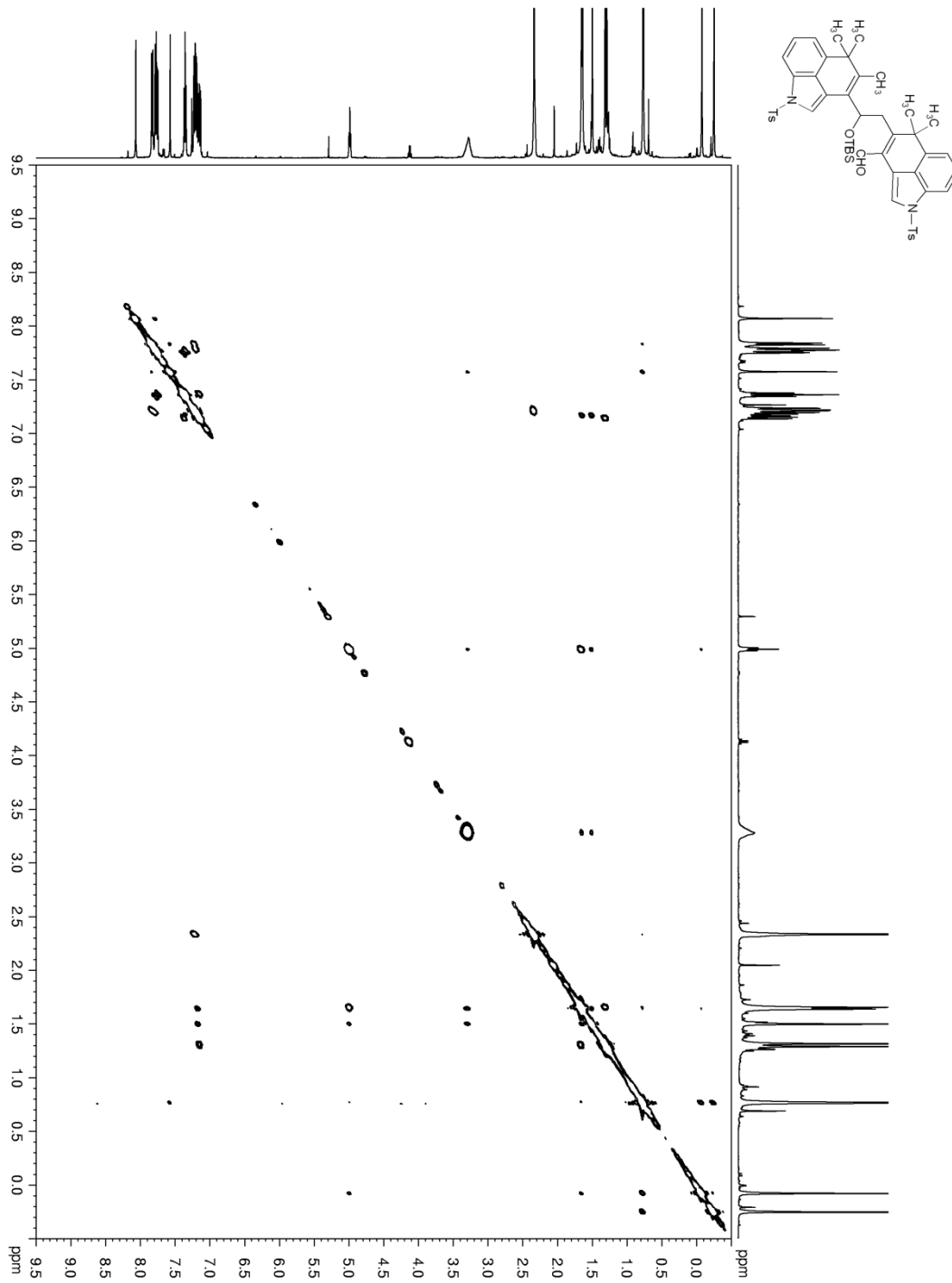


Figure 138. ^1H NMR Spectrum (600 MHz, CDCl_3) of 577

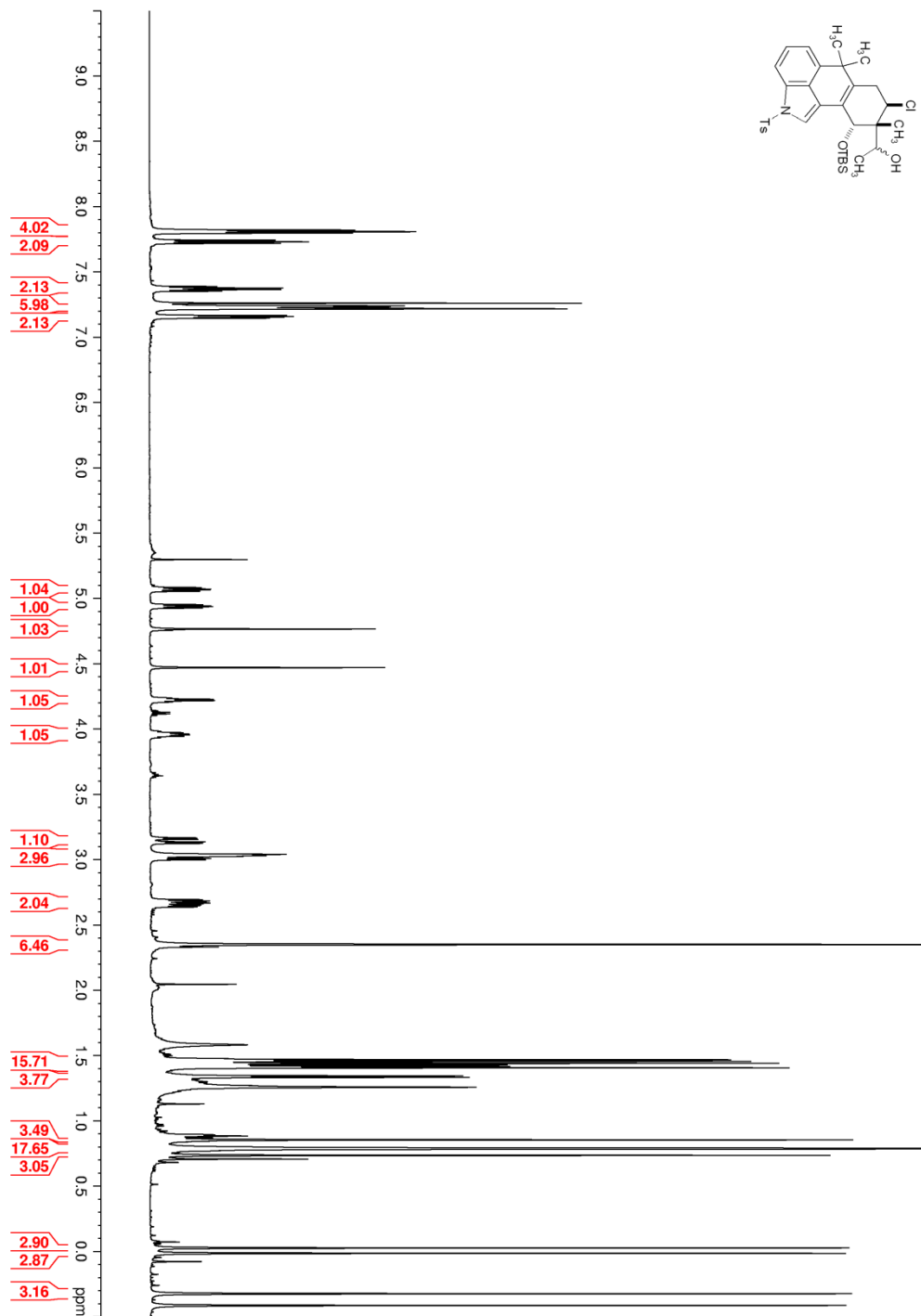


Figure 139. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 577

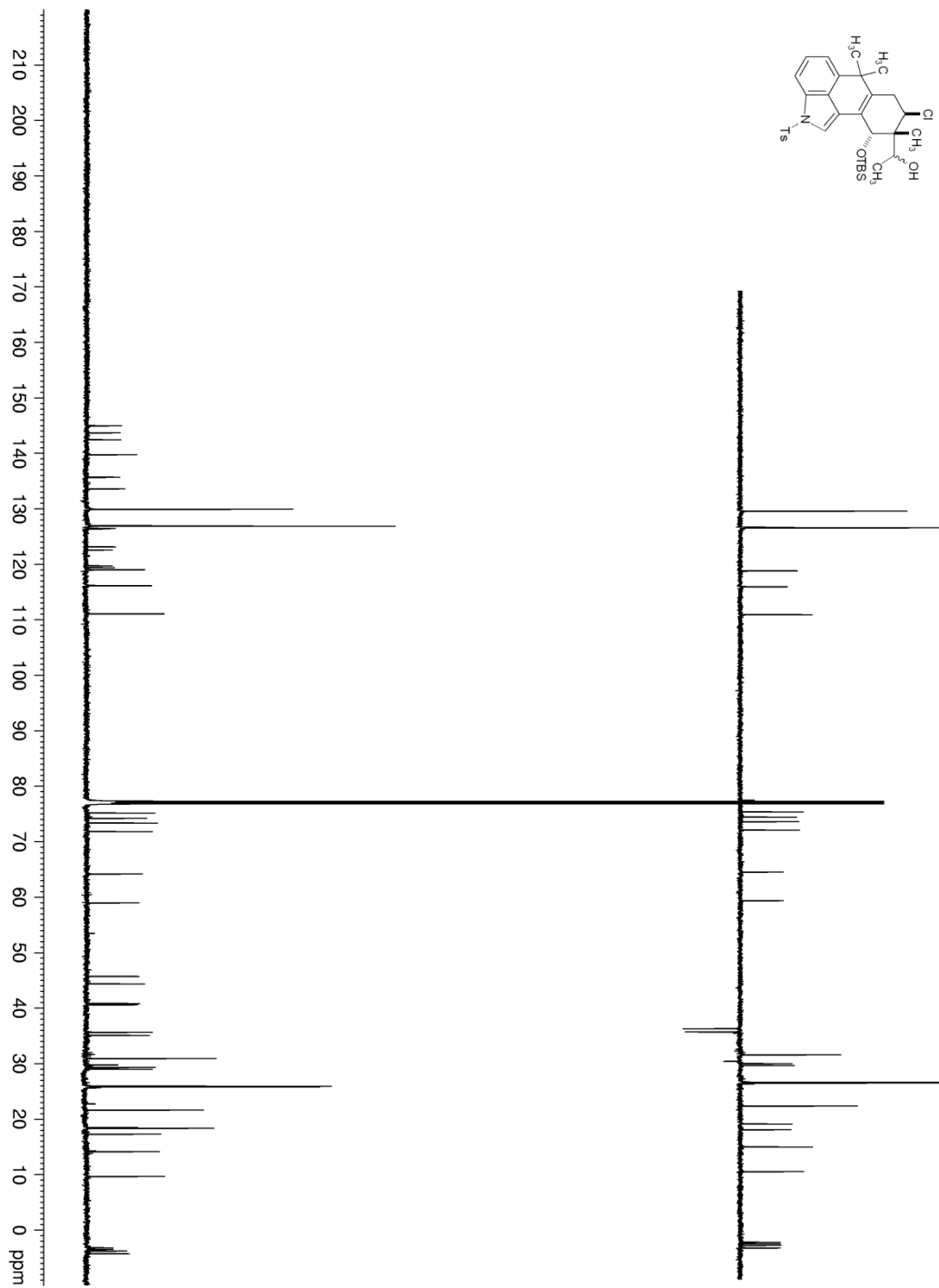


Figure 140. ^1H NMR Spectrum (600 MHz, CDCl_3) of 578

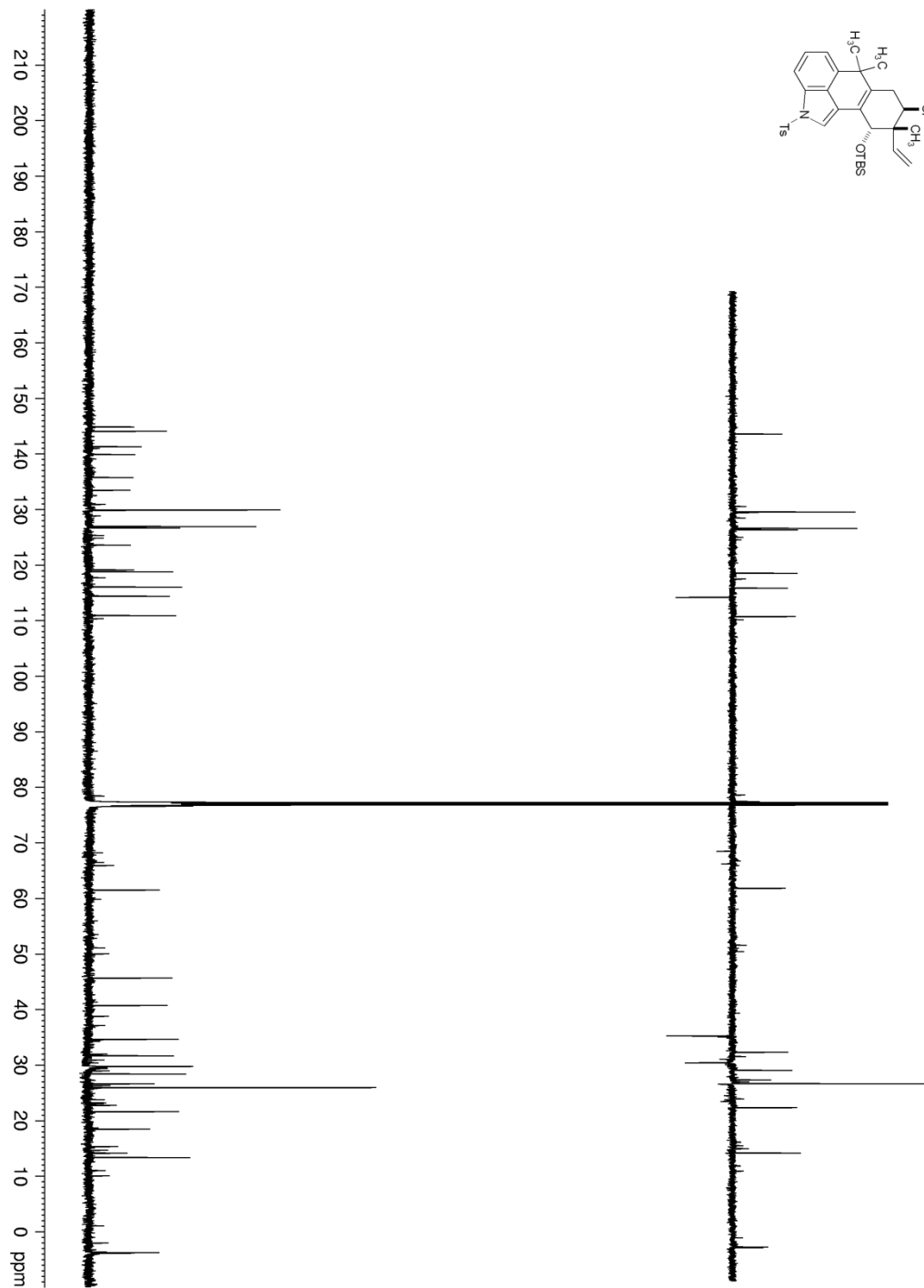


Figure 141. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 578

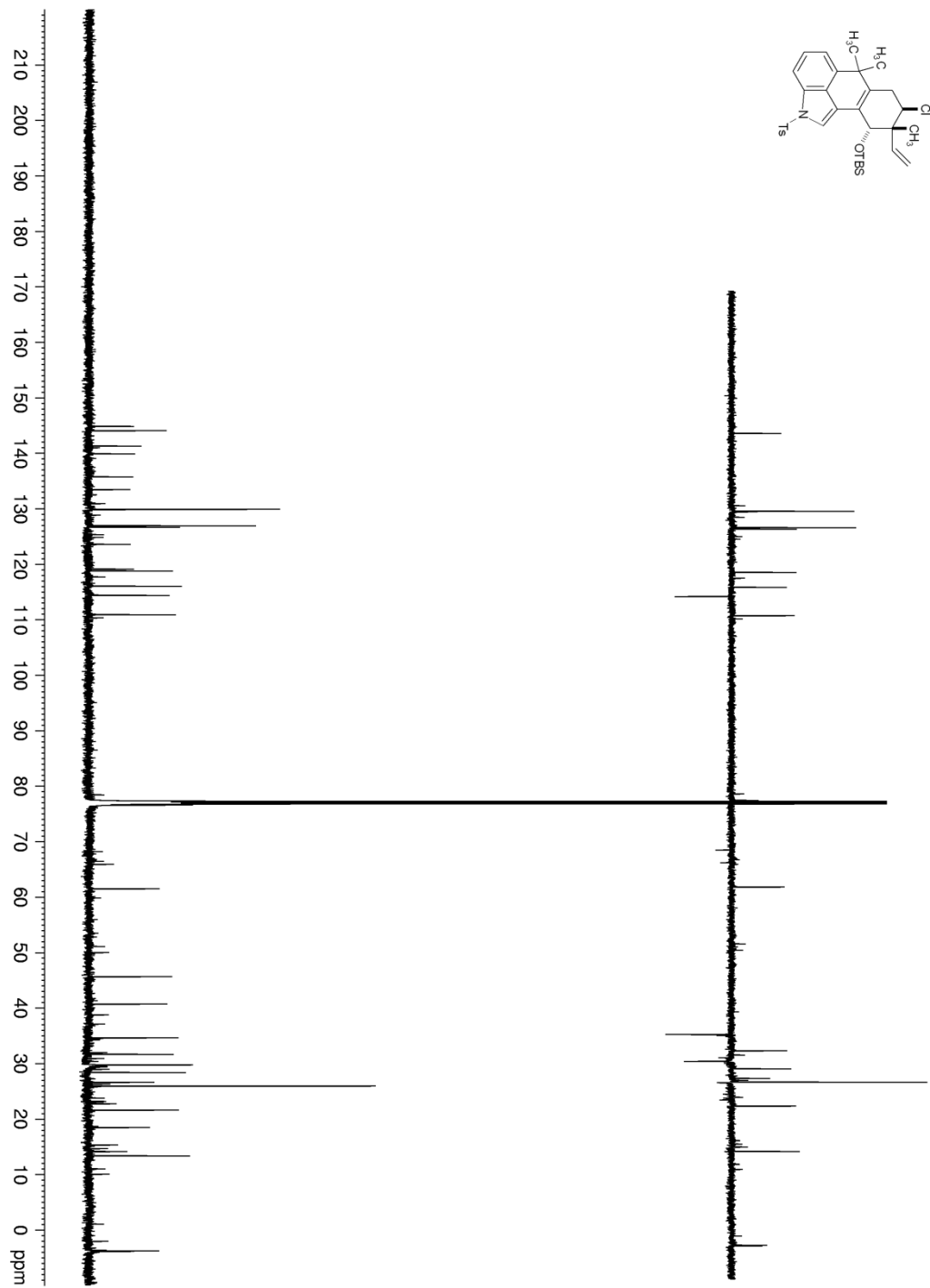


Figure 142. ^1H NMR Spectrum (600 MHz, CDCl_3) of 579

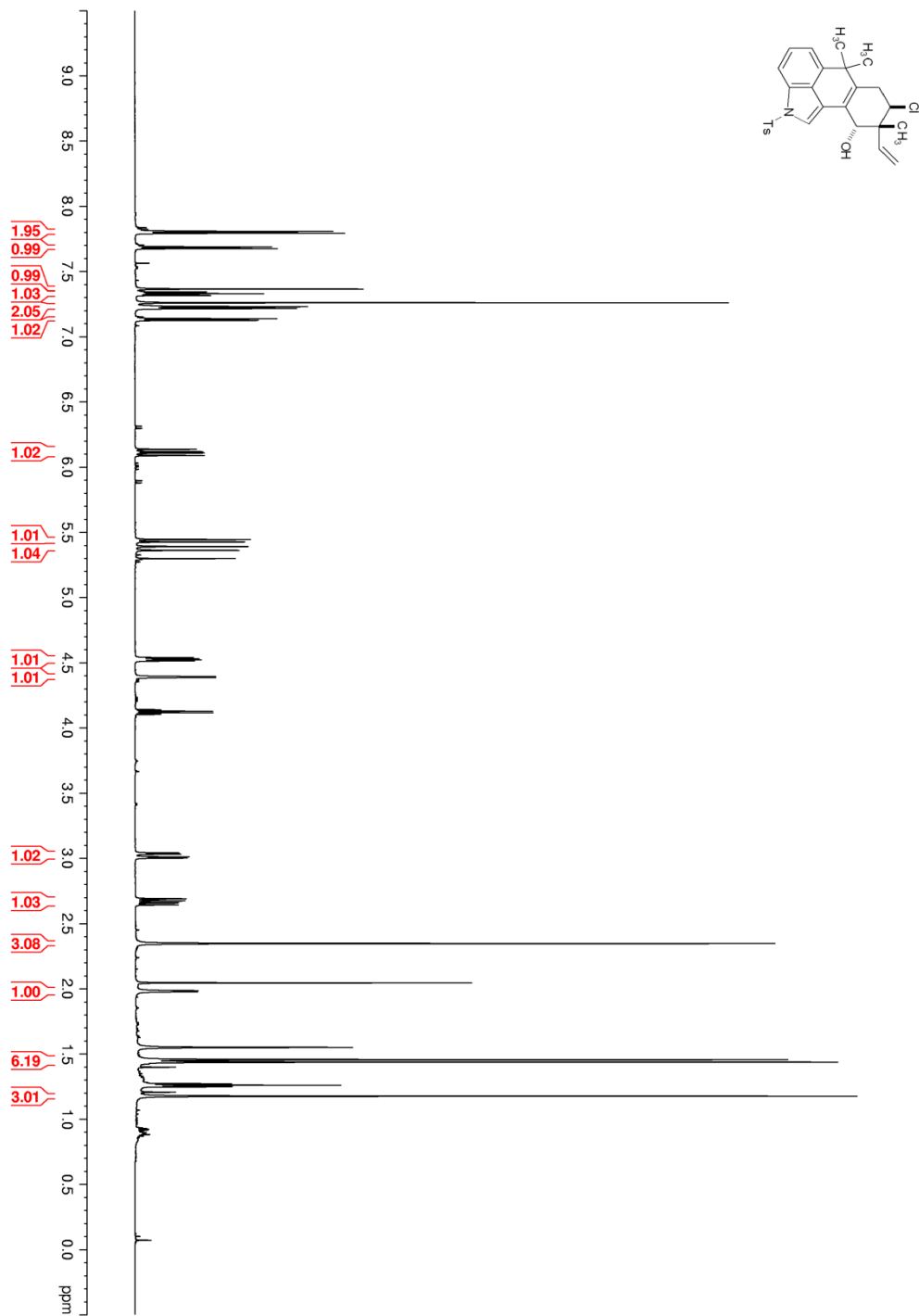


