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Supporting Information

Metal-free Direct Amidation of Peptidyl Thiol Esters with α-Amino Acid Esters

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A. General Information.

^{1}H and ^{13}C NMR spectra were recorded on Bruker AV400 spectrometers (400 MHz and 100 MHz, respectively). All ^{1}H chemical shifts are reported in ppm (δ) relative to TMS (0.00); ^{13}C shifts are reported in ppm (δ) relative to $CDCl_3$ (77.16). Data are reported in the following order: chemical shifts are given (δ); multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), app (apparent); coupling constants, *J*, are reported (Hz); integration is provided. Peaks are reported (cm^{-1}).

Analytical thin-layer chromatography (TLC) was performed on Merck silica gel aluminium sheets with F-254 indicator. Visualization was accomplished by UV light, or with solutions of K_2CO_3/$KMnO_4$ in water. Solvents for reactions and chromatography were reagent grade and used as received. Flash column chromatography was performed by the method of Still[1] with 32-63 μm silica gel 60. HPLC analyses were achieved by using a chiral HPLC equipped with a chiralpak column with *n*-hexanes: 2-propanol as the mobile phase. The HPLC is SHIMADZU (SPD-10A VP Plus) and Agilent Technologies (1260 Infinity). High Resolution MS: Bruker APEX III 7.0 Tesla IonSpec 4.7 Tesla FTMS and Thermo scientific LTQ ORBITRAP XL. IR spectra were recorded on a JASCO FT/IR-300 instrument and are reported in wave numbers (cm^{-1}). Optical rotations were recorded on WZZ-2SS polarimeter.

All reactions requiring inert atmospheres were carried out under dry argon in oven-dried glassware. Melting points were obtained on a micro-melting apparatus and the data were uncorrected. "Brine" refers to a saturated aqueous solution of NaCl.

All the *N*-Cbz-amino acids and amino acid esters, *N*, *N*'–dicyclohexylcarbodiimide (DCC), 4-methylbenzenethiol, 1-hydroxybenzotriazole (HOBt), were purchased from Aladdin. *N*-Cbz-amino thiol esters of high enantiopurity were prepared by using the method of Lanny S. L. (DCC/DMAP/*p*-Thiocresol)[2].

The amino acid esters were prepared according to literature procedures from the hydrochloride salts.

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B. Experimental Procedures

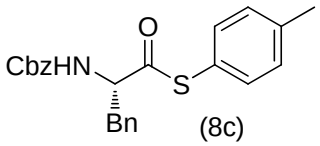
B1. Synthesis of Thiol Esters

Thiol esters were prepared from the corresponding *N*-Cbz-amino acids. Thioesters **8a**[3], **8b**[4] were prepared from the literature methods precisely .

General Procedure A: The Preparation of Thiol Esters Derived from N-Cbz- Amino Acids

4-Methylbenzenethiol (10.5 mmol) and 1-hydroxybenzotriazole (15 mmol) were added to a solution of the *N*-Cbz-amino acid (10 mmol) in dry ethyl acetate (10 mL) at 0 °C followed by *N, N′*-dicyclohexylcarbodiimide (10 mmol). The mixture was stirred for 24h at room temperature and the reaction progress was monitored by TLC analysis. At the end of the reaction a few drops of 50% acetic acid in ethyl acetate were added. The mixture was filtered through Celite™ and the organic phase was washed with sat. $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by recrystallization (solvent, ethyl acetate and petroleum ether) or flash chromatography (silica gel, ethyl acetate in petroleum ether) affording the desired product [2].

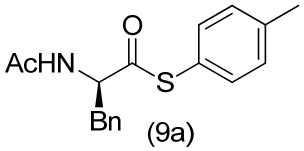
B1.1. *N*-Cbz-L-phenylalanine *p*-toluene thiol ester (8c) [2]



(8c)

Following the general procedure A, 4-methylbenzenethiol (1.302 g, 10.5 mmol) and 1-hydroxybenzotriazole (2.025 g, 15.0 mmol) were added to a solution of *N*-Cbz-L-phenylalanine (2.990 g, 10 mmol) in dry ethyl acetate 10 mL at 0 °C followed by *N, N′*-dicyclohexylcarbodiimide (2.060 g, 10.0 mmol). The mixture was stirred for 24 h at room temperature and the reaction progress was monitored by TLC analysis (25% ethyl acetate in petroleum ether, UV light, phenylalanine *p*-toluene thiol ester R_f =0.46). At the end of the reaction a few drops of 50 % acetic acid in ethyl acetate were added. The mixture was filtered through Celite™ and the organic phase was washed with $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by recrystallization (solvent, ethyl acetate and petroleum ether) affording the title compound as a white crystal 3.447 g (85% yield). m.p. 116-117 °C; $[\alpha]_D^{20}$ -66.6 (c 0.424, $CHCl_3$), lit: [2] $[\alpha]_D^{20}$ -66.0 (c 1.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37-7.22 (m, 12H), 7.16-7.14 (m, 2H), 5.29(d, J = 8.8 Hz, 1H), 5.11 (q, J = 12.8 Hz, 2H), 4.85-4.80 (m, 1H), 3.19-3.08 (m, 2H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 199.3, 155.7, 139.9, 136.1, 135.4, 134.6, 130.2, 129.5, 128.8, 128.6, 128.3, 128.1, 127.3, 123.4, 67.3, 61.4, 38.4, 21.4; HRMS (ESI) Calcd for: $C_{24}H_{23}NNaO_3S^{+1}$ ($[M+Na]^+$): 428.1291. Found: 428.1282; HPLC conditions: CHIRAL PAK AD-H, *n*-hexane/*i*-PrOH = 7:3, flow rate = 0.65 mL/min, detector 230 nm, t_R = 17.9 min, >99% ee.

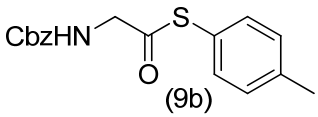
B1.2. *N*-Ac-D-phenylalanine *p*-toluene thiol ester (9a)



(9a)

4-methylbenzenethiol (0.77 g, 6.171 mmol) and 1-hydroxybenzotriazole (1.14 g, 8.415 mmol) were added to a solution of *N*-Ac-D-phenylalanine (1.16 g, 5.61 mmol) in dioxane 10 mL at 0 °C followed by *N, N′*-dicyclohexylcarbodiimide (1.16 g, 5.61 mmol) which was dissolved in 10mL ethyl acetate. The mixture was stirred for 24 h at room temperature and the reaction progress was monitored by TLC analysis (30% ethyl acetate in petroleum ether, UV light, phenylalanine *p*-toluene thiol ester R_f=0.2). At the end of the reaction the mixture was filtered through Celite™ . The filtrate was concentrated *in vacuo* to remove the dioxane , and then diluted with 10mL ethyl acetate , washed with $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 30% ethyl acetate in petroleum ether) affording the title compound as a white solid 1.32 g (75% yield). m.p. 156-158 °C; $[\alpha]_D^{20}$ +58.2 (c 0.660, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31-7.14 (m, 9H), 6.56 (d, *J* = 7.9 Hz, 1H), 5.07 (td, *J* = 7.9, 5.8 Hz, 1H), 3.18 (dd, *J* = 14.0, 5.6 Hz, 1H), 3.10-3.01 (m, 1H), 2.34 (s, 3H), 1.93 (d, *J* = 3.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 199.0, 170.3, 139.9, 135.8, 134.6, 130.2, 129.4, 128.7, 127.2, 123.4, 59.8, 38.2, 23.0, 21.4; HRMS (ESI) Calcd for: $C_{18}H_{19}NNaO_2S^{+1}$ ($[M+Na]^+$): 336.1029. Found: 336.1035; HPLC conditions: Lux 3u Cellulose-2, *n*-hexane/*i*-PrOH=8:2, flow rate = 1.0mL /min, detector 206 nm), t_R = 10.0 min, 54% ee.

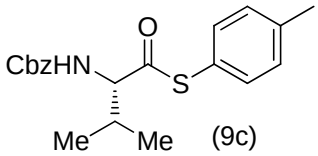
B1.3. *N*-Cbz- glycine *p*-toluene thiol ester (9b)



(9b)

4-methylbenzenethiol (2.981 g, 24 mmol) and 1-hydroxybenzotriazole (4.050 g, 30 mmol) were added to a solution of *N*-Cbz-Glycine acid (4.1832 g, 20 mmol) in dry ethyl acetate 40 mL at 0 °C followed by *N, N′*-dicyclohexylcarbodiimide (4.120 g, 20.0 mmol). The mixture was stirred for 24 h at room temperature and the reaction progress was monitored by TLC analysis (R_f=0.8, 50% ethyl acetate in petroleum ether, UV light). At the end of the reaction a few drops of 50 % acetic acid in ethyl acetate were added. The mixture was filtered through Celite™ and the organic phase was washed with $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by recrystallization (solvent, ethyl acetate and petroleum ether, a few ethanol) affording the title compound as a white crystal 5.235 g (83% yield). TLC (R_f = 0.3, silica gel, 25% ethyl acetate in ethyl acetate in petroleum ether); m.p. 92-94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42-7.09 (m, 9H), 5.65 (s, 1H), 5.14 (d, *J* = 9.3 Hz, 2H), 4.12 (d, *J* = 5.3 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 196.8, 156.4, 140.1, 136.2, 134.7, 130.3, 128.6, 128.3, 128.2, 122.9, 67.4, 50.6, 21.4; HRMS (ESI) Calcd for: $C_{17}H_{17}NNaO_3S^{+1}$ ($[M+Na]^+$): 338.0821. Found: 338.0820.

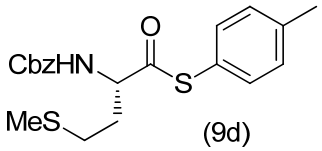
B1. 4. *N*-Cbz-L-valine *p*-toluene thiol ester (9c)[5]



(9c)

Following the general procedure A, 4-methylbenzenethiol (1.302 g, 10.5 mmol) and 1-hydroxybenzotriazole (2.025 g, 15.0 mmol) were added to a solution of *N*-Cbz-L-valine (2.512 g, 10 mmol) in dry ethyl acetate 10 mL at 0 ^{o}C followed by *N, N'*-dicyclohexylcarbodiimide (2.060 g, 10.0 mmol). The mixture was stirred for 24h at room temperature and the reaction progress was monitored by TLC analysis (25% ethyl acetate in petroleum ether, UV light, phenylalanine *p*-toluene thiol ester R_f=0.38). At the end of the reaction a few drops of 50 % acetic acid in ethyl acetate were added. The mixture was filtered through Celite™ and the organic phase was washed with $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by recrystallization (solvent: ethyl acetate and petroleum ether) affording the title compound as a white crystal 3.04 g (85% yield). TLC (R_f = 0.52, silica gel, 25% ethyl acetate in petroleum ether). m.p. 60-64 °C; $[\alpha]_D^{20}$ -35.9 (c 0.985, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39-7.32 (m, 5H), 7.29-7.18 (m, 4H), 5.34 (d, *J* = 9.2 Hz, 1H), 5.16 (s, 2H), 4.49 (dd, *J* = 9.5, 4.6 Hz, 1H), 2.36 (d, *J* = 7.4 Hz, 3H), 2.33 (dd, *J* = 9.2, 4.2 Hz, 1H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 199.2, 156.3, 139.9, 136.14, 134.6, 130.1, 128.6, 128.3, 128.2, 123.5, 67.4, 65.7, 31.3, 21.4, 19.5, 16.9; RMS (ESI) Calcd for: $C_{20}H_{23}NNaO_3S^{+1}$ ($[M+Na]^+$): 380.1291. Found: 380.1287.

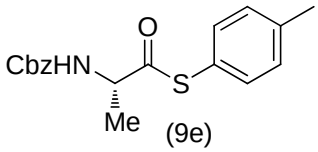
B1.5. *N*-Cbz-L-methionine *p*-toluene thiol ester (9d) [2]



(9d)

Following the general procedure A, 4-methylbenzenethiol (1.302 g, 10.5 mmol) and 1-hydroxybenzotriazole (2.025 g, 15.0 mmol) were added to a solution of *N*-Cbz-L-methionine (2.833 g, 10 mmol) in dry ethyl acetate 10 mL at 0 °C followed by *N, N'*-dicyclohexylcarbodiimide (2.060 g, 10.0 mmol). The mixture was stirred for 24 h at room temperature and the reaction progress was monitored by TLC analysis (25% ethyl acetate in petroleum ether, UV light, phenylalanine *p*-toluene thiol ester R_f=0.38). At the end of the reaction a few drops of 50% acetic acid in ethyl acetate were added. The mixture was filtered through Celite™ and the organic phase was washed with $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by recrystallization (solvent, ethyl acetate and petroleum ether) affording the title compound as a white crystal 3.35 g (86% yield). TLC (R_f = 0.38, silica gel, 25% ethyl acetate in petroleum ether); m.p. 143-144 °C; $[\alpha]_D^{20}$ -33.6 (c 0.422, $CHCl_3$), lit: [2] $[\alpha]_D^{20}$ -34.9 (c 1.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43-7.32 (m, 5H), 7.30-7.20 (m, 4H), 5.47 (d, *J* = 8.7 Hz, 1H), 5.17 (s, 2H), 4.75-4.69 (m, 1H), 2.66-2.52 (m, 2H), 2.38 (s, 3H), 2.30-2.18 (m, 1H), 2.11 (s, 3H), 2.05-1.94 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 199.2, 155.9, 140.0, 136.1, 134.6, 130.2, 128.6, 128.4, 128.2, 123.2, 67.41, 60.1, 32.0, 30.0, 21.4, 15.5; HRMS (ESI) Calcd for: $C_{20}H_{23}NNaO_3S_2^{+1}$ ($[M+Na]^+$): 412.1012. Found: 412.1006

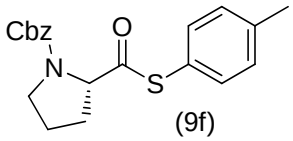
B1.6. *N*-Cbz-L-alanine *p*-toluene thiol ester (9e)[6]



(9e)

Following the general procedure A, 4-methylbenzenethiol (1.302 g, 10.5 mmol), 1-hydroxy-benzotriazole (2.025 g, 15.0 mmol), *N*-Cbz-L-alanine(2.232 g, 10 mmol), dry ethyl acetate 10 mL, *N,N'*-dicyclohexylcarbodiimide (2.060 g, 10.0 mmol), The crude product was purified by recrystallization (solvent, ethyl acetate and petroleum ether). The title compound was prepared as a white crystal 2.635 g (80% yield). TLC (25% ethyl acetate in petroleum ether, UV light, phenylalanine *p*-toluene thiol ester R_f =0.38); m.p. 58-62°C; $[\alpha]_D^{20}$ -28.3 (c 0.710, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.40-7.16 (m, 9H), 5.35-5.24 (m, 1H), 5.21-5.09 (m, 2H), 4.67-4.51 (m, 1H), 2.37 (s, 3H), 1.46 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 199.9, 155.6, 139.9, 136.1, 134.6, 130.1, 128.6, 128.3, 128.2, 123.3, 67.3, 56.6, 21.4, 19.0; HRMS (ESI) Calcd for: $C_{18}H_{19}NNaO_3S^{+1}$ ($[M+Na]^+$): 352.0978, found: 352.0972.

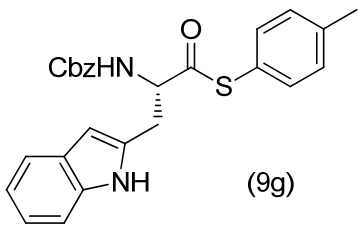
B1.7. *N*-Cbz-L-proline *p*-toluene thiol ester (9f) [2]



(9f)

Following the general procedure A, 4-methylbenzenethiol (1.302 g, 10.5 mmol), 1-hydroxybenzotriazole (2.025 g, 15.0 mmol), *N*-Cbz-L-proline (2.493 g, 10 mmol), dry ethyl acetate 10 mL, *N, N'*-dicyclohexylcarbodiimide (2.060 g, 10.0 mmol), The crude product was purified by recrystallization (solvent, ethyl acetate and petroleum ether). The title compound was prepared as a white crystal 2.1 g (60% yield). TLC (R_f = 0.29, silica gel, 25% ethyl acetate in petroleum ether); m.p. 61-62 °C; $[\alpha]_D^{20}$ -111.5 (c 0.487, $CHCl_3$), lit: [2] $[\alpha]_D^{20}$ -112.9 (c 0.78, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.45-7.23 (m, 6H), 7.16 (dt, *J* = 26.7, 8.4 Hz, 3H), 5.34-5.04 (m, 2H), 4.64 (dd, J = 8.4, 3.2 Hz, 0.4H), 4.54 (dd, J = 8.8, 3.2 Hz, 0.6H), 3.74-3.48 (m, 2H), 2.35 (s, 3H), 2.26-2.02 (m, 3H), 1.97-1.85 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.6, 200.2, 155.2 154.5, 139.7, 139.6, 136.6, 136.4, 134.6, 134.5, 130.1, 128.5, 128.1, 127.9, 123.9, 123.6, 67.3, 66.4, 66.0, 47.3, 46.9, 31.7, 30.7, 24.1, 23.4, 21.4; HRMS (ESI) Calcd for: $C_{20}H_{21}NNaO_3S^{+1}$ ($[M+Na]^+$): 378.1134. Found: 378.1131.

B1.8. *N*-Cbz-L-tryptophan *p*-toluene thiol ester (9g) [2]

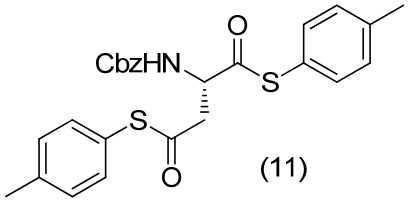


(9g)

Following the general procedure A, 4-methylbenzenethiol (1.302 g, 10.5 mmol), 1-hydroxybenzotriazole (2.025 g, 15.0 mmol), *N*-Cbz-L-tryptophan (3.383 g, 10 mmol), dry ethyl acetate 10 mL, *N, N'*-dicyclohexylcarbodiimide (2.060 g, 10.0 mmol). The crude product was

purified by flash chromatography (silica gel, 25%ethyl acetate in petroleum ether). The title compound was prepared as a pale yellow solid 4.09 g (92% yield). TLC (R_f= 0.17, silica gel, 25% ethyl acetate in ethyl acetate in petroleum ether); m.p. 51-52.5 °C; $[\alpha]_D^{20}$ -79.3 (c 0.677, $CHCl_3$), lit: [2] $[\alpha]_D^{20}$ -79.6 (c 1.25, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.18 (s, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.36-7.24 (m, 6H), 7.23-7.07 (m, 6H), 6.94 (s, 1H), 5.38 (d, *J* = 8.6 Hz, 1H), 5.12 (s, 2H), 4.89-4.84 (m, 1H), 3.38 (dd, *J* = 14.8, 5.8 Hz, 1H), 3.28 (dd, *J* = 14.7, 5.5 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.2, 155.9, 139.9, 136.2, 136.1, 134.6, 130.1, 128.6, 128.3, 128.1, 127.5, 123.6, 123.3, 122.4, 119.9, 118.9, 111.3, 109.3, 67.3, 61.0, 28.3, 21.4; HRMS (ESI) Calcd for: $C_{26}H_{24}N_2NaO_3S^{+1}$ ($[M+Na]^+$): 467.1400. Found: 467.1395.

B1.9. *N*-Cbz-L-aspartic acid *p*-toluene thiol ester. (11)



(11)

4-methylbenzenethiol (2.604 g, 21 mmol) and 1-hydroxybenzotriazole (4.050 g, 30 mmol) were added to a solution of *N*-Cbz-L-aspartic acid (2.672 g, 10 mmol) in dry ethyl acetate 20 mL at 0 °C followed by *N, N'*-dicyclohexylcarbodiimide (4.120 g, 20.0 mmol). The mixture was stirred for 24 h at room temperature and the reaction progress was monitored by TLC analysis (R_f = 0.38, 25% ethyl acetate in petroleum ether, UV light). At the end of the reaction a few drops of 50 % acetic acid in ethyl acetate were added. The mixture was filtered through Celite™ and the organic phase was washed with $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by recrystallization (solvent, ethyl acetate and petroleum ether) affording the title compound as a white crystal 4.08 g (85% yield). TLC (R_f= 0.38, silica gel, 25% ethyl acetate in ethyl acetate in petroleum ether); m.p. 111-114 °C; $[\alpha]_D^{20}$ -97.4 (c 0.176, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45-7.30 (m, 5H), 7.27-7.14 (m, 8H), 5.97 (d, *J* = 9.8 Hz, 1H), 5.19 (s, 2H), 4.87-4.79 (m, 1H), 3.51 (dd, *J* = 17.1, 4.6 Hz, 1H), 3.09 (dd, *J* = 17.1, 4.3 Hz, 1H), 2.37 (d, *J* = 2.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 198.5, 196.8, 155.8, 140.3, 139.9, 136.0, 134.6, 134.6, 130.2, 130.1, 128.6, 128.3, 128.1, 123.5, 123.1, 67.5, 57.6, 44.5, 29.7, 21.4; IR (film): 3321.76，3031.12，2925.72, 2853.73, 1701.16, 1497.42, 1402.57, 1312.51, 1243.34, 1047.35, 987.28, 920.96, 807.45, 741.33, 698.50, 474.91 cm^{-1}; HRMS (MALDI) Calcd for $C_{26}H_{25}NO_4S_2Na^{+1}$ ($[M+Na]^+$): 502.1117. Found: 502.1117.

B2. Synthesis of Free Amine

General Method B: The Preparation of Amino Acid Ester Free Amine[7]

The amino acid ester hydrochloride salt (10 mmol) was mixed with tetrahydrofuran(THF) (20 mL) in a 50 mL, round-bottom flask. Triethylamine (200 mmol) was added dropwise to the stirred solution and the mixture was then stirred for 4-24 h at room temperature. The solution was filtered and washed with 10 mL of THF. Concentration of the THF filtrate *in vacuo* yielded the amino acid ester free amine (**6a**, **6b-d**, **6e**, **10**). Yield (60-99%).

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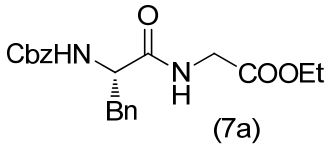
B3. Amidation of thioesters with amines in the presence of silyl compounds.

General Method C: The Preparation of N-Cbz–dipeptide-OMe/(-OEt)

N-Cbz-amino acid thiol ester (1.0 mmol, 1.0 equiv) was added to a polar solvent (4 mL, EtOH or others) in a 10 mL, round-bottom flask. Stir until the thiol ester dissolved, then added silyl compound (1.0 mmol, 1.0 equiv), amino acid ester free amine (2.0 mmol, 2.0 equiv) in it. The mixture was heated at 40 ^{o}C for 18 h-72 h, then cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue dissolved in ethyl acetate (20 mL) then washed successively with 1M aqueous HCl (4 mL), 2M aqueous NaOH (5 mL), brine (5 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated to dryness. The crude product was purified by flash chromatography (silica gel, first use 25% ethyl acetate in petroleum ether, then use 10% MeOH in DCM to wash the chromatography to get the product).

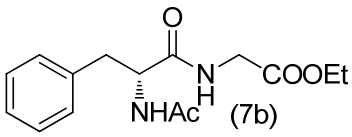
B3.1. Coupling of *N*-Cbz-L-phenylalanine *p*-toluene thiol ester with Gly–OEt to get (7a) [8]



(7a)

Following the general procedure C, Phe-thiol ester **8a**, **8b**, **8c** (0.493 mmol) was added to EtOH (2 mL) in a 10 mL, round-bottom flask. Stir until the thiol ester dissolved, then added BSA or other silyl compound (0.493 mmol, Table 2), Gly–OEt (0.493 mmol or 0.986 mmol Table 1) in it. The mixture was heated at 40 ^{o}C for 18 h, then cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (15 mL) then washed successively with 1M aqueous HCl (4 mL), 2M aqueous NaOH (4 mL), and brine (4 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to dryness. The crude product was purified by flash chromatography (silica gel, first use 25% ethyl acetate in petroleum ether, then use 10% MeOH in DCM wash the chromatography to get the product). The product was prepared as a white crystal. The yields are showed in Table 1 and Table 2. m.p. 111-112 ºC; $[\alpha]_D^{20}$ -17.0 (c 0.370, EtOH), lit: [9] $[\alpha]_D^{27}$ -17.1 (c=0.57, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35-7.10 (m, 10H), 6.98 (s, 1H), 5.88 (d, *J* = 6.8 Hz, 1H), 5.00 (dd, *J* = 30.2, 12.3 Hz, 2H), 4.58 (d, *J* = 6.5 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.04- 3.65 (m, 2H), 3.13 (dd, *J* = 13.6, 6.0 Hz, 1H), 2.99 (dd, *J* = 13.6, 7.6 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.7, 169.6, 156.2, 136.6, 136.2, 129.3, 128.6, 128.5, 128.1, 127.9, 126.9, 66.9, 61.5, 56.0, 41.3, 38.5, 14.1; HRMS (ESI) Calcd for: $C_{21}H_{24}N_2NaO_5^{+1}$ ($[M+Na]^+$): 407.1577. Found: 407.1575; HPLC conditions: CHIRAL PAK AD-H, *n*-hexane/*i*-PrOH = 85:15, flow rate = 0.65 mL/min, detector 230 nm), t_R = 41.0 min. >99% ee.

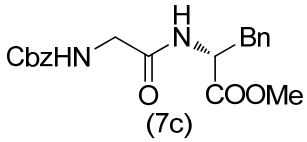
B3.2. Coupling of *N*-Ac-D-phenylalanine *p*-toluene thiol ester with Gly–OEt to get (7b)



(7b)

Following the general procedure C, *N*-Ac-D-Phe-thiol ester (350mg, 1.12 mmol) (54% ee) was added to EtOH (4 mL) in a 25 mL, round-bottom flask. Stir until the thiol ester dissolved, then added BSA (227.8mg, 1.12mmol), Gly–OEt (230.3mg, 2.24mmol) in it. The mixture was heated at 40 ^{o}C for 24 h, then cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (15 mL) then washed successively with 1M aqueous HCl (4 mL), 2M aqueous NaOH (4 mL), and brine (4 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to dryness. The crude product was purified by flash chromatography (silica gel, first use 50% ethyl acetate in petroleum ether, then use 10% MeOH in DCM wash the chromatography to get the product). The title compound was prepared as a solid 298mg (91% yield). m.p. 133-138^{o}C; $[\alpha]_D^{20}$ +2.0 (c 0.501, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62 (s, 1H), 7.42 (s, 1H), 7.22 (t, *J* = 8.5 Hz, 5H), 5.08-4.72 (m, 1H), 4.14 (q, *J* = 7.0 Hz, 2H), 3.93 (d, *J* = 5.1 Hz, 2H), 3.13 (dt, *J* = 20.2, 7.9 Hz, 1H), 2.98 (dd, *J* = 13.6, 7.9 Hz, 1H), 1.90 (s, 3H), 1.24 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.3, 170.7, 169.5, 136.9, 129.3, 128.4, 126.7, 61.3, 54.3, 54.2, 41.3, 38.3, 38.2 22.8, 14.1; HRMS (ESI) Calcd for: $C_{15}H_{20}N_2NaO_4^{+1}$([M+Na]$^+$): 315.1315. Found: 315.1321; HPLC conditions: Lux 3u Cellulose-2, *n*-hexane/*i*-PrOH = 7:3, flow rate = 1.0mL /min, detector 206 nm, t_R = 13.5 min. 54% ee.

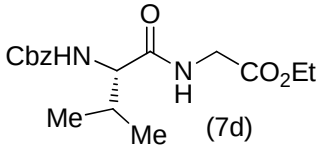
B3.3. Coupling of *N*-Cbz-glycine-*p*-toluene thiol ester with L-Phe–OMe to get (7c) [10]



(7c)

Following the general procedure C, Gly-*p*-toluene thiol ester (405.3 mg, 1.285 mmol) was added to EtOH (5 mL) in a 25 mL, round-bottom flask. Stir until the thiol ester dissolved, then added BSA (261.4 mg, 1.285 mmol), L-Phe–OMe (460 mg, 2.57 mmol) in it. The mixture was heated at 40 ^{o}C for 24 h, then cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (15 mL) then washed successively with 1M aqueous HCl (4 mL), 2M aqueous NaOH (4 mL) and brine (4 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to dryness. The crude product was purified by flash chromatography (use 50% ethyl acetate in petroleum ether to get the product). The title compound was prepared as a colorless oil 372mg (78% yield). $[\alpha]_D^{20}$ +15.0 (c 0.113, EtOH).; lit: [10] $[\alpha]_D^{25}$ +15.2 (c 1.02, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.27-7.06 (m, 8H), 6.98 (d, *J* = 6.8 Hz, 2H), 6.87 (d, *J* = 7.0 Hz, 1H), 5.75 (s, 1H), 5.03-4.90 (m, 2H), 4.75 (dd, *J* = 13.9, 6.2 Hz, 1H), 3.70 (t, *J* = 5.5 Hz, 2H), 3.55 (s, 3H), 2.95 (qd, *J* = 13.8, 6.1 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=171.9, 169.1, 156.7, 136.3, 135.8, 129.3, 128.6, 128.5, 128.2, 128.1, 127.1, 67.1, 53.3, 52.4, 44.3, 37.8; HRMS (ESI) Calcd for: $C_{20}H_{22}N_2NaO_5^{+1}$([M+Na]$^+$): 393.1421. Found: 393.1426; HPLC conditions: Lux 3 μ Cellulose-2, *n*-hexane/*i*-PrOH = 6:4, flow rate= 1.0 mL /min, detector 210 nm, t_R = 16.2 min. >99% ee.

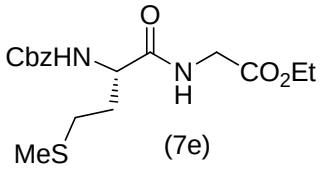
B3.4. Coupling of *N*-Cbz-L-valine *p*-toluene thiol ester with Gly–OEt to get (7d) [9]



(7d)

Following the general procedure C, Val *p*-toluene thiol ester (200 mg, 0.559 mmol) was added to EtOH (2 mL) in a 10 mL, round-bottom flask. Stir until the thiol ester dissolved, then added BSA (113.8 mg, 0.559 mmol), Gly–OEt (115.4 mg, 1.119 mmol) in it. The mixture was heated at 40 ^{o}C for 72 h, then cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (15 mL) then washed successively with 1M aqueous HCl (4 mL), 2M aqueous NaOH (4mL), brine (4mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated to dryness. The crude product was purified by flash chromatography (first use 25% ethyl acetate in petroleum ether, then use 10% MeOH in DCM wash the chromatography to get the product). The title compound was prepared as a white solid 148.5 mg (79% yield). m.p. 144-145 ^{o}C; $[\alpha]_D^{20}$ -25.3 (c 0.42, EtOH), lit: [9] $[\alpha]_D^{23}$ -25.2 (c=0.62, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59-7.28 (m, 5H), 6.50 (s, 1H), 5.40 (d, *J* = 8.5 Hz, 1H), 5.17-5.03 (m, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.14-3.93 (m, 3H), 2.17 (dq, *J* = 13.2, 6.6 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.96 (dd, *J* = 19.0, 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.5, 169.6, 156.4, 136.2, 128.6, 128.2, 128.1, 67.1, 61.6, 60.3, 41.3, 31.0, 19.2, 17.7, 14.1; HRMS (ESI) Calcd for: $C_{17}H_{24}N_2NaO_5^{+1}$ ($[M+Na]^+$): 359.1577. Found: 359.1576.

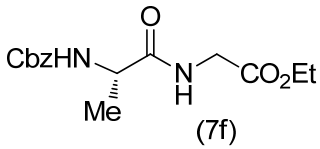
B3.5. Coupling of *N*-Cbz-L-methionine *p*-toluene thiol ester with Gly–OEt to get (7e) [9]



(7e)

Following the general procedure C, Met-*p*-toluene thiol ester (200 mg, 0.516 mmol) was added to EtOH (2 mL) in a 10 mL, round-bottom flask. Stir until the thiol ester dissolved, then added BSA (105 mg, 0.516 mmol), Gly-OEt (106.4 mg, 1.032 mmol) in it. The mixture was heated at 40 ^{o}C for 72 h, then cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (15 mL) then washed successively with 1M aqueous HCl (4 mL), 2M aqueous NaOH (4 mL), brine (4 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated to dryness. The crude product was purified by flash chromatography (first use 25% ethyl acetate in petroleum ether, then use 10% MeOH in DCM wash the chromatography to get the product). The title compound was prepared as a solid 151.3 mg (80% yield). m.p.74-76 ^{o}C; $[\alpha]_D^{20}$ −19.5 (c 0.21, EtOH), lit: [9] $[\alpha]_D^{22}$ −19.4 (c=2.19, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61-7.27 (m, 5H), 6.70 (s, 1H), 5.57 (d, *J* = 7.9 Hz, 1H), 5.20-5.04 (m, 2H), 4.44 (dd, *J* = 14.1, 6.8 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.03 (ddd, *J* = 23.1, 18.3, 5.4 Hz, 2H), 2.60 (t, *J* = 7.0 Hz, 2H), 2.34-1.85 (m, 5H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.3, 169.5, 156.1, 136.1, 128.6, 128.3, 128.1, 67.2, 61.7, 53.7, 41.3, 31.5, 29.9, 15.1, 14.1; HRMS (ESI) Calcd for: $C_{17}H_{24}N_2NaO_5S^{+1}$ ($[M+Na]^+$): 391.1298. Found: 391.1296.

B3.6. Coupling of *N*-Cbz-L-alanine *p*-toluene thiol ester with Gly–OEt to get (7f) [8]

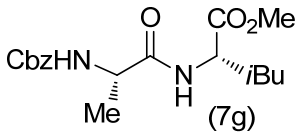


(7f)

Following the general procedure C, Ala-*p*-toluene thiol ester (200 mg, 0.607 mmol) was added

to EtOH (2 mL) in a 10 mL, round-bottom flask. Stir until the thiol ester dissolved, then added BSA (123.5 mg, 0.607 mmol), Gly-OEt (125 mg, 1.214 mmol) in it. The mixture was heated at 40 ^{o}C for 36 h, then cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (15 mL) then washed successively with 1M aqueous HCl (4 mL), 2M aqueous NaOH (4 mL), brine (4 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated to dryness. The crude product was purified by flash chromatography (first use 25% ethyl acetate in petroleum ether, then use 10% MeOH in DCM wash the chromatography to get the product). The title compound was prepared as a solid 181.4 mg (97% yield). m.p. 98-100 ºC; $[\alpha]_D^{20}$ -22.0 (c 0.191, EtOH), lit: [9] $[\alpha]_D^{21}$ -22.2 (c 2.43, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43-7.27 (m, 5H), 6.80 (s, 1H), 5.56 (d, *J* = 6.9 Hz, 1H), 5.10 (q, *J* = 12.2 Hz, 2H), 4.39-4.26 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.00 (d, *J* = 5.1 Hz, 2H), 1.39 (d, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.7, 169.7, 156.1, 136.2, 128.5, 128.2, 128.1, 67.0, 61.6, 50.4, 41.3, 18.6, 14.1; HRMS (ESI) Calcd for: $C_{15}H_{20}N_2NaO_5^{+1}$ ($[M+Na]^+$): 331.1264. Found: 331.1264.

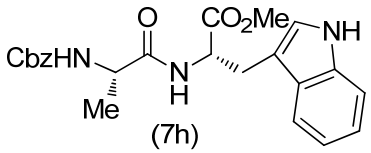
B3.7. Coupling of *N*-Cbz-L-alanine-*p*-toluene thiol ester with L-Leu–OMe to get (7g) [8]



(7g)

Following the general procedure C, Ala-*p*-toluene thiol ester (200 mg, 0.607 mmol) was added to EtOH (2 mL) in a 10 mL, round-bottom flask. Stir until the thiol ester dissolved, then added BSA (123.5 mg, 0.607 mmol), Leu–OMe (176.2 mg, 1.214 mmol) in it. The mixture was heated at 40 ^{o}C for 48 h, then cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (15 mL) then washed successively with 1M aqueous HCl (4 mL), 2M aqueous NaOH (4 mL), brine (4 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated to dryness. The crude product was purified by flash chromatography (first use 25% ethyl acetate in petroleum ether, then use 10% MeOH in DCM wash the chromatography to get the product). The title compound was prepared as a solid 148.9 mg (70% yield). m.p. 72-73 ºC; $[\alpha]_D^{20}$ -9.9 (c 0.789, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27-7.23 (m, 5H), 6.90 (d, *J* = 7.9 Hz, 1H), 5.72 (d, *J* = 7.6 Hz, 1H), 5.01 (s, 2H), 4.51 (td, *J* = 8.6, 4.8 Hz, 1H), 4.38-4.23 (m, 1H), 3.61 (d, *J* = 9.2 Hz, 3H), 1.54 (dd, *J* = 12.7, 7.7 Hz, 2H), 1.29 (d, *J* = 7.0 Hz, 4H), 0.82 (d, *J* = 5.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.3, 172.5, 156.0, 136.2, 128.5, 128.1, 127.9, 66.9, 52.3, 50.7, 50.3, 41.2, 24.8, 22.8, 21.8; HRMS (ESI) Calcd for: $C_{18}H_{26}N_2NaO_5^{+1}$ ($[M+Na]^+$): 373.1734. Found: 373.1737.

B3.8. Coupling of *N*-Cbz-L-alanine *p*-toluene thiol ester with L-Trp–OMe to get (7h) [11]



(7h)

Following the general procedure C, Ala-*p*-toluene thiol ester (200 mg, 0.607 mmol) was added to EtOH (2 mL) in a 10mL, round-bottom flask. Stir until the thiol ester dissolved, then added BSA (123.5 mg, 0.607 mmol), Trp–OMe (265 mg, 1.214 mmol) in it. The mixture was heated at

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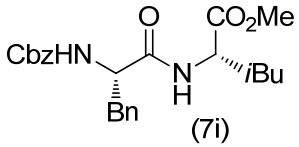
40 °C for 72 h, then cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (15 mL) then washed successively with 1M aqueous HCl (4 mL), 2M aqueous NaOH (4 mL), brine (4 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated to dryness. The crude product was purified by flash chromatography (first use 25% ethyl acetate in petroleum ether, then use 10% MeOH in DCM wash the chromatography to get the product). The title compound was prepared as a solid 185.1 mg (72% yield). m.p. 119-122 °C; $[\alpha]_D^{20}$-4.6 (c 0.618, MeOH), lit: [12] $[\alpha]_D^{20}$-4.9 (MeOH, 32 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.34 (s, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.38-7.23 (m, 6H), 7.10 (dt, *J* = 28.1, 7.3 Hz, 2H), 6.89 (s, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 5.49 (d, *J* = 7.7 Hz, 1H), 5.00 (dd, *J* = 34.7, 12.2 Hz, 2H), 4.92-4.82 (m, 1H), 4.27 (s, 1H), 3.60 (d, *J* = 18.0 Hz, 3H), 3.26 (d, *J* = 5.3 Hz, 2H), 1.30-1.24 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.1, 171.9, 155.8, 136.3, 136.1, 128.6, 128.2, 128.1, 127.5, 123.1, 122.2, 119.6, 118.5, 111.3, 109.6, 66.9, 52.9, 52.5, 50.4, 27.5, 18.6; HRMS (ESI) Calcd for: $C_{23}H_{25}N_3NaO_5^{+1}$ ($[M+Na]^+$): 446.1686. Found: 446.1688.

