Supporting Information

Hydroxy-directed peptide bond formation from *α*-amino acid-derived inert esters enabled by boronic acid catalysis

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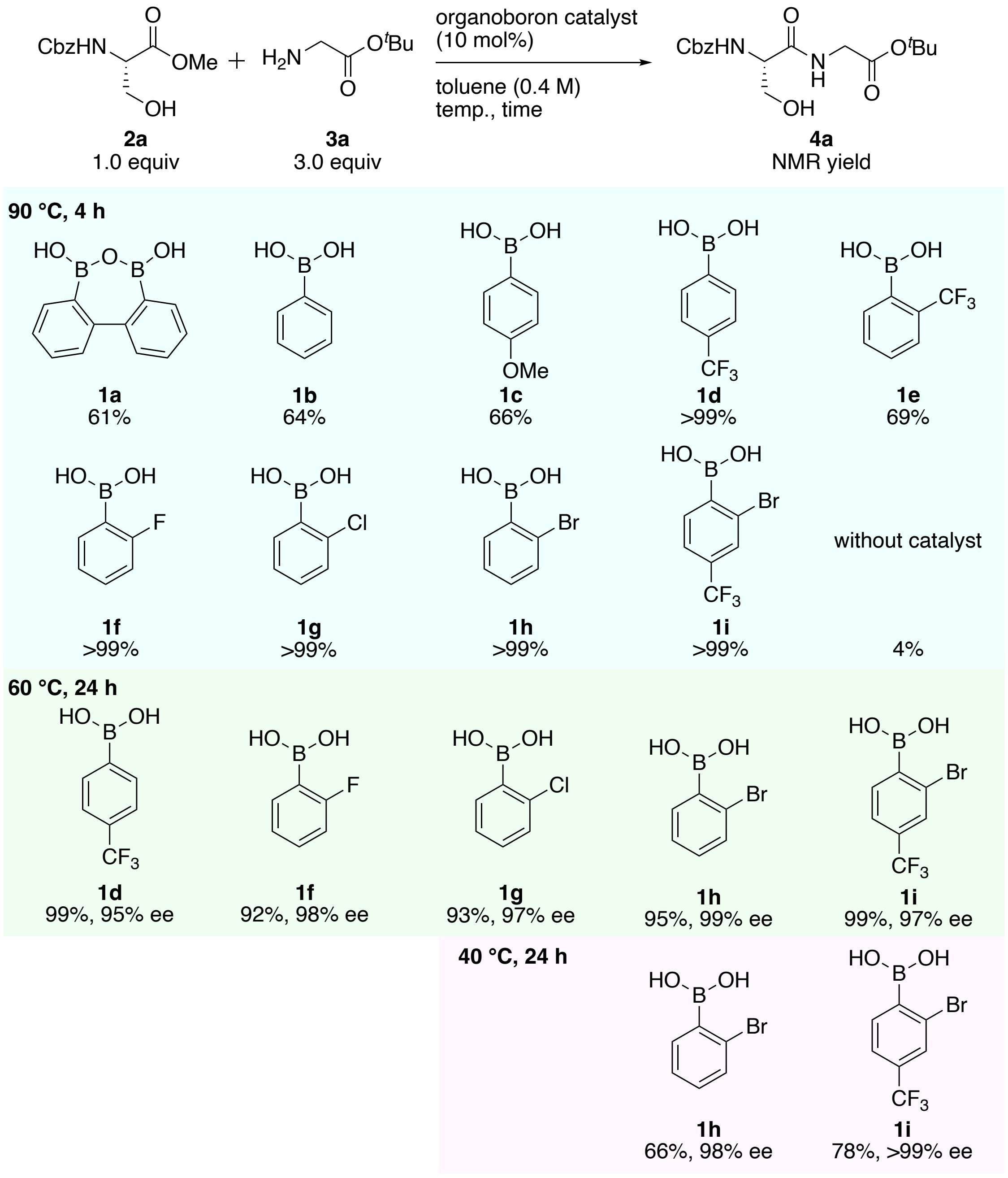
1. General information

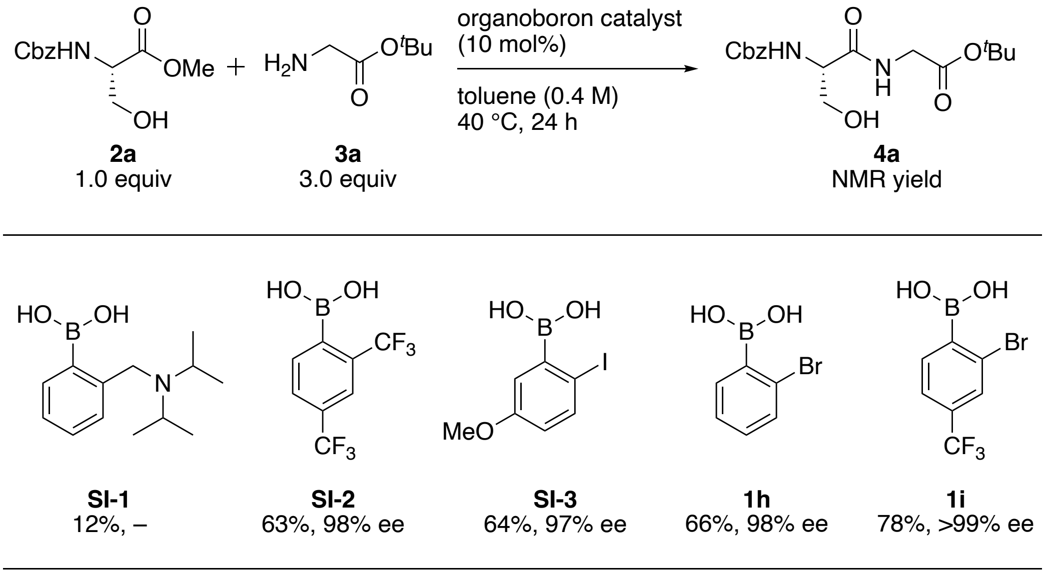
Melting points (mp) were obtained on AS ONE ATM-02 melting point apparatus. IR spectra were recorded on an FT/IR460-plus IR spectrometer and absorbance bands are reported in wavenumber (cm^{-1}). Optical rotation was recorded on a JASCO DIP-1000 polarimeter and reported as follows: $[\alpha]_D$, concentration (g/100 mL), and solvent. NMR spectra were recorded on Agilent Technologies 400-MR DD2 (400 MHz for ^{1}H, 100 MHz for ^{13}C), 400-MR (400 MHz for ^{1}H, 100 MHz for ^{13}C), JEOL EX-270 spectrometer (270 MHz for ^{1}H), JEOL JNM ECP-500 spectrometer (500 MHz for ^{1}H, 126 MHz for ^{13}C). ^{1}H NMR data are reported as follows; chemical shift in parts per million (ppm) downfield or upfield from $CDCl_3$ (δ 7.26), integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, quint = quintet, dd = double doublet, ddd = double double doublet, dt = double triplet, and m = multiplet), and coupling constants (Hz). ^{13}C NMR chemical shifts are reported in ppm downfield or upfield from $CDCl_3$ (δ 77.0). Mass spectra were measured with JEOL JMS-AX505HA, JMS-700 MStation, and JEOL JMS-T100LP spectrometers. Thin-layer chromatography (TLC) was carried out on Merck 60F-254 or Fuji NH KP20610 (NH) precoated silica gel plates and were visualized by fluorescence quenching under UV light. Column chromatography was performed using Silica Gel 60N (spherical, neutral, 63-210 μm) (Kanto Chemical Co., Inc.). Analytical high performance liquid chromatography (HPLC) was performed on a JASCO PU-2089 intelligent HPLC pump with JASCO UV-2075 intelligent UV/VIS detector. Detection was performed at 254 nm. CHIRALPAKR IA (f 0.46 cm × 25 cm) from Daicel were used. Retention times (t_R) and peak ratios were determined with ChromNAV. Air- and/or moisture-sensitive reactions were carried out under nitrogen atmosphere using oven-dried glassware. 2-bromo-4-(trifluoromethyl)phenylboronic acid (**1i**), *N*-protecting serine or threonine derivatives **2a**–**2d**, amino esters **3m**, and amino esters HCl salt **3a**–**3l**, **3n**–**3r**·HCl were purchased. Molecular sieves 4A was finely ground in mortar and heated with a microwave oven (2 min for 3 times) and then placed under vacuum for 10 min prior to use.

2. Screening of organoboron catalysts

SI-Scheme 1.

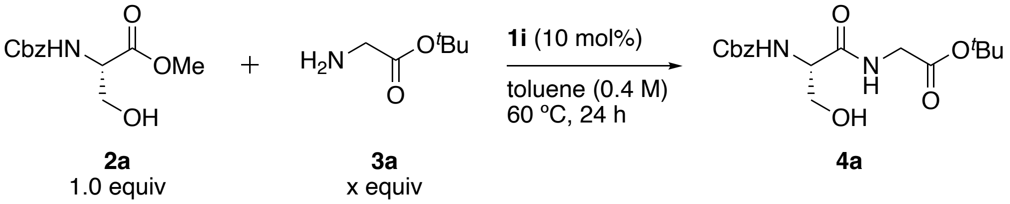


SI-Scheme 2.


CbzHN
OMe
OH
2a
1.0 equiv
+
H_2N
O^tBu
3a
3.0 equiv
organoboron catalyst
(10 mol%)
toluene (0.4 M)
40 °C, 24 h
CbzHN
N
H
OH
O^tBu
4a
NMR yield
SI-1
12%, –
SI-2
63%, 98% ee
SI-3
64%, 97% ee
1h
66%, 98% ee
1i
78%, >99% ee

3. Supplemental data for the catalytic peptide bond formation using *β*-hydroxy-*α*-amino esters catalyzed by 1i

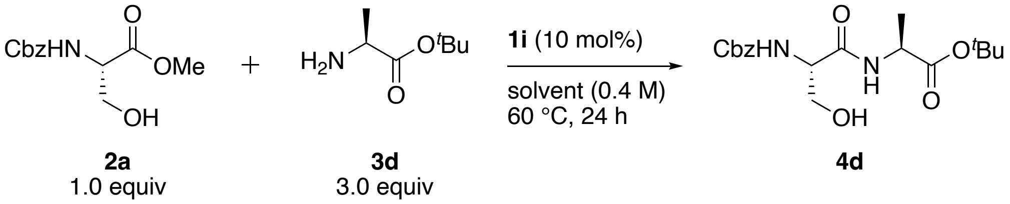
SI-Table 1. Optimization of amino ester 3 equivalent



entry	x (equiv)	yield (%)[a]	ee (%)[b]
1	1.0	60	98
2	1.5	92	98
3	**3.0**	**99[96]**[c]	**97**

[a]Determined by ^{1}H NMR of a crude mixture of products.
[b]Determined by chiral HPLC analysis.
[c]Isolated yield.

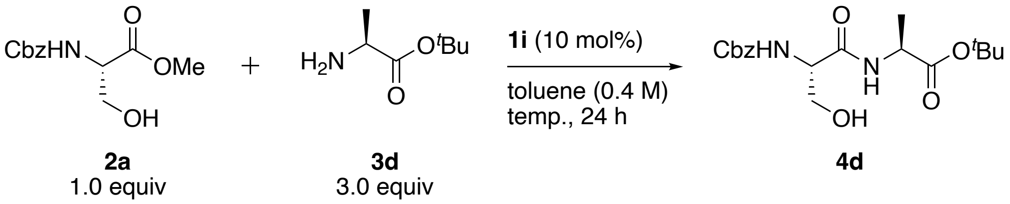
SI-Table 2. Effect of solvent



entry	solvent	yield (%)[a]
1	**toluene**	**79**
2	DCE	51
3	CPME	57
4	EtOAc	34

[a]Determined by ^{1}H NMR of a crude mixture of products.
[b]Isolated yield.
DCE = 1,2-dichloroethane
CPME = cyclopentyl methyl ether

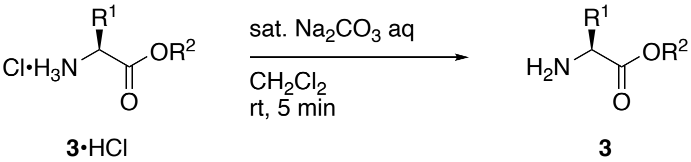
SI-Table 3. Optimization of reaction temperature



entry	temp. (°C)	yield (%)[a]	dr[b]
1	40	28	>99 : 1
2	60	79	99 : 1
3	70	82	98 : 2
4	**80**	**96[89]**[c]	**97 : 3**
5	90	97	92 : 8

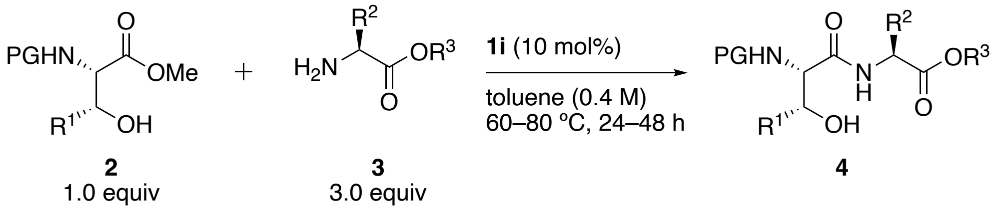
[a] Determined by ^{1}H NMR of a crude mixture of products.
[b] Determined by chiral HPLC analysis.
[c] Isolated yield.

4. Preparation of amino esters 3



Sat. Na_2CO_3 aq (3.0 mL) was added to a solution of amino ester hydrochloric salt **3**•HCl (0.9 mmol) in CH_2Cl_2 (3.0 mL) at room temperature. After stirring for 5 min, the reaction mixture was separated and aqueous layer was extracted three times with CH_2Cl_2. The combined organic layer was washed with brine and dried over Na_2SO_4. Filtration and concentration under reduced pressure furnished the crude product of **3**, which was used for the reactions without further purification.

5. Procedure for the catalytic peptide bond formation of *β*-hydroxy-*α*-amino esters and characterization of *β*-hydroxy-*α*-amino ester-derived dipeptides 4 (Scheme 2, Scheme 3)



General Procedure A

Boronic acid **1i** (5.38 mg, 20.0 μmol, 10.0 mol%) was added to a solution of *N*-protecting serine or threonine derivative **2** (0.200 mmol, 1.0 equiv) and amino ester **3** (0.600 mmol, 3.0 equiv) in toluene (0.5 mL, 0.40 M) at room temperature. After stirring for 24–48 h at 60–80 °C, the reaction mixture was cooled to room temperature. The reaction mixture was quenched by 1 M HCl and the resulting mixture was extracted with CH_2Cl_2. The combined organic layer was successively washed with sat. $NaHCO_3$ aq., H_2O, brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by silica gel column chromatography to give the corresponding dipeptide **4**.

General Procedure B

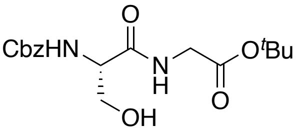
Boronic acid **1i** (5.38 mg, 20.0 μmol, 10.0 mol%) was added to a solution of *N*-protecting serine derivative **2** (0.200 mmol, 1.0 equiv) and amino ester **3** (0.600 mmol, 3.0 equiv) in toluene (0.5 mL, 0.40 M) at room temperature. After stirring for 24–48 h at 80 °C, the reaction mixture was cooled to room temperature. Concentration under reduced pressure furnished the crude product, which was purified by silica gel column chromatography to give the corresponding dipeptide **4**.

General Procedure C

Boronic acid **1i** (5.38 mg, 20.0 μmol, 10.0 mol%) was added to a solution of *N*-protecting serine derivative **2** (0.200 mmol, 1.0 equiv) and HCl salt of amino ester **3** (0.600 mmol, 3.0 equiv) in toluene (0.5 mL, 0.40 M) in the presence of MS 4A (400 mg/0.200 mmol) at room temperature. After stirring for 24 h at 80 °C, the reaction mixture was cooled to room temperature and filtered through a pad of Celite with EtOAc. Concentration under reduced pressure furnished the crude product, which was purified by silica gel column chromatography to give the corresponding dipeptide **4**.

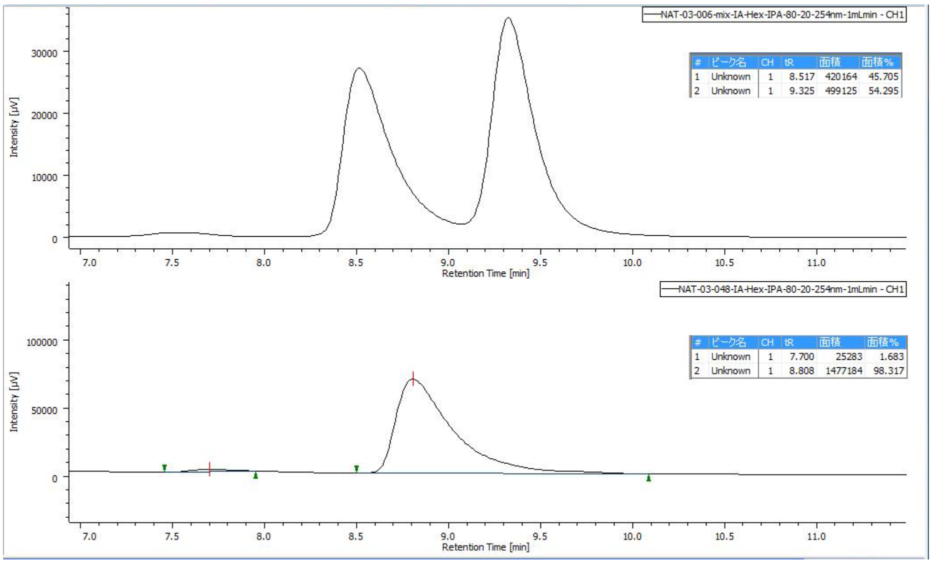
Authentic samples of peptides were prepared from L-, D- or DL-amino acids, and used as references for HPLC analysis.

Cbz-Ser-Gly-O^{t}Bu (4a)[1]



4a

Compound **4a** was prepared according to the procedure A from Cbz-Ser-OMe (**2a**) (50.7 mg, 0.200 mmol) and H-Gly-O^{t}Bu (**3a**) (78.7 mg, 0.600 mmol) at 60 °C for 24 h. Yield 96% (67.7 mg, 0.192 mmol, 97% ee). Purified by column chromatography (silica gel, 4:1 CH_2Cl_2/EtOAc). Data for **4a**; colorless oil; R_f = 0.27 (CH_2Cl_2/EtOAc = 2:1); $[\alpha]_D^{25}$ –6.3° (*c* = 1.0, $CHCl_3$); IR (neat) ν = 3379, 3017, 2352, 1720, 1527, 1370, 1217, 1158, 1063, 757 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.39–7.31 (m, 5H), 6.99 (br, 1H), 5.90 (d, *J* = 7.3 Hz, 1H), 5.13 (s, 2H), 4.30 (br, 1H), 4.08 (dd, *J* = 11.3, 2.4 Hz, 1H), 3.93 (d, *J* = 5.4 Hz, 2H), 3.68 (dd, *J* = 11.3, 5.1 Hz, 1H), 2.92 (br, 1H), 1.46 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 169.0, 156.4, 136.0, 128.5, 128.3, 128.1, 82.7, 67.3, 63.0, 55.7, 42.1, 28.0; HRMS (ESI) m/z calcd for $C_{17}H_{24}N_2NaO_6$ $[M+Na]^+$ 375.1532, found 375.1528.

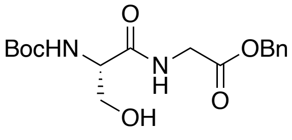


#	ピーク名	CH	tR	面積	面積%
1	Unknown	1	8.517	420164	45.705
2	Unknown	1	9.325	499125	54.295

#	ピーク名	CH	tR	面積	面積%
1	Unknown	1	7.700	25283	1.683
2	Unknown	1	8.808	1477184	98.317

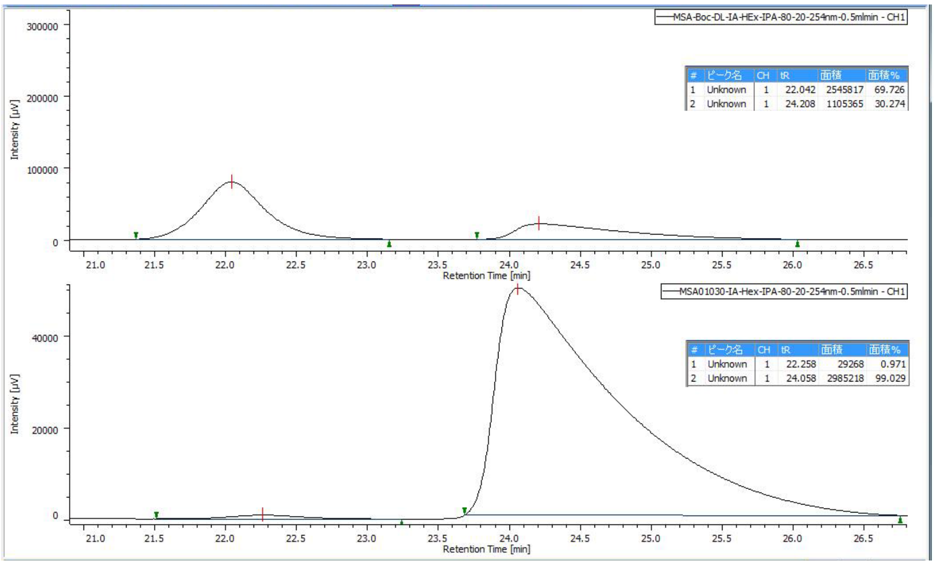
The ee was determined by chiral HPLC analysis [CHIRALPAK IA(ϕ 0.46 cm × 25 cm), hexane / IPA = 80 : 20, 254 nm, flow rate 1.0 mL/min, t^R = 7.7 min (minor), 8.8 min (major)]

Boc-Ser-Gly-OBn (4b)[1]



4b

Compound **4b** was prepared according to the procedure A from Boc-Ser-OMe (**2b**) (43.8 mg, 0.200 mmol) and H-Gly-OBn (**3b**) (99.1 mg, 0.600 mmol) at 60 °C for 24 h. Yield 62% (43.8 mg, 0.124 mmol, 98% ee). Purified by column chromatography (silica gel, 4:1 CH_2Cl_2/EtOAc). Data for **4b**; colorless oil; $R_f = 0.28$ (CH_2Cl_2/EtOAc = 2:1); $[\alpha]_D^{25}$ –9.1° ($c = 1.0$, $CHCl_3$); IR (neat) ν = 3667, 3316, 2979, 2448, 1746, 1538, 1392, 1164, 1058, 852, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.33 (m, 5H), 7.03 (br, 1H), 5.51 (br, 1H), 5.20 (d, J = 12.0 Hz, 1H), 5.17 (d, J = 12.0 Hz, 1H), 4.21 (br, 1H), 4.16–4.12 (m, 2H), 4.05 (dd, J = 18.5, 5.5 Hz, 1H), 3.66 (dd, J = 11.0, 4.5 Hz, 1H) 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 169.7, 156.0, 135.0, 128.7, 128.6, 128.4, 80.6, 67.4, 63.0, 55.1, 41.4, 28.3; HRMS (ESI) m/z calcd. for $C_{17}H_{24}N_2Na_1O_6[M+Na]^+$ 375.1532, found 375.1535.

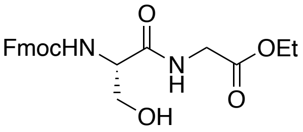


#	ピーク名	CH	tR	面積	面積%
1	Unknown	1	22.042	2545817	69.726
2	Unknown	1	24.208	1105365	30.274

#	ピーク名	CH	tR	面積	面積%
1	Unknown	1	22.258	29268	0.971
2	Unknown	1	24.058	2985218	99.029

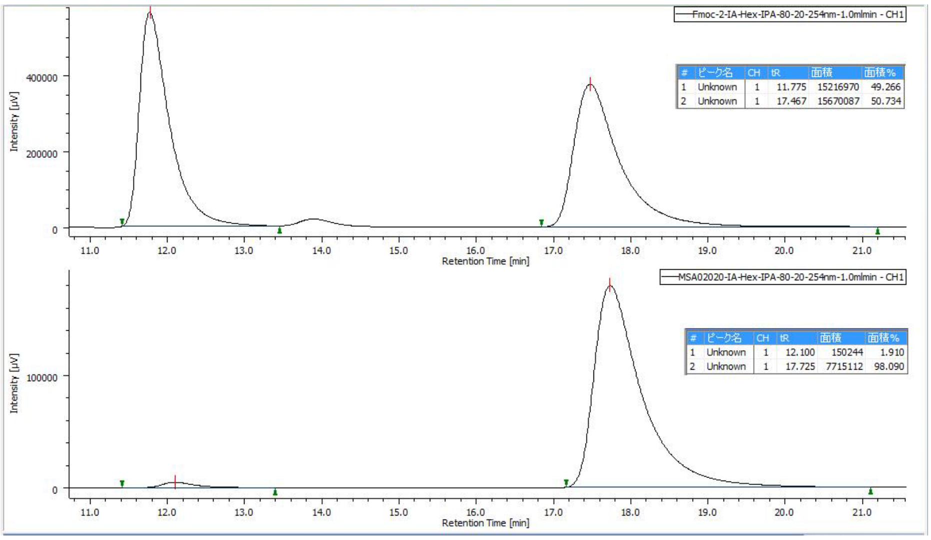
The ee was determined by chiral HPLC analysis [CHIRALPAK IA(ϕ 0.46 cm × 25 cm), hexane / IPA = 80 : 20, 254 nm, flow rate 0.5 mL/min, t^R = 22.3 min (minor), 24.1 min (major)]

Fmoc-Ser-Gly-OEt (4c)[1]



4c

Compound **4c** was prepared according to the procedure A from Fmoc-Ser-OMe (**2c**) (68.3 mg, 0.200 mmol) and H-Gly-OEt (**3c**) (61.9 mg, 0.600 mmol) at 60 °C for 24 h. Yield 65% (53.7 mg, 0.130 mmol, 96% ee). Purified by column chromatography (silica gel, 2:1 CH_2Cl_2/EtOAc). Data for **4c**; white solid; $R_f = 0.28$ (CH_2Cl_2/EtOAc = 2:1); $[\alpha]_D^{25}$ –10.1° (c = 1.0, $CHCl_3$); IR (KBr) ν = 3067, 2889, 1930, 1584, 1448, 1296, 1220, 1116, 929, 726, 570 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.77 (d, J = 7.3 Hz, 2H), 7.59 (d, J = 7.3 Hz, 2H), 7.41 (t, J = 7.3 Hz, 2H), 7.32 (t, J = 7.3 Hz, 2H), 6.87 (br, 1H), 5.81–5.77 (m, 1H), 4.46 (d, J = 6.8 Hz, 1H), 4.25–4.17 (m, 5H), 4.04 (d, J = 5.7 Hz, 1H), 3.72–3.66 (m, 1H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 170.0, 156.5, 143.6, 141.3, 127.8, 127.7, 127.1, 125.0, 124.0, 120.1, 120.0, 67.3, 62.9, 61.8, 55.7, 47.0, 41.4, 14.0; HRMS (ESI) m/z calcd. for $C_{22}H_{24}N_2Na_1O_6[M+Na]^+$ 435.1532, found 435.1525.

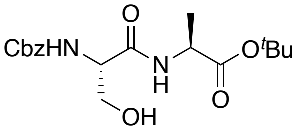


#	ピーク名	CH	tR	面積	面積%
1	Unknown	1	11.775	15216970	49.266
2	Unknown	1	17.467	15670087	50.734

#	ピーク名	CH	tR	面積	面積%
1	Unknown	1	12.100	150244	1.910
2	Unknown	1	17.725	7715112	98.090

The ee was determined by chiral HPLC analysis [CHIRALPAK IA(ϕ 0.46 cm × 25 cm), hexane / IPA = 80 : 20, 254 nm, flow rate 1.0 mL/min, t_R = 12.1 min (minor), 17.7 min (major)]

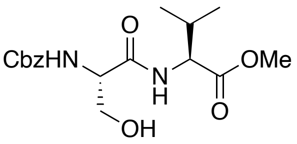
Cbz-Ser-Ala-O^{t}Bu (4d)[1]



4d

Compound **4d** was prepared according to the procedure A from Cbz-Ser-OMe (**2a**) (50.7 mg, 0.200 mmol) and H-Ala-O^{t}Bu (**3d**) (87.1 mg, 0.600 mmol) at 80 °C for 24 h. Yield 89% (65.4 mg, 0.179 mmol). Purified by column chromatography (silica gel, 3:1 CH_2Cl_2/EtOAc). Data for **4d**; yellow oil; R_f = 0.26 (CH_2Cl_2/EtOAc = 3:1); $[\alpha]_D^{25}$ –4.5° (*c* = 1.0, $CHCl_3$); IR (neat) ν = 3413, 2981, 1722, 1520, 1370, 1218, 1151, 1059, 846, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.28 (m, 5H), 7.08 (br, 1H), 5.92 (d, *J* = 7.5 Hz, 1H), 5.11 (s, 2H), 4.43 (quint, *J* = 7.5 Hz, 1H), 4.30 (br, 1H), 4.00 (dd, *J* = 11.0, 2.5 Hz, 1H), 3.67 (dd, *J* = 11.0, 6.0 Hz, 1H), 1.45 (s, 9H), 1.35 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 170.4, 156.3, 136.0, 128.5, 128.2, 128.0, 82.4, 67.1, 63.0, 55.5, 48.9, 27.9, 17.8; HRMS (ESI) m/z calcd. for $C_{18}H_{26}N_2NaO_6[M+Na]^+$ 389.1689, found 389.1677.

