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4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium Toluene-4-sulfonate (DMT/NMM/TsO$^-$) Universal Coupling Reagent for Synthesis in Solution

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4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium toluene-4-sulfonate (DMT/NMM/TsO$^-$), a representative member of the inexpensive and environmentally-friendly *N*-triazinylammonium family of sulfonates, has been found to be a very effective coupling reagent for the synthesis of amides, esters and peptides in solution. This study confirms the usefulness of DMT/NMM/TsO$^-$ for peptide synthesis in solution, starting from Z-, Fmoc- and Boc-protected substrates as well as unnatural building blocks. Peptide synthesis with DMT/NMM/TsO$^-$ produced high yields, with high crude product purity and low risk of racemization. In all cases, stoichiometric amounts of reagents were used and the standard synthetic procedure, without the need for time-consuming optimization stages or expensive chromatographic purification. DMT/NMM/TsO$^-$ was also found to be very useful for the synthesis of oligopeptides using a fragment coupling strategy.

Keywords: triazine-based coupling reagent • peptide • ester • coupling of fragments • standard protocol

Introduction

A wide range of coupling reagents is available for peptide synthesis [1-9]. Nevertheless, synthetic methods require further improvement to facilitate difficult coupling, involving less reactive or sterically-hindered substrates. It is also necessary to reduce the costs of peptide manufacturing, isolation and purification and to eliminate hazardous or environmentally harmful components, procedures and side products.

In this study, an innovative strategy was developed for improving coupling. Excessive over-activation of the acylating component, which usually elicits a side reaction, was avoided. At the same time, high effectiveness was achieved by introducing into the synthetic pathway leading to the formation

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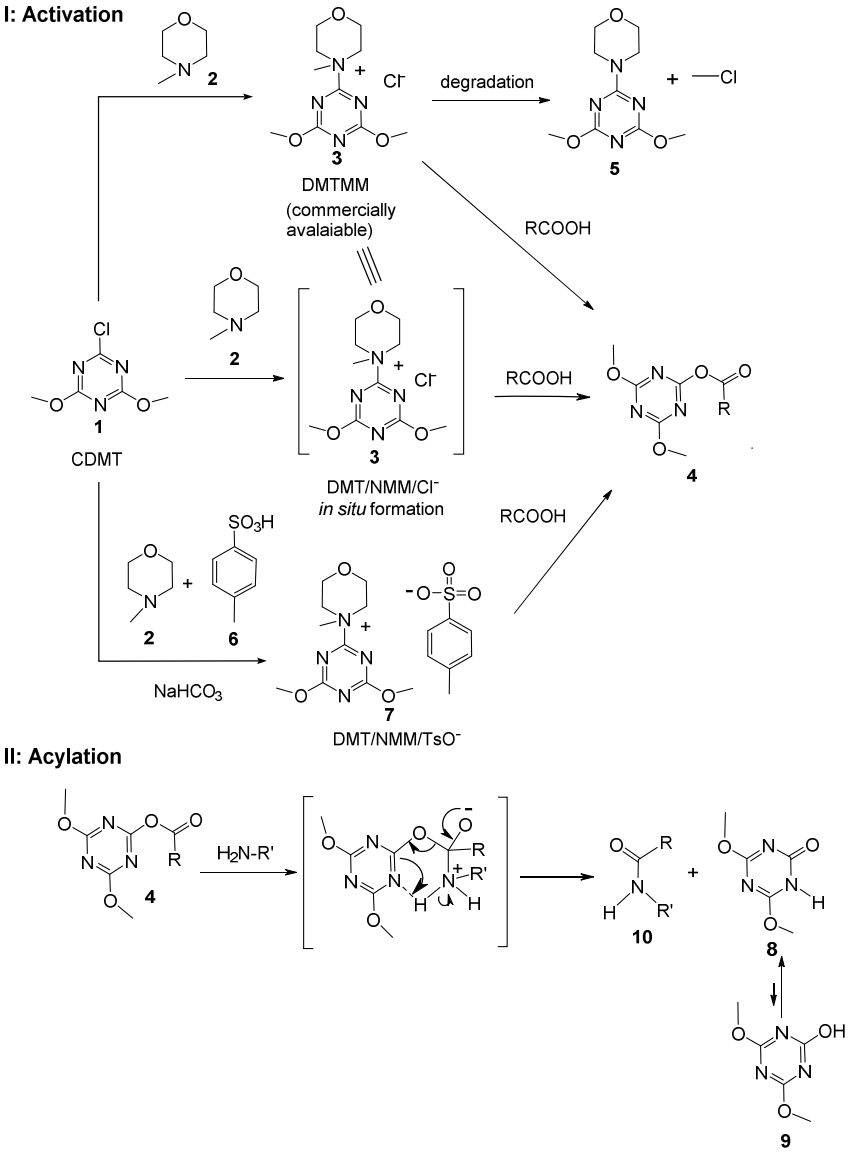
of amide or ester bonds an additional, synchronous and thermodynamically highly favored process, involving rearrangement of the side product.

The goal was reached by designing the "superactive ester" **4** [10] giving activation "push" by electron withdrawing effect of 1,3,5-triazine ring [11], amplified by the synchronous "pull" caused by additional stabilization of the strongly acidic 2-hydroxy-1,3,5-triazine **9** side-product through the fast, highly thermodynamically favored process of intramolecular neutralization by basic nitrogen atoms of the triazine ring (Scheme 1, pathway II: acylation). Moreover, proceeding *via* the cyclic 6-membered transition state, this process is facilitated by the Thorpe-Ingold effect, enhancing coupling of sterically-hindered substrates.



Scheme 1. Coupling using triazine reagents. *In situ* synthesis of DMT/NMM/Cl⁻ (**3**), activation of carboxylic acid to 2-acyloxy-4,6-dimethoxy-1,3,5-triazine (**4**), degradation of DMT/NMM/Cl⁻ (**3**) to inactive coupling reagent compound **4**, synthesis of stable DMT/NMM/TsO⁻ (**7**), intramolecular transfer of the proton from the tetrahedral intermediate to the triazine nitrogen leading to the thermodynamically-preferred form of the amide function of triazinone **8** leaving group.

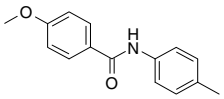
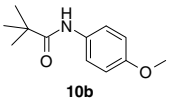
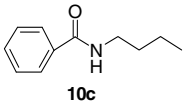
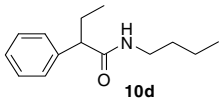
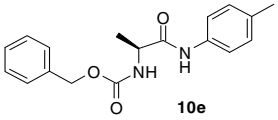
The substrates necessary for the preparation of the "superactive esters" were neither expensive nor environmentally harmful. The scope of the procedure leading to triazine superactive ester formation was very broad [12]. However, the multi-stage *in situ* procedure of triazine superactive ester formation by treating the carboxylic component with 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) in the presence of *N*-methylmorpholine was complicated to perform. Attempts to simplify the synthetic procedure by using *N*-methyl-N-(4,6-dimethoxy-1,3,5-triazin-2-yl)morpholinium chloride (**3**) (DMT/NMM/Cl), identified as a reactive intermediate, were ambiguous (Scheme 1, pathway I).

Kunishima et al. [15] describe **3** (using the acronym DMTMM) as a universal reagent for the synthesis of peptides and esters [16-20]. However, the efficacy of coupling under standard conditions for peptide synthesis (in anhydrous DMF) has been found to be unsatisfactory [13], especially in the case of SPPS [14]. Studies have further revealed that, under anhydrous conditions, quaternary ammonium chloride DMT/NMM/Cl is prone to demethylation in a process [21] analogous to the Von Braun reaction [22], yielding methyl chloride and non-reactive 2-(morpholi-4-yl)-4,6-dimethoxy-1,3,5-triazine (**5**) (Scheme 1, pathway I). To make the proposed strategy of general use, it was necessary to eliminate difficulties caused by the insufficient stability of *N*-triazinylammonium chloride **3**. Substitution of the nucleophilic chloride anion with the less nucleophilic sulphonate produced a collection of stable coupling reagents with diverse reactivities (Scheme 1, pathway I). Screening their synthetic potential revealed p-toluenesulphonate **7** to be the most expedient for SPPS [23]. Because acylating components are used in large excess in SPPS, attempts were made to investigate the use of **7** under standard conditions in representative syntheses in solution. The utility of DMT/NMM/TsO^- was tested for the synthesis of amides, esters and peptides, including oligopeptides, using the step by step and fragment coupling strategy. No excess of reagents was used, and all reactions were performed following standard synthetic procedures, without optimization stages.

Results and Discussion

An effective coupling reagent should allow the synthesis of various carboxylic acid (amino acid) derivatives, including amides, esters, thioesters and peptides, with high yields and without losing optical homogeneity. In the first stage of our study, attempts were made to verify the usefulness of DMT/NMM/TsO^- for amide synthesis. As in the case of other classic reagents, condensation mediated by **7** occurs in two stages. The first stage involves activation of the carboxyl function of acid, leading to the formation of the appropriate superactive esters **4**. Acylation of the nucleophile occurs in the second stage. Formation of super-active esters following the treatment of carboxylic acids with DMT/NMM/TsO^- was confirmed by TLC analysis using 4-(4-nitrobenzyl)pyridine (NBP) [24], which enables visualization of the activation product **4**. DMT/NMM/TsO^- was been found to be an effective reagent for the synthesis of amides **10** derived from both aromatic and aliphatic acids and amines (see Table 1). In all cases, stoichiometric quantities of reagents were used. The reaction yields were in the range of 88-99% and the purity of the crude amides **10a-e**, isolated after a simple washing procedure, were determined using RP-HPLC as being in the range of 89-99%.

Table 1. Synthesis of Amides **10a-e** with DMT/NMM/TsO$^-$.

Entry	Product	Purity [%]	Yield [%]
1.1	 **10a**	93	99
1.2	 **10b**	98	92
1.3	 **10c**	95	90
1.4	 **10d**	89	93
1.5	 **10e**	99	88

From a technical standpoint, the very high purity of the final crude products, which were purified only by washing the reaction mixture with aqueous solutions of $NaHCO_3$ and $NaHSO_4$, is very important. Our results show that using DMT/NMM/TsO$^-$ as a coupling reagent enables costly and time-consuming chromatographic purification processes to be avoided.

In the next stage of our investigation, we evaluated the utility of DMT/NNM/TsO$^-$ for ester **11** synthesis. Acylation of alcohols, which are less nucleophilic than amines, usually requires more vigorous reaction conditions and the use of more powerful acylating reagents.

Because of their orthogonality, we studied the synthesis of allyl esters of *N*-protected amino acids (see Table 2, entry 2.1-2.7). The allyl esters of Fmoc-Asp(OtBu)-OAll and Fmoc-Glu (OtBu)-OAll were found to be particularly useful for the synthesis of cyclic peptides, producing yields of 86% and 96%, respectively. The results of comparative studies on the synthesis of allyl esters of Fmoc-Asp (OtBu)-OAll with classical carbodiimide, uronium and phosphonium salts coupling reagents (Table 2, entry 2.8.-2.11) clearly indicated the usefulness and the advantage of DMT/NMM/TsO$^-$ as a coupling reagent in the synthesis of esters in solution. Synthesis of active esters (Pfp - pentafluorophenyl and NSu - N-hydrosycuccinimide) also occurred in the presence of DMT/NMM/TsO$^-$, with satisfactory yields in the range of 77-88%.

Table 2. Synthesis of esters **11a-n** of carboxylic acids using DMT/NNM/TsO$^-$ as a coupling reagent.

Entry	Ester	Yield [%]	Purity [%]	%L / %D [a]
2.1	Allyl ester of 4-methoxybenzoic acid (**11a**)	82	99	-
2.2	Fmoc–L-Ala-OAll (**11b**)	86	88	100/0
2.3	Fmoc–L-Phe-OAll (**11c**)	87	95	99.5/0.5
2.4	Fmoc-L-Glu-(OtBu)-OAll (**11d**)	77	93	100/0
2.5	Fmoc-L-Ser(tBu)-OAll (**11e**)	82	93	99.6/0.4
2.6	Fmoc-L-Lys(Boc)-OAll (**11f**)	96	96	99.5/0.5
2.7	Fmoc-L-Asp-(OtBu)-OAll (**11g**)	86	99	100/0
2.8	Fmoc-L-Asp-(OtBu)-OAll (**11g**) by using DCC	70	92	-
2.9	Fmoc-L-Asp-(OtBu)-OAll (**11g**) by using TBTU	70	99	-
2.10	Fmoc-L-Asp-(OtBu)-OAll (**11g**) by using HATU	72	98	-
2.11	Fmoc-L-Asp-(OtBu)-OAll (**11g**) by using BOP	59	99	-
2.12	Fmoc-L-Asp-(OtBu)-OPfp (**11h**)	88	93	100/0
2.13	Fmoc-L-Ala-OPfp (**11i**)	83	88	100/0
2.14	Fmoc-L-Ala-ONSu (**11j**)	78	95	100/0
2.15	Fmoc-L-Ala-SPh (**11k**)	94	97	100/0
2.16	Fmoc-L-Ser(tBu)-SPh (**11l**)	90	96	99/1
2.17	Fmoc-L-Ala-S$(CH_2)_3CH_3$ (**11m**)	88	95	99/1
2.18	Fmoc-L-Ser(tBu)-S$(CH_2)_3CH_3$ (**11n**)	80	97	98/2

[a] Enantiomeric purities were determined by GC analysis on a ChirasilVal column after degradation of peptides to amino acids and subsequent formation of volatile N-Tfa-amino acid-OMe.

The versatility of DMT/NMM/TsO$^-$ for the synthesis of thioesters of *N*-protected amino acids was especially interesting. In all cases, the yields and purity of the crude products were exceptionally high. It should be emphasized that, regardless of both the structure of the activated amino acid and of the thiol used, no racemization of the final product was observed. During the derivatization protocol, racemization may occur under acidic hydrolysis, resulting in low D enantiomer content.

In the next stage of our research, we investigated the utility of DMT/NMM/TsO$^-$ for peptide synthesis in solution. It had been demonstrated that DMT/NMM/TsO$^-$ can be very efficient for the synthesis of orthogonally-protected dipeptides **12** with Z, Boc and Fmoc protecting groups, derived from a broad range of natural and unnatural hindered amino acids (Table 3). In solution, all protected dipeptides were obtained with very high purity, evaluated by LC-MS analysis. Homogeneous products were obtained, isolated and purified by simple extraction, including in the cases of the sterically-hindered aminoisobutyric acid derivatives, and of serine and threonine with an *O*-protected in the side chain by a bulky *t*-Bu group. The yields of the reaction ranged from 70-98%, and purity from 88-99% (see Table 3).

Table 3. Dipeptides **12a-u** synthesized in solution with DMT/NMM/TsO$^-$.

Entry	Dipeptide	Yield [%]	Purity [%]	%L / %D [a]	
				N-term.	C-term
3.1	Z-Aib-L-Ala-OMe (**12a**)	85	95	-	100/0
3.2	Z-Aib-L-Phe-OMe (**12b**)	81	99	-	100/0
3.3	Z-Aib-L-Leu-OMe (**12c**)	84	99	-	100/0
3.4	Z-L-Ala-L-Phe-OMe (**12d**)	74	80	98.5/1.5	99/1
3.5	Z-L-Phe-L-Leu-OMe (**12e**)	71	90	98.1/1.9	100/0
3.6	Z-L-Phe-L-Ala-OMe (**12f**)	77	89	98.4/1.6	100/0
3.7	Z-L-Phe-L-Phe-OMe (**12g**)	74	93	97.5/2.5	97.5/2.5
3.8	Z-L-Tyr(Z)-L-Ala-OMe (**12h**)	70	94	100/0	100/0
3.9	Z-L-Tyr(Z)-L-Tyr-OMe (**12i**)	73	86	100/0	100/0
3.10	Fmoc-L-Phe-L-Phe-OMe (**12j**)	87	84	100/0	100/0
3.11	Fmoc-L-Ala-L-Leu-OMe (**12k**)	87	96	100/0	100/0
3.12	Fmoc-L-Ala-L-Ala-OMe (**12l**)	91	98	100/0	100/0
3.13	Fmoc-L-Ala-L-Phe-OMe (**12m**)	88	98	100/0	100/0
3.14	Fmoc-L-Pro-L-Ala-OMe (**12n**)	98	99	100/0	100/0
3.15	Fmoc-L-Asp(OtBu)-L-Ala-OMe (**12o**)	77	98	100/0	100/0
3.16	Fmoc-L-Ser(tBu)-L-Ala-OMe (**12p**)	88	96	100/0	98.8/1.2
3.17	Fmoc-L-Thr(tBu)-L-Ala-OMe (**12q**)	75	95	100/0	98.8/1.2
3.18	Boc-Aib-L-Ala-OMe (**12r**)	74	99	-	100/0
3.19	Boc-L-Trp-L-Ala-OMe (**12s**)	71	85	*	100/0
3.20	Boc-L-Ala-L-Phe-OMe (**12t**)	68	99	100/0	99/1
3.21	Boc-Orn(Z)-Leu-OMe (**12u**)	89	100	100/0	100/0

[a] Enantiomeric purities were determined by GC analysis on a ChirasilVal column after degradation of peptides to amino acids and subsequent formation of volatile N-Tfa-amino acid-OMe.

