Electronic Supplementary Material (ESI) for RSC Advances.

Supporting Information

1. Figures and Tables

2. Chemistry

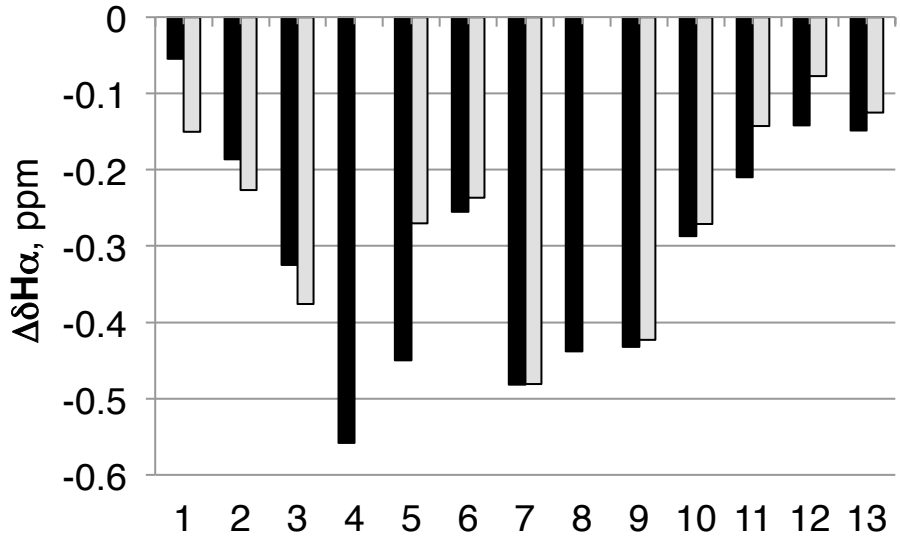


Fig. S1. Bar graph showing the ΔδHα values (ΔδHα = δHαobserved – δHαRC, ppm) as a function of residue number for peptides **11** (in black) and **8a** (in grey). The chemical shift values reported for Wishart et al. 1995 for unstructured hexapeptides were taken as reference for the random coil state ($\delta H\alpha^{RC}$).

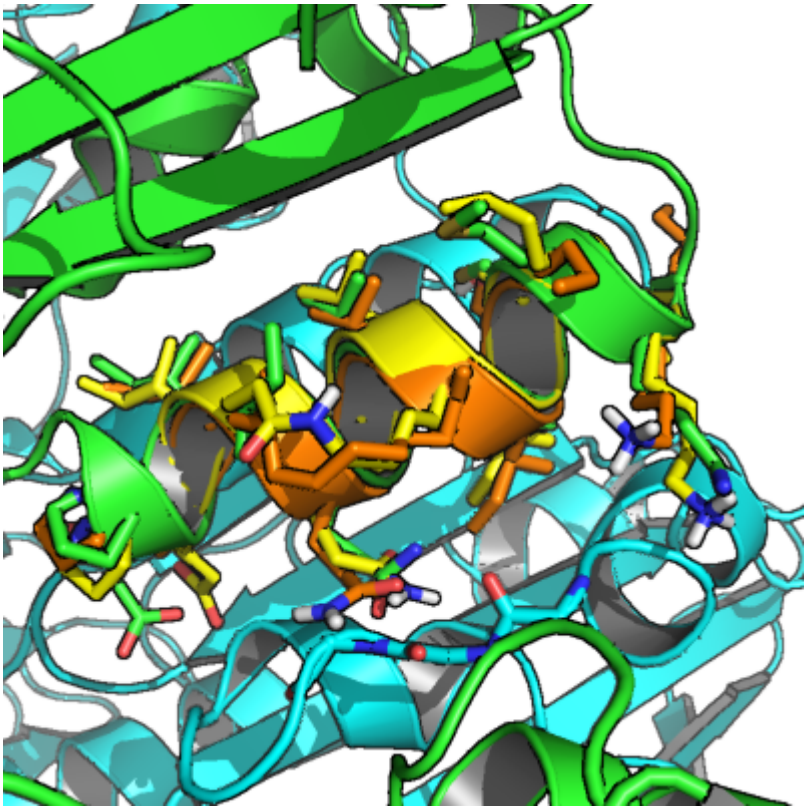


Fig. S2 Superimposition of the best two calculated structures of peptide **8a** (carbon atoms coloured in orange) and **11** (carbon atoms coloured in yellow) with the α-helix Pro435-Met447 (green) of Li-TryR (PDB id. 2JK6).

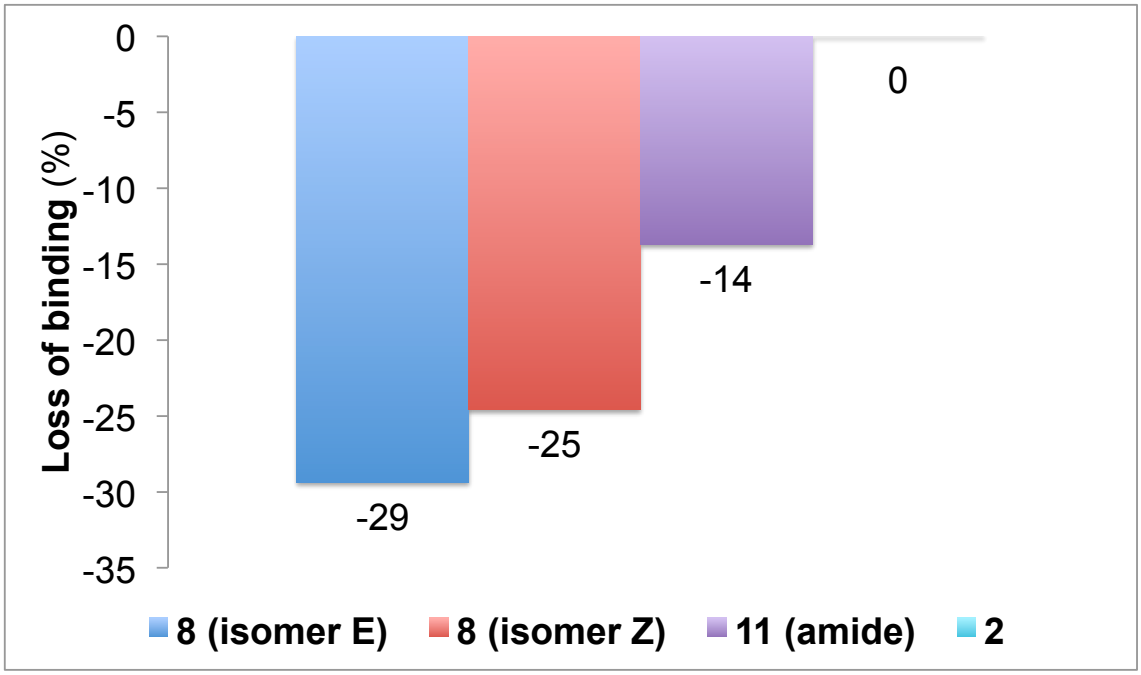


Fig. S3. Relative loss of binding (%) observed for the cyclic peptides **8** (*E* and *Z* isomers) and **11** (amide bridges) with the Li-TryR monomer along the respective MD simulations when the total binding energy is compared with linear counterpart **2** under the same simulation conditions.

