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4-(4,6-Di[2,2,2-trifluoroethoxy]-1,3,5-triazin-2-yl)-4-methylomorpholinium Tetrafluoroborate. Triazine-Based Coupling Reagents Designed for Coupling Sterically Hindered Substrates

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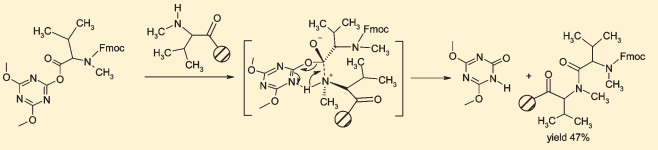
Supporting Information

ABSTRACT: 4-(4,6-Di[2,2,2-trifluoroethoxy]-1,3,5-triazin-2-yl)-4-methylomorpholinium tetrafluoroborate (DFET/NMM/BF_4) was prepared and used as a reagent for coupling sterically hindered substrates. The formation of the appropriate triazine "superactive" ester in a reaction of DFET/NMM/BF_4 with carboxylic acids was confirmed. The efficiency of the reagent has been studied in the synthesis of Leu-enkephaline pentapeptide carried out on a Fmoc-RinkAmide-AM-PS resin, by systematically modifying the -Gly-Gly- fragment for *N*-methyl or α,α-disubstituted residues and compared with the efficiency of classic aminium salt 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) under a variety of reaction conditions. In syntheses of Aib−Aib (Aib: α-aminoisobutyric acid), MeVal-MeVal, and MeLeu-MeLeu, the considerably superior performance of enkephaline analogues was obtained for DFET/NMM/BF_4 relative to TBTU, regardless of reaction conditions. Analysis of the couplings involving triazine reagent suggests that factors controlling efficiency of coupling sterically hindered substrates are the structure of the leaving group permitting formation of the cyclic intermediate or cyclic transition state and the absence of strongly solvating solvents. It has to be considered as highly probable that the absence of strongly solvating milieu favors cyclic intermediates or the cyclic transition state. Arrangement of both components into the cyclic intermediate or cyclic transition state by accumulation of the geminal (vicinal) substituents effect (known as the Thorpe−Ingold effect) would compensate retardation of the coupling process caused by steric hindrance.



INTRODUCTION

In recent years, most of the peptides used in combating various diseases as well as peptides showing activity as insecticides, contraceptives, growth promoters, metabolism regulators, and many other uses have been prepared using unnatural building blocks such as noncoded amino acids. The main reason for practicing this approach is the expected increase of the resistance of unnatural structures toward metabolic degradation, prolonged activity, reduced dosage, and more convenient application. In most cases, these advantageous effects of incorporation of an unnatural moiety into the peptide chain exclude application of biological approaches for their preparation, and therefore that depends only on a successful chemical synthetic strategy.

Currently, the arsenals of available reagents and strategies for the coupling are adequate for successful assembly of peptides from the 20 coded amino acids in solution and on a solid support, but often they are found insufficient or even fail in the case of their unnatural analogues or the so-called difficult sequences.[1−10] The most frustrating syntheses involve the concourse of poor reactive and sterically hindered building blocks because stronger activation and prolonged coupling time may severely deteriorate the yield and purity of the required peptide.

The acidity of the additive, either used in combination with carbodiimide or contained into a stand-alone coupling reagent, is a critical factor in the efficiency of peptide bond formation. However, sterical effects are also involved in this process, which become more influential as the size of the peptide fragment increases. In most of the cases, an approach to improve the efficiency of the coupling reagent by expansion of its structure remains not fruitful because introduction of any additional structural fragments enlarges the size of the reagent, spoiling the effect of increased reactivity. Therefore, most of the attempts were made to shrink the reagent fragment participating at the stage most sensitive to the steric effects, which for the classic mechanism of peptide bond synthesis is the formation of the tetrahedral intermediate during the aminolysis step. Nowadays, only few reagents were designed in accord with this inspirational

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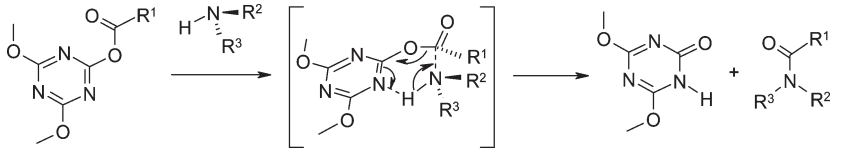
Scheme 1. Intramolecular Cyclic Transition State Postulated for Coupling Involving Triazine "Superactive Esters"



strategy. All of them are based on good leaving groups of size smaller than standard HOBt, HOAt, or 6-Cl-HOBt. The additional goal of the process of declining the size of the leaving group was elimination of the explosive property caused by instability of the triazole fragment.[11] One of the first and most promising responses to this problem was coupling reagents based on the ethyl 2-cyano-2-(hydroxyimino)acetate (Oxyma) oxime frame, which contains high electron-withdrawing substituents, increasing the acidity of the additive and consequently the reactivity.[12] Its parent uronium salt, COMU, incorporating a hydrogen bond acceptor in the iminium part resulted in performances superior to reagents described previously.[13−15]

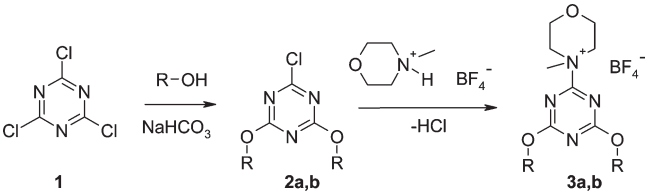
The alternative process of size diminution gave coupling reagents based on the use of pyridine,[16,17] pyrimidine,[18] or triazine[19−22] as leaving group. In all cases, an additional mechanistic benefit originating from structural features of azines predisposed for the aminolysis proceeding via a cyclic, concerted transition state, similar to the one envisaged for 7-HOAt[23] (Scheme 1), has been anticipated. However, for relatively less reactive derivatives of pyridine and pyrimidine, this benefit has been less significant than in the case of much more electron-deficient triazines.[24,25]

Bearing in mind the Thorpe−Ingold effect,[26] we hypothesized that increased substitution in substrates could favor formation of the cyclic intermediate or transition state (at least compared to the linear transition state or linear intermediate) by tethering the two reacting centers and finally support acylation of sterically hindered substrates.[27−30] In general, intramolecular reactions occur more rapidly than their intermolecular counterparts owing to their more favorable entropy change on passing to the transition state.[31] When five- and six-membered rings are formed, like the one proposed for 4-(4,6-di[2,2,2-trifluoroethoxy]-1,3,5-triazin-2-yl)-4-methylomorpholinium tetrafluoroborate (DFET), this entropic contribution produces a favorable ΔG and equilibrium constant. This would compensate the well-known effect of retardation of synthetic processes by increased steric hindrance of substrates. To verify this assumption, we undertake systematic studies on incorporation of N-alkylated amino acids and on 2,2-disubstituted amino acids comparing different coupling reagents.

