Tetrahedron 64 (2008) 10538–10545

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Solid-phase synthesis of 5-arylhistidines via a microwave-assisted Suzuki–Miyaura cross-coupling

Vanessa Cerezo [a], Muriel Amblard [b], Jean Martinez [b], Pascal Verdié [b], Marta Planas [a], Lidia Feliu [a,*]

[a] Laboratori d'Innovació en Processos i Productes de Síntesi Orgànica (LIPPSO), Departament de Química, Universitat de Girona, Campus de Montilivi, 17071 Girona, Spain
[b] Institut des Biomolécules Max Mousseron (IBMM), UMR 5247 CNRS, Université Montpellier 1, Université Montpellier 2, Faculté de Pharmacie, 15 Av. C. Flahault, BP 14 491, 34093 Montpellier Cedex 5, France

ARTICLE INFO

Article history:
Received 6 August 2008
Received in revised form 26 August 2008
Accepted 27 August 2008
Available online 3 September 2008

Keywords:
Histidine
Arylation
Suzuki–Miyaura cross-coupling
Microwave
Biaryl peptides
Solid-phase synthesis

ABSTRACT

Microwave irradiation efficiently promoted the solid-phase Suzuki–Miyaura reaction of a 5-bromohistidine with various arylboronic acids in the presence of a palladium catalyst. This methodology allowed the synthesis of peptides bearing a histidine residue substituted at position 5 of the imidazole ring with a phenyl, a substituted phenyl, a pyridyl, or a thienyl ring, as well as with the benzene ring of a tyrosine residue.

1. Introduction

Imidazoles bearing an aryl substituent at position 4(5) have shown a number of biological properties of potential interest including antifungal activity, potent β-glucosidase or activin receptor-like kinase 5 (ALK5) inhibition, as well as neuropeptide Y 5 (NPY5) receptor antagonist activity.[1] 4(5)-Arylimidazoles also occur naturally in the form of 5-arylhistidines. For example, 5-arylhistidines are central structures of compounds such as the active site of the heme-copper oxidases, and cytotoxic and antifungal marine peptides.[2]

Despite their interest, the preparation of 5-arylhistidines still remains an important synthetic challenge, including as key step the arylation of the position 4(5) of the imidazole ring. So far, several methods for the synthesis of 4(5)-arylimidazoles have been reported in the literature, but they have never been applied to the derivatization of a histidine residue.[3] Most of these protocols provide moderate yields and/or require drastic conditions.

With this in mind, we focused our current studies on biaryl amino acids in the development of an efficient methodology toward the preparation of 5-arylhistidines. Recently, we have reported the synthesis of these amino acid derivatives in solution via a microwave-assisted Suzuki–Miyaura cross-coupling of a 5-bromohistidine with various arylboronic acids.[4]

In recent years, a large number of diverse chemical transformations have been transferred from solution to solid-phase, enabling the design and synthesis of combinatorial libraries for drug discovery research.[5] In particular, the Suzuki–Miyaura coupling has been adapted to solid-phase and has found several applications to the discovery of novel compounds.[6] In this line of view, we envisioned that the solid-phase Suzuki–Miyaura reaction would emerge as a successful approach toward peptides bearing 5-arylhistidine residues.

In the present study, we describe an efficient solid-phase synthesis of 5-arylhistidines by arylation of the position 4(5) of the imidazole ring via a microwave-assisted Suzuki–Miyaura cross-coupling.

2. Results and discussion

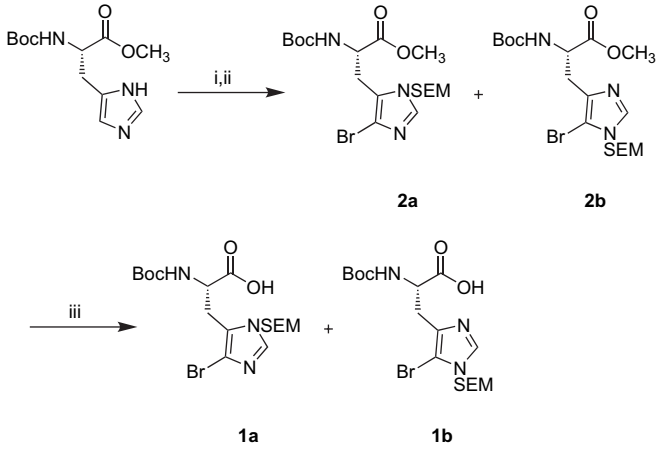
2.1. Synthesis of SEM-protected 5-bromohistidines

Bromohistidines **1** were selected to study the solid-phase arylation of the position 4(5) of the imidazole ring. The Boc group was chosen as N^{α}-amino protection because this group was expected to be stable to the basic conditions and the high temperature of the Suzuki–Miyaura reaction. To avoid racemization of the histidine residue during the coupling step to the solid support, the imidazole

* Corresponding author. Tel.: +34 972 418274; fax: +34 972 418150.
E-mail address: lidia.feliu@udg.edu (L. Feliu).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.08.077

ring was protected with the 2-(trimethylsilyl)ethoxymethyl (SEM) group. This group can be easily introduced, is stable to the standard Fmoc/*t*-Bu solid-phase peptide synthesis protocol and can be removed during the acidic cleavage step. Bromohistidines **1** were prepared following the protocol previously described in our group (Scheme 1).[4] Commercially available Boc–His–OMe was brominated by treatment with *N*-bromosuccinimide (NBS) and alkylated with SEMCl affording a regioisomeric mixture of the SEM-protected 5-bromohistidines **2** with a 73% overall yield. To be able to compare the Suzuki–Miyaura arylation of either the mixture or a single isomer, **2a** and **2b** were separated by reverse-phase preparative HPLC. Final hydrolysis of the methyl ester of **2** with LiOH led to histidines **1** with a 93% yield.



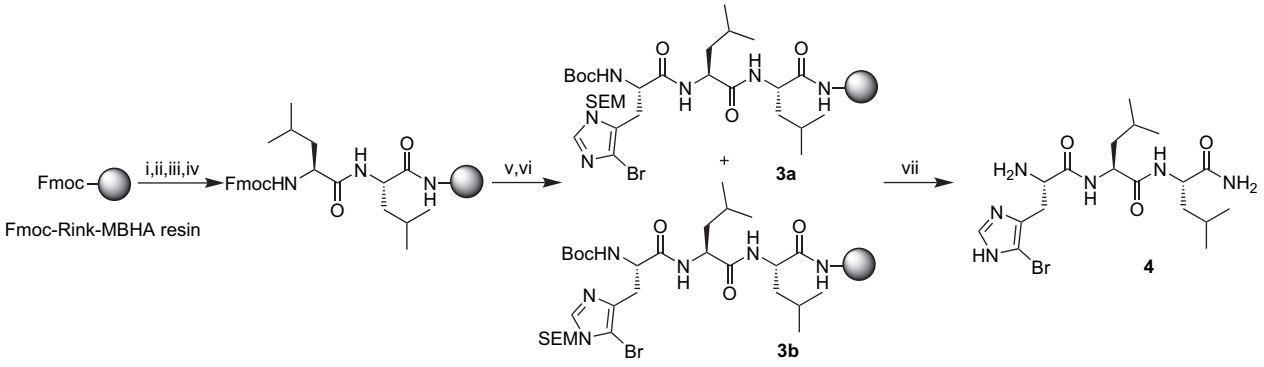
Scheme 1. Reagents and conditions: (i) NBS, CH_3CN, 0 °C; (ii) (a) DBU, DMF, 0 °C, (b) SEMCl, 0 °C to rt, 73% (two steps); (iii) LiOH, THF, MeOH, H_2O, 25 °C, 93%.

2.2. Synthesis of H–His(5-Ph)-Leu-Leu–NH_2

To investigate the feasibility of the solid-phase arylation of the imidazole ring of a histidine residue, a model peptide incorporating the SEM-protected 5-bromohistidines **1** was constructed onto a Rink amide resin. The tripeptidyl resin **3** was prepared following Fmoc/*t*-Bu strategy by sequential coupling and deprotection steps using standard conditions (Scheme 2). Fmoc–Leu–OH couplings and Fmoc removal were performed under microwave irradiation. The mixture of histidine derivatives **1a** and **1b** was coupled at room temperature affording the regioisomeric tripeptidyl resins **3a** and **3b**. An aliquot of this mixture was treated with TFA/CH_2Cl_2 under stirring for 3 h at room temperature. The resulting H–His(5-Br)-Leu-Leu–NH_2 (**4**) was obtained with 99% purity and was fully characterized by ^1H and ^{13}C NMR, and mass spectrometry.

