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Graphical Abstract

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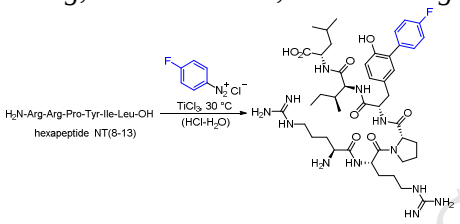

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ABSTRACT

The radical arylation of the phenolic side chain of tyrosine in peptides has been investigated. Aryl radicals were generated from aryldiazonium salts using titanium(III) chloride as stoichiometric reductant. Due to the high selectivity with which 3-aryltyrosine derivatives were formed, this reaction type represents a new strategy for the direct functionalization of peptides.

1. Introduction

Radical arylation reactions have recently become an increasingly popular strategy for the synthesis of biaryl compounds.[1,2] Since such transformations are formally comparable to aromatic C-H activations,[3,4] simple starting materials can be used in comparison with established Suzuki-type cross-coupling reactions.[5] Moreover, good regioselectivities have been obtained in radical arylations of donor-substituted benzenes including phenols[6-8] and anilines.[9] The radical arylation of L-tyrosine,[10] which can essentially be carried out in the complete absence of protecting groups, and which does not lead to partial racemization at the stereocenter of the amino acid thereby represents a particularly valuable alternative to known transition-metal catalyzed protocols.[11] 3-Aryltyrosines prepared through such arylation reactions were recently applied in the synthesis of a highly subtype-selective neurotensin receptor ligand **1** (Figure 1).[10b,12] The neurotensin receptor subtype 2 (NTS2) appears to be involved in antinociceptive activity and hypothermia, whereas NTS1 is considered to be largely responsible for the control of dopamine-mediated, neuroleptic effects.[13,14] A significant drawback with regard to a future structural optimization of ligand **1** however is that each hexapeptide has to be prepared separately through multistep solid-phase peptide synthesis (SPPS).[15]

Against this background, it appeared as a challenging task to investigate the direct radical arylation of tyrosine residues in peptides, since this could provide a far easier access to further derivatives of ligand **1** bearing diversely substituted aryl moieties in 3-position of the tyrosine unit. Arylation at the aromatic core of tyrosine incorporated in peptides has so far been achieved through a two-step sequence comprising electrophilic iodination and subsequent Suzuki cross-coupling.[16-18] Since the initial iodination step thereby preferably provides 3,5-diiodinated tyrosines, this strategy is mainly suited for the synthesis of 3,5-diarylated derivatives.

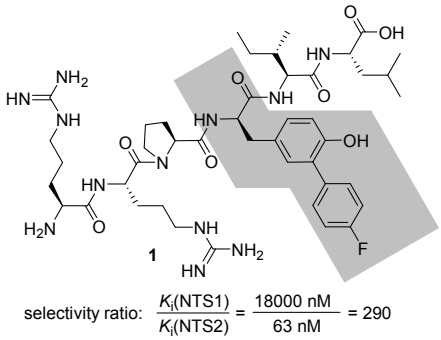


Figure 1. Neurotensin receptor subtype 2 (NTS2) ligand **1** with high selectivity over NTS1.

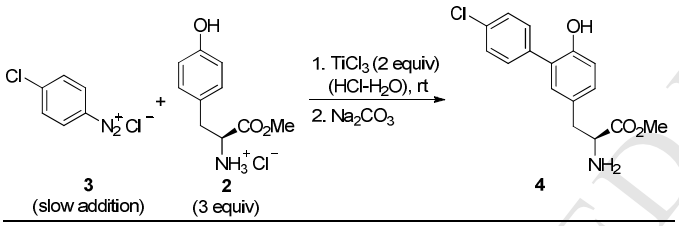
With regard to a selective radical arylation of tyrosine in peptides, which might generally be complicated by the high reactivity of aryl radicals towards many organic functional groups,[19] it was interesting to notice that the backbone of peptides had been found to be largely inert towards the attack of electrophilic hydroxyl radicals.[20] Among all carbon-centered radicals, aryl radicals can also be considered as electrophilic.[21]

In this article, we now report first results on the direct radical arylation of tyrosine residues in peptides and, in particular, on the preparation of further derivatives of NTS2 ligand **1**.

2. Results and discussion

In a first series of experiments, we investigated whether the previously reported titanium(III)-mediated arylation of L-tyrosine methyl ester (**2**) with 4-chlorophenyldiazonium chloride (**3**) (Table 1, entry 1) could also be conducted with substoichiometric amounts of the reductant. Table 1 contains selected results from this series (see Supporting Information for further experiments). Radical arylations of electron-rich benzenes can basically proceed as chain reactions requiring the reductant only as initiator,[7,22] and with regard to an arylation of peptides, lower amounts of titanium(III) would facilitate work-up as well as separation. The yield of 22% from the experiment with 0.1 equivalents of titanium(III) chloride demonstrated that a chain transfer does indeed occur (entry 3, 10% theoretical yield for non-chain reaction), but that it is not effective enough to allow for useful conversions of **2**. Addition of zinc to regenerate titanium(III) ions could not improve this result (entry 4). The negative effect of titanium(IV) ions formed in the reaction course became apparent from the reaction reported in entry 5, as the yield was even lower than with 0.5 equivalents of titanium(III) chloride (entry 2). Lower amounts of the radical acceptor **2** also decreased the yield to 38% and 31% (entries 6 and 7), which indicated that a good conversion relative to the tyrosine unit will most probably require a significant excess of diazonium ions.

