Solid-phase based total synthesis of Jasplakinolide by means of ring-closing metathesis methodology

René Tannert, Tai-Shan Hu, Hans-Dieter Arndt* and Herbert Waldmann*

Universität Dortmund, Fakultät Chemie, Otto-Hahn-Str. 6, D-44227 Dortmund, Germany, and Max-Plank-Institut für Molekulare Physiologie, Otto-Hahn-Str. 11, D-44227 Dortmund, Germany

hans-dieter.arndt@mpi-dortmund.mpg.de
herbert.waldmann@mpi-dortmund.mpg.de

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General Methods

All solvents, when not purchased in suitable purity or dryness, were distilled using standard methods. Alternatively, solvents (HPLC grade) were passed under argon atmosphere through alumina columns (MBraun solvent purification system). Deionized water was used for all experiments. D-Tryptophan was donated by Degussa. All reagents were purchased from commercial suppliers (Acros, Alfa Aesar, Fluka, Novabiochem, Sigma-Aldrich) and used without purification. LiCl was dried at $T = 110^\circ$C and $p < 1$ mbar for 15 h. Within a description of a reaction workup the term “concentration” refers to removal of the solvent under reduced pressure using a rotary evaporator followed by connection of the sample to fine vacuum ($p < 0.1$ mbar).

Analytical Thin Layer Chromatography (TLC) was carried out on Merck precoated silica gel plates (60F-254) using ultraviolet light irradiation at 254 nm or KMnO$_4$ solution as staining reagent (1 g KMnO$_4$, 6.6 g K$_2$CO$_3$, 1.7 mL 5% NaOH solution, 100 mL H$_2$O). Column chromatography was performed using silica gel from J. T. Baker (particle size 40-60 µm) and applying a pressure of 0.3-0.5 bar. Column dimensions are described by height ($h$) and diameter ($d$).

Capillary Gas Chromatography (GC) was conducted using a HP 6890 GC system equipped with a HP-5MS column (24.8 m x 201 µm x 0.33 µm).

Analytical HPLC was performed on an Agilent 1100 machine using a Macherey-Nagel C18 gravity 3 µm reversed phase column. The separations were started at 10% MeCN (with 0.1% TFA) in H$_2$O (with 0.1% TFA) with a flow of 1 mL·min$^{-1}$, and the MeCN proportion was linearly increased after 1 min to 100% over a period of 7 min and then kept at that proportion for a period of 7 min.

Preparative HPLC was performed on an Agilent system equipped with a Macherey Nagel C18 gravity 5 µm reversed phase column. Separations were performed with an isocratic proportion of 50% MeCN in H$_2$O (with 0.1% TFA) applying a flow of 20 mL·min$^{-1}$.

Melting points were determined with a Büchi Melting Point B-540 apparatus (uncorrected). Optical rotations were measured in a Schmidt + Haensch Polartronic HH8 polarimeter at 589 nm, with values given in 10$^{-1}$ deg cm$^2$ g$^{-1}$ and concentrations $c$ given in g/100mL.  

$^1$H- and $^{13}$C-NMR spectra were recorded on Varian Unity Inova 600 (599.8 MHz ($^1$H) and 150.8 MHz ($^{13}$C)), Bruker DRX 500 (500.1 MHz ($^1$H) and 125.8 MHz ($^{13}$C)), Bruker DRX 400 (400 MHz ($^1$H) and 100.5 MHz ($^{13}$C)) and Varian Mercury VX 400 (400.1 MHz ($^1$H) and 100.6 MHz ($^{13}$C)) spectrometers. Chemical shifts are expressed in parts per million (ppm) and
the spectra are calibrated to residual solvent signals of CDCl$_3$ (7.26 ppm ($^1$H) and 77.0 ppm ($^{13}$C)), CD$_2$OD (3.31 ppm ($^1$H) and 49.0 ppm ($^{13}$C)), C$_6$D$_6$ (7.16 ppm ($^1$H) and 128.0 ppm ($^{13}$C)), DMSO (2.50 ppm ($^1$H) and 39.43 ppm ($^{13}$C)), and D$_2$O (4.79 ppm ($^1$H)), respectively. Coupling constants are given in Hertz (Hz) and the following notations indicate the multiplicity of the signals: s (singlet), d (doublet), t (triplet), q (quartet), qui (quintet), sext (sextet), sept (septet), m (multiplet), app (apparent), br (broad signal). Unless otherwise stated, spectra were recorded at 27°C.

Fourier transform infrared spectroscopy (FT-IR) spectra were obtained with a Bruker Tensor 27 spectrometer (ATR, neat).

Low Resolution Mass Spectra were recorded on a Thermo Finnigan LCQ ESI spectrometer (source voltage 70 keV). High Resolution FAB Spectra were recorded on a Jeol SX 102 A (matrix: meta-nitrobenzyl alcohol). A Thermo DFS High Resolution Magnetic Sector MS (Double Focusing Mass Spectrometer) device was used to record EI (source voltage 70 keV; reference substance: perfluorokerosene, resolution: 10000) and CI (methane gas; source voltage 120 keV; reference substance: Ultramark 2500F, resolution: 10000) spectra, respectively. High Resolution ESI Spectra were recorded on a Thermo Electron LTQ Orbitrap (source voltage 3.8 kV, resolution: 60000) spectrometer.

**Abbreviations**

Bn = benzyl, CI = chemical ionization, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Dec = 3-methyl-4,9-decadien-2-ol, DIAD = diisopropyl azodicarboxylate, DIC = $N$,$N'$-diisopropylcarbodiimide, DIPEA = $N$,$N$-diisopropylethylamine, DMAP = 4-(dimethylamino)pyridine, DMF = $N$,$N$-dimethylformamide, EDC·HCl = $N$-Ethyl-$N'$-(3-dimethylaminopropyl)carbodiimide hydrochloride, EI = electron impact, ESI = electrospray ionization, FAB = fast atom bombardment, Fmoc = 9-Fluorenylmethoxycarbonyl, FmocOSu = $N$-(9-Fluorenylmethoxycarbonyloxy)succinimide, HFIP = 1,1,1,3,3,3-hexafluoroisopropanol, HOBr = 1-hydroxybenzotriazole, Htn = ($2S,6R,8S$)-8-hydroxy-2,4,6-trimethylnon-4-enoic acid, NMP = 1-methylpyrrolidin-2-one, Mhx = ($2S,4R$)-4-methylhex-5-enol, Pea = 2,4-dimethylpent-4-enoic acid; TBAF = tetra-$n$-butylammonium fluoride, TFA = trifluoroacetic acid; THF = tetrahydrofuran, Und = ($2S,4R$)-4-methylundeca-5,10-dien-2-ol, TIPS = triisopropylsilyl, TIPSCI = triisopropylsilyl chloride.
Experimental Section

Under an argon atmosphere, a 25 mL-solid phase reaction vessel was charged with polystyrene-bound 2-chlorotrityl chloride (200-400 mesh; 4.2 g; 5.8 mmol), N-Fmoc-O-TIPS-protected β-tyrosine (0.72 eq, 4.2 mmol, 2.3 g), and CH$_2$Cl$_2$ (10mL). DIPEA (2.9 eq, 17 mmol, 2.9 mL) was added in one portion at 23°C via syringe, and the suspension was shaken (200 rpm) at 23°C for 2 h. The resin was drained and washed with anhydrous CH$_2$Cl$_2$ (1x 10 mL), anhydrous CH$_2$Cl$_2$/MeOH/DIPEA (17:2:1 v/v/v; 3x 7 mL), CH$_2$Cl$_2$ (4x 10 mL), N,N'-dimethylformamide (3x 10 mL), and CH$_2$Cl$_2$ (3x 10 mL). The resulting resin 18 was dried (0.5 mbar, 23°C) for 14 h. Its amino acid loading was determined to be 0.88 mmol·g$^{-1}$ by Fmoc-deprotection of a small resin sample (2x 4 mg) using DBU/piperidine/NMP (2:2:96 v/v) and subsequent measuring of the UV-absorption ($\lambda=304$ nm) against a blank sample.$^2$

