Supporting Information
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Supporting Information for:

A Cyclooligomerisation Approach to Backbone Modified Cyclic Peptides Bearing Guanidinium Arms

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**General Procedures:** All reactions were performed under an atmosphere of dry nitrogen, unless otherwise specified. Most reagents were commercially available reagent grade chemicals and were used without further purification. Dimethylformamide was dried over 4 Å molecular sieves prior to use. Dichloromethane was dried over CaH₂ and distilled prior to use. Melting points were determined using a Gallenkamp melting point apparatus and are reported in degrees Celsius (uncorrected). ¹H Nuclear magnetic resonance spectra were recorded at a frequency of 300 MHz or at a frequency of 400 MHz and are recorded as parts per million (ppm) downfield shift with deuterochloroform (δ_H 7.26), deuteromethanol (δ_H 3.34) or d₆-DMSO (δ_H 3.50), as internal references, unless otherwise stated. ¹³C Nuclear magnetic resonance spectra were recorded at a frequency of 75.47 MHz or at a frequency of 100.62 MHz and are reported as parts per million (ppm) downfield shift with deuterochloroform (δ_C 77.0) deuteromethanol (δ_C 49.0) or d₆-DMSO (δ_C 39.5) as an internal reference, unless otherwise stated. Optical rotations were measured on a dual wavelength polarimeter in a 2.5 cm cell using the indicated spectroscopic grade solvents. Analytical reverse phase high performance liquid chromatography (RP-HPLC) was performed using a Sunfire™ C₁₈ column (5 µm, 2.1 x 150 mm ID). Flow rate was maintained at 0.2 mL/min over a linear gradient from 0 % to 100 % solvent B (solvent A: 100:0.01 v/v Milli-Q water/TFA, solvent B: 100:0.01 v/v acetonitrile/TFA) over 30 min and eluent monitored from 210 to 320 nm. Preparative RP-HPLC was performed using a Sunfire™ PrepC₁₈ OBD™ column (5 µm, 19 x 150 mm ID). Flow rate was maintained at 7.0 mL/min over a linear gradient from 0 % to 100 % solvent B (solvent A: 100:0.01 v/v Milli-Q water/TFA, solvent B: 100:0.01 v/v acetonitrile/TFA) over 45 min and eluent monitored at wavelengths 214 and 280 nm. N,N’-di-Boc-N’-triflyl-guanidine,¹ Boc-Dab(Z)-OH²,³ and Boc-Dpr(Z)-OH²,³ were prepared according to literature procedures.
Z-Arg(Boc)-Thr-OBn (5)

Threonine benzyl ester.HCl (0.37 g, 1.2 mmol) was dissolved in N,N-dimethylformamide (5 mL) and diisopropylethylamine (19.3 mL, 177 mmol). This solution was added to a solution of Z-Arg(Boc)-OH (0.66 g, 1.3 mmol), HBTU (0.53 g, 1.4 mmol) and HOBt.H2O (0.21 g, 1.4 mmol) in N,N-dimethylformamide (5 mL) and the resulting solution stirred for 16 h at ambient temperature. Aq. 10% citric acid (50 mL) was then added and the mixture was extracted with ethyl acetate (2 x 50 mL). The combined organic fractions were then washed with 0.5 M HCl (50 mL), saturated aqueous NaHCO3 solution (50 mL), H2O (50 mL) and brine (50 mL) then dried (MgSO4). The solvent was removed under reduced pressure and the resulting crude product was purified by flash chromatography (4:1→1:1 hexane/EtOAc) to give 5 (0.73 g, 58%) as a colourless foam; [α]25D +9 (c = 0.7, CH2Cl2); δH (400 MHz; CDCl3) 8.36 (1H, br s), 7.36 – 7.28 (10H, m), 7.16 (1H, d, J 8.8 Hz), 5.99 (1H, d, J 8.1 Hz), 5.83 (1H, d, J 7.8 Hz), 5.21 – 5.06 (4H, m), 4.62 - 4.60 (1H, m), 4.38 – 4.31 (2H, m), 3.37 – 3.33 (2H, m), 1.87 – 1.81 (1H, m), 1.76 – 1.60 (4H, m), 1.48 – 1.45 (18 H, m), 1.15 (6H, d, J 6.3 Hz). δc (100 MHz; CDCl3) 172.3, 170.4, 163.1, 156.3, 156.2, 153.1, 136.1, 135.2, 128.6, 128.4, 128.2, 128.1, 128.0, 83.2, 79.5, 68.0, 67.3, 67.0, 57.6, 54.6, 40.3, 40.1, 29.2, 28.2, 28.0, 25.3, 20.0.

Z-Arg(Boc)-Thr(Oxz)-OBn (6)

Diethylaminosulfur trifluoride (0.17 mL, 1.3 mmol) was added dropwise to a cold solution (-78 °C) of 5 (0.20 g, 0.43 mmol) in CH2Cl2 (6.4 mL). After stirring for 3 h at -78 °C, the reaction mixture was then quenched with anhydrous K2CO3 (0.27 g, 1.9 mmol), and was allowed to warm to room temperature. The mixture was poured into sat. aq. NaHCO3 (10 mL) and the product was extracted with CH2Cl2 (3 x 10 mL). The combined organic layers were dried (MgSO4) and concentrated in vacuo leaving a yellow oil. This was immediately dissolved in anhydrous CH2Cl2 (6.4 mL) to give a pale brown solution which was cooled to 0 °C. Bromotrichloromethane (0.13 mL, 1.3 mmol) was added to the solution, followed by DBU (0.19 mL, 1.3 mmol). The solution turned a dark brown colour, the ice bath was removed and the reaction mixture was stirred at room temperature for 16h, then quenched with saturated aqueous NH4Cl (20 mL). The mixture was extracted with EtOAc (3 x 10 mL) then the combined organic layers were concentrated under reduced pressure to give a brown oil which was purified by flash chromatography (EtOAc/hexane, 2:5) to give the oxazole 6 as a yellow oil (0.17 g, 60%); [α]25D +63 (c = 0.2, CH2Cl2); δH (400 MHz; CDCl3) 11.46 (1H, br s), 8.31 (1H, m), 7.43 – 7.32 (10H, m), 5.83 (1H, d, J 8.5 Hz), 5.35 (2H, s), 5.11 (2H, s), 4.98
– 4.93 (1H, m), 3.49 – 3.33 (2H, m), 2.57 (3H, s), 2.02 – 1.83 (2H, m), 1.66 – 1.60 (2H, m), 1.48 (9H, s), 1.46 (9H, s). δ\textsubscript{C} (100 MHz; CDCl\textsubscript{3}) 163.4, 161.9, 161.7, 156.6, 156.2, 155.8, 153.2, 136.1, 128.5, 128.4, 129.3, 128.0, 127.4, 83.2, 79.3, 67.0, 66.6, 49.3, 40.1, 30.9, 28.2, 28.0, 25.4, 12.2. MS (ESI) m/z 702 (M+Na)^+ 100%; HRMS: (M+Na)^+ found 702.3112, C\textsubscript{35}H\textsubscript{45}N\textsubscript{5}O\textsubscript{9}Na requires (M+Na)^+ 702.3110.

**H\textsubscript{2}N-Arg(Boc)\textsubscript{2}-Thr(Oxz)-OH (7)**

Pd/C (10 mol%, 16 mg) was added to a solution of 6 (0.11 g, 0.16 mmol) in MeOH (6.5 mL) in a single-necked, round bottom flask fitted with a 3-way tap attached to a balloon of H\textsubscript{2}(g). The flask was evacuated (water aspirator) and then filled with H\textsubscript{2}(g), and the process repeated five times. The reaction mixture was then stirred under a H\textsubscript{2}(g) atmosphere for 5h, after which the contents of the flask were filtered through a pad of Celite, the Celite washed several times (CH\textsubscript{3}Cl/MeOH/NH\textsubscript{3}(aq) 90:9:1), the organic fractions combined, and the solvent removed under reduced pressure to give 7 as a colourless solid (0.044 g, 60%) which was used without further purification. MS (ESI) m/z = 456 [M+H]^+ (100), 478 [M+Na]^+ (42).

