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Article

Synthesis of Biphenyl Tyrosine Via Cross-Coupling Suzuki-Miyaura Reaction Using Aryltrifluoroborate Salts

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We reported a fast and easy method for obtaining biarylic units from tyrosine derivatives via Suzuki-Miyaura cross-coupling using a variety of substituted and unsubstituted potassium aryl- and heteroaryltrifluoroborate salts. The scope of the methodology was also extended to the formation of bis-tyrosine linked dipeptide bonds, leading to biologically interesting compounds. Some biarylic units were obtained as free amino acids through the one step cleavage reaction in good yields.

Keywords: tyrosine, boron, aryltrifluoroborates, cross-coupling, Suzuki-Miyaura

Introduction

The biaryl subunit is an important structural motif that can be found in many compounds including natural products and polymers,[1] especially modified aromatic amino acids that are present in various pharmaceuticals, which are currently under development or have already been introduced to the market.[2]

Naturally found in fungal cell wall proteins,[3] dityrosine is found as a dimer formed by 3,3'-biaryl bond formation, as well as a biaryl ether moiety in which the tyrosine units are linked through an oxygen atom. This latter is present in isotrityrosine and pulcherosine, which have been isolated from bacteria[4] and plants.[5] Biaryl subunits are routinely obtained by employing palladium as a catalyst via Suzuki-Miyaura cross-coupling, as reported recently by Monteiro and co-workers[6] in the synthesis of pharmaceutical compounds, although Bedford *et al.*[1] reported the rhodium catalyzed direct ortho-arylation of 2-tert-butyl protected tyrosine using aryl bromide substrates. One known biaryl compound is the 3-arylated tyrosine moiety present in the antibacterial arylomycin A_2 (Figure 1), isolated from *Streptomyces* strain TU6075.[7,8] Roberts *et al.*[9] exploited the latter compound by Suzuki-Miyaura reaction for the formation of the biaryl unit. Barluenga and co-workers[10] performed in one-pot mode the iodination and arylation of 3,5-diiodotyrosine side chains of biologically active peptides by a Suzuki-Miyaura cross-coupling reaction.

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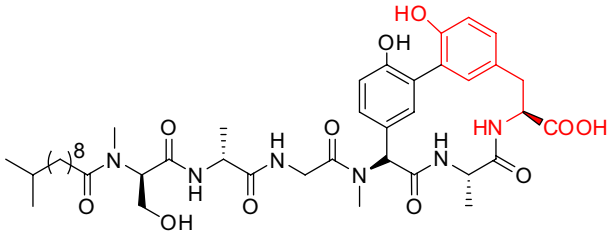
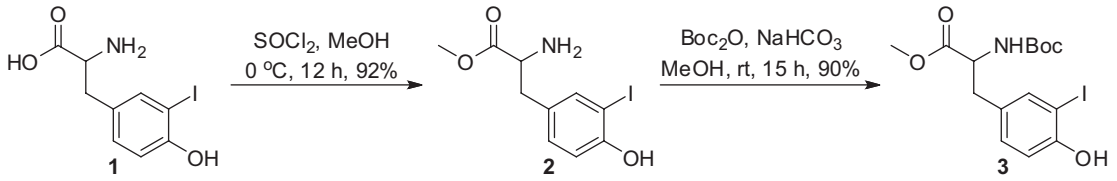


Figure 1. Arylomycin A_2.

There are some biologically important tyrosine fragments, including monocyclic peptides such as K-13, noncompetitive inhibitor of angiotensin I-converting enzyme and a weak inhibitor of aminopeptidase B,[11] isolated from *Micromonospora halophytica ssp. exilisia* and synthetically exploited by Ma and co-workers,[12] bicyclic bouvardins, an antitumor agent, complex polycyclic antibiotics such as chloropeptins, an anti-human immunodeficiency virus (HIV) drug[13] and teicoplanin, used in the prophylaxis and treatment of serious infections caused by Gram-positive bacteria.[14] The molecular structure and interesting biological activity make these compounds attractive synthetic targets.

Results and Discussion

For our preliminary studies, we used commercially available 3-iodotyrosine without the prior protection **1** or **2** directly for Suzuki coupling, but the product was not observed. Therefore, tyrosine was esterified with methanol in the presence of thionyl chloride and the amino group protected with *tert*-butyloxycarbonyl group (Boc) **3** (Scheme 1).[15,16]



Scheme 1. 3-Iodotyrosine protection.

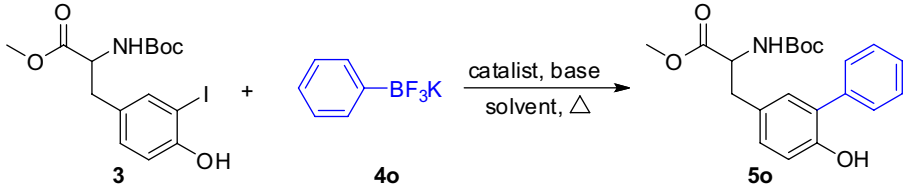
The study of the optimal reaction conditions was carried out using the coupling between phenyltrifluoroborate (**4o**) and *N-tert*-butyloxycarbonyl-3-iodotyrosine methyl ester (**3**) in MeOH with K_2CO_3; a yield of 73% of **5o** was observed as a model study (Table 1, entry 1).

Using K_2CO_3 as the base, other palladium catalysts were tested, resulting in the desired products; however, these were obtained in low to moderate yields (Table 1, entries 2-5 and 9). Only trietylamine was used as a different base, but this led to the cross-coupled product in 20% yield (Table 1, entry 8) and no improvement was achieved by replacing conventional heating with microwave (Table 1, entry 6). When MeOH was replaced with toluene, the yield of **5o** was obtained in trace amounts only (Table 1, entry 7). The catalytic amount of $Pd(OAc)_2$ was 0.05 mmol. Under basic conditions and an alcoholic environment, the saponification of the methyl ester was not observed, as described by Stefani *et al.*[17]

With the optimized reaction conditions in hand, the substrate scope of this Pd-catalyzed cross-coupling reaction was investigated. Different substituents on the aromatic ring of aryltrifluoroborate salts were tested, and the products were generally afforded in low to good yields (Table 2). Aryltrifluoroborates bearing electron-withdrawing groups such as CN, CHO, and Cl substituents, all in the *para*-position, were suitable substrates, giving the corresponding cross-coupled products in low to moderate yields ranging from 17% to 50% (Table 2, entries 1, 5 and 10). Aryltrifluoroborate bearing the CO_2H group did not yield the desired product under the reaction conditions (Table 2, entry 12), 43% of start material was intact recovered, we believed that the remaining material decomposed. Other aspects observed as the presence of homocoupling product from organotrifluoroborate salt and a possible lability of tyrosine under the cross coupling conditions prevented the formation of desired products in better yields.

