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Solid-phase synthesis of biaryl cyclic peptides by borylation and microwave-assisted intramolecular Suzuki–Miyaura reaction

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ABSTRACT

Miyaura borylation and Suzuki–Miyaura cross-coupling have been combined to set up an efficient strategy for the solid-phase synthesis of biaryl cyclic peptides. The Miyaura borylation was the key step in obtaining the linear peptidyl resin precursor containing both the boronate and the halogenated derivative of an aromatic amino acid. The Suzuki–Miyaura macrocyclization was performed under microwave irradiation leading to biaryl cyclic peptides of different ring sizes.

1. Introduction

The biaryl motif is an important substructure of many bioactive and functional molecules and has been the focus of synthetic chemists during the last years.[1] In particular, biaryl amino acids are valuable synthetic intermediates for the preparation of a plethora of biologically active compounds, and their incorporation in peptide and peptidomimetic drugs is considered a useful approach to improve the biological activity of such compounds.[2]

Several methods have proven to be effective for the preparation of biaryl amino acids.[1] Among them, the Suzuki–Miyaura cross-coupling of an aryl halide and an aryl boron derivative has emerged as one of the most reliable reactions to create the aryl–aryl bond.[3] This reaction has been efficiently applied for accessing biaryl cyclic peptides, such as arylomycins, biphenomycins, or RP-66453.[4] However, up to now, the synthesis of this type of compounds has only been conducted in solution. The solid-phase synthesis of biaryl peptides has been scarcely reported and is restricted to the preparation of linear sequences involving the coupling of a polymer-bound halogenated aromatic amino acid and an aryl boron in solution.[5]

Recently, we have described an alternative approach for the preparation of biaryl peptides through solid-phase Miyaura borylation of a phenylalanine residue followed by Suzuki–Miyaura cross-coupling with a range of aryl halides.[6] This approach is advantageous because it avoids the synthesis and purification of the amino acid boronate in solution, and is amenable to the preparation of peptide boronates in a flexible manner under mild conditions. Moreover, it allows the preparation of a large diversity of biaryl peptides from a single boronopeptide intermediate because the number of commercially available aryl halides is larger than that of arylborons.

Within our current interest in cyclic peptides, in this work we envisioned that this methodology could be extended to the solid-phase synthesis of biaryl bridged macrocycles. The key steps of this strategy would be the synthesis, via a Miyaura borylation, of the linear peptide containing both the boronate and the halogenated derivative of an aromatic amino acid, and the Suzuki–Miyaura macrocyclization for the formation of the aryl–aryl bond. Performing the borylation and the macrocyclization on solid support would benefit from the advantages inherent to the solid-phase synthesis, and would represent a convergent and versatile approach for the preparation of biaryl cyclic compounds. Based on these considerations, we report herein an efficient solid-phase synthesis of biaryl-containing cyclic peptides.

2. Results and discussion

2.1. Arylation of boronopeptidyl resins with halogenated aromatic amino acids

We first set up to examine the feasibility of the arylation of boronopeptidyl resins with halogenated aromatic amino acids through a Suzuki–Miyaura cross-coupling. For this study we used

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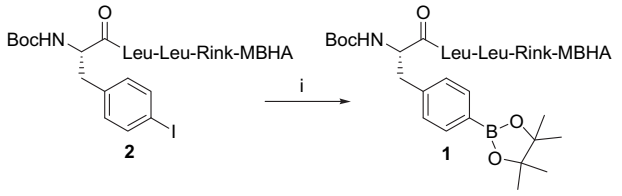
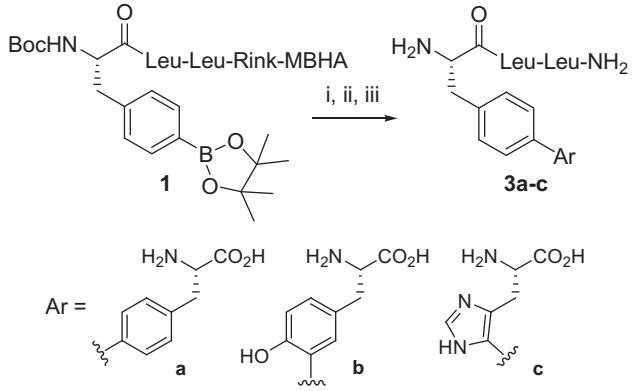
the boronophenylalanine peptidyl resin Boc-Phe(4-BPin)-Leu-Leu-Rink-MBHA (**1**), which was prepared following our recently reported methodology (Scheme 1).[6]



Scheme 1. Solid-phase Miyaura borylation of a iodophenylalanyltripeptide. Reagents and conditions: (i) B_2Pin_2, $PdCl_2$(dppf), dppf, KOAc, DMSO, 80 °C, 24 h.

Accordingly, resin Boc-Phe(4-I)-Leu-Leu-Rink-MBHA (**2**) was treated with bis(pinacolato)diboron (B_2Pin_2), $PdCl_2$(dppf), 1,1′-bis (diphenylphosphanyl)ferrocene (dppf), and KOAc in DMSO at 80 °C for 24 h. The resulting boronopeptidyl resin was then subjected to arylation with Boc-Phe(4-I)-OMe,[7] Boc-Tyr(3-I,SEM)-OMe[8] or a mixture of Boc-His(5-Br,1-SEM)-OMe and Boc-His(5-Br,3-SEM)-OMe[8] under the conditions previously optimized for the arylation of phenylalanine boronates with aryl halides (SEM=[2-(trimethylsilyl)ethoxy]methyl) (Table 1).[6] The reaction was carried out using $Pd_2(dba)_3$, P(*o*-tolyl)$_3$, and KF in DME/EtOH/H_2O under microwave irradiation (MWI) at 120 °C for 30 min. After hydrolysis of the methyl ester with LiOH in THF, the resulting biaryl peptidyl resins were cleaved with TFA/triisopropylsilane (TIS)/H_2O. HPLC and ESI-MS analysis of the crude reaction mixtures showed the formation of the expected biaryl tetrapeptides in good purities. Cross-coupling of the boronopeptidyl resin **1** with the iodophenylalanine **a** and the iodotyrosine **b** led to the biaryl peptides **3a** and **3b** with 92 and 79% purity, respectively. Moreover, **1** reacted with bromohistidines **c** affording the biaryl peptide **3c** in 42% purity. This result is especially noteworthy because cross-couplings involving the imidazole ring of a histidine have been shown to be challenging.[8] Purification of the crude reaction mixtures by column chromatography afforded the corresponding biaryl peptides **3a**–**c** in 12–62% yield, and these products were fully characterized by mass spectrometry, and ^{1}H and ^{13}C NMR. 2D-COSY, HSQC, and HMBC experiments were carried out to completely assign all the proton and carbon signals. HPLC and NMR analysis of tetrapeptide **3a** pointed out the occurrence of two isomers. Further analysis by ^{1}H NMR at low temperature in MeOH-d_4 confirmed that they corresponded to two different conformers. For biaryl tetrapeptides **3b** and **3c**, the NMR spectra showed the presence of only one stereoisomer. These results revealed that no epimerization occurred during the borylation and Suzuki–Miyaura cross-coupling steps.

Table 1
Solid-phase Suzuki–Miyaura arylation of boronotripeptidyl resin **1** with halogenated amino acid derivatives



i) $Pd_2(dba)_3$, P(*o*-tolyl)$_3$, ArX, KF, DME/EtOH/H_2O, MWI, 120 ºC, 30 min. ii) LiOH, THF/H_2O, rt, 24 h. iii) TFA/TIS/H_2O, rt, 2 h.

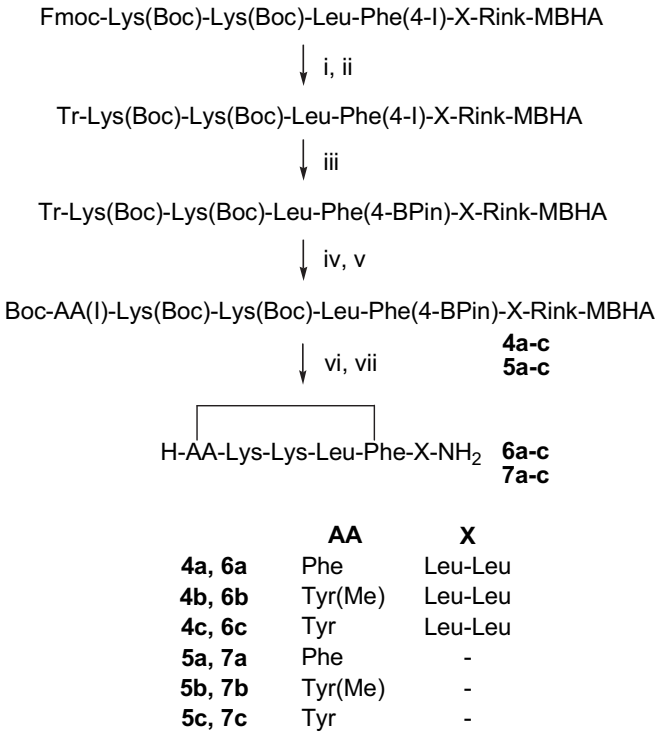
ArX	Peptide	Purity[a] (%)	Yield[b] (%)
Boc-Phe(4-I)-OMe	**3a**	92	62
Boc-Tyr(3-I,SEM)-OMe	**3b**	79	48
Boc-His(5-Br,1-SEM)-OMe and Boc-His(5-Br,3-SEM)-OMe	**3c**	42	12

[a] Percentage determined by HPLC at 220 nm from the crude reaction mixture.
[b] Isolated yield.

