C-Alkylation of Peptides Containing Aminomalonate[1]) and (Amino)(cyano)acetate Residues

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Dedicated to Professor *Heinrich Nöth* on the occasion of his 70th birthday

N-Acetyl-, *N*-[(*tert*-butoxy)carbonyl](Boc)-, and *N*-[(benzyloxy)carbonyl](Z)-protected tri-, penta-, and heptapeptide methyl esters, **1**–**8**, with a central aminomalonate (Ama) (allyl, methyl, benzyl, or *tert*-butyl) or (amino)(cyano)acetate (Aca) residue have been prepared by conventional techniques (*Schemes 4–6*). The new peptides with acidic backbone-bound CH groups can be *C*-alkylated with primary alkyl, allyl, and benzyl halides, under mildly basic conditions (1 equiv. MeONa or *t*-BuOK in THF); also, they can be added to *Michael* acceptors such as acrylates, acrylonitrile, methyl vinyl ketone, or nitrostyrene (catalytic amounts of alkoxide bases in THF) (*Schemes 7–16*). In most cases, the products, **48**–**100**, are formed in excellent yields (average of 77%); one of the epimeric products prevails (2:1 to > 20:1), and the epimers have been separated, isolated in pure form, and fully characterized (without configurational assignments); addition of the co-solvent 3,4,5,6-tetrahydro-1,3-dimethylpyrimidin-2(1*H*)-one (DMPU) or of LiBr may improve or even reverse the ratio of epimeric products formed; the heptapeptide derivative **8** had to be solubilized for alkylations in THF by the addition of 30 equiv. of LiBr. Cleavage of the Ama groups (benzyl with H_2/Pd-C, *t*-Bu with HCl/Et_2O) gave carboxylate derivatives which are actually peptides containing the alkylated aminomalonic acid, the lower homolog of aspartic acid, as residue in the central position. These acids are quite resistant to decarboxylation which had to be achieved by heating at reflux in THF in the presence of 2 equiv. of LiBr and of catalytic amounts of pyridine (*Schemes 17* and *18*). A one-step removal of the allyl aminomalonate group is possible with Pd/PPh_3/formate (*Scheme 19*). The resulting peptides, **101**–**115**, were formed as separable 1:1 mixtures of two epimers. The CN group of the alkylated Aca residue can be removed reductively (Na/NH_3; *Scheme 20*). The value of the new method is compared with that of existing methods of peptide-backbone modification.

1. Introduction. – Modified natural peptides and proteins are widely used for investigations of structure-activity correlations. Usually, these oligopeptides are prepared by stepwise procedures [2]. In contrast, methods based on the chemical modification of intact peptides would be more attractive and more economical for the preparation of a multitude of derivatives, without having to repeat the peptide synthesis for each modification.

Over the past ten years, we have developed a methodology by which new side chains can be attached *via* enolates of sarcosine or glycine residues within a peptide chain [3–5]. Analogous modifications using nucleophilic reactivity have also been reported by other groups [6]. The generation of electrophilic glycine equivalents within peptides using electrochemical decarboxylation [7], oxidative cleavage of serine or threonine residues [8], or bromination with *N*-bromosuccinimide [9] has also been realized.

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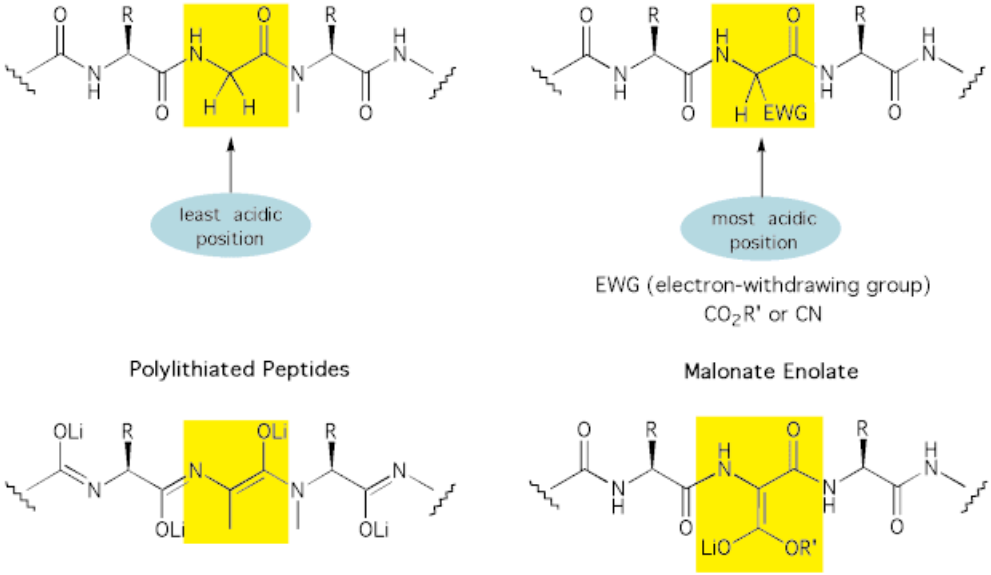
[1]) For a preliminary communication, see [1].

[2]) Part of the Dissertation No. 12307 of *T.M.*, ETH-Zürich, 1997.

In previous papers [3–5] about peptide enolates, we demonstrated that linear and cyclic oligopeptides containing up to eleven amino acids can be alkylated at glycine or sarcosine residues *via* polylithiated derivatives. The glycine- or sarcosine-enolate reactive sites were generated by deprotonation of the least acidic position in the peptide backbone using strong bases. However, this procedure was only applicable if an *N*-alkylated amino acid was incorporated adjacent to the peptide-enolate unit in the direction of the C-terminus. Also special precautions were necessary for providing anhydrous and oxygen-free conditions. The purpose of this paper is to describe a project for reversing this situation [9]: the position to be substituted is now the most acidic one in the molecule (*Scheme 1*). This goal should be achieved by substitution of one α-CH proton of a glycine residue by an electron-withdrawing group, *e.g.*, a carboxyalkyl (CO_2R') or a CN group.

Scheme 1



In other words, the incorporation of an *a*mino*m*alonic *a*cid monoester (*Ama* monoester)[3]) or an *a*mino*c*yano*a*cetic-acid (*Aca*) building block into a peptide should render the adjacent backbone CH group the most acidic position within the molecule. Weaker bases and, therefore, milder conditions could be used for nucleophile generation. The modification of oligopeptides, that are not *N*-alkylated should be then possible. The synthetic potential of this approach (*i.e.*, application of the classical malonic-ester synthesis to peptides) is indicated in *Scheme 2*.

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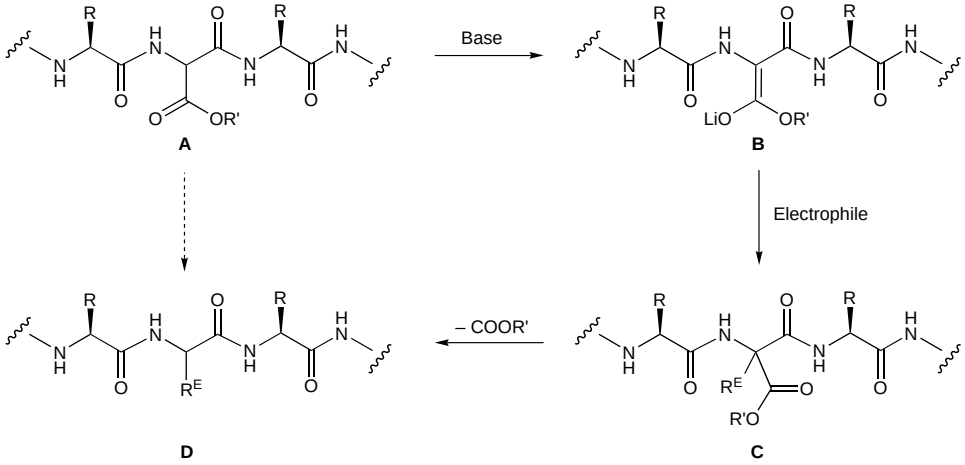
[3]) Ama-Containing peptides are not unknown in the literature: a diketopiperazine [10], a tripeptide [11], and some peptide isosteres [12], containing at least one Ama building block, have been reported. Ama was also detected in alkaline hydrosylates of proteins of *E. coli*; a content of 0.3 Ama/1000 amino acids was found. The origin of the Ama residues is still unclear; it has been demonstrated that Ama is not formed from any of the 20 proteinogenic amino acids during the hydrolysis procedure [13].

Scheme 2



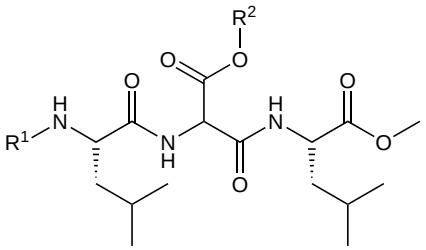
Deprotonation of **A** gives the new enolate derivative **B** (geometry (*E*/*Z*) of the enolate double bond is unknown). The subsequent alkylation of **B** leads to the corresponding α,α-disubstituted derivative **C**, which is finally converted to the modified peptide **D** by cleavage of the electron-withdrawing group.

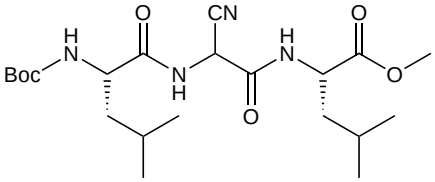
2. Ama- and Aca-Containing Peptides, the Starting Materials. – The peptides **1**–**8** containing three to seven amino acids were prepared. The Ama or Aca building block was always positioned in the middle of the peptides. The other amino-acid components were chosen according to previous work [3]. Except in **1** and **8**, the ester group of the Ama side chain was designed to be cleaved selectively.

We prepared the Ama-monoester building blocks in a straightforward manner[4]) (*Scheme 3*). The *N*-protected glycine esters were doubly deprotonated by lithium diisopropylamide (LDA)/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) and carboxylated with CO_2 gas, yielding the corresponding *N*-protected Ama monoesters (**9**–**12**). Treatment of **10** with CH_2N_2 gave the Ama-diester derivative **13**, which is required for the preparation of **8**. Using the same deprotonation-carboxylation procedure, Boc-protected amino-acetonitrile **14** could be converted to Boc-Aca-OH (**15**). The building blocks **9**–**12** and **15** were used without further purification. Surprisingly, these building blocks could be activated and incorporated into peptides by conventional methods, without any 'decarboxylation problems'.

The assembly of the peptides **1**–**8** is schematically presented in *Schemes 4*–*6* (intermediates **16**–**47**). Except for **8**, all peptides were built up from C to N terminus. The *N*-protected amino acids (Z- or Boc-) were activated by isobutyl chlorocarbonate (in THF)/*N*-methylmorpholine (NMM); dicyclohexylcarbodiimide (DCC)/1-hydroxy-1*H*-benzotriazole (HOBt) or 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC)/HOBt was employed for the coupling of the *N*-protected Ama building blocks.

[4]) Another method for the preparation of this half ester has been described by *U. Schmidt et al.* [14].



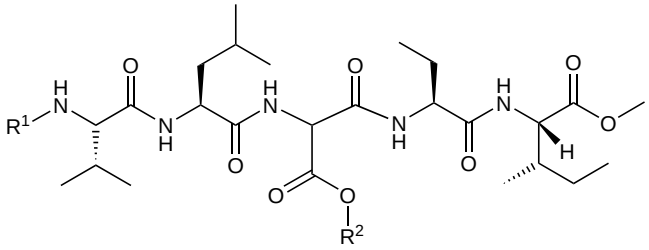


1 R^1 = Boc, R^2 = Me

2 R^1 = Boc, R^2 = Bn

3 R^1 = Ac, R_2 = *t*-Bu

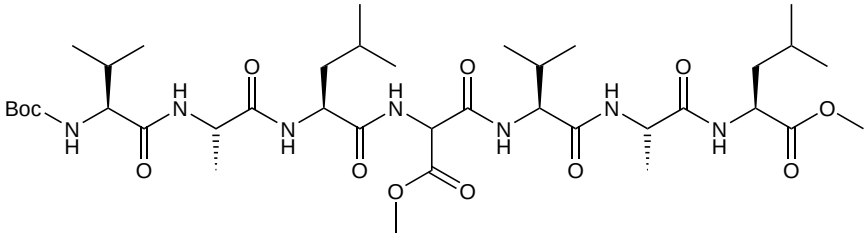
4



5 R^1 = Z, R^2 = *t*-Bu

6 R^1 = Boc, R^2 = Bn

7 R^1 = Boc, R^2 = All



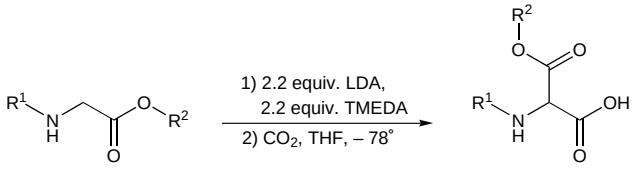
8

We exclusively used sat. HCl/Et_2O solution for removal of the Boc protecting group, and Pd/C under H_2 for cleavage of the Z group.

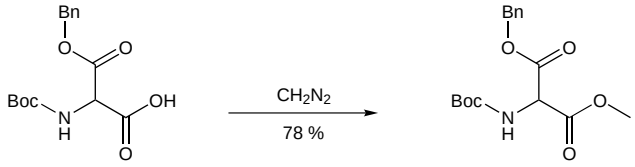
Finally, the heptapeptide **8** was assembled by a fragment-condensation technique (*Scheme 6*): the two peptide fragments, H-Val-Ala-Leu-OMe (**40**) and Boc-Val-Ala-Leu-Ama(OMe)-OH (**47**), were first built up using the strategy described above. The reaction of **40** and **47** was carried out in THF at 0° in the presence of EDC/HOBt as activating reagents (→ **8**, 50%).

The peptide derivatives were obtained as mixtures of two epimers which could not be separated, with one exception: a single epimer of the *tert*-butyl malonate **3**

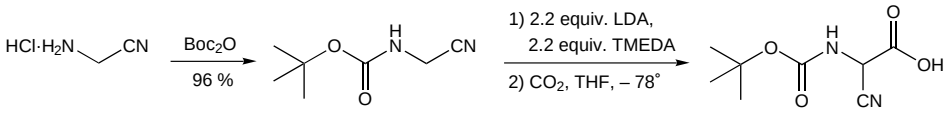
Scheme 3



Product	R^1	R^2
9	CO_2CMe_3 (Boc)	Me
10	Boc	Bn
11	Boc	All
12	CO_2Bn (Z)	*t*-Bu



10 **13**

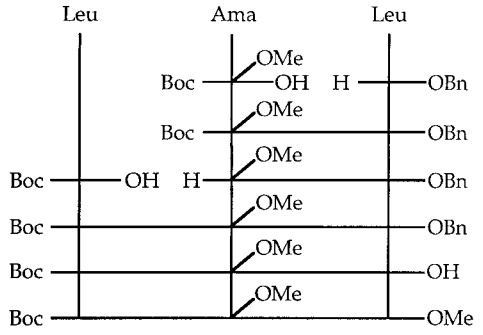


14 **15**

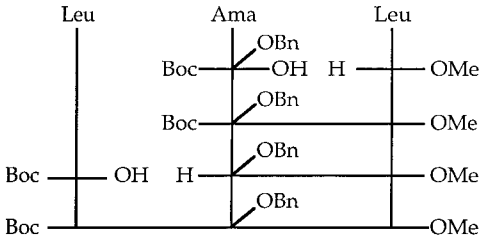
(unknown configuration) separated from the workup solution. The peptide derivatives **3**, **5**, and **8** were rather insoluble in organic solvents. For details of the oligopeptide syntheses, see *Exper. Part* and standard procedures [15].

3. Deprotonation and Alkylation of the Ama-Containing Peptides 1–3, 5–8, and the Aca-Containing Tripeptide 4. – The deprotonation and subsequent alkylation were carried out first with the Boc-tripeptide diester **1**. We chose NaOMe in MeOH as base, which was employed in slight stoichiometric exces (1.3 equiv.) for alkylation and substoichiometrically (0.3 equiv.) for *Michael* additions to acrylic-acid derivatives, methyl vinyl ketone, and nitrostyrene. The reactions were usually carried out in THF at 0°. As can be seen from *Scheme 7*, the tripeptide **1** reacted with a wide range of different electrophiles. Using these conditions, the methylated product **48** was obtained in 84% yield. All other alkyl halides also gave good results: EtI (→ **49**), BuI (→ **50**), allyl and benzyl bromide (→ **51** and **52**, resp.), and cyclohex-2-enyl bromide (→ **53**). This procedure could also be successfully used for *Michael* additions of the enolate of **1** to methyl acrylate (→ **54**), to *tert*-butyl acrylate (→ **55**), acrylonitrile (→ **56**), and methyl

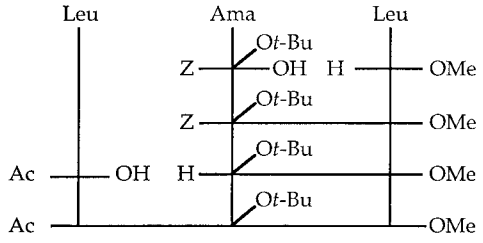
Scheme 4



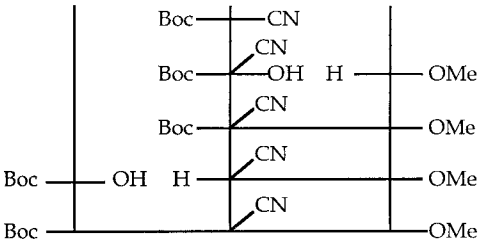
Product	Yield [%]
9	
16	73
17	quant.
18	82
19	quant.
1	quant.



Product	Yield [%]
10	
20	69
21	quant.
2	77

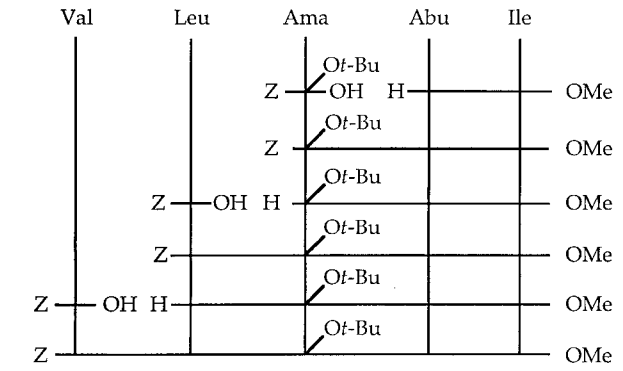


Product	Yield [%]
12	
22	69
23	quant.
3	79

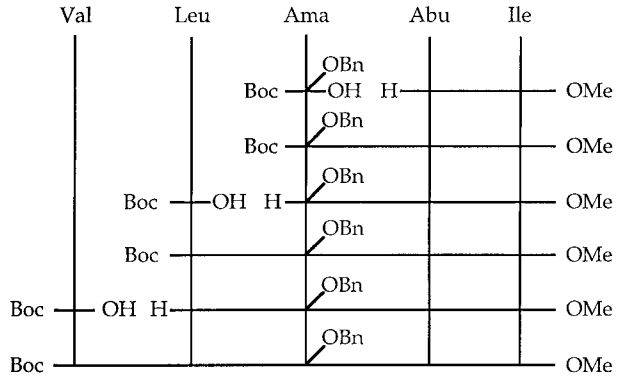


Product	Yield [%]
14	96
15	
24	69
25	quant.
4	77

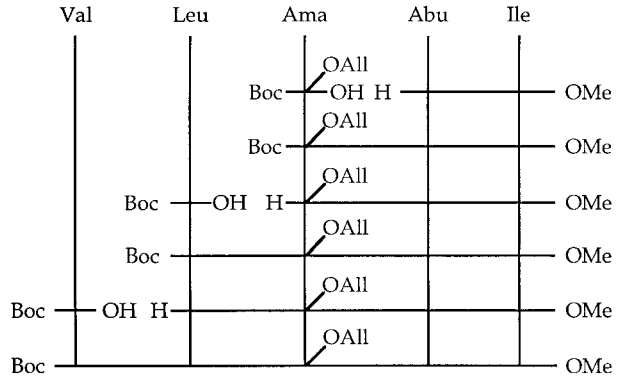
Scheme 5



Product	Yield [%]
26	99
27	69
28	quant.
29	96
30	quant.
5	81



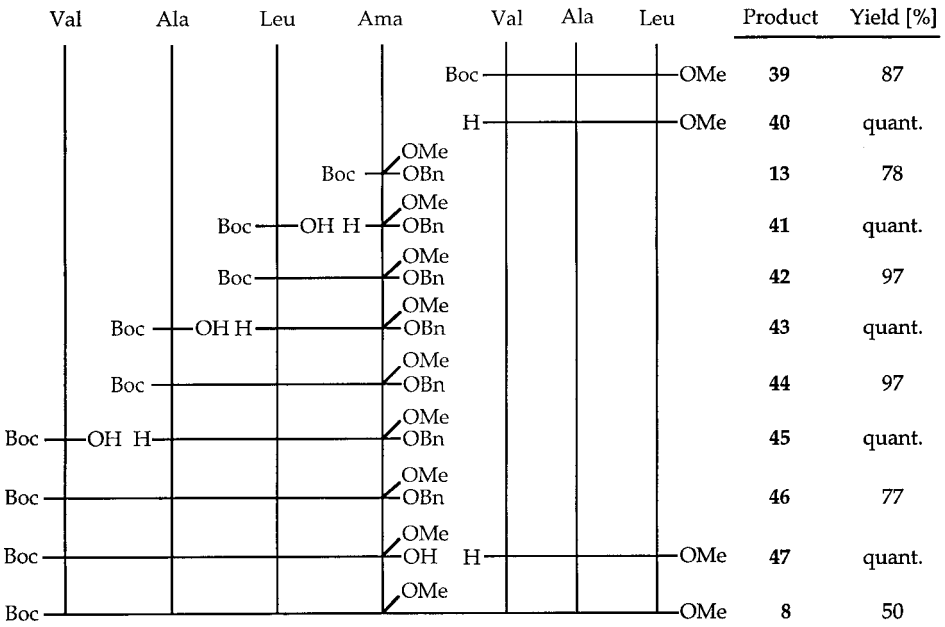
Product	Yield [%]
31	67
32	quant.
33	95
34	quant
6	85



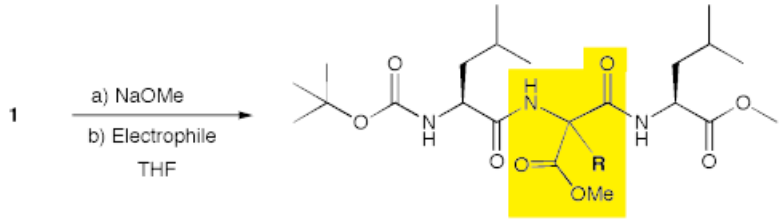
Product	Yield [%]
35	65
36	quant.
37	95
38	quant.
7	97

vinyl ketone (→ **57**). The reaction of **1** with nitrostyrene led to the formation of adduct **58**. In all cases, the products were obtained as 1 : 1 mixture of two diastereoisomers; in the case of **53** and **58**, four isomers were detected by ^{1}H-NMR analysis. All attempts to separate the diastereoisomers were unsuccessful.

Scheme 6



Scheme 7

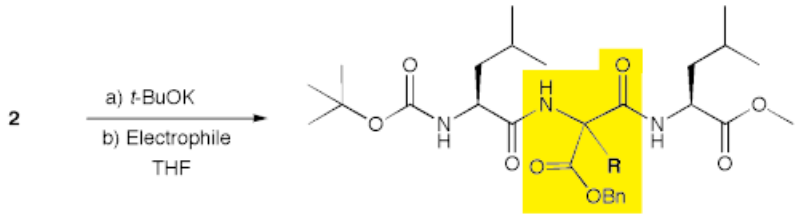


Electrophile	Product[a])	R	Yield [%]
MeI	**48**	Me	84
EtI	**49**	Et	61
BuI	**50**	Bu	31
CH_2=$CHCH_2Br$	**51**	CH_2CH=CH_2	85
BnBr	**52**	Bn	81
Cyclohex-2-enyl bromide	**53**[b])	cyclohex-2-en-1-yl	79
Methyl acrylate	**54**	$CH_2CH_2CO_2Me$	90
tert-Butyl acrylate	**55**	$CH_2CH_2CO_2{}^tBu$	86
Acryl nitrile	**56**	CH_2CH_2CN	89
Methyl vinyl ketone	**57**	CH_2CH_2COMe	70
Nitrostyrene	**58**[b])	$CH(Ph)CH_2NO_2$	57

[a]) 1 : 1 Mixture of two diastereoisomers. [b]) Four isomers were detected by ^{1}H-NMR.

Applying the same procedure, the benzyl malonate **2** could be readily alkylated with MeI (→ **59**), EtI (→ **60**), allyl bromide (→ **61**), and BnBr (→ **62**), or again, added in a *Michael* fashion to methyl acrylate (→ **63**), to *tert*-butyl acrylate (→ **64**), to acrylonitrile (→ **65**), and to methyl vinyl ketone (→ **66**) (*Scheme 8*). We noticed a pronounced effect of added LiBr on the diastereoselectivity of this alkylation[5]). The product ratio for the methylation of **2** increased from 1:1 (no LiBr) to almost 6:1 (3 equiv. of LiBr). An enhancement of the diastereoselectivity by adding 3 equiv. of LiBr was also observed for the alkylation with allyl (2:1) and benzyl bromide (3:1). In contrast, for the *Michael* addition of **2** no LiBr was required to obtain products which were enriched in one epimer. The best result was obtained using *tert*-butyl acrylate as electrophile (dr 20:1). The configuration of the major products formed was not determined.

Scheme 8



Electrophile	LiBr [equiv.]	Product	R	Yield [%]	dr[a])
MeI	0	**59**	Me	88	1:1
MeI	3	**59**	Me	88	5.5:1
MeI	5	**59**	Me	79	5:1
EtI	3	**60**	Et	34	2:1
CH_2=$CHCH_2Br$	0	**61**	CH_2CH=CH_2	72	1:1
CH_2=$CHCH_2Br$	3	**61**	CH_2CH-CH_2	64	2:1
BnBr	0	**62**	Bn	70	1:1
BnBr	3	**62**	Bn	63	3:1
Methyl acrylate	0	**63**	$CH_2CH_2CO_2Me$	84	5:1
tert-Butyl acrylate	0	**64**	$CH_2CH_2CO_2{}^tBu$	95	20:1
Acryl nitrile	0	**65**	CH_2CH_2CN	92	2:1
Methyl vinyl ketone	0	**66**	CH_2CH_2COMe	88	3:1

[a]) The diastereoselectivity was determined by ^{1}H-NMR spectroscopy.

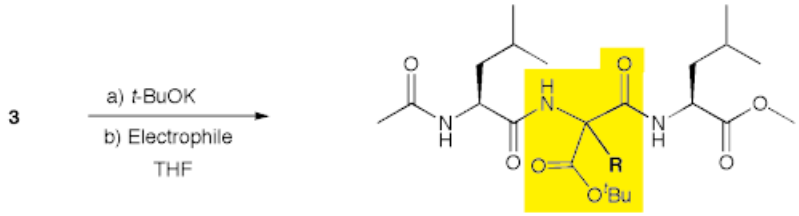
Finally, the *tert*-butyl malonate **3** could be used for alkylations both as a single isomer and as a 1:1 mixture of two isomers (*Scheme 9*). In this case, LiBr was necessary for better solubilization[6]). In the methylation of **3** (single isomer), we found again that the selectivity could be increased by the addition of LiBr. The best result was obtained by adding 3 equiv. of LiBr (→ **67**; 86%, dr 12:1). If **3** was used as a 1:1 mixture of diastereoisomers, the methylated product **67** was obtained with reduced selectivity (2.5:1). This result indicates that the deprotonation of the two epimers probably leads to different (*E*)/(*Z*)-enolate mixtures, and that each of these enolates might give one of

5) For a general discussion of this effect, see [3a].

6) Peptides can be solubilized in THF and other organic solvents by addition of salts, an effect which turned out to be especially strong with Li salts [16].

the two possible diastereoisomers preferentially. As can be seen from *Scheme 9*, using malonate **3** as a single isomer and 3 equiv. of LiBr, the alkylation products, **68**–**73**, were obtained in excellent yields, and some of them were highly enriched in one epimer. The selectivities range from 2 : 1 for the ethylation (→ **68**) up to 12 : 1 for the reaction with methyl acrylate (→ **71**). Without adding LiBr, the additon of the enolate of **3** to methyl acrylate gave a preference for one isomer of only 4.5 : 1.

Scheme 9



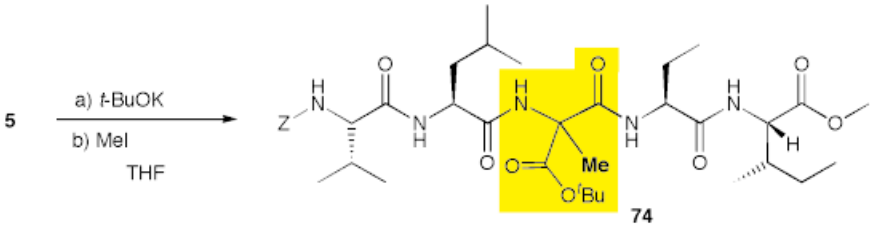
Entry[a])	Electrophile	LiBr [equiv.]	Product	R	Yield [%]	dr[b])
1	MeI	0	**67**	Me	89	3 : 1
2	MeI	3	**67**	Me	88	2.5 : 1
3	MeI	0	**67**	Me	89	5 : 1
4	MeI	3	**67**	Me	86	12 : 1
5	MeI	5	**67**	Me	90	9 : 1
6	EtI	3	**68**	Et	35	2 : 1
7	CH_2=$CHCH_2$	3	**69**[c])	CH_2CH=CH_2	48	4 : 1
8	BnBr	3	**70**[c])	Bn	66	4 : 1
9	Methyl acrylate	0	**71**	$CH_2CH_2CO_2Me$	91	4.5 : 1
10	Methyl acrylate	3	**71**	$CH_2CH_2CO_2Me$	90	12 : 1
11	Acrylonitrile	3	**72**	CH_2CH_2CN	88	3 : 1
12	Methyl vinyl ketone	3	**73**	CH_2CH_2COMe	91	4 : 1

a) For *Entry 1* and *2*, **3** was used as a 1 : 1 mixture. For *Entries 3–12*, the educt was used as a single isomer of unknown configuration. [b]) The diastereoselectivity was determined by ^{1}H-NMR spectroscopy. [c]) Separated by FC.

Because of the excellent results obtained in the tripeptide malonate cases, we next tested the alkylation of Ama-containing pentapeptide derivative **5**. In this case, *t*-BuOK was used as base, and it was necessary to add LiBr to achieve good solubilization[5]) in THF. In the methylation of **5**, the selectivity could be increased in the presence of increasing amounts of LiBr (*Scheme 10*); but, compared to the tripeptide cases, the enhancement was rather poor. The best result was achieved by adding 25 equiv. of LiBr (→ **74**; 88%, dr 3 : 1). A stronger effect on the diastereoselectivity was observed by adding 3,4,5,6-tetrahydro-1,3-dimethylpyrimidin-2(1*H*)-one (DMPU)[7]) as a co-solvent instead of LiBr. Using a 5 : 1 mixture of THF/DMPU, the methylated product **74** was obtained as a 5 : 1 mixture of two isomers. With less DMPU, the selectivity decreased (dr 3 : 1 with THF/DMPU 7.5 : 1). The methylation of **5** in other solvents (except in 1,2-dimethoxyethane (DME)) in combination with DMPU gave similar selectivities (see *Scheme 10*).

7) For reviews describing the co-solvent effect of DMPU, see the corresponding chapter in [3a].

Scheme 10



Solvent		LiBr [equiv.]	Yield [%]	dr[a])
THF		2	77	1:1.2
THF		10	82	2.2:1
THF		25	91	3:1
THF		30	92	2:1
THF/DMPU[b])	5:1	0	85	3:1
THF/DMPU	5:1	0	92	5:1
Et_2O/DMPU	5:1	0	86	4.7:1
CH_2Cl_2/DMPU	5:1	0	84	4.7:1
Toluene/DMPU	5:1	0	93	4.3:1
DME[c])/DMPU	5:1	0	90	1:1

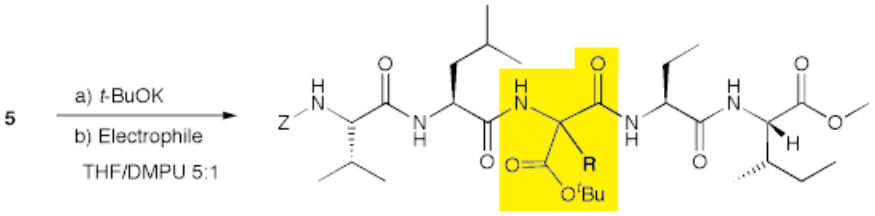
[a]) The diastereoselectivity was determined by HPLC (*LiChrosorb*; hexane/i-PrOH 96:4). [b]) DMPU: 3,4,5,6-Tetrahydro-1,3-dimethylpyrimidin-2(1*H*)-one. [c]) DME: 1,2-Dimethoxyethane.

As can be seen from *Scheme 11*, under optimized conditions (THF/DMPU 5:1; *t*-BuOK; 0°), a multitude of electrophiles reacted with the enolate derivative of **5** giving yields of up to 95% (**74**–**84**). Even less activated electrophiles, *e.g.*, EtI or BuI, could be used successfully (→**75** and **76**). The products are in some cases highly enriched in one epimer. The best results were obtained for the reaction with *tert*-butyl acrylate: only one isomer was detected in the crude product by ^{1}H-NMR spectroscopy (→**82**; 87%, dr >95:5)! The selectivities for the other reactions ranged from 2:1 (addition to methyl vinyl ketone) to 9:1 (benzylation). In this case, all product mixtures (except **80**) could be separated by chromatographic methods. For isolation and identification of these products, see *Exper. Part*. The configuration of the products at the alkylated Ama residue was not determined.

The results obtained for the alkylations of the pentapeptide **6**, with the Ama benzyl ester incorporated, are shown in *Scheme 12*. Using the standard reaction condition (*t*-BuOK; THF; 0°), the alkylation products, **85**–**90**, were isolated in 60–90% yield and were highly enriched in one epimer. No Li salt for solubilization was necessary in this case. The product **89** derived from the addition to *tert*-butyl acrylate was obtained diastereoisomerically pure. Except in the case of **87** and **88**, the diastereoisomeric products could be chromatographically separated. For isolation and full identification of these products, see *Exper. Part*. The major product of the benzylated derivative **86a**[8]) gave crystals from MeOH suitable for X-ray analysis (*Fig. 1*). According to the crystal structure, the new stereogenic center in **86a** has (*S*)-configuration.

[8]) We use **a** and **b** throughout this paper for specifying the two epimers of peptide alkylation products.

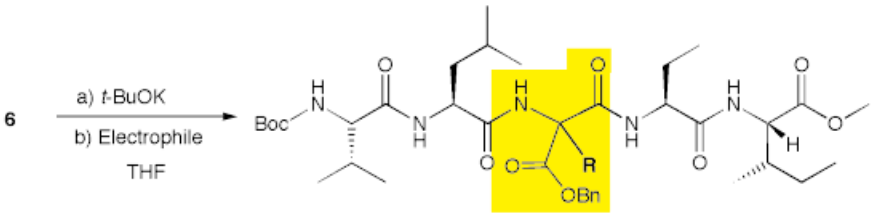
Scheme 11



Electrophile	Product[a])	R	Yield [%]	dr[b])
MeI	**74**	Me	85	5:1
EtI	**75**	Et	70	4:1
BuI	**76**	Bu	37	2.3:1
CH_2=$CHCH_2Br$	**77**	CH_2CH=CH_2	95	4.8:1
BnBr	**78**	Bn	89	9:1
$ClCH_2NHCOPh$	**79**	$CH_2NHCOPh$	86	2:1
Cyclohex-2-enyl bromide	**80**[c])	cyclohex-2-en-1-yl	74	–
Methyl acrylate	**81**	$CH_2CH_2CO_2Me$	85	4:1
tert-Butyl acrylate	**82**	$CH_2CH_2CO_2{}^tBu$	87	> 95:5[d])
Acrylonitrile	**83**	CH_2CH_2CN	86	4:1
Methyl vinyl ketone	**84**	CH_2CH_2COMe	91	2:1

[a]) The two diastereoisomers were separated using chromatographic methods. [b]) The diastereoselectivity was determined by HPLC (*LiChrosorb*). [c]) Not separated. [d]) Only one diastereoisomer was detected in the ^{1}H-NMR spectrum of the crude product.

Scheme 12



Electrophile	Product[a])	R	Yield [%]	dr[b])
CH_2=$CHCH_2Br$	**85**	CH_2CH=CH_2	62	2.3:1
BnBr	**86**	Bn	81	5.5:1
Cyclopent-2-enyl bromide	**87**[c])	cyclopent-2-en-1-yl	64	–
Cyclohex-2-enyl bromide	**88**[c])	cyclohex-2-en-1-yl	76	–
tert-Butyl acrylate	**89**	$CH_2CH_2CO_2{}^tBu$	89	> 95:5[d])
Acrylonitrile	**90**	CH_2CH_2CN	85	4:1

[a]) The two diastereoisomers were separated using chromatographic methods. [b]) The diastereoselectivity was determined by HPLC (*LiChrosorb*). [c]) Not separated. [d]) Only one diastereoisomer was detected in the ^{1}H-NMR spectrum of the crude product.

For the benzylation of **6**, we showed that the variation of solvent and base has a dramatic effect on the selectivity. As can be seen in *Scheme 13*, using the same base but changing the solvent, the selectivity could be increased. Changing the solvent from THF to CH_2Cl_2/DMPU, the selectivity rose from 5.3:1 to more than 9:1. A reversal of

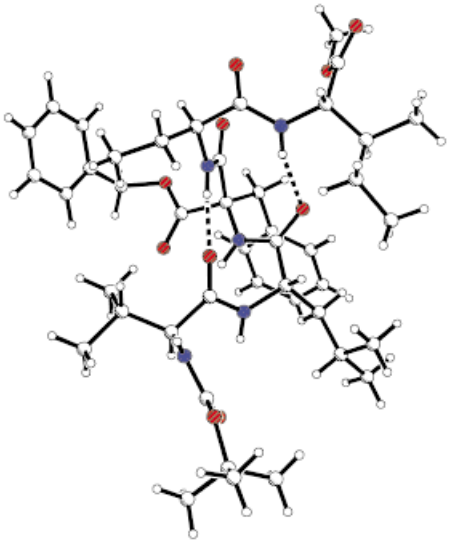
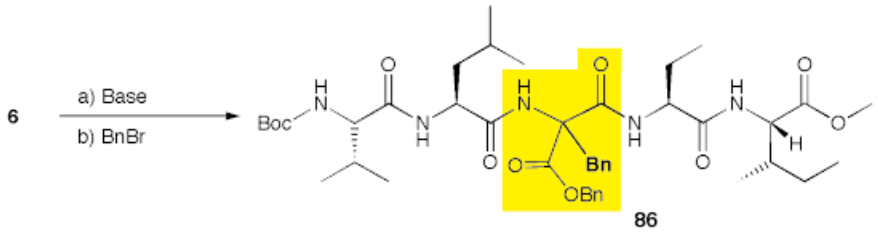


Fig. 1. *X-Ray crystal structure of the pentapeptide derivative* **86a**. O-Atoms in red, N-atoms in blue. The structure was determined by *P. B. Rheiner.*

the selectivity was observed by changing the base: using BuLi as base, the pentapeptide **6** was benzylated to give preferentially product **86b** with (*R*)-configuration on the new stereogenic center (up to 1:6); on the other hand, deprotonation with *t*-BuOK and benzylation led preferentially to the product (9:1) of (*S*)-configuration.

Scheme 13

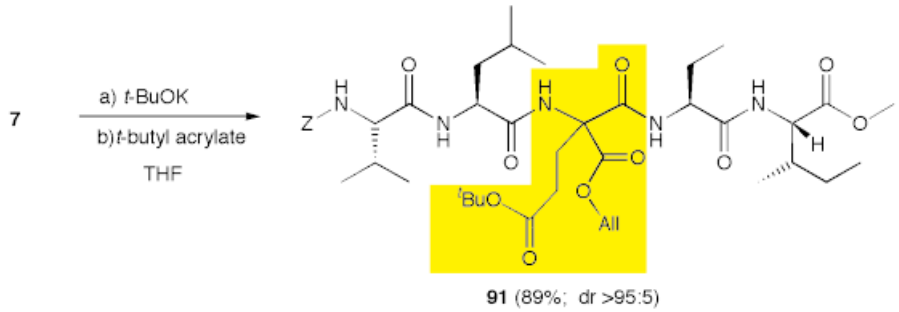


Solvent		Base	Yield [%]	Ratio[a]) (*S*)/(*R*)
THF		*t*-BuOK	82	5.3:1
THF		LDA	73	1:1
THF		BuLi	78	1:2.3
THF/DMPU	20:3	*t*-BuOK	72	4.5:1
THF/DMPU	20:3	*t*-BuOLi	91	4:1
THF/DMPU	20:3	BuLi	77	1:2
Et_2O/DMPU	20:3	*t*-BuOK	78	4.3:1
Et_2O/DMPU	20:3	BuLi	90	1:6
CH_2Cl_2/DMPU	20:3	*t*-BuOK	65	9.2:1
CH_2Cl_2/DMPU	20:3	BuLi	90	1:1.5

[a]) The diastereoselectivity was determined by HPLC (*LiChrosorb*; hexane/i-PrOH 97:3).

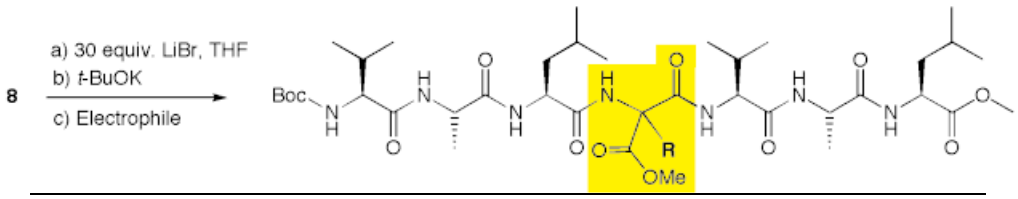
The pentapeptide **7** was added, in a *Michael* fashion, to *tert*-butyl acrylate (→**91**) applying the same conditions mentioned above. According to ^{1}H-NMR analysis of the crude product, the derivative **91** was obtained as a single diastereoisomer of unknown configuration (*Scheme 14*).

Scheme 14



For the solubilization of the heptapeptide **8** in THF, at least 30 equiv. of LiBr were necessary. The solution thus obtained was then treated with base (*t*-BuOK) and electrophile under the standard conditions. The results are summarized in *Scheme 15*. The products, **92**–**95**, were isolated in high yields. The selectivities were in the same range as found for the pentapeptide derivatives. Again, the reaction with *tert*-butyl acrylate gave a single diastereoisomer (**95** of unknown configuration) as determined by HPLC analysis.

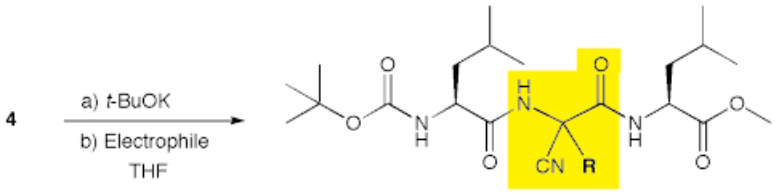
Scheme 15



Electrophile	Product	R	Yield [%]	dr
Allyl bromide	**92**	$CH_2CH{=}CH_2$	52	6.2 : 1
Acrylonitrile	**93**	CH_2CH_2CN	86	3 : 1
Methyl vinyl ketone	**94**	CH_2CH_2COMe	75	4 : 1
tert-Butyl acrylate	**95**	$CH_2CH_2CO_2{}^t$Bu	85	> 95 : 5

Finally, the Aca-containing tripeptide **4** could be deprotonated and alkylated using the same conditions optimized for the aminomalonate cases. As can be seen from *Scheme 16*, the products, **96**–**100**, were obtained in very good yields, albeit as 1 : 1 mixtures of epimers (four stereoisomers of **99**). Compared to the aminomalonate derivatives, the epimer pairs could be separated by flash chromatography much more readily. The configuration of the products was not determined.

Scheme 16



Electrophile	Product[a])	R	Yield [%]
MeI	**96**	Me	82
CH_2=$CHCH_2Br$	**97**	CH_2CH=CH_2	74
BnBr	**98**	Bn	67
Cyclohex-2-enyl bromide	**99**[b])	cyclohex-2-en-1-yl	70
tert-Butyl acrylate	**100**	$CH_2CH_2CO_2{}^tBu$	88

[a]) 1:1 Mixture of two diastereoisomers, readily separated. [b]) Four isomers were detected by ^{1}H-NMR; not separated.