Figure 143. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 579

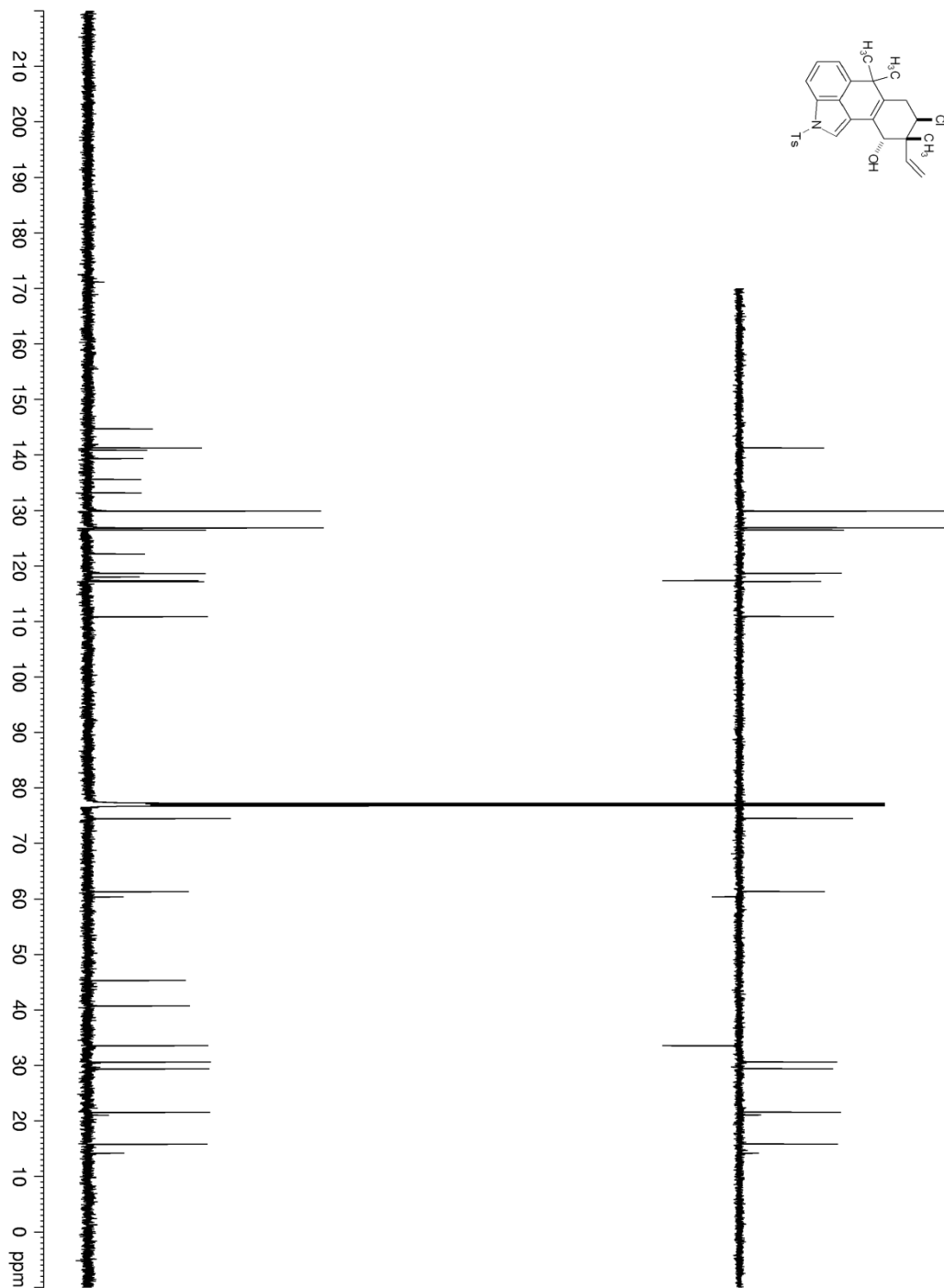


Figure 144. ^1H NMR Spectrum (400 MHz, CDCl_3) of 587

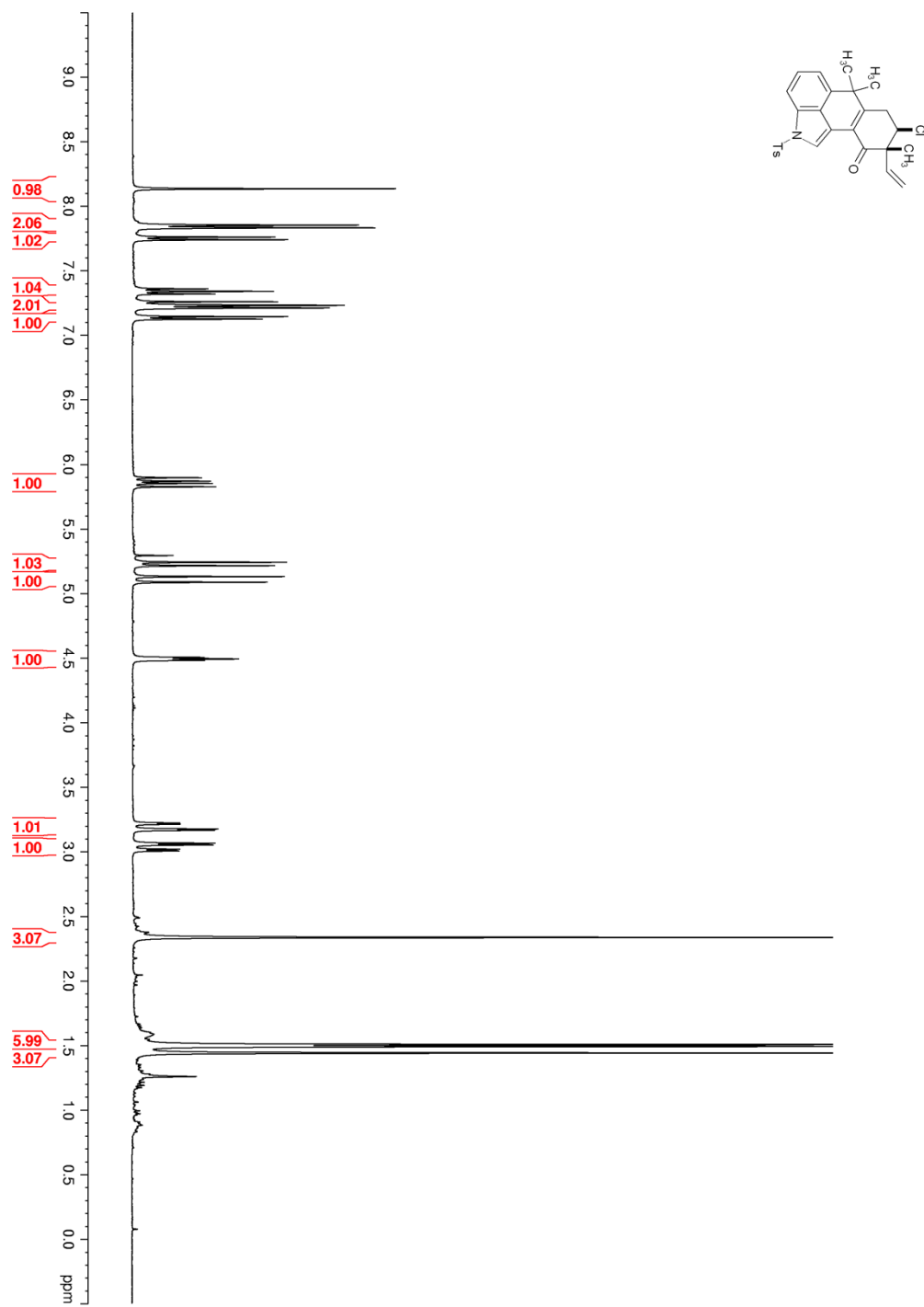


Figure 145. ^{13}C NMR Spectrum (100 MHz, CDCl_3) of 587

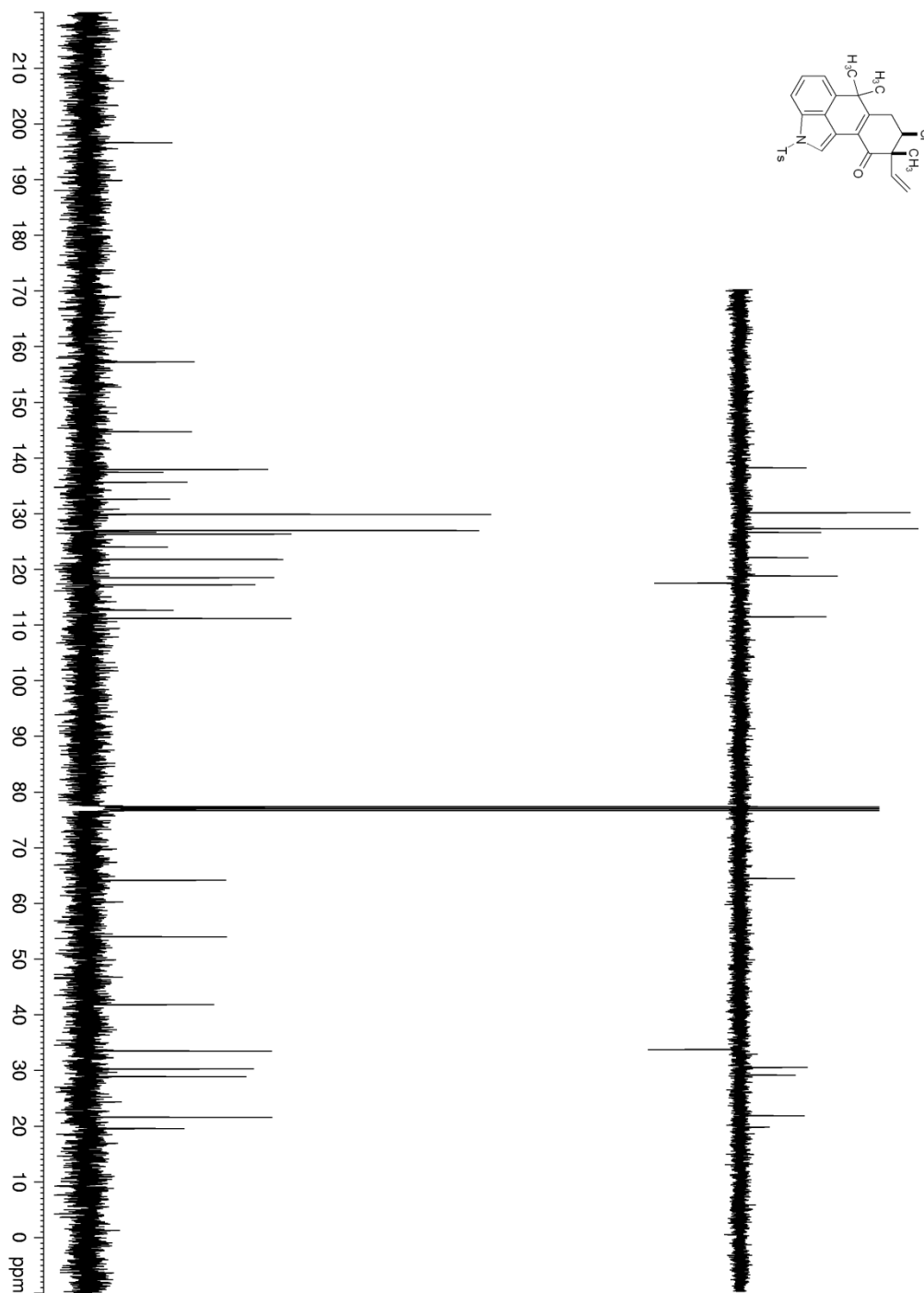


Figure 146. ^1H NMR Spectrum (400 MHz, CDCl_3) of 588

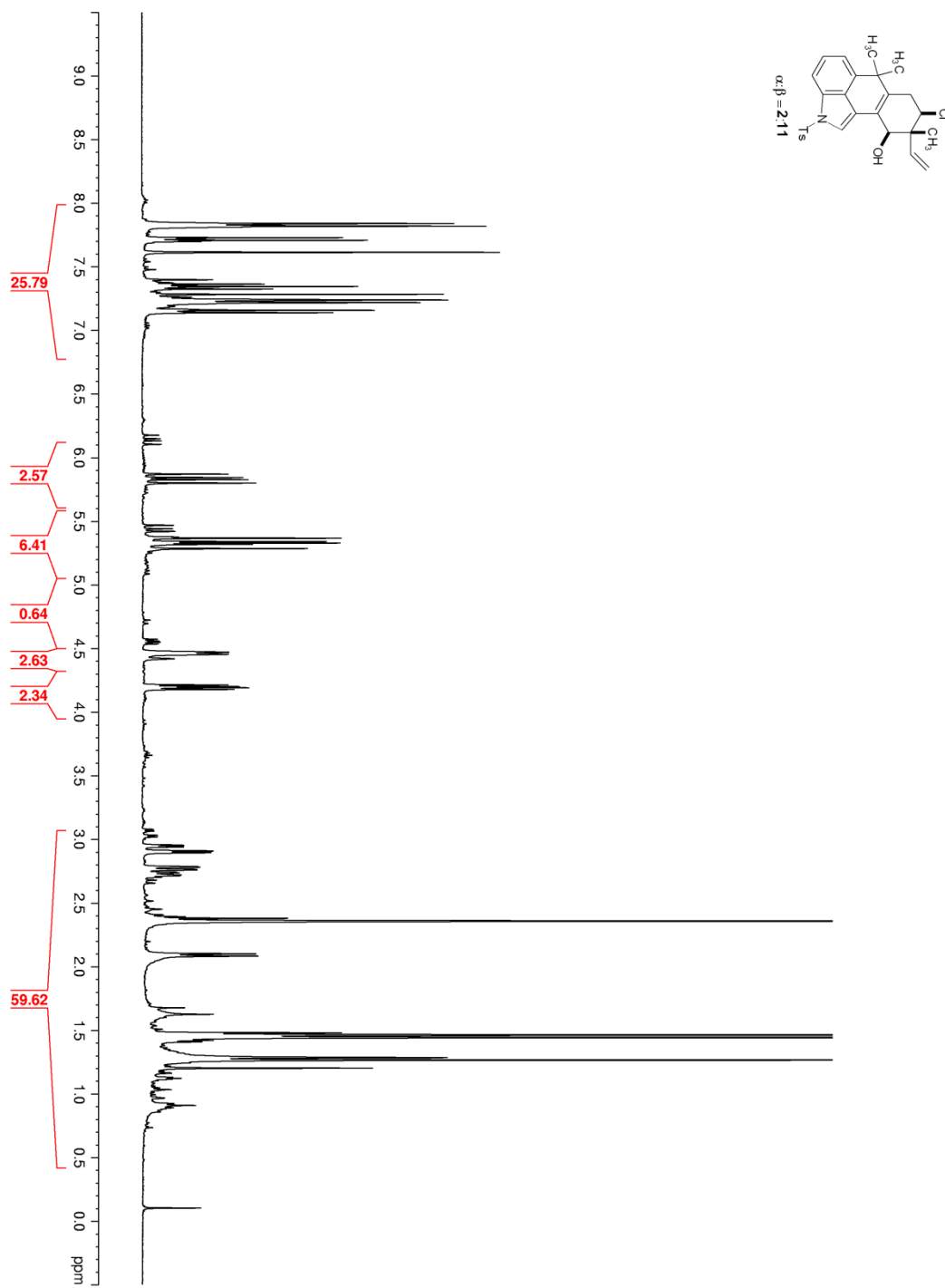


Figure 147. ^{13}C NMR Spectrum (100 MHz, CDCl_3) of 588

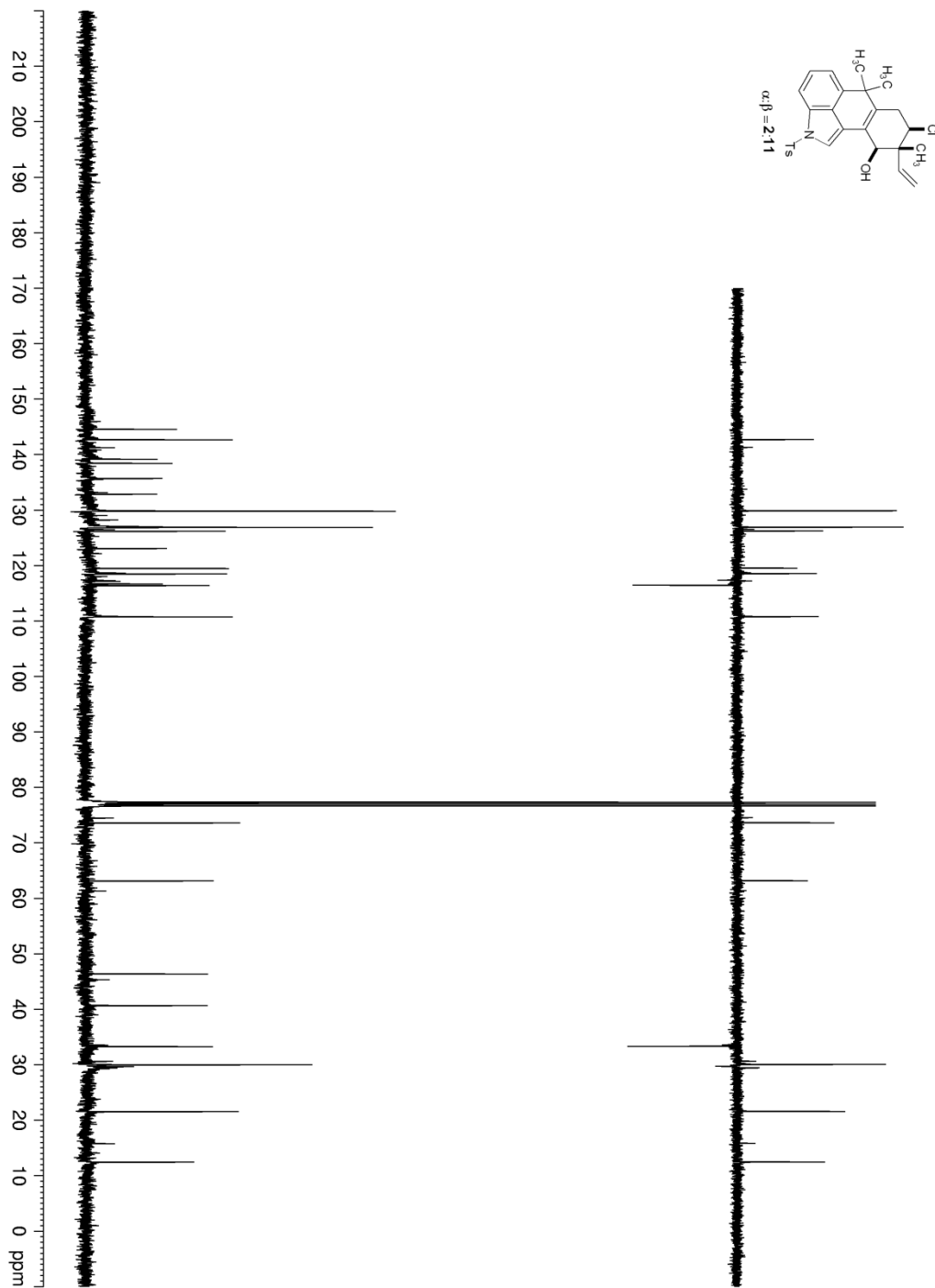


Figure 148. ¹H NMR Spectrum (500 MHz, CDCl₃) of 596

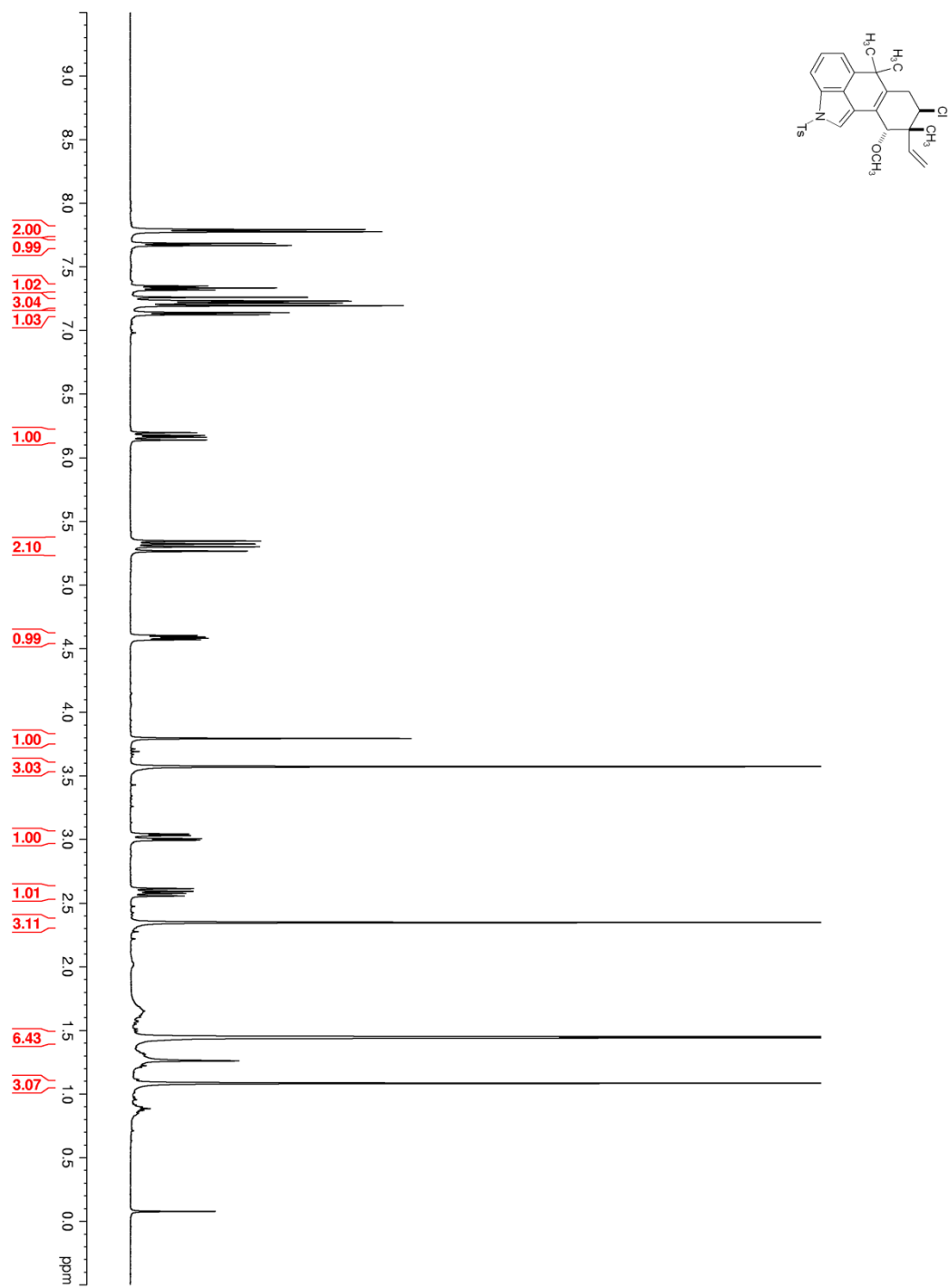