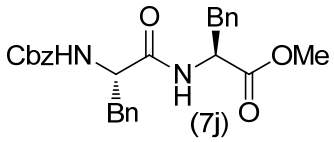
B3.9. Coupling of *N*-Cbz-L-pheylalanine *p*-toluene thiol ester with L-Leu–OMe to get (7i) [8]



(7i)

Following the general procedure C, Phe-*p*-toluene thiol ester (200 mg, 0.493 mmol) was added to EtOH (2 mL) in a 10 mL, round-bottom flask. Stir until the thiol ester dissolved, then added BSA (100.3 mg, 0.493 mmol), Leu–OMe (143.1 mg, 0.986 mmol) in it. The mixture was heated at 40 °C for 48 h, then cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (15 mL) then washed successively with 1M aqueous HCl (4 mL), 2M aqueous NaOH (4 mL), brine (4 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated to dryness. The crude product was purified by flash chromatography (first use 25% ethyl acetate in petroleum ether, then use 10% MeOH in DCM wash the chromatography to get the product). The title compound was prepared as a solid 111.3 mg (53% yield). m.p. 110-112 °C. $[\alpha]_D^{20}$ -5.1 (c 0.536, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36-7.13 (m, 10H), 6.64 (d, *J* = 7.9 Hz, 1H), 5.62 (d, *J* = 8.2 Hz, 1H), 5.04 (s, 2H), 4.61-4.45 (m, 2H), 3.66 (d, *J* = 10.4 Hz, 3H), 3.06 (d, *J* = 6.1 Hz, 2H),1.60-1.54(m, 2H) 1.39-1.19 (m, 1H), 0.90-0.80 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.9, 170.9, 156.0, 136.5, 136.4, 136.2, 129.4, 128.5, 128.2, 128.0, 126.9, 67.0, 56.0, 52.3, 50.8, 41.3, 38.5, 24.7, 22.7; HRMS (ESI) Calcd for: $C_{24}H_{30}N_2NaO_5^{+1}$ ($[M+Na]^+$): 449.2047. Found: 449.2042.

B3.10. Coupling of *N*-Cbz-L-phenylalanine *p*-toluene thiol ester with L-Phe–OMe to get (7j)[13]

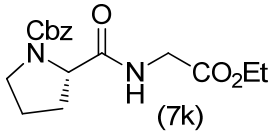


(7j)

Following the general procedure C, Phe-*p*-toluene thiol ester (307.6 mg, 0.758 mmol) was added to EtOH (2 mL) in a 10mL, round-bottom flask. Stir until the thiol ester dissolved, then added BSA (154.3 mg, 0.758 mmol), Phe–OMe (271.9 mg, 1.517 mmol) in it. The mixture was

heated at 40 °C for 72 h, then cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (20 mL) then washed successively with 1M aqueous HCl (6 mL), 2M aqueous NaOH (6 mL), brine (6 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated to dryness. The crude product was purified by flash chromatography (first use 25% ethyl acetate in petroleum ether, then use 10% MeOH in DCM wash the chromatography to get the product). The title compound was prepared as a solid 211 mg (60% yield). m.p. 134–136 °C; $[\alpha]_D^{20}$ -22.1 (c 0.541, $CHCl_3$), lit: [13] $[\alpha]_D$ -21.9, ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37-7.18 (m, 11H), 7.13 (d, *J* = 6.7 Hz, 2H), 6.90 (dd, *J* = 6.5, 2.8 Hz, 2H), 6.36 (d, *J* = 7.7 Hz, 1H), 5.32 (d, *J* = 7.6 Hz, 1H), 5.10-5.01 (m, 2H), 4.83 (dt, *J* = 8.0, 5.9 Hz, 1H), 4.52-4.33 (m, 1H), 3.66 (d, *J* = 4.4 Hz, 3H), 3.08-2.88 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=171.5, 170.5, 155.9, 136.3, 136.1, 135.5, 129.4, 129.2, 128.8, 128.6, 128.6, 128.2, 128.1, 127.2, 127.1, 67.1, 56.2, 53.0, 52.4, 38.5, 37.8; HRMS (ESI) Calcd for: $C_{27}H_{28}N_2NaO_5^{+1}$ ($[M+Na]^+$): 483.1890. Found: 483.1890.

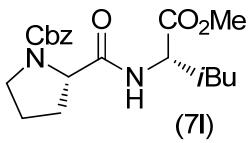
B3.11. Coupling of *N*-Cbz-L-proline *p*-toluene thiol ester with Gly–OEt to get (7k) [9]



(7k)

Following the general procedure C, Pro-*p*-toluene thiol ester (200 mg, 0.563 mmol) was added to EtOH (2 mL) in a 10mL, round-bottom flask. Stir until the thiol ester dissolved, then added BSA (114.47 mg, 0.563 mmol), Gly–OEt (116 mg, 1.125 mmol) in it. The mixture was heated at 40 °C for 36 h, then cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (15 mL) then washed successively with 1M aqueous HCl (4 mL), 2M aqueous NaOH (4 mL), brine (4 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated to dryness. The crude product was purified by flash chromatography (first use 25% ethyl acetate in petroleum ether, then use 10% MeOH in DCM wash the chromatography to get the product). The title compound was prepared as a colorless oil 160 mg (85% yield). $[\alpha]_D^{20}$ -60.4 (c 0.264, AcOEt), lit: [9] $[\alpha]_D^{22}$ -60.4 (c=2.43, AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 (d, *J* = 20.0 Hz, 5H), 6.79 (br s, 0.37H, 2-NH in one of rotamers), 5.15 (dd, *J* = 25.9, 11.9, 2H), 4.37 (d, *J* = 18.2, 1H), 4.24-4.10 (m, 2H), 4.06-3.73 (m, 2H), 3.50 (d, *J* = 43.6 Hz, 2H), 2.22 (d, *J* = 54.8 Hz, 1H), 1.98 (dd, *J* = 37.9, 20.8 Hz, 3H), 1.25 (dd, *J* = 9.0, 4.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.2, 169.7, 155.9, 136.4, 128.4, 128.0, 127.8, 67.2, 61.2, 60.4, 47.0, 41.3, 28.9, 24.4, 14.1; HRMS (ESI) Calcd for: $C_{17}H_{22}N_2NaO_5^{+1}$ ($[M+Na]^+$): 357.1421. Found: 357.1421.

B3.12. Coupling of *N*-Cbz-L-proline *p*-toluene thiol ester with L-Leu–OMe to get (7l) [14]

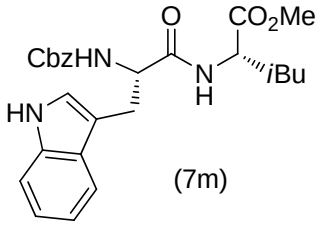


(7l)

Following the general procedure C, Pro-*p*-toluene thiol ester (200 mg, 0.563 mmol) was added to EtOH (2 mL) in a 10 mL, round-bottom flask. Stir until the thiol ester dissolved, then added BSA (114.4 mg, 0.563 mmol), Leu–OMe (163.4 mg, 1.125 mmol) in it. The mixture was heated at

40 °C for 48 h, then cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (15 mL) then washed successively with 1M aqueous HCl (4 mL), 2M aqueous NaOH (4 mL), brine (4 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated to dryness. The crude product was purified by flash chromatography (first use 25% ethyl acetate in petroleum ether, then use 10% MeOH in DCM wash the chromatography to get the product). The title compound was prepared as a colorless oil 116.5 mg (55% yield). $[\alpha]_D^{20}$ -63.0 (c 0.187, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43-7.25 (m, 5H), 7.14 (d, *J* = 5.9 Hz, 0.6H), 6.39 (d, *J* = 5.8 Hz, 0.4H), 5.17 (dd, *J* = 23.5, 12.4 Hz, 2H), 4.53-4.30 (m, 2H), 3.81-3.33 (m, 5H), 2.15 (s, 1H), 1.91 (d, *J* = 5.5 Hz, 2H), 1.68-1.41 (m, 3H), 1.26(m, 1H) 0.89 (d, *J* = 5.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=173.2, 171.4, 156.1, 136.5, 128.5, 128.1, 127.8, 67.3, 60.2, 52.2, 50.9, 46.9, 41.2, 31.0, 28.1, 24.9, 22.8. HRMS (ESI) Calcd for: $C_{20}H_{28}N_2NaO_5^{+1}$ ($[M+Na]^+$): 399.1890. Found: 399.1893.

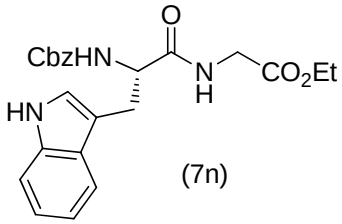
B3.13. Coupling of Z-L-Trp-*p*-toluene thiol ester with L-Leu–OMe to get (7m)



(7m)

Following the general procedure C, Trp-*p*-toluene thiol ester (200 mg, 0.45 mmol) was added to EtOH (2 mL) in a 10 mL, round-bottom flask. Stir until the thiol ester dissolved, then added BSA (91.5 mg, 0.45 mmol), Leu–OMe (130.6 mg, 0.9 mmol) in it. The mixture was heated at 40 °C for 48 h, then cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (15 mL) then washed successively with 1M aqueous HCl (4 mL), 2M aqueous NaOH (4 mL), brine (4 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated to dryness. The crude product was purified by flash chromatography (first use 25% ethyl acetate in petroleum ether, then use 10% MeOH in DCM wash the chromatography to get the product). The title compound was prepared as a solid 119.1 mg (57% yield). m.p. 73-75 °C; $[\alpha]_D^{20}$ +50.5 (c 0.129, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.59 (d, *J* = 16.1 Hz, 1H), 7.63 (t, *J* = 12.2 Hz, 1H), 7.29 (d, *J* = 20.6 Hz, 6H), 7.20-6.94 (m, 3H), 6.37 (s, 1H), 5.67 (s, 1H), 5.06 (d, *J* = 12.1 Hz, 2H), 4.58-4.47 (m, 1H), 4.13 (ddd, *J* = 19.1, 13.1, 7.1 Hz, 1H), 3.73-3.67 (m, 1H), 3.61 (s, 2H), 3.53-3.41 (m, 1H), 3.29 (d, *J* = 13.6 Hz, 1H), 3.18 (dd, *J* = 14.6, 7.4 Hz, 1H),1.49-1.40(m, 2H) 0.92-0.82 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.9, 171.2, 156.1, 136.3, 128.6, 128.2, 128.1, 127.4, 123.6, 122.1, 119.7, 118.8, 111.30, 110.2, 67.0, 60.8, 52.3, 44.1, 41.4, 24.7, 22.6, 21.9; HRMS (ESI) Calcd for: $C_{26}H_{31}N_3NaO_5^{+1}$ ($[M+Na]^+$): 488.2156. Found: 488.2153.

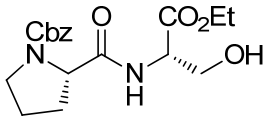
B3.14. Coupling of *N*-Cbz-L-tryptophan *p*-toluene thiol ester with Gly–OEt to get (7n) [15]



(7n)

Following the general procedure C, Trp-*p*-toluene thiol ester (200 mg, 0.45 mmol) was added to EtOH (2 mL) in a 10 mL, round-bottom flask. Stir until the thiol ester dissolved, then added BSA (91.5 mg, 0.45 mmol), Gly–OEt (92.8 mg, 0.9 mmol) in it. The mixture was heated at 40 ^{o}C for 36 h, then cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (15 mL) then washed successively with 1M aqueous HCl (4 mL), 2M aqueous NaOH (4 mL), brine (4 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated to dryness. The crude product was purified by flash chromatography (first use 25% ethyl acetate in petroleum ether, then use 10% MeOH in DCM wash the chromatography to get the product). The title compound was prepared as a solid 175.3 mg (92% yield). m.p. 70-72 °C; $[\alpha]_D^{20}$ -3.1 (c 0.263, $CHCl_3$), lit: [15] *N*-Cbz-D-Trp-Gly-OEt $[\alpha]_D^{25}$ 2.9 (c 0.23, $CHCl_3$); *N*-Cbz-L-Trp-Gly-OEt $[\alpha]_D^{25}$ -3.1 (c 0.215, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.60 (s, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.22-6.81 (m, 9H), 6.68 (s, 1H), 5.75 (d, *J* = 7.6 Hz, 1H), 4.89 (q, *J* = 12.3 Hz, 2H), 4.48 (d, *J* = 6.6 Hz, 1H), 3.92 (q, *J* = 7.1 Hz, 2H), 3.67 (dd, *J* = 5.3, 2.5 Hz, 2H), 3.10 (d, *J* = 5.7 Hz, 2H), 1.04 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=172.3, 169.7, 156.3, 136.3, 128.6, 128.2, 128.0, 127.6, 123.7, 122.0, 119.5, 118.6, 111.5, 109.9, 67.0, 61.5, 55.6, 41.4, 28.5, 14.1; HRMS (ESI) Calcd for: $C_{23}H_{25}N_3NaO_5^{+1}$ ($[M+Na]^+$): 446.1686. Found: 446.1689.

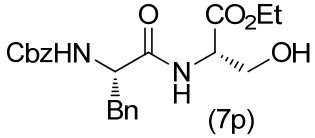
B3.15 Coupling of *N*-Cbz-L-proline *p*-toluene thiol ester with L-Ser–OEt to get (7o)



(7o)

Following the general procedure C, Pro-*p*-toluene thiol ester (200 mg, 0.563 mmol) was added to EtOH (2 mL) in a 10 mL, round-bottom flask. Stir until the thiol ester dissolved, then added BSA (100.3 mg, 0.563 mmol), Ser–OEt (149.8 mg, 1.125 mmol) in it. The mixture was heated at 40 ^{o}C for 48 h, then cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (15 mL) then washed successively with 1M aqueous HCl (4 mL), 2M aqueous NaOH (4 mL), brine (4 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated to dryness. The crude product was purified by flash chromatography (first use 25% ethyl acetate in petroleum ether, then use 10% MeOH in DCM wash the chromatography to get the product). The title compound was prepared as a colorless oil 123.7 mg (60% yield). $[\alpha]_D^{20}$ -43.3 (c 0.116, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 (d, *J* = 27.5 Hz, 5H), 7.18 (d, *J* = 7.0 Hz, 1H), 5.24-4.97 (m, 2H), 4.67-4.48 (m, 1H), 4.34-4.26 (m, 1H), 4.21 (dt, *J* = 16.3, 8.0 Hz, 2H), 3.94 (d, *J* = 22.2 Hz, 2H), 3.77 (s, 1H), 3.55 (ddt, *J* = 16.7, 10.2, 5.6 Hz, 2H), 2.25-1.79 (m, 4H), 1.28 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.2, 170.4, 155.6, 136.4, 128.5, 128.1, 127.9, 67.4, 62.4, 61.8, 60.7, 55.2, 47.1, 29.5, 24.6, 14.1; IR (film): 3325.78, 2935.24, 1741.36, 1677.60, 1535.08, 1420.80, 1355.94, 1200.94, 1122.32, 1086.88, 1029.02, 765.21, 698.88 cm^{-1}; HRMS (MALDI) Calcd for $C_{18}H_{24}N_2O_6Na^{+1}$ ($[M+Na]^+$):387.1527. Found: 387.1527.

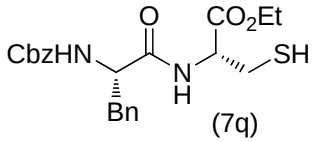
B3.16. Coupling of *N*-Cbz-L-phenylalanine *p*-toluene thiol ester with L-Ser–OEt to get (7p)



(7p)

Following the general procedure C, Phe-*p*-toluene thiol ester (200 mg, 0.493 mmol) was added to EtOH (2 mL) in a 10 mL, round-bottom flask. Stir until the thiol ester dissolved, then added BSA (100.3 mg, 0.4932 mmol), Ser–OEt (131.3 mg, 0.986 mmol) in it. The mixture was heated at 40 ^{o}C for 72 h, then cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (15 mL) then washed successively with 1M aqueous HCl (4 mL), 2M aqueous NaOH (4 mL), brine (4 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated to dryness. The crude product was purified by flash chromatography (first use 25% ethyl acetate in petroleum ether, then use 10% MeOH in DCM wash the chromatography to get the product). The title compound was prepared as a solid 123.7mg (61% yield). m.p. 100-103 ^{o}C; $[\alpha]_D^{20}$ +14.6 (c 0.189, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.48 (d, *J* = 7.7 Hz, 1H), 7.22 (ddd, *J* = 12.3, 9.1, 4.9 Hz, 10H), 5.97 (dd, *J* = 22.2, 8.1 Hz, 1H), 5.09-4.96 (m, 2H), 4.93 (dd, *J* = 16.0, 7.9 Hz, 1H), 4.63-4.54 (m, 2H), 4.18-4.10 (m, 2H), 3.84 (d, *J* = 4.3 Hz, 1H), 3.65 (s, 1H), 3.13-2.95 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=171.9, 170.3, 156.5, 136.5, 136.1, 129.4, 128.5, 128.5, 128.1, 127.9, 126.9, 67.0, 62.7, 61.9, 56.2, 54.9, 38.6, 14.1; IR (film): 3306.51, 3032.82, 2935.37, 1663.81, 1534.58, 1452.39, 1376.02, 1339.12, 1256.47, 1300.52, 1053.70, 743.23, 699.12 cm^{-1}; HRMS (MALDI) Calcd for $C_{22}H_{26}N_2O_6Na^{+1}$ ($[M+Na]^+$): 437.1683. Found: 437.1683;

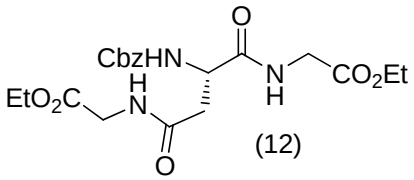
B3.17. Coupling of *N*-Cbz-L-phenylalanine *p*-toluene thiol ester with L-Cys–OEt to get (7q)



(7q)

Following the general procedure C, Phe-*p*-toluene thiol ester (200 mg, 0.493 mmol) was added to EtOH (2 mL) in a 10 mL, round-bottom flask. Stir until the thiol ester dissolved, then added BSA (100.3 mg, 0.493 mmol), Cys–OEt (147.1 mg, 0.986 mmol) in it. The mixture was heated at 40 ^{o}C for 36 h, then cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (15 mL) then washed successively with 1M aqueous HCl (4 mL), 2M aqueous NaOH (4 mL), brine (4 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated to dryness. The crude product was purified by flash chromatography (first use 25% ethyl acetate in petroleum ether, then use 10% MeOH in DCM wash the chromatography to get the product). The title compound was prepared as a solid 148.6 mg (70% yield). m.p. 120-122^{o}C. $[\alpha]_D^{20}$ +37.3 (c 0.159, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39-7.10 (m, 10H), 6.88 (dd, *J* = 64.5, 6.7 Hz, 1H), 5.45 (dd, *J* = 59.1, 8.0 Hz, 1H), 5.11-5.01 (m, 2H), 4.85-4.73 (m, 1H), 4.51 (dd, *J* = 34.1, 7.1 Hz, 1H), 4.25-4.10 (m, 2H), 3.21-2.85 (m, 4H), 2.32 (s, 1H), 1.25 (dd, *J* = 13.3, 7.0 Hz, 3H); ^{13}C NMR (101 MHz, CDCl3) δ = 170.8, 169.9, 155.9, 137.9, 136.3, 130.0, 129.3, 129.1, 128.6, 128.1, 127.1, 67.1, 62.1, 55.9, 53.8, 38.4, 26.7, 14.1; IR (film): 3299.10, 3032.01, 2928.81, 1736.27, 1663.16, 1535.27, 1450.95, 1374.04, 1254.29, 1209.80, 1113.53, 1034.06, 744.24, 699.27 cm^{-1}. HRMS (MALDI) Calcd for $C_{22}H_{26}N_2O_5SNa^{+1}$ ($[M+Na]^+$): 453.1455. Found: 453.1455.

B3.18. Coupling of *N*-Cbz-L-aspartic bis-*p*-toluene thiol ester with Gly–OEt to get (12) [16]



(12)

Following the general procedure C, N-Cbz-L-aspartic bis-*p*-toluene thiol ester (200 mg, 0.417 mmol) was added to EtOH (2 mL) in a 10 mL, round-bottom flask. Stir until the thiol ester dissolved, then added BSA (170 mg, 0.834 mmol), Gly–OEt (172 mg, 1.668 mmol) in it. The mixture was heated at 40 ^{o}C for 48 h, then cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (15 mL) then washed successively with 1M aqueous HCl (6 mL), 2M aqueous NaOH (6 mL), brine (6 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated to dryness. The crude product was purified by flash chromatography (first use 25% ethyl acetate in petroleum ether, then use 10% MeOH in DCM wash the chromatography to get the product). The title compound was prepared as a solid 150 mg (82% yield). m.p. 142-144^{o}C; $[\alpha]_D^{20}$ +8.9 (c 0.105, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35 (t, *J* = 5.9 Hz, 5H), 6.65 (s, 1H), 6.39 (d, *J* = 7.4 Hz, 1H), 5.71 (d, *J* = 7.4 Hz, 1H), 5.12 (d, *J* = 7.0 Hz, 2H), 4.61 (s, 1H), 4.26-3.85 (m, 8H), 3.05-2.59 (m, 2H), 1.31-1.23 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.3, 171.0, 169.8, 169.6, 156.2, 136.1, 128.5, 128.2, 128.1, 67.2, 61.7, 61.5, 51.6, 41.5, 41.5, 37.6, 14.1, 14.1. HRMS (ESI) Calcd for: $C_{20}H_{27}N_3NaO_8^{+1}$ ($[M+Na]^+$): 460.1690. Found: 460.1692.

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C. HPLC Spectra

The useless peaks were not integrated.

C1. Investigate the existence of racemization.

C1.1. *N*-Cbz-Phe-STol react with Gly-OEt to get the *N*-Cbz-Phe-Gly-OEt(7a)

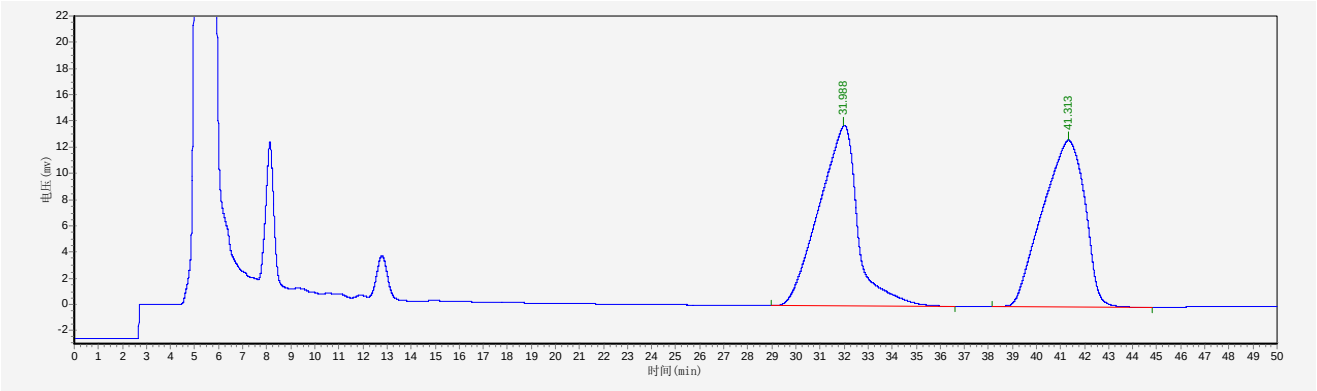
HPLC conditions:

Equipment: SPD-10A, VP, Plus, SHIMADZU. Column temperature：room temperature. Flow rate：0.650 mL/min. Mobile phase：*n*-hexane：*i*-propanol = 85:15. UV detection：230 nm. Column：CHIRAL PAK AD-H, 4.6mm I.D. ×250mm, 5μm.

Sample processing：

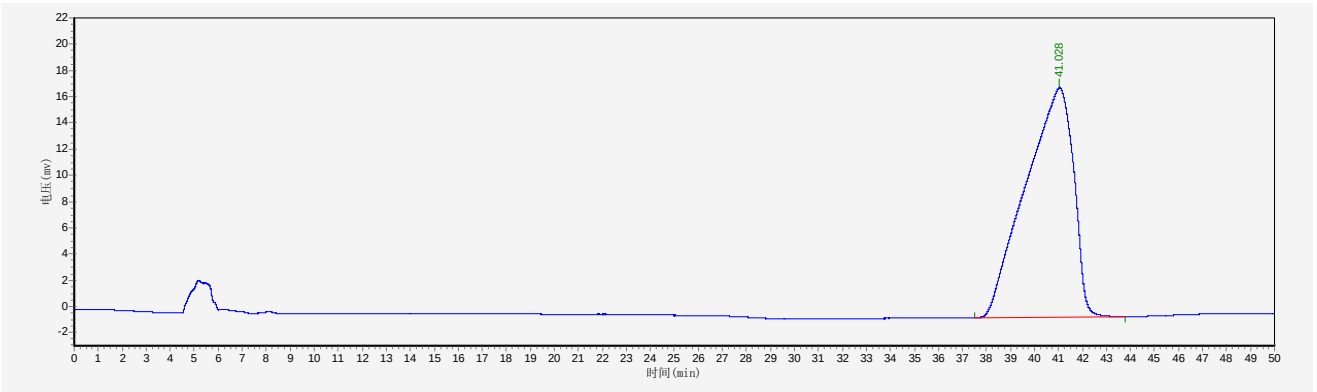
After the reaction finished, the solvent was evaporated under reduced pressure, and the residue purified by flash chromatography (silica gel, 25% ethyl acetate in petroleum ether and 10% MeOH in DCM). After removal of the solvents, the product was dissolved in *i*-propanol, filtered through microporous membrane, and finally injected into the HPLC.

C1.1.1. *N*-Cbz-(D,L)-Phe-Gly-OEt, HPLC spectra:



Peak	Ret. Time (min)	Height (mV)	Area (μV*s)	Area (%)
1	31.988	13.768	1545274.875	49.92
2	41.313	12.692	1550409.000	50.08

C1.1.2. N-Cbz-L-Phe-Gly-OEt, HPLC spectra:



Peak	Ret. Time (min)	Height (mV)	Area (μV*s)	Area (%)
1	41.028	17.502	2423128.750	100

C1.2. *N*-Cbz-Gly-STol react with Phe-OMe to get the *N*-Cbz-Gly-Phe -OMe(7c)

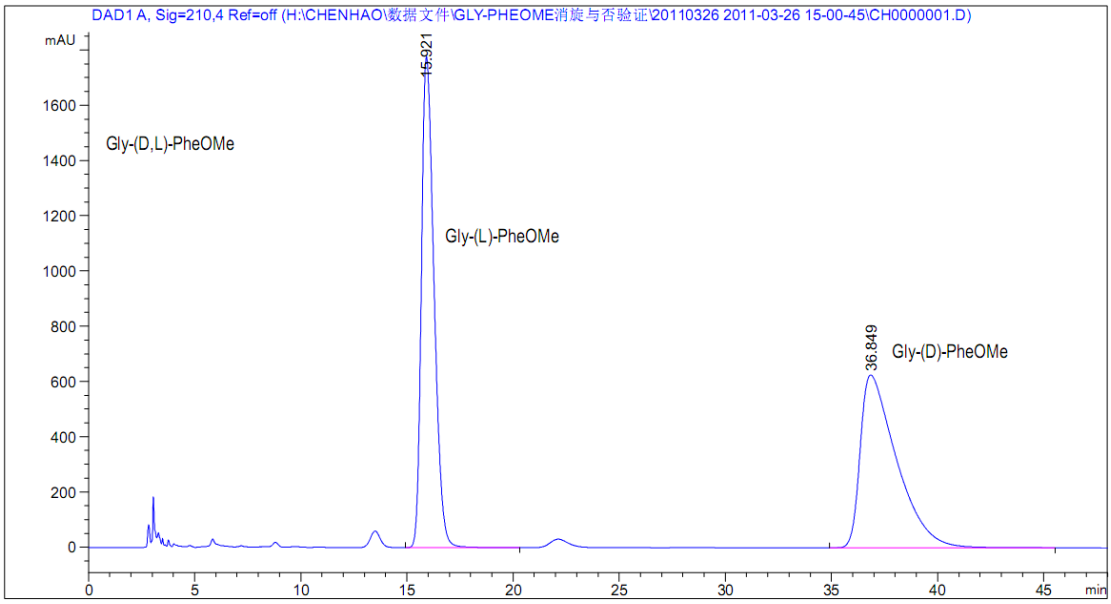
HPLC conditions:

Equipment: Agilent Technologies(1260 Infinity). Column temperature：room temperature. Flow rate：1.0 mL/min. Mobile phase：*n*-hexane：*i*-propanol = 60:40. UV detection：210 nm. Column：Lux 3u Cellulose-2, 250×4.60mm.

Sample processing：

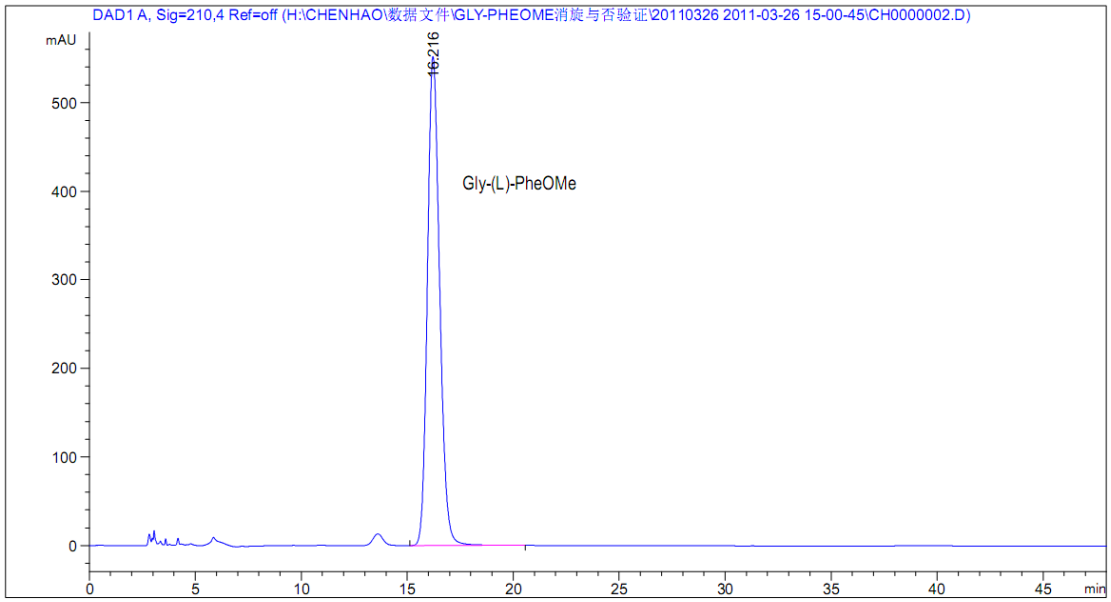
After the reaction finished, the solvent was evaporated under reduced pressure, and the residue purified by flash chromatography (silica gel, 25% ethyl acetate in petroleum ether and 10% MeOH in DCM). After removal of the solvents, the product was dissolved in *i*-propanol, filtered through microporous membrane, and finally injected into the HPLC.

C1.2.1. N-Cbz-Gly-(D,L)-Phe-OMe, HPLC spectra:



Peak	Ret. Time (min)	Height ((mAU)	Area ((mAU *s)	Area (%)
1	15.921	1777.00452	7.31054e4	49.5792
2	36.849	625.47485	7.43463e4	50.4208

C1.2.2. N-Cbz-Gly-(L)-Phe-OMe, HPLC spectra:



Peak	Ret. Time (min)	Height ((mAU)	Area ((mAU *s)	Area (%)
1	16.216	552.12628	2.20933e4	100

C1.3. *N*-Ac-Phe-STol react with Gly-OEt to get the *N*-Ac-Phe-Gly-OEt(7b)

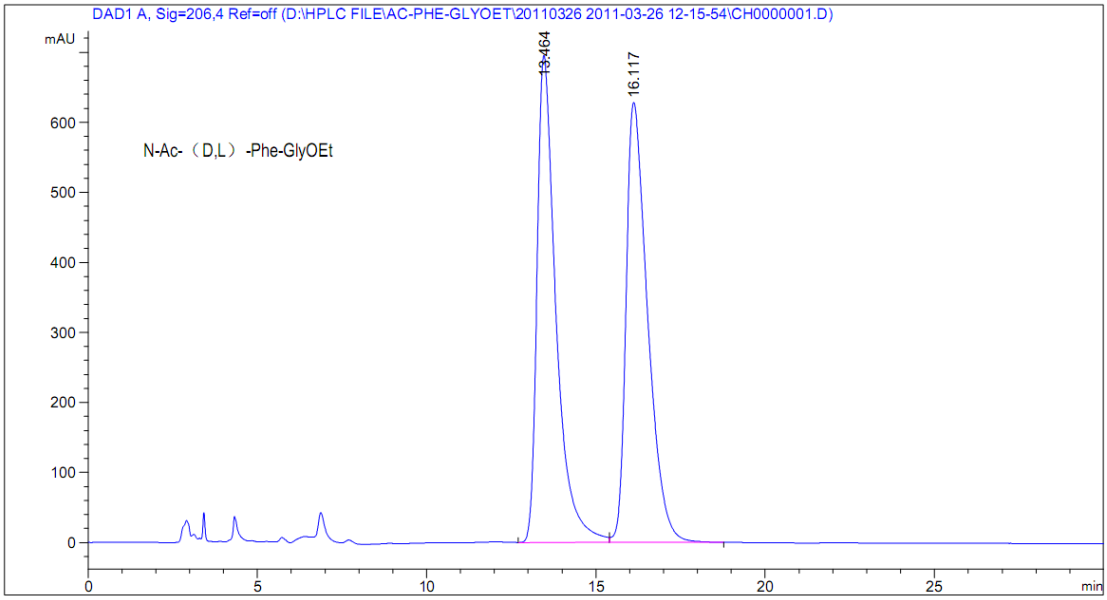
HPLC conditions:

Equipment: Agilent Technologies(1260 Infinity). Column temperature：room temperature. Flow rate：1.0 mL/min. Mobile phase：*n*-hexane：*i*-propanol = 70:30. UV detection：206 nm. Column：Lux 3u Cellulose-2, 250×4.60mm.

Sample processing：

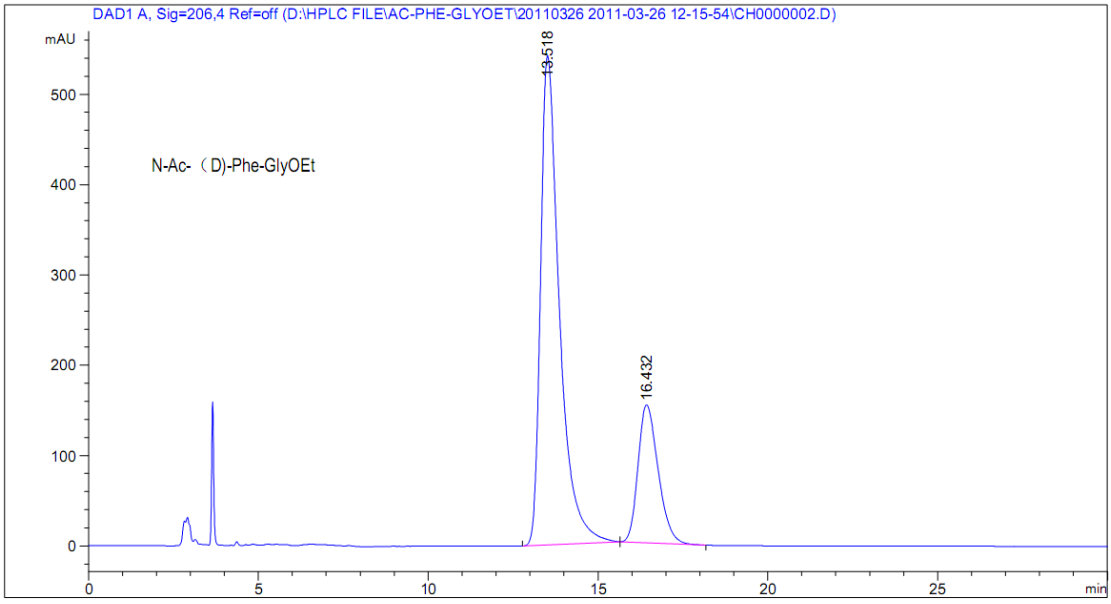
After the reaction finished, the solvent was evaporated under reduced pressure, and the residue purified by flash chromatography (silica gel, 50% ethyl acetate in petroleum ether and 10% MeOH in DCM). After removal of the solvents, the product was dissolved in *i*-propanol, filtered through microporous membrane, and finally injected into the HPLC.

C1.3.1. N-Ac-(D,L)-Phe-Gly-OEt, HPLC spectra:



Peak	Ret. Time (min)	Height (mAU)	Area ((mAU *s)	Area (%)
1	13.464	695.54041	2.69970e4	49.3010
2	16.117	628.43127	2.77625e4	50.6990

C1.3.2. N-Ac-(D)-Phe-Gly-OEt, HPLC spectra:



Peak	Ret. Time (min)	Height (mAU)	Area (mAU*s)	Area (%)
1	13.518	541.74762	2.08598e4	76.8303
2	16.432	152.69974	6290.67285	23.1697

C1.3.3. Start material *N*-Ac-Phe-STol, HPLC spectra：

HPLC conditions:

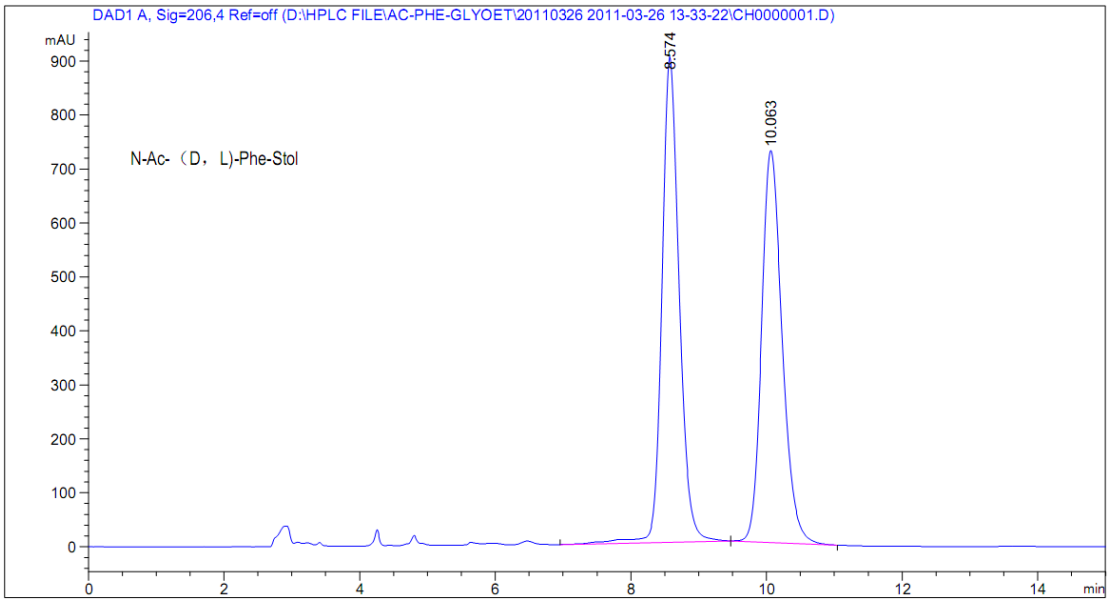
Equipment: Agilent Technologies(1260 Infinity). Column temperature: room temperature. Flow rate: 1.0 mL/min. Mobile phase：*n*-hexane: *i*-propanol = 80:20. UV detection: 206 nm.

Column: Lux 3u Cellulose-2.