Table 1. Arylation of methyl L-tyrosinate (**2**).



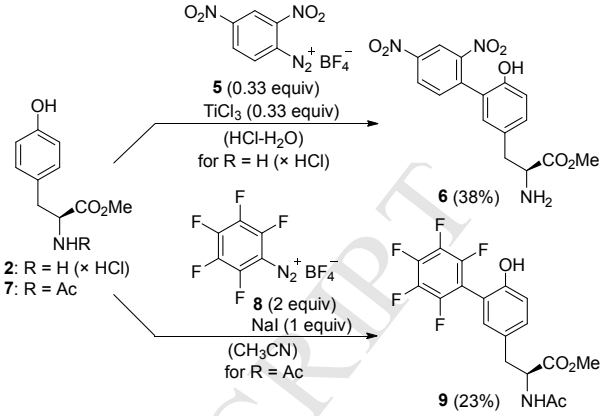
3 (slow addition) **2** (3 equiv) **4**

entry	variation of standard conditions[a]	yield **4** (%)[b]
1	--	56
2	$TiCl_3$ (0.5 equiv)	35
3	$TiCl_3$ (0.1 equiv)	22
4	$TiCl_3$ (0.1 equiv) + Zn (10 equiv)	18
5	$TiCl_3$ (1 equiv) + $TiCl_4$ (1 equiv)	29
6	**2** (1.5 equiv)	38
7	**2** (1 equiv)	31

[a]Standard conditions: Slow addition of **3** (2 mmol) in HCl/H_2O (0.4 M, 5 mL) to a mixture of **2** (6 mmol) and $TiCl_3$ (4 mmol, 4 mL of 1 M soln. in 3 M HCl) in H_2O (6 mL) over 10-15 min at rt. [b]Yield determined by ^{1}H-NMR using dimethyl terephthalate as internal standard.

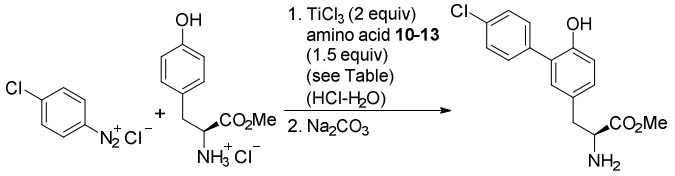
Radical arylations of arenes are more easy to conduct as chain reactions when electron-deficient diazonium salts are employed.[22] In that case, the diazonium ions are stronger oxidants,[23] and reduction of them can occur along with rearomatization of the cyclohexadienyl adduct arising from the radical addition step.[22] For such reactions, the 2,4-dinitrophenyldiazonium salt **5** and the pentafluoro derivative **8** have been found to be particularly well suited (Scheme 1).[24] Due to good solubility of **5** in water, the arylation of L-tyrosine methyl ester (**2**) could be conducted under conditions comparable to those reported in Table 1. The experiment with the pentafluorophenyldiazonium salt **8**, in contrast, had to be performed in acetonitrile. The use of sodium iodide as initiator had earlier been reported by Kochi.[24] In both reactions, the desired products **6** or **9** were obtained again with high regioselectivity, but not with better yields than those obtained before with the 4-chlorophenyldiazonium salt **3** (Table 1). Interestingly, 3-pentafluorophenyltyrosine derivatives comparable to **9** have not been described in literature so far, although they could be valuable building blocks for investigations by magnetic resonance tomography (MRT).[25]

Scheme 1. Arylations with reactive diazonium ions.



In further experiments, alternative aryl radical sources, including phenylazocarboxylate salts[26] in the presence of acid and phenylhydrazine in combination with manganese dioxide,[9b] were investigated. Since the comparably low yields of 3-aryltyrosines obtained from these attempts further supported the special aptitude of the reductive conditions based on titanium(III) chloride, we turned to evaluate the effect of other amino acids on the arylation reaction. Based on literature reports and earlier observations, it can be expected that cysteine[27] and methionine[28] have a significant negative impact on radical arylations through either hydrogen atom transfer from the thiol group or homolytic substitution at the sulfur atoms of the thioether. Our study thus focused on phenylalanine **10**, histidine **11,** tryptophan **12** and lysine **13**, which were used as methyl esters in separate competition experiments (Table 2).

Table 2. Competition experiments with aromatic amino acid methyl esters.



3 (slow addition) **2** (1.5 equiv) **4**

entry	competing amino acid[a]	yield **4** (%)[b]
1	--	38
2	L-phenylalanine methyl ester (×HCl) (**10**)	22
3	L-histidine methyl ester (×HCl) (**11**)	28
4	L-tryptophan methyl ester (×HCl) (**12**)	7
5	L-lysine methyl ester (×HCl) (**13**)	22

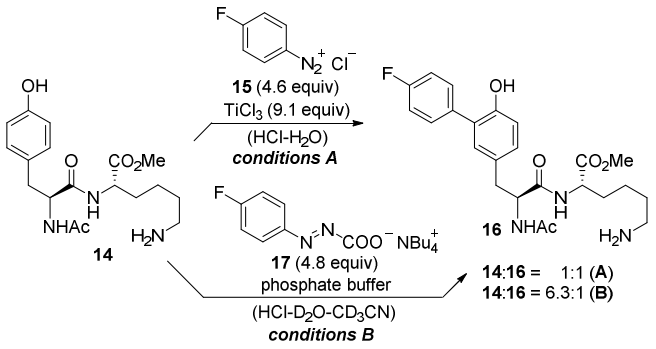
[a]Standard conditions: Slow addition of **2** (2 mmol) in HCl/H_2O (0.4 M, 5 mL) to a mixture of **2** (3 mmol), methyl ester-protected amino acid **10-13** (3 mmol) and $TiCl_3$ (4 mmol, 4 mL of 1 M soln. in 3 M HCl) in H_2O (6 mL) over 10-15 min at rt. [b]Yield determined by ^{1}H-NMR using dimethyl terephthalate as internal standard.