**Boc-Orn(Z)-Thr-OMe (10)**

Threonine methyl ester.HCl (7.47 g, 44.3 mmol) was dissolved in dry CH\textsubscript{2}Cl\textsubscript{2} (65 mL), N,N-dimethylformamide (36 mL) and N-methylmorpholine (19.3 mL, 177 mmol). To this solution Boc-Orn(Z)-OH (16.2 g, 44.3 mmol), EDC.HCl (9.35 g, 48.8 mmol) and HOBT.H\textsubscript{2}O (7.47 g, 48.8 mmol) were added and the resulting solution stirred for 22 h at ambient temperature. The solvent was subsequently removed under reduced pressure to give a yellow-orange residue which was partitioned between 0.5 M HCl (60 mL) and EtOAc (60 mL). The aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic fractions were then washed with 0.5 M HCl (50 mL), saturated aqueous NaHCO\textsubscript{3} solution (50 mL), H\textsubscript{2}O (50 mL) and brine (50 mL) then dried (MgSO\textsubscript{4}). The solvent was removed under reduced pressure and the resulting crude product was purified by flash chromatography (silica gel; CHCl\textsubscript{3}/MeOH/NH\textsubscript{3} [90:9:1]) to give 10 (18.1 g, 85 %) as a pale yellow oil; [α]\textsubscript{D}\textsuperscript{20} = -11.0; δ\textsubscript{H} (400 MHz; CDCl\textsubscript{3}) 7.33-7.32 (5H, m), 5.43 (1H, br s), 5.29 (1H, br s), 5.07 (2H, s), 4.57 (1H, d, J 9.0 Hz), 4.33-4.30 (2H, m), 3.70 (3H, s), 3.31 (2H, br s), 3.16 (1H, m), 1.85 (1H, m), 1.63 (1H, m), 1.60-1.57 (2H, m), 1.41 (9H, s), 1.19 (3H, d, J 6.0 Hz). δ\textsubscript{C} (100 MHz; CDCl\textsubscript{3}) 172.9, 171.4, 157.0, 155.9, 136.5, 128.56, 128.53, 128.1, 80.1, 68.0, 66.8, 57.6, 53.6, 52.5, 40.5, 29.9, 28.3, 25.9,
19.9. MS (ESI) m/z 504 [(M+Na)^+], 100; 985 [(2M+Na)^+, 77]; HRMS: found [M+Na]^+ 504.2315, C_{23}H_{25}N_{3}NaO_{8} requires [M+Na]^+ 504.2316.

**Boc-Dab(Z)-Ser-OMe (11)**

DMF (24 mL) was added to a solution of Boc-Dab(Z)-OH (3.0 g, 8.6 mmol), HCl.H-Ser-OMe (1.5 g, 9.4 mmol), EDC-HCl (2.5 g, 12.9 mmol), and HOBT (1.7 g, 12.9 mmol) in CH_2Cl_2 (30 mL) followed by NMM (3.0 mL, 25.8 mmol), and the mixture was stirred at 0 °C for 10 min and then allowed to warm to room temperature. After stirring for 16 h, the reaction mixture was poured into a 10 % aqueous solution of citric acid and extracted with EtOAc (3 x 70 mL). The combined organic layers were washed with 10 % aq. citric acid (50 mL), sat. aq. NaHCO_3 (50 mL), water (50 mL), brine (50 mL), and dried (MgSO_4). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (EtOAc/hexane, 3:2) to give dipeptide 11 as a colourless solid (2.7 g, 70 %); mp 95-97 °C (lit. 89-93 °C, [α]_20^D -4.3 (c 1.1, CHCl_3) [lit. [α]_20^D -30.4 (c 1.0, DMF)].

**Boc-Dpr(Z)-Ser-OMe (12)**

DMF (24 mL) was added to a solution of Boc-Dpr(Z)-OH (2.9 g, 8.7 mmol), HCl.H-Ser-OMe (1.5 g, 09.6 mmol), EDC (2.5 g, 13.1 mmol), and HOBT (1.8 g, 13.1 mmol) in CH_2Cl_2 (30 mL) followed by NMM (2.9 mL, 26.1 mmol), and the mixture was stirred at 0 °C for 10 min and then allowed to warm to room temperature. After stirring for 16 h, the reaction mixture was poured into a 10 % aqueous solution of citric acid and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with 10 % aq. citric acid (50 mL), sat. aq. NaHCO_3 (50 mL), water (50 mL), brine (50 mL), and dried (MgSO_4). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (EtOAc/hexane, 2:1) to give dipeptide 12 as a colourless solid (3.3 g, 87 %); mp 90-91 °C; [α]_20^D -5.7 (c 1.0, CHCl_3); ^1H NMR (CDCl_3, 200 MHz): δ 7.58 (m, 1H), 7.26-7.31 (m, 5H), 5.83-5.90 (m, 2H), 5.07 (s, 2H), 4.59-4.63 (m, 1H), 4.34 (m, 1H), 3.91 (s, 2H), 3.72 (s, 3H), 3.54 (m, 2H), 1.41 (s, 9H), OH not observed; ^13C NMR (CDCl_3, 75 MHz): δ 171.1, 170.8, 157.5, 156.2, 136.4, 128.6, 128.2, 128.1, 80.7, 67.2, 62.5, 55.1, 52.8, 43.1, 28.4, one signal obscured or overlapping; MS (ESI) m/z = 439 [M+Na]^+.

**Boc-Orn(Z)-Thr(Oxz)-OMe (13)**

Dipeptide 10 (17.5 g, 36.3 mmol) was dissolved in CH_2Cl_2 (520 ml) at room temperature and cooled to -78 °C. Diethylaminosulfur trifluoride (14.4 mL, 109 mmol) was added dropwise
over 5 min via syringe and the resulting mixture was stirred at -78 °C for 3.5h. The reaction was quenched with solid K$_2$CO$_3$ (22.6 g, 163 mmol) and allowed to return to room temperature before being transferred to a separating funnel and further diluted with CH$_2$Cl$_2$ (500 mL). The organics were washed with sat. aq. NaHCO$_3$ (2 x 500 ml) and brine (500 ml), dried (MgSO$_4$) and concentrated in vacuo leaving an orange oil. This was immediately dissolved in CH$_2$Cl$_2$ (520 ml) giving a pale orange solution which was cooled to 0 °C then DBU (16.3 ml, 109 mmol) followed by bromotrichloromethane (10.7 ml, 109 mmol) were each added dropwise over 5 min. The solution turned a dark brown colour, the ice bath was removed and the reaction mixture was stirred at room temperature for 16h. Evaporation of CH$_2$Cl$_2$ left a dark brown oil which was redissolved in EtOAc (700 ml) and the organics were washed with saturated aq. NH$_4$Cl solution (2 x 500 ml). The aqueous fractions were back extracted with EtOAc (2 x 300 ml) and the combined organics were washed with brine (600 ml), dried (MgSO$_4$) and concentrated in vacuo leaving a dark brown oil. This was purified by flash column chromatography (2:5 →1:1 EtOAc/hexane elution) giving 13 as a colourless foam (9.9 g, 59 %); [$\alpha$]$_{D}^{20}$ -20.7 (c = 1.5, CHCl$_3$); $\delta$$_H$ (400 MHz; CDCl$_3$) 7.33-7.32 (5H, m), 5.25 (1H, m), 5.06 (2H, m), 4.92 (1H, m), 4.86 (1H, m), 3.88 (3H, s), 3.20 (2H, m), 2.58 (3H, s), 1.92 (1H, m), 1.79 (1H, m), 1.61-1.52 (2H, m), 1.41 (9H, s). $\delta$$_C$ (100 MHz; CDCl$_3$) 162.6, 162.2, 156.6, 156.4, 155.2, 136.6, 128.5, 128.1, 128.0, 127.3, 80.2, 66.7, 52.1, 48.5, 40.5, 31.7, 28.3, 26.0, 12.1. MS (ESI) m/z 484 [(M+Na)$^+$, 100], 945 [(2M+Na)$^+$, 33]; HRMS: found [M+Na]$^+$ 484.2059, C$_{23}$H$_{31}$N$_3$NaO$_7$ requires [M+Na]$^+$ 484.2054.

