Electronic Supplementary Information (ESI)

Tandem deprotection/coupling for peptide synthesis in water at room temperature

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1. General Information

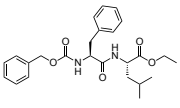
A solution of 2 wt % TPGS-750-M/H_20 was prepared by dissolving TPGS-750-M in degassed HPLC grade water and was stored under argon. TPGS-750-M was made as previously described[1] and is available from Sigma-Aldrich (catalog #733857). All commercially available reagents were used without further purification. Thin layer chromatography (TLC) was done using Silica Gel 60 F254 plates (Merck, 0.25 mm thick). Flash chromatography was done in glass columns using Silica Gel 60 (EMD, 40-63 μm). ^{1}H and ^{13}C NMR were recorded at 25 °C either on a Varian Unity Inova 400 MHz, a Varian Unity Inova 500 MHz or on a Varian Unity Inova 600 MHz spectrometers in $CDCl_3$ or MeOD with residual $CHCl_3$ (^{1}H = 7.27 ppm, ^{13}C = 77.16 ppm) or MeOH (^{1}H = 4.78 ppm, ^{13}C = 49.0 ppm) as internal standards. Chemical shifts are reported in parts per million (ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, bd = broad doublet, t = triplet, q = quartet, quin = quintet, m = multiplet), coupling constant (if applicable) and integration.

Chiral HPLC data were collected using a Shimadzu LC-20AT Prominence liquid chromatograph coupled with Shimadzu SPD-M20A Prominence diode array detector. HPLC method ran using HPLC grade isopropanol and hexanes through a Lux 5u Cellulose-2 (250 x 4.6 mm) column.

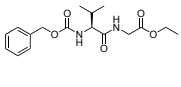
HRMS data were recorded on a Waters Micromass LCT TOF ES+ Premier mass spectrometer using ESI ionization.

[1] B. H. Lipshutz, S. Ghorai, A. R. Abela, R. Moser, T. Nishikata, C. Duplais, A. Krasovskiy, *J. Org. Chem.* **2011**, *76*, 4379.

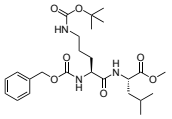
2. Scope of the reaction



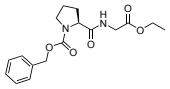
Cbz-L-Phe-L-Leu-OEt (2a)
99 %



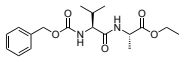
Cbz-L-Val-Gly-OEt (2b)
26 % (95 %)[1]



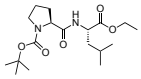
Cbz-L-Orn(Boc)-L-Leu-OMe (2c)
91 %



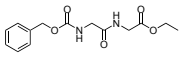
Cbz-L-Pro-Gly-OEt (2d)
42 % (85 %)[1]



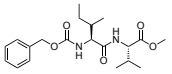
Cbz-L-Val-L-Ala-OEt (2e)
72 % (49 %)[1]



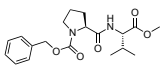
Boc-L-Pro-L-Leu-OEt (2f)
84 %



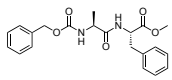
Cbz-Gly-Gly-OEt (2g)
30 % (63 %)[1]



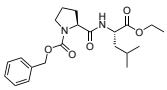
Cbz-L-Ile-L-Val-OMe (2h)
70 %



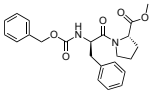
Cbz-L-Pro-L-Val-OMe (2i)
88 %



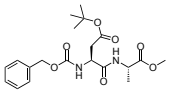
Cbz-L-Ala-L-Phe-OMe (2j)
82 %



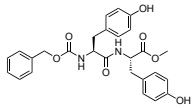
Cbz-L-Pro-L-Leu-OEt (2k)
94 %



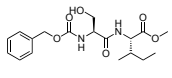
Cbz-D-Phe-L-Pro-OMe (2l)
83 %



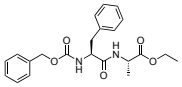
Cbz-L-Asp(OtBu)-L-Ala-OMe (2m)
74 % (83 %)[1]



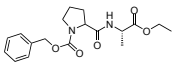
Cbz-L-Tyr-L-Tyr-OMe (2n)
84 %



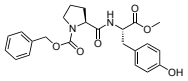
Cbz-L-Ser-L-Ile-OMe (2o)
44 % (82 %)[1]



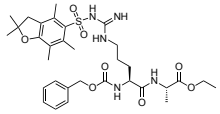
Cbz-L-Phe-L-Ala-OEt (2p)
85 %



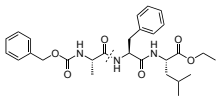
Cbz-LPro-L-Ala-OEt (2q)
65 %



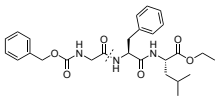
Cbz-LPro-L-Tyr-OMe (2r)
71 %



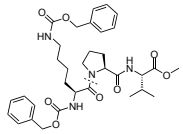
Cbz-L-Arg(Pbf)-L-Ala-OEt (2s)
41 % (75 %)[1]



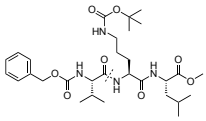
Cbz-L-Ala-L-Phe-L-Leu-OEt (3a)
92 %



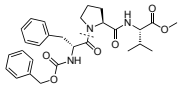
Cbz-Gly-L-Phe-L-Leu-OEt (3b)
82 %



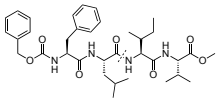
Cbz-L-Lys(Cbz)-L-Pro-L-Val-OMe (3c)
51 % (65 %)[1]



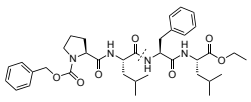
Cbz-L-Val-L-Orn(Boc)-L-Leu-OMe (3d)
51 % (79 %)[1]



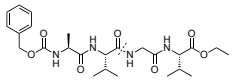
Cbz-D-Phe-L-Pro-L-Val-OMe (3e)
66 %



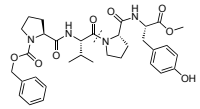
Cbz-L-Phe-L-Leu-L-Ile-L-Val-OMe (4a)
70 %



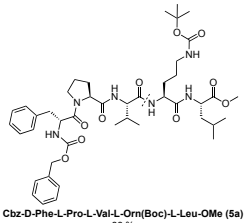
Cbz-L-Pro-L-Leu-L-Phe-L-Leu-OEt (4b)
89 %



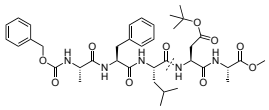
Cbz-L-Val-Gly-L-Val-L-Ala-OEt (4c)
60 %



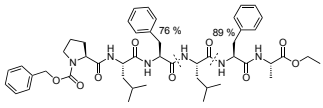
Cbz-L-Pro-L-Val-L-Pro-L-Tyr-OMe (4d)
86 %



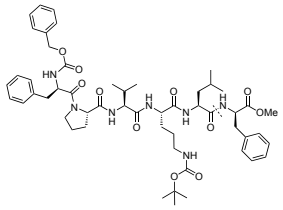
Cbz-D-Phe-L-Pro-L-Val-L-Orn(Boc)-L-Leu-OMe (5a)
88 %



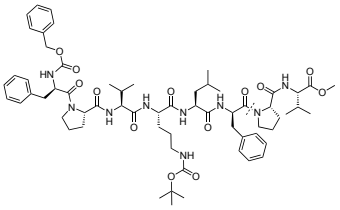
Cbz-L-Ala-L-Phe-L-Leu-L-Asp(OtBu)-L-Ala-OMe (5b)
89 %[1]



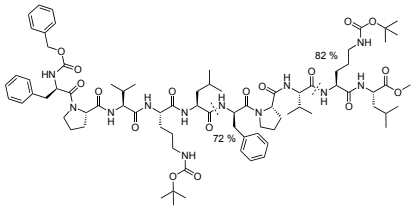
Cbz-L-Pro-L-Leu-L-Phe-L-Leu-L-Phe-L-Ala-OEt (6a)
89 % (76 %)



Cbz-D-Phe-L-Pro-L-Val-L-Orn(Boc)-L-Leu-D-Phe-OMe (6b)
75 % (coupling step only)



Cbz-D-Phe-L-Pro-L-Val-L-Orn(Boc)-L-Leu-D-Phe-L-Pro-L-Val-OMe (8a)
86 %



Cbz-D-Phe-L-Pro-L-Val-L-Orn(Boc)-L-Leu-D-Phe-L-Pro-L-Val-L-Orn(Boc)-L-Leu-OMe (10a)
82 % (72 %)

3. General procedure for dipeptide formation

To a microwave vial were added *N*-terminal-protected amino acid (1.0 equiv) and amino ester (1.0 equiv) in a 2 wt % solution of TPGS-750-M/$H_2$0 [0.5 M], followed by 2,6-lutidine (3.05 equiv). If noted in the text, 10 wt % THF was also added. After 5 min, COMU (1.05 equiv) was added. The reaction was then stirred vigorously at rt (20-25 °C) until completion. The product was extracted with methyl *t*-butyl ether (MTBE; 10 mL) or a 1:1 mixture of hexanes/EtOAc. The organic layer was washed with a solution of HCl 1 M (2 x 5 mL), with a saturated solution of sodium carbonate (2 x 5 mL) and finally brine (1 x 5 mL). The solution was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield the desired peptide. These peptides can be used without further purification but yields were determined after flash chromatography on silica with a gradient of hexanes:EtOAc: 100:0 / 90:10 / 75:25 / 50:50 (100 mL each).

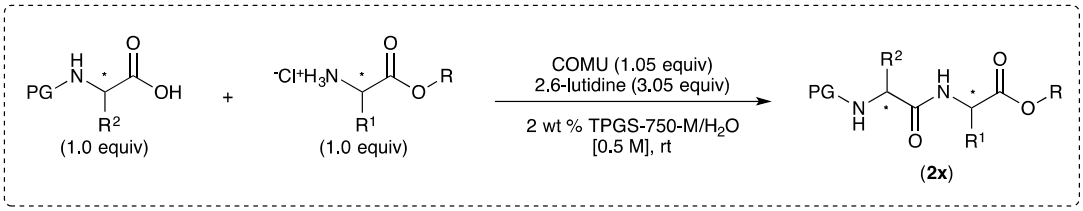
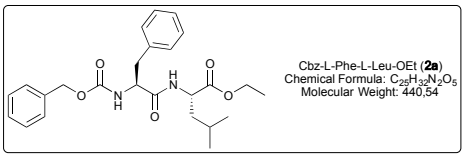
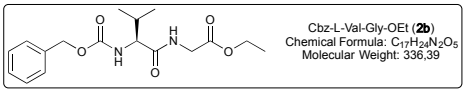


Figure 1 : General Scheme for the Dipeptide Synthesis

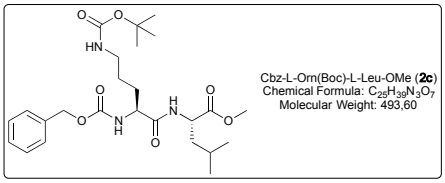
Preparation of Dipeptides



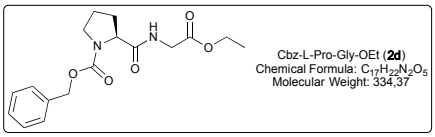
Synthesis of Cbz-L-Phe-L-Leu-OEt (**2a**):
Scale: 0.2 mmol
Yield: 99% (0.087 g)
Aspect: white powder – **mp:** 106-107 °C
R_f = 0.85 (1:1 hexanes/EtOAc) – Cerium Ammonium Molybdate stain
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 6H), 7.26 – 7.16 (m, 4H), 6.11 (bd, J = 8.2 Hz, 1H), 5.28 (bd, *J* = 6.1 Hz, 1H), 5.10 (d, *J* = 2.7 Hz, 2H), 4.54 (td, *J* = 8.5, 5.3 Hz, 1H), 4.44 (bd, *J* = 8.2 Hz, 1H), 4.16 (qd, *J* = 7.1, 3.5 Hz, 2H), 3.14 (dd, *J* = 13.9, 6.4 Hz, 1H), 3.06 (dd, *J* = 13.9, 6.9 Hz, 1H), 1.54 – 1.41 (m, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.90 (dd, *J* = 8.5, 6.3 Hz, 6H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 170.5, 155.9, 136.3, 136.1, 129.4, 128.6, 128.5, 128.2, 128.0, 127.0, 67.0, 61.3, 56.0, 50.9, 41.5, 38.4, 24.7, 22.7, 22.0, 14.1.



Synthesis of Cbz-L-Val-Gly-OEt (**2b**):
Scale: 0.64 mmol
Yield: 95% (0.20 g in presence of 10% THF) – 26% (0.06 g without THF)
Aspect: white powder – **mp:** 150-151 °C
R_f = 0.43 (1:1 hexanes/AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 5H), 6.81 (s, 1H), 5.60 (d, *J* = 8.9 Hz, 1H), 5.09 (q, *J* = 12.2 Hz, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.11 (dq, *J* = 9.6, 3.6, 3.1 Hz, 1H), 4.00 (ddd, *J* = 62.0, 18.1, 5.3 Hz, 2H), 2.15 (dt, *J* = 13.4, 6.1 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.96 (dd, *J* = 21.9, 6.8 Hz, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 171.8, 169.8, 156.6, 136.3, 128.6, 128.2, 128.1, 67.1, 61.6, 60.3, 41.3, 31.2, 19.3, 17.9, 14.2.

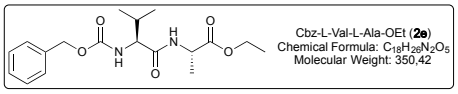


Synthesis of Z-L-Orn(Boc)-L-Leu-OMe (**2c**):
Scale: 0.32 mmol
Yield: 91% (0.143 g)
Aspect: white powder – **mp:** 75 °C
R_f = 0.66 (1:1 hexanes/AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H), 6.90 (s, 1H), 5.62 (d, *J* = 8.4 Hz, 1H), 5.09 (s, 2H), 4.82 (s, 1H), 4.55 (ddd, *J* = 9.4, 8.0, 4.8 Hz, 1H), 4.41 (s, 1H), 3.70 (s, 3H), 3.33 (s, 3H), 3.11 – 3.00 (m, 1H), 2.15 – 1.82 (m, 2H), 1.60 (dddd, *J* = 45.1, 18.0, 13.3, 8.1 Hz, 6H), 1.43 (s, 9H), 0.92 (dd, *J* = 9.6, 6.2 Hz, 6H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 172.0, 156.8, 156.4, 136.4, 128.6, 128.2, 128.1, 79.4, 67.0, 53.4, 52.3, 51.0, 40.9, 30.4, 28.5, 26.3, 24.9, 23.0, 21.7.
MS (ESI) 516.2 $[M+Na]^+$
HRMS (ESI): *m/z* calc. for $[C_{25}H_{39}N_3O_7Na]$: 516.2686, found 516.2667.

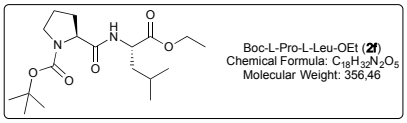


Synthesis of Cbz-L-Pro-Gly-OEt (**2d**):
Scale: 1.8 mmol

Yield: 85% (0.50 g in presence of 10% THF) – 42% (0.25 g without THF)
Aspect: colorless oil
R_f = 0.14 (1:1 hexanes/AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.26 (m, 5H), 7.15 (bs, 0.5H), 6.51 (bs, 0.5H), 5.18 (d, *J* = 12.4 Hz, 1H, rotamer 1), 5.15 – 5.05 (m, 1H, rotamer 2), 4.37 (d, *J* = 24.9 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.00 (d, *J* = 16.4 Hz, 2H), 3.49 (d, *J* = 52.0 Hz, 2H), 2.23 (d, *J* = 78.9 Hz, 1H), 2.09 – 1.83 (m, 3H), 1.26 (t, *J* = 7.2 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 172.0, 169.8, 169.6, 156.1, 155.0, 136.4, 128.5, 128.1, 127.9, 67.4, 61.4, 60.8, 60.5, 47.5, 47.1, 41.4, 41.1, 31.1, 28.7, 24.5, 23.6, 14.2.

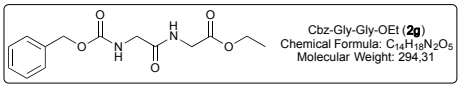


Synthesis of Cbz-L-Val-L-Ala-OEt (**2e**):
Scale: 1.2 mmol
Yield: 72% (0.30 g without THF) – 49% (0.21 g in presence of 10% THF)
Aspect: white powder – **mp:** 140-141 °C
R_f = 0.47 (1:1 hexanes/AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 6.64 (d, *J* = 7.4 Hz, 1H), 5.54 (d, *J* = 8.9 Hz, 1H), 5.17 – 5.04 (m, 2H), 4.56 (p, *J* = 7.2 Hz, 1H), 4.20 (tt, *J* = 7.2, 3.4 Hz, 2H), 4.07 (dd, *J* = 9.0, 6.3 Hz, 1H), 2.11 (dp, *J* = 13.4, 6.5, 5.7 Hz, 1H), 1.39 (d, *J* = 7.2 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.96 (dd, *J* = 21.6, 6.8 Hz, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 171.1, 156.6, 136.3, 128.6, 128.3, 128.1, 67.2, 67.1, 63.3, 61.7, 60.3, 48.2, 31.5, 19.2, 18.3, 18.0, 14.2.
MS (ESI) 373.1 $[M+Na]^+$
HRMS (ESI): *m/z* calc. for $[C_{18}H_{26}N_2O_5Na]$: 373.1740, found 373.1733.

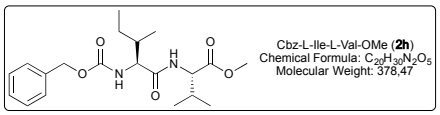


Synthesis of Boc-Pro-Leu-OEt (**2f**)
Scale: 0.64 mmol
Yield: 84% (0.191 g)
Aspect: white powder – **mp:** 84-85 °C
R_f =0.43 (1:1 hexanes/AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (s, 1H), 6.42 (s, 1H), 4.71 – 4.45 (m, 1H), 4.45 – 4.22 (m, 1H), 4.18 (qd, *J* = 7.2, 6.7, 2.5 Hz, 2H), 3.65 – 3.29 (m, 2H), 2.36 (s, 1H), 2.15 (s, 1H), 1.88 (p, *J* = 6.3, 5.8 Hz, 2H), 1.79 – 1.53 (m, 4H), 1.47 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.93 (d, *J* = 6.2 Hz, 6H).

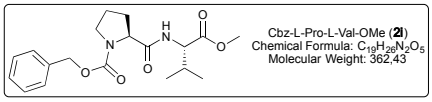
^{13}C NMR (151 MHz, $CDCl_3$) δ 172.8, 172.7, 171.9, 171.8, 155.9, 154.7, 80.9, 80.4, 61.2, 59.7, 51.0, 50.7, 47.1, 42.0, 41.4, 31.0, 29.8, 28.4, 27.8, 24.9, 23.8, 23.0, 22.0, 14.3.



Synthesis of Cbz-Gly-Gly-OEt (**2g**)
Scale: 0.2 mmol
Yield: 63% (0.0559 g in presence of 10% THF) – 30% (0.0162 g without THF)
Aspect: pale yellow crystal – **mp:** 80-81 °C
R_f = 0.62 (AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H), 6.90 (bs, 1H), 5.82 (bs, 1H), 5.11 (s, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.99 (d, *J* = 5.4 Hz, 2H), 3.91 (d, *J* = 5.8 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 169.7, 156.9, 136.3, 128.6, 128.3, 128.2, 67.3, 61.7, 44.5, 41.3, 14.2.
MS (ESI) 317.1 $[M+Na]^+$
HRMS (ESI): *m/z* calc. for $[C_{14}H_{18}N_2O_5Na]$: 317.1113, found 317.1110.

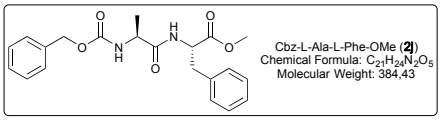


Synthesis of Cbz-L-Ile-L-Val-OMe (**2h**)
Scale: 1.7 mmol
Yield: 70% (0.47 g)
Aspect: white powder – **mp:** 130-131 °C
R_f = 0.71 (1:1 hexanes/AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H), 6.38 (d, *J* = 8.7 Hz, 1H), 5.40 (d, *J* = 8.9 Hz, 1H), 5.12 (s, 2H), 4.54 (dd, *J* = 8.7, 4.9 Hz, 1H), 4.12 – 4.05 (m, 1H), 3.74 (s, 3H), 2.17 (h, *J* = 6.7 Hz, 1H), 1.93 – 1.83 (m, 1H), 1.53 (ddp, *J* = 15.3, 7.7, 3.7 Hz, 1H), 1.16 (ddt, *J* = 14.4, 9.4, 7.2 Hz, 1H), 0.92 (td, *J* = 14.3, 13.5, 6.7 Hz, 12H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 172.2, 171.3, 156.4, 136.4, 128.6, 128.3, 128.1, 67.2, 59.8, 57.2, 52.3, 37.5, 31.3, 24.9, 19.0, 17.9, 15.5, 11.5.
MS (ESI) 401.2 $[M+Na]^+$
HRMS (ESI): *m/z* calc. for $[C_{20}H_{30}N_2O_5Na]$: 401.2052, found 401.2036.

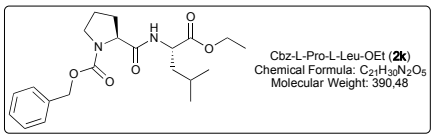


Synthesis of Cbz-L-Pro-L-Val-OMe (**2i**)

Scale: 0.3 mmol
Yield: 83% (0.09 g)
Aspect: yellow oil
Rf = 0.39 (1:1 hexanes/AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 – 7.26 (m, 4H), 7.26 – 7.18 (m, 1H), 6.40 (s, 1H), 5.26 – 5.05 (m, 2H), 4.56 – 4.30 (m, 2H), 3.84 – 3.39 (m, 5H), 2.49 – 1.82 (m, 6H), 0.87 (dd, *J* = 13.9, 6.8 Hz, 6H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 171.4, 155.7, 154.7, 136.3, 67.0, 60.4, 60.0, 57.1, 56.7, 51.7, 47.2, 46.7, 30.8, 27.9, 24.4, 23.4, 18.7, 17.4.

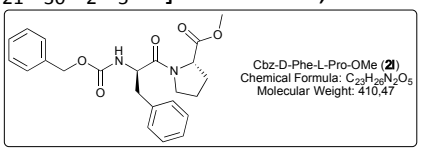


Synthesis of Cbz-L-Ala-L-Phe-OMe (**2j**)
Scale: 0.86 mmol
Yield: 82% (0.22 g)
Aspect: white powder – **mp:** 89-90 °C
Rf = 0.45 (1:1 hexanes/AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 – 7.27 (m, 5H), 7.27 – 7.05 (m, 5H), 6.38 (bs, 1H), 5.19 (bs, 1H), 5.11 (q, *J* = 12.2 Hz, 2H), 4.86 (dt, *J* = 7.8, 5.9 Hz, 1H), 4.22 (t, *J* = 7.0 Hz, 1H), 3.74 (s, 3H), 3.16 (dd, *J* = 13.9, 5.8 Hz, 1H), 3.09 (dd, *J* = 13.9, 6.0 Hz, 1H), 1.35 (d, *J* = 7.0 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.9, 171.8, 156.0, 136.3, 135.8, 129.4, 128.7, 128.7, 128.3, 128.2, 127.3, 67.2, 53.3, 52.5, 50.5, 38.0, 18.5, 6.2.

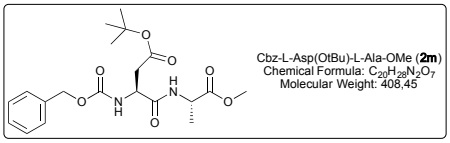


Synthesis of Cbz-L-Pro-L-Leu-OEt (**2k**)
Scale: 1.1 mmol
Yield: 94% (0.40 g)
Aspect: white powder – **mp:** 63-64 °C
R_f = 0.50 (1:1 hexanes/AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 5H), 7.11 – 7.02 (bs, 1H), 6.34 (bs, 1H), 5.16 (q, *J* = 15.5, 14.0 Hz, 2H), 4.52 (s, 1H), 4.36 (t, *J* = 12.2 Hz, 2H), 4.24 – 4.06 (m, 2H), 3.78 – 3.36 (m, 3H), 2.33 (s, 1H), 2.15 (s, 1H), 2.02 – 1.74 (m, 4H), 1.70 – 1.37 (m, 3H), 1.33 – 1.18 (m, 3H), 0.89 (dd, *J* = 6.3, 2.9 Hz, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7 (major rotamer), 172.6 (minor rotamer), 172.0 (minor rotamer), 171.4 (major rotamer), 156.1 (major rotamer), 155.0 (minor rotamer),

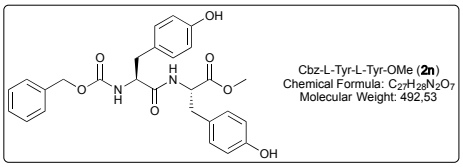
136.5, 136.3, 128.5, 128.0, 127.8, 67.3, 61.2, 60.7 (minor rotamer), 60.3 (major rotamer), 51.1 (major rotamer), 50.6 (minor rotamer), 47.5 (minor rotamer), 47.0 (major rotamer), 41.3, 31.0, 28.2, 24.9, 24.6, 23.6, 22.8, 22.0, 14.2.
MS (ESI) 413.2 $[M+Na]^+$
HRMS (ESI): *m/z* calc. for $[C_{21}H_{30}N_2O_5Na]$: 413.2052, found 413.2065.



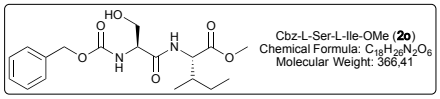
Synthesis of Cbz-D-Phe-L-Pro-OMe (**2l**)
Scale: 3.9 mmol
Yield: 83% (1.3 g)
Aspect: white powder
Rf = 0.40 (1:1 hexanes/AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.10 (m, 10H), 5.76 – 5.67 (m, 1H), 5.17 – 5.06 (m, 2H), 4.71 (td, *J* = 8.9, 5.5 Hz, 1H), 4.30 (dd, *J* = 8.4, 3.8 Hz, 1H), 3.70 (d, *J* = 2.2 Hz, 3H), 3.65 – 3.49 (m, 2H), 3.08 (dd, *J* = 13.1, 5.4 Hz, 1H), 2.96 (dd, *J* = 12.9, 9.3 Hz, 1H), 2.66 (dt, *J* = 9.4, 6.9 Hz, 1H), 2.30 – 1.94 (m, 1H), 1.98 – 1.80 (m, 3H), 1.52 (qd, *J* = 6.9, 4.7 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 170.0, 155.6, 136.5, 136.3, 129.6, 129.3, 128.5, 128.5, 128.1, 128.1, 128.0, 127.1, 66.9, 58.8, 54. 1, 52.3, 46.9, 40.3, 29.0, 24.5.
MS (ESI) 433.1 $[M+Na]^+$
HRMS (ESI): *m/z* calc. for $[C_{23}H_{26}N_2O_5Na]$: 433.1740, found 433.1754.



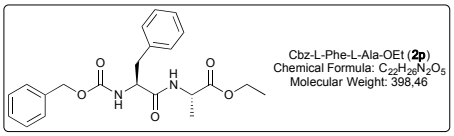
Synthesis of Cbz-L-Asp(tBu)-L-Ala-OMe (**2m**)
Scale: 1.2 mmol
Yield: 83% (0.40 g in presence of 10% THF) – 74% (0.35 g without THF)
Aspect: white powder – **mp:** 79-80 °C
Rf = 0.39 (1:1 hexanes/AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 4H), 7.12 (d, *J* = 7.4 Hz, 1H), 6.06 (d, *J* = 8.5 Hz, 1H), 5.09 (s, 2H), 4.51 (dq, *J* = 21.7, 7.1 Hz, 2H), 3.68 (s, 3H), 2.84 (dd, *J* = 17.0, 4.9 Hz, 1H), 2.62 (dd, *J* = 17.1, 6.6 Hz, 1H), 1.40 (s, 9H), 1.34 (d, *J* = 7.2 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 170.8, 170.2, 155.9, 136.1, 128.4, 128.1, 128.0, 81.6, 70.4, 67.0, 52.2, 51.0, 48.2, 37.6, 27.9, 17.8.
MS (ESI) 431.1 $[M+Na]^+$
HRMS (ESI): *m/z* calc. for $[C_{20}H_{28}N_2O_7Na]$: 431.1794, found 431.1774.



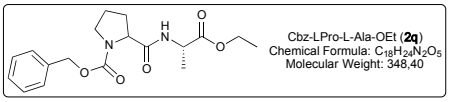
Synthesis of Cbz-L-Tyr-L-Tyr-OMe (**2n**)
Scale: 0.15 mmol
Yield: 84% (0.064 g)
Aspect: white powder– **mp:** 67-68 °C
Rf = 0.10 (1:1 hexanes/AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.29 (m, 5H), 7.15 (bd, *J* = 8.0 Hz, 0.7H), 7.08 – 7.04 (bd, *J* = 8.5 Hz, 0.5H), 6.99 (bd, *J* = 7.7 Hz, 1H), 6.81 (m, 2H), 6.66 (dd, *J* = 8.5, 6.9 Hz, 3H), 6.19 (d, *J* = 7.9 Hz, 1H), 5.67 (s, 1H), 5.38 (d, *J* = 8.1 Hz, 1H), 5.10 (s, 2H), 4.79 – 4.68 (m, 1H), 4.36 (bs, 1H), 3.70 (d, *J* = 4.1 Hz, 3H), 3.05 – 2.85 (m, 4H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 171.1, 156.3, 155.3, 136.0, 130.6, 130.4, 128.7, 128.4, 128.3, 128.2, 127.0, 115.8, 67.5, 56.4, 53.6, 52.6, 37.8, 37.0, 29.8.
MS (ESI) 515.1 $[M+Na]^+$
HRMS (ESI): *m/z* calc. for $[C_{27}H_{28}N_2O_7Na]$: 515.1794, found 515.1799.



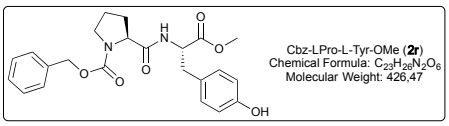
Synthesis of Cbz-L-Ser-L-Ile-OMe (**2o**)
Scale: 1.2 mmol
Yield: 82% (0.36 g in presence of 10% THF) – 44% (0.19 g without THF)
Aspect: pale yellow oil
Rf = 0.15 (1:1 hexanes/AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 4H), 7.22 (bd, *J* = 8.5 Hz, 1H), 6.05 (d, *J* = 7.6 Hz, 1H), 5.17 – 5.05 (m, 2H), 4.53 (dd, *J* = 8.5, 5.0 Hz, 1H), 4.34 (dt, *J* = 10.9, 4.7 Hz, 1H), 3.98 (dd, *J* = 11.3, 4.1 Hz, 1H), 3.77 – 3.64 (m, 4H), 1.95 – 1.85 (m, 1H), 1.39 (dqd, *J* = 14.6, 7.3, 4.3 Hz, 1H), 1.21 – 1.10 (m, 1H), 0.93 – 0.85 (m, 6H).
13C NMR (126 MHz, $CDCl_3$) δ 172.5, 171.1, 156.7, 136.1, 128.6, 128.3, 128.1, 67.3, 62.9, 57.0, 55.5, 52.3, 37.4, 25.1, 15.6, 11.6.
MS (ESI) 389.1 $[M+Na]^+$
HRMS (ESI): *m/z* calc. for $[C_{18}H_{26}N_2O_6Na]$: 389.1689, found 389.1686.



Synthesis of Cbz-L-Phe-L-ALa-OMe (**2p**)
Scale: 3.9 mmol
Yield: 85% (1.32 g)
Aspect: white powder – **mp:** 210-212 °C
Rf = 0.61 (1:1 hexanes/AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.12 (m, 11H), 6.77 (d, *J* = 7.2 Hz, 1H), 5.65 (d, *J* = 8.3 Hz, 1H), 5.06 (q, *J* = 12.3 Hz, 2H), 4.50 (dq, *J* = 14.3, 7.4 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.15 – 3.00 (m, 2H), 1.32 (d, *J* = 7.1 Hz, 4H), 1.26 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 170.4, 155.7, 136.1, 135.9, 129.0, 128.2, 128.2, 127.8, 127.6, 126.6, 66.6, 61.2, 55.7, 47.9, 38.3, 17.9, 13.8.
MS (ESI) 421.2 $[M+Na]^+$
HRMS (ESI): *m/z* calc. for $[C_{22}H_{26}N_2O_5Na]$: 421.1740, found 421.1742.

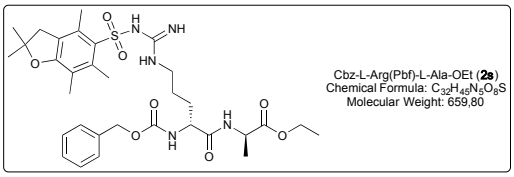


Synthesis of Cbz-L-Pro-L-Ala-OMe (**2q**)
Scale: 0.8 mmol
Yield: 65% (0.18 g)
Aspect: pale yellow oil
Rf = 0.29 (1:1 hexanes/AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.27 (m, 5H), 7.19 – 7.01 (bs, 1H), 6.47 (bs, 1H), 5.16 (s, 2H), 4.57 – 4.41 (m, 1H), 4.41 – 4.25 (m, 1H), 4.25 – 4.08 (m, 2H), 3.68 – 3.35 (m, 2H), 2.22 (m, 2H), 2.06 – 1.82 (m, 3H), 1.46 – 1.17 (m, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 171.4, 156.1, 155.0, 136.5, 128.6, 128.1, 128.0, 61.5, 60.8, 60.5, 48.3, 48.1, 47.6, 47.1, 31.1, 29.8, 28.6, 24.6, 23.7, 18.3, 14.2.
MS (ESI) 371.1 $[M+Na]^+$
HRMS (ESI): *m/z* calc. for $[C_{18}H_{24}N_2O_5Na]$: 371.1583, found 371.1592.



Synthesis of Cbz-L-Pro-L-Tyr-OMe (**2r**)
Scale: $6.6.10^{-4}$ mol
Yield: 71% (0.20 g)

Aspect: yellow oil
R_f = 0.61 (1:1 hexanes/AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.28 (m, 4H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.91 (t, *J* = 9.1 Hz, 2H), 6.80 – 6.63 (m, 2H), 6.46 – 6.36 (m, 1H), 5.27 – 5.01 (m, 2H), 4.82 (q, *J* = 6.8 Hz, 1H), 4.32 (t, *J* = 14.4 Hz, 1H), 3.69 (d, *J* = 22.2 Hz, 3H), 3.44 (ddd, *J* = 26.8, 15.4, 6.6 Hz, 2H), 3.09 (d, *J* = 13.1 Hz, 1H), 3.00 – 2.78 (m, 1H), 2.30 – 1.56 (m, 4H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 171.7, 155.5, 136.4, 130.4, 128.6, 128.3, 128.1, 127.2, 115.5, 67.6, 60.8, 60.4, 53.6, 52.5, 47.5, 47.0, 37.3, 28.5, 24.5.
MS (ESI) 449.1 $[M+Na]^+$
HRMS (ESI): *m/z* calc. for $[C_{23}H_{26}N_2O_6Na]$: 449.1689, found 449.1702.