RESULTS AND DISCUSSION

The measurements of nitrogen kinetic isotope effects[32] in the reaction model for difficult coupling involving sterically hindered trimethylacetic acid and aniline used as a less nucleophilic amino component provided data compatible with fast release of the leaving group but not enough characteristics to confirm unequivocally the mechanism via cyclic transition state. One could expect that decreasing electron density in the triazine ring would favor attack of the nucleophilic amino component on the activated carboxylic function, simultaneously sustaining the character of triazine as an excellent leaving group. If this modification would be sufficient for promoting the cyclic intermediate in a coupling reaction, substantial intensification of coupling sterically hindered substrates has to be observed.

Scheme 2. Synthesis of 2-Chloro-4,6-di (2,2,2,-trifluoroethoxy)-1,3,5-triazine (CDFET, 2b) and 4-Di(4,6-[2,2,2-trifluoroethoxy]-1,3, 5-triazyn-2-yl)-4-methylomorpholinium Tetrafluoroborate (DFET/NMM/BF_4, 3b)



a=CH_3-	**2a**, yield 86%	**3a**, yield 70%
b=CF_3CH_2-	**2b**, yield 52%	**3b**, yield 43%

To increase the reactivity of classic triazine-based coupling reagents **2a**, methoxy groups at positions 2 and 4 in the triazine ring were substituted with much more strongly electron-withdrawing 2,2,2-trifluoroethoxy substituents. Synthesis of 2-chloro-4,6-di(2,2,2-trifluoroethoxy)-1,3,5-triazine (CDFET, **2b**) was accomplished in the two-phase system by treatment of cyanuric chloride with an equivalent amount of 2,2,2-trifluoroethanol in the presence of sodium bicarbonate with 52% yield (Scheme 2).

Contrary to the well-known rule of thumb declaring that substitution of chlorine atoms in cyanuric chloride with other groups proceeds under gradually more vigorous conditions, introduction of the trifluoroethoxy group enhanced the reactivity of triazine. This strongly favored substitution of the next reactive group in the 1,3,5-triazine ring and promoted formation of persubstituted derivatives. Therefore, isolation of **2b** from the mixture of products required fractional distillation affording all three possible triazines substituted with mono-, di-, and tri-(2,2,2-trifluoroethoxy) groups.

Stable solid coupling reagent **3b** was prepared according to a classic procedure[33] by treatment of **2b** with *N*-methylmorpholinium tetrafluoroborate in the presence of sodium bicarbonate in 43% yield. This procedure, reducing the danger of partial hydrolysis, was found much more convenient for the preparation of highly reactive **3b** than the recently proposed method[20,34] involving transformation in aqueous medium, considered as being less suitable for the highly reactive substrate.

Coupling experiments in solution confirmed the expectations and demonstrated the synthetic usability of **3b**. The activation of carboxylic function proceeded substantially faster than in the case of analogue **3a** (R = CH_3)[20] (Scheme 3).

Even in the case of sterically hindered carboxylic components **4b**, monitoring of the activation process shows the complete consumption of an equimolar amount of reagent within 15 min.

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Scheme 3. Activation of 4-Methoxybenzoic Acid (4a) and Trimethylacetic Acid (4b) and with 3b

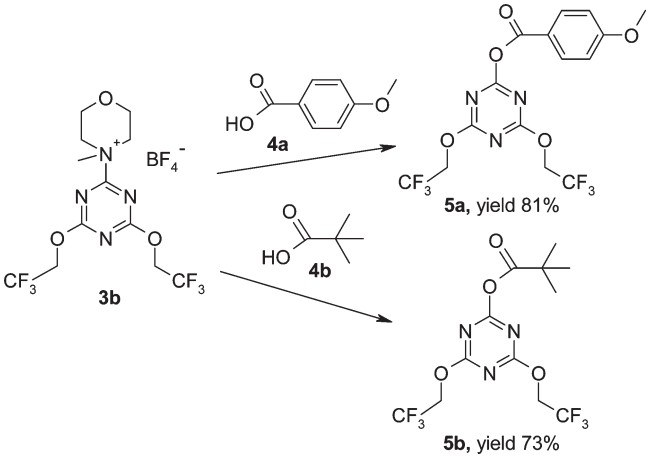

Table 1. Synthesis of Peptides in Solution Using 3b

				Pg-Aaa-Bbb-OMe[b]	
entry	peptide	yield %	purity[a] %	Aaa L/D %	Bbb L/D %[c]
1	Z-Aib-Aib-OMe[d]	89	94.2	-	-
2	Fmoc-Phe-Ala-OMe	98	97.1	99.5/0.5	98.9/1.1
3	Boc-Leu-Val-OMe	93	82.4	98.2/1.8	99.7/0.3
4	Boc-Pro-Phe-OMe	94	96.4	100/0	99.8/0.2
5	Z-Aib-Leu-OMe[d]	91	96.2	-	99.2/0.8

[a] HPLC method. [b] Determined by GC on a ChromasilVal column after hydrolysis to amino acids. [c] Unspecific partial racemization accompanying hydrolytic degradation. [d] Z: benzoxycarbonyl. Aib: α-aminoisobutyric acid.

The formation of appropriate triazine "superactive" ester was confirmed by the presence of a characteristic band at 1757 and 1786 cm^{-1} in the IR spectrum of both 2-acyloxy-4,6-di(2,2,2-trifluoroethoxy)-1,3,5-triazines (**5a,b**) obtained in 73−81% yield, respectively (Scheme 3).

In the case of procedures involving **3a**, the isolation of neutral product obtained in the coupling reaction was less convenient because less soluble appropriate hydroxy-1,3,5-triazines are formed as side product. Therefore, to completely remove this side product, it was necessary to prolong the washing procedure of crude preparation. The coupling results obtained for the selected peptides are compiled below in Table 1.