Figure 150. ¹H NMR Spectrum (400 MHz, CDCl₃) of 597

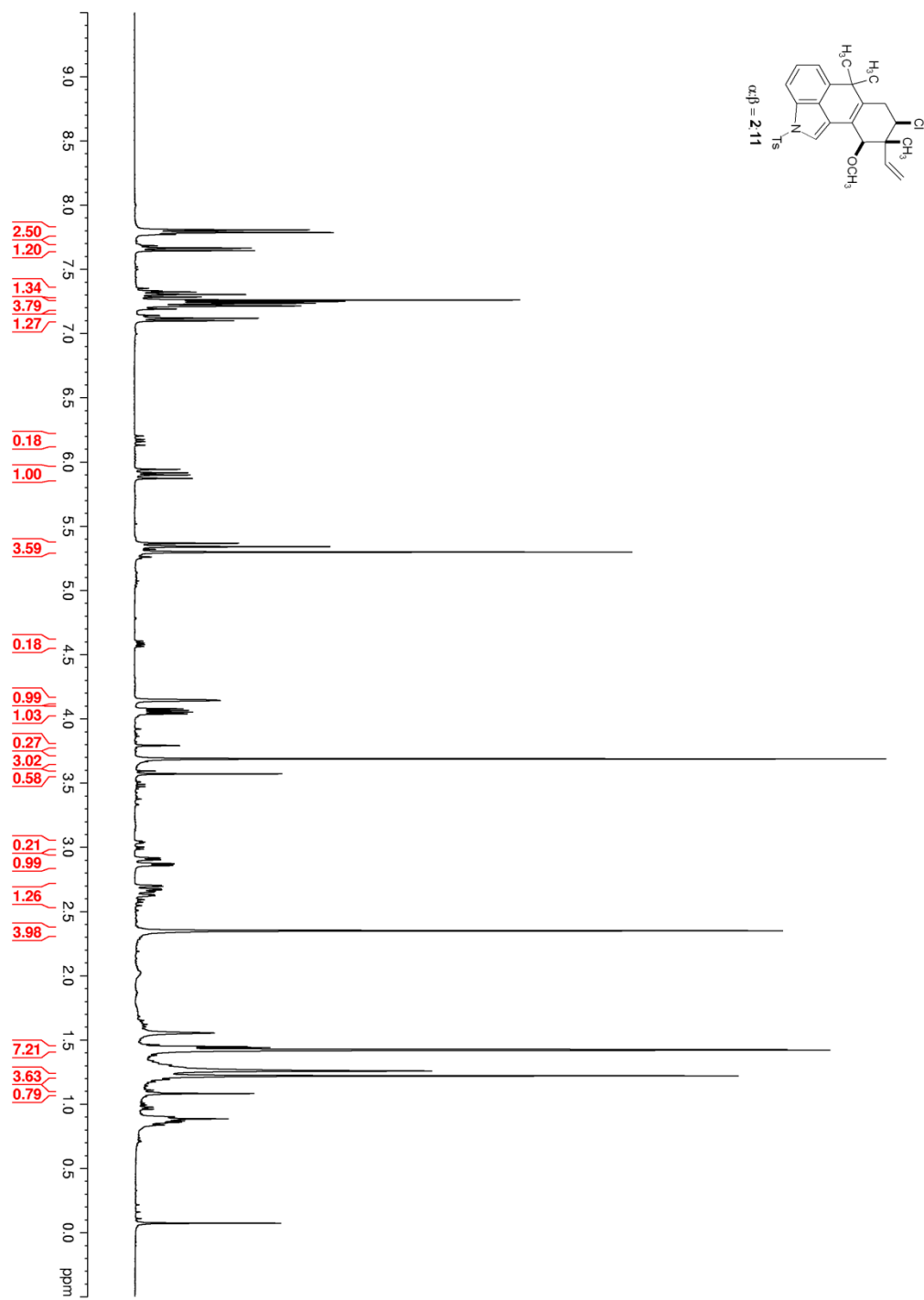


Figure 151. ^{13}C NMR Spectrum (100 MHz, CDCl_3) of 597

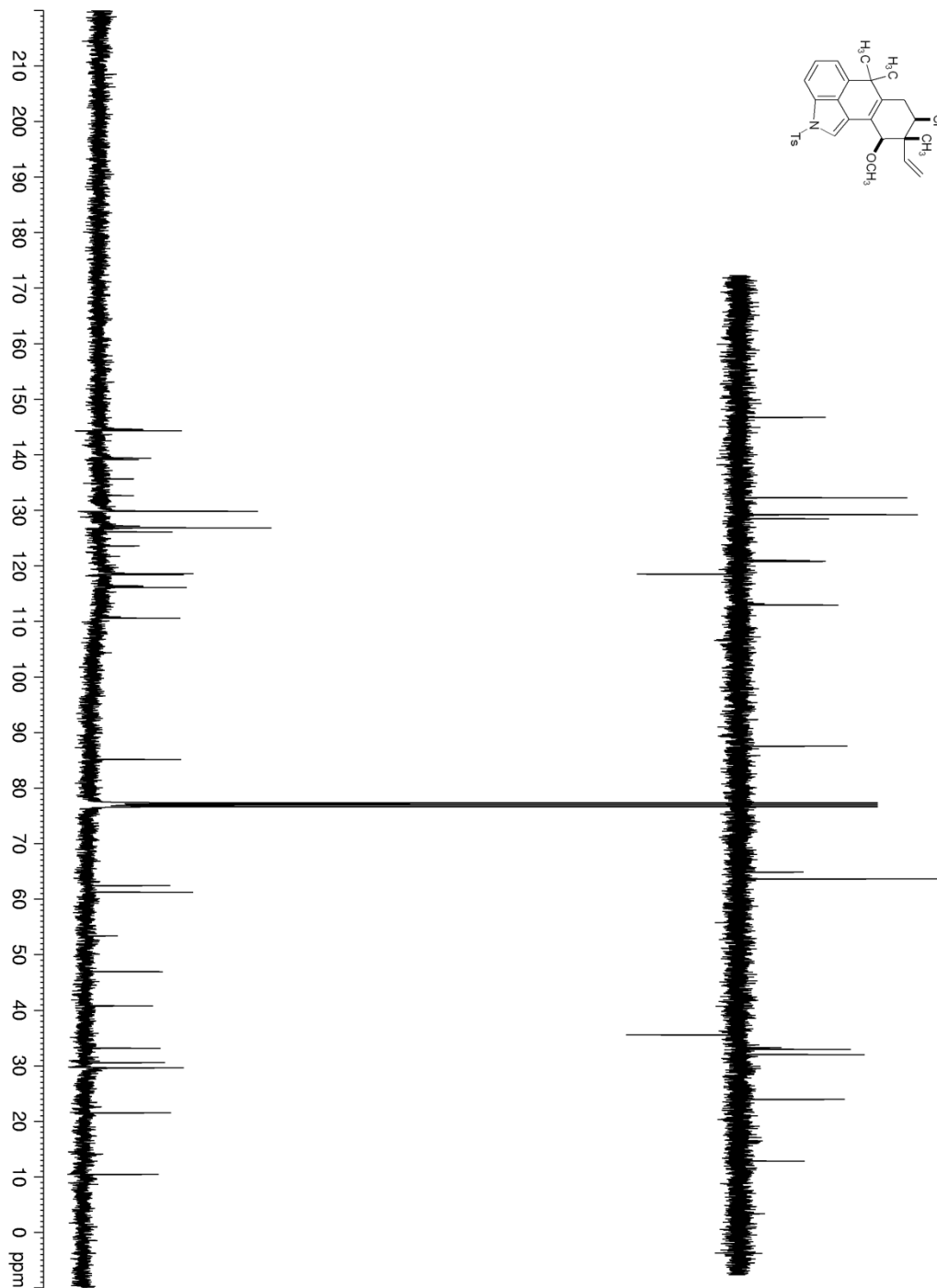


Figure 152. ¹H NMR Spectrum (600 MHz, CDCl₃) of 598

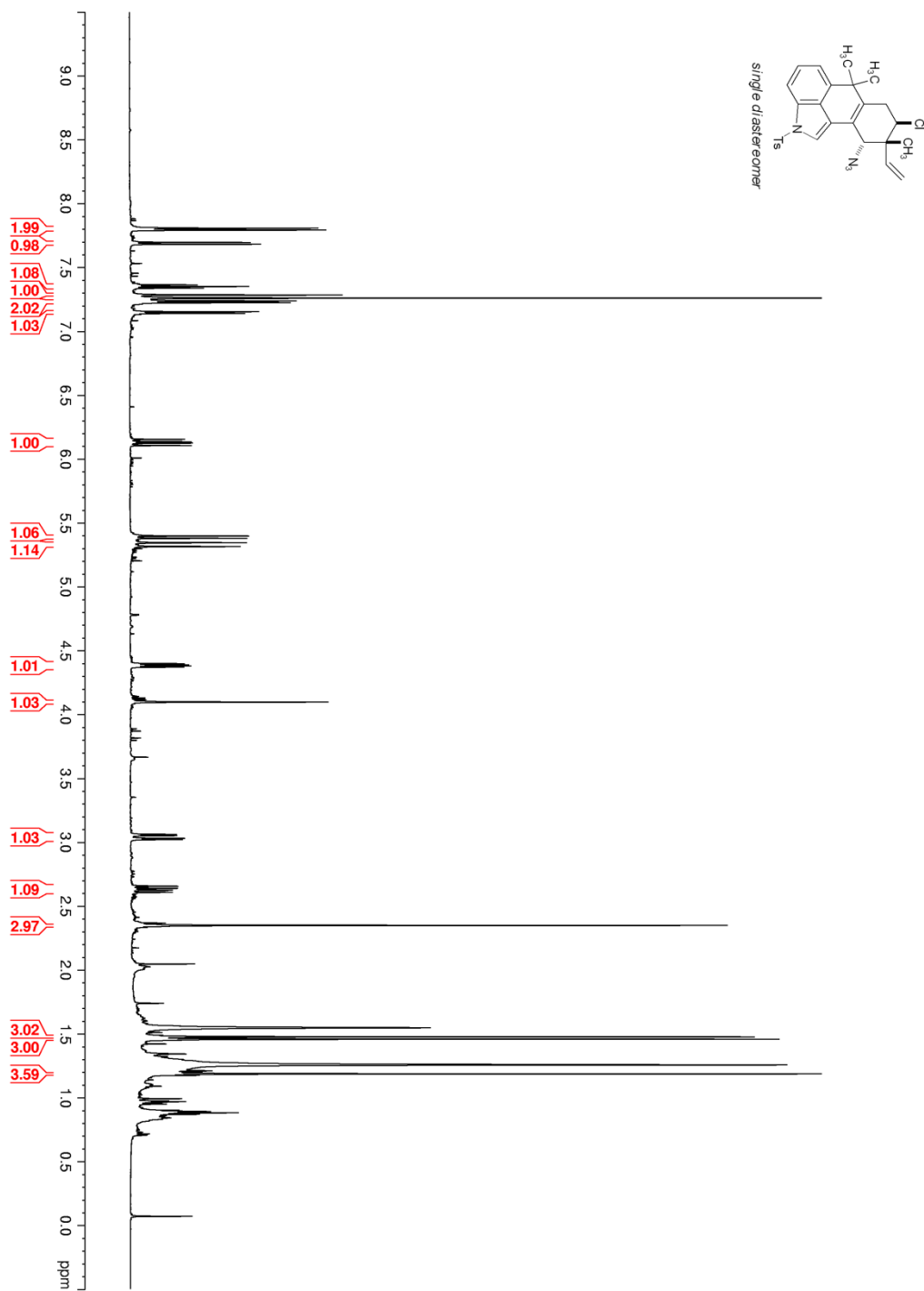


Figure 153. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 598

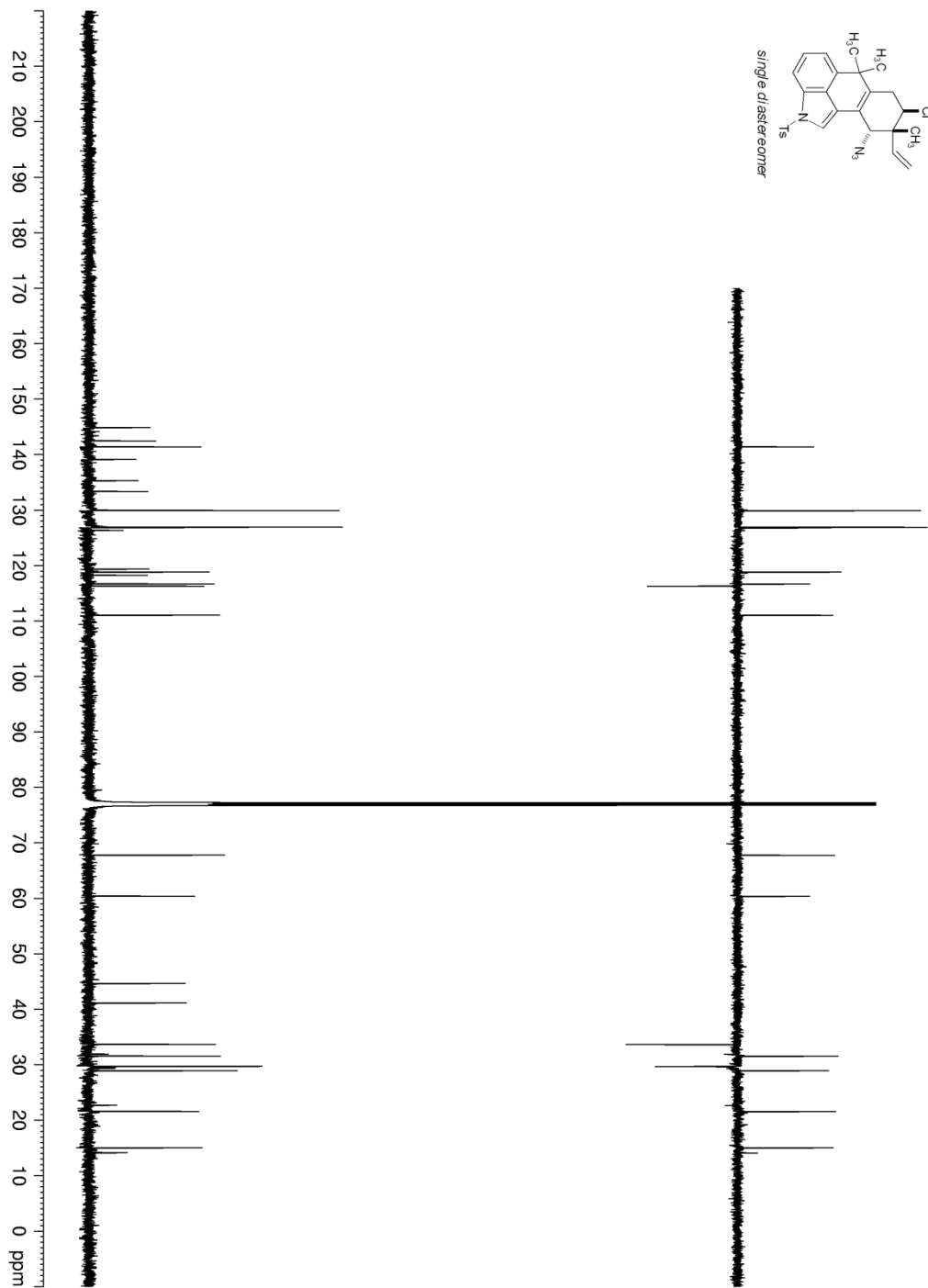


Figure 154. HSQC Spectrum (150 MHz, CDCl₃) of 598

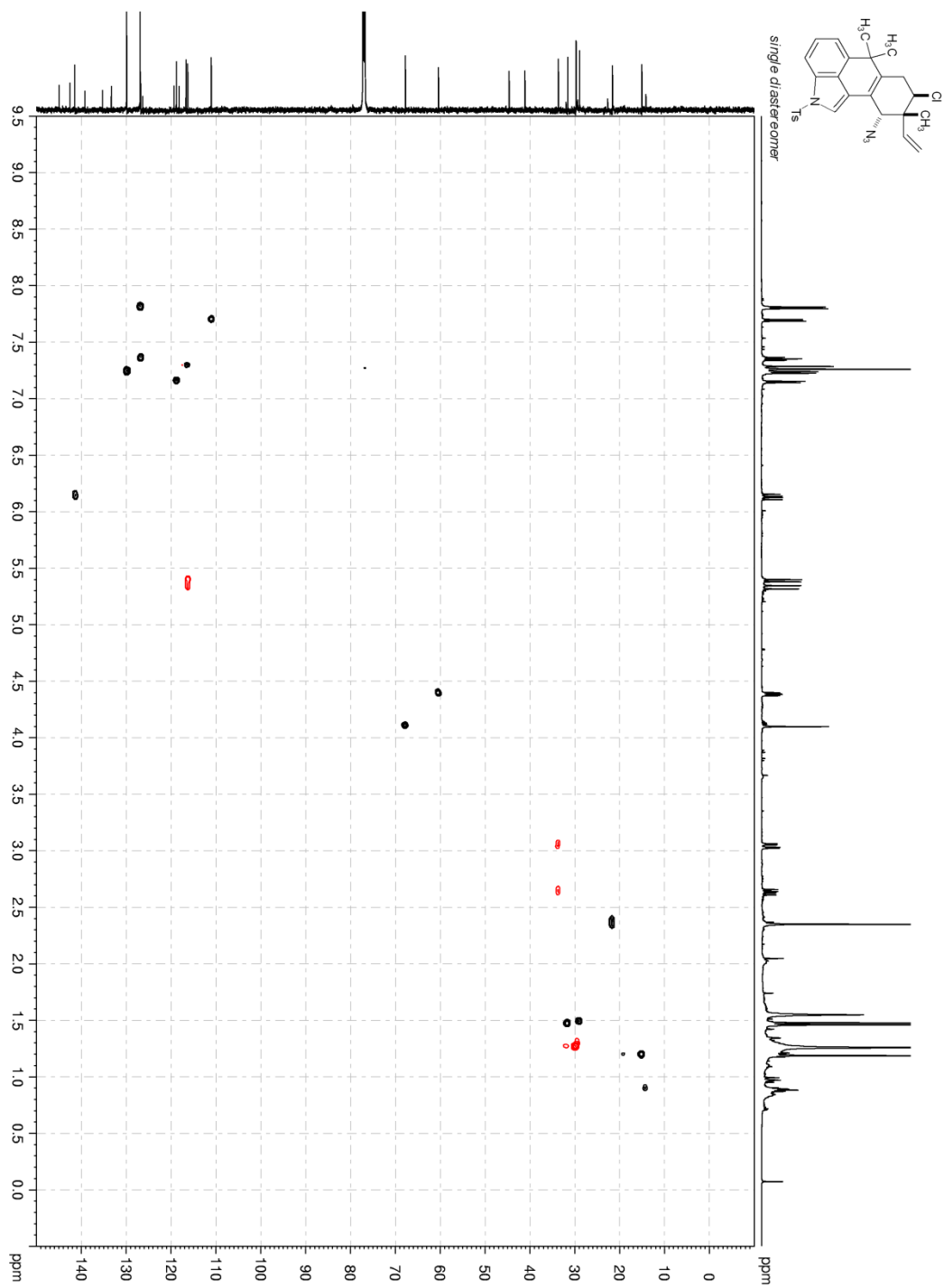


Figure 155. HMBC Spectrum (150 MHz, CDCl₃) of 598

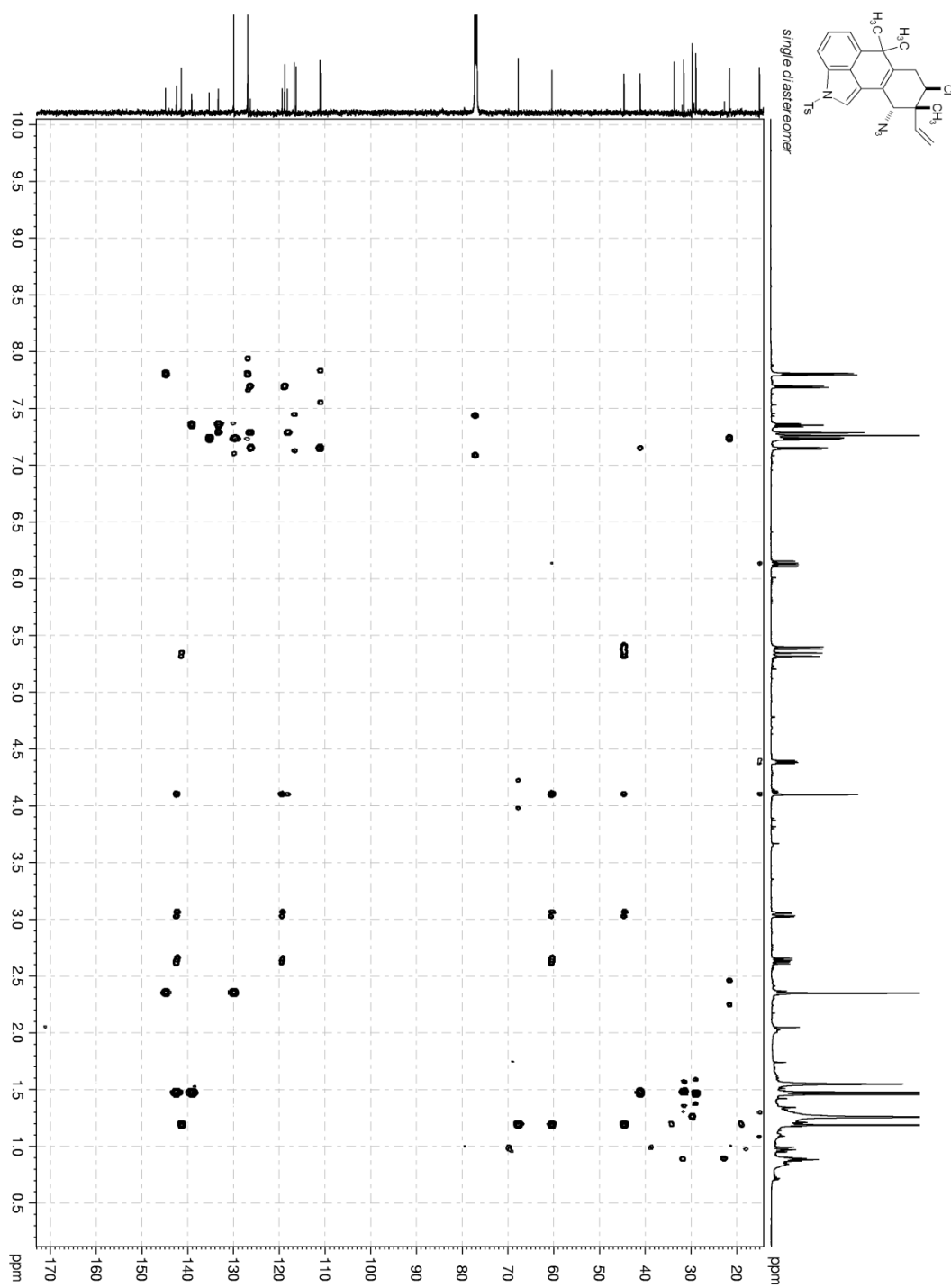