Synthesis of Cbz-L-Arg(Pbf)-L-Ala-OEt (**2s**)
As the counterion of Cbz-Arg(Pbf)-OH is a cyclohexylammonium, 2.0 equiv of this amino acid, as well as 2.0 equiv of COMU were used.
Scale: $1.0.10^{-4}$ mol
Yield: 75% (0.024 g in presence of 10% THF) – 41% (0.013 g without THF)
Aspect: yellow oil
R_f = 0.58 (AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 3.6 Hz, 5H), 6.79 (s, 1H), 6.23 (s, 2H), 6.00 (s, 1H), 5.89 (d, *J* = 8.1 Hz, 0H), 5.06 (t, *J* = 3.0 Hz, 2H), 4.53 – 4.33 (m, 1H), 4.28 – 4.11 (m, 1H), 3.67 (t, *J* = 10.3 Hz, 1H), 3.24 (s, 2H), 2.94 (s, 2H), 2.58 (d, *J* = 2.9 Hz, 3H), 2.50 (s, 3H), 2.09 (s, 3H), 1.80 (d, *J* = 15.0 Hz, 3H), 1.72 – 1.52 (m, 6H), 1.46 (s, 6H), 1.40 (d, *J* = 7.3 Hz, 1H), 1.27 (td, *J* = 11.8, 11.3, 5.4 Hz, 4H), 1.10 (q, *J* = 12.3, 11.5 Hz, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.1, 170.8, 158.9, 156.5, 138.5, 136.4, 132.8, 132.4, 128.6, 128.3, 128.0, 128.0, 124.8, 117.7, 86.6, 67.1, 61.7, 56.1, 48.8, 32.8, 32.7, 29.8, 28.7, 25.5, 25.1, 19.4, 18.1, 14.2, 12.6.
MS (ESI) 682.3 $[M+Na]^+$
HRMS (ESI): *m/z* calc. for $[C_{32}H_{45}N_2O_8SNa]$: 682.2886, found 682.2896.

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4. General procedure for Cbz-deprotection/coupling in 1-pot

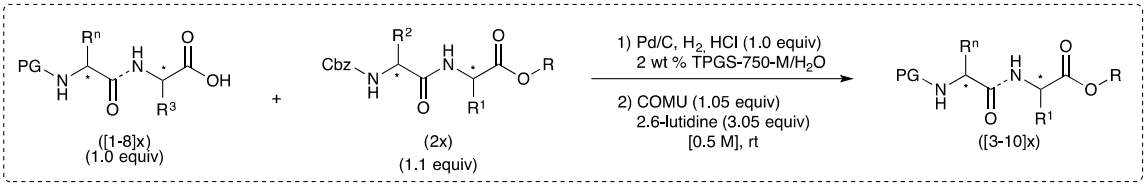
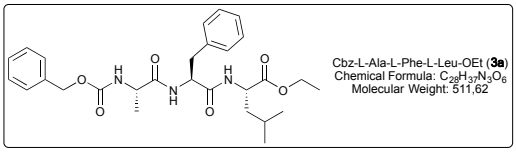


Figure 2 : General Scheme for the One-Pot Deprotection/Coupling Step - Access to Longer Peptides

To a microwave vial was added the Cbz-protected dipeptide **2x** (1.1 equiv, [0.5 M]) followed by a solution of HCl (12 M; 1.0 equiv) in a 2 wt % solution of TPGS-750-M/H_2O. After dissolution, Pd/$C_{10\%}$ (10 wt %) was added. The vial was purged twice with hydrogen gas (balloon) and kept under H_2 atmosphere for 2 h at rt (20-25 °C). The reaction was followed by TLC (1:1 mixture of hexanes/EtOAc – UV and ninhydrin). After completion, the vial was purged with argon for 0.5 h. If noted in the text, 10% THF was then added. The next *N*-protected-amino acid or peptide (hydrolyzed according to the literature)[2] (1.0 equiv) and COMU (3.05 equiv) were added. After 5 min, 2.6-lutidine (3.05 equiv) was added and the reaction was stirred for 2 h at rt (20-25 °C). The product was filtered through a pad of Celite® and extracted with MTBE or a 1:1 mixture of hexanes/EtOAc (10 mL). The organic layer was washed with a solution of HCl (1 M; 2 x 5 mL), with a saturated solution of sodium carbonate (2 x 5 mL) and brine (1 x 5 mL). The solution was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield the desired peptide, which can be used without further purification. Yields were determined after flash chromatography with a gradient of hexanes:EtOAc: 100 / 90:10 / 75:25 / 50:50 / 25:75 / 0:100 (100 mL each)

Preparation of Tripeptides



Synthesis of Cbz-L-Ala-L-Phe-L-Leu-OEt (**3a**) [from Cbz-L-Ala-OH + **2a**]
Scale: 0.6 mmol
Yield: 92% (0.285 g)
Aspect: white powder – **mp:** 129-130 °C
R_f = 0.39 (1:1 Hexanes/AcOEt) – Cerium Ammonium Molybdate stain

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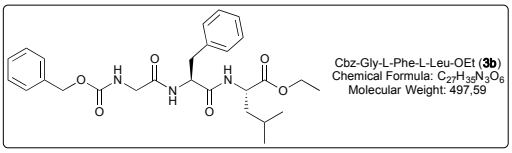
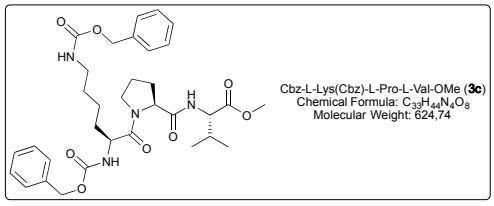
[2] G. S. Hamilton; Y-Q. Wu; D. C. Limburg; D. E. Wilkinson; M. J. Vaal; J-H. Li; C. Thomas; W. Huang; H. Sauer; D. T. Ross; R. Soni; Y. Chen; H. Guo; P. Howorth; H. Valentine; S. Liang; D. Spicer; M. Fuller; J. P. Steiner. *J. Med. Chem*. **2002**, *45*, 3549-3557.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 5H), 7.27 – 7.15 (m, 5H), 6.81 (bd, *J* = 7.7 Hz, 1H), 6.56 (bd, *J* = 7.7 Hz, 1H), 5.41 (d, *J* = 7.2 Hz, 1H), 5.16 – 4.99 (dd, *J* = 50.0, 12.2 Hz, 2H), 4.73 (q, *J* = 7.2 Hz, 1H), 4.52 (td, *J* = 8.5, 5.3 Hz, 1H), 4.24 (d, *J* = 7.1 Hz, 1H), 4.15 (qd, *J* = 7.1, 1.6 Hz, 2H), 3.08 (d, *J* = 6.7 Hz, 2H), 1.54 (dddd, *J* = 42.2, 21.4, 9.9, 6.5 Hz, 3H), 1.31 (d, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 6H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 172.4, 172.4, 170.5, 156.0, 136.4, 136.3, 129.4, 128.6, 128.5, 128.3, 128.1, 127.0, 67.1, 61.3, 54.2, 51.0, 50.7, 41.4, 38.2, 24.8, 22.8, 22.1, 18.7, 14.2.
MS (ESI) 534.2 $[M+Na]^+$
HRMS (ESI): *m/z* calc. for $[C_{28}H_{37}N_3O_6Na]$: 534.2580, found 534.2560.

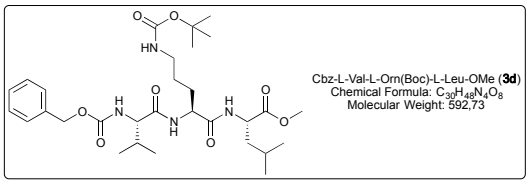


Synthesis of Cbz-Gly-L-Phe-L-Leu-OEt (**3b**) [from Cbz-Gly-OH + **2a**]
Scale: 0.3 mmol
Yield: 82% (0.125 g)
Aspect: yellow syrup
R_f = 0.30 (1:1 Hexanes/AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.10 (m, 10H), 6.86 (bd, *J* = 8.1 Hz, 1H), 5.83 (bt, *J* = 5.6 Hz, 1H), 5.09 (s, 2H), 4.80 (q, *J* = 7.2 Hz, 1H), 4.51 (td, *J* = 8.3, 5.2 Hz, 1H), 4.13 (qd, *J* = 7.1, 1.2 Hz, 2H), 3.84 (t, *J* = 5.5 Hz, 2H), 3.04 (t, *J* = 7.8 Hz, 2H), 1.62 – 1.42 (m, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.90 – 0.83 (d, *J* = 4.8 Hz, 6H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 170.7, 169.2, 156.7, 136.4, 129.5, 128.6, 128.2, 128.1, 127.0, 67.2, 61.4, 54.4, 51.1, 44.5, 41.4, 38.5, 31.7, 24.8, 22.7, 22.1, 14.2.
MS (ESI) 520.2 $[M+Na]^+$
HRMS (ESI): *m/z* calc. for $[C_{27}H_{35}N_3O_6Na]$: 520.2424, found 520.2433.

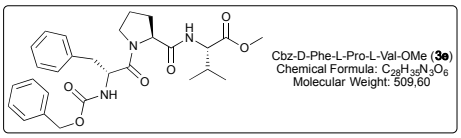


Synthesis of Cbz-L-Lys(Cbz)-L-Pro-L-Val-OMe (**3c**) [from Cbz-L-Lys(Cbz)-OH + **2i**]
Scale: 0.27 mmol
Yield: 65% (0.17 g in presence of 10% THF) – 51% (0.09 g without THF)
Aspect: pale yellow syrup
R_f = 0.36 (1:1 Hexanes/AcOEt) – Cerium Ammonium Molybdate stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 10H), 6.95 (d, *J* = 8.7 Hz, 1H), 5.64 (d, *J* = 8.6 Hz, 1H), 5.27 (t, *J* = 6.2 Hz, 1H), 5.09 (d, *J* = 6.3 Hz, 4H), 4.61 – 4.45 (m, 2H), 3.71 (s, 3H), 3.77 – 3.53 (m, 1H), 3.27 – 3.11 (m, 2H), 2.28 (dt, *J* = 11.5, 3.8 Hz, 1H), 2.21 – 2.08 (m, 2H), 1.98 (ddd, *J* = 15.8, 11.3, 6.9 Hz, 2H), 1.81 – 1.20 (m, 9H), 0.88 (dd, *J* = 9.7, 6.8 Hz, 6H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4, 172.0, 171.1, 156.7, 156.2, 136.9, 136.4, 128.6, 128.6, 128.3, 128.2, 128.1, 67.1, 66.7, 60.2, 57.4, 52.3, 52.2, 47.6, 40.6, 32.6, 31.3, 29.8, 29.4, 27.8, 25.3, 22.0, 19.1, 17.7.
MS (ESI) 647.3 $[M+Na]^+$
HRMS (ESI): *m/z* calc. for $[C_{33}H_{44}N_4O_8Na]$: 647.3057, found 647.3056.



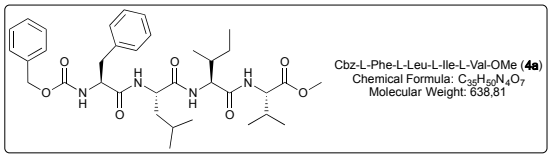
Synthesis of Cbz-L-Val-L-Orn(Boc)-L-Leu-OMe (**3d**) [from Cbz-L-Val-OH + **2c**]
Scale: 0.1 mmol (0.027 g)
Yield: 79% (0.05 g in presence of 10% THF) – 51% (0.03 g without THF)
Aspect: white powder – **mp:** 153-155 °C
R_f = 0.21 (1:1 Hexanes/AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 7.05 (d, *J* = 22.6 Hz, 2H), 5.74 – 5.48 (m, 1H), 5.18 – 5.03 (m, 2H), 4.87 (s, 1H), 4.69 – 4.63 (m, 1H), 4.53 (dddd, *J* = 9.5, 7.3, 5.0, 2.1 Hz, 1H), 4.16 – 4.05 (m, 1H), 3.70 (s, 3H), 3.31 (d, *J* = 12.5 Hz, 1H), 3.06 (d, *J* = 14.2 Hz, 1H), 2.17 – 1.78 (m, 3H), 1.74 – 1.49 (m, 6H), 1.43 (s, 9H), 0.99 – 0.82 (m, 12H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 171.8, 171.7, 156.9, 156.6, 136.5, 128.6, 128.2, 128.1, 79.4, 67.1, 60.4, 52.3, 52.0, 51.0, 40.8, 39.3, 31.5, 29.7, 28.6, 26.6, 24.9, 23.0, 21.7, 19.3, 18.0.
MS (ESI) 615.3 $[M+Na]^+$
HRMS (ESI): *m/z* calc. for $[C_{30}H_{48}N_4O_8Na]$: 615.3370, found 615.3395.



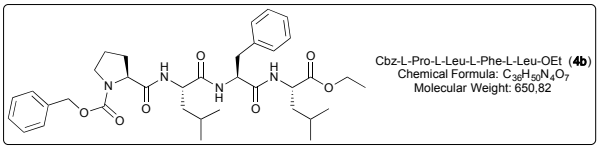
Synthesis of Cbz-D-Phe-L-Pro-L-Val-OMe (**3e**) [from Cbz-D-Phe-OH + **2i**]
Scale: 0.6 mmol
Yield: 66% (0.219 g)
Aspect: yellow syrup
R_f = 0.36 (1:1 Hexanes/AcOEt) – Cerium Ammonium Molybdate stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.6 Hz, 1H), 7.40 – 7.16 (m, 10H), 5.65 (d, *J* = 8.2 Hz, 1H), 5.16 – 4.96 (m, 2H), 4.66 (q, *J* = 8.0 Hz, 1H), 4.53 – 4.37 (m, 2H), 3.68 (s, 3H), 3.56 (td, *J* = 9.1, 2.6 Hz, 1H), 3.01 (d, *J* = 7.8 Hz, 2H), 2.56 (td, *J* = 9.7, 7.1 Hz, 1H), 2.24 (ddt, *J* = 12.0, 6.7, 2.1 Hz, 1H), 2.13 (tdd, *J* = 13.8, 6.3, 4.1 Hz, 1H), 1.90 – 1.76 (m, 1H), 1.59 – 1.39 (m, 2H), 0.84 (dd, *J* = 6.9, 3.1 Hz, 6H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 171.7, 170.6, 155.8, 136.3, 135.9, 129.4, 128.6, 128.5, 128.2, 128.0, 127.3, 67.0, 60.0, 57.4, 54.3, 52.0, 47.0, 39.3, 30.9, 27.1, 24.3, 19.1, 17.7.
MS (ESI) 532.2 $[M+Na]^+$
HRMS (ESI): *m/z* calc. for $[C_{28}H_{35}N_3O_6Na]$: 532.2424, found 532.2440.

Preparation of Tetrapeptides

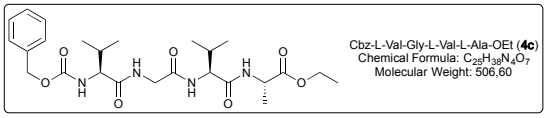


Synthesis of Cbz-L-Phe-L-Leu-L-Ile-L-Val-OMe (**4a**) [from **2a** + **2h**]
Scale: $6.9.10^{-5}$ mol
Yield: 70% (0.031 g)
Aspect: white powder – **mp:** 194-195 °C
R_f = 0.7 (100% AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (bs, 1H), 7.69 (bs, 1H), 7.41 (bs, 1H), 7.34 – 7.05 (m, 10H), 6.13 – 5.97 (m, 1H), 5.02 (dd, *J* = 93.8, 12.5 Hz, 2H), 4.85 (q, *J* = 7.3 Hz, 1H), 4.76 (q, *J* = 8.0 Hz, 1H), 4.71 – 4.57 (m, 3H), 3.73 (s, 3H), 3.01 (td, *J* = 12.7, 11.4, 6.4 Hz, 2H), 2.14 (dq, *J* = 13.3, 6.7 Hz, 1H), 1.83 (d, *J* = 14.0 Hz, 3H), 1.53 (dddd, *J* = 50.4, 27.4, 12.2, 5.2 Hz, 4H), 1.37 – 1.18 (m, 3H), 1.10 (ddd, *J* = 13.4, 9.4, 6.9, 1H), 0.99 – 0.78 (m, 24H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 185.4, 172.7, 172.3, 171.7, 171.1, 136.6, 129.5, 128.5, 128.4, 128.0, 128.0, 126.8, 66.8, 58.0, 57.1, 52.3, 51.6, 42.4, 39.2, 37.3, 31.3, 29.8, 25.3, 24.9, 22.8, 22.6, 19.1, 18.0, 15.4, 11.6.
MS (ESI) 661.3 $[M+Na]^+$
HRMS (ESI): *m/z* calc. for $[C_{35}H_{50}N_4O_7Na]$: 661.3577, found 661.3566.

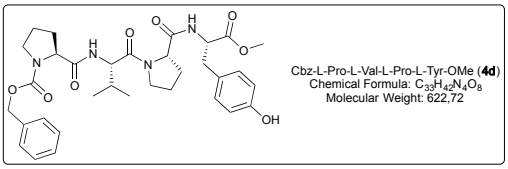


Synthesis of Cbz-L-Pro-L-Leu-L-Phe-L-Leu-OEt (**4b**) [from **2k** + **2a**]

Scale: $9.25.10^{-5}$ mol
Yield: 89% (0.0535 g)
Aspect: white powder – **mp:** 148-150 °C
$\mathbf{R_f}$ = 0.21 (1:1 Hexanes/AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.15 (m, 5H), 6.89 (bd, *J* = 8.4 Hz, 1H), 6.82 (bd, *J* = 6.5 Hz, 1H), 6.67 (bd, *J* = 8.3 Hz, 1H), 5.16 (d, *J* = 4.1 Hz, 2H), 4.74 (q, *J* = 7.6 Hz, 1H), 4.55 – 4.50 (m, 1H), 4.28 – 4.11 (m, 2H), 3.51 (dq, *J* = 15.5, 8.5, 7.4 Hz, 2H), 3.28 (dd, *J* = 14.6, 5.6 Hz, 1H), 3.10 – 3.00 (m, 1H), 2.21 – 1.79 (m, 4H), 1.68 – 1.44 (m, 2H), 1.35 (ddd, *J* = 14.5, 9.6, 5.7 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.00 – 0.72 (m, 6H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 172.4, 172.3, 171.6, 170.8, 156.5, 137.2, 136.1, 129.2, 128.7, 128.6, 128.5, 128.4, 127.9, 126.8, 67.7, 61.2, 60.9, 53.8, 52.8, 51.1, 47.2, 41.1, 40.0, 37.3, 29.8, 28.6, 25.0, 24.8, 23.0, 21.9, 21.7, 14.2.
MS (ESI) 673.3 $[M+Na]^+$
HRMS (ESI): *m/z* calc. for $[C_{36}H_{50}N_4O_7Na]$: 673.3577, found 673.3583.



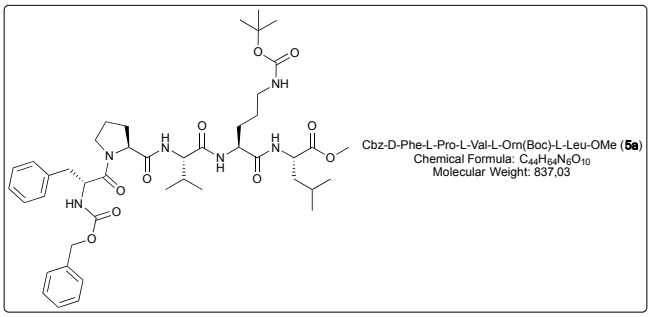
Synthesis of Cbz-L-Val-L-Gly-L-Val-L-Ala-OEt (**4c**) [from **2b** + **2e**]
Scale: 0.11 mmol
Yield: 60% (0.33 g)
Aspect: White powder – **mp:** 170-171 °C
$\mathbf{R_f}$ = 0.44 (100% AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (bs, 1H), 7.33 (m, 5H), 7.15 (bd, *J* = 7.6 Hz, 1H), 7.06 (bd, *J* = 8.9 Hz, 1H), 5.80 (bd, *J* = 8.7 Hz, 1H), 5.17 – 5.01 (m, 2H), 4.56 (p, *J* = 7.3 Hz, 1H), 4.47 (t, *J* = 8.0 Hz, 1H), 4.28 – 4.11 (m, 3H), 3.97 (dd, *J* = 16.5, 4.7 Hz, 1H), 2.10 (dq, *J* = 13.5, 6.7 Hz, 2H), 1.36 (d, *J* = 7.2 Hz, 3H), 1.31 – 1.21 (m, 3H), 0.95 (ddd, *J* = 13.7, 6.8, 3.8 Hz, 12H).
^{13}C NMR (101 MHz, MeOD) δ 175.0, 174.0, 173.2, 171.3, 158.8, 138.2, 129.5, 129.0, 128.8, 67.7, 62.6, 62.3, 59.9, 43.5, 32.0, 31.5, 19.7, 19.6, 18.7, 17.3, 14.5.
MS (ESI) 529.3 $[M+Na]^+$
HRMS (ESI): *m/z* calc. for $[C_{25}H_{38}N_4O_7Na]$: 529.2638, found 529.2654.



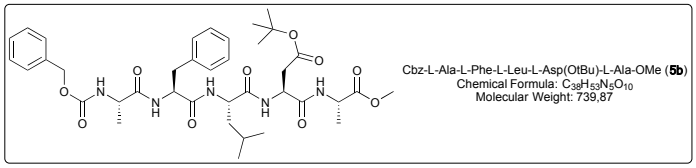
Synthesis of Cbz-L-Pro-L-Val-L-Pro-L-Tyr-OMe (**4d**) [from **2i** + **2r**]
Scale: 0.35 mmol

Yield: 86% (0.13 g) in presence of 10% THF
Aspect: Yellow oil
R_f = 0.17 (100% AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.28 (m, 5H), 7.19 (bd, *J* = 8.4 Hz, 1H), 7.07 (bd, *J* = 8.1 Hz, 0.2H), 6.97 (m, 2H), 6.86 – 6.66 (m, 2H), 5.26 – 5.00 (m, 2H), 4.67 (q, *J* = 6.4 Hz, 1H), 4.53 (m, 2H), 4.37 (m, 1H), 4.16 – 4.06 (m, 0.4H), 3.72 (d, *J* = 9.3 Hz, 3H), 3.68 – 3.34 (m, 4H), 3.27 – 3.22 (m, 0.5H), 3.12 – 2.91 (m, 2H), 2.85 (s, 1H), 2.28 – 1.69 (m, 10H), 0.89 (t, *J* = 4.7 Hz, 3H), 0.76 (dd, *J* = 13.1, 6.6 Hz, 3H).
13C NMR (126 MHz, $CDCl_3$) δ 172.5, 172.0, 171.7, 171.1, 155.9, 155.7, 136.5, 136.5, 130.5, 130.4, 130.2, 128.6, 128.6, 128.3, 128.2, 128.0, 127.6, 115.7, 67.5, 66.8, 61.1, 60.6, 60.1, 56.0, 55.4, 54.0, 53.8, 52.4, 47.7, 47.4, 47.1, 38.5, 31.3, 29.8, 28.8, 27.9, 25.1, 24.7, 24.2, 23.8, 19.6, 17.7.
MS (ESI) 645.3 $[M+Na]^+$
HRMS (ESI): *m/z* calc. for $[C_{33}H_{42}N_4O_8Na]$: 645.2900, found 645.2910.

Preparation of Pentapeptides

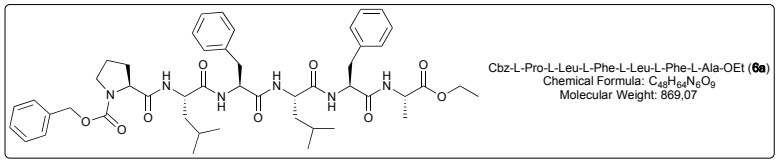


Synthesis of Cbz-D-Phe-L-Pro-L-Val-L-Orn(Boc)-L-Leu-OMe (**5a**) [from **3e** + **2c**]
Scale: 0.10 mmol
Yield: 88% (0.081 g)
Aspect: white crystalline powder – **mp:** 66-68 °C
Rf = 0.64 (100% AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (bs, 0.5H), 7.41 – 7.16 (m, 10H), 6.96 (d, J = 18.8 Hz, 2H), 6.72 (d, J = 53.6 Hz, 1H), 5.61 – 5.45 (m, 0.5H), 5.19 – 4.93 (m, 2H), 4.89 (d, J = 12.4 Hz, 1H), 4.56 (s, 1H), 4.49 – 4.26 (m, 2H), 4.27 – 4.11 (m, 2H), 3.79 (td, J = 9.1, 7.8, 4.0 Hz, 1H), 3.72 (s, 3H), 3.40 (d, J = 43.8 Hz, 1H), 3.16 – 2.92 (m, 3H), 2.77 (s, 1H), 2.60 (s, 1H), 2.39 (s, 1H), 2.06 – 1.49 (m, 10H), 1.49 – 1.29 (m, 9H), 1.13 – 0.72 (m, 12H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 173.2, 172.8, 172.2, 171.6, 157.1, 156.7, 135.8, 129.4, 128.7, 128.6, 128.3, 127.5, 79.6, 67.2, 61.6, 59.9, 55.3, 54.1, 52.4, 50.9, 40.5, 37.6, 29.4, 28.8, 28.5, 28.5, 27.3, 24.9, 24.6, 23.2, 21.7, 19.8, 18.7.
MS (ESI) 859.4 $[M+Na]^+$
HRMS (ESI): *m/z* calc. for $[C_{44}H_{64}N_6O_{10}Na]$: 859.4582, found 859.4563.



Synthesis of Cbz-L-Ala-L-Phe-L-Leu-L-Asp(OtBu)-L-Ala-OMe (**5b**) [from **3a** + **2m**]
Scale: 0.16 mmol
Yield: 89% (0.106 g)
Aspect: white powder – **mp:** 201-202 °C
R_f = 0.54 (100% AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.34 (m, 2H), 7.30 (ddd, *J* = 8.0, 6.3, 2.1 Hz, 4H), 7.20 – 7.12 (m, 3H), 6.87 (m, 1H), 6.79 – 6.67 (m, 1H), 5.29 (dd, *J* = 15.9, 6.9 Hz, 1H), 5.18 (d, *J* = 3.7 Hz, 1H), 5.01 (d, *J* = 12.1 Hz, 1H), 4.92 – 4.82 (m, 1H), 4.78 (d, J = 12.1 Hz, 1H), 4.59 – 4.46 (m, 2H), 4.42 – 4.31 (m, 1H), 4.07 (m, 1H), 3.73 (s, 3H), 3.22 (dd, *J* = 14.5, 5.8 Hz, 1H), 3.08 (dd, *J* = 14.2, 5.8 Hz, 1H), 2.90 (dd, *J* = 16.3, 5.5 Hz, 1H), 2.73 (dd, *J* = 16.2, 8.1 Hz, 1H), 1.82 – 1.62 (m, 3H), 1.55 (ddd, *J* = 14.1, 10.9, 4.4 Hz, 1H), 1.48 – 1.42 (d, *J* = 7.2 Hz, 3H), 1.41 (d, *J* = 1.2 Hz, 9H), 1.36 (d, *J* = 7.2 Hz, 3H), 0.90 (dd, *J* = 12.9, 6.5, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 173.1, 172.1, 171.6, 170.6, 170.3, 156.8, 135.8, 135.5, 129.3, 129.1, 128.8, 128.8, 128.7, 128.1, 128.1, 127.5, 81.3, 67.6, 54.9, 53.0, 52.5, 52.2, 49.9, 48.5, 40.0, 37.4, 36.5, 28.1, 24.7, 23.4, 21.2, 17.9, 17.6.
MS (ESI) 762.3 $[M+Na]^+$
HRMS (ESI): *m/z* calc. for $[C_{38}H_{53}N_5O_{10}Na]$: 762.3690, found 762.3707.

Preparation of Hexapeptides



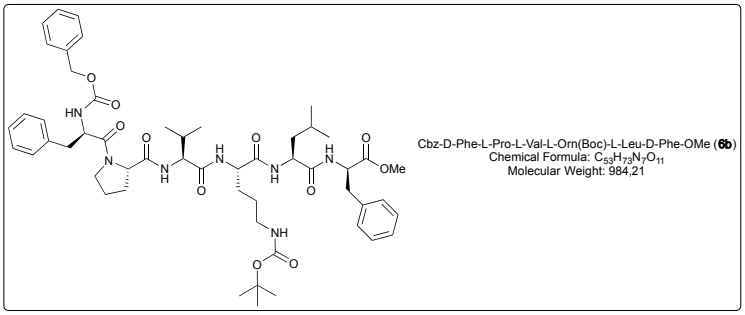
Synthesis of Cbz-L-Pro-L-Leu-L-Phe-L-Leu-L-Phe-L-Ala-OEt (**6a**) [from **4b** + **2p**]
Scale: $4.6.10^{-5}$ mol
Yield: 89% (0.081 g)
Aspect: white powder – **mp:** 210 °C (degradation)
R_f = 0.66 (100% AcOEt) – Cerium Ammonium Molybdate stain
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.05 (m, 15H), 7.00 (bd, *J* = 6.7 Hz, 1H), 6.84 (bd, *J* = 5.9 Hz, 1H), 5.15 (s, 2H), 4.71 (ddd, *J* = 10.7, 8.7, 4.2 Hz, 1H), 4.50 (dq, *J* = 29.0, 7.0, 6.4 Hz, 2H), 4.25 (t, *J* = 7.5 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.11 (dd, *J* = 7.2, 4.4 Hz, 1H), 3.98

(dt, *J* = 8.9, 4.4 Hz, 1H), 3.58 – 3.44 (m, 3H), 3.21 (tt, *J* = 15.1, 8.6 Hz, 1H), 2.93 (dd, *J* = 14.2, 10.8 Hz, 1H), 2.03 – 1.83 (m, 4H), 1.68 (s, 6H), 1.58 (t, *J* = 6.6 Hz, 2H), 1.46 (d, *J* = 7.3 Hz, 3H), 1.40 (d, *J* = 5.3 Hz, 3H), 1.32 – 1.22 (m, 3H), 0.98 – 0.76 (m, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 173.2, 172.6, 172.4, 172.0, 171.2, 157.0, 138.4, 136.4, 135.9, 129.5, 129.1, 128.9, 128.9, 128.7, 128.2, 128.0, 127.3, 126.3, 68.1, 61.3, 60.7, 55.1, 54.7, 54.4, 53.5, 48.6, 47.4, 40.0, 39.2, 37.0, 36.1, 28.1, 25.0, 24.9, 24.7, 23.3, 22.9, 21.7, 20.9, 17.8, 14.3.

MS (ESI) 891.4 $[M+Na]^+$

HRMS (ESI): m/z calc. for $[C_{48}H_{64}N_6O_9Na]$: 891.4633, found 891.4626.



Synthesis of Cbz-D-Phe-L-Pro-L-L-Orn(Boc)-L-Leu-D-Phe-OMe (**6b**)

This hexapeptide was obtained with a [5a +H-D-Phe-OMe] coupling step procedure.

Scale: $7.8.10^{-5}$ mol

Yield: 75% (0.057 g)

Aspect: white powder – **mp:** 82-84 °C

Rf = 0.64 (100% AcOEt) – Cerium Ammonium Molybdate stain

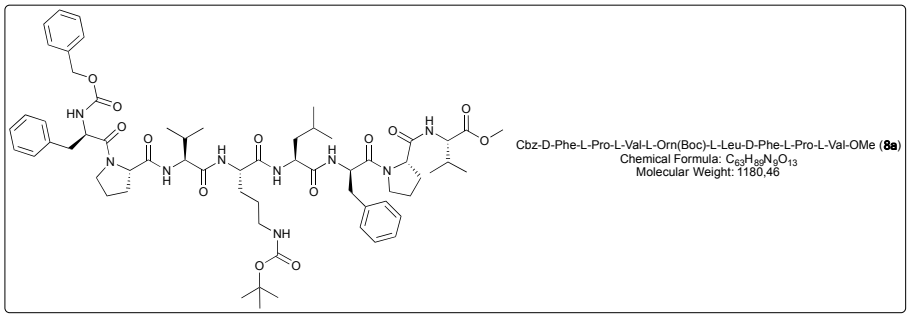
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (bd, *J* = 5.9 Hz, 1H), 7.41 – 7.15 (m, 15H), 7.09 (bd, *J* = 8.4 Hz, 1H), 6.83 (bd, *J* = 7.1 Hz, 1H), 5.73 – 5.64 (m, 1H), 5.05 (d, *J* = 12.1 Hz, 1H), 4.95 – 4.82 (m, 1H), 4.66 (q, *J* = 7.5 Hz, 1H), 4.50 – 4.35 (m, 3H), 4.11 (dddt, *J* = 26.1, 20.7, 13.9, 7.0 Hz, 4H), 3.89 – 3.74 (m, 1H), 3.62 (s, 3H), 3.48 (d, *J* = 15.6 Hz, 1H), 3.14 (ddd, *J* = 26.3, 14.3, 7.8 Hz, 4H), 2.90 (td, *J* = 10.7, 8.3, 4.5 Hz, 1H), 2.68 (dd, *J* = 20.8, 12.2 Hz, 1H), 2.24 (ddd, *J* = 27.9, 14.8, 6.7 Hz, 1H), 2.11 – 1.54 (m, 15H), 1.51 – 1.25 (m, 9H), 1.02 (t, *J* = 6.5 Hz, 6H), 0.90 (d, *J* = 6.6 Hz, 6H).

13C NMR (101 MHz, $CDCl_3$) δ 173.2, 173.2, 173.2, 172.1, 157.3, 136.9, 135.8, 135.7, 135.5, 129.4, 129.2, 128.6, 128.6, 128.6, 128.4, 128.3, 128.1, 127.9, 127.4, 126.6, 67.1, 66.9, 61.8, 61.5, 60.9, 54.4, 52.3, 52.0, 50.9, 47.4, 40.6, 40.4, 39.4, 37.7, 37.3, 37.1, 29.7, 29.3, 28.8, 28.3, 25.1, 24.8, 24.6, 23.3, 23.1, 21.5, 21.1, 19.6.

MS (ESI) 1006.5 $[M+Na]^+$

HRMS (ESI): m/z calc. for $[C_{53}H_{73}N_7O_{11}Na]$: 1006.5266, found 1006.5281.

Prepapration of Octapeptides



Synthesis of Cbz-D-Phe-L-Pro-L-L-Orn(Boc)-L-Leu-D-Phe-L-Pro-L-Val-OMe (**8a**) [from **6a** + **2i**]

Scale: $4.1.10^{-5}$ mol

Yield: 86% (0.049 g)

Aspect: white powder – **mp:** 75-76 °C

Rf = 0.44 (100% AcOEt) – Cerium Ammonium Molybdate stain

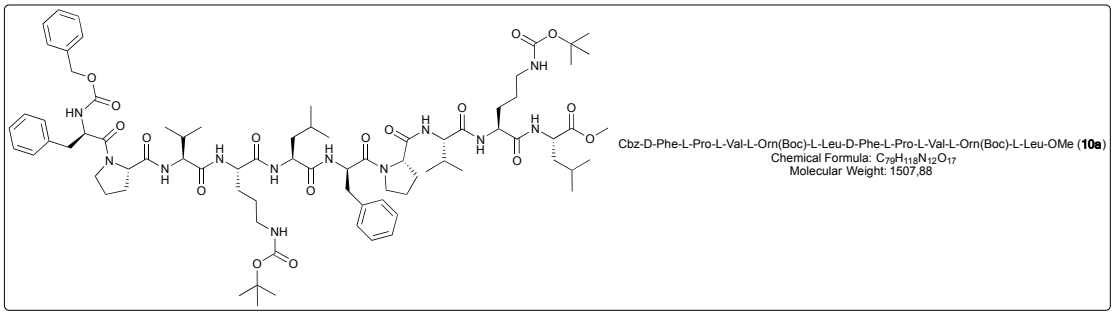
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (bs, 1H), 7.49 (bs, 1H), 7.42 (bs, 1H), 7.35 – 7.11 (m, 15H), 6.93 – 6.74 (bd, 2H), 4.97 (d, *J* = 12.2 Hz, 2H), 4.91 – 4.70 (m, 2H), 4.44 – 4.25 (m, 3H), 4.19 (dd, *J* = 8.5, 6.7 Hz, 1H), 4.04 (ddd, *J* = 15.7, 12.1, 7.7 Hz, 2H), 3.74 (s, 1H), 3.67 – 3.53 (m, 3H), 3.46 (d, *J* = 8.7 Hz, 1H), 3.17 – 2.95 (m, 4H), 2.86 (d, *J* = 11.9 Hz, 1H), 2.68 – 2.51 (m, 1H), 2.30 (td, *J* = 9.8, 7.0 Hz, 1H), 2.19 – 2.04 (m, 3H), 2.00 – 1.45 (m, 14H), 1.26 (d, *J* = 7.2 Hz, 12H), 1.02 – 0.74 (m, 15H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 173.3, 173.1, 172.4, 172.3, 171.8, 171.7, 171.5, 157.4, 156.6, 135.9, 135.7, 129.7, 129.7, 129.4, 128.8, 128.7, 128.5, 128.5, 128.4, 128.2, 127.6, 127.1, 79.8, 67.1, 61.9, 60.4, 58.4, 57.9, 56.2, 55.6, 54.2, 52.1, 52.0, 47.6, 46.8, 40.7, 39.7, 37.6, 31.0, 30.2, 29.8, 28.5, 25.3, 24.8, 24.1, 23.6, 21.3, 19.8, 19.5, 18.9.

