Supporting Information

Stereocontrolled and Efficient Total Synthesis of (-)-Stephanotic Acid Methyl Ester and (-)-Celogentin C

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General information

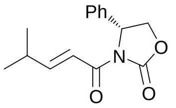
All reagents were obtained from commercial suppliers unless otherwise stated. Tetrahydro- furan (THF) was distilled from potassium sodium alloys; dichloromethane and acetonitrile were distilled from calcium hydride; N, N-Dimethylformamide (DMF) was distilled from magnesium sulfate under vacuum; Methanol was distilled from magnesium methoxide. Flasks were flame-dried under vacuum and cooled under a stream of nitrogen or argon.

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 or triketohydrindene hydrate in ethanol.

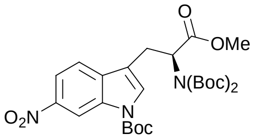
^{1}H NMR were recorded at 300 MHz or 400 MHz NMR spectrometer, ^{13}C NMR at 75 MHz or 100 MHz NMR spectrometer unless otherwise stated. The following abbreviations are used for the multiplicities: s: singlet, d: doublet, t: triplet, m: multiplet, br s: broad singlet for proton spectra. Coupling constants (J) are reported in Hertz (Hz). Infrared spectra were recorded with a thin layer of the product on a KBr disk.

The following abbreviations are used: **EtOAc**; ethyl acetate; **THF**: Tetrahydrofuran; **DMF**: N, N-Dimethylformamide; **Boc$_2$O**: di-tert-butyldicarbonate; **HOAc**: acetic acid; **DMAP**: 4-Dimethylaminopyridine; **EDCI**: 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide Hydrochloride; **HATU**: O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate; **HBTU**: O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate; **HOBt**: 1-Hydroxybenzotriazole; **DIPEA**: diisopropylethylamine; **NBS**: N-Bromosuccinimide

Experimental procedure and physical data



Compound 4.[1,2,3] To the solution of (2E)-isohexenoic acid (2.67 g, 23.4 mmol) and Et_3N (2.5 equiv) in THF (volume corresponded to 0.2 M of the oxazolidinone) was added trimethylacetyl chloride (2.62 g, 21.7 mmol) at -20 ^{o}C. A white solid was formed instantaneously. The mixture was stirred at -20 ^{o}C for 2.0 h. Lithium chloride (0.92 g, 21.6 mmol) was added, followed by the oxazolidinone (2.92 g, 17.9 mmol). The mixture was allowed to warm to room temperature slowly and stirred for 4.0 h. The reaction was quenched by addition of saturated NH_4Cl and the solution was extracted with EtOAc; The organic layer was washed subsequently with saturated $NaHCO_3$, brine and water, dried over anhydrous Na_2SO_4 and filtered. EtOAc was removed in vacuo, and the residue was purified by flash column chromatography(silica gel, 12% EtOAc in petroleum ether) provided the desired product **4** (4.33 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.30 (m, 5H), 7.22 (dd, J = 15.6, 1.2 Hz, 1H), 7.05 (dd, J = 15.6, 6.6 Hz, 1H), 5.48 (dd, J = 8.7, 3.9 Hz, 1H), 4.68 (t, J = 9.0 Hz, 1H), 4.26 (dd, J = 9.0, 3.9 Hz, 1H), 2.52 (m, 1H), 1.07 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 158.2, 153.8, 139.2, 129.1 (2C), 128.6, 126.0 (2C), 117.6, 69.8, 57.6, 31.3, 21.1, 21.0.



Compound 10. [5] To a stirred suspension of nitration of 6-nitro-L-tryptophan **8** [4] (6.39 g, 25.7 mmol) in dry MeOH (90 mL) was added slowly Me_3SiCl (25.0 mL, 196 mmol) in an ice-cold bath. After the addition was completed, The ice-cold bath was removed and the reaction was stirred at room temperature for 18.0 h. Then, Et_3N (50 mL, 361 mmol) and $(Boc)_2O$ (8.9 g, 40.8 mmol) were sequentially added. The reaction mixture was stirred until TLC showed complete protection. The solvent was removed under reduced pressure and the residue was extracted between water and EtOAc (3 × 60 mL).The combined organic layers were dried over Na_2SO_4, and then evaporated in vacuo.

To a solution of above crude product in dry CH_3CN (90 mL) was added DMAP (650 mg,

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[1] Ho, G. J.; Mathre, D. J. *J. Org. Chem.* **1995**, *60*, 2271-2273.

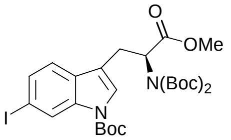
[2] Lin, J.; Liao, S.; Han, Y.; Qiu, W.; Hruby, V. J. *Tetrahedron*: *Asymmetry* **1997**, *8*, 3213-3221.

[3] Liao, S.; Shenderovich, M. D.; Lin, J.; Hruby, V. J. *Tetrahedron* **1997**, *53*, 16645-16662.

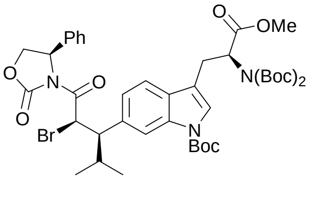
[4] Moriya, T.; Hagio, K.; Yoneda, N. *Bull. Chem. Soc. Jpn.* **1975,** *48*, 2217-2218.

[5] Jia, Y.; Bois-Choussy, M.; Zhu, J. *Org. Lett.* **2007**, *9*, 2401-2404.

5.3 mmol) and $(Boc)_2O$ (12.4 g, 56.9 mmol) at room temperature. The mixture was stirred for 1 h,after which time TLC showed that some starting material still remained. More $(Boc)_2O$ (4.4 g, 20.2 mmol) was added and the mixture was additionally stirred overnight. The solvent was evaporated, and the crud purified by silica gel column chromatography to afford **10** (8.59 g, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.14 (dd, J = 8.7, 2.1 Hz, 1H), 7.68 (s, 1H), 7.64 (d, J = 8.7 Hz, 1H), 5.19 (dd, J = 9.9, 5.3 Hz, 1H), 3.77 (s, 3H), 3.55 (dd, J = 15.0, 5.3 Hz, 1H), 3.39 (dd, J = 15.0, 9.9 Hz, 1H), 1.69 (s, 9H), 1.39 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 151.9 (2C), 148.6, 144.9, 135.3, 134.1, 129.3, 119.0, 117.7, 116.6, 111.5, 84.9, 83.1 (2C), 57.8, 52.3, 27.8 (3C), 27.5 (6C), 25.2.

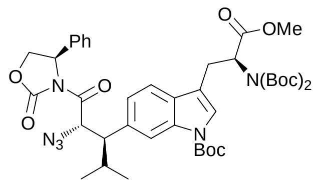


Compound 6.[5] To a solution of nitro-tryptophane **10** (8.59 g, 15.3 mmol) and Zn dust (50.0 g) in CH_2Cl_2 (180 mL) was slowly added HOAc (14.0 mL) at 0 °C. The solution was stirred at room temperature for 20 min and then the solution was filtered. The filtrate was washed with sat. aqueous $NaHCO_3$, H_2O and brine, dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was dissolved in THF (112 mL), H_2O (79 mL) and 5% HCl (43 mL). $NaNO_2$ was slowly added to the solution at 0 °C. After being stirred at 0 °C for 5 min, the mixture was added to the solution of KI (15.8 g 95.2 mmol) and I_2 (4.06 g 16.0 mmol) in H_2O (150 mL), then the resulting reaction mixture was continued to stir at room temperature for 1.0 h. The reaction mixture was basified to pH 7-8 with sat. aqueous $NaHCO_3$, extracted with EtOAc, and the combined organic phases were washed with sat. aqueous $NaHSO_3$, H_2O and brine, dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, 10-15% EtOAc in petroleum ether, then CH_2Cl_2 again) to provide the desired product **6** (7.08 g, 72%) and deiodo product (0.80 g 10%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.27 (s, 1H), 7.23 (d, J = 7.8 Hz, 1H), 5.12 (dd, J = 9.9, 5.1 Hz, 1H), 3.72 (s, 3H), 3.44 (dd, J = 15.0, 5.1 Hz, 1H), 3.29 (dd, J = 15.0, 9.9 Hz, 1H), 1.60 (s, 9H), 1.30 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 151.7 (2C), 149.0, 136.3, 131.3, 129.8, 124.4, 124.1, 120.4, 116.3, 88.7, 83.9, 83.0 (2C), 58.0, 52.3, 28.0 (3C), 27.6 (6C), 25.3.



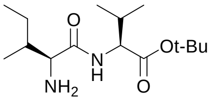
Compound 12. To a solution of iodo-tryptophane **6** (1.29 g, 2.0 mmol) in dry THF (4.0 mL) was added *i*-PrMgCl (2.0 M, 1.0 mL, 2.0 mmol) dropwise at -30 °C and the reaction mixture was stirred at the same temperature for 30 min. $CuBr{\cdot}Me_2S$ (83 mg, 0.4 mmol) was added to the reaction at -30 °C and the mixture was warmed to -20 °C over 20 min. The unsaturated amide **4** (519 mg, 2.0 mmol) in dry THF (2.0 mL) was added slowly at -15 to -10

°C. After being stirred at the same temperature for 4.0 h, the reaction mixture was cooled to -78 °C, and NBS (357 mg, 2.0 mmol) in dry THF (5.0 mL) was added. After an additional 2.0 h, the mixture was slowly warmed to 0 °C and then was stirred at 0 °C for 2.0 h. the reaction mixture was quenched with saturated $NaHSO_3$ and extracted with EtOAc (3 × 30 mL). The combined organic phase was washed with water (30 mL), brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 12% - 17% EtOAc in petroleum ether) to afford the desired product **12** (1.11 g, 65%). $[\alpha]_D^{30}$ –64.5 (*c* 1.00, MeOH); IR (neat): 2979, 1784, 1735, 1481, 1442, 1370, 1326, 1257, 1139, 1087, 851, 765, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.91 (s, 1H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.40 (s, 1H), 7.37-7.32 (m, 5H), 7.05 (d, *J* = 8.2 Hz, 1H), 6.36 (d, *J* = 10.4 Hz, 1H), 5.46 (dd, *J* = 8.8, 4.4 Hz, 1H), 5.21 (dd, *J* = 10.0, 4.6 Hz, 1H), 4.82 (t, *J* = 8.8 Hz, 1H), 4.30 (dd, *J* = 8.8, 4.4 Hz, 1H), 3.76 (s, 3H), 3.50 (dd, *J* = 15.2, 4.6 Hz, 1H), 3.45 (dd, *J* = 10.4, 5.2 Hz, 1H), 3.34 (dd, *J* = 15.2, 10.0 Hz, 1H), 2.09 (m, 1H), 1.65 (s, 9H), 1.32 (s, 18H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 170.7, 167.9, 152.9, 151.6, 149.6, 137.7, 135.1, 134.1, 129.7, 129.1, 128.8, 125.8, 124.5, 118.1, 116.3, 83.5, 82.9, 70.0, 58.1, 53.8, 52.2, 30.8, 28.1, 27.7, 25.6, 21.9, 17.9; HRMS (ESI) *m/z* calcd for $C_{42}H_{58}BrN_4O_{11}$ $(M + NH_4)^+$ 873.3280; found 873.3279.



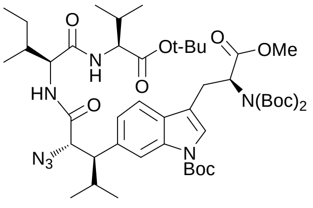
Compound 13. To a solution of compound **12** (5.74 g, 6.7 mmol) in DMF (21 mL) was added NaN_3 (1.14 g, 17.5 mmol) in one portion at room temperature. After being stirred for one day, DMF was removed under vacuum. the residue was diluted with EtOAc (50 mL) and water (50 mL), and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with water (2 × 50 mL), brine (2 × 50 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 10%-12% EtOAc in petroleum ether) to afford the desired product **13** (4.52 g, 82%). $[\alpha]_D^{34}$ –29.9 (*c* 1.00, MeOH); IR (neat): 2978, 2104, 1785, 1736, 1698, 1482, 1443, 1370, 1329, 1267, 1255, 1158, 1141, 1089, 851, 762, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.77 (s, 1H), 7.47 (s, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.69 (t, *J* = 7.6 Hz, 2H), 6.35 (d, *J* = 7.6 Hz, 2H), 5.78 (d, *J* = 11.6 Hz, 1H), 5.26 (dd, *J* = 8.8, 4.4 Hz, 1H), 5.23 (dd, *J* = 10.0, 5.0 Hz, 1H), 4.57 (t, *J* = 8.8 Hz, 1H), 4.02 (dd, *J* = 8.8, 4.4 Hz, 1H), 3.78 (s, 3H), 3.55 (dd, *J* = 14.8, 5.0 Hz, 1H), 3.38 (dd, *J* = 14.8, 10.0 Hz, 1H), 3.22 (dd, *J* = 11.6, 4.0 Hz, 1H), 2.34 (m, 1H), 1.66 (s, 9H), 1.35 (s, 18H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 170.7, 169.4, 152.8, 151.7, 149.3, 137.0, 134.9, 132.1, 129.7, 128.2, 127.7, 125.0, 124.6, 124.5, 118.3, 116.1, 115.9, 83.8, 82.9, 69.5, 58.9, 57.7, 57.3, 52.4, 52.2, 28.5, 28.0, 27.7, 25.4, 21.0,

17.1; HRMS (ESI) *m/z* calcd for $C_{42}H_{54}N_6NaO_{11}$ $(M + Na)^+$ 841.3743; found 841.3738.



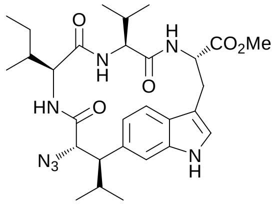
L-isoleucyl-L-valine tert-butyl ester 14. A solution of valine tert-butyl ester (113 mg, 0.65 mmol) and N-Cbz-L-isoleucine (193 mg, 0.73 mmol) in dry THF (3.0 mL) at 0 ºC was treated with HOBt (97 mg, 0.72 mmol), EDCI (193 mg, 1.01 mmol), and DIPEA (0.25 mL, 186 mg, 1.44 mmol). The reaction mixture was stirred at 0 °C for 1 h and at room temperature overnight. Water was added to the mixture, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 15 mL), and the combined organic layers were washed with water (20 mL), brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography(silica gel, 12% EtOAc in petroleum ether) to give the crude product N-Cbz-L-isoleucyl-L-valine tert-butyl ester.

To a solution of above crude product in MeOH (1.5 mL) was added HCO_2NH_4 (214 mg, 3.40 mmol) and 10% Pd/C (47 mg). The resulting mixture was stirred under H_2 (1 atm) at room temperature for 16 h, then filtered through filter paper and concentrated in vacuo. the residue was purified by flash column chromatography (silica gel, 1% Et_3N in CH_2Cl_2) to afford **14** (136 mg) in a total yield of 60% for two steps. $[\alpha]_D^{20}$ –37.6 (*c* 1.00, MeOH); IR (neat): 3330, 2966, 2934, 2877, 1733, 1665, 1509, 1370, 1150, 848 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.4 Hz, 1H), 4.39 (dd, *J* = 9.0, 4.2 Hz, 1H), 3.29 (d, *J* = 3.6 Hz, 1H), 2.15 (m, 1H), 1.96 (m, 1H), 1.51 (br s, 2H), 1.44 (s, 9H), 1.35 (m, 1H), 1.09 (m, 1H), 0.96-0.85 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 171.3, 81.6, 59.9, 56.9, 37.8, 31.1, 27.8 (3C), 23.6, 18.9, 17.4, 15.9, 11.7; HRMS (ESI) *m/z* calcd for $C_{15}H_{31}N_2O_3$ $(M + H)^+$ 287.2329; found 287.2334.



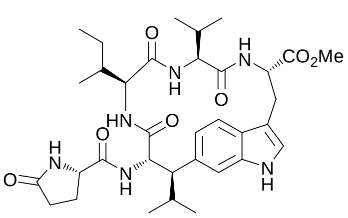
Compound 15. To a solution of azido compound **13** (409 mg, 0.50 mmol) in THF (6.0 mL) was added water (2.0 mL). The solution was stirred at 0 °C for 15 min, and then 30% H_2O_2 (0.45 mL, 8 equiv.) was added dropwise followed by dropwise addition of lithium hydroxide monohydrate (81 mg, 1.93 mmol) in water (1.0 mL). The resulting mixture was stirred at 0 °C for 6 h. The reaction was quenched with saturated Na_2SO_3 and stirred at room temperature for 30 min. The mixture was acidified with 6 N HCl to pH = 2 and extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with water (30 mL), brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo to give crud product, which was used directly in the next step.

A solution of above acid and amine **14** in dry THF (3.0 mL) at 0 °C was treated with HATU (263 mg, 0.69 mmol) and DIPEA (0.30 mL, 223 mg, 1.73 mmol). The resulting mixture was stirred at room temperature for 1 d. The reaction mixture was diluted with EtOAc. The organic phase was washed with 1% HCl (20 mL), saturated $NaHCO_3$ (20 mL), water (20 mL), brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 12% - 17% EtOAc in petroleum ether) to afford the desired product **15** (367 mg) in a total yield of 78% for two steps. $[\alpha]_D^{22}$ –35.0 (*c* 1.00, MeOH); IR (neat): 3401, 2975, 2108, 1736, 1699, 1655, 1516, 1443, 1370, 1257, 1155, 1088, 851, 768 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.36 (s, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 8.1 Hz, 1H), 6.14 (d, *J* = 8.4 Hz, 1H), 5.18 (dd, *J* = 10.2, 5.0 Hz, 1H), 4.34 (d, *J* = 5.4 Hz, 1H), 4.28 (dd, *J* = 8.7, 4.8 Hz, 1H), 4.08 (t, *J* = 7.8 Hz, 1H), 3.75 (s, 3H), 3.48 (dd, *J* = 15.0, 5.0 Hz, 1H), 3.29 (dd, *J* = 15.0, 10.2 Hz, 1H), 3.02 (dd, *J* = 8.4, 5.4 Hz, 1H), 2.52 (m, 1H), 2.08-2.01 (m, 2H), 1.64 (s, 9H), 1.43 (s, 9H), 1.31 (s, 18H), 1.31-1.15 (m, 1H), 1.04 (d, *J* = 6.3 Hz, 3H), 0.85-0.66 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 170.5, 170.2, 168.2, 151.6, 149.4, 135.5, 129.6, 124.4, 123.9, 118.6, 116.2, 115.5, 83.4, 82.9, 82.0, 67.0, 58.0, 57.7, 57.6, 55.0, 52.3, 36.9, 31.2, 28.8, 28.1, 27.9, 27.7, 25.5, 24.9, 21.4, 20.4, 18.7, 17.6, 14.9, 11.1; HRMS (ESI) *m/z* calcd for $C_{48}H_{75}N_7NaO_{12}$ $(M + Na)^+$ 964.5366; found 964.6365.



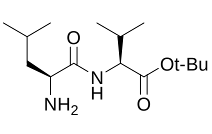
Compound 16. Trifluoroacetic acid (5.0 mL) was added slowly to a solution of compound **15** (283 mg, 0.30 mmol) in CH_2Cl_2 (5.0 mL) at ^oC. After 2.0 h the reaction mixture was concentrated ensuring all excess trifluoroacetic had been removed. The residue was dissolved in anhydrous DMF (150 mL), cooled to 0 ^oC, DIPEA (0.75 mL, 4.31 mmol) and HATU (1.14 g, 3.0 mmol) were added sequentially. The reaction mixture was allowed to warm to room temperature, was stirred for 9 days, and then was concentrated. The residue was dissolved in EtOAc (50 mL) and was washed with 1% HCl (20 mL), saturated $NaHCO_3$ (2 × 30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 60% - 90% EtOAc in petroleum ether) to give the product **16** (82 mg, 48%). $[\alpha]_D^{27}$ –18.5 (*c* 1.00, MeOH); IR (neat): 3328, 2965, 2101, 1745, 1661, 1513, 1460, 1384, 1211 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.48 (d, *J* = 8.4 Hz, 1H), 7.01 (s, 1H), 6.98 (s, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 5.48 (m, 1H), 4.03 (d, *J* = 8.4 Hz, 1H), 3.92 (d, *J* = 11.6 Hz, 1H), 3.83 (d, *J* = 6.0 Hz, 1H), 3.78 (s, 3H), 3.48 (dd, *J* = 14.8, 5.6 Hz, 1H), 3.20-3.11 (m, 2H), 2.32 (m, 1H), 2.02 (m, 1H), 1.64 (m, 1H), 1.45 (m, 1H), 1.11 (m, 1H), 1.03 (d, *J* = 6.4 Hz, 3H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.92-0.89 (m, 12H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.7, 172.2, 171.7, 171.1, 138.4, 131.2, 127.1, 125.6, 120.2, 118.7, 115.8, 110.0, 66.6, 60.0, 59.4, 53.4, 52.8, 51.9, 38.9, 32.4, 30.1, 28.7, 26.0, 22.0, 19.0, 18.9, 15.9, 11.0; HRMS (ESI) *m/z* calcd for $C_{29}H_{42}N_7O_5$ $(M + H)^+$

568.3242; found 568.3247.



