Original β,γ-diamino acid as inducer of a γ-turn mimic in short peptides.

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Supporting information

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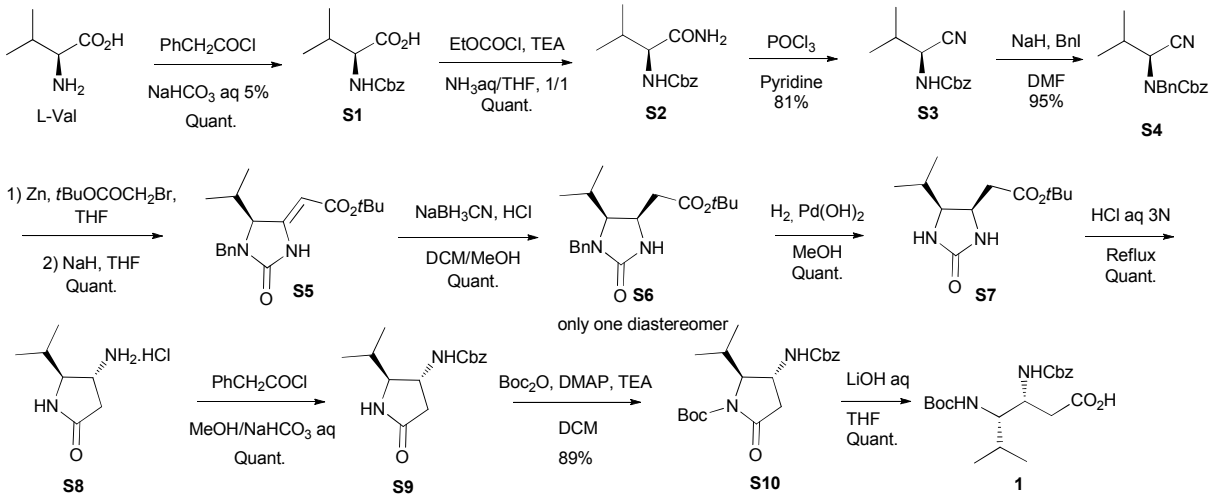
General information

Unless otherwise stated, all reactions were conducted under an atmosphere of dry argon gas. THF was distilled over sodium/benzophenone under argon. Dimethylformamide was purchased from Aldrich with a peptide synthesis grade. All other reagents were used as received. Flash chromatography was performed on Kieselgel 60 (35-70 µm) silica gel. Infrared spectra were recorded in dichloromethane (5mM) on an FT-IR spectrophotometer. ^{1}H NMR were measured at 250, 300, 400 or 500 MHz using $CDCl_3$ as solvent. Chemical shifts are reported in δ units to 0.01 ppm precision with coupling constants reported to 0.1 Hz precision using residual solvent as an internal reference. Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, bs = broad singlet. ^{13}C NMR were measured at 62.5 or 125 MHz using $CDCl_3$ as solvent. Chemical shifts are reported in δ units to 0.1 ppm precision using residual solvent as an internal reference. Mass spectra were measured on a Microtof-Q Bruker Daltonics spectrometer at the Institut de Chimie Moléculaire et des Matériaux (ICMMO) Mass Spectrometry Laboratory.

DIPEA stands for diisopropylethylamine, EDCI stands for 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, HOBt stands for hydroxybenzotriazole, TEA stands for triethylamine, TFA stands for trifluoroacetic acid.

Synthesis of compound 1



The synthesis of compound **1** has been performed as already described (see reference 11 in the paper) starting from 10 g of L-valine with the following slight modifications:

- purification by column chromatography was necessary only on compounds **S4** and **S10**.

- in the synthesis of compound **S7**, Pd/C was replaced by $Pd(OH)_2$.

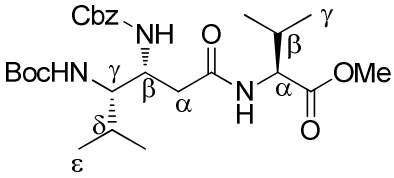
- in the synthesis of compound **S10** only 0.1 equivalent of DMAP was used (instead of 0.2 as reported in reference 11)

In these conditions, compound **1** was obtained in 68% yield (22g of compound **1** were obtained).

Synthesis of peptides

General procedure for Boc-deprotection: The *N*-Boc-protected peptide was dissolved in freshly distilled dichloromethane (concentration of the solution: 50 mM) under argon. TFA (10 equiv.) was added and the mixture was stirred at room temperature for 3h. The solution was concentrated and dried under vacuum. The residue was used in a coupling reaction step with no further purification.

Boc-(L)β,γ-Val-OMe



To a solution of L-valine methylester hydrochloride (127 mg, 761 µmol, 1 equiv.), EDCI (175 mg, 913 µmol, 1.2 equiv.), HOBt (123 mg, 913 µmol, 1.2 equiv.), DIPEA (200 µL, 1.14 mmol, 1.5 equiv.) in DMF (8 mL) was added Boc-β,γ-OH (300 mg, 761 µmol, 1 equiv.) in DMF (8 mL). The mixture was stirred overnight at room temperature. The solution was diluted with ethylacetate (30 mL). The organic layer was washed with an aqueous citric acid solution (2M) (3 x 15 mL), with a saturated $NaHCO_3$ solution (2 x 20 mL) and with brine (3 x 20 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated. 384 mg of a white powder were recovered and used further without any purification (quantitative yield).

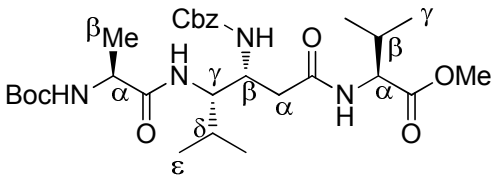
^{1}H NMR (300MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.0 Hz, 1H, NH_{val}), 7.40-7.28 (m, 5H, $H_{aromatic}$), 5.65 (d, *J* = 9.5 Hz, 1H, NH_{cbz}), 5.12 (s, 2H, CH_2Ph), 4.78 (d, *J* = 9.6 Hz, 1H, $NH_{\beta,\gamma}$), 4.45 (dd, *J* = 7.7, 5.4 Hz, 1H, $H_{\alpha\ val}$), 3.98 (m, 1H, $H_{\beta\ \beta,\gamma}$), 3.73 (s, 3H, OCH_3), 3.80-3.66 (m, 1H, $H_{\gamma\ \beta,\gamma}$), 2.56-2.52 (m, 2H, $H_{\alpha\ \beta,\gamma}$), 2.23 (m, 1H, $H_{\beta\ val}$), 2.05 (m, 1H, $H_{\delta\ \beta,\gamma}$), 1.46 (s, 9H, $C(CH_3)_3$), 0.99-0.89 (m, 12H, $H_{\varepsilon\ \beta,\gamma} + H_{\gamma\ val}$).

^{13}C NMR (62.5MHz, $CDCl_3$): δ 172.7, 171.1, 157.2, 156.2, 136.7, 128.5, 128.0, 80.0, 66.7, 58.0, 57.7, 52.2, 50.4, 37.3, 30.2, 28.3, 28.2, 20.3, 19.1, 17.7, 16.2.

ESI-MS: Calculated for $C_{26}H_{41}N_3NaO_7$: 530.2837 $[M+Na]^+$, observed: 530.2811 $[M+Na]^+$

IR (5 mM, CH_2Cl_2) ν (cm^{-1}) 3423, 3291, 1717, 1695.

Boc-Ala-(L)β,γ-Val-OMe 4a



The dipeptide (40 mg, 79 µmol, 1 equiv.) was deprotected at the *N*-terminal position according to the above reported procedure. To a solution of the deprotected peptide (79 µmol, 1 equiv.), EDCI (18 mg, 95 µmol, 1.2 equiv.), HOBt (13 mg, 95 µmol, 1.2 equiv.), DIPEA (20 µL, 118 µmol, 1.5 equiv.) in

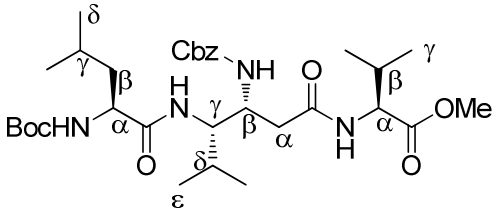
DMF (1 mL) was added BocAlaOH (15 mg, 79 µmol, 1 equiv.) in DMF (0.4 mL). The mixture was stirred overnight at room temperature. The solution was diluted with ethylacetate (15 mL). The organic layer was washed with an aqueous citric acid solution (2M) (3 x 10 mL), with a saturated $NaHCO_3$ solution (2 x 10 mL) and with brine (3 x 10mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography (SiO_2, Heptane/AcOEt, 30/70, v/v) to afford 17 mg of a white powder (37 % yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, *J*=6.2 Hz, 1H, NH_{val}), 7.43-7,30 (m, 5H, $H_{aromatic}$), 6.77 (d, *J*=9.2 Hz, 1H, $NH_{\beta,\gamma}$), 6.04 (d, *J*=9.0 Hz, 1H, NH_{Cbz}), 5.11 (bs, 2H, CH_2Ph), 4.92 (d, *J*=6.3 Hz, 1H, NH_{ala}), 4.42 (m, 1H, $H_{\alpha\ val}$), 4.30 (m, 1H, $H_{\beta\ \beta,\gamma}$), 4.09 (m, 1H, $H_{\alpha\ ala}$), 3.76 (s, 3H,OCH_3), 3.58 (m, 1H, $H_{\gamma\ \beta,\gamma}$), 2.56 (dd, *J*=4.0 Hz, *J*=14.5 Hz, 1H, $H_{\alpha 2\ \beta,\gamma}$), 2.46 (dd, *J*=4.5 Hz, *J*=14.5 Hz, 1H, $H_{\alpha 1\ \beta,\gamma}$), 2.20 (m, 1H, $H_{\beta\ val}$), 2.07 (m, 1H, $H_{\delta\ \beta,\gamma}$), 1.46 (s, 9H, $C(CH_3)_3$), 1.38 (d, *J*=7.0 Hz, 3H, $H_{\beta\ ala}$), 1.00-0.94 (m, 6H, $H_{\gamma\ val}$), 0.96-0.89 (m, 6H, $H_{\varepsilon\ \beta,\gamma}$)

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.7, 173.2, 172.1, 156.1, 136.6, 128.3, 127.8, 80.5, 66.5, 57.8, 57.6, 52.1, 50.8, 49.7, 37.3, 30.1, 28.7, 28.2, 20.5, 19.0, 17.9, 17.7, 17.1

ESI-MS: Calculated for $C_{29}H_{46}N_4NaO_8$: 601.3208 $[M+Na]^+$, observed: 601.3186 $[M+Na]^+$
IR (5 mM, CH_2Cl_2) ν (cm^{-1}) 3419, 3340, 1719, 1698, 1673.