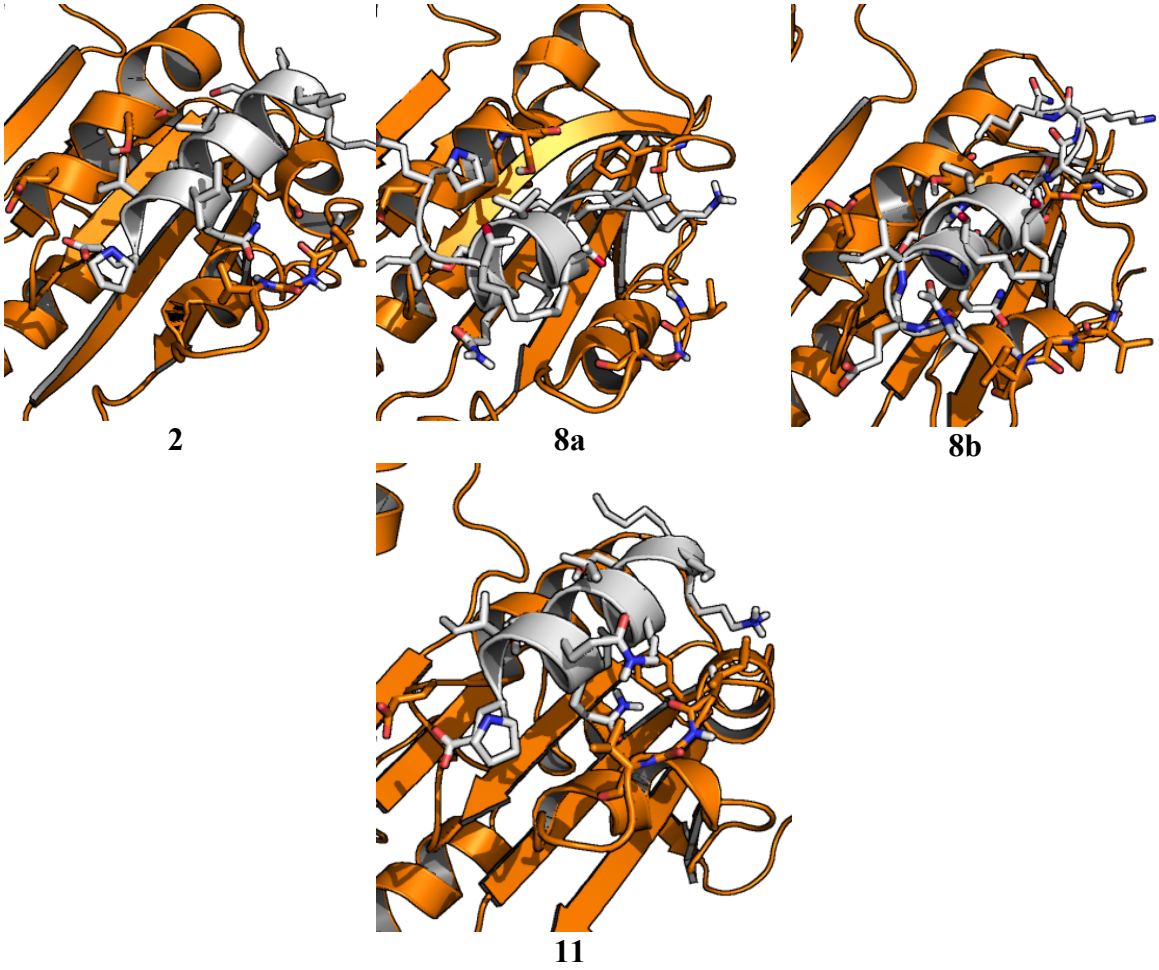
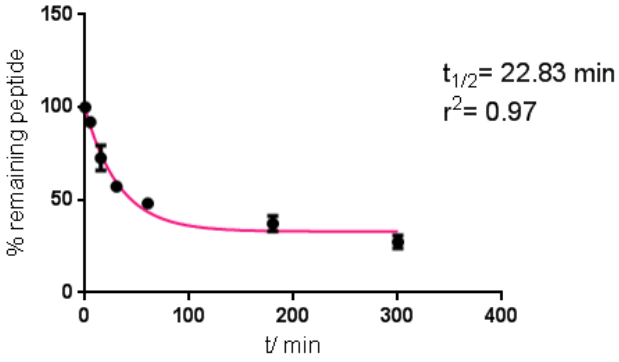
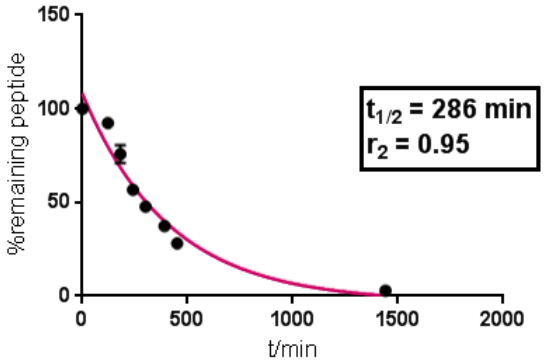


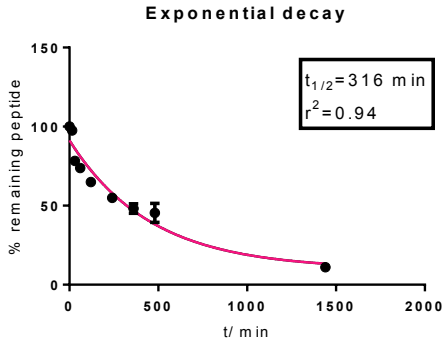
Fig. S4. Detail of the representative structure of the major clusters calculated along the last 20 ns of the MD trajectories of peptide **2**, **8a**, **8b** and **11** (carbon atoms coloured in grey) using the module ptraj implement in the AmberTools 14.



linear peptide



5a



11

Fig. S5 Proteolytic stability of peptide **2** (linear), **5a** (all-hydrocarbon) and **11** (lactam-bridged).