Stephanotic acid methyl ester 2. A solution of compound **16** (80 mg, 0.14 mmol) in MeOH (3.0 mL) was degassed for 20 min, then HCO_2NH_4 (115 mg) and 10% Pd/C (190 mg) was added sequentially. The reaction mixture was stirred under argon at room temperature for 10 h and filtered through filter paper. The filter pad was washed with MeOH, and the filtrate was concentrated. The residue was dissolved in EtOAc (30 mL) and was washed with saturated $NaHCO_3$ (10 mL), H_2O (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give crud product, which was used directly in the next step.

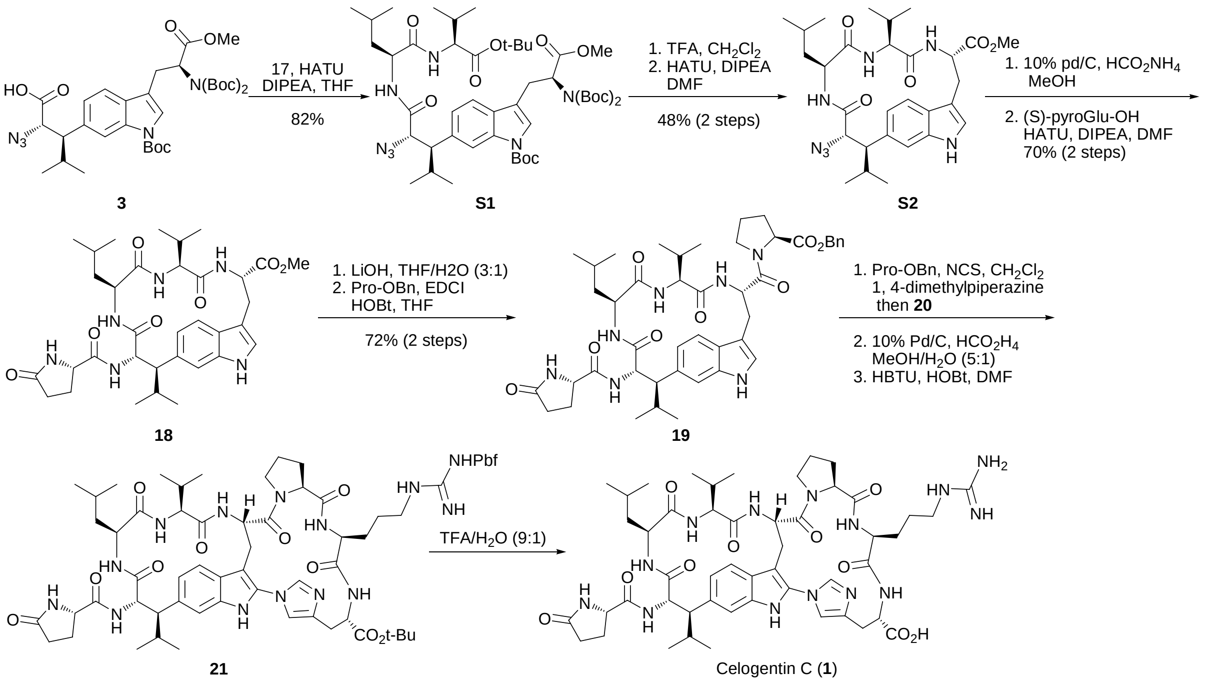
A solution of above crud product in dry DMF (2.0 mL) at 0 °C was treated with (S)-Pyroglutamic acid (32 mg, 0.25 mmol), DIPEA (0.1 mL, 0.58 mmol) and HATU (107 mg, 0.28 mmol). The reaction mixture was allowed to warm to room temperature overnight and the solvent was removed under vacuum. The residue was dissolved in EtOAc (30 mL) and was washed with HCl (1M; 10 mL), saturated $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 3% - 4% MeOH in CH_2Cl_2) to give stephanotic acid methyl ester **2** (64 mg, 70%). $[\alpha]_D^{22}$ –112.4 (*c* 0.50, MeOH); ^1H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H), 8.52 (d, J = 9.2 Hz, 1H), 8.30 (d, J = 10.0 Hz, 1H), 7.87 (s, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 6.99-6.97 (m, 3H), 6.88 (s, 1H), 5.23 (m, 1H), 4.86 (t, J = 10.4 Hz, 1H), 4.11 (dd, J = 8.8, 3.6 Hz, 1H), 3.88 (dd, J = 7.6, 6.0 Hz, 1H), 3.76 (dd, J = 10.4, 8.4 Hz, 1H), 3.65 (s, 3H), 3.27 (m, 1H), 3.13 (dd, J = 15.2, 8.8 Hz, 1H), 2.99 (dd, J = 11.6, 3.6 Hz, 1H), 2.24 (m, 1H), 2.13 (m, 1H), 2.08 (m, 2H), 2.01 (m, 1H), 1.71 (m, 1H), 1.62 (m, 1H), 1.22 (m, 2H), 0.92 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H), 0.77 (d, J = 8.6 Hz, 3H), 0.68-0.63 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.5, 172.2, 171.8, 170.7, 170.0, 169.7, 136.1, 129.8, 125.5, 123.5, 119.0, 117.8, 114.4, 108.4, 58.0, 57.7, 55.2, 55.1, 52.0, 51.9, 51.1, 37.2, 30.5, 29.0, 27.1, 26.8, 25.6, 24.1, 21.8, 18.7, 17.9, 17.3, 15.4, 10.4; HRMS (ESI) *m/z* calcd for $C_{34}H_{49}N_6O_7$ $(M + H)^+$ 653.3657; found 653.3664.



L-leucyl-L-valine tert-butyl ester 17. A solution of valine tert-butyl ester (5.19 g, 30.0 mmol) and N-Cbz-L-leucine (8.05 g, 30.4 mmol) in dry CH_2Cl_2 (100 mL) at 0 °C was treated with HOBt (4.72 g, 35.0 mmol), EDCI (7.72 g, 40.3 mmol), and DIPEA (13.0 mL, 9.65 g, 74.8 mmol). The resulting mixture was stirred at 0 °C for 1 h and at room temperature for 1 d. The reaction mixture was washed with saturated $NaHCO_3$ (50 mL), water (50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 12% EtOAc in petroleum ether) to give the product N-Cbz-L-leucyl-L-valine tert-butyl ester. $[\alpha]_D^{31}$ –46.5 (*c* 1.00, MeOH); IR (neat): 3313, 2963, 1733, 1701, 1658, 1548, 1458, 1369, 1270, 1239, 1148 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.29 (m, 5H), 6.41 (d, *J* = 8.4 Hz, 1H), 5.22 (d, *J* = 7.2 Hz, 1H), 5.11 (s, 2H), 4.40 (dd, *J* = 8.8, 4.4 Hz, 1H), 4.21 (m, 1H), 2.13 (m, 1H), 1.70-1.62 (m, 2H), 1.53 (m, 1H), 1.46 (s, 9H), 0.94-0.87 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 170.7, 156.1, 136.2, 128.5 (2C), 128.1, 128.0 (2C), 81.9, 67.0, 57.4, 53.6, 41.3, 31.4, 28.0 (3C), 24.6, 22.9, 22.0, 18.8, 17.5; HRMS (ESI) *m/z* calcd for $C_{23}H_{37}N_2O_5$ $(M + H)^+$ 421.2697; found 421.2691.

To a solution of above product (5.66 g, 13.5 mmol) in MeOH (40.0 mL) was added 10% Pd/C (319 mg). The resulting mixture was stirred under H_2 (4 atm) at room temperature for 12 h, then filtered through filter paper and concentrated in vacuo to afford the desired product **17** (3.79 g, 98%), which was directly used for next reaction.

Compound **18** was prepared from compound **3** according to the same procedure as that described for stephanotic acid methyl ester **2**; Compound **S3** and Celogentin C was prepared according to the literature procedure [6] (Scheme 1).



Scheme 1

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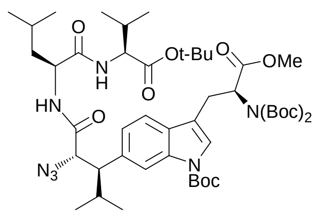
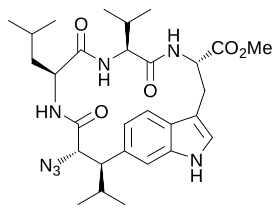
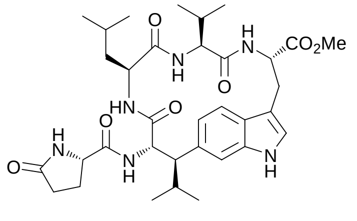
[6] Ma, B.; Litvinov, D. N.; He, L.; Banerjee, B.; Castle, S. L. *Angew. Chem. Int. Ed.* **2009**, *48*, 6104-6107.



Compound S1. $[\alpha]_D^{31}$ –40.0 (*c* 1.00, MeOH); IR (neat): 3336, 2976, 2109, 1736, 1698, 1661, 1520, 1442, 1370, 1257, 1142, 1087, 851, 768 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.34 (s, 1H), 7.03 (dd, J = 8.0, 1.2 Hz, 1H), 6.42 (d, J = 8.0 Hz, 1H), 6.38 (d, J = 8.8 Hz, 1H), 5.16 (dd, J = 10.0, 4.8 Hz, 1H), 4.33 (d, J = 5.2 Hz, 1H), 4.29-4.21 (m, 2H), 3.72 (s, 3H), 3.46 (dd, J = 14.8, 4.8 Hz, 1H), 3.28 (dd, J = 14.8, 10.0 Hz, 1H), 2.99 (dd, J = 8.8, 5.2 Hz, 1H), 2.49 (m, 1H), 2.04 (m, 1H), 1.62(s, 9H), 1.41 (s, 9H), 1.45-1.38 (m, 1H), 1.29 (s, 18H), 1.29-1.13 (m, 2H), 1.02 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 6.8 Hz, 6H), 0.75 (d, J = 6.8 Hz, 3H), 0.72 (d, J = 6.4 Hz, 3H), 0.68 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.4, 170.2, 168.1, 151.4, 149.1, 135.2, 129.4, 124.2, 123.3, 118.3, 115.9, 115.5, 83.1, 82.5, 81.4, 66.7, 57.8, 57.3, 54.8, 52.0, 51.5, 40.3, 30.9, 28.6, 27.8, 27.7, 27.4, 25.2, 24.0, 22.4, 21.5, 21.2, 20.1, 18.5, 17.4; HRMS (ESI) *m/z* calcd for $C_{48}H_{79}N_8O_{12}$ $(M + NH_4)^+$ 959.5812; found 959.5816.

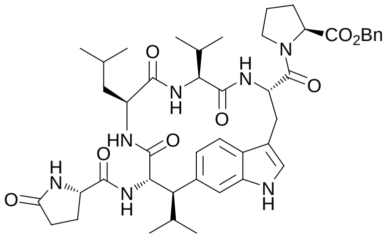


Compound S2. $[\alpha]_D^{24}$ –23.5 (*c* 1.00, MeOH); IR (neat): 3318, 2960, 2101, 1743, 1659, 1630, 1519, 1457, 1387, 1370, 1218 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.48 (d, J = 8.4 Hz, 1H), 7.03 (s, 1H), 6.98 (s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 5.47 (dd, J = 10.4, 6.0 Hz, 1H), 4.30 (dd, J = 9.2, 6.4 Hz, 1H), 3.91 (d, J = 11.2 Hz, 1H), 3.83 (d, J = 7.6 Hz, 1H), 3.77 (s, 3H), 3.49 (dd, J = 15.2, 6.0 Hz, 1H), 3.16 (dd, J = 15.2, 10.4 Hz, 1H), 3.12 (dd, J = 11.2, 5.2 Hz, 1H), 2.31 (m, 1H), 2.04 (m, 1H), 1.56 (m, 1H), 1.48-1.36 (m, 2H), 1.01 (d, J = 7.2 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 0.91-0.86 (m, 12H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.61, 173.58, 172.0, 170.8, 138.4, 131.1, 127.2, 125.6, 120.1, 118.7, 115.9, 110.0, 66.5, 59.5, 53.8, 53.4, 52.9, 52.0, 44.0, 32.5, 30.1, 28.6, 25.9, 23.3, 22.0, 21.7, 19.0, 18.82, 18.78; HRMS (ESI) *m/z* calcd for $C_{29}H_{42}N_7O_5$ $(M + H)^+$ 568.3242; found 568.3241.



Compound 18. $[\alpha]_D^{34}$ –200.5 (*c* 1.00, MeOH); IR (neat): 3310, 2960, 1741, 1649, 1521, 1456, 1368, 1264, 1214 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H), 8.53 (d, J = 8.8 Hz, 1H), 8.39 (d, J = 10.0 Hz, 1H), 7.86 (s, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 6.98 (s, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.90 (s, 1H), 6.80 (d, J = 8.0 Hz, 1H), 5.22 (m, 1H), 4.86 (t, J = 10.4 Hz, 1H), 4.11 (dd, J = 8.4, 2.8 Hz, 1H), 4.03 (t, J = 9.2 Hz, 1H), 3.88 (t, J = 7.0 Hz, 1H), 3.65 (s, 3H), 3.28 (m, 1H), 3.15 (dd, J = 15.2, 8.4 Hz, 1H), 2.99 (dd, J = 11.8, 3.0 Hz, 1H), 2.24 (m, 1H), 2.12-2.04 (m, 4H), 1.70 (m, 1H), 1.40-1.35 (m, 2H), 1.23 (m, 1H), 0.91 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H), 0.85 (d, J = 6.0 Hz, 3H), 0.79-0.75 (m, 6H), 0.69 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100

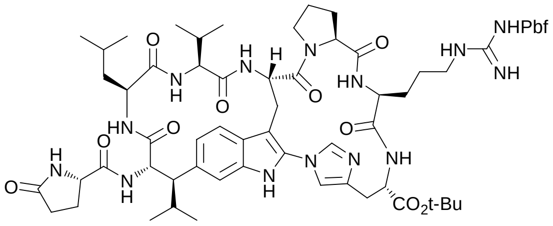
MHz, DMSO-*d*$_6$) δ 177.4, 172.3, 172.1, 171.7, 169.9, 169.8, 136.0, 129.9, 125.6, 123.4, 119.0, 117.7, 114.5, 108.4, 58.2, 55.14, 55.05, 52.0, 51.9, 51.7, 51.3, 42.9, 30.5, 29.0, 27.0, 26.8, 25.5, 23.7, 23.1, 21.8, 20.9, 18.6, 17.6, 17.3; HRMS (ESI) *m/z* calcd for $C_{34}H_{49}N_6O_7$ (M + H)$^+$ 653.3657; found 653.3651.



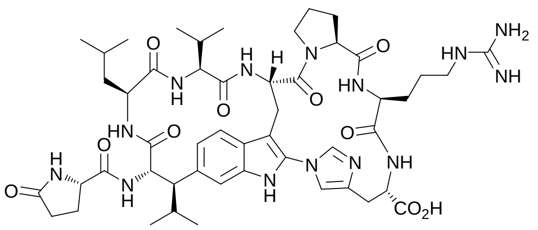
Compound 19.[7] To a solution of compound **18** (33 mg, 0.05 mmol) in THF/H$_2$O (3:1, 2.0 mL) was added lithium hydroxide monohydrate (21 mg, 0.50 mmol) at 0 ^{o}C. The resulting mixture was stirred at 0 ^{o}C for 3 h. The reaction mixture was acidified with 6 N HCI to pH = 2 and was diluted with EtOAc (30 mL). The mixture was dried over Na$_2$SO$_4$, and concentrated in vacuo to give crud product, which was used directly in the next step.

A solution of above crud product and L-proline benzyl ester (20 mg, 0.10 mmol) in anhydrous THF (3.0 mL) was treated with HOBt (13 mg, 0.10 mmol), EDCI (21 mg, 0.11 mmol) and DIPEA (25 μL, 0.14 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 2 days. The reaction was treated with saturated NaHCO$_3$ (5 mL) and extracted with CH$_2$Cl$_2$ (6×5 mL). The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. Preparative TLC (silica gel, 1:10 MeOH/CH$_2$Cl$_2$ elution) afforded **19** (30 mg, 72%). $[\alpha]_D^{34}$ –128.0 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.63 (s, 1H), 8.51 (d, *J* = 9.2 Hz, 1H), 8.33 (d, *J* = 9.2 Hz, 1H), 7.86 (s, 1H), 7.39-7.38 (m, 5H), 7.35-7.34 (m, 2H), 6.98 (s, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.87 (s, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 5.31 (m, 1H), 5.18 (d, *J* = 12.4 Hz, 1H), 5.12 (d, *J* = 12.4 Hz, 1H), 4.85 (t, *J* = 10.2 Hz, 1H), 4.41 (dd, *J* = 8.4, 5.6 Hz, 1H), 4.11 (dd, *J* = 8.4, 2.8 Hz, 1H), 4.02 (m, 1H), 3.90-3.82 (m, 2H), 3.76 (m, 1H), 3.23 (dd, *J* = 15.2, 4.6 Hz, 1H), 3.04 (dd, *J* = 15.2, 7.6 Hz, 1H), 2.98 (dd, *J* = 11.6, 3.2 Hz, 1H), 2.28-2.20 (m, 2H), 2.13-2.06 (m, 4H), 2.03-1.95 (m, 2H), 1.85 (m, 1H), 1.69 (m, 1H), 1.39-1.34 (m, 2H), 1.24 (m, 1H), 0.85 (d, *J* = 6.8 Hz, 6H), 0.80-0.75 (m, 9H), 0.69 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 177.5, 172.2, 171.9, 171.8, 170.0, 169.5, 169.2, 135.9, 129.5, 128.5, 128.1, 128.0, 126.0, 124.2, 118.7, 117.9, 114.3, 108.0, 66.0, 58.7, 57.6, 55.2, 55.0, 52.0, 51.7, 50.0, 46.7, 42.8, 30.3, 29.0, 28.6, 26.8, 26.2, 25.6, 24.9, 23.8, 23.2, 21.8, 20.9, 18.8, 17.7, 17.3; HRMS (ESI) *m/z* calcd for $C_{45}H_{60}N_7O_8$ (M + H)$^+$ 826.4498; found 826.4496.