**Boc-Dab(Z)-Ser(Oxz)-OMe (14)**

Diethylaminosulfur trifluoride (6.0 mL, 4.9 mmol) was added dropwise to a cold solution (-78 °C) of 11 (2.0 g, 4.5 mmol) in CH$_2$Cl$_2$ (65 mL). After stirring for 2 h at -78 °C, the reaction mixture was quenched with anhydrous K$_2$CO$_3$ (0.9 g, 6.7 mmol), and was allowed to warm to room temperature. The mixture was poured into sat. aq. NaHCO$_3$ (100 mL) and the product was extracted with CH$_2$Cl$_2$ (3 x 100 mL). The combined organic layers were dried (MgSO$_4$) and concentrated in vacuo leaving a brown oil. This was immediately dissolved in anhydrous CH$_2$Cl$_2$ (65 mL) to give a pale brown solution which was cooled to 0 °C. Bromotrichloromethane (1.3 mL, 13.4 mmol) was added to the solution, followed by DBU (2.0 mL, 3.4 mmol). The solution turned a dark brown colour, the ice bath was removed and the reaction mixture was stirred at room temperature for 16h, then quenched with saturated aqueous NaHCO$_3$ (200 mL). The mixture was extracted with EtOAc (3 x 100 mL) then the combined organic layers were dried (Na$_2$SO$_4$) then concentrated under reduced pressure to
give a brown oil which was purified by flash chromatography (EtOAc/hexane, 3:2) to give the oxazole 14 as a light brown oil (1.7 g, 90%); $[\alpha]^{20}_D$ -39.9 (c 1.1, CHCl$_3$); $^1$H NMR (CDCl$_3$, 200 MHz): $\delta$ 8.14 (s, 1H), 7.29 (m, 5H), 5.43 (m, 2H), 5.01-5.09 (m, 3H), 3.90 (s, 3H), 3.18-3.49 (m, 2H), 1.90-2.21 (m, 2H), 1.36 (s, 9H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 164.9, 161.5, 156.6, 155.7, 144.3, 136.6, 133.3, 128.6, 128.2, 80.7, 66.8, 52.4, 43.7, 37.2, 35.0, 28.4, one signal obscured or overlapping; MS (ESI) m/z 456 [M+Na]$^+$ HRMS (ESI) calcd. for C$_{21}$H$_{27}$N$_3$O$_7$Na [M+Na]$^+$ 456.1741, found 456.1741; Anal. Calc. C 58.2, H 6.3, N 9.7; found. C 58.3, H 6.3, N 9.65.

**Boc-Dpr(Z)-Ser(Oxz)-OMe (15)**

Diethylaminosulfur trifluoride (1.09 mL, 8.33 mmol) was added dropwise to a cold solution (-78 °C) of 12 (3.33 g, 7.57 mmol) in CH$_2$Cl$_2$ (108 mL). After stirring for 2 h at -78 °C, the reaction mixture was then quenched with anhydrous K$_2$CO$_3$ (1.57 g, 11.4 mmol), and was allowed to warm to room temperature. The mixture was poured into sat. aq. NaHCO$_3$ (50 mL) and the product was extracted with CH$_2$Cl$_2$ (3 x 40 mL). The combined organic layers were dried (MgSO$_4$) and concentrated in vacuo leaving a brown oil. This was immediately dissolved in anhydrous CH$_2$Cl$_2$ (108 mL) to give a pale brown solution which was cooled to 0 °C. Bromotrichloromethane (2.24 mL, 22.7 mmol) was added to the solution, followed by DBU (3.40 mL, 22.7 mmol). The solution turned a dark brown colour, the ice bath was removed and the reaction mixture was stirred at room temperature for 16h, then quenched with saturated aqueous NaHCO$_3$ (50 mL). The mixture was extracted with EtOAc (3 x 40 mL) then the combined organic layers were dried (Na$_2$SO$_4$) then concentrated under reduced pressure to give a brown oil which was purified by flash chromatography (EtOAc/hexane, 2:3) to give the oxazole 15 (2.23 g, 70 %) as a colourless oil. $[\alpha]^{20}_D$ -29.2 (c 1.2, CHCl$_3$), $^1$H NMR (CDCl$_3$, 200 MHz): $\delta$ 8.11 (s, 1H), 7.26 (m, 5H), 5.80-5.83 (m, 1H), 5.52 (br s, 1H), 5.00 (m, 3H), 3.83 (s, 3H), 3.65-3.67 (m, 2H), 1.36 (s, 9H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 163.2, 161.4, 156.8, 155.3, 144.5, 136.3, 133.2, 128.5, 128.1, 128.1, 80.4, 66.9, 52.2, 49.5, 43.6, 28.2; MS (ESI) m/z 442 [M+Na]$^+$ HRMS (ESI) calcd. for C$_{20}$H$_{27}$N$_3$O$_7$Na [M+Na]$^+$ 442.1585, found 442.1580; Anal. Calc. C 57.3, H 6.0, N 10.0; found. C 57.2, H 6.0, N 10.0.

**Boc-Orn(Z)-Thr(Oxz)-OH (13a)**

The ester 13 (3.76 g, 8.14 mmol) was dissolved in methanol (50 mL) and water (16 mL) and to this solution NaOH (0.98 g, 24.4 mmol) was added at room temperature. The resulting reaction mixture was stirred for 20 h after which time TLC showed complete conversion of
the starting material. The reaction mixture was subsequently acidified with 2 M HCl (15 mL) and extracted into EtOAc (3 × 50 mL) with the addition of brine (100 mL). The combined organic fractions were dried (Na₂SO₄) and then concentrated under reduced pressure to afford the desired carboxylic acid 13a (3.64 g, quant.) as a colourless solid. [α]D⁰ = -38.5 (c 1.0, CHCl₃). 

1H NMR (CDCl₃, 200 MHz): δ 7.35-7.20 (m, 5H), 5.96-5.76 (br m, 1H), 5.09 (s, 2H), 5.03-4.83 (br m, 2H), 3.23 (m, 2H), 2.61 (s, 3H), 1.98-1.44 (m, 4H), 1.41 (s, 9H), OH not observed.

13C NMR (CDCl₃, 75 MHz): δ 164.6, 163.5, 157.1, 156.6, 155.7, 136.6, 128.5, 128.0, 127.2, 79.9, 66.6, 48.5, 40.9, 40.4, 31.4, 28.3, 26.0, 11.9. MS (ESI) m/z = 470 [M+Na]⁺. HRMS (ESI) calcd. for C₂₂H₂₉N₃O₇Na [M+Na]⁺ 470.1898, found 470.1899.

**Boc-Dab(Z)-Ser(Oxz)-OH (14a)**

The ester 14 (1.5 g, 3.4 mmol) was dissolved in methanol (40 mL) and water (13 mL) and to this solution NaOH (0.4 g, 10.2 mmol) was added at room temperature. The reaction mixture was stirred for 20 h after which time TLC showed complete conversion of the starting material. A 10% aq. solution of citric acid (200 mL) was added then the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (Na₂SO₄) and the solvent was removed under reduced pressure to give 14a (1.1 g, 76%) as a pale yellow oil which was used without further purification in the next step. 1H NMR (CD₃OD, 300 MHz): δ 8.11 (s, 1H), 7.30 (m, 5H), 5.05-5.11 (m, 3H), 3.20 (m, 2H), 2.01-2.11 (m, 2H), 1.42 (s, 9H), 2 x NH and OH not observed; 13C NMR (CD₃OD, 75 MHz): δ 168.8, 165.6, 159.3, 158.1, 143.2, 140.2, 138.7, 129.8, 129.4, 129.3, 81.3, 67.9, 48.4, 38.7, 34.7, 29.1.

