Supporting Information

Total Synthesis of Rugulovasine A

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General information

Proton NMR (^{1}H) were recorded at 400 MHz NMR spectrometer, Carbon NMR (^{13}C) at 100 MHz NMR spectrometer unless otherwise stated. The following abbreviations are used for the multiplicities: s: singlet, d: doublet, t: triplet, m: multiplet, br s: broad singlet for proton spectra. Coupling constants (*J*) are reported in Hertz (Hz).

Infrared spectra were recorded with a thin layer of the product on a KBr disk and reported in frequency of absorption (cm^{-1}).

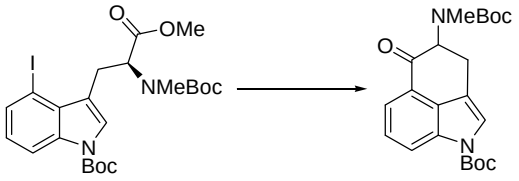
High resolution mass spectral (HRMS) data were obtained with an ionization mode of ESI.

Flash chromatography was performed using silica gel (200-300 mesh) with solvents distilled prior to use. Visualization was achieved under a UV lamp (254 nm and 365 nm), and by developing the plates with phosphomolybdic acid in ethanol.

All reagents were obtained from commercial suppliers unless otherwise stated.

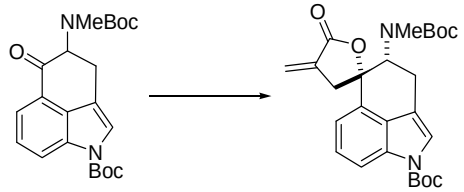
The following abbreviations are used: **FCC**: flash column chromatography; **PE**: petroleum ether; **EtOAc**: ethyl acetate; **DCM**: dichloromethane; **THF**: tetrahydrofuran; **TMSOTf**: trimethylsilyl trifluoromethanesulfonate; **DMSO**: dimethylsulfoxide.

Experimental procedure and physical data



7 **6**

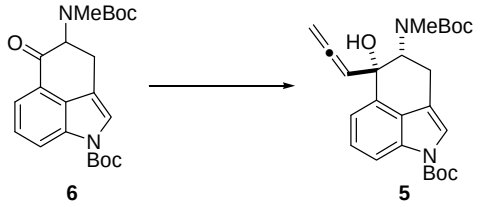
Compound 6: Compound **7** (250 mg, 0.46 mmol) was dissolved in anhydrous THF (9 mL) and cooled to -100 ^{o}C (liquid nitrogen, ethanol bath) with stirring under argon. To this solution was added *t*-Buli (0.62 mL, 1.6 M in pantane, 0.99 mmol) dropwise over 10 min, maintaining the temperature at -100 ^{o}C. After the reaction mixture was stirred at -100 ^{o}C for 1h, the temperature was allowed to slowly warm to -78 ^{o}C, where it was stirred for 1 h and then allowed to slowly warm to 0 ^{o}C. After remaining at 0 ^{o}C for 1 h, the solution then poured into saturated $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine (2 × 10 mL), dried over Na_2SO_4, filtered and evaporated. The residue was purified by FCC (DCM-EtOAc, 50 : 1) to afford the compound **6** (143 mg, 80% yield) as yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) Mixture of rotamers δ 8.13 (brs, 1 H), 7.74-7.67 (m, 1 H), 7.47-7.36 (m, 2 H), 5.27-5.20 (m, 0.6 H), 4.78-4.74 (m, 0.4 H), 3.50-3.28 (m, 2 H), 2.99 (s, 1.2 H), 2.94 (s, 1.8 H), 1.67 (s, 9 H), 1.50 (s, 5.4 H), 1.36 (s, 3.6 H); ^{13}C NMR (100 MHz, $CDCl_3$) Mixture of rotamers δ 193.5, 192.8, 156.3, 155.6, 149.5, 133.7, 133.6, 125.7, 125.4, 125.3, 121.9, 120.3, 120.2, 119.3, 119.2, 113.6, 113.5, 84.2, 80.2, 80.0, 63.3, 61.8, 32.9, 32.0, 28.4, 28.3, 28.1, 25.8, 25.1; IR (KBr) 2918, 2849, 1737, 1699, 1600, 1447, 1390, 1369, 1354, 1337, 1258, 1151, 1113, 1071 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{22}H_{29}N_2O_5$ $(M + H)^+$ 401.2071; found 401.2074.



6 **4**

Compound 4: Compound **6** (120 mg, 0.3 mmol) was dissolved in THF (4.4 mL) and cooled to 0 ^{o}C with stirring under argon. To this solution was added I_2 (3.8 mg, 0.015 mmol), activated Zn powder (51 mg, 0.78 mmol) and ethyl α-(bromomethyl)acrylate (113 mg, 0.63 mmol). The

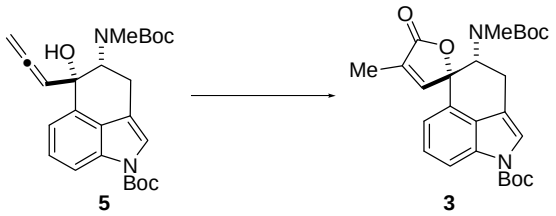
mixture was stirred at 50 °C for 12 h. Then saturated aqueous NH_4Cl was added, and the aqueous phase was extracted with EtOAc (3 × 15mL). The organic layer was combined, washed with brine (2 × 15 mL) and dried over Na_2SO_4, filtered and evaporated. The residue was purification by FCC (DCM-EtOAc, 50:1) to afforded the compound **4** (126 mg, 90% yield) as yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) Mixture of rotamers δ 7.95 (brs, 1 H), 7.35-7.29 (m, 2 H), 7.19 (s, 0.7 H), 7.17 (s, 0.3 H), 6.29 (s, 1 H), 5.72 (s, 1 H), 4.85-4.83 (m, 0.7 H), 4.61 (brs, 0.3 H), 3.54-3.35 (m, 3 H), 2.94 (m, 1 H), 2.90 (s, 3 H), 1.67 (s, 9 H), 1.47 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) Mixture of rotamers δ 169.3, 157.0, 155.6, 149.8, 136.1, 135.5, 133.5, 130.1, 128.6, 125.4, 121.6, 120.7, 120.1, 118.0, 117.7, 116.0, 114.9, 84.1, 83.8, 80.8, 80.4, 57.6, 56.7, 33.9, 31.9, 31.0, 29.7, 29.3, 28.3, 28.2, 23.0, 22.7, 22.6, 14.1; IR (KBr) 2976, 2927, 2855, 1769, 1738, 1689, 1479, 1444, 1392, 1367, 1340, 1258, 1149, 1112, 1031, 995, 940, 902, 883, 854, 787, 767 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{26}H_{36}N_3O_6$ $(M + NH_4)^+$ 486.2599; found 486.2600.



6 **5**

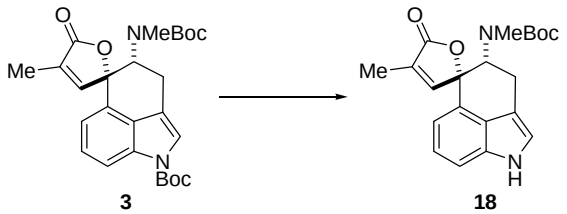
Compound 5: Lithium aluminum hydride (0.22 mL, 2.4 M in THF 0.53 mmol) was added portionwise to a suspension of chromium(III) chloride (165 mg, 1.04 mmol) in THF (2.3 mL) at 0 °C under an argon atmosphere. Immediate gas evolution occurred with darkening of the initial purple color, which finally turned dark brown. After the gas evolution had ceased, the reaction mixture was stirred for an additional 15 minutes at 25 °C. Propargylbromide (0.21 mL, 10 M in toluene, 2.1 mmol) was added in one portion, then 0.46 mL HMPA was added. Then a solution of compound **6** (105 mg, 0.26 mmol) in THF (2.3 mL) was added dropwise over 10 minutes. The resulting mixture was stirred at 35 °C for 12 h and poured into ice cold water. The organic layer was separated and the rest was extracted with EtOAc (3 × 15 mL). The combined organic layer were washed with brine (2 × 15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by FCC (DCM-EtOAc, 50:1) to afford compound **5** (47 mg, 66% brsm) as brown oil with recovery of compound **6** (39 mg); ^{1}H NMR (400 MHz, $CDCl_3$) Mixture of rotamers δ 7.87 (brs, 1 H), 7.30-7.23 (m, 3 H), 5.57-5.39 (m, 1 H), 5.11-4.99 (m, 2 H), 4.44 (m, 1 H), 3.46-3.43 (m,

1 H), 3.01-2.91 (m, 4 H), 1.67 (s, 9 H), 1.48-1.41 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) Mixture of rotamers δ 207.0, 157.1, 155.8, 150.0, 134.9, 133.6, 128.0, 125.1, 119.5, 118.2, 116.0, 115.1, 114.9, 96.0, 95.7, 83.5, 80.3, 79.9, 79.3, 74.5, 58.6, 30.6, 28.4, 28.2, 22.7, 22.5, 22.2, 14.2, 14.1; IR (KBr) 3435, 2977, 2932, 1959, 1732, 1689, 1479, 1442, 1390, 1368, 1340, 1299, 1280, 1250, 1151, 1134, 1108, 1069, 1047, 926, 881, 853, 761 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{50}H_{65}N_4O_{10}$ $(2M + H)^+$ 881.4695; found 881.4716.