2.2. Synthesis of biaryl cyclic peptides

In view of the excellent results obtained, the synthesis of biaryl cyclic peptides via a solid-phase intramolecular Suzuki–Miyaura arylation was attempted. This approach involved first the preparation of the linear peptidyl resins containing the required boronate and halogenated amino acid derivatives.

For this purpose, we planned the synthesis of the resins Boc-AA(I)-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Leu-Leu-Rink-MBHA (**4a**–**c**) and Boc-AA(I)-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA (**5a**–**c**), where AA(I) corresponds to Phe(4-I) (**a**), Tyr(3-I,Me) (**b**) or Tyr(3-I,SEM) (**c**) (Scheme 2). SEM and methyl protecting groups of the tyrosine residue served to ensure the stability of the hydroxyl function under the reaction conditions. We first assayed the preparation of **4a** starting from Boc-Phe(4-BPin)-Leu-Leu-Rink-MBHA (**1**).



	AA	X
4a, 6a	Phe	Leu-Leu
4b, 6b	Tyr(Me)	Leu-Leu
4c, 6c	Tyr	Leu-Leu
5a, 7a	Phe	-
5b, 7b	Tyr(Me)	-
5c, 7c	Tyr	-

Scheme 2. Solid-phase Suzuki–Miyaura cyclization. Reagents and conditions: (i) piperidine/DMF (3:7), 10 min. (ii) TrCl, DIEA, DMF, rt, 3 h. (iii) $PdCl_2$(dppf), dppf, B_2Pin_2, KOAc, DMSO, 80 °C, 24 h. (iv) TFA/H_2O/CH_2Cl_2 (0.2:1:98.8), 20 min. (v) Boc-Phe(4-I)-OH, Boc-Tyr(3-I,Me)-OH or Boc-Tyr(3-I,SEM)-OH, ethyl cyanoglyoxylate-2-oxime, DIPCDI, DMF, rt, 3 h. (vi) $Pd_2(dba)_3$, P(*o*-tolyl)$_3$, KF, DME/EtOH/H_2O, MWI, 120 °C, 30 min. (vii) TFA/TIS/H_2O, rt, 2 h.

Selective removal of the Boc group with TMSOTf in the presence of lutidine,[9] followed by coupling of Fmoc-Leu-OH yielded Fmoc-Leu-Phe(4-BPin)-Leu-Leu-NH_2 (86% purity). However, elongation of the peptide sequence by subsequent Fmoc removal and coupling of two Fmoc-Lys(Boc)-OH residues resulted in the decomposition of the boronate into the phenolic compound as shown by HPLC and mass spectrometry analysis. Therefore, an alternative strategy for the

synthesis of **4a**–**c** was devised, which was based on the formation of the boronate at the last steps of the synthesis (Scheme 2). In particular, this strategy consisted on (i) the preparation of Fmoc-Lys(Boc)-Lys(Boc)-Leu-Phe(4-I)-Leu-Leu-Rink-MBHA; (ii) replacement of the Fmoc group by a trityl to overcome its instability under the Miyaura borylation conditions; (iii) formation of the boronate using the conditions described above; (iv) trityl removal, and (v) coupling of the corresponding iodophenylalanine or iodotyrosine derivative. Acidolytic cleavage of an aliquot of the resulting resins **4a**–**c** yielded the corresponding boronopeptides in purities ranging from 72 to 81%. This strategy was applied for the preparation of peptidyl resins **5a**–**c** and led to the expected borylated sequences in 76–89% purity. All boronopeptides were characterized by HRMS. These results strengthened the usefulness of our methodology for the solid-phase borylation of peptides under Miyaura conditions.

With the properly functionalized peptidyl resins **4a**–**c** and **5a**–**c** in hand, we set out to examine the macrocyclization by way of an intramolecular Suzuki–Miyaura reaction (Scheme 2 and Fig. 1). Exposure of resins **4a**–**c** and **5a**–**c** to $Pd_2(dba)_3$, P(*o*-tolyl)$_3$, and KF in DME/EtOH/H_2O under microwave irradiation at 120 °C for 30 min provided the expected biaryl cyclic peptides **6a**–**c** and **7a**–**c** in 72–79% purity. Pure compounds were obtained in 23–35% yield after purification by column chromatography and were characterized by mass spectrometry and ^{1}H NMR, which was consistent with the formation of the biaryl bond.

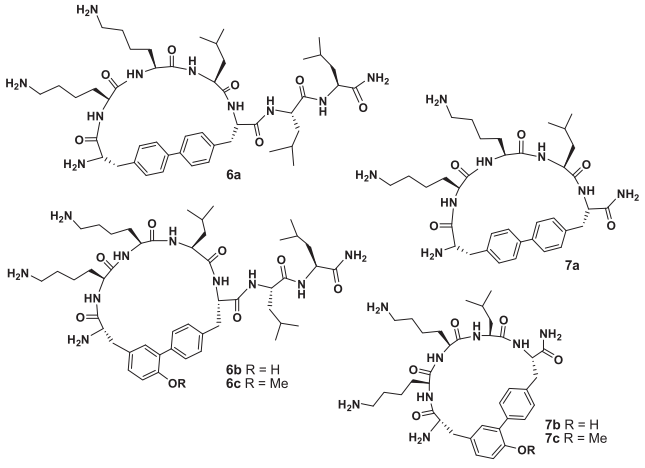


Fig. 1. Structures of biaryl cyclic peptides **6a**–**c** and **7a**–**c**.

Finally, we evaluated the applicability of the intramolecular Suzuki–Miyaura macrocyclization to the preparation of biaryl cyclic peptides of different ring sizes (Table 2, Fig. 2). Linear peptidyl resins **8**–**12**, which contained 3, 4, 6, 7 or 8 amino acids were prepared and cyclized via aryl–aryl bond formation following the strategy depicted in Scheme 2. Acidolytic cleavage of an aliquot of resins **8**–**12** allowed the characterization by mass spectrometry of the linear precursors. Cyclization of the peptidyl resin **10** containing six residues was the most troublesome, leading to the biaryl cyclic peptide **15** in 36% purity together with a mixture of byproducts that could not be identified. The other cyclizations gave biaryl cyclic peptides **13**, **14**, **16**, and **17** in purities ranging from 70 to 84%. The structure of all biaryl cyclic peptides was confirmed by HRMS.

Table 2
Results of the synthesis of biaryl cyclic peptides **13**–**17**

Linear peptidyl resin	Cyclic peptide	Purity[a] (%)
Boc-Phe(4-I)-Leu-Phe(4-BPin)-Rink-MBHA (**8**)	**13**	71
Boc-Phe(4-I)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA (**9**)	**14**	70
Boc-Phe(4-I)-Phe-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA (**10**)	**15**	36
Boc-Phe(4-I)-Lys(Boc)-Phe-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA (**11**)	**16**	84
Boc-Phe(4-I)-Lys(Boc)-Lys(Boc)-Phe-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA (**12**)	**17**	77

[a] Percentage determined by HPLC at 220 nm from the crude reaction mixture.

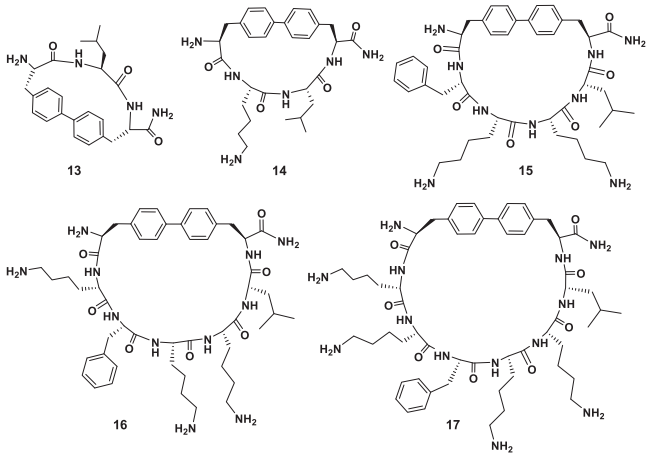


Fig. 2. Structures of biaryl cyclic peptides **13**–**17**.