On the other hand, aryltrifluoroborate bearing electron-donor groups as CH_3O, CH_3, C_2H_5S, *tert*-butyl, OH and NH_2 undergo the reaction leading to the cross-coupled products with yields ranging from 19% to 79% (Table 2, entries 2-4, 6-9, 14 and 16). The reaction seems to be sensitive to steric hindrance, as noted in the case of the methyl group when present in the *ortho*, *meta* and *para* position on the aromatic ring, leading to diminishing yields such as 33, 47 and 62%, respectively (Table 2, entries 6-8). Neutral aromatic rings, such as benzene and naphthalene, gave

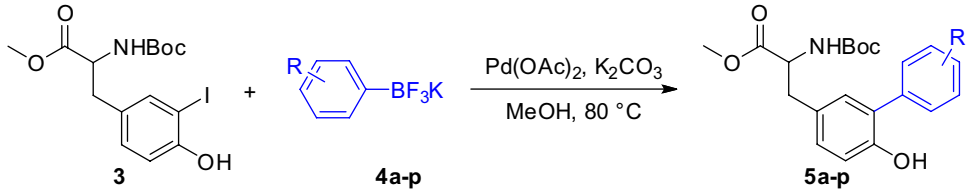
Table 1. Survey for palladium-catalyzed coupling of aryltrifluoroborates with 3-iodotyrosine[a]



entry	Catalyst	Base	Solvent	time / h	Yield / %[b]
1	$Pd(OAc)_2$	K_2CO_3	MeOH	7	73
2	$PdCl_2(dppf).CH_2Cl_2$	–	–	12	33
3	$Pd(PPh_3)_4$	–	–	12	48
4	$PdCl_2(PPh_3)_2$	–	–	12	61
5	PdPEPPSI-IPr	–	–	12	54
6	$Pd(OAc)_2$	–	–	3	traces[c]
7	$Pd(OAc)_2$	–	Toluene	12	traces
8	$Pd(OAc)_2$	TEA	MeOH	12	20
9	$PdCl_2(dppf).CH_2Cl_2$	–	–	12	46

[a]Conditions: **3** (0.5 mmol), **4o** (0.5 mmol), catalyst (10 mol%), base (1.5 mmol), solvent (4 mL), 80°C; [b]isolated yield; [c]reaction under microwave irradiation.

Table 2. Substrate scope of cross-coupling reaction of aryltrifluoroborates to iodo-tyrosine



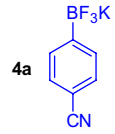
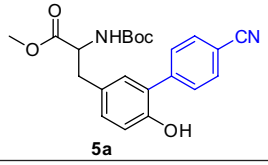
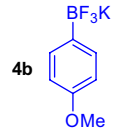
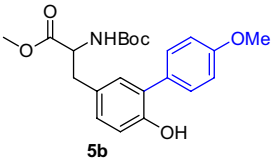
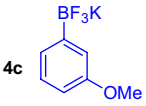
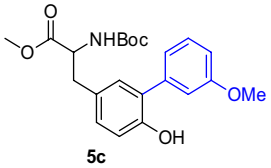
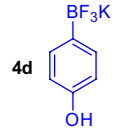
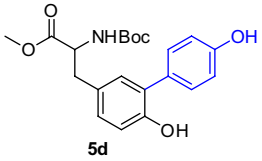
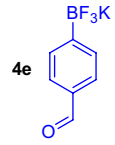
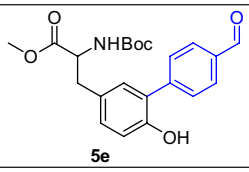
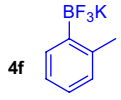
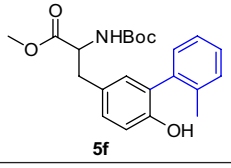
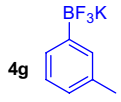
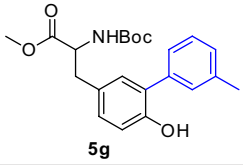
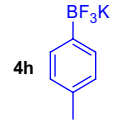
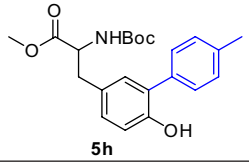
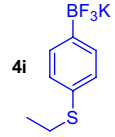
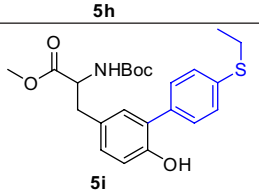
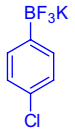
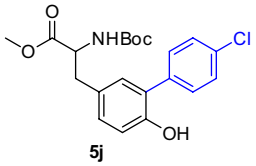
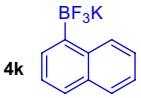
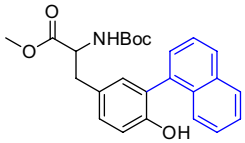
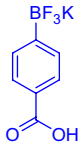
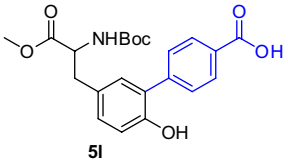
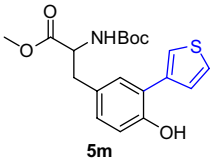
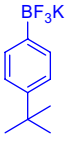
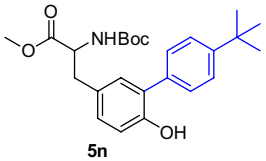
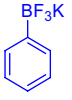
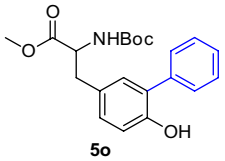
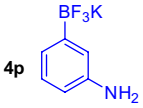
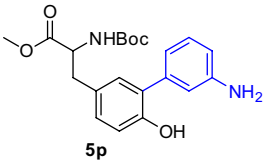
entry	RBF_3K	Product	time / h	Yield / %[a]
1	 **4a**	 **5a**	10	50
2	 **4b**	 **5b**	8	79
3	 **4c**	 **5c**	8	77
4	 **4d**	 **5d**	12	57
5	 **4e**	 **5e**	12	17
6	 **4f**	 **5f**	12	33
7	 **4g**	 **5g**	12	47
8	 **4h**	 **5h**	8	62
9	 **4i**	 **5i**	12	45

Table 2. Substrate scope of cross-coupling reaction of aryltrifluoroborates to iodo-tyrosine (cont.)