The results summarized in Table 2 show that the electron-deficient imidazole unit of histidine **11** (entry 3), which can be considered as protonated under the strongly acidic conditions, has the least impact on the arylation of tyrosine **2**. The presence of phenylalanine **10** or lysine **13** reduced the yield of **4** more significantly from 38% to 22% (entries 1, 2 and 5). Indole, which occurs in the side chain of tryptophan, and which is known to be

an efficient acceptor for aryl radicals led to only 7% of **4** (entry 4).[10a,29] Remarkably, arylation products besides **4** were only detected in the competition experiment with tryptophan **12**. The fact that the other amino acids **10**, **11** and **13** are not attacked by aryl radicals, and merely increase hydrogen abstraction to give volatile chlorobenzene, is beneficial with regard to the radical arylation of peptides.

In the next step, the reductive titanium(III)-mediated arylation was applied to the dipeptide AcHN-Tyr-Lys-OMe (**14**) (Scheme 2, conditions A). In contrast to the reactions reported before (Table 1), and due to the value of the peptidic component, a significant excess of 4-fluorophenyldiazonium chloride (**15**) (4.6 equiv) and titanium(III) chloride (9.1 equiv) was now used.[30] Thus, the titanium-based arylation provided a promising reactant-to-product ratio of 1:1. Purification of the arylated dipeptide **16** was achieved through washing with diethyl ether to remove unpolar side products, followed by solid phase extraction and preparative HPLC. After washing with diethyl ether, analysis of the crude reaction mixture by ^{1}H-NMR revealed no significant products other than **16** and unreacted dipeptide **14**.

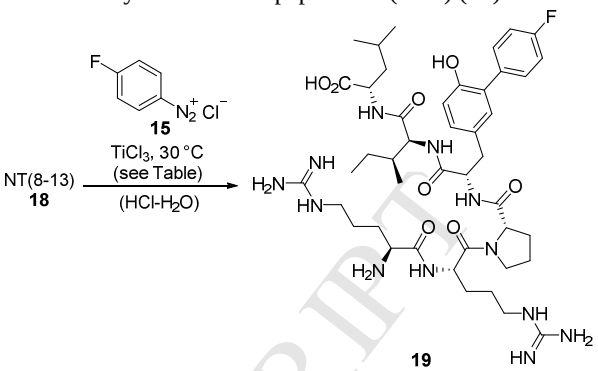
Scheme 2. Arylation of dipeptide AcHN-Tyr-Lys-OMe (**14**).



Although not successful in preliminary attempts with tyrosine **2**, we again evaluated the acid-induced reaction of phenylazocarboxylate **17** as metal-free alternative for the arylation of **14** (Scheme 2, conditions B).[26] If effective, such reaction could benefit from the highly efficient access to ^{18}F-labelled derivatives of **17**[31] and provide radiolabeled peptides. However, only a low conversion of **14** could be achieved under conditions B, which further supports the special role of titanium(III) ions in radical arylations of phenols. Since the overall conditions A and B are more or less identical if one ignores the presence of titanium ions, a possible explanation for the vast difference in outcome could be that titanium(III) ions are able to increase the reactivity of phenol as a radical acceptor.[32]

A series of arylation experiments was then carried out with hexapeptide NT(8-13) (**18**) (Table 3). The conditions including 4.6 equivalents of 4-fluorophenyldiazonium chloride (**15**) and 9.1 equivalents of titanium(III) chloride turned out to be the most successful, since a favorable reactant-to-product ratio of 1.3:1 could be achieved in this way (entry 1). The selectivity of the arylation at the tyrosine unit was confirmed by product ion (tandem) mass spectrometry (see Supporting Information). Lower as well as larger amounts of the diazonium salt **15** and titanium(III) chloride resulted in lower conversions of the hexapeptide **18** (entries 2-5). Not unexpectedly, the experiments using large amounts of both reactants (entries 5 and 6) were significantly complicated by the elaborate removal of the titanium ions during work-up. Beneficially, analysis of the crude reaction mixtures by ^{1}H-NMR spectroscopy indicated that no significant side-products were formed from **18** other than the arylated peptide **19**. Unpolar products such as fluorobenzene arising from hydrogen abstraction by the aryl radical,[19] or 4,4'-difluoroazobenzene formed from aryl radical addition to the diazonium salt **15**,[33] could easily be removed through washing of the crude reaction mixture with diethyl ether.

