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Solid-Phase Synthesis of Biaryl Cyclic Peptides Containing a 3-Aryltyrosine

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A concise and efficient solid-phase synthesis of biaryl cyclic peptides containing a Phe–Tyr or a Tyr–Tyr linkage has been accomplished. The key steps include a Miyaura borylation of a resin-bound 3-iodotyrosine and a microwave-assisted Suzuki–Miyaura reaction for the formation of the macrocycle. First, the feasibility of the solid-phase Miyaura borylation of a 3-iodotyrosyltripeptide was established. Then, the Suzuki–Miyaura reaction was applied to the cross-coupling of linear 3-boronotyrosine-containing peptidyl resins with iodobenzene and with halogenated aromatic amino acids. Finally, this methodology was extended to the synthesis of biaryl cyclic peptides through the preparation of a linear peptidyl resin containing both the required boronate and halogenated derivatives, followed by a microwave-assisted Suzuki–Miyaura macrocyclization.

Introduction

Biaryl cyclic peptides have been subject to the attention of synthetic chemists during the last few years due to their interesting biological activity.[1] Biaryl compounds have been mainly prepared in solution using a Suzuki–Miyaura cross-coupling reaction for the formation of the biaryl linkage.[2] The solid-phase synthesis of biaryl peptides has scarcely been reported, being limited to linear sequences and involving the coupling of a polymer-bound halogenated aromatic amino acid with an arylboron in solution.[3]

We have described the solid-phase synthesis of biaryl cyclic peptides containing an arylphenylalanine residue.[4] All the key steps of this approach were performed on a solid support and entail (i) Miyaura borylation of a 4-iodophenylalanine peptide; (ii) chain elongation to afford a linear peptide containing both the boronate and the halogenated amino acid derivative, and (iii) Suzuki–Miyaura macrocyclization for the formation of the aryl–aryl bond. Recently, James et al. reported a complementary study for the synthesis of arylphenylalanine-containing cyclic peptides, but they prepared the corresponding boronophenylalanine derivative in solution.[5] In our methodology, both borylation and macrocyclization are performed on the solid support, and therefore it benefits from the advantages inherent to solid-phase synthesis. In particular, performing the borylation on the solid support avoids the synthesis and purification of the amino acid boronate in solution. Therefore, this strategy is amenable to the preparation of biaryl cyclic peptides in a flexible and convergent manner under mild conditions.

We envisioned that this methodology could be extended to the formation of biaryl linkages involving a tyrosine residue. This would represent an efficient strategy for the synthesis of natural biaryl cyclic peptides bearing an aryltyrosine, such as biphenomycins, RP-66453, or glycopeptide antibiotics, and the strategy could be extended to allow the preparation of analogues. In this paper, we report the results from our work in this area, in which we studied the effectiveness of the solid-phase Miyaura borylation of 3-iodotyrosine peptides and of the Suzuki–Miyaura macrocyclization of conveniently functionalized linear peptidyl resins.

Results and Discussion

Solid-Phase Synthesis of Boronotyrosines

Miyaura borylation of a 3-iodotyrosine residue on solid support was investigated using Boc-Tyr(3-BPin,SEM)-Leu-Leu-Rink-MBHA (**1a**; Boc = *tert*-butyloxycarbonyl; SEM = 2-(trimethylsilyl)ethoxymethyl; BPin = pinacolboranyl) and Boc-Tyr(3-BPin,Me)-Leu-Leu-Rink-MBHA (**1b**) as model systems (Scheme 1). SEM and methyl protecting groups served to ensure the stability of the hydroxy functionality under the reaction conditions. Thus, we prepared the required halogenated resins Boc-Tyr(3-I,SEM)-Leu-Leu-Rink-MBHA (**2a**) and Boc-Tyr(3-I,Me)-Leu-Leu-Rink-MBHA (**2b**) by coupling Boc-Tyr(3-I,SEM)-OH or Boc-Tyr(3-I,Me)-OH[3d] to H-Leu-Leu-Rink-MBHA. This dipeptidyl resin was constructed from Fmoc-Rink-MBHA

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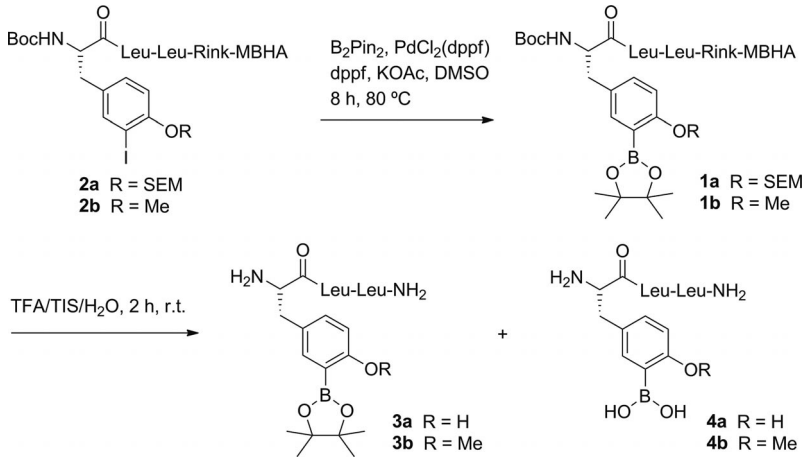


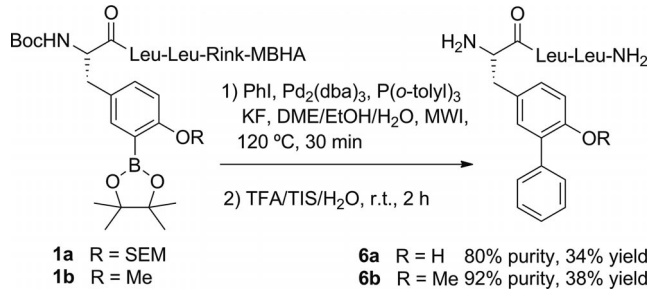
Scheme 1. Solid-phase Miyaura borylation of a 3-iodotyrosyltripeptide.

following an Fmoc/*t*Bu strategy by sequential coupling and deprotection steps using standard protocols. Treatment of an aliquot of the resulting resins **2a** and **2b** with TFA/TIS/H_2O (95:2.5:2.5; TFA = trifluoroacetic acid; TIS = triisopropylsilane) for 2 h at room temperature gave H-Tyr(3-I)-Leu-Leu-NH_2 and H-Tyr(3-I,Me)-Leu-Leu-NH_2 in 97 and 92% purity, respectively. These compounds were characterized by mass spectrometry.