Fmoc-D-abrine (10) (2.5 eq, 8.4 mmol, 3.7 g), HOBt (2.5 eq, 8.4 mmol, 1.3 g) and DIC (2.5 eq, 8.4 mmol, 1.3 mL) were successively dissolved in DMF (40 mL), shaken for 1 min, and then added to the drained resin 18 (5.5 g, 0.61 mmol·g$^{-1}$, 3.3 mmol) at 23°C. The suspension was shaken (200 rpm) for 2 h and then washed with DMF (2x 40 mL). Fmoc-cleavage was performed by treatment of the resin with piperidine/DMF (1:4 v/v; 2x 20 mL) for 20 min followed by washing with DMF (4x 25 mL). A solution of Fmoc-L-Ala-OH (2.3 eq, 7.6 mmol, 2.3 g), HATU (2.3 eq, 7.6 mmol, 2.9 g), HOAt (2.3 eq, 7.6 mmol, 1.0 g) and DIPEA (4.6 eq, 15.3 mmol, 2.6 mL) in DMF (40 mL) was added to the resin at 23°C. The
suspension was shaken (200 rpm) for 2.5 h and then washed with DMF (2x 40 mL). The coupling procedure was then repeated once. Fmoc-cleavage was performed by treatment of the resin with piperidine/DMF (1:4 v/v; 2x 20 mL) for 20 min followed by washing with DMF (4x 25 mL). A solution of (S)-2,4-dimethyl-4-pentenoic acid (2.3 eq, 7.6 mmol, 0.97 g), HATU (2.3 eq, 7.6 mmol, 2.9 g), HOAt (2.3 eq, 7.6 mmol, 1.0 g) and DIPEA (4.6 eq, 15.3 mmol, 2.6 mL) in DMF (40 mL) was added to the resin at 23°C. The suspension was shaken (200 rpm) for 2.5 h and then washed with DMF (4x 25 mL) and CH₂Cl₂ (4x 25 mL). For cleavage, the resin was treated with AcOH/TFE/CH₂Cl₂ (1:1:8 v/v/v; 2 × 40 mL) for 1.5 h. After filtration, cyclohexane (60 mL) was added to the filtrate. After concentration, column chromatography (4% - 10% MeOH in CH₂Cl₂) of the resulting crude peptide gave the desired acid 19 as a colorless wax (1.6 g, 3.3 mmol, 66%) besides the desilylated byproduct, also as a colorless wax (0.28 g, 0.50 mmol, 15%).

Rᵣ=0.21 (CHCl₃/MeOH 20:1); LC: tᵣ=9.94min; [α]D²³ +32.5 (c 1.2 in CHCl₃); νmax/cm⁻¹ = 3296, 2943, 2867, 1734, 1641, 1603, 1541, 1510 and 1457 cm⁻¹; δH(400 MHz, CDCl₃) mixture of rotamers (ratio >12:1), major rotamer: 8.29 (1H, s, Trp2-NH), 7.58 (1H, d, 3J 7.6, Trp4-H), 7.32 (1H, d, 3J 7.6, Trp7-H), 7.16 (1H, t, 3J 7.6, Trp6-H), 7.12 (2H, d, 3J 8.6, βTyr2-H, βTyr3-H), 7.10 (1H, t, 3J 7.6, Trp5-H), 6.94 (1H, d, 3J 1.8, Trp2-H), 6.92 (1H, d, 3J 8.6, βTyrβ-NH), 6.80 (2H, d, 3J 8.6, βTyr3-H, βTyr5-H), 6.54 (1H, d, 3J 7.0, Alaα-NH), 5.63 (1H, dd, 3J 10.5 and 5.7, Trpα-H), 5.39 (1H, td, 3J 8.6 and 4.9, βTyrβ-H), 4.75 (1H, s, Pea5-H₆), 4.69 (1H, s, Pea5-H₆), 4.68 (1H, dq, 3J 7.0 and 7.0, Alaα-H), 3.36 (1H, dd, 3J 5.7, 2J 15.8, Trpβ-H₆), 3.25 (1H, dd, 3J 10.5, 2J 15.8, Trpβ-H₆), 2.93 (3H, s, Trp-NCH₃), 2.85 (1H, dd, 3J 4.9, 2J 15.0, βTyrα-H₆), 2.76 (1H, dd, 3J 8.6, 2J 15.0, βTyrα-H₆), 2.50-2.41 (1H, m, Pea2-H), 2.34 (1H, dd, 3J 6.5, 2J 14.3, Pea3-H₆), 2.03 (1H, dd, 3J 8.3, 2J 14.3, Pea3-H₆), 1.66 (3H, s, Pea7-H₃), 1.29-1.19 (3H, m, TIPS), 1.10 (3H, d, 3J 6.2, Pea6-H₃), 1.08 (18H, d, 3J 7.3, TIPS) and 0.88 (3H, d, 3J 7.0, Alaα-H₃); δC(100 MHz, CDCl₃) 177.6 (Pea-1), 174.3 (Ala-C=O), 172.2 (Trp-C=O), 169.1 (βTyr-C=O), 155.4 (βTyr-γ), 142.6 (Pea-4), 136.1 (Trp-7a), 132.9 (βTyr-1), 127.4 (Trp-3a), 127.3 (2x, βTyr-2, βTyr-6), 122.1 (Trp-6), 122.1 (Trp-2), 120.0 (2x, βTyr-3, βTyr-5), 119.9 (Trp-5), 118.5 (Trp-4), 112.6 (Pea-5), 111.1 (Trp-3), 110.8 (Trp-7), 56.3 (Trp-α), 49.5 (βTyr-β), 45.7 (Ala-α), 41.6 (Pea-3), 40.6 (βTyr-α), 38.8 (Pea-2), 30.5 (Trp-NCH₃), 22.9 (Trp-β), 22.2 (Pea-7), 17.9 (6x, TIPS), 17.1 (Ala-β), 16.6 (Pea-6) and 12.7 (3x, TIPS); m/z (ESI): calc. for C₄₀H₇₀N₄O₆Si [M+H]+: 719.4198, found 719.4202.
Pea-Ala-D-2-Br-N-MeTrp-βTyr(TIPS)-OH (20)