The obtained yields were spanned in the range from 89 to 98. Thus, even the most hindered sequences were obtained in reasonable good yield. All preparative inconveniences caused by the lower solubility of 2-hydroxy-4,6-di(2,2,2,-trifluoroethoxy)-1,3,5-triazine were eliminated when **3b** was applied in SPPS; therefore, this procedure involving **3b** was considered as more precise for comparison of reactivity of coupling reagents. The model peptides selected for the comparative studies were based on the Leu-enkephaline pentapeptide, by systematically modifying the -Gly-Gly- fragment for *N*-methyl or α,α-disubstituted residues. In the performed experiments, the efficiency of classic aminium salt 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) was compared with triazine reagent DFET/NMM/BF_4 (**3b**) under a variety of reaction conditions. The syntheses of enkephaline analogues were carried out on a Fmoc-RinkAmide-AM-PS resin, studying the introduction of the last three residues onto H-Phe-Leu-resin. The composition of products was determined by LC-MS, and the amount of incomplete sequences was determined based on UV absorbance at 220 nm.

In the synthesis of the "less" sterically hindered sarcosine-containing analogue **7** under conditions optimized for uronium coupling reagents, the productivity of TBTU was comparable with DFET/NMM/BF_4 (**3b**) (see Table 2, entries 1−4 and 5−7).

However, in the case of Aib analogue **8** under more demanding conditions with short, 1 min preactivation time, significantly different results were obtained for both compared coupling reagents (Table 3). Application of TBTU for Aib-Aib coupling prolonged to 240 min gave the expected enkephaline analogue in yields not exceeding 24%, with 72−77% des-Aib side products present as the predominant impurity. Considerably superior performance was obtained for DFET/NMM/BF_4 (**3b**) relative to TBTU, regardless of reaction conditions. The crucial factor controlling the coupling with TBTU and especially DFET/NMM/BF_4 (**3b**) was found to be the character of the solvent used in the synthesis. In the case of strongly solvating DMF solution (Table 3, entries 5−7), the yields of the final product were poor. However, decreasing the solvating ability of solvent by gradually increasing the amount of DCM from 0 to 100% (entries 7−10), the most suitable solvent during activation of the carboxylic substrate[35] significantly promoted the coupling, raising the yield of the final product from 8 to 71% even for shorter 30 min coupling time. It is worthy to notice that dilution of DCM with strongly solvating 1,1,3,3-tetramethylurea (TMU) depressed the efficiency of coupling, yielding final products in only 19% yield (Table 3, entry 10 vs 12), whereas an opposite tendency was observed in DMF (entry 7 vs 11). Further improvements of results were obtained by prolongation of difficult coupling of Aib residues to 120 min. The best, 82% yield again was obtained in the composition of solvents with the dominating fraction of less polar DCM.

It has been found that also the presence of additives, such as HOAt, HOBt, Oxyma, or HODMT, in the reaction mixture could substantially modify the coupling results. On one hand, addition of classic HOBt severely deteriorated coupling process (entry 15), increasing the amount of des-Aib peptide to 86%, whereas on the other hand HOAt, HODMT, and especially Oxyma increased the efficiency of peptide bond formation. The performance of HODMT was slightly superior to that of HOAt. The most beneficial was addition of Oxyma[36] (Table 3, entry 17) affording pentapeptide **9** in 94% yield, the highest percentage achieved in this peptide system. Again, this propitious result of Oxyma was purged away by addition of DMF to reacting mixture (entry 20).

Considerable diversification of coupling results was found also in the case of incorporation of consecutive *N*-methylleucine residues into the peptide chain. For TBTU, the yield of expected enkephalin analogue was in the range 1−11% (Table 4, entries 1 and 2), whereas in experiments with DFET/NMM/BF_4 (**3b**), even in DMF solution the final product was obtained in 66−79% yield (entries 3 and 4). For both reagents, a minimum preactivation time of 1 min is recommended to enhance active ester formation (entries 2, 4 vs 1, 3).

Generally recognized as one of the most extremely difficult couplings, introduction of N-MeVal into N-MeVal-Phe-Leu-resin was studied during assembly of enkephalin analogue

Table 2. Synthesis of Tyr-Sar-Sar-Phe-Leu Enkephaline Analogue (7), Preactivation 1 min

entry	coupling reagent	base	coupling time [min]	solvent	pentapeptide [%]	des-Sar [%]
1	TBTU	DIPEA	5	DMF	99.06	0.58
2	TBTU	NMM	5	DMF	99.10	0.58
3	TBTU	-	5	DMF:DCM (1:1)	98.39	0.10
4	**3b**	NMM	5	DMF	96.94	2.49
5	**3b**	NMM	5	DMF:DCM (1:1)	96.84	2.48

Table 3. Synthesis of Tyr-Aib-Aib-Phe-Leu Enkephaline Analogue (8), Preactivation 1 min

entry	coupling reagent	base	additive	coupling time [min]	solvent	penta peptide [%]	des-Aib	des-Tyr	des-2Aib	des-AibTyr
1	TBTU	NMM		5 min each	DMF	0.67	96.12	0.12	0.2	2.88
2	TBTU	NMM	-	30/2 × 120/30	"	18.41	77.78	2.64	0.65	0.53
3	TBTU	NMM	-	30/2 × 120/30	DMF:DCM (1:1)	21.16	74.79	2.89	0.57	0.59
4	TBTU	NMM	-	30/2 × 120/30	DMF:DCM (1:8)	23.02	72.32	3.51	0.57	0.58
5	**3b**	NMM	-	5 min each	DMF	11.16	85.03	0.26	0.19	3.36
6	**3b**	NMM[a]		30 each	"	8.02	90.35	--	0.76	0.87
7	**3b**	NMM		30 each	DMF:DCM (1:1)	21.71	77.02	--	0.94	0.32
8	**3b**	NMM	-	30 each	DMF:DCM (1:8)	39.41	59.68	--	0.76	0.12
9	**3b**	NMM	-	30 each	DCM	70.90	28.21	--	0.83	0.06
10	**3b**	NMM	-	30 each	TMU:DMF (1:4)	12.38	86.73	--	0.81	0.07
11	**3b**	NMM	-	30 each	TMU:DCM (1:4)	18.93	80.27	--	0.72	0.06
12	**3b**	NMM		30/2 × 120/30	DMF	33.65	65.40	--	0.74	0.20
13	**3b**	NMM		30/2 × 120/30	DMF:DCM (1:1)	55.37	44.29	--	0.16	0.19
14	**3b**	NMM		30/2 × 120/30	DMF:DCM (1:8)	82.32	17.32	0.05	0.11	0.19
15	**3b**	NMM	HOBt	30/2 × 120/30	DMF:DCM (1:1)	12.86	86.24	--	0.63	0.26
16	**3b**	NMM	HOAt	30/2 × 120/30	DMF:DCM (1:1)	64.81	34.17	--	0.81	0.21
17	**3b**	NMM	Oxyma	30/2 × 120/30	DMF:DCM (1:1)	94.15	4.86	--	0.85	0.15
18	**3b**	NMM	HODMT	30/2 × 120/30	DMF:DCM (1:1)	66.75	33.03	--	0.13	0.09
19	**3b**	NMM	-	30/60/30	DCM[b]	63.35	36.09	--	0.51	--
20	**3b**	NMM	Oxyma	30/2 × 120/30	DCM[b]	48.79	50.70	--	0.32	0.18