Table 3. Arylation of hexapeptide NT(8-13) (**18**).



entry	conditions[a] **15** (equiv)	conditions[a] $TiCl_3$ (equiv)	ratio **18**:**19**[b]
1	4.6	9.1	1.3:1
2	3.4	6.3	2.1:1
3	3.4	3.4	4.0:1
4	2.3	4.2	5.4:1
5	6.3	12.6	2.0:1
6	12.6	25.2	--[c]

[a]General conditions: Slow addition of 4-fluorophenyldiazonium chloride (**15**) (0.2 M) over 20 minutes to a solution of NT(8-13) (**18**) (5.23 µmol or 10.5 µmol) and $TiCl_3$ (in 2 M hydrochloric acid) in water (0.5 mL or 1.0 mL) under argon atmosphere at 30° C. [b]Ratio determined by ^{1}H-NMR spectroscopy (integration of characteristic aromatic signals). [c]Integration of characteristic signals not possible.

Finally, the optimized conditions (Table 3, entry 1) were applied to the arylation of NT(8-13) (**18**) with 3-bromophenyldiazonium chloride, which provided the arylated hexapeptide **20** in a reactant-product ratio of 1.5:1. This ratio is similar to that reached in the preparation of **19**.

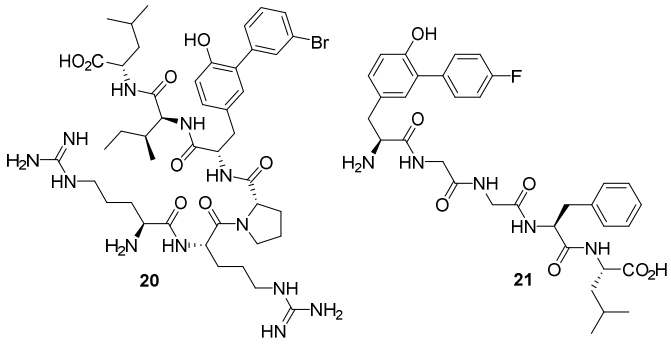


Figure 2. Variation of diazonium salt and peptide.

The unfavorable effect of phenylalanine, which was already observed in the competition experiment (Table 2), became again noticable in the arylation of the Phe-containing pentapetide Leu-enkephalin with 4-fluorophenyldiazonium chloride (**15**). Under comaprable conditions (**15** (3.0 equiv), $TiCl_3$ (5.5 equiv)), a lower reactant-to-product ratio of 3:1 was achieved in the reaction yielding the arylated pentapeptide **21** (c.f. entry 2, Table 3). Remarkably, this low conversion is not due to a competing arylation of the phenylalanine side-chain, but to an increased formation of non-polar products such as fluorobenzene and difluororazobenzene. In the two reactions leading to **20** and **21**,

peptidic side-products were only observed in small amounts relative to desired arylation products.

In summary, we have shown that reasonable conversions can be obtained in direct radical arylations of peptides using diazonium salts and titanium(III) chloride as reductant. Such reactions can provide a more straightforward access to a compound library of functionalized peptides, since the strategy does not require the preparation of each peptide through solid-phase synthesis. The fact that no significant peptidic side-products were observed, supports the assumption that peptide backbone is largely stable towards electrophilic radicals. Ongoing work includes the preparation of further arylated derivatives of hexapeptide NT(8-13) as well as investigations on a possibly activating effect of titanium(III) ions in radical arylations of phenols. Moreover, and despite the high reactivitiy of aryl radicals towards many substrates, radical arylations could become a new strategy for the late-stage functionalization of complex biomolecules.[34]

3. Experimental part

3.1. General techniques

Column chromatography was performed on silica gel, 230 - 400 mesh ASTM. TLC plates were visualized with UV. All reagents were purchased from commercial sources and used without additional purification. Hexapeptide NT(8-13) was prepared according to literature procedures (see also Supporting Information).[35] ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on Bruker Avance 600 or Avance 360 spectrometers using either $CDCl_3$, CD_3OD, CD_3CN or D_2O as solvent with TMS or C_6F_6 (for ^{19}F NMR) as reference. Mass spectra were recorded on a Jeol GC mate II spectrometer using electron ionization. Electrospray ionization MS (ESI-MS) measurements were performed on a UHR-TOF Bruker Daltonik (Bremen, Germany) maXis plus, an ESI-quadrupole time-of-flight (qToF) mass spectrometer capable of resolution of at least 60.000 FWHM. LC-MS Waters-system Bridge C18 analytical column, 4.6×50 mm, 3.5 µm, flow rate: 1:23 ml/min) coupled to a Waters ACQUITY QDa mass detector equipped with an ESI-trap. Parameters: CH_3CN in H_2O 10-90% in 17 min, 0.1% formic acid. Column chromatography on silica gel was used for purification unless otherwise noted. Purification of arylated peptides by preparative HPLC was performed on a Jasco HPLC-UV system (Jasco, Groß-Umstadt, Germany) which included a PU-2087Plus pump with degasser, an AS-2057Plus autosampler and an UV-2077Plus detector. A Nucleodur C18ce column (5 µM particle size; 10 × 250 mM, Macherey-Nagel, Düren, Germany) was used for separation. Samples were dissolved in 0.1% formic acid, injected (about 10 mg in 500 µL volume) and eluted at a flow rate of 3.0 mL/min at room temperature. Fractions were collected manually. Data acquisition and processing was carried out by ChromPass 1.8 software. Chromatograms were recorded at 220, 260 and 280 nm. Sample clean-up by SPE was performed with Strata C18E (55 µm, 70 Å) tubes (Phenomenex, Aschaffenburg, Germany). After conditioning of the resin with 2 mL of CH_3CN and 2 mL of 0.1% TFA, 10 mg of sample (dissolved in 0.1% TFA) were loaded per column. After 2 washing steps with 2 mL of 0.1% TFA, peptides were eluted with 1.5 mL of 60% CH_3CN, 0.1% TFA. Subsequently, samples were dried by lyophilization.

