Supplementary Material
Stereoselective synthesis and structure determination of a bicyclo[3.3.2]decapeptide

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This paper is dedicated to Prof. Pierre Vogel, a master of bicyclic molecules, on the occasion of his 70th Birthday

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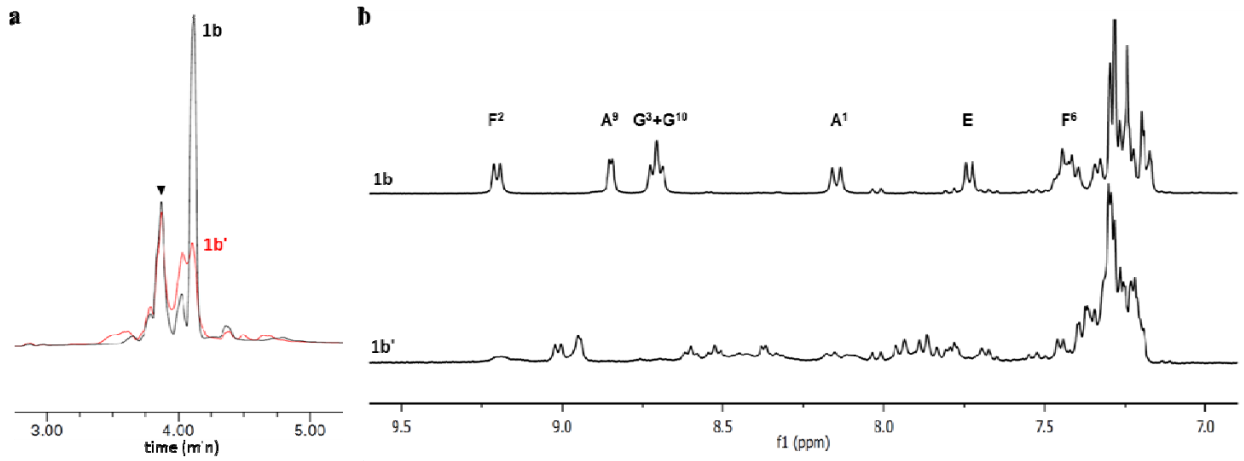
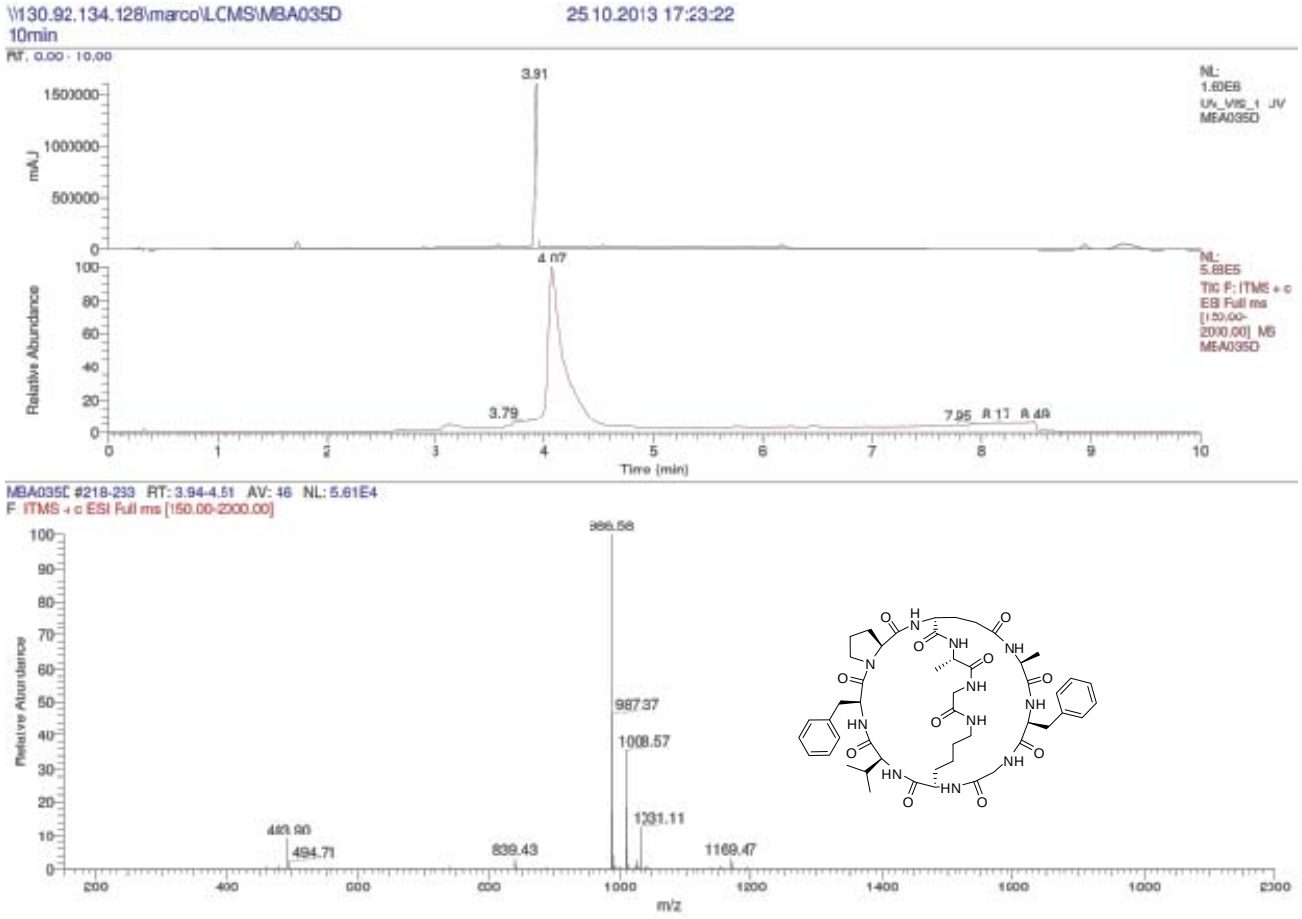
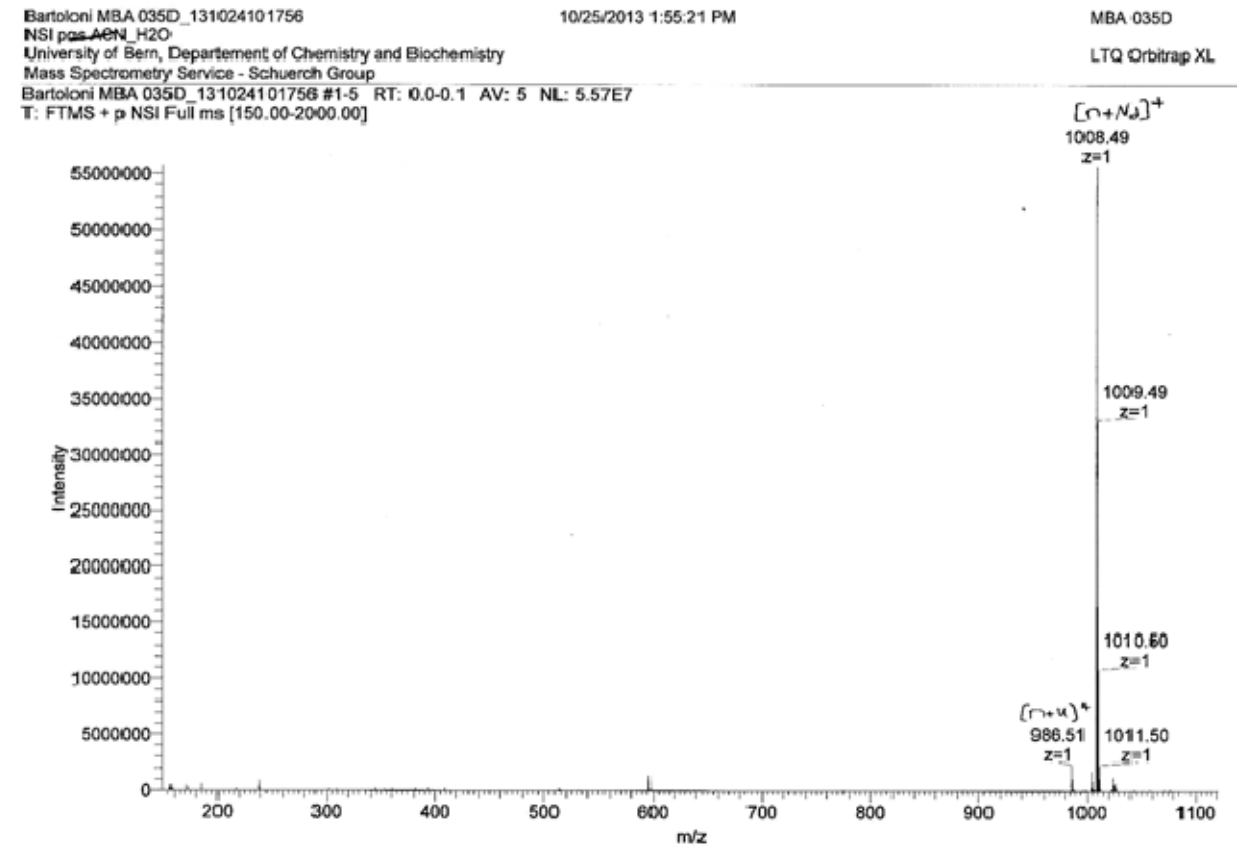