The borylation was first attempted under the conditions previously described for the preparation of resin-bound phenylalanine boronates.[6] Resins **2a** and **2b** were treated with bis(pinacolato)diboron (B_2Pin_2) (4 equiv.), $PdCl_2$-(dppf) (0.18 equiv.), 1,1′-bis(diphenylphosphanyl)ferrocene (dppf; 0.09 equiv.), and KOAc (6 equiv.), in DMSO at 80 °C for 24 h (Scheme 1). In both cases, acidolytic cleavage of the resulting resins gave the corresponding borylated products with low purities. Moreover, mass spectrometry analysis of the crude reaction mixtures resulting from **2a** and **2b** showed the presence of H-Tyr-Leu-Leu-NH_2 (**5a**) and H-Tyr(Me)-Leu-Leu-NH_2 (**5b**) as the respective major products. These tripeptides resulted from protodeborylation of resins **1** or deiodination of resins **2**. Since the formation of such by-products has been reported to increase in the presence of transition metals, such as palladium, and with long heating times,[7] the borylation was attempted with a shorter reaction time. Carrying out the reaction for 8 h, the amount of **5a** and **5b** was reduced to less than 10%, and the corresponding boronopeptides (i.e., **3a** + **4a** and **3b** + **4b**) were obtained in 60 and 78% purity, respectively. As previously reported, peptide boronic acids **4a** and **4b** could be formed by hydrolysis of the pinacol ester functionality of the corresponding boronate during HPLC analysis.[7,8]

Arylation of Resin-Bound Boronotyrosine-Containing Peptides

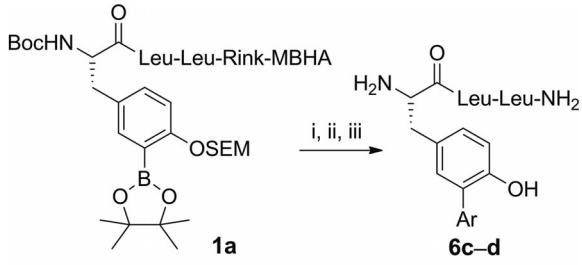
With resin-bound tyrosine boronates **1a** and **1b** in hand, we attempted their arylation with iodobenzene by a Suzuki–Miyaura cross-coupling (Scheme 2).[4,6] Thus, resins **1a** and **1b** were treated with iodobenzene (5 equiv.), $Pd_2(dba)_3$ (0.2 equiv.), P(*o*-tolyl)$_3$ (0.4 equiv.), and KF (4 equiv.) in DME/EtOH/H_2O (9:9:2; DME = 1,2-dimethoxyethane) under microwave irradiation at 120 °C for 30 min. Acidolytic cleavage of the resulting resins with TFA/TIS/H_2O (95:2.5:2.5) gave the corresponding biaryl tripeptides **6a** and **6b** in 80 and 92% purity, respectively. These compounds were purified by column chromatography, and were obtained in 34 and 38% yield, respectively. They were characterized by NMR spectroscopy and mass spectrometry.

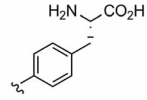
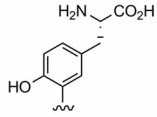


Scheme 2. Solid-phase arylation of resins **1a** and **1b** with PhI.

Bearing in mind our aim of preparing biaryl cyclic peptides, we then studied the feasibility of the arylation of a boronopeptidyl resin with a halogenated aromatic amino acid. In particular, Boc-Tyr(3-BPin,SEM)-Leu-Leu-Rink-MBHA (**1a**) was treated with the methyl ester derivatives Boc-Phe(4-I)-OMe[9] and Boc-Tyr(3-I,SEM)-OMe[3d] under the conditions described above (Scheme 3). After arylation and hydrolysis of the methyl ester with LiOH in THF, the resulting biaryl peptidyl resins were cleaved with TFA/TIS/H_2O. HPLC and ESI-MS analysis of the crude reaction mixtures showed the presence of the expected biaryl tetrapeptides (i.e., **6c** and **6d**), in 64 and 61% purity, respectively, together with a small amount of the protodeborylated product, H-Tyr-Leu-Leu-NH_2 (**5a**, 8–9%). Purification of these crude reaction mixtures by column chromatography gave the corresponding biaryl peptides (i.e., **6c** and **6d**) in 44 and 55% yield, respectively. These products were fully characterized by mass spectrometry, and ^1H and ^{13}C NMR spec-

troscopy. Moreover, 2D COSY, HSQC and HMBC experiments were carried out to completely assign all the proton and carbon signals. The NMR spectra showed the presence of a single stereoisomer, revealing that no epimerization occurred during the borylation and Suzuki–Miyaura cross-coupling steps.



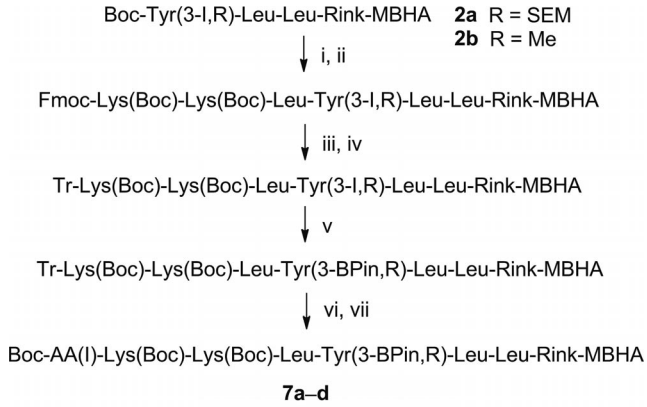
	Ar	Purity (%)	Yield (%)
6c		64	44
6d		61	55

Reagents and conditions: i) Boc-Phe(4-I)-OMe or Boc-Tyr(3-I,SEM)-OMe, $Pd_2(dba)_3$, P(*o*-tolyl)$_3$, KF, DME/EtOH/H_2O, MWI, 120 °C, 30 min; ii) LiOH, THF, r.t., 24 h; iii) TFA/TIS/H_2O, r.t., 2 h.

Scheme 3. Solid-phase arylation of resin **1a** with halogenated aromatic amino acids.