Figure 156. NOESY Spectrum (600 MHz, CDCl₃) of 598

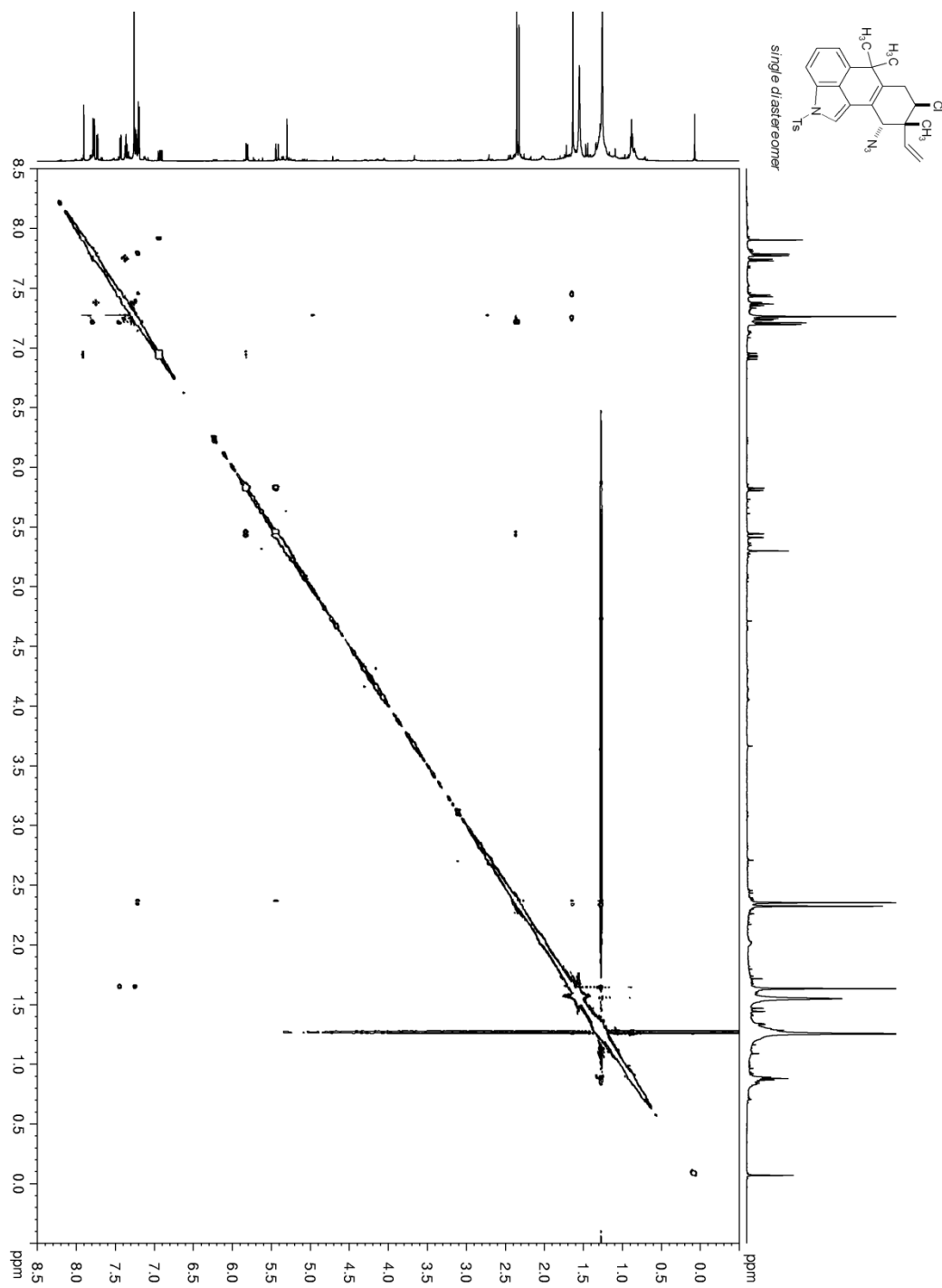


Figure 157. ^1H NMR Spectrum (400 MHz, CDCl_3) of 600

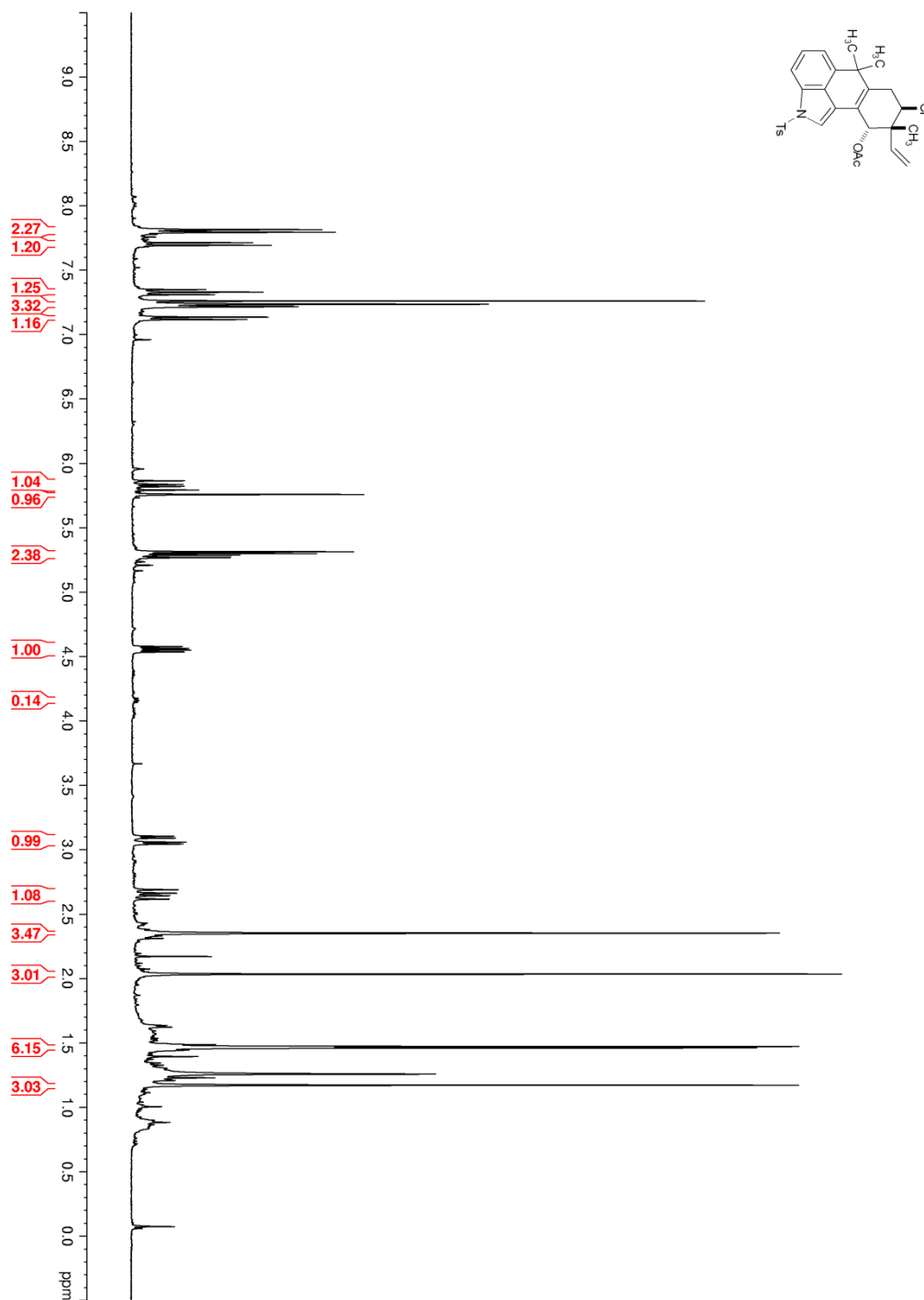


Figure 158. ^{13}C NMR Spectrum (100 MHz, CDCl_3) of 600

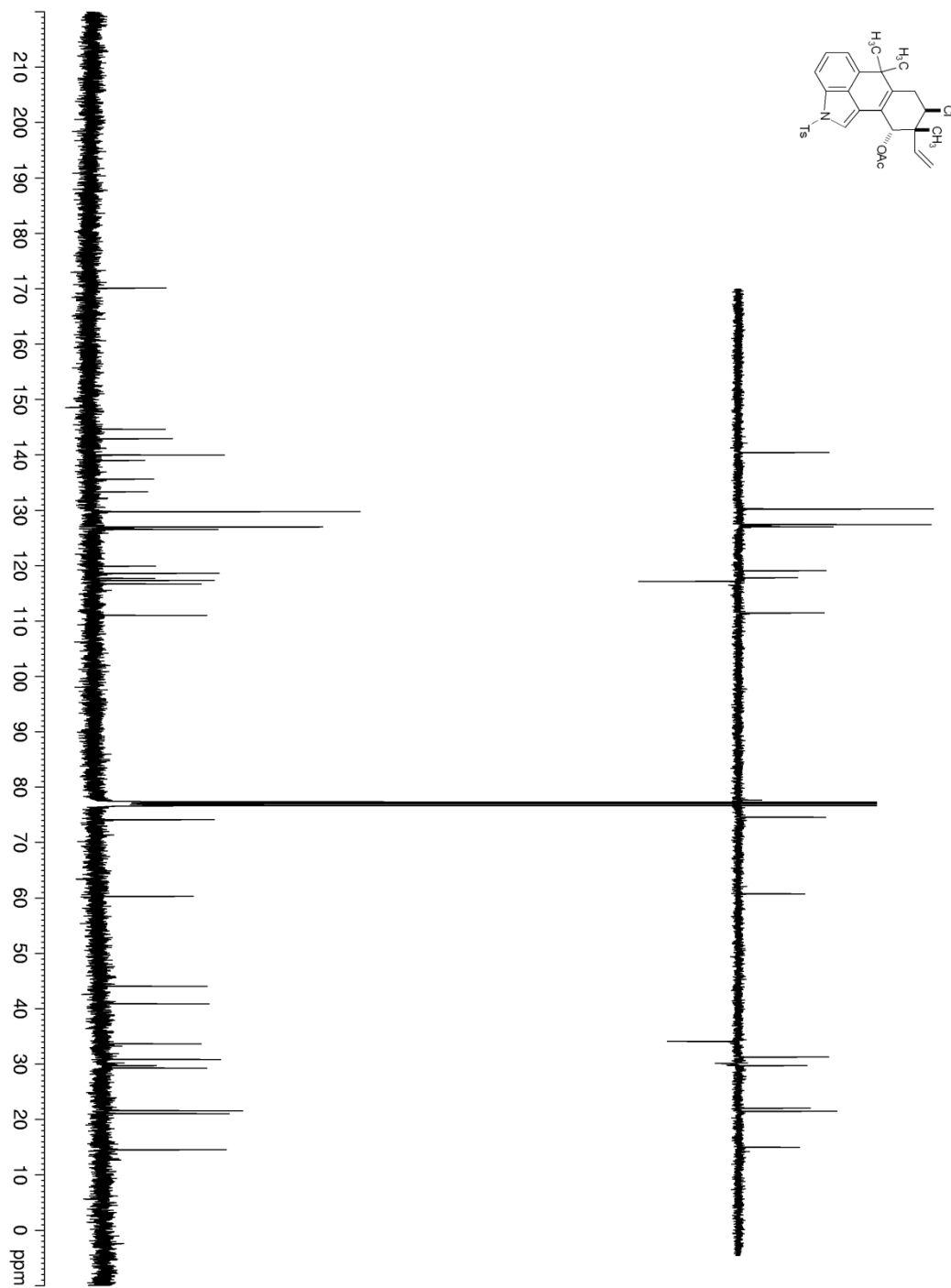


Figure 159. ^1H NMR Spectrum (400 MHz, CDCl_3) of 601

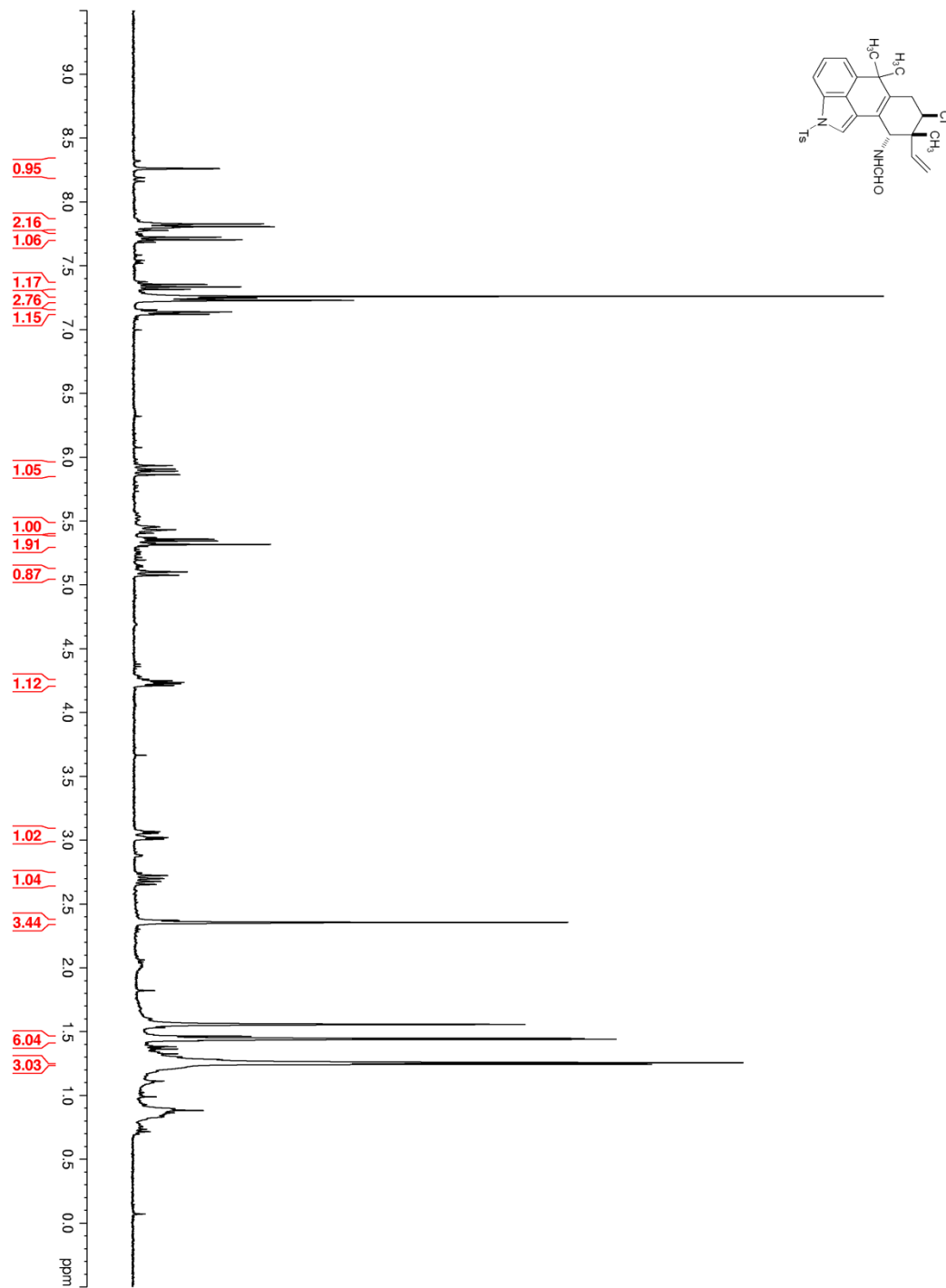


Figure 160. ^{13}C NMR Spectrum (125 MHz, CDCl_3) of 601

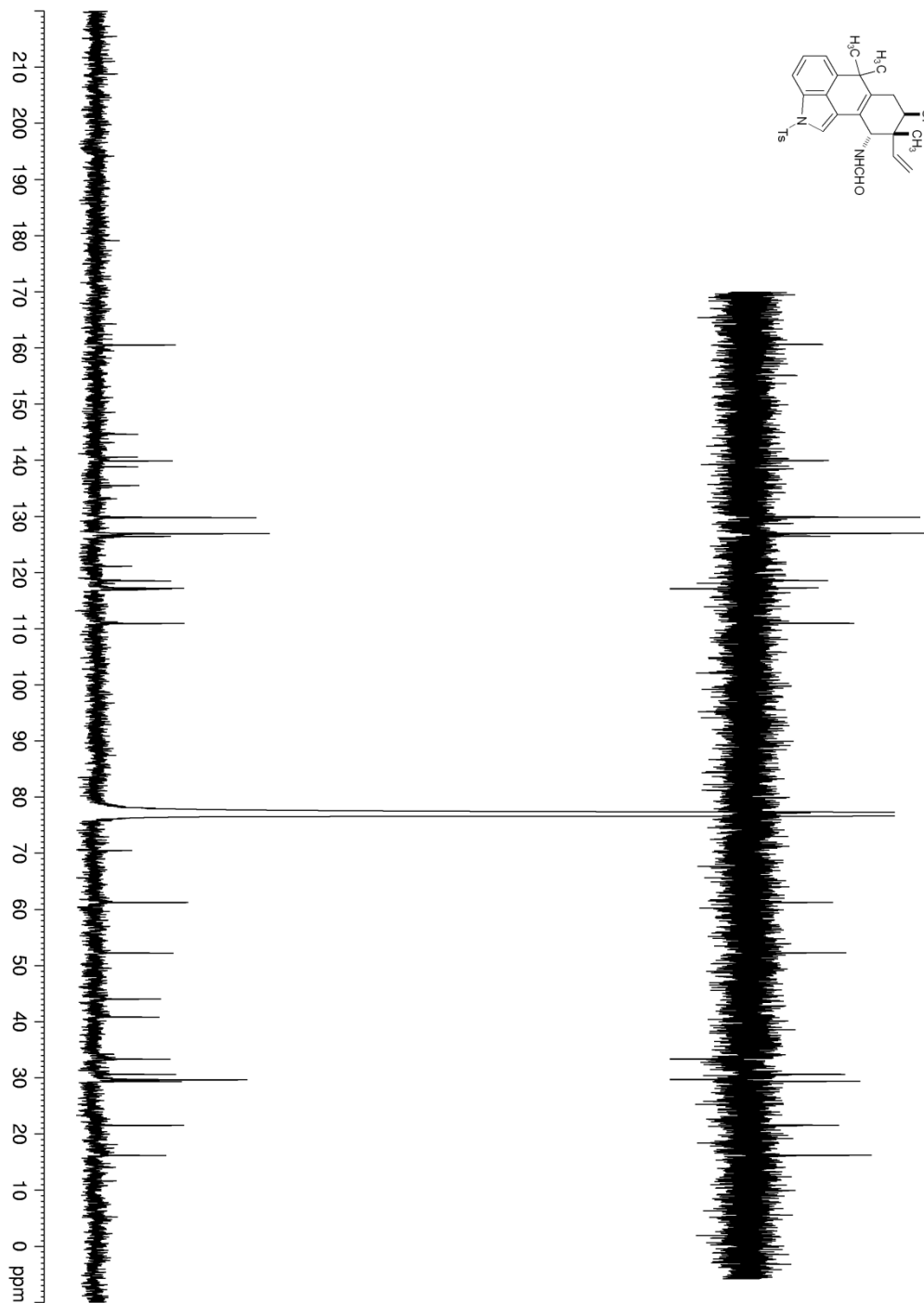


Figure 161. ^1H NMR Spectrum (600 MHz, CDCl_3) of 602 (hapalindole K)

