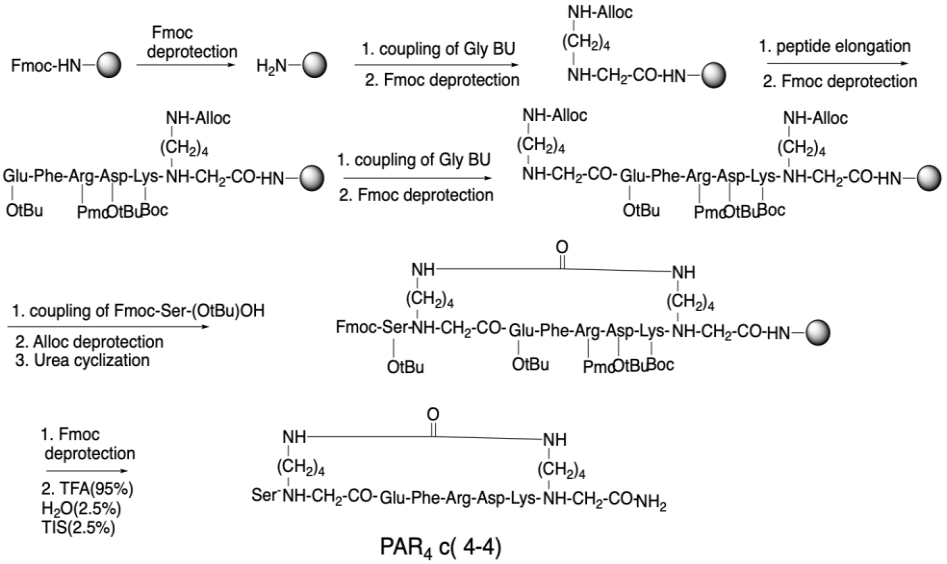
Peptide Synthesis:



The backbone cyclic P*c*(4-4) peptide was synthesized by Fmoc SPPS as shown in the scheme above. The two other peptides PAR_4 c(2-2) and PAR_4 c(6-6) composing altogether the mini-library were prepared in a similar scheme. All reactions that were performed on solid support utilized Fmoc chemistry for the Nα protection. Reaction mixtures were shaken using Bigger Bill orbital shaker. Pre-activation tubes were stirred over a vortex. Excluding the cleavage procedure, all other reactions on the solid support were performed under basic conditions of pH 8-9. The process of the reactions was monitored by HPLC/MS following "small cleavage" procedure. The synthesis via solid support was performed in a vessel equipped with a sintered glass bottom. Fmoc Rink Amide methylbenzhydrylamine (Fmoc Rink Amide-MBHA) resin (loading capacity 0.66 mmol/g resin) was the solid support for this synthesis. The equivalents of all reagents used in SPPS were calculated with respect to the resin loading capacity and weight. The volume of the solvents in all reactions was fixed to 30 mL to maintain constant concentration of reagents. After cleavage from resin the crude final peptides were lyophilized, dissolved in TDW/ACN 1:1 mixture, and analyzed by HPLC/MS.

The coupling protocol*:* A solution of Fmoc-N^{α}-AA-OH (3 equiv.) and HOAt (3 equiv.) in NMP was prepared and cooled down to 0°C. HATU (3 equiv.) was then added for pre-activation of the amino acid prior to reaction with the peptidyl-resin, and the solution was shaken at 0°C for 3 minutes. The pre-activated solution was added to the

peptidyl-resin and the mixture was shaken for 60 minutes. The procedure was repeated twice. The resin beads were washed with 30 mL NMP (4 × 2 min) and DCM (2 × 2 min).

Fmoc removal: For the removal of Fmoc protecting group, a solution of 20% piperidine in NMP was added to the peptidyl-resin. The reaction was performed in a vessel shaken at room temperature for 30 minutes. The reaction was repeated once using fresh solution of 20% piperidine in NMP. At the end of the second cycle, the peptidyl-resin beads were washed with 30 mL of NMP (4 x 2min), and DCM (2 x 2min).

Alloc removal: For the removal of Alloc protecting group the peptidyl-resin was added to a saturated argon solution composed of acetic acid (5%), N-methyl morpholin (2.5%), and DCM (92.5%) and the mixture was shaken for 5 minutes, after which tetrakis (triphenylphosphine) palladium(0) Pd(PPh3)4 (0.1 equiv.) was added. The reaction mixture was shaken vigorously in dark and under argon for three hours, after which the peptidyl-resin beads were washed with 30 mL solution of 0.5% v/v DIPEA in DMF (5 X 2 min), 0.5% sodium diethyldithiocarbamate trihydrate salt in DMF (5 X 2 min), and DCM (5 X 2 min).

