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for

Conformationally Constrained Mimics of the Membrane-Proximal Domain of FceRIa

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1. Materials and methods

(2*S*,4*R*)-*N*-Boc-4-hydroxyproline and Fmoc-OSu were received from Bachem. Boc-Ser-OH, $(Boc)_2O$, trifluoroethanol (TFE), triisopropylsilane (TIS), N-hydroxybenzotriazole monohydrate (HOBt) and Fmoc-Allylgly-OH were received from Fluka. Fmoc-Trp(Boc)-OH, Fmoc-Tyr(*t*Bu)-OH, Fmoc-Glu(O*t*Bu)-OH dihydrate, Fmoc-Arg(Pbf)-OH, Fmoc-Ala-OH, Boc-Lys(Boc)-OH dicyclohexylammonium salt, *O*-(Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU) were received from Novabiochem.

Benzylidene-bis-(tricyclohexylphosphine)-dichlororuthenium (1st generation Grubbs catalyst), benzylidene-[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene] dichloro(tricyclohexylphosphine)-ruthenium (2nd generation Grubbs catalyst), and dichloro(O-isopropoxyphenylmethylene)-(tricyclohexyphosphine) ruthenium (Hoveyda-Grubbs-catalyst) were received from Aldrich.

H-Leu-2-Cl-Trt and H-Tyr(*t*Bu)-2-Cl-Trt resins were received from Novabiochem. For solid-phase peptide synthesis, peptide grade DMF and NMP (Fluka) was used.

NMR spectra were recorded on a Bruker Avance 400 spectrometer (resonance frequencies 400.13 for ^{1}H and 100.61 MHz for ^{13}C) or a Bruker Avance 500 (resonance frequencies 500.13 for ^{1}H and 125.77 MHz for ^{13}C) equipped with a 5mm inverse broadband probe head with z-gradients at room temperature with standard Bruker pulse programs. Chemical shifts are given in values of ppm, referenced to residual solvent signals (7.26 for ^{1}H, 77.0 for ^{13}C in $CDCl_3$, 2.49 and 39.6 in DMSO, 3.31 and 49.0 in CD_3OD, respectively). ^{1}H NMR data were collected with 32k complex data points and were apodized with a Gaussian window function (lb = -0.5 and gb = 0.2) prior to Fourier transformation. ^{13}C-jmod spectra with WALTZ16 ^{1}H decoupling were acquired using 64k data points. Signal to noise enhancement was achieved by multiplication of the FID with an exponential window function (lb= 1Hz).

All two-dimensional experiments were performed with 1k x 256 data points, the number of transients (8 – 128 scans) and the sweep widths were optimized individually. In the homonuclear ^{1}H,^{1}H-COSY (Bruker pulse program *cosygpqf*), TOCSY (*mlevph*), and ROESY (*roesyph.2*) experiments the relaxation delay was set to 1.5 s, and the 90° pulse length to 11.2 µs. The resulting FID's were zero-filled to a 2k x 1k data matrix and apodized with a sine function for the COSY and a shifted sine function (in the case of TOCSY and ROESY) in both the ω1 and ω2 dimensions prior to Fourier transformation. The TOCSY was run with the MLEV17 spin lock sequence and a mixing time of 100 ms. Heteronuclear spectra were recorded with 1k x 256 data points, zero-filled to a 1k x 512 data matrix, and apodized in both dimensions with a shifted sine function. HSQC experiments (*hsqcetgpsp*) were acquired by using adiabatic pulses for inversion of ^{13}C and garp-sequence for broadband ^{13}C-decoupling, optimized for ^{1}J(CH) = 145 Hz. The 90° ^{13}C pulse length was 12.0 µs. ^{1}H,^{13}C long-range spectra HMBC (*hmbcgplpndqf*) were run with ^nJ(CH) set to 8Hz.

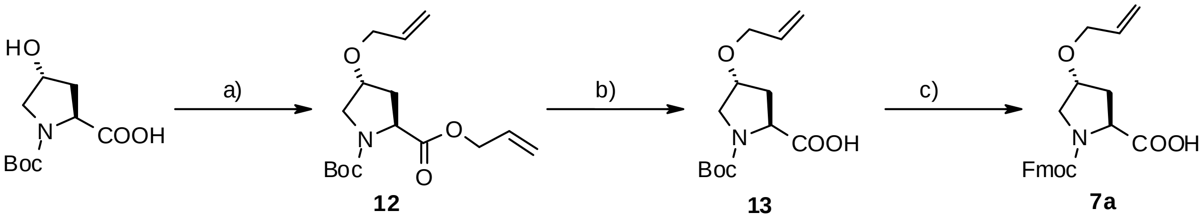
Mass spectra were recorded on Waters Micromass ZQ equipment in combination with an Agilent Series 1100 injection system using ESI or APCI as ionization conditions. High-resolution mass spectra were recorded on a Bruker Daltonics 9.4T APEX-III FT mass spectrometer.

HPLC was performed on Hewlett Packard Series 1100/1200 equipment with a Waters XTerra RP-18 3.5 µm, 4.6x50 mm cartridge. Solvent A = 30 mM phosphate buffer pH 4.5, solvent B = 95% aq. acetonitrile. Gradient: 0.5 min A:B = 95:5, then in 7 min to A:B = 5:95. Preparative HPLC was performed on a Gilson preparative HPLC system (Pump 322, UV/VIS Detector 155, Liquid Handler 215) with a Waters XTerra Prep MS C18 column (5 uM, 19 x 150 mm and an appropriate gradient between solvent A = water and solvent B = 95% aq. acetonitrile.

Liquid chromatography was performed on a Biotage SP4 system. Reaction progress was monitored with Merck 60 F254 HPTLC silica gel plates. Optical rotations were measured on a Perkin-Elmer 341 Polarimeter using a 10 cm cuvette. All chemical transformations requiring exclusion of moisture and oxygen were performed under an atmosphere of dry argon. Solid-phase reactions were performed on an orbital shaker at room temperature using standard solid phase reaction vessels.

2. Synthesis of the amino acid building blocks 7a,b, 8 and 9

2.1. Synthesis of *N*-Fmoc-(2*S*,4*R*)-4-*O*-allyl-hydroxyproline (7a)



a) NaH, allyl bromide; b) LiOH; c) 1. TFA, 2. FmocOSu

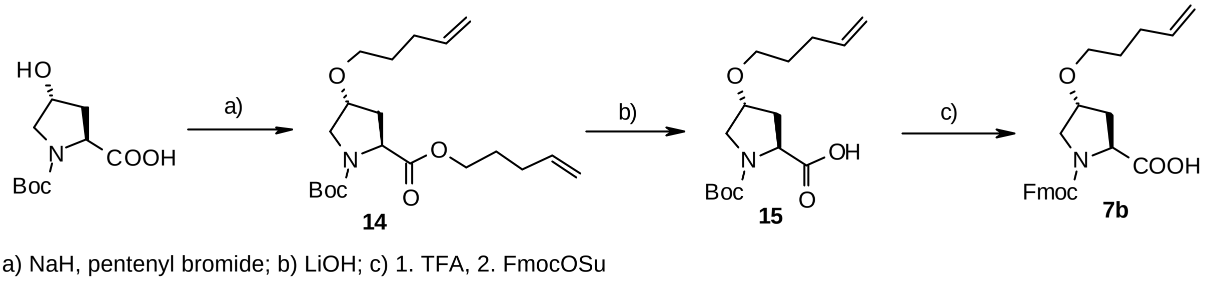
2.1.1. N-Boc-(2*S*,4*R*)-4-*O*-allyl-hydroxyproline allyl ester (12): To a suspension of 95 % sodium hydride (471 mg, 18.6 mmol) in 10 mL dry DMF a solution of (2*S*,4*R*)-*N*-Boc-4-hydroxyproline (2.00 g, 8.5 mmol) in 20 mL DMF was added dropwise within 20 min at room temperature. The mixture was stirred for additional 30 min, then allyl bromide (1.95 mL, 22.1 mmol) was added dropwise. The resulting clear solution was stirred overnight at room temperature. The reaction was quenched by addition of 50 mL water. The pH was adjusted to 2 – 3 by addition of 5M hydrochloric acid and the mixture was thoroughly extracted with ether. The combined ether extracts were washed with brine, dried over $MgSO_4$ and evaporated. Purification by column chromatography (Biotage Si40+M column, gradient: cyclohexane/ethyl acetate 90:10 to 80:20 over 8 column volumes) gave **12** (1.88 g, 71 %) as a colourless oil. MS (ESI+): *m/z* = 334 [M+Na]$^+$; HR-MS [M+Na]$^+$ = $C_{16}H_{25}NO_5Na$, calcd 334.1625; found 334.1625; ^{1}H NMR ([D_6]DMSO, 400 MHz, approx. 2:3 rotameric mixture) *d* = 1.31 and 1.37 (s, 9H), 1.96 (m, 1H), 2.32 (m, 1H), 3.42 (m, 2H), 3.94 (m, 2H), 4.08 (m, 1H), 4.20 (m, 1H), 4.50 – 4.63 (m, 2H), 5.16 (m, 2H), 5.25 (m, 2H), 5.88 (m, 2H); ^{13}C NMR ([D_6]DMSO, 100 MHz, major rotamer): *d* = 28.2 (q), 36.2 (t), 52.0 (t), 58.0 (d), 65.4 (t), 69.5 (t), 75.9 (d), 79.7 (s), 117.0 (t), 118.7 (t), 132.7 (d), 135.5 (d), 153.4 (s), 172.6 (s).

2.1.2. *N*-Boc-(2*S*,4*R*)-4-*O*-allyl-hydroxyproline (13): To a solution of **12** (1.20 g, 3.9 mmol) in THF/methanol 3:1 (8 mL) was added a solution of lithium hydroxide (185 mg, 7.7 mmol) in 2 mL water. After 3 h stirring at room temperature TLC indicated complete consumption of the starting material. The solution was concentrated in vacuo and partitioned between 1 N hydrochloric acid and ethyl acetate. The aqueous layer was extracted twice with ethyl acetate and the combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave **13** (1.06 g, quantitative yield) as a colorless solid that was used in the next step without further purification. MS (ESI+): *m/z* = 272 [MH]$^+$, 294

[*M*+Na]$^+$; HR-MS: [*M*-H]$^+$ = $C_{13}H_{20}NO_5$, calcd 270.1347; found 270.1347; ^{1}H NMR ([D$_6$]-DMSO, 400 MHz, 3:2 mixture of rotamers): *d* = 1.32 and 1.37 (s, 9H), 1.95 and 2.26 (m, 2H), 3.38 (m, 2H), 3.93 (m, 2H), 4.07 (m, 2H), 5.12 (ddd, *J* = 11.4, 3.5 and 1.4 Hz, 1H), 5.22 (ddd, *J* = 17.2, 3.5 and 1.7 Hz, 1H), 5.85 (ddt, *J* = 17.2, 11.4 and 5.3 Hz, 1H); ^{13}C NMR ([D$_6$]-DMSO, 100 MHz, major rotamer): *d* = 28.5 (q), 36.2 (t), 51.9 (t), 58.1 (d), 69.5 (t), 76.0 (d), 79.4 (s), 117.0 (t), 135.6 (d), 153.6 (s), 174.6 (s). Dicyclohexylamine salt (recrystallized from *n*-hep-tane): m.p.: 123 – 124 °C, [a]$_D^{20}$ = -27.9 (c = 1.0, MeOH)

2.1.3. N-Fmoc-(2*S*,4*R*)-4-*O*-allyl-hydroxyproline (7a): To a solution of **13** (754 mg, 2.8 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (5 mL) and the mixture was stirred at room temperature for 90 min. Toluene (20 mL) was added, the mixture was evaporated to dryness and dried in vacuo to yield 727 mg of a colorless solid. This material was dissolved in dichloromethane/DMF 95:5 (12 mL) and diisopropylethylamine (950 µL, 5.6 mmol) was added. The resulting mixture was cooled in an ice bath and Fmoc-OSu (1.41 g, 4.2 mmol) was added in one portion. The resulting clear solution was stirred for 30 min at 0 °C and then overnight at room temperature. For workup the solution was evaporated and the residue was partitioned between 1 N hydrochloric acid and dichloromethane. The aqueous layer was extracted twice with dichloromethane and the combined organic layers were dried over $MgSO_4$ and evaporated. Purification by column chromatography (Biotage Si25+M, dichloromethane/isopropanol 95:5 + 0.1% acetic acid) gave **7a** (1.10 g, quantitative yield) as a colorless oil. MS (ESI+): *m/z* = 416 [*M*+Na]$^+$; HR-MS: [*M*+Na]$^+$ = $C_{23}H_{23}NO_5Na$, calcd 416.1468; found 416.1468; ^{1}H NMR ([D$_6$]DMSO, 400 MHz, ca 3:2 mixture of rotamers): *d* = 1.90 and 2.11 (m, 1H), 2.31 and 2.42 (m, 1H), 3.42 – 3.57 (m, 2H), 3.89 – 4.03 (m, 2H), 4.11 – 4.21 and 4.25 – 4.39 (m, 3H), 5.15 (m, 1H), 5.26 (m, 1H), 5.88 (m, 1H), 7.33 (m, 2H), 7.42 (m, 2H), 7.65 (m, 2H), 7.90 (m, 2H), 12.67 (br. s, 1H); ^{13}C NMR ([D$_6$]DMSO, 100 MHz, major rotamer): *d* = 35.4 (t), 46.9 (d), 58.1 (d), 67.0 (t), 69.4 (t), 76.7 (d), 116.9 (t), 120.5, 125.6, 127.5, 128.1, 135.5 (5d), 141.1, 144.1, 154.4, 173.7 (3s).

2.2. Synthesis of *N*-Fmoc-(2*S*,4*R*)-4-*O*-pent-4-enyl-hydroxyproline (7b)



a) NaH, pentenyl bromide; b) LiOH; c) 1. TFA, 2. FmocOSu

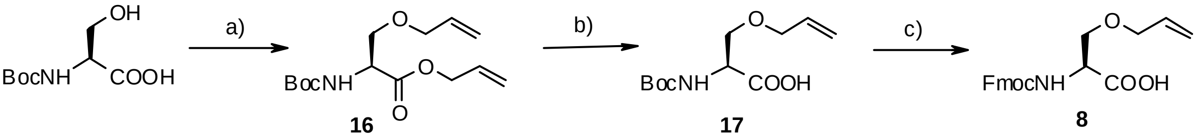
2.2.1. *N*-Boc-(2*S*,4*R*)-4-*O*-pent-4-enyl-hydroxyproline pent-4-enyl ester (14): Following the procedure given for the synthesis of **12,** this compound was prepared from (2*S*,4*R*)-*N*-Boc-4-hydroxyproline (2.00 g, 8.5 mmol), 95 % sodium hydride (471 mg, 18.6 mmol), and 5-bromo-1-pentene (2.6 mL, 22 mmol) as a colorless oil, yield = 1.06 g (34 %). MS (ESI+): *m/z* = 390 [*M*+Na]$^+$; HR-MS: [*M*+Na]$^+$ = $C_{20}H_{33}NO_5Na$, calcd 390.2251; found 390.2250; ^{1}H NMR ([D$_6$]DMSO, 500 MHz, approx. 2:3 rotameric mixture) *d* = 1.31 and 1.37 (s, 9H), 1.54 (m, 2H), 1.65 (m, 2H), 1.93 (m, 1H), 2.00 – 2.11 (m, 4H), 2.26 (m, 1H), ca. 3.3 – 3.45 (m, 4H), 3.97 – 4.10 (m, 3H), 4.14 (m, 1H), 4.98 (m, 4H), 5.78 (m, 2H); ^{13}C NMR ([D$_6$]DMSO, 125 MHz, major rotamer): *d* = 27.7 (t), 28.3 (q), 28.8 (t), 29.9 (t), 30.2 (t), 36.3 (t), 51.9 (t), 58.1 (d), 64.4 (t), 67.9 (t), 76.3 (d), 79.6 (s), 115.4 (t), 115.8 (t), 138.1 (d), 138.7 (d), 153.4 (s), 173.0 (s).