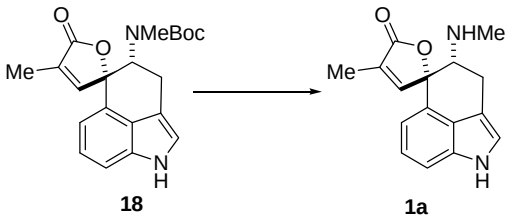


5 **3**

Compound 3: To allenyl alcohol **5** (88 mg, 0.2 mmol) in 2,4,6-collidine (3 mL) was added $Ru_3(CO)_{12}$ (25 mg, 0.1 mmol) in a 20 mL, two-necked, creased flask. The flask was flushed with 1 atm of CO. After the reaction was stirred for 2 h at 100 °C, the CO was released. The reaction mixture was poured into brine and extracted with EtOAc (3 × 15 mL). The organic layer was combined and washed with saturated aqueous $KHSO_4$ solution, brine, saturated aqueous $NaHCO_3$ solution, and brine. The solvent was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FCC (DCM-EtOAc, 50:1) to afford compound **3** as pale yellow oil (54 mg, 58%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1 H), 7.42-7.14 (m, 3 H), 6.92-6.89 (m, 1 H), 4.88 (dd, J = 4.4, 12.8 Hz, 0.76 H), 4.70 (dd, J = 4.0, 12.4 Hz, 0.24 H), 3.45-3.38 (m, 1 H), 3.05-2.91 (m, 4 H), 2.06-2.03 (m, 3 H), 1.68 (s, 9 H), 1.44 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 173.2, 156.0, 154.8, 149.8, 149.5, 148.5, 133.6, 131.3, 130.3, 128.7, 126.6, 125.3, 125.2, 120.5, 120.3, 119.5, 119.4, 116.5, 116.4, 114.8, 88.5, 87.8, 83.8, 80.5, 80.1, 56.9, 55.9, 30.9, 30.5, 28.5, 28.3, 28.2, 23.4, 22.8, 10.7, 10.6; IR (KBr) 2982, 2917, 2849, 1740, 1690, 1443, 1390, 1372, 1337, 1242, 1149, 1047 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{52}H_{64}N_4O_{12}Na$ $(2M + Na)^+$ 959.4413; found 959.4393.

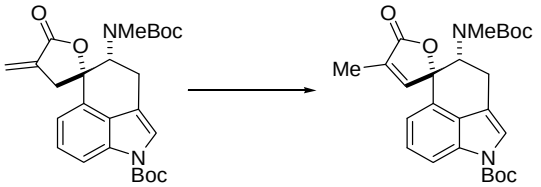


Compound 18: To a solution of **3** (90 mg, 0.19 mmol) in MeOH/THF (3 : 1, 4 mL) was added Cs_2CO_3 (309 mg, 0.95 mmol). After stirring for 36 h at room temperature, the solution was poured into brine and extracted with EtOAc (3 × 15 mL). The combined organic layer were dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by FCC (PE-EtOAc, 4:1) to afford compound **18** as pale liquid (51 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) Mixture of rotamers δ 8.39 (s, 0.26 H), 8.31 (s, 0.74 H), 7.36-7.20 (m, 3 H), 7.15-7.09 (m, 1 H), 6.98-6.94 (m, 1 H), 6.94-6.75 (m, 1 H), 4.93 (dd, J = 4.4, 12.4 Hz, 0.7 H), 4.77 (dd, J = 4.8, 12.4 Hz, 0.3 H), 3.55-3.44 (m, 1 H), 3.09-2.93 (m, 4 H), 2.06-2.04 (m, 3 H), 1.45-1.43 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) Mixture of rotamers δ 174.2, 173.6, 156.0, 155.0, 150.1, 149.1, 134.1, 130.9, 130.0, 126.3, 126.3, 126.2, 123.0, 122.8, 119.1, 118.9, 115.9, 112.1, 112.0, 110.2, 89.3, 88.6, 80.4, 79.9, 57.4, 56.6, 31.0, 30.7, 28.5, 28.3, 23.7, 23.2, 10.7, 10.6; IR (KBr) 3339, 2976, 2926, 2854, 1754, 1686, 1479, 1449, 1389, 1369, 1346, 1240, 1150, 1030 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{25}N_2O_4$ $(M+H)^+$ 369.1809; found 369.1821.



Compound 1a: Compound **18** (15.0 mg, 0.041 mmol) was dissolved in dried DCM (0.5 mL), and cooled to 0 ^{o}C under an argon atmosphere. 2,6-lutidine (21.8 mg, 0.20 mmol) and TMSOTf (36.5 mg , 0.16 mmol) was added, then the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with saturated aqueous NaCl followed by addition of DCM (10 mL). The organic layer was separated, and the aqueous phase was further extracted with DCM (2 × 10 mL). The combined organic phases were dried over Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by FCC (DCM-MeOH, 20 : 1) to give the product **1a** as pale yellow liquid (9.5 mg, 87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (1, 1 H), 7.30 (d, J = 7.6 Hz, 1

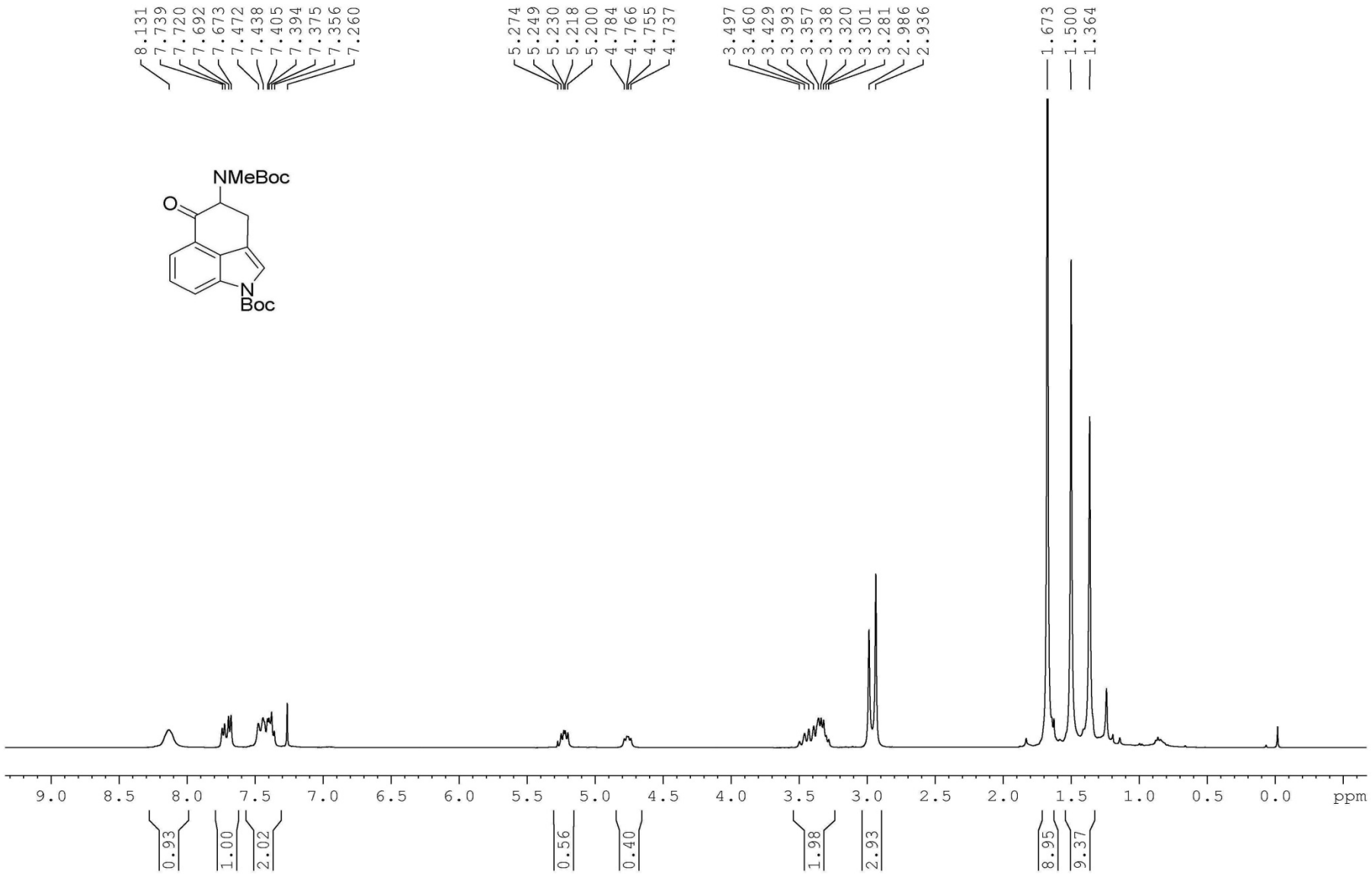
H), 7.15 (t, J = 7.6 Hz, 1 H), 6.98 (s, 1 H), 6.85 (d, J = 7.2 Hz, 1 H), 5.29-5.25 (m, 1 H), 3.18-3.16 (m, 1 H), 3.07-3.01 (m, 1 H), 2.49 (s, 3 H), 2.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 150.6, 134.0, 126.5, 123.0, 119.5, 115.0, 111.4, 109.9, 88.5, 63.1, 35.0, 29.7, 25.3, 10.8; IR (KBr) 3338, 3061, 2925, 2854, 2802, 1748, 1660, 1620, 1603, 1449, 1373, 1346, 1243, 1140, 1049, 754 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{17}N_2O_2$ $(M+H)^+$ 269.1285; found 269.1279.