**Boc-Dpr(Z)-Ser(Oxz)-OH (15a)**

The ester 15 (2.24 g, 5.34 mmol) was dissolved in methanol (57 mL) and water (19 mL) then NaOH (0.64 g, 16 mmol) was added to the reaction mixture. The reaction mixture was stirred for 20 h after which time TLC showed complete conversion of the starting material. A 10% aq. solution of citric acid (50 mL) was added, and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (Na₂SO₄), and the solvent was removed under reduced pressure to give 15a (1.42 g, 66%) as a pale yellow oil which was used without further purification in the next step. 1H NMR (CD₃OD, 200 MHz): δ 7.98 (s, 1H), 7.32 (m, 5H), 5.05 (m, 3H), 3.31 (m, 2H), 1.29 (s, 9H), NH and OH not observed; MS (ESI) m/z 428 [M+Na]⁺.
CF₃COOH. H₂N-Orn(Z)-Thr(Oxz)-OH (16)

Trifluoroacetic acid (60 mL) was added to a solution of 13a (2.71 g, 6.07 mmol) in anhydrous dichloromethane (20 mL) under an atmosphere of nitrogen. The resulting reaction mixture was stirred for 4.5 h. Trifluoroacetic acid and dichloromethane were subsequently removed under reduced pressure followed by azeotropic removal of residual reagents with toluene to give 16 (2.80 g, quant.) as a brown foam. ¹H NMR (CD₃OD, 200 MHz): δ 7.42-7.18 (m, 5H), 5.07 (s, 2H), 4.59 (br m, 1H), 3.17 (m, 2H), 2.64 (s, 3H), 2.14-1.97 (br m, 2H), 1.62-1.50 (br m, 2H), NH and OH not observed. ¹³C NMR (CD₃OD, 75 MHz): δ 164.9, 162.9, 159.1, 159.0, 158.8, 158.6, 138.1, 129.4, 129.2, 128.9, 128.6, 67.3, 40.7, 30.0, 26.3, 24.1, 12.1. MS (ESI) m/z = 348 [M]+. HRMS (ESI) calcd. for C₁₇H₂₂N₃O₅ [M]+ 348.1554, found 348.1557.

CF₃COOH. H₂N-Dab(Z)-Ser(Oxz)-OH (17)

Trifluoroacetic acid (30 mL) was added to a solution of 14a (1.0 g, 2.4 mmol) in anhydrous dichloromethane (10 mL) under an atmosphere of nitrogen. The resulting reaction mixture was stirred for 4.5 h. Trifluoroacetic acid and dichloromethane were subsequently removed under reduced pressure followed by azeotropic removal of residual reagents with toluene to give 17 (1.0 g, quant.) as a brown foam which was used immediately in the next reaction.

CF₃COOH. H₂N-Dpr(Z)-Ser(Oxz)-OH (18)

Trifluoroacetic acid (30 mL) was added to a solution of 15a (1.3 g, 3.2 mmol) in anhydrous dichloromethane (10 mL) under an atmosphere of nitrogen. The resulting reaction mixture was stirred for 4.5 h. Trifluoroacetic acid and dichloromethane were subsequently removed under reduced pressure followed by azeotropic removal of residual reagents with toluene to give the desired TFA salt 18 (1.3 g, quant.) as a brown foam which was used immediately in the next reaction.

Boc-Orn(Z)-Thr(Oxz)-OPfp (25)

Pyridine (0.14 mL, 1.73 mmol) and pentafluorophenyl 2,2,2-trifluoroacetate (0.44 mL, 1.89 mmol) were added to a solution of 13a (0.70 g, 1.58 mmol) in CH₂Cl₂ (3 mL) and DMF (2 mL). The reaction mixture was stirred at room temperature under nitrogen for 21 h. The solvent was removed in vacuo then the residue was re-dissolved in EtOAc (50 mL) and washed with 0.1 M HCl (3 x 30 mL), 5% NaHCO₃ (3 x 30 mL) and brine (30 mL). The organic solution was dried over MgSO₄ and concentrated under reduced pressure to give 25 as
a pale yellow foam (0.88 g, 91%); mp: 55-57 °C; \([\alpha]^{20}_{D} -18.8\) (c = 0.96, CHCl₃); \(\delta_H\) (400 MHz; CDCl₃) 7.33-7.32 (5H, m), 5.25 (1H, m), 5.07 (2H, s), 4.96 (1H, m), 4.91 (1H, m), 3.25-3.21 (2H, m), 2.66 (3H, s), 1.98 (1H, m), 1.84 (1H, m), 1.65-1.54 (2H, m), 1.43 (9H, s).

\(\delta_C\) (100 MHz; CDCl₃) 163.1, 159.9, 157.8, 156.5, 155.2, 136.5, 128.5, 128.2, 128.1, 125.3, 80.5, 66.7, 48.6, 40.5, 31.5, 28.3, 26.1, 12.4 ppm. MS (ESI) \(m/z\) 636 [(M+Na)⁺, 100]; HRMS: found [M+Na]⁺ 636.1750, C₂₈H₂₈F₅N₃NaO₇ requires [M+Na]⁺ 636.1740.

**Boc-Dab(Z)-Ser(Oxz)-OPfp (26)**

Pyridine (0.17 mL, 2.09 mmol) and pentafluorophenyl 2,2,2-trifluoroacetate (0.39 mL, 2.28 mmol) were added to a solution of 14a (0.81 g, 1.9 mmol) in CH₂Cl₂ (2 mL) and DMF (1 mL). The reaction mixture was stirred at room temperature under nitrogen for 21 h. The solvent was removed in vacuo then the residue was re-dissolved in EtOAc (50 mL) and washed with 0.1 M HCl (3 x 50 mL), 5% NaHCO₃ (3 x 50 mL) and brine (50 mL). The organic solution was dried over MgSO₄ and concentrated under reduced pressure to give 26 as a pale yellow solid (0.6 g, 51%); mp 129-132 °C; \([\alpha]^{20}_{D} -35.2\) (c 1.0, CHCl₃); \(^1\)H NMR (CDCl₃, 200 MHz): \(\delta\) 8.34 (s, 1H), 7.26 (m, 5H), 5.62-5.72 (m, 2H), 4.97-5.03 (m, 3H), 3.16-3.41 (m, 2H), 1.98-2.19 (m, 2H), 1.37 (s, 9H); \(^{13}\)C NMR (CDCl₃, 75 MHz): \(\delta\) 164.8, 161.1, 157.2, 155.9, 144.2, 139.8, 136.5, 136.1, 133.2, 131.9, 128.6, 128.5, 128.3, 81.3, 67.2, 46.7, 37.2, 34.4, 28.2, one signal obscured or overlapping; MS (ESI) \(m/z\) 608 [M+Na]⁺ HRMS calcld. for C₂₆H₂₆F₅N₃O₇Na [M+Na]⁺ 608.1427, found 608.1420.

