# Enantioselective Solid-Phase Peptide Synthesis Using Traceless Chiral Coupling Reagents and Racemic Amino Acids

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Dedicated to Prof. *Dieter Seebach* on the occasion of his 75th birthday

The enantioselective condensing reagent 4,6-dimethoxy-1,3,5-triazine (DMT)/strychnine/$BF_4^-$ was obtained by treatment of 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) with strychnine tetrafluoroborate. The reagent was useful under typical conditions of solid-phase peptide synthesis (SPPS) with enantiomerically homogeneous substrates. By SPPS, desired dipeptides were obtained in 84–94% yield using 4 equiv. of racemic Fmoc-Ala, Fmoc-Phe, and/or Fmoc-Tyr for 1 equiv. of *Wang* resin loaded with Gly, Ala, Leu, Phe, Glu(*t*Bu), and/or Pro, respectively. For all three Fmoc-protected amino acids, the configuration of the enantiomer preferred under SPPS conditions was independent of the structure of the acylated component and identical to that established in condensations proceeding in solution. In all cases, the enantiomer ratios L/D (er) were in a similar range, and varied from 9:92 to 2:98 for alanine, and from 90:10 to 100:0 for aromatic amino acids. The synthesis of Ac-L-Lys(Ac)-D-Ala-D-Ala-OH from racemic Fmoc-Ala gave an L/D ratio of 10:90 for the esterification of *Wang* resin, and 0:100 for the formation of peptide bonds.

**1. Introduction.** – *Methods of Enantioselective Acylation.* Ready access to a whole range of chiral building blocks is essential to derive full profits from the systematic exploration of a diversity of peptide structures by using the latest methods of combinatorial chemistry and high throughput screening. The classical approach based on asymmetric synthesis or resolution of a racemic precursor seems to be non-optimal, because most substrates are used in minute amounts in single experiments only, and usually they are discarded after a preliminary selection procedure as not promising. Therefore, an approach based on the enantiomer-differentiating transformation of racemic substrates, which are usually easily available, would be welcome as more advantageous and less time-consuming than the long-established procedures based on racemate resolution or asymmetric synthesis. Such an approach would be considered the most convenient procedure based on coupling chiral building blocks, such as amino acids used for the construction of complex peptide molecules. Although several chiral coupling reagents and chiral acylation catalysts have been proposed for the synthesis of enantiomerically enriched peptides directly from racemic substrates, including optically active *N*-hydroxysuccinimide [1–6], diacylamines [7–14], chiral 4-(dimethylamino)pyridine (DMAP) analogs [15–23], 1-methyl-1*H*-imidazole [24–30],

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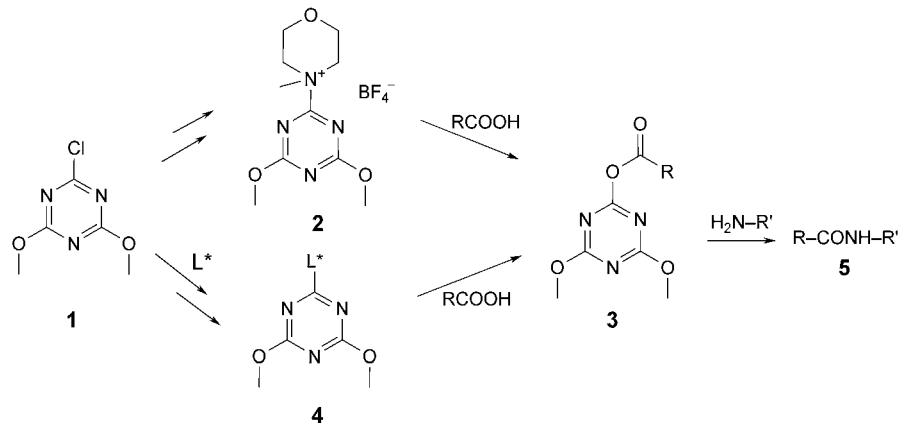
benzotetramisol [31], tertiary amines [32–36] and phosphines [37–45], and others [46–55] as chiral auxiliaries, so far none of the proposed enantioselective coupling methods has been acceptable for peptide synthesis because of the unpredictable configuration, enantiomeric purity, and yield of the final product.

The unpredictability of the enantioselective synthesis of peptides is caused by the fairly complex mechanism of this process, consisting of two subsequent stages. In the first one, the carboxylic group is activated, followed by aminolysis of the activated species in the second step. In both of these elementary stages, tetrahedral intermediates are formed with additional stereogenic centers at the C-atom of the former carboxylic group. Moreover, both the formation and decay of the tetrahedral intermediates, proceeding *via* multiple transition states, depend on the multifaceted matching/dismatching effects of all the stereogenic centers of all the reacting molecules.

**2. Chiral 1,3,5-Triazine-Based Coupling Reagents for Enantiomerically Enriched (Pure) Peptides Directly from Racemic Substrates.** – Recently, we solved the problem of unpredictable enantioselective synthesis of peptides from racemic substrates. This was accomplished by substantial simplification of interactions between stereogenic centers. To achieve this, traceless enantioselective coupling reagents were designed with the chiral fragment departing after the activation of a carboxylic component. According to this concept, such reagents are prepared by temporary attachment of the chiral fragment to a classical peptide-bond-forming agent. Thus, after selection of the enantiomer at the activation stage and departure of the chiral component, the activated intermediate is converted to a well-known form of a conventional acylating species. To date, the only traceless reagent according to the concept presented above has been obtained by modification of the 1,3,5-triazine-based coupling reagent **2** with the chiral fragment integrated in the ammonium leaving group L*, departing as HL* after activation with the formation of the 'classic' 1,3,5-triazin-2-yl 'superactive' ester **3** [56–59] (*Scheme 1*).

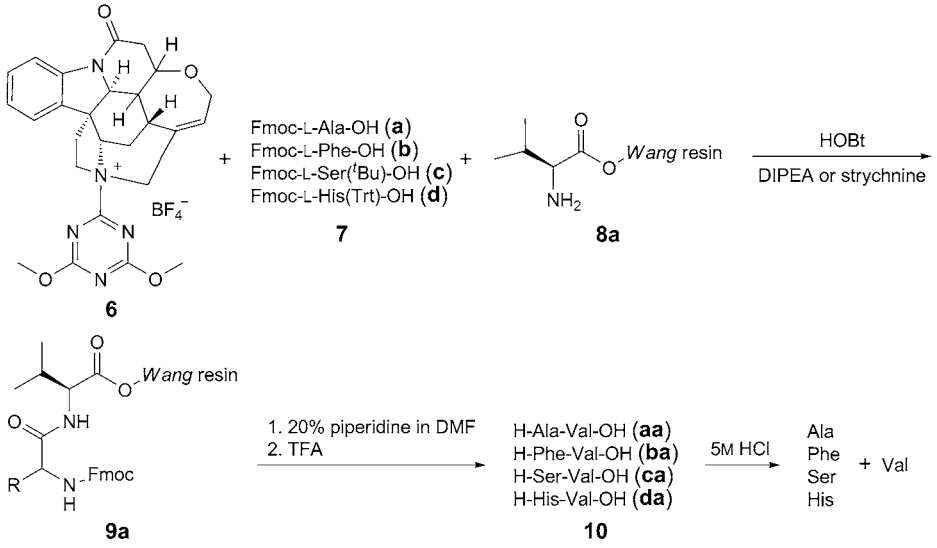
Scheme 1. *Enantioselective Activation of the Carboxylic Component with the Traceless Coupling Reagent* **4** *Affords the Activated Carboxylic Component* **3** *Identical to the Product of Activation with the Classic Achiral Reagent* ***2***



Thus, for every racemic carboxylic component, the results of synthesis may be predicted from a single model experiment. On the other hand, any modification of the chiral fragment necessary to access the preferred configuration or to improve enantiomeric enrichment gives exactly the same acylating intermediate, which significantly facilitates the synthetic protocol. Triazine coupling reagents containing strychnine (DMT/strychnine/$BF_4^-$) [60] or brucine (DMT/brucine/$BF_4^-$) [61] as the chiral fragment have proved highly effective in the synthesis of enantiomerically enriched or even enantiomerically homogeneous peptides from racemic substrates in the solution phase.

**3. Attempts to Exploit of Chiral Traceless Coupling Reagents in the Solid-Phase Peptide Synthesis (SSPS).** – It is well-known that enantiomeric enrichment obtained in an enantioselective process is substantially enhanced by a greater excess of the racemic substrate. However, in syntheses proceeding in solution, the excess of the substrate used may severely impede the isolation of the final product. Therefore, one can presume that this drawback could be completely eliminated under conditions of SPPS. The application of a racemic substrate in a reasonably increased excess should enhance enantioselectivity, unify enantiomeric enrichment for homologous substrates, and be advantageous for the final yield as well purity of the product. To verify the potential of this approach, the enantioselective coupling reagent **6** was obtained by treatment of 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT; **1**) with strychnine tetrafluoroborate as described in [60] and used in SPPS. In preliminary experiments, we confirmed the versatility of **6** under conditions of the SPPS standard protocol involving optically pure *N*-protected amino acids, an augmented amount of tertiary amine, and a variety of additives [62] (*Scheme 2*).

Scheme 2. *The Selection of Conditions for Peptide-Bond Formation Using Chiral Triazine Coupling Reagents in SPPS*



In the study, enantiomerically pure amino acids prone to racemization, *i.e.*, Fmoc-L-Phe-OH (**7b**), Fmoc-L-Ser(*t*Bu)-OH (**7c**), and Fmoc-L-His(Trt)-OH (**7d**), were used as substrates[1]) (*Table 1*).

Table 1. *Solid-Phase Peptide Synthesis Using DMT/Strychnine/$BF_4^-$* (**6**). In all reactions, 4 equiv. of *N*-protected L-amino acids, 2 equiv. of DMT/strychnine/$BF_4^-$, 4 equiv. of tertiary amine, and 1 equiv. of amino component (Val-*Wang* resin) were used.

| *Entry* | C-Comp. **7** | Amine | Product **10** | Yield [%] | er[1]) C-Comp. (L/D) | er[1]) N-Comp. (L/D) |
|---|---|---|---|---|---|---|
| *1* | Ala (**a**) | $EtN^iPr_2$ | H-L-Ala-L-Val-OH (**10aa**) | 91 | 100 : 0 | 100 : 0 |
| *2* | Ala (**a**) | Strychnine | H-L-Ala-L-Val-OH (**10aa**) | 90 | 100 : 0 | 100 : 0 |
| *3* | Phe (**b**) | $EtN^iPr_2$ | H-L-Phe-L-Val-OH (**10ba**) | 93 | 99.8 : 0.2 | 100 : 0 |
| *4* | Phe (**b**) | Strychnine | H-L-Phe-L-Val-OH (**10ba**) | 92 | 100 : 0 | 100 : 0 |
| *5* | Ser (**c**) | $EtN^iPr_2$ | H-L-Ser-L-Val-OH (**10ca**) | 90 | 99.7 : 0.3 | 100 : 0 |
| *6* | Ser (**c**) | Strychnine | H-L-Ser-L-Val-OH (**10ca**) | 91 | 99.8 : 0.2 | 100 : 0 |
| *7* | His (**d**) | $EtN^iPr_2$ | H-L-His-L-Val-OH (**10da**) | 89 | 99.5 : 0.5 | 100 : 0 |
| *8* | His (**d**) | Strychnine | H-L-His-L-Val-OH (**10da**) | 88 | 99.6 : 0.4 | 100 : 0 |

It has been found that the presence of strychnine or DIPEA ($EtN^iPr_2$) does not alter the solid-phase coupling procedure with **6** as a reagent for peptide-bond formation. In some cases, minimal racemization of C-components was observed; however, rather than being the result of epimerization, this may be due to rather harsh conditions of hydrolysis of peptides to amino acids, which was indispensable for the evaluation of their enantiomeric composition by gas chromatography on chiral stationary phase.