Arylation of the histidine residue of resin **3** via a microwave-assisted Suzuki–Miyaura cross-coupling was then studied. The reaction conditions were optimized by using phenylboronic acid (Table 1). For each experiment, aliquots of resin were subjected to the corresponding reaction conditions and, after acidolytic cleavage, the obtained crude product mixture was analyzed by LC/MS. To promote the SEM group removal during the cleavage step, stirring and time exposure to TFA were found to be essential. When the cleavage was performed with TFA/CH_2Cl_2 (95:5) for 2 h under stirring (entries 6 and 7), the percentage of SEM-protected compounds decreased compared to those experiments carried out without stirring (entries 1–5). Using TFA/CH_2Cl_2 (95:5) and stirring the resin for 3 h afforded only 2% of SEM-protected tripeptide (entry 8).

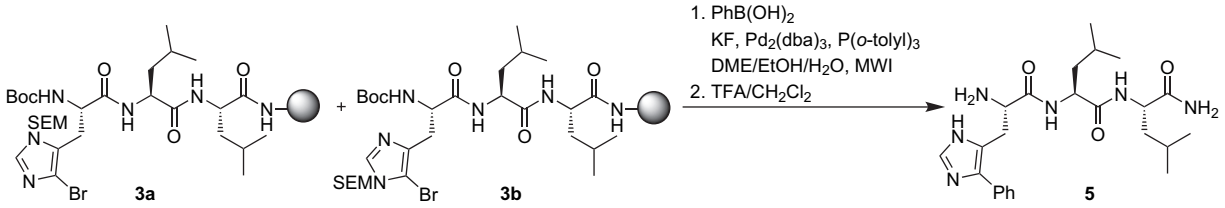
The Suzuki–Miyaura reaction was initially attempted using the catalyst, base, solvent, and temperature that gave the best results for the synthesis of 5-arylhistidines in solution.[4] Thus, the coupling was conducted by using $PhB(OH)_2$ (2 equiv), $Pd_2(dba)_3$ (0.1 equiv), and KF (2 equiv) in toluene/EtOH/H_2O (9:1:0.2) under microwave irradiation at 110 °C for 10 min (Table 1, entry 1). Under these conditions only the starting material was recovered. Using DME/EtOH/H_2O (9:9:2) and performing the reaction at 170 °C, traces of the 5-phenylhistidine tripeptide **5** were detected (entry 2). Taking into account that the reagent concentration is a key parameter in solid-phase reactions,[7] the solvent volume was reduced ca. threefold (entry 3). In this case, a significant increase of the arylated product was observed (37% including **5** and SEM-protected **5**). To improve this result, reactions were run using a larger excess of reagents (entries 4–6). The use of $PhB(OH)_2$ (4 equiv), $Pd_2(dba)_3$ (0.2 equiv), and KF (4 equiv) led to the highest percentage of arylated product (81% including **5** and SEM-protected **5**) and no starting material was detected (entry 5). An increase of the amount of reagents did not improve the results (entry 6). A prolonged microwave irradiation exposure (15 min) slightly enhanced the formation of the arylated peptide (84% including **5** and SEM-protected **5**, entry 7). Even though the cross-coupling reaction of either resin **3a** or **3b** yields the same 5-phenylhistidine tripeptide after the cleavage step, we examined this reaction using a single isomer of **3**. Notably, the obtained result was similar to that of the mixture.



Scheme 2. Reagents and conditions: (i), (iii), and (v) piperidine/DMF, MWI, 75 °C; (ii) and (iv) Fmoc–Leu–OH, HBTU, DIEA, DMF, MWI, 75 °C; (vi) **1a** and **1b**, HBTU, DIEA, DMF, 25 °C; (vii) TFA/CH_2Cl_2, 3 h, stirring.

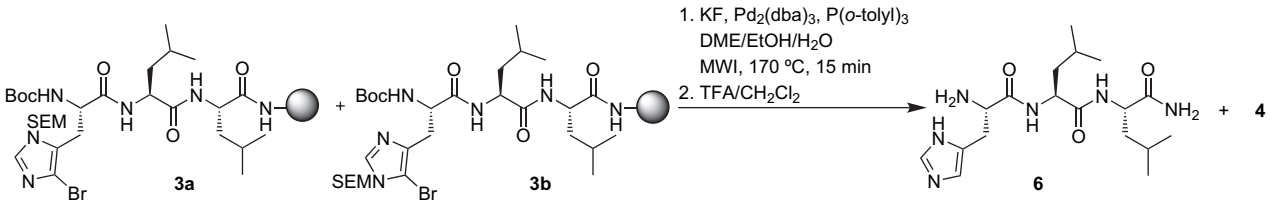
It should be noted that the above crude product mixtures proved to contain a byproduct (4–12%) derived from the reductive dehalogenation of bromohistidines **3** (Scheme 3). This side-reaction has been proposed to proceed by the protonation of arylpalladium intermediates with water or other protic sources and has also been

Table 1
Microwave-assisted arylation of 5-bromohistidine tripeptidyl resins **3a** and **3b** with $PhB(OH)_2$



Entry[a]	$PhB(OH)_2$ (equiv)	$Pd_2(dba)_3$ (equiv)	P(*o*-tolyl)$_3$ (equiv)	KF (equiv)	Solvent	Volume (mL)	*T* (°C)	*t* (min)	**6**[b] (%)	**4** (%)	**4**-SEM[c] (%)	**5** (%)	**5**-SEM[d] (%)
1[e]	2	0.1	0.2	2	Tol/EtOH/H_2O[f]	4	110	10	—[g]	35	34	—	—
2[e]	2	0.1	0.2	2	DME/EtOH/H_2O[h]	4	170	10	—	21	17	3	4
3[e]	2	0.1	0.2	2	DME/EtOH/H_2O	1.2	170	10	4	3	12	8	29
4[e]	3	0.15	0.3	3	DME/EtOH/H_2O	1.2	170	10	6	9	13	20	45
5[e]	4	0.2	0.4	4	DME/EtOH/H_2O	1.2	170	10	12	—	—	52	29
6[i]	5	0.25	0.5	5	DME/EtOH/H_2O	1.2	170	10	11	—	—	63	16
7[i]	4	0.2	0.4	4	DME/EtOH/H_2O	1.2	170	15	11	—	—	67	17
8[j]	4	0.2	0.4	4	DME/EtOH/H_2O	1.2	170	15	10	—	—	83	2

[a] Each experiment was carried out with 50 mg of resins **3a** and **3b** (0.94 mmol/g).
[b] Percentage determined by HPLC at 214 nm from the crude reaction mixture.
[c] Compound **4**-SEM corresponds to SEM-protected 5-bromohistidine tripeptide **4**.
[d] Compound **5**-SEM corresponds to SEM-protected 5-phenylhistidine tripeptide **5**.
[e] Cleavage was carried out for 2 h without stirring.
[f] Toluene/EtOH/H_2O (9:1:0.2).
[g] Not detected.
[h] DME/EtOH/H_2O (9:9:2).
[i] Cleavage was carried out for 2 h under stirring.
[j] Cleavage was carried out for 3 h under stirring.



Scheme 3. Obtention of the dehalogenated compound **6**.

reported for Suzuki–Miyaura cross-couplings involving bromoimidazole derivatives.[3b,8] Nolan and co-workers have recently described the dehalogenation of aryl chlorides using a palladium catalyst and a base in isopropanol under microwave heating.[8a] Based on this report, resin **3** was subjected to the Suzuki–Miyaura conditions but in the absence of $PhB(OH)_2$, leading to 58% of dehalogenated compound **6** (Scheme 3). Attempts to reduce the amount of **6** were performed by carrying out the cross-coupling reaction in DME as solvent. Unexpectedly, despite the absence of protic solvents, the formation of the dehalogenated product (10%) was not avoided. In addition, only a 47% of arylated product **5** was formed and a 39% of starting material **4** was recovered.