4. Removal of the Electron-Withdrawing Groups (CO_2R and CN). – According to *Scheme 2*, the last step on the way to modified peptides is the removal of the activating group. In the classical malonic-ester syntheses, this has been traditionally effected *via* a two-step procedure: cleavage of the ester group, followed by thermal decarboxylation of the acid formed[9]). For the cases at hand, we proceeded as follows: the benzyl-ester groups of the derivatives of benzyl malonates **2** and **6** were smoothly cleaved by hydrogenolysis (H_2/Pd-C/MeOH); the *tert*-butyl-ester groups of the *tert*-butyl malonates derived from **3** or **5** were readily removed with HCl in Et_2O. No spontaneous decarboxylation was observed, and the acids formed are stable and can be stored for several days without any decomposition. Without further purification, the acids were then decarboxylated using 2 equiv. of LiBr and catalytic amount of pyridine in THF under reflux. Other methods such as radical decarboxylation, following *Barton*'s [19] or *Kochi*'s procedure [20], failed completely.

As can be seen from the data presented in *Schemes 17* and *18*, the tripeptide derivatives **101**–**106** and the pentapeptide derivatives **107**–**115** were cleaved and decarboxylated in high yields, using the above-mentioned two-step procedure. The new peptide derivatives were formed as 1:1 mixtures of epimers. No side reactions of any functionality and no epimerization of the other stereogenic centers were detectable. In most cases, the isomers could be separated chromatographically. The configuration of the central amino-acid residue was determined by derivatization and gas chromatography following *Bayer*'s procedure [21] (see *Exper. Part*).

The use of an allylic ester group in the Ama side chain opens an alternative route for the removal of the activating group. *Tsuji* and co-workers reported a simple one-step method for the conversion of substituted allyl malonates to monocarboxylic acids and

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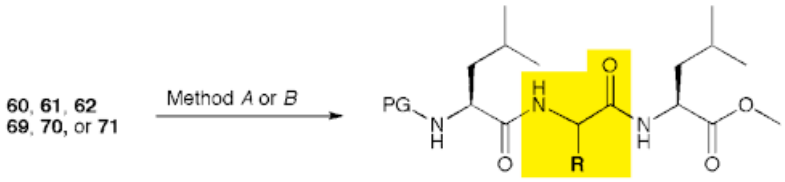
9) Another method for the dealkoxycarbonylations of malonates has been reviewed by *Krapcho*. This process involves the use of H_2O, H_2O with added salts, or anhydrous salts in dipolar aprotic media such as DMSO [17]. In addition, *Ho* reported that malonates can be converted to carboxylic acids by treatment with (iodo)trimethylsilane [18]. Both procedures are carried out at rather high temperatures ($\geq 100°$).

Scheme 17

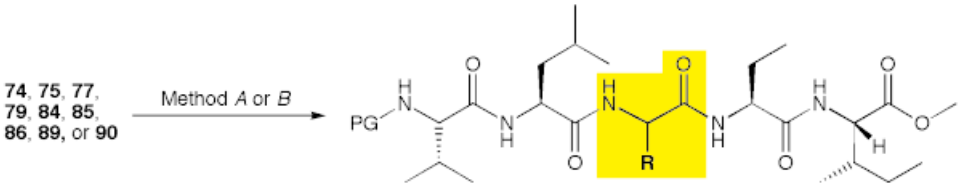


101–106

Method[a])	Educt	Product[b])	PG	R	Yield [%]
A	**60**	**101**	Boc	Me	76
A	**61**	**102**	Boc	CH_2CH_2Me	91
A	**62**	**103**	Boc	cyclohexyl	81
B	**69**	**104**	Ac	$CH_2CH{=}CH_2$	94
B	**70**	**105**	Ac	CH_2Ph	84
B	**71**	**106**	Ac	$CH_2CH_2CO_2CMe_3$	96

[a]) Method *A: i*) Pd/C, H_2, MeOH, 4–10 h; *ii*) 2 equiv. LiBr, cat. pyridine, THF, Δ, 6–10 h. Method *B: i*) sat. HCl/Et_2O, 10 h; *ii*) 2 equiv. LiBr, cat. pyridine, THF, Δ, 6–10 h. [b]) 1:1 Mixture of two diastereoisomers; products **104**–**106** separated by FC.

Scheme 18



107–115

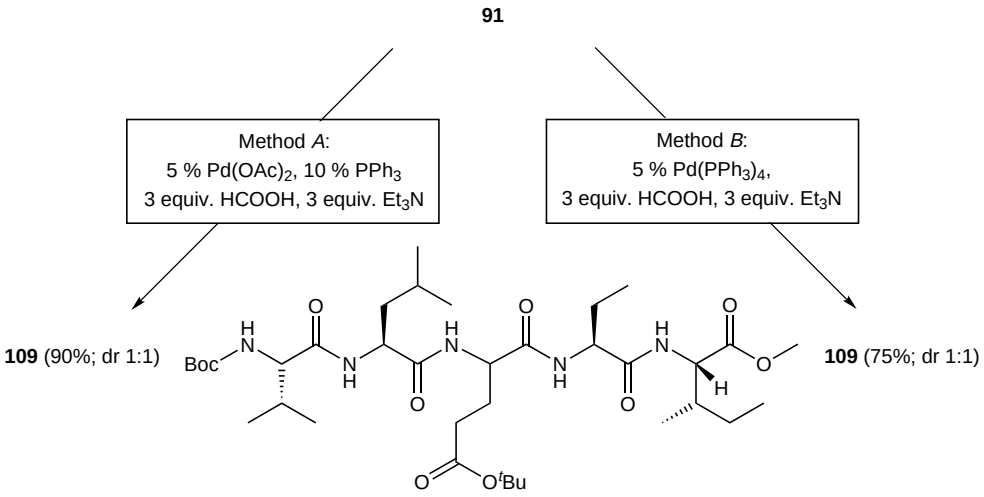
Method[a])	Educt	PG	Product[b])	R	Yield [%]
A	**85**	Boc	**107**	CH_2CH_2Me	76
A	**86**	Boc	**108**	CH_2Ph	74
A	**89**	Boc	**109**	$CH_2CH_2CO_2CMe_3$	87
A	**90**	Boc	**110**	CH_2CH_2CN	74
B	**74**	Z	**111**	Me	87
B	**75**	Z	**112**	Et	79
B	**77**	Z	**113**	$CH_2CH{=}CH_2$	78
B	**79**	Z	**114**[c])	$CH_2NHCOPh$	74
B	**84**	Z	**115**	CH_2CH_2COMe	85

[a]) Method *A: i*) Pd/C, H_2, MeOH, 4–10 h; *ii*) 2 equiv. LiBr, cat. pyridine, THF, Δ, 6–10 h. Method *B: i*) sat. HCl/Et_2O, 10 h; *ii*) 2 equiv. LiBr, cat. pyridine, THF, Δ, 6–10 h. [b]) 1:1 Mixture of two diastereoisomers; readily separated by FC. [c]) Not separated.

esters in the presence of a Pd catalyst under mild conditions [22]. The treatment of the allylic-ester derivative **91** with tertiary amine salts of HCO_2H, catalyzed by Pd^0-phosphine complex at r.t. leads to evolution of CO_2 and propene, giving the

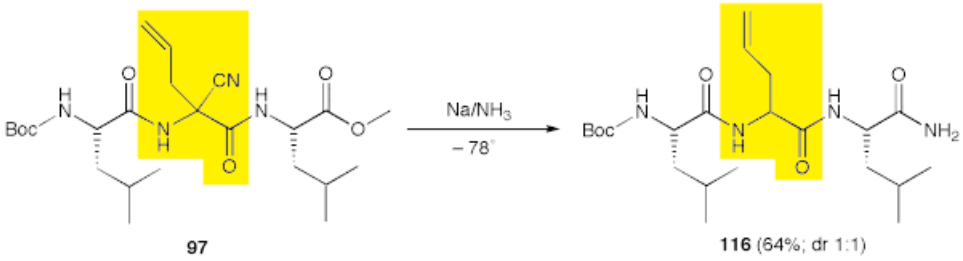
decarboxylated peptide derivative **109** in high yield (*Scheme 19*). Better results were achieved by the *in situ* generation of the Pd^0-phosphine complex starting from Pd^{II} (*Method A* in *Scheme 19:* $Pd(OAc)_2$, PPh_3), as compared to the use of pre-formed Pd^0-phosphine complex (*Method B*). Again, the peptide derivative was formed as a 1:1 mixture of separable isomers in both cases. No further attempts were made to optimize this reaction.

Scheme 19



Finally, the decyanation of the Aca-containing peptide derivative **97** could be achieved, using a procedure published by *Rychnovsky et al.* [23] (*Scheme 20*): a solution of **97** in THF was added to a solution of Na in liquid NH_3 at $-78°$ [10]). In addition to the decyanation, an amidation of the C-terminal methyl-ester group occurred under these conditions, and the peptide amide **116** was formed, in good yield, as a 1:1 mixture of diastereoisomers.

Scheme 20



[10]) It was reported that the reaction of tertiary mononitriles with solvated electrons produces exclusively the corresponding hydrocarbon. Whereas the primary and the secondary nitriles not only undergo cleavage of the C–CN bond but also reduction to the amine, the reaction of tridecanenitrile with Li in $EtNH_2$ gives a 2:1 mixture of the corresponding hydrocarbon and the amine [24].

5. Structure Analysis of the Ama- and Aca-Containing Peptides. – The structure of the peptides with CO_2R and CN substituents, as shown in the *Schemes 7–16*, is compatible with all spectroscopic data given in the *Exper. Part.* When possible and appropriate, the peptides were also submitted to elemental analysis and degradation to their components, followed by GC analysis on chiral columns [21]. As mentioned in the previous sections, the configurations at the CO_2R- and CN-substituted stereogenic centers is unknown in almost all cases. There was not enough time, within the present investigation, to do extensive structural work by NMR and CD spectroscopy, or by X-ray analysis (few of the new compounds were actually crystalline!). Thus, we mention here only two examples.

The *CD spectroscopy* has been used successfully to investigate the secondary structure of peptides and proteins in solution: characteristic troughs between 200 and 230 nm in the CD spectra of peptides are associated with β-sheet and α-helix secondary structures, respectively [25]. An overlay of the CD spectra of the pentapeptides **86a** and **86b** in 2,2,2-trifluoroethanol (TFE) at 0.2 mM concentration in shown in *Fig. 2,a:* both CD curves are typical for peptides with no defined secondary structure [25]. In contrast, the CD spectrum of the heptapeptide derivative **95** in TFE shows two characteristics: a shoulder at 220 nm ($[\theta] = -4.0 \cdot 10^4$) and a strong minimum at 206 nm ($[\theta] = -6.8 \cdot 10^4$); as can be seen from *Fig. 2,b*, the use of MeOH instead of TFE does not change the general pattern of the CD spectrum of **95**. The CD curves observed for **95** indicate the presence of a defined secondary structure. The conclusion would be that **95** has a 3_{10}-helical structure [26][27]. This is in contrast to 'normal' peptides of which distinct secondary structures are observed in solution only when they are built of 10–15 amino-acid residues[11]). In fact, **95** contains a geminally disubstituted central amino acid, and these are known to be helix-inducing!

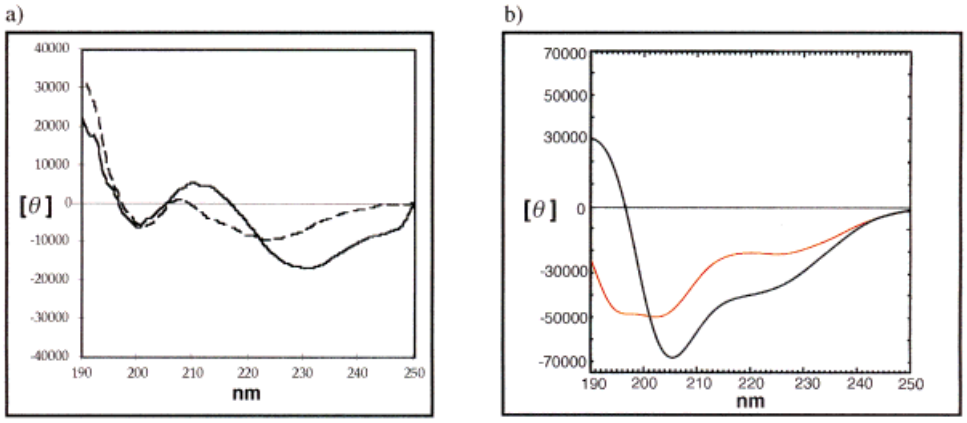


Fig. 2. *CD Spectra of two Ama-containing peptides. a*) Overlay of the CD spectra (molar ellipticity $[\theta]$ in 10 deg cm^2mol^{-1}) of the epimeric pentapeptides **86a** (—) and **86b** (- - -) in 2,2,2-trifluoroethanol (TFE) at 0.2 mM concentration. *b*) Overlay of the CD spectra of the heptapeptide **95** in MeOH (red) and TFE (black) at 0.2 mM concentration.

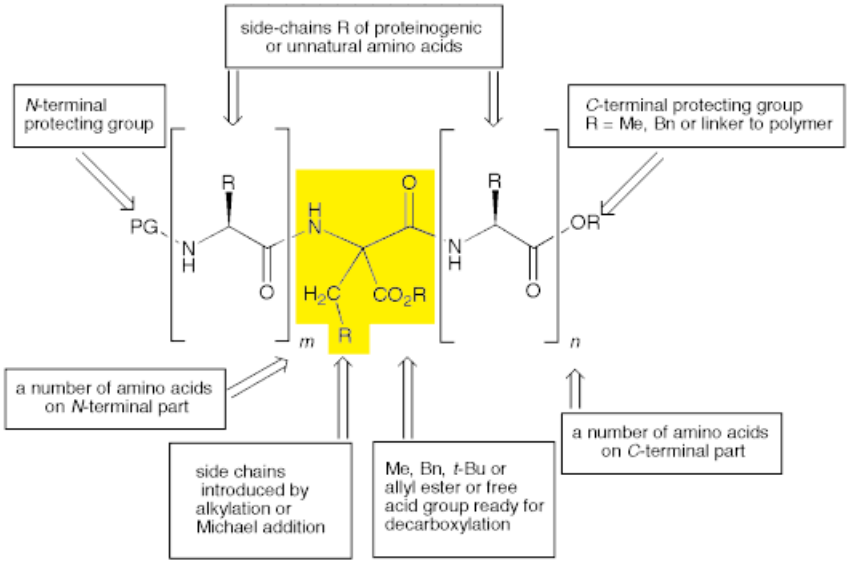
[11]) Exceptions to this rule are observed *i*) with peptides containing *proline* or other turn-inducing amino acids [28], *ii*) with peptides containing *several* or *only* α,α-disubstituted amino acids (*e.g.*, Aib) [30], and *iii*) with homopeptides, consisting of sequences of the *same* amino acid [31].

An *X-ray crystal-structure analysis* of Boc-Val-Leu-(CO_2Bn)Phe-Abu-Ile-OMe (**86a**) was possible: this pentapeptide derivative gave crystals from MeOH suitable for X-ray analysis (*Fig. 1*). The compound forms a perfect right-handed 3_{10}-helix, stabilized by two intramolecular C=O···H–N H-bonds. As deduced from the CD spectrum above (*Fig. 2,a*), there can be little of this conformation in solution.

6. Discussion of the Results and Conclusions. – The readily prepared *N*-Boc- or *N*-Z-protected amino-malonic acid half-esters **9**–**12** (PG-NH-CH(CO_2R)-CO_2H≡PG-Ama-OH) and the related (amino)(cyano)acetic acid **15** (Boc-NH-CH(CN)-CO_2H≡Boc-Aca-OH) can be used as building blocks in conventional peptide solution synthesis (without special modifications of the usual coupling and handling procedures). This was demonstrated by incorporation of the Ama and Aca residues in the central positions of tri-, penta-, and heptapeptides **1**–**8**. There is no doubt – in our minds – that these residues could be incorporated in other positions along peptide chains (*Scheme 21*). The resulting Ama-containing peptides can then be alkylated under mildly basic conditions by primary alkyl halides, by primary and secondary allyl halides, by *N*-(chloromethyl) amides, and by *Michael* acceptors (such as acrylates, acrylonitriles, or nitroolefins). By this peptidic backbone alkylation, a tertiary stereogenic center is introduced, and the new side-chain may be a simple alkyl group, or it may be functionalized (C=C bond, ester, CN, amino, NO_2 group); there are hundreds of possible electrophiles commercially available (just skim through a fine-chemicals catalog!). The products of alkylation are often formed with high diastereoselectivity (*Schemes 8–15*), and the geminally disubstituted Ama residue in the peptide chain appears to exhibit the well-known helix-inducing effect (*Figs. 1* and *2*). Depending upon the type of Ama ester group, deprotection by hydrogenation (CO_2Bn), by treatment with acid (CO_2(*t*-Bu)) or with Pd(PPh_3)$_4$/formate (CO_2Allyl) leads to the free carboxylic acids (lower homologs of α-branched aspartic-acid residues in the peptide chain), which are remarkably resistant to loss of CO_2 (!), or to the decarboxylated peptides with the electrophilically introduced side chain at the former Ama position (*Schemes 17–19*). Thus, three types of modified peptides become available: those with various branched Ama ester residues, the corresponding acids, and conventional peptides with one non-proteinogenic residue of L- and D-configuration. Furthermore, we have demonstrated that peptides with geminal substitution by a CN and an alkyl group at one of the residues (of (*R*)- and (*S*)-configuration) can be readily prepared. Of course, it should also be possible to incorporate more than one Ama and/or Aca residue at various positions of a peptide. Finally, we are confident that solid-phase peptide synthesis is feasible with the Boc-Ama and Boc-Aca derivatives described herein. Thus, a highly *combinatorial* approach to the synthesis of new types of modified peptides is at hand!

A comparison of the Ama/Aca strategy (*A*) with our previous method (*B*) of polylithiated peptide back-bone modification (*Scheme 1*) reveals the following similarities and differences, and relative advantages and disadvantages. *i*) For both methods, a peptide with a special amino acid (Ama, Aca for *A*, *N*-methyl-amino acid(s) for *B* [4]) has to be prepared. *ii*) A peptide with a single side chain is formed directly in *B*, and only after two additional steps, *i.e.*, ester cleavage and decarboxylation or decyanation in *A*. *iii*) On the other hand, in the new method *A*, the ester, acid, and

Scheme 21



nitrile intermediates are interesting modified peptides of their own. *iv*) After removal of the acidifying CO_2R or CN groups in method *A*, 1:1 mixtures – albeit readily separable – of diastereoisomeric peptides are obtained, while there is usually rather high stereoselectivity of alkylations with polylithiated peptides in *B*. *v*) The greatest advantage of the new method are the much milder conditions and less expensive reagents for the alkylation step: 1 equiv. or catalytic amounts of a Na or K alkoxide base at room temperature for *A vs.* many equiv. of a Li base ($LiNR_2$ or *t*-BuLi) at dry-ice temperature for *B*!

Experimental Part

1. *Abbreviations.* Abu: (*R*)-2-aminobutyric acid; Ama: aminomalonic acid, Aca: (amino)(cyano)acetic acid, Boc_2O: di(*tert*-butyl)dicarbonate, DCC: dicyclohexylcarbodiimide, DIPA: diisopropylamine, EDC: 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, FC: flash chromatography, HOBt: 1-hydroxy-1*H*-benzotriazole), NMM: *N*-methylmorpholine, TMEDA: *N*,*N*,*N*′,*N*′-tetramethylenediamine; three-letter amino-acid abbreviations are used for α-amino acids.

2. *General.* THF used for carboxylation and coupling reactions was freshly distilled over K under Ar. DIPA and TMEDA were distilled from CaH_2. Solvents for chromatography and for workup were distilled over P_2O_5. Amino-acid derivatives were purchased from *Senn*, *Bachem*, and *Degussa*. BuLi was used as a 1.5M soln. in hexane. All other chemicals for reactions were used as purchased from *Fluka*. TLC: *Merck* silica gel *60* F_{254} anal. plates: detection with UV and by placing in a Cl_2 tank for 5 min, then staining with a soln. of *N*,*N*,*N*′,*N*′-tetramethyl-4,4′-methylenebis[aniline]. FC: *Merck* silica gel *60* (40–63 μm). GC: *Chirasil-Val*® column (*Macherey-Nagel*, 25 m, 0.4 mm); *Carlo-Erba-Fractovap 4160-HRGC*; injector temp. 220°; detector temp. 220° (FID); carrier gas: 0.5 bar H_2; temp. program: 3 min 85°, 4°/min until 180°. Anal. HPLC: *Kontron* HPLC system; UV detector *Uvikon LCD-75*, programmer *200*, integrator *Shimadzu C-R 1B Chromatopak*; *LiChrosorb Si-60* column (*Knauer* 7 μm, 250 × 4 mm). Prep. HPLC: *Knauer* HPLC system; pump type *64*, programmer *50*, UV detector variable-wavelength monitor, *LiChrosorb Si-60* column (*Knauer* 7 μm, 250 × 35 mm). Optical rotation: *Perkin-Elmer-241* polarimeter (10 cm, 1 ml cell). Circular dichroism (CD): *Jasco J-710*; recording from 190 to 250 nm at r.t.; 1-mm cell; average of 5 scans, corrected for the baseline; peptide concentration 0.2 mM; molar ellipticity θ in $deg \cdot cm^2 \cdot dmol^{-1}$ (λ in nm); smoothing by *Jasco* software. M.p.:

Büchi 510; uncorrected. ^{1}H-NMR: *Bruker-AMX-II-500* (500 MHz), *-AMX-400* (400 MHz), *-AMX-300* (300 MHz), or *Varian-Gem-200* (200 MHz) spectrometer. ^{13}C-NMR: *Bruker-AMX-II-500* (125 MHz), *-AMX-400*(100 MHz), *-AMX-300* (75 MHz), or *Varian-Gem-200* (50 MHz) spectrometer. Signals of epimers in italics. MS: *VG ZAB2-SEQ* spectrometer (FAB).

3. *General Procedures.* 3.1. *Carboxylation of Glycine Derivatives* (*GP 1*): To a soln. of DIPA (2.2 equiv.) and TMEDA (2.2 equiv.) in THF, BuLi (2.2 equiv.) was added at $-78°$ (dry ice). After 30 min stirring, a soln. of the glycine derivative (1 equiv.) in THF was added slowly ($T \leq -70°$), and stirring was continued for 1 h at $-78°$. Then, CO_2 was bubbled into the mixture through a needle for 1 h. The cooling bath was removed after 10 min, because the soln. became thick. The mixture was allowed to warm to r.t. and acidified to pH 1 with 1N H_2SO_4 soln. The two layers were separated, and the aq. layer was extracted twice with Et_2O. The combined org. layers were dried ($MgSO_4$), filtered, and evaporated. The obtained Ama-acid derivatives were used without further purification.

3.2. *Coupling with Isobutyl Chloroformate* (*GP 2*). To a soln. of the carboxy component (1 equiv.) in dry THF, NMM (1 equiv.) and isobutyl chloroformate (1 equiv.) were added at $-15°$. After 10 min, a cold (0°) soln. of the salt of the amino component (1 equiv.) and NMM (1 equiv.) in THF and DMF was added dropwise ($T \leq -10°$). After 30–60 min, the cooling bath was removed, and the soln. was warmed to r.t. Stirring was continued for 12 h. The mixture was then diluted with AcOEt and washed with 5% citric acid, sat. aq. $NaHCO_3$, and sat. aq. NaCl soln. All aq. layers were additionally extracted twice with AcOEt. The combined org. layers were dried ($MgSO_4$), filtered and evaporated.

3.3. *Coupling with DCC* (*GP 3*). To a soln. of the carboxy component (1 equiv.) and the salt of the amino component (1 equiv.) in THF at 0°, NMM (2 equiv.) was added. After 15 min, HOBt (1.1 equiv.) and DCC (1.1 equiv.) were added successively. After 1 h, the mixture was allowed to warm to r.t., and stirring was continued for 12 h. Then, the white precipitate was filtered off. Workup of the filtrate according to *GP 2*.

3.4. *Coupling with EDC* (*GP 4*). A stirred soln. of the amino-ester hydrochloride (1 equiv.) in THF under Ar was treated with NMM (1 equiv.) at 0° (ice bath). This mixture was added to a soln. of the carboxy component (1 equiv.) in THF and DMF. Then, HOBt (1.2 equiv.) and EDC (1.2 equiv.) were added successively. The mixture was allowed to warm at r.t., and stirring was continued for 12 h. Workup according to *GP 2*.

4. *Synthesis of the Starting Materials.* 4.1. *Synthesis of Boc-Leu-Ama(OMe)-Leu-OMe* (**1**). *Boc-Gly-OMe.* A colorless soln. of 20.0 g (115 mmol) of Boc-Gly-OH in 100 ml of Et_2O was treated with a soln. of CH_2N_2, until the soln. became yellow. Excess CH_2N_2 was destroyed by adding AcOH. Drying ($MgSO_4$) and evaporation gave 21.6 g (quant.) of Boc-Gly-OMe. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.46 (*s*, 9 H); 3.75 (*s*, 3 H); 3.92 (*d*, $J = 7$, 2 H); 5.08 (*m*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 28.32 (Me); 42.30 (CH_2); 52.24 (Me); 80.02 (C); 155.73 (C); 170.87 (C). FAB-MS: 190 (1, $[M+1]^+$), 134 (23), 90 (13), 67 (100).

Boc-Ama(OMe)-OH (**9**). According to *GP 1*, with DIPA (24.4 ml, 172 mmol), TMEDA (25.82 ml, 172 mmol), and BuLi (118.6 ml, 172 mmol) in THF (300 ml), and Boc-Gly-OMe (15.0 g, 85.7 mmol) in THF (100 ml). After workup 19.9 g (quant.) of **9** were obtained. Colorless oil. Used without further purifications. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.45 (*s*, 9 H); 3.8 (*s*, 3 H); 4.8, 5.0 (2 br. *s*, 1 H); 5.7 (br. *m*, 1 H); 7.7 (br. *m*, 1 H).

Boc-Ama(OMe)-Leu-OBn (**16**). According to *GP 3*, with **9** (19.9 g, 85.7 mmol), TsOH·H-Leu-OBn (34.48 g, 87.5 mmol), HOBt (13.41 g, 85.7 mmol), NMM (9.64 ml, 85.7 mmol), and DCC (18.97 g, 91.5 mmol) in THF (250 ml) and DMF (60 ml). FC (hexane/AcOEt 3:2): 30.85 g (73%) of **16**. White foam. ^{1}H-NMR (400 MHz, $CDCl_3$; 2 epimers): 0.88–0.95 (*m*, 6 H); 1.44, *1.45* (2*s*, 9 H); 1.54–1.69 (*m*, 3 H); 3.74, 3.79 (2*s*, 3 H); 4.60–4.68 (*m*, 1 H); 4.89–4.91 (*m*, 1 H); 5.11–5.19 (*m*, 2 H); 5.79–5.85 (*m*, 1 H); 6.86, *6.91* (2*d*, $J =$ 6.5, 8.0, 1 H); 7.29–7.39 (*m*, 5 H). ^{13}C-NMR (100 MHz, $CDCl_3$; 2 epimers): 21.77, *21.79* (Me); 22.76, *22.80* (Me); 24.77, *24.81* (CH); 28.21, *28.31* (Me); 41.12, *41.33* (CH_2); 51.35 (CH); 53.17, *53.21* (Me); 57.75, *57.85* (CH); 67.20 (CH_2); 80.00, *80.70* (C); 126.95, *127.54* (CH); 128.24, *128.47* (CH); 128.51, *128.62* (CH); 135.23 (C); 155.23, *155.73* (C); 164.82, *164.91* (C); 168.00, *168.11* (C); 171.97, *172.01* (C).

H-Ama(OMe)-Leu-OBn·HCl (**17**·HCl). To a soln. of **16** (15.0 g, 34.37 mmol) in Et_2O (30 ml), a sat. HCl/Et_2O soln. (100 ml) was added, and the mixture was stirred at r.t. for 12 h. After evaporation 13.24 g (quant.) of **17**·HCl were obtained. Yellow foam. ^{1}H-NMR (200 MHz, $CDCl_3$; 2 epimers): 0.81–0.95 (*m*, 6 H); 1.55–1.75 (*m*, 3 H); 3.74, *3.82* (2*s*, 3 H); 4.50–4.63 (*m*, 1 H); 5.05–5.25 (*m*, 3 H); 5.64–5.78 (*m*, 1 H); 7.27–7.43 (*m*, 5 H); 7.5, *8.0* (2*d*, $J = 8$, 1 H); 9.0 (br. *m*, 3 H). FAB-MS: 359 (1, $[M+23]^+$), 337 (100, $[M+1]^+$), 201 (9), 178 (7).

Boc-Leu-Ama(OMe)-Leu-OBn (**18**). According to *GP 2* with **17**·HCl (11.5 g, 34.2 mmol), Boc-Leu-OH·H_2O (8.72 g, 35 mmol), HOBt (4.73 g, 35 mmol), NMM (3.85 ml, 35 mmol), and DCC (8.3 g, 40 mmol) in THF (200 ml); 2 h at 0° and 20 h at r.t. FC (hexane/AcOEt 1:1): 13.34 g (82%) of **18**. White foam. ^{1}H-NMR (400 MHz, $CDCl_3$; 2 epimers): 0.88–0.95 (*m*, 12 H); 1.45 (*s*, 9 H); 1.56–1.72 (*m*, 6 H); 3.75, *3.79* (2*s*, 3 H);

4.15–4.20 (*m*, 1 H); 4.57–4.66 (*m*, 1 H); 4.82, *4.89* (2*d*, *J* = 7.5, 6.5, 1 H); 5.09–5.20 (*m*, 3 H); 6.93, *7.04* (2*d*, *J* = 8.0, 7.5, 1 H); 7.23–7.41 (*m*, 6 H). ^{13}C-NMR (100 MHz, $CDCl_3$; 2 epimers): 21.72 (Me); 21.77 (Me); 22.75 (Me); 23.00, *23.03* (Me); 24.77 (CH); 24.81 (CH); 28.28 (Me); 40.89 (CH_2); 41.22 (CH_2); 51.43, *51.36* (CH); 53.05 (CH); 53.22, *53.33* (Me); 56.49, *56.58* (CH); 67.20 (CH_2); 80.29 (C); 126.99, *127.63* (CH); 128.26, *128.31* (CH); 128.62, *128.64* (CH); 135.23, *135.32* (C); 155.57 (C); 164.25, *164.69* (C); 167.34, *167.42* (C); 171.86, *171.93* (C); 172.78, *172.90* (C). FAB-MS: 672 (39, $[M+23]^+$), 550 (27, $[M+1]^+$), 494 (34), 451 (29), 450 (91), 337 (92), 222 (29), 176 (41), 91 (100).

Boc-Leu-Ama(OMe)-Leu-OH (**19**). A suspension of **18** (10.66 g, 19 mmol), and 10% Pd/C (0.5 g) in MeOH (40 ml) was stirred at r.t. under H_2 (balloon) for 12 h. Filtration (*Celite*) and evaporation gave 8.94 g (quant.) of **19**. White foam. ^{1}H-NMR (500 MHz, $CDCl_3$; 2 epimers): 0.92–0.96 (*m*, 12 H); 1.45 (*s*, 9 H); 1.63–1.75 (*m*, 6 H); 3.49 (*s*, 3 H); 4.13, *4.28* (2*m*, 1 H); 4.57–4.62 (*m*, 1 H); 5.02–5.15 (*m*, 1 H); 5.32 (*d*, *J* = 6.0, 1 H); 7.15, *7.22* (2*d*, *J* = 7.0, 7.9, 1 H); 7.50–7.55 (br. *m*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$; 2 epimers): 21.74 (Me); 21.78 (Me); 22.85 (Me); 24.02 (Me); 24.74 (CH); 24.85 (CH); 28.28 (Me); 40.95 (CH_2); 41.30 (CH_2); 51.26, *51.38* (CH); 53.11, *53.40* (Me); 56.56, *56.72* (CH); 164.63 (C); 167.43 (C); 173.22 (C); 174.78 (C). FAB-MS: 482 (20, $[M+23]^+$), 460 (6, $[M+1]^+$), 404 (15), 360 (35), 247 (54), 132 (20), 86 (100).

Boc-Leu-Ama(OMe)-Leu-OMe (**1**). A soln. of **19** (8.94 g, 19 mmol) in Et_2O (150 ml) was treated with CH_2N_2 until the soln. became yellow. Excess CH_2N_2 was destroyed by adding some drops of AcOH. Drying ($MgSO_4$) and evaporation gave 8.97 g (quant.) of **1**. ^{1}H-NMR (300 MHz, CD_3OD; 2 epimers): 0.88–0.96 (*m*, 12 H); 1.43, *1.44* (2*s*, 9 H); 1.48–1.72 (*m*, 6 H); 3.70 (*s*, 3 H); 3.75, *3.77* (2*s*, 3 H); 4.13–4.17 (br. *m*, 1 H); 4.44–4.49 (*m*, 1 H); 4.55–4.9 (br. *m*, 1 H). ^{13}C-NMR (75 MHz, CD_3OD; 2 epimers): 21.59, *21.78* (Me); 23.22, *23.39* (Me); 25.80 (CH); 28.66 (Me); 41.39 (CH_2); 41.73 (CH_2); 52.49 (Me); 52.72 (CH); 53.49 (Me); 54.50 (CH); 57.68 (CH); 158.15 (C); 167.43 (CH); 168.86 (C); 174.07, *174.21* (C); 175.81 (C).

4.2. *Synthesis of Boc-Leu-Ama(OBn)-Leu-OMe* (**2**). *Boc-Ama(OBn)-OH* (**10**). According to *GP 1*, with DIPA (22.67 ml, 160 mmol), TMEDA (24.02 ml, 160 mmol), and BuLi (106.6 ml, 160 mmol) in THF (300 ml), and Boc-Gly-OBn (20.7 g, 78.5 mmol) in THF (100 ml). After workup, 25.3 g (quant.) of **10** were obtained. Colorless oil. Used without further purification. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.45 (*m*, 9 H); 4.8–4.9 (*m*, 1 H); 5.05 (*d*, *J* = 10, 1 H); 5.2–5.46 (*m*, 2 H); 5.6–5.7 (*m*, 1 H); 7.25–7.4 (*m*, 5 H).

Boc-Ama(OBn)-Leu-OMe (**20**). According to *GP 3*, with **10** (23.4 g, 78 mmol), TsOH·H-Leu-OMe (25.39 g, 80 mmol). NMM (8.81 ml, 80 mmol), and DCC (17.33 g, 85 mmol) in THF (300 ml) and DMF (100 ml). FC (hexane/AcOEt 2 : 1): 20.31 g (60%) of **20**. Colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$; 2 epimers): 0.84–0.96 (*m*, 6 H); 1.42, *1.43* (2*s*, 9 H); 1.47–1.67 (*m*, 3 H); 3.69, *3.71* (2*s*, 3 H); 4.54–4.61 (*m*, 1 H); 4.93–4.97 (*m*, 1 H); 5.17–5.28 (*m*, 2 H); 5.83 (*d*, *J* = 6.5, 1 H); 6.83, *6.90* (2*d*, *J* = 7.9, 7.5, 1 H); 7.31–7.38 (*m*, 5 H). ^{13}C-NMR (100 MHz, $CDCl_3$; 2 epimers): 21.73, *21.78* (Me); 22.69, *22.78* (Me); 24.70, *24.74* (CH); 28.21, *28.30* (Me); 41.16, *41.42* (CH_2); 51.16, *51.25* (CH); 52.34, *52.38* (Me); 57.95 (CH); 68.05, *68.15* (CH_2); 80.60 (C); 126.94, *127.48* (CH); 128.42, *128.47* (CH); 128.61, *128.65* (CH); 134.77 (C); 155.16 (C); 164.59 (C); 167.48, *167.59* (C); 172.51, *172.59* (C).

H-Ama(OBn)-Leu-OMe·HCl (**21**·HCl). To a soln. of **20** (9.00 g, 19.15 mmol) in 30 ml of Et_2O, a sat. HCl/Et_2O soln. (125 ml) was added, and the mixture was stirred at r.t. for 12 h. After evaporation, 7.01 g (quant.) of **21**·HCl were obtained. Yellow foam. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.80–1.00 (*m*, 6 H); 1.50–1.70 (*m*, 3 H); 3.60 (*s*, 3 H); 3.80–4.00 (*m*, 1 H); 4.35–4.50 (*m*, 1 H); 5.15–5.35 (*m*, 2 H); 5.65–5.85 (*m*, 1 H); 7.20–7.45 (*m*, 5 H); 8.25–9.00 (br. *m*, 3 H).

Boc-Leu-Ama(OBn)-Leu-OMe (**2**). According to *GP 2*, with **20** (14.68 g, 41 mmol), Boc-Leu-OH·H_2O (11.03 g, 45 mmol), NMM (5.04 ml, 45 mmol), and isobutyl chloroformate (5.98 ml, 45 mmol) in THF (300 ml). FC (hexane/AcOEt 3 : 1): 15.03 g (67%) of **2**. ^{1}H-NMR (400 MHz, $CDCl_3$; 2 epimers): 0.84–0.94 (*m*, 12 H); 1.43, *1.44* (2*s*, 9 H); 1.45–1.80 (*m*, 6 H); 3.69, *3.71* (2*s*, 3 H); 4.10–4.29 (*m*, 1 H); 4.52–4.58 (*m*, 1 H); 4.84, *4.93* (2*d*, *J* = 8.8, 8.8, 1 H); 5.11–5.27 (*m*, 3 H); 6.80–6.90 (*m*, 1 H); 7.15–7.25 (*m*, 1 H); 7.28–7.38 (*m*, 5 H). ^{13}C-NMR (100 MHz, $CDCl_3$; 2 epimers): 21.75 (CH_3); 21.77 (Me); 22.67, *22.75* (Me); 22.98, *23.05* (Me); 24.71 (CH); 24.74 (CH); 28.26, *28.27* (Me); 41.07, *41.20* (CH_2); 41.33, *41.39* (CH_2); 51.25, *51.36* (CH); 52.36, *52.40* (Me); 52.95, *53.08* (CH); 56.66, *56.74* (CH); 68.22, *68.33* (CH_2); 80.16, *80.32* (C); 128.39, *128.50* (CH); 128.54, *128.64* (CH); 128.68 (CH); 134.62, *134.67* (C); 155.55 (C); 164.15 (C); 166.79, *166.82* (C); 172.38, *172.50* (C); 172.76, *172.81* (C). FAB-MS: 572 (2, $[M+23]^+$), 550 (9, $[M+1]^+$), 494 (12), 450 (16), 337 (18), 146 (32), 91 (100).

4.3. *Synthesis of Ac-Leu-Ama(O^{t}Bu)-Leu-OMe* (**3**). *Z-Ama(O^{t}Bu)-OH* (**12**). According to *GP 1*, with DIPA (15.4 ml, 108 mmol), TMEDA (16.21 ml, 108 mmol), and BuLi (75 ml, 108 mmol) in THF (300 ml), and Z-Gly-OtBu (14.4 g, 54 mmol) in THF (100 ml). After workup, 16.9 g (quant.) of **12** were obtained. Colorless oil. Used without further purification. ^{1}H-NMR (200 MHz, $CDCl_3$; 2 epimers): 1.35–1.5 (br. *m*, 9 H); 4.8, *4.9* (2*d*, *J* = 8, 8, 1 H); 5.15 (*s*, 2 H); 5.85, *6.9* (2*d*, *J* = 8.0, 8.0, 1 H); 7.3–7.4 (*m*, 5 H); 7.6–7.8 (br. *m*, 1 H).

Z-Ama(O^{t}Bu)-Leu-OMe (**22**). According to *GP 3*, with **12** (16.7 g, 54 mmol), TsOH·H-Leu-OMe (17.45 g, 55 mmol), HOBt (7.35 g, 55 mmol), NMM (6 ml, 55 mmol), and DCC (12.4 g, 60 mmol) in THF (200 ml). FC (hexane/AcOEt 3:1): 16.27 g (69%) of **22**. ^{1}H-NMR (300 MHz, $CDCl_3$; 2 epimers): 0.8–1.0 (*m*, 6 H); 1.47, *1.50* (2*s*, 9 H); 1.5–1.75 (*m*, 3 H); 3.72, *3.73* (2*s*, 3 H); 4.55–4.7 (*m*, 1 H); 4.83 (*d*, *J* = 7.0, 1 H); 5.12 (*s*, 2 H); 5.95 (*m*, 1 H); 6.7–6.85 (br. *m*, 1 H); 7.3–7.45 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$; 2 epimers): 21.69, *21.81* (Me); 22.69 (Me); 24.67, *24.71* (CH); 27.70 (Me); 41.44, *41.52* (CH_2); 51.09 (Me); 52.28, *52.39* (CH); 58.57, *58.72* (CH); 67.11 (CH_2); 83.89, *84.22* (C); 127.87, *127.97* (CH); 128.09 (CH); 128.42 (CH); 136.05 (C); 155.84 (C); 161.43 (C); 165.84, *166.13* (C); 172.53, *172.57* (C). FAB-MS: 873 (3, $[2M+1]^+$), 739 (4), 459 (5, $[M+23]^+$), 437 (15, $[M+1]^+$), 381 (100), 336 (11).

H-Ama(O^{t}Bu)-Leu-OMe (**23**). A suspension of **22** (16.0 g, 36.8 mmol) and 10% Pd/C (0.4 g) in MeOH (60 ml) was stirred under H_2 for 12 h at r.t. After filtration (*Celite*) and evaporation, 10.9 g (quant.) of **23** were obtained. ^{1}H-NMR (200 MHz, $CDCl_3$; 2 epimers): 0.85–0.95 (*m*, 6 H); 1.46 (*s*, 9 H); 1.5–1.7 (*m*, 3 H); 2.20 (*s*, 2 H); 3.71, *3.72* (2*s*, 3 H); 4.04, *4.11* (2*s*, 1 H); 4.53–4.70 (*m*, 1 H); 7.35–7.5 (*m*, 1 H). FAB-MS: 605 (34, $[2M+1]^+$), 303 (38, $[M+1]^+$), 247 (100), 185 (31), 146 (60), 86 (71), 67.1 (61).

Ac-Leu-Ama(O^{t}Bu)-Leu-OMe (**3**). According to *GP 2*, with Ac-Leu-OH (6.58 g, 38 mmol), **23** (10.9 g, 36 mmol), NMM (4.18 ml, 38 mmol), and isobutyl chloroformate (4.96 ml, 38 mmol) in THF (170 ml). After workup, the combined org. layers were evaporated without further drying. The residue was stirred for 30 min in 50 ml of hot AcOEt. After cooling to r.t., the white precipitate was collected by filtration and then dried for 4 h under h.v.: 8.80 g (50%) of **3**. The filtrate was then cooled to $-20°$ (ice-NaCl bath), and additional 5.3 g (29%) of **3** could be isolated. The first fraction contained only one epimer, whereas the second fraction was a 1:1 mixture of the two possible epimers. Major isomer: $[\alpha]_D^{r.t.} = -42.6$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.92–0.94 (*m*, 12 H); 1.53 (*s*, 9 H); 1.48–1.7 (*m*, 6 H); 2.02 (*s*, 3 H); 3.72 (*s*, 3 H); 4.56–4.66 (*m*, 2 H); 5.01–5.03 (*m*, 1 H); 6.21 (br. *s*, 1 H); 7.01 (br. *s*, 1 H); 7.29 (br. *s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.94 (Me); 22.07 (Me); 22.76 (Me); 22.96 (Me); 23.14 (Me); 24.82 (CH); 27.80 (Me); 41.52 (CH_2); 51.24 (CH); 51.46 (CH); 52.32 (Me); 57.29 (CH); 84.29 (C); 164.50 (C); 165.45 (C); 170.04 (C); 172.18 (C); 172.60 (C). FAB-MS: 915 (10, $[2M+1]^+$), 457 (33, $[M+1]^+$), 401 (54), 306 (10), 246 (27), 202 (18), 155 (55), 153 (52), 127 (68), 85 (100).

4.4. *Synthesis of Boc-Leu-Aca-Leu-OMe* (**4**). N-*Boc-Aminoacetonitrile* (**14**). To a soln. of aminoacetonitrile hydrochloride (4.58 g, 50 mmol) in dioxane (100 ml), H_2O (50 ml), and 1N NaOH soln. (50 ml), Boc_2O (12.0 g, 55 mmol) was added at 0°. After 24 h stirring at r.t., the mixture was diluted with CH_2Cl_2. The aq. layer was extracted twice with 100 ml of CH_2Cl_2. The combined org. layers were washed twice with aq. sat. NaCl soln., dried ($MgSO_4$), and evaporated: 7.50 g (96%) of **14**. Colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.45 (*s*, 9 H); 4.06 (*d*, *J* = 5.7, 2 H); 5.11 (*s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 28.06 (Me); 28.94 (CH_2); 81.15 (C); 116.61 (C); 155.08 (C).

Boc-Aca-OH (**15**). According to *GP 1*, with DIPA (3.63 ml, 25.6 mmol), TMEDA (3.84 ml, 25.6 mmol), and BuLi (18.2 ml, 25.6 mmol) in THF (20 ml), and Boc-aminoacetonitrile (2.0 g, 12 mmol) in THF (10 ml). After workup, 2.32 g (90%) of **15** were obtained. Colorless oil. Used without purification. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.45 (*s*, 9 H); 5.00 (*s*, 0.5 H); 5.25 (*d*, 0.5 H); 5.80 (*d*, 0.5 H); 7.10 (*s*, 0.5 H); 10.1 (br. *s*, 1 H).