Synthesis of Biaryl Cyclic Peptides

To achieve our final goal, we set out to examine the synthesis of biaryl cyclic peptides with the aim of achieving ring closure by solid-phase formation of the aryl–aryl bond under the conditions of the Suzuki–Miyaura cross-coupling. This approach involved the preparation of linear peptidyl resins containing the required boronate and halogenated amino acid derivatives, followed by macrocyclization. Thus, we prepared the peptidyl resins Boc-AA(I)-Lys(Boc)-Lys(Boc)-Leu-Tyr(3-BPin,R)-Leu-Leu-Rink-MBHA (**7a**–**d**) where AA(I) corresponds to Phe(4-I), Tyr(3-I,Me) or Tyr(3-I,SEM), and R is Me or SEM (Scheme 4). Since in previous studies we had observed that the boronate functionality decomposed into the phenolic compound after several Fmoc removal and coupling steps,[4] we decided to form the boronate in the last steps of the synthesis. Therefore, we first prepared Fmoc-Lys(Boc)-Lys(Boc)-Leu-Tyr(3-I,R)-Leu-Leu-Rink-MBHA (R = Me or SEM) starting from resins Boc-Tyr(3-I,SEM)-Leu-Leu-Rink-MBHA (**2a**) and Boc-Tyr(3-I,Me)-Leu-Leu-Rink-MBHA (**2b**). After Boc removal by treatment with trimethylsilyl triflate (TMSOTf) and 2,6-lutidine in CH_2Cl_2 for 1 h, the peptidyl chain was elongated. Then we replaced the Fmoc group by a trityl group to overcome the instability of Fmoc under the Miyaura borylation conditions. Next, the boronate was formed using the conditions described above, which led to Tr-Lys(Boc)-Lys(Boc)-Leu-Tyr(3-BPin,R)-Leu-Leu-Rink-MBHA (R = Me or SEM). Trityl group removal and coupling of the corresponding 4-iodophenylalanine or 3-iodotyrosine derivative gave peptidyl resins **7a**–**d**. Acidolytic cleavage of an aliquot of these resins yielded the expected borylated peptides in purities ranging from 30–62%. The cleaved peptides were characterized by HRMS.



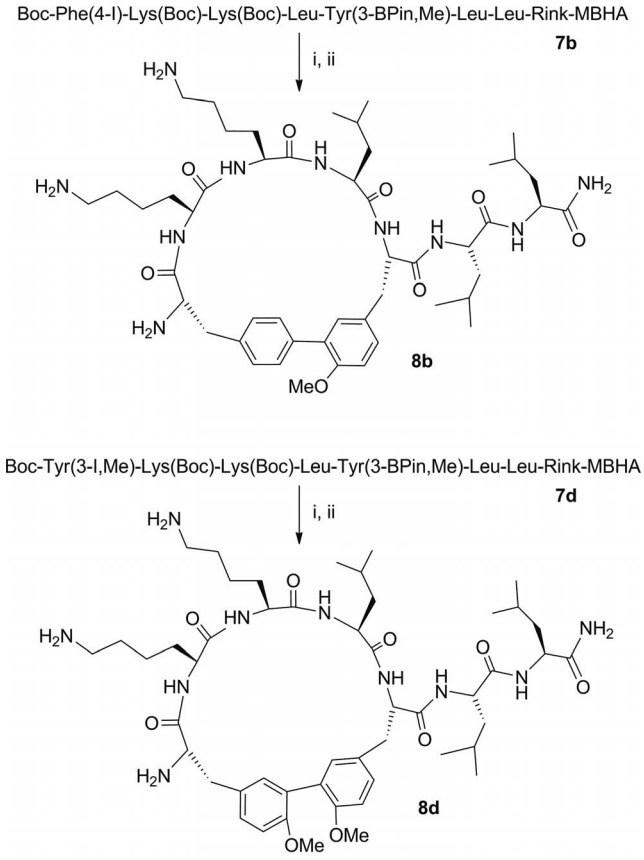
	Aa	R
7a	Phe	SEM
7b	Phe	Me
7c	Tyr(SEM)	SEM
7d	Tyr(Me)	Me

Reagents and conditions: (i) 1 M TMSOTf, 1.5 M 2,6-lutidine in CH_2Cl_2, r.t., 1 h; (ii) chain elongation; coupling steps: Fmoc-Aa-OH, ethyl cyanoglyoxylate 2-oxime, DIPCDI, DMF, r.t., 1 h; Fmoc removal: piperidine/DMF (3:7), 2 x 10 min; (iii) piperidine/DMF (3:7), 2 x 10 min; (iv) TrCl, DIEA, DMF, r.t., 3 h; (v) B_2Pin_2, $PdCl_2$(dppf), dppf, KOAc, DMSO, 80 °C, 8 h; (vi) TFA/H_2O/CH_2Cl_2 (0.2:1:98.8), 20 min; (vii) Boc-Phe(4-I)-OH, Boc-Tyr(3-I,Me)-OH or Boc-Tyr(3-I,SEM)-OH, ethyl cyanoglyoxylate 2-oxime, DIPCDI, DMF, r.t., 3 h.

Scheme 4. Synthesis of linear peptidyl resins **7a**–**d**.

Cyclization of resins **7a**–**d** by Suzuki–Miyaura cross-coupling was attempted using $Pd_2(dba)_3$, P(*o*-tolyl)$_3$, and KF in DME/EtOH/H_2O under microwave irradiation at 120 °C for 30 min. After cleavage, HPLC and ESI-MS analysis of the crude reaction mixtures showed that only resin **7b** had cyclized to form the expected biaryl cyclic peptide **8b**, and in low purity (<10%). In all reactions a major product derived from the simultaneous protodeborylation and dehalogenation of the corresponding linear precursor was observed. In order to improve these results, the macrocyclization was tested using SPhos instead of P(*o*-tolyl)$_3$.[10] Under these conditions, biaryl cyclic peptides **8b** and **8d** were formed in 47 and 33% purity, respectively (Scheme 5). These compounds were purified by column chromatography and were obtained in 16 and 22% yield, respectively. **8b** and **8d** were characterized by mass spectrometry and ^{1}H NMR spectroscopy, and the data were consistent with the formation of the biaryl bond. In the case of **8b**, only one

steroisomer was observed. NMR analysis of **8d** indicated the presence of two conformers, which was confirmed by performing further ^{1}H NMR experiments at high temperature in [D$_6$]DMSO. As expected, raising the temperature resulted in the coalescence of the proton signals.



Scheme 5. Synthesis of biaryl cyclic peptides **8b** and **8d**.

Conclusions

We have developed a convenient strategy for the modification of tyrosine peptides through solid-phase borylation and subsequent arylation. This methodology can be considered to be a useful approach for the synthesis of linear and cyclic 3-aryltyrosine-containing peptides. Moreover, this work constitutes the first example of a solid-phase intramolecular Suzuki–Miyaura cross-coupling for the formation of biaryl cyclic peptides containing a Tyr–Tyr linkage. We expect that this approach will find applications in the synthesis of natural products or biaryl-containing analogues.