Moreover, all couplings proceeded with exceedingly low racemization (epimerization) of the activated *N*-terminal amino acid residue. Only in the case of the *C*-terminal amino acid residue was some racemization observed, particularly for the *C*-terminal phenylalanine residue. This may have been caused by the harsh conditions of acidolytic degradation of the peptides to amino acids prior to determination of their enantiomeric purity.

DMT/NMM/TsO$^-$ was also successfully applied in [2 + 1] fragment coupling (see Table 4) and [2 + 3] fragment coupling (see Table 5).

Table 4. Tripeptides **13a-d** synthesized in solution with DMT/NMM/TsO$^-$ using the [2+1] strategy.

Entry	Tripeptide	Yield [%]	Purity [%]	H_2N-X_1-X_2-X_3-COOH %L / %D [a]		
				X_1	X_2	X_3
4.1	Boc-L-Ala-Gly-L-Phe-OMe (**13a**)	78	90	100/0	-	98/2
4.2	Boc-L-Ala-Gly-L-Ala-OMe (**13b**)	81	91	100/0	-	100/0
4.3	Boc-L-Ala-L-Trp-L-Ala-OMe (**13c**)	84	92	100/0	*	100/0
4.3	Boc-L-Ala-Aib-L-Leu-OMe (**13d**)	90	88	100/0	-	100/0

[a] Enantiomeric purities were determined by GC analysis on a ChirasilVal column after degradation of peptides to amino acids and subsequent formation of volatile N-Tfa-amino acid-OMe.

In the case of tripeptide synthesis, the yield of the reaction ranged from 78-90% (Table 4). The lowest yield was observed in the case of activation of the glycine residue (peptide **13a**). This may indicate that over-activation occurred, despite the progress of the formation of the superactive triazine ester being controlled, resulting in the degradation of the reactive intermediates and thus a lower reaction yield. The purity of the crude products in all cases was high, at around 90%.

Table 5. [2+3] strategy for synthesis of pentapeptides **14a-d** in solution with DMT/NMM/TsO$^-$.

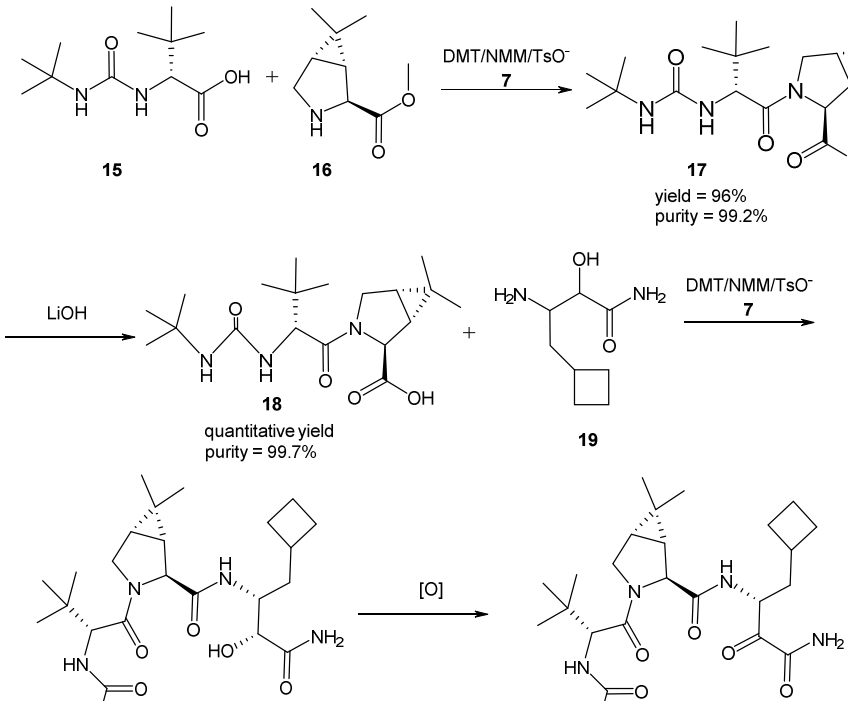
Entry	Pentapeptide	Yield [%]	Purity [%]	H_2N-X_1-X_2-X_3-X_4-X_5-COOH %L / %D [a]				
				X_1	X_2	X_3	X_4	X_3
5.1	Z-L-Phe-L-Phe-L-Ala-Aib-L-Leu-OMe (**14a**)	75	99	99/1	99/1	99/1	-	100/0
5.2	Z-L-Tyr(Z)-L-Tyr-L-Ala-L-Ala-L-Phe-OMe (**14b**)	71	95	99/1	99/1	100/0	100/	99/1
5.3	Z-L-Ala-L-Phe-L-Ala–L-Trp-L-Ala-OMe (**14c**)	76	89	98/2	97/3	98/2	-	98/2
5.4	Z-L-Tyr(Z)-L-Ala-L-Ala-Gly-L-Phe-OMe (**14d**)	70	98	100/0	99/1	99/1	-	98/2

[a] Enantiomeric purities were determined by GC analysis on a ChirasilVal column after degradation of peptides to amino acids and subsequent formation of volatile N-Tfa-amino acid-OMe.

Pentapeptides **14a-14d** were obtained using the [2 + 3] strategy for fragment coupling, with DMT/NMM/TsO$^-$ as the coupling reagent. The reaction yields were satisfactory, at above 70%, even though in all cases the stoichiometry of the reagents used in the syntheses was maintained. The purity of the raw products proved to be very high, in the range of 89-99%. The lowest purity was observed for the pentapeptide Z-AlaPheAlaTrpAla-OMe (**14c**). However, the most important

evidence proving the high efficiency of DMT/NMM/TsO$^-$ for the coupling of fragments was the optical purity of the final products. No loss of enantiomeric homogeneity was observed in any of the synthesized peptides. As previously mentioned, the low content of amino acid D-enantiomers could be the result of peptide racemization, occurring under the harsh conditions of acid hydrolysis (5 M HCl, 20 h, 100°C) to free amino acids. Nevertheless, even in the case of the epimerization-sensitive amino acid residue in position 2, L enantiomere content was in the range of 97-99%.

DMT/NMM/TsO$^-$ was furthermore used successfully in the synthesis of peptide derivatives composed of unnatural amino acids. Reagent **7** was used in the synthesis of a peptide antiviral drug, known by its commercial name as Boceprevir [25, 26] (Scheme 2). In the first stage, dipeptide **17** was obtained, and in the second step precursor **20** of Boceprevir was obtained using the [2 + 1] fragment coupling strategy.



Scheme 2. Synthesis of Boceprevir using DMT/NMM/TsO$^-$ (**7**) as a coupling reagent.

All synthetic steps necessary for the preparation of **20** were included within an optimized one-pot procedure, without the isolation of superactive intermediate 2-acyloxy-4,6-dimethoxy-1,3,5-triazine. The yield and purity of the synthesized products allowed Boceprevir to be obtained with a crude product purity of 99.3%. It was thus possible to obtain pharmaceutical-grade purity after the crystallization step.

Studies on the effectiveness of standard methods of peptide synthesis in the preparation of Boceprevir intermediates showed that none of the tested approaches did not afforded the final

products with high purity. Data presented in table 6 show the results of the synthesis of dipeptide 17 and tripeptide 20 by using the active ester method (TBTU, EDC/HOBt), mixed anhydride methods (isobutyl chloroformate), and acid chloride method (bis(trichloromethyl)carbonate).

Table 6. Synthesis of peptides **17** and **20** with classical coupling reagents.

Synthesis of dipeptide 17				
Method of coupling	Purity of crude product [%][a]	Yield [%]	Purity after preparative HPLC [%]	Yield [%]
TBTU	66	75	93.6	63
EDC/HOBt	80.5	72	-	-
mixed anhydride method isobutyl chloroformate	91	85	93.2	79
acid chlorides method bis(trichloromethyl)carbonate (BTC)	92	82	-	-
Synthesis of tripeptide 20				
Method of coupling	Crude product		Products after preparative HPLC	
TBTU	Fr I - 38% - product		Fr I: purity = 99.3%, yield = 32%,	
	Fr II - 22% - depsipeptide		Fr II: purity = 99.8%, yield = 22%	
	Fr III - 15% - dipeptide **17**		Fr III: purity = 99.9%, yield = 15%	
EDC/HOBt	Fr I - 51% - product		Fr I: purity = 99.9 %, yield = 40%	
	Fr II - 23% - depsipeptide		Fr II: purity = 98.9%, yield = 18%	
	Fr III - 26% - dipeptide 17		Fr II: purity = 99.6%,yield = 17%	

[a] HPLC 50-90%B in 20 min

In all cases, it was necessary to purify by preparative chromatography of both intermediates in order to obtain satisfactory purity of the final products, which is technically disadvantageous as it reduces the yield as well as increases the cost and time.

Conclusions

4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium toluene-4-sulfonate (DMT/NMM/TsO^-), an inexpensive and environmentally-friendly member of the of *N*-triazinylammonium family of sulfonates, has been identified as a very effective coupling reagent for the synthesis of amides, esters and peptides in solution. In this study, it was confirmed that DMT/NMM/TsO^- can be used with Z-, Fmoc- and Boc protected substrates as well as unnatural building blocks for the synthesis of esters, thioesters, dipeptides and oligopeptides, with high yield, high crude product purity and low levels of epimerization. Stoichiometric amounts of the reagents and standard synthetic procedures were used, without any optimization stages. The results show that, in many cases, it is possible to avoid time-consuming and costly chromatographic purification processes. DMT/NMM/TsO^- was also found to be very useful for the synthesis of oligopeptides. Using the fragment coupling strategy, final peptides were obtained with high yields and very high purity, while most importantly preserving enantiomeric homogeneity. This is particularly significant given that it is recommended to apply

additives when using classic coupling reagents, to suppress racemization. Thus, DMT/NMM/TsO^- can be considered as an effective tool for screening studies, allowing the preparation of diversified products with satisfactory purity and yield. Moreover, after careful optimization even complex products derived by coupling unusual building blocks can be obtained with high efficiency and to pharmacological standards, while omitting chromatographic purification.

Experimental Section

General information

Thin-layer chromatography experiments were performed on silica gel (Merck; 60 Å F254). Spots were visualized with UV light (254 and 366 nm) and with 1% ethanolic 4-(4-nitrobenzyl)pyridine (NBP).

Melting points were determined using a Büchi apparatus, model 510.

Analytical RP-HPLC was performed with a Waters 600S HPLC system (Waters 2489 UV/Vis detector, Waters 616 pump, Waters 717 plus autosampler, HPLC manager software from Chromax) using a C18 column (25 cm x 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 UV detection at 220 nm, Rt in min.

LC/MS spectra were recorded with a Waters ZQ 2000 Micromas or MS Bruker microOTOF-QIII.

IR spectra were recorded as KBr pellets or film with a Bruker ALPHA spectrometer or a PerkinElmer Spectrum 100.

^1H and ^{13}C NMR spectra were recorded with a Bruker Avance DPX 250 (250 MHz) spectrometer, with chemical shifts (ppm) relative to TMS used as an internal standard. Multiplicities are marked as s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet.

Gas chromatography (GC) – Shimadzu GC-14A, FID (H2/air), split 1:50. Column: capilar Chirasil-Val (25 m x 0,32 mm, thickness of film 0.2 µm, carrier gas: hel, pressure 0.45 atm. Temperature program: 4 min in 90°C, next 4°C/min to 190°C and 3 min at 90°C.

*Synthesis of 4-methoxy-N-(4-methylphenyl)benzamide (**10a**). Typical Procedure*

4-Methoxy-benzoic acid (0.152 g, 1 mmol) and DIPEA (0.088 mL, 0.5 mmol) were added to a vigorously stirred solution of DMT/NMM/TsO^- (7) (0.413 g, 1 mmol) in CH_2Cl_2 (5 mL), cooled to 0°C. Stirring was continued until the disappearance of condensing reagent **7** (TLC analysis, staining with 0.5% solution of NBP). Activation time: 40 min. After this time, p-tolylamine (0.107 g, 1 mmol) was added and the mixture stirred for an additional 2h at 0°C. The mixture was left overnight at room temperature. The mixture was diluted with CH_2Cl_2 (10 mL) and the solution was washed successively with water, 0.5 M aqueous $NaHSO_4$, water, 0.5 M aqueous $NaHCO_3$ and with water again. The organic layer was dried using $MgSO_4$, filtered, and concentrated to dryness. The residue was dried under a vacuum with P_2O_5 and KOH to a constant weight, affording 0.239 g 4-methoxy-*N*-*p*-tolyl-benzamide (**10a**), yield = 99%, mp = 143-145°C, lit. [27] mp = 145-148°C.

Analysis: for $C_{15}H_{15}NO_2$ (241.29): calculated: C 74.67%, H 6.27%, N 5.80%, O 13.26%, found: C 74.69%, H 6.25%, N 5.78%.

LC-MS: 242.68 ($[M+H]^+$ $C_{15}H_{16}NO_2^+$, calc. 241.29).

Anal. RP-HPLC (3–97%B in 30 min): Rt = 22.81 min, purity 93%.

IR (film/NaCl): v = 3339, 3031, 2963, 2862, 1651, 1596, 1514, 1500, 1402, 1308, 1237, 1101, 1031 [cm^{-1}].

^{1}H-NMR (250 MHz; $CDCl_3$) δ = 2.30 (s, 3H, CH_3); 3.84 (s, 3H, OCH_3); 6.93 (d, 2H, J = 8.6 Hz, -C_6H_4-OCH_3); 7.13 (d, 2H, J = 8.1 Hz, -C_6H_4-CH_3); 7.47 (d, 2H, J = 8.1 Hz, -C_6H_4-CH_3); 7.81 (d, 2H, J= 8.6 Hz , -C_6H_4-OCH_3) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.3, 55.5, 113.6, 120.7, 129.6, 130.1, 132.5, 139.2, 160.1, 165.1 [ppm].

Synthesis of *N*-(4-methoxy-phenyl)-2,2-dimethyl-propionamide (**10b**)

Starting materials: 2,2-dimethyl-propionic acid (0.102 g, 1 mmol); 4-methoxy-phenylamine (0.123 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.088 mL, 0.5 mmol). Activation time: 45 min. Product: *N*-(4-methoxy-phenyl)-2,2-dimethyl-propionamide: 0.191 g, yield = 92%, mp = 122-124˚C, lit. [28] mp = 124-126°C.

Analysis: for $C_{12}H_{17}NO_2$ (207.27): calculated: C 69.54%, H 8.27%, N 6.76%, O 15.44%, found: C 69.56%, H 8.26%, N 6.74%.

LC-MS: 208.68 ($[M+H]^+$ $C_{12}H_{18}NO_2^+$, calc. 207.27).

Anal. RP-HPLC (3–97%B in 30 min): Rt = 19.87 min, purity 98%.

IR (film/NaCl): v = 3303, 3130, 3009, 1644m 1622, 1602, 1579, 1542, 1509, 1459, 1312, 1246, 1170, 1033 [cm^{-1}].

^{1}H-NMR (250 MHz; $CDCl_3$) δ = 1.09 (s, 9H, $(CH_3)_3$-); 3.71 (s, 3H, OCH_3); 6.79 (d, 2H, J = 8.6 Hz, -C_6H_4-OCH_3); 7.24 (d, 2H, J = 8.2 Hz, -C_6H_4-NH) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 27.5, 39.8, 55.6, 114.8, 122.2, 137.1, 160.1, 172.1 [ppm].