Boc-Aca-Leu-OMe (**24**). According to *GP 3*, with **15** (2.30 g, 11.0 mmol), TsOH·H-Leu-OMe (3.80 g, 12 mmol), HOBt (1.62 g, 12 mmol), NMM (1.32 ml, 12 mmol), and DCC (2.72 g, 13 mmol) in THF (20 ml; 16 h at r.t.). After workup and purification with FC (hexane/AcOEt 3:1), 1.92 g (51%) of **24** were obtained. ^{1}H-NMR (300 MHz, $CDCl_3$; 2 epimers): 0.92–0.94 (*m*, 6 H); 1.33 (*s*, 9 H); 1.58–1.88 (*m*, 3 H); 3.75 (*s*, 3 H); 4.58–4.65 (*m*, 1 H); 5.24 (br. *s*, 1 H); 5.79, *5.91* (2 br. *s*, 1 H); 7.00, *7.16* (2*d*, *J* = 7.8, 8.1, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.57 (Me); 22.59 (Me); 24.64 (CH); 28.01 (Me); 40.92 (CH_2); 45.76 (CH); 51.60 (CH); 52.58 (CH_2); 82.07 (C); 115.24 (C); 154.58 (C); 162.40 (C); 172.87 (C). FAB-MS: 655 (12, $[2M+1]^+$), 328 (21, $[M+1]^+$), 272 (100), 240 (6), 212 (49).

H-Aca-Leu-OMe·HCl (**25**·HCl). To a soln. of **24** (0.240 g, 0.73 mmol) in Et_2O (10 ml), a sat. HCl/Et_2O soln. (30 ml) was added, and the mixture was stirred at r.t. for 5 h. After evaporation, 0.19 g (98%) of **25**·HCl were obtained. White foam. ^{1}H-NMR (300 MHz, CD_3OD; 2 epimers): 0.89–0.99 (*m*, 6 H); 1.64–1.76 (*m*, 3 H); 3.732, *3.738* (2*s*, 3 H); 4.50–4.59 (*m*, 1 H); 4.65, *4.68* (2*s*, 1 H). ^{13}C-NMR (75 MHz, CD_3OD; 2 epimers): 21.54 (Me); 23.16, *23.22* (Me); 25.92, *25.98* (CH); 40.93, *41.38* (CH_2); 52.71, *52.89* (CH); 52.90, *53.06* (CH); 56.66, *56.64* (CH); 111.37 (C); 165.33 (C); 174.09, *174.57* (C).

Boc-Leu-Aca-Leu-OMe (**4**). According to *GP 2*, with Boc-Leu-OH·H_2O (0.180 g, 0.72 mmol), **25**·HCl (0.190 g, 0.72 mmol), NMM (0.16 ml, 1.44 mmol), and isobutyl chloroformate (0.10 ml, 0.72 mmol) in THF (5 ml) and DMF (5 ml). FC (hexane/AcOEt 1:1): 0.20 g (63%) of **4**. Light-yellow foam. ^{1}H-NMR (400 MHz, $CDCl_3$; 2 epimers): 0.91–0.96 (*m*, 12 H); 1.45 (*s*, 9 H); 1.50–1.74 (*m*, 6 H); 3.75, *3.78* (2*s*, 3 H); 4.21, *4.33*

(2 br. *m*, 1 H); 4.56–4.64 (*m*, 1 H); 5.12, *5.31* (2 br. *s*, 1 H); 5.46, *5.52* (2*d*, *J* = 5.7, 7.6, 1 H); 7.73 (br. *s*, 1 H); 7.80 (*d*, *J* = 7.2, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$; 2 epimers): 21.65, *21.80* (Me); 22.69, *22.77* (Me); 22.95 (Me); 23.00 (Me); 24.71, *24.76* (CH); 24.83 (CH); 28.31 (Me); 40.71, *40.79* (CH_2); 40.90, *41.02* (CH_2); 43.88 (CH); 44.39 (CH); 51.51, 51.77 (CH); 52.58, *52.71* (Me); 80.82 (C); 114.72, *115.04* (C); 155.97, *155.38* (C); 161.85, *162.03* (C); 172.48 (C); 173.32, *173.46* (C). FAB-MS: 1322 (2, $[3M+1]^+$), 881 (26, $[2M+1]^+$), 781 (15), 725 (14), 441 (29, $[M+1]^+$), 385 (61), 341 (100).

4.5. *Synthesis of Z-Val-Leu-Ama(O^{t}Bu)-Abu-Ile-OMe* (**5**). *Boc-Abu-Ile-OH*. A suspension of Boc-Abu-Ile-OBn (40.63 g, 0.1 mmol) and 10% Pd/C (0.54 g) in MeOH (200 ml) was stirred for 12 h under H_2 (balloon) at r.t. Filtration (*Celite*) and evaporation gave 31.56 g (99.7%) of Boc-Abu-Ile-OH. $[\alpha]_D^{r.t.} = +33.9$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.89–0.94 (*m*, 9 H); 1.16–1.26 (*m*, 1 H); 1.39–1.53 (*m*, 1 H); 1.43 (*s*, 9 H); 1.61–1.68 (*m*, 1 H); 1.78–1.85 (*m*, 1 H); 1.92–1.99 (*m*, 1 H); 4.09–4.11 (br. *m*, 1 H); 4.59 (*dd*, *J* = 4.9, 8.5, 1 H); 5.29–5.30 (br. *m*, 1 H); 6.91–7.00 (br. *m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.91 (Me); 11.54 (Me); 15.32 (Me); 24.84 (CH_2); 25.44 (CH_2); 27.91 (Me); 37.64 (CH_2); 55.73 (CH); 56.51 (CH); 80.26 (C); 156.02 (C); 172.48 (C); 174.75 (C). FAB-MS: 1290 (0.3, $[M+23]^+$), 993 (2, $[3M+23]^+$), 655 (28, $[2M+23]^+$), 339 (82, $[M+23]^+$), 317 (58, $[M+1]^+$), 261 (100), 217 (64).

Boc-Abu-Ile-OMe. A soln. of Boc-Abu-Ile-OH (31.00 g, 97.9 mmol) in Et_2O (150 ml) was treated with CH_2N_2, until a yellow color appeared. Excess CH_2N_2 was destroyed by adding a few drops of AcOH. Drying ($MgSO_4$) and evaporation gave 32.36 g (quant.) of Boc-Abu-Ile-OMe. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.83–0.93 (*m*, 9 H); 1.05–1.21 (*m*, 1 H); 1.40 (*s*, 9 H); 1.36–1.45 (*m*, 1 H); 1.54–1.70 (*m*, 1 H); 1.75–1.92 (*m*, 2 H); 3.68 (*s*, 3 H); 4.00–4.10 (*m*, 1 H); 4.53 (*dd*, *J* = 5.0, 8.5, 1 H); 5.18 (*d*, *J* = 7.5, 1 H); 6.65 (*d*, *J* = 7.5, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.87 (Me); 11.29 (Me); 15.29 (Me); 24.91 (CH_2); 25.39 (CH_2); 28.15 (Me); 37.68 (CH); 51.92 (Me); 55.62 (CH); 56.29 (CH); 79.75 (C); 155.59 (C); 171.84 (C); 172.10 (C). FAB-MS: 330 (0.4, $[M+1]^+$), 197 (7.9), 158 (11), 102 (37), 86 (16), 58 (100).

HCl · H-Abu-Ile-OMe (**26** · HCl). To a soln. of Boc-Abu-Ile-OMe (32.0 g, 99 mmol) in Et_2O (100 ml), a sat. HCl/Et_2O soln. (300 ml) was added, and the mixture was stirred at r.t. for 12 h. After evaporation, 25.73 g (quant.) of **26** · HCl were obtained. White foam. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.80–1.00 (br. *m*, 9 H); 1.20–1.55 (br. *m*, 2 H); 1.85–2.15 (br. *m*, 3 H); 3.67 (*s*, 3 H); 4.35–4.55 (br. *m*, 2 H); 8.15–8.30 (br. *m*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 8.94 (Me); 11.49 (Me); 15.44 (Me); 24.95 (CH_2); 25.28 (CH_2); 36.65 (CH); 51.91 (Me); 54.28 (CH); 57.72 (CH); 169.27 (C); 171.73 (C). FAB-MS: 691 (1, $[3M+1]^+$), 461 (23, $[2M+1]^+$), 231 (100, $[M+1]^+$), 154 (26), 146 (24), 137 (20), 136 (20).

Z-Ama(O^{t}Bu)-Abu-Ile-OMe (**27**). According to *GP 3*, with **12** (15.70 g, 50 mmol), **26** · HCl (14.67 g, 50 mmol), HOBt (7.43 g, 55 mmol), NMM (12.12 ml, 100 mmol), and DCC (11.35 g, 65 mmol) in THF (500 ml); 48 h at r.t. FC (AcOEt/hexane 1 : 2): 25.34 g (69%) of **27**. White foam. M.p. 125.4–127.6. ^{1}H-NMR (300 MHz, $CDCl_3$; 2 epimers): 0.85–0.95 (*m*, 9 H); 1.17–1.20 (*m*, 1 H); 1.30–1.50 (*m*, 1 H); 1.46 (*s*, 9 H); 1.60–1.78 (*m*, 1 H); 1.80–2.00 (*m*, 2 H); 3.70 (*s*, 3 H); 4.35–4.45 (*m*, 1 H); 4.52–4.60 (*m*, 1 H); 4.78–4.88 (*m*, 1 H); 5.13 (*s*, 2 H); 6.00–6.10 (*m*, 1 H); 6.40–6.55 (*m*, 1 H); 6.92, *7.02* (2*d*, *J* = 7.5, 7.5, 1 H); 7.28–7.40 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$; 2 epimers): 9.57 (Me); 11.57 (Me); 15.41 (Me); 25.02, *25.14* (CH_2); 26.03, *26.27* (CH_2); 27.72, *27.85* (Me); 37.87 (CH); 52.13 (Me); 54.58 (CH); 56.47, *56.54* (CH); 58.67, *58.81* (CH); 67.18 (CH_2); 83.90, *84.17* (C); 128.07 (CH); 128.46 (CH); 136.15 (C); 155.82, *155,88* (C); 164.7 (C); 165.75, *166.04* (C); 170.52, *170.55* (C); 172.14 (C). FAB-MS: 1043 (19, $[2M+1]^+$), 522 (66, $[M+1]^+$), 466 (100), 146 (26).

H-Ama(O^{t}Bu)-Abu-Ile-OMe (**28**). A suspension of **27** (24.66 g, 47.3 mmol), and 10% Pd/C (0.5 g) in MeOH (200 ml) was stirred under H_2 (balloon) at r.t. for 18 h. Filtration (*Celite*) and evaporation yielded 18.32 g (quant.) of **28**. ^{1}H-NMR (300 MHz, $CDCl_3$; 2 epimers): 0.85–0.93 (*m*, 9 H); 1.10–1.25 (*m*, 1 H); 1.30–1.5 (*m*, 1 H); 1.47, *1.48* (2*s*, 9 H); 1.62–1.72 (*m*, 1 H); 1.80–1.91 (*m*, 2 H); 2.01 (br. *m*, 2 H); 3.71 (*s*, 3 H); 4.01, *4.02* (2*s*, 1 H); 4.38–4.43 (*m*, 1 H); 4.52–4.56 (*m*, 1 H); 6.60–6.67 (*m*, 1 H); 7.44, *7.53* (2*d*, *J* = 8, 8, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$: 2 epimers): 9.58 (Me); 11.41 (Me); 15.33 (Me); 24.96 (CH_2); 25.62; *25.95* (CH_2); 27.70 (Me); 37.49 (CH); 51.90, *52.09* (CH_2); 54.06, *54.28* (CH); 56.39 (CH); 59.13 (CH); 82.81, *82.96* (C); 168.33, *168.40* (C); 169.24, *169.37* (C); 170.98 (C); 172.04 (C). FAB-MS: 775 (100, $[2M+1]^+$), 756 (88), 388 (23, $[M+1]^+$), 146 (82).

Z-Leu-Ama(O^{t}Bu)-Abu-Ile-OMe (**29**). According to *GP 2*, with Z-Leu-OH (13.26 g, 50 mmol), **28** (18.32 g, 47.3 mmol), NMM (11.0 ml, 100 mmol), and isobutyl chloroformate (6.53 ml, 50 mmol) in THF (400 ml) and DMF (20 ml). After workup and evaporation, the residue was stirred for 2 h in refluxing Et_2O. Filtration and drying of the solid gave 29.36 g (96%) of **29**. White amorpous solid. M.p. > 160° (dec.). ^{1}H-NMR (300 MHz, (D_6)DMSO; 2 epimers): 0.80–0.90 (*m*, 15 H); 1.12–1.24 (*m*, 1 H); 1.37, *1.37* (2*s*, 9 H); 1.41–1.89 (*m*, 7 H); 3.61, *3.61* (2*s*, 3 H); 4.11–4.24 (*m*, 1 H); 4.33–4.40 (*m*, 1 H); 4.97–5.10 (*m*, 3 H); 7.28–7.39

(*m*, 5 H); 7.48, *7.69* (2*d*, *J* = 8.5, 8.5, 1 H); 8.10 (*d*, *J* = 7.5, 0.3 H); 8.23–8.34 (*m*, 2 H); 8.51 (*d*, *J* = 8, 0.7 H). ^{13}C-NMR (75 MHz, (D_6)DMSO; 2 epimers): 9.67, *9.83* (Me); 11.01, *11.10* (Me); 15.31 (Me); 21.13 (Me); 22.91, *23.04* (Me); 24.12 (CH); 24.66, *24.79* (CH_2); 25.52 (CH_2); 27.31, *27.41* (Me); 36.06 (CH); 40.45 (CH_2); 51.44 (Me); 52.79, *53.08* (CH); 53.47, *53.56* (CH); 56.28, *56.42* (CH); 56.81 (CH); 65.27 (CH_2); 81.54, *81.76* (C); 127.42, *127.51* (CH); 127.63 (CH); 128.22 (CH); 136.98 (C); 155.83 (C); 164.80, *165.09* (C); 166.32, *166.48* (C); 170.95, *171.27* (C); 171.69 (C); 172.30, *172.50* (C). FAB-MS: 1269 (16, $[2M+1]^+$), 1135 (9), 657 (21, $[M+23]^+$), 635 (100, $[M+1]^+$), 579 (60), 305 (29), 231 (24), 176 (22), 154 (49), 146 (49).

H-Leu-Ama(O^{t}Bu)-Abu-Ile-OMe (**30**). A suspension of **29** (29.0 g, 44.8 mmol), and 10% Pd/C (1.5 g) in MeOH (400 ml) and DMF (100 ml) was stirred under H_2 (balloon) at r.t. for 12 h. After filtration (*Celite*) and evaporation, 23.06 g (quant.) of **30** were obtained. White powder. ^{1}H-NMR (300 MHz, $CDCl_3$; 2 epimers): 0.81–1.00 (*m*, 15 H); 1.09–1.28 (*m*, 1 H); 1.34–1.48 (*m*, 3 H); 1.48, *1.50* (2*s*, 9 H); 1.62–2.03 (*m*, 6 H); 3.42–3.48 (*m*, 1 H); 3.73 (*s*, 3 H); 4.40–4.47 (*m*, 1 H); 4.54–4.60 (*m*, 1 H); 4.99, *5.06* (2*d*, *J* = 7, 7.3, 1 H); 6.64, *6.67* (2*d*, *J* = 6.6, 8.4, 1 H); 7.16, *7.21* (2*d*, *J* = 7.9, 7.9, 1 H); 8.19, *8.26* (2*d*, *J* = 7, 7.3, 1 H). ^{13}C-NMR (85 MHz, $CDCl_3$; 2 epimers): 9.69 (Me); 11.56 (Me); 15.50 (Me); 21.36 (Me); 23.40 (Me); 24.81 (CH); 25.08, *25.20* (CH_2); 25.70, *25.86* (CH_2); 27.80, *27.90* (Me); 37.75 (CH); 43.81, *43.92* (CH_2); 52.14 (Me); 53.41 (CH); 54.83 (CH); 56.58 (CH); 57.04, *57.32* (CH); 83.87, *84.03* (C); 165.35 (C); 165.91 (C); 170.63 (C); 172.18 (C); 176.11, *176.26* (C). FAB-MS: 1001 (89, $[2M+1]^+$), 501 (100, $[M+1]^+$), 445 (67), 231 (33), 146 (81).

Z-Val-Leu-Ama(O^{t}Bu)-Abu-Ile-OMe (**5**). According to *GP 2*, with Z-Val-OH (12.54 g, 50 mmol), **30** (23.00 g, 44.8 mmol), NMM (11.0 ml, 50 mmol), and isobutyl chloroformate (6.53 ml, 50 mmol) in THF (350 ml) and DMF (100 ml). During the washing and extraction steps, a white precipitate appeared in the org. layers: 18.78 g (55%) of **5**. The aq. layers were extracted twice with 200 ml of AcOEt. The combined org. layers were dried ($MgSO_4$) and evaporated. The residue was stirred in 100 ml of AcOEt for 1 h at 60°. After cooling to r.t., 9.43 g (26%) of **5** were obtained. Total yield: 28.21 g (81%) of **5**. White powder. ^{1}H-NMR (300 MHz, (D_6)DMSO; 2 epimers): 0.80–0.89 (*m*, 21 H); 1.11–1.24 (*m*, 1 H); 1.35, *1.37* (2*s*, 9 H); 1.41–1.78 (*m*, 7 H); 1.92–1.98 (*m*, 1 H); 3.61, *3.61* (2*s*, 3 H); 3.84–3.89 (*m*, 1 H); 4.15–4.22 (*m*, 1 H); 4.32–4.53 (*m*, 2 H); 4.98–5.10 (*m*, 3 H); 7.28–7.36 (*m*, 6 H); 7.97, *8.07* (2*d*, *J* = 8, 8, 1 H); 8.23–8.32 (*m*, 1.5 H); 8.50 (*d*, *J* = 8, 0.5 H). ^{13}C-NMR (75 MHz, (D_6)DMSO; 2 epimers): 9.67, *9.80* (Me); 11.00, *11.10* (Me); 15.31 (Me); 18.00 (Me); 19.19 (Me); 21.21 (Me); 22.69, *23.11* (Me); 23.95 (CH); 24.66, *24.79* (CH_2); 25.54 (CH_2); 27.30, *27.41* (Me); 30.13, *30.20* (CH); 36.05 (CH); 40.59, *40.68* (CH_2); 50.46, *50.79* (CH); 51.46 (Me); 53.41, *53.53* (CH); 56.22, *56.42* (CH); 56.81 (CH); 60.13 (CH); 65.25 (CH_2); 81.47, *81.67* (C); 127.50 (CH); 127.63 (CH); 127.79 (CH); 128.22 (CH); 137.04 (C); 155.95 (C); 164.76, *164.99* (C); 166.27, *166.41* (C); 170.91, *170.98* (C); 171.27 (C); 171.67 (C); 171.95, *172.05* (C). FAB-MS: 1490 (9, $[2M+23]^+$), 1468 (10, $[2M+1]^+$), 756 (100, $[M+23]^+$), 734 (55, $[M+1]^+$), 678 (48), 656 (30), 600 (21), 404 (48), 347 (22), 231 (28), 176 (28), 146 (49).

4.6. *Synthesis of Boc-Val-Leu-Ama(OBn)-Abu-Ile-OMe* (**6**). *Boc-Ama(OBn)-Abu-Ile-OMe* (**31**). According to *GP 3*, with **10** (24.68 g, 80 mmol), **26** · HCl (24.20 g, 81 mmol), HOBt (11.4 g, 80 mmol), NMM (17.6 ml, 160 mmol), and DCC (18.5 g, 90 mmol) in THF (300 ml) and DMF (60 ml). FC (hexane/AcOEt 3 : 1): 28.07 g (67%) of **31**. White foam. ^{1}H-NMR (300 MHz, $CDCl_3$; 2 epimers): 0.73–0.90 (*m*, 9 H); 1.05–1.20 (*m*, 1 H); 1.40 (*s*, 9 H); 1.33–1.58 (*m*, 1 H); 1.60–1.75 (*m*, 1 H); 1.80–1.91 (*m*, 2 H); 3.70 (*s*, 1 H); 4.46–4.57 (*m*, 2 H); 5.00 (*d*, *J* = 7, 1 H); 5.10–5.26 (*m*, 2 H); 5.96 (*d*, *J* = 8, 1 H); 6.88–6.93 (*m*, 1 H); 7.22–7.26 (*m*, 1 H); 7.30–7.35 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$; 2 epimers): 9.31, *9.43* (Me); 11.42 (Me); 15.27 (Me); 24.98 (CH_2); 25.58 (CH_2); 28.09 (Me); 37.57 (CH); 51.99 (Me); 54.43, *54.58* (CH); 56.42 (CH); 57.89 (CH); 67.86, *67.96* (CH_2); 80.34, *80.41* (C); 128.13 (CH); 128.37 (CH); 128.43 (CH); 134.66 (C); 155.04 (C); 164.74, *164.98* (C); 167.41 (C); 170.47, *170.55* (C); 172.04 (C). FAB-MS: 1565 (2, $[3M+1]^+$), 1043 (52, $[2M+1]^+$), 522 (95, $[M+1]^+$), 466 (100), 146 (83).

HCl · H-Ama(OBn)-Abu-Ile-OMe (**32** · HCl). To a soln. of **31** (19.70 g, 37.0 mmol) in Et_2O (30 ml), a sat. HCl/Et_2O soln. (300 ml) was added, and the mixture was stirred at r.t. for 12 h. After evaporation, 16.76 g (quant.) of **32** · HCl were obtained. White foam. ^{1}H-NMR (300 MHz, $CDCl_3$; 2 epimers): 0.64–0.69 (*m*, 2 H); 0.77–0.88 (*m*, 7 H); 1.16–1.29 (*m*, 1 H); 1.30–1.45 (*m*, 1 H); 1.55–1.95 (*m*, 3 H); 3.59, *3.62* (2*s*, 3 H); 4.36–4.60 (*m*, 2 H); 5.09–5.28 (*m*, 2 H); 5.43, *5.55* (2 br. *s*, 1 H); 7.21–7.37 (*m*, 5.5 H); 7.65 (br. *d*, 0.5 H); 8.60–8.84 (br. *m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$; 2 epimers): 9.67, *9.81* (Me); 11.25, *11.39* (Me); 15.32, *15.38* (Me); 25.13, *25.31* (CH_2); 25.50, *25.73* (CH_2); 36.70, *37.11* (CH); 51.99 (Me); 55.75, *55.93* (CH); 56.69, *56.99* (CH); 69.02 (CH_2); 128.07 (CH); 128.32 (CH); 128.46 (CH); 134.09, *134.23* (C); 162.23, *162.45* (C); 164.43, *164.60* (C); 170.91, *171.53* (C); 172.24, *172.57* (C). FAB-MS: 843 (36, $[2M+1]^+$), 422 (100, $[M+1]^+$), 231 (32), 146 (65).

Boc-Leu-Ama(OBn)-Abu-Ile-OMe (**33**). According to *GP 2*, with Boc-Leu-OH · H_2O (9.97 g, 40 mmol), **32** (16.71 g, 37 mmol), NMM (8.8 ml, 80 mmol), and isobutyl chloroformate (5.3 ml, 40 mmol) in THF

(300 ml). After workup, 24.42 g (95%) of **33** were obtained. For anal. purposes, **33** was purified by FC (hexane/AcOEt 2:1). ^{1}H-NMR (300 MHz, $CDCl_3$; 2 epimers): 0.75–0.80 (*m*, 2 H); 0.84–0.92 (*m*, 13 H); 1.09–1.20 (*m*, 1 H); 1.30–1.55 (*m*, 2 H); 1.42 (*s*, 9 H); 1.55–1.75 (*m*, 3 H); 1.75–1.95 (*m*, 2 H); 3.72 (*s*, 3 H); 4.15–4.30 (*m*, 1 H); 4.35–4.50 (*m*, 1 H); 4.55–4.60 (*m*, 1 H); 5.10–5.28 (*m*, 3 H); 6.78, *6.83* (2*d*, *J* = 7.5, 7.5, 1 H); 7.10 (*d*, *J* = 7.5, 0.5 H); 7.28–7.36 (*m*, 5.5 H); 7.45–7.55 (br. *m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$; 2 epimers): 9.67, *9.89* (Me); 11.52 (Me); 15.40 (Me); 21.69, *21.84* (Me); 22.58 (Me); 24.66, *24.95* (CH); 25.12, *25.28* (CH_2); 25.45 (CH_2); 28.26 (Me); 37.66, *37.80* (CH); 41.25, *41.36* (CH_2); 52.10, *52.18* (Me); 52.91, *53.39* (CH); 55.03, *55.25* (CH); 56.42, *56.53* (CH); 56.74, *57.04* (CH); 68.14, *68.29* (CH_2); 80.01, *80.37* (C); 128.31 (CH); 128.54 (CH); 128.63 (CH); 134.66 (C); 155.72 (C); 164.41, *164.75* (C); 166.67, *166.80* (C); 170.62 (C); 172.14, *172.59* (C); 172.88, *173.02* (C). FAB-MS: 1269 (4, $[2M+1]^+$), 635 (22, $[M+1]^+$), 534(52), 433(26), 348(23), 230(37), 145(79), 90(100).

HCl · H-Leu-Ama(OBn)-Abu-Ile-OMe (**34** · HCl). A soln. of **33** (24.0 g, 37 mmol) in sat. HCl/Et_2O soln. (300 ml) was stirred at r.t. for 12 h and then evaporated to yield 21.11 g (quant.) of **34** · HCl. Yellow foam. ^{1}H-NMR (300 MHz, $CDCl_3$; 2 epimers): 0.71–0.96 (*m*, 15 H); 1.12–1.27 (*m*, 1 H); 1.33–1.43 (*m*, 1 H); 1.60–1.84 (*m*, 7 H); 3.69 (*s*, 9 H); 4.34–4.70 (*m*, 4 H); 5.03–5.23 (*m*, 2 H); 5.65–5.68 (br. *m*, 1 H); 7.24–7.37 (*m*, 5 H); 8.19–8.47 (br. *m*, 4 H). ^{13}C-NMR (85 MHz, $CDCl_3$; 2 epimers): 9.65, *9.94* (Me); 11.57 (Me); 15.51 (Me); 22.31 (Me); 22.49 (CH); 24.27 (CH); 25.22, *25.38* (CH_2); 25.73, *26.13* (CH_2); 37.20, *37.45* (CH); 40.35 (CH_2); 52.08, *52,57* (Me); 55.16 (CH); 56.68 (CH); 56.90, *56.98* (CH); 68.14, *68.36* (CH_2); 128.38 (CH); 128.63 (CH); 134.69 (C); 164.73 (C); 166.81 (C); 169.87, *170.07* (C); 171.23, *171.85* (C); 172.50 (C). FAB-MS: 1604 (2, $[3M+1]^+$), 1069 (29, $[2M+1]^+$), 535 (100, $[M+1]^+$), 390(7), 305(9), 231(15), 176(22), 146(26), 90(89), 86(88).

Boc-Val-Leu-Ama(OBn)-Abu-Ile-OMe (**6**). According to *GP 2*, with Boc-Val-OH (8.69 g, 40 mmol), **34** · HCl (21.11 g, 37 mmol), NMM (8.8 ml, 80 mmol), and isobutyl chloroformate (5.3 ml, 40 mmol) in THF (300 ml). FC (hexane/AcOEt 2:1): 23.95 g (85%) of **6**. Yellowish foam. ^{1}H-NMR (300 MHz, (D_6)DMSO; 2 epimers): 0.73–0.88 (*m*, 21 H); 1.14–1.19 (*m*, 1 H); 1.36 (*s*, 9 H); 1.40–1.82 (*m*, 7 H); 1.84–1.97 (*m*, 1 H); 3.60 (*s*, 3 H); 3.70–3.80 (*m*, 1 H); 4.15–4.22 (*m*, 1 H); 4.32–4.40 (*m*, 1 H); 4.40–4.58 (*m*, 1 H); 5.07–5.19 (*m*, 2 H); 5.25, *5.35* (2*d*, *J* = 7.6, 8.0, 1 H); 6.70, 6.74 (2*d*, *J* = 9.2, 9.3, 1 H); 7.28–7.38 (*m*, 5 H); 7.85, *7.96* (2*d*, *J* = 8.3, 8.4, 1 H); 8.16, *8.22* (2*d*, *J* = 7.7, 7.7, 1 H); 8.33, *8.52* (2*d*, *J* = *7.7, 8.0, 1* H); 8.47, *8.62* (2*d*, *J* = 8.0, 8.3, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$; 2 epimers): 9.26, *9.66* (Me); 11.42, *11.53* (Me); 15.16, *15.21* (Me); 18.04, *18.30* (Me); 19.12, *19.27* (Me); 22.12, *22.33* (Me); 22.77, *23.00* (Me); 24.45 (CH); 24.81, *25.03* (CH_2); 26.31, *26.57* (CH_2); 28.30 (Me); 31.31, *31.82* (CH); 37.59, *38.04* (CH); 42.30 (CH_2); 51.08 (CH); 52.01, *52.11* (Me); 54.01, *54.44* (CH); 56.02, *56.30* (CH); 56.35, *56.58* (CH); 59.5, *59.57* (CH); 67.06, *67.79* (CH_2); 78.90, *79.09* (C); 127.29, *127.88* (CH); 128.37, *128.47* (CH); 134.81, *134.09* (C); 155.78, *155.96* (C); 164.16, *165.17* (C); 166.50, *166.85* (C); 170.76, *171.12* (C); 171.66, *171.79* (C); 172.47, *172.63* (C); 172.76, *172.93* (C). FAB-MS: 1468 (15, $[2M+1]^+$), 1368(2), 734 (31, $[M+1]^+$), 533(17), 422(15), 231(15), 146(28), 116(16).

4.7. *Synthesis of Boc-Val-Leu-Ama(OAll)-Abu-Ile-OMe* (**7**). *Boc-Gly-OAll*. To a cold (0°) soln. of Boc-Gly-OH (8.75 g, 50 mmol) and allylic alcohol (3.8 ml, 55 mmol) in CH_2Cl_2 (100 ml), DMAP (0.610 g, 5 mmol) and DCC (11.34 g, 55 mmol) were added. A white precipitate appeared. After 3 h, the solid was filtered off. The org. soln. was washed with 50 ml of aq. sat. $NaHCO_3$ and sat. NaCl soln. The org. phase was dried ($MgSO_4$) and evaporated. After purification with FC (pentane/Et_2O 3:1), Boc-Gly-OAll (10.34 g, 96%) was obtained. Colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.37 (*s*, 9 H); 3.74 (*d*, *J* = 5.8, 2 H); 4.46–4.50 (*m*, 2 H); 5.06–5.26 (*m*, 2 H); 5.45 (br. *s*, 1 H); 5.72–5.92 (*m*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 27.76 (Me); 43.12 (CH_2); 65.47 (CH_2); 81.73 (C); 117.34 (CH_2); 132.58 (CH); 156.07 (C); 169.03 (C).

Boc-Ama(OAll)-OH (**11**). According to *GP 1*, with DIPA (2.9 ml, 20 mmol), TMEDA (3.06 ml, 20 mmol), and BuLi (14.61 ml, 20 mmol) in THF (60 ml), and Boc-Gly-OAll (2.0 g, 9.29 mmol) in THF (20 ml). After workup, 2.26 g (quant.) of **11** were obtained. Colorless oil. Used without further purification. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.44 (*s*, 9 H); 4.60–4.85 (*m*, 2 H); 5.05 (*m*, 0.5 H); 5.23–5.45 (*m*, 2 H); 5.60–5.70 (br. *d*, 0.5 H); 5.90–6.05 (*m*, 1 H); 7.50 (br. *s*, 1 H); 10.25 (br. *s*, 1 H).

Boc-Ama(OAll)-Abu-Ile-OMe (**35**). According to *GP 4*, with **11** (0.58 g, 2.3 mmol), **26** · HCl (0.508 g, 2.3 mmol), NMM (2.04 ml, 4.6 mmol), HOBt (0.76 g, 5 mmol), and EDC (0.955 g, 5 mmol) in THF (20 ml). FC (hexane/AcOEt 2:1): 0.688 g (65%) of **35**. White foam. R_f (AcOEt/hexane 1:1) 0.58. ^{1}H-NMR (400 MHz, $CDCl_3$: 2 epimers): 0.87–0.94 (*m*, 9 H); 1.08–1.21 (*m*, 1 H); 1.35–1.44 (*m*, 1 H); 1.443, *1.449* (2*s*, 9 H); 1.64–1.75 (*m*, 1 H); 1.85–1.96 (*m*, 2 H); 3.73, *3.74* (2*s*, 3 H); 4.37–4.44 (*m*, 1 H); 4.56, *4.57* (2*dd*, J_1 = 4.9, 8.5, J_2 = 4.9, 8.6, 1 H); 4.64–4.74 (*m*, 2 H); 4.92 (br. *m* 1 H); 5.24–5.28 (*m*, 1 H); 5.32–5.38 (*m*, 1 H); 5.80–5.82 (br. *m*, 1 H); 5.85–5.96 (*m*, 1 H); 6.50–6.52 (br. *m*, 1 H); 7.00–7.03 (br. *m*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$: 2 epimers): 9.46, *9.56* (Me); 11.50 (Me); 15.40 (Me); 25.04, *15.10* (CH_2); 25.53 (Me); 28.19 (Me);

37.73 (CH); 52.10 (Me); 54.70, *54.80* (CH); 56.48, *56.54* (CH); 57.93 (CH); 66.90, *66.96* (CH_2); 80.67 (C); 119.26, *119.51* (CH_2); 130.92, *131.01* (CH); 155.15 (C); 164.87, *165.07* (C); 167.22 (C); 170.38, *170.44* (C); 172.03 (C). FAB-MS: 1414 (4, $[3M+1]^+$), 943 (100, $[2M+1]^+$), 472 (50, $[M+1]^+$), 416 (32).

HCl · H-Ama(OAll)-Abu-Ile-OMe (**36** · HCl). In sat. HCl/Et_2O soln. (30 ml), **35** (0.650 g, 1.3 mmol) was disolved, and the mixture was stirred at r.t. for 4 h. After evaporation, 0.58 g (quant.) of **36** · HCl were obtained. White foam. ^{1}H-NMR (300 MHz, CD_3OD; 2 epimers): 0.87–1.03 (*m*, 9 H); 1.14–1.40 (*m*, 2 H); 1.40–1.60 (*m*, 1 H); 1.63–1.95 (*m*, 3 H); 3.71 (*s*, 3 H); 4.34–4.51 (*m*, 2 H); 4.70–4.95 (*m*, 3 H); 5.24–5.44 (*m*, 2 H); 5.88–6.08 (*m*, 1 H); 8.28, *8.50* (2*d*, *J* = 8.7, 7.9, 1 H); 8.64, *8.78* (2*d*, *J* = 7.9, 7.4, 1 H). ^{13}C-NMR (300 MHz, CD_3OD; 2 epimers): 10.35, *10.61* (Me); 11.79 (Me); 16.06 (Me); 26.43 (CH_2); 26.82, *26.89* (CH_2); 38.39, *38.42* (CH); 52.58 (Me); 56.43, *56.57* (CH); 58.42 (CH); 58.55 (CH); 68.96, *69.08* (CH_2); 120.17, *120.46* (CH_2); 132.48, *132.59* (CH); 163.57, *163.86* (C); 165.90 (C); 173.51, *173.75* (C); 174.30 (C). FAB-MS: 745 (26, $[2M+1]^+$), 373 (100, $[M+1]^+$), 199 (13).

Boc-Leu-Ama(OAll)-Abu-Ile-OMe (**37**). According to *GP 4*, with Boc-Leu-OH · H_2O (0.947 g, 3.8 mmol), **36** · HCl (1.50 g, 3.67 mmol), HOBt (0.518 g, 3.87 mmol), NMM (0.83 ml, 7.6 mmol), and EDC (0.747 g, 3.87 mmol) in THF (30 ml). FC (hexane/AcOEt 2 : 1): 1.37 g (66%) of **37**. White foam. ^{1}H-NMR (400 MHz, CD_3OD; 2 epimers): 0.87–0.98 (*m*, 15 H); 1.20–1.33 (*m*, 1 H); 1.44 (*s*, 9 H); 1.44–1.63 (*m*, 3 H); 1.65–1.74 (*m*, 2 H); 1.83–1.94 (*m*, 2 H); 3.696, *3.698* (2*s*, 3 H); 4.15–4.18 (br. *m*, 1 H); 4.31–4.38 (*m*, 2 H); 4.62–4.72 (*m*, 2 H); 5.19–5.24 (*m*, 2 H); 5.30–5.36 (*m*, 1 H); 5.87–5.97 (*m*, 1 H). ^{13}C-NMR (100 MHz, CD_3OD; 2 epimers): 10.50, *10.64* (Me); 11.73, *11.76* (Me); 14.45 (Me); 16.03, *16.05* (Me); 21.86, *21.94* (Me); 23.48 (Me); 23.71 (CH_2); 25.93 (CH); 26.34 (CH_2); 26.43, *26.46* (CH_2); 28.75 (Me); 32.76 (CH_2); 38.16, *38.35* (CH); 41.81, *41.95* (CH_2); 52.42 (Me); 54.45, *54.60* (CH); 56.23, *56.38* (CH); 58.25 (CH); 58.41 (CH); 80.74, *80.81* (C); 118.94, *119.14* (CH_2); 12.82, *132.89* (CH); 157.94 (C); 167.02, *167.54* (C); 167.96, *168.18* (C); 173.37, *173.45* (C); 173.53, *173.92* (C); 175.61, *175.67* (C). FAB-MS: 1169 (8, $[2M+1]^+$), 607 (17, $[M+23]^+$), 585 (75, $[M+1]^+$), 529 (24), 485 (100), 384 (34), 372 (16), 299 (46), 231 (24), 199 (23), 146 (56).

HCl · H-Leu-Ama(OAll)-Abu-Ile-OMe (**38** · HCl). In sat. HCl/Et_2O soln. (30 ml), **37** (1.351 g, 2.3 mmol) was dissolved, and the mixture was stirred at r.t. for 10 h. After evaporation, 1.166 g (quant.) of **38** · HCl were obtained. White foam. ^{1}H-NMR (400 MHz, CD_3OD; 2 epimers): 0.89–1.03 (*m*, 15 H); 1.21–1.28 (*m*, 1 H); 1.44–1.51 (*m*, 1 H); 1.65–1.82 (*m*, 4 H); 1.84–1.91 (*m*, 1 H); 3.70, *3.70* (2*s*, 3 H); 4.04–4.10 (*m*, 1 H); 4.33–4.40 (*m*, 2 H); 4.63–4.74 (*m*, 2 H); 5.20–5.38 (*m*, 3 H); 5.88–5.98 (*m*, 1 H); 8.17 (*d*, *J* = 8.2, 1 H); 8.27 (*d*, *J* = 8.0, 1 H). ^{13}C-NMR (100 MHz, CD_3OD; 2 epimers): 10.41, *10.61* (Me); 11.70, *11.76* (Me); 16.00, *16.03* (Me); 22.19, *22.25* (Me); 23.06, *23.12* (Me); 25.40 (CH); 26.37, *26.44* (CH_2); 26.61, *26.67* (CH_2); 38.27, *38.30* (CH); 38.35, *38.37* (CH); 41.62, *41.71* (CH_2); 52.44, *52.48* (Me); 52.82 (CH); 56.16, *56.20* (CH); 56.37, *56.41* (CH); 58.28, *58.37* (CH); 67.80, *67.93* (CH_2); 119.09, *119.33* (CH_2); 132.77, *132.85* (CH); 166.85, *167.05* (C); 167.71, *168.09* (C); 170.84, *170.86* (C); 173.37, *173.39* (C); 173.59, *173.61* (C); 173.96, *174.05* (C). FAB-MS: 970 (54, $[2M+1]^+$), 485 (100, $[M+1]^+$), 372 (7), 255 (11), 199 (19).

Boc-Val-Leu-Ama(OAll)-Abu-Ile-OMe (**7**). According to *GP 4*, with Boc-Val-OH (0.543 g, 2.5 mmol), **38** · HCl (1.14 g, 2.26 mmol), NMM (0.6 ml, 5.5 mmol), HOBt (0.421 g, 2.75 mmol), and EDC (0.527 g, 2.75 mmol) in THF (30 ml). FC (hexane/AcOEt 3 : 2): 1.49 g (97%) of **7**. White foam. ^{1}H-NMR (400 MHz, (D_6)DMSO; 2 epimers): 0.78–0.87 (*m*, 21 H); 1.09–1.28 (*m*, 1 H); 1.37 (*s*, 9 H); 1.37–1.51 (*m*, 4 H); 1.53–1.72 (*m*, 2 H); 1.74–1.80 (*m*, 1 H); 1.88–1.98 (*m*, 1 H); 3.614, *3.616* (2*s*, 3 H); 3.74–3.78 (br. *m*, 1 H); 4.15–4.22 (*m*, 1 H); 4.32–4.44 (*m*, 1 H); 4.46–4.62 (*m*, 4 H); 5.14–5.21 (*m*, 1 H); 5.26–5.33 (*m*, 2 H); 5.79–5.89 (*m*, 1 H); 6.68, *6.71* (2*d*, *J* = 9.3, 9.4, 1 H); 7,85, *7.94* (2*d*, *J* = 8.1, 8.2, 1 H); 8.12, *8.20* (2*d*, *J* = 7.9, 7.7, 1 H); 8.31 (*d*, *J* = 7.7, 0.5 H); 8.41–8.44 (*m*, 1 H); 8.59 (*d*, *J* = 8.3, 1 H). ^{13}C-NMR (D_6)DMSO; 2 epimers): 9.62, *9.73* (Me); 11.04, *11.12* (Me); 15.28, *15.31* (Me); 18.12, *19.18* (Me); 21.22, *21.29* (Me); 21.96, *22.29* (Me); 22.98, *23.13* (Me); 23.84 (CH); 24.67, *24.79* (CH_2); 25.61, *25.48* (CH_2); 28.05 (Me); 30.00, *30.10* (CH); 36.04, *36.09* (CH); 40.76 (CH_2); 50.32, *50.61* (CH); 51.46, *51.49* (Me); 53.50 (CH); 56.02, *56.24* (CH); 56.40 (CH); 59.64, *59.72* (CH); 65.23 (CH_2); 77.87 (C); 117.33, *117.47* (CH_2); 131.81 (CH); 155.25 (C); 164.58, *164.63* (C); 166.98, *167.17* (C); 170.84, *171.09* (CH); 171.17, *171.23* (C); 171.64 (C); 171.71 (C); 172.21, *172.31* (C). FAB-MS: 1367 (11, $[2M+1]^+$), 684 (39, $[M+1]^+$), 584 (100), 539 (10), 483 (26), 398 (37), 372 (38), 354 (20).

4.8. *Synthesis of Boc-Val-Ala-Leu-Ama(OMe)-Val-Ala-Leu-OMe* (**8**). *Boc-Ala-Leu-OBn*. According to *GP 2*, with Boc-Ala-OH (5.29 g, 28 mmol), TsOH · H-Leu-OBn (11.02 g, 28 mmol), NMM (6.17 ml, 56 mmol), and isobutyl chloroformate (3.66 ml, 28 mmol) in THF (60 ml), and DMF (20 ml). After workup, 11.03 g (quant.) of Boc-Ala-Leu-OBn were obtained. Colorless oil. $[\alpha]_D^{r.t.} = -46.6$ ($c = 1.05$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.88 (*d*, *J* = 6.2, 6 H); 1.30 (*d*, *J* = 7, 3 H); 1.41 (*s*, 9 H); 1.51–1.66 (*m*, 3 H); 4.18–4.25 (*m*, 1 H); 4.60–4.66 (*m*, 1 H); 5.19, 5.15 (2*AB*, J_{AB} = 12.0, 2 H); 5.25 (br. *d*, *J* = 6.5, 1 H); 6.82 (br. *d*, *J* = 6.4, 1 H); 7.30–7.36 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 18.06 (Me); 21.64 (Me); 22.67 (CH); 24.56 (Me); 28.15 (Me); 41.07

(CH_2); 50.65 (CH); 66.82 (CH_2); 70.83 (C); 128.02 (CH); 128.18 (CH); 128.40 (CH); 135.25 (C); 155.35 (C); 172.45 (C). FAB-MS: 785 (9, $[2M+1]^+$), 393 (50, $[M+1]^+$), 337 (87), 293 (43), 229 (13), 201 (10), 91 (100).

HCl · H-Ala-Leu-OBn. To a soln. of Boc-Ala-Leu-OBn (11.03 g, 28 mmol) in Et_2O (20 ml), sat. HCl/Et_2O soln. (150 ml) was added, and the mixture was stirred at r.t. for 12 h. After evaporation, 13 g (quant.) of HCl · H-Ala-Leu-OBn were obtained. Colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.75–1.00 (br. *m*, 6 H); 1.45–1.80 (br. *m*, 6 H); 4.30–4.55 (br. *m*, 2 H); 5.00–5.20 (br. *m*, 2 H); 7.20–7.35 (br. *m*, 5 H); 8.00–8.35 (br. *m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.85 (Me); 21.88 (Me); 22.67 (Me); 24.68 (CH); 39.96 (CH_2); 49.72 (CH); 51.94 (CH); 67.09 (CH_2); 128.23 (CH); 128.52 (CH); 135.30 (C); 170.10 (C); 172.28 (C).

