Electronic Supplementary Material (ESI) for Chemical Communications

Constrained α/γ-Peptide: a New Stable Extended Structure in Solution without any Hydrogen Bond and Characterized by a Four-Fold Symmetry.

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Supporting information

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I- General information

Unless otherwise stated, all reactions were conducted in oven dried glassware under an atmosphere of dry argon gas. Diethylether and THF were distilled over sodium/benzophenone ketyl under argon. All other reagents were used as received. Flash chromatography was performed on Kieselgel 60 (35-70 µm) silica gel. Infrared spectra were recorded as thin films on NaCl plates using an FT-IR spectrophotometer. Mass spectra were measured on a MAT95S Finnigan-Thermo spectrometer at the Institut de Chimie Moléculaire et des Matériaux (ICMMO) Mass Spectrometry Laboratory. One dimensional ^{1}H NMR spectra were recorded on Bruker spectrometers operating at 250, 300, 360, 400 or 500 MHz using $CDCl_3$, $(CD_3)_2SO$ or D_2O as solvent. Chemical shifts are reported in δ units to 0.01 ppm precision with coupling constants (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. One dimensional ^{13}C NMR were measured at 62.5, 75, 90, 100 or 125 MHz using $CDCl_3$, $(CD_3)_2SO$ or D_2O as solvent. Chemical shifts are reported in δ units to 0.1 ppm precision using residual solvent as an internal reference.

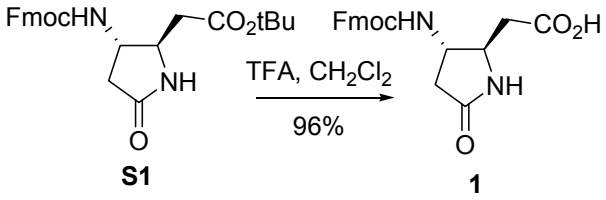
Purifications of the oligomers were performed using a Dionex HPLC semi-preparative system (P580) with a diode array detector (UVD340S), and a Gilson 215 liquidhandler. The separations were accomplished with a C18 Interchim column (UP5NEC: 5µm, 10mm I.D. × 250 mm L).

Two dimensional ^{1}H-^{1}H and ^{1}H-^{13}C spectra were recorded on a Bruker Avance III spectrometer operating at a ^{1}H frequency of 500 MHz and equipped with a triple resonance, z-axis pulsed-field-gradient cryogenic probehead, optimized for ^{1}H detection. Complete proton assignments of the tetramer 2, hexamer 3 and octamer 4 were obtained from the analysis of a 2D total correlation spectroscopy (TOCSY) experiment using a 80 ms DIPSI-2 mixtime, and 2D rotating frame Overhauser effect spectroscopy (ROESY) experiments (300 ms mixing time). Homonuclear experiments were typically collected as 1024 (t1) and 4096 (t2) time-domain matrices over a spectral width of 10 ppm, with 8 scans per t1 increment. Carbon assignment was deduced from heteronuclear 2D ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC spectra, using a 512 (t1) x 1024 (t2) or a 1024 (t1) x 4096 (t2) time-domain matrices, rescpectively, with 16 scans per t1 increment. CH_2-TROSY experiments were typically collected as 512 (t1) and 4096 (t2) time-domain matrices over a spectral width of 10 ppm, with 32 scans per t1 increment. Data were processed with the TOPSPIN 2.0 software (Bruker). Unless specified otherwise, shifted sine-bell window functions were applied in both indirect and direct detected dimensions and extensive zero-filling prior to Fourier transformation was used to yield high digital resolution. Spectra

were analyzed using CARA software.[1] Homonuclear $^3J_{HN_{H\gamma}}$ vicinal couplings in Lac residue were directly obtained from amide resonances in 1D proton spectra. Homonuclear $^3J_{H\alpha_{H\beta}}$ or $^3J_{H\gamma_{H}\delta}$ couplings were extracted from the doublets obtained in the CH_2-TROSY experiments. Finally, some structural relevant heteronuclear scalar couplings ($^3J_{HNC\beta}$, $^3J_{HNC\delta}$, $^3J_{HN'C\delta}$ and $^3J_{HN'C\alpha}$ and $^3J_{HNC'}$) were possibly measured in phase-sensitive HMBC experiments.[2]

II- Procedures and characterisation data of all new compounds

Syntheses (and characterisation data) of compound **S1** and **S2**, starting from aspartic acid (6 or 7 steps) is described elsewhere.[3]



2-((2*R*,3*S*)-3-(((9H-fluoren-9-yl)methoxy)carbonylamino)-5-oxopyrrolidin-2-yl)acetic acid (1)

To a stirred solution of compound **S1** (2.08 g, 4.77 mmol) at 0°C in dry CH_2Cl_2 (30 mL) was added dropwise trifluoroacetic acid (11 mL, 148 mmol). The mixture was then stirred at room temperature for 4h. The reaction mixture was poured into a separatory funnel, EtOAc was added and the organic layer was washed with 2M HCl, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material **1** was used without further purification.

Yield: 96% (1.74g, 4.58mmol); yellow solid; mp: 123°C.

^{1}H NMR (250MHz, MeOD) δ (ppm) **:** 2.30 (dd , *J*=6.0 , 17.0 Hz , 1H) , 2.53 (dd , *J*=8.1 , 17.0 Hz , 1H) , 2.66-2.80 (m , 2H) , 3.79 (m , 1H) , 4.08 (m , 1H) , 4.23 (t , *J*=6.5Hz , 1H) , 4.39-4.48 (m , *J*=6.5 Hz , 2H) , 7.29-7.46(m , 4H) , 7.67 (d , *J*=7.2 Hz , 2H) , 7.82 (d , *J*=7.2 Hz , 2H).

^{13}C NMR (62.5 MHz, DMSO) δ (ppm) 36.7, 40.9, 47.2, 51.9, 57.4, 65.8, 120.6, 125.6, 127.5, 128.1, 141.2, 144.3, 156.1, 172.5, 174.4

HRMS (electrospray) (M+Na) calculated 403.1276, found 403.1264.

IR (thin film, CH_2Cl_2) ν (cm^{-1}) 3384, 1683, 1264.

$[\alpha]_D^{20}$ = + 3.9 (c=0.47, MeOH).

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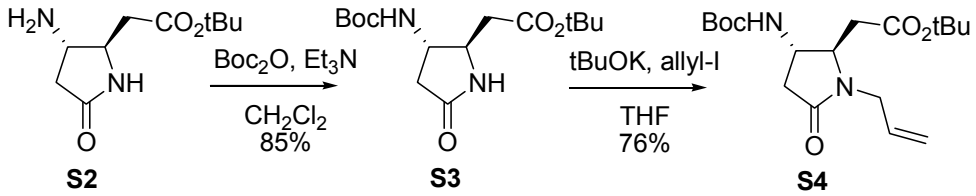
[1] Keller R. Computer-Aided Resonance Assignment, version 1.2.3. http://cara.nmr.ch/doku.php
[2] A.Meissner, O. W. Soerensen, *Magn. Reson. Chem*. 2001, **39**, 49-52.
[3] C. T. Hoang, F. Bouillère, S. Johannesen, A. Zulauf, C. Panel, D. Gori, A. Pouilhès, V. Alezra, C. Kouklovsky, *J. Org. Chem.* 2009, **74**, 4177-4187.