Synthesis of *N*-Butyl-benzamide (**10c**)

Starting materials: benzoic acid (0.122 g, 1 mmol); butylamine (0.073 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.088 mL, 0.5 mmol). Activation time: 40 min. Product: *N*-Butyl-benzamide: 0.159 g, yield = 90%, mp = 41-44°C, lit. [29] mp = 42-43^{o}C.

Analysis: for $C_{11}H_{15}NO$ (177.25): calculated: C 74.54%, H 8.53%, N 7.90%, O 9.03%, found: C 74.55%, H 8.55%, N 7.92%.

LC-MS: 178.66 ($[M+H]^+$ $C_{11}H_{16}NO^+$, calc. 177.25).

Anal. RP-HPLC (3–97%B in 30 min): Rt = 19.56 min, purity 95%.

IR (film/NaCl): v = 3314, 2958, 2931, 1635, 1578, 1536, 1490, 1465, 1365, 1304, 1223, 1151, 1074 [cm^{-1}].

^{1}H-NMR (250 MHz; $CDCl_3$) δ = 0.87 (t, 3H, J = 6.5 Hz, CH_3-CH_2-); 1.37-1.49 (m, 4H, -CH_2-CH_2-); 3.36 (q, 2H, J = 4.8 Hz, -NH-CH_2-); 7.47-7.51 (m, 3H, C_6H_5-); 7.82 (d, 2H, J = 6.9 Hz, C_6H_5-) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 13.5, 20.1, 31.4, 39.5, 127.5, 128.2, 130.1, 133.1, 167.2 [ppm].

Synthesis of *N*-butyl-2-phenyl-butyramide (**10d**)

Starting materials: 2-phenyl-butyric acid (0.164 g, 1 mmol); butylamine (0.073 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.088 mL, 0.5 mmol). Activation time: 40 min. Product: *N*-butyl-2-phenyl-butyramide: 0.204 g, yield = 93%, mp = 61-63°C.

Analysis: for $C_{14}H_{21}NO$ (219.33): calculated: C 76.67%, H 9.65%, N 6.39%, O 7.29%, found: C 76.65%, H 9.63%, N 7.27%.

LC-MS: 220.84 ($[M+H]^+$ $C_{14}H_{22}NO^+$, calc. 219.33).

Anal. RP-HPLC (3–97%B in 30 min): Rt = 21.17 min, purity 89%.

IR (film/NaCl): v = 3298, 2960, 2931, 2873, 1641, 1544, 1495, 1454, 1365, 1273, 1227, 1189, 1115, 1031 [cm^{-1}].

^{1}H-NMR (250 MHz; $CDCl_3$) δ = 0.81 (t, 3H, J = 6.4 Hz, CH_3-CH_2-); 0.86 (t, 3H, J = 6.6 Hz, CH_3-CH_2-); 1.22-1.29 (m, 4H, -CH_2-CH_2-); 1.52-1.72 (m, 2H, CH_3-CH_2-); 3.19 (q, 2H, J = 4.9 Hz, -NH-CH_2-); 3.65 (dd, 1H, J_1 = 6.5 Hz, J_2 = 4.1 Hz, -CH-CH_2-); 7.47-7.51 (m, 3H, C_6H_5-); 7.82 (d, 2H, J = 6.9 Hz, C_6H_5-) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 11.5, 13.8, 20.5, 26.4, 31.5, 39.6, 47.4, 127.5, 126.3, 128.9, 138.1, 172.4 [ppm].

Synthesis of (R)-3-methyl-*N*-*p*-tolyl-succinamic acid benzyl ester (**10e**)

Starting materials: Z-L-Ala-OH (0.223 g, 1 mmol), *p*-tolylamine (0.107 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.088 mL, 0.5 mmol). Activation time: 30 min. Product: (R)-3-methyl-*N*-*p*-tolyl-succinamic acid benzyl ester: 0.275 g, yield = 88%, mp = 121-123°C.

Anal. RP-HPLC (3–97%B in 30 min): Rt = 16.22 min, purity 99%.

LC-MS: 313.87 ($[M+H]^+$ $C_{18}H_{21}N_2O_3^+$, calc. 312.37).

IR (film/NaCl): v = 3302, 3278, 3123, 2971, 1686, 1654, 1597, 1562, 1451, 1323, 1243, 1202, 1105, 1071, 1027 [cm^{-1}].

^{1}H-NMR (250 MHz; $CDCl_3$) δ = 1.43 (d, 3H, J = 7.5 Hz, CH_3-CH-); 2.31 (s, 3H, CH_3-C_6H_4-); 4.11 (q, 1H, J = 7.5 Hz, CH_3-CH-); 5.08 (bs, 2H, -CH_2O-); 7.13 (dd, 2H, J_1 = 3.9 Hz, J_2 = 7.3 Hz, C_6H_4-); 7.35-7.39 (m, 5H, C_6H_5-); 7.58 (dd, 2H, J_1 = 3.9 Hz, J_2 = 7.3 Hz, C6H4-) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 18.7, 21.6, 50.2, 66.5, 120.5, 127.8, 128.2, 128.9, 129.8 130.1, 137.6, 156.8, 168.9 [ppm].

*Synthesis of allyl 4-methoxybenzoate (**11a**). Typical Procedure*

4-Methoxy-benzoic acid (0.152 g, 1 mmol) and DIPEA (0.088 mL, 0.5 mmol) were added to a vigorously stirred solution of DMT/NMM/TsO^- (**7**) (0.413 g, 1 mmol) in CH_2Cl_2 (5 mL), cooled to 0°C. Stirring was continued until the disappearance of condensing reagent **7** (TLC analysis, staining with 0.5% solution of NBP). Activation time: 40 min. After this time, allyl alcohol (0.058 g, 1 mmol) and DIPEA (0.176 mL, 1 mmol) were added, and the mixture stirred for an additional 2h at 0°C. The mixture was left overnight at room temperature. The mixture was diluted with CH_2Cl_2 (10 mL), and the solution was washed successively with water, 0.5 M aqueous $NaHSO_4$, water, 0.5 M aqueous $NaHCO_3$ and with water again. The organic layer was dried using $MgSO_4$, filtered and concentrated to dryness. The residue was dried under a vacuum with P_2O_5 and KOH to a constant weight, affording 0.158 g allyl 4-methoxybenzoate (**11a**), yield = 82%, bp = 128-133°C (p = 1.0 Torr), lit. [30] bp = 130-140°C (p = 1.3 Torr). Anal. RP-HPLC (3-97%B in 30 min): Rt = 17.77 min, purity 99%.

LC-MS: 192.91 $[M]^+$ $C_{11}H_{12}O_3^+$, calc. 192.22.

IR (film/NaCl): v = 2928, 1692, 1548, 1560, 1536, 1500, 1464, 136, 1304, 1272, 1192, 1116, 788 [cm^{-1}].

^{1}H-NMR (250 MHz; $CDCl_3$): δ = 3.88 (s, 3H, CH_3O); 4.81 (d, 2H, J = 6 Hz, -O-CH_2-CH=CH_2); 5.24-5.43 (m, 2H, -CH_2-CH=CH_2); 5.98-6.09 (m, 1H, -CH_2-CH=CH_2); 6.91 (d, 2H, J = 8 Hz, arom.); 8.17 (d, 2H, J = 8 Hz, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ: 55.5, 65.6, 113.9, 118.2, 123.0, 132.0, 132.7, 166.5 [ppm].

Synthesis of Fmoc-L-Ala-OAll (**11b**)

Starting materials: Fmoc-L-Ala-OH (0.311 g, 1 mmol), DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol), allyl alcohol (0.058 g, 1 mmol). Activation time: 40 min. Product: Fmoc-L-Ala-OAll (**11b**): 0.302 g, yield = 86%, oil. Anal. RP-HPLC (20–97%B in 30 min): Rt = 6.18 min, purity 88%.

LC-MS: 352.88 ($[M+H]^+$ $C_{21}H_{22}NO_4^+$, calc. 351.41).

IR (film/NaCl): v = 3344, 2928, 1724, 1508, 1448, 1336, 1252, 1204, 1072, 764 [cm^{-1}].

^{1}H-NMR (250 MHz; $CDCl_3$): δ = 1.41 (d, 3H, J = 10 Hz, CH_3-CH-); 4.20 (t, 1H, J = 6.5 Hz, -$CHCH_2O$); 4.39-4.46 (m, 3H, -$CHCH_2O$ + CH_3-CH-); 4.66 (d, 2H, J = 6 Hz, -O-CH_2-CH=CH_2); 5.24-5.37 (m, 3H, -CH_2-CH=CH_2 + -OCO-NH-); 5.93 (m, 1H, -CH_2-CH=CH_2); 7.31 (t, 2H, J = 7 Hz, arom.); 7.40 (t, 2H, J = 7 Hz, arom.); 7.59 (d, 2H, J = 7 Hz, arom.); 7.76 (d, 2H, J = 7 Hz, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 18.6, 47.1, 49.5, 65.4, 66.8, 118.1, 119.8, 125.1, 127.1, 128.6, 132.1, 142.6, 160.1, 172.8 [ppm].

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 5.23 (L-Ala); L/D = 100/0.

Synthesis of Fmoc-L-Phe-OAll (**11c**)

Starting materials: Fmoc-L-Phe-OH (0.387 g, 1 mmol), DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol), allyl alcohol (0.058 g, 1 mmol). Activation time: 45 min. Product: Fmoc-L-Phe-

OAll (**11c**): 0.372 g, yield = 87%, mp = 103-105°C, lit. [31] mp = 105-106°C. Anal. RP-HPLC (20–97%B in 30 min): Rt = 8.33 min, purity 95%.

LC-MS: 428.88 ($[M+H]^+$ $C_{27}H_{26}NO_4^+$, calc. 427.50).

IR (film/NaCl): v = 3320, 3032, 2944, 1728, 1512, 1448, 1340, 1192, 1052, 760, 704 [cm^{-1}].

^{1}H-NMR (250 MHz; $CDCl_3$): δ = 3.06 (broad d, 2H, J = 6.5 Hz, CH-CH_2-C_6H_5); 4.17-4.23 (m, 1H, -O-CH_2-CH-); 4.30-4.44 (m, 2H, -O-CH_2-CH-); 4.61 (d, 2H, J = 6 Hz, -O-CH_2-CH=CH_2); 4.72 (q, 1H, J = 6.5 Hz, -CH-CH_2-C_6H_5); 5.23-5.34 (m, 3H, -CH_2-CH=CH_2 + -OCO-NH-); 5.86 (m, 1H, -CH_2-CH=CH_2); 7.09-7.77 (m, 13H, arom) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 38.3, 47.1, 54.7, 65.4, 66.8, 118.1, 120.1, 125.1, 127.2, 128.7, 129.1, 132.1, 136.4, 142.2, 156.1, 171.6 [ppm].

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 21.15 (D-Phe), Rt = 21.45 (L-Phe), L/D = 99.5/0.5.

Synthesis of Fmoc-L-Glu(OtBu)-OAll (**11d**)

Starting materials: Fmoc-L-Glu(OtBu)-OH (0.426 g, 1 mmol), DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol), allyl alcohol (0.058 g, 1 mmol). Activation time: 45 min. Product: Fmoc-L-Glu(OtBu)-OAll (**11d**): 0.358 g, yield = 77%, mp = 67-69°C, lit. [32] mp = 69-70°C. Anal. RP-HPLC (20–97%B in 30 min): Rt = 7.73 min, purity 93%.

LC-MS: 465.95 ($[M+H]^+$ $C_{27}H_{32}NO_6^+$, calc. 465.55).

IR (film/NaCl): v = 2976, 2928, 1724, 1512, 1448, 1368, 1332, 1152, 1056, 784 [cm^{-1}].

^{1}H-NMR (250 MHz; $CDCl_3$): δ = 1.44 (s, 9H, $(CH_3)_3$CO-); 1.90-2.40 (m, 4H, -CH_2-CH-); 4.22 (t, 1H, J = 7 Hz, -CH-CH_2-O-); 4.30-4.45 (m, 2H, -CH-CH_2-O-); 4.64 (d, 2H, J = 6 Hz, -OCH_2CH=CH_2); 5.20-5.40 (m, 2H, OCH_2CH=CH_2); 5.46 (m, 1H, NH); 5.89 (m, 1H, OCH_2CH=CH_2); 7.31 (t, 2H, J = 7 Hz, arom.); 7.40 (t, 2H, J = 7 Hz, arom.); 7.59 (d, 2H, J = 7 Hz, arom.); 7.76 (d, 2H, J = 7 Hz, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 28.0, 28.3, 31.6, 47.1, 53.8, 65.4, 66.9, 81.0, 118.9, 120.1, 125.2, 127.1, 128.7, 132.1, 142.2, 156.1, 171.1, 172.2 [ppm].

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 14.88 (L-Glu), L/D = 100/0.

Synthesis of Fmoc-L-Ser(tBu)-OAll (**11e**)

Starting materials: Fmoc-L-Ser(tBu)-OH (0.383 g, 1 mmol), DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol), allyl alcohol (0.058 g, 1 mmol). Activation time: 35 min. Product: Fmoc-L-Ser(tBu)-OAll (**11e**): 0.347 g, yield = 82%, mp = 59-62°C. lit. [33] mp = 58-60°C. Anal. RP-HPLC (20–97%B in 30 min): Rt = 7.07 min, purity 93%.

LC-MS: 424.82 ($[M+H]^+$ $C_{25}H_{30}NO_5^+$, calc. 423.51).

IR (film/NaCl): v = 3448, 2976, 1724, 1508, 1448, 1392, 1364, 1336, 1192, 1104, 984, 784, 648 [cm^{-1}].

^{1}H-NMR (250 MHz; $CDCl_3$): δ = 1.20 (s, 9H, $-OC(CH_3)_3$); 3.62 (dd, 1H, J_1 = 9 Hz, J_2 = 6 Hz, -CH-CH_2-O-); 3.87 (dd, 1H, J_1 = 9 Hz, J_2 = 6 Hz, -CH-CH_2-O-); 4.23-4.29 (m, 1H, $-CHCH_2O-$); 4.36-4.54 (m, 3H, $-CHCH_2O-$ + $-CHCH_2OC(CH_3)_3$); 4.68 (d, 2H, J = 7 Hz, $-OCH_2CH=CH_2$); 5.22-5.38 (m, 2H, $OCH_2CH=CH_2$); 5.62 (broad d, 1H, J = 4.5 Hz, NH); 5.66 (m, 1H, $OCH_2CH=CH_2$); 7.26 (t, 2H, J = 7 Hz, arom.); 7.37 (t, 2H, J = 7 Hz, arom.); 7.60 (d, 2H, J = 7 Hz, arom.); 7.75 (d, 2H, J = 7 Hz, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 27.6, 47.1, 54.6, 65.4, 55.8, 69.4, 73.1, 118.1, 119.9, 125.0, 127.2, 128.6, 132.1, 142.2, 152.3, 171.7 [ppm].

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 10.32 (L-Ser), Rt = 10.64 (D-Ser) L/D = 99.6/0.4.

Synthesis of Fmoc-L-Lys(Boc)-OAll (**11f**)

Starting materials: Fmoc-L-Lys(Boc)-OH (0.468 g, 1 mmol), DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol), allyl alcohol (0.058 g, 1 mmol). Activation time: 50 min. Product: Fmoc-L-Lys(Boc)-OAll (**11f**): 0.488 g, yield = 96%, mp = 120-122°C, lit. [34] mp = 123°C. Anal. RP-HPLC (20–97%B in 30 min): Rt = 8.25 min, purity 96%.

LC-MS: 509.92 ($[M+H]^+$ $C_{29}H_{37}N_2O_6^+$, calc. 508.62).

IR (film/NaCl): v = 2936, 1720, 1504, 1448, 1368, 1248, 1168, 752 [cm^{-1}].