MS (ESI) 1202.7 $[M+Na]^+$

HRMS (ESI): m/z calc. for $[C_{63}H_{89}N_9O_{13}Na]$: 1202.6477, found 1202.6478.

Preparation of the Decapeptide



Synthesis of Cbz-D-Phe-L-Pro-L-Val-L-Orn(Boc)-L-Leu-D-Phe-L-Pro-L-Val-L-Orn(Boc)-L-Leu-OMe (**10a**) [from **8a** + **2c**]

Scale: $2.3.10^{-5}$ mol

Yield: 82% (0.028 g)

Aspect: white powder – **mp:** 170-172 °C

Rf = 0.74 (100% AcOEt) – Cerium Ammonium Molybdate stain

^{1}H NMR (400 MHz, MeOD) δ 7.54 (m, 0.5H), 7.31 – 7.05 (m, 15H), 6.63 – 6.43 (m, 1H), 5.08 – 4.91 (m, 2H), 4.60 (dd, *J* = 9.2, 6.6 Hz, 1H), 4.56 – 4.40 (m, 1H), 4.36 (dd, *J* = 10.0, 5.0 Hz, 2H), 4.22 (ddd, *J* = 24.2, 8.6, 4.6 Hz, 4H), 4.14 – 3.94 (m, 3H), 3.61 (s, 5H), 3.55 – 3.38 (m, 2H), 3.12 – 2.81 (m, 8H), 2.81 – 2.58 (m, 2H), 2.19 – 2.00 (m, 2H), 1.85 – 1.40 (m, 22H), 1.34 (s, 15H), 1.28 – 1.09 (m, 5H), 0.95 – 0.74 (m, 24H).

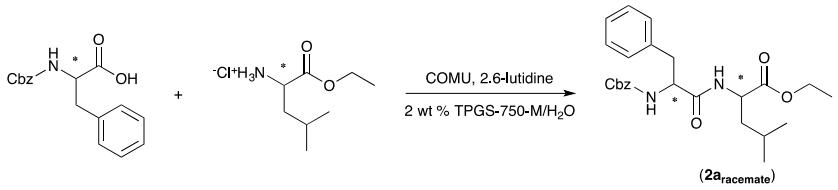
^{13}C NMR (101 MHz, MeOD) δ 174.4, 174.3, 174.2, 173.3, 173.3, 173.3, 173.3, 173.1, 173.1, 159.6, 158.6, 137.7, 130.6, 130.5, 130.2, 129.6, 129.5, 129.5, 129.4, 129.1, 128.9, 128.6, 128.2, 80.0, 61.9, 60.8, 55.0, 54.2, 52.7, 52.1, 41.3, 41.0, 38.6, 31.0, 30.3, 30.1, 28.8, 27.4, 25.8, 25.4, 23.5, 22.3, 21.8, 21.7, 19.8, 19.0, 14.5.

MS (ESI) 1529.9 $[M+Na]^+$

HRMS (ESI): m/z calc. for $[C_{79}H_{118}N_{12}O_{17}Na]$: 1529.8635, found 1529.8611.

5. Racemization studies

a. Racemate



Synthesis of *Z*-DL-Phe-DL-Leu-OEt (2a$_{racemate}$)

To a microwave vial were added Cbz-DL-Phe-OH (1.0 equiv) and HCl•DL-Leu-OEt (1.0 equiv) in a 2 wt % solution of TPGS-750-M/H_2O [0.5 M], followed by 2.6-lutidine (3.05 equiv). After 5 min, COMU (1.05 equiv) was added. The reaction was stirred at rt until completion. The product was extracted with EtOAc (10 mL). The organic layer was washed with a solution of HCl 1 M (2 x 5 mL), with a saturated solution of sodium carbonate (2 x 5 mL) and brine (1 x 5 mL). The solution was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield the desired peptide. The product **2a$_{racemate}$** was purified by flash chromatography on silica with a gradient starting from 100% hexanes to a 1:1 ratio of hexanes/EtOAc. The product (0.75 mg/mL) was then analyzed by chiral HPLC at an absorbance of 210 nm. The method ran at 1.25 mL/min using 5% v/v isopropanol/hexanes through a Lux 5u Cellulose-2 (250 x 4.6 mm) column. The ratio between the two couples of enantiomers is 60:40 (determined by ^{1}H NMR).

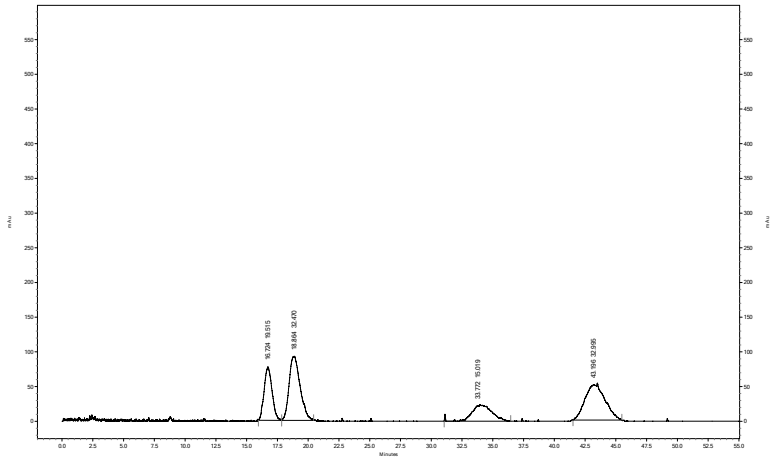
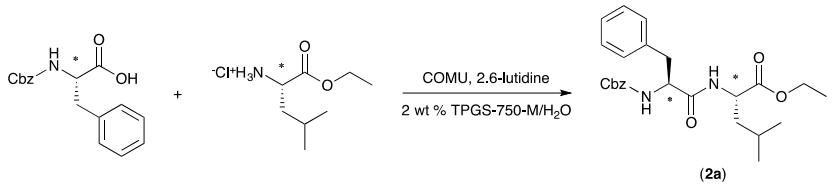


*Figure 3 : Chiral HPLC spectra of Cbz-DL-Phe-DL-Le-OEt (**2a$_{racemate}$**)*

	Peak 1	Peak 2	Peak 3	Peak 4
Time (min)	16.724	18.864	33.772	43.196
Area (%)	19.515	32.470	15.019	32.995

a. Coupling step



Compound **2a** obtained by the coupling between Cbz-L-Phe-OH and HCl•L-Leu-OEt was analyzed with the same method at a concentration of 0.75 mg/mL. One peak was identified at 16.692 min. The enantiomeric excess is > 99%.

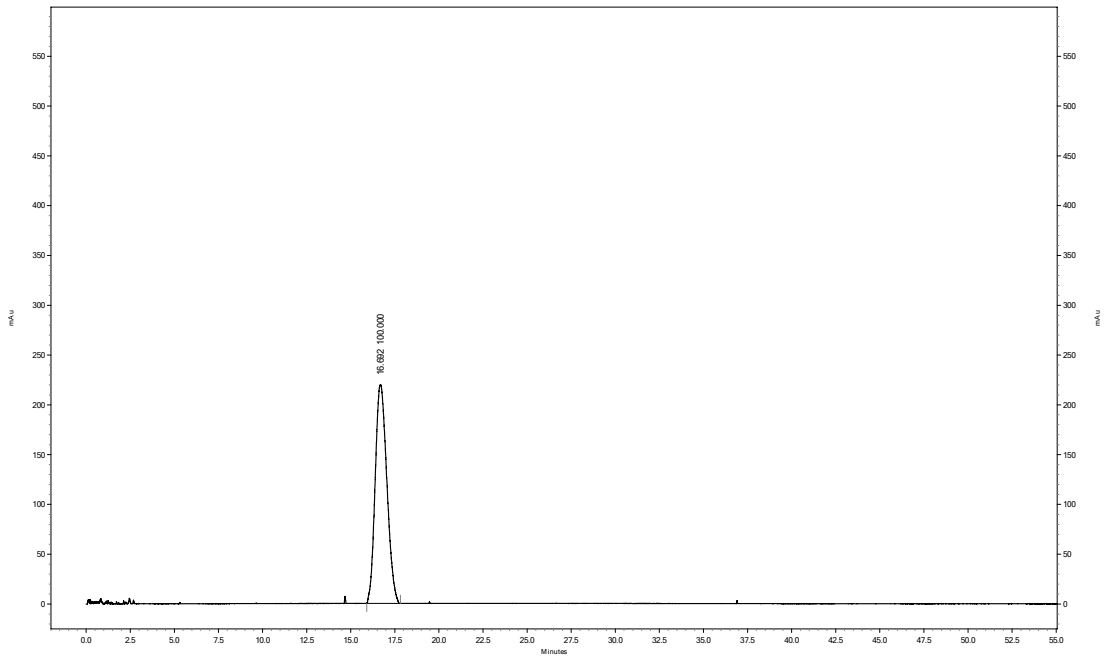
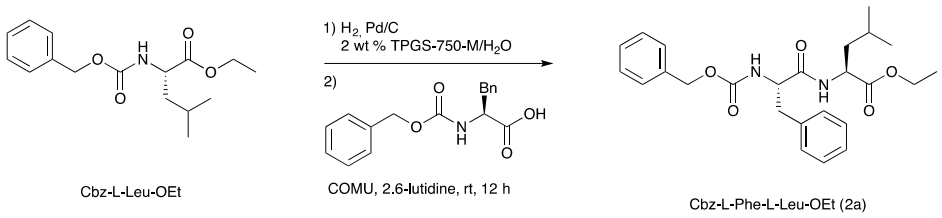


*Figure 4 : Chiral HPLC spectra of Cbz-L-Phe-L-Leu-OEt (**2a**)- coupling step*

	Peak 1
Time (min)	16.692
Area (%)	100

b. Tandem deprotection/coupling step



Compound **2a** obtained by the deprotection of Cbz-L-Leu-OEt followed by, in a 1-pot fashion, coupling with Cbz-L-Phe-OH which was analyzed with the same method at a concentration of 0.75 mg/mL. One peak was identified at 16.800 min. The enantiomeric excess is > 99%.

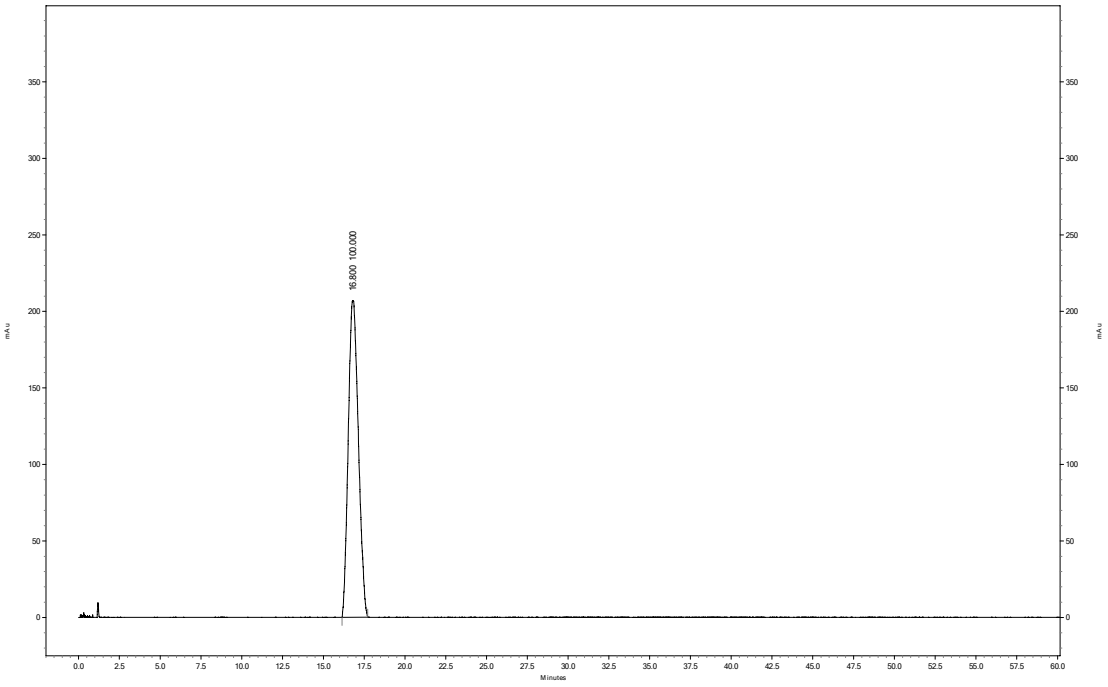
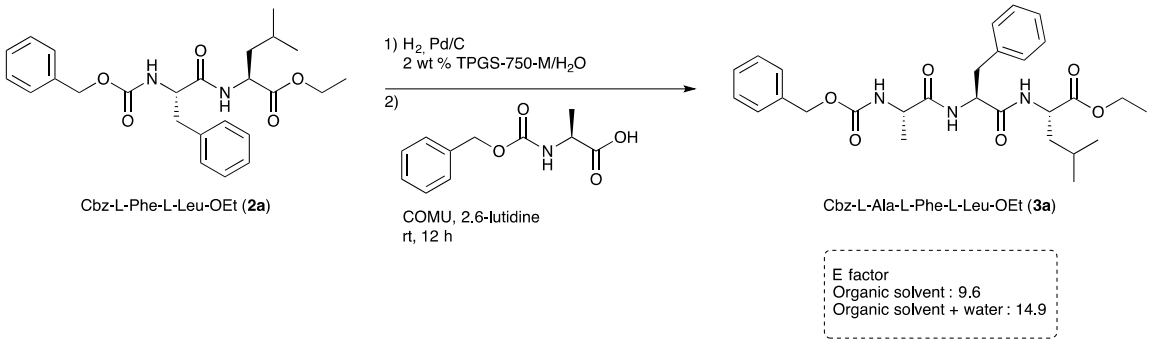


*Figure 5 : Chiral HPLC spectra of Cbz-L-Phe-L-Leu-OEt (**2a**) obtained by tandem deprotection/coupling step*

	Peak 1
Time (min)	16.800
Area (%)	100

6. E Factors



To a microwave vial was added Cbz-L-Phe-L-Leu-OEt **2a** (1.86 g, 4.06 mmol, 1.1 equiv) followed by $Pd/C_{10\%}$ (0.186 g, 10 wt %) in a 2 wt % solution of TPGS-750-M/H_2O [8.1 mL, 0.5 M]. The vial was purged twice with hydrogen gas (balloon) and kept under H_2 atmosphere for 2 h at rt. The vial was purged with argon for 0.5 h. Cbz-L-Ala-OH (0.78 g, 3.5 mmol, 1.0 equiv) and COMU (1.57 g, 3.7 mmol, 3.05 equiv) were added. After 5 min, 2.6-lutidine (1.2 mL, 10.7 mmol, 3.05 equiv) was added and the reaction was stirred overnight at rt. The product was then filtered through a pad of Celite® and extracted with MTBE (20 mL). The organic layer was washed with a solution of HCl (1 M) and then with a saturated solution of sodium carbonate. The solution was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield the desired peptide **3a** as a white powder with a global yield of 86 % (1.53 g).

E_{factor} calculation (organic solvent):

$$E_{factor} = \frac{m_{solvent}}{m_{product}} = \frac{20 \times 0.74}{1.534} = 9.6$$

E_{factor} calculation (organic solvent + water):

$$E_{factor} = \frac{m_{solvent}}{m_{product}} = \frac{20 \times 0.74 + 8.1}{1.534} = 14.9$$