***tert*-butyl 2-((2*R*,3*S*)-3-(*tert*-butoxycarbonylamino)-5-oxopyrrolidin-2-yl)acetate (S3)**

To a stirred solution of compound **S2** (100 mg, 0.47 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise TEA (72 µL, 0.51 mmol) and $(Boc)_2O$ (204 mg, 0.93 mmol). The mixture was then stirred at room temperature for 2h. The reaction mixture was poured into a separatory funnel, EtOAc was added and the organic layer was washed with 10% aqueous citric acid, brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (CH_2Cl_2/MeOH: 97/3) to give pure **S3**.

Yield: 85% (125mg, 0.39mmol); white solid; mp: 155°C.

^{1}H NMR (250MHz, $CDCl_3$) δ (ppm) **:** 1.48 (s , 18H) , 2.21 (dd , *J*=5.7 , 16.9 Hz , 1H) , 2.37 (dd , *J*=10.5 , 16.9 Hz , 1H) , 2.63-2.84 (m , 2H) , 3.75 (m , 1H) , 4.00 (m , 1H) , 5.26 (d , *J*=6.4 Hz , 1H) , 6.47 (bs , 1H).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm) 28.2, 28.5, 36.8, 40.4, 51.7, 58.1, 80.2, 81.9, 155.4, 170.7, 174.7.

HRMS (electrospray) (M+Na) calculated 337.1739, found 337.1739.

IR (thin film, CH_2Cl_2) ν (cm^{-1}) 3305, 2978, 1701, 1159.

$[\alpha]_D^{20}$ = +31.4 (c=1.03, CH_2Cl_2).

***tert*-butyl 2-((2*R*,3*S*)-1-allyl-3-(*tert*-butoxycarbonylamino)-5-oxopyrrolidin-2-yl)acetate (S4)**

The compound **S3** (53 mg, 0,168 mmol) was dissolved in dry THF (2 mL). Then the solution was added directly on freshly sublimated *t*BuOK (28.4 mg, 0.253 mmol). After 20min of vigorous stirring at room temperature, allyl iodide was added dropwise (23 µL, 0.253 mmol). The mixture was then stirred at room temperature for 1h and concentrated under reduced pressure. The crude material was purified by flash chromatography (CH_2Cl_2/MeOH: 95/5) to give pure **S4**. Crystals of S4 was obtained by slow evaporation of ethanol solution.

Yield: 76% (45mg, 0.128mmol); white crystalline solid; mp: 132°C.

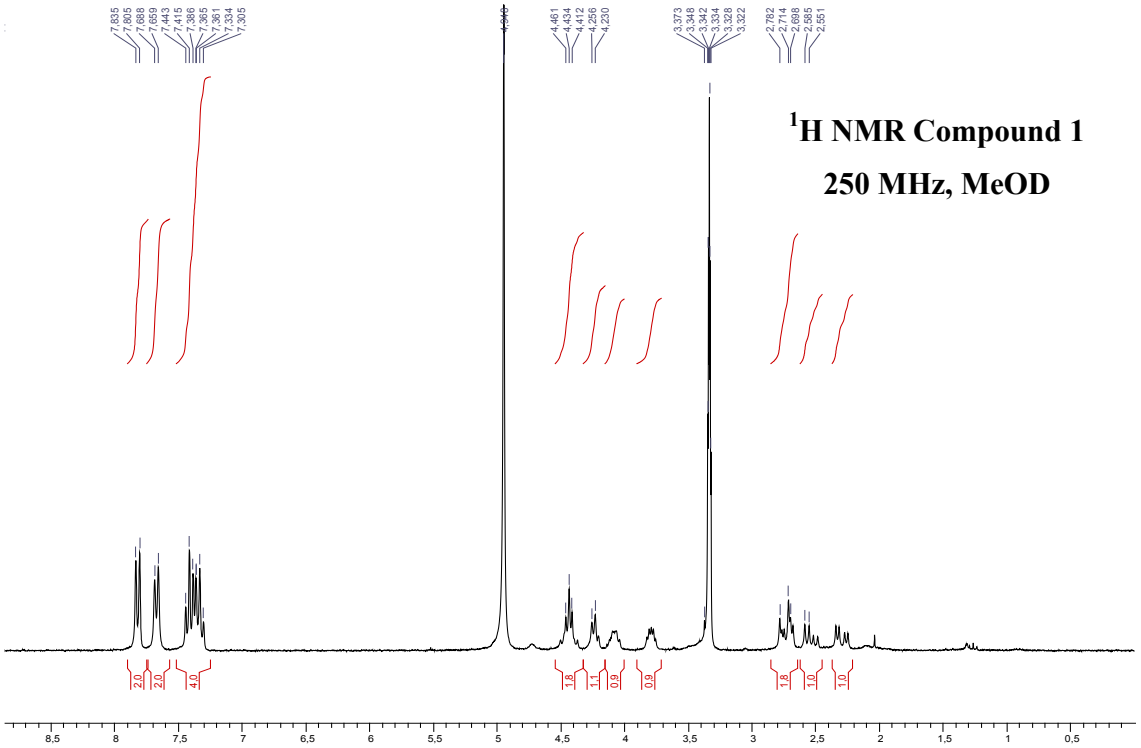
^{1}H NMR (300MHz, $CDCl_3$) δ (ppm) **:** 1.42 (s , 9H) , 1.43 (s , 9H) , 2.25 (dd , *J*=3.7 , 17.5 Hz , 1H) , 2.52 (dd , *J*=6.1 , 15.7 Hz , 1H), 2.62 (dd , *J*=4.5Hz , 15.7 Hz , 1H), 2.86 (dd , *J*=8.2Hz , 17.5 Hz , 1H) , 3.53 (dd , *J*=6.8Hz , 15.5 Hz , 1H) , 3.76 (m , 1H) , 4.08 (m , 1H) , 4.25 (dd , *J*=5.2Hz , 15.5 Hz , 1H) , 5.11 (d , *J*=6.3Hz , 1H) , 5.18 (dd , *J*=1.2Hz , 10.1 Hz , 1H) , 5.20 (dd , *J*=1.2 Hz , 16.9 Hz , 1H) , 5.71 (dddd , *J*=5.2Hz , *J*=6.8 Hz , *J*=10.1 Hz , *J*=16.9 Hz , 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 28.1, 28.5, 37.6, 38.2, 43.4, 49.9, 62.1, 80.2, 81.7, 118.3, 132.4, 155.4, 169.7, 172.4.

HRMS (electrospray) (M+Na) calculated 377.2047, found 377.2039.