Fmoc-D-bromoabrine (11) (1.5 eq, 0.54 mmol, 0.28 g), HOBt (1.5 eq, 0.54 mmol, 73 mg) and DIC (1.5 eq, 0.54 mmol, 0.11 mL) were successively dissolved in NMP (5 mL), shaken for 1 min, and then added to the drained resin 18 (0.55 g, 0.65 mmol·g⁻¹, 0.36 mmol) at 23°C. The suspension was shaken (200 rpm) for 2 h and then washed with NMP (3x 10 mL). Fmoc-cleavage was performed by treatment of the resin with DBU/piperidine/NMP (2:2:96 v/v; 5x 10 mL) and NMP (3x 10 mL). A solution of Fmoc-L-Ala-OH (3.0 eq, 1.1 mmol, 0.34 g), HATU (3.0 eq, 1.1 mmol, 0.41 g), HOAt (3.0 eq, 1.1 mmol, 0.15 g) and DIPEA (6.0 eq, 2.2 mmol, 0.38 mL) in DMF (5 mL) was added to the resin at 23°C. The suspension was shaken (200 rpm) for 14 h and then washed with NMP (3x 10 mL). The resin was then treated with DBU/piperidine/NMP (2:2:96 v/v; 5x 10 mL) and NMP (3x 10 mL). A solution of (S)-2,4-dimethyl-4-pentenoic acid (3.0 eq, 1.1 mmol, 0.14 g), HOBt (3.0 eq, 1.1 mmol, 0.15 g) and DIC (3.0 eq, 1.1 mmol, 0.23 mL) were successively dissolved in NMP (5 mL), shaken for 1 min, and then added to the resin. The suspension was shaken (200 rpm) for 11 h and then washed with NMP (4x 10 mL) and CH₂Cl₂ (3x 10 mL). For cleavage, the resin was treated with HFIP/CH₂Cl₂ (1:4 v/v; 5 mL) for 2 h followed by evaporation of the solvent in an argon stream and drying in fine vacuum (p = 0.1 mbar). Column chromatography (h = 12 cm, d = 2 cm, 2% - 4% MeOH in CHCl₃) of the resulting crude peptide gave acid 20 (80 mg, 0.10 mmol, 28%) as a colorless wax.
$R_f=0.42$ (CH$_2$Cl$_2$/MeOH 10:1); LC: $t_R=10.07$ min; $\left[\alpha\right]_D^{23}+29.3$ (c 0.83 in CHCl$_3$); $\nu_{\text{max}}$/cm$^{-1} = 2944$, 2867, 1645, 1511 and 1453 cm$^{-1}$; $\delta_H$/CDCl$_3$ mixture of rotamers (ratio 9:1), major rotamer: 8.42 (1H, s, Trp2-NH$_3$), 7.51 (1H, d, $^3J$ 7.6, Trp4-H), 7.26-7.23 (1H, m, Trp7-H), 7.13-7.04 (4H, m, Trp6-H, $\beta$Tyr2-H, $\beta$Tyr6-H, Trp5-H), 6.87 (1H, d, $^3J$ 8.4, $\beta$Tyr$\beta$-NH), 6.80 (2H, d, $^3J$ 8.4, $\beta$Tyr3-H, $\beta$Tyr5-H), 5.68 (1H, dd, $^3J$ 8.8 and 7.6, Trp$\alpha$-H), 5.37 (1H, td, $^3J$ 8.1 and 5.4, $\beta$Tyr$\beta$-H), 4.72 (1H, s, Pea5-H$_a$), 4.65 (1H, s, Pea5-H$_b$), 4.59 (1H, dq, $^3J$ 7.1 and 7.1, Ala$\alpha$-NH$_3$), 4.52 (2H, d, $^3J$ 8.4, $\beta$Tyr$\beta$-NH), 3.41-3.36 (1H, m, Trp$\beta$-H$_a$), 3.29-3.24 (1H, m, Trp$\beta$-H$_b$), 2.99 (3H, s, Trp-NC$_3$H$_3$), 2.83 (1H, dd, $^3J$ 5.4, $^2J$ 15.0, $\beta$Tyr$\alpha$-H), 2.74 (1H, dd, $^3J$ 8.1, $^2J$ 15.0, $\beta$Tyr$\alpha$-H), 2.45-2.27 (2H, m, Pea2-H, Pea3-H$_a$), 2.07-1.96 (1H, m, Pea3-H$_b$), 1.63 (3H, s, Pea7-H$_3$), 1.29-1.18 (3H, m, TIPS), 1.09 (18H, d, $^3J$ 7.2, TIPS), 1.06 (3H, d, $^3J$ 6.8, Pea6-H$_3$) and 0.62 (3H, d, $^3J$ 7.1, Ala$\beta$-H$_3$); $\delta_C$/CDCl$_3$ 177.5 (Pea-1), 174.1 (Ala-C=O), 172.1 (Trp-C=O), 168.9 ($\beta$Tyr-C=O), 155.4 ($\beta$Tyr-4), 142.5 (Pea-4), 136.0 (Trp-7a), 132.8 ($\beta$Tyr-1), 127.5 (Trp-3a), 127.4 (2x, $\beta$Tyr-2, $\beta$Tyr-6), 122.3 (Trp-6), 120.1 (Trp-5), 119.9 (2x, $\beta$Tyr-3, $\beta$Tyr-5), 118.2 (Trp-4), 112.6 (Pea-5), 110.5 (Trp-3), 110.4 (Trp-7), 109.0 (Trp-2), 55.6 (Trp-\alpha), 49.6 ($\beta$Tyr-$\beta$), 45.5 (Ala-\alpha), 41.6 (Pea-3), 40.5 ($\beta$Tyr-\alpha), 38.7 (Pea-2), 30.7 (Trp-NCH$_3$), 23.0 (Trp-\beta), 22.1 (Pea-7), 17.9 (6x, TIPS), 17.6 (Pea-6), 17.0 (Ala-\beta) and 12.6 (3x, TIPS); $m/z$ (ESI): calc. for C$_{40}$H$_{58}^{79}$BrN$_4$O$_6$Si [M+H]$^+$: 797.3304, found 797.3311.

Pea-Ala-$D$-$N$-MeTrp-$\beta$Tyr(TIPS)-O-Mhx (4)
The peptidic acid 19 (44 mg, 61 µmol) was placed in a 5 mL-flask equipped with a stirring bar was dissolved in a mixture of anhydrous CH$_2$Cl$_2$ (3 mL) and anhydrous N,N-dimethylformamide (0.2 mL) under argon atmosphere. At 23°C alcohol 16 (4.0 eq, 0.24 mmol, 36 mg), DMAP (2.0 eq, 0.12 mmol, 15 mg), DIPEA (2.0 eq, 0.12 mmol, 22 µL), and EDC-HCl (2.0 eq, 0.12 mmol, 23 mg) were added consecutively to the colorless solution. The mixture was stirred for 18.5 h, diluted with AcOEt (5 mL), and washed with saturated aqueous NH$_4$Cl solution (1x 4 mL, 1x 5 mL). The aqueous layer was extracted with AcOEt (1x 5 mL), and the combined organic extracts were washed with brine (1x 5 mL), dried with MgSO$_4$, filtered, and concentrated. Column chromatography (h = 14.5 cm, d = 1 cm; 30% - 50% AcOEt in cyclohexane) of the crude product yielded peptidic diene 4 as a colorless wax (37 mg, 45 µmol, 74 %).

$R_t=0.36$ (AcOEt/cyclohexane 1:1); LC: $t_R=12.53$ min; [$\alpha$]$_D^{23}+13.8$ (c 0.82 in CHCl$_3$); $\delta$(500 MHz, CDCl$_3$) mixture of rotamers (ratio >8:1), major rotamer: 8.05 (1H, s, Trp2-NH), 7.60 (1H, d, $3J$ 7.8, Trp4-H), 7.32 (1H, d, $3J$ 7.8, Trp7-H), 7.17 (1H, t, $3J$ 7.8, Trp6-H), 7.13-7.09 (2H, m, Trp5-H, $\beta$Tyr$\beta$-NH), 7.08 (2H, d, $3J$ 8.6, $\beta$Tyr2-H, $\beta$Tyr6-H), 6.94 (1H, d, $3J$ 2.0, Trp2-H), 6.76 (2H, d, $3J$ 8.6, $\beta$Tyr3-H, $\beta$Tyr5-H), 6.31 (1H, d, $3J$ 6.3, Ala$\alpha$-NH), 5.63 (1H, ddd, $3J$ 17.4, 10.3 and 7.6, Mhx5-H), 5.55 (1H, dd, $3J$ 10.4 and 6.0, Trpa-H), 5.35 (1H, dt, $3J$ 7.7 and 7.0, $\beta$Tyr$\beta$-H), 4.91 (1H, d, $3J$ 17.4, Mhx6-H$_{trans}$), 4.87 (1H, d, $3J$ 10.3, Mhx6-H$_{cis}$), 4.89-4.81 (1H, m, Mhx2-H), 4.77 (1H, s, Pea5-H$_a$), 4.70 (1H, s, Pea5-H$_b$), 4.66-4.58 (1H, m, Ala$\alpha$-H), 3.46 (1H, dd, $3J$ 6.0, $2J$ 15.7, Trp$\beta$-H$_a$), 3.21 (1H, dd, $3J$ 10.4, $2J$ 15.7, Trp$\beta$-H$_b$), 2.94 (3H, s, Trp-NCH$_3$), 2.87 (1H, dd, $3J$ 7.0, $2J$ 15.2, $\beta$Tyr$\alpha$-H$_a$), 2.73 (1H, dd, $3J$ 7.0, $2J$ 15.2, $\beta$Tyr$\alpha$-H$_b$), 2.45-2.35 (2H, m, Pea2-H, Pea3-H$_a$), 2.10-1.99 (2H, m, Mhx4-H, Pea3-H$_b$), 1.68 (3H, s, Pea7-H$_3$), 1.57 (1H, ddd, $3J$ 7.5 and 7.5, $2J$ 14.1, Mhx3-H$_a$), 1.30-1.18 (4H, m, Mhx3-H$_b$, TIPS), 1.10 (3H, d, $3J$ 6.2, Mhx1-H$_3$), 1.08 (18H, d, $3J$ 7.3, TIPS), 1.10-1.06 (m, 3H, Pea6-H$_3$), 0.96 (3H, d, $3J$ 6.8, Ala$\beta$H$_3$) and 0.90 (3H, d, $3J$ 6.7, Mhx7-H$_3$); $\delta_c$(100 MHz, CDCl$_3$) 175.9 (Pea-1), 173.8 (Ala-C=O), 170.4 (Trp-C=O), 168.9 ($\beta$Tyr-C=O), 155.4 ($\beta$Tyr-4), 143.7 (Mhx-5), 142.8 (Pea-4), 136.1 (Trp-7a), 132.9 ($\beta$Tyr-1), 127.5 (2x, $\beta$Tyr-2, $\beta$Tyr-6), 127.4 (Trp-3a), 122.1 (Trp-2/Trp-6), 122.0 (Trp-6/Trp-2), 119.7 (2x, $\beta$Tyr-3, $\beta$Tyr-5), 119.5 (Trp-5), 118.6 (Trp-4), 112.7 (Mhx-6), 112.4 (Pea-5), 111.2 (Trp-3), 111.0 (Trp-7), 69.6 (Mhx-2), 56.9 (Trp-$\alpha$), 49.4 ($\beta$Tyr-$\beta$), 45.7 (Ala-$\alpha$), 42.4 (Mhx-3), 41.8 (Pea-3), 40.9 ($\beta$Tyr-$\alpha$), 38.8 (Pea-2), 34.3 (Mhx-4), 31.0 (Trp-NCH$_3$), 23.4 (Trp-$\beta$), 22.2 (Pea-7), 20.0 (2x, Mhx-7, Mhx-1), 17.9 (6x, TIPS), 17.2 (Ala-$\beta$), 17.0 (Pea-6) and 12.6 (3x, TIPS); $m/z$ (ESI): calc. for C$_{47}$H$_{71}$N$_4$O$_6$Si [M+H]$^+$: 815.5137, found 815.5144.