Figure S1. Comparison between **1b** and **1b'**. (a) Superimposition of RP-HPLC chromatogram of the second cyclization reactions, 2 h after start. The peak marked by a triangle corresponds to the phosphinoxide byproduct of PyBOP. (b) Amide proton regions of ^{1}H-NMR spectra of **1b** and **1b'** (CD_3OD). **1b** displays a single set of amide protons, assigned according to labels (missing amide protons are concealed by the signals of the aromatic side chains, between 7.0 and 7.5 ppm, as revealed by COSY spectra), whereas **1b'** exhibits a complex spectrum, probably derived from a conformational mixture.





NMR (experimental details) – NMR data were acquired in DMSO-d_6 at 298 K using a Bruker AvanceII 400 MHz NMR spectrometer. 1D ^{1}H-NMR data were acquired with 64 transients into 32K data points over a ppm width of 12 ppm. A relaxation delay of 6 s was applied between transients. 2D ^{1}H-TOCSY NMR data were acquired over a frequency width of 12 ppm in both F_2 and F_1 into 2K complex data points in F_2 using 256 t_1 increments. A relaxation delay of 2 s between transients was used for all experiments. ^{1}H-TOCSY data were recorded using 32 transients. The 2D TOCSY NMR data were acquired with a spin-lock time of 70 ms. Data were processed using standard apodizing functions prior to Fourier transformation.
2D ^{1}H-^{13}C HSQC NMR data were acquired, with ^{13}C decoupling during the acquisition period, over an F2 frequency width of 12 ppm into 2K complex data points. 32 transients were accumulated for each of 128 *t*1 increments over an F1 frequency width of 180 ppm centered at 90 ppm. Phase-sensitive data were acquired in a sensitivity-improved manner using an echo-antiecho acquisition mode.

^{1}H-NMR characterization of 1b (DMSO-d_6)