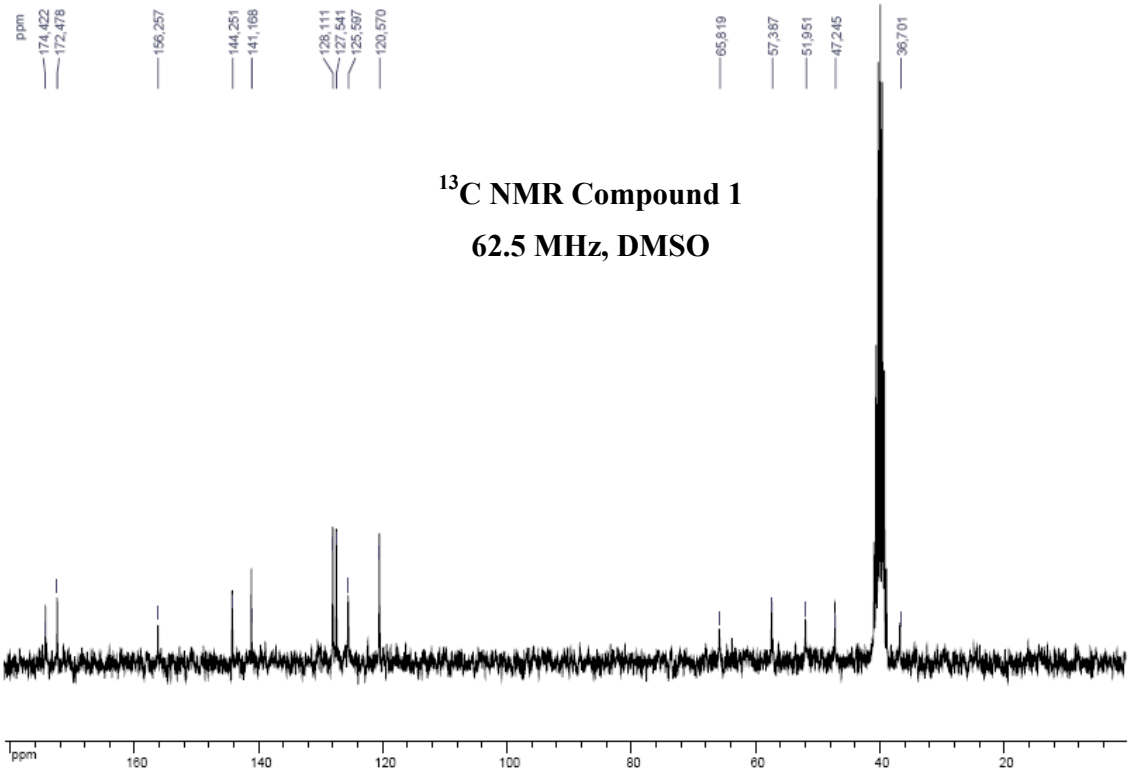
IR (thin film, CH_2Cl_2) ν (cm^{-1}) 3310, 1684, 1645, 1517, 1158. $[\alpha]_D^{20}$ = +17.1 (c=0.80, CH_2Cl_2).