3.2. Compounds

Methyl L-3-(4-chlorophenyl)tyrosinate (**4**) (Table 1)

A degassed solution of 4-chloroaniline (10.0 mmol, 1.28 g) in hydrochloric acid (3 N, 10 mL) and water (10 mL) was treated at 0 °C with a degassed solution of sodium nitrite (10.0 mmol, 0.69 g) in water (5 mL) by dropwise addition over a period of 10 minutes, followed by additional stirring for 20 minutes at 0 °C. An aliquot of this 0.4 M ice-cooled solution of 4-chlorophenyldiazonium chloride (**3**) (2.00 mmol, 5 mL) was added dropwise by a syringe pump to a vigorously stirred, degassed mixture of methyl tyrosinate hydrochloride (**2**) (6.00 mmol, 1.39 g) in water (6 mL) and titanium(III) chloride (4.00 mmol, 4 mL of a ca. 1 M solution in 3 N hydrochloric acid) under nitrogen atmosphere at room temperature within 10-15 minutes. After stirring for 10 more minutes, the pH of the crude mixture was adjusted to a value of 8-9 by the use of satd. aqueous solution of sodium carbonate. Threefold extraction with diethyl ether (3 × 75 mL), washing of the combined organic phases with a satd. aqueous solution of sodium chloride, drying over sodium sulfate and concentration in vacuo led to the crude product mixture, which was analyzed by ^{1}H NMR spectroscopy (56% yield determined by internal standard dimethyl terephthalate). Purification by column chromatography (silica gel, CH_2Cl_2/MeOH = 10:1) gave methyl 3-(4-chloro-phenyl)-tyrosinate (**4**).

R_f = 0.5 (CH_2Cl_2/MeOH 10:1); colorless solid; ^{1}H NMR (360 MHz, CD_3OD) δ (ppm) = 2.94 (dd, *J* = 6.0 Hz, *J* = 13.9 Hz, 1 H), 3.02 (dd, *J* = 7.0 Hz, *J* = 13.9 Hz, 1 H), 3.71 (s, 3 H), 3.83 (dd, *J* = 6.0 Hz, *J* = 7.0 Hz, 1 H), 6.85 (d, *J* = 8.3 Hz, 1 H), 7.01 (dd, 2.2 Hz, *J* = 8.6 Hz, 1 H), 7.09 (d, *J* = 2.2 Hz, 1 H), 7.37 (d, *J* = 8.6 Hz, 2 H), 7.54 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (91 MHz, CD_3OD) δ (ppm) = 39.9 (CH_2), 49.9 (CH_3), 56.4 (CH), 117.3 (CH), 128.6 (C_q), 128.7 (C_q), 129.0 (2 × CH), 130.7 (CH), 131.9 (2 × CH), 132.4 (CH), 133.6 (C_q), 138.7 (C_q), 154.6 (C_q), 175.3 (C_q); MS (EI) m/z (%): 307 (3) [^{37}Cl-M$^+$], 305 (8) [^{35}Cl-M$^+$], 248 (4), 246 (10), 219 (42), 217 (100), 181 (15), 152 (10), 136 (10), 107 (58), 88 (58), 70 (9), 57 (21), 43 (60); HRMS (EI) calcd. for $C_{16}H_{16}{}^{35}ClNO_3$ [M$^+$]: 305.0819, found: 305.0821.[10a]

Competition experiments (Table 2)

An aliquot of the previously prepared 0.4 M ice-cooled solution of 4-chlorophenyldiazonium chloride (**3**) (2.00 mmol, 5 mL) was added dropwise by a syringe pump to a vigorously stirred, degassed mixture of methyl tyrosinate hydrochloride (**2**) (3.00 mmol, 695 mg) and a second methyl ester-protected amino acid **10**-**13** (3.00 mmol) in water (6 mL) and titanium(III) chloride (4.00 mmol, 4 mL of a ca. 1 M solution in 3 N hydrochloric acid) under nitrogen atmosphere at room temperature within 10-15 minutes. After stirring for 10 more minutes, the pH of the crude mixture was adjusted to a value of 8-9 by the use of satd. aqueous sodium carbonate. Threefold extraction with diethyl ether (3 x 75 mL), washing of the combined organic phases with a satd. aqueous solution of sodium chloride, drying over sodium sulfate and concentration in vacuo led to a crude product. The yield of **4** was determined by ^{1}H NMR using dimethyl terephthalate as internal standard.

Methyl L-3-(2,4-dinitro)tyrosinate (**6**) (Scheme 1)

A mixture of 2,4-dinitroaniline (5.00 mmol, 915 mg) and tetrafluoroboric acid (50%, 71.4 mmol, 12.5 mL) was cooled to –5 °C. A pre-cooled solution of sodium nitrite (5.00 mmol, 345 mg) in water (2.5 mL) was dropwise added over a period of 20 minutes. The precipitate was filtered off and subsequently washed with cold tetrafluoroboric acid, ethanol and diethyl ether. The resulting 2,4-dinitrophenyldiazonium tetrafluoroborate (**5**) was dried in vacuo and stored at −18 °C.