Boc-Val-Ala-Leu-OBn. According to *GP 2*, with Boc-Val-OH (6.08 g, 28 mmol), HCl · H-Ala-Leu-OBn (9.13 g, 28 mmol) NMM (6.17 ml, 56 mmol), and isobutyl chloroformate (3.66 ml, 28 mmol) in THF (80 ml). FC (hexane/AcOEt 2 : 1): 11.11 g (87%) of Boc-Val-Ala-Leu-OBn. White solid. M.p. 136.9–138.0°. $[\alpha]_D^{r.t.} = -54.7$ ($c = 1.05$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.88–0.95 (*m*, 12 H); 1.35 (*d*, $J = 6.5$, 3 H); 1.44 (*s*, 9 H); 1.50–1.65 (*m*, 3 H); 2.05–2.17 (*m*, 1 H); 3.90–3.98 (*m*, 1 H); 4.50–4.65 (*m*, 2 H); 5.10–5.21 (*m*, 3 H); 6.70 (*d*, $J = 7.3$, 1 H); 6.79 (*d*, $J = 7.0$, 1 H); 7.30–7.40 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.66 (Me); 18.29 (Me); 19.15 (Me); 21.71 (Me); 22.68 (Me); 24.63 (CH); 28.24 (Me); 31.03 (CH); 41.00 (CH_2); 48.59 (CH); 50.83 (CH); 59.62 (CH); 66.90 (CH_2); 79.71 (C); 128.13 (CH); 128.25 (CH); 128.45 (CH); 135.34 (C); 155.82 (C); 171.51 (C); 171.94 (C); 172.45 (C). FAB-MS: 1475 (0.7, $[3M+1]^+$), 983 (20, $[2M+1]^+$), 492 (74, $[M+1]^+$), 436 (51), 392 (15), 293 (23), 222 (75), 91 (100).

Boc-Val-Ala-Leu-OH. A suspension of Boc-Val-Ala-Leu-OBn (2.50 g, 5.1 mmol) and 10% Pd/C (0.1 g) in MeOH (60 ml) was stirred under H_2 (balloon) at r.t. for 12 h. Filtration (*Celite*) and evaporation gave 2.01 g (quant.) of Boc-Val-Ala-Leu-OH. Anal. data in agreement with those reported in [32].

Boc-Val-Ala-Leu-OMe (**39**). To a soln. of Boc-Val-Ala-Leu-OH (2.01 g, 5.1 mmol) in Et_2O (60 ml), CH_2N_2 was added, until the color of the soln. became yellow. Excess CH_2N_2 was destroyed by adding a few drops of AcOH. Drying ($MgSO_4$) and evaporation gave 2.10 g (quant.) of **39**. White solid. Anal. data in agreement with those reported in [32]. M.p. 159.5–162°. $[\alpha]_D^{r.t.} = -47.2$ ($c = 1.9$, $CHCl_3$).

HCl · H-Val-Ala-Leu-OMe (**40** · HCl). To a soln. of **39** (2.74 g, 6.59 mmol) in Et_2O (20 ml), sat. HCl/Et_2O soln. (60 ml) was added and the mixture was stirred at r.t. for 12 h. After evaporation, 2.08 g (quant.) of **40** · HCl were obtained. White foam. Anal. data in agreement with those reported in [32].

Boc-Ama(OBn)-OMe (**13**). According to *GP 1*, with DIPA (7.0 ml, 50 mmol), TMEDA (7.5 ml, 50 mmol), BuLi (33.3 ml, 25.6 mmol) in THF (80 ml), and Boc-Gly-OBn (5.3 g, 20 mmol) in THF (60 ml). After workup, the org. layer was treated with CH_2N_2, until the soln. became yellow. Excess CH_2N_2 was destroyed by adding some drops of AcOH. Drying ($MgSO_4$), evaporation, and purification by FC (hexane/AcOEt 3 : 1) gave 5.04 g (78%) of **13**. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.43 (*s*, 9 H); 3.74 (*s*, 3 H); 5.03 (*d*, $J = 7.5$, 1 H); 5.17 (*AB*, $J_{AB} = 12.4$, 1 H); 5.27 (*AB*, $J_{AB} = 12.2$, 1 H); 5.55 (*d*, $J = 7$, 1 H); 7.33–7.35 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 28.14 (Me); 53.17 (Me); 57.39 (CH); 67.90 (CH_2); 80.70 (C); 128.05 (CH); 128.23 (CH); 128.52 (CH); 134.76 (C); 154.65 (C); 166.36 (C); 166.91 (C).

H-Ama(OMe)-OBn · HCl (**41** · HCl). To a soln. of **13** (4.90 g, 15.1 mmol) in Et_2O (10 ml), sat. HCl/Et_2O soln. (50 ml) was added, and the mixture was stirred at r.t. for 12 h. After evaporation, 3.89 g (quant.) of **41** · HCl were obtained. White oil. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.74 (*s*, 3 H); 5.16 (*m*, 3 H); 7.25–7.33 (*m*, 5 H); 8.40–9.50 (br. *s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 54.18 (Me); 55.82 (CH); 69.03 (CH_2); 128.29 (CH); 128.49 (CH); 134.38 (C); 163.42 (C); 163.79 (C).

Boc-Leu-Ama(OMe)-OBn (**42**). According to *GP 4*, with Boc-Leu-OH · H_2O (3.98 g, 16 mmol), **41** · HCl (3.70 g, 14.2 mmol), NMM (3.5 ml, 32 mmol), HOBt (2.16 g, 16 mmol), and EDC (3.45 g, 18 mmol) in THF (100 ml). FC (hexane/AcOEt 1 : 1): 6.44 g (97%) of **42**. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.90–0.94 (*m*, 6 H); 1.43 (*s*, 9 H); 1.43–1.51 (*m*, 1 H); 1.61–1.75 (*m*, 2 H); 3.74 (*s*, 3 H); 4.15–4.30 (br. *m*, 1 H); 4.85–4.93 (br. *m*, 1 H); 5.16–5.28 (*m*, 3 H); 7.15–7.21 (br. *m*, 1 H); 7.30–7.38 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.77 (Me); 22.93 (Me); 24.61 (CH); 28.22 (Me); 40.99 (CH_2); 52.68 (CH); 53.27 (Me); 56.21 (CH); 68.04 (CH_2); 80.25 (C); 128.10 (CH); 128.52 (CH); 128.55 (CH); 134.69 (C); 165.76 (C); 165.81 (C); 166.32 (C); 172.46 (C). FAB-MS: 873 (11, $[2M+1]^+$), 773 (3), 437 (58, $[M+1]^+$), 381 (100), 337 (80), 224 (30), 175 (21).

HCl · H-Leu-Ama(OMe)-OBn (**43** · HCl). A soln. of **42** (2.0 g, 4.56 mmol) in sat. HCl/Et_2O (30 ml) was stirred at r.t. for 12 h and then evaporated to yield 1.70 g (quant.) of **43** · HCl. ^{1}H-NMR (300 MHz, $CDCl_3$; 2 epimers): 0.89–0.99 (*m*, 6 H); 1.65–1.90 (*m*, 3 H); 3.69, *3.71* (2*s*, 3 H); 4.40–4.55 (br. *m*, 1 H); 5.10–5.36 (*m*, 3 H); 7.31 (*m*, 5 H); 8.25–8.45 (*m*, 4 H). ^{13}C-NMR (75 MHz, CD_3OD; 2 epimers): 22.22 (Me); 23.19 (Me); 25.39 (CH); 41.80 (CH_2); 52.88 (CH); 53.92 (Me); 57.80 (CH); 69.24 (CH_2); 129.64 (CH); 129.71 (CH); 129.94 (CH); 136.91 (C); 167.47, *167.53* (C); 168.03 (C); 171.24 (C). FAB-MS: 674 (5, $[2M+1]^+$), 338 (100, $[M+1]^+$), 306 (26), 288 (12), 154 (32).

Boc-Ala-Leu-Ama(OMe)-OBn (**44**). According to *GP 2*, with Boc-Ala-OH (0.87 g, 4.6 mmol), **43**·HCl (1.70 g, 4.56 mmol), NMM (1.01 ml, 9.2 mmol), and isobutyl chloroformate (0.6 ml, 4.6 mmol) in THF (80 ml), and DMF (10 ml). After workup, 2.25 g (97%) of **44** were obtained. ^{1}H-NMR (300 MHz, $CDCl_3$; 2 epimers): 0.87–0.93 (*m*, 6 H); 1.32, *1.33* (2*d*, *J* = 6.8, 6.8, 3 H); 1.42 (*s*, 9 H); 1.51–1.69 (*m*, 3 H); 3.744, *3.749* (2*s*, 3 H); 4.10–4.20 (*m*, 1 H); 4.50–4.57 (*m*, 1 H); 5.00 (*d*, *J* = 6.5, 1 H); 5.15–5.28 (*m*, 3 H); 6.63 (*d*, *J* = 6.8, 1 H); 7.17–7.19 (br. *m* 1 H); 7.31–7.39 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$; 2 epimers): 17.88 (Me); 21.75 (Me); 22.92 (Me); 24.54 (CH); 28.22 (Me); 40.56, *40.63* (CH_2); 49.95 (CH); 51.25 (CH); 53.27 (Me); 56.23 (CH); 68.04 (CH_2); 80.24 (C); 128.13 (CH); 128.53 (CH); 134.69 (C); 155.56 (C); 165.68 (C); 166.25 (C); 171.72 (C); 172.86 (C). FAB-MS: 1523 (1, $[3M+1]^+$), 1015 (67, $[2M+1]^+$), 508 (100, $[M+1]^+$), 452(98), 408(12), 229(52), 224(59), 201(33).

H-Ala-Leu-Ama(OMe)-OBn·HCl (**45**·HCl). A soln. of **44** (2.20 g, 4.34 mmol) in sat. HCl/Et_2O (100 ml) was stirred at r.t. for 10 h and then evaporated to yield 1.92 g (quant.) of **45**·HCl. ^{1}H-NMR (300 MHz, CD_3OD; 2 epimers): 0.90–0.97 (*m*, 6 H); 1.50 (*d*, *J* = 7.1, 3 H); 1.52–1.73 (*m*, 3 H); 3.73, *3.74* (2*s*, 3 H); 3.96–4.05 (*m*, 1 H); 4.53–4.59 (*m*, 1 H); 5.15–5.28 (*m*, 3 H); 7.31–7.36 (*m*, 5 H). ^{13}C-NMR (75 MHz, CD_3OD; 2 epimers): 17.82 (Me); 22.03 (Me); 23.50 (Me); 25.90 (CH); 41.86, *41.90* (CH_2); 50.03, *50.26* (CH); 53.07 (Me); 53.80 (CH); 57.77, *57.80* (CH); 69.11 (CH_2); 129.63 (CH); 129.85 (CH); 129.92 (CH); 136.97 (C); 167.65, *167.76* (C); 168.20, *168.31* (C); 171.43 (C); 174.68 (C). FAB-MS: 1222 (5, $[3M+1]^+$), 815 (60, $[2M+1]^+$), 408 (100, $[M+1]^+$), 337(10), 224(19), 185(47).

Boc-Val-Ala-Leu-Ama(OMe)-OBn (**46**). According to *GP 2*, with Boc-Val-OH (0.956 g, 4.4 mmol), **45**·HCl (1.90 g, 4.3 mmol), NMM (0.96 ml, 8.8 mmol), isobutyl chloroformate (4.5 ml, 4.4 mmol), and THF (70 ml). After workup, 2.45 g (94%) **46** were obtained. The residue was stirred in AcOEt for 1 h at 60°. 1.97 g (77%) of **46**. White solid. ^{1}H-NMR (300 MHz, $CDCl_3$; 2 epimers): 0.85–0.93 (*m*, 12 H); 1.34 (*d*, *J* = 7, 3 H); 1.42 (*s*, 9 H); 1.50–1.70 (*m*, 3 H); 2.04–2.13 (*m*, 1 H); 3.71, *3.74* (2*s*, 3 H); 4.00–4.10 (*m*, 1 H); 4.57–4.64 (*m*, 1 H); 4.68–4.73 (*m*, 1 H); 5.10–5.35 (*m*, 4 H); 6.97–7.06 (*m*, 2 H); 7.29–7.37 (*m*, 5 H); 7.52–7.61 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$; 2 epimers): 17.73 (Me); 18.50 (Me); 19.26 (Me); 22.02 (Me); 22.86, *22.89* (Me); 24.63, *24.65* (CH); 28.33 (Me); 30.98, *31.03* (CH); 41.05, *41.11* (CH_2); 48.78, *48.83* (CH); 51.36, *51.39* (CH); 53.22 (Me); 56.22, *56.26* (CH); 59.84 (CH); 67.99, *68.03* (CH_2); 79.89 (C); 128.09 (CH); 128.17 (CH); 128.52, *128.58* (CH); 134.86 (C); 156.05 (C); 165.86, *165.96* (C); 166.38, *166.49* (C); 171.70 (C); 172.02 (C); 172.28 (C). FAB-MS: 1820 (0.9, $[3M+1]^+$), 1213 (28, $[2M+1]^+$), 607 (100, $[M+1]^+$), 507(25), 384(16), 337(31), 328(44), 215(26).

Boc-Val-Ala-Leu-Ama(OMe)-OH (**47**). A mixture of **46** (1.012 g, 2.0 mmol), 10% Pd/C (50 mg), and MeOH (50 ml) was stirred under a H_2 (balloon) at r.t for 12 h. Filtration (*Celite*) and evaporation gave 1.04 g (quant.) of **47**. ^{1}H-NMR (300 MHz, (D_6)DMSO; 2 epimers): 0.78–0.88 (*m*, 12 H); 1.17–1.23 (*m*, 3 H); 1.37 (*s*, 9 H); 1.42–1.47 (*m*, 2 H); 1.54–1.65 (*m*, 1 H); 1.90–1.96 (*m*, 1 H); 3.61, *3.62* (2*s*, 3 H); 3.70–3.92 (*m*, 3 H); 4.30–4.42 (*m*, 2.5 H); 4.65–4.70 (br. *m*, 0.5 H); 6.73 (*d*, *J* = 8.9, 0.5 H); 7.85–7.99 (br. *m*, 1 H); 7.97 (*d*, *J* = 8.4, 0.5 H); 8.07–8.34 (*m*, 1.5 H). ^{13}C-NMR (75 MHz, (D_6)DMSO; 2 epimers): 17.85 (Me); 18.14, *18.30* (Me); 19.10 (Me); 21.32, *21.54* (Me); 22.92 (Me); 23.02 (Me); 23.99 (CH); 28.10 (Me); 30.33 (CH); 40.59, *40.99* (CH_2); 47.73 (CH); 50.41, *50.56* (CH); 50.66, *51.57* (CH); 52.28, *52.36* (Me); 56.41 (CH); 58.95, *59.41* (CH); 77.96 (C); 155.38 (C); 166.81 (C); 167.67, *167.80* (C); 170.10, *170.76* (C); 171.76, *171.86* (C); 171.95, *172.23* (C). FAB-MS: 1638(22), 1616(25), 1077(49), 1055 (46, $[2M+23]^+$), 539 (100, $[M+23]^+$), 517 (43, $[M+1]^+$), 443(21), 417(21), 395(35), 328(25), 247(35), 215(27), 117(45), 116(30).

Boc-Val-Ala-Leu-Ama(OMe)-Val-Ala-Leu-OMe (**8**). According to *GP 4*, with **47** (1.188 g, 2.3 mmol), **40**·HCl (0.809 g, 2.3 mmol), HOBt (0.31 g, 2.3 mmol), NMM (2.5 ml, 2.3 mmol), EDC (0.55 g, 2.8 mmol), and THF (100 ml); 1 h at 0° and 24 h at r.t. The mixture was concentrated under h.v., and the residue was stirred for 2 h in H_2O. The white precipitate was filtered off and washed with H_2O. The solid was then stirred for 2 h in AcOEt at 60°. Drying under h.v.: 0.973 g (50%) of **8**. White powder. ^{1}H-NMR (300 MHz, (D_6)DMSO; 2 epimers): 0.74–0.85 (*m*, 24 H); 1.14 (*d*, *J* = 6.8, 3 H); 1.16 (*d*, *J* = 7.1, 3 H); 1.34 (*s*, 9 H); 1.38–1.58 (*m*, 6 H); 1.87–1.95 (*m*, 2 H); 3.57 (*s*, 3 H); 3.59, *3.62* (2*s*, 3 H); 3.73–3.78 (*m*, 1 H); 4.15–4.44 (*m*, 5 H); 5.21, *5.33* (2*d*, *J* = 7.7, 8.1, 1 H); 6.69 (*d*, *J* = 8.7, 1 H); 7.81, *7.83* (2*d*, *J* = 7.7, 7.7, 1 H); 7.97, *7.99* (2*d*, *J* = 5.9, 7.4, 1 H); 8.06, *8.15* (2*d*, *J* = 8.4, 7.1, 1 H); 8.16 (*d*, *J* = 7.7, 1 H); 8.20, *8.27* (2*d*, *J* = 7.4, 8.4, 1 H); 8.35, *8.53* (2*d*, *J* = 7.8, 9.3, 1 H). ^{13}C-NMR (75 MHz, (D_6)DMSO; 2 epimers): 17.55, *17.76* (Me); 17.85, *17.95* (Me); 18.19 (Me); 18.89 (Me); 19.10 (Me); 21.14 (Me); 21.30 (Me); 21.37 (Me); 22.72 (Me); 22.97 (Me); 23.11 (Me); 23.99 (CH); 24.05 (CH); 28.11 (Me); 30.33 (CH); 30.80, *31.06* (CH); 40.68 (CH_2); 47.74 (CH); 50.11 (CH); 50.71 (CH); 51.81 (Me); 52.46 (Me); 56.15 (CH); 57.46 (CH); 59.45 (CH); 78.05 (C); 155.63, *155.66* (C); 165.28 (C); 168.20, *168.42* (C); 169.86 (C); 170.25, *171.04* (C); 172.14 (C); 172.40 (C); 172.52 (C); 173.11 (C). GC: 3.28 (L-Ala); 4.55 (L-Val); 5.16 (Gly); 7.75 (L-Leu).

5. *Alkylations. General Procedure* (*GP 5*). Dried LiBr (if used) and the peptide were dissolved in THF and cosolvent (if used). The soln. was cooled to 0° (ice bath) under Ar. Then, the base (NaOMe, as a soln in MeOH, or solid *t*-BuOK) was added. After 10 min, the appropriate electrophile (3 equiv.) was added. The mixture was worked up by addition of 1N HCl and AcOEt. The org. phases were washed twice with sat. aq. NaCl soln. All aq. layers were extracted twice with AcOEt. The combined org. phases were dried ($MgSO_4$) and evaporated.

5.1. *Alkylation* **1**. *Boc-Leu-(CO$_2$Me)Ala-Leu-OMe* (**48a/b**). According to *GP 5*, with **1** (1.50 g, 3.27 mmol), MeI (0.62 ml, 9.81 mol), NaOMe soln. (3.5 ml, 3.5 mmol), and THF (40 ml); 2.5 h. FC (hexane/AcOEt 1:1): 1.34 g (84%) of **48a/b** as a 1:1 mixture of epimers. ^{1}H-NMR (400 MHz, $CDCl_3$; 2 epimers): 0.84–0.96 (*m*, 12 H); 1.45 (*s*, 9 H); 1.48–1.72 (*m*, 6 H); 1.80 (*s*, 3 H); 3.71, *3.73* (2*s*, 3 H); 3.75, *3.77* (2*s*, 3 H); 4.04–4.13 (*m*, 1 H); 4.53–4.59 (*m*, 1 H); 4.88 (*m*, 1 H); 6.77, *6.84* (2*d*, *J* = 7, 7, 1 H); 7.46, *7.53* (2*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$; 2 epimers): 21.65, *21.68* (Me); 21.84, *21.95* (Me); 22.70, *22.79* (Me); 22.84 (Me); 22.97, *22.99* (Me); 24.66, *24.76* (CH); 24.85, *24.90* (CH); 28.26 (Me); 40.87 (CH_2); 51.29, *51.36* (CH); 52.36 (Me); 52.96 (Me); 53.35, *53.46* (CH); 62.75, *63.00* (C); 80.15, *80.32* (C); 155.57, *155.78* (C); 167.39, *167.63* (C); 170.87, *170.95* (C); 171.74 (C); 172.49, *172.58* (C). FAB-MS: 510 (67, $[M+23]^+$), 488 (68, $[M+1]^+$), 432(41), 388(25), 275(83), 146(55), 86(100).

Boc-Leu-(CO$_2$Me)Abu-Leu-OMe (**49a/b**). According to *GP 5*, with **1** (0.473 g, 1 mmol), EtI (0.25 ml, 3 mmol), NaOMe soln. (1.2 ml, 1.2 mmol), and THF (15 ml); 16 h. FC (hexane/AcOEt 2:1): 0.317 g (61%) of **49a/b** as a 1:1 mixture of epimers. ^{1}H-NMR (200 MHz, $CDCl_3$; 2 epimers): 0.7–0.85 (*m*, 3 H); 1.4 (*s*, 9 H); 1.4–1.8 (*m*, 6 H); 2.15–2.3 (*m*, 1 H); 2.4–2.6 (*m*, 1 H); 3.67, *3.69* (*s*, 3 H); 3.71, *3.74* (*s*, 3 H); 4.00–4.17 (*m*, 1 H); 4.45–4.60 (*m*, 1 H); 4.8–5.0 (br. *m*, 1 H); 6.65–6.85 (br. *m*, 1 H); 7.45, *7.55* (2*s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$; 2 epimers): 7.38, *7.51* (Me); 21.36, *21.60* (Me); 21.66, *21.80* (Me); 22.69 (Me); 22.82 (Me); 24.52, *24.66* (CH); 24.74 (CH); 26.23, *26.59* (CH_2); 28.12 (Me); *40.47*, 40.61 (CH_2); 40.73 (CH_2); 51.17 (CH); 52.23, *52.97* (Me); 53.07, *53.25* (Me); 66.84, *67.17* (C); 166.63, *166.89* (C); 170.68, *170.82* (C); 171.65, *171.70* (C); 172.52 (C); 172.65 (C). FAB-MS: 1003 (8, $[2M+1]^+$), 524 (14, $[M+23]^+$), 502 (100, $[M+1]^+$), 446(40), 402(12), 289(22), 115(12).

Boc-Leu-(Bu)Ama(OMe)-Leu-OMe (**50a/b**). According to *GP 5*, with **1** (0.473 g, 1 mmol), BuI (0.34 ml, 3 mmol), 1.2 ml of NaOMe soln. (1M in MeOH), and THF (15 ml); 10 h. FC (hexane/AcOEt 3:1): 0.164 g (31%) of **50a/b** as a 1:1 mixture of epimers. ^{1}H-NMR (200 MHz, $CDCl_3$; 2 epimers): 0.75–0.90 (*m*, 15 H); 0.90–1.65 (*m*, 10 H); 1.38, *1.39* (2*s*, 9 H); 2.05–2.25 (*m*, 1 H); 2.25–2.55 (*m*, 1 H); 3.64, *3.65*, 3.67, *3.70* (4*s*, 6 H); 3.95–4.15 (*m*, 1 H); 4.45–4.55 (*m*, 1 H); 4.85–5.00 (*m*, 1 H); 6.70–6.95 (*m*, 1 H); 7.40–7.55 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$; 2 epimers): 13.62 (Me); 21.25 (Me); 21.59 (Me); 21.75 (Me); 22.12 (Me); 22.65 (CH_2); 22.74 (Me); 24.44, *24.51* (CH); 24.62, *24.68* (CH); 25.11 (CH_2); 25.25 (CH_2); 25.37 (Me); 28.06 (Me); 32.87 (CH_2); 40.41, *40.57* (CH_2); 40.75 (CH_2); 51.09 (CH); 52.00, *52.15* (CH); 52.99 (Me); 53.15 (Me); 66.24, *66.59* (CH_2); 80.11, *80.38* (C); 155.51 (C); 166.67, 166.83, *166.96* (C); 170.66, *170.80* (C); 171.60, *171.69* (C); 172.45, *172.51* (C). FAB-MS: 1059 (2, $[2M+1]^+$), 530 (75, $[M+1]^+$), 474(35), 430(14), 317(59), 257(26), 144(100), 86(79).

Boc-Leu-(All)Ama(OMe)-Leu-OMe (**51a/b**). According to *GP 5*, with **1** (0.473 g, 1 mmol), allyl bromide (0.25 ml, 3 mmol), NaOMe soln. (1.2 ml, 1.2 mmol), and THF (15 ml); 3 h. FC (hexane/AcOEt 2:1): 0.417 g (81%) of **51a/b** as a 1:1 mixture of epimers. ^{1}H-NMR (400 MHz, $CDCl_3$; 2 epimers): 0.89–0.96 (*m*, 12 H); 1.45 (*s*, 9 H); 1.52–1.73 (*m*, 6 H); 3.00–3.09 (*m*, 1 H); 3.14–3.22 (*m*, 1 H); 3.71, *3.72* (2*s*, 3 H); 3.76, *3.78* (2*s*, 3 H); 4.10–4.13 (*m*, 1 H); 4.53–4.59 (*m*, 1 H); 4.85 (*d*, *J* = 7, 1 H); 5.09–5.14 (*m*, 2 H); 5.51–5.62 (*m*, 1 H); 6.83, *6.96* (2*d*, *J* = 9, 9, 1 H); 7.39, *7.45* (*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$; 2 epimers): 21.50, *21.64* (Me); 21.76, *21.88* (Me); 22.80, *22.82* (Me); 22.97 (Me); 24.68 (CH); 24.81 (CH); 28.26 (Me); 37.43, *37.77* (CH_2); 40.88 (CH_2); 40.92 (CH_2); 5.28 (CH); 52.32 (Me); 53.36 (Me); 53.47 (CH); 65.95 (C); 120.08, *120.40* (Me); 130.79, *131.11* (CH); 166.01, *166.40* (C); 170.06, *170.20* (C); 171.66 (C); 172.48 (C). FAB-MS: 536 (100, $[M+23]^+$), 514 (60, $[M+1]^+$), 458(33), 414(15), 313(27).

Boc-Leu-(CO$_2$Me)Phe-Leu-OMe (**52a/b**). According to *GP 5*, with **1** (0.473 g, 1 mmol), BnBr (0.35 ml, 3 mmol), NaOMe soln. (1.2 ml, 1.2 mmol), and THF (15 ml); 4 h. FC (hexane/AcOEt 1:1): 0.486 g (86%) of **52a/b** as a 1:1 mixture of epimers. ^{1}H-NMR (400 MHz, $CDCl_3$; 2 epimers): 0.90–0.87 (*m*, 12 H); 1.42 (*s*, 3 H); 1.55–1.71 (*m*, 6 H); 3.71–3.72 (*m*, 2 H); 3.73, *3.75* (2*s*, 3 H); 3.79, *3.81* (2*s*, 3 H); 4.02–4.06 (*m*, 1 H); 4.53–4.60 (*m*, 1 H); 4.79–4.80 (*m*, 1 H); 6.83, *7.17* (2*d*, *J* = 8, 8, 1 H); 7.00–7.05, *7.20–7.24* (2*m*, 5 H); 7.27, *7.34* (2*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$; 2 epimers): 21.38, *21.45* (Me); 21.60, *21.66* (Me); 22.86 (Me); 23.07 (Me); 24.67 (CH); 24.84 (CH); 28.22, *28.24* (Me); 37.65 (CH_2); 40.63 (CH_2); 41.67 (CH_2); 51.30, *51.36* (CH); 52.25, *52.35* (Me); 53.30, *53.45* (Me); 54.00 (CH); 67.59 (C); 80.65 (C); 127.14, *127.25* (CH); 128.29, *128.30* (CH); 129.89, *130.00* (CH); 135.36 (C); 155.97 (C); 166.51 (C); 170.03, *170.18* (C); 171.16, *171.58* (C); 172.45, *172.65* (C). FAB-MS: 586 (36, $[M+23]^+$), 564 (40, $[M+1]^+$), 508(23), 363(25), 291(25), 178(100).

Boc-Leu-(cyclohex-2-enyl)Ama(OMe)-Leu-OMe (**53a–d**). According to *GP 5*, with **1** (0.473 g, 1.0 mmol), cyclohex-2-enyl bromide (0.35 ml, 3 mmol), NaOMe soln. (1.2 ml, 1.2 mmol), and THF (15 ml); 3 h. FC (hexane/AcOEt 2:1): 0.436 g (79%) of **53a–d** as a mixture of four diastereoisomers. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.83–0.95 (*m*, 12 H); 1.44 (*s*, 9 H); 1.36–1.81 (*m*, 10 H); 1.95–2.05 (br. *m*, 2 H); 3.13–3.30 (*m*, 1 H); 3.70, 3.71, 3.71, 3.71, 3.73, 3.74, 3.77 (7*s*, 6 H); 4.10–4.20 (*m*, 1 H); 4.50–4.60 (*m*, 1 H); 4.82–4.92 (*m*, 1 H); 5.62–5.69 (*m*, 1 H); 5.0–6.00 (*m*, 1 H); 6.84–7.06 (4*s*, 1 H); 7.53, 7.63, 7.93, 8.05 (4*d*, 1 H). FAB-MS: 576.3 (22, $[M+23]^+$), 554.3 (88, $[M+1]^+$), 498(28), 341(61), 281(15), 259(13), 168(92), 146(43), 130(22), 108(26), 86(100), 56(94).

Boc-Leu-(CO_2Me)Glu(OMe)-Leu-OMe (**54a/b**). According to *GP 5*, with **1** (0.473 g, 1 mmol), methyl acrylate (0.27 ml, 3 mmol), and NaOMe soln. (0.15 ml, 0.3 mmol) in THF (20 ml); 3 h. FC (hexane/AcOEt 5:3): 0.504 g (90%) of **54a/b** as a 1:1 mixture of epimers. ^{1}H-NMR (400 MHz, $CDCl_3$; 2 epimers): 0.89–0.97 (*m*, 12 H); 1.44, *1.46* (2*s*, 9 H); 1.56–1.72 (*m*, 6 H); 2.13–2.26 (*m*, 1 H); 2.28–2.35 (*m*, 1 H); 2.54–2.66 (*m*, 1 H); 2.76–2.85 (*m*, 1 H); 3.65 (*s*, 3 H); 3.71, 3.73, 3.75, 3.79 (4*s*, 6 H); 4.04–4.11 (*m*, 1 H); 4.49–4.57 (*m*, 1 H); 4.85 (*m*, 1 H); 6.78, *6.92* (2*d*, $J=8$, 8, 1 H); 7.55, *7.68* (2*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$; 2 epimers): 21.57 (Me); 21.73 (Me); 22.80 (Me); 22.95, *23.01* (Me); 24.65, *24.81* (CH); 24.87, *24.90* (CH); 28.25 (Me); 28.39 (CH_2); 28.63 (CH_2); 40.55 (CH_2); 40.77 (CH_2); 51.40, *51.46* (CH); 51.83 (Me); 52.35 (Me); 52.41 (Me); 53.39, *53.53* (CH); 65.51, *65.90* (C); 80.18 (C); 166.15, *166.53* (C); 170.00, *170.24* (C); 171.90 (C); 172.33, *172.37* (C); 173.05 (C). FAB-MS: 582 (83, $[M+23]^+$), 560 (44, $[M+1]^+$), 460(26), 359(24), 347(27).

Boc-Leu-(CO_2Me)Glu(O^{t}Bu)-Leu-OMe (**55a/b**). According to *GP 5*, with **1** (0.473 g, 1 mmol), *tert*-butyl acrylate (0.27 ml, 3 mmol), and NaOMe soln. (0.15 ml, 0.3 mmol) in THF (20 ml); 2 h. FC (hexane/AcOEt 3:2): 0.515 g (86%) of **55a/b** as a 1:1 mixture of epimers. ^{1}H-NMR (400 MHz, $CDCl_3$; 2 epimers): 0.89–0.97 (*m*, 12 H); 1.42 (*s*, 9 H); 1.45, *1.46* (2*s*, 9 H); 1.55–1.73 (*m*, 6 H); 2.03–2.11 (*m*, 1 H); 2.13–2.27 (*m*, 1 H); 2.47–2.60 (*m*, 1 H); 2.66–2.77 (*m*, 1 H); 3.71, *3.72* (2*s*, 3 H); 3.75, *3.78* (2*s*, 3 H); 4.05–4.13 (*m*, 1 H); 4.50–4.58 (*m*, 1 H); 4.88–4.90 (*m*, 1 H); 6.93, *6.98* (2*d*, $J=8$. 7, 1 H); 7.61, *7.72* (2*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$; 2 epimers): 21.56 (Me); 21.78 (Me); 22.83 (Me); 22.96, *23.01* (Me); 24.64, *24.78* (CH); 24.84, *24.88* (CH); 28.06, *28.06* (Me); 28.28 (Me); 28.79, *28.96* (CH_2); 29.97, *30.03* (CH_2); 40.47, *40.58* (CH_2); 51.35, *51.46* (CH); 52.21, *52.33* (Me); 53.33 (Me); 53.47 (CH); 65.50, *65.87* (C); 80.07, *80.34* (C); 80.76 (C); 155.55, *155.71* (C); 166.35, *166.62* (C); 170.05 (C); 170.34, *170.38* (C); 171.94, *172.02* (C); 172.35, *172.38* (C). FAB-MS: 624 (59, $[M+23]^+$), 602 (63, $[M+1]^+$), 546(12), 446(48), 345(33), 333(39).

Boc-Leu-(CH_2CH_2CN)Ama(OMe)-Leu-OMe (**56a/b**). According to *GP 5*, with **1** (0.473 g, 1 mmol), acrylonitrile (0.20 ml, 3 mmol), and NaOMe soln. (0.15 ml, 0.3 mmol) in THF (20 ml); 2.5 h. FC (hexane/AcOEt 3:2): 0.47 g (89%) of **56a/b** as a 1:1 mixture of epimers. ^{1}H-NMR (400 MHz, $CDCl_3$; 2 epimers): 0.89–0.98 (*m*, 12 H); 1.46, *1.47* (2*s*, 3 H); 1.48–1.74 (*m*, 6 H); 2.21–2.38 (*m*, 2 H); 2.61–2.77 (*m*, 1 H); 2.89–2.97 (*m*, 1 H); 3.71, *3.74* (2*s*, 3 H); 3.78, *3.82* (2*s*, 3 H); 4.01–4.10 (*m*, 1 H); 4.50–4.56 (*m*, 1 H); 4.88, 4.94 (2*d*, $J=7$. 7, 1 H); 6.57, *6.96* (2*d*, $J=7$. 7, 1 H); 7.63, *7.69* (2*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$; 2 epimers): 11.85, *12.00* (CH_2); 21.49 (Me); 21.57 (Me); 22.78 (Me); 23.01 (Me); 24.71, *24.90* (CH); 24.95, *24.97* (CH); 28.24 (Me); 28.89 (CH_2); 40.07, *40.21* (CH_2); 40.34, *40.57* (CH_2); 51.51 (CH); 52.38, *52.58* (Me); 53.72, *53.90* (Me); 54.23 (CH); 65.29, *65.60* (C); 80.60, *81.00* (C); 118.56, *118,87* (C); 155.80, *156.12* (C); 165.26, *165.74* (C); 169.42, *169.54* (C); 171.89, *172.03* (C); 172.25, *172.34* (C). FAB-MS: 549 (25, $[M+23]^+$), 527 (80, $[M+1]^+$), 471(27), 427(86), 314(49).

Boc-Leu-($CH_2CH_2COCH_3$)Ama(OMe)-Leu-OMe (**54a/b**). According to *GP 5*, with **1** (0.236 g, 0.5 mmol), methyl vinyl ketone (0.13 ml, 1.5 mmol), and NaOMe soln. (0.07 ml, 0.15 mmol) in THF (20 ml); 0.75 h. FC (hexane/AcOEt 3:2): 0.192 g (70%) of **57a/b** as a 1:1 mixture of epimers. ^{1}H-NMR (200 MHz, $CDCl_3$; 2 epimers): 0.8–0.95 (*m*, 12 H); 1.41, *1.43* (2*s*, 9 H); 1.43–1.8 (*m*, 6 H); 2.0, *2.1* (2*s*, 3 H); 2.2–2.7 (*m*, 4 H); 3.68, *3.70* (2*s*, 3 H); 3.71, *3.75* (2*s*, 3 H); 4.0–4.2 (*m*, 2 H); 4.4–4.5 (*m*, 1 H); 4.8–4.95 (*m*, 1 H); 6.9, *7.0* (2*d*, $J=8$, 1 H); 7.5, *7.7* (2*s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$; 2 epimers): 21.44 (Me); 21.63 (Me); 21.85 (Me); 22.71 (Me); 22.84 (Me); 22.90 (Me); 24.52 (CH); 24.77 (CH); 27.66 (Me); 28.17 (Me); 29.69, *29.76* (CH_2); 37.57, *37.92* (CH_2); 40.30 (CH_2); 40.58 (CH_2); 51.34 (CH); 52.27 (Me); 53.25 (Me); 53.34 (CH); 65.28, *65.69* (C); 80.35 (C); 155.60 (C); 166.49, *166.80* (C); 169.98, *170.30* (C); 172.11 (C); 172.36 (C); 207 (C). FAB-MS: 1087 (6, $[2M+1]^+$), 566 (45, $[M+23]^+$), 544 (100, $[M+1]^+$), 488(15), 444(23), 342(19), 313(85), 299(14), 158(12).

Boc-Leu-($CHPhCH_2NO_2$)Ama(OMe)-Leu-OMe (**58a–d**). According to *GP 5*, with **1** (0.236 g, 0.5 mmol), nitro styrene (0.224 g, 1.5 mmol), and NaOMe soln. (0.07 ml, 0.15 mmol) in THF (20 ml); 4.5 h. FC (hexane/AcOEt 3:1): 0.178 g (57%) of **58a–d** as a mixture of four diastereoisomers. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.85–1.07 (*m*, 12 H); 1.41, *1.46* (2*s*, 3 H); 1.54–1.83 (*m*, 6 H); 3.69, *3.70* (2*s*, 3 H); 3.72, *3.73* (2*s*, 3 H); 3.99–4.13 (*m*, 1 H); 4.54–4.61 (*m*, 1 H); 4.76–4.94 (*m*, 2 H); 5.09 (*d*, $J=5$, 1 H); 5.32–5.53 (*m*, 1 H); 6.62, *6.78* (2*d*, $J=$

8, 8, 1 H); 7.09–7.42 (*m*, 5 H); 7.63, *7.65* (2*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.31, *21.38* (Me); 21.41, *21.47* (Me); 22.79, *22.89* (Me); 23.21, *23.38* (Me); 24.35, *24.66* (CH); 24.77, *24.91* (CH); 28.16, *28.25* (Me); 40.31 (CH_2); 40.45 (CH_2); 47.99 (CH); 51.20, *51.40* (CH); 51.48 (Me); 52.15 (Me); 53.77, *53.97* (CH); 68.17 (C); 77.80 (CH_2); 81.49 (C); 128.64 (CH); 128.78 (CH); 128.94 (CH); 134.29 (C); 164.37 (C); 168.51 (C); 172.20 (C); 172.87 (C). FAB-MS: 645 (15, $[M+23]^+$), 623 (23, $[M+1]^+$), 576 (810), 410 (44), 190 (45).

5.2. *Alkylation of* **2**. *Boc-Leu-(CO$_2$Bn)Ala-Leu-OMe* (**59a/b**). According to *GP 5*, with **2** (0.40 g, 0.72 mmol), MeI (0.14 ml, 2.1 mmol), and *t*-BuOK (106 mg, 0.94 mmol) in THF (15 ml); 2 h. FC (hexane/AcOEt 3:1): 0.324 g (80%) of **59a/b** as a 1:1 mixture of two epimers. ^{1}H-NMR (500 MHz, $CDCl_3$; 2 epimers): 0.82–0.97 (*m*, 12 H); 1.43 (*s*, 9 H); 1.44–1.65 (*m*, 6 H); 1.81, *1.82* (2*s*, 3 H); 3.69, *3.71* (2*s*, 3 H); 4.08–4.14 (*m*, 1 H); 4.51–4.55 (*m*, 1 H); 4.78, *4.84* (2*d*, $J=7$, 7, 1 H); 5.12–5.24 (*m*, 2 H); 6.63, *6.79* (2*d*, $J=8$, 8, 1 H); 7.29–7.39 (*m*, 5 H); 7.43, *7.56* (2*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$; 2 epimers): 21.69 (Me); 21.84 (Me); 22.73 (Me); 22.79, *22.83* (Me); 22.93, *23.02* (Me); 24.58, *24.73* (CH); 24.78, *24.85* (CH); 28.25, *28.27* (Me); 40.88 (CH_2); 40.95 (CH_2); 51.33 (CH); 52.33, *52.40* (Me); 52.78, *53.28* (CH); 62.78, *62.99* (C); 68.25, *68.30* (CH_2); 127.00, *127.67* (CH); 128.41, *128.46* (CH); 128.53, *128.57* (CH); 134.79, *134.89* (C); 167.31, *167.55* (C); 170.21 (C); 171.64 (C); 172.43, *172.52* (C). FAB-MS: 586 (22, $[M+23]^+$), 564 (17, $[M+1]^+$), 508 (14), 351 (21), 275 (14).

Boc-Leu-(CO$_2$Bn)Abu-Leu-OMe (**60a/b**). According to *GP 5*, with **2** (0.40 g, 0.72 mmol), LiBr (189 mg, 2.1 mmol), EtI (0.18 ml, 2.1 mmol), and *t*-BuOK (106 mg, 0.94 mmol) in THF (15 ml); 24 h. FC (hexane/AcOEt 3:1): 0.138 g (34%) of **60a/b** as a 2:1 mixture of epimers. ^{1}H-NMR (200 MHz, $CDCl_3$; 2 epimers): 0.7–0.8 (*m*, 3 H); 0.8–0.95 (*m*, 12 H); 1.43, *1.45* (2*s*, 9 H); 1.3–1.7 (*m*, 6 H); 2.15–2.3 (*m*, 1 H); 2.5–2.65 (*m*, 1 H); 3.69, *3.70* (2*s*, 3 H); 4.0–4.15 (*m*, 1 H); 4.5–4.6 (*m*, 1 H); 4.8, *4.9* (2br. *m*, 1 H); 5.1–5.3 (*m*, 2 H); 6.65, *6.78* (2br. *s*, 1 H); 7.25-7.35 (*m*, 5 H); 7.4, *7.6* (2*s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$; 2 epimers): 7.26, *7.39* (Me); 21.42, *21.73* (Me); 22.62, *22.72* (Me); 22.88 (Me); 24.40 (CH); 24.62 (CH); 26.40, *26.78* (Me); 28.08 (Me); 40.59 (CH_2); 40.71 (CH_2); 51.22 (CH); 52.20 (Me); 53.44 (CH); 66.81, *67.07* (C); 68.08, *68.17* (CH_2); 80.23 (C); 128.51 (CH); 134.92 (C); 155.50 (C); 166.48, *166.76* (C); 170.09 (C); 171.52, *171.62* (C); 172.44 (C). FAB-MS: 600 (12, $[M+23]^+$), 578 (100, $[M+1]^+$), 522 (54), 478 (15), 377 (24), 365 (37), 229 (12), 192 (16).

Boc-Leu-(All)Ama(OBn)-Leu-OMe (**61a/b**). According to *GP 5, with* ***2*** (0.40 g, 0.72 mmol), LiBr (189 mg, 2.1 mmol), allyl bromide (0.18 ml, 2.1 mmol), and *t*-BuOK (106 mg, 0.94 mmol) in THF (15 ml); 10 h. FC (hexane/AcOEt 2:1): 0.267 g (64%) of **61a/b** as a 2:1 mixture of epimers. ^{1}H-NMR (400 MHz, $CDCl_3$; 2 epimers): 0.83–0.95 (*m*, 12 H); 1.43 (*s*, 9 H); 1.40–1.72 (*m*, 6 H); 2.97–3.03 (*m*, 1 H); 3.19–3.24 (*m*, 1 H); 3.69, *3.70* (2*s*, 3 H); 4.08–4.11 (*m*, 1 H); 4.49–4.57 (*m*, 1 H); 4.81 (*m*, 1 H); 5.06–5.23 (*m*, 4 H); 5.43–5.59 (*m*, 1 H); 6.72, *6.90* (2*d*, $J=7.5$, 8, 1 H); 7.28–7.38 (*m*, 5 H); 7.45, *7.50*, (2*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$; 2 epimers): 21.55 (Me); 21.68 (Me); 22.74, *22.78* (Me); 22.92, *23.00* (Me); 24.59 (CH); 24.76 (CH); 28.27 (Me); 37.97 (CH_2); 40.92 (CH_2); 51.27, *51.32* (CH); 52.32 (Me); 52.90 (CH); 65.41, *65.89* (C); 68.30, *68.38* (CH_2); 80.06 (C); 120.09, *120.44* (CH_2); 127.00, *127.67* (CH); 128.41, *128.51* (CH); 128.53, *128.56* (CH); 130.61, *130.67* (CH); 134.73, *134.77* (C); 155.46 (C); 165.84, *166.26* (C); 169.47, *169.55* (C); 171.48, *171.61* (C); 172.43, *172.48* (C). FAB-MS: 612 (13, $[M+23]^+$), 590 (44, $[M+1]^+$), 534 (17), 389 (10), 377 (21), 204 (26).