The absence of racemization of the acylating components in the presence of DMT/strychnine/$BF_4^-$ (**6**) under SPPS conditions prompted us to apply **6** as a chiral coupling reagent in the synthesis of peptides directly from racemic *N*-protected amino acids under such conditions. The usefulness of **6** was then evaluated by the SPPS of dipeptides using racemic Fmoc-alanine, Fmoc-phenylalanine, and Fmoc-tyrosine as starting materials. In all cases syntheses were performed on *Wang* resin[2]). The process involved two steps: *i*) activation of the racemic Fmoc-protected C-component (2 equiv.) by using DMT/strychnine/$BF_4^-$ (**6**) to yield enantiomerically enriched active ester **3**; *ii*) acylation of an N-component anchored to *Wang* resin **8** (*Scheme 3*).

The configurational preferences and enantiomeric enrichment of the selected racemic *N*-protected substrates in syntheses proceeding in solution were determined previously in independent condensation experiments. As expected, for all three amino acids the enantiomers kinetically selected under SPPS conditions were independent of the structure of the acylated component and were the same as those established previously in condensations proceeding in solution [60], which opens a new venue for the synthetic application of traceless chiral coupling reagents (*Table 2*).

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[1]) The configuration and optical purity of isolated products were determined after hydrolytic degradation to amino acids, and the subsequent derivatization and separation of enantiomers by GC on a *Chirasil* Val capillary column.

[2]) Preliminary results were published in [63].

Scheme 3. *Synthesis of Dipeptides from Racemic Fmoc-Protected Amino Acids Using DMT/Strychnine/$BF_4^-$* (**6**) *under SPPS Conditions*

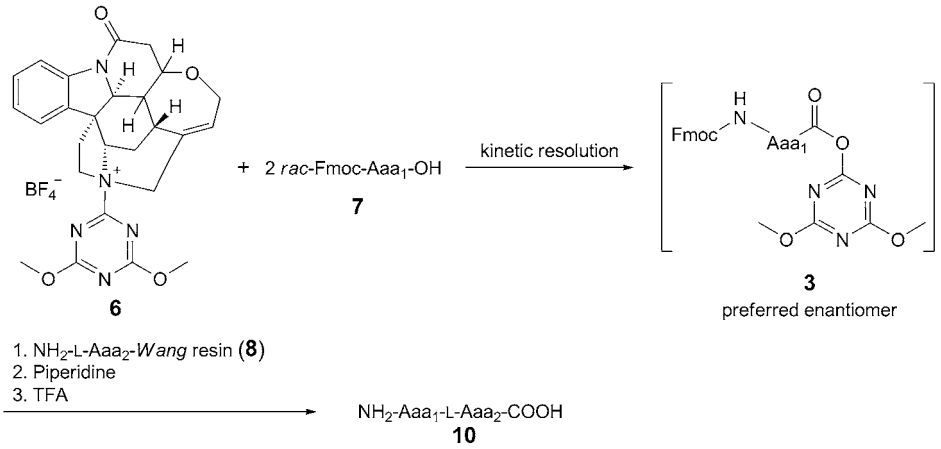



Table 2. *Synthesis of Enantiomerically Enriched Peptides Using DMT/Strychnine/$BF_4^-$* (**6**) *Directly from Racemic Starting Materials.* In all experiments, 4 equiv. of racemic *N*-protected amino acid (**7**), 2 equiv. of DMT/strychnine/$BF_4^-$ (**6**), 0.4 equiv. of strychnine, and 1 equiv. of amino acid anchored to *Wang* resin, **8**, were used; activation time of racemic C-component, 15 min.

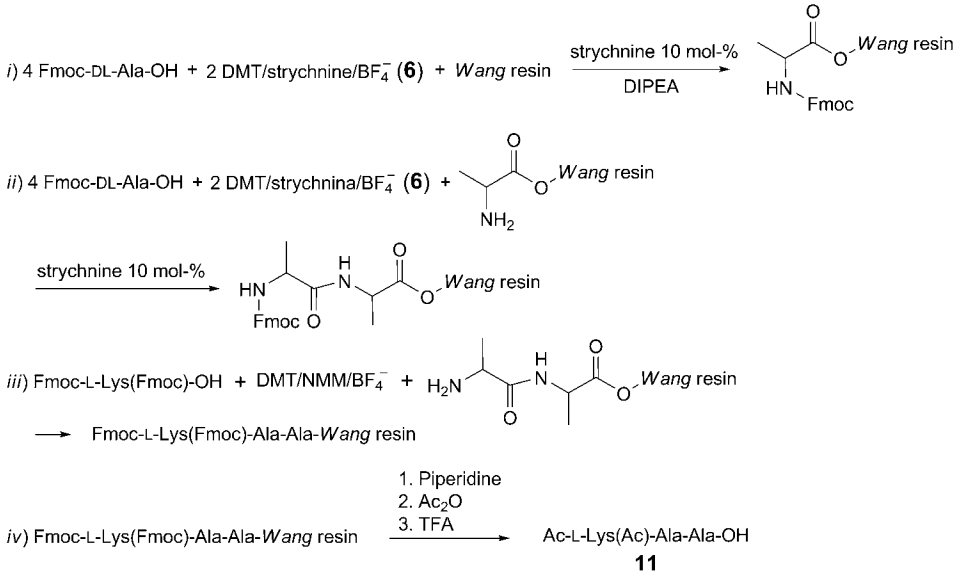
| *Entry* | Racemic C-Component **7** | $NH_2$-Aaa–*Wang* resin **8** | Product prepared **10** | Yield [%] | er[1]) N-Termini amino acid (L/D) |
|---|---|---|---|---|---|
| *1* | Fmoc-Ala-OH (**7a**) | $NH_2$-Gly– (**8b**) | H-D-Ala-Gly-OH (**10ab**) | 93 | 2 : 98 |
| *2* | | $NH_2$-L-Leu– (**8c**) | H-D-Ala-L-Leu-OH (**10ac**) | 91 | 5 : 95 |
| *3* | | $NH_2$-L-Phe– (**8d**) | H-D-Ala-L-Phe-OH (**10ad**) | 92 | 8 : 92 |
| *4* | | $NH_2$-L-Glu(O$^t$Bu)– (**8e**) | H-D-Ala-L-Glu-OH (**10ae**) | 89 | 3 : 97 |
| *5* | | NH-L-Pro– (**8f**) | H-D-Ala-L-Pro-OH (**10af**) | 94 | 4 : 96 |
| *6* | Fmoc-Phe-OH (**7b**) | $NH_2$-Gly– (**8b**) | H-L-Phe-Gly-OH (**10bb**) | 90 | 90 : 10 |
| *7* | | $NH_2$-L-Leu– (**8c**) | H-L-Phe-L-Leu-OH (**10bc**) | 92 | 100 : 0 |
| *8* | | $NH_2$-L-Ala– (**8g**) | H-L-Phe-L-Ala-OH (**10bg**) | 94 | 98 : 2 |
| *9* | | $NH_2$-L-Glu(O$^t$Bu)– (**8e**) | H-L-Phe-L-Glu-OH (**10be**) | 88 | 98 : 2 |
| *10* | | NH-L-Pro– (**8f**) | H-L-Phe-L-Pro-OH (**10bf**) | 90 | 96 : 4 |
| *11* | Fmoc-Tyr-OH (**7e**) | $NH_2$-Gly– (**8b**) | H-L-Tyr-Gly-OH (**10eb**) | 89 | 89 : 11 |
| *12* | | $NH_2$-L-Leu– (**8c**) | H-L-Tyr-L-Leu-OH (**10ec**) | 93 | 100 : 0 |
| *13* | | $NH_2$-L-Ala– (**8g**) | H-L-Tyr-L-Ala-OH (**10eg**) | 92 | 100 : 0 |
| *14* | | $NH_2$-L-Phe– (**8d**) | H-L-Tyr-L-Phe-OH (**10ed**) | 91 | 98 : 2 |
| *15* | | $NH_2$-L-Glu(O$^t$Bu)– (**8e**) | H-L-Tyr-L-Glu-OH (**10ee**) | 88 | 100 : 0 |
| *16* | | NH-L-Pro– (**8f**) | H-L-Tyr-L-Pro-OH (**10ef**) | 89 | 99 : 1 |

The versatility of the traceless chiral coupling reagents was further confirmed in the synthesis of the peptide Ac-L-Lys(Ac)-D-Ala-D-Ala-OH (**11**)[3]), which is a component

[3]) The cell wall of many bacteria consist of peptides containing D-Ala-D-Ala fragment, which is the target for glycopeptide antibiotics, often regarded as drugs of last resort in *Gram*-positive bacteria infections [65–67].

of bacterial cell walls. The synthesis of **11** was achieved on *Wang* resin using racemic Fmoc-Ala-OH and enantiomerically homogeneous Fmoc-L-Lys(Fmoc)-OH (*Scheme 4*).

Scheme 4. *Synthesis of Ac-L-Lys(Ac)-D-Ala-D-Ala-OH Using DMT/Strychnine/$BF_4^-$* (**6**)




The first stage of synthesis involved the anchoring of alanine residues to *Wang* resin. It is already known that anchoring *N*-protected amino acids to HO resins *via* ester bonds proceeds less readily than *via* the formation of amide bonds, and requires a stoichiometric amount of tertiary amine in order to activate the OH group of the solid support [64]. In several cases, a basic environment is considered an important feature promoting the partial racemization of the activated component. As expected, the attachment of the first alanine residue to the resin proceeded enantioselectively with the D-Ala/L-Ala ratio of 90:10 (*Table 3*).