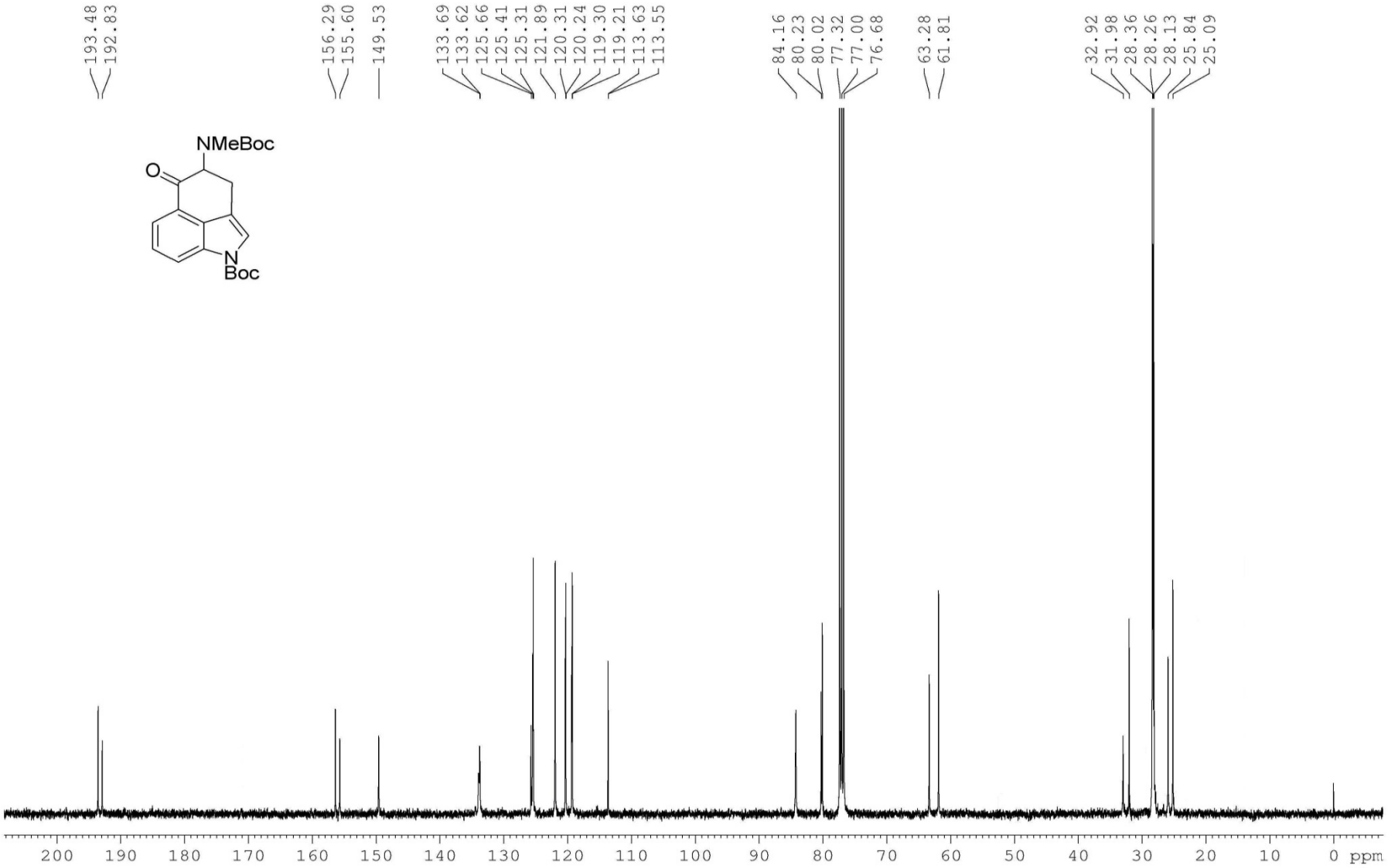
4 **3**

Convertion of compound 4 to compound 3: To compound **4** (37 mg, 0.08 mmol) in dioxane (0.8 mL) was added $Ru_3(CO)_{12}$ (5 mg, 0.008 mmol) and Et_3N (8 mg, 0.08 mmol). The solution was stirred for 2 h at 100 °C. The reaction mixture was poured into brine and extracted with EtOAc (3 × 5 mL). The organic layer was combined and washed brine. The solvent was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FCC (DCM-EtOAc, 50:1) to afford compound **3** as pale yellow oil (35 mg, 95%).

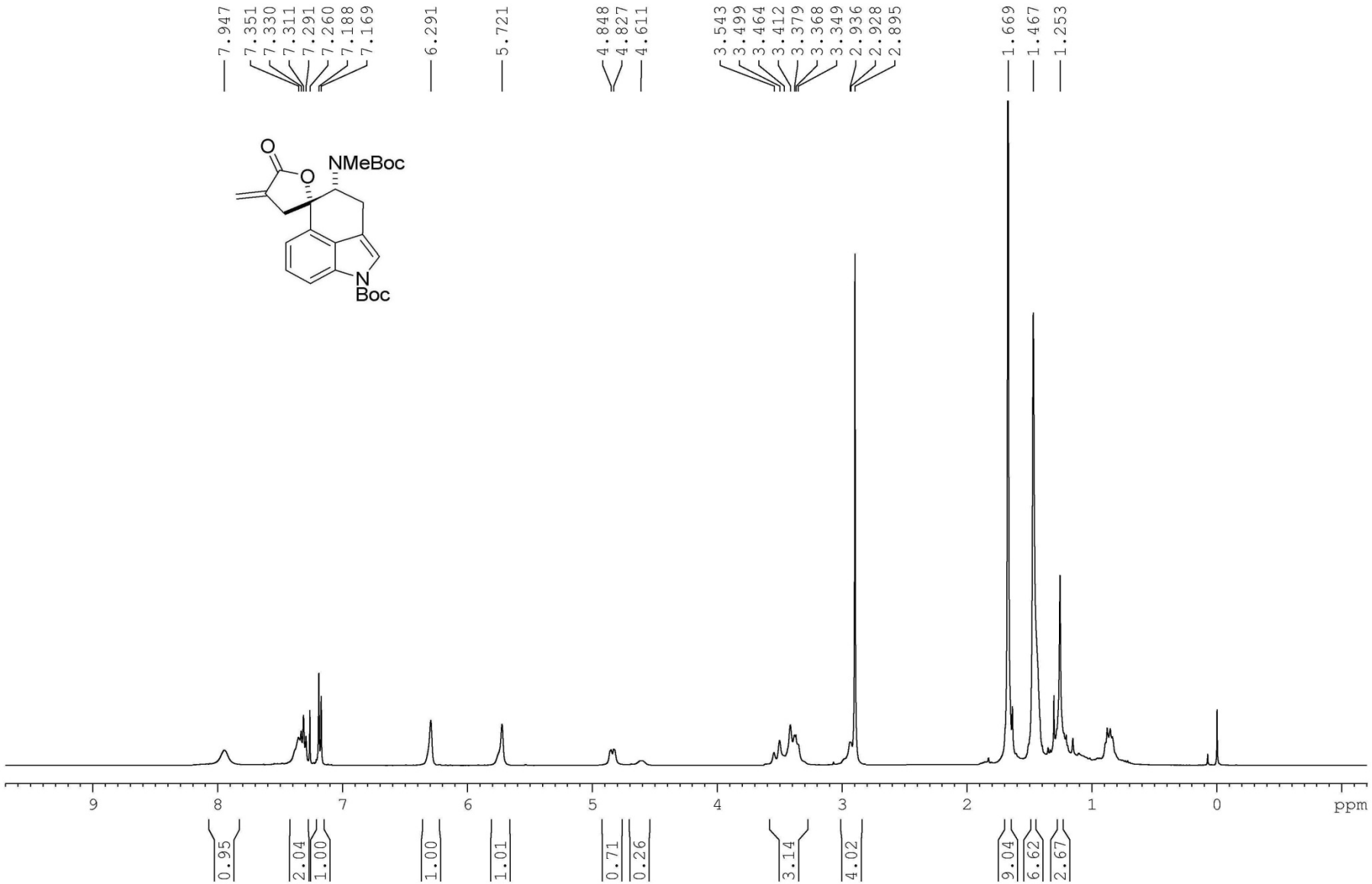
^{1}H-NMR of compound 6 (400 MHz, $CDCl_3$)