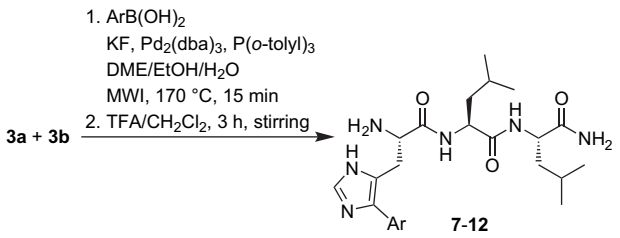
2.3. Synthesis of H–His(5-Ar)-Leu-Leu–NH_2

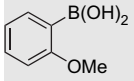
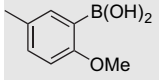
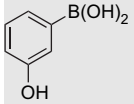
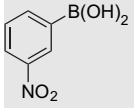
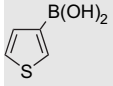
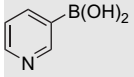
We explored the applicability of the Suzuki–Miyaura reaction to the coupling of 5-bromohistidine tripeptidyl resin **3** with other arylboronic acids possessing substituted benzene, pyridine, and thiophene rings (Table 2). All reactions, which were carried out using 150 mg of resin **3**, afforded the desired 5-arylhistidine tripeptides **7**–**12** in purities ranging from 52 to 83% (including the corresponding SEM-protected peptide derivatives). Couplings with 5-methyl-2-methoxyphenylboronic acid and 3-nitrophenylboronic acid gave the highest percentages of arylated product (83 and 80%, respectively, calculated from the non-protected and SEM-protected biaryl tripeptide). In addition to the presence of starting material (2–15%), all the crude reaction mixtures contained also compound **6** (4–36%). Similar to previous studies, coupling of 3-pyridylboronic acid with **3** was found to be difficult.[9] It was necessary to repeat the reaction three times to obtain **12** with 52% purity (Table 2). The 5-arylhistidine tripeptides were purified by reverse-phase preparative HPLC and fully characterized by mass spectrometry, and ^1H and ^{13}C NMR. 2D-COSY and HMQC experiments were carried out to completely assign all the proton and carbon signals. In the case of compounds **7** and **10**, each proton of the amide groups gave rise to two separate NMR peaks at room temperature. This was attributed to the presence of two different conformers, a hypothesis that was confirmed by performing high temperature ^1H NMR experiments in DMSO-d_6. As expected, raising the temperature resulted in the coalescence of the amide protons.

2.4. Synthesis of peptides containing 5-(3-tyrosyl)histidines

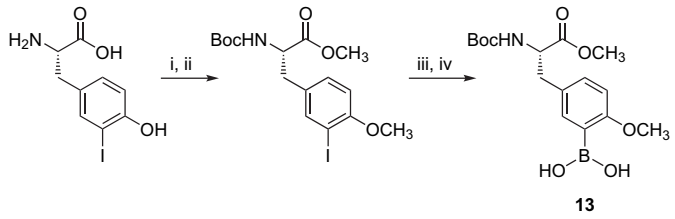
Extension of the above methodology to the synthesis of peptides containing tyrosine–histidine cross-links was studied. For this purpose, the tyrosine-3-boronic acid derivative **13** was prepared from protected 3-iodo-L-tyrosine[10] by Miyaura borylation with bis(pinacolato)diboron[11] and hydrolysis (Scheme 4). Next, Suzuki–Miyaura coupling of 5-bromohistidine tripeptidyl resin **3** with **13** was investigated (Fig. 1). When resin **3** was treated with tyrosine boronic acid **13** (4 equiv), $Pd_2(dba)_3$ (0.2 equiv), and KF (4 equiv) in DME/EtOH/H_2O (9:9:2) under microwave irradiation at 170 °C for

Table 2
Microwave-assisted arylation of 5-bromohistidine tripeptidyl resins **3a** and **3b** with various arylboronic acids



$ArB(OH)_2$	**6**[a] (%)	**4** (%)	**4**-SEM[b] (%)	Peptide	Pept (%)	Pept-SEM[c] (%)
	10	15	—[d]	**7**[e]	61	4
	4	4	7	**8**[e]	75	8
	13	2	—	**9**[e]	65	7
	20	—	—	**10**[e]	73	7
	9	—	—	**11**[e]	70	—
	36	—	—	**12**[f]	52	—

[a] Percentage determined by HPLC at 214 nm from the crude reaction mixture.
[b] Compound **4**-SEM corresponds to SEM-protected 5-bromohistidine tripeptide **4**.
[c] Pept-SEM corresponds to SEM-protected 5-arylhistidine tripeptides **7**–**12**.
[d] Not detected.
[e] Reaction conditions: $ArB(OH)_2$ (4 equiv), $Pd_2(dba)_3$ (0.2 equiv), P(*o*-tolyl)$_3$ (0.4 equiv), KF (4 equiv) in DME/EtOH/H_2O (9:9:2).
[f] Reaction conditions: the resin was treated three times with conditions specified in footnote e.



Scheme 4. Reagents and conditions: (i) Boc_2O, Et_3N, MeOH, rt; (ii) (a) Cs_2CO_3, DMF, (b) CH_3I, rt, 79% (two steps); (iii) bis(pinacolato)diboron, $PdCl_2$(dppf), KOAc, DMSO, 80 °C; (iv) CH_3CN/H_2O, 75 °C, 63% (two steps).

30 min, 22% of 5-(3-tyrosyl)histidine peptide was formed but 39% of starting material **4** was recovered. A second treatment for other 30 min at 170 °C resulted in the decomposition of the tripeptidyl resin. Next, experiments were performed at 140 °C. Resin **3** was exposed to the above reagents under microwave irradiation for two periods of 30 min and 1 h, respectively. Under these conditions, 5-(3-tyrosyl)histidine peptide **14** was formed (18%) together with its acid derivative **15** (49%). Similar to previous reactions, it was also observed the formation of the dehalogenated product **6** (19%) and the presence of starting material **4** (12%). To promote complete hydrolysis, the resin obtained from the Suzuki–Miyaura reaction

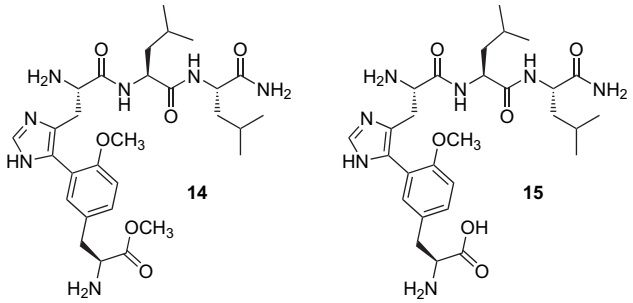


Figure 1. Structure of 5-(3-tyrosyl)histidines **14** and **15**.

was exposed to LiOH (5 equiv) in THF/H_2O (7:1) leading to 67% of the 5-(3-tyrosyl)histidine acid derivative **15**.

3. Conclusion

In conclusion, we have developed a straightforward solid-phase synthesis of 5-arylhistidines. The imidazole ring of a histidine residue has been derivatized with phenyl, substituted phenyl, pyridyl, thienyl groups but also with a tyrosine derivative. This study constitutes the first solid-phase Suzuki–Miyaura coupling involving the imidazole ring of a histidine. The application of this methodology to the generation of combinatorial libraries is under investigation.

4. Experimental section

4.1. General methods

Commercially available reagents were used throughout without purification. Solvents were purified and dried by passing through an activated alumina purification system (MBraun SPS-800) or by conventional distillation techniques. Melting points (capillary tube) were measured with an Electrothermal digital melting point apparatus IA 91000 and were uncorrected. IR spectra were recorded on a Mattson-Galaxy Satellite FT-IR using a single reflection ATR system as a sampling accessory.

Analytical thin layer chromatography (TLC) was performed on precoated TLC plates, silica gel 60 F_{254} (Merck). The spots on the TLC plates were visualized with UV/vis light (254 nm) and/or stained with a solution of potassium permanganate (1,5 g/100 mL H_2O). Flash chromatography (FC) purifications were performed on silica gel 60 (230–400 mesh, Merck).

All compounds were analyzed under standard analytical HPLC conditions on a Beckman Gold apparatus composed of the 126 solvent module, the 168 detector, and the 32 Karat software, on a C_{18} reverse-phase column (VWR chromolith column, 50×3.9 mm): 0–100% B linear gradient over 3 min at a flow rate of 5 mL/min. Solvent A was 0.1% aqueous TFA and solvent B was 0.1% TFA in CH_3CN. Detection was performed at 214 nm and 254 nm. Preparative HPLC (Waters 4000 apparatus) was carried out on a C_{18} reverse-phase column (Deltapak column, 100×40 mm, 15 μm, 100 Å) at a flow rate of 50 mL/min. Linear gradients of 0.1% aqueous TFA and 0.1% TFA in CH_3CN were run from 100:0 to 70:30 over 30 min (condition A); from 100:0 to 90:10 over 10 min and from 90:10 to 70:30 over 40 min (condition B); from 100:0 to 85:15 over 15 min and from 85:15 to 70:30 over 30 min (condition C) with UV detection at 214 nm.