2.2.2. N-Boc-(2*S*,4*R*)-4-*O*-pent-4-enyl-hydroxyproline (15): Following the procedure given for for the synthesis of **13,** this compound was obtained in 99 % yield (2.2 mmol scale) from *N*-Boc-(2*S*,4*R*)-4-*O*-pent-4-enyl-hydroxyproline pent-4-enyl ester (**14**) as a colorless oil. MS (ESI+): *m/z* = 322 [*M*+Na]$^+$; HR-MS: [*M*-H]$^+$ = $C_{15}H_{24}NO_5$, calcd 298.1660; found 298.1660; ^{1}H NMR ([D$_6$]DMSO, 400 MHz, ca 3:2 mixture of rotamers): *d* = 1.33 and 1.37 (s, 9H), 1.53 (m, 2H), 1.93 (m, 1H), 2.02 (m, 2H), 2.24 (m, 1H), 3.36 (m, 4H), 4.01 (m, 1H), 4.06 (dd, *J* = 17 and 8.8 Hz, 1H), 4.93 (dd, *J* = 10.2 and ca 1 Hz, 1H), 4.99 (ddt, *J* = 17.1, 3.6 and 1.7 Hz, 1H), 5.78 (ddt, *J* = 17.1, 10.2 and 6.6 Hz, 1H), 12.6 (br, s, 1H); ^{13}C NMR ([D$_6$]DMSO, 100 MHz, major rotamer): *d* = 27.9 (q), 28.4 (t), 29.8 (t), 35.8 (t), 51.4 (t), 57.7 (d), 67.4 (t), 76.0 (d), 79.0 (t), 115.0 (t), 138.3 (d), 153.2 (s), 174.2 (s).

Dicyclohexylamine salt (recrystallized from n-heptane): m.p.: 112 – 114 °C; $[a]_D^{20}$ = - 26.7 (c = 1.01, MeOH).

2.2.3. N-Fmoc-(2*S*,4*R*)-4-*O*- pent-4-enyl -hydroxyproline (7b): Following the procedure given for for the synthesis of **7a** this compound was prepared in quantitative yield (1.3 mmol scale) from *N*-Boc-(2*S*,4*R*)-4-*O*-pent-4-enyl-hydroxyproline (**15**) as a colorless oil. MS (ESI+): *m/z* = 444 [*M*+Na]$^+$; HR-MS: [*M*+H]$^+$= $C_{25}H_{28}NO_5$, calcd 422.1962; found 422.1962; ^{1}H NMR ([D$_6$]DMSO, 400 MHz, ca 3:2 mixture of rotamers): *d* = 1.56 (m, 2H), 1.96 and 2.10 (m, 1H), 2.28 and 2.39 (m, 1H), 3.35 – 3.55 (m, 4H, partly obscured by water signal), 4.07 (m 1H), 4.11 – 4.21 and 4.26 – 4.37 (m, 4H), 4.95 (ddt, *J* = 10.2, 2 and 1 Hz, 1H), 5.01 (ddt, *J* = 17.2, 3.6 and 2 Hz, 1H), 5.80 (m, 1H), 7.33 (m, 2H), 7.42 (m, 2H), 7.65 (m, 2H), 7.89 (m, 2H), 12.4 (br. s, 1H); ^{13}C NMR ([D$_6$]DMSO, 100 MHz, major rotamer): *d* = 28.8 (t), 30.2 (t), 35.4 (t), 46.9 (d), 51.8 (t), 58.1 (d), 66.9 (t), 67.8 (t), 77.0 (d), 115.3 (t), 120.5 (d), 125.6 (d), 127.5 (d), 128.1 (d), 138.6 (d), 141.1 (s), 144.1 (s), 154.4 (s), 173.7 (s).

2.3. Synthesis of Fmoc-Ser(Allyl)-OH (8)



a) NaH, allyl bromide; b) LiOH; c) 1. TFA, 2. FmocOSu

2.3.1. *N*-Boc-*O*-allyl-(*L)*-serine allyl ester (16): Following the procedure given for for the synthesis of **12,** this compound was prepared from *N*-Boc-(*L*)-serine (2.00 g, 9.75 mmol), 95 % sodium hydride (542 mg, 21.5 mmol), and allyl bromide (2.25 mL, 25.5 mmol) as a colorless oil, yield = 1.82 g (65 %). MS (ESI+): *m/z* = 308 [M+Na]$^+$; HR-MS: [M+Na]$^+$ = $C_{14}H_{23}NO_5Na$, calcd 308.1468; found 308.1468; ^{1}H NMR (CDCl$_3$, 400 MHz): *d* = 1.45 (s, 9H), 3.66 (dd, *J* = 9.4 and 3.3 Hz, 1H), 3.89 (dd, *J* = 9.4 and 3.0 Hz, 1H), 3.95 (dddd, *J* = 13.0, 5.5, 1.3 and 1.3 Hz, 1H), 4.0 (dddd, *J* = 13.0, 5.7, 1.3 and 1.3 Hz, 1H), 4.45 (m, 1H), 4.63 (dddd, *J* = 13.5, 5.5, 1.3 and 1.3 Hz, 1H), 4.70 (dddd, *J* = 13.5, 5.5, 1.3 and 1.3 Hz), 5.18 (ddd, *J* = 10.4, 2.9 and 1.3 Hz, 1H), 5.33 (ddd, *J* = 17.2, 2.9 and 1.3 Hz, 1H), 5.24 (m, 2H), 5.85 (ddt, *J* = 17.2, 10.4 and 5.5 Hz, 1H), 5.85 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz): *d* = 28.7 (q), 54.5 (d), 66.3 (t), 70.4 (t), 72.6 (t), 117.8 (t), 118.8 (t), 132.1 (d), 134.4 (d), 170.8 (s). $C(CH_3)_3$ and COO*t*Bu signals were hidden in the noise.

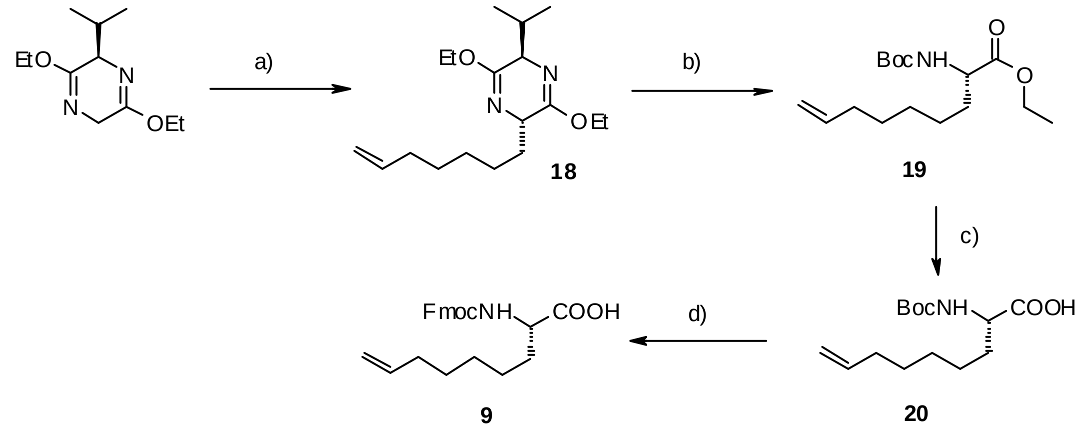
2.3.2. *N*-Boc-*O*-allyl-(*L*)-serine (17): Following the procedure given for for the synthesis of **13**, this compound was prepared in 99 % yield (6 mmol scale) from *N*-Boc-*O*-allyl-(*L*)-serine allyl ester (**16**) as a colorless oil. MS (ESI+): *m/z* = 246 [MH$^+$], 268 [M+Na]$^+$; HR-MS: [M-H]$^+$ = $C_{11}H_{18}NO_5$, calcd 244.1191; found 244.1191; ^{1}H NMR ([D$_6$]DMSO, 400 MHz): *d* = 1.36 (s, 9H), 3.59 (m, 2H), 3.92 (m, 2H), 4.11 (m, 1H), 5.12 (ddd, *J* = 10.4, 3.5 and 1.4 Hz, 1H), 5.22 (ddd, *J* = 17.3, 3.5 and 1.8 Hz, 1H), 5.83 (ddt, *J* = 17.3, 10.4 and 5.4 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 12.6 (br. s, 1H); ^{13}C NMR ([D$_6$]DMSO, 100 MHz): *d* = 28.2 (q), 53.8 (d), 69.2 (t), 71.1 (t), 78.2 (s), 116.6 (t), 135.0 (d), 155.4 (d), 172.0 (s).

Dicyclohexylamine salt (recrystallized from n-heptane): m.p.: 121 – 122 °C; $[a]_D^{20}$ = + 13.0 (c = 1.0, MeOH).

2.3.3. Fmoc-Ser(Allyl)-OH (8): Following the procedure given for for the synthesis of **7a**, this compound was prepared in 99 % yield (0.8 mmol scale) from *N*-Boc-*O*-allyl-L-serine **(17)** as a colorless oil. MS (ESI+): *m/z* = 390 [M+Na]$^+$; HR-MS: [M+Na]$^+$ = $C_{21}H_{21}NO_5$-Na, calcd 390.1312; found 390.1312; ^{1}H NMR ([D$_6$]DMSO, 400 MHz): *d* = 3.65 (m, 2H), 3.97 (m, 2H), 4.22 (m, 2H), 4.28 (m, 2H), 5.15 (ddd, *J* = 10.5, 3.5 and 1.3 Hz, 1H), 5.26 (ddd, *J* = 17.3, 3.5 and 1.7 Hz, 1H), 5.88 (ddt, *J* = 17.3, 10.5 and 5.3 Hz, 1H), 7.33 (dd, *J* = 7.4 Hz, 2H), 7.42 (dd, *J* = 7.4 Hz, 2H), 7.64 (br. d, *J* = 8.2 Hz, 1H), 7.74 (d, *J* = 7.4 Hz, 2H), 7.89 (d, *J*

= 7.4 Hz, 2H), 12.6 (br. s, 1H); ^{13}C NMR ([D$_6$]DMSO, 100 MHz): *d* = 47.0 (d), 54.6 (d), 66.1 (t), 69.4 (t), 71.5 (t), 117.0 (t), 120.5, 125.7, 127.4, 128.0, 135.3 (5t), 141.1, 144.2, 156.4, 172.0 (4s).

2.4. Synthesis of *N*-Fmoc-(*S*)-2-amino-8-nonenoic acid (9)



a) n-BuLi, heptenyl bromide;b) HCl; c) LiOH; d) 1. TFA, 2. FmocOSu

2.4.1. (2*S*,5*R*)-3,6-Diethoxy-2-hept-6-enyl-5-isopropyl-2,5-dihydro-pyrazine (18): *n*-Butyllithium (1.6N in hexane, 3.25 mL, 5.2 mmol) was added dropwise to a stirred solution of (2*S*)-3,6-diethoxy-2-isopropyl-2,5-dihydro-pyrazine (1.06 g, 5 mmol) in THF (10 mL) with cooling in a dry-ice/acetone bath. After 10 min at -78 °C, 7-bromo-1-heptene (762 mL, 5 mmol) was added dropwise. After 3 h the mixture was allowed to warm to room temperature. The solvent was evaporated and the residue was partitioned between ether and water. The organic layer was dried over MgSO$_4$ and evaporated. Purification by chromatography on silica (column: Biotage Si25+S; gradient: cyclohexane/ethylacetate 100:0 to 90:10 over 8 column volumes) gave **18** (717 mg, 47%) as a colorless oil. MS (ESI+): *m/z* = 309 [*M*+H]$^+$; HR-MS: [*M*+H]$^+$ = $C_{18}H_{33}N_2O_2$, calcd 309.2537; found 309.2535; ^{1}H NMR ([D$_6$]DMSO, 400 MHz): *d* = 0.63 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 1.17 – 1.37 (m, 6H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.0 Hz, 3H), 1.64 (m, 2H), 1.96 (m, 2H), 2.19 (dsp, *J* = 6.8 and 3.4 Hz, 1H), 3.86 (dd, *J* = 3.9 and 3.4 Hz, 1H), 3.95 (dt, *J* = 6.2 and 3.9 Hz, 1H), 4.03 – 4.15 (m, 4H), 4.93 (ddt, *J* = 10.3, 3.2 and ca 2 Hz, 1H), 4.98 (ddt, *J* = 17.1, 6.7 and ca 2 Hz, 1H), 5.78 (ddt, *J* = 17.1, 10.3 and 6.7 Hz, 1H); ^{13}C NMR ([D$_6$]DMSO, 100 MHz): *d* = 14.6 (q), 14.7 (q), 16.8 (q), 19.5 (q), 24.2 (t), 28.5 (t), 28.7 (t), 31.5 (d), 33.4 (t), 33.9 (t), 55.0 (d), 60.1(d), 2x 60.4 (2t), 115.1 (t), 139.2 (d), 162.5 (s), 163.2 (s).