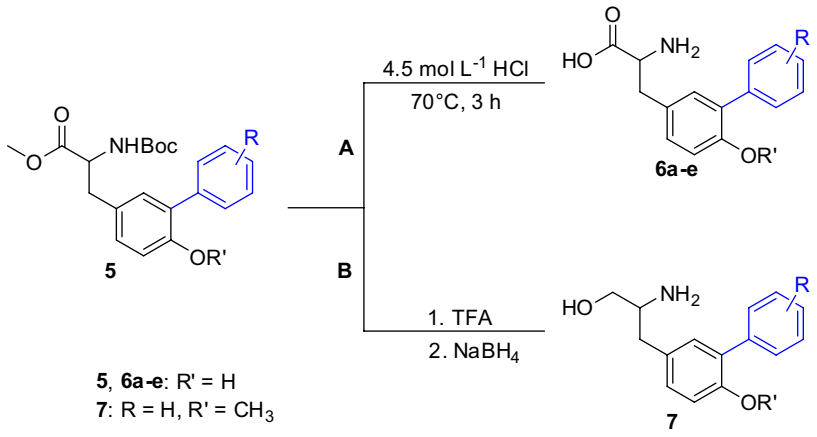
entry	RBF_3K	Product	time / h	Yield / %[a]
10	**4j** 	 **5j**	12	36
11	**4k** 	 **5k**	12	50
12	**4l** 	 **5l**	12	nr
13	**4m** 	 **5m**	12	89
14	**4n** 	 **5n**	12	74
15	**4o** 	 **5o**	7	73
16	**4p** 	 **5p**	12	19

[a]Yields refer to isolated pure products.

moderate to good yields (Table 2, entries 11 and 15, 50% and 73%, respectively) and heterocyclic thiophene gave the highest yield in the series, 89% (Table 2, entry 13).

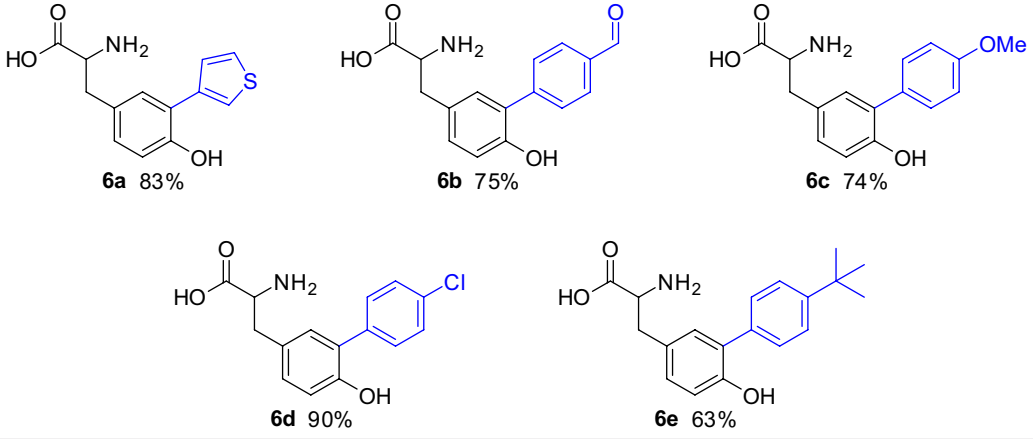
The next step was the direct conversion of the *N*-Boc-amino ester products into the correspondent free amino acid as hydrochloride salts **6a-e** (Table 3) through the one-step cleavage reaction with 4.5 mol L^{-1} HCl at 70 °C for 3 h[18] (Scheme 2, route A). Alternatively, the *N*-Boc-amino ester **5o** was first converted into free amino ester with trifluoroacetic acid[19] in 82% yield, which could be used after a simple filtration through a short pad of silica gel. The crude product was reduced into the respective amino alcohol **7** in 55% yield using sodium borohydride[20] (Scheme 2, route B).

Next, we did the synthesis of dipeptides[21] that could be subjected to cross-coupling reaction. For this purpose, the compounds 3-phenyl-tyrosine methyl ester **8**, obtained from selective amino deprotection of **5o** in the presence of trifluoroacetic acid (TFA) in dichloromethane (DCM) and 3-iodo-*N*-tert-butyloxycarbonyltyrosine **9**, were coupled using *N*-*N*'-diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole (HOB*t*) in DCM for 15 h. After purification, the resulting dipeptide **10** was isolated in 52% yield. With the iodine present in the peptide fragment, this



Scheme 2. Functional group transformations.

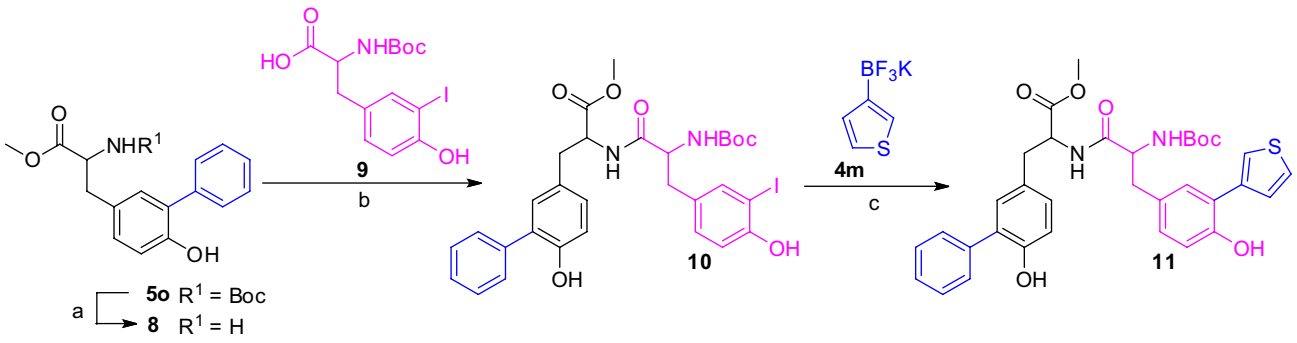
Table 3. Free amino acids[a]