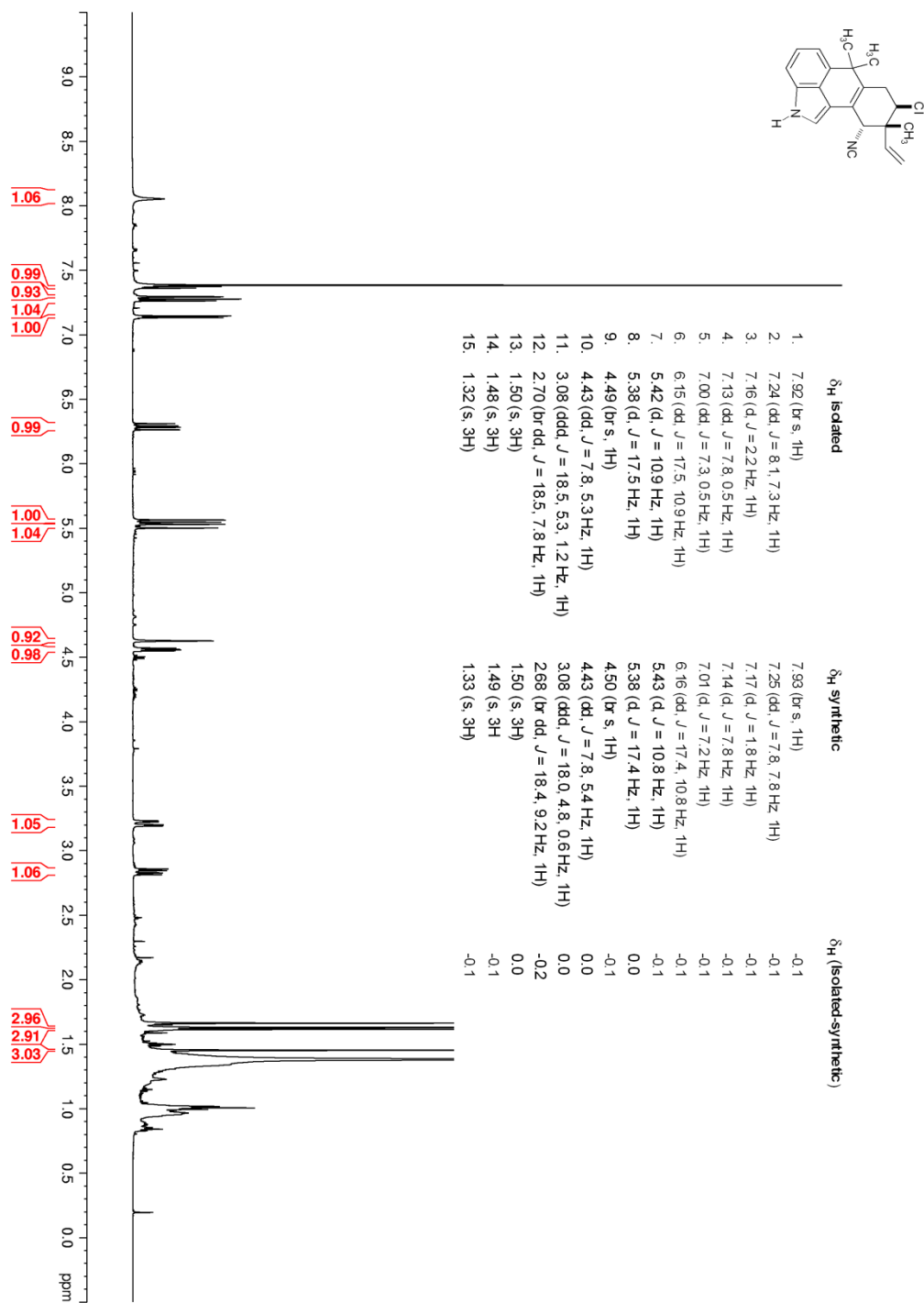


Figure 162. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 602 (hapalindole K)

