Electronic Supplementary Information

Continuous flow synthesis of β- amino acids from α-amino acids via Arndt-Eistert homologation

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General remarks

^{1}H-NMR spectra were recorded on a 300 MHz instrument. ^{13}C-NMR spectra were recorded on the same instrument at 75 MHz. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet. Analytical HPLC analysis (Shimadzu LC20) was carried out on a C18 reversed-phase (RP) analytical column (150 × 4.6 mm, particle size 5 μm) at 37 °C using a mobile phase A (water–acetonitrile 90 : 10 (v/v) + 0.1% TFA) and B (MeCN + 0.1% TFA) at a flow rate of 1.5 mL/min. The following gradient was applied: linear increase from solution 30% B to 100% B in 8 min, hold at 100% solution B for 2 min. All solvents and chemicals were obtained from standard commercial vendors and were used without any further purification. Diazald was synthesized following a literature procedure.[S1] The known products were characterized by ^{1}H NMR, ^{13}C NMR and mass spectrometry and identified by comparison of the spectra with those reported in the literature. The new compounds **7c** and **7g** were further characterized by HRMS. Proof of purity was obtained by ^{1}H NMR and HPLC-UV spectroscopy.

CAUTION: CH_2N_2 is a highly toxic, carcinogenic and very explosive gas. The reactions present herein should not be undertaken without stringent hazard assessment and proper safety precautions put in place.

The photoreactor should be wrapped with aluminium foil to block the dangerous UV radiation. Protection glasses against UV radiation should be used during the operation of the system.

Construction of the photoreactor

The photoreactor consists of a 3 mL perfluoroalkoxy (PFA) coil surrounding a commercial germicide compact fluorescent UV light (254 nm) (UVL, Figure S1). The support for the coil was constructed using two round bottom flask cork supports (CSP, Figure S1) with 5.5 cm of diameter. The two supports (CSP) were connected using five metal sticks (STK, Figure S1). The PFA tube was coiled around the support (Figure S1). The compact fluorescent UV light was introduced through the top hole of the support. The lamp was kept cooled using an air cooling device on the bottom of the support (CD, Figure S2). The Support was wrapped with aluminium foil to block the dangerous UV radiation (Figure S2).

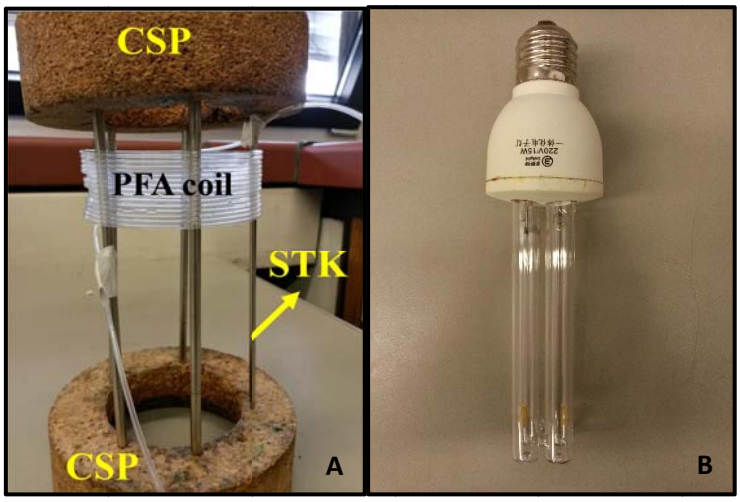


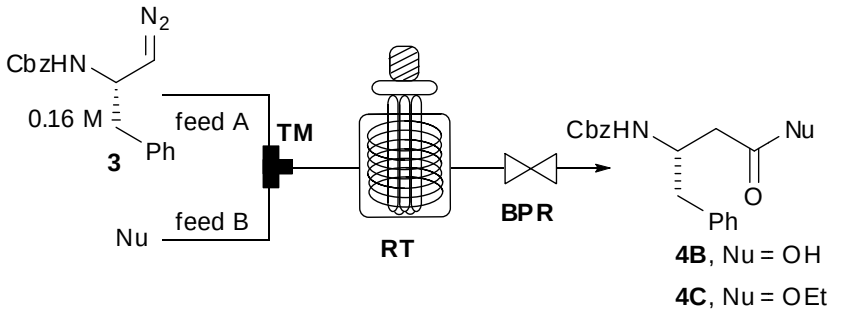
Figure S1: A- Support for the photoreactor. Two round bottom flask cork supports (CSP) with 5.5 cm of diameter were connected using five metal sticks (STK). The PFA tube was coiled around the support; **B**- commercial germicide compact fluorescent UV light.

Optimization study of the continuous flow photochemical Wolff rearrangement

Feed A (0.16 M THF solution of diazoketone **3B**) and feed B (mixture of THF and the nucleophile) pumped at 150 µl.min^{-1} were carried into a T-mixer (**TM**), and the resultant mixture then went through the photoreactor (**RT**) for a specific time according to the volume of the reactor (Table S1). To avoid segmented flow and to obtain stable flow rates and predictable residence times throughout the photoreactor (**RT**), a back-pressure regulator (**BPR**, 6.9 bar) was attached at the end of the stream (Table S1, Figure S2).

With the black compact lamp, we were able to obtain the homologated product **4B** in good yields but the reaction proved to be very slow (entry 1, Table S1). A powerful 100W compact fluorescent lamp was shown to be ineffective providing less than 10% of conversion (not shown in Table S1). A commercial germicide compact fluorescent UV lamp proved to be more effective, enabling good yields of **4B** in just 5 – 10 min residence time (entry 3 and 4, Table S1). Using EtOH as nucleophile afforded the homologated product **4C** in higher yields (entry 5, Table S1).

Table S1: Optimization of the continuous flow photochemical Wolff rearrangement



entry	Source of light	Nu	Residence Time (min)	Yields (%)
1	black compact lamp (365 nm)	H_2O/THF 1:1	80	58 (**4B**)
2	UV compact lamp (254 nm)	H_2O/THF 1:1	40	45(**4B**)
3	UV compact lamp (254 nm)	H_2O/THF 1:1	10	57(**4B**)
4	UV compact lamp (254 nm)	H_2O/THF 1:1	5	55(**4B**)
5	UV compact lamp (254 nm)	EtOH/THF 1:1	10	65(**4C**)

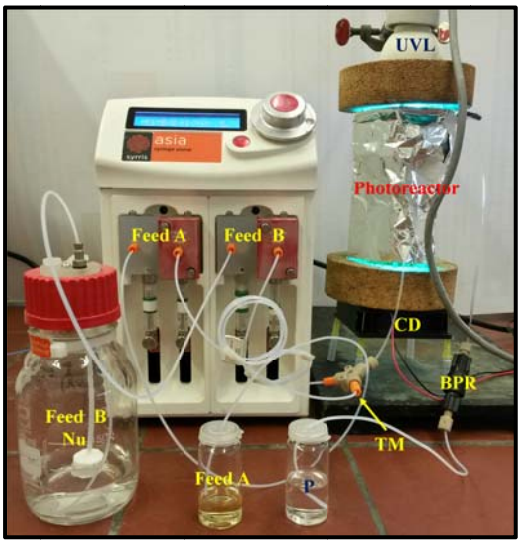
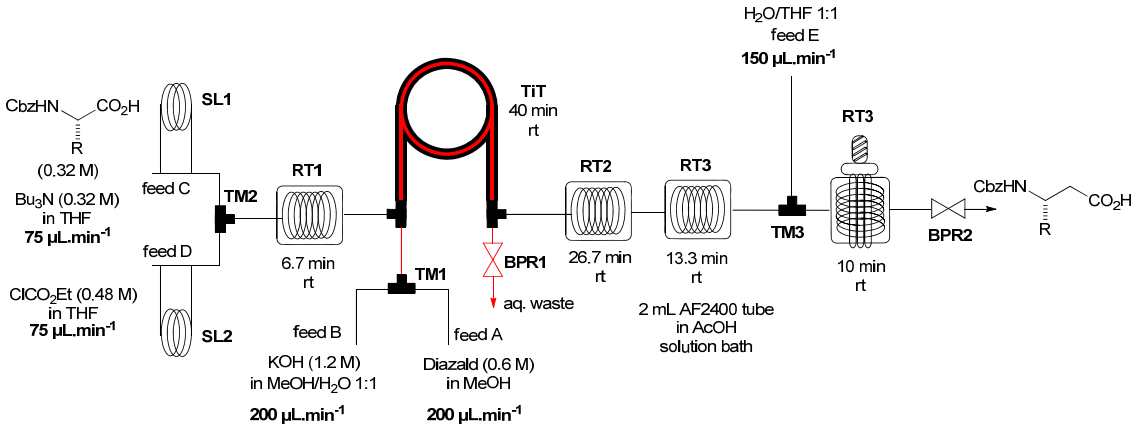


Figure S2: Feed A (0.16 M THF solution of diazoketone **3**) and feed B (mixture of THF and the nucleophile) pumped at 150 µl.min^{-1} were carried into a T-mixer (**TM**), and the resultant mixture then went through the photoreactor at 300 µL.min^{-1} to assure a residence time of 10 min in the photoreactor. In order to obtain stable flow rates and predictable residence times throughout the photoreactor, a back-pressure regulator (**BPR**, 6.9 bar) was attached at the end of the stream.

Continuous process to obtain β-amino acids from α-amino acids via the Arndt Eistert homologation sequence.

Feed A (0.6 M solution of Diazald in MeOH) and feed B (1.2 M solution of KOH in MeOH/H_2O 1:1) were pumped into a T-mixer (**TM1**) by two syringe pumps at flow rates of 200 µL/min each (Asia Syrris). The combined mixture went through a PFA tubing (600 µL internal volume) and then further through the inner tube of the tube-in-tube reactor (**TiT**, room temperature). The mixture leaving the inner tube was quenched into conc. AcOH. Feed C (2 mL of a 0.32 M solution of *N*-Cbz-*L*-phenylalanine **1B** and Bu_3N in dry THF) and feed D (2 mL 0.48 M solution of ethyl chloroformate in dry THF) were pumped into a T-mixer (**TM2**) by two further syringe pumps at flow rates of 75 µL/min each (Asia Syrris). The combined mixture went through a coil reactor (**RT1**, 1 mL internal volume, room temperature) and then further through the outer tube of the tube-in-tube reactor (**TiT**). The mixture leaving the outer tube went through a second coil reactor (**RT2**, 4 mL internal volume, room temperature) and then through a coil of gas-permeable Teflon AF-2400 (**RT3**, 2 mL internal volume). The degassed stream was mixed with an appropriated nucleophile from feed E (1:1 mixture of THF/H_2O or EtOH) in a T-mixer (**TM3**) (Asia Syrris). The new mixture went through the photoreactor (**RT4**, 3mL internal volume) The product was collected in a flask. In the case that EtOH was used as the nucleophile, after collection was finished, the solvent was removed and the residue was purified by flash chromatography with AcOEt/petroleum ether as eluent. When H_2O was used as a nucleophile, the THF was removed and the aqueous phase was extracted 3 times with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered and concentrated and the residue was purified by flash chromatography with AcOEt/petroleum ether as eluent (1% of AcOH was added to the eluent)



Scheme S1 Continuous process to obtain β-amino acids from α-amino acids via the Arndt Eistert homologation sequence