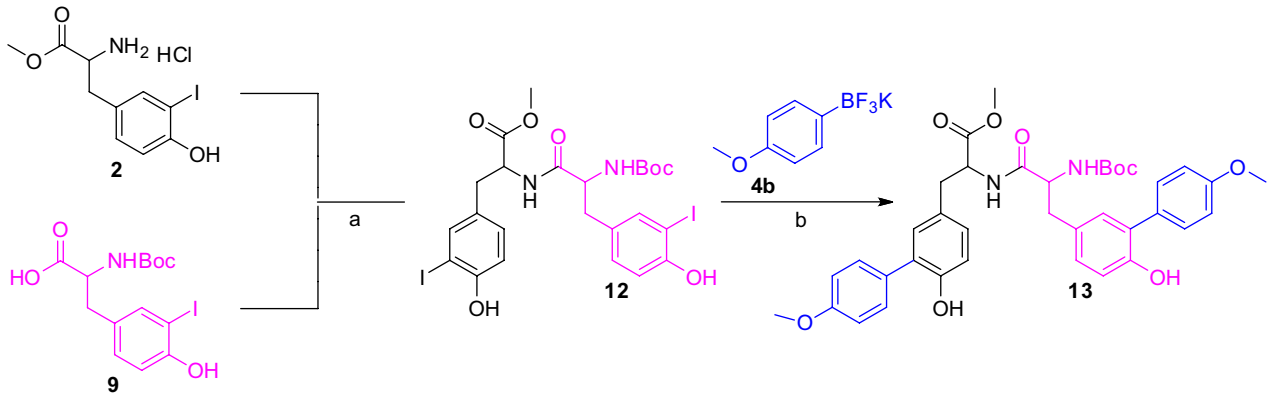
[a]Yields refer to isolated pure products. Compounds **6a** to **6e** were obtained as hydrochloride salts.

offered the opportunity of a new cross-coupling reaction showing the versatility to form different biarylic subunits in peptides fragments. To evidence this fact, dipeptide **10** was reacted with organotrifluoroborate salt **4m** under Pd catalysis to give the compound **11** in 42% yield (Scheme 3).

Similarly, the dipeptide **12** was achieved via peptide bond between compounds **2** as hydrochloride salt and **9** in 48% yield. Enticed by the possibility of bis cross-coupling at the same time, due to the presence of iodine atoms on the aromatic rings, we performed the cross-coupling reaction using two equivalents of potassium 4-methoxyphenyltrifluoroborate salt **4b**, leading exclusively to the compound **13**, from which, after flash chromatography, the product could be obtained with high purity in 61% yield (Scheme 4).



Scheme 3. (a) TFA, DCM, rt, 12 h (yield 63%); (b) HOB*t*, DIC, DCM, rt, 15 h (yield 52%); (c) $Pd(OAc)_2$, K_2CO_3, MeOH, 12 h, 70 °C, (yield 42%).



Scheme 4. (a) HOB*t*, DIC, TEA, DCM, rt, 15 h (yield 48%); (b) $Pd(OAc)_2$, K_2CO_3, MeOH, 10 h (yield 61%).

Surprisingly, the formation of the single coupling product was not observed during the reaction.

Conclusions

In conclusion, we have demonstrated that the cross-coupling of 3-iodotyrosine with potassium heteroaryl- and aryltrifluoroborate salts can be carried out using $Pd(OAc)_2$ as the catalyst. Both activated and deactivated species of trifluoroborate salts can be coupled, proven to be suitable nucleophiles. Subsequently, the obtained biphenyl tyrosines were transformed into the corresponding free amino acid as hydrochloride salts. The coupled tyrosine was converted in dipeptides and the submitted to the cross-coupling reaction with heteroaryl- and aryltrifluoroboate salts leading to products in moderate to good yields. The structures of all products were characterized by ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR, and high resolution mass spectrometry (HRMS) analysis.

Experimental

All reactions were carried out under a nitrogen atmosphere; all compounds were characterized by ^{1}H NMR, ^{13}C NMR and electrospray ionization-mass spectrometry (ESI-MS). Copies of the ^{1}H, and ^{13}C spectra can be found at the end of the Supplementary Information (SI) section. NMR spectra were recorded on a 300 MHz instrument. All ^{1}H NMR experiments are reported in δ units, parts *per* million (ppm), and were measured relative to the signals for tetramethylsilane (TMS) (0.00 ppm). All ^{13}C NMR spectra are reported in ppm relative to deuteron-chloroform (77.23 ppm), unless otherwise stated, and all were obtained with ^{1}H decoupling. For HRMS, previously lyophilized samples were dissolved in methanol and deposited into the 96 well plate of the SIL-20A autosampler for ESI-MS analysis in an IT-TOF mass spectrometer system (Shimadzu). Typically, 0.1 µL sample aliquots were injected and infused into the instrument in 50% acetonitrile, containing 0.5% formic acid under a constant flow rate of 0.2 mL min^{-1}. Instrument control, data acquisition and processing were performed by the LCMS Solution suite (Shimadzu). ESI conditions: source temperature 200 °C, cone voltage 4.5 kV, detector voltage 1.57 kV, nebulizing gas flow 1.5 L min^{-1}. Solvents and reagents were of analytical grade or the highest grade commercially available and were used without further purification. Palladium catalysts, 3-iodotyrosine and potassium aryltrifluroborate salts (**4a**-**p**) were purchased from Sigma-Aldrich and used as received.

General procedure for Suzuki-Miyaura cross-coupling reaction (**5a-p**)

To a two-necked 25 mL round-bottomed flask under a nitrogen atmosphere containing $Pd(OAc)_2$ (11.23 mg, 10 mol%), potassium trifluoroborate salt (0.5 mmol), L-*N*-*t*-butyloxycarbonyltyrosine methyl ester (210.5 mg, 0.5 mmol), and dry MeOH (4 mL) were added K_2CO_3 (207.6 mg, 1.5 mmol). The reaction mixture was stirred and heated at 80 °C. The reaction was monitored by thin layer chromatography (TLC). Then the reaction mixture was diluted with ethyl acetate and washed with saturated solution of NH_4Cl (3 × 20 mL), the organic phase was collected, dried with $MgSO_4$, filtered and the solvent was removed under vacuum. Purification by silica flash chromatography (eluting with ethyl acetate/hexane 2:8).

N-*tert*-Butyloxycarbonyl-*m*-(4-cyanophenyl)-tyrosine methyl ester (**5a**): Yield 99 mg (50%); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, 2H, *J* 8.1 Hz), 7.56 (d, 2H, *J* 8.1 Hz), 6.93 (s, 1H), 6.92 (d, 1H, *J* 7.6 Hz), 6.74 (d, 1H, *J* 7.6 Hz), 4.99 (d, 1H, *J* 6.4 Hz), 4.48 (d, 1H, *J* 5.6 Hz), 3.64 (s, 3H), 3.05-2.87 (m, 2H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.42, 155.19, 152.23, 142.84,

132.11 (2C), 131.32, 130.61, 129.93 (2C), 128.34, 126.52, 118.92, 116.61, 110.66, 80.28, 60.52, 52.35, 37.57, 28.29 (3C); HRMS (ESI-TOF) *m/z* calcd.: for $C_{22}H_{24}N_2O_5$ + Na^+: 419.1583; found: 419.1576.

