Supporting Information for

Crystallographic Characterization of the α/β-Peptide 14/15-Helix

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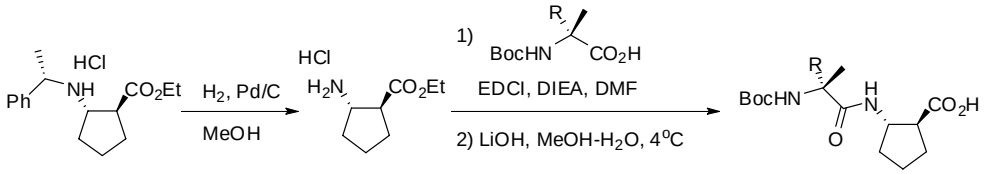
Complete Reference 14

Gong, B.; Zeng, H.; Zhu, J.; Yuan, L.; Han, Y.; Cheng, S.; Furukawa, M.; Parra, R. D.; Kovalevsky, A. Y.; Mills, J. L.; Skrzypczak-Jankun, E.; Martinovic, S.; Smith, R. D.; Zheng, C.; Szyperski, T.; Zeng, X. C. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 11583.

Peptide Synthesis and Purification

α/β-Peptides **2** and **3** were synthesized by a fragment condensation strategy in solution using Boc-Aib-ACPC-OH (**4**) and Boc-Ala-ACPC-OH (**5**). Dipeptide fragments **4** and **5** were prepared in three steps from the known ACPC intermediate (Scheme S1).[1] Coupling reactions between peptide fragments were mediated by (*N*,*N*-dimethylamino)-propyl-3-ethylcarbodiimide hydrochloride (EDCI) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP). Boc-protected amino acids and coupling reagents were purchased from Sigma-Aldrich and Chem-Impex. X-ray quality crystals of **2** and **3** were grown from a chloroform/diethyl ether mixture and by evaporation of a methanol/water mixture, respectively.



R = Me, Boc-Aib-ACPC-OH (**4**)
H, Boc-Ala-ACPC-OH (**5**)

Scheme S1. Preparation of dipeptide fragments **4** and **5**.

Boc-Ala-ACPC-Aib-ACPC-Aib-ACPC-Aib-ACPC-OBn (2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.5 Hz, 2H), 7.95 (s, 1H), 7.88 (s, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.40-7.25 (m, 6H), 7.18 (d, *J* = 8.1 Hz, 1H), 5.87 (d, *J* = 3.4 Hz, 1H), 5.15 (ABq, J_{AB} = 12.6 Hz, Δυ = 0.16 ppm, 2H), 4.56 (quintet, *J* = 6.4 Hz, 1H), 4.42-4.26 (m, 3H), 4.05 (m, 1H), 3.20 (q, *J* = 7.4 Hz), 2.49-2.26 (m, 3H), 2.24-1.57 (m, 24H), 1.54 (s, 3H), 1.47 (br s, 12H), 1.44 (s, 3H), 1.43 (s, 3H), 1.41 (s, 3H), 1.40 (s, 3H), 1.38 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.10, 175.65, 175.33, 175.22, 174.29, 174.18, 173.54, 156.22, 136.71, 128.57, 128.03, 128.00, 80.52, 77.43, 66.22, 57.01, 56.83, 56.76, 55.23, 55.13, 54.75, 53.37, 53.02, 52.94, 52.22, 49.55, 33.11, 33.01, 32.58, 32.48, 29.87, 29.70, 28.56, 28.39, 28.09, 27.81, 27.77, 27.49, 24.53, 24.47, 24.21, 24.11, 23.93, 23.81, 23.72, 17.99; **MALDI-TOF MS** 979.3 $[M+H]^+$, 1001.3 $[M+Na]^+$, 1017.2 $[M+K]^+$.