7. ^{1}H and ^{13}C NMR spectral analyses

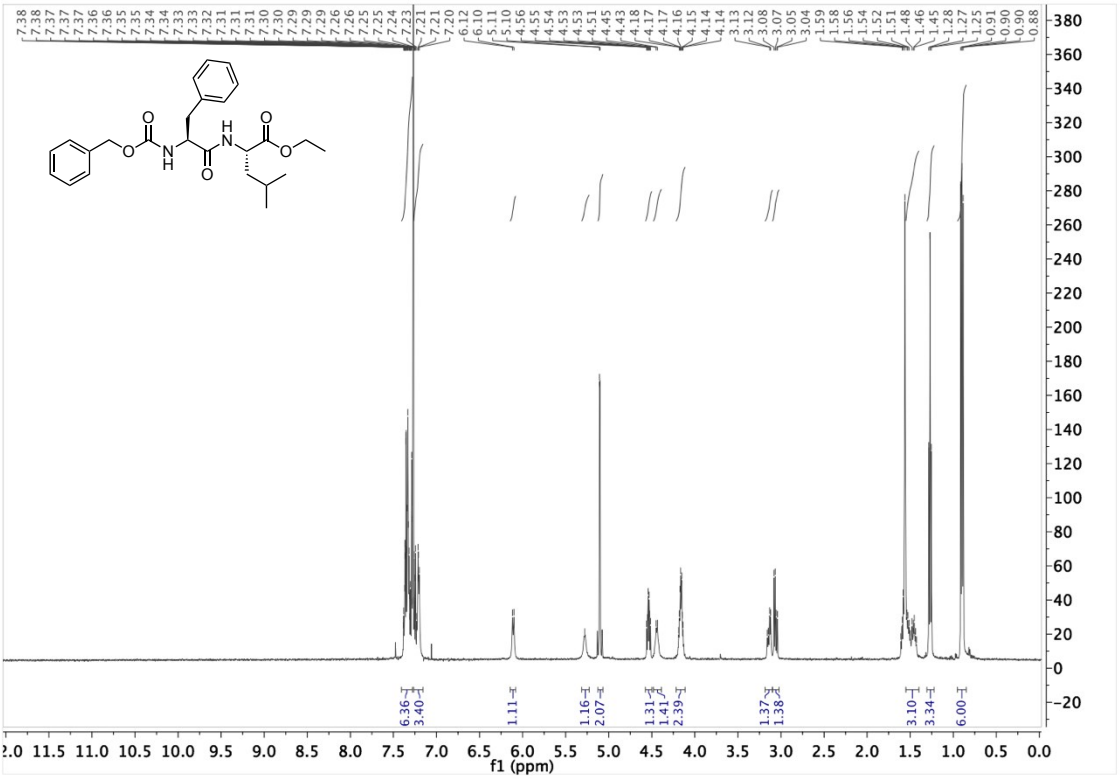


*Figure 6 : NMR ^{1}H of Cbz-L-Phe-L-Leu-OEt (**2a**)*

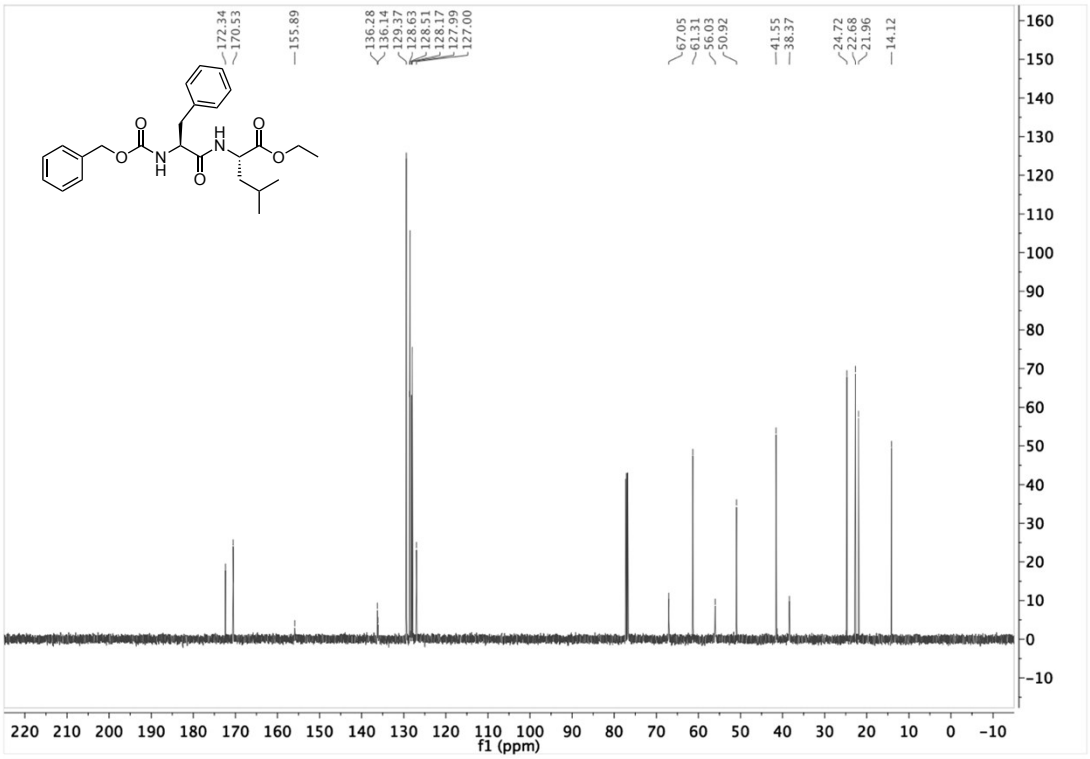


*Figure 7 : NMR ^{13}C of Cbz-L-Phe-L-Leu-OEt (**2a**)*

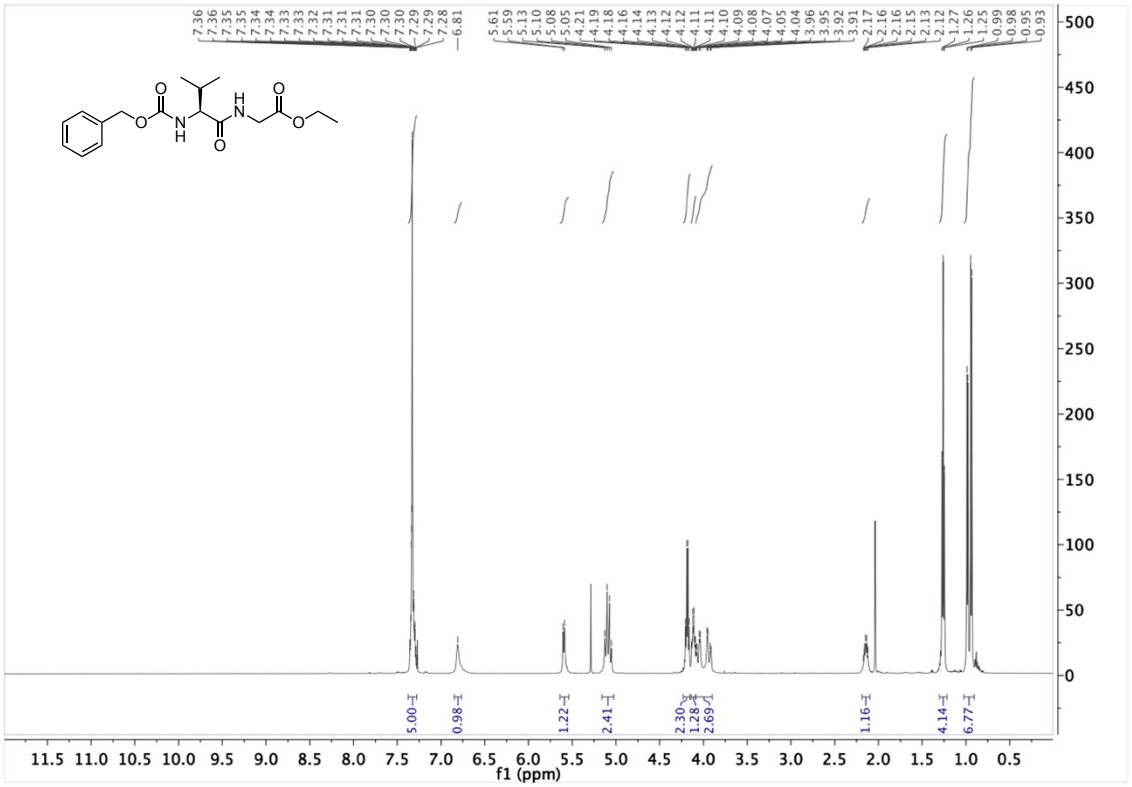


*Figure 8 : NMR [1]H of Cbz-L-Val-Gly-OEt (**2b**)*

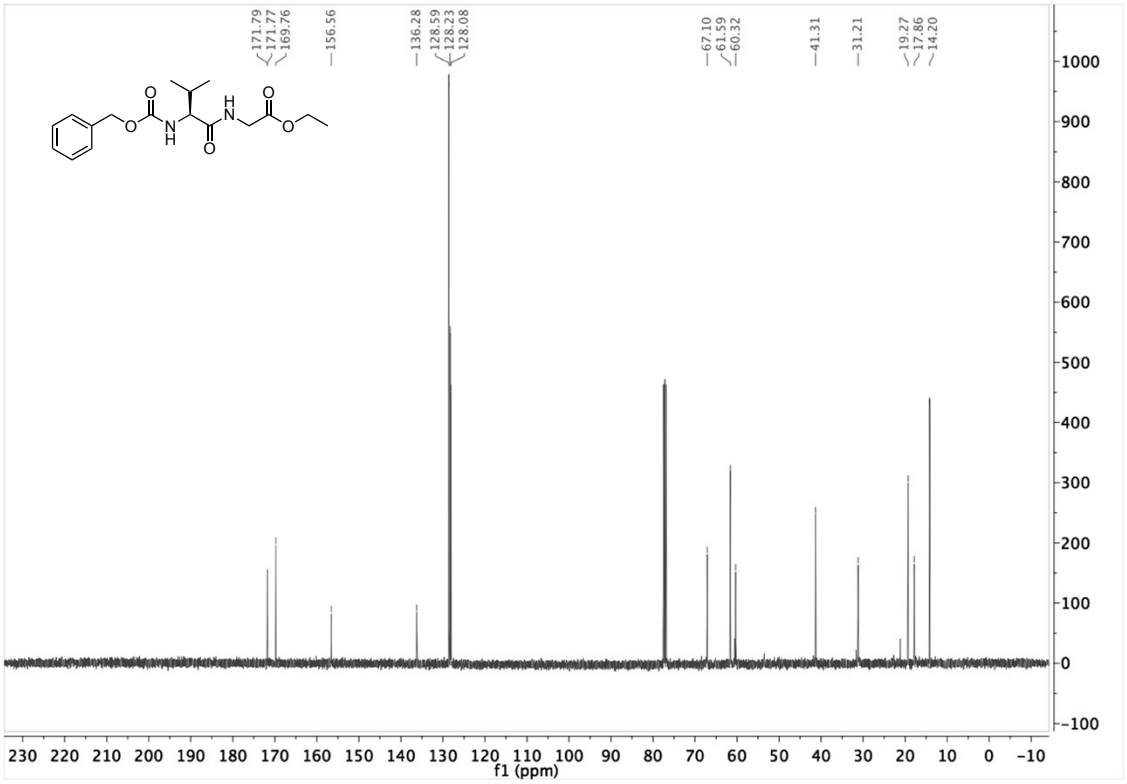


*Figure 9 : NMR [13]C of Cbz-L-Val-Gly-OEt (**2b**)*

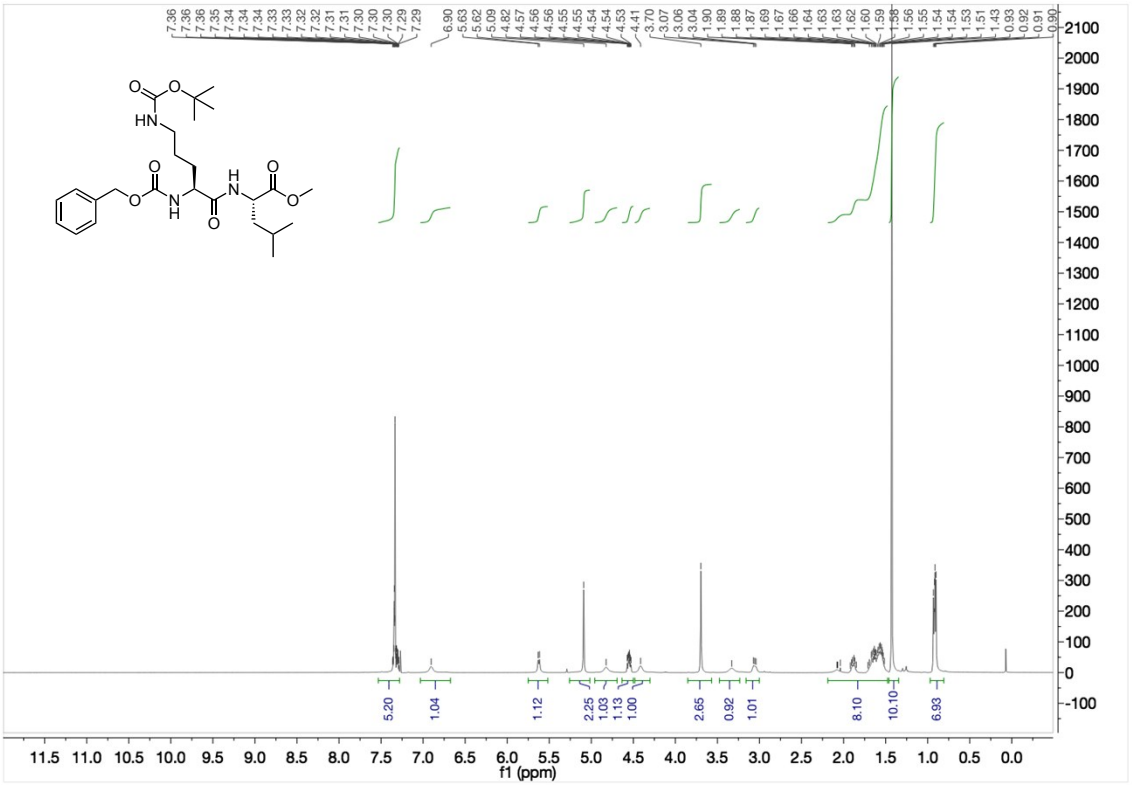


*Figure 10 : NMR ^{1}H of Cbz-L-Orn(Boc)-L-Leu-OMe (**2c**)*

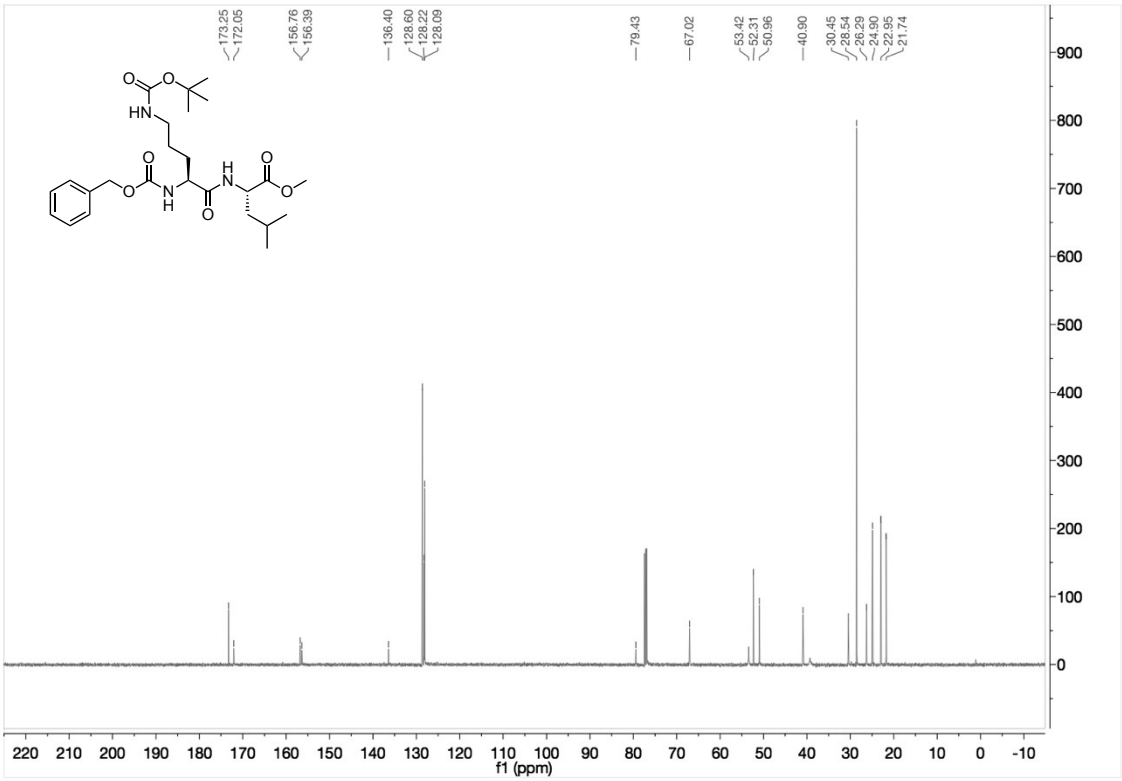


*Figure 11 : NMR ^{13}C of Cbz-L-Orn(Boc)-L-Leu-OMe (**2c**)*

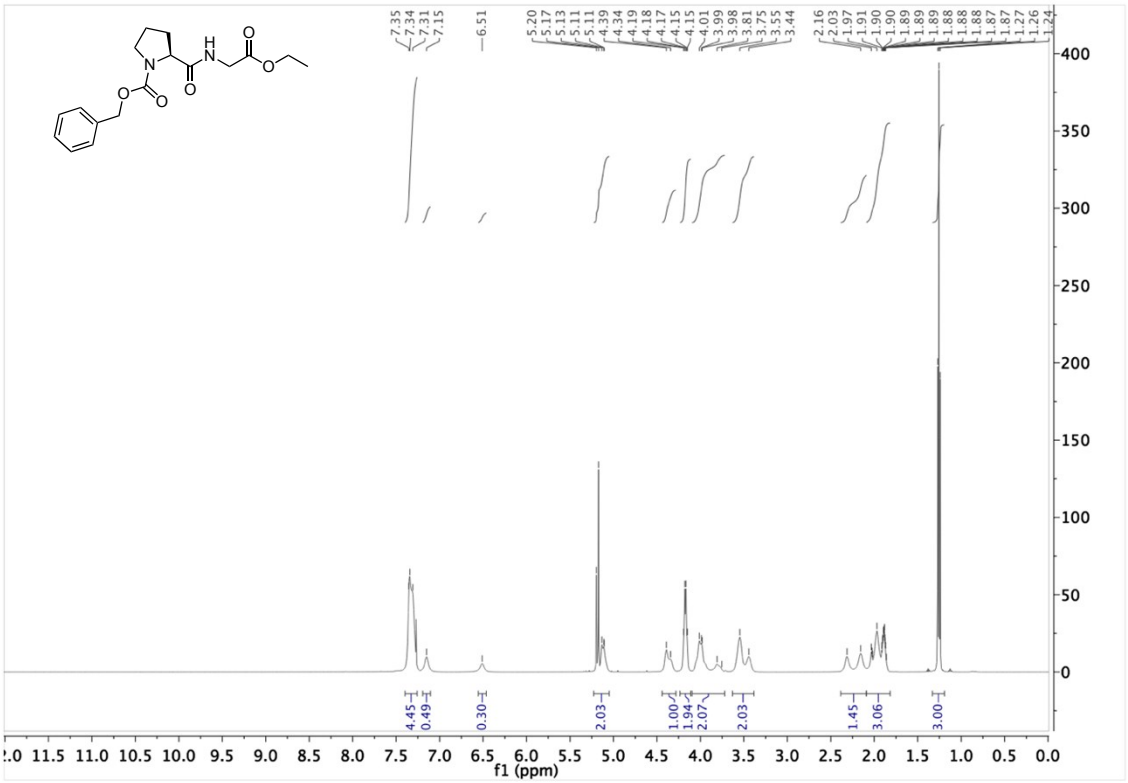


*Figure 12 : NMR [1]H of Cbz-Pro-Gly-OEt (**2d**)*

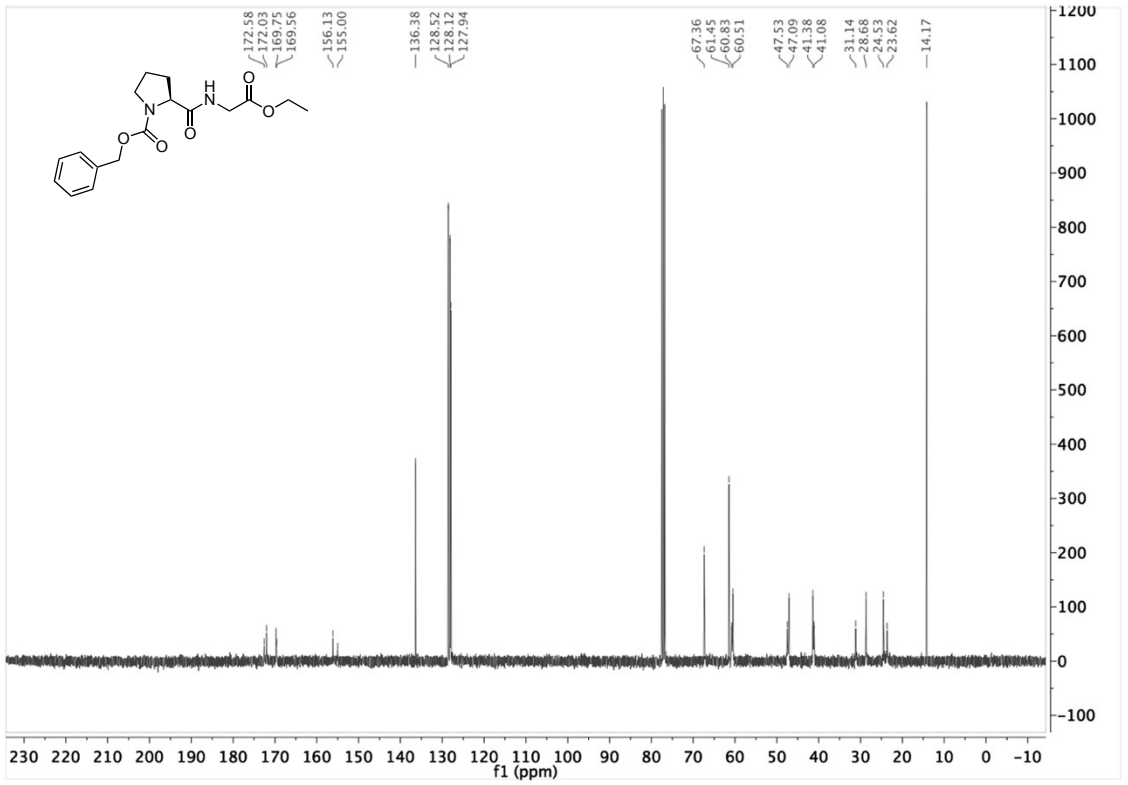


*Figure 13 : NMR [13]C of Cbz-L-Pro-Gly-OEt (**2d**)*

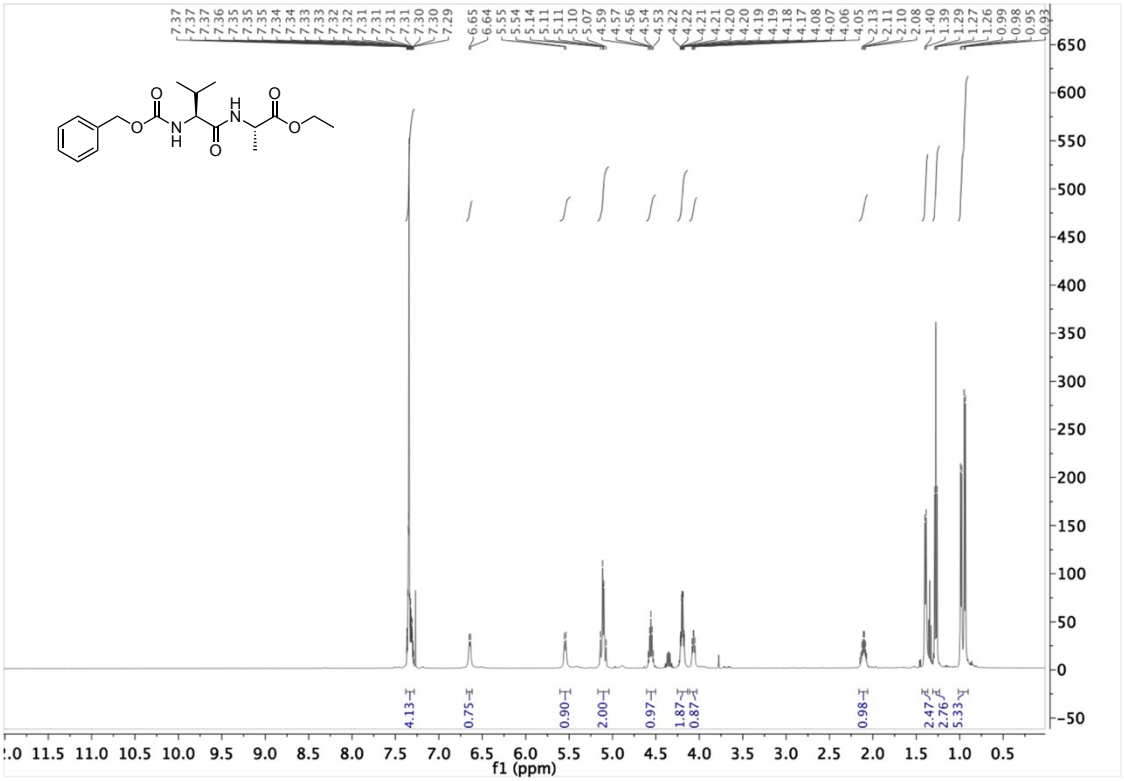


*Figure 14 : NMR ^{1}H of Cbz-L-Val-L-Ala-OEt (**2e**)*

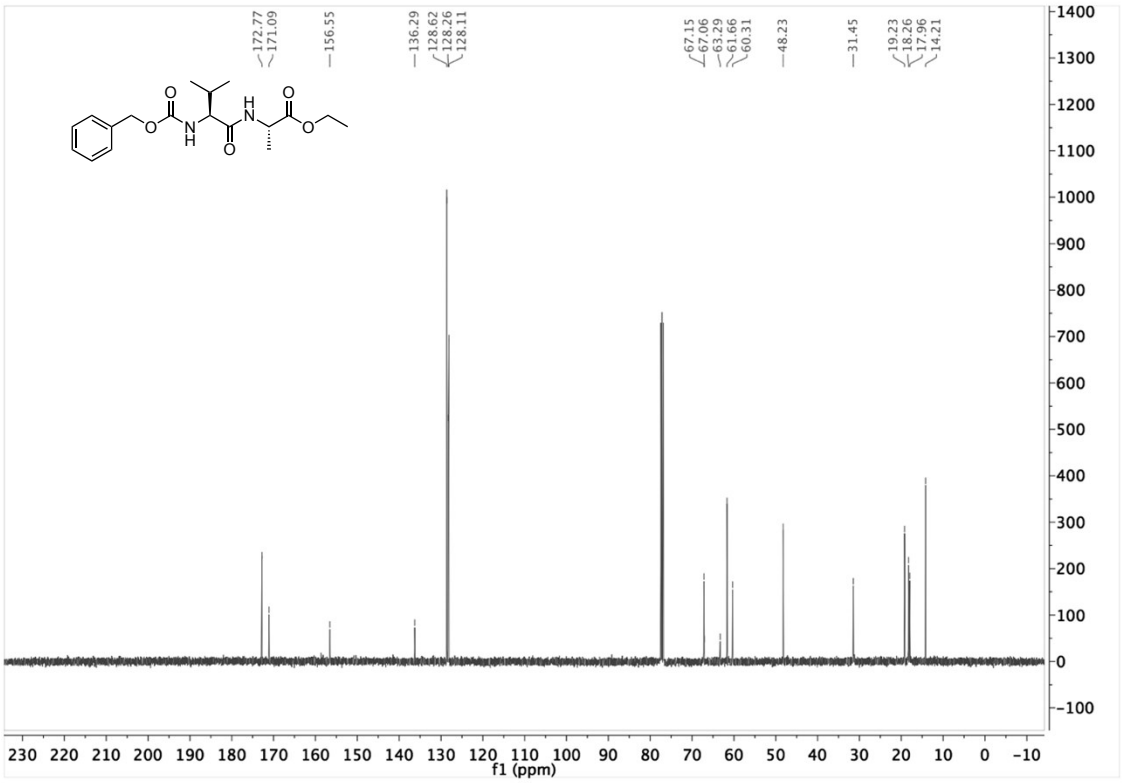


*Figure 15 : NMR ^{13}C of Cbz-L-Val-L-Ala-OEt (**2e**)*

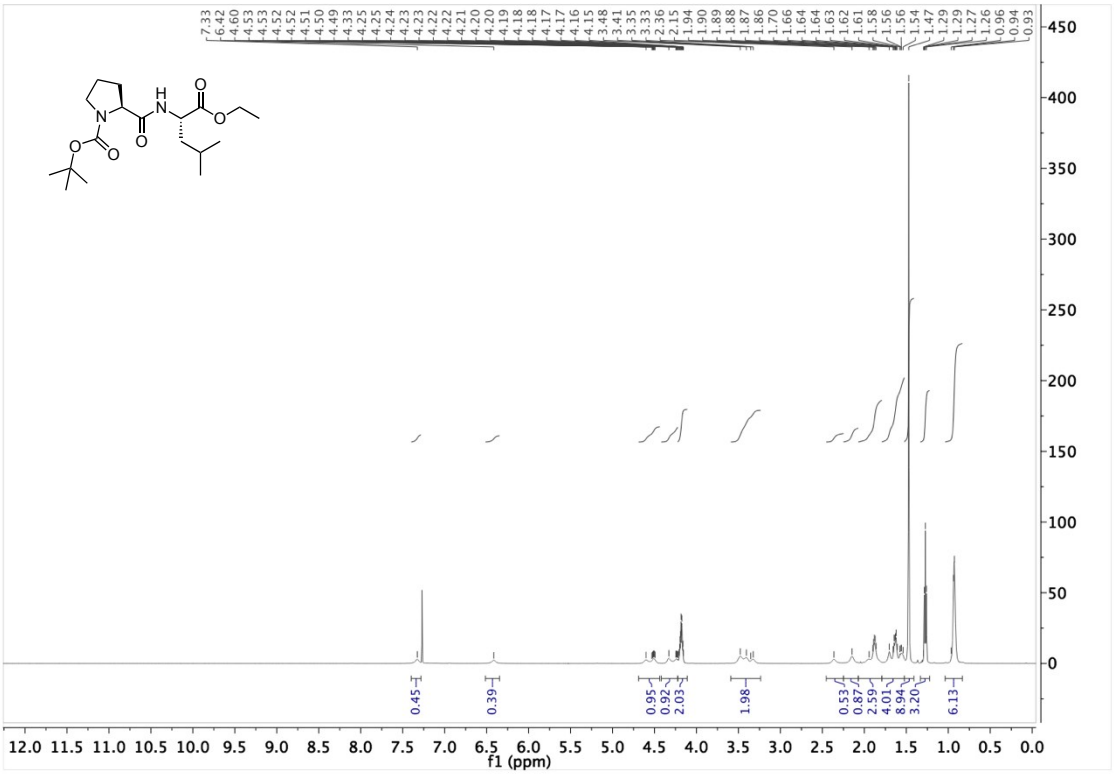


*Figure 16 : NMR ^{1}H of Boc-L-Pro-L-Leu-OEt (**2f**)*

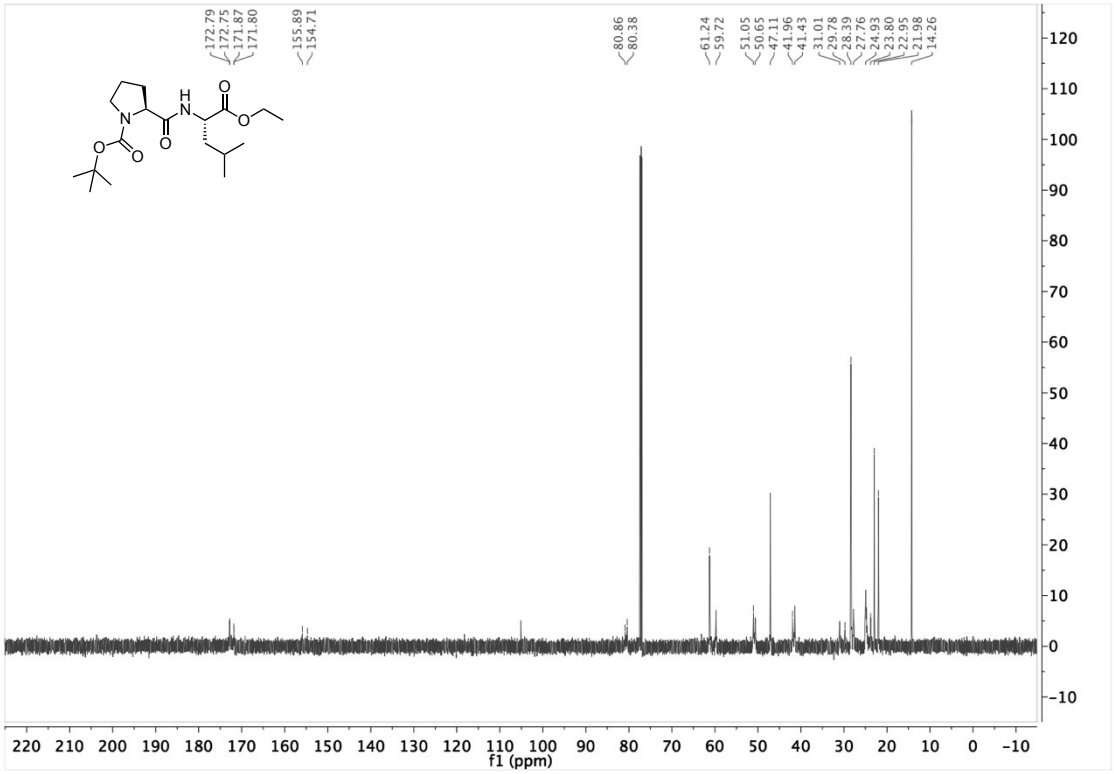


*Figure 17 : NMR ^{13}C of Boc-L-Pro-L-Leu-OEt (**2f**)*

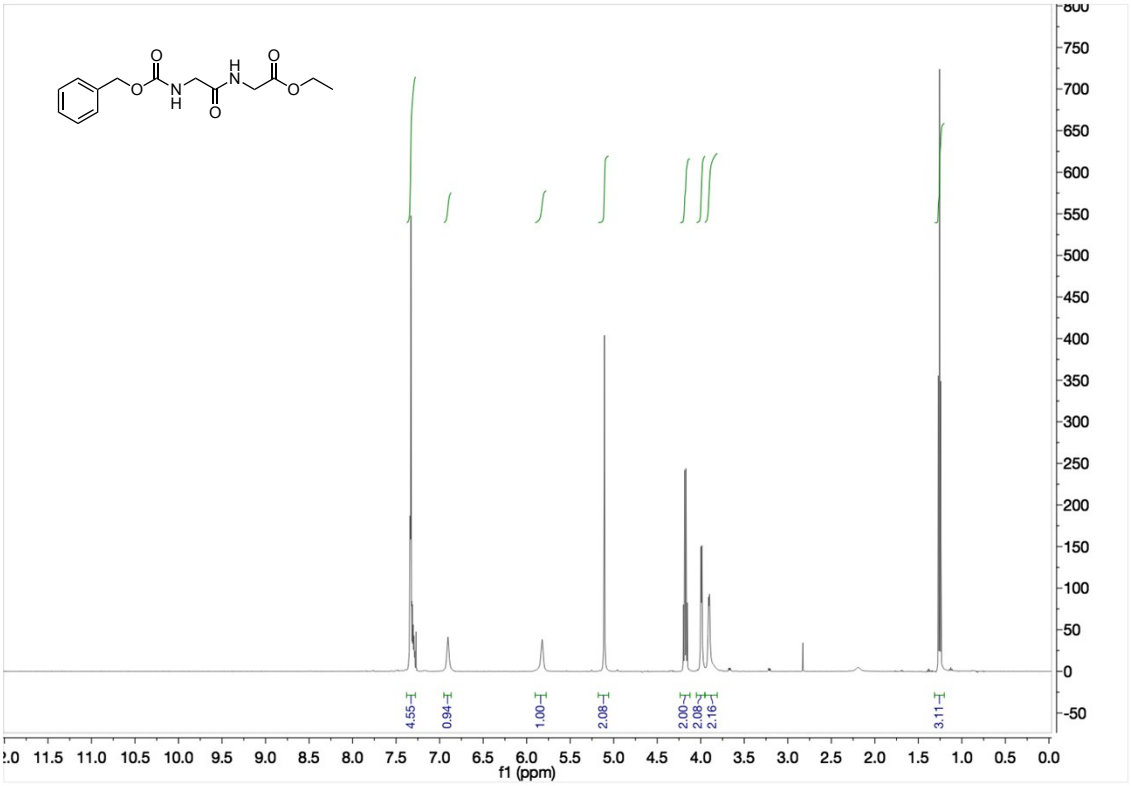


*Figure 18 : NMR ^{1}H of Cbz-Gly-Gly-OEt (**2g**)*

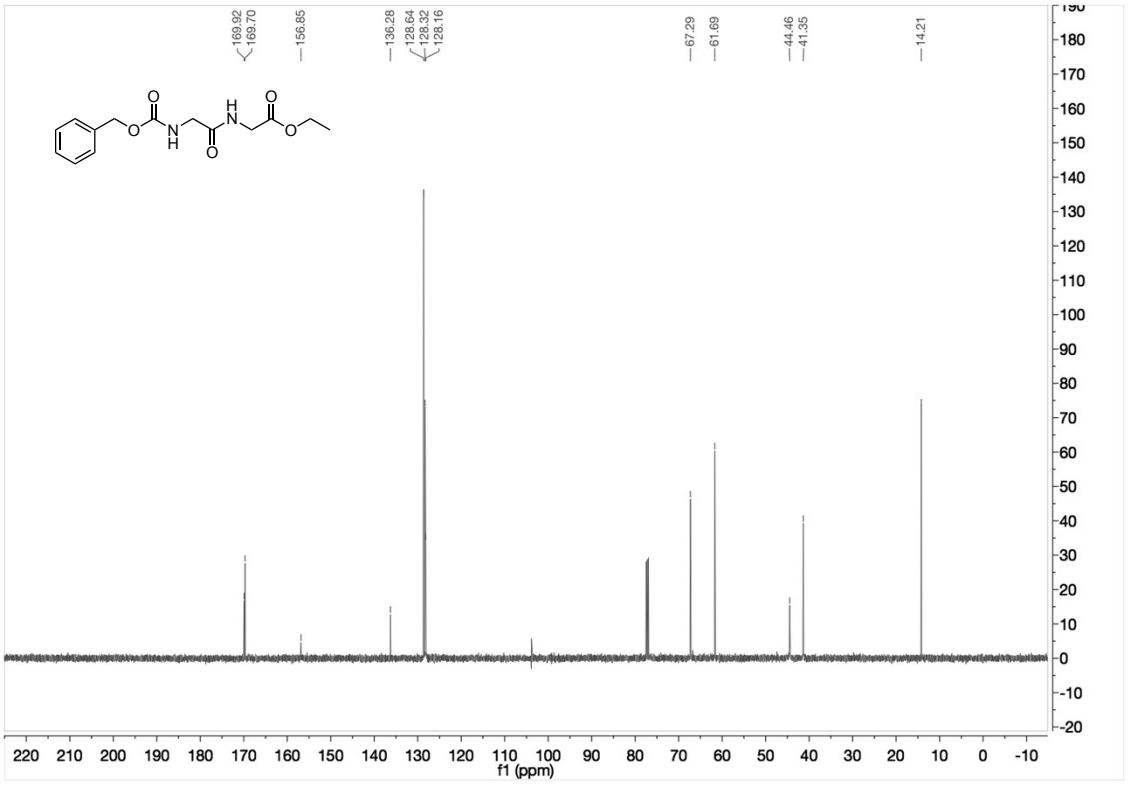


*Figure 19 : NMR ^{13}C of Cbz-Gly-Gly-OEt (**2g**)*

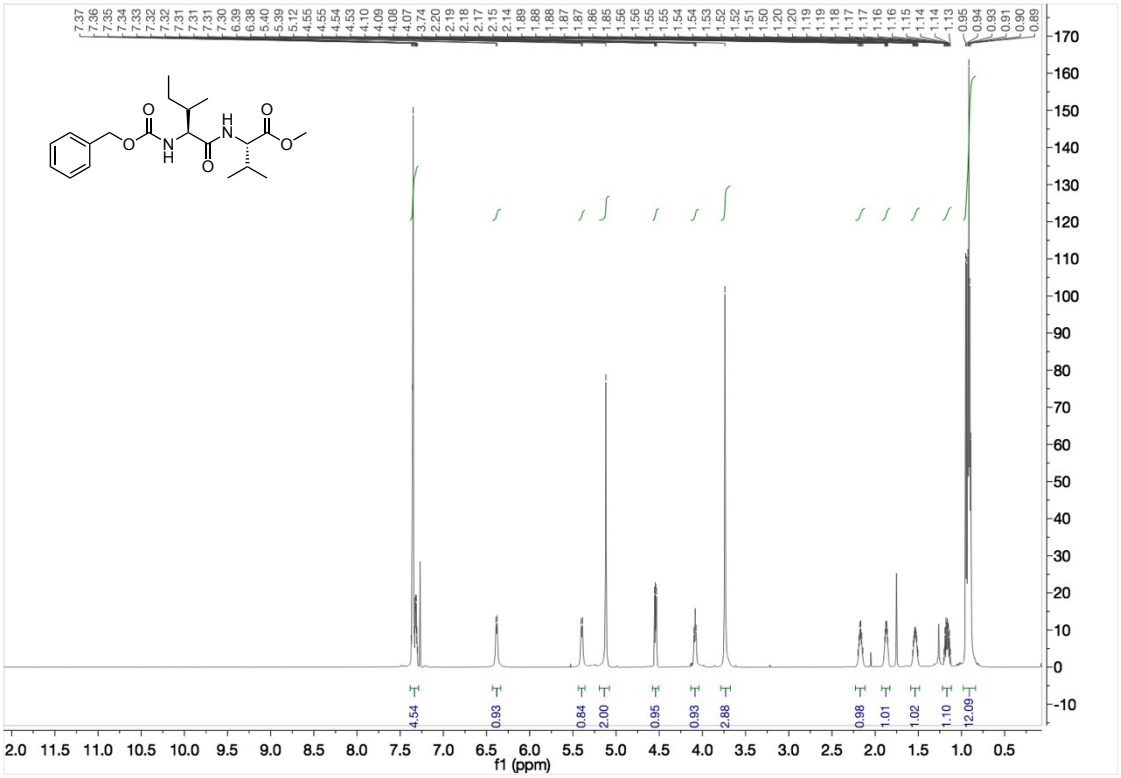