Boc-Leu-(L)β,γ-Val-OMe 4b



The dipeptide (340 mg, 671 µmol, 1 equiv.) was deprotected at the *N*-terminal position according to the above reported procedure. To a solution of L-Boc-leucine (155 mg, 671 µmol, 1 equiv.), EDCI (154 mg, 805 µmol, 1.2 equiv.), HOBt (109 mg, 805 µmol, 1.2 equiv.), DIPEA (175 µL, 1.0 mmol, 1.5 equiv.) in DMF (3 mL) was added the deprotected dipeptide in DMF (3 mL). The mixture was stirred overnight at room temperature. The solution was diluted with ethylacetate (15 mL). The organic layer was washed with an aqueous citric acid solution (2M) (3 x 10 mL), with a saturated $NaHCO_3$ solution (2 x 10 mL) and with brine (3 x 10mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography (SiO_2, 100% AcOEt) to afford 415 mg of a white powder (quantitative yield).

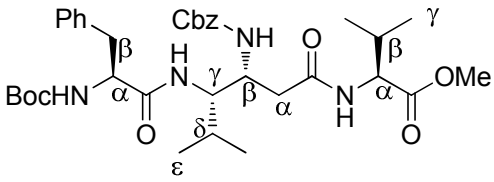
^{1}H NMR (250MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.9 Hz, 1H, NH_{val}), 7.37-7.32 (m, 5H, $H_{aromatic}$), 6.88 (d, *J* = 9.2 Hz, 1H, $NH_{\beta,\gamma}$), 6.09 (d, *J* = 9.2 Hz, 1H, NH_{cbz}), 5.11 (s, 2H, CH_2Ph), 4.97 (d, *J* = 7.3 Hz, 1H, NH_{leu}), 4.43 (dd, *J* = 7.9, 5.6 Hz, 1H, $H_{\alpha\ val}$), 4.35 (m, 1H, $H_{\beta\ \beta,\gamma}$), 4.05 (dt, *J* = 7.2, 2.0 Hz 1H, $H_{\alpha\ leu}$), 3.76 (s, 3H, OCH_3), 3.53 (m, 1H, $H_{\gamma\ \beta,\gamma}$), 2.55 (dd, *J*=14.3, 4.1 Hz, 1H, $H_{\alpha 2\ \beta,\gamma}$), 2.45 (dd, *J*=14.3, 4.1 Hz, 1H, $H_{\alpha 1\ \beta,\gamma}$), 2.29-2.03 (m, 2H, $H_{\beta\ val}$ + $H_{\delta\ \beta,\gamma}$), 1.79-1.60 (m, 3H, $H_{\beta\ leu}$ + $H_{\gamma\ leu}$), 1.45 (s, 9H, $C(CH_3)_3$), 0.99-0.88 (m, 18H, $H_{\delta\ leu}$ + $H_{\varepsilon\ \beta,\gamma}$ + $H_{\gamma\ val}$)

^{13}C NMR (62.5MHz, $CDCl_3$): δ 176.6, 172.7, 172.6, 156.4, 155.6, 136.7, 128.3, 128.2, 127.8, 79.8, 66.7, 58.1, 57.9, 52.2, 52.0, 41.7, 38.6, 30.2, 28.3, 26.4, 24.8, 22.9, 21.8, 20.5, 19.0, 17.9, 17.4

ESI-MS: Calculated for $C_{32}H_{52}N_4NaO_8$: 643.3677 $[M+Na]^+$, observed: 643.3669 $[M+Na]^+$

IR (5 mM, CH_2Cl_2) ν (cm^{-1}) 3415, 3339, 1723, 1703, 1698, 1675

Boc-Phe-(L)β,γ-Val-OMe 4c



The dipeptide (51 mg, 101 µmol, 1 equiv.) was deprotected at the *N*-terminal position according to the above reported procedure. To a solution of the deprotected peptide (101 µmol, 1 equiv.), EDCI (23 mg, 122 µmol, 1.2 equiv.), HOBt (16.5 mg, 122 µmol, 1.2 equiv.), DIPEA (35 µL, 202 µmol, 2 equiv.) in DMF (1.5 mL) was added BocPheOH (27 mg, 101 µmol, 1 equiv.) in DMF (1.5 mL). The mixture was stirred overnight at room temperature. The solution was diluted with ethylacetate (20 mL). The organic layer was washed with an aqueous citric acid solution (2M) (3 x 15 mL), with a saturated $NaHCO_3$ solution (2 x 15 mL) and with brine (3 x 15mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography (SiO_2, Heptane/AcOEt, 30/70, v/v) to afford 29 mg of a white powder (44 % yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, *J*=7.9 Hz, 1H, NH_{val}), 7.38-7,22 (m, 10H, $H_{aromatic}$), 6.31 (d, *J*=9.8 Hz, 1H, $NH_{\beta,\gamma}$), 5.73 (d, *J*=9.2 Hz, 1H, NH_{cbz}), 5.08 (bs, 2H, CH_2Ph), 4.89 (d, *J*=7.6 Hz, 1H, NH_{phe}), 4.42 (m, 1H, $H_{\alpha\ val}$), 4.34 (m, 1H, $H_{\alpha\ phe}$), 4.04 (m, 1H, $H_{\beta\ \beta,\gamma}$), 3.74 (s, 3H, OCH_3), 3.69 (m, 1H, $H_{\gamma\ \beta,\gamma}$), 3.09 (dd, *J*=7.4 Hz, *J*=13.8 Hz, 1H, $H_{\beta 2\ phe}$), 3.02 (dd, *J*=7.0 Hz, *J*=13.8 Hz, 1H, $H_{\beta 1\ phe}$), 2.25 (dd, *J*=14.8, 3.2 Hz, 1H, $H_{\alpha 2\ \beta,\gamma}$), 2.19 (m, 1H, $H_{\beta\ val}$), 2.14 (dd, *J*=14.8, 4.5 Hz, 1H, $H_{\alpha 1\ \beta,\gamma}$), 1.97 (m, 1H, $H_{\delta\ \beta,\gamma}$), 1.42 (s, 9H, $C(CH_3)_3$), 0.98 (d, *J*=6.8 Hz, 3H, $H_{\gamma\ val}$), 0.96 (d, *J*=6.8 Hz, 3H, $H_{\gamma\ val}$), 0.88-0.79 (m, 6H, $H_{\varepsilon\ \beta,\gamma}$)

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.9, 172.3, 171.5, 156.0, 155.8, 136.5, 136.3, 129.2, 128.8, 128.3, 127.8, 127.1, 80.6, 66.6, 57.8, 57.8, 57.4, 56.3, 52.1, 49.7, 37.5, 36.9, 30.2, 28.4, 28.3, 19.0, 17.9, 16.7

ESI-MS: Calculated for $C_{35}H_{50}N_4NaO_8$: 677.3526 $[M+Na]^+$, observed: 677.3518 $[M+Na]^+$

IR (5 mM, CH_2Cl_2) ν (cm^{-1}) 3417, 3339, 1717, 1667.

Coupling constants and NOE correlations of peptides

Coupling constants of **Boc-Ala-β,γ-Val-OMe 4a** in $CDCl_3$ at 293K in Hz

J ^{1}H-^{1}H(Hz)	Ala	β,γ	Val
^3J (H^{α}-H^{N})	6.3	-	6.2
^3J (H^{γ}-H^{N})	-	9.2	-
^3J (H^{β}-H^{N})	-	9.0	-
^3J ($H^{\alpha1}$-H^{β})	-	4.5	-
^3J ($H^{\alpha2}$-H^{β})	-	4.0	-

Coupling constants of **Boc-Leu-β,γ-Val-OMe 4b** in $CDCl_3$ at 293K in Hz

J ^{1}H-^{1}H(Hz)	Leu	β,γ	Val
^3J (H^{α}-H^{N})	7.3	-	7.9
^3J (H^{γ}-H^{N})	-	9.2	-
^3J (H^{β}-H^{N})	-	9.2	-
^3J (H^{α}-H^{β})	2.0	-	5.6
^3J ($H^{\alpha1}$-H^{β})	-	4.1	-
^3J ($H^{\alpha2}$-H^{β})	-	4.1	-

Coupling constants of **Boc-Phe-β,γ-Val-OMe 4c** in $CDCl_3$ at 293K in Hz

J ^{1}H-^{1}H(Hz)	Phe	β,γ	Val
^3J (H^{α}-H^{N})	7.6	-	7.9
^3J (H^{γ}-H^{N})	-	9.6	-
^3J (H^{β}-H^{N})	-	9.2	-
^3J (H^{α}-$H^{\beta1}$)	7.0	-	-
^3J (H^{α}-$H^{\beta2}$)	7.4	-	-
^3J ($H^{\alpha1}$-H^{β})	-	4.5	-
^3J ($H^{\alpha2}$-H^{β})	-	3.2	-

Inter-residue NOEs observed in the ROESY NMR spectrum of **Boc-Ala-β,γ-Val-OMe 4a** ($CDCl_3$, 500 MHz, 293K).