^{1}H-NMR (250 MHz; $CDCl_3$): δ = 1.36-1.80 (m, 6H, $-CH_2-(CH_2)_3$); 1.48 (s, 9H, $(CH_3)_3COO$); 3.10-3.12 (m, 2H, $-NHCH_2(CH_2)_3$); 4.22-4.25 (m, 1H, $-CHCH_2O-$); 4.38-4.42 (m, 3H, $-CHCH_2O-$ + $-CH(CH_2)_4$); 4.66 (d, 2H, J = 6 Hz, $-OCH_2CH=CH_2$); 5.42-5.39 (m, 3H, $OCH_2CH=CH_2$ + NHCO); 5.95 (m, 1H, $OCH_2CH=CH_2$); 7.26 (t, 2H, J = 7 Hz, arom.); 7.37 (t, 2H, J = 7 Hz, arom.); 7.60 (d, 2H, J = 7 Hz, arom.); 7.75 (d, 2H, J = 7 Hz, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 22.1, 28.2, 29.4, 31.4, 40.6, 47.1, 53.5, 65.4, 66.9, 80.1, 118.1, 119.9, 125.1, 127.2, 128.6, 132.1, 142.2, 156.2, 171.6 [ppm].

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 11.43 (L-Lys), Rt = 11.04 (D-Lys) L/D = 99.5/0.5.

Synthesis of Fmoc-L-Asp(OtBu)-OAll (**11g**)

Starting materials: Fmoc-L-Asp(OtBu)-OH (0.411 g, 1 mmol), DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol), allyl alcohol (0.058 g, 1 mmol). Activation time: 40 min. Product: Fmoc-L-Asp(OtBu)-OAll (**11g**): 0.388 g, yield = 86%, mp = 79-81°C, lit. [35] mp = 82-83°C. Anal. RP-HPLC (20-97%B in 30 min): Rt = 7.06 min, purity 99%.

LC-MS: 453.12 ($[M+H]^+$ $C_{26}H_{30}NO_6^+$, calc. 451.52).

IR (film/NaCl): v = 3438, 2942, 1724, 1507, 1463, 1448, 1369, 1336 [cm^{-1}].

^{1}H-NMR (250 MHz; $CDCl_3$): δ = 1.45 (s, 9H, $(CH_3)_3CO$-); 2.80, 2.95 (d AB, 2H, J_1 = 16 Hz, J_2 = 4 Hz, -$OCOCH_2CH$-); 4.20-4.55 (m, 4H, -$CHCH_2OCONH$- + -$OCOCH_2CH$-); 4.65 (d, 2H, J = 6 Hz, -$OCH_2CH{=}CH_2$); 5.20-5.40 (m, 2H, -$OCH_2CH{=}CH_2$); 5.81 (d, 1H, J = 7.5 Hz, NH); 5.93 (m, 1H, CH_2-$CH{=}CH_2$); 7.31 (t, 2H, J = 7 Hz, arom.); 7.40 (t, 2H, J = 7 Hz, arom.); 7.59 (d, 2H, J = 7 Hz, arom.); 7.76 (d, 2H, J = 7 Hz, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 28.3, 31.6, 47.1, 53.8, 65.4, 66.9, 81.0, 118.9, 120.1, 125.2, 127.1, 128.7, 132.1, 142.2, 156.1, 171.1, 172.2 [ppm].

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min Rt = 14.13 (L-Asp), L/D = 100/0.

Synthesis of Fmoc-L-Asp(OtBu)-OAll (**11g**) in the presence DCC

Starting materials: Fmoc-L-Asp(OtBu)-OH (0.411 g, 1 mmol), DCC (0.206 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol), allyl alcohol (0.058 g, 1 mmol). Activation time: 40 min. Product: Fmoc-L-Asp(OtBu)-OAll (**11g**): 0.316 g, yield = 70%, anal. RP-HPLC (20–97%B in 30 min): Rt = 7.04 min, purity 92%. Product identical to that described above.

Synthesis of Fmoc-L-Asp(OtBu)-OAll (**11g**) in the presence TBTU

Starting materials: Fmoc-L-Asp(OtBu)-OH (0.411 g, 1 mmol), TBTU (0.321 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol), allyl alcohol (0.058 g, 1 mmol). Activation time: 40 min. Product: Fmoc-L-Asp(OtBu)-OAll (**11g**): 0.316 g, yield = 70%, anal. RP-HPLC (20–97%B in 30 min): Rt = 7.05 min, purity 99%. Product identical to that described above.

Synthesis of Fmoc-L-Asp(OtBu)-OAll (**11g**) in the presence HATU

Starting materials: Fmoc-L-Asp(OtBu)-OH (0.411 g, 1 mmol), HATU (0.380 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol), allyl alcohol (0.058 g, 1 mmol). Activation time: 40 min. Product: Fmoc-L-Asp(OtBu)-OAll (**11g**): 0.325 g, yield = 72%, anal. RP-HPLC (20–97%B in 30 min): Rt = 7.06 min, purity 98%. Product identical to that described above.

Synthesis of Fmoc-L-Asp(OtBu)-OAll (**11g**) in the presence BOP

Starting materials: Fmoc-L-Asp(OtBu)-OH (0.411 g, 1 mmol), BOP (0.442 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol), allyl alcohol (0.058 g, 1 mmol). Activation time: 40 min. Product: Fmoc-L-Asp(OtBu)-OAll (**11g**): 0.266 g, yield = 59%, anal. RP-HPLC (20–97%B in 30 min): Rt = 7.05 min, purity 99%. Product identical to that described above.

Synthesis of Fmoc-L-Asp(OtBu)-OPfp (**11h**)

Starting materials: Fmoc-L-Asp(OtBu)-OH (0.411 g, 1 mmol), DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol), pentafluorophenol (0.184 g, 1 mmol). Activation time: 40 min. Product: Fmoc-L-Asp(OtBu)-OPfp (**11h**): 0.508 g, yield = 88%, mp. = 93-95°C, lit. [36] mp. = 94.6-95.8°C, $[\alpha]_D^{20}$

= -2.4 (c = 1.0, $CHCl_3$), lit. [37] $\alpha]_D^{20}$ = -2.5 (c = 1.0, $CHCl_3$). Anal. RP-HPLC (20–97%B in 30 min): Rt = 8.77 min, purity 93%.

LC-MS: 578.91 ($[M+H]^+ C_{29}H_{25}F_5NO_6^+$, calc. 577.51).

IR (film/NaCl): v = 3320, 3027, 2966, 1738, 1513, 1441, 1347, 1244, 1190, 1050, 767, 709 [cm^{-1}].

^{1}H-NMR (250 MHz; $CDCl_3$): δ = 1.38 (s, 9H); 2.97 (d, 2H, J = 6.2 Hz); 4.38 (d, 2H, J = 3.1 Hz); 4.49 (t, 1H, J = 3.1 Hz); 5.06 (t, 1H, J = 6.2 Hz); 5.53 (d, 1H, J = 7.0 Hz, OCO-NH-); 7.29 (t, 2H, J = 7.2 Hz, arom.); 7.39 (t, 2H, J = 7.2 Hz, arom.); 7.58 (d, 2H, J = 7.2 Hz, arom.); 7.75 (d, 2H, J = 7.2 Hz, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 28.0, 36.1, 47.1, 53.8, 66.9, 119.9, 125.1, 127.2, 128.6, 138.3, 139.1, 141.0, 142.2, 156.1, 171.5, 172.3 [ppm].

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min Rt = 14.13 (L-Asp), L/D = 100/0.

Synthesis of Fmoc-L-Ala-OPfp (**11i**)

Starting materials: Fmoc-L-Ala-OH (0.311 g, 1 mmol), DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol), pentafluorophenol (0.184 g, 1 mmol). Activation time: 30 min. Product: Fmoc-L-Ala-OPfp (**11i**): 0.396 g, yield = 83%, mp = ,172-174°C, lit. [38] mp = 171-173°C, $[\alpha]_D^{20}$ = -22.5 (c = 1.0, $CHCl_3$), lit. [39] $[\alpha]_D^{20}$ = -22.2 (c = 1.0, $CHCl_3$). Anal. RP-HPLC (20–97%B in 30 min): Rt = 7.01 min, purity 88%.

LC-MS: 478.89 ($[M+H]^+ C_{24}H_{17}F_5NO_4^+$, calc. 477.39).

IR (film/NaCl): v = 3322, 3030, 2965, 1742, 1510, 1440, 1340, 1245, 1192, 1050, 760, 704 [cm^{-1}].

^{1}H-NMR (250 MHz; $CDCl_3$): δ = 1.44 (d, 3H, J = 7.4 Hz); 4.38 (d, 2H, J = 3.1 Hz); 4.49 (t, 1H, J = 3.1 Hz); 4.62 (q, 1H, J = 7.4 Hz); 5.53 (d, 1H, J = 7.0 Hz, OCO-NH-); 7.29 (t, 2H, J = 7.2 Hz, arom.); 7.39 (t, 2H, J = 7.2 Hz, arom.); 7.58 (d, 2H, J = 7.2 Hz, arom.); 7.75 (d, 2H, J = 7.2 Hz, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 18.6, 49.5, 47.1, 66.9, 119.9, 125.1, 127.2, 128.8, 138.3, 139.1, 141.2, 155.9, 171.5 [ppm].

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 5.23 (L-Ala); L/D = 100/0.

Synthesis of Fmoc-L-Ala-ONSu (**11j**)

Starting materials: Fmoc-L-Ala-OH (0.311 g, 1 mmol), DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol), N-hydroxysusuccinimide (0.115 g, 1 mmol). Activation time: 30 min. Product: Fmoc-L-Ala-ONSu (**11j**): 0.319 g, yield = 78%, oil, $[\alpha]_D^{20}$ = -23.1 (c = 1.0, $CHCl_3$), lit. [40] $[\alpha]_D^{20}$ = -23 (c = 1.0, $CHCl_3$). Anal. RP-HPLC (20–97%B in 30 min): Rt = 6.81 min, purity 95%.

LC-MS: 409.91 ($[M+H]^+ C_{22}H_{21}N_2O_6^+$, calc. 408.41).

IR (film/NaCl): v = 3320, 3035, 2960, 1748, 1501, 1440, 1346, 1248, 1188, 1052, 761, 705 [cm^{-1}].

^{1}H-NMR (250 MHz; $CDCl_3$): δ = 1.44 (d, 3H, J = 7.4 Hz); 2.83 (ddd, 4H, J = 15.0 Hz, J = 8.1 Hz, J = 4.3 Hz); 4.38 (d, 2H, J = 3.1 Hz); 4.49 (t, 1H, J = 3.1 Hz); 4.62 (q, 1H, J = 7.4 Hz); 5.53 (d, 1H, J = 7.0 Hz, OCO-NH-); 7.29 (t, 2H, J = 7.2 Hz, arom.); 7.39 (t, 2H, J = 7.2 Hz, arom.); 7.58 (d, 2H, J = 7.2 Hz, arom.); 7.75 (d, 2H, J = 7.2 Hz, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 18.1, 25.6, 47.1, 50.3, 66.9, 119.9, 125.1, 127.2, 128.6, 142.2, 155.9, 169.1, 169.7 [ppm].

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 5.23 (L-Ala); L/D = 100/0.

Synthesis of Fmoc-L-Ala-SPh (**11k**)

Starting materials: Fmoc-L-Ala-OH (0.311 g, 1 mmol), DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol), thiophenol (0.110 g, 1 mmol). Activation time: 30 min. Product: Fmoc-L-Ala-SPh (**11k**): 0.383 g, yield = 94%, oil. Anal. RP-HPLC (20–97%B in 30 min): Rt = 7.21 min, purity 97%.

LC-MS: 404.89 ($[M+H]^+$ $C_{24}H_{22}NO_3S^+$, calc. 403.50).

IR (film/NaCl): v = 3321, 3030, 2965, 1752, 1510, 1440, 1340, 1245, 1192, 1050, 771, 714 [cm^{-1}].

^{1}H-NMR (250 MHz; $CDCl_3$): δ = 1.44 (d, 3H, J = 7.4 Hz); 4.38 (d, 2H, J = 3.1 Hz); 4.49 (t, 1H, J = 3.1 Hz); 4.62 (q, 1H, J = 7.4 Hz); 5.53 (d, 1H, J = 7.0 Hz, OCO-NH-); 7.17 (t, 1H, J = 7.5 Hz, arom); 7.24 (dd, 2H, J = 7.5 Hz, J = 7.9 Hz, arom); 7.29 (t, 2H, J = 7.2 Hz, arom.); 7.39 (t, 2H, J = 7.2 Hz, arom.); 7.48 (d, 2H, J = 7.8 Hz, arom); 7.58 (d, 2H, J = 7.2 Hz, arom.); 7.75 (d, 2H, J = 7.2 Hz, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 20.3, 47.2, 58.7, 66.9, 119.9, 125.1, 127.4, 128.6, 129.1, 131.4, 134.8, 142.2, 155.5, 193.4 [ppm].

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 5.23 (L-Ala); L/D = 100/0.

Synthesis of Fmoc-L-Ser(tBu)-SPh (**11l**)

Starting materials: Fmoc-L-Ser(tBu)-OH (0.383 g, 1 mmol), DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol), thiophenol (0.110 g, 1 mmol). Activation time: 45 min. Product: Fmoc-L-Ser(tBu)-SPh (**11l**): 0.428 g, yield = 90%, oil, $[\alpha]_D^{20}$ = -25.7 (c = 1.0, $CHCl_3$), lit. [41] $[\alpha]_D^{20}$ = -23.8 (c = 0.8, $CHCl_3$). Anal. RP-HPLC (20–97%B in 30 min): Rt = 7.96 min, purity 96%.

LC-MS: 477.03 ($[M+H]^+$ $C_{28}H_{30}NO_4S^+$, calc. 475.61).

IR (film/NaCl): v = 3323, 3031, 2960, 1744, 1502, 1449, 1340, 1243, 1188, 1057, 760, 710 [cm^{-1}].

^{1}H-NMR (250 MHz; $CDCl_3$): δ = 1.29 (9H, s); 4.38 (d, 2H, J = 3.1 Hz); 4.49 (t, 1H, J = 3.1 Hz); 4.68 (d, 2H, J = 6.8 Hz); 4.71 (t, 1H, J = 6.8 Hz); 5.53 (d, 1H, J = 7.0 Hz, OCO-NH-); 7.17 (t, 1H, J = 7.5 Hz, arom); 7.24 (dd, 2H, J = 7.5 Hz, J = 7.9 Hz, arom); 7.29 (t, 2H, J = 7.2 Hz, arom.); 7.39 (t, 2H, J = 7.2 Hz, arom.); 7.48 (d, 2H, J = 7.8 Hz, arom); 7.58 (d, 2H, J = 7.2 Hz, arom.); 7.75 (d, 2H, J = 7.2 Hz, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 27.6, 47.2, 58.1, 66.9, 69.3, 73.5, 119.9, 125.1, 127.1, 128.6, 129.1, 131.4, 134.6, 142.2, 155.5, 193.4 [ppm].

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 10.32 (L-Ser), Rt = 10.64 (D-Ser) L/D = 99/1.

Synthesis of Fmoc-L-Ala-S$(CH_2)_3CH_3$ (**11m**)

Starting materials: Fmoc-L-Ala-OH (0.311 g, 1 mmol), DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol), butanethiol (0.091 g, 1 mmol). Activation time: 30 min. Product: Fmoc-L-Ala-S$(CH_2)_3CH_3$ (**11m**): 0.337 g, yield = 88%, oil. Anal. RP-HPLC (20–97%B in 30 min): Rt = 7.31 min, purity 95%.

LC-MS: 384.95 ($[M+H]^+$ $C_{22}H_{26}NO_3S^+$, calc. 383.51).

IR (film/NaCl): v = 3320, 3037, 2960, 1750, 1510, 1449, 1345, 1245, 1192, 1050, 762, 709 [cm^{-1}].

^{1}H-NMR (250 MHz; $CDCl_3$): δ = 0.89 (3H, t, J = 6.5 Hz); 1.29-1.33 (m, 4H); 1.44 (d, 3H, J = 7.4 Hz); 3.35 (2H, t, J = 7.2 Hz); 4.38 (d, 2H, J = 3.1 Hz); 4.49 (t, 1H, J = 3.1 Hz); 4.62 (q, 1H, J = 7.4 Hz); 5.53 (d, 1H, J = 7.0 Hz, OCO-NH-); 7.29 (t, 2H, J = 7.2 Hz, arom.); 7.39 (t, 2H, J = 7.2 Hz, arom.); 7.58 (d, 2H, J = 7.2 Hz, arom.); 7.75 (d, 2H, J = 7.2 Hz, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 13.7, 20.3, 21.9, 30.1, 31.2, 47.1, 58.1, 66.9, 119.9, 125.1, 127.2, 128.6, 142.2, 155.5, 193.4 [ppm].