*Figure 20 : NMR ^{1}H of Cbz-L-Ile-L-Val-OMe (**2h**)*

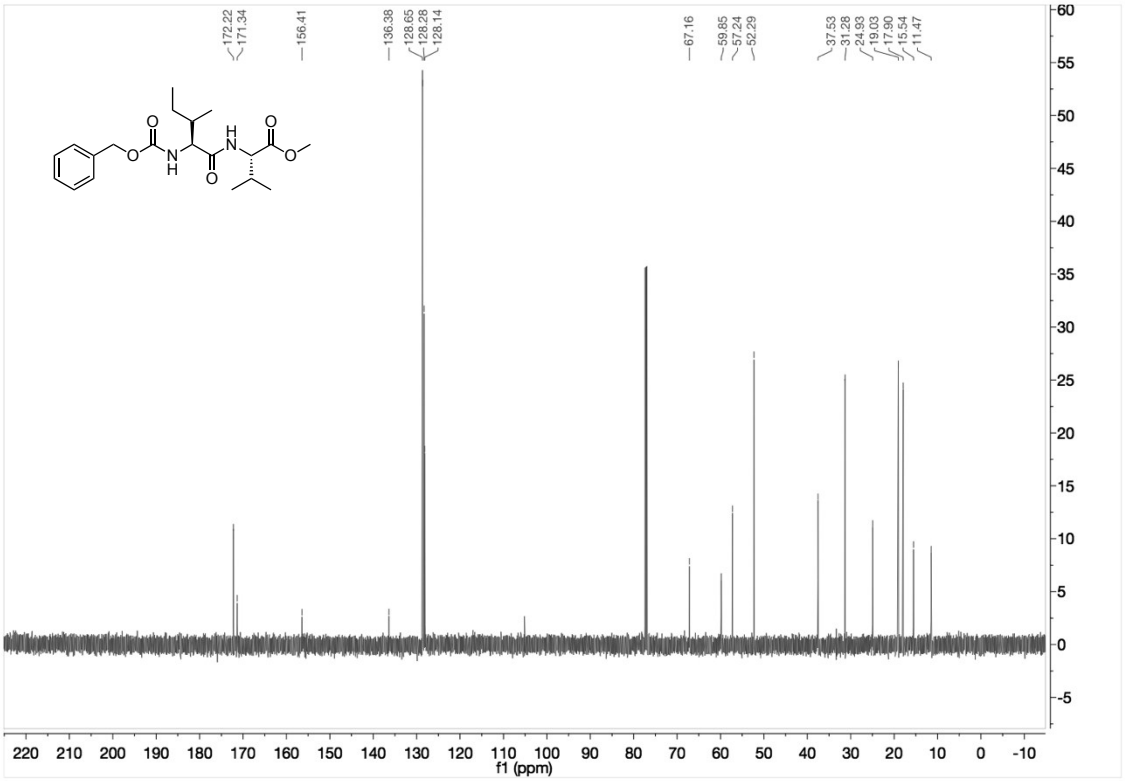


*Figure 21 : NMR ^{13}C of Cbz-L-Ile-L-Val-OMe (**2h**)*

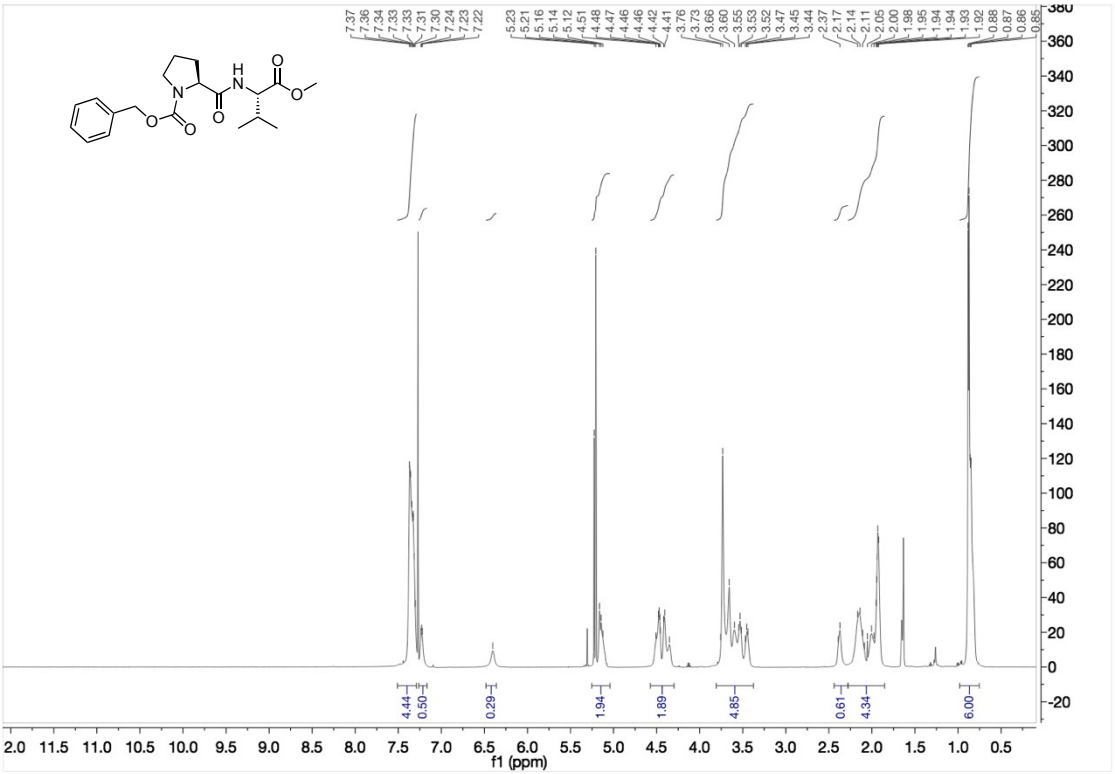


*Figure 22 : NMR ^{1}H of Cbz-L-Pro-L-Val-OMe (**2i**)*

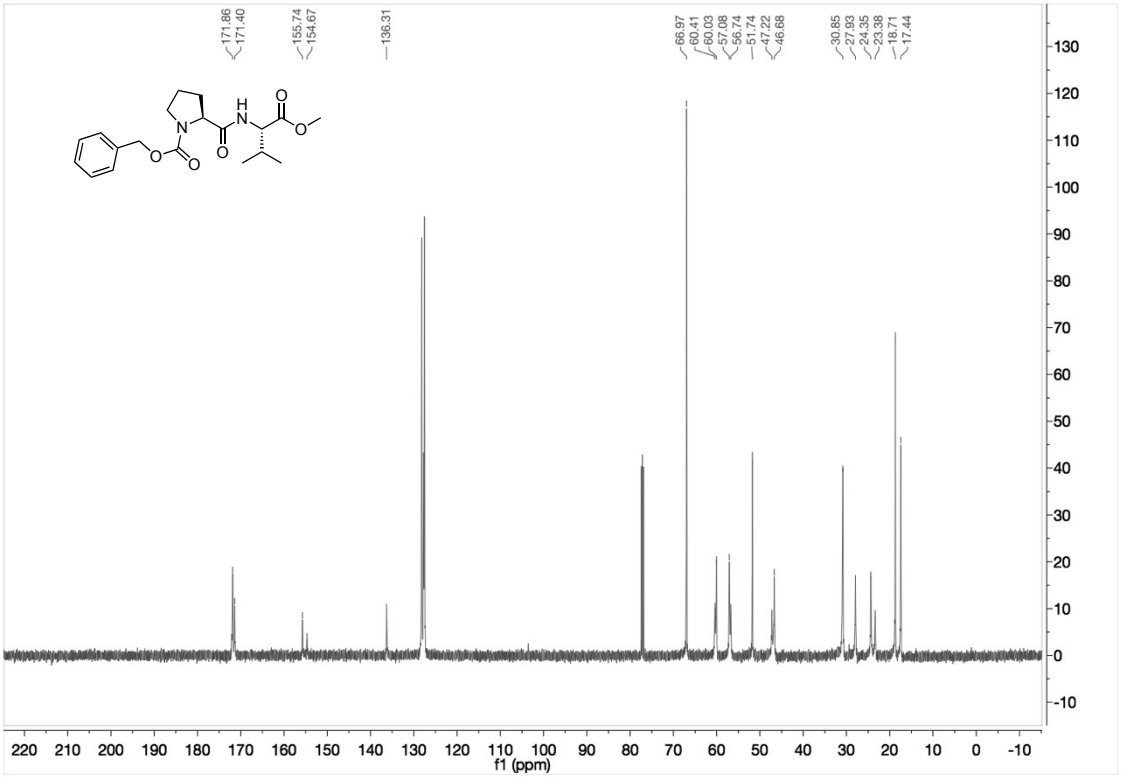


*Figure 23 : NMR ^{13}C of Cbz-L-Pro-L-Val-OMe (**2i**)*

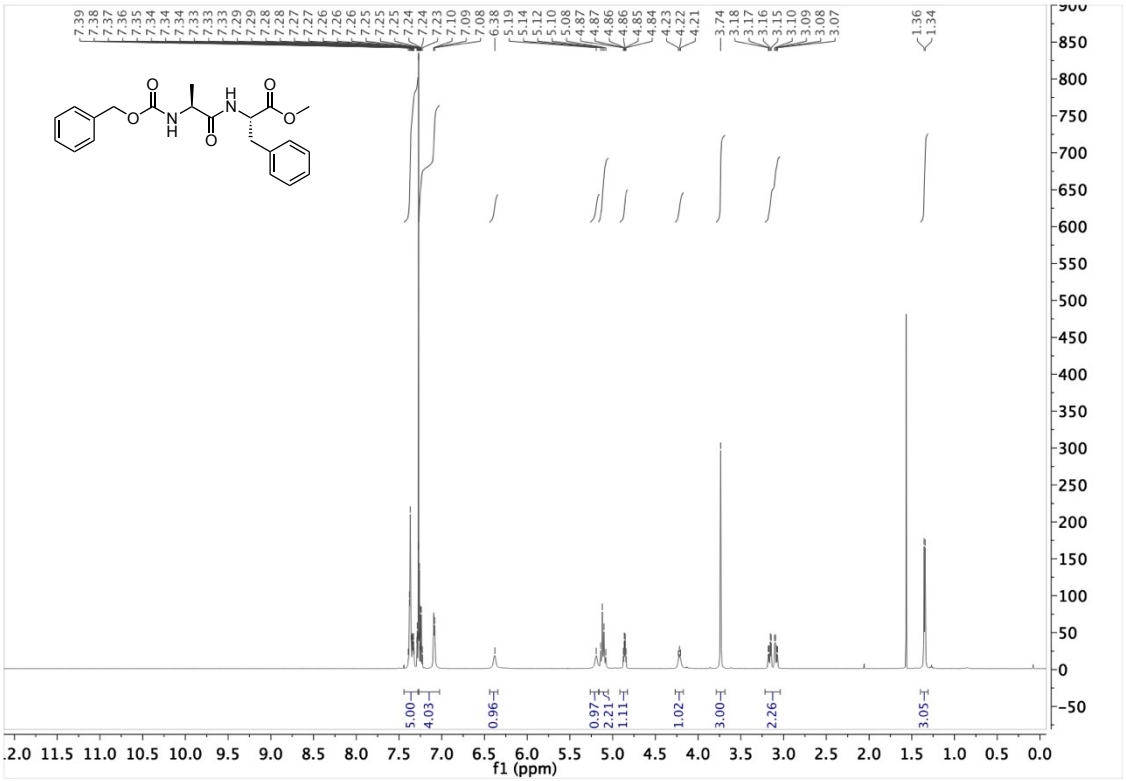


*Figure 24 : NMR ^{1}H of Cbz-L-Ala-L-Phe-OMe (**2j**)*

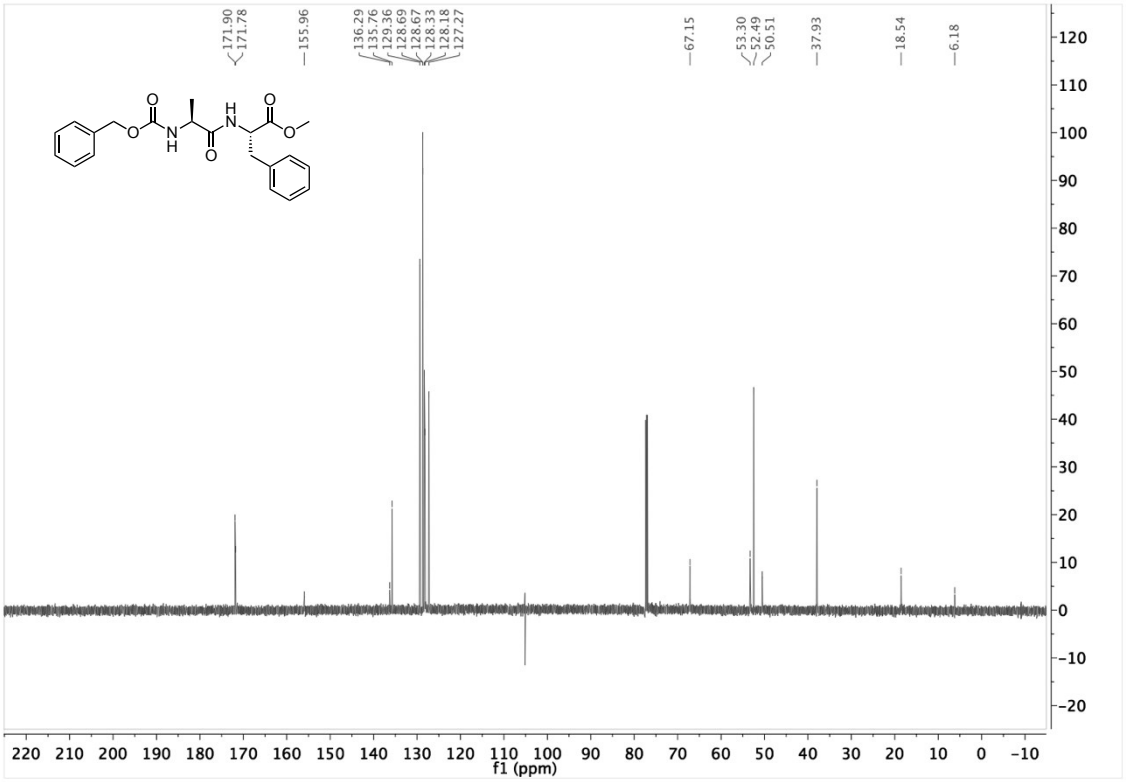


*Figure 25 : NMR ^{13}C of Cbz-L-Ala-L-Phe-OMe (**2j**)*

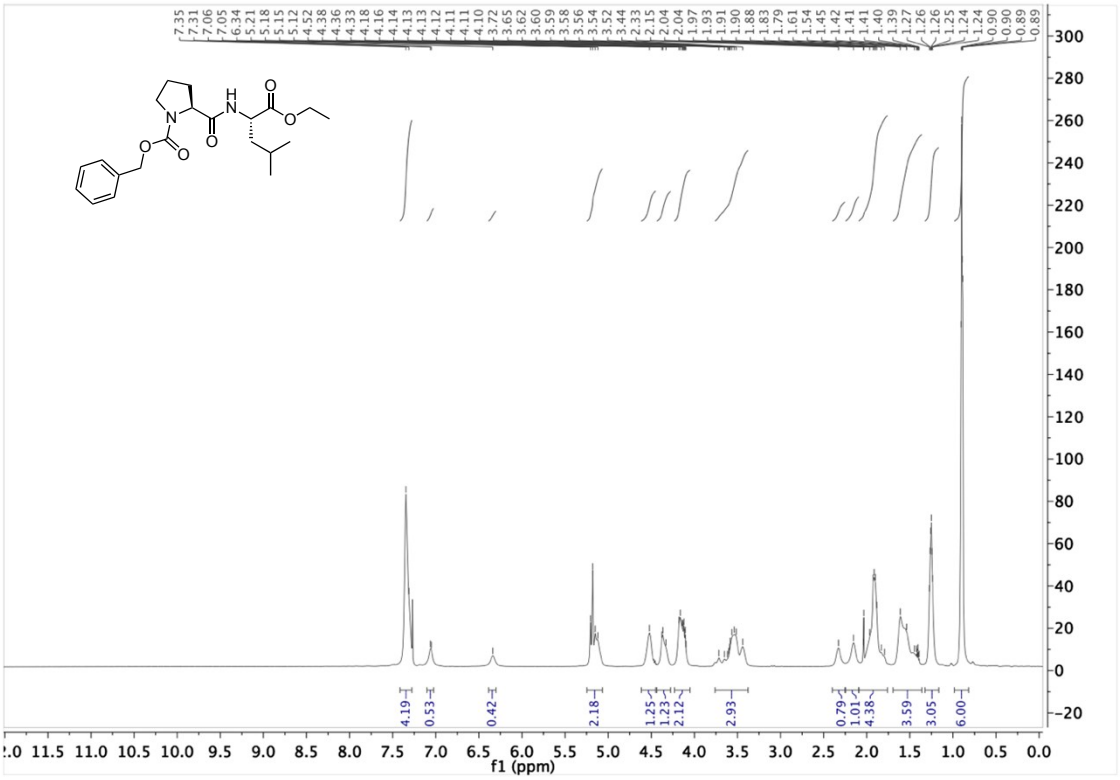


*Figure 26 : NMR ^{1}H of Cbz-L-Pro-L-Leu-OEt (**2k**)*

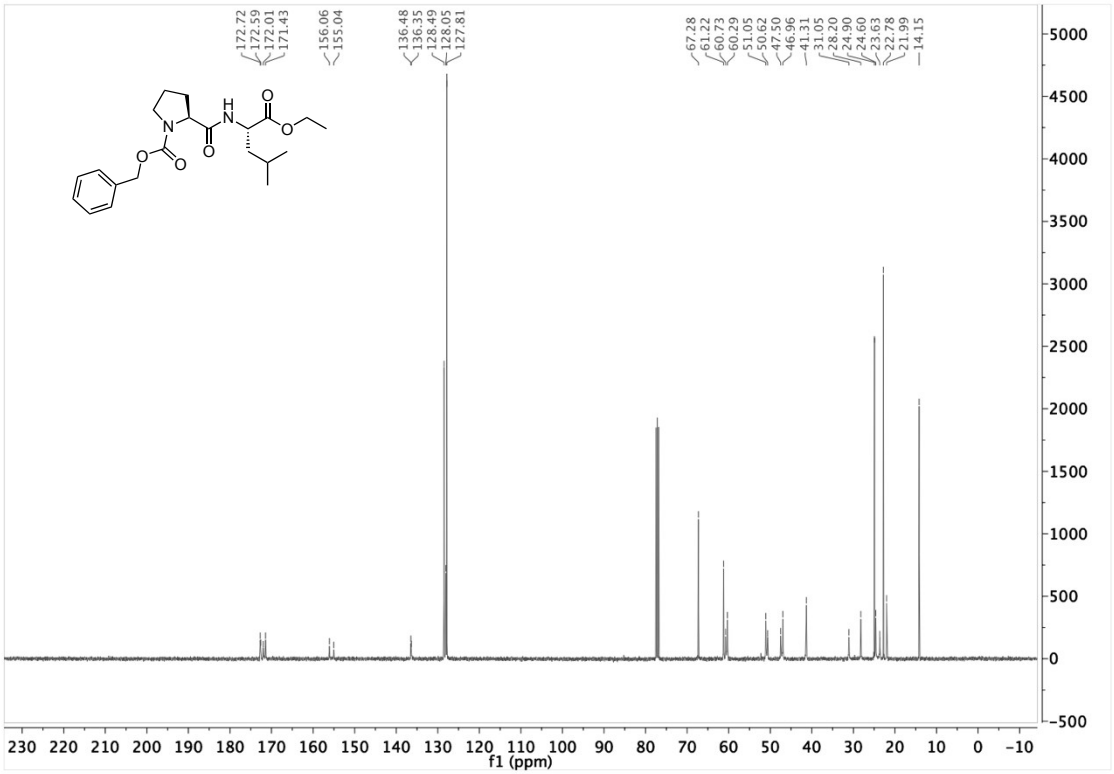


*Figure 27 : NMR ^{13}C of Cbz-L-Pro-L-Leu-OEt (**2k**)*

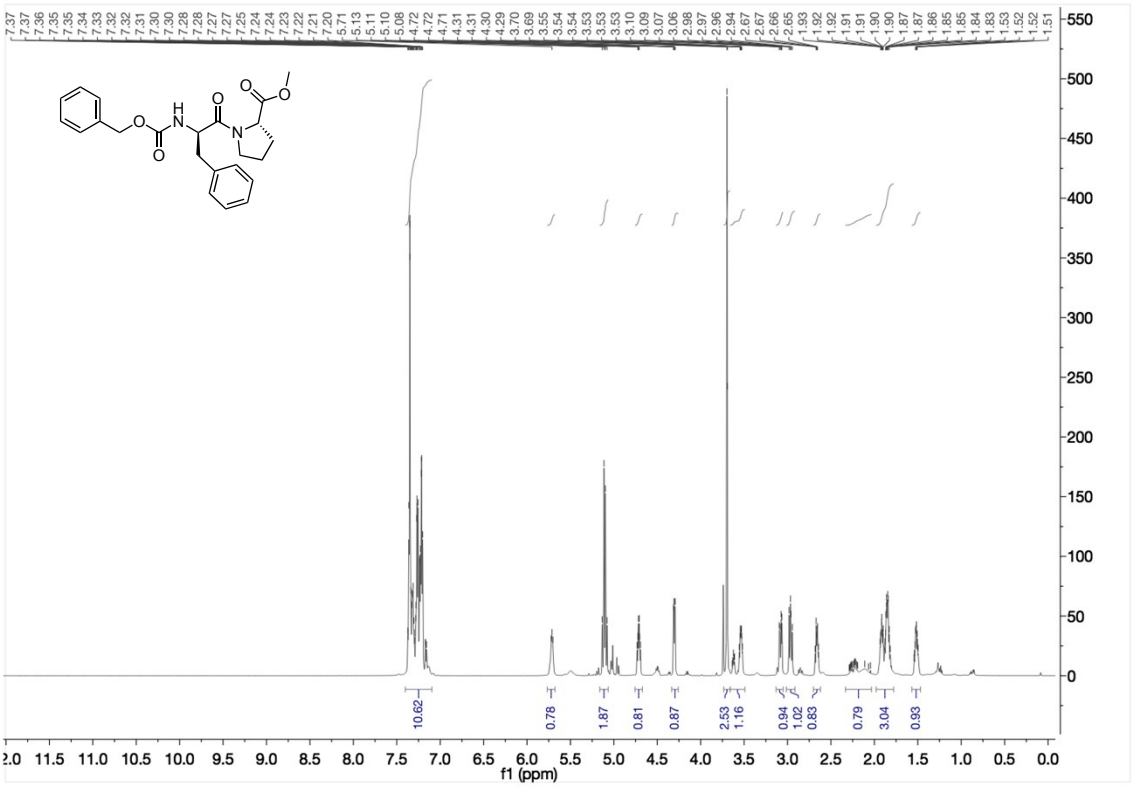


*Figure 28: NMR ^{1}H of Cbz-D-Phe-L-Pro-OMe (**2l**)*

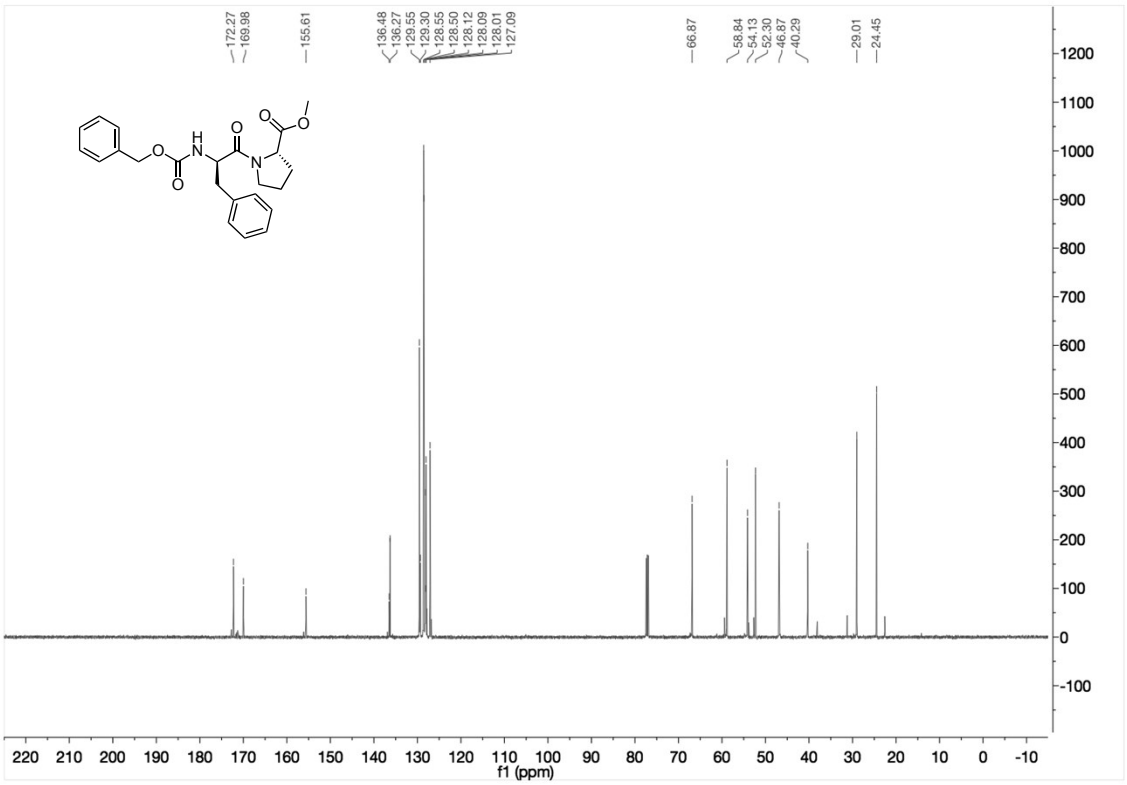


*Figure 29 : NMR ^{13}C of Cbz-D-Phe-L-Pro-OMe (**2l**)*

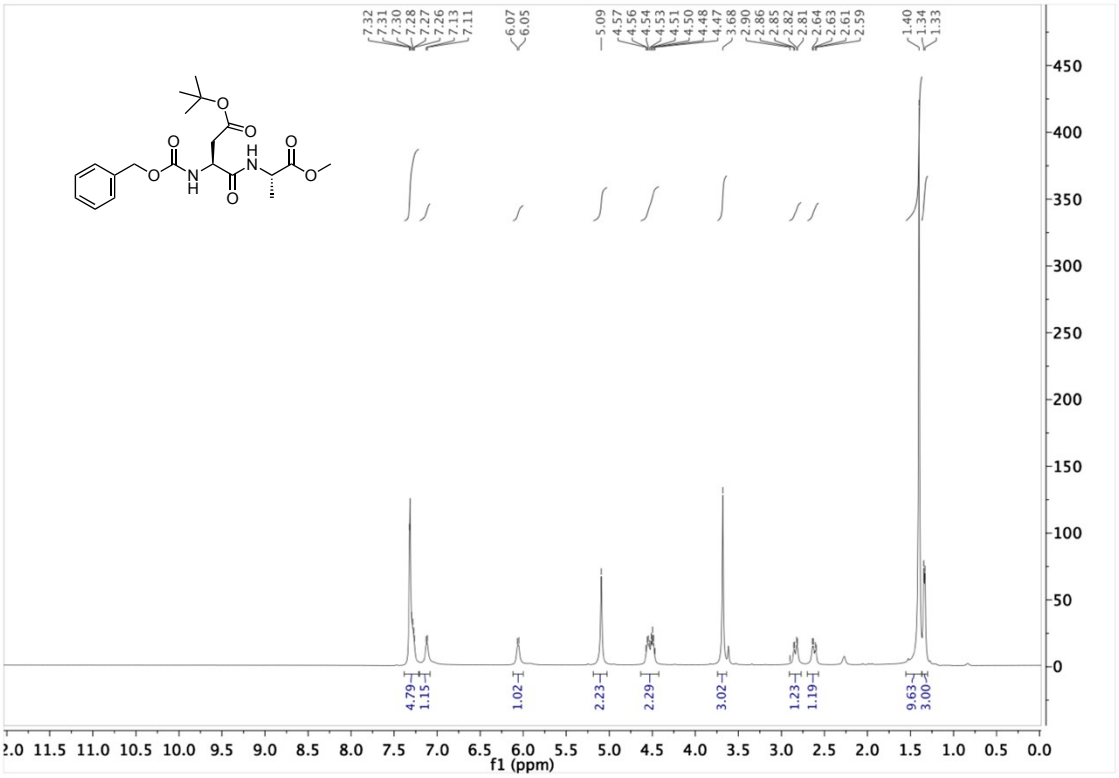


*Figure 30 : NMR ^{1}H of Cbz-L-Asp(tBu)-L-Ala-OMe (**2m**)*

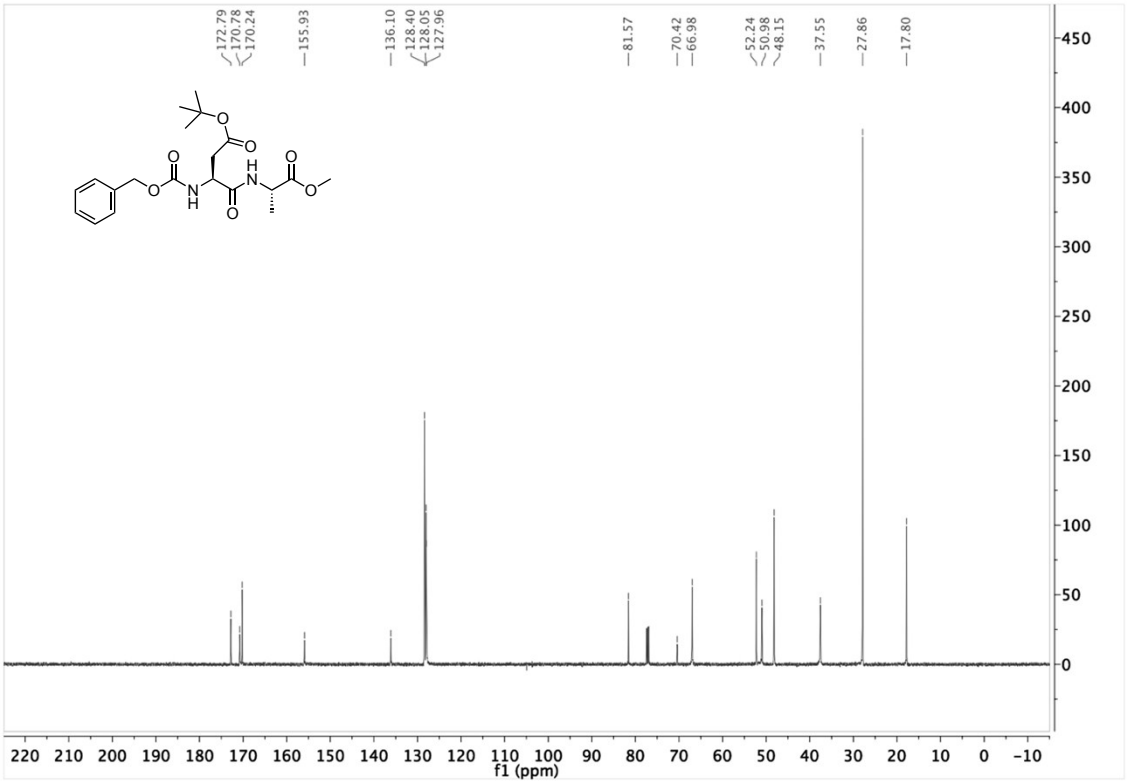


*Figure 31 : NMR ^{13}C of Cbz-L-Asp(tBu)-L-Ala-OMe (**2m**)*

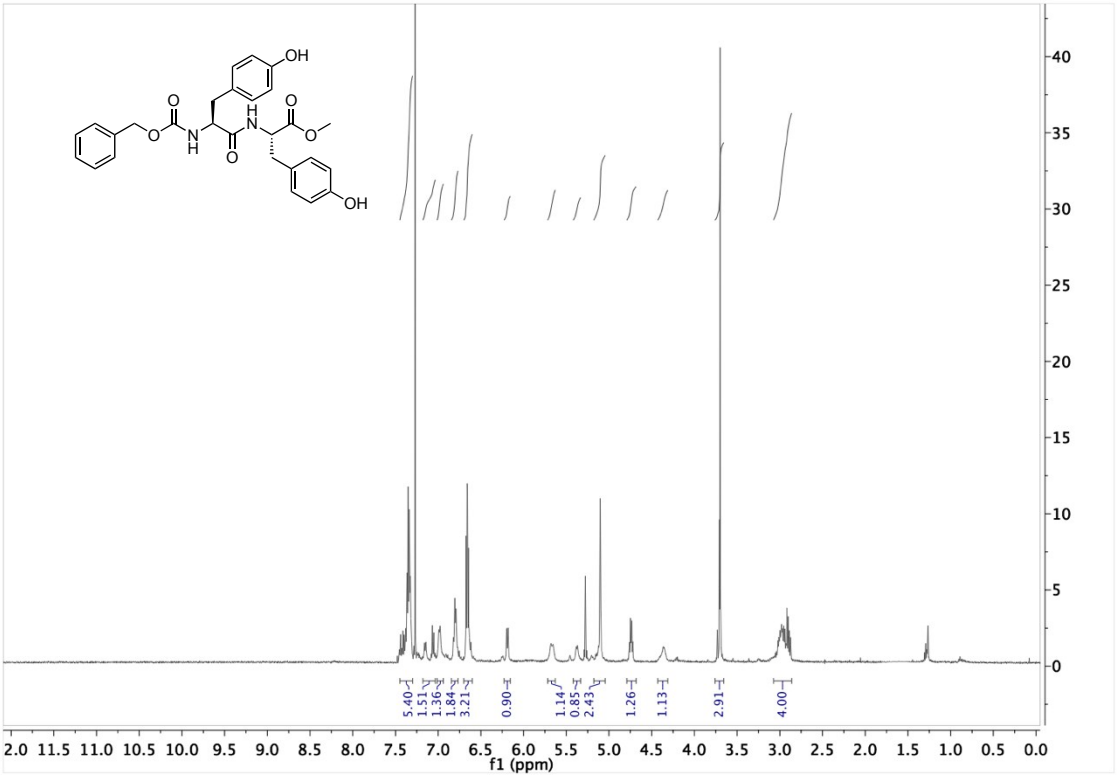


*Figure 32 : NMR ^{1}H of Cbz-L-Tyr-L-Tyr-OMe (**2n**)*

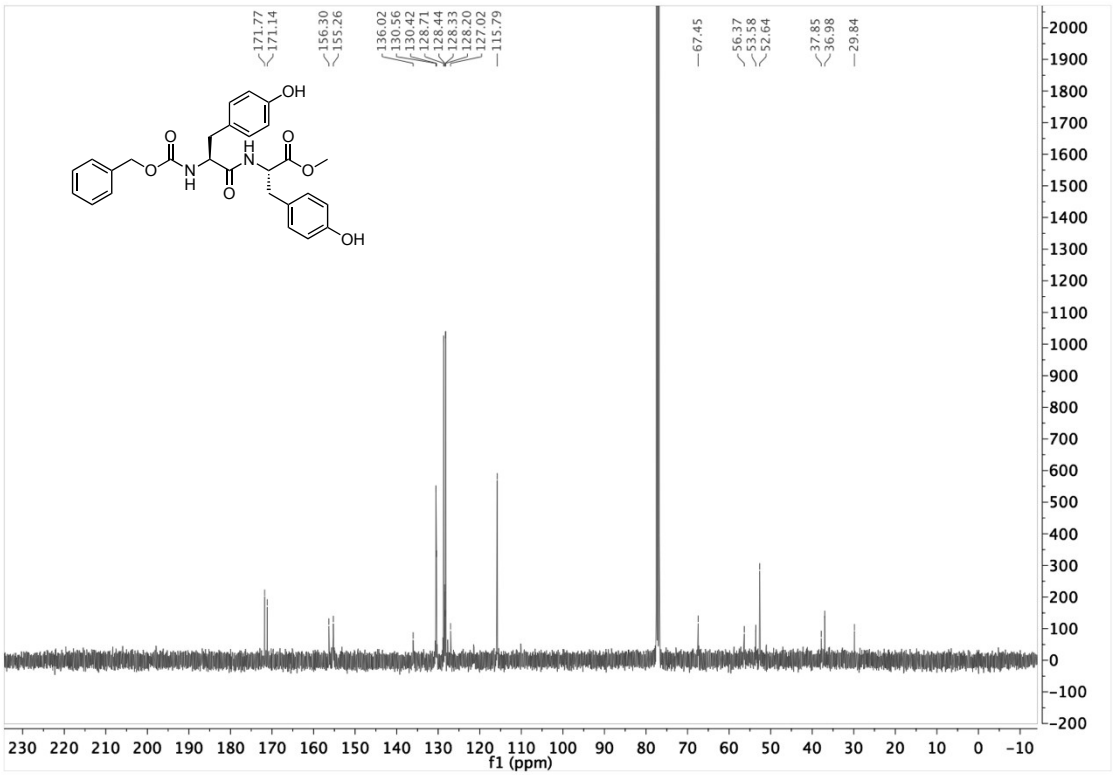


*Figure 33 : NMR ^{13}C of Cbz-L-Tyr-L-Tyr-OMe (**2n**)*

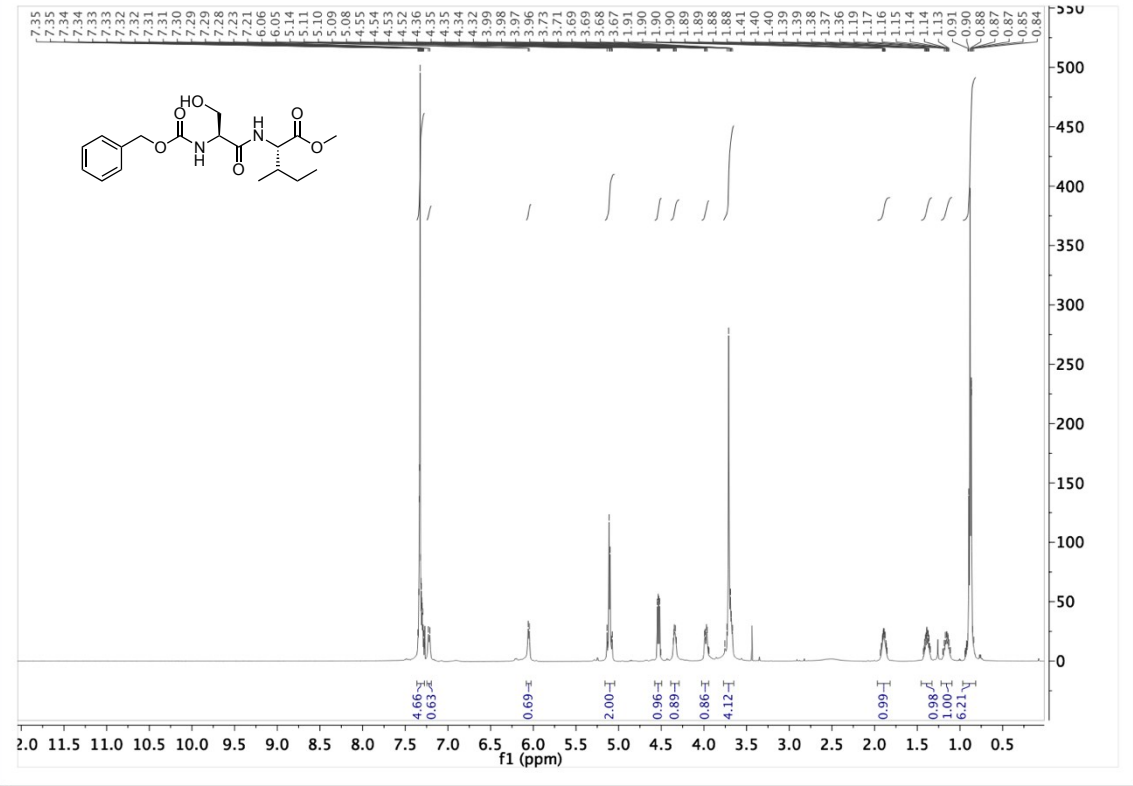


*Figure 34 : NMR ^{1}H of Cbz-L-Ser-L-Ile-OMe (**2o**)*

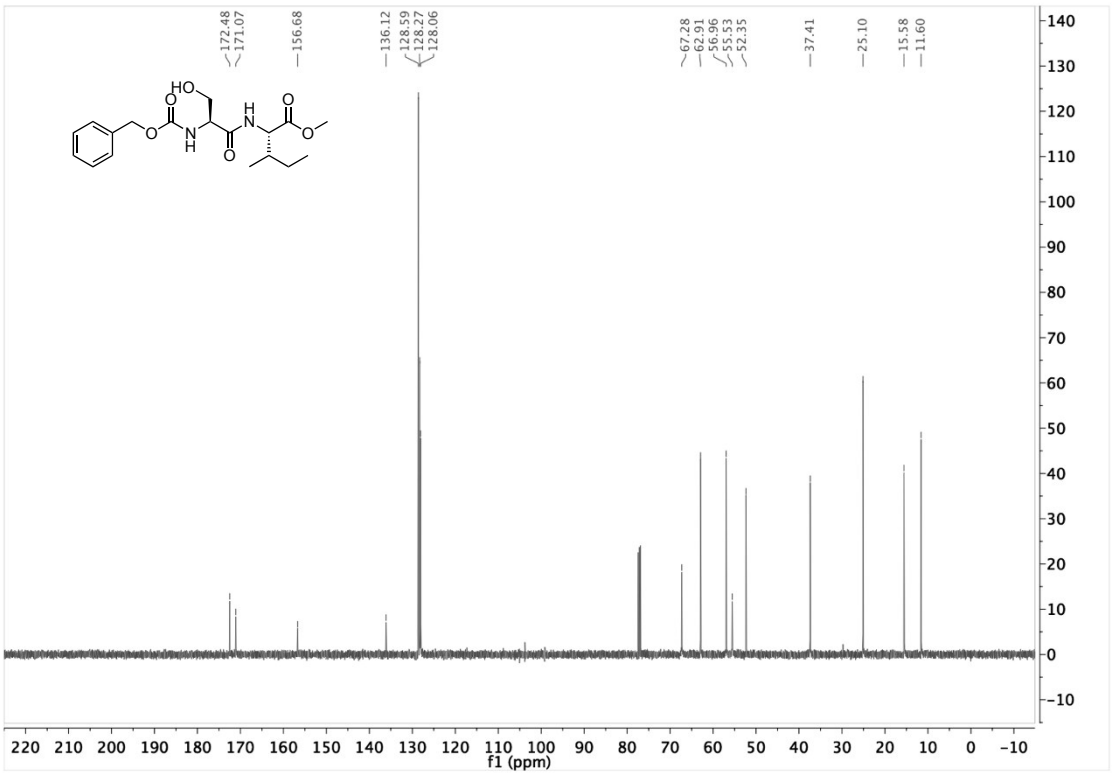