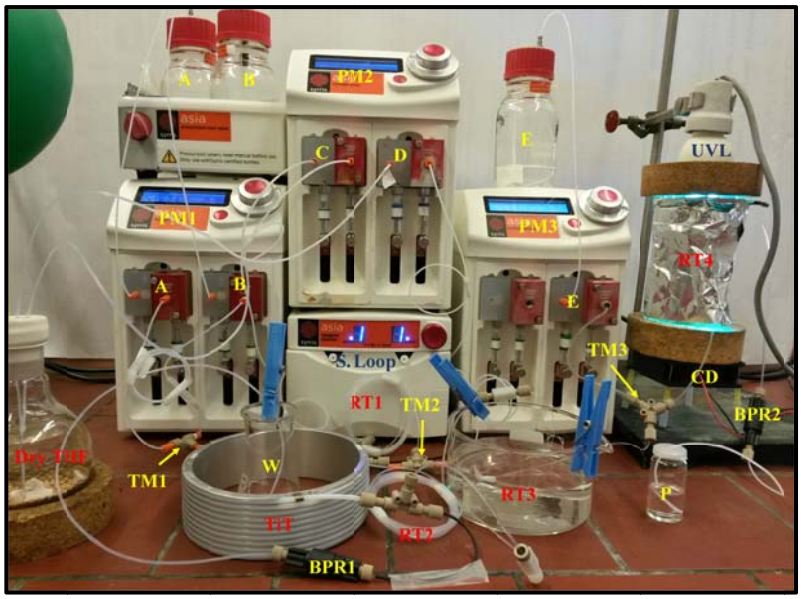


Figure S3: Continuous flow set-up. Feed A (A; Diazald) and feed B (B; KOH in MeOH/H_2O 1:1) were pumped into a T-mixer (**TM1**) by two syringe pumps (**PM1**; Asia syringe pump module). The combined mixture went through a PFA tubing (1.6 mm i.d., 600 µL internal volume) and then further through the inner tube of the tube-in-tube reactor (**TiT**). The mixture leaving the inner tube (yellow out_{inner}, **Figure S4**) was quenched into conc. AcOH (**W**). Feed C (dry THF pumped through sample loop – 0.32 M solution of protected amino acid and Bu_3N in dry THF) and feed D (dry THF pumped through sample loop – 0.48 M solution of ethyl chloroformate (ECF) in dry THF), were pumped into a T-mixer (**TM2**) by two syringe pumps (**PM2**; Asia syringe pump module). The combined mixture went through a 1 mL coil reactor **(RT1**) and then further through the outer tube of the tube-in-tube reactor (**TiT**). The mixture leaving the outer tube went through a 4 mL coil reactor (**RT2**) and thereafter throug a 2 mL coil of gas-permeable Teflon AF-2400 (**RT3**, immersed in a bath of AcOH in MeOH). The degassed stream is mixed with an appropriate nucleophile from feed E in a T-mixer (**TM3**) (**PM3**, Asia syringe pump module). This stream went through the photoreactor (**RT4**) and was collected (**P**). Back-pressure regulators (**BPR2**) (6.9 bar) were attached after **RT4** and to the outlet of the inner tube of the tube-in-tube reactor (**BPR1**) (6.9 bar) (Scheme S1)

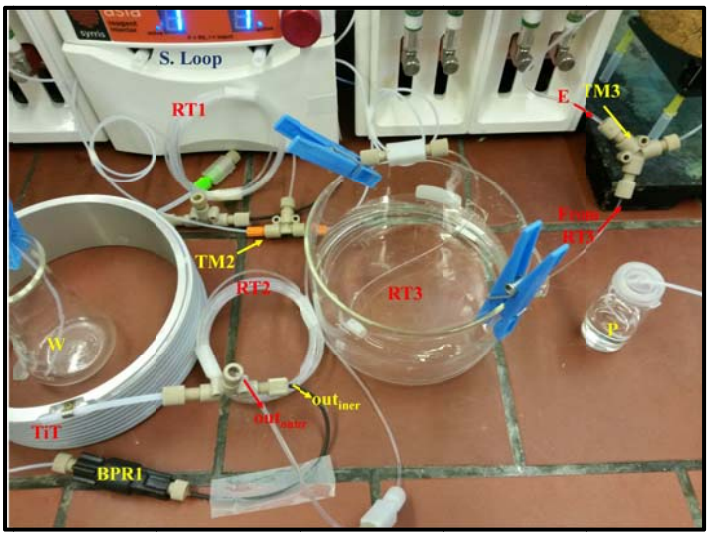
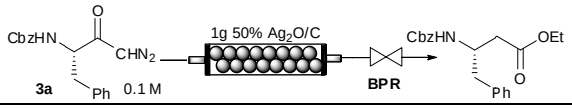


Figure S4: Detail of the setup. **RT1** (1 mL coil reactor); **TiT** (tube-in tube reactor); **TM2** (T-mixer 2); **RT2** (4mL coil reactor), **RT3** (2 mL coil of gas-permeable Teflon AF-2400 in a bath of AcOH in MeOH); **TM3** (T-mixer 3); E (feed of nucleophile); **W** (quench solution of AcOH); **BPR1** (back-pressure regulator 1); **P** (collected product)

Silver-catalyzed approach

A mixture of 1g 50% silver oxide and charcoal (previously mechanically mixed for 30 min), was used to pack an Omnifit column (6.6mm/100mm) (http://www.omnifit.com/). The column was fitted into a Syrris heating block (http://www.syrris.com) to allow for temperature control. A 5.2 bar back- pressure regulator was attached at the outlet of reactor. A 2 mL solution of diazoketone **3** (0.1 M THF/EtOH 1:1) was pumped through the column at the flow rates shown in Table S1. The outlet stream was collected for 35 min. The conversion was determined by HPLC. The collected product was concentrated and purified by chromatography, affording the homologated product in 71% yield, as a white solid (Figure S5).

Table S1 Continuous flow silver catalyzed Wolff rearrangement



entry	Flow rate (μL)	T (°C)	Residence Time (min)	Conversion (%)[#]
1	400	r.t	5	76
2	400	60	5	93
3	200	60	10	100 (71)

#conversion determined by HPLC analysis

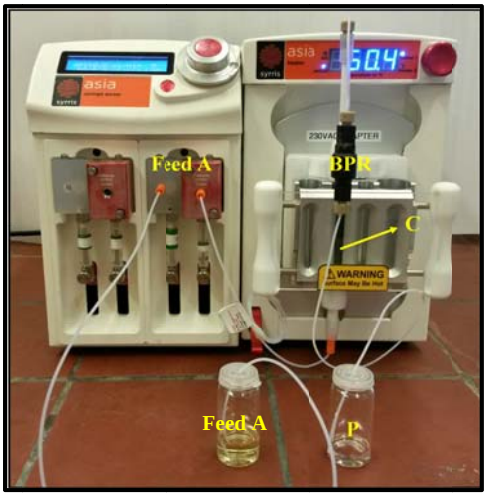


Figure S5: Feed A (0.1 M solution of diazoketone **3** in THF/EtOH 1:1) was pumped through the column (**C**), at 60 °C. Collected product (**P**).

Characterization data

(*S*)-Benzyl (4-diazo-3-oxo-1-phenylbutan-2-yl)carbamate (3): mp: 85-87°C (lit.[S2] 84 °C); $[\alpha]_D^{20}$ -43.2 (c 1.02, $CHCl_3$), lit.[S3] : $[\alpha]_D^{22}$ -42 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.14 (m, 10H), 5.46 (d, *J* = 7.0 Hz, 1H), 5.23 (s, 1H), 5.10 (s, 2H), 4.51 (br d, *J* = 6.9 Hz, 1H), 3.06 (d, *J* = 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.74, 155.72, 136.15, 136.01, 129.34, 128.71, 128.56, 128.25, 128.08, 127.11, 67.06, 58.86, 54.64, 38.51; FT-IR (KBr, cm^{-1}) 3326, 3033, 2950, 2103, 1685, 1632, 1527, 1464, 1370, 1249, 1198, 1112880, 636, 575; *R*f: 0.39 (50% EtOAc/ petroleum ether).

(*S*)-3-((tert-Butoxycarbonyl)amino)-4-phenylbutanoic acid (4a): 80 mg (0.29 mmol, 45%, white solid); mp: 99-101°C (lit.[S4] 104-107 °C); $[\alpha]_D^{20}$ -16.1 (c 0.99, $CHCl_3$), lit.[S5] : $[\alpha]_D^{22}$ -16.0 (c 0.98, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 9.23 (s, 1H), 7.49 – 7.08 (m, 6H), 5.08 (s, 1H), 4.35 – 3.87 (m, 1H), 3.10 – 2.76 (m, 2H), 2.71 – 2.33 (m, 2H), 1.42 (s, *J* = 9H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ 176.81, 156.33, 155.26, 137.60, 129.39, 128.55, 126.63, 81.05, 79.68, 48.64, 40.29, 37.44, 28.32; FT-IR (KBr, cm^{-1}) 3364, 3026, 2979, 2923, 1686, 1519, 1430, 1415, 1366, 1265, 1164, 1082, 1049, 1026, 853; *R*f: 0.27 (50% EtOAc/ petroleum ether, 1% AcOH).

(*S*)-3-(((Benzyloxy)carbonyl)amino)-4-phenylbutanoic acid (4b): 80 mg (0.26 mmol, 40%, white solid); mp: 116 - 118°C (lit.[S6] 116 - 118 °C); $[\alpha]_D^{20}$ -32.0 (c 1.20, $CHCl_3$), lit[S3] : $[\alpha]_D^{22}$ -36.0 (c 0.90, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.00 (m, 10H), 5.40 – 5.24 (m, 1H), 5.09 (s, 2H), 4.39 – 4.13 (m, 1H), 3.10 – 2.80 (m, 2H), 2.72 – 2.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ 176.54, 155.71, 137.30, 136.34, 129.34, 128.64, 128.53, 128.16, 128.08, 126.79, 66.78, 49.17, 40.13, 37.18; FT-IR (KBr, cm^{-1}) 3329, 3030, 2919, 1694, 1532, 1496, 1454, 1416, 1374, 1258, 1083, 772, 748; *R*f: 0.35 (50% EtOAc/ petroleum ether, 1% AcOH); *R*f: 0.15 (30% acetone DCM).

(*S*)-Ethyl 3-(((benzyloxy)carbonyl)amino)-4-phenylbutanoate (4c): 118 mg (0.34 mmol, 54%, white solid): mp:70-73 °C; $[\alpha]_D^{20}$ -14.0 (c 0.92, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.11 (m, 10H), 5.35 (d, *J* = 8.3 Hz, 1H), 5.09 (s, 2H), 4.33 – 4.21 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.52 – 2.76 (m, 2H), 2.60 – 2.40 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 171.53, 155.59, 137.49, 136.52, 129.36, 128.57, 128.50, 128.07, 128.02, 126.68, 66.59, 60.68, 49.36, 40.25, 37.53, 14.20; FT-IR (KBr, cm^{-1}) 3347, 3033, 2980, 2905, 1776, 1887, 1602, 1533, 1498, 1443, 1376, 1313, 1167, 1024, 872; HRMS (ESI) calcd for $C_{20}H_{24}NO_4$ $[M+H]^+$, 342,17053, found 342,16996; *R*f: 0.45 (5% EtOAc/ DCM).

(*R*)-4-(Benzyloxy)-3-((tert-butoxycarbonyl)amino)butanoic acid (4d): 67 mg (0.22 mmol, 34%, viscous yellowish oil); ^1H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 7.41 – 7.26 (m, 5H), 5.22 (br m, 1H), 4.53 (s, 1H), 4.16 (br m, 1H), 3.66 – 3.48 (m, 2H), 2.78 – 2.58 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ 176.14, 155.40, 137.82, 128.40, 127.74, 127.62, 79.74, 73.21, 70.94, 47.09, 36.15, 28.34; FT-IR (KBr, cm^{-1}) 3375, 3058, 2978, 1740, 1681, 1454, 1294, 1247, 1096, 1026, 884, 776; HRMS (ESI) calcd for $C_{16}H_{24}NO_5$ $[M+H]^+$, 310,16545, found 310.16487; *R*f: 0.33 (40% EtOAc/ petroleum ether, 1% AcOH).

(*S*)-3-(((Benzyloxy)carbonyl)amino)butanoic acid (4e): 79 mg (0.33 mmol, 52%, White solid): mp: 99–102 °C (lit[S6] 104–106 °C); $[\alpha]_D^{20}$ -14.5 (c 1.99, $CHCl_3$), lit[S7]: $[\alpha]_D^{25}$ -15.7 (c 1.04, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.26 (m, 5H), 5.43 – 5.23 (m, 1H), 5.25 – 4.99 (m, 2H), 4.22 – 4.02 (m, 1H), 2.68 – 2.46 (m, 2H), 1.28 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.53, 155.68, 136.35, 128.55, 128.17, 66.78, 43.79, 40.22, 20.29; FT-IR (KBr, cm^{-1}) 3307, 3031, 2971, 2931, 1685, 1535, 1452, 14,17, 1251, 1088, 1061, 950, 693; *R*f: 0.31 (40% EtOAc/ petroleum ether, 1% AcOH).