III- ^{1}H and ^{13}C NMR spectra of new monomeric compounds



^{1}H NMR Compound 1

250 MHz, MeOD

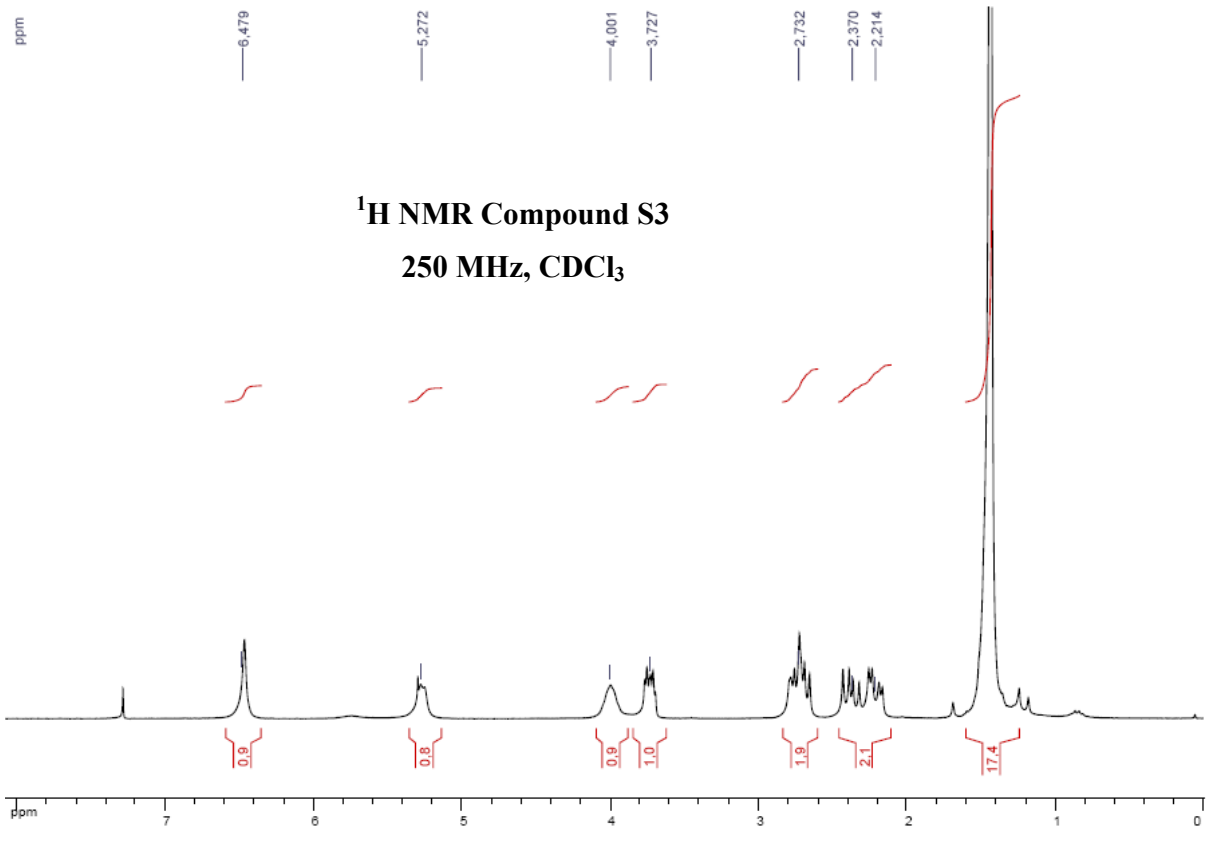


^{13}C NMR Compound 1

62.5 MHz, DMSO

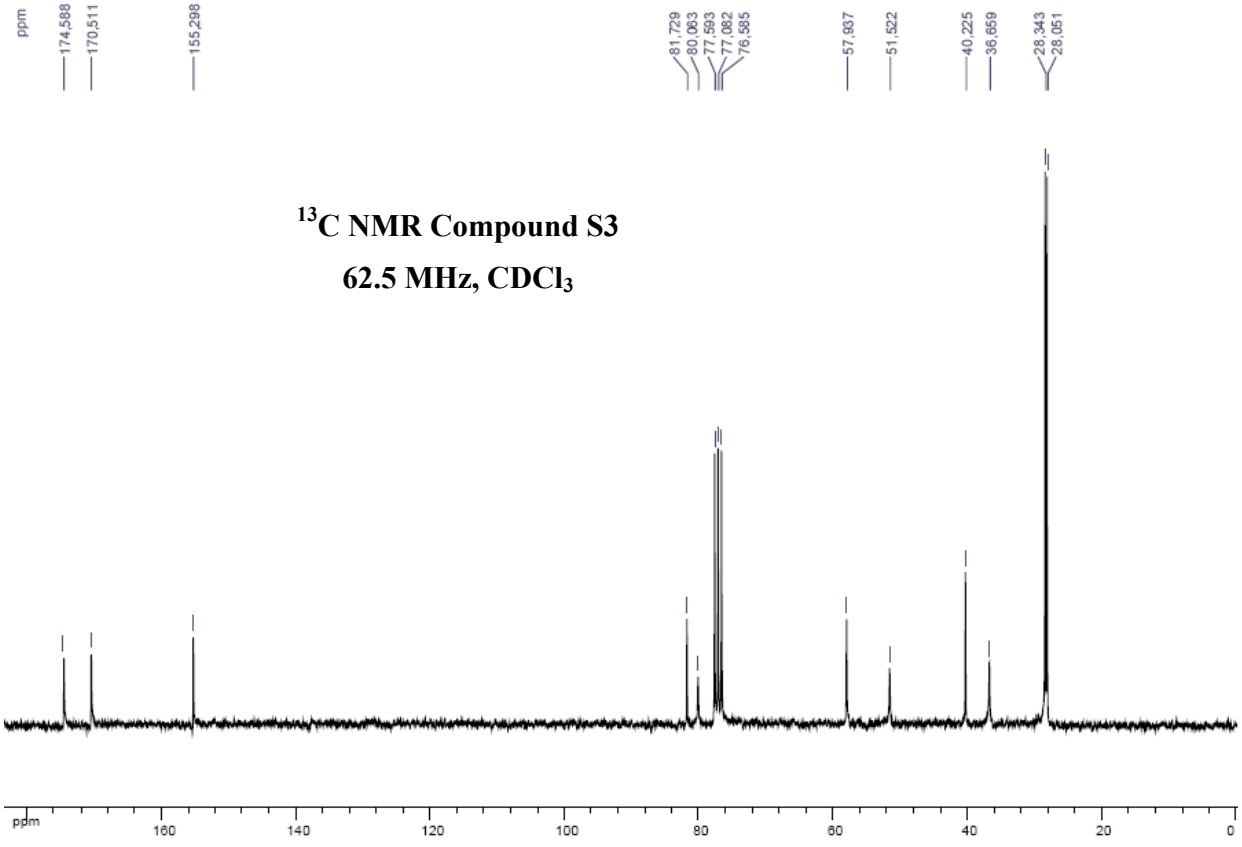
^{1}H NMR Compound S3

250 MHz, $CDCl_3$



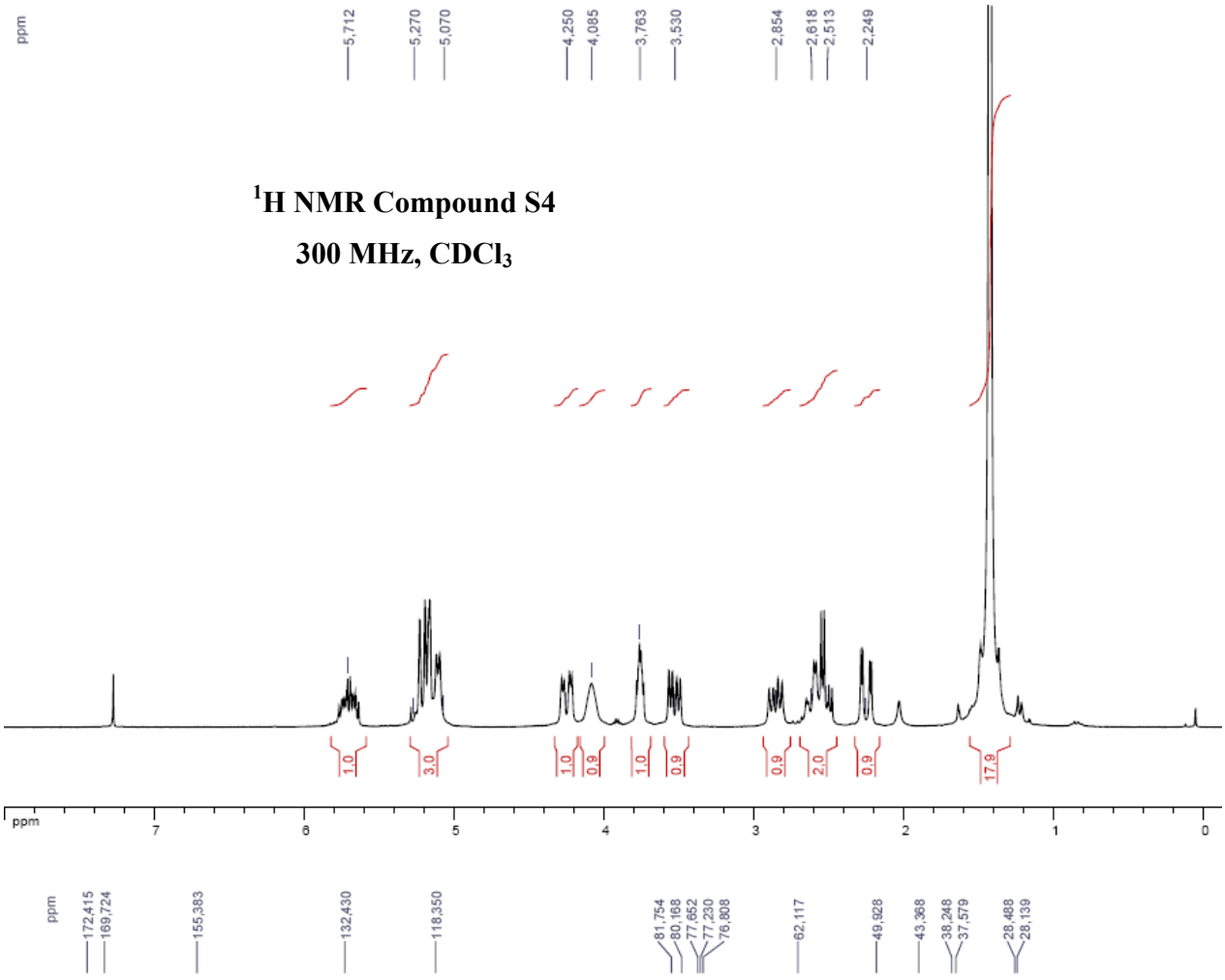
^{13}C NMR Compound S3

62.5 MHz, $CDCl_3$



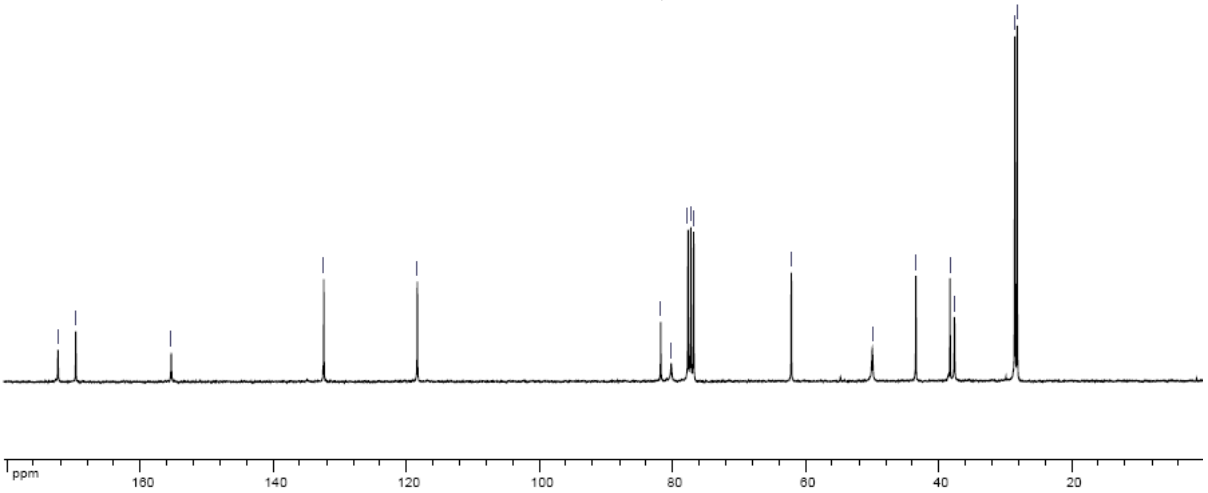
^{1}H NMR Compound S4

300 MHz, $CDCl_3$



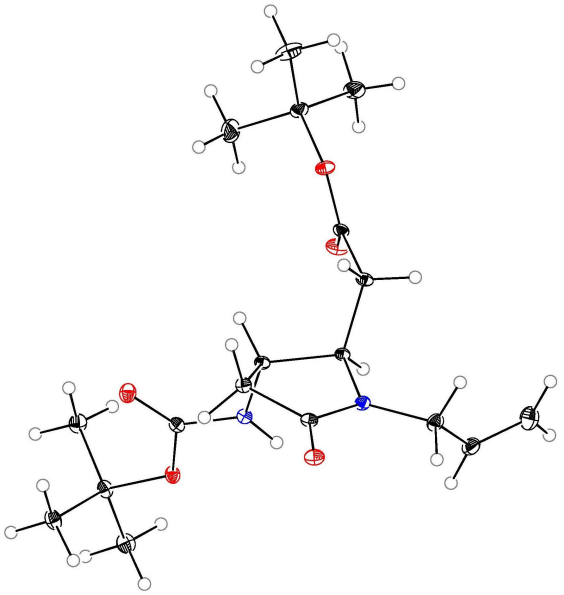
^{13}C NMR Compound S4

75 MHz, $CDCl_3$



IV- Crystallographic data of compound S4.

Figure S1: ORTEP drawing of S4. Ellipsoids are drawn at the 50 % probability level.



Single-crystal X-ray structure analyses: Details of the crystal data, data collection and refinement are given in Table S1. The diffraction intensities were collected with graphite-monochromatized Mo Kα radiation. Data collection and cell refinement were carried out using a Bruker Kappa X8 APEX II diffractometer. The temperature of the crystal was maintained at the selected value (100K) by means of a 700 series Cryostream cooling device to within an accuracy of ±1 K. Intensity data were corrected for Lorenz-polarization and absorption factors. The structures were solved by direct methods using SHELXS-97[4], and refined against F^2 by full-matrix least-squares methods using SHELXL-97 with anisotropic displacement parameters for all non-hydrogen atoms. All calculations were performed by using the Crystal Structure crystallographic software package WINGX[5]. The structures were drawn using ORTEP3.

Treatment on H: H atoms of the structure were added from the difference Fourier map, and refined by the riding model.

4. (a) [SHELXS-97] G. M. Sheldrick, SHELXS-97, *Program for Crystal Structure Solution, University of Göttingen, Göttingen, Germany* **1997**.
(b) [SHELXL-97] G. M. Sheldrick, SHELXL-97, *Program for the refinement of crystal structures from diffraction data, University of Göttingen, Göttingen, Germany* **1997**.
5. [WINGX] L.J. Farrugia, *J. Appl. Cryst.* 1999, **32**, 837.

CCDC 798420 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_ request/cif.

Table S1: Summary of X-ray crystallographic data for **S4**.

	S4
Empirica formula	$C_{18}\ H_{30}\ N_2\ O_5$
Formula weight	354.44
Temperature (K)	100(1)
Wavelength (Å)	0.71069
Crystal system	monoclinic
Space group	*P* 2_1 (no.4)
Unit cell dimensions	
a (Å)	5.7347(3)
b (Å)	17.0484(9)
c (Å)	10.2113(6)
α (°)	90
β (°)	96.0450(10)
γ (°)	90
U ($Å^3$)	992.78(9)
Z	2
$D_{calc.}$ ($Mg.m^{-3}$)	1.186
Absorption coefficient (mm^{-1})	0.086