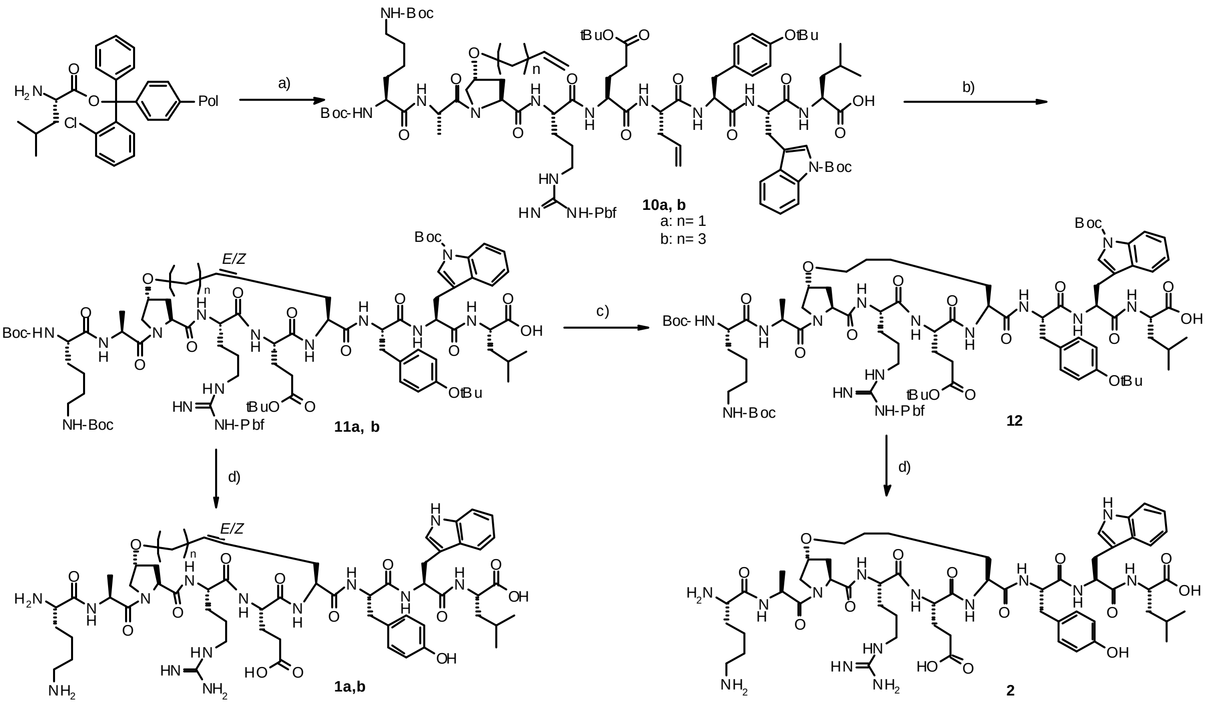
2.4.2. *N*-Boc-(S)-2-amino-8-nonenoic acid ethyl ester (19): A solution of **18** (589 mg, 1.9 mmol) in 1N hydrochloric acid (5 mL) and acetonitrile (5 mL) was stirred at room temperature. After 1 h TLC (cyclohexane/ethyl acetate 9:1) indicated complete consumption of the starting material. The solution was evaporated to approx. half its volume, diluted with water and washed with ether. The aqueous layer was made alkaline by addition of aq. ammonia. The resulting mixture was extracted three times with ether, the combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated to yield a mixture of (*S*)-2-amino-8-nonenoic acid ethyl ester and L-valine ethyl ester as a yellow oil. This mixture was disolved in dioxane (5 mL) and Boc_2O (500 mg, 2.3 mmol) was added with stirring at room temperature. After 4h the mixture was evaporated and the residue was purified by chromatography on silica (Biotage Si 40+S column; gradient: cyclohexane/ ethylacetate 95:5 to 80:20 over 5 column volumes) to yield **19** (375 mg, 66 %) as a colorless oil. MS (ESI+): *m/z* = 322 $[M+Na]^+$, 621 $[2M+Na]^+$; HR-MS: $[M+Na]^+$ = $C_{16}H_{29}NO_4Na$, calcd 322.1989; found 322.1989; ^1H NMR ($[D_6]$DMSO, 400 MHz): *d* = 1.15 (t, *J* = 7.1Hz, 3H), 1.19 – 1.33 (m, 6H), 1.36 (s, 9H), 1.55 (m, 2H), 1.98 (m, 2H), 3.86 (m, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 4.92 (dd, *J* = 10.2 and 1.2 Hz, 1H), 4.98 (ddt, *J* = 17.2, 3.2 and ca 2 Hz, 1H), 5.76 (ddt, *J* = 17.2, 10.2 and 6.7 Hz, 1H), 7.16 (br. d, *J* = 7.6 Hz, 1H).

2.4.3. *N*-Boc-(*S*)-2-amino-8-nonenoic acid (20): Following the procedure given for for the synthesis of **13** this compound was prepared in quantitative yield (1.2 mmol scale) from *N*-Boc-(*S*)-2-amino-8-nonenoic acid ethyl ester (**19**) as a colorless oil. MS (ESI+): *m/z* = 272 $[M+H]^+$; HR-MS: $[M+Na]^+$ = $C_{14}H_{25}NO_4Na$, calcd 294.1676; found 294.1676; ^1H NMR ($[D_6]$DMSO, 400 MHz): *d* = 1.21 – 1.35 (m, 6H), 1.36 (s, 9H), 1.47 – 1.52 (m, 2H), 1.97 (m, 2H), 3.81 (m, 1H), 4.92 (ddt, *J* = 10.2, 2.2 and 1 Hz, 1H), 4.97 (ddt, *J* = 17.2, 3.7 and 2.2 Hz, 1H), 5.77 (ddt, *J* = 17.2, 10.2 and 6.7 Hz), 6.96 (d, *J* = 7.8 Hz).

Dicyclohexylamine salt (recrystallized from n-heptane): m.p.: 82 - 84 °C; $[a]_D^{21}$ = + 11.9 (c = 0.52, MeOH).

2.4.4. *N*-Fmoc-(*S*)-2-amino-8-nonenoic acid (9): Following the procedure given for for the synthesis of **7a** this compound was prepared in 85 % yield (1 mmol scale) from *N*-Boc-(*S*)-2-amino-8-nonenoic acid (**20**) as a colorless solid. MS (ESI+): *m/z* = 416 $[M+Na]^+$; HR-MS: $[M+Na]^+$ = $C_{24}H_{27}NO_4Na$, calcd 416.1832; found 416.1832; ^1H NMR ($[D_6]$DMSO, 500 MHz): *d* = 1.30 – 1.46 (m, 6H), 1.55 – 1.70 (m, 2H), 1.98 (m, 2H), 3.90 (m, 1H), 4.21 (m, 1H), 4.25 (m, 2H), 4.92 (d, *J* = 10.1 Hz, 1H), 4.97 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.77 (ddt, *J* = 17.1, 10.1, 6.6 Hz, 1H), 7.31 (dd, *J* = 7.4 Hz, 2H), 7.40 (dd, *J* = 7.4 Hz, 2H), 7.58 (d, *J* = 8 Hz, 1H), 7.70 (dd, *J* = 7.4, 2.3 Hz, 2H), 7.87 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR ($[D_6]$DMSO, 125 MHz): *d* = 25.8 (t), 28.4 (t), 28.5 (t), 31.2 (t), 33.5 (t), 47.1 (d), 54.2 (d), 66.0 (t), 115.1 (t), 120.5 (d), 125.7 (d), 127.5 (d), 128.1 (d), 139.2 (d), 141.2 (s), 144.3 (s), 156.6 (s), 174.4 (s).

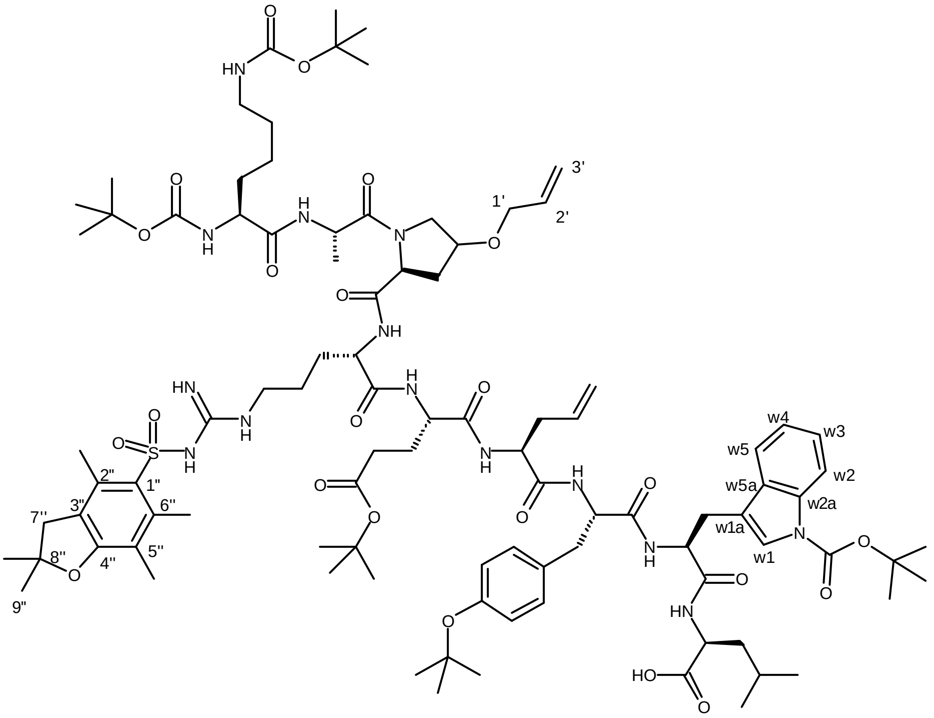
3. Synthesis of cyclic peptides 1a and 2



a) Fmoc-AA-OH, HBTU, HOBt, *i*Pr_2NEt, *N*-methyl pyrrolidone, RT, 1h; b) [$RuCl_2(PCy_3)_2(=CHPh)$], CH_2Cl_2, reflux; c) H_2, Pd/C, EtOH, rt; d) CF_3COOH/(*i*Pr)$_3$SiH/H_2O (v/v/v) = 95/2.5/2.5.

3.1. N-Boc-Lys(Boc)-Ala-(4*R*)Hyp(4-OAllyl)-Arg(Pbf)-Glu(O*t*Bu)-Allylgly-Tyr(*t*Bu)-Trp(Boc)-Leu (10a): H-Leu-2-Cl-Trt resin (150 mg, loading: 0.74 mmol/g) was placed in a 50 mL solid phase reactor and swelled with NMP (5 mL). To a solution of HBTU (155 mg, 0.4 mmol), HOBt-monohydrate (83 mg, 0.53 mmol) and Fmoc-Trp(Boc)-OH (239 mg, 0.44 mmol) in 5 mL NMP was added diisopropyl ethyl amine (155 µL, 0.89 mmol) and the resulting solution was stirred at room temperature for 2 min. This solution was added to the resin and shaken at room temperature for 1 h. The solvent was then filtered off and the resin was washed thoroughly with DMF (5 x 5 mL) and NMP (5 x 5 mL). The N-terminal Fmoc group was cleaved by double treatment with 20% piperidine in NMP (5 mL) followed by washing with NMP (10 x 5 mL). This coupling/Fmoc-deprotection procedure was repeated with Fmoc-Tyr(*t*Bu)-OH (209 mg, 0.44 mmol), Fmoc-Allylgly-OH (153 mg, 0.44 mmol), Fmoc-Glu(O*t*Bu)-OH dihydrate (199 mg, 0.44 mmol), Fmoc-Arg(Pbf)-OH (294 mg, 0.44 mmol), **6a** (178 mg, 0.44 mmol), Fmoc-Ala-OH monohydrate (149 mg, 0.44 mmol) and Boc-Lys(Boc)-OH dicyclohexylammonium salt (239 mg, 0.44 mmol). After the last couplimg step the resin was thoroughly washed with DMF, dichloromethane, methanol and finally again with dichloromethane (5 x 5 mL of each) and dried in vacuo for 30 min. The resin was swelled by addition of dichloromethane and treated for10 min each with dichloromethane/TFE/acetic acid 3:1:1 (*v/v/v*, 5 x 5 mL). The resin was finally rinsed with dichloromethane/TFE 1:1 (*v/v*, 5 mL) and the combined filtrates were co-evaporated with toluene. The crude product was purified by preparative HPLC followed by lyophilisation to yield 159 mg (76 %) of 10a as a fluffy, colorless solid. HPLC: t_R = 7.37 min, purity > 99 %; MS (ESI+): *m/z* = 963 [*M*+2Na] $^{2+}$, 1881 [*M*+H]$^+$, 1902 [*M*+Na]$^+$, 1925 [*M*-H+2Na]$^+$; HR-MS: [*M*H]$^+$ = $C_{95}H_{143}N_{14}O_{23}S$, calcd 1880.0166; found1880.0171; [*M*+Na]$^+$ = $C_{95}H_{142}N_{14}O_{23}SNa$, calcd 1901.9985; found 1901.9985

Table S1: ^{1}H (500 MHz) and ^{13}C (100 MHz) NMR data of **10a** in [D_6]DMSO



Amiono acid	**Position**	*d* (**^{1}H**)	*d* (**^{13}C**)
Lysine (K)	α–NH	6.77 (d, *J*= 7.8 Hz)	
	C_α	3.85	54.20
	C_β	1.51 + 1.41	31.68
	$C_?$	1.24 + 1.18	22.93
	C_δ	1.30	29.26
	C_ε	2.84	39.6
	ε-NH	6.69 (t, *J* = 5.5 Hz)	
Alanine (A)	NH	7.92 (d, *J* = 8.0 Hz)	
	C_α	4.50	46.13
	C_β	1.13 (d, *J* = 6.9 Hz)	17.11
Hydroxyproline	C_α	4.35 (t, *J* = 7.8 Hz)	58.45
(Hyp)	C_β	2.12 + 1.88	34.76
	C_γ	4.13	76.58

	C_δ	3.70 (br.d, *J* = 11.0 Hz)	51.94
	C_δ	3.61 (br.dd, *J* = 11.0 + 4.1 Hz)	
	1’	3.93	69.04
	2’	5.83	135.10
	3’a	5.21 (dd, *J* = 17.2 + 1.6 Hz)	116.54
	3’b	5.10 (dd, *J* = 10.5 + 1.6 Hz)	
Arginine (R)	NH	8.05 (d, *J* = 7.6 Hz)	
	C_α	4.12	52.53
	C_β	1.63 + 1.47	28.8
	C_γ	1.42	25.4
	C_δ	3.00	40.0
	C_ε		
	1’’		134.3
	2’’		131.50
	3’’		124.36
	4’’		157.52
	5’’		116.30**
	6’’		137.33
	7’’		42.54
	8’’		86.33
	9’’	1.38 (s, 6H)	28.26
	2’’-Me	2.40 (s, 3H)	19.01
	5’’-Me	1.97 (s, 3H)	12.33
	6’’-Me	2.45 (s, 3H)	17.65
Glutamic acid (E)	NH	7.78 (d, *J* = 8.0 Hz)	
	C_α	4.18	51.69
	C_β	1.83 + 1.66	27.36
	C_γ	2.15	31.23
Allylgylcine	NH	7.75 (d, *J* = 8.2 Hz)	
	C_α	4.23	52.15*
	C_β	2.28 and 2.15	36.13
	C_γ	5.56	134.00
	C_δ	4.93 (d, *J* = 17.4 Hz)	117.41
	C_δ	4.86 (d, *J* = 10.5 Hz)	
Tyrosine (Y)	NH	7.89 (d, *J* = 8.0 Hz)	
	C_α	4.40	54.00