S8
The peptidic acid 20 (72 mg, 90 µmol) was esterified with olefinic alcohol 16 (4.0 eq, 0.36 mmol, 52 mg) as described above for ester 4. Column chromatography \( (h = 11 \text{ cm}, d = 1 \text{ cm}; 20\% - 50\% \text{ AcOEt in cyclohexane}) \) of the crude product yielded the desired peptidic diene 5 as colorless wax (31 mg, 35 µmol, 39%).

\[ R_f=0.53 \text{ (AcOEt/cyclohexane 1:1); LC: } t_R=12.87 \text{ min}; [\alpha]_D^{23} +27.6 \text{ (c 1.0 in CHCl}_3); v_{\text{max}}/\text{cm}^{-1} = 3272, 2931, 2867, 1734, 1640 \text{ and } 1511 \text{ cm}^{-1}; \delta_H(500 \text{ MHz, CDCl}_3) \text{ mixture of rotamers (ratio 7:1), major rotamer: 8.43 (1H, s, Trp2-NH), 7.51 (1H, d, } ^3J 8.0, \text{ Trp4-H), 7.22 (1H, d, } ^3J 8.0, \text{ Trp7-H), 7.13-7.09 (3H, m, Trp6-H, } \beta\text{Tyr2-H, } \beta\text{Tyr6-H), 7.09-7.01 (2H, m, Trp5-H, } \beta\text{Tyr\beta-NH), 6.77 (2H, d, } ^3J 9.0, \beta\text{Tyr3-H, } \beta\text{Tyr5-H), 6.20 (1H, d, } ^3J 6.5, \text{ Alaα-NH), 5.62 (1H, ddd, } ^3J 17.0, 10.3 \text{ and } 7.5, \text{ Mhx5-H), 5.58 (1H, dd, } ^3J 11.0 \text{ and } 5.5, \text{ Trpα-H), 5.38 (1H, dt, } ^3J 7.0 \text{ and } 6.8, \beta\text{Tyrβ-H), 4.91-4.81 (1H, m, Mhx2-H), 4.91 (1H, d, } ^3J 17.0, \text{ Mhx6-H}^{\text{trans}), 4.87 (1H, d, } ^3J 10.3, \text{ Mhx6-H}^{\text{cis}), 4.74 (1H, s, Pea5-H}_a, 4.66 (1H, s, Pea5-H}_b, 4.52 (1H, dq, } ^3J 6.5 \text{ and } 6.5, \text{ Alaα-H), 3.42 (1H, dd, } ^3J 5.5, ^2J 15.3, \text{ Trpβ-H}_a, 3.22 (1H, dd, } ^3J 11.0, ^2J 15.3, \text{ Trpβ-H}_b, 2.97 (3H, s, Trp-NCH}_3), 2.89 (1H, dd, } ^3J 6.8, ^2J 15.4, \beta\text{Tyrα-H}_a, 2.74 (1H, dd, } ^3J 6.8, ^2J 15.4, \beta\text{Tyrβ-H}_b, 2.39-2.28 (2H, m, Mhx4-H, Pea3-H}_a), 2.07-1.95 (2H, m, Pea2-H, Pea3-H}_b), 1.65 (3H, s, Pea7-H}_3), 1.61-1.52 (1H, m, Mhx3-H}_a), 1.30-1.17 (4H, m, Mhx3-H}_b, \text{TIPS), 1.10 (3H, d, } ^3J 6.0, \text{ Mhx1-H}_3) 1.08 (18H, d, } ^3J 7.5, \text{TIPS), 1.06 (3H, d, } ^3J 7.0,
Pea6-\(H_3\), 0.90 (3H, d, \(^3J\) 7.0, Mhx-7-\(H_3\)) and 0.72 (3H, d, \(^3J\) 6.5, Ala\(\beta\)-\(H_3\)); \(\delta\)\(_C\)(125 MHz, CDCl\(_3\)): 176.0 (Pea-1), 173.7 (Ala-C=O), 170.4 (Trp-C=O), 168.7 (\(\beta\)Tyr-C=O), 155.4 (\(\beta\)Tyr-4), 143.7 (Mhx-5), 142.7 (Pea-4), 136.0 (Trp-7a), 132.7 (\(\beta\)Tyr-1), 127.6 (2x, \(\beta\)Tyr-2, \(\beta\)Tyr-6), 127.4 (Trp-3a), 122.3 (Trp-6), 120.0 (Trp-5), 119.8 (2x, \(\beta\)Tyr-3, \(\beta\)Tyr-5), 118.2 (Trp-4), 112.7 (Mhx-6), 112.4 (Pea-5), 110.6 (Trp-3), 110.4 (Trp-7), 109.0 (Trp-2), 69.5 (Mhx-2), 56.6 (Trp-\(\alpha\)), 49.5 (\(\beta\)Tyr-\(\beta\)), 45.5 (Ala-\(\alpha\)), 42.3 (Mhx-3), 41.7 (Pea-3), 40.8 (\(\beta\)Tyr-\(\alpha\)), 38.6 (Mhx-4), 34.2 (Pea-2), 32.0 (Trp-NCH\(_3\)), 23.5 (Trp-\(\beta\)), 22.2 (Pea-7), 20.0 (Mhx-1), 20.0 (Mhx-7), 17.9 (6x, TIPS), 17.0 (Pea-6), 16.6 (Ala-\(\beta\)) and 12.6 (3x, TIPS); \(m/z\) (ESI): calc. for C\(_{47}\)H\(_{70}\)BrN\(_4\)O\(_6\)Si [M+H]\(^+\): 893.4243, found 893.4253.

The peptidic acid 19 (50 mg, 70 \(\mu\)mol) was esterified with olefinic alcohol 17 (4.0 eq, 0.28 mmol, 64 mg) as described above for ester 4. Column chromatography (\(h\) = 14.5 cm, \(d\) = 1 cm; 25% - 40% AcOEt in cyclohexane) of the crude product yielded the desired peptidic diene 6 as colorless wax (42 mg, 48 \(\mu\)mol, 68%).

\(R_f\)=0.56 (AcOEt/cyclohexane 3:2); LC: \(t_R=15.53\) min; \(\alpha\)\(_D\)=+18.3 (c 1.0 in CHCl\(_3\)); \(\delta\)\(_\text{H}(400\) MHz, CDCl\(_3\)) mixture of rotamers (ratio 10:1), major rotamer: 8.12 (1H, s, Trp2-NH), 7.59 (1H, d, \(^3J\) 7.8, Trp4-H), 7.32 (1H, d, \(^3J\) 7.7, Trp7-H), 7.17 (1H, t, \(^3J\) 7.7, Trp6-H), 7.13-7.07 (3H, m, Trp5-H, \(\beta\)Tyr2-H, \(\beta\)Tyr6-H), 6.94 (1H, s, Trp2-H), 6.76 (2H, d, \(^3J\) 8.4, \(\beta\)Tyr3-H, \(\beta\)Tyr5-H), 6.33 (1H, d, \(^3J\) 6.2, Ala\(\alpha\)-NH), 5.79 (ddt, \(^3J\) 17.0, 10.2 and 6.6, 1H, Und10-H), 5.55
(dd, $^3J$ 10.4 and 5.9, 1H, Trpα-H), 5.36 (1H, dt, $^3J$ 7.6 and 7.0, βTyrβ-H), 5.26 (1H, dd, $^3J$ 10.8 and 7.2, Und6-H), 5.10 (1H, dd, $^3J$ 10.2 and 10.2, Und5-H), 4.99 (1H, d, $^3J$ 17.0, Und11-Htrans), 4.94 (1H, d, $^3J$ 10.2, Und11-Hcis), 4.82-4.72 (1H, m, Und2-H), 4.77 (1H, s, Pea5-Htrans), 4.70 (1H, s, Pea5-Hcis), 4.66-4.56 (1H, m, Alaα-H), 3.46 (1H, dd, $^3J$ 5.9, $^2J$ 15.8, Trpβ-Ha), 3.21 (1H, dd, $^3J$ 10.4, $^2J$ 15.8, Trpβ-Hb), 2.94 (3H, s, Trp-NC3-H3), 2.86 (1H, dd, $^3J$ 7.0, $^2J$ 15.1, βTyrα-Ha), 2.73 (1H, dd, $^3J$ 7.0, $^2J$ 15.1, βTyrα-Hb), 2.47-2.32 (3H, m, Pea2-H, Pea3-Ha, Und4-H), 2.10-1.91 (5H, m, Pea3-Hb, Und7-H2, Und9-H2), 1.68 (3H, s, Pea7-H3), 1.52-1.37 (3H, m, Und3-Ha, Und8-H2), 1.34-1.16 (4H, m, Und3-Hb, TIPS), 1.13-1.02 (24H, m, Und1-H3, TIPS, Pea6-H3), 0.95 (3H, d, $^3J$ 6.8, Alaβ-H3) and 0.86 (3H, d, $^3J$ 6.6, Und12-H3);