Boc-Leu-(CO$_2$Bn)Phe-Leu-OMe (**62a/b**). According to *GP 5*, with **2** (0.40 g, 0.72 mmol), BnBr (0.26 ml, 2.1 mmol), and *t*-BuOK (106 mg, 0.94 mmol) in THF (15 ml); 4.5 h. FC (hexane/AcOEt 3:1): 0.326 g (70%) of **62a/b** (1:1). The two epimers were separated by FC (hexane/AcOEt 4:1).

Data of **62a**: R_f 0.25 (hexane/AcOEt 2:1). $[\alpha]_D^{rt} = -37.7$ ($c=1.0$, MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.84–0.93 (*m*, 12 H); 1.39 (*s*, 9 H); 1.46–1.71 (*m*, 6 H); 3.70 (*s*, 3 H); 3.70 (*AB*, $J_{AB}=14.1$, 1 H); 3.78 (*AB*, $J_{AB}=14.1$, 1 H); 3.99–4.06 (*m*, 1 H); 4.51 (*ddd*, $J=5.6$, 8.7, 8.7, 1 H); 4.74 (*d*, $J=5.3$, 1 H); 5.33 (*s*, 2 H); 6.87–6.89 (*m*, 2 H); 7.10–7.17 (*m*, 4 H); 7.34–7.39 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.46 (Me); 21.55 (Me); 22.82 (Me); 23.08 (Me); 24.80 (CH); 28.25 (Me); 37.87 (CH_2); 40.78 (CH_2); 51.46 (CH); 52.21 (Me); 53.93 (CH); 67.49 (C); 68.57 (CH_2); 80.63 (C); 127.07 (CH); 128.22 (CH); 128.64 (CH); 128.93 (CH); 130.00 (CH); 134.56 (C); 135.22 (C); 155.90 (C); 166.41 (C); 171.17 (C); 172.46 (C). FAB-MS: 1279 (12, $[2M+1]^+$), 663 (14, $[M+23]^+$), 640 (100, $[M+1]^+$), 584 (28), 540 (5), 427 (20), 291 (11), 254 (27).

Data of **62b**: R_f 0.28 (hexane/AcOEt 2:1). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.82–0.91 (*m*, 12 H); 1.40–1.61 (*m*, 6 H); 1.40 (*s*, 9 H); 3.58 (*AB*, $J_{AB}=14.2$, 1 H); 3.71 (*s*, 3 H); 3.81 (*AB*, $J_{AB}=14.2$, 1 H); 4.00–4.07 (*m*, 1 H); 4.55–4.60 (*m*, 1 H); 4.92 (*d*, $J=8.1$, 1 H); 5.10–5.22 (*m*, 2 H); 6.84 (*d*, $J=8.1$, 1 H); 6.96–6.99 (*m*, 2 H); 7.13–7.16 (*m*, 3 H); 7.25 (*s*, 1 H); 7.26–7.32 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.42 (Me); 21.52 (Me); 22.63 (Me); 22.90 (Me); 24.47 (CH); 28.11 (Me); 38.23 (CH_2); 40.58 (CH_2); 40.96 (CH_2); 51.10 (CH); 52.17 (Me); 52.89 (CH); 66.97 (C); 68.28 (CH_2); 79.91 (C); 127.02 (CH); 128.07 (CH); 128.43 (CH); 128.50 (CH); 129.93 (CH); 134.44 (C); 155.29 (C); 165.41 (C); 169.38 (C); 171.51 (C); 172.47 (C). FAB-MS: 1279 (11, $[2M+1]^+$), 640 (100, $[M+1]^+$), 584 (28), 540 (9), 427 (16), 291 (11), 254 (23).

Boc-Leu-(CO_2Bn)Glu(OMe)-Leu-OMe (**63a/b**). According to *GP 5*, with **2** (0.10 g, 0.18 mmol), methyl acrylate (0.05 ml, 54 mmol), and *t*-BuOK (10 mg, 0.08 mmol) in THF (15 ml); 5 h. FC (hexane/AcOEt 3:1): 96 mg (84%) of **63a/b** as a 5:1 mixture of epimers. ^{1}H-NMR (300 MHz, $CDCl_3$; 2 epimers): 0.82–0.90 (*m*, 12 H); 1.34–1.71 (*m*, 6 H); *1.42*, 1.43 (2*s*, 9 H); 2.05–2.18 (*m*, 1 H); 2.23–2.34 (*m*, 1 H); 2.51–2.64 (*m*, 1 H); 2.80–2.93 (*m*, 1 H); 3.63 (*s*, 3 H); 3.68, *3.70* (2*s*, 3 H); 4.06–4.12 (*m*, 1 H); 4.44–4.53 (*m*, 1 H); 4.77, *4.85* (2*d*, J = 5.9, 1 H); 5.11–5.25 (*m*, 2 H); *6.69*, 6.89 (2*d*, J = 8.0, 7.7, 1 H); 7.30–7.37 (*m*, 5 H); *7.50*, 7.71 (2*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$; 2 epimers): 21.62, *21.91* (Me); 22.75, *22.90* (Me); 23.04 (Me); 24.58, *24.79* (CH); 24.85 (CH); 28.26 (Me); 28.55 (CH_2); 28.78 (CH_2); 40.58 (CH_2); 40.78 (CH_2); 51.49 (CH); 51.76 (Me); 52.31 (Me); 53.63 (CH); 65.55, *65.87* (C); 68.39, *68.49* (CH_2); 80.44 (C); 128.57 (CH); 134.69, *134.76* (C); 155.70 (C); 166.03, *166.45* (C); 169.42 (C); 171.87 (C); 172.24, *172.31* (C); 173.02 (C).

Boc-Leu-(CO_2Bn)Glu(O^{t}Bu)-Leu-OMe (**64a/b**). According to *GP 5*, with **2** (0.276 g, 0.5 mmol), *tert*-butyl acrylate (0.22 ml, 1.5 mmol), and *t*-BuOK (16 mg, 0.13 mmol) in THF (15 ml); 2 h. FC (hexane/AcOEt 2:1): 0.324 g (95%) of **64a/b** as a 20:1 mixture of epimers. ^{1}H-NMR (300 MHz, $CDCl_3$; 2 epimers): 0.83–0.95 (*m*, 12 H); 1.40 (*s*, 9 H); 1.43 (*s*, 9 H); 1.51–1.66 (*m*, 6 H); 1.97–2.07 (*m*, 1 H); 2.15–2.25 (*m*, 1 H); 2.45–2.55 (*m*, 1 H); 2.72–2.82 (*m*, 1 H); 3.68, *3.70* (2*s*, 3 H); 4.06–4.10 (*m*, 1 H); 4.45–4.55 (*m*, 1 H); 4.77 (br. *d*, 1 H); 5.13 (*AB*, J_{AB} = 12.1, 1 H); 5.23 (*AB*, J_{AB} = 12.1, 1 H); 6.93 (*d*, J = 7, 1 H); 7.30–7.32 (*m*, 5 H); 7.74 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$; 2 epimers): 21.65 (Me); 22.78 (Me); 23.04 (Me); 24.76 (CH); 24.82 (CH); 28.06 (Me); 28.29 (Me); 29.00 (CH_2); 29.97 (CH_2); 40.66 (CH_2); 40.79 (CH_2); 51.47 (CH); 52.28 (Me); 53.59 (CH); 65.90 (C); 68.40 (Me); 80.35 (C); 80.72 (C); 128.54 (CH); 134.85 (CH); 155.65 (C); 166.54 (C); 169.49 (C); 171.92 (C); 172.31 (C). FAB-MS: 1355 (14, $[2M+1]^+$), 678 (100, $[M+1]^+$), 622(18), 566(17), 522(45), 420(23), 409(25), 377(24), 236(229, 146(27).

Boc-Leu-(CH_2CH_2CN)Ama(OBn)-Leu-OMe (**65a/b**). According to *GP 5*, with **2** (0.276 g, 0.5 mmol), acrylonitrile (0.10 ml, 1.5 mmol), and *t*-BuOK (16 mg, 0.13 mmol) in THF (15 ml); 3.5 h. FC (hexane/AcOEt 2:1): 0.266 g (88%) of **65a/b** as a 3:1 mixture of epimers.

Data of **65a** (major isomer): R_f 0.83 (hexane/AcOEt 1:1). $[\alpha]_D^{r.t.} = -40.1$ (c = 0.95, MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.82–0.88 (*m*, 12 H); 1.37–1.66 (*m*, 6 H); 1.43 (*s*, 9 H); 2.25–2.43 (*m*, 2 H); 2.57–2.67 (*m*, 1 H); 2.94–3.04 (*m*, 1 H); 3.72 (*s*, 3 H); 4.03 (*ddd*, J = 5.3, 7.4, 9.4, 1 H); 4.44–4.52 (*m*, 1 H); 4.89 (*d*, J = 7.3, 1 H); 5.17 (*s*, 2 H); 6.45 (*d*, J = 7.8, 1 H); 7.26–7.36 (*m*, 5 H); 7.54 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 11.71 (CH_2); 21.47 (Me); 21.73 (Me); 22.71 (Me); 22.89 (Me); 24.54 (CH); 24.79 (CH); 28.21 (Me); 29.26 (CH_2); 40.13 (CH_2); 40.27 (CH_2); 51.44 (CH); 52.60 (Me); 53.21 (CH); 65.21 (C); 68.73 (CH_2); 118.87 (C); 128.63 (CH); 128.76 (CH); 134.30 (C); 155.75 (C); 165.08 (C); 168.77 (C); 171.99 (C); 172.21 (C). FAB-MS: 1205 (1, $[2M+1]^+$), 603 (21, $[M+1]^+$), 547(15), 503(44), 390(3), 217(3), 146(15), 91(100).

Data of **65b** (minor isomer): R_f 0.81 (hexane/AcOEt 1:1). $[\alpha]_D^{r.t.} = -37.0$ (c = 0.4, MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.82–0.94 (*m*, 12 H); 1.25–1.68 (*m*, 6 H); 1.44 (*s*, 9 H); 2.11–2.35 (*m*, 2 H); 2.62–2.72 (*m*, 1 H); 2.90–3.00 (*m*, 1 H); 3.69 (*s*, 3 H); 3.97–4.04 (*m*, 1 H); 4.44–4.52 (*m*, 1 H); 4.78 (br. *d*, 1 H); 5.17 (*AB*, J_{AB} = 11.8, 1 H); 5.25 (*AB*, J_{AB} = 11.8, 1 H); 6.84 (*d*, J = 7.5, 1 H); 7.30–7.36 (*m*, 5 H); 7.70 (*s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 11.73 (CH_2); 21.29 (Me); 21.48 (Me); 22.59 (Me); 22.91 (Me); 24.72 (CH_2); 28.11 (Me); 28.65 (CH_2); 40.05 (CH_2); 40.52 (CH_2); 51.51 (CH); 52.27 (Me); 54.05 (C); 65.47 (C); 68.93 (CH_2); 80.90 (C); 118.61 (C); 128.70 (CH); 128.77 (CH); 128.83 (CH); 134.10 (C); 165.71 (C); 168.95 (C); 172.00 (C); 172.32 (C). Anal. calc. for $C_{31}H_{46}N_4O_8$: C 61.78, N 7.69, H 9.30; found: C 61.66, N 7.47, H 9.28.

Boc-Leu-(CH_2CH_2COMe)Ama(OBn)-Leu-OMe (**66a/b**). According to *GP 5*, with **2** (0.276 g, 0.5 mmol), methyl vinyl ketone (0.19 ml, 1.5 mmol), and *t*-BuOK (16 mg, 0.13 mmol) in THF (15 ml); 2 h. FC (hexane/AcOEt 3:1): 0.287 g (92%) of **66a/b** as a 2:1 mixture of epimers. ^{1}H-NMR (400 MHz, $CDCl_3$; 2 epimers): 0.83–0.95 (*m*, 12 H); 1.31–1.75 (*m*, 6 H); 1.42, *1.44* (2*s*, 9 H); 2.07, *2.09* (2*s*, 3 H); 2.22–2.55 (*m*, 3 H); 2.69–2.79 (*m*, 1 H); 3.68, *3.70* (2*s*, 3 H); 4.02–4.09 (*m*, 1 H); 4.43–4.51 (*m*, 1 H); 4.76, *4.82* (2 br. *m*, 1 H); 5.12–5.23 (*m*, 2 H); 6.76, *6.92* (2*d*, J = 6.5, 7.9, 1 H); 7.26–7.35 (*m*, 5 H); 7.43, *7.70* (2*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$; 2 epimers): 21.54 (Me); 21.57 (Me); 21.60, *21.84* (Me); 22.74 (Me); 22.89 (Me); 23.05 (Me); 24.54, *24.76* (CH); 24.83 (CH); 27.88 (CH_2); 28.00 (CH_2); 28.26 (Me); 29.75, *29.83* (CH); 37.58, *37.89* (CH_2); 40.46, *40.60* (CH_2); 40.71, *40.95* (CH_2); 51.47 (CH); 52.29, *52.37* (Me); 53.00 (CH); 53.68 (CH); 65.47, *65.77* (C); 68.32, *68.39* (CH_2); 80.36 (C); 128.55 (CH); 128.59 (CH); 128.62 (CH); 134.71, *134.80* (C); 155.72 (C); 166.40, 166.73 (C); 169.46, *169.65* (C); 171.89, *171.97* (C); 172.30 (C); 207.37, *207.46* (C). FAB-MS: 1240 (1, $[2M+1]^+$), 643 (2, $[M+23]^+$), 620 (32, $[M+1]^+$), 520(6), 389(33), 234(16), 146(14), 90(100), 86(45). Anal. calc. for $C_{32}H_{49}N_3O_9$: C 62.02, N 6.78, H 7.97; found: C 62.10, N 6.74, H 8.07.

5.3. *Alkylation of* **3**. *Ac-Leu-(CO_2^{t}Bu)Ala-Leu-OMe* (**67a/b**). According to *GP 5*, with **3** (0.10 g, 0.21 mmol), LiBr (57 mg, 0.65 mmol), MeI (0.04 ml, 0.63 mmol), and *t*-BuOK (35 mg, 0.25 mmol) in THF (15 ml); 4 h. FC (Et_2O): 91 mg (89%) of **67a/b** as a 12:1 mixture of epimers. ^{1}H-NMR (200 MHz, $CDCl_3$; 2

epimers): 0.8–0.95 (*m*, 12 H); 1.4 (*s*, 9 H); 1.4–1.7 (*m*, 6 H); 1.70 (*s*, 3 H); 2.00, *2.04 (2s*, 3 H); 3.66, *3.69* (2*s*, 3 H); 4.4–4.65 (*m*, 2 H); 6.35 (*d*, *J* = 8, 1 H); 6.85 (*d*, *J* = 8, 1 H); 7.45, *7.50* (2*s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 21.63 (Me); 21.92 (Me); 22.76 (Me); 22.96 (Me); 24.70 (CH); 27.48 (Me); 40.98 (CH_2); 41.26 (CH_2); 51.04 (CH); 51.50 (CH); 52.20 (Me); 63.32 (C); 83.41 (C); 168.03 (C); 169.04 (C); 170.34 (C); 171.30 (C); 172.73 (C). FAB-MS: 472 (7, $[M+1]^+$), 416(41), 261(19), 227(24), 156(33), 128(56), 85(100), 72.8(47).

Ac-Leu-(CO$_2$^{t}Bu)Abu-Leu-OMe (**68a/b**). According to *GP 5*, with **3** (0.20 g, 0.43 mmol), LiBr (113 mg, 1.31 mmol), EtI (0.11 ml, 1.31 mmol), and *t*-BuOK (70 mg, 0.56 mmol) in THF (15 ml); 24 h. FC (Et_2O): 0.073 g (35%) of **68a/b** as a 2:1 mixture of epimers. ^{1}H-NMR (300 MHz, $CDCl_3$; 2 epimers): 0.72–0.76 (*m*, 3 H); 0.87–0.95 (*m*, 12 H); 1.44, *1.46* (2*s*, 9 H); 1.21–1.69 (*m*, 6 H); 1.98, *2.01* (2*s*, 3 H); 2.15–2.24 (*m*, 1 H); 2.40–2.50 (*m*, 1 H); 3.70, *3.71* (2*s*, 3 H); 4.44–4.62 (*m*, 2 H); 5.94, *6.03* (2*d*, *J* = 8.1, 8.1, 1 H); 6.60, *6.70* (2*d*, *J* = 8.1, 8.1, 1 H); 7.27, *7.35* (2*s*, 1 H). ^{1}H-NMR (75 MHz, $CDCl_3$; 2 epimers): 7.32, *7.53* (Me); 21.39, *21.49* (Me); 21.83 (Me); 22.65, *22.73* (Me); 22.88 (Me); 24.50, *24.55* (CH); 24.63, *24.69* (CH); 26.31 (Me); 27.46 (Me); 40.81 (CH_2); 41.14, *41.21* (CH_2); 41.52 (CH_2); 50.98, *51.05* (CH); 51.58, *51.68* (Me); 51.26 (CH); 67.30, *67.47* (C); 83.27, *83.43* (C); 166.66, *167.03* (C); 168.77, *168.92* (C); 170.23, *171.04* (C); 172.59 (C); 172.70 (C). FAB-MS: 971 (6, $[2M+1]^+$), 486 (38, $[M+1]^+$), 430(100), 275(22), 241 (33), 156(31), 128(55), 85.9(84).

Ac-Leu-(All)Ama(O^{t}Bu)-Leu-OMe (**69a/b**). According to *GP 5*, with **3** (0.20 g, 0.43 mmol), LiBr (113 mg, 1.31 mmol), allyl bromide (0.11 ml, 1.31 mmol), and *t*-BuOK (70 mg, 0.56 mmol) in THF (15 ml); 12 h. FC (Et_2O): 0.103 g (48%) of **69a/b** as a 2:1 mixture of epimers.

Data of **69a**: R_f 0.41 (hexane/AcOEt 1:1). M.p. 118.3–120.5°. $[\alpha]_D^{r.t.} = -69.5$ (*c* = 0.92, MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.88–0.96 (*m*, 6 H); 1.45 (*s*, 9 H); 1.45–1.69 (*m*, 6 H); 2.02 (*s*, 3 H); 2.97 (*ABX*, J_{AB} = 14.4, J_{AX} = 7.2, 1 H); 3.13 (*ABX*, J_{AB} = 14.4, J_{AX} = 7.3, 1 H); 3.71 (*s*, 3 H); 4.45–4.54 (*m*, 1 H); 4.56–4.62 (*m*, 1 H); 5.07–5.13 (*m*, 2 H); 5.47 5.61 (*m*, 1 H); 5.95 (*d*, *J* = 7.9, 1 H); 6.79 (*d*, *J* = 8.3, 1 H); 7.32 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.68 (Me); 22.07 (Me); 22.87 (Me); 23.12 (Me); 24.76 (CH); 24.85 (CH); 27.67 (Me); 37.77 (CH_2); 41.24 (CH_2); 41.53 (CH_2); 51.17 (CH); 51.79 (CH); 52.27 (Me); 66.45 (C); 83.80 (C); 119.87 (CH_2); 131.25 (CH); 166.54 (C); 168.10 (C); 170.07 (C); 170.95 (C); 172.58 (C). FAB-MS: 498 (7, $[M+1]^+$), 442(37), 341(17), 281(139, 253(18), 207(15), 156(20), 147(29), 128(59), 72(100).

Data of **69b**: R_f 0.37 (hexane/AcOEt 1:1). M.p. 138.5–140.0°. $[\alpha]_D^{r.t.} = -52.5$ (*c* = 0.92, MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.93–1.00 (*m*, 12 H); 1.45 (*s*, 9 H); 1.40–1.68 (*m*, 6 H); 2.02 (*s*, 3 H); 2.97 (*ABX*, J_{AB} = 14.6, J_{AX} = 7.0, 1 H); 3.15 (*ABX*, J_{AB} = 14.6, J_{AX} = 7.0, 1 H); 3.71 (*s*, 3 H); 4.43–4.64 (*m*, 2 H); 5.06–5.08 (*m*, 1 H); 5.14 (*s*, 1 H); 5.45–5.62 (*m*, 1 H); 5.82 (*d*, *J* = 7.9, 1 H); 6.78 (*d*, *J* = 8.3, 1 H); 7.29 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.54 (Me); 21.92 (Me); 22.72 (Me); 23.00 (Me); 24.62 (CH); 24.72 (CH); 27.54 (Me); 37.67 (CH_2); 41.41 (CH_2); 51.06 (CH); 51.67 (CH); 52.20 (Me); 83.80 (C); 119.91 (CH_2); 131.27 (CH); 166.63 (C); 168.22 (C); 170.16 (C); 171.01 (C); 172.70 (C).

Ac-Leu-(CO$_2$^{t}Bu)Phe-Leu-OMe (**70a/b**). According to *GP 5*, with **3** (0.20 g, 0.43 mmol), LiBr (113 mg, 1.31 mmol), BnBr (0.15 ml, 1.31 mmol), and *t*-BuOK (70 mg, 0.56 mmol) in THF (15 ml); 10 h. FC (Et_2O): 0.157 g (66%) of **70a/b** as a 4:1 mixture of epimers.

Data of **70a**: R_f 0.52 (hexane/AcOEt 1:1). M.p. 135.5–137.5°. $[\alpha]_D^{r.t.} = -66.3$ (*c* = 0.80, MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.86–0.91 (*m*, 12 H); 1.45 (*s*, 9 H); 1.42–1.64 (*m*, 6 H); 1.96 (*s*, 3 H); 3.54 (*AB*, J_{AB} = 14.0, 1 H); 3.76 (*AB*, J_{AB} = 14.0, 1 H); 3.74 (*s*, 3 H); 4.31–4.39 (*m*, 1 H); 4.56–4.62 (*m*, 1 H); 6.08 (*d*, *J* = 7.8, 1 H); 6.75 (*d*, *J* = 8.4, 1 H); 7.01–7.04 (*m*, 2 H); 7.14 (*s*, 1 H); 7.16–7.20 (*m*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.79 (Me); 21.86 (Me); 22.83 (Me); 22.99 (Me); 23.10 (Me); 24.56 (C); 24.70 (CH); 27.70 (Me); 38.26 (CH_2); 41.33 (CH_2); 41.46 (CH_2); 51.25 (Me); 51.88 (CH); 52.43 (CH); 67.59 (C); 84.29 (C); 127.40 (CH); 128.40 (CH); 130.30 (CH); 135.33 (C); 166.29 (C); 168.62 (C); 170.47 (C); 171.50 (C); 173.01 (C). FAB-MS: 548 (18, $[M+1]^+$), 492(100), 400(10), 346(19), 336(34), 303(48), 293(27), 291(38).

Data of **70b**: R_f 0.43 (hexane/AcOEt 1:1). M.p. 161.0–162.5°. $[\alpha]_D^{r.t.} = -64.8$ (*c* = 1.03, MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.89–0.96 (*m*, 12 H); 1.46 (*s*, 9 H); 1.54–1.69 (*m*, 6 H); 1.97 (*s*, 3 H); 3.61 (*AB*, J_{AB} = 14.3, 1 H); 3.71 (*AB*, J_{AB} = 14.3, 1 H); 3.71 (*s*, 3 H); 4.39–4.46 (*m*, 1 H); 4.52–4.59 (*m*, 1 H); 5.76 (*d*, *J* = 7.4, 1 H); 6.83 (*d*, *J* = 8.1, 1 H); 7.03–7.06 (*m*, 2 H); 7.19–7.24 (*m*, 4 H). ^{13}C-NMR (40 MHz, $CDCl_3$): 21.66 (Me); 21.73 (Me); 22.74 (Me); 22.87 (Me); 23.00 (Me); 24.71 (CH); 27.57 (Me); 37.98 (CH_2); 40.96 (CH_2); 41.41 (CH_2); 51.28 (Me); 51.85 (CH); 52.17 (CH); 67.50 (C); 84.11 (C); 127.09 (CH); 128.11 (CH); 130.01 (CH); 135.25 (C); 166.65 (C); 168.14 (C); 170.17 (C); 170.80 (C); 172.49 (C). FAB-MS: 1095 (8, $[2M+1]^+$), 570 (6, $[M+23]^+$), 548 (30, $[M+1]^+$), 492(100), 303(10), 128(11).

Ac-Leu-(CO$_2$^{t}Bu)Glu(OMe)-Leu-OMe (**71a/b**). According to *GP 5*, with **3** (0.10 g, 0.21 mmol), LiBr (113 mg, 1.31 mmol), methyl acrylate (0.06 ml, 63 mmol), and *t*-BuOK (6 mg, 0.06 mmol) in THF (15 ml); 4 h. FC (Et_2O): 0.108 g (91%) of **71a/b** as a 4:1 mixture of epimers. The major isomer was isolated by precipitation from AcOEt/hexane.

Major isomer: R_f 0.39 (hexane/AcOEt 1:1). M.p. 138.8–140.2°. $[\alpha]_D^{r.t.} = -40.5$ ($c = 1.04$, MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.92–0.97 (*m*, 12 H); 1.45 (*s*, 9 H); 1.38–1.73 (*m*, 6 H); 2.03 (*s*, 3 H); 2.15 (*ddd*, $J = 6.0$, 10.1, 16.2, 1 H); 2.27 (*ddd*, $J = 6.2$, 9.2, 16.2, 1 H); 2.52 (*ddd*, $J = 6.0$, 9.6, 14.5, 1 H); 2.73 (*ddd*, $J = 6.1$, 10.1, 14.5, 1 H); 3.65 (*s*, 3 H); 3.70 (*s*, 3 H); 4.44–4.60 (*m*, 2 H); 5.89 (*d*, $J = 7.9$, 1 H); 6.89 (*d*, $J = 8.2$, 1 H); 7.56 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.67 (Me); 21.93 (Me); 22.78 (Me); 22.90 (Me); 23.10 (Me); 24.85 (CH); 27.60 (Me); 28.75 (CH_2); 28.86 (CH_2); 41.06 (CH_2); 41.23 (CH_2); 51.23 (CH); 51.83 (CH); 51.83 (Me); 52.26 (Me); 66.31 (C); 83.89 (C); 166.66 (C); 167.96 (C); 170.13 (C); 171.23 (C); 172.42 (C); 173.15 (C). FAB-MS: 544 (18, $[M+1]^+$), 488 (72), 333 (13), 299 (38), 287 (19), 159 (19), 128 (68), 85 (100). Anal. calc. for $C_{26}H_{45}N_3O_9$: C 57.44, H 8.34, N 7.73; found: C 57.22, H 8.39, N 7.67.

Ac-Leu-(CH_2CH_2CN)Ama(O^{t}Bu)-Leu-OMe (**72a/b**). According to *GP 5*, with **3** (0.202 g, 0.43 mmol), LiBr (113 mg, 1.3 mmol), acrylonitrile (0.18 ml, 2.1 mmol), and *t*-BuOK (14 mg, 0.14 mmol) in THF (15 ml); 2 h. FC (Et_2O): 0.202 g (91%) of **72a/b** as a 3:1 mixture of epimers. ^{1}H-NMR (400 MHz, $CDCl_3$; 2 epimers): 0.90–0.98 (*m*, 12 H); 1.44, *1.46* (2*s*, 3 H); 1.50–1.76 (*m*, 6 H); 2.02, *2.06* (2*s*, 3 H); 2.16–2.39 (*m*, 2 H); 2.51–2.66 (*m*, 1 H); 2.78–2.93 (*m*, 1 H); *3.71*, 3.74 (2*s*, 3 H); 4.39–4.47 (*m*, 1 H); 4.50–4.57 (*m*, 1 H); *5.94*, 6.02 (2*d*, $J = 7.1$, 7.7, 1 H); 6.50, *6.74* (2*d*, $J = 8.0$, 8.1, 1 H); 7.47, *7.56* (2*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$; 2 epimers): 11.90, *12.13* (CH_2); 21.40, *21.69* (Me); 21.89 (Me); 22.81, *22.85* (Me); 22.93, *22.99* (Me); 23.06 (Me); 24.75, *24.79* (CH); 24.91, *24.93* (CH); 27.58, *27.61* (Me); 28.70 (CH_2); 29.15 (CH_2); 40.24, *40.51* (CH_2); 40.78, *41.17* (CH_2); 51.40 (CH); 51.88 (CH); 52.38 (CH); 52.61 (Me); 84.45, *84.86* (C); 118.87, *119.20* (C); 165.65, *165.88* (C); 167.38, *167.72* (C); 170.48, *170.85* (C); 171.22, *171.30* (C); 172.36 (C). FAB-MS: 511 (8, $[M+1]^+$), 455 (29), 266 (11), 256 (12), 207 (14), 156 (32), 147 (41), 128 (51), 85 (78), 72 (100).

Ac-Leu-(CH_2CH_2COMe)Ama(O^{t}Bu)-Leu-OMe (**73a/b**). According to *GP 5*, with **3** (0.15 g, 0.32 mmol), LiBr (85.4 mg, 0.96 mmol), methyl vinyl ketone (0.08 ml, 0.96 mmol), and *t*-BuOK (10 mg, 0.07 mmol) in THF (15 ml); 2 h. FC (Et_2O): 0.151 g (88%) of **73a/b** as a 4:1 mixture of epimers. ^{1}H-NMR (300 MHz, $CDCl_3$; 2 epimers): 0.89–1.05 (*m*, 12 H); 1.45, *1.48* (2*s*, 9 H); 1.47–1.79 (*m*, 6 H); *1.98*, 2.04 (2*s*, 3 H); 2.13 (*s*, 3 H); 2.21–2.67 (*m*, 4 H); 3.70, *3.72* (2*s*, 3 H); 4.41–4.48 (*m*, 1 H); 4.51–4.58 (*m*, 1 H); 5.97 (*d*, $J = 7.6$, 1 H); 7.01 (*d*, $J = 8.1$, 1 H); 7.37, *7.61* (2*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$; 2 epimers): 21.72 (Me); 21.94 (Me); 22.82 (Me); 22.93 (Me); 23.11 (Me); 24.60, *24.88* (CH); 27.67 (Me); 27.96 (CH_2); 29.84 (Me); 38.16 (CH_2); 40.97 (CH_2); 41.14, *42.53* (CH_2); 51.27, *51.44* (CH); 52.08 (CH); 52.26 (Me); 66.35 (C); 83.77 (C); 167.06 (C); 168.07 (C); 170.30 (C); 171.43 (C); 172.51 (C); 207.85 (C). FAB-MS: 1055 (2, $[2M+1]^+$), 528 (17, $[M+1]^+$), 472 (38), 299 (24), 255 (37), 156 (22), 128 (52), 85 (100), 56 (35).

5.4. *Alkylation of* **5**. *Z-Val-Leu-(CO_2^{t}Bu)Ala-Abu-Ile-OMe* (**74a/b**). According to *GP 5*, with **5** (0.200 g, 0.27 mmol), MeI (0.05 ml, 0.81 mmol), and *t*-BuOK (40 mg, 0.35 mmol) in THF (20 ml) and DMPU (2.5 ml); 6 h. FC (hexane/AcOEt 2:1): 0.18 g (88%) of **74a/b** as a 5:1 mixture of epimers. Separated by HPLC (hexane/i-PrOH 96.5:3.5).

Data of **74a**: R_f 0.31 (hexane/AcOEt 1:1). t_R 9.96 min (hexane/i-PrOH 96.5:3.5). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.85–0.95 (*m*, 21 H); 1.12–1.27 (*m*, 1 H); 1.36–1.53 (*m*, 2 H); 1.43 (*s*, 9 H); 1.60–1.67 (*m*, 3 H); 1.70 (*s*, 3 H); 1.81–1.93 (*m*, 2 H); 2.06–2.14 (*m*, 1 H); 3.70 (*s*, 3 H); 3.98–4.02 (*m*, 1 H); 4.46–4.48 (*m*, 1 H); 4.57 (*dd*, $J = 5.4$, 8.5, 1 H); 4.55–4.61 (*m*, 1 H); 5.05–5.12 (*m*, 2 H); 5.59 (br. *d*, 1 H); 6.52 (*d*, $J = 7.2$, 1 H); 6.72 (*d*, $J = 7.7$, 1 H); 7.11 (br. *d*, 1 H); 7.28–7.36 (*m*, 5 H); 7.66 (*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 9.90 (Me); 11.47 (Me); 15.42 (Me); 17.79 (Me); 19.33 (Me); 21.52 (Me); 22.13 (Me); 22.83 (Me); 24.66 (CH); 25.13 (CH_2); 25.06 (CH_2); 27.67 (Me); 31.08 (CH); 37.70 (CH); 41.37 (CH_2); 51.55 (CH); 52.13 (Me); 54.80 (CH); 56.52 (CH); 60.50 (CH); 63.48 (C); 67.00 (CH_2); 83.37 (C); 127.97 (CH); 128.15 (CH); 128.53 (CH); 136.31 (C); 156.52 (C); 167.84 (C); 168.80 (C); 170.86 (C); 170.95 (C); 171.63 (C); 172.61 (C). FAB-MS: 1495 (10, $[2M+1]^+$), 770 (42, $[M+23]^+$), 748 (92, $[M+1]^+$), 692 (64), 518 (24), 503 (32), 462 (35), 418 (100), 347 (57), 284 (36).

Data of **74b**: M.p. 77.0–80.0°. R_f 0.31 (hexane/AcOEt 1:1). t_R 12.35 min (hexane/i-PrOH 96.5:3.5). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.84–0.97 (*m*, 21 H); 1.13–1.35 (*m*, 1 H); 1.36–1.52 (*m*, 1 H); 1.44 (*s*, 9 H); 1.60–1.78 (*m*, 2 H); 1.69 (*s*, 3 H); 1.80–1.99 (*m*, 3 H); 2.08–2.17 (*m*, 1 H); 3.71 (*s*, 3 H); 4.04 (*dd*, $J = 6.3$, 8.0, 1 H); 4.40 (*ddd*, $J = 4.7$, 8.0, 8.0, 1 H); 4.47 (*dd*, $J = 6.5$, 8.4, 1 H); 4.38–4.49 (*m*, 1 H); 5.06–5.13 (*m*, 2 H); 5.35 (*d*, $J = 7.6$, 1 H); 6.92 (*d*, $J = 7.4$, 1 H); 6.98 (*d*, $J = 8.7$, 1 H); 7.29 (*m*, 6 H); 7.70 (*d*, $J = 6.0$, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 9.82 (Me); 11.29 (Me); 14.01 (Me); 15.43 (Me); 17.69 (Me); 19.40 (Me); 21.81 (Me); 21.97 (Me); 22.72 (Me); 24.72 (CH); 25.16 (CH_2); 25.22 (CH_2); 27.57 (Me); 30.69 (CH); 37.12 (CH); 40.40 (CH_2); 51.55 (CH); 52.03 (Me); 54.78 (CH); 56.77 (CH); 60.49 (CH); 62.66 (CH); 67.19 (CH_2); 83.61 (CH); 128.11 (CH); 182.21 (CH); 128.53 (CH); 136.11 (C); 156.60 (C); 168.44 (C); 170.32 (C); 171.13 (C); 171.61 (C); 171.83 (C); 172.90 (C). FAB-MS: 1495 (17, $[2M+1]^+$), 770 (14, $[M+23]^+$), 748 (93, $[M+1]^+$), 692 (100), 518 (15), 503 (16), 462 (24), 418 (74), 347 (38), 284 (27).

Z-Val-Leu-(CO_2^{t}Bu)Abu-Abu-Ile-OMe (**75a/b**). According to *GP 5*, with **5** (0.733 g, 1.0 mmol), EtI (0.25 ml, 3.0 mmol), and *t*-BuOK (145 mg, 1.3 mmol) in THF (40 ml) and DMPU (5 ml); 16 h. FC (hexane/AcOEt 2:1): 0.535 g (70%) of **75a/b** as a 4:1 mixture of epimers. The epimers were separated by HPLC (hexane/i-PrOH 96.5:3.5).

Data of **75a**: t_R 13.41 min (hexane/i-PrOH 96.5:3.5). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.65 (*dd*, *J* = 7.4, 7.4, 3 H); 0.75–0.98 (*m*, 18 H); 1.08–1.20 (*m*, 1 H); 1.25–1.56 (*m*, 3 H); 1.41 (*s*, 9 H); 1.63–1.88 (*m*, 6 H); 2.00–2.16 (*m*, 2 H); 2.32–2.39 (*m*, 1 H); 3.65 (*s*, 3 H); 3.94 (*dd*, *J* = 8.1, 8.1, 1 H); 4.62 (*dd*, *J* = 5.2, 9.3, 1 H); 4.76–4.91 (*m*, 2 H); 5.05 (*AB*, J_{AB} = 12.1, 2 H); 6.10–6.29 (*m*, 1 H); 6.34 (*d*, *J* = 7.1, 1 H); 6.53 (*d*, *J* = 9.0, 1 H); 7.26–7.38 (*m*, 5 H); 7.70–7.89 (br. *s*, 1 H); 8.10–8.24 (br. *s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 7.44 (Me); 10.01 (Me); 11.45 (Me); 15.17 (Me); 18.10 (Me); 19.33 (Me); 22.56 (Me); 22.76 (Me); 24.55 (CH); 24.84 (CH_2); 26.53 (CH_2); 26.64 (CH_2); 27.77 (Me); 30.96 (CH); 38.08 (CH); 41.78 (CH_2); 51.80 (Me); 52.23 (CH); 53.93 (CH); 56.31 (CH); 60.86 (CH); 66.87 (CH_2); 67.83 (C); 82.84 (C); 128.08 (CH); 128.27 (CH); 128.71 (CH); 136.68 (C); 156.89 (C); 166.84 (C); 168.81 (C); 170.92 (C); 171.71 (C); 172.61 (C); 173.34 (C). FAB-MS: 1524 (19, $[2M+1]^+$), 762 (100, $[M+1]^+$), 706 (62), 617 (20), 432 (34), 347 (27), 347 (27).

Data of **75b**: t_R 20.47 min (hexane/i-PrOH 96.5 3.5). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.71–0.97 (*m*, 21 H); 1.14–1.30 (*m*, 4 H); 1.44 (*s*, 9 H); 1.46–1.51 (*m*, 1 H); 1.60–1.78 (*m*, 3 H); 1.93–2.04 (*m*, 2 H); 2.06–2.19 (*m*, 2 H); 2.27–2.36 (*m*, 1 H); 3.71 (*s*, 3 H); 4.07 (*dd*, *J* = 6.3, 8.2, 1 H); 5.09 (*AB*, J_{AB} = 12.2, 2 H); 5.36 (*d*, *J* = 8.3, 1 H); 6.99 (*d*, *J* = 7.1, 1 H); 7.10 (*d*, *J* = 8.7, 1 H); 7.26 (*s*, 1 H); 7.29–7.35 (*m*, 5 H); 7.94 (*d*, *J* = 8.2, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 7.90 (Me); 10.05 (Me); 11.25 (Me); 15.46 (Me); 17.67 (Me); 19.44 (Me); 22.05 (Me); 22.61 (Me); 24.73 (CH); 25.05 (CH_2); 25.21 (CH_2); 27.39 (CH_2); 27.59 (Me); 30.68 (CH); 36.92 (CH); 40.52 (CH_2); 51.67 (Me); 52.03 (CH); 54.81 (CH); 56.86 (CH); 60.32 (CH); 66.54 (C); 67.13 (CH_2); 83.59 (C); 128.09 (CH); 128.19 (CH); 128.52 (CH); 136.16 (C); 156.53 (C); 167.84 (C); 169.86 (C); 171.26 (C); 171.47 (C); 171.97 (C); 172.99 (C). FAB-MS: 784 (29, $[M+23]^+$), 762 (44, $[M+1]^+$), 706 (100), 628 (34), 572 (10), 532 (20), 476 (35), 432 (76), 347 (36).

Z-Val-Leu-(Bu)Ama(O^{t}Bu)-Abu-Ile-OMe (**76a/b**). According to *GP 5*, with **5** (0.500 g, 0.68 mmol), BuI (0.23 ml, 2.04 mmol), and *t*-BuOK (99 mg, 0.88 mmol) in THF (40 ml) and DMPU (5 ml); 24 h. FC (hexane/AcOEt 2:1): 0.181 g (37%) of **76a/b** as a 2.3:1 mixture of epimers. The epimers were separated by HPLC (hexane/i-PrOH 96.5:3.5).

Data of **76a**: t_R 7.04 min (hexane/i-PrOH 96.5:3.5). $[\alpha]_D^{r.t.} = -47.7$ (*c* = 1.00, EtOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.70–1.00 (*m*, 24 H); 1.05–1.25 (*m*, 5 H); 1.25–1.95 (*m*, 7 H); 1.43 (*s*, 9 H); 2.00–2.19 (*m*, 2 H); 2.28–2.40 (*m*, 1 H); 3.66 (*s*, 3 H); 3.93–3.98 (*m*, 1 H); 4.60 (*dd*, *J* = 5.3, 9.0, 1 H); 4.68–4.75 (*m*, 2 H); 5.01–5.12 (*m*, 2 H); 5.90 (br. *s*, 1 H); 6.48 (*d*, *J* = 7.5, 1 H); 6.64 (*d*, *J* = 8.7, 1 H); 7.29–7.36 (*m*, 6 H); 7.84 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.88 (Me); 11.49 (Me); 13.70 (Me); 15.35 (Me); 17.97 (Me); 19.33 (Me); 22.28 (CH_2); 22.42 (Me); 22.84 (Me); 24.65 (CH); 25.19 (CH_2); 25.30 (CH_2); 26.35 (CH_2); 27.74 (Me); 31.04 (CH); 32.65 (CH_2); 38.00 (CH); 41.92 (CH_2); 51.54 (CH); 52.25 (Me); 54.34 (CH); 56.41 (CH); 60.76 (CH); 66.98 (CH_2); 67.27 (C); 83.20 (C); 128.16 (CH); 128.32 (CH); 128.73 (CH); 136.64 (C); 156.81 (C); 167.07 (C); 168.78 (C); 171.03 (C); 171.24 (C); 172.08 (C); 173.12 (C). FAB-MS: 1580 (14, $[2M+1]^+$), 790 (100, $[M+1]^+$), 734 (62), 645 (27), 545 (15), 504 (12), 460 (27), 346 (15).

Data of **71b**: t_R 15.22 min (hexane/i-PrOH 96.5:3.5). $[\alpha]_D^{r.t.} = -49.9$ (*c* = 1.00, EtOH). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.84–0.97 (*m*, 24 H); 1.11–1.34 (*m*, 5 H); 1.44 (*s*, 9 H); 1.44–1.52 (*m*, 2 H); 1.59–1.80 (*m*, 3 H); 1.93–2.16 (*m*, 4 H); 2.21–2.32 (*m*, 1 H); 3.71 (*s*, 3 H); 4.07 (*dd*, *J* = 6.2, 8.5, 1 H); 4.36–4.43 (*m*, 2 H); 4.47 (*dd*, *J* = 6.7, 8.7, 1 H); 5.05–5.14 (*m*, 2 H); 5.34 (*d*, *J* = 8.1, 1 H); 6.89 (*d*, *J* = 7.3, 1 H); 7.06 (*d*, *J* = 8.7, 1 H); 7.18 (*s*, 1 H); 7.27–7.35 (*m*, 5 H); 7.84 (*d*, *J* = 8.5, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 10.02 (Me); 11.29 (Me); 13.78 (Me); 15.50 (Me); 17.71 (Me); 19.45 (Me); 22.17 (Me); 22.40 (CH_2); 22.60 (Me); 24.79 (CH); 25.10 (CH_2); 25.28 (CH_2); 25.83 (CH_2); 27.64 (Me); 30.77 (CH); 33.78 (CH_2); 37.06 (CH); 40.65 (CH_2); 51.79 (CH); 51.99 (Me); 54.90 (CH); 56.87 (CH); 60.41 (CH); 66.20 (C); 67.12 (CH_2); 83.61 (C); 128.09 (CH); 128.19 (CH); 128.54 (CH); 136.28 (C); 156.51 (C); 167.87 (C); 169.94 (C); 171.24 (C); 171.36 (C); 171.95 (C); 172.92 (C). FAB-MS: 1580 (13, $[2M+1]^+$), 812 (35), 790 (69, $[M+1]^+$), 734 (100), 645 (5), 545 (10), 460 (17), 346 (6).

Z-Val-Leu-(All)Ama(O^{t}Bu)-Abu-Ile-OMe (**77a/b**). According to *GP 5*, with **5** (0.733 g, 1.0 mmol), allyl bromide (0.25 ml, 3.0 mmol), and *t*-BuOK (145 mg, 1.3 mmol) in THF (40 ml) and DMPU (5 ml); 6 h. FC (hexane/AcOEt 2:1): 0.735 g (95%) of **77a/b** as a 4.8:1 mixture of epimers, which were separated by HPLC (hexane/i-PrOH 96.5:3.5).