(*R*)-5-(Benzyloxy)-3-((tert-butoxycarbonyl)amino)-5-oxopentanoic acid (4f): 79 mg (0.24 mmol, 37%, white solid): mp: 101-103 °C (lit[S4] 96-99); $[\alpha]_D^{20}$ +1.6 (c 2.04, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 7.43 – 7.30 (m, 5H), 5.49 – 5.33 (m, 1H), 5.14 (s, *J* = 8.4 Hz, 2H), 4.44 – 4.25 (m, 1H), 2.83 – 2.49 (m, 4H), 1.51 – 1.37 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ 175.90, 171.13, 155.10, 135.52, 128.61, 128.37, 128.27, 79.88, 66.63, 44.21, 38.10, 37.92, 28.32; FT-IR (KBr, cm^{-1}) 3375, 2978, 2931, 1740, 1682, 1523, 1366, 1247, 1199, 1057, 950, 692; HRMS (ESI) calcd for $C_{17}H_{24}NO_6$ $[M+H]^+$, 338,16036, found 338,15978; *R*f: 0.42 (40% EtOAc/ petroleum ether, 1% AcOH).

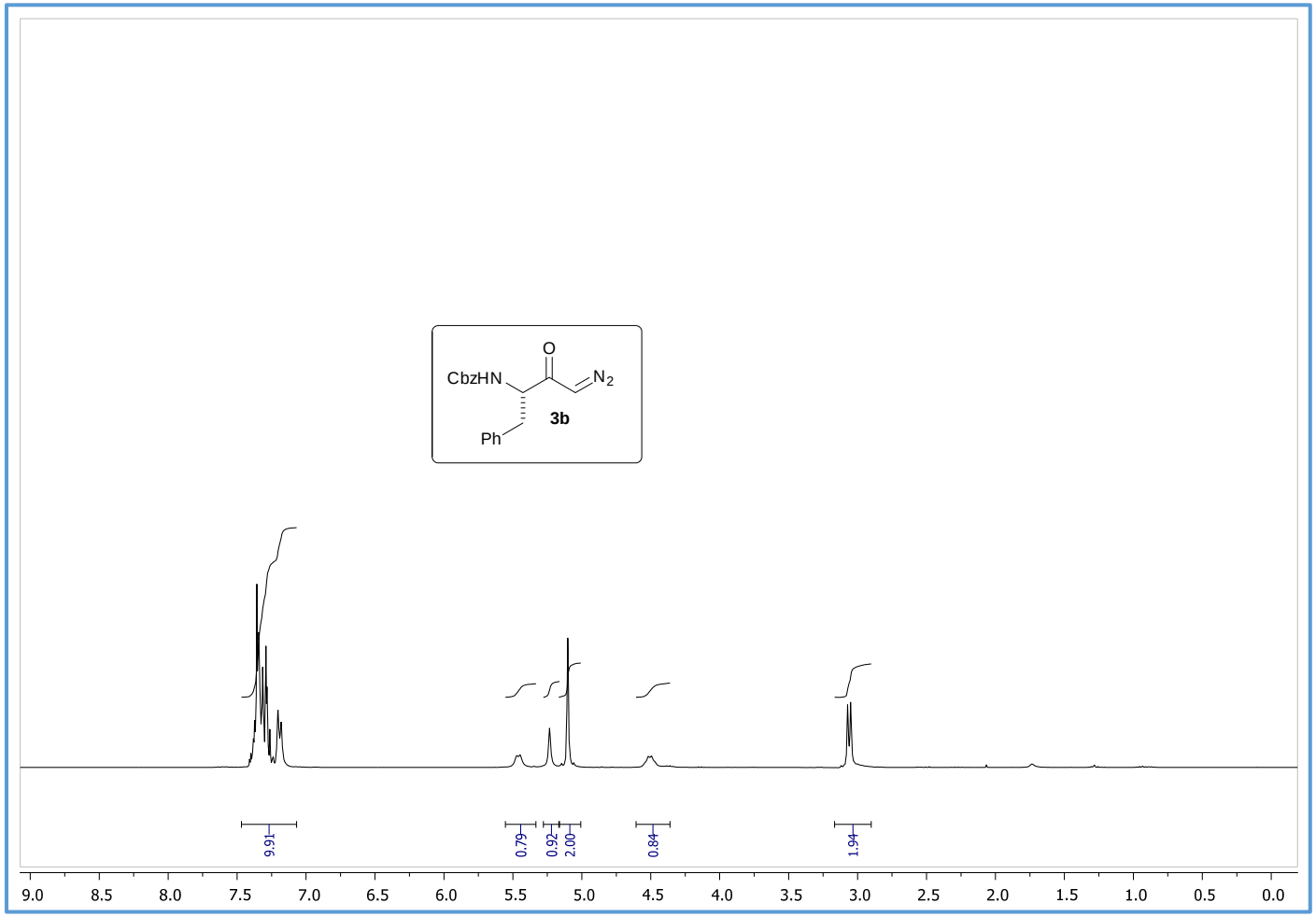
(*R*)-3-(((Benzyloxy)carbonyl)amino)-4-methylpentanoic acid (4g): 64 mg (0.24 mmol, 38%, white solid): mp: 89-91 °C; $[\alpha]_D^{20}$ -24.7 (c 3.14, $CHCl_3$), lit[S8]: $[\alpha]_D^{20}$ -16.5 (c 1.10, $CHCl_3$), lit[S6]:

$[\alpha]_D^{23}$ -33.6 (c 0.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 – 6.80 (m, 5H), 4.83 – 4.70 (m, 1H), 4.70 – 4.57 (m, 2H), 3.45 – 3.28 (m, 1H), 2.18 – 1.98 (m, 2H), 1.49 – 1.29 (m, 1H), 0.46 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.26, 156.62, 136.92, 129.04, 128.60, 67.57, 54.26, 37.67, 32.51, 20.28, 19.50; FT-IR (KBr, cm^{-1}) 3334, 3036, 2958, 2872, 1689, 1530, 1412, 1354, 1241, 1154, 1028, 929, 777, 731; *R*f: 0.22 (40% EtOAc/ petroleum ether, 1% AcOH).

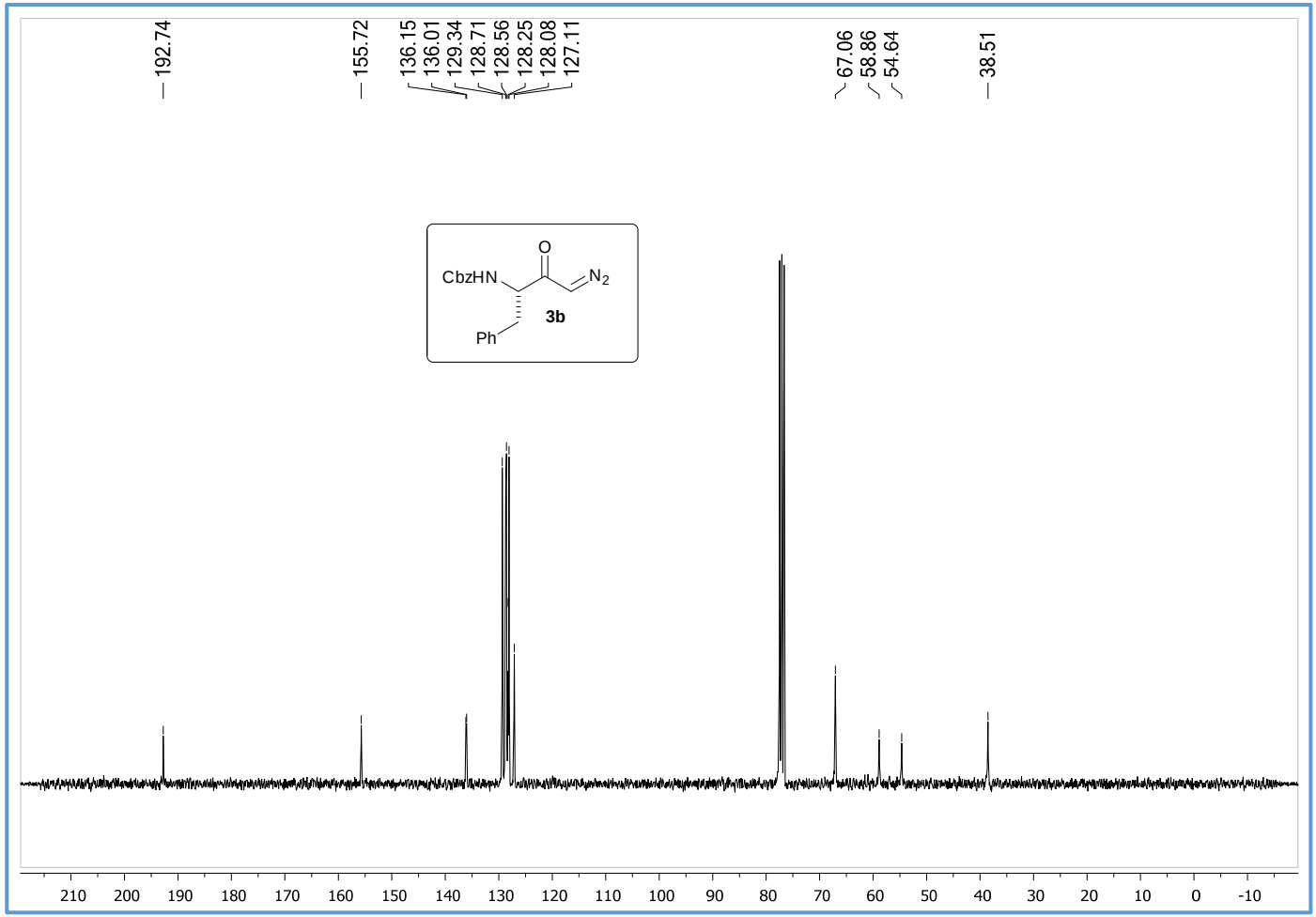
(*S*)-2-(1-(tert-Butoxycarbonyl)pyrrolidin-2-yl)acetic acid (4h): 61 mg (0.27 mmol, 42%, white solid): mp: 101-104 °C (lit[S9] 98-99 °C); $[\alpha]_D^{20}$ -39.0 (c 0.99, DMF), lit[S9]: $[\alpha]_D^{20}$ -38.6 (c 1.41, DMF); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 8.90 (br s, *J* = 250.4 Hz, 1H), 4.35 – 4.00 (m, 1H), 3.57 – 3.24 (m, 2H), 2.88 (br m, 1H), 2.34 (dd, *J* = 15.4, 9.4 Hz, 1H), 2.17 – 1.99 (m, 1H), 1.94 – 1.69 (m, 3H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ 176.91, 154.63, 80.04, 54.00, 46.64, 39.22, 31.21, 28.56, 23.59, 22.94; FT-IR (KBr, cm^{-1}) 3307, 3031, 2968, 2932, 1684, 1535, 1452, 1418, 1300, 1251, 1117, 250, 730; *R*f: 0.30 (50% EtOAc/ petroleum ether, 1% AcOH).