*Figure 35 : NMR ^{13}C of Cbz-L-Ser-L-Ile-OMe (**2o**)*

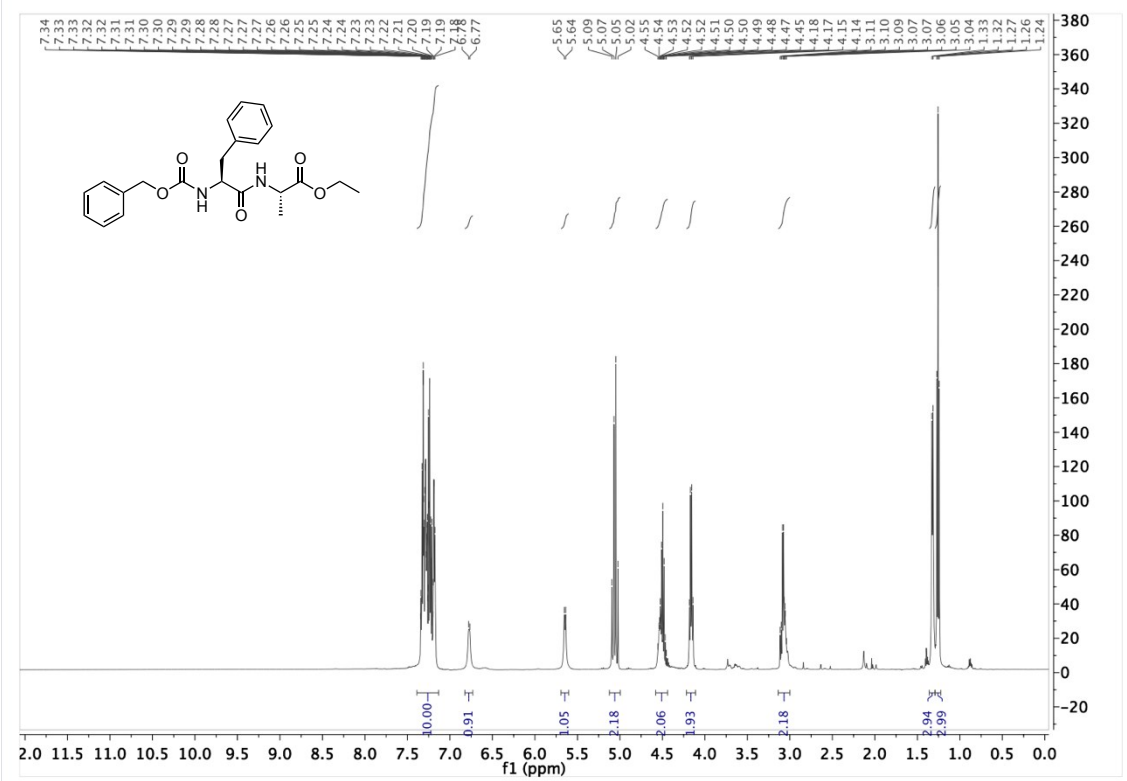


*Figure 36 : NMR ^{1}H of Cbz-L-Phe-L-ALa-OMe (**2p**)*

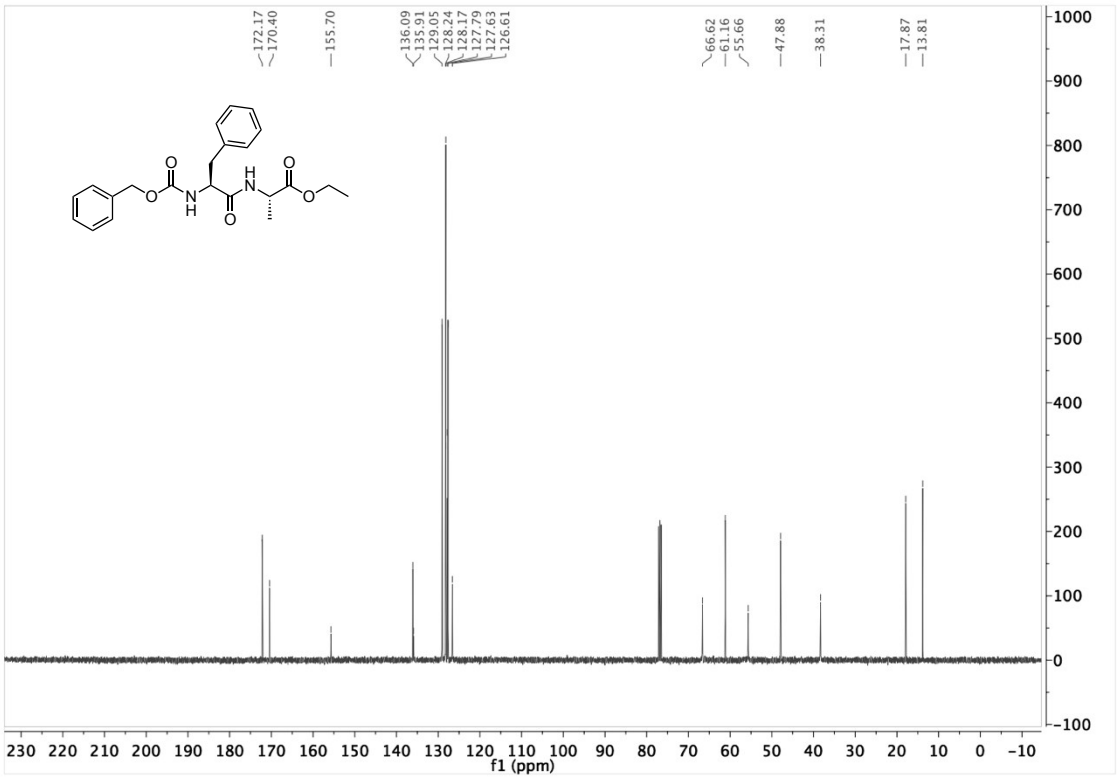


*Figure 37 : NMR ^{13}C of Cbz-L-Phe-L-Ala-OMe (**2p**)*

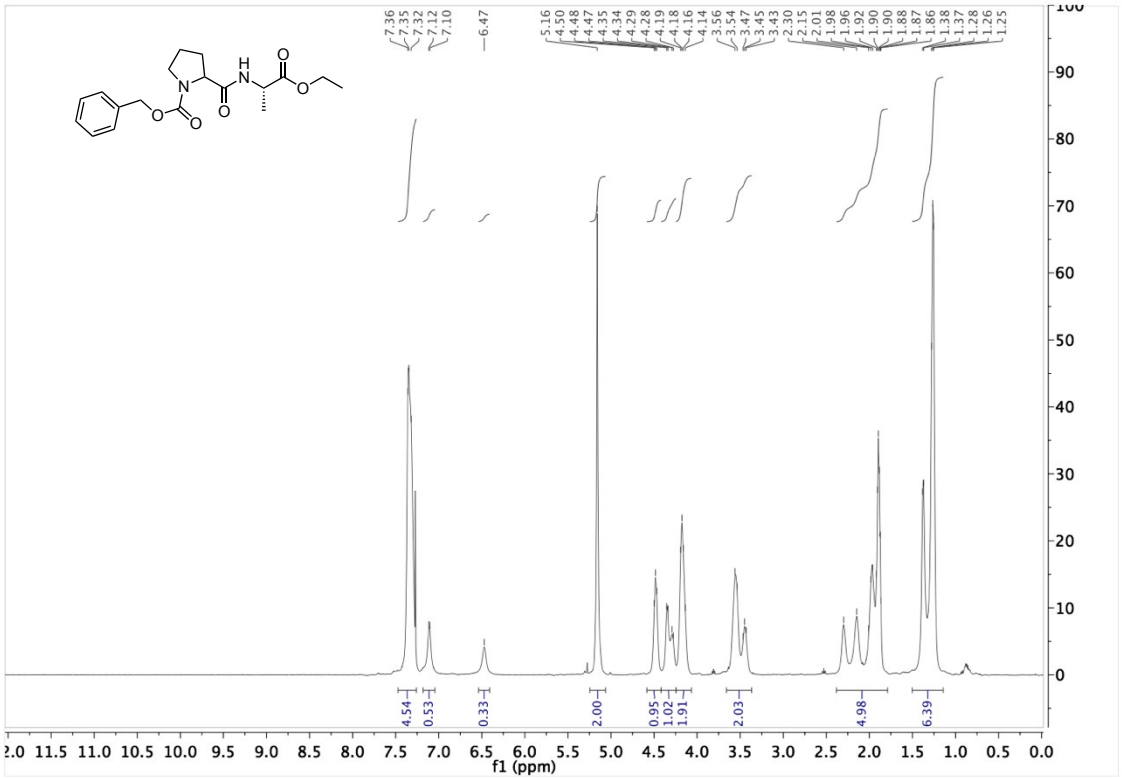


*Figure 38 : NMR [1]H of Cbz-L-Pro-L-ALa-OMe (**2q**)*

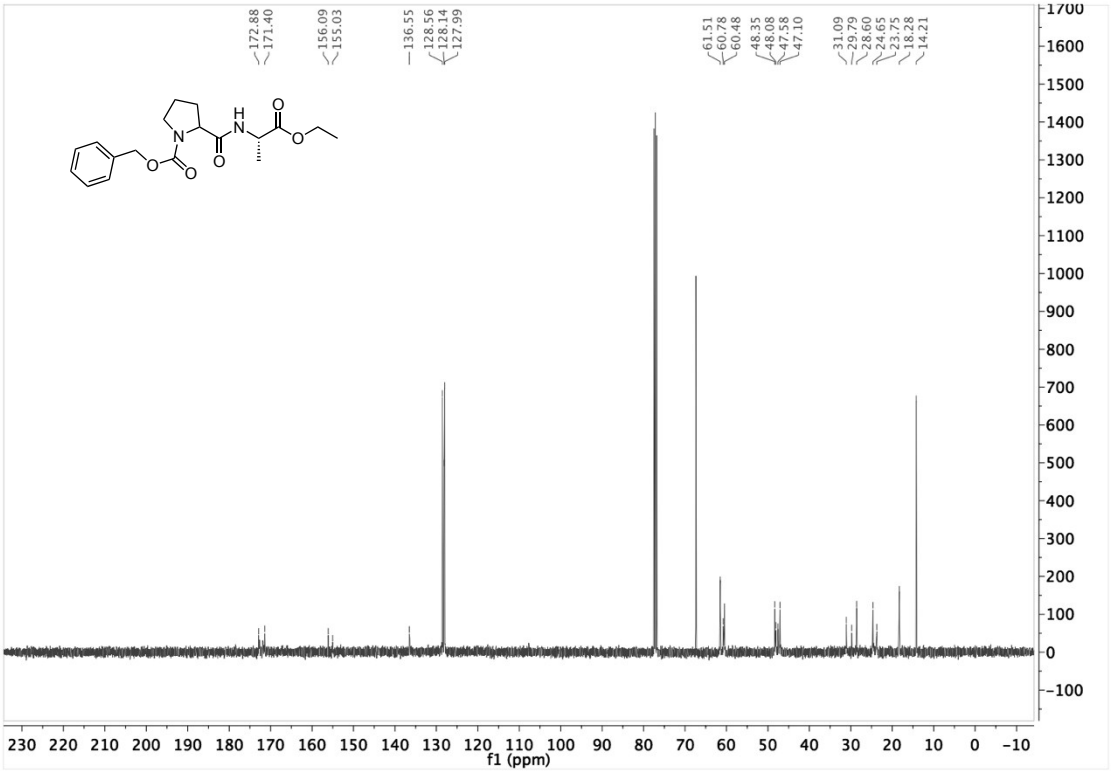


*Figure 39 : NMR [13]C of Cbz-L-Pro-L-ALa-OMe (**2q**)*

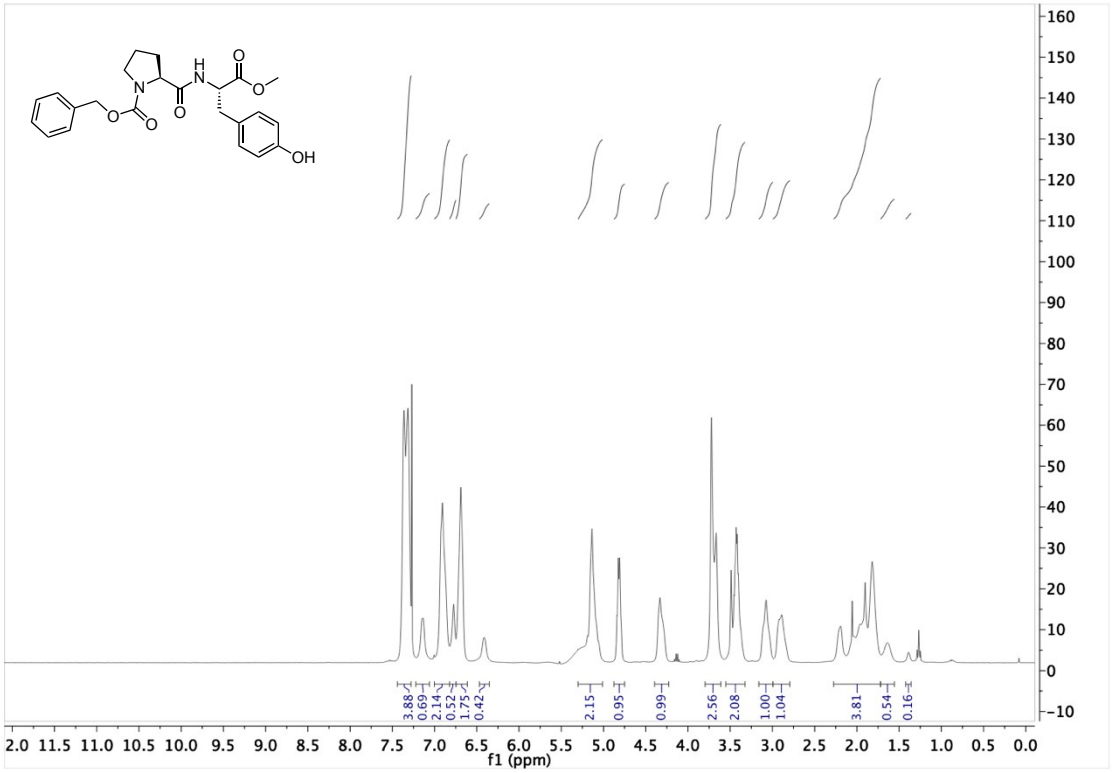


*Figure 40 : NMR ^{1}H of Cbz-L-Pro-L-Tyr-OMe (**2r**)*

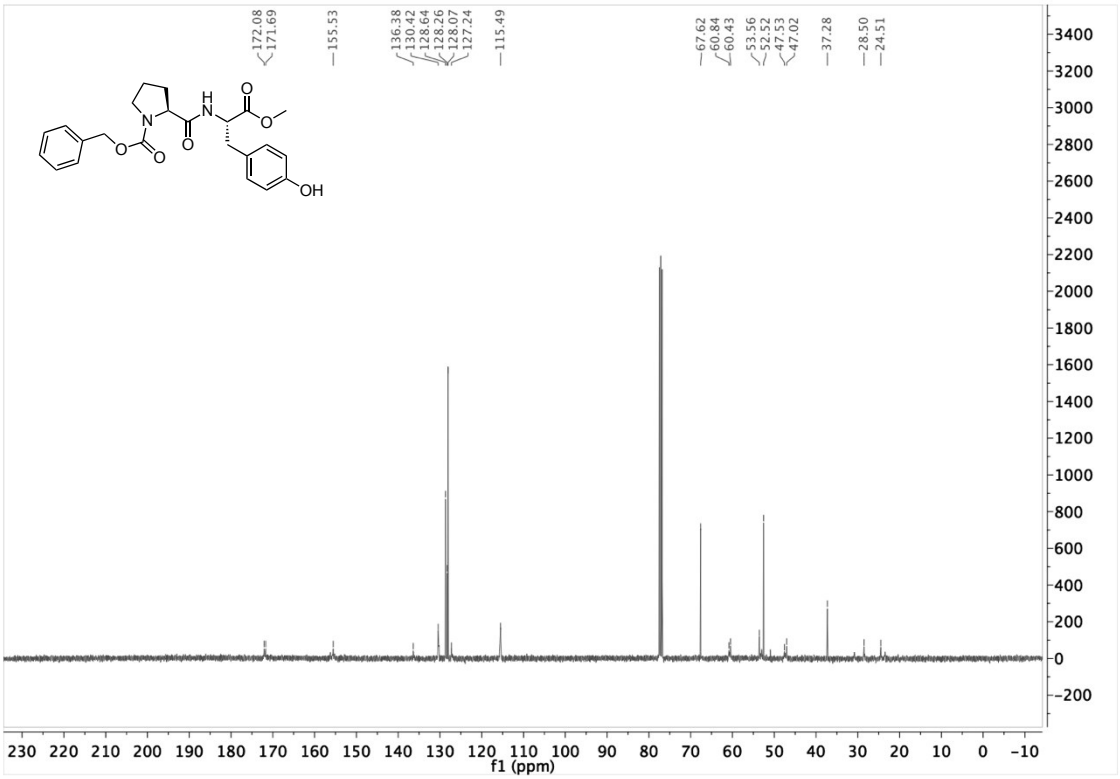


*Figure 41 : NMR ^{13}C of Cbz-L-Pro-L-Tyr-OMe (**2r**)*

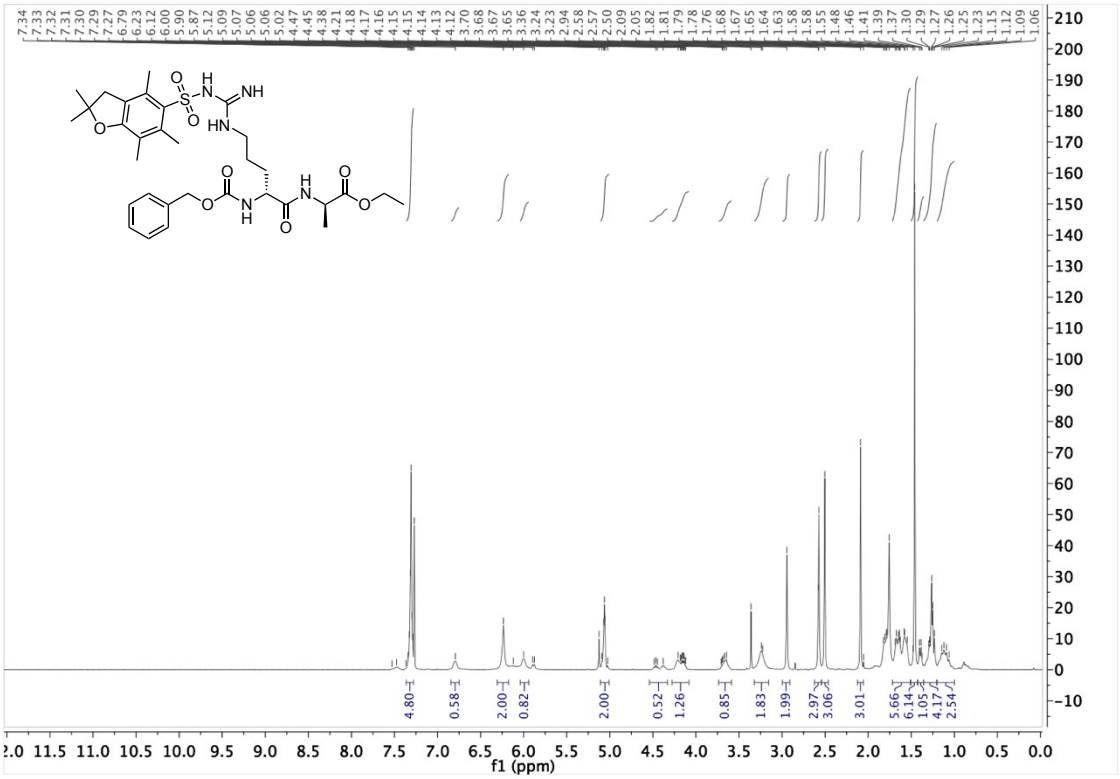


*Figure 42 : NMR ^{1}H of Cbz-L-Arg(Pbf)-L-Ala-OEt (**2s**)*

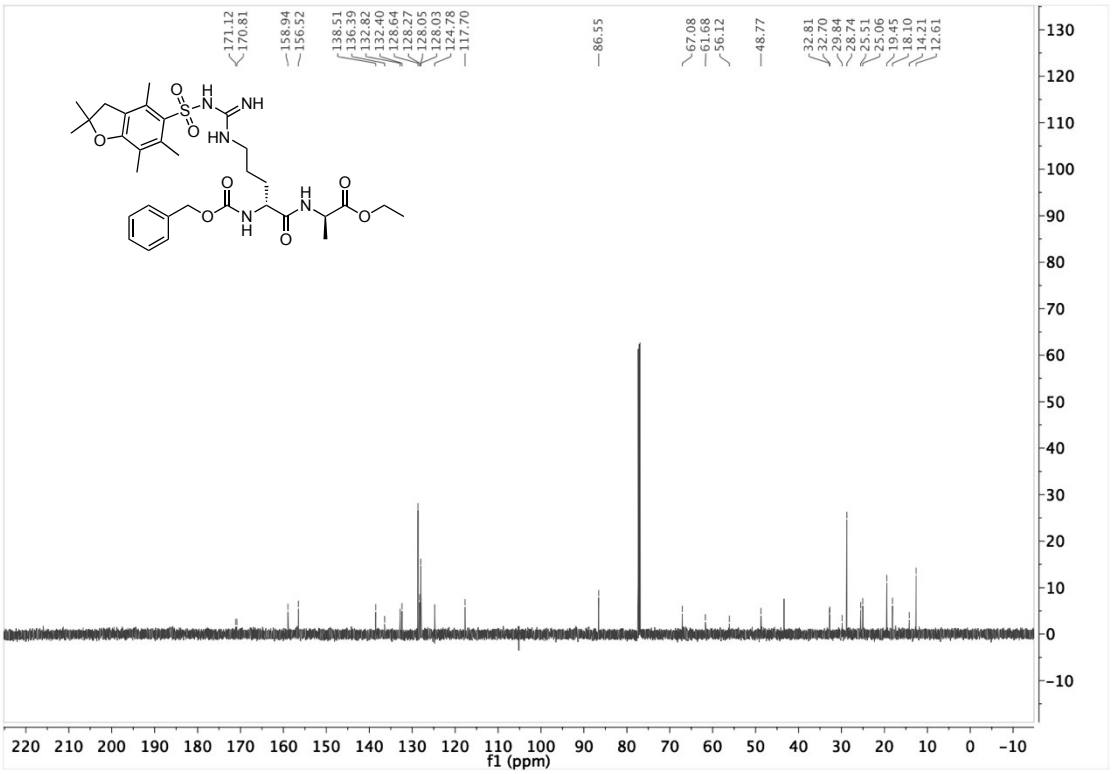


*Figure 43 : NMR ^{13}C of Cbz-L-Arg(Pbf)-L-Ala-OEt (**2s**)*

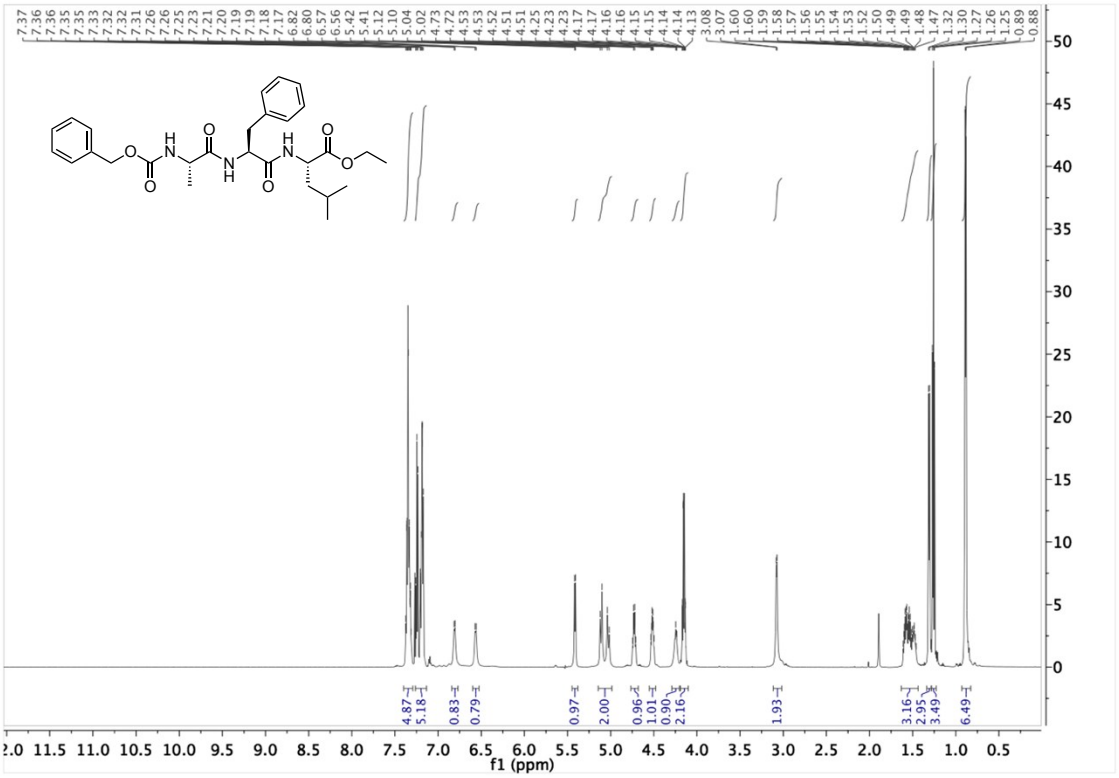


*Figure 44 : NMR ^{1}H of Cbz-L-Ala-L-Phe-L-Leu-OEt (**3a**)*

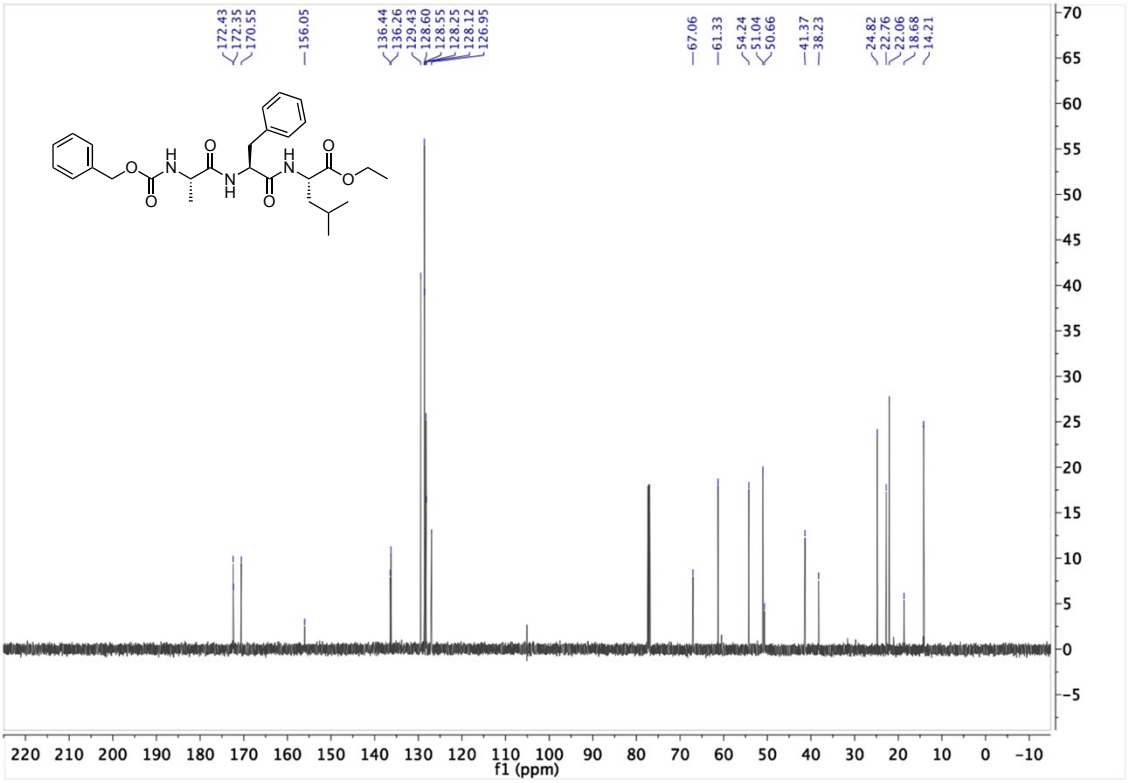


*Figure 45 : NMR ^{13}C of Cbz-L-Ala-L-Phe-L-Leu-OEt (**3a**)*

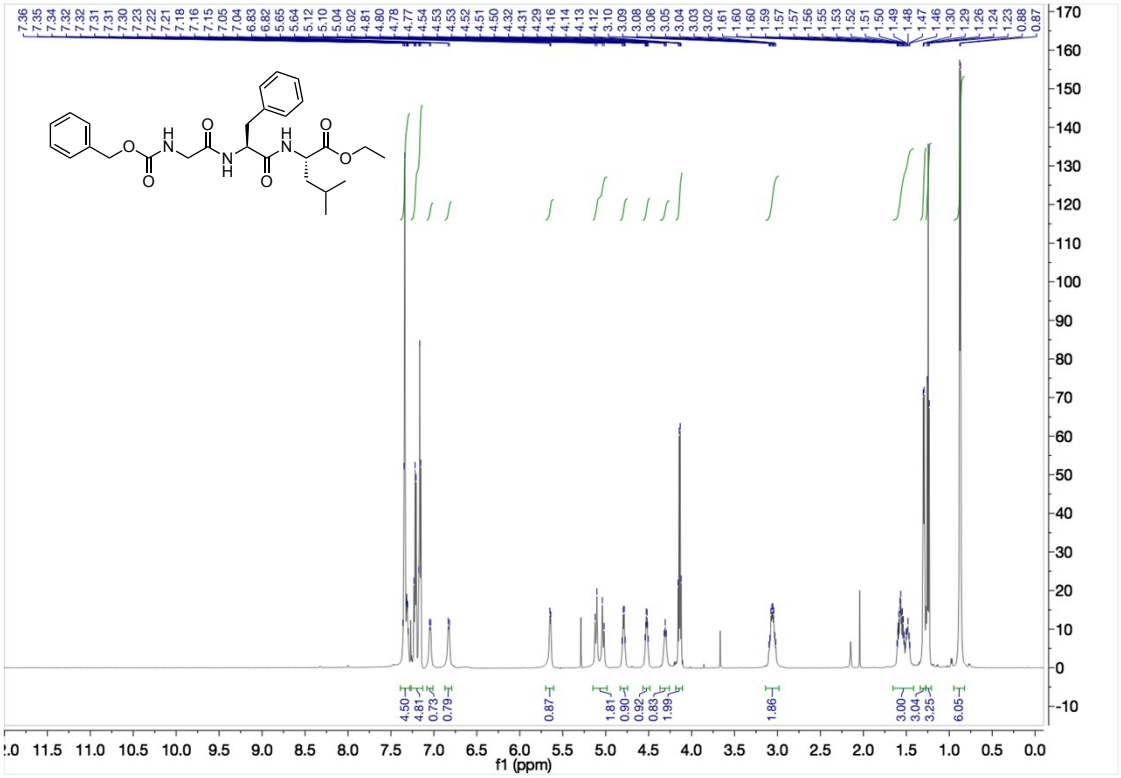


*Figure 46 : NMR ^{1}H of Cbz-Gly-L-Phe-L-Leu-OEt (**3b**)*

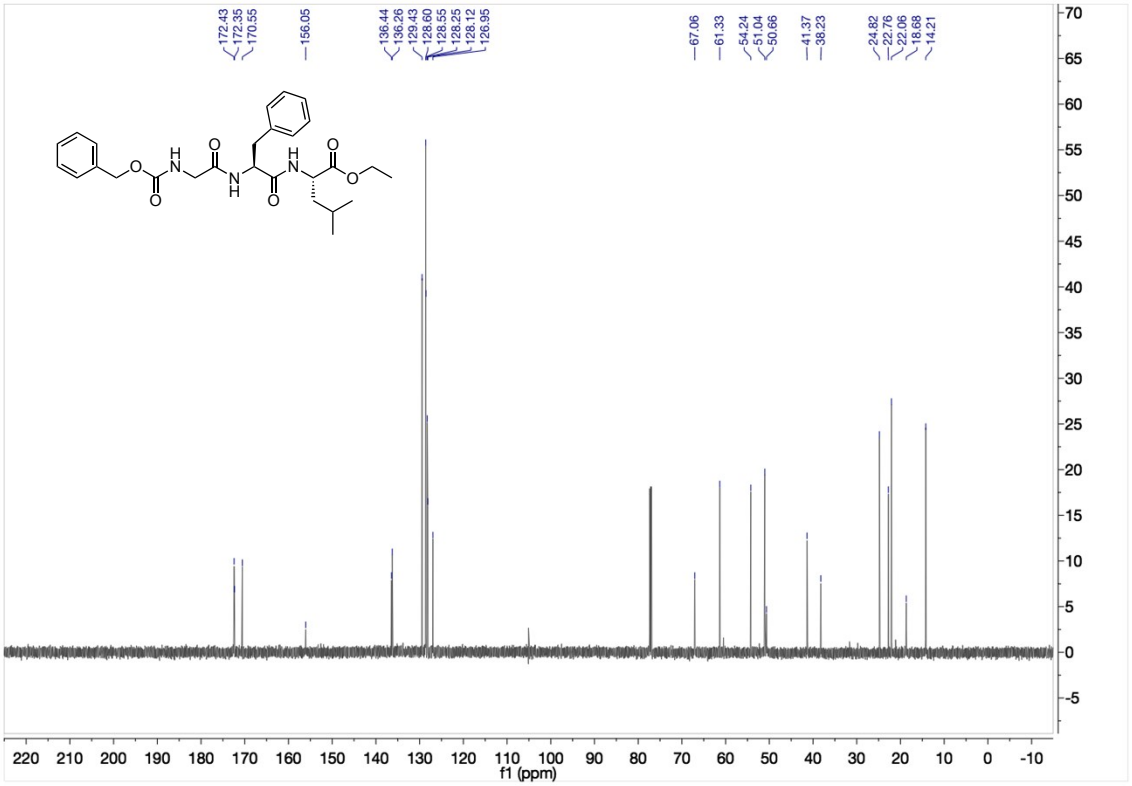


*Figure 47 : NMR ^{13}C of Cbz-Gly-L-Phe-L-Leu-OEt (**3b**)*

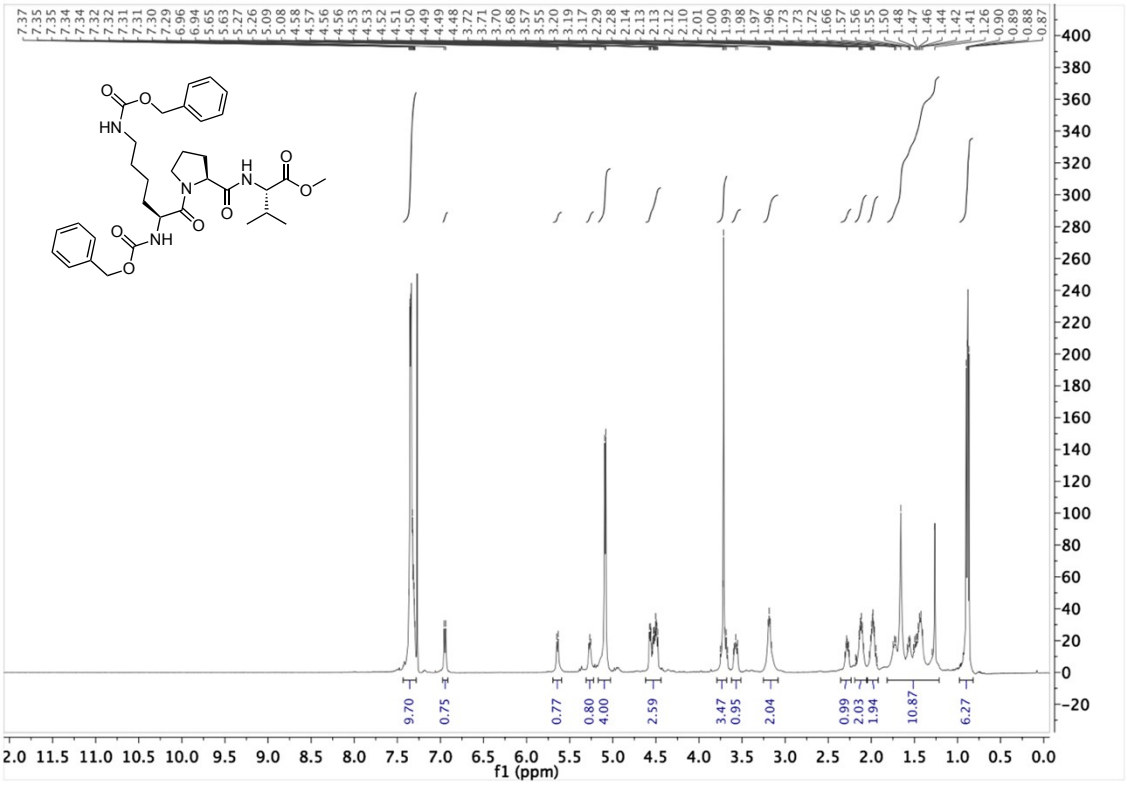


*Figure 48 : NMR ^{1}H of Cbz-L-Lys(Cbz)-L-Pro-L-Val-OMe (**3c**)*

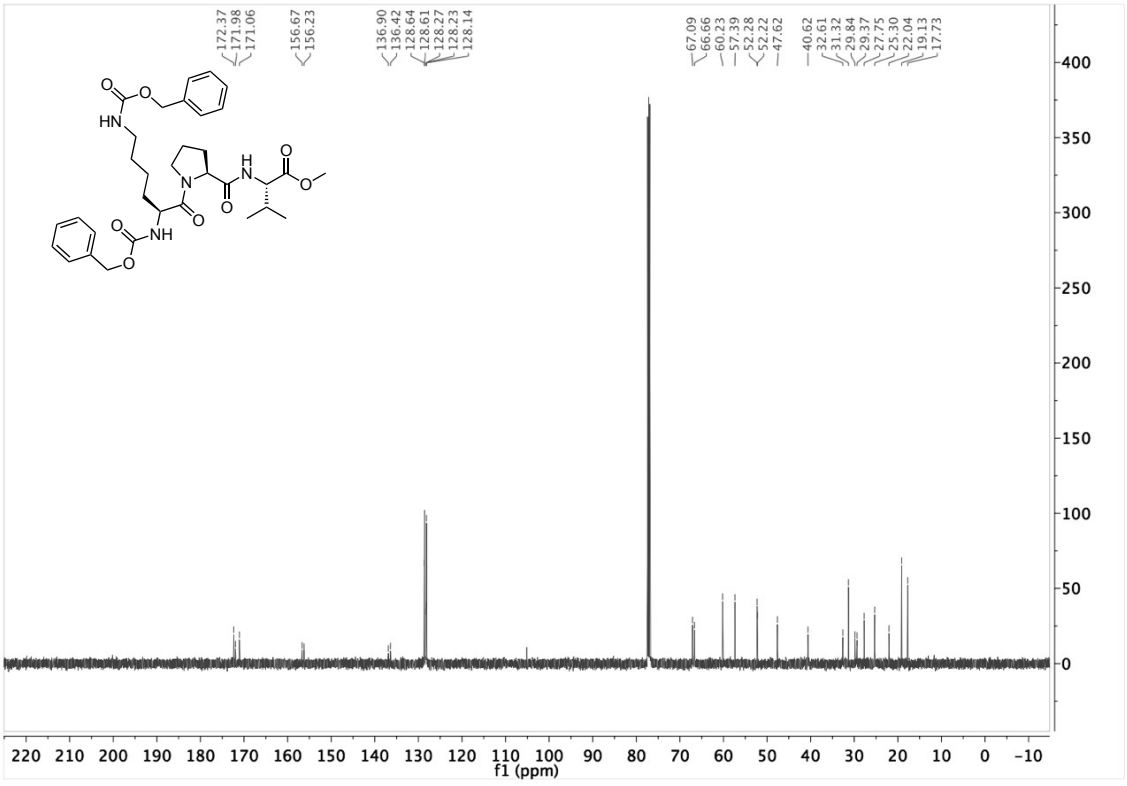


*Figure 49 : NMR ^{13}C of Cbz-L-Lys(Cbz)-L-Pro-L-Val-OMe (**3c**)*