Compound S3. $[\alpha]_D^{25}$ –24.0 (*c* 0.50, CH$_2$Cl$_2$), lit [7] $[\alpha]_D^{25}$ –28.0 (*c* 0.067, CH$_2$Cl$_2$); ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.42 (s, 1H), 8.75 (d, *J* = 9.6 Hz, 1H), 8.51 (d, *J* = 8.8 Hz, 1H), 8.38 (d, *J* = 9.2 Hz, 1H), 8.31 (d, *J* = 10.0 Hz, 1H), 7.87 (s, 1H), 7.85 (s, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.33 (s, 1H), 7.02 (br s, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H),

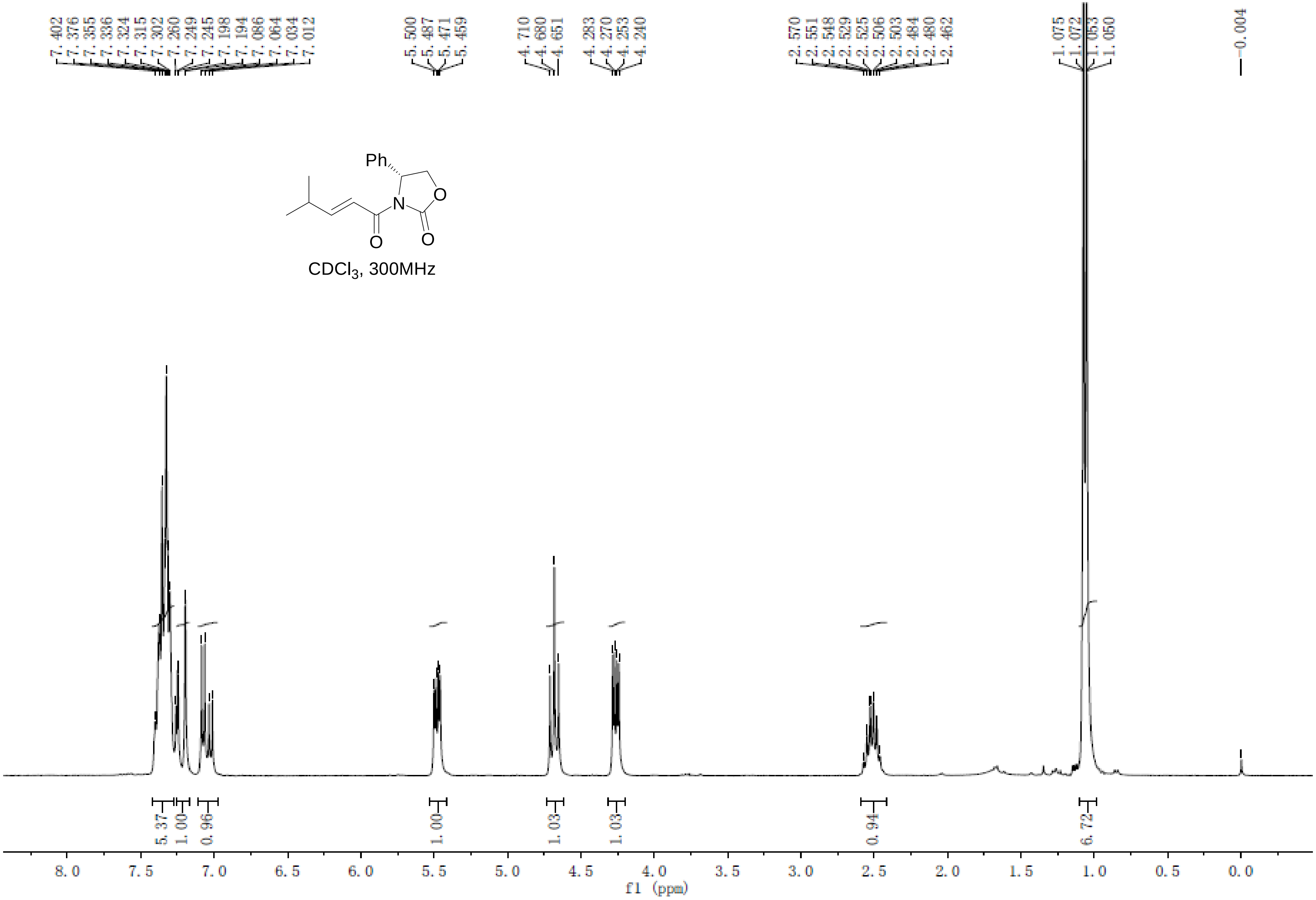


6.85 (s, 1H), 6.66 (br s, 1H), 6.59 (d, J = 5.2 Hz, 1H), 6.38 (br s, 1H), 5.69 (m, 1H), 4.88-4.79 (m, 2H), 4.14-4.07 (m, 3H), 4.03-3.92 (m, 2H), 3.90-3.84 (m, 1H), 3.56 (t, J = 7.8 Hz, 1H), 3.19-3.13 (m, 2H), 3.06 (d, J = 2.8 Hz, 1H), 3.03-2.98 (m, 2H), 2.95 (s, 2H), 2.78 (dd, J = 16.4, 12.4 Hz, 1H), 2.59 (t, J = 14.0 Hz, 1H), 2.47 (s, 3H), 2.42 (s, 3H), 2.26-2.19 (m, 2H), 2.15-2.12 (m, 1H), 2.10-2.02 (m, 4H), 1.99 (s, 3H), 1.88-1.82 (m, 1H), 1.77-1.69 (m, 3H), 1.62 (m, 1H), 1.50-1.37 (m, 3H), 1.41 (s, 9H), 1.39 (s, 3H), 1.38 (s, 3H), 1.25 (m, 1H), 1.18-1.12 (m, 1H), 0.82 (d, J = 6.4 Hz, 3H), 0.77 (d, J = 6.4 Hz, 3H), 0.72 (d, J = 6.8 Hz, 3H), 0.69-0.65 (m, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.4, 172.1, 171.5, 171.3, 171.1, 170.8, 170.0, 169.3, 169.1, 157.4, 156.0, 138.2, 137.4, 137.2, 134.2, 132.7, 131.4, 130.6, 129.4, 125.0, 124.3, 119.4, 116.6, 116.2, 113.8, 99.9, 86.2, 81.5, 61.6, 57.2, 55.1, 54.7, 52.2, 51.2, 50.4, 47.2, 46.8, 42.5, 41.4, 31.5, 31.2, 29.9, 29.0, 28.3, 27.6, 27.5, 26.5, 26.1, 25.5, 25.1, 24.4, 23.9, 23.1, 21.8, 20.9, 18.9, 18.7, 18.1, 17.6, 17.0, 12.2; HRMS (ESI) m/z calcd for $C_{67}H_{95}N_{14}O_{13}S$ (M + H)$^+$ 1335.6918; found 1335.6820.

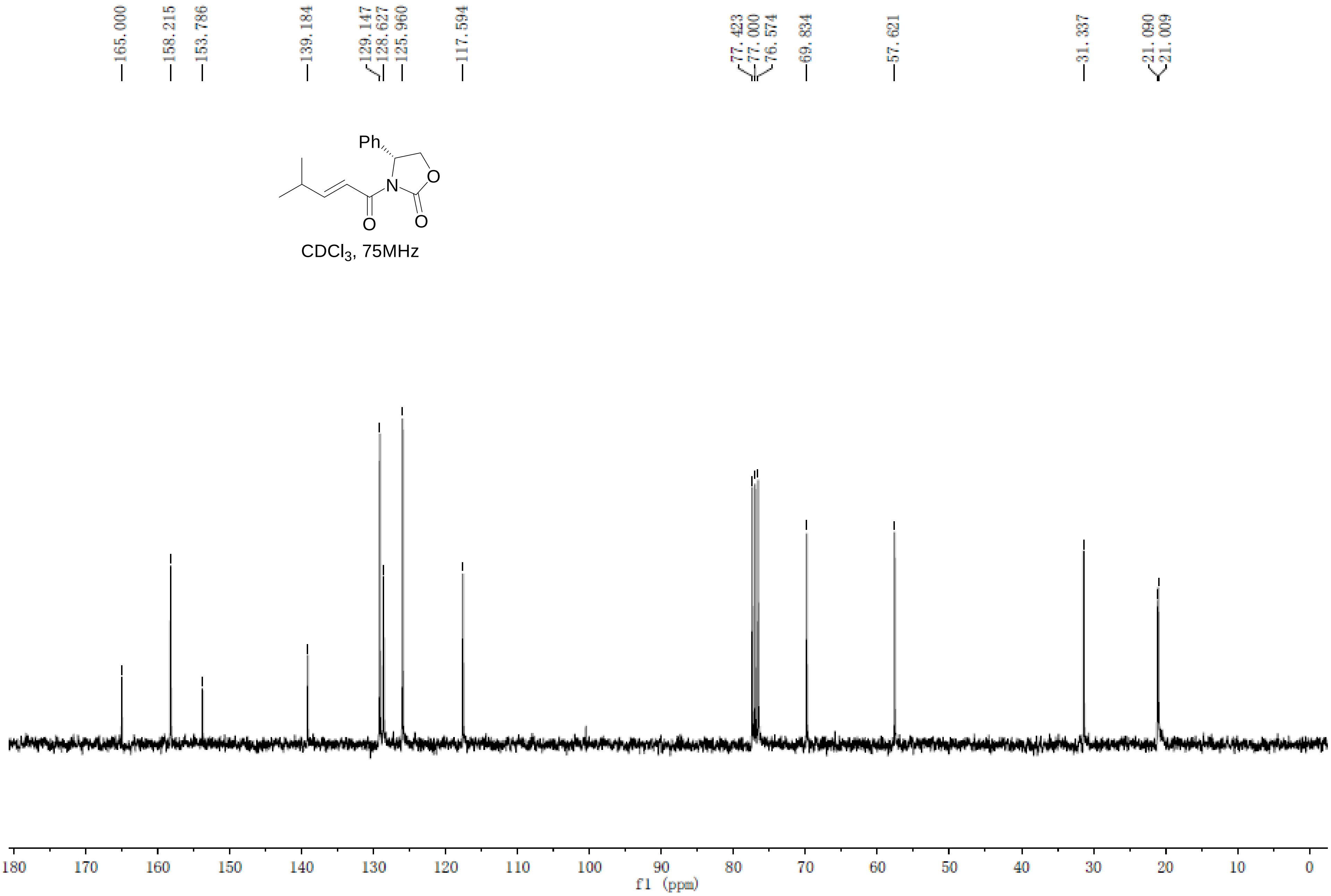


Celogentin C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 9.33 (s, 1H), 8.81 (d, J = 8.8 Hz, 1H), 8.54 (d, J = 8.8 Hz, 1H), 8.34 (d, J = 9.6 Hz, 1H), 8.14 (d, J = 8.8 Hz, 1H), 7.88 (s, 1H), 7.76 (s, 1H), 7.62 (br s, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.95 (d, J = 10.4 Hz, 1H), 6.94 (s, 1H), 6.81 (d, J = 6.4 Hz, 1H), 5.62 (dd, J = 15.8, 9.0 Hz, 1H), 4.90 (t, J = 10.6 Hz, 1H), 4.83 (t, J = 10.4 Hz, 1H), 4.20 (dd, J = 15.8, 9.0 Hz, 1H), 4.15-4.09 (m, 2H), 3.99-3.94 (m, 2H), 3.82-3.74 (m, 1H), 3.56 (t, J = 7.6 Hz, 1H), 3.42 (d, J = 16.0 Hz, 1H), 3.32 (dd, J = 15.4, 5.8 Hz, 1H), 3.12-3.06 (m, 3H), 2.93 (dd, J = 15.2, 12.8 Hz, 1H), 2.59 (dd, J = 15.2, 11.6 Hz, 1H), 2.27-2.20 (m, 2H), 2.16-2.12 (m, 1H), 2.12-2.06 (m, 2H), 2.03-1.96 (m, 2H), 1.87-1.74 (m, 3H), 1.72-1.65 (m, 1H), 1.63-1.58 (m, 1H), 1.48-1.37 (m, 4H), 1.23-1.15 (m, 1H), 0.83 (d, J = 6.4 Hz, 3H), 0.77 (d, J = 6.0 Hz, 1H), 0.73-0.70 (m, 9H), 0.67 (d, J = 6.0Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.4, 172.1, 171.3, 171.2, 170.9, 169.3, 169.1, 156.8, 136.5, 132.8, 131.5, 131.1, 128.6, 124.9, 119.5, 114.0, 100.9, 61.6, 57.2, 55.1, 54.7, 52.1, 51.3, 49.9, 47.2, 46.9, 41.5, 40.5, 31.1, 29.7, 29.0, 26.6, 25.5, 25.0, 23.9, 23.0, 21.7, 20.9, 18.6, 18.2, 17.0; HRMS (ESI) m/z calcd for $C_{45}H_{60}N_7O_8$ (M + H)$^+$ 1027.5472; found 1027.5455.

