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Solid-Phase Synthesis of a Pepticinnamin E Library

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Abstract—Pepticinnamin E is a naturally occurring bisubstrate inhibitor of farnesyltransferase. Based on the structure of the natural product, a compound library was synthesized by variation of eight structural parameters. Following three different routes, a total of 51 analogues was synthesized on the polymeric support in 6–11-step parallel syntheses. Overall yields ranged from 3 to 63%, and the compounds were obtained with >90% purity.

Introduction

Proteins with intrinsic GTPase-activity are involved in a multitude of important biological processes like signal transduction and vesicular trafficking. The biological function often critically depends on the post-translational modification of these proteins with lipid residues. A prime example are the Ras proteins which serve as molecular switches in growth-factor mediated mitogenic signalling events. The crucial biological role of the Ras proteins is highlighted by the fact that mutations in the Ras genes are found in approximately 30% of all human tumours.[1,2]

Oncogenic Ras only serves as a molecular switch for the transduction of growth signals if the Ras is *S*-farnesylated at the C-terminus and if located at the plasma membrane. Thus, inhibitors of the enzyme protein farnesyltransferase (PFT), which catalyzes the transfer of a farnesyl residue from farnesylpyrophosphate (FPP) to the cysteine embedded in a C-terminal CAAX amino acid sequence occurring in non-matured Ras (Scheme 1), are of particular interest as new antitumor therapeutic agents. However, despite the fact that several PFT-inhibitors are in advanced clinical trials, some of the most important and fundamental aspects of this application of the signal transduction therapy[3] remain unclear. The crucial substrate of PFT, the farnesylation of which is suppressed by these compounds, is still unknown.[2] In this context, inhibitors which induce apoptosis (i.e., programmed cell death), and which are bisubstrate inhibitors of the PFT, are of particular interest.[2,4]

To investigate these biological questions in a focussed but flexible manner, a class of potential PFT inhibitors are required, the structure of which can be varied rapidly and efficiently by combinatorial solid-phase synthesis. This approach should furnish inhibitors which are competitive to the protein substrate, to the farnesylpyrophosphate, or even to both substrates, as well as substances which induce apoptosis in Ras-transformed cells but not in the untransformed wild cells.

In this article we report on the solid-phase synthesis of a library of potential PFT-inhibitors that is based on the structure of a naturally occurring bisubstrate inhibitor.[5a] In the accompanying paper, the biological investigation of the compound collection and the delineation of a structure–activity relationship are described.[5b]

Results and Discussion

Starting point for the synthesis of a library of potential farnesyltransferase inhibitors was pepticinnamin E **1**, a naturally occurring bisubstrate inhibitor of the enzyme.[6] The peptidic natural product is composed of five building blocks (Fig. 1). The central tripeptide embodies three aromatic amino acids. Tyrosine **4** is *D*-configured while DOPA-derivative **6** and phenylalanine **5** are *N*-methylated. A lipophilic cinnamic acid derivative **2** is

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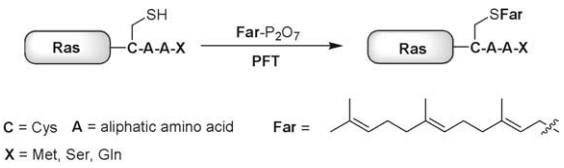


Scheme 1. Farnesylation of Ras-proteins by protein farnesyltransferase (PFT).

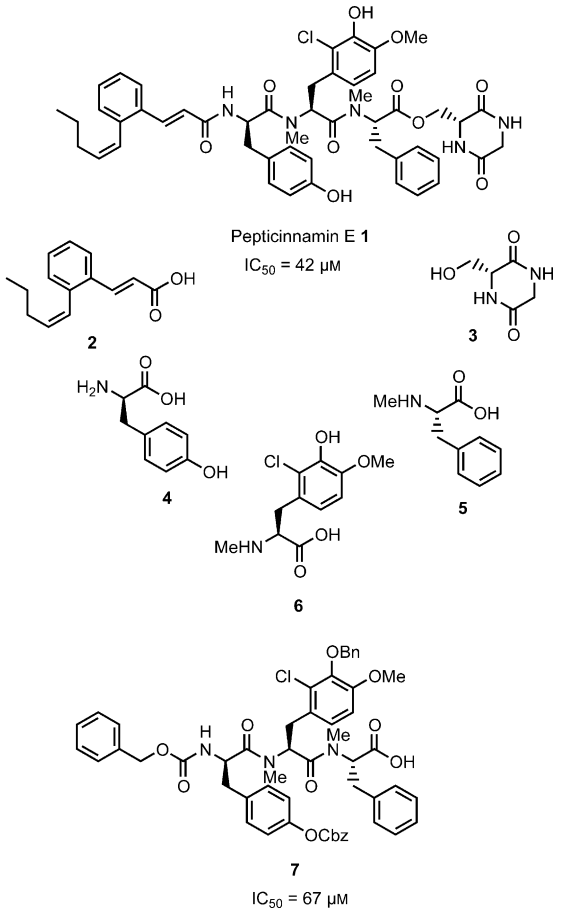


Figure 1. Structure of the farnesyltransferase-inhibitor pepticinnamin E and its components.

attached to the N-terminus of the tripeptide, and the C-terminus is esterified with a diketopiperazine via the side chain alcohol of a serine incorporated into this heterocycle.

It is prudent to speculate that lipophilic structural unit **2** occupies the farnesylpyrophosphate binding site of farnesyltransferase, and that building blocks **3**–**6** imitate the CAAX recognition sequence of the Ras protein (compare Scheme 1).[1,7] In this respect, it should be noted that *N*-acylated tripeptide **7**, an intermediate in the synthesis of pepticinnamin E, displays an inhibitory activity that is similar to the potency of the natural product (Fig. 1).

In the total synthesis of pepticinnamin E[7] first the core tripeptide had to be built up followed by attachment of the pentenylcinnamic acid and the diketopiperazine. Drawing from this successfully realized strategy, a library of pepticinnamin E analogues was developed by

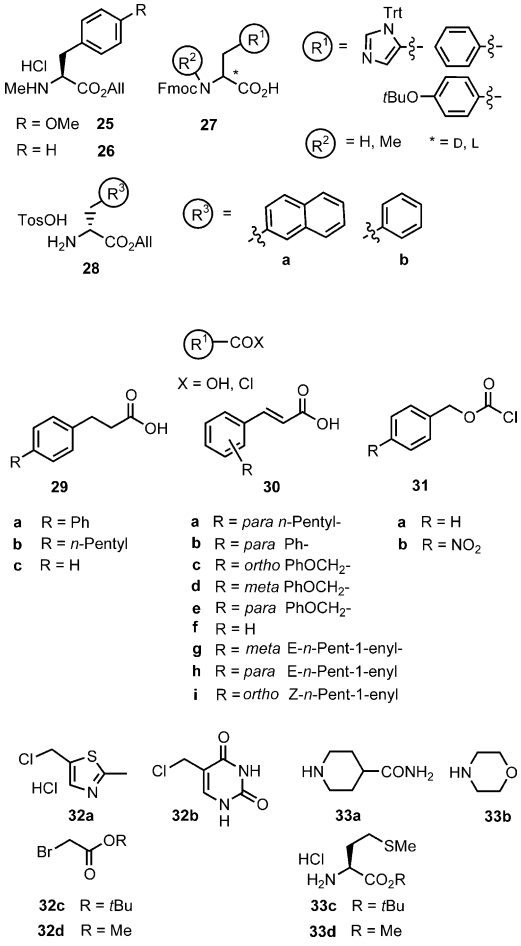
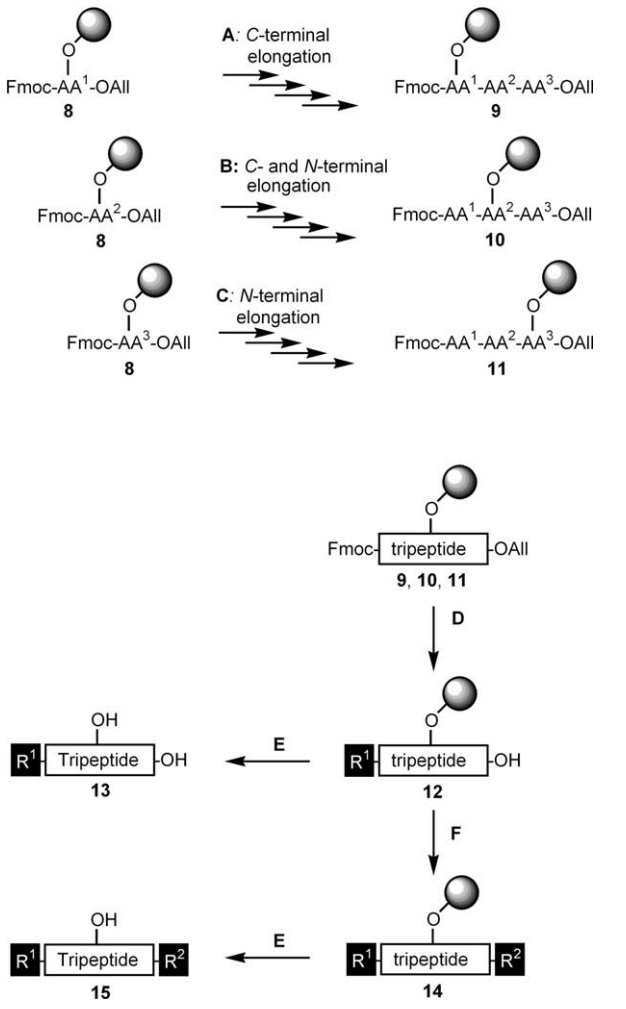
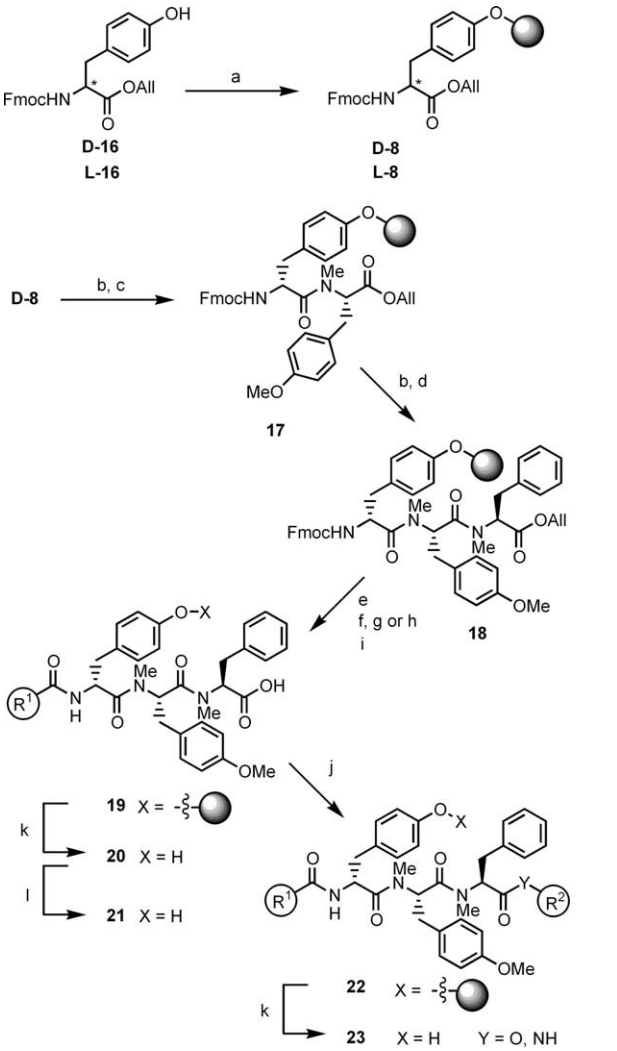


Figure 2. Building blocks used for the solid phase synthesis.

variation of the structure of all five building blocks (Fig. 2). In particular, the lipophilic N-terminal group, the amino acid side chains and the polar C-terminus, as well as the degree of *N*-methylation were varied. To this end, it was planned to attach the first amino acid to a polymeric carrier via the aromatic hydroxyl group of a tyrosine (Scheme 2). Depending on the amino acid chosen for resin attachment the subsequent chain elongation should proceed in C-terminal-, N-terminal- or alternating C- and N-terminal direction (routes A, B and C, see Scheme 2). Different immobilized tripeptide intermediates **9**, **10** and **11** formed thereby would then be deprotected at their N-termini followed by attachment of lipophilic carboxylic acids and liberation of the C-terminus (step D, Scheme 2). Release of acylated tripeptides **13** from the polymeric carrier would give a set of compounds analogous to chain-shortened farnesyltransferase inhibitor **7** (step E, Scheme 2). Coupling of polymer-bound intermediate **12** to polar building blocks would yield immobilized esters and amides **14**. These ultimately would be released to deliver analogues **15** of pepticinnamin E mimicking all building blocks incorporated in the natural product (step E, Scheme 2). From a preparative point of view the coupling of the sterically demanding *N*-methylated amino acids which additionally are prone to racemization and side reactions[8] was considered particularly challenging. Also, efficient acylation reactions with acrylic acid derivatives often is



Scheme 2. Planned synthesis of a pepticinnamin E library.



Scheme 3. (a) DEAD, PPh_3, THF, 0 °C, 1 h, rt, 12 h, loading-level: 0.40–0.53 mmol g^{-1}, 53–59%; (b) $Pd(PPh_3)_4$, $PhSiH_3$ or NMA, THF, 24 h; (c) **25**, HATU, HOAt, *i*PrNEt$_2$, NMP; 48 h; (d) **26**, PyAOP, HOAt, *i*PrNEt$_2$, NMP; 48 h; (e) piperidine/DMF 1/4, 10–40 min; (f) **29**, HATU, HOAt, *i*PrNEt$_2$, NMP, 12–24 h; (g) **30**, PyAOP, DMAP, *i*PrNEt$_2$, CH_2Cl_2/DMF 1/2, 12–17 h; (h) **31**, HOAt, DMAP, *i*PrNEt$_2$, CH_2Cl_2/DMF 2/1, 7–20 h; (i) $Pd(PPh_3)_4$, morpholine, THF, 4 h; (j) **33**, PyAOP, *i*PrNEt$_2$, NMP, 16 h (Y = NH); (h) Cs_2CO_3, KI, **32**, DMF, 24 h, rt (X = Br) or 24–48 h, 50 °C (X = Cl) (Y = O); (l) TFA/H_2O 95/5, 4–24 h; (m) 10% Pd/C, H_2, MeOH, 8 h.

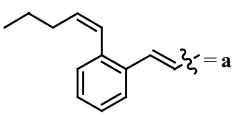
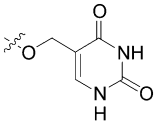
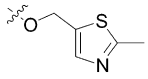
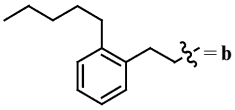
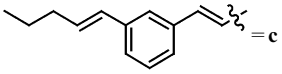
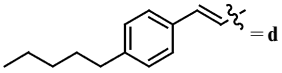
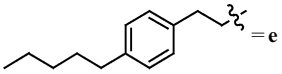
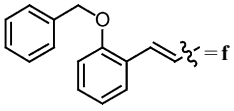
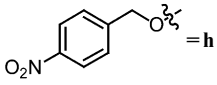
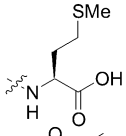
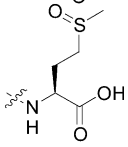
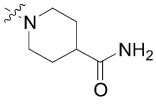
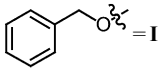
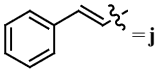
accompanied by unwanted side reactions and complications.[9] As polymeric carrier, the Wang resin was chosen which embodies an acid-labile linking group. The base-labile Fmoc-urethane was employed for temporary masking of the N-terminus, and the C-terminus of the intermediates was protected as palladium^0 (Pd^0)-sensitive allyl ester. These three types of blocking groups are orthogonally stable to each other.

C-Terminal elongation of the peptide chain (route A)

Orthogonally protected tyrosine building blocks **16** were attached to the Wang resin by means of a Mitsunobu reaction[10] with loading loading levels of 0.4–0.53 mmol g^{-1} (54–59%; determined with the Fmoc method[11]).

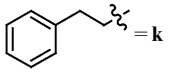
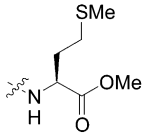
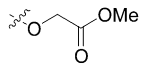
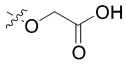
For the synthesis of tripeptide **18** by C-terminal elongation the allyl ester was removed from **D-8** by Pd^0-catalyzed allyl transfer to phenylsilane or *N*-methylaniline as trapping nucleophiles. Attachment of *N*-methylated building block **25** could then successfully be achieved by employing HATU as highly reactive coupling reagent. In contrast, further chain elongation with building block **26** to give tripeptide **18** turned out to be problematic. After cleavage of the allyl ester application of numerous coupling reagents including HATU, TFFH and PyBroP resulted in incomplete conversion and substantial racemization (Scheme 3). The best results were obtained with PyAOP resulting in 89% conversion and 7% epimerization of the activated amino acids. Double coupling led to an increase of yield to 94% accompanied with 9% racemization. These findings are not unexpected. It has been reported previously that efficient coupling of sterically demanding *N*-methylated amino acids requires particular coupling reagents and conditions,[8] in particular on the solid phase. Also, the C-terminal chain elongation of peptides frequently is accompanied by epimerization,[12,13] and *N*-methylated amino acids are also known to be prone to racemization.[14] In the light of these findings the results recorded in the synthesis of solid-phase bound *N*-methylated tripeptide **18** can be regarded as fairly satisfying.

Table 1. Results for the synthesis of pepticinnamin E analogues via route A

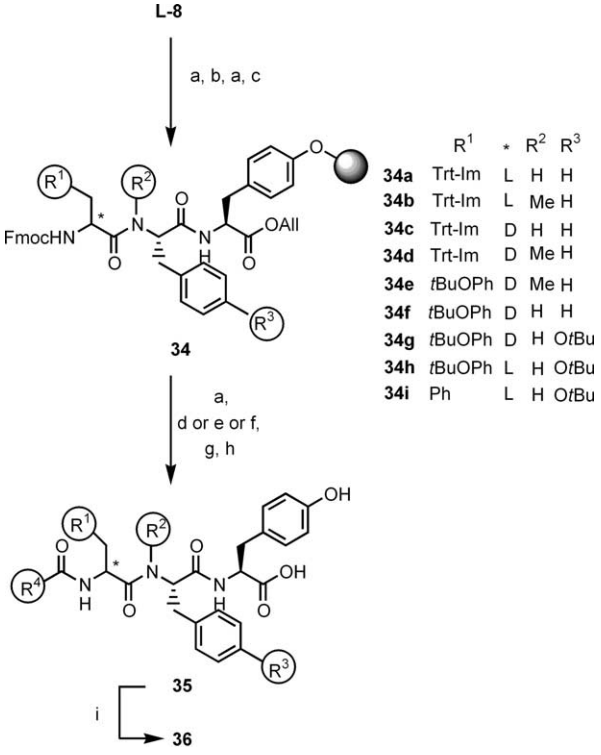
Entry	Compd	R^1	Y–R^2	Yield (yield/step) (%)	Purity
1	**23/1**	 = **a**		14 (80)	>95
2	**23/2**	**a**		10 (77)	>95
3	**20/1**	**a**	–OH	12 (76)	>95
4	**21**	 = **b**	–OH	14 (78)	>95
5	**20/2**	 = **c**	–OH	13 (77)	>95
8	**20/3**	 = **d**	–OH	13 (77)	95
10	**20/4**	 = **e**	–OH	18 (81)	>95
12	**20/5**	 = **f**	–OH	10 (75)	>95
13	**20/6**	Fm = **g**	–OH	11 (76)	>95
14	**23/4**	 = **h**		10 (77)	>95
15	**23/5**	**h**		5 (72)	>95
16	**23/6**	**h**		13 (78)	60
17	**20/7**	**h**	–OH	5 (69)	>95
18	**20/8**	 = **I**	–OH	13 (77)	>95
19	**20/9**	 = **j**	–OH	13 (77)	>95

(*continued on next page*)

Table 1 (*continued*)

Entry	Compd	R^1	$Y-R^2$	Yield (yield/step) (%)	Purity
20	**23/7**	 = **k**		8 (76)	91
21	**23/8**	**k**		28 (87)	>95
22	**23/9**	**k**		40 (90)	>95
23	**23/10**	**k**	–OAll	31 (85)	>95
24	**20/10**	**k**	–OH	36 (88)	95

In the next step of the synthesis, the Fmoc-urethane was cleaved under basic conditions and cinnamic and hydrocinnamic acid derivatives **30** and **29** as well as chloroformic acid esters **31** were attached to the N-terminus. While the coupling reactions with **29** and **31** proceeded smoothly in the presence of HATU/HOAt and DMAP/HOAt, respectively, efficient activation of the unsaturated acids **30** could only be achieved with PyAOP/DMAP. Subsequent liberation of the C-terminus by Pd^0-mediated allyl transfer to morpholine yielded resin-bound tripeptides **19**, which were then released from the solid support by repeated treatment with trifluoroacetic acid/H_2O 95/5. Under these conditions, the use of additional scavenging reagents was not necessary.[15] After purification by HPLC, tripeptides **20**, which can be regarded as analogues to compound **7**, were obtained with >95% purity and acceptable overall yields. Hydrogenation of the double bonds incorporated into the *N*-acyl substituents yielded further analogues with saturated carbon chains.



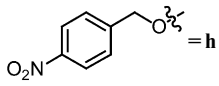
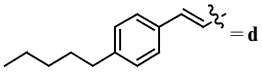
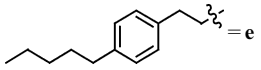
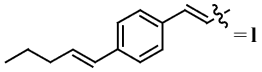
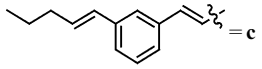
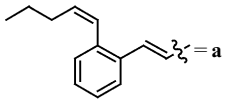
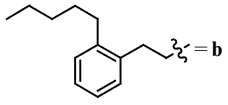
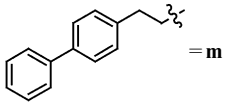
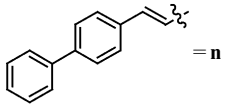
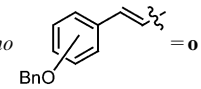
Scheme 4. (a) Piperidine/DMF 1/4, 2×5 min or 2×20 min; (b) **27**, HATU, *i*PrNEt$_2$, NMP, 2.5 h; (c) **27**, HATU, *i*PrNEt$_2$, NMP or DIC, HOAt, DMF, 14 h; (d) **29**, HATU, HOAt, *i*PrNEt$_2$, NMP, 12–24 h; (e) **30**, PyAOP, DMAP, *i*PrNEt$_2$, CH_2Cl_2/DMF 2/1, 12–24 h; (f) **31**, HOAt, DMAP, *i*PrNEt$_2$, CH_2Cl_2/DMF 2/1, 7–10 h; (g) Pd(PPh$_3$)$_4$, morpholine, THF, 4–16 h; (h) TFA/H_2O 95/5, 4–5 h; (i) 10% Pd/C, H_2, dioxane, 8 h.

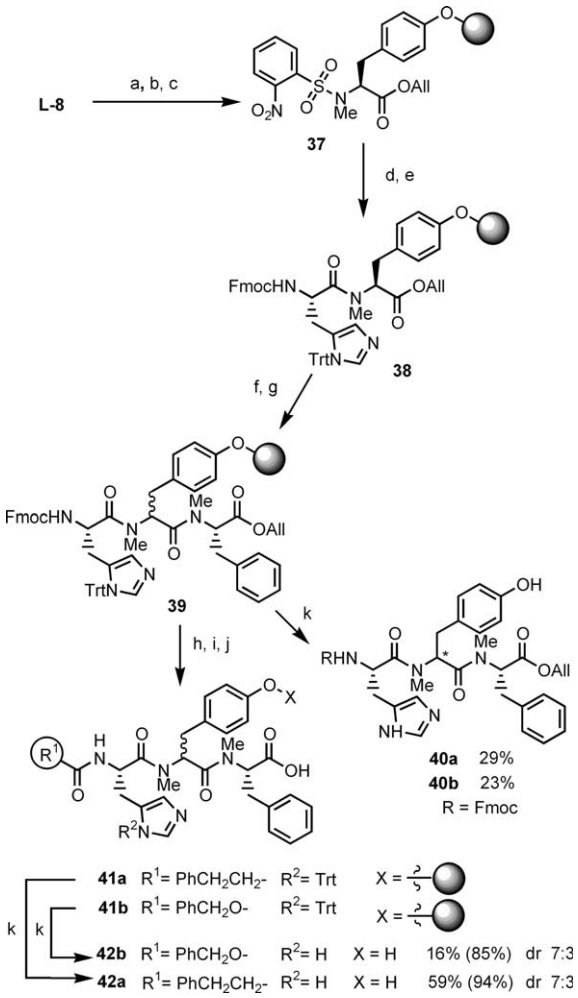
Furthermore, polymer-bound carboxylic acids **19** were converted to amides **22** by activation with PyAOP. Coupling to primary amino acids **33** proceeded efficiently under these conditions without any epimerization. In addition, conversion of the carboxylic acids to the cesium salts followed by alkylation with alkyl halides **32** yielded C-terminal esters. Compounds **23** (see Table 1) were finally released from the resin under the conditions described above.