Yellow solid; yield 1.17 g (83%); ^{1}H NMR (600 MHz, CD_3OD / D_2O) δ (ppm) = 7.94 (d, *J* = 8.2 Hz, 1 H), 8.66 (dd, *J* = 2.2 Hz, *J* = 8.2 Hz, 1 H), 9.02 (d, *J* = 2.2 Hz, 1 H); ^{13}C NMR

(151 MHz, CD_3OD / D_2O) δ (ppm) = 119.7 (CH), 120.6 (C_q), (CH_2), 52.5 (CH_3), 60.5 (CH), 112.1-112.5 (m, C_q), 113.4 (C_q), 116.5 (CH), 127.2 (C_q), 131.5 (CH), 132.5 (CH), 136.4-138.5 (m, 2 × C_q), 139.6-141.6 (m, C_q), 143.5-145.2 (m, 2 × C_q), 153.6 (C_q), 170.6 (C_q), 172.1 (C_q); MS (EI) m/z (%): 403 (5) [M^+], 345 (19), 344 (100), 313 (23), 302 (20), 274 (13), 273 (71), 88 (32), 60 (14), 43 (34); HRMS (EI) calcd. for $C_{18}H_{14}F_5NO_4$ [M^+]: 403.0843, found: 403.0845.

Titanium(III) chloride (1.00 mmol, 1 mL of a ca. 1 M solution in 3 N hydrochloric acid) was added dropwise by a syringe pump to a vigorously stirred, degassed mixture of methyl L-tyrosinate hydrochloride (**2**) (3.00 mmol, 695 mg) and 2,4-dinitrophenyldiazonium tetrafluoroborate (**5**) (1.00 mmol, 282 mg) in hydrochloric acid (3 N, 3 mL) under nitrogen atmosphere within 10-15 minutes. After stirring for 10 more minutes, the pH of the crude mixture was adjusted to a value of 8-9 by the use of satd. aqueous sodium carbonate. Threefold extraction with ethyl acetate (3 × 75 mL), washing of the combined organic phases with a satd. aqueous solution of sodium chloride, drying over sodium sulfate and concentration in vacuo led to the crude product. Purification by column chromatography (silica gel, CH_2Cl_2/MeOH = 25:1→10:1) gave methyl L-3-(2,4-dinitrophenyl)tyrosinate (**6**).

R_f = 0.1 (CH_2Cl_2/MeOH 25:1); colorless solid; yield 139 mg (38%); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 2.86 (dd, *J* = 7.8 Hz, *J* = 13.9 Hz, 1 H), 3.10 (dd, *J* = 6.7 Hz, *J* = 14.1 Hz, 1 H), 3.75 (s, 3 H), 3.76-3.80 (s, 1 H), 6.53 (d, *J* = 8.8 Hz, 1 H), 7.05-7.07 (m, 2 H), 7.58 (d, *J* = 8.5 Hz, 1 H), 8.41 (dd, *J* = 2.4 Hz, *J* = 8.5 Hz, 1 H), 8.76 (d, *J* = 2.3 Hz, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm) = 39.4 (CH_2), 51.9 (CH_3), 55.0 (CH), 115.5 (CH), 119.5 (CH), 123.2 (CH), 126.5 (CH), 128.0 (C_q), 129.9 (CH), 131.5 (C_q), 133.7 (CH), 139.6 (C_q), 146.3 (C_q), 149.2 (C_q), 152.7 (C_q), 174.9 (C_q); MS (EI) m/z (%): 361 (2) [M^+], 302 (16), 274 (9), 273 (17), 256 (21), 181 (10), 89 (23), 88 (100), 33 (12); HRMS (EI) calcd. for $C_{16}H_{15}N_3O_7$ [M^+]: 361.0910, found: 361.0909.

Methyl L-3-(pentafluorophenyl)tyrosinate (**9**) (Scheme 1)

A solution of pentafluoroaniline (5.00 mmol, 916 mg) in dry acetonitrile (1 mL) is added dropwise to a mixture of pulverized nitrosyl tetrafluoroborate (5.00 mmol, 915 mg) in dry acetonitrile (1 mL) at –30 °C over a period of 30 minutes. After stirring for 1 hour at –30 °C, dry dichloromethane (7.5 mL) was added and the resulting precipitate was filtered off. Drying in vacuo led to the desired pentafluorophenyldiazonium tetraflurorborate (**8**).

Yellow solid; yield 1.07 g (76%); ^{13}C NMR (151 MHz, CD_3CN) δ (ppm) = 96.1 (m, C_q), 139.8 (d, J_{CF} = 260.5 Hz, 2 × C_q), 149.0 (dd, J_{CF} = 15.6 Hz, J_{CF} = 282.4 Hz, C_q), 154.4 (d, J_{CF} = 279.3 Hz, 2 × C_q); ^{19}F NMR (282 MHz, CD_3CN) δ (ppm) = –120.1, –123.7, –151.9, –153.0.

A solution of sodium iodide (0.50 mmol, 75 mg) in acetonitrile (1 mL) was added dropwise by a syringe pump to a mixture of the doubly protected tyrosine derivative **7** (0.50 mmol, 119 mg) and pentafluorophenyldiazonium tetrafluoroborate (**8**) (1.00 mmol, 282 mg) in acetonitrile (5.8 mL) under nitrogen atmosphere within 15 minutes. After addition of an aqueous solution of sodium thiosulfate (0.05 M, 30 mL), the reaction mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with satd. aqueous solution of sodium chloride, dried over sodium sulfate and concentrated in vacuo. Purification by column chromatography (silica gel, EtOAc/hexanes = 3:1) gave the desired product **9**.