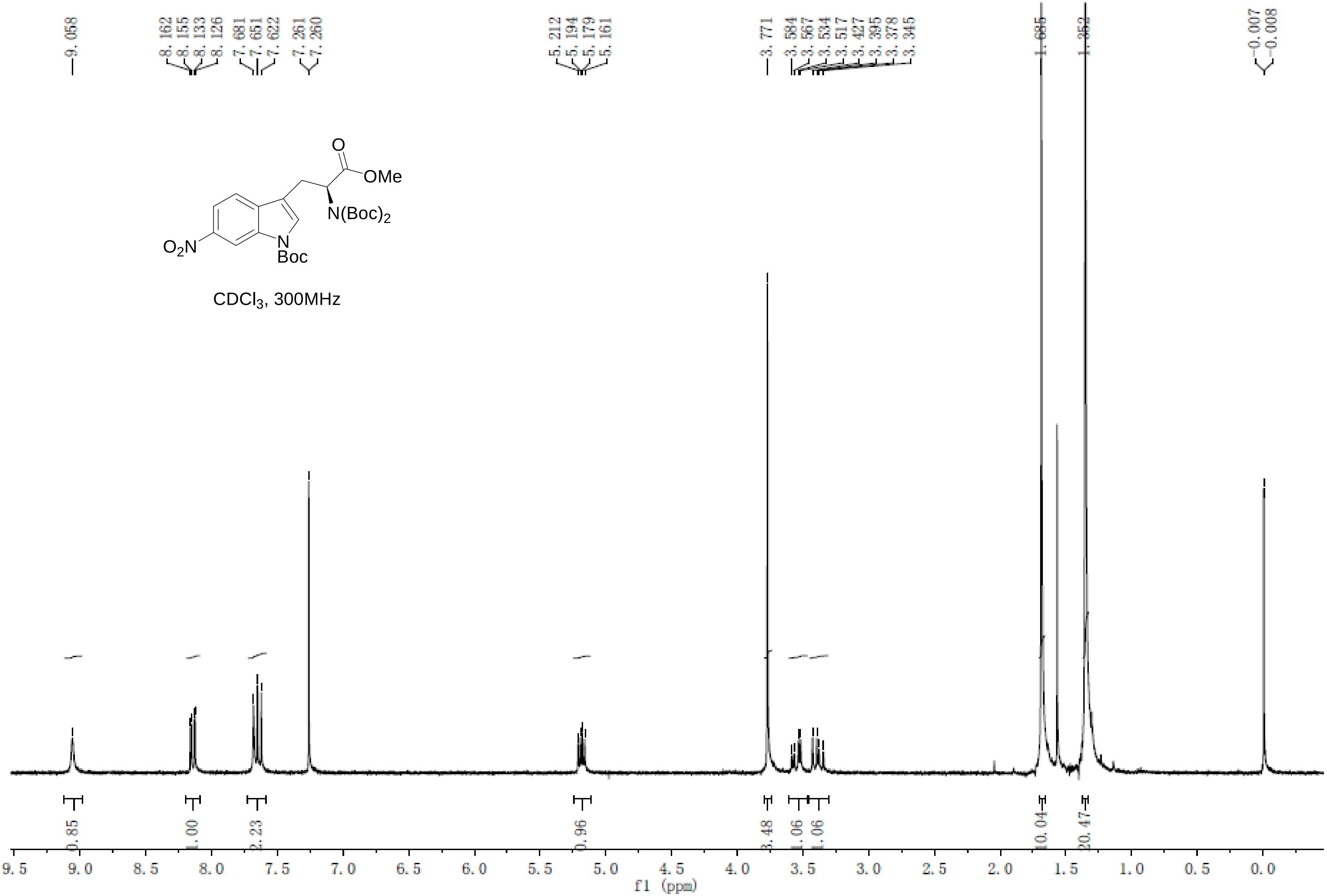
^{1}H-NMR of compound 4



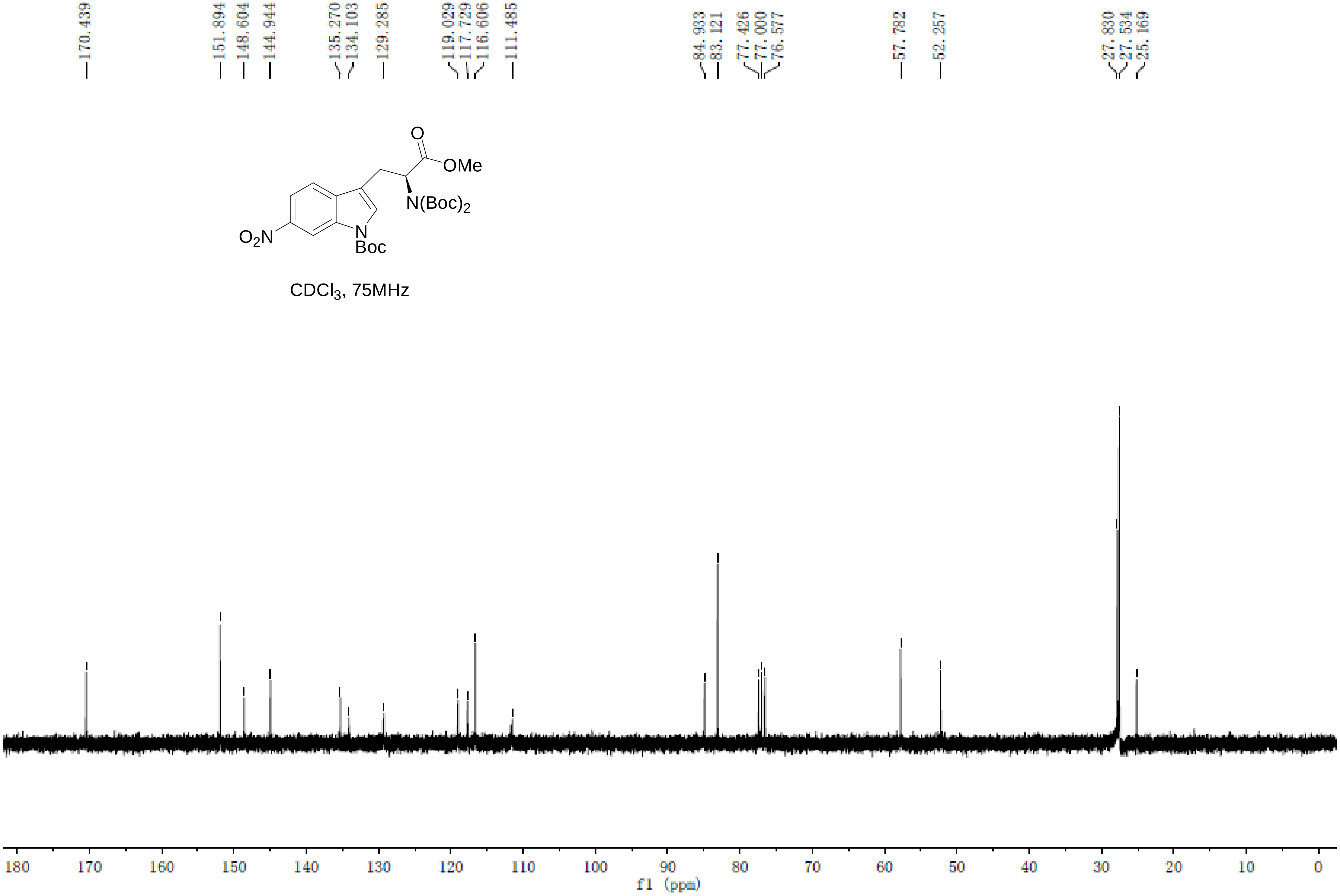
^{13}C-NMR of compound 4



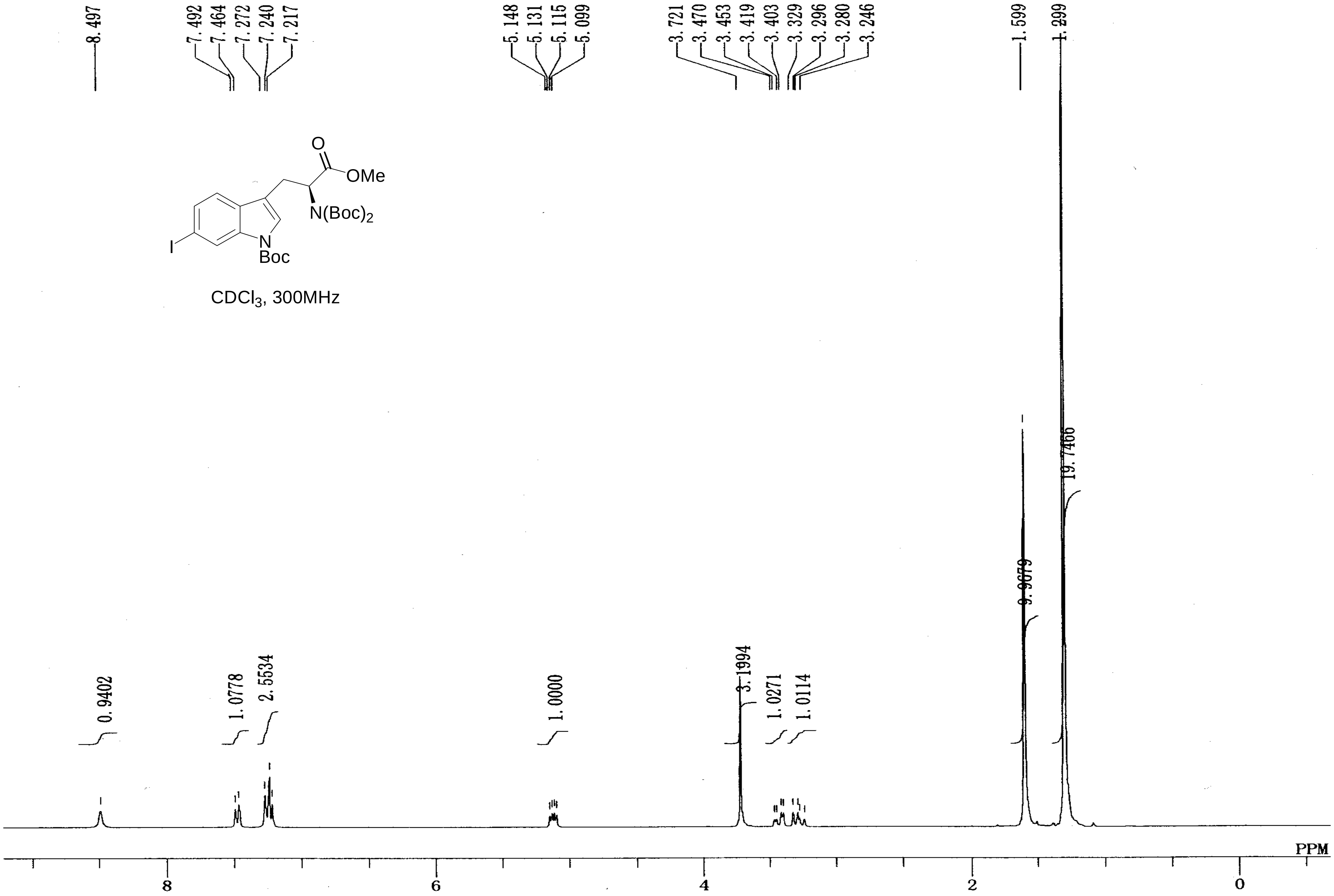
^{1}H-NMR of compound 10



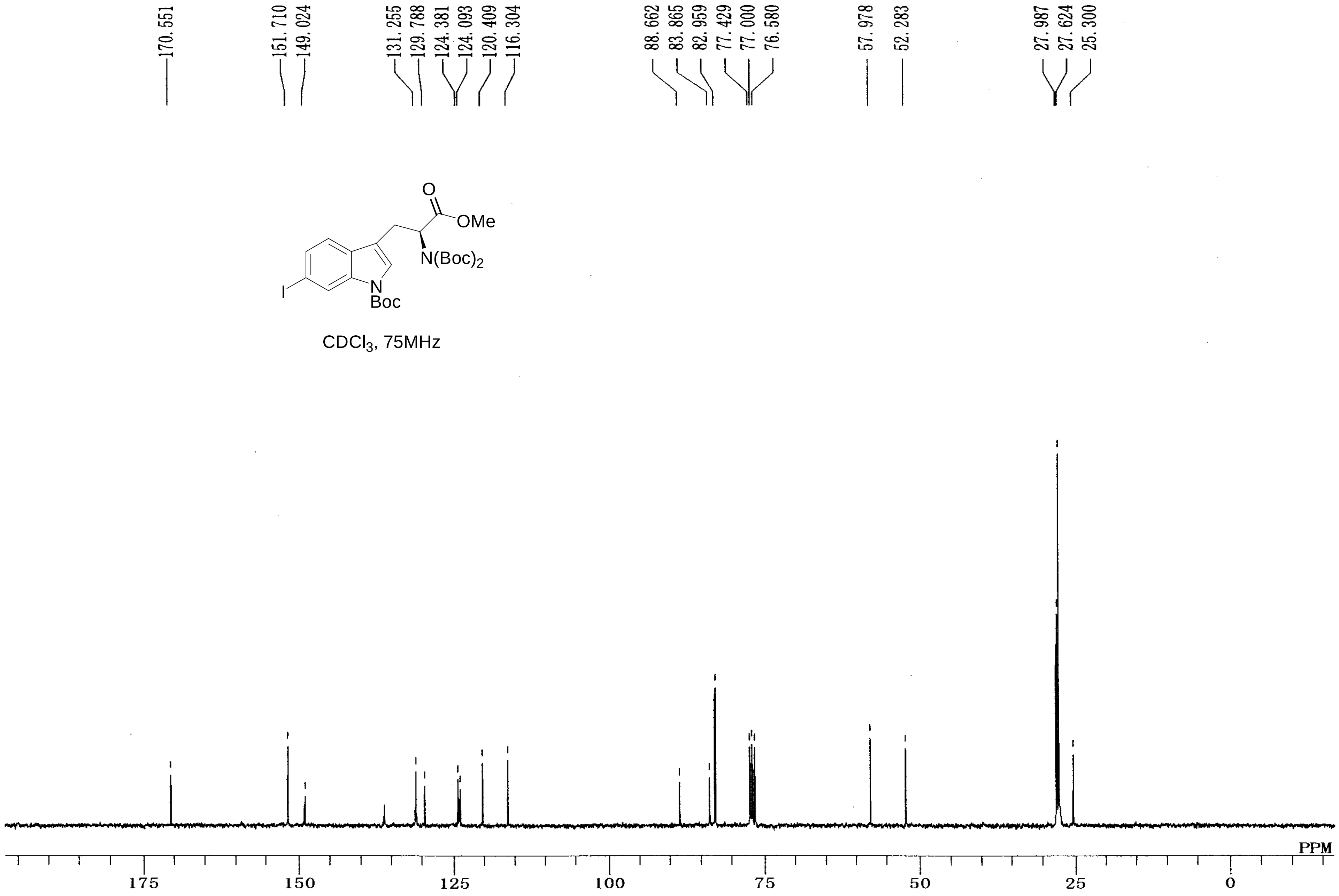
^{13}C-NMR of compound 10



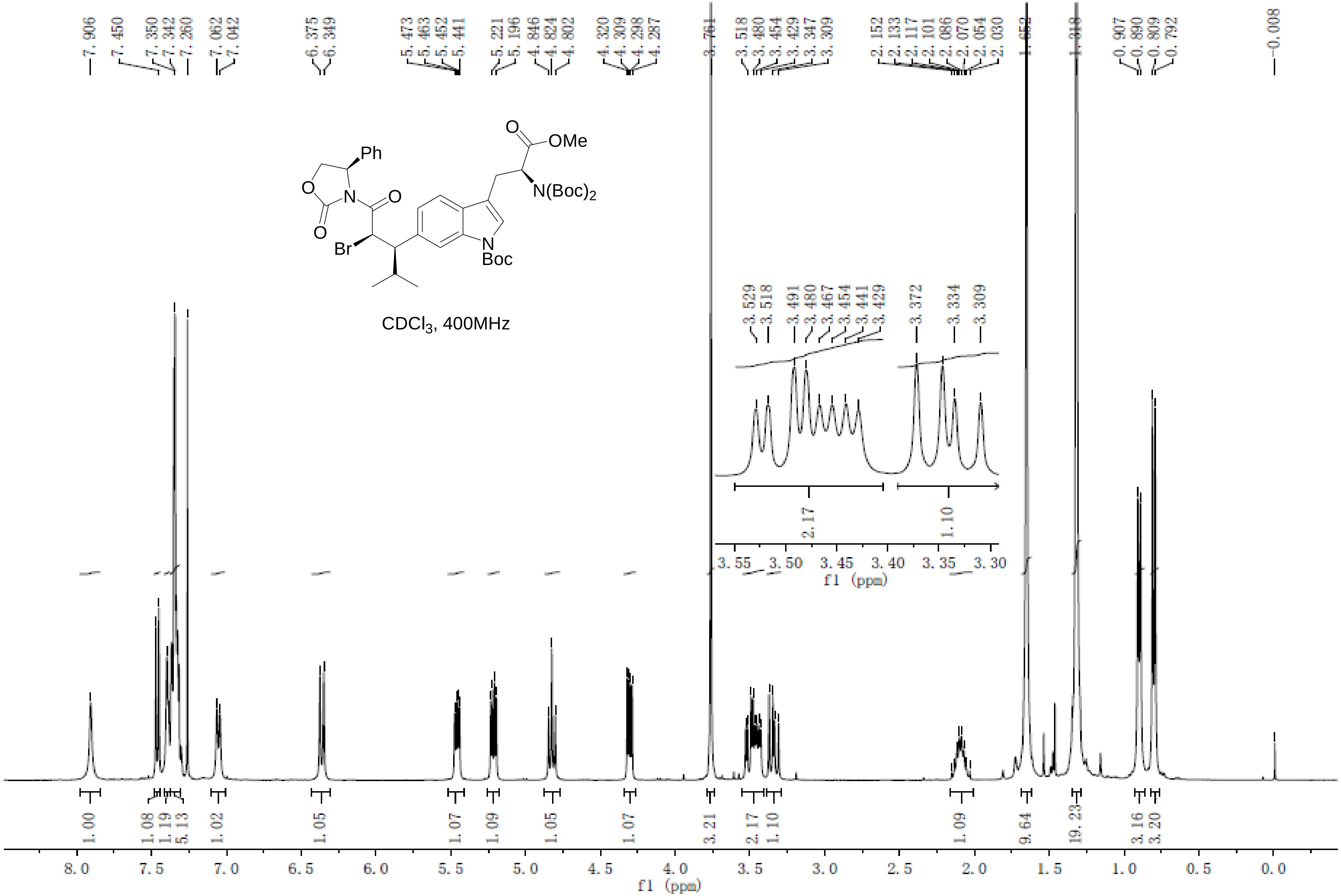
^{1}H-NMR of compound 6



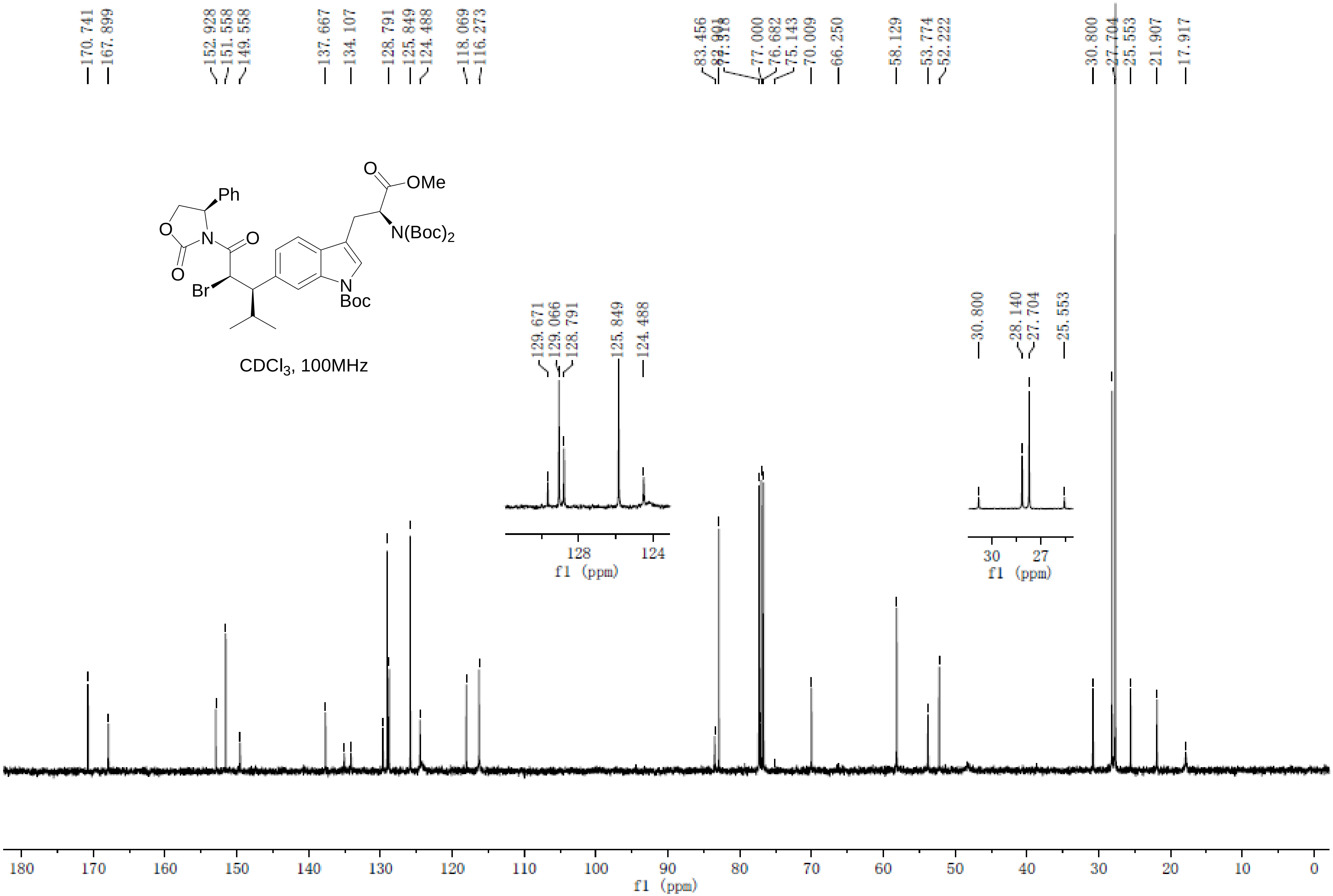
^{13}C-NMR of compound 6



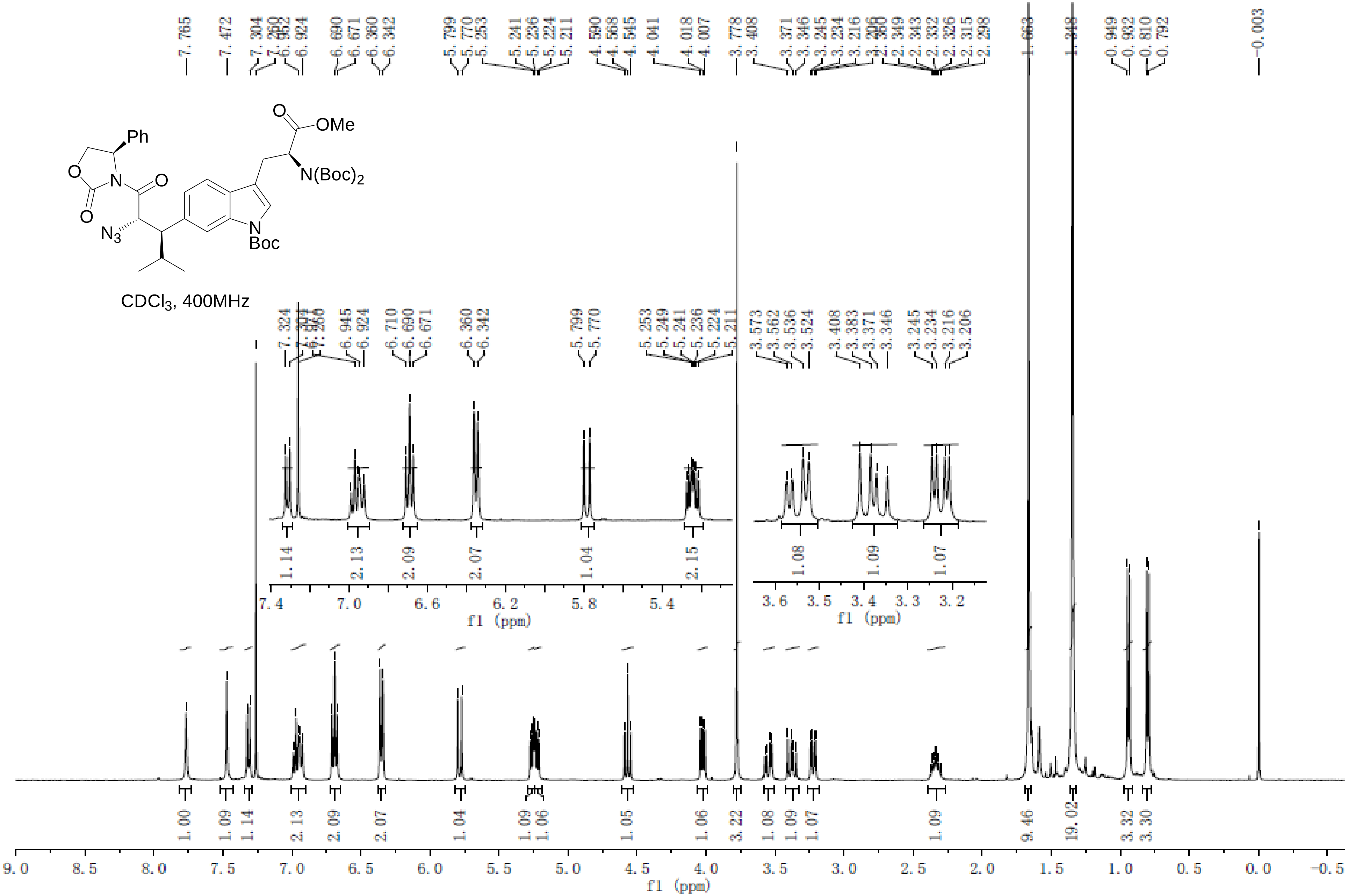