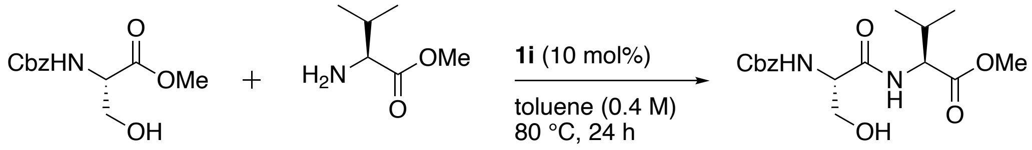
Cbz-Ser-Val-OMe (4e)[1]



4e

Condition A: Compound **4e** was prepared according to the procedure A from Cbz-Ser-OMe (**2a**) (50.7 mg, 0.200 mmol) and H-Val-OMe (**3e**) (78.7 mg, 0.600 mmol) at 80 °C for 24 h. Yield >99% (69.8 mg, 0.198 mmol). Purified by column chromatography (silica gel, 4:1 CH_2Cl_2/EtOAc). Condition B: Compound **4e** was also prepared according to the procedure C from Cbz-Ser-OMe (**2a**) (50.7 mg, 0.200 mmol) and H-Val-OMe•HCl (**3e**•HCl) (100.6 mg, 0.600 mmol) at 80 °C for 24 h. Yield 81% (57.1 mg, 0.162 mmol). Purified by column chromatography (silica gel, 4:1 CH_2Cl_2/EtOAc). Data for **4e**; colorless oil; R_f = 0.31 (CH_2Cl_2/EtOAc = 2:1); $[\alpha]_D^{25}$ –9.7° (*c* = 1.0, $CHCl_3$); IR (neat) ν = 3670, 3330, 2966, 2448, 1669, 1531, 1216, 1147, 1061, 752 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.30 (m, 5H), 6.90 (d, *J* = 8.5 Hz, 1H), 5.82 (d, *J* = 7.0 Hz, 1H), 5.16 (d, *J* = 12.5 Hz, 1H), 5.11 (d, *J* = 12.5 Hz, 1H), 4.50 (dd, *J* = 8.5, 4.5 Hz, 1H), 4.29–4.26 (m, 1H), 4.10 (dd, *J* = 11.5, 3.0 Hz, 1H), 3.75 (s, 3H), 3.66 (dd, *J* = 11.5, 5.5 Hz, 1H), 2.23–2.14 (m, 1H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 171.1, 156.6, 136.0, 128.5, 128.2, 128.0, 67.2, 62.8, 57.4, 55.1, 52.3, 30.7, 19.0, 17.6; HRMS (ESI) m/z calcd. for $C_{17}H_{24}N_2NaO_6[M+Na]^+$ 375.1532, found 375.1528.

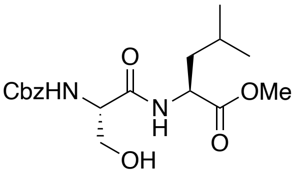
Cbz-Ser-Val-OMe (4e)[1]: 1 mmol scale reaction



2a 1.0 equiv; **3e** 3.0 equiv; **4e** >99%, >20:1 dr

Boronic acid **1i** (26.9 mg, 0.100 mol, 10.0 mol %) was added to a solution of Cbz-Ser-OMe (**2a**) (253.3 mg, 1.00 mmol, 1.0 equiv) and H-Val-OMe (**3e**) (393.5 mg, 3.00 mmol, 3.0 equiv) in toluene (2.5 mL, 0.40 M) at room temperature. After stirring for 24 h at 80 °C, the reaction mixture was cooled to room temperature. The reaction mixture was quenched by 1 M HCl and the resulting mixture was extracted with CH_2Cl_2. The combined organic layer was successively washed with sat. $NaHCO_3$ aq., H_2O, brine, dried over Na_2SO_4, filtered, and concentration in vacuo. The crude material was purified by silica gel column chromatography (4:1 CH_2Cl_2/EtOAc) to give Cbz-Ser-Val-OMe (**4e**) (351.4 mg, 0.997 mmol, >99%, >20:1 dr) as a colorless oil.

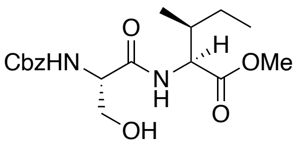
Cbz-Ser-Leu-OMe (4f)[1]



4f

Compound **4f** was prepared according to the procedure A from Cbz-Ser-OMe (**2a**) (50.7 mg, 0.200 mmol) and H-Leu-OMe (**3f**) (87.1 mg, 0.600 mmol) at 80 °C for 24 h. Yield 94% (68.8 mg, 0.188 mmol). Purified by column chromatography (silica gel, 4:1 CH_2Cl_2/EtOAc). Data for **4f**; colorless oil; $R_f = 0.33$ (CH_2Cl_2/EtOAc = 2:1); $[\alpha]_D^{26}$ −10.1° ($c = 1.0$, $CHCl_3$); IR (neat) ν = 3420, 2958, 1722, 1670, 1512, 1439, 1346, 1216, 1151, 1062, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.30 (m, 5H), 6.79 (br, 1H), 5.80 (d, $J = 6.8$ Hz, 1H), 5.14 (d, $J = 12.4$ Hz, 1H), 5.11 (d, $J = 12.4$ Hz, 1H), 4.61–4.55 (m, 1H), 4.30–4.26 (m, 1H), 4.06 (dd, $J = 11.2, 2.8$ Hz, 1H), 3.74 (s, 3H), 3.65 (dd, $J = 11.2, 6.0$ Hz, 1H), 3.28 (br, 1H), 1.69–1.51 (m, 3H), 0.92 (d, $J = 6.4$ Hz, 3H), 0.91 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 170.9, 156.4, 136.0, 128.5, 128.2, 128.0, 67.2, 63.0, 55.2, 52.5, 51.1, 40.7, 24.8, 22.8, 21.6; HRMS (ESI) m/z calcd. for $C_{18}H_{26}N_2NaO_6[M+Na]^+$ 389.1689, found 389.1666.

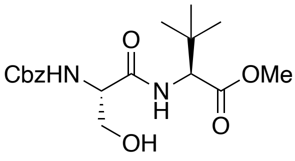
Cbz-Ser-Ile-OMe (4g)[2]



4g

Compound **4g** was prepared according to the procedure A from Cbz-Ser-OMe (**2a**) (50.7 mg, 0.200 mmol) and H-Ile-OMe (**3g**) (87.1 mg, 0.600 mmol) at 80 °C for 24 h. Yield 87% (63.8 mg, 0.174 mmol). Purified by column chromatography (silica gel, 4:1 CH_2Cl_2/EtOAc). Data for **4g**; colorless oil; $R_f = 0.30$ (CH_2Cl_2/EtOAc = 3:1); $[\alpha]_D^{25}$ −3.1° ($c = 1.0$, $CHCl_3$); IR (neat) ν = 3320, 2964, 1730, 1531, 1215, 1961, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.30 (m, 5H), 6.91 (d, $J = 7.6$ Hz, 1H), 5.81 (d, $J = 7.2$ Hz, 1H), 5.16 (d, $J = 12.0$ Hz, 1H), 5.11 (d, $J = 12.0$ Hz, 1H), 4.54 (dd, $J = 8.0, 4.4$ Hz, 1H), 4.29–4.25 (m, 1H), 4.11–4.06 (m, 1H), 3.74 (s, 3H), 3.69–3.62 (m, 1H) 3.14 (br, 1H), 1.94–1.86 (m, 1H), 1.43–1.34 (m, 1H), 1.20–1.09 (m, 1H), 0.92–0.84 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 171.0, 156.5, 136.0, 128.5, 128.2, 128.0, 67.2, 62.8, 56.8, 55.2, 52.3, 37.3, 25.0, 15.5, 11.5; HRMS (ESI) m/z calcd. for $C_{18}H_{26}N_2NaO_6[M+Na]^+$ 389.1689, found 389.1676.

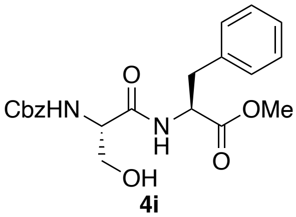
Cbz-Ser-Tle-OMe (4h)



4h

Compound **4h** was prepared according to the procedure A from Cbz-Ser-OMe (**2a**) (50.7 mg, 0.200 mmol) and H-Tle-OMe (**3h**) (87.1 mg, 0.600 mmol) at 80 °C for 24 h. Yield 98% (72.2 mg, 0.197 mmol). Purified by column chromatography (silica gel, 4:1 CH_2Cl_2/EtOAc). Data for **4h**; white solid; R_f = 0.20 (CH_2Cl_2/EtOAc = 4:1); $[\alpha]_D^{25}$ –27.8° (*c* = 1.0, $CHCl_3$); IR (KBr) ν = 3401, 3276, 2960, 2727, 1962, 1720, 1639, 1509, 1359, 1221, 1056, 759 cm^{-1}; mp 85–87 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 7.35–7.30 (m, 5H), 7.20 (d, *J* = 9.2 Hz, 1H), 5.95 (d, *J* = 7.6 Hz, 1H), 5.16 (d, *J* = 12.2 Hz, 1H), 5.10 (d, *J* = 12.2 Hz, 1H), 4.37 (d, *J* = 9.2 Hz, 1H), 4.30–4.25 (m, 1H), 4.06 (dd, *J* = 11.6, 3.0 Hz, 1H), 3.71 (s, 3H), 3.65 (dd, *J* = 11.6, 5.7 Hz, 1H), 2.84 (br, 1H), 0.94 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 170.9, 156. 7, 136.0, 128.5, 128.2, 128.0, 67.3, 62.5, 60.5, 55.0, 51.9, 34.4, 26.5; HRMS (ESI) m/z calcd for $C_{18}H_{26}N_2NaO_6$ $[M+Na]^+$ 389.1689, found 389.1686.

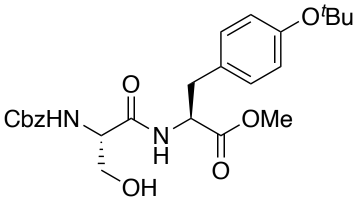
Cbz-Ser-Phe-OMe (4i)[3]



4i

Compound **4i** was prepared according to the procedure A from Cbz-Ser-OMe (**2a**) (50.7 mg, 0.200 mmol) and H-Phe-OMe (**3i**) (108 mg, 0.600 mmol) at 80 °C for 24 h. Yield >99% (79.9 mg, 0.200 mmol). Purified by column chromatography (silica gel, 40:1 Et_2O/MeOH). Data for **4i**; colorless amorphous; R_f = 0.30 (hexane/EtOAc = 2:3); $[\alpha]_D^{25}$ +9.9° (*c* = 1.0, $CHCl_3$); IR (neat) ν = 3271, 3017, 1743, 1552, 1447, 1179, 1028, 910, 771 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.31 (m, 5H), 7.28–7.21 (m, 3H), 7.10–7.09 (m, 2H), 6.88 (d, *J* = 5.5 Hz, 1H), 5.69 (d, *J* = 7.0 Hz, 1H), 5.12 (d, *J* = 12.0, 1H), 5.08 (d, *J* = 12.0 Hz, 1H), 4.85 (dt, *J* = 7.0, 5.5 Hz, 1H), 4.22–4.19 (m, 1H), 4.02 (dd, *J* = 11.5, 2.5 Hz, 1H), 3.74 (s, 3H), 3.59 (dd, *J* = 11.5, 5.5 Hz, 1H), 3.17 (dd, *J* = 13.5, 7.0 Hz, 1H), 3.03 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.34 (br, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 170.6, 156.4, 135.9, 135.5, 129.1, 128.7, 128.6, 128.3, 128.1, 127.3, 67.3, 62.8, 55.1, 53.3, 52.6, 37.6; HRMS (ESI) m/z calcd for $C_{21}H_{24}N_2NaO_6$ $[M+Na]^+$ 423.1532, found 423.1521.

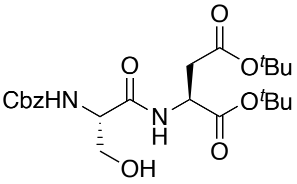
Cbz-Ser-Tyr(^{t}Bu)-OMe (4j)[1]



4j

Compound **4j** was prepared according to the procedure A from Cbz-Ser-OMe (**2a**) (50.7 mg, 0.200 mmol) and H-Tyr(^{t}Bu)-OMe (**3j**) (150.8 mg, 0.600 mmol) at 80 °C for 24 h. Yield 97% (91.4 mg, 0.193 mmol). Purified by column chromatography (silica gel, 4:1 CH_2Cl_2/EtOAc). Data for **4j**; yellow oil; $R_f = 0.30$ (CH_2Cl_2/EtOAc = 3:1); $[\alpha]_D^{25}$ +11.4° (c = 1.0, $CHCl_3$); IR (neat) ν = 3418, 2979, 2097, 1664, 1507, 1366, 1217, 1160, 1059, 896, 753 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 7.03–6.98 (m, 2H), 6.93–6.88 (m, 3H), 5.70 (br, 1H), 5.15–5.11 (m, 2H), 4.81–4.80 (m, 1H), 4.21 (br, 1H), 4.01 (br, 1H), 3.72 (s, 3H), 3.61–3.58 (m, 1H), 3.13–3.07 (m, 1H), 3.05–2.95 (m, 1H), 2.17 (br, 1H), 1.31 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 170.6, 156.4, 154.6, 135.9, 130.3, 129.6, 128.6, 128.3, 128.1, 124.3, 78.5, 67.3, 62.8, 55.1, 53.4, 52.5, 37.0, 28.8; HRMS (ESI) m/z calcd. for $C_{25}H_{32}N_2NaO_7[M+Na]^+$ 495.2107, found 495.2089.

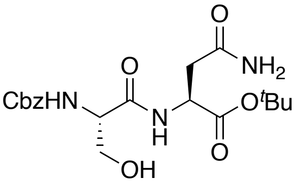
Cbz-Ser-Asp(^{t}Bu)-O^{t}Bu (4l)



4l

Compound **4l** was prepared according to the procedure A from Cbz-Ser-OMe (**2a**) (50.7 mg, 0.200 mmol) and H-Asp(^{t}Bu)-O^{t}Bu (**3l**) (147 mg, 0.600 mmol) at 80 °C for 24 h. Yield 93% (86.6 mg, 0.186 mmol). Purified by column chromatography (silica gel, 2:1 CH_2Cl_2/EtOAc). Data for **4l**; white solid; $R_f = 0.36$ (CH_2Cl_2/EtOAc = 2:1); $[\alpha]_D^{23}$ +21.5° (c = 1.0, $CHCl_3$); IR (KBr) ν = 3355, 3263, 3073, 2981, 1736, 1561, 1457, 1366, 1270, 1173, 1055, 909, 755, 701, 553 cm^{-1}; mp 137–139 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.29 (m, 5H), 7.19 (d, J = 8.5 Hz, 1H), 5.81 (d, J = 9.0 Hz, 1H), 5.11 (s, 2H), 4.72 (dt, J = 9.0, 4.5 Hz, 1H), 4.32–4.28 (m, 1H), 4.03 (dd, J = 11.5, 3.0 Hz, 1H), 3.69 (dd, J = 11.5, 6.5 Hz, 1H), 2.87 (dd, J = 16.5, 4.5 Hz, 1H), 2.70 (dd, J = 16.5, 4.5 Hz, 1H), 1.45 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 170.0, 169.8, 156.1, 136.1, 128.5, 128.1, 128.0, 83.0, 82.0, 67.1, 63.3, 55.8, 49.4, 37.0, 28.0, 27.8; HRMS (ESI) m/z calcd for $C_{23}H_{34}N_2NaO_8$ $[M+Na]^+$ 489.2213, found 489.2218.

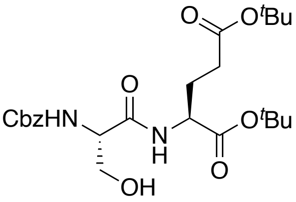
Cbz-Ser-Asn-O^{t}Bu (4m)



4m

Compound **4m** was prepared according to the procedure A from Cbz-Ser-OMe (**2a**) (50.7 mg, 0.200 mmol) and H-Asn-O^{t}Bu (**3m**) (113 mg, 0.600 mmol) at 80 °C for 48 h in toluene (0.2 M) in the absence of MS 4A (400 mg). Yield 91% (74.9 mg, 0.183 mmol). Purified by column chromatography (silica gel, 19:1 CH_2Cl_2/MeOH). Data for **4m**; yellow amorphous; $R_f = 0.31$ (CH_2Cl_2/MeOH = 9:1); $[\alpha]_D^{24}$ +12.8° (c = 1.0, $CHCl_3$); IR (neat) ν = 3340, 2980, 1672, 1524, 1410, 1370, 1217, 1157, 1059, 845, 756 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.82 (d, J = 7.0 Hz, 1H), 7.33–7.28 (m, 5H), 6.40 (br, 2H), 5.09 (s, 2H), 4.67 (br, 1H), 4.32 (br, 1H), 3.95 (dd, J = 10.5, 2.4 Hz, 1H), 3.79 (br, 1H), 3.69 (dd, J = 10.5, 3.2 Hz, 1H), 2.76 (br, 1H), 1.42 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 170.9, 170.0, 156.4, 136.2, 128.5, 128.1, 128.0, 82.8, 67.0, 63.0, 56.5, 50.0, 37.0, 27.8; HRMS (ESI) m/z calcd for $C_{19}H_{27}N_3NaO_7$ $[M+Na]^+$ 432.1747, found 432.1746.

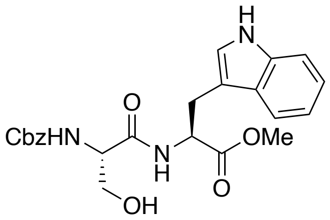
Cbz-Ser-Glu(^{t}Bu)-O^{t}Bu (4n)



4n

Compound **4n** was prepared according to the procedure A from Cbz-Ser-OMe (**2a**) (50.7 mg, 0.200 mmol) and H-Glu(^{t}Bu)-O^{t}Bu (**3n**) (156 mg, 0.600 mmol) at 80 °C for 24 h. Yield 90% (86.6 mg, 0.180 mmol). Purified by column chromatography (silica gel, 40:1 Et_2O/MeOH). Data for **4n**; white solid; $R_f = 0.21$ (hexane/EtOAc = 2:1); $[\alpha]_D^{26}$ −19.1° (c = 1.0, MeOH); IR (KBr) ν = 3478, 3314, 2984, 2367, 1727, 1544, 1367, 1260, 1154, 1016, 848, 759 cm^{-1}; mp 96–97 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.29 (m, 5H), 7.13 (d, J = 8.0 Hz, 1H), 5.84 (d, J = 7.0 Hz, 1H), 5.12 (s, 2H), 4.46 (dt, J = 8.0, 4.5 Hz, 1H), 4.30–4.27 (m, 1H), 4.04 (dd, J = 11.5, 3.0 Hz, 1H), 3.66 (dd, J = 11.5, 6.5 Hz, 1H), 2.61 (br, 1H), 2.34–2.23 (m, 2H), 2.17–2.10 (m, 1H), 1.95–1.87 (m, 1H), 1.46 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 171.0, 170.7, 156.3, 136.1, 128.5, 128.2, 128.0, 82.8, 81.0, 67.2, 63.2, 55.7, 52.7, 31.5, 28.0, 27.9, 26.8; HRMS (ESI) m/z calcd for $C_{24}H_{36}N_2NaO_8$ $[M+Na]^+$ 503.2369, found 503.2389.

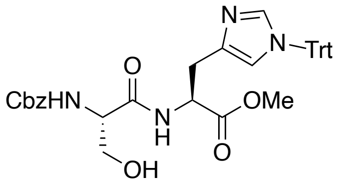
Cbz-Ser-Trp-OMe (4o)[4]



4o

Compound **4o** was prepared according to the procedure A from Cbz-Ser-OMe (**2a**) (50.7 mg, 0.200 mmol) and H-Trp-OMe (**3o**) (131 mg, 0.600 mmol) at 80 °C for 24 h. Yield 75% (65.9 mg, 0.150 mmol). Purified by column chromatography (silica gel, 40:1 Et$_2$O/MeOH). Data for **4o**; brown amorphous; R$_f$ = 0.32 (Et$_2$O/MeOH = 40:1); $[\alpha]_D^{24}$ +22.3° (c = 1.0, CHCl$_3$); IR (neat) ν = 3629, 3317, 3016, 2953, 1713, 1670, 1525, 1457, 1342, 1217, 1060, 761 cm^{-1}; ^{1}H NMR (270 MHz, CDCl$_3$) δ 8.46 (br, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.33–7.24 (m, 6H), 7.20 (br, 1H), 7.16–7.04 (m, 2H), 6.91 (d, J = 1.9 Hz, 1H), 5.98 (br, 1H), 5.04 (d, J = 12.4 Hz, 1H), 4.99 (d, J = 12.4 Hz, 1H), 4.87 (dt, J = 8.1, 5.4 Hz, 1H), 4.28–4.22 (m, 1H), 3.84 (dd, J = 11.3, 3.2 Hz, 1H), 3.63 (s, 3H), 3.56 (dd, J = 11.3, 5.7 Hz, 1H), 3.27 (d, J = 5.4 Hz, 2H), 3.07 (br, 1H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 172.3, 170.7, 156.4, 136.0, 128.5, 128.2, 128.1, 128.0, 127.2, 123.3, 122.0, 119.4, 118.2, 111.4, 109.1, 67.1, 62.7, 55.7, 52.9, 52.5, 27.1; HRMS (ESI) m/z calcd for $C_{23}H_{25}N_3NaO_6$ [M+Na]$^+$ 462.1641, found 462.1653.

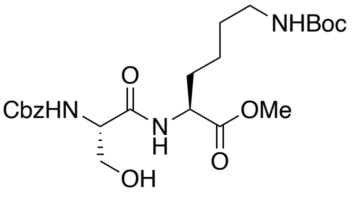
Cbz-Ser-His(Trt)-OMe (4p)



4p

Compound **4p** was prepared according to the procedure B from Cbz-Ser-OMe (**2a**) (50.7 mg, 0.200 mmol) and H-His(Trt)-OMe (**3p**) (247 mg, 0.600 mmol) at 80 °C for 24 h. Yield 70% (88.0 mg, 0.139 mmol). Purified by column chromatography (silica gel, 30:1 Et$_2$O/MeOH). Data for **4p**; yellow amorphous; R$_f$ = 0.27 (Et$_2$O/MeOH = 30:1); $[\alpha]_D^{25}$ +8.3° (c = 1.0, CHCl$_3$); IR (neat) ν = 3414, 3015, 2952, 1724, 1672, 1495, 1445, 1333, 1216, 1133, 1059, 760 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.45–7.29 (m, 16H), 7.10–7.05 (m, 6H), 6.53 (s, 1H), 6.14 (br, 1H), 5.14 (d, J = 12.5 Hz, 1H), 5.11 (d, J = 12.5 Hz, 1H), 4.81–4.78 (m, 1H), 4.24 (br, 1H), 4.13 (br d, J = 11.5 Hz, 1H), 3.71 (dd, J = 11.5, 4.5 Hz, 1H), 3.58 (s, 3H), 3.31 (dd, J = 15.0, 2.5 Hz, 1H), 2.90 (dd, J = 15.0, 5.0 Hz, 1H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 171.2, 170.8, 156.0, 141.7, 138.4, 136.2, 129.7, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 120.0, 67.0, 63.1, 57.4, 53.2, 52.4, 28.7; HRMS (ESI) m/z calcd for $C_{37}H_{37}N_4O_6$ [M+H]$^+$ 633.2713, found 633.2720.

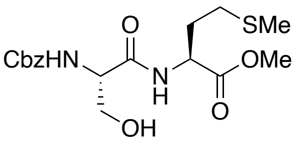
Cbz-Ser-Lys(Boc)-OMe (4q)[5]



4q

Compound **4q** was prepared according to the procedure B from Cbz-Ser-OMe (**2a**) (50.7 mg, 0.200 mmol) and H-Lys(Boc)-OMe (**3q**) (156 mg, 0.600 mmol) at 80 °C for 48 h. Yield 92% (88.7 mg, 0.184 mmol). Purified by column chromatography (silica gel, 1:1 CH_2Cl_2/EtOAc). Data for **4q**; white solid; $R_f = 0.26$ (CH_2Cl_2/EtOAc = 1:1); $[\alpha]_D^{26}$ –10.9° (*c* = 1.0, MeOH); IR (KBr) ν = 3469, 3335, 2956, 2371, 1687, 1526, 1365, 1254, 1174, 1065, 869, 746, 697, 613 cm^{-1}; mp 104–105 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 7.35–7.28 (m, 5H), 7.25–7.22 (m, 1H), 6.02 (d, *J* = 7.8 Hz, 1H), 5.11 (s, 2H), 4.79 (br, 1H), 4.59–4.52 (m, 1H), 4.35–4.29 (m, 1H), 4.03 (dd, *J* = 10.5, 2.4 Hz, 1H), 3.71–3.65 (m, 4H), 3.25 (br, 1H), 3.04 (br, 1H), 1.90–1.78 (m, 1H), 1.72–1.59 (m, 1H), 1.50–1.17 (m, 14H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 170.9, 156.4, 156.2, 136.0, 128.5, 128.1, 128.0, 79.3, 67.1, 62.8, 55.7, 52.5, 52.1, 40.0, 31.2, 29.2, 28.3, 22.3; HRMS (ESI) m/z calcd for $C_{23}H_{35}N_3NaO_8$ $[M+Na]^+$ 504.2322, found 504.2315.

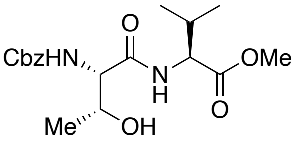
Cbz-Ser-Met-OMe (4r)[6]



4r

Compound **4r** was prepared according to the procedure A from Cbz-Ser-OMe (**2a**) (50.7 mg, 0.200 mmol) and H-Met-OMe (**3r**) (97.9 mg, 0.600 mmol) at 80 °C for 24 h. Yield 65% (49.7 mg, 0.129 mmol). Purified by column chromatography (silica gel, 4:1 CH_2Cl_2/EtOAc). Data for **4r**; white solid; $R_f = 0.32$ (CH_2Cl_2/EtOAc = 1:1); $[\alpha]_D^{26}$ –21.7° (*c* = 1.0, MeOH); IR (KBr) ν = 3301, 3073, 2932, 2344, 1727, 1655, 1543, 1439, 1249, 1019, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.28 (m, 5H), 5.93 (d, *J* = 7.0 Hz, 1H), 5.11 (s, 2H), 4.70 (dt, *J* = 8.0, 5.0 Hz, 1H), 4.33–4.29 (m, 1H), 4.02 (dd, *J* = 11.5, 2.5 Hz, 1H), 3.74 (s, 3H), 3.72–3.66 (m, 1H), 3.46 (br, 1H), 2.50 (br, 2H), 2.19–2.12 (m, 1H), 2.06 (s, 3H), 2.01–1.94 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4, 170.9, 156.4, 135.9, 128.5, 128.2, 128.0, 67.2, 62.9, 55.5, 52.7, 51.7, 30.9, 29.9, 15.4; HRMS (ESI) m/z calcd for $C_{17}H_{24}N_2NaO_6S$ $[M+Na]^+$ 407.1253, found 407.1250.

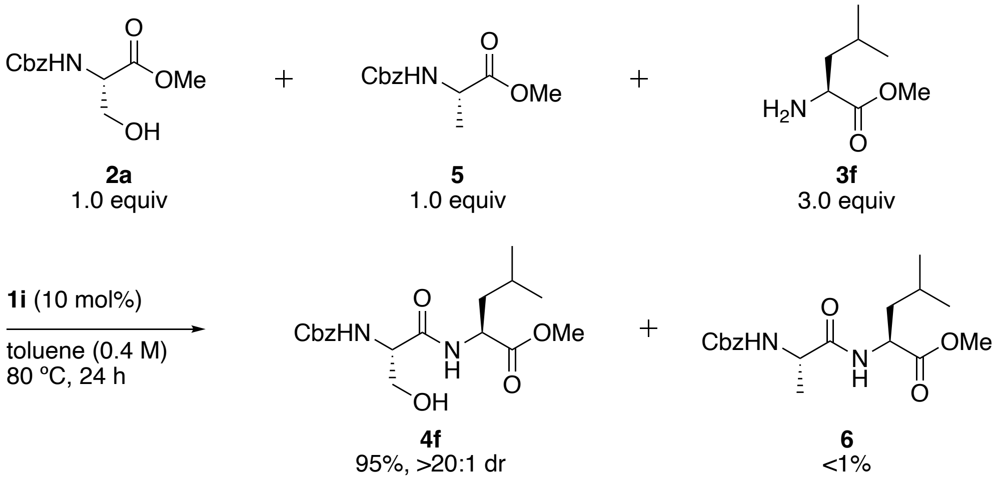
Cbz-Thr-Val-OMe (4s)



4s

Compound **4s** was prepared according to the procedure A from Cbz-Thr-OMe (**2d**) (53.5 mg, 0.200 mmol) and H-Val-OMe (**3e**) (78.7 mg, 0.600 mmol) at 80 °C for 48 h. Yield 91% (66.9 mg, 0.183 mmol). Purified by column chromatography (silica gel, 4:1 CH_2Cl_2/EtOAc). Data for **4s**; colorless oil; $R_f = 0.34$ (CH_2Cl_2/EtOAc = 4:1); $[\alpha]_D^{26}$ –29.4° ($c = 1.0$, $CHCl_3$); IR (neat) ν = 3327, 2967, 1739, 1663, 1531,1215, 1147, 1065, 740, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.29 (m, 5H), 7.07 (d, $J = 9.0$ Hz, 1H), 5.87 (d, $J = 7.5$ Hz, 1H), 5.15 (d, $J = 12.0$ Hz, 1H), 5.09 (d, $J = 12.0$ Hz, 1H), 4.48 (dd, $J = 9.0$, 5.5 Hz, 1H), 4.34–4.30 (m, 1H), 4.20 (dd, $J = 7.5$, 2.5 Hz, 1H), 3.73 (s, 3H), 2.63 (br, 1H), 2.20–2.13 (m, 1H), 1.18 (d, $J = 7.0$ Hz, 1H, 3H), 0.89 (d, $J = 6.5$ Hz, 1H, 3H), 0.86 (d, $J = 6.5$ Hz, 1H, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 171.1, 156.9, 136.0, 128.5, 128.2, 128.0, 67.2, 66.8, 58.1, 57.3, 52.2, 30.7, 19.0, 17.9, 17.5; HRMS (ESI) m/z calcd for $C_{18}H_{26}N_2NaO_6$ $[M+Na]^+$ 389.1689, found 389.1707.