Sample processing：

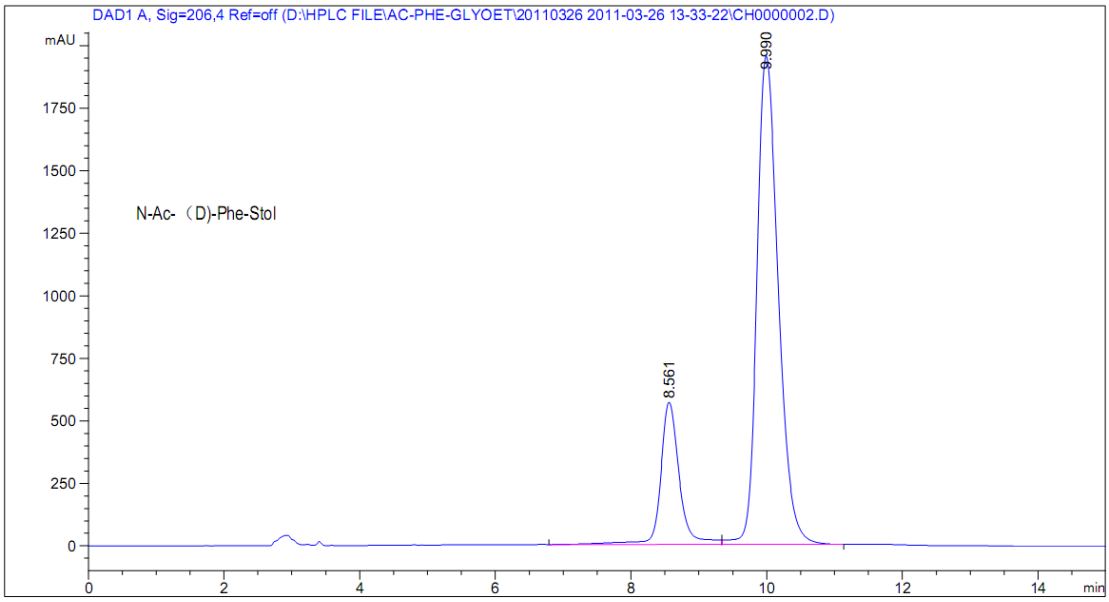
After the reaction finished, the mixture was filtered through Celite™. The filtrate was concentrated *in vacuo* to remove the dioxane, and then diluted with ethyl acetate, washed with $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The mixture was purified by flash chromatography to get the product. The product was dissolved in *i*-propanol, filtered through microporous membrane, and finally injected into the HPLC.

C1.3.3.1. *N*-Ac-(D, L)-Phe-STol, HPLC spectra：



Peak	Ret. Time (min)	Height (mAU)	Area ((mAU*s)	Area (%)
1	8.574	899.89282	1.59783e4	51.1049
2	10.063	726.38019	1.52873e4	48.8951

C1.3.3.2. *N*-Ac-(D)-Phe-STol, HPLC spectra：



Peak	Ret. Time (min)	Height (mAU)	Area (mAU*s)	Area (%)
1	8.561	568.82086	9485.23926	23.1355
2	9.990	1952.10535	3.15133e4	76.8645

C2. Investigate chemical kinetics

C2.1 Reaction use EtOH as the solvent

HPLC conditions:

Equipment: SPD-10A, VP, Plus, SHIMADZU. Column temperature: room temperature. Flow rate：0.650 mL/min. Mobile phase：*n*-hexane：*i*-propanol =70:30. UV detection：230nm. Column：CHIRAL PAK AD-H, 4.6mm I.D. ×250mm, 5μm.

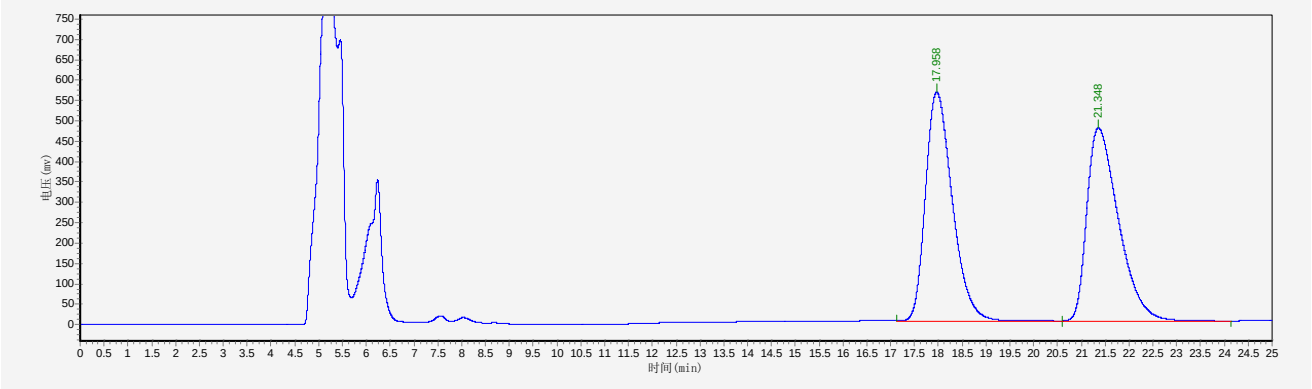
Sample processing：

a. The reaction solvent: In the reaction, the sample was collected at a certain time by injector. Then the sample was evaporated under reduced pressure. The residue was dissolved in *i*-propanol, filtered through microporous membrane, and finally injected into the HPLC.

b. Start material: Get 4mg start material, then dissolved in 1mL *i*-propanol, filtered by microporous membrane, and finally injected into the HPLC.

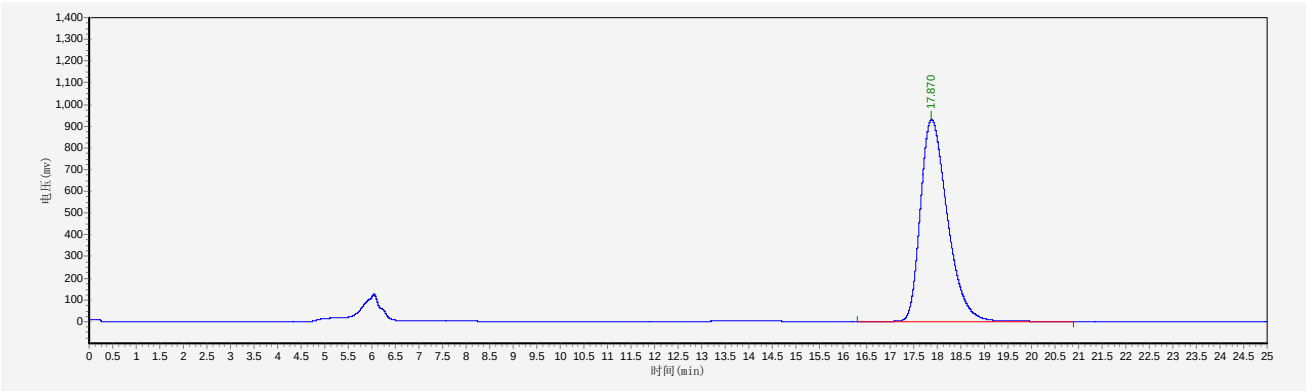
c. Product: Get 4mg product, then dissolved in 1mL *i*-propanol, filtered by microporous membrane, and finally injected into the HPLC.

C2.1.1. Start material: *N*-Cbz-(D,L)-phenylalanine *p*-toluene thiol ester



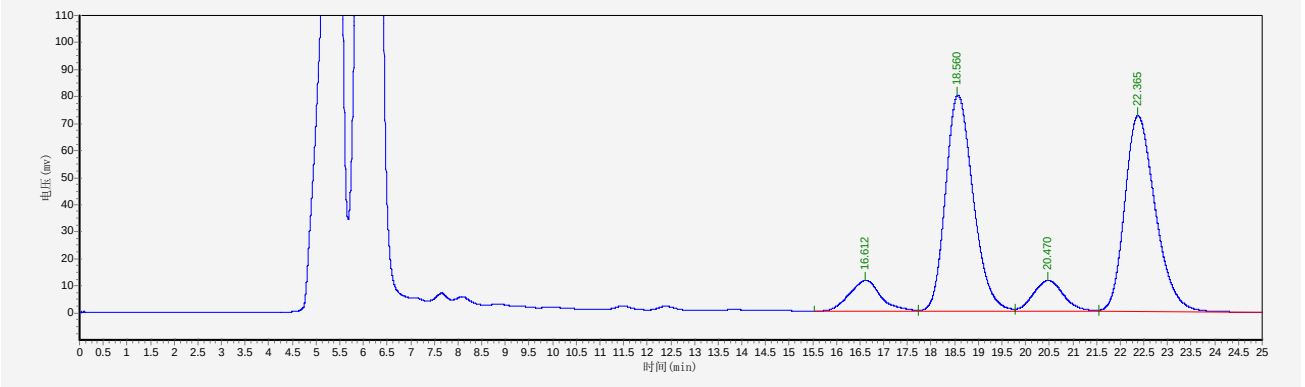
Peak	Ret. Time (min)	Height (mV)	Area (μV*s)	Area (%)
1	17.958	569.069	22960394.000	51.34
2	21.348	473.813	21759190.000	48.66

C2.1.2. Start material: *N*-Cbz-L-phenylalanine *p*-toluene thiol ester



Peak	Ret. Time (min)	Height (mV)	Area (μV*s)	Area (%)
1	17.870	930.470	36900280.000	100.00

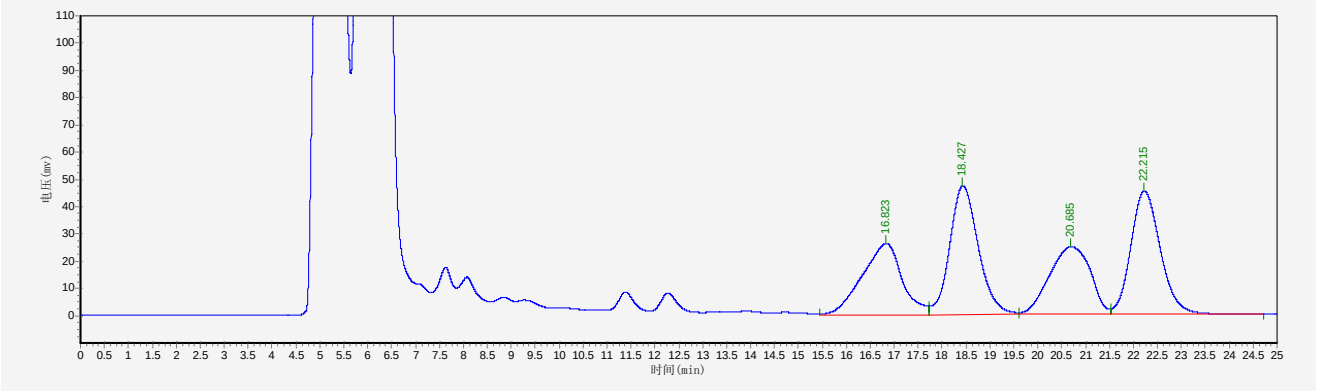
C2.1.3. *N*-Cbz-(D,L)-Phe-STol react with Gly–OEt for 1 h



Peak	Ret. Time (min)	Height (mV)	Area (μV*s)	Area (%)
1	16.612	11.361	528726.875	6.98
2	18.560	80.025	3259035.250	43.03

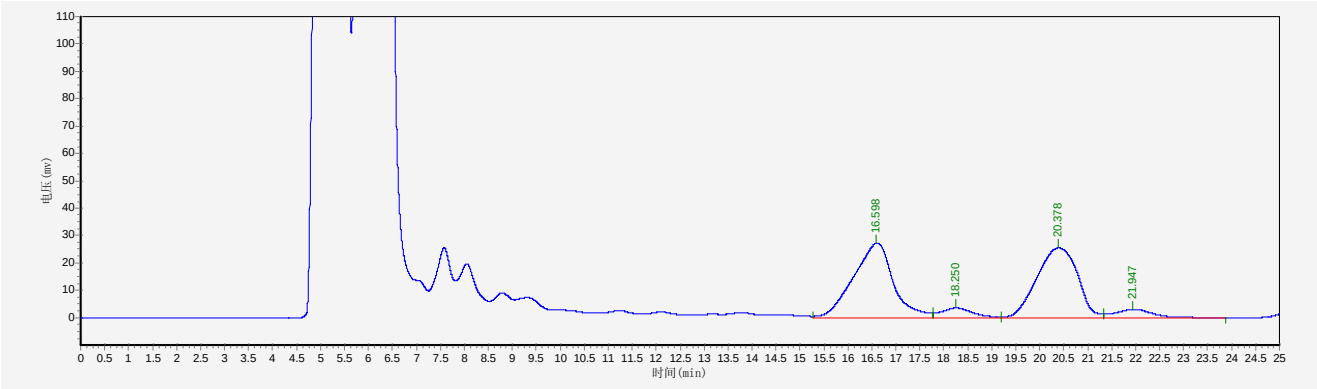
3	20.470	11.391	518382.063	6.85
4	22.365	72.555	3266930.000	43.14

C2.1.4. *N*-Cbz-(D,L)-Phe-STol react with Gly–OEt for 5 h



Peak	Ret. Time (min)	Height (mV)	Area (μV*s)	Area (%)
1	16.823	26.206	1520707.625	22.01
2	18.427	47.243	1964845.250	28.44
3	20.685	24.847	1474677.375	21.35
4	22.215	45.278	1947567.125	28.19

C2.1.5. *N*-Cbz-(D,L)-Phe-STol react with Gly–OEt for 18 h



Peak	Ret. Time (min)	Height (mV)	Area (μV*s)	Area (%)
1	16.598	27.579	1610442.125	45.73
2	18.250	3.777	182280.016	5.18
3	20.378	25.758	1532545.875	43.52
4	21.947	3.336	196408.359	5.58

C2.2 Reaction use NMP as the solvent

HPLC conditions:

Equipment: Agilent Technologies(1260 Infinity). Column temperature：room temperature. Flow rate：1.0 mL/min. Mobile phase：*n*-hexane：*i*-propanol = 70:30. UV detection：206 nm. Column：Lux 3u Cellulose-2, 250×4.60mm.

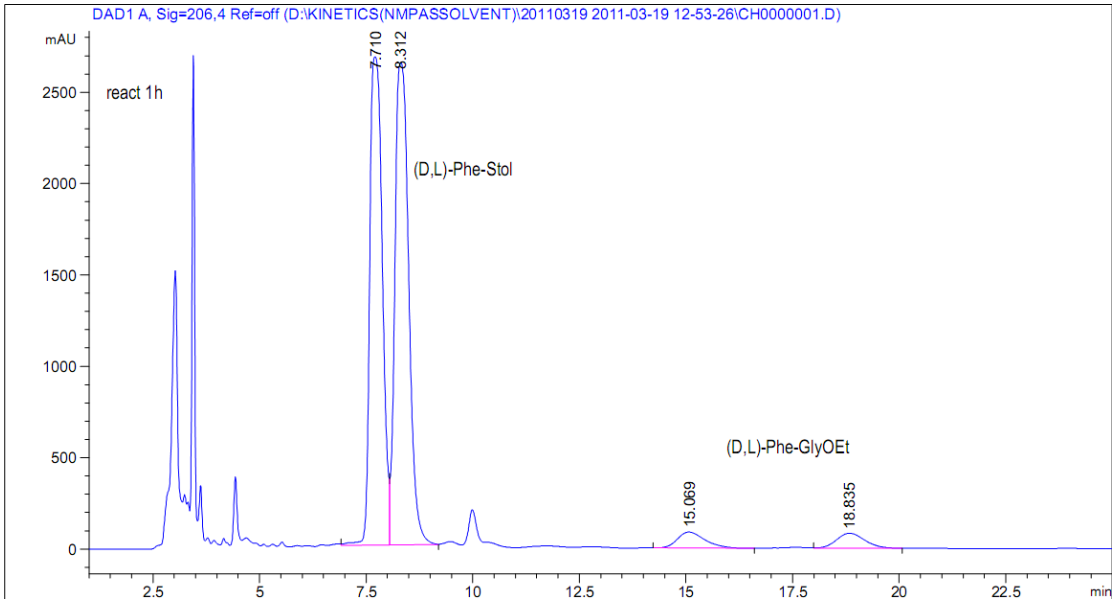
Sample processing：

a. The reaction solvent: The reaction solvent: In the reaction, the sample was collected at a certain time by injector. The sample was diluted with ethyl acetate, and washed with water, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was dissolved in *i*-propanol, filtered through microporous membrane, and finally injected into the HPLC.

b. Start material: Get 4mg start material, then dissolved in 1mL *i*-propanol, filtered by microporous membrane, and finally injected into the HPLC.

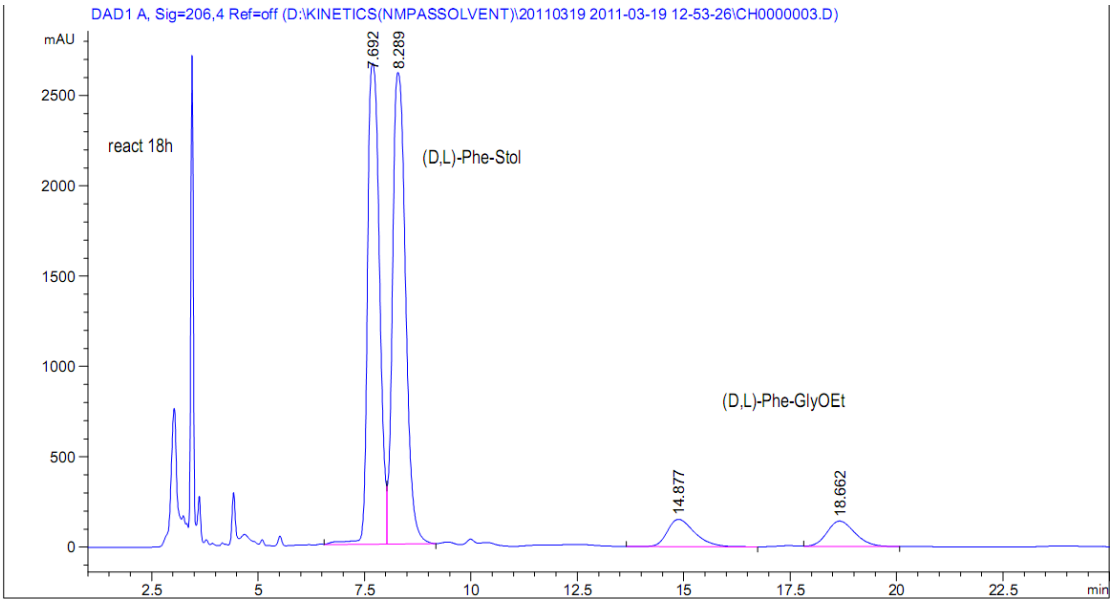
c. Product: Get 4mg product, then dissolved in 1mL *i*-propanol, filtered by microporous membrane, and finally injected into the HPLC.

C2.2.1. *N*-Cbz-(D,L)-Phe-Stol react with Gly-OEt for 1h



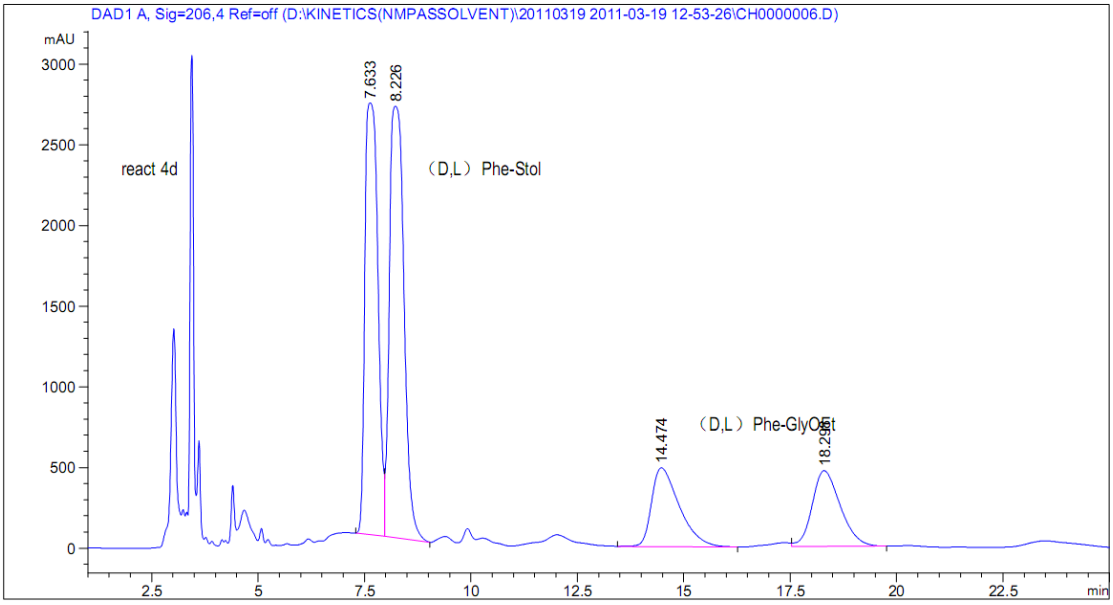
Peak	Ret. Time (min)	Height (mAU)	Area (mAU *s)	Area (%)
1	7.710	2672.16406	5.45662e4	44.7908
2	8.312	2640.55078	5.95345e4	48.8691
3	15.069	87.83057	3935.59253	3.2305
4	18.835	82.64775	3788.08545	3.1095

C2.2.2. *N*-Cbz-(D,L)-Phe-Stol react with Gly-OEt for 18h



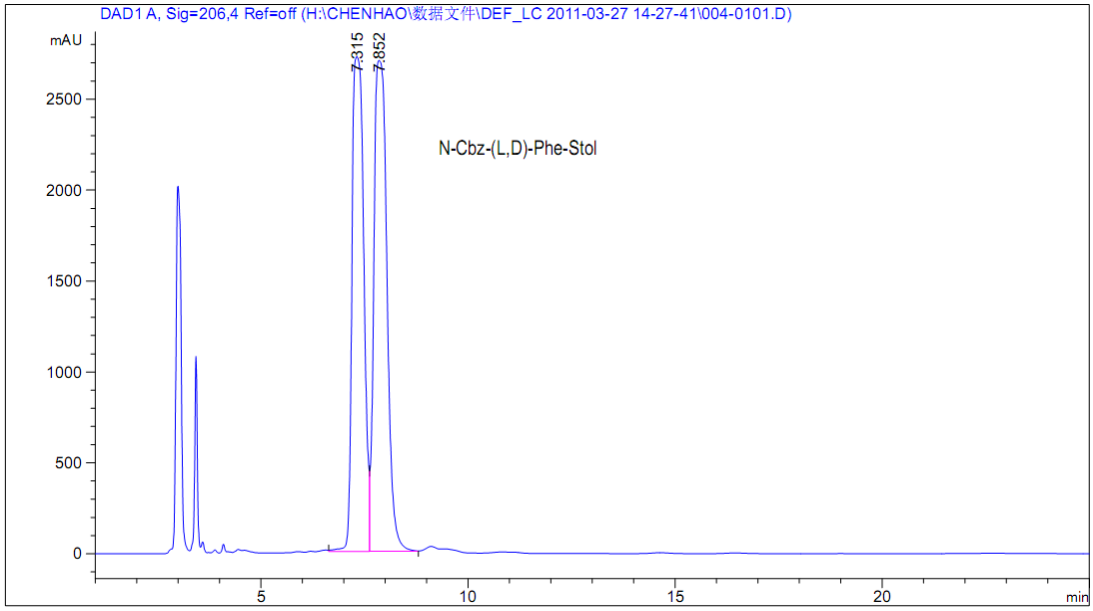
Peak	Ret. Time (min)	Height (mAU)	Area (mAU *s)	Area (%)
1	7.692	2661.97876	5.18226e4	42.9379
2	8.289	2610.66870	5.55978e4	46.0659
3	14.877	151.53903	6766.75879	5.6066
4	18.662	141.79852	6504.79199	5.3896

C2.2.3. *N*-Cbz-(D,L)-Phe-Stol react with Gly-OEt for 4d



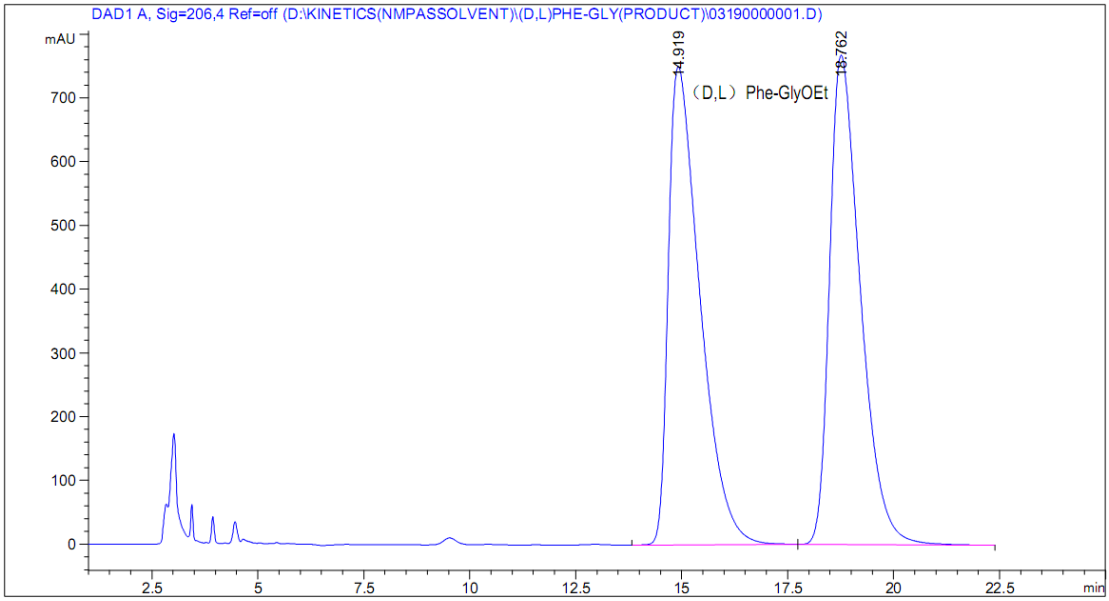
Peak	Ret. Time (min)	Height (mAU)	Area (mAU *s)	Area (%)
1	7.633	2675.54614	5.68328e4	34.5679
2	8.226	2674.62061	6.39087e4	38.8718
3	14.474	487.56213	2.20132e4	13.3893
4	18.298	469.85529	2.16544e4	13.1711

C2.2.4. The start material N-Cbz-(D,L)-Phe-STol:



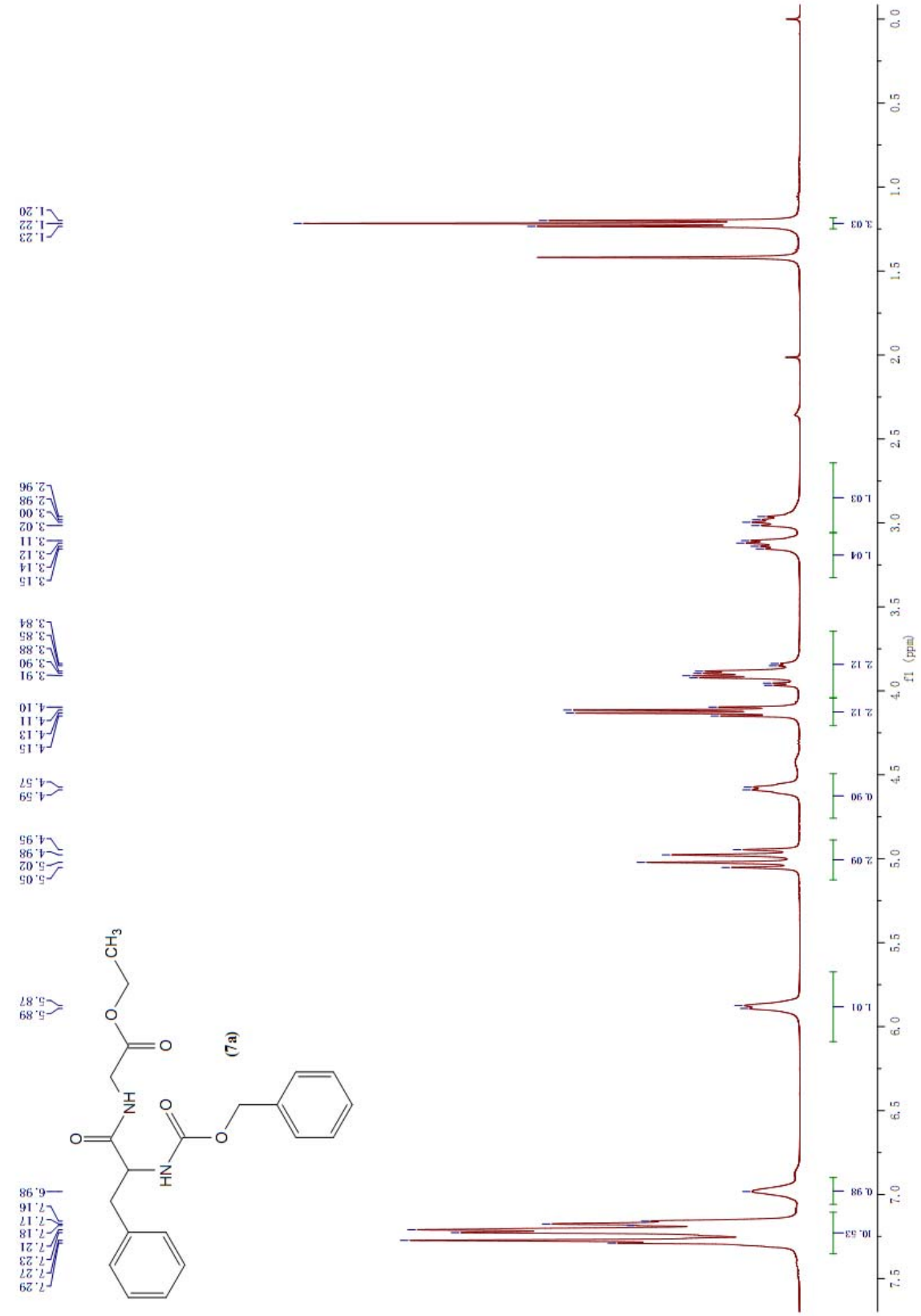
Peak	Ret. Time (min)	Height ((mAU)	Area ((mAU *s)	Area (%)
1	7.315	2721.65137	5.36457e4	47.5559
2	7.852	2700.37158	5.91599e4	52.4441

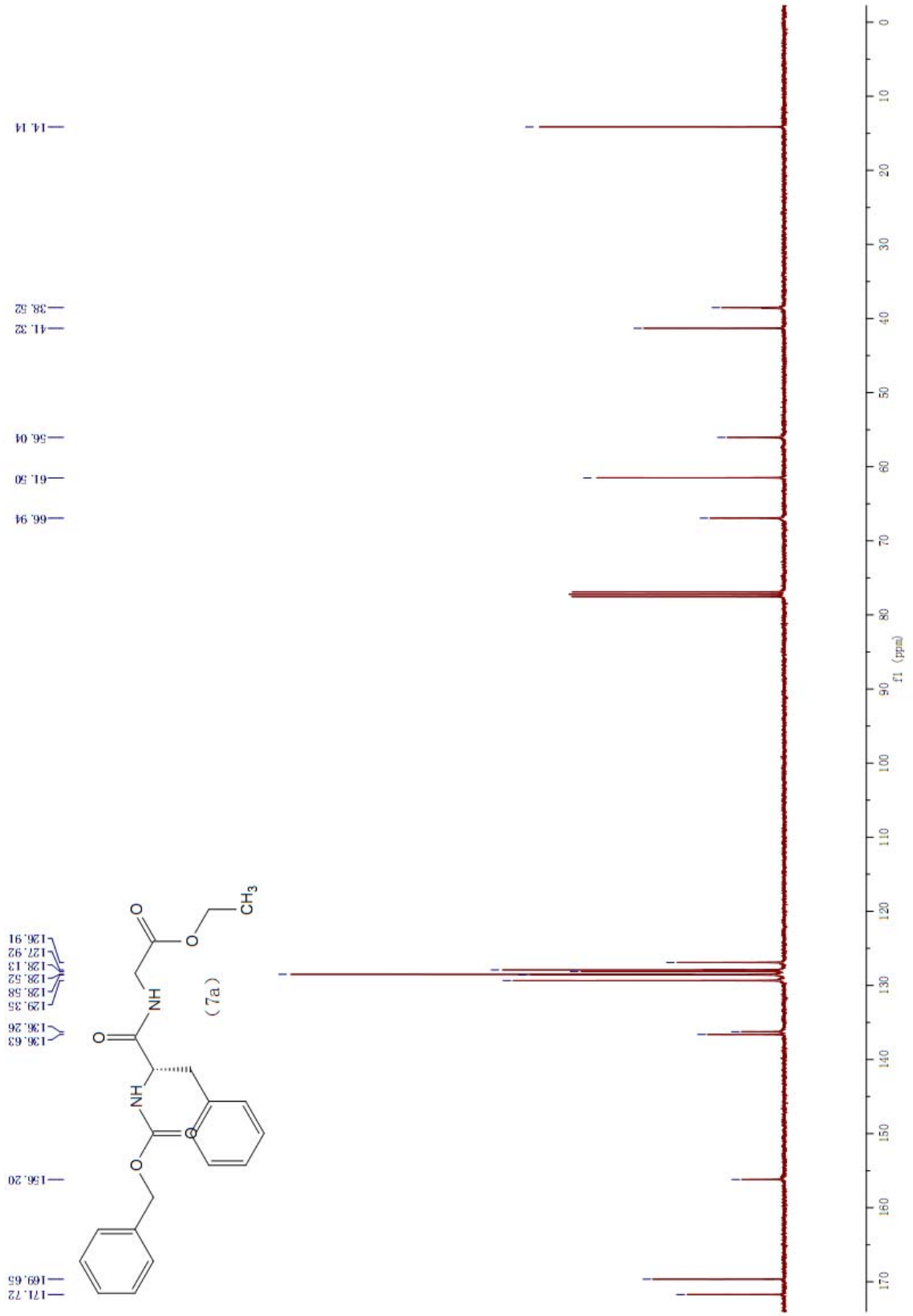
C2.2.5. The product N-Cbz-(D,L)-Phe-Gly-OMe:



Peak	Ret. Time (min)	Height ((mAU)	Area ((mAU *s)	Area (%)
1	14.919	750.08289	3.88838e4	50.0411
2	18.762	767.60815	3.88199e4	49.9589