3. Conclusion

In conclusion, we have established the viability of the solid-phase borylation and Suzuki–Miyaura arylation for the synthesis of biaryl cyclic peptides of three to eight residues. This work shows that the Suzuki–Miyaura reaction can be applied to the cross-coupling of boronophenylalanine-containing peptidyl resins with halogenated aromatic amino acids. Moreover, it constitutes the first example of solid-phase intramolecular Suzuki–Miyaura cross-coupling for the formation of biaryl cyclic peptides. We expect that this methodology could find applications in the synthesis of natural products and in the diversity-oriented synthesis of biaryl-containing macrocycles.

4. Experimental section

4.1. General methods

Commercially available reagents were used throughout without purification. Solvents were purified and dried by passing them through an activated alumina purification system (MBraun SPS-800) or by conventional distillation techniques.

Flash chromatography purifications were performed on C_{18}-reversed phase silica gel 100 not endcapped (230–400 mesh, Fluka).

All compounds were analyzed under standard analytical HPLC conditions with a Dionex liquid chromatography instrument composed of an UV/vis Dionex UVD170U detector, a P680 Dionex bomb, an ASI-100 Dionex automatic injector, and CHROMELEON 6.60 software. Detection was performed at 220 nm. Method A: Analysis was carried out with a Kromasil 100 C_{18} (250 mm×4.6 mm, 3.5 μm) column with a 2–100% B linear gradient over 28 min at a flow rate of 1 mL/min. Solvent A was 0.1% aq TFA, and solvent B was 0.1% TFA in CH_3CN. Method B: Analysis was carried out with a Kromasil 100 C_{18} (40×4.6 mm, 3.5 μm) column with a 2–100% B linear gradient over 7 min at a flow rate of 1 mL/min.

ESI-MS analyses were performed with an Esquire 6000 ESI ion Trap LC/MS (Bruker Daltonics) instrument equipped with an electrospray ion source. The instrument was operated in the positive ESI (+) ion mode. Samples (5 μL) were introduced into the mass spectrometer ion source directly through an HPLC autosampler. The mobile phase (80:20 CH_3CN/H_2O at a flow rate of 100 μLmin^{-1}) was delivered by a 1100 Series HPLC pump (Agilent). Nitrogen was

employed as both the drying and nebulizing gas. HRMS were recorded under conditions of ESI with a Bruker MicroTof-Q instrument using a hybrid quadrupole time-of-flight mass spectrometer (University of Zaragoza). Samples were introduced into the mass spectrometer ion source directly through a 1100 Series Agilent HPLC autosampler and were externally calibrated using sodium formate. The instrument was operated in the positive ESI (+) ion mode.

^{1}H and ^{13}C NMR spectra were measured with a Bruker 300 or 400 MHz NMR spectrometer. Chemical shifts were reported as δ values (ppm) directly referenced to the solvent signal.

Microwave-assisted reactions were performed with an Ethos SEL labstation microwave (Milestone) equipped with a dual magnetron (1600 W). The time, temperature, and power were controlled with the EasyControl software. The temperature was monitored through the ATC-400FO Automatic Fiber Optic Temperature Control System immersed in a standard Milestone reference vessel. This equipment regulates the power to achieve and maintain the selected temperature.

4.2. General method for the arylation of linear peptides via a solid-phase Suzuki–Miyaura reaction

A 5 mL quartz vial was charged with the boronopeptidyl resin Boc-Phe(4-BPin)-Leu-Leu-Rink-MBHA (**1**),[6] the halogenated aromatic amino acid conveniently protected (5 equiv), $Pd_2(dba)_3$ (0.2 equiv), P(*o*-tolyl)$_3$ (0.4 equiv), and KF (4 equiv). Thoroughly degassed DME/EtOH/H_2O (9:9:2, 1–1.5 mL) was then added under nitrogen. The reaction mixture was heated at 120 °C under microwave irradiation for 30 min. After this time, the resin was washed with DMF (6×1 min), EtOH (6×1 min), CH_2Cl_2 (6×1 min), and Et_2O (3×1 min). An aliquot of the resulting biaryl peptidyl resin was cleaved with TFA/H_2O/TIS (95:2.5:2.5) whilst being stirred for 2 h at room temperature. Following TFA evaporation and Et_2O extraction, the crude peptide was dissolved in H_2O/CH_3CN, lyophilized, and analyzed by HPLC.

The rest of the biaryl peptidyl resin was hydrolyzed by the treatment with LiOH (5 equiv) in THF/H_2O (7:1) at room temperature for 24 h. After the reaction time, the solvent was removed and the resin was washed with DMF (3×1 min), MeOH (2×1 min), H_2O (2×1 min), DMF (3×1 min), and CH_2Cl_2 (3×1 min). The resulting biaryl peptide was released from the solid support by treatment with TFA/H_2O/TIS (95:2.5:2.5) with stirring for 2 h at room temperature. Following TFA evaporation and Et_2O extraction, the crude peptide was dissolved in H_2O/CH_3CN, lyophilized, analyzed by HPLC, and purified by reverse-phase column chromatography. Biaryl peptides were characterized by MS and NMR.

*4.2.1. Linear biaryl peptide **3a**.* Starting from resin Boc-Phe(4-BPin)-Leu-Leu-Rink-MBHA (**1**, 100 mg), the Suzuki–Miyaura reaction was performed following the general procedure using Boc-Phe(4-I)-OMe.[7] After the reaction time, acidolytic cleavage of an aliquot of the biaryl peptidyl resin afforded the corresponding methyl ester (87% purity). t_R=16.84 and 17.20 min (method A). MS (ESI): m/z=568.3 $[M+H]^+$, 590.3 $[M+Na]^+$. After hydrolysis, the crude biaryl peptide **3a** was obtained in 92% purity. Elution with H_2O/MeOH/TFA (80:20:0.2) yielded pure **3a** (15.9 mg, 62% yield). t_R=16.28 and 16.64 min (method A). ^{1}H NMR (400 MHz, CD_3CN+D_2O): δ=0.84–0.90 [m, 12H, 4×CH_3(δ)-Leu], 1.50–1.60 [m, 6H, 2×CH(γ)-Leu, 2×CH_2(β)-Leu], 3.16–3.32 [m, 4H, CH_2(β)-Phe], 4.17–4.32 [m, 4H, 2×CH(α)-Leu, 2×CH(α)-Phe], 7.33–7.37 [m, 4H, CH_{arom}-2, CH_{arom}-6, CH_{arom}-3′, CH_{arom}-5′], 7.60–7.64 [m, 4H, CH_{arom}-3, CH_{arom}-5, CH_{arom}-2′, CH_{arom}-6] ppm. ^{1}H NMR (400 MHz, CD_3OD): δ=0.91–1.00 [m, 12H, 4×CH_3(δ)-Leu], 1.56–1.75 [m, 6H, 2×CH(γ)-Leu, 2×CH_2(β)-Leu], 3.06 [dd, J=8.8, 14.0 Hz, 1H, CH_2(β)-Phe], 3.15 [dd, J=8.0, 14.4 Hz, 1H, CH_2(β)-Phe], 3.32–3.39 [m, 2H, CH_2(β)-Phe], 4.03 [dd, J=5.2, 8.0 Hz, 1H, CH(α)-Phe], 4.17 [dd, J=5.2, 8.8 Hz, 1H, CH(α)-Phe], 4.41–4.52 [m, 2H, 2×CH(α)-Leu], 7.39 [m, 4H, CH_{arom}-2, CH_{arom}-6, CH_{arom}-3′, CH_{arom}-5′], 7.62 [d, J=8.0 Hz, 4H, CH_{arom}-3, CH_{arom}-5, CH_{arom}-2′, CH_{arom}-6] ppm. ^{13}C NMR (100 MHz, CD_3CN+D_2O): δ=21.90, 23.25, 23.33 [4×CH_3(δ)-Leu], 25.33, 25.56 [2×CH(γ)-Leu], 36.28, 37.16 [2×CH_2(β)-Phe], 41.23, 41.36 [2×CH_2(β)-Leu], 52.56, 53.44 [2×CH(α)-Leu], 55.06 [2×CH(α)-Phe], 128.28 [CH_{arom}-3, CH_{arom}-5, CH_{arom}-2′, CH_{arom}-6′], 131.15, 131.22 [CH_{arom}-2, CH_{arom}-6, CH_{arom}-3′, CH_{arom}-5′], 134.43, 134.83 [C_{arom}-1, C_{arom}-4′], 140.48 [C_{arom}-4, C_{arom}-1′], 168.95, 173.19, 176.31 [4×CO] ppm. MS (ESI): m/z=554.3 $[M+H]^+$. HRMS (ESI): calcd for $C_{30}H_{44}N_5O_5$ 554.3337; found 554.3362.