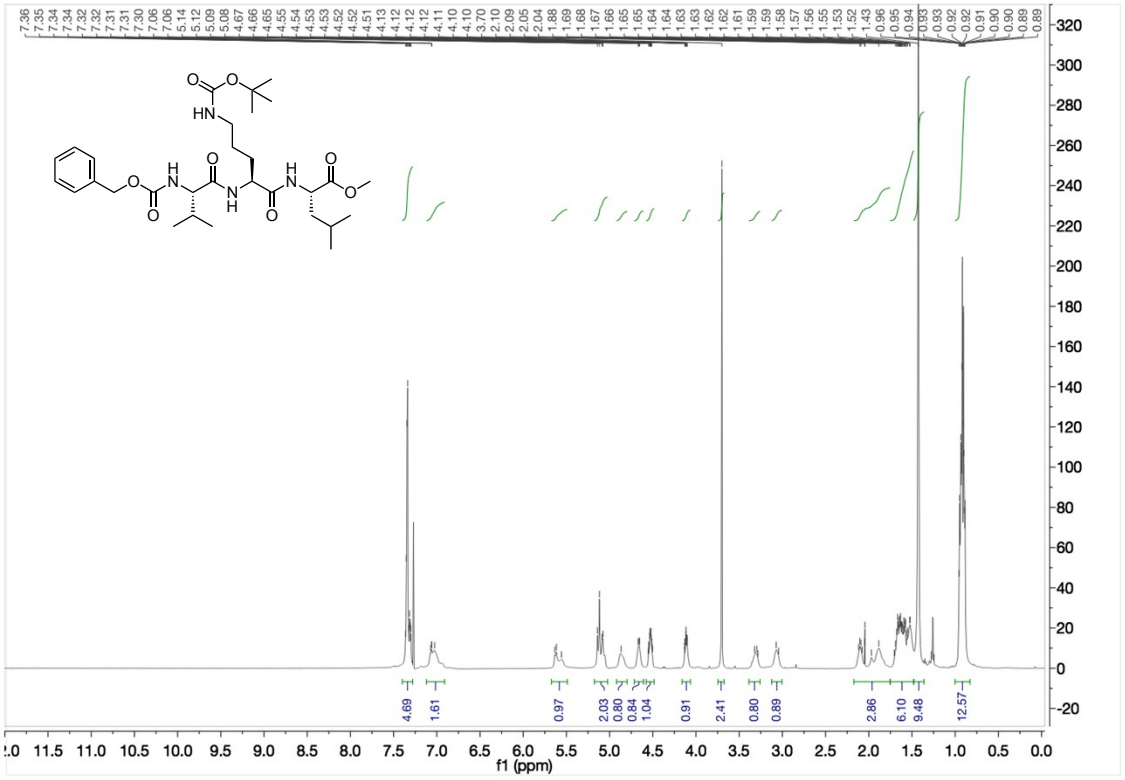


*Figure 50 : NMR ^{1}H of Cbz-L-Val-L-L-Leu-OMe (**3d**)*

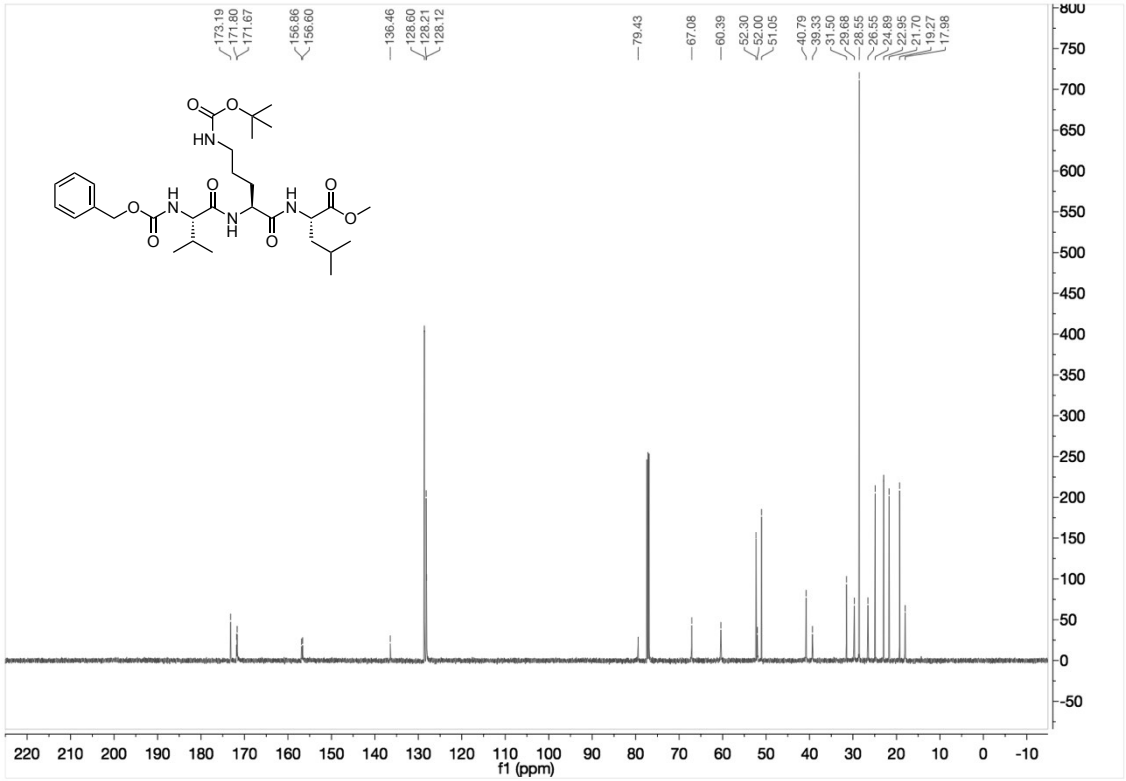


*Figure 51 : NMR ^{13}C of Cbz-L-Val-L-Orn(Boc)-L-Leu-OMe (**3d**)*

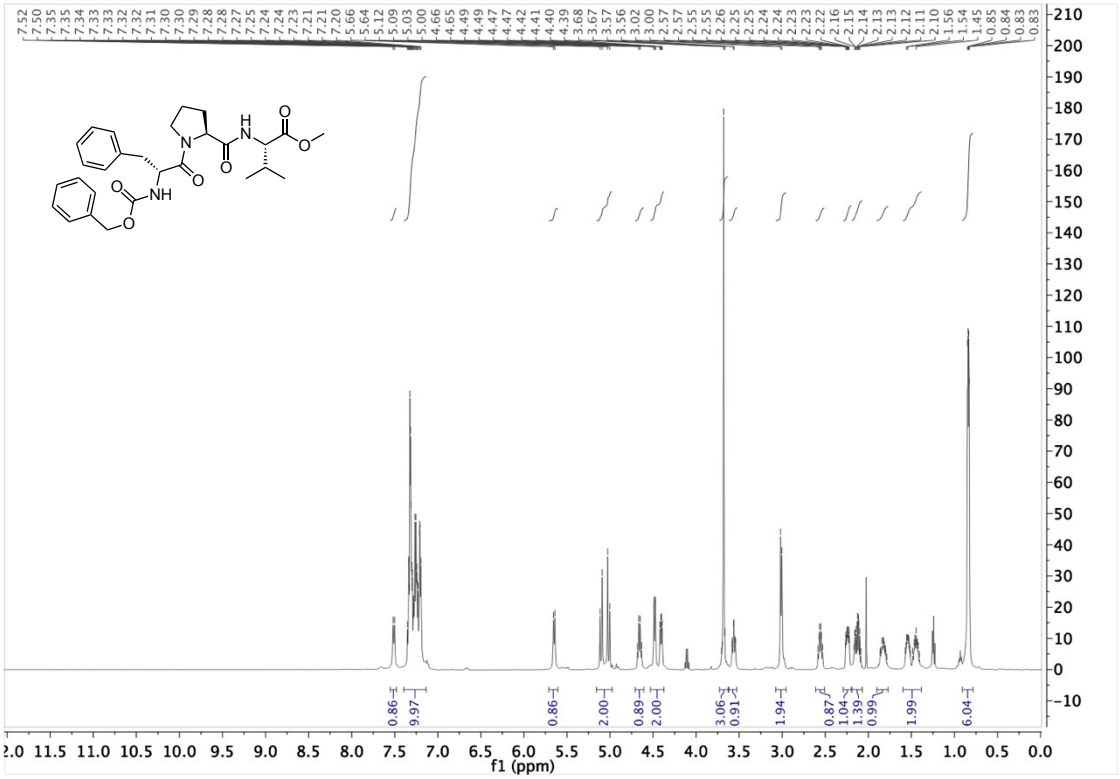


*Figure 52 : NMR ^{1}H of Cbz-D-Phe-L-Pro-L-Val-OMe (**3e**)*

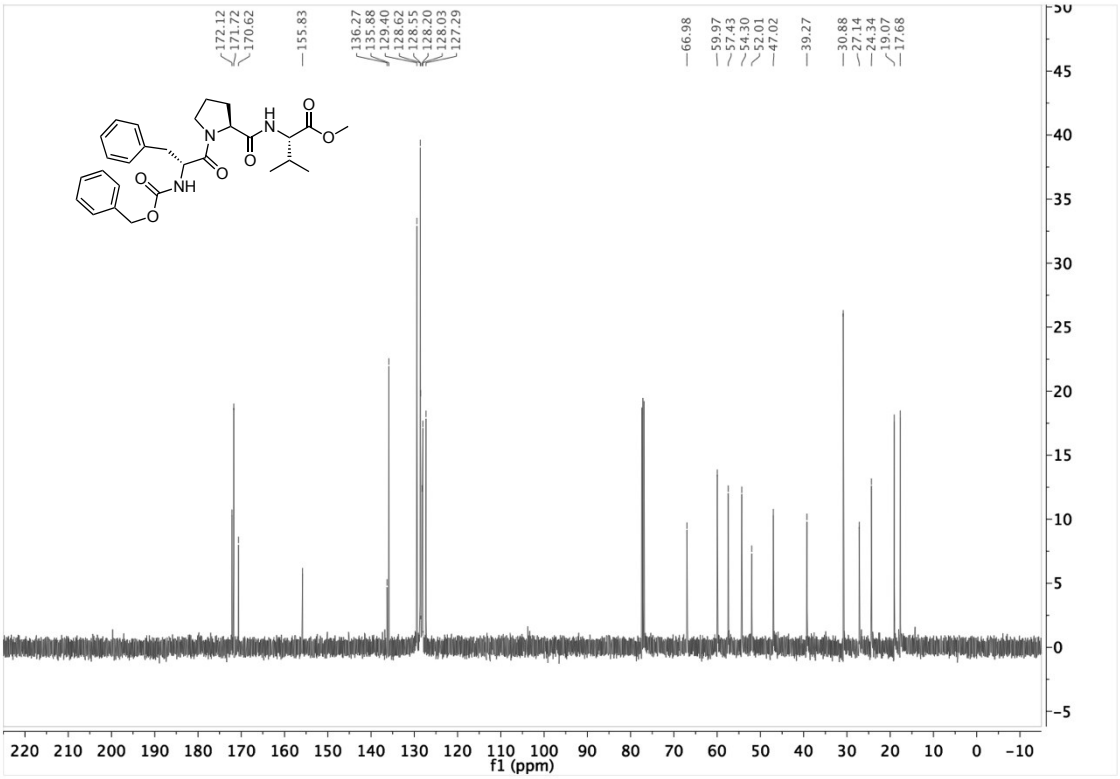


*Figure 53 : NMR ^{13}C of Cbz-D-Phe-L-Pro-L-Val-OMe (**3e**)*

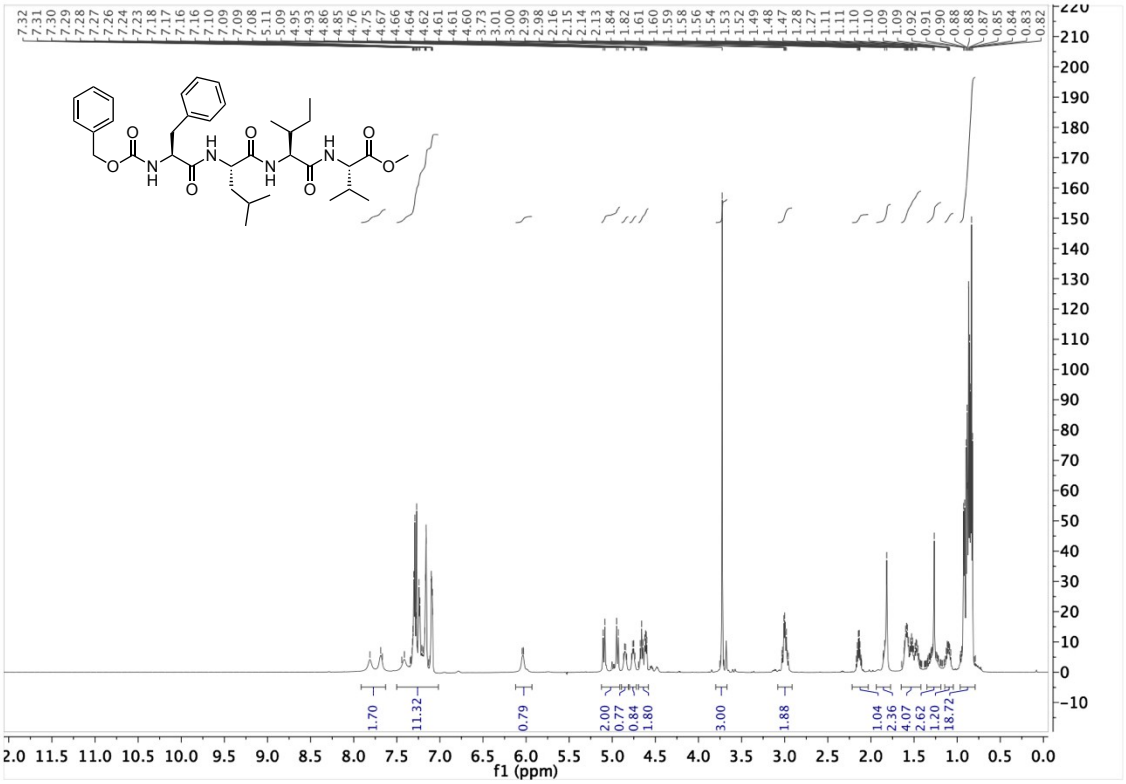


*Figure 54: NMR ^{1}H of Cbz-L-Phe-L-Leu-L-Ile-L-Val-OMe (**4a**)*

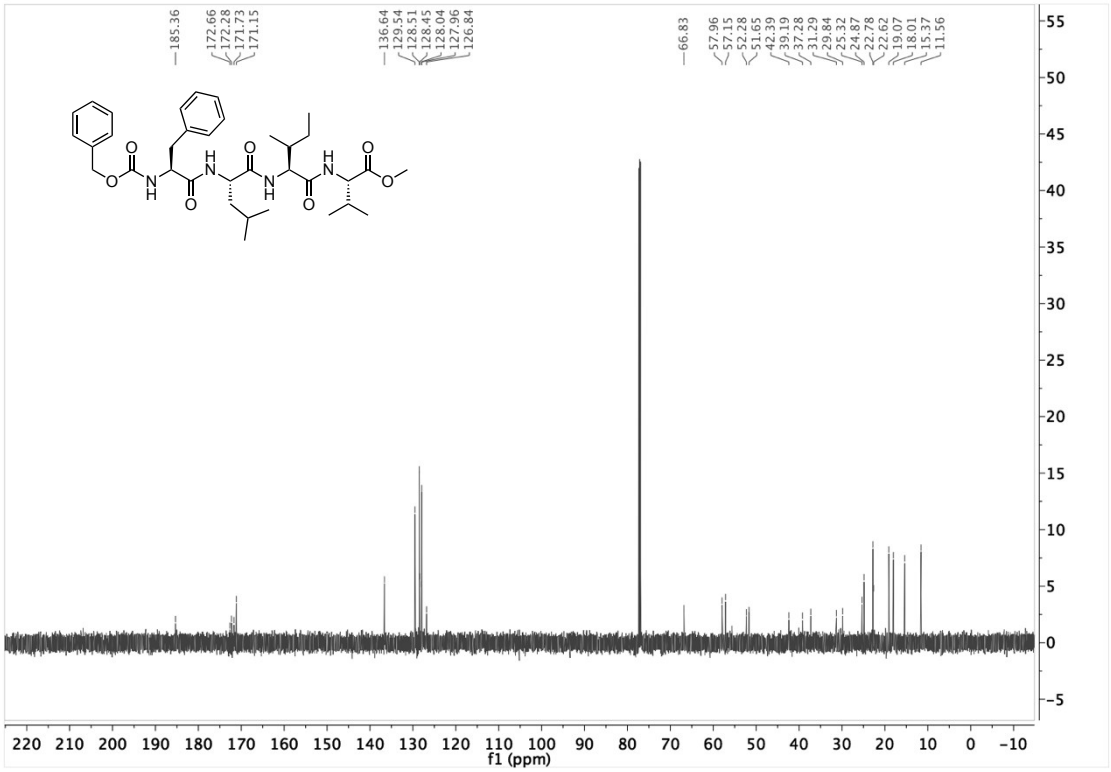


*Figure 55 : ^{13}C of Cbz-L-Phe-L-Leu-L-Ile-L-Val-OMe (**4a**)*

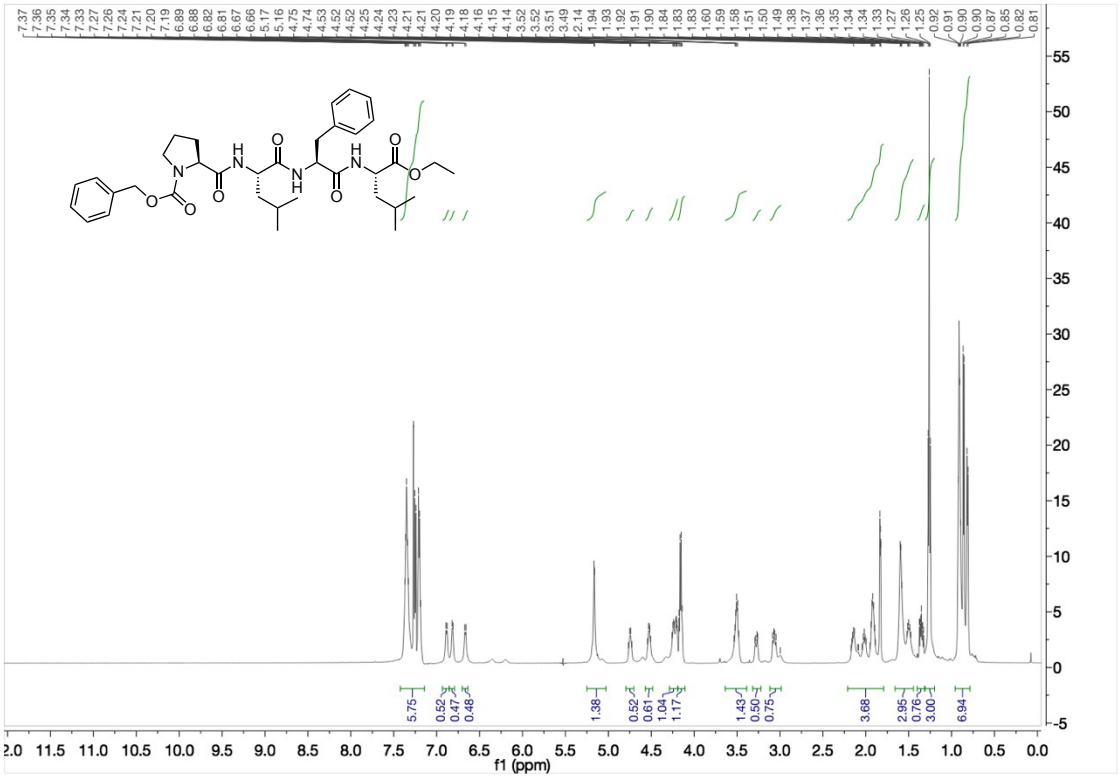


*Figure 56 : ^{1}H Z-Pro-Leu-Phe-Leu-OEt (**4b**)*

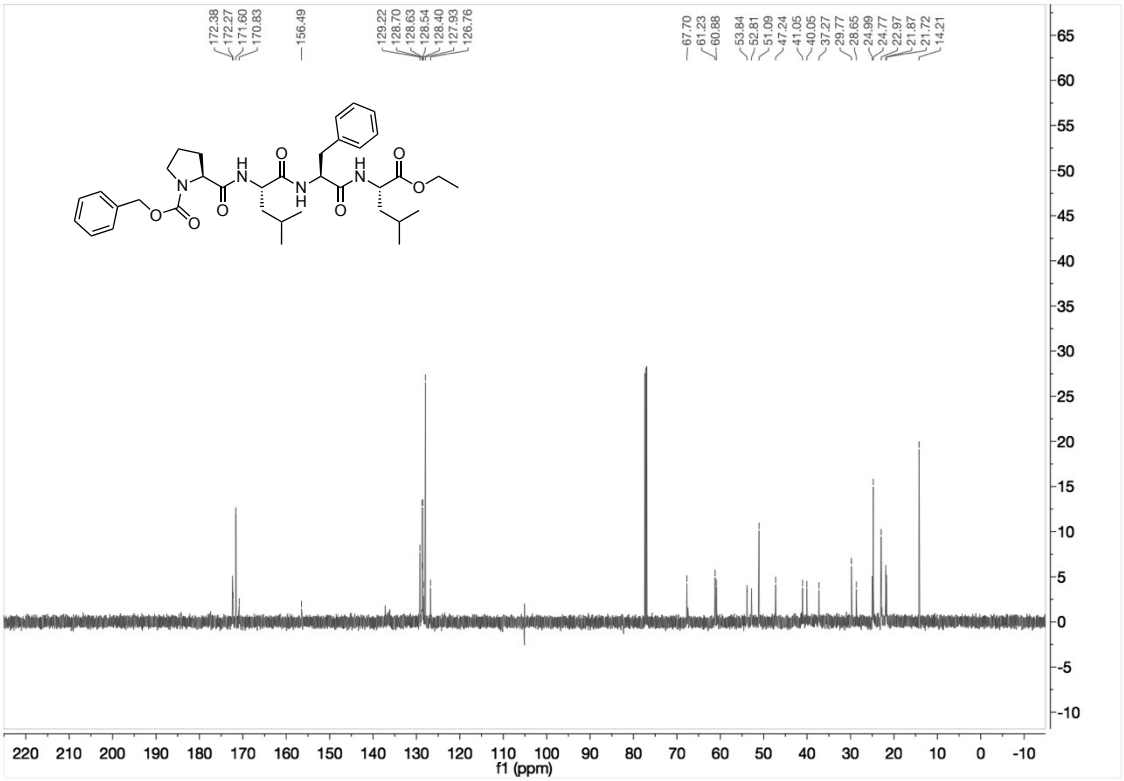


*Figure 57 :^{13}C Z-Pro-Leu-Phe-Leu-OEt (**4b**)*

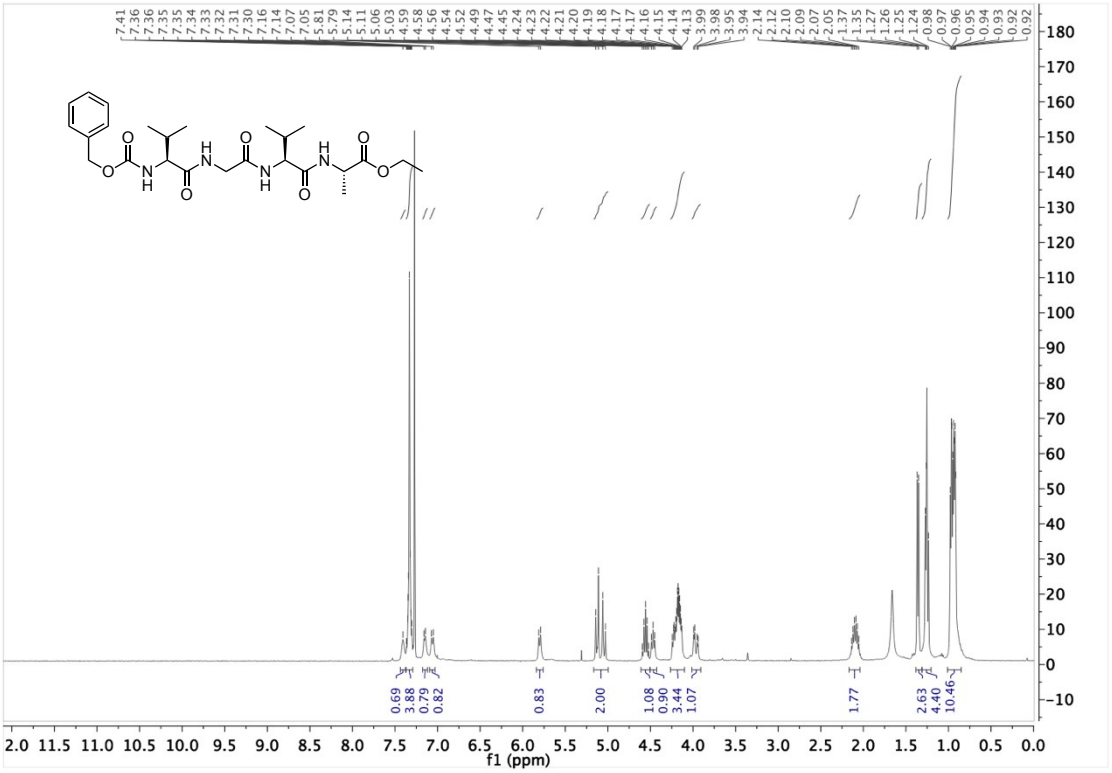


*Figure 58 : NMR ^{1}H of Cbz-L-Val-Gly-L-Val-L-Ala-OEt (**4c**)*

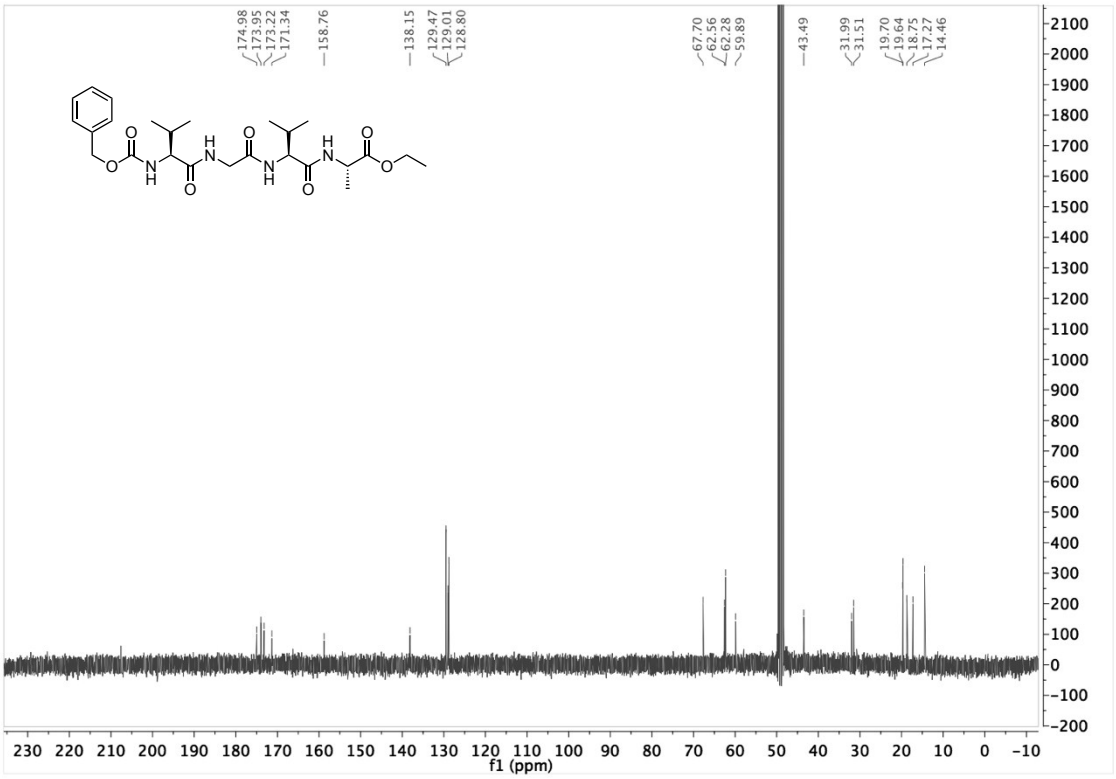


*Figure 59 : NMR ^{13}C of Cbz-L-Val-Gly-L-Val-L-Ala-OEt (**4c**)*

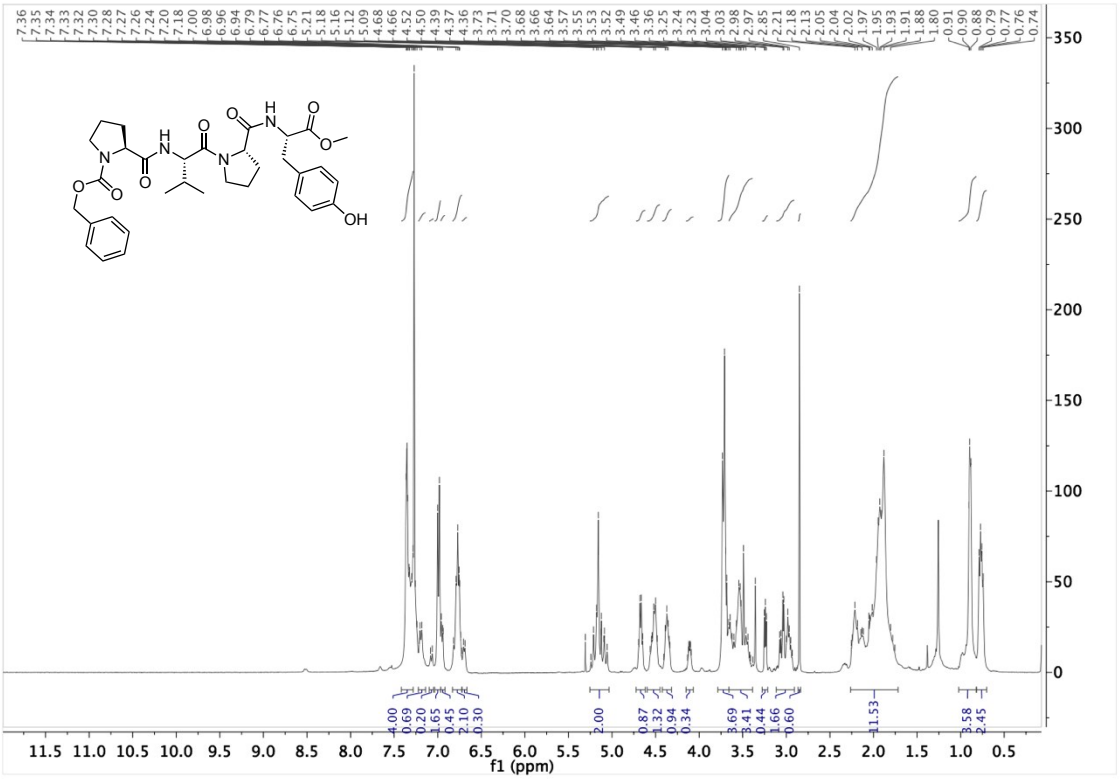


*Figure 60 : NMR ^{1}H of Cbz-L-Pro-L-Val-L-Pro-L-Tyr-OMe (**4d**)*

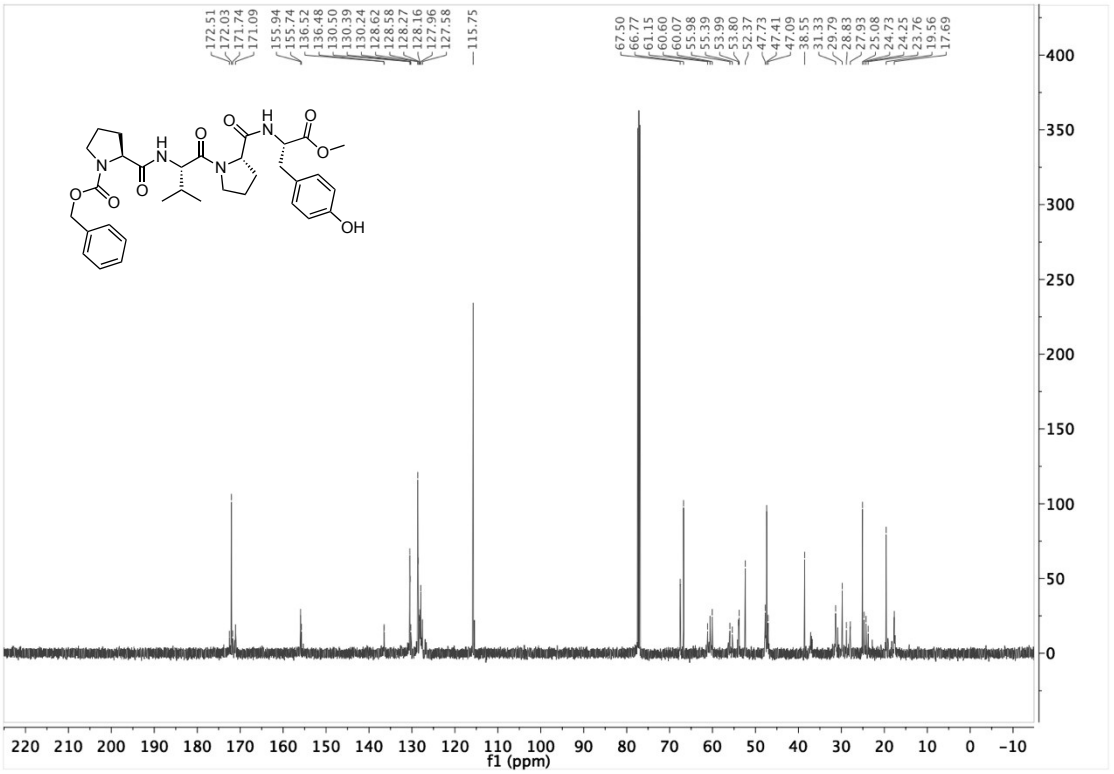


*Figure 61 : NMR ^{13}C of Cbz-L-Pro-L-Val-L-Pro-L-Tyr-OMe (**4d**)*

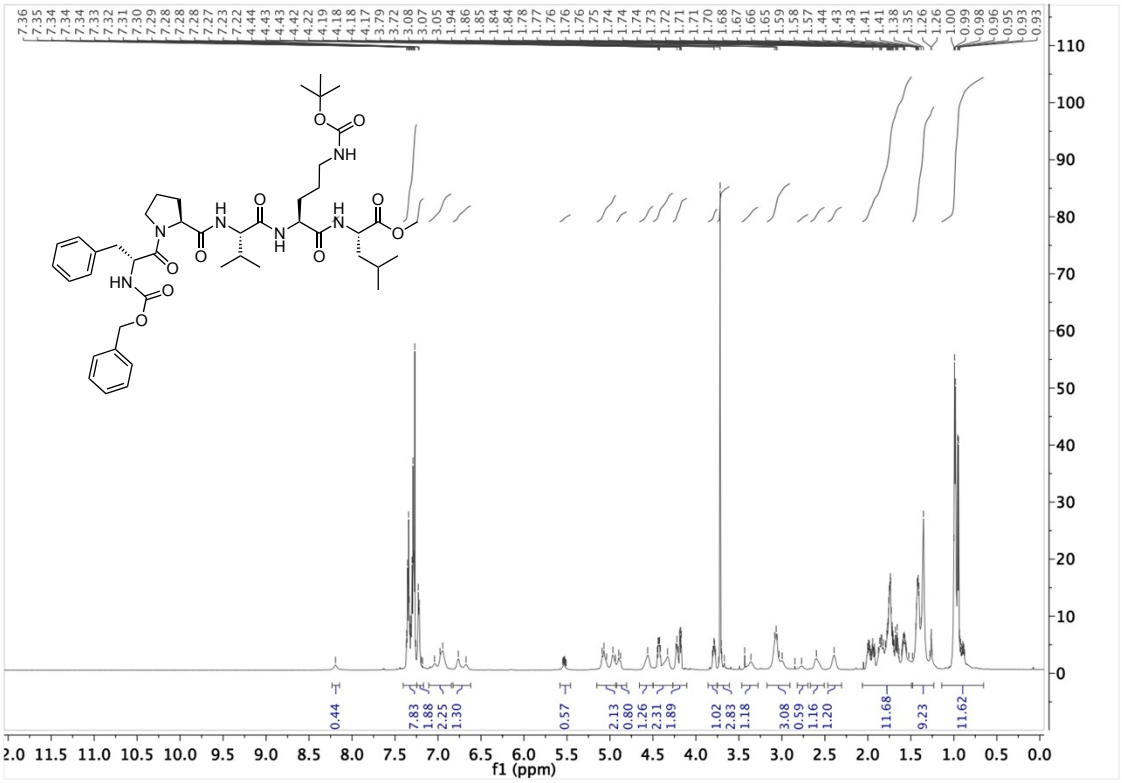


*Figure 62 : NMR ^{1}H of Cbz-D-Phe-L-Pro-L-Val-L-Orn(Boc)-L-Leu-OMe (**5a**)*

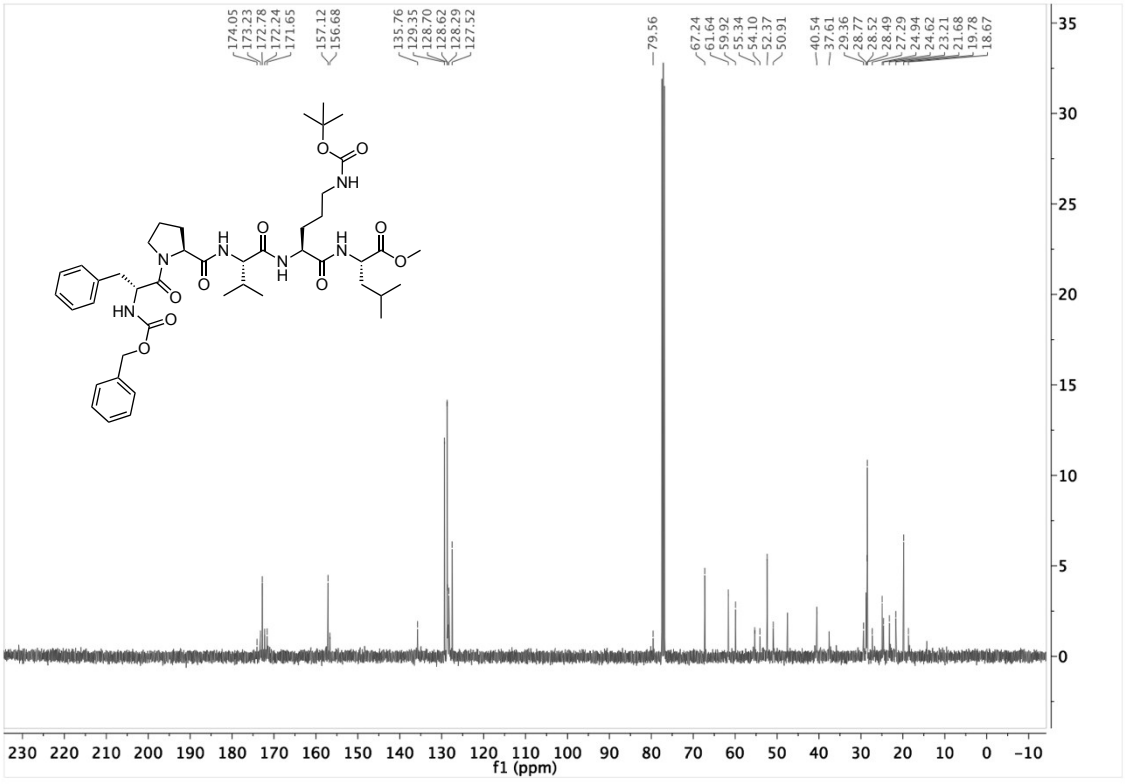


*Figure 63 : NMR ^{13}C of Cbz-D-Phe-L-Pro-L-Val-L-Orn(Boc)-L-Leu-OMe (**5a**)*