D. NMR spectra

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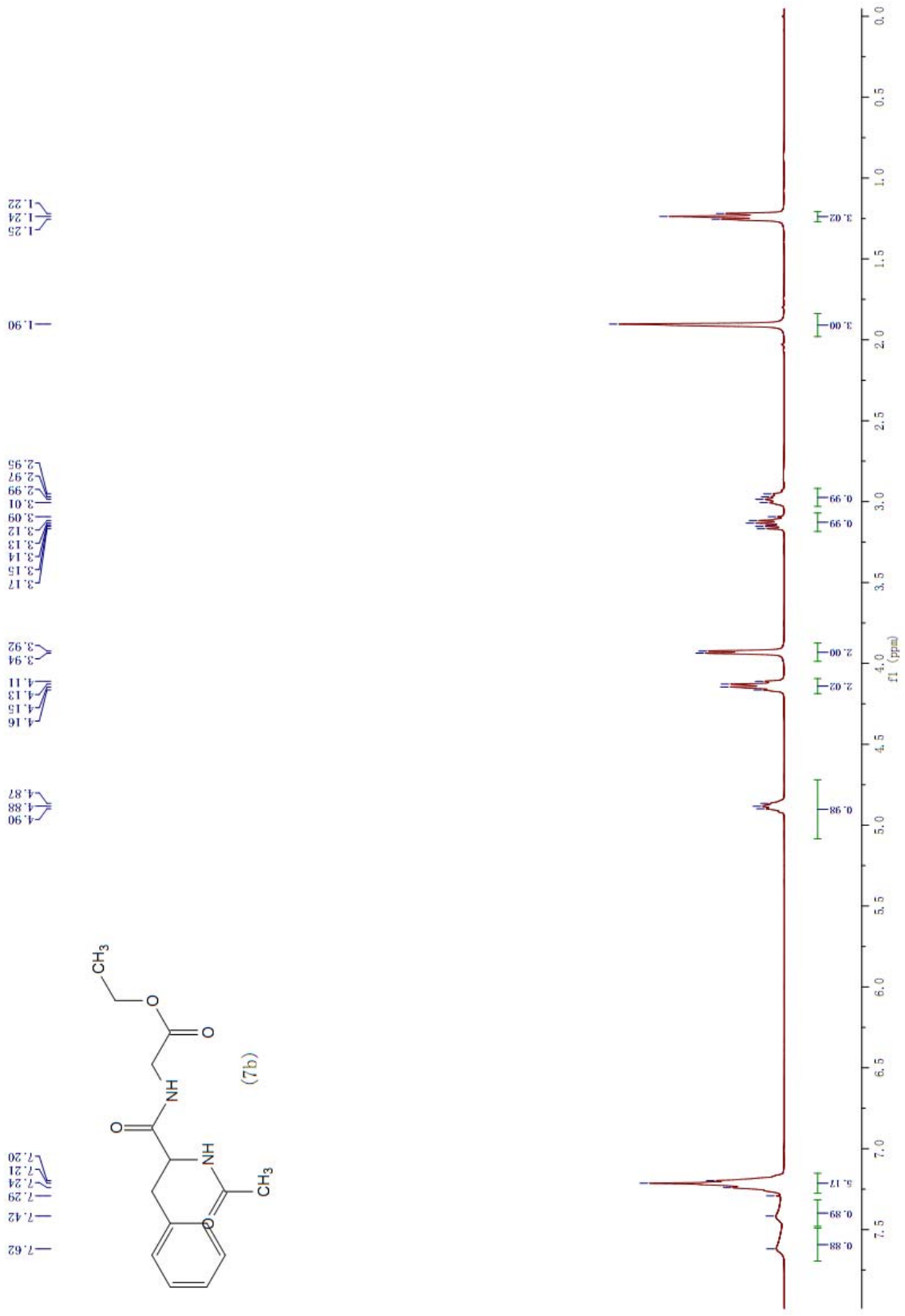
38.52
41.32
56.04
61.50
66.94
136.91
127.92
128.13
128.52
128.58
129.35
136.26
136.63
156.20
169.65
171.72
(7a)
f1 (ppm)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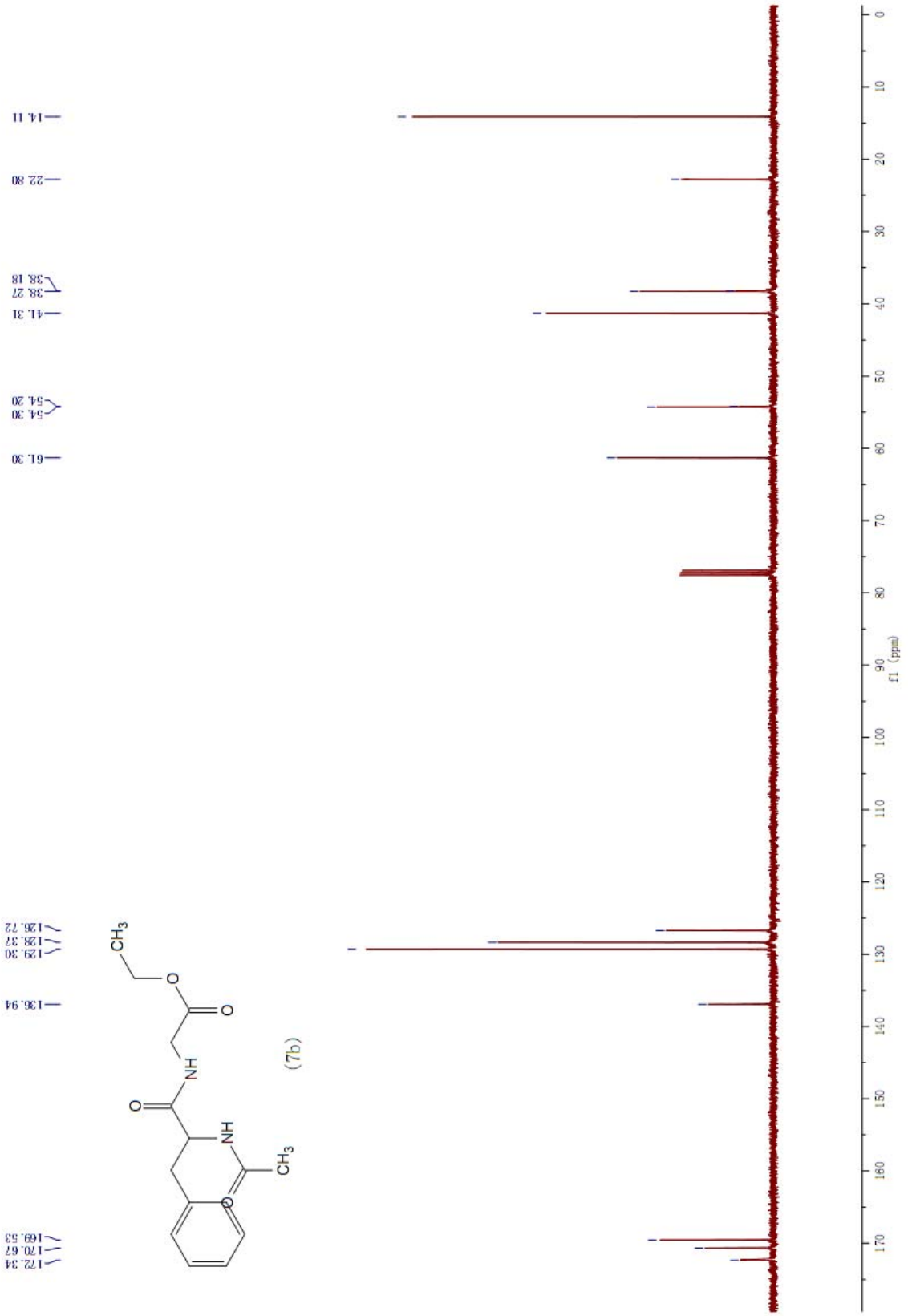
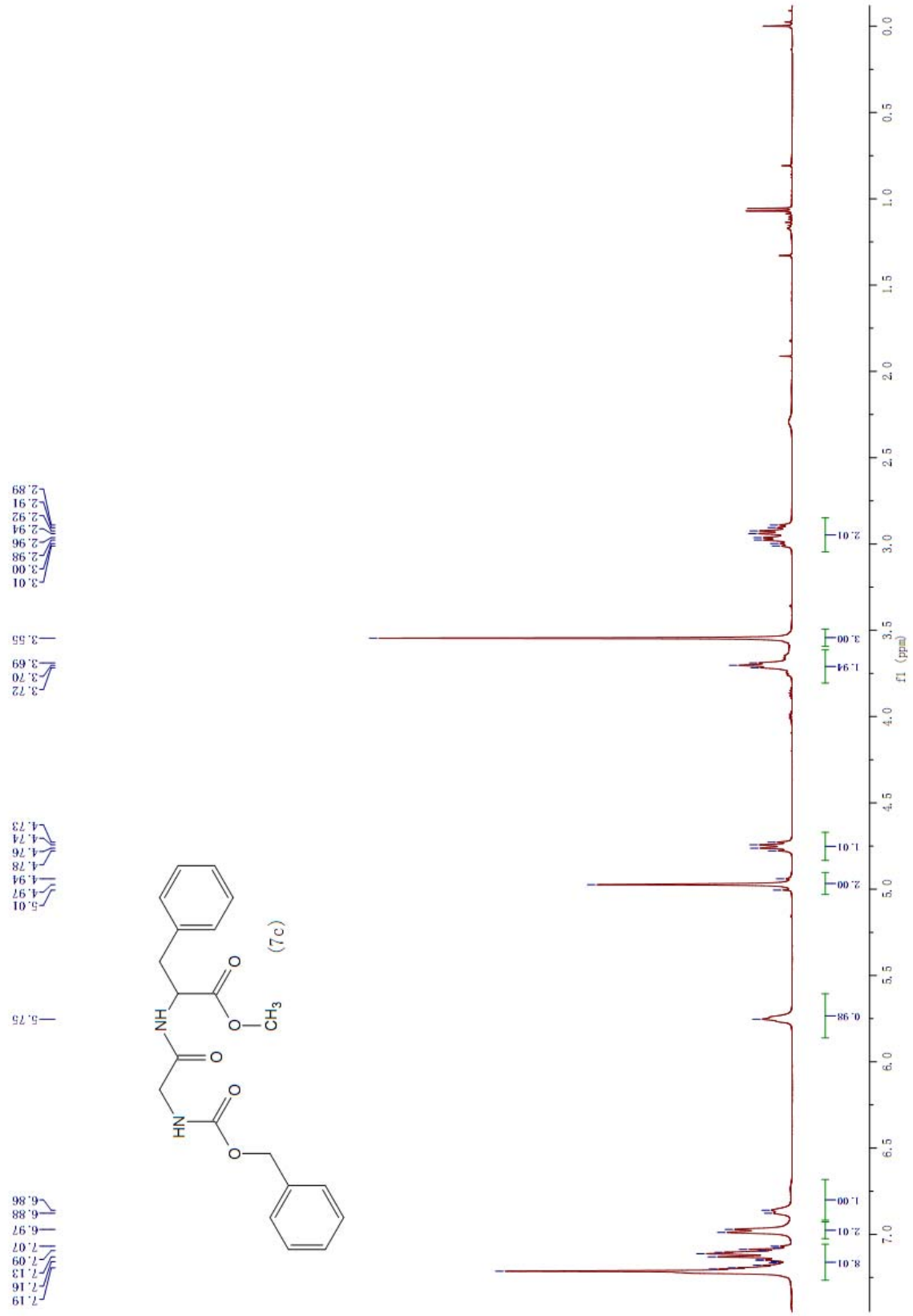
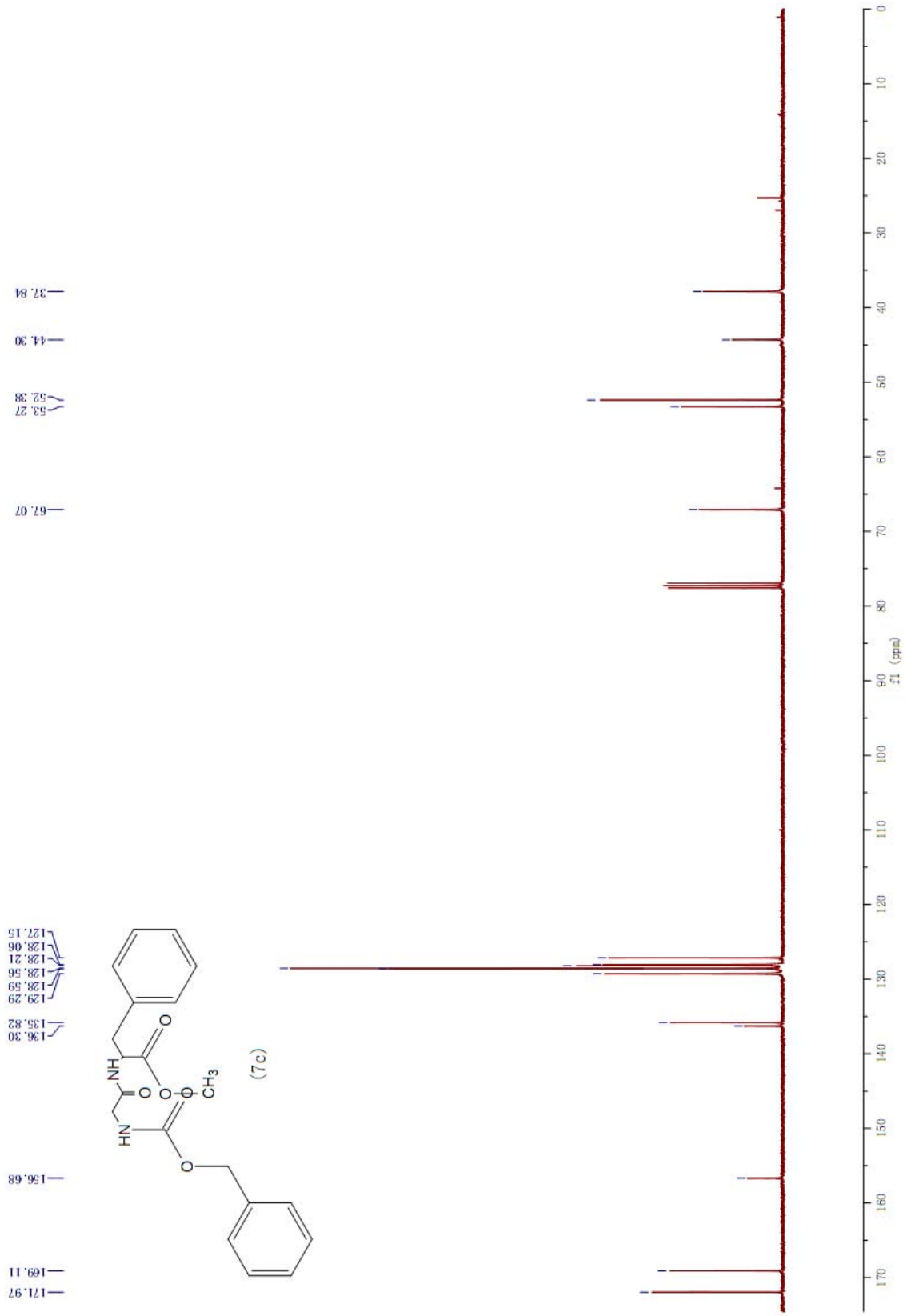
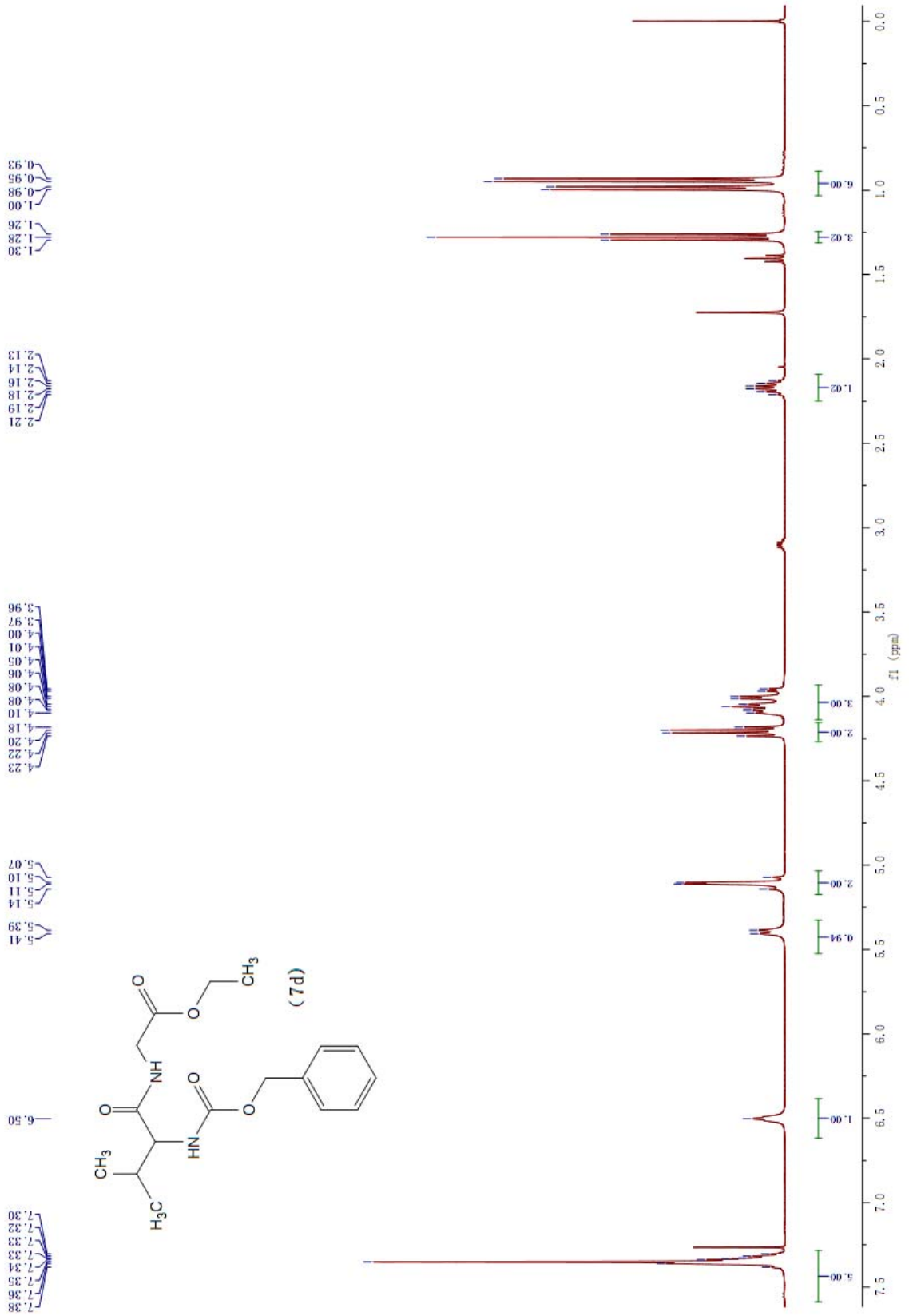
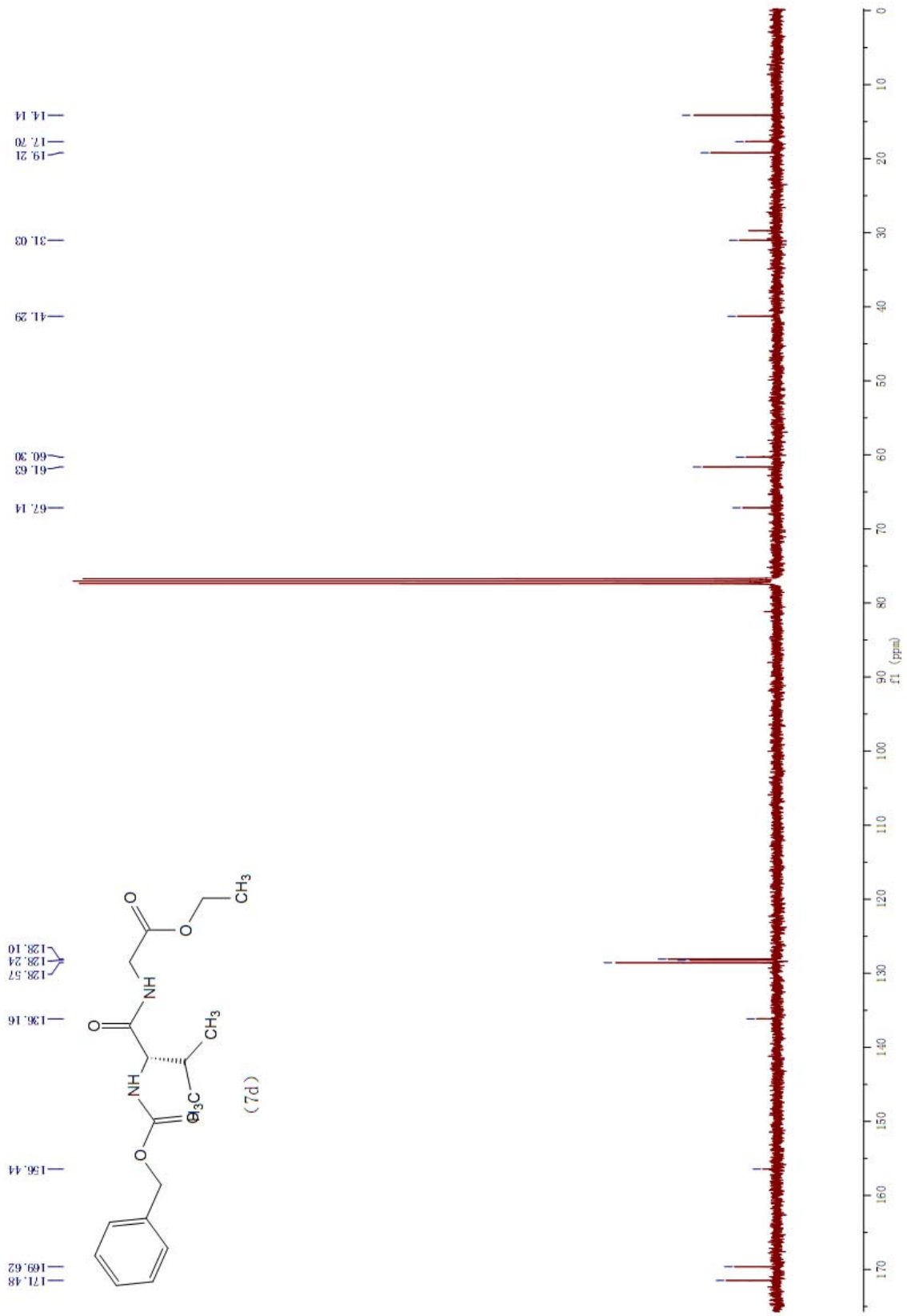
1.24
1.25
1.90
2.95
2.97
2.99
3.01
3.09
3.12
3.13
3.14
3.15
3.17
3.92
3.94
4.11
4.13
4.15
4.16
4.87
4.88
4.90
7.20
7.21
7.24
7.29
7.42
7.62
CH3
O
O
NH
O
NH
CH3
O
(7b)
3.02
3.00
0.99
0.99
2.00
2.02
0.98
5.17
0.89
0.88
f1 (ppm)

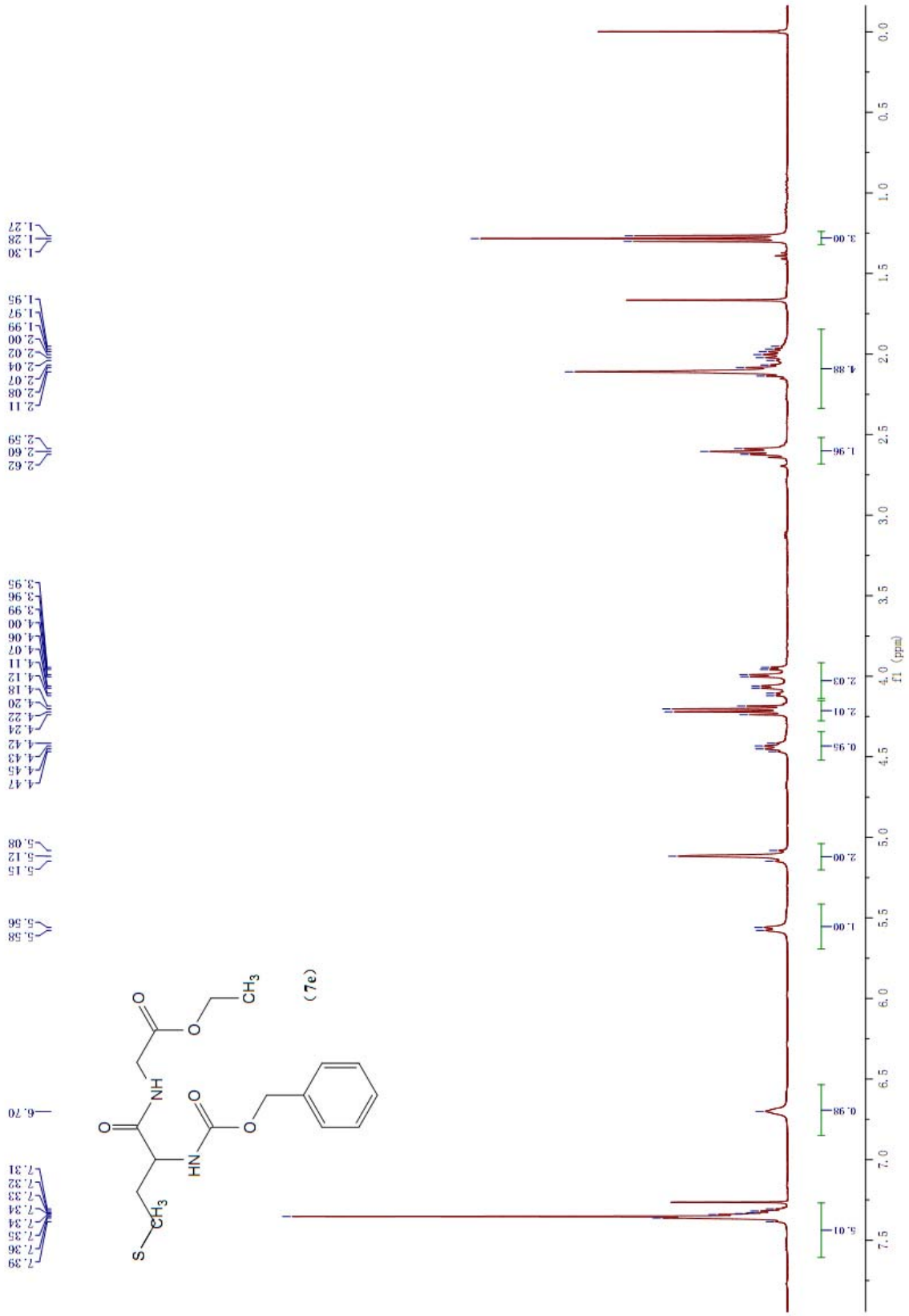

14.11
22.80
38.18
38.27
41.31
54.20
54.30
61.30
136.72
128.37
129.30
136.94
169.53
170.67
172.34
CH3
O
O
NH
O
NH
CH3
O
(7b)
f1 (ppm)

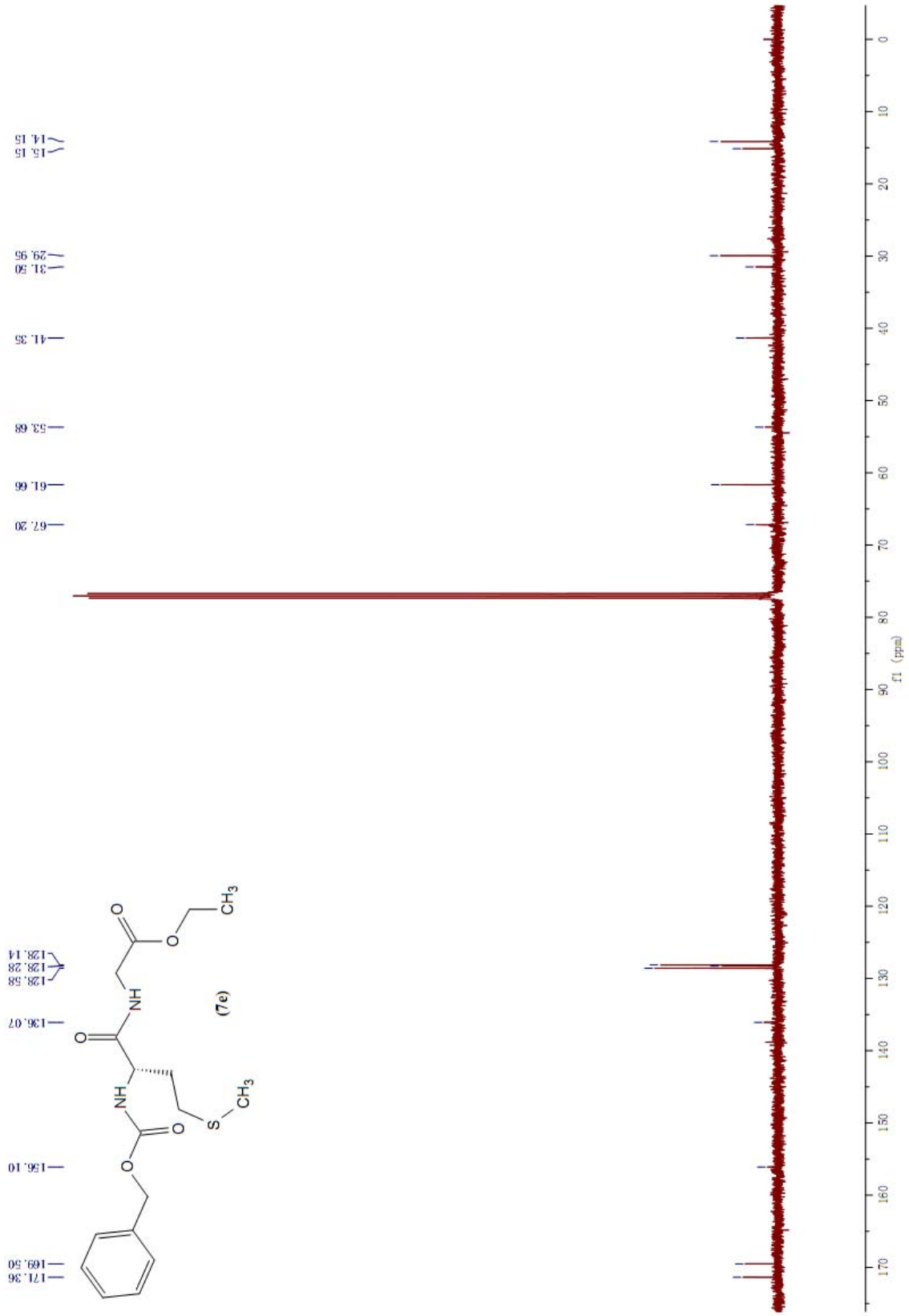

(7c)
f1 (ppm)

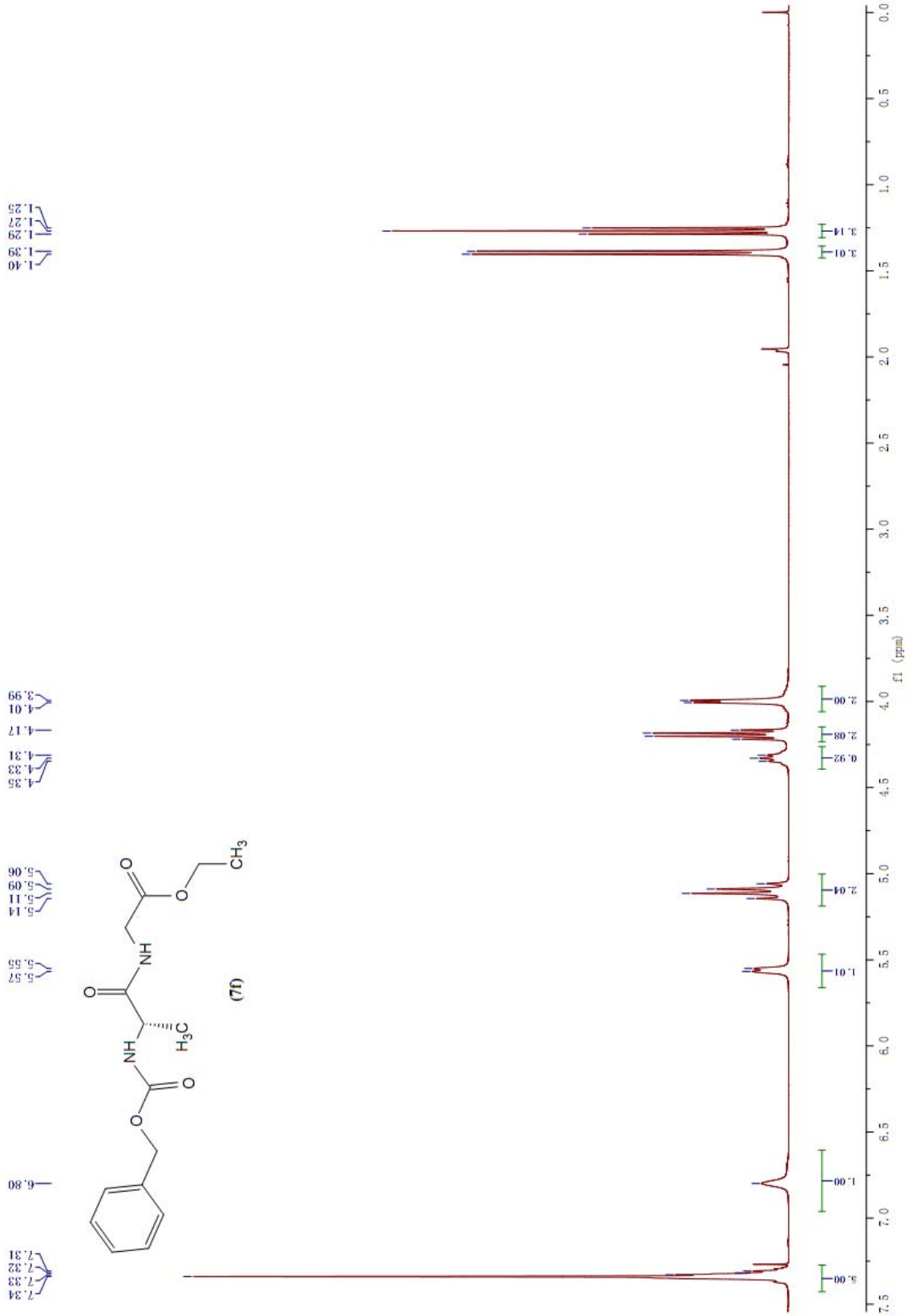

171.97
169.11
156.68
136.30
135.82
129.29
128.59
128.56
128.21
128.06
127.15
67.07
53.27
52.38
44.30
37.84
(7c)
f1 (ppm)


(7d)
f1 (ppm)


14.14
17.70
19.21
31.03
41.29
60.30
61.63
67.14
128.10
128.24
128.57
136.16
156.44
169.62
171.48
(7d)
f1 (ppm)


(7e)
f1 (ppm)


14.15
15.15
29.95
31.50
41.35
53.68
61.66
67.20
128.14
128.28
128.58
136.07
156.10
169.50
171.36
(7e)
f1 (ppm)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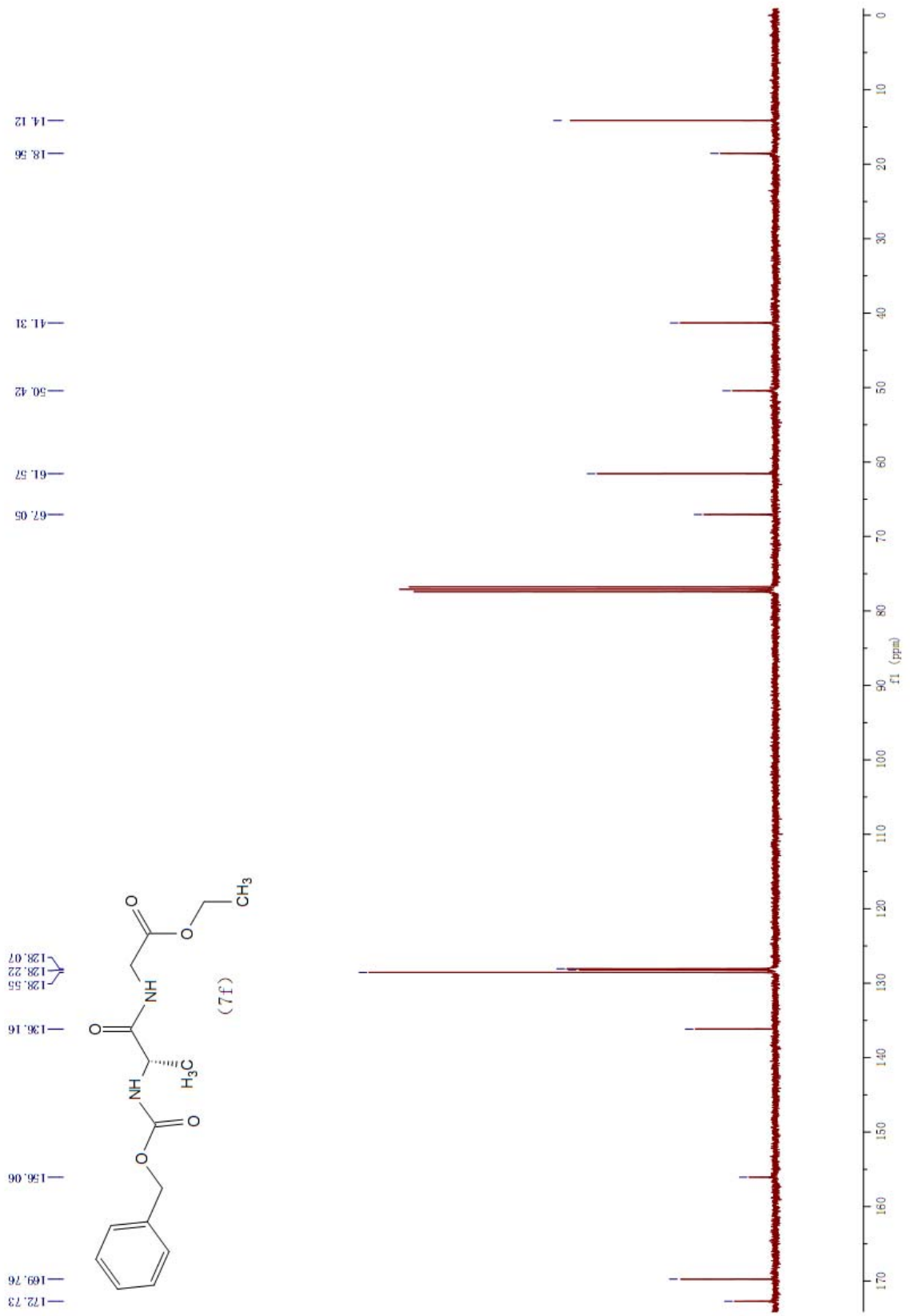
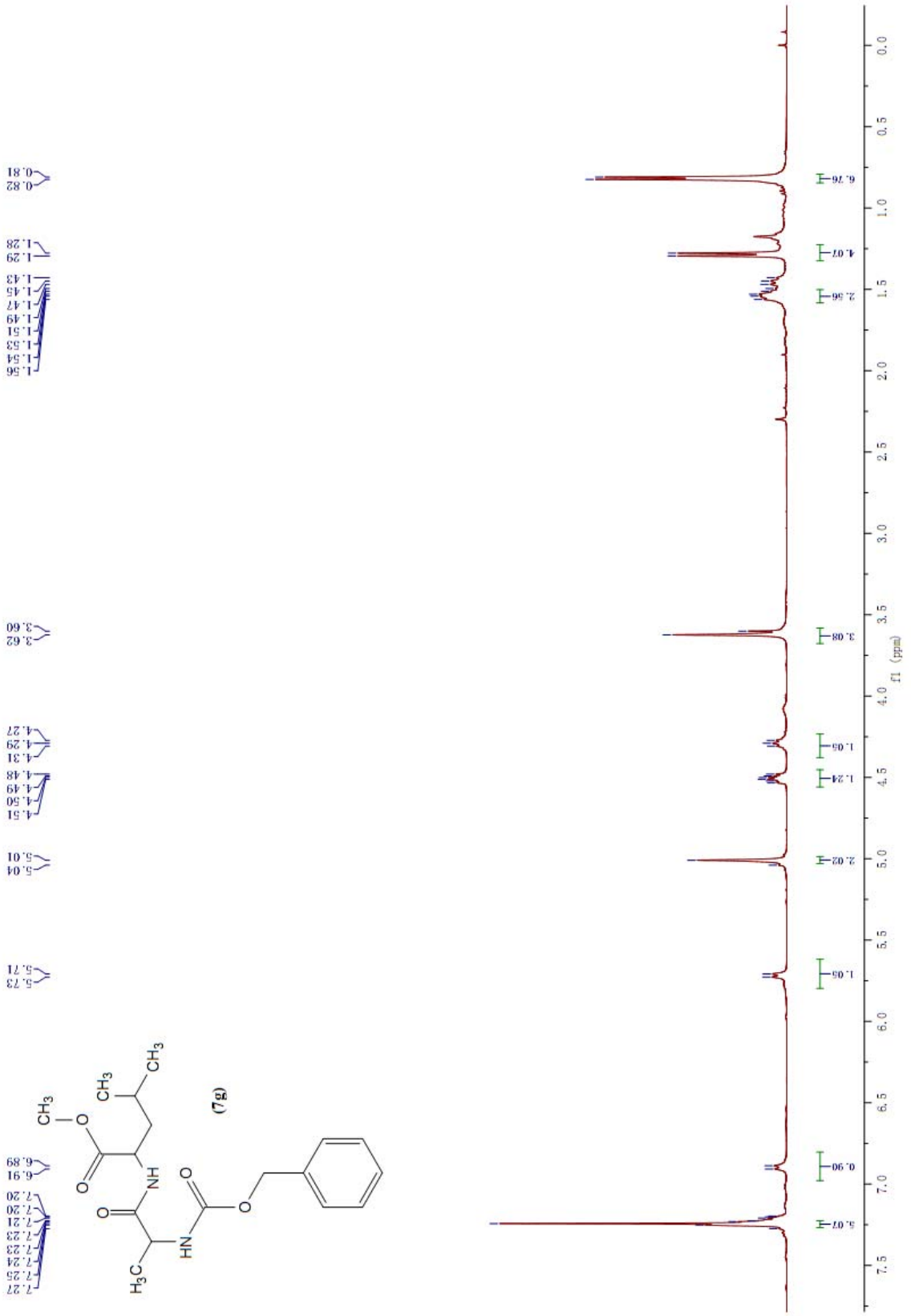
1.27
1.29
1.39
1.40
3.99
4.01
4.17
4.31
4.33
4.35
5.06
5.09
5.11
5.14
5.55
5.57
6.80
7.31
7.32
7.33
7.34
3.14
3.01
2.00
2.08
0.92
2.04
1.01
1.00
5.00
f1 (ppm)
(7f)