LC/MS analysis was performed on a LC/MS system consisting of a Waters Alliance 2690 HPLC, coupled to a Micromass Quatro Micro spectrometer (electrospray ionization mode, ESI^+). All analyses were carried out using Onyx Monolithic C_{18} 25×4.6 mm reverse-phase column (Phenomenex). A flow rate of 1.5 ml/min and

a gradient of 0–100% B over 4 min were used (solvent A was 0.1% HCOOH in water and solvent B 0.1% HCOOH in acetonitrile). Positive ion electrospray mass spectra were acquired at a solvent flow rate of 100 μL/min. Nitrogen was used for both the nebulizing gas and the drying gas. Data were acquired in the scan mode from *m*/*z* 200 to 1200 in 0.1 s intervals, 10 scans were summed to produce the final spectrum. High resolution mass spectra (HRMS) were determined under conditions of ESI on a Bruker MicroTof-Q instrument using a lock-spray source.

The microwave-assisted synthesis was performed by using the Discover SPPS Microwave Manual Peptide Synthesizer (CEM Corporation). ^{1}H and ^{13}C NMR spectra were measured on a Bruker 200, 300, or 400 MHz NMR spectrometer. Chemical shifts were reported as δ values (ppm) directly referenced to the solvent signal.

4.2. Synthesis of SEM-protected 5-bromohistidines 1

4.2.1. Methyl 5-bromo-N(α)-tert-butoxycarbonyl-L-histidinate

N-Bromosuccinimide (2.6 g, 14.8 mmol) was added to a solution of methyl *N*(α)-*tert*-butoxycarbonyl-L-histidinate (4.0 g, 14.8 mmol) in dry acetonitrile (80 mL) at 0 °C. The reaction mixture was stirred at this temperature under Ar for 30 min. Then, pyridine (32 μL) was added and the mixture was concentrated in vacuo. Triethylamine (3.2 mL) was added to the concentrated solution. Removal of the solvent gave a residue, which was purified by column chromatography. Elution with EtOAc/hexane (2:1) afforded methyl 5-bromo-*N*(α)-*tert*-butoxycarbonyl-L-histidinate as a white solid (4.9 g, 95%). t_R 1.02 min; mp 156–158 °C; IR (neat) 3359, 3079, 1693, 1526, 1434, 1323, 1244, 1166 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.37 (s, 9H, $(CH_3)_3C$), 2.94 (dd, *J*=6.6 and 15.4 Hz, 1H, CH_2-β), 3.13 (dd, *J*=5.4 and 15.4 Hz, 1H, CH_2-β), 3.71 (s, 3H, OCH_3), 4.43–4.46 (m, 1H, CH-α), 5.28 (br s, 1H, NH–Boc), 7.43 (s, 1H, CH-2$_{imid}$), 10.43 (br s, 1H, NH_{imid}); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.94 ($(CH_3)_3C$), 30.31 (CH_2-β), 53.52 (OCH_3), 53.66 (CH-α), 81.56 ($C(CH_3)_3$), 115.62 (C-5$_{imid}$), 124.03 (C-4$_{imid}$), 135.55 (CH-2$_{imid}$), 156.30 (CONH), 172.67 (COO); MS (ESI) *m*/*z* (%) 348.0 (100), 350.0 (96) $[M+H]^+$, 695.1 (4), 697.1(9), 699.1 (4) $[2M+H]^+$, 248.0 (18), 250.0 (16) $[M-Boc+H]^+$; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{19}BrN_3O_4$ $[M]^+$ 348.0553, 350.0522, found 348.0544, 350.0521; calcd for $C_{12}H_{18}BrN_3NaO_4$ $[M]^+$ 370.0373, 372.0352, found 370.0362, 372.0351.

*4.2.2. Methyl 5-bromo-N(α)-tert-butoxycarbonyl-N(π)-[2-(trimethylsilyl)ethoxymethyl]-L-histidinate (**2a**) and methyl 5-bromo-N(α)-tert-butoxycarbonyl-N(τ)-[2-(trimethylsilyl)ethoxymethyl]-L-histidinate (**2b**)*

DBU (1.5 mL, 9.9 mmol) was added to a solution of methyl 5-bromo-*N*(α)-*tert*-butoxycarbonyl-L-histidinate (2.3 g, 6.6 mmol) in dry DMF (17 mL) at 0 °C. The reaction mixture was stirred at this temperature under Ar for 1.5 h. After this time, 2-(trimethylsilyl)-ethoxymethyl chloride was added (1.3 mL, 9.9 mmol) and the mixture was stirred for 3 h while the temperature was allowed to warm to room temperature. The reaction mixture was then poured into water (150 mL) and the product was extracted with toluene/EtOAc (1:1, 3×40 mL). The organic layers were combined, washed with brine (50 mL), and dried over anhydrous magnesium sulfate. Removal of the solvent afforded a pale yellow oil, which was purified by column chromatography. Elution with hexane/EtOAc (60:40) gave **2** as a colorless oil (2.4 g, 77%). t_R 1.75 and 1.90 min; IR (neat) 2953, 1713, 1489, 1364, 1248, 1207, 1164, 1090, 834 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.03 (s, 9H, $(CH_3)_3Si$), 0.89–0.97 (m, 2H, CH_2Si), 1.42 (s, 6.8H, $(CH_3)_3C$), 1.46 (s, 2.2H, $(CH_3)_3C$), 3.04 (dd, *J*=8.4 and 15.2 Hz, 1H, CH_2-β), 3.18 (dd, *J*=6.2 and 15.2 Hz, 1H, CH_2-β), 3.50–3.58 (m, 2H, CH_2O), 3.74 (s, 0.8H, OCH_3), 3.78 (s, 2.2H, OCH_3), 4.57–4.68 (m, 1H, CH-α), 5.26–5.32 (m, 2H, NCH_2O), 5.86 (br s, 1H, CONH), 7.48 (s, 0.8H, CH-2$_{imid}$), 7.65 (s, 0.2H, CH-2$_{imid}$); ^{13}C NMR (50 MHz, $CDCl_3$) δ −0.79 ($(CH_3)_3Si$), 18.26 (CH_2Si), 27.74, 29.94 (CH_2-β), 28.92, 29.02 ($(CH_3)_3C$), 52.89, 53.36 (CH-α and OCH_3), 67.15, 68.04 (CH_2O), 75.46, 75.59 (NCH_2O), 80.27, 80.79 ($(CH_3)_3C$), 102.76, 118.38 (C-5$_{imid}$), 125.06, 137.28 (C-4$_{imid}$), 137.76, 138.82 (CH-2$_{imid}$), 155.60, 155.63 (CONH), 172.43, 172.87 (COO); HRMS (ESI) *m*/*z* calcd for $C_{18}H_{33}BrN_3O_5Si$ $[M]^+$ 478.1367, 480.1345, found 478.1375, 480.1352; calcd for $C_{18}H_{32}BrN_3NaO_5Si$ $[M]^+$ 500.1187, 502.1190, found 500.1199, 502.1197.