		Boc	Ala	β,γ	Val	OMe
i, i+1	H^{α}-H^{α}					
	H^{β}-$H^{N\beta,\gamma}$					
	H^{α}-$H^{N\beta,\gamma}$					
	$H^{\alpha 1}$-H^{N}					
	$H^{\alpha 2}$-H^{N}					
	H^{β}-H^{N}					
	H^{γ}-H^{N}					
i, i+2	H^{α}-H^{γ}					
	H^{α}-H^{N}					

(**strong**, **medium**, **weak**)

Inter-residue NOEs observed in the NOESY NMR spectrum of **Boc-Leu-β,γ-Val-OMe 4b** ($CDCl_3$, 500 MHz, 293K)

		Boc	Leu	β,γ	Val	OMe
i, i+1	H^{α}-$H^{N\beta,\gamma}$					
	H^{N}-H^{N}					
	$H^{\alpha 2}$-H^{N}					
	H^{β}-H^{β}					
	H^{δ}-H^{α}					
	H^{γ}-H^{N}					

(**strong**, **medium**, **weak**)

Inter-residue NOEs observed in the NOESY NMR spectrum of **Boc-Phe-β,γ-Val-OMe 4c** ($CDCl_3$, 500 MHz, 293K)

		Boc	Phe	β,γ	Val	OMe
i, i+1	H^{α}-H^{N}					
	H^{N}-$H^{N\beta,\gamma}$					
	$H^{\alpha 1}$-H^{N}					
	$H^{\alpha 2}$-H^{N}					
	H^{β}-H^{N}					
	H^{γ}-H^{N}					
i, i+2	H^{α}-H^{N}					
i, i+3	HBoc-H^{N}					

(**strong**, **medium**, **weak**)

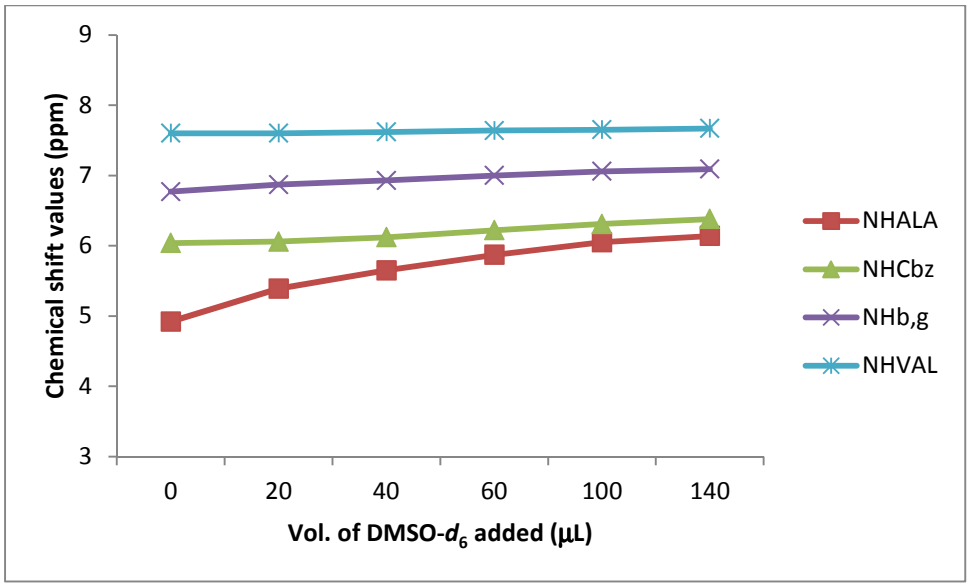
Titrations: δ (ppm) versus total volume (in µL) of added DMSO in 500 µL of a 5 mM solution of tripeptide in $CDCl_3$.

After addition of 140 µL of DMSO : $\Delta\delta = 0.07$ Å for **Boc-Ala-β,γ-Val-OMe 4a**

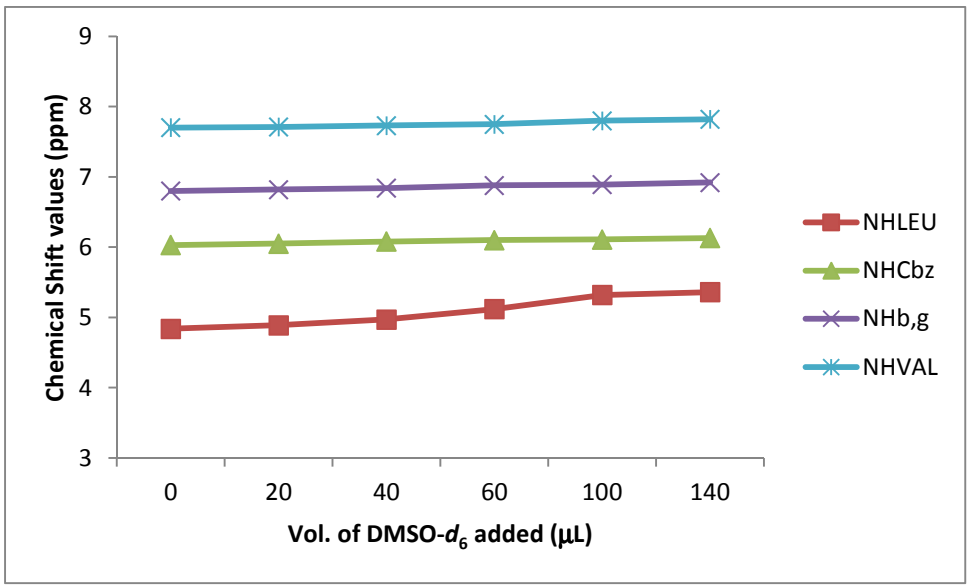
After addition of 140 µL of DMSO : $\Delta\delta = 0.12$ Å for **Boc-Leu-β,γ-Val-OMe 4b**

After addition of 60 µL of DMSO : $\Delta\delta = 0.03$ Å for **Boc-Phe-β,γ-Val-OMe 4c**