*4.2.2. Linear biaryl peptide **3b**.* Starting from resin Boc-Phe(4-BPin)-Leu-Leu-Rink-MBHA (**1**, 100 mg), the Suzuki–Miyaura reaction was performed following the general procedure using Boc-Tyr(3-I,SEM)-OMe.[8] After the reaction time, acidolytic cleavage of an aliquot of the biaryl peptidyl resin afforded the corresponding methyl ester (82% purity). t_R=16.47 min (method A). MS (ESI): m/z=584.3 $[M+H]^+$. After hydrolysis, the crude biaryl peptide **3b** was obtained in 79% purity. Elution with H_2O/MeOH/TFA (70:30:0.2) yielded pure **3b** (12.5 mg, 48% yield). t_R=15.96 min (method A). ^{1}H NMR (400 MHz, CD_3OD): δ=0.94–0.98 [m, 12H, 4×CH_3(δ)-Leu], 1.57–1.73 [m, 6H, 2×CH(γ)-Leu, 2×CH_2(β)-Leu], 2.99–3.30 [m, 4H, CH_2(β)-Tyr, CH_2(β)-Phe], 4.04–4.27 [m, 2H, CH(α)-Phe, CH(α)-Tyr], 4.39–4.51 [m, 2H, 2×CH(α)-Leu], 6.90 [d, J=7.8 Hz, 1H, CH_{arom}-3′], 7.10 [d, J=7.8 Hz, 1H, CH_{arom}-4′], 7.21 [s, 1H, CH_{arom}-6′], 7.33 [d, J=7.8 Hz, 2H, CH_{arom}-2, CH_{arom}-6], 7.56 [d, J=7.8, 2H, CH_{arom}-3, CH_{arom}-5] ppm. ^{13}C NMR (100 MHz, CD_3OD): δ=21.91, 21.98, 23.32, 23.40 [4×CH_3(δ)-Leu], 25.73, 25.84 [2×CH(γ)-Leu], 38.21 [CH_2(β)-Tyr, CH_2(β)-Phe], 41.81, 42.06 [2×CH_2(β)-Leu], 53.31 [CH(α)-Leu], 55.45 [CH(α)-Tyr, CH(α)-Phe], 117.38 [CH_{arom}-3′], 126.88 [C_{arom}-5′], 129.74 [C_{arom}-1′], 130.21 [CH_{arom}-2, CH_{arom}-6], 130.68 [CH_{arom}-4′], 131.07 [CH_{arom}-3, CH_{arom}-5], 132.53 [CH_{arom}-6′], 133.98 [C_{arom}-1], 139.39 [C_{arom}-4], 155.07 [C_{arom}-2′], 169.58, 174.04 [4×CO] ppm. MS (ESI): m/z=570.3 $[M+H]^+$. HRMS (ESI): calcd for $C_{30}H_{44}N_5O_6$ 570.3286; found 570.3306; calcd for $C_{30}H_{43}N_5NaO_6$ 592.3106; found 592.3110.

*4.2.3. Linear biaryl peptide **3c**.* Starting from resin Boc-Phe(4-BPin)-Leu-Leu-Rink-MBHA (**1**, 100 mg), the Suzuki–Miyaura reaction was performed following the general procedure using a regioisomeric mixture of Boc-His(5-Br,3-SEM)-OMe and Boc-His(5-Br,1-SEM)-OMe.[3] After the reaction time, acidolytic cleavage of an aliquot of the biaryl peptidyl resin afforded the corresponding methyl ester (37% purity). t_R=14.68 min (method A). After hydrolysis, the crude biaryl peptide **3c** was obtained in 42% purity. Elution with H_2O/MeOH/TFA (90:10:0.2) yielded pure **3c** (3 mg, 12% yield). t_R=14.59 min (method A). ^{1}H NMR (400 MHz, CD_3OD): δ=0.94–0.99 [m, 12H, 4×CH_3(δ)-Leu], 1.57–1.73 [m, 6H, 2×CH(γ)-Leu, 2×CH_2(β)-Leu], 3.08–3.13 [m, 1H, CH_2(β)-Phe], 3.27–3.35 [m, 1H, CH_2(β)-Phe], 3.43–3.48 [m, 2H, CH(β)-His], 4.03–4.09 [m, 1H, CH(α)-His], 4.14–4.17 [m, 1H, CH(α)-Phe], 4.34 [dd, J=5.2, 9.6 Hz, 1H, CH(α)-Leu], 4.47 [m, 1H, CH(α)-Leu], 7.44 [d, J=7.6 Hz, 2H, CH_{arom}-2, CH_{arom}-6], 7.54 [d, J=7.6 Hz, 2H, CH_{arom}-3, CH_{arom}-5], 7.58 [s, 1H, CH_{imid}], 8.74 [br s, 1H, NH] ppm. ^{13}C NMR (100 MHz, CD_3OD): δ=23.30, 23.39, 23.49 [4×CH_3(δ)-Leu], 25.74, 25.94 [2×CH(γ)-Leu, CH_2(β)-His], 38.35 [CH_2(β)-Phe], 41.68, 41.89 [CH_2(β)-Leu], 53.40 [2×CH(α)-Leu], 55.28 [CH(α)-Phe, CH(α)-His], 129.76 [CH_{arom}-3, CH_{arom}-5], 131.58 [CH_{arom}-2, CH_{arom}-6], 169.41, 174.01 [4×CO] ppm. MS (ESI): m/z=544.2 $[M+H]^+$. HRMS (ESI): calcd for $C_{27}H_{42}N_7O_5$ 544.3242; found 544.3242; calcd for $C_{27}H_{41}N_7NaO_5$ 566.3061; found 566.3046.

4.3. Solid-phase synthesis of cyclic biaryl peptides 6a–c, 7a–c, and 13–17

4.3.1. General method for solid-phase peptide synthesis. Peptidyl resins were synthesized manually by the solid-phase method using

standard Fmoc chemistry. Fmoc-Rink-MBHA resin (0.56 mmol/g) was used as solid support. Couplings of the corresponding amino acids Fmoc-Leu-OH, Fmoc-Phe(4-I)-OH, Fmoc-Phe-OH, Fmoc-Lys (Boc)-OH (4 equiv) were performed using ethyl cyanoglyoxylate-2-oxime (4 equiv), *N*,*N*′-diisopropylcarbodiimide (DIPCDI) (4 equiv) in DMF at room temperature for 1 h. The completion of the reactions was monitored by the Kaiser test.[10] Fmoc group removal was achieved with piperidine/DMF (3:7, 2+10 min). After each coupling and deprotection step, the resin was washed with DMF (6×1 min) and CH_2Cl_2 (3×1 min) and air-dried. Once the peptide sequence was completed, the Fmoc group was removed and the trityl group was introduced using TrCl (10 equiv) and *N*,*N*-diisopropylethylamine (DIEA) (10 equiv) in DMF at room temperature for 3 h. Then, the resin was washed with DMF (6×1 min) and CH_2Cl_2 (3×1 min) and air-dried. An aliquot of the resulting peptidyl resin was cleaved with TFA/H_2O/triisopropylsilane (TIS) (95:2.5:2.5) whilst being stirred for 2 h at room temperature. Following TFA evaporation and Et_2O extraction, the crude peptide was dissolved in H_2O/CH_3CN, lyophilized, analyzed by HPLC, and characterized by MS.

4.3.1.1. Tr-Lys(Boc)-Lys(Boc)-Leu-Phe(4-I)-Leu-Leu-Rink-MBHA. This peptidyl resin was prepared following the general method for solid-phase peptide synthesis. Acidolytic cleavage of an aliquot of this peptidyl resin afforded H-Lys-Lys-Leu-Phe(4-I)-Leu-Leu-NH_2 (73% purity). t_R=6.69 min (method B). MS (ESI): m/z=443.6 $[M+2H]^{2+}$, 886.4 $[M+H]^+$.

4.3.1.2. Tr-Lys(Boc)-Lys(Boc)-Leu-Phe(4-I)-Rink-MBHA. This pept idyl resin was prepared following the general method for solid-phase peptide synthesis. Acidolytic cleavage of an aliquot of this peptidyl resin afforded H-Lys-Lys-Leu-Phe(4-I)-NH_2 (54% purity). t_R=6.27 min (method B). MS (ESI): m/z=330.6 $[M+2H]^{2+}$, 660.2 $[M+H]^+$, 682.1 $[M+Na]^+$.