N-Terminal elongation of the peptide chain (route C)

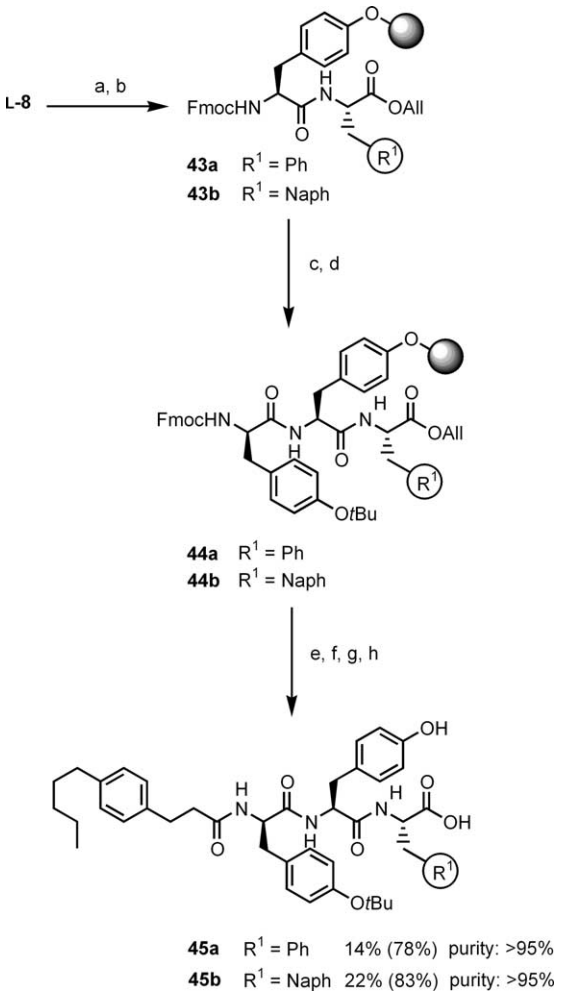
As an alternative, the C-terminal amino acid was employed for attachment to the resin, and the peptide chain was elongated in the N-terminal direction via sequential Fmoc-deprotection and coupling steps (Scheme 4). Monitoring the reactions with the ninhydrin test[15,16] and examination of tripeptides **34** by HPLC revealed that the couplings proceeded with high yield and without racemization. If histidine was attached to the peptide, the couplings were carried out with diisopropyl carbodiimide (DIC) and HOAt, since histidine derivatives are prone to racemization under basic conditions.

Table 2. Results for the synthesis of pepticinnamin E analogues via route C

Entry	Compd	R^1	R^2	*	R^3	R^4	Yield (per step) (%)	Purity
1	**35/1**	 = **i**	HOPh–	D	Me	H	14 (78)	78
2	**35/2**	**i**	HOPh–	D	H	H	18 (81)	>95
3	**35/3**	**i**	HOPh–	D	H	OH	21 (82)	>95
4	**35/4**	**i**	HOPh–	L	H	OH	31 (86)	>95
5	**35/5**	**i**	Ph–	L	H	H	18 (81)	>95
6	**35/6**	**i**	Imid	L	H	H	24 (84)	95
7	**35/7**	**i**	Imid	L	Me	H	24 (84)	85
8	**35/8**	**i**	Imid	D	Me	H	24 (84)	>95
9	**35/9**	 = **h**	Imid	D	H	H	58 (81)	>95
10	**35/10**	 = **d**	HOPh–	D	H	H	31 (86)	>95
11	**35/11**	**d**	Imid	D	H	H	15 (79)	95
12	**35/12**	 = **e**	Imid	D	H	H	24 (84)	>95
13	**35/13**	**e**	Imid	L	H	H	19 (81)	93
14	**35/14**	**e**	Imid	L	Me	H	30 (86)	>95
15	**35/15**	**e**	Imid	D	Me	H	24 (84)	>95
16	**35/16**	 = **l**	Imid	D	H	H	3 (65)	*E*/*Z*-mixt. 1:1
17	**35/17**	 = **c**	Imid	D	H	H	13 (77)	>95
18	**35/18**	 = **a**	Imid	D	H	H	38 (89)	90
19	**36**	 = **b**	Imid	D	H	H	30 (86)	95
20	**35/19**	 = **m**	Imid	D	H	H	34 (87)	>95
21	**35/20**	 = **n**	Imid	D	Me	H	21 (82)	*E*/*Z*-mixt. 1.7/1
22	**35/21**	*ortho*  = **o**	Imid	D	H	H	10 (75)	*E*/*Z*-mixt. 1/2.5
23	**35/22**	*ortho* **o**	Imid	L	H	H	13 (77)	89
24	**35/23**	*meta* **o**	Imid	L	H	H	21 (82)	91
25	**35/24**	*meta* **o**	Imid	D	H	H	28 (85)	*E*/*Z*-mixt. 1.7/1
26	**35/25**	*para* **o**	Imid	L	H	H	11 (76)	*E*/*Z*-mixt. 1.6/1
27	**35/26**	*para* **o**	Imid	D	H	H	10 (75)	>95



Scheme 5. (a) Piperidine/DMF 1/4, 215 min; (b) *o*-$NO_2C_6H_4SO_2Cl$, lutidine, CH_2Cl_2, 11 h; (c) *p*-NO_2PhSO_3Me, MTBD, DMF, 1.5 h, (d) DBU, 2-mercaptoethanol, DMF, 1 h; (e) Fmoc-l-His(Trt)OH, DIC, HOAt, lutidine, DMF, 24 h; (f) $Pd(PPh_3)_4$, NMA, THF; 24 h, (g) **26**, PyAOP, *i*PrNEt$_2$, NMP, 24 h; (h) **31**, DMAP, HOAt, *i*PrNEt$_2$, DMF/CH_2Cl_2, 8 h; (i) **29c**, HATU, HOAt, *i*PrNEt$_2$, NMP, 8 h; (j) $Pd(PPh_3)_4$, morpholine, THF, 24 h; (k) TFA/H_2O 95/5, 24 h.



Scheme 6. (a) $Pd(PPh_3)_4$, NMA, THF; (b) **26**, PyAOP, *i*PrNEt$_2$, NMP, 8 h; (c) piperidine/DMF 1/4, 2×5 min; (d) Fmoc-D-Tyr(*t*Bu)OH, HATU, *i*PrNEt$_2$, NMP, 14 h; (e) **29**, HATU, HOAt, *i*PrNEt$_2$, NMP, 12 h; (f) $Pd(PPh_3)_4$, morpholine, THF, 24 h. TFA/H_2O 95/5, 3.5 h.

After deprotection of the N-termini, they were acylated with cinnamic acids, hydrocinnamic acids and chloroformic acid esters, the C-terminal carboxylic acid was liberated and *N*-acylated tripeptides **35** were released from the polymeric carrier as described above. Hydrogenation yielded compounds **36** embodying a saturated acyl chain. The results of the synthesis are given in Table 2.

Surprisingly, in the products **35** with a *para*-pentenyl-, phenyl- and benzyloxy-substituted cinnamic acid substituent (Table 2, entries, 16, 21, 22, 25 and 26) *E*/*Z*-isomerization of the originally *E*-configured double bond occurred. This was proven by LC–MS and NMR analysis and comparison of the chemical shifts and coupling constants with literature data[17] for *E*- and *Z*-configured cinnamic acid amides. Such isomerizations of cinnamic acid derivatives have been observed before. They occur under the influence of light,[18] are favored when electron-donating substituents are present at the aromatic ring[17] and are promoted by Brønstedt and Lewis acids.[19]

N- and C-terminal elongation of the peptide chain (route B)

In the third approach, the central amino acid was linked to the solid support and *N*-methylated according to Miller et al.[20] (Scheme 5). After removal of the Fmoc group from tyrosine **L-8** the 1-nitrobenzenesulfonic acid amide was formed and the N–H proton was abstracted with a guanidine base. Treatment with methyl-*p*-nitrobenzenesulfonate yielded desired intermediate **37**. After removal of the sulfonamide blocking group a histidine building block was introduced under weakly basic conditions without recordable epimerization. Next the allyl ester was cleaved and the C-terminal amino acid was introduced. In the presence of PyAOP as coupling reagent, conversion was quantitative but two diastereomeric compounds were formed due to epimerization of the central amino acid upon activation. After cleavage from the solid support, isomers **40a** and **40b** could be separated by hplc. In addition, **39** was converted to *N*-acylated tripeptides **41a** and **41b** according to the methods described above, and isomers **42a** and **42b** were released from the solid support under acidic conditions.

Finally, peptides **45** were synthesized by reversal of the order of the chain extension steps, that is by elongating the peptide chain first in the C-terminal direction followed by acylation of the N-terminus. To this end, **L-8** was first converted to polymer-bound dipeptides **42** which then yielded access to tripeptide intermediates **44** (Scheme 6). Epimerization was not detected in any of the coupling steps. Compounds **44** were then converted into peptides **45** according to the methods described above.

Conclusion

Employing four different synthesis routes, a collection of 51 pepticinnamin E analogues was synthesized by variation of up to eight structural parameters. The syntheses proceeded in 6–11 steps on the polymeric support and yielded the desired compounds in 3–63% overall yield which corresponds to an average yield per step of 65–91% (in the majority of the cases >80% are reached). With a few exceptions, the compounds were obtained in quantities more than sufficient for subsequent biological evaluation and with >90% purity.

The library contains compounds with a structure that is close to the natural product itself (e.g., **23**/**1**) or which embody at least the twice *N*-methylated backbone of pepticinnamin E which may be prone to adopting a β-turn conformation (see Table 1). In addition, analogues were synthesized that carry only one *N*-methyl group (Table 2) and which should adopt a different conformation. Furthermore, several compounds embody a histidine as N-terminal amino acid. Its imidazole group may serve as a good ligand for the Zn^{2t} in the active site of farnesyltransferase.

The synthesized compounds were investigated in different enzymatic farnesyltransferase assays and in cell-assays with Ras-transformed cancer cell lines. The results of these investigations and the delineation of a structure–activity relationship are described in the accompanying paper.[5b]

Experimental

General

All melting points were determined using a Büchi 530 or a Büchi B 540 apparatus and are uncorrected. Optical rotations $[\alpha]_D^{20}$ were measured with a Perkin–Elmer polarimeter 241 or 341. TLC was performed on Kieselgel $60F_{254}$ (Merck). Column chromatography is referred to flash chromatography and was performed on silica gel (230–400 mesh). IR spectra were recorded on a Bruker IFS 88 Fourier-Transform-IR-spektrometer. Elemental analyses were measured with an Elementar CHN-Rapid Analysator. NMR spectra were recorded with Bruker AC 250, Bruker AM 400, Varian Mercury 400 and Bruker DRX 500. The signal of the residual protonated solvent ($CDCl_3$ or CD_3OD) was taken as reference [^{1}H: δ, 7.24 ($CHCl_3$) or 3.31 (CH_3OH), ^{13}C: δ, 77.0 ($CHCl_3$) or 49.0 (CH_3OH)]. Values in square brackets indicate rotamers. Mass spectra were recorded on the following spectrometers: EI = Finnigan MAT MS70, FAB = Finnigan MAT MS 70 (3-nitrobenzylalcohol (NBA) as matrix), MALDI-TOF = Perseptive Biosystems Voyager BioSpectrometry Workstation or Voyager-DE Pro BioSpectrometry™ Workstation (2.5 dihydroxybenzoic acid (DHB) as matrix), ESI = Finnigan Thermoquest LCQ (ESI 1) or Waters ZMD 2000 (ESI 2). If not indicated otherwise, the ESI-mass spectrometers were coupled with analytical HPLC-systems: ESI-1, coupled with HP Modell 1100/Hewlett Packard; column: VP 50/10 Nucleosil C18PPN/ Macherey-Nagel, 100×5 mm, 5-μm particle size; detection: 210, 220, 254 and 305 nm; flow rate: 1 mL/min eluent gradient ($CH_3CN/H_2O/HCO_2H$): A: 45/55/0.1 to 90/10/0.1 in 30 min; B: 20/80/0.1 to 90/10/0.1 in 30 min. ESI 2, coupled with Waters 2790 with 996 DAD-Detector, column: RPC18 Synergy MAX, 50×2 mm, 3.5-μm particle size/ Phenomenex, detection: 254 nm; flow rate: 1.1 mL/min; eluent-gradient: ($CH_3CN/H_2O/HCO_2H$): 2.5/97.5/ 0.05%, to 97.5/2.5/0.05% in 4 min. For analytical HPLC was used HP Modell 1100/Hewlett Packard; column: VP 50/10 Nucleosil C18PPN/Macherey-Nagel, 100×5 mm, 5-μm particle size, detection: 210, 220, 254 and 305 nm; flow rate: 1 mL/min; eluent gradients are indicated for the appropriate compound. For preparative HPLC a Pro Star 215/Varian with Varian detector model 340 was used, column: VP 250/21 Nucleosil C18PPN, 100×5 mm, 5 μm particle size/Macherey–Nagel, detection: 210 or 305 nm; flow rate: 10 mL/min; eluent-gradient: (CH_3CN/H_2O/TFA): 20/80/0.05% to 80/20/ 0.05%, 30 min; The used Wang resin (100–200 mesh, 1% DVB) was supplied by Novabiochem and Advanced ChemTech. The solid-phase synthesis of the compounds **6** were performed on an Argonaut Technologies Quest-210-Synthesizer.

Compound **16** was synthesized by azeotropic esterification[21] of tyrosine, followed by standard Fmoc-protection under Schotten–Baumann conditions.

Compound **30i** was synthesized as published before.[6] Cinnamic acid derivatives **30a**–**h** were synthesized by standard knoevenagel-condensation starting from the commercial aldehydes. Hydrogenation of **30a**, **30b** and **30f** furnished the hydrocinnamic acids **29a**–**c**.

Amino acid allyl esters **28a** and **28b** were synthesized by azeotropic esterification according to standard procedures.[21]

3-(2-Naphthyl)-L-alanine allyl ester hydrotosylate (28b). Yield 96%; brownish solid, R_f = 0.28 [ethyl acetate/ cyclohexane 2/1, 2% NEt_3 (v/v)]; HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–90/10/0.1 in 40 min, 50 °C): R_t = 9.83 min; mp: 188 °C; $[\alpha]_D^{20}$ −4.9 (*c* 0.51, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 2.37 (s, 3H), 3.38–3.46 (d, ^3J = 6.8 Hz, 2H), 4.46 (t, ^3J = 6.8 Hz, 1H), 4.68–4.70 (m, 2H), 5.19–5.30 (m, 2H), 5.81-5.88 (m, 1H), 7.24 (d, ^3J = 8.4 Hz, 2H), 7.38–7.41 (m, 1H), 7.49–7.52 (m, 2H), 7.71–7.76 (m., 1H), 7.72 (d, ^3J = 8.2 Hz, 2H), 7.83–7.90 (m, 3H); ^{13}C NMR (100.6 MHz, CD_3OD): δ 21.30, 37.56, 55.11, 67.84,

119.80, 126.91, 127.15, 127.38, 127.94, 128.63, 128.71, 129.60, 129.82, 132.29, 132.69, 134.21, 134.89, 141.72, 143.35, 169.71; MS (EI, 70 eV, *m/z*): 255 (M^+); HRMS (FAB): calcd for $C_{16}H_{18}O_2$ $[M+H]^+$ 256.1338; found: 256.1361.

The *N*-methylated amino acid building blocks **25** and **26** were synthesized in three steps starting from the appropriate Boc-protected amino acids by *N*-methylation,[22] alkylation of the carboxylic function by allylbromide[23] and standard Boc cleavage by HCl in Et_2O.

***N*,*O*-Dimethyl-L-tyrosine allyl ester hydrochloride (25).** Overall yield (three steps): 84%, white solid; $R_f=0.25$ [ethyl acetate/cyclohexane 3/1, 1% NEt_3 (v/v)]; mp: 107 °C; $[\alpha]_D^{20}$ +9.4 (*c* 0.5, MeOH); ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.77 (s, 3H, NCH_3), 3.28–3.37 (m, 1H), 3.53–3.61 (m, 1H), 3.76 (s, 3H), 4.05 (m, 1H), 4.57 (d, $^3J=5.9$ Hz, 2H), 5.19–5.26 (m, 2H), 5.66–5.82 (m, 1H), 6.82 (d, $^3J=8.4$ Hz, 2H), 7.20 (d, $J=8.4$ Hz, 2H), 9.59 (bs, 1H), 10.53 (bs, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 32.10, 35.08, 55.22, 62.67, 66.91, 114.24, 119.92, 125.87, 130.44, 130.53, 159.05, 167.46; IR (KBr): 3476, 3003, 2913, 2839, 2698, 2449, 1745, 1653, 1605, 1575, 1465, 1453, 1397, 1252; MS (EI, 70 eV, *m/z*): 249 (2) [M^+-HCl], 164 (35) [$M^+-HCl-CO_2-C_3H_5$], 128 (100) [$M^+-NCH_3-OCH_2-OC_3H_5$], 121 (23) [$CH_2C_6H_4OCH_3^+$], 82 (5) [$2\times C_4H_{10}^+$], 41 (11) [$C_3H_5^+$]; anal. calcd for $C_{14}H_{30}ClNO_3$ (285.77): C 58.84, H 7.05, N 4.90; found: C 59.00, H 6.93, N 4.78.

***N*-Methyl-L-phenylalanine allyl ester hydrochloride (26).** Overall yield (three steps): 79%, white solid; $R_f=0.27$ [ethyl acetate/cyclohexane 3/1, 1% NEt_3 (v/v)]; mp: 111–112 °C; $[\alpha]_D^{20}$ −17.2 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.78 (s, 3H), 3.32–3.42 (m, 1H), 3.62–3.69 (m, 1H), 4.09 (m, 1H), 4.55 (d, $^3J=6.0$ Hz, 2H), 5.15–5.21 (m, 2H), 5.61–5.77 (m, 1H), 7.21–7.34 (m, 5H), 9.81 (s, 1H), 10.61 (br. s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 31.94, 35.85, 62.45, 66.85, 119.84, 127.63, 128.84, 129.31, 130.46, 134.13, 167.41; IR (KBr): 3494, 2936, 2737, 2698, 2424, 1755, 1653, 1605, 1575, 1472 (CH), 1456 (CH), 1397 (CH_3), 1264; MS (FAB, *m/z*): 219.969 $[M+H]^+$; anal calcd for $C_{13}H_{18}ClNO_2$ (255.74): C 61.05, H 7.09, N 5.48; found: C 61.11, H 6.96, N 5.45.

3-(3-(1-*E*-*n*-Pentenyl)phenyl)-*E*-acrylic acid (30g). A solution of 3-bromobenzaldehyde (117 μL, 1.0 mmol), pent-1-enylboronic acid[24] (137 mg, 1.2 mmol), CsF (365 mg, 2.4 mmol) and $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) in 4 mL degassed DME was stirred at 100 °C for 14 h under argon atmosphere. After cooling to room temperature water was added and the aqueous phase was extracted with ethyl acetate. After drying of the organic phases over $MgSO_4$ the solvent was evaporated in vacuo. To the residue was added a solution of malonic acid (125 mg, 1.2 mmol) and piperidine (9.9 μL, 0.1 mmol) in 1 mL pyridine and the reaction mixture was stirred at 100 °C for 6 h. Then a mixture of ice and concentrated HCl were added. The aqueous phase was extracted with Et_2O, the combined organic phases were dried over $MgSO_4$. After concentration in vacuo chromatography on silica gel [ethyl acetate/cyclohexane 1/2, 1% HOAc (v/v) afforded **30g** (140 mg, 65%) as yellowish solid; $R_f=0.40$ (ethyl acetate/cyclohexane 1/1, 1% HOAc (v/v)]; HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C): $R_t=10.72$ min; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (t, $^3J=7.2$ Hz, 3H), 1.55 (m, 2H), 2.24 (m, 2H), 6.27–6.33 (m, 1H), 6.40 (d, $^3J_{trans}=15.8$ Hz, 1H), 6.48 (d, $^3J_{trans}=16.0$, 1H), 7.37–7.40 (m, 2H), 7.50 (s, 1H), 7.34 (d, $^3J=7.6$ Hz, 1H), 7.80 (d, $^3J_{trans}=16.0$ Hz, 1H), 12.40 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.03, 22.72, 35.38, 117.64, 126.24, 126.89, 128.44, 129.28, 129.37, 132.42, 134.47, 138.91, 147.39, 173.08; MS (ESI-1): 215.1 $[M-H]^-$; HRMS (FAB, *m/z*): calcd for $C_{14}H_{17}O_2$ $[M+H]^+$: 217.1229, found: 217.1256.

3-(4-(1-*E*-*n*-Pentenyl)phenyl)-*E*-acrylic acid (30h). The synthesis was performed according to the procedure described above for the synthesis of **30g** starting from 4-bromobenzaldehyde. Purification by cristallization from cyclohexane afforded **30h** [141 mg, 65%, as a yellowish solid; $R_f=0.40$ (ethyl acetate/cyclohexane 1/1, 1% HOAc (v/v)]; HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C): $R_t=11.58$ min; mp: 175 °C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, $^3J=7.2$ Hz), 1.55 (m, 2H), 2.15 (m, 2H), 6.21–6.28 (m, 1H), 6.32 (d, $^3J_{trans}=16.0$ Hz, 1H), 6.33 (d, $^3J_{trans}=16.0$ Hz, 1H), 7.29 (d, $^3J=8.4$ Hz, 2H), 7.40 (d, $^3J=8.4$ Hz, 2H), 7.60 (d, $^3J_{trans}=16.0$ Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.08, 23.43, 36.18, 118.31, 127.35, 129.38, 130.54, 133.49, 134.09, 141.36, 146.04, 170.41; MS (ESI-1): 215.1 $[M-H]^-$; HRMS (FAB): calcd for $C_{14}H_{17}O_2$ $[M+H]^+$: 217.1229, found: 217.1252.

General procedure for the pd^0-catalysed cleavage of allyl esters on the solid phase (GP P1)

Variant A. The resin (0.6 mmol) was washed under argon atmosphere twice with 5 mL THF, 5 mL CH_2Cl_2 and the appropriate dry and degassed solvent. After swelling in the solvent for some min 10–20 mol% $Pd(PPh_3)_4$-catalyst and 10–30 equiv phenylsilane were added and the mixture was shaken under argon and under light exclusion. After filtration of the resin, it was washed with 2×5 mL CH_2Cl_2, DMF/H_2O 1/1 (v/v), DMF, MeOH und CH_2Cl_2.

Variant B. The resin (0.6 mmol) was washed under argon atmosphere twice with 5 mL THF, 5 mL CH_2Cl_2 and dry and degassed NMA/THF [1/5 (v/v)]. After swelling in 10 mL NMA/THF [1/5 (v/v)] for some min 10–20 mol% $Pd(PPh_3)_4$ catalyzator were added and the mixture was shaken under argon and under light exclusion. After filtration of the resin it was washed with 2×5 mL CH_2Cl_2, DMF/H_2O 1/1 (v/v), DMF, MeOH und CH_2Cl_2.

Variant C. The resin (0.6 mmol) was washed under argon atmosphere twice with 5 mL THF, 5 mL CH_2Cl_2

and morpholine/THF [1/9 (v/v)]. After swelling in 10 mL morpholine/THF mixture [1/5 (v/v)] for some min 10–20 mol% $Pd(PPh_3)_4$ catalyzator were added and the mixture was shaken under argon and under light exclusion. After filtration of the resin, it was washed with 2×5 mL CH_2Cl_2, DMF/H_2O 1/1 (v/v), DMF, MeOH und CH_2Cl_2.