Boc-Ala-ACPC-Aib-ACPC-Aib-ACPC-Aib-ACPC-Aib-OBn (3): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20-8.06 (m, 2H), 7.90 (s, 1H), 7.88 (s, 1H), 7.83 (s, 1H), 7.60 (d, *J* = 7.3 Hz), 7.38-7.23 (m, 6H), 7.08 (d, *J* = 7.3 Hz), 5.84 (br s, 1H), 5.14 (ABq, J_{AB} = 12.6 Hz, Δυ = 0.05 ppm, 2H), 4.46-4.26 (m, 4H), 4.03 (m, 1H), 2.77 (q, *J* = 8.0 Hz), 2.53-2.31 (m, 3H), 2.17-1.66 (m, 24H), 1.64 (s, 3H), 1.58 (s, 3H), 1.54 (s, 3H), 1.47 (s, 9H), 1.46 (d, *J* = 3.8 Hz), 1.44 (s, 3H), 1.42 (s, 3H), 1.41 (s, 3H), 1.40 (s, 3H), 1.39 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.55, 175.23, 175.05, 174.96, 174.42, 174.39, 174.30, 174.20, 174.13, 156.34, 136.68, 128.49, 127.97, 127.92, 80.62, 77.43, 66.54, 57.00, 56.88, 56.77, 56.10, 55.08, 52.59, 52.48, 51.42, 33.07, 32.73, 32.51, 32.49, 28.73, 27.85, 27.80, 27.57, 25.78, 24.31, 24.13, 23.78, 23.73, 23.69, 18.06, 18.01; **MALDI-TOF MS** 1064.5 $[M+H]^+$, 1086.5 $[M+Na]^+$, 1102.5 $[M+K]^+$.

Crystallographic Experimental Section

The crystal structures have been deposited at the Cambridge Crystallographic Data Centre with deposition number CCDC 640722 (**2**) and 640729 (**3**).

Data Collection for Octamer 2

A colorless crystal with approximate dimensions 0.4 x 0.4 x 0.3 mm^3 was selected under oil under ambient conditions and attached to the tip of a nylon loop. The crystal was mounted in a stream of cold nitrogen at 100(2) K and centered in the X-ray beam by using a video camera.

The crystal evaluation and data collection were performed on a Bruker CCD-1000 diffractometer with Mo K_α (λ = 0.71073 Å) radiation and the diffractometer to crystal distance of 4.9 cm.

The initial cell constants were obtained from three series of ω scans at different starting angles. Each series consisted of 20 frames collected at intervals of 0.3º in a 6º range about ω with the exposure time of 10 seconds per frame. A total of 252 reflections was obtained. The reflections were successfully indexed by an automated indexing routine built in the SMART program. The final cell constants were calculated from a set of 9472 strong reflections from the actual data collection.

The data were collected by using the hemisphere data collection routine. The reciprocal space was surveyed to the extent of a full sphere to a resolution of 0.80 Å. A total of 86034 data were harvested by collecting five sets of frames with 0.25º scans in ω with an exposure time 52 sec per frame. These highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements.[2]

Structure Solution and Refinement for Octamer 2

The systematic absences in the diffraction data were uniquely consistent for the space group $P2_12_12$ that yielded chemically reasonable and computationally stable results of refinement.[2]

A successful solution by the direct methods provided most non-hydrogen atoms from the *E*-map. The remaining non-hydrogen atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients. Atom C(21) is disordered over two positions in a 56:44 ratio.

The final least-squares refinement of 645 parameters against 13157 data resulted in residuals *R* (based on F^2 for $I \geq 2\sigma$) and *wR* (based on F^2 for all data) of 0.0487 and 0.1366, respectively. The final difference Fourier map was featureless.

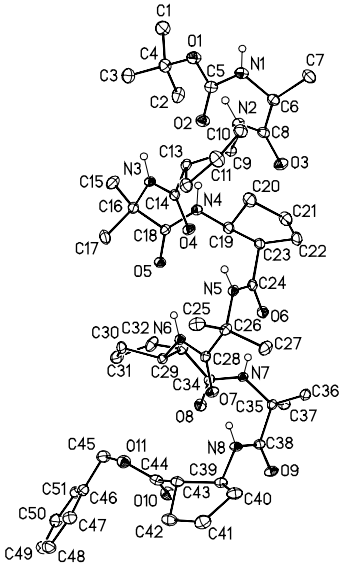


Figure S1. Molecular drawing of octamer **2** shown with 30% probability ellipsoids. Only the preferred orientation of atom C(21) is shown. All hydrogen atoms except the amide hydrogens have been omitted for clarity.

Table S1. Crystal data and structure refinement for octamer **2**.