4.3.2. General method for solid-phase Miyaura borylation. A 25 mL round-bottomed flask was charged with the corresponding iodopeptidyl resin, bis(pinacolato)diboron (B_2Pin_2) (4 equiv), $PdCl_2$(dppf) (0.18 equiv), and 1,1′-bis(diphenylphosphanyl)ferrocene (dppf) (0.09 equiv). A thoroughly sonicated solution of KOAc (6 equiv) in degassed anhydrous DMSO (20 μL/mg of resin) was then added, and the mixture was heated at 80 °C for 24 h. Then, the resin was washed with DMSO (6×1 min), MeOH (6×1 min), CH_2Cl_2 (6×1 min), and Et_2O (3×1 min). An aliquot of the resulting boronopeptidyl resin was cleaved with TFA/H_2O/TIS (95:2.5:2.5) whilst being stirred for 2 h at room temperature. Following TFA evaporation and Et_2O extraction, the crude peptide was dissolved in H_2O/CH_3CN, lyophilized, analyzed by HPLC, and characterized by MS.

4.3.2.1. Tr-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Leu-Leu-Rink-MBHA. This peptidyl resin was prepared starting from Tr-Lys(Boc)-Lys(Boc)-Leu-Phe(4-I)-Leu-Leu-Rink-MBHA (600 mg) following the general method for solid-phase Miyaura borylation. Acidolytic cleavage of an aliquot of this peptidyl resin afforded H-Lys-Lys-Leu-Phe(4-BPin)-Leu-Leu-NH_2 (56% purity) and H-Lys-Lys-Leu-Phe(4-B$(OH)_2$)-Leu-Leu-NH_2 (22% purity), resulting from partial hydrolysis of the pinacol boronate during HPLC analysis. t_R=6.08 min (boronic acid), 6.75 min (boronate) (method B). MS (ESI): m/z=804.5 $[M+H]^+$, 886.5 $[M+H]^+$, 908.5 $[M+Na]^+$.

4.3.2.2. Tr-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA. This peptidyl resin was prepared starting from Tr-Lys(Boc)-Lys(Boc)-Leu-Phe(4-I)-Rink-MBHA (400 mg) following the general method for solid-phase Miyaura borylation. Acidolytic cleavage of an aliquot of this peptidyl resin afforded H-Lys-Lys-Leu-Phe(4-BPin)-NH_2 (67% purity) and H-Lys-Lys-Leu-Phe(4-B$(OH)_2$)-NH_2 (11% purity), resulting from partial hydrolysis of the pinacol boronate during HPLC analysis. t_R=5.31 min (boronic acid), 6.39 min (boronate) (method B). MS (ESI): m/z=330.7 $[M+2H]^{2+}$, 578.3 $[M+H]^+$, 660.3 $[M+H]^+$.

4.3.2.3. Tr-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA. This peptidyl resin was prepared starting from Tr-Lys(Boc)-Leu-Phe(4-I)-Rink-MBHA (90 mg) following the general method for solid-phase Miyaura borylation. Acidolytic cleavage of an aliquot of this peptidyl resin afforded H-Lys-Leu-Phe(4-BPin)-NH_2 and H-Lys-Leu-Phe (4-B$(OH)_2$)-NH_2. MS (ESI): m/z=450.2 $[M+H]^+$, 532.3 $[M+H]^+$.

4.3.2.4. Tr-Phe-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA. This peptidyl resin was prepared starting from Tr-Phe-Lys(Boc)-Lys(Boc)-Leu-Phe(4-I)-Rink-MBHA (90 mg) following the general method for solid-phase Miyaura borylation. Acidolytic cleavage of an aliquot of this peptidyl resin afforded H-Phe-Lys-Lys-Leu-Phe(4-BPin)-NH_2 (37% purity) and H-Phe-Lys-Lys-Leu-Phe(4-B$(OH)_2$)-NH_2 (30% purity), resulting from partial hydrolysis of the pinacol boronate during HPLC analysis. t_R=14.52 min (boronic acid), 18.54 min (boronate) (method A). MS (ESI): m/z=807.5 $[M+H]^+$.

4.3.2.5. Tr-Lys(Boc)-Phe-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA. This peptidyl resin was prepared starting from Tr-Lys (Boc)-Phe-Lys(Boc)-Lys(Boc)-Leu-Phe(4-I)-Rink-MBHA (65 mg) following the general method for solid-phase Miyaura borylation. Acidolytic cleavage of an aliquot of this peptidyl resin afforded H-Lys-Phe-Lys-Lys-Leu-Phe(4-BPin)-NH_2 (35% purity) and H-Lys-Phe-Lys-Lys-Leu-Phe(4-B$(OH)_2$)-NH_2 (28% purity), resulting from partial hydrolysis of the pinacol boronate during HPLC analysis. t_R=14.45 min (boronic acid), 18.12 min (boronate) (method A). MS (ESI): m/z=853.5 $[M+H]^+$, 935.5 $[M+H]^+$.

4.3.2.6. Tr-Lys(Boc)-Lys(Boc)-Phe-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA. This peptidyl resin was prepared starting from Tr-Lys(Boc)-Lys(Boc)-Phe-Lys(Boc)-Lys(Boc)-Leu-Phe(4-I)-Rink-MB HA (100 mg) following the general method for solid-phase Miyaura borylation. Acidolytic cleavage of an aliquot of this peptidyl resin afforded H-Lys-Lys-Phe-Lys-Lys-Leu-Phe(4-BPin)-NH_2 (48% purity) and H-Lys-Lys-Phe-Lys-Lys-Leu-Phe(4-B$(OH)_2$)-NH_2 (28% purity), resulting from partial hydrolysis of the pinacol boronate during HPLC analysis. t_R=14.10 min (boronic acid), 17.61 min (boronate) (method A). MS (ESI): m/z=1093.5 $[M-H+TFA]^-$, 1175.5 $[M-H+TFA]^-$.

4.3.3. General method for the solid-phase synthesis of the linear precursors ***4a–c***, ***5a–c***, *and* ***8–12***. The boronopeptidyl resins obtained following the procedure described in section 4.3.2 were treated with TFA/H_2O/CH_2Cl_2 (0.2:1:98.8, 2×1 min, 1×20 min), and then washed with DMF (3×1 min), DIEA/DCM (1:19) (3×1 min), and DMF (3×1 min). The corresponding halogenated amino acid Boc-Phe(4-I)-OH, Boc-Tyr(3-I,Me)-OH or Boc-Tyr(3-I,SEM)-OH was coupled using ethyl cyanoglyoxylate-2-oxime (3 equiv), DIPCDI (3 equiv) in DMF at room temperature for 3 h. The resin was washed with DMF (6×1 min) and CH_2Cl_2 (3×1 min) and air-dried. The completion of the reaction was monitored by the Kaiser test. An aliquot of the resulting peptidyl resin was cleaved with TFA/H_2O/TIS (95:2.5:2.5) whilst being stirred for 2 h at room temperature. Following TFA evaporation and Et_2O extraction, the crude peptide was dissolved in H_2O/CH_3CN, lyophilized, analyzed by HPLC, and characterized by MS.

*4.3.3.1. Boc-Phe(4-I)-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Leu-Leu-Rink-MBHA (****4a****).* This peptidyl resin was prepared starting from Tr-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Leu-Leu-Rink-MBHA following the general method using Boc-Phe(4-I)-OH[7] as halogenated amino acid. Acidolytic cleavage of an aliquot of the resulting

peptidyl resin afforded H-Phe(4-I)-Lys-Lys-Leu-Phe(4-BPin)-Leu-Leu-NH_2 (52% purity) and H-Phe(4-I)-Lys-Lys-Leu-Phe(4-B$(OH)_2$)-Leu-Leu-NH_2 (25% purity), resulting from partial hydrolysis of the pinacol boronate during HPLC analysis. t_R=6.67 min (boronic acid), 7.27 min (boronate) (method B). MS (ESI): m/z=1077.4 $[M+H]^+$, 1159.4 $[M+H]^+$, 1181.4 $[M+Na]^+$.

*4.3.3.2. Boc-Tyr(3-I,Me)-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Leu-Leu-Rink-MBHA (**4b**).* This peptidyl resin was prepared starting from Tr-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Leu-Leu-Rink-MBHA following the general method using Boc-Tyr(3-I,Me)-OH[8] as halogenated amino acid. Acidolytic cleavage of an aliquot of the resulting peptidyl resin afforded H-Tyr(3-I,Me)-Lys-Lys-Leu-Phe(4-BPin)-Leu-Leu-NH_2 (59% purity) and H-Tyr(3-I,Me)-Lys-Lys-Leu-Phe(4-B$(OH)_2$)-Leu-Leu-NH_2 (13% purity), resulting from partial hydrolysis of the pinacol boronate during HPLC analysis. t_R=6.53 min (boronic acid), 7.11 min (boronate) (method B). MS (ESI): m/z=595.4 $[M+2H]^{2+}$, 1107.4 $[M+H]^+$, 1189.5 $[M+H]^+$.