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 5.20 (D-Ala), Rt = 5.23 (L-Ala), L/D = 99/1.

Synthesis of Fmoc-L-Ser(tBu)-S$(CH_2)_3CH_3$ (**11n**)

Starting materials: Fmoc-L-Ser(tBu)-OH (0.383 g, 1 mmol), DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol), butanethiol (0.091 g, 1 mmol). Activation time: 45 min. Product: Fmoc-L-Ser(tBu)-S$(CH_2)_3CH_3$ (**11n**): 0.364 g, yield = 80%, oil. Anal. RP-HPLC (20-97%B in 30 min): Rt = 8.11 min, purity 97%.

LC-MS: 457.12 ($[M+H]^+$ $C_{26}H_{34}NO_4S^+$, calc. 455.62).

IR (film/NaCl): v = 3322, 3031, 2955, 1748, 1510, 1441, 1340, 1241, 1190, 1050, 778, 702 [cm^{-1}].

^{1}H-NMR (250 MHz; $CDCl_3$): δ = 0.89 (3H, t, J = 6.5 Hz); 1.29 (13H, s); 1.29-1.33 (m, 4H); 3.35 (2H, t, J = 7.2 Hz); 3.87 (2H d, J = 6.8 Hz), 4.38 (d, 2H, J = 3.1 Hz); 4.49 (t, 1H, J = 3.1 Hz); 4.62 (1H, dt, J = 3.10

Hz, J = 6.85 Hz); 5.53 (d, 1H, J = 7.0 Hz, OCO-NH-); 7.29 (t, 2H, J = 7.2 Hz, arom.); 7.39 (t, 2H, J = 7.2 Hz, arom.); 7.58 (d, 2H, J = 7.2 Hz, arom.); 7.75 (d, 2H, J = 7.2 Hz, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 13.3, 21.9, 27.6, 30.2, 31.1, 47.2, 58.1, 66.9, 69.3, 73.5, 119.9, 125.1, 127.3, 128.7, 142.2, 155.5, 193.4 [ppm].

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 10.32 (L-Ser), Rt = 10.64 (D-Ser) L/D = 98/2.

*Synthesis of Z-Aib-Ala-OMe (**12a**): Typical Procedure*

Z-Aib-OH (0.237 g, 1 mmol) and DIPEA (0.088 mL, 0.5 mmol) were added to a vigorously stirred solution of DMT/NMM/TsO^- (0.413 g, 1 mmol) in CH_2Cl_2 (5 mL), cooled to 0°C. The stirring was continued until the disappearance of a condensing reagent **5** (TLC analysis, staining with 0.5% solution of NBP), activation time = 1 h. After which time, HCl*L-Ala-OMe (0.139 g, 1 mmol) and DIPEA (0.176 mL, 1 mmol) were added and the mixture stirred for an additional 2 h at 0°C. The mixture was left overnight at room temperature. The mixture was diluted with CH_2Cl_2 (10 mL) and the solution was washed successively with water, 0.5 M aqueous $NaHSO_4$, water, 0.5 M aqueous $NaHCO_3$ and with water again. The organic layer was dried with $MgSO_4$, filtered and concentrated to dryness. The residue was dried under a vacuum with P_2O_5 and KOH to a constant weight, affording 0. 277 g Z-Aib-Ala-OMe, yield = 85%, mp = 67-68°C, lit. [42] mp = 68.6-69.6°C. Anal. RP-HPLC (50-100%B in 30 min): Rt = 5.77 min, purity 95%.

IR (film/NaCl): ν = 3678, 3608, 3430, 3017, 2965, 2398, 1734, 1672, 1512, 1451, 1420, 1250, 1224, 1191, 1170, 1151, 1086, 1066, 1020 [cm^{-1}].

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.36 (d, 3H, J = 7.1 Hz, CH_3-CH-); 1.53, 1.54 (s, 3H + 3H, $(CH_3)_2$C-); 3.74 (s, 3H, CH_3O-); 4.46 (qu, 1H, J = 7.1 Hz, CH_3CH-); 5.10 (s, 2H, -CH_2O-); 5.34 (s, 1H, NH-COO), 6.80 (broad d, 1H, J = 7 Hz, NH); 7.28-7.36 (s, 5H, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 17.7, 25.1, 48.1, 52.3, 58.1, 66.5, 127.9, 128.5, 128.9, 155.6, 172.9, 175,6 [ppm].

LC/MS: 323.3 ([M+H]$^+$, $C_{16}H_{22}N_2O_5^+$; calc. 322.36).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 5.23 (L-Ala); L/D = 100/0; Rt = 6.88 (Aib).

Synthesis of Z-Aib-Phe-OMe (**12b**)
Starting materials: Z-Aib-OH (0.237 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Phe-OMe*HCl (0.216 g, 1 mmol). Product: Z-Aib-Phe-OMe (0.323 g, 81%), mp = 96-97°C, lit. [42] mp = 94.5-95.5°C. Anal. RP-HPLC (50–100%B in 30 min): Rt = 6.52 min, purity 99%.

IR (film/NaCl): ν = 3422, 3019, 2950, 1731, 1672, 1498, 1452, 1362, 1258 [cm^{-1}].

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.47 (s, 6H, $(CH_3)_2C$-); 3.08 (d, 2H, J = 7 Hz, -CH_2CH-); 3.71 (s, 3H, CH_3O-); 4.84 (q, 1H, J = 7 Hz, -CH_2CH-); 5.07 (s, 2H, -CH_2O-); 5.27 (s, 1H, NH-COO); 6.68 (d, 1H, J = 7 Hz, CONH), 7.06-7.82 (m,10H, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 25.1, 37.6, 52.3, 53.5, 58.1, 66.5, 127.8, 128.1, 128.5, 128.9, 129.1, 136.3, 155.6, 171.3, 175.6, [ppm].

LC/MS: 399.5 ($[M+H]^+$, $C_{22}H_{26}N_2O_5^+$; calc. 398.5).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 6.78 (Aib); Rt = 21.45 (L-Phe); L/D = 100/0.

Synthesis of Z-Aib-Leu-OMe (**12c**)

Starting materials: Z-Aib-OH (0.237 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Leu-OMe*HCl (0.182 g, 1 mmol). Product: Z-Aib-Leu-OMe (0.306 g, 84%), mp = 78-80°C, lit. [43] mp = 77-80°C. Anal. RP-HPLC (50–100%B in 30 min): Rt = 6.40 min, purity 99%.

IR (film/NaCl): v = 3684, 3620, 3433, 2975, 2895, 2400, 1735, 1717, 1680, 1559, 1512, 1417 [cm^{-1}].

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.91 (d, 6H, J = 6 Hz, $(CH_3)_2$-CH-); 1.45-1.7 (m, 3H, -CH_2CH-); 1.53, 1.55 (s + s, 3H + 3H, $(CH_3)_2C$-); 3.71 (s, 3H, CH_3O-); 4.59 (dt, 1H, J_1 = 8.1 Hz, J_2 = 4.5 Hz, -CH_2CH-); 5.09 (s, 2H, -CH_2O-); 5.31 (s, 1H, NHCOO); 6.61 (d, 1H, J = 5 Hz, NH); 7.35 (s, 5H, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 22.6, 24.6, 25.1, 38.2, 52.3, 53.8, 58.1, 66.5, 127.9, 128.5, 128.9, 155.6, 172.8, 175.6 [ppm].

LC/MS: 365.4 ($[M+H]^+$, $C_{19}H_{28}N_2O_5^+$; calc. 364.5).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 6.49 (Aib); Rt = 10.65 (L-Leu); L/D = 100/0.

Synthesis of Z-Ala-Phe-OMe (**12d**)

Starting materials: Z-Ala-OH (0.223 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Phe-OMe*HCl (0.216 g, 1 mmol). Product: Z-Ala-Phe-OMe (0.284 g, 74%), mp = 102-103°C, lit. [44] mp = 104-106°C. Anal. RP-HPLC (50–100%B in 30 min): Rt = 7.11 min, purity 80%.

IR (film/NaCl): v = 3306, 3088, 3064, 2951, 1719, 1660, 1584, 1521, 1497, 1364, 1212, 1178, 1114, 1068 [cm^{-1}].

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.44 (d, 3H, J = 6.2 Hz, CH_3-CH-); 3.19 (dd, 2H, J_1 = 4.1 Hz, J_2 = 7.2 Hz, -CH_2-CH-); 3.65 (s, 3H, CH_3O-); 4.31 (q, 1H, J = 6.2 Hz, CH_3-CH-); 4.75 (q, 1H, J = 6.9 Hz, -CH_2-CH-); 5.04 (s, 2H, -CH_2-O-); 7.27-7.36 (m, 10H, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 17.5, 37.6, 50.5, 52.3, 53.2, 66.5, 127.9, 128.3, 128.6, 128.9, 129.1, 136.3, 154.4, 171.3, 172.2 [ppm].

LC/MS: 385.5 ([M+H]$^+$, $C_{21}H_{24}N_2O_5^+$; calc. 384.4).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 5.20 (D-Ala), Rt = 5.23 (L-Ala), L/D = 98.5/1.5; Rt = 21.15 (D-Phe), Rt = 21.45 (L-Phe), L/D = 99/1.

Synthesis of Z-Phe-Leu-OMe (**12e**)

Starting materials: Z-Phe-OH (0.299 g, 1 mmol); DMT/NMM/TsO$^-$ (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Leu-OMe*HCl (0.182 g, 1 mmol). Product: Z-Phe-Leu-OMe (0.303 g, 71%), mp = 109-111°C, lit. [45] mp = 110-112C. Anal. RP-HPLC (50-100%B in 30 min): Rt = 7.95 min, purity 90%.

IR (film/NaCl): v = 3377, 3080, 2956, 2868, 1746, 1691, 1656, 1541, 1454, 1434, 1368, 1260, 1222, 1147, 1055 [cm^{-1}].

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.90 (d, 6H, J = 6.1 Hz, $(CH_3)_2$-CH-); 1.44-1.72 (m, 3H, -CH_2CH-); 3.20 (dd, 2H, J_1 = 4.1 Hz, J_2 = 7.2 Hz, -CH_2-CH-); 3.62 (s, 3H, CH_3O-); 4.51 (dt, 1H, J_1 = 8.1 Hz, J_2 = 4.5 Hz, -CH_2CH-); 4.77 (q, 1H, J = 6.9 Hz, -CH_2-CH-); 7.25-7.41 (m, 10H, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 22.6, 24.6, 38.2, 38.6, 52.3, 53.8, 55.8, 66.5, 127.9, 128.5, 128.7, 128.9, 129.1, 137.1, 155.8, 170.9, 172.8 [ppm].

LC/MS: 427.5 ([M+H]$^+$, $C_{24}H_{30}N_2O_5^+$; calc. 426.5).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 10.65 (L-Leu), L/D = 100/0; Rt = 21.16 (D-Phe), Rt = 21.44 (L-Phe), L/D = 98.1/1.9.

Synthesis of Z-Phe-Ala-OMe (**12f**)

Starting materials: Z-Phe-OH (0.299 g, 1 mmol); DMT/NMM/TsO$^-$ (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Ala-OMe*HCl (0.139 g, 1 mmol). Product: Z-Phe-Ala-OMe (0.296 g, 77%), mp = 122-124°C, lit. [46] mp = 125-126°C. Anal. RP-HPLC (50–100%B in 30 min): Rt = 6.98 min, purity 89%.

IR (film/NaCl): v = 3294, 3031, 2950, 1735, 1690, 1645, 1530, 1454, 1371, 1284, 1236, 1216, 1140, 1045 [cm^{-1}].

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.44 (d, 3H, J = 6.1 Hz, CH_3-CH-); 3.21 (dd, 2H, J_1 = 4.1 Hz, J_2 = 7.4 Hz, -CH_2-CH-); 3.64 (s, 3H, CH_3O-); 4.32 (q, 1H, J = 6.1 Hz, CH_3-CH-); 4.75 (q, 1H, J = 7.1 Hz, -CH_2-CH-); 5.04 (s, 2H, -CH_2-O-); 7.26-7.39 (m, 10H, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 17.7, 38.4, 47.8, 52.3, 55.8, 66.5, 129.2, 127.9, 128.5, 128.7, 128.9, 137.1, 155.8, 171.2, 172.9 [ppm].

LC/MS: 385.4 ([M+H]+, C21H24N2O5+; calc. 384.4).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 5.23 (L-Ala), L/D = 100/0; Rt = 21.14 (D-Phe), Rt = 21.45 (L-Phe), L/D = 98.4/1.6.

Synthesis of Z-Phe-Phe-OMe (**12g**)

Starting materials: Z-Phe-OH (0.299 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Phe-OMe*HCl (0.216 g, 1 mmol). Product: Z-Phe-Phe-OMe (0.341 g, 74%), mp = 133-136°C, lit. [47] mp = 136-138°C. Anal. RP-HPLC (50–100%B in 30 min): Rt = 8.12 min, purity 93%.

IR (film/NaCl): v = 3304, 3274, 3064, 2961, 1733, 1686, 1652, 1535, 1494, 1453, 1384, 1286, 1258, 1197, 1083 [cm^{-1}].

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 2.89-3.19 (m, 4H, (-CH_2-CH-)$_2$); 3.55 (s, 3H, CH_3O-); 4.81-4.88 (m, 2H, (-CH_2-CH-)$_2$); 5.03 (s, 2H, -CH_2-O-); 7.06-7.77 (m, 15H, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 37.6, 38.4, 52.4, 53.2, 55.8, 66.5, 127.9, 128.5, 128.7, 128.9, 129.1, 137.1, 155.8, 170.9, 171.3 [ppm].

LC/MS: 461.6 ([M+H]$^+$, $C_{27}H_{28}N_2O_5^+$; calc. 460.5).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 21.15 (D-Phe), Rt = 21.44 (L-Phe), L/D = 97.5/2.5.

Synthesis of Z-Tyr(Z)-Ala-OMe (**12h**)

Starting materials: Z-Tyr(Z)-OH (0.449 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Ala-OMe*HCl (0.139 g, 1 mmol). Product: Z-Tyr(Z)-Ala-OMe (0.376 g, 70%), mp = 178-180°C. Anal. RP-HPLC (50–100%B in 30 min): Rt = 9.02 min, purity 94%.

IR (film/NaCl): v = 3302, 3065, 3035, 2951, 1748, 1656, 1508, 1449, 1374, 1204, 1048, 1033 [cm^{-1}].

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.22 (d, 3H, J = 6.4 Hz, CH_3-CH-); 2.16 (dd, 2H, J_1 = 4.6 Hz, J_2 = 8.4 Hz, -CH_2-CH-); 3.52 (s, 3H, CH_3O-); 4.11 (q, 1H, J = 6.4 Hz, CH_3-CH-); 4.53-4.60 (m, 1H, -CH_2-CH-); 5.05 (s, 2H, -CH_2-O-); 5.18 (s, 2H, -CH_2-O-); 7.16-7.55 (m, 14H, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 17.7, 38.5, 47.8, 52.3, 55.8, 66.5, 70.3, 114.6, 127.9, 128.5, 128.9, 129.8, 153.1, 155.8, 171.2, 172.9 [ppm].

LC/MS: 535.5 ([M+H]$^+$, $C_{29}H_{30}N_2O_8^+$; calc. 534.6).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 5.22 (L-Ala), L/D = 100/0; Rt = 23.55 (L-Tyr), L/D = 100/0.

Synthesis of Z-Tyr(Z)-Tyr-OMe (**12i**)

Starting materials: Z-Tyr(Z)-OH (0.449 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Tyr-OMe*HCl (0.232 g, 1 mmol). Product: Z-Tyr(Z)-Tyr-OMe (0.457 g, 73%), mp = 182-185°C. Anal. RP-HPLC (50–100%B in 30 min): Rt = 9.16 min, purity 86%.

IR (film/NaCl): v = 3303, 3033, 2953, 1748, 1659, 1589, 1508, 1446, 1371, 1204, 1110, 1048, 1019 [cm^{-1}].