F (0 0 0)	384
Reflection collected	19619
Independent reflections (Rint)	9587 (0.0345)
Observed reflections (I >2σ(I))	8202
Final *R* indices [$I > 2\sigma I$]	R1=0.0414, wR2= 0.1001
Final *R* indices (all data)	R1=0.0525, wR2= 0.1053
S	1.014
$(\Delta\ \rho)_{max,\ min}$ [e $Å^{-3}$]	0.379 ; -0.252
Flack Parameter[6]	0.1(3)

[6] H. D. Flack, *Acta Cryst.* 1983, **A39**, 876-881

V- General procedure for peptide syntheses (tetramer 2, hexamer 3, octamer 4)

Peptide syntheses were performed manually in a glass apparatus fitted with a sintered glass. Solvents and soluble reagents were removed by suction. Washings between deprotection, coupling and subsequent deprotection steps were carried out with DMF (2x1min), MeOH, CH_2Cl_2, DMF, CH_2Cl_2.

- Fmoc group removal

The Fmoc goup was removed using 20% piperidine in DMF (45min).

- Solid phase peptide backbone elongation

All syntheses were carried out with Rink Amide resin (88 mg, 0.0965 mmol) by a Fmoc solid phase strategy. Couplings of each Fmoc monomer derivative (0.145 mmol) was carried out with HATU (55 mg, 0.145 mmol) and DIPEA (48 µL, 0.289 mmol) in DMF (1.5 mL) for 1h at room temperature. Couplings were monitored by the Kaiser test.

- Cleavage from the resin

Cleavage of the oligomers from the resin was performed by treatment with TFA/H_2O (95:5) for 1h. The resin was then washed with TFA. The TFA solution was concentrated in vacuo, solubilized in water and lyophilized to afford crude oligomers.

The crude peptides were finally purified by preparative RP-HPLC.

For compound **2**, eluent: gradient of acetonitrile (2% to 5%) with water (less than 0.1% TFA) and with a flow of 2mL/min. (Retention time: 8,4 min).

For compound **3**, eluent: gradient of acetonitrile (1% to 5%) with water (less than 0.1% TFA) and with a flow of 2mL/min. (Retention time: 8.1 min).

For compound **4**, after a first purification on the Dionex system, an ultimate purification was performed using a Waters HPLC semi-preparative system. The separation was accomplished with a Waters column (symmetry RP8 prep column: 7mm I.D. × 300 mm L). Eluent: gradient of acetonitrile (30% to 90%) with water (less than 0.1% TFA) and with a flow of 1mL/min (Retention time : 12.1 min).

Tables with ^{1}H and ^{13}C chemical shifts of oligomers **2-4** are given in the following.

VI- Characterization data and NMR studies of tetramer 2, hexamer 3 and octamer 4.

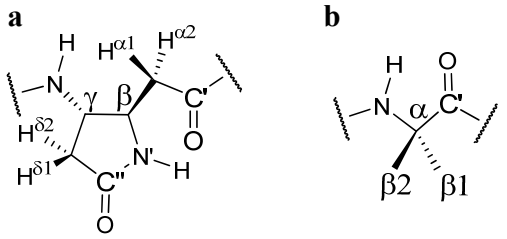
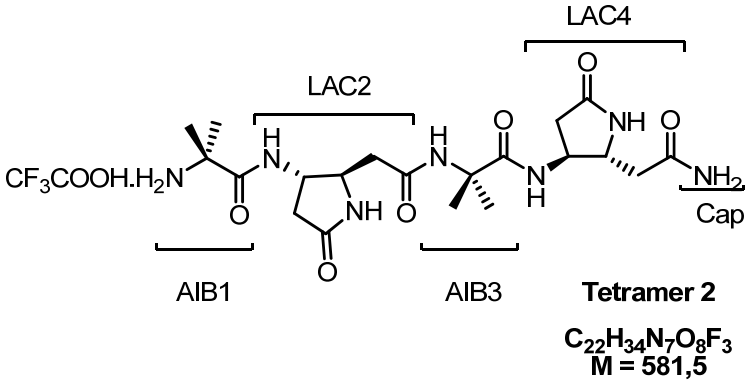


Figure S2: Nomenclature used for LAC (a) and AIB (b) amino acid residues.