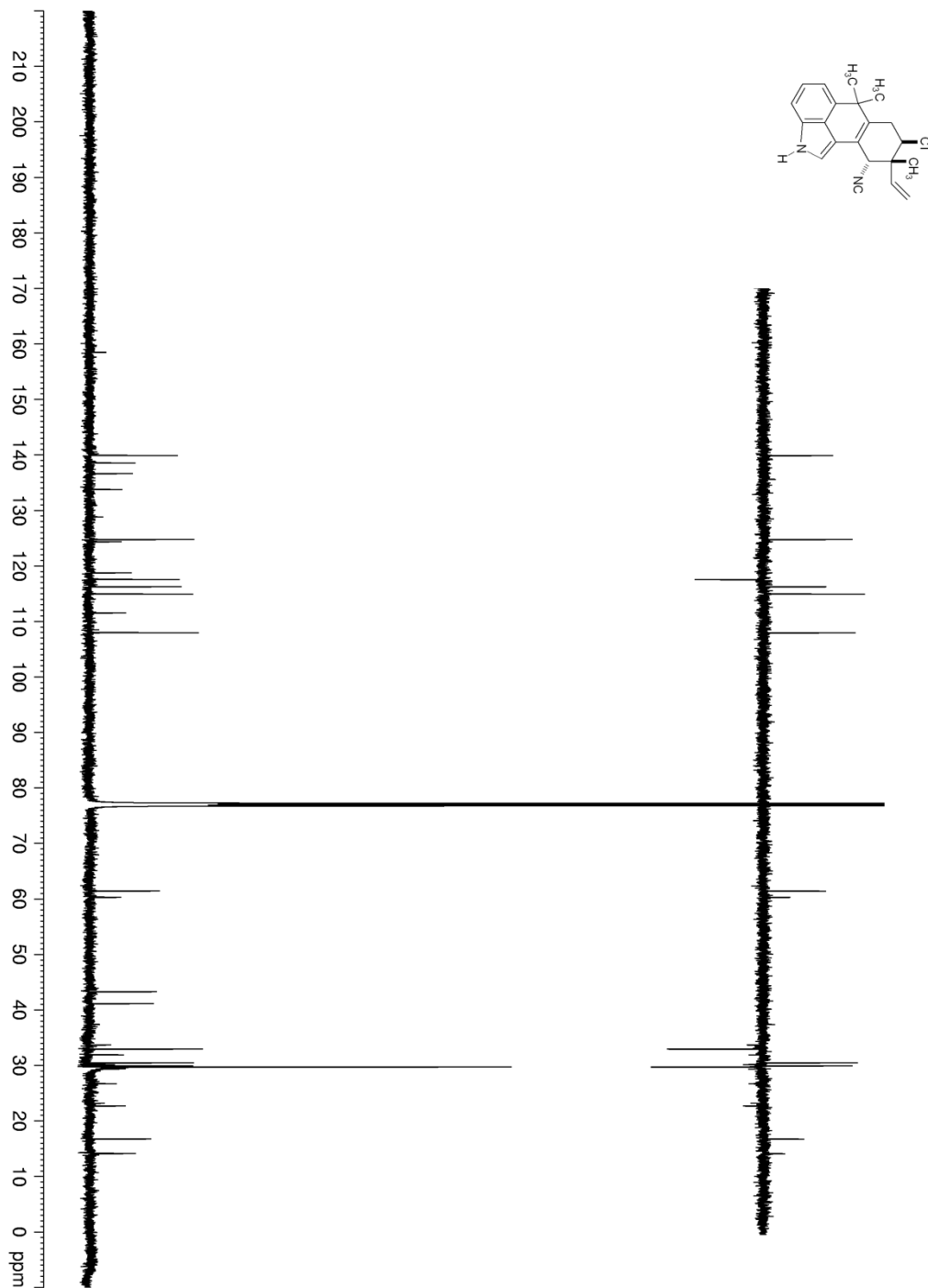


Figure 163. ^1H NMR Spectrum (500 MHz, CDCl_3) of 603

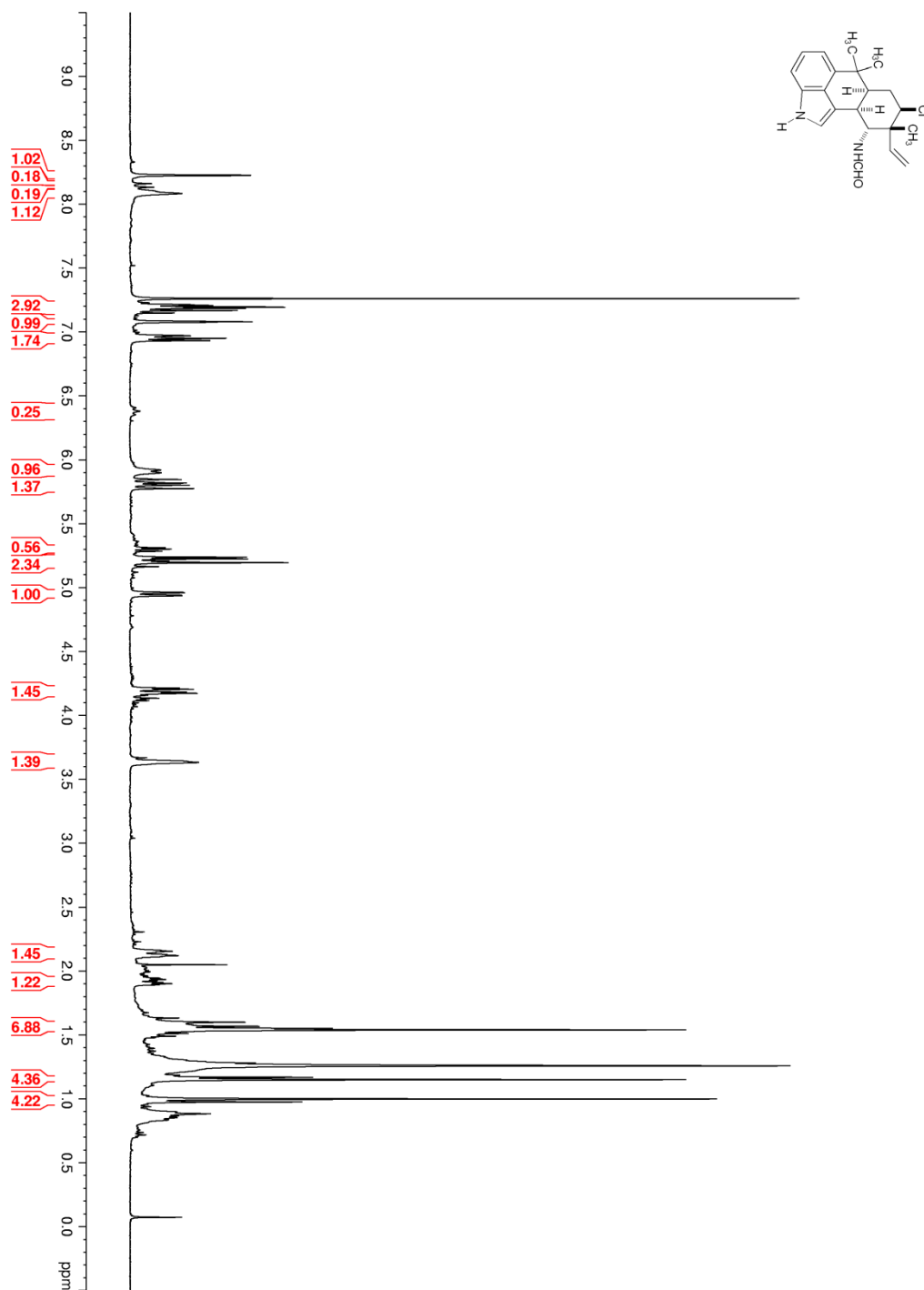


Figure 164. ^{13}C NMR Spectrum (125 MHz, CDCl_3) of 603

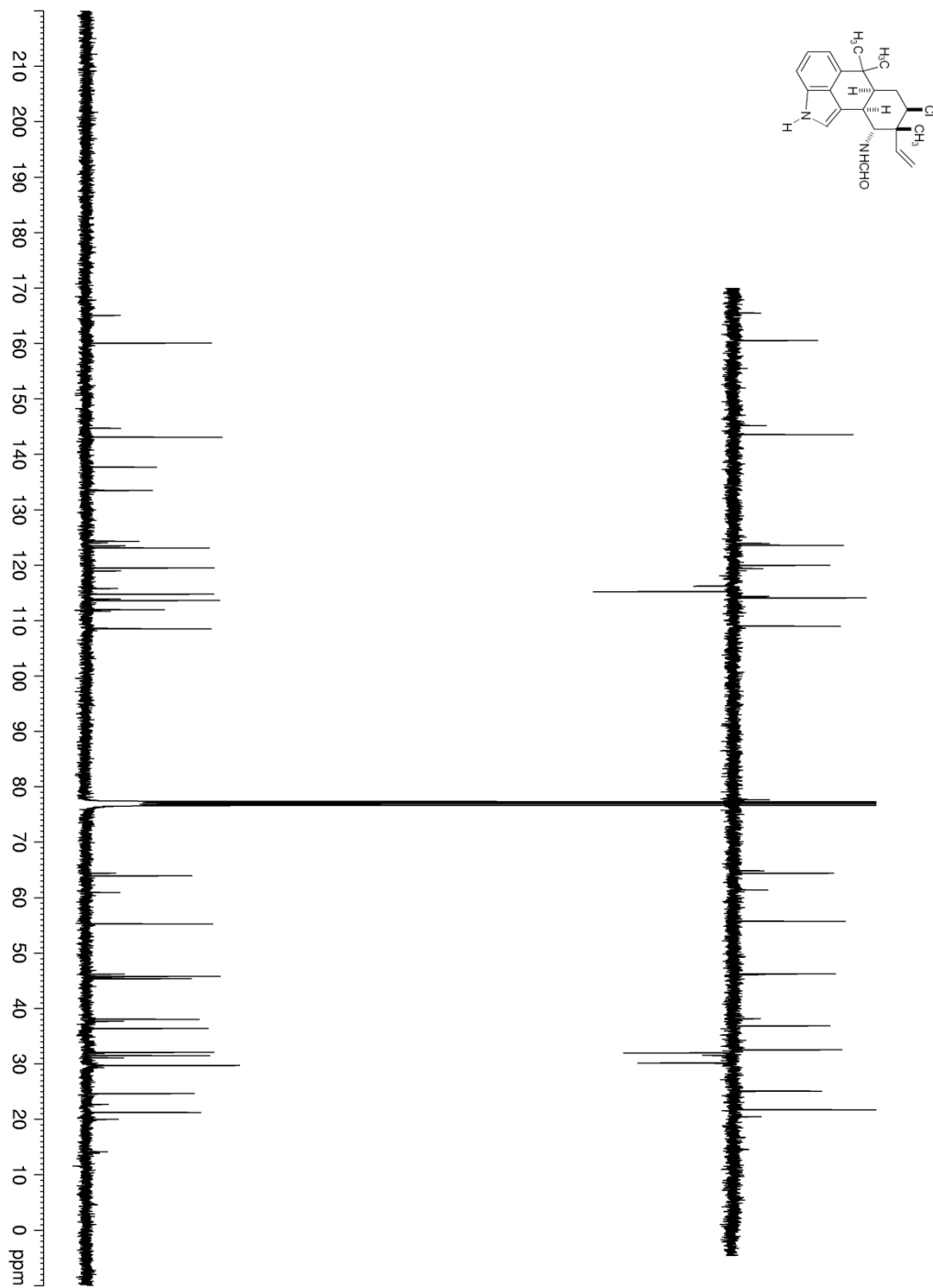


Figure 165. ^1H NMR Spectrum (600 MHz, CDCl_3) of 604

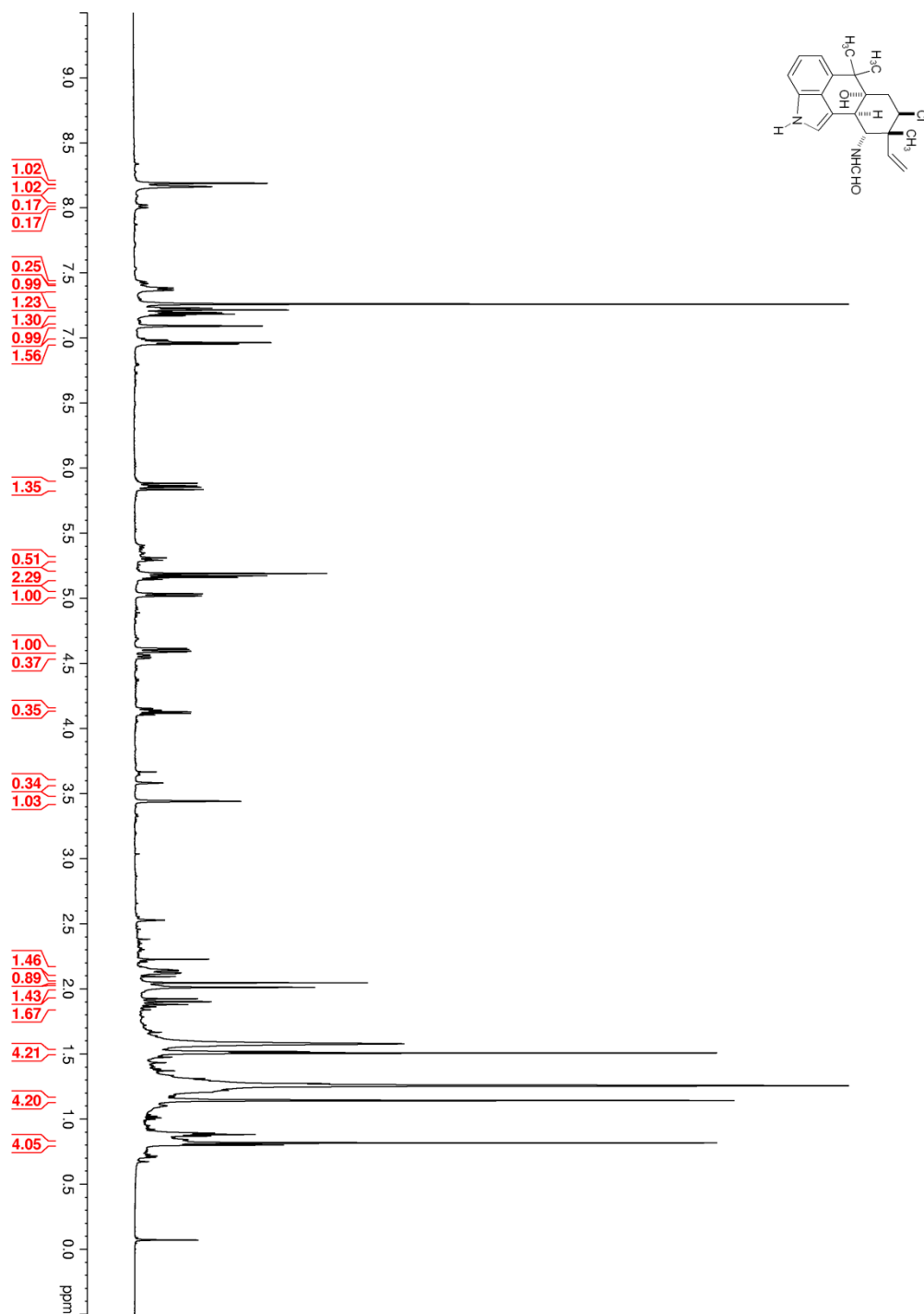


Figure 166. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 604

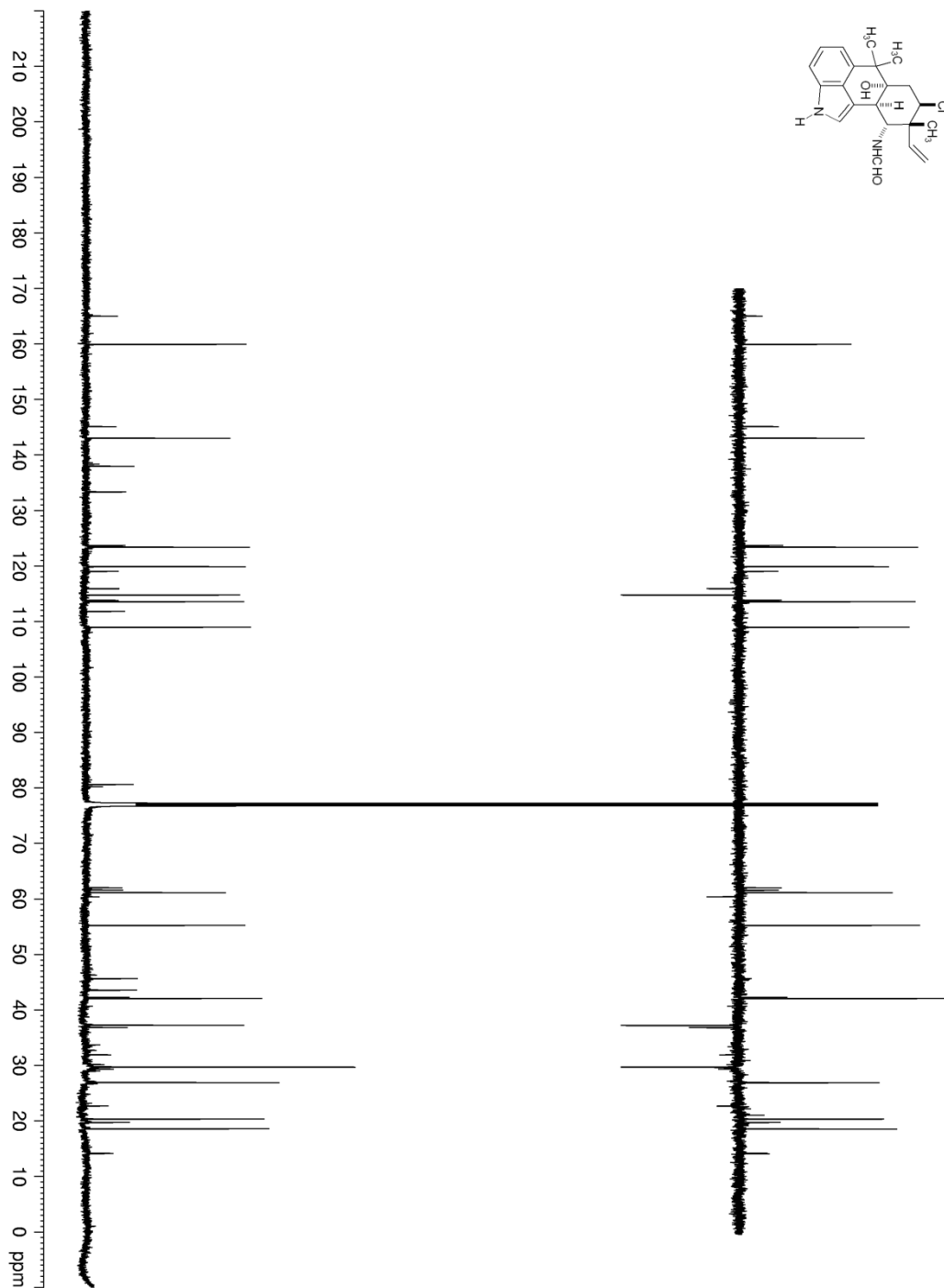


Figure 167. HSQC Spectrum (150 MHz, CDCl₃) of 604

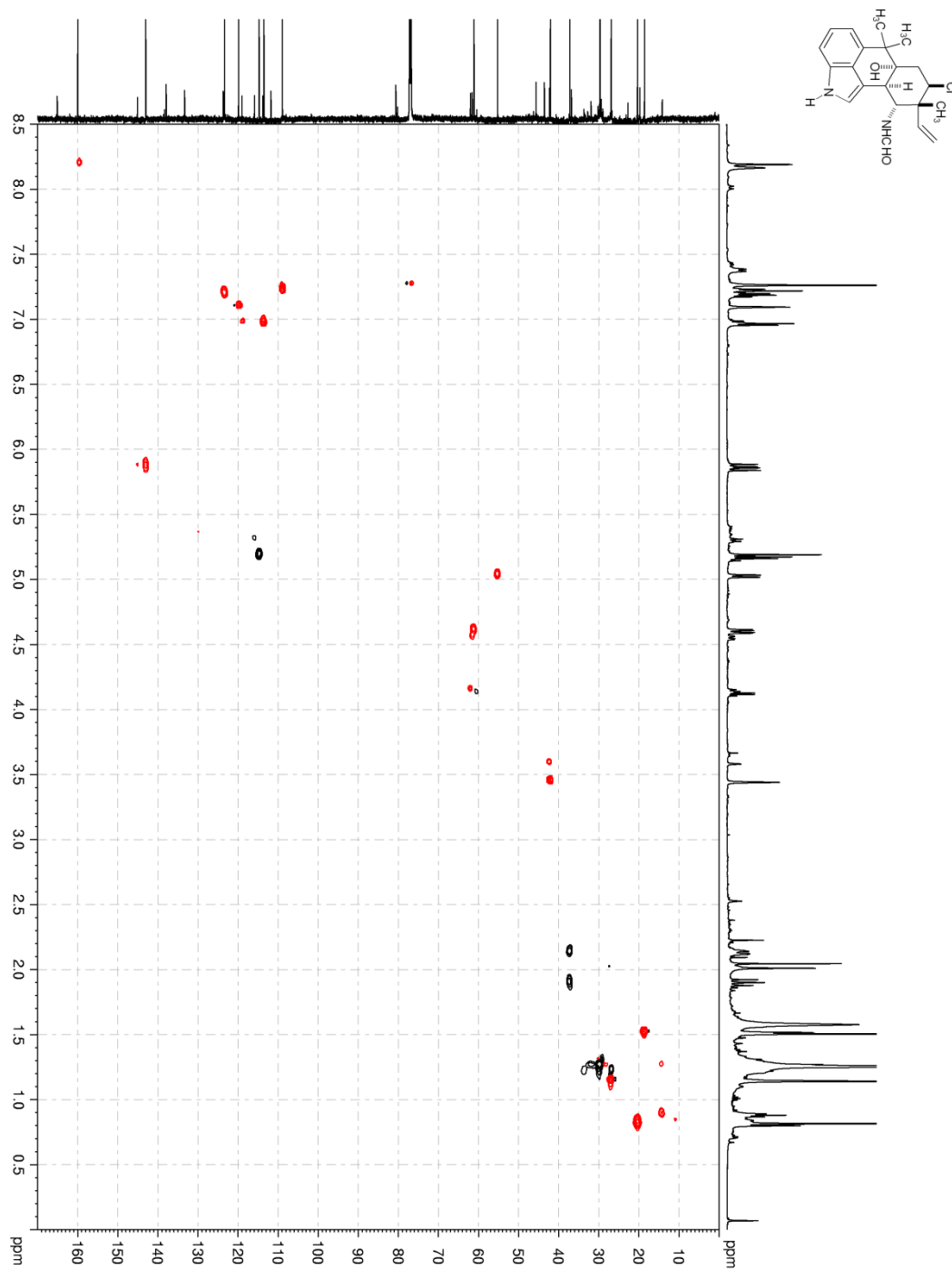


Figure 168. NOESY Spectrum (600 MHz, CDCl₃) of 604

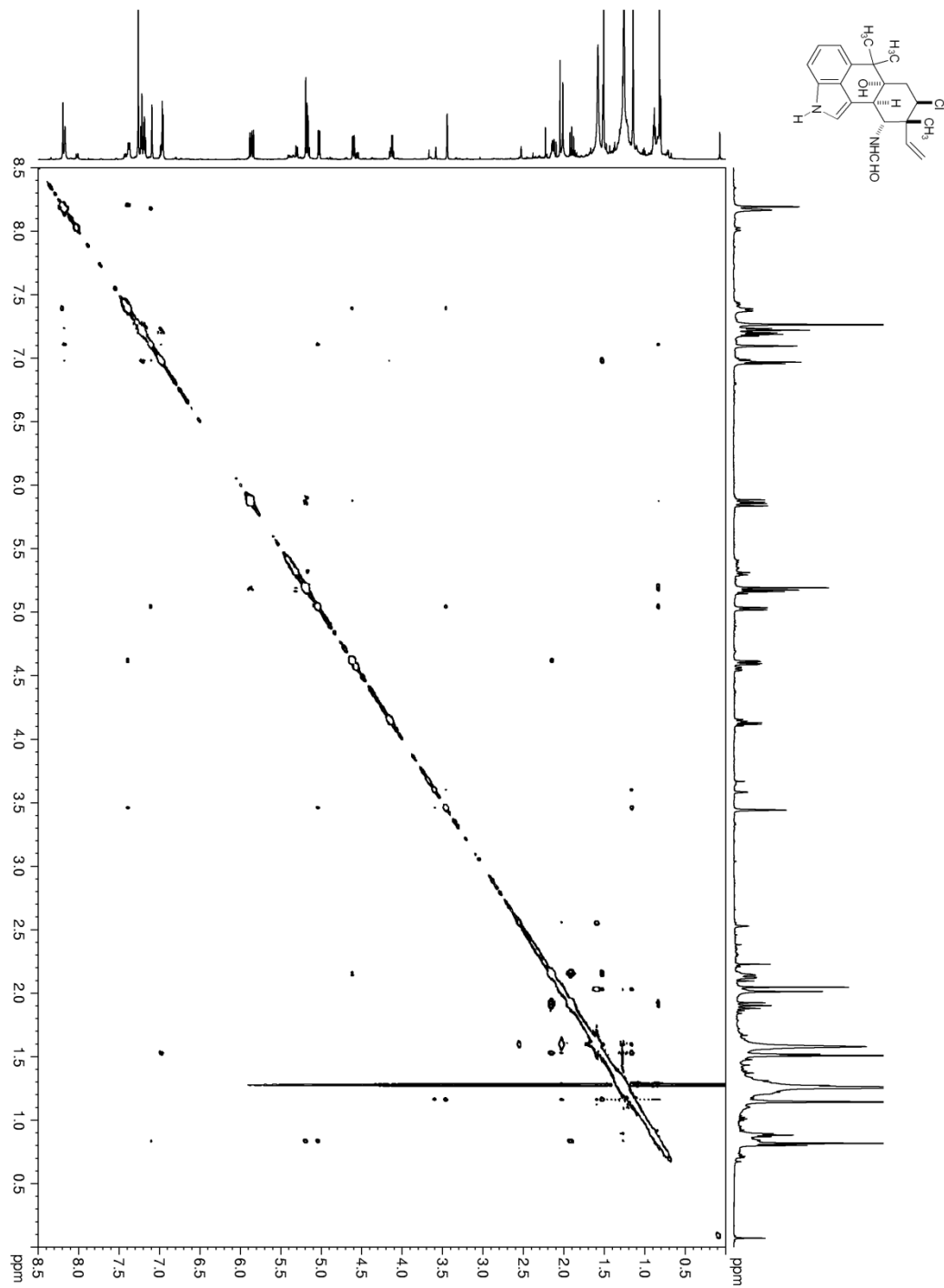


Figure 169. ¹H NMR Spectrum (400 MHz, CDCl₃) of 605

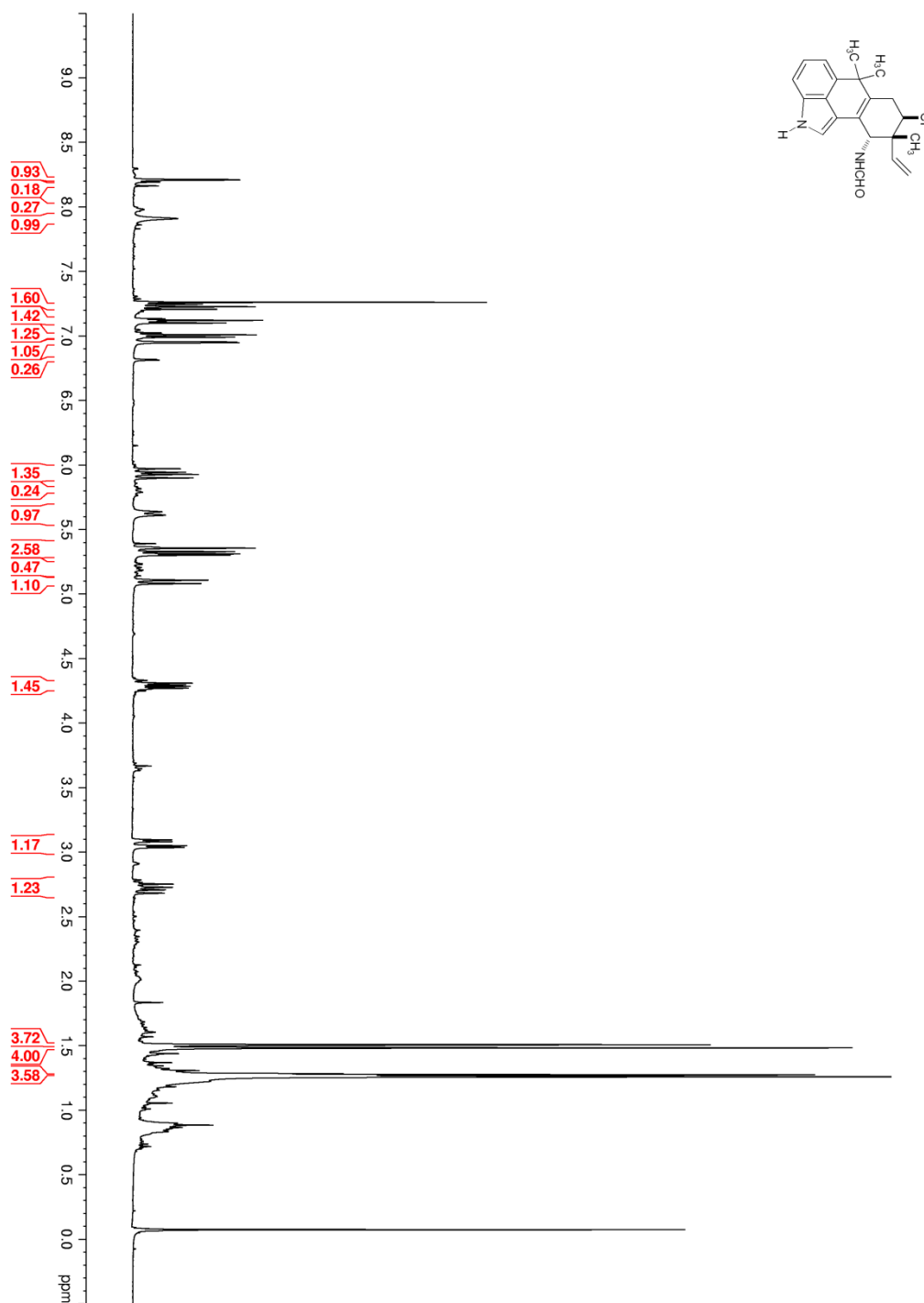


Figure 170. ^{13}C NMR Spectrum (100 MHz, CDCl_3) of 605

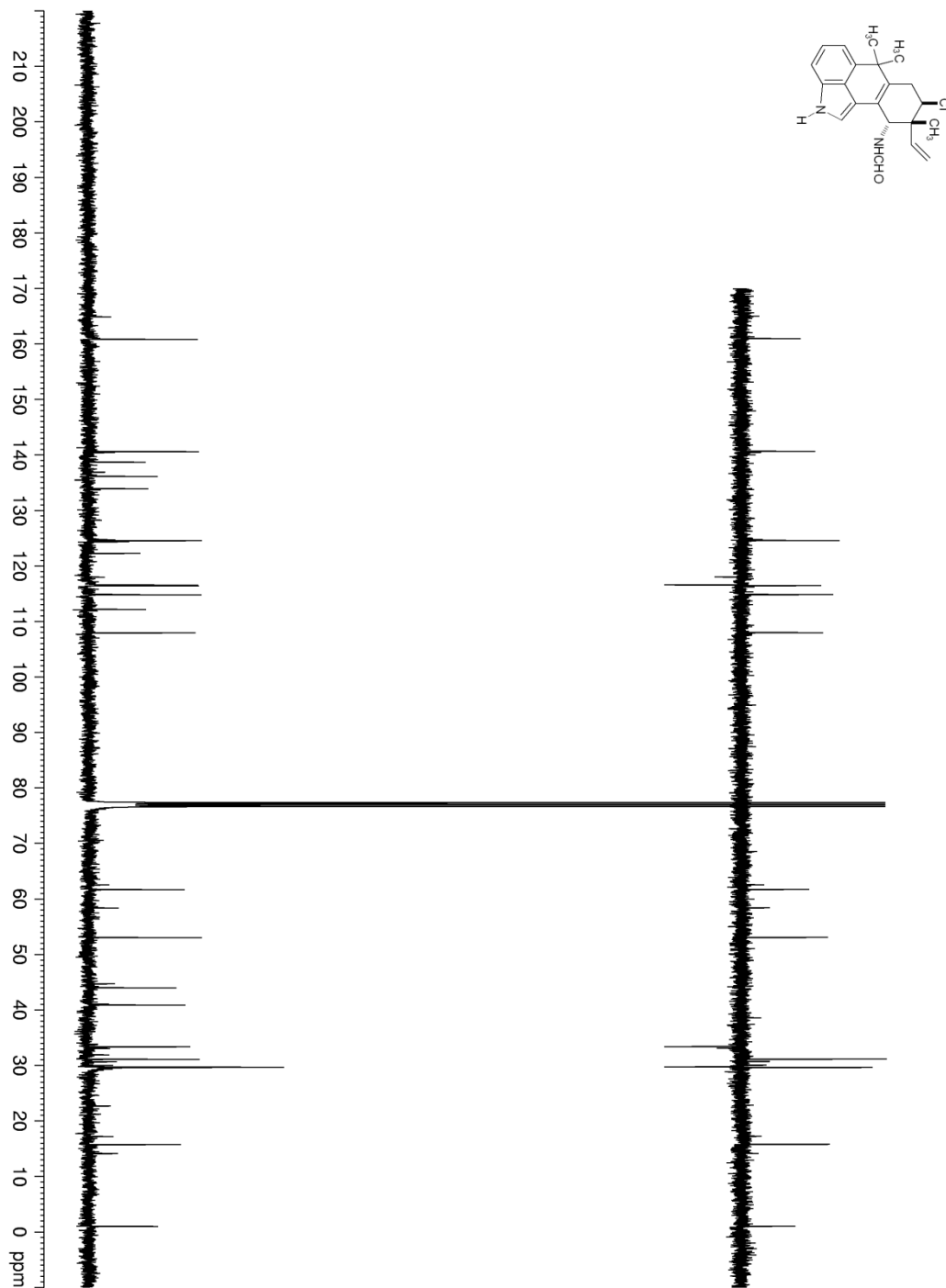


Figure 171. ¹H NMR Spectrum (600 MHz, CDCl₃) of 606 (hapalindole A)

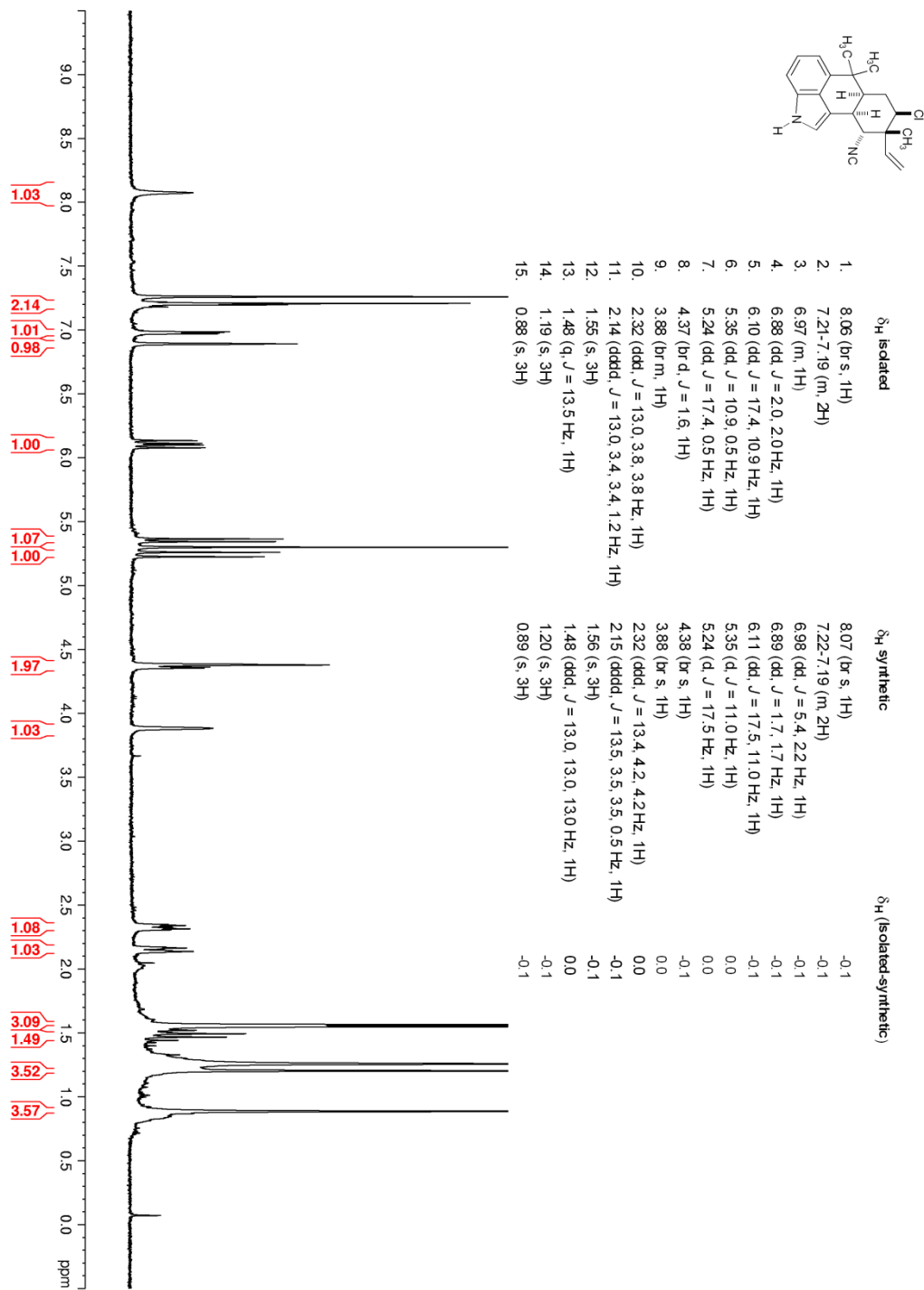


Figure 172. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 606 (hapalindole A)