**Boc-Dpr(Z)-Ser(Oxz)-OPfp (27)**

Pyridine (0.25 mL, 3.07 mmol) and pentafluorophenyl 2,2,2-trifluoroacetate (0.63 mL, 3.63 mmol) were added to a solution of 15a (1.17 g, 2.79 mmol) in CH₂Cl₂ (5 mL) and DMF (3 mL). The reaction mixture was stirred at room temperature under nitrogen for 21 h. The solvent was removed in vacuo, then the residue was re-dissolved in EtOAc (50 mL) and washed with 0.1 M HCl (3 x 50 mL), 5% NaHCO₃ (3 x 50 mL) and brine (50 mL). The organic solution was dried over MgSO₄ and concentrated under reduced pressure to give the desired pentafluorophenyl ester as a pale yellow solid (1.55 g, 98%); mp 128-130 °C; \([\alpha]^{20}_{D} -24.3\) (c 1.0, CHCl₃); \(^1\)H NMR (CDCl₃, 200 MHz): \(\delta\) 8.26 (s, 1H), 7.27 (m, 5H), 5.64 (m, 2H), 5.08 (s, 2H), 3.53 (m, 2H), 1.26 (s, 9H), NH not observed; \(^{13}\)C NMR (CDCl₃, 75 MHz): \(\delta\) 164.1, 161.5, 156.9, 155.7, 146.9, 143.9, 139.8, 136.2, 136.2, 130.8, 128.7, 128.4, 128.3, 80.9, 67.3, 49.8, 43.7, 28.4, one signal overlapping; MS (ESI) \(m/z\) 593 [M+Na]⁺ HRMS (ESI) calcld. for C₂₅H₂₄F₅N₃O₇Na [M+Na]⁺ 594.1270, found 594.1269.
Cyclo[Orn(Z)-Thr(Oxz)]₃ (19) and Cyclo[Orn(Z)-Thr(Oxz)]₄ (22)

**Method 2:** Under an atmosphere of nitrogen, pentafluorophenyl diphenylphosphinate (FDPP) (0.94 g, 2.4 mmol) and diisopropylethylamine (1.1 mL, 6.4 mmol) were added to a solution of 16 (0.75 g, 1.6 mmol) in anhydrous DMF (35 mL). The resulting solution was stirred at ambient temperature for 5 days after which time the solvent was removed under reduced pressure. The residue was partitioned between EtOAc (70 mL) and 2 M HCl (10 mL). The organic phase was isolated and the aqueous phase further extracted with EtOAc (2 × 25 mL). The combined organic phases were then washed with 1 M NaOH (2 × 15 mL), H₂O (2 × 15 mL) and brine (25 mL). The solvent was removed under vacuum to give a brown oil which was purified by flash chromatography (silica gel; hexane/EtOAc 1:4 → neat EtOAc) to provide the cyclic trimer 19 (100 mg, 19 %) as a colourless foam; data identical to that reported in the main text. Traces of the cyclic tetramer 22 were observed by LCMS of the crude reaction mixture but this compound was not isolated.

Cyclic Peptide: [Dab(Z)-Ser(Oxz)]₃ (20)

**Method 1:** Diisopropylethylamine (1.1 mL, 6.4 mmol) was added to a solution of 17 (0.95 g, 2.1 mmol) in anhydrous N,N-dimethylformamide (43 mL) then FDPP (1.26 g, 3.3 mmol) was added. The resulting reaction mixture was stirred at ambient temperature for 4 days after which time the solvent was removed under reduced pressure to give a brown residue which was partitioned between 1 M HCl (15 mL) and EtOAc (20 mL). The aqueous layer was further extracted with EtOAc (2 × 20 mL). The combined organic layers were then washed with 5 % lithium chloride (2 × 20 mL), water (15 mL), and brine (15 mL) followed by concentrating under reduced pressure to give the crude product as a brown oil, which was subsequently purified by flash chromatography (silica gel, EtOAc/Hexane 2:1) followed by preparative TLC (EtOAc/Hexane 3:1) to afford cyclic trimer 20 (0.14 g, 21 %) as a colourless oil. [α]D²⁰ -187 (c 0.7, CHCl₃); ¹H NMR (CDCl₃, 200 MHz): δ 8.39 (d, J 7.2 Hz, 3H), 8.19 (s, 3H), 7.35 (m, 15H), 5.87 (m, 3H), 5.32 (m, 3H), 5.13 (s, 6H), 3.14-3.60 (m, 6H), 1.87-2.35 (m, 6H); ¹³C NMR (CDCl₃, 75 MHz): δ 163.9, 160.4, 156.6, 142.2, 136.6, 135.1, 128.6, 128.2, 128.2, 66.8, 46.1, 37.1, 36.0; MS (ESI) m/z 926 [M+Na]⁺ HRMS (ESI) calcd. for C₄₅H₄₅N₀₁₂Na [M+Na]⁺ 926.3088, found 926.3080. Traces of the cyclic tetramer 23 were observed by LCMS of the crude reaction mixture but this compound was not isolated.
**Method 2:** Compound 26 (0.54 g, 0.92 mmol) was dissolved in CH$_2$Cl$_2$ (2 ml) and trifluoroacetic acid (8 ml) was added in one portion. The reaction mixture was stirred at room temperature for 3 h and the solvents were removed to give the trifluoroacetate salt 29 a yellow foam. This was dissolved in DMF (18 ml) and diisopropylethylamine (0.8 ml, 4.6 mmol) was added in one portion. The solution was stirred at room temperature for 3 days then the DMF was removed *in vacuo* to give a brown oil. This was dissolved in DMF (1.8 ml) and diisopropylethylamine (0.8 ml, 4.6 mmol) was added in one portion. The solution was stirred at room temperature for 3 days then the DMF was removed *in vacuo* to give a brown oil. The crude product was purified by flash chromatography (EtOAc: CH$_2$Cl$_2$ 3:1) giving the cyclic trimer 20 as a colourless solid (0.07 g, 24%). Data identical to that obtained above. Traces of the cyclic tetramer 23 were observed by LCMS of the crude reaction mixture but this compound was not isolated.

**Cyclic Peptide: [Dpr(Z)-Ser(Oxz)]$_3$ (21) and [Dpr(Z)-Ser(Oxz)]$_4$ (24)**

**Method 1:** Diisopropylethylamine (1.14 mL, 6.52 mmol) was added to a solution of 18 (0.79 g, 1.88 mmol) in anhydrous DMF (38 mL) then FDPP (1.10 g, 2.87 mmol) was added. The resulting reaction mixture was stirred at ambient temperature for 4 days after which time the solvent was removed under reduced pressure to give a brown residue which was partitioned between 1 M HCl (20 mL) and EtOAc (20 mL). The aqueous layer was further extracted with EtOAc (2 x 30 mL). The combined organic layers were then washed with 5 % lithium chloride (2 x 20 mL), water (15 mL), and brine (15 mL) followed by concentrating under reduced pressure to give the crude product as a brown oil, which was subsequently purified by flash chromatography (silica gel, EtOAc/Hexane 2:1) followed by preparative TLC (EtOAc/Hexane 3:1) to afford cyclic trimer 21 (0.15 g, 27%) and cyclic tetramer 24 (0.06 g, 11%) as colourless oils. Cyclic trimer 21: $[\alpha]_D^{20} + 19.9$ (c 0.9, CHCl$_3$); $^1$H NMR (CDCl$_3$, 200 MHz): $\delta$ 8.43 (d, $J$ 5.8 Hz, 3H), 8.14 (s, 3H), 7.29 (m, 15H), 5.59 (br s, 3H), 5.18 (m, 3H), 5.02 (m, 6H), 3.71 (m, 6H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 164.3, 160.4, 155.5, 142.3, 136.2, 135.4, 128.7, 128.4, 128.3, 67.2, 46.4, 36.5; MS (ESI) m/z 884 [M+Na]$^+$ HRMS calcd. for C$_{42}$H$_{39}$N$_9$O$_{12}$Na [M+Na]$^+$ 884.2610, found 824.2600. Cyclic tetramer 24: $[\alpha]_D^{20}$ -38 (c 1, CHCl$_3$); $^1$H NMR (CDCl$_3$, 200 MHz): $\delta$ 8.14 (s, 4H), 7.83 (br s, 4H), 7.26 (m, 20H), 5.50 (m, 4H), 5.00 (s, 8H), 3.74 (m, 8H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 165.4, 161.4, 156.7, 143.8, 136.1, 134.4, 128.8, 128.5, 128.3, 66.7, 46.0, 35.8; MS (ESI) m/z 1171 [M+Na]$^+$ HRMS (ESI) calcd. for C$_{56}$H$_{52}$N$_{12}$O$_{16}$Na [M+Na]$^+$ 1171.3517, found 1171.3519.
Method 2: Compound 27 (1.53 g, 2.68 mmol) was dissolved in CH₂Cl₂ (8 ml) and trifluoroacetic acid (22 ml) was added in one portion. The reaction mixture was stirred at room temperature for 3 h and the solvents were removed to give the trifluoroacetate salt 30 as an orange foam. This was dissolved in DMF (54 ml) and diisopropylethylamine (2.29 ml, 13.4 mmol) was added in one portion. The pale orange solution was stirred at room temperature for 3 days then the DMF was removed in vacuo to give a red-brown oil. This was redissolved in EtOAc (60 ml) and washed with 1M HCl solution (50 ml) and brine (50 ml), the organics were then dried (MgSO₄) and concentrated in vacuo leaving a brown oil. The crude product was purified by flash chromatography (EtOAc/CH₂Cl₂ 10:1) giving the cyclic trimer 21 as a colourless foam (0.32 g, 41%). Data identical to that obtained above. The cyclic tetramer 24 was observed by LCMS of the crude reaction mixture but this compound was not isolated.