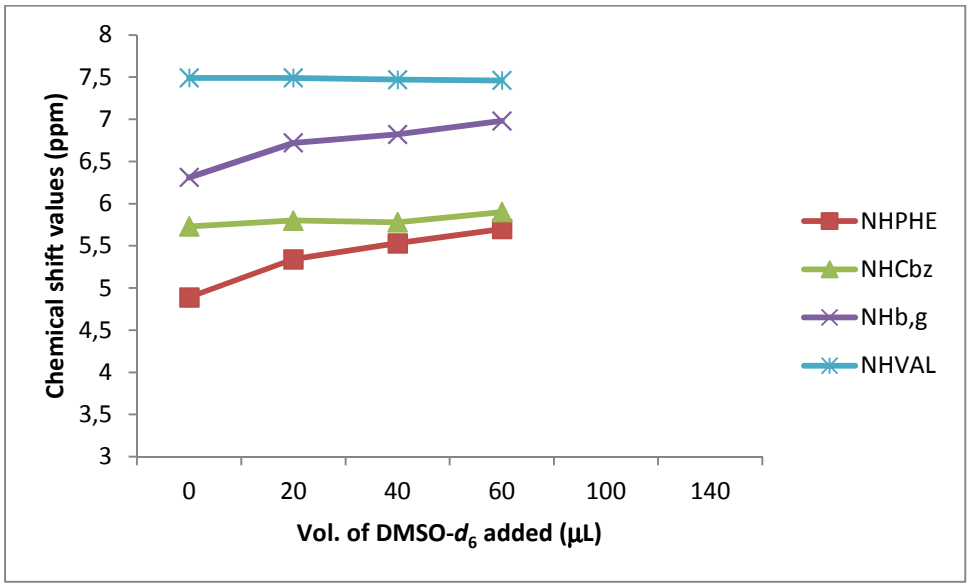
Boc-Ala-β,γ-Val-OMe 4a

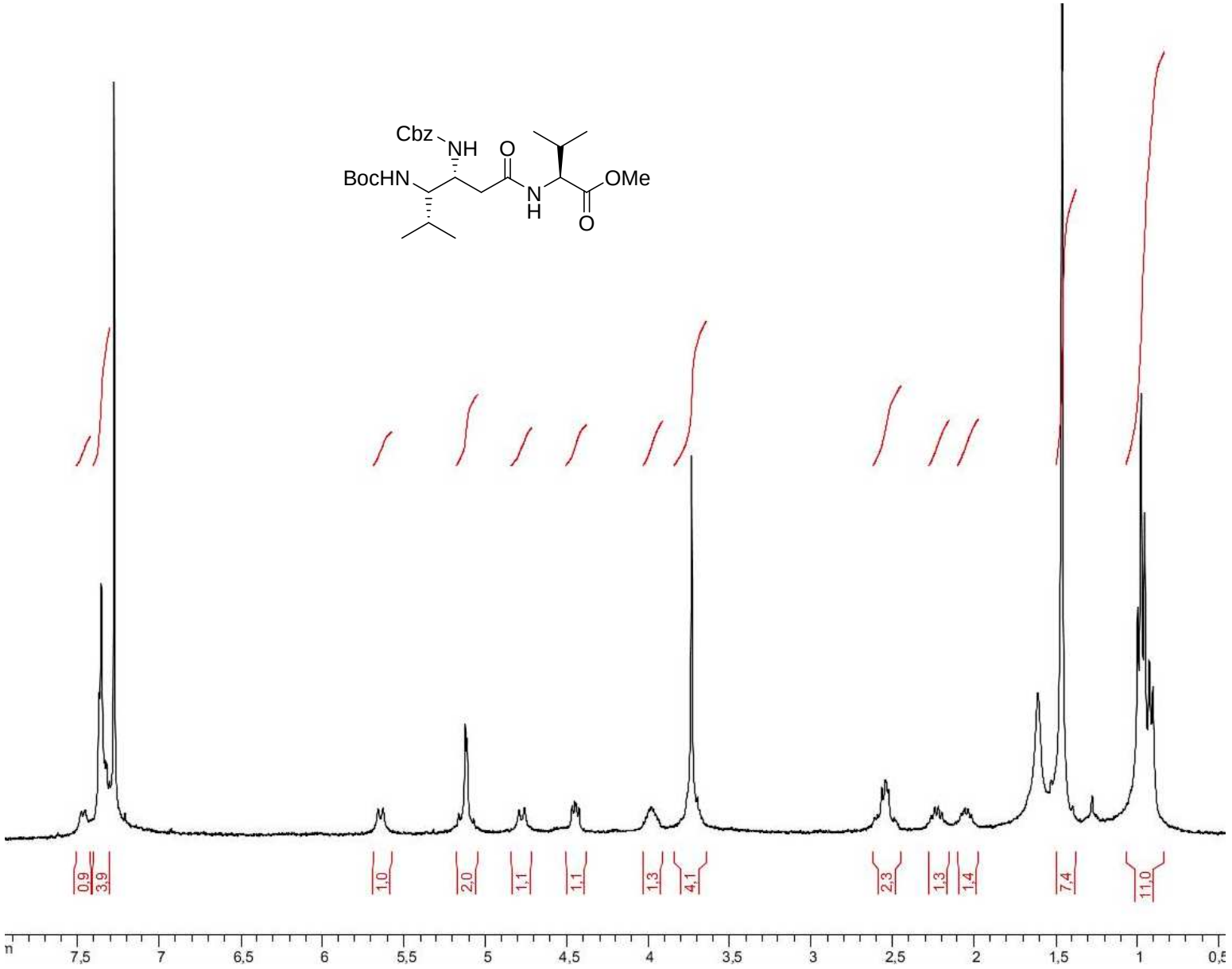


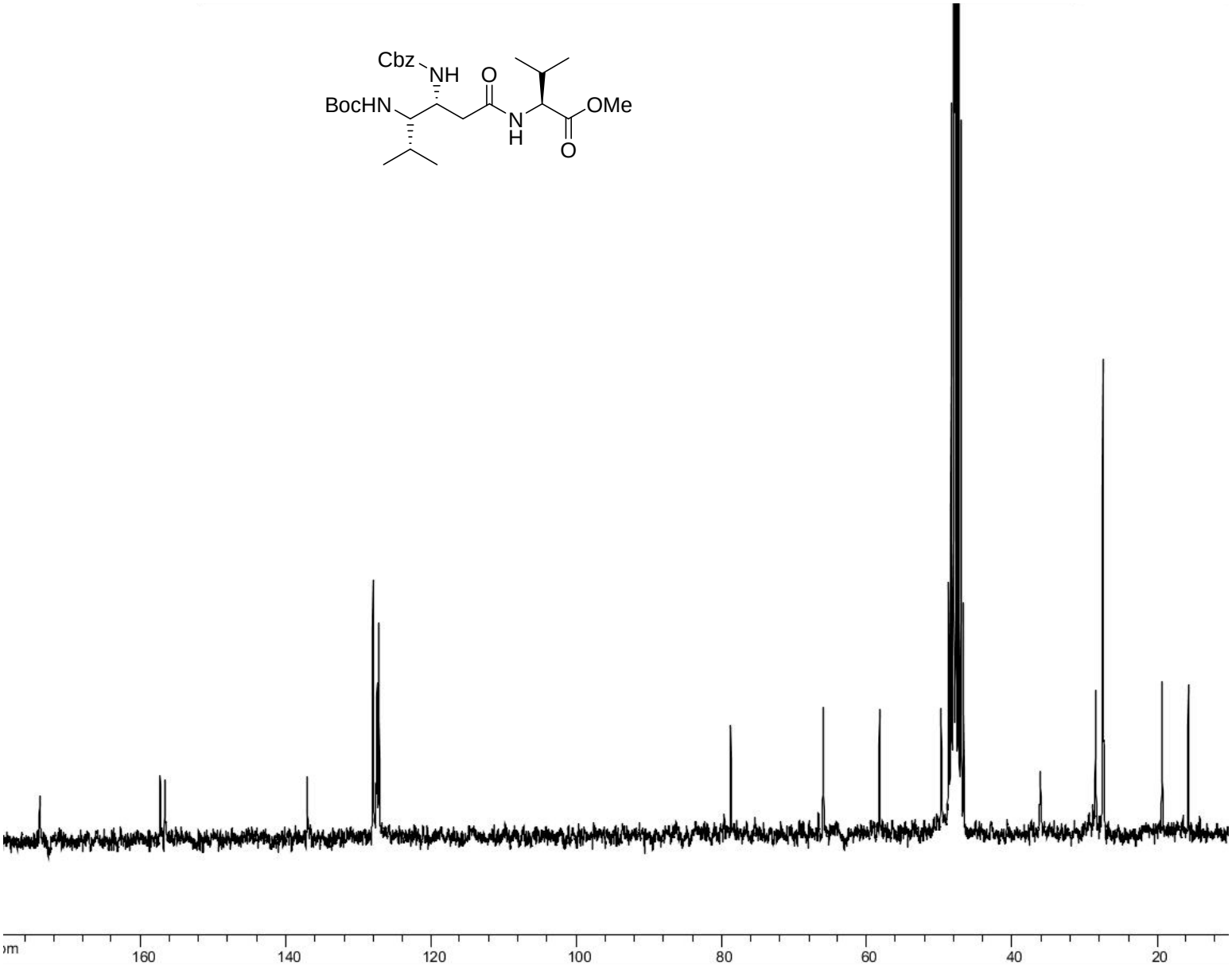
Boc-Leu-β,γ-Val-OMe 4b

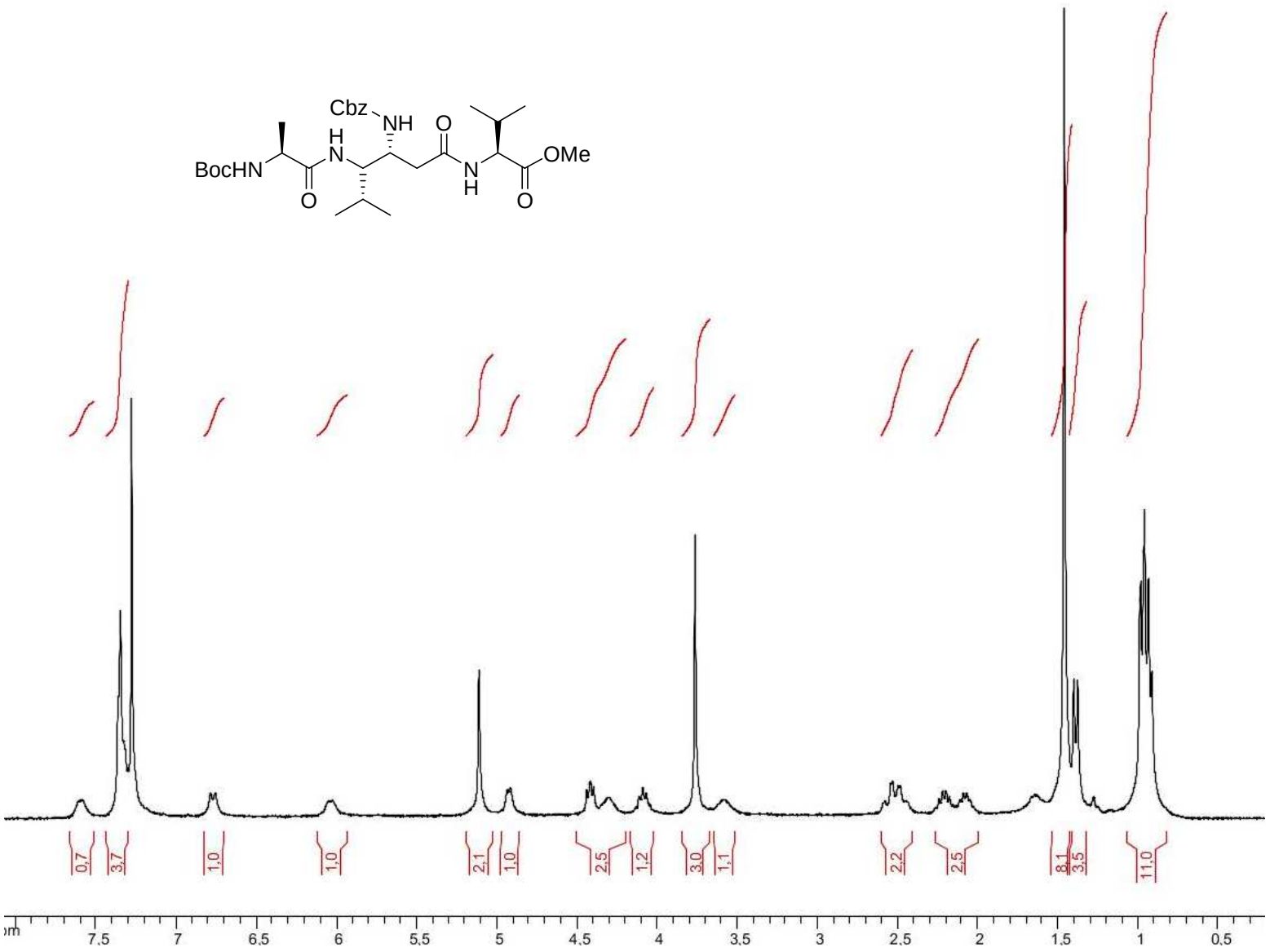


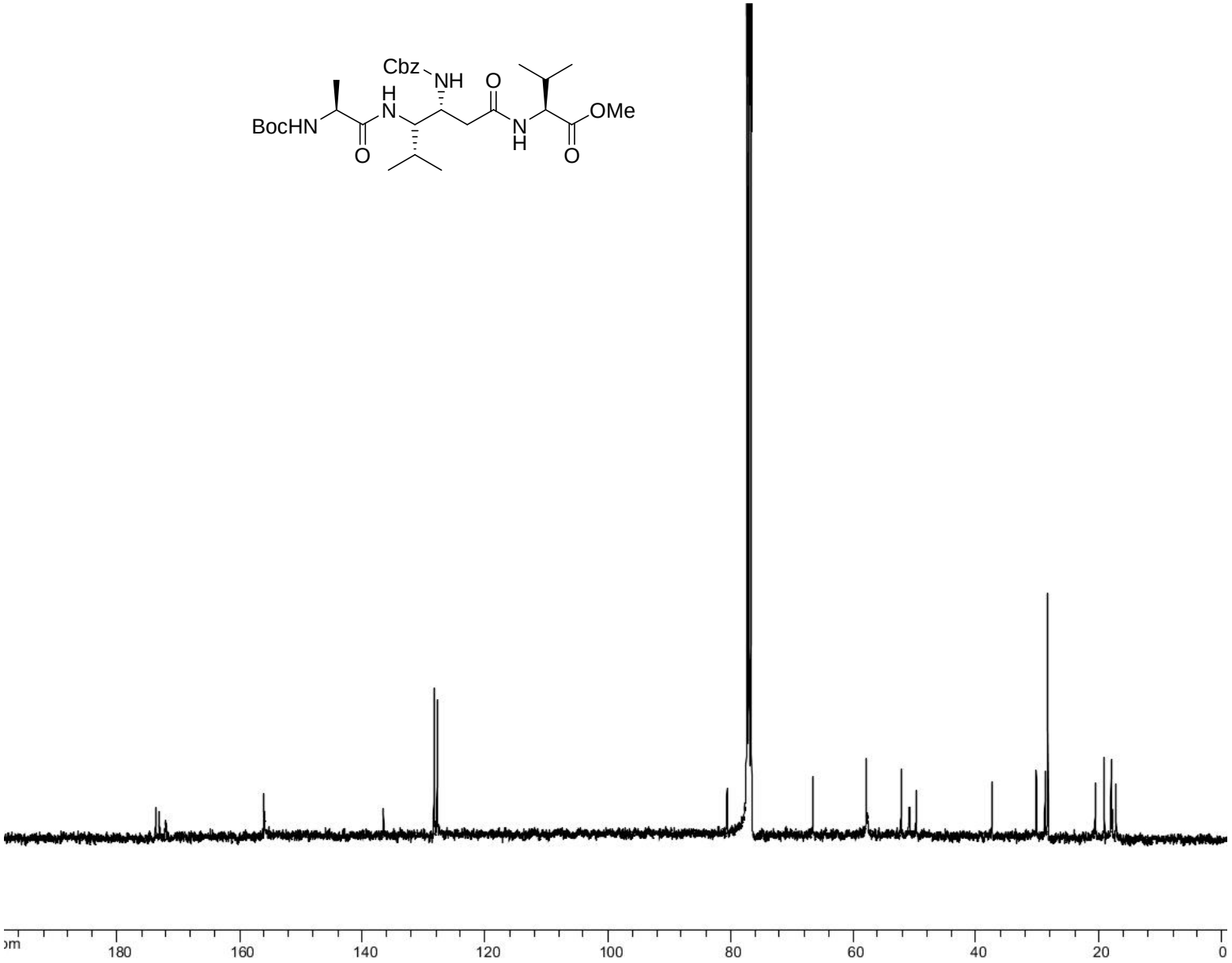
Boc-Phe-β,γ-Val-OMe 4c

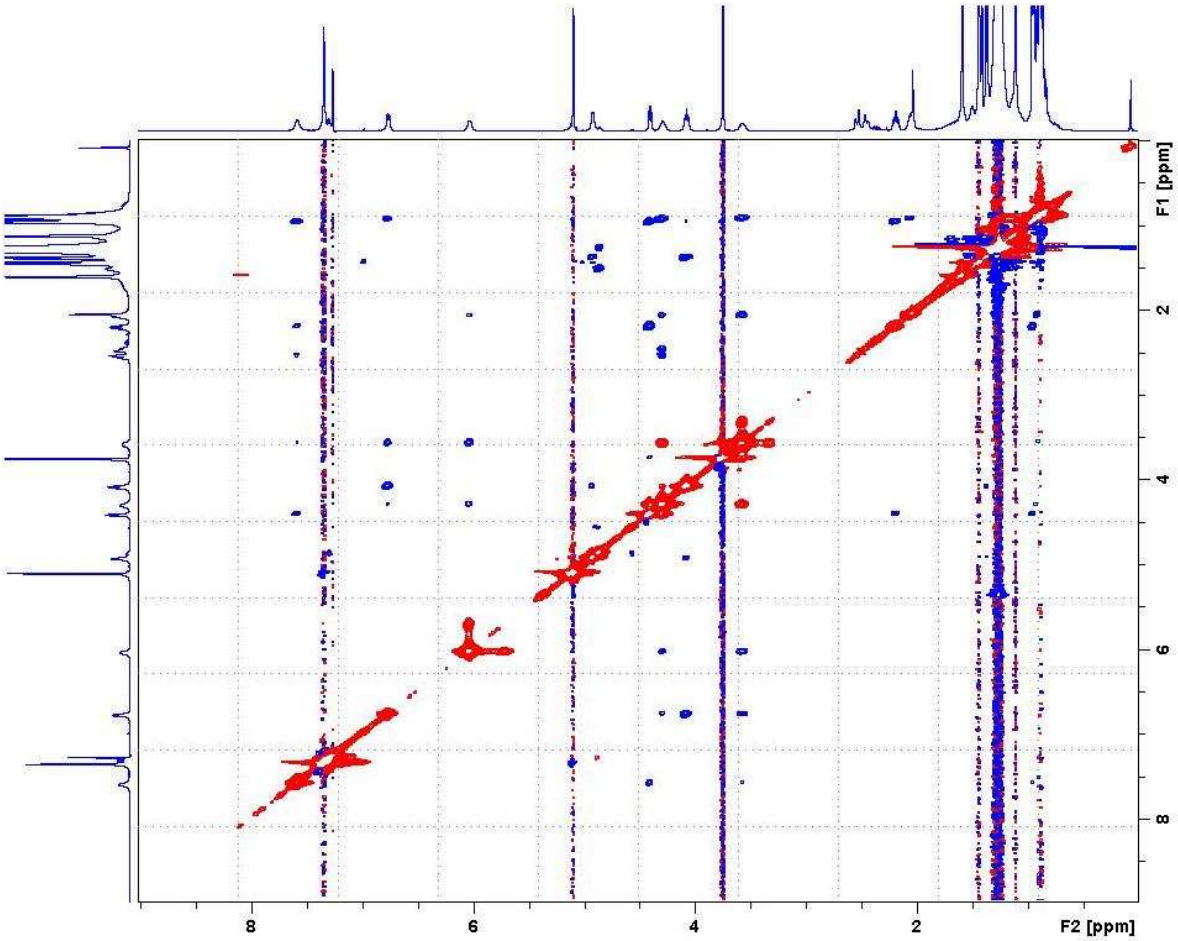




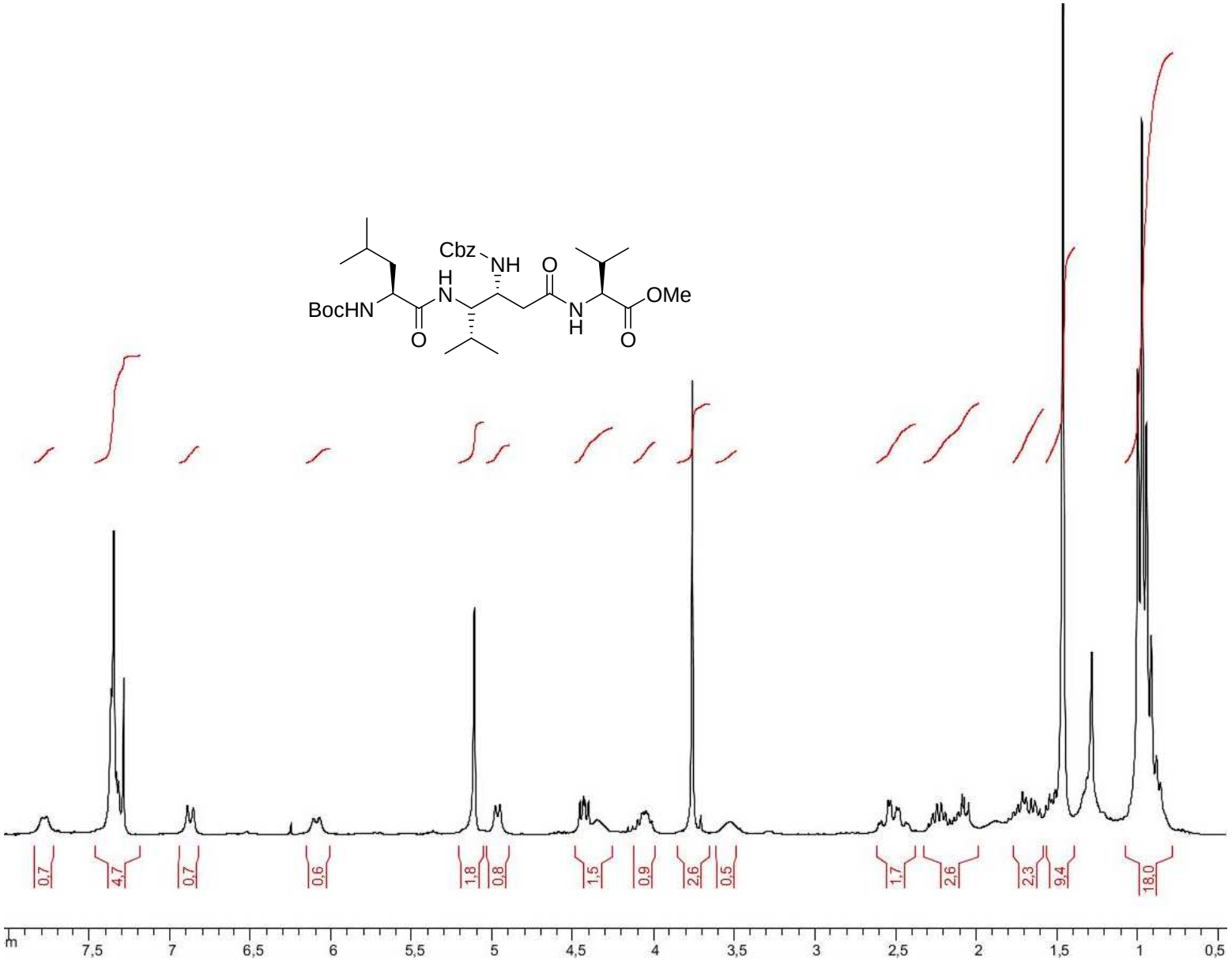


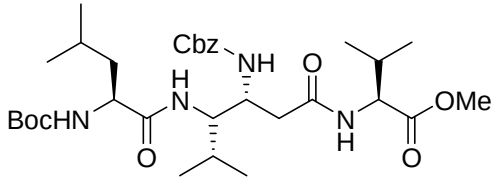


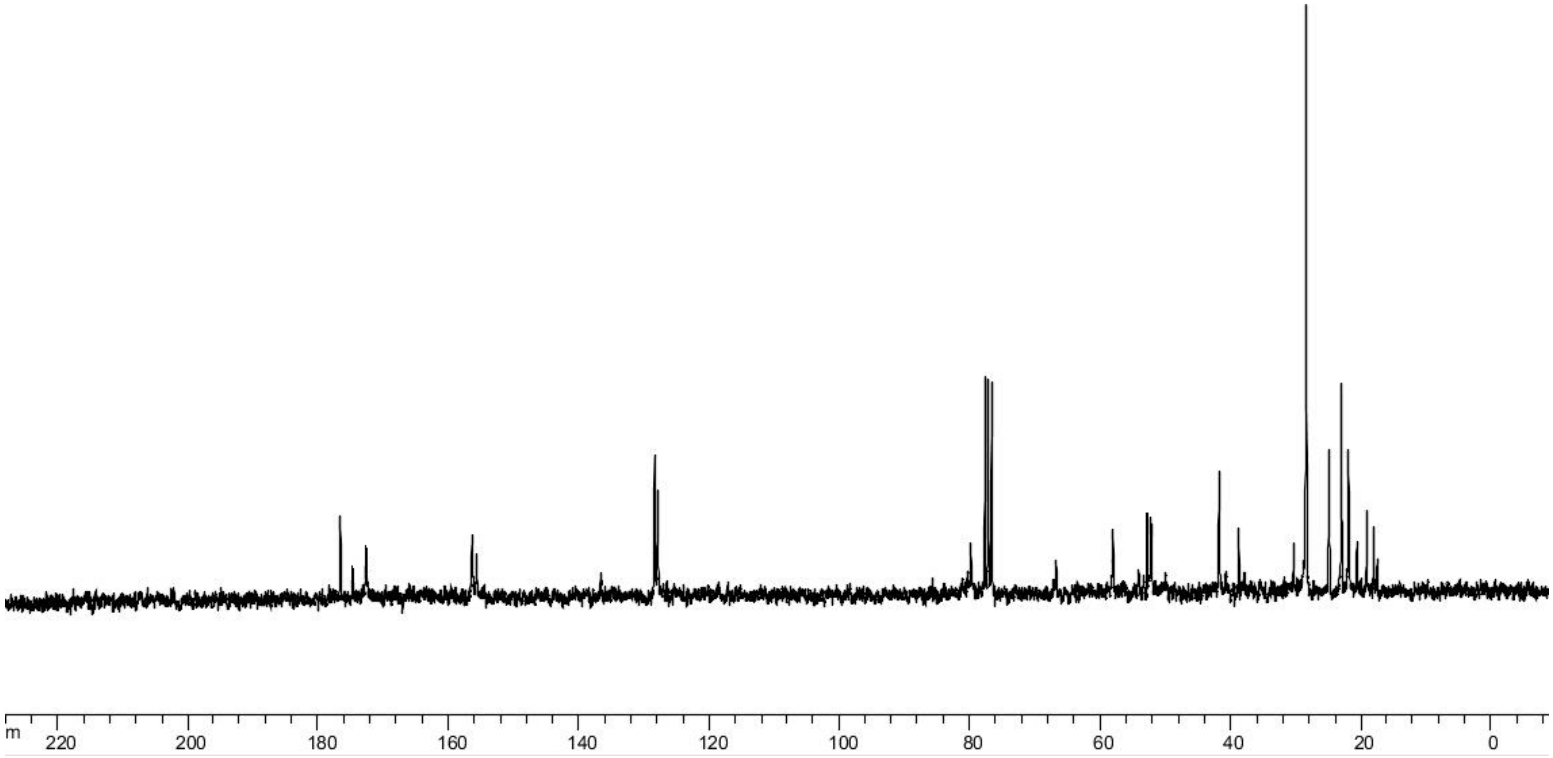


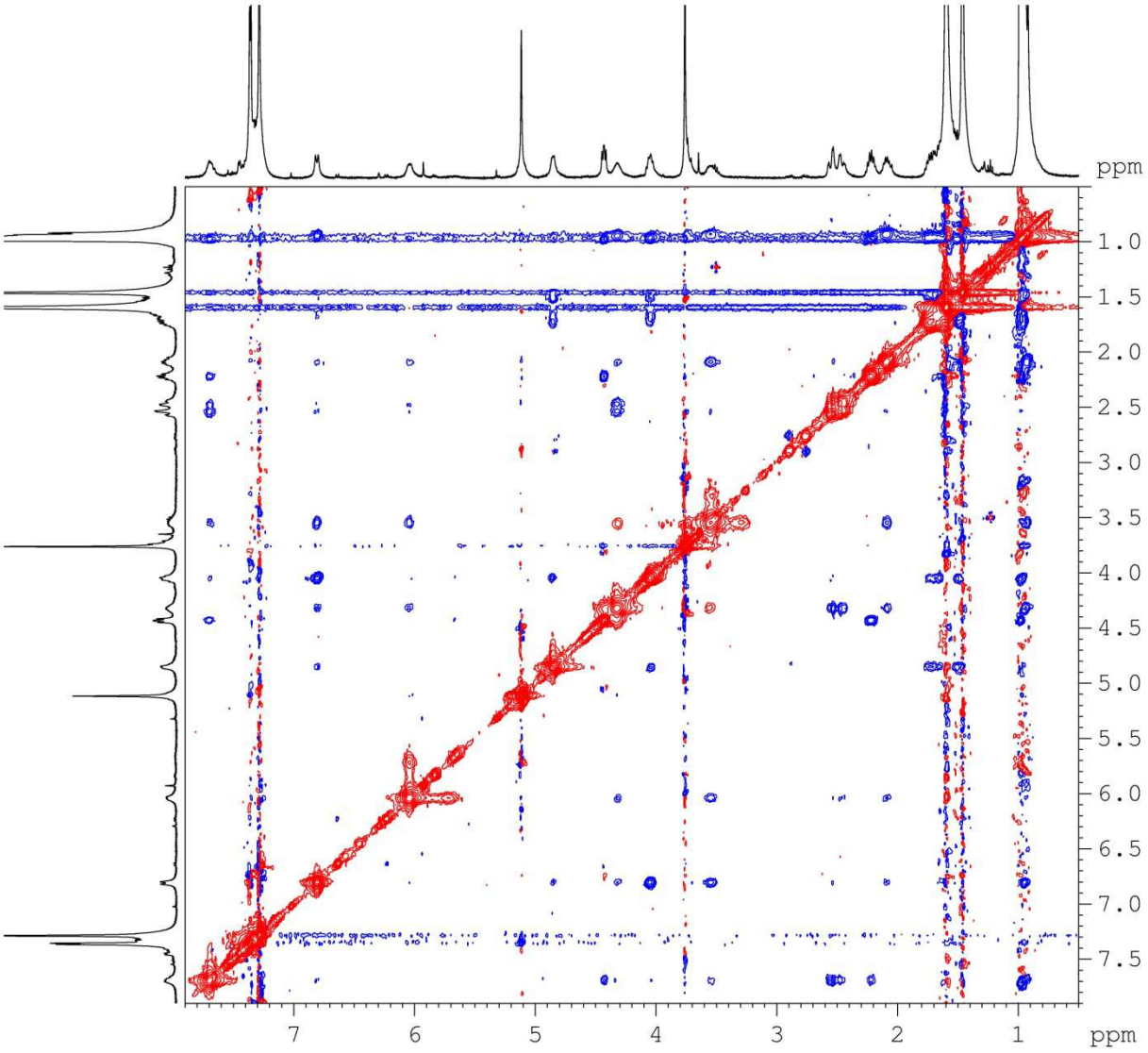


NOESY of **Boc-Ala-β,γ-Val-OMe 4a** 500 MHz, $CDCl_3$

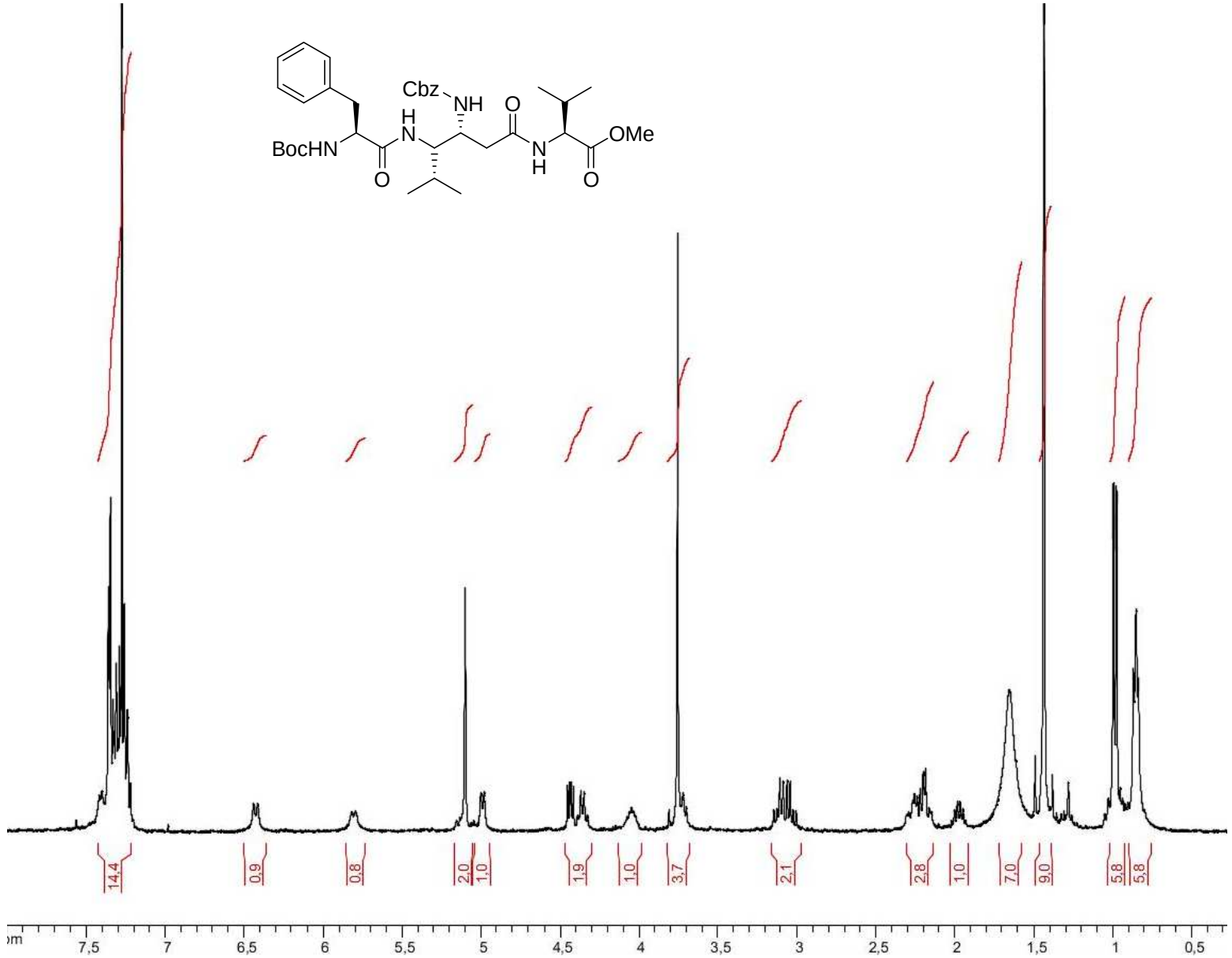


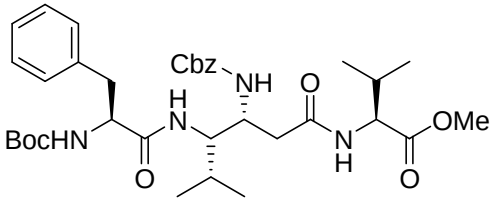


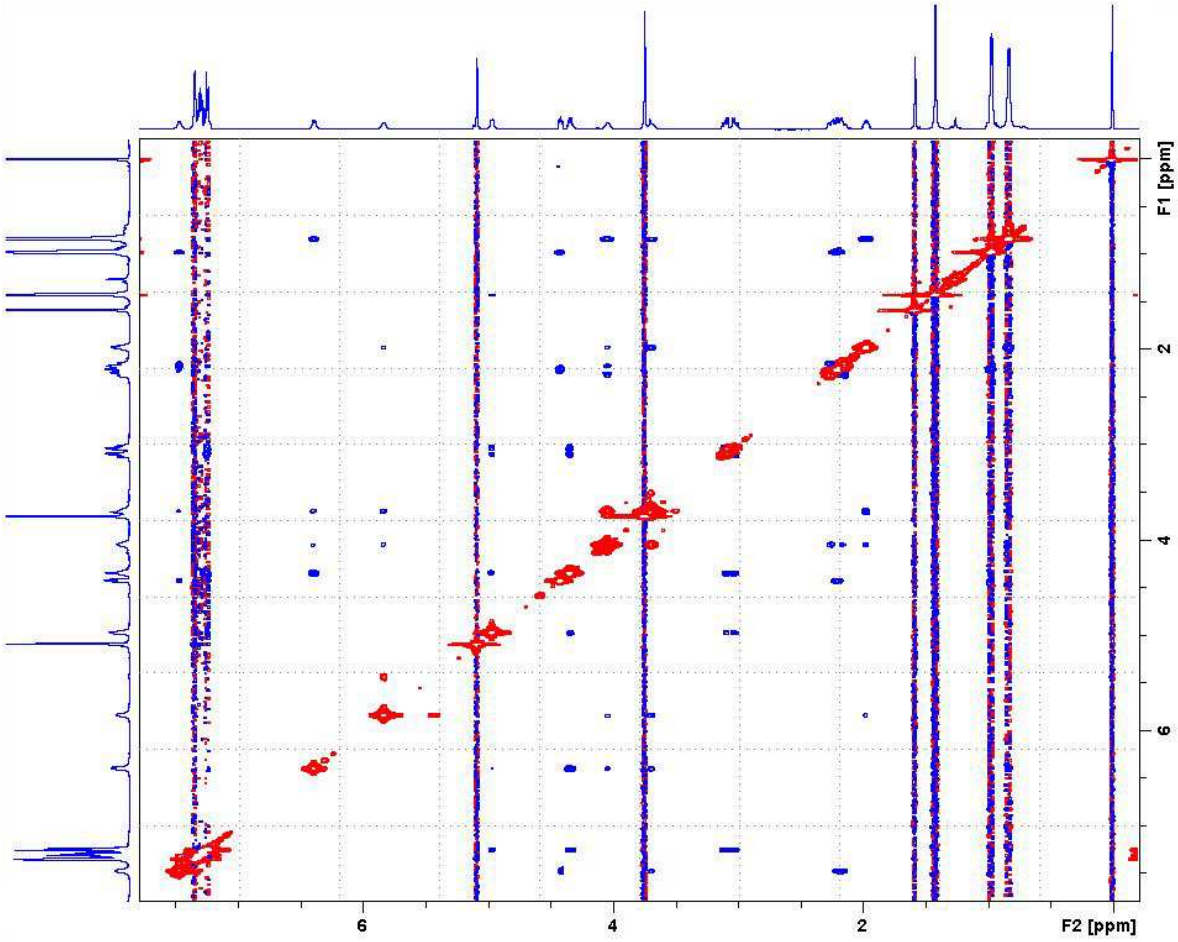




NOESY of **Boc-Leu-β,γ-Val-OMe 4b** 400 MHz, $CDCl_3$







NOESY of **Boc-Phe-β,γ-Val-OMe 4c** 500 MHz, $CDCl_3$

Molecular dynamics (MD) studies: All molecular dynamics simulations were performed using the Amber 11 software package and Amber force fields.[1] The β,γ-diamino acid and the peptides moieties were created using the LEaP program and parameterized by the Antechamber program suite.