Table 3. *Synthesis of Ac-L-Lys(Ac)-D-Ala-D-Ala-OH* (**11**) *Using DMT/Strychnine/$BF_4^-$* (**6**) *Directly from Racemic Fmoc-Ala-OH*

| *Entry* | Step | Product | er[1]) Ala (D/L) |
|---|---|---|---|
| *1* | I | Fmoc-Ala-*Wang* resin | 90:10 |
| *2* | II | Fmoc-Ala-Ala-*Wang* resin | 95:5 |
| *3* | III | Fmoc-L-Lys(Fmoc)-Ala-Ala-*Wang* resin | 95:5 |

The second step of the synthesis was also based on the enantiomer-differentiating activation of racemic Fmoc-Ala-OH, yielding the dipeptide Fmoc-Ala-Ala anchored to the *Wang* resin. In this step, the enantiomer ratio (er) determined as the total for both Ala residues was D/L 95:5. The obtained result shows that the incorporation of the second alanine residue in the peptide chain occurred in an almost completely

enantiospecific way, yielding the product of the expected DD configuration. The last synthetic step was completed in the presence of the classical achiral triazine-based coupling reagent DMT/NMM/$BF_4^-$ (**2**) [59] using optically homogenous Fmoc-L-Lys(Fmoc)-OH. An examination of the enantiomeric composition of the final product isolated after acetylation and cleavage from the resin reconfirmed the expected configurations for all stereogenic centers.

**4. Conclusions and Outlook.** – The application of chiral (1,3,5-triazin-2-yl)ammonium tetrafluoroborates has paved the way for using racemic *N*-protected amino acids as substrates in SPPS. The most advantageous aspect of this approach is the predictability of SPPS coupling conditions, configuration, and the optical purity of the final product based on a simple coupling experiment, even if the model experiment is performed in solution. Moreover, SPPS involving excess acylating reagent should be regarded as particularly favorable for stereoisomer-differentiating reactions due to the inherent advantage of this methodology under excess conditions.

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## Experimental Part

*General. Abbreviations.* DMAP, 4-(dimethylamino)pyridine; Fmoc, [(9*H*-fluoren-9-yl)methoxy]-carbonyl; DMT/NMM/$BF_4^-$, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium tetrafluoroborate; DMT/strychnine/$BF_4^-$, *N*-(4,6-dimethoxy-1,3,5-triazin-2-yl)strychninium tetrafluoroborate; HOBt, 1-hydroxybenzotriazole TFA, $CF_3COOH$; TIPS, $(i\text{-}Pr)_3SiH$; h.v., 0.1 – 0.01 Torr; TNBS, 2,4,6-trinitrobenzenesulfonic acid.

GC: FID ($H_2$/air); split 1:50; *Chirasil* L-Val cap. column (25 m × 0.25 mm); carrier gas, He; pressure, 135 kPa. $^1$H-NMR Spectra: *Bruker Avance DPX 250* (250 MHz) spectrometer; $\delta$ in ppm rel. to $Me_4Si$ as internal standard, *J* in Hz. LC/MS Spectra: *Dionex UltiMate 3000*.

1. *Peptide Synthesis.* Amino acids were purchased from *Novabiochem* or *Bachem*. *Wang* resin and Fmoc-Aaa-*Wang* resin were purchased from *Novabiochem*.

*Manual Solid-Phase Peptide Synthesis* (SPPS). All peptides were synthesized on *Merck-Heidolph Paraller Synthesis-1* by Fmoc methodology [68].

*Coupling Procedure by Using DMT/Strychnine/$BF_4^-$* (**6**; *GP 1*). Two equiv. of amino acid, 4 equiv. of $EtN^iPr_2$ or strychnine, 2 equiv. of HOBt, and 2 equiv. of DMT/strychnine/$BF_4^-$ (**6**) as a coupling reagent were dissolved in DMF (3 – 5 ml), added to the resin (1 equiv.), and shaken for 30 min. The completion of the reaction was monitored by TNBS [69] or *Kaiser* test [70].

*Deprotection* (*GP 2*). The Fmoc group was removed by a soln. of 20% piperidine in DMF (2 × 5 min).

*Cleavage from the Resin* (*GP 3*). The peptides were cleaved from the resin using TFA/$Et_3SiH$/$H_2O$ 9.5:2.5:2.5 (*ca.* 2 ml/0.1 g of resin). Cleavage was performed during 2 h, then the resin was filtered off, and the filtrate was evaporated. To the residue, $Et_2O$ was added to precipitate the peptide. The resulting solid was filtered off, and washed with $Et_2O$. The product was dissolved in $H_2O$ and lyophilized. The final products were obtained as a TFA salts.

2. *Enantiomer-Differentiating Solid-Phase Peptide Synthesis* (*SPPS*) *by Using DMT/Strychnine/$BF_4^-$* (**6**; *GP 4*). To the vigorously stirred soln. of DMT/strychnine/$BF_4^-$ (**6**; 2 equiv.) in MeCN (3 ml), cooled to 0°, strychnine (0.40 equiv.) was added, and, after 5 min, the soln. was treated with the appropriate racemic carboxylic acid (4 equiv.). The stirring was continued for additional 15 min, and then the soln. was added to freshly prepared amino component (1 equiv.; Fmoc deprotection according *GP 2*)

anchored to the *Wang* resin. Shaking was continued for 1 h. After filtration of soln., the resin was washed with DMF (3 × 5 ml) and $CH_2Cl_2$ (3 × 5 ml).

*Anal. RP-HPLC.* Performed on a *Waters 600S* HPLC system (*Waters 2489* UV/VIS detector, *Waters 616* pump type, *Waters 717 plus Autosampler* type; HPLC manager, *Chromax*) using a *Vydac* $C_{18}$ column (25 cm × 4.6 mm, 5 mm; *Sigma*). HPLC was performed with a gradient of 0.1% TFA in $H_2O$ (*A*) and 0.08% TFA in MeCN (*B*), at a flow rate of 1 ml/min with the UV detection at 220 nm; $t_R$ in min.

3. *Hydrolysis of Products of Coupling to Amino Acid* (*GP 5*). Peptide (5 mg) was treated with redistilled, constant boiling HCl in the sealed tube at 100° for 20 h. The soln. was concentrated to dryness, and the residue was dissolved with redistilled $H_2O$ and concentrated again. Remaining salt was dried overnight in a vacuum desiccator under $P_2O_5$ and then treated with anh. MeOH sat. with dry HCl (2 ml) for 12 h at r.t. MeOH was evaporated, and the residue was dried overnight in a vacuum desiccator under $P_2O_5$, then suspended in $CH_2Cl_2$ and treated with $(CF_3CO)_2O$ (50 µl) for 12 h at r.t. The soln. was analyzed on a *Chirasil* L-Val cap. column (25 m × 0.25 mm); split, 1:50; He was used as carrier gas.

*H-L-Ala-L-Val-OH* (**10aa**; *Table 1*, *Entry 1*). Fmoc-Val-*Wang* resin (100 mg, 0.75 mmol/g, 0.075 mmol) was pre-swollen in $CH_2Cl_2$ (5 ml) for 1 h, and then Fmoc group was removed according to *GP 2*. Subsequently, the peptide chain was elongated with Fmoc-Ala-OH (47 mg, 0.15 mmol) in the presence of DMT/strychnine/$BF_4^-$ (84 mg, 0.15 mmol), HOBt (20 mg, 0.15 mmol), and $EtN^iPr_2$ (54 µl, 0.30 mmol; *GP 1*). After deprotection (*GP 2*), dipeptide was cleaved from the resin (*GP 3*) and lyophilized to give 21 mg of **10aa** as a TFA salt. Anal. RP-HPLC (0–10% *B* in 20 min): $t_R$ 8.11 min, purity > 98%. GC: hydrolysate has been derivatized according to *GP 5*; chromatography conditions: temp. 90°, 4 min; 90–200°, 4°/min; 200°, 3 min; $t_R$ 4.00 (L-Ala), 3.81 (D-Ala); L/D 100:0; 5.19 (L-Val), 5.15 (D-Val); L/D 100:0. $^1$H-NMR (250 MHz, $D_2O$): 0.95, 0.97 (*dd*, *J* = 6.0, $Me_2CH$); 1.44 (*d*, *J* = 7.1, *Me*CH); 2.08–2.10 (*m*, $Me_2CH$); 4.01–4.04 (*m*, 1 H, CH–CH); 4.59 (*q*, *J* = 7.5, MeC*H*); 5.40 (*d*, *J* = 8.5, NHCOO); 6.31 (*d*, *J* = 6, NH). LC/MS: 189.82 ($[M+H]^+$, $C_8H_{17}N_2O_3^+$; calc. 189.23).

*H-L-Ala-L-Val-OH* (**10aa**; *Table 1*, *Entry 2*). Fmoc-Val-*Wang* resin (100 mg, 0.75 mmol/g, 0.075 mmol) was pre-swollen in $CH_2Cl_2$ (5 ml) for 1 h, and then Fmoc group was removed according to *GP 2*. Subsequently, the peptide chain was elongated with Fmoc-Ala-OH (47 mg, 0.15 mmol) in the presence of DMT/strychnine/$BF_4^-$ (84 mg, 0.15 mmol), HOBt (20 mg, 0.15 mmol), and strychnine (100 mg, 0.30 mmol; *GP 1*). After deprotection (*GP 2*), dipeptide was cleaved from the resin (*GP 3*) and lyophilized to give 20 mg of **10aa** as a TFA salt. Anal. RP-HPLC (0–10% *B* in 20 min): $t_R$ 8.12 min, purity > 98%. GC: hydrolysate has been derivatized according to *GP 5*; chromatography conditions: temp. 90°, 4 min; 90–200°, 4°/min; 200°, 3 min; $t_R$ 4.00 (L-Ala), 3.81 (D-Ala); L/D 100:0; 5.19 (L-Val), 5.15 (D-Val); L/D 100:0. $^1$H-NMR (250 MHz, $D_2O$): identical to those described above. LC/MS: 189.82 ($[M+H]^+$, $C_8H_{17}N_2O_3^+$; calc.189.23).

*H-L-Phe-L-Val-OH* (**10ba**; *Table 1*, *Entry 3*). Fmoc-Val-*Wang* resin (100 mg, 0.75 mmol/g, 0.075 mmol) was pre-swollen in $CH_2Cl_2$ (5 ml) for 1 h, and then Fmoc group was removed according to *GP 2*. Subsequently, the peptide chain was elongated with Fmoc-Phe-OH (58 mg, 0.15 mmol) in the presence of DMT/strychnine/$BF_4^-$ (84 mg, 0.15 mmol), HOBt (20 mg, 0.15 mmol), and $EtN^iPr_2$ (54 µl, 0.30 mmol; *GP 1*). After deprotection (*GP 2*), dipeptide was cleaved from the resin (*GP 3*) and lyophilized to give 26 mg of **10ba** as a TFA salt. Anal. RP-HPLC (0–10% *B* in 20 min): $t_R$ 9.11 min, purity > 98%. GC: hydrolysate has been derivatized according to *GP 5*; chromatography conditions: temp. 90°, 4 min; 90–200°, 4°/min; 200°, 3 min; $t_R$ 18.89 (L-Phe), 18.44 (D-Phe); L/D 99.8:0.2; 5.19 (L-Val), 5.15 (D-Val); L/D 100:0. $^1$H-NMR (250 MHz, $D_2O$): 0.94, 0.96 (*dd*, *J* = 6.0, $Me_2CH$); 2.12 (*m*, 1 H, $Me_2CH$); 3.10, 3.14 (*d*, *AB* system, *J* = 14.0, 5.0, $CHCH_2Ph$); 4.00–4.08 (*m*, 1 H, CH–CH); 4.85 (*q*, *J* = 6.5, 1 H, $PhCH_2$–C*H*); 5.75 (br., NH); 7.08–7.32 (*m*, 6 arom. H, NH). LC/MS: 265.47 ($[M+H]^+$, $C_{14}H_{21}N_2O_3^+$; calc. 265.33).