General procedure for the base mediated cleavage of Fmoc-protecting groups on the solid support (GP P2)

To the resin (0.5 mmol/g, 50 μmol) were added 3 mL piperidine/DMF 1/4 (v/v) and the mixture was shaken between 5 and 30 min. After filtration, the procedure was repeated and the resin was filtered and washed with 4×5 mL DMF, 4×5 mL MeOH und 4×5 mL CH_2Cl_2.

General procedure for the C-terminal coupling of amino acid allyl esters on solid support (GP P3)

Variant A. To polymeric support (0.50 mmol/g, 0.50 mmol) swollen in NMP was added a solution of 3–6 equiv of HATU, 1–2 equiv of HOAt and 3–6 equiv of DIEA in NMP. After shaking for 30–60 min the resin is filtered, washed with 2×5 mL NMP and a solution of 3–6 equiv of the amino component and 6–12 equiv of DIEA in NMP were added. After shaking for several hours the resin is filtered off, washed with 3×5 mL DMF, 3×5 mL DMF/H_2O 1/1 (v/v), 3×5 mL DMF, 3×5 mL MeOH und 4×5 mL CH_2Cl_2 and dried in vacuo.

Variant B. To a solution of 3–6 equiv of PyAOP, 3–6 equiv of the amino-component and by choice 1–2 equiv of HOAt in NMP, 12–15 equiv of DIEA were added and the solution was immediately added to a pre-swollen (for 10 min) suspension of the polymer bound compound (0.50 mmol/g, 0.50 mmol) in NMP. After shaking for several hours, the resin is filtered off, washed with 3×5 mL DMF, 3×5 mL DMF/H_2O 1/1 (v/v), 3×5 mL DMF, 3×5 mL MeOH und 4×5 mL CH_2Cl_2 and dried in vacuo.

General procedure for the N-terminal attachment of Fmoc-amino acids GP P4

Variant A. To a solution of 3–5 equiv of the appropriate Fmoc-amino acid, 2.8–4.8 equiv of HATU and by choice 1 equiv of HOAt in NMP were added 10–16 equiv of DIEA and the mixture was shaken for some minutes. This mixture was shaken then for several hours, the resin was filtered off, washed with 3×5 mL DMF, 3×5 mL DMF/H_2O 1:1, 3×5 mL DMF, 3×5 mL MeOH and 4×5 CH_2Cl_2 and dried in vacuo.

Variant B. To a solution of 4–6 equiv of the Fmoc-amino acid, HOAt and by choice 2,6-lutidine in 15 mL dry DMF were added 4–6 equiv of *N*,*N*′-diisopropylcarbodiimide. After shaking the solution for 5 minutes this solution is added to a mixture of pre-swollen polymer (0.50 mmol/g, 1.0 mmol) in 10 mL DMF. After shaking for several hours, the resin is filtered off, washed with 5×5 mL DMF, 5×5 mL DMF/H_2O 1/1 (v/v), 5×5 mL DMF, 5×5 mL MeOH und 8×5 mL CH_2Cl_2 and dried in vacuo.

General procedure for the cleavage from the solid support (GP P5)

Variant A. After washing the resin twice with 5 mL CH_2Cl_2 a mixture of TFA and the appropriate scavenger reagent is added. After shaking for several hours, the solid support is filtered off and washed with 5 mL TFA, 5 mL $CHCl_3$, 2×5 mL CH_2Cl_2, 5 mL MeOH and 5 mL toluene. The combined filtrates were evaporated in vacuo. HPLC purification, followed by lyophilization afforded the product.

Variant B. After washing the resin twice with 5 mL CH_2Cl_2, the polymer-bound compound was reacted several times for different periods of time with mixtures of TFA/CH_2Cl_2/H_2O 47/47/6 (v/v/v) and with TFA/H_2O 95/5 (v/v). The resin was filtered off, washed with 3×5 mL CH_2Cl_2, 2×5 mL EtOH and 5 mL toluene. The combined filtrates were evaporated in vacuo. HPLC purification, followed by lyophilization afforded the product.

General procedure for the N-terminal coupling of acrylic acid derivatives on solid support (GP P8)

After washing the polymer (0.5 mmol/g, 0.15 mmol) with 2×5 mL THF, 2×5 mL CH_2Cl_2 and swelling in 3 mL DMF for 30 min, 10 equiv of DIEA were added. A solution of 3–6 equiv of the acrylic acid, PyAOP and HOAt in 6 mL of a mixture of dry DMF/CH_2Cl_2 1/1 (v/v) was added. After shaking for 1 min, 0.5 equiv of DMAP were added and the mixture was shaken for several hours. The resin was filtered, washed with 3×5 mL DMF, 3×5 mL DMF/H_2O 1/1, 3×5 mL DMF, 3×5 mL MeOH and 3×5 mL CH_2Cl_2 and dried in vacuo.

General procedure for the N-terminal coupling of saturated carboxylic acids on solid support (GP P9)

To a solution of 3–5 equiv carboxylic acid, 2.8–4.8 equiv of HATU and by choice 1 equiv of HOAt in 10 mL NMP were added 10–15 equiv of DIEA and the mixture was shaken for some minutes. Afterwards, the pre-activated mixture was added to the polymer-bound compound (0.50 mmol/g, 55 μmol) in 5 mL NMP. After shaking for several hours, the resin is filtered off, washed with 3×5 mL DMF, 3×5 mL DMF/H_2O 1/1 (v/v), 3×5 mL DMF, 3×5 mL MeOH and 3×5 mL CH_2Cl_2 and dried in vacuo.

General procedure for the N-terminal coupling of benzylchloroformiates on solid support (GP P10)

To a solution of 3–6 equiv of HOAt, 0.1–1 equiv of DMAP and 10–15 equiv of DIEA in 6 mL of a mixture of dry CH_2Cl_2/DMF 1/1 (v/v), were added slowly 10–20 equiv of benzylchloroformiate at 0 °C. After 10 min at 0 °C, the mixture was added to the polymer-bound compound (0.5 mmol/g, 0.15 mmol) in 3 mL dry CH_2Cl_2 and the suspension was shaken for several

hours at room temperature. The polymer is filtered off, washed with 3×5 mL DMF, 3×5 mL DMF/H_2O 1/1, 3×5 mL DMF, 3×5 mL MeOH and 3×5 mL CH_2Cl_2 and dried in vacuo.

General procedure for the electrophilic attachment (GP P11):

Variant A. To the polymer-bound compound (200 mg, 100 μmol) was added a solution of 10 equiv of Cs_2CO_3 in 0.5 mL H_2O, 0.5 mL EtOH and 3 mL DMF and the mixture was shaken for 5 h under exclusion of light. After filtering off the resin and washing with DMF, EtOH, CH_2Cl_2 and dry DMF, 1 mL dry DMF, variable equiv of the halogenide and by choice 1–2 equiv of KI (1–2 equiv) were added and the mixture was shaken for several hours under exclusion of light. The resin is filtered off then, washed with DMF (4×5 mL), DMF/H_2O 1:1 (4×5 mL), DMF (4×5 mL), MeOH (2×5 mL) und CH_2Cl_2 (6×5 mL) and dried in vacuo.

Variant B. After washing the polymer-bound compound (200 mg, 100 μmol) with dry THF (2×5 mL), CH_2Cl_2 (2×5 mL) and DMF (2×5 mL), 1 mL dry DMF, Cs_2CO_3 (10 equiv) and halogenide (10–20 equiv) were added. The mixture was shaken for several hours under exclusion of light and was worked up and dried according to variant A.

General procedure for the nucleophilic attachment (GP P12)

After washing of the polymer-bound compound (100 mg, 50 μmol) with a mixture of 8×2 mL MeOH/CH_2Cl_2 1/1, 1% HOAc, 3×5 mL THF, 3×5 mL CH_2Cl_2 and 2×5 mL NMP, a solution of 5–6 equiv of amino component, 5–6 equiv of PyAOP and 1 equiv of HOAt in 6 mL NMP were added, followed by addition of 12–19 equiv of DIEA. The mixture was shaken for several hours, then, the resin is filtered off, washed with 4×5 mL DMF, DMF/H_2O 1/1, 4×5 mL DMF, 2×5 mL MeOH und 5×5 mL CH_2Cl_2 and dried in vacuo.

Synthesis of polymer-bound compound 8

After washing Wang-resin (500 mg, 1.29 mmol/g, 0.65 mmol) with 2×5 mL THF and 2×5 mL CH_2Cl_2 drying it in vacuo and swelling in 4 mL dry THF, a solution of **16** (865 mg, 1.95 mmol) and PPh_3 (511 mg, 1.95 mmol) in 4 mL THF was added. A solution of DEAD (303 μL, 1.95 mmol) was added slowly at 0 °C. After 1 h at 0 °C, the mixture was shaken at room temperature for 24 h. The resin was filtered off, washed with 2×5 mL THF, 2×5 CH_2Cl_2, 2×5 DMF, 2×5 mL DMF/H_2O 1/1 (v/v), 2×5 DMF, 2×5 MeOH und 2×5 CH_2Cl_2 and dried in vacuo; IR (KBr): 3530, 3430, 3083, 3060, 3026, 2923, 2848, 1944, 1873, 1802, 1734, 1602, 1507, 1493, 1452, 1182, 1068, 1028; loading: 0.53 mmol/g, 59% (according to Fmoc-determination[10]); analysis after TFA-cleavage from a resin sample: HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C): R_t = 11.52 min, purity >95%, R_f = 0.45 [ethyl acetate/hexane 1/1 (v/v)]). These determined analytic results correspond to the data of **16**.

For the blocking of unreacted hydroxy functions of the Wang linker, the resin is reacted with a solution of 1.5 mL pyridine and 1.5 mL acetic anhydride in 20 mL CH_2Cl_2 for 30 min. The polymer is then filtered off, washed with 3×10 mL CH_2Cl_2, 3×10 mL DMF, 3×10 mL MeOH and 2×10 mL CH_2Cl_2 and dried in vacuo.

Solid-phase bound *N*-9-fluorenylmethoxycarbonyl-D-tyrosyl-*N*,*O*-dimethyl-L-tyrosine allyl ester (17). Compound **D-8** (2.00 g, 0.50 mmol/g, 1.04 mmol) was reacted with $Pd(PPh_3)_4$ in 50 mL NMA/THF for 24 h according to GP P1. Then the resin bound compound was pre-activated with HATU (1.54 g 4.05 mmol), HOAt (184 mg, 1.35 mmol) and DIEA (690 μL, 4.05 mmol) in 5 mL NMP for 60 min and then coupled with **25** (1.16 g, 4.05 mmol) and DIEA (1.05 mL) in 10 mL NMP for 24 h. IR (KBr): 3434, 3083, 3060, 3026, 2925, 2852, 1945, 1874, 1802, 1731, 1650, 1602, 1583, 1511, 1494, 1453, 1423, 1365, 1239, 1181; analysis after TFA-cleavage from a resin sample: The starting material was completely transformed into **17**. R_f = 0.40 [ethyl acetate/hexane 1/1, 1% HOAc (v/v)]; HPLC (A1): R_t = 17.72 min, purity: >95%; HRMS (FAB): calcd for $C_{38}H_{39}N_2O_7$ $[M+H]^+$: 635.2757, found: 635.2893.

Solid-phase bound *N*-9-Fluorenylmethoxycarbonyl-D-tyrosyl-*N*,*O*-dimethyl-L-tyrosyl-*N*-methyl-L-phenylalanine allyl ester (18). According to GP P1 compound **17** (6.46 g, 0.50 mmol/g, 3.23 mmol) was reacted with $Pd(PPh_3)_4$ in 50 mL NMA/THF 1/4 (v/v) for 24 h. Then resin bound compound (2.16 g) was coupled with **26** (731 mg, 3.24 mmol), PyAOP (1.69 g, 3.24 mmol), HOAt (147 mg, 1.08 mmol) and DIEA (2.22 mL, 13.0 mmol) for 42 h in 20 mL NMP. Analysis after TFA-cleavage from a resin sample: HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min): R_t = 8.48 min [11%, Fmoc-Tyr-Me(OMe)Tyr-OH], 17.28 min (7%, **18**, Epimer 1), 17.62 min (82%, **18**, Epimer 2); LC–MS (ESI-1, Grad. A): 595.2 $[M+H]^+$, R_t = 10.01 min [Fmoc-Tyr-Me(OMe)Tyr-OH]; 818.4 $[M+Na]^+$, R_t = 20.45 min (**18**, Epimer 1); 818.4 $[M+Na]^+$, R_t = 20.89 min (**18**, Epimer 2); **18**: HRMS (FAB): calcd for $C_{48}H_{49}N_3O_8$ $[M+H]^+$ 796.3597, found: 796.3550.

***N*-3-(2-(1-*Z*-*n*-Pentenyl)phenyl)-*E*-acryloyl-D-tyrosyl-*N*,*O*-dimethyl-L-tyrosyl-*N*-methyl-L-phenylalanine-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidine-5-ylmethylester (23/1).** According to GP P2, the polymer-bound compound **18** (260 mg, 0.50 mmol/g, 0.13 mmol) was reacted for 2×10 min with 5 mL piperidine/DMF, respectively. Then the polymer bound compound was coupled with **30i** (130 mg, 0.60 mmol), PyAOP (313 mg, 0.60 mmol), HOAt (82 mg, 0.60 mmol), DMAP (18 mg, 0.15 mmol) and DIEA (257 μL, 1.5 mmol) in 9 mL DMF/CH_2Cl_2 for 20 h according to GP P8. After cleavage of the allyl group with $Pd(PPh_3)_4$ in 8 mL morpholine/THF mixture for 4 h according to GP P1 variant C the C-terminus was alkylated by reaction with **32b** (209 mg, 1.3 mmmol), Cs_2CO_3 (424 mg, 1.3 mmol) and KI (43 mg, 0.26 mmol) in 5 mL DMF according to GP P11 variant A for 24 h at room temperature and for 24 h at 50 °C. Then the product is cleaved from the resin by treatment with 2×10 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v/v) for 2×20

min and with 2×15 mL TFA/H_2O 95/5 (v/v) for 2×30 min according to GP P5 variant B. Purification by HPLC afforded **23**/**1** (13 mg, 13%, nine steps) as a white solid; R_f = 0.64 [ethyl acetate/EtOH 5/1 (v/v)]; HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–60/40/0.1 in 60 min, 50 °C): R_t = 50.41 min, purity: >95%; mp: >250 (decomp); $[\alpha]_D^{20}$ −50.2 (*c* 0.64, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 0.79 (t, ^3J = 7.5 Hz, 3H), 1.34 (m, 2H), 1.93 (td, ^3J = 7.34 Hz, ^3J = 1.5 Hz, 2H), 2.14–2.23 (dd, ^2J = 15.0 Hz, ^3J = 6.0 Hz, 1H), 2.43–2.48 (dd, ^2J = 15.0 Hz, ^3J = 7.5 Hz, 1H), 2.56 [2.57] (s, 3H), 2.67–2.70 (m, 2H), 2.87 [2.88] (s, 3H), 2.96–3.04 (m, 2H), 3.70 [3.73] (s, 3H), 4.61–4.65 [4.72–4.74] (m, 1H), 4.87–4.91 (m, 2H), 4.96–5.02 [5.07–5.11] (m, 1H), 5.36–5.39 (m, 1H), 5.59–5.63 (m, 1H), 5.73–5.78 (m, 1H), 6.48 (d, $^3J_{cis}$ = 10.6 Hz, 1H), 6.50 (d, $^3J_{trans}$ = 15.8 Hz, 1H), 6.64–6.70 (m, 3H), 6.80–6.89 (m, 3H), 6.91–6.94 (m, 1H), 7.00–7.02 (m, 1H), 7.12–7.19 (m, 4H), 7.21–7.37 (m, 5H), 7.53–7.58 (m, 1H), 7.64 (d, $^3J_{trans}$ = 15.8 Hz, 1H); LC–MS (ESI): 854.4 $[M-H]^-$, 856.1 $[M+H]^+$, 878.3 $[M+Na]^+$; R_t = 11.80 min; MS (MALDI-TOF): 878.93 $[M+Na]^+$, 894.88 $[M+K]^+$; HRMS (FAB): calcd for $C_{40}H_{54}N_5O_9$ $[M+H]^+$: 856.3922, found: 856.3941.

***N*-(3-(2-(1-*Z*-*n*-Pentenyl)phenyl)-*E*-acryloyl-D-tyrosyl-*N*,*O*-dimethyl-L-tyrosyl-*N*-methyl-L-phenylalanine-2-methyl-thiazole-5-yl methyl ester (23/2).** According to GP P2, the polymer-bound compound **18** (260 mg, 0.50 mmol/g, 0.13 mmol) was reacted for 2×20 min with 5 mL piperidine/DMF, respectively. Then the polymer-bound compound was coupled with **30i** (97 mg, 450 μmol), PyAOP (235 mg, 450 μmol), HOAt (61 mg, 450 μmol), DMAP (18 mg, 150 μmol) and DIEA (257 μL, 1.5 mmol) in 9 mL DMF/CH_2Cl_2 for 17 h according to GP P8. After cleavage of the allyl group with $Pd(PPh_3)_4$ in 8 mL morpholine/THF mixture for 4 h according to GP P1 variant C, the C-terminus was alkylated by reaction with **32a** (209 mg, 1.3 mmol), Cs_2CO_3 (977 mg, 3 mmol) and KI (25 mg, 150 μmol) in 5 mL DMF according to GP P11 variant B for 24 h at 50 °C. Then the product is cleaved from the resin by treatment with 2×10 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v/v) for 30 and 60 min and with 2×5 mL TFA/H_2O 95/5 (v/v) for 2×2 h according to GP P5 variant B. Purification by HPLC afforded **23/2** (15 mg, 14%, nine steps) as a brownish solid; HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–90/10/0.1 in 30 min, 50 °C): R_t = 23.17 min, purity: >95%; mp: 87–89 °C; $[\alpha]_D^{20}$ −72.1 (*c* 0.59, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 0.79 [0.80] (t, ^3J = 7.2 Hz, 3H), 1.35 (q, ^3J = 7.2 Hz, 2H), 1.92–1.96 (m, 2H), 2.35–2.40 (m, 1H), 2.40 (s, 3H), 2.56–2.58 (m, 1H), 2.56 [2.58] (s, 3H), 2.64–2.67 (m, 1H), 2.66 (s, 1H), 2.77–2.79 (m, 2H), 3.70 [3.73] (s, 3H), 4.76–4.81 (m, 1H), 4.87–4.91 [4.99–5.10] (m, 1H), 5.17 (s, 2H) 5.40–5.44 (m, 1H), 5.75–5.83 (m, 1H), 6.49–6.55 (m, 1H), 6.53 (d, $^3J_{trans}$ = 15.8 Hz, 2H) 6.63–6.75 (m, 3H), 6.82–6.89 (m, 4H), 6.99–7.00 (d, ^3J = 8.4 Hz), 7.12–7.18 (m, 5H), 7.25–7.32 (m, 4H), 7.55 [7.60] (d, ^3J = 7.6 Hz, 1H), 7.66 [7.71] (d, $^3J_{trans}$ = 15.8 Hz, 1H); LC–MS (ESI-2): 843.10 $[M+H]^+$, R_t = 3.25 min; MS (MALDI-TOF): 865.7 $[M+Na]^+$; HRMS (FAB): calcd for $C_{49}H_{55}N_4O_7S$ $[M+H]^+$: 843.3791, found: 843.3803.

***N*-3-(2-(1-*Z*-*n*-Pentenyl)phenyl)-*E*-acryloyl-D-tyrosyl-*N*,*O*-dimethyl-L-tyrosyl-*N*-methyl-L-phenylalanine (21/1).** According to GP P2, the polymer-bound compound **18** (260 mg, 0.50 mmol/g, 0.13 mmol) was reacted twice for 20 min with 5 mL piperidine/DMF. Then the polymer bound compound was coupled with **30i** (112 mg, 520 μmol), PyAOP (313 mg, 600 μmol), HOAt (82 mg, 600 μmol), DMAP (18 mg, 150 μmol) and DIEA (205 μL, 1.2 mmol) in 9 mL DMF/CH_2Cl_2 for 20 h according to GP P8. Cleavage of the allyl group with $Pd(PPh_3)_4$ in 8 mL morpholine/THF mixture for 4 h according to GP P1 furnishes the polymer bound compound.

***N*-3-(2-(1-*Z*-*n*-pentenyl)phenyl)-*E*-acryloyl-D-tyrosyl-*N*,*O*-dimethyl-L-tyrosyl-*N*-methyl-L-phenylalanine (19/1).** The product is cleaved from the resin by treatment with 2×10 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v/v) for 10 and 20 min and with 2×5 mL TFA/H_2O 95/5 (v/v) for 30 and 180 min according to GP P5 variant B. Purification by HPLC afforded **21/1** (11 mg, 12%, eight steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C): R_t = 11.96 min, purity: >95%; mp: 93–94 °C; $[\alpha]_D^{20}$ −63.6 (*c* 0.11, MeOH); ^{1}H NMR (400 MHz, CD_3OD): 0.81–0.87 [0.92–1.0] (t, ^3J = 7.4 Hz, 3H), 1.33–1.42 (m, 2H), 1.94–2.0 [2.03–2.09] (m, 2H), 2.13–2.43 (m, 1H), 2.32 [2.41] (s, 3H), 2.43–2.70 (m, 1H), 2.56 [2.57] (s, 3H), 2.67–2.70 (m, 2H), 2.96–3.04 (m, 2H), 3.70 [3.73] (s, 3H), 4.67–4.73 (m, 1H), 5.45–5.51 (m, 1H), 5.68–5.74 [5.78–5.86] (m, 1H), 5.92–6.08 (m, 1H), 6.40 (d, $^3J_{cis}$ = 11.3 Hz, 1H), 6.54 (d, $^3J_{trans}$ = 15.6 Hz, 1H). 6.61–6.77 (m, 3H), 6.80–6.89 (m, 3H), 6.91–6.94 (m, 1H), 7.00–7.02 (m, 1H), 7.12–7.19 (m, 7H), 7.21–7.37 (m, 2H), 7.72 (d, $^3J_{trans}$ = 16.0 Hz, 1H); LC–MS (ESI-2): 730.1 $[M-H]^-$, R_t = 3.02 min; MS (MALDI-TOF): 754.9 $[M+Na]^+$; HRMS (FAB, *m*/*z*): calcd for $C_{44}H_{50}N_3O_7$ $[M+H]^+$ 732.3649, found 732.3664.

***N*-3-[2-(*n*-Pentyl)phenyl]propionyl-D-tyrosyl-*N*,*O*-dimethyl-L-tyrosyl-*N*-methyl-L-phenylalanine (21).** Compound **19/1** (230 mg, 0.50 mmol/g, 114 μmol) is treated with 10 mL TFA/triisopropylsilane/H_2O 95/5/5 (v/v) for 18 h. After purification by HPLC, the residue was dissolved 5 mL methanol, Pd (50 mg, 10% on charcoal) was added and the mixture was stirred for 6 h under hydrogen atmosphere. After filtration over Celite, washing with methanol (2×5 mL) and evaporation of the solvents furnished **21** (12 mg, 14%, nine steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C): R_t = 14.72 min, purity: >95%; mp: 119–122 °C; $[\alpha]_D^{20}$ −27.8 (*c* 0.32, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 0.87–0.91 (m, 3H), 1.28–1.39 (m, 4H), 1.53–1.56 (m, 2H), 2.11–2.21 (m, 3H), 2.36–2.46 (m, 1H), 2.58–2.70 (m, 4H), 2.80–2.94 (m, 3H), 2.82 (s, 3H), 3.43–3.48 (m, 2H), 3.68 [3.72] (s, 3H), 4.61–4.72 (m, 1H), 5.04–5.16 [5.36–5.44] (m, 1H), 5.63–5.74 (m, 1H), 6.58–6.67 (m, 4H), 6.75–6.80 (m, 4H), 7.06–7.12 (m, 5H), 7.22–7.27 (m, 4H); LC–MS (ESI-1, Grad. A): 736.2 $[M+H]^+$, 758.5 $[M+Na]^+$; R_t = 15.80 min; MS (MALDI-TOF): 758.7 $[M+Na]^+$; HRMS (FAB): calcd for $C_{44}H_{54}N_3O_7$ $[M+H]^+$: 736.3962, found: 736.3937.