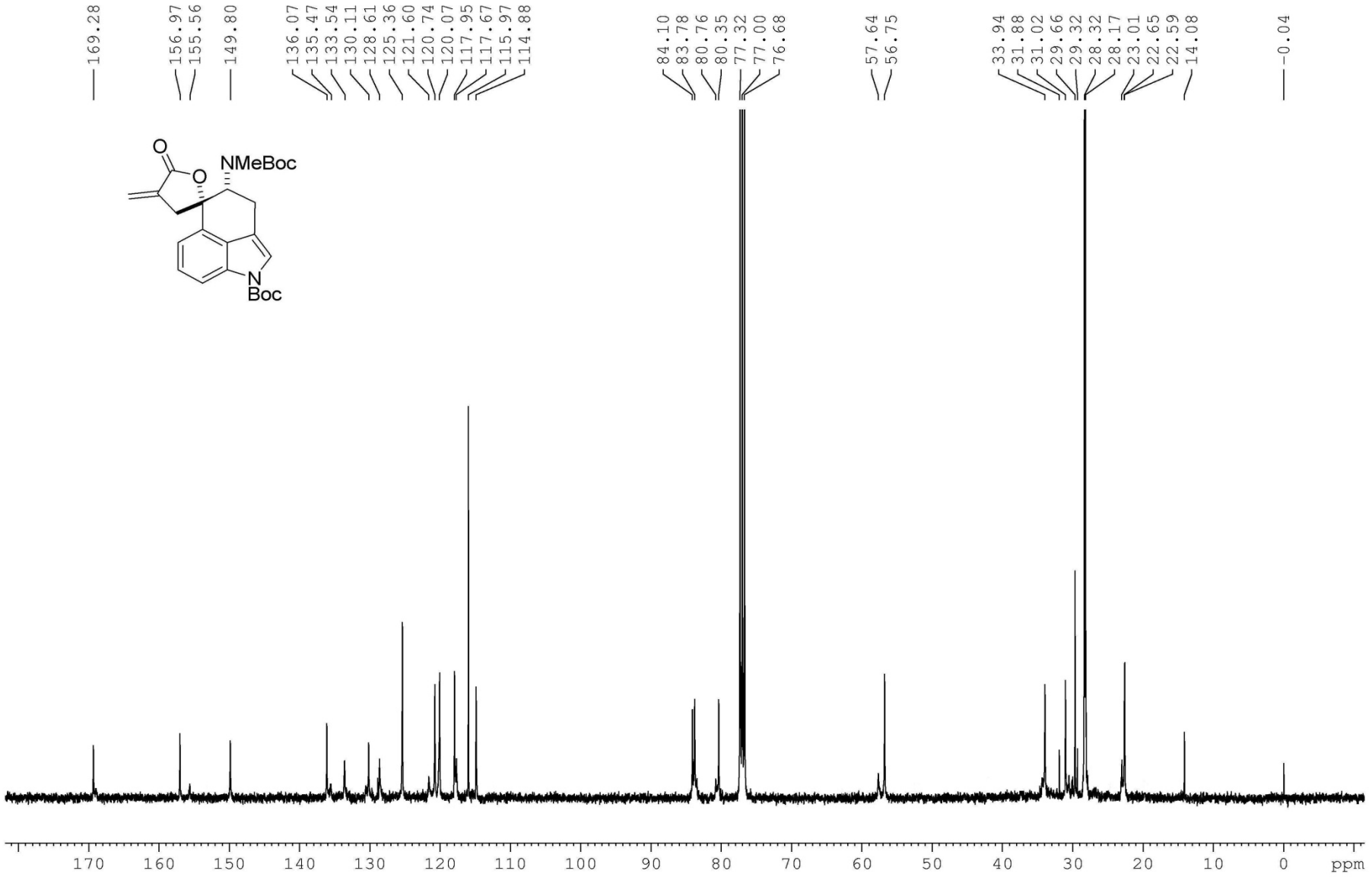
^{13}C-NMR of compound 6 (100 MHz, $CDCl_3$)



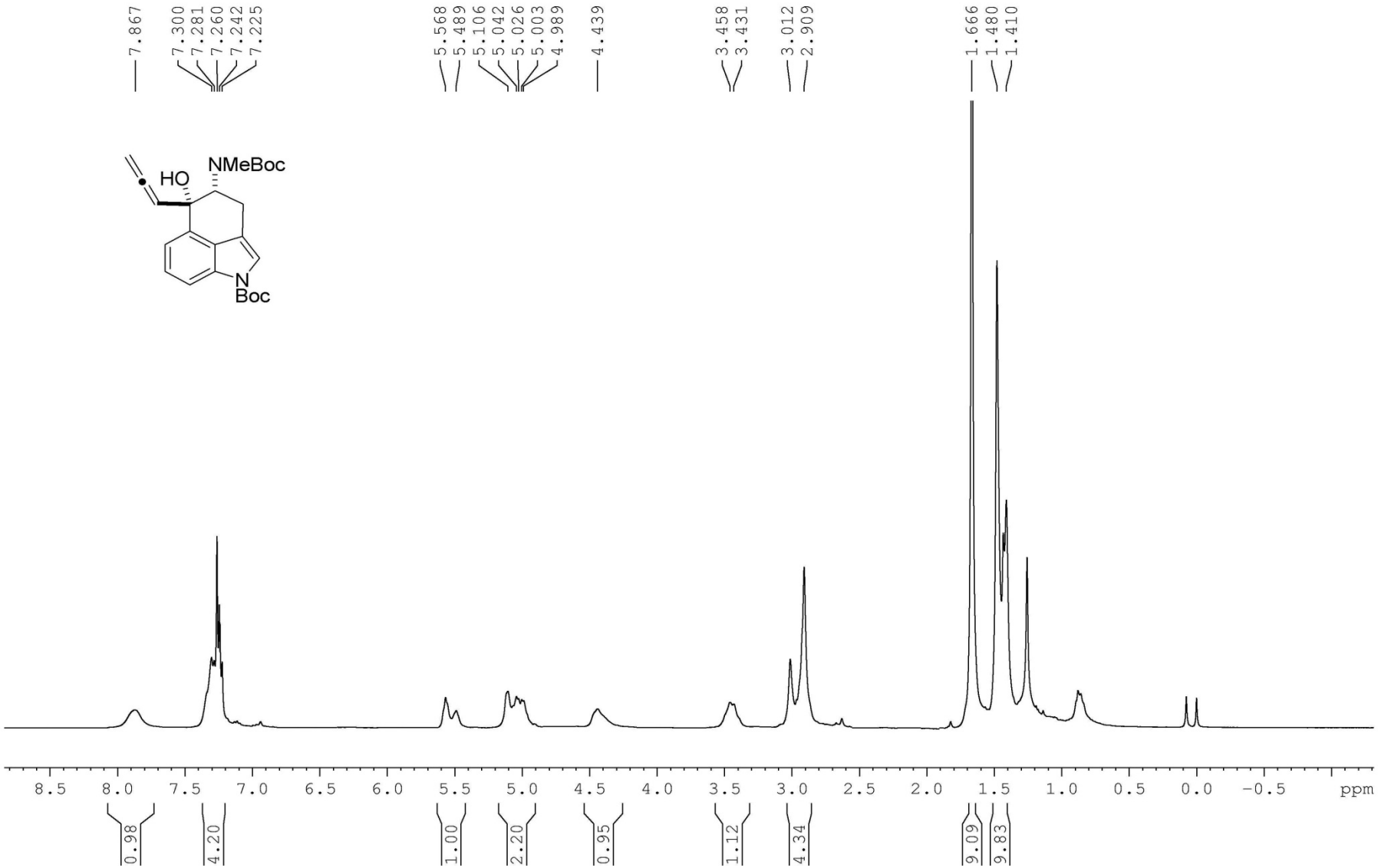
^{1}H-NMR of compound 4 (400 MHz, $CDCl_3$)