*4.2.3. 5-Bromo-N(α)-tert-butoxycarbonyl-N(π)-[2-(trimethylsilyl)ethoxymethyl]-L-histidine (**1a**) and 5-bromo-N(α)-tert-butoxycarbonyl-N(τ)-[2-(trimethylsilyl)ethoxymethyl]-L-histidine (**1b**)*

An aqueous solution of LiOH (1.6 M, 10.5 mmol) was added to a solution of **2** (1.8 g, 3.8 mmol) in THF/MeOH (1:1, 14.6 mL). The reaction mixture was stirred at room temperature for 1.5 h. After this time, the organic solvents were evaporated under reduced pressure. The resulting residue was adjusted to pH 5–6 by addition of 1 N HCl followed by extraction with EtOAc (3×50 mL). The organic layers were combined, washed with brine (50 mL), and dried over anhydrous magnesium sulfate. Removal of the solvent afforded histidine derivatives **1** as a white solid (1.7 g, 93%). t_R 1.65 and 1.70 min; mp 107–109 °C; IR (neat) 3317, 2954, 1711, 1681, 1366, 1247, 1159, 1100, 835 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.03 (s, 9H, $(CH_3)_3Si$), 0.91–1.02 (m, 2H, CH_2Si), 1.43 (s, 6.8H, $(CH_3)_3C$), 1.48 (s, 2.2H, $(CH_3)_3C$), 3.05–3.32 (m, 2H, CH_2-β), 3.52–3.62 (m, 2H, CH_2O), 4.55–4.65 (m, 1H, CH-α), 5.32 (s, 1.5H, NCH_2O), 5.36 (s, 0.5H, NCH_2O), 5.50 (d, *J*=7.4 Hz, 1H, CONH), 7.71 (s, 0.8H, CH-2$_{imid}$), 8.06 (s, 0.2H, CH-2$_{imid}$), 11.05 (br s, 1H, COOH); ^{13}C NMR (50 MHz, $CDCl_3$) δ −0.74 ($(CH_3)_3Si$), 18.33 (CH_2Si), 27.53, 29.76 (CH_2-β), 28.95, 29.11 ($(CH_3)_3C$), 53.36, 53.78 (CH-α), 67.45, 67.87 (CH_2O), 76.04, 76.47 (NCH_2O), 80.28, 80.96 ($(CH_3)_3C$), 104.66, 116.20 (C-5$_{imid}$), 126.10, 135.20 (C-4$_{imid}$), 137.87, 138.45 (CH-2$_{imid}$), 155.82, 156.01 (CONH), 173.87, 174.31 (COO); HRMS (ESI) *m*/*z* calcd for $C_{17}H_{31}BrN_3O_5Si$ $[M]^+$ 464.1211, 466.1197, found 464.1219, 466.1201.

4.3. Synthesis of methyl *N*(α)-*tert*-butoxycarbonyl-3-borono-4-methoxy-L-tyrosinate (13)

4.3.1. Methyl N(α)-tert-butoxycarbonyl-3-iodo-4-methoxy-L-tyrosinate

Triethylamine (2.2 mL, 24.3 mmol) was added to a solution of 3-iodo-L-tyrosine[10] (4.5 g, 22.1 mmol) in anhydrous methanol (43 mL) at 0 °C. A solution of Boc_2O (5.91 g, 26.2 mmol) in anhydrous methanol (35 mL) was then added dropwise. The reaction mixture was stirred for 1.5 h while the temperature was allowed to warm to room temperature. After this time, the mixture was concentrated in vacuo and then adjusted to pH 4 by addition of 1 N HCl. The solution was transferred to a separatory funnel and extracted with EtOAc (50 mL). The organic layer was washed with brine (50 mL), dried over anhydrous magnesium sulfate, and evaporated in vacuo to yield *N*(α)-*tert*-butoxycarbonyl-3-iodo-L-tyrosine. IR (neat) 3355, 3319, 1681, 1503, 1367, 1250, 1157 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45 (s, 9H, $(CH_3)_3C$), 2.95–3.20 (m, 2H, CH_2-β), 4.51–4.53 (m, 1H, CH-α), 5.20 (br s, 1H, CONH), 6.86 (d, *J*=8.2 Hz, 1H, CH_{arom}-5), 7.06 (d, *J*=8.2 Hz, 1H, CH_{arom}-6), 7.52 (s, 1H, CH_{arom}-2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 29.01 ($(CH_3)_3C$), 37.28 (CH_2-β), 55.38 (CH-α), 81.32 ($C(CH_3)_3$), 85.98 (C_{arom}-3), 115.84 (CH_{arom}-5), 130.75 (C_{arom}-1), 131.70 (CH_{arom}-6), 139.86 (CH_{arom}-2), 154.93 (C_{arom}-4), 156.32 (CONH), 176.53 (COO); HRMS (ESI) *m*/*z* calcd for $C_{14}H_{18}INNaO_5$ $[M]^+$ 430.0122, found 430.0137.

N(α)-*tert*-Butoxycarbonyl-3-iodo-L-tyrosine was added to a solution of Cs_2CO_3 (8.35 g, 25.4 mmol) in anhydrous DMF (76 mL) and the reaction mixture was stirred at room temperature for 15 min. Methyl iodide (3.3 mL, 53.0 mmol) was then added and the mixture was stirred at room temperature overnight. After this time, the reaction mixture was concentrated under reduced pressure and

acidified to pH 5–6 by addition of 1 N HCl. The resulting solution was extracted with EtOAc (100 mL), the organic layer was washed with brine (100 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography. Elution with hexane/EtOAc (80:20) gave methyl *N*(α)-*tert*-butoxycarbonyl-3-iodo-4-methoxy-L-tyrosinate as a pale yellow solid (7.60 g, 79% calculated from 3-iodo-L-tyrosine). t_R 1.87 min; mp 63–65 °C; IR (neat) 3333, 1736, 1702, 1510, 1495, 1366, 1255, 1223, 1151, 1048, 1016, 822 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.46 (s, 9H, $(CH_3)_3C$), 2.96 (dd, *J*=5.8 and 13.8 Hz, 1H, CH_2-β), 3.08 (dd, *J*=5.6 and 13.8 Hz, 1H, CH_2-β), 3.76 (s, 3H, OCH_3), 3.88 (s, 3H, CO_2CH_3), 4.53–4.56 (m, 1H, CH_2-α), 5.02 (br s, 1H, CONH), 6.77 (d, *J*=8.4 Hz, 1H, CH_{arom}-5), 7.10 (dd, *J*=2.2 and 8.4 Hz, 1H, CH_{arom}-6), 7.57 (d, *J*=2.2 Hz, CH_{arom}-2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.97 ($(CH_3)_3C$), 37.64 (CH_2-β), 52.92 (CO_2CH_3), 55.17 (CH-α), 57.03 (OCH_3), 80.71 ($C(CH_3)_3$), 86.61 (C_{arom}-3), 111.54 (CH_{arom}-5), 130.92 (C_{arom}-1), 130.95 (CH_{arom}-6), 140.91 (CH_{arom}-2), 155.65 (CONH), 157.94 (C_{arom}-4), 172.77 (COO); HRMS (ESI) *m*/*z* calcd for $C_{16}H_{22}INNaO_5$ $[M]^+$ 458.0435, found 458.0425.

4.3.2. Methyl N(α)-tert-butoxycarbonyl-3-borono-4-methoxy-L-tyrosinate (**13**)

A solution of *N*(α)-*tert*-butoxycarbonyl-3-iodo-4-methoxy-L-tyrosinate (0.99 g, 2.28 mmol) in degassed DMSO (10 mL) was added to a solution of bis(pinacolato)diboron (1.18 g, 4.56 mmol), $PdCl_2$(dppf) (0.11 g, 0.13 mmol), and KOAc (0.90 g, 9.13 mmol) in degassed DMSO (5 mL). The mixture was stirred under nitrogen at 80 °C for 7 h. After this time, brine (50 mL) was added and the resulting solution was extracted with EtOAc (3×100 mL). The combined organic extracts were washed with brine (3×50 mL) and dried over anhydrous magnesium sulfate. Removal of the solvent gave a dark brown oil, which was purified by column chromatography. Elution with hexane/EtOAc (83:17) afforded a mixture of the expected boronate together with the boronic acid derivative as a pale yellow oil. This mixture was dissolved in acetonitrile/H_2O (1:1, 40 mL) and was stirred at 75 °C for 4 h. The resulting solution was lyophilized to afford a white solid, which was purified by column chromatography. Elution with hexane/EtOAc (3:1) afforded the pinacol boronic ester (104 mg, 10%) and elution with hexane/EtOAc (1:1) gave methyl *N*(α)-*tert*-butoxycarbonyl-3-borono-4-methoxy-L-tyrosinate (**13**) (540 mg, 63%). t_R 1.45 min; mp 126–127 °C; IR (neat) 3352, 1737, 1686, 1518, 1494, 1362, 1344, 1234, 1153, 1043, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 9H, $(CH_3)_3C$), 3.02 (dd, *J*=5.6 and 13.8 Hz, 1H, CH_2-β), 3.07 (dd, *J*=5.5 and 13.8 Hz, 1H, CH_2-β), 3.73 (s, 3H, OCH_3), 3.89 (s, 3H, CO_2CH_3), 4.52–4.55 (m, 1H, CH-α), 5.03 (br s, 1H, CONH), 5.54 (br s, 2H, $B(OH)_2$), 6.85 (d, *J*=8.4 Hz, 1H, CH_{arom}-5), 7.23 (dd, *J*=2.2 and 8.4 Hz, 1H, CH_{arom}-6), 7.58 (d, *J*=2.2 Hz, 1H, CH_{arom}-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.41 ($(CH_3)_3C$), 37.60 (CH_2-β), 52.41 (CO_2CH_3), 54.73 (CH-α), 55.95 (OCH_3), 80.30 ($C(CH_3)_3$), 110.34 (C_{arom}-3), 110.84 (CH_{arom}-5), 128.64 (C_{arom}-1), 133.75 (CH_{arom}-6), 137.87 (CH_{arom}-2), 155.37 (CONH), 163.85 (C_{arom}-4), 172.53 (COO); HRMS (ESI) *m*/*z* calcd for $C_{16}H_{24}BNNaO_7$ $[M]^+$ 376.1538, found 376.1538.