Spectroscopic data

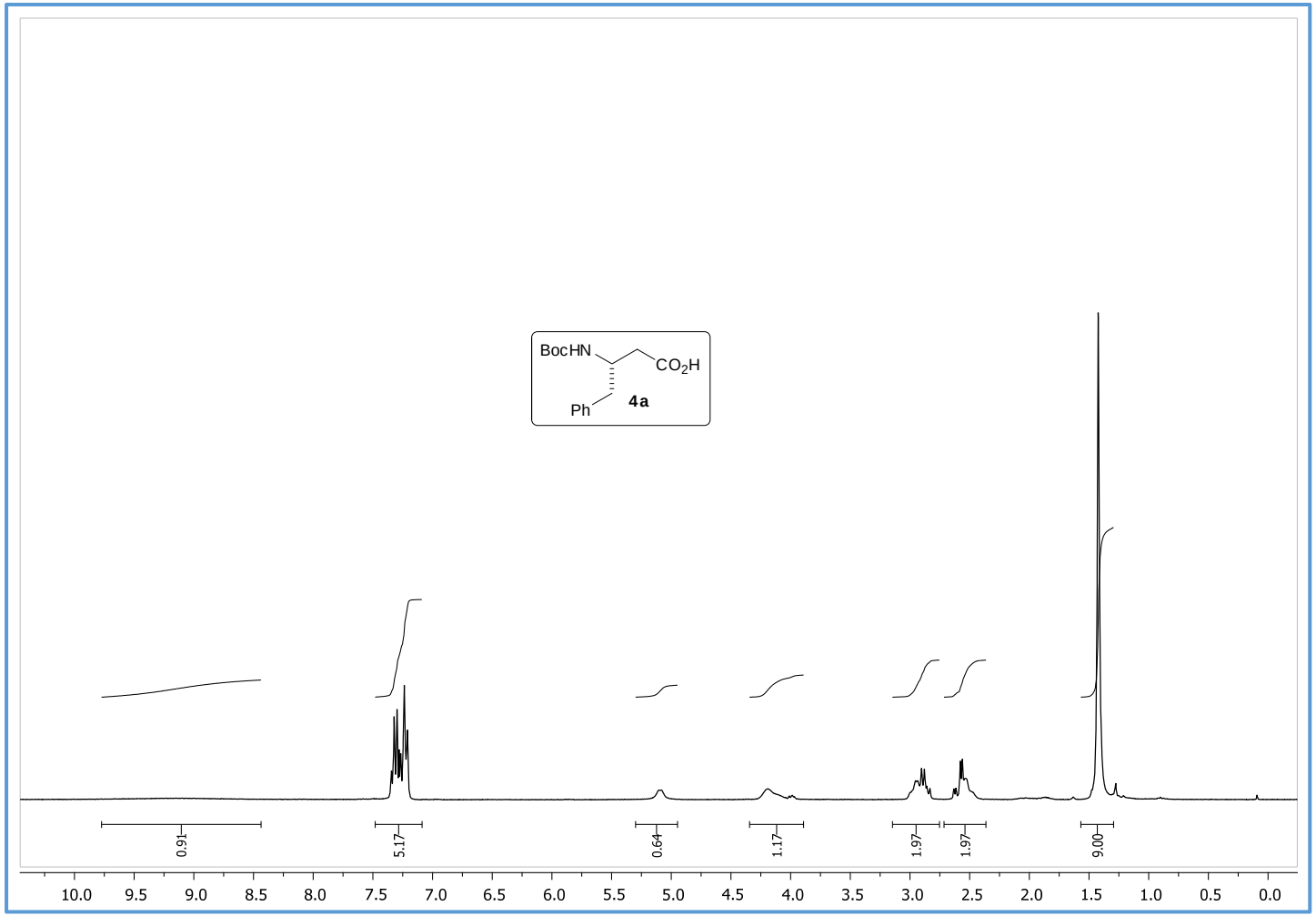
^{1}H NMR of (*S*)-benzyl (4-diazo-3-oxo-1-phenylbutan-2-yl)carbamate 3b



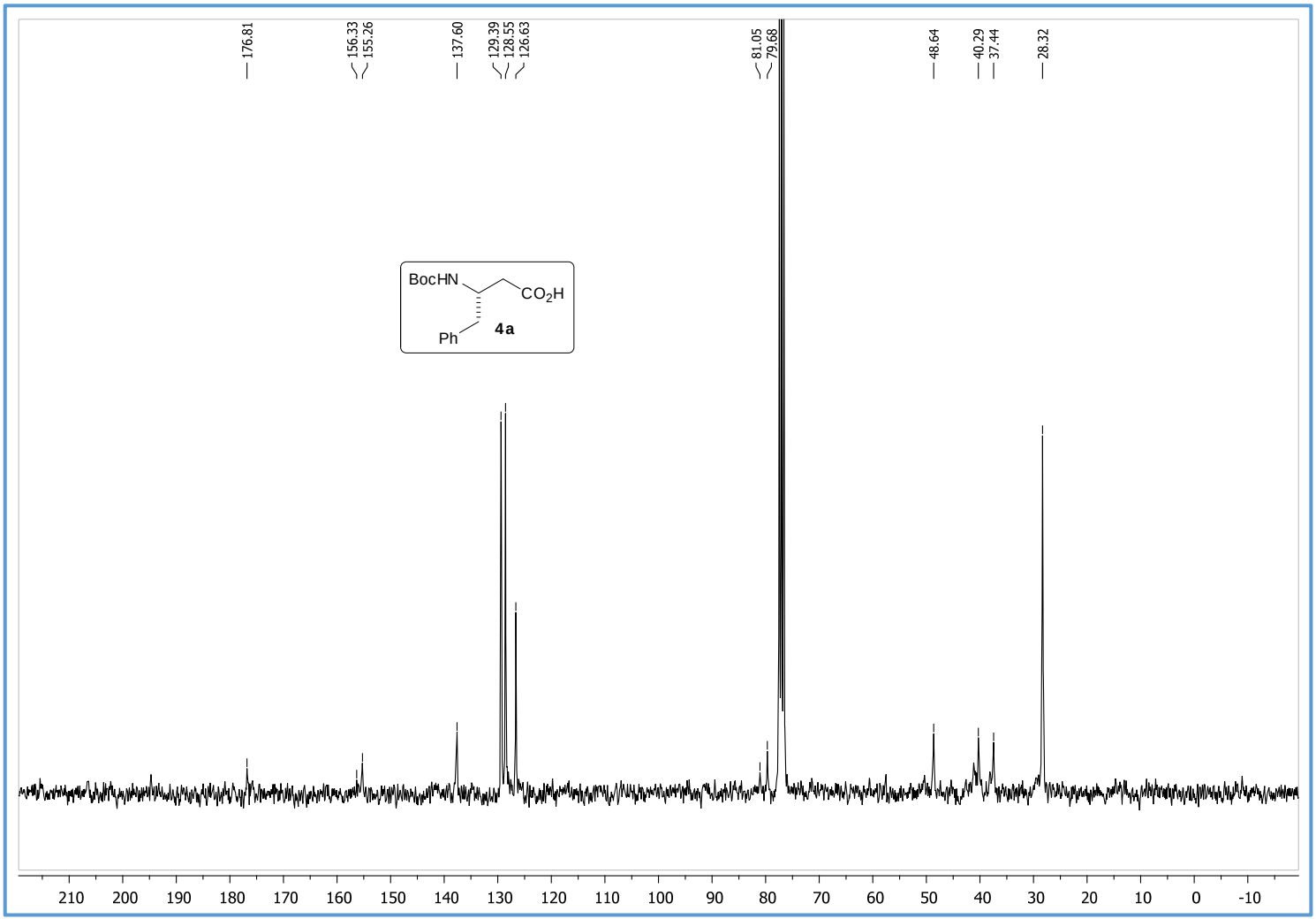
^{13}C NMR of (*S*)-benzyl (4-diazo-3-oxo-1-phenylbutan-2-yl)carbamate 3b



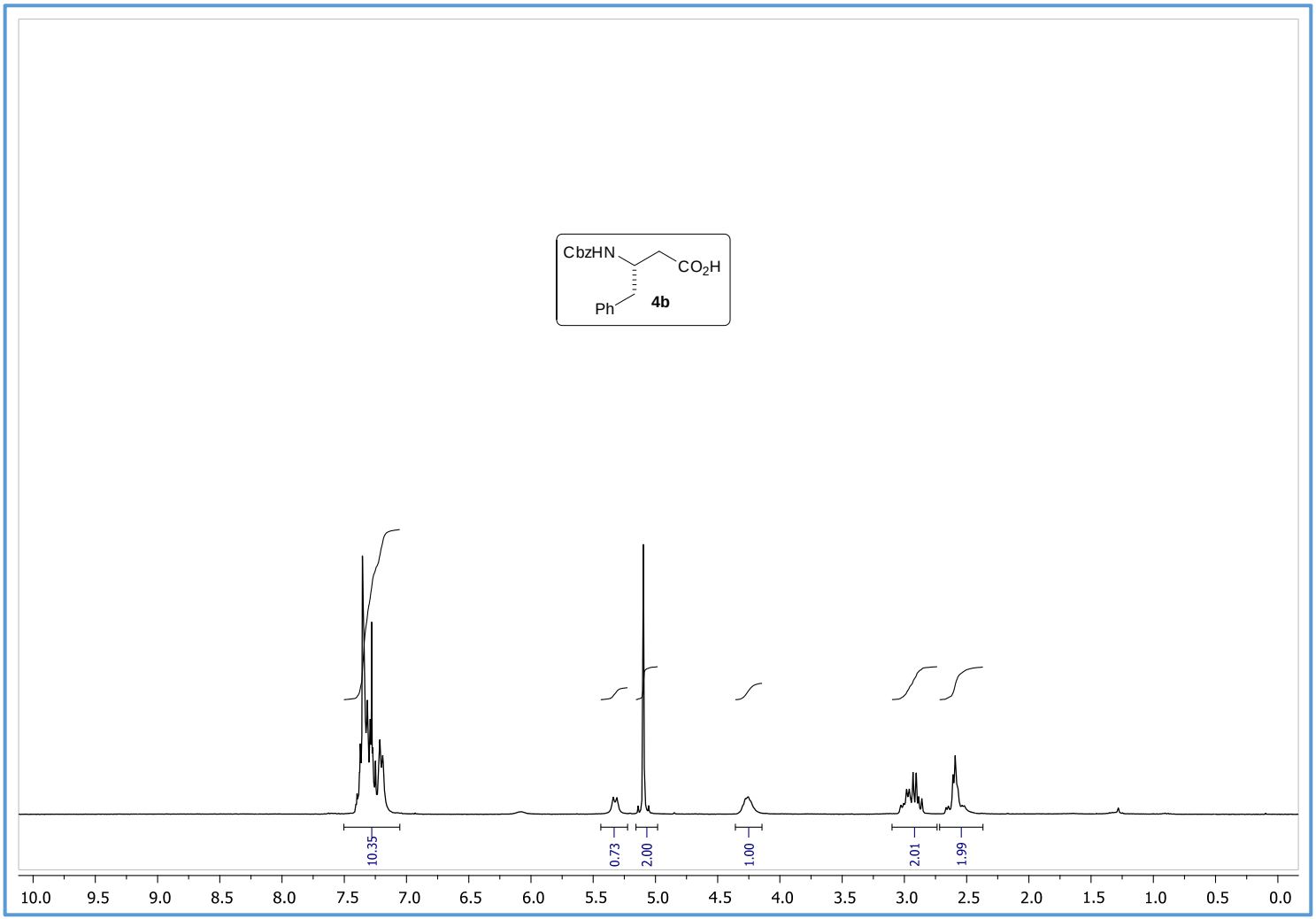
^{1}H NMR of (*S*)-3-((tert-butoxycarbonyl)amino)-4-phenylbutanoic acid 4a



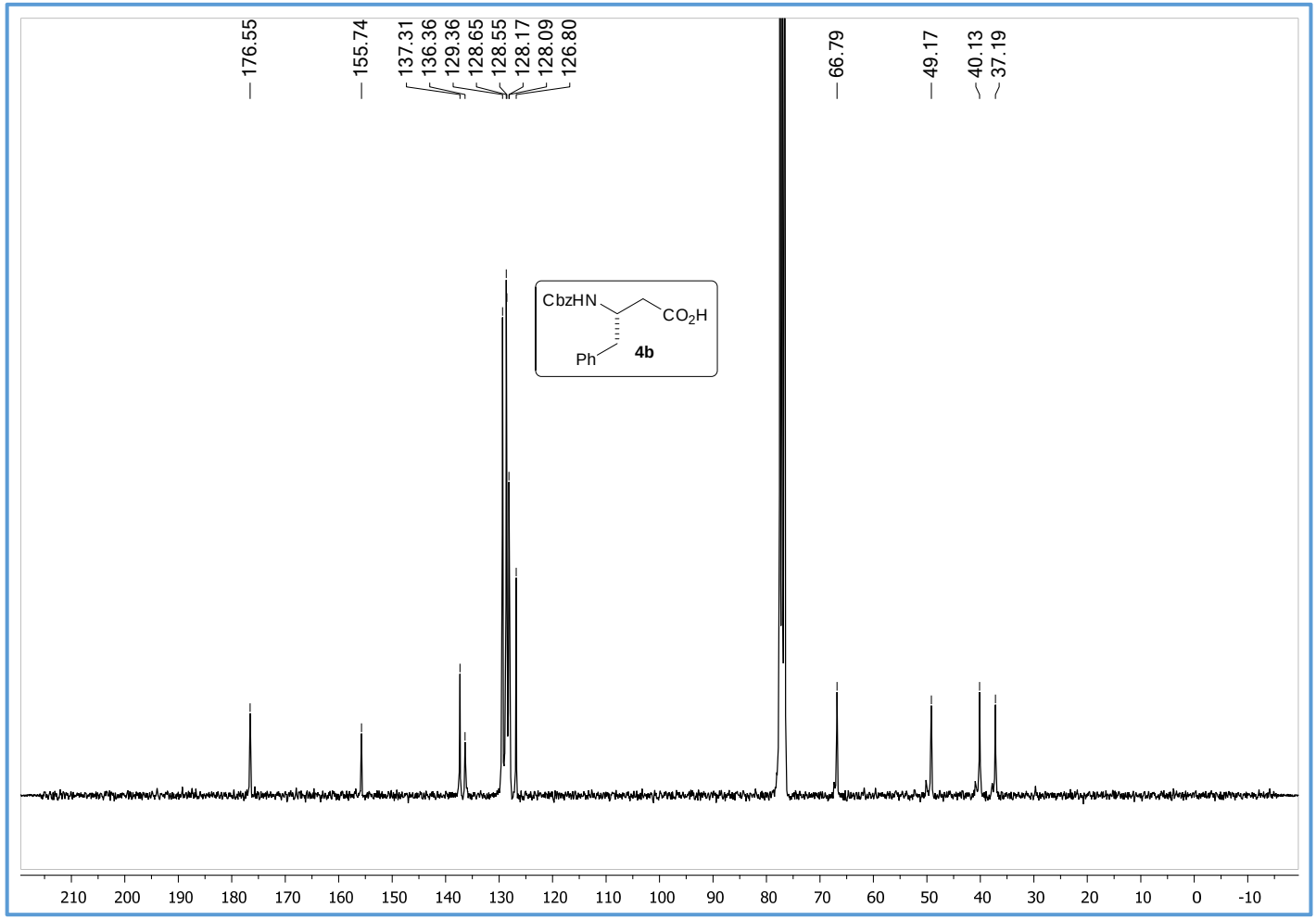
^{13}C NMR of (*S*)-3-((tert-butoxycarbonyl)amino)-4-phenylbutanoic acid 4a