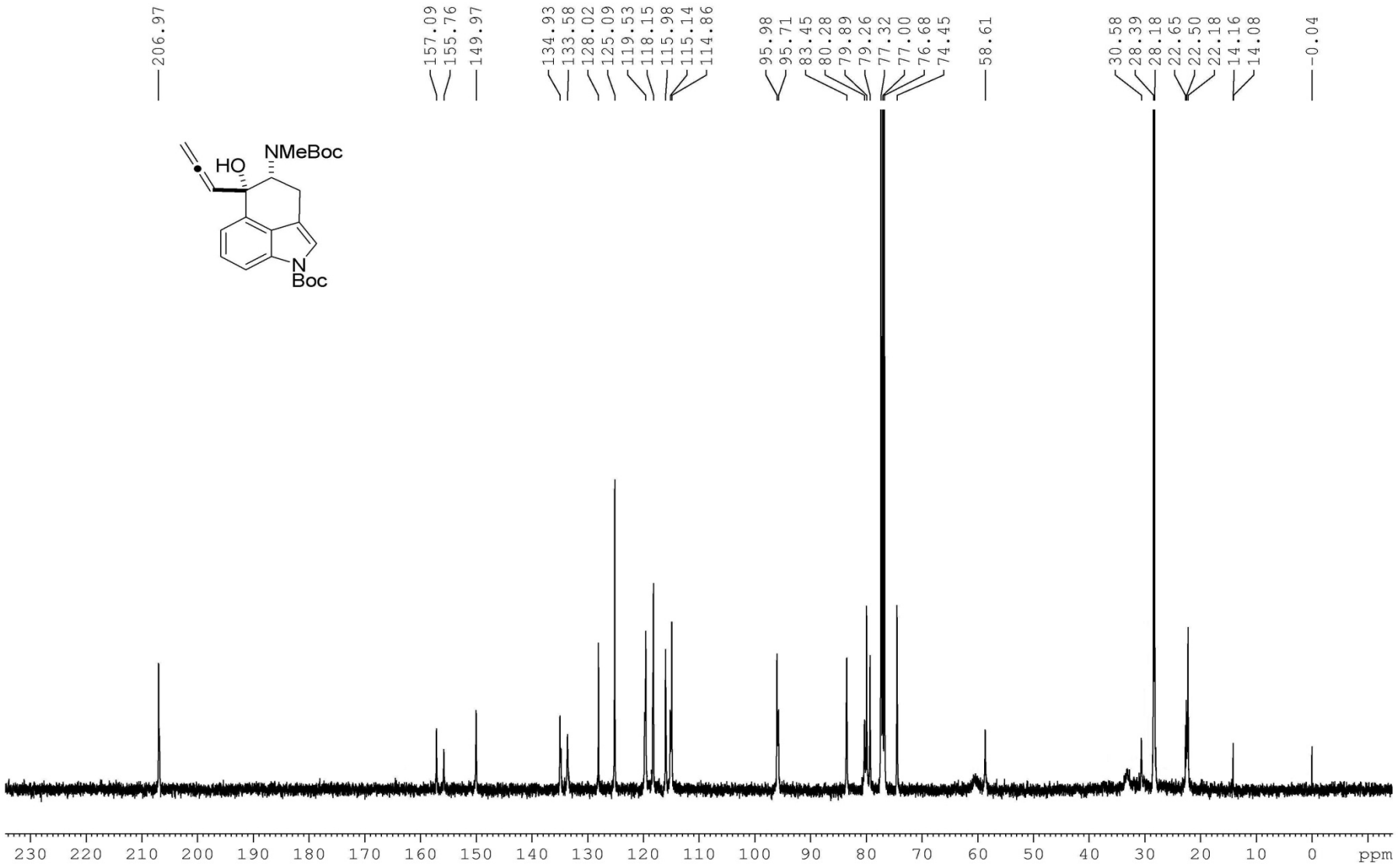
^{13}C-NMR of compound 4 (100 MHz, $CDCl_3$)



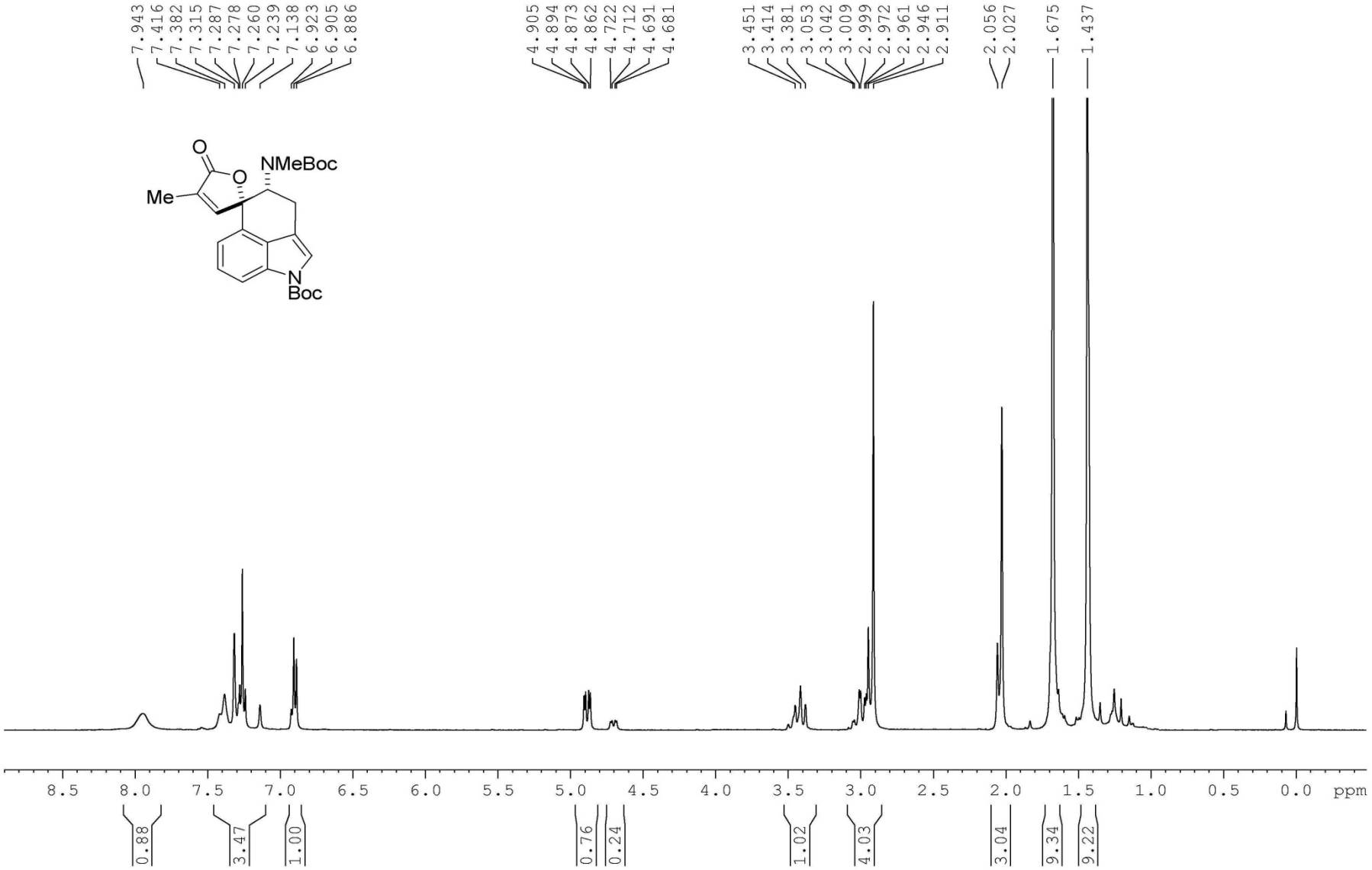
^{1}H-NMR of compound 5 (400 MHz, $CDCl_3$)