^{1}H-NMR of compound 12



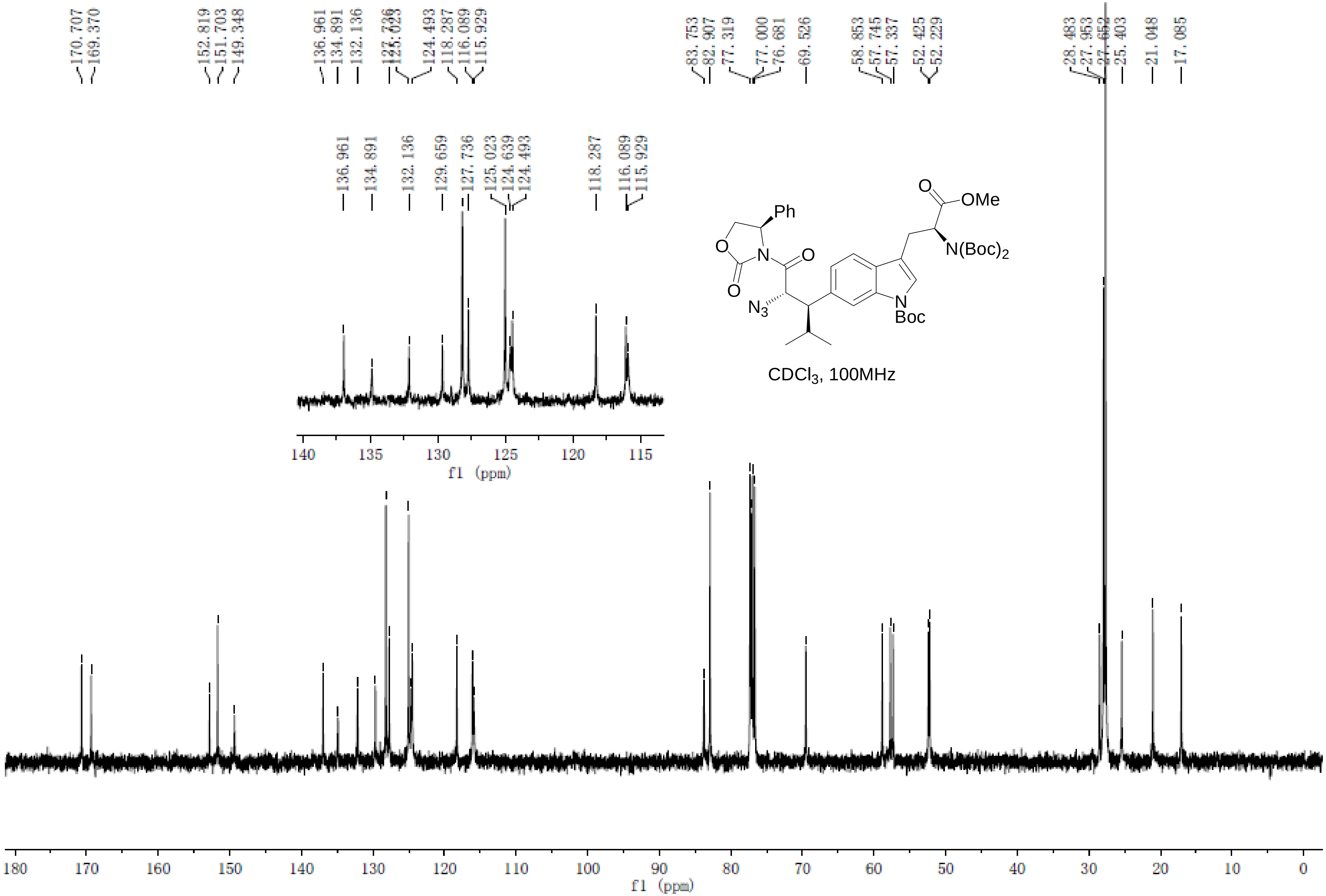
^{13}C-NMR of compound 12



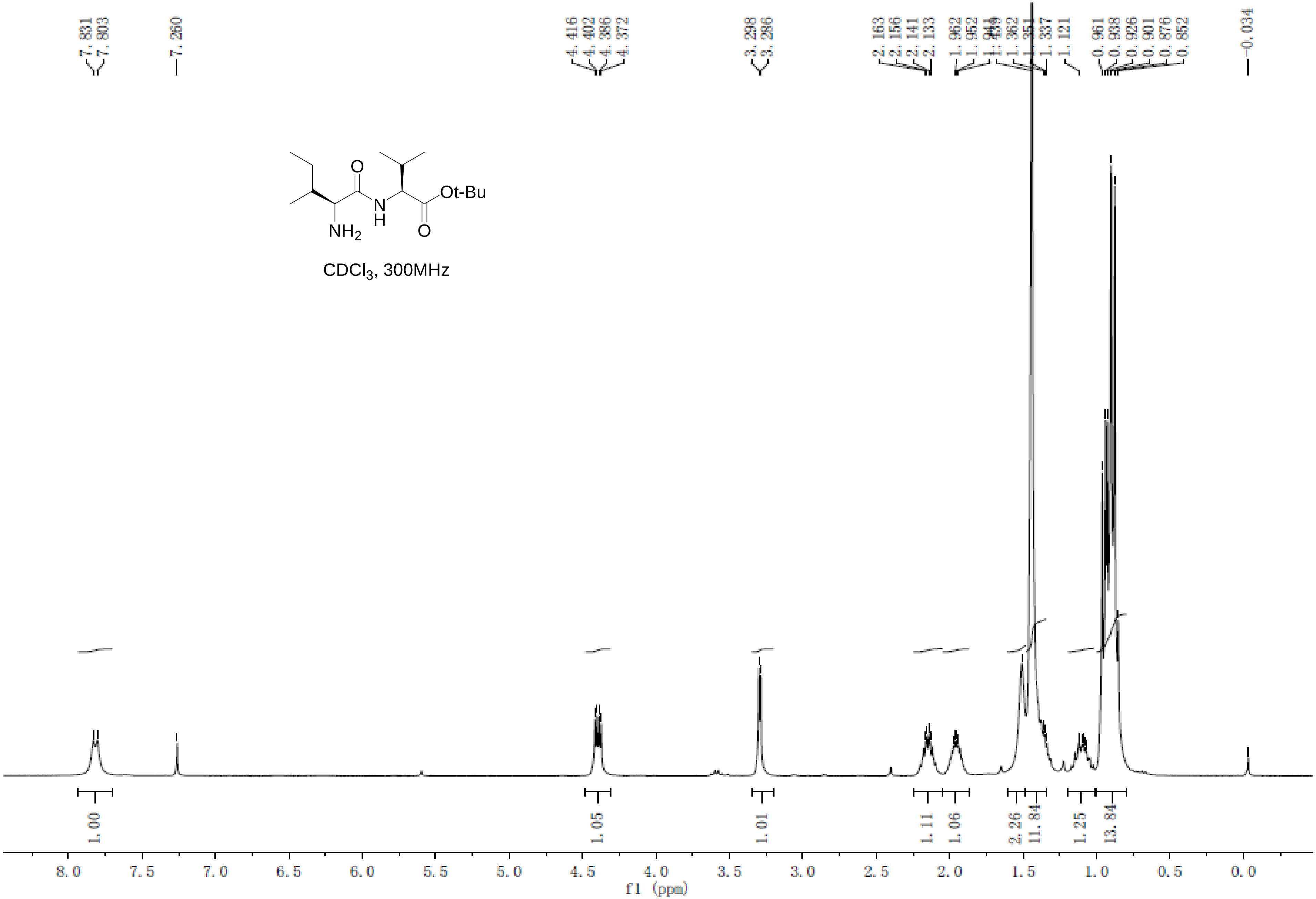
^{1}H-NMR of compound 13



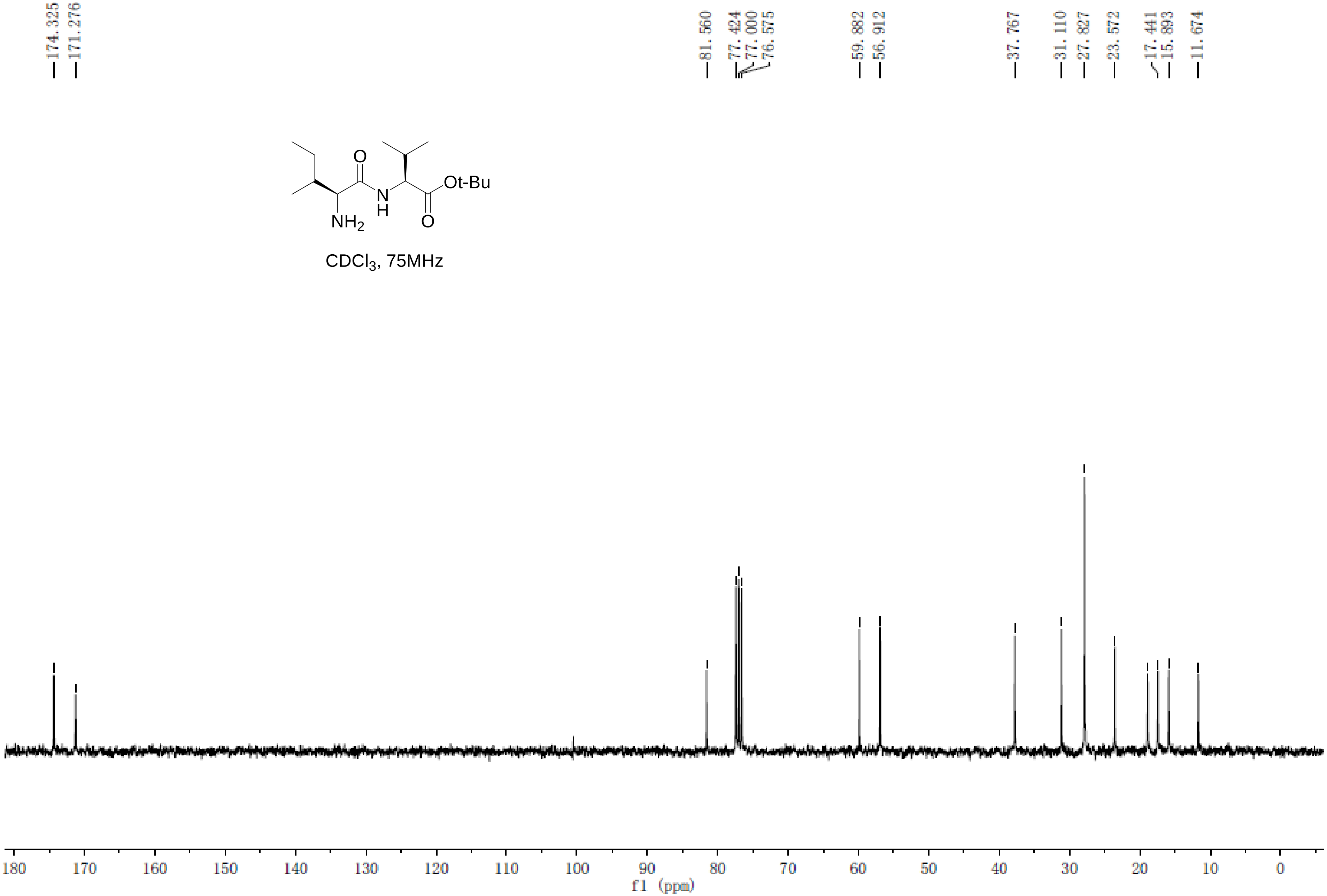
^{13}C-NMR of compound 13



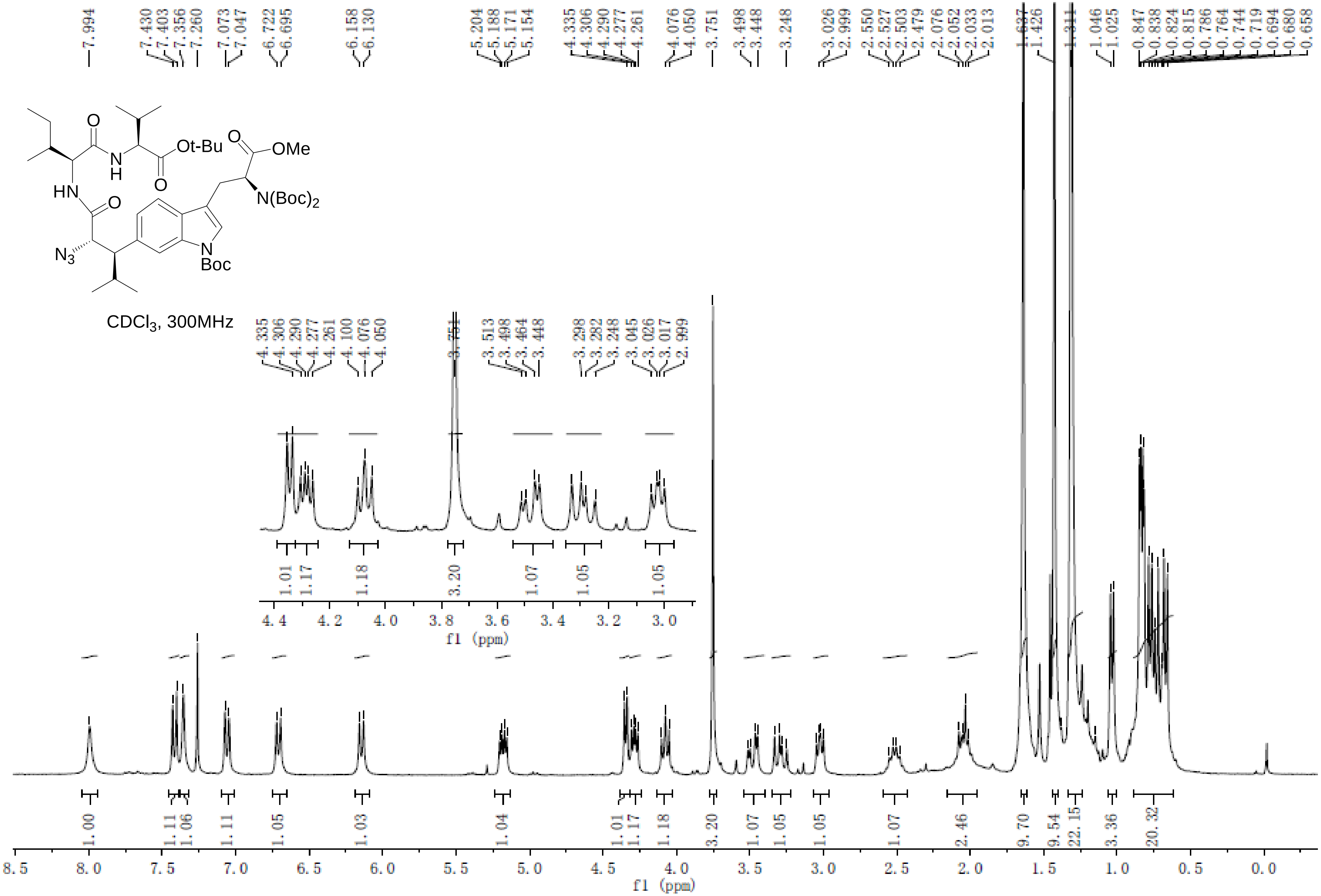
^{1}H-NMR of compound 14



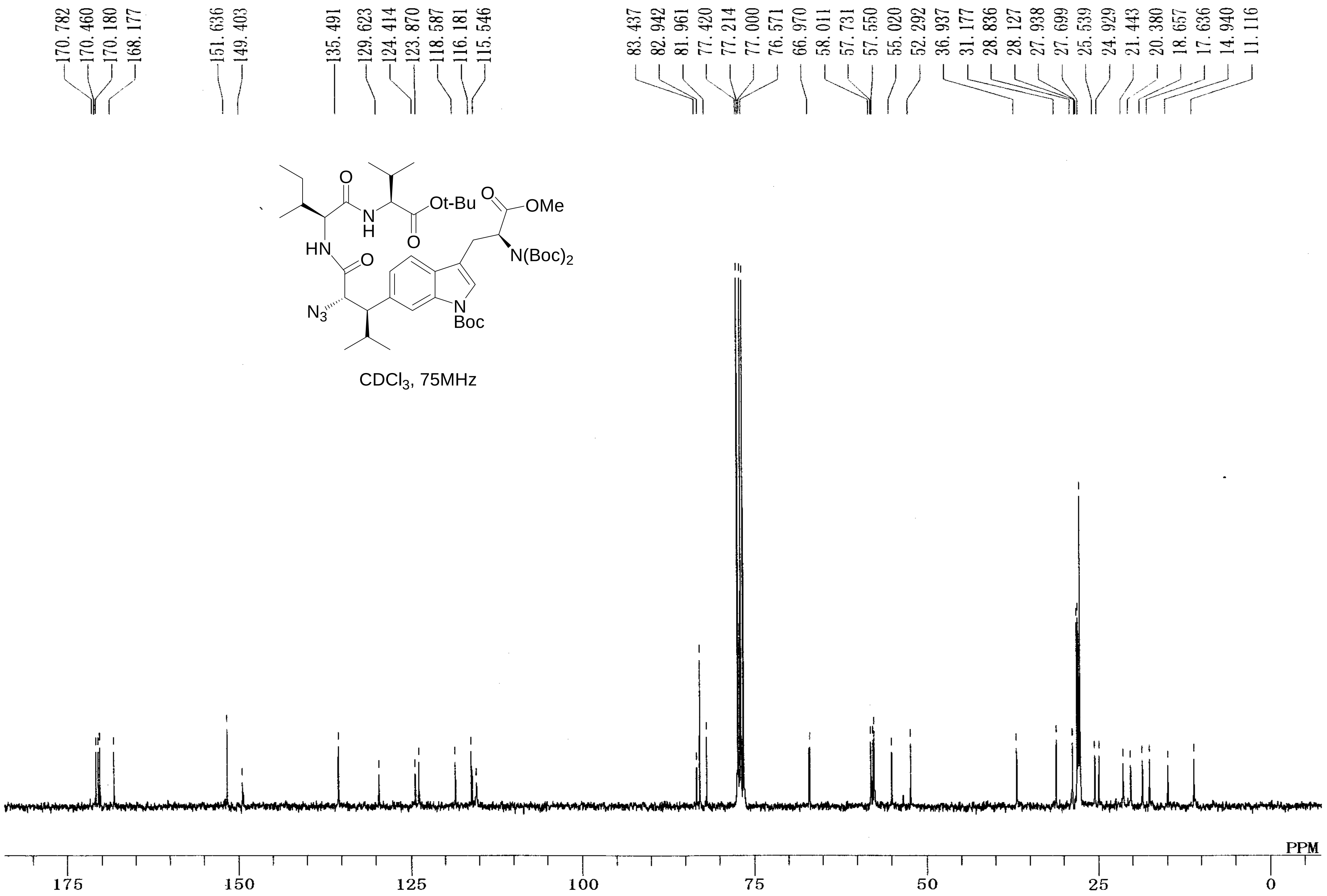
^{13}C-NMR of compound 14



^{1}H-NMR of compound 15