[1] Rectangular boxes of chloroform molecules (approximately 8 Å solvent layer on each side) were added. For the chloroform solvent model, the corresponding parameters of Amber 11 were used.

Simulated annealing. Each Simulation started with the peptide minimization (5000 steps). The energy-minimized structure was then subjected to a simulated annealing under NMR constraints. The ideal interatomic distances *d* were deduced from the volume integrals on the NOESY or ROESY spectra using the distance between geminal protons for the distance calibration. Three ranges of distance constraints have been then defined for peptide **4a**: $(d\text{-}0.25) \leq d \leq (d\text{+}0.25)$ for 1.8 Å < *d* < 3 Å ; $(d\text{-}0.5) \leq d \leq (d\text{+}0.5)$ for 3 Å < *d* < 4 Å ; and $(d\text{-}0.75) \leq d \leq (d\text{+}0.75)$ for 4 Å < *d*. Three ranges of distance constraints have been then defined for peptide **4a** and **4c**: $(d\text{-}0.5) \leq d \leq (d\text{+}0.5)$ for 1.8 Å < *d* < 3 Å ; $(d\text{-}0.75) \leq d \leq (d\text{+}0.75)$ for 3 Å < *d* < 4 Å ; and $(d\text{-}1) \leq d \leq (d\text{+}1)$ for 4 Å < *d.* Dihedrals were directly constrained by the Amber package using the *J* couplings determined on the ^{1}H spectra, and properly parameterized Karpluss coefficients.[2] The simulated annealing protocol consisted of 20000 steps including a heating stage (900 K) followed by a cooling to 0 K. For each peptide, 200 structures were calculated starting from extended folds. The ten lowest-energy structures were selected and were used to define the NMR structure ensemble.

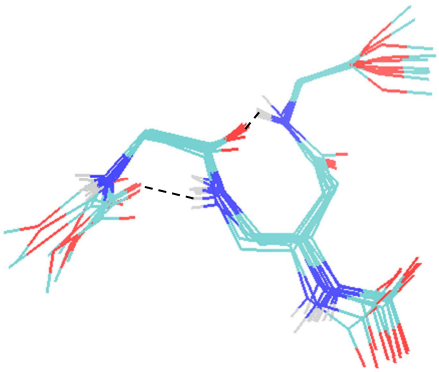
Dynamics. The lowest energy structure obtained by simulated annealing was subjected to a molecular dynamics simulation. Pressure and temperature were equilibrated at 1 bar and 300 K, respectively. First, the solvent box was minimized over 10000 steps, peptide being fixed. Second, the whole system was minimized over 2500 steps. Third, the