R_f = 0.4 (EtOAc/hexanes 3:1); colorless solid; yield 46 mg (23%); ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm) = 1.98 (s, 3 H), 2.98 (dd, *J* = 6.2 Hz, *J* = 14.1 Hz, 1 H), 3.12 (dd, *J* = 5.7 Hz, *J* = 14.1 Hz, 1 H), 3.74 (s, 3 H), 4.88 (dd, *J* = 6.0 Hz, *J* = 14.1 Hz, 1 H), 6.10 (d, *J* = 8.1 Hz, 1 H), 6.83 (d, *J* = 8.3 Hz, 1 H), 6.90 (d, *J* = 2.1 Hz, 1 H), 7.07 (dd, *J* = 2.2 Hz, *J* = 8.4 Hz, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 22.8 (CH_3), 37.2

4-Fluorophenyldiazonium chloride

A degassed solution of 4-fluoroaniline (10.0 mmol, 0.96 mL) in hydrochloric acid (3 N, 10 mL) and water (10 mL) was treated at 0 °C with a degassed solution of sodium nitrite (10.0 mmol, 0.69 g) in water (5 mL) by dropwise addition over a period of 20 minutes, followed by additional stirring for 30 minutes at 0 °C. The mixture was diluted with further hydrochloric acid (3 N, 10 mL) and water (15 mL) for a final concentration of (0.2 M (10 mmol / 50 mL)).

AcHN-(3-(4-fluorophenyl)-Tyr)-Lys-OMe **16**

Conditions A (Scheme 2): To a solution of AcHN-Tyr-Lys-OMe (**14**) (18.4 µmol, 8.80 mg) in water (1 mL) titanium(III) chloride (168 µmol, 126 µL, in 2 M hydrochloric acid, 1.33 mmol/mL) was added. Under argon atmosphere at 30° C a solution of 4-fluorophenyldiazonium chloride (0.2 M, 84.0 µmol, 420 µL) was added over 20 minutes and the mixture was stirred for further 25 minutes at this temperature. The reaction mixture was washed with diethyl ether (3 × 2.5 mL) and the water phase was lyophilized. After removal of titanium salts by solid phase extraction, the water phase was lyophilized again and ^{1}H NMR spectrum was recorded of the crude reaction mixture. The ratio of starting material to product was determined as 1:1. Purification by preparative HPLC (solvents A (water 0.1% formic acid) and B (acetonitrile, 0.1% formic acid): from 5 to 50% B at 35 min and to 100% B at 55 min, followed by a wash and re-equilibration step (total run time was 61 min), led to **16** as white powder.

Conditions B (Scheme 2): Dipeptide AcHN-Tyr-Lys-OMe (5.2 µmol, 2.5 mg) was dissolved in phosphate buffer (30.0 mg NaH_2PO_4, 35.8 mg Na_2HPO_4 in 0.55 mL deuterated water with diluted hydrochloric acid (2 M), pH 4-5) and under air atmosphere was added 4-fluorophenylazocarboxylate (25 µmol) (synthesized as described in ref. 26a) in a acetonitrile-d_3-deuterated water solution (150 µL / 50 µL) over 60 minutes. ^{1}H NMR spectrum was recorded from the crude reaction mixture. The ratio of starting material to product was determined as 6.3:1.

^{1}H NMR (600 MHz, CD_3OD): δ (ppm) = 1.42-1.49 (m, 2 H), 1.58-1.72 (m, 3 H), 1.84-1.89 (m, 1 H), 1.92 (s, 3 H), 2.84-2.91 (m, 3 H), 3.02 (dd, *J* = 6.5 Hz, *J* = 13.9 Hz, 1 H), 3.63 (s, 3 H), 4.44 (dd, *J* = 4.7 Hz, *J* = 9.7 Hz, 1 H), 4.50 (dd, *J* = 6.6 Hz, *J* = 8.5 Hz, 1 H), 6.81 (d, *J* = 8.2 Hz, 1 H), 7.04 (dd, *J* = 2.3 Hz, *J* = 8.3 Hz, 1 H) 7.09 (t, J_{HF} = 8.9 Hz, *J* = 8.9 Hz, 2 H), 7.15 (d, *J* = 2.2 Hz, 1 H), 7.56 (dd, J_{HF} = 5.5 Hz, *J* = 8.9 Hz, 2 H); LC-MS (ESI) *m/z*: 460.25 $[M+H]^+$. HRMS (ESI) calcd. for $C_{24}H_{30}FN_3O_5$ $[M+H]^+$ 460.2242, found: 460.2242.

H_2N-Arg-Arg-Pro-(3-(4-fluorophenyl)-Tyr)-Ile-Leu-OH **19** (Table 3)

To a solution of NT(8-13) triformiate (**18**) (10.5 µmol, 10.4 mg) in water (1 mL) titanium(III) chloride (92.0 µmol, 69.2 µL, in 2 M hydrochloric acid, 1.33 mmol/mL) was added. Under argon atmosphere at 30° C the 4-fluorophenyldiazonium chloride solution (0.2 M, 48.0 µmol, 240 µL) was added over 20 minutes and the reaction mixture was stirred for further 25 minutes. The reaction mixture was washed with diethyl ether (3 × 2.5 mL) and the water phase was lyophilized. After removal of titanium salts by solid phase extraction, the water phase was