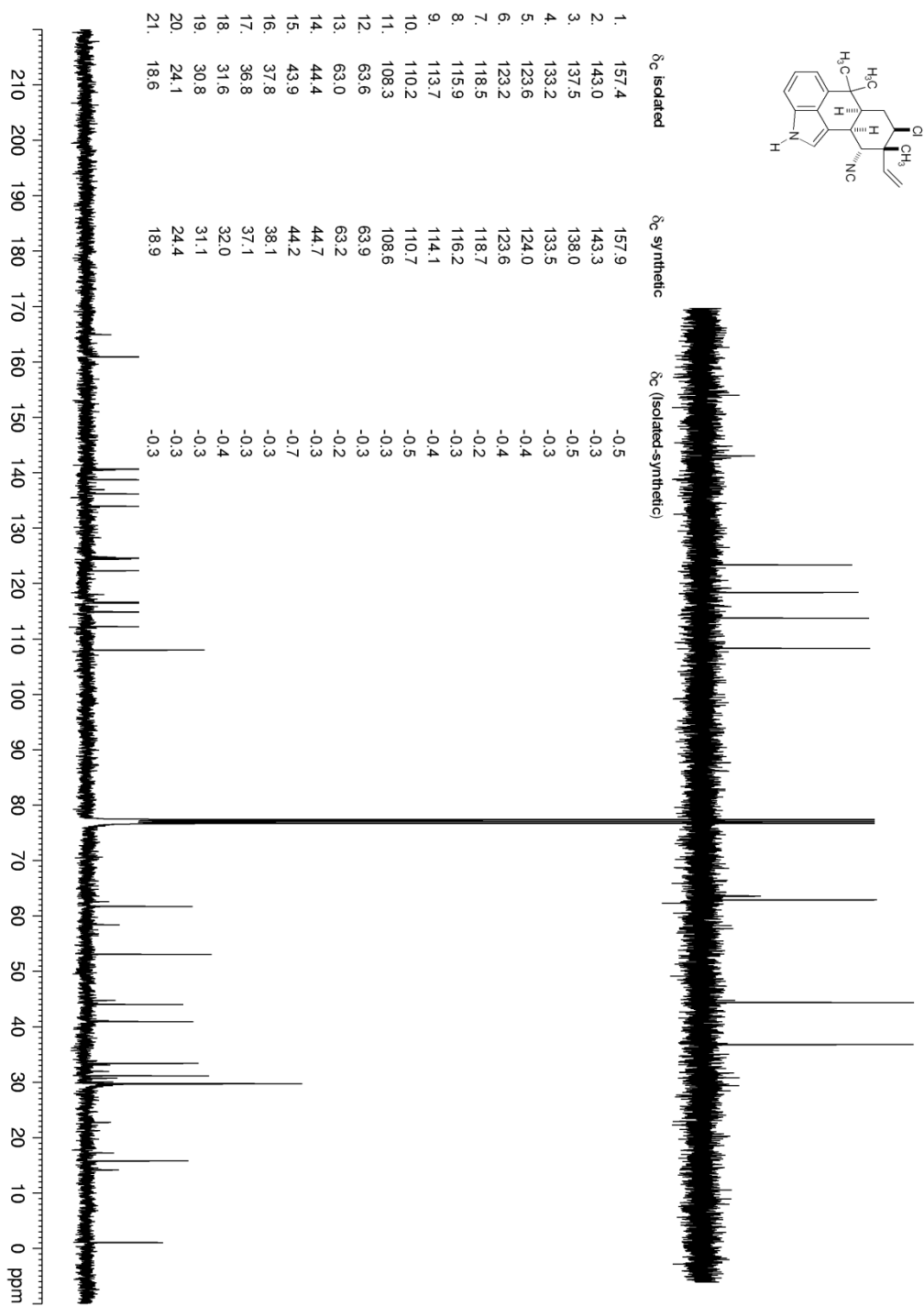


Figure 173. ^1H NMR Spectrum (600 MHz, CDCl_3) of 607

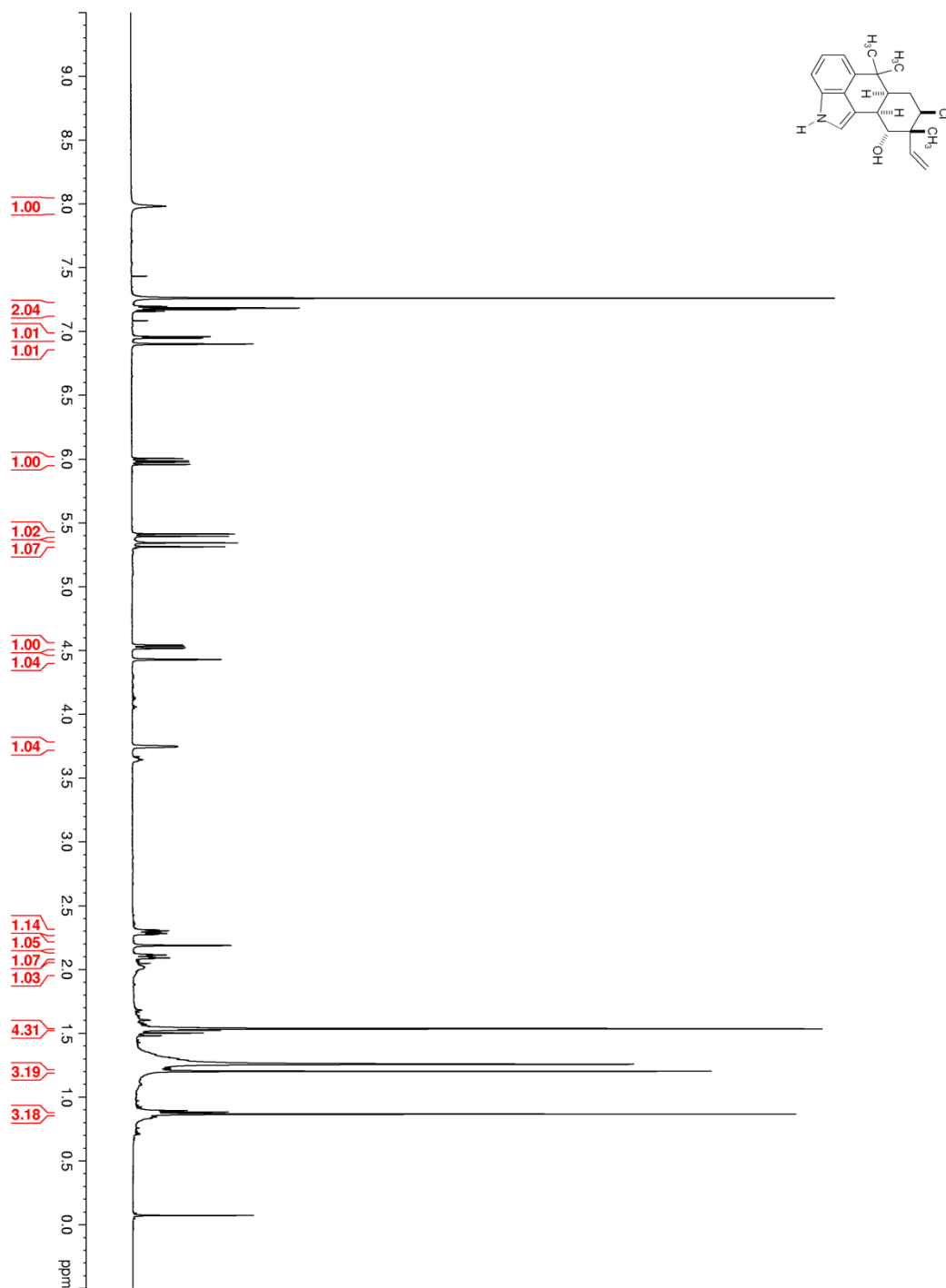


Figure 174. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 607

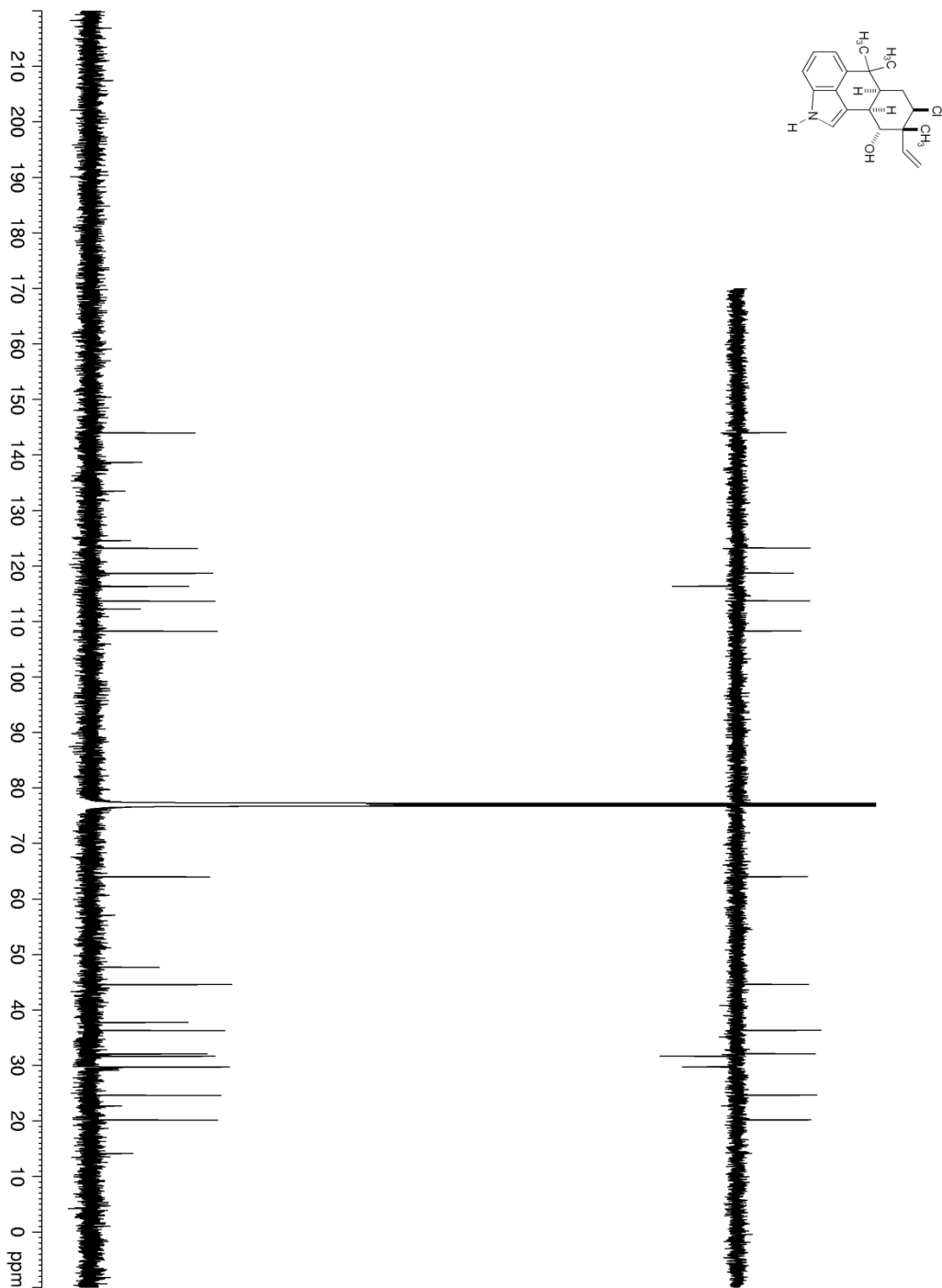


Figure 175. HSQC Spectrum (150 MHz, CDCl₃) of 607

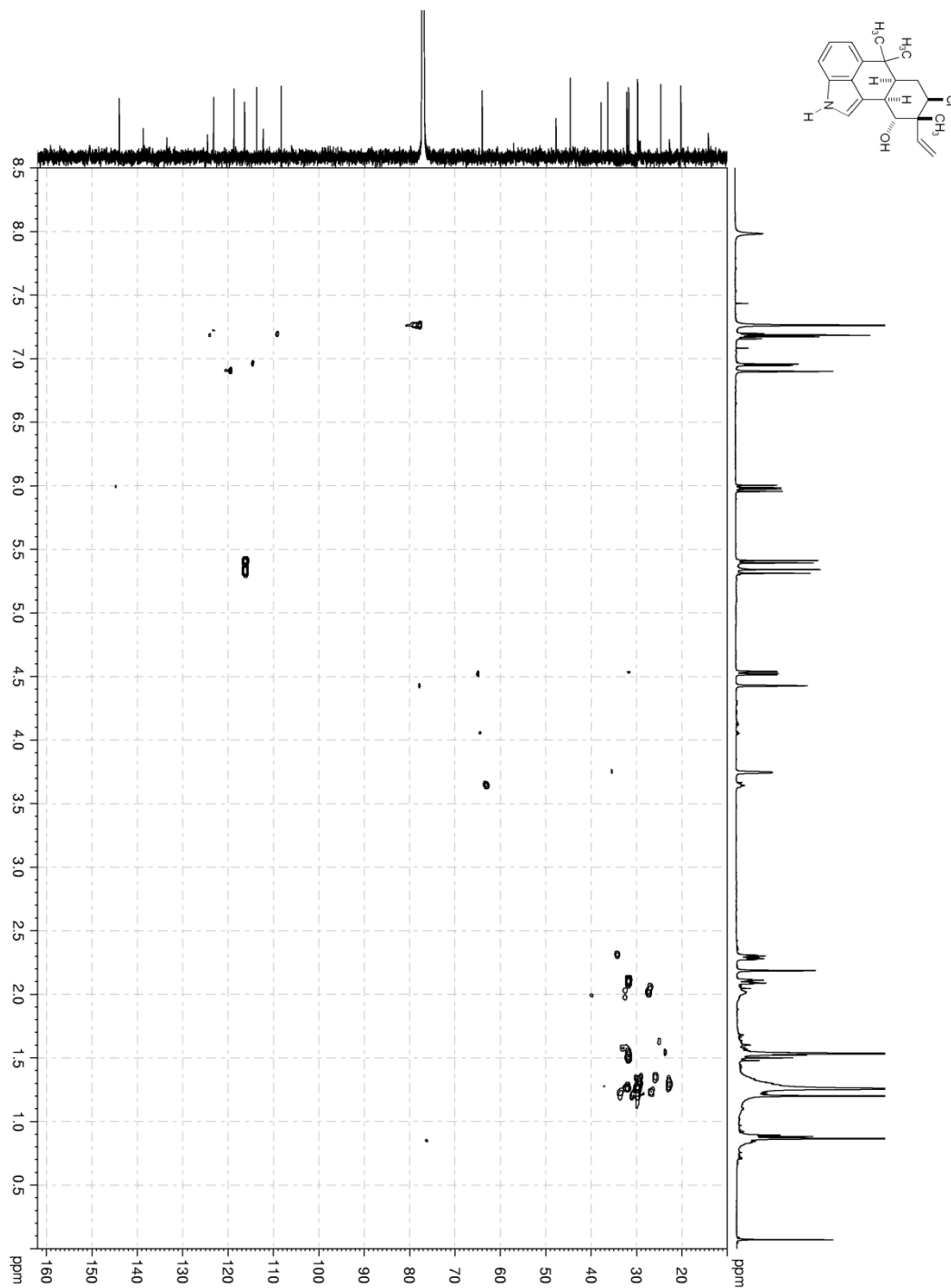


Figure 176. NOESY Spectrum (600 MHz, CDCl₃) of 607

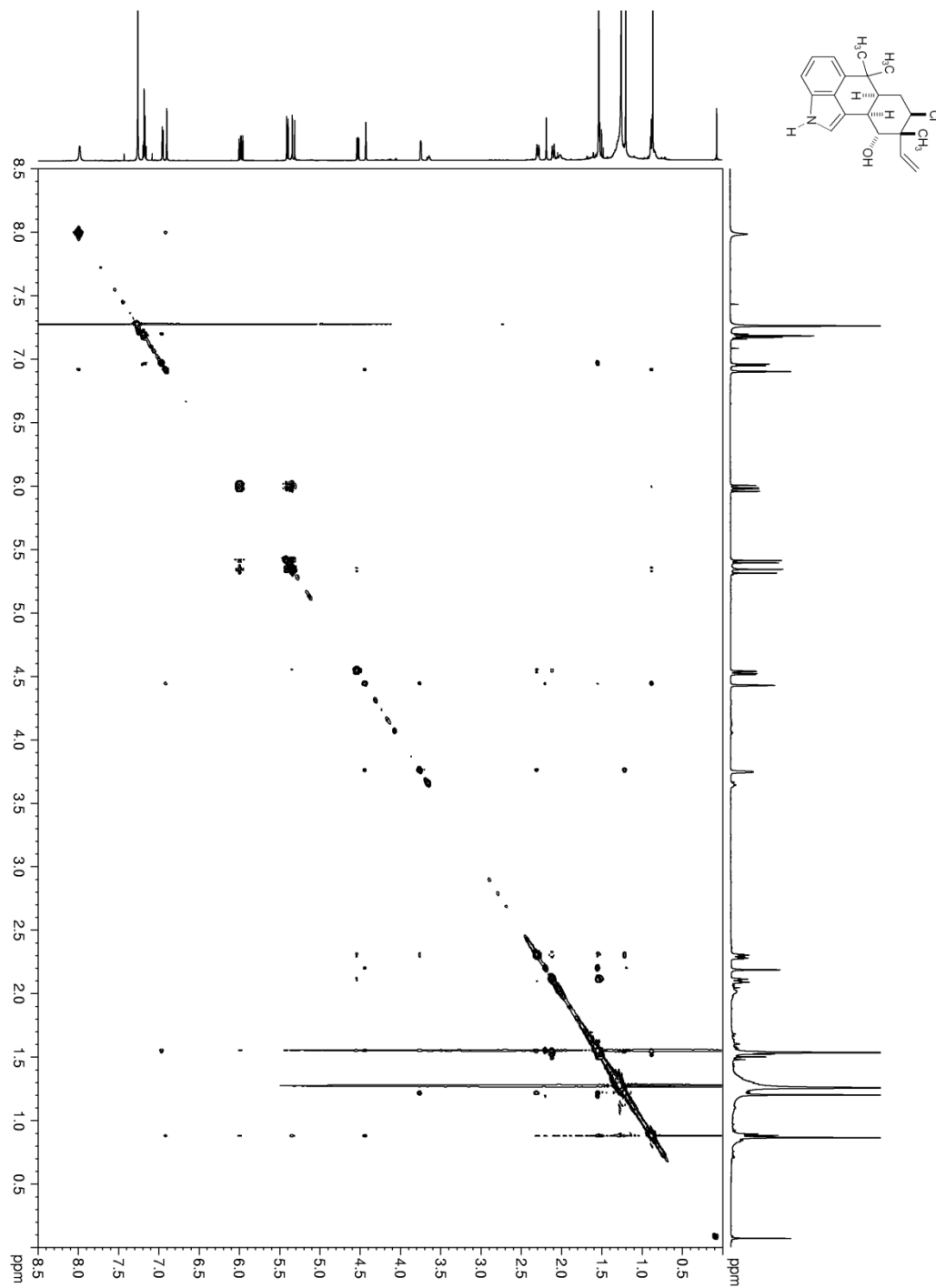


Figure 177. ^1H NMR Spectrum (400 MHz, CDCl_3) of 609

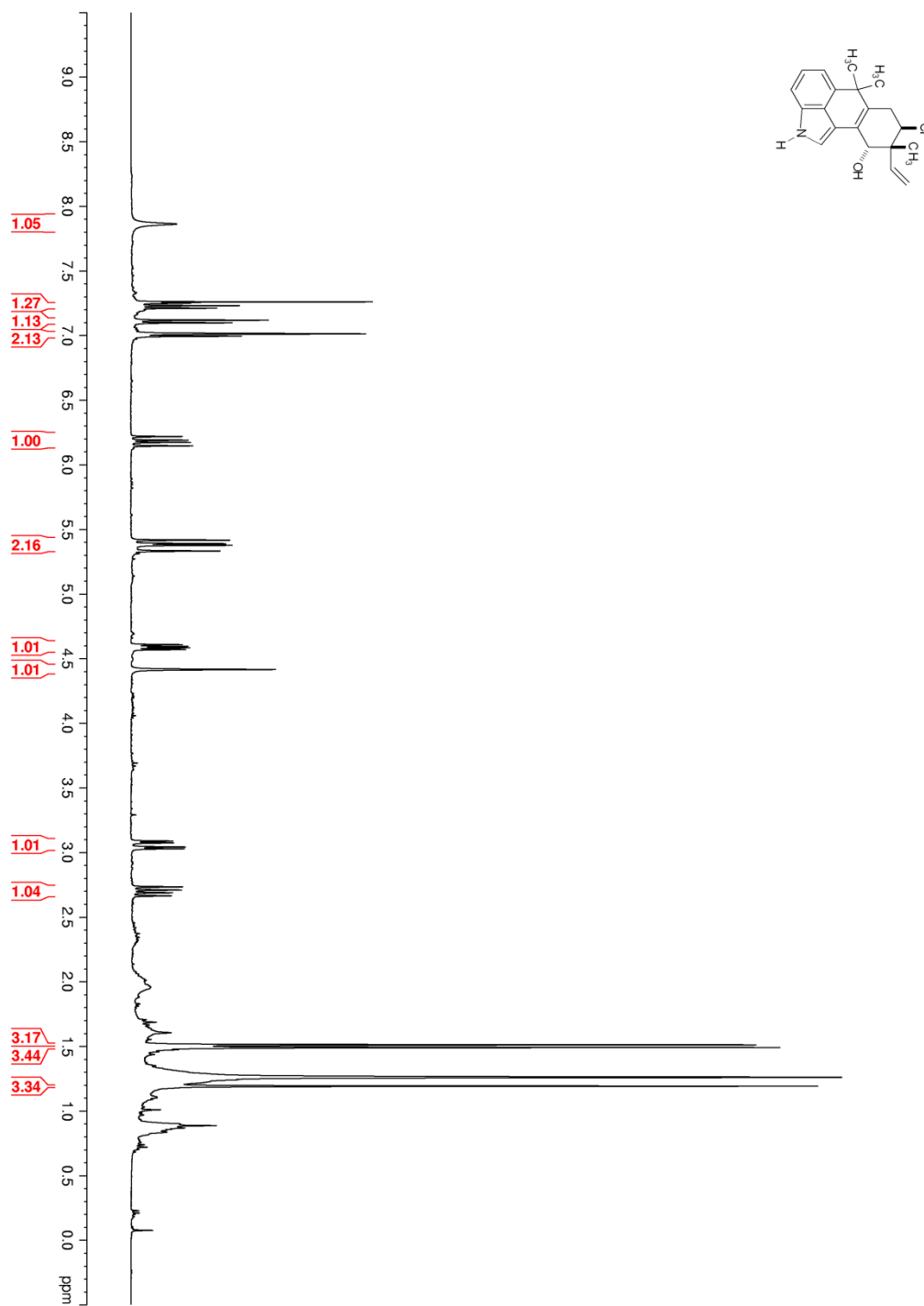