Experimental Section

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} reverse-phase silica gel 100 (not end-capped; 230–400 mesh, Fluka). All compounds were analyzed under standard analytical HPLC conditions with a Dionex liquid chromatography instrument or with an Agilent Technologies 1200 Series HPLC instrument. Detection was performed at 220 nm. Method A: Analysis was carried out using the Dionex instrument 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. Method B: Analysis was carried out using the Dionex instrument with a Kromasil 100 C_{18} (40 mm × 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. Method C: Analysis was carried out using the Agilent instrument 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. Method D: Analysis was carried out using the Agilent instrument with a Kromasil 100 C_{18} (40 mm × 4.6 mm, 3.5 μm) column with a 2–100% B linear gradient over 10 min at a flow rate of 1 mL/min. Solvent A was 0.1% aqueous TFA, and solvent B was 0.1% TFA in CH_3CN. ESI-MS analyses were performed with an Esquire 6000 ESI ion-trap LCMS (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 μL/min) was delivered by a 1100 Series HPLC pump (Agilent). Nitrogen was used as both the drying and nebulizing gas. HRMS were recorded under ESI conditions 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 Bruker 300 or 400 MHz NMR spectrometers. Chemical shifts are 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 Easy-Control 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. Microwave-assisted reactions were also performed with a single mode Discover S-Class labstation microwave (CEM) (0–300 W). The time, temperature, and power were controlled with the Synergy software. The temperature was monitored through an infrared sensor in the floor of the cavity.

Boc-Tyr(3-I,SEM)-Leu-Leu-Rink-MBHA (2a): This peptidyl resin was synthesized manually by the solid-phase method using standard Fmoc chemistry. Fmoc-Rink-MBHA resin (0.56 mmol/g) was used as solid support. Fmoc-Leu-OH (4 equiv.) and Boc-Tyr(3-I,SEM)-OH[3d] were coupled using ethyl cyanoglyoxylate 2-oxime (3 equiv.) and *N*,*N*′-diisopropylcarbodiimide (DIPCDI) (3 equiv.) in DMF at room temperature for 3 h. The completion of the reactions was checked by the Kaiser test.[11] Fmoc group removal was achieved with piperidine/DMF (3:7, 2 + 8 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. An aliquot of Boc-Tyr(3-I,SEM)-Leu-Leu-Rink-MBHA (**2a**) was cleaved with TFA/H_2O/triisopropylsilane (TIS) (95:2.5:2.5) whilst 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 characterized by MS. H-Tyr(3-I)-Leu-Leu-NH_2 was obtained in 97% purity. t_R = 6.49 min (Method B). MS (ESI): *m/z* = 533.0 $[M + H]^+$, 555.0 $[M + Na]^+$.

Boc-Tyr(3-I,Me)-Leu-Leu-Rink-MBHA (2b): This peptidyl resin was synthesized manually by the solid-phase method using standard Fmoc chemistry. Fmoc-Rink-MBHA resin (0.56 mmol/g) was used as solid support. Fmoc-Leu-OH (4 equiv.) and Boc-Tyr(3-I,Me)-OH[3d] were coupled using ethyl cyanoglyoxylate 2-oxime (3 equiv.) and DIPCDI (3 equiv.) in DMF at room temperature for 3 h. The completion of the reactions was checked by the Kaiser test.[11] Fmoc group removal was achieved with piperidine/DMF (3:7, 2 + 8 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. An aliquot of Boc-Tyr(3-I,Me)-Leu-Leu-Rink-MBHA (**2b**) was cleaved with TFA/H_2O/TIS (95:2.5:2.5) whilst 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 characterized by MS. H-Tyr(3-I,Me)-Leu-Leu-NH_2 was obtained in 92% purity. t_R = 6.86 min (Method B). MS (ESI): *m/z* = 547.0 $[M + H]^+$, 569.0 $[M + Na]^+$, 585.0 $[M + K]^+$.

General Method for the Borylation of Linear Peptidyl Resins 2a and 2b by a Miyaura Reaction: A 25 mL round-bottomed flask was charged with the appropriate 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 mL/mg of resin) was then added, and the mixture was heated at 80 °C for 8 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.

Boc-Tyr(3-BPin,SEM)-Leu-Leu-Rink-MBHA (1a): This peptidyl resin was prepared starting from Boc-Tyr(3-I,SEM)-Leu-Leu-Rink-MBHA (**2a**, 600 mg) following the General Method for solid-phase Miyaura borylation. Acidolytic cleavage of an aliquot of this peptidyl resin gave H-Tyr(3-BPin)-Leu-Leu-NH_2 (**3a**, 23% purity) and H-Tyr[3-B(OH)$_2$]-Leu-Leu-NH_2 (**4a**, 37% purity), resulting from partial hydrolysis of the pinacol boronate during HPLC analysis. t_R = 6.11 min (boronic acid), 7.12 min (boronate) (Method B). HRMS (ESI): calcd. for $C_{21}H_{36}BN_4O_6$ 451.2726; found 451.2729; calcd. for $C_{27}H_{46}BN_4O_6$ 533.3510; found 533.3511.

Boc-Tyr(3-BPin,Me)-Leu-Leu-Rink-MBHA (1b): This peptidyl resin was prepared starting from Boc-Tyr(3-I,Me)-Leu-Leu-Rink-MBHA (**2b**, 380 mg) following the General Method for solid-phase Miyaura borylation. Acidolytic cleavage of an aliquot of this peptidyl resin gave H-Tyr(3-BPin,Me)-Leu-Leu-NH_2 (**3b**, 29% purity) and H-Tyr[3-B(OH)$_2$,Me]-Leu-Leu-NH_2 (**4b**, 49% purity), resulting from partial hydrolysis of the pinacol boronate during HPLC analysis. t_R = 6.28 min (boronic acid), 7.06 min (boronate) (Method B). MS (ESI): *m/z* = 465.2 $[M_{B(OH)2} + H]^+$, 547.3 $[M_{BPin} + H]^+$. HRMS (ESI): calcd. for $C_{22}H_{38}BN_4O_6$ 465.2879; found 465.2897; calcd. for $C_{28}H_{48}BN_4O_6$ 547.3666; found 547.3683; calcd. for $C_{28}H_{47}BN_4NaO_6$ 569.3486; found 569.3485.

General Method for the Arylation of Linear Peptides by a Solid-Phase Suzuki–Miyaura Reaction: A 5 mL quartz vial was charged with the appropriate boronopeptidyl resin, the aryl halide or 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. When necessary, the rest of the biaryl peptidyl resin was hydrolyzed by treatment with LiOH (5 equiv.) in THF/H_2O (7:1) at room temperature for 24 h. After the reaction was finished, 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 spectroscopy.