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 2.19 (dd, 2H, J_1 = 4.6 Hz, J_2 = 8.4 Hz, -CH_2-CH-); 3.08 (dd, 2H, J_1 = 4.6, J_2 = 8.0 Hz, -CH_2-CH-); 3.55 (s, 3H, CH_3O-); 4.53-4.60 (m, 1H, -CH_2-CH-); 4.80-4.91 (m, 1H, -CH_2-CH-); 5.05 (s, 2H, -CH_2-O-); 5.18 (s, 2H, -CH_2-O-); 6.32 (d, 2H, J = 7.1 Hz, C_6H_4-); 6.97 (d, 2H, J = 7.2 Hz, C_6H_4-); 7.33-7.55 (m, 14H, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 37.6, 38.4, 52.5, 53.2, 55.8, 66.5, 70.3, 115.7, 116.6, 127.9, 128.5, 128.9, 129.8, 130.5, 153.1, 155.8, 170.9, 171.3 [ppm].

LC/MS: 627.7 ($[M+H]^+$, $C_{35}H_{34}N_2O_9^+$; calc. 626.7).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 23.55 (L-Tyr), L/D = 100/0.

Synthesis of Fmoc-Phe-Phe-OMe (**12j**)

Starting materials: Fmoc-Phe-OH (0.387 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Phe-OMe*HCl (0.216 g, 1 mmol). Product: Fmoc-Phe-Phe-OMe (0.477 g, 87%), mp = 169-171°C. Anal. RP-HPLC (50-100%B in 30 min): Rt = 11.54 min, purity 84%.

IR (film/NaCl): v = 3422, 1729, 1680, 1494, 1452, 1401, 1320 [cm^{-1}].

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 2.96 broad d, 2H, J = 6.5 Hz, -CH-CH_2-C_6H_5); 3.08 (broad d, 2H, J = 6.5 Hz, -CH-CH_2-C_6H_5); 3.55 (s, 3H, CH_3O-); 4.13-4.22 (m, 1H, -O-CH_2-CH-); 4.25-4.45 (m, 4H, -O-CH_2-CH- + (-CH-CH_2-C_6H_5)$_2$); 5.38 (broad d, 1H, J = 5 Hz,

OCONH); 7.15-7.35 (m, 13H, arom. + NH), 7,43 (t, 2H, J = 7.5 Hz, arom.); 7.52 (t, 2H, J = 6.5 Hz, arom.); 7.76 (d, 2H, J = 7.5 Hz, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 37.6, 38.4, 47.1, 52.3, 53.2, 55.8, 66.9, 119.9, 125.1, 127.1, 128.4, 128.7, 120.9, 129.1, 142.2, 155.5, 170.9, 171.3 [ppm].

LC/MS: 549.7 ($[M+H]^+$, $C_{34}H_{32}N_2O_5^+$; calc. 548.6).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 21.45 (L-Phe); L/D = 100/0.

Synthesis of Fmoc-Ala-Leu-OMe (**12k**)

Starting materials: Fmoc-Ala-OH (0.329 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Leu-OMe*HCl (0.182 g, 1 mmol). Product: Fmoc-Ala-Leu-OMe (0.381 g, 87%), mp = 123-125°C, lit. [48] mp = 124-126°C. Anal. RP-HPLC (50–100%B in 30 min): Rt = 10.92 min, purity 96%.

IR (film/NaCl): v = 3608, 3422, 3017, 2973, 1739, 1711, 1676, 1506, 1448 [cm^{-1}].

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.88 (d, 6H, J = 4 Hz, $(CH_3)_2$-CH-); 1.39 (d, 3H, J = 7 Hz, CH_3CH-); 1.50-2.05 (m, 3H, $(CH_3)_2CHCH_2$-); 3.71 (s, 3H, CH_3O-); 4.20 (t, 1H, J = 3 Hz, -$CHCH_2O$-); 4.26-4.40 (m, 1H, CH-NH); 4.38 (d, 2H, J = 3 Hz, -$CHCH_2O$); 4.59 (m, 1H, $CHCH_2CH$); 5.53 (d, 1H, J = 7 Hz, OCO-NH-);

6.56 (d, 1H, J = 7 Hz, CO-NH-); 7.29 (t, 2H, J = 7 Hz, arom.); 7.39 (t, 2H, J = 7 Hz, arom.); 7.58 (d, 2H, J = 7 Hz, arom.); 7.75 (d, 2H, J = 7 Hz, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 17.5, 22.4, 24.4, 38.2, 47.1, 50.5, 52.4, 53.8, 66.9, 119.9, 125.1, 127.1, 128.6, 142.2, 155.9, 172.2, 172.8 [ppm].

LC/MS: 439.6 ([M+H]$^+$, $C_{25}H_{30}N_2O_5^+$; calc. 438.5).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 5.48 (L-Ala), L/D = 100/0; Rt = 10.88 (L-Leu), L/D = 100/0.

Synthesis of Fmoc-Ala-Ala-OMe (**12l**)

Starting materials: Fmoc-Ala-OH (0.329 g, 1 mmol); DMT/NMM/TsO$^-$ (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Ala-OMe*HCl (0.139 g, 1 mmol). Product: Fmoc-Ala-Ala-OMe (0.361 g, 91%), mp = 189-190°C, lit. [49] mp = 195-196°C. Anal. RP-HPLC (50–100%B in 30 min): Rt = 8.35 min, purity 98%.

IR (film/NaCl): v = 3119, 3008, 1740, 1718, 1675, 1504, 1450, 1376, 1314 [cm^{-1}].

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.40 (d, 3H + 3H, J = 7.5 Hz, CH_3-CH-); 3.74 (s, 3H, CH_3O-); 4.20 (t, 1H, J = 6.5 Hz, -$CHCH_2O$); 4.20-4.30 (m, 1H, CH_3CH); 4.40 (d, 2H, J = 6.5 Hz, -$CHCH_2O$); 4.58 (q, 1H, J = 7.5 Hz, CH_3-CH); 5.45 (broad d, 1H, J = 7 Hz, NHCOO); 6.54 (broad d, 1H, NH); 7.31 (t, 2H, J = 7 Hz, arom.); 7.43 (t, 2H, J = 7 Hz, arom.); 7.60 (d, 2H, J = 7 Hz, arom.); 7.76 (d, 2H, J = 7 Hz, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 17.1, 17.5, 47.1, 47.8, 50.5, 52.2, 66.9, 119.9, 125.1, 127.1, 128.6, 142.2, 155.9, 172.3, 172.9 [ppm].

LC/MS: 397.5 ([M+H]$^+$, $C_{22}H_{24}N_2O_5^+$; calc. 396.4).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 5.66 (L-Ala), L/D = 100/0.

Synthesis of Fmoc-Ala-Phe-OMe (**12m**)

Starting materials: Fmoc-Ala-OH (0.329 g, 1 mmol); DMT/NMM/TsO$^-$ (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Phe-OMe*HCl (0.216 g, 1 mmol). Product: Fmoc-Ala-Phe-OMe (0.416 g, 88%), mp = 159-160°C, lit. [49] mp = 160°C.

Anal. RP-HPLC (50–100%B in 15 min): Rt = 10.95 min, purity 98%.

IR (film/NaCl): v = 3678, 3616, 3430, 3012, 2407, 1742, 1719, 1680, 1603, 1502, 1448, 1363 [cm^{-1}].

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.35 (d, 3H, J = 6.5 Hz, CH_3-CH-); 3.08, 3.15 (d AB system, 2H, J_1 = 14 Hz, J_2 = 6 Hz, -CH_2-C_6H_5); 3.71 (s, 3H, CH_3O-); 4.20 (t, 1H, J = 7.5 Hz, -$CHCH_2O$-); 4.15-4.40 (m, 1H, CH); 4.42 (d, 2H, J = 7.5 Hz, -$CHCH_2O$); 4.85 (q, 1H, J = 6 Hz, -CH_2CH-); 5.30 (broad d, 1H, J = 7 Hz, -NHCOO); 6.42 (broad d, 1H, J = 6.5 Hz, -NHCOO); 7.08-7.72 (m, 13H, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 17.5, 37.6, 47.1, 50.5, 52.3, 53.2, 66.9, 119.9, 125.1, 127.1, 128.4, 128.7, 128.9, 129.1, 142.2, 155.9, 171.3, 172.2[ppm].

LC/MS: 473.6 ($[M+H]^+$, $C_{28}H_{28}N_2O_5^+$; calc. 472.5).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 5.28 (L-Ala), L/D = 100/0; Rt = 22.16 (L-Phe), L/D = 100/0.

Synthesis of Fmoc-Pro-Ala-OMe (**12n**)

Starting materials: Fmoc-Pro-OH (0.337 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Ala-OMe*HCl (0.139 g, 1 mmol). Product: Fmoc-Pro-Ala-OMe (0.414 g, 98%), mp = 90-92°C, lit. [50] mp = 92-94°C. Anal. RP-HPLC (50–100%B in 10 min): Rt = 8.90 min, purity 99%.

IR (film/NaCl): ν = 3350, 3170, 3100, 1740, 1670, 1530, 1430, 1360, 1340, 1270, 1210 [cm^{-1}].

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.37 (d, 3H, J = 6 Hz, CH_3-CH-); 1.60-2.50 (m, 4H, -CH_2-CH_2-); 3.40-3.80 (m, 2H, N-CH_2-); 3.72 (s, 3H, CH_3-O-); 4.15-4.45 (m, 4H, -O-CH_2-CH- + -O-CH_2-CH- + N-CH-); 4.53 (qu, 1H, J = 6 Hz, CH_3CH); 7.08 (broad s, 1H, NH); 7.31 (t, 2H, J = 7 Hz, arom.); 7.40 (t, 2H, J = 7 Hz, arom.); 7.57 (broad d, 2H, J = 7 Hz, arom.); 7.76 (d, 2H, J = 7 Hz, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 17.7, 23.0, 28.6, 46.2, 47.1, 47.8, 52.2, 58.8, 67.5, 119.9, 125.1, 127.1, 128.6, 142.2, 154.5, 172.0, 172.9 [ppm].

LC/MS: 423.6 ($[M+H]^+$, $C_{24}H_{26}N_2O_5^+$; calc. 422.5).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 4.91 (L-Ala), L/D = 100/0; Rt = 11.67 (L-Pro), L/D = 100/0.

Synthesis of Fmoc-Asp(OtBu)-Ala-OMe (**12o**)

Starting materials: Fmoc-Asp(tBu)-OH (0.412 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Ala-OMe*HCl (0.139 g, 1 mmol). Product: Fmoc-Asp(tBu)-Ala-OMe (0.382 g, 77%), oil. Anal. RP-HPLC (50–100%B in 15 min): Rt = 11.26 min, purity 98%.

IR (film/NaCl): ν = 3410, 3090, 2990, 1750, 1740, 1710, 1675, 1540, 1450, 1375 [cm^{-1}].

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.40 (d, 3H, J = 7 Hz, CH_3-CH-); 1.46 (s, 9H, -$OC(CH_3)_3$); 2.57 (dd, 1H, J_1 = 17 Hz, J_2 = 7 Hz, -OCO-CH_2-CH-); 2.92 (dd, 1H, J_1 = 17 Hz, J_2 = 4 Hz, -OCO-CH_2-CH-); 3.73 (s, 3H, CH_3O-); 4.26 (t, 1H, J = 7 Hz, -CH-CH_2O-); 4.42 (d, 2H, J = 7 Hz, -CH-CH_2O-); 4.48-4.60 (m, 2H, CH_3CH- + OCO-CH_2-CH-); 5.97 (d, 1H, J = 7 Hz, NH); 7.07 (d, 1H, J = 5 Hz, NH); 7.31 (t, 2H, J = 7 Hz, arom.); 7.41 (t, 2H, J = 7 Hz, arom.); 7.58 (d, 2H, J = 7 Hz, arom.); 7.77 (d, 2H, J = 7 Hz, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 17.7, 28.1, 37.9, 47.1, 47.8, 52.4, 53.6, 66.9, 81.4, 119.9, 125.1, 127.1, 128.6, 142.2, 155.5, 172.3, 172.5, 172.9 [ppm].

LC/MS: 497.7 ($[M+H]^+$, $C_{27}H_{32}N_2O_7^+$; calc. 496.6).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 5.13 (L-Ala), L/D = 100/0; Rt = 14.13 (L-Asp), L/D = 100/0.

Synthesis of Fmoc-Ser(tBu)-Ala-OMe (**12p**)

Starting materials: Fmoc-Ser(tBu)-OH (0.383 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Ala-OMe*HCl (0.139 g, 1 mmol). Product: Fmoc-Ser(tBu)-Ala-OMe (0.412 g, 88%), mp = 83-84°C, lit. [50] mp = 84-86°C. Anal. RP-HPLC (50–100%B in 15 min): Rt = 11.38 min, purity 96%.

IR (film/NaCl): v = 3410, 3320, 2990, 1740, 1720, 1670, 1480, 1440, 1375, 1210 [cm^{-1}].

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.24 (s, 9H, $-OC(CH_3)_3$); 1.45 (d, 3H, J = 7 Hz, CH_3-CH-); 3.39 (dd, 1H, J_1 = 9 Hz, J_2 = 6 Hz, -CH-CH_2-O-); 3.75 (s, 3H, CH_3O-); 3.80 (dd, 1H, J_1 = 9 Hz, J_2 = 6 Hz, -CH-CH_2-O-); 4.20-4.25 (m, 2H, -$CHCH_2$O- +-NH-CH-CH_2O); 4.39 (d, 2H, J = 7 Hz, -$CHCH_2$O); 4.58 (qu, 1H, J = 7 Hz, CH_3CH-); 5.79 (broad d, 1H, J = 4 Hz, NH); 7.30 (t, 2H, J = 7 Hz, arom.); 7.39 (t, 2H, J = 7 Hz, arom.); 7.45 (broad m, 1H, NH); 7.60 (d, 2H, J = 7 Hz, arom.); 7.75 (d, 2H, J = 7 Hz, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 17.7, 27.6, 38.3, 47.1, 47.8, 52.3, 66.9, 69.3, 73.5, 119.9, 125.1, 127.1, 128.6, 142.2, 155.5, 171.3, 172.9 [ppm].

LC/MS: 469.6 ([M+H]$^+$, $C_{26}H_{32}N_2O_6^+$; calc. 468.6).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 4.69 (D-Ala), Rt = 5.16 (L-Ala), L/D = 98.8/1.2; Rt = 10.32 (L-Ser), L/D = 100/0.

Synthesis of Fmoc-Thr(tBu)-Ala-OMe (**12q**)

Starting materials: Fmoc-Thr(tBu)-OH (0.396 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Ala-OMe*HCl (0.139 g, 1 mmol). Product: Fmoc-Thr(tBu)-Ala-OMe (0.362 g, 75%), mp = 148-150°C, lit. [50] mp = 149-151°C. Anal. RP-HPLC (50–100%B in 15 min): Rt = 13.03 min, purity 95%.

IR (film/NaCl): v = 3380, 3290, 1755, 1720, 1675, 1535, 1480, 1280, 1220 [cm^{-1}].

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.10 (d, 3H, J = 6 Hz, (CH_3-CH-O-); 1.31 (s, 9H, $-OC(CH_3)_3$); 1.44 (d, 3H, J = 7 Hz, CH_3-CH-); 3.76 (s, 3H, CH_3O-); 4.10-4.25 (m, 3H, -$CHCH_2$O- + CH-O-CH-CH-NH); 4.38 (d, 2H, J = 7 Hz, -$CHCH_2$O); 4.52 (qu, 1H, J = 7 Hz, CH_3CH-); 6.00 (d, 1H, J = 4 Hz, NH); 7.24 (m, 1H, NH); 7.30 (t, 2H, J = 7 Hz, arom.); 7.39 (t, 2H, J = 7 Hz, arom.); 7.60 (d, 2H, J = 7 Hz, arom.); 7.75 (d, 2H, J = 7 Hz, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 17.2, 17.7, 28.3, 47.1, 47.8, 52.3, 66.9, 72.8, 73.7, 119.9, 125.1, 127.1, 128.6, 142.2, 155.5, 170.6, 172.9 [ppm].

LC/MS: 483.6 ([M+H]$^+$, $C_{27}H_{34}N_2O_6^+$; calc. 482.6).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 4.67 (D-Ala), Rt = 5.11 (L-Ala), L/D = 98.8/1.2; Rt = 7.34 (L-Thr), L/D = 100/0.