[a] 2 equiv of NMM was used instead of the regular 6 equiv. [b] Aib-Aib coupling.

Table 4. Synthesis of Tyr-MeLeu-MeLeu-Phe-Leu Enkephaline Analogue (9) with Coupling Time of 5 Min Each

entry	coupling reagent	base	preactivation time [min]	solvent	pentapeptide [%]	des-MeLeu	des-Tyr	des-MeLeu,Tyr
1	TBTU	NMM	1	DMF	10.75	53.25	13.81	20.59
2	"	NMM	0	"	1.37	24.91	5.93	66.95
3	**3b**	NMM	1	"	78.74	6.05	10.32	1.14
4	**3b**	NMM	0	"	66.14	15.65	11.66	2.78

Table 5. Synthesis of Tyr-MeVal-MeVal-Phe-Leu Enkephaline Analogue (10), Preactivation 1 min

entry	coupling reagent	base	coupling time [min]	solvent	pentapeptide [%]	des-MeVal	des-Tyr	des-2 MeVal	des-MeVal,Tyr
1	TBTU	NMM	5 min each	DMF	0.15	4.36	5.11	0.07	90.31
2	TBTU	NMM	2 × 120 min each	DMF/DCM (1:8)	0.22	16.05	7.34	0.51	75.89
3	**3b**	NMM	5 min each	DMF	8.87	37.18	31.21	0.26	22.49
4	**3b**	NMM	2 × 120 min each	DMF:DCM (1:8)	46.9	32.31	12.31	0.72	7.76

10 (Table 5). TBTU gave unsatisfactory results even if the total coupling time was prolonged to 240 min. Much better results were obtained using DFET/NMM/BF_4 (**3b**) (Table 5, entries 3, 4 vs 1, 2). Even for short 5 min couplings in DMF as solvent, identified previously as unfavorable, superior performance was observed. Besides the pentapeptide, obtained in 9% yield, tetrapeptides with the single amino acid deletion dominated in the mixture of products.

A substantial increase of yield to 47% was obtained by prolongation of coupling time and reduction of solvating power of the solvent used in the coupling procedure, by increasing the percentage of DCM.

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CONCLUSIONS

The increased steric hindrance of substrates always disturbed coupling of amino acids. In the search for the universal remedy, the contraction of the leaving group gave some effects and simple acyl chlorides, and more reactive acyl fluorides supervene more sophisticated approaches. Careful analysis of the couplings involving triazine reagent strongly suggest a presence of the additional factor controlling efficiency of coupling sterically hindered substrates, besides the acidity of the leaving group. These are the structure of the leaving group permitting formation of a cyclic intermediate or a cyclic transition state and the absence of solvents strongly solvating hydrogen of the acylated nucleophile. It has to be considered as highly probable that, in the case of activation of the carboxylic function by a triazine-based coupling reagent triazine "superactive esters" which are able to acylate amino components (and especially N-alkylated amio components) via cyclic intermediates or cyclic transition state, in the weakly solvating dichloromethane solution, this mechanism of acylation is dominating. The consequence of arrangement of both components into the cyclic intermediate or cyclic transition state is their stabilization by accumulation of geminal (vicinal) substituents, known as the Thorpe−Ingold effect.[26] This would compensate (at least partially) retardation of the coupling process caused by steric hindrance, and the excellent results with Aib-Aib coupling evaluate the compensation as extensive to consider it as the important factor in designing the structure of coupling reagents.

GENERAL METHODS

NMR spectra were recorded on 250 or 700 MHz spectrometers using the solvent peak as an internal reference. Multiplicities are indicated, s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), m (multiplet); coupling constants (J) are in Hertz (Hz).

IR spectra were recorded as KBr pellets or film.

Analysis of experiments regarding dipeptide formation in solution were carried out using a Vydac C-18 column, detection at 220 nm, gradient from 10% to 50% B in 15 min, flow 1 mL/min; A: 0.1% TFA in water, B: 0.1% TFA in mixture 90% acetonitrile and 10% water.

Experiments of efficiency during assembly of enkephalin analogues in the solid phase were performed using a Waters SunFire C18 (3.5 μm, 4.6 × 100 mm) column, with detection at 220 nm. Solvents used were A: H_2O/0.045% TFA and B: CH_3CN/0.036% TFA,with a flow of 1 mL/min.

Gas chromatography (GC)−FID (H_2/air), Split 1:50, column capillary Chirasil-Val (25 m × 0.32 mm, thickness film 0.2 μm, carier gas hel −pressure 0.45 atm. Temperature program: 4 min in 90 °C, next 4 °C/min to 190 °C and 3 min in 190 °C.

2-Chloro-4,6-di[2,2,2-trifluoroethoxy]-1,3,5-triazine (2b). Cyanuric chloride (92.2 g; 0.5 mol) was gradually added to the vigorously stirred suspension of sodium bicarbonate (126 g; 1.5 mol) in 2,2,2-trifluoroethanol (86.3 mL; 1.2 mol) diluted with chloroform (40 mL) in such a rate to maintain the temperature of the reacting mixture in the range 25−30 °C. Stirring was continued at 25−30 °C until no more cyanuric chloride was detected (TLC; R_f = 0.85; chloroform), then heated to gentle reflux until all intermediate product was consumed (TLC; R_f = 0.72; chloroform). Then, the reacting mixture was cooled to room temperature, further diluted with chloroform (50 mL), and thoroughly washed with 1% aqueous $NaHCO_3$ solution (4 × 500 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Crude oil was distilled under reduced pressure using a column with a rotating band. Fraction 152−155 °C/27 mmHg. was collected yielding 2-chloro-4,6-di[2,2,2-trifluoroethoxy]-1,3,5-triazine (**2b**) (81 g; 52% yield).