Biaryl Linear Peptide 6a: Starting from resin Boc-Tyr(3-BPin,SEM)-Leu-Leu-Rink-MBHA (**1a**, 100 mg), the Suzuki–Miyaura reaction was performed following the General Procedure using 4-iodobenzene as the aryl halide. After the reaction was finished, acidolytic cleavage of an aliquot of the biaryl peptidyl resin gave **6a** in 80% purity. Elution with H_2O/MeOH/TFA (80:20:0.2) yielded pure **6a** (7.5 mg, 34% yield). t_R = 3.09 min (Method D). ^1H NMR (400 MHz, CD_3OD): δ = 0.92–0.99 [m, 12 H, 4 × $CH_3(\delta)$-Leu], 1.53–1.74 [m, 6 H, 2 CH(γ)-Leu, 2 $CH_2(\beta)$-Leu], 2.88–2.94 [m, 1 H, $CH_2(\beta)$-Tyr], 3.25–3.34 [m, 1 H, $CH_2(\beta)$-Tyr], 4.08 [dd, *J* = 4.4, 9.2 Hz, 1 H, CH(α)-Tyr], 4.41 [dd, *J* = 5.6, 10.0 Hz, 1 H, CH(α)-Leu], 4.48 [dd, *J* = 6.4, 9.2 Hz, 1 H, CH(α)-Leu], 6.90 [d, *J* = 8.2 Hz, 1 H, CH_{arom}-5], 7.10 [dd, *J* = 2.2, 8.2 Hz, 1 H, 6-H_{arom}], 7.26 [d, *J* = 2.2 Hz, 1 H, 2-H_{arom}], 7.29 [tt, *J* = 1.4, 8.4 Hz, 1 H, 4′-H_{arom}], 7.39 [t, *J* = 8.4 Hz, 2 H, 3′-H_{arom}, 5′-H_{arom}], 7.58 [dt, *J* = 1.4, 8.4 Hz, 2 H, 2′-H_{arom}, 6′-H_{arom}] ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 21.96, 22.06, 23.42, 23.47 [4 $CH_3(\delta)$-Leu], 25.85, 25.91 [2 CH(γ)-Leu], 37.97 [$CH_2(\beta)$-Tyr], 41.88, 42.21 [2 $CH_2(\beta)$-Leu], 52.79, 53.41 [2 CH(α)-Leu], 55.79 [CH(α)-Tyr], 117.68 [CH_{arom}-5], 126.51 [C_{arom}-1], 127.89 [CH_{arom}-4′], 129.02 [CH_{arom}-3′, CH_{arom}-5′], 130.42 [CH_{arom}-2′, CH_{arom}-6′], 130.48 [CH_{arom}-6], 130.54 [C_{arom}-3], 132.83 [CH_{arom}-2], 139.86 [C_{arom}-1′], 155.24 [C_{arom}-4], 169.88 [CO-Tyr], 174.10, 177.21 [2 CO-Leu] ppm. MS (ESI): *m/z* = 483.1 $[M + H]^+$. HRMS (ESI): calcd. for $C_{27}H_{39}N_4O_4$ 483.2966; found 483.2978; calcd. for $C_{27}H_{38}N_4NaO_4$ 505.2785; found 505.2797.

Biaryl Linear Peptide 6b: Starting from resin Boc-Tyr(3-BPin,Me)-Leu-Leu-Rink-MBHA (**1b**, 150 mg), the Suzuki–Miyaura reaction was performed following the General Procedure using 4-iodobenzene as the aryl halide. After the reaction was finished, acidolytic cleavage of an aliquot of the biaryl peptidyl resin gave **6b** in 92% purity. Elution with H_2O/MeOH/TFA (60:40:0.2) yielded pure **6b** (12.5 mg, 38% yield). t_R = 7.31 min (Method B). ^1H NMR (400 MHz, CD_3OD): δ = 0.92–0.99 [m, 12 H, 4 $CH_3(\delta)$-Leu], 1.53–1.75 [m, 6 H, 2 CH(γ)-Leu, 2 $CH_2(\beta)$-Leu], 2.95 [dd, *J* = 9.2, 14.4 Hz, 1 H, $CH_2(\beta)$-Tyr], 3.25–3.34 [m, 1 H, $CH_2(\beta)$-Tyr], 3.80 [s, 3 H, OCH_3], 4.12 [dd, *J* = 4.4, 9.2 Hz, 1 H, CH(α)-Tyr], 4.41 [dd, *J* = 5.2, 9.6 Hz, 1 H, CH(α)-Leu], 4.48 [dd, *J* = 6.4, 8.4 Hz, 1 H, CH(α)-Leu], 7.06 [d, *J* = 8.2 Hz, 1 H, 5-H_{arom}], 7.26 [dd, *J* = 2.4, 8.2 Hz, 1 H, 6-H_{arom}], 7.28–7.32 [m, 2 H, 2-H_{arom}, 4′-H_{arom}], 7.38 [t, *J* = 8 Hz, 2 H, 3′-H_{arom}, 5′-H_{arom}], 7.51 [dt, *J* = 1.6, 8.4 Hz,

2 H, 2′-H_{arom}, 6′-H_{arom}] ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 21.95, 22.08, 23.44, 23.49 [4 CH_3(δ)-Leu], 25.86, 25.91 [2 CH(γ)-Leu], 37.92 [CH_2(β)-Tyr], 41.90, 42.22 [2 CH_2(β)-Leu], 52.76, 53.36 [2 CH(α)-Leu], 55.73 [CH(α)-Tyr], 56.13 [OCH_3], 113.18 [CH_{arom}-5], 127.63 [C_{arom}-1], 128.04 [CH_{arom}-4′], 128.94 [CH_{arom}-3′, CH_{arom}-5′], 130.58 [CH_{arom}-2′, CH_{arom}-6′], 130.76 [CH_{arom}-6], 132.65 [C_{arom}-3], 132.83 [CH_{arom}-2], 139.74 [C_{arom}-1′], 157.65 [C_{arom}-4], 169.77 [CO-Tyr], 174.12, 177.20 [2 CO-Leu] ppm. MS (ESI): *m/z* = 497.2 $[M + H]^+$. HRMS (ESI): calcd. for $C_{28}H_{41}N_4O_4$ 497.3122; found 497.3118.

Biaryl Linear Peptide 6c: Starting from resin Boc-Tyr(3-BPin,SEM)-Leu-Leu-Rink-MBHA (**1a**, 120 mg), the Suzuki–Miyaura reaction was performed following the General Procedure using Boc-Phe(4-I)-OMe[9] as the aryl halide. After the reaction was finished, acidolytic cleavage of an aliquot of the biaryl peptidyl resin gave the corresponding methyl ester in 70% purity. t_R = 6.17 min (Method B). MS (ESI): *m/z* = 584.3 $[M + H]^+$.