Figure 178. ^{13}C NMR Spectrum (100 MHz, CDCl_3) of 609

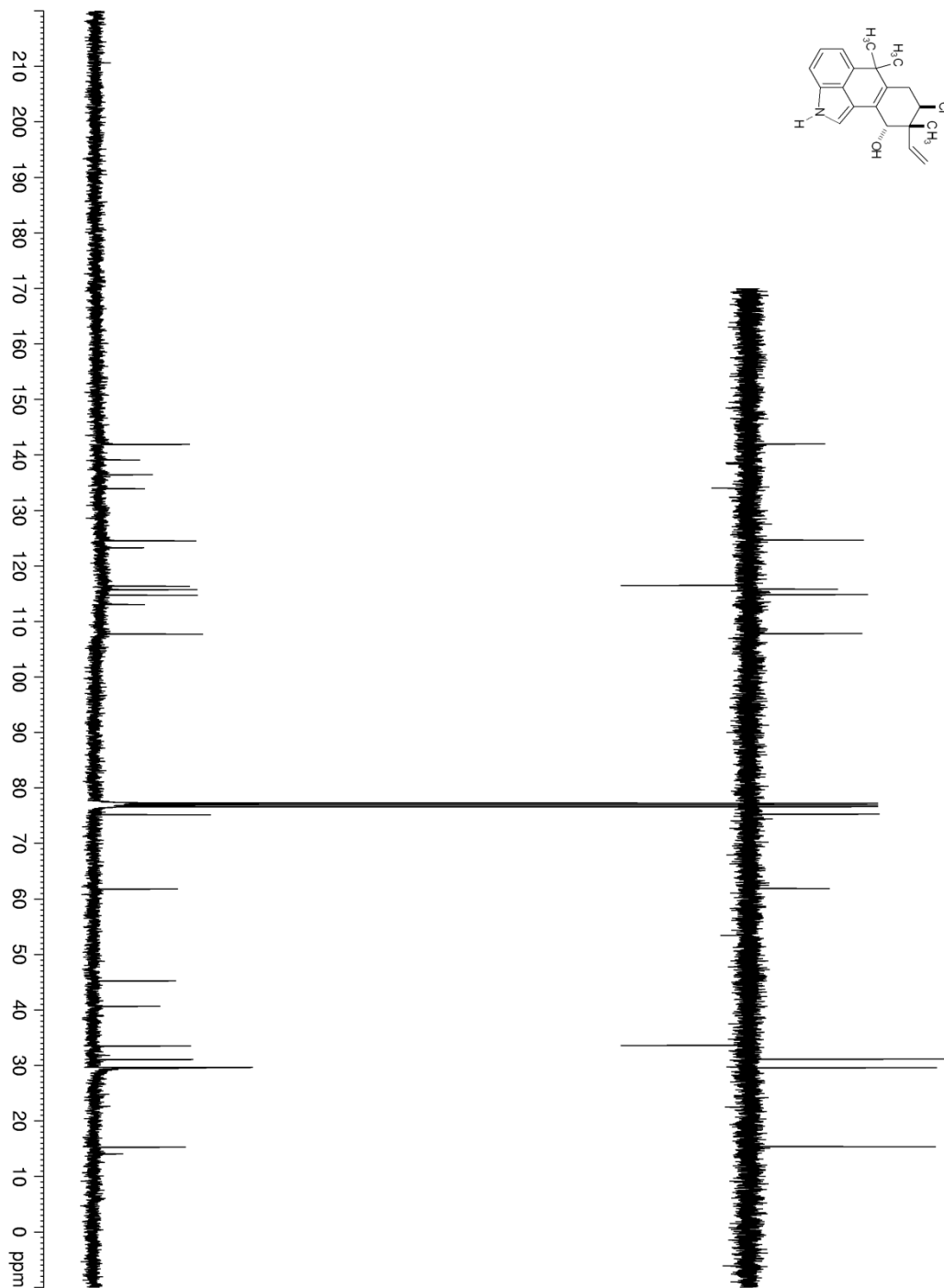


Figure 179. ^1H NMR Spectrum (600 MHz, CDCl_3) of 610

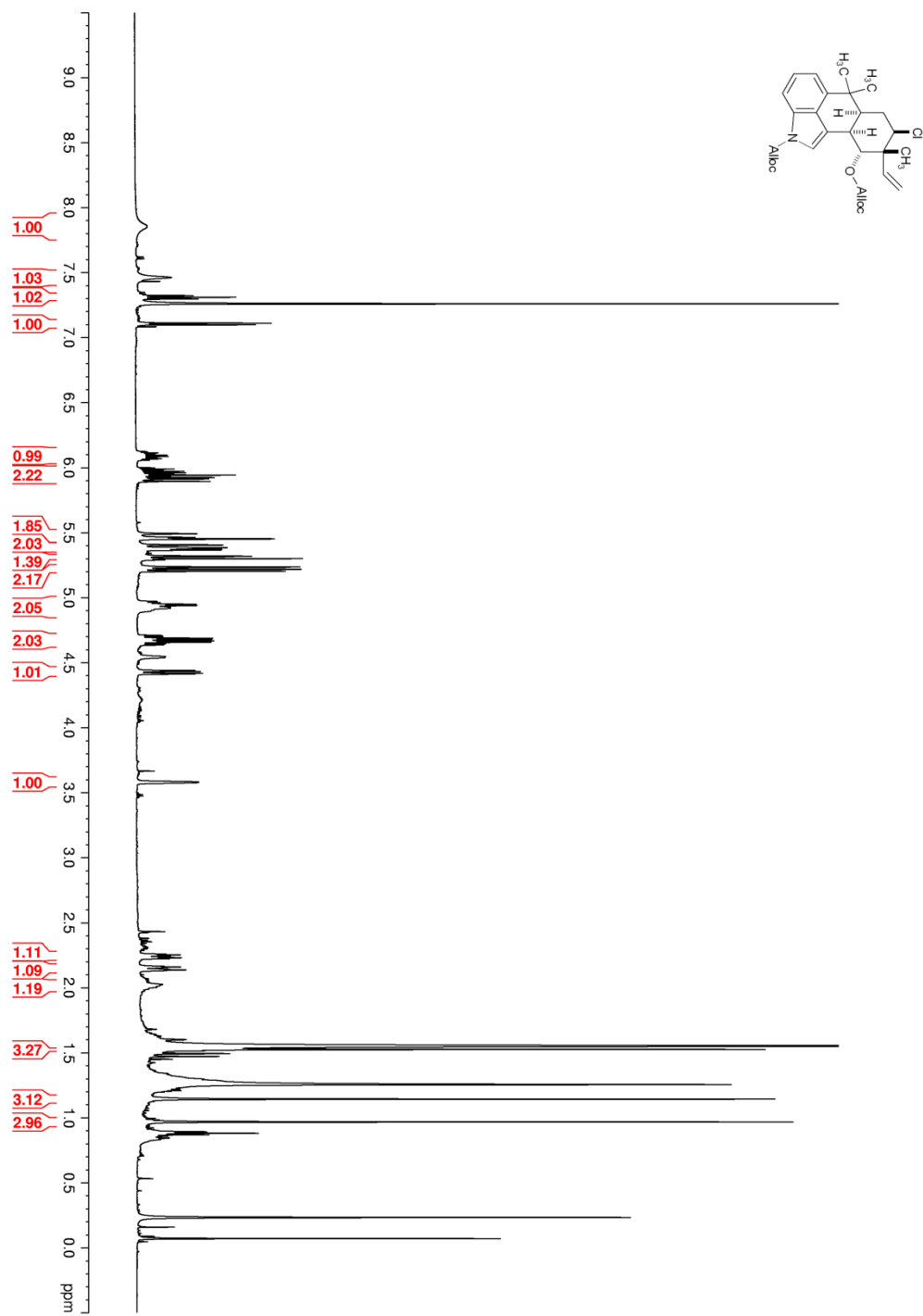


Figure 180. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 610

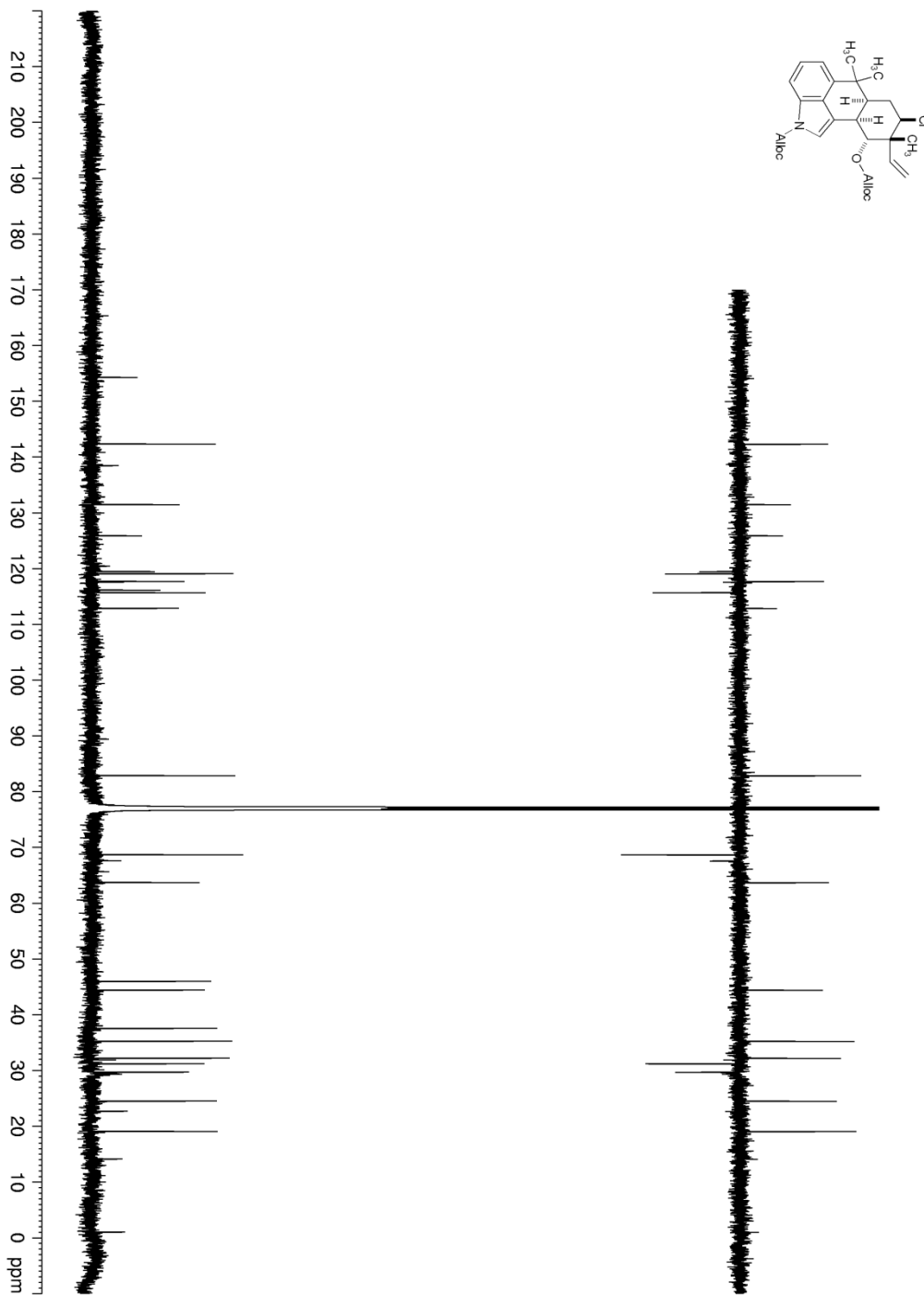


Figure 181. ¹H NMR Spectrum (600 MHz, CDCl₃) of 611

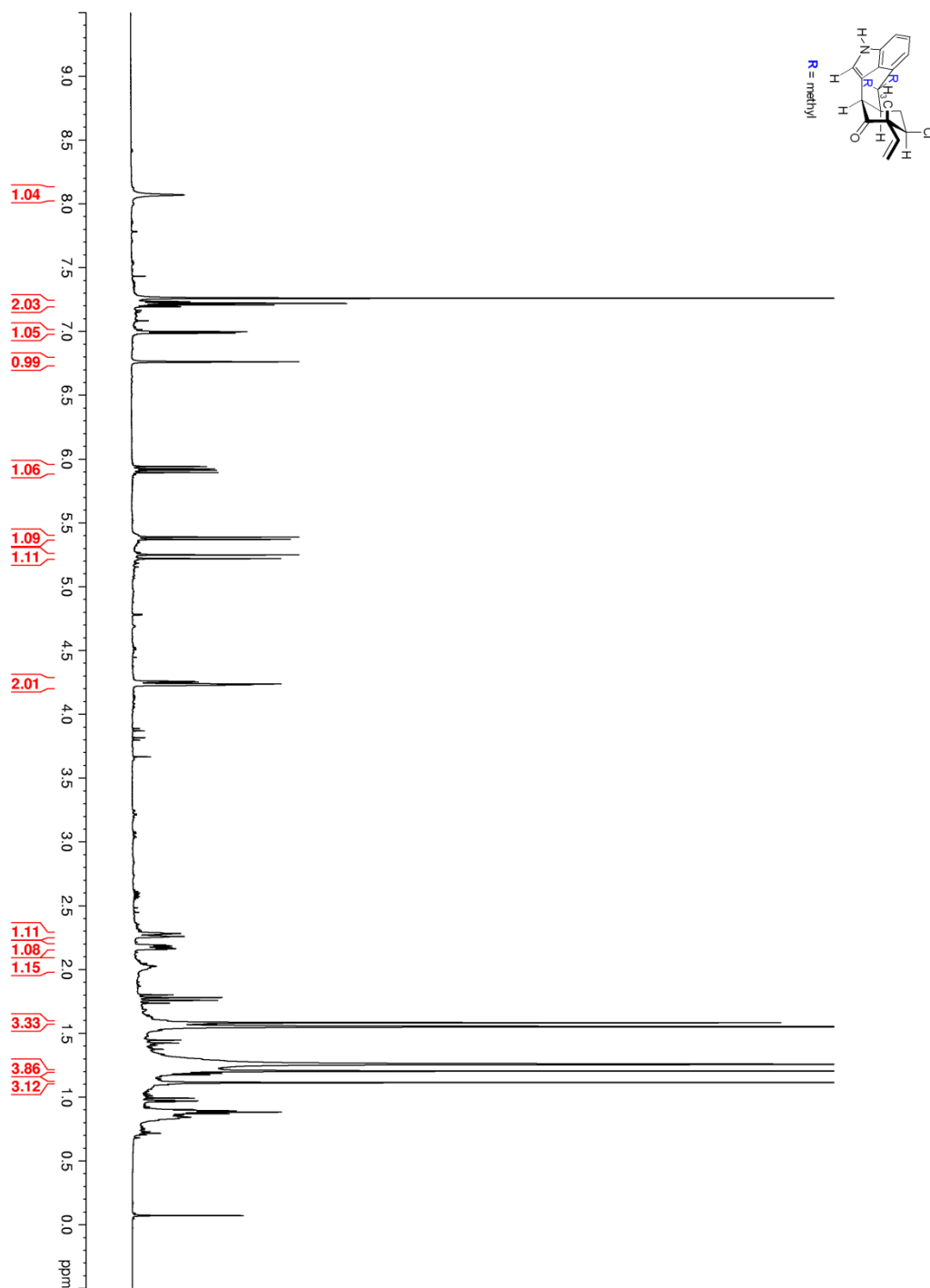


Figure 182. ^{13}C NMR Spectrum (150 MHz, CDCl_3) of 611

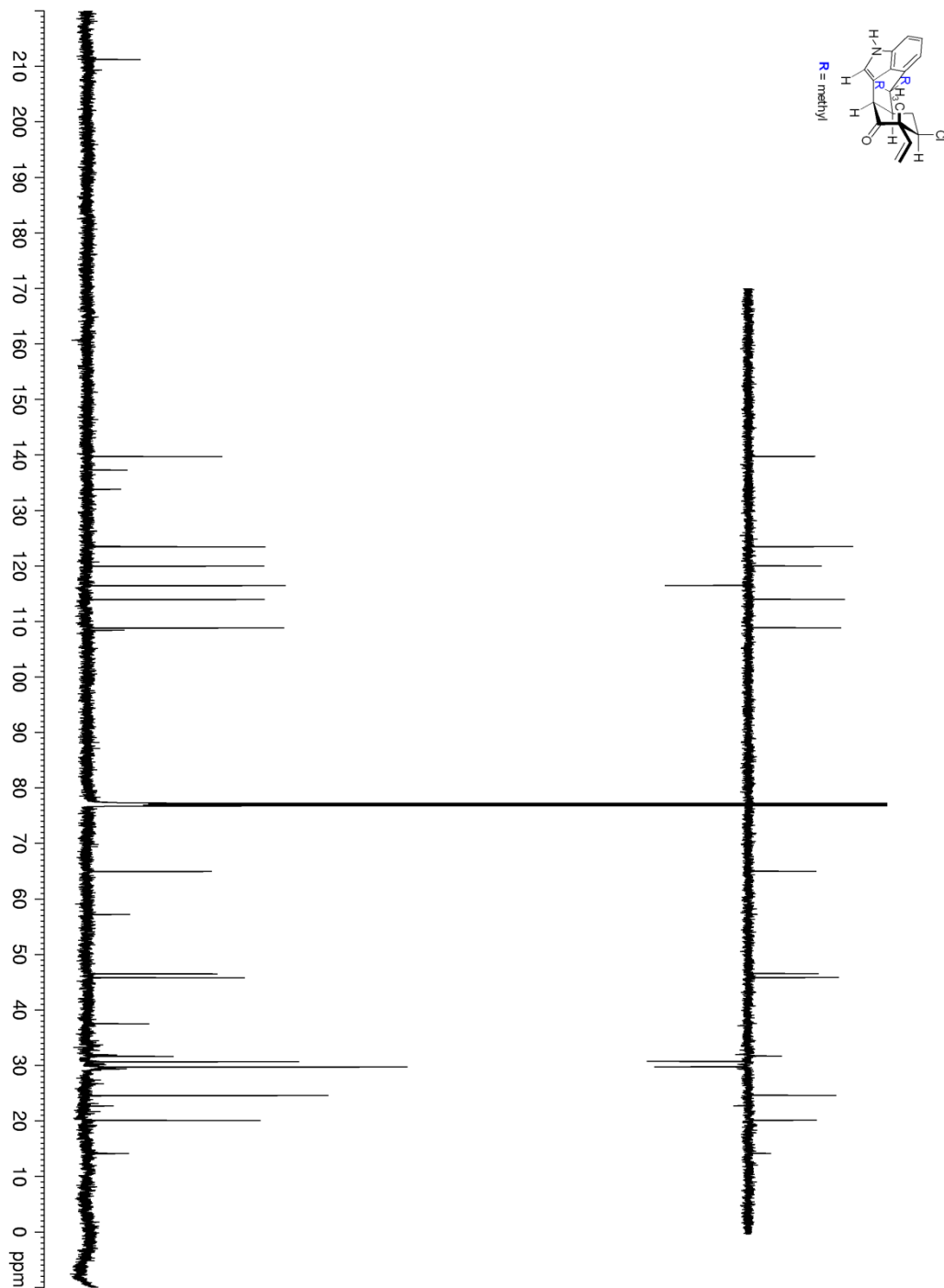


Figure 183. ^1H NMR Spectrum (500 MHz, CDCl_3) of 612