*H-L-Phe-L-Val-OH* (**10ba**; *Table 1*, *Entry 4*). Fmoc-Val-*Wang* resin (100 mg, 0.75 mmol/g, 0.075 mmol) was pre-swollen in $CH_2Cl_2$ (5 ml) for 1 h, and then Fmoc group was removed according to *GP 2*. Subsequently, the peptide chain was elongated with Fmoc-Phe-OH (58 mg, 0.15 mmol) in the presence of DMT/strychnine/$BF_4^-$ (84 mg, 0.15 mmol), HOBt (20 mg, 0.15 mmol), and strychnine (100 mg, 0.30 mmol; *GP 1*). After deprotection (*GP 2*), dipeptide was cleaved from the resin (*GP 3*) and lyophilized to give 26 mg of **10ba** as a TFA salt. Anal. RP-HPLC (0–10% *B* in 20 min): $t_R$ 9.12 min, purity > 98%. GC: hydrolysate has been derivatized according to *GP 5*; chromatography conditions:

temp. 90°, 4 min; 90–200°, 4°/min; 200°, 3 min; $t_R$ 18.88 (L-Phe), 18.43 (D-Phe); L/D = 100:0; 5.18 (L-Val), 5.15 (D-Val); L/D 100:0. $^1$H-NMR (250 MHz, $D_2O$): product identical to those described above. LC/MS: 265.47 ($[M+H]^+$, $C_{14}H_{21}N_2O_3^+$; calc. 265.33).

*H-L-Ser-L-Val-OH* (**10ca**; *Table 1*, *Entry 5*). Fmoc-Val-*Wang* resin (100 mg, 0.75 mmol/g, 0.075 mmol) was pre-swollen in $CH_2Cl_2$ (5 ml) for 1 h, and then Fmoc group was removed according to *GP 2*. Subsequently, the peptide chain was elongated with Fmoc-Ser($^t$Bu)-OH (57 mg, 0.15 mmol) in the presence of DMT/strychnine/$BF_4^-$ (84 mg, 0.15 mmol), HOBt (20 mg, 0.15 mmol), and Et$N^i$Pr$_2$ (54 µl, 0.30 mmol; *GP 1*). After deprotection (*GP 2*), dipeptide was cleaved from the resin (*GP 3*) and lyophilized to give 21 mg of **10ca** as a TFA salt. Anal. RP-HPLC (0–10% *B* in 20 min): $t_R$ 7.76 min, purity >98%. GC: hydrolysate has been derivatized according to *GP 5*; chromatography conditions: temp. 90°, 4 min; 90–200°, 4°/min; 200°, 3 min; $t_R$ 7.75 (L-Ser), 7.79 min (D-Ser); L/D 99.7:0.3; 5.18 (L-Val), 5.15 (D-Val); L/D 100:0. $^1$H-NMR (250 MHz, $D_2O$): 0.94, 0.97 (*dd*, *J* = 6.1, *Me*$_2$CH); 2.12 (*m*, Me$_2$C*H*); 3.36 (*dd*, *J* = 8.1, 4.0, 1 H, CH–C*H*$_2$O); 3.81 (*dd*, *J* = 8.1, 4.0, 1 H, CH–C*H*$_2$O); 4.00–4.08 (*m*, 1 H, CH–CH); 4.19–4.25 (*m*, 1 H, NH–CHCH$_2$O); 5.75 (br., NH). LC/MS: 204.21 ($[M+H]^+$, $C_8H_{17}N_2O_4^+$; calc. 204.23).

*H-L-Ser-L-Val-OH* (**10ca**; *Table 1*, *Entry 6*). Fmoc-Val-*Wang* resin (100 mg, 0.75 mmol/g, 0.075 mmol) was pre-swollen in $CH_2Cl_2$ (5 ml) for 1 h, and then Fmoc group was removed according to *GP 2*. Subsequently, the peptide chain was elongated with Fmoc-Ser($^t$Bu)-OH (57 mg, 0.15 mmol) in the presence of DMT/strychnine/$BF_4^-$ (84 mg, 0.15 mmol), HOBt (20 mg, 0.15 mmol), and strychnine (100 mgl, 0.30 mmol; *GP 1*). After deprotection (*GP 2*), dipeptide was cleaved from the resin (*GP 3*) and lyophilized to give 22 mg of **10ca** as a TFA salt. Anal. RP-HPLC (0–10% *B* in 20 min): $t_R$ 7.77 min, purity >98%. GC: hydrolysate has been derivatized according to *GP 5*; chromatography conditions: temp. 90°, 4 min; 90–200°, 4°/min; 200°, 3 min; $t_R$ 7.75 (L-Ser), 7.78 (D-Ser); L/D = 99.8:0.2; 5.17 (L-Val), 5.14 (D-Val); L/D 100:0. $^1$H-NMR (250 MHz, $D_2O$): identical to those described above LC/MS: 204.22 ($[M+H]^+$, $C_8H_{17}N_2O_4^+$; calc. 204.23).

*H-L-His-L-Val-OH* (**10da**; *Table 1*, *Entry 7*). Fmoc-Val-*Wang* resin (100 mg, 0.75 mmol/g, 0.075 mmol) was pre-swollen in $CH_2Cl_2$ (5 ml) for 1 h, and then Fmoc group was removed according to *GP 2*. Subsequently, the peptide chain was elongated with Fmoc-His(Trt)-OH (93 mg, 0.15 mmol) in the presence of DMT/strychnine/$BF_4^-$ (84 mg, 0.15 mmol), HOBt (20 mg, 0.15 mmol), and Et$N^i$Pr$_2$ (54 µl, 0.30 mmol) (*GP 1*). After deprotection (*GP 2*), dipeptide was cleaved from the resin (*GP 3*) and lyophilized to give 25 mg of **10da** as a TFA salt. Anal. RP-HPLC (0–10% *B* in 20 min): $t_R$ 6.11 min, purity >98%. GC: hydrolysate has been derivatized according to *GP 5*; chromatography conditions: temp. 90°, 4 min; 90–200°, 4°/min; 200°, 3 min; $t_R$ 30.36 (L-His), 30.41 (D-His); L/D 99.5:0.5; 5.17 (L-Val), 5.14 (D-Val); L/D 100:0. $^1$H-NMR (250 MHz, $D_2O$): 0.94, 0.97 (*dd*, *J* = 6.1, *Me*$_2$CH); 2.12–2.15 (*m*, Me$_2$C*H*); 2.84, 3.03 (*d*, *AB* system, *J* = 14.0, 4.0, 2 H, CH–C*H*$_2$–C=CH–NH); 4.00–4.06 (*m*, 1 H, CH–CH); 4.61 (*q*, *J* = 6.5, 1 H, CH–C*H*$_2$C$_3$H$_3$N$_2$); 5.88 (br., NH); 7.78 (br., NH). LC/MS: 255.37 ($[M+H]^+$, $C_{11}H_{19}N_4O_3^+$; calc. 255.29).

*H-L-His-L-Val-OH* (**10da**; *Table 1*, *Entry 8*). Fmoc-Val-*Wang* resin (100 mg, 0.75 mmol/g, 0.075 mmol) was pre-swollen in $CH_2Cl_2$ (5 ml) for 1 h, and then Fmoc group was removed according to *GP 2*. Subsequently, the peptide chain was elongated with Fmoc-His(Trt)-OH (93 mg, 0.15 mmol) in the presence of DMT/strychnine/$BF_4^-$ (84 mg, 0.15 mmol), HOBt (20 mg, 0.15 mmol), and strychnine (100 mg, 0.30 mmol; *GP 1*). After deprotection (*GP 2*), dipeptide was cleaved from the resin (*GP 3*) and lyophilized to give 26 mg of **10da** as a TFA salt. Anal. RP-HPLC (0–10% *B* in 20 min) $t_R$ 6.10 min, purity >98%. GC: hydrolysate has been derivatized according to *GP 5*; chromatography conditions: temp. 90°, 4 min; 90–200°, 4°/min; 200°, 3 min; $t_R$ 30.36 (L-His), 30.40 (D-His); L/D 99.6:0.4; 5.16 (L-Val), 5.14 (D-Val); L/D 100:0. $^1$H-NMR (250 MHz, $D_2O$): identical to those described above. LC/MS: 255.38 ($[M+H]^+$, $C_{11}H_{19}N_4O_3^+$; calc. 255.29).

*H-D-Ala-Gly-OH* (**10ab**; *Table 2*, *Entry 1*). Fmoc-Gly-*Wang* resin (100 mg, 0.77 mmol/g, 0.077 mmol) was pre-swollen in $CH_2Cl_2$ (5 ml) for 1 h, and then Fmoc group was removed according to *GP 2*. Subsequently, the peptide chain was elongated with Fmoc-DL-Ala-OH (96 mg, 0.308 mmol) in the presence of DMT/strychnine/$BF_4^-$ (86 mg, 0.154 mmol) and strychnine (9 mg, 0.028 mmol; *GP 4*). After deprotection (*GP 2*) dipeptide was cleaved from the resin (*GP 3*) and lyophilized to give 19 mg of **10ab** as a TFA salt. Anal. RP-HPLC (0–10% *B* in 20 min): $t_R$ 7.26 min, purity >98%. GC: hydrolyzate

has been derivatized according to *GP 5*; chromatography conditions: temp. 90°, 4 min; 90–200°, 4°/min; 200°, 3 min; $t_R$ 5.19 (Gly), 4.13 (L-Ala), 3.79 (D-Ala); L/D 2:98. $^1$H-NMR (250 MHz, $D_2O$): 1.41 (*d*, *J* = 6.5, *Me*CH); 3.96 (*d*, *J* = 4.0, NH–C*H*$_2$COO); 4.39 (*m*, MeC*H*); 6.61 (br. *s*, NH). LC/MS: 147.55 ([*M* + H]$^+$, $C_5H_{11}N_2O_3^+$; calc. 147.15).

*H*-D-*Ala*-L-*Leu-OH* (**10ac**; *Table 2*, *Entry 2*). Fmoc-L-Leu-*Wang* resin (100 mg, 0.86 mmol/g, 0.086 mmol) was pre-swollen in $CH_2Cl_2$ (5 ml) for 1 h, and then Fmoc group was removed according to *GP 2*. Subsequently, the peptide chain was elongated with Fmoc-DL-Ala-OH (108 mg, 0.344 mmol) in the presence of DMT/strychnine/$BF_4^-$ (96 mg, 0.172 mmol) and strychnine (12 mg, 0.034 mmol; *GP 4*). After deprotection (*GP 2*), dipeptide was cleaved from the resin (*GP 3*) and lyophilized to give 25 mg of **10ac** as a TFA salt. Anal. RP-HPLC (0–10% *B* in 20 min): $t_R$ 7.92 min, purity > 98%. GC: hydrolysate has been derivatized according to *GP 5*; chromatography conditions: temp. 90°, 4 min; 90–200°, 4°/min; 200°, 3 min; $t_R$ 8.56 (L-Leu), 4.16 (L-Ala), 3.79 (D-Ala); L/D 5:95. $^1$H-NMR (250 MHz, $D_2O$): 0.91 (*d*, *J* = 6.0, *Me*$_2$CH); 1.34 (*d*, *J* = 7.1, *Me*CH); 1.45–1.7 (*m*, *Me*CH); 4.46 (*qu*, *J* = 7.1, MeC*H*); 4.59 (*dt*, *J* = 8.0, 4.5, CH$_2$C*H*); 6.61 (*d*, *J* = 5, NH). LC/MS: 203.38 ([*M* + H]$^+$, $C_9H_{19}N_2O_3^+$; calc. 203.26).