After hydrolysis, crude biaryl peptide **6c** was obtained in 64% purity. Elution first with H_2O/MeOH/TFA (90:10:0.2) in reverse phase, and then with CH_2Cl_2/MeOH/AcOH (5:3:1) in normal phase yielded pure **6c** (14.4 mg, 44% yield). t_R = 6.04 min (Method B). ^1H NMR (400 MHz, CD_3OD): δ = 0.89–0.95 [m, 12 H, 4 CH_3(δ)-Leu], 1.54–1.70 [m, 6 H, 2 CH(γ)-Leu, 2× CH_2(β)-Leu], 2.80–2.93 [m, 1 H, CH_2(β)], 3.13–3.19 [m, 1 H, CH_2(β)], 3.19–3.30 [m, 2 H, CH_2(β)], 4.01–4.11 [m, 2 H, CH(α)-Tyr, CH(α)-Phe], 4.34–4.45 [m, 2 H, 2 CH(α)-Leu], 6.86 [d, *J* = 8.0 Hz, 1 H, 5-H_{arom}], 7.06–7.09 [m, 1 H, 6-H_{arom}], 7.22 [d, *J* = 1.6 Hz, 1 H, 2-H_{arom}], 7.31 [d, *J* = 8.0 Hz, 2 H, 3′-H_{arom}, 5′-H_{arom}], 7.57 [d, *J* = 8.0 Hz, 2 H, 2′-H_{arom}, 6′-H_{arom}] ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 20.51, 20.59, 21.97, 22.06 [4 CH_3(δ)-Leu], 24.40, 24.48 [2 CH(γ)-Leu], 35.87, 36.46 [CH_2(β)-Phe, CH_2(β)-Tyr], 40.40, 40.73 [2 CH_2(β)-Leu], 52.08 [CH(α)-Leu], 54.25 [CH(α)-Phe, CH(α)-Tyr], 116.12 [CH_{arom}-5], 125.17 [C_{arom}-1], 128.42 [C_{arom}-3], 128.75 [CH_{arom}-3′, CH_{arom}-5′], 129.33 [C_{arom}-4′], 129.74 [CH_{arom}-2′, CH_{arom}-6′], 130.22 [CH_{arom}-6], 131.24 [CH_{arom}-2], 138.05 [C_{arom}-1′], 153.80 [C_{arom}-4], 168.49, 170.30, 173.04 [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 570.3277.

Biaryl Linear Peptide 6d: Starting from resin Boc-Tyr(3-BPin,SEM)-Leu-Leu-Rink-MBHA (**1a**, 120 mg), the Suzuki–Miyaura reaction was performed following the General Procedure using Boc-Tyr(3-I,SEM)-OMe[3d] as the aryl halide. After the reaction was finished, acidolytic cleavage of an aliquot of the biaryl peptidyl resin gave the corresponding methyl ester in 61% purity. t_R = 6.08 min (Method B). MS (ESI): *m/z* = 600.3 $[M + H]^+$.

After hydrolysis, crude biaryl peptide **6d** was obtained in 61% purity. Elution first with H_2O/MeOH/TFA (90:10:0.2) in reverse phase, and then with CH_2Cl_2/MeOH/AcOH (5:3:1) in normal phase yielded pure **6d** (12.8 mg, 55% yield). t_R = 5.96 min (Method B). ^1H NMR (400 MHz, CD_3OD): δ = 0.92–0.98 [m, 12 H, 4 CH_3(δ)-Leu], 1.55–1.75 [m, 6 H, 2 CH(γ)-Leu, 2 CH_2(β)-Leu], 2.89–2.95 [m, 1 H, CH_2(β)-Tyr], 3.11 [dd, *J* = 8.4, 14.8 Hz, 1 H, CH_2(β)-Tyr], 3.25–3.37 [m, 2 H, CH_2(β)-Tyr], 4.10 [dd, *J* = 4.4, 9.2 Hz, 1 H, CH(α)-Tyr], 4.18–4.21 [m, 1 H, CH(α)-Tyr], 4.39 [dd, *J* = 5.2, 10.0 Hz, 1 H, CH(α)-Leu], 4.47 [t, *J* = 7.6 Hz, 1 H, CH(α)-Leu], 6.93 [dd, *J* = 5.2, 8.8 Hz, 2 H, 3′-H_{arom}, 5-H_{arom}], 7.15–7.18 [m, 4 H, 2-H_{arom}, 6-H_{arom}, 4′-H_{arom}, 6′-H_{arom}] ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 21.95, 22.05, 23.41, 23.52 [4 CH_3(δ)-Leu], 25.85, 25.94 [2 CH(γ)-Leu], 36.57, 37.86 [2 CH_2(β)-Tyr], 41.86, 42.20 [2 CH_2(β)-Leu], 52.86, 53.44 [CH(α)-Leu], 55.82 [2 CH(α)-Tyr], 117.50, 117.57 [CH_{arom}-5, CH_{arom}-3′], 126.85, 127.43, 127.48 [C_{arom}], 131.65 [CH_{arom}-2, CH_{arom}-6, CH_{arom}-4′, CH_{arom}-6′], 133.56 [C_{arom}], 155.20 [C_{arom}-2′, C_{arom}-4], 170.10, 174.45 [CO] ppm. MS (ESI): *m/z* = 586.3 $[M + H]^+$. HRMS (ESI): calcd. for $C_{30}H_{44}N_5O_7$ 586.3235; found 586.3220.

General Method for the Synthesis of 3-Iodotyrosylpeptidyl Resins: 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, Boc-Tyr(3-I,Me)-OH,[3d] Boc-Tyr(3-I,SEM)-OH,[3d] or Fmoc-Lys(Boc)-OH (4 equiv.) were performed using ethyl cyanoglyoxylate 2-oxime (4 equiv.) and DIPCDI (4 equiv.) in DMF at room temperature for 1 h. The completion of the reactions was monitored by the Kaiser test.[11] Fmoc group removal was achieved with piperidine/DMF (3:7, 2× 10 min). The Boc group of the tyrosine residue was removed by treatment with trimethylsilyl triflate (TMSOTf; 1 M in CH_2Cl_2) and 2,6-lutidine (1.5 M in CH_2Cl_2) at room temperature (2× 30 min).[12] 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 complete, the N-terminal 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/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.