4.4. Synthesis of H–His(5-Ar)-Leu-Leu–NH_2

4.4.1. Synthesis of bromotripeptidyl resin **3**

The bromotripeptidyl resin **3** was synthesized manually by the solid-phase method using standard Fmoc chemistry. Fmoc–Rink–MBHA resin (0.94 mmol/g) was used as solid support. Couplings of Fmoc–Leu–OH (3 equiv) were performed using HBTU (3 equiv) and DIEA (3 equiv) in DMF under microwave irradiation (5 min, 75 °C, 50 W). SEM-protected 5-bromohistidines **1** were coupled using the same conditions but at room temperature. The completion of the reactions was checked by the Kaiser and the TNBS tests. Fmoc group removal was achieved with 20% piperidine in DMF under microwave irradiation (3 min, 75 °C, 50 W). After each coupling and deprotection step, the resin was washed with DMF (×3), MeOH (×1), and CH_2Cl_2 (×3), and air dried.

4.4.1.1. H–His(5-Br)-Leu-Leu–NH_2 (**4**).

An aliquot of the bromotripeptidyl resin **3** was cleaved with TFA/CH_2Cl_2 (95:5) under stirring for 3 h at room temperature. Following TFA evaporation and diethyl ether extraction, the crude peptide was dissolved in H_2O/CH_3CN (50:50 v/v containing 0.1% TFA), lyophilized, and purified by reverse-phase preparative HPLC using condition A to afford H–His(5-Br)-Leu-Leu–NH_2 (**4**). t_R 0.92 min; ^1H NMR (400 MHz, CD_3CN) δ 0.92–0.97 (m, 12H, 4×CH_3(δ)–Leu), 1.53–1.66 (m, 2H, 2×CH(γ)–Leu), 1.69–1.75 (m, 4H, 2×CH_2(β)–Leu), 3.27 (dd, *J*=6.7 and 15.8 Hz, 1H, CH_2(β)–His), 3.34 (dd, *J*=5.2 and 15.8 Hz, 1H, CH_2(β)–His), 4.30–4.40 (m, 3H, 3×CH(α)), 6.15 (s, 1H, $CONH_2$), 6.63 (s, 1H, $CONH_2$), 7.62 (d, *J*=7.3 Hz, 1H, CONH), 7.80 (d, *J*=6.0 Hz, 1H, CONH), 8.19 (s, 1H, CH_{imid}-2); ^{13}C NMR (100 MHz, CD_3CN) δ 20.45, 20.73, 22.29, 22.37 (4×CH_3(δ)–Leu), 24.46, 24.58 (2×CH(γ)–Leu), 25.96 (CH_2(β)–His), 40.07, 40.14 (2×CH_2(β)–Leu), 52.13, 52.17, 52.91 (3×CH(α)), 124.25 (C_{imid}-4), 136.02 (CH_{imid}-2), 167.36, 173.43, 174.63 (3×CO); MS (ESI) *m*/*z* (%) 459.13 (100), 461.13 (96) $[M+H]^+$.

4.4.2. General method for the microwave-assisted Suzuki–Miyaura cross-coupling

A 25 mL reaction vessel containing a magnetic stir bar was charged with bromotripeptidyl resin **3** (300 mg), which was first swelled in a degassed mixture of DME/EtOH/H_2O (9:9:2, 1.2 mL) for 15 min under argon atmosphere. Then, $Pd_2(dba)_3$ (0.2 equiv), P(*o*-tolyl)$_3$ (0.4 equiv), KF (4 equiv), and the corresponding boronic acid (4 equiv) were added. The mixture was irradiated at 170 °C for 15 min at 300 W. After the reaction time, upon cooling, the solvent was removed and the resin was washed with DMF (×3), EtOH (×3), and CH_2Cl_2 (×3). The aryltripeptides were released from the solid support by treatment with TFA/CH_2Cl_2 (95:5) under stirring for 3 h at room temperature. Following TFA evaporation and diethyl ether extraction, the crude peptides were dissolved in H_2O/CH_3CN (50:50 v/v containing 0.1% TFA), lyophilized, and purified by reverse-phase preparative HPLC.

4.4.2.1. H–His(5-Ph)–Leu-Leu–NH_2 (**5**).

This peptide was purified using condition A. t_R 1.02 min; ^1H NMR (400 MHz, CD_3CN) δ 0.92–0.97 (m, 12H, 4×CH_3(δ)–Leu), 1.49–1.68 (m, 6H, 2×CH(γ)–Leu, 2×CH_2(β)–Leu), 3.43 (d, *J*=6.9 Hz, 2H, CH_2(β)–His), 4.22–4.34 (m, 2H, 2×CH(α)–Leu), 4.49 (t, *J*=6.9 Hz, 1H, CH(α)–His), 5.99 (s, 1H, $CONH_2$), 6.67 (s, 1H, $CONH_2$), 7.44 (d, *J*=7.6 Hz, 1H, CONH), 7.48–7.55 (m, 3H, CH_{arom}-3, CH_{arom}-4, CH_{arom}-5), 7.59 (dd, *J*=1.8 and 8.1 Hz, 2H, CH_{arom}-2, CH_{arom}-6), 8.20 (d, *J*=6.0 Hz, 1H, CONH), 8.55 (s, 1H, CH_{imid}-2); ^{13}C NMR (100 MHz, CD_3CN) δ 20.63, 20.86, 22.31 (4×CH_3(δ)–Leu), 24.37, 24.51 (2×CH(γ)–Leu), 26.27 (CH_2(β)–His), 40.22, 40.45 (2×CH_2(β)–Leu), 51.87, 52.39, 52.91 (3×CH(α)), 123.19 (C_{imid}), 126.96 (C_{imid}), 128.39 (CH_{arom}-2, CH_{arom}-6), 129.16 (CH_{arom}-3, CH_{arom}-5), 129.45 (CH_{arom}-4), 131.67 (C_{arom}-1), 134.24 (CH_{imid}-2), 167.65, 172.84, 174.47 (3×CO); MS (ESI) *m*/*z* (%) 456.9 (100) $[M+H]^+$, 479.1 (10) $[M+Na]^+$.

4.4.2.2. Biarylic peptide **7**.

This peptide was purified using condition C. t_R 1.05 min; ^1H NMR (300 MHz, CD_3CN) δ 0.84–0.93 (m, 12H, 4×CH_3(δ)–Leu), 1.51–1.57 (m, 6H, 2×CH_2(β)–Leu, 2×CH(γ)–Leu), 3.28 (d, *J*=6.6 Hz, 1H, CH_2(β)–His), 3.85 (s, 3H, OCH_3), 4.13–4.33 (m, 3H, 2×CH(α)–Leu, CH(α)–His), 5.79 (s, 0.6H, $CONH_2$), 5.87 (s, 0.4H, $CONH_2$), 6.43 (s, 0.4H, $CONH_2$), 6.53 (s, 0.6H, $CONH_2$), 6.75 (d, *J*=5.5 Hz, 0.6H, CONH), 6.86 (d, *J*=7.1 Hz, 0.6H, CONH), 7.09 (t, *J*=7.9 Hz,1H, CH_{arom}-5), 7.15 (d, *J*=7.9 Hz,1H, CH_{arom}-3), 7.31 (d, *J*=7.5 Hz, 0.4H, CONH), 7.38 (dd, *J*=1.6 and 7.9 Hz, 1H, CH_{arom}-6), 7.52 (td, *J*=1.6 and 7.9 Hz, 1H, CH_{arom}-4), 7.85 (d, *J*=6.0 Hz, 0.4H, CONH), 8.56 (s, 1H, CH_{imid}-2); ^{13}C NMR (100 MHz, CD_3CN) δ 20.07,

20.16, 20.44, 20.51, 21.91, 21.96, 22.02, 22.09 (CH_3(δ)–Leu), 24.12, 24.16, 24.22 (CH(γ)–Leu), 25.98 (CH_2(β)–His), 39.65, 39.83, 40.11 (CH_2(β)–Leu), 51.04, 51.63, 51.79, 52.55, 52.61 (CH(α)–Leu, CH(α)–His), 55.19 (OCH_3), 111.51 (CH_{arom}-3), 114.06 (C_{arom}-1), 120.67 (CH_{arom}-5), 123.28 (C_{imid}), 128.13 (C_{imid}), 130.89 (CH_{arom}-6), 131.67 (CH_{arom}-4), 133.42 (CH_{imid}-2), 156.67 (C_{arom}-2), 171.17, 172.25, 173.22 (CO); MS (ESI) *m*/*z* (%) 487.3 (100) $[M+H]^+$.