Data of **77a**: R_f 0.40 (hexane/AcOEt 1:1). t_R 9.71 min (hexane/i-PrOH 96.5:3.5). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.78 (*dd*, *J* = 7.4, 7.4, 3 H); 0.82–0.86 (*m*, 6 H); 0.89–0.97 (*m*, 12 H); 1.11–1.18 (*m*, 1 H); 1.34–1.52 (*m*, 3 H); 1.41 (*s*, 9 H); 1.66–1.70 (*m*, 3 H); 1.70–1.77 (*m*, 1 H); 2.02–2.06 (*m*, 1 H); 2.86 (*ABX*, J_{AB} = 14.4,

J_{AX} = 8.4, 1 H); 3.09 (*ABX*, J_{AB} = 14.4, J_{AX} = 6.0, 1 H); 3.65 (*s*, 3 H); 3.92–3.96 (*m*, 1 H); 4.63 (*dd*, *J* = 5.1, 9.1, 1 H); 4.75–4.85 (br. *m*, 2 H); 4.89–4.92 (*m*, 1 H); 5.01–5.12 (*m*, 3 H); 5.47–5.49 (*m*, 1 H); 6.20 (br. *s*, 1 H); 6.39 (br. *d*, 1 H); 6.60 (*d*, *J* = 9.3, 1 H); 7.31–7.32 (*m*, 5 H); 8.06 (*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 9.84 (Me); 11.44 (Me); 15.36 (Me); 18.06 (Me); 19.30 (Me); 22.42 (Me); 22.77 (Me); 24.52 (CH); 24.97 (CH_2); 26.69 (CH_2); 27.69 (Me); 30.83 (CH); 37.76 (CH_2); 38.10 (CH); 41.82 (CH_2); 51.58 (CH); 52.09 (Me); 53.87 (CH); 56.20 (CH); 60.75 (CH); 66.73 (C); 66.73 (CH_2); 83.00 (C); 119.85 (CH_2); 127.81 (CH); 128.01 (CH); 128.43 (CH); 130.91 (CH); 136.40 (C); 156.57 (C); 165.75 (C); 167.93 (C); 170.77 (C); 171.09 (C); 172.12 (C); 172.91 (C). FAB-MS: 1547 (6, $[2M+1]^+$), 774 (100, $[M+1]^+$), 718 (58), 629 (24), 529 (17), 444 (43), 347 (30), 310 (28), 234 (21).

Data of **77b**: R_f 0.36 (hexane/AcOEt 1:1). t_R 14.12 min (hexane/i-PrOH 96.5:3.5). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.85–0.97 (*m*, 21 H); 1.14–1.27 (*m*, 1 H); 1.43 (*s*, 9 H); 1.43–1.50 (*m*, 1 H); 1.59–1.76 (*m*, 3 H); 1.89 (*s*, 1 H); 1.92–2.04 (*m*, 2 H); 2.08–2.17 (*m*, 1 H); 2.92 (*ABX*, J_{AB} = 14.1, J_{AX} = 7.6, 1 H); 3.05 (*ABX*, J_{AB} = 14.1, J_{AX} = 7.2, 1 H); 3.71 (*s*, 3 H); 4.04 (*dd*, *J* = 6.4, 8.5, 1 H); 4.32–4.39 (*m*, 2 H); 4.47 (*dd*, *J* = 6.4, 8.5, 1 H); 5.11 (*s*, 2 H); 5.14–5.15 (*m*, 1 H); 5.32 (*d*, *J* = 8.1, 1 H); 5.51–5.61 (*m*, 1 H); 6.83 (*d*, *J* = 5.8, 1 H); 7.00 (*d*, *J* = 8.5, 1 H); 7.32–7.37 (*m*, 6 H); 7.60 (*d*, *J* = 8.1, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 10.13 (Me); 11.35 (Me); 15.46 (Me); 17.76 (Me); 19.49 (Me); 21.91 (Me); 22.69 (Me); 24.74 (CH); 25.15 (CH_2); 25.24 (CH_2); 27.68 (Me); 30.53 (CH); 37.06 (CH); 38.10 (CH_2); 40.63 (CH_2); 52.01 (Me); 52.36 (CH); 55.10 (CH); 56.90 (CH); 60.36 (CH); 65.86 (C); 67.23 (CH_2); 84.00 (C); 120.22 (CH_2); 128.11 (CH); 128.26 (CH); 128.58 (CH); 130.80 (CH); 136.14 (C); 156.60 (C); 167.09 (C); 168.87 (C); 171.21 (C); 171.39 (C); 172.23 (C); 172.70 (C). FAB-MS: 1547 (16, $[2M+1]^+$), 1413 (3), 774 (100, $[M+1]^+$), 718 (77), 640 (14), 544 (27), 488 (22), 444 (59), 347 (40), 30 (40).

Z-Val-Leu-(CO$_2$^{t}Bu)Phe-Abu-Ile-OMe (**78a/b**). According to *GP 5*, with **5** (0.733 g, 1.0 mmol), BnBr (0.35 ml, 3.0 mmol), and *t*-BuOK (145 mg, 1.3 mmol) in THF (40 ml) and DMPU (5 ml); 8 h. FC (hexane/AcOEt 2:1): 0.735 g (89%) of **78a/b** as a 9:1 mixture of epimers, which were separated by HPLC (hexane/i-PrOH 96.5:3.5).

Data of **78a**: t_R 6.6 min (hexane/i-PrOH 96.5:3.5). $[\alpha]_D^{rt.} = -49.9$ (*c* = 1.0, EtOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.82–0.96 (*m*, 21 H); 1.12–1.28 (*m*, 1 H); 1.29–1.79 (*m*, 5 H); 1.83–1.98 (*m*, 2 H); 2.07–2.18 (*m*, 1 H); 3.53 (*AB*, J_{AB} = 14.0, 1 H); 3.71 (*AB*, J_{AB} = 14.0, 1 H); 3.73 (*s*, 3 H); 4.00 (*dd*, *J* = 6.2, 8.6, 1 H); 4.31 (*ddd*, *J* = 5.8, 7.7, 7.7, 1 H); 4.60 (*dd*, *J* = 5.3, 8.5, 1 H); 5.08 (*s*, 2 H); 5.43 (*d*, *J* = 8.6, 1 H); 6.57 (*d*, *J* = 7.4, 1 H); 6.64 (*d*, *J* = 8.6, 1 H); 6.90 (*d*, *J* = 7.8, 1 H); 6.98–7.00 (*m*, 3 H); 7.12–7.17 (*m*, 3 H); 7.20 (*s*, 1 H); 7.28–7.38 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.96 (Me); 11.51 (Me); 15.46 (Me); 17.68 (Me); 19.31 (Me); 21.93 (Me); 22.87 (Me); 24.63 (CH); 25.27 (CH_2); 25.88 (CH_2); 27.69 (Me); 31.03 (CH); 37.73 (CH); 38.12 (CH_2); 41.07 (CH_2); 51.56 (CH); 52.20 (Me); 55.21 (CH); 56.64 (CH); 60.48 (CH); 67.01 (CH_2); 67.67 (C); 83.99 (C); 127.14 (CH); 127.98 (CH); 128.12 (CH); 128.50 (CH); 130.05 (CH); 134.87 (C); 136.30 (C); 156.40 (C); 166.02 (C); 167.73 (C); 170.78 (C); 170.96 (C); 171.27 (C); 172.52 (C). FAB-MS: 1648 (61, $[2M+1]^+$), 1514 (19), 846 (28, $[M+23]^+$), 824 (100, $[M+1]^+$), 768 (93), 679 (35), 579 (37), 494 (41), 360 (37), 347 (38), 231 (39).

Data of **78b**: t_R 10.66 min (hexane/i-PrOH 96.5:3.5). $[\alpha]_D^{rt.} = -36.6$ (*c* = 1.0, EtOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.80–0.95 (*m*, 21 H); 1.12–1.28 (*m*, 1 H); 1.40–1.53 (*m*, 1 H); 1.44 (*s*, 9 H); 1.64–1.74 (*m*, 3 H); 1.92–2.04 (*m*, 2 H); 2.08–2.17 (*m*, 1 H); 3.50 (*AB*, J_{AB} = 13.8, 1 H); 3.69 (*AB*, J_{AB} = 13.8, 1 H); 3.71 (*s*, 3 H); 4.00 (*dd*, *J* = 6.5, 8.6, 1 H); 4.10–4.28 (*m*, 1 H); 4.34 (*ddd*, *J* = 4.4, 8.4, 8.4, 1 H); 4.46 (*dd*, *J* = 6.6, 8.6, 1 H); 5.10 (*s*, 2 H); 5.27 (*d*, *J* = 8.2, 1 H); 6.78 (*d*, *J* = 5.2, 1 H); 7.05–7.08 (*m*, 3 H); 7.21–7.23 (*m*, 4 H); 7.28–7.37 (*m*, 5 H); 7.56 (*d*, *J* = 8.1, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 10.27 (Me); 11.31 (Me); 15.45 (Me); 17.76 (Me); 19.56 (Me); 21.58 (Me); 22.73 (Me); 24.68 (CH); 24.97 (CH_2); 25.23 (CH_2); 27.68 (Me); 30.15 (CH); 36.89 (CH); 38.85 (CH_2); 40.38 (CH_2); 51.91 (Me); 52.81 (CH); 55.37 (CH); 56.95 (CH); 60.27 (CH); 67.23 (CH); 67.23 (CH_2); 84.34 (C); 127.31 (CH); 128.07 (CH); 128.21 (CH); 128.56 (CH); 130.11 (CH); 134.81 (C); 136.06 (C); 156.61 (C); 166.99 (C); 168.67 (C); 171.29 (C); 172.55 (C). FAB-MS: 1648 (44, $[2M+1]^+$), 1514 (5), 846 (17, $[M+23]^+$), 824 (100, $[M+1]^+$), 768 (97), 679 (10), 594 (19), 579 (18), 494 (25), 391 (25), 360 (17), 347 (17), 231 (18).

Z-Val-Leu-(PhCONHCH$_2$)Ama(O^{t}Bu)-Abu-Ile-OMe (**79a/b**). According to *GP 5*, with **5** (0.733 g, 1.0 mmol), *N*-(chloromethyl)benzamide (0.508 g, 3.0 mmol), and *t*-BuOK (145 mg, 1.3 mmol) in THF (40 ml) and DMPU (5 ml); 6 h. FC (hexane/AcOEt 7:3): 0.750 g (86%) of **79a/b** as a 2:1 mixture of epimers. Separation by FC (hexane/AcOEt 3:1).

Data of **79a**: R_f 0.19 (hexane/AcOEt 7:3). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.90–0.99 (*m*, 21 H); 1.10–1.30 (*m*, 1 H); 1.44 (*s*, 9 H); 1.40–1.80 (*m*, 5 H); 1.80–2.15 (*m*, 3 H); 3.66 (*s*, 3 H); 3.94–4.04 (*m*, 1 H); 4.19–4.26 (*m*, 2 H); 4.28–4.38 (*m*, 2 H); 4.43 (*dd*, *J* = 6.5, 8.6, 1 H); 5.11 (*s*, 2 H); 5.29 (*d*, *J* = 8.1, 1 H); 6.55 (*d*, *J* = 6.6, 1 H); 7.6–7.50 (*m*, 9 H); 7.50–7.65 (*m*, 1 H); 7.80–7.95 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.73 (Me); 11.23 (Me); 15.39 (Me); 17.38 (Me); 19.13 (Me); 21.81 (Me); 22.62 (Me); 24.51 (CH); 24.89 (CH_2); 25.23

(CH_2); 27.54 (Me); 30.55 (CH); 36.73 (CH); 40.48 (CH_2); 43.18 (CH_2); 51.84 (Me); 52.68 (CH); 55.35 (CH); 57.16 (CH); 60.12 (CH); 67.24 (C); 67.56 (CH_2); 84.29 (C); 127.65 (CH); 128.23 (CH); 128.38 (CH); 128.46 (CH); 128.67 (CH); 131.92 (CH); 133.41 (C); 136.16 (C); 156.69 (C); 166.86 (C); 167.75 (C); 168.68 (C); 171.35 (C); 171.94 (C); 172.46 (C). FAB-MS: 1756 (26, $[2M+23]^+$), 1734 (30, $[2M+1]^+$), 889 (52, $[M+23]^+$), 867 (97, $[M+1]^+$), 789 (7), 668 (12), 391 (38), 371 (11), 149 (100).

Data of **79b**: R_f 0.16 (hexane/AcOEt 7:3). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.82–0.94 (*m*, 21 H); 1.10–1.19 (*m*, 1 H); 1.21–1.58 (*m*, 3 H); 1.43 (*s*, 9 H); 1.65–2.08 (*m*, 5 H); 3.63 (*s*, 3 H); 3.94–4.00 (*m*, 1 H); 4.10 (*ABX*, $J_{AB}=13.9$, $J_{AX}=5.5$, 1 H); 4.19–4.27 (*m*, 1 H); 4.30–4.35 (*m*, 1 H); 4.34 (*ABX*, $J_{AB}=13.9$, $J_{AX}=6.9$, 1 H); 4.49 (*dd*, $J=5.7$, 8.5, 1 H); 5.09 (*s*, 2 H); 5.18 (*d*, $J=7.3$, 1 H); 6.69 (br. *s*, 1 H); 6.92 (*d*, $J=5.5$, 1 H); 7.29–7.53 (*m*, 10 H); 7.71–7.85 (*m*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 10.14 (Me); 11.43 (Me); 15.44 (Me); 17.75 (Me); 19.43 (Me); 21.66 (Me); 22.75 (Me); 24.74 (CH); 25.19 (CH_2); 27.62 (Me); 30.39 (CH); 37.10 (CH); 40.23 (CH_2); 43.27 (CH_2); 51.96 (Me); 53.28 (CH); 55.66 (CH); 56.67 (CH); 60.36 (CH); 67.28 (C); 67.34 (CH_2); 84.74 (C); 127.48 (CH); 128.12 (CH); 128.34 (CH); 128.37 (CH); 128.60 (CH); 131.66 (CH); 133.82 (C); 136.01 (C); 156.62 (C); 166.84 (C); 166.92 (C); 168.19 (C); 171.09 (C); 172.46 (C); 172.49 (C). FAB-MS: 1734 (4, $[2M+1]^+$), 889 (51, $[M+23]^+$), 867 (100, $[M+1]^+$), 811 (38), 734 (13), 678 (11), 668 (12), 537 (13), 416 (11).

Z-Val-Leu-(cyclohex-2-enyl)Ama(O^{t}Bu)-Abu-Ile-OMe (**80a–d**). According to *GP 5*, with **5** (0.733 g, 1.0 mmol), cyclohex-2-enyl bromide (0.34 ml, 3.0 mmol), and *t*-BuOK (145 mg, 1.3 mmol) in THF (40 ml) and DMPU (5 ml); 10 h. FC (hexane/AcOEt 2:1) gave 0.607 g (74%) of **80a–d** as a mixture of four isomers. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.83–0.99 (*m*, 21 H); 1.05–1.24 (*m*, 1 H); 1.41, *1.44* (2*s*, 9 H); 1.27–2.15 (*m*, 14 H); 2.96–3.05 (br. *m*, 1 H); 3.68, *3.69*, *3.72* (3*s*, 3 H); 4.12–4.17 (*m*, 1 H); 4.36–4.47 (*m*, 2 H); 4.51–4.69 (*m*, 1 H); 5.03–5.14 (*m*, 2 H); 5.38–5.43 (*m*, 1 H); 5.53–5.82 (*m*, 3 H); 7.20–7.45 (*m*, 8 H); 8.46, *8.73* (2*d*, $J=8.1$, 8.1, 1 H). FAB-MS: 1629 (7, $[2M+1]^+$), 836 (28, $[M+23]^+$), 814 (64, $[M+1]^+$), 758 (100), 730 (11), 569 (20), 484 (39), 350 (35).

Z-Val-Leu-(CO$_2$^{t}Bu)Glu(OMe)-Abu-Ile-OMe (**81a/b**). According to *GP 5*, with **5** (0.200 g, 0.27 mmol), methyl acrylate (0.1 ml, 0.9 mmol), LiBr (118 mg, 0.9 mmol), and *t*-BuOK (10 mg, 0.09 mmol) in THF (20 ml); 4 h. FC (Et_2O/pentane 9:1): 0.191 g (85%) of **81a/b** as a 4:1 mixture of epimers. Separation by HPLC (hexane/i-PrOH 96.5:3.5).

Data of **81a**: $[\alpha]_D^{rt}=-40.7$ ($c=0.9$, EtOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.86–0.95 (*m*, 21 H); 1.12–1.37 (*m*, 2 H); 1.44 (*s*, 9 H); 1.51–1.85 (*m*, 4 H); 1.88–1.94 (*m*, 2 H); 2.06–2.26 (*m*, 3 H); 2.45–2.55 (*m*, 1 H); 2.63–2.73 (*m*, 1 H); 3.62 (*s*, 3 H); 3.70 (*s*, 3 H); 3.96–4.01 (*m*, 1 H); 4.34–4.41 (*m*, 1 H); 4.50–4.53 (*m*, 1 H); 4.56 (*dd*, $J=5.4$, 8.7, 1 H); 5.09 (*s*, 2 H); 5.50 (*d*, $J=8.4$, 1 H); 6.50 (*d*, $J=7.5$, 1 H); 6.86–6.89 (*m*, 2 H); 7.28–7.35 (*m*, 5 H); 7.60 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.96 (Me); 11.44 (Me); 15.44 (Me); 17.73 (Me); 19.35 (Me); 20.07 (Me); 22.88 (Me); 24.73 (CH); 25.33 (CH_2); 25.44 (CH_2); 27.73 (Me); 28.61 (CH_2); 28.68 (CH_2); 30.99 (CH); 37.68 (CH); 41.26 (CH_2); 51.69 (CH); 51.76 (Me); 52.08 (Me); 55.35 (CH); 56.64 (CH); 60.58 (CH); 66.36 (C); 67.10 (CH_2); 84.03 (C); 128.03 (CH); 128.18 (CH); 128.97 (CH); 136.38 (C); 156.61 (C); 166.84 (C); 168.00 (C); 170.69 (C); 171.27 (C); 171.58 (C); 172.56 (C); 173.02 (C). FAB-MS: 1662 (12, $[2M+23]^+$), 1640 (69, $[2M+1]^+$), 820 (100, $[M+1]^+$), 764 (63), 675 (17), 575 (23), 490 (27).

Data of **81b**: $[\alpha]_D^{rt}=-42.7$ ($c=1.01$, EtOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.84–0.97 (*m*, 21 H); 1.11–1.37 (*m*, 2 H); 1.44 (*s*, 9 H); 1.60–1.81 (*m*, 3 H); 1.88–2.03 (*m*, 3 H); 2.07–2.18 (*m*, 1 H); 2.25–2.31 (*m*, 2 H); 2.43–2.63 (*m*, 2 H); 3.65 (*s*, 3 H); 3.71 (*s*, 3 H); 4.05 (*dd*, $J=6.2$, 8.3, 1 H); 4.34–4.42 (*m*, 2 H); 4.46 (*dd*, $J=6.5$, 8.6, 1 H); 5.10 (*s*, 2 H); 5.33 (*d*, $J=8$, 1 H); 6.87 (*d*, $J=7.1$, 1 H); 6.99 (*d*, $J=8.5$, 1 H); 7.29–7.36 (*m*, 5 H); 7.54 (*s*, 1 H); 7.78 (*d*, $J=8.1$, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 10.00 (Me); 11.30 (Me); 15.49 (Me); 17.71 (Me); 19.45 (Me); 22.00 (Me); 22.69 (Me); 24.80 (CH); 25.08 (CH_2); 25.26 (CH_2); 27.64 (Me); 28.84 (CH_2); 29.21 (CH_2); 30.65 (CH); 37.13 (CH); 40.61 (CH_2); 51.85 (CH); 52.02 (Me); 55.07 (CH); 56.84 (CH); 60.46 (CH); 65.68 (C); 67.20 (CH_2); 84.26 (C); 128.09 (CH); 128.22 (CH); 128.55 (CH); 136.24 (CH); 156.58 (C); 167.26 (C); 169.29 (C); 171.08 (C); 171.73 (C); 172.01 (C); 172.78 (C); 172.86 (C). FAB-MS: 1662 (6, $[2M+23]^+$), 1640 (93, $[2M+1]^+$), 820 (100, $[M+1]^+$), 764 (84), 590 (21), 575 (19), 490 (28).

Z-Val-Leu-(CO$_2$^{t}Bu)Glu(O^{t}Bu)-Abu-Ile-OMe (**82**). According to *GP 5*, with **5** (0.733 g, 1.0 mmol), *tert*-butyl acrylate (0.43 ml, 3.0 mmol), and *t*-BuOK (33 mg, 0.3 mmol) in THF (40 ml) and DMPU (5 ml); 6 h. FC (hexane/AcOEt 2:1) gave 0.749 g (87%) of **82**. Diastereoisomerically pure.

Data of **82**: R_f 0.38 (AcOEt/hexane 1:1). $[\alpha]_D^{rt}=-43.5$ ($c=1.01$, EtOH). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.58 0.70 (*m*, 21 H); 0.80–0.97 (*m*, 1 H); 1.16 (*s*, 9 H); 1.81 (*s*, 9 H); 1.14–1.25 (*m*, 1 H); 1.31–1.54 (*m*, 3 H); 1.68–1.78 (*m*, 2 H); 1.80–1.89 (*m*, 1 H); 1.91–1.95 (*m*, 2 H); 2.10–2.24 (*m*, 3 H); 3.45 (*s*, 3 H); 3.80 (*dd*, $J=$ 6.4, 8.2, 1 H); 4.11 (*ddd*, $J=4.5$, 8.2, 8.2, 1 H); 4.16–4.22 (*m*, 2 H); 4.83 (*AB*, $J_{AB}=12$, 2 H); 5.09 (*d*, $J=8.3$, 1 H); 6.68 (*d*, $J=7.3$, 1 H); 6.81 (*d*, $J=8.7$, 1 H); 7.02–7.11 (*m*, 5 H); 7.33 (*s*, 1 H); 7.67 (*d*, $J=8.2$, 1 H).

^{13}C-NMR (100 MHz, $CDCl_3$): 9.97 (Me); 11.25 (Me); 15.46 (Me); 17.68 (Me); 19.42 (Me); 22.09 (Me); 22.61 (Me); 24.70 (CH); 24.89 (CH_2); 25.19 (CH_2); 27.59 (Me); 28.02 (Me); 29.49 (CH_2); 30.22 (CH_2); 30.76 (CH); 36.95 (CH); 40.69 (CH_2); 51.69 (CH); 52.07 (Me); 54.88 (CH); 56.82 (CH); 60.7 (CH_2); 65.47 (C); 67.10 (CH_2); 81.03 (C); 84.08 (C); 128.07 (CH); 128.17 (CH); 128.51 (CH); 136.17 (CH); 156.52 (C); 167.52 (C); 169.70 (C); 171.14 (C); 171.79 (C); 171.86 (C); 172.95 (C). FAB-MS: 1724 (11, $[2M+1]^+$), 1589 (8), 884 (26), 862 (100, $[M+1]^+$), 806 (26), 728 (59), 476 (44).

Boc-Val-Leu-(CH_2CH_2CN)Ama(O^tBu)-Abu-Ile-OMe (**83a/b**). According to *GP 5*, with **5** (0.733 g, 1.0 mmol), acrylonitrile (0.19 ml, 3.0 mmol), and *t*-BuOK (33 mg, 0.3 mmol) in THF (40 ml) and DMPU (5 ml); 6 h. FC (hexane/AcOEt 2:1) gave 0.680 g (86%) of **83a/b** as a 4:1 mixture of epimers. Separated by FC (hexane/AcOEt 3:1, gradient).

Data of **83a**: R_f 0.38 (AcOEt/hexane 1:1). t_R 15.40 min (hexane/i-PrOH 96.5:3.5). $[\alpha]_D^{r.t.} = -39.1$ ($c = 0.80$, EtOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.78 (*dd*, $J = 7.2, 7.2, 3$ H); 0.87–0.97 (*m*, 18 H); 1.12–1.22 (*m*, 1 H); 1.35–1.57 (*m*, 2 H); 1.42 (*s*, 3 H); 1.66–1.91 (*m*, 6 H); 2.05–2.12 (*m*, 1 H); 2.23–2.39 (*m*, 2 H); 2.42–2.47 (*m*, 1 H); 2.80–2.85 (*m*, 1 H); 3.66 (*s*, 3 H); 3.89 (*dd*, $J = 7.8, 7.8, 1$ H); 4.61–4.65 (*m*, 2 H); 4.68–4.78 (br. *m*, 1 H); 5.06 (*AB*, $J_{AB} = 12.2$, 2 H); 6.10 (br. *s*, 1 H); 6.37 (*d*, $J = 5.9$, 1 H); 6.70 (*d*, $J = 8.7$, 1 H); 7.16–7.38 (*m*, 6 H); 8.10 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.81 (Me); 11.50 (Me); 11.90 (Me); 15.33 (Me); 18.13 (Me); 19.31 (Me); 22.53 (Me); 24.52 (CH); 25.23 (CH_2); 26.49 (CH_2); 27.72 (Me); 29.39 (CH_2); 30.62 (CH); 38.09 (CH_2); 41.14 (CH_2); 52.01 (CH); 52.27 (Me); 54.45 (CH); 56.34 (CH); 61.02 (CH); 65.98 (CH_2); 68.04 (C); 84.02 (C); 118.73 (C); 128.14 (CH); 128.37 (CH); 128.74 (CH); 136.52 (C); 156.91 (C); 165.69 (C); 167.65 (C); 171.08 (C); 171.50 (C); 172.94 (C); 173.28 (C). FAB-MS: 1596 (15, $[2M+23]^+$), 1574 (64, $[2M+1]^+$), 1440 (11), 809 (61, $[M+23]^+$), 787 (89, $[M+1]^+$), 731 (100), 642 (23), 542 (20), 457 (49).

Data of **83b**: R_f 0.31 (AcOEt/hexane 1:1). t_R 29.80 min (hexane/i-PrOH 96.5:3.5). $[\alpha]_D^{r.t.} = -40.3$ ($c = 1.00$, EtOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.80–1.00 (*m*, 21 H); 1.09–1.25 (*m*, 1 H); 1.44 (*s*, 9 H); 1.54–1.73 (*m*, 4 H); 1.80–1.96 (*m*, 2 H); 2.11–2.20 (*m*, 2 H); 2.25–2.30 (*m*, 2 H); 2.60–2.80 (*m*, 2 H); 3.69 (*s*, 3 H); 4.02–4.07 (*m*, 1 H); 4.27–4.41 (*m*, 2 H); 4.49 (*dd*, $J = 5.9, 8.4, 1$ H); 5.10 (*s*, 2 H); 5.40 (*d*, $J = 8.1$, 1 H); 6.93–6.96 (br. *m*, 2 H); 7.26–7.34 (*m*, 6 H); 7.60 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.82 (Me); 11.22 (Me); 12.06 (Me); 15.24 (Me); 17.62 (Me); 19.32 (Me); 21.26 (Me); 22.72 (Me); 24.63 (CH); 25.02 (CH_2); 25.24 (CH_2); 27.43 (Me); 28.53 (CH_2); 30.11 (CH); 37.10 (CH_2); 39.80 (CH_2); 51.94 (Me); 52.97 (CH); 55.07 (CH); 56.66 (CH); 60.32 (CH); 65.90 (CH_2); 67.24 (C); 85.12 (C); 118.85 (C); 128.12 (CH); 128.34 (CH); 128.62 (CH); 136.01 (C); 156.80 (C); 166.05 (C); 167.46 (C); 171.02 (C); 171.98 (C); 172.49 (C); 172.91 (C). FAB-MS: 1596 (20, $[2M+23]^+$), 1440 (28), 1574 (75, $[2M+1]^+$), 809 (43, $[M+23]^+$), 787 (93, $[M+1]^+$), 731 (100), 653 (17), 542 (10), 457 (33).

Z-Val-Leu-(CH_2CH_2COMe)Ama(O^tBu)-Abu-Ile-OMe (**84a/b**). According to *GP 5*, with **5** (0.733 g, 1.0 mmol), methyl vinyl ketone (0.25 ml, 3.0 mmol), and *t*-BuOK (33 mg, 0.3 mmol) in THF (40 ml) and DMPU (5 ml); 6 h. FC (hexane/AcOEt 2:1): 0.733 g (91%) of **84a/b** as a 2:1 mixture of epimers. Separated by FC (hexane/AcOEt 4:1).

Data of **84a**: R_f 0.24 (hexane/AcOEt 1:1). $[\alpha]_D^{r.t.} = -56.7$ ($c = 1.07$, EtOH). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.86–0.95 (*m*, 21 H); 1.14–1.27 (*m*, 1 H); 1.35–1.59 (*m*, 2 H); 1.43 (*s*, 9 H); 1.50–1.69 (*m*, 3 H); 1.83–1.96 (*m*, 3 H); 2.08 (*s*, 3 H); 2.04–2.15 (*m*, 1 H); 2.32–2.48 (*m*, 3 H); 2.55–2.61 (*m*, 1 H); 3.69 (*s*, 3 H); 4.00 (*dd*, $J = 6.8, 8.0, 1$ H); 4.40–4.45 (*m*, 1 H); 4.52–4.55 (*m*, 1 H); 4.56 (*dd*, $J = 5.3, 8.7, 1$ H); 5.09 (*AB*, $J_{AB} = 12.4$, 2 H); 5.55 (*d*, $J = 8.4$, 1 H); 6.51 (*d*, $J = 7.4$, 1 H); 6.92 (*d*, $J = 7.8$, 1 H); 6.97 (*d*, $J = 8.5$, 1 H); 7.28–7.37 (*m*, 5 H); 7.65 (*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 9.89 (Me); 11.43 (Me); 15.39 (Me); 17.69 (Me); 19.30 (Me); 22.00 (Me); 22.80 (Me); 24.60 (CH); 25.18 (CH_2); 25.57 (CH_2); 27.63 (Me); 27.73 (CH_2); 29.73 (Me); 30.84 (CH); 37.63 (CH); 37.90 (CH_2); 41.20 (CH_2); 51.58 (CH); 52.06 (C); 55.05 (CH); 56.48 (CH); 60.46 (CH); 66.11 (C); 67.03 (CH_2); 83.71 (C); 127.98 (CH); 128.15 (CH); 128.50 (CH); 136.19 (C); 156.45 (C); 166.98 (C); 168.17 (C); 170.75 (C); 171.21 (C); 171.62 (C); 172.55 (C); 207.30 (C). FAB-MS: 1609 (56, $[2M+1]^+$), 14741 (15), 827 (22, $[M+23]^+$), 805 (100, $[M+1]^+$), 748 (73), 670 (20), 559 (22), 474 (35), 340 (28).

Data of **84b**: R_f 0.20 (hexane/AcOEt 1:1). $[\alpha]_D^{r.t.} = -44.7$ ($c = 1.0$, EtOH). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.85–0.97 (*m*, 21 H); 1.13–1.28 (*m*, 1 H); 1.38–1.5 (*m*, 1 H); 1.44 (*s*, 9 H); 1.60–1.81 (*m*, 3 H); 1.87–1.88 (*m*, 1 H); 1.93–2.02 (*m*, 2 H); 2.05–2.16 (*m*, 1 H); 2.13 (*s*, 3 H); 2.36–2.49 (*m*, 4 H); 3.71 (*s*, 3 H); 4.07 (*dd*, $J = 6.2, 8.1, 1$ H); 4.36 (*ddd*, $J = 4.5, 8.1, 8.1, 1$ H); 4.40–4.46 (*m*, 1 H); 4.46 (*dd*, $J = 6.6, 8.6, 1$ H); 5.09 (*AB*, $J_{AB} = 12$, 2 H); 5.34 (*d*, $J = 8.4$, 1 H); 6.91 (*d*, $J = 7.5$, 1 H); 7.03 (*d*, $J = 8.6$, 1 H); 7.29–7.38 (*m*, 5 H); 7.56 (*s*, 1 H); 7.91 (*d*, $J = 8.0$). ^{13}C-NMR (100 MHz, $CDCl_3$): 10.02 (Me); 11.26 (Me); 15.45 (Me); 17.67 (Me); 19.43 (Me); 21.98 (Me); 22.67 (Me); 24.73 (CH); 24.97 (CH_2); 25.21 (CH_2); 27.59 (Me); 28.31 (CH_2); 29.81 (Me); 30.65 (CH); 37.01 (CH); 38.10 (CH_2); 40.43 (CH_2); 51.71 (Me); 52.02 (CH); 54.98 (CH); 56.78 (CH); 60.36 (CH); 65.42 (C); 67.17 (CH_2); 84.09 (C); 128.10 (CH); 128.21 (C); 128.53 (CH); 136.12 (C); 156.65 (C); 167.61

(C); 169.70 (C); 171.10 (C); 171.89 (C); 172.92 (C); 207.28 (C). FAB-MS: 1630(54), 1609 (68, $[2M+1]^+$), 1474(11), 827 (65, $[M+23]^+$), 826(100), 805 (87, $[M+1]^+$), 748(60), 726(25), 670(7), 659(15), 574(12), 474(24), 340(19).

5.5. *Alkylation of* **6**. *Boc-Val-Leu-(All)Ama(OBn)-Abu-Ile-OMe* (**85a/b**). According to *GP 5*, with **6** (1.00 g, 1.36 mmol), allyl bromide (0.34 ml, 4.08 mmol), and *t*-BuOK (199 mg, 1.77 mmol) in THF (40 ml); 10 h. FC (hexane/AcOEt 2:1): 0.658 g (62%) of **85a/b** as a 2.3:1 mixture of epimers. Separated by HPLC (hexane/i-PrOH 97:3).

Data of **85a**: t_R 16.9 min (hexane/i-PrOH 98:2). M.p. 183.5–186.0°. $[\alpha]_D^{rt} = -28.7$ ($c = 0.79$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.66–0.78 (*m*, 6 H); 0.81–0.92 (*m*, 15 H); 1.07–1.25 (*m*, 1 H); 1.41 (*s*, 9 H); 1.34–1.67 (*m*, 4 H); 1.80–1.85 (*m*, 1 H); 1.96–2.04 (*m*, 1 H); 2.91 (*ABX*, $J_{AB} = 14.5$, $J_{AX} = 8.3$, 1 H); 3.14 (*ABX*, $J_{AB} = 14.3$, $J_{AX} = 63$, 1 H); 3.72 (*s*, 3 H); 3.79 (*dd*, $J = 8.2$, 8.2, 1 H); 4.60 (*dd*, $J = 5$, 9, 1 H); 4.60–4.72 (*m*, 2 H); 4.91 (*ABX*, $J_{AB} = 10.1$, $J_{AX} \leq 1.5$, 1 H); 5.03 (*ABX*, $J_{AB} = 16.4$, $J_{AX} \leq 1$, 1 H); 5.04 (*AB*, $J_{AB} = 12$, 1 H); 5.18 (*AB*, $J_{AB} = 12$, 1 H); 5.39–5.53 (*m*, 1 H); 5.65–5.67 (br. *m*, 1 H); 6.25 (*d*, $J = 7.4$, 1 H); 6.66 (*d*, $J = 8.9$, 1 H); 7.25–7.31 (*m*, 5 H); 7.45–7.51 (br. *m*, 1 H); 8.01 (br. *s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.63 (Me); 11.48 (Me); 15.39 (Me); 18.06 (Me); 19.28 (Me); 22.03 (Me); 22.69 (Me); 24.46 (CH); 25.01 (CH_2); 26.27 (CH_2); 28.28 (Me); 30.60 (CH); 38.02 (CH); 38.02 (CH_2); 41.42 (CH_2); 51.55 (CH); 52.06 (Me); 54.06 (CH); 56.31 (CH); 60.31 (CH); 66.22 (C); 68.26 (CH_2); 79.53 (C); 120.26 (CH_2); 128.50 (CH); 128.82 (CH); 130.54 (CH); 134.78 (C); 155.96 (C); 165.37 (C); 169.10 (C); 170.94 (C); 171.23 (C); 172.39 (C); 172.53 (C). FAB-MS: 1547 (14, $[2M+1]^+$), 774 (59, $[M+1]^+$), 674(17), 629(16), 573(28), 488(21), 391(39), 204(40), 149(100).

Data of **85b**: t_R 25.9 min (hexane/i-PrOH 98:2). M.p. 154.5–156.0°. $[\alpha]_D^{rt} = -64.2$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.80–0.95 (*m*, 21 H); 1.13–1.28 (*m*, 1 H); 1.43 (*s*, 9 H); 1.43–1.53 (*m*, 1 H); 1.58–1.71 (*m*, 3 H); 1.89–2.12 (*m*, 3 H); 2.99 (*ABX*, $J_{AB} = 14.2$, $J_{AX} = 7.6$, 1 H); 3.11 (*ABX*, $J_{aB} = 14.1$, $J_{AX} = 7.0$, 1 H); 3.72 (*s*, 3 H); 3.89 (*dd*, $J = 8.4$, 6.8, 1 H); 4.24–4.33 (*m*, 2 H); 4.48 (*dd*, $J = 8.5$, 6.3, 1 H); 4.98 (*d*, $J = 8.3$, 1 H); 5.03 (*dd*, $J = 12$, 1.3, 1 H); 5.07 (*d*, $J = 3.8$, 1 H); 5.19 (*s*, 2 H); 5.40–5.54 (*m*, 1 H); 6.83 (*d*, $J = 5.9$, 1 H); 6.97 (*d*, $J = 8.5$, 1 H); 7.28–7.35 (*m*, 5 H); 7.37 (*s*, 1 H); 7.51 (*d*, $J = 8$, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 10.06 (Me); 11.37 (Me); 15.41 (Me); 19.55 (Me); 21.59 (Me); 22.80 (Me); 24.55 (CH); 24.93 (CH_2); 25.23 (CH_2); 28.26 (Me); 29.89 (CH); 37.05 (CH); 37.90 (CH_2); 40.11 (CH_2); 51.85 (CH); 51.93 (Me); 55.41 (CH); 56.78 (CH); 59.80 (CH); 65.90 (C); 68.28 (CH_2); 80.26 (C); 120.51 (CH_2); 128.44 (CH); 128.54 (CH); 130.54 (CH); 134.59 (C); 156.09 (C); 166.09 (C); 169.67 (C); 171.16 (C); 171.57 (C); 172.47 (C); 172.96 (C). FAB-MS: 1547 (11, $[2M+1]^+$), 774 (100, $[M+1]^+$), 674(87), 629(17), 573(27), 488(73), 391(18), 204(93), 149(73).

Boc-Val-Leu-(CO_2Bn)Phe-Abu-Ile-OMe (**86a/b**). According to *GP 5*, with **6** (1.00 g, 1.36 mmol), BnBr (0.48 ml, 4.08 mmol), and *t*-BuOK (199 mg, 1.77 mmol) in THF (40 ml); 6 h. FC (hexane/AcOEt 2:1): 0.910 g (81%) of **86a/b** as a 5.5:1 mixture of epimers. Separated by HPLC (hexane/i-PrOH 97:3).

Data of **86a**: t_R 14.8 min (hexane/i-PrOH 98:2). M.p. 154.5–155.5°. $[\alpha]_D^{rt} = -58.5$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.72 (*dd*, $J = 7.4$, 7.4, 3 H); 0.85–0.93 (*m*, 18 H); 1.16–1.26 (*m*, 1 H); 1.36–1.54 (*m*, 1 H); 1.42 (*s*, 9 H); 1.57–1.69 (*m*, 2 H); 1.90–2.09 (*m*, 3 H); 3.57 (*AB*, $J_{AB} = 13.8$, 1 H); 3.72 (*s*, 3 H); (*AB*, $J_{AB} = 13.7$, 1 H); 3.83 (*dd*, $J = 7.7$, 7.7, 1 H); 4.13–4.16 (*m*, 1 H); 4.27 (*ddd*, $J = 4.1$, 8.6, 8.6, 1 H); 4.47 (*dd*, $J = 6.5$, 8.4, 1 H); 4.92 (*d*, $J = 8.3$, 1 H); 5.20 (*AB*, $J_{AB} = 12$, 2 H); 6.77 (*d*, $J = 5$, 1 H); 6.84 (*d*, $J = 8.2$, 1 H); 6.84 (*d*, $J = 7.8$, 1 H); 7.08–7.22 (*m*, 5 H); 7.23 (*s*, 1 H); 7.34 (*s*, 5 H); 7.43 (*d*, $J = 8.1$, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 10.19 (Me); 11.39 (Me); 15.44 (Me); 17.85 (Me); 19.64 (Me); 21.36 (Me); 22.88 (Me); 24.57 (CH); 24.82 (CH_2); 25.27 (CH_2); 28.25 (Me); 29.47 (CH); 37.00 (CH); 38.71 (CH_2); 40.04 (CH_2); 51.89 (Me); 53.25 (CH); 55.71 (CH); 56.91 (CH); 59.78 (CH); 67.33 (C); 68.45 (CH_2); 80.37 (C); 127.28 (CH); 128.29 (CH); 128.64 (CH); 128.86 (CH); 129.90 (CH); 134.40 (C); 134.69 (C); 156.14 (C); 166.32 (C); 169.49 (C); 171.33 (C); 171.46 (C); 172.34 (C); 173.38 (C). FAB-MS: 1649 (47, $[2M+1]^+$), 846(47), 825 (70, $[M+1]^+$), 724(100), 538(39), 231(28), 154(21), 146(27), 120(23).

Data of **86b**: t_R 24.3 min (hexane/i-PrOH 98:2). M.p. 108.3–111.0°. $[\alpha]_D^{rt} = -28.0$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.75–0.96 (*m*, 21 H); 1.10–1.65 (*m*, 6 H); 1.43 (*s*, 9 H); 1.75–2.00 (*m*, 2 H); 2.00–2.15 (*m*, 1 H); 3.55 (*AB*, $J_{AB} = 14$, 1 H); 3.74 (*s*, 3 H); 3.76 (*AB*, $J_{AB} = 13.5$, 1 H); 3.85 (*dd*, $J = 8.7$, 6.5, 1 H); 4.22–4.29 (*m*, 1 H); 4.37–4.45 (*m*, 1 H); 4.58 (*dd*, $J = 5$, 8.4, 1 H); 5.12 (br. *d*, $J = 8$, 1 H); 5.19 (*AB*, $J_{AB} = 17$, 2 H); 6.49 (*d*, $J = 7.5$, 1 H); 6.52 (*d*, $J = 6.5$, 1 H); 6.90 (*d*, $J = 6.4$, 2 H); 6.96 (*d*, $J = 7.8$, 1 H); 7.10–7.17 (*m*, 3 H); 7.19 (*s*, 1 H); 7.34 (*s*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.72 (Me); 11.56 (Me); 15.46 (Me); 17.77 (Me); 19.33 (Me); 21.71 (Me); 22.92 (Me); 24.46 (CH); 25.20 (CH_2); 25.60 (CH_2); 28.25 (Me); 30.58 (CH); 37.71 (CH); 38.35 (CH_2); 41.60 (CH_2); 51.60 (CH); 52.23 (Me); 55.15 (CH); 56.65 (CH); 60.06 (CH); 67.31 (C); 68.53 (CH_2); 0.00 (C); 127.22 (CH); 128.23 (CH); 128.60 (CH); 128.71 (CH); 128.89 (CH); 129.97 (CH); 134.34 (C); 134.47 (C); 155.80 (C); 165.44 (C); 168.97 (C); 170.47 (C); 171.26 (C); 171.81 (C); 172.31 (C). FAB-MS: 1649 (8, $[2M+1]^+$), 825 (29, $[M+1]^+$), 724(12), 538(9), 391(47), 254(22), 231(8),

154 (299, 149 (100), 146 (10), 137 (31), 120 (12). Anal. calc. for $C_{44}H_{65}N_5O_{10}$: C 64.13, H 7.95, N 8.50; found: C 64.10, H 7.84, N 8.49.

Boc-Val-Leu-(cyclopent-2-enyl)Ama(OBn)-Abu-Ile-OMe (**87a–d**). According to *GP 5*, with **6** (0.733 g, 1.0 mmol), cyclopent-2-enyl bromide (0.44 ml, 3.0 mmol), and *t*-BuOK (145 mg, 1.3 mmol) in THF (40 ml); 14 h. FC (hexane/AcOEt 7:3): gave 0.511 g (64%) of **87a–d** as a mixture of four diastereoisomers (unseparated). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.78–0.84 (*m*, 6 H); 0.87–0.94 (*m*, 15 H); 1.16–1.27 (*m*, 1 H); 1.42 (*s*, 9 H); 1.35–1.67 (*m*, 4 H); 1.69–2.09 (*m*, 8 H); 2.17–2.30 (*m*, 2 H); 3.54–3.57 (*m*, 1 H); 3.72, *3.73* (2*s*, 3 H); 3.90–3.99 (*m*, 1 H); 4.33–4.42 (*m*, 1 H); 4.43–4.50 (*m*, 2 H); 5.06–5.09 (*m*, 1 H); 5.11–5.17 (*m*, 2 H); 5.54–5.56, *5.72–5.74* (2*m*, 1 H); 5.83–5.85 (*m*, 1 H); 6.92, *6.97* (2*d*, *J* = 7.7, 7.5, 1 H); 7.00–7.16 (*m*, 2 H); 7.30–7.36 (*m*, 5 H); 8.09 (br. *s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 10.20, *10.08* (Me); 11.25, *11.28* (Me); 15.47, *15.50* (Me); 17.66 (Me); 19.57, *19.59* (Me); 22.12, *22.24* (Me); 22.48, *22.62* (Me); 24.18, *24.27* (CH_2); 24.47, *24.49* (CH); 24.78, *24.81* (CH_2); 25.33 (CH_2); *28.30* (Me); 30.66, *30.73* (CH); 31.7, *31.85* (CH_2); 36.94, *37.02* (CH); 39.76, *39.90* (CH_2); 50.98 (CH); 51.63, *51.81* (CH); 52.05 (Me); 55.15, *55.19* (CH); 56.71 (CH); 67.66, *67.86* (C); 67.95, *68.08* (CH_2); 79.75, *79.85* (C); 128.50 (CH); 128.53 (CH); 128.59 (CH); 128.82 (CH); 134.64 (CH); 134.69 (CH); 134.70 (C); 134.91 (CH); 155.93 (C); 167.50, *167.59* (C); 170.6 (C); 172.01 (C); 171.24, *171.29* (C); 172.37, *172.53* (C); 173.06, *173.13* (C).