Empirical formula	$C_{51}\ H_{78}\ N_8\ O_{11}$	
Formula weight	979.21	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12$	
Unit cell dimensions	a = 27.761(4) Å	α= 90°.
	b = 18.604(3) Å	β= 90°.
	c = 10.2474(15) Å	γ = 90°.
Volume	5292.6(14) $Å^3$	
Z	4	
Density (calculated)	1.229 Mg/m^3	
Absorption coefficient	0.087 mm^{-1}	
F(000)	2112	
Crystal size	0.40 x 0.40 x 0.30 mm^3	
Theta range for data collection	1.32 to 28.30°.	
Index ranges	-37<=h<=36, -24<=k<=24, -13<=l<=13	
Reflections collected	86034	
Independent reflections	13157 [R(int) = 0.0459]	
Completeness to theta = 28.30°	99.9 %	
Absorption correction	multiscan with sadabs	
Max. and min. transmission	0.9744 and 0.9661	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	13157 / 2 / 645	
Goodness-of-fit on F^2	1.005	
Final R indices [I>2sigma(I)]	R1 = 0.0487, wR2 = 0.1326	
R indices (all data)	R1 = 0.0518, wR2 = 0.1366	
Absolute structure parameter	n/a	
Largest diff. peak and hole	0.405 and -0.253 $e.Å^{-3}$	

Data Collection for Nonamer 3

A colorless crystal with approximate dimensions 0.43 x 0.40 x 0.24 mm^3 was selected under oil under ambient conditions and attached to the tip of a nylon loop. The crystal was mounted in a stream of cold nitrogen at 100(2) K and centered in the X-ray beam by using a video camera.

The crystal evaluation and data collection were performed on a Bruker CCD-1000 diffractometer with Mo K_α (λ = 0.71073 Å) radiation and the diffractometer to crystal distance of 4.9 cm.

The initial cell constants were obtained from three series of ω scans at different starting angles. Each series consisted of 20 frames collected at intervals of 0.3º in a 6º range about ω with the exposure time of 50 seconds per frame. A total of 297 reflections was obtained. The reflections were successfully indexed by an automated indexing routine built in the SMART program. The final cell constants were calculated from a set of 9472 strong reflections from the actual data collection.

The data were collected by using the full sphere data collection routine to survey the reciprocal space to the extent of a full sphere to a resolution of 0.95 Å. A total of 62681 data were harvested by collecting four sets of frames with 0.36º scans in ω and one set with 0.45º scans in φ with an exposure time 60 sec per frame. These highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements.[2]

Structure Solution and Refinement for Nonamer 3

The systematic absences in the diffraction data were consistent for the space group $P4_32_12$ that yielded chemically reasonable and computationally stable results of refinement.[2]

A successful solution by the direct methods provided most non-hydrogen atoms from the *E*-map. The remaining non-hydrogen atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the

neighboring atoms with relative isotropic displacement coefficients. Atoms C31 is disordered over two positions in a 76(1):24(1) ratio, atom C41 is disordered over two positions in a 71(2):29(2) ratio, and C49-C55 in a 1:1 ratio. Restraints and constraints were applied to ensure a computationally stable refinement. The water molecule resides on a crystallographic two-fold axis.

The final least-squares refinement of 700 parameters against 4442 data resulted in residuals *R* (based on F^2 for $I \geq 2\sigma$) and *wR* (based on F^2 for all data) of 0.0617 and 0.1638, respectively. The final difference Fourier map was featureless.

References

(1) Lee, H. -S.; LePlae, P. R.; Porter, E. A.; Gellman, S. H. *J. Org. Chem.* **2001**, *66*, 3597.

(2) Bruker-AXS. (2000-2003) SADABS V.2.05, SAINT V.6.22, SHELXTL V.6.10 & SMART 5.622 Software Reference Manuals. Bruker-AXS, Madison, Wisconsin, USA.