TLC: R_f (chloroform) = 0.65. ^{1}H NMR (250 MHz; $CDCl_3$) δ = 4.89 (q, J_{3H-F} = 7.9 Hz, 4H, CH_2) [ppm]. MS: 312.03 $[M + 1]^+$. ^{13}C NMR (175 MHz; $CDCl_3$) δ = 64.46; 122.29; 171.32; 173.67 [ppm]. Anal. Calcd for $C_7H_4ClF_6N_3O_2$: C, 26.99%; H, 1.29%; Cl, 11.38%; F, 36.59%; N, 13.49%; O, 10.27%. Found: C, 27.31%; H, 1.36%.

4-(4,6-Di[2,2,2-Trifluoroethoxy]-1,3,5-triazin-2-yl)-4-methylomorpholinium Tetrafluoroborate (3b). The suspension of $NaHCO_3$ (16.8 g, 0.2 mol) and 2-chloro-4,6-di[2,2,2-trifluoroethoxy]-1,3,5-triazine (31.16 g, 0.1 mol) in acetonitrile (50 mL) was cooled to 0 °C in the ice−salt bath, and then a solution of *N*-methylmorpholinium tetrafluoroborate (18.90 g, 0.1 mol) in 20 mL of acetonitrile was added. Stirring was continued until 2-chloro-4,6-di[2,2,2-trifluoroethoxy]-1,3,5-triazine was not detected by TLC (about 4 h). The mixture was filtered, and precipitate was washed with acetonitrile (4 × 20 mL). The combined filtrates were concentrated to dryness. Crude oil was diluted with 5 mL of acetonitrile and participated 100 mL of THF. After recrystallization of the solid residue from the mixture acetonitrile/THF, 4-(4,6-di[2,2,2-trifluoroethoxy]-1,3,5-triazyn-2-yl)-4-methylomorpholinium tetrafluoroborate was obtained (19.95 g; 43%) as a white crystalline solid which decomposed when heated above 250 °C.

^{1}H NMR (250 MHz; CD_3CN) δ = 3.43 (s, 3H); 3.74−3.83 (m, 4H); 4.00−4.05 (m, 2H); 4.46−4.51 (m, 2H); 5.07 (q, J_{3H-F} = 8.4 Hz, 4H) [ppm]. ^{13}C NMR (175 MHz; CD_3CN) δ = 53.6; 60.4; 61.5; 65.0; 122.6; 171.4; 172.6 [ppm]. MS: 377.12 $[M - BF_4]^+$. Anal. Calcd for $C_{12}H_{15}BF_{10}N_4O_3$: C, 31.06%; H, 3.26%; B, 2.33%; F, 40.94%; N, 12.07%; O, 10.34%. Found: C, 31.84%; H, 3.68%.

2-Acyloxy-4,6-di[2,2,2-trifluoroethoxy]-1,3,5-triazine (5a, b): Typical Procedure. The appropriate carboxylic acid (1 mmol) and NMM (22 μL, 0.2 mmol) were added to a vigorously stirred solution of **3b** (0.464 g, 1 mmol) in THF (5 mL) and CH_3CN (1 mL), cooled to 0 °C. Stirring was continued until 4-(4,6-di[2,2,2-trifluoroethoxy]-1,3,5-triazin-2-yl)-4-methylomorpholinium tetrafluoroborate was not detected by TLC (about 15 min). The mixture was concentrated to dryness and the residue suspended in THF (5 mL) and filtered. Filtrate was concentrated to dryness again. The residue was dried under vacuum with P_2O_5 and KOH to constant weight affording neutral products **5a** or **5b**.

4-Methoxybenzoic Acid 4,6-Di[2,2,2-trifluoroethoxy]-[1,3,5]triazin-2-yl Ester (5a). The solution of 4-(4,6-di[2,2,2-trifluoroethoxy]-1,3,5-triazin-2-yl)-4-methylomorpholinium tetrafluoroborate (0.464 g, 1 mmol) and 4-methoxybenzoic acid (0.152 g, 1 mmol) in 5 mL of THF and 1 mL of CH_3CN was cooled to 0 °C in the ice−salt bath, and then NMM (22 μL, 0.2 mmol) was added. Stirring was continued until 4-(4,6-di[2,2,2-trifluoroethoxy]-1,3,5-triazin-2-yl)-4-methylomorpholinium tetrafluoroborate was not detected by TLC (about 15 min). The mixture was concentrated to dryness and the residue suspended in THF (5 mL) and filtered. Filtrate was concentrated to dryness again. 4-Methoxybenzoic acid 4,6-di[2,2,2-trifluoroethoxy]-[1,3,5]triazin-2-yl ester was obtained (yield 0.346 g; 81%) as oil.

IR (film) = 1757 [cm^{-1}]. ^{1}H NMR (700 MHz; $CDCl_3$) δ = 3.90 (s, 3H, $\underline{CH_3}$−O−Ph); 4.87 (q, J_{3H-F} = 7.9 Hz, 4H, $CF_3-\underline{CH_2}-O$); 6.96 (d, J_{3H-H} = 7 Hz, 2H, $\underline{CH}-C-O-CH_3$); 8.09 (d, J_{3H-H} = 7 Hz, 2H, $\underline{CH}-C-CO$) [ppm]. ^{13}C NMR (175 MHz; $CDCl_3$) δ = 55.5; 64.2; 114.2; 119.4; 122.4; 133.0; 161.3; 165.0; 171.3; 172.7 [ppm].