***N*-3-(3-(1-*E*-Pentenyl)phenyl)-*E*-acryloyl-D-tyrosyl-*N,O*-dimethyl-L-tyrosyl-*N*-methyl-L-phenylalanine (20/2).** According to GP P2, the polymer-bound compound **18** (240 mg, 0.50 mmol/g, 0.12 mmol) was reacted twice for 20 min with 5 mL piperidine/DMF. The polymer-bound compound was then coupled with **30g** (97 mg, 450 μmol), PyAOP (235 mg, 450 μmol), HOAt (61 mg, 450 μmol), DMAP (18 mg, 150 μmol) and DIEA (257 μmol, 1.5 mmol) in 9 mL DMF/CH_2Cl_2 for 66 h according to GP P8. Cleavage of the allyl group with $Pd(PPh_3)_4$ in 8 mL morpholine/THF mixture for 4 h furnished polymer-bound.

***N*-3-(3-(1-*E*-Pentenyl)phenyl)-*E*-acryloyl-D-tyrosyl-*N,O*-dimethyl-L-tyrosyl-*N*-methyl-L-phenylalanine (19/2).** According to GP P1, the product is cleaved from the resin by treatment with 2×10 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v/v) for 10 and 30 min and with 2×5 mL TFA/H_2O 95/5 (v/v) for 60 and 120 min according to GP P5 variant B. Purification by HPLC afforded **20/2** (12 mg, 13%, eight steps) as a white solid; HPLC (A2, HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–90/10/0.1 in 40 min, 50 °C) R_t = 26.21 min, purity: >95%; mp: 127–129 °C, $[\alpha]_D^{20}$ −64.1 (*c* 0.32, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 [0.94] (t, ^3J = 8.0 Hz, 3H), 1.26–1.34 (m, 2H), 1.43–1.50 (m, 2H), 2.25–2.57 (m, 2H), 2.31 [2.43] s, 3H) 2.63–2.92 (m, 2H), 2.78 [2.87] (s, 3H), 3.04–3.14 (m, 1H), 3.22–3.34 (m, 1H), 3.73 [3.74] (s, 3H), 4.79–4.83 (m, 1H), 5.03–5.15 (m, 1H), 5.37–5.41 (m, 1H), 5.77–5.84 (m, 1H), 6.28–6.42 (m, 3H), 6.67–6.90 (m, 8H), 7.09–7.21 (m, 2H), 7.18–7.23 (m, 4H), 7.27–7.35 (m, 3H), 7.43 [7.56] (d, $^3J_{trans}$ = 15.6 Hz, 1H); LC–MS (ESI 2): 730.07 $[M-H]^-$, R_t = 3.10 min, MS (MALDI-TOF): 754.8 $[M+Na]^+$; HRMS (FAB): calcd for $C_{44}H_{50}N_3O_7$ $[M+H]^+$: 732.3649, found 732.3627.

***N*-3-[4-(*n*-Pentyl)phenyl)]-*E*-acryloyl-D-tyrosyl-*N,O*-dimethyl-L-tyrosyl-*N*-methyl-L-phenylalanine (20/3).** According to GP P2, the polymer-bound compound **18** (240 mg, 0.50 mmol/g, 0.12 mmol) was reacted for 2×20 min with 5 mL piperidine/DMF, respectively. Then the polymer-bound compound was coupled with **30a** (105 mg, 480 μmol), PyAOP (313 mg, 600 μmol), DMAP (18 mg, 150 μmol), HOAt (82 mg, 600 mg) und DIEA (257 μL, 1.5 mmol) in 9 mL DMF/CH_2Cl_2 for 66 h according to GP P8. After cleavage of the allyl group with $Pd(PPh_3)_4$ in 8 mL morpholine/THF mixture for 4 h according to GP P1, the product is cleaved from the resin by treatment with 2×5 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v/v) for 10 and 30 min and with 2×5 mL TFA/H_2O 95/5 (v/v) for 60 and 120 min according to GP P5 variant B. Purification by HPLC afforded **20/3** (12 mg, 13%, eight steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 40/55/0.1–90/10/0.1 in 30 min, 50 °C): R_t = 14.33 min, purity: 95%; mp: 134 °C; $[\alpha]_D^{20}$ −49.6 (*c* 0.22, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85–0.88 (m, 3H), 1.26–1.34 (m, 6H), 1.55–1.61 (m, 2H), 1.80–2.16 (m, 2H), 2.27–2.55 (m, 3H), 2.32 [2.43] (s, 3H) 2.63–2.92 (m, 1H), 3.05–3.14 (m, 1H), 3.22–3.33 (m, 1H), 3.73 [3.75] (s, 3H), 4.79–4.82 (m, 1H), 5.05–5.15 (m, 1H), 5.38–5.41 (m, 1H), 5.77–5.84 (m, 1H), 6.28 [6.35] (d, ^3J = 15.6 Hz, 1H), 6.60–6.91 (m, 8H), 7.09–7.21 (m, 5H), 7.29–7.45 (m, 4H), 7.56 (d, ^3J = 15.6 Hz, 1H); LC–MS (ESI-2): 732.14 $[M-H]^-$, R_t = 3.18 min; MS (MALDI-TOF): 757.1 $[M+Na]^+$, 773.1 $[M+K]^+$; HRMS (FAB): calcd for $C_{44}H_{52}N_3O_7$ $[M+H]^+$: 734.3805, found: 734.3831.

***N*-3-[4-(*n*-Pentyl)phenyl)]propionyl-D-tyrosyl-*N,O*-dimethyl-L-tyrosyl-*N*-methyl-L-phenylalanine (20/4).** According to GP P2, the polymer-bound compound **18** (260 mg, 0.50 mmol/g, 130 μmol) was reacted for 2×20 min with 5 mL piperidine/DMF, respectively. Then the polymer-bound compound was coupled with **29b** (99 mg, 450 μmol), HATU (171 mg, 450 μmol), HOAt (20 mg, 150 μmol) und DIEA (257 μL, 1.5 mmol) in 8 mL NMP for 66 h according to GP P9. After cleavage of the allyl group with $Pd(PPh_3)_4$ in 8 mL morpholine/THF mixture for 4 h according to GP P1, the product is cleaved from the resin by treatment with 2×5 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v/v) for 10 and 30 min and with 2×5 mL TFA/H_2O 95/5 (v/v) for 60 and 120 min according to GP P5 variant B. Purification by HPLC afforded **20/4** (16 mg, 17%, eight steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C) R_t = 21.34 min, purity: >95%; mp: 101 °C; $[\alpha]_D^{20}$ −71.7 (*c* 0.54, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 0.85 (t, ^3J = 6.9 Hz, 3H), 1.28–1.35 (m, 4H), 1.53–1.57 (m, 2H), 1.80–2.16 (m, 2H), 2.27–2.58 (m, 7H), 2.67–2.73 (m, 2H), 2.82–2.91 (m, 2H), 2.93 [2.95] (s, 3H), 3.00–3.10 [3.13–3.25] (m, 1H), 3.33–3.41 (m, 1H), 3.68 [3.71] (s, 3H), 4.54–4.62 (m, 1H), 4.84–4.94 (m, 1H), 5.02–5.11 (m, 1H), 6.52 (d, ^3J = 8.4 Hz, 2H), 6.60 [6.66] (d, ^3J = 8.4 Hz, 2H), 6.71–6.83 (m, 4H), 7.18 (d, ^3J = 7.8 Hz, 2H), 7.04 (d, ^3J = 8.0 Hz, 2H), 7.11–7.22 (m, 3H), 7.24–7.29 (m, 2H); LC–MS (ESI-2): 734.16 $[M-H]^-$; R_t = 3.15 min; MS (MALDI-TOF): 758.7 $[M+H]^+$; HRMS (FAB): calcd for $C_{44}H_{54}N_3O_7$ $[M+H]^+$: 736.3962, found: 736.3942.

***N*-3-(2-Benzyloxyphenyl)-*E*-acryloyl-D-tyrosyl-*N,O*-dimethyl-L-tyrosyl-*N*-methyl-L-phenylalanine (20/5).** According to GP P2, the polymer-bound compound **18** (260 mg, 0.50 mmol/g, 130 μmol) was reacted twice for 20 min with 5 mL piperidine/DMF, respectively. Then the polymer-bound compound was coupled with **30c** (114 mg, 450 μmol), PyAOP (235 mg, 450 μmol), DMAP (18 mg, 150 μmol), HOAt (61 mg, 450 μmol) and DIEA (257 μL, 1.5 mmol) for 66 h according to GP P8. After cleavage of the allyl group with $Pd(PPh_3)_4$ in 8 mL morpholine/THF mixture for 4 h according to GP P1, the product is cleaved from the resin by treatment with 2×5 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v/v) for 10 and 30 min and with 2×5 mL TFA/H_2O 95/5 (v/v) for 60 and 120 min according to GP P5 variant B. Purification by HPLC afforded **20/5** (10 mg, 10%, eight steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C): R_t = 10.03 min, purity: >95%; mp: 120 °C; $[\alpha]_D^{20}$ −88.0 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 2.23–2.70 (m, 4H), 2.32 [2.58] (s, 3H), 2.79–3.00 (m, 4H), 3.21–3.28 (m, 1H), 3.70 [3.73] (s, 3H), 4.72–4.80 [4.85–4.96] (m, 1H), 5.08 (m, 2H), 5.05–5.19 (m, 1H), 5.50 (m, 1H), 5.94–5.98 (m, 1H), 6.62–6.84 (m, 7H), 6.88 (d, ^3J = 8.6 Hz, 1H), 6.92–7.02 (m, 4H), 7.08–7.18 (m, 4H), 7.19–7.36 (m, 5H), 7.40–7.46 (m, 1H), 7.54–7.61 (d, $^3J_{trans}$ = 15.4 Hz, 1H); LC–MS (ESI-2): 768.1 $[M-H]^-$; R_t = 2.86 min; MS (MALDI-TOF): 792.9 $[M+Na]^+$; HRMS (FAB): calcd for $C_{46}H_{48}N_3O_8$ $[M+H]^+$: 770.3441, found: 770.3428.

***N*-9-Fluorenylmethoxycarbonyl-D-tyrosyl-*N,O*-dimethyl-L-tyrosyl-*N*-methyl-L-phenylalanine (20/6).** According to GP P1 variant B, polymer-bound compound **18** (230 mg, 0.50 mmol/g, 115 μmol) was reacted with $Pd(PPh_3)_4$ in 10 mL NMA/THF 1/4 (v/v) for 16 h. Then the product was cleaved from the resin for 19 h according to GP P5 variant A with 10 mL TFA/triisopropylsilane/H_2O 95/5/5 (v/v). Purification by HPLC afforded **20/6** (10 mg, 11%, six steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C): $R_t = 9.87$ min, purity: >95%; mp: 223 °C; $[\alpha]_D^{20}$ −18.9 (*c* 0.26, MeOH); ^1H NMR (400 MHz, $CDCl_3$): δ 2.18–2.70 (m, 4H), 2.31 [2.50] (s, 3H) 2.81 [2.89] (s, 3H), 3.02–3.09 (m, 1H), 3.21–3.37 (m, 1H), 3.75 [3.76] (s, 3H), 4.15–4.18 (m, 1H), 4.25–4.55 (m, 2H), 4.63–4.69 (m, 1H), 4.95–4.97 [5.17–5.21] (m, 1H), 5.48–5.50 [5.54–5.62] (m, 1H), 6.67 (d, $^3J = 8.4$ Hz, 2H), 6.72–6.81 (m, 3H), 6.84–6.92 (m, 3H), 7.12–7.14 (m, 1H), 7.18–7.22 (m, 2H), 7.23–7.31 (m, 4H), 7.39 (t, $^3J = 6.8$ Hz, 2H), 7.50–7.54 (m, 2H), 7.75 (d, $^3J = 7.0$ Hz, 2H); LC–MS (ESI-1, Grad. A): 756.1 $[M+H]^+$, 778.2 $[M+Na]^+$, 754.1 $[M-H]^-$, $R_t = 13.27$ min; MS (MALDI-TOF): 778.8 $[M+Na]^+$, 794.8 $[M+K]^+$.

***N*-4-Nitro-benzyloxycarbonyl-D-tyrosyl-*N,O*-dimethyl-L-tyrosyl-*N*-methyl-L-phenylalanyl-L-methionine (23/4).** According to GP P2, the polymer-bound compound **18** (260 mg, 0.50 mmol/g, 0.13 mmol) was reacted for 2×20 min with 5 mL piperidine/DMF, respectively. Then the polymer bound compound was coupled with **31b** (129 mg, 600 μmol), DMAP (18 mg, 150 μmol), HOAt (82 mg, 600 μmol) and DIEA (205 μL, 1.2 mmol) in 9 mL DMF/CH_2Cl_2 for 17 h according to GP P10. After cleavage of the allyl group with $Pd(PPh_3)_4$ in 8 mL morpholine/THF mixture for 4 h according to GP P1 variant C the compound was reacted with *t*butylmethionine hydrochloride (145 mg, 600 μmol), PyAOP (313 mg, 600 μmol), HOAt (20 mg, 150 μmol) und DIEA (257 μL, 1.5 mmol) for 16 h in 5 mL NMP according to GP P12. Then the product is cleaved from the resin by treatment with 2×10 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v/v) for 10 and 30 min and with 2×5 mL TFA/H_2O 95/5 (v/v) for 60 and 120 min according to GP P5 variant B. Purification by HPLC afforded **23/4** (11 mg, 10%, nine steps) as a yellowish solid; HPLC (A2, HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1-90/10/0.1 in 30 min, 50 °C) $R_t = 6.99$ min, purity: >95%; mp: 122 °C; $[\alpha]_D^{20}$ −23.4 (*c* 0.30, MeOH); ^1H NMR (400 MHz, $CDCl_3$): δ 1.82–2.18 (m, 2H), 2.19 [2.24] (s, 3H), 2.31–2.72 (m, 6H), 2.80–3.03 (m, 6H), 3.30–3.32 (m, 2H), 3.70 [3.72] (s, 3H), 4.36-4.46 [4.61–4.68] (m, 1H), 4.74–4.83 (m, 1H) 4.98–5.28 (m, 2H), 5.42–5.68 (m, 2H), 6.68–6.82 (m, 5H), 6.88–6.95 (m, 3H), 7.12–7.24 (m, 5H), 7.33–7.46 (m, 2H), 8.18 (d, $^3J = 8.8$ Hz, 2H); LC–MS (ESI-1, Grad. B) 866.2 $[M+Na]^+$; $R_t = 23.30$ min; MS (MALDI-TOF): 867.1 $[M+Na]^+$.

In a second fraction, ***N*-4-nitro-benzyloxycarbonyl-D-tyrosyl-*N,O*-dimethyl-L-tyrosyl-*N*-methyl-L-phenylalanine** (**20/7**) was isolated (4 mg, 5%) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C) $R_t = 6.66$ min, purity: >95%; mp: 115 °C; $[\alpha]_D^{20}$ −10.0 (*c* 0.29, MeOH); ^1H NMR (400 MHz, $CDCl_3$): δ 2.28–2.63 (m, 5H), 2.74–2.99 (m, 6H), 3.00–3.02 (m, 1H), 3.66 [3.67] (s, 3H), 3.92–3.95 (m, 1H), 4.50–5.55 (m, 1H), 5.05–5.11 (m, 2H), 5.44–5.46 (m, 1H), 6.61–6.80 (m, 10H), 6.92–7.11 (m, 3H), 7.32–7.39 (m, 2H), 8.09–8.18 (m, 2H); LC–MS (ESI-2): 735.00 $[M+Na]^+$; $R_t = 2.58$ min; MS (MALDI-TOF): 735.7 $[M+Na]^+$.

In a third fraction was isolated ***N*-4-nitro-benzyloxycarbonyl-D-tyrosyl-*N,O*-dimethyl-L-tyrosyl-*N*-methyl-L-phenylalanyl-L-methionine sulfoxide (23/5)** (5.2 mg, 5%) as a yellowish solid; LC–MS (ESI-1, Grad. B): 882.3 $[M+Na]^+$; $R_t = 18.27$ min, purity: >95%.

***N*-4-Nitro-benzyloxycarbonyl-D-tyrosyl-*N,O*-dimethyl-L-tyrosyl-*N*-methyl-L-phenylalanyl-piperidine-4-carboxylic amide (23/6).** According to GP P2, the polymer-bound compound **18** (260 mg, 0.50 mmol/g, 0.13 mmol) was reacted for 2×20 min with 5 mL piperidine/DMF, respectively. Then the polymer-bound compound was coupled with **31b** (129 mg, 600 μmol), DMAP (18 mg, 150 μmol), HOAt (82 mg, 600 μmol) und DIEA (205 μL, 1.2 mmol) in 9 mL DMF/CH_2Cl_2 for 17 h according to GP P10. After cleavage of the allyl group with $Pd(PPh_3)_4$ in 8 mL morpholine/THF mixture for 4 h according to GP P1 variant C the compound was reacted with 4-piperidine-amide (77 mg, 600 μmol), PyAOP (313 mg, 600 μmol), HOAt (20 mg, 150 μmol) and DIEA (257 μL, 1.5 mmol) in 5 mL NMP for 16 h according to GP P12. Then the product was cleaved from the resin by treatment with 2×10 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v/v) for 10 and 30 min and with 2×5 mL TFA/H_2O 95/5 (v/v) for 60 and 120 min according to GP P5 variant B. Purification by HPLC afforded **23/6** (11 mg, 13%, nine steps) as yellow solid as an unseparable 3/2 compound mixture; HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C): $R_t = 6.34$ min (isomer 1); $R_t = 6.63$ min (isomer 2); mp: 105 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 1.71–1.78 (m, 2H), 2.17–2.24 (m, 2H), 2.36–2.76 (m, 8H), 2.80–3.14 (m, 5H), 3.37–3.39 (m, 2H), 3.62–3.69 (m, 2H), 3.75 [3.76] (s, 3H), 4.36–4.46 [4.61–4.68] [4.74–4.83] (m, 1H), 4.98–5.28 (m, 2H), 5.42–5.68 (m, 2H), 6.68–6.82 (m, 5H), 6.88–6.95 (m, 3H), 7.12–7.24 (m, 5H), 7.33–7.46 (m, 2H), 8.18 (d, $^3J = 8.8$ Hz, 2H); LC–MS (ESI-2): 845.10 $[M+Na]^+$, $R_t = 2.36$ min; MS (MALDI-TOF): 845.8 $[M+Na]^+$.

***N*-Benzyloxycarbonyl-D-tyrosyl-*N,O*-dimethyl-L-tyrosyl-*N*-methyl-L-phenylalanine (20/8).** According to GP P2, the polymer-bound compound **18** (260 mg, 0.50 mmol/g, 130 μmol) was reacted for 2×20 min with 5 mL piperidine/DMF, respectively. Then the polymer-bound compound was coupled with **31a** (85 μL, 600 μmol), DMAP (18 mg, 150 μmol), HOAt (82 mg, 600 μmol) and DIEA (205 μL, 1.2 mmol) for 20 h in 9 mL DMF/CH_2Cl_2 according to GP P10. After cleavage of the allyl group with $Pd(PPh_3)_4$ in 8 mL morpholine/THF mixture for 4 h according to GP P1, the product is cleaved from the resin by treatment with 2×5 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v/v) for 10 and 20 min and with 2×5 mL TFA/H_2O 95/5 (v/v) for 30 and 180 min according to GP P5 variant B. Purification by HPLC afforded **20/**

8 (11 mg, 12%, eight steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C): $R_t = 6.87$ min; mp: 112 °C; $[\alpha]_D^{20}$ −127.1 (*c* 0.24, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.17–2.45 (m, 2H), 2.27 [2.42] (s, 3H) 2.46–2.91 (m, 2H), 2.76 [2.86] (s, 3H), 2.98–3.09 (m, 1H), 3.21–3.37 (m, 1H), 3.72 [3.75] (s, 3H), 4.40–4.42 [4.59–4.63] (m, 1H), 4.86–5.05 (m, 2H), 5.11–5.14 (m, 1H), 5.41–5.44 [5.62–5.66] (m, 1H), (m, 8H), 7.12–7.22 (m, 4H), 7.28–7.32 (m, 6H); LC–MS (ESI-2): 666.07 $[M-H]^-$, $R_t = 2.60$ min, purity: >95%; MS (MALDI-TOF): 691.0 $[M+Na]^+$; HRMS (FAB): calcd for $C_{38}H_{42}N_3O_8$ $[M+H]^+$: 668.2972, found: 668.2987.

***N*-3-Phenyl-*E*-acryloyl-D-tyrosyl-*N,O*-dimethyl-L-tyrosyl-*N*-methyl-L-phenylalanine (20/9).** According to GP P2, the polymer-bound compound **18** (260 mg, 0.50 mmol/g, 130 μmol) was reacted twice for 20 min with 5 mL piperidine/DMF, respectively. Then the polymer-bound compound was coupled with **30f** (77 mg, 0.52 mmol), PyAOP (313 mg, 600 μmol), DMAP (18 mg, 150 μmol), HOAt (82 mg, 600 μmol) and DIEA (205 μL, 1.2 mmol) for 20 h in 9 mL DMF/CH_2Cl_2 according to GP P8. After cleavage of the allyl group with $Pd(PPh_3)_4$ in 8 mL morpholine/THF mixture for 4 h according to GP P1, the product is cleaved from the resin by treatment with 2×5 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v/v) for 10 and 20 min and with 2×5 mL TFA/H_2O 95/5 (v/v) for 30 and 180 min according to GP P5 variant B. Purification by HPLC afforded **20/9** (11 mg, 13%, eight steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C): $R_t = 6.38$ min, purity: >95%; mp: 114–116 °C; $[\alpha]_D^{20}$ −10.0 (*c* 0.12, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29–2.58 (m, 2H), 2.29 [2.42] (s, 3H) 2.68–2.91 (m, 2H), 2.79 [2.88] (s, 3H), 3.04–3.14 (m, 1H), 3.22–3.34 (m, 1H), 3.73 [3.75] (s, 3H), 4.13–4.15 (m, 1H), 4.81–4.84 [5.03–5.08] (m, 1H), 5.12–5.16 [5.37–5.41] (m, 1H), 6.31 [6.39] (d, $^3J = 15.6$ Hz, 1H), 6.66–6.92 (m, 8H), 7.09–7.11 (m, 5H), 7.19–7.21 (m, 3H), 7.29–7.35 (m, 1H), 7.37–7.47 (m, 1H), 7.58 (d, $^3J = 15.6$ Hz, 1H); LC–MS (ESI-2): 662.1 $[M-H]^-$, $R_t = 2.55$ min; MS (MALDI-TOF): 686.7 $[M+Na]^+$; HRMS (FAB): calcd for $C_{39}H_{42}N_3O_7$ $[M+H]^+$: 664.3023, found: 664.2990.

***N*-3-Phenylpropionyl-D-tyrosyl-*N,O*-dimethyl-L-tyrosyl-*N*-methyl-L-phenylalanineallyl ester (23/10).** According to GP P2, the polymer-bound compound **18** (960 mg, 0.50 mmol/g, 0.48 mmol) was reacted twice for 20 min with 5 mL piperidine/DMF. The polymer-bound compound was then coupled with **29c** (264 mg, 1.75 mmol), HATU (627 mg, 1.65 mmol), HOAt (75 mg, 0.55 mmol) and DIEA (941 μL, 5.5 mmol) in 15 mL NMP according to GP P9 for 4.5 h furnishing the polymer bound intermediate *N*-3-phenylpropionyl-D-tyrosyl-*N,O*-dimethyl-L-tyrosyl-*N*-methyl-L-phenylalanine allyl ester (**22/10**). A sample of the intermediate (168 mg, 0.52 mmol/g, 87 μmol) was treated with 10 mL TFA/triisopropylsilane/H_2O 90/5/5 (v/v/v). Purification by HPLC afforded **23/10** (19 mg, 31%, seven steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–100/0/0.1 in 30 min, 50 °C): $R_t = 14.65$ min, purity: >95%; mp: 77–80 °C; $[\alpha]_D^{20}$ −122.1 (*c* 0.33, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29–2.62 (m, 5H), 2.34 [2.59] (s, 3H), 2.56–2.83 (m, 3H), 2.79 [2.87] (s, 3H), 3.04–3.12 (m, 1H), 3.27–3.35 (m, 1H), 3.71 [3.73] (s, 3H), 4.60 (d, $^3J = 5.8$ Hz, 2H), 4.82–5.08 (m, 2H), 5.20–5.33 (m, 2H), 5.50 (t, $^3J = 7.5$ Hz, 1H), 5.73–5.91 (m, 1H), 6.13–6.22 (m, 1H), 6.58–6.64 (m, 3H), 6.72–6.75 (m, 2H), 6.79–6.83 (m, 2H), 6.93–6.95 (m, 1H), 7.10–7.19 (m, 6H), 7.21–7.27 (m, 4H); MS (MALDI-TOF): 728.7 $[M+Na]^+$, 744.7 $[M+K]^+$; LC–MS (ESI-1, Grad. A): 728.4 $[M+Na]^+$, $R_t = 13.41$ min; FAB (3-NBA): 706.4 $[M+H]^+$, 728.3 $[M+Na]^+$; HRMS (FAB) calcd for $C_{42}H_{48}N_3O_7$ $[M+H]^+$: 706.3492, found: 706.3398.