Cyclo[Orn-Thr(Oxz)]₃ trishydrobromide (31)
A solution of HBr in acetic acid (45% v/v, 5 mL) was added to 19 (71.2 mg, 72.1 µmol). The reaction mixture was stirred for 15 h at ambient temperature to give a deep orange solution which was subsequently combined with anhydrous ether (20 mL) to give a colourless precipitate. The precipitate was triturated with anhydrous ether (total volume ~200 mL) until the ethereal layer became clear followed by the removal of remaining solvent under reduced pressure to give the trihydrobromide salt 31 as a brown solid (57.5 mg, 69.4 µmmol, 96%). ¹H NMR (CD₃OD/CDCl₃, 200 MHz): δ 8.59 (d, J 5.5 Hz, 3H), 5.30-5.10 (m, 3H), 3.10-2.94 (m, 6H), 2.65 (s, 9H), 2.42-1.55 (m, 12H) [H₃N⁺ not observed]. ¹³C NMR (CDCl₃, 75 MHz): δ 162.8, 162.0, 155.9, 79.5, 40.3, 32.7, 25.1, 24.2, 11.6. MS (ESI) m/z = 294 [M-H⁺]²⁺. HRMS (ESI) calcd. for C₂₇H₄₁N₉O₆²⁺ [M-H⁺]²⁺ 293.6585, found 293.6584.

Cyclo[Dab-Ser(Oxz)]₃ trishydrobromide (32)
Under an atmosphere of argon, a solution of HBr in acetic acid (45 % v/v, 5 mL) was added to 20 (0.07 g, 0.08 mmol). The reaction mixture was stirred for 3 h at ambient temperature to give a dark orange solution which was subsequently combined with anhydrous ether (15 mL) to give a colourless precipitate. The precipitate was triturated with anhydrous ether (total volume 200 mL) until the ethereal layer became clear followed by the removal of remaining solvent under reduced pressure to give the trihydrobromide salt 32 as a colourless solid (0.06 g, 100 %) which was used without further purification in the next step. ¹H NMR (CD₃OD,
200 MHz): \(\delta\) 8.85- 8.88 (m, 3H), 8.58 (s, 3H), 5.45 (br s, 3H), 3.17-3.31 (m, 6H), 2.30-2.50 (m, 6H), \(\text{NH}_3^+\) obscured or overlapping; \(^{13}\text{C}\) NMR (CD\(_3\)OD, 75 MHz): \(\delta\) 163.8, 162.3, 144.5, 136.1, 47.1, 37.7, 33.9; MS (ESI) \(m/z\) 502 [M-2H\(^+\)].

**Cyclo[Dpr-Ser(Oxz)]\(_3\) trishydrobromide (33)**

Under an atmosphere of argon, a solution of HBr in acetic acid (45 \% v/v, 13 mL) was added to 21 (0.17 g, 0.20 mmol). The reaction mixture was stirred for 3 h at ambient temperature to give a dark orange solution which was subsequently combined with anhydrous ether (30 mL) to give a colourless precipitate. The precipitate was triturated with anhydrous ether (total volume 250 mL) until the ethereal layer became clear followed by the removal of remaining solvent under reduced pressure to give the desired trihydrobromide salt 33 as a colourless solid (0.14 g, 100 \%) which was used without further purification in the next step. \(^1\text{H}\) NMR (CD\(_3\)OD, 200 MHz): \(\delta\) 8.88 (d, \(J\) 6.2 Hz, 3H), 8.65 (s, 3H), 5.64-5.66 (m, 3H), 3.56-3.71 (m, 6H), \(\text{NH}_3^+\) obscured or overlapping.

**Cyclo[Orn-Thr(Oxz)]\(_4\) tetrahydrobromide (34)**

Under an atmosphere of argon, a solution of HBr in acetic acid (33 \% v/v, 2.4 mL) was added to 22 (44 mg, 0.03 mmol) The reaction mixture was stirred for 16 h at ambient temperature to give a dark orange solution which was subsequently combined with anhydrous ether (10 mL) to give a colourless precipitate. The precipitate was triturated with anhydrous ether (8 x 20 mL) until the ethereal layer became clear followed by the removal of remaining solvent under reduced pressure to give the desired tetrahydrobromide salt 34 as a colourless solid (30 mg, 83 \%); \(\delta\)\(_H\) (200 MHz; CD\(_3\)OD) 5.39-5.21 (m, 4H), 3.11-3.01 (m, 8H), 2.59 (s, 12H), 2.23-1.65 (m, 16H), \(\text{NH}, \text{NH}_3^+\) not observed; MS (ESI) \(m/z\) 391 [M+2H\(^2+\)].

**Cyclo[Arg(Boc)\(_2\)-Thr(Oxz)]\(_3\) (8)**

**Method 1:** To a suspension of 31 (0.12 g, 0.15 mmol) in CH\(_2\)Cl\(_2\) (5 mL), diisopropylethylamine (0.14 mL, 0.75 mmol) was added and the solution stirred at room temperature for 15 mins. \(\text{N,N’-di-Boc-N’’-trifyl-guanidine}\) (0.32 g, 0.83 mmol) in CH\(_2\)Cl\(_2\) (2 mL) was added via cannula and the reaction mixture stirred at room temperature for 21 h. The mixture was diluted with CH\(_2\)Cl\(_2\) (10 mL) and washed with 2 M NaHSO\(_4\) (10 mL), NaHCO\(_3\) (10 mL), brine (10 mL), dried (MgSO\(_4\)) and concentrated under reduced pressure to give a pale brown foam. The crude material was purified by flash chromatography (2:3 hexane:E\(\text{TAc}\)) to give 8 as a colourless foam (0.16 g, 82\%); \([\alpha]^{20}_D\) -1.0 (c = 3.5, CHCl\(_3\)); \(\delta\)\(_H\)
Method 2: To a solution of 31 (35 mg, 0.04 mmol) in DMF (1.2 ml), DIPEA (33 µl, 0.19 mmol) was added. The mixture was stirred at room temperature for 10 min, after which time \(N,N'\)-bis(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine (55 mg, 0.18 mmol) was added. The reaction mixture was stirred for 48 h then the DMF was evaporated in vacuo and the residue was dissolved in EtOAc (5 ml). The organics were washed with 1M HCl solution (5 ml) and brine (5 ml), dried (MgSO\(_4\)) and concentrated in vacuo to give a colourless oil which was purified by flash column chromatography (1:2 → 3:2 EtOAc–hexane elution) to give 8 (30 mg, 54 %) as a colourless oil. Data identical to that obtained above.