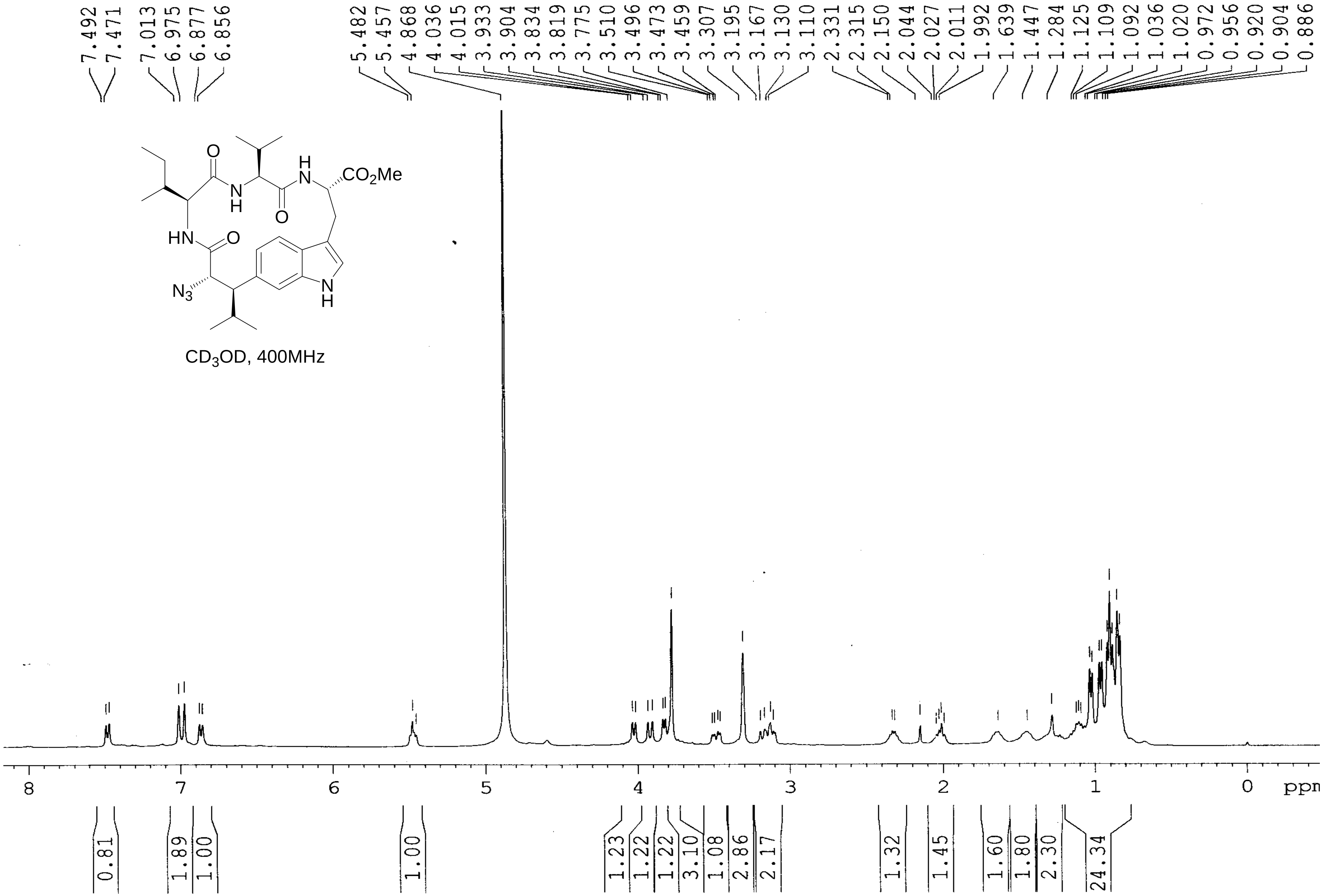


^{13}C-NMR of compound 15

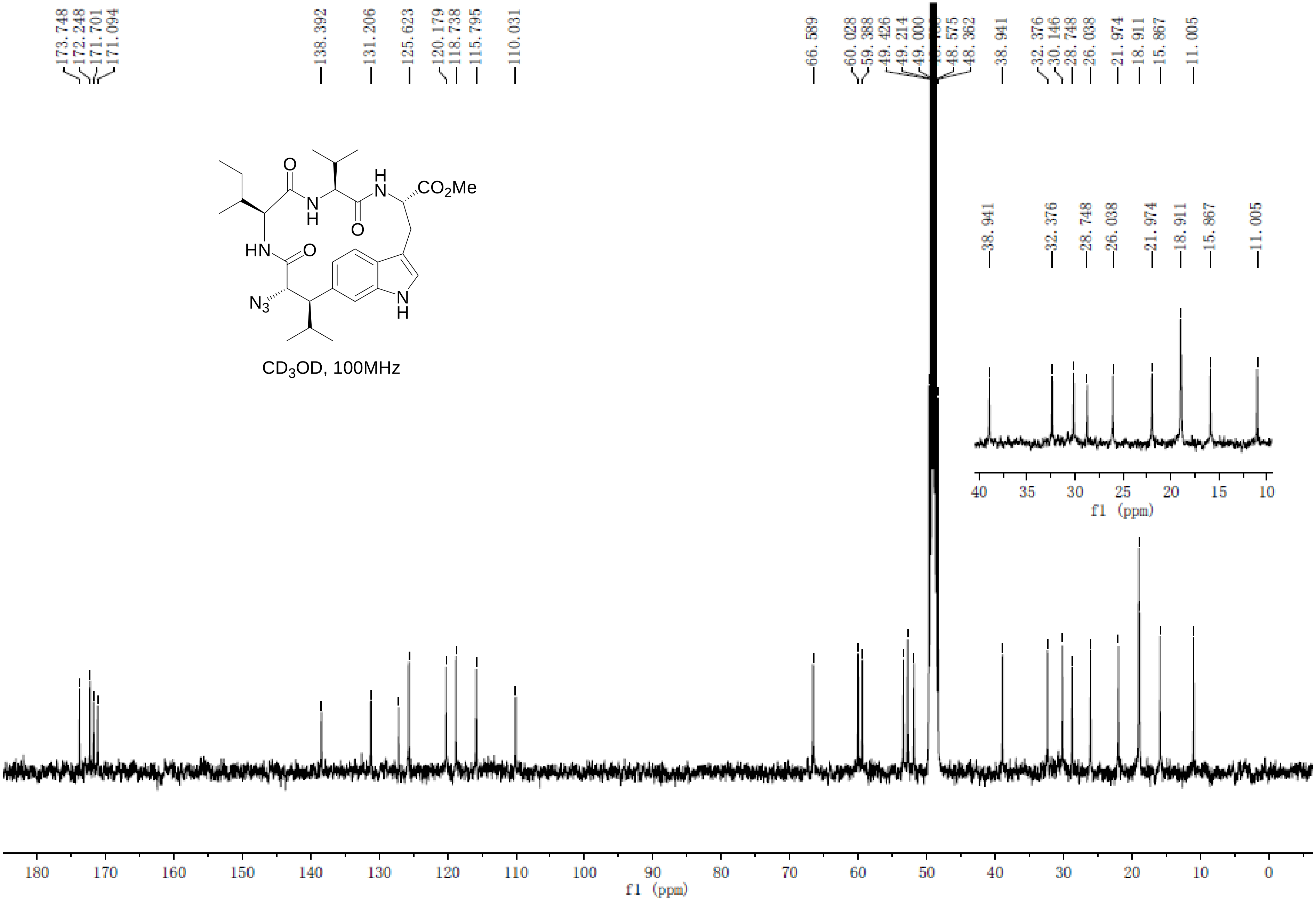


CDCl$_3$, 75MHz

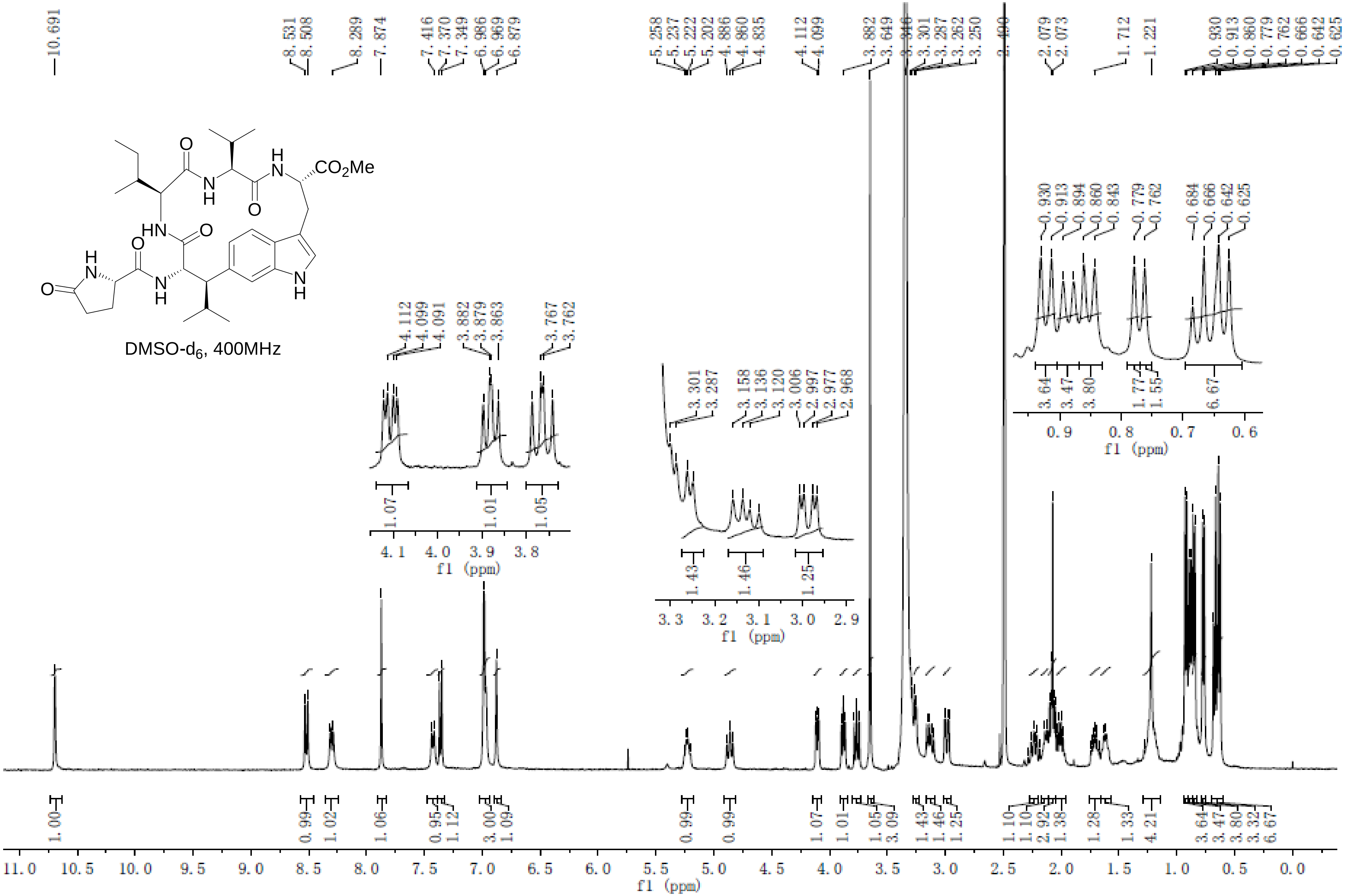
^{1}H-NMR of compound 16



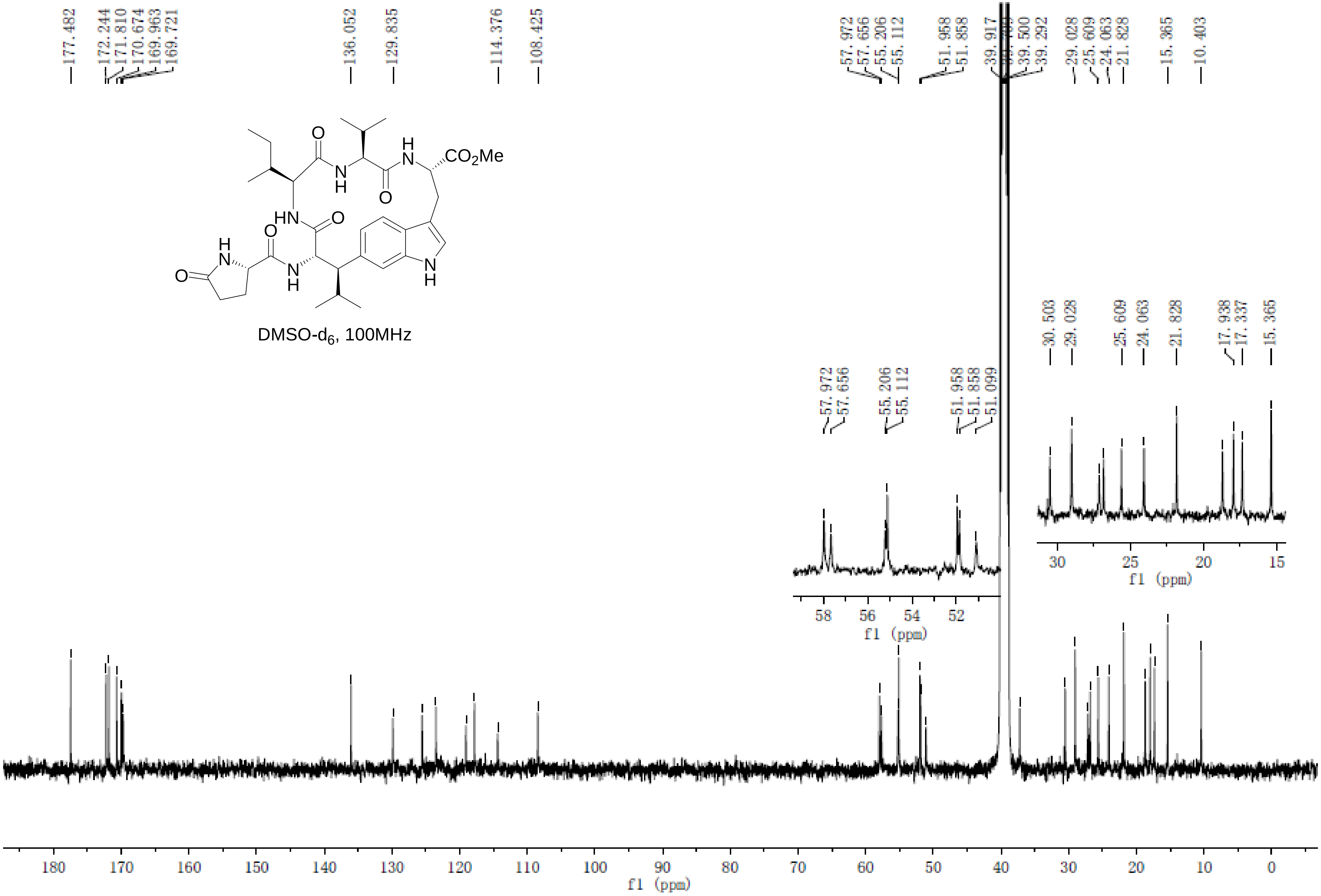
^{13}C-NMR of compound 16



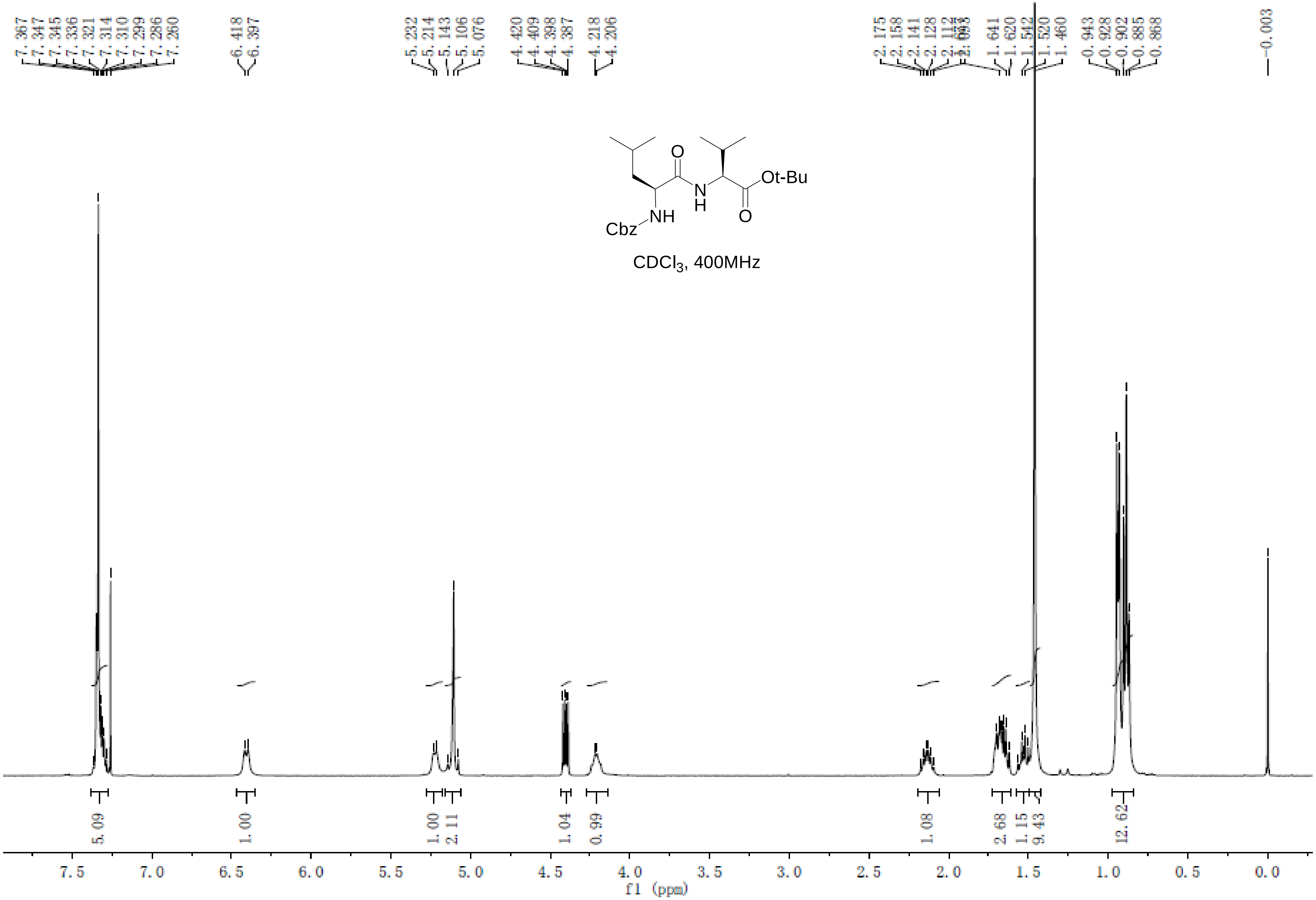
^{1}H-NMR of stephanotic acid methyl ester 2



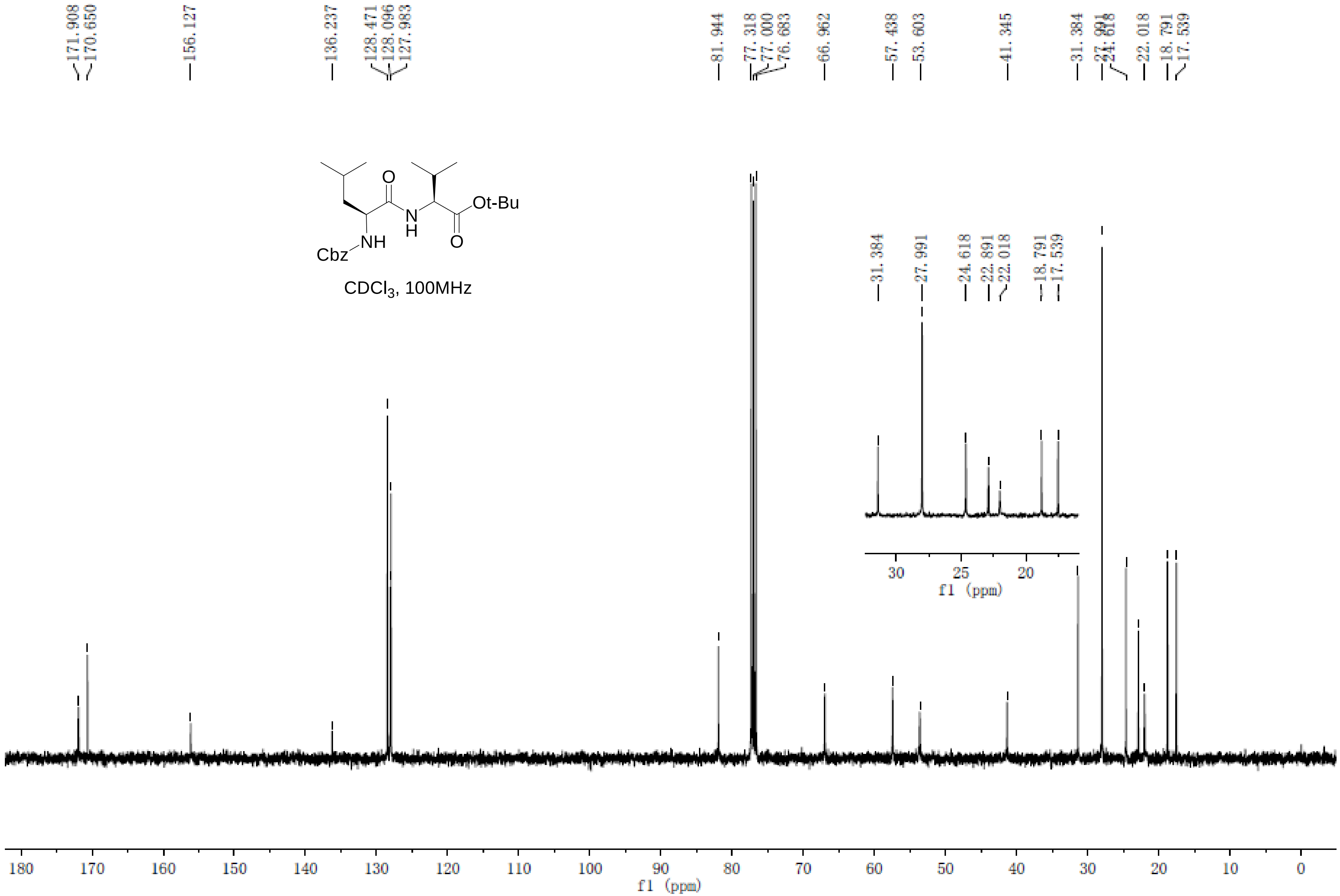
^{13}C-NMR of stephanotic acid methyl ester 2