***N*-3-Phenylpropionyl-D-tyrosyl-*N,O*-dimethyl-L-tyrosyl-*N*-methyl-L-phenylalanine (20/10).** Resin-bound compound **22/10** (132 mg, 0.50 mmol/g, 66 μmol) was reacted with $Pd(PPh_3)_4$ in 10 mL morpholine/THF mixture for 5 h according to GP P1 variant C furnishing polymer-bound ***N*-3-phenylpropionyl-D-tyrosyl-*N,O*-dimethyl-L-tyrosyl-*N*-methyl-L-phenylalanine** (**19/10**). Cleavage from the solid support by 10 mL TFA/triisopropylsilane/H_2O 90/5/5 (v/v/v) for 12 h and then with 10 mL TFA/H_2O 95/5 (v/v) for 12 h, followed by purification by HPLC affording **20/10** (23 mg, 53%) as a light brown solid; HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–100/0/0.1 in 30 min): $R_t = 8.73$ min, purity: 95%; mp: 126 °C; $[\alpha]_D^{20}$ −105.1 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16–2.53 (m, 4H), 2.24 [2.32] (s, 3H), 2.56–2.83 (m, 4H), 2.65 [2.76] (s, 3H), 2.93–3.03 (m, 1H), 3.12–3.29 (m, 1H), 3.63 (s, 3H), 4.17–4.28 (m, 1H), 4.63–4.72 [4.73–4.84] (m, 1H), 4.97 [5.30] (t, $^3J = 7.3$ Hz, 1H), 6.48–6.82 (m, 8H), 6.91–7.26 (m, 10H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 29.67 [29.94], 30.31, 31.28, 31.39, 33.94, 34.92, 36.81, 37.80, 50.10 [50.54], 53.78, 55.23 [55.26], 55.92 [60.88], 113.78 [113.85], 115.57 [15.67], 126.33 [126.38], 126.70 [127.12], 128.18 [128.26], 128.33 [128.54], 128.58 [128.64], 128.81 [128.98], 129.00 [130.06], 130.16 [130.40], 130.81, 136.78, 137.26, 140.06 [140.20], 155.41 [155.59], 158.31 [158.43], 168.99, 169.84, 171.71, 172.50; LC–MS (ESI-1, Grad. A): 664.3 $[M-H]^-$, $R_t = 8.18$ min; MS (MALDI-TOF): 687.70 $[M+Na]^+$, 703.33 $[M+K]^+$; HRMS (FAB) calcd for $C_{39}H_{44}N_3O_7$ $[M+H]^+$: 666.3179, found: 666.3164.

***N*-3-Phenylpropionyl-D-tyrosyl-*N,O*-dimethyl-L-tyrosyl-*N*-methyl-L-phenylalanyl-L-methionine methyl ester (23/7).** Compound **19/10** (126 mg, 0.50 mmol/g, 63 μmol) was reacted twice with **33c** (66 mg, 380 μmol), PyAOP (197 mg, 378 μmol), HOAt (8.6 mg, 63 μmol) and DIEA (108 μL, 630 μmol) in 3 mL NMP for 8 h according to GP P12, followed by cleavage from the resin according to GP P5 variant B for 12 h with 10 mL TFA/triisopropylsilane/H_2O 90/5/5 (v/v/v). Purification by HPLC afforded **23/7** (4 mg, 8%, nine steps) as light brown solid; HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–65/35/0.1 in 60 min, 50 °C): $R_t = 31.98$ min, purity: 91%; mp: 80 °C; $[\alpha]_D^{20}$ −63.6 (*c* 0.11, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.71–2.22 (m, 11H) 1.23 (s, 3H), 2.23–2.68 (m, 8H), 2.84 (s, 3H), 2.93 (m, 1H), 3.58 (s, 3H), 3.70 (s, 3H), 4.48–4.59 (m, 1H), 5.05–5.14 (m, 1H), 5.15–5.23 [5.39–5.47] (m, 1H), 6.05–6.13 [6.29–6.34] (m, 1H), 6.44–6.62 (m, 3H), 6.64–6.83 (m, 5H), 7.08–7.20 (m, 10H);

LC–MS (ESI): 833.3 $[M+Na]^+$, $R_t = 12.54$ min; MS (MALDI-TOF): 833.8 $[M+Na]^+$, 849.8 $[M+K]^+$; HRMS (FAB): calcd for $C_{45}H_{54}N_3O_9S$ $[M+H]^+$: 812.3581, found: 812.3396.

***N*-3-Phenylpropionyl-D-tyrosyl-*N*,*O*-dimethyl-L-tyrosyl-*N*-methyl-L-phenylalanine-methoxycarbonylmethylester (23/8).** Compound **19/10** (80 mg, 0.50 mmol/g, 40 μmol) was reacted first with Cs_2CO_3 (293 mg, 0.9 mmol) and then with methyl-bromoacetate (166 μL, 1.8 mmol) in 1 mL DMF for 44 h according to GP P11 variant A. Afterwards, cleavage from the resin according to GP P5 variant B for 12 h with 10 mL TFA/triisopropylsilan/H_2O 90/5/5 (v/v/v) and purification by HPLC afforded **23/8** (11 mg, 38%, nine steps) as white solid; HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–100/0/0.1 in 30 min, 50 °C): $R_t = 12.17$ min, purity: >95%; $R_f = 0.31$ [ethyl acetate/hexane 2/1, 1% HOAc (v/v)]; mp: 110 °C; $[\alpha]_D^{20}$ −119.4 (*c* 0.32, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.00–2.11 (m, 1H), 2.29–2.55 (m, 5H), 2.66 (s, 3H), 2.70–2.79 (dd, $^2J = 15.8$ Hz, $^3J = 8.0$ Hz, 2H), 2.85 [2.98] (s, 3H), 3.01–3.10 (m, 1H), 3.27–3.37 (m, 1H), 3.70 [3.71] (s, 3H), 3.77 [3.72] (s, 3H), 4.44 [4.61] (d, $^2J = 15.8$ Hz, 1H), 4.67 (d, $^2J = 15.8$ Hz, 1H), 4.77–4.82 (m, 2H), 5.11–5.15 (m, 1H), 5.46–5.50 (t, $^3J = 7.7$ Hz, 1H), 6.26–6.31 (m, 1H), 6.56–6.64 (m, 3H), 6.71–6.74 (d, $^3J = 8.3$ Hz, 2H), 6.78–6.83 (d, $^3J = 8.5$ Hz, 2H), 6.97–6.98 (d, $^3J = 6.0$ Hz, 1H), 7.08–7.20 (m, 5H), 7.23–7.26 (m, 4H), 7.33–7.42 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 29.88, 30.38, 31.43 [31.51], 33.44, 34.59, 37.26 [37.42], 37.98, 49.99 [50.19], 52.43 [52.48], 53.61, 54.89 [55.38], 59.64 [60.36], 61.15 [61.48], 113.74, [113.80], 115.33, [115.38], 126.26 [126.30], 126.84 [126.97], 127.24, 128.17 [128.24], 128.40 [128.52], 128.63 [128.73], 128.82 [128.98], 130.18 [130.32], 136.63, 135.34, 140.31, 140.34, 155.03, 158.46, 167.83, 169.55, 169.75, 171.45, 171.88; LC–MS (ESI-1, Grad. A): 736.2 $[M-H]^-$, 760.5 $[M+Na]^+$, $R_t = 12.23$ min; MS (MALDI-TOF): 738.85 $[M+H]^+$, 759.17 $[M+Na]^+$, 775.45 $[M+K]^+$; HR-MS (FAB): calcd for $C_{42}H_{48}N_3O_9$ $[M+H]^+$: 738.3391, found: 738.3405.

***N*-3-Phenylpropionyl-D-tyrosyl-*N*,*O*-dimethyl-L-tyrosyl-*N*-methyl-L-phenylalanyl-carboxymethylester (23/9).** Compound **19/10** (144 mg, 0.50 mmol/g, 72 μmol) was reacted first with Cs_2CO_3 (450 mg, 1.5 mmol) and then with **32d** (488 μL, 3.0 mmol) in 6 mL DMF for 44 h according to GP P11 variant A. Afterwards, the product was cleaved from the resin according to GP P5 variant B for 12 h by treatment with 10 mL TFA/triisopropylsilane/H_2O 90/5/5 (v/v/v) and 10 mL TFA/H_2O 95/5 (v/v). Purification by HPLC afforded **23/9** (10 mg, 35%, nine steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C): $R_t = 9.11$ min, purity: >95%; mp: 95–97 °C; $[\alpha]_D^{20}$ −93.1 (*c* 0.39, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.93–1.98 (t, $^3J = 7.8$ Hz, 1H), 2.21–2.43 (m, 4H), 2.40 [2.50] (s, 3H), 2.61–2.74 (m, 3H), 2.71 [2.86] (s, 3H), 2.92–3.05 (m, 1H), 3.18–3.29 (m, 1H), 3.64 [3.65] (s, 3H), 4.41–4.67 (m, 2H), 4.78–4.95 (m, 2H), 5.39–5.44 (t, $^3J = 7.7$ Hz, 1H), 6.52–6.63 (m, 3H), 6.68 (d, $^3J = 8.5$ Hz, 2H), 6.74 (d, $^3J = 8.3$ Hz, 2H), 6.76 (m, 1H), 7.01 (d, $^3J = 7.2$ Hz, 2H), 7.04–7.13 (m, 3H), 7.14–7.23 (m, 4H), 7.25–7.32 (m, 1H); LC–MS (ESI-1, Grad. A): 724.0 $[M+H]^+$, $R_t = 7.45$ min; MS (MALDI-TOF): 746.8 $[M+Na]^+$, 762.8 $[M+K]^+$; HRMS (FAB): calcd for $C_{41}H_{45}NaN_3O_9$ $[M+H]^+$ 746.3053, found: 724.3063.

***N*-Benzyloxycarbonyl-D-tyrosyl-*N*-methyl-L-phenylalanyl-L-tyrosine (35/1).** Starting from **l-8** (300 mg, 0.40 mmol/g, 120 μmol) the appropriate tripeptide was built up by sequenzial N-terminal deblocking by treatment with 2×5 mL piperidine/DMF for 2×5 min according to GP P2 and attachment of FmocMePheOH (169 mg, 420 μmol) for 2.5 h and of Fmoc-D-Tyr(*t*Bu)OH (193 mg, 420 μmol) for 14 h by coupling with HATU (148 mg, 390 μmol) in the presence of DIEA (134 μL, 780 μmol) in 5 mL NMP according to GP P4 variant A furnishing **34e**. Then, after N-terminal deblocking according to GP P2 and reaction with **31a** (73 μL, 520 μmol), DMAP (16 mg, 130 μmol), HOAt (71 mg, 520 μmol) and DIEA (178 μL, 1.04 mmol) in 7.5 mL DMF/CH_2Cl_2 according to GP P10 for 10 h followed by the liberation of the C-terminus according GP P1 variant C for 16 h. The product was cleaved from the resin by treatment with 2×5 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v/v) for 30 and 60 min and with 2×5 mL TFA/H_2O 95/5 (v/v) for 2×1.5 h, according to GP P5 variant B affording **92/21** (11 mg, 14%, eight steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–90/10/0.1 in 40 min, 50 °C): $R_t = 15.74$ min, purity: 78%; mp: 116–117 °C; $[\alpha]_D^{20}$ +23.6 (*c* 0.11, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 2.28–2.40 (m, 1H), 2.47 (s, 3H), 2.60–2.69 (m, 1H), 2.75–2.87 (m, 2H), 3.05–3.16 (m, 2H), 4.46–4.50 (m, 1H), 4.56–4.60 (m, 1H), 4.95 (d, $^2J = 12.5$ Hz, 1H), 5.03 (d, $^2J = 12.5$ Hz, 1H), 5.39–5.42 (t, $^3J = 5.5$ Hz, 1H), 6.56 (d, $^3J = 8.6$ Hz, 2H), 6.62 (d, $^3J = 8.4$ Hz, 2H), 6.75 (d, $^3J = 8.4$ Hz, 2H), 6.93 (d, $^3J = 8.4$ Hz, 2H), 7.11–7.13 (m, 3H), 7.17–7.25 (m, 7H); LC–MS (ESI-2): 638.04 $[M-H]^-$, $R_t = 2.22$ min; MS (MALDI-TOF): 662.6 $[M+Na]^+$, 678.6 $[M+K]^+$; HR-MS (FAB, *m*/*z*): calcd for $C_{36}H_3N_3NaO_8$ $[M+Na]^+$ 662.2478, found: 662.2502.

***N*-Benzyloxycarbonyl-D-tyrosyl-L-phenylalanyl-L-tyrosine (35/2).** Starting from **L-8** (300 mg, 0.40 mmol/g, 120 μmol) the appropriate tripeptide was built up by sequenzial N-terminal deblocking by treatment with 2×5 mL piperidine/DMF for 2×5 min according to GP P2 and attachment of FmocPheOH (163 mg, 420 μmol) for 2.5 h and of Fmoc-D-Tyr(*t*Bu)OH (193 mg, 420 μmol) for 14 h by coupling with HATU (148 mg, 390 μmol) in the presence of DIEA (134 μL, 780 μmol) in 5 mL NMP according to GP P4 variant A, furnishing **34f**. Then, after N-terminal deblocking according to GP P2 and reaction with **31a** (73 μL, 520 μmol), DMAP (16 mg, 130 μmol), HOAt (71 mg, 520 μmol) and DIEA (178 μL, 1.04 mmol) in 7.5 mL DMF/CH_2Cl_2 according to GP P10 for 10 h followed by the liberation of the C-terminus according GP P1 variant C for 16 h. The product was cleaved from the resin by treatment with 2×5 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v/v) for 30 and 60 min and with 2×5 mL TFA/H_2O 95/5 (v/v) for 2×1.5 h, according to GP P5 variant B affording **35/2** (14 mg, 18%, eight steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–90/10/0.1 in 40 min, 50 °C)

R_t = 14.54 min, purity: >95%; mp: 165 °C; $[\alpha]_D^{20}$ +1.0 (*c* 0.35, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 2.52 (dd, ^2J = 13.5 Hz, ^3J = 8.8 Hz, 1H), 2.72 (dd, ^2J = 14.1 Hz, ^3J = 8.8 Hz, 2H), 2.86 (dd, ^2J = 14.1 Hz, ^3J = 8.4 Hz, 1H), 2.95–3.06 (m, 2H), 4.15–4.18 (m, 1H), 4.50–4.56 (m, 2H), 4.90 (d, ^2J = 12.5 Hz, 1H), 5.01 (d, ^2J = 12.5 Hz, 1H), 6.57 (d, ^3J = 8.4 Hz, 2H), 6.62 (d, ^3J = 8.4 Hz, 2H), 6.81 (d, ^3J = 8.2 Hz, 2H), 7.02 (d, ^3J = 8.6 Hz, 2H), 7.10–7.16 (m, 4H), 7.19–7.25 (m, 5H); LC–MS (ESI-2): 624.48 $[M-H]^-$; R_t = 3.88 min; MS (MALDI-TOF): 648.5 $[M+Na]^+$, 664.5 $[M+K]^+$; HRMS (FAB): calcd for $C_{35}H_{36}N_3O_8$ $[M+H]^+$ 626.2502, found: 626.2523.

***N*-Benzyloxycarbonyl-D-tyrosyl-L-tyrosyl-L-tyrosine (35/3).** Starting from **L-8** (300 mg, 0.40 mmol/g, 120 μmol) the appropriate tripeptide was built up by sequenzial N-terminal deblocking by treatment with 2×5 mL piperidine/DMF for 2×5 min according to GP P2 and attachment of Fmoc-D-Tyr(*t*Bu)OH (193 mg, 420 μmol) for 2.5 h and of Fmoc-D-Tyr(*t*Bu)OH (193 mg, 420 μmol) for 14 h by coupling with HATU (148 mg, 390 μmol) in the presence of DIEA (134 μL, 780 μmol) in 5 mL NMP according to GP P4 variant A, furnishing **34g**. Then, after N-terminal deblocking according to GP P2 and reaction with **31a** (73 μL, 520 μmol), DMAP (16 mg, 130 μmol), HOAt (71 mg, 520 μmol) and DIEA (178 μL, 1.04 mmol) in 7.5 mL DMF/CH_2Cl_2 according to GP P10 for 10 h followed by the liberation of the C-terminus according GP P1 variant C for 16 h. The product was cleaved from the resin by treatment with 2×5 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v/v) for 30 and 60 min and with 2×5 mL TFA/H_2O 95/5 (v/v) for 2×1.5 h, according to GP P5 variant B, affording **35/3** (16 mg, 21%, eight steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–90/10/0.1 in 40 min, 50 °C): R_t = 11.33 min, purity: >95%; mp: 142–144 °C; $[\alpha]_D^{20}$ +1.1 (*c* 0.54, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 2.53 (dd, ^2J = 13.9 Hz, ^3J = 8.6 Hz, 1H), 2.65 (dd, ^2J = 14.1 Hz, ^3J = 8.6 Hz, 1H), 2.77 (dd, ^2J = 14.1 Hz, ^3J = 5.8 Hz, 2H), 2.87 (m, 2H), 3.03 (dd, ^3J = 8.6 Hz, 1H) 4.17 (dd, ^3J = 8.9 Hz, ^3J = 5.7 Hz, 1H), 4.47–4.53 (m, 2H), 4.89 (d, ^2J = 12.5 Hz, 1H), 5.01 (d, ^2J = 12.5 Hz, 1H), 6.58–6.65 (m, 6H), 6.82 (d, ^3J = 8.4 Hz, 2H), 6.87 (d, ^3J = 8.4 Hz, 2H), 6.96 (d, ^3J = 8.4 Hz, 2H), 7.20–7.23 (m, 5H); LC–MS (ESI 2): 640.77 $[M-H]^-$; R_t = 1.88 min; MS (MALDI-TOF): 664.8 $[M+Na]^+$, 680.8 $[M+K]^+$; HRMS (FAB): calcd for $C_{35}H_{36}N_3O_9$ $[M+H]^+$ 642.2452, found: 642.2417.

***N*-Benzyloxycarbonyl-L-tyrosyl-L-tyrosyl-L-tyrosine (35/4).** Starting from **L-8** (400 mg, 0.30 mmol/g, 120 μmol) the appropriate tripeptide was built up by sequenzial N-terminal deblocking by treatment with 2×5 mL piperidine/DMF for 2×5 min according to GP P2 and attachment of Fmoc-L-Tyr(*t*Bu)OH (193 mg, 420 μmol) for 2.5 h and of Fmoc-L-Tyr(*t*Bu)OH (193 mg, 420 μmol) for 14 h by coupling with HATU (148 mg, 390 μmol) in the presence of DIEA (134 μL, 780 μmol) in 5 mL NMP according to GP P4 variant A, furnishing **34h**. Then, after N-terminal deblocking according to GP P2 and reaction with **31a** (73 μL, 520 μmol), DMAP (16 mg, 130 μmol), HOAt (71 mg, 520 μmol) and DIEA (178 μL, 1.04 mmol) in 7.5 mL DMF/CH_2Cl_2 according to GP P10 for 10 h followed by the liberation of the C-terminus according GP P1 variant C for 16 h. The product was cleaved from the resin by treatment with 2×5 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v/v) for 30 and 60 min and with 2×5 mL TFA/H_2O 95/5 (v/v) for 2×1.5 h, according to GP P5 variant B affording **35/4** (24 mg, 31%, eight steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–90/10/0.1 in 40 min, 50 °C): R_t = 11.20 min, purity: >95%; mp: 126 °C; $[\alpha]_D^{20}$ −12.7 (*c* 0.45, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 2.57 (dd, ^2J = 13.7 Hz,^3J = 9.6 Hz, 1H), 2.71 (dd, ^2J = 14.1 Hz, ^3J = 8.6 Hz, 1H), 2.82–2.87 (m, 2H), 2.91–3.07 (m, 2H), 4.19 (dd, ^3J = 9.4 Hz, ^3J = 4.9 Hz, 1H), 4.50 (dd, ^3J = 8.0 Hz, ^3J = 5.5 Hz, 2H), 4.88 (d, ^2J = 12.5 Hz, 1H), 4.98 (d, ^2J = 12.5 Hz, 1H), 6.58–6.63 (m, 6H), 6.90–6.95 (m, 6H), 7.15–7.26 (m, 5H); LC–MS (ESI-2): 640.00 $[M-H]^-$, R_t = 1.90 min; MS (MALDI-TOF): 664.5 $[M+Na]^+$; HRMS (FAB): calcd for $C_{35}H_{36}N_3O_9$ $[M+H]^+$: 642.2452, found: 642.2462.

***N*-Benzyloxycarbonyl-L-phenylalanyl-L-phenylalanyl-L-tyrosine (35/5).** Starting from **L-8** (300 mg, 0.40 mmol/g, 120 μmol) the appropriate tripeptide was built up by sequenzial N-terminal deblocking by treatment with 2×5 mL piperidine/DMF for 2×5 min according to GP P2 and attachment of FmocPheOH (163 mg, 420 μmol) for 2.5 h and of FmocPheOH (163 mg, 420 μmol) for 14 h by coupling with HATU (148 mg, 390 μmol) in the presence of DIEA (134 μL, 780 μmol) in 5 mL NMP according to GP P4 variant A furnishing **34i**. Then, after N-terminal deblocking according to GP P2 and reaction with **31a** (73 μL, 520 μmol), DMAP (16 mg, 130 μmol), HOAt (71 mg, 520 μmol) and DIEA (178 μL, 1.04 mmol) in 7.5 mL DMF/CH_2Cl_2 according to GP P10 for 10 h followed by the liberation of the C-terminus according GP P1 variant C for 16 h. The product was cleaved from the resin by treatment with 2×5 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v/v) for 30 and 60 min and with 2×5 mL TFA/H_2O 95/5 (v/v) for 2×1.5 h, according to GP P5 variant B affording **35/5** (13 mg, 18%, eight steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–90/10/0.1 in 40 min, 50 °C) R_t = 14.54 min, purity: >95%; mp: 201–202 °C; $[\alpha]_D^{20}$ −20.0 (*c* 0.39, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 2.52 (m, 1H), 2.78–2.94 (m, 3H), 2.98–3.08 (m, 2H), 4.26 (dd, ^2J = 9.8 Hz, ^3J = 4.9 Hz, 1H), 4.50 (dd, ^2J = 7.8 Hz, ^3J = 5.5 Hz, 1H), 4.58 (dd, ^2J = 8.4 Hz, ^3J = 5.5 Hz, 1H), 4.90 (d, ^2J = 12.5 Hz, 1H), 4.94 (d, ^2J = 12.5 Hz, 1H), 6.63 (d, ^3J = 8.6 Hz, 2H), 6.96 (d, ^3J = 8.6 Hz, 2H), 7.08–7.22 (m, 15H); LC–MS (ESI 2): 608.47 $[M-H]^-$; R_t = 2.43 min; MS (MALDI-TOF): 632.9 $[M+Na]^+$, 648.8 $[M+Na]^+$; HRMS (FAB): calcd for $C_{35}H_{36}N_3O_7$ $[M+H]^+$ 610.2553, found: 610.2554.