14.12
18.56
41.31
50.42
61.57
67.05
128.07
128.22
128.55
136.16
156.06
169.76
172.73
(7f)
f1 (ppm)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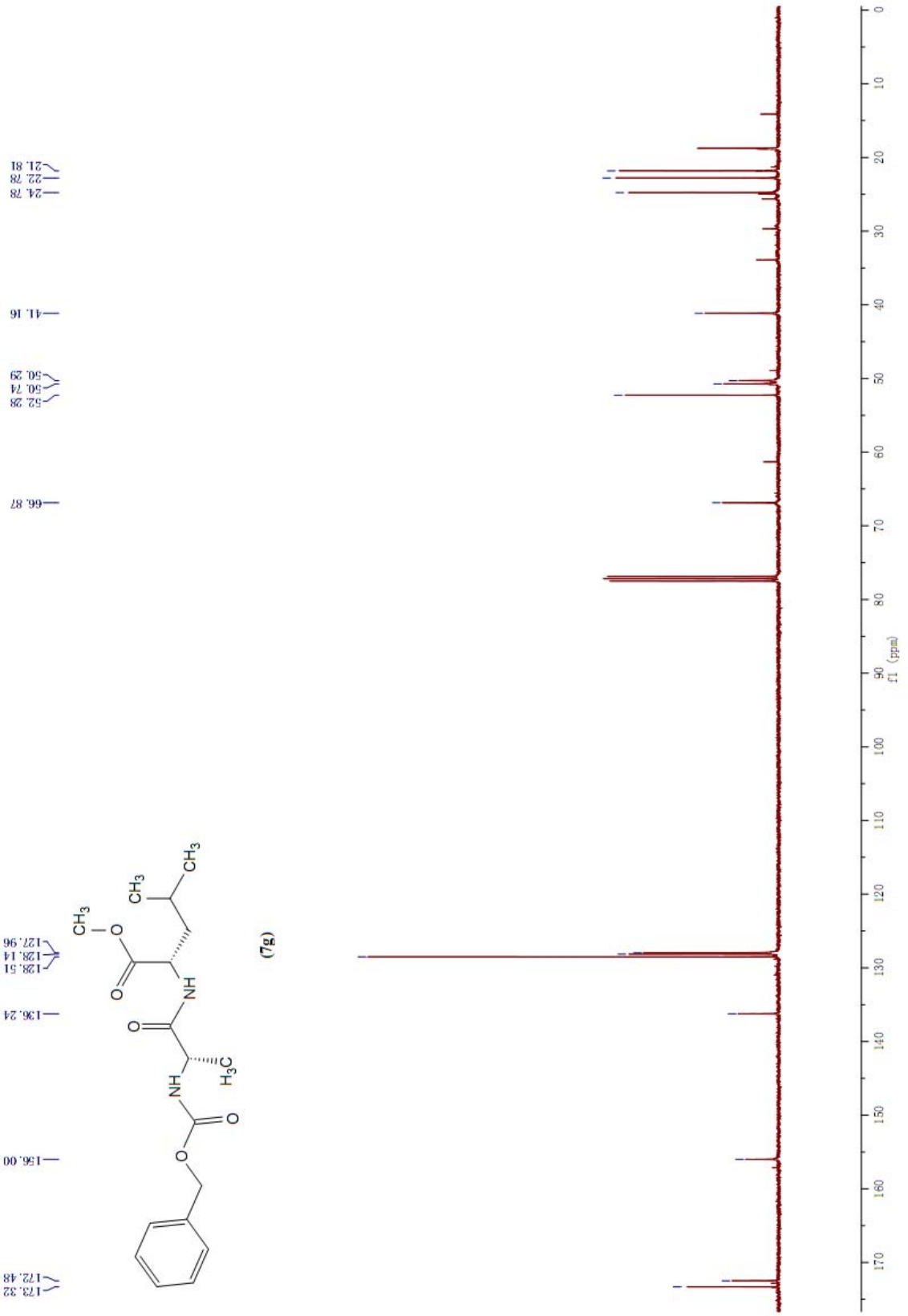
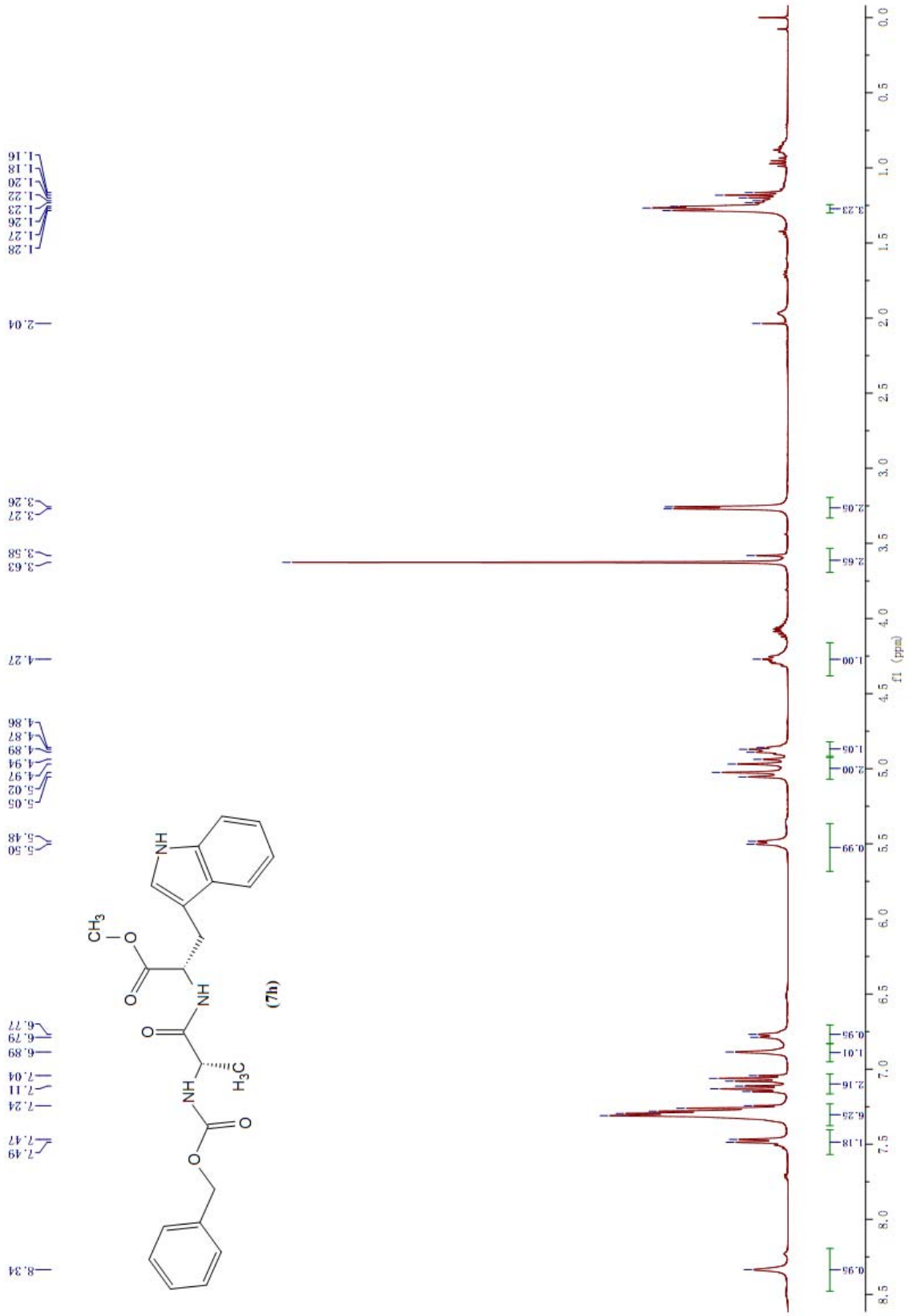
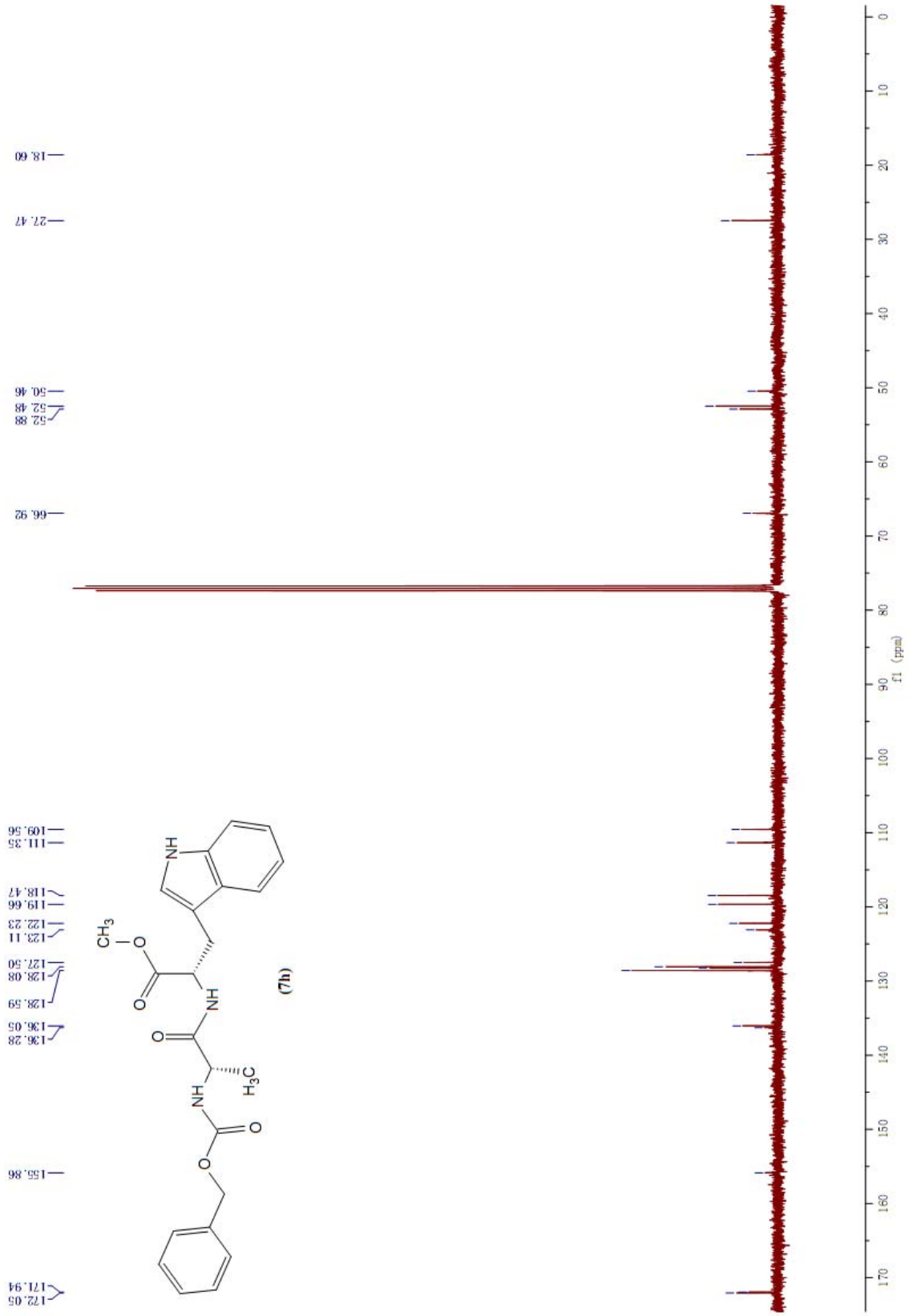
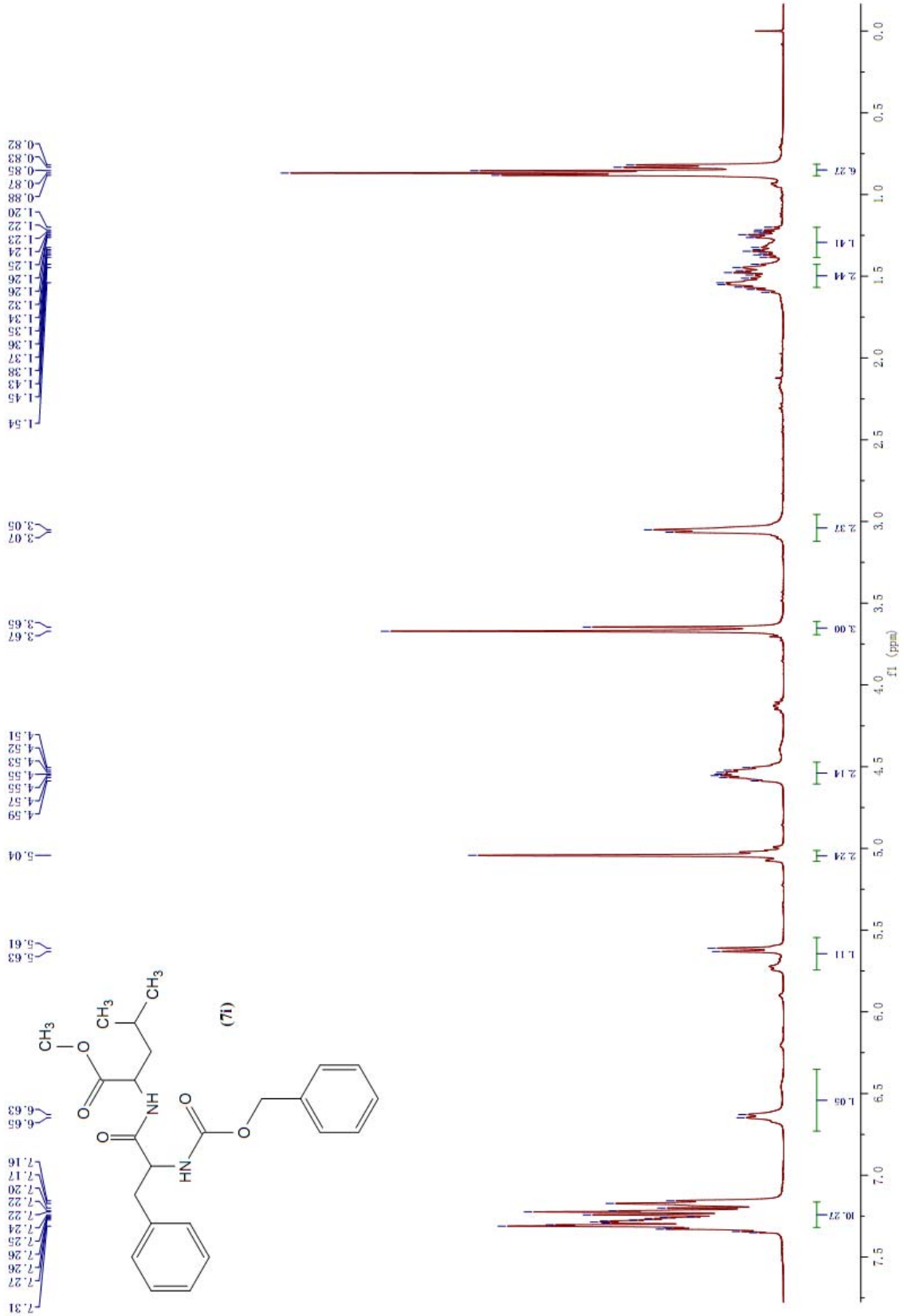
0.82
1.28
1.29
1.43
1.45
1.47
1.49
1.51
1.53
1.54
1.56
3.60
3.62
4.27
4.29
4.31
4.48
4.49
4.50
4.51
5.01
5.04
5.71
5.73
6.89
6.91
7.20
7.20
7.21
7.23
7.23
7.24
7.25
7.27
CH3
O
O
CH3
CH3
NH
O
HN
O
O
H3C
(7g)
6.76
4.07
2.56
3.08
1.09
1.24
2.02
1.08
0.90
5.07
f1 (ppm)

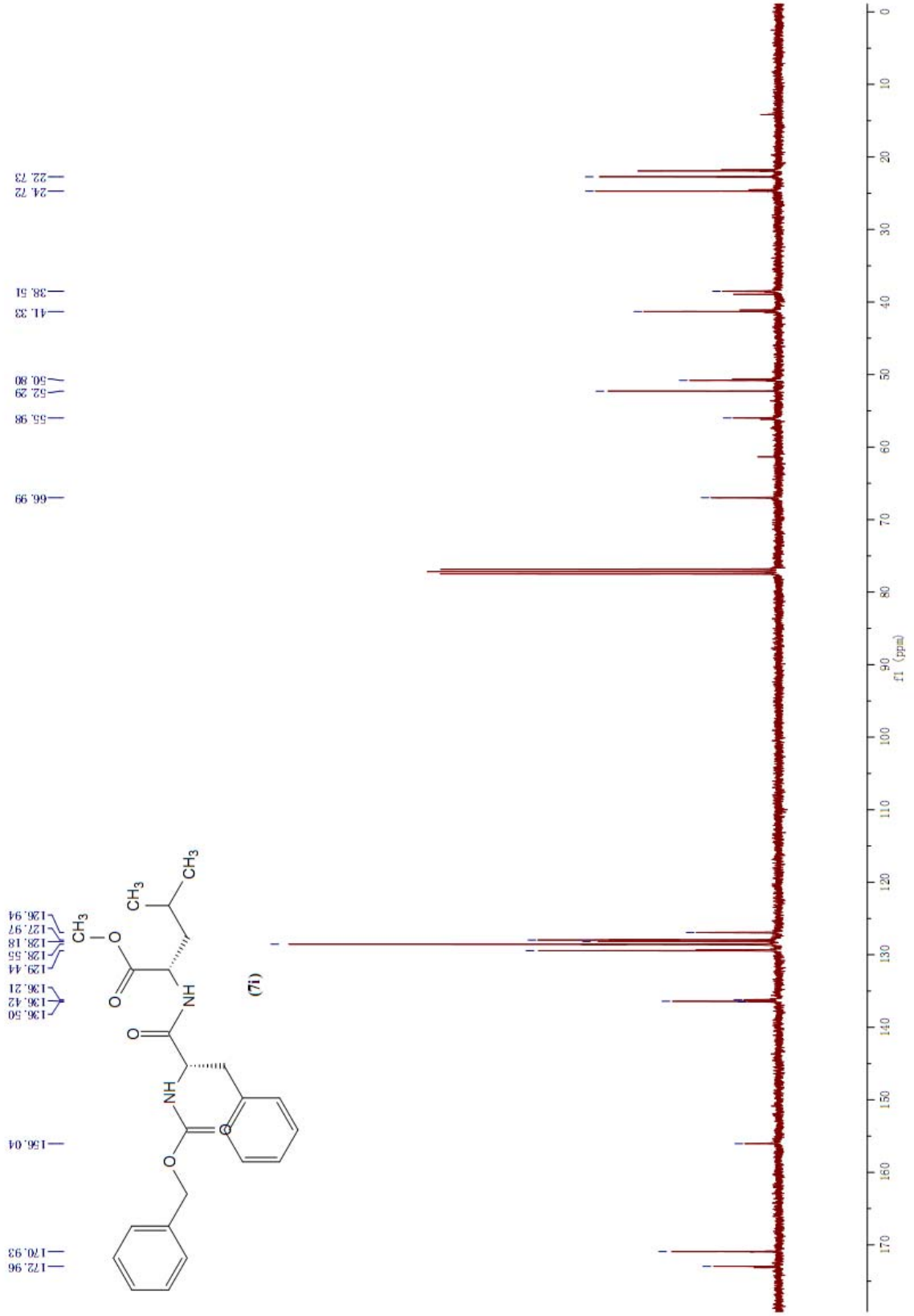

21.81
22.78
24.78
41.16
50.29
50.74
52.28
66.87
127.96
128.14
128.51
136.24
156.00
172.48
173.32
f1 (ppm)

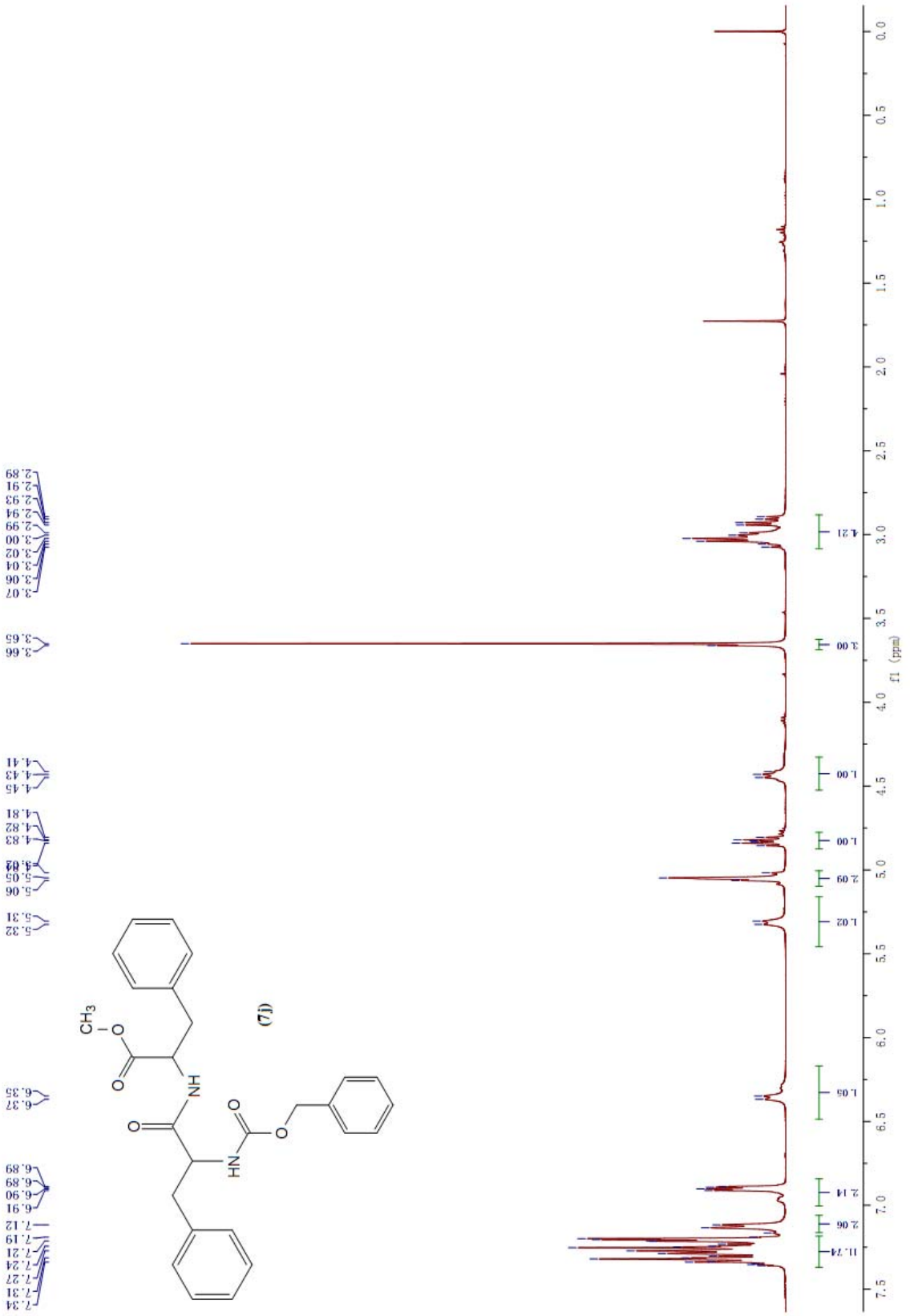
(7g)

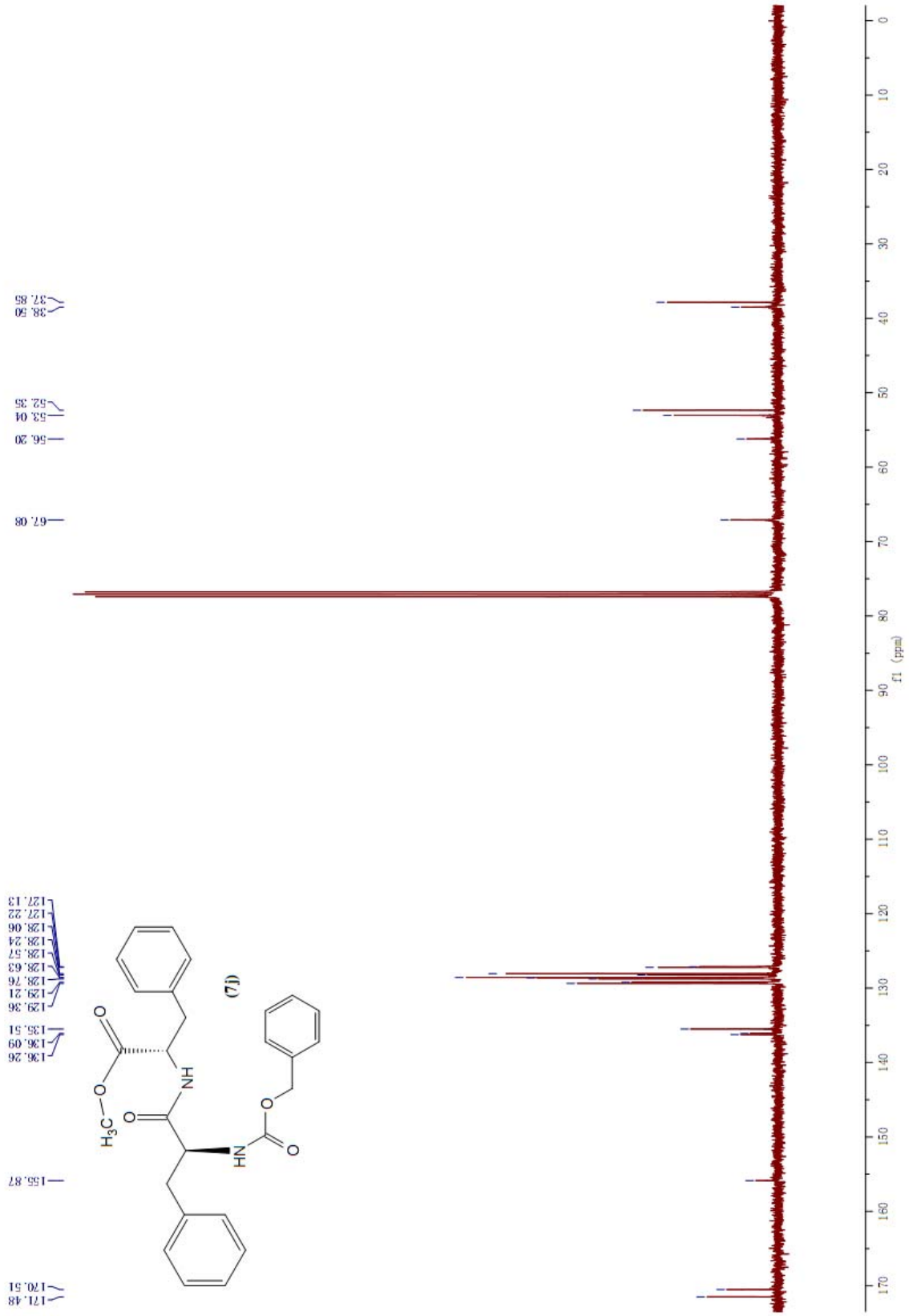

1.16
1.18
1.20
1.22
1.23
1.26
1.27
1.28
2.04
3.26
3.27
3.58
3.63
4.27
4.86
4.87
4.89
4.94
4.97
5.02
5.05
5.48
5.50
6.77
6.79
6.89
7.04
7.11
7.24
7.47
7.49
8.34
NH
CH3
O
O
NH
O
NH
H3C
O
O
(7h)
3.23
2.05
2.63
1.00
1.05
2.00
0.99
0.93
1.01
2.16
6.25
1.18
0.93
f1 (ppm)


18.60
27.47
50.46
52.48
52.88
66.92
109.56
111.35
118.47
119.66
122.23
123.11
127.50
128.08
128.59
136.05
136.28
155.86
171.94
172.05
(7h)
f1 (ppm)


(7i)
f1 (ppm)


22.73
24.72
38.51
41.33
50.80
52.29
55.98
66.99
126.94
127.97
128.18
128.55
129.44
136.21
136.42
136.50
156.04
170.93
172.96
CH3
CH3
CH3
O
O
NH
O
NH
O
O
O
(7i)
f1 (ppm)


(7j)
f1 (ppm)


171.48
170.51
155.87
136.26
136.09
135.51
129.36
129.21
128.76
128.63
128.57
128.24
128.06
127.22
127.13
67.08
56.20
53.04
52.35
38.50
37.85
(7j)
f1 (ppm)

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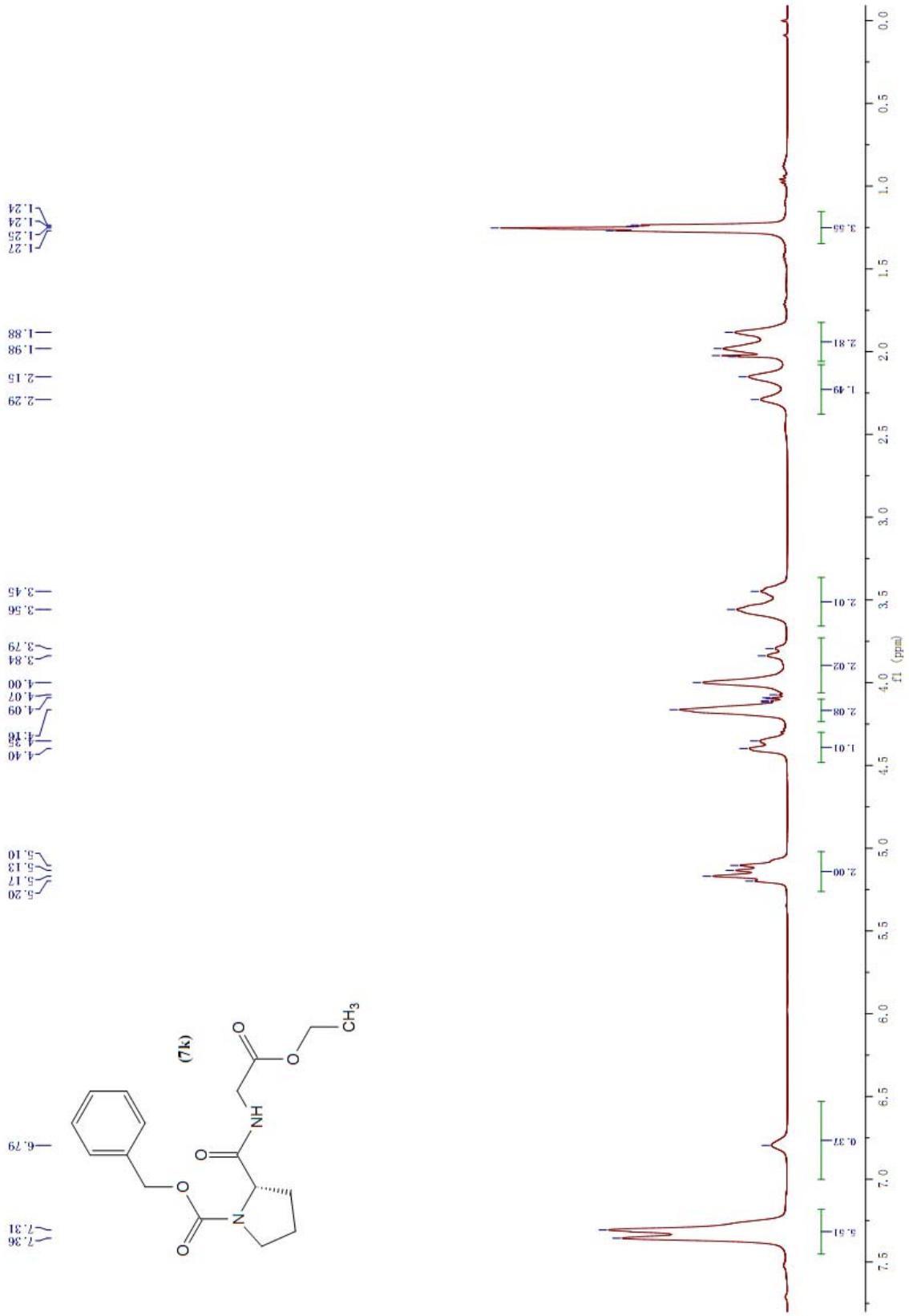
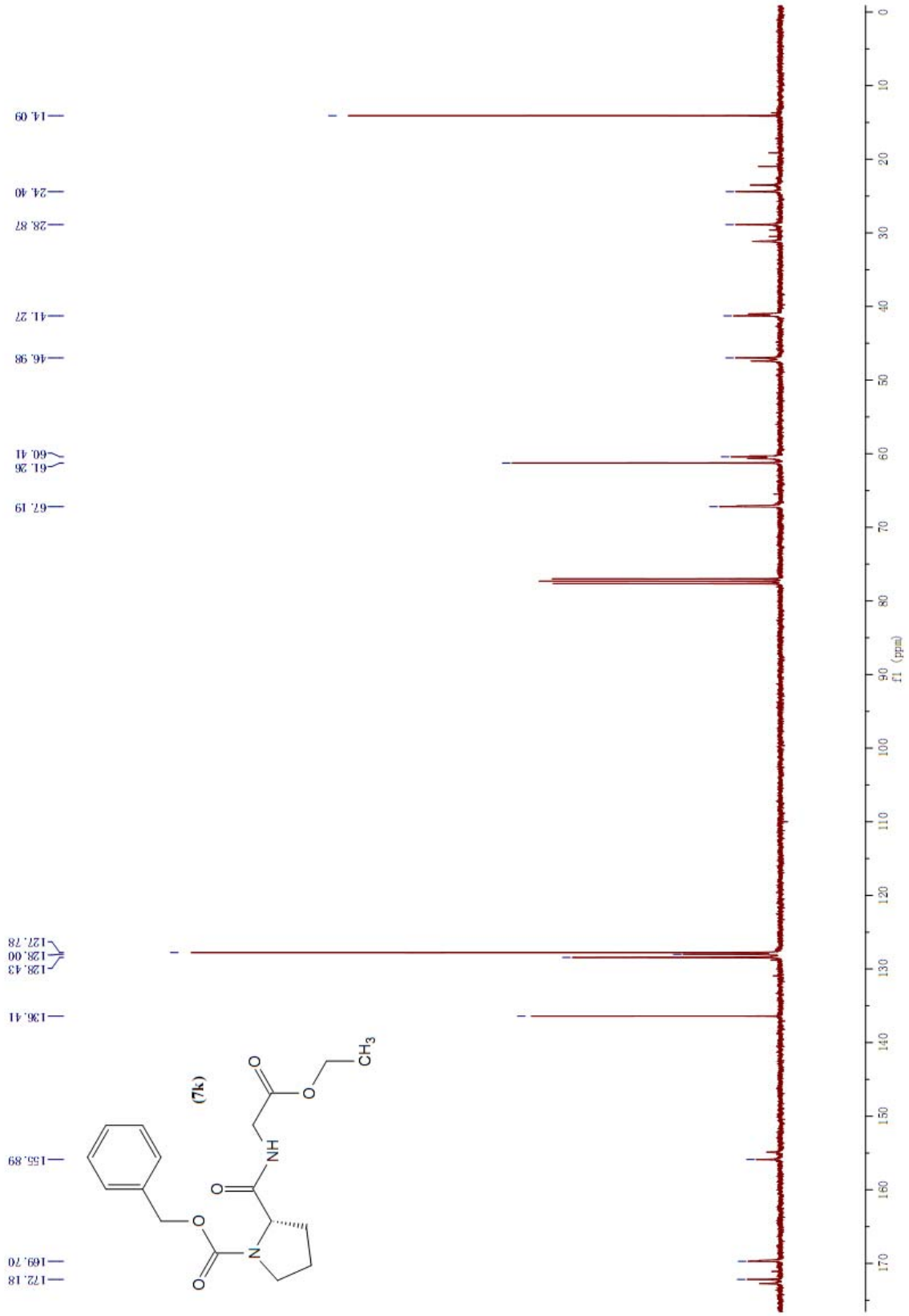
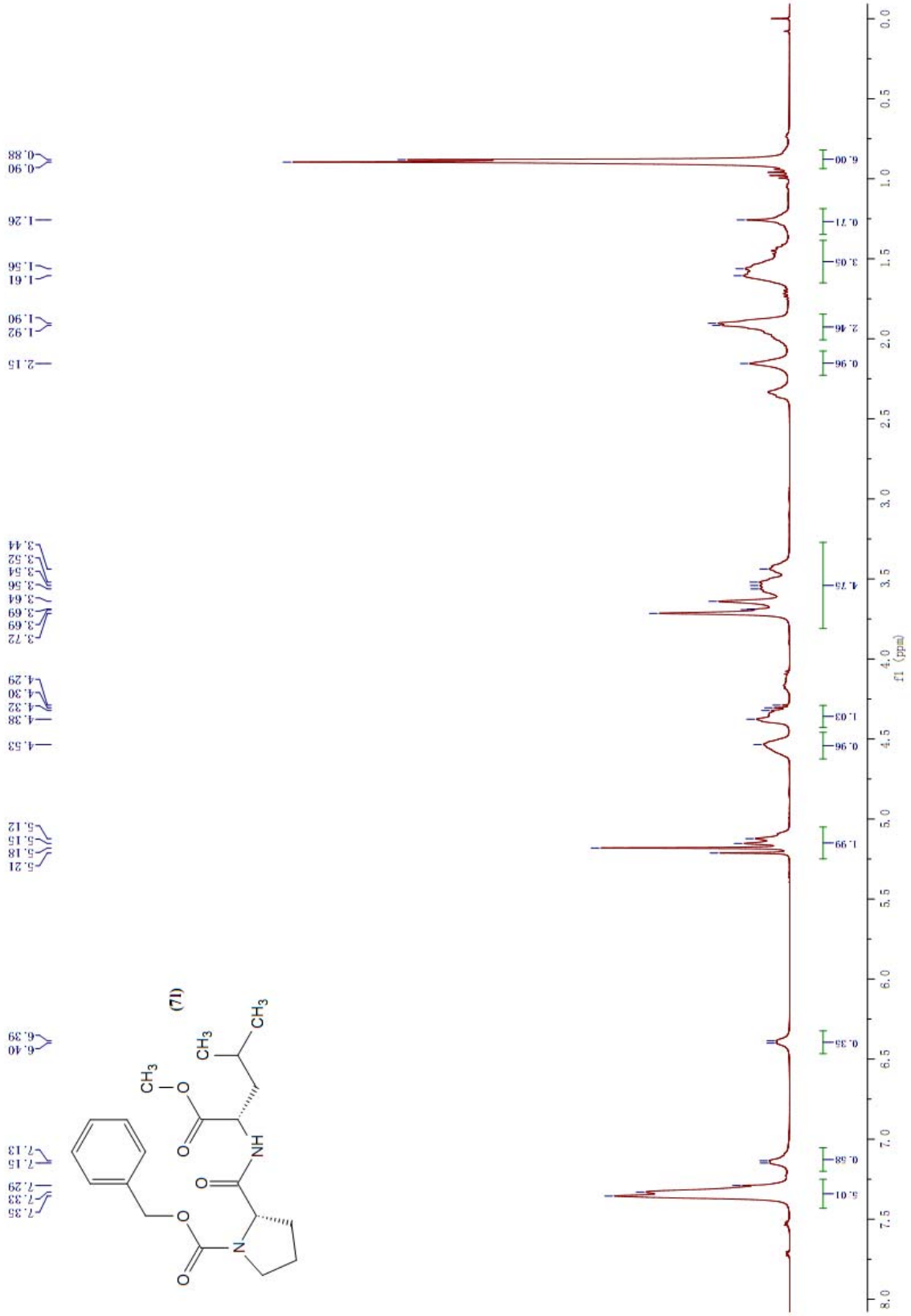
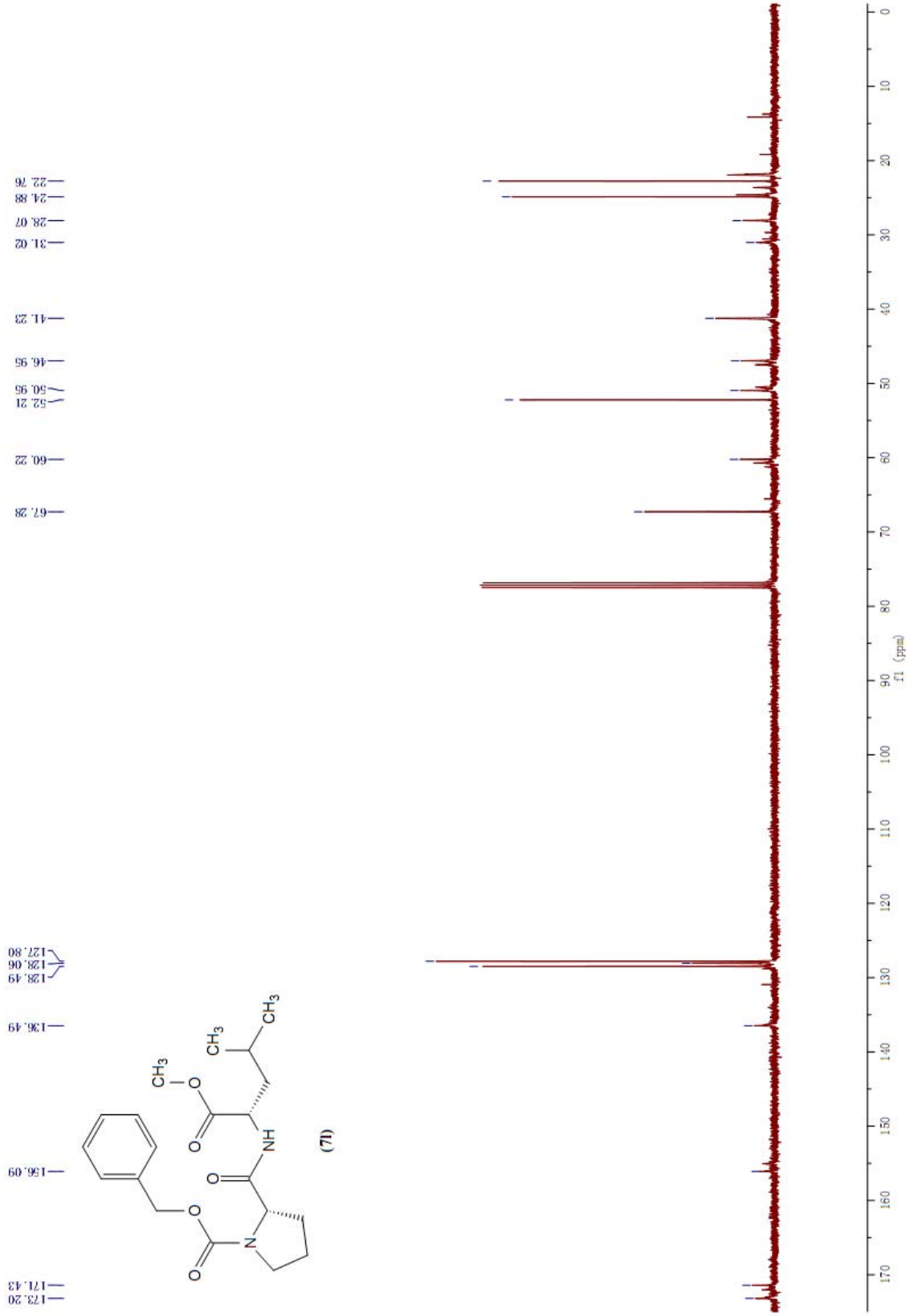
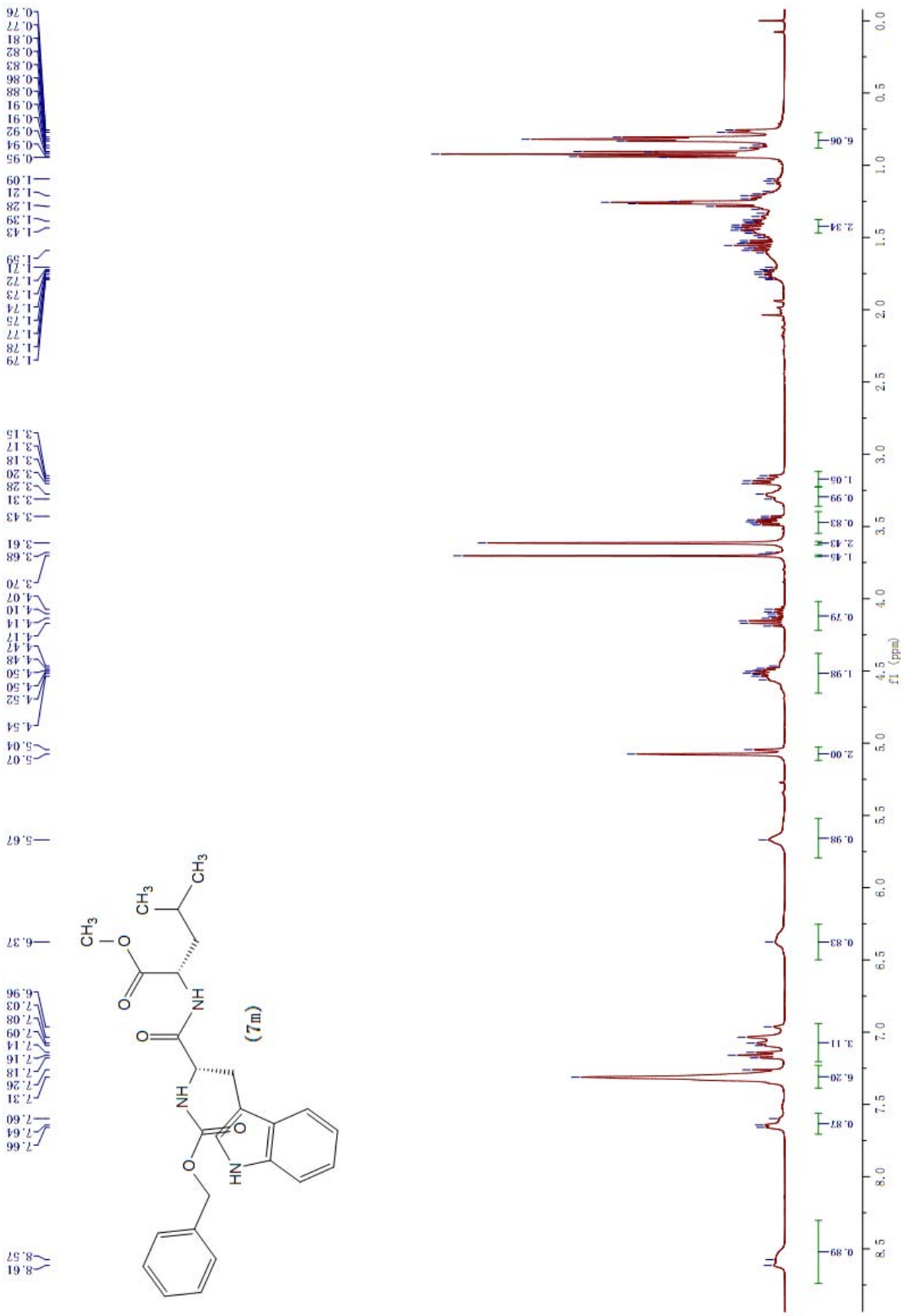
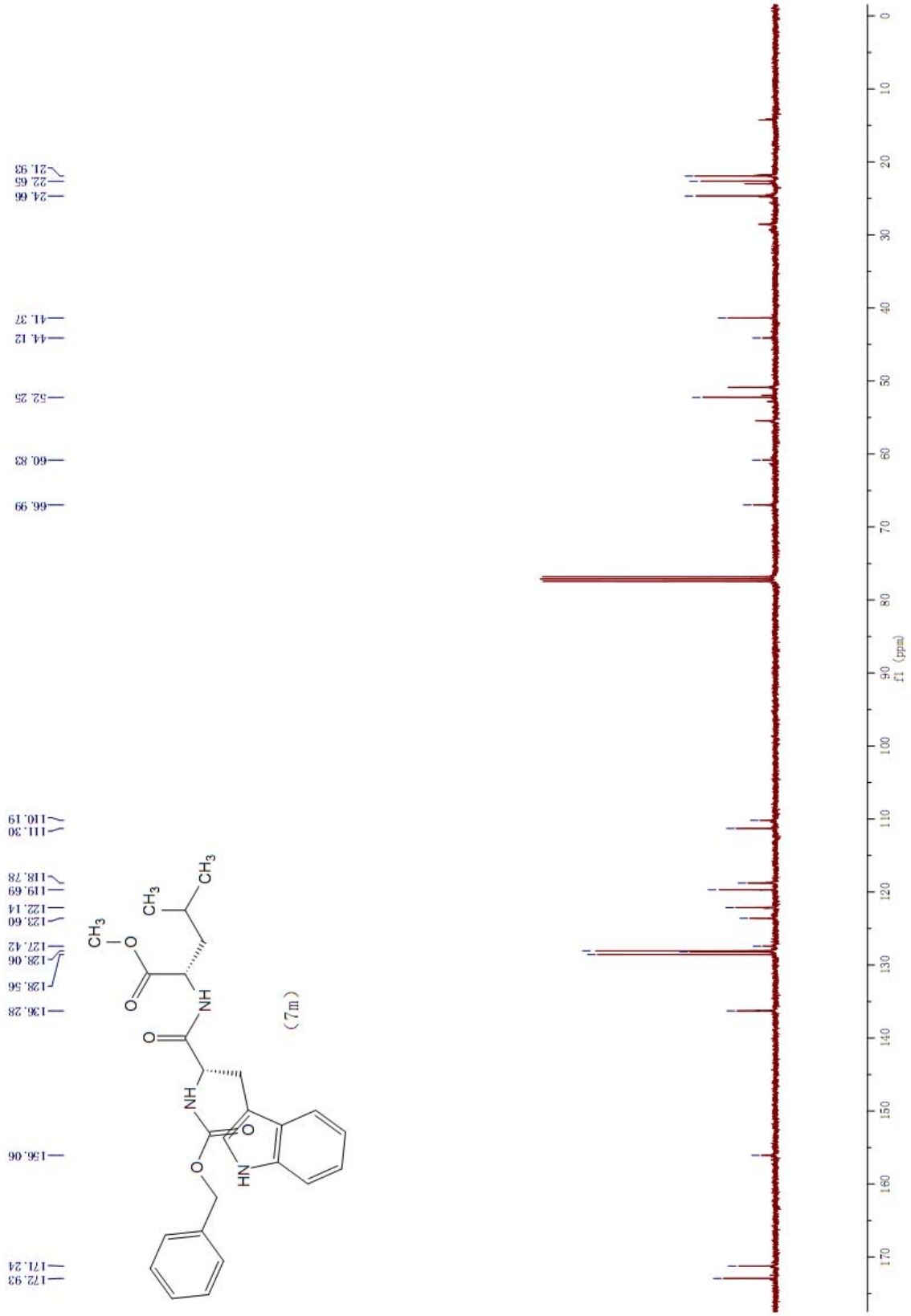