N-tert-Butyloxycarbonyl-*m*-(4-methoxyphenyl) tyrosine methyl ester (**5b**): Yield 158 mg (79%); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.28 (m, 2H), 6.92-6.88 (m, 4H), 6.80-6.77 (m, 1H), 4.96 (d, 1H, *J* 6.6 Hz), 4.48-4.44 (m, 1H), 3.77 (s, 3H), 3.64 (s, 3H), 3.03-2.81 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.49, 159.26, 154.30, 151.84, 139.07, 131.17, 130.88, 130.22, 129.95, 129.38, 127.92, 115.92, 115.05, 114.55, 80.03, 55.33, 52.30, 52.22, 37.50, 28.31 (3C); HRMS (ESI-TOF) *m/z* calcd.: for $C_{22}H_{27}NO_6$ + Na^+: 424.1736; found: 424.1729.

N-tert-Butyloxycarbonyl-*m*-(3-methoxyphenyl) tyrosine methyl ester (**5c**): Yield 154 mg (77%); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.7.26 (m, 1H), 6.95-6.78 (m, 6H), 4.95 (s, 1H), 4.50-4.41 (m, 1H), 3.75 (s, 3H), 3.63 (s, 3H), 3.03-2.87 (m, 2H), 1.22 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.47, 160.17, 155.18, 151.77, 138.50, 131.03, 130.19, 129.86, 127.95, 121.23, 116.06, 115.05, 114.63, 113.49, 80.05, 55.01, 54.59, 52.23, 37.50, 28.30 (3C); HRMS (ESI-TOF) *m/z* calcd.: for $C_{22}H_{27}NO_6$ + Na^+: 424.1736; found: 424.1732.

N-tert-Butyloxycarbonyl-*m*-(4-hydroxyphenyl)tyrosine methyl ester (**5d**): Yield 110 mg (57%); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.18 (m, 1H), 6.90-6.86 (m, 3H), 6.84 (s, 1H), 6.77 (d, 2H, *J* 8.7 Hz), 5.00 (d, 1H, *J* 7.8 Hz), 4.48 (d, 1H, *J* 6.3 Hz), 3.62 (s, 3H), 2.95 (ddd, 2H, *J* 5.8, 13.8, 19.1 Hz), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.65, 155.34, 151.66, 138.47, 130.98, 130.95, 130.40 (2C), 129.82, 127.91 (2C), 120.81, 116.09, 114.99, 80.33, 60.52, 54.64, 52.35, 28.28 (3C); HRMS (ESI-TOF) *m/z* calcd.: for $C_{21}H_{25}NO_6$ + Na^+: 410.1580; found: 410.1576.

N-tert-Butyloxycarbonyl-*m*-(4-formylphenyl)tyrosine methyl ester (**5e**): Yield 33 mg (17%); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.94 (s, 1H), 7.78 (d, 1H, *J* 7.6 Hz), 7.70 (d, 1H, *J* 7.6 Hz), 7.52 (t, 1H, *J* 7.6 Hz), 6.97-6.91 (m, 2H), 6.78 (d, 1H, *J* 8.0 Hz), 5.70 (s, 1H), 4.97 (d, 1H, *J* 7.5 Hz), 4.05 (d, 1H, *J* 6.1 Hz), 3.65 (s, 3H); 3.06-2.89 (m, 2H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.21, 172.43, 155.15, 151.88, 138.64, 136.77, 135.20 (2C), 131.38, 130.58, 130.24, 129.35, 128.57, 126.93, 116.45, 80.16, 54.59, 52.31, 37.61, 28.29 (3C); HRMS (ESI-TOF) *m/z* calcd.: for $C_{22}H_{25}NO_6$ + Na^+: 422.1580; found: 422.1577.

N-tert-Butyloxycarbonyl-*m*-(*o*-tolyl)tyrosine methyl ester (**5f**): Yield 63 mg (33%); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.11 (m, 5H), 6.95-6.92 (m, 1H), 6.83-6.77 (m, 1H), 4.90 (s, 1H), 4.47 (d, 1H, *J* 5.4 Hz), 3.61 (s, 3H), 3.02-2.89 (m, 2H), 2.08 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.41, 151.72, 141.63, 137.32, 135.63, 131.10, 129.88, 129.28, 128.54, 127.72, 127.13, 126.42, 125.52, 115.48, 79.92, 54.59, 52.15, 37.53, 28.30 (3C), 19.72; HRMS (ESI-TOF) *m/z* calcd.: for $C_{22}H_{27}NO_5$ + Na^+: 408.1787; found: 408.1779.

N-tert-Butyloxycarbonyl-*m*-(*m*-tolyl)tyrosine methyl ester (**5g**): Yield 90.5 mg (47%); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (t, 1H, *J* 7.6 Hz), 7.06-6.98 (m, 3H), 6.80-6.77 (m, 2H), 6.70-6.67 (m, 1H), 4.82 (s, 1H), 4.37 (d, 1H, *J* 5.7 Hz), 3.52 (s, 3H), 2.92-2.75 (m, 2H), 2.21 (s, 3H), 1.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.46, 155.13, 151.77, 138.88, 137.02, 131.13, 129.72, 129.68, 129.03, 128.56, 128.30, 127.94, 126.03, 115.95, 79.95, 60.41, 52.18, 37.50, 28.29 (3C), 21.46; HRMS (ESI-TOF) *m/z* calcd.: for $C_{22}H_{27}NO_5$ + Na^+: 408.1787; found: 408.1784.

N-tert-Butyloxycarbonyl-*m*-(*p*-tolyl)tyrosine methyl ester (**5h**): Yield 119 mg (62%); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, 2H, *J* 7.9 Hz), 7.11 (d, 2H, *J* 7.9 Hz), 6.82 (d, 2H, *J* 6.3 Hz), 6.71 (d, 1H, *J* 8.8 Hz), 4.88 (s, 1H), 4.41 (d, 1H, *J* 6.0 Hz), 3.55 (s, 3H), 2.95-2.82 (m, 2H), 2.24 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.49, 155.17, 151.89, 137.53, 135.69, 134.17, 133.84, 131.18, 129.77, 129.53, 128.91, 128.22, 127.89, 115.96, 80.00, 54.58, 52.20, 37.49, 28.30 (3C), 21.19; HRMS (ESI-TOF) *m/z* calcd.: for $C_{22}H_{27}NO_5$ + Na^+: 408.1787; found: 408.1785.