General procedure for the synthesis of polymer bound tripeptides 34a–d (GP P13)

Starting from **L-8** (2.1 g, 0.40 mmol/g, 840 μmol) the appropriate tripeptide was built up by sequenzial N-terminal deblocking by treatment with 2×10 mL piperidine/DMF for 2×5 min according to GP P2 and coupling of FmocMePheOH or FmocPheOH (1.08 g, 2.67 mmol), HATU (958 mg, 2.52 mmol) in the presence of

DIEA (913 μL, 5.34 mmol) in 20 mL NMP according to GP P4 variant A for 2.5 h and of Fmoc-D-His(Trt)OH or Fmoc-L-His(Trt)OH (193 mg, 420 μmol), DIC (520 μL, 3.36 mmol) and HOAt (457 mg, 3.36 mmol) for 14 h in 25 mL DMF for 14 h according to GP P4 variant B.

Polymer-bound N^{α}-9-Fluorenylmethoxycarbonyl-(N^{Im}-triphenylmethyl)-D-histidyl-L-phenylalanyl-L-tyrosine allyl ester (34a). Reaction of **L-8** with FmocPheOH and Fmoc-D-His(Trt)OH according to GP P13 furnished **34a**; ninhydrine-test:[15] negative.

Polymer-bound N^{α}-9-fluorenylmethoxycarbonyl-(N^{Im}-triphenylmethyl)-L-histidyl-L-phenylalanyl-L-tyrosine allyl ester (34b). Reaction of **L-8** with FmocPheOH and Fmoc-L-His(Trt)OH according to GP P13 furnished **34b**; ninhydrine-test:[15] negative.

Analysis of samples of **34a** and **34b** after cleavage from the resin: LC–MS (ESI-1, Grad. A): 742.3 $[M+H]^+$, $R_t = 1.95$ min (Fmoc-His-Phe-Tyr-OH).

Polymer-bound N^{α}-9-fluorenylmethoxycarbonyl-(N^{Im}-triphenylmethyl)-D-histidyl-*N*-methyl-L-phenylalanyl-L-tyrosine allyl ester (34c). Reaction of **L-8** with FmocMePheOH and Fmoc-D-His(Trt)OH according to GP P13 furnished **34c**; ninhydrine-test:[15] negative.

Polymer-bound N^{α}-9-fluorenylmethoxycarbonyl-(N^{Im}-triphenylmethyl)-L-histidyl-*N*-methyl-L-phenylalanyl-L-tyrosine allyl ester (34d). Reaction of **L-8** with FmocMePheOH and Fmoc- L-His(Trt)OH according to GP P13 furnished **34d**; ninhydrine-test:[15] negative.

Analysis of samples of **34c** and **34d** after cleavage from the resin: LC–MS (ESI-1, Grad. A): 742.3 $[M+H]^+$, $R_t = 1.95$ min (Fmoc-His-MePhe-Tyr-OH).

General procedure for the synthesis of the tripeptides 35/6–35/8 (GP P14)

According to GP P2, the polymer-bound tripeptide 34 (400 mg, 0.40 mmol/g, 160 μmol) was N-terminally deblocked by piperidine/DMF treatment for 2×5 min, followed by coupling with 31a (113 μL, 800 μmol), DMAP (24 mg, 200 μmol), HOAt (109 mg, 800 μmol) and DIEA (274 μL, 1.6 mmol) in DMF/CH_2Cl_2 2/1 (v/v) for 12 h. After the liberation of the C-terminus with $Pd(PPh_3)_4$ in 5 mL morpholine/THF for 16 h according to GP P1 variant C, the product was cleaved from the resin by treatment with 2×5 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v) for 2×45 min and 2×5 mL TFA/H_2O 95/5 (v/v) for 2×1.5 h According to GP P5, variant B followed by HPLC purification affording the appropriate product.

N^{α}-Benzyloxycarbonyl-L-histidyl-L-phenylalanyl-L-tyrosine hydrotrifluoroacetate (35/6). Starting from tripeptide **34b** reaction according to GP P14 furnishes **35/6** (28 mg, 24%, eight steps) as a slightly yellow solid; HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–70/30/0.1 in 30 min, 50 °C): $R_t = 10.24$ min, purity: 95%; mp: 129 °C; $[\alpha]_D^{20}$ −7.3 (*c* 0.56, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 2.88–2.98 (m, 3H), 3.06–3.14 (m, 3H), 4.36–4.40 (t, $^3J = 6.8$ Hz, 1H), 4.58 (dd, $^3J = 5.3$ Hz, $^3J = 8.4$ Hz, 1H), 4.63 (dd, $^3J = 5.3$ Hz, $^3J = 9.0$ Hz, 1H), 5.04 (s, 2H), 6.68 (d, $^3J = 8.6$ Hz, 2H), 7.06 (d, $^3J = 8.6$ Hz, 2H), 7.16–7.27 (m, 5H), 7.31–7.34 (m, 5H), 8.63 (s, 1H); LC–MS (ESI-2): 600.08 $[M+H]^+$, 622.05 $[M+Na]^+$; $R_t = 1.45$ min; MS (MALDI-TOF): 600.4 $[M+H]^+$, 622.4 $[M+Na]^+$; HRMS (FAB, *m*/*z*): calcd for $C_{32}H_{34}N_5O_7$ $[M+H]^+$ 600.2458, found: 600.2476.

N^{α}-Benzyloxycarbonyl-L-histidyl-*N*-methyl-L-phenylalanyl-L-tyrosine hydrotrifluoroacetate (35/7). Starting from tripeptide **34d** reaction according to GP P14 furnishes **35/7** (28 mg, 24%, eight steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–70/30/0.1 in 30 min, 50 °C): $R_t = 10.82$ min, purity: >85; mp: 127 °C; $[\alpha]_D^{20}$ −64.2 (*c* 0.88, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 2.44–2.59 (m, 2H), 2.74–2.97 (m, 5H), 3.13–3.28 (m, 2H), 4.51–4.61 (m, 1H), 4.67–4.71 (m, 2H), 4.97–5.00 (m, 1H), 5.06–5.09 (m, 1H), 6.67 (d, $^3J = 8.6$ Hz, 2H), 6.92 [6.97] (d, $^3J = 8.6$ Hz, 2H), 7.13–7.20 (m, 6H), 7.26–7.34 (m, 5H), 8.68 [8.73] (s, 1H); LC–MS (LC–ESI 2): 614.08 $[M+H]^+$, 636.07 $[M+Na]^+$; $R_t = 1.49$ min, MS (MALDI-TOF): 614.7 $[M+H]^+$, 636.7 $[M+Na]^+$; HRMS (FAB): calcd for $C_{33}H_{36}N_5O_7$ $[M+H]^+$: 614.2615, found: 614.2637.

N^{α}-Benzyloxycarbonyl-D-histidyl-*N*-methyl-L-phenylalanyl-L-tyrosine hydrotrifluoroacetate (35/8). Starting from tripeptide **34c** reaction according to GP P14 furnishes **35/8** (28 mg, 24%, eight steps) as a white solid. HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–70/30/0.1 in 30 min, 50 °C) $R_t = 9.74$ min, purity: >95%; mp: 128 °C; $[\alpha]_D^{20}$ −52.2 (*c* 0.51, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 2.48–2.51 (m, 2H), 2.66 (s, 3H), 2.73–2.83 (m, 2H), 3.09 (dd, $^2J = 14.1$ Hz, $^3J = 4.50$ Hz, 1H), 3.18 (dd, $^2J = 14.7$ Hz, $^3J = 5.09$, 1H), 4.58–4.61 (m, 2H), 4.93 (d, $^2J = 12.5$ Hz, 1H), 5.01 (d, $^2J = 12.3$ Hz, 1H), 5.36 (dd, $^3J = 11.15$ Hz, $^3J = 5.1$ Hz, 1H), 6.56 [6.61] (d, $^3J = 8.6$ Hz, 2H), 6.90–7.01 (m, 1H), 6.93 [6.99] (d, $^3J = 8.6$ Hz, 2H), 7.07–7.17 (m, 5H), 7.18–7.32 (m, 5H), 8.55 [8.58] (s, 1H); LC–MS (LC-ESI 2): 614.08 $[M+H]^+$, 636.07 $[M+Na]^+$, $R_t = 1.42$ min; MS (MALDI-TOF): 614.9 $[M+H]^+$, 636.9 $[M+Na]^+$; HRMS (FAB): calcd for $C_{33}H_{36}N_5O_7$ $[M+H]^+$: 614.2615, found: 614.2650.

N^{α}-4-Nitro-benzyloxycarbonyl-D-histidyl-L-phenylalanyl-L-tyrosine hydrotrifluoroacetate (35/9). According to GP P2 the polymer-bound tripeptide **34a** (300 mg, 0.40 mmol/g, 120 μmol) was N-terminally deblocked by piperidine/DMF treatment for 2×5 min, followed by coupling with **31b** (112 mg, 520 μmol), DMAP (16 mg, 130 μmol), HOAt (71 mg, 520 μmol) and DIEA (178 μL, 1.04 mmol) in 7.5 mL DMF/CH_2Cl_2 1/2 (v/v) for 20 h. After the liberation of the C-terminus with $Pd(PPh_3)_4$ in 5 mL morpholine/THF for 16 h according to GP P1 variant C, the product was cleaved from the resin by treatment with 2×5 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v) for 2×45 min and 2×5 mL TFA/H_2O 95/5 (v/v) for 2×1.5 h According to GP P5 variant B followed by HPLC purification affording **35/9** (45 mg, 58%, eight steps) as a light yellow solid; HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–90/10/0.1 in 40 min, 50 °C) $R_t = 8.96$

min, purity: >95%; mp: 124 °C; $[\alpha]_D^{20}$ +3.9 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 2.64–2.81 (m, 3H), 2.88–3.04 (m, 3H), 4.27 (dd, ^3J = 6.1 Hz, ^3J = 7.8 Hz, 1H), 4.47 (dd, ^3J = 5.1 Hz, ^3J = 8.41 Hz, 1H), 4.53 (dd, ^3J = 4.7 Hz, ^3J = 9.8 Hz, 1H), 5.02 (s, 2H), 6.53 (d, ^3J = 8.4 Hz, 2H), 6.83 (s, 1H), 6.90 (d, ^3J = 8.6 Hz, 2H), 7.03–7.09 (m, 5H), 7.39 (d, ^3J = 8.4 Hz, 2H), 8.05 (d, ^3J = 8.80 Hz, 2H), 8.51 (s, 1H); MS (MALDI-TOF): 645.6 $[M+H]^+$, 667.6 $[M+Na]^+$; HRMS (FAB):, calcd for $C_{32}H_{33}N_6O_9$ $[M+H]^+$: 645.2309, found: 645.2295.

***N*-3-[(4-(*n*-Pentyl)phenyl]-*E*-acryloyl-D-tyrosyl-L-phenylalanyl-L-tyrosine (35/10).** Starting from **L-8** (400 mg, 0.30 mmol/g, 120 μmol), the appropriate tripeptide was built up by sequenzial N-terminal deblocking by treatment with 2×5 mL piperidine/DMF for 2×5 min according to GP P2 and attachment of FmocPheOH (163 mg, 420 μmol) for 2.5 h and of Fmoc-D-Tyr(*t*-Bu)OH (193 mg, 420 μmol) for 14 h by coupling with HATU (148 mg, 390 μmol) in the presence of DIEA (134 μL, 780 μmol) in 5 mL NMP according to GP P4 variant A furnishing **34f**. Then, after N-terminal deblocking according to GP P2 and reaction with **30a** (85 mg μL, 390 μmol) and PyAOP (203 mg, 390 μmol) in the presence of DIEA (223 μL, 1.3 mmol) in 7.5 mL DMF/CH_2Cl_2 for 18 h according to GP P8, followed by the liberation of the C-terminus according GP P1 variant C for 16 h. The product was cleaved from the resin by treatment with 2×5 mL $TFA/CH_2Cl_2/H_2O$ 47/47/6 (v/v/v) for 30 and 60 min and with 2×5 mL TFA/H_2O 95/5 (v/v) for 2×1.5 h, according to GP P5 variant B affording **35/10** (26 mg, 31%, eight steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–90/10/0.1 in 40 min, 50 °C): R_t = 22.25 min, purity: >95%; mp: 131–132 °C; $[\alpha]_D^{20}$ −1.4 (*c* 0.58, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 0.82 (t, ^3J = 7.5 Hz, 3H), 1.22–1.29 (m, 4H), 1.52–1.56 (m, 2H), 2.53 (t, ^3J = 7.4 Hz, 2H), 2.61 (dd, ^2J = 13.9 Hz, ^3J = 8.0 Hz, 1H), 2.71 (dd, ^2J = 14.1 Hz, ^3J = 8.8 Hz, 1H), 2.79 (dd, ^2J = 14.1 Hz, ^3J = 6.5 Hz, 1H), 2.88 (dd, ^2J = 13.9 Hz, ^3J = 8.4 Hz, 1H), 2.96 (dd, ^2J = 14.1 Hz, ^3J = 5.1 Hz, 1H), 3.04 (dd, ^2J = 14.1 Hz, ^3J = 5.1 Hz, 1H), 4.49–4.55 (m, 3H), 6.48 (d, $^3J_{trans}$ = 15.6 Hz, 1H), 6.57 (d, ^3J = 8.6 Hz, 2H), 6.60 (d, ^3J = 8.6 Hz, 2H), 6.82 (d, ^3J = 8.8 Hz, 2H), 6.97 (d, ^3J = 8.6 Hz, 2H), 7.03 (d, ^3J = 8.4 Hz, 2H), 7.09–7.13 (m, 5H), 7.36 (d, ^3J = 8.2 Hz, 2H), 7.56 (d, $^3J_{trans}$ = 15.6 Hz, 1H); LC–MS (ESI-2): 690.84 $[M-H]^-$, R_t = 2.63 min; MS (MALDI-TOF): 714.6 $[M+Na]^+$; HR-MS (FAB, *m*/*z*): calcd for $C_{41}H_{46}N_3O_7$ $[M+H]^+$: 632.3336, found: 692.3332.

***N*$^{\alpha}$-3-[4-(*n*-Pentyl)phenyl]-*E*-acryloyl-D-histidyl-L-phenylalanyl-L-tyrosine hydrotrifluoroacetate (35/11).** According to GP P2 the polymer bound tripeptide **34a** (300 mg, 0.40 mmol/g, 120 μmol) was N-terminally deblocked by piperidine/DMF treatment for 2×5 min, followed by coupling with **30a** (105 mg, 480 μmol), PyAOP (250 mg, 480 μmol), DMAP (15 mg, 120 μmol) and DIEA (103 μL, 600 μmol) in 3 mL DMF/CH_2Cl_2 for 24 h. After the liberation of the C-terminus with $Pd(PPh_3)_4$ in 5 mL morpholine/THF for 16 h according to GP P1 variant C the product was cleaved from the resin by treatment with 2×5 mL $TFA/CH_2Cl_2/H_2O$ 47/47/6 (v/v) for 10 and 20 min and 2×5 mL TFA/H_2O 95/5 (v/v) for 30 min and 180 min according to GP P5 variant B followed by HPLC purification affording **35/11** (14 mg, 15%, eight steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C): R_t = 16.19 min, purity: 95%; mp: 149 °C; $[\alpha]_D^{20}$ −5.3 (*c* 0.53, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 0.90 (t, ^3J = 7.0 Hz, 3H), 1.28–1.36 (m, 4H), 1.62 (quint, ^3J = 7.6 Hz, 2H), 2.62 (t, ^3J = 7.6 Hz, 2H), 2.81 (dd, ^2J = 14.1 Hz, ^3J = 9.8 Hz, 1H), 2.90–2.97 (m, 2H), 3.08–3.16 (m, 3H), 4.58 (dd, ^3J = 5.28 Hz, ^3J = 8.6 Hz, 1H), 4.65 (dd, ^3J = 4.7 Hz, ^3J = 9.2 Hz, 1H), 4.71 (m, 1H), 6.55 (d, $^3J_{trans}$ = 15.6 Hz, 1H), 6.67 (d, ^3J = 8.6 Hz, 2H), 6.95 (s, 1H), 7.04 (d, ^3J = 8.4 Hz, 2H), 7.15–7.26 (m, 8H), 7.45 (d, ^3J = 8.2 Hz, 1H), 7.50 (d, $^3J_{trans}$ = 15.6 Hz, 1H), 8.64 (s, 1H); LC–MS (ESI-1, Grad. A): 666.3 $[M+H]^+$, 688.3 $[M+Na]^+$, 664.4 $[M-H]^-$; R_t = 17.78 min; MS (MALDI-TOF): 666.7 $[M+H]^+$, 688.7 $[M+Na]^+$, 704.6 $[M+K]^+$; HRMS (FAB): calcd for $C_{38}H_{44}N_5O_6$ $[M+H]^+$: 666.3292, found: 666.3317.

***N*$^{\alpha}$-3-[4-(*n*-Pentyl)phenyl]propionyl-D-histidyl-L-phenylalanyl-L-tyrosine hydrotrifluoroacetate (35/12).** According to GP P2, the polymer-bound tripeptide **34a** (300 mg, 0.40 mmol/g, 120 μmol) was N-terminally deblocked by piperidine/DMF treatment for 2×5 min, followed by coupling with **29b** (106 mg, 480 μmol), HATU (175 mg, 460 μmol), HOAt (27 mg, 200 μmol) and DIEA (342 μL, 2.0 mmol) in 5 mL NMP for 24 h. After the liberation of the C-terminus with $Pd(PPh_3)_4$ in 5 mL morpholine/THF for 16 h according to GP P1 variant C the product was cleaved from the resin by treatment with 2×5 mL $TFA/CH_2Cl_2/H_2O$ 47/47/6 (v/v) for 10 and 20 min and 2×5 mL TFA/H_2O 95/5 (v/v) for 30 and 180 min according to GP P5 variant B followed by HPLC purification affording **92/34** (23 mg, 24%, eight steps) as a light yellow solid; HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C): R_t = 16.69 min, purity: 95%; mp: 130–131 °C; $[\alpha]_D^{20}$ +7.6 (MeOH, *c* 1.0); ^{1}H NMR (400 MHz, CD_3OD): δ 0.87 (t, ^3J = 6.8 Hz, 3H, CH_3), 1.15–1.37 (m, 4H), 1.55 (quint, ^3J = 7.6 Hz, 2H), 2.41–2.55 (m, 2H), 2.54 (t, ^3J = 7.6 Hz, 2H), 2.79 (m, 4H), 2.90–3.02 (m, 2H), 3.10–3.16 (m, 2H), 4.55–4.64 (m, 3H), 6.68 (d, ^3J = 8.4 Hz, 2H), 6.88 (s, 1H), 7.08–7.11 (m, 6H), 7.14–7.22 (m, 5H), 8.64 (s, 1H); LC–MS (ESI-1, Grad. A): 668.4 $[M+H]^+$, 690.3 $[M+Na]^+$, 666.4 $[M-H]^-$; R_t = 17.27 min; MS (MALDI-TOF): 668.8 $[M+H]^+$, 690.8 $[M+Na]^+$; HRMS (FAB, *m*/*z*): calcd for $C_{38}H_{46}N_5O_6$ $[M+H]^+$: 668.3448, found: 668.3418.

General procedure for the synthesis of tripeptides 35/13–35/15 (GP P15)

According to GP P2, the polymer-bound tripeptide 34 (400 mg, 0.40 mmol/g, 160 μmol) was N-terminally deblocked by piperidine/DMF treatment for 2×5 min, followed by coupling with **29b** (110 mg, 500 μmol), HATU (175 mg, 460 μmol), HOAt (27 mg, 200 μmol) und DIEA (342 μL, 2.0 mmol) in 5 mL NMP für 12 h. After the liberation of the C-terminus with $Pd(PPh_3)_4$ in 5 mL morpholine/THF for 16 h according to GP P1 variant C the product was cleaved from the resin by treatment with 2×5 mL $TFA/CH_2Cl_2/H_2O$ 47/47/6 (v/v) for 2×45 min and 2×5 mL TFA/H_2O 95/5 (v/v) for

2×1.5 h according to GP P5 variant B followed by HPLC purification affording the appropriate product.

N^{α}-3-[4-(*n*-Pentyl)phenyl]propionyl-L-histidyl-L-phenylalanyl-L-tyrosine hydrotrifluoroacetate (35/13). Starting from tripeptide **34b**, reaction according to GP P15 furnished 35/13 (24 mg, 19%, eight steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–70/30/0.1 in 30 min, 50 °C): $R_t = 20.04$ min, purity: 93%; mp: >210 °C (decomp.); $[\alpha]_D^{20}$ −13.2 (*c* 0.19, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 0.87 (t, $^3J = 6.8$ Hz, 3H), 1.25–1.36 (m, 4H), 1.52–1.59 (quint, $^3J = 7.6$ Hz, 2H), 2.44 (t, $^3J = 8.4$ Hz, 2H), 2.54 (t, $^3J = 7.6$ Hz, 2H), 2.79 (t, $^3J = 7.6$ Hz, 2H), 2.81–2.94 (m, 3H), 3.00–3.13 (m, 3H), 4.56 (dd, $^3J = 5.1$ Hz, $^3J = 8.2$ Hz, 1H), 4.56–4.62 (m, 2H), 6.67 (d, $^3J = 8.6$ Hz, 2H), 6.93 (s, 1H), 7.04 (d, $^3J = 8.6$ Hz, 2H), 7.04–7.08 (m, 4H), 7.17–7.25 (m, 5H), 8.58 (s, 1H); LC–MS (ESI 2): 668.17 $[M+H]^+$, 690.15 $[M+Na]^+$, $R_t = 1.94$ min; MS (MALDI-TOF): 668.8 $[M+H]^+$, 690.8 $[M+Na]^+$; HRMS (FAB): calcd for $C_{38}H_{46}N_5O_6$: 668.3448, found: 668.3433.

N^{α}-3-[4-(*n*-Pentyl)phenyl]propionyl-L-histidy-*N*-methyl-L-phenylalanyl-L-tyrosine hydrotrifluoroacetate (35/14). Starting from tripeptide **34d**, reaction according to GP P15 furnished **35/14** (38 mg, 30%, eight steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–90/10/0.1 in 40 min, 50 °C) $R_t = 18.36$ min, purity: >95%; mp: 120 °C; $[\alpha]_D^{20}$, −12.3 (*c*, 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ, 0.87 (m, 3H), 1.29 (m, 4H), 1.54 (m, 2H), 2.33–2.45 (m, 4H), 2.52 (s, 3H), 2.65–2.71 (m, 2H), 2.79–2.92 (m, 4H), 3.12–3.23 (m, 2H), 4.55–4.67 (m, 1H), 4.94–5.00 (m, 1H), 5.27–5.39 (m, 1H), 6.67 (m, 2H), 6.94–6.96 (m, 3H), 7.02–7.20 (m, 9H), 8.71 (s, 1H); LC–MS (ESI-2):, 682.18 $[M+H]^+$, 704.16 $[M+Na]^+$, $R_t = 1.99$ min; MS (FAB): 682.3 $[M+H]^+$, 704.3 $[M+Na]^+$; HRMS (FAB): calcd for $C_{39}H_{48}N_5O_6$ $[M+H]^+$: 682.3605, found: 682.3625.

N^{α}-3-[4-(*n*-Pentyl)phenyl]propionyl-D-histidyl-*N*-methyl-L-phenylalanyl-L-tyrosine hydrotrifluoroacetate (35/15). Starting from tripeptide **34c**, reaction according to GP P15 furnished **35/15** (27 mg, 21%, eight steps) as a slightly yellow solid. HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–70/10/0.1 in 30 min, 50 °C) $R_t = 18.95$ min, purity: >95%; mp: 127 °C; $[\alpha]_D^{20}$ −20.0 (*c* 0.75, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 0.86 (t, $^3J = 7.0$ Hz, 3H), 1.29–1.31 (m, 4H), 1.54 (quint, $^3J = 7.4$ Hz, 2H), 2.32–2.39 (m, 1H), 2.46–2.54 (m, 3H), 2.60 (dd, $^2J = 15.3$ Hz, $^3J = 6.3$ Hz, 2H), 2.70 (s, 3H), 2.78 (t, $^3J = 7.2$ Hz, 2H), 2.86–2.92 (m, 4H), 4.56 (dd, $^3J = 5.1$ Hz, $^3J = 8.2$ Hz, 1H), 4.56–4.62 (m, 2H), 6.67 (d, $^3J = 8.6$ Hz, 2H), 6.93 (s, 1H), 7.04 (d, $^3J = 8.6$ Hz, 2H), 7.04–7.08 (m, 4H), 7.17–7.25 (m, 5H), 8.58 (s, 1H); LC–MS (ESI-2): 682.18 $[M+H]^+$, 704.16 $[M+Na]^+$, $R_t = 1.92$ min; HRMS (FAB): calcd for $C_{39}H_{47}N_5O_6$ $[M+H]^+$ 682.3605, found: 682.3615.