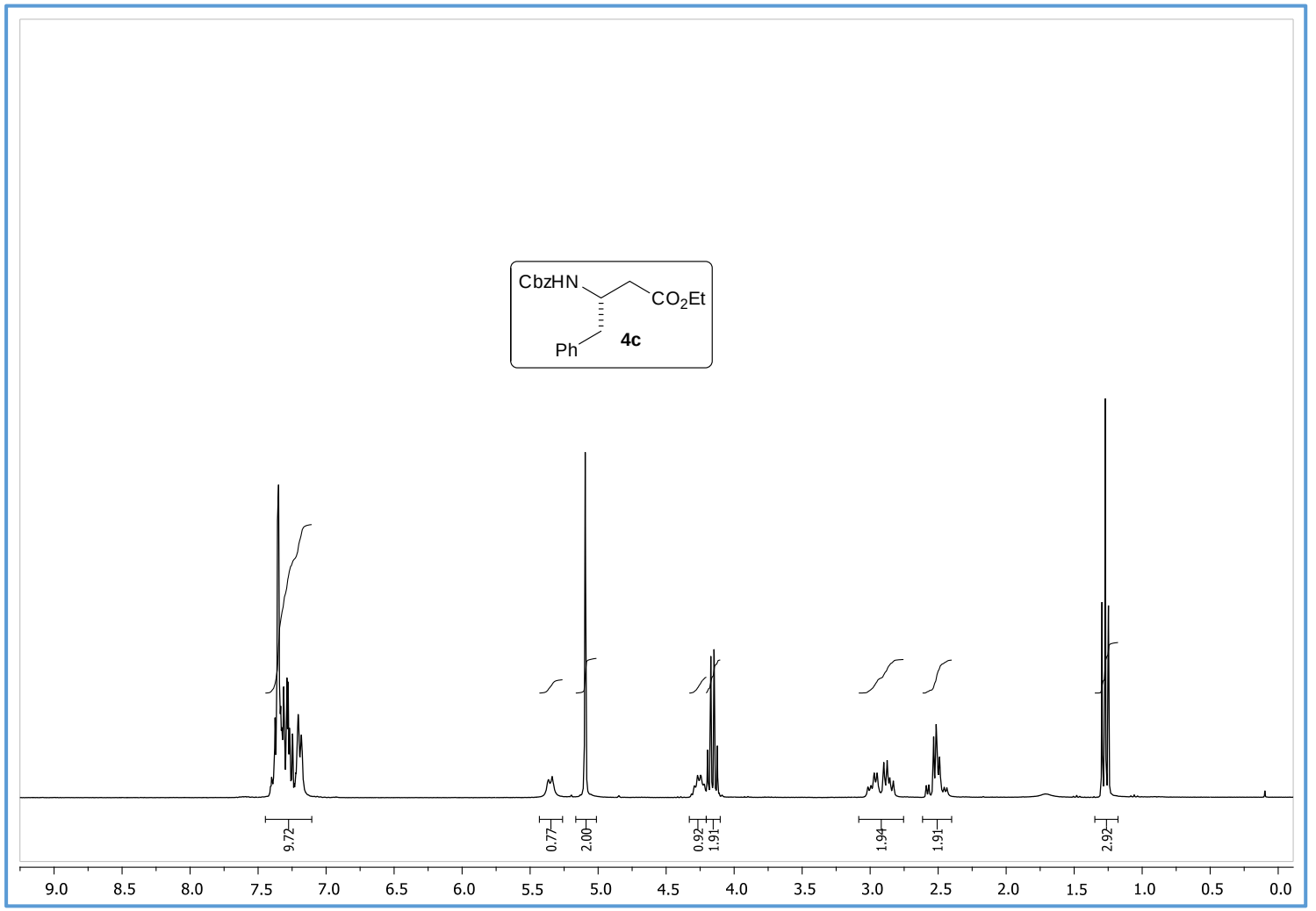
^{1}H NMR of (*S*)-3-(((benzyloxy)carbonyl)amino)-4-phenylbutanoic acid 4b



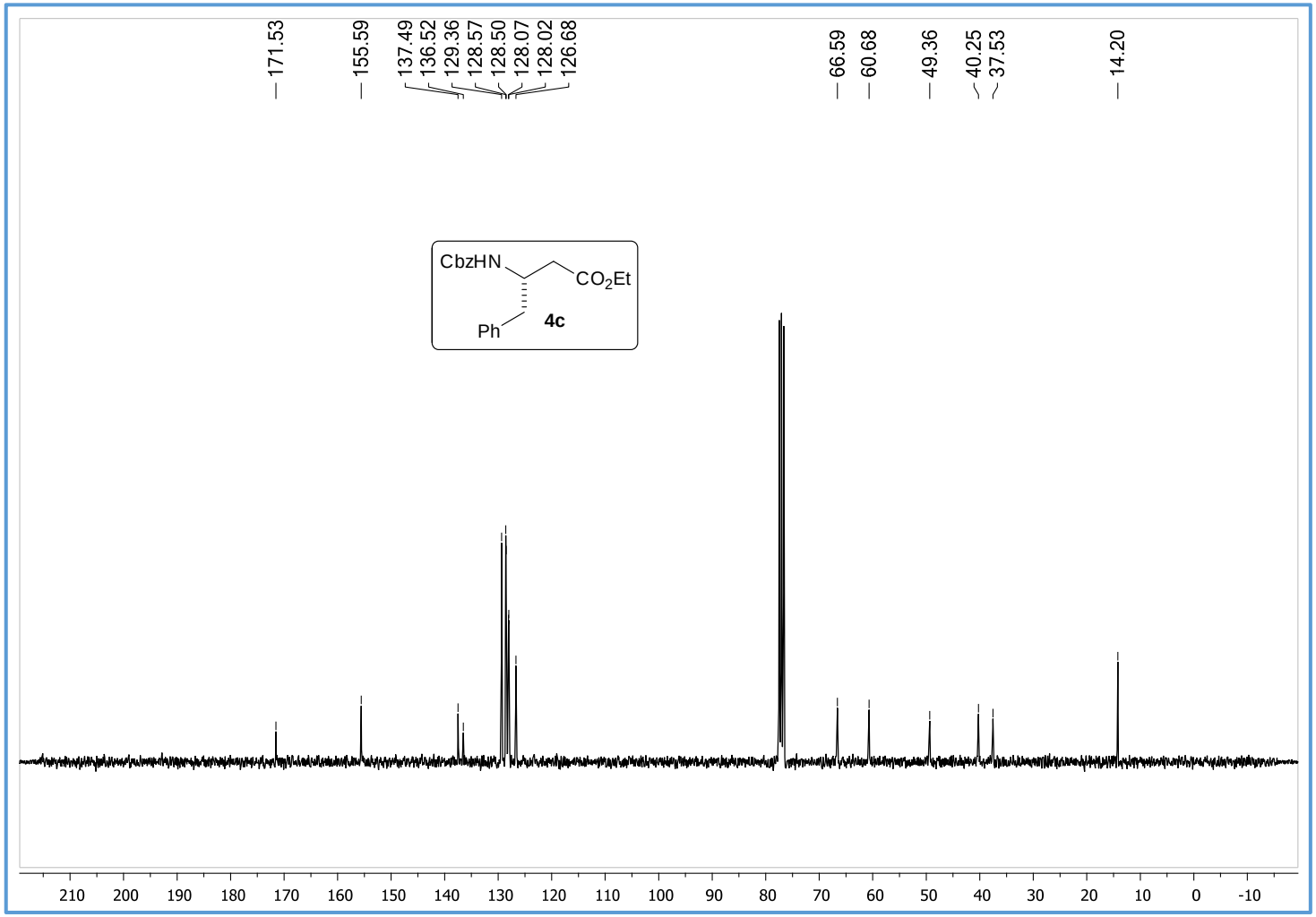
^{13}C NMR of (*S*)-3-(((benzyloxy)carbonyl)amino)-4-phenylbutanoic acid 4b



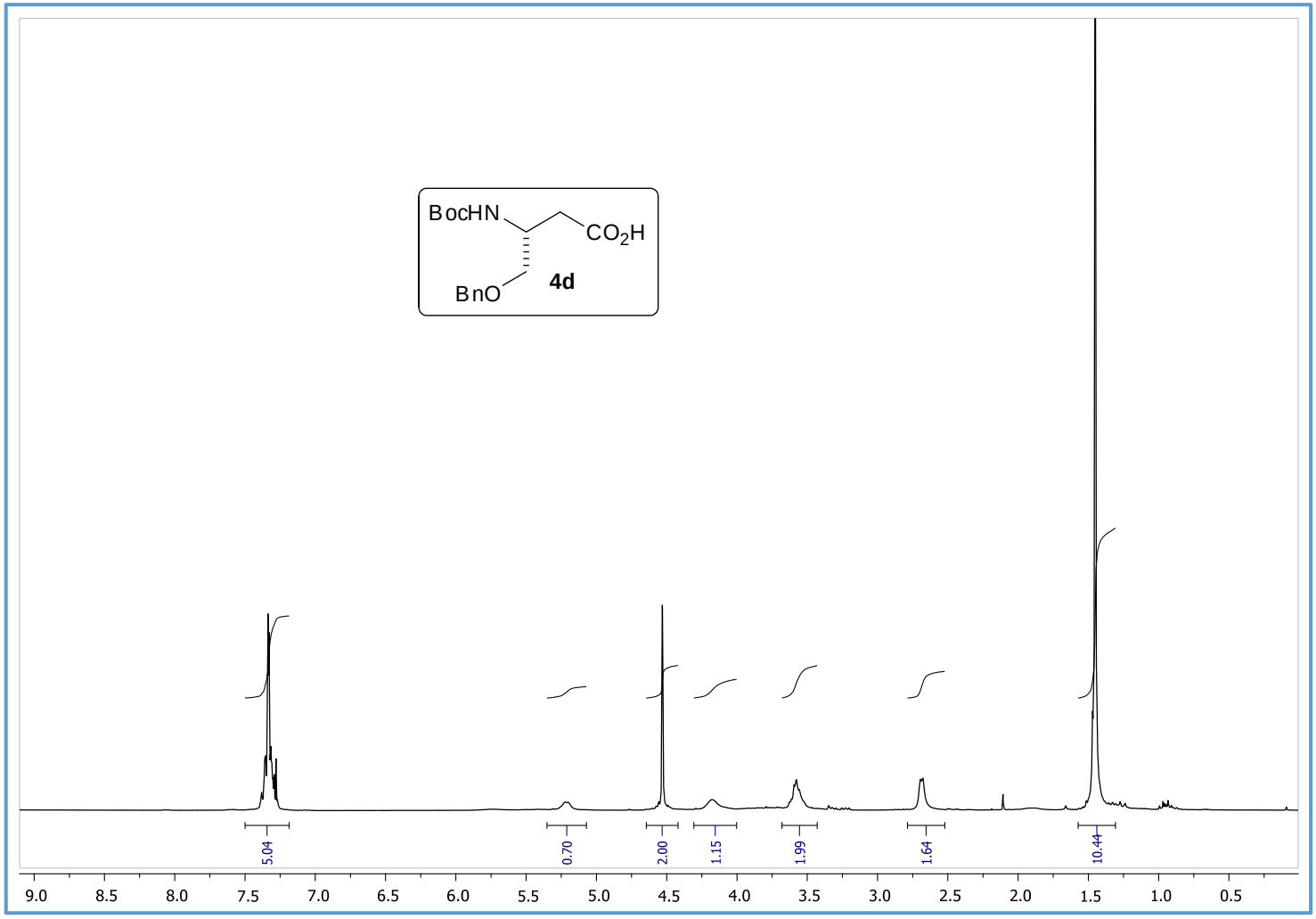
^{1}H NMR of (*S*)-ethyl 3-(((benzyloxy)carbonyl)amino)-4-phenylbutanoate 4c