### Cyclo[Dab(Boc\(_2\)Guanidinyl)-Ser(Oxz)]\(_3\) (35)

**Method 1:** To a suspension of 32 (0.04 g, 0.05 mmol) in CH\(_2\)Cl\(_2\) (1 mL), diisopropylethylamine (40 µL, 0.23 mmol) was added and the solution stirred at room temperature for 15 mins. \(N,N'\)-bis(tert-butoxycarbonyl)-\(N''\)-trifyl-guanidine (0.08 g, 0.2 mmol) in CH\(_2\)Cl\(_2\) (1 mL) was added via cannula and the reaction mixture stirred at room temperature for 21 h. The mixture was diluted with CH\(_2\)Cl\(_2\) (10 mL) and washed with 0.1 M HCl (2 x 10 mL), sat. NaHCO\(_3\) (10 mL), brine (10 mL), dried (MgSO\(_4\)) and concentrated under reduced pressure to give a brown oil. The crude material was purified by flash chromatography (1:1 hexane:EtOAc) to give 35 as a colourless precipitate (0.03 g, 48 %); [\(\alpha\)]\(_{D}\)\(^{25}\) -90 (c = 1.5, CH\(_2\)Cl\(_2\)); \(\delta_H\) (400 MHz; CDCl\(_3\)) 11.46 (3H, s), 8.67 (3H, t, \(J\) 5.5 Hz), 8.44 (3H, d, \(J\) 6.8 Hz), 8.22 (3H, s), 5.30 – 5.26 (3H, m), 3.84 – 3.79 (3H, m), 3.42 – 3.39 (3H, m), 2.47 – 2.39 (3H, m), 2.09 – 2.02 (3H, m), 1.47 (54H, s). \(\delta_C\) (100 MHz; CDCl\(_3\)) 163.5, 163.2, 159.9, 156.1, 152.8, 142.0, 135.0, 83.0, 79.3, 46.4, 36.6, 34.8, 28.3, 28.0 ppm. MS (ESI) m/z 1250 \([M+Na]^+\), 100%; HRMS: \([M+Na]^+\) found 1250.5746, \(C_{54}H_{81}N_{15}O_{18}\) requires \([M+Na]^+\) 1250.5776.

**Method 2:** Under an atmosphere of nitrogen, diisopropylethylamine (0.06 mL, 0.35 mmol) was added to a solution of 32 (0.06 g, 0.08 mmol) and \(N,N'\)-bis(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine (0.10g, 0.33 mmol) in anhydrous \(N,N\)-dimethylformamide (1.5 mL). The resulting reaction mixture was stirred at ambient temperature for 16 h after which
time the solvent was removed under reduced pressure to give a brown residue which was partitioned between 1 M HCl (5 mL) and EtOAc (10 mL). The aqueous layer was further extracted with EtOAc (2 x 10 mL). The combined organic layers were then washed with 5 % lithium chloride (2 x 10 mL), water (10 mL), and brine (10 mL) followed by concentrating under reduced pressure to give the crude product as a brown oil, which was subsequently purified by flash chromatography (EtOAc/Hexane 2:1 → CHCl₃/MeOH 9:1) to afford guanidinium cyclic trimer 35 (0.06 g, 57 %) as a colourless oil. Data identical to that obtained above.

Cyclo[Δpr(Boc₂Guanidinyl)-Ser(Oxz)]₃ (36)

**Method 1:** To a suspension of 33 (0.08 g, 0.11 mmol) in CH₂Cl₂ (2 mL), diisopropylethylamine (94 µL, 0.51 mmol) was added and the solution stirred at room temperature for 15 mins. N,N'-bis(tert-butoxycarbonyl)-N''-triflyl-guanidine (0.21 g, 0.54 mmol) in CH₂Cl₂ (1 mL) was added via cannula and the reaction mixture stirred at room temperature for 21 h. The mixture was diluted with CH₂Cl₂ (10 mL) and washed with 0.1 M HCl (2 x 10 mL), sat. NaHCO₃ (10 mL), brine (10 mL), dried (MgSO₄) and concentrated under reduced pressure to give a colourless precipitate. The crude material was purified by flash chromatography (1:2 hexane:EtOAc) to give the product 36 as a colourless oil (0.06 g, 42%); [α]²⁵⁺⁺ +17 (c = 1, CH₂Cl₂); δ₁H (300 MHz; CDCl₃) 11.40 (3H, br s), 8.78 (3H, m), 8.50 (3H, d, J 6.2 Hz), 8.18 (3H, s), 5.26 (3H, m), 4.06 – 3.91 (6H, m), 1.50 (27H, s), 1.36 (9H, s). δ₁C (75 MHz; CDCl₃) 163.3, 161.9, 159.9, 156.8, 153.0, 142.3, 135.1, 83.5, 79.3, 48.1, 44.4, 28.2 ppm. MS (ESI) m/z 1208 (M+Na)⁺ 100%; HRMS: (M+Na)⁺ found 1208.5301, C₅₁H₇₅N₁₅O₁₈Na requires (M+Na)⁺ 1208.5307.

**Method 2:** Under an atmosphere of nitrogen, diisopropylethylamine (0.15 mL, 0.87 mmol) was added to a solution of 33 (0.14 g, 0.20 mmol) and N,N'-bis(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine (0.26 g, 0.83 mmol) in anhydrous N,N-dimethylformamide (4.0 mL). The resulting reaction mixture was stirred at ambient temperature for 16 h after which time the solvent was removed under reduced pressure to give a brown residue which was partitioned between 1 M HCl (10 mL) and EtOAc (10 mL). The aqueous layer was further extracted with EtOAc (2 x 10 mL). The combined organic layers were then washed with 5 % lithium chloride (2 x 10 mL), water (15 mL), and saturated brine (15 mL) followed by concentrating under reduced pressure to give the crude product as a brown oil, which was
purified by flash chromatography (EtOAc/Hexane 1:1) to give 36 (0.11 g, 46 %) as a colourless oil. Data identical to that obtained above.

**Cyclo[Arg(Boc)-Thr(Oxz)]₄ (9)**

To a solution of 34 (30 mg, 0.03 mmol) in DMF (0.54 ml) was added diisopropylethylamine (21 µl, 0.12 mmol). The mixture was stirred at room temperature for 10 min, after which time N,N'-bis(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine (36 mg, 0.12 mmol) was added. The reaction mixture was stirred for 48 h then the DMF was evaporated in vacuo and the residue was dissolved in EtOAc (5 ml). The organics were washed with 1M HCl solution (5 ml), dried (MgSO₄) and concentrated in vacuo leaving a colourless oil which was purified by flash column chromatography (1:2 → 2:1 EtOAc - hexane elution) to give 9 (11 mg, 23 %) as a colourless oil; [α]²⁰D -59.8 (c = 1.1, CHCl₃); δH (400 MHz; CDCl₃) 11.49 (4H, br s), 8.40 (4H, br s), 7.25 (4H, d, J 8.2 Hz), 5.39 (4H, app dt, J 8.2, 7.2 Hz), 3.54 (8H, m), 2.61 (12H, s), 2.16-2.02 (8H, m), 1.74-1.65 (8H, m), 1.50 (72H, s). δC (100 MHz; CDCl₃) 161.1, 161.0, 156.0, 154.3, 153.3, 128.6, 83.5, 80.0, 45.6, 40.7, 29.8, 28.3, 28.1, 25.7, 11.9. MS (ESI) m/z 1772 ([M+Na]+, 100), 1750 ([M+H]+, 35); HRMS: found [M+2H]²⁺ 875.4613, C₈₀H₁₂₆N₂₀O₂₄ requires [M+2H]²⁺ 875.4621.

**Cyclo[Arg-Thr(Oxz)]₃-(CF₃CO₂H)₃ [1.(CF₃CO₂H)₃]**

Compound 8 (54 mg, 0.04 mmol) was dissolved in a mixture of CH₂Cl₂ (1 ml) and trifluoroacetic acid (3 ml) and the reaction mixture was stirred at room temperature for 2 h. The solvents were removed in vacuo and the above process was repeated a second time to ensure complete Boc deprotection. Once again the solvents were removed leaving a brown oil. This was purified by preparative HPLC (gradient 2-70% B in A over 45 mins, retention time = 18.1 mins) to give 1.(CF₃CO₂H)₃ (39 mg, 90 %) as a fluffy colourless solid after lyophilisation from tert-BuOH; mp 85-88 °C; [α]²⁰D -27.2 (c = 1.1, MeOH); δH (400 MHz; D₂O) 5.17 (3H, t, J 5.6 Hz), 3.26 (6H, t, J 6.6 Hz), 2.63 (9H, s), 2.17 (3H, m), 2.01 (3H, m), 1.74 (3H, m), 1.56 (3H, m), NH/NH₂ not observed. δC (100 MHz; D₂O) 162.0, 160.3, 156.7, 155.3, 127.3, 47.7, 40.4, 30.1, 23.0, 110.0. MS (ESI) m/z 357 [(M-H⁻)²⁺, 100], 238 [(M)³⁺, 80], 413 [(M+ CF₃CO₂⁻)²⁺, 23], 712 [(M-2H⁺)⁺, 21], 826 [(M-H⁻+ CF₃CO₂⁻)⁺, 15], 940 [(M+2(CF₃CO₂⁻)⁻, 18]; HRMS: found [M]³⁺ 238.1300, C₃₀H₄₈N₁₅O₆ requires [M]³⁺ 238.1299.