Boc-Val-Leu-(cyclohex-2-enyl)Ama(OBn)-Abu-Ile-OMe (**88a–d**). According to *GP 5*, with **6** (1.00 g, 1.36 mmol), cyclohex-2-enyl bromide (0.47 ml, 4.08 mmol), and *t*-BuOK (199 mg, 1.77 mmol) in THF (40 ml); 10 h. FC (hexane/AcOEt 2:1): 0.842 g (76%) of **88a–d** as a mixture of four diastereoisomers (unseparated). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.72–0.97 (*m*, 21 H); 1.11–1.26 (*m*, 1 H); 1.27–2.09 (*m*, 15 H); 1.414, *1.417* (2*s*, 9 H); 2.95–3.05 (br. *m*, 1 H); 3.69, *3.70*, *3.71*, *3.72* (4*s*, 3 H); 3.96–4.02 (*m*, 1 H); 4.35–4.53 (*m*, 3 H); 5.08–5.16 (*m*, 3 H); 5.47–5.50 (*m*, 0.5 H); 5.68–5.80 (*m*, 2.5 H); 7.07, *7.12* (2*d*, *J* = 8.1, 8.4, 1 H); 7.20–7.37 (*m*, 6 H); 8.16, *8.32* (2*d*, *J* = 7.8, 7.8, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 10.08; 10.13; 10.84; 11.19; 15.55; 16.78; 17.63; 19.59; 21.64; 22.21; 22.39; 22.58; 23.89; 24.10; 24.48; 24.72; 25.38; 25.71; 28.34; 30.75; 36.85; 39.75; 39.96; 41.53; 41.62; 50.77; 52.16; 55.13; 55.21; 56.85; 59.82; 68.12; 68.27; 68.46; 79.79; 124.41; 124.54; 128.74; 128.81; 131.36; 131.54; 134.94; 156.18; 167.76; 167.96; 171.26; 171.34; 171.61; 171.68; 172.78; 172.83; 172.91; 173.10; 173.52; 173.65. FAB-MS: 1628 (4, $[2M+1]^+$), 836 (26, $[M+23]^+$), 814 (63, $[M+1]^+$), 714 (100), 669 (19), 613 (23), 528 (34), 502 (23).

Boc-Val-Leu-(CO_2Bn)Glu(O^{t}Bu)Abu-Ile-OMe (**89**). According to *GP 5*, with **6** (1.00 g, 1.36 mmol), *tert*-butyl acrylate (0.59 ml, 4.08 mmol) and *t*-BuOK (20 mg, 0.17 mmol) in THF (40 ml); 6 h. FC (hexane/AcOEt 2:1): 1.05 g (89%) of **89** (diastereoisomerically pure). t_R 25.5 min (hexane/i-PrOH 98:2). $[\alpha]_D^{r.t.} = -58.1$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.81–0.94 (*m*, 21 H); 1.14–1.25 (*m*, 1 H); 1.41 (*s*, 9 H); 1.43 (*s*, 9 H); 1.40–1.51 (*m*, 1 H); 1.7–1.75 (*m*, 3 H); 1.91–1.99 (*m*, 3 H); 2.04–2.16 (*m*, 3 H); 2.44–2.59 (*m*, 2 H); 3.72 (*s*, 3 H); 3.91 (*dd*, *J* = 6.6, 8.6, 1 H); 4.29–4.34 (*m*, 2 H); 4.49 (*dd*, *J* = 6.3, 8.6, 1 H); 5.02 (*d*, *J* = 8.2, 1 H); 5.18 (*s*, 2 H); 6.81 (*d*, *J* = 6.7, 1 H); 6.98 (*d*, *J* = 8.7, 1 H); 7.30–7.36 (*m*, 5 H); 7.68 (*s*, 1 H); 7.70 (*d*, *J* = 10, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 10.00 (Me); 11.37 (Me); 15.46 (Me); 17.81 (Me); 19.52 (Me); 21.81 (Me); 22.78 (Me); 24.57 (CH); 24.85 (CH_2); 25.25 (CH_2); 28.04 (Me); 29.35 (Me); 29.35 (CH_2); 30.12 (CH_2); 30.32 (CH); 37.18 (CH); 40.25 (CH_2); 52.06 (CH); 55.33 (CH); 56.70 (CH); 59.82 (CH); 65.48 (C); 68.35 (CH_2); 80.04 (C); 81.03 (C); 128.43 (CH); 128.59 (CH); 128.66 (CH); 134.68 (C); 156.04 (C); 166.95 (C); 170.33 (C); 171.11 (C); 171.73 (C); 172.00 (C); 172.29 (C); 172.68 (C). FAB-MS: 1724 (52, $[2M+1]^+$), 885 (28), 862 (66, $[M+1]^+$), 762 (49), 706 (100), 688 (17), 520 (24), 236 (32), 231 (21), 154 (20), 146 (32).

Boc-Val-Leu-(CH_2CH_2CN)Ama(OBn)-Abu-Ile-OMe (**90a/b**). According to *GP 5*, with **6** (0.50 g, 0.68 mmol), acryl nitrile (0.13 ml, 2.04 mmol), and *t*-BuOK (10 mg, 0.1 mmol) in THF (40 ml); 10 h. FC (hexane/AcOEt 2:1): 0.434 g (85%) of **90a/b** as a 4:1 mixture of epimers. Separated by FC (hexane/AcOEt 4:1).

Data of **90a**: $[\alpha]_D^{r.t.} = -52.0$ ($c = 1.02$, EtOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.69 (*dd*, *J* = 7.5, 7.4, 3 H); 0.74 (*d*, *J* = 6.3, 3 H); 0.80 (*d*, *J* = 6.4, 3 H); 0.87–0.93 (*m*, 12 H); 1.10–1.25 (*m*, 1 H); 1.33–1.69 (*m*, 6 H); 1.41 (*s*, 9 H); 1.82–1.92 (*m*, 1 H); 2.02–2.08 (*m*, 1 H); 2.19–2.37 (*m*, 2 H); 2.45–2.55 (*m*, 1 H); 2.83–2.93 (*m*, 1 H); 3.73 (*s*, 3 H); 3.77–3.82 (*m*, 1 H); 4.49–4.66 (*m*, 2 H); 4.60 (*dd*, *J* = 4.9, 8.9, 1 H); 5.08 (*AB*, J_{AB} = 11.9, 1 H); 5.19 (*AB*, J_{AB} = 11.9, 1 H); 5.58 (br. *d*, 1 H); 6.29 (*d*, *J* = 7.0, 1 H); 6.70 (*d*, *J* = 8.5, 1 H); 7.12 (br. *d*, 1 H); 7.27–7.33 (*m*, 5 H); 8.04 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.58 (Me); 11.49 (Me); 11.90 (CH_2); 15.37 (Me); 18.03 (Me); 19.28 (Me); 22.04 (Me); 22.72 (Me); 24.50 (CH); 25.24 (CH_2); 25.97 (CH_2); 28.32 (Me); 29.58 (CH_2); 30.46 (CH); 37.97 (CH); 40.76 (CH_2); 51.93 (CH); 52.08 (Me); 54.64 (CH); 56.42 (CH); 60.45 (CH); 65.37 (C); 68.69 (CH_2); 79.87 (C); 118.41 (C); 128.64 (C); 128.77 (CH); 128.93 (CH); 134.50 (C); 156.01 (C); 164.99 (C); 168.51 (C); 170.59 (C); 171.63 (C); 172.53 (C); 172.76 (C). FAB-MS: 1573 (6, $[2M+1]^+$), 787 (77, $[M+1]^+$), 687 (100), 642 (8), 586 (23), 457 (49).

Data of **90b**: $[\alpha]_D^{r.t.} = -42.2$ ($c = 1.15$, EtOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.75–0.80 (*m*, 3 H); 0.81–0.98 (*m*, 18 H); 1.12–1.34 (*m*, 1 H); 1.44 (*s*, 9 H); 1.53–1.74 (*m*, 5 H); 1.87–1.96 (*m*, 2 H); 2.07–2.16 (*m*, 1 H); 2.20–2.25 (*m*, 2 H); 2.68–2.87 (*m*, 2 H); 3.72 (*s*, 3 H); 3.87 (*dd*, $J = 7.4$, 7.4, 1 H); 4.17–4.27 (*m*, 2 H); 4.50 (*dd*, $J = 5.8$, 8.5, 1 H); 4.90 (*d*, $J = 7.8$, 1 H); 5.16–5.27 (*m*, 2 H); 6.78–6.81 (br. *m*, 2 H); 7.24 (*d*, $J = 9.0$, 1 H); 7.30–7.37 (*m*, 5 H); 7.64 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 10.02 (Me); 11.46 (Me); 12.19 (CH_2); 15.43 (Me); 17.85 (Me); 19.57 (Me); 21.29 (Me); 22.97 (Me); 24.78 (CH); 25.01 (CH_2); 25.27 (CH_2); 28.28 (Me); 28.57 (CH_2); 29.50 (CH); 37.37 (CH); 39.74 (CH_2); 51.94 (Me); 53.46 (CH); 55.76 (CH); 56.76 (CH); 60.17 (CH); 65.83 (C); 68.97 (CH_2); 80.72 (C); 118.56 (C); 128.60 (CH); 128.69 (CH); 128.86 (CH); 134.32 (C); 156.30 (C); 165.47 (C); 168.44 (C); 170.87 (C); 171.88 (C); 172.20 (C); 173.46 (C). FAB-MS: 1573 (13, $[2M + 1]^+$), 809 (14, $[M + 23]^+$), 878 (44, $[M + 1]^+$), 687 (100), 642 (2), 586 (4), 457 (14).

5.6. *Alkylation of* **7**. *Boc-Val-Leu-(CO_2All)Glu(O^tBu)-Abu-Ile-OMe* (**91**). According to *GP 5*, with **7** (0.983 g, 1.47 mmol), *tert*-butyl acrylate (0.65 ml, 4.5 mmol), and *t*-BuOK (33 mg, 0.33 mmol) in THF (40 ml); 2 h. FC (hexane/AcOEt 2:1): 1.039 g (89%) of **91** (diastereoisomerically pure). $[\alpha]_D^{r.t.} = -43.4$ ($c = 1.00$, EtOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.84–0.95 (*m*, 21 H); 1.13–1.25 (*m*, 1 H); 1.35–1.52 (*m*, 2 H); 1.41 (*s*, 9 H); 1.42 (*s*, 9 H); 1.62–1.76 (*m*, 3 H); 1.89–2.12 (*m*, 3 H); 2.15–2.21 (*m*, 2 H); 2.41–2.57 (*m*, 2 H); 3.71 (*s*, 3 H); 3.93 (*dd*, $J = 6.5$, 8.4, 1 H); 4.31–4.43 (*m*, 2 H); 4.49 (*dd*, $J = 6.2$, 8.4, 1 H); 4.62–4.64 (*m*, 2 H); 5.04 (*d*, $J = 8.4$, 1 H); 5.23 (*dd*, $J = 1.2$, 10.4, 1 H); 5.28–5.34 (*m*, 1 H); 5.78–5.91 (*m*, 1 H); 6.83 (*d*, $J = 6.8$, 1 H); 6.97 (*d*, $J = 8.7$, 1 H); 7.71 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 10.05 (Me); 11.36 (Me); 15.46 (Me); 17.81 (Me); 19.54 (Me); 21.95 (Me); 22.79 (Me); 24.65 (CH); 24.91 (CH); 25.27 (CH_2); 28.07 (Me); 28.33 (Me); 29.43 (CH); 30.20 (CH_2); 30.43 (CH_2); 37.18 (CH_2); 40.43 (CH_2); 52.04 (Me); 52.19 (CH); 55.33 (CH); 56.85 (CH); 59.95 (CH); 65.50 (C); 67.32 (CH_2); 80.23 (C); 81.24 (C); 119.67 (CH_2); 131.15 (CH); 156.36 (C); 167.42 (C); 170.56 (C); 171.44 (C); 172.08 (C); 172.39 (C); 172.91 (C); 173.07 (C). FAB-MS: 1625 (3, $[2M + 1]^+$), 834 (46, $[M + 23]^+$), 812 (67, $[M + 1]^+$), 712 (52), 667 (13), 656 (100), 638 (17), 470 (18).

5.7. *Alkylation of* **8**. *General Procedure for Alkylation of* **8** (*GP 6*). The heptapeptide **8** and 30 equiv. of LiBr were dissolved in THF under Ar and cooled to 0° (ice bath). Then, *t*-BuOK was added. After 10 min, 3 equiv. of the electrophile were added. The mixture was stirred at 4° for several h. For the workup, the mixture was diluted with AcOEt and washed with 1N HCl and sat. NaCl soln. The aq. phases were extracted twice with AcOEt. The combined org. layers were dried ($MgSO_4$) and evaporated.

Boc-Val-Ala-Leu-(All)Ama(OMe)-Val-Ala-Leu-OMe (**92a**/**b**). According to *GP 6*, with **8** (0.407 g, 0.5 mmol), LiBr (1.30 g, 15.0 mmol), *t*-BuOK (72 mg, 0.65 mmol), and allyl bromide (0.12 ml, 1.5 mmol) in THF (100 ml); 60 h. FC (hexane/AcOEt 1:4): 0.222 g (52%) **92a**/**b** as a 6.2:1 mixture of two epimers. Separation by FC (hexane/AcOEt 1:2).

Data of **92a**: ^{1}H-NMR (300 MHz, CD_3OD): 0.83–0.95 (*m*, 24 H); 1.34 (*d*, $J = 7.1$, 3 H); 1.37 (*d*, $J = 7.1$, 3 H); 1.43 (*s*, 9 H); 1.55–1.68 (*m*, 6 H); 1.95–2.15 (*m*, 2 H); 2.90–3.05 (*m*, 2 H); 3.68 (*s*, 3 H); 3.71 (*s*, 3 H); 3.88 (*d*, $J = 6.4$, 1 H); 4.20 (*d*, $J = 7.1$, 1 H); 4.30–4.49 (*m*, 5 H); 5.03–5.11 (*m*, 2 H); 5.50–5.73 (*m*, 1 H). ^{13}C-NMR (300 MHz, CD_3OD): 17.95 (Me); 18.36 (Me); 19.70 (Me); 19.76 (Me); 21.82 (Me); 23.28 (Me); 23.35 (Me); 25.66 (CH); 25.79 (CH); 28.68 (Me); 32.08 (CH); 38.77 (CH_2); 41.44 (CH_2); 48.33 (CH); 49.19 (CH); 50.14 (CH); 52.11 (Me); 52.65 (Me); 52.99 (CH); 53.66 (CH); 60.26 (CH); 61.47 (CH); 67.21 (CH_2); 80.74 (C); 120.57 (CH_2); 132.51 (CH); 151.24 (C); 168.57 (C); 171.39 (C); 172.88 (C); 174.15 (C); 174.37 (C); 174.91 (C). FAB-MS: 902 (3), 876 (55, $[M + 23]^+$), 854 (100, $[M + 1]^+$), 754 (33), 709 (21), 638 (32), 582 (13), 483 (38), 391 (47), 328 (11).

Data of **92b**: ^{1}H-NMR (500 MHz, $CDCl_3$): 0.88–0.97 (*m*, 21 H); 0.99 (*d*, $J = 6.9$, 3 H); 1.41 (*d*, $J = 7.2$, 3 H); 1.45 (*d*, $J = 7.3$, 3 H); 1.47 (*s*, 9 H); 1.53–1.59 (*m*, 1 H); 1.64–1.76 (*m*, 5 H); 2.10–2.17 (*m*, 1 H); 2.43–2.49 (*m*, 1 H); 2.99–3.08 (*m*, 2 H); 3.71 (*s*, 3 H); 3.78 (*s*, 3 H); 3.91–4.05 (*m*, 1 H); 4.13–4.17 (*m*, 1 H); 4.24 (*dd*, $J = 4.6$, 7.3, 1 H); 4.37–4.40 (br. *m*, 1 H); 4.45–4.51 (*m*, 1 H); 4.52–4.56 (*m*, 1 H); 5.05–5.11 (*m*, 3 H); 6.62 (*d*, $J = 5.8$, 1 H); 7.02 (*d*, $J = 8.1$, 1 H); 7.28 (*d*, $J = 7.9$, 1 H); 7.50 (*d*, $J = 9.4$, 1 H); 7.49 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 17.05 (Me); 17.09 (Me); 17.30 (Me); 18.13 (Me); 19.26 (Me); 19.29 (Me); 21.76 (Me); 22.01 (Me); 22.33 (Me); 22.92 (Me); 24.59 (CH); 24.72 (CH); 28.27 (Me); 28.85 (CH); 30.15 (CH); 37.20 (CH_2); 40.02 (CH_2); 40.72 (CH_2); 49.36 (CH); 49.96 (CH); 50.92 (CH); 52.12 (Me); 53.51 (Me); 53.99 (CH); 60.31 (CH); 60.82 (CH); 66.07 (C); 80.98 (C); 120.05 (CH_2); 131.12 (CH); 156.72 (C); 167.75 (C); 169.74 (C); 170.70 (C); 172.14 (C); 172.51 (C); 172.78 (C); 173.10 (C); 173.61 (C). FAB-MS: 1730 (2, $[2M + 23]^+$), 1708 (1, $[2M + 1]^+$), 876 (100, $[M + 23]^+$), 854 (41, $[M + 1]^+$), 754 (19), 638 (8), 483 (6).

Boc-Val-Ala-Leu-(CH_2CH_2CN)Ama(OMe)-Val-Ala-Leu-OMe (**93a**/**b**). According to *GP 6*, with **8** (0.122 g, 0.15 mmol), LiBr (0.39 g, 4.5 mmol), *t*-BuOK (5 mg, 0.04 mmol), and acrylonitrile (20 µl, 0.45 mmol) in THF (40 ml); 48 h. FC (hexane/AcOEt 1:4): 0.102 g (78%) **93a**/**b** as a 4:1 mixture of two diastereoisomers.

Data of **93b**: ^{1}H-NMR (500 MHz, $CDCl_3$): 0.86–1.01 (*m*, 24 H); 1.17–1.41 (*m*, 2 H); 1.44 (*d*, *J* = 7.1, 3 H); 1.45 (*d*, *J* = 7.1, 3 H); 1.49 (*s*, 9 H); 1.61–1.78 (*m*, 4 H); 2.07–2.15 (*m*, 1 H); 2.28–2.37 (*m*, 2 H); 2.38–2.43 (*m*, 1 H); 2.68–2.72 (*m*, 2 H); 3.71 (*s*, 3 H); 3.83 (*s*, 3 H); 3.92 (*dd*, *J* = 5.7, 4.4, 1 H); 4.14–4.26 (*m*, 3 H); 4.39–4.46 (*m*, 1 H); 4.52–4.58 (*m*, 1 H); 5.38 (br. *s*, 1 H); 6.89 (*d*, *J* = 4.6, 1 H); 7.08 (*d*, *J* = 8.2, 1 H); 7.25 (*d*, *J* = 8.0, 1 H); 7.35 (*d*, *J* = 6.7, 1 H); 7.58 (*d*, *J* = 6.1, 1 H); 7.74 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 12.19 (CH_2); 17.16 (Me); 17.20 (Me); 17.56 (Me); 19.23 (Me); 19.23 (Me); 19.27 (Me); 21.74 (Me); 21.79 (Me); 22.44 (Me); 22.98 (Me); 24.61 (CH); 24.93 (CH); 28.21 (CH_2); 28.29 (Me); 28.98 (CH); 29.93 (CH); 39.83 (CH_2); 40.74 (CH_2); 49.82 (CH); 50.84 (CH); 50.92 (CH); 52.17 (Me); 53.82 (Me); 54.38 (CH); 61.05 (CH); 61.40 (CH); 65.43 (C); 81.19 (C); 118.70 (C); 157.16 (C); 167.41 (C); 168.48 (C); 170.90 (C); 172.87 (C); 173.02 (C); 173.21 (C); 173.50 (C); 174.12 (C). FAB-MS: 1756 (7, $[2M+23]^+$), 1734 (4, $[2M+1]^+$), 889 (100, $[M+23]^+$), 867 (47, $[M+1]^+$), 767 (23, $[M-100]^+$), 391 (10).

Boc-Val-Ala-Leu-(CH$_2$CH$_2$COMe)Ama(OMe)-Val-Ala-Leu-OMe (**94a**/**b**). According to *GP 6*, with **8** (0.122 g, 0.15 mmol), LiBr (0.39 g, 4.5 mmol), *t*-BuOK (5 mg, 0.04 mmol), and methyl vinyl ketone (40 µl, 0.45 mmol) in THF (40 ml); 48 h. FC (hexane/AcOEt 1:4): 0.114 g (78%) **94a**/**b** as a 3:1 mixture of epimers (not separated). ^{1}H-NMR (400 MHz, CD_3OD): 0.87–0.97 (*m*, 24 H); 1.35–1.41 (*m*, 6 H); 1.45, *1.46* (2*s*, 9 H); 1.58–1.71 (*m*, 6 H); 1.94–2.24 (*m*, 2 H); 2.10, *2.11* (2*s*, 3 H); 2.42–2.52 (*m*, 4 H); 3.695, *3.699*, 3.71, *3.76* (4*s*, 6 H); 3.86–3.92 (*m*, 1 H); 4.10–4.12, *4.19–4.21* (2*m*, 1 H); 4.25–4.52 (*m*, 6 H). ^{13}C-NMR (100 MHz, $CDCl_3$; 2 epimers): 17.87, 17.97, 18.07, 18.14, 18.39, 18.53, 18.63, 18.75, 19.76, 19.81, 19.87, 21.89, 21.92, 21.99, 22.29, 23.09, 23.35, 23.40 (18 Me); 25.72, 25.82, 25.84, 25.88 (4 CH); 28.16 (CH_2); 28.78 (Me); 28.90 (CH); 29.90, 29.96 (2 CH_2); 31.31, 31.91, 32.00 (3 CH); 38.54, 41.17, 41.36, 41.43, 41.48 (5 CH_2); 50.20, 50.53, 50.65, 50.99, 52.16, 52.23 (6 CH); 52.67 (Me); 53.05 (CH); 53.70, *54.01* (Me); 54.49, 60.45, 61.33, 61.56, 61.66 (5 CH); 66.48, *66.97* (C); 80.76 (C); 158.26, *158.41* (C); 168.95, *169.52* (C); 171.03, 171.87, 172.82, 174.25, 174.34, 174.44, 174.53, 174.78, 175.01, 175.91 (C); 209.29, *209.57* (C). FAB-MS: 906 (54, $[M+23]^+$), 884 (100, $[M+1]^+$), 826 (12), 785 (35), 739 (24), 668 (30), 612 (12), 513 (14).

Boc-Val-Ala-Leu-(CO$_2$Me)Glu(O^{t}Bu)-Val-Ala-Leu-OMe (**95**). According to *GP 6*, with **8** (0.162 g, 0.2 mmol), LiBr (0.521 g, 6.0 mmol), *t*-BuOK (30 mg, 0.2 mmol), and *tert*-butyl acrylate (0.08 ml, 0.6 mmol) in THF (40 ml); 60 h. FC (hexane/AcOEt 1:4): 0.161 g (85%) **95** (diastereoisomerically pure). $[\alpha]_D^{r.t.} = -66.8$ ($c = 0.98$, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.73–0.99 (*m*, 24 H); 1.41 (*s*, 9 H); 1.41 (*d*, *J* = 6.8, 3 H); 1.44 (*d*, *J* = 7.3, 3 H); 1.47 (*m*, 9 H); 1.55–1.77 (*m*, 6 H); 2.03–2.21 (*m*, 3 H); 2.44–2.52 (*m*, 3 H); 3.71 (*s*, 3 H); 3.78 (*s*, 3 H); 3.97 (br. *dd*, *J* = 5.4, 5.4, 1 H); 4.20–4.26 (*m*, 2 H); 4.32–4.40 (br. *m*, 1 H); 4.42–4.52 (*m*, 2 H); 5.16 (br. *d*, 1 H); 6.64 (*d*, *J* = 5.6, 1 H); 7.00 (*d*, *J* = 7.7, 1 H); 7.27 (*d*, *J* = 7.4, 1 H); 7.48 (*d*, *J* = 6.3, 1 H); 7.60–7.63 (*m*, 1 H); 7.63 (*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 16.89 (Me); 16.94 (Me); 17.44 (Me); 18.10 (Me); 19.21 (Me); 19.36 (Me); 21.78 (Me); 22.01 (Me); 22.40 (Me); 22.86 (Me); 24.57 (CH); 24.73 (CH); 28.01 (Me); 28.24 (Me); 28.34 (CH_2); 28.83 (CH); 30.03 (CH_2); 30.19 (CH); 39.84 (CH_2); 40.67 (CH_2); 40.35 (CH); 50.00 (CH); 50.99 (CH); 52.09 (CH); 53.43 (CH); 53.53 (Me); 60.06 (CH); 60.75 (CH); 65.28 (C); 80.74 (C); 80.82 (C); 156.65 (C); 168.01 (C); 170.43 (C); 170.80 (C); 171.43 (C); 172.04 (C); 172.67 (C); 172.78 (C); 173.06 (C); 173.43 (C). FAB-MS: 1906 (25, $[2M+23]^+$), 1884 (10, $[2M+1]^+$), 965 (48, $[M+23]^+$), 964 (100), 942 (46, $[M+1]^+$), 842 (21), 786 (24), 515 (14), 471 (13), 301 (12), 215 (17).

5.8. *Alkylation of* **4**. *Boc-Leu-(CN)Ala-Leu-OMe* (**96a**/**b**). According to *GP 5*, with **4** (1.321 g, 3.0 mmol), *t*-BuOK (0.504 g, 4.5 mmol), and MeI (0.56 ml, 9.0 mmol) in THF (80 ml); 4 h. FC (hexane/AcOEt 3:1): 0.550 g (40%) of **96a** and 0.570 g (41%) of **96b**.

Data of **96a**: $[\alpha]_D^{r.t.} = -31.8$ ($c = 1.00$, EtOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.90–0.94 (*m*, 12 H); 1.44 (*s*, 9 H); 1.62–1.72 (*m*, 6 H); 1.84 (*s*, 3 H); 3.73 (*s*, 3 H); 4.05–4.13 (br. *s*, 1 H); 4.53–4.60 (*m*, 1 H); 4.96 (*d*, *J* = 6.8, 1 H); 6.85 (*d*, *J* = 6.8, 1 H); 7.42 (*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.59 (Me); 21.67 (Me); 22.65 (Me); 22.78 (Me); 24.09 (Me); 24.50 (CH); 24.64 (CH); 28.12 (Me); 39.95 (CH_2); 40.81 (Me); 51.68 (CH); 52.39 (Me); 52.60 (CH); 52.97 (C); 80.83 (C); 117.59 (C); 156.35 (C); 165.67 (C); 172.45 (C).

Data of **96b**: R_f 0.11 (hexane/AcOEt 2:1). $[\alpha]_D^{r.t.} = -56.9$ ($c = 1.01$, EtOH). ^{1}H-NMR (200 MHz, $CDCl_3$): 0.92–0.97 (*m*, 12 H); 1.46 (*s*, 9 H); 1.54–1.76 (*m*, 6 H); 1.86 (*s*, 3 H); 3.73 (*s*, 3 H); 3.99–4.09 (*m*, 1 H); 4.50–4.61 (*m*, 1 H); 5.31 (*d*, *J* = 7.5, 1 H); 7.27–7.29 (br. *m*, 1 H); 7.49 (*s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 21.48 (Me); 21.57 (Me); 22.69 (Me); 22.91 (Me); 24.15 (Me); 24.53 (CH); 28.14 (Me); 39.22 (CH_2); 40.56 (CH_2); 51.51 (CH); 52.27 (Me); 52.97 (CH); 53.63 (C); 80.84 (C); 117.59 (C); 156.22 (C); 166.28 (C); 172.63 (C). FAB-MS: 909 (23, $[2M+1]^+$), 809 (8), 640 (7), 477 (11, $[M+23]^+$), 455 (35, $[M+1]^+$), 399 (54), 355 (100), 215 (19).

Boc-Leu-(All)Aca-Leu-OMe (**97a**/**b**). According to *GP 5*, with **4** (0.442 g, 1.0 mmol), *t*-BuOK (0.131 g, 1.3 mmol), and allyl bromide (0.26 ml, 3.0 mmol) in THF (40 ml); 10 h. FC (hexane/AcOEt 3:1): 0.179 g (37%) of **97a** and 0.177 g (37%) of **97b**.

Data of **97a**: R_f 0.40 (hexane/AcOEt 2:1). $[\alpha]_D^{r.t.} = -43.0$ ($c = 1.00$, EtOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.91–0.96 (*m*, 12 H); 1.45 (*s*, 9 H); 1.53–1.77 (*m*, 6 H); 2.81 (*ABX*, $J_{AB} = 14.0$, $J_{AX} = 7.5$, 1 H); 2.95 (*ABX*, $J_{AB} = 14.0$, $J_{AX} = 7.0$, 1 H); 3.74 (*s*, 3 H); 4.11–4.20 (br. *m*, 1 H); 4.51–4.63 (*m*, 1 H); 4.93 (br. *d*, $J =$ 5.8, 1 H); 5.30–5.39 (*m*, 2 H); 5.72–5.93 (*m*, 1 H); 6.86 (*d*, $J = 7.9$, 1 H); 7.26 (*s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 21.51 (Me); 21.67 (Me); 22.65 (Me); 22.75 (Me); 24.49 (CH); 24.62 (CH); 28.11 (Me); 39.78 (CH_2); 40.75 (CH_2); 40.84 (CH_2); 51.67 (Me); 52.30 (CH); 52.74 (CH); 56.49 (C); 80.74 (C); 116.61 (C); 122.93 (CH_2); 128.80 (CH); 156.20 (C); 164.57 (C); 172.13 (C); 172.13 (C); 172.28 (C). FAB-MS: 983 (17, $[2M + 23]^+$), 961 (42, $[2M + 1]^+$), 861 (12), 503 (43, $[M + 23]^+$), 481 (39, $[M + 1]^+$), 425 (100), 381 (25).

Data of **97b**: R_f 0.24 (hexane/AcOEt 2:1). $[\alpha]_D^{r.t.} = -56.0$ ($c = 1.02$, EtOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.81–0.95 (*m*, 12 H); 1.44 (*s*, 9 H); 1.60–1.75 (*m*, 6 H); 2.79–2.94 (*m*, 2 H); 3.71 (*s*, 3 H); 3.91–4.01 (*m*, 1 H); 4.48–4.59 (*m*, 1 H); 5.12–5.16 (*m*, 1 H); 5.31–5.39 (*m*, 2 H); 5.78–5.99 (*m*, 1 H); 7.13–7.24 (*m*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 21.50 (Me); 21.63 (Me); 22.74 (Me); 22.96 (Me); 24.52 (CH); 24.68 (CH); 28.23 (Me); 39.09 (Me); 40.68 (Me); 41.34 (CH_2); 51.63 (Me); 52.27 (CH); 53.22 (CH); 56.55 (C); 81.03 (C); 116.52 (C); 122.74 (CH_2); 129.34 (CH); 156.01 (C); 164.90 (C); 171.72 (C); 172.52 (C). FAB-MS: 983 (7, $[2M + 23]^+$), 961 (73, $[2M + 1]^+$), 861 (29), 805 (13), 666 (14), 503 (22, $[M + 23]^+$), 481 (60, $[M + 1]^+$), 425 (70), 381 (100).

Boc-Leu-(CN)Phe-Leu-OMe (**98a/b**). According to *GP 5*, with **4** (0.448 g, 1.0 mmol), *t*-BuOK (0.131 g, 1.3 mmol), and BnBr (0.36 ml, 3.0 mmol) in THF (40 ml); 6 h. FC (pentane/Et_2O 2:1): 0.155 g (29%) of **98a**, 30 mg (5.6%) **98a/b**, and 0.173 g (32%) of **98b**.

Data of **98a**: R_f 0.46 (hexane/AcOEt 2:1). $[\alpha]_D^{r.t.} = -59.6$ ($c = 0.95$, EtOH). ^{1}H-NMR (200 MHz, $CDCl_3$): 0.92–0.96 (*m*, 12 H); 1.43 (*s*, 9 H); 1.46–1.74 (*m*, 6 H); 3.38 (*AB*, $J_{AB} = 13.7$, 1 H); 3.48 (*AB*, $J_{AB} = 13.7$, 1 H); 3.72 (*s*, 3 H); 4.09–4.12 (*m*, 1 H); 4.54–4.62 (*m*, 1 H); 4.81 (*d*, $J = 7.5$, 1 H); 6.64 (*d*, $J = 7.9$, 1 H); 7.20 (*s*, 1 H); 7.28–7.38 (*m*, 5 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 21.70 (Me); 22.62 (Me); 22.78 (Me); 24.56 (CH); 28.11 (Me); 40.11 (CH_2); 41.19 (CH_2); 42.21 (CH_2); 51.79 (CH_2); 52.33 (CH); 52.90 (CH); 57.89 (C); 80.74 (C); 116.80 (C); 128.48 (CH); 128.48 (CH); 130.38 (CH); 131.85 (C); 164.29 (C); 172.00 (C); 172.09 (C). FAB-MS: 1061 (10, $[2M + 1]^+$), 961 (6), 880 (7), 553 (17, $[M + 23]^+$), 531 (27, $[M + 1]^+$), 475 (100), 431 (25).

Data of **98b**: R_f 0.46 (hexane/AcOEt 2:1). $[\alpha]_D^{r.t.} = -36.8$ ($c = 0.99$, EtOH). ^{1}H-NMR (200 MHz, $CDCl_3$): 0.88–0.97 (*m*, 12 H); 1.31–1.77 (*m*, 6 H); 1.46 (*s*, 9 H); 3.42 (*s*, 2 H); 3.74 (*s*, 3 H); 3.96–4.05 (*m*, 1 H); 4.46–4.57 (*m*, 1 H); 4.90 (*d*, $J = 7.0$, 1 H); 6.89 (*d*, $J = 7.0$, 1 H); 7.08 (*s*, 1 H); 7.28–7.34 (*m*, 5 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 21.64 (Me); 21.70 (Me); 22.53 (Me); 22.75 (Me); 24.43 (CH); 24.53 (CH); 28.18 (Me); 39.57 (CH_2); 40.84 (CH_2); 42.21 (CH_2); 51.67 (Me); 52.33 (CH); 53.00 (CH); 58.11 (C); 80.96 (C); 116.61 (C); 128.54 (CH); 129.12 (CH); 130.32 (CH); 132.13 (C); 156.10 (C); 164.82 (C); 172.00 (C); 172.32 (C). FAB-MS: 1592 (2, $[3M + 1]^+$), 1083 (11, $[2M + 23]^+$), 1061 (83, $[2M + 1]^+$), 961 (40), 905 (17), 553 (31, $[M + 23]^+$), 531 (63, $[M + 1]^+$), 475 (75), 431 (100).

Boc-Leu-(cyclohex-2-enyl)Gly(CN)-Leu-OMe (**99a–d**). According to *GP 5*, with **4** (0.442 g, 1.0 mmol), *t*-BuOK (0.144 g, 1.3 mmol), and cyclohex-2-enyl bromide (0.35 ml, 3.0 mmol) in THF (40 ml); 10 h. FC (pentane/Et_2O 2:1): 0.363 g (74%) of **99a–d** as mixture of four isomers (not separated). ^{1}H-NMR (200 MHz, $CDCl_3$): 0.91–0.95 (*m*, 12 H); 1.44 (*s*, 9 H); 1.24–1.87 (*m*, 10 H); 2.05–2.15 (*m*, 3 H); 3.06–3.20 (br. *m*, 1 H); 3.70 (*s*, 3 H); 3.90–3.95 (br. *m*, 1 H); 4.53–4.58 (*m*, 1 H); 5.05 (*s*, 1 H); 5.75–5.78 (*m*, 1 H); 6.06–6.10 (*m*, 1 H); 6.85, *7.00* (2*s*, 1 H); 7.05, *7.26* (2*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.12 (CH_2); 21.36, *21.46* (Me); 21.52, *21.63* (Me); 22.67, *22.82* (Me); 22.90 (Me); 24.37 (CH); 24.51 (CH); 24.55 (CH_2); 24.61 (CH_2); 24.71 (CH_2); 28.09 (Me); 38.49 (CH_2); 40.51, *40.82* (CH_2); 41.69, *42.33* (CH); 51.53, *51.63* (CH); 51.73 (Me); 52.21, *53.39* (CH); 60.66, *60.91* (C); 81.17 (C); 115.95 (C); 122.81, *123.70* (C); 134.07, *134.75* (CH); 156.17 (C); 164.36, *164.83* (C); 171.56 (CH); 172.70 (C).

Boc-Leu-(CN)Glu(O^{t}Bu)-Leu-OMe (**100a/b**). According to *GP 5*, with **4** (0.440 g, 1.0 mmol), *t*-BuOK (36 mg, 0.3 mmol), and *tert*-butyl acrylate (0.45 ml, 3.0 mmol) in THF (40 ml); 10 h. FC (hexane/AcOEt 3:1): 0.187 g (33%) of **100a**, 0.101 mg (17%) **100a/b**, and 0.215 g (37%) of **100b**.

Data of **100a**: R_f 0.46 (hexane/AcOEt 2:1). $[\alpha]_D^{r.t.} = -34.6$ ($c = 1.06$, EtOH). ^{1}H-NMR (200 MHz, $CDCl_3$): 0.92–0.98 (*m*, 12 H); 1.43–1.79 (*m*, 6 H); 1.48 (*s*, 9 H); 1.49 (*s*, 9 H); 2.31–2.42 (*m*, 2 H); 2.68–2.74 (*m*, 2 H); 3.75 (*s*, 3 H); 4.00–4.15 (br. *m*, 1 H); 4.52–4.60 (*m*, 1 H); 4.86 (*d*, $J = 5.8$, 1 H); 7.30 (*d*, $J = 7.5$, 1 H); 8.41 (*s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 21.45 (Me); 21.67 (Me); 22.75 (Me); 22.84 (Me); 24.68 (CH); 27.92 (Me); 28.14 (Me); 30.65 (CH_2); 31.60 (CH_2); 40.49 (CH_2); 51.63 (Me); 52.30 (CH); 53.38 (CH); 58.20 (C); 80.68 (C); 82.36 (C); 116.55 (C); 165.62 (C); 172.28 (C); 173.71 (C). FAB-MS: 1159 (12, $[2M + 23]^+$), 1137 (13, $[2M + 1]^+$), 1037 (21), 591 (65, $[M + 23]^+$), 569 (41, $[M + 1]^+$), 513 (22), 457 (100), 413 (75).

Data of **100b**: R_f 0.34 (hexane/AcOEt 2:1). $[\alpha]_D^{r.t.} = -46.7$ ($c = 1.00$, EtOH). ^{1}H-NMR (200 MHz, $CDCl_3$): 0.91–0.97 (*m*, 12 H); 1.45 (*s*, 9 H); 1.48 (*s*, 9 H); 1.53–1.80 (*m*, 6 H); 2.35–2.41 (*m*, 2 H); 2.68–2.74 (*m*, 2 H); 3.71 (*s*, 3 H); 3.86–3.89 (*m*, 1 H); 4.49–4.60 (*m*, 1 H); 5.16 (*d*, $J = 6.2$, 1 H); 7.44 (*d*, $J = 7.0$, 1 H); 8.79 (*s*, 1 H).

^{13}C-NMR (50 MHz, $CDCl_3$): 21.35 (Me); 21.45 (Me); 22.69 (Me); 22.97 (Me); 24.30 (CH); 24.56 (CH); 27.89 (Me); 28.11 (Me); 30.56 (CH_2); 31.76 (CH_2); 38.91 (CH_2); 40.30 (CH_2); 51.41 (Me); 52.08 (CH); 53.41 (CH); 58.58 (C); 80.71 (C); 82.42 (C); 116.58 (C); 155.97 (C); 165.78 (C); 172.03 (C); 172.82 (C); 174.19 (C). FAB-MS: 1137 (4, $[2M+1]^+$), 1037 (4), 569 (16, $[M+1]^+$), 513 (11), 457 (11), 413 (100).

6. *Decarboxylation of Ama-Containing Peptides. General Procedure for the Decarboxylation of Ama(OBn)-Containing Peptides* (*GP 7*). The peptide was disolved in MeOH, and 10% Pd/C was added. The suspension was stirred at r.t. under H_2 (balloon). The reaction went to completion within 8–10 h (TLC). The mixture was then filtered (*Celite*) and evaporated. The residue (*without further purification*) was dissolved in THF, and 2 equiv. of LiBr and 0.3 equiv. of pyridine were added. The mixture was then heated to reflux for 4–6 h. After diluting with AcOEt, the mixture was washed twice with 1N HCl and once with sat. NaCl soln. The aq. layers were re-extracted twice with AcOEt. The combined org. layers were dried ($MgSO_4$) and evaporated.

General Procedure for the Decarboxylation of Ama(O^{t}Bu)-Containing Peptides (*GP 8*). The peptide was dissolved in Et_2O, and sat. HCl/Et_2O soln. was added. The reaction went to completion within 4–10 h (TLC). Then, the mixture was evaporated and dried under h.v. for 15 min. The decarboxylation was accomplished according to *GP 7*.

General Procedure for GC Analysis. In a screw-capped vial, 10 mg of peptide were hydrolyzed with conc. HCl soln. at 110° for 10 h. Then, H_2O was removed in an airflow, and *ca.* 1 ml of anh. 4M HCl in i-PrOH was added. The soln. was heated at 110° for 1 h, then the solvent removed in an airflow, and *ca.* 0.1 ml of CH_2Cl_2 and 0.05 ml of pentafluoropropionic anhydride were added. Heating at 110° for 15 min, followed by removal of the solvent in an airflow, gave the derivatives of individual amino acids.

*Boc-Leu-*D/L*-Ala-Leu-OMe* (**101a/b**). According to *GP 7*, with **59a/b** (150 mg, 0.31 mmol) and Pd/C (10 mg) in MeOH (10 ml); 4 h. After evaporation, the residue and LiBr (36 mg, 0.42 mmol) were dissolved in THF (20 ml). Then, pyridine (10 µl, 0.1 mmol) was added. The suspension was heated at reflux for 10 h. FC (hexane/AcOEt 1:1): 103 mg (76%) of **101a/b** as a 1:1 mixture of epimers (not separated). ^{1}H-NMR (200 MHz, $CDCl_3$): 0.94–0.98 (*m*, 12 H); 1.39 (*d*, *J* = 7.0, 3 H); 1.46 (*s*, 9 H); 1.48–1.72 (*m*, 6 H); 3.73, *3.74* (2*s*, 3 H); 4.04–4.10 (*m*, 1 H); 4.43–4.64 (*m*, 2 H); 4.87–4.95 (*m*, 1 H); 6.60–6.70 (*m*, 1.5 H); 6.83 (*d*, *J* = 7.5, 0.5 H). ^{13}C-NMR (200 MHz, $CDCl_3$): 17.57 (Me); 21.76 (Me); 22.69 (Me); 22.88 (Me); 24.72 (CH); 28.21 (Me); 41.16 (CH_2); 41.32 (CH_2); 48.46, *48.71* (CH); 50.81 (CH); 52.17 (Me); 53.13 (C); 80.33 (C); 155.81 (C); 172.03 (C); 172.70 (C); 173.17 (C). FAB-MS: 1289 (5, $[3M+1]^+$), 859 (23, $[2M+1]^+$), 430 (97, $[M+1]^+$), 374 (35), 330 (52), 217 (42), 146 (88), 86 (100).