2,2-Dimethylpropionic Acid 4,6-Di[2,2,2-Trifluoroethoxy]-[1,3,5]triazin-2-yl Ester (5b). The solution of 4-(4,6-di[2,2,2-trifluoroethoxy]-1,3,5-triazin-2-yl)-4-methylomorpholinium tetrafluoroborate (0.464 g, 1 mmol) and 2,2-dimethylpropionic acid (0.102 g, 1 mmol) in 5 mL of THF and 1 mL of CH_3CN was cooled to 0 °C in the ice−salt bath, and then NMM (22 μL, 0.2 mmol) was added. Stirring was continued until 4-(4,6-di[2,2,2-trifluoroethoxy]-1,3,5-triazin-2-yl)-4-methylomorpholinium tetrafluoroborate was not detected by TLC (about 15 min). The mixture was concentrated to dryness and the

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residue suspended in THF (5 mL) and filtered. Filtrate was concentrated to dryness again. 2,2-Dimethylpropionic acid 4,6-di[2,2,2-trifluoroethoxy]-[1,3,5]triazin-2-yl ester was obtained (yield 0.275 g; 73%) as oil.

IR (film) = 1786 [cm^{-1}]. ^1H NMR (250 MHz; CD_3CN) δ = 1.36 (s, 9H); 4.86 (q, J_{3H-F} = 7.9 Hz, 4H) [ppm]. ^{13}C NMR (175 MHz; $CDCl_3$) δ = 26.4; 39.6; 62.2; 122.4; 171.5; 172.8; 173.5 [ppm].

Formation of the Peptide Bond in Solution, Synthesis of Z-Aib-Aib-OMe. Typical Procedure. The solution of 4-(4,6-di[2,2,2-trifluoroethoxy]-1,3,5-triazin-2-yl)-4-methylomorpholinium tetrafluoroborate (0.464 g, 1 mmol) and Z-Aib-OH (0.237 g, 1 mmol) in 5 mL of THF was cooled to 0 °C in the ice−salt bath, and then NMM (30 μL, 0.27 mmol) was added. Stirring was continued until 4-(4,6-di[2,2,2-trifluoroethoxy]-1,3,5-triazin-2-yl)-4-methylomorpholinium tetrafluoroborate was not detected by TLC (about 20 min). After this time, H-Aib-OMe·HCl (0.154 g, 1 mmol) and NMM (110 μL, 1 mmol) were added. The reaction was left overnight at room temperature. The mixture was concentrated to dryness, and the residue was dissolved in 30 mL of ethyl acetate and washed with water (2 × 15 mL), 1 N $NaHSO_4$ (2 × 15 mL), water (2 × 15 mL), 1 N $NaHCO_3$ (3 × 15 mL), water (3 × 15 mL), and brine (1 × 20 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Z-Aib-Aib-OMe was obtained (0.299 g; 89%) as a white crystalline solid, mp 98−100 °C, lit.[37] mp 99−100 °C.

HPLC: t_R = 13.28 min, purity = 94.2%. ^1H NMR (250 MHz; $CDCl_3$) δ = 1.49 (s, 12H); 3.76 (s, 3H); 5.08 (s, 2H); 5.22−5.27 (m, 1H); 6.86−6.91 (m, 1H); 7.28−7.36 (m, 5H) [ppm].

Fmoc-Phe-Ala-OMe. The solution of 4-(4,6-di[2,2,2-trifluoroethoxy]-1,3,5-triazin-2-yl)-4-methylomorpholinium tetrafluoroborate (0.464 g, 1 mmol) and Fmoc-Phe-OH (0.387 g, 1 mmol) in 5 mL of THF was cooled to 0 °C in the ice−salt bath, and then NMM (30 μL, 0.27 mmol) was added. Stirring was continued until 4-(4,6-di[2,2,2-trifluoroethoxy]-1,3,5-triazin-2-yl)-4-methylomorpholinium tetrafluoroborate was not detected by TLC (about 15 min). After this time H-Ala-OMe·HCl (0.140 g, 1 mmol) and NMM (110 μL, 1 mmol) were added. The reaction was left overnight at room temperature. The mixture was concentrated to dryness and dissolved in ethyl acetate (30 mL) and washed with water (2 × 15 mL), 1 N $NaHSO_4$ (2 × 15 mL), water (2 × 15 mL), 1 N $NaHCO_3$ (3 × 15 mL), water (3 × 15 mL), and brine (1 × 20 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Fmoc-Phe-Ala-OMe was obtained (0.463 g; 98%) as a white crystalline solid, mp 172−175 °C, lit.[38] mp 177−179 °C.

HPLC: t_R = 14.13 min, purity = 97.1%. GC: t_R = 3.36 min (D-Ala); t_R = 3.87 (L-Ala) L/D = 98,87/1,13; t_R = 18.40 (D-Phe); t_R = 18.95 (L-Phe) L/D = 99.47/0.53. ^1H NMR (250 MHz, $CDCl_3$) δ = 1.26 (d, J = 7.1, 3H), 2.98 (d, J = 7.0 Hz, 2H), 3.63 (s, 3H), 4.12 (t, J = 6.8 Hz, 1H), 4.25−4.45 (m, 4H, 2×CH), 5.31 (s, 1H), 6.26 (s, 1H), 7.10−7.70 (m, 13H) [ppm].

Boc-Leu-Val-OMe. The solution of 4-(4,6-di[2,2,2-trifluoroethoxy]-1,3,5-triazin-2-yl)-4-methylomorpholinium tetrafluoroborate (0.464 g, 1 mmol) and Boc-Leu-OH (0.231 g, 1 mmol) in 5 mL of THF was cooled to 0 °C in the ice−salt bath, and then NMM (30 μL, 0.27 mmol) was added. Stirring was continued until 4-(4,6-di[2,2,2-trifluoroethoxy]-1,3,5-triazin-2-yl)-4-methylomorpholinium tetrafluoroborate was not detected by TLC (about 20 min). After this time H-Val-OMe·HCl (0.168 g, 1 mmol) and NMM (110 μL, 1 mmol) were added. The reaction was left overnight at room temperature. The mixture was concentrated to dryness, and the residue was dissolved in 30 mL of ethyl acetate and washed with water (2 × 15 mL), 1 N $NaHSO_4$ (2 × 15 mL), water (2 × 15 mL), 1 N $NaHCO_3$ (3 × 15 mL), water (3 × 15 mL), and brine (1 × 20 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Boc-Leu-Val-OMe was obtained (0.320 g; 93%) as a white crystalline solid which melted in the range 95−98 °C, lit.[39] mp 125−126 °C.