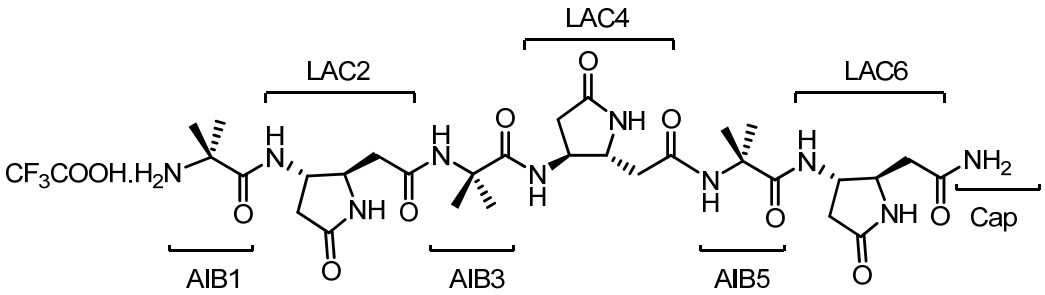
Tetramer 2: HRMS (electrospray) m/z $[M+Na]^+$ calculated 490.2385, found 490.2385.

Table S2: ^{1}H-NMR Chemical Shifts in ppm of tetramer 2 (DMSO-d_6, 500 MHz, 293K)

Residue	H^N	$H^{N'}$	$H^{\alpha1}$/ $H^{\alpha2}$	H^{β}	H^{γ}	$H^{\delta2}$/ $H^{\delta1}$
AIB1	8.15			1.44		
LAC2	8.54	7.72	2.31/2.38	3.67	4.12	2.07/2.58
AIB3	8.01			1.29, 1.31		
LAC4	7.81	7.52	2.19/2.39	3.61	4.06	2.13/2.41

Table S3: ^{13}C-NMR Chemical Shifts in ppm of tetramer 2 (DMSO-d_6, 500 MHz, 293K)

Residue	C^{α}	C^{β}	C^{γ}	C^{δ}
AIB1		23.22		
LAC2	40.45	56.93	50.20	35.79
AIB3		24.49, 25.33		
LAC4	39.67	56.62	49.96	35.96



Hexamer 3
$C_{32}H_{49}N_{10}O_{11}F_3$
M = 806,8

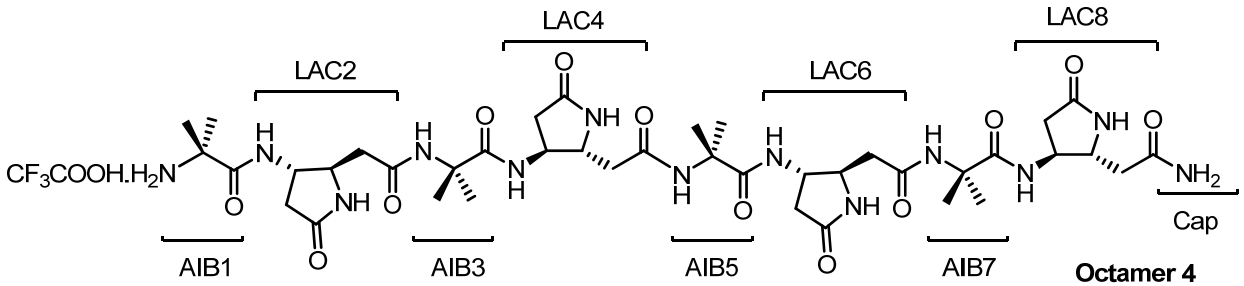
Hexamer 3: HRMS (electrospray) m/z $[M+Na]^+$ calculated 693.3678, found 693.3679.

Table S4: ^{1}H-NMR Chemical Shifts in ppm of hexamer 3 (DMSO-d_6, 500 MHz, 293K)

Residue	H^N	$H^{N'}$	$H^{\alpha1}$/ $H^{\alpha2}$	H^{β}	H^{γ}	$H^{\delta2}$/ $H^{\delta1}$
AIB1	8.18			1.44		
LAC2	8.56	7.67	2.32/2.38	3.66	4.13	2.07/2.58
AIB3	8.00			1.30		
LAC4	7.85	7.53	2.24/2.39	3.60	4.08	2.15/2.40
AIB5	7.97			1.28, 1.31		
LAC6	7.82	7.44	2.20/2.39	3.61	4.07	2.15/2.40

Table S5: ^{13}C-NMR Chemical Shifts in ppm of hexamer 3 (DMSO-d_6, 500 MHz, 293K)

Residue	C^{α}	C^{β}	C^{γ}	C^{δ}	C'/C''
AIB1	56.20	23.34			171.52/-
LAC2	40.43	57.07	50.21	35.82	168.98/174.03
AIB3	56.77	24.45, 24.70			174.19/-
LAC4	40.24	56.97	49.82	35.91	169.34/174.24
AIB5	55.79	25.26, 25.54			174.09/-
LAC6	39.66	56.62	50.03	35.91	172.11/174.01



Octamer 4: HRMS (electrospray) m/z $[M+Na]^+$ calculated 940.4611, found 940.4601.

Table S6: ^{1}H-NMR Chemical Shifts in ppm of octamer 4 (DMSO-d_6, 500 MHz, 293K)

Residue	H^N	$H^{N'}$	$H^{\alpha1}$/ $H^{\alpha2}$	H^β	H^γ	$H^{\delta2}$/ $H^{\delta1}$
AIB1	8.140			1.440		
LAC2	8.554	7.695	2.314/2.374	3.666	4.129	2.068/2.595
AIB3	8.015			1.298, 1.312		
LAC4	7.874	7.499	2.242/2.392	3.598	4.085	2.146/2.411
AIB5	7.988			1.291, 1.317		
LAC6	7.881	7.484	2.242/2.395	3.597	4.101	2.159/2.391
AIB7	7.967			1.284, 1.313		
LAC8	7.835	7.459	2.193/2.404	3.606	4.074	2.149/2.388

Table S7 : ^{13}C-NMR Chemical Shifts in ppm of octamer 4 (DMSO-d_6, 500 MHz, 293K)

Residue	C^α	C^β	C^γ	C^δ	C'/C''
AIB1	56.36	23.19, 23.22			171.55/-
LAC2	40.42	56.99	50.18	35.75	169.01/174
AIB3	55.78	24.63, 25.40			174.19/-
LAC4	40.11	56.97	49.74	35.73	169.34/174
AIB5	55.81	24.52, 25.39			174.21/-
LAC6	40.11	56.84	49.74	35.73	169.4/174
AIB7	55.81	24.43, 25.20			174.23/-
LAC8	39.61	56.54	49.97	35.90	172.11/174