Table S1. Structural statistics for the ensemble of the 20 lowest target function NMR structures of peptides **8a** and **11**.

		8a	**11**
Number of distance restraints	Intraresidue (i – j = 0)	48	50
	Sequential (|i – j| = 1)	38	31
	Medium range (1 < |i – j| < 5)	13	11
	Total number	99	92
Number of dihedral angle constraints	ϕ angles	12	12
	ψ angles	10	12
	Total number	22	24
Average maximum violations per structure	Distance (Å)	0.04±0.00	0.00±0.00
	Dihedral angle (º)	0.2 ± 0.2	0.00±0.00
Averaged structure energies	CYANA target function value	0.23±0.02	$2\ 10^{-9} \pm 2\ 10^{-9}$
Pairwise RMSd (Å)	Backbone atoms	0.5 ± 0.2	0.6 ± 0.2
	All heavy atoms	1.3 ± 0.2	1.4 ± 0.2
Ramachandran plot (%)	Residues in most favoured regions	100	100
	Residues in additional allowed regions	0.0	0.0
	Residues in generously allowed regions	0.0	0.0
	Residues in disallowed regions	0.0	0.0

Table S2. Total and per-residue binding energies (kcal mol^{-1}) calculated with MM-ISMSA after analyzing the corresponding MD simulations of the system peptide:Li-TryR monomer. Only the last 20 ns of the 30 ns of each MD trajectories have been taken into account.

Total energy (kcal mol^{-1})

2 (linear prototype)	**8a** (*E* isomer)	**8b** (*Z* isomer)	**11** (amide)
-73.8 ± 4.4	-52.1 ± 6.1	-55.6 ± 4.1	-63.7 ± 5.7

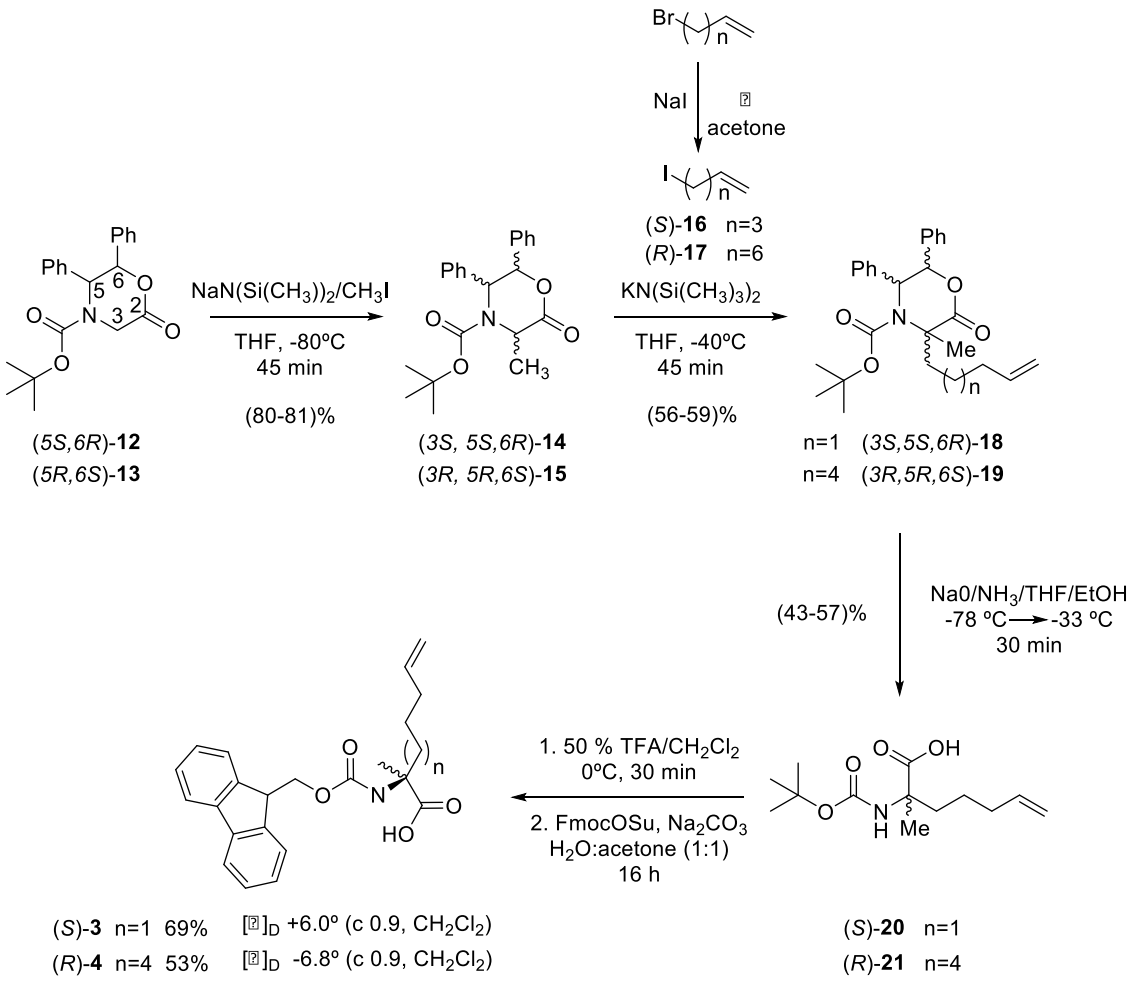
Energy per residue (kcal mol^{-1})

2 (linear prototype)		**8a** (*E* isomer)		**8b** (*E* isomer)		**11** (amide)	
Residue	Energy	Residue	Energy	Residue	Energy	Residue	Energy
D453	-6.1	*S440*	-5.2	*T457*	-4.3	*V460*	-6.7
I437	-5.8	*T457*	-5.0	*I437*	-4.1	*I458*	-4.8
T457	-5.7	*V460*	-4.8	*T463*	-4.0	*C444*	-4.8
V460	-5.2	*I437*	-4.1	*F454*	-3.7	*T457*	-4.7
S440	-4.5	*T463*	-3.1	*S440*	-3.4	*I437*	-4.4
T463	-3.8			*E436*	-3.1	*S440*	-4.4
F454	-3.7					*T463*	-3.8
L468	-3.5					*D453*	-3.4
C444	-3.4						
V441	-3.0						

2. CHEMISTRY

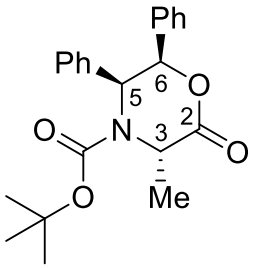
2.1.Asymmetric synthesis of the α,α-disubstituted amino acids (*S*)-**3** and (*R*)-**4**.