Tr-Lys(Boc)-Lys(Boc)-Leu-Tyr(3-I,SEM)-Leu-Leu-Rink-MBHA: This peptidyl resin was prepared following the General Method for the synthesis of 3-iodotyrosylpeptidyl resins. Acidolytic cleavage of an aliquot of this peptidyl resin gave H-Lys-Lys-Leu-Tyr(3-I)-Leu-Leu-NH_2 in 68% purity. t_R = 17.86 min (Method A). MS (ESI): *m/z* = 902.4 $[M + H]^+$.

Tr-Lys(Boc)-Lys(Boc)-Leu-Tyr(3-I,Me)-Leu-Leu-Rink-MBHA: This peptidyl resin was prepared following the General Method for the synthesis of 3-iodotyrosylpeptidyl resins. Acidolytic cleavage of an aliquot of this peptidyl resin gave H-Lys-Lys-Leu-Tyr(3-I,Me)-Leu-Leu-NH_2 in 73% purity. t_R = 18.94 min (Method A).

General Method for Miyaura Borylation of the Above Hexapeptidyl Resins: A 25 mL round-bottomed flask was charged with the corresponding 3-iodotyrosylpeptidyl resin, B_2Pin_2 (4 equiv.), $PdCl_2$(dppf) (0.18 equiv.), and dppf (0.09 equiv.). A thoroughly sonicated solution of KOAc (6 equiv.) in degassed anhydrous DMSO (20 mL/mg of resin) was then added, and the mixture was heated at 80 °C for 8 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.

Tr-Lys(Boc)-Lys(Boc)-Leu-Tyr(3-BPin,SEM)-Leu-Leu-Rink-MBHA: This peptidyl resin was prepared starting from Tr-Lys(Boc)-Lys(Boc)-Leu-Tyr(3-I,SEM)-Leu-Leu-Rink-MBHA following the General Method for solid-phase Miyaura borylation. Acidolytic cleavage of an aliquot of this resin gave H-Lys-Lys-Leu-Tyr(3-BPin)-Leu-Leu-NH_2 (27% purity) and H-Lys-Lys-Leu-Tyr[3-B$(OH)_2$]-Leu-Leu-NH_2 (33% purity), resulting from partial hydrolysis of the pinacol boronate during HPLC analysis. t_R = 16.80 (boronic acid), 20.53 (boronate) (Method A). MS (ESI): *m/z* = 820.5 $[M_{B(OH)2} + H]^+$, 902.4 $[M_{BPin} + H]^+$.

Tr-Lys(Boc)-Lys(Boc)-Leu-Tyr(3-BPin,Me)-Leu-Leu-Rink-MBHA: This peptidyl resin was prepared starting from Tr-Lys(Boc)-Lys-(Boc)-Leu-Tyr(3-I,Me)-Leu-Leu-Rink-MBHA following the General Method for solid-phase Miyaura borylation. Acidolytic cleavage of an aliquot of this peptidyl resin gave H-Lys-Lys-Leu-Tyr[3-$B(OH)_2$,Me]-Leu-Leu-NH_2 (41% purity), resulting from hydrolysis of the pinacol boronate during HPLC analysis. t_R = 17.17 (boronic acid) (Method A). MS (ESI): *m/z* = 834.5 $[M_{B(OH)2} + H]^+$, 856.5 $[M_{B(OH)2} + Na]^+$, 916.5 $[M_{BPin} + H]^+$, 938.4 $[M_{BPin} + Na]^+$.

General Method for the Synthesis of the Linear Precursors 7a–d: The corresponding boronopeptidyl resin was 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/CH_2Cl_2 (1:19) (3× 1 min), and DMF (3× 1 min). The corresponding halogenated amino acid Boc-Phe(4-I)-OH,[9] Boc-Tyr(3-I,Me)-OH[3d] or Boc-Tyr(3-I,SEM)-OH[3d] 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.[11] 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.

Boc-Phe(4-I)-Lys(Boc)-Lys(Boc)-Leu-Tyr(3-BPin,SEM)-Leu-Leu-Rink-MBHA (7a): This peptidyl resin was prepared starting from Tr-Lys(Boc)-Lys(Boc)-Leu-Tyr(3-BPin,SEM)-Leu-Leu-Rink-MBHA following the General Method using Boc-Phe(4-I)-OH as halogenated amino acid. Acidolytic cleavage of an aliquot of the resulting peptidyl resin gave H-Phe(4-I)-Lys-Lys-Leu-Tyr[3-B-$(OH)_2$]-Leu-Leu-NH_2 (30% purity), resulting from hydrolysis of the pinacol boronate during HPLC analysis. t_R = 15.11 min (Method C). MS (ESI): *m/z* = 1093.3 $[M_{B(OH)2} + H]^+$, 1175.1 $[M_{BPin} + H]^+$.

Boc-Phe(4-I)-Lys(Boc)-Lys(Boc)-Leu-Tyr(3-BPin,Me)-Leu-Leu-Rink-MBHA (7b): This peptidyl resin was prepared starting from Tr-Lys(Boc)-Lys(Boc)-Leu-Tyr(3-BPin,Me)-Leu-Leu-Rink-MBHA following the General Method using Boc-Phe(4-I)-OH as halogenated amino acid. Acidolytic cleavage of an aliquot of the resulting peptidyl resin gave H-Phe(4-I)-Lys-Lys-Leu-Tyr[3-$B(OH)_2$,Me]-Leu-Leu-NH_2 (51% purity), resulting from hydrolysis of the pinacol boronate during HPLC analysis. t_R = 15.41 min (Method C). MS (ESI): *m/z* = 1107.4 $[M_{B(OH)2} + H]^+$, 1189.3 $[M_{BPin} + H]^+$.

Boc-Tyr(3-I,SEM)-Lys(Boc)-Lys(Boc)-Leu-Tyr(3-BPin,SEM)-Leu-Leu-Rink-MBHA (7c): This peptidyl resin was prepared starting from Tr-Lys(Boc)-Lys(Boc)-Leu-Tyr(3-BPin,SEM)-Leu-Leu-Rink-MBHA following the General Method using Boc-Tyr(3-I,SEM)-OH as halogenated amino acid. Acidolytic cleavage of an aliquot of the resulting peptidyl resin gave H-Tyr(3-I)-Lys-Lys-Leu-Tyr(3-BPin)-Leu-Leu-NH_2 (26% purity) and H-Tyr(3-I)-Lys-Lys-Leu-Tyr[3-$B(OH)_2$]-Leu-Leu-NH_2 (36% purity), resulting from partial hydrolysis of the pinacol boronate during HPLC analysis. t_R = 17.69 min (boronic acid), 20.88 (boronate) (Method A). MS (ESI): *m/z* = 1109.3 $[M_{B(OH)2} + H]^+$, 1191.3 $[M_{BPin} + H]^+$.