*4.3.3.3. Boc-Tyr(3-I,SEM)-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Leu-Leu-Rink-MBHA (**4c**).* This peptidyl resin was prepared starting from Tr-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Leu-Leu-Rink-MBHA following the general method using Boc-Tyr(3-I,SEM)-OH[8] as halogenated amino acid. Acidolytic cleavage of an aliquot of the resulting peptidyl resin afforded H-Tyr(3-I)-Lys-Lys-Leu-Phe(4-BPin)-Leu-Leu-NH_2 (42% purity) and H-Tyr(3-I)-Lys-Lys-Leu-Phe(4-B$(OH)_2$)-Leu-Leu-NH_2 (39% purity), resulting from partial hydrolysis of the pinacol boronate during HPLC analysis. t_R=6.47 min (boronic acid), 7.13 min (boronate) (method B). MS (ESI): m/z=1093.2 $[M+H]^+$, 1175.2 $[M+H]^+$.

*4.3.3.4. Boc-Phe(4-I)-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA (**5a**).* This peptidyl resin was prepared starting from Tr-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA following the general method using Boc-Phe(4-I)-OH[7] as halogenated amino acid. Acidolytic cleavage of an aliquot of the resulting peptidyl resin afforded H-Phe(4-I)-Lys-Lys-Leu-Phe(4-BPin)-NH_2 (54% purity) and H-Phe(I)-Lys-Lys-Leu-Phe(B$(OH)_2$)-NH_2 (22% purity), resulting from partial hydrolysis of the pinacol boronate during HPLC analysis. t_R=5.79 min (boronic acid), 6.72 min (boronate) (method B). MS (ESI): m/z=851.2 $[M+H]^+$, 933.3 $[M+H]^+$, 955.3 $[M+Na]^+$.

*4.3.3.5. Boc-Tyr(3-I,Me)-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA (**5b**).* This peptidyl resin was prepared starting from Tr-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA following the general method using Boc-Tyr(3-I,Me)-OH[8] as halogenated amino acid. Acidolytic cleavage of an aliquot of the resulting peptidyl resin afforded H-Tyr(3-I,Me)-Lys-Lys-Leu-Phe(4-BPin)-NH_2 (71% purity) and H-Tyr(3-I,Me)-Lys-Lys-Leu-Phe(4-B$(OH)_2$)-NH_2 (18% purity), resulting from partial hydrolysis of the pinacol boronate during HPLC analysis. t_R=6.01 min (boronic acid), 6.89 min (boronate) (method B). MS (ESI): m/z=881.2 $[M+H]^+$, 963.2 $[M+H]^+$.

*4.3.3.6. Boc-Tyr(3-I,SEM)-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA (**5c**).* This peptidyl resin was prepared starting from Tr-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA following the general method using Boc-Tyr(3-I,SEM)-OH[8] as halogenated amino acid. Acidolytic cleavage of an aliquot of the resulting peptidyl resin afforded H-Tyr(3-I)-Lys-Lys-Leu-Phe(4-BPin)-NH_2 (67% purity) and H-Tyr(3-I,Me)-Lys-Lys-Leu-Phe(4-B$(OH)_2$)-NH_2 (21% purity), resulting from partial hydrolysis of the pinacol boronate during HPLC analysis. t_R=5.76 min (boronic acid), 6.72 min (boronate) (method B). MS (ESI): m/z=867.2 $[M+H]^+$, 949.3 $[M+H]^+$.

*4.3.3.7. Boc-Phe(4-I)-Leu-Phe(4-BPin)-Rink-MBHA (**8**).* This peptidyl resin was prepared starting from Tr-Leu-Phe(4-BPin)-Rink-MBHA following the general method using Boc-Phe(4-I)-OH[7] as halogenated amino acid. Acidolytic cleavage of an aliquot of the resulting peptidyl resin afforded H-Phe(4-I)-Leu-Phe(4-BPin)-NH_2. MS (ESI): m/z=677.1 $[M+H]^+$.

*4.3.3.8. Boc-Phe(4-I)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA (**9**).* This peptidyl resin was prepared starting from Tr-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA following the general method using Boc-Phe(4-I)-OH[7] as halogenated amino acid. Acidolytic cleavage of an aliquot of the resulting peptidyl resin afforded H-Phe(4-I)-Lys-Leu-Phe(4-BPin)-NH_2 and H-Phe(4-I)-Lys-Leu-Phe(4-B$(OH)_2$)-NH_2. MS (ESI): m/z=723.1 $[M+H]^+$, 805.2 $[M+H]^+$.

*4.3.3.9. Boc-Phe(4-I)-Phe-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA (**10**).* This peptidyl resin was prepared starting from Tr-Phe-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA following the general method using Boc-Phe(4-I)-OH[7] as halogenated amino acid. Acidolytic cleavage of an aliquot of the resulting peptidyl resin afforded H-Phe(4-I)-Phe-Lys-Lys-Leu-Phe(4-BPin)-NH_2 and H-Phe(4-I)-Phe-Lys-Lys-Leu-Phe(4-B$(OH)_2$)-NH_2. MS (ESI): m/z=998.3 $[M+H]^+$, 1080.3 $[M+H]^+$.

*4.3.3.10. Boc-Phe(4-I)-Lys(Boc)-Phe-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA (**11**).* This peptidyl resin was prepared starting from Tr-Lys(Boc)-Phe-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA following the general method using Boc-Phe(4-I)-OH[7] as halogenated amino acid. Acidolytic cleavage of an aliquot of the resulting peptidyl resin afforded H-Phe(4-I)-Lys-Phe-Lys-Lys-Leu-Phe(4-BPin)-NH_2 (38% purity) and H-Phe(4-I)-Lys-Phe-Lys-Lys-Leu-Phe(4-B$(OH)_2$)-NH_2 (23% purity), resulting from partial hydrolysis of the pinacol boronate during HPLC analysis. t_R=16.81 min (boronic acid), 19.62 min (boronate) (method A).

*4.3.3.11. Boc-Phe(4-I)-Lys(Boc)-Lys(Boc)-Phe-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA (**12**).* This peptidyl resin was prepared starting from Tr-Lys(Boc)-Lys(Boc)-Phe-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA following the general method using Boc-Phe(4-I)-OH[7] as halogenated amino acid. Acidolytic cleavage of an aliquot of the resulting peptidyl resin afforded H-Phe(4-I)-Lys-Lys-Phe-Lys-Lys-Leu-Phe(4-BPin)-NH_2 (45% purity) and H-Phe(4-I)-Lys-Lys-Phe-Lys-Lys-Leu-Phe(4-B$(OH)_2$)-NH_2 (29% purity), resulting from partial hydrolysis of the pinacol boronate during HPLC analysis. t_R=15.83 min (boronic acid), 18.58 min (boronate) (method A). MS (ESI): m/z=627.8 $[M+2H]^{2+}$, 1254.4 $[M+H]^+$.

4.3.4. General method for the cyclization via a Solid-phase Suzuki–Miyaura reaction. A 5 mL quartz vial was charged with the linear precursor incorporating the borono and iodo functionalities, $Pd_2(dba)_3$ (0.2 equiv), P(*o*-tolyl)$_3$ (0.4 equiv), and KF (4 equiv). Thoroughly degassed DME/EtOH/H_2O (9:9:2, 1–1.9 mL) was then added under nitrogen. The reaction mixture was heated at 120 °C under microwave irradiation for 30 min. After this time, the resin was washed with DMF (6×1 min), EtOH (6×1 min), CH_2Cl_2 (6×1 min), and Et_2O (3×1 min). The resulting cyclic biaryl peptidyl resin was cleaved with TFA/H_2O/TIS (95:2.5:2.5) whilst being stirred for 2 h at room temperature. Following TFA evaporation and Et_2O extraction, the crude peptide was dissolved in H_2O/CH_3CN, lyophilized, analyzed by HPLC, and purified by reverse-phase column chromatography. Cyclic biaryl peptides were characterized by MS and NMR.