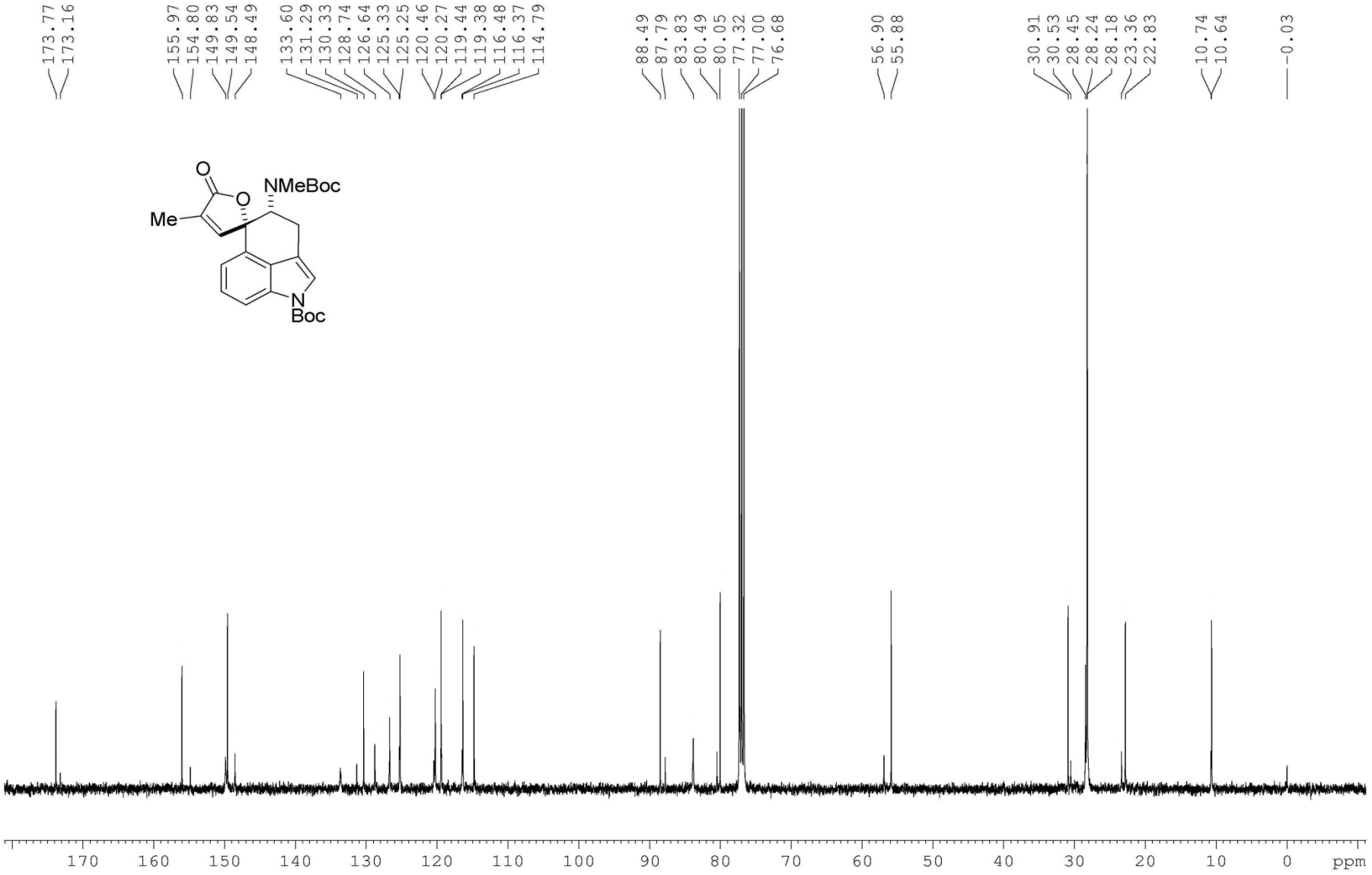
^{13}C-NMR of compound 5 (100 MHz, $CDCl_3$)



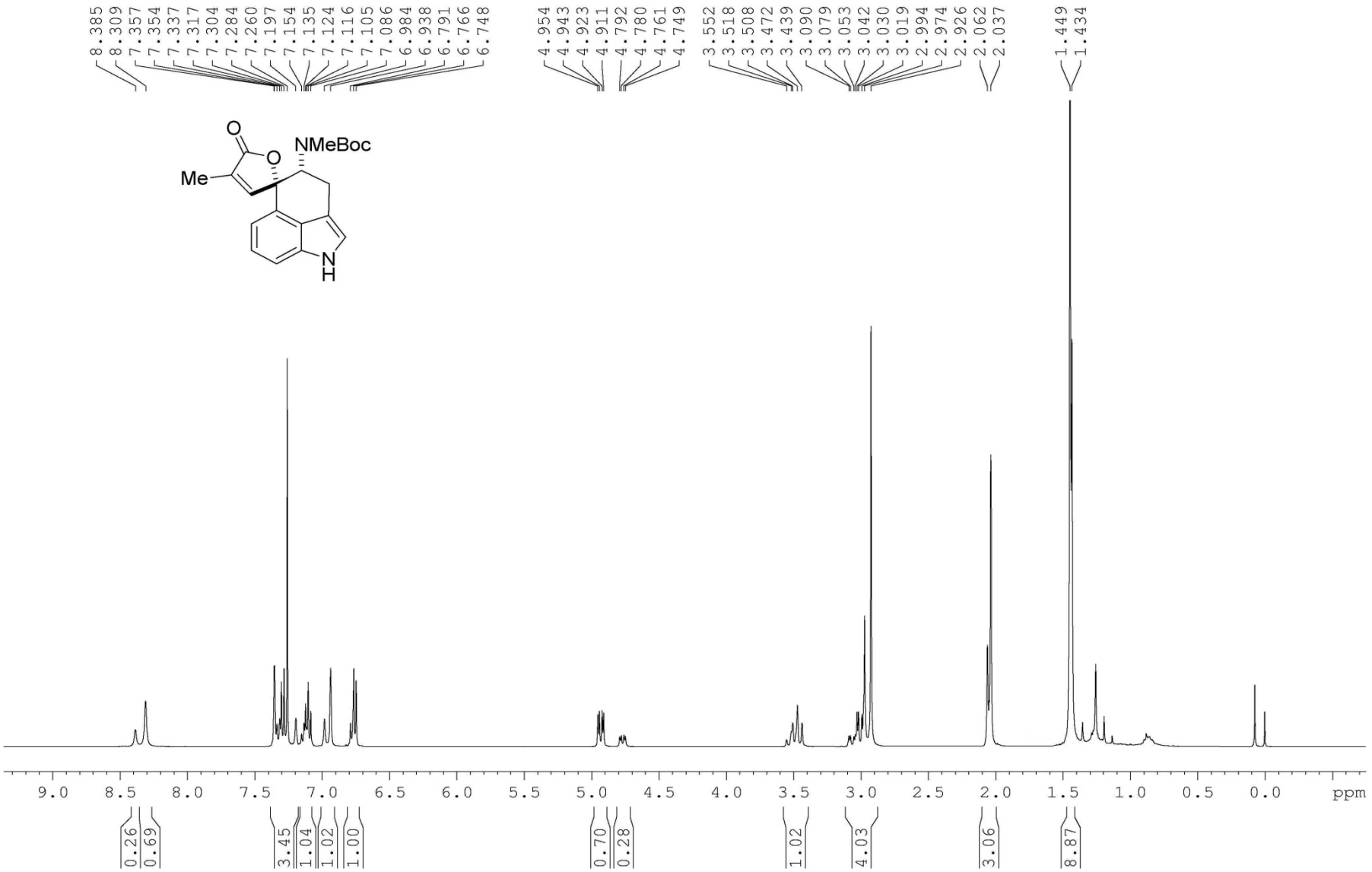
^{1}H-NMR of compound 3 (400 MHz, $CDCl_3$)



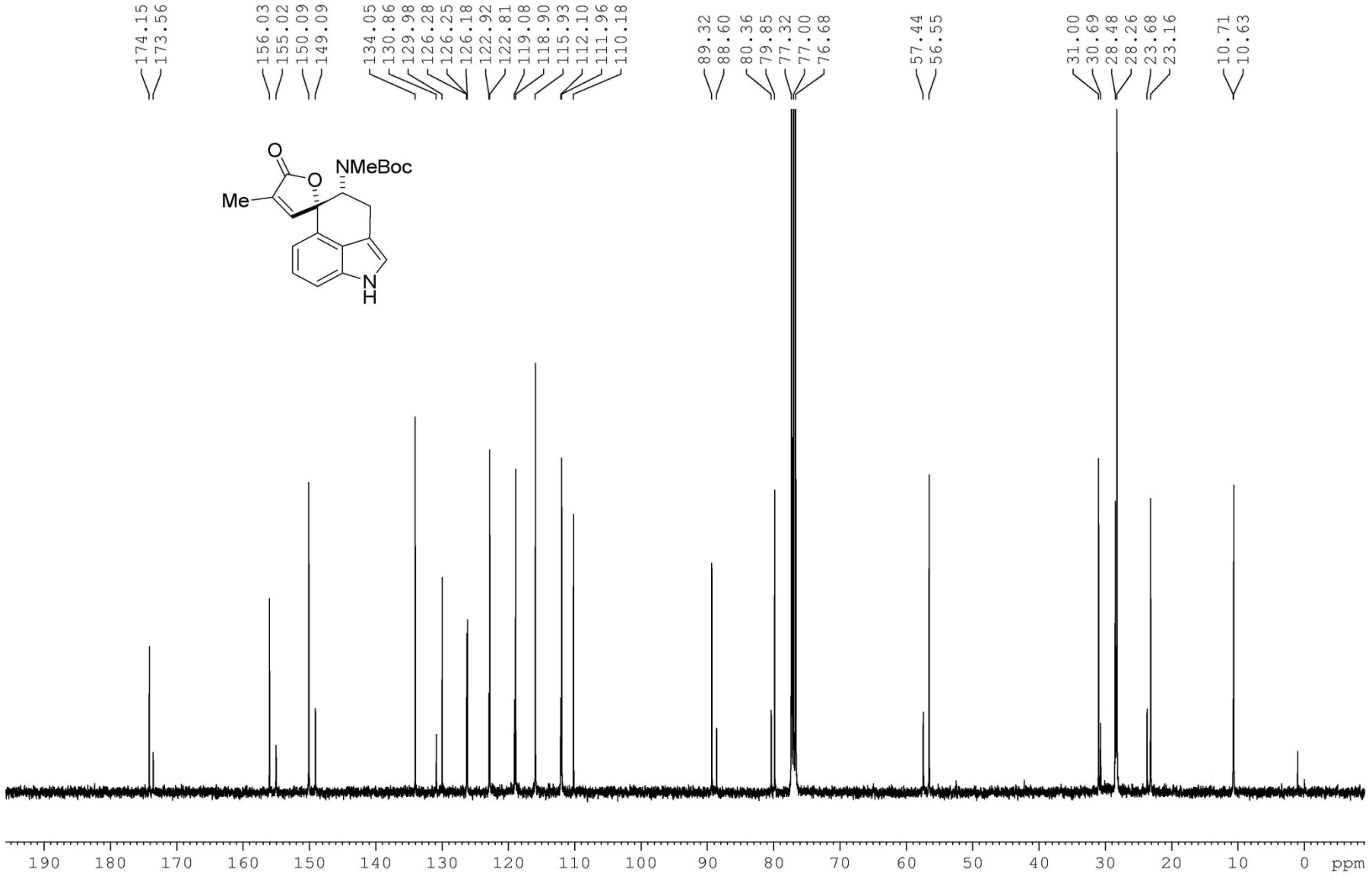
^{13}C-NMR of compound 3 (100 MHz, $CDCl_3$)