$\delta$C(100 MHz, CDCl3) 175.9 (Pea-1), 173.8 (Ala-C=O), 170.3 (Trp-C=O), 168.9 (βTyr-C=O), 155.3 (βTyr-4), 142.8 (Pea-4), 138.7 (Und-10), 136.0 (Trp-7α), 135.2 (Und-5), 132.9 (βTyr-1), 128.4 (Und-6), 127.5 (2x, βTyr-2, βTyr-6), 127.3 (Trp-3α), 122.0 (2x, Trp-6, Trp-2), 119.7 (2x, βTyr-3, βTyr-5), 119.4 (Trp-5), 118.5 (Trp-4), 114.5 (Und-11), 112.4 (Pea-5), 111.1 (Trp-3), 111.0 (Trp-7), 69.9 (Und-2), 56.9 (Trp-α), 49.5 (βTyr-β), 45.7 (Ala-α), 43.1 (Und-3), 41.8 (Pea-3), 41.0 (βTyr-α), 38.7 (Pea-2), 33.3 (Und-9), 31.0 (Trp-NCH3), 29.0 (Und-8), 28.3 (Und-4), 26.8 (Und-7), 23.3 (Trp-β), 22.2 (Pea-7), 21.3 (Und-12), 19.7 (Und-1), 17.9 (6x, TIPS), 17.2 (Ala-β), 16.9 (Pea-6) and 12.6 (3x, TIPS); $\nu_{\text{max}}$/cm$^{-1}$ = 3307, 2930, 2867, 1732, 1639 and 1510 cm$^{-1}$; $m/z$ (ESI): calc. for C$_{52}$H$_{79}$N$_4$O$_6$Si [M+H]$^+$: 883.5763, found 883.5771.

cyclo-[Ala-D-N-MeTrp-βTyr-O-Htn] (2 + 7)

Standard RCM:
The peptidic diene 4 (34 mg, 42 µmol) was placed in a 50 mL-two-neck flask equipped with a stirring bar and dissolved in anhydrous toluene (40 mL). Argon was bubbled through the
colorless solution via canula at 23 °C for 15 min. A cooler was placed on one neck, and the flask was placed in an oil bath at 120 °C, and argon purging was continued for another 20 min. Catalyst 21 (0.30 Äq., 13 µmol, 11 mg) was dissolved in anhydrous toluene (0.8 mL), and the resulting dark solution was added in one portion via syringe to the diene solution. The solution was cooled down to 23 °C and concentrated to give a dark-brown wax. Column chromatography (h = 16 cm, d = 1 cm; 60% AcOEt in cyclohexane) of the crude product yielded cyclo-[Ala-D-N-MeTrp-βTyr-O(TIPS)-(E)-Htn] (5.8 mg, 7.4 µmol, 18%) and cyclo-[Ala-D-N-MeTrp-βTyr-O(TIPS)-(Z)-Htn] (7.4 mg, 9.4 µmol, 23%) as colorless waxes.

Relay-RCM:
Peptidic diene 6 (39 mg, 44 µmol) was subjected to ring-closing metathesis according to the procedure described above for RCM starting from precursor 4. Column chromatography (h = 13.5 cm, d = 1 cm; 25% - 60% AcOEt in cyclohexane) of the crude product yielded cyclodepsipeptides cyclo-[Ala-D-N-MeTrp-βTyr-O(TIPS)-(E)-Htn] (11.7 mg, 15 µmol, 34%) and cyclo-[Ala-D-N-MeTrp-βTyr-O(TIPS)-(Z)-Htn] (11 mg, 13 µmol, 30%) as colorless waxes.

\[E\]-isomer:

Rf=0.32 (AcOEt/cyclohexane 3:2); LC: tR=11.96 min; [α]D\text{23} +27.5 (c 0.40 in CHCl3); δH(600 MHz, CDCl3) 7.95 (1H, s, Trp2-NH), 7.62 (1H, d, 3J 7.8, Trp4-H), 7.44 (1H, d, 3J 9.0, βTyr-β-NH), 7.34 (1H, d, 3J 7.8, Trp7-H), 7.19 (1H, td, 4J 1.1, 3J 7.8, Trp6-H), 7.13 (1H, td, 4J 0.9, 3J 7.8, Trp5-H), 7.00 (2H, d, 3J 8.6, βTyr2-H, βTyr6-H), 6.95 (1H, d, 3J 2.1, Trp2-H),
6.78 (2H, d, $^3J$ 8.6, $\beta$Tyr3-$H$, $\beta$Tyr5-$H$), 6.73 (1H, d, $^3J$ 6.4, Alaα-$NH$), 5.66 (1H, dd, $^3J$ 9.9 and 6.5, Trpα-$H$), 5.30 (1H, ddd, $^3J$ 9.0, 5.5 and 4.6, $\beta$Tyrβ-$H$), 4.81-4.74 (2H, m, Htn5-$H$, Alaα-$H$), 4.62 (1H, ddd, $^3J$ 10.2, 6.3 and 4.1, Htn8-$H$), 3.40 (1H, ddd, $^4J$ 0.7, $^3J$ 6.5, $^2J$ 15.7, Trpβ-$H_a$), 3.23 (1H, dd, $^3J$ 9.9, $^2J$ 15.7, Trpβ-$H_b$), 2.94 (3H, s, Trp-NCH$_3$), 2.69 (1H, dd, $^3J$ 4.6, $^2J$ 15.1, $\beta$Tyrα-$H_a$), 2.59 (1H, dd, $^3J$ 5.5, $^2J$ 15.1, $\beta$Tyrα-$H_b$), 2.55 (1H, ddd, $^3J$ 11.5, 7.0 and 2.5, Htn2-$H$), 2.39 (1H, dd, $^3J$ 11.5, $^2J$ 15.9, Htn3-$H_a$), 2.29-2.20 (1H, m, Htn6-$H$), 1.91 (1H, app d, $^2J$ 15.7, Htn3-$H_b$), 1.58 (3H, s, Htn11-$H_b$), 1.31 (1H, ddd, $^3J$ 11.3, 3.2, $^2J$ 14.0, Htn7-$H_a$), 1.27-1.21 (3H, m, TIPS), 1.15 (3H, d, $^3J$ 7.0, Htn10-$H_3$), 1.15-1.10 (1H, m, Htn7-$H_b$), 1.09 (18H, d, $^3J$ 7.4, TIPS), 1.05 (3H, d, $^3J$ 6.3, Htn9-$H_3$), 1.01 (3H, d, $^3J$ 6.7, Alaβ-$H_3$) and 0.83 (3H, d, $^3J$ 6.7, Htn12-$H_3$); $\delta$C(100 MHz, CDCl$_3$) 174.9 (Htn-1), 174.2 (Ala-C=O), 170.5 (Trp-C=O), 168.9 ($\beta$Tyr-C=O), 155.3 ($\beta$Tyr-4), 136.1 (Trp-7a), 133.8 (Htn-4), 132.9 ($\beta$Tyr-1), 127.8 (Htn-5), 127.6 (Trp-3a), 127.0 (2x, $\beta$Tyr-2, $\beta$Tyr-6), 122.2 (Trp-2), 121.9 (Trp-6), 119.8 (2x, $\beta$Tyr-3, $\beta$Tyr-5), 119.5 (Trp-5), 118.6 (Trp-4), 111.1 (Trp-7), 111.0 (Trp-3), 70.4 (Htn-8), 55.9 (Trp-α), 48.7 ($\beta$Tyr-β), 46.2 (Ala-α), 43.5 (Htn-7), 40.6 (Htn-3), 40.1 ($\beta$Tyr-α), 39.8 (Htn-2), 30.2 (Trp-NCH$_3$), 29.2 (Htn-6), 22.8 (Htn-12), 22.2 (Trp-β), 19.0 (Htn-9), 18.6 (Htn-10), 17.9 (8x, Ala-β, Htn-11, TIPS) and 12.6 (3x, TIPS); m/z (ESI): calc. for C$_{45}$H$_{97}$N$_4$O$_{16}$Si [M+H]$^+$: 787.4824, found 787.4828.