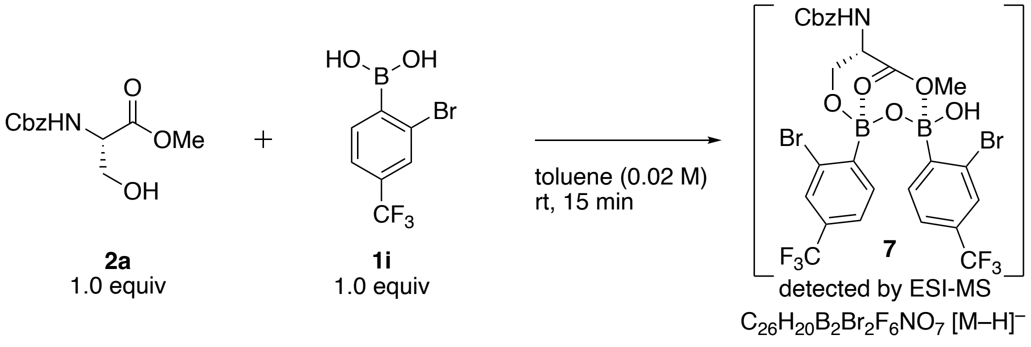
6. Competition experiment (Scheme 4A)



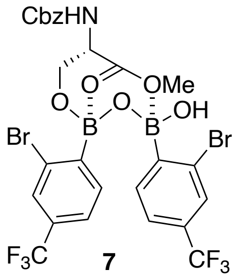
Boronic acid **1i** (5.38 mg, 20.0 μmol, 10.0 mol%) was added to a solution of Cbz-Ser-OMe (**2a**) (50.7 mg, 0.200 mmol, 1.0 equiv), Cbz-Ala-OMe (**5**) (47.5 mg, 0.200 mmol, 1.0 equiv) and H-Leu-OMe (**3f**) (87.1 mg, 0.600 mmol, 3.0 equiv) in toluene (0.5 mL, 0.40 M) at room temperature. After stirring for 24 h at 80 °C, the reaction mixture was cooled to room temperature. The reaction mixture was quenched by 1 M HCl and the resulting mixture was extracted with CH_2Cl_2. The combined organic layer was successively washed with sat. $NaHCO_3$ aq., H_2O, brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Compound **6** was not detected by ^1H NMR analysis of the crude product. The crude product was purified by silica gel column chromatography (eluent, 4:1 CH_2Cl_2/EtOAc) to give the corresponding peptide **4f** (69.5 mg, 0.190 mmol, 95%, >20:1 dr) as a colorless oil.

7. Detection of presumed reaction intermediate (Scheme 4B)

ESI-MS analysis



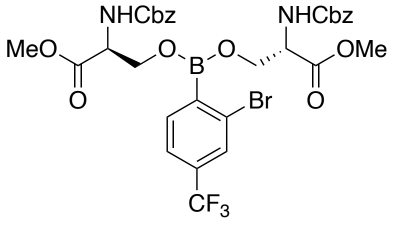
Boronic acid **1i** (2.69 mg, 10.0 μmol, 1.0 equiv) was added to a solution of Cbz-Ser-OMe (**2a**) (2.53 mg, 10.0 μmol, 1.0 equiv) in toluene (0.5 mL, 0.02 M) at room temperature. After stirring for 15 min at room temperature, ESI-MS (SI-Figure 1) was recorded using methanol as an eluent. The negative ESI-LRMS spectrum shown in SI-Figure 1 gave a peak corresponding to the expected intermediate **7**. The ESI-HRMS analysis showed *m/z* peak at 751.9701 ($C_{26}H_{20}{}^{11}B_2{}^{79}Br_2F_6NO_7$ [M–H]$^-$, calcd *m/z* 751.9697). Other peaks such as complex **SI-4** (**1i** : **2a** = 1 : 2) and dimer of boronic acid **SI-5** were also detected by the negative ESI-MS analysis.



7

${}^{12}C_{26}{}^{1}H_{20}{}^{11}B_2{}^{79}Br_2{}^{19}F_6{}^{14}N^{16}O_7$ [M–H]$^-$

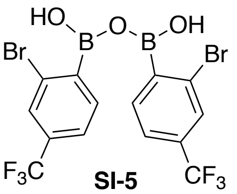
calcd m/z: 751.9697
found m/z: 751.9701



SI-4

${}^{12}C_{31}{}^{1}H_{30}{}^{11}B^{79}Br^{19}F_3{}^{14}N_2{}^{16}O_{10}$ [M–H]$^-$

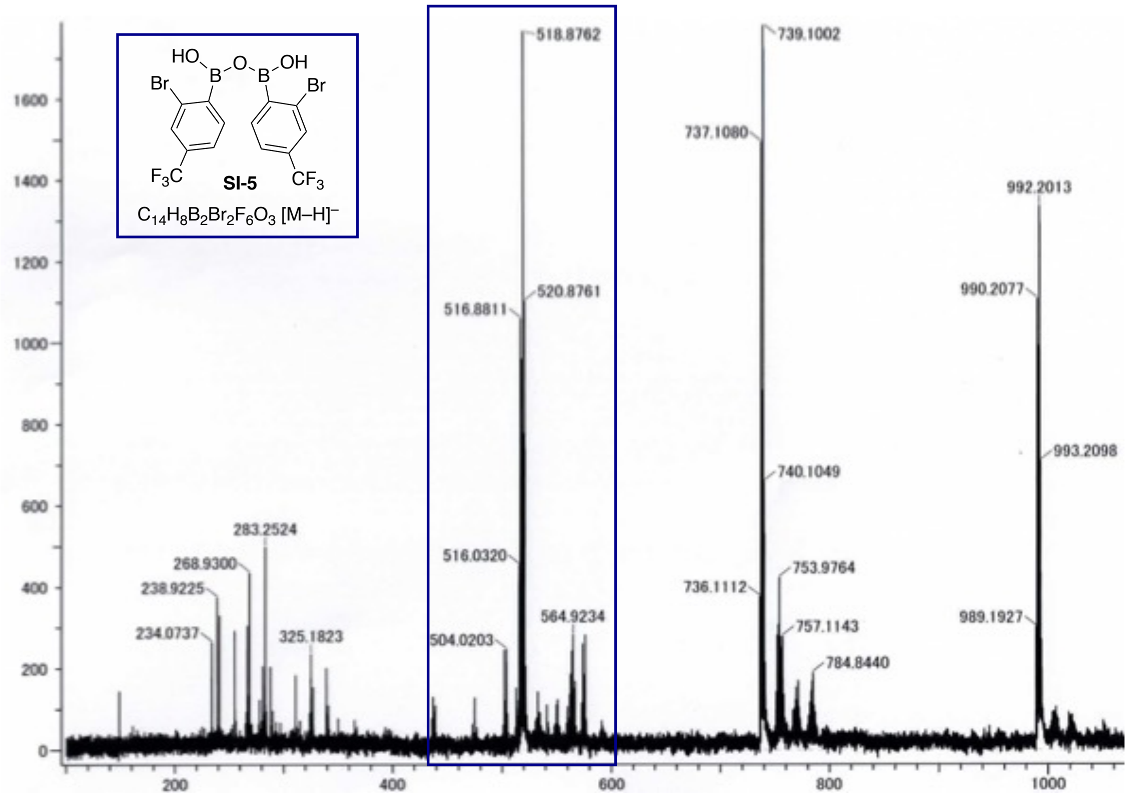
calcd m/z: 737.1129
found m/z: 737.1096



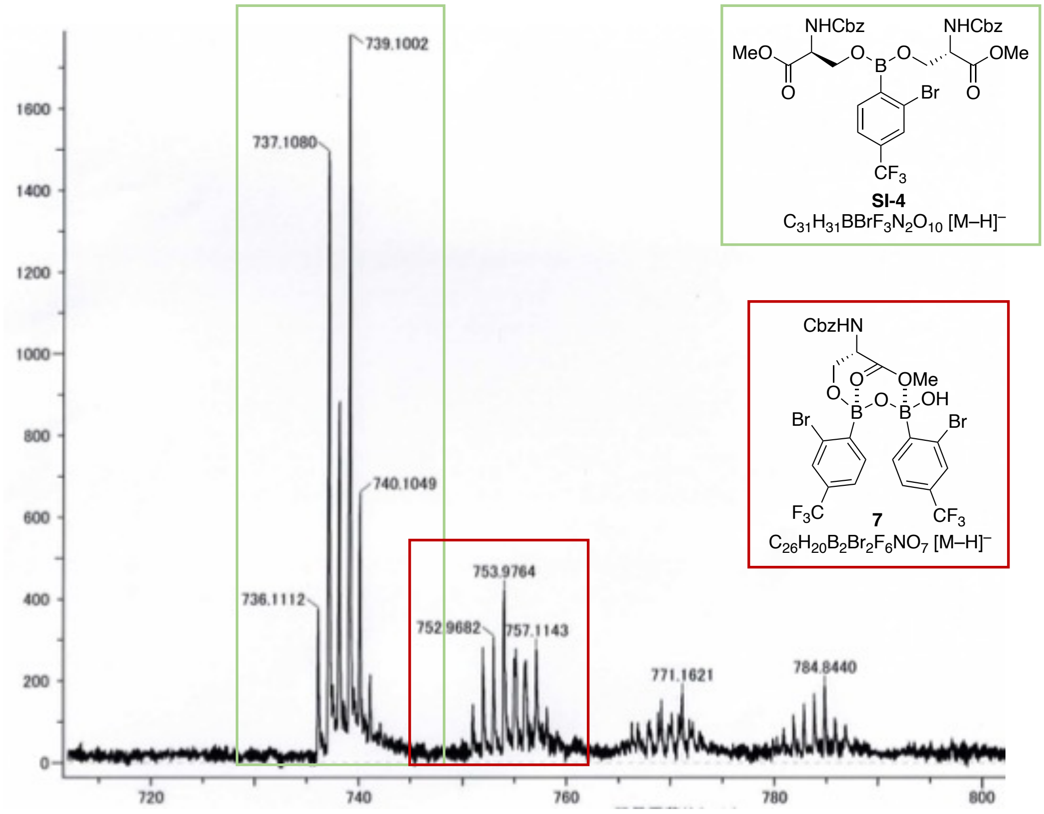
SI-5

${}^{12}C_{14}{}^{1}H_8{}^{11}B_2{}^{79}Br_2{}^{19}F_6{}^{16}O_3$ [M–H]$^-$

calcd m/z: 516.8852
found m/z: 516.8862

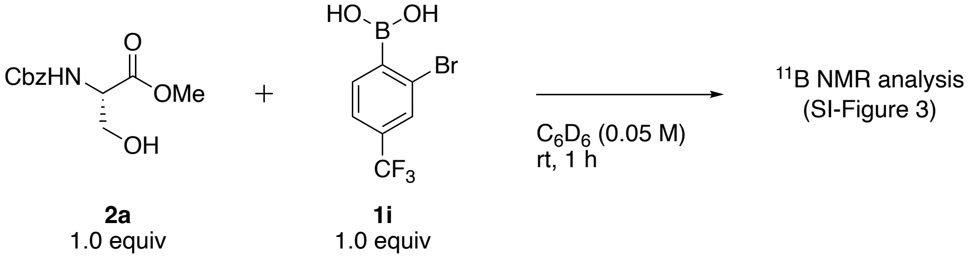


SI-Figure 1. Negative ESI-LRMS spectrum

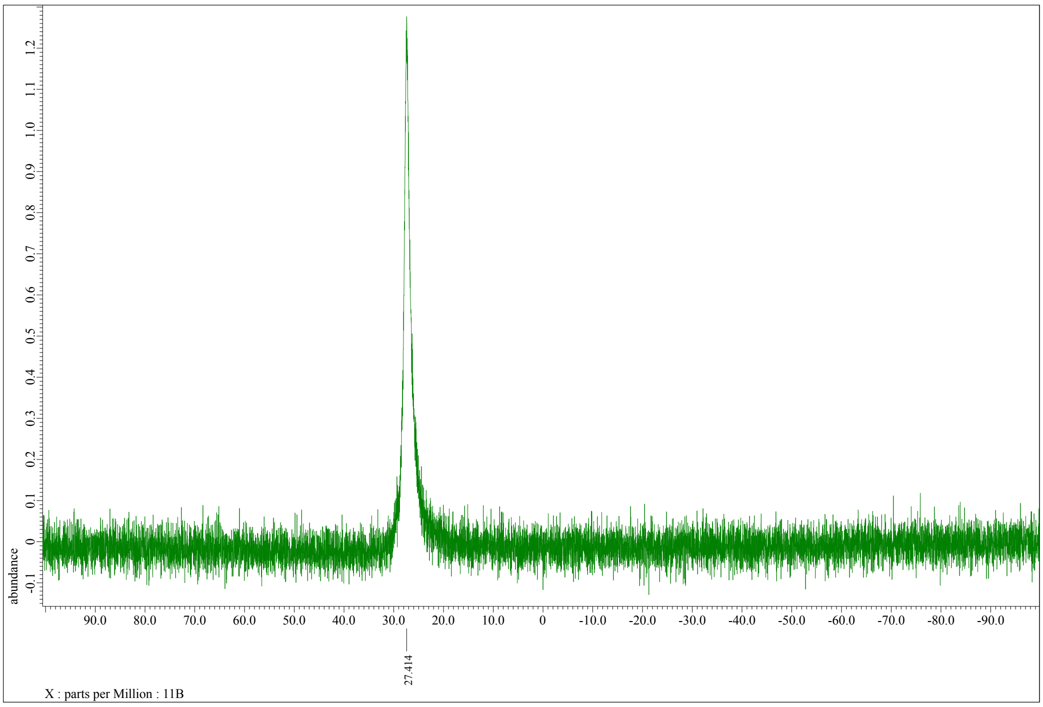


SI-Figure 2. Enlarged view of negative ESI-LRMS spectrum shown SI-Figure 1.

^{11}B NMR analysis



Boronic acid **1i** (5.38 mg, 20.0 μmol, 1.0 equiv) was added to a solution of Cbz-Ser-OMe (**2a**) (5.07 mg, 20.0 μmol, 1.0 equiv) in C_6D_6 (0.5 mL, 0.05 M) at room temperature. After stirring for 1 h at room temperature, ^{11}B NMR was recorded (SI-Figure 3).

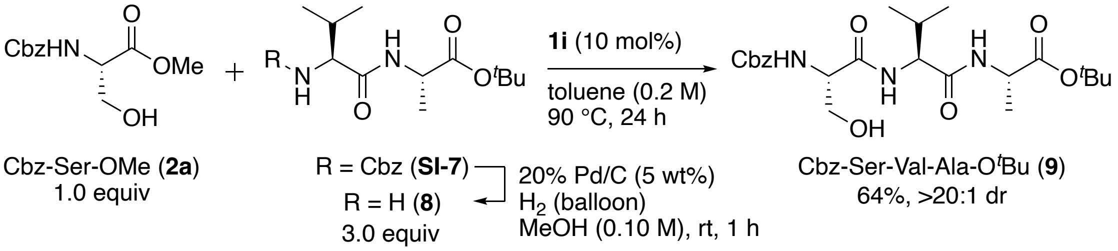


SI-Figure 3. The ^{11}B-NMR spectrum of an equimolar mixture of Cbz-Ser-OMe (2a) and boronic acid 1i in C_6D_6.

The ^{11}B-NMR of a mixture of Cbz-Ser-OMe (**2a**) and boronic acid **1i** in C_6D_6 suggested a tri-coordinated boron structure instead of the expected tetra-coordinated boron structure, probably due to the weak coordination of the ester functional group. (SI-Figure 3).

8. Application to the catalytic synthesis of oligopeptides (Scheme 4C)

Cbz-Ser-Val-Ala-O*ᵗ*Bu (9)

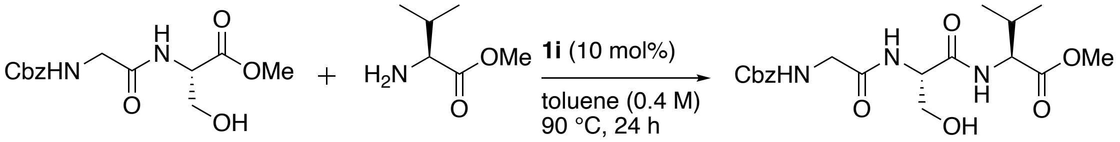


20% Pd/C (22.8 mg, 5 wt%) was added to a solution of Cbz-Val-Ala-O*ᵗ*Bu (**SI-7**) (114 mg, 0.300 mmol, 3.0 equiv) in MeOH (3.0 mL, 0.10 M) at room temperature and the atmosphere was filled with H_2 (1 atm, balloon). After stirred for 1 h, the resulting mixture was filtered through a pad of Celite® and the resulting filtrate was concentrated under reduced pressure to furnish the crude product, which was subjected to the next step without further purification.

Boronic acid **1i** (2.69 mg, 10.0 μmol, 10.0 mol%) was added to a solution of Cbz-Ser-OMe (**2a**) (25.3 mg, 0.100 mmol, 1.0 equiv) and H-Val-Ala-O*ᵗ*Bu (**8**) (73.3 mg, 0.300 mmol, 3.0 equiv) in toluene (0.5 mL, 0.20 M) at room temperature. After stirring for 24 h at 90 °C, the reaction mixture was cooled to room temperature. The reaction mixture was quenched by 1 M HCl and the resulting mixture was extracted with CH_2Cl_2. The combined organic layer was successively washed with sat. $NaHCO_3$ aq., H_2O, brine, dried over Na_2SO_4, filtered, and concentration in vacuo. The crude material was purified by silica gel column chromatography (1:1 CH_2Cl_2/EtOAc) to give Cbz-Ser-Val-Ala-O*ᵗ*Bu (**9**) (30.0 mg, 0.064 mmol, 64%, >20:1 dr) as a white solid.

Data for **9**; white solid; R_f = 0.31 (CH_2Cl_2/EtOAc = 1:1); $[\alpha]_D^{26}$ –20.0° (*c* = 1.0, $CHCl_3$); IR (KBr) ν = 3287, 2980, 2344, 1641, 1534, 1369, 1261, 1152, 1028, 695 cm^{-1}; mp 168–170 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.27 (m, 5H), 7.18 (d, *J* = 8.5 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.02 (d, *J* = 7.5 Hz, 1H), 5.10 (s, 2H), 4.44–4.40 (m, 2H), 4.35–4.32 (m, 1H), 3.95 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.66 (dd, *J* = 11.0, 7.0 Hz, 1H), 2.63 (br, 2H), 2.18–2.14 (m, 1H), 1.43 (s, 9H), 1.32 (d, *J* = 6.5 Hz, 1H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 171.2, 170.6, 156.3, 136.1, 128.5, 128.2, 128.0, 82.1, 67.0, 63.0, 59.0, 55.6, 48.8, 30.6, 27.9, 19.2, 18.2, 17.8; HRMS (ESI) m/z calcd for $C_{23}H_{35}N_3NaO_7$ $[M+Na]^+$ 488.2373, found 488.2387.

Cbz-Gly-Ser-Val-OMe (11)



Cbz-Gly-Ser-OMe (**10**)
1.0 equiv

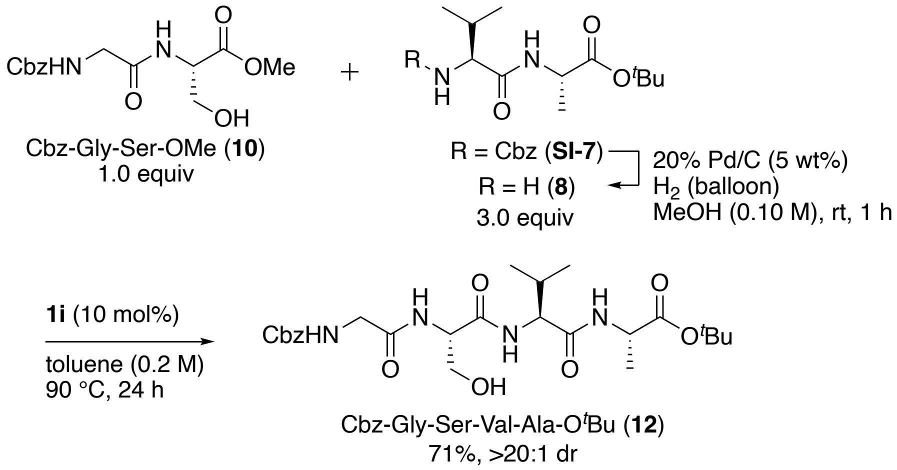
H-Val-OMe (**3e**)
3.0 equiv

Cbz-Gly-Ser-Val-OMe (**11**)
87%, >20:1 dr

Boronic acid **1i** (5.38 mg, 20.0 μmol, 10.0 mol%) was added to a solution of Cbz-Gly-Ser-OMe (**10**) (62.1 mg, 0.200 mmol, 1.0 equiv) and H-Val-OMe (**3e**) (78.7 mg, 0.600 mmol, 3.0 equiv) in toluene (0.5 mL, 0.40 M) at room temperature. After stirring for 24h at 90 °C, the reaction mixture was cooled to room temperature. The reaction mixture was quenched by 1 M HCl and the resulting mixture was extracted with CH_2Cl_2. The combined organic layer was successively washed with sat. $NaHCO_3$ aq., H_2O, brine, dried over Na_2SO_4, filtered, and concentration in vacuo. The crude material was purified by silica gel column chromatography (20:1 Et_2O/MeOH) to give Cbz-Gly-Ser-Val-OMe (**11**) (71.4 mg, 0.174 mmol, 87%, >20:1 dr) as a yellow oil.

Data for **11**; yellow oil; $R_f = 0.23$ (Et_2O/MeOH = 20:1); $[\alpha]^{26}_{D}$ $-13.1°$ ($c = 1.0$, $CHCl_3$); IR (neat) $\nu = 3319, 3018, 2966, 1728, 1659, 1529, 1439, 1217, 1153, 1051, 999, 757\ cm^{-1}$; ^1H NMR (270 MHz, $CDCl_3$) δ 7.43 (br, 1H), 7.40 (br, 1H), 7.34–7.28 (m, 5H), 5.93–5.89 (m, 1H), 5.09 (s, 2H), 4.68–4.62 (m, 1H), 4.46 (dd, $J = 8.1, 4.9$ Hz, 1H), 3.97–3.90 (m, 3H), 3.75–3.64 (m, 4H), 3.43 (br, 1H), 2.22–2.10 (m, 1H), 0.91 (d, $J = 6.8$ Hz, 3H), 0.88 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 170.7, 170.0, 156.7, 136.1, 128.5, 128.2, 128.0, 67.1, 62.6, 55.6, 54.2, 52.3, 44.3, 30.6, 18.9, 17.7; HRMS (ESI) m/z calcd for $C_{19}H_{27}N_3NaO_7$ $[M+Na]^+$ 432.1747, found 432.1751.

Cbz-Gly-Ser-Val-Ala-O^{t}Bu (12)



20% Pd/C (22.8 mg, 5 wt%) was added to a solution of Cbz-Val-Ala-O^{t}Bu (**SI-7**) (114 mg, 0.300 mmol, 3.0 equiv) in MeOH (3.0 mL, 0.10 M) at room temperature and the atmosphere was filled with H_2 (1 atm, balloon). After stirred for 1 h, the resulting mixture was filtered through a pad of Celite® and the resulting filtrate was concentrated under reduced pressure to furnish the crude product, which was subjected to the next step without further purification.

Boronic acid **1i** (2.69 mg, 10.0 μmol, 10.0 mol%) was added to a solution of Cbz-Gly-Ser-OMe (**10**) (31.0 mg, 0.100 mmol, 1.0 equiv) and H-Val-Ala-O^{t}Bu (**8**) (73.3 mg, 0.300 mmol, 3.0 equiv) in toluene (0.5 mL, 0.20 M) at room temperature. After stirring for 24 h at 90 °C, the reaction mixture was cooled to room temperature. The reaction mixture was quenched by 1 M HCl and the resulting mixture was extracted with CH_2Cl_2. The combined organic layer was successively washed with sat. $NaHCO_3$ aq., H_2O, brine, dried over Na_2SO_4, filtered, and concentration in vacuo. The crude material was purified by silica gel column chromatography (1:9 CH_2Cl_2/EtOAc) to give Cbz-Gly-Ser-Val-Ala-O^{t}Bu (**12**) (37.0 mg, 0.071 mmol, 71%, >20:1 dr) as a white solid.

Data for **12**; white solid; R_f = 0.30 (CH_2Cl_2/EtOAc = 1:9); $[\alpha]_D^{26}$ –16.1° (c = 1.0, $CHCl_3$); IR (KBr) ν = 3266, 3088, 2963, 2371, 1735, 1620, 1560, 1455, 1367, 1235, 1159, 1056, 937, 752, 696 590 cm^{-1}; mp 168–171 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.37–7.31 (m, 5H), 7.13 (br, 1H), 6.82–6.80 (m, 2H), 5.49 (br, 1H), 5.12 (s, 2H), 4.60–4.56 (m, 1H), 4.43 (dt, J = 7.8, 4.1Hz, 1H), 4.34–4.31 (m, 1H), 4.01 (br d, J = 4.6 Hz, 1H), 3.95 (d, J = 2.7 Hz, 2H), 3.62 (dd, J = 5.4, 3.8 Hz, 1H), 2.28–2.21 (m, 1H), 1.45 (s, 9H), 1.35 (d, J = 3.8 Hz, 3H), 0.98 (d, J = 3.5 Hz, 3H), 0.93 (d, J = 3.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 170.9, 170.8, 169.4, 156.7, 136.2, 129.5, 128.5, 128.2, 128.0, 82.0, 67.1, 63.1, 59.0, 54.5, 48.9, 44.3, 30.9, 27.9, 19.2, 18.0; HRMS (ESI) m/z calcd for $C_{25}H_{38}N_4NaO_8$ $[M+Na]^+$ 545.2587, found 545.2595.

9. References

(1) M. Koshizuka, K. Makino and N. Shimada, *Org. Lett.*, 2020, **22**, 8658–8664.

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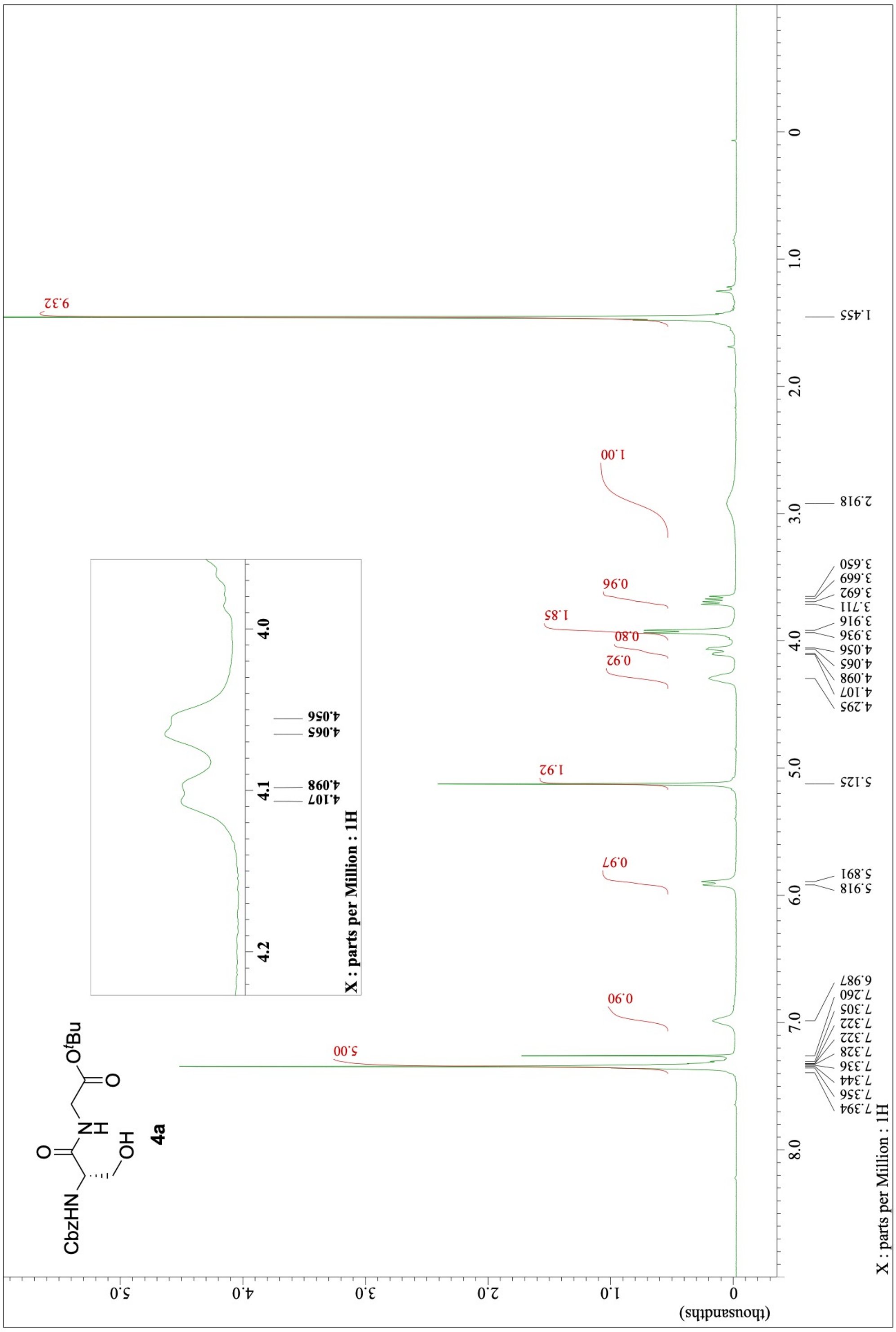
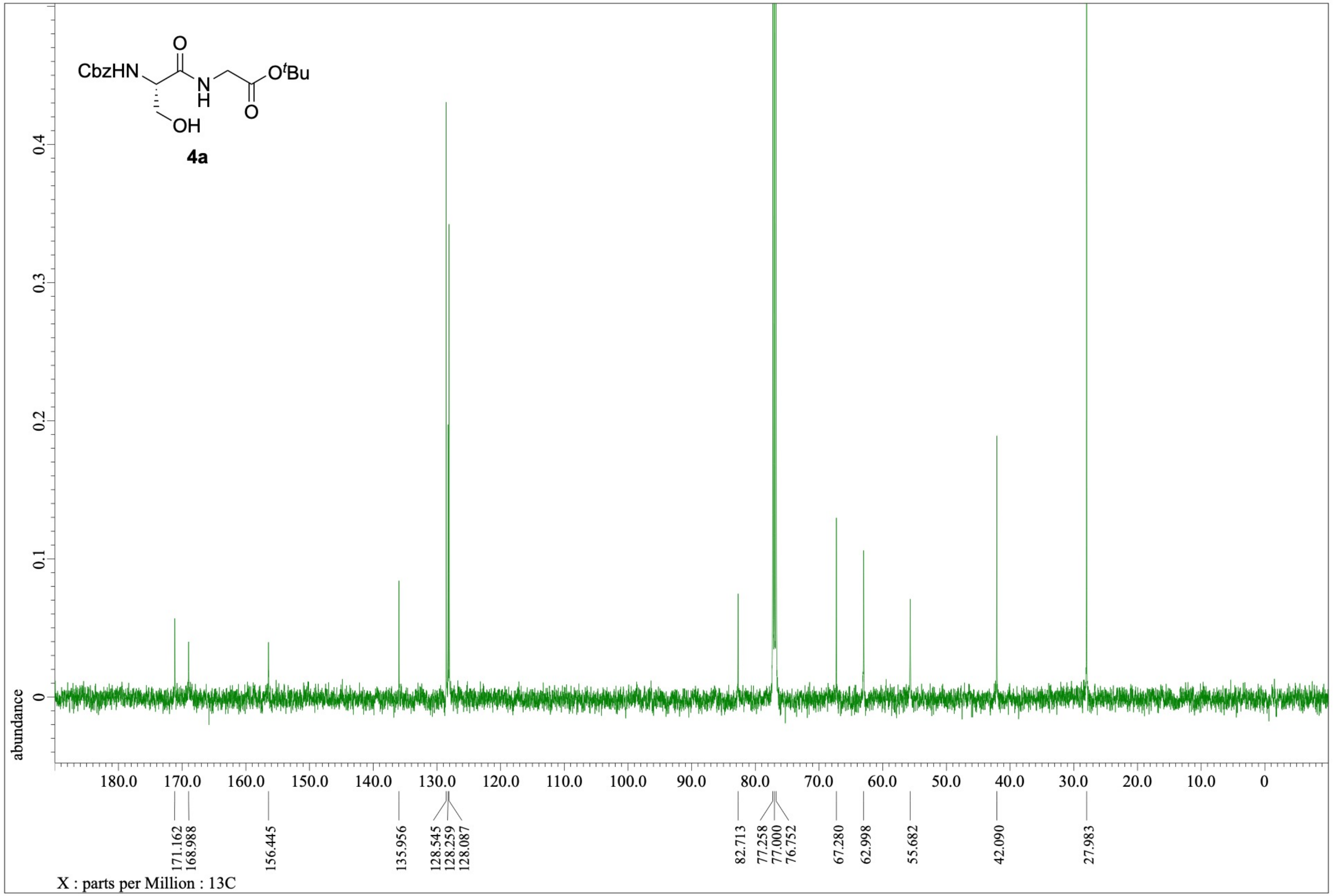
10. ^{1}H and ^{13}C NMR spectra