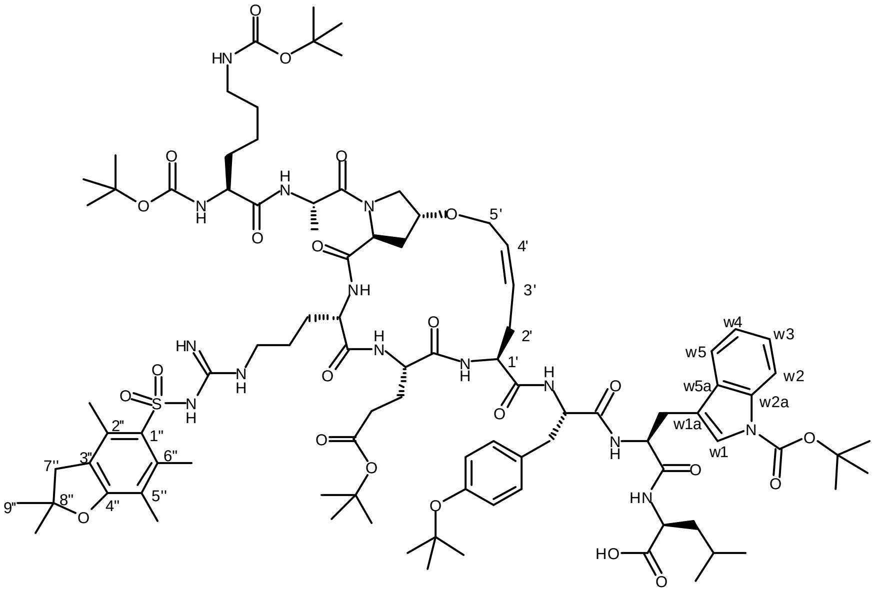
	C_β	2.87	36.39
	C_β	2.70 (dd, J = 14.2 and 8.7 Hz)	
	$C_?$		132.10
	C_δ	6.98 (d, J = 8.5 Hz)	129.62
	C_ε	6.73 (d, J = 8.5 Hz)	123.32
	C		153.43
Tryptophane	NH	8.02 (d, J = 7.7 Hz)	
(W)	C_α	4.65	52.06*
	C_β	3.08 (dd, J = 14.9 and 4.6 Hz) and 2.91	27.61
	C_1	7.51 (s)	124.16
	C_{1a}		116.26**
	C_2	8.00 (d, J = 7.6 Hz)	114.65
	C_{2a}		134.74
	C_3	7.29 (t, J =7.6 Hz)	124.29
	C_4	7.22 (t, J = 7.6 Hz)	122.46
	C_5	7.67 (d, J = 7.6 Hz)	119.49
	C_{5a}		130.44
Leucine (L)	NH	8.25 (d, J = 7.8 Hz)	
	$C_?$	4.25	50.35
	C_β	1.52	40.1
	C_γ	1.61	24.33
	C_δ	0.87 (d, J = 6.6 Hz)	22.91
	C_δ	0.83 (d, J = 6.6 Hz)	21.40
	COOH	12.4-12.7 (br.s)	
COO and CON:			173.81, 171.80, 171.74, 171.45, 171.36, 170.94, 170.83, 170.75, 170.62, 170.48
Boc-NCO			156.10, 155.62, 155.37, 149.10
t-Bu-Cq			83.43, 79.68, 78.05, 77.57, 77.38
tBu-CH_3		1.56, 1.34, 1.33, 1.21	28.59, 28.35, 27.78, 27.74

*), **) : interchangeable

3.2. Peptide 11a: To a solution of 10a (69 mg, 36 µmol) in dry dichloromethane was added 1st generation Grubbs catalyst (6 mg, 7.2 µmol) under inert conditions and the solution was heated to reflux. Monitoring the reaction by HPLC indicated complete consumption of the starting material after 16 h. After cooling the mixture was evaporated and the residue was purified by preparative HPLC followed by lyophilisation to yield **11a** (17.3 mg, 26 %) as a fluffy white solid. HPLC: two partially resolved peaks, t_R = 7.09 and 7.15 min, purity > 96 %; MS (ESI+): *m/z* = 949 [*M*+2Na]$^{2+}$, 1874 [*M*+Na]$^+$ 1896 [*M*-H+2Na]$^+$; HR-MS: [*M*+H]$^+$ = $C_{93}H_{139}N_{14}O_{23}S$, calcd 1851.9853; found 1851.98589 [*M*+Na]$^+$ = $C_{93}H_{138}N_{14}O_{23}SNa$, calcd 1873.9672; found 1873.9670.

NMR (Table S2) shows a 1:1-mixture of two sets of signals. One signal set is consistent with a *Z* double bond (positive ROESY-crosspeak between H-3' and H-4'). Overlapping resonances [*d*(H-3', H-4') = 5.33 ppm] prohibit an unambiguous assignment of the double bond geometry of the second signal set. Both sets of signals remain intact at *T* = 350 K; this indicates the presence of *E/Z*-isomers rather than rotamers.

Table S2: ^{1}H (500 MHz) and ^{13}C (100 MHz) NMR data of **11a** in [D$_6$]DMSO



Amino Acid	position	*d* (^{1}H)*	*d* (^{13}C)*
Lysine (K)	α-NH	6.38	
	C?	3.86	54.15
	Cβ	1.53 and 1.40	31.80
	Cγ	1.20	22.94
	Cδ	1.30	29.33
	Cε	2.85	39.70
	ε-NH	6.70	
Alanine (A)	NH	7.90 // 7.67	
	Cα	4.46 // 4.24	45.93 // 45.70
	Cβ	1.15 (d, *J* = 6.4 Hz) //	17.02 // 16.91

		1.13 (d, J = 6.4 Hz)	
Hydroxyproline (Hyp)	C_{α}	4.38	57.92 // 57.57
	C_{β}	2.07 and 1.86 // 1.91	35.14 // 34.55
	C_{γ}	4.20	76.67 // 72.71
	C_{δ}	3.79 and 3.21 // 3.77 and 3.41	51.25 // 52.44
Arginine (R)	NH	8.19	
	C_{α}	4.14 // 4.02	52.22 // 52.83
	C_{β}	1.60	28.2
	C_{γ}	1.42	25.56
	C_{δ}	3.03	40.00
	C_{ε}		
	1’’		134.30
	2’’		131.50
	3’’		124.38
	4’’		157.52
	5’’		116.30**
	6’’		137.35
	7’’	2.94	42.57
	8’’		86.35
	9’’	1.39	
	2’’-Me	2.41	19.03
	5’’-Me	1.99	12.34
	6’’-Me	2.46	17.67
Glutamic acid (E)	NH	8.02 and 7.88	
	C_{α}	4.27 and 4.21	51.62 // 51.91
	C_{β}	2.03 and 1.50 // 2.03 and 1.60	27.10 // 26.40
	C_{γ}	2.07 and 1.95	30.5
Tyrosine (Y)	NH	8.07 // 7.96	
	C_{α}	4.45 // 4.41	54.15
	C_{β}	2.88 and 2.69	36.97
	C_{γ}		132.21
	C_{δ}	7.02 (d, J= 8.5 Hz)	129.71 // 129.66
	C_{ε}	6.75 (d, J = 8.5 Hz)	123.31 // 123.28
	C		153.49 // 153.46

Tryptophane	NH	8.11	
(W)	C_α	4.71 // 4.65	51.93 // 52.14
	C_β	3.09 and 2.92	27.66
	C_1	7.53 // 7.52	123.98
	C_{1a}		116.25**
	C_2	8.01	114.67
	C_{2a}		134.74
	C_3	7.29	124.31
	C_4	7.22	122.47
	C_5	7.69 (d, *J* = 8.0 Hz) // 7.66 (d, *J* = 8.0 Hz)	119.51
	C_{5a}		130.48 // 130.45
Leucine (L)	NH	8.29	
	C_α	4.25	50.38
	C_β	1.52	40.1
	C_γ	1.61	24.36
	C_δ	0.87 (d, J= 6.4 Hz)	22.91
	C_δ	0.83 (d, J= 6.4 Hz)	21.42
1’-NH		7.61 (d, *J* = 8.5 Hz) // 7.25	
1’		4.36 // 4.33	51.96 // 51.22
2’		2.30 + 2.15 // 2.25	30.60 // 34.10
3’		5.26 // 5.33	128.09 // 129.18
4’		5.44 // 5.33	130.26 // 130.03
5’		4.05 and 3.94 // 3.87 and 3.63	65.07 // 68.54
COO bzw. CON			173.85, 173.82, 171.72, 171.52, 171.46, 171.26, 171.14, 170.82, 170.69, 170.63, 170.43
Boc-NCO			156.14, 155.64, 155.37, 149.11
*t*Bu-Cq			83.46, 80.75, 80.71, 78.04, 77.62, 77.41
9’’ + tBu-CH$_3$		1.56, 1.35, 1.22	28.61, 28.38, 28.36, 28.28, 27.74, 27.67

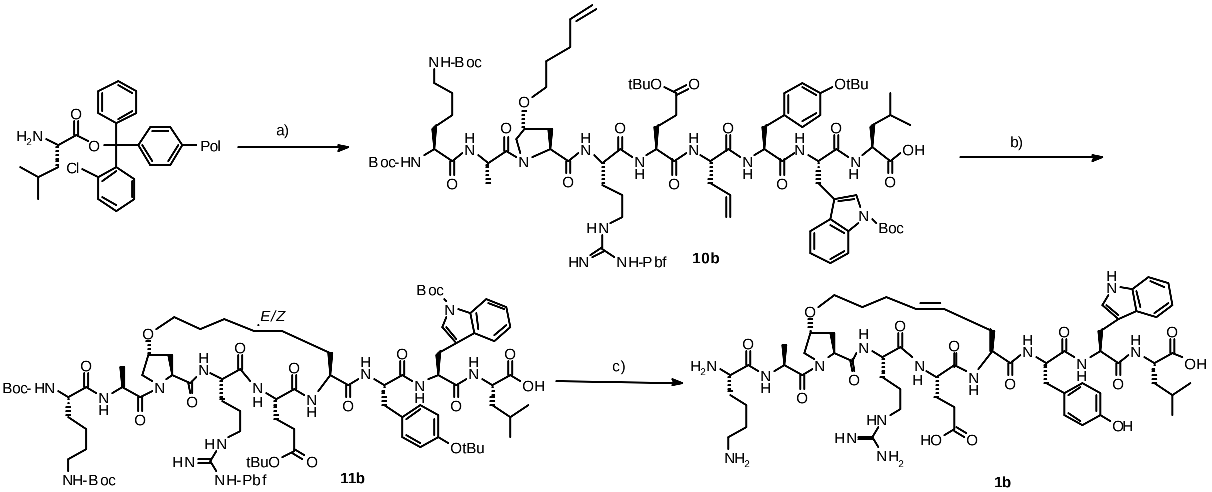
*) the two signal sets are separated by // **) interchangeable

3.3. Peptide 12: A mixture of 11a (10.0 mg, 5.4 µmol) and 10 % Pd/C (1.0 mg) in methanol (5mL) was stirred under an atmosphere of hydrogen at room temperature for 16 h. The mixture was filtered through celite and the filter cake was thoroughly washed with methanol. The combined filtrates were evaporated and the residual oil was taken up in dioxane/water and subjected to lyophilisation to yield peptide 12 (10.0 mg, 100 %) as a fluffy white solid. ^{1}H NMR confirmed the absence of olefinic protons. HPLC: t_R = 7.02 min, purity = 95 %; MS (ESI+): *m/z* = 950 $[M+2Na]^{2+}$, 1876 $[M+Na]^+$ 1898 $[M\text{-}H+2Na]^+$; HR-MS: $[M+Na]^+$ = $C_{93}H_{140}N_{14}O_{23}SNa$, calcd 1875.9829; found 1875.9834; $[M\text{-}H+2Na]^+$ = $C_{93}H_{139}N_{14}O_{23}SNa_2$, calcd 1897.9648; found 1897.9643.

3.4. Peptide 1a: Peptide 11a (10.0 mg, 2.7 µmol) was dissolved in TFA/TIS/H_2O 95:2.5:2.5 (*v/v/v*, 2 mL) and the solution was stirred at room temperature for 5 h. The mixture was then cooled in an ice bath and cold diethyl ether was added until precipitation commenced. The mixture was kept at 4 °C overnight, the solids were then isolated by centrifugation. The pellet was washed with cold ether and taken up in aqueous dioxane. Lyophilisation gave **1a** (6.4 mg, quant.) as a colorless, fluffy solid. HPLC: t_R = 3.15 min, purity = 80 %; MS (ESI+): *m/z* = 594 $[M+2H]^{2+}$, 1187 $[MH]^+$; HR-MS: $[MH]^+$ = $C_{57}H_{83}N_{14}O_{14}$, calcd 1187.62077; found 1187.62044.

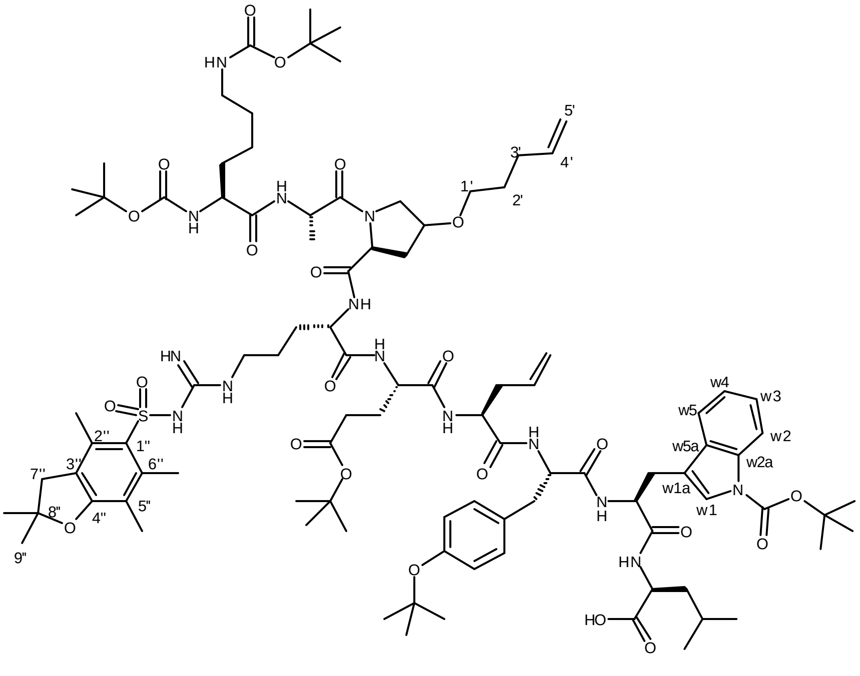
3.5. Peptide 2: Peptide 2 was prepared in quantitative yield by treating 12 (12.9 mg, 6.9 µmol) with TFA:TIS:H_2O 95:2.5:2.5 (2 mL) following the protocol given for the synthesis of **1a**. HPLC: t_R = 3.006 min, purity = 96 %; MS (ESI+): *m/z* = 595 $[M+2H]^{2+}$, 1189 $[MH]^+$; HR-MS: $[MH]^+$ = $C_{57}H_{85}N_{14}O_{14}$, calcd 1189.63642; found 1189.63567; $[M+Na]^+$ = $C_{57}H_{84}N_{14}O_{14}Na$, calcd 1211.61836; found 1211.61854.

4. Synthesis of cyclic peptide 1b



a) Fmoc-AA-OH, HBTU, HOBt, *i*Pr_2NEt, *N*-methyl pyrrolidone, rt, 1h; b) [$RuCl_2(PCy_3)_2$(=CHPh)], CH_2Cl_2, reflux; c) $CF_3COOH/(iPr)_3SiH/H_2O$ (v/v/v) = 95/2.5/2.5.