*H*-D-*Ala*-L-*Phe-OH* (**10ad**; *Table 2*, *Entry 3*). Fmoc-L-Phe-*Wang* resin (100 mg, 0.86 mmol/g, 0.086 mmol) was pre-swollen in $CH_2Cl_2$ (5 ml) for 1 h, and then Fmoc group was removed according to *GP 2*. Subsequently, the peptide chain was elongated with Fmoc-DL-Ala-OH (108 mg, 0.344 mmol) in the presence of DMT/strychnine/$BF_4^-$ (96 mg, 0.172 mmol) and strychnine (12 mg, 0.034 mmol; *GP 4*). After deprotection (*GP 2*), dipeptide was cleaved from the resin (*GP 3*) and lyophilized to give 28 mg of **10ad** as a TFA salt. Anal. RP-HPLC (0–10% *B* in 20 min) $t_R$ 8.11 min, purity > 98%. GC: hydrolyzate has been derivatized according to *GP 5*; chromatography conditions: temp. 90°, 4 min; 90–200°, 4°/min; 200°, 3 min; $t_R$ 18.92 (L-Phe), 4.01 (L-Ala), 3.81 (D-Ala); L/D 8:92. $^1$H-NMR (250 MHz, $D_2O$): 1.34 (*d*, *J* = 7.0, *Me*CH); 3.08 (*d*, *J* = 7.0, C*H*$_2$CH); 4.45 (*q*, *J* = 7.0, MeC*H*); 4.84 (*q*, *J* = 7.0, CH$_2$C*H*); 6.68 (*d*, *J* = 7.1, CONH); 7.06–7.82 (*m*, 5 arom. H). LC/MS: 237.39 ([*M* + H]$^+$, $C_{12}H_{17}N_2O_3^+$; calc.237.27).

*H*-D-*Ala*-L-*Glu-OH* (**10ae**; *Table 2*, *Entry 4*). Fmoc-L-Glu(O$^t$Bu)-*Wang* resin (100 mg, 0.81 mmol/g, 0.081 mmol) was pre-swollen in $CH_2Cl_2$ (5 ml) for 1 h, and then Fmoc group was removed according to *GP 2*. Subsequently, the peptide chain was elongated with Fmoc-DL-Ala-OH (101 mg, 0.324 mmol) in the presence of DMT/strychnine/$BF_4^-$ (91 mg, 0.162 mmol) and strychnine (11 mg, 0.032 mmol; *GP 4*). After deprotection (*GP 2*), dipeptide was cleaved from the resin (*GP 3*) and lyophilized to give 24 mg of **10ae** as a TFA salt. Anal. RP-HPLC (0–10% *B* in 20 min): $t_R$ 5.25 min, purity > 98%. GC: hydrolysate has been derivatized according to *GP 5*; chromatography conditions: temp. 90°, 4 min; 90–200°, 4°/min; 200°, 3 min; 8.11 min (L-Glu); $t_R$ 4.00 (L-Ala), 3.82 (D-Ala); L/D 3:97. $^1$H-NMR (250 MHz, $D_2O$): 1.28 (*d*, *J* = 6.5, *Me*CH)); 2.05 (*q*, *J* = 7.2, 2 H, CH–CH$_2$CH$_2$); 2.33 (*t*, *J* = 6.8, 2 H, CH$_2$–CH$_2$); 4.09 (*q*, *J* = 6.5, MeC*H*); 4.33–4.51 (*m*, 1 H, CHCOO*H*). LC/MS: 219.44 ([*M* + H]$^+$, $C_8H_{15}N_2O_5^+$; calc. 219.21).

*H*-D-*Ala*-L-*Pro-OH* (**10af**; *Table 2*, *Entry 5*). Fmoc-L-Pro-*Wang* resin (100 mg, 0.76 mmol/g, 0.076 mmol) was pre-swollen in $CH_2Cl_2$ (5 ml) for 1 h, and then Fmoc group was removed according to *GP 2*. Subsequently, the peptide chain was elongated with Fmoc-DL-Ala-OH (95 mg, 0.304 mmol) in the presence of DMT/strychnine/$BF_4^-$ (85 mg, 0.152 mmol) and strychnine (10 mg, 0.030 mmol; *GP 4*). After deprotection (*GP 2*), dipeptide was cleaved from the resin (*GP 3*) and lyophilized to give 21 mg of **10af** as a TFA salt. Anal. RP-HPLC (0–10% *B* in 20 min): $t_R$ 6.11 min, purity > 98%. GC: hydrolysate has been derivatized according to *GP 5*; chromatography conditions: temp. 90°, 4 min; 90–200°, 4°/min; 200°, 3 min; $t_R$ 10.81 (L-Pro), 4.19 (L-Ala), 3.89 (D-Ala); L/D 4:96. $^1$H-NMR (250 MHz, $D_2O$): 1.37 (*d*, *J* = 6.0, *Me*CH); 1.60–2.50 (*m*, CH$_2$–CH$_2$); 3.40–3.80 (*m*, N–CH$_2$); 4.18–4.28 (*m*, N–CH); 4.43 (*q*, *J* = 6.0, MeC*H*); 7.08 (br. *s*, NH). LC/MS: 187.40 ([*M* + H]$^+$, $C_8H_{15}N_2O_3^+$; calc. 187.21).

*H*-L-*Phe-Gly-OH* (**10bb**; *Table 2*, *Entry 6*). Fmoc-Gly-*Wang* resin (100 mg, 0.77 mmol/g, 0.077 mmol) was pre-swollen in $CH_2Cl_2$ (5 ml) for 1 h, and then Fmoc group was removed according to *GP 2*. Subsequently, the peptide chain was elongated with Fmoc-DL-Phe-OH (119 mg, 0.308 mmol) in the presence of DMT/strychnine/$BF_4^-$ (86 mg, 0.154 mmol) and strychnine (10 mg, 0.031 mmol; *GP 4*). After deprotection (*GP 2*), dipeptide was cleaved from the resin (*GP 3*) and lyophilized to give 23 mg of **10bb** as a TFA salt. Anal. RP-HPLC (0–10% *B* in 20 min): $t_R$ 8.02 min, purity > 98%. GC: hydrolysate has been derivatized according to *GP 5*; chromatography conditions: temp. 90°, 4 min; 90–200°, 4°/min; 200°, 3 min; $t_R$ 4.96 (Gly), 18.16 (L-Phe), 17.82 (D-Phe); L/D 90:10. $^1$H-NMR (250 MHz, $D_2O$): 3.08 (br. *d*,

$J = 6.5$, CH–C$H_2$Ph); 3.92, 4.00 (*d*, *AB* system, $J = 14.0$, 8.0, NH–C$H_2$COO); 4.25 – 4.45 (*m*, C*H*–$CH_2$Ph); 7.15 – 7.35 (*m*, 6 arom. H, NH). LC/MS: 223.65 ($[M+H]^+$, $C_{11}H_{15}N_2O_3^+$; calc. 223.25).

*H*-L-*Phe*-L-*Leu-OH* (**10bc**; *Table 2*, *Entry 7*). Fmoc-L-Leu-*Wang* resin (100 mg, 0.86 mmol/g, 0.086 mmol) was pre-swollen in $CH_2Cl_2$ (5 ml) for 1 h, and then Fmoc group was removed according to *GP 2*. Subsequently, the peptide chain was elongated with Fmoc-DL-Phe-OH (133 mg, 0.344 mmol) in the presence of DMT/strychnine/$BF_4^-$ (96 mg, 0.172 mmol) and strychnine (12 mg, 0.034 mmol; *GP 4*). After deprotection (*GP 2*), dipeptide was cleaved from the resin (*GP 3*) and lyophilized to give 31 mg of **10bc** as a TFA salt. Anal. RP-HPLC (0 – 10% *B* in 20 min): $t_R$ 8.92 min, purity > 98%. GC: hydrolysate has been derivatized according to *GP 5*; chromatography conditions: temp. 90°, 4 min; 90 – 200°, 4°/min; 200°, 3 min; $t_R$ 8.61 (L-Leu), 18.81 (L-Phe), 18.38 (D-Phe); L/D 100 : 0. $^1$H-NMR (250 MHz, $D_2O$): 0.91 (*d*, $J = 6.0$, *Me*$_2$CH); 1.45 – 1.7 (*m*, $CH_2CH$); 3.08 (*d*, $J = 7.0$, C$H_2$CH); 4.55 (*dt*, $J = 8.0$, 4.5, $CH_2$C*H*); 4.84 (*q*, $J = 7.0$, $CH_2$C*H*); 6.68 (*d*, $J = 7.0$, CONH); 7.06 – 7.52 (*m*, 5, arom. H). LC/MS: 279.79 ($[M+H]^+$, $C_{15}H_{23}N_2O_3^+$; calc. 279.35).

*H*-L-*Phe*-L-*Ala-OH* (**10bg**; *Table 2*, *Entry 8*). Fmoc-L-Ala-*Wang* resin (100 mg, 0.96 mmol/g, 0.096 mmol) was pre-swollen in $CH_2Cl_2$ (5 ml) for 1 h, and then Fmoc group was removed according to *GP 2*. Subsequently, the peptide chain was elongated with Fmoc-DL-Phe-OH (149 mg, 0.384 mmol) in the presence of DMT/strychnine/$BF_4^-$ (108 mg, 0.192 mmol) and strychnine (13 mg, 0.038 mmol) (*GP 4*). After deprotection (*GP 2*), dipeptide was cleaved from the resin (*GP 3*) and lyophilized to give 32 mg of **10bg** as a TFA salt. Anal. RP-HPLC (0 – 10% *B* in 20 min): $t_R$ 7.53 min, purity > 98%. GC: hydrolysate has been derivatized according to *GP 5*; chromatography conditions: temp. 90°, 4 min; 90 – 200°, 4°/min; 200°, 3 min; $t_R$ 4.00 (L-Ala), 18.90 (L-Phe), 18.54 (D-Phe); L/D 98 : 2. $^1$H-NMR (250 MHz, $D_2O$): 1.42 (*d*, $J = 6.5$, *Me*CH); 3.08 (*d*, $J = 7.0$, C$H_2$CH); 4.31 (*q*, $J = 6.5$, MeC*H*); 4.80 (*q*, $J = 7.0$, $CH_2$C*H*); 6.65 (*d*, $J =$ 7.0, CONH); 7.05 – 7.45 (*m*, 5 arom. H). LC/MS: 237.88 ($[M+H]^+$, $C_{12}H_{17}N_2O_3^+$; calc. 237.27).