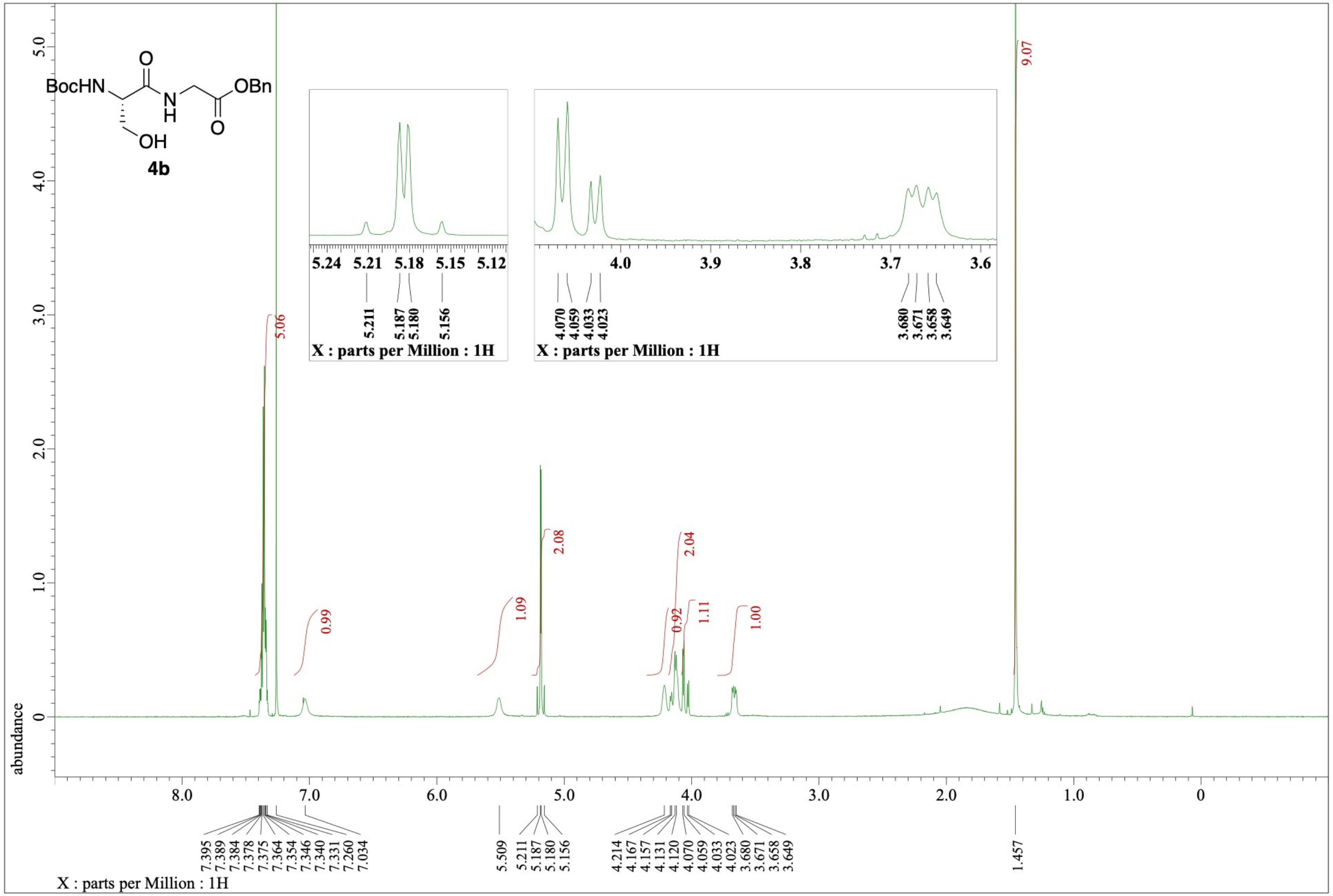


^{1}H NMR spectrum of 4a (270 MHz, CDCl$_3$)

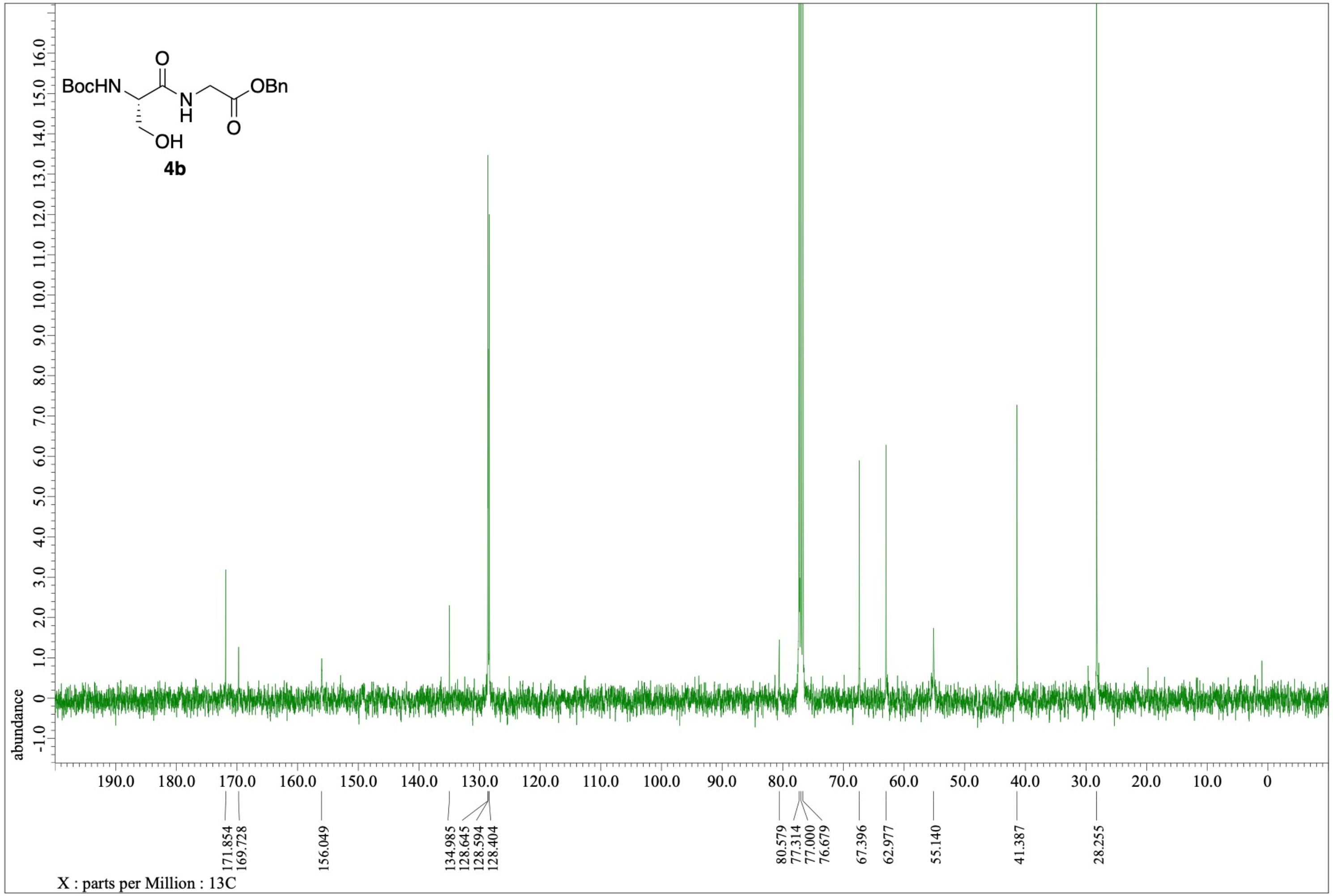
^{13}C NMR spectrum of 4a (126 MHz, CDCl$_3$)



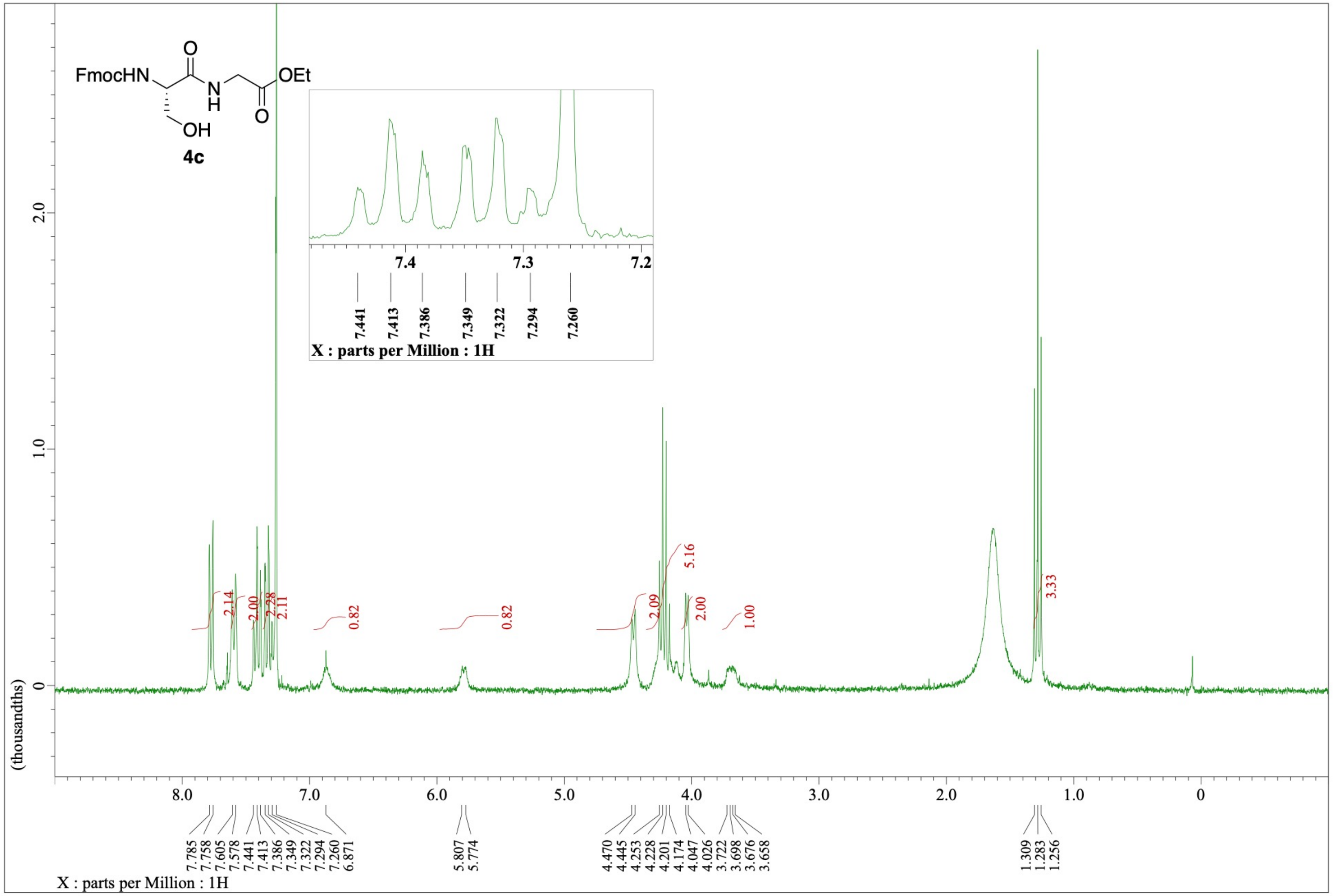
^{1}H NMR spectrum of 4b (500 MHz, $CDCl_3$)



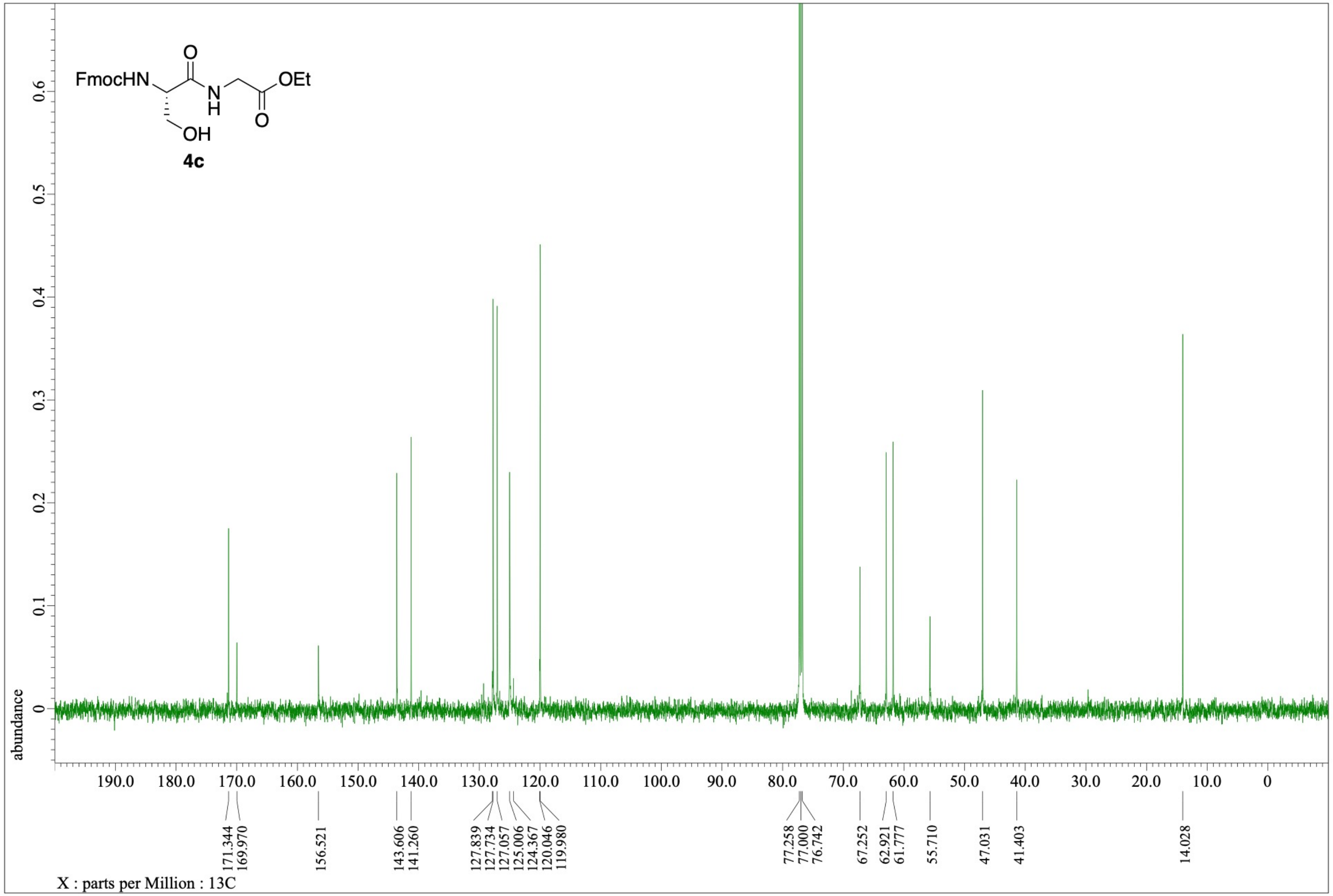
^{13}C NMR spectrum of 4b (100 MHz, $CDCl_3$)



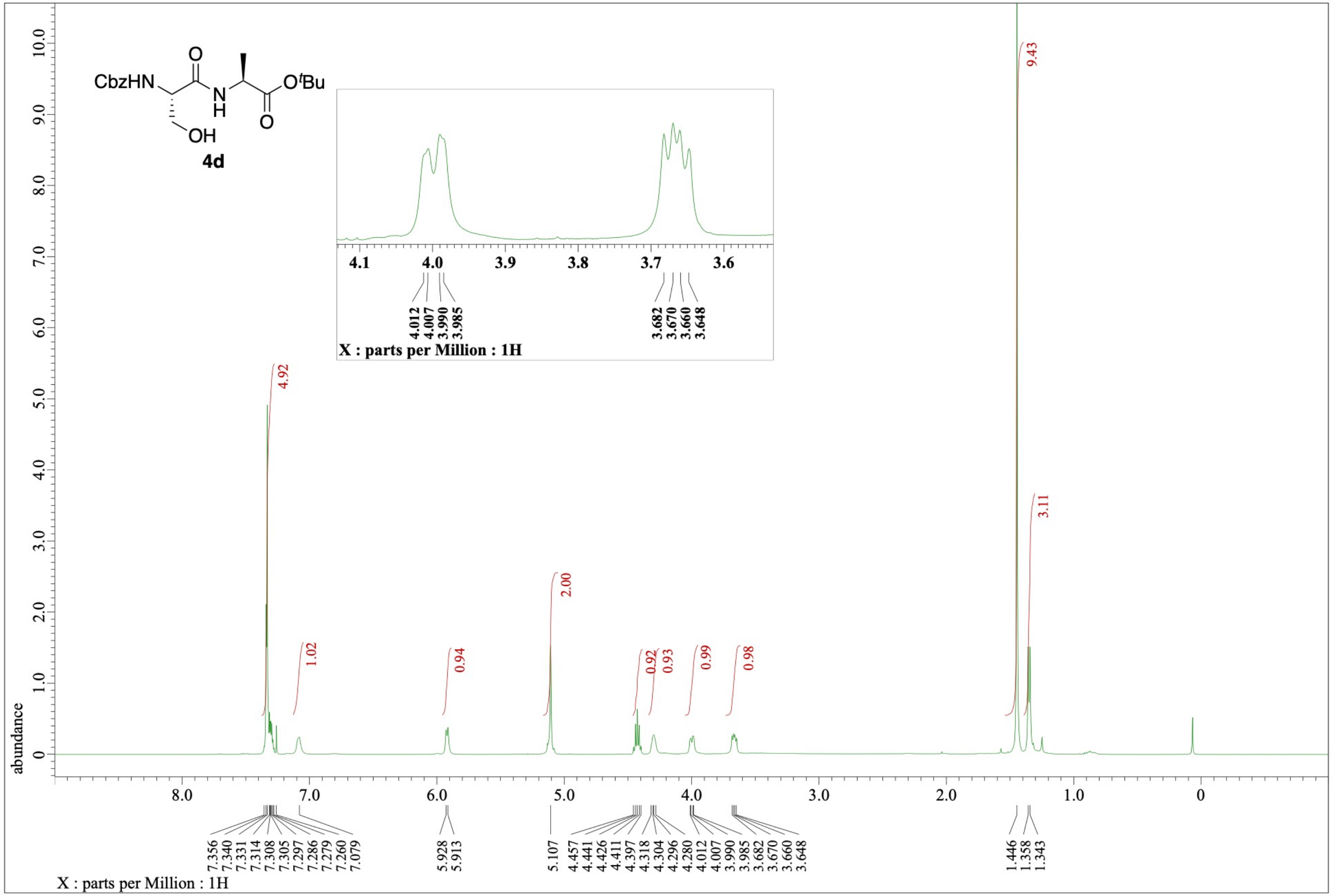
^{1}H NMR spectrum of 4c (270 MHz, CDCl$_3$)



^{13}C NMR spectrum of 4c (126 MHz, CDCl$_3$)



^{1}H NMR spectrum of 4d (500 MHz, $CDCl_3$)



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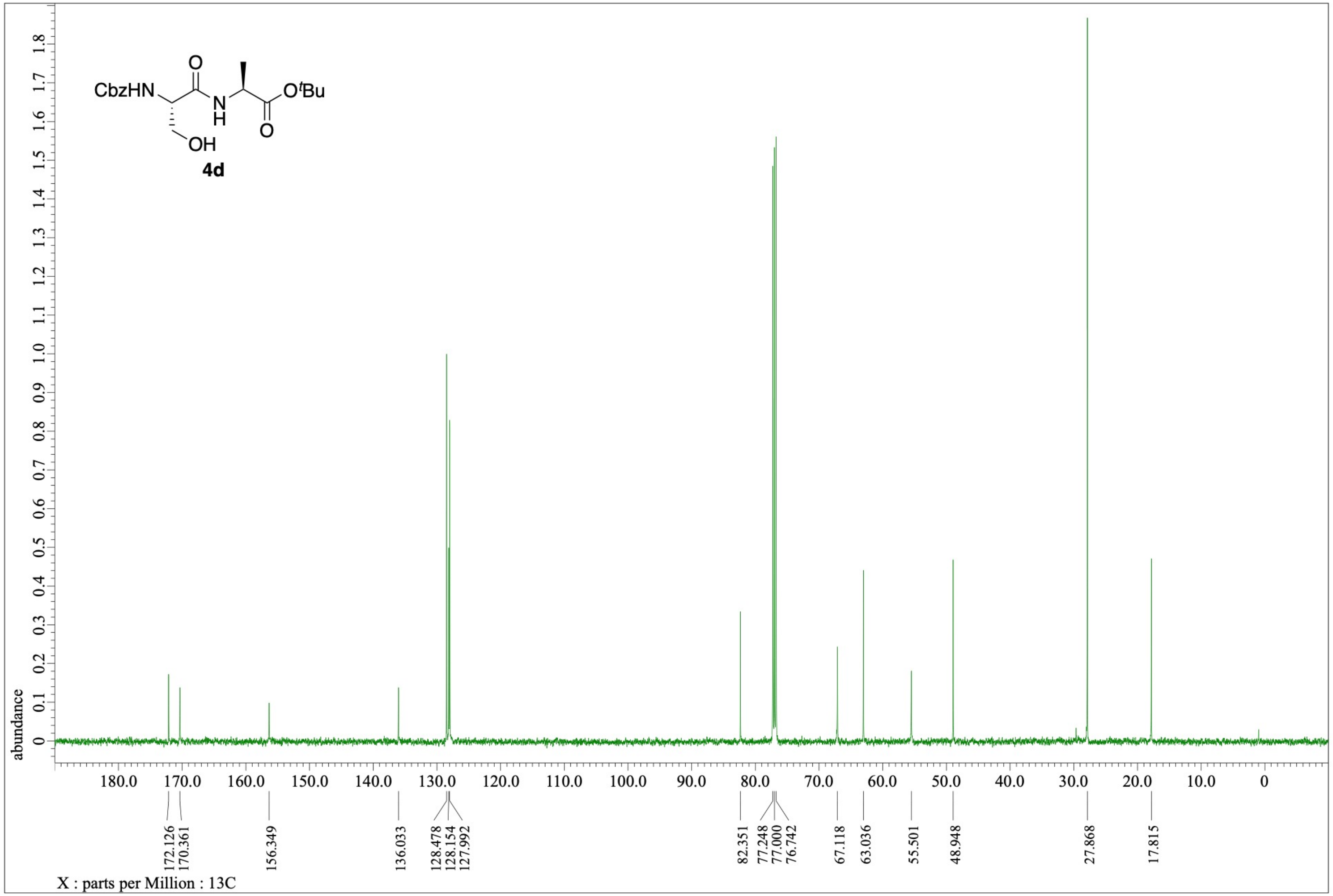
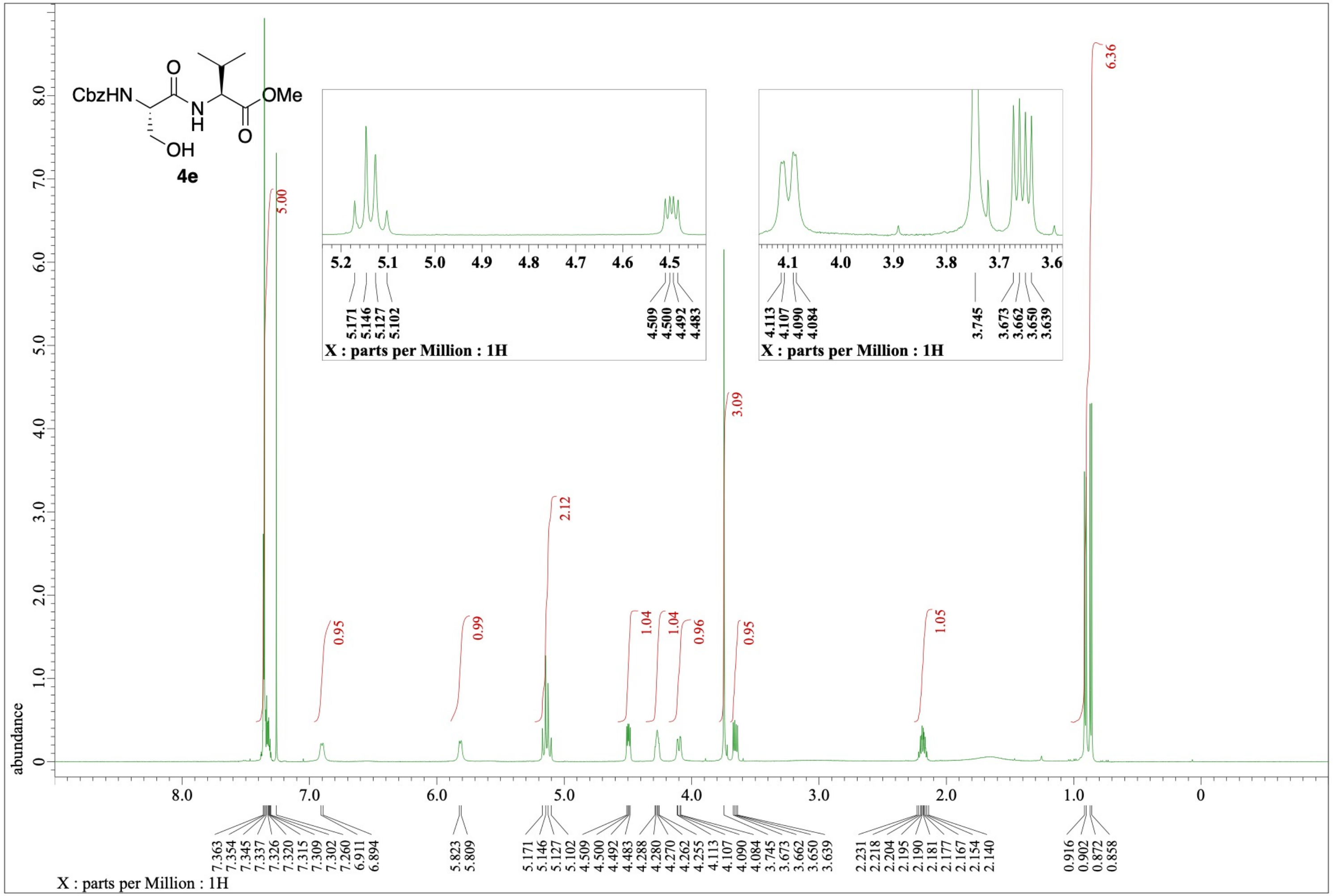
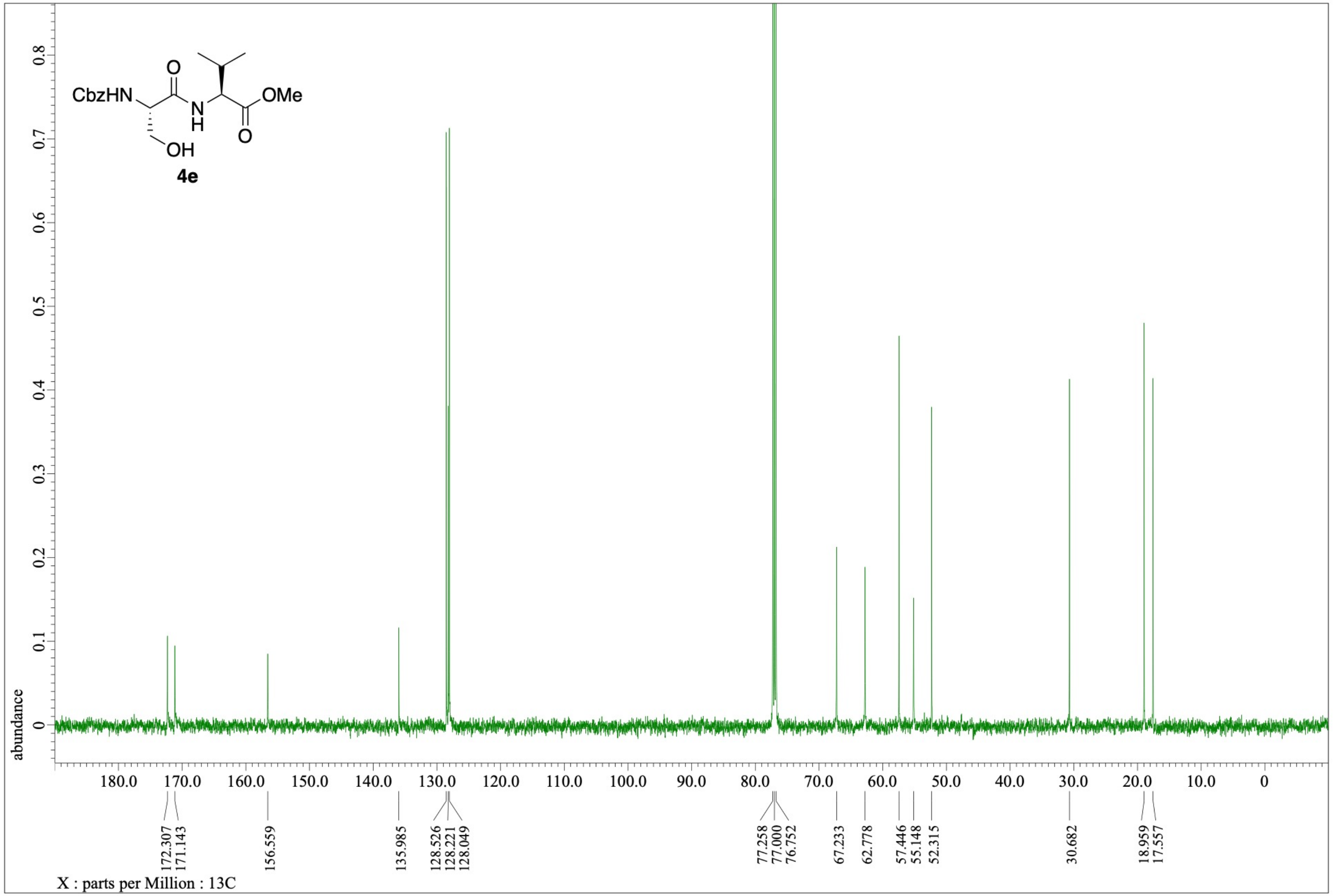