N-tert-Butyloxycarbonyl-*m*-(4-ethylthylphenyl)tyrosine methyl ester (**5i**): Yield 97 mg (45%); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (s, 4H), 6.89 (d, 2H, *J* 6.6 Hz), 6.77 (d, 1H, *J* 8.8 Hz), 5.62 (s, 1H), 4.96 (d, 1H, *J* 7.3 Hz), 4.49-4.41 (m, 1H), 3.63 (s, 3H), 3.03-2.97 (m, 2H), 2.90 (q, 2H, *J* 7.3 Hz), 1.32 (s, 9H), 1.27 (t, 3H, *J* 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.45, 155.18, 151.86, 139.08, 136.47, 134.60, 131.14, 129.71, 129.49, 129.12, 128.04, 127.65, 116.16, 115.04, 80.04, 60.45, 54.57, 52.24, 28.30 (3C), 27.48, 14.37; HRMS (ESI-TOF) *m/z* calcd.: for $C_{23}H_{29}NO_5S$ + Na^+: 454.1664; found: 454.1659.

N-tert-Butyloxycarbonyl-*m*-(4-chlorophenyl)tyrosine methyl ester (**5j**): Yield 73 mg (36%); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (s, 4H), 6.92-6.89 (m, 2H), 6.77 (d, 1H, *J* 7.9 Hz), 4.92 (s, 1H), 4.48 (d, 1H, *J* 4.9 Hz), 3.64 (s, 3H), 3.04-2.88 (m, 2H), 1.33 (s, 9H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 172.39, 155.08, 151.68, 135.72, 133.71, 131.18, 130.46 (2C), 130.02, 129.07 (2C), 128.29, 127.09, 116.26, 80.05, 60.42, 52.24, 37.51, 28.30 (3C); HRMS (ESI-TOF) *m/z* calcd.: for $C_{21}H_{24}ClNO_5 + Na^+$: 428.1241; found: 428.1240.

N-tert-Butyloxycarbonyl-*m*-(naphthalene-1-yl)tyrosine methyl ester (**5k**): Yield 105 mg (50%); yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84-7.74 (m, 4H), 7.49 (dd, 1H, *J* 1.6, 8.5 Hz), 7.44 (m, 2H), 7.00 (d, 1H, *J* 2.0 Hz), 6.93 (dd, 1H, *J* 2.2, 8.5 Hz), 6.85 (m, 1H), 5.70 (s, 1H), 4.98 (d, 1H, *J* 7.5 Hz), 4.50 (d, 1H, *J* 6.3 Hz), 3.62 (s, 3H), 3.05-2.88 (m, 2H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.50, 155.20, 152.05, 134.68, 133.57, 132.69, 131.43, 129.86, 128.76, 128.20, 128.11, 128.04, 127.84, 127.74, 127.21, 126.49, 126.31, 116.20, 80.07, 60.45, 52.24, 37.56, 28.32 (3C); HRMS (ESI-TOF) *m/z* calcd.: for $C_{25}H_{27}NO_5 + Na^+$: 444.1787; found: 428.1782.

N-tert-Butyloxycarbonyl-*m*-(tiophen-3-yl)tyrosine methyl ester (**5m**): Yield 168 mg (89%); brow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.35 (m, 2H), 7.22-7.18 (m, 1H), 7.02 (s, 1H), 6.89-6.88 (m, 2H), 6.79-6.76 (m, 1H), 5.57 (s, 1H), 4.94 (d, 1H, *J* 5.8 Hz), 4.48 (d, 1H, *J* 6.0 Hz), 3.64 (s, 3H), 3.03-2.93 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.46, 155.14, 151.94, 137.44, 130.59, 129.53, 128.06, 128.02, 126.54, 123.06, 123.01, 116.16, 80.06, 54.57, 52.23, 37.53, 28.30 (3C); HRMS (ESI-TOF) *m/z* calcd.: for $C_{19}H_{23}NO_5S + Na^+$: 400.1195; found: 400.1191.

N-tert-Butyloxycarbonyl-*m*-(4-*tert*-butylphenyl) tyrosine methyl ester (**5n**): Yield 157 mg (74%); yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.31 (m, 4H), 6.91-6.78 (m, 3H), 5.52 (d, 1H, *J* 19.8 Hz), 4.94 (s, 1H), 4.48 (s, 1H), 3.62 (s, 3H), 2.96 (s, 2H), 1.32 (s, 9H), 1.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.50, 155.19, 151.88, 150.79, 134.11, 134.07, 131.21, 129.56, 128.70, 128.13, 127.94, 126.07, 115.98, 79.99, 54.60, 52.22, 37.53, 37.50, 34.64, 31.34 (3C), 28.31 (3C); HRMS (ESI-TOF) *m/z* calcd.: for $C_{25}H_{33}NO_5 + H^+$: 428.2437; found: 428.2432.

N-tert-Butyloxycarbonyl-*m*-phenyltyrosine methyl ester (**5o**): Yield 135 mg (73%); colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, 4H, *J* 4.4 Hz), 7.42-7.35 (m, 1H), 7.01-6.98 (m, 2H), 6.90-6.87 (m, 1H), 5.66 (d, 1H, *J* 5.3 Hz), 4.57 (d, 1H, *J* 6.1 Hz), 3.72 (s, 3H), 3.13-3.03 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.48, 155.17, 151.82, 137.22, 131.25, 129.73, 129.08 (2C), 129.02 (2C), 128.25, 127.98, 127.71, 116.09, 80.04, 54.58, 50.69, 37.48, 28.29 (3C); HRMS (ESI-TOF) *m/z* calcd.: for $C_{21}H_{25}NO_5 + Na^+$: 394.1630; found: 394.1627.

N-tert-Butyloxycarbonyl-*m*-(3-aminophenyl)tyrosine methyl ester (**5p**): Yield 36 mg (19%); yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, 1H, *J* 7.5 Hz), 6.99 (d, 1H, *J* 7.5 Hz), 6.78 (s, 1H), 6.71-6.68 (m, 2H), 6.60 (d, 1H, *J* 7.5 Hz), 6.52 (s, 1H), 4.79 (d, 1H, *J* 6.1 Hz), 4.36 (d, 1H, *J* 6.6 Hz), 3.52 (s, 3H), 2.93-2.76 (m, 2H), 1.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.46, 146.15, 142.65, 130.76, 130.38, 129.78, 129.53, 127.91, 118.80, 117.69, 115.28, 114.62, 114.10, 113.94, 52.19, 28.30 (3C); HRMS (ESI-TOF) *m/z* calcd.: for $C_{21}H_{26}N_2O_5 + Na^+$: 409.1739; found: 409.1738.