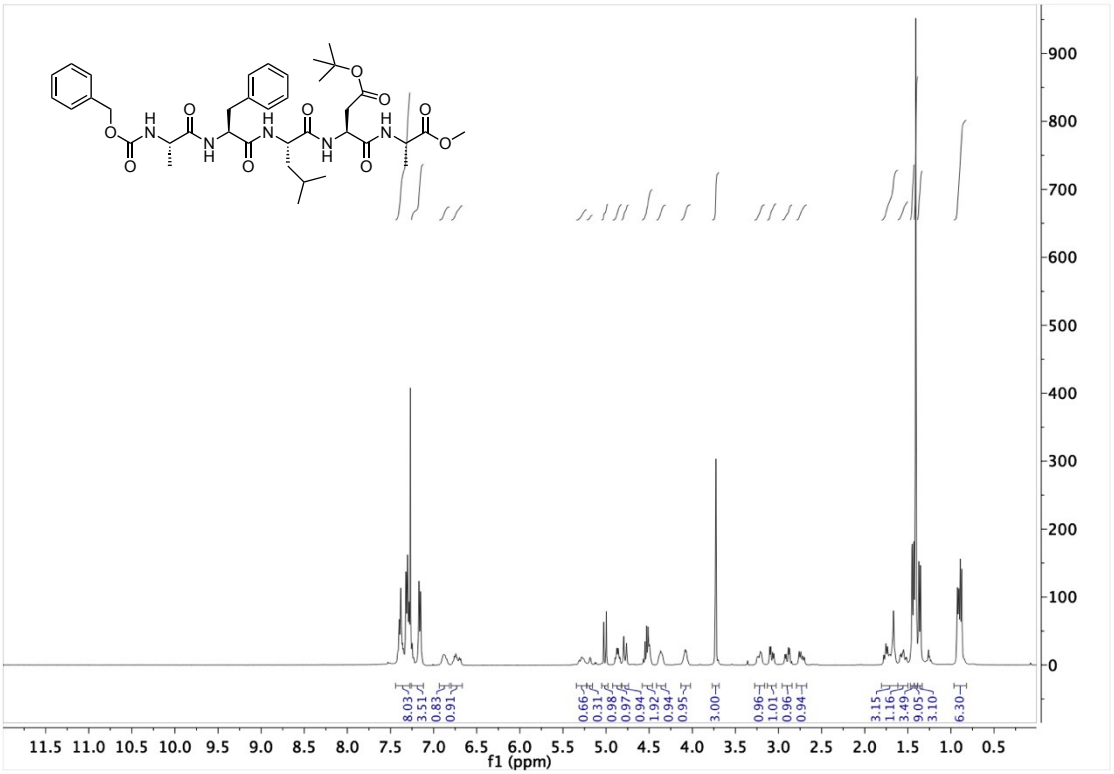


*Figure 64 : NMR ^{1}H of Cbz-L-Ala-L-Phe-L-Leu-Asp(OtBu)-Ala-OMe (**5b**)*

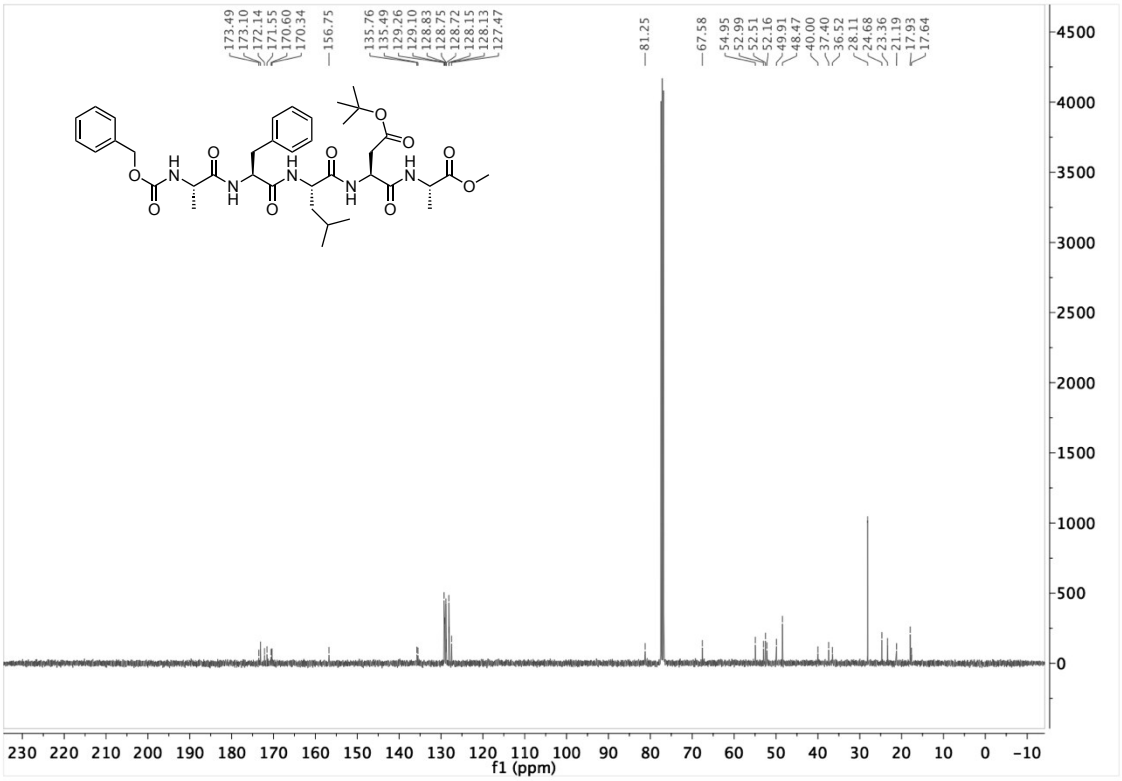


*Figure 65 : NMR ^{13}C of Cbz-L-Ala-L-Phe-L-Leu-Asp(OtBu)-Ala-OMe (**5b**)*

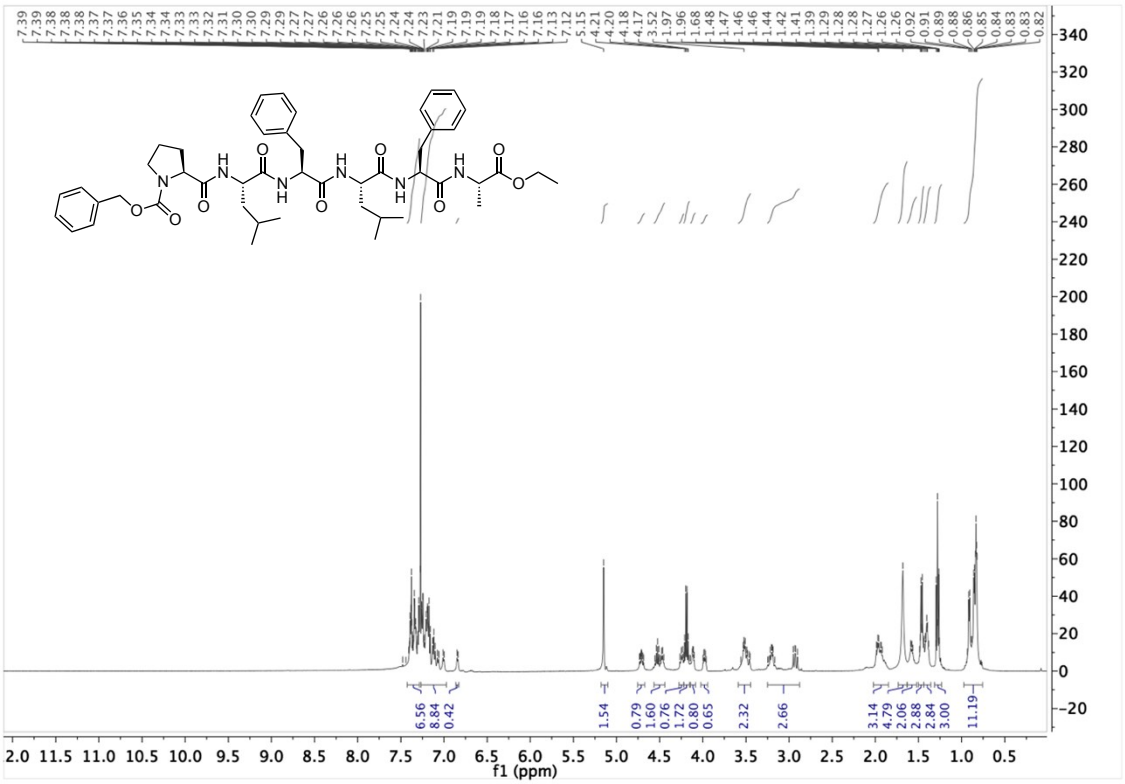


*Figure 66 : NMR ^{1}H of Cbz-L-Pro-L-Leu-L-Phe-L-Leu-L- Phe-L-Ala-OEt (**6a**)*

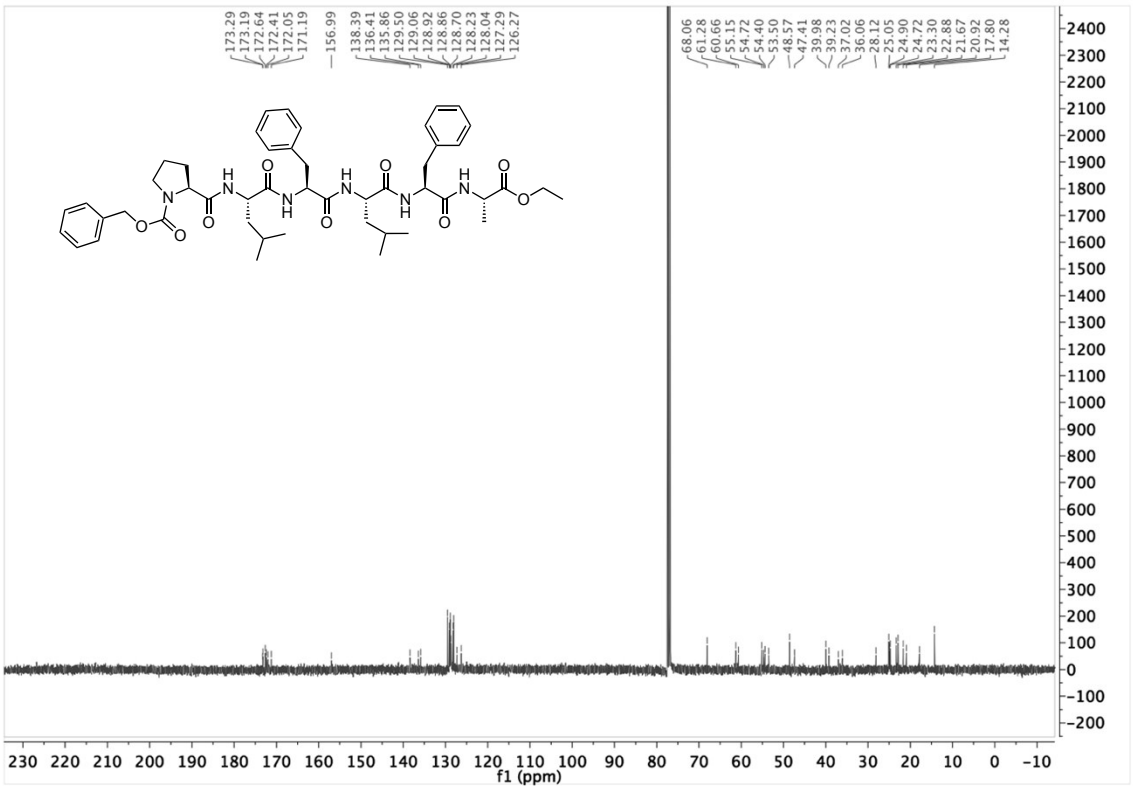


*Figure 67 : NMR ^{13}C of Cbz-L-Pro-L-Leu-L-Phe-L-Leu-L-Phe-L-Ala-OEt (**6a**)*

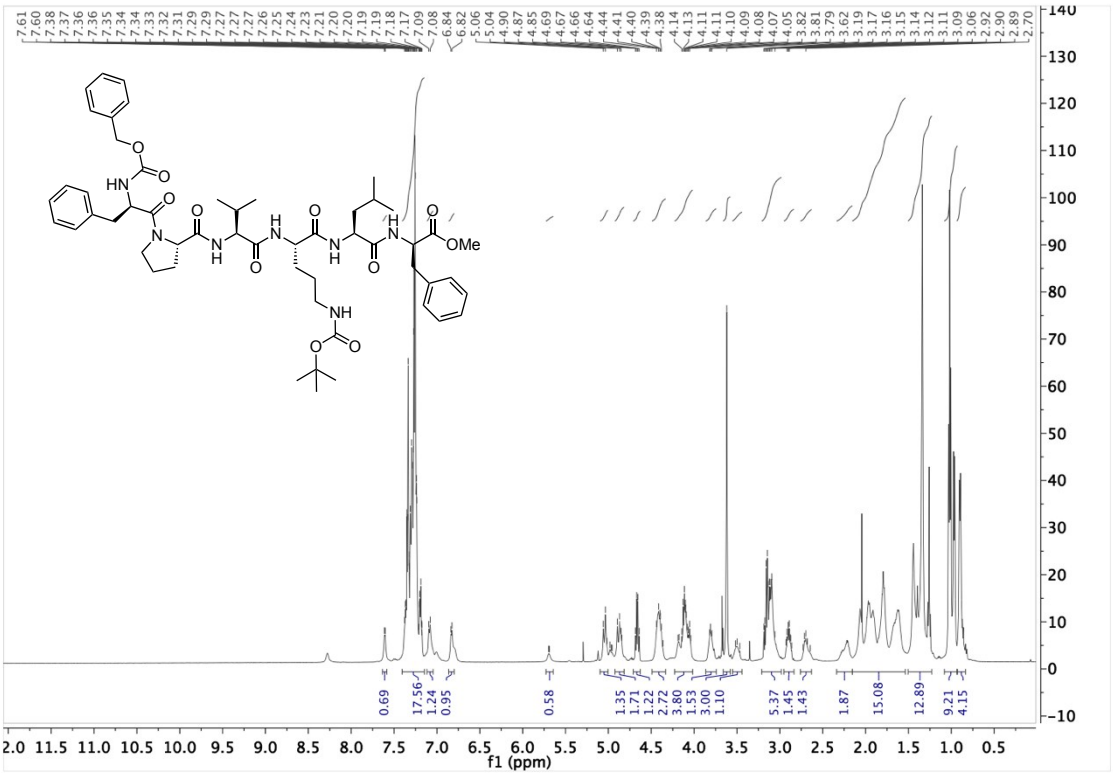


*Figure 68 : NMR [1]H of Cbz-D-Phe-L-Pro-L-Val-L-Orn(Boc)-L-Leu-D-Phe-OMe (**6b**)*

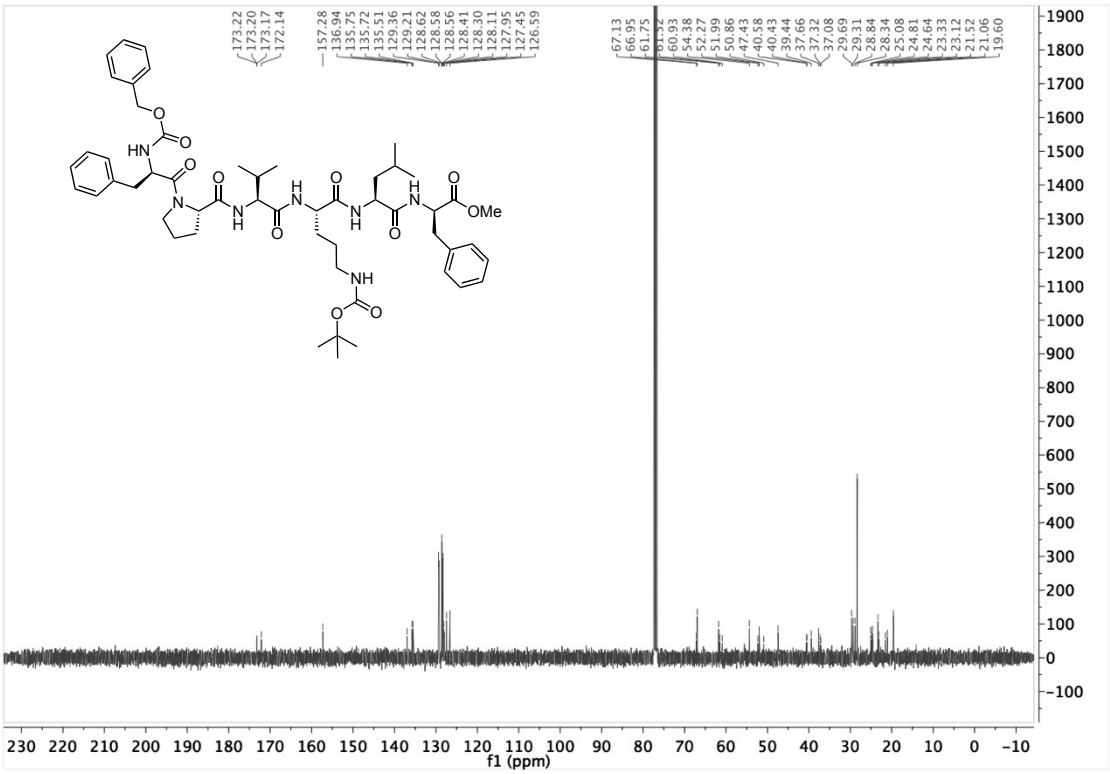


*Figure 69: NMR [13]C of Cbz-D-Phe-L-Pro-L-Val-L-Orn(Boc)-L-Leu-D-Phe-OMe (**6b**)*

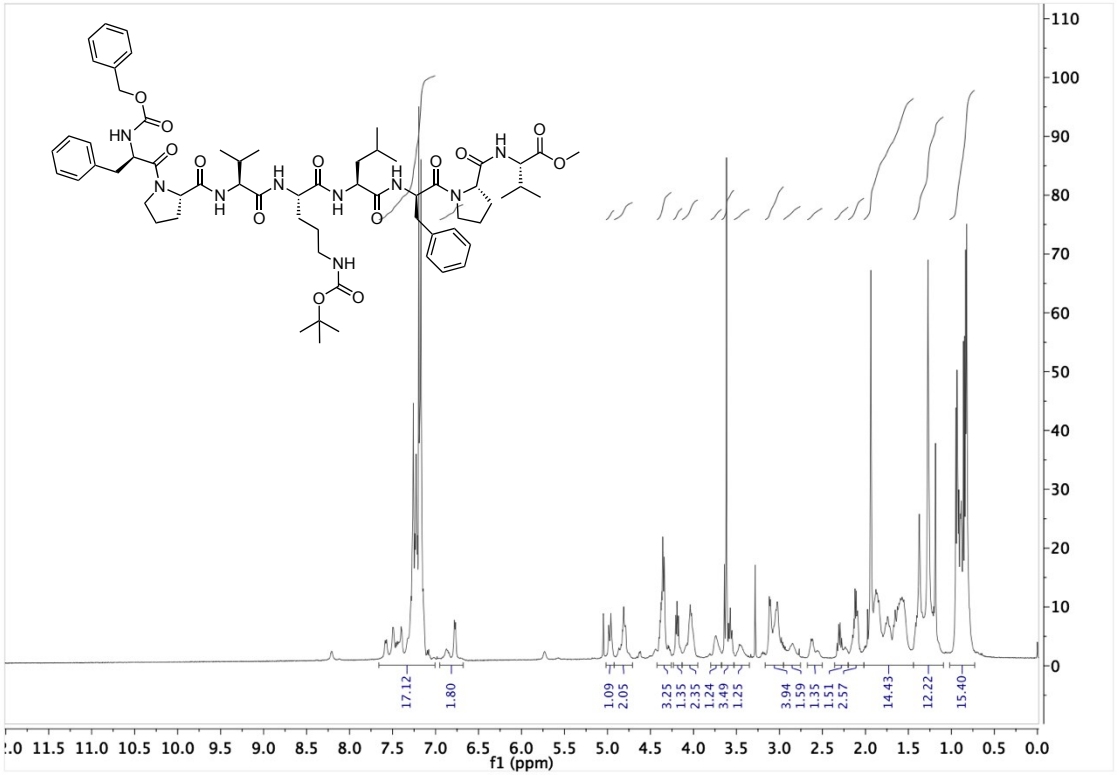


*Figure 70 : NMR ^{1}H of Cbz-D-Phe-L-Pro-L-Val-L-Orn(Boc)-L-Leu-D-Phe-L-Pro-L-Val-OMe (**8a**)*

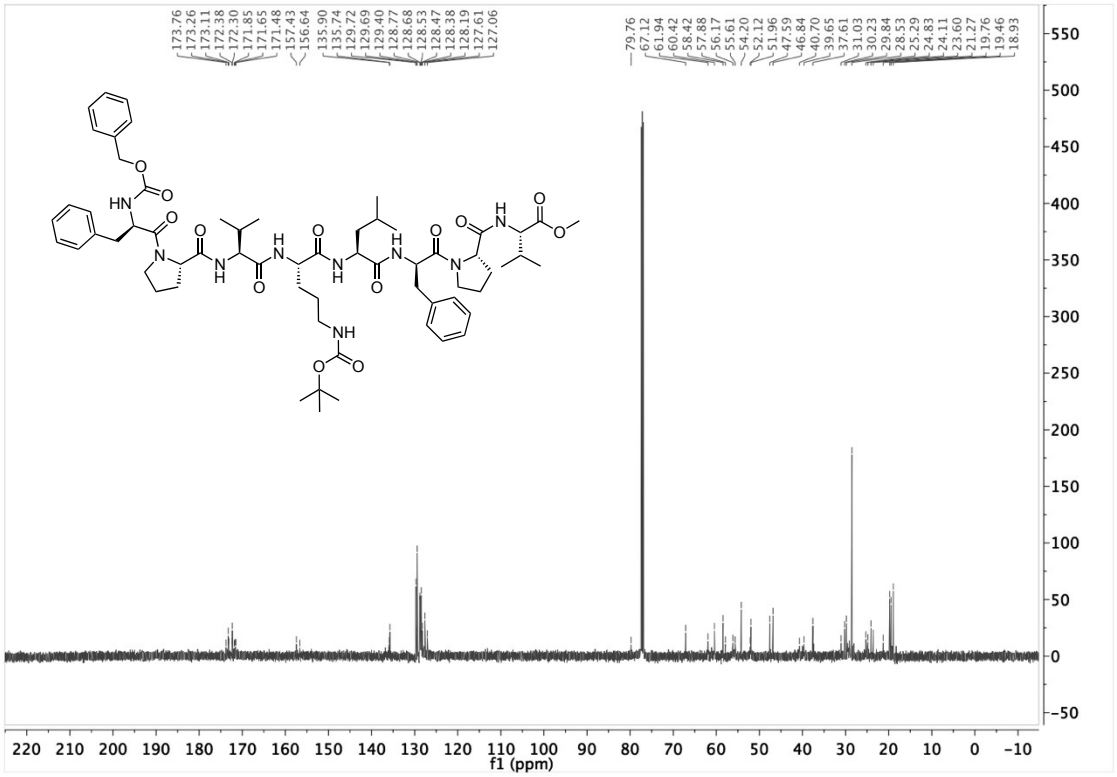


*Figure 71 : NMR ^{13}C of Cbz-D-Phe-L-Pro-L-Val-L-Orn(Boc)-L-Leu-D-Phe-L-Pro-L-Val-OMe (**8a**)*

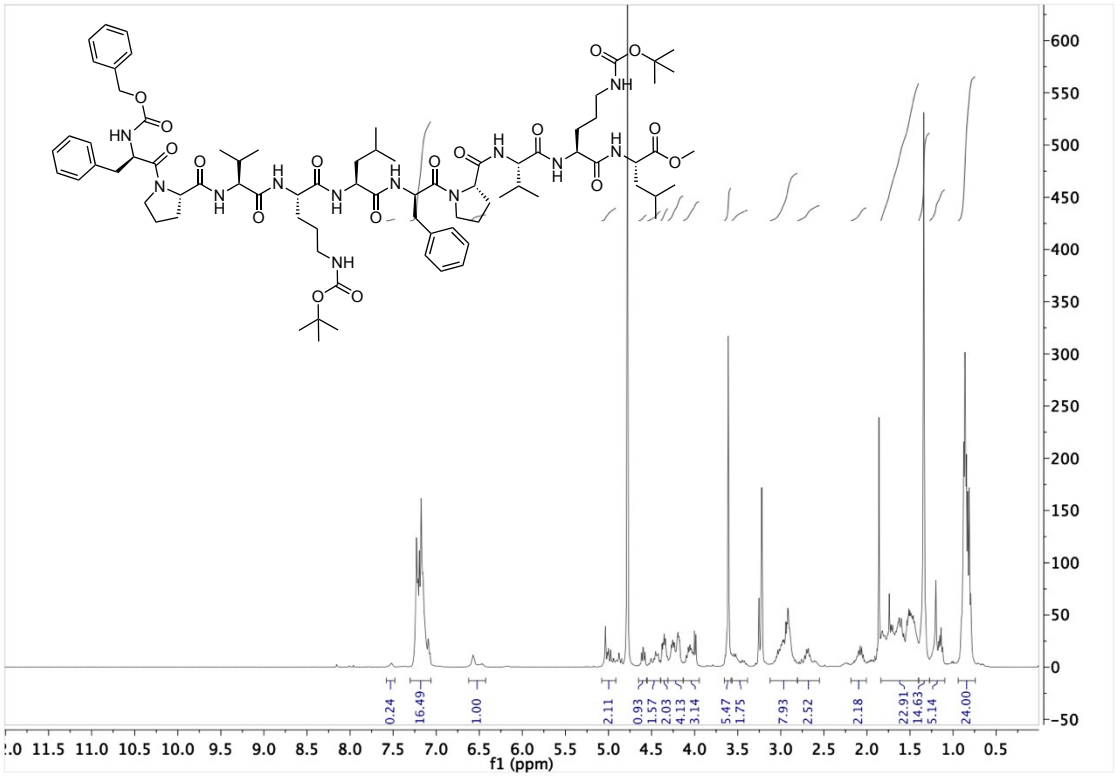


*Figure 72 : NMR ^{1}H of Cbz-D-Phe-L-Pro-L-Val-L-Orn(Boc)-L-Leu-D-Phe-L-Pro-L-Val-L-Orn(Boc)-L-Leu-OMe (**10a**)*

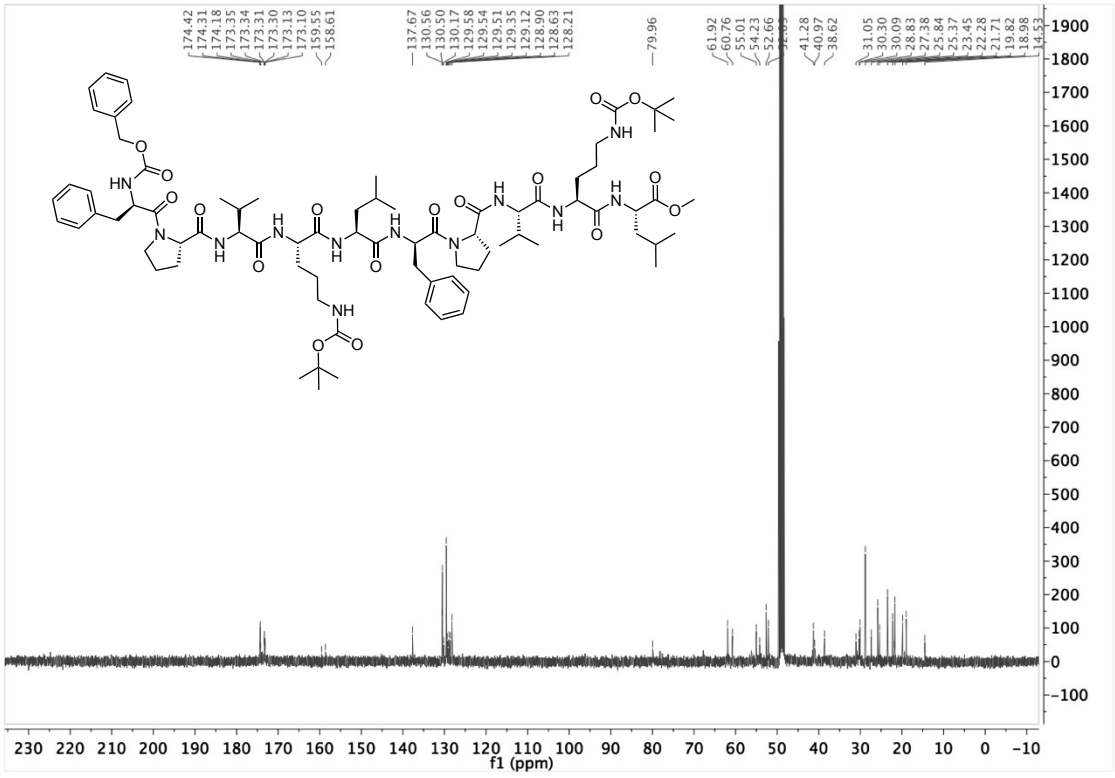


*Figure 73 : NMR ^{13}C of Cbz-D-Phe-L-Pro-L-Val-L-Orn(Boc)-L-Leu-D-Phe-L-Pro-L-Val-L-Orn(Boc)-L-Leu-OMe (**10a**)*

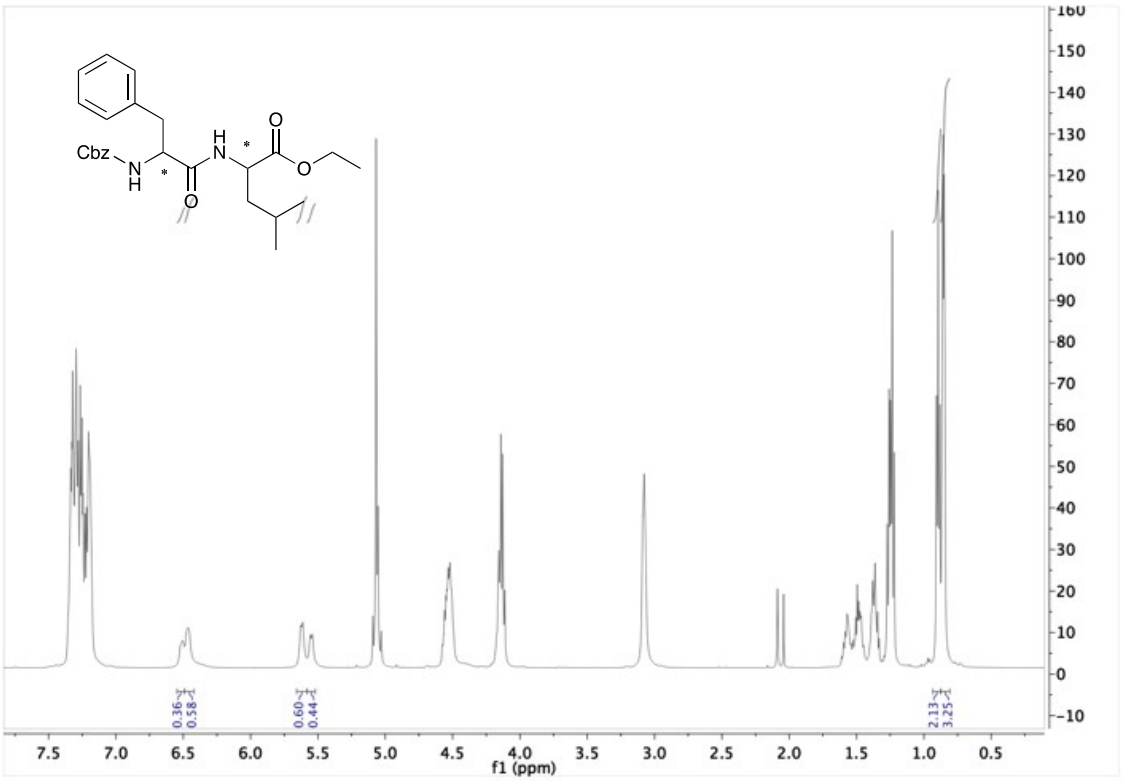


*Figure 74 : NMR ^{1}H of Cbz-DL-Phe-DL-Leu-OEt (**2a**$_{racemate}$)*