N^{α}-3-[4-(1-*E*-*n*-Pentenyl)phenyl)]-*E*/*Z*-acryloyl-D-histidyl-L-phenylalanyl-L-tyrosine hydrotrifluoroacetate (35/16). According to GP P2, the polymer-bound tripeptide **34a** (300 mg, 0.40 mmol/g, 120 μmol) was N-terminally deblocked by piperidine/DMF treatment for 2×5 min, followed by coupling with **30h** (60 mg, 270 μmol), PyAOP (250 mg, 480 μmol), DMAP (15 mg, 120 μmol), DIEA (205 μL, 1.2 mmol) in 7.5 mL DMF/CH_2Cl_2 for 24 h According to GP P8. After the liberation of the C-terminus with $Pd(PPh_3)_4$ in 5 mL morpholine/THF for 16 h according to GP P1 variant C the product was cleaved from the resin by treatment with 2×5 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v) for 10 and 20 min and 2×5 mL TFA/H_2O 95/5 (v/v) for 30 min and 180 min according to GP P5 variant B followed by HPLC purification affording **35/16** (3 mg, 3%, eight steps) as a light brown solid as a mixture of *E*- und *Z*-isomer (*E*/*Z* = 1:1, according to ^{1}H NMR); HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C): $R_t = 16.19$ min; HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–90/10/0.1 in 30 min, 50 °C): $R_t = 13.47$ min (isomer 1), $R_t = 15.41$ min (isomer 2); mp: 165 °C; $[\alpha]_D^{20}$ +6.3 (*c* 0.24, MeOH); ^{1}H NMR (400 MHz, CD_3OD) *Z*-isomer: δ 0.96 (m, 3H), 1.27–1.30 (m, 2H), 1.49–1.52 (m, 2H), 2.72–2.78 (m, 6H), 4.56–4.72 (m, 3H), 5.93 (d, $^3J_{cis} = 12.7$ Hz, 1H), 6.30–6.39 (m, 2H), 6.65–6.68 [6.74–6.77] (m, 2H), 6.89 (m, 1H), 6.99 (d, $^3J = 8.2$ Hz, 1H), 7.15–7.27 (m, 7H), 7.39 (t, $^3J = 8.8$ Hz, 2H), 7.47 (d, $^3J = 8.8$ Hz, 1H), 8.54 (s, 1H, His); *E*-isomer: δ 0.96 (m, 3H), 1.27–1.30 (m, 2H), 1.49–1.52 (m, 2H), 2.72–2.78 (m, 6H), 4.56–4.72 (m, 3H), 6.30–6.39 (m, 2H), 6.56 (d, $^3J_{trans} = 15.9$ Hz, 1H), 6.74–6.77 (m, 2H), 6.93 (m, 1H), 7.04 (d, $^3J = 8.2$ Hz, 1H), 7.15–7.27 (m, 6H), 7.39 (t, $^3J = 8.8$ Hz, 2H), 7.47 (d, $^3J = 8.8$ Hz, 1H), 7.47 (d, $^3J = 16.0$ Hz, 1H), 8.56 (s, 1H); LC–MS (ESI-1, Grad. A): 664.3 $[M+H]^+$, 686.3 $[M+Na]^+$; $R_t = 16.06$ min (isomer 1), $R_t = 17.67$ min (isomer 2); MS (MALDI-TOF): 664.9 $[M+H]^+$, 686.9 $[M+Na]^+$; HR-MS (FAB, *m*/*z*): calcd for $C_{38}H_{42}N_5O_6$ $[M+H]^+$ 664.3135, found: 664.3096.

N^{α}-3-[3-(1-*E*-*n*-Pentenyl)phenyl)]-*E*-acryloyl-D-histidyl-L-phenylalanyl-L-tyrosine hydrotrifluoroacetate (35/17). According to GP P2, the polymer-bound tripeptide **34a** (150 mg, 0.40 mmol/g, 60 μmol) was N-terminally deblocked by piperidine/DMF treatment for 2×5 min, followed by coupling with **30g** (39 mg, 180 μmol), PyAOP (94 mg, 180 μmol), DMAP (7 mg, 60 μmol), HOAt (8 mg, 60 μmol), DIEA (103 μL, 600 μmol) in 3 mL DMF/CH_2Cl_2 for 24 h according to GP P8. After the liberation of the C-terminus with $Pd(PPh_3)_4$ in 5 mL morpholine/THF for 16 h according to GP P1 variant C the product was cleaved from the resin by treatment with 2×5 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v) for 10 and 20 min and 2×5 mL TFA/H_2O 95/5 (v/v) for 30 min and 180 min according to GP P5 variant B followed by HPLC purification affording **35/17** (6 mg, 13%, eight steps) as a white solid. HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C); $R_t = 15.85$ min, purity: >95%; mp: 144 °C; $[\alpha]_D^{20}$ −4.2 (MeOH, *c* 0.33); ^{1}H NMR (400 MHz, CD_3OD): δ 0.97 (t, $^3J = 7.2$ Hz, 3H), 1.49–1.55 (m, 2H), 2.17–2.23 (m, 2H), 2.81 (dd, $^2J = 14.1$ Hz, $^3J = 10.0$, 1H), 2.91–2.97 (m, 2H), 3.09–3.19 (m, 3H), 4.48–4.52 (m, 1H), 4.58–4.66 (m, 2H), 6.29–6.34 (m, 1H), 6.41 (d, $^3J_{trans} = 16.0$ Hz, 1H), 6.60 (d, $^3J = 15.6$ Hz, 1H), 6.67 (d, $^3J = 8.6$ Hz, 2H), 6.95 (s, 1H), 7.04 (d, $^3J = 8.4$ Hz, 2H), 7.16–7.24 (m, 4H), 7.29–7.33 (m, 1H), 7.37 (m, 2H), 7.50–7.54 (m, 2H), 7.73 (d, $^3J = 15.8$ Hz, 1H), 8.40 (s, 1H); LC–MS (LC–ESI 1): 664.3 $[M+H]^+$, 686.3 $[M+Na]^+$, $R_t = 16.06$ min; MS

(MALDI-TOF): 664.7 $[M+H]^+$, 686.7 $[M+Na]^+$, 702.7 $[M+K]^+$; HRMS (FAB): calcd for $C_{38}H_{41}NaN_5O_6$ $[M+Na]^+$: 686.2955, found: 686.2938.

N^{α}-3-[2-(1-*Z*-*n*-Pentenyl)phenyl]-*E*-acryloyl-D-histidyl-L-phenylalanyl - L - tyrosin - hydrotrifluoroacetate (35/18). According to GP P2, the polymer-bound tripeptide **34a** (300 mg, 0.40 mmol/g, 120 μmol) was N-terminally deblocked by piperidine/DMF treatment for 2×5 min, followed by coupling with **30i** (104 mg, 480 μmol), PyAOP (250 mg, 480 μmol), DMAP (15 mg, 120 μmol), DIEA (205 μL, 1.2 mmol) in 3 mL DMF/CH_2Cl_2 for 24 h according to GP P8. Liberation of the C-terminus with $Pd(PPh_3)_4$ in 5 mL morpholine/THF for 16 h according to GP P1 variant C furnished the polymer bound compound **N^{α}-3-[2-(1-*Z*-*n*-pentenyl)phenyl]-*E*-acryloyl-D-histidyl-L-phenylalanyl-L-tyrosine-hydrotrifluoroacetate**. The product was cleaved from the resin by treatment with 2×5 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v) for 10 and 20 min and 2×5 mL TFA/H_2O 95/5 (v/v) for and 180 min according to GP P5 variant B followed by HPLC purification affording **35/18** (35 mg, 38%, eight steps) as a yellowish solid. HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C): R_t = 14.90 min, purity: 90%; mp: 134 °C; $[\alpha]_D^{20}$ +7.0 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 0.76 (t, ^3J = 7.2 Hz, 3H, CH_2CH_3), 1.28–1.33 (m, 2H), 1.89–1.95 (m, 2H), 2.72–2.78 (dd, ^2J = 13.9 Hz, ^3J = 10.0 Hz, 1H), 2.86–2.95 (m, 2H), 2.99–3.10 (m, 3H), 4.48–4.52 (m, 1H), 4.58–4.66 (m, 2H), 5.63–5.80 (m, 1H), 6.46 (d, $^3J_{cis}$ = 11.1 Hz, 1H), 6.51 (d, $^3J_{trans}$ = 15.6 Hz, 1H), 6.61 (d, ^3J = 8.6 Hz, 2H), 6.87 (s, 1H), 7.00 (d, ^3J = 8.6 Hz, 2H), 7.08–7.16 (m, 6H), 7.21–7.27 (m, 2H), 7.59 (d, ^3J = 7.0 Hz, 1H), 7.73 (d, $^3J_{trans}$ = 15.8 Hz, 1H), 8.40 (s, 1H); LC–MS (ESI-1 Grad. A): 662.4 $[M-H]^-$, 664.3 $[M+H]^+$, 686.3 $[M+Na]^+$; R_t = 15.53 min; MS (MALDI-TOF): 664.9 $[M+H]^+$, 686.9 $[M+Na]^+$, 702.9 $[M+K]^+$; HRMS (FAB): calcd for $C_{38}H_{42}N_5O_6$ $[M+H]^+$: 664.3135, found: 664.3150.

N^{α}-3-[2-(*n*-Pentyl)phenyl]propionyl-D-histidyl-L-phenylalanyl-L-tyrosin hydrotrifluoroacetate (36). Starting from **34a** (300 mg, 0.40 mmol/g, 120 μmol) polymer-bound compound **N^{α}-3-[2-(1-*Z*-*n*-pentenyl)phenyl]-*E*-acryloyl-D-histidyl-L-phenylalanyl-L-tyrosine-hydrotrifluoroacetate** was synthesized according to the procedure described for **35/18**. After cleavage from the resin the product by treatment with 2×5 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v) for 10 and 20 min and 2×5 mL TFA/H_2O 95/5 (v/v) for 30 and 180 min according to GP P5 variant B the cleaving solutions were concentrated in vacuo. The residue was dissolved in 5 mL dioxane, Pd (50 mg, 10% on charcoal) was added and the suspension was stirred for 8 h under an hydrogen atmosphere. After filtration over Celite, the filtrate was concentrated. Purification by HPLC and lyophilisation afforded 36 (28 mg, 30%, eight steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C): R_t = 14.70 min, purity: >95%; mp: 120–121 °C; $[\alpha]_D^{20}$ +7.2 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 0.89 (t, ^3J = 7.2 Hz, 3H), 1.31–1.35 (m, 4H), 1.52–1.58 (m, 2H), 2.43–2.49 (m, 2H), 2.60 (t, ^3J = 7.8 Hz, 2H), 2.73–2.89 (m, 4H), 2.92–3.03 (m, 2H), 3.10–3.15 (m, 2H), 4.55–4.64 (m, 3H), 6.68 (d, ^3J = 8.6 Hz, 2H), 6.85 (s, 1H), 7.04–7.09 (m, 7H), 7.15–7.22 (m, 4H), 8.60 (s, 1H); LC–MS (ESI-1, Grad. A): 668.3 $[M+H]^+$, 690.3 $[M+Na]^+$, 666.5 $[M-H]^-$, R_t = 16.33 min; MS (MALDI-TOF): 668.5 $[M+H]^+$, 690.5 $[M+Na]^+$; HR-MS (FAB, *m*/*z*): calcd for $C_{38}H_{46}N_5O_6$ $[M+H]^+$: 668.3448, found: 668.3421.

N^{α}-3-(4-Biphenyl)-*E*-acryloyl-D-histidyl-L-phenylalanyl-L-tyrosine-hydrotrifluoroacetate (35/19). According to GP P2, the polymer-bound tripeptide **34a** (300 mg, 0.40 mmol/g, 120 μmol) was N-terminally deblocked by piperidine/DMF treatment for 2×5 min, followed by coupling with **29a** (109 mg, 480 μmol), HATU (186 mg, 480 μmol), HOAt (16 mg, 120 μmol) und DIEA (205 μL, 1.2 mmol) in 5 mL NMP für 24 h. After the liberation of the C-terminus with $Pd(PPh_3)_4$ in 5 mL morpholine/THF for 16 h according to GP P1 variant C the product was cleaved from the resin by treatment with 2×5 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v) for 10 and 20 min and 2×5 mL TFA/H_2O 95/5 (v/v) for and 180 min according to GP P5 variant B followed by HPLC purification affording **35/19** (32 mg, 34%, eight steps) as a yellowish solid. HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C): R_t = 13.00 min, purity: >95%; mp: 118–119 °C; $[\alpha]_D^{20}$ +8.9 (*c* 1.00; MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 2.41–2.45 (m, 2H), 2.63–2.93 (m, 6H), 2.99–3.04 (m, 2H), 4.29 (t, ^3J = 7.0 Hz, 1H), 4.35 (dd, ^3J = 5.9 Hz, ^3J = 8.6 Hz, 1H), 4.66 (dd, ^3J = 5.5 Hz, ^3J = 8.8 Hz, 1H), 6.58 (d, ^3J = 8.6 Hz, 2H), 6.78 (m, 1H), 6.94 (d, ^3J = 8.4 Hz, 2H), 7.04–7.15 (m, 7H), 7.16–7.21 (m, 2H), 7.27–7.40 (m, 2H), 7.39 (d, ^3J = 7.8 Hz, 2H), 7.45 (d, ^3J = 7.8 Hz, 2H), 8.49 (s, 1H). LC–MS (ESI-1, Grad. A): 674.3 $[M+H]^+$; R_t = 13.63 min; MS (MALDI-TOF): 674.9 $[M+H]^+$, 696.9 $[M+Na]^+$, 712.9 $[M+K]^+$; HRMS (FAB): calcd for $C_{39}H_{40}N_5O_6$ $[M+H]^+$ 674.2979, found: 674.2947.

N^{α}-3-(4-Biphenyl)-*E*/*Z*-acryloyl-D-histidyl-*N*-methyl-L-phenylalanyl-L-tyrosine hydrotrifluoroacetate (35/20). According to GP P2, the polymer-bound tripeptide **34a** (400 mg, 0.40 mmol/g, 160 μmol) was N-terminally deblocked by piperidine/DMF treatment for 2×5 min, followed by coupling with **30b** (179 mg, 800 μmol), PyAOP (417 mg, 800 μmol), HOAt (109 mg, 800 μmol), DMAP (25 mg, 200 μmol), DIEA (343 μL, 2.0 mmol) in 7 mL DMF/CH_2Cl_2 2/1 (v/v) for 18 h according to GP P8. After the liberation of the C-terminus with $Pd(PPh_3)_4$ in 5 mL morpholine/THF for 16 h according to GP P1 variant C, the product was cleaved from the resin by treatment with 2×5 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v) for 2×45 min and 2×5 mL TFA/H_2O 95/5 (v/v) for 2×1.5 h according to GP P5 variant B followed by HPLC purification affording **35/20** (27 mg, 21%) as a white solid as a mixture of *E*- and *Z*-isomer (*E*/*Z* = 1.6/1, according to ^{1}H NMR). HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–70/30/0.1 in 30 min, 50 °C): R_t = 15.20 min (*E*-isomer), R_t = 16.34 min (*Z*-isomer); mp: 161 °C; $[\alpha]_D^{20}$ −43.9 (*c* 0.59, MeOH); ^{1}H NMR (400 MHz, CD_3OD): *Z*-isomer: δ 2.29–2.43 [2.59–2.70] (m, 1H), 2.42 [2.58] (s, 3H), 2.81–3.05 (m, 4H), 3.06–3.28 (m, 2H), 4.50–4.68 (m, 1H), 5.01–5.20 (m, 1H), 5.31–5.50 (m, 1H), 4.68–4.72 (m, 1H), 5.86 [5.96] [6.01] (d, $^3J_{cis}$ = 12.5 Hz, 1H), 6.58 (d, ^3J = 8.4 Hz, 2H), 6.65–6.69

[6.78–6.82] [6.88–6.93] (m, 1H), 6.97–7.01 (m, 1H), 7.09–7.25 (m, 9H), 7.32–7.36 (m, 1H), 7.41–7.45 (m, 3H), 7.52–7.56 (m, 1H), 7.59–7.70 (m, 7H), 8.65 [8.70] [8.73] (s, 1H); *E*-isomer: δ 2.29–2.43 [2.59–2.70] (m, 1H), 2.42 [2.58] (s, 3H), 2.81–3.05 (m, 4H), 3.06–3.28 (m, 2H), 4.50–4.68 (m, 1H), 5.01–5.20 (m, 1H), 5.31–5.50 (m, 1H), 4.68–4.72 (m, 1H), 6.46 [6.56] (d, $^3J_{trans}$ = 15.8 Hz, 1H), 6.58 (d, ^3J = 8.4 Hz, 2H), 6.65–6.69 [6.78–6.82] [6.88–6.93] (m, 1H), 6.97–7.01 (m, 1H), 7.09–7.25 (m, 8H), 7.32–7.36 (m, 1H), 7.41–7.45 (m, 3H), 7.52–7.56 (m, 1H), 7.59–7.70 (m, 8H), 8.65 [8.70] [8.73] (s, 1H); LC–MS (ESI-1, Grad. B): 686.2 $[M+H]^+$, 708.3 $[M+Na]^+$, R_t = 14.22 min (isomer 1), R_t = 15.31 (isomer 2); MS (MALDI-TOF): 686.1 $[M+H]^+$; HRMS (FAB): calcd for $C_{40}H_{40}N_5O_6$ $[M+H]^+$: 686.2979, found: 686.3008.

General procedure for the synthesis of the compounds 35/21–35/26 (GP P16)

According to GP P2, the polymer-bound tripeptide **34a** or **34b** (400 mg, 0.40 mmol/g, 160 μmol) was N-terminally deblocked by piperidine/DMF treatment for 2×5 min, followed by coupling with **30c**, **30d**, or **30e** (122 mg, 480 μmol), PyAOP (250 mg, 480 μmol), DMAP (20 mg, 160 μmol) and DIEA (274 μL, 1.6 mmol) in 7 mL DMF/CH_2Cl_2 2/1 (v/v) for 18 h. After the liberation of the C-terminus with $Pd(PPh_3)_4$ in 5 mL morpholine/THF for 16 h according to GP P1 variant C the product was cleaved from the resin by treatment with 2×5 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v) for 2×45 min and 2×5 mL TFA/H_2O 95/5 (v/v) for 2×1.5 h according to GP P5 variant B followed by HPLC purification affording the appropriate product.

N^{α}-3-[2-(Benzyloxy)phenyl]-*E*-acryloyl-L-histidyl-L-phenylalanyl-L-tyrosine hydrotrifluoroacetate (35/21). Reaction with **30c** starting from tripeptide **34b** according to GP P16 furnished **35/21** (16 mg, 13%, eight steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–70/30/0.1 in 30 min, 50 °C): R_t = 15.61 min, purity: 89%; mp: 118 °C; $[\alpha]_D^{20}$ −3.7 (*c* 0.43, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 2.80 (d, ^3J = 9.8 Hz, 1H), 2.89–2.95 (m, 2H), 3.07–3.15 (m, 3H), 4.58 (d, ^3J = 5.3 Hz, 1H), 4.64 (d, ^3J = 4.9 Hz, 1H), 4.68–4.72 (m, 1H), 5.09 (s, 2H), 6.56 (d, $^3J_{trans}$ = 15.8 Hz, 1H), 6.66 (d, ^3J = 8.4 Hz, 2H), 6.92-7.05 (m, 2H), 7.02–7.17 (m, 8H), 7.27–7.37 (m, 5H), 7.42 (d, ^3J = 7.2 Hz, 2H), 7.56 (d, $^3J_{trans}$ = 15.8 Hz, 1H), 8.63 (s, 1H); LC–MS (ESI-1, Grad. B): 700.4 $[M-H]^-$, 702.3 $[M+H]^+$, R_t = 19.21 min; MS (Maldi-TOF): 703.09 $[M+H]^+$, 725.59 $[M+Na]^+$; HRMS (FAB): calcd for $C_{40}H_{40}N_5O_7$, $[M+H]^+$; 702.2928, found: 702.2937.

N^{α}-3-[2-(benzyloxy)phenyl]-*E*/*Z*-acryloyl-D-histidyl-L-phenylalanyl-L-tyrosine hydrotrifluoroacetate (35/22). Reaction with **30c** starting from tripeptide **34a** according to GP P16 furnished **35/22** (13 mg, 10%, eight steps) as a white solid as a mixture of *E*- and *Z*-isomer (*E*/*Z* = 1/2.5, according to ^{1}H NMR); HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–90/10/0.1 in 40 min, 50 °C): R_t = 14.12 min (*Z*-isomer), R_t = 14.50 min (*E*-isomer); mp: 127 °C; $[\alpha]_D^{20}$ −15.3 (*c* 0.50, MeOH); ^{1}H NMR (400 MHz, CD_3OD): *Z*-isomer: δ 2.74–3.10 (m, 6H), 4.43–4.58 (m, 3H), 5.04 (s, 2H), 5.90 (d, $^3J_{cis}$ = 12.5 Hz, 1H), 6.60 (d, ^3J = 8.4 Hz, 2H), 6.71–6.75 (m, 1H), 6.79–6.82 (m, 1H), 6.93–6.97 (m, 3H), 7.10–7.12 (m, 6H), 7.25–7.33 (m, 3H), 7.36–7.42 (m, 3H), 7.53 (d, ^3J = 8.8 Hz, 1H), 8.27 (s, 1H); *E*-isomer: δ 2.74–3.10 (m, 6H), 4.43–4.58 (m, 3H), 5.14 (s, 2H), 6.54 (d, $^3J_{trans}$ = 15.8 Hz, 1H), 6.60 (d, ^3J = 8.4 Hz, 2H), 6.71–6.75 (m, 1H), 6.79–6.82 (m, 1H), 6.93–6.97 (m, 3H), 7.10–7.12 (m, 6H), 7.25–7.33 (m, 3H), 7.36–7.42 (m, 3H), 7.53 (d, ^3J = 8.8 Hz, 1H), 8.31 (s, 1H); LC–MS (ESI-1, Grad. B): 702.3 $[M+H]^+$, 724.3 $[M+Na]^+$, R_t = 17.77 min (isomer 1), 702.3 $[M+H]^+$, 724.3 $[M+Na]^+$, R_t = 18.73 min (isomer 2).

N^{α}-3-[3-(Benzyloxy)phenyl]-*E*-acryloyl-L-histidyl-L-phenylalanyl-L-tyrosin-hydrotrifluoroacetate (35/23). Reaction with **30d** starting from tripeptide **34b** according to GP P16 furnished **35/23** (28 mg, 21%, eight steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–70/30/0.1 in 30 min, 50 °C): R_t = 16.72 min, purity: 91%; mp: 147 °C; $[\alpha]_D^{20}$ −23.9 (*c* 0.90, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 2.80–3.21 (m, 3H) 3.07–3.15 (m, 3H), 4.56 (dd, ^3J = 5.3 Hz, ^3J = 8.4 Hz, 1H), 4.61 (dd, ^3J = 5.3, ^3J = 9.2 Hz, 1H), 4.71–4.73 (m, 1H), 5.07 (s, 2H), 6.52 (d, ^3J = 15.6 Hz, 1H), 6.65 (d, ^3J = 8.6 Hz, 2H), 6.98–7.04 (m, 3H), 7.06–7.20 (m, 8H), 7.24–7.37 (m, 4H), 7.38–7.42 (m, 2H), 7.45 (d, ^3J = 15.8 Hz, 1H), 8.62 (s, 1H); LC-MS (ESI-1, Grad. B): 700.4 $[M-H]^-$, 702.3 $[M+H]^+$, 724.3 $[M+Na]^+$, R_t = 20.76 min; MS (MALDI-TOF): 703.66 $[M+H]^+$, 725.80 $[M+Na]^+$; HRMS (FAB): calcd for $C_{40}H_{40}N_5O_7$ $[M+H]^+$: 702.2928, found: 702.2945.