peptide remained fixed and the solvent box was warmed at 300 K while volume was kept constant (50000 steps, i.e. 50 ps). Fourth, the whole system was warmed at constant temperature (50000 steps, i.e. 50 ps). Fifth, the whole system was equilibrated at constant temperature (300 K) and pressure (1 bar) (50000 steps, i.e. 50 ps). Finally, molecular dynamics simulations were performed at constant temperature and concentration for 50 ns using 1 fs time steps. Coordinates and energies were recorded every 2000 steps, allowing analyses of trajectories. Two restraints were applied for the MD simulations of each peptide:

Boc-Ala-β,γ-Val-OMe (**4a**) : $2.5 < H_{\alpha\ ala}\text{-}NH_{val} < 3.5$ Å and $3.5 < H_{\alpha\ ala}\text{-}H_{\gamma\ val} < 5$ Å
Boc-Leu-β,γ-Val-OMe (**4b**): $2 < NH_{leu}\text{-}H_{\gamma\ leu} < 3$ Å and $2 < NH_{val}\text{-}H_{\gamma\ \beta,\gamma} < 3$ Å
Boc-Phe-β,γ-Val-OMe (**4c**) : $2 < NH_{val}\text{-}H_{\gamma\ \beta,\gamma} < 3.5$ Å and $3 < NH_{val}\text{-}H_{\alpha\ phe} < 5$ Å