Table S8: Coupling constants of tetramer 2 in DMSO-d_6 at 293K in Hz

J (Hz)	Lac 2	Lac 4
^3J (H^{β}-$H^{N'}$)	<1.5	<1.5
^3J (H^{γ}-$H^{\delta1}$)	8,3	8,8
^3J (H^{γ}-$H^{\delta2}$)	3,9	6,6
^3J (H^{β}-$H^{\alpha1}$)	7,6	8,1
^3J (H^{β}-$H^{\alpha2}$)	5,2	4,2
^3J (H^{N}-H^{γ})	6,9	7,5

Table S9: Coupling constants of hexamer 3 in DMSO-d_6 at 293K in Hz

J ^{1}H-^{1}H(Hz)	Lac 2	Lac 4	Lac 6	Aib 3	Aib 5
^3J (H^{β}-$H^{N'}$)	3.1	<1.7	2.7	-	-
^3J (H^{γ}-$H^{\delta1}$)	8.2	9.1	9.1	-	-
^3J (H^{γ}-$H^{\delta2}$)	3.6	6.4	6.8	-	-
^3J (H^{β}-$H^{\alpha1}$)	7.7	8	8.3	-	-
^3J (H^{β}-$H^{\alpha2}$)	5.4	4.4	4.3	-	-
^3J (H^{N}-H^{γ})	6.7	7.7	7.5	-	-
J ^{1}H-^{13}C(Hz)	Lac 2	Lac 4	Lac 6	Aib 3	Aib 5
^3J (H^{N}-C^{β})	2.2	2.2	2.2	-	-
^3J (H^{N}-C^{δ})	2.5	2.5	2.5	-	-
^3J ($H^{N'}$-C^{γ})	6.8	7.0	7.1	-	-
^3J ($H^{N'}$-C^{α})	<1.7	<1.7	<1.7	-	-
^3J (H^{N}-C')	-	-	-	2.9	3.0

Table S10: Coupling constants of octamer 4 in DMSO-d_6 at 293K in Hz

J ^{1}H-^{1}H (Hz)	Lac 2	Lac 4	Lac 6	Lac 8	Aib 3	Aib 5	Aib 7
^3J (H^{β}-$H^{N'}$)	1.0	1.0	1.0	1.0	-	-	-
^3J (H^{γ}-$H^{\delta1}$)	8.3	8.8	8.8	8.7	-	-	-
^3J (H^{γ}-$H^{\delta2}$)	4.2	6.3	6.9	6.6	-	-	-

^3J (H^{β}-$H^{\alpha 1}$)	7.4	8.1	8.1	8.2	-	-	-
^3J (H^{β}-$H^{\alpha 2}$)	5.6	4.4	4.2	4.5	-	-	-
^3J (H^{N}-H^{γ})	6.9	7.7	7.8	7.6	-	-	-
J ^{1}H-^{13}C(Hz)	**Lac 2**	**Lac 4**	**Lac 6**	**Lac 8**	**Aib 3**	**Aib 5**	**Aib 7**
^3J (H^{N}-C^{β})	2.2	2.2	2.2	2.2	-	-	-
^3J (H^{N}-C^{δ})	2.5	2.5	2.5	2.5	-	-	-
^3J ($H^{N'}$-C^{γ})	6.8	7.0	7.0	7.1	-	-	-
^3J ($H^{N'}$-C^{α})	<1.8	<1.8	<1.8	<1.8	-	-	-
^3J (H^{N}-C')	-	-	-	-	2.9	3.0	3.0

Table S 11: Inter-residue NOEs observed in the ROESY NMR spectrum of tetramer 2 (DMSO-d_6, 500 MHz, 293K, τm = 300 ms)

		Aib1	Lac2	Aib3	Lac4	Cap
i, i+1	H^{N}-H^{N}					
	$H^{N'}$-H^{N}					
	CH_3^{β}-$H^{\delta 2}$					
	CH_3^{β}-$H^{\alpha 2}$					
	CH_3^{β}-H^{β}					
	CH_3^{β}-H^{γ}					
	$H^{\alpha 1}$-H^{N}					
	$H^{\alpha 2}$-H^{N}					
	H^{β}-H^{N}					
	H^{γ}-H^{N}					
	CH_3^{β}-H^{N}					

(**strong, medium, weak**)

Table S 12: Inter-residue NOEs observed in the ROESY NMR spectrum of hexamer 3 (DMSO-d_6, 500 MHz, 293K, τm = 300 ms)

		Aib1	Lac2	Aib3	Lac4	Aib5	Lac6	Cap
i, i+1	H^{N}-H^{N}							
	$H^{N'}$-H^{N}							
	CH_3^{β}-$H^{\delta 2}$							
	CH_3^{β}-$H^{\alpha 2}$							
	CH_3^{β}-H^{β}							
	CH_3^{β}-H^{γ}							
	$H^{\alpha 1}$-H^{N}							
	$H^{\alpha 2}$-H^{N}							
	H^{β}-H^{N}							
	H^{γ}-H^{N}							
	CH_3^{β}-H^{N}							
i, i+2	$H^{N'}$-H^{N}							

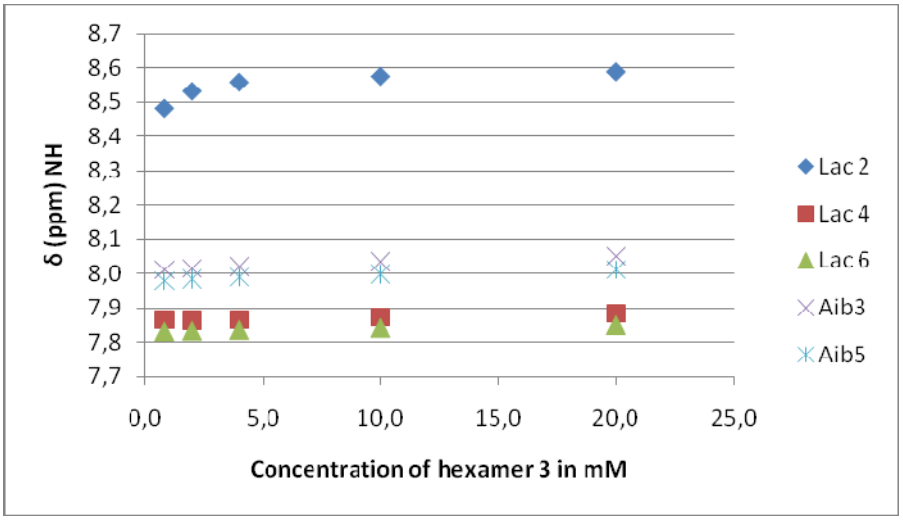
(**strong, medium, weak**)

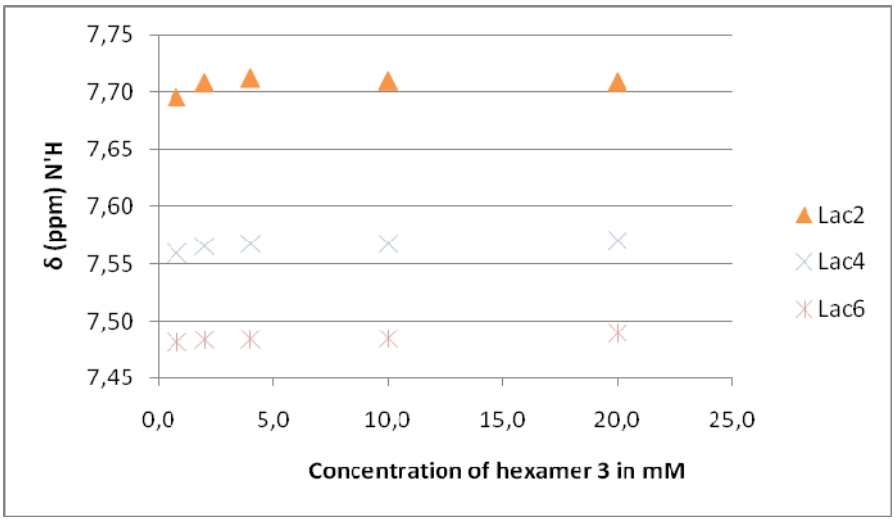
Table S 13: Inter-residue NOEs observed in the ROESY NMR spectrum of octamer 4 (DMSO-d_6, 500 MHz, 293K, τm = 300 ms)