N^{α}-3-[3-(benzyloxy)phenyl]-*E*/*Z*-acryloyl-D-histidyl-L-phenylalanyl-L-tyrosine hydrotrifluoroacetate (35/24). Reaction with **30d** starting from tripeptide **34a** according to GP P16 furnished **35/24** (37 mg, 28%) as a white solid as a mixture of *E*- und *Z*-isomer (*E*/*Z* = 1.7/1, according to ^{1}H NMR); HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–90/10/0.1 in 30 min, 50 °C): R_t = 14.76 min (*Z*-isomer), R_t = 15.72 min (*E*-isomer); mp: 144 °C; $[\alpha]_D^{20}$ −3.5 (*c* 0.48, MeOH); ^{1}H NMR (400 MHz, CD_3OD) *Z*-isomer: δ 2.69–2.88 (m, 3H), 2.94–3.09 (m, 3H), 4.50–4.59 (m, 3H), 4.98 (s, 2H), 5.78 (d, ^3J = 12.7 Hz, 1H), 6.59–6.61 (m, 2H), 6.81–6.89 (m, 2H), 6.92–7.01 (m, 4H), 7.05–7.17 (m, 5H), 7.20–7.45 (m, 7H), 8.52 (s, 1H); *E*-isomer: δ = 2.69–2.88 (m, 3H), 2.94–3.09 (m, 3H), 4.50–4.59 (m, 3H), 5.05 (s, 2H), 6.41 (d, ^3J = 15.6 Hz, 1H), 6.59–6.61 (m, 2H), 6.81–6.89 (m, 2H), 6.92–7.01 (m, 4H), 7.05–7.17 (m, 5H), 7.20–7.45 (m, 7H), 8.54 (s, 1H); LC–MS (ESI-1, Grad. B): 702.3 $[M+H]^+$, 724.3 $[M+Na]^+$, R_t = 14.07 min (isomer 1), 702.3 $[M+H]^+$, 724.3 $[M+Na]^+$, R_t = 15.02 min (isomer 2); MS (MALDI-TOF): 704.2 $[M+H]^+$, 725.6 $[M+Na]^+$.

N^{α}-3-[4-(benzyloxy)phenyl]-*E*/*Z*-acryloyl-L-histidyl-L-phenylalanyl-L-tyrosine hydrotrifluoroacetate (35/25). Reaction with **30e** starting from tripeptide **34b** according to GP P16 furnished **35/25** (14 mg, 11%, eight steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–90/10/0.1 in 30 min, 50 °C): R_t = 15.84 min (*Z*-isomer), R_t = 16.78 min (*E*-isomer); mp: 145 °C; $[\alpha]_D^{20}$ −22.2 (*c* 0.55, MeOH); ^{1}H NMR (400 MHz, CD_3OD) *Z*-iso-

mer: δ 2.80–2.91 (m, 2H), 2.97–3.17 (m, 4H), 4.54–4.78 (m, 3H), 5.04 (s, 2H), 5.79 (d, $^3J_{cis}$ = 12.5 Hz, 1H), 6.64–6.67 (m, 3H), 6.86 (d, ^3J = 8.8 Hz, 1H), 6.98–7.04 (m, 5H), 7.07–7.18 (m, 2H), 7.26–7.51 (m, 9H), 8.60 (s, 1H). *E*-isomer: δ 2.80–2.91 (m, 2H), 2.97–3.17 (m, 4H), 4.54–4.78 (m, 3H), 5.09 (s, 2H), 6.41 (d, $^3J_{trans}$ = 15.8 Hz, 1H), 6.64–6.67 (m, 3H), 6.86 (d, ^3J = 8.8 Hz, 1H), 6.98–7.04 (m, 5H), 7.07–7.18 (m, 2H), 7.26–7.51 (m, 9H), 8.62 (s, 1H); LC–MS (ESI-1, Grad. B): 702.3 $[M+H]^+$, 724.3 $[M+Na]^+$, R_t = 15.22 min (isomer 1); 702.3 $[M+H]^+$, 724.3 $[M+Na]^+$, R_t = 16.16 min (isomer 2); MS (MALDI-TOF): 703.9 $[M+H]^+$, 725.5 $[M+Na]^+$; HRMS (FAB): calcd for $C_{40}H_{40}N_5O_7$ $[M+H]^+$ 702.2928, found: 702.2859.

N^{α}-3-[4-(Benzyloxy)phenyl]-*E*-acryloyl-D-histidyl-*N*-L-phenylalanyl-L-tyrosin hydrotrifluoroacetate (35/26). Reaction with **30e** starting from tripeptide **34a** according to GP P16 furnished **35/26** (27 mg, 19%, eight steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–90/10/0.1 in 40 min, 50 °C): R_t = 13.48 min, purity: >95%; mp: 127 °C; $[\alpha]_D^{20}$ +5.5 (*c* 0.33, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 2.74 (d, ^2J = 13.9 Hz, ^3J = 9.8 Hz, 1H), 2.83–2.90 (m, 2H), 3.01–3.09 (m, 3H), 4.51 (dd, ^3J = 5.3 Hz, ^3J = 8.3 Hz, 1H), 4.69 (dd, ^3J = 4.7 Hz, ^3J = 9.6 Hz, 1H), 4.65 (dd, ^3J = 6.5 Hz, ^3J = 7.4 Hz, 1H), 4.83 (s, 2H), 6.52 (d, $^3J_{trans}$ = 15.8 Hz, 1H), 6.55–6.63 (m, 3H), 6.68–6.77 (m, 1H), 6.87 (s, 1H), 6.93–6.99 (m, 2H), 7.07–7.15 (m, 11H), 7.31 (d, ^3J = 7.6 Hz, 1H), 7.88 (d, $^3J_{trans}$ = 15.8 Hz, 1H), 8.51 (s, 1H); LC–MS (ESI-2): 702.38 $[M+H]^+$, R_t = 1.70 min; MS (MALDI-TOF): 702.6 $[M+H]^+$, 724.6 $[M+Na]^+$.

Solid-phase bound *N*-methyl,*N*-(*o*-nitro-benzolsulfonyl)-L-tyrosine allyl ester (37). According to GP P2, polymer-bound compound **L-8** (2.80 g, 0.50 mmol/g, 1.4 mmol) was reacted twice with 10 mL piperidine/DMF for 15 min, then it was coupled with *o*-nitrobenzenesulfonic acid chloride (1.24 g, 5.6 mmol) and 2,6-lutidine (813 μL, 7.0 mmol) in 10 mL CH_2Cl_2. After shaking the suspension for 11 h under argon atmosphere, the resin was filtered off and washed with 3×5 mL CH_2Cl_2, 3×5 mL DMF/H_2O 1/1 (v/v), 3×5 mL DMF, 3×5 mL MeOH und 5×5 mL CH_2Cl_2 and finally with 8×5 mL dry THF, 4×5 mL dry CH_2Cl_2 and 2×5 mL dry DMF under argon. To the polymer bound compound were added 5 mL dry DMF, MTBD (603 μL, 4.2 mmol) and afterwards a solution of methyl-4-nitrobenzenesulfonate (1.22 g, 5.6 mmol) 15 mL DMF. After shaking for 1.5 h, the resin is filtered off, washed with 2×10 mL DMF, 2×10 mL MeOH and 3×10 mL CH_2Cl_2 and dried in vacuo. Analysis of a sample of the polymer: The analytical data confirms the complete reaction of the starting material. HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min): R_t = 8.67 min, purity: >95%; MS [EI, 70 eV, *m*/*z* (%)]: 420 (7) $[M^+]$, 335 (14) $[M^+-C_3H_5-CO_2]$, 149 (49), $[M^+-CO_2-SO_2C_6H_4NO_2-C_3H_5-OH]$, 107 (100) $[C_7H_7O^+]$, 77 (4), $[C_6H_5^+]$; HRMS (EI, 70 eV, *m*/*z*): calcd for $C_{19}H_{20}N_2O_7S$ $[M^+]$: 420.0991, found: 420.0999.

Polymer-bound N^{α}-9-Fluorenylmethoxycarbonyl-L-histidyl-*N*-methyl-L-tyrosine-allyl ester (38). To polymer-bound compound **37** (2.70 g, 0.50 mmol/g, 1.35 mmol) were added 15 mL dry DMF and after swelling for some min, DBU (1.05 mL, 7 mmol) and 2-mercaptoethanol (981 mL, 14 mmol). The suspension was shaken for 1 h, whereby the solution becomes yellow-green. After filtering the resin was washed with 3×5 mL DMF, 3×5 mL DMF/H_2O 1/1 (v/v), 3×5 mL DMF, 3×5 mL MeOH and 4×5 mL CH_2Cl_2 and dried in vacuo. Then the deprotected, polymer-bound compound (1.20 g, 0.50 mmol/g, 600 μmol) was reacted with Fmoc-L-His(Trt)OH (2.08 g, 3.36 mmol), *N*,*N*-diisopropylcarbodiimide (520 μL, 3.36 mmol), HOAt (457 mg, 3.36 mmol) and lutidine (390 μL, 3.36 mmol) in 15 mL DMF for 24 h according GP P4 variant B furnishing **38**. Ninhydrine test:[15] negative; analysis after cleavage from a polymer sample: HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C): R_t = 5.13 min; LC–MS (ESI-1, Grad. A): 595.4 $[M+H]^+$, 617.3 $[M+Na]^+$, R_t = 4.22 min.

N^{α}-9-Fluorenylmethoxycarbonyl-L-histidyl-*N*-methyl-L/D-tyrosine-*N*-methyl-L-phenylalanine allyl ester hydrotrifluoracetate (40). According to GP P1 variant B, polymer-bound compound **38** (1.20 g, 0.50 mmol/g, 600 μmol) was reacted with $Pd(PPh_3)_4$ in 15 mL THF/NMA 4/1 (v/v), then it was coupled with **26** (569 mg, 2.52 mmol), PyAOP (1.32 g, 2.52 mmol), HOAt (114 mg, 840 μmol) and DIEA (1.29 mL, 7.56 mmol) in 15 mL NMP according to GP P3 variant B furnishing the polymer-bound product **39**.

Treatment of **39** twice with TFA/H_2O/EMS 90/5/5 for 2×2.5 h and HPLC-purification furnished two isomers **40a** and **40b** of the tripeptide **N^{α}-9-fluorenylmethoxycarbonyl-L-histidyl-*N*-methyl-L/D-tyrosine-*N*-methyl-L-phenylalaninallyl ester-hydrotrifluoroacetate.**

40a. 38 mg, 29%, seven steps, brownish solid; HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C): R_t = 6.35 min, purity: >95%; mp: 115–116 °C, $[\alpha]_D^{20}$ −100.7 (*c* 1.0, MeOH), ^{1}H NMR (400 MHz, CD_3OD): δ 2.34–2.54 (m, 2H), 2.40 [2.54] (s, 3H), 2.67–3.05 (m, 3H), 2.53 [2.74] (s, 3H), 3.11–3.18 (m, 1H), 4.01–4.08 [4.22–4.30] (m, 1H), 4.37–4.59 (m, 4H), 4.61–4.68 (m, 1H), 4.80 (m, 2H), 5.03–5.34 (m, 3H), 5.78–5.85 (m, 1H), 6.55 (d, ^3J = 8.4 Hz, 2H), 6.80 (m, 2H), 6.90 (m, 1H), 7.04–7.06 (m, 2H), 7.10–7.19 (m, 5H), 7.22–7.28 (m, 2H), 7.58 (d, ^3J = 7.6 Hz, 2H), 7.67 (d, ^3J = 7.4 Hz, 2H), 8.56 (s, 1H); LC-MS (ESI 1, Grad. B): 756.2 $[M+H]^+$, 778.4 $[M+Na]^+$, R_t = 12.09 min.

40b. 31 mg, 23%, brownish solid; HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C): R_t = 7.99 min, purity: 90%; mp: 113–114 °C; $[\alpha]_D^{20}$ −192.3 (*c* 0.20, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 2.38–3.23 (m, 12H), 4.09–4.20 (m, 1H), 4.37–4.59 (m, 2H), 4.49–4.70 (m, 2H), 4.72–4.85 (m, 2H), 5.14–5.25 (m, 2H), 5.50 (m, 1H), 5.79–5.89 (m, 1H), 6.62 (d, ^3J = 8.4 Hz, 2H), 6.80–6.83 (m, 2H), 7.00–7.01 [7.02–7.04] (m, 1H), 7.09–7.21 (m, 5H), 7.27–7.31 (m, 2H), 7.37–7.40 (t, ^3J = 7.4 Hz, 2H), 7.57 (d, ^3J = 7.4 Hz, 2H), 7.78 (d, ^3J = 7.6 Hz, 2H), 8.67 (s, 1H); LC–ESI (ESI-1, Grad. B): 756.3 $[M+H]^+$, R_t = 14.02 min;

HRMS (FAB): calcd for $C_{44}H_{45}N_5O_7$ $[M+H]^+$ 756.3397, found: 756.3410.

N^{α}-Benzyloxycarbonyl-L-histidyl-*N*-methyl-L/D-tyrosyl-*N*-methyl-L-phenylalanine hydrotrifluoroacetate (42b). According to GP P2, polymer-bound compound 39 (336 mg, 0.52 mmol/g, 175 μmol) was reacted twice with 6 mL piperidine/DMF for 15 min, then it was coupled with 18a (191 μL, 1.12 mmol), DMAP (14 mg, 112 μmol), HOAt (152 mg, 1.12 mmol) and DIEA (383 μL, 2.24 mmol) in 9 mL DMF/CH_2Cl_2 for 8 h according to GP P10. After deblocking of the carboxylic function with $Pd(PPh_3)_4$ in 10 mL morpholine/THF for 24 h according to GP P1 variant C the product is cleaved from the resin by treatment with TFA/H_2O/TES 90/5/5 (v/v/v) for 24 h according to GP P5 variant A affording 42b (21 mg, 16%) as a brown solid as a diastereomeric mixture (7:3); HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–90/10/0.1 in 40 min, 50 °C): $R_t = 11.33$ min (isomer 1), $R_t = 11.83$ min (Isomer 2); mp: 109 °C; $[\alpha]_D^{20}$ −65.3 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 2.34–3.22 (m, 12H), 4.58–4.78 (m, 2H), 5.08–5.14 (m, 1H), 5.41–5.49 (m, 2H), 6.56–6.71 (m, 3H), 6.91 (m, 1H), 6.98–7.03 (m, 1H), 7.08–7.35 (m, 10H), 8.63–8.67 (m, 1H); LC-MS (ESI-1, Grad A): 628.2 $[M+H]^+$, 650.2 $[M+Na]^+$, $R_t = 2.43$ (isomer 1), $R_t = 2.48$ (isomer 2); MS (MALDI-TOF): 628.62 $[M+H]^+$, 650.61 $[M+Na]^+$; HRMS (FAB): calcd for $C_{34}H_{38}N_5O_7$ $[M+H]^+$ 628.2771, found: 628.2761.

N^{α}-3-Phenylpropionyl-L-histidyl-*N*-methyl-L/D-tyrosyl-*N*-methyl-L-phenylalanin-hydrotrifluoroacetate (42a). According to GP P2, polymer-bound compound **39** (336 mg, 0.52 mmol/g, 175 μmol) was reacted twice with 6 mL piperidine/DMF for 15 min, then it was coupled with **29c** (135 mg, 896 μmol), HATU (319 mg, 840 μmol), HOAt (38 mg, 280 μmol) and DIEA (479 μL) in 9 mL NMP for 8 h according to GP P9. After deblocking of the carboxylic function with $Pd(PPh_3)_4$ in 10 mL morpholine/THF for 24 h according to GP P1 variant C the product is cleaved from the resin by treatment with TFA/H_2O/TES 90/5/5 (v/v/v) for 24 h according to GP P5 variant A affording **42a** (66 mg, 50%) as a brown solid as a diastereomeric mixture (7/3); HPLC (A2, CH_3CN/H_2O/TFA, 20/80/0.1–90/10/0.1 in 50 min, 50 °C) $R_t = 17.88$ min (isomer 1), $R_t = 19.14$ min (isomer 2); mp: 122 °C; $[\alpha]_D^{20}$ −71.8 (*c* 0.32, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 2.29–3.23 (m, 16H), 4.58–4.64 (m, 1H), 5.08–5.14 (m, 1H), 5.28–5.48 (m, 1H), 6.56–6.75 (m, 3H), 6.85–6.93 (m, 1H), 7.01–7.04 (m, 1H), 7.13–7.38 (m, 10H), 8.61 [8.64] (m, 1H). LC–MS (ESI-1, Grad A): 626.2 $[M+H]^+$, 648.3 $[M+Na]^+$; 2.50 min; HRMS (FAB): calcd for $C_{35}H_{41}N_5O_6$ $[M+H]^+$ 626.2979, found: 626.2958.

General procedure for the synthesis of dipeptides of type 43 (GP P17)

According to GP P1 variant B, polymer-bound compound **L-8** (400 mg, 0.41 mmol/g, 162 μmol) was C-terminally deblocked with $Pd(PPh_3)_4$ in 5 mL NMA/THF followed by coupling with 3 equiv of **28a** or **28b**, PyAOP (256 mg, 490 μmol) and DIEA (528 μL, 3.10 mmol) according to GP P3 in 5 mL NMP for 8 h affording dipeptides **43**.

General procedure for the synthesis of dipeptides of type 44 (GP P18)

According to GP P2, polymer-bound compounds **43** were N-terminally deblocked with 2×5 mL piperidine/DMF for 2×3 min, followed by coupling with Fmoc-D-Tyr(*t*Bu)OH (223 mg, 486 μmol) by reaction with HATU (170 mg, 440 μmol), HOAt (22 mg, 162 μmol) and DIEA (277 μL, 162 μmol) in 5 mL NMP for 14 h according to GP P4 variant A affording the polymer bound compounds **44**.

Polymer bound *N*-9-Fluorenylmethoxycarbonyl-(*O*-*tert*-butyl)-D-tyrosyl-L-tyrosyl-L-phenylalanine allyl ester (44a). Reaction of **L-8** (400 mg, 0.41 mmol/g, 162 μmol) with **28a** (185 mg, 490 μmol) according to GP P17 furnished the dipeptide **43a** which was reacted with Fmoc-D-Tyr(*t*Bu)OH according to GP P18 affording **44a**; Ninhydrine test: negative; TFA-cleavage from a polymer sample furnished the deprotected compound Fmoc-Tyr-Tyr-Ph-OH: HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C): $R_t = 16.81$ min; LC–MS (ESI-1, Grad. A): 754.1 $[M+H]^+$, $R_t = 13.58$ min; $C_{45}H_{43}N_3O_8$ (753.84).

Polymer-bound *N*-9-Fluorenylmethoxycarbonyl-(*O*-*tert*-butyl)-D-tyrosyl-L-tyrosyl-L-3-(2-naphthyl)alanine allyl ester (44b). Reaction of **L-8** (400 mg, 0.41 mmol/g, 162 μmol) with **28b** (209 mg, 490 μmol) according to GP P17 furnished the dipeptide **43b** which was reacted with Fmoc-D-Tyr(*t*Bu)OH according to GP P18 affording **44b**. Ninhydrine Test:[15] negative; TFA-cleavage from a polymer sample furnished the deprotected compound Fmoc-Tyr-Tyr-Naph-OH: HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C): $R_t = 13.96$ min; MS (MALDI-TOF): 827.0 $[M+Na]^+$, 842.9 $[M+K]^+$; Fmoc-Tyr-Tyr-Naph-OH: $C_{49}H_{45}N_3O_8$ (803.91).

General procedure for the synthesis of tripeptides of the type *N*-3-[(4-(*n*-pentyl)phenyl]propionyl-D-Tyr-Tyr-X-OH (GP P19)

According to GP P2, the polymer-bound tripeptide **44** (400 mg, 0.41 mmol/g, 162 μmol) was reacted twice with 5 mL piperidine/DMF for 5 min, the compound is then reacted with **29b** (117 mg, 530 μmol), HATU (188 mg, 480 μmol), HOAt (22 mg, 162 μmol) and DIEA (277 μL, 1.62 mmol) in 5 mL NMP for 12 h according to GP P9. After deblocking of the carboxylic function with $Pd(PPh_3)_4$ in 10 mL morpholine/THF for 24 h according to GP P1 variant C the product is cleaved from the resin by treatment with 2×5 mL TFA/CH_2Cl_2/H_2O 47/47/6 (v/v/v) for 2×15 min and with 2×5 mL TFA/H_2O 95/5 (v/v) for 2×1.5 h according to GP P5 variant B.

***N*-3-[(4-(*n*-pentyl)phenyl]propionyl-D-tyrosyl-L-tyrosyl-L-phenylalanine (45a).** Starting from tripeptide **44a** reaction according to GP P19 furnishes **45a** (16 mg, 14%, eight steps) as a white solid; HPLC (A2, CH_3CN/H_2O/

TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C): $R_t = 8.25$ min, purity: >95%; mp: 214 °C; $[\alpha]_D^{20}$ −1.1 (*c* 0.47, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 0.74 (t, $^3J = 6.8$ Hz, 3H), 1.16–1.18 (m, 4H), 1.42–1.47 (m, 2H), 2.26–2.32 (m, 2H), 2.39–2.43 (m, 2H), 2.51–2.61 (m, 2H), 2.65–2.72 (m, 4H), 2.86–2.91 (m, 1H), 3.03–3.07 (m, 1H), 4.26–4.33 (m, 2H), 4.51–4.54 (m, 1H), 6.51–6.55 (m, 4H), 6.61 (d, $^3J = 8.4$ Hz), 6.70 (d, $^3J = 8.4$ Hz, 2H), 6.92–7.15 (m, 9H); LC–MS (ESI-1, Grad. A): 694.2 $[M+H]^+$, 716.4 $[M+Na]^+$; $R_t = 11.78$ min; MS (MALDI-TOF): 694.9 $[M+H]^+$, 716.8 $[M+Na]^+$; HRMS (FAB): calcd for $C_{41}H_{48}N_3O_7$ $[M+H]^+$ 694.3492, found: 694.3522.

***N*-3-[(4-(*n*-Pentyl)phenyl]propionyl-D-tyrosyl-L-tyrosyl-L-3-(2-naphthyl)alanine (45b).** Starting from tripeptide **44b** reaction according to GP P19 furnishes **45b** (26 mg, 22%, eight steps) as a white solid; HPLC (A2, CH_3CN/H_2O/TFA, 45/55/0.1–90/10/0.1 in 30 min, 50 °C) $R_t = 9.74$ min, purity: >95%; mp: 102 °C; $[\alpha]_D^{20}$ +2.0 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3MeOD): δ 0.78 (t, $^3J = 6.94$ Hz, 3H), 1.20–122 (m, 4H), 1.46–1.49 (m, 2H), 2.24–2.29 (m, 2H), 2.45 (t, $^3J = 7.8$ Hz, 2H), 2.48–2.62 (m, 2H), 2.63–2.75 (m, 4H), 3.06–3.11 (dd, $^2J = 13.9$ Hz, $^3J = 7.8$ Hz, 1H), 3.23–3.28 (m, 1H), 4.29 (t, $^3J = 7.0$ Hz, 1H), 4.35 (dd, $^3J = 5.9$ Hz, $^3J = 7.8$ Hz, 1H), 4.66 (dd, $^3J = 5.5$ Hz, $^3J = 7.6$ Hz, 1H), 6.52–6.57 (m, 4H), 6.64 (d, $^3J = 8.4$ Hz, 2H), 6.68 (d, $^3J = 8.4$ Hz, 2H), 6.94 (d, $^3J = 8.2$ Hz), 6.98 (d, $^3J = 8.2$ Hz, 2H), 7.18 (dd, $^3J = 8.4$ Hz, $^4J = 1.8$ Hz, 1H), 7.30–7.34 (m, 2H), 7.52 (s, 1H), 7.61–7.68 (m, 3H); LC–MS (ESI 1, Grad. A): 744.2 $[M+H]^+$, 766.4 $[M+Na]^+$, $R_t = 14.45$ min; MS (MALDI-TOF): 766.5 $[M+Na]^+$; HRMS (FAB): calcd for $C_{45}H_{50}N_3O_7$ $[M+H]^+$: 744.3649, found: 744.3660.

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