General amino acid deprotection procedure (**6a-e**)

The protected amino acid (0.25 mmol) was heated at 70 °C with 4.5 mol L^{-1} HCl (2 mL) for 3 h. After cooling, the aqueous phase was diluted with water (10 mL) and washed with diethyl ether (10 mL). The aqueous phase was then evaporated under reduced pressure delivering a solid, which was triturated with diethyl ether. After decanting and drying, the product was obtained.[15]

3-(Tiophen-3-yl)tyrosine hydrochloride (**6a**): Yield 62 mg (83%); white solid; ^1H NMR (300 MHz, D_2O) δ 7.59 (s, 1H), 7.46-7.43 (m, 1H), 7.35 (d, 1H, *J* 4.0 Hz, 1H), 7.24 (s, 1H), 7.06 (d, 1H, *J* 8.3 Hz), 6.92 (d, 1H, *J* 8.2 Hz), 4.20 (t, 1H, *J* 6.5 Hz), 3.19 (dd, 1H, *J* 6.5, 14.7 Hz), 3.06 (dd, 1H, *J* 6.5, 14.7 Hz); ^{13}C NMR (75 MHz, D_2O) δ 171.69, 152.45, 137.54, 130.76, 129.52, 128.15, 125.99 (2C), 123.78, 123.69, 116.90, 54.44, 34.93; HRMS (ESI-TOF) *m/z* calcd.: for $C_{13}H_{13}NO_3S + H^+$: 264.0694; found: 264.0689.

3-(4-Formylphenyl)tyrosine hydrochloride (**6b**): Yield 60 mg (75%); white solid; ^1H NMR (300 MHz, D_2O) δ 9.80 (s, 1H), 7.85 (s, 1H), 7.79 (d, 1H, *J* 7.6 Hz), 7.71 (d, 1H, *J* 7.6 Hz), 7.52 (t, 1H, *J* 7.6 Hz), 7.15-7.12 (m, 1H), 7.04 (s, 1H), 6.95 (d, 1H, *J* 8.2 Hz), 4.22 (t, 1H, *J* 6.5 Hz), 3.19 (dd, 1H, *J* 6.5, 14.7 Hz), 2.95 (dd, 1H, *J* 6.5, 14.7 Hz); ^{13}C NMR (75 MHz, D_2O) δ 196.32, 171.75, 152.37, 138.50, 135.98, 135.76, 131.60, 130.49, 129.37, 129.32, 129.10, 127.75, 126.21, 116.85, 54.47, 34.94; HRMS (ESI-TOF) *m/z* calcd.: for $C_{16}H_{15}NO_4 + H^+$: 286.1079; found: 286.1072.

3-(4-Methoxyphenyl)tyrosine hydrochloride (**6c**): Yield 59 mg (74%); white solid; ^1H NMR (300 MHz, D_2O) δ 7.35 (d, 2H, *J* 4.0 Hz), 7.16-7.07 (m, 1H), 7.03 (s, 1H), 6.96 (d, 2H, *J* 9.0 Hz), 6.92-6.84 (m, 1H), 4.21 (t, 1H, *J* 6.0 Hz), 3.79 (s, 3H), 3.21-3.03 (m, 2H); ^{13}C NMR (75 MHz, D_2O) δ 171.61, 158.21, 152.23, 131.58, 130.89, 130.47, 130.42, 129.51, 128.82, 126.04, 116.70, 116.07, 114.05, 55.46,

54.39, 34.91; HRMS (ESI-TOF) *m/z* calcd.: for $C_{16}H_{17}NO_4$ + H^+: 288.1236; found: 288.1230.

3-(4-Chlorophenyl)tyrosine hydrochloride (**6d**): Yield 73 mg (90%); white solid; ^{1}H NMR (300 MHz, D_2O) δ 7.41 (s, 2H), 7.17-7.12 (m, 2H), 7.10-6.95 (m, 1H), 6.86 (d, 2H, *J* 8.3 Hz), 4.22-4.18 (m, 1H), 3.26-3.06 (m, 2H); ^{13}C NMR (75 MHz, D_2O) δ 171.95, 155.17, 152.31, 131.59, 131.53, 130.98 (2C), 130.89, 130.69, 128.51, 125.91, 116.02 (2C), 53.58, 34.95; HRMS (ESI-TOF) *m/z* calcd.: for $C_{15}H_{14}ClNO_3$ + H^+: 292.0740; found: 292.0732.

3-(4-*tert*-Butylphenyl)tyrosine hydrochloride (**6e**): Yield 55 mg (63%); white solid; ^{1}H NMR (300 MHz, D_2O) δ 7.20-7.05 (m, 4H), 7.01-6.82 (m, 3H), 3.92-3.84 (m, 1H), 3.01-2.84 (m, 2H), 0.99 (s, 9H); ^{13}C NMR (75 MHz, D_2O) δ 169.70, 152.57, 149.58, 134.94, 134.89, 131.54, 128.97 (2C), 128.66, 126.03, 124.99 (2C), 116.57, 67.85, 33.98, 31.00, 25.07 (3C); HRMS (ESI-TOF) *m/z* calcd.: for $C_{19}H_{24}NO_3$ + H^+: 314.1756; found: 314.1750.

General amino alcohol procedure (**7**)

A solution of **5** (128 mg, 0.5 mmol) and TFA (1.5 mL) in DCM (3 mL) was stirred until complete consume of start material, monitored by TLC. After, $NaHCO_3$ saturated solution was added slowly, the mixture was extracted with DCM, the organic layer was collected, dried with $MgSO_4$, filtered and the solvent was removed under vacuum. A MeOH (4 mL) solution of **8** was cooled to 0 °C, and $NaBH_4$ (8 equivalent) was added in one portion. The resulting solution was stirred under ambient temperature for 24 h. After the reaction was complete (monitored by TLC), the organic solvents were evaporated under vacuum. Water (5 mL) was added, and after phase separation, the corresponding aqueous phase was extracted with EtOAc (3 × 3 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and then concentrated under high vacuum. The crude product was purified directly by silica gel column chromatography[17] (eluting with ethyl acetate/hexane 9:1).

O-Methyl-3-(phenyl)tyrosinol (**7**): Yield 35 mg (55%); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-741 (m, 2H), 7.34-7.29 (m, 2H), 7.26-7.23 (m, 1H), 7.06-7.01 (m, 2H), 6.84 (d, 1H, *J* 8.9 Hz, 1H), 3.70 (s, 1H), 3.62-3.56 (m, 2H), 3.39-3.34 (m, 1H), 3.75-3.69 (m, 1H), 3.56-3.49 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.32, 138.29, 131.64, 130.94, 130.19, 129.48 (2C), 129.17, 128.01 (2C), 127.02, 111.60, 65.29, 55.72, 54.36, 29.10; HRMS (ESI-TOF) *m/z* calcd.: for $C_{16}H_{19}NO_2$ + H^+: 258.1494; found: 258.1485.