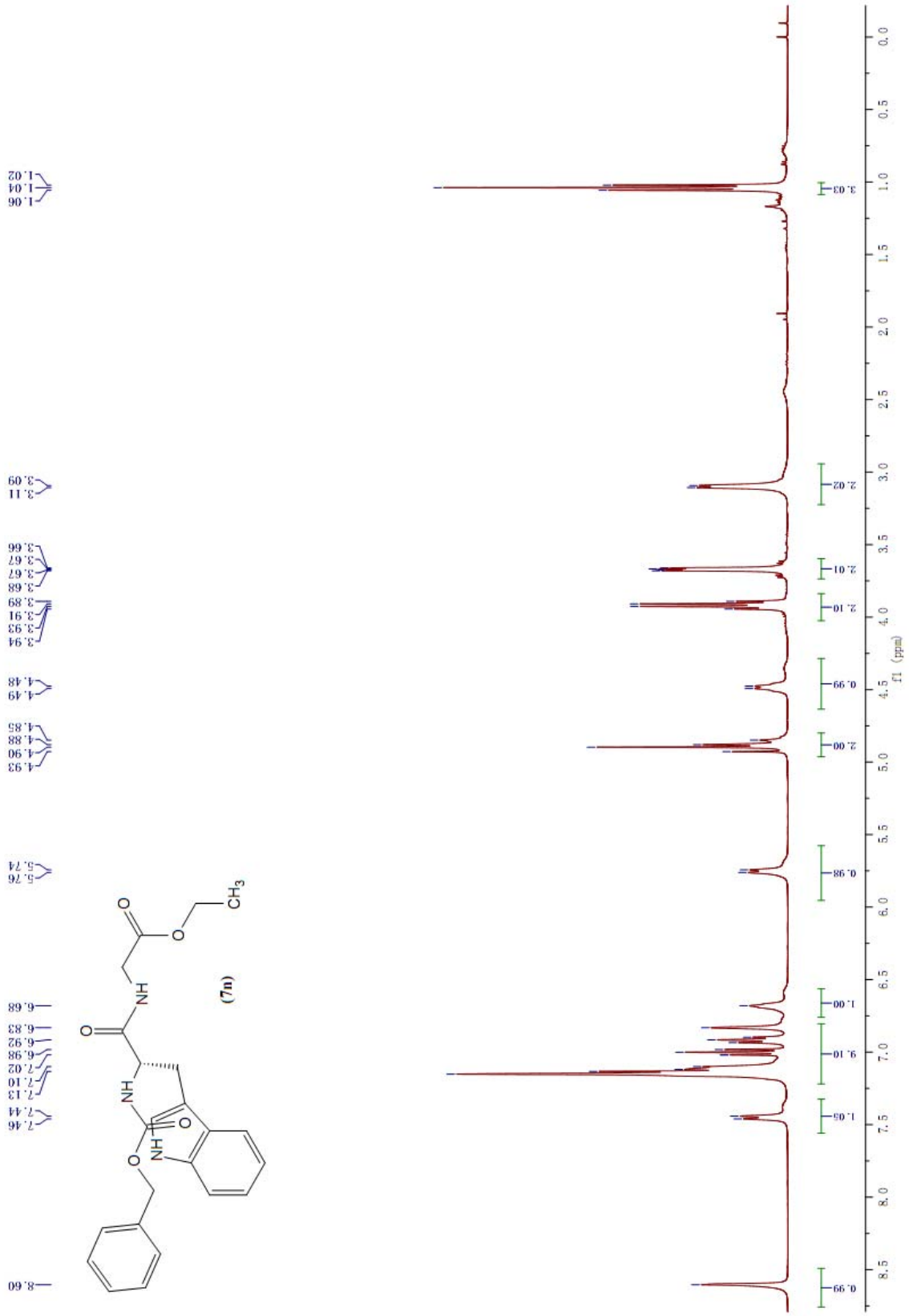

14.09
24.40
28.87
41.27
46.98
60.41
61.36
67.19
127.78
128.00
128.43
136.41
155.89
169.70
172.18
(7k)
O
O
CH3
NH
O
O
N
O
f1 (ppm)

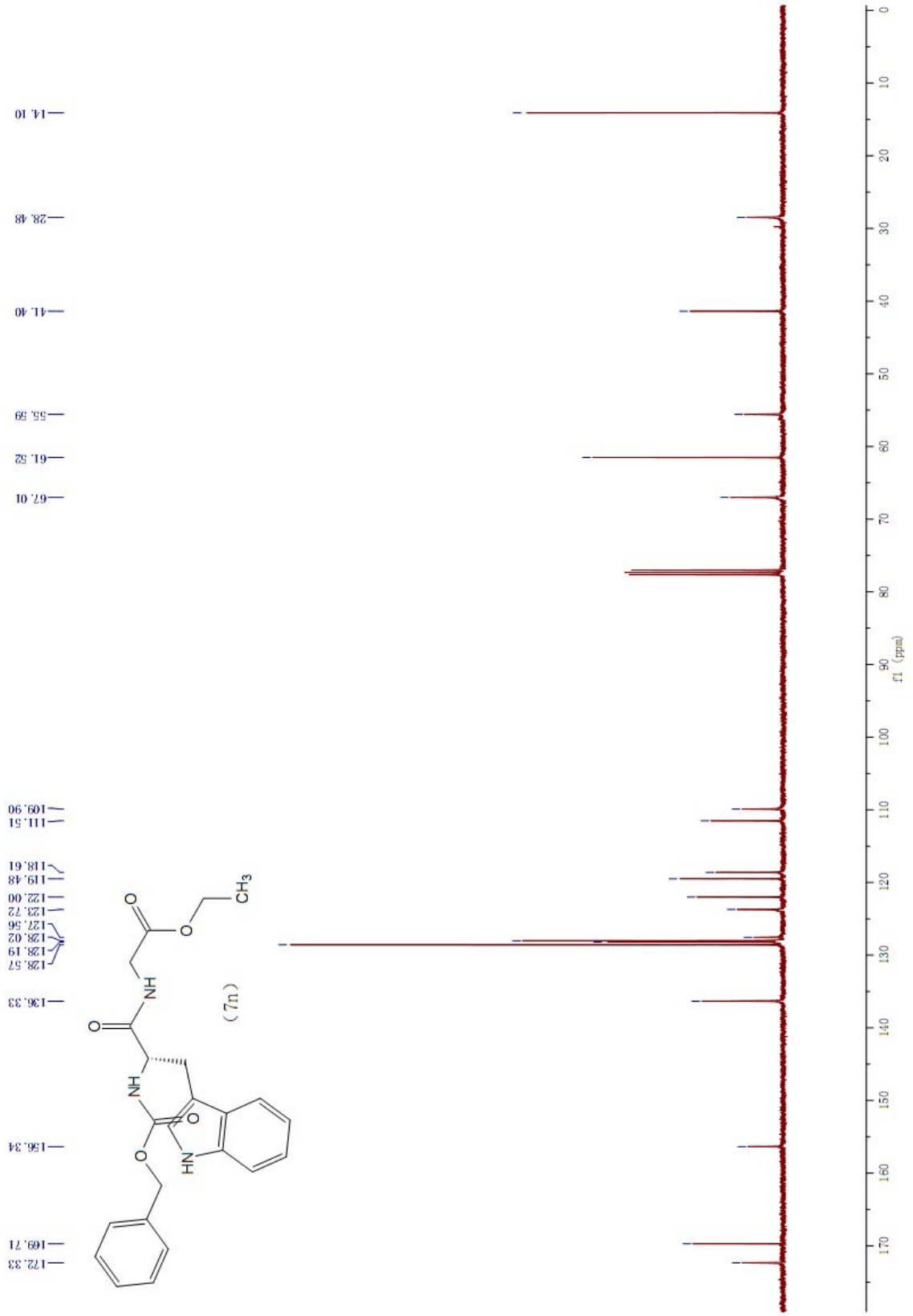

(7l)
CH3
CH3
CH3
O
O
NH
O
O
O
N
0.88
0.90
1.26
1.56
1.61
1.90
1.92
2.15
3.44
3.52
3.54
3.56
3.64
3.69
3.69
3.72
4.29
4.30
4.32
4.38
4.53
5.12
5.15
5.18
5.21
6.39
6.40
7.13
7.15
7.29
7.33
7.35
6.00
0.71
3.05
2.46
0.96
4.75
1.03
0.96
1.99
0.35
0.58
5.01
f1 (ppm)

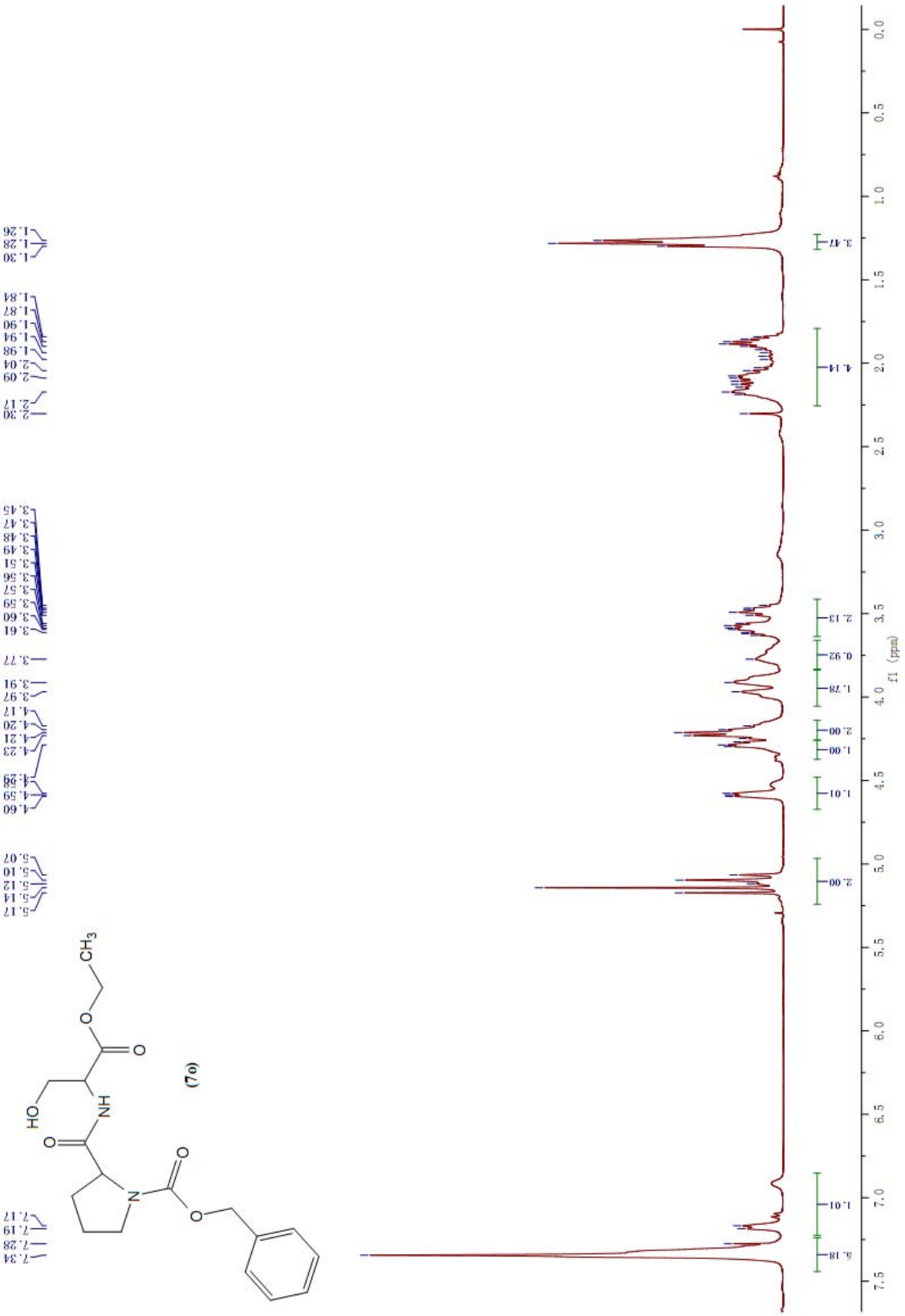

22.76
24.88
28.07
31.02
41.23
46.96
50.96
52.21
60.22
67.28
127.80
128.06
128.49
136.49
156.09
171.43
173.20
CH3
CH3
CH3
O
O
O
NH
O
O
N
O
(7l)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)

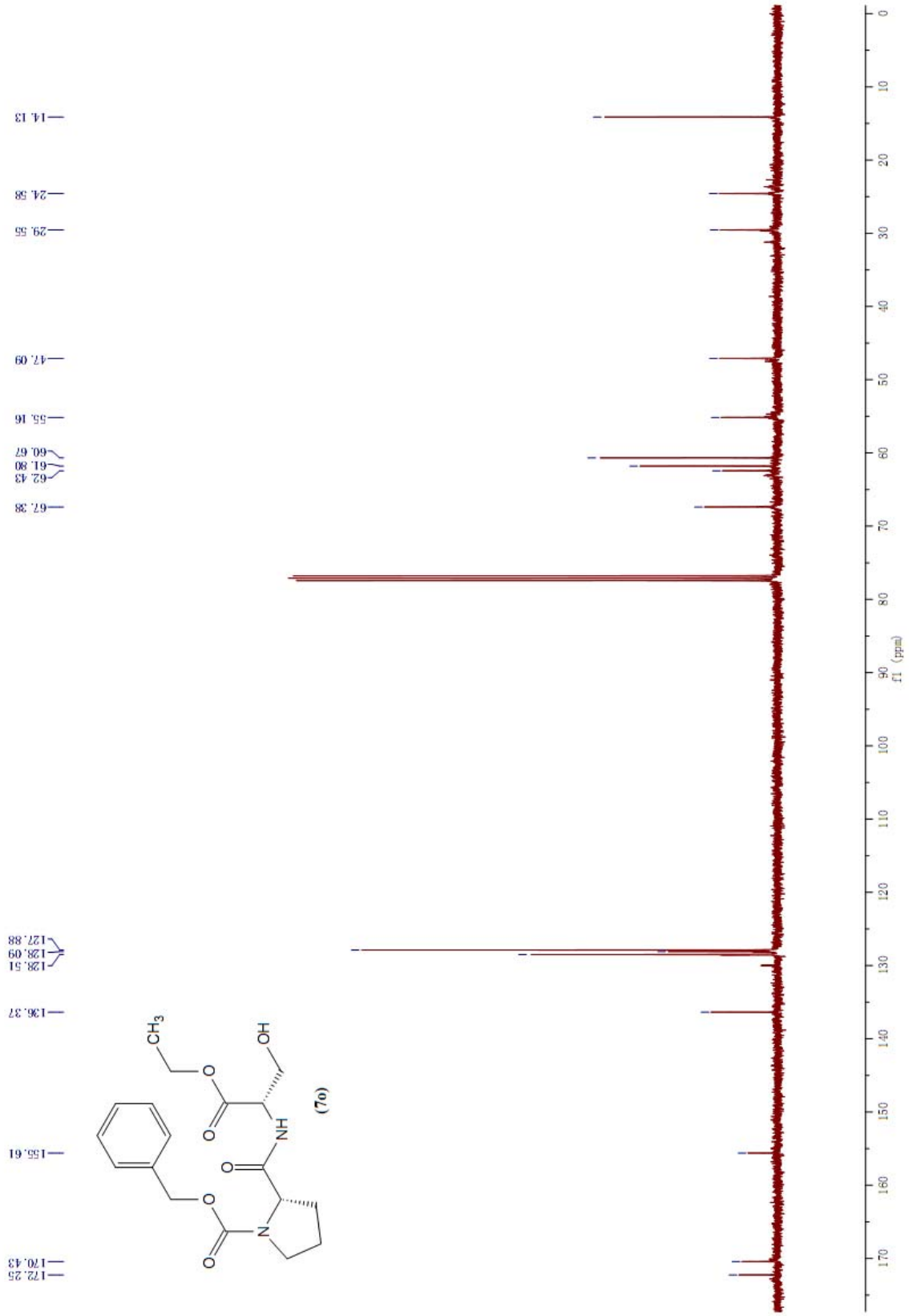

(7m)
f1 (ppm)

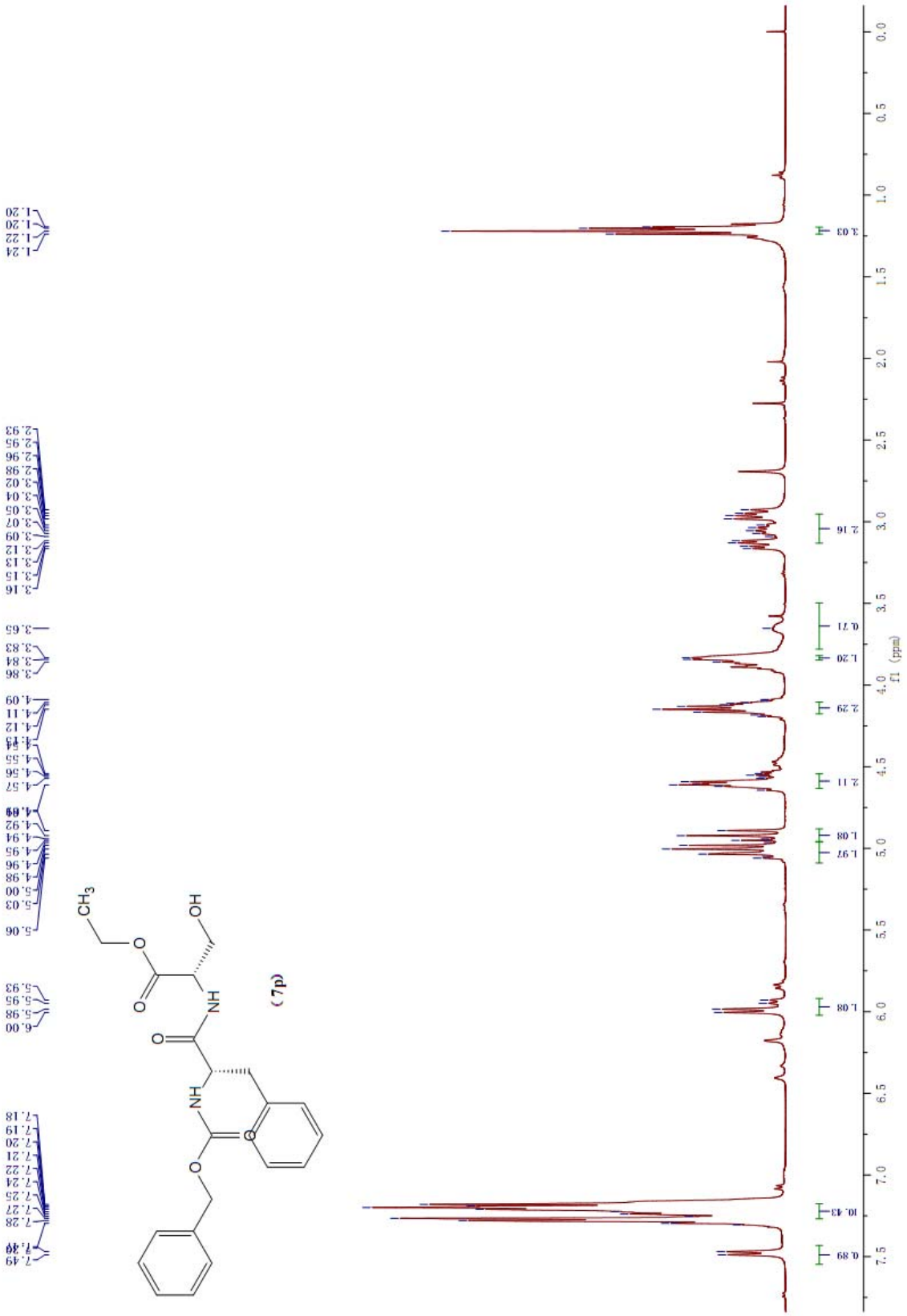

21.93
22.65
24.66
41.37
44.12
52.25
60.83
66.99
110.19
111.30
118.78
119.69
122.14
123.60
127.42
128.06
128.56
136.28
156.06
171.24
172.93
CH3
CH3
CH3
O
O
NH
O
NH
O
NH
O
(7m)
f1 (ppm)

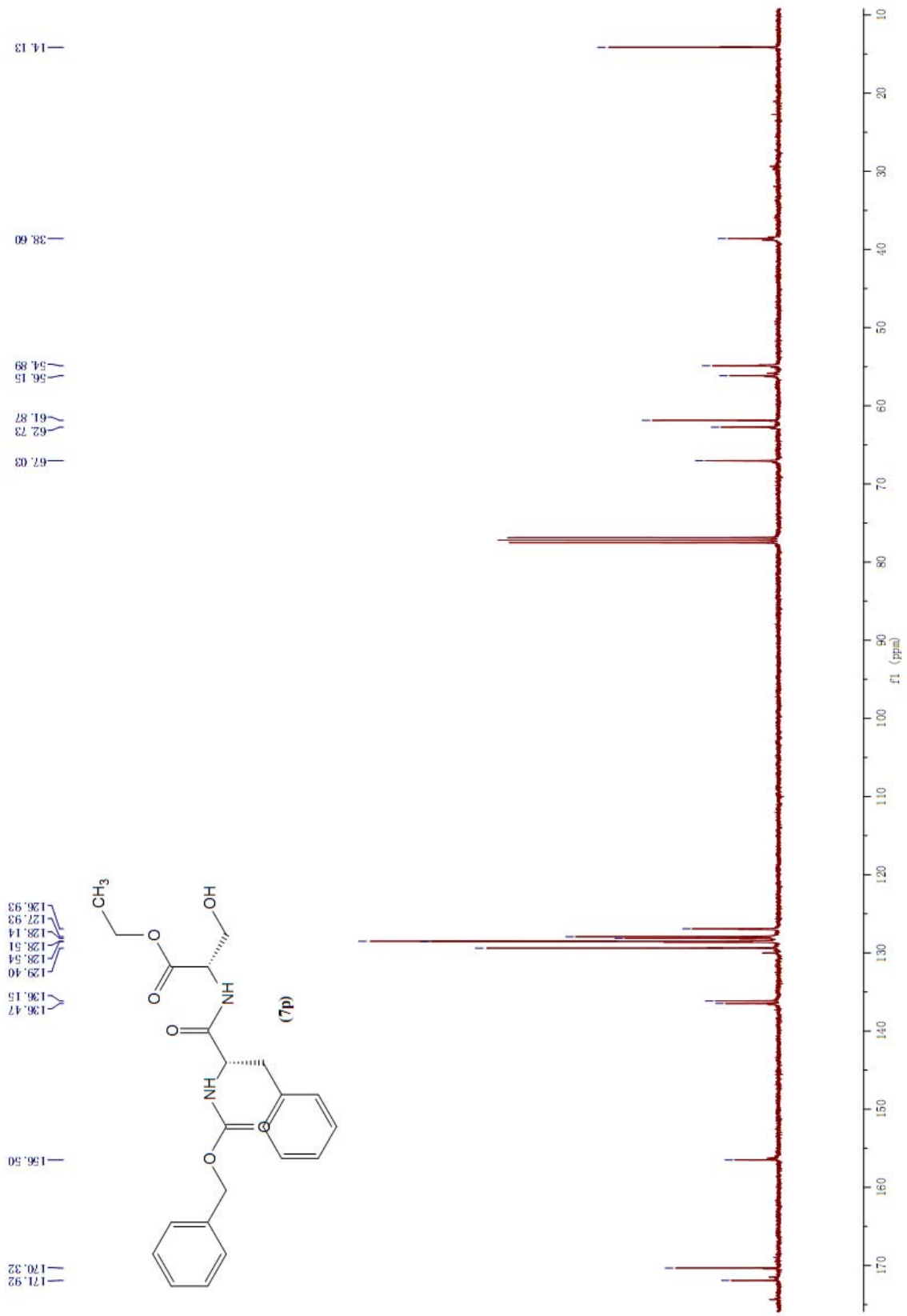

1.02
1.04
1.06
3.09
3.11
3.66
3.67
3.67
3.68
3.89
3.91
3.93
3.94
4.48
4.49
4.85
4.88
4.90
4.93
5.74
5.76
6.68
6.83
6.92
6.98
7.02
7.10
7.13
7.44
7.46
8.60
(7n)
NH
NH
NH
O
O
O
O
O
CH3
3.03
2.02
2.01
2.10
0.99
2.00
0.98
1.00
9.10
1.03
0.99
f1 (ppm)

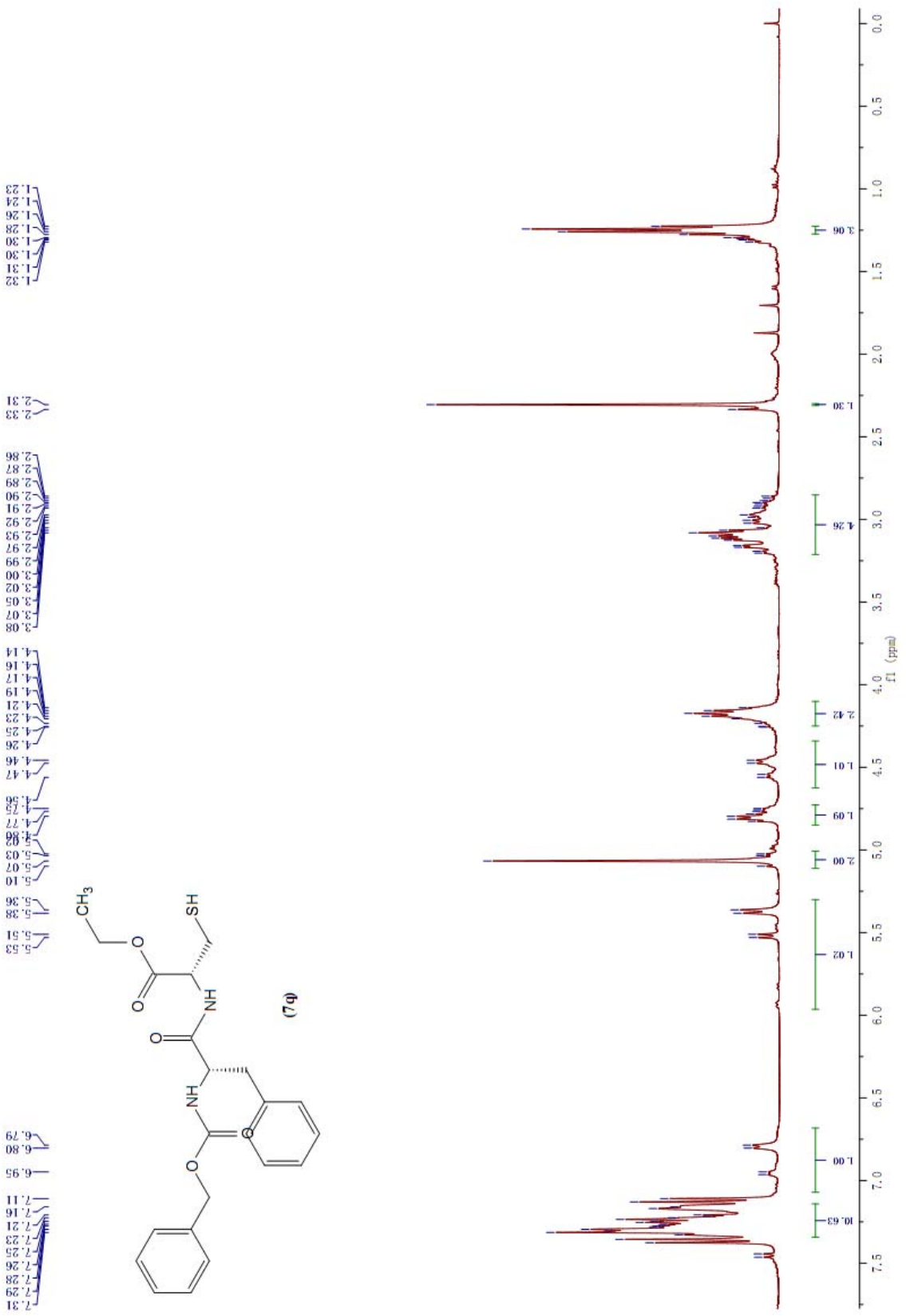

14.10
28.48
41.40
55.59
61.52
67.01
109.90
111.51
118.61
119.48
122.00
123.72
127.56
128.02
128.19
128.57
136.33
156.34
169.71
172.33
(7n)
f1 (ppm)

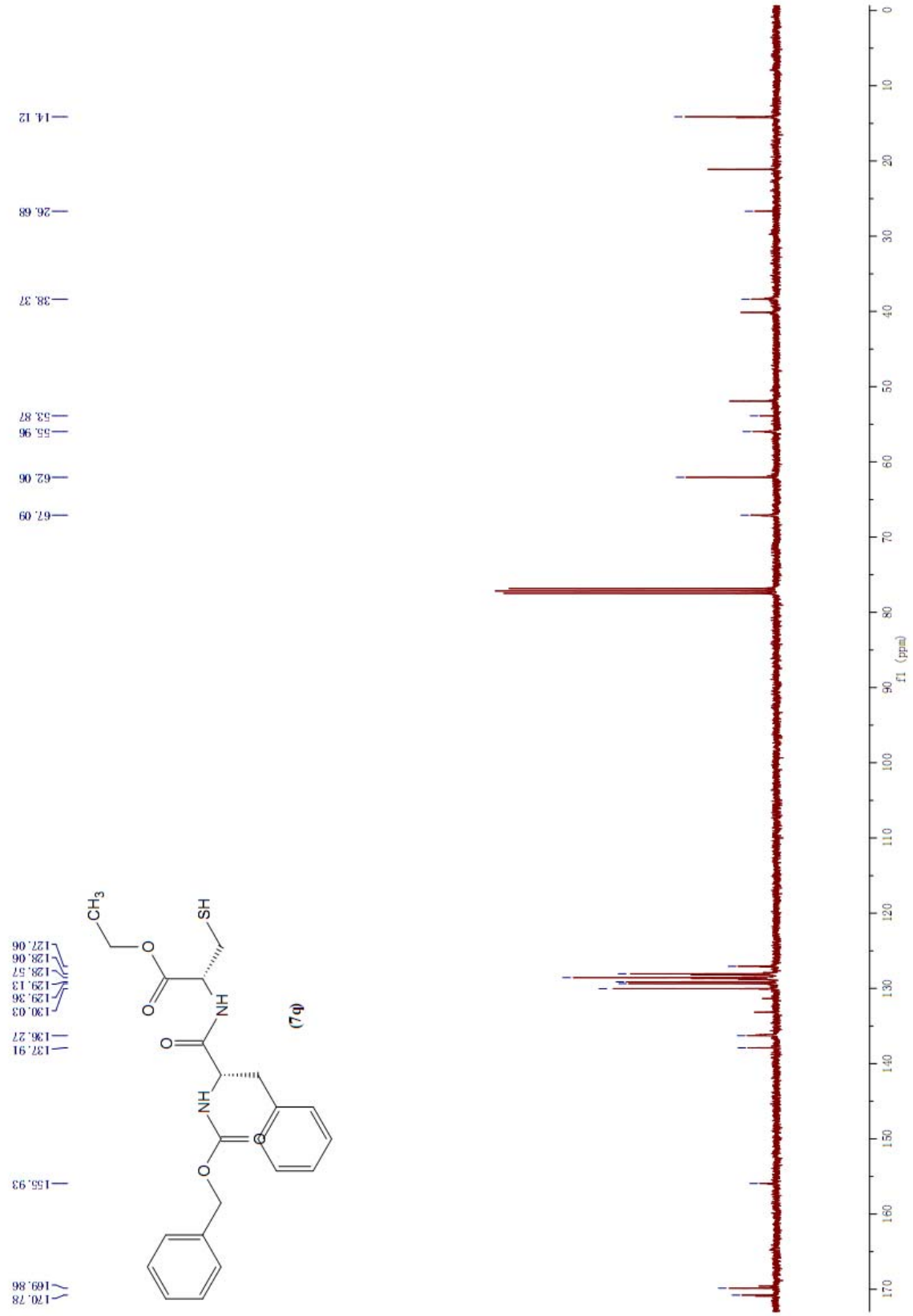

(7ω)
f1 (ppm)