Urea Cyclization: After the removal of the Alloc groups from the peptidyl-resin, the on-resin urea cyclization was carried out as follows: the peptidyl-resin was washed with NMP (5 X 2 min) and DCM (3 X 2min), followed by adding a solution of BTC (0.33 equiv.). After 2 hours DIPEA (10 equiv.) in DCM was added to the peptidyl-resin. The mixture was shaken for 5 hours, after which the resin beads were washed with 30 mL of DCM (4 x 2min), and DMF (2 x 2min).

Cleavage protocol: In this method, a simultaneous removal of the synthesized peptides from the solid support, together with the acid labile protecting groups on their side chains was performed by the following procedure: After washing the resin with DMF (2 x 2min), DCM (4 x 2min), iPA (4 x 2min), and diethyl ether (4X2min), The resin was dried in vacuum at RT. A solution of 30 ml pre-cooled solution (at 0^{o}C) composed of TFA (95%), TDW (2.5%), and TIS (2.5%) was added to a dried and desiccated 2.1 g peptide-resin beads. The reaction mixture was kept standing at 0^{o}C for 30 minutes after which it was shaken for 150 minutes at room temperature. The TFA solution containing the cleaved peptide was then separated from the resin beads *via* filtration and the TFA was partially evaporated by a stream of nitrogen. Cold di t-butyl ether was added to the remaining volume of TFA, and the mixture was centrifuged to separate scavengers and

other hydrophobic impurities from the precipitated peptide. Diethyl ether was then removed from the precipitate by decanting. The cycle of precipitation, centrifugation, and decanting was repeated three times. The precipitate was dissolved in 10 mL ACN/TDW (1:1) (relative to 2.1g peptide-resin beads) and the solution was lyophilized overnight prior to purification *via* preparative HPLC. The lyophilized crude product was obtained as fluffy white solid.

Preparative high performance liquid chromatography (HPLC): The crude peptides were dissolved in TDW/ACN 1:1 mixture, filtered through a 0.45 μm PTFE filters and injected in 5-10 mL volumes to a reversed phase preparative HPLC column of Vydac (C18, 22 × 250 mm, 10 μm). The analysis utilized a Merck-Hitachi L-6200A pump and L-7400 variable wavelength detector recording at 220 nm at room temperature. The gradient of the mobile phase consisted of A: TDW (0.1% v/v TFA) and B: ACN (0.085% v/v TFA). First, the column was equilibrated for 5 minutes at 95% A, then linear gradient was applied from 5 to 40 minutes to reach 95% B. The mobile phase remained for 5 minutes at 95% B for column equilibration. The gradient was returned back to the starting conditions (95% A, 5% B) within 5 minutes, and kept at this point for additional 5 minutes for column equilibration. The flow rate of the mobile phase was 9 mL/min. The collected fractions were analyzed by MS, lyophilized, and injected to an analytical HPLC column to determine the degree of purity.

Analytical high performance liquid chromatography (HPLC): All samples were dissolved in TDW/ACN 1:1 mixture, filtered through a 0.45 μm PTFE filters and injected to a reversed phase analytical HPLC column of Vydac (C18, 4.6 × 250 mm, 10 μm). The analysis utilized a Merck-Hitachi L-7100 pump and L-7400 variable wavelength detector recording at 220 nm at room temperature. The gradient of the mobile phase consisted of A: TDW (0.1% v/v TFA) and B: ACN (0.085% v/v TFA). First, the column was equilibrated for 5 minutes at 95% A, then linear gradient was applied from 5 to 20 minutes to reach 95% B. The mobile phase remained for 5 minutes at 95% B for column equilibration. The gradient was returned back to the starting conditions (95% A, 5% B) within 5 minutes, and kept at this point for additional 5 minutes for column equilibration. The flow rate of the mobile phase was 1 mL/min. The collected fractions were further analyzed by MS (Fig S7).

Mass spectrometry (MS): Mass spectra were acquired on a LCQ Fleet Ion Trap mass spectrometer (Thermo Scientific) utilizing electrospray ionization. For high resolution mass spectrometry (HRMS) analyses, the spectra were recorded on an Agilent 6550 iFunnel Q-TOF LC/MS system.