Synthesis of Boc-Aib-Ala-OMe (**12r**)

Starting materials: Boc-Aib-OH (0.203 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Ala-OMe*HCl (0.139 g, 1 mmol). Product: Boc-Aib-Ala-OMe (0.213 g, 74%), mp = 194-96°C, lit. [51] mp = 95-95.5°C. Anal. RP-HPLC (50–100%B in 15 min): Rt = 10.22 min, purity 99%.

IR (film/NaCl): v = 3320, 1756, 1688, 1668, 1656, 1516, 1368, 1280, 1252, 1168, 1088, 772 [cm^{-1}].

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.44 (s, 9H, $(CH_3)_3$-C-O-); 1.48 (s, 3H, CH_3-CH-); 1.51 (s, 6H, CH_3C-CH_3); 3.72 (s, 3H, -COO-CH_3); 4.55-4.64 (m, 1H, -CH-$COOCH_3$) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 17.7, 25.1, 28.2, 48.1, 52.1, 79.6, 58.1, 156.8, 172.9, 175.6 [ppm].

LC/MS: 289.96 ([M+H]$^+$, $C_{13}H_{25}N_2O_5^+$; calc. 288.35).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 6.49 (Aib); Rt = 5.11 (L-Ala), L/D = 100/0.

Synthesis of Boc-L-Trp-Ala-OMe (**12s**)

Starting materials: Boc-L-Trp-OH (0.304 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Ala-OMe*HCl (0.139 g, 1 mmol). Product: Boc-L-Trp-Ala-OMe (0.276 g, 71%), mp = 110-112°C, lit. [52] mp = 112-113°C. Anal. RP-HPLC (50–100%B in 15 min): R t = 12.81 min, purity 85%.

IR (film/NaCl): v = 3344,1668, 1504, 1468, 1456, 1368, 1216, 1192, 1164, 1056, 792, 664 [cm^{-1}].

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.26 (d, 3H, J = 7 Hz, CH_3-CH-); 1.43 (s, 9H, $(CH_3)_3$-C-O-); 3.12-3.38 (m, 2H, CH_2-); 3.66 (s, 3H, -COO-CH_3); 4.40-4.51 (m, 1H, -NHCH-CH_3); 5.04-5.21 (m, 1H, CH-); 7.09-7.37 + 7.64-7.67 (m, 5H, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 17.7, 27.7, 28.2, 47.8, 52.0, 53.6, 80.0, 109.8, 111.6, 118.7, 120.2, 122.2, 124.4, 127.6, 136.1, 155.3, 172.5, 172.9, [ppm].

LC/MS: 390.96 ([M+H]$^+$, $C_{20}H_{28}N_3O_5^+$; calc. 389.46).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 5.11 (L-Ala), L/D = 100/0.

Synthesis of Boc-L-Ala-L-Phe-OMe (**12t**)

Starting materials: Boc-L-Ala-OH (0.189 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Phe-OMe*HCl (0.238 g, 1 mmol). Product: Boc-L-Ala-L-Phe-OMe (0.238 g, 68%), mp = 79-83°C, lit. [53] mp = 80°C. Anal. RP-HPLC (50–100%B in 15 min): Rt = 10.97 min, purity 99%.

IR (film/NaCl): v = 3312, 2976, 1680, 1516, 1444, 1368, 1312, 1164, 1048, 756, 704, 664 [cm^{-1}].

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.29 (d, 3H, J = 7 Hz, CH_3-CH-); 1.43 (s, 9H, $(CH_3)_3$-C-O-); 3.03-3.23 (m, 2H, CH_2-C_6H_5); 3.68 (s, 3H, -COO-CH_3); 4.06-4.19 (m, 1H, -NH-CH-CH_3); 4.84 (q, 1H, J = 6 Hz, CH-CH_2-C_6H_5); 6.85 (broad d, 1H, -NH-); 7.09-7.27 (m, 5H, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 17.7, 28.1, 38.4, 47.8, 52.3, 55.6, 80.0, 128.7, 128.9, 129.1, 155.3, 171.2, 172.9 [ppm].

LC/MS: 351.94 ([M+H]$^+$, $C_{18}H_{27}N_2O_5^+$; calc. 350.42).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 5.11 (L-Ala), L/D = 100/0; Rt = 22.16 (L-Phe), Rt = 22.36 (D-Phe) L/D = 99/1.

Synthesis of Boc-L-Orn(Z)-L-Leu-OMe (**12u**)

Starting materials: Boc-L-Orn(Z)-OH (0.366 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Leu-OMe*HCl (0.182 g, 1 mmol). Product: Boc-L-Orn(Z)-L-Leu-OMe (0.439 g, 89%), mp = 84-86°C, lit. [54] mp = 85-88°C. Anal. RP-HPLC (50–100%B in 15 min): Rt = 11.05 min, purity 100%.

IR (film/NaCl): v = 3583, 2620, 3447, 3019, 2976, 2400, 1707, 1517, 1424 [cm^{-1}].

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.86 (d, 6H, J = 8.5 Hz, $(CH_3)_2$-CH-); 1.30-2.00 (m, 7H, -CH_2CH- + -$CH_2CH_2CH_2$CH-); 1.43 (s, 9H, $(CH_3)_3$C-); 3.15 (q, 2H, J = 4,5 Hz, -NH-$CH_2CH_2CH_2$CH-); 3.58 (m, 1H, -CH_2-CH-CONH-); 3.69 (s, 3H, -COO-CH_3); 4.55 (q, 1H, J = 4.0 Hz, -CONH-CH-CH_2-); 4.95 (broad s, 1H, NH); 5.07 (AB, 2H, J = 8.5 Hz, -CH_2O-); 5.21 (m, 1H, NH); 6.95 (broad s 1H, NH); 7.35 (s, 5H, arom.) [ppm].

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 22.6, 24.8, 25.7, 28.2, 28.7, 40.0, 40.4, 52.1, 53.5, 53.8, 66.5, 80.0, 127.9, 128.5, 128.9, 155.3, 156.3, 172.5, 172.8 [ppm].

LC/MS: 494.92 ([M+H]$^+$, $C_{25}H_{40}N_3O_7^+$; calc. 493.61).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 11.03 (L-Orn) L/D = 100/0; Rt = 10.88 (L-Leu), L/D = 100/0.

Synthesis of Boc-Ala-Gly-Phe-OMe (**13a**)

Starting materials: Boc-Ala-Gly-OH (0.246 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Phe-OMe*HCl (0.238 g, 1 mmol). Product: Boc-Ala-Gly-Phe-OMe (0.318 g, 78%), oil, $[\alpha]_D^{20}$ = -25 (c = 1.0, $CHCl_3$). Anal. RP-HPLC (50–100%B in 15 min): Rt = 8.82 min, purity 90%.

IR (film/NaCl): v = 3136, 3064, 3048, 2976, 1680, 1632, 1360, 1160, 1048, 856, 760, 704, 648 [cm^{-1}].

^{1}H-NMR ($CDCl_3$): δ = 1.28 (d, 3H, J = 8 Hz, CH_3 Ala); 1.43 (s, 9H, $(CH_3)_3$C Boc); 3.19 (t, 2H, J = 6 Hz, -CH_2-CH- Phe); 3.90 (s, 3H, -COO-CH_3); 3.93-3.97 (m, 2H, -CH_2- Gly); 4.36 (q, 1H, J = 5 Hz, -CH- Ala); 4.82 (q, 1H, J = 6 Hz, -CH- Phe), 5.13 (broad d, 1H, -NH-); 6.97 (broad d, 1H, -NH-); 7.08-7.31 (m, 5H, C_6H_5- Phe) [ppm].

LC/MS: 408.97 ([M+H]$^+$, $C_{20}H_{30}N_3O_6^+$; calc. 407.47).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 4.55 (L-Ala), L/D = 100/0; Rt = 6.78 (Gly); Rt = 20.11 (D-Phe), Rt = 20.38 (L-Phe), L/D = 98/2.

Synthesis of Boc-Ala-Gly-Ala-OMe (**13b**)

Starting materials: Boc-Ala-Gly-OH (0.246 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Ala-OMe*HCl (0.139 g, 1 mmol). Product: Boc-Ala-Gly-Ala-OMe (0.268 g, 81%), oil, $[\alpha]_D^{20}$ = -15 (c = 1.0, MeOH), lit. [55] $\alpha]_D^{20}$ = -7 (c = 1.0, CH_2Cl_2). Anal. RP-HPLC (50–100%B in 15 min): Rt = 9.48 min, purity 91%.

IR (NaCl/film): v = 3352, 3128, 2984, 1748, 1632, 1512, 1360, 1164, 1028, 856, 736, 648 [cm^{-1}].

^{1}H-NMR ($CDCl_3$): δ = 1.27 (d, 3H, J = 8 Hz, CH_3 Ala); 1.36 (d, 3H, J = 8 Hz, CH_3 Ala); 1.41 (s, 9H, $(CH_3)_3$C- Boc);3.71-3.89 (m, 2H, -CH_2- Gly); 3.94 (s, 3H, -COO-CH_3);4.38-4.41 (m, 1H, -CH- Ala); 4.59-4.85 m, 1H, -CH- Ala); 6.01 (broad d, 1H, -NH-) [ppm].

LC/MS: 332.89 ([M+H]$^+$, $C_{14}H_{26}N_3O_6^+$; calc. 331.37).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 4.66 (L-Ala), L/D = 100/0; Rt = 6.72 (Gly).

Synthesis of Boc-Ala-Trp-Ala-OMe (**13c**)

Starting materials: Boc-Ala-Trp-OH (0.375 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Ala-OMe*HCl (0.139 g, 1 mmol). Product: Boc-Ala-Trp-Ala-

OMe (0.387 g, 84%), oil, $[\alpha]_D^{20}$ =-16,45 (c = 1.0, EtOH). Anal. RP-HPLC (50–100%B in 15 min): Rt = 8.40 min, purity 92%.

IR (NaCl/film): v = 3344, 3128, 2928, 1632, 1604, 1532, 1456, 1368, 1216, 1164, 792, 664 [cm^{-1}].

^{1}H-NMR ($CDCl_3$): δ = 1.24 (d, 3H, J = 8 Hz, CH_3 Ala); 1.33 (d, 3H, J = 8 Hz, CH_3 Ala); 1.41 (s, 9H, $(CH_3)_3$C- Boc); 3.15 (dd, 1H, J_1 = 5 Hz, J_2 = 10 Hz, -CH_2CH- Trp); 3.40 (dd, 1H, J_1 = 3 Hz, J_2 = 7 Hz, -CH_2CH- Trp); 3.67 (s, 3H, -COO-CH_3); 4.07-4.12 (m, 1H, -CH-): 4.39-4.45 (m, 1H, -CH-); 4.67-4.74 (m, 1H, -CH-), 4.76 (broad d, 1H, -NH-); 6.45 (broad d, 1H, -NH-); 6.75 (broad d, 1H, -NH-); 7.13-7.71 (m, 5H, arom. Trp); 8.14 (s, 1H, NH Trp) [ppm].

LC/MS: 461.94 ([M+H]$^+$, $C_{23}H_{33}N_4O_6^+$; calc. 460.53).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 4.77 (L-Ala) L/D = 100/0.

Synthesis of Boc-Ala-Aib-Leu-OMe (**13d**)

Starting materials: Boc-Ala-Aib-OH (0.274 g, 1 mmol); DMT/NMM/TsO$^-$ (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Leu-OMe*HCl (0.182 g, 1 mmol). Product: Boc-Ala-Aib-Leu-OMe (0.361 g, 90%), oil, $[\alpha]_D^{20}$ = -18 (c = 1.0, $CHCl_3$). Anal. RP-HPLC (50–100%B in 15 min): Rt = 7.18 min, purity 88%.

IR (NaCl/film): v = 3320, 3128, 2936, 1756, 1648, 1612, 1516, 1448, 1368, 1252, 1088, 772 [cm^{-1}].

^{1}H-NMR ($CDCl_3$): δ = 0.93 (d, 6H, J = 8 Hz, $(CH_3)_2$CH- Leu); 1.26 (d, 3H, J = 7 Hz, CH_3 Ala); 1.54 (s, 9H, $(CH_3)_3$C- Boc); 1.56 (s, 6H, $(CH_3)_2$C- Aib); 1.57-1.69 (m, 3H. –$CHCH_2$- Leu); 3.72 (s, 3H, -COO-CH_3), 4.04 (t, 1H, J = 5 Hz, -CH- Leu); 4.56 (qu, 1H, J = 6 Hz, -CH- Ala); 4.61 (broad d, 1H, -NH-); 6.60 (broad d, 1H, -NH-); 6.99 (broad d, 1H, -NH-) [ppm].

LC/MS: 403.11 ([M+H]$^+$, $C_{19}H_{36}N_3O_6^+$; calc. 401.51).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 4.57 (L-Ala), L/D = 100/0; Rt = 6.54 (Aib); Rt = 10.66 (L-Leu), L/D = 100/0.

Synthesis of Z-Phe-Phe-Ala-Aib-Leu-OMe (**14a**)

Starting materials: Z-Phe-Phe-OH (0.446 g, 1 mmol); DMT/NMM/TsO$^-$ (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Ala-Aib-Leu-OMe*HCl (0.338 g, 1 mmol). Product: Z-Phe-Phe-Ala-Aib-Leu-OMe (0.547 g, 75%), mp = 70-71°C, $[\alpha]_D^{20}$ = -7,79 (c = 1, MeOH). Anal. RP-HPLC (50–100%B in 15 min): Rt = 5.38 min, purity 99%.

LC/MS: 730.96 ([M+H]$^+$, $C_{40}H_{52}N_5O_8^+$; calc. 729.88).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 4.46 (D-Ala), Rt = 4.58 (L-Ala), L/D = 99/1; Rt = 6.54 (Aib); Rt = 10.66 (L-Leu), L/D = 100/0; R_t = 20.11 (D-Phe), Rt = 20.38 (L-Phe), L/D = 99/1.

Synthesis of Z-Tyr(Z)-Tyr-Ala-Ala-Phe-OMe (**14b**)

Starting materials: Z-Tyr(Z)-Tyr-OH (0.613 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Ala-Ala-Phe-OMe*HCl (0.358 g, 1 mmol). Product: Z-Tyr(Z)-Tyr-Ala-Ala-Phe-OMe (0.651 g, 71%), mp = 72-72°C, $[\alpha]_D^{20}$ = 3,79 (c = 1, MeOH). Anal. RP-HPLC (50–100%B in 15 min): Rt = 6.81 min., purity 95%.

LC/MS: 917.52 ($[M+H]^+$, $C_{50}H_{54}N_5O_{12}^+$; calc. 916.01).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 4.55 (L-Ala), L/D = 100/0; Rt = 20.21 (D-Phe), Rt = 20.55 (L-Phe), L/D = 99/1; Rt = 24.98 (L-Tyr), Rt = 25.08 (D-Tyr), L/D = 99/1.

Synthesis of Z-Ala-Phe-Ala-Trp-Ala-OMe (**14c**)

Starting materials: Z-Ala-Phe-OH (0.371 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Ala-Trp-Ala-OMe*HCl (0.397 g, 1 mmol). Product: Z-Ala-Phe-Ala-Trp-Ala-OMe (0.542 g, 76%), mp = 85-87ºC, $[\alpha]_D^{20}$ = -29.34 (c = 1, MeOH). Anal. RP-HPLC (50–100%B in 15 min): Rt = 9.18 min, purity 89%.

LC/MS: 714.31 ($[M+H]^+$, $C_{38}H_{45}N_6O_8^+$; calc. 712.81).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; Rt = 4.44 (D-Ala), Rt = 4.58 (L-Ala), L/D = 98/2; Rt = 20.25 (D-Phe), Rt = 20.75 (L-Phe), L/D = 97/3.

Synthesis of Z-Tyr(Z)-Ala-Ala-Gly-Phe-OMe (**14d**)

Starting materials: Z-Tyr(Z)-Ala-OH (0.521 g, 1 mmol); DMT/NMM/TsO^- (0.413 g, 1 mmol); DIPEA (0.264 mL, 1.5 mmol) and H-Ala-Gly-Phe-OMe*HCl (0.344 g, 1 mmol). Product: Z-Tyr(Z)-Ala-Ala-Gly-Phe-OMe (0.570 g, 70%), mp = = 92,94ºC, $[\alpha]_D^{20}$ = 10.99 (c=1, MeOH). Anal. RP-HPLC (50-100%B in 15 min): Rt = 12.64 min, purity 98%.