HPLC: t_R = 11.42 min, purity = 82.4%. GC: t_R = 7.37 min (D-Leu); t_R = 7.97 (L-Leu) L/D = 98,24/1,76; t_R = 4,57 (D-Val); t_R = 7,76 (L-Val) L/D = 99.75/0.25. ^1H NMR (250 MHz; $CDCl_3$) δ = 0.89−0.96 (m, 12H); 1.44 (s, 9H); 1.49−1.53 (m, 1H); 1.61−1.64 (m, 3H); 3.74 (s, 3H); 4.03−4.16 (m, 1H); 4.51−4.56 (m, CH); 4.85−4.88 (m, 1H); 6.52−6.58 (m, 1H) [ppm].

Boc-Pro-Phe-OMe. The solution of 4-(4,6-di[2,2,2-trifluoroethoxy]-1,3,5-triazin-2-yl)-4-methylomorpholinium tetrafluoroborate (0.464 g, 1 mmol) and Boc-Pro-OH (0.215 g, 1 mmol) in 5 mL of THF was cooled to 0 °C in the ice−salt bath, and then NMM (30 μL, 0.27 mmol) was added. Stirring was continued until 4-(4,6-di[2,2,2-trifluoroethoxy]-1,3,5-triazin-2-yl)-4-methylomorpholinium tetrafluoroborate was not detected by TLC (about 20 min). After this time H-Phe-OMe·HCl (0.216 g, 1 mmol) and NMM (110 μL, 1 mmol) were added. The reaction was left overnight at room temperature. The mixture was concentrated to dryness and dissolved in 30 mL of ethyl acetate and washed with water (2 × 15 mL), 1 N $NaHSO_4$ (2 × 15 mL), water (2 × 15 mL), 1 N $NaHCO_3$ (3 × 15 mL), water (3 × 15 mL), and brine (1 × 20 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Boc-Pro-Phe-OMe was obtained (354 mg; 94%) as oil. Lit.[40] mp. 65−66 °C.

HPLC: t_R = 10.09 min, purity = 96.4%. GC: t_R = 10,91 min (L-Pro) L/D = 100; t_R = 18.52 (D-Phe); t_R = 19.36 (L-Phe) L/D = 99.79/0.21. ^1H NMR (250 MHz; $CDCl_3$) δ = 1.43 (s, 9H); 1.50−1.80 (m, 2H); 1.79−2.10 (m, 2H); 2.97−3.23 (m, 2H); 3.29−3.32 (m, 2H); 3.72 (s, 3H); 4.13−4.34 (m, 1H); 4.72−4.93 (m, 1H); 6.40−6.52 (m, 1H); 7.08−7.31 (m, 5H) [ppm].

Z-Aib-Leu-OMe. The solution of 4-(4,6-di[2,2,2-trifluoroethoxy]-1,3,5-triazin-2-yl)-4-methylomorpholinium tetrafluoroborate (0.464 g, 1 mmol) and Z-Aib-OH (0.237 g, 1 mmol) in 5 mL of THF was cooled to 0 °C in the ice−salt bath, and then NMM (30 μL, 0.27 mmol) was added. Stirring was continued until 4-(4,6-di[2,2,2-trifluoroethoxy]-1,3,5-triazin-2-yl)-4-methylomorpholinium tetrafluoroborate was not detected by TLC (about 20 min). After this time, H-Leu-OMe·HCl (0.181 g, 1 mmol) and NMM (110 μL, 1 mmol) were added. The reaction was left overnight at room temperature. The mixture was concentrated to dryness, and the residue was dissolved in 30 mL of ethyl acetate and washed with water (2 × 15 mL), 1 N $NaHSO_4$ (2 × 15 mL), water (2 × 15 mL), 1 N $NaHCO_3$ (3 × 15 mL), water (3 × 15 mL), and brine (1 × 20 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Z-Aib-Leu-OMe was obtained (0.332 g; 91%) as a white crystalline solid which melted in the range 81−84 °C, lit.[20] mp 78−80 °C.

HPLC: t_R = 13.56 min, purity = 96.2%. GC: t_R = 3.22 min (Aib); t_R = 7.46 (D-Leu); t_R = 8.11 (L-Leu) L/D = 99.23/0.77. ^1H NMR (250 MHz; $CDCl_3$) δ = 0.91 (d, 6H, J_{3H-H} = 6.5 Hz); 1.53−1.55 (s, 6H); 1.57−1.68 (m, 3H); 3.71 (s, 3H); 4.52−4.64 (t, 1H, J = 6 Hz); 5.09 (s, 2H); 5.32−5.35 (m, 1H); 6.69−6.77 (m, 1H); 7.33−7.36 (m, 5H) [ppm].

Synthesis of H-Phe-Leu-RinkAmide-AM-PS. Dipeptide H-Phe-Leu-RinkAmide-AM-PS was manually assembled on Fmoc-Rink Amide-aminomethyl-PS-resin (5 g, 0.59 $mmolg^{-1}$), after Fmoc removal with piperidine in DMF (20%, 2 × 10 min). The resin was washed with DMF (× 10), DCM (× 10), and DMF (× 10). Residues were introduced after 30 min coupling, with preactivation of Fmoc-amino acids (3 equiv) with HBTU (3 equiv) and DIPEA (6 equiv) in 30 mL of DMF for 1 min. The resin was then washed with DMF (× 10), DCM (× 10), and DMF (× 10) prior to the next cycle of deprotection/coupling. Quantitative incorporation was checked at each step by use of the Kaiser test for primary amines. Sample cleavage (10 mg) with TFA/H_2O (95:5) confirmed the dipeptide in >99.5% purity, as analyzed by reversed-phase HPLC and ESI-MS ($[M + H]^+$ = 278.21). The purity was checked on reversed-phase HPLC, using a 0% to 100% linear gradient of A in B over 8 min, with detection at 220 nm. The t_R of the dipeptide H-Phe-Leu-NH_2 was 3.55 min.