Starting from the commercially available chiral diphenyloxazinones **12** and **13**, the procedure described by described by Williams and colleges[61] taking into account the modifications reported by Verdine group[54] was followed.



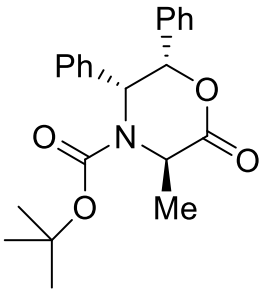
Scheme S1. Assymetric synthesis of quaternary amino acids (*S*)-**3** and (*R*)-**4**.

(*3S,5S,6R*)-5,6-diphenyl-4-(*terc*-butoxycarbonyl)-3-methyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (14)[6].



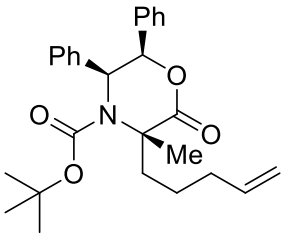
White solid (80%). **M.p.** (hexane:AcOEt, 4:1): 201-202 ºC M.p. ref. 202-204 ºC. **HPLC** (Agilent, 10% to 100% of water in 10 min): 9.91 min (> 98% analytical purity). **$[\alpha]^{rt}_D$** –65.5 º (c 0.2, CH_2Cl_2); $[\alpha]^{25}_D$ (ref.[6]) -61.0 º (c 0.2, CH_2Cl_2). **^{1}H-RMN** (300 MHz, DMSO-*d*$_6$): δ 1.04 (s, 6H, tBu), 1.40 (s, 3H, tBu), 1.71 (m, 3H, α-CH_3), 4.89 (m, 1H, α-CH), 5.15 (m, 1H, benzyl), 6.26 (m, 1H, benzyl), 6.52 (m, 2H, Ar), 7.00-7.34 (m, 8H, Ar).

(*3R,5R,6S*)-5,6-diphenyl-4-(*terc*-butoxycarbonyl)-3-methyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (**15**)**[6]**.



White solid (81%). **M.p.** (hexane:AcOEt, 4:1): 198-199 ºC. **HPLC** (Agilent, 10% to 100% of water in 10 min): 9.90 min (> 98*%* analytical purity).**$[\alpha]^{rt}_D$** +67.0 º (c 0.2, CH_2Cl_2); $[\alpha]^{25}_D$ –65.5 º (c 0.2, CH_2Cl_2) of its enantiomer.**^{1}H-RMN** (300 MHz, DMSO-*d*$_6$): δ 1.04 (s, 6H, tBu), 1.40 (s, 3H, tBu), 1.65-1.76 (m, 3H, α-CH_3), 4.98-4.80 (q, *J* = 7.3 Hz, 1H, α-CH), 5.05-5.27 (m, 1H, benzyl), 6.23-6.30 (m, 1H, benzyl), 6.47-6.56 (m, 2H, Ar), 7.00-7.31 (m, 8H, Ar).

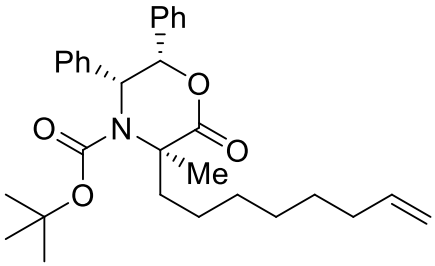
(*3S,5S,6R*)-5,6-diphenyl-4-(*terc*-butoxycarbonyl)-3-methyl-3-(4'-pentenyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (**18**)



To a solution of **14** (166 mg, 0.45 mmol) and freshly prepared 1-iodine-4-pentenyl[7] (**16**, 2.26 mmol, 5.0 eq.) in dry THF (6 mL) at -40 ºC, a solution of 1.0 M $KN(TMS)_2$ in THF (900 μL, 0.90 mmol) was added dropwise for 10 min under argon atmosphere. Then, the mixture was stirred at this temperature for 35 min. After the reaction was completed, the mixture was poured over AcOEt (10 mL), washed with H_2O (3 x 15 mL) and brine (1 x 15 mL), and dried over anh. Na_2SO_4. The organic phase was filtered and concentrated under reduced pressure. The resulting crude was purified by CCTLC (hexane:AcOEt, 5:1) to give a colorless oil (116 mg, 59%) that was identified as **18**. **HPLC** (Agilent, 10% to 100% of water in 10 min):

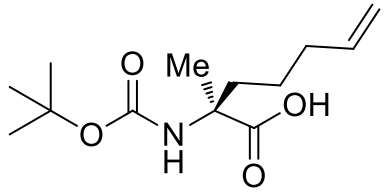
11.31 min (92% analytical purity). **[α]$^{rt}_{D}$** + 25.2 º (c 3.1, CH_2Cl_2). **^{1}H-RMN** (400 MHz, DMSO-*d*$_6$): δ 1.04-1.85 (m, 14H, $C_\beta H_2$, α-CH_3, tBu), 2.07 (q, 2H, γ-CH_2 allyl, *J* = 7.0 Hz), 2.50 (m, 8H, α-CH_2), 5.03 (m, 2H, ε-CH_2 vinyl), 5.81 (dtd, 1H, δ-CH vinyl, *J* = 6.8, 6.6, 3.3 Hz), 6.23 (d, 2H, CH-Ph, *J* = 3.2 Hz), 6.87 (bs, 2H, Ar), 7.07-7.32 (m, 8H, Ar). **^{13}C-RMN** (100 MHz, DMSO-*d*$_6$): δ 23.8 (β-CH_2), 28.7 (CH_3, ^{t}Bu, Boc), 33.8 (γ-CH_2), 64.2 (CH, CHPh), 115.7 (ε-CH_2), 126.0, 128.0, 128.5, 129.3, 135.6, 135.9, (C-Ar), 138.1 (δ-CH), 151.7 (C=O, Boc), 173.2 (C=O, lactone). **EM** (ESI +) *m/z:* 458.3 $[M+Na]^+$ (100%), 336.3 $[M\text{-Boc}]^+$ (80%), 195.1 [M-(1,2-diphenyl-1-hydroxyethane)]$^+$ (70%). **Elemental analysis** (%) calculated for $C_{27}H_{33}NO_4$ C 74.45, H 7.64, N 3.22; found C 74.16, H 7.91, N 3.49.