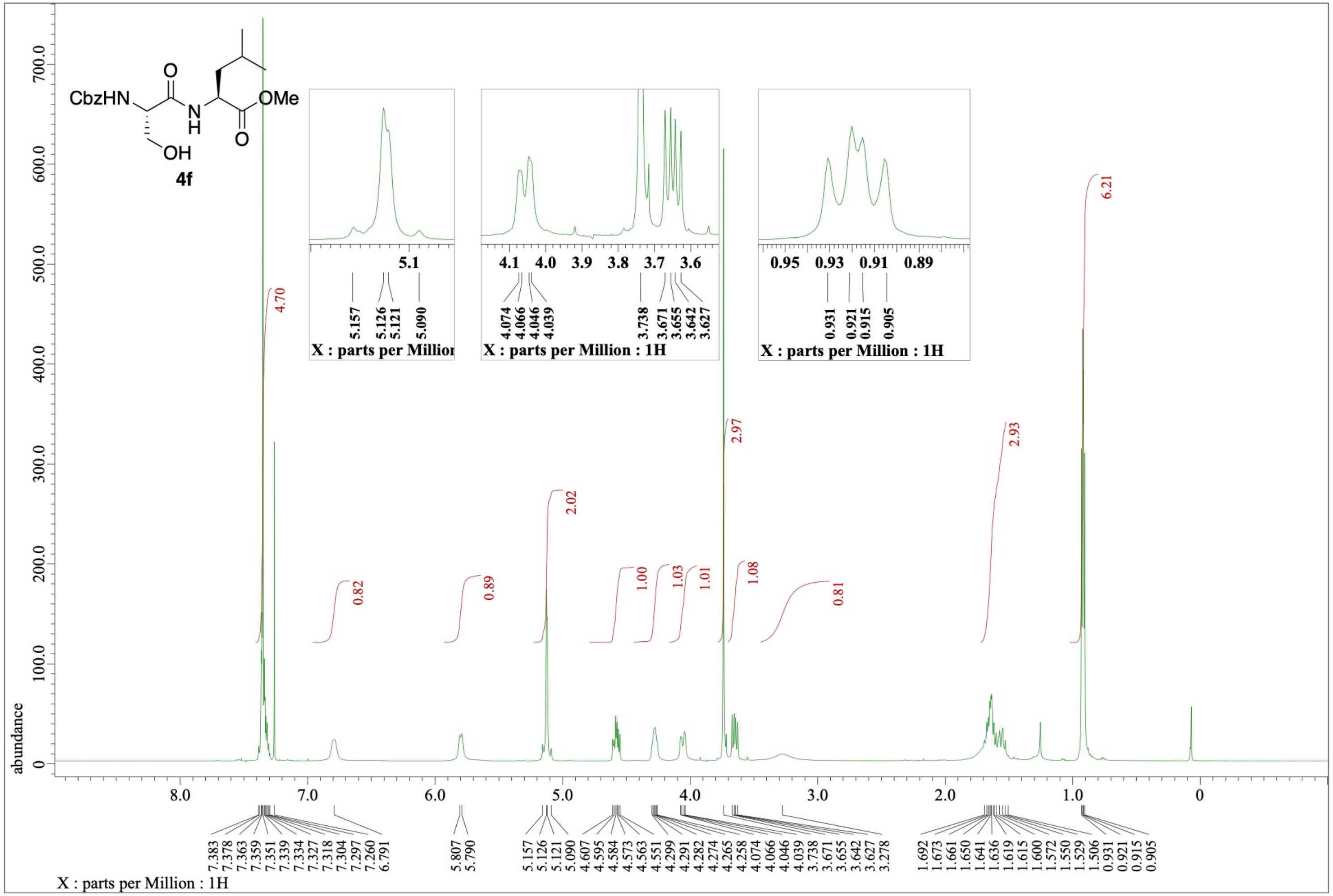
^{1}H NMR spectrum of 4e (500 MHz, $CDCl_3$)



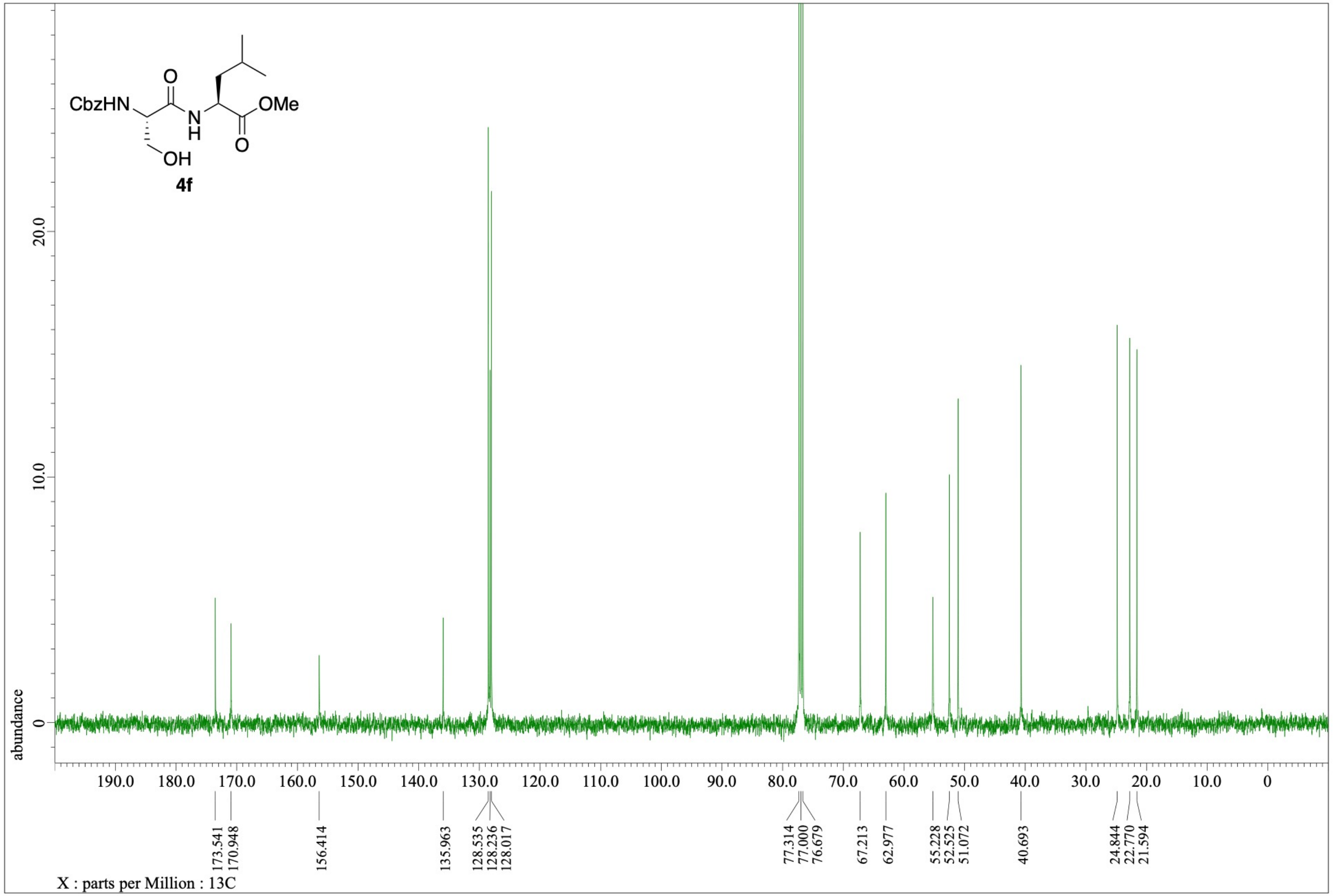
^{13}C NMR spectrum of 4e (126 MHz, CDCl$_3$)



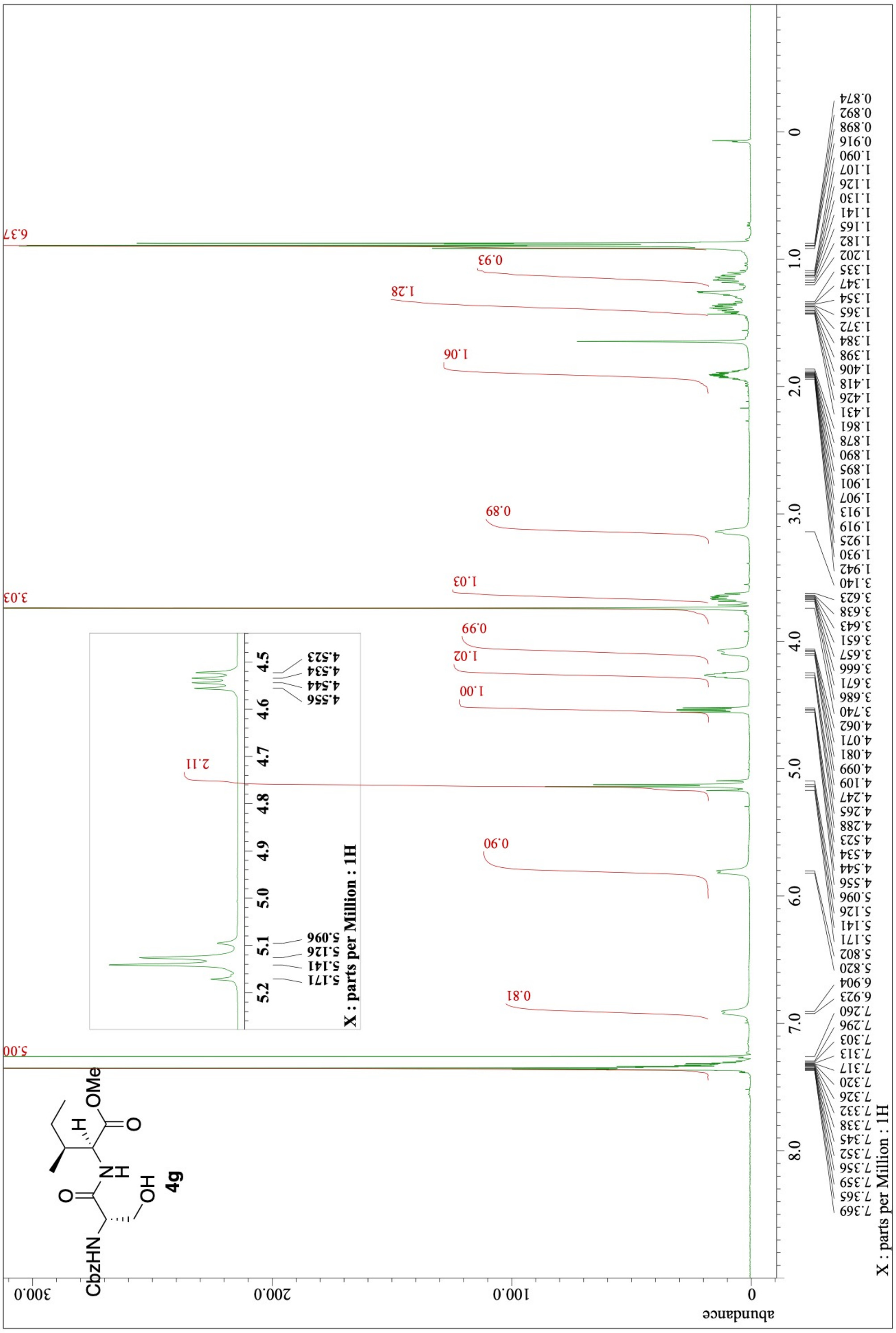
^{1}H NMR spectrum of 4f (400 MHz, $CDCl_3$)



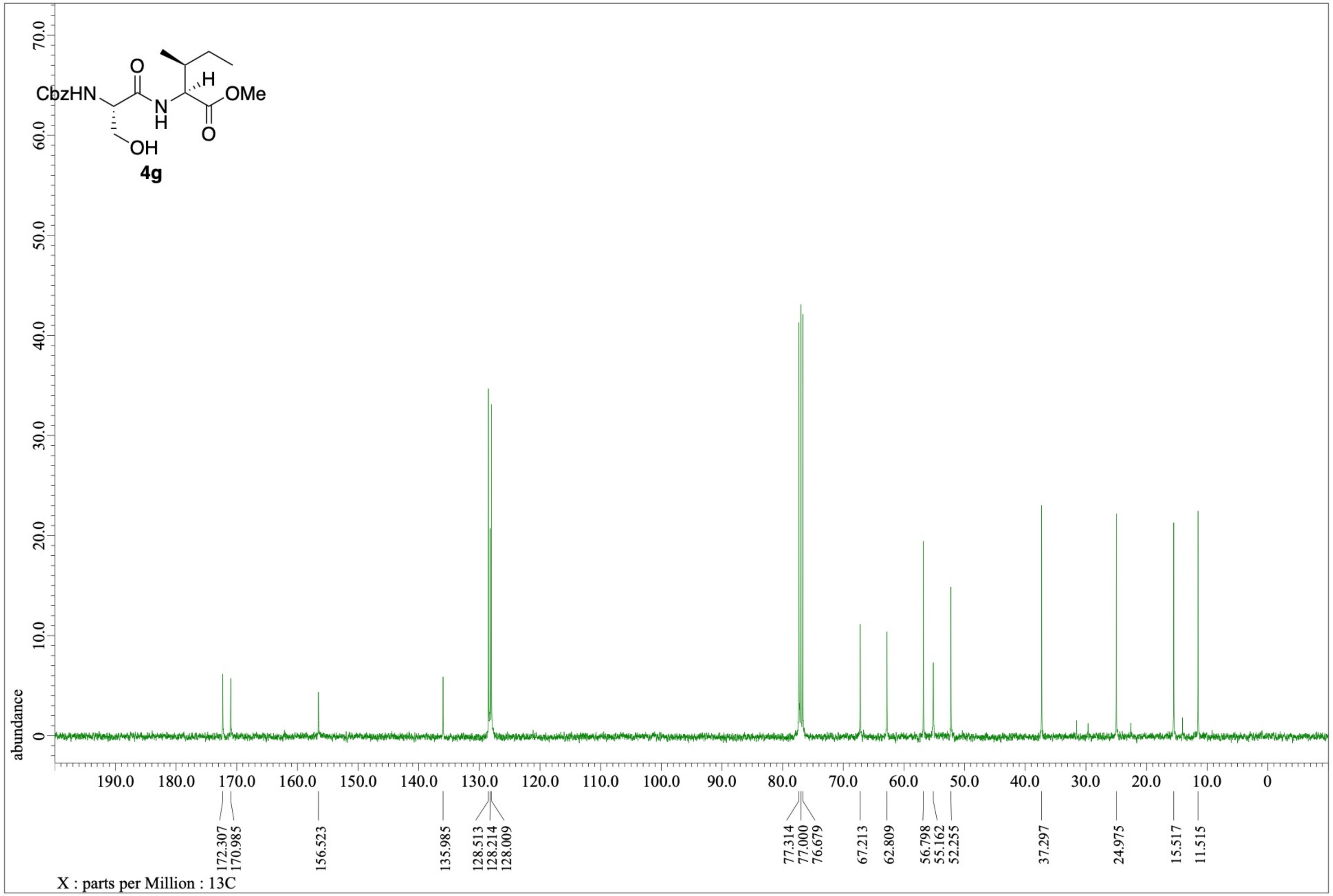
^{13}C NMR spectrum of 4f (100 MHz, $CDCl_3$)



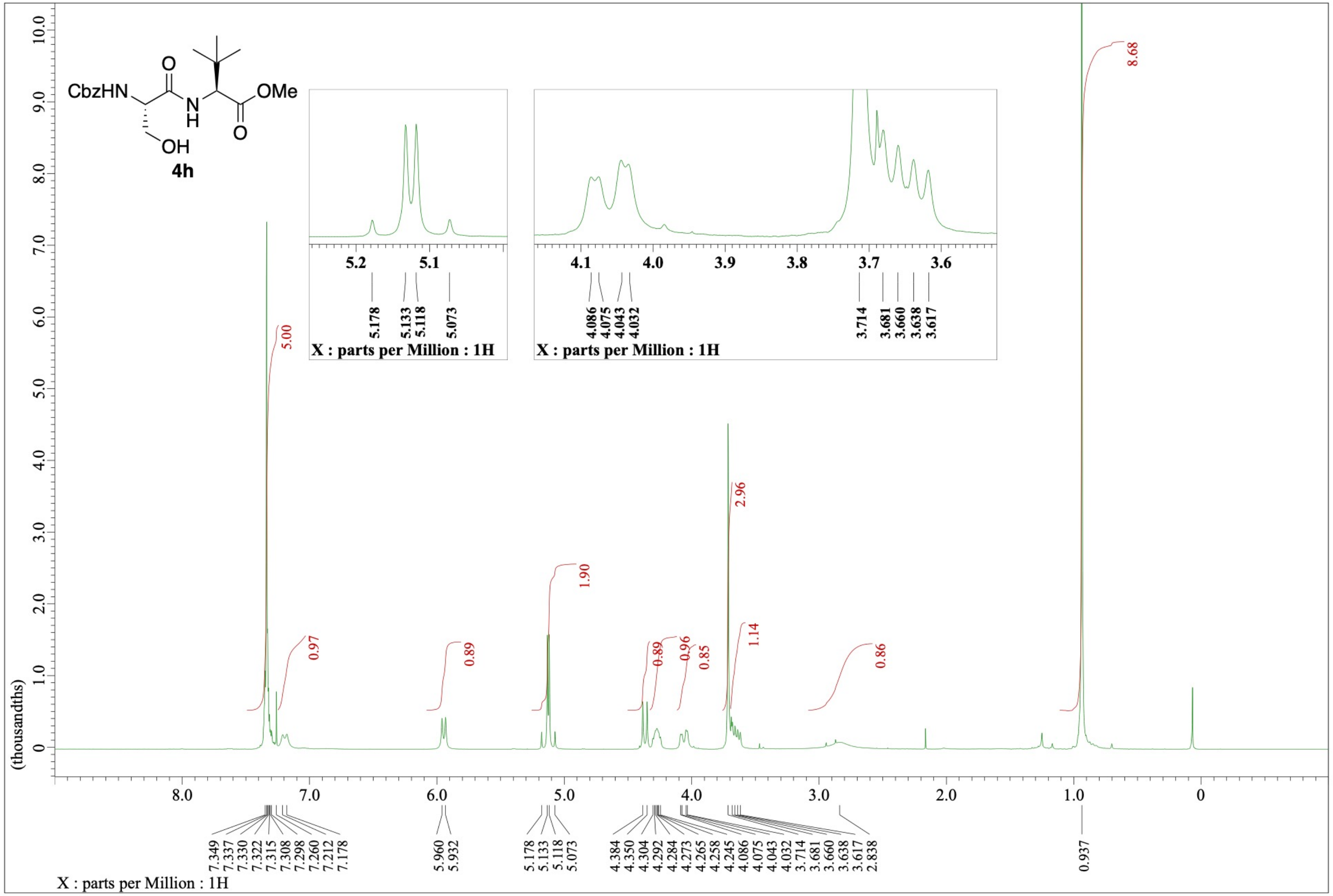
^1H NMR spectrum of 4g (400 MHz, $CDCl_3$)



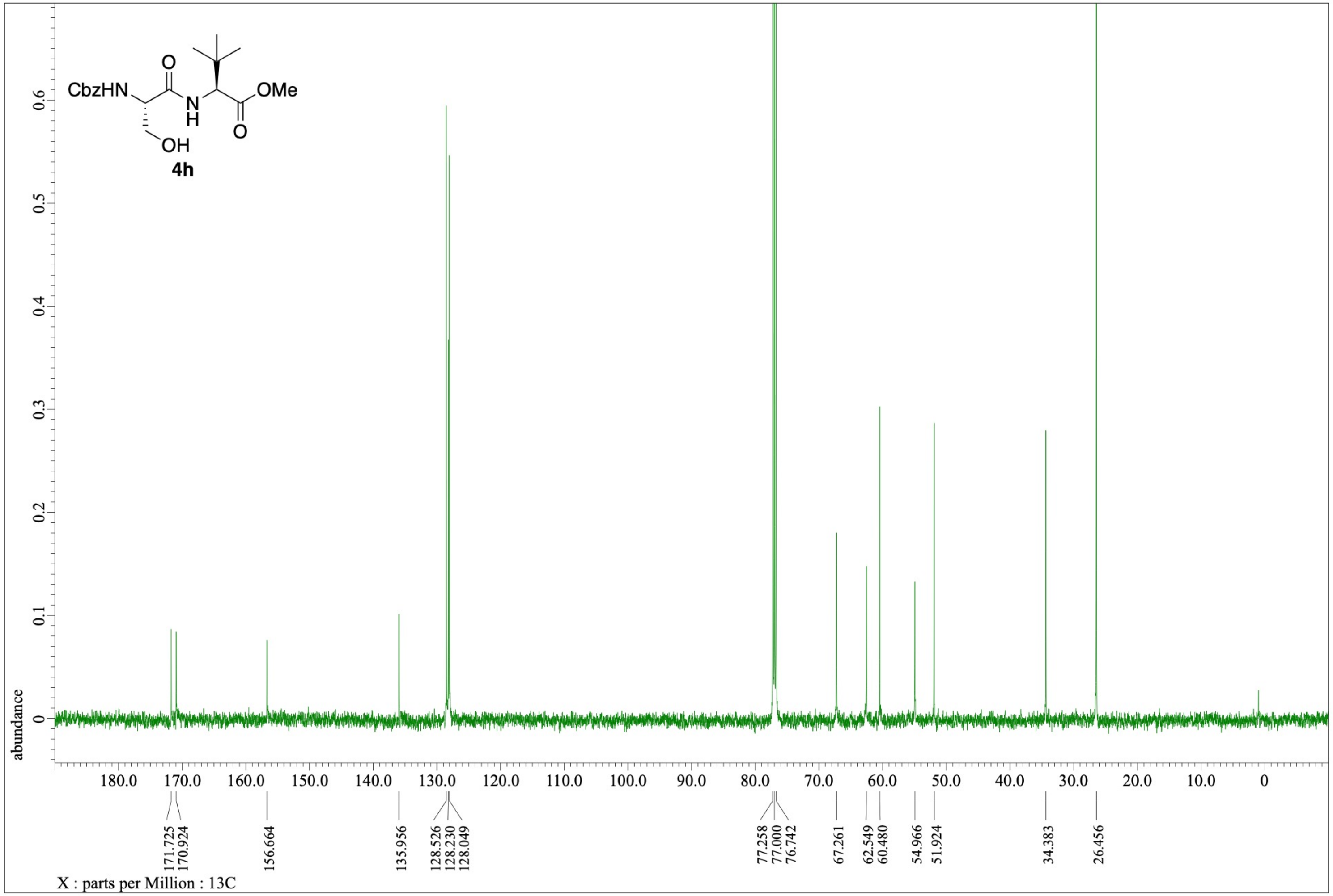
^{13}C NMR spectrum of 4g (100 MHz, CDCl$_3$)



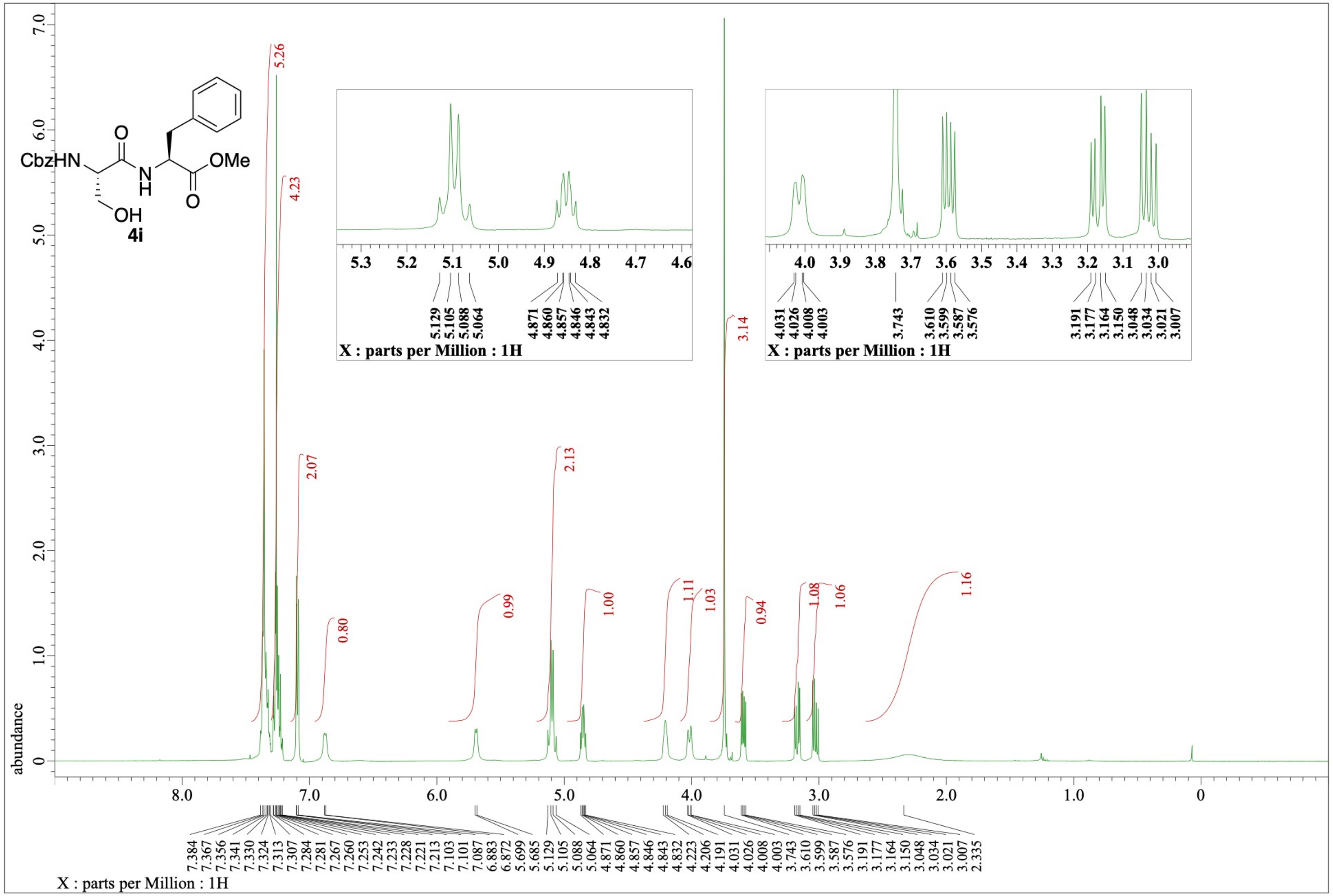
^{1}H NMR spectrum of 4h (270 MHz, $CDCl_3$)