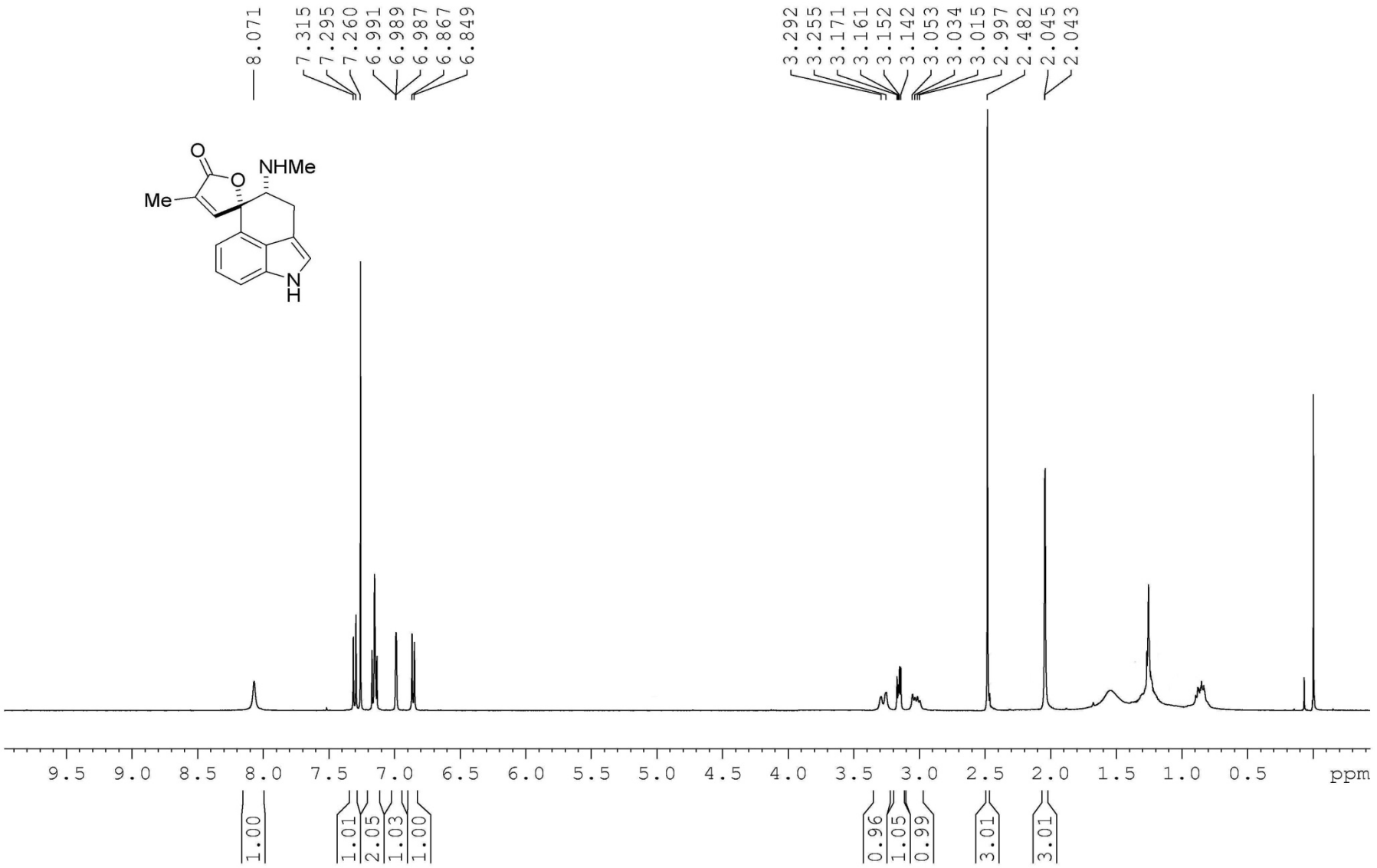
^{1}H-NMR of compound 18 (400 MHz, $CDCl_3$)



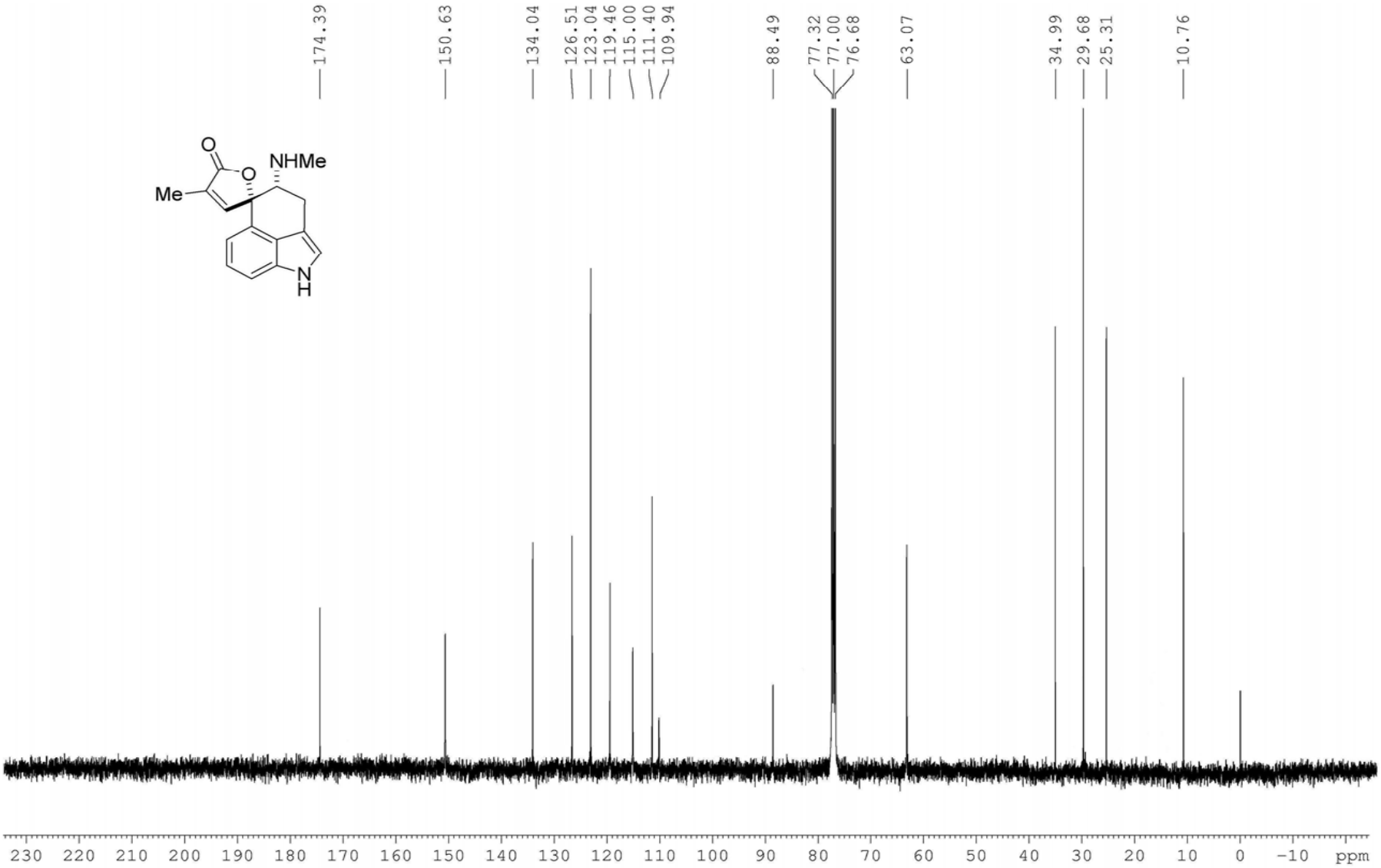
^{13}C-NMR of compound 18 (100 MHz, $CDCl_3$)