(*3R,5R,6S*)-5,6-diphenyl-4-(*terc*-butoxycarbonyl)-3-methyl-3-(7'-octenyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (19)



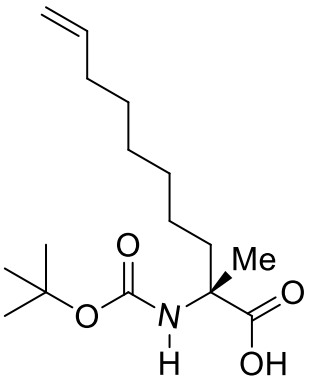
Following the described procedure for **18**, a solution of **15** (235 mg, 0.64 mmol) and freshly prepared 1-iodine-4-pentenyl[7] (**17**, 1.94 mmol, 3.0 eq.) in dry THF (8 mL) was reacted with 1.0 M $KN(TMS)_2$ in THF (1.30 mL, 1.30 mmol, 2.0 eq.) for 45 min. The resulting crude was purified by CCTLC (hexane:AcOEt, 6:1) to obtain 170 mg (56%) of a amorphous white solid identified as **19**. **HPLC** (Agilent, 10% to 100% of water in 10 min): 12.26 min (> 98% analytical purity). **[α]$^{rt}_{D}$** -29.0 º (c 3.4, CH_2Cl_2). **^{1}H-RMN** (400 MHz, $CDCl_3$): δ 1.16-1.90 (m, 20H, β–CH_2, γ-CH_2, δ-CH_2, ε-CH_2, α-CH_3, tBu), 1.95-2.34 (m, 3H, CH_2 allyl, $C_\alpha H_2$), 2.50 (m, 1H, $C_\alpha H_2$), 4.94 (m, 2H, CH_2 vinyl), 5.78 (dtd, 1H, CH vinyl, *J* = 6.9, 6.6, 3.3 Hz), 5.96 (d, 2H, benzyl, *J* = 3.1 Hz), 6.86-7.43 (m, Ar, 10H). **^{13}C-RMN** (100 MHz, $CDCl_3$): δ 25.1 (β-CH_2), 28.6, 28.9 (CH_3, ^{t}Bu-Boc), 29.1 (γ-CH_2), 29.6 (δ-CH_2), 33.4 (CH_2 allyl), 39.3 (α-CH_2), 41.4 (α-CH_2), 64.2 (C, Cα), 80.6 (CH, benzyl), 81.2 (C, Boc), 82.0 (CH, benzyl), 114.5 (CH_2, vinyl), 125.9 , 127.9, 128.4, 129.1 (CH-Ar), 135.5 (C-Ar), 135.9 (C-Ar), 139.1 (CH, vinyl), 152.6 (C=O, Boc), 154.1 (C=O, Boc), 173.2 (C=O, lactone). **EM** (ESI +) *m/z:* 378.3 $[M\text{-Boc}]^+$ (100%), 500.3 $[M+Na]^+$ (90%). **Elemental analysis** (%) calculated for $C_{30}H_{39}NO_4$ C 75.44, H 8.23, N 2.92; found C 75.23, H 8.51, N 3.12.

Boc-α-(4'-pentenyl)-*(S)*-Ala-OH (**20**)



To a mixture of Na (237 mg, 10.38 mmol) in dry TFH saturated with NH_3 (6 mL) at -78 ºC, a solution of **18** (348 mg, 0.81 mmol) and absolute EtOH (600 μL) in dry THF (9 mL) was added dropwise. The reaction temperature was allowed to heat until -33 ºC in 30 min, an excess of NH_4Cl was added and the mixture was stirred until it got room temperature. Then, H_2O (3 mL) was added and the organic phase was extracted with Et_2O (1 x 9 mL). The aqueous phase was acidified until pH = 2 with a solution of 3.0 N HCl and extracted with AcOEt (3 x 9 mL). The organic phases were combined, dried over anh. Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude was purified by CCTLC (CH_2Cl_2:MeOH, 95:5) to give 90 mg (43%) of a white solid identified as (*S*)-**20**. **M.p.** (CH_2Cl_2) 97-98 ºC. **HPLC** (Agilent; 10% to 100% of water in 10 min): 7.87 min (83% analytical purity). $[\alpha]^{rt}_D$ + 12.7 º (c 2.1, CH_2Cl_2). **^{1}H-RMN** (400 MHz, acetone-d_6): δ 1.29-1.60 (m, 14H, α-CH_3, β-CH_2 , Boc), 1.84 (td, 1H, γ-CH_2, *J* = 12.5, 5.0 Hz), 1.94-2.10 (m, 7H, acetona, γ-CH_2, α-CH_2), 4.96 (m, 2H, CH_2 vinyl), 5.79 (m, 1H, CH_2 vinyl), 5.80 (dtd, 1H, CH vinyl, *J* = 10.3, 6.7, 6.0 Hz), 6.06 (bs, 1H, NH). **^{13}C-RMN** (100 MHz, acetone-d_6): δ 24.3 (α-CH_3), 28,7 (CH_3, Boc), 34.6 (γ-CH_2), 37.0 (α-CH_2), 62.5 (C, α-C), 78.9 (C, Boc), 115.0 (CH_2, vinyl), 139.6 (CH, vinyl), 155.2 (C=O, Boc). **EM** (ESI +) *m/z:* 280.0 $[M+Na]^+$ (100%), 180.1 $[M-Boc+H]^+$ (40%), 224.1 $[M-allyl+H]^+$ (50%).

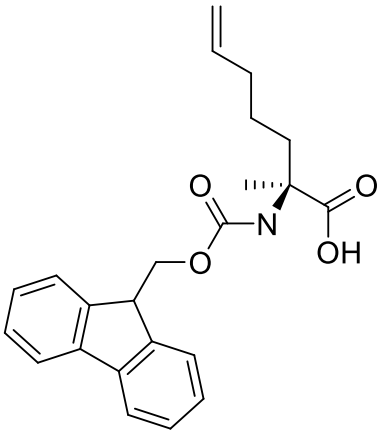
Boc-α-(7'-octenyl)-*(R)*-Ala-OH (**21**)