General Procedure of the Synthesis of H-Tyr-Sar-Sar-Phe-Leu-NH_2 on the Solid Phase (7). H-Tyr-Sar-Sar-Phe-Leu-NH_2 was synthesized on the solid phase from H-Phe-Leu-RinkAmide-AM-PS (0.1 g, 0.59 mmol g^{-1}). The resin was swelled with DMF (× 10) and DCM (× 10), and the next step was started by washing with solvent (× 5). Residues were introduced after using different coupling times (see Table 3), with 1 min preactivation of Fmoc-amino acids (3 equiv) with the corresponding coupling reagent (3 equiv) and base (6 equiv) in 0.6 mL of solvent. After coupling, resin was washed with DMF (× 10), DCM (× 10), and DMF (× 5). The Fmoc residue was removed by using 20% piperidine in DMF (2 × 10 min) and washed with DMF (× 10) and DCM (× 10). The peptide chain was cleaved from the resin with TFA/H_2O (95:5) over 2 h at room temperature. The solution was filtered, and the resin was washed with DCM (5 × 1 mL), which was removed together with TFA under nitrogen flow. The crude peptide was purified with cold Et_2O (3 × 2 mL), and after lyophilization, purity was checked on reversed-phase HPLC, using a 17% to 18% linear gradient of A in B over 15 min.

The purity of H-Tyr-Sar-Sar-Phe-Leu-NH_2 was determined based on signal t_R = 9.35 min, $[M + H]^+$ = 583.36. Des-Sar t_R = 8.72 min, $[M + H]$ = 512.90.

General Procedure of the Synthesis of H-Tyr-Aib-Aib-Phe-Leu-NH_2 on the Solid Phase (8). H-Tyr-Aib-Aib-Phe-Leu-NH_2 was assembled on the solid phase from H-Phe-Leu-RinkAmide-AM-PS (0.1 g, 0.59 $mmol^{-1}g$). The resin was swelled with DMF (× 10) and DCM (× 10). The step was started from washing with solvent (× 5). Residues were introduced after different coupling times (see Table 4), with 1 min preactivation of Fmoc-amino acids (3 equiv) with coupling reagent (3 equiv) and base (6 equiv) in 0.6 mL of solvent. After coupling, resin was washed with DMF (× 10), DCM (× 10), and DMF (× 5). The Fmoc residue was removed by using 20% piperidine in DMF (2 × 10 min) and washed with DMF (× 10) and DCM (× 10). The peptide chain was cleaved from the resin with TFA/H_2O (95:5) over 2 h at room temperature. The solution was filtered, and the resin was washed with DCM (5 × 1 mL), which was removed together with TFA under nitrogen flow. The crude peptide was purified with cold Et_2O (3 × 2 mL), and after lyophilization, purity was checked on reversed-phase HPLC, using a 15−35% linear gradient of A in B over 8 min.

The purity of H-Tyr-Aib-Aib-Phe-Leu-NH_2 was determined based on signal t_R = 7.30 min, $[M + H]^+$ = 611.40. Des-Aib t_R = 7.39 min, $[M + H]^+$ = 526.31. Des-Tyr t_R = 5.74 min, $[M + H]^+$ = 448.29. Des-2Aib t_R = 4.75 min, $[M + H]^+$ = 441.32. Des-TyrAib t_R = 4.12 min, $[M + H]^+$ = 363.30.

General Procedure of the Synthesis of H-Tyr-MeLeu-MeLeu-Phe-Leu-NH_2 on the Solid Phase (9). H-Tyr-MeLeu-MeLeu-Phe-Leu-NH_2 was elongated on the solid phase from H-Phe-Leu-RinkAmide-AM-PS (0.1 g, 0.59 mmol g^{-1}). The resin was swelled with DMF (× 10) and DCM (× 10). The step was started from wash with solvent (× 5). Residues were introduced by means of 5 min couplings and various preactivation times (see Table 5) of Fmoc-amino acids (3 equiv) with coupling reagent (3 equiv) and base (6 equiv) in 0.6 mL of DMF. After coupling, resin was washed with DMF (× 10), DCM (× 10), and DMF (× 5). Fmoc residue was removed by using 20% piperidine in DMF (2 × 10 min) and washed with DMF (× 10) and DCM (× 10). The peptide chain was cleaved from the resin with TFA/H_2O (95:5) over 2 h at room temperature. The solution was filtered, and the resin was washed with DCM (5 × 1 mL), which was removed together with TFA under nitrogen flow. The crude peptide was purified with cold Et_2O (3 × 2 mL), and after lyophilization, purity was checked on reversed-phase HPLC, using a 15−50% linear gradient of A in B over 8 min.

Purity of H-Tyr-MeLeu-MeLeu-Phe-Leu-NH_2 was determined based on signal t_R = 7.93 min, $[M + H]^+$ = 695.46. Des-MeLeu t_R = 6.19 min, $[M + H]^+$ = 568.36. Des-Tyr t_R = 6.83 min, $[M + H]^+$ = 532.40. Des-TyrMeLeu t_R = 4.56 min, $[M + H]^+$ = 405.29.

General Procedure of Synthesis of H-Tyr-MeVal-MeVal-Phe-Leu-NH_2 on the Solid Phase (10). H-Tyr-MeVal-MeVal-Phe-Leu-NH_2 was assembled on the solid phase from H-Phe-Leu-RinkAmide-AM-PS (0.1 g, 0.59 mmol g^{-1}). The resin was swelled with DMF (× 10) and DCM (× 10). The step was started from washing with solvent (× 5). Residues were introduced after various coupling times (see Table 5), with 1 min preactivation of Fmoc-amino acids (3 equiv) with coupling reagent (3 equiv) and base (6 equiv) in 0.6 mL of solvent. After coupling, resin was washed with DMF (× 10), DCM (× 10), and DMF (× 5). Fmoc residue was removed by using 20% piperidine in DMF (2 × 10 min) and washed with DMF (× 10) and DCM (× 10). The peptide chain was cleaved from the resin with TFA/H_2O (95:5) over 2 h at room temperature. The solution was filtered, and the resin was washed with DCM (5 × 1 mL), which was removed together with TFA under nitrogen flow. The crude peptide was purified with cold Et_2O (3 × 2 mL), and after lyophilization, purity was checked on reversed-phase HPLC, using a 15−35% linear gradient of A in B over 8 min.

The purity of H-Tyr-MeVal-MeVal-Phe-Leu-NH_2 was determined based on signal t_R = 8.04 min. $[M + H]^+$ = 667.48. Des-MeVal t_R = 6.41 min. $[M + H]^+$ = 554.38. Des-Tyr, t_R = 7.51 min. $[M + H]^+$ = 504.36. Des-2 MeVal t_R = 4.90 min. $[M + H]^+$ = 441.31. Des-TyrMeVal t_R = 4.11 min. $[M + H]^+$ = 391.30.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR and MS spectra for new compounds, and copies of HPLC and GC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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