4.4.2.3. Biarylic peptide ***8***. This peptide was purified using condition A. t_R 1.13 min; ^{1}H NMR (400 MHz, CD_3CN) δ 0.87–0.96 (m, 12H, 4×CH_3(δ)–Leu), 1.52–1.71 (m, 6H, 2×CH(γ)–Leu, 2×CH_2(β)–Leu), 2.34 (s, 3H, CH_3), 3.30 (dd, *J*=6.6 and 14.8 Hz, 1H, CH_2(β)–His), 3.35 (dd, *J*=6.6 and 14.8 Hz, 1H, CH_2(β)–His), 3.85 (s, 3H, OCH_3), 4.26–4.34 (m, 2H, 2×CH(α)–Leu), 4.40 (t, *J*=6.6 Hz, 1H, CH(α)–His), 5.94 (s, 1H, $CONH_2$), 6.54 (s, 1H, $CONH_2$), 7.06 (d, *J*=8.5 Hz, 1H, CH_{arom}-3), 7.22 (d, *J*=1.8 Hz,1H, CH_{arom}-6), 7.34 (dd, *J*=1.8 and 8.5 Hz, 1H, CH_{arom}-4), 7.41 (d, *J*=7.8 Hz, 1H, CONH), 8.05 (d, *J*=6.0 Hz, 1H, CONH), 8.56 (s, 1H, CH_{imid}-2); ^{13}C NMR (100 MHz, CD_3CN) δ 19.37 (CH_3), 20.51, 20.78 (2×CH(γ)–Leu), 22.28, 22.34, 24.41, 24.51 (4×CH_3(δ)–Leu), 26.48 (CH_2(β)–His), 40.08, 40.42 (2×CH_2(β)–Leu), 51.88, 52.21, 52.94 (3×CH(α)), 55.51 (OCH_3), 111.78 (CH_{arom}-3), 114.44 (C_{arom}-1), 123.89 (C_{imid}), 128.42 (C_{imid}), 130.41 (CH_{arom}-4), 131.50 (C_{arom}-5), 132.13 (CH_{arom}-6), 133.72 (CH_{imid}-2), 154.86 (C_{arom}-2), 167.59, 173.09, 174.17 (3×CO); MS (ESI) *m*/*z* (%) 501.3 (100) $[M+H]^+$.

4.4.2.4. Biarylic peptide ***9***. This peptide was purified using condition B. t_R 0.96 min; ^{1}H NMR (400 MHz, CD_3CN) δ 0.89–0.95 (m, 12H, 4×CH_3(δ)–Leu), 1.51–1.61 (m, 4H, 2×CH_2(β)–Leu), 1.62–1.70 (m, 2H, 2×CH(γ)–Leu), 3.37 (dd, *J*=8.4 and 15.5 Hz, 1H, CH_2(β)–His), 3.48 (dd, *J*=5.2 and 15.5 Hz, 1H, CH_2(β)–His), 4.30–4.36 (m, 2H, 2×CH(α)–Leu), 4.42 (dd, *J*=5.2 and 8.4 Hz, 1H, CH(α)–His), 6.03 (s, 1H, $CONH_2$), 6.59 (s, 1H, $CONH_2$), 6.96 (ddd, *J*=0.8, 2.0, and 8.0 Hz,1H, CH_{arom}-4), 7.05 (ddd, *J*=0.8, 2.0, and 8.0 Hz,1H, CH_{arom}-6), 7.14 (t, *J*=2.0 Hz, 1H, CH_{arom}-2), 7.38 (t, *J*=8.0 Hz, 1H, CH_{arom}-5), 7.44 (d, *J*=7.6 Hz, 1H, CONH), 7.84 (d, *J*=5.8 Hz, 1H, CONH), 8.60 (s, 1H, CH_{imid}-2); ^{13}C NMR (100 MHz, CD_3CN) δ 20.41, 20.79, 22.30, 22.34 (4×CH_3(δ)–Leu), 24.45, 24.52 (2×CH(γ)–Leu), 26.23 (CH_2(β)–His), 39.89, 40.44 (2×CH_2(β)–Leu), 52.11 (CH(α)–Leu), 52.16 (CH(α)–His), 53.04 (CH(α)–Leu), 115.05 (CH_{arom}-2), 117.35 (CH_{arom}-4), 119.29 (CH_{arom}-6), 122.28 (C_{imid}), 127.40 (C_{imid}), 130.61 (CH_{arom}-5), 131.88 (C_{arom}-1), 134.04 (CH_{imid}-2), 157.86 (C_{arom}-3), 167.40, 173.76, 174.36 (3×CO); MS (ESI) *m*/*z* (%) 473.3 (100) $[M+H]^+$.

4.4.2.5. Biarylic peptide ***10***. This peptide was purified using condition A. t_R 1.07 min; ^{1}H NMR (400 MHz, CD_3CN) δ 0.86–0.96 (m, 12H, 4×CH_3(δ)–Leu), 1.51–1.73 (m, 6H, 2×CH_2(β)–Leu, 2×CH(γ)–Leu), 3.48 (d, *J*=6.6 Hz, 2H, CH_2(β)–His), 4.16–4.22 (m, 0.37H, CH(α)–Leu), 4.24–4.28 (m, 1H, CH(α)–Leu), 4.30–4.35 (m, 0.63H, CH(α)–Leu), 4.46 (t, *J*=6.6 Hz, 1H, CH(α)–His), 5.92 (s, 0.37H, $CONH_2$), 6.03 (s, 0.63H, $CONH_2$), 6.60 (s, 1H, $CONH_2$), 6.86 (d, *J*=6.1 Hz, 0.37H, CONH), 6.96 (d, *J*=7.9 Hz, 0.37H, CONH), 7.44 (d, *J*=7.4 Hz, 0.63H, CONH), 7.78 (t, *J*=8.0 Hz, 1H, CH_{arom}-5), 7.99 (ddd, *J*=1.0, 2.1, and 8.0 Hz, 1H, CH_{arom}-6), 8.12 (d, *J*=6.1 Hz, 0.63H, CONH), 8.35 (ddd, *J*=1.0, 2.1, and 8.0 Hz, 1H, CH_{arom}-4), 8.43 (t, *J*=2.1 Hz, 1H, CH_{arom}-2), 8.62 (s, 1H, CH_{imid}-2); ^{13}C NMR (100 MHz, CD_3CN) δ 20.50, 20.81, 20.85, 22.25, 22.30, 22.32, 22.43 (CH_3(δ)–Leu), 24.42, 24.51, 24.53 (CH(γ)–Leu), 25.90 (CH_2(β)–His), 39.97, 40.09, 40.17, 40.35 (CH_2(β)–Leu), 51.95 (CH(α)–Leu), 52.20 (CH(α)–His), 52.88 (CH(α)–Leu), 123.34 (CH_{arom}-2), 123.79 (C_{imid}), 123.89 (CH_{arom}-4), 128.06 (C_{imid}), 129.71 (C_{arom}-1), 130.24 (CH_{arom}-5), 134.51 (CH_{imid}-2), 134.68 (CH_{arom}-6), 148.26 (C_{arom}-3), 167.07, 171.17, 172.27, 172.77, 174.04, 174.64 (CO); MS (ESI) *m*/*z* (%)502.3 (100) $[M+H]^+$.