4.1. N-Boc-Lys(Boc)-Ala-(4R)Hyp(4-pent-5-enyl)-Arg(Pbf)-Glu(OtBu)-Allylgly-Tyr-(*t*Bu)-Trp(Boc)-Leu (10b): Peptide **10b** was prepared in 67 % yield (0.11 mmol scale) by the protocol given for the synthesis of **10a**. HPLC: t_R = 7.59 min, purity > 99 %; MS (ESI+): *m/z* = 977 [*M*+2Na] $^{2+}$, 1908 [*M*+H]$^+$, 1930 [*M*+Na]$^+$; HR-MS: [*M*+H]$^+$ = $C_{97}H_{147}N_{14}O_{23}S$, calcd 1908.0479; found 1908.0474; [*M*+Na]$^+$ = $C_{97}H_{146}N_{14}O_{23}SNa$, calcd 1930.0298; found 1930.0300.



Amino acid	position	*d* (^{1}H)	*d* (^{13}C)
Lysine (K)	α-NH	6.79 (d, *J* = 8.3 Hz)	

	C_α	3.85	54.21
	C_β	1.52 and 1.40	31.24
	C_γ	1.22	22.96
	C_δ	1.30	29.29
	C_ε	2.84	39.75
	ε-NH	6.72	
Alanine (A)	NH	7.93 (d, *J* = 7.2 Hz)	
	C_α	4.49	46.17
	C_β	1.13 (d, *J* = 6.8 Hz)	17.15
Hydroxyproline	C_α	4.34	58.48
(Hyp)	C_β	2.10 and 1.87	34.80
	C_γ	4.06	77.00
	C_δ	3.66 (br.d, *J* = 11.2 Hz) 3.60 (br.dd, *J* = 11.2 and 4.2 Hz)	51.95
	1’	3.35	67.58
	2’	1.53	28.60
	3’	2.01	29.87
	4’	5.77 (ddt, *J*= 17.1, 10.3 and 6.6 Hz)	138.30
	5’a	4.97 (d, *J* = 17.1 Hz)	115.02
	5’b	4.92 (d, *J* = 10.3 Hz)	
Arginine (R)	NH	8.07 (d, *J* = 7.7 Hz)	
	C_α	4.12	52.58
	C_β	1.63 and 1.46	28.82
	C_γ	1.42	25.34
	C_δ	3.01	40.10
	ε–NH	6.60 - 6.30	
	1’’		134.31
	2’’		131.52
	3’’		124.39
	4’’		157.54
	5’’		116.28
	6’’		137.36
	7’’	2.92	42.56
	8’’		86.36
	9’’	1.38	28.36
	2’’-Me	2.40	19.04

	5''-Me	1.97	12.35
	6''-Me	2.45	17.68
Glutamic acid (E)	NH	7.79	
	C_α	4.18	51.70
	C_β	1.83 and 1.66	27.45
	C_γ	2.16	31.24
Allyl glycine	NH	7.77	
	C_α	4.22	52.17*
	C_β	2.28 and 2.15	36.14
	C_γ	5.56 (ddt, *J* = 17.1, 10.2 and 6.8 Hz)	134.03
	C_δ	4.93 (d, *J* = 17.1 Hz) 4.85 (d, *J* = 10.2 Hz)	117.43
Tyrosine (Y)	NH	7.91 (d, *J* = 8.1 Hz)	
	C_α	4.40	54.02
	C_β	2.87 and 2.70 (dd, *J* = 14.3 and 9.0 Hz)	36.96
	C_γ		132.13
	C_δ	6.99 (d, *J* = 8.3 Hz)	129.65
	C_ε	6.73 (d, *J* = 8.3 Hz)	123.35
	C		153.45
Tryptophane (W)	NH	8.04 (d, *J* = 8.1 Hz)	
	C_α	4.65	52.07*
	C_β	3.08 (dd, *J* = 14.8 and 4.4 Hz) and 2.91 (dd, *J* = 14.8 and 6.8 Hz)	27.63
	C_1	7.51	124.18
	C_{1a}		116.72
	C_2	8.00 (d, *J* = 7.9Hz)	114.68
	C_{2a}		134.75
	C_3	7.29 (t, *J* = 7.9Hz)	124.32
	C_4	7.22 (t, *J* = 7.9Hz)	122.49
	C_5	7.68 (d, *J* = 7.9Hz)	119.51
	C_{5a}		130.46
Leucine (L)	NH	8.29 (d, *J* = 7.9Hz)	

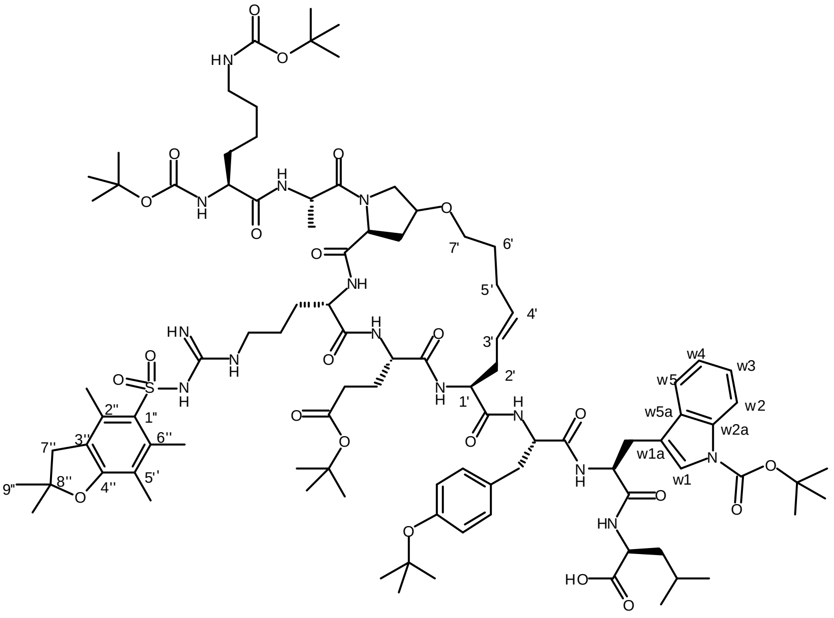
C_α	4.25	50.37
C_β	1.52	40.10
C_γ	1.62	24.35
C_δ	0.87 (d, J = 6.4 Hz)	22.94
C_δ	0.83 (d, J = 6.4 Hz)	21.42
COO and. CON		173.85, 171.63, 171.49, 171.44, 170.86, 170.78, 170.64, 170.50
Boc-NCO and NH=C(NH-)$_2$		56.12, 155.64, 155.40, 149.12
*t*Bu-Cq		83.45, 79.70, 78.07, 77.59
*t*Bu-CH_3:	1.56, 1.34, 1.33, 1.20	28.60, 28.27, 27.79, 27.75

*) interchangeable

4.2. Peptide 11b: Peptide **11b** was prepared from **10b** in 44 % yield (25 µmol scale) by the protocol given for the synthesis of **11a** using 20 mol% 1st generation Grubbs catalyst and a reaction time of 3.5 h. HPLC: t_R = 7.27 min, purity > 99 %; MS (ESI+): m/z = 962 $[M+2Na]^{2+}$, 1880 $[MH]^+$, 1902 $[M+Na]^+$; HR-MS: $[MH]^+$ = $C_{95}H_{143}N_{14}O_{23}S$, calcd 1880.0166; found 1880.0176; $[M+Na]^+$ = $C_{95}H_{142}N_{14}O_{23}SNa$, calcd 1901.9986; found 1901.9971; $[M\text{-}H+Ca]^+$ = $C_{95}H_{141}N_{14}O_{23}SCa$, calcd 1917.9635; found 1917.9631.

The NMR of this material (Table S3) shows a 9:1-mixture of two sets of signals. In other experiments using the same catalyst a ratio of up to 20:1 was found. The main component has an *E* double bond as deduced from the coupling constant ($J_{3',4'}$= 15.4 Hz). The relevant signals of the minor component could not be unambiguously assigned due to a high signal/noise ratio. Both sets of signals remain intact at T = 350 K which indicates the presence of a *Z* isomer rather than rotamers as minor component.

Table S3: ^{1}H (500 MHz) and ^{13}C (100 MHz) NMR data of **11b** in [D$_6$]DMSO (main component only)



Amino acid	**Position**	*d* (**^{1}H)***	*d* (**^{13}C)***
Lysine (K)	α-NH	6.77	
	C_α	3.85	54.20
	C_β	1.52 and1.41	31.63
	C_γ	1.25 and 1.18	22.88
	C_δ	1.30	29.40
	C_ε	2.85	39.69
	ε-NH	6.50 – 6.30	
Alanine (A)	NH	7.90	
	C_α	4.43	45.88
	C_β	1.13	17.09
Hydroxyproline (P)	C_α	4.40	57.84
	C_β	2.29 and 1.89	34.67
	C_γ	4.07	76.05
	C_δ	3.84 and 3.24	50.89
Arginine (R)	NH	8.35	
	C_α	3.91	54.20
	C_β	1.67 and 1.50	28.5
	C_γ	1.46	25.84
	C_δ	3.03	39.96

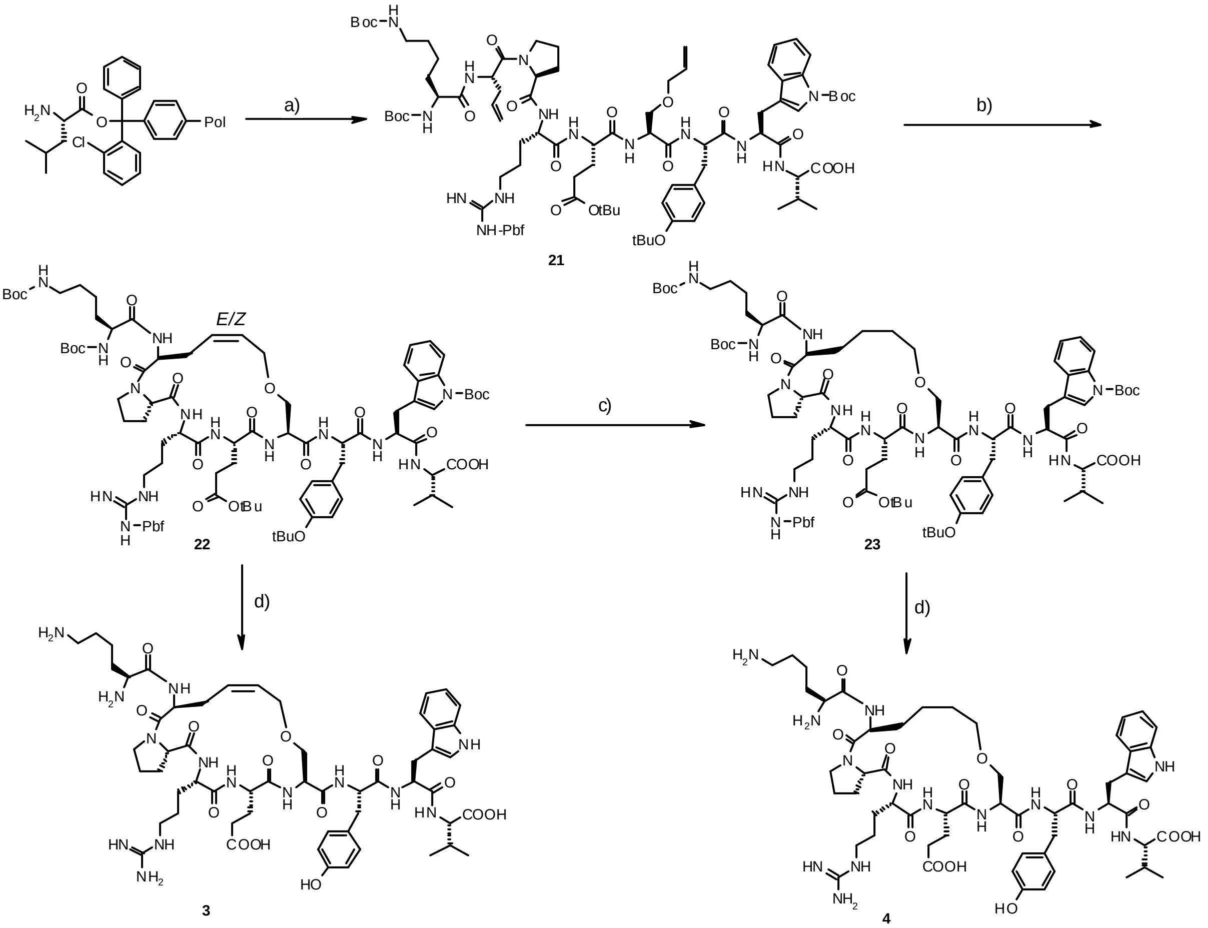
	ε–NH	6.80 – 6.30	
	1’’		134.22
	2’’		131.45
	3’’		124.30
	4’’		157.51
	5’’		116.25
	6’’		137.25
	7’’	2.94	42.57
	8’’		86.31
	9’’	1.39	
	2’’-Me	2.41	19.00
	5’’-Me	1.99	12.31
	6’’-Me	2.47	17.66
Glutamic acid (E)	NH	7.33	
	C_α	4.27	50.90
	C_β	1.85 and 1.68	28.20
	C_γ	2.12	30.82
Tyrosine (Y)	NH	8.09	
	C_α	4.43	54.11
	C_β	2.88 and 2.74	36.78
	C_γ		132.2
	C_δ	7.00 (d, *J* = 8.2 Hz)	129.54
	C_ε	6.75 (d, *J* = 8.2 Hz)	123.35
	C		not detected
Tryptophane (W)	NH	8.02	
	C_α	4.65	52.26
	C_β	3.08 and 2.90	27.65
	C_1	7.53	124.17
	C_{1a}		116.2
	C_2	8.00 (d, *J* = 8.0 Hz)	114.77
	C_{2a}		134.6
	C_3	7.30 (t, *J* = 8.0 Hz)	124.32
	C_4	7.23 (t, *J* = 8.0 Hz)	122.41
	C_5	7.69 (d, *J* = 8.0 Hz)	119.51
	C_{5a}		130.3
Leucine (L)	NH	8.26	

	C_α	4.23	50.60
	C_β	1.52	40.25
	C_γ	1.63	24.37
	C_δ	0.88 (d, *J* =6.4 Hz)	22.89
	C_δ	0.84 (d, *J* =6.4 Hz)	21.51
	NH	8.14	
	1’	4.17	53.00
	2’	2.27 and 2.12	29.50
	3’	5.15	124.88
	4’	5.27	131.88
	5’	2.19 and 1.85	23.06
	6’	1.45	28.4
	7’	3.37 and 3.26	68.30
$\underline{C}$OO, $\underline{C}$ON, Boc-N$\underline{C}$O			not detected
*t*Bu-Cq			83.38, 79.68, 77.45
9’’ and *t*Bu-$\underline{C}H_3$		1.56, 1.35, 1.33, 1.22	28.58, 28.35, 28.27, 27.75

*) major component only

4.3. Peptide 1b: Peptide **1b** was prepared in quantitative yield by treating **11b** (12 mg, 6.3 µmol) with TFA/ TIS/H_2O 95:2.5:2.5 (2 mL) following the protocol given for the synthesis of 1a. HPLC: t_R = 3.36 min, purity = 93 %; MS (ESI+): *m/z* = 608 $[M+2H]^{2+}$, 1215 $[MH]^+$; HR-MS: $[MH]^+$ = $C_{59}H_{87}N_{14}O_{14}$, calcd 1215.65207; found 1215.65215.