Z-isomer:

$R_t$=0.42 (AcOEt/cyclohexane 3:2); LC: $t_R$=12.01 min; [$\alpha$]$_D^{23}$ =+20.5 (c 0.39 in CHCl$_3$); $\delta$H(600 MHz, CDCl$_3$) 7.95 (1H, s, Trp2-NH), 7.62 (1H, d, $^3J$ 7.8, Trp4-$H$), 7.33 (1H, d, $^3J$ 7.8, Trp7-$H$), 7.18 (1H, td, $^4J$ 1.0, $^3J$ 7.8, Trp6-$H$), 7.14 (1H, d, $^3J$ 8.6, $\beta$Tyrβ-NH), 7.12 (1H, td, $^4J$ 0.9, $^3J$ 7.8, Trp5-$H$), 7.01 (2H, d, $^3J$ 8.6, $\beta$Tyr2-$H$, $\beta$Tyr6-$H$), 6.95 (1H, d, $^3J$ 1.7, Trp2-$H$),
6.77 (2H, d, J 8.6, βTyr3-H, βTyr5-H), 6.60 (1H, d, J 6.7, Alaα-NH), 5.59 (1H, dd, J 9.6 and 6.7, Trpα-H), 5.20 (1H, ddd, J 8.8, 8.6 and 4.5, βTyrβ-H), 5.02 (1H, d, J 9.3, Htn5-H), 4.78 (1H, dq, J 6.7/6.7, Alaα-H), 4.73 (1H, ddd, J 8.2, 6.4 and 3.3, Htn8-H), 3.37 (1H, ddd, J 0.7, 6.7, 2J 15.8, Trpβ-Hα), 3.22 (1H, dd, J 9.6, 2J 15.8, Trpβ-Hb), 2.99 (3H, s, Trp-NC3), 2.68 (1H, dd, J 4.5, 15.9, βTyr-Ha), 2.62 (1H, dd, J 8.8, 15.9, βTyr-Hb), 2.57 (1H, dd, J 9.2, 15.9, Htn3-Ha), 2.49 (2H, m, Htn2-H, Htn6-H), 1.96 (1H, dd, J 4.2, 15.9, Htn3-Hb), 1.51 (1H, ddd, J 8.2, 7.9, 14.3, Htn7-Ha), 1.33 (1H, ddd, J 6.5, 3.3, 14.3, Htn7-Hb), 1.27-1.19 (3H, m, TIPS), 1.17 (3H, d, J 6.9, Htn10-Ha), 1.10 (3H, d, J 6.7, Alaβ-H), 1.08 (18H, d, J 7.4, TIPS), 1.05 (3H, d, J 6.4, Htn9-Ha) and 0.84 (3H, d, J 6.7, Htn12-Ha); δC (100 MHz, CDCl3) 174.8 (Htn-1), 174.6 (Ala-C=O), 170.0 (Trp-C=O), 168.9 (βTyr-C=O), 155.2 (βTyr-4), 136.1 (Trp-7a), 133.7 (Htn-5), 133.3 (βTyr-1), 130.7 (Htn-4), 127.3 (Trp-3a), 127.2 (2x, βTyr-2, βTyr-6), 122.1 (Trp-6), 122.0 (Trp-2), 119.7 (2x, βTyr-3, βTyr-5), 119.5 (Trp-5), 118.6 (Trp-4), 111.1 (Trp-7), 111.0 (Trp-3), 70.8 (Htn-8), 55.8 (Trp-α), 48.9 (βTyr-β), 45.7 (Ala-α), 43.9 (Htn-7), 40.3 (βTyr-α), 39.1 (Htn-2), 35.6 (Htn-3), 30.5 (Trp-NCH3), 29.8 (Htn-6), 23.5 (Trp-β), 22.8 (Htn-12) 21.2 (Htn-9), 21.2 (Htn-10), 18.6 (Ala-β), 17.9 (6x, TIPS), 17.8 (Htn-11) and 12.6 (3x, TIPS); m/z (ESI): calc. for C_{45}H_{67}N_{4}O_{6}Si [M+H]^+: 787.4824, found 787.4828.

cyclo-[Ala-D-N-MeTrp-βTyr-O-(E)-Htn] (3) (desbromo Jasplakinolide)

Cyclo-[Ala-D-N-MeTrp-βTyr-O(TIPS)-(E)-Htn] (4.0 mg, 5.1 µmol) was placed in a 5-mL flask equipped with a stirring bar and dissolved in THF (1 mL). A solution of TBAF (1.0 eq, 5.1 µmol) in THF (1.0 M, 5.1 µL) was added dropwise at 23°C. The reaction mixture was
stirred for 30 min, and then concentrated. Column chromatography \((h = 3 \text{ cm}, d = 1 \text{ cm}; 3\% \text{ MeOH in CH}_2\text{Cl}_2)\) of the crude product yielded desilylated peptide 3 (2.6 mg, 4.1 µmol, 80%) as pale brown wax.