4.4.2.6. Biarylic peptide ***11***. This peptide was purified using condition C. t_R 1.01 min; ^{1}H NMR (400 MHz, CD_3CN) δ 0.86–0.92 (m, 12H, 4×CH_3(δ)–Leu), 1.48–1.68 (m, 6H, 2×CH(γ)–Leu, 2×CH_2(β)–Leu), 3.42 (dd, *J*=5.6 and 16.2 Hz, 1H, CH_2(β)–His), 3.48 (dd, *J*=5.3 and 16.2 Hz, 1H, CH_2(β)–His), 4.20–4.26 (m, 1H, CH(α)–Leu), 4.28–4.34 (m, 1H, CH(α)–Leu), 4.47 (t, *J*=5.4 Hz, 1H, CH(α)–His), 6.06 (s, 1H, $CONH_2$), 6.71 (s, 1H, $CONH_2$), 7.44 (dd, *J*=1.2 and 5.0 Hz, 1H, $CH_{thienyl}$-5), 7.52 (d, *J*=7.4 Hz, 1H, CONH), 7.58 (dd, *J*=2.9 and 5.0 Hz, 1H, $CH_{thienyl}$-4), 7.83 (dd, *J*=1.2 and 2.9 Hz, 1H, $CH_{thienyl}$-2), 8.17 (d, *J*=6.2 Hz, 1H, CONH), 8.45 (s, 1H, CH_{imid}-2); ^{13}C NMR (100 MHz, CD_3CN) δ 20.31, 20.54, 21.92, 21.97 (4×CH_3(δ)–Leu), 24.02, 24.19 (2×CH(γ)–Leu), 26.20 (CH_2(β)–His), 39.89, 40.06 (2×CH_2(β)–Leu), 51.57, 51.98, 52.65 (3×CH(α)), 115.04 (C_{arom}), 122.73 (C_{arom}), 124.66 (C_{arom}), 126.39 ($CH_{thienyl}$-2), 127.10 ($CH_{thienyl}$-4), 127.16 ($CH_{thienyl}$-5), 133.63 (CH_{imid}-2), 167.50, 172.51, 174.26 (3×CO); MS (ESI) *m*/*z* (%) 463.2 (100) $[M+H]^+$, 485.0 (20) $[M+Na]^+$.

4.4.2.7. Biarylic peptide ***12***. Following the general procedure, the Suzuki–Miyaura reaction was carried out by treating resin **3** three times with using $Pd_2(dba)_3$ (0.2 equiv), P(*o*-tolyl)$_3$ (0.4 equiv), KF (4 equiv), and 3-pyridylboronic acid (4 equiv). This peptide was purified using condition B. t_R 0.90 min; ^{1}H NMR (300 MHz, CD_3CN) δ 0.84–0.92 (m, 12H, 4×CH_3(δ)–Leu), 1.52–1.638 (m, 6H, 2×CH(γ)–Leu, 2×CH_2(β)–Leu), 3.42–3.46 (m, 2H, CH_2(β)–His), 4.25–4.29 (m, 2H, 2×CH(α)–Leu), 4.39–4.44 (m, 1H, CH(α)–His), 5.95 (s, 1H, $CONH_2$), 6.47 (s, 1H, $CONH_2$), 7.27 (d, *J*=7.6 Hz, 1H, CONH), 7.78 (br s, 1H, CH_{py}-5), 7.97 (d, *J*=5.6 Hz, 1H, CONH), 8.34 (d, *J*=7.8 Hz, 1H, CH_{py}-6), 8.42 (s, 1H, CH_{imid}-2), 8.72 (br s, 1H, CH_{pyr}-4), 9.00 (br s, 1H, CH_{pyr}-2); MS (ESI) *m*/*z* (%) 458.2 (35) $[M+H]^+$.

4.4.2.8. Biarylic peptide ***15***. Following the general procedure, the Suzuki–Miyaura reaction was carried out by treating resin **3** with $Pd_2(dba)_3$ (0.2 equiv), P(*o*-tolyl)$_3$ (0.4 equiv), KF (4 equiv), and tyrosine-3-boronic acid **13** (4 equiv) at 140 °C for two periods of 30 min and 1 h, respectively. After the corresponding washes, the resin was treated 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), MeOH (×2), H_2O (×2), DMF (×3), and CH_2Cl_2 (×3). The biarylic peptide **15** was released from the solid support by treatment with TFA/CH_2Cl_2 (95:5) under stirring for 3 h at room temperature. Following TFA evaporation and diethyl ether extraction, the crude peptide was dissolved in H_2O/CH_3CN (50:50 v/v containing 0.1% TFA), and lyophilized. t_R 14.72 min; MS (ESI) *m*/*z* (%) 574.4 (33) $[M+H]^+$.

Acknowledgements

V.C. is the recipient of a predoctoral fellowship from the University of Girona. This work was supported by grant AGL2006-13564-C02-02/AGR from MEC of Spain.

References and notes

1. (a) For a recent review about imidazoles, see: Bellina, F.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 4571–4624; (b) Ellis, G. P.; Epstein, C.; Fitzmaurice, C.; Golberg, L.; Lord, G. H. *J. Pharm. Pharmacol.* **1964**, *16*, 400–407; (c) Li, Y.-K.; Hsu, H.-S.; Chang, L.-F.; Chen, G. *J. Biochem.* **1998**, *123*, 416–422; (d) Kim, D.-K.; Jang, Y.; Lee, H. S.; Park, H. J.; Yoo, J. *J. Med. Chem.* **2007**, *50*, 3143–3147; (e) Elliott, R. L.; Oliver, R. M.; LaFlamme, J. A.; Gillaspy, M. L.; Hammond, M.; Hank, R. F.; Maurer, T. S.; Baker, D. L.; DaSilva-Jardine, P. A.; Stevenson, R. W.; Mack, C. M.; Cassella, J. V. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3593–3596.
2. (a) Tomson, F.; Bailey, J. A.; Gennis, R. B.; Unkefer, C. J.; Li, Z.; Silks, L. A.; Martinez, R. A.; Donohoe, R. J.; Dyer, R. B.; Woodruff, W. H. *Biochemistry* **2002**, *41*, 14383–14390; (b) Faulkner, D. J.; He, H.; Unson, M. D.; Bewley, C. A.; Garson, M. J. *Gazz. Chim. Ital.* **1993**, *123*, 301–307; (c) Bewley, C. A.; He, H.; Williams, D. H.; Faulkner, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 4314–4321.
3. (a) Primas, N.; Mahatsekake, C.; Bouillon, A.; Lancelot, J.-C.; Sopkovà-de Oliveira Santos, J.; Lohier, J.-F.; Rault, S. *Tetrahedron* **2008**, *64*, 4596–4601; (b) Bellina, F.; Cauteruccio, S.; Di Fiore, A.; Marchetti, C.; Rossi, R. *Tetrahedron* **2008**, *64*, 6060–6072 and references therein.
4. Cerezo, V.; Afonso, A.; Planas, M.; Feliu, L. *Tetrahedron* **2007**, *63*, 10445–10453.

5. Dolle, R. E.; Le Bourdonnec, B.; Goodman, A. J.; Morales, G. A.; Salvino, J. M.; Zhang, W. *J. Comb. Chem.* **2007**, *9*, 855–902.
6. (a) Haug, B. E.; Stensen, W.; Svendsen, J. S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2361–2364; (b) Cousaert, N.; Willand, N.; Gesquière, J.-C.; Tartar, A.; Déprez, D.; Deprez-Poulain, R. *Tetrahedron Lett.* **2008**, *49*, 2743–2747; (c) Le Quement, S. T.; Nielsen, T. E.; Meldal, M. *J. Comb. Chem.* **2008**, *10*, 447–455; (d) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2008**, *64*, 3047–3101.
7. Amblard, M.; Fehrentz, J.-A.; Martinez, J.; Subra, G. *Mol. Biotechnol.* **2006**, *33*, 239–254.
8. (a) Navarro, O.; Kaur, H.; Mahjoor, P.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 3173–3180; (b) Cepanec, I. *Synthesis of Biaryls*; Elsevier: Amsterdam, 2004.
9. (a) Kondolff, I.; Doucet, H.; Santelli, M. *Synlett* **2005**, 2057–2061; (b) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.
10. Chiarello, J.; Joullie, M. M. *Synth. Commun.* **1988**, *18*, 2211–2223.
11. Ishiyama, T.; Murate, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508–7510.