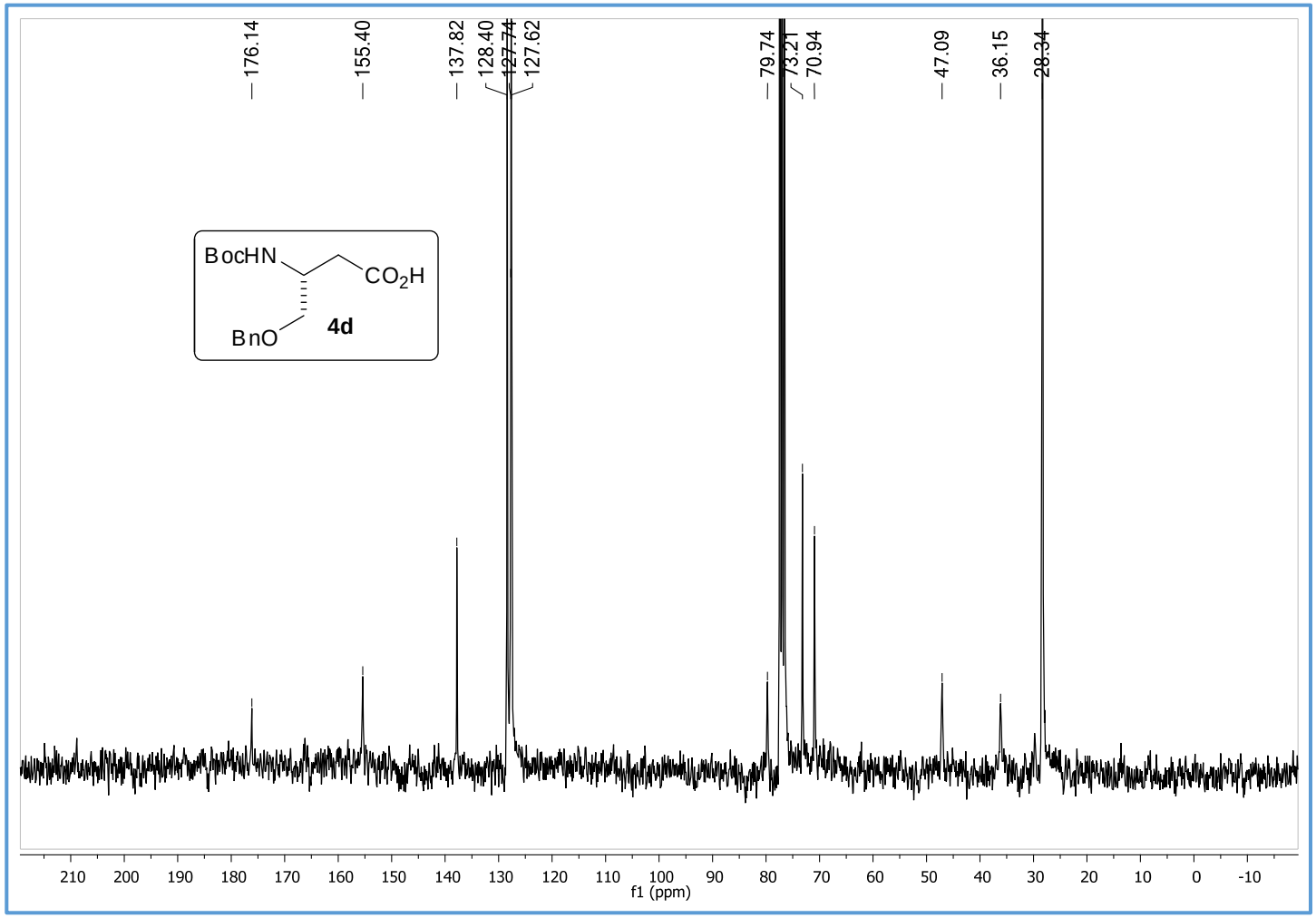
^{13}C NMR of (*S*)-ethyl 3-(((benzyloxy)carbonyl)amino)-4-phenylbutanoate 4c



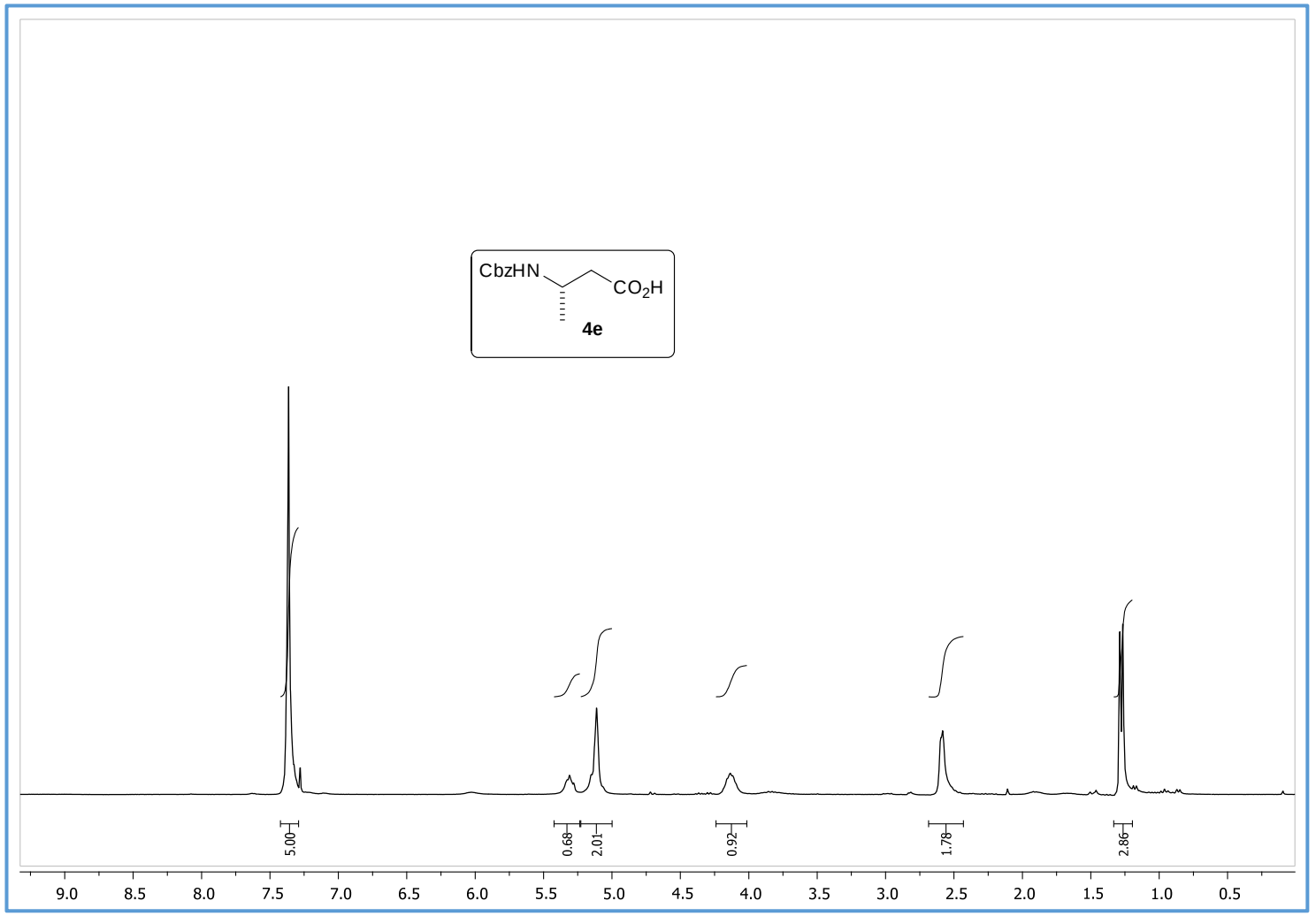
^{1}H NMR of (*R*)-4-(benzyloxy)-3-((tert-butoxycarbonyl)amino)butanoic acid 4d



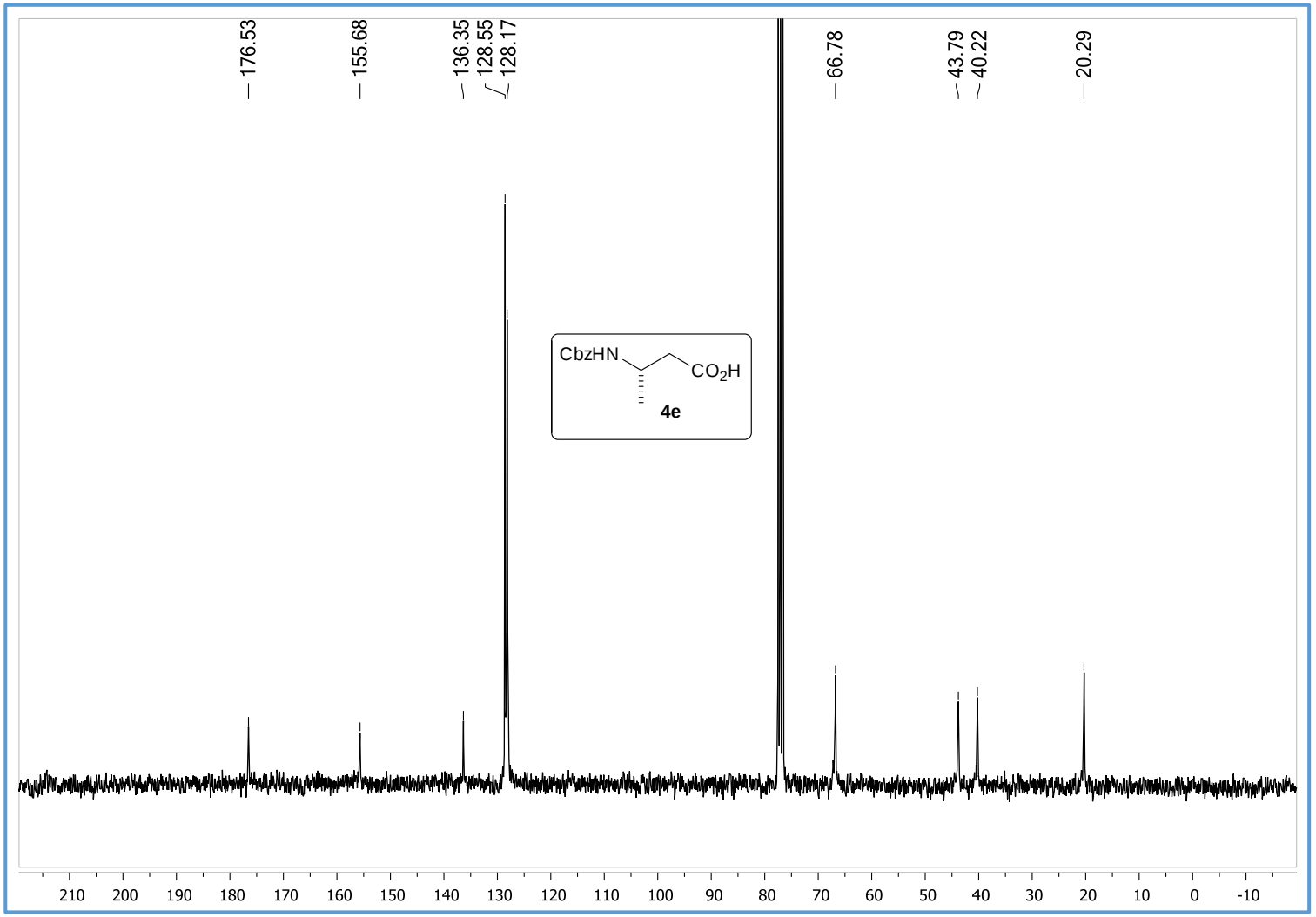
^{13}C NMR of (*R*)-4-(benzyloxy)-3-((tert-butoxycarbonyl)amino)butanoic acid 4d