*4.3.4.1. Cyclic biaryl peptide **6a**.* Starting from resin Boc-Phe(4-I)-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Leu-Leu-Rink-MBHA (**4a**) (178 mg), Suzuki–Miyaura cyclization followed by acidolytic cleavage afforded the cyclic biaryl peptide **6a**, which was dissolved in H_2O/CH_3CN, lyophilized, analyzed by HPLC (74% purity) and purified by reverse-phase column chromatography. Elution with

H_2O/MeOH/TFA (70:30:0.2) yielded pure **6a** (15 mg, 28% yield). t_R=17.48 min (method A). ^{1}H NMR (400 MHz, CD_3OD): δ=0.93–0.98 [m, 18H, 6×CH_3(δ)-Leu], 1.20–1.74 [m, 21H, 3×CH(γ)-Leu, 3×CH_2(β)-Leu, 2×CH_2(β)-Lys, 2×CH_2(γ)-Lys, 2×CH_2(δ)-Lys], 2.84–2.93 [m, 6H, CH_2(β)-Phe, 2×CH_2(ε)-Lys], 3.25–3.33 [m, 2H, CH_2(β)-Phe], 4.05–4.11 [m, 1H, CH(α)-Phe], 4.34–4.46 [m, 5H, 2×CH(α)-Lys, 3×CH(α)-Leu], 4.69–4.72 [m, 1H, CH(α)-Phe], 7.29 [d, J=8.0 Hz, 4H, CH_{arom}-2, CH_{arom}-6, CH_{arom}-3′, CH_{arom}-5′], 7.67 [d, J=8.0 Hz, 4H, CH_{arom}-3, CH_{arom}-5, CH_{arom}-2′, CH_{arom}-6′] ppm. MS (ESI): m/z=905.6 $[M+H]^+$. HRMS (ESI): calcd for $C_{48}H_{78}N_{10}O_7$ 453.3022; found 453.3034; calcd for $C_{48}H_{77}N_{10}O_7$ 905.5971; found 905.5969; calcd for $C_{48}H_{76}N_{10}NaO_7$ 927.5791; found 927.5772.

*4.3.4.2. Cyclic biaryl peptide **6b**.* Starting from resin Boc-Tyr(3-I,Me)-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Leu-Leu-Rink-MBHA (**4b**) (182 mg), Suzuki–Miyaura cyclization followed by acidolytic cleavage afforded the cyclic biaryl peptide **6b**, which was dissolved in H_2O/CH_3CN, lyophilized, analyzed by HPLC (72% purity) and purified by reverse-phase column chromatography. Elution with H_2O/MeOH/TFA (70:30:0.2) yielded pure **6b** (12.7 mg, 23% yield). t_R=17.63 min (method A). ^{1}H NMR (400 MHz, CD_3OD): δ=0.91–0.98 [m, 18H, 6×CH_3(δ)-Leu], 1.16–1.71 [m, 21H, 3×CH(γ)-Leu, 3×CH_2(β)-Leu, 2×CH_2(β)-Lys, 2×CH_2(γ)-Lys, 2×CH_2(δ)-Lys], 2.70–2.72 [m, 2H CH_2(ε)-Lys], 2.83–2.93 [m, 3H, CH_2(ε)-Lys, CH_2(β)-Phe], 3.13–3.19 [m, 3H, CH_2(β)-Phe, CH_2(β)-Tyr], 3.78 [s, 3H, OCH_3], 4.09–4.15 [m, 2H, CH(α)-Tyr, CH(α)-Lys], 4.18–4.49 [m, 3H, 3×CH(α)-Leu], 4.57–4.64 [m, 2H, CH(α)-Phe, CH(α)-Lys], 7.05 [d, J=8.6 Hz, 1H, CH_{arom}-3′], 7.22 [s, 1H, CH_{arom}-6′], 7.24 [dd, J=2.4, 8.6 Hz, 1H, CH_{arom}-4′], 7.32 [d, J=8.2 Hz, 2H, CH_{arom}-2, CH_{arom}-6], 7.49 [d, J=8.2 Hz, 2H, CH_{arom}-3, CH_{arom}-5] ppm. MS (ESI): m/z=468.3 $[M+2H]^{2+}$, 935.6 $[M+H]^+$, 957.5 $[M+Na]^+$. HRMS (ESI): calcd for $C_{49}H_{80}N_{10}O_8$ 468.3075; found 468.3098; calcd for $C_{49}H_{79}N_{10}O_8$ 935.6077; found 935.6057; calcd for $C_{49}H_{78}N_{10}NaO_8$ 957.5896; found 957.5875.

*4.3.4.3. Cyclic biaryl peptide **6c**.* Starting from resin Boc-Tyr(3-I,SEM)-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Leu-Leu-Rink-MBHA (**4c**) (195 mg), Suzuki–Miyaura cyclization followed by acidolytic cleavage afforded the cyclic biaryl peptide **6c**, which was dissolved in H_2O/CH_3CN, lyophilized, analyzed by HPLC (79% purity) and purified by reverse-phase column chromatography. Elution with H_2O/MeOH/TFA (70:30:0.2) yielded pure **6c** (20.5 mg, 35% yield). t_R=17.18 min (method A). ^{1}H NMR (400 MHz, CD_3OD): δ=0.87–0.97 [m, 18H, 6×CH_3(δ)-Leu], 1.45–1.70 [m, 21H, 3×CH(γ)-Leu, 3×CH_2(β)-Leu, 2×CH_2(β)-Lys, 2×CH_2(γ)-Lys, 2×CH_2(δ)-Lys], 2.66–2.73 [m, 2H, CH_2(ε)-Lys], 2.81–2.91 [m, 3H, CH_2(ε)-Lys, CH_2(β)-Phe], 3.07–3.18 [m, 3H, CH_2(β)-Tyr, CH_2(β)-Phe], 4.07–4.14 [m, 2H, CH(α)-Tyr, CH(α)-Lys], 4.27–4.54 [m, 3H, 3×CH(α)-Leu], 4.57–4.61 [m, 2H, CH(α)-Phe, CH(α)-Lys], 6.88 [d, J=8.0 Hz, 1H, CH_{arom}-3′], 7.09 [dd, J=2.0, 8.0 Hz, 1H, CH_{arom}-4′], 7.24–7.25 [m, 1H, CH_{arom}-6′], 7.32 [d, J=8.2 Hz, 2H, CH_{arom}-4, CH_{arom}-6], 7.60 [d, J=8.2 Hz, 2H, CH_{arom}-3, CH_{arom}-5] ppm. MS (ESI): m/z=921.6 $[M+H]^+$. HRMS (ESI): calcd for $C_{48}H_{78}N_{10}O_8$ 461.2997; found 461.3017; calcd for $C_{48}H_{77}N_{10}O_8$ 921.5920; found 921.5900; calcd for $C_{48}H_{76}N_{10}NaO_8$ 943.5740; found 943.5713.

*4.3.4.4. Cyclic biaryl peptide **7a**.* Starting from resin Boc-Phe(4-I)-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA (**5a**) (135 mg), Suzuki–Miyaura cyclization followed by acidolytic cleavage afforded the cyclic biaryl peptide **7a**, which was dissolved in H_2O/CH_3CN, lyophilized, analyzed by HPLC (76% purity) and purified by reverse-phase column chromatography. Elution with H_2O/MeOH/TFA (90:10:0.2) yielded pure **7a** (8.3 mg, 25% yield). t_R=14.60 min (method A). ^{1}H NMR (400 MHz, CD_3OD): δ=0.85–0.90 [m, 6H, 2×CH_3(δ)-Leu], 1.20–1.62 [m, 15H, CH(γ)-Leu, CH_2(β)-Leu, 2×CH_2(β)-Lys, 2×CH_2(γ)-Lys, 2×CH_2(δ)-Lys], 2.84–3.02 [m, 6H, CH_2(β)-Phe, 2×CH_2(ε)-Lys], 3.22–3.39 [m, 2H, CH_2(β)-Phe], 4.03 [dd, J=5.2, 12.0 Hz, 1H, CH(α)-Phe], 4.11–4.14 [m, 1H, 2×CH(α)-Lys], 4.348–4.40 [m, 1H, CH(α)-Leu], 4.67–4.72 [m, 1H, CH(α)-Phe], 7.26 [d, 8.2 Hz, 4H, CH_{arom}-2, CH_{arom}-6, CH_{arom}-3′, CH_{arom}-5′], 7.67 [d, J=8.2 Hz, 4H, CH_{arom}-3, CH_{arom}-5, CH_{arom}-2′, CH_{arom}-6′] ppm. ^{13}C NMR (100 MHz, CD_3OD): δ=21.49 [CH_2(γ)-Lys], 23.50, 23.69 [2×CH_3(δ)-Leu], 25.66 [CH(γ)-Leu], 28.24 [CH_2(β)-Lys, CH_2(δ)-Lys], 38.15 [CH_2(β)-Phe], 38.69 [CH_2(β)-Phe], 40.43 [2×CH_2(ε)-Lys], 41.39 [CH(β)-Leu], 51.94 [CH(α)-Leu], 54.32 [CH(α)-Phe, CH(α)-Lys], 55.77 [CH(α)-Phe], 127.83, 127.95 [CH_{arom}-3, CH_{arom}-5, CH_{arom}-2′, CH_{arom}-6′], 130.88 [CH_{arom}-2, CH_{arom}-6, CH_{arom}-3′, CH_{arom}-5′], 131.38 [C_{arom}], 134.53 [C_{arom}], 137.56 [C_{arom}], 140.90 [C_{arom}], 168.81, 175.91 [CO] ppm. MS (ESI): m/z=679.4 $[M+H]^+$. HRMS (ESI): calcd for $C_{36}H_{56}N_8O_5$ 340.2181; found 340.2167; calcd for $C_{36}H_{55}N_8O_5$ 679.4290; found 679.4273; calcd for $C_{36}H_{54}N_8NaO_5$ 701.4109; found 701.4086.