5. Synthesis of cyclic peptides 3 and 4

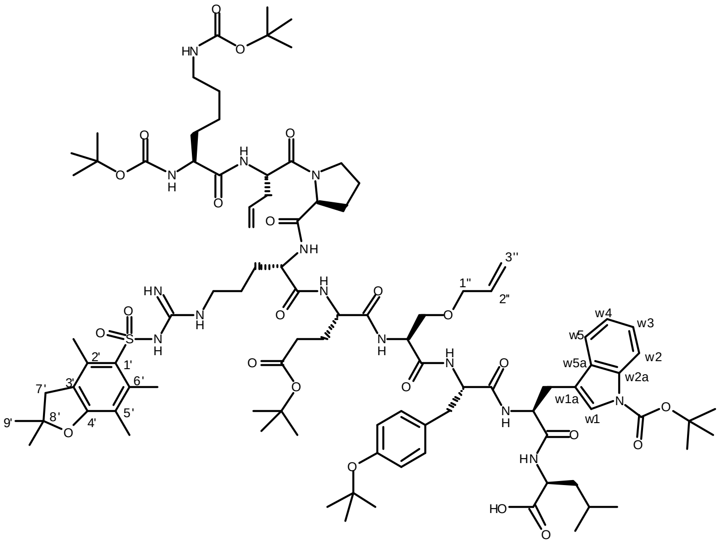


a) Fmoc-AA-OH, HBTU, HOBt, *i*Pr_2NEt, *N*-methyl pyrrolidone, rt, 1h; b) $[RuCl_2(PCy_3)_2(=CHPh)]$, CH_2Cl_2, reflux; c) H_2, Pd/C, EtOH, rt; d) CF_3COOH/(*i*Pr)$_3$SiH/H_2O (v/v/v) = 95/2.5/2.5

5.1. *N*-Boc-Lys(Boc)-Allylgly-Pro-Arg(Pbf)-Glu(OtBu)-Ser(OAllyl)-Tyr(tBu)-Trp-(Boc)-Leu (21)

Peptide **21** was prepared in 75 % yield (0.15 mmol scale) by the protocol given for the synthesis of **10a**. HPLC: t_R = 7.22 min, purity > 99 %; MS (ESI+): *m/z* = 963 [M^{2+}+Na], 1881 [*M*+H]$^+$, 1903 [*M*+Na]$^+$, 1925 [*M*-H+2Na]$^+$; HR-MS: [*M*H]$^+$ = $C_{95}H_{143}N_{14}O_{23}S$, calcd 1880.0166; found 1880.0160; [*M*+Na]$^+$ = $C_{95}H_{142}N_{14}O_{23}SNa$, calcd 1901.9985; found 1902.0000

Table S5: ^{1}H (500 MHz) and ^{13}C (100 MHz) NMR data of **21** in [D$_6$]DMSO



Amino Acid	**Position**	*d* (**^{1}H)**	*d* (**^{13}C)**
Lysine (K)	α-NH	6.81 (d, *J* = 8.0 Hz)	
	C_α	3.84	54.45
	C_β	1.51 and 1.42	31.67
	C_γ	1.25 and 1.17	22.9
	C_δ	1.30	29.25
	C_ε	2.84	39.8
	ε-NH	6.71	
Allylglycine	NH	7.84 (d, *J* = 7.8 Hz)	
	C_α	4.51	50.00
	C_β	2.38 and 2.24	35.78
	C_γ	5.75	134.05
	C_δ	5.06 (d, *J* = 17.3 Hz)	117.68
		4.96 (d, *J* = 10.5 Hz)	
Proline (P)	C_α	4.33	59.39
	C_β	1.97 and 1.80	29.07
	C_γ	1.86 and 1.80	24.50
	C_δ	3.57 and 3.50	46.94
Arginine (R)	NH	7.88 (d, *J* = 8.2 Hz)	
	C_α	4.24	51.78
	C_β	1.68 and 1.46	29.60
	C_γ	1.44	25.30

	C_δ	3.01	40.0
	C_ε		
	C_ε-NH	6.3 – 6.7 (3H)	
	1’		134.3
	2’		131.50
	3’		124.37
	4’		157.53
	5’		116.28
	6’		137.35
	7’	2.93 (s, 2H)	42.57
	8’		86.35
	9’	1.38 (s, 6H)	28.24
	2’-Me	2.40 (s, 3H)	19.03
	5’-Me	1.98 (s, 3H)	12.34
	6’-Me	2.46 (s, 3H)	17.67
Glutamic Acid (E)	NH	8.10 (d, *J* = 7.3 Hz)	
	C_α	4.03	52.56*
	C_β	1.87 + 1.75	26.93
	C_γ	2.16	31.38
Serine (S)	NH	7.95 (d, *J* = 8.0 Hz)	
	C_α	4.42	52.63*
	C_β	3.43 (dd, *J* = 10.1 and 5.3 Hz)	69.50
	1’’	3.84	71.09
	2’’	5.75	134.97
	3’’	5.15 (br.d, *J* = 17.2 Hz)	116.55
		5.03 (br.d, *J* = 11.0 Hz)	
Tyrosine (Y)	NH	7.92 (d, *J* = 8.0 Hz)	
	C_α	4.40	54.02
	C_β	2.87	36.89
	C_β	2.70 (dd, *J* = 14.0 + 8.7 Hz)	
	C_γ		132.07
	C_δ	6.98 (d, *J* = 8.3 Hz)	129.74
	C_ε	6.72 (d, *J* = 8.3 Hz)	123.27
	C		153.45
Tryptophane (W)	NH	8.08 (d, *J* = 8.2 Hz)	

	C_α	4.65	52.08
	C_β	3.08 (dd, *J* = 15.4 + 5.3 Hz)	27.6
	C_1	7.52	124.19
	C_{1a}		116.28
	C_2	8.01 (d, *J* = 8.2 Hz)	114.67
	C_{2a}		134.75
	C_3	7.29 (t, *J* = 8.0 Hz)	124.31
	C_4	7.22 (t, *J* = 7.8 Hz)	122.47
	C_5	7.68 (d, *J*= 7.8 Hz)	119.51
	C_{5a}		130.43
Leucine (L)	NH	8.29 (d, *J* = 7.8 Hz)	
	C_α	4.24	50.41
	C_β	1.53	40.1
	C_γ	1.62	24.35
	C_δ	0.88 (d, *J* = 6.6 Hz)	22.92
	C_ε	0.84 (d, *J* = 6.6 Hz)	21.44
COO bzw. CON			173.85, 171.97, 171.52, 171.38, 171.19, 170.87, 170.79, 170.51, 169.61, 169.31
Boc-NCO			156.12, 155.63, 155.34, 149.11
-Bu-Cq			83.46, 80.61, 78.12, 77.59, 77.40
*t*Bu-CH_3		1.56, 1.35, 1.34, 1.21	28.61, 28.37, 28.35, 27.75, 27.66, 27.64

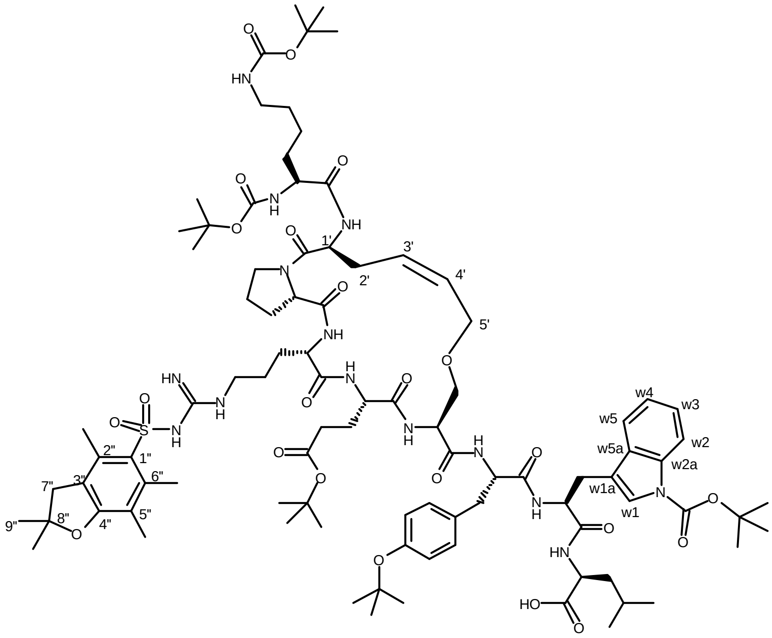
*) interchangeable

5.2. Peptide 22

Peptide **22** was prepared in 62 % yield (22 µmol scale) by the protocol given for the synthesis of **11a** using 20 mol% 1st generation Grubbs catalyst and a reaction time of 2 h. HPLC: t_R = 7.047 min, purity = 96 %; MS (ESI+): *m/z* = 949 [*M*+2Na]$^{2+}$, 1852 [*M*H]$^+$, 1874 [*M*+Na]$^+$, 1897 [*M*-H+2Na]$^+$; HR-MS: [*M*+Na]$^+$ = $C_{93}H_{138}N_{14}O_{23}SNa$, calcd 1873.9672; found 1873.9677; [*M*-H+2Na]$^+$ = $C_{93}H_{137}N_{14}O_{23}SNa_2$, calcd 1895.9492; found 1895.9492

The NMR spectrum of the product of this reaction (Table S6) shows an approx. 4:1 mixture of two sets of signals. The NMR of the minor component is consistent with an *E* double bond (*J* = 15.3 Hz, positive ROESY-crosspeaks between H-3’ and H-5’, and between H-4´and H-2´). Overlapping resonances [*d*(H-3’, H-4’) = 5.46 ppm] prohibit an unambigiuos assignment of the double bond geometry of the major signal set. Both sets of signals remain intact at *T* = 350 K; this indicates the presence of E/Z isomers rather than rotamers.

Table S6: ^{1}H- (500 MHz) and ^{13}C- (100 MHz) NMR data of **22** in [D$_6$]DMSO



Amino acid	**Position**	***d*** **(^{1}H)**	***d*** **(^{13}C)***
Lysine (K)	α-NH	6.83 // 6.71	
	C_{α}	3.84 // 3.80	54.24 // 54.75
	C_{β}	1.49 and 1.40	31.38
	C_{γ}	1.25 and 1.17	22.90
	C_{δ}	1.30	29.30
	C_{ε}	2.84	39.58
	ε-NH	6.40	
Proline (P)	C_{α}	4.25 // 4.16 // 4.12	59.51 // 60.50 // 60.65
	C_{β}	2.02 and 1.77	29.33
	C_{γ}	1.78	24.35
	C_{δ}	3.52	47.1
Arginine (R)	NH	7.63 // 7.81	
	C_{α}	4.12 // 4.01	52.36 // 52.77
	C_{β}	n.d.	n.d.
	C_{γ}	n.d.	n.d.
	C_{δ}	3.01 // 3.04	40.0

	C_ε		
	1’’		134.33
	2’’		131.52
	3’’		124.41
	4’’		157.54
	5’’		116.3*
	6’’		137.36
	7’’	2.94	42.56
	8’’		86.38
	9’’	1.38	
	2’’-Me	2.40	19.03
	5’’-Me	1.98	12.36
	6’’-Me	2.46	17.68
Glutamic acid (E)	NH	8.01 // 7.68	
	C_α	4.18 // 4.16	51.7
	C_β	2.03 and 1.66 // 1.98 and 1.70	26.7 // 27.13
	C_γ	2.19 and 2.13 // 2.24 and 2.09	30.55 // 31.09
Serine (S)	NH	7.72 // 7.83	
	C_α	4.37 // 4.54	53.27 // 52.66
	C_β	3.50 // 3.53 and 3.45 // 3.23	69.2 // 69.6 // 69.96
Tyrosine (Y)	NH	7.93 // 7.88 // 8.14	
	C_α	4.48 // 4.39	53.70 // 54.04
	C_β	2.86 and 2.70 // 2.93 and 2.63	36.92 // 37.15
	C_γ		132.30 // 132.13
	C_δ	6.99 (d, J = 7.8 Hz) // 7.05 (d, J = 7.8 Hz)	129.76
	C_ε	6.73 (d, J = 7.8 Hz) // 6.76 (d, J = 7.8 Hz)	123.30
	C		153.46
Tryptophane (W)	NH	8.27 // 8.08	
	C_α	4.65	52.13
	C_β	3.09 and 2.92	27.56
	C_1	7.51 // 7.52	124.33**

	C_{1a}		116.45
	C_2	8.01 (d, J= 8.0 Hz)	114.69
	C_{2a}		134.77
	C_3	7.29 (t, *J* = 8.0 Hz)	124.39**
	C_4	7.22 (t, *J* = 8.0 Hz)	122.49
	C_5	7.68	119.51
	C_{5a}		130.44
Leucine (L)	NH	8.28 // 8.24	
	C_α	4.25	50.30
	C_β	1.52	40.1
	C_γ	1.62	24.34
	C_δ	0.83 (d, *J* = 6.4 Hz)	21.42
	C_δ	0.87 (d, *J* = 6.4 Hz)	22.93
1’-NH		7.80 (*E*) // 7.90 (*Z*)	
1’		4.45 (*E*) // 4.49 (*Z*)	50.23 (*E*) // 49.94 (*Z*)
2’		2.32 and 2.23 (*E*) // 2.35 (*Z*)	35.19 (*E*) // 29.48 (*Z*)
3’		5.78 (*J* = 15.3 Hz, *E*) // 5.46 (*Z*)	127.4 (*E*) // 127.8 (*Z*)
4’		5.51 (*E*) // 5.46 (*Z*)	129.8 (*E*) // 129.5 (*Z*)
5’		3.79 (*E*) // 3.92 and 3.85	70.70 (*E*) // 66.38 (*Z*)
COO and CON			173.85, 171.55, 171.33, 170.87, 170.60
Boc-NCO			156.14, 155.66, 149.13
tBu-Cq			83.47, 80.71, 78.19, 77.43
*t*Bu-CH_3		1.56, 1.34, 1.21	28.63, 28.59, 28.39, 28.36, 28.26, 28.20, 27.76, 27.69