\(R_t=0.27\) (AcOEt/cyclohexane 4:1); LC: \(t_R=7.48\) min; \([\alpha]_D^{23}+9.6\) (c 0.25 in MeOH); 
\(\delta\)H (600 MHz, CDCl\(_3\)) 8.02 (1H, s, Trp2-N\(\text{H}\)), 7.62 (1H, d, \(\text{J} 7.8, \text{Trp4-H}\)), 7.45 (1H, d, \(\text{J} 8.6, \beta\text{Tyr}3-N\text{H}\)), 7.34 (1H, d, \(\text{J} 7.8, \text{Trp7-H}\)), 7.19 (1H, td, \(\text{J} 0.9, \text{J} 7.8, \text{Trp6-H}\)), 7.13 (1H, td, \(\text{J} 0.8, \text{J} 7.8, \text{Trp5-H}\)), 6.98 (2H, d, \(\text{J} 8.5, \beta\text{Tyr}2-\beta\text{Tyr}6-\text{H}\)), 6.92 (1H, d, \(\text{J} 8.5, \beta\text{Tyr}2-\text{H}\)), 6.72-6.68 (1H, m, Ala\(\alpha\)-N\text{H})), 6.71 (2H, d, \(\text{J} 8.6, \beta\text{Tyr}3-\beta\text{Tyr}5-\text{H}\)), 5.65 (1H, dd, \(\text{J} 9.7\) and \(\text{J} 6.7, \text{Trp}\alpha-\text{H}\)), 5.28 (1H, dt, \(\text{J} 8.6\) and \(\text{J} 5.4, \beta\text{Tyr}\beta-\text{H}\)), 4.82-4.75 (2H, m, Htn5-\text{H}, Ala\(\alpha\)-\text{H})), 4.64 (1H, ddd, \(\text{J} 10.2, \text{J} 6.4\) and \(\text{J} 4.2, \text{Htn8-}\text{H}\)), 3.41 (1H, ddd, \(\text{J} 0.5, \text{J} 6.7\) and \(\text{J} 15.6, \beta\text{Tyr}a-\text{H}\)), 3.21 (1H, dd, \(\text{J} 9.7, \text{J} 15.6, \beta\text{Tyr}b-\text{H}\)), 2.95 (3H, s, Trp-NC\text{H})), 2.69 (1H, dd, \(\text{J} 5.4, \text{J} 15.0, \beta\text{Tyr}a-\text{H}\)), 2.60 (1H, dd, \(\text{J} 5.4, \text{J} 15.0, \beta\text{Tyr}b-\text{H}\)), 2.53 (1H, ddd, \(\text{J} 11.4, \text{J} 7.0\) and \(\text{J} 2.7, \text{Htn2-}\text{H}\)), 2.37 (1H, dd, \(\text{J} 11.4, \text{J} 15.6, \text{Htn3-}\text{H}\)), 2.29-2.21 (1H, m, Htn6-\text{H})), 1.93 (1H, app d, \(\text{J} 15.6, \text{Htn3-}\text{H}\)), 1.59 (3H, s, Htn, 11-\text{H}_3)), 1.37-1.31 (1H, m, Htn7-\text{H}_3)), 1.19-1.15 (1H, m, Htn7-\text{H}_3)), 1.15 (3H, d, \(\text{J} 7.0, \text{Htn10-}\text{H}_3)), 1.07 (3H, d, \(\text{J} 6.4, \text{Htn9-}\text{H}_3)), 1.02 (3H, d, \(\text{J} 6.7, \text{Ala}\beta\text{-H}_3)) and 0.84 (3H, d, \(\text{J} 6.6, \text{Htn12-}\text{H}_3)); \(\delta\)C (150 MHz, CDCl\(_3\)) 175.0 (Htn-1), 174.3 (Htn5-\text{C}=\text{O}), 170.5 (Trp-\text{C}=\text{O}), 169.0 (\beta\text{Tyr}-\text{C}=\text{O}), 155.1 (\beta\text{Tyr}-4), 136.1 (Trp-7a), 133.9 (Htn-4), 132.0 (\beta\text{Tyr}-1), 127.8 (Htn-5), 127.3 (2x, \beta\text{Tyr}-2, \beta\text{Tyr}-6), 127.2 (Trp-3a), 122.0 (Trp-6/Trp-2), 121.9 (Trp-2/Trp-6), 119.6 (Trp-5), 118.5 (Trp-4), 115.4 (2x, \beta\text{Tyr}-3, \beta\text{Tyr}-5), 111.1 (Trp-3), 110.8 (Trp-7), 70.5 (Htn-8), 56.1 (Trp-\alpha)), 48.9 (\beta\text{Tyr}-\beta), 46.2 (Ala-\alpha), 43.5 (Htn-7), 40.8 (Htn-3), 40.2 (2x, \beta\text{Tyr}-\alpha, Htn-2), 29.7 (Trp-NCH\(_3\)), 29.2 (Htn-6), 23.0 (Trp-\beta), 21.9 (Htn-12), 20.4 (Htn-10), 18.0 (Htn-9/Htn-11), 17.9 (Ala-\beta) and 17.8 (Htn-11/Htn-9); \(m/z\) (ESI): calc. for C\(_{36}\)H\(_{47}\)N\(_{4}\)O\(_{6}\) [M+H]\(^{+}\): 631.3490, found 631.3488.
The desilylation of cyclo-[Ala-D-N-MeTrp-βTyr-O-(Z)-Htn] (4.5 mg, 5.7 µmol) was performed according to the procedure described for 3. Column chromatography (h = 8 cm, d = 1 cm; 3% - 10% MeOH in CH$_2$Cl$_2$) of the crude product yielded desilylated peptide 7 (2.9 mg, 4.6 µmol, 80%) as a colorless wax.

$R_f=0.45$ (AcOEt/cyclohexane 4:1); LC: $t_R=7.65$ min; $[\alpha]_D^{23} +8.0$ (c 0.23 in CHCl$_3$); $\nu_{\text{max}}$/cm$^{-1} = 3312, 2927, 2855, 1731, 1636$ and $1517$; $\delta_H$(600 MHz, CDCl$_3$) 8.07 (1H, s, Trp2-NH), 7.60 (1H, d, $^3J$ 7.6, Trp4-H), 7.35-7.31 (2H, m, Trp7-H, βTyrβ-NH), 7.16 (1H, td, $^3J$ 7.6, Trp6-H), 7.10 (1H, td, $^3J$ 7.6, Trp5-H), 6.99 (2H, d, $^3J$ 8.4, βTyr2-H, βTyr6-H), 6.88 (1H, s, Trp2-H), 6.67 (2H, d, $^3J$ 8.4, βTyr3-H, βTyr5-H), 6.35 (1H, d, $^3J$ 6.3, Alaα-NH), 5.64 (1H, dd, $^3J$ 9.1 and 6.9, Trpα-H), 5.18 (1H, ddd, $^3J$ 8.8, 8.4 and 5.1, βTyrβ-H), 5.04 (1H, d, $^3J$ 9.1, Htn5-H), 4.78 (1H, ddd, $^3J$ 9.0, 6.4 and 2.8, Htn8-H), 4.69 (1H, dq, $^3J$ 6.9 and 6.3, Alaα-H), 3.45 (1H, dd, $^3J$ 6.9, $^2J$ 15.8, Trpβ-H$_a$), 3.18 (1H, dd, $^3J$ 9.1, $^2J$ 15.8, Trpβ-H$_b$), 3.02 (3H, s, Trp-NCH$_3$), 2.74 (1H, dd, $^3J$ 8.8, $^2J$ 16.1, βTyrα-H$_a$), 2.68 (1H, dd, $^3J$ 5.1, $^2J$ 16.1, βTyrα-H$_b$), 2.53-2.40 (3H, m, Htn6-H, Htn2-H, Htn3-H$_a$), 2.16 (1H, dd, $^3J$ 3.7, $^2J$ 14.0, Htn3-H$_b$), 1.65 (3H, s, Htn11-H$_3$), 1.49 (1H, ddd, $^3J$ 9.0 and 6.8, $^2J$ 14.4, Htn7-H$_a$), 1.35-1.23 (1H, m, Htn7-H$_b$), 1.16 (3H, d, $^3J$ 6.6, Htn10-H$_3$), 1.08 (3H, d, $^3J$ 6.9, Alaβ-H$_3$), 1.07 (3H, d, $^3J$ 6.4, Htn9-H$_3$) and 0.84 (3H, d, $^3J$ 6.6, Htn12-H$_3$); $\delta_C$(150 MHz, CDCl$_3$) 175.0 (Htn-1), 174.6 (Ala-C=O), 169.8 (Trp-C=O), 168.7 (βTyr-C=O), 155.1 (βTyr-4), 136.0 (Trp-7a), 133.8 (Htn-5), 132.7 (βTyr-1), 130.4 (Htn-4), 127.3 (2x, βTyr-2, βTyr-6), 127.1 (Trp-3a), 121.9 (Trp-6), 121.7 (Trp-2), 119.3 (Trp-5), 118.4 (Trp-4), 115.2 (2x, βTyr-3, βTyr-5), 111.0 (Trp-3), 110.8...
(Trp-7), 70.3 (Htn-8), 56.0 (Trp-α), 49.2 (βTyr-β), 45.5 (Ala-α), 43.8 (Htn-7), 40.1 (βTyr-α),
39.0 (Htn-6), 35.1 (Htn-3), 30.6 (Trp-NCH₃), 29.3 (Htn-6), 23.6 (Htn-11), 22.6 (Trp-β), 20.8
(Htn-9), 20.8 (Htn-12), 17.6 (Htn-10) and 17.1 (Ala-β); m/z (ESI): calc. for C₃₆H₄₁N₄O₆

![Chemical Structure](image)

cyclo-[Ala-D-2-Br-N-MeTrp-βTyr-O-Htn] (1 + 8)

Peptidic diene 5 (30 mg, 34 µmol) was subjected to ring-closing metathesis according to the
procedure described above for compound 3. Column chromatography (h = 12 cm, d = 1 cm;
20% - 50% AcOEt in cyclohexane) of the crude metathesis product yielded an E/Z-mixture of
cyclo-[Ala-D-2-Br-N-MeTrp-βTyr(TIPS)-O-Htn] (12 mg, 14 µmol, 42%) as a pale brown wax that was subjected to desilylation according to the procedure described for compound 3.
Column chromatography (h = 6 cm, d = 1 cm; 30% - 80% AcOEt in cyclohexane) followed
by preparative HPLC yielded 1 (jasplakinolide) (2.3 mg, 3.2 µmol, 10% from 5) and its Z-
isomer 8 (4.2 mg, 5.9 µmol, 18% from 5), both as colorless waxes.
Jasplakinolide (Jaspamide) (1)