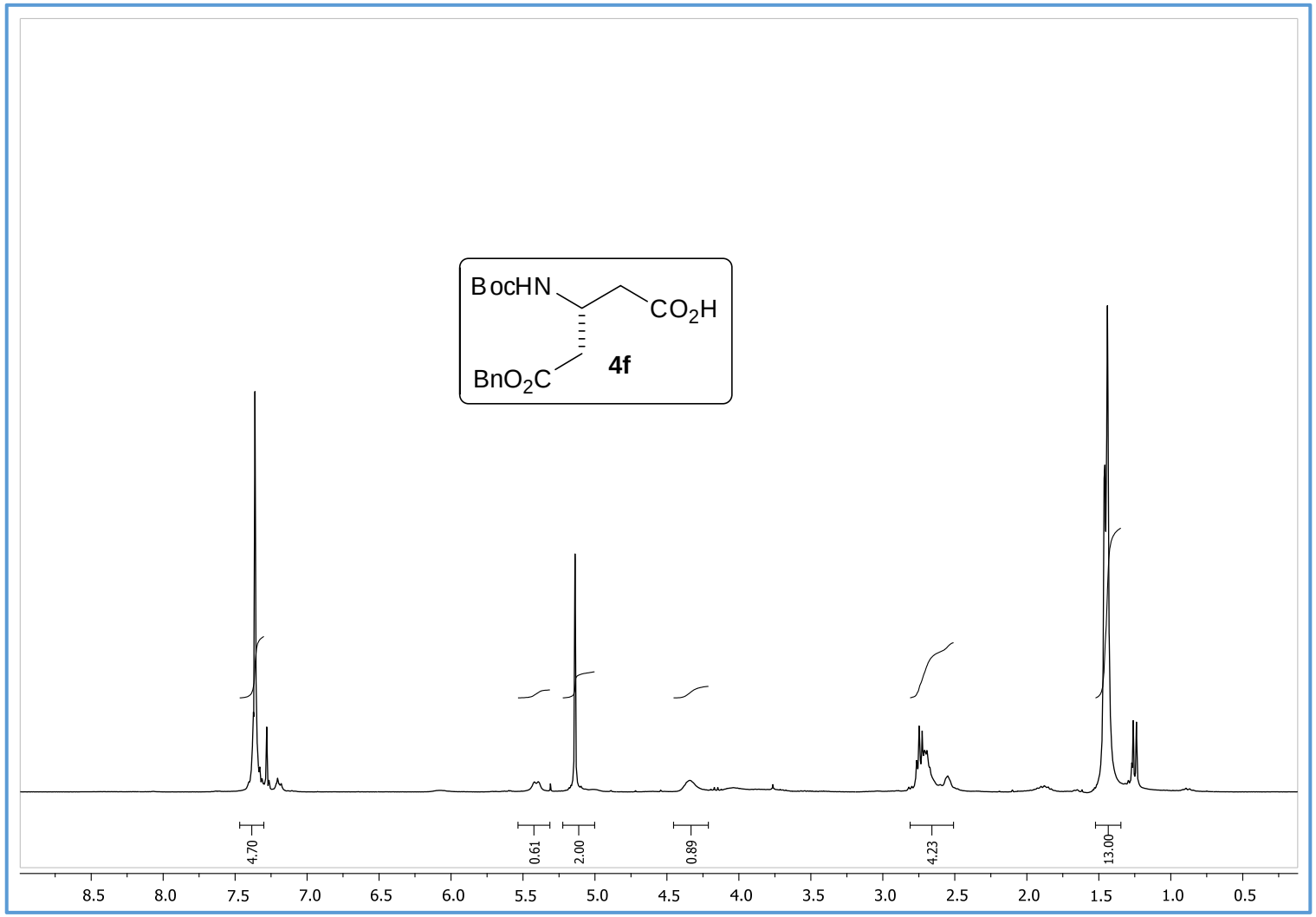
^{1}H NMR of (*S*)-3-(((benzyloxy)carbonyl)amino)butanoic acid 4e



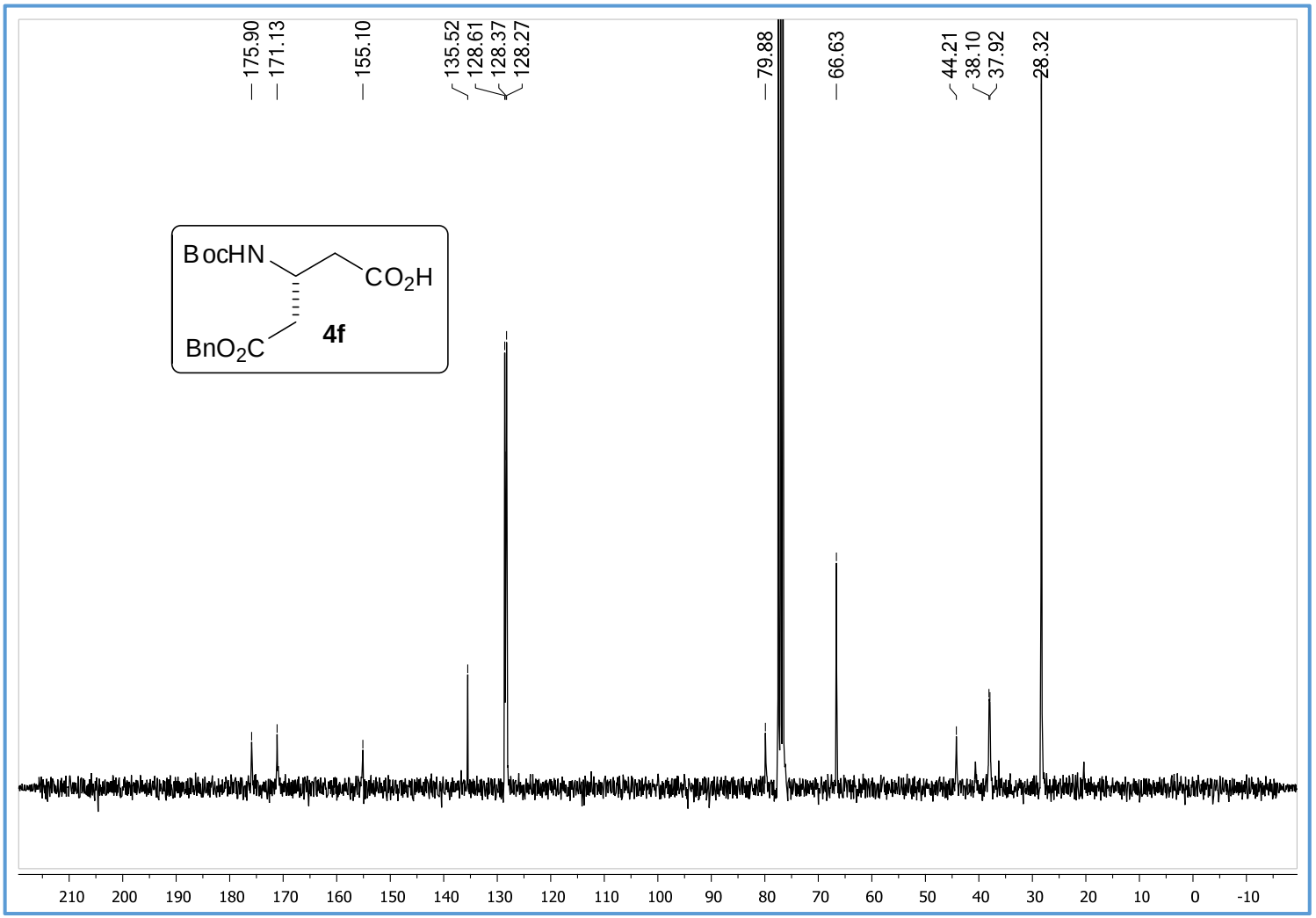
^{13}C NMR of (*S*)-3-(((benzyloxy)carbonyl)amino)butanoic acid 4e



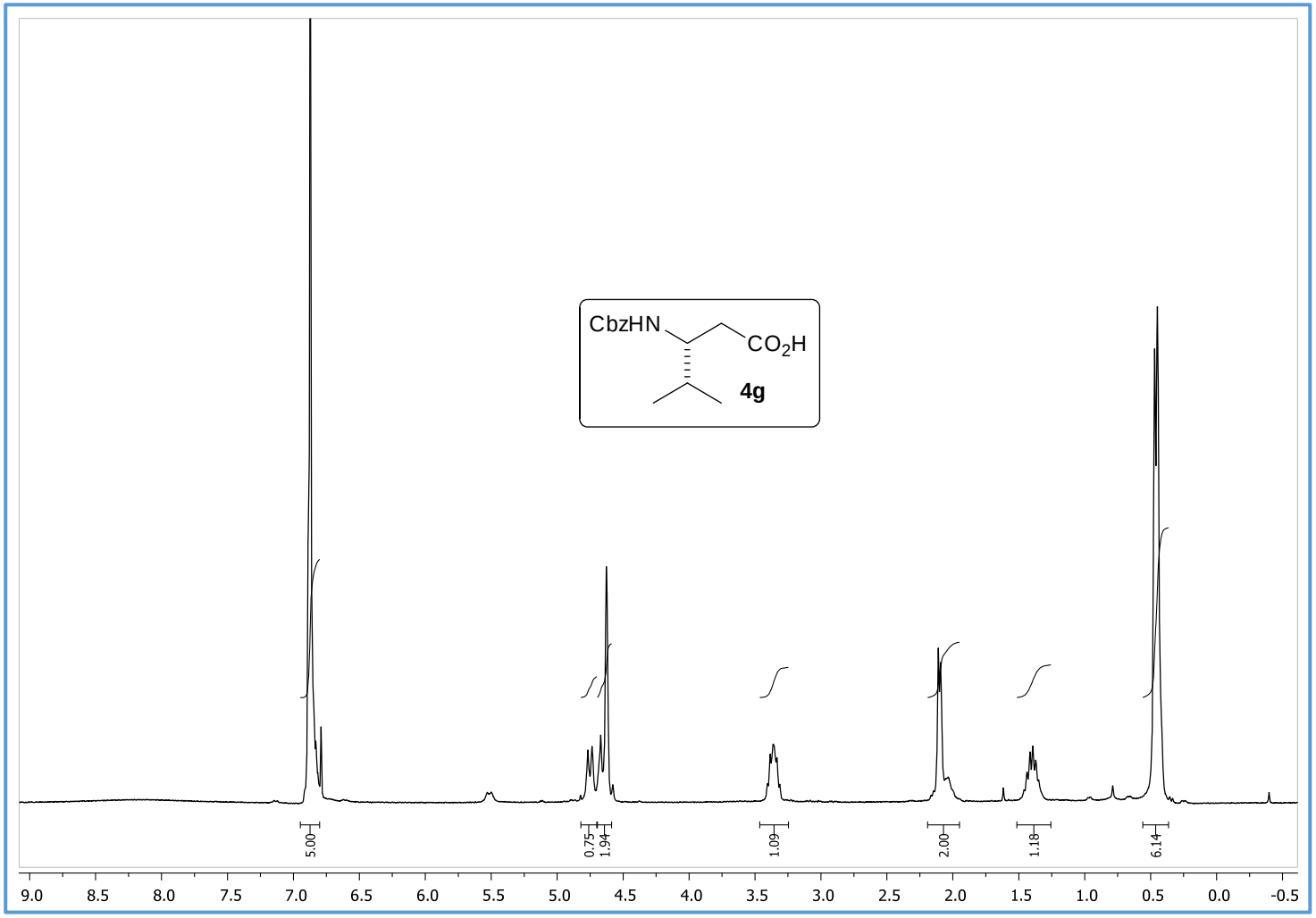
^{1}H NMR of (*R*)-5-(benzyloxy)-3-((tert-butoxycarbonyl)amino)-5-oxopentanoic acid 4f