*H*-L-*Phe*-L-*Glu-OH* (**10be**; *Table 2*, *Entry 9*). Fmoc-L-Glu(O*t*Bu)-*Wang* resin (100 mg, 0.81 mmol/g, 0.081 mmol) was pre-swollen in $CH_2Cl_2$ (5 ml) for 1 h, and then Fmoc group was removed according to *GP 2*. Subsequently, the peptide chain was elongated with Fmoc-DL-Phe-OH (125 mg, 0.324 mmol) in the presence of DMT/strychnine/$BF_4^-$ (91 mg, 0.162 mmol) and strychnine (11 mg, 0.032 mmol; *GP 4*). After deprotection (*GP 2*), dipeptide was cleaved from the resin (*GP 3*) and lyophilized to give 29 mg of **10be** as a TFA salt. Anal. RP-HPLC (0 – 10% *B* in 20 min): $t_R$ 6.05 min, purity > 98%. GC: hydrolysate has been derivatized according to *GP 5*; chromatography conditions: temp. 90°, 4 min; 90 – 200°, 4°/min; 200°, 3 min; $t_R$ 8.11 (L-Glu), 18.90 (L-Phe), 18.54 (D-Phe); L/D 98 : 2. $^1$H-NMR (250 MHz, $D_2O$): 2.08 (*q*, $J = 6.1$, 2 H, $CH_2$–$CH_2$); 2.35 (*t*, $J = 5.8$, 2 H, $CH_2$–$CH_2$); 3.44, 3.19 (*dd*, $J = 2.8$, 7.8, C$H_2$CH); 4.16 (*t*, $J =$ 5.9, C*H*–$CH_2$); 4.80 (*q*, $J = 7.0$, $CH_2$C*H*); 6.65 (*d*, $J = 7.0$, CONH); 7.05 – 7.45 (*m*, 5 arom. H). LC/MS: 295.61 ($[M+H]^+$, $C_{14}H_{19}N_2O_5^+$; calc. 295.31).

*H*-L-*Phe*-L-*Pro-OH* (**10bf**; *Table 2*, *Entry 10*). Fmoc-L-Pro-*Wang* resin (100 mg, 0.76 mmol/g, 0.076 mmol) was pre-swollen in $CH_2Cl_2$ (5 ml) for 1 h, and then Fmoc group was removed according to *GP 2*. Subsequently, the peptide chain was elongated with Fmoc-DL-Phe-OH (118 mg, 0.304 mmol) in the presence of DMT/strychnine/$BF_4^-$ (85 mg, 0.152 mmol) and strychnine (10 mg, 0.030 mmol; *GP 4*). After deprotection (*GP 2*), dipeptide was cleaved from the resin (*GP 3*) and lyophilized to give 26 mg of **10bf** as a TFA salt. Anal. RP-HPLC (0 – 10% *B* in 20 min): $t_R$ 7.95 min, purity > 98%. GC: hydrolysate has been derivatized according to *GP 5*; chromatography conditions: temp. 90°, 4 min; 90 – 200°, 4°/min; 200°, 3 min; $t_R$ 10.43 (L-Pro), 18.81 (L-Phe), 18.44 (D-Phe); L/D 96 : 4. $^1$H-NMR (250 MHz, $D_2O$): 1.40 – 2.88 (*m*, $CH_2$-$CH_2$); 3.01, 3.16 (*d*, *AB* system, $J = 14.0$, 7.0, PhC$H_2$); 3.30 – 3.60 (*m*, N–$CH_2$); 4.15 – 4.30 (*m*, CO-N-CH-CO); 4.85 (*d*, $J = 7.0$, PhC$H_2$–C*H*); 6.42 (br. *s*, NH); 7.00 – 7.49 (*m*, 5 arom. H). LC/MS: 263.72 ($[M+H]^+$, $C_{14}H_{19}N_2O_3^+$; calc. 263.31).

*H*-L-*Tyr-Gly-OH* (**10eb**; *Table 2*, *Entry 11*). Fmoc-Gly-*Wang* resin (100 mg, 0.77 mmol/g, 0.077 mmol) was pre-swollen in $CH_2Cl_2$ (5 ml) for 1 h, and then Fmoc group was removed according to *GP 2*. Subsequently, the peptide chain was elongated with Fmoc-DL-Tyr-OH (124 mg, 0.308 mmol) in the presence of DMT/strychnine/$BF_4^-$ (86 mg, 0.154 mmol) and strychnine (10 mg, 0.031 mmol; *GP 4*). After deprotection (*GP 2*), dipeptide was cleaved from the resin (*GP 3*) and lyophilized to give 24 mg of **10eb** as a TFA salt. Anal. RP-HPLC (0 – 10% *B* in 20 min): $t_R$ 6.18 min, purity > 98%. GC: hydrolysate has been derivatized according to *GP 5*; chromatography conditions: temp. 90°, 4 min; 90 – 200°, 4°/min; 200°, 3 min; $t_R$ 5.05 (Gly), 22.86 (L-Tyr), 22.49 (D-Tyr); L/D 89 : 11. $^1$H-NMR (250 MHz, $D_2O$): 3.05, 3.10

(*d*, *AB* system, $J = 12.0$, 4.0, CH–C$H_2$C$_6$H$_4$OH); 3.96 (*d*, $J = 4.0$, 2 H, NH–C$H_2$COO); 4.65 (*q*, $J = 6.5$, HOC$_6$H$_4$CH$_2$–C*H*); 5.83 (br., NH); 6.47 (*d*, $J = 8.0$, 2 arom. H); 6.99 (*d*, $J = 8.0$, 2 arom. H). LC/MS: 239.55 ($[M+H]^+$, $C_{11}H_{15}N_2O_4^+$; calc. 239.25).

*H*-L-*Tyr*-L-*Leu-OH* (**10ec**; *Table 2*, *Entry 12*). Fmoc-L-Leu-*Wang* resin (100 mg, 0.86 mmol/g, 0.086 mmol) was pre-swollen in $CH_2Cl_2$ (5 ml) for 1 h, and then Fmoc group was removed according to *GP 2*. Subsequently, the peptide chain was elongated with Fmoc-DL-Tyr-OH (139 mg, 0.344 mmol) in the presence of DMT/strychnine/$BF_4^-$ (96 mg, 0.172 mmol) and strychnine (12 mg, 0.034 mmol; *GP 4*). After deprotection (*GP 2*), dipeptide was cleaved from the resin (*GP 3*) and lyophilized to give 33 mg of **10ec** as a TFA salt. Anal. RP-HPLC (0–10% *B* in 20 min): $t_R$ 9.08 min, purity >98%. GC: hydrolysate has been derivatized according to *GP 5*; chromatography conditions: temp. 90°, 4 min, 90–200°, 4°/min, 200°, 3 min; $t_R$ 8.29 (L-Leu), 22.76 (L-Tyr), 22.46 (D-Tyr); L/D 100 : 0. $^1$H-NMR (250 MHz, $D_2O$): 0.92 (*d*, $J = 6.0$, *Me*$_2$CH); 1.42–1.72 (*m*, $CH_2CH$); 3.01, 3.07 (*d*, *AB* system, $J = 12.0$, 4.0, CH–C$H_2$C$_6$H$_4$OH); 4.58 (*dt*, $J = 8.0$, 4.0, $CH_2$C*H*); 4.76 (*q*, $J = 6.5$, HOC$_6$H$_4$CH$_2$–C*H*); 5.75 (br., NH); 6.39 (*d*, $J = 8.0$, 2 arom. H); 6.96 (*d*, $J = 8.0$, 2 arom. H). LC/MS: 295.70 ($[M+H]^+$, $C_{15}H_{23}N_2O_4^+$; calc. 295.35).

*H*-L-*Tyr*-L-*Ala-OH* (**10eg**; *Table 2*, *Entry 13*). Fmoc-L-Ala-*Wang* resin (100 mg, 0.96 mmol/g, 0.096 mmol) was pre-swollen in $CH_2Cl_2$ (5 ml) for 1 h, and then Fmoc group was removed according to *GP 2*. Subsequently, the peptide chain was elongated with Fmoc-DL-Tyr-OH (155 mg, 0.384 mmol) in the presence of DMT/strychnine/$BF_4^-$ (108 mg, 0.192 mmol) and strychnine (13 mg, 0.038 mmol; *GP 4*). After deprotection (*GP 2*), dipeptide was cleaved from the resin (*GP 3*) and lyophilized to give 32 mg of **10eg** as a TFA salt. Anal. RP-HPLC (0–10% *B* in 20 min): $t_R$ 8.41 min, purity >98%. GC: hydrolysate has been derivatized according to *GP 5*; chromatography conditions: temp. 90°, 4 min; 90–200°, 4°/min; 200°, 3 min; $t_R$ 4.01 (L-Ala), 22.75 (L-Tyr), 22.46 (D-Tyr); L/D 100 : 0. $^1$H-NMR (250 MHz, $D_2O$): 1.36 (*d*, $J = 7.0$, *Me*CH); 3.04, 3.11 (*d*, *AB* system, $J = 12.0$, 4.0, CH–C$H_2$C$_6$H$_4$OH); 4.44 (*qu*, $J = 7.0$, MeC*H*); 4.75 (*q*, $J = 6.5$, HOC$_6$H$_4$CH$_2$–C*H*); 5.87 (br., NH); 6.46 (*d*, $J = 8.0$, 2 arom. H); 6.95 (*d*, $J = 8.0$, 2 arom. H). LC/MS: 253.76 ($[M+H]^+$, $C_{12}H_{17}N_2O_4^+$; calc.253.27).

*H*-L-*Tyr*-L-*Phe-OH* (**10ed**; *Table 2*, *Entry 14*). Fmoc-L-Phe-*Wang* resin (100 mg, 0.86 mmol/g, 0.086 mmol) was pre-swollen in $CH_2Cl_2$ (5 ml) for 1 h, and then Fmoc group was removed according to *GP 2*. Subsequently, the peptide chain was elongated with Fmoc-DL-Tyr-OH (139 mg, 0.344 mmol) in the presence of DMT/strychnine/$BF_4^-$ (96 mg, 0.172 mmol) and strychnine (12 mg, 0.034 mmol; *GP 4*). After deprotection (*GP 2*), dipeptide was cleaved from the resin (*GP 3*) and lyophilized to give 35 mg of **10ed** as a TFA salt. Anal. RP-HPLC (0–10% *B* in 20 min): $t_R$ 11.23 min, purity >98%. GC: hydrolysate has been derivatized according to *GP 5*; chromatography conditions: temp. 90°, 4 min; 90–200°, 4°/min; 200°, 3 min; $t_R$ 18.99 (L-Phe), 23.34 (L-Tyr), 22.46 (D-Tyr); L/D 98 : 2. $^1$H-NMR (250 MHz, $D_2O$): 3.01, 3.07 (*d*, *AB* system, $J = 12.0$, 4.0, CH–C$H_2$C$_6$H$_4$OH); 3.11, 315 (*d*, *AB* system, $J = 14.0$, 5.0, CH–C$H_2$Ph); 4.76 (*q*, $J = 6.5$, HOC$_6$H$_4$CH$_2$–C*H*); 4.88 (*q*, $J = 6.5$, PhCH$_2$–C*H*); 5.77 (br., NH); 6.36 (*d*, $J = 8.0$, 2 arom. H); 6.90 (*d*, $J = 8.0$, 2 arom. H); 7.06–7.35 (*m*, 5 arom. H). LC/MS: 329.81 ($[M+H]^+$, $C_{18}H_{21}N_2O_4^+$; calc. 329.37).