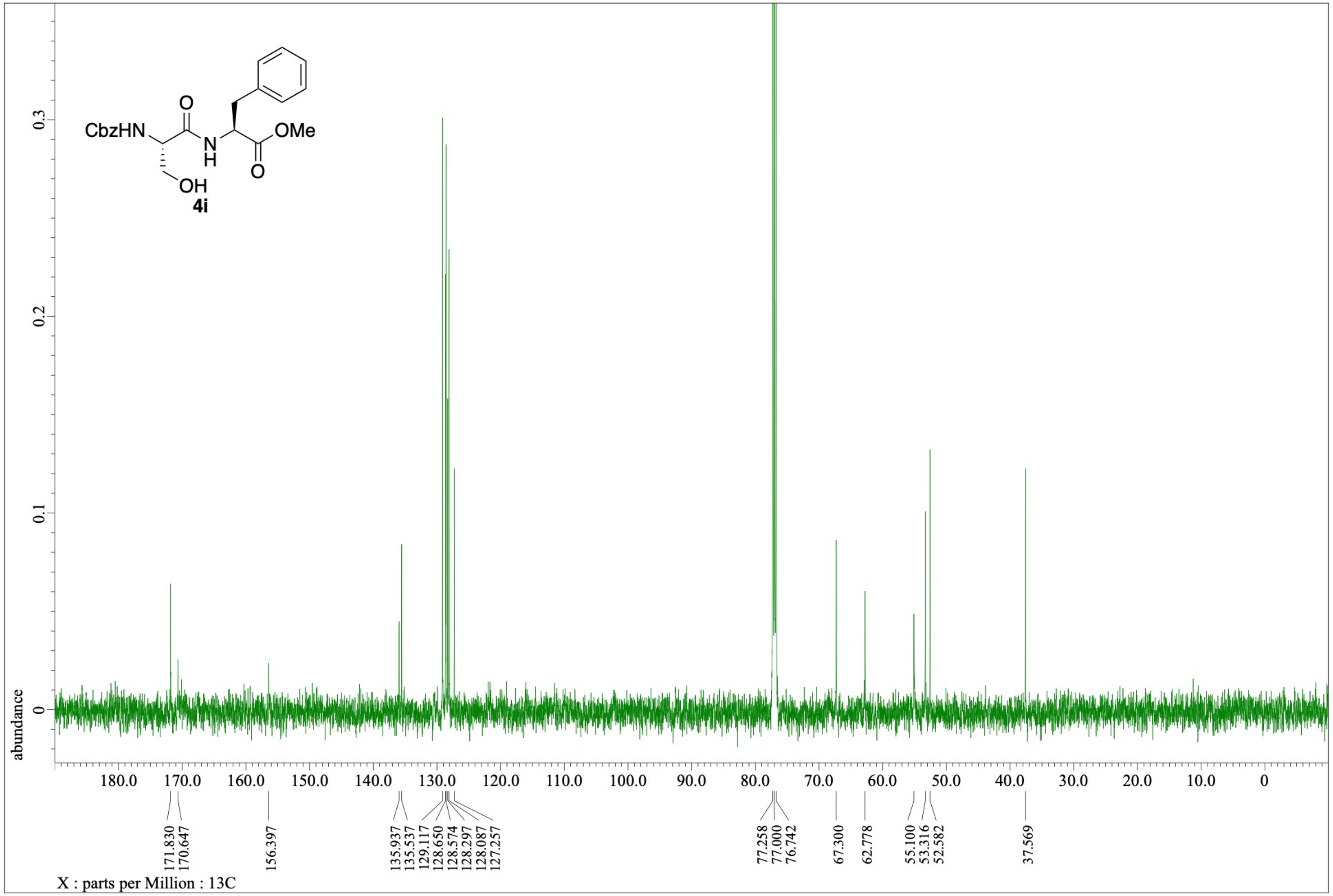
^{13}C NMR spectrum of 4h (126 MHz, $CDCl_3$)



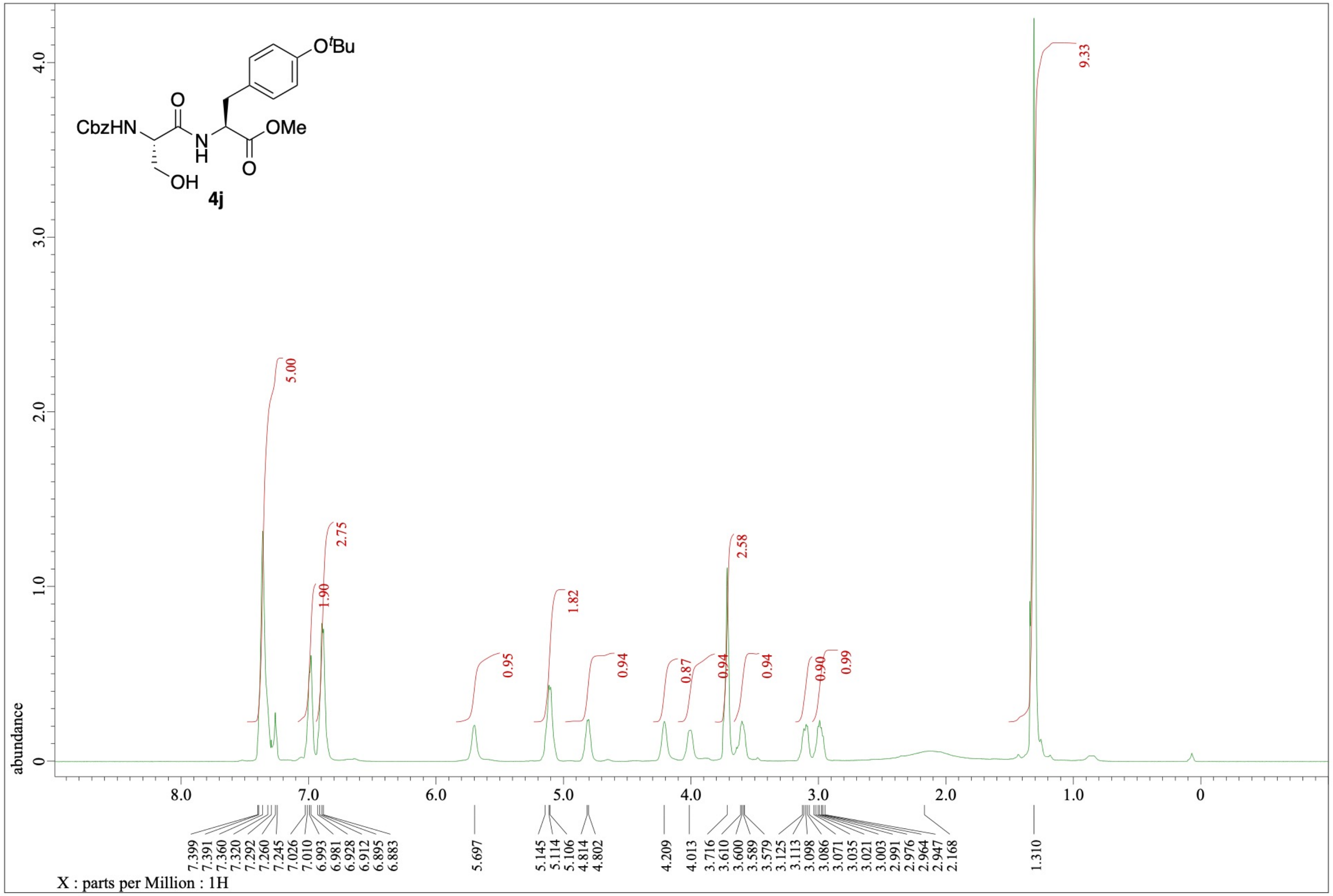
^{1}H NMR spectrum of 4i (500 MHz, $CDCl_3$)



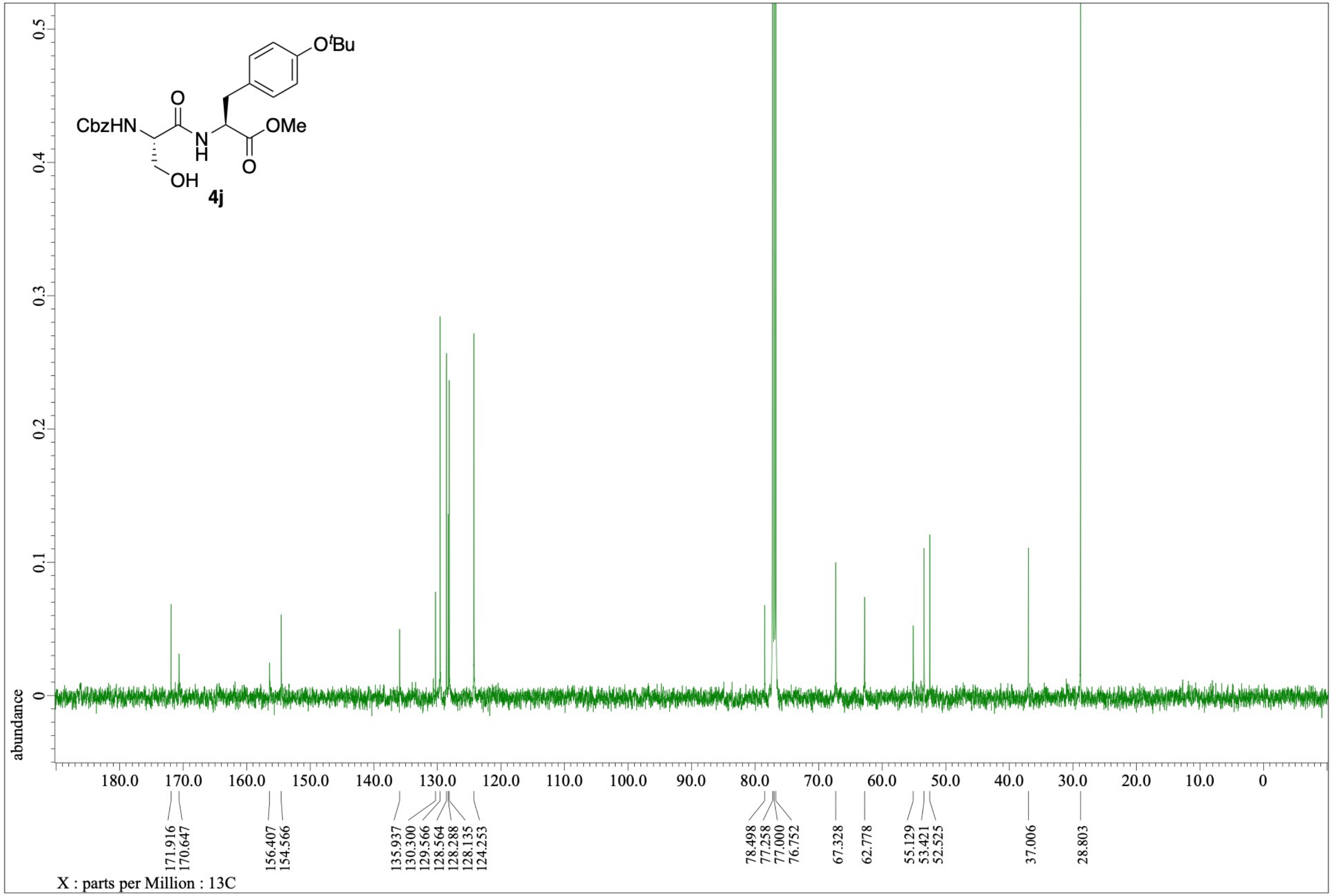
^{13}C NMR spectrum of 4i (126 MHz, $CDCl_3$)



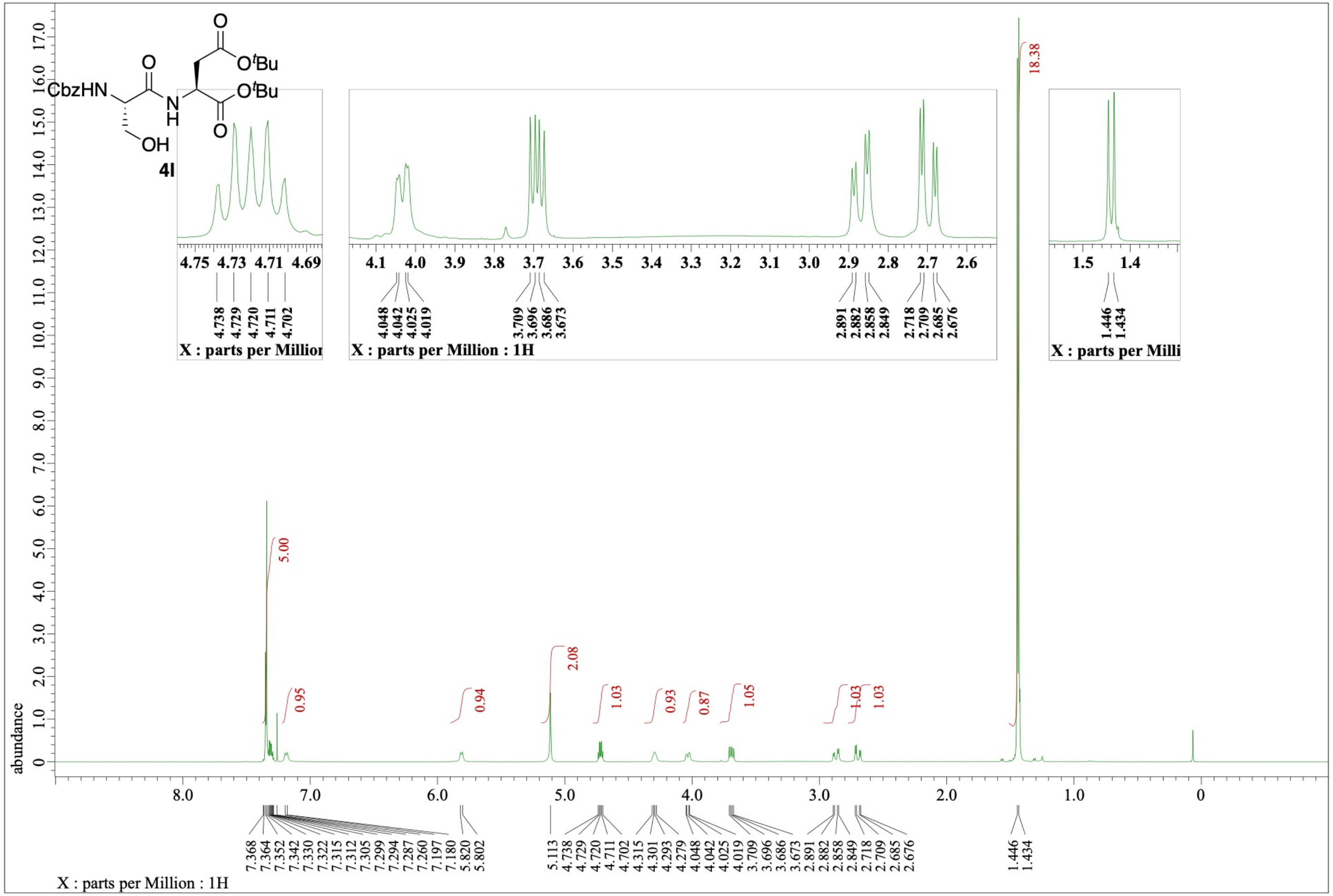
^{1}H NMR spectrum of 4j (500 MHz, CDCl$_3$)



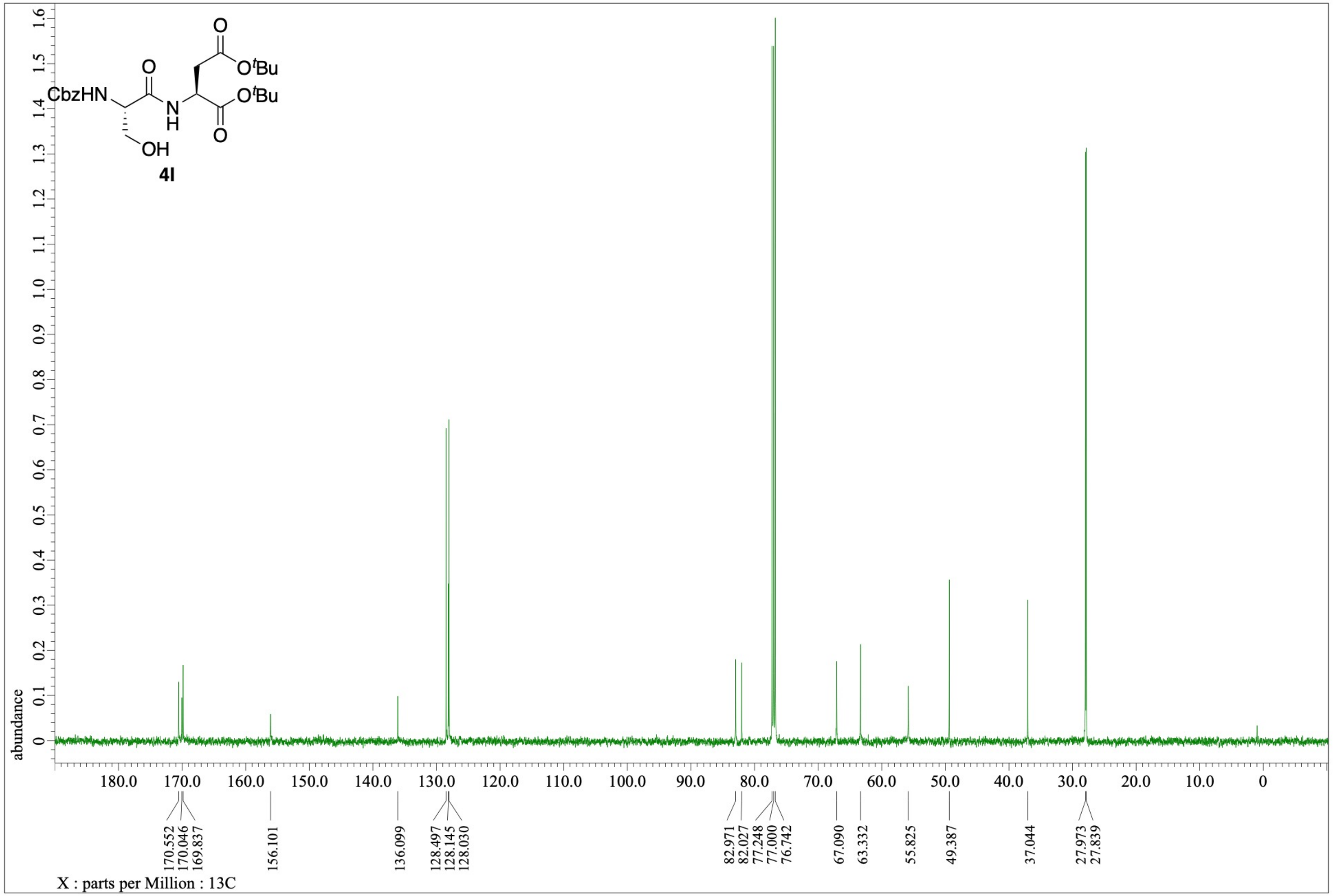
^{13}C NMR spectrum of 4j (126 MHz, $CDCl_3$)



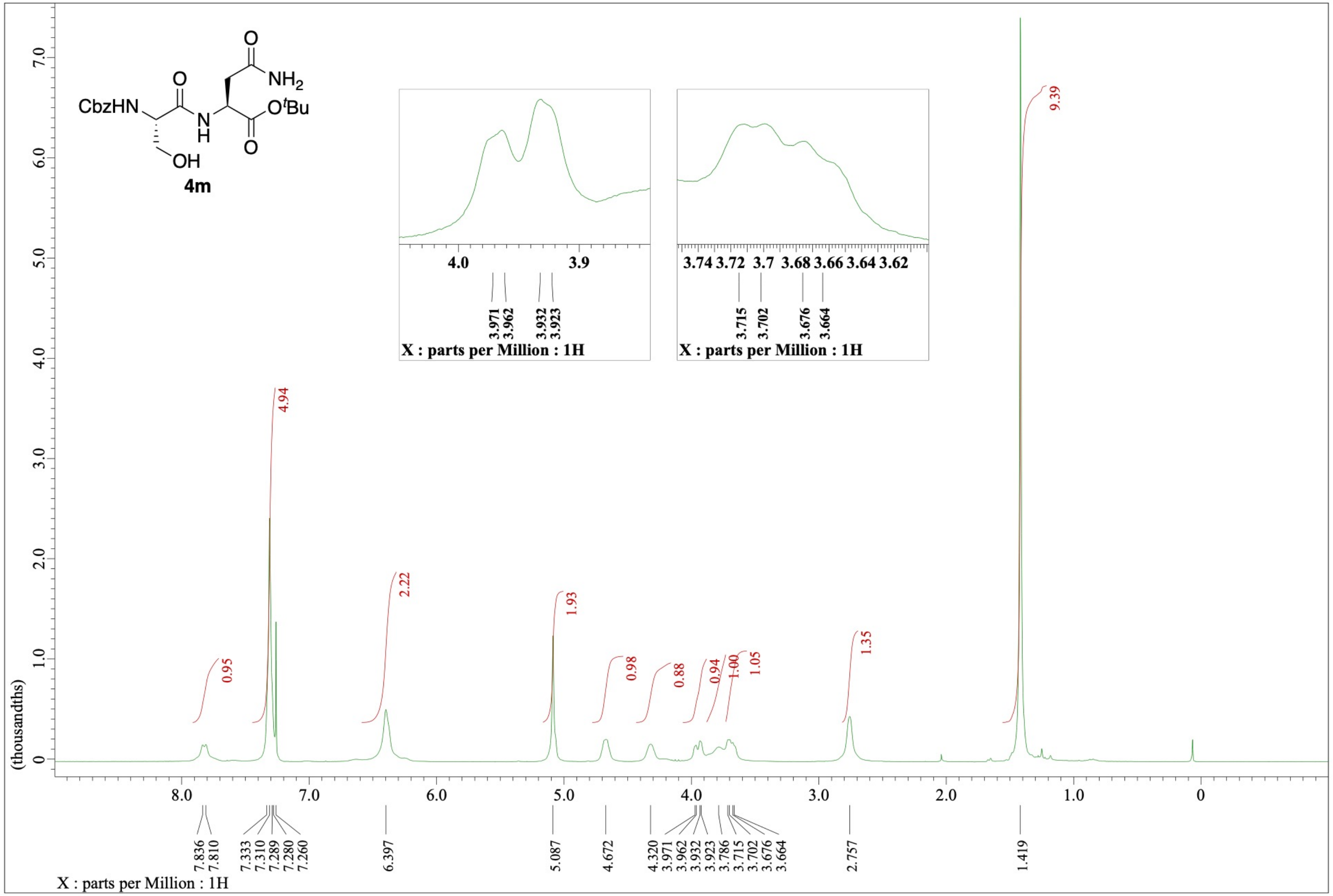
^{1}H NMR spectrum of 4l (500 MHz, CDCl$_3$)



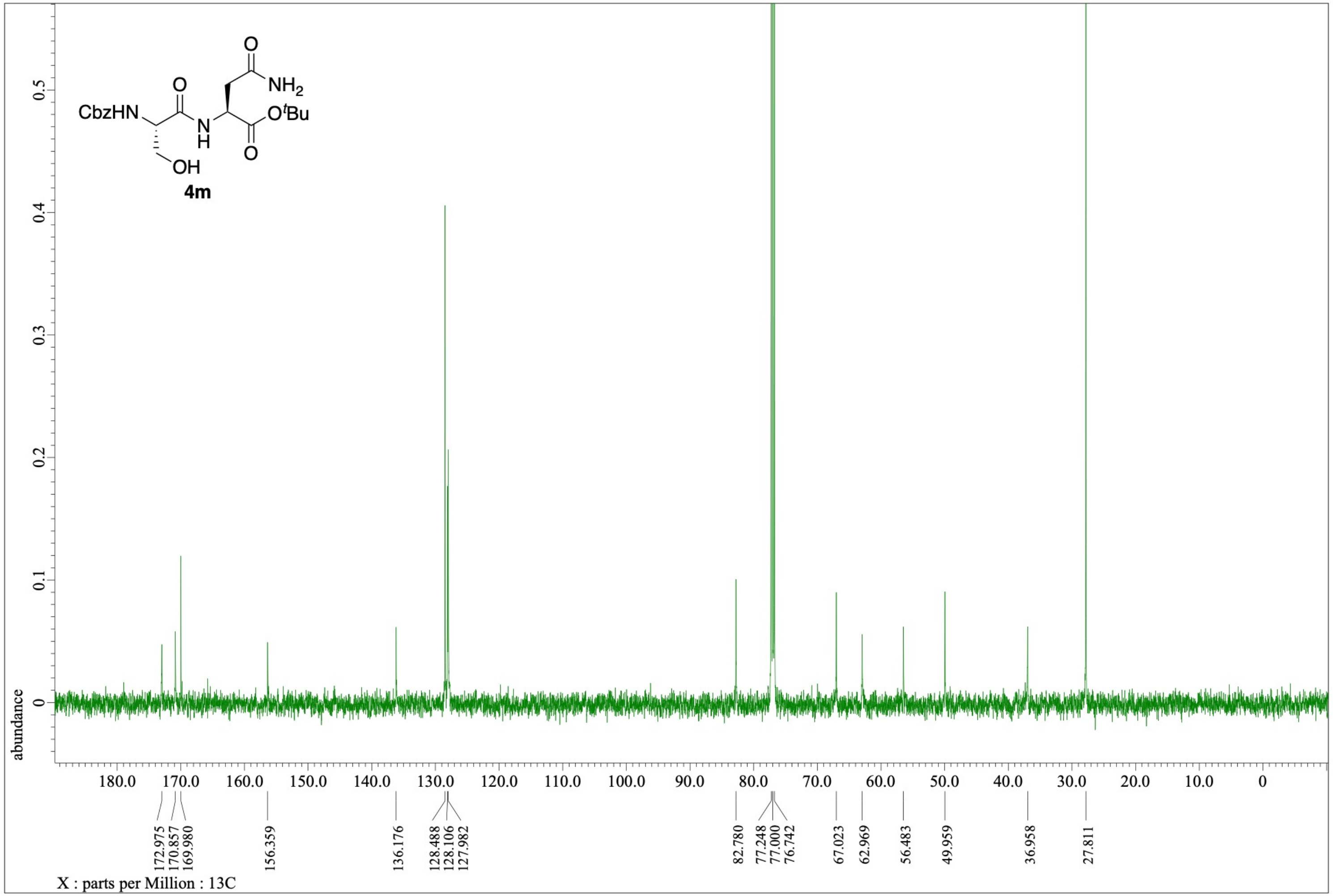
^{13}C NMR spectrum of 4l (126 MHz, $CDCl_3$)



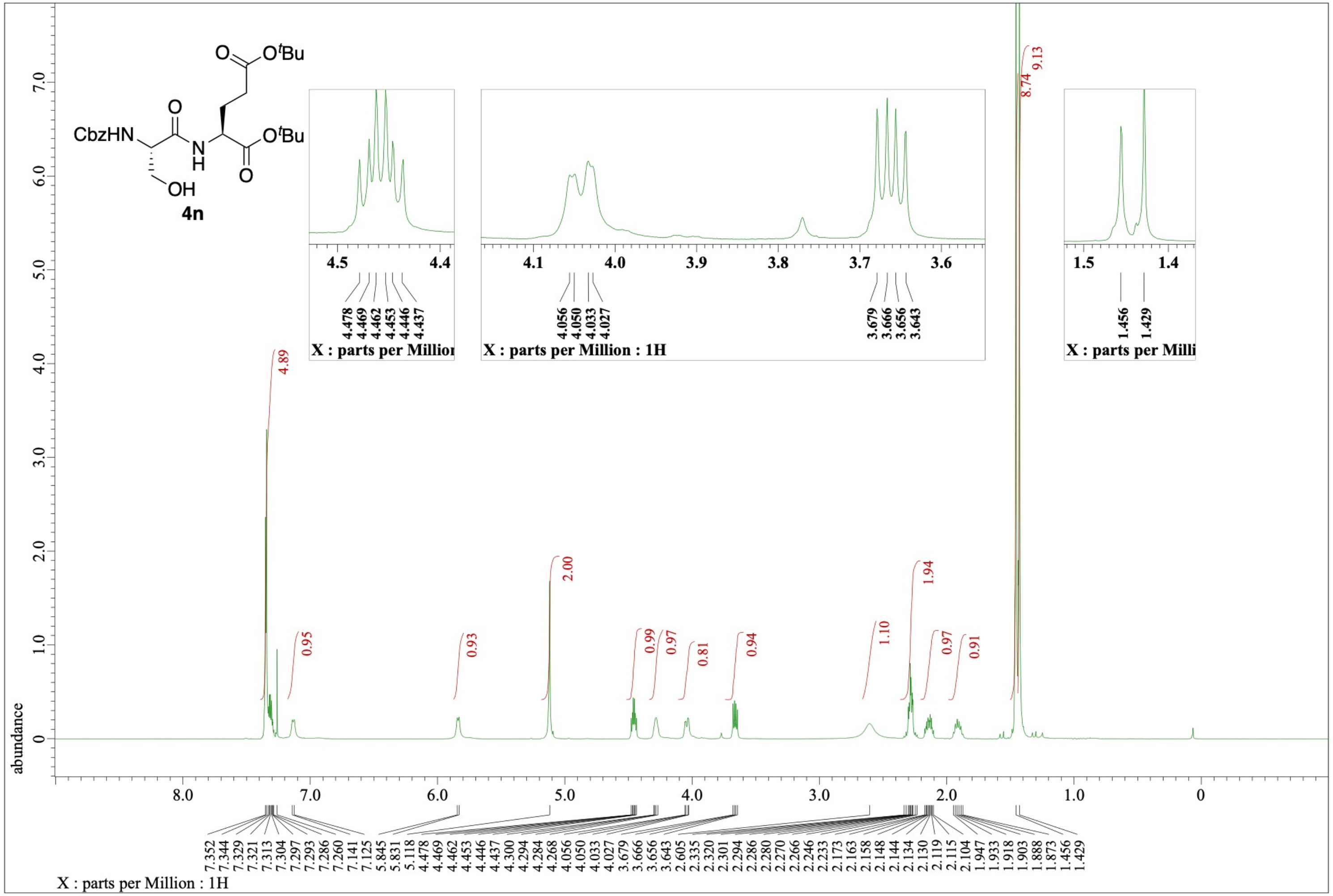
^1H NMR spectrum of 4m (270 MHz, $CDCl_3$)