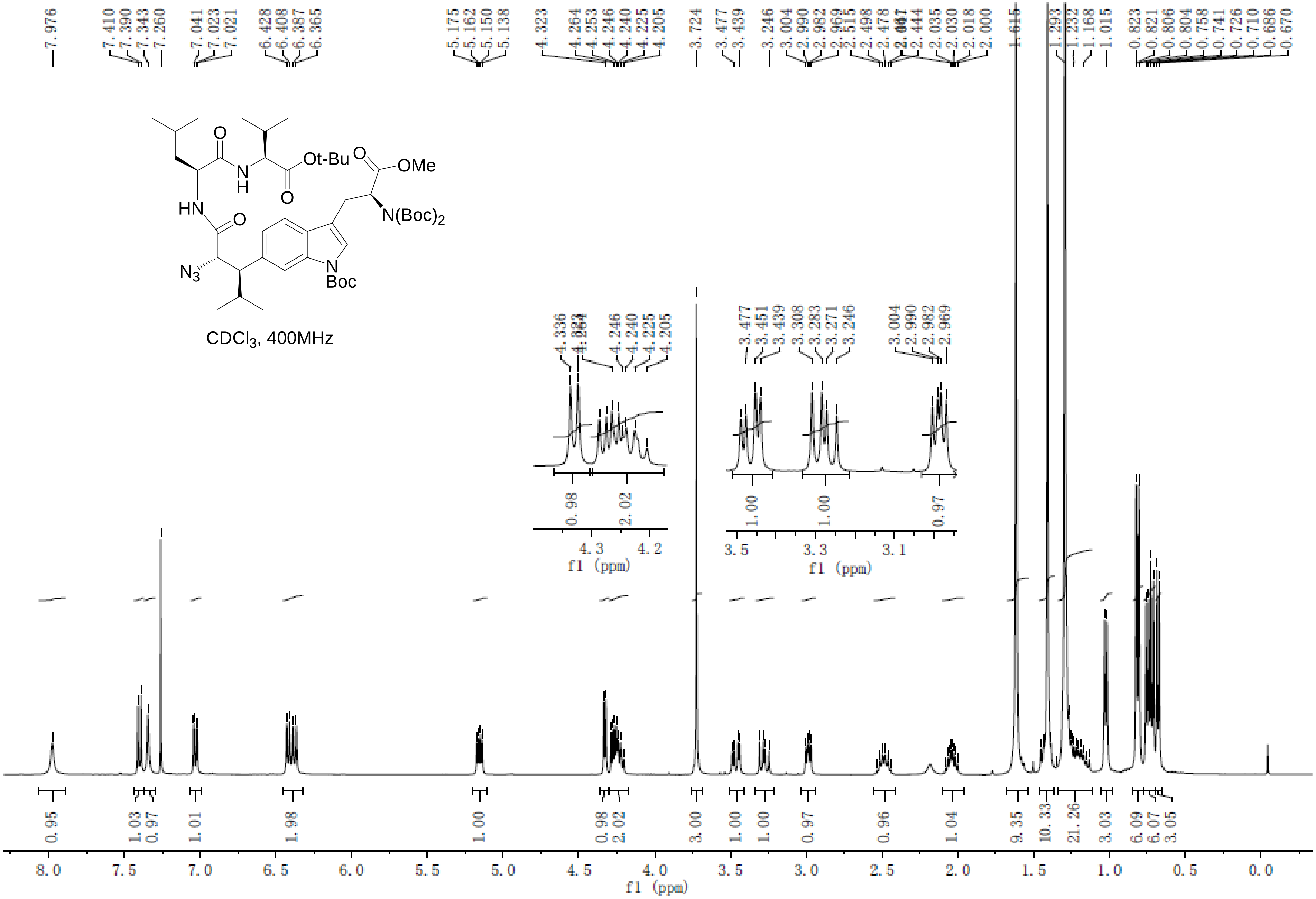
^{1}H-NMR of N-Cbz-L-leucyl-L-valine tert-butyl ester



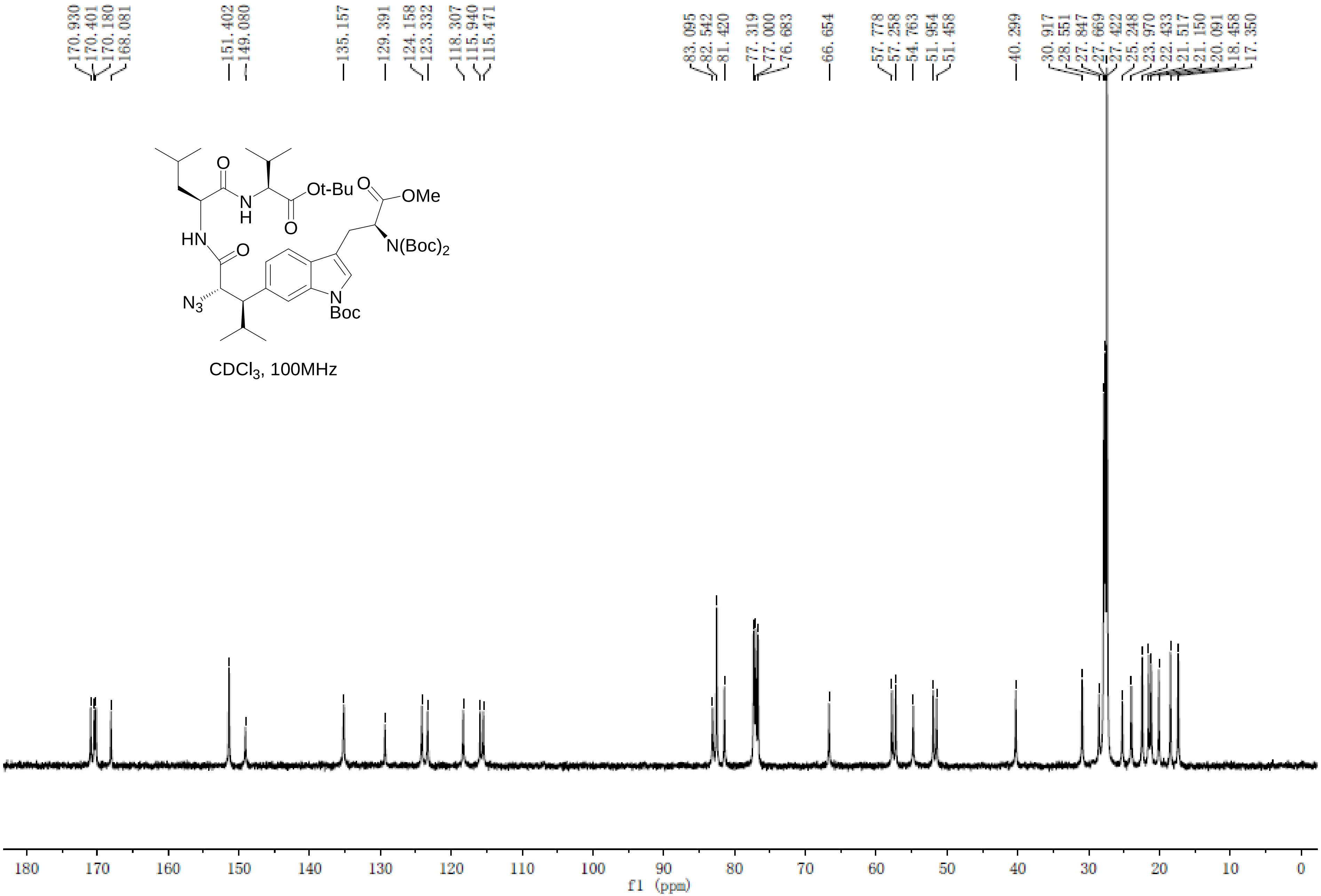
^{13}C-NMR of N-Cbz-L-leucyl-L-valine tert-butyl ester