*H*-L-*Tyr*-L-*Glu-OH* (**10ee**; *Table 2*, *Entry 15*). Fmoc-L-Glu(O$^t$Bu)-*Wang* resin (100 mg, 0.81 mmol/g, 0.081 mmol) was pre-swollen in $CH_2Cl_2$ (5 ml) for 1 h, and then Fmoc group was removed according to *GP 2*. Subsequently, the peptide chain was elongated with Fmoc-DL-Tyr-OH (131 mg, 0.324 mmol) in the presence of DMT/strychnine/$BF_4^-$ (91 mg, 0.162 mmol) and strychnine (11 mg, 0.032 mmol; *GP 4*). After deprotection (*GP 2*), dipeptide was cleaved from the resin (*GP 3*) and lyophilized to give 30 mg of **10ee** as a TFA salt. Anal. RP-HPLC (0–10% *B* in 20 min): $t_R$ 7.15 min, purity >98%. GC: hydrolysate has been derivatized according to *GP 5*; chromatography conditions: temp. 90°, 4 min; 90–200°, 4°/min; 200°, 3 min; $t_R$ 8.10 (L-Glu), 23.34 (L-Tyr), 22.46 (D-Tyr); L/D 100 : 0. $^1$H-NMR (250 MHz, $D_2O$): 2.04 (*q*, $J = 6.8$, 2 H, $CH_2$–$CH_2$); 2.35 (*t*, $J = 5.7$, 2 H, $CH_2$–$CH_2$); 3.04, 3.11 (*d*, *AB* system, $J = 12.0$, 4.0, CH–C$H_2$C$_6$H$_4$OH); 4.14 (*t*, $J = 6.9$, 1 H, $CH_2$C*H*); 4.75 (*q*, $J = 6.5$, HOC$_6$H$_4$CH$_2$–C*H*); 5.87 (br., NH); 6.46 (*d*, $J = 8.0$, 2 arom. H); 6.95 (*d*, $J = 8.0$, 2 arom. H). LC/MS: 311.71 ($[M+H]^+$, $C_{14}H_{19}N_2O_6^+$; calc. 311.31).

*weiterH*-L-*Tyr*-L-*Pro-OH* (**10ef**; *Table 2*, *Entry 16*). Fmoc-L-Pro-*Wang* resin (100 mg, 0.76 mmol/g, 0.076 mmol) was pre-swollen in $CH_2Cl_2$ (5 ml) for 1 h, and then Fmoc group was removed according to *GP 2*. Subsequently, the peptide chain was elongated with Fmoc-DL-Tyr-OH (123 mg, 0.304 mmol) in the presence of DMT/strychnine/$BF_4^-$ (85 mg, 0.152 mmol) and strychnine (10 mg, 0.030 mmol; *GP 4*). After

deprotection (*GP 2*), dipeptide was cleaved from the resin (*GP 3*) and lyophilized to give 26 mg of **10ef** as a TFA salt. Anal. RP-HPLC (0–10% *B* in 20 min): $t_R$ 8.28 min, purity >98%. GC: hydrolysate has been derivatized according to *GP 5*; chromatography conditions: temp. 90°, 4 min; 90–200°, 4°/min; 200°, 3 min; $t_R$ 10.43 (L-Pro), 23.33 (L-Tyr), 22.46 (D-Tyr); L/D 99:1. $^1$H-NMR (250 MHz, $D_2O$): 1.40–2.88 (*m*, $CH_2$–$CH_2$); 3.04, 3.11 (*d*, *AB* system, $J$ = 12.0, 4.0, CH–C$H_2$C$_6$H$_4$OH); 4.14 (*t*, $J$ = 6.9, $CH_2$C*H*); 3.30–3.60 (*m*, N–$CH_2$); 4.15–4.30 (*m*, CO-N-CH-CO); 4.75 (*q*, $J$ = 6.5, HOC$_6$H$_4$C$H_2$–C*H*); 6.46 (*d*, $J$ = 8.0, 2 arom. H); 6.95 (*d*, $J$ = 8.0, 2 arom. H). LC/MS: 279.70 ([$M$ + H]$^+$, $C_{14}H_{19}N_2O_4^+$; calc. 279.31).

*Ac-L-Lys(Ac)-D-Ala-D-Ala-OH* (**11**): *Anchoring Fmoc-D-Ala-OH to* Wang *Resin* (*Table 3*, *Entry 1*). To the vigorously stirred soln. of DMT/strychnine/$BF_4^-$ (**6**) (0.308 g, 0.55 mmol) in MeCN (5 ml), cooled to 0°, strychnine (37 mg, 0.11 mmol) was added, and after 5 min the soln. was treated with the appropriate racemic carboxylic acid (0.242 g, 1.1 mmol). The stirring was continued for additional 15 min, then the soln. was added to the pre-swollen (in $CH_2Cl_2$ for 1 h) *Wang* resin (0.250 g, 1.1 mmol/g, 0.275 mmol) treated with stoichiometric amount of EtN$^i$Pr$_2$ (50 µl, 0.275 mmol) and cat. amount of DMAP (5 mg), and the suspension was shaked for 10 h. The resin was then filtered, washed with $CH_2Cl_2$ (4 ml, 6 × 1 min), and dried under h.v. overnight. The level of alanine-residue attachment to *Wang* resin [71] was estimated as 0.95 mmol/g of the modified resin. In the next step, the Fmoc-Ala-*Wang* resin was covered with DMF (5 ml), and unreacted OH groups were capped using $Ac_2O$ (0.281 g, 2.75 mmol) and DMAP (3 mg, 0.027 mmol) dissolved in DMF (0.5 ml) for 1–2 h under Ar bubbling. The resin was then washed with DMF (5 ml, 5 × 1 min) and $CH_2Cl_2$ (5 ml, 5 × 1 min), and then the Fmoc group was removed according to *GP 2*. A small amount of Ala-*Wang* resin (50 mg) was treated with TFA/$Et_3SiH$/$H_2O$ 9.5:2.5:2.5 (5 ml). Cleavage was performed during 2 h, then the resin was filtered off, and the filtrate was evaporated. The solid residue was derivatizated according to *GP 5*; chromatography conditions: temp. 90°, 4 min; 90–200°, 4°/min; 200°, 3 min; $t_R$ 4.00 (L-Ala), 3.81 (D-Ala); D/L 90:10.

*Incorporation of Second Residue of* D-*Ala to* D-*Ala*-Wang *Resin* (*Table 3*, *Entry 2*). Subsequently, the peptide chain was elongated with Fmoc-DL-Ala-OH (0.236 g, 0.760 mmol) in the presence of DMT/strychnine/$BF_4^-$ (0.213 g, 0.38 mmol) and strychnine (25 mg, 0.076 mmol; *GP 4*). After deprotection (*GP 2*), 50 mg of Ala-Ala-*Wang* resin was treated with TFA/$Et_3SiH$/$H_2O$ 9.5:2.5:2.5 (5 ml). Cleavage was performed during 2 h, then the resin was filtered off, and the filtrate was evaporated. Solid residue was dissolved in $H_2O$ (5 ml) and lyophilized to give 11 mg of D-Ala-D-Ala as a TFA salt. Anal. RP-HPLC (0–10% *B* in 20 min): $t_R$ 6.11 min, purity >98%. GC: hydrolysate has been derivatized according to *GP 5*; chromatography conditions: temp. 90°, 4 min; 90–200°, 4°/min, 200°; 3 min; $t_R$ 4.01 (L-Ala), 3.81 (D-Ala); D/L 95:5. LC/MS: 161.73 ([$M$ + H]$^+$, $C_6H_{13}N_2O_3^+$; calc.161.17).

*Incorporation of Lys Residue to* D-*Ala*-D-*Ala*-Wang *Resin* (*Table 3*, *Entry 3*). Fmoc-Lys(Fmoc)-OH (0.284 mmol), EtN(i-Pr)$_2$ (102 µl, 0.568 mmol), HOBt (0.284 mmol), and DMT/NMM/$BF_4^-$ (**2**; 93 mg, 0.284 mmol) as a coupling reagent were dissolved in DMF (5 ml) and added to D-Ala-D-Ala-*Wang* resin (150 mg, 0.95 mmol/g, 0.142 mmol) and shaken for 30 min. The completion of the reaction was confirmed by TNBS test. After Fmoc deprotection (*GP 2*), tripeptide was as covered with DMF (3 ml), and free amino groups were acetylated using $Ac_2O$ (0.290 g, 2.84 mmol.) and DMAP (3 mg, 0.028 mmol) dissolved in DMF (0.3 ml) for 2 h under Ar bubbling. The resin was then washed with DMF (5 ml, 5 × 1 min) and $CH_2Cl_2$ (5 ml, 5 × 1 min). Tripeptide was cleaved from the resin (*GP 3*) and lyophilized to give 45 mg of **11**.

*Anal. RP-HPLC* (0–34% *B* in 20 min). $t_R$ 10.11 min, purity >97%. GC: hydrolysate has been derivatized according to *GP 5*; chromatography conditions: temp. 90°, 4 min; 90–200°, 4°/min; 200°, 3 min; $t_R$ 4.01 (L-Ala), 3.81 (D-Ala); D/L 95:5; 11.03 (L-Lys), 11.28 (D-Lys); D/L 0:100. $^1$H-NMR (250 MHz, $CD_3OD$): 1.25 (*q*, $J$ = 4.8, 2 H, $CH_2$–$CH_2$–$CH_2$); 1.43 (*d*, $J$ = 6.9, *Me*CH); 1.48 (*d*, $J$ = 6.9, *Me*CH); 1.55 (*q*, $J$ = 4.7, 2 H, $CH_2$–$CH_2$–$CH_2$); 1.80 (*q*, $J$ = 6.1, 2 H, $CH_2$–$CH_2$–$CH_2$); 1.85 (*s*, 2 MeCO); 3.01, 3.06 (*dt*, $J$ = 2.4, 5.9, NHC$H_2$); 4.11 (*q*, $J$ = 6.9, MeC*H*); 4.41 (*t*, $J$ = 5.5, C*H*–$CH_2$); 4.53 (*q*, $J$ = 6.9, MeC*H*); 7.2–7.9 (*m*, 4 NH). LC/MS: 372.53 ($M^+$, $C_{16}H_{28}N_4O_6^+$; calc. 372.42).