**Cyclo[Arg-Thr(Oxz)]₃-(HCl)₃ (1.3HCl)**
Stannic chloride (97 µL, 0.84 mmol) was added to a solution of 8 (0.09 g, 0.07 mmol) in EtOAc (0.8 mL) and the mixture was stirred at room temperature under an atmosphere of nitrogen for 16 h. The excess stannic chloride and EtOAc were removed in vacuo and the remaining yellow solid dissolved in methanol. Diethyl ether was added until the formation of a colourless precipitate which was separated from the mother liquor by centrifugation giving 1.3HCl as a colourless solid (0.06 g, quant.) \([\alpha]_{20}^{25} -42.5 \text{ (c = 0.04 , MeOH)}; \delta_{\text{H}} \text{(400 MHz; DMSO-}d_6\text{) 8.38 (3H, d, J 6.6 Hz), 7.8 (3H, t, J 5.5 Hz), 5.19 (6H, m), 3.17 (6H, m), 2.64 (9H, s), 2.05 (3H, m), 1.92 (3H, m)\text{.} Arg \text{ NH/ NH}_2 \text{ not observed.} \delta_{\text{C}} \text{(100 MHz; DMSO-}d_6\text{) 161.7, 161.0, 157.8, 154.5, 128.6, 48.1, 32.2, 25.3, 12.3, (one signal obscured or overlapping) MS (ESI) m/z 356.7 \text{ [(M-H)}^+\text{] } 100\text{], 238.2 \text{ [M}^3+\text{, } 40\text{]; HRMS: found [M] }^3\text{+ 238.1297, C}_{30}\text{H}_{48}\text{N}_{15}\text{O}_6\text{ }^3\text{+ requires [M]}^3\text{+ 238.1299.}}

**Cyclo[Dab(guanidinyl)-Thr(Oxz)]_3.(HCl)_3 (2.3HCl)**

Stannic chloride (31 µL, 0.27 mmol) was added to a solution of 35 (0.03 g, 0.02 mmol) in EtOAc (0.2 mL) and the mixture was stirred at room temperature under an atmosphere of nitrogen for 16 h. The excess stannic chloride and EtOAc were removed in vacuo and the remaining yellow solid dissolved in methanol. Diethyl ether was added until the formation of a colourless precipitate which was separated from the mother liquor by centrifugation giving 2.3HCl as a colourless solid (12 mg, 81%); \([\alpha]_{25}^{20} -33.8 \text{ (c = 1.2, DMSO:MeOH 50:50)}; \delta_{\text{H}} \text{(400 MHz; DMSO-}d_6\text{) 8.83 (3H, s), 8.53 (3H, d, J 6.9 Hz), 7.77 (3H, m), 5.34 – 5.29 (3H, m), 3.28 (6H, m), 2.26 – 2.06 (6H, m), guanidinium \text{ NH/ NH}_2 \text{ not observed.} \delta_{\text{C}} \text{(100 MHz; DMSO-}d_6\text{) 162.7, 159.2, 156.8, 143.0, 134.5, 45.6, 37.0, 33.3. MS (ESI) m/z 314.5 \text{ [(M-H)}^+\text{] } 100\%\text{], 210 \text{ [(M)}^3\text{+, } 56\%\text{]; HRMS: found [M-2H}^+\text{] + 628.2816, C}_{24}\text{H}_{32}\text{N}_{15}\text{O}_6\text{ }^3\text{+ requires 628.2811.}}

**Cyclo[Dpr(guanidinyl)-Thr(Oxz)]_3.(HCl)_3 (3.3HCl)**

Stannic chloride (91 µL, 0.79 mmol) was added to a solution of 36 (0.08 g, 0.07 mmol) in EtOAc (0.6 mL) and the mixture was stirred at room temperature under an atmosphere of nitrogen for 16 h. The excess stannic chloride and EtOAc were removed in vacuo and the remaining yellow solid dissolved in methanol. Diethyl ether was added until the formation of a colourless precipitate which was separated from the mother liquor by centrifugation giving 3.3HCl as a colourless solid (0.04 g, quant.); \([\alpha]_{20}^{25} +8 \text{ (c = 0.1 , MeOH)}; \delta_{\text{H}} \text{(400 MHz; DMSO-}d_6\text{) 8.95 (3H, s), 8.48 (3H, d, J 6.7 Hz), 7.83 – 7.80 (3H, m), 7.37 (6H, br s), 5.45 – 5.41 (3H, m), 3.86 – 3.71 (6H, m).} \delta_{\text{C}} \text{(100 MHz; DMSO-}d_6\text{) 161.9, 160.1, 158.4, 144.6,}
135.5, 49.6, 48.5, 44.3. MS (ESI) m/z 658 [(M+2(Cl))⁺, 53%], 586 [(M-2H)⁺, 22%], 622 [(M-H⁺+Cl)⁺, 18%]; HRMS: [(M-H⁺+Cl)⁺] found 622.2126, C₂₁H₂₀N₁₅O₆Cl⁺ requires [(M-H⁺+Cl)⁺] 622.2108.

**Cyclo[Arg-Thr(Oxz)]₄·(CF₃CO₂H)₄ [4.(CF₃CO₂H)₄]**

Compound 9 (11 mg, 0.006 mmol) was dissolved in a mixture of CH₂Cl₂ (1 ml) and trifluoroacetic acid (3ml) and the reaction mixture was stirred at room temperature for 2h. The solvents were removed *in vacuo* and the above process was repeated a second time to ensure complete Boc deprotection. Once again the solvents were removed leaving a brown oil. This was purified by preparative HPLC (gradient 2-70% B in A over 45 mins, retention time = 16.5 min) to give [4.(CF₃CO₂H)₄] (8 mg, quant.) as a fluffy colourless solid after lyophilisation from tert-BuOH; mp 97-99 °C; [α]₂₀D -60.0 (c = 0.6, MeOH); δH (400 MHz; D₂O) 5.31 (4H, dd, J 9.5, 5.2 Hz), 3.27 (8H, t, J 7.0 Hz), 2.52 (12H, s), 2.21-2.13 (4H, m), 2.08-1.97 (4H, m), 1.79-1.69 (8H, m), NH/NH₂ not observed. δC (100 MHz; D₂O) 163.5, 161.1, 156.8, 156.0, 127.5, 46.0, 40.4, 28.9, 24.3, 11.1. MS (ESI) m/z 317 [(M-H⁺)³⁺, 100], 238 [(M)⁴⁺, 37], 355 [(M+CF₃CO₂⁻)]³⁺, 18], 475 [(M-2H⁺)²⁺, 51], 532 [(M-H⁺+ CF₃CO₂⁻)²⁺, 20], 589 [(M+2(CF₃CO₂⁻)²⁻, 24], 1292 [M+3(CF₃CO₂⁻)⁺, 8; HRMS: found [M]⁴⁺ 238.1298, C₄₀H₆₄N₂₀O₈ requires [M]⁴⁺ 238.1299.
References


3) Bergmann, M.; Zervas, L. Ber. 1932, 65, 1192.


7) Compound 33 has previously been synthesized in the free amine form; Mink, D; Mecozzi, S.; Rebek, Jr J. Tetrahedron Lett. 1998, 39, 5709.