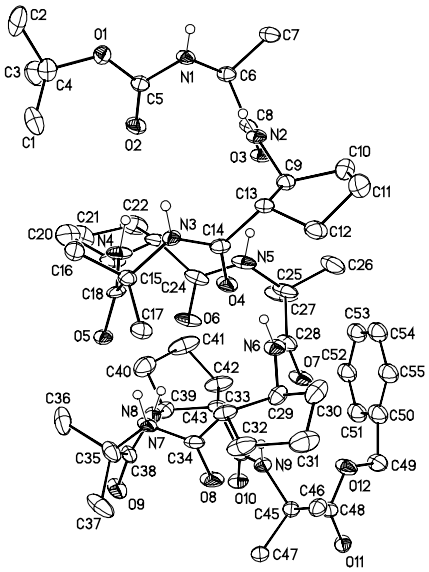


Figure S2. Molecular drawing of nonamer **3** shown with 40% probability ellipsoids. The solvent molecules, minor components of the disordered atoms, and non-amido hydrogen atoms are omitted.

Table S2. Crystal data and structure refinement for nonamer **3**.

Empirical formula	$C_{55}\ H_{85}\ N_9\ O_{12}$. MeOH . ½ H_2O	
Formula weight	1105.37	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Tetragonal	
Space group	$P4_32_12$	
Unit cell dimensions	a = 14.7772(7) Å	α= 90°.
	b = 14.7772(7) Å	β= 90°.
	c = 56.444(5) Å	γ = 90°.
Volume	12325.4(14) $Å^3$	
Z	8	
Density (calculated)	1.191 Mg/m^3	
Absorption coefficient	0.085 mm^{-1}	
F(000)	4776	
Crystal size	0.43 x 0.40 x 0.24 mm^3	
Theta range for data collection	1.95 to 22.03°.	
Index ranges	-15<=h<=15, -15<=k<=15, -59<=l<=59	
Reflections collected	62681	
Independent reflections	4442 [R(int) = 0.0553]	
Completeness to theta = 22.03°	99.9 %	
Absorption correction	Multi-scan with SADABS	
Max. and min. transmission	0.9798 and 0.9642	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4442 / 1449 / 700	
Goodness-of-fit on F^2	1.214	
Final R indices [I>2sigma(I)]	R1 = 0.0617, wR2 = 0.1576	
R indices (all data)	R1 = 0.0712, wR2 = 0.1638	
Absolute structure parameter	N/A	
Largest diff. peak and hole	0.427 and -0.232 $e.Å^{-3}$	

Table S3. Hydrogen bonds for octamer **2** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2)-H(2)...O(10)#1	0.88	2.15	2.968(2)	154.8
N(3)-H(3)...O(9)#1	0.88	2.10	2.8459(19)	142.6
N(4)-H(4)...O(2)	0.88	2.29	3.135(2)	160.1
N(5)-H(5)...O(4)	0.88	1.97	2.8190(19)	162.9
N(6)-H(6)...O(5)	0.88	2.08	2.870(2)	148.7
N(7)-H(7)...O(6)	0.88	2.05	2.9295(19)	176.9
N(8)-H(8)...O(7)	0.88	1.99	2.8116(19)	155.9

Symmetry transformations used to generate equivalent atoms:
#1 x-1/2,-y+3/2,-z+1

Table S4. Hydrogen bonds for nonamer **3** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(9)#1	0.88	2.05	2.882(5)	158.4
N(2)-H(2)...O(10)#1	0.88	2.24	2.977(5)	141.1
N(3)-H(3)...O(11)#1	0.88	2.25	2.910(5)	131.6
N(4)-H(4)...O(2)[a]	0.88	2.78	3.461(6)	135.8
N(5)-H(5)...O(3)	0.88	2.11	2.944(5)	158.8
N(6)-H(6)...O(4)	0.88	2.07	2.868(5)	150.1
N(7)-H(7)...O(5)	0.88	2.09	2.940(5)	163.0
N(8)-H(8)...O(6)	0.88	2.12	2.925(5)	151.4
N(9)-H(9)...O(7)	0.88	2.21	2.917(5)	136.7
N(9)-H(9)...O(8)[a]	0.88	2.80	3.282(6)	116.3
O(13)-H(13A)...O(14)	0.84	2.06	2.858(7)	158.8
O(14)-H(14A)...O(3)	0.8400(12)	2.04(4)	2.803(4)	151(7)

a. possible hydrogen bonding interaction
Symmetry transformations used to generate equivalent atoms:
#1 -y+3/2,x+1/2,z-1/4