## REFERENCES


[1] K. Takeda, K. Tsuboyama, A.Suzuki, H. Ogura, *Chem. Pharm. Bull.* **1985**, *33*, 2545.
[2] T. Teramoto, M. Deguchi, T. Kurosaki, *Tetrahedron Lett*. **1981**, *22*, 1109.
[3] T. Teramoto, T. Kurosaki, *Tetrahedron Lett*. **1977**, *18*, 1523.
[4] S. W. Markowicz, J. Karolak-Wojciechowska, *Pol. J. Chem*. **1994**, *68*, 1973.
[5] H. R. Kricheldorf, M. Au, T. Mang, *Int. J. Pept. Protein Res.* **1985**, *26*, 149.
[6] H. R. Kricheldorf, T. Mang, *Makromol. Chem*. **1982**, *183*, 2093.
[7] Y. Murakami, K. Kondo, K. Miki, Y. Akiyama, T. Watanabe, Y. Yokoyama, *Tetrahedron Lett*. **1997**, *38*, 3751.
[8] K. Kondo, Y. Murakami, *Chem. Pharm. Bull*. **1998**, *46*, 1217.
[9] K. Kondo, T. Kurosaki, Y. Murakami, *Synlett* **1998**, 725.
[10] A. G. Al-Sehemi, R. S. Atkinson, J. Fawcett, D. R. Russel, *J. Chem. Soc., Perkin Trans. 1* **2000**, 4413.
[11] E. J. Günster, R. C. Scholtz, *Makromol. Ch*em. **1980**, *181*, 643.
[12] D. A. Evans, J. C. Andersen, M. K. Taylor, *Tetrahedron Lett*. **1993**, *34*, 5563.
[13] P. W. Jencks, M. Gilchrist, *J. Am. Chem. Soc.* **1968**, *90*, 2622.
[14] N. Maezaki, A. Furusawa, S. Uchida, T. Tanaka, *Tetrahedron* **2001**, *57*, 9309.
[15] C. E. Garret, G. C. Fu, *J. Am. Chem. Soc*. **1998**, *120*, 7479.
[16] S. Arai, S. Bellemin-Laponnaz, G. C. Fu, *Angew. Chem*. **2001**, *113*, 240; S. Arai, S. Bellemin-Laponnaz, G. C. Fu, *Angew. Chem., Int. Ed.* **2001**, *40*, 234.
[17] S. A. Shaw, P. Aleman, J. Christy, J. W. Kampf, P. Va, E. Vedejs, *J. Am. Chem. Soc*. **2006**, *128*, 925.
[18] A. H. Mermerian, G. C. Fu, *Angew. Chem*. **2005**, *117*, 971; A. H. Mermerian, G. C. Fu, *Angew. Chem., Int. Ed*. **2005**, *44*, 949.
[19] A. C. Spivey, F. Zhu, M. B. Mitchell, S. G. Davey, R. L. Jarvest, *J. Org. Chem*. **2003**, *68*, 7379.
[20] T. Kawabata, R. Stragies, T. Fukaya, Y. Nagaoka, H. Schedel, K. Fuji, *Tetrahedron Lett*. **2003**, *44*, 1545.
[21] G. Priem, B. Pelotier, S. J. F. Madonald, M. S. Anson, I. B. Campbell, *J. Org. Chem*. **2003**, *68*, 3844.
[22] C. O. Dalaigh, S. J. Hynes, J. E. O'Brien, T. McCabe, D. J. Maher, G. W. Watson, S. J. Connon, *Org. Biomol. Chem*. **2006**, *4*, 2785.
[23] M. Anstiss, A. Nelson, *Org. Biomol. Chem*. **2006**, *4*, 4135.
[24] E. R. Jarvo, S. J. Miller, *Tetrahedron* **2002**, *58*, 2481.
[25] M. P. Sibi, S. Maneyem, *Tetrahedron* **2000**, *56*, 8033.
[26] G. T. Copeland, E. R. Jarvo, S. J. Miller, *J. Org. Chem*. **1998**, *63*, 6784.
[27] G. T. Copeland, S. J. Miller, *J. Am. Chem. Soc*. **1999**, *121*, 4306.
[28] R. F. Harris, A. J. Nation, G. T. Copeland, S. J. Miller, *J. Am. Chem. Soc*. **2000**, *122*, 11270.
[29] M. M. Vasbinder, E. R. Jarvo, S. J. Miller, *Angew. Chem*. **2001**, *113*, 2906; M. M. Vasbinder, E. R. Jarvo, S. J. Miller, *Angew. Chem., Int. Ed*. **2001**, *40*, 2824.
[30] V. B. Birman, E. W. Uffman, H. Jiang, X. Li, C. J. Kilbane, *J. Am. Chem. Soc*. **2004**, *126*, 12226.
[31] V. B. Birman, X. Li, *Org. Lett*. **2006**, *8*, 1351.
[32] R. Wegler, *Liebigs Ann. Chem*. **1932**, *498*, 62.
[33] T. Oriyama, Y. Hori, K. Imai, R. Sasaki, *Tetrahedron Lett*. **1996**, *37*, 8543.
[34] T. Sano, K. Imai, K. Ohashi, T. Oriyama, *Chem. Lett*. **1999**, *28*, 265.
[35] T. Oriyama, K. Imai, T. Sano, T. Hosoya, *Tetrahedron Lett*. **1998**, *39*, 3529.
[36] D. Terakado, H. Koutaka, T. Oriyama, *Tetrahedron: Asymmetry* **2005**, *16*, 1157.
[37] E. Vedejs, S. T. Diner, *J. Am. Chem. Soc*. **1993**, *115*, 3358.
[38] E. Vedejs, N. S. Bennett, L. M. Conn, S. T. Diver, M. Gingras, S. Lin, P. A. Oliver, M. J. Peterson, *J. Org. Chem.* **1993**, *58*, 7286.
[39] H. Aida, K. Mori, Y. Yamaguchi, S. Mizuta, T. Moriyama, T. Fujimoto, *Org. Lett.* **2012**, *14*, 812.
[40] P. A. MacNeil, N. K. Roberts, B. Bosnisch, *J. Am. Chem. Soc.* **1981**, *103*, 2273.
[41] S. Gladiali, A. Dore, D. Fabbri, O. De Lucchi, M. Manassero, *Tetrahedron: Asymmetry* **1994**, *5*, 511.
[42] M. J. Burk, J. E. Feaster, R. L. Harlow, *Tetrahedron: Asymmetry* **1991**, *2*, 569.
[43] E. Vedejs, O. Daugulis, L. A. Harper, J. A. MacKay, D. R. Powell, *J. Org. Chem*. **2003**, *68*, 5020.
[44] J. A. MacKay, E. Vedejs, *J. Org. Chem*. **2004**, *69*, 6934.

[45] J. L. Methot, W. R. Roush, *Adv. Synth. Catal*. **2004**, *346*, 1035.
[46] S. Srseniyadis, A. Valleix, A. Wagner, C. Mioskowski, *Angew. Chem*. **2004**, *116*, 3376; S. Srseniyadis, A. Valleix, A. Wagner, C. Mioskowski, *Angew. Chem., Int. Ed*. **2004**, *43*, 3314.
[47] B. Pelotier, G. Priem, S. J. F. Macdonald, M. S. Anson, R. J. Upton, I. B. Campbell, *Tetrahedron Lett*. **2005**, *46*, 9005.
[48] C. A. Lewis, B. R. Sculimbrene, Y. Xu, S. J. Miller, *Org. Lett*. **2005**, *7*, 3021.
[49] V. B. Birman, H. Jiang, X. Li, *Org. Lett*. **2007**, *9*, 3237.
[50] Y. Kosugi, M. Akakura, K. Ishihara, *Tetrahedron* **2007**, *63*, 6191.
[51] S. D. Stamatov, J. Stawinski, *Org. Biomol. Chem*. **2007**, *5*, 3787.
[52] A. V. Karnik, S. S. Kamath, *J. Org. Chem*. **2007**, *72*, 7435.
[53] G. T. Notte, T. Sammakia, P. J. Steel, *J. Am. Chem. Soc.* **2005**, *127*, 13502.
[54] D. Terakado, T. Oriyama, *Org. Synth*. **2006**, *83*, 70.
[55] A. Moretto, C. Peggion, F. Formaggio, M. Crisma, B. Kaptein, Q. B. Broxterman, C. Toniolo, *Chirality* **2005**, *17*, 481.
[56] Z. J. Kaminski, *Int. J. Peptide Protein Res.* **1994**, *43*, 312.
[57] Z. J. Kaminski, P. Paneth, M. O'Leary, *J. Org. Chem*. **1991**, *56*, 5716.
[58] Z. J. Kaminski, P. Paneth, J. Rudzinski, *J. Org. Chem*. **1998**, *63*, 4248.
[59] Z. J. Kaminski, B. Kolesinska, J. Kolesinska, G. Sabatino, M. Chelli, P. Rovero, M. Blaszczyk, M. L. Glowka, A. M. Papini, *J. Am. Chem. Soc.* **2005**, *127*, 16912.
[60] B. Kolesinska, K. Kasperowicz, M. Sochacki, A. Mazur, S. Jankowski, Z. J. Kaminski, *Tetrahedron Lett*. **2010**, *51*, 20.
[61] B. Kolesinska, Z. J. Kaminski, *Org. Lett*. **2009**, *11*, 765.
[62] M. Goodman, in 'Methods of Organic Chemistry (Houben–Weyl)', Vol. E 22c, Eds. M. Goodman, A. Felix, L. Moroder, C. Toniolo, Thieme, Stuttgart, 2003.
[63] B. Kolesińska, Peptides 2008, Proceedings of the 30th European Peptide Symposium, Eds. H. Lankinen, The Finnish Peptide Society, Helsinki, 2008, 82.
[64] M.-C. Pozo Carrero, B. Kolesinska, G. Sabatino, M. Chelli, P. Rovero, Z. J. Kaminski, A. M. Papini, Peptides 2004, Proceedings of the 28th European Peptide Symposium, Ed. M. Flegl, M. Fridkin, C. Gilon, J. Slaninowa, Kenes Int., Praga, 2004, 257.
[65] J. Rao, G. M. Whitesides, *J. Am. Chem. Soc*. **1997**, *119*, 10286.
[66] O. Hernout, K. Berthoin, I. Delattre, P. M. Tulkens, S. Carryn, J. Marchand-Brynaert, *Bioorg. Med. Chem. Lett*. **2007**, *17*, 5758.
[67] W. W. Navarre, O. Schneewind, *Microbiol. Mol. Biol. Rev.* **1999**, *63*, 174.
[68] L. A. Carpino, G. Y. Han, *J. Org. Chem*. **1972**, *37*, 3404.
[69] A. Oded, R. A. Houghten, *Pept. Res.* **1990**, *3*, 42.
[70] E. Kaiser, R. L. Colescott, C. D. Bossinger, P. I. Cook, *Anal. Biochem.* **1970**, *34*, 595.
[71] M. Gude, J. Ryf, P. D. White, *Lett. Pept. Sci.* **2002**, *9*, 203.

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