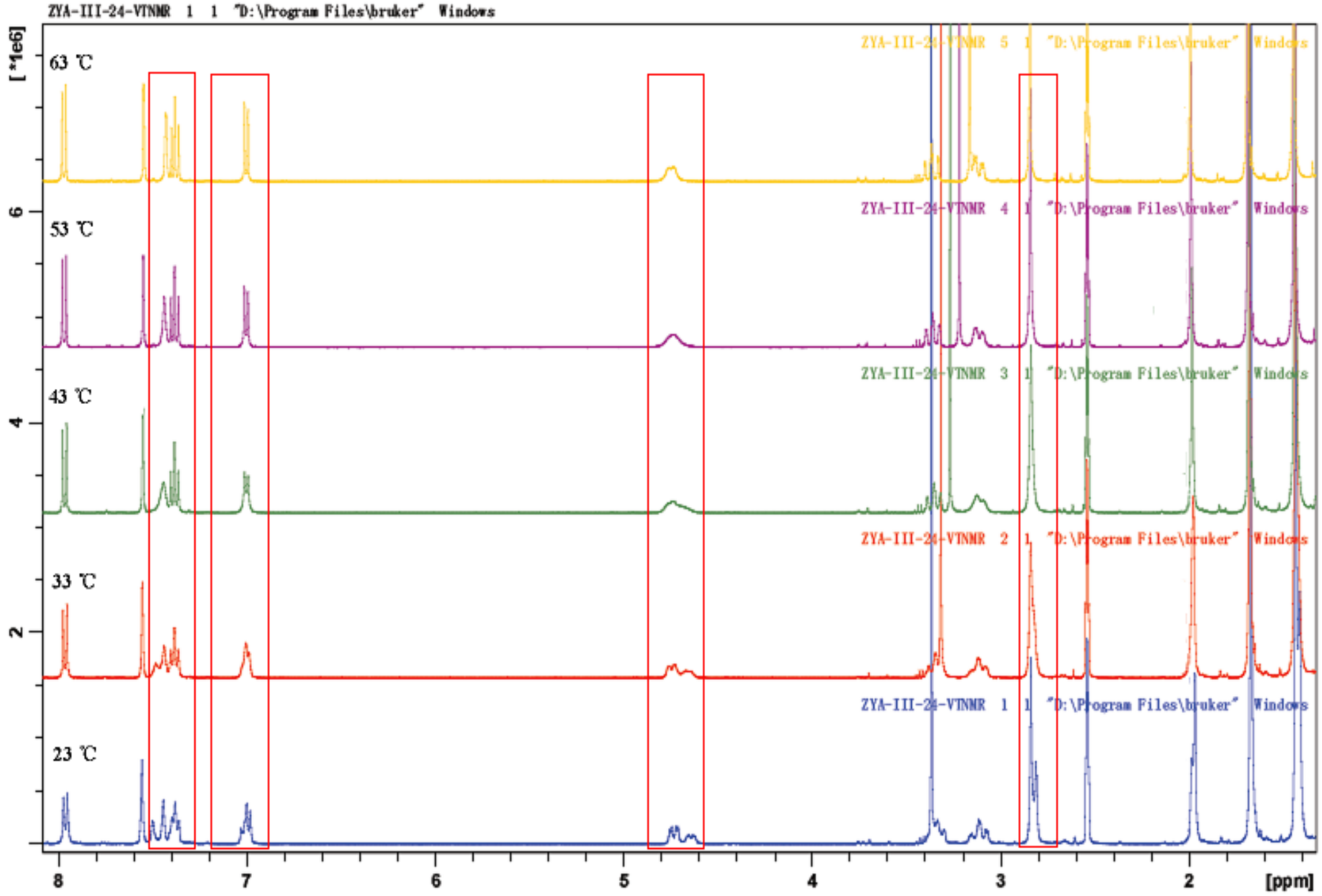
^{1}H-NMR of compound 1a (400 MHz, $CDCl_3$)



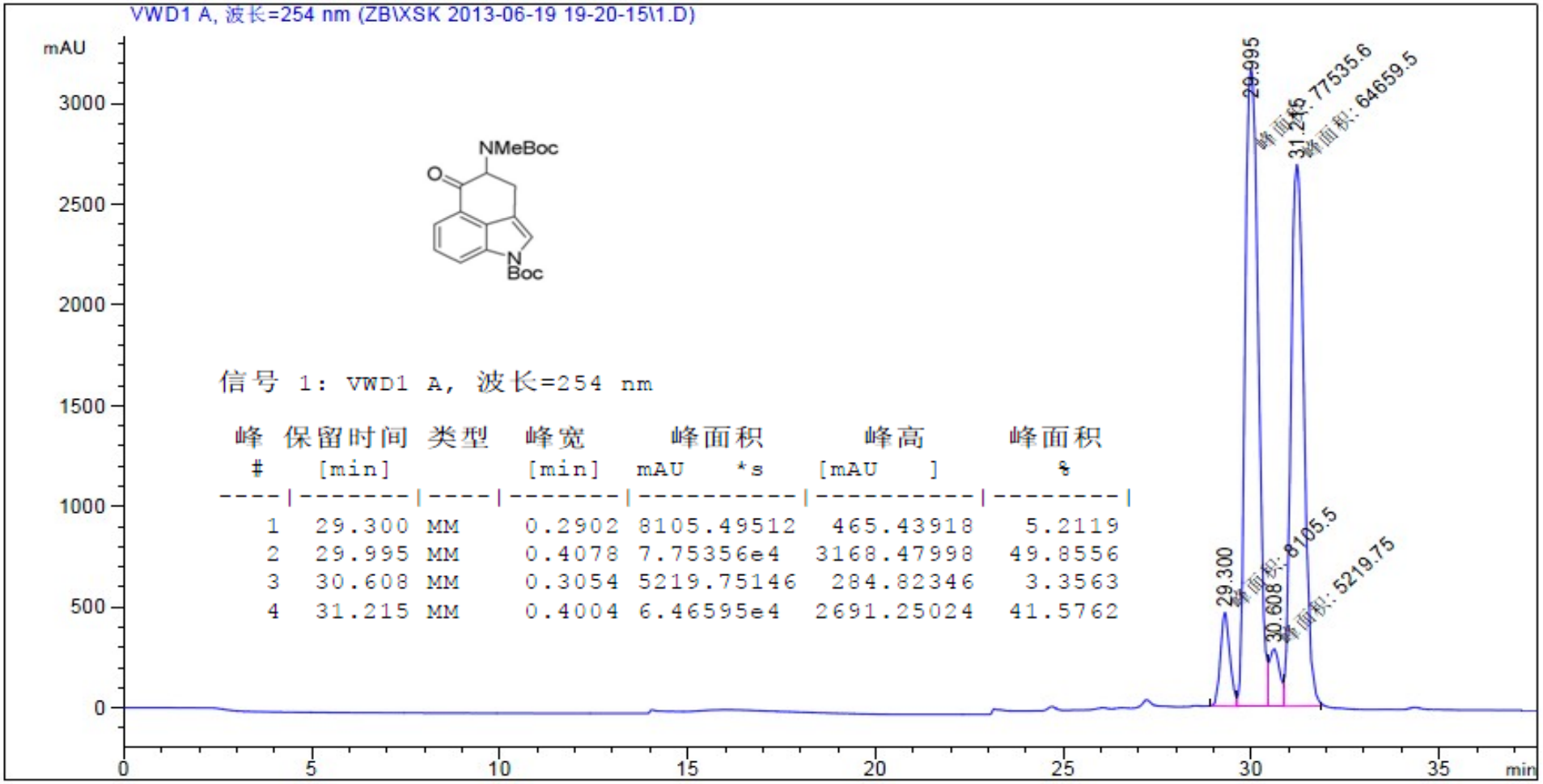
^{13}C-NMR of compound 1a (100 MHz, $CDCl_3$)



VT ^{1}H NMR of compound 3 (400MHz, DMSO-d_6, 23 °C to 63 °C)



Chiral HPLC analysis of compound 10



(Information about Chiral HPLC analysis of compound **10**: AD – H; 0.46 * 25; Iso : Hex = 30 : 70, 10 min; Iso : Hex = 40 : 60, 10 min; Iso : Hex = 50 : 50, 10 min; Iso : Hex = 80: 20, 10 min; 2mL/min, 254 nm)