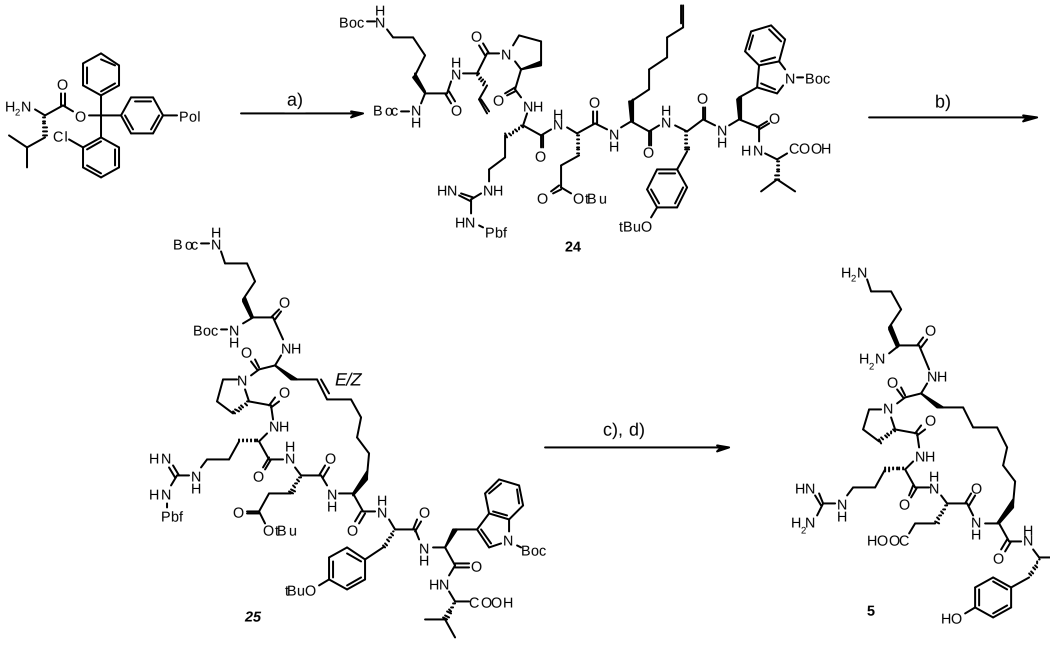
*) the two signal sets are separated by // **): interchangeable

5.3. Peptide 23: Peptide 23 was prepared in quantitative yield by hydrogenation of **22** (9 mg, 4.8 µmol) with 0.9 mg 10% Pd/C in methanol (5 mL) following the protocol given for the synthesis of peptide **12**. ^{1}H NMR confirmed the absence of olefinic protons. HPLC: t_R = 7.053 min, purity = 96 % (220 nm); MS (ESI+): *m/z* = 949 [*M*-H+2Na]$^{2+}$, 1854 [*M*H]$^+$, 1876 [*M*+Na]$^+$, 1899 [*M*-H+2Na]$^+$; HR-MS: [*M*H]$^+$ = $C_{93}H_{141}N_{14}O_{23}S$, calcd 1854.0009; found 1854.0012; [*M*+Na]$^+$ = $C_{93}H_{140}N_{14}O_{23}SNa$, calcd 1875.9829; found 1875.9827.

5.4. Peptide 3: Treatment of **22** (23 mg, 12.3 µmol) with TFA/TIS/H_2O 95:2.5:2.5 (5 mL) as described for the synthesis of **1a** gave the peptide **3** (16.0 mg, quant.) as a fluffy white solid after lyophilisation. HPLC: t_R = 2.96 min, purity = 90 % (220 nm); MS (ESI+): m/z = 594 $[M+2H]^{2+}$, 616 $[M+2Na]^{2+}$, 1187 $[MH]^+$; HR-MS: $[M+H]^+$ = $C_{57}H_{83}N_{14}O_{14}$, calcd 1187.6208; found 1187.6206; $[M+Na]^+$ = $C_{57}H_{82}N_{14}O_{14}Na$, calcd 1209.6027; found 1209.6027.

5.5. Peptide 4: Treatment of **23** (9.0 mg, 4.8 µmol) with TFA/TIS/H_2O 95:2.5:2.5 (1 mL) as described for the synthesis of **1a** gave the peptide **4** (5.4 mg, 94 %) as a fluffy white solid after lyophilisation. HPLC: t_R = 3.13 min, purity = 90 % (220 nm); MS (ESI+): m/z = 595 $[M+2H]^{2+}$, 617 $[M+2Na]^{2+}$, 1189 $[MH]^+$; HR-MS: $[MH]^+$ = $C_{57}H_{85}N_{14}O_{14}$, calcd1189.63642; found 1189.63663.

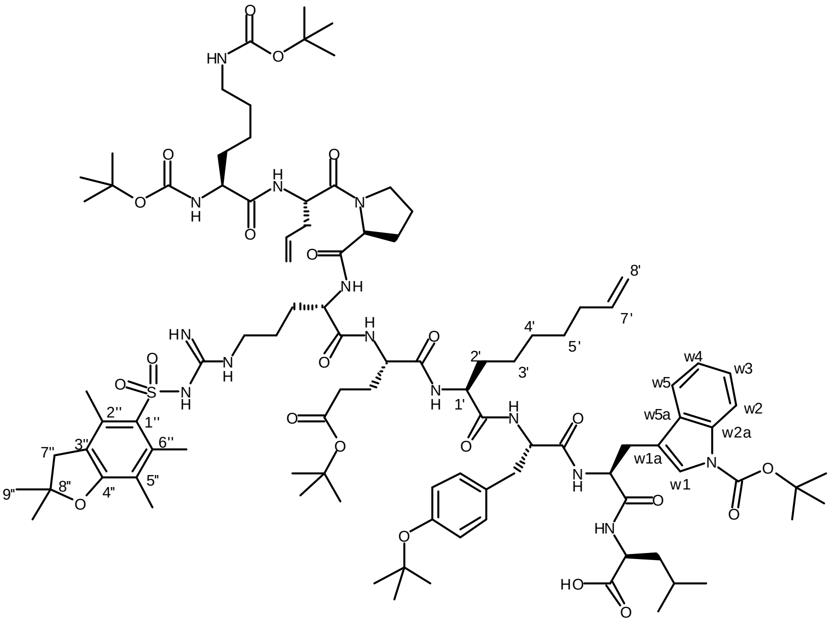
6. Synthesis of cyclic peptide 5



a) Fmoc-AA-OH, HBTU, HOBt, *i*Pr_2NEt, *N*-methyl pyrrolidone, rt, 1h; b) $[RuCl_2(PCy_3)_2(=CHPh)]$, CH_2Cl_2, reflux; c) H_2, Pd/C, EtOH, rt; d) $CF_3COOH/(iPr)_3SiH/H_2O$ (v/v/v) = 95/2.5/2.5

6.1. N-Boc-Lys(Boc)-Allylgly-Pro-Arg(Pbf)-Glu(OtBu)-Hept-7-enylgly-Tyr(tBu)-Trp(Boc)-Leu (24): Peptide **24** was prepared in 60 % yield (0.11 mmol scale) by the protocol given for the synthesis of **10a**. HPLC: t_R = 7.75 min, purity > 99 %; MS (ESI+): m/z = 972 $[M+Ca]^{2+}$, 1906 $[MH]^+$, 1944 $[M-H+Ca]^+$; HR-MS: $[MH]^+$ = $C_{98}H_{149}N_{14}O_{22}S$, calcd 1906.0686; found 1906.0712; $[M-H+Ca]^+$ = $C_{98}H_{147}N_{14}O_{22}SCa$, calcd 1944.0156; found 1944.0176.

Table S7: ^{1}H (500 MHz) and ^{13}C (100 MHz) NMR data of **24** in [D$_6$]DMSO.



Amino acid	position	? (^{1}H)	? (^{13}C)
Lysine (K)	α-NH	8.11	
	C_α	3.99	55.80
	C_β	1.69 and 1.56	32.71
	C_γ	1.34	23.84
	C_δ	1.44	30.26
	C_ε	3.00	40.74
Allylglycine	NH	7.96	
	C_α	4.63	52.15
	C_β	2.52 and 2.36	36.38
	C_γ	5.80	n.d.
	C_δ	5.10 (d, *J* = 17.2 Hz)	118.60
		5.02 (d, *J* = 10.0 Hz)	
Proline (P)	C_α	4.40	61.30
	C_β	2.13 and 1.95	30.16
	C_γ	2.04 and 1.94	25.80
	C_δ	3.76 and 3.63	48.42
Arginine (R)	NH	n.d.	
	C_α	4.36	53.9
	C_β	1.83 and 1.71	29.57
	C_γ	n.d.	n.d.

	C_δ	3.15	41.30
	7’’	2.97	43.66
	9’’	1.44	
	2’’-Me	2.50	19.42
	5’’-Me	2.06	12.29
	6’’-Me	2.56	18.22
Glutamic acid (E)	NH	8.13	
	C_α	4.36	53.9
	C_β	2.09 and 1.91	28.09
	C_γ	2.30 (t, J = 7.8 Hz)	32.18
Hepten-7-ylglycine	NH	8.11	
	1’	4.05	55.41
	2’	1.57 and 1.48	31.73
	3’ / 4’	1.14 and 1.03	26.20
	5’	1.30	29.6
	6’	2.30	34.54
	7’	5.80	n.d.
	8’	4.98 (d, J = 17.2 Hz)	114.60
		4.91 (d, J = 10.3 Hz)	
Tyrosine (Y)	NH	8.21	
	C_α	4.51	56.42
	C_β	3.14 and 2.68 (dd, J = 14.0 and 10.8 Hz)	37.25
	C_γ		
	C_δ	7.04 (d, J = 8.3 Hz)	130.36
	C_δ	6.82 (d, J = 8.3 Hz)	124.87
	C		
Tryptophane (W)	NH	8.19	
	C_α	4.81	54.17
	C_β	3.28	28.09
	C_1	7.59	125.14
	C_{1a}		
	C_2	8.09 (d, J = 8.0 Hz)	115.85
	C_{2a}		

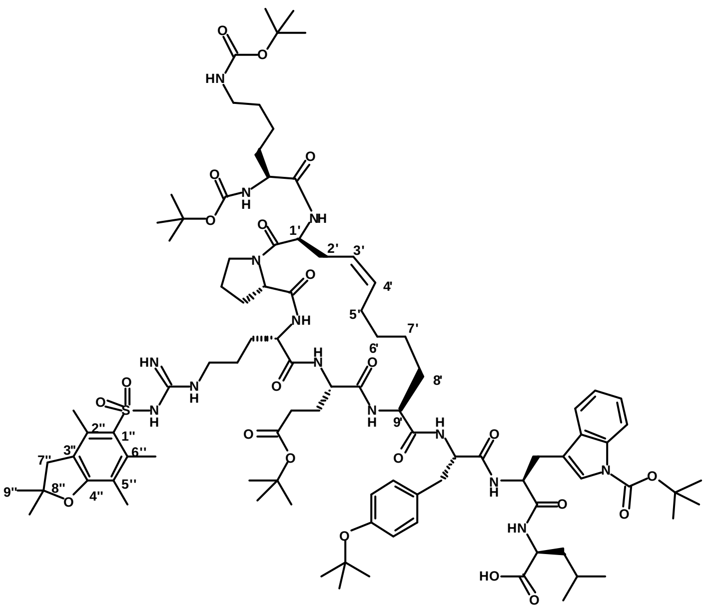
	C_3	7.29 (t, J = 7.6 Hz)	125.26
	C_4	7.23 (t, J = 7.6 Hz)	123.41
	C_5	7.71 (d, J = 7.6 Hz)	120.08
	C_{5a}		
Leucine (L)	NH	8.27 (d, J = 7.8 Hz)	
	C_α	4.39	52.27
	C_β	1.64	41.31
	C_γ	1.60	26.16
	C_δ	0.94 (d, J = 6.4 Hz)	23.15
	C_δ	0.88 (d, J = 6.4 Hz)	21.91
9``-CH_3, *t*Bu-CH_3		1.29, 1.42, 1.65	28.2, 28.4, 29.0

6.2. Peptide 25

Peptide **25** was prepared from **24** in 51 % yield (21 µmol scale) by the protocol given for the synthesis of **11a** using 20 mol% 1st generation Grubbs catalyst and a reaction time of 2 h. HPLC: t_R = 7.51 min, purity = 94 %; MS (ESI+): *m/z* = 961 [*M*+2Na] $^{2+}$, 1900 [*M*+Na]$^+$,1922 [*M*-H+2Na]$^+$; HR-MS: [*M*+Na]$^+$ = $C_{96}H_{144}N_{14}O_{22}SNa$, calcd 1900.0193; found 1900.0185; [*M*-H+2Na]$^+$ = $C_{96}H_{143}N_{14}O_{22}SNa_2$, calcd 1922.0012; found 1922.0010.

The ^{1}H NMR (Table S8) shows an approx 2:1-mixture of two sets of signals. The signals of the main component is consistent with a *E*-double bond (*J* = 15.4 Hz). The configuration of the double bond of the second signal set could not be unambiguously assigned due to overlapping resonances [*d*(H-3’, H-4’) = 5.33/5.34 ppm]. Both sets of signals remain intact at *T* = 350 K which indicates the presence of *E/Z*-isomers rather than rotamers.

Table S8: ^{1}H (500 MHz) and ^{13}C (100 MHz) NMR data of **25** in [D$_6$]DMSO.



Amino Acid	**Position**	*d* (^{1}H)*	*d* (^{13}C)*
Lysine (K)	α-NH	6.82	
	C_α	3.86	54.33
	C_β	1.50 and 1.42	31.74
	C_γ	1.21	22.90
	C_δ	1.31	30.21
	C_ε	2.85	39.68
	ε-NH	6.4	
Proline (P)	C_α	4.37 // 4.33	59.25 // 59.67
	C_β	2.00 and 1.87	28.5
	C_γ	1.76 and 1.56	24.57
	C_δ	3.62 and 3.33 // 3.56 and 3.47	47.15 // 46.85
Arginine (R)	NH	7.10	
	C_α	4.16	52.43
	C_β	1.15	n.d.
	C_γ		n.d.
	C_δ	3.05 and 2.95	40.04
	C_ε		
	1’’		134.77
	2’’		131.51
	3’’		124.38