The procedure described for **20** was followed from **19** (300 mg, 0.63 mmol). The resuting crude was purified by CCTLC (CH_2Cl_2:MeOH, 95:5) to give 108 mg (57%) of a white solid that was identified as (*R*)-**21**. **M.p.** (hexane) 180-181 ºC. **HPLC** (Agilent, 10% to 100% of water in 10 min): 9.50 min (> 98% analytical purity). $[\alpha]^{ta}_D$ -6.5 º (c 0.9, CH_2Cl_2). **^{1}H-RMN** (400 MHz, acetone-d_6): δ 1.25-1.52 (m, 21H, β-CH_2, α-CH_3, γ-CH_2, δ-CH_2, ε-CH_2, ω-CH_2, tBu), 1.84 (m, 1H, CH_2 allyclic), 1.94-2.14 (m, 6H, acetone, α-CH_2, CH_2 allyl), 4.94 (m,

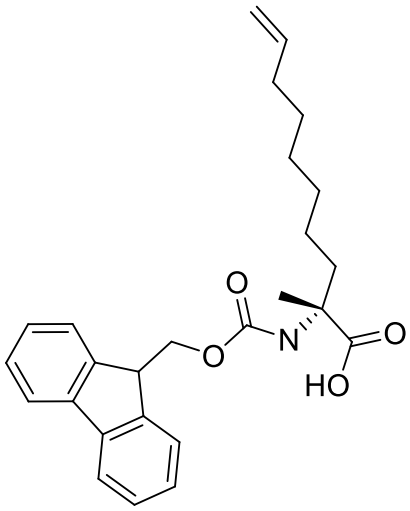
2H, CH_2 vinyl), 5.80 (m, 1H, CH vinyl), 5.99 (bs, 1H, NH carbamate). **^{13}C-RMN** (100 MHz, acetone-*d_6*): δ 23.55 (α-CH_3), 24.6 (β-CH_2), 28.6 (CH_3, Boc), 29.6 (γ-CH_2, δ-CH_2), 30.3 (ε-CH_2), 34.5 (CH_2 allyl), 37.6 (α-CH_2), 59.8 (C, α-C), 79.0 (C, Boc), 114.8 (CH_2 vinyl), 139.9 (CH vinyl), 155.2 (C=O, Boc), 176.2 (C=O, acid). **HRMS** (ESI +) *m/z:* Calculated for $C_{16}H_{29}NO_4$ 299.2097; found $[M+H]^+$ 300.2160.

Fmoc-α-(4'-pentenyl)-*(S)*-Ala-OH (3)[8]



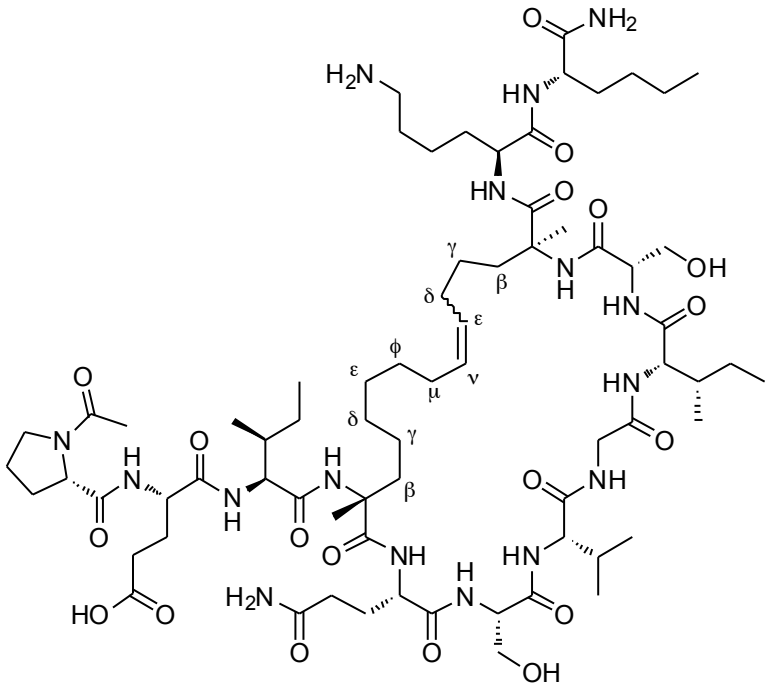
To a solution of (*S*)-**20** (78 mg, 0.3 mmol) in CH_2Cl_2 (1.5 mL) at 0 ºC was added TFA (1.5 mL). The mixture was stirred for 30 min at this temperature, concentrated under reduced pressure with oil bomb. The crude was the redisolved in a mixture of H_2O:acetona (1:1, 9 mL) and reacted with FmocOSu (111 mg, 0.33 mmol) and Na_2CO_3 (96 mg, 0.9 mmol) for 16 h at room temperature. The mixture was acidified until pH = 3 adding 0.1 N HCl. The solution was extracted with AcOEt (3 x 6 mL), the organic phases dried over anh. Na_2SO_4, filtered, and concentrated under reduced pressure. The final crude was purified by CCTLC (CH_2Cl_2:MeOH, 95:5) to give 78 mg (69%) of a white foam identified as (*S*)-**3**[8]. **HPLC** (Agilent, 10% to 100% of water in 10 min): 10.65 min (> 98% analytical purity). **$[\alpha]^{rt}_D$** +6.0 º (c 1.1, CH_2Cl_2). **^{1}H-RMN** (400 MHz, DMSO-*d_6*): δ 1.10-1.37 (m, 5H, α-CH_3, β-CH_2), 1.67 (m, 1H, γ-CH_2), 1.91 (m, 3H, γ-CH_2, α-CH_2), 4.21 (m, 2H, CH_2-Fmoc), 4.29 (m, 1H, CH-Fmoc), 4.93 (m, 2H, CH_2 vinyl), 5.73 (dtd, 1H, CH vinyl, *J* = 10.3, 6.7, 6.0 Hz), 6.94 (bs, 1H, NH), 7.32 (t, 2H, $H_{2,7}$-Fmoc, *J* = 7.5 Hz), 7.41 (t, 2H, $H_{3,6}$-Fmoc, *J* = 7.5 Hz), 7.65 (d, 2H, $H_{1,8}$-Fmoc, *J* = 7.5 Hz), 7.89 (d, 2H, $H_{4,5}$-Fmoc, *J* = 7.5 Hz). **^{13}C-RMN** (100 MHz, DMSO-*d_6*): δ 23.5 (β-CH_2), 28.9 (α-CH_3), 28.8 (CH_2), 33.5 (α-CH_2), 35.7 (γ-CH_2), 46.8 (CH-Fmoc), 58.9 (C, α-C), 64.7 (CH_2-Fmoc), 114.4 (CH_2 vinyl), 120.1 ($C_{4,5}$-Fmoc), 125.0 ($C_{1,8}$-Fmoc), 127.0, 127.5 ($C_{2,7}$-Fmoc, $C_{3,6}$-Fmoc), 138.9 (CH vinyl), 140.7, 143.9, 144.0 (C-Fmoc), 153.6 (C=O, Fmoc), 176.2 (C=O, acid). **EM** (ESI +) *m/z:* 458.3 $[M+K]^+$ (100%), 336.2 $[M-(CH_2)_6CHCH_2+H]^+$ (100%), 380.2 [M-allyl+H]$^+$ (60%), 195.1 [M-fulvene+H]$^+$ (40%).