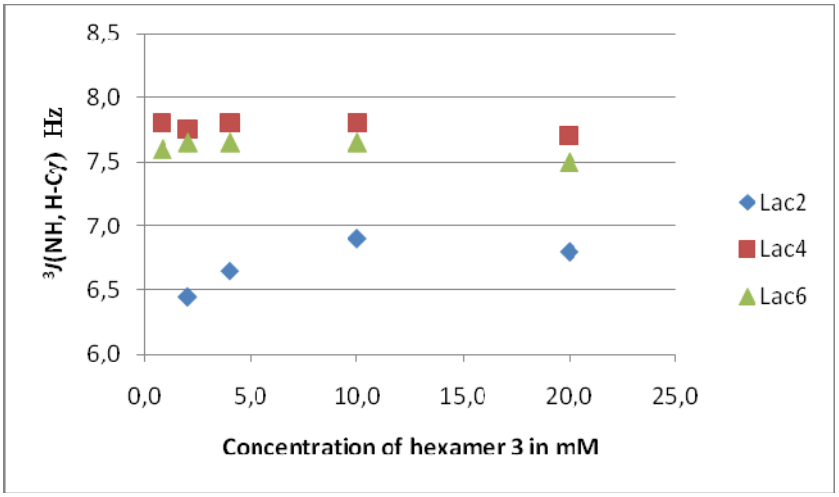
		Aib1	Lac2	Aib3	Lac4	Aib5	Lac6	Aib7	Lac8	Cap
i, i+1	H^N-H^N									
	$H^{N'}$-H^N									
	CH_3^{β}-$H^{\delta 2}$									
	CH_3^{β}-$H^{\alpha 2}$									
	CH_3^{β}-H^{β}									
	CH_3^{β} -H^{γ}									
	$H^{\alpha 1}$-H^N									
	$H^{\alpha 2}$-H^N									
	H^{β}-H^N									
	H^{γ}-H^N									
	CH_3^{β}-H^N									
i, i+2	$H^{N'}$-H^N									

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

Figure S3: Concentration studies of hexamer 3 in DMSO-d_6 (concentration range: 0.8 mM to 20 mM)







VII- Structure calculations of tetramer 2, hexamer 3 and octamer 4.

Simulated annealing (SA) calculations were carried out with the program DYNAMO[7] 2.1 and consisted of three stages. The first stage comprised an initialization period of 1000 steps (3 fs long) of molecular dynamics at 4000K and very tight temperature control. In a second stage, the coordinates were allowed to cook at 4000K with loose temperature control for 4000 steps. In the final stage, the structure was annealed by slowly reducing the temperature from 4000 K to 0 K over the space of 20000 molecular dynamic steps (3 fs long). In the first two stages, force constants were set as follows: 1000 kcal.mol^{-1}.Å^{-2}, 250 kcal.mol^{-1}.rad^{-2}, 50 kcal.mol^{-1}.rad^{-2}, 2 kcal.mol^{-1}.Å^{-2} for bonds, angles, impropers and NOE

[7] F. Delaglio Dynamo NMR Molecular Structure Engine, version 2.1. http://spin.niddk.nih.gov/NMRPipe/dynamo/

constraints, respectively. No Van der Waals interactions were operative. During the final stage, bonds force constant was maintained at 1000 kcal.mol^{-1}.Å^{-2}, both angles and impropers to 500 kcal.mol^{-1}.rad^{-2}, NOE term was increased exponentially from 2 to 30 kcal.mol^{-1}.Å^{-2}. The Van der Waals interactions and *J*-coupling restraints were slowly introduced during cooling to reach the final values of 4 kcal.mol^{-1}.Å^{-2} and 1 kcal.mol^{-1}.rad^{-2}, respectively.

NMR constraints consisted of 12, 18 and 24 ^{1}H-^{1}H vicinal *J*-coupling constants (Tables S8-S10) as well as 47, 70 and 84 NOE for tetramer **2**, hexamer **3** and octamer **4**, respectively (Tables S14-S16). Additionally, 14 and 19 heteronuclear ^{1}H-^{13}C ^{3}*J*-couplings have been used for the structure calculations of hexamer 3 and octamer 4, respectively (Tables S8-S10). ^{1}H-^{1}H *J*-coupling values have been measured from 1D and/or 2D ROESY spectra. ^{1}H-^{13}C *J*-coupling values have been extracted from 2D phase-sensitive HMBC spectra.[8] Karplus parameters have been set to the following values: A=8.77, B=-1.18, C=1.62 for $^{3}J_{H\delta H\gamma}$ and $^{3}J_{H\alpha H\beta}$; A=6.51, B=-1.76, C=1.60 for $^{3}J_{H_N,H\beta}$ and $^{3}J_{H_NH\gamma}$; A=5.70, B=-2.70, C=0.10 for $^{3}J_{H_NC\beta}$, $^{3}J_{H_NC\delta}$, $^{3}J_{H_N,C\gamma}$ and $^{3}J_{H_N,C\alpha}$; and A=4.70, B=-1.50, C=0.10 for $^{3}J_{H_NC'}$.[9] The volumes of the ROESY cross peaks were converted into upper distance bounds of *ca* 2.8, 3.8 or 5.0 Å. For each oligomer 200 structures have been calculated starting from an extended fold. Typical final energies (kcal.mol-1) of tetramer **2** were 23,3 ± 0.5 ; 1.4 ± 0.1; 1.0 ± 0.1 ; 11.5 ± 0.2 ; 7.0 ± 0.3 and 4.7 ± 0.2 for *J*-coupling, bond, impropers, angle, NOE and Van der Waals force constants, respectively. Typical final energies (kcal.mol-1) of hexamer **3** were 47,4 ± 0.6 ; 2.6 ± 0.1; 0.8 ± 0.1 ; 17.0 ± 1.0 ; 14.4 ± 1.1 and 8.7 ± 0.3 for *J*-coupling, bond, impropers, angle, NOE and Van der Waals force constants, respectively. Typical final energies (kcal.mol-1) of octamer **4** were 63,8 ± 3.4 ; 3.7 ± 0.2; 1.0 ± 0.2 ; 23.8 ± 0.8 ; 17.2 ± 2.3 and 12.7 ± 0.4 for *J*-coupling, bond, impropers, angle, NOE and Van der Waals force constants, respectively.

[8] D.O. Cicero, G. Barbato, R. Bazzo, *J Magn Reson*, 2001, 209-213.
[9] (a) J.M. Schmidt *J Biomol NMR*. 2007, **37**: 287-301. (b) E. Hansen, *Prog. NMR Spect*, 1981, **14,** 175-296.