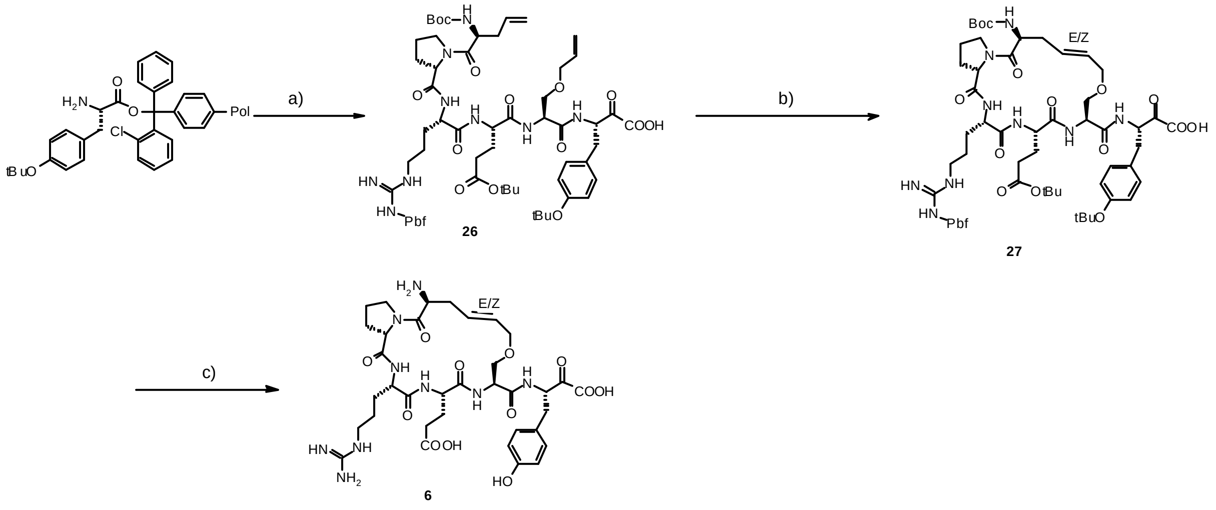
	4’’		157.54
	5’’		116.39 // 116.33**
	6’’		137.33
	7’’	2.93	42.56
	8’’		86.35
	9’’	1.38	
	2’’-Me	2.40	21.48
	5’’-Me	1.97	12.34
	6’’-Me	2.46	17.67
Glutamic Acid (E)	NH	8.13 // 8.07	
	C_α	3.86	53.17
	C_β	2.02 and 1.76	25.90
	C_γ	2.18	31.74
Tyrosine (Y)	NH	8.07 // 7.88	
	C_α	4.45	53.90
	C_β	2.95 and 2.60	37.02
	C_γ		132.26 // 132.35
	C_δ	7.03 (d, *J* = 8.3 Hz)	129.75
	C_ε	6.74 (d, *J* = 8.3 Hz)	123.20
	C		153.49
Tryptophane (W)	NH	8.19 // 8.10	
	C_α	4.63 // 4.59	52.08
	C_β	3.09 and 2.96	27.33
	C_1	7.56 // 7.53	124.30
	C_{1a}		116.31 // 116.29**
	C_2	8.01 (d, *J*= 8.0 Hz)	114.67
	C_{2a}		134.77
	C_3	7.29 (t, *J* = 7.8 Hz)	124.30
	C_4	7.22 (t, *J* = 7.8 Hz)	122.49
	C_5	7.71 // 7.69	119.51
	C_{5a}		130.38 // 130.34
Leucine (L)	NH	8.23 // 8.19	
	C_α	4.24	50.50
	C_β	1.52	40.14
	C_γ	1.61	24.33
	C_δ	0.87 (d, *J* = 6.4 Hz)	19.02

C_δ	0.83 (d, *J* = 6.4 Hz)	22.93
1’-NH	7.87 // 7.91	
1’	4.39 // 4.50	50.60 // 50.22
2’	2.34 + 2.18 // 2.51 + 2.27	35.50 // 29.67
3’	5.33 // 5.30	123.87 // 125.30
4’	5.49 (*J* = 15.4 Hz) // 5.34	133.36 // 131.58
5’	1.93 and 1.78 // 1.92	30.20 // 26.29
9’	3.97	53.90
9’-NH	6.92	
COO and CON		173.87, 172.28, 172.20, 171.87, 171.81, 171.58, 171.43, 171.11, 171.04, 170.97, 170.94, 170.90, 170.38
Boc-NCO		156.12, 155.66, 155.40, 155.34, 149.13
*t*Bu-Cq		83.45 // 83.41, 79.79 // 79.74, 78.13, 77.51, 77.49, 77.43
*t*Bu-CH_3	1.57, 1.35, 1.33, 1.20	28.60, 28.58, 28.36, 28.26, 27.78

*) the two signal sets are separated by // ; **) interchangeable

6.3. Peptide 5: Following the protocol given for the synthesis of **12**, a mixture of peptide 25 (4.5 mg, 2.4 µmol) and 10 % Pd/C (1 mg) in methanol (2 mL) was hydrogenated at atmospheric pressure for 6 h. The mixture was filtered through celite and evaporated to dryness. ^1H NMR indicated the complete absence of olefinic protons. The residue was taken up in TFA/TIS/H_2O 95:2.5:2.5 (*v/v/v*, 1 mL) and the solution was stirred at room temperature for 2 hours following by precipitation with ice-cold ether. The pellet was washed with ether and purified by preparative HPLC to yield 5 (1.5 mg, 51%) as a colorless fluffy solid after lyophilisation. HPLC: t_R = 3.57 min, purity = 95 %; MS (ESI+): *m/z* = 608 $[M+2H]^{2+}$, 1215 $[MH]^+$; HR-MS: $[MH]^+$ = $C_{60}H_{91}N_{14}O_{13}$, calcd 1215.68846; found 1215.68805

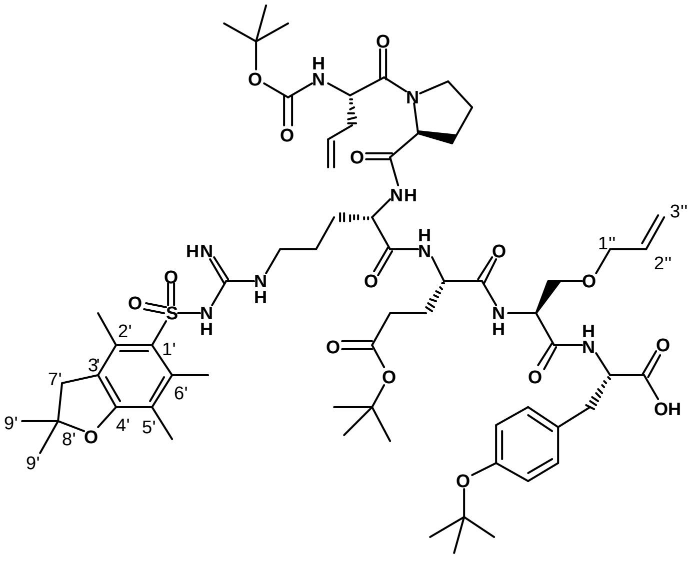
7. Synthesis of cyclic peptide 6



a) Fmoc-AA-OH, HBTU, HOBt, *i*Pr_2NEt, *N*-methyl pyrrolidone, RT, 1h; b) $[RuCl_2(PCy_3)_2(=CHPh)]$, CH_2Cl_2, reflux; c) $CF_3COOH/(iPr)_3SiH/H_2O$ (v/v/v) = 95/2.5/2.5

7.1. *N*-Boc-Allylgly-Pro-Arg(Pbf)-Glu(OtBu)-Ser(OAllyl)-Tyr(*t*Bu) (26): Peptide **26** was prepared in 85 % yield (0.17 mmol scale) by the protocol given for the synthesis of **10a** starting from H-Tyr(tBu)-2Cl-Trt resin (200 mg, loading 0.88 mmol/g). HPLC: t_R = 6.21 min, purity > 99 %; MS (ESI+): *m/z* = 649 $[M+2Na]^{2+}$, 1252 $[MH]^+$, 1274 $[M+Na]^+$; HR-MS: $[M+Na]^+$ = $C_{62}H_{93}N_9O_{16}SNa$, calcd 1274.6353; found 1274.6349; $[M-H+2Na]^+$ = $C_{62}H_{92}N_9O_{16}SNa_2$, calcd 1296.6173; found 1296.6175

Table S9: ^1H (500 MHz) and ^{13}C (100 MHz) NMR data of **16** in $[D_6]DMSO$.



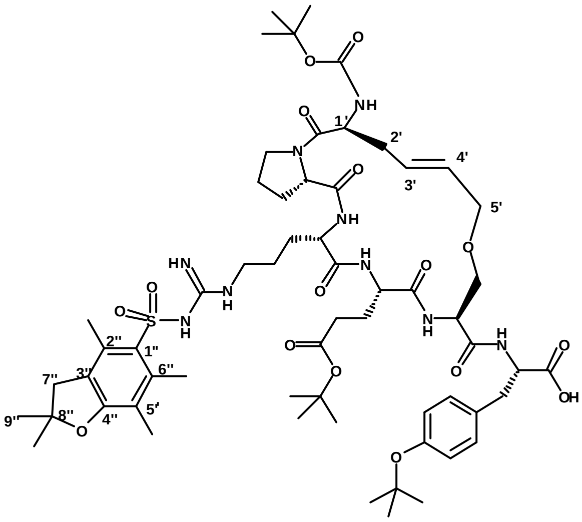
Amino Acid	**position**	*d* (**^{1}H**)	*d* (**^{13}C**)
Allylglycine	NH	6.89 (d, *J* = 6.9 Hz)	
	C_α	4.20	51.91
	C_β	2.33 and 2.21	35.35
	C_γ	5.79	134.48
	C_δ	5.10	117.58
	C_ε	4.99 (d, *J* = 9.9 Hz)	
Proline (P)	C_α	4.36	59.43
	C_β	2.01 and 1.80	29.01
	C_γ	1.89 and 1.83	24.61
	C_δ	3.60 and 3.51	46.90
Arginine (R)	NH	7.91 (d, *J* = 8.0 Hz)	
	C_α	4.25	51.73
	C_β	1.68 and 1.48	29.50
	C_γ	1.44	25.23
	C_δ	3.02	40.0
	1’		134.3
	2’		131.50
	3’		124.37
	4’		157.52
	5’		116.32
	6’		137.34
	7’	2.95 (s, 2H)	42.57
	8’		86.35
	9’	1.39 (s, 6H)	28.38
	2’-Me	2.42 (s, 3H)	19.04
	5’-Me	1.99 (s, 3H)	12.35
	6’-Me	2.47 (s, 3H)	17.68
Glutamic Acid (E)	NH	8.10 (d, *J* = 7.5 Hz)	
	C_α	4.05	52.53
	C_β	1.88 + 1.76	27.00
	C_γ	2.18	31.45
Ser(OAll)	NH	7.95 (d, *J* = 8.3 Hz)	
	CO		169.48
	C_α	4.50	52.53

	C_β	3.47	69.73
	1’’	3.90	71.11
	2’’	5.79	135.05
	3’’a	5.21 (dd, *J* = 17.2 and 1.4 Hz)	116.56
	3’’b	5.10	
Tyrosine (Y)	NH	8.12 (d, *J* = 8.5 Hz)	
	CO		
	C_α	4.37	53.62
	C_β(a)	2.98 (dd, *J* = 14.0 and 5.3 Hz)	36.04
	C_β(b)	2.85 (dd, *J* = 14.0 and 8.2 Hz)	
	C_γ		131.99
	C_δ	7.09 (d, *J* = 8.3 Hz)	129.75
	C_ε	6.83 (d, *J* = 8.3 Hz)	123.43
	C		153.64
	COOH	12.7 (br.s)	
COO and CON			171.50, 171.34, 171.30, 170.81, 170.40
Boc-NCO, $R_?$			155.33, 156.13
*t*Bu-C_q			80.64, 78.14, 77.70
*t*Bu-CH_3		1.36, 1.34, 1.24	28.62, 28.25, 27.68

7.2. Peptide 27: Peptide **27** was prepared in from 26 in 34 % yield (41 µmol scale) by the protocol given for the synthesis of **11a** byb using 20 mol% 1st generation Grubbs catalyst and a reaction time of 16 h. HPLC: t_R = 5.83 min, purity = 96 %; MS (ESI+): *m/z* = 1247 $[M+Na]^+$,1269 $[M\text{-}H+2Na]^+$; HR-MS: $[M+Na]^+$ = $C_{60}H_{89}N_9O_{16}SNa$, calcd 1246.6040; found 1246.6033; $[M\text{-}H+2Na]^+$ = $C_{60}H_{88}N_9O_{16}SNa_2$, calcd 1268.5860; found 1268.5853.

The NMR of **27** (Table S9) shows an approx 5:4-mixture of two components. The NMR data of the minor component is compatible with an *E*-configured double bond (*J* = 15.5 Hz and a positive ROESY-crosspeak between H-3’ and H-5’). Overlapping resonances prohibit an unambigiuos assignment of the double bond geometry of the second signal set. Both sets of signals remain intact at *T* = 350 K.

Table S9: ^{1}H (500 MHz) and ^{13}C (100 MHz) NMR data of **27** in [D$_6$]DMSO.



Amino acid	**Position**	***d* (^{1}H) (*Z* // *E*)**	***d* (^{13}C) (*Z* // *E*)**
Proline (P)	C_α	4.29 // 4.21	59.57 // 60.47
	C_β	2.01 // 1.80	29.25 // 29.45
	C_γ	1.80 // 1.84	24.50
	C_δ	3.51 // 3.59	47.08
Arginine (R)	NH	7.86 // 7.80	
	C_α	4.17 // 3.99	52.3 // 52.9
	C_β	[a]	[a]
	C_γ	[a]	[a]
	C_δ	3.02	39.96
	ε-NH	7.00 – 6.60	
	1’’		134.3
	2’’		131.50
	3’’		124.38
	4’’		157.52
	5’’		116.32
	6’’		137.34
	7’’	2.94	42.57
	8’’		86.37
	9’’	1.39	28.36
	2’’-Me	2.41	19.02
	5’’-Me	1.99	12.35
	6’’-Me	2.47	17.66
Glutamic acid (E)	NH	8.03 // 7.65	

	C_α	[a] // 4.00	[a]
	C_β	[a] // 1.87	[a]
	C_γ	2.26 + 2.07 // 2.14	31.10 // 31.68
Serine (S)	NH	7.70 // 7.74	
	C_α	4.40 // 4.45	53.30 // 53.20
	C_β	3.54 // 3.55 and 3.48	69.80 // 69.95
Tyrosine (Y)	NH	8.17 // 8.26	
	$C_?$	4.34 // 4.40	53.70 // 53.41
	C_β	2.97 and 2.84 // 3.01 and 2.77	36.12 // 36.28
	C_γ		132.10
	$C_?$	7.07	129.78
	C_ε	6.81	123.43
	C		153.63
	1'-NH	6.86 // 6.92	
	1'	4.15 // 4.27	[a] // 52.24
	2'	2.30 and 2.23 // 2.35 and 2.23	35.12 // 29.32
	3'	5.80 // 5.53 (*J* = 15.5 Hz)	127.43 // 127.73
	4'	5.53	129.7
	5'	3.84 //3.92 and 3.74	70.86 // 65.68
	<u>C</u>OO and. <u>C</u>ON		172.89, 172.80, 172.63, 171.87, 171.52, 171.42, 171.24, 171.16, 170.77, 170.66, 170.44, 170.22, 169.42, 169.19
	Boc-N<u>C</u>O		156.16, 156.13, 155.69, 155.57
	*t*Bu-Cq		80.74, 80.70, 78.27, 77.71, 77.67
	*t*Bu-<u>C</u>H_3:	1.36, 1.35, 1.34, 1.33, 1.24	28.63, 28.22, 27.69

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[a] could not be resolved due to signal overlap

7.3. Peptide 6: Treatment of 27 (8.0 mg, 6.5 µmol) with TFA/TIS/H_2O 95:2.5:2.5 (1 mL) as described for the synthesis of 1a gave the peptide 6 (5.0 mg, 88 %) as a fluffy white solid after lyophilisation. HPLC: t_R = 0.993 min, purity = 94 %; MS (ESI+): *m/z* = 402.5 [*M*-H+2Na]$^{2+}$, 760 [*M*H]$^+$, 782 [*M*+Na]$^+$; HR-MS: [*M*H]$^+$ = $C_{34}H_{50}N_9O_{11}$ calcd 760.36243; found 760.36260.

References

[1] U. Groth, C. Schmeck, U. Schöllkopf, *Ann. Chem.* **1993**, *3*, 321-3233.