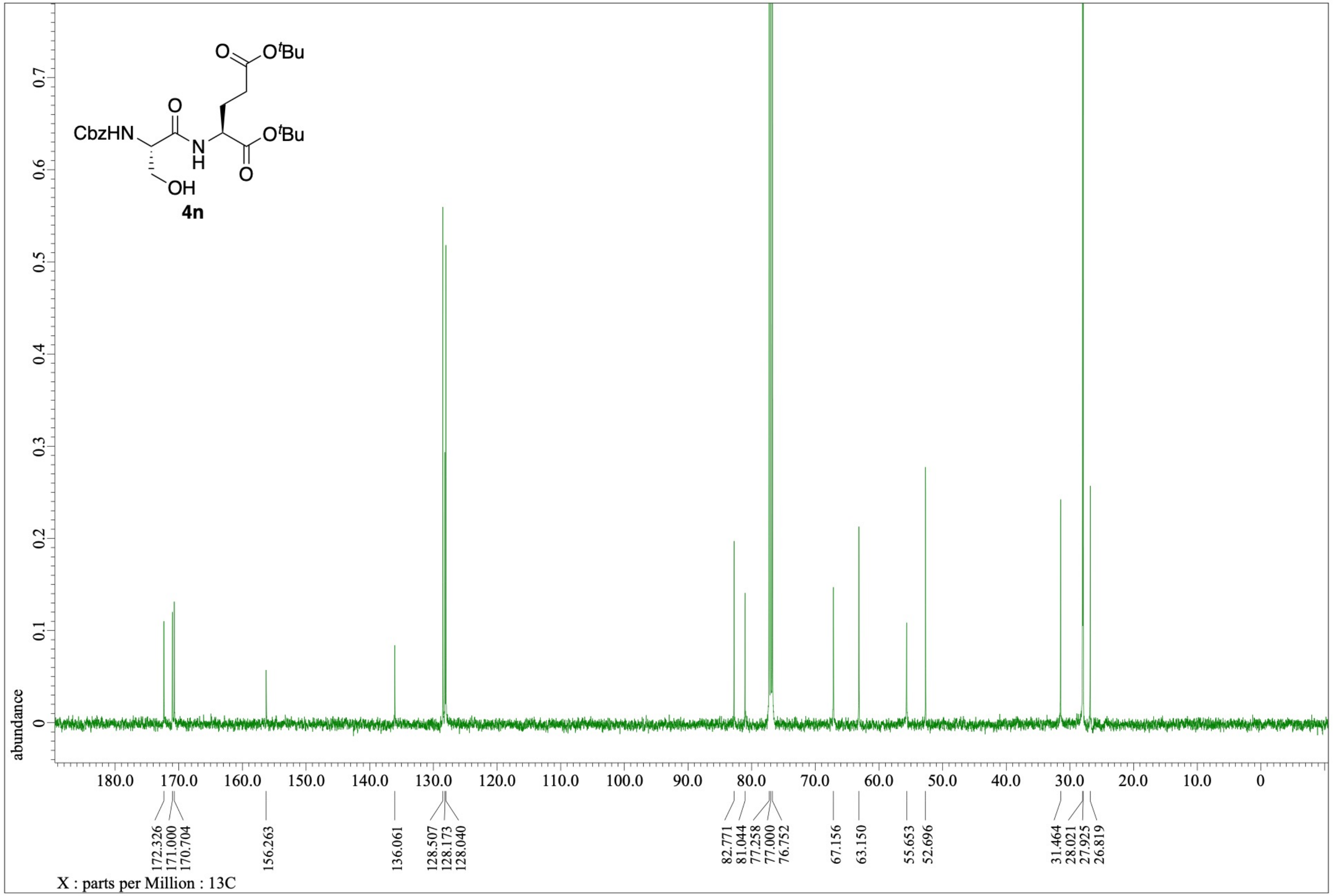
^{13}C NMR spectrum of 4m (126 MHz, $CDCl_3$)



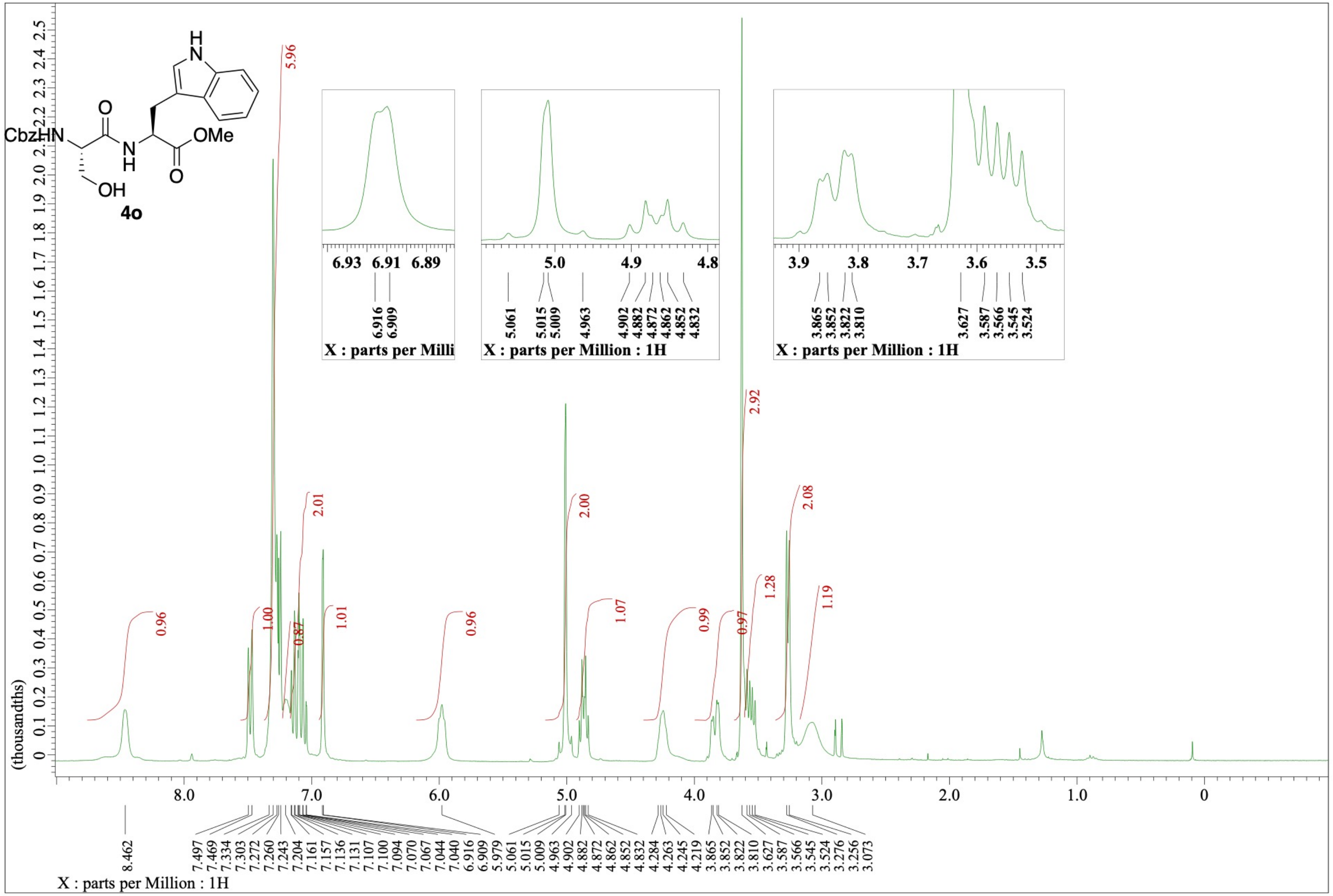
^{1}H NMR spectrum of 4n (500 MHz, $CDCl_3$)



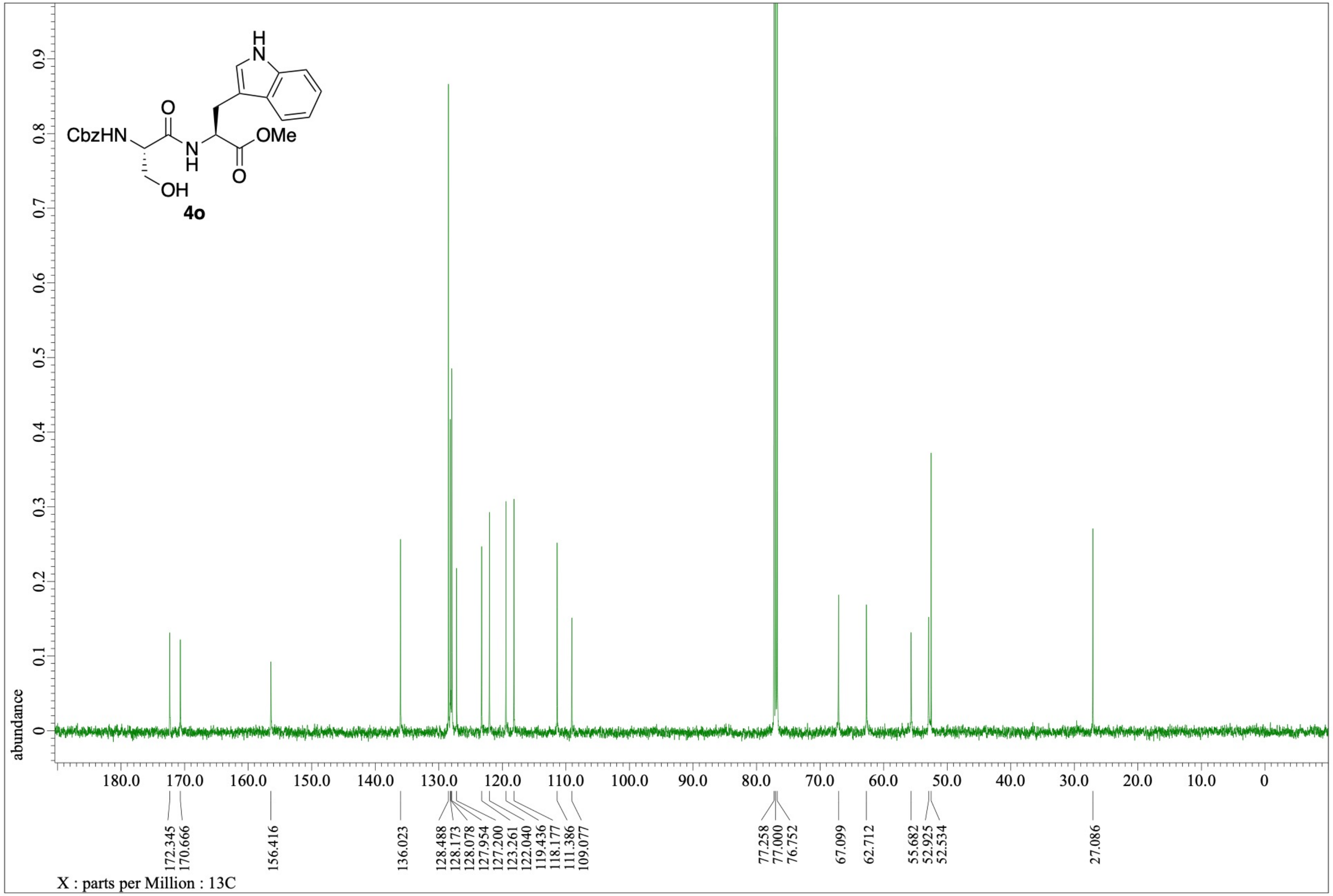
^{13}C NMR spectrum of 4n (126 MHz, $CDCl_3$)



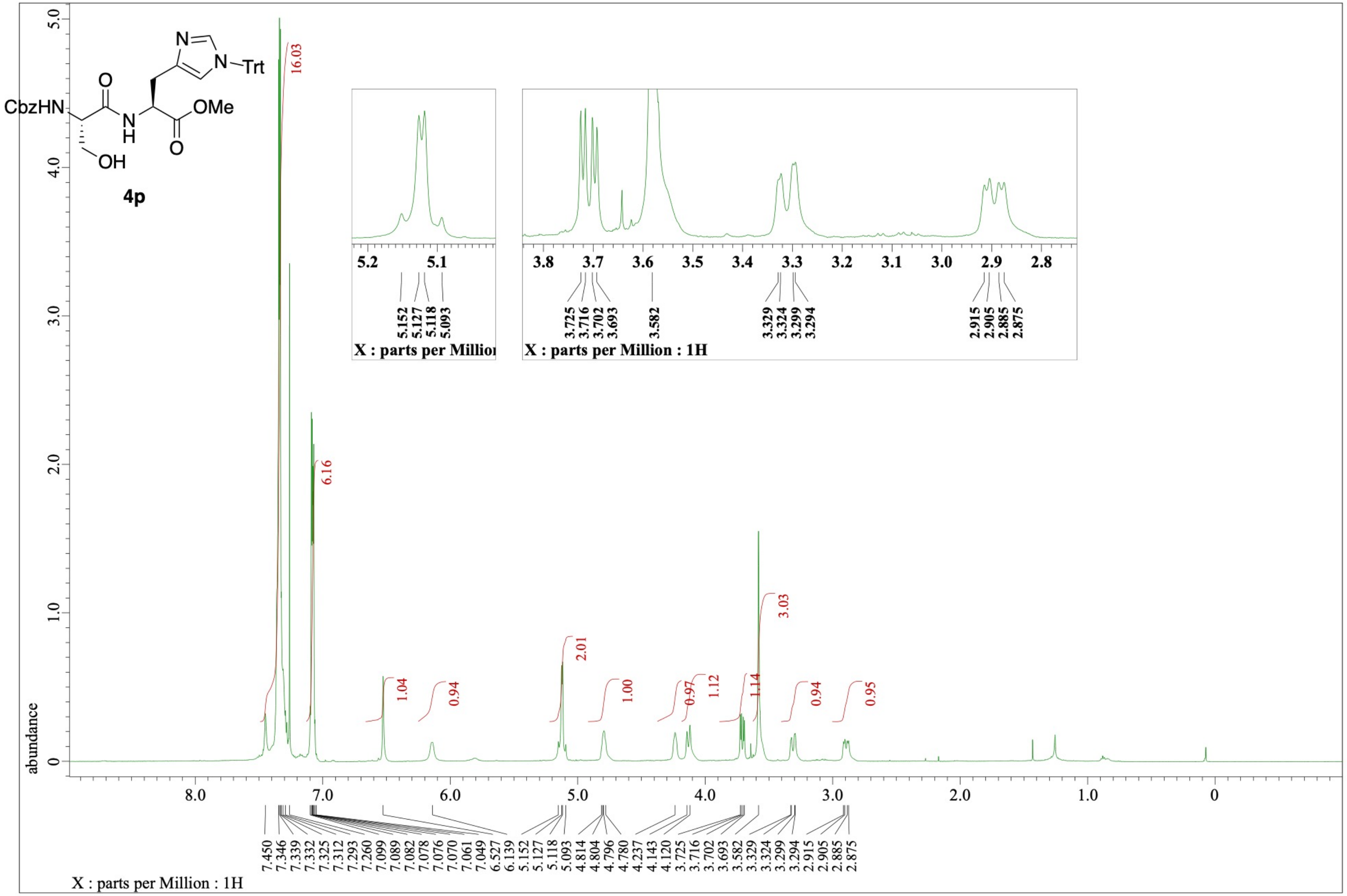
^{1}H NMR spectrum of 4o (270 MHz, $CDCl_3$)



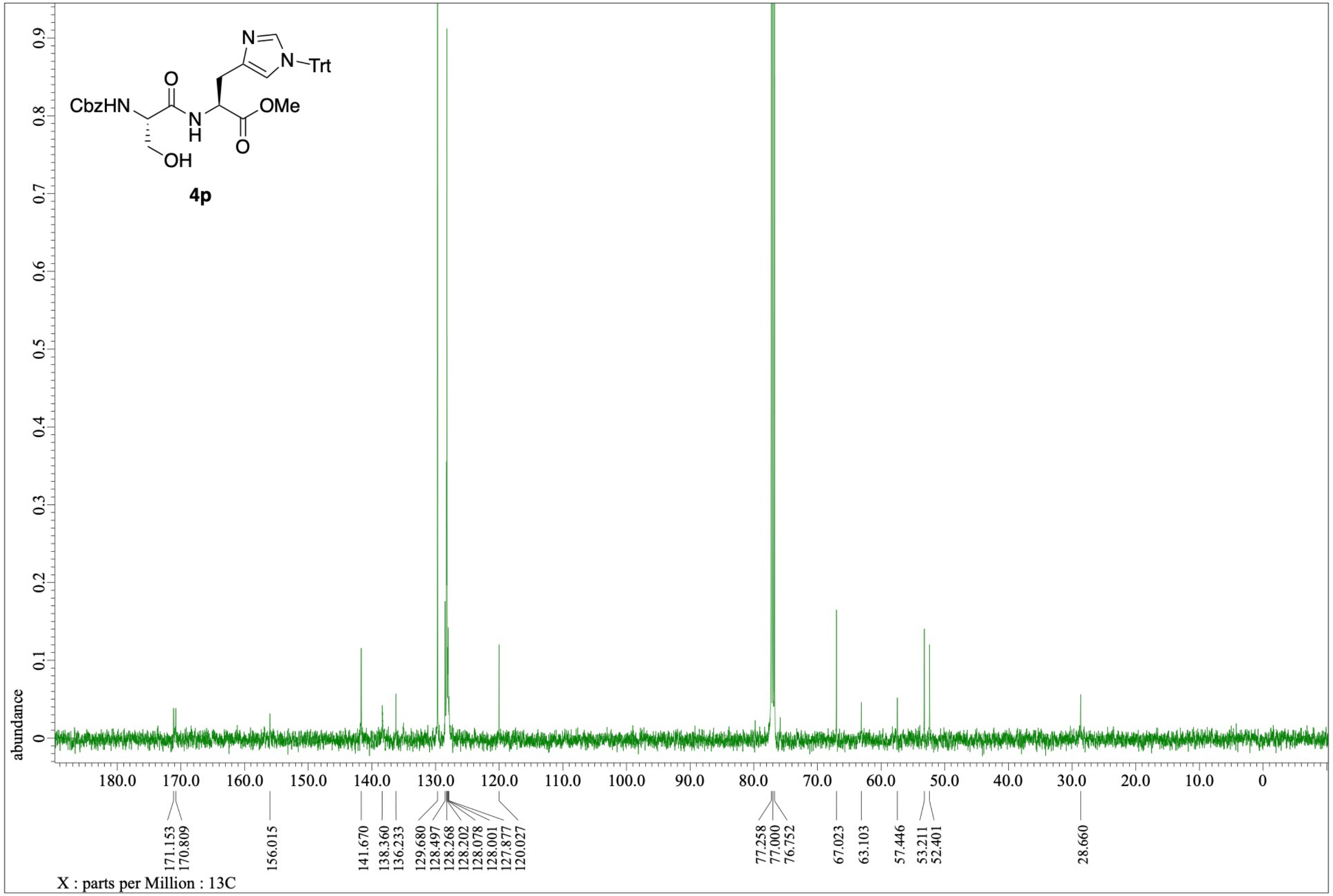
^{13}C NMR spectrum of 4o (126 MHz, $CDCl_3$)



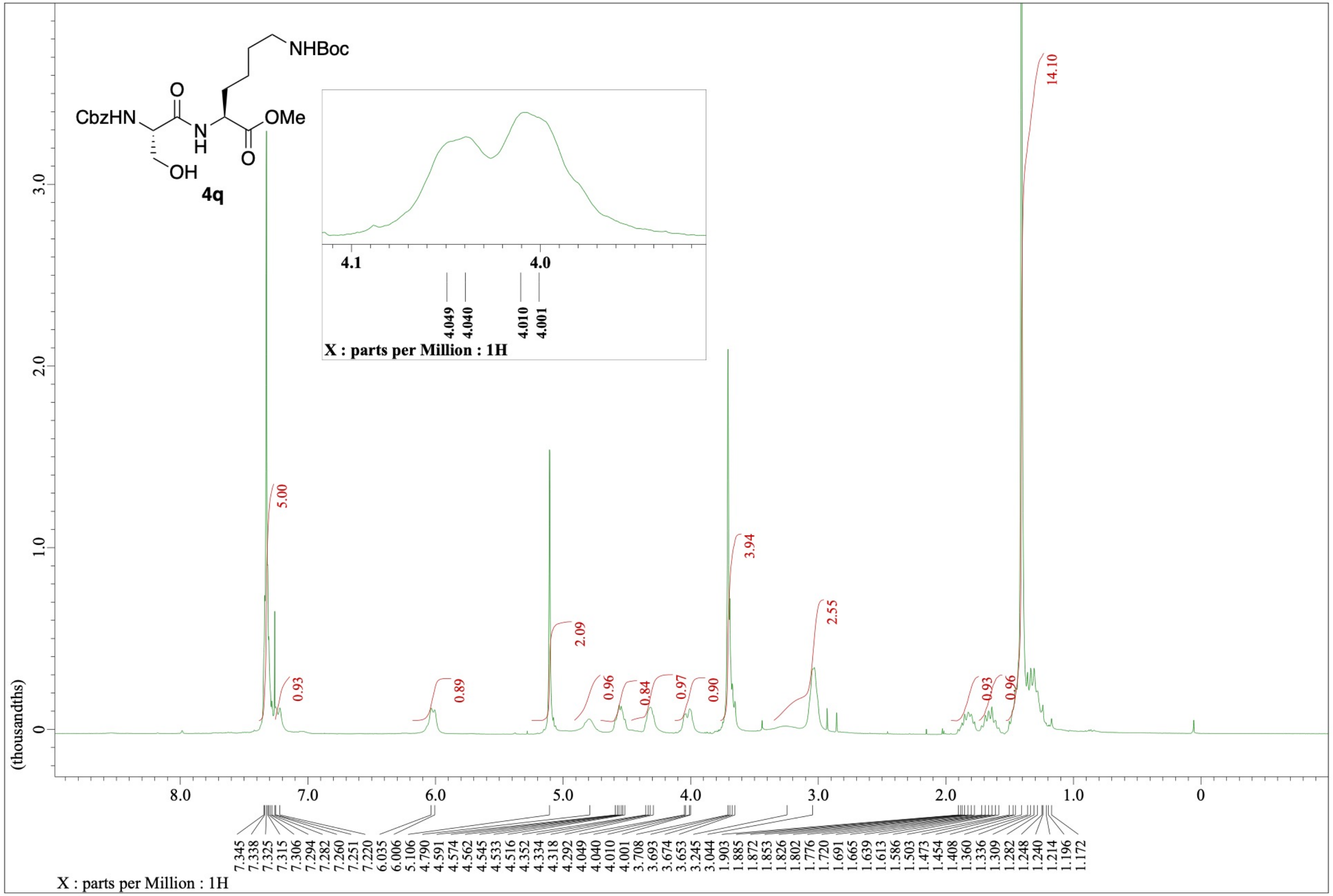
^{1}H NMR spectrum of 4p (500 MHz, $CDCl_3$)



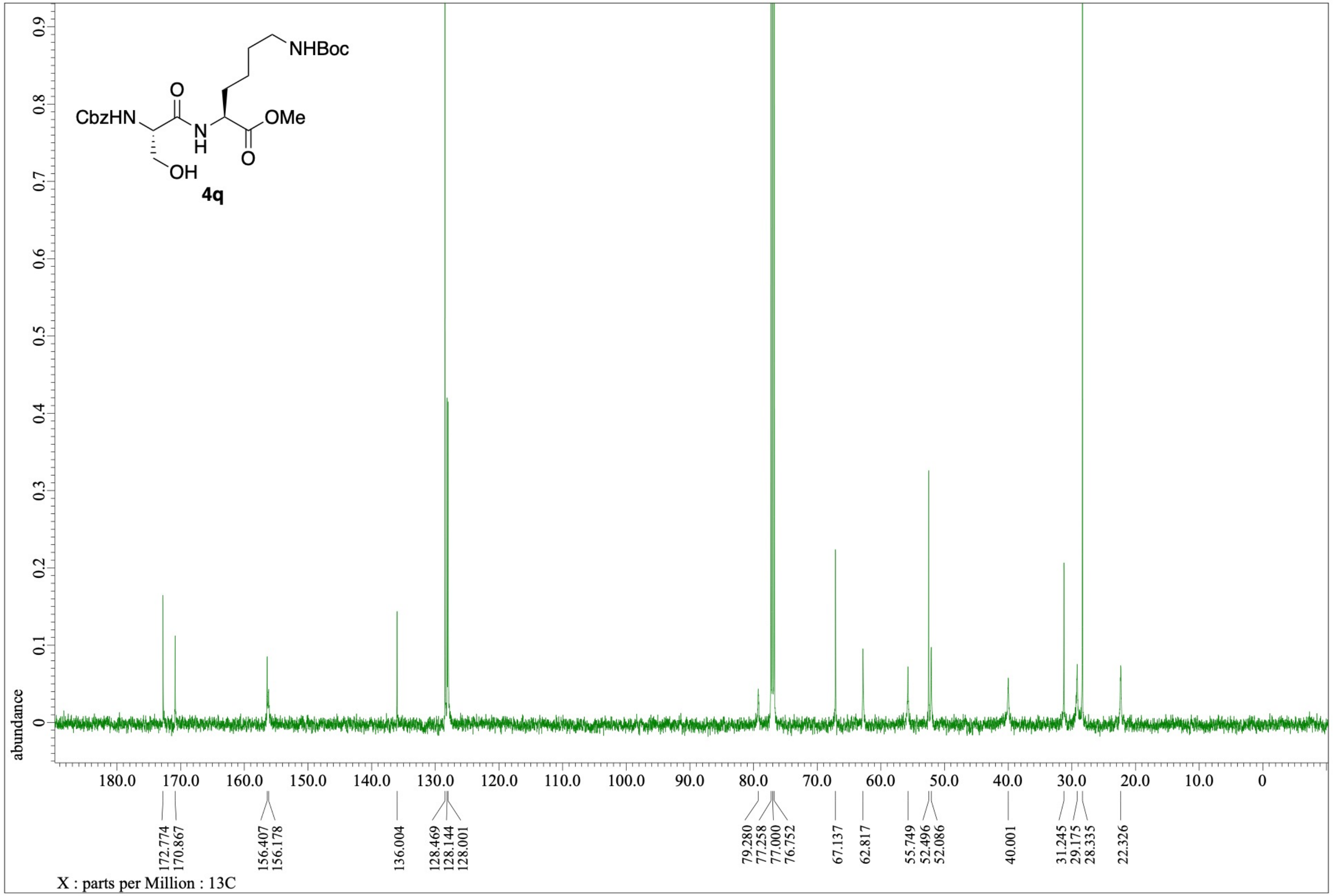
^{13}C NMR spectrum of 4p (126 MHz, CDCl$_3$)



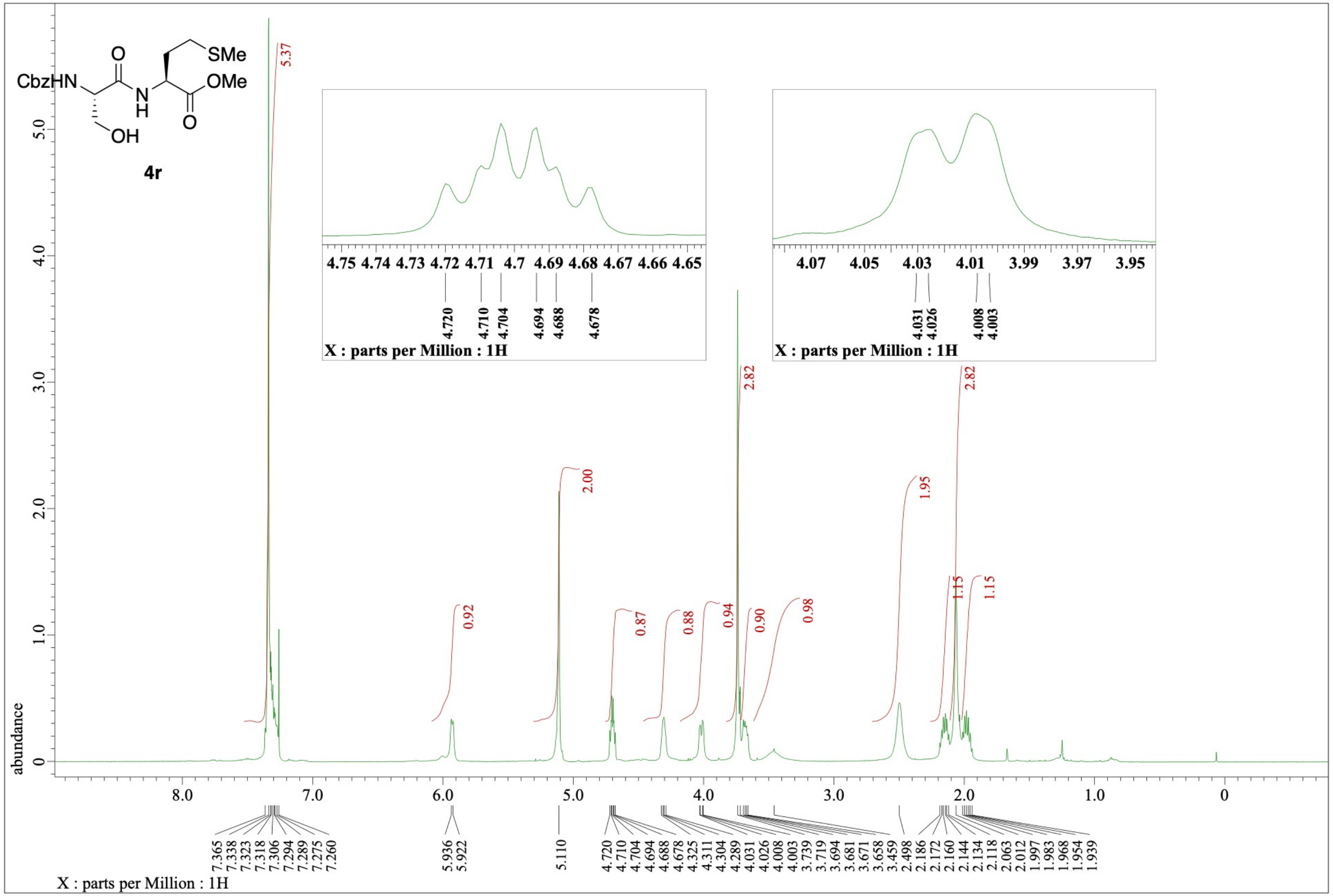
^{1}H NMR spectrum of 4q (270 MHz, CDCl$_3$)