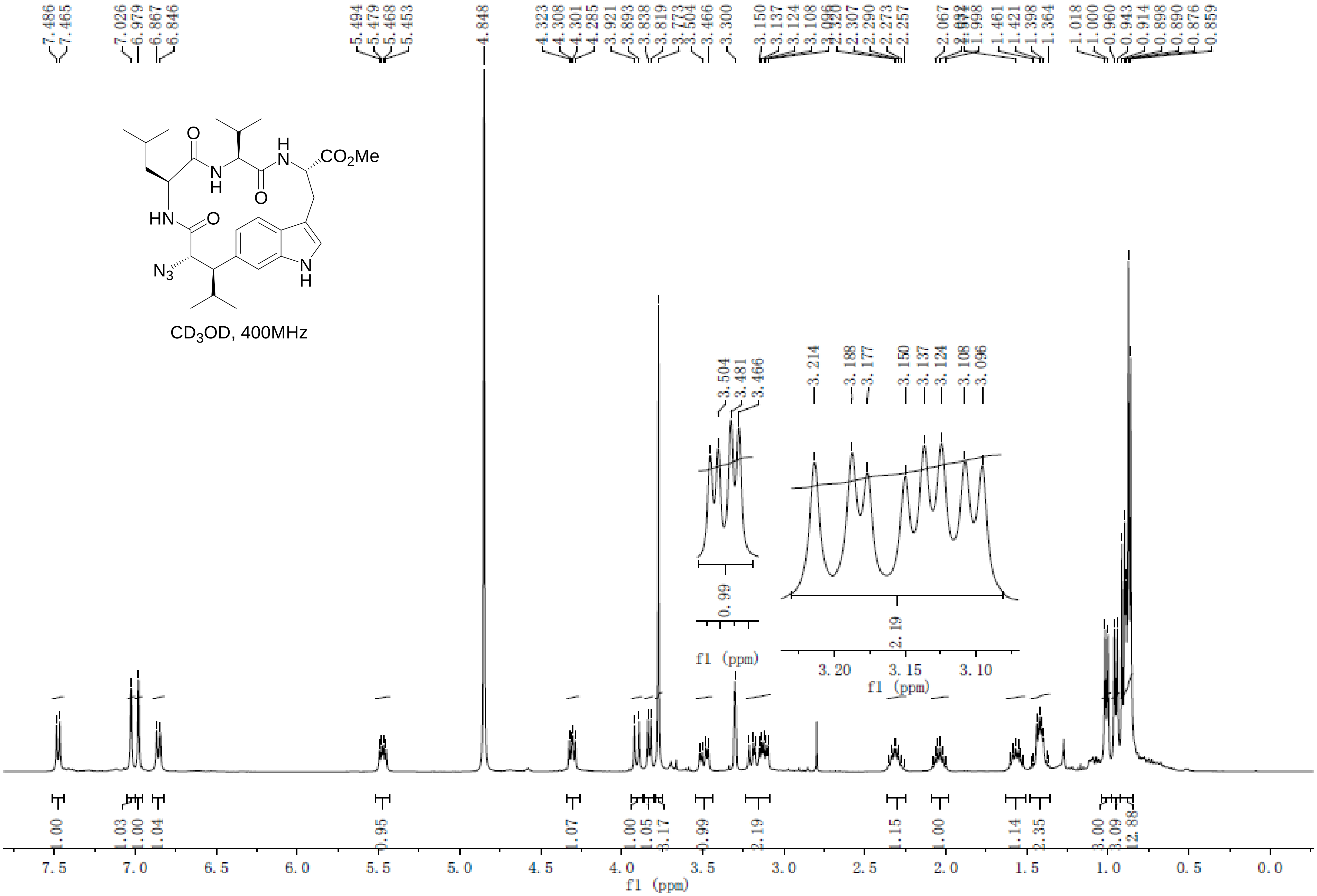
^{1}H-NMR of compound S1



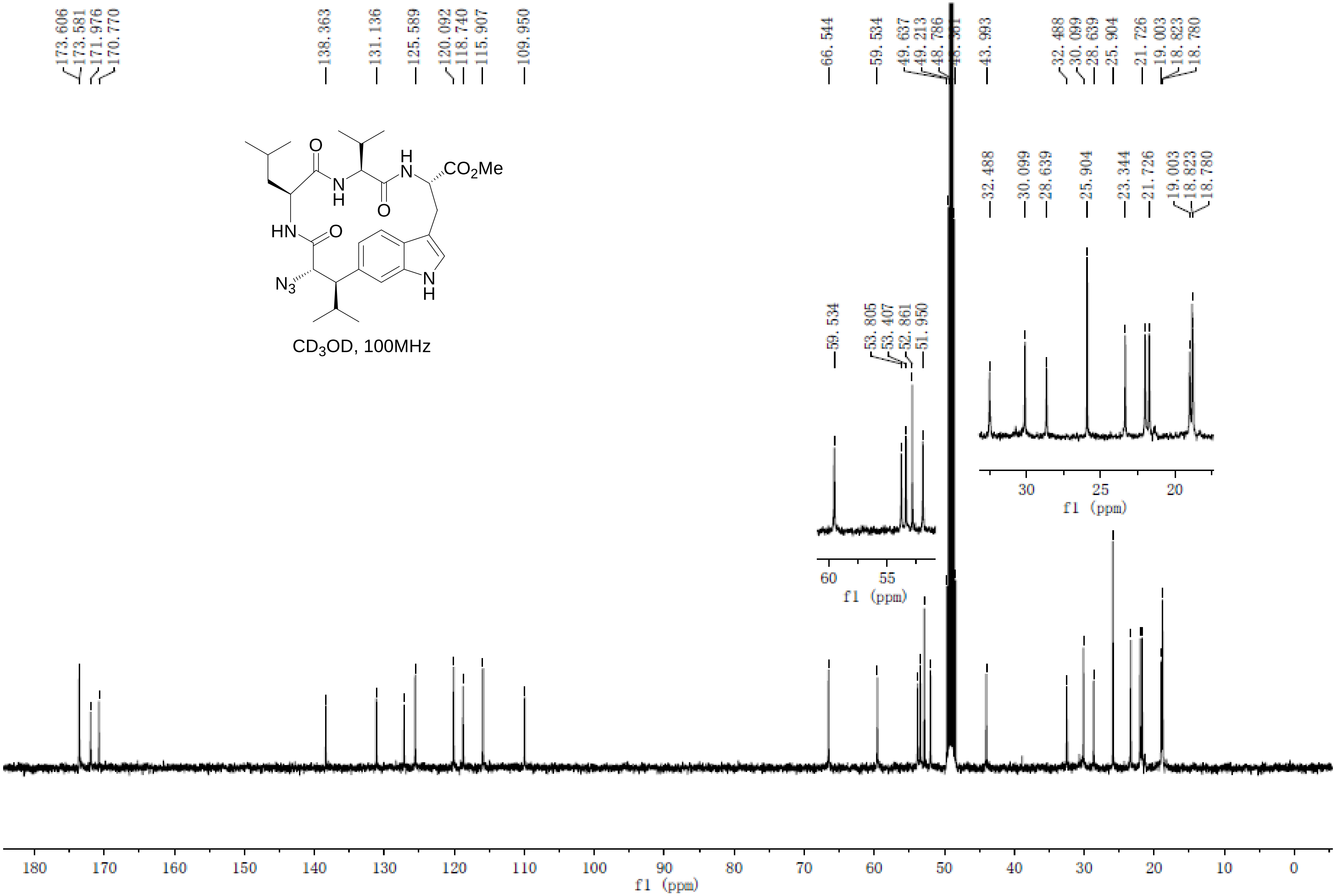
^{13}C-NMR of compound S1



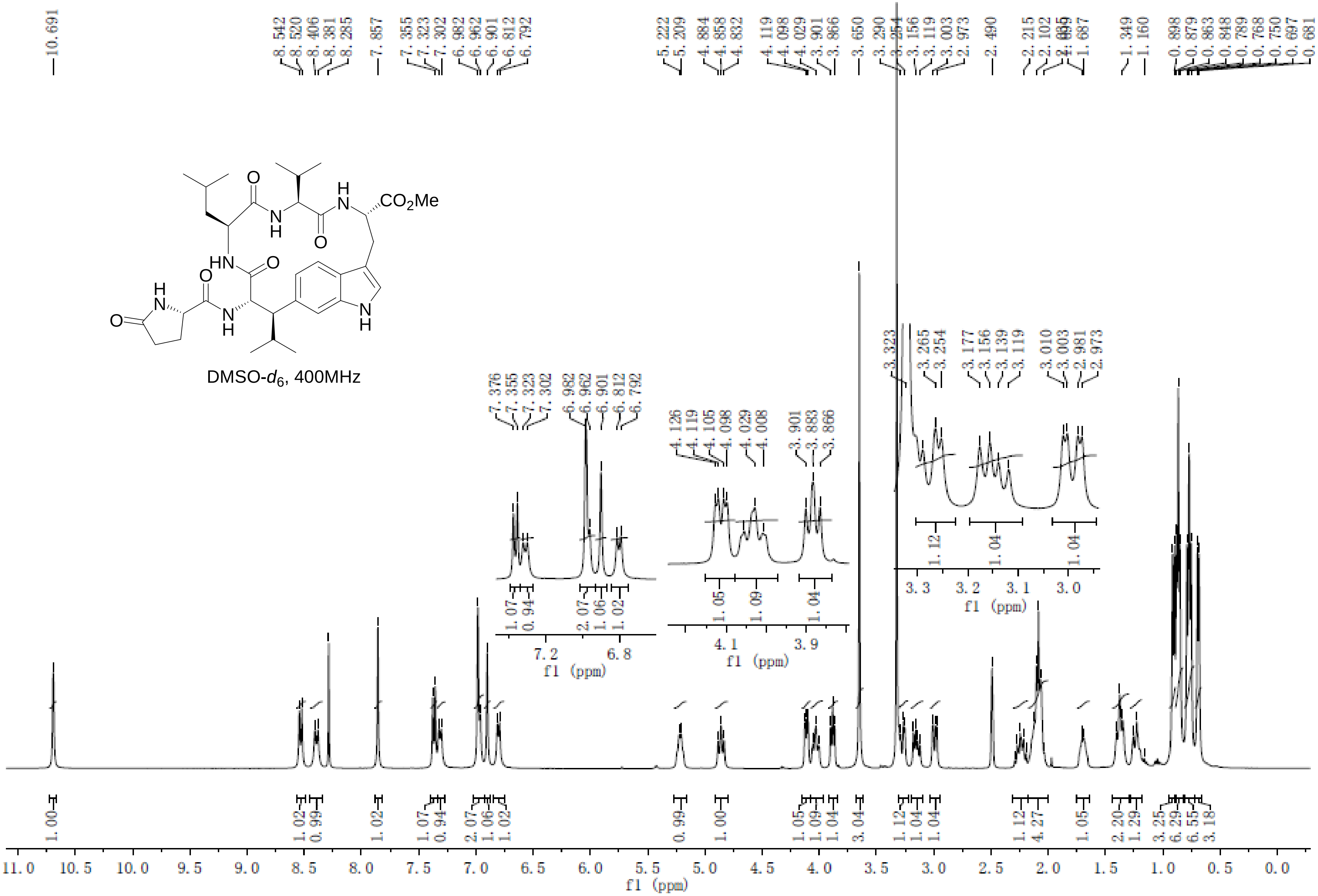
^{1}H-NMR of compound S2



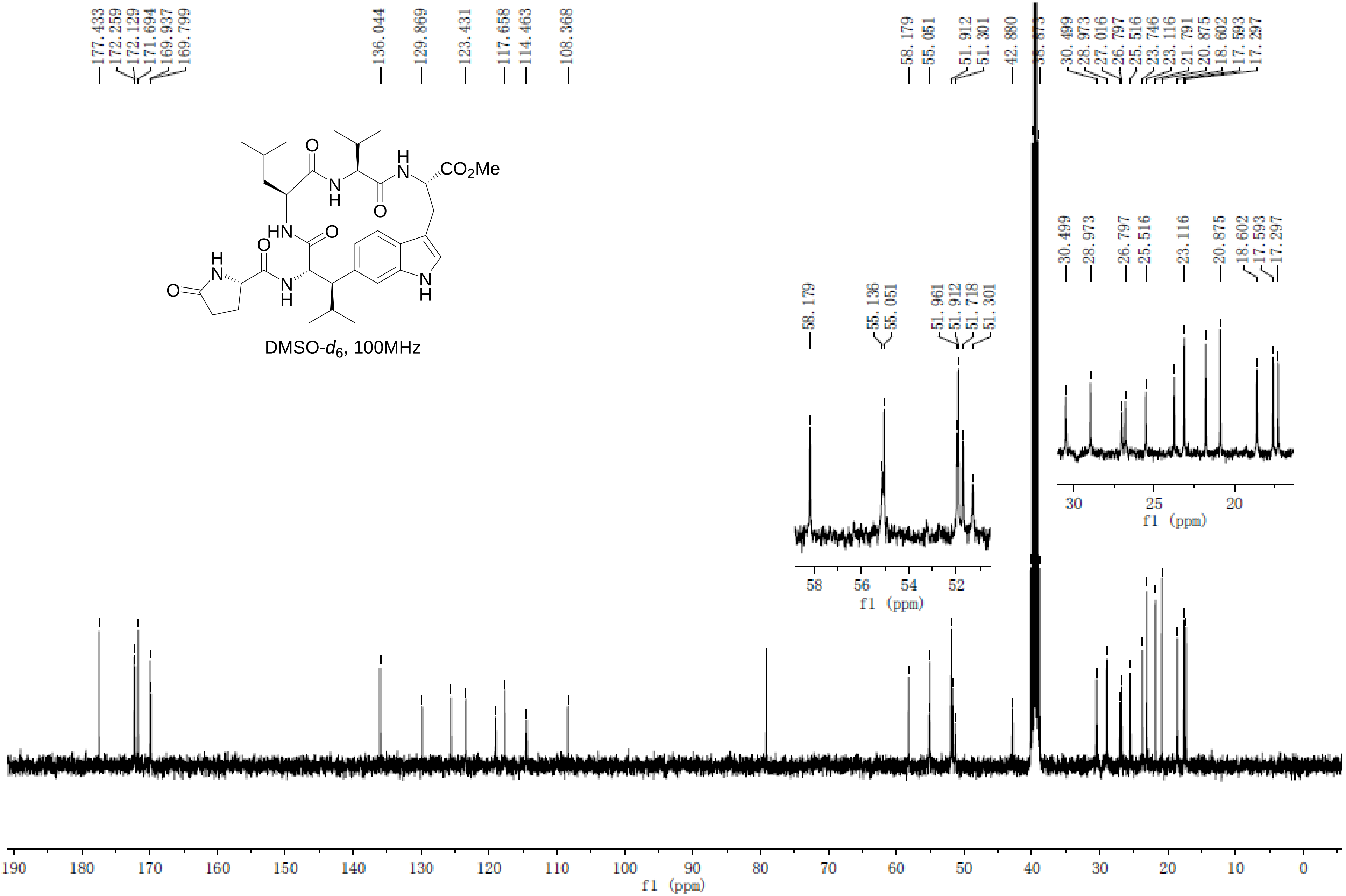
^{13}C-NMR of compound S2



^{1}H-NMR of compound 18

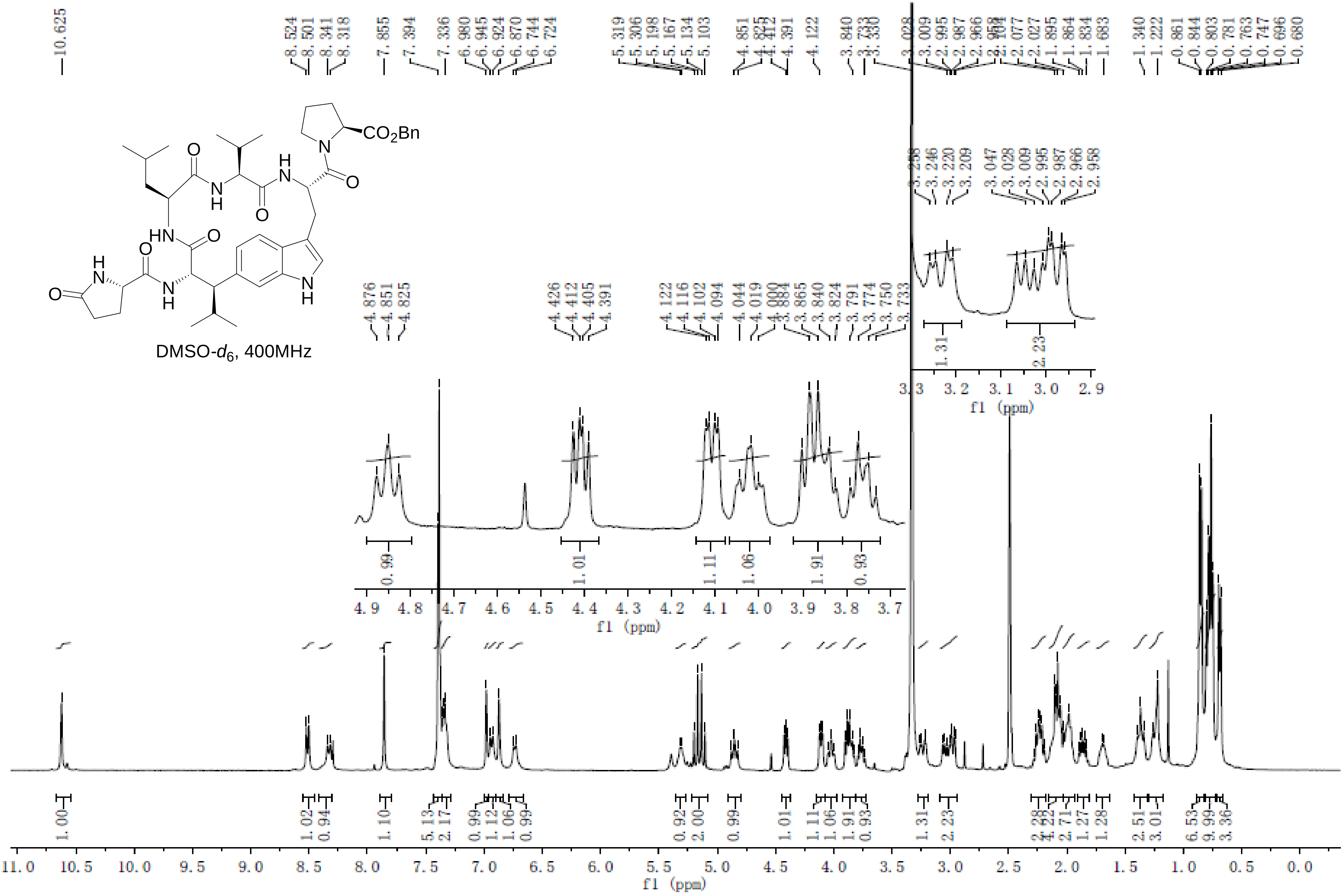


^{13}C-NMR of compound 18

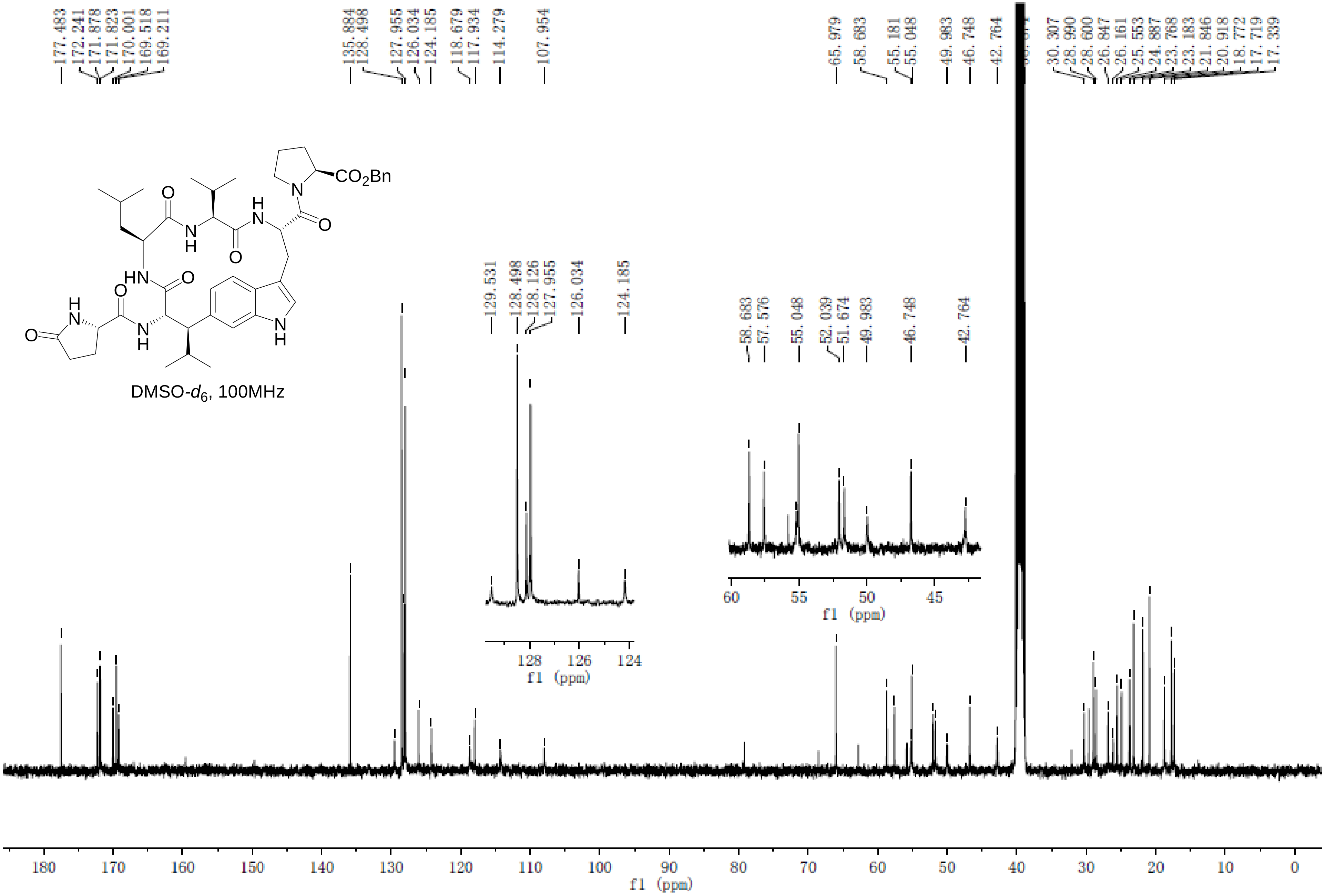


DMSO-d_6, 100MHz

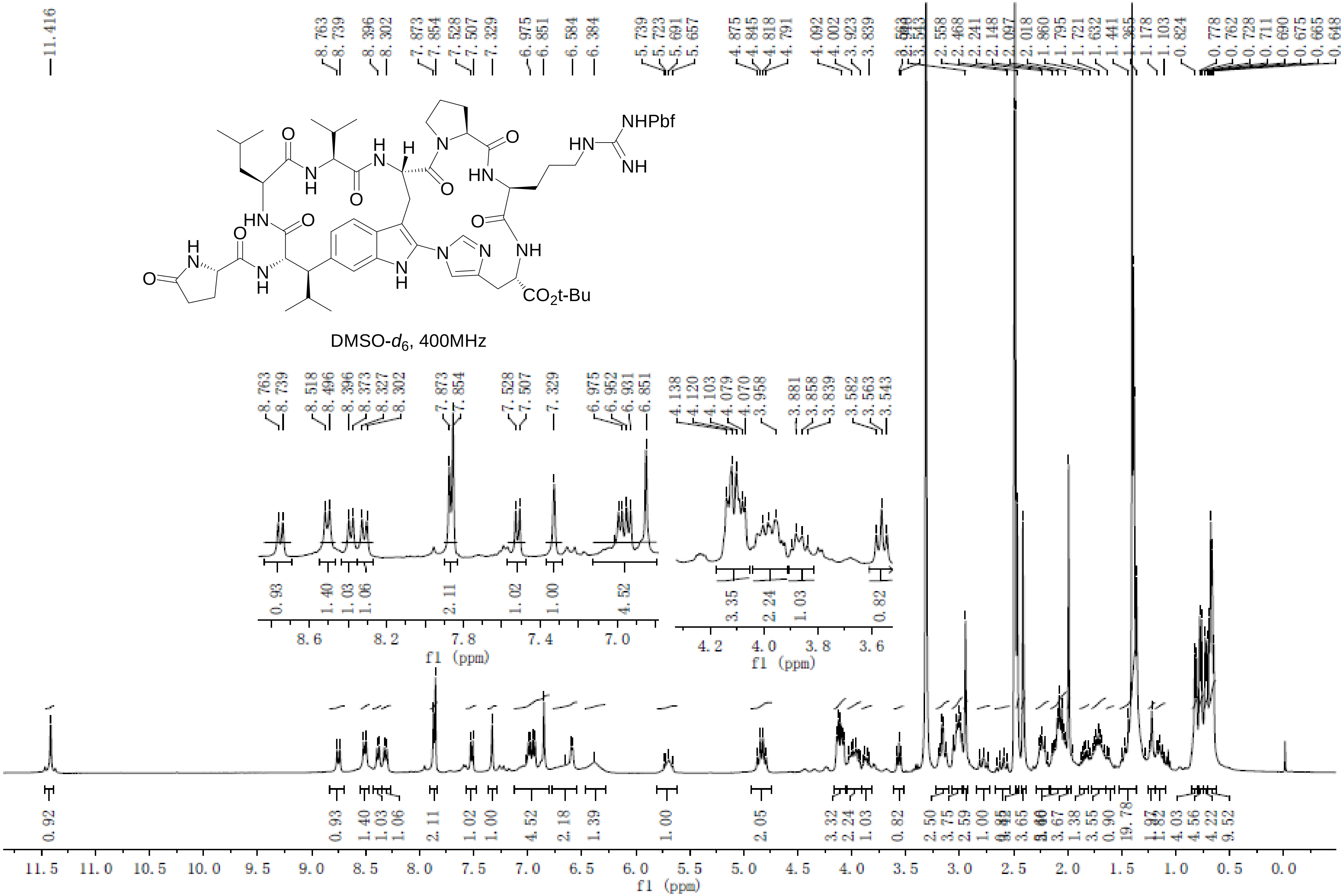
^{1}H-NMR of compound 19



^{13}C-NMR of compound 19

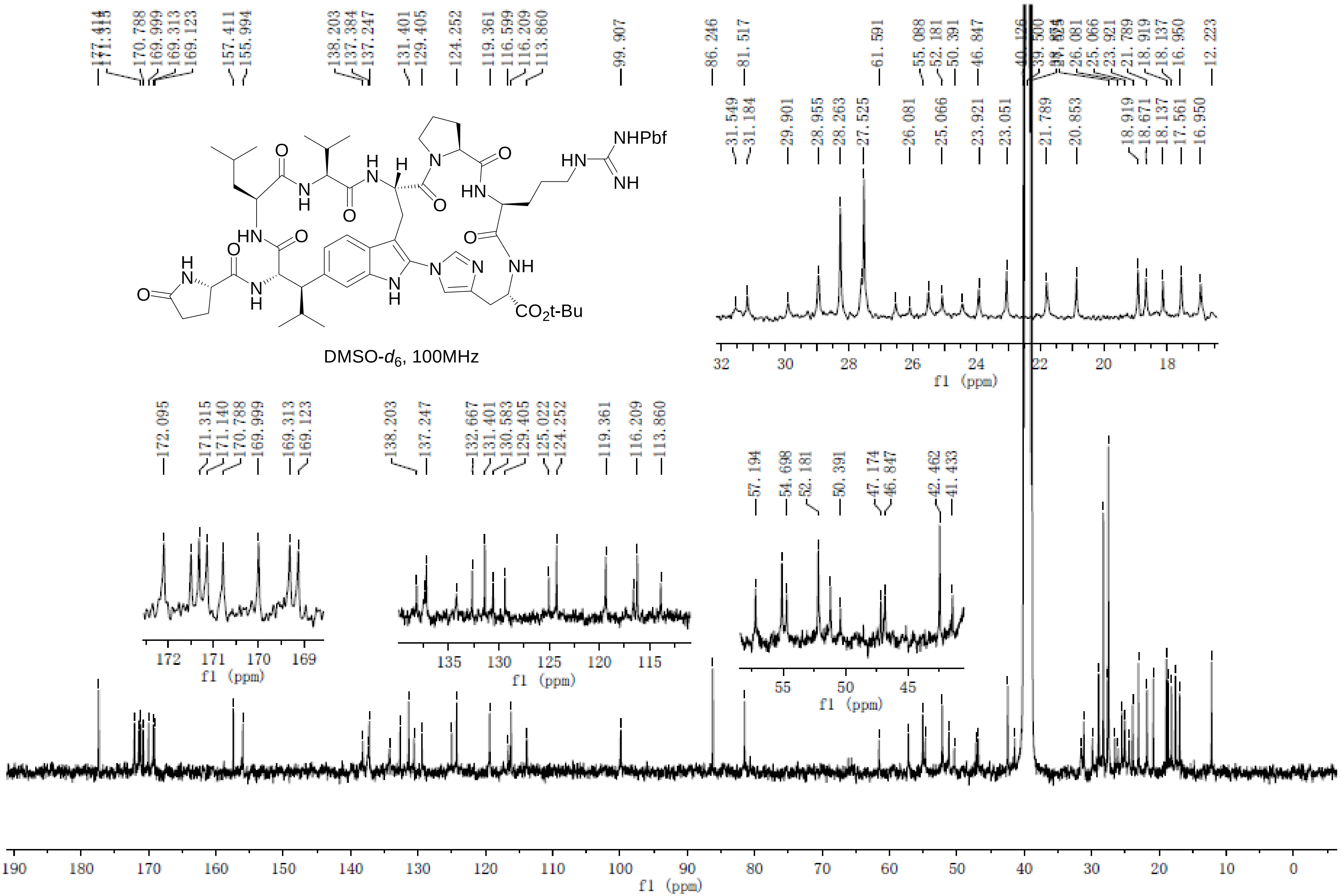


^{1}H-NMR of compound S3

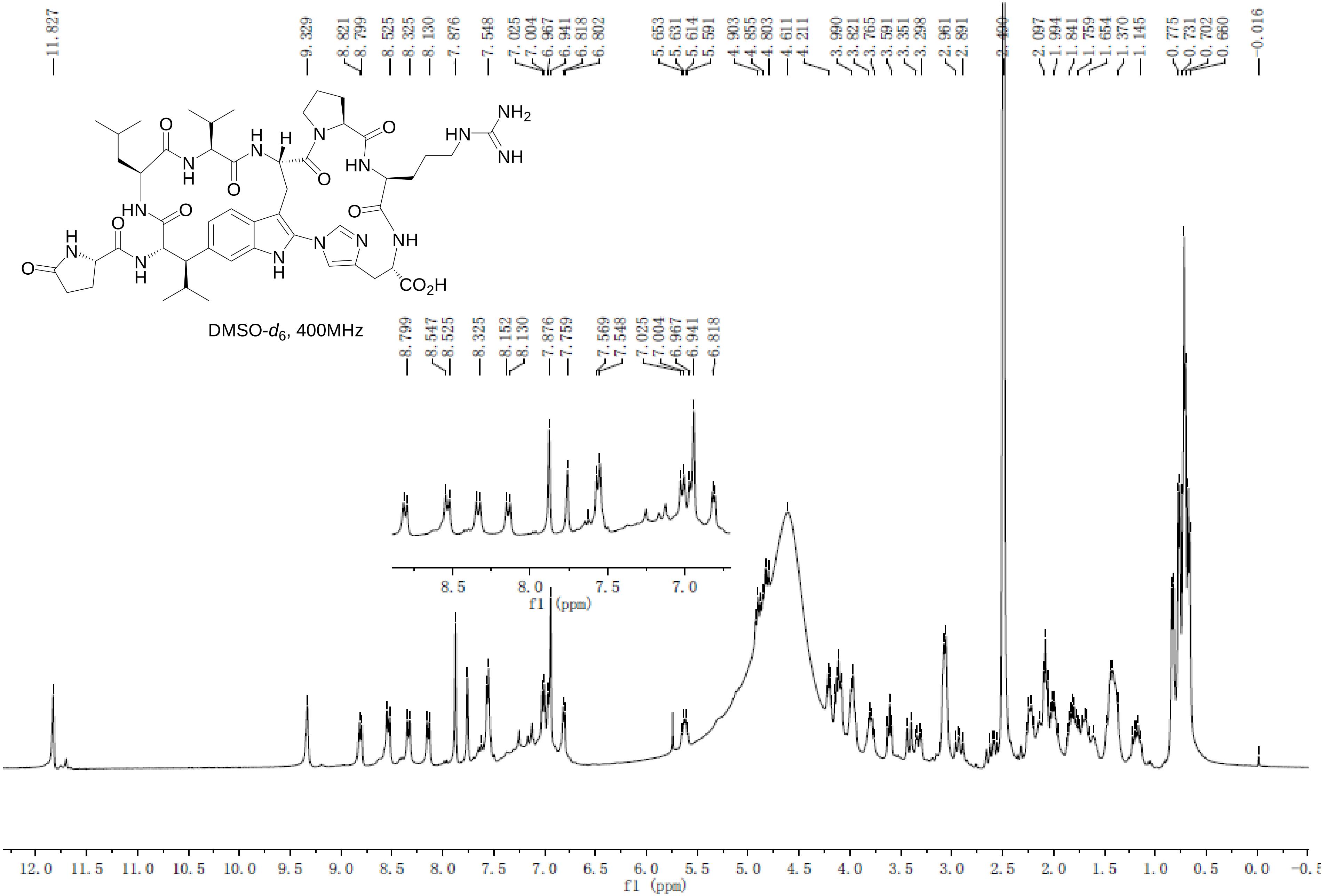


DMSO-d_6, 400MHz

^{13}C-NMR of compound S3



^{1}H-NMR of Celogentin C (1)



^{13}C-NMR of Celogentin C (1)