*4.3.4.5. Cyclic biaryl peptide **7b**.* Starting from resin Boc-Tyr(3-I,Me)-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA (**5b**) (167 mg), Suzuki–Miyaura cyclization followed by acidolytic cleavage afforded the cyclic biaryl peptide **7b**, which was dissolved in H_2O/CH_3CN, lyophilized, analyzed by HPLC (75% purity) and purified by reverse-phase column chromatography. Elution with H_2O/MeOH/TFA (90:10:0.2) yielded pure **7b** (12.6 mg, 30% yield). t_R=14.56 min (method A). ^{1}H NMR (400 MHz, CD_3OD): δ=0.92–0.96 [m, 6H, 2×CH_3(δ)-Leu], 1.18–1.61 [m, 15H, CH(γ)-Leu, CH_2(β)-Leu, 2×CH_2(β)-Lys, 2×CH_2(γ)-Lys, 2×CH_2(δ)-Lys], 2.69–2.76 [m, 2H, CH_2(ε)-Lys], 2.83–2.99 [m, 3H, CH_2(ε)-Lys, CH_2(β)-Phe], 3.14–3.16 [m, 2H, CH_2(β)-Tyr], 3.21 [dd, J=2.8, 14.0 Hz, 1H, CH_2(β)-Phe], 3.78 [s, 3H, OCH_3], 4.06–4.10 [m, 2H, CH(α)-Tyr, CH(α)-Lys], 4.33–4.36 [m, 1H, CH(α)-Leu], 4.53 [dd, J=5.8, 8.6 Hz, 1H, CH(α)-Lys], 4.59 [dd, J=2.8, 12.0 Hz, 1H, CH(α)-Phe], 7.05 [d, J=8.4 Hz, 1H, CH_{arom}-3′], 7.23–7.26 [m, 2H, CH_{arom}-4′, CH_{arom}-6′], 7.30 [d, J=8.2 Hz, 2H, CH_{arom}-2, CH_{arom}-6], 7.48 [d, J=8.2 Hz, 2H, CH_{arom}-3, CH_{arom}-5] ppm. MS (ESI): m/z=709.4 $[M+H]^+$. HRMS (ESI): calcd for $C_{37}H_{58}N_8O_6$ 355.2234; found 355.2232; calcd for $C_{37}H_{57}N_8O_6$ 709.4396; found 709.4372; calcd for $C_{37}H_{56}N_8NaO_6$ 731.4215; found 731.4188.

*4.3.4.6. Cyclic biaryl peptide **7c**.* Starting from resin Boc-Tyr(3-I,SEM)-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA (**5c**) (185 mg), Suzuki–Miyaura cyclization followed by acidolytic cleavage afforded the cyclic biaryl peptide **7c**, which was dissolved in H_2O/CH_3CN, lyophilized, analyzed by HPLC (76% purity) and purified by reverse-phase column chromatography. Elution with H_2O/MeOH/TFA (90:10:0.2) yielded pure **7c** (13 mg, 30% yield). t_R=13.59 min (method A). ^{1}H NMR (400 MHz, CD_3OD): δ=0.92–0.97 [m, 6H, 2×CH_3(δ)-Leu], 1.18–1.67 [m, 15H, CH(γ)-Leu, CH_2(β)-Leu, 2×CH_2(β)-Lys, 2×CH_2(γ)-Lys, 2×CH_2(δ)-Lys], 2.61–2.75 [m, 2H, CH_2(ε)-Lys], 2.80–2.94 [m, 3H, CH_2(ε)-Lys, CH_2(β)-Phe], 3.12–3.13 [m, 2H, CH_2(β)-Tyr], 3.21 [dd, J=2.8, 14.0 Hz, 1H, CH_2(β)-Phe], 4.06–4.10 [m, 2H, CH(α)-Lys, CH(α)-Tyr], 4.37–4.40 [m, 1H, CH(α)-Leu], 4.52–4.58 [m, 2H, CH(α)-Lys, CH(α)-Phe], 6.89 [d, J=8.2 Hz, 1H, CH_{arom}-3′], 7.09 [dd, 1H, J=2.4, 8.2 Hz, CH_{arom}-4′], 7.31 [d, 2H, J=8.2 Hz, CH_{arom}-2, CH_{arom}-6], 7.53 [br s, 1H, CH_{arom}-6′], 7.59 [d, 2H, J=8.2 Hz, CH_{arom}-3, CH_{arom}-5] ppm. MS (ESI): m/z=695.4 $[M+H]^+$. HRMS (ESI): calcd for $C_{36}H_{56}N_8O_6$ 348.2156; found 348.2145; calcd for $C_{36}H_{55}N_8O_6$ 695.4239; found 695.4225; calcd for $C_{36}H_{54}N_8NaO_6$ 717.4059; found 717.4047.

*4.3.4.7. Cyclic biaryl peptide **13**.* Starting from resin Boc-Phe(4-I)-Leu-Phe(4-BPin)-Rink-MBHA (**8**) (21 mg), Suzuki–Miyaura cyclization followed by acidolytic cleavage afforded the cyclic biaryl peptide **13**, which was dissolved in H_2O/CH_3CN, lyophilized, and analyzed by HPLC (71% purity). t_R=17.22 min (method A). MS (ESI): m/z=423.2 $[M+H]^+$. HRMS (ESI): calcd for $C_{24}H_{31}N_4O_3$ 423.2391; found 423.2391.

*4.3.4.8. Cyclic biaryl peptide **14**.* Starting from resin Boc-Phe(4-I)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA (**9**) (60 mg), Suzuki–Miyaura cyclization followed by acidolytic cleavage afforded the cyclic biaryl peptide **14**, which was dissolved in H_2O/CH_3CN, lyophilized, and analyzed by HPLC (70% purity). t_R=16.72 min (method A). MS (ESI): m/z=276.1 $[M+2H]^{2+}$, 551.2 $[M+H]^+$. HRMS (ESI): calcd for $C_{30}H_{43}N_6O_4$ 551.3340; found 551.3330.

*4.3.4.9. Cyclic biaryl peptide **15**.* Starting from resin Boc-Phe(4-I)-Phe-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA (**10**) (65 mg), Suzuki–Miyaura cyclization followed by acidolytic cleavage afforded the cyclic biaryl peptide **15**, which was dissolved in H_2O/CH_3CN, lyophilized, and analyzed by HPLC (36% purity). t_R=15.23 min (method A). MS (ESI): m/z=413.7 $[M+2H]^{2+}$, 826.4 $[M+H]^+$. HRMS (ESI): calcd for $C_{45}H_{65}N_9O_6$ 413.7523; found 413.7530.

*4.3.4.10. Cyclic biaryl peptide **16**.* Starting from resin Boc-Phe (4-I)-Lys(Boc)-Phe-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA (**11**) (38 mg), Suzuki–Miyaura cyclization followed by acidolytic cleavage afforded the cyclic biaryl peptide **16**, which was dissolved in H_2O/CH_3CN, lyophilized, and analyzed by HPLC (84% purity). t_R=16.05 min (method A). MS (ESI): m/z=477.7 $[M+2H]^{2+}$, 954.5 $[M+H]^+$. HRMS (ESI): calcd for $C_{51}H_{77}N_{11}O_7$ 477.7998; found 477.8007; calcd for $C_{51}H_{76}N_{11}O_7$ 954.5924; found 954.5876.

*4.3.4.11. Cyclic biaryl peptide **17**.* Starting from resin Boc-Phe(4-I)-Lys(Boc)-Lys(Boc)-Phe-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA (**12**) (60 mg), Suzuki–Miyaura cyclization followed by acidolytic cleavage afforded the cyclic biaryl peptide **17**, which was dissolved in H_2O/CH_3CN, lyophilized, and analyzed by HPLC (77% purity). t_R=15.19 min (method A). MS (ESI): m/z=541.8 $[M+2H]^{2+}$, 1082.5 $[M+H]^+$. HRMS (ESI): calcd for $C_{57}H_{90}N_{13}O_8$ 361.5673; found 361.5690; calcd for $C_{57}H_{89}N_{13}O_8$ 541.8473; found 541.8498; calcd for $C_{57}H_{88}N_{13}O_8$ 1082.6873; found 1082.6829.

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Supplementary data

Supplementary data HPLC, MS, and NMR spectra for peptides **3**–**17** and for their corresponding precursors are provided. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.01.084. These data include MOL files and InChIKeys of the most important compounds described in this article.

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