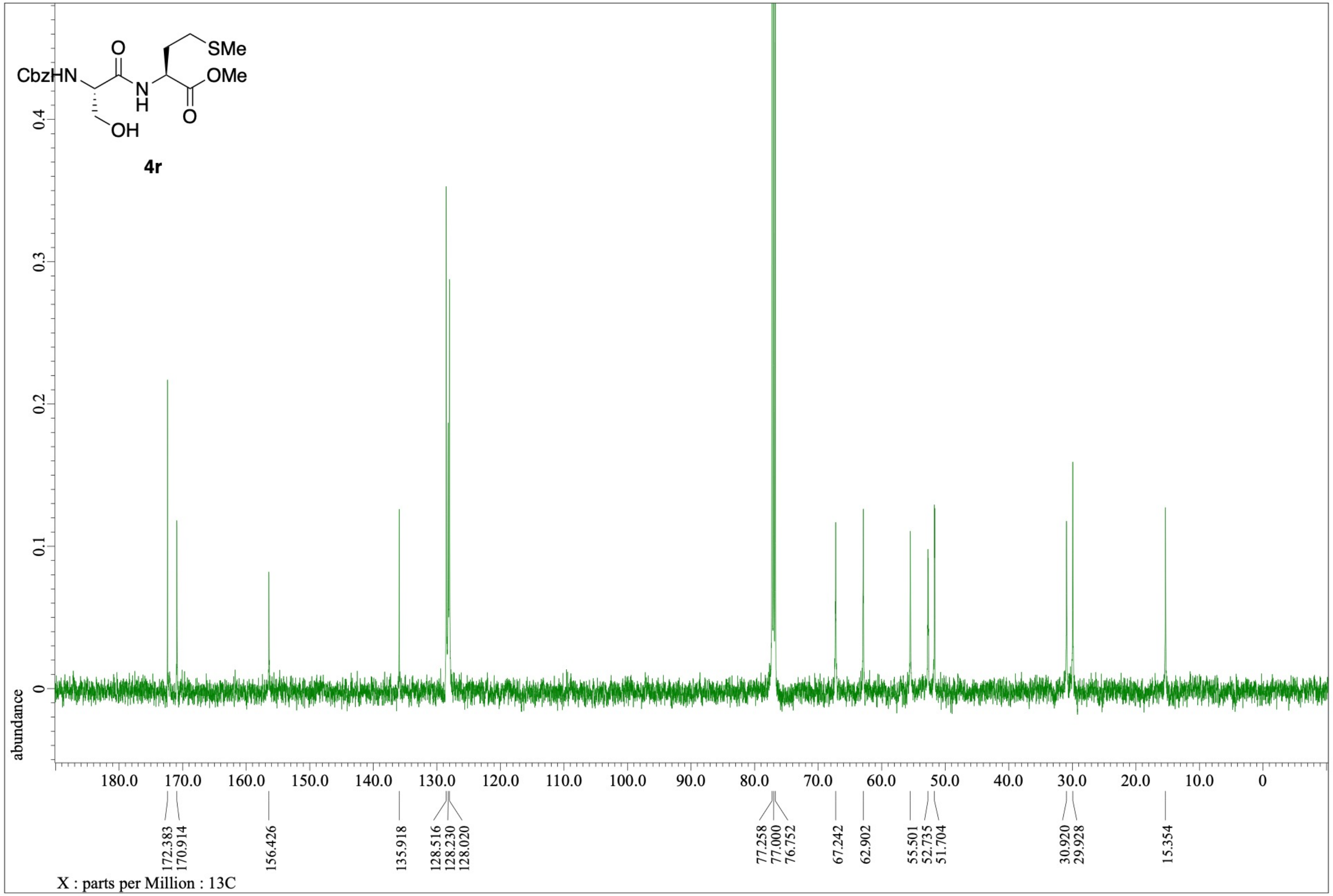
^{13}C NMR spectrum of 4q (126 MHz, CDCl$_3$)



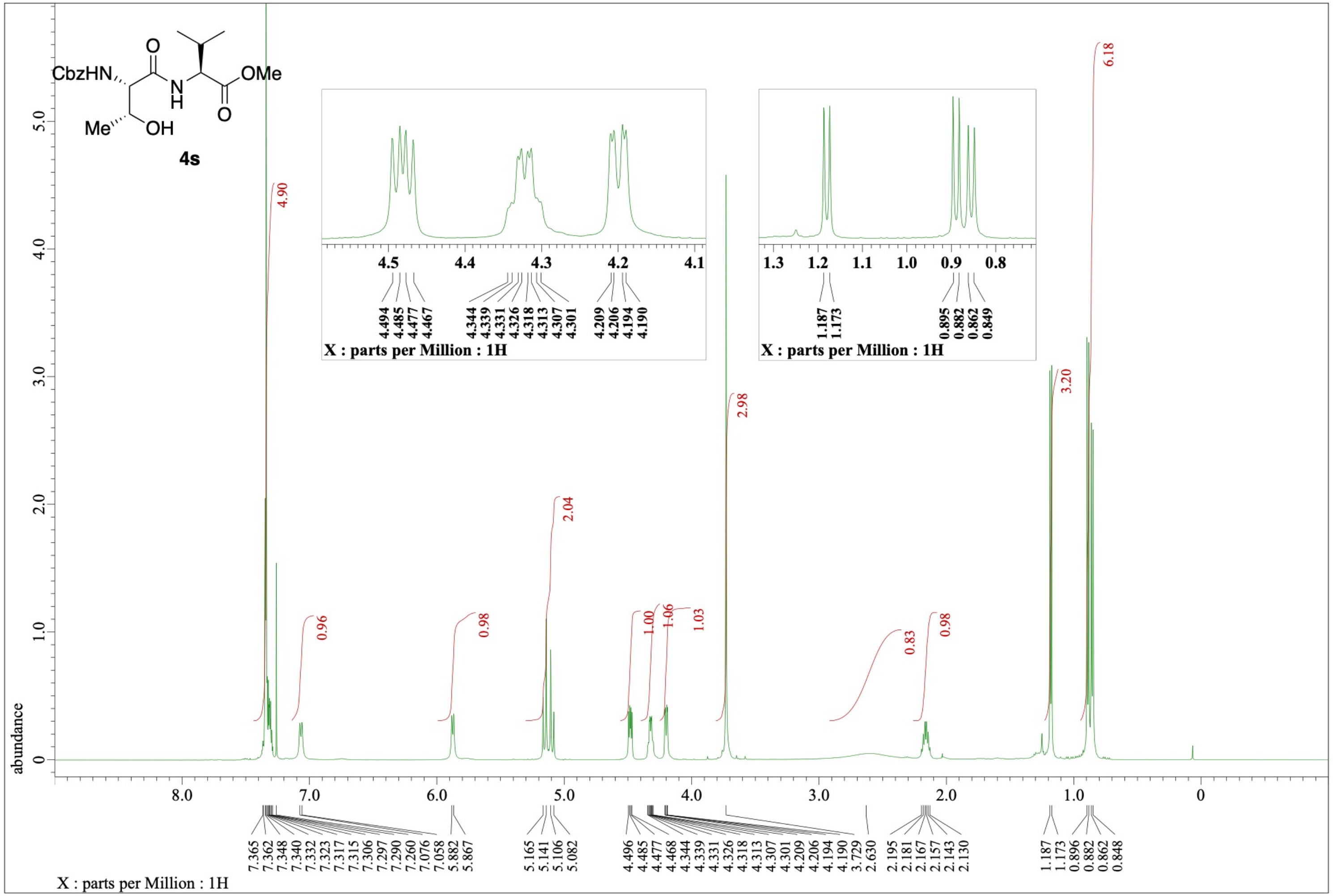
^{1}H NMR spectrum of 4r (500 MHz, $CDCl_3$)



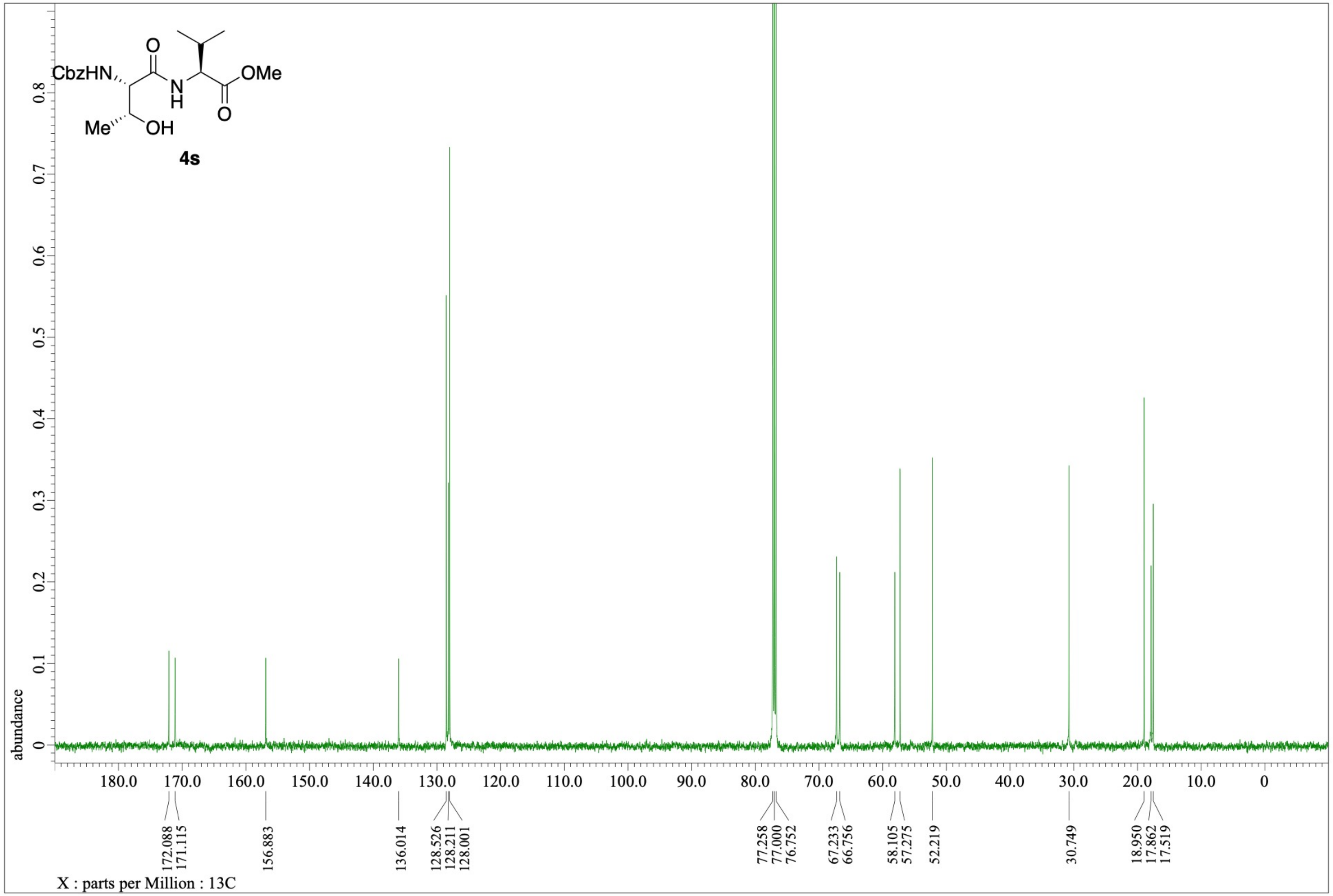
^{13}C NMR spectrum of 4r (126 MHz, $CDCl_3$)



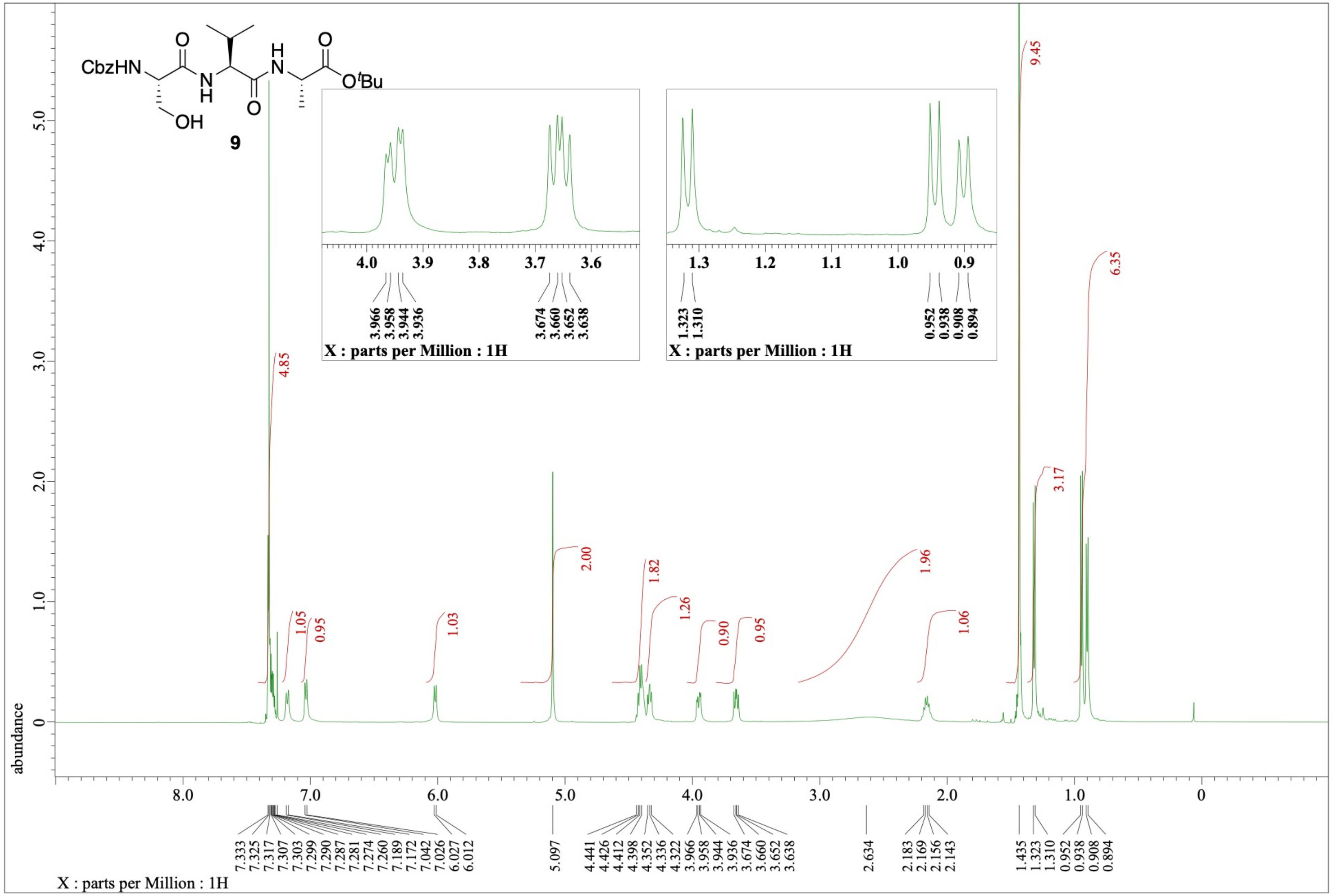
^{1}H NMR spectrum of 4s (500 MHz, CDCl$_3$)



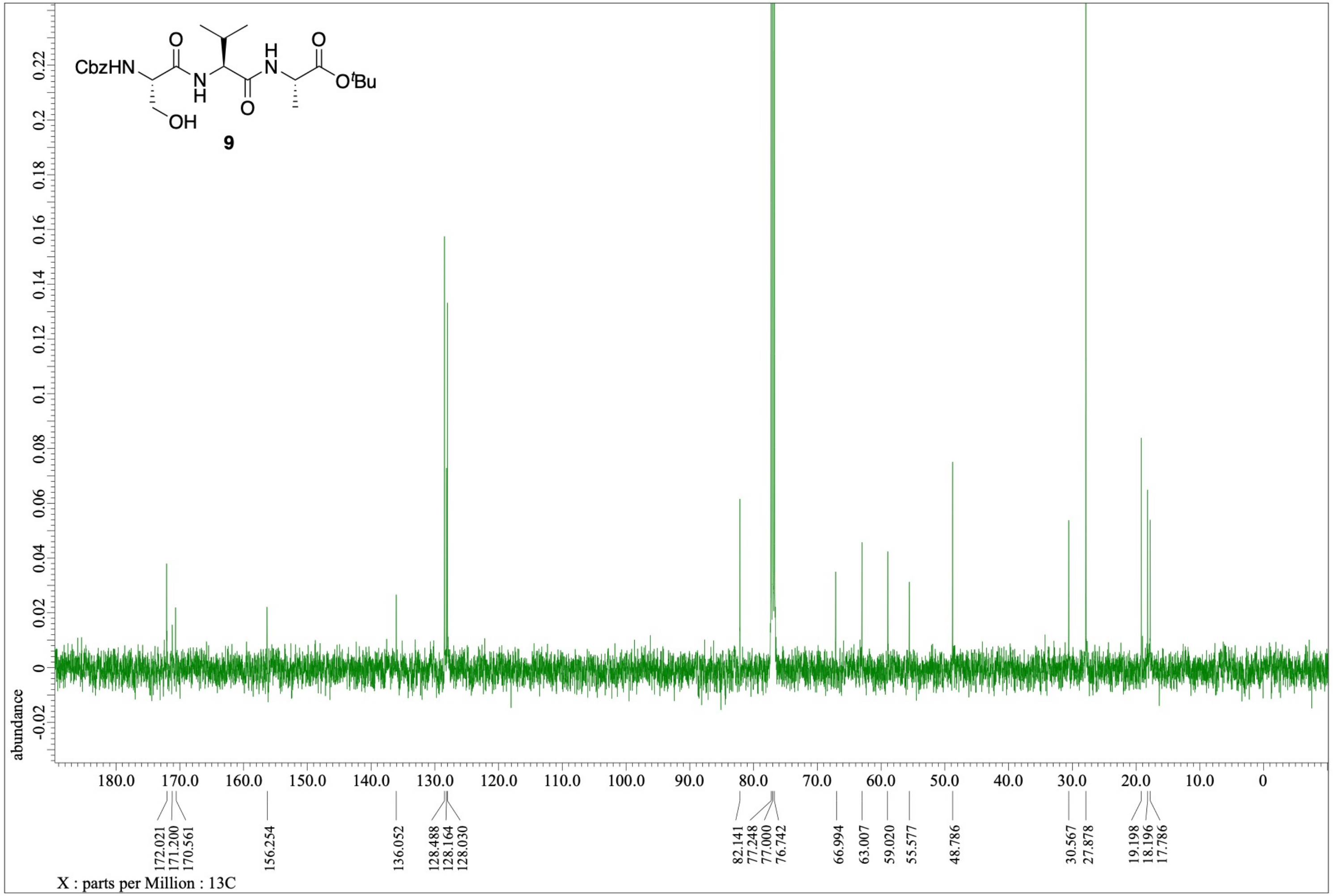
^{13}C NMR spectrum of 4s (126 MHz, CDCl$_3$)



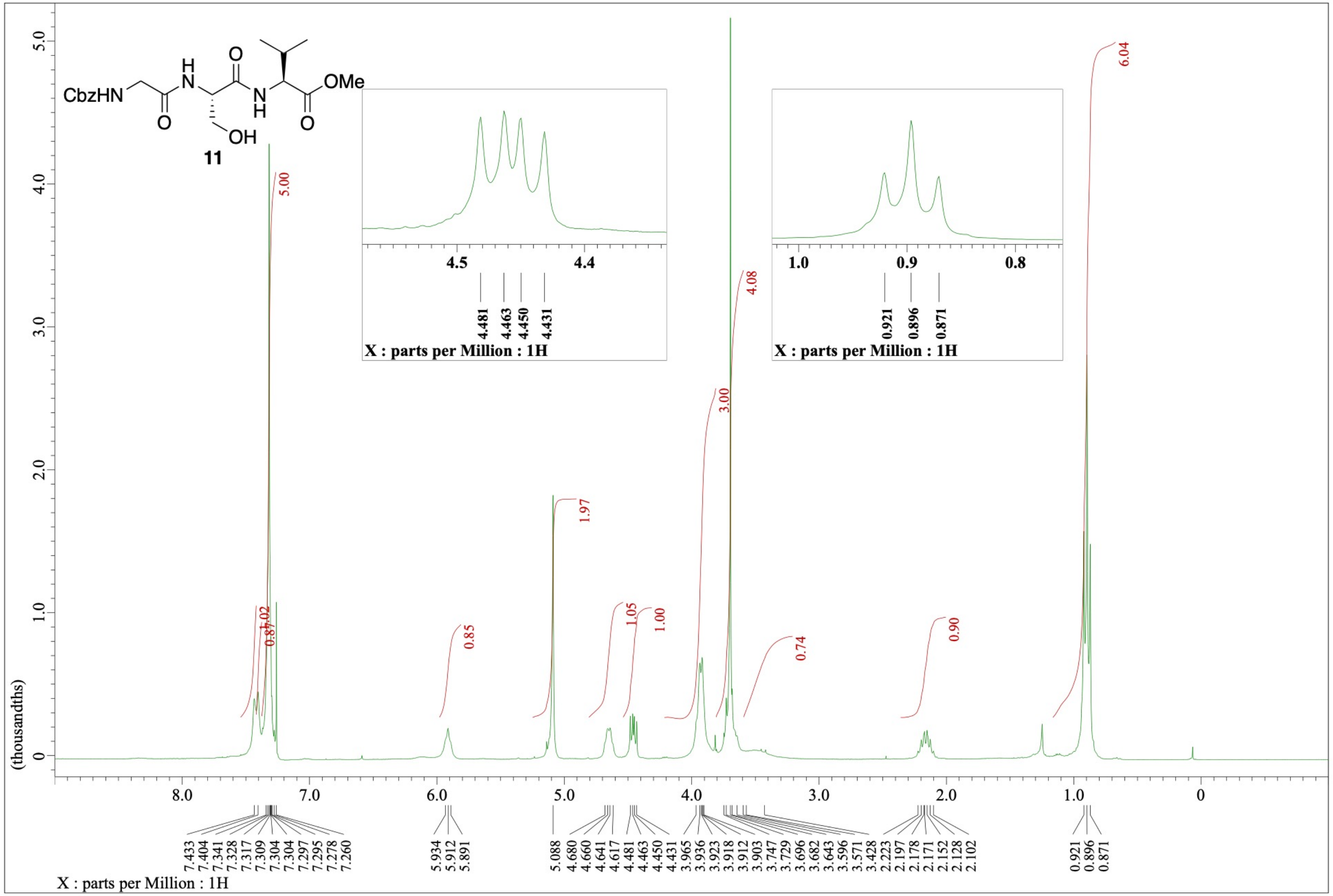
^{1}H NMR spectrum of 9 (500 MHz, $CDCl_3$)



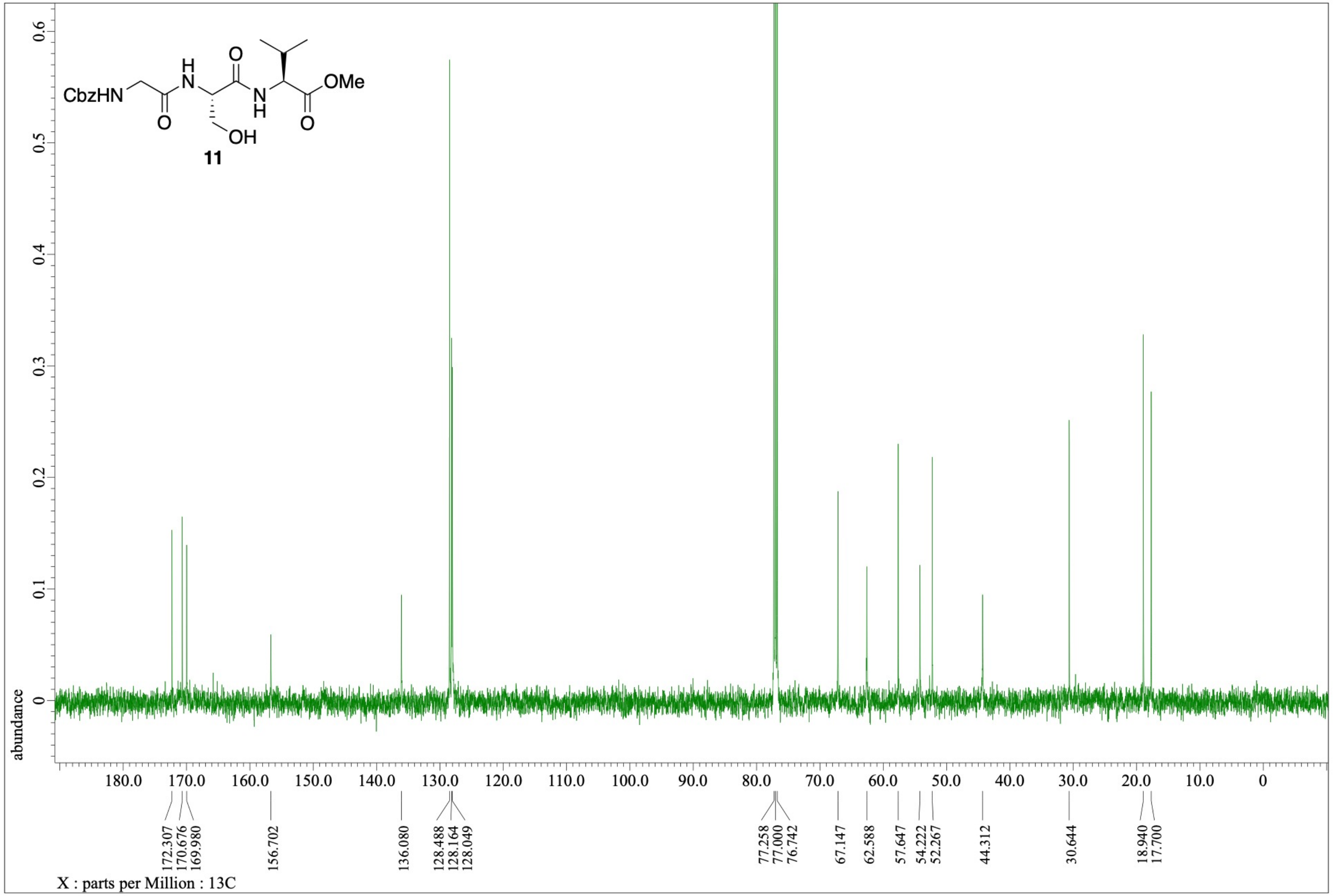
^{13}C NMR spectrum of 9 (126 MHz, CDCl$_3$)



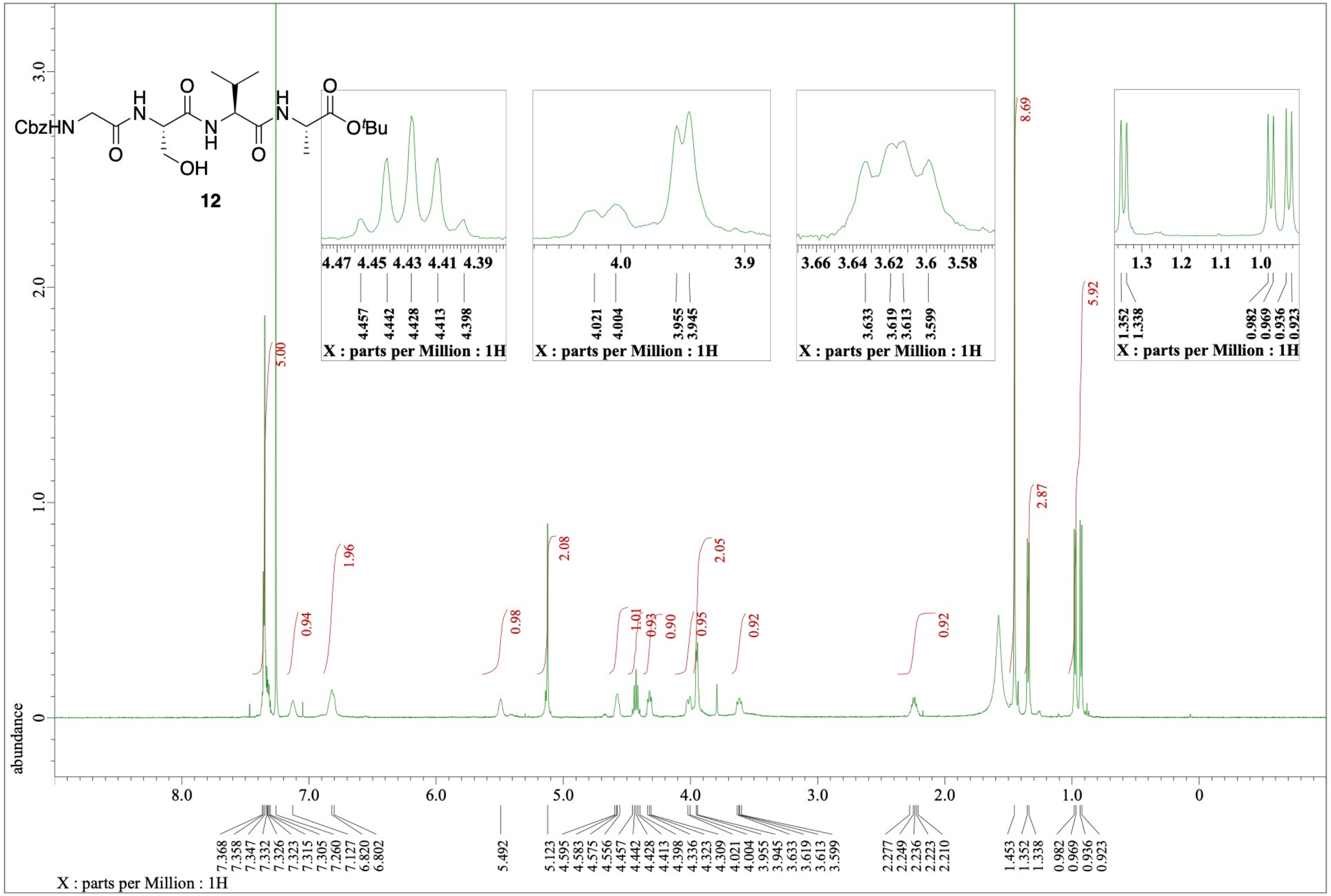
^{1}H NMR spectrum of 11 (270 MHz, CDCl$_3$)



^{13}C NMR spectrum of 11 (126 MHz, $CDCl_3$)



^{1}H NMR spectrum of 12 (270 MHz, CDCl$_3$)



^{13}C NMR spectrum of 12 (126 MHz, CDCl$_3$)