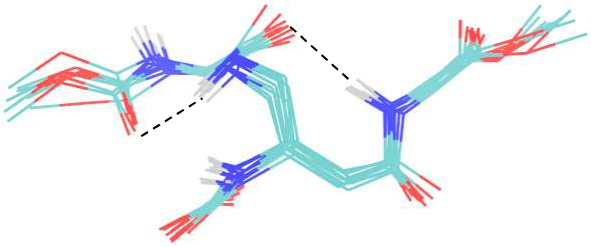
Analysis of hydrogen bonding was conducted by measurement of distances between proton of amides groups and oxygen of carbonyl groups for each snapshots of the trajectory using the ptraj program.[1]

[1] a) D. A. Case, T. Cheatham, T. Darden, H. Gohlke, R. Luo, K. M. Merz, A. Onufriev, C. Simmerling, B. Wang, R. Woods, *J. Computat. Chem.*, 2005, **26**, 1668. b) D.A. Case, T.A. Darden, T.E. Cheatham, III, C.L. Simmerling, J. Wang, R.E. Duke, R. Luo, R.C. Walker, W. Zhang, K.M. Merz, B. Roberts, B. Wang, S. Hayik, A. Roitberg, G. Seabra, I. Kolossváry, K.F. Wong, F. Paesani, J. Vanicek, J. Liu, X. Wu, S.R. Brozell, T. Steinbrecher, H. Gohlke, Q. Cai, X. Ye, J. Wang, M.-J. Hsieh, G. Cui, D.R. Roe, D.H.Mathews, M.G. Seetin, C. Sagui, V. Babin, T. Luchko, S. Gusarov, A. Kovalenko, and P.A. Kollman (2010), AMBER 11, University of California, San Francisco.
[2] C. Pérez, F. Lohr, H. Ruterjans, J. M. Schmidt, *J. Am. Chem. Soc.* 2001, **123**, 7081.

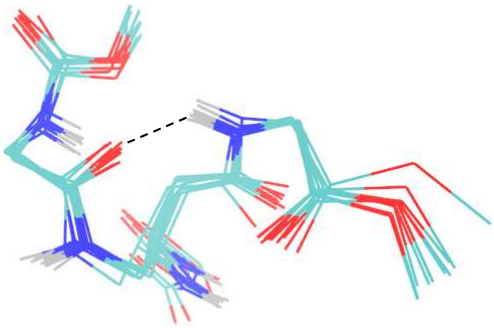
Overlay of the 10 lowest energy structures of **Boc-Ala-β,γ-Val-OMe 4a**



Overlay of the 10 lowest energy structures of **Boc-Leu-β,γ-Val-OMe 4b**

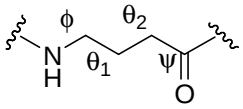


Overlay of the 10 lowest energy structures of **Boc-Phe-β,γ-Val-OMe 4c**



Dihedrals

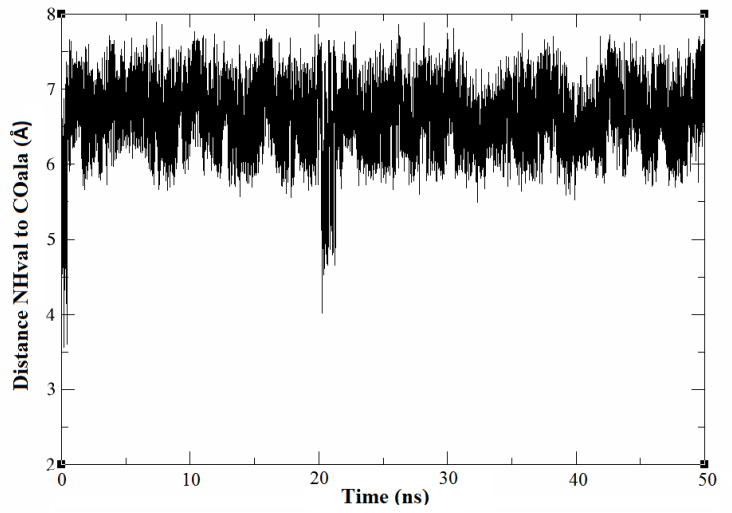
Averaged β,γ-Val backbone dihedral angles with RMSD obtained on the 10 lowest energy structures for peptides **4a**, **4b**, and **4c**



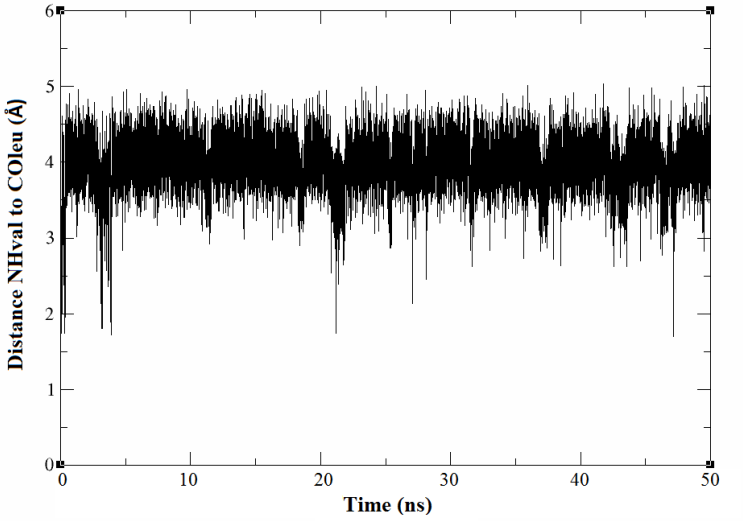
Peptides	ϕ	Θ_1	Θ_2	Ψ
Boc-Ala-β,γ-Val-OMe	-115 ± 8	56 ± 4	-94 ± 3	96 ± 6
Boc-Phe-β,γ-Val-OMe	-83 ± 2	73 ± 3	57 ± 7	-126 ± 6
Boc-Leu-β,γ-Val-OMe	-70 ± 4	175 ±4	-96 ± 6	43 ± 6

Trajectories obtained for peptides (a) **4a**, (b) **4b** and (c) **4c** in the time course of the MD simulation. NH….O=C distances revealing the formation of 9-membered ring hydrogen bond

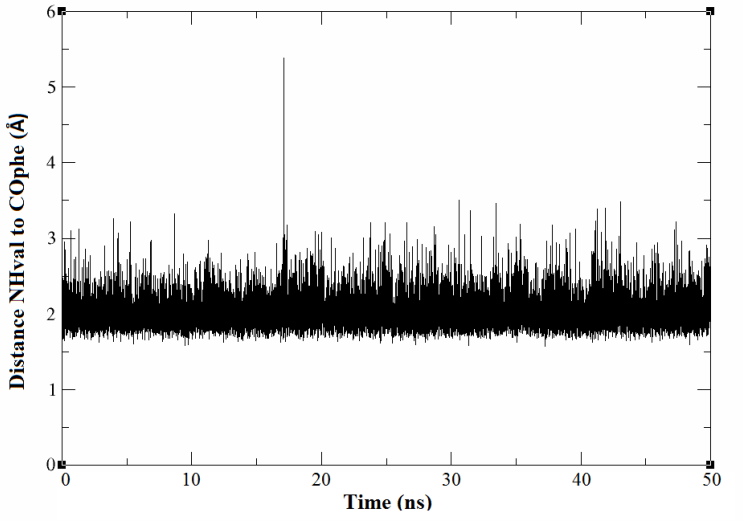
(a)



(b)

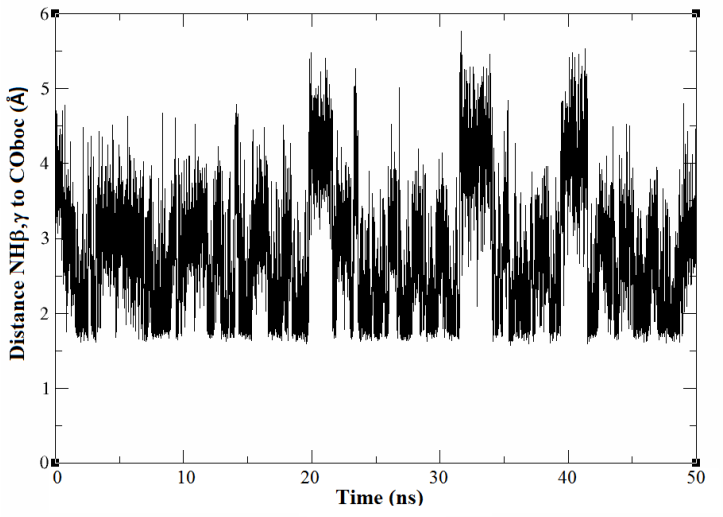


(c)

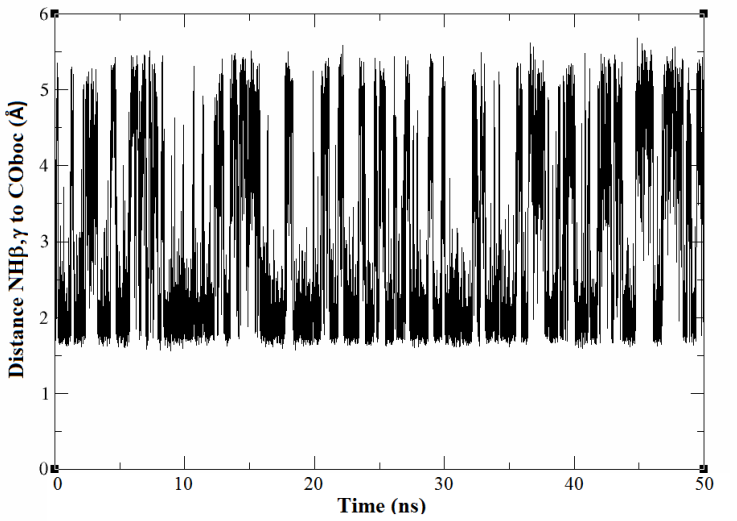


Trajectories obtained for peptides (a) **4a**, (b) **4b** and (c) **4c** in the time course of the MD simulation. NH….O=C distances revealing the formation of 7-membered ring hydrogen bond

(a)



(b)



(c)