Synthesis of dipeptides **10**

A solution of **9** (203 mg, 0.5 mmol) in dry DCM was cooled to 0 °C and 1-hydroxybenzotriazole (1.1 equivalent) was added, followed by *N-N'*-diisopropylcarbodiimide (1.2 equivalent). After 1 h, the mixture was allowed to warm to room temperature then compound **5o** dissolved in DCM was added. The reaction mixture was stirred for 15 h. The urea was filtered out, the supernatant was dried to get the crude compound.[18] Purification by silica flash chromatography (eluting with ethyl acetate/hexane 5:5).

N-tert-Butyloxycarbonyl-di-tyrosine methyl ester (**10**): Yield 171 mg (52%); white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.35 (m, 5H), 6.88 (d, 1H, *J* 7.5 Hz), 6.82 (s, 1H), 6.77-6.76 (m, 2H), 6.68 (d, 1H, *J* 8.2 Hz), 6.35 (d, 1H, *J* 7.5 Hz), 5.78 (s, 1H), 4.95 (s, 1H), 4.73-4.67 (m, 1H), 4.17 (s, 1H), 3.61 (s, 3H), 2.96-2.93 (m, 2H), 2.81-2.79 (m, 2H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.52, 170.83, 155.35, 154.33, 151.93, 139.10, 137.12, 131.08, 130.82, 130.19, 129.68, 129.06 (5C), 128.38, 127.75, 127.53, 116.21, 115.17, 85.30, 52.46, 42.38, 37.19, 37.01, 28.27 (3C), 23.45; HRMS (ESI-TOF) *m/z* calcd.: for $C_{30}H_{33}IN_2O_7$ + H^+: 661.1411; found: 661.1407.

For compound **11**, see general procedure for Suzuki-Miyaura cross-coupling reaction.

N-tert-Butyloxycarbonyl-di-tyrosine methyl ester (**11**): Yield 64 mg (42%); white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.28 (m, 7H), 7.22-7.19 (m, 1H), 7.07 (s, 1H), 6.86-6.79 (m, 2H), 6.76-6.67 (m, 3H), 6.30 (d, 1H, *J* 7.5 Hz), 6.11 (s, 1H), 5.75 (s, 1H), 4.96 (s, 1H), 4.69-4.65 (m, 1H), 4.22 (s, 1H), 3.55 (s, 3H), 2.95-2.75 (m, 4H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.52, 171.07, 152.12, 151.90, 137.51, 137.13, 131.02, 130.59, 129.68, 129.29, 129.05 (4C), 129.03 (2C), 128.36, 128.09, 127.71, 127.56, 126.05, 123.05, 116.41, 116.17, 60.44, 53.44, 52.30, 42.34, 37.18, 28.25 (3C), 23.45, 14.19; HRMS (ESI-TOF) *m/z* calcd.: for $C_{34}H_{36}N_2O_7S$ + H^+: 617.2321; found: 617.2318.

A solution of **9** (203 mg, 0.5 mmol) in dry DCM was cooled to 0 °C and 1-hydroxybenzotriazole (1.1 equivalent) was added, followed by *N-N'*-diisopropylcarbodiimide (1.2 equivalent). After 1 h, the mixture was allowed to warm to room temperature, then compound **2** dissolved in DMF was added, followed by triethylamine (TEA) (1.2 equivalent). The reaction mixture was stirred for 15 h. The precipitated dicyclohexylurea was filtered off and washed with DCM. The filtrated was evaporated under high

vacuum, the crude compound was acidified under ice cold condition with 1 mol L^{-1} HCl to pH 2-3 and extracted with DCM, the organic layer was collected, dried with $MgSO_4$, filtered and the solvent was removed under vacuum.[5] Purification by silica flash chromatography (eluting with ethyl acetate/hexane 5:5).

N-tert-Butyloxycarbonyl-di-tyrosine methyl ester (**12**): Yield 170 mg (48%); yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, 1H, *J* 1.8 Hz), 7.36 (d, 1H, *J* 1.8 Hz), 7.25-7.20 (m, 2H), 7.00 (d, 1H, *J* 7.9 Hz), 6.86 (dd, 1H, *J* 1.8, 8.3 Hz), 6.78 (d, 1H, *J* 8.0 Hz), 6.66 (d, 1H, *J* 7.7 Hz), 5.19 (d, 1H, *J* 7.2 Hz), 4.74 (dd, 1H, *J* 6.0, 13.0 Hz), 4.47 (d, 1H, *J* 7.8 Hz), 4.30 (s, 1H), 3.69 (s, 3H), 3.02-2.89 (m, 4H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.35 (2C), 157.55, 155.57, 154.78, 154.67, 139.28 (2C), 130.72, 130.62, 129.83, 129.13, 115.31, 115.26, 84.93, 60.55, 53.48, 52.64, 42.34, 28.32 (3C), 23.46, 14.19; HRMS (ESI-TOF) *m/z* calcd.: for $C_{24}H_{28}I_2N_2O_7 + H^+$: 710.2973; found: 710.2965.

For compound **13**, see general procedure for Suzuki-Miyaura cross-coupling reaction.

N-tert-Butyloxycarbonyl-di-tyrosine methyl ester (**13**): Yield 102 mg (61%); white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, 4H, *J* 8.4 Hz), 7.02-6.96 (m, 6H), 6.87-6.79 (m, 4H), 6.42 (d, 1H, *J* 7.6 Hz), 5.70 (s, 1H), 5.04 (s, 1H), 4.80-4.74 (m, 1H), 4.32 (s, 1H), 3.84 (s, 6H), 3.65 (s, 3H), 2.99-2.88 (m, 4H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.53, 171.05, 159.22, 159.20, 151.93, 131.17, 130.99, 130.21, 129.31, 128.31, 128.06, 128.02, 127.54, 116.08, 116.01, 114.53, 114.48, 55.34 (2C), 53.44, 52.28, 42.32, 28.25 (3C), 23.46; HRMS (ESI-TOF) *m/z* calcd.: for $C_{38}H_{32}N_2O_9 + H^+$: 671.2969; found: 671.2960.

Supplementary Information

Supplementary information (experimental details and analytical data for all new compounds, as well as the copies of ^{1}H and ^{13}C NMR spectra) is available free of charge at http://jbcs.sbq.org.br as PDF file.

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