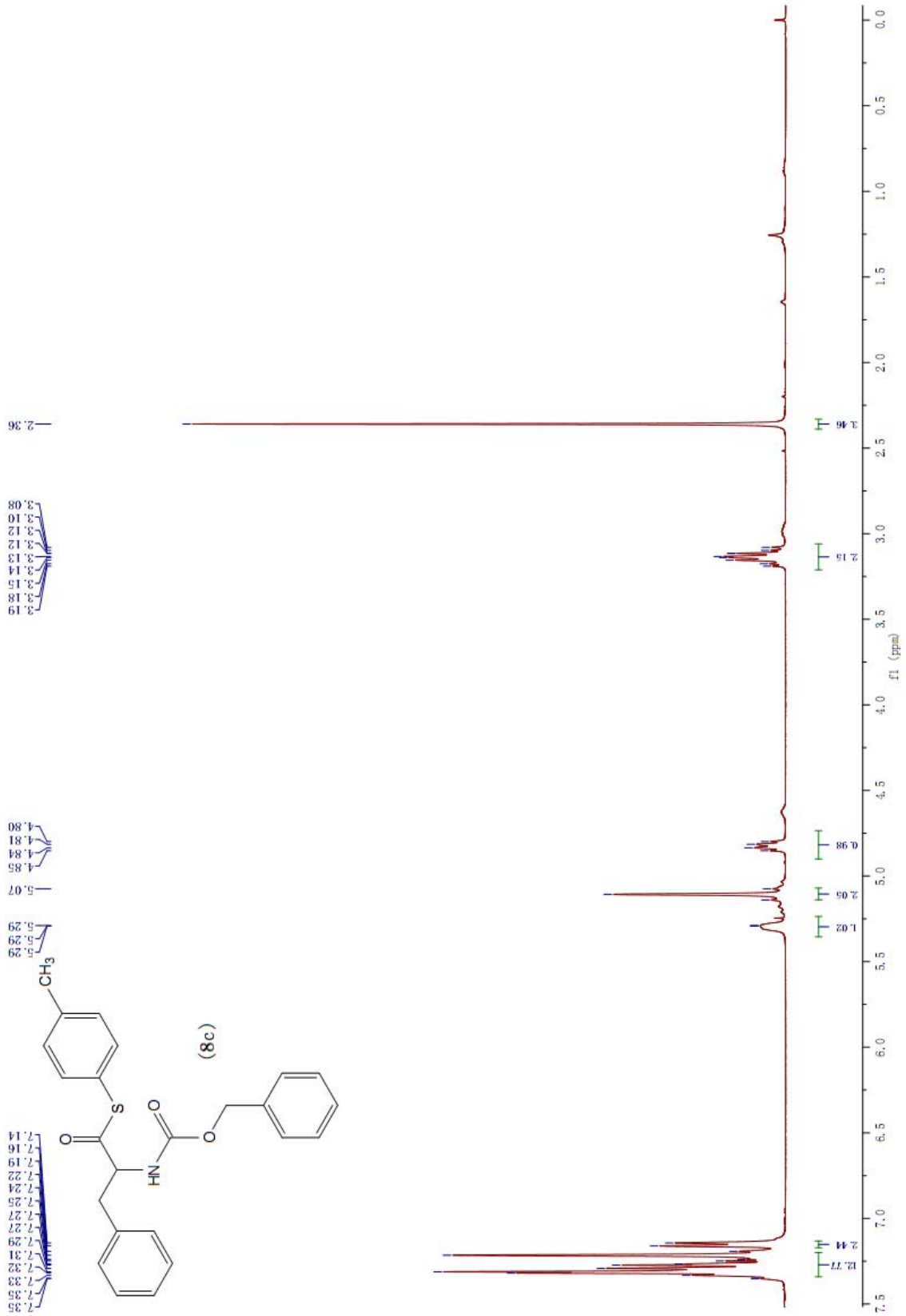

14.13
24.58
29.55
47.09
55.16
60.67
61.80
62.43
67.38
127.88
128.09
128.51
136.37
155.61
170.43
172.25
f1 (ppm)
(7o)

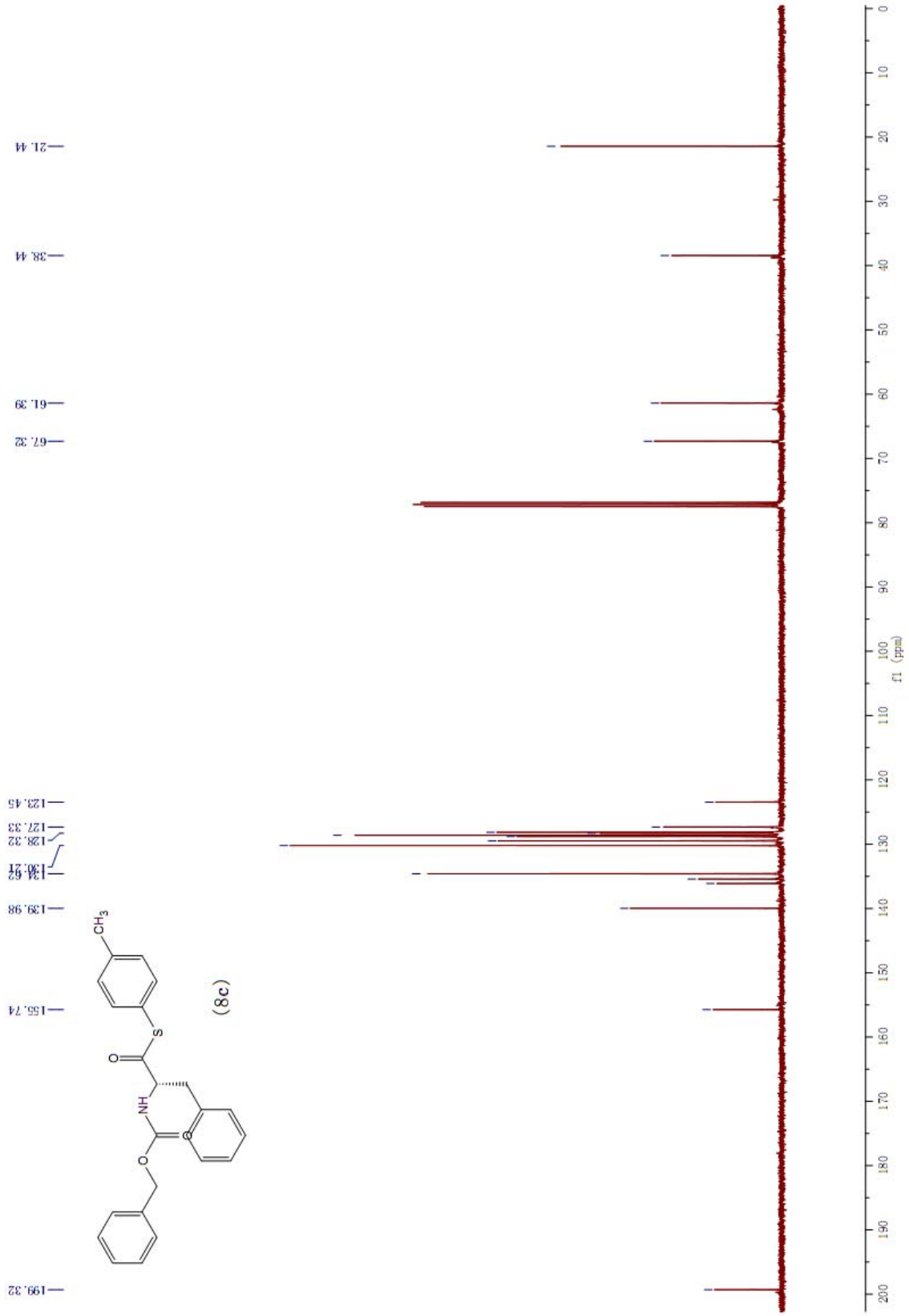

CH3
O
OH
NH
O
NH
O
O
(7p)
f1 (ppm)

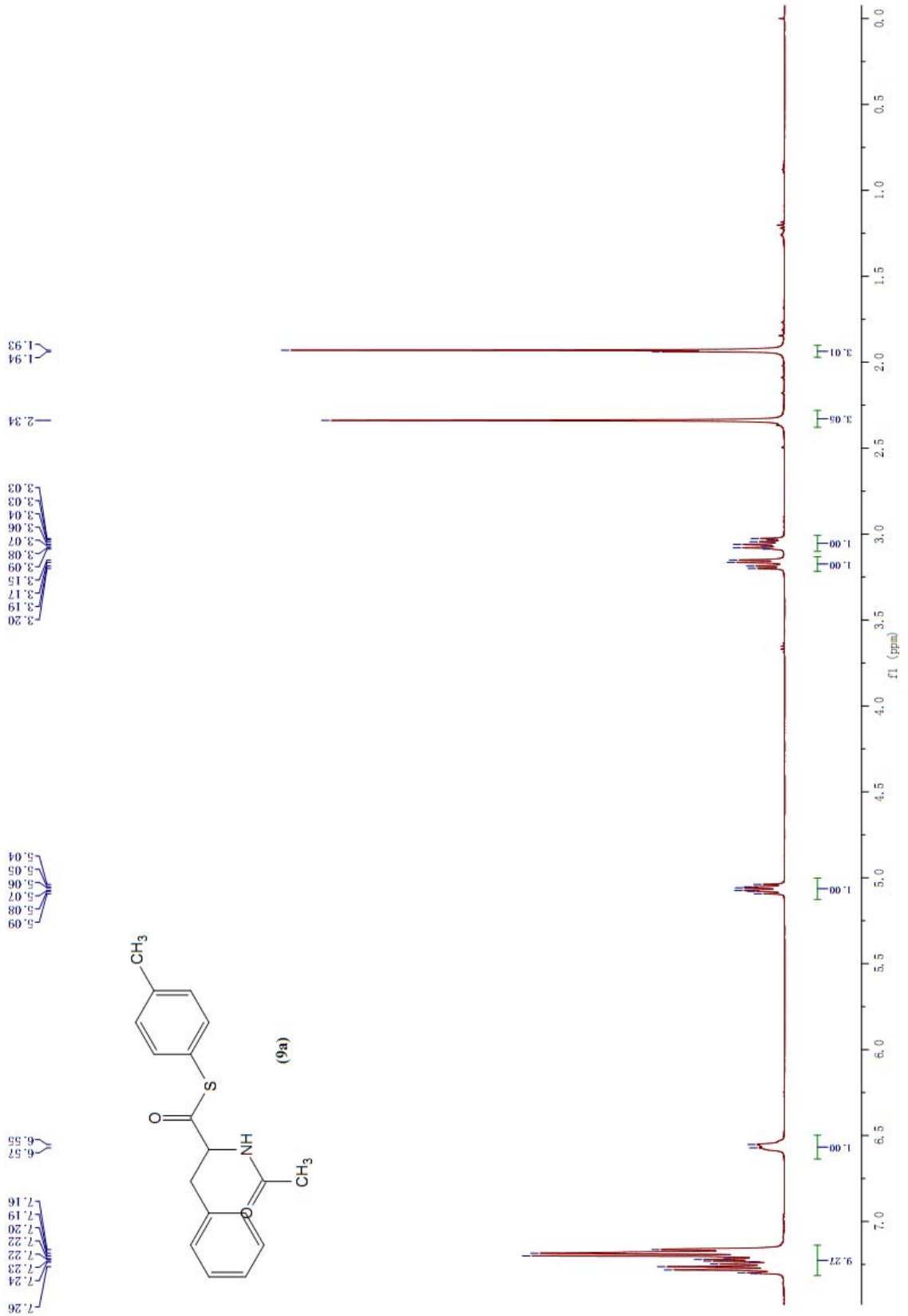

14.13
38.60
54.89
56.15
61.87
62.73
67.03
129.40
128.54
128.51
128.14
127.93
136.93
136.47
136.15
156.50
170.32
171.92
(7p)
f1 (ppm)

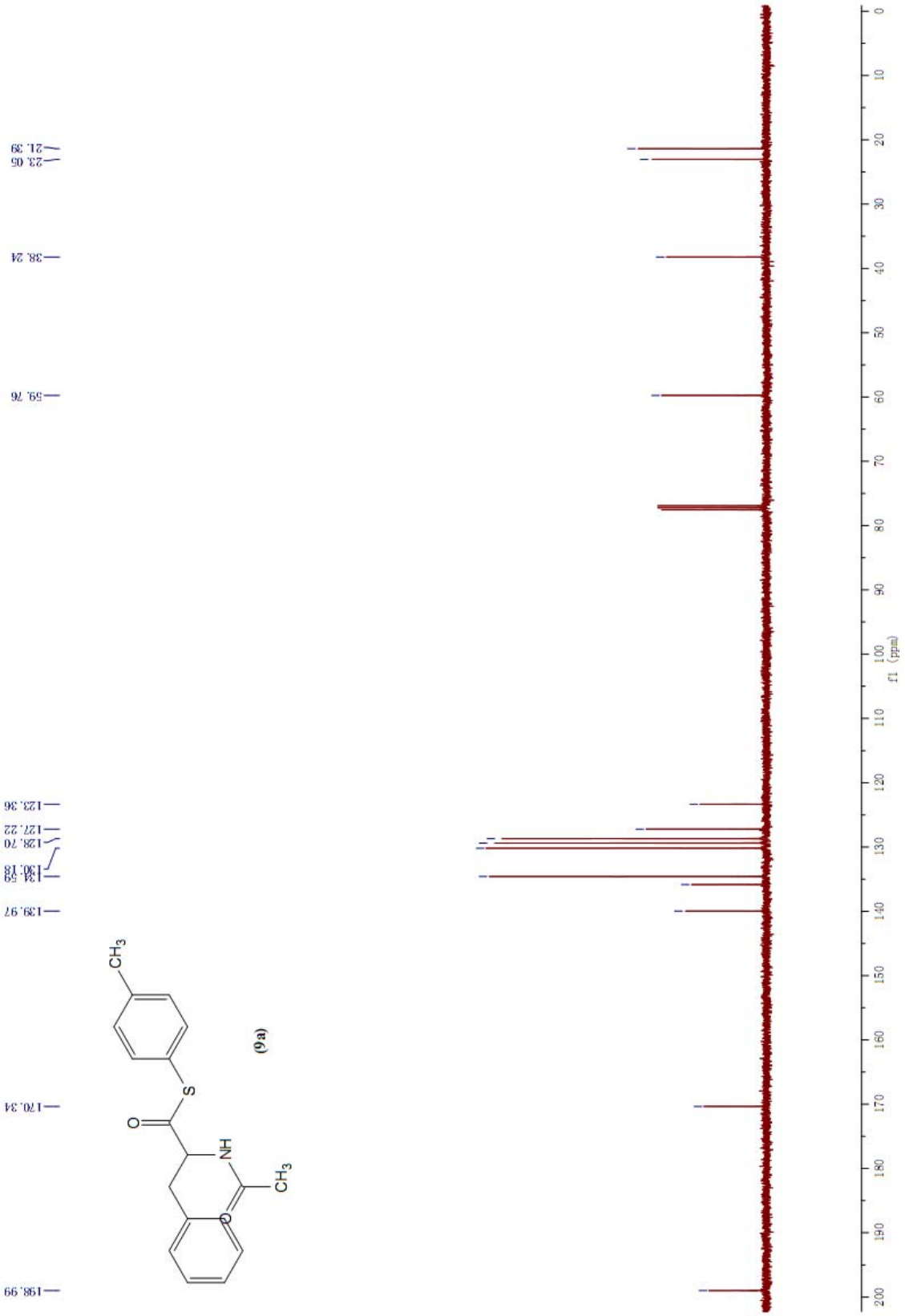

(7q)
f1 (ppm)

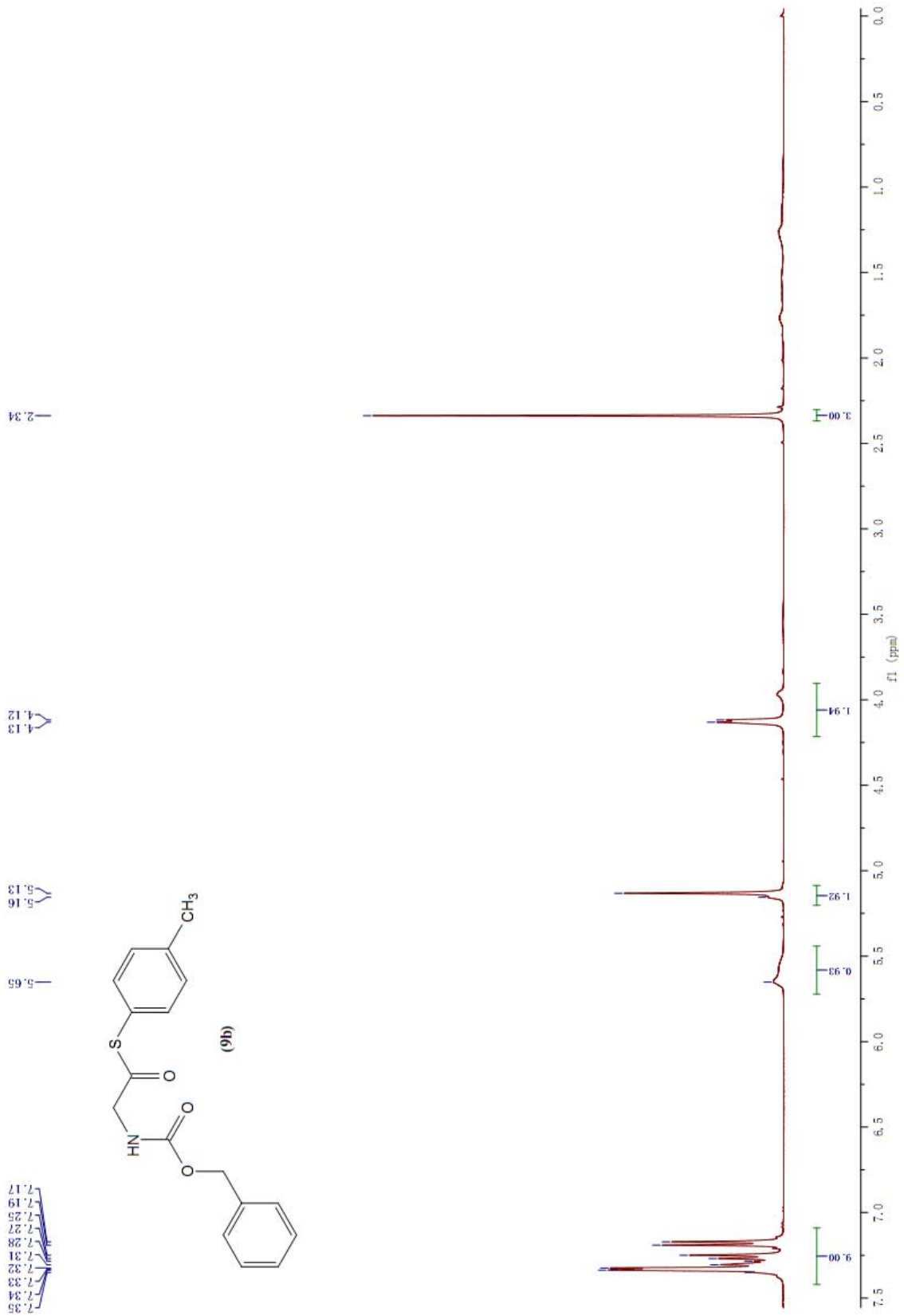

14.12
26.68
38.37
53.87
55.96
62.06
67.09
127.06
128.06
128.57
129.13
129.36
130.03
136.27
137.91
155.93
169.86
170.78
CH3
SH
O
NH
(7q)
f1 (ppm)

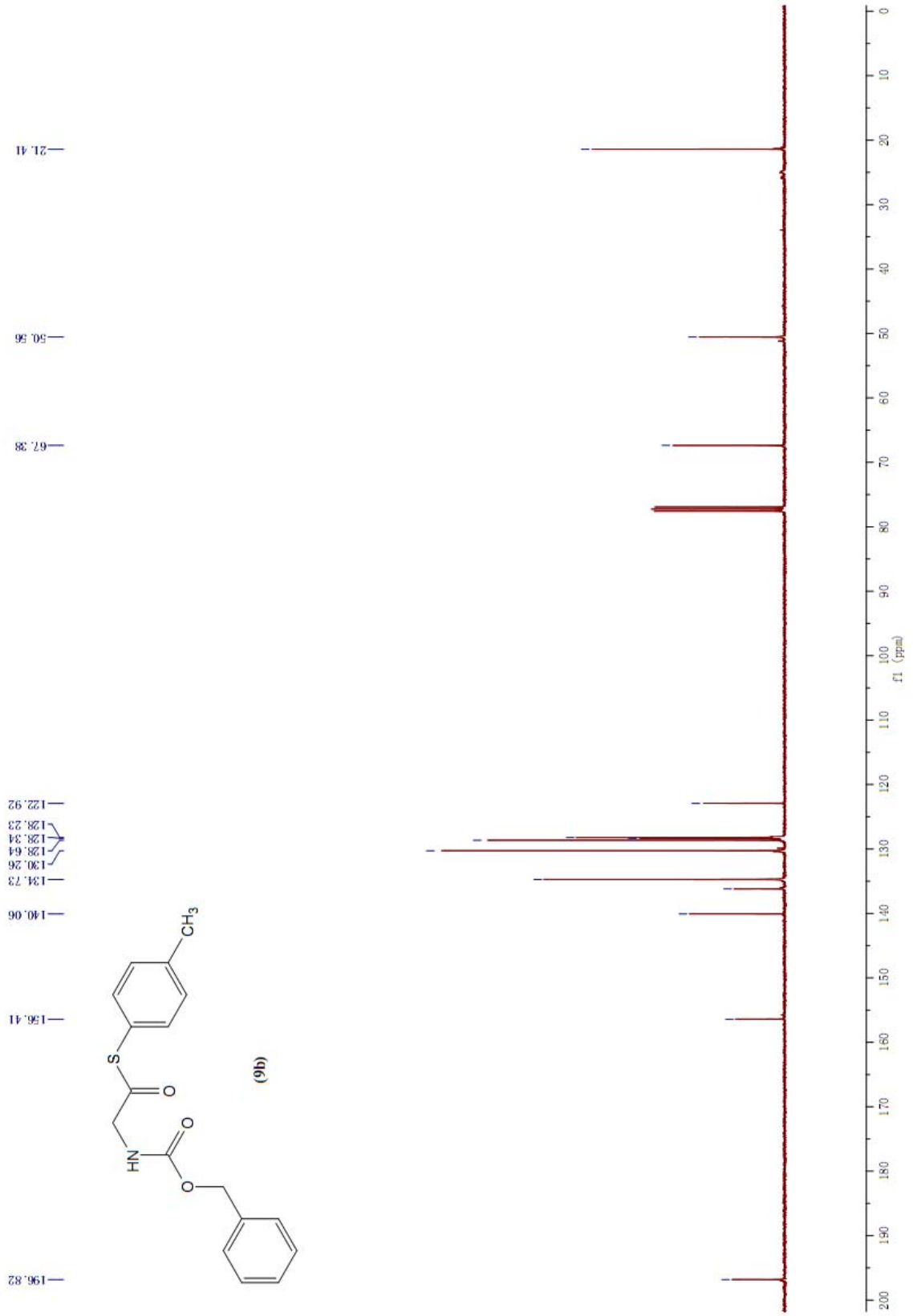

(8c)
CH3
S
O
HN
O
O
f1 (ppm)

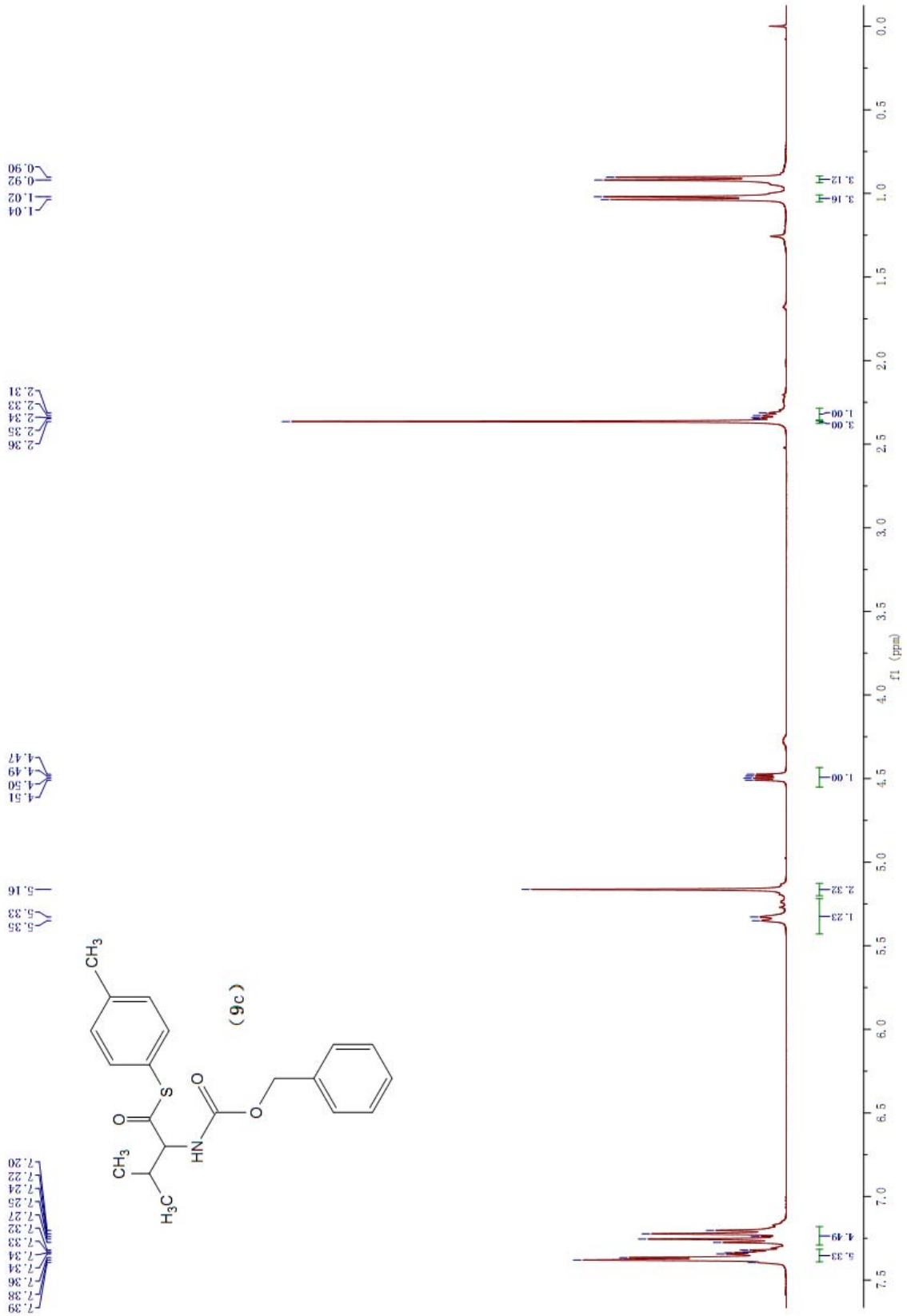

21.44
38.44
61.39
67.32
123.45
127.33
128.32
130.21
134.62
139.98
155.74
199.32
CH3
S
O
NH
O
O
(8c)
f1 (ppm)

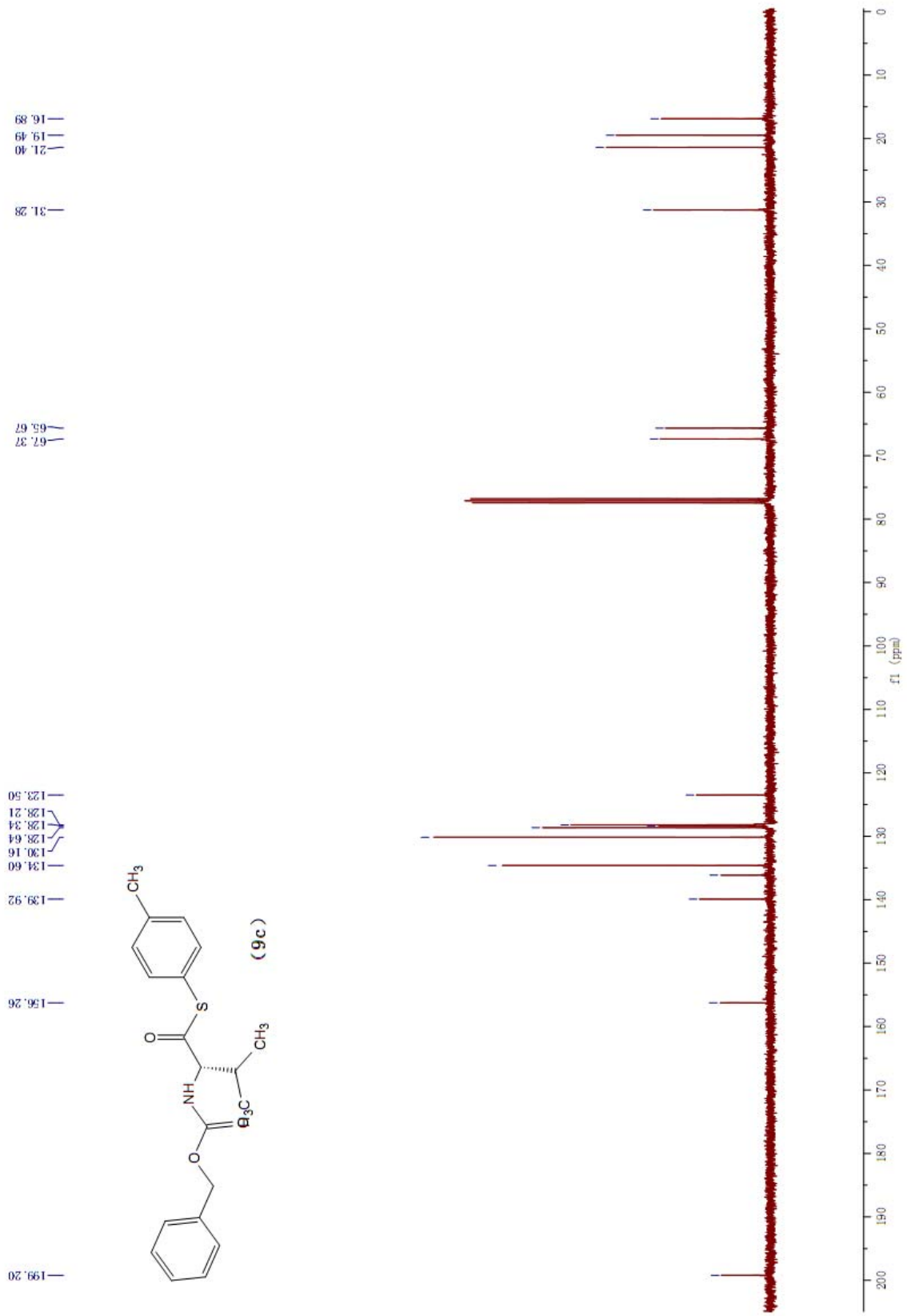

1.93
1.94
2.34
3.03
3.03
3.04
3.06
3.07
3.08
3.09
3.15
3.17
3.19
3.20
5.04
5.05
5.06
5.07
5.08
5.09
6.55
6.57
7.16
7.19
7.20
7.22
7.22
7.23
7.24
7.26
CH3
S
O
NH
CH3
O
(9a)
3.01
3.09
1.00
1.00
1.00
1.00
9.27
f1 (ppm)

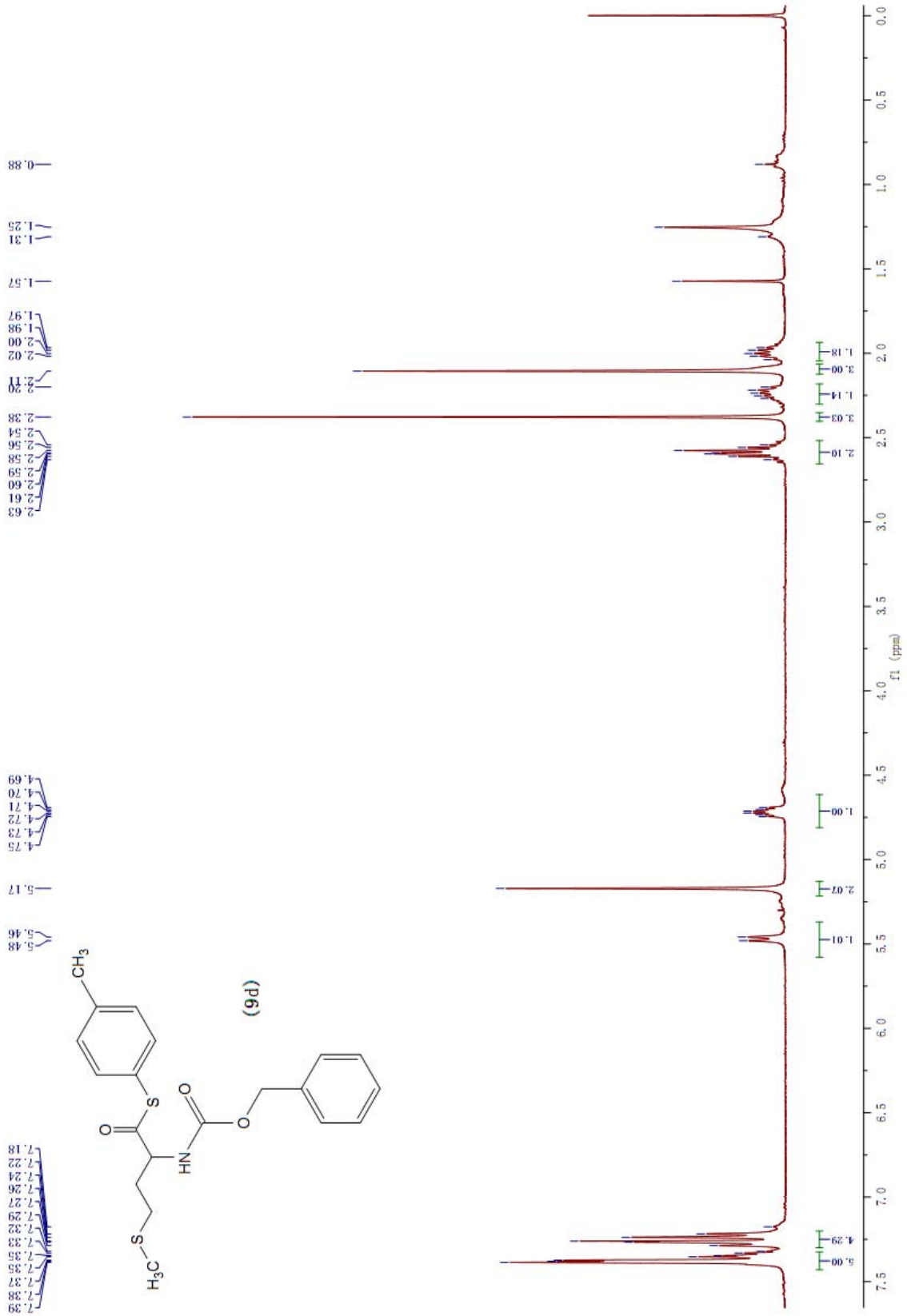

21.39
23.05
38.24
59.76
123.36
127.22
128.70
130.18
134.59
139.97
170.34
198.99
CH3
S
O
NH
CH3
O
(9a)
f1 (ppm)


2.34
4.12
4.13
5.13
5.16
5.65
7.17
7.19
7.25
7.27
7.28
7.31
7.32
7.33
7.34
7.35
CH3
S
O
HN
O
O
(9b)
3.00
1.94
1.92
0.93
9.00
f1 (ppm)


21.41
50.56
67.38
122.92
128.23
128.34
128.64
130.26
134.73
140.06
156.41
196.82
CH3
S
O
HN
O
O
(9b)
f1 (ppm)


(9c)
f1 (ppm)


16.89
19.49
21.40
31.28
65.67
67.37
123.50
128.21
128.34
128.64
130.16
134.60
139.92
156.26
199.20
CH3
S
O
NH
H3C
CH3
O
(9c)
f1 (ppm)


(9d)
f1 (ppm)