Fmoc-α-(7'-octenyl)-*(R)*-Ala-OH (4)[8]

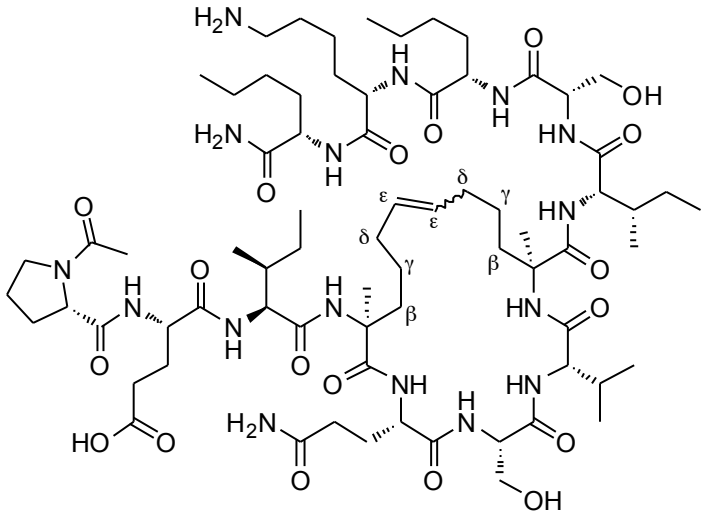


The procedure described for **2** was followed from (*R*)-**21** (100 mg, 0.30 mmol). The final crude was purified by flash chromatography in silica gel (hexane:acetone, 1:1) to give 67 mg (53%) of a colorless oil that was identified as (*R*)-**4**[8]. **HPLC** (Agilent, 10% to 100% of water in 10 min): 10.65 min (> 98% analytical purity). $[\alpha]^{rt}_{D}$ -6.8 º (c 0.9, CH_2Cl_2). **^{1}H-RMN** (400 MHz, DMSO-d_6): δ 1.10-1.44 (m, 11H, β-CH_2, γ-CH_2, δ-CH_2, ε-CH_2, α-CH_3), 1.69 (m, 2H, α-CH_2), 1.99 (dt, 6.8 Hz, CH_2 allyl, J = 7.3 Hz), 4.22 (m, 3H, CH_2-Fmoc. CH-Fmoc), 4.96 (m, 2H, CH_2 vinyl), 5.77 (dtd, 1H, CH vinyl, J = 10.2, 6.6, 3.2 Hz), 7.32 (t, 2H, $H_{2,7}$-Fmoc, J = 7.5 Hz), 7.40 (t, 2H, $H_{3,6}$-Fmoc, J = 7.5 Hz), 7.71 (d, 2H, $H_{1,8}$-Fmoc, J = 7.5 Hz), 7.89 (d, 2H, $H_{4,5}$-Fmoc, J = 7.5 Hz), 12.40 (bs, 1H, acid). **^{13}C-RMN** (100 MHz, DMSO-d_6): δ 22.5 (α-CH_3), 23.2, 28.2, 28.4, 29.1 (β-CH_2, γ-CH_2, δ-CH_2, ε-CH_2), 33.17 (α-CH_2), 36.6 (CH_2 vinyl), 46.7 (CH-Fmoc), 58.3 (α-C, C), 65.2 (CH_2-Fmoc), 114.7 (CH_2 vinyl), 120.1, 125.3, 127.1, 127.6 (CH-Fmoc), 138.8 (CH, vinyl), 140.7, 143.9 (C-Fmoc), 154.7 (C=O, Fmoc), 175.4 (C=O, acid). **EM** (ESI +) *m/z:* 458.3 $[M+K]^+$ (100%), 336.2 $[M-(CH_2)_6CHCH_2+H]^+$ (100%), 380.2 $[M-allyl+H]^+$ (60%), 195.1 $[M-fulvene+H]^+$ (40%).

2.2.^{1}H- and ^{13}C-NMR chemical shifts (δ) of stapled peptides **5a, 8a** and **11**.



Stapled peptide **5a,b**



Stapled peptide **8a,b**

Table S3. *^{1}H- and ^{13}C-NMR chemical shifts (δ, ppm from DSS) of stapled peptide **5a** in 30% TFE in H_2O/D_2O 9:1 v/v at pH 5.5 and 25ºC.*

Residue	*NH*	*α-CH*	*β-CH*	*Others*
Pro1	-	4.25 (*65.7*)	2.00, 2.33 (*33.2*)	Ac 2.20 (*25.1*); γ-CH_2 2.01, 2.13 (*28.3*); δ-CH_2 3.64, 3.87 (*52.2*)
Glu2	9.32	4.13 (*60.4*)	2.06** (*29.7*)	2.37** (*37.4*);
Ile3	7.70	3.82 (*65.5*)	2.08 (*33.2*)	δ-CH_3 0.91 (*13.1*); γ-CH_3 0.93 (*17.8*); γ-CH_2 1.18, 1.59 (*29.0*);
(D)-Ala4	7.85	-	1.50, 2.31 (*39.6*)	γ-CH_2 1.18, 1.72 (*26.3*); δ-CH_2 1.11, 1.40 (*35.5*); ε-CH_2 - ; ϕ-CH_2 -; μ-CH_2 1.98, 2.10 (*36.3*); ν-CH 5.35 (-)
Gln5	8.12	4.01 (*60.4*)	2.14** (*30.2*)	γ-CH_2 2.38, 2.48 (*35.4*); $CONH_2$ 6.67, 7.09
Ser6	7.73	4.29 (*63.0*)	3.99, 4.10 (*64.1*)	
Val7	8.59	3.77 (*67.0*)	2.13 (*32.9*)	γ-CH_3 0.98, 1.05 (*22.6, 22.9*)
Gly8	8.60	3.85, 3.91 (*48.2*)		
Ile9	7.86	3.93 (*65.4*)	1.99 (*39.2*)	δ-CH_3 0.91 (*13.9*); γ-CH_3 0.97 (*18.1*); γ-CH_2 1.25, 1.76 (*29.9*)
Ser10	7.59	4.11 (*65.6*)	3.97** (*64.1*)	
Ala11	8.25	-	1.74, 1.98 (*42.7*)	β–CH_3 - γ-CH_2 1.34** (-); δ-CH_2 1.87, 1.95 (*35.5*); ε-CH 5.43 (-);
Lys12	7.57	4.16 (*59.0*)	1.88** (*33.8*)	γ-CH_2 1.52, 1.62 (*26.1*); δ-CH_2 1.33 (*30.1*); ε-CH_2 3.00 (*43.2*); NH_2 –
Nle13	7.99	4.17 (*58.7*)	1.88** (*34.5*)	γ-CH_2 1.51** (*31.7*); δ-CH_2 1.33** (*25.4*); ε-CH_3 0.88 (*16.6*); $CONH_2$ terminal 6.92, 7.33