Boc-Tyr(3-I,Me)-Lys(Boc)-Lys(Boc)-Leu-Tyr(3-BPin,Me)-Leu-Leu-Rink-MBHA (7d): This peptidyl resin was prepared starting from Tr-Lys(Boc)-Lys(Boc)-Leu-Tyr(3-BPin,Me)-Leu-Leu-Rink-MBHA following the General Method using Boc-Tyr(3-I,Me)-OH as halogenated amino acid. Acidolytic cleavage of an aliquot of the resulting peptidyl resin gave H-Tyr(3-I,Me)-Lys-Lys-Leu-Tyr[3-$B(OH)_2$,Me]-Leu-Leu-NH_2 (45% purity), resulting from hydrolysis of the pinacol boronate during HPLC analysis. t_R = 18.94 min (boronic acid) (Method A). MS (ESI): *m/z* = 1137.3 $[M_{B(OH)2} + H]^+$, 1219.1 $[M_{BPin} + H]^+$.

General Method for the Cyclization by a Solid-Phase Suzuki–Miyaura Reaction – Synthesis of Biaryl Cyclic Peptides 8b and 8d: A 5 mL quartz vial was charged with the linear precursor incorporating the borono and iodo functionalities, $Pd_2(dba)_3$ (0.2 equiv.), SPhos (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 biaryl cyclic 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. Biaryl cyclic peptides were characterized by MS and NMR spectroscopy.

Biaryl Cyclic Peptide 8b: Starting from resin Boc-Phe(4-I)-Lys-(Boc)-Lys(Boc)-Leu-Tyr(3-BPin,Me)-Leu-Leu-Rink-MBHA (**7b**, 134 mg), Suzuki–Miyaura cyclization followed by acidolytic cleavage gave biaryl cyclic peptide **8b** (47% purity). Elution with H_2O/MeOH/TFA (60:40:0.2) yielded pure **8b** (6.9 mg, 16% yield). t_R = 6.51 min (Method B). ^1H NMR (300 MHz, CD_3OD): δ = 0.87–0.97 [m, 18 H, 6 CH_3(δ)-Leu], 1.29–1.72 [m, 21 H, 3 CH(γ)-Leu, 3 CH_2(β)-Leu, 2 CH_2(β)-Lys, 2 CH_2(γ)-Lys, 2 CH_2(δ)-Lys], 2.81–2.91 [m, 4 H, 2 CH_2(ε)-Lys], 3.06–3.18 [m, 4 H, CH_2(β)-Tyr, CH_2(β)-Phe], 3.79 [s, 3 H, OCH_3], 4.22–4.56 [m, 7 H, CH(α)-Tyr, CH(α)-Phe, 3 CH(α)-Leu, 2 CH(α)-Lys], 6.99 [d, *J* = 8.7 Hz, 1 H, 5-H_{arom}], 7.16 [dd, *J* = 1.6, 8.7 Hz, 1 H, 6-H_{arom}], 7.32 [d, *J* = 8.1 Hz, 2 H, 3′-H_{arom}, 5′-H_{arom}], 7.44 [d, *J* = 1.6 Hz, 1 H, 2-H_{arom}], 7.65 [d, *J* = 8.1 Hz, 2 H, 2′-H_{arom}, 6′-H_{arom}], 7.78–8.03 (m, 4 H, NH) ppm. MS (ESI): *m/z* = 468.3 $[M + 2H]^{2+}$, 935.7 $[M + H]^+$.

Biaryl Cyclic Peptide 8d: Starting from resin Boc-Tyr(3-I,Me)-Lys-(Boc)-Lys(Boc)-Leu-Tyr(3-BPin,Me)-Leu-Leu-Rink-MBHA (**7d**, 123 mg), Suzuki–Miyaura cyclization followed by acidolytic cleavage gave biaryl cyclic peptide **8d** (33% purity). Elution with H_2O/MeOH/TFA (60:40:0.2) yielded pure **8d** (9 mg, 22% yield). t_R = 6.59 min (Method B). ^1H NMR (300 MHz, CD_3OD): δ = 0.86–0.98 [m, 18 H, 6 CH_3(δ)-Leu], 1.29–1.81 [m, 21 H, 3 CH(γ)-Leu, 3 CH_2(β)-Leu, 2 CH_2(β)-Lys, 2 CH_2(γ)-Lys, 2 CH_2(δ)-Lys], 2.70–2.92 [m, 4 H, 2 CH_2(ε)-Lys], 3.07–3.23 [m, 4 H, 2 CH_2(β)-Tyr], 3.73 [s, 2.6 H, OCH_3], 3.74 [s, 0.4 H, OCH_3], 3.77 [s, 2.6 H, OCH_3], 3.79 [s, 0.4 H, OCH_3], 4.15–4.50 [m, 7 H, 2 CH(α)-Tyr, 3 CH(α)-Leu, 2 CH(α)-Lys], 6.88–7.07 [m, 2 H, 3′-H_{arom}, 5-H_{arom}], 7.11–7.33 [m, 3 H, 2-H_{arom}, 4′-H_{arom}, 6-H_{arom}], 7.75 [s, 1 H, 6′-H_{arom}], 7.82–8.19 [m, 1 H, NH] ppm. MS (ESI): *m/z* = 965.7 $[M + H]^+$, 987.7 $[M + Na]^+$.

Supporting Information (see footnote on the first page of this article): Copies of HPLC chromatograms and mass spectra of compounds. Copies of ^1H and ^{13}C NMR spectra of **6a–d**, **8b**, and **8d**.

Acknowledgments

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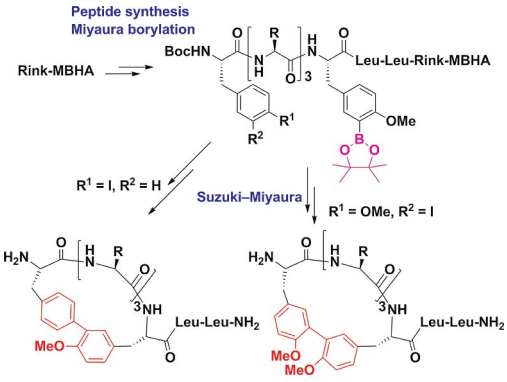

Biaryl cyclic peptides containing a Phe–Tyr or a Tyr–Tyr linkage have been synthesized by solid-phase Miyaura borylation and microwave-assisted Suzuki–Miyaura macrocyclization.

Keywords: Synthetic methods / Solid-phase synthesis / Microwave chemistry / Cyclization / Cross-coupling / Macrocycles / Peptides / Biaryls / Boronates