LC/MS: 811.38 ($[M+H]^+$, $C_{43}H_{48}N_5O_{11}^+$; calc. 809.88).

GC: the hydrolysate was derivatized according to the standard procedure; chromatography conditions: temperature 60-150°C, 4°C/min, 150°C, 5 min, 150-180°C, 40°C/min; R_t = 4.38 (D-Ala), Rt

= 4.50 (L-Ala), L/D = 99/1; Rt = 6.75 (Gly); Rt = 20.22 (D-Phe), Rt = 20.85 (L-Phe), L/D = 98/2; Rt = 24.98 (L-Tyr), L/D = 100/0.

*Synthesis of Boceprevir (**21**)*

Coupling of (2R)-2-(3-tert-butyl-ureido)-3,3-dimethyl-butyric acid (**15**) with methyl (1R,2S,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate hydrochloride (**16**). Synthesis of dipeptide **17**

Methylene chloride (50 mL) was placed in a round-bottomed flask and cooled in a water-ice bath to 0°C. To the vigorously stirred solvent were added sequentially: DMT/NMM/TsO^- (**7**) (2.07 g, 5 mmol); (*2R*)-2-(3-tert-butyl-ureido)-3,3-dimethyl-butyric acid (**15**) (1.51 g, 5 mmol); methyl (*1R,2S,5S*)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate hydrochloride (**16**) (1.03 g, 5 mmol) and NMM (0.825 mL, 7.5 mmol). Mixing was continued for 12 h, allowing the temperature to rise slowly from 0°C to 20°C. The mixture was then diluted with methylene chloride (20 mL) and washed successively with water (30 mL), 1M $NaHSO_4$ (30 mL), water (30 mL), 1M $NaHCO_3$ (30 mL) and with water again (30 mL). The organic layer was dried over anhydrous $MgSO_4$. After evaporation of the solvent, the product was dried in a vacuum desiccator to a constant weight over P_2O_5. A final weight of 1.81 g was obtained, yielding 96% dipeptide **17**. Anal. RP-HPLC (3-97% B, in 55 min): Rt = 27.9 min, purity 99.2%.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.12 (s, 9H, -$(CH_3)_3$C-CH-); 1.38 (s, 3H, -$(CH_3)_2$C-); 1.39 (s, 3H, -$(CH_3)_2$C-); 1.40-1.43 (m, 1H, -CH-); 1.53-1.55 (m, 1H, -CH-); 1.69 (s, 9H, -$(CH_3)_3$C-NH-); 3.85 (s, 3H, CH_3O-); 4.17-4.23 (m, 1H, -CH_2-); 4.29-4.32 (m, 1H, -CH_2-); 4.45-4.50 (m, 1H, -CH-COO); 4.57, (s, 1H, -CH-) [ppm].

HR-MS: 382.2838 ($[M + H]^+$, $C_{20}H_{36}N_3O_4^+$; calculated 382.52).

Synthesis of dipeptide **17** by using TBTU as a coupling reagent

Starting materials: (2R)-2-(3-tert-butyl-ureido)-3,3-dimethyl-butyric acid (**15**) (0.604 g, 2 mmol); methyl (1R,2S,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate hydrochloride (**16**) (0.453 g, 2.2 mmol); TBTU (0.706 g, 2.2 mmol); DIPEA (792 µL, 4.4 mmol), methylene chloride (10 mL). The mixture was then diluted with methylene chloride (10 mL) and washed successively with water (20 mL), 1M $NaHSO_4$ (20 mL), water (20 mL), 1M $NaHCO_3$ (20 mL) and with water again (20 mL). The organic layer was dried over anhydrous $MgSO_4$. A final weight of 0.572 g was obtained, yielding 75% dipeptide **17**. Anal. RP-HPLC (50-90% B): Rt = 8.07 min, purity 66%. After preparative HPLC was obtained 0.481 g, yield = 63%. Anal. RP-HPLC (50-90% B): Rt = 7.97 min, purity 93.6%. NMR and MS identical to those described above.

Synthesis of dipeptide **17** by using EDC/HOBt as a coupling reagent

Starting materials: (2R)-2-(3-tert-butyl-ureido)-3,3-dimethyl-butyric acid (**15**) (0.604 g, 2 mmol); methyl (1R,2S,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate hydrochloride (**16**) (0.453 g, 2.2 mmol); HOBt (0.271 g, 2 mmol); EDC (0.383 g, 2 mmol); DIPEA (792 µL, 4.4 mmol), methylene chloride (10 mL). A final weight of 0.549 g was obtained, yielding 72% dipeptide **17**. Anal. RP-HPLC (50-90% B): Rt = 8.08 min, purity 80.5%. NMR and MS identical to those described above.

Synthesis of dipeptide **17** in the presence of isobutyl chloroformate

Starting materials: (2R)-2-(3-tert-butyl-ureido)-3,3-dimethyl-butyric acid (**15**) (0.604 g, 2 mmol); methyl (1R,2S,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate hydrochloride (**16**); isobutyl chloroformate (0.273 g, 2 mmol); NMM (440 µL, 4 mmol); methylene chloride (7 mL); DMF (3 mL). A final weight of 0.648 g was obtained, yielding 85% dipeptide **17**. Anal. RP-HPLC (50-90% B): Rt = 8.01 min, purity 85%. After preparative HPLC was obtained 0.603 g, yield = 79%. Anal. RP-HPLC (50-90% B): Rt = 8.02 min, purity 93.2%. NMR and MS identical to those described above.

Synthesis of dipeptide **17** in the presence of bis(trichloromethyl)carbonate

Starting materials: (2R)-2-(3-tert-butyl-ureido)-3,3-dimethyl-butyric acid (**15**) (0.604 g, 2 mmol); methyl (1R,2S,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate hydrochloride (**16**); bis(trichloromethyl)carbonate (0.199 g, 0.67 mmol);

2,4,6-trimethylpyridine (0.801 g, 6.6 mmol); THF (10 mL). A final weight of 0.626 g was obtained, yielding 82% dipeptide **17**. Anal. RP-HPLC (50-90% B): Rt = 8.05 min, purity 92%. NMR and MS identical to those described above.

Basic hydrolysis of the dipeptide **17**. Synthesis of dipeptide **18**

To dipeptide **17** (1.81 g, 4.8 mmol) in MeOH : THF (1:1) solution (30 mL) was added dropwise 1M LiOH (10 mL). Stirring was continued for 4 h (substrate disappearance based on TLC: DCM : MeOH 9 : 1). The organic solvents were evaporated on a vacuum evaporator and ethyl acetate (30 mL) was added to the residue. The solution was acidified with 1M aqueous HCl to pH 2 while stirring. The organic layer was dried over anhydrous $MgSO_4$. After evaporation of the solvent, the product was dried in a vacuum desiccator to a constant weight over P_2O_5. Dipeptide with a quantitative yield of 1.76 g was obtained. Anal. RP-HPLC (3–97%B, in 55 min): Rt = 21.3 min, purity 99.7%.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.11 (s, 9H, -$(CH_3)_3$C-CH-); 1.16 (s, 3H, -$(CH_3)_2$C-); 1.16 (s, 3H, -$(CH_3)_2$C-); 1.30-1.31 (m, 1H, -CH-); 1.37 (s, 9H, -$(CH_3)_3$C-NH-); 1.39-1.40 (m, 1H, -CH-); 4.20-4.25 (m, 1H, -CH_2-); 4.25-4.28 (m, 1H, -CH_2-); 4.47-4.53 (m, 1H, -CH-COO); 4.54-4.56 (m, 1H, -CH-) [ppm].

HR-MS: 368.2702 ([M + H]$^+$, $C_{19}H_{34}N_3O_4^+$; calculated 368.49).

Coupling of dipeptide **18** with hydrochloride (2R, 3S) 3-amino-4-cyclobutylo-2-hydroxybutyroamide hydrochloride (**19**). Synthesis of tripeptide **20**.

Methylene chloride (50 mL) was placed in a round-bottomed flask and cooled in a water-ice bath to 0^{o}C. To the vigorously stirred solvent were added DMT/NMM/TsO$^-$ (1.74 g, 4.2 mmol); dipeptide **18** (1.54 g, 4.2 mmola) and NMM (0.23 mL, 2.1 mmol). Stirring was continued until all DMT/NMM/TsO$^-$ had been consumed (TLC, DCM : MeOH 9 : 1; visualization by 0.5% solution of NBP in EtOH). After 25 min, to the solution were added hydrochloride 3-amino-4-cyclobutylo-2-hydroxybutyroamide hydrochloride (**19)** (0.88 g, 4.2 mmol) and NMM (0.46 mL, 4.2 mmol) in DMF (10 mL). Mixing was continued for 12 h, allowing the temperature to slowly rise from 0^{o}C to 20^{o}C. In the next step, water (30 mL) was added and the solution was extracted by DCM (4 x 15 ml). The combined organic layers were washed with water (30 mL), 1M $NaHSO_4$ (30 mL), water (30 mL), 1M $NaHCO_3$ (30 mL) and with water (30 mL) again. The organic layer was dried over anhydrous $MgSO_4$. After evaporation of the solvent, the product was dried in a vacuum desiccator to a constant weight over P_2O_5. Finally, 2.06 g, yielding 94% of tripeptide **20** was obtained. Anal. RP-HPLC (3–97%B, in 55 min): Rt = 29.1 min, purity 93.9%.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.00 (s, 3H, -$(CH_3)_2$C-); 1.09 (s, 9H, -$(CH_3)_3$C-CH-); 1.14 (s, 3H, -$(CH_3)_2$C-); 1.30-1.34 (m, 1H, -CH-); 1.38 (s, 9H, -$(CH_3)_3$C-NH-); 1.41-1.45 (m, 1H, -CH-); 1.82-1.95 (m, 1H, -CH- + m, 2H, -CH_2- + m, 6H, -$(CH_2)_3$-); 3.98 (qu, 1H,-CH-); 4.13-4.27 (m, 1H, -CH_2-); 4.23-4.25 (m, 1H, -CH_2-); 4.47-4.54 (m, 1H, -CH-); 5.35 (d, 1H, -CH-); 5.41 (t, 1H, -CHOH) [ppm].

HR-MS: 522,3967 ([M + H]$^+$, $C_{27}H_{48}N_5O_5^+$; calculated 522,71).

Synthesis of tripeptide **20** by using TBTU as a coupling reagent

Starting materials: dipeptide **18** (0.367 g, 1 mmol), hydrochloride 3-amino-4-cyclobutylo-2-hydroxybutyroamide hydrochloride (**19**) (0.209 g, 1 mmol), TBTU (0.321 g, 1 mmol); DIPEA (360 µL, 2 mmol); methylene chloride (6 mL). Finally it was obtained 0.531 g of product. Anal. RP-HPLC (50-90% B): Rt = 4.11 min, content = 38% (tripeptide 20); Rt = 4.35 min, content = 22% (depsipeptide); Rt = 4.81 min, content = 15% (dipeptide 17, starting material). After preparative HPLC were obtained: Fr I (tripeptide 20): Rt = 4.05 min, purity = 99.3%, yield = 32% (0.170 g); Fr II (depsipeptide): Rt = 4.29 min, purity = 99.8%, yield = 22% (0.115 g); Fr III (dipeptide 17): Rt = 4.81 min, purity = 99.9%, yield = 15%.

Synthesis of tripeptide **20** in the presence EDC and HOBt

Starting materials: dipeptide **18** (0.367 g, 1 mmol), hydrochloride 3-amino-4-cyclobutylo-2-hydroxybutyroamide hydrochloride (**19**) (0.209 g, 1 mmol), EDC (0.155 g, 1 mmol); HOBt (0.153 g, 1

mmol); DIPEA (360 µL, 2 mmol); methylene chloride (6 mL). Finally it was obtained 0.451 g of product. Anal. RP-HPLC (50-90% B): Rt = 3.09 min, content = 43% (tripeptide 20); Rt = 3.24 min, content = 18% (depsipeptide); Rt = 3.87 min, content = 17% (dipeptide 17, starting material). After preparative HPLC were obtained: Fr I (tripeptide 20): Rt = 4.05 min, purity = 99.9%, yield = 40% (0.209 g); Fr II (depsipeptide): Rt = 4.28 min, purity = 98.9%, yield = 18% (0.009 g); Fr III (dipeptide 17): Rt = 4.80 min, purity = 99.6%, yield = 17%.

Oxidation of tripeptide **20** to Boceprevir **21**

To a round-bottomed flask equipped with a magnetic stirrer and a dropping funnel containing tripeptide 20 (0.64 g, 1.2 mmol) were added: TEMPO (0.095 g, 0.06 mmol), NaBr (0.17 g, 1.2 mmol) and a mixture of toluene (10 mL), ethyl acetate (4 mL) and water (1 mL). With intense stirring the solution was cooled to 0^{o}C, and a water solution of NaClO (2 mL, 3.3 mmol) with 8.8 mL of 1M $NaHCO_3$ was added dropwise. On detecting the disappearance of the tripeptide **20** (TLC: AcOEt : hexane : AcOH 9 : 1 : 0,1) the phases were separated. The aqueous layer was extracted three times with diethyl ether (10 mL). The combined organic layers were washed with a solution of 0.08 mg KJ in 20 mL of 10% $NaHSO_4$, 10% $Na_2S_2O_3$ (20 mL) and brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$. After evaporation of the solvent, the product was dried in a vacuum desiccator to a constant weight over P_2O_5. Finally, 0.62 g yielding 98% of tripeptide **21** was obtained. Anal. RP-HPLC (3–97%B, in 55 min): Rt = 29.41 min, purity 99.3%.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.90 (s, 3H, -$(CH_3)_2$C-); 1.04 (s, 9H, -$(CH_3)_3$C-CH-); 1.06 (s, 3H, -$(CH_3)_2$C-); 1.29-1.30 (m, 1H, -CH-); 1.32 (s, 9H, -$(CH_3)_3$C-NH-); 1.38-1.40 (m, 1H, -CH-); 1.60-1.66 (m, 1H, -CH- + m, 2H, -CH_2- + m, 6H, -$(CH_2)_3$-); 3.73-3.84 (m, 1H, -CH_2-); 4.14-4.20 (m, 1H, -CH_2-); 4.45-4.50 (m, 1H, -CH-); 5.35 (d, 1H, -CH-); 6,51 (t, 1H, -CHCO-) [ppm].

^{13}C NMR (210 MHz, $CDCl_3$): δ = 12.28 (-CH_2-CH_2-CH_2-); 17.90 (-$(CH)_2$C-$(CH_3)_2$-); 18.57 (-$(CH_3)_2$C-$(CH)_2$-); 20.73 (-$(CH)_2$C-$(CH_3)_2$-); 26.11 (-$(CH_3)_3$C-CH-); 27.19 (-CH_2-CH_2-CH_2-); 29.01 (-$(CH_3)_3$C-NH-); 32.02 (-CH_2-CH-CH_2-); 34.41 (-CH_2-cbut); 38.34 (-$(CH_3)_3$C-CH-); 48.23 (-N-CH_2-CH-); 49.77 (-$(CH_3)_3$C-NH-); 52.78 (-NH-CH-C(O)-C(O)-); 57.72 (-N-CH-C(O)-NH-); 59.87 (-$(CH_3)_3$C-CH-); 157.06 (-NH-C(O)-NH-); 161.31 (-C(O)-NH_2); 170.14 ($(CH_3)_3$-C-C(O)-); 173.38 (-C(O)-NH-CH-C(O)-); 195.87 (-C(O)-C(O)-NH_2) [ppm].

IR (film): υ = 3324 (N-H), 2959 (C-H), 1622-1261 (C=O), 1540 (N-H), 1434-1364 (C-H), 1313-1043 (C-N), 752-589 (C-H) [cm^{-1}].

HR-MS: 520,3798 ($[M + H]^+$, $C_{27}H_{46}N_5O_5^+$; calculated 520,69).

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Author Contribution Statement

Justyna Fraczyk – synthesis of amides and peptides; Zbigniew J. Kaminski – Boceprevir synthesis and discussion of results; Joanna Katarzynska – Boceprevir synthesis using TBTU and EDC/ HOBt as coupling reagents; Beata Kolesinska – synthesis of esters, peptides and Boceprevir, preparation of manuscript.

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