\( R_f = 0.65 \) (AcOEt/cyclohexane 4:1); LC: \( t_R = 7.70 \) min; m.p. 110°C (decomposition); \( [\alpha]_D^{23} +11.0 \) (c 0.18 in MeOH) (lit., \( +35 \) (c 2.4 in MeOH); \( \nu_{\text{max}} / \text{cm}^{-1} = 3211, 3065, 2978, 1663, 1647, 1636, 1517 \) and 1449 cm\(^{-1}\); \( \delta \)H (600 MHz, CDCl\(_3\)) 8.06 (1H, s, Trp2-NH), 7.60 (1H, d, \( J = 7.9 \), Trp4-NH), 7.54 (1H, d, \( J = 7.8 \), \( \beta \)-Tyr\( \beta\)-NH), 7.54 (1H, d, \( J = 7.8 \), \( \beta \)-Tyr\( \beta\)-NH), 7.27-7.24 (1H, m, Trp7-NH), 7.16 (1H, d, \( J = 7.9 \), Trp6-NH), 7.11 (1H, d, \( J = 7.9 \), Trp5-NH), 7.04 (2H, d, \( J = 8.6 \), \( \beta \)-Tyr2-NH, \( \beta \)-Tyr6-NH), 6.88-6.85 (1H, m, Ala\( \alpha\)-NH), 6.74 (2H, d, \( J = 8.6 \), \( \beta \)-Tyr3-NH, \( \beta \)-Tyr5-NH), 5.82 (1H, dd, \( J = 10.6 \) and 6.1, Trp-\( \alpha\)-H), 5.31-5.26 (1H, m, \( \beta \)-Tyr\( \beta\)-H), 4.74 (1H, dq, \( J = 6.7 \) and 6.7, Ala\( \alpha\)-H), 4.70 (1H, d, \( J = 10.1 \), Htn5-H), 4.61-4.55 (1H, m, Htn8-H), 3.36 (1H, dd, \( J = 6.1 \), \( J = 15.4 \), Trp\( \beta\)-H\( \alpha\)), 3.23 (1H, dd, \( J = 10.6 \), \( J = 15.4 \), Trp\( \beta\)-H\( \beta\)), 2.99 (3H, s, Trp-NCH\(_3\)), 2.68 (1H, dd, \( J = 4.8 \), \( J = 15.1 \), \( \beta \)-Tyr\( \alpha\)-H\( \alpha\)), 2.62 (1H, dd, \( J = 5.3 \), \( J = 15.1 \), \( \beta \)-Tyr\( \alpha\)-H\( \beta\)), 2.56-2.50 (1H, m, Htn2-H), 2.35 (1H, dd, \( J = 11.6 \), \( J = 16.4 \), Htn3-H\( \alpha\)), 2.30-2.21 (1H, m, Hdn6-H), 1.90 (1H, app d, \( J = 16.4 \), Htn3-H\( \beta\)), 1.56 (3H, s, Htn11-H\( \delta\)), 1.31-1.25 (2H, m, Htn7-H\( \delta\)), 1.12 (3H, d, \( J = 7.0 \), Htn10-H\( \beta\)), 1.05 (3H, d, \( J = 6.3 \), Htn9-H\( \beta\)), 0.81 (3H, d, \( J = 6.6 \), Htn12-H\( \beta\)) and 0.74 (3H, d, \( J = 6.7 \), Ala\( \beta\)-H\( \beta\)); \( m/z \) (ESI): calc. for \( C_{36}H_{46}^{79}\text{Br}_{4}N_{6}O_{6} \) [M+H]\(^+\): 709.2595, found 709.2595.
cis-Jasplakinolide (cis-Jaspamide) (8)

$R_f=0.65$ (AcOEt/cyclohexane 4:1); LC: $t_R=7.93$ min; m.p. 110 - 112°C (decomposition); $[\alpha]_D^{23} +21.0$ (c 0.34 in MeOH); $v_{max}/\text{cm}^{-1} = 3206, 3065, 2975, 1663, 1646, 1637, 1517$ and 1448 cm$^{-1}$; $\delta_H(500 \text{MHz, CDCl}_3) 8.11 (1\text{H, s, Trp2-}NH)$, 7.49 (1H, d, $^3J 7.8$, Trp4-)$H$, 7.37 (1H, d, $^3J 8.1$, $\beta$Tyr-$\beta$-NH), 7.23 (1H, d, $^3J 7.8$, Trp7-)$H$, 7.14 (1H, t, $^3J 7.8$, Trp6-)$H$, 7.09 (1H, t, $^3J 7.8$, Trp5-)$H$, 7.03 (2H, d, $^3J 8.5$, $\beta$Tyr2-)$H$, $\beta$Tyr6-)$H$, 6.70 (2H, d, $^3J 8.5$, $\beta$Tyr3-)$H$, $\beta$Tyr5-)$H$, 6.47 (1H, d, $^3J 8.1$, Ala$\alpha$-NH), 5.74 1H, (dd, $^3J 10.3/6.1$, Trp$\alpha$-$H$), 5.16 (1H, td, $^3J 8.1/4.6$, $\beta$Tyr$\beta$-$H$), 5.00 (1H, d, $^3J 9.1$, Htn5-$H$), 4.79-4.73 (1H, m, Htn8-$H$), 4.61-4.55 (1H, m, Ala$\alpha$-NH), 3.35 (1H, dd, $^3J 6.1$, $^2J 15.4$, Trp$\beta$-$H_a$), 3.22 (1H, dd, $^3J 10.2$, $^2J 15.2$, Trp$\beta$-$H_b$), 3.03 (3H, s, Trp-NC$_3$H$_3$), 2.74 (1H, dd, $^3J 8.1$, $^2J 16.2$, $\beta$Tyr$\beta$-$H_a$), 2.62 (1H, dd, $^3J 4.6$, $^2J 16.2$, $\beta$Tyr$\beta$-$H_b$), 2.52-2.41 (2H, m, Htn2-$H$, Hdn6-$H$), 2.39 (1H, dd, $^3J 8.6$, $^2J 14.3$, Htn3-$H_a$), 2.16 (1H, dd, $^3J 3.6$, $^2J 14.3$, Htn3-$H_b$), 1.62 (3H, s, Htn11-$H$), 1.50-1.43 (1H, m, Htn7-$H_a$), 1.34-1.26 (1H, m, Htn7-$H_b$), 1.13 (3H, d, $^3J 6.9$, Htn10-$H$), 1.08 (3H, d, $^3J 6.2$, Htn9-$H$), 0.82 (3H, d, $^3J 6.8$, Htn12-$H$), and 0.81 (3H, d, $^3J 7.3$, Ala$\beta$-$H_3$); $\delta_C(125 \text{MHz, CDCl}_3) 176.0$ (Htn-1), 174.8 (Ala-C=O), 170.2 (Trp-C=O), 169.1 ($\beta$Tyr-C=O), 155.2 ($\beta$Tyr-4), 134.1 (Trp-7a), 134.1 (Htn-5), 133.0 ($\beta$Tyr-1), 130.3 (Htn-4), 127.5 (2x, $\beta$Tyr-2, $\beta$Tyr-6), 127.5 (Trp-3a), 122.4 (Trp-6), 121.6 (Trp-3), 120.3 (Trp-5), 118.3 (Trp-4), 115.5 (2x, $\beta$Tyr-3, $\beta$Tyr-5), 110.4 (Trp-7), 107.2 (Trp-2), 70.5 (Htn-8), 55.6 (Trp-α), 49.7 ($\beta$Tyr-β), 45.8 (Ala-α), 44.1 (Htn-7), 40.3 ($\beta$Tyr-α), 39.2 (Htn-2), 35.4 (Htn-3), 31.2 (Trp-NCH$_3$), 29.5 (Htn-6), 23.9 (Htn-11), 21.9 (Trp-β), 21.1 (Htn-9), 21.0 (Htn-12), 17.7 (Htn-10) and 16.7 (Ala-β); $m/z$ (ESI): calc. for C$_{36}$H$_{46}$BrN$_4$O$_6$ [M+H]$^+$: 709.2595, found 709.2596.
References

**Supplementary Material (ESI) for Chemical Communications**

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![Chemical Structure](image)

**4**

$^1$H; 500 MHz

CDCl$_3$
$^{13}$C; 100 MHz
CDCl$_3$
Supplementary Material (ESI) for Chemical Communications
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5

$^1$H; 500 MHz
CDCl$_3$
$^1$H; 400 MHz

CDCl$_3$
Supplementary Material (ESI) for Chemical Communications
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$^1$H; 600 MHz
CDCl$_3$
13C; 150 MHz
CDCl₃
$^{1}H; 600 \text{ MHz}$

$\text{CDCl}_3$
Supplementary Material (ESI) for Chemical Communications
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$(^1H-^{13}C)$ gHSQC; 600 MHz, CDCl$_3$
$^1$H; 500 MHz
CDCl$_3$
$^{1}H$-gHMBC; 500 MHz, CDCl$_3$
Supplementary Material (ESI) for Chemical Communications
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$^1$H; 600 MHz
CDCl$_3$