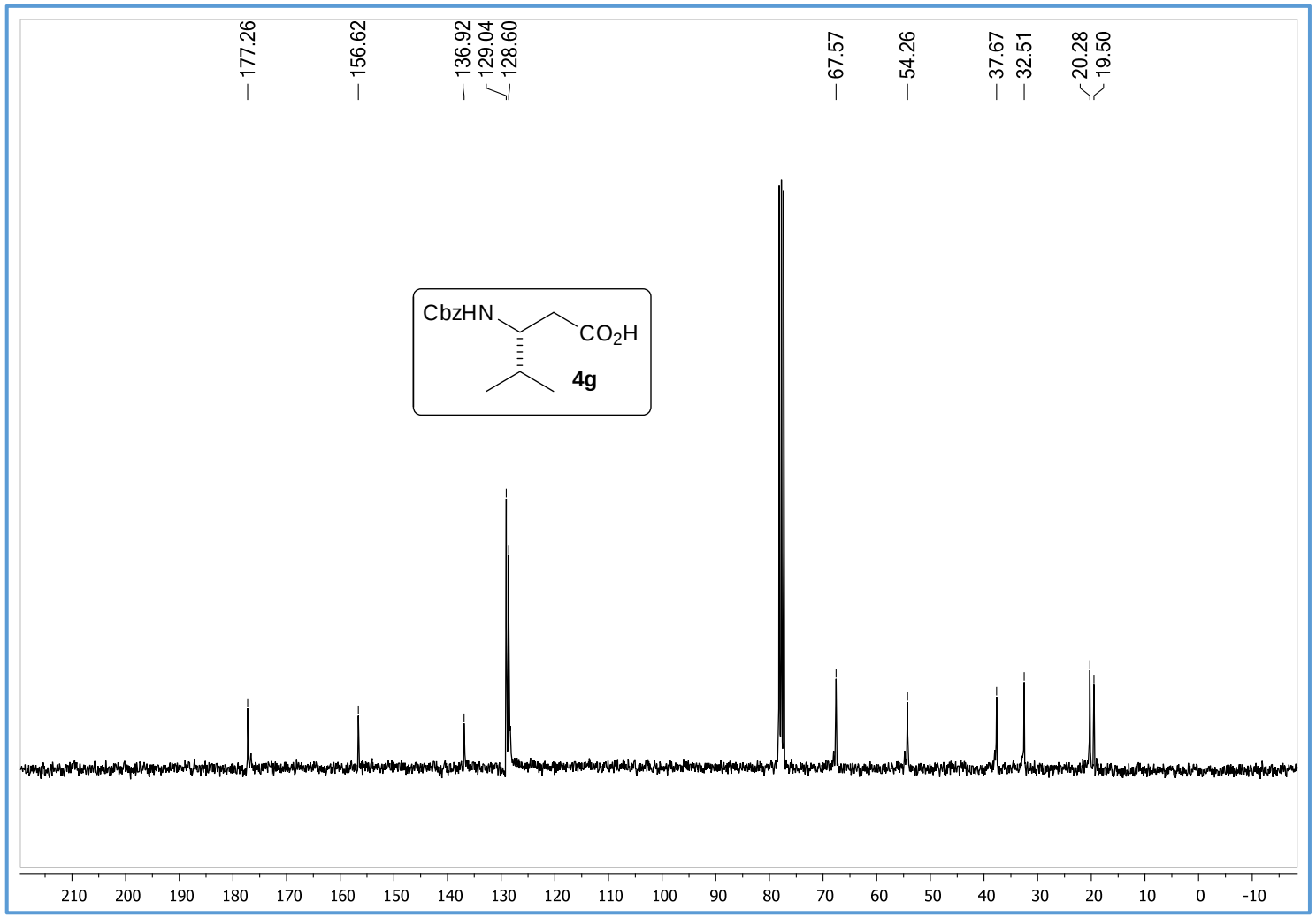
^{13}C NMR of (*R*)-5-(benzyloxy)-3-((tert-butoxycarbonyl)amino)-5-oxopentanoic acid 4f



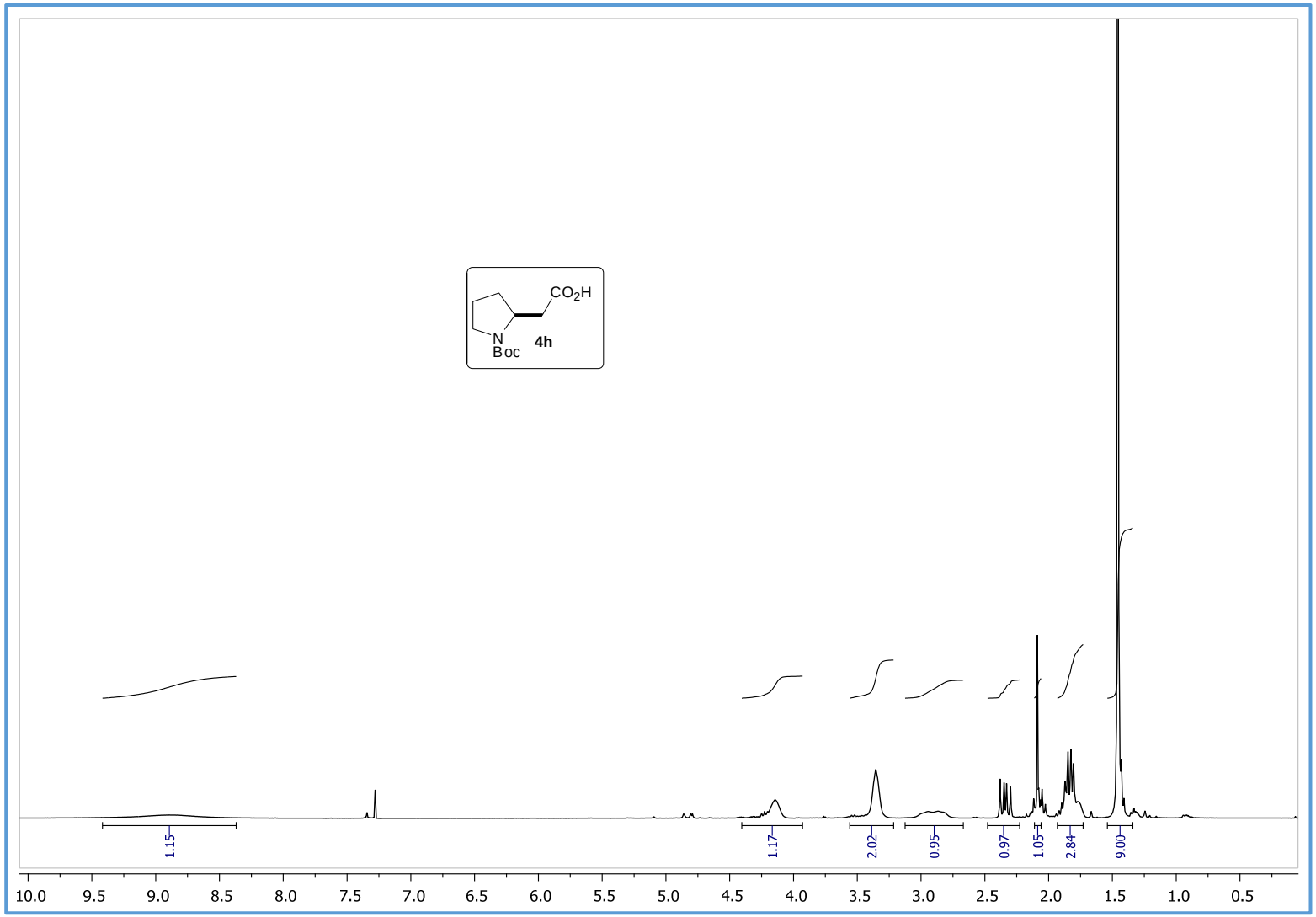
^{1}H NMR of (*R*)-3-(((benzyloxy)carbonyl)amino)-4-methylpentanoic acid 4g



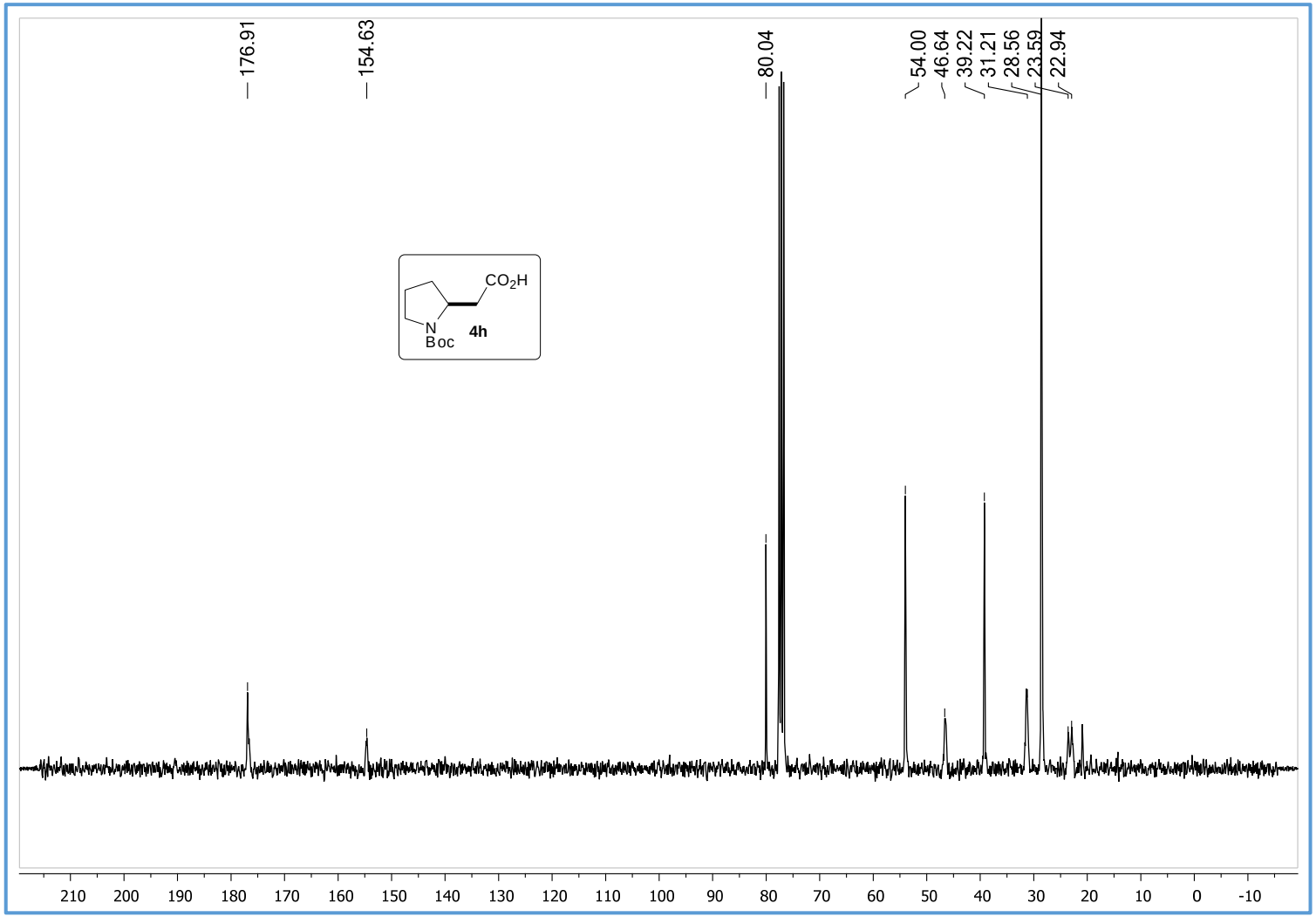
^{13}C NMR of (*R*)-3-(((benzyloxy)carbonyl)amino)-4-methylpentanoic acid 4g



^{1}H NMR of (*S*)-2-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)acetic acid 4h



^{13}C NMR of (*S*)-2-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)acetic acid 4h



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