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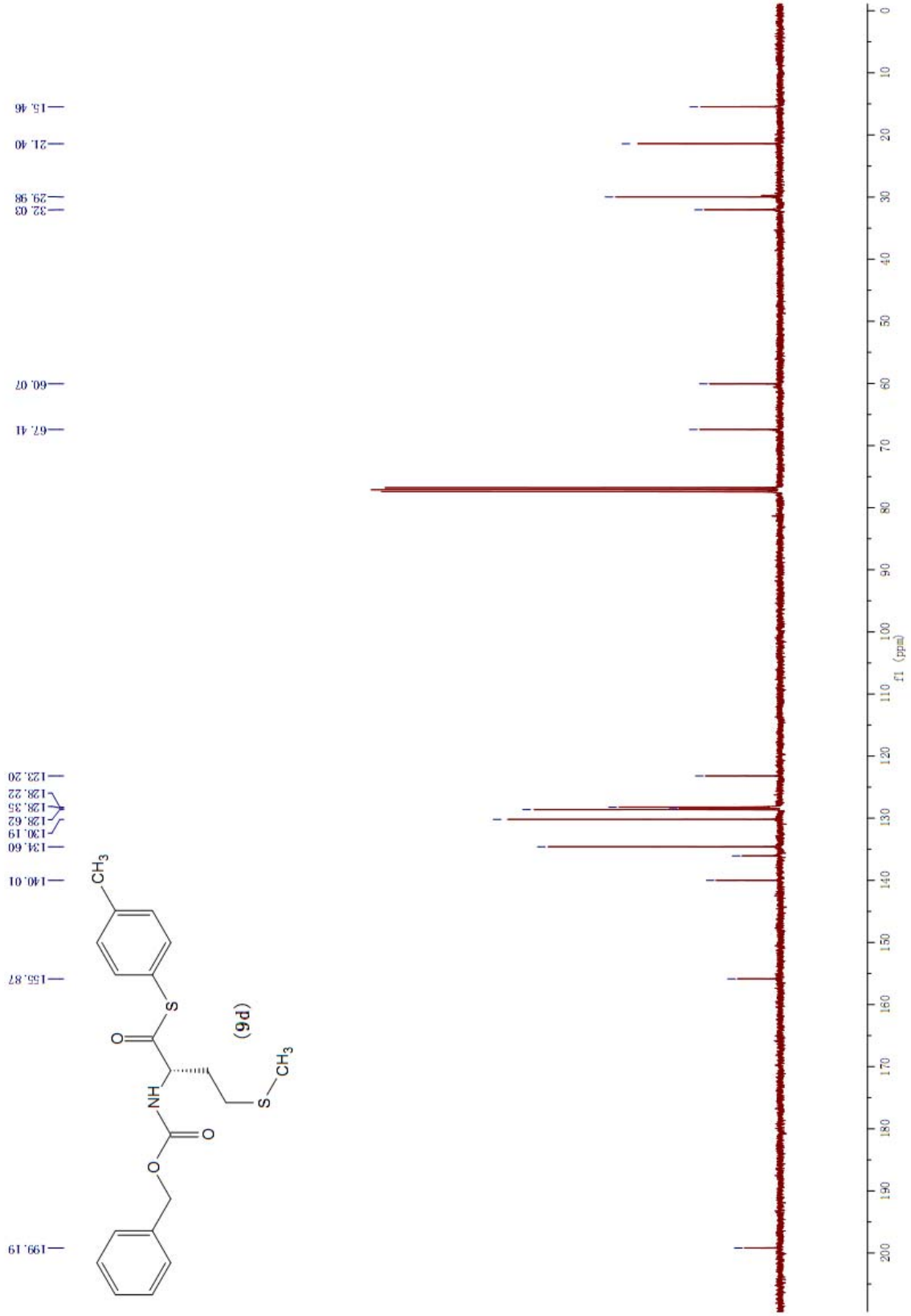
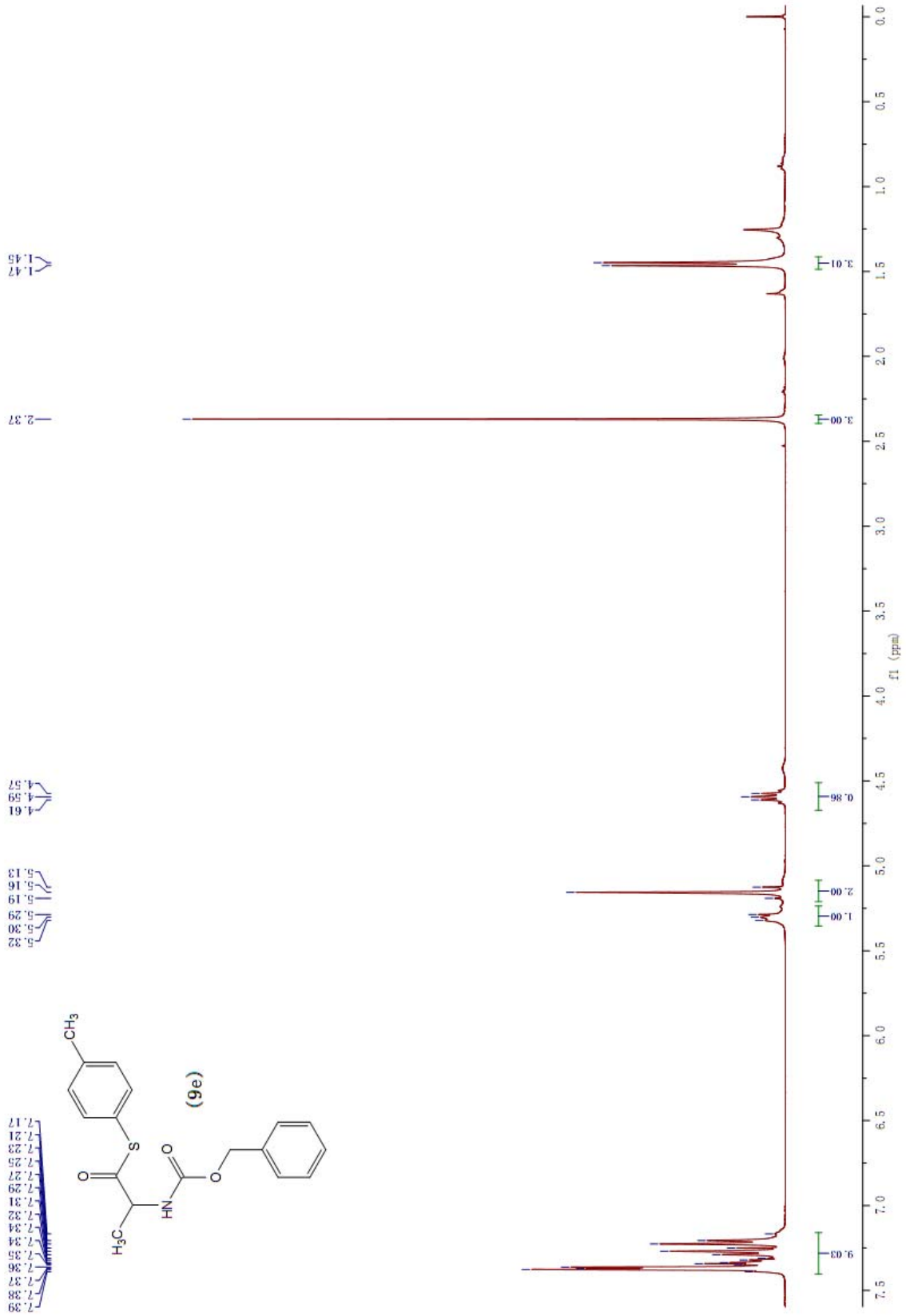
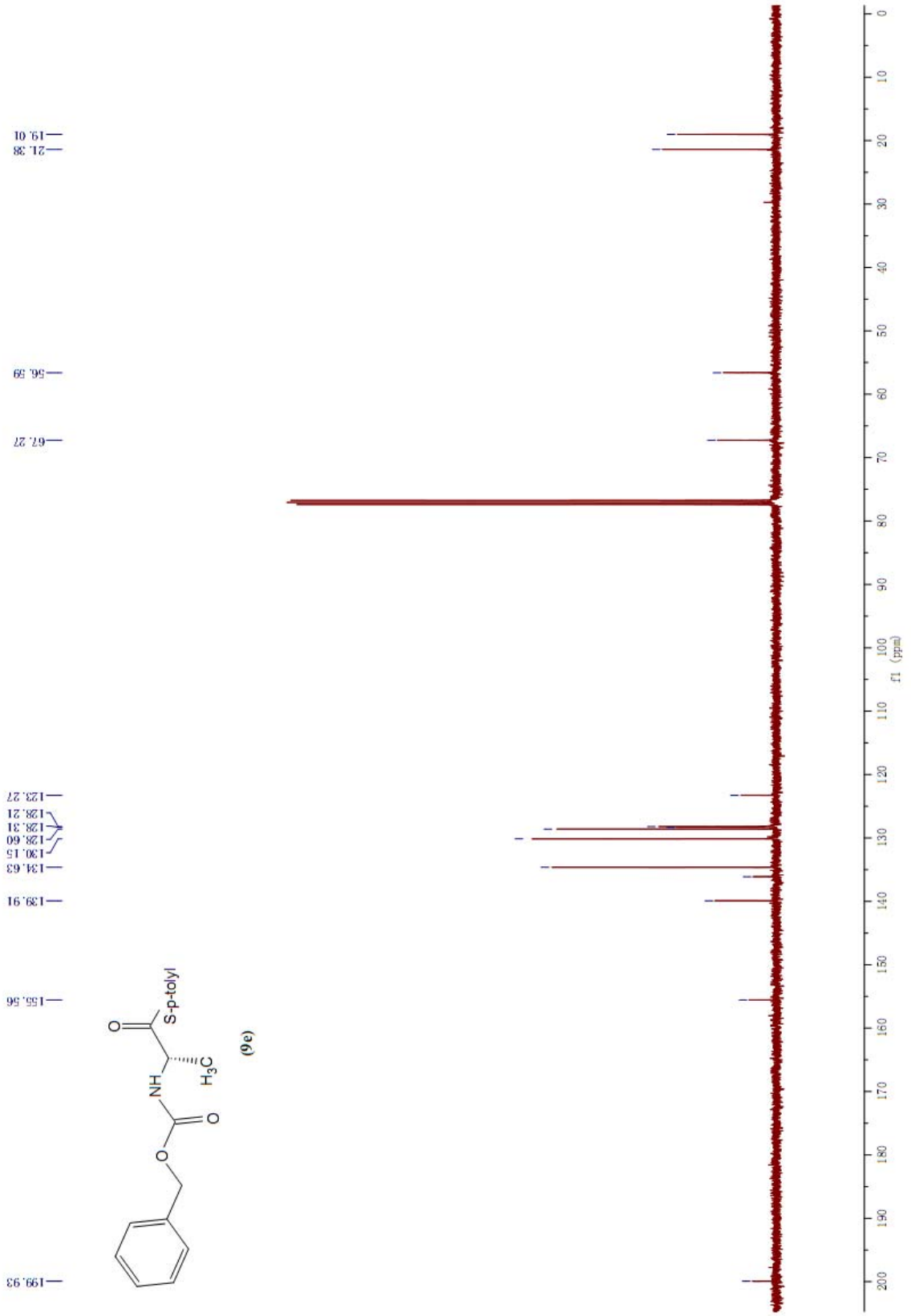
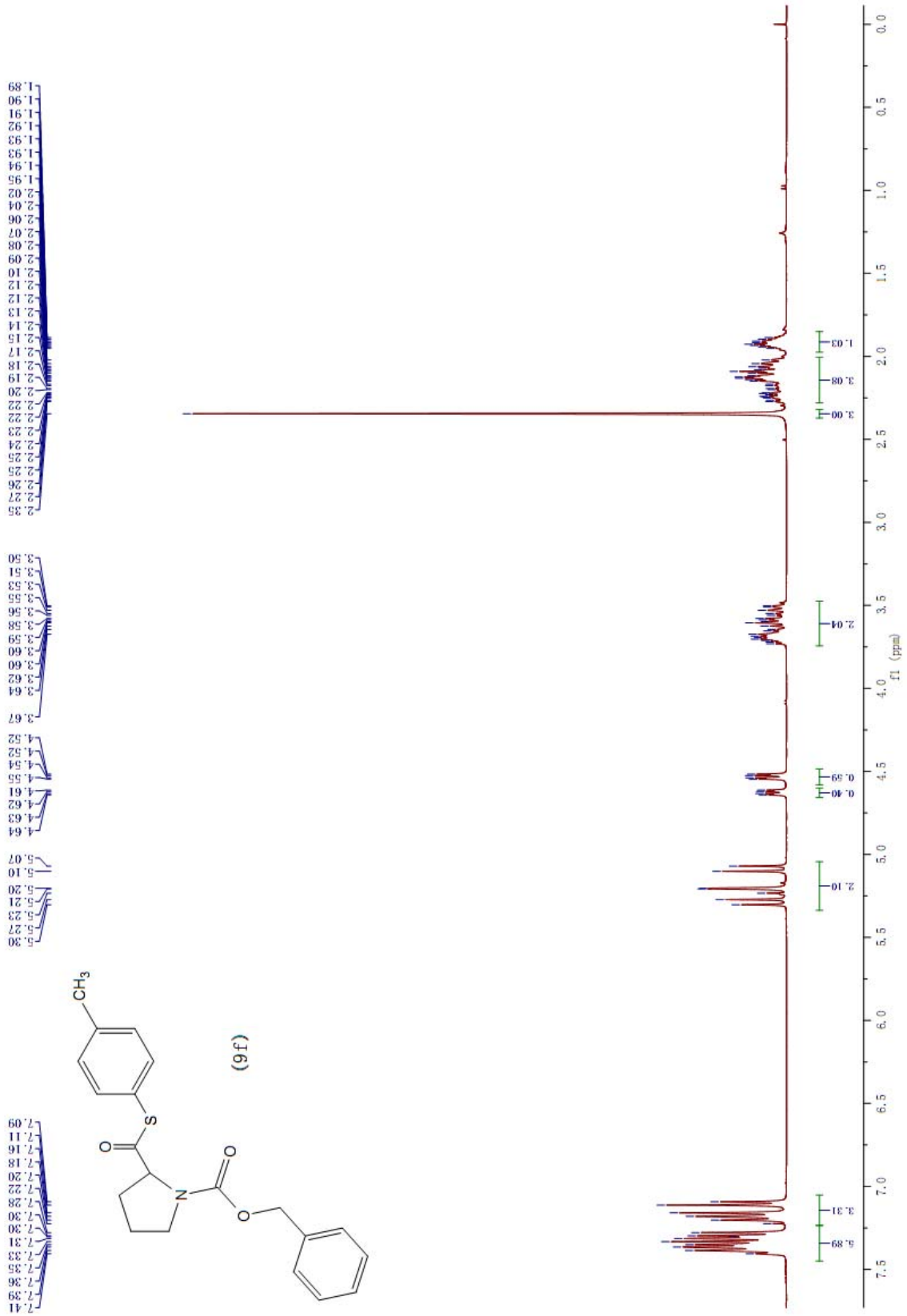
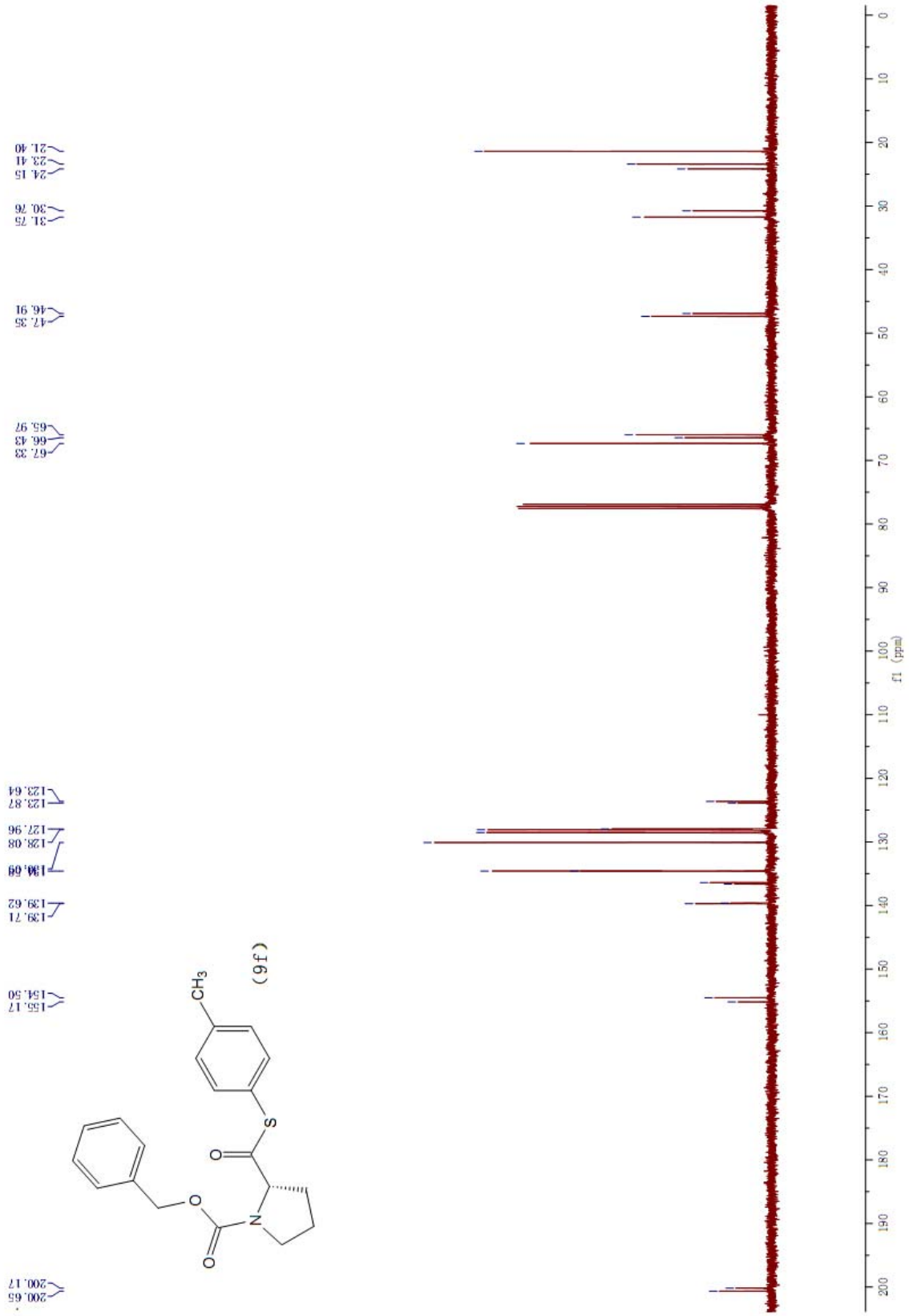
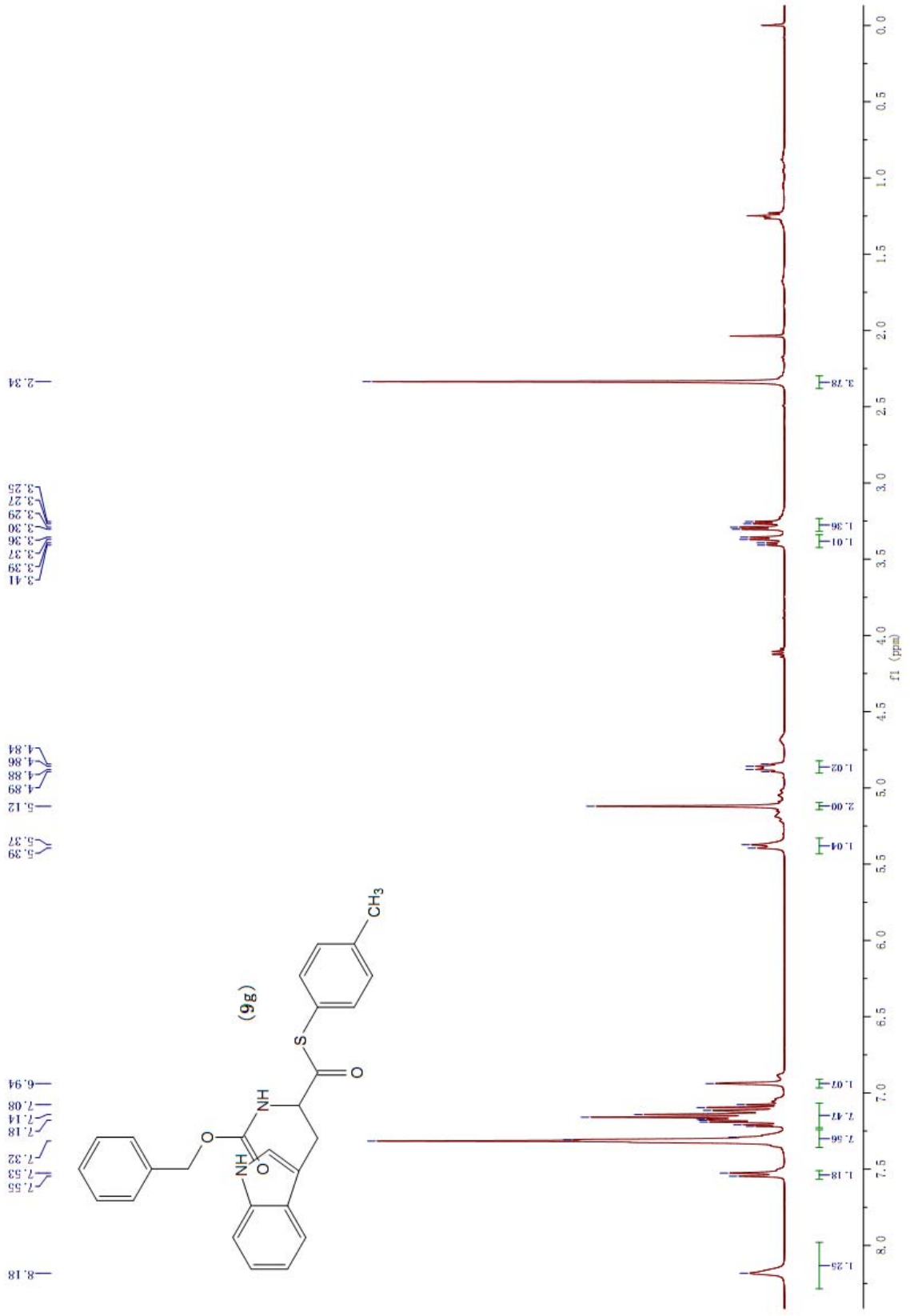


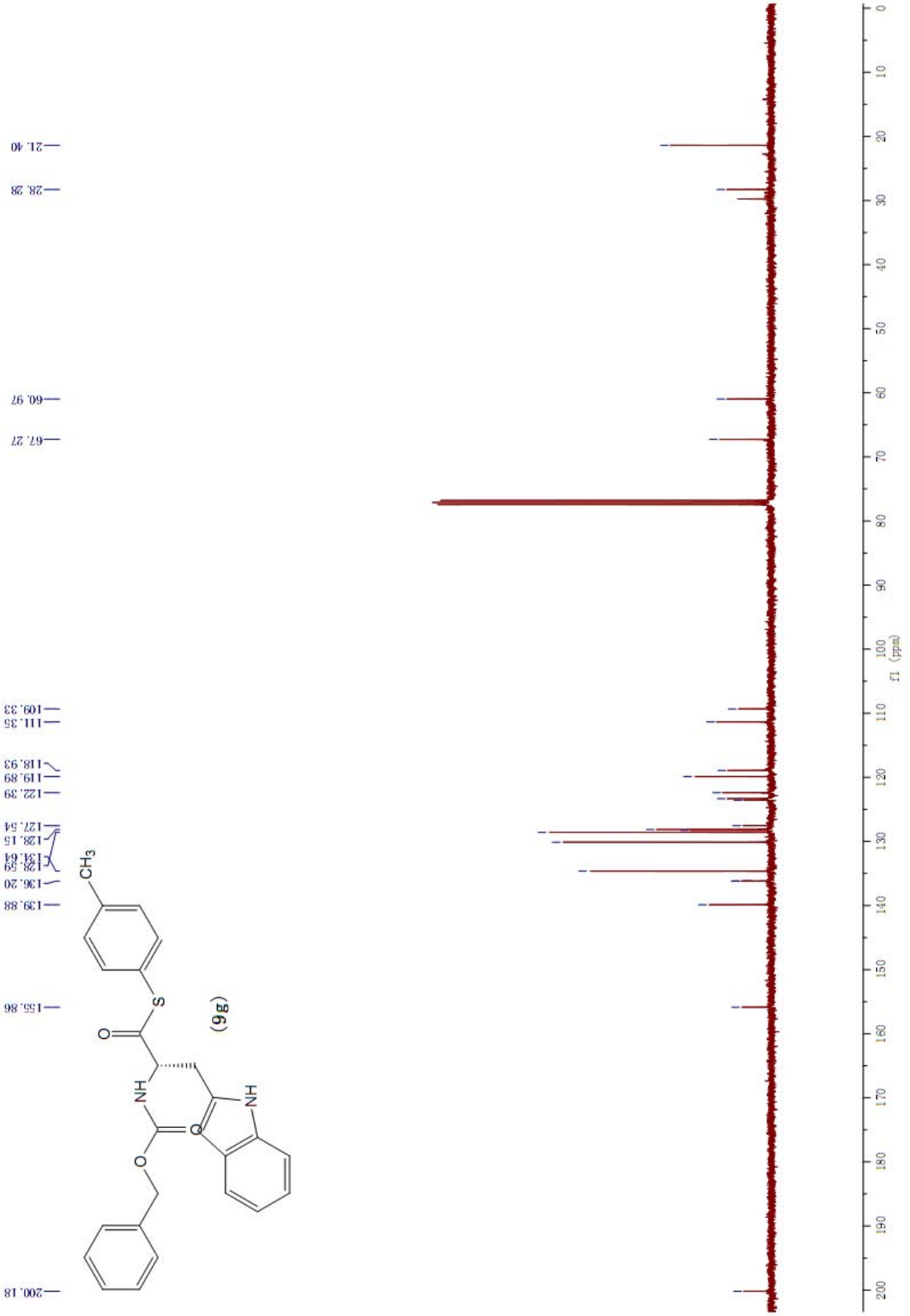

1.45
1.47
2.37
4.57
4.59
4.61
5.13
5.16
5.19
5.29
5.30
5.32
7.17
7.21
7.23
7.25
7.27
7.29
7.31
7.32
7.34
7.34
7.35
7.36
7.37
7.38
7.39
CH3
S
O
O
HN
O
H3C
(9e)
3.01
3.00
0.86
2.00
1.00
9.03
f1 (ppm)

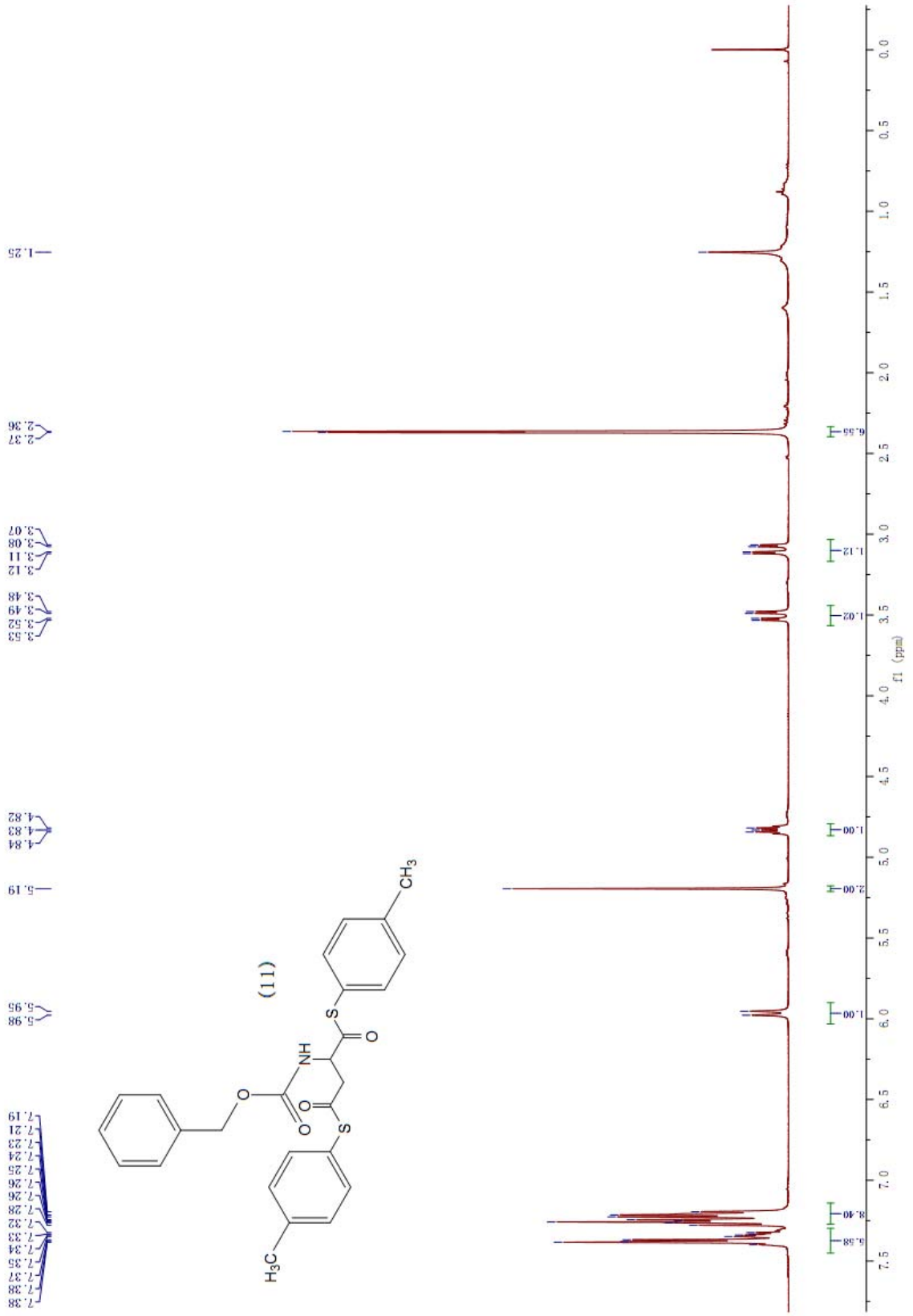

19.01
21.38
56.59
67.27
123.27
128.21
128.31
128.60
130.15
134.63
139.91
155.56
199.93
S-p-tolyl
O
NH
H3C
O
O
(9e)
f1 (ppm)

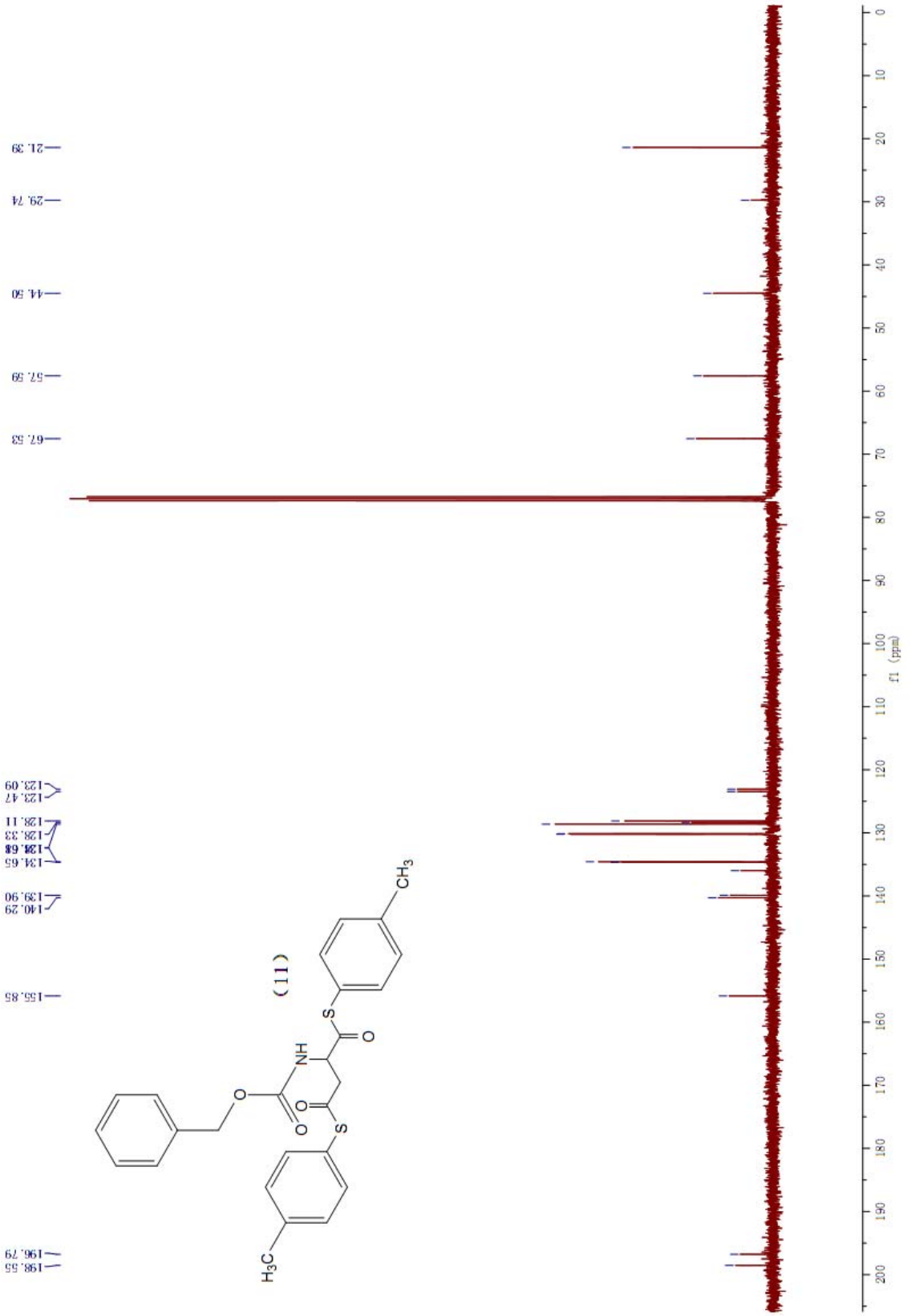

CH3
S
O
N
O
O
(9f)
f1 (ppm)

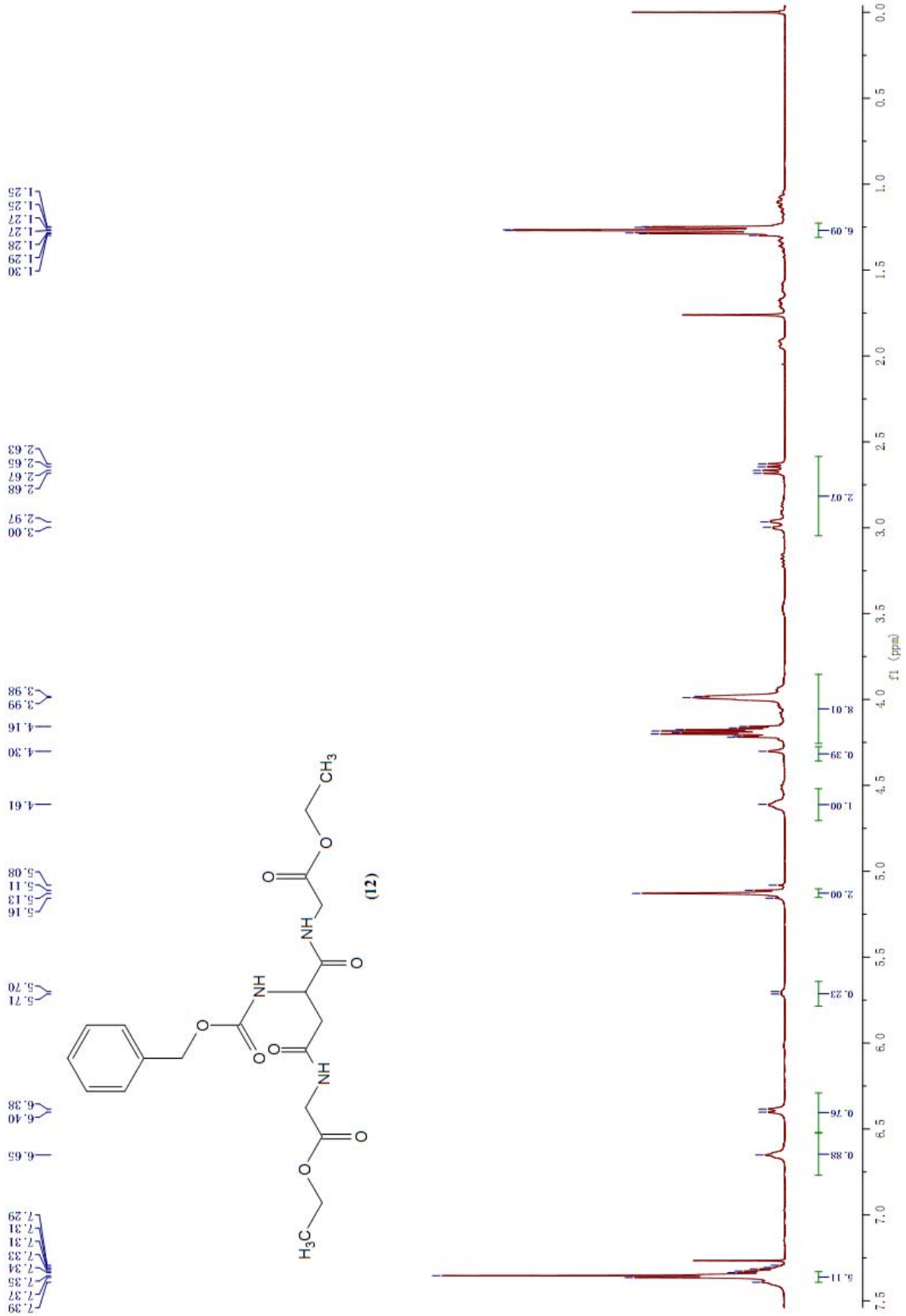

21.40
23.41
24.15
30.76
31.75
46.91
47.35
65.97
66.43
67.33
123.64
123.87
127.96
128.08
139.62
139.71
154.50
155.17
200.17
200.65
CH3
S
O
O
O
N
(9f)
f1 (ppm)

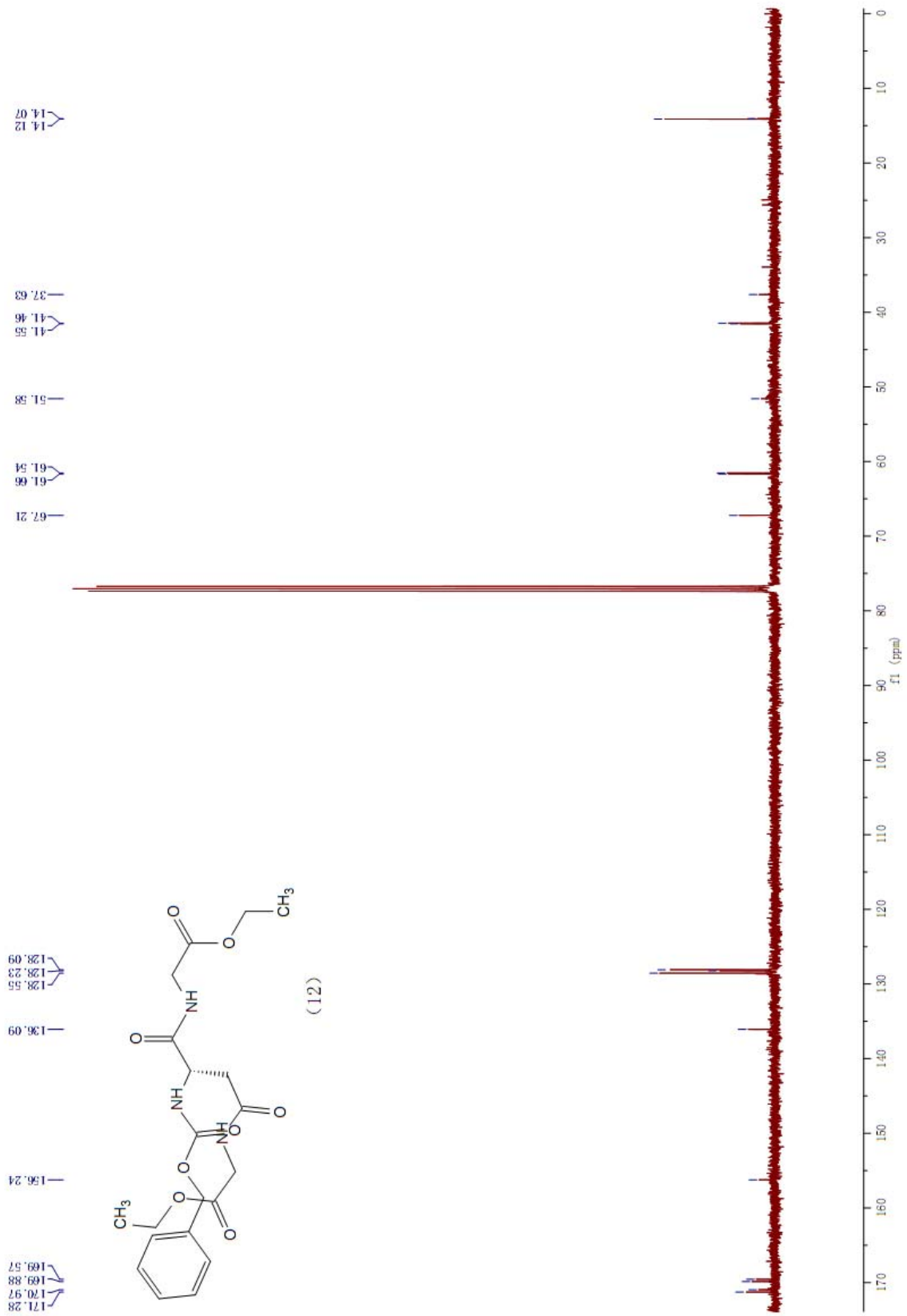

(9g)
CH3
S
O
NH
O
NH
O
2.34
3.25
3.27
3.29
3.30
3.36
3.37
3.39
3.41
4.84
4.86
4.88
4.89
5.12
5.37
5.39
6.94
7.08
7.14
7.18
7.32
7.53
7.55
8.18
3.78
1.36
1.01
1.02
2.00
1.04
1.07
7.47
7.56
1.18
1.28
f1 (ppm)


21.40
28.28
60.97
67.27
109.33
111.35
118.93
119.89
122.39
127.54
128.15
128.59
134.64
136.20
139.88
155.86
200.18
CH3
S
O
NH
O
O
NH
(9g)
f1 (ppm)


(11)
CH3
H3C
NH
O
S
f1 (ppm)


21.39
29.74
44.50
57.59
67.53
123.09
123.47
128.11
128.33
134.65
139.90
140.29
155.85
196.55
196.79
(11)
CH3
H3C
NH
O
S
f1 (ppm)


1.25
1.25
1.27
1.27
1.28
1.29
1.30
2.63
2.65
2.67
2.68
2.97
3.00
3.98
3.99
4.16
4.30
4.61
5.08
5.11
5.13
5.16
5.70
5.71
6.38
6.40
6.65
7.29
7.31
7.31
7.33
7.34
7.35
7.37
7.39
6.09
2.07
8.01
0.39
1.00
2.00
0.23
0.76
0.88
5.11
f1 (ppm)
(12)


14.07
14.12
37.63
41.46
41.55
51.58
61.54
61.66
67.21
128.09
128.23
128.55
136.09
156.24
169.57
169.88
170.97
171.28
(12)
f1 (ppm)