lyophilized again and ^{1}H NMR spectrum was recorded. The ratio of **18** to **19** is determined to 1.3:1. Purification of the crude reaction mixture was done by preparative HPLC (solvents A (water 0.1% trifluoroacetic acid) and B (acetonitrile, 0.1% trifluoroacetic acid): from 5 to 50% B at 70 min and to 100% B at 90 min, followed by a wash and re-equilibration step (total run time was 106 min). Characteristic ^{1}H NMR signals (600 MHz, CD_3OD): δ (ppm) = 6.81 (d, J = 8.2 Hz, 1 H), 7.04 (dd, J = 2.2 Hz, J = 8.2 Hz, 1 H) 7.10 (t, J_{HF} = 8.8 Hz, J = 8.8 Hz, 2 H), 7.15 (d, J = 2.2 Hz, 1 H), 7.58 (dd, J_{HF} = 5.5 Hz, J = 8.8 Hz, 2 H); LC-MS (ESI) *m/z*: 911.74 $[M+H]^+$. HRMS (ESI) calcd. for $C_{44}H_{67}FN_{12}O_8$ $[M+H]^+$ 911.5262, found: 911.5262; calcd. for $C_{44}H_{67}FN_{12}O_8$ $[M+2H]^+$ 456.2667, found: 456.2667.

H_2N-Arg-Arg-Pro-(3-(3-bromophenyl)-Tyr)-Ile-Leu-OH **20** (Figure 2)

A degassed solution of 3-bromoaniline (10.0 mmol, 1.09 mL) in hydrochloric acid (3 N, 10 mL) and water (10 mL) was treated at 0 °C with a degassed solution of sodium nitrite (10.0 mmol, 0.69 g) in water (5 mL) by dropwise addition over a period of 20 minutes, followed by additional stirring for 30 minutes at 0 °C. The mixture is diluted with further hydrochloric acid (3 N, 10 mL) and water (15 mL) for a final concentration of (0.2 M (10 mmol / 50 mL)).

To a solution of NT(8-13) triformiate (**18**) (5.3 µmol, 5.0 mg) in water (1 mL) titanium(III) chloride (48.0 µmol, 36.0 µL, in 2 M hydrochloric acid, 1.33 mmol/mL) was added. Under argon atmosphere at 30° C the 3-bromophenyldiazonium chloride solution (0.2 M, 24.0 µmol, 120 µL) was added over 20 minutes and the reaction mixture was stirred for further 25 minutes. The reaction mixture was washed with diethyl ether (3 × 2.5 mL) and the water phase was lyophilized. After removal of titan residues by solid phase extraction, the water phase was lyophilized again and ^{1}H NMR spectrum was recorded. The ratio of **18** to **20** is determined to 1.5:1. Purification of the crude reaction mixture was done by preparative HPLC (solvents A (water 0.1% trifluoroacetic acid) and B (acetonitrile, 0.1% trifluoroacetic acid): from 5 to 50% B at 70 min and to 100% B at 90 min, followed by a wash and re-equilibration step (total run time was 106 min). LC-MS (ESI) *m/z*: 973.01 $[(^{81}Br)M+H]^+$; HRMS (ESI) calcd. for $C_{44}H_{67}{}^{79}BrN_{12}O_8$ $[M+H]^+$ 971.4461, found: 973.4451, calcd. for $C_{44}H_{67}{}^{79}BrN_{12}O_8$ $[M+2H]^+$ 486.2267, found 487.2262.

H_2N-(3-(4-fluorophenyl)-Tyr)-Gly-Gly-Phe-Leu-OH **21** (Figure 2)

To a solution of Leu-enkephalin (72.0 µmol, 40.0 mg) in water (2 mL) titanium(III) chloride (396 µmol, 396 µL in 3 M hydrochloric acid, 1.0 mmol/mL) was added. Under argon atmosphere at 30° C the 4-fluorophenyldiazonium chloride solution (0.2 M, 216 µmol, 1.08 mL) was added over 20 minutes and the reaction mixture was stirred for further 25 minutes. The reaction mixture was washed with diethyl ether (3 × 2.5 mL) and the water phase was lyophilized. After removal of titanium salts by solid phase extraction, the water phase was lyophilized again and ^{1}H NMR spectrum was recorded. The ratio of Leu-enkephalin to **21** was determined to 3:1. Purification of the crude reaction mixture was done by preparative HPLC (solvents A (water 0.1% trifluoroacetic acid) and B (acetonitrile, 0.1% trifluoroacetic acid): from 10 to 50% B at 70 min and to 100% B at 90 min, followed by a wash and re-equilibration step (total run time was 106 min). Characteristic ^{1}H NMR signals (600 MHz, CD_3OD): δ (ppm) = 6.90 (d, J = 7.7 Hz, 1 H), 7.09-7.13 (m, 3 H), 7.17-7.22 (m, 2 H), 7.24-7.30 (m, 4 H), 7.58 (dd, J_{HF} = 5.7 Hz, J = 7.8 Hz, 2 H); HRMS (ESI) calcd. for $C_{34}H_{40}FN_5O_7$ $[M+H]^+$ 650.2985, found: 650.2985, calcd. for $C_{34}H_{40}FN_5O_7$ $[M+Na]^+$ 672.2804, found: 672.2804.

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Supplementary data

^{1}H NMR spectra of compounds **6, 9, 14** and **16**, ^{13}C NMR spectra of compounds **6**, **9** and **14**, HPLC chromatograms of compounds **16** and **19-21**, UHPLC chromatograms of compounds **16** and **19-21**, and product ion (tandem) mass spectra of compounds **19-21** are available as Supporting Information.

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