residue	*proton*	*δ (ppm)*	*J (Hz)*
Ala1	NH	8.03	^{3}J(NH-αCH) = 8.17
	αCH	4.43	^{3}J(βCH-αCH) = 7.16
	βCH_3	1.04	
Phe2	αNH	8.92	^{3}J(NH-αCH) = 5.96
	αCH	4.07	^{3}J(β"CH-αCH) = 9.38
	β'CH	3.15	^{2}J(β"CH-β'CH) = 14.10
	β"CH	2.87	
	2,6H	6.98	
	3,5H	7.12	
	4H	7.10	
Gly3	NH	8.60	
	α'CH	3.50	
	α"CH	3.79	
^{D}Lys4	αNH	7.17	
	αCH	4.09	
	βCH_2	1.48	
	γCH_2	1.12	
	δ'CH	1.90	
	δ"CH	1.13	
	ε'CH	3.16	
	ε"CH	2.81	
	εNH	7.17	
Val5	αNH	7.05	^{3}J(γ'CH-βCH) = 6.80
	αCH	3.49	^{3}J(γ"CH-βCH) = 7.07
	βCH	1.89	
	$\gamma' CH_3$	0.87	
	$\gamma'' CH_3$	0.58	
Phe6	αNH	7.23	^{3}J(NH-αCH) = 9.40
	αCH	4.90	^{3}J(β'CH-αCH) = 5.81
	β'CH	2.94	^{3}J(β"CH-αCH) = 8.69
	β"CH	2.62	^{2}J(β'CH-β"CH) = 14.10
	2,6H	6.98	
	3,5H	7.12	
	4H	7.10	
Pro7	αCH	4.14	
	β'CH	2.03	
	β"CH	1.63	
	γ'CH	1.84	
	γ"CH	1.77	
	$\delta' CH_2$	3.65	
	$\delta'' CH_2$	3.22	
Glu8	NH	7.62	^{3}J(NH-αCH) = 6.26
	αCH	4.41	
	β'CH	2.43	
	β"CH	1.67	
	γ'CH	2.17	
	γ"CH	1.88	
Ala9	NH	8.62	^{3}J(NH-αCH) = 2.33
	αCH	3.97	^{3}J(βCH-αCH) = 7.02
	βCH_3	1.18	
Gly10	NH	8.60	
	α'CH	3.50	
	α"CH	3.79	

Table S1. Backbone and side-chain torsion angles of **1b** (degrees). Residues marked with an asterisk belong to protomer 2.

	φ	ψ	ω	χ^1	χ^2	χ^3	χ^4	χ^5
Ala1	–137.680	151.906	–178.925					
Phe2	54.754	41.230	177.412	–73.879	–3.209 177.135			
Gly3	74.234	0.905	–173.982					
^{D}Lys4	129.027	–3.758	178.928 178.624[a]	70.440	–156.291	–169.981	–175.802	120.957[b]
Val5	–54.018	–43.314	176.462	–64.786 171.637				
Phe6	–110.888	113.610	177.658	–53.842	–63.971 115.734			
Pro7	–54.582	142.281	–178.011	–12.439	12.212	6.679	–1.825	8.772
Glu8	–169.161	160.898	–170.123	60.269	–170.314	–79.722 (O) 95.062 (N)		
Ala9	–58.078	140.164	171.154					
Gly10	83.183	5.088	178.675					
Ala1*	–158.358	162.982	174.373					
Phe2*	62.285	53.289	165.219	–58.872	–53.387 125.177			
Gly3*	62.981	30.024	175.758					
^{D}Lys4*	81.243	2.576	179.556 174.247[a]	68.465	–171.354	–176.800	178.987	141.519[b]
Val5*	–68.092	–31.277	179.650	–69.773 168.060				
Phe6*	–100.506	123.590	168.668	–78.257	–166.875 11.874			
Pro7*	–68.395	138.776	178.615	29.836	–36.902	29.055	–10.565	–11.916
Glu8*	–171.305	144.972	–168.510	56.979	–174.915	–67.717 (O) 114.943 (N)		
Ala9*	–54.500	133.288	166.307					
Gly10*	95.968	–5.592	175.215					

[a] $C^{\varepsilon}(^{D}Lys4)$–$N^{\varepsilon}(^{D}Lys4)$–C'(Gly10)–$C^{\alpha}$(Gly10)
[b] $C^{\delta}(^{D}Lys4)$–$C^{\varepsilon}(^{D}Lys4)$–$N^{\varepsilon}(^{D}Lys4)$–C'(Gly10)

Table S2. Intramolecular hydrogen bonds for **1b**. Residues marked with an asterisk belong to protomer 2.

donor	acceptor	distance (Å)	angle N···O=C (°)
Ala1 N	Phe6 O	2.92	157.727
^{D}Lys4 N	Ala1 O	3.03	123.505
Phe6 N	Ala1 O	3.23	139.421
^{D}Lys4 N^{ε}	Glu8 O	3.19	137.340
Val5 N	Phe2 O	3.44	104.163
Ala1*N	Phe6* O	3.00	139.175
^{D}Lys4* N	Ala1* O	3.27	114.338
Phe6* N	Ala1* O	3.02	147.075
^{D}Lys4* N^{ε}	Glu8* O	3.21	138.455
Val5* N	Phe2* O	3.12	112.703