Table S4. *^{1}H- and ^{13}C-NMR chemical shifts (δ, ppm from DSS) of stapled peptide **8a** in 30% TFE in H_2O/D_2O 9:1 v/v at pH 5.5 and 25ºC.*

Residuo	*NH*	*α-CH*	*β-CH*	*Others*
Pro1	-	4.27 (*66.1*)	1.99, 2.36 (*33.6*)	Ac 2.21 (*24.7*); γ-CH_2 2.03, 2.16 (-); δ-CH_2 3.63, 3.88 (-)
Glu2	9.00	4.12 (*60.8*)	2.08, 2.08 (-)	2.41, 2.49 (-)
Ile3	7.64	3.79 (*65.8*)	2.10 (*38.9*)	δ-CH_3 0.94 (*12.7*); γ-CH_3 0.94 (*17.2*); γ-CH_2 1.17, 1.60 (-)
Ala4	7.81	-	1.93, 2.13 (-)	β-CH_3 1.51 (22.3); γ-CH_2 1.69, 1.69 (-); δ-CH_2 1.71, 2.07 (-); ε-CH 5.35 (-)
Gln5	8.50	4.07 (*61.3*)	2.19, 2.27 (-)	γ-CH_2 2.43, 2.60 (*35.7*); $CONH_2$ 6.32, 6.49
Ser6	7.74	4.23 (*63.4*)	4.06, 4.06 (-)	
Val7	7.75	3.64 (*68.6*)	2.38 (*32.9*)	γ-CH_3 0.96, 1.03 (*21.1, 22.6*)
Ala8	8.37	-	1.51, 2.18 (-)	β-CH_3 1.49 (21.4); γ-CH_2 1.52, 1.52 (-); δ-CH_2 1.66, 2.17 (-); ε-CH 5.48 (-)
Ile9	8.45	3.75 (*66.9*)	1.94 (*39.4*)	δ-CH_3 0.90 (*13.6*); γ-CH_3 0.98 (*18.0*); γ-CH_2 1.23, 1.50 (-)
Ser10	7.84	4.20 (*63.8*)	4.05, 4.05 (-)	
Nle11	8.22	4.18 (*60.7*)	1.87, 1.97 (*34.4*)	γ-CH_2 1.35, 1.60 (*29.0*) δ-CH_2 1.30, 1.30 (*25.4*); ε-CH_2 0.86 (16.1)
Lys12	8.17	4.24 (*59.0*)	2.01, 2.07 (-)	γ-CH_2 1.50, 1.58 (*25.6*); δ-CH_2 1.74, 1.74 (*29.6*); ε-CH_2 3.01, 3.01 (*43.3*)
Nle13	8.45	4.20 (*59.3*)	1.89, 1.89 (*34.8*)	γ-CH_2 1.51,1.51 (-); δ-CH_2 1.33, 1.33 (*25.3*); ε-CH_3 0.89 (*16.1*); $CONH_2$ 6.78, 7.19

Table S5. *^{1}H-and ^{13}C-NMR chemical shifts (δ, ppm from DSS) of stapled peptide **11** in 30% TFE in H_2O/D_2O 9:1 v/v at pH 5.5 and 25ºC.*

Residue	*HN*	*α-CH*	*β-CH*	*Others*
Pro1	-	4.36 (*65.0*)	2.03, 2.40 (*32.7*)	Ac 2.23 (*24.5*); γ-CH_2 1.99, 2.04 (-); δ-CH_2 3.67, 3.91 (-)
Glu2	9.42	4.17 (*59.8*)	2.09, 2.09 (*28.8*)	γ-CH_2 2.41, 2.41 (*36.4*)
Ile3	7.71	3.85 (*64.6*)	2.08 (*38.0*)	δ-CH_3 0.94 (*12.4*); γ-CH_3 0.93 (*16.9*); γ-CH_2 1.21, 1.63 (-)
Glu4	7.90	3.79 (*61.5*)	1.90, 2.57 (-)	γ-CH_2 2.31, 2.57 (*34.8*)
Gln5	8.18	3.89 (*59.8*)	2.12, 2.22 (-)	γ-CH_2 2.48, 2.50 (*34.8*); $CONH_2$ 6.65, 7.30
Ser6	7.77	4.22 (-)	4.01, 4.18 (-)	
Val7	8.28	3.64 (*67.5*)	2.32 (*32.0*)	γ-CH_3 0.97, 1.07 (*21.2, 22.4*)
Lys8	7.97	3.88 (-)	1.82, 1.91 (-)	γ-CH_2 1.16, 1.43 (-); δ-CH_2 1.65, 1.65 (-); ε-CH 2.67, 3.56 (42.7)
Ile9	8.29	3.74 (*65.8*)	1.94 (*38.5*)	δ-CH_3 0.87 (*13.0*); γ-CH_3 0.96 (*17.3*); γ-CH_2 1.17, 1.83 (-)
Ser10	8.08	4.18 (-)	4.00, 4.14 (-)	
Nle11	8.18	4.11 (*59.5*)	1.86, 1.92 (-)	γ-CH_2 1.62, 1.62 (*31.2*) δ-CH_2 1.31, 1.31 (*24.9*); ε-CH_2 0.86 (15.7)
Lys12	7.96	4.18 (*58.1*)	2.00, 2.04 (-)	γ-CH_2 1.52, 1.59 (*25.2*); δ-CH_2 1.73, 1.73 (*29.3*); ε-CH_2 3.01, 3.01 (*42.5)*; ζ-NH_2 7,04
Nle13	8.19	4.17 (-)	1.82, 1.87 (-)	γ-CH_2 1.50, 1.50 (-); δ-CH_2 1.32, 1.32 (*24.8*); ε-CH_3 0.88 (*15.8*); $CONH_2$ 6.90, 7.19