Boc-Leu-Nva-Leu-OMe (**102a/b**). According to *GP 7*, with **51a/b** (399 mg, 0.67 mmol) and Pd/C (10 ml) in MeOH (30 ml); 12 h. After evaporation, the residue and LiBr (114 mg, 1.13 mmol) were dissolved in THF (20 ml). Then, pyridine (10 µl, 0.1 mmol) was added. The suspension was heated at reflux for 10 h. FC (hexane/AcOEt 2:1): 0.285 mg (92%) of **102a/b** as a 1:1 mixture of epimers (not separated). ^{1}H-NMR (300 MHz, CD_3OD): 0.75–0.96 (*m*, 15 H); 1.28–1.79 (*m*, 10 H); 1.43, *1.43* (2*s*, 9 H); 3.69, *3.69* (2*s*, 3 H); 4.00–4.10 (*m*, 1 H); 4.35–4.46 (*m*, 2 H). ^{13}C-NMR (300 MHz, CD_3OD): 14.02, *14.19* (Me); 19.88, *19.99* (CH_2); 21.89, *21.97* (Me); 22.07, *22.28* (Me); 23.36, *23.44* (Me); 23.55 (Me); 25.95, *26.03* (CH); 28.83, *28.88* (Me); 35.27, *35.61* (CH_2); 41.51, *41.54* (CH_2); 41.96, *42.17* (CH_2); 52.17, *52.35* (CH); 52.82 (Me); 54.18, *54.31* (CH); 54.61, *55.15* (CH); 80.84 (C); 158.27 (C); 174.59 (C); 174.74, *174.78* (C); 175.82, *176.13* (C). FAB-MS: 480 (10, $[M+23]^+$), 460 (100), 458 (38, $[M+1]^+$), 404 (70), 360 (27), 326 (23), 314 (12), 280 (31), 258 (35), 247 (25), 206 (26).

Boc-Leu-(cyclohexyl)Gly-Leu-OMe (**103a/b**). According to *GP 7*, with **53a–d** (162 mg, 0.25 mmol) and Pd/C (10 mg) in MeOH (10 ml); 12 h. After evaporation the residue and LiBr (44 mg, 0.5 mmol) were dissolved in THF (20 ml). Then, pyridine (10 µl, 0.1 mmol) was added. The mixture was heated at reflux for 10 h. After workup, 109 mg (81%) of **103a/b** were obtained as a 1:1 mixture of epimers. One isomer was isolated by precipitation (AcOEt/hexane).

Data of **103a**: ^{1}H-NMR (300 MHz, $CDCl_3$): 0.89–0.93 (*m*, 12 H); 0.93–1.24 (*m*, 6 H); 1.43 (*s*, 9 H); 1.43–1.73 (*m*, 11 H); 3.27 (*s*, 3 H); 4.08–4.15 (br. *m*, 1 H); 4.26 (*m*, 1 H); 4.57–4.59 (*m*, 1 H); 4.98 (*d*, *J* = 7.5, 1 H); 6.52 (*d*, *J* = 8.1, 1 H); 6.64 (*d*, *J* = 8.7, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.72 (Me); 21.96 (Me); 22.64 (Me); 22.75 (Me); 24.64 (CH); 25.74 (CH_2); 25.95 (CH_2); 28.15 (Me); 29.38 (CH_2); 40.06 (CH); 40.76 (CH_2); 41.24 (CH_2); 50.58 (CH); 52.18 (Me); 53.16 (CH); 57.87 (CH); 80.07 (C); 155.81 (C); 170.89 (C); 172.62 (C); 173.17 (C). FAB-MS: 1493 (0.4, $[3M+1]^+$), 995 (26, $[2M+1]^+$), 520 (24, $[M+23]^+$), 498 (92, $[M+1]^+$), 442 (45), 398 (15), 353 (13), 297 (33), 269 (23).

Ac-Leu-(All)Gly-Leu-OMe (**104/b**). According to *GP 8*, with **69a/b** (150 mg, 0.30 mmol) and sat. HCl/Et_2O soln. (20 ml); 4 h. The residue and LiBr (52 mg, 0.6 mmol) were dissolved in THF (20 ml). Then, pyridine (10 µl, 0.1 mmol) was added. The mixture was heated at reflux for 6 h. FC (hexane/AcOEt 1:1): 47.3 mg (39%) of **104a**, 36.3 mg (30%) **104b**, and 17.3 mg (15%) **104a/b**.

Data of **104a**: ^{1}H-NMR (300 MHz, $CDCl_3$): 0.84–0.93 (*m*, 12 H); 1.50–1.71 (*m*, 3 H); 1.95 (*s*, 3 H); 2.43–2.61 (*m*, 2 H); 3.70 (*s*, 3 H); 4.15–4.27 (*m*, 1 H); 4.53–4.62 (*m*, 2 H); 5.08–5.14 (*m*, 2 H); 5.66–5.80 (*m*, 1 H); 6.47 (*d*, *J* = 6.5, 1 H); 6.84 (*d*, *J* = 8.7, 1 H); 7.32 (*d*, *J* = 8.1, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.33 (Me); 22.35 (Me); 22.64 (Me); 22.78 (Me); 24.53 (CH); 28.77 (Me); 36.05 (CH_2); 40.42 (CH_2); 40.48 (CH_2); 50.74 (Me); 52.02 (CH); 52.13 (CH); 52.94 (CH); 118.85 (CH_2); 133.29 (CH); 170.91 (C); 171.05 (C); 172.74 (C); 173.90 (C). FAB-MS: 795 (3, $[2M+1]^+$), 398 (46, $[M+1]^+$), 371 (23).

Data of **104b**: ^{1}H-NMR (300 MHz, $CDCl_3$): 0.92–1.00 (*m*, 12 H); 1.45–1.74 (*m*, 6 H); 2.02 (*s*, 3 H); 2.40–2.65 (*m*, 2 H); 3.74 (*s*, 3 H); 4.51–4.67 (*m*, 3 H); 5.09–5.19 (*m*, 2 H); 5.65–5.86 (*m*, 1 H); 6.39 (*d*, *J* = 8.3, 1 H); 6.98 (*d*, *J* = 7.9, 1 H); 7.00 (*d*, *J* = 7.9, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.73 (Me); 22.18 (Me); 22.69 (Me); 22.94 (Me); 24.68 (CH); 36.40 (CH_2); 41.22 (CH_2); 41.41 (CH_2); 50.71 (Me); 51.57 (CH); 52.20 (CH); 52.30 (CH); 118.96 (CH_2); 132.80 (CH); 170.25 (C); 170.73 (C); 172.32 (C); 173.27 (C). FAB-MS: 1192 (0.5, $[3M+1]^+$), 795 (24, $[2M+1]^+$), 420 (25, $[M+23]^+$), 398 (100, $[M+1]^+$), 243 (11).

Ac-Leu-Phe-Leu-OMe (**105a/b**). According to *GP 8*, with **70a/b** (150 mg, 0.31 mmol) and sat. HCl/Et_2O soln. (20 ml); 4 h. Then, the residue and LiBr (60 mg, 0.60 mmol) were dissolved in THF (20 ml). Then, pyridine (10 µl, 0.1 mmol) was added. The mixture was heated at reflux for 6 h. After workup, 160 mg (94%) of **105a/b** were obtained as a 1:1 mixture. One isomer could be separated by precipitation (AcOEt/hexane).

Data of **105a**: ^{1}H-NMR (300 MHz, $CDCl_3$): 0.82–0.90 (*m*, 12 H); 1.44–1.64 (*m*, 6 H); 1.94 (*s*, 3 H); 3.05–3.08 (*m*, 2 H); 3.69 (*s*, 3 H); 4.46–4.55 (*m*, 2 H); 4.70–4.80 (*m*, 1 H); 6.12 (*d*, *J* = 7.9, 1 H); 6.67 (*d*, *J* = 8.3, 1 H); 6.91 (*d*, *J* = 7.9, 1 H); 7.17–7.26 (*m*, 5 H). ^{13}C-NMR (300 MHz, $CDCl_3$): 21.82 (Me); 22.20 (Me); 22.71 (Me); 23.00 (Me); 24.74 (CH); 37.88 (CH_2); 41.06 (CH_2); 41.28 (CH_2); 50.80 (CH); 51.69 (Me); 54.17 (CH); 126.87 (CH); 128.52 (CH); 129.34 (CH); 136.46 (C); 170.17 (C); 170.42 (C); 171.98 (C); 172.80 (C). FAB-MS: 1343 (0.9, $[3M+1]^+$), 895 (32, $[2M+1]^+$), 448 (100, $[M+1]^+$), 303 (33), 293 (55).

Ac-Leu-Glu(OMe)-Leu-OMe (**106a/b**). According to *GP 8*, with **71a/b** (180 mg, 0.33 mmol) and sat. HCl/Et_2O soln. (30 ml); 4 h. The resulting residue and LiBr (60 mg, 0.79 mmol) were dissolved in THF (20 ml). Then, pyridine (10 µl, 0.1 mmol) was added. The mixture was heated at reflux for 6 h. FC (hexane/AcOEt 1:1): 67.8 mg (46%) of **106a** and 73.5 mg (50%) **106b**.

Data of **106a**: ^{1}H-NMR (300 MHz, $CDCl_3$): 0.85–0.92 (*m*, 12 H); 1.50–1.65 (*m*, 6 H); 1.94 (*s*, 3 H); 1.94–2.03 (*m*, 1 H); 2.12–2.20 (*m*, 1 H); 2.25–2.55 (*m*, 2 H); 3.64 (*s*, 3 H); 3.67 (*s*, 3 H); 4.30–4.37 (*m*, 1 H); 4.48–4.56 (*m*, 2 H); 6.64 (*d*, *J* = 7.1, 1 H); 7.39 (*d*, *J* = 8.4, 1 H); 7.53 (*d*, *J* = 8.1, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.38 (Me); 22.02 (Me); 22.56 (Me); 22.72 (Me); 24.55 (CH); 24.63 (CH); 26.60 (CH_2); 30.01 (CH_2); 40.51 (CH_2); 40.61 (CH_2); 50.64 (CH); 51.74 (Me); 52.06 (Me); 52.39 (CH); 52.55 (CH); 170.92 (C); 173.08 (C); 173.55 (C); 174.16 (C). FAB-MS: 1330 (1, $[3M+1]^+$), 887 (13, $[2M+1]^+$), 467 (3, $[M+23]^+$), 444 (100, $[M+1]^+$), 391 (15), 299 (17), 289 (12).

Data of **106b**: ^{1}H-NMR (300 MHz, $CDCl_3$): 0.92–0.95 (*m*, 12 H); 1.46–1.71 (*m*, 6 H); 1.94–2.19 (*m*, 2 H); 2.03 (*s*, 3 H); 2.47–2.55 (*m*, 2 H); 3.70 (*s*, 3 H); 3.74 (*s*, 3 H); 4.40–4.61 (*m*, 3 H); 6.04 (*d*, *J* = 7.5, 1 H); 6.96 (*d*, *J* = 7.9, 1 H); 7.10 (*d*, *J* = 7.5, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.70 (Me); 21.99 (Me); 23.27 (Me); 25.83 (CH); 25.88 (CH); 28.14 (CH_2); 30.83 (CH_2); 41.26 (CH_2); 41.81 (CH_2); 52.17 (Me); 53.36 (CH); 53.56 (CH); 173.73 (C); 174.62 (C); 175.12 (C); 175.33 (C). FAB-MS: 1330 (1, $[3M+1]^+$), 887 (49, $[2M+1]^+$), 467 (1, $[M+23]^+$), 444 (100, $[M+1]^+$), 391 (4), 299 (19), 289 (9).

*Boc-Val-Leu-*L*-Nva-Abu-Ile-OMe* (**107a**) *and Boc-Val-Leu-*D*-Nva-Abu-Ile-OMe* (**107b**). According to *GP 7*, with **85a/b** (0.200 g, 0.25 mmol) and Pd/C (10 mg) in MeOH (20 ml); 12 h. The resulting residue and LiBr (39 mg, 0.44 mmol) were dissolved in THF (20 ml). Then, pyridine (10 µl, 0.1 mmol) was added. The mixture was then heated at reflux for 6 h. FC (hexane/AcOEt 1:1): 0.126 mg (76%) of **107a/b**. The mixture was separated with FC (hexane/AcOEt 2:1 → 1:1).

Data of **107a**: M.p. 212–214°. ^{1}H-NMR (400 MHz, CD_3OD): 0.90–0.97 (*m*, 24 H); 1.20–1.54 (*m*, 4 H); 1.43 (*s*, 9 H); 1.55–1.73 (*m*, 5 H); 1.75–2.02 (*m*, 4 H); 3.70 (*s*, 3 H); 3.83 (*d*, *J* = 7.2, 1 H); 4.27–4.33 (*m*, 3 H); 4.36 (*d*, *J* = 6.3, 1 H). ^{13}C-NMR (100 MHz, CD_3OD): 10.74 (Me); 11.67 (Me); 13.88 (Me); 15.99 (Me); 18.66 (Me); 19.85 (Me); 20.20 (CH_2); 22.29 (Me); 23.16 (Me); 25.83 (CH); 26.21 (CH_2); 26.40 (CH_2); 28.74 (Me); 31.96 (CH); 34.65 (CH_2); 38.24 (CH); 41.50 (CH_2); 52.42 (Me); 53.93 (CH); 54.67 (CH); 56.06 (CH); 58.29 (CH); 61.6 (CH); 80.57 (C); 158.17 (C); 173.53 (C); 174.31 (C); 174.35 (C); 174.59 (C); 174.89 (C). FAB-MS: 1285 (2, $[2M+1]^+$), 664 (17, $[M+23]^+$), 642 (47, $[M+1]^+$), 497 (7), 391 (100), 371 (24).

Data of **107b**: ^{1}H-NMR (400 MHz, CD_3OD): 0.88–0.96 (*m*, 24 H); 1.19–1.49 (*m*, 5 H); 1.44 (*s*, 9 H); 1.53–1.92 (*m*, 7 H); 1.98–2.12 (*m*, 1 H); 3.70 (*s*, 3 H); 3.84 (*d*, *J* = 7.0, 1 H); 4.24 (*dd*, *J* = 5.9, 8.1, 1 H); 4.36 (*dd*, *J* = 5.8, 8.7, 1 H); 4.37 (*d*, *J* = 5.9, 1 H); 4.43–4.47 (*m*, 1 H). ^{13}C-NMR (100 MHz, CD_3OD): 10.57 (Me); 11.71 (Me); 14.03 (Me); 15.96 (Me); 15.96 (Me); 18.69 (Me); 19.75 (Me); 20.11 (CH_2); 22.04 (Me); 23.45 (Me); 25.79 (CH); 26.28 (CH_2); 26.43 (CH_2); 28.72 (Me); 31.82 (CH_2); 35.26 (CH_2); 38.36 (CH); 41.76 (CH_2);

52.38 (Me); 53.20 (CH); 54.47 (CH); 55.86 (CH); 58.19 (CH); 61.88 (CH); 69.12 (CH_2); 80.65 (C); 158.17 (C); 173.38 (C); 174.10 (C); 174.52 (C); 174.58 (C). FAB-MS: 664 (7, $[M+23]^+$), 642 (100, $[M+1]^+$), 542 (23), 497 (39), 441 (44), 412 (21), 356 (69), 312 (20), 257 (63).

*Boc-Val-Leu-*L*-Phe-Abu-Ile-OMe* (**108a**) *and Boc-Val-Leu-*D*-Phe-Abu-Ile-OMe* (**108b**). According to *GP 7*, with **86a**/**b** (0.211 g, 0.256 mmol) and Pd/C (10 mg) in MeOH (20 ml); 10 h. The residue and LiBr (35 mg, 0.4 mmol) were dissolved in THF (20 ml). Then, pyridine (10 µl, 0.1 mmol) was added. The mixture was heated at reflux for 10 h. FC (hexane/AcOEt 1:1): 53.1 mg (38%) of **108a**, 37.5 mg (27%) of **108b**, and 12.1 mg (9%) of **108a**/**b**.

Data of **108a**: $[\alpha]_D^{r.t.} = -15.9$ ($c = 1.9$, TFE). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.78 (*dd*, $J = 7.4, 7.4, 3$ H); 0.82–0.91 (*m*, 18 H); 1.11–1.23 (*m*, 1 H); 1.36–1.40 (*m*, 1 H); 1.41 (*s*, 9 H); 1.49–1.64 (*m*, 2 H); 1.72–1.83 (*m*, 1 H); 1.85–1.90 (*m*, 2 H); 1.98–2.08 (*m*, 1 H); 3.00 (*ABX*, $J_{AB} = 13.8$, $J_{AX} = 7.9$, 1 H); 3.20 (*ABX*, $J_{AB} = 13.8$, $J_{AX} = 6.8$, 1 H); 3.73 (*s*, 3 H); 4.40–4.41 (br. *m*, 1 H); 4.38–4.41 (br. *m*, 1 H); 4.44–4.49 (*m*, 1 H); 4.56 (*dd*, $J = 5.2, 8.7$, 1 H); 4.78–4.84 (*m*, 1 H); 5.11 (br. *d*, 1 H); 6.91–6.93 (br. *m*, 2 H); 7.13 (*d*, $J = 8.1$, 1 H); 7.17–7.27 (*m*, 6 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 9.89 (Me); 11.49 (Me); 15.44 (Me); 17.89 (Me); 19.29 (Me); 22.29 (Me); 24.47 (CH); 25.19 (CH_2); 25.41 (CH_2); 28.29 (Me); 31.05 (CH); 37.79 (CH); 37.79 (CH_2); 40.90 (CH_2); 52.08 (Me); 52.24 (CH); 54.35 (CH); 54.97 (CH); 56.34 (CH); 59.92 (CH); 80.02 (C); 126.83 (CH); 128.51 (CH); 129.28 (CH); 136.82 (C); 155.96 (C); 170.66 (C); 171.34 (C); 172.04 (C); 172.89 (C). FAB-MS: 1401 (12, $[2M+23]^+$), 1379 (35, $[2M+1]^+$), 712 (67, $[M+23]^+$), 690 (100, $[M+1]^+$), 590 (33), 545 (21), 489 (34), 404 (20), 257 (21).

Data of **108b**: ^{1}H-NMR (300 MHz, CD_3OD): 0.84–0.95 (*m*, 21 H); 1.20–1.27 (*m*, 1 H); 1.43 (*s*, 9 H); 1.30–1.55 (*m*, 2 H); 1.57–1.70 (*m*, 2 H); 1.71–1.99 (*m*, 4 H); 2.91 (*ABX*, $J_{AB} = 14.0$, $J_{AX} = 8.7$, 1 H); 3.13 (*ABX*, $J_{AB} = 14.3$, $J_{AX} = 5.3$, 1 H); 3.70 (*s*, 3 H); 3.83 (*d*, $J = 7.2$, 1 H); 4.33 (*dd*, $J = 6.2, 8.1$, 1 H); 4.37 (*d*, $J = 5.9$, 1 H); 4.40 (*dd*, $J = 5.6, 9.3$, 1 H); 4.66 (*dd*, $J = 5.3, 8.7$, 1 H); 7.13–7.35 (*m*, 5 H). ^{13}C-NMR (75 MHz, CD_3OD): 10.49 (Me); 11.72 (Me); 15.96 (Me); 18.61 (Me); 19.84 (Me); 22.01 (Me); 23.39 (Me); 25.65 (CH); 26.33 (CH_2); 26.64 (CH_2); 28.69 (Me); 31.80 (CH); 38.32 (CH_2); 38.67 (CH); 42.02 (CH_2); 52.39 (Me); 53.12 (CH); 55.64 (CH); 55.84 (CH); 58.29 (CH); 61.71 (CH); 80.64 (C); 127.85 (CH); 129.58 (CH); 130.48 (CH); 138.43 (C); 158.29 (C); 173.32 (C); 173.65 (C); 174.24 (C); 174.55 (C); 174.67 (C). FAB-MS: 1379 (5, $[2M+1]^+$), 1279 (5), 827 (11), 690 (100, $[M+1]^+$), 590 (41), 545 (36), 489 (31), 404 (34), 257 (24), 231 (25).

Boc-Val-Leu-(CH_2CH_2CN)Gly-Abu-Ile-OMe (**110a**/**b**). According to *GP 7*, with **90a**/**b** (0.25 g, 0.31 mmol) and Pd/C (10 mg) in MeOH (50 ml), 12 h. Then, the residue and LiBr (53 mg, 0.62 mmol) were dissolved in THF (20 ml). Then, pyridine (10 µl, 0.1 mmol) was added. The mixture was heated at reflux for 6 h. FC (hexane/AcOEt 1:1 →3:7): 0.130 g (63%) of **110a**/**b** as a 1:1 mixture of epimers. Separation with FC (hexane/AcOEt 2:1 →1:1.

Data of **110a**: GC: 5.15 (L-Abu), 5.36 (L-Val), 7.28 (L-Ile), 8.69 (L-Leu), 18.63 (D-Glu). ^{1}H-NMR (400 MHz, CD_3OD): 0.90–0.98 (*m*, 21 H); 1.07–1.31 (*m*, 1 H); 1.43 (*s*, 9 H); 1.47–1.55 (*m*, 1 H); 1.63–1.76 (*m*, 4 H); 1.80–2.02 (*m*, 4 H); 2.22–2.30 (*m*, 1 H); 2.44–2.58 (*m*, 2 H); 3.71 (*s*, 3 H); 3.82 (*d*, $J = 7.0$, 1 H); 4.26–4.32 (*m*, 2 H); 4.37 (*d*, $J = 6.1$, 1 H); 4.44 (*dd*, $J = 4.6, 9.7$, 1 H). ^{13}C-NMR (100 MHz, CD_3OD): 10.69 (Me); 11.75 (Me); 14.58 (CH_2); 16.05 (Me); 18.73 (Me); 19.81 (Me); 22.05 (Me); 23.30 (Me); 25.92 (CH); 26.35 (CH_2); 26.45 (CH_2); 28.58 (CH_2); 28.81 (Me); 31.94 (CH); 38.33 (CH); 41.02 (CH_2); 52.46 (Me); 53.57 (CH); 54.22 (CH); 56.22 (CH); 58.34 (CH); 61.92 (CH); 80.77 (C); 120.28 (C); 158.42 (C); 172.61 (C); 173.55 (C); 174.30 (C); 174.91 (C); 175.30 (C). FAB-MS: 1307 (4, $[2M+1]^+$), 677 (73, $[M+23]^+$), 654 (73, $[M+1]^+$), 555 (100), 454 (8), 368 (11), 324 (12).

Data of **110b** (traces of **110a**): ^{1}H-NMR (300 MHz, CD_3OD): 0.88–0.98 (*m*, 21 H); 1.27–1.30 (*m*, 1 H); 1.44 (*s*, 9 H); 1.43–2.30 (*m*, 10 H); 2.45–2.55 (*m*, 2 H); 3.70 (*s*, 3 H); 3.80–3.86 (*m*, 1 H); 4.25–4.48 (*m*, 3 H). FAB-MS: 1307 (7, $[2M+1]^+$), 676 (37, $[M+23]^+$), 654 (100, $[M+1]^+$), 554 (44), 508 (11), 454 (14), 367 (12), 324 (12).

*Boc-Val-Leu-*D*-Glu(O^{t}Bu)-Abu-Ile-OMe* (**109a**) *and Boc-Val-Leu-*L*-Glu(O^{t}Bu)-Abu-Ile-OMe* (**109b**). *a*) According to *GP 7*, with **89** (0.200 g, 0.23 mmol) and Pd/C (10 mg) in MeOH (20 ml); 12 h. The residue and LiBr (40 mg, 0.46 mmol) were dissolved in THF (20 ml). Then, pyridine (0.01 ml, 0.12 mmol) was added. The mixture was heated at reflux for 10 h. FC (hexane/AcOEt 1:1): 144 g (87%) of **109a**/**b** as a 1:1 mixture of epimers. Separation with FC (hexane/AcOEt 2:1 →1:1) gave 41 mg of **109a**, and 65 mg of **109b**.

b) The peptide derivative **91** (100 mg, 0.12 mmol) was dissolved in THF (7 ml). $Pd(OAc)_2$ (1.4 mg, 0.006 mmol), PPh_3 (3.2 mg, 0.012 mmol), HCO_2H (14.2 µl, 0.36 mmol), and Et_3N (50 µl, 0.036 mmol) were added, and the mixture was stirred for 24 h at r.t. The soln. was diluted with 20 ml of AcOEt. The org. phase was washed with 1N HCl and aq. sat. NaCl soln. The aq. layers were extracted twice with AcOEt. The combined org. phases were dried ($MgSO_4$) and evaporated. FC (hexane/AcOEt 2:3): gave 84.9 mg (90%) of **109a**/**b** as a 1:1 mixture of epimers.

c) The peptide derivative (100 mg, 0.12 mmol) **91** was dissolved in THF (7 ml). $Pd(PPh_3)_4$ (7.2 mg, 0.006 mmol), HCO_2H (14.2 µl, 0.36 mmol), and Et_3N (50 µl, 0.036 mmol) were added. The mixture was then stirred for 24 h at r.t. Workup acording to *b* and FC (hexane/AcOEt 2:3) gave 67.1 mg (75%) of **109a/b** as a 1:1 mixture of epimers.

Data of **109a**: R_f 0.26 (AcOEt/hexane 1.5:1). M.p. 204–207°. $[\alpha]_D^{rt.} = -22.8$ ($c = 0.99$, EtOH). GC: 5.28 (L-Abu), 5.48 (L-Val), 7.46 (L-Ile), 8.87 (L-Leu), 18.76 (D-Glu). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.78–0.94 (*m*, 21 H); 1.12–1.27 (*m*, 1 H); 1.42 (*s*, 9 H); 1.43 (*s*, 9 H); 1.35–1.40 (*m*, 1 H); 1.53–1.61 (*m*, 1 H); 1.62–1.75 (*m*, 3 H); 1.86–1.99 (*m*, 3 H); 2.05–2.18 (*m*, 2 H); 2.24–2.40 (*m*, 1 H); 3.74 (*s*, 3 H); 3.94 (br. *m*, 1 H); 4.41–4.46 (*m*, 2 H); 4.52–4.56 (*m*, 1 H); 4.58 (*dd*, $J = 5.2, 8.7$, 1 H); 5.08 (br. *s*, 1 H); 6.90 (br. *s*, 1 H); 7.02 (br. *d*, $J = 6.9$, 1 H); 7.08 (*d*, $J = 8.0$, 1 H); 7.36 (*d*, $J = 8.4$, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 10.07 (Me); 11.52 (Me); 15.44 (Me); 17.89 (Me); 19.39 (Me); 21.99 (Me); 22.94 (Me); 24.77 (CH); 25.21 (CH_2); 25.36 (CH_2); 27.06 (CH_2); 28.08 (Me); 28.31 (Me); 30.86 (CH); 31.73 (CH_2); 37.87 (CH); 40.67 (CH_2); 52.16 (Me); 52.24 (CH); 52.54 (CH); 55.09 (CH); 56.34 (CH); 60.09 (CH); 80.16 (C); 80.78 (C); 156.06 (C); 170.96 (C); 171.33 (C); 172.14 (C); 172.44 (C); 172.53 (C); 173.01 (C). FAB-MS: 1456 (16, $[2M+1]^+$), 728 (100, $[M+1]^+$), 672 (5), 628 (16), 572 (26), 471 (10), 386 (11), 257 (16).

Data of **109b**: R_f 0.16 (AcOEt/hexane 1.5:1). M.p. >215° (dec.). GC: 5.14 (L-Abu), 5.34 (L-Val), 7.26 (L-Ile), 8.66 (L-Leu), 18.81 (L-Glu). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.84–0.93 (*m*, 21 H); 1.11–1.26 (*m*, 1 H); 1.40 (*s*, 9 H); 1.44 (*s*, 9 H); 1.40–1.76 (*m*, 5 H); 1.83–1.97 (*m*, 3 H); 2.03–2.17 (*m*, 2 H); 2.20–2.30 (*m*, 2 H); 3.73 (*s*, 3 H); 4.04 (br. *s*, 1 H); 4.60–4.85 (br. *m*, 4 H); 5.60 (br. *s*, 1 H); 7.27 (br. *s*, 1 H); 7.45 (br. *s*, 1 H); 7.68 (br. *s*, 1 H); 8.01 (br. *s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 10.04 (Me); 11.53 (Me); 15.48 (Me); 18.29 (Me); 19.33 (Me); 22.22 (Me); 22.94 (Me); 24.91 (CH); 25.10 (CH_2); 25.65 (CH_2); 28.10 (Me); 28.42 (Me); 28.42 (CH_2); 31.06 (CH); 31.93 (CH_2); 37.64 (CH); 41.77 (CH_2); 52.14 (Me); 52.61 (CH); 54.45 (CH); 56.70 (CH); 60.42 (CH); 80.04 (C); 80.67 (C); 156.58 (C); 171.53 (C); 171.95 (C); 172.29 (C); 172.51 (C); 172.61 (C); 172.76 (C). FAB-MS: 1456 (19, $[2M+1]^+$), 1356 (5), 750 (13, $[M+23]^+$), 728 (100, $[M+1]^+$), 628 (9), 583 (16), 572 (11), 527 (6), 471 (9), 391 (25). Anal. calc. for $C_{35}H_{63}N_5O_{10}$: C 58.80, H 8.89, N 9.81; found: C 58.65, H 8.84, N 9.65.

*Z-Val-Leu-*D*-Ala-Abu-Ile-OMe* (**111a**) *and Z-Val-Leu-*L*-Ala-Abu-Ile-OMe* (**111b**). According to *GP 8*, **74a/b** (0.254 g, 0.34 mmol) and sat. HCl/Et_2O soln. (20 ml); 10 h. The residue and LiBr (59 mg, 0.68 mmol) were dissolved in THF (20 ml). Then, pyridine (10 µl, 0.1 mmol) was added. The mixture was heated at reflux for 5 h. FC (hexane/AcOEt 1:1): 0.181 g (87%) of **111a/b** as a 1:1 mixture of epimers. Separated by FC (hexane/AcOEt 2:1 →1:1).

Data of **111a**: GC: 4.04 (D-Ala), 5.44 (L-Abu), 5.65 (L-Val), 7.61 (L-Ile), 9.00 (L-Leu). ^{1}H-NMR (400 MHz, CD_3OD): 0.88–0.97 (*m*, 21 H); 1.20–1.28 (*m*, 1 H); 1.37 (*d*, $J = 7.2$, 3 H); 1.43–1.53 (*m*, 1 H); 1.56–1.73 (*m*, 4 H); 1.80–1.94 (*m*, 2 H); 2.00–2.07 (*m*, 1 H); 3.69 (*s*, 3 H); 3.89–3.91 (*m*, 1 H); 4.29–4.36 (*m*, 4 H); 5.04–5.13 (*m*, 2 H); 7.27–7.37 (*m*, 5 H). ^{13}C-NMR (100 MHz, CD_3OD): 10.68 (Me); 11.67 (Me); 15.97 (Me); 17.84 (Me); 18.54, *18.65* (Me); 19.71, *19.77* (Me); 21.84, *21.99* (Me); 23.34, *23.48* (Me); 25.88 (CH); 26.25 (CH_2); 26.40 (CH_2); 31.79 (CH); 38.19 (CH); 41.21, *41.93* (CH_2); 50.46 (CH); 52.40 (Me); 53.74 (CH); 56.05 (CH); 58.32 (CH); 62.32, *62.43* (CH); 67.77, *67.91* (CH_2); 128.89 (CH); 128.97, *129.04* (CH); 129.47 (CH); 138.13 (C); 158.99 (C); 173.53 (C); 174.20, *174.33* (C); 174.45 (C); 174.52 (C); 174.95 (C). FAB-MS: 1297 (2, $[2M+1]^+$), 671 (15, $[M+23]^+$), 649 (89, $[M+1]^+$), 515 (13), 504 (19), 419 (27), 348 (13).

Data of **111b**: ^{1}H-NMR (400 MHz, CD_3OD): 0.90–0.94 (*m*, 21 H); 1.24–1.33 (br. *m*, 1 H); 1.34 (*d*, $J = 6.1$, 3 H); 1.40–1.75 (br. *m*, 5 H); 1.75–1.95 (br. *m*, 2 H); 2.00–2.10 (br. *m*, 1 H); 3.69 (*s*, 3 H); 3.92 (*d*, $J = 6.6$, 1 H); 4.30–4.42 (*m*, 4 H); 5.09 (*s*, 2 H); 7.25–7.35 (*m*, 5 H). ^{13}C-NMR (100 MHz, CD_3OD): 10.58 (Me); 11.71 (Me); 15.94 (Me); 17.98 (Me); 18.71 (Me); 19.71 (Me); 21.86 (Me); 23.46 (Me); 25.82 (CH); 26.29 (CH_2); 26.40 (CH_2); 31.75 (CH); 38.34 (CH); 41.46 (CH_2); 50.43 (CH); 52.36 (Me); 55.94 (CH); 58.23 (CH); 62.53 (CH); 67.79 (CH_2); 128.83 (CH); 129.03 (CH); 129.48 (CH); 138.18 (C); 158.88 (C); 173.37 (C); 174.16 (C); 174.44 (C); 174.53 (C); 174.71 (C). FAB-MS: 1297 (3, $[2M+1]^+$), 1162 (6), 648 (100, $[M+1]^+$), 514 (27), 503 (40), 418 (59), 347 (40).

*Z-Val-Leu-*D*-Abu-Abu-Ile-OMe* (**112a**) *and Z-Val-Leu-*L*-Abu-Abu-Ile-OMe* (**112b**). According to *GP 8*, **75a/b** (0.25 g, 0.32 mmol) and sat. HCl/Et_2O soln. (20 ml), 10 h. The residue and LiBr (57 mg, 0.66 mmol) were dissolved in THF (20 ml). Then, pyridine (10 µl, 0.1 mmol) was added, and the mixture was heated at reflux for 6 h. FC (hexane/AcOEt 1:1): 0.179 g (79%) of **112a/b** as a 1:1 mixture of epimers. Separated by FC (hexane/AcOEt 2:1 →1:1).

Data of **112a**: GC: 5.17 (D-Abu), 5.42 (L-Abu), 5.64 (L-Val), 7.63 (L-Ile), 9.05 (L-Leu). ^{1}H-NMR (400 MHz, CD_3OD): 0.87–0.97 (*m*, 24 H); 1.18–1.27 (*m*, 1 H); 1.44–1.54 (*m*, 1 H); 1.64–1.74 (*m*, 5 H); 1.81–1.94 (*m*, 3 H); 2.02–2.07 (*m*, 1 H); 3.69 (*s*, 3 H); 3.90 (*d*, $J = 7$, 1 H); 4.22 (*dd*, $J = 5.2, 9$, 1 H); 4.30–4.36 (*m*, 3 H);

5.08 (AB, J_{AB} = 12.4, 2 H); 7.28–7.37 (m, 5 H). ^{13}C-NMR (100 MHz, CD_3OD): 10.77 (Me); 10.89 (Me); 11.66 (Me); 15.97 (Me); 18.66 (Me); 19.78 (Me); 22.13 (Me); 23.24 (Me); 25.87 (CH); 26.24 (CH_2); 26.40 (CH_2); 31.79 (CH); 38.15 (CH); 38.15 (CH); 41.32 (CH_2); 52.41 (Me); 53.75 (CH); 56.03 (CH); 56.46 (CH); 58.31 (CH); 67.88 (CH_2); 128.98 (CH); 129.04 (CH); 129.47 (CH); 138.14 (C); 158.96 (C); 173.54 (C); 174.28 (C); 174.35 (C); 174.41 (C); 174.89 (C). FAB-MS: 1323 (4, $[2M+1]^+$), 1189 (4), 684 (21, $[M+23]^+$), 662 (99, $[M+1]^+$), 528 (39), 517 (89), 432 (100), 347 (89), 316 (22), 257 (25).

Data of **112b**: ^{1}H-NMR (400 MHz, CD_3OD): 0.87–0.94 (m, 24 H); 1.18–1.29 (m, 1 H); 1.41–1.51 (m, 1 H); 1.52–1.69 (m, 5 H); 1.76–1.91 (m, 3 H); 1.99–2.08 (m, 1 H); 3.69 (s, 3 H); 3.96 (d, J = 7.1, 1 H); 4.30 (dd, J = 5.7, 8.2, 1 H); 4.35 (dd, J = 6.0, 8.1, 1 H); 4.38 (d, J = 5.9, 1 H); 5.05–5.12 (m, 2 H); 7.26–7.36 (m, 5 H). ^{13}C-NMR (100 MHz, CD_3OD): 10.60 (Me); 10.74 (Me); 11.71 (Me); 15.96 (Me); 18.72 (Me); 19.76 (Me); 22.03 (Me); 23.48 (Me); 25.82 (CH); 26.28 (CH_2); 26.50 (CH_2); 31.94 (CH); 38.36 (CH); 41.74 (CH_2); 52.39 (Me); 53.18 (C); 55.81 (C); 55.98 (C); 58.18 (CH); 62.29 (CH); 67.73 (CH_2); 128.82 (CH); 129.02 (CH); 129.48 (CH); 138.19 (C); 158.77 (C); 173.42 (C); 173.87 (C); 174.15 (C); 174.30 (C); 174.58 (C). FAB-MS: 1323 (4, $[2M+1]^+$), 1189 (4), 684 (25, $[M+23]^+$), 662 (100, $[M+1]^+$), 528 (20), 517 (49), 432 (66), 347 (67), 316 (11), 257 (17).

Z-Val-Leu-(All)Gly-Abu-Ile-OMe (**113a/b**). According to *GP 8*, **77a/b** (0.262 g, 0.33 mmol) and sat. HCl/Et_2O soln. (20 ml); 10 h. The residue and LiBr (57 mg, 0.66 mmol) were dissolved in THF (20 ml). Then, pyridine (10 µl, 0.1 mmol) was added, and the mixture was heated at reflux for 6 h. FC (hexane/AcOEt 2:1 →1:1): 0.134 g of **113a** and 0.123 g of **113b**. The purification by precipitation (AcOEt/hexane) gave finally 0.101 g (45%) of **113a** and 0.073 g (32%) of **113b**.

Data of **113a**: ^{1}H-NMR (400 MHz, $CDCl_3$): 0.82–0.91 (m, 21 H); 1.10–1.15 (m, 1 H); 1.34–1.41 (m, 1 H); 1.56–1.88 (m, 6 H); 1.90–1.96 (m, 1 H); 2.45–2.60 (m, 2 H); 3.59 (s, 3 H); 4.35 (br. s, 1 H); 4.55 (dd, J = 5.5, 8.4, 1 H); 4.70–5.00 (br. m, 2 H); 5.05–5.13 (m, 5 H); 5.74–5.84 (m, 1 H); 5.93 (br. s, 1 H); 7.26–7.36 (m, 5 H); 7.45–7.90 (br. m, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 9.69 (Me); 11.48 (Me); 15.31 (Me); 18.04 (Me); 19.40 (Me); 23.01 (Me); 23.24 (Me); 24.70 (CH); 25.18 (CH_2); 26.55 (CH_2); 31.98 (CH); 38.11 (CH); 42.25 (CH_2); 51.82 (CH); 51.98 (Me); 52.13 (CH); 54.04 (CH); 56.37 (CH); 59.96 (CH); 67.02 (CH_2); 118.29 (CH_2); 128.00 (CH); 128.12 (CH); 128.40 (CH); 133.25 (CH); 136.58 (C); 156.69 (C); 170.61 (C); 171.03 (C); 171.25 (C); 171.84 (C); 172.84 (C). FAB-MS: 1347 (6, $[2M+1]^+$), 674 (100, $[M+1]^+$), 529 (33), 444 (24), 347 (19), 231 (10).

Data of **113b**: ^{1}H-NMR (400 MHz, $CDCl_3$): 0.80–1.00 (m, 21 H); 1.00–2.15 (m, 9 H); 2.25–2.45 (m, 2 H); 3.69 (s, 3 H); 4.34–4.48 (m, 1 H); 4.60–4.72 (m, 1 H); 4.88–5.26 (m, 8 H); 5.60–5.82 (m, 1 H); 6.40–6.60 (br. m, 1 H); 7.26–7.30 (m, 5 H); 7.80 (br. s, 1 H); 8.10 (br. s, 1 H); 8.60 (br. s, 1 H). FAB-MS: 696 (3, $[M+23]^+$), 674 (24, $[M+1]^+$), 529 (5), 444 (6), 391 (100), 371 (19), 347 (3).

Z-Val-Leu-(CH_2NHCOPh)Gly-Abu-Ile-OMe (**114a/b**). According to *GP 8*, with **79a/b** (0.35 g, 0.4 mmol), and sat. HCl/Et_2O (50 ml); 10 h. The residue and LiBr (70 mg, 0.8 mmol) were dissolved in THF (20 ml). Then, pyridine (10 µl, 0.1 mmol) was added, and the mixture was heated at reflux for 6 h. Precipitation with AcOEt/hexane gave 0.231 g (74%) of **114a/b** as a 1:1 mixture of epimers. One epimer could be separated by a second precipitation from AcOEt/hexane.

Data of **114b**: ^{1}H-NMR (400 MHz, CD_3OD): 0.78 (d, J = 5.2, 3 H); 0.84 (d, J = 5.2, 3 H); 0.87–0.96 (m, 18 H); 1.18–1.41 (m, 2 H); 1.41–1.64 (m, 3 H); 1.65–1.77 (m, 1 H); 1.79–1.92 (m, 2 H); 2.00–2.07 (m, 1 H); 3.68 (s, 3 H); 3.75 (ABX, J_{AB} = 13.8, J_{AX} = 8.6, 1 H); 3.82 (ABX, J_{AB} = 13.8, J_{AX} = 4.9, 1 H); 3.90 (d, J = 7.0, 1 H); 4.22–4.28 (m, 1 H); 4.33 (dd, J = 5.7, 8.4, 1 H); 4.35 (d, J = 6.1, 1 H); 4.66 (dd, J = 5.2, 8.2, 1 H); 5.04–5.11 (m, 2 H); 7.25–7.36 (m, 5 H); 7.42–7.46 (m, 2 H); 7.50–7.54 (m, 1 H); 7.72–7.83 (m, 2 H). ^{13}C-NMR (100 MHz, CD_3OD): 10.80 (Me); 11.74 (Me); 16.03 (Me); 18.70 (Me); 19.80 (Me); 22.09 (Me); 23.19 (Me); 25.78 (CH); 26.29 (CH_2); 26.45 (CH_2); 31.86 (CH); 38.27 (CH); 41.10 (CH_2); 42.10 (CH_2); 52.45 (Me); 54.16 (CH); 54.87 (CH); 56.38 (CH); 58.36 (CH); 62.40 (CH); 67.98 (CH_2); 128.51 (CH); 128.97 (CH); 129.09 (CH); 129.52 (CH); 129.58 (CH); 132.90 (CH); 135.26 (C); 138.14 (C); 159.05 (C); 170.57 (C); 172.09 (C); 173.58 (C); 174.42 (C); 174.59 (C); 175.12 (C). FAB-MS: 1556 (14, $[2M+23]^+$), 1534 (22, $[2M+1]^+$), 1400 (14), 789 (70, $[M+23]^+$), 767 (100, $[M+1]^+$), 633 (24), 537 (14), 416 (11).

Data of **114a/b**: FAB-MS: 1538 (6), 769 (100), 767 (18, $[M+1]^+$), 636 (24), 538 (21), 491 (26), 416 (16), 405 (53).

Z-Val-Leu-(CH_2CH_2COMe)Gly-Abu-Ile-OMe (**115a/b**). According to *GP 8*, **84a/b** (0.370 g, 0.46 mmol) and sat. HCl/Et_2O soln. (20 ml), 6 h. The residue and LiBr (80.3 mg, 0.92 mmol) were dissolved in THF (20 ml). Then, pyridine (10 µl, 0.1 mmol) was added, and the mixture was heated at reflux for 4 h. FC (hexane/AcOEt 1:1) gave 0.112 g (34%) of **115a** and 0.172 g (51%) of **115b**.

Data of **115a**: M.p. 192.5–195.0°. ^{1}H-NMR (400 MHz, CD_3OD): 0.87–0.97 (m, 21 H); 1.17–1.28 (m, 1 H); 1.43–1.51 (m, 1 H); 1.53–1.73 (m, 3 H); 1.75–1.96 (m, 3 H); 2.00–2.16 (m, 2 H); 2.12 (s, 3 H); 2.53–2.59

(*m*, 2 H); 3.69 (*s*, 3 H); 3.89 (*d*, *J* = 6.6, 1 H); 4.29–4.34 (*m*, 4 H); 5.05 (*AB*, J_{AB} = 12.3, 1 H); 5.12 (*AB*, J_{AB} = 12.3, 1 H); 7.27–7.38 (*m*, 5 H). ^{13}C-NMR (100 MHz, CD_3OD): 10.70 (Me); 11.68 (Me); 15.98 (Me); 18.65 (Me); 19.73 (Me); 21.87 (Me); 23.36 (Me); 25.91 (CH); 26.27 (CH_2); 26.40 (CH_2); 26.68 (CH_2); 29.88 (Me); 31.68 (CH); 38.17 (CH); 40.34 (CH_2); 41.06 (CH_2); 52.41 (Me); 53.77 (CH); 54.09 (CH); 56.04 (CH); 58.32 (CH); 62.67 (CH); 68.00 (CH_2); 129.05 (CH); 129.47 (CH); 138.09 (C); 159.13 (C); 173.51 (C); 173.89 (C); 174.31 (C); 174.57 (C); 174.92 (C); 210.28 (C). FAB-MS: 1413 (7), 726 (49, $[M+23]^+$), 707 (100), 704 (77, $[M+1]^+$), 561 (34), 475 (16).

Data of **115b**: ^{1}H-NMR (400 MHz, (D_6)DMSO): 0.81–0.87 (*m*, 21 H); 1.15–1.22 (*m*, 1 H); 1.37–1.68 (*m*, 6 H); 1.77–1.83 (*m*, 2 H); 1.95–1.97 (*m*, 1 H); 2.03 (*s*, 3 H); 2.41–2.50 (*m*, 4 H); 3.61 (*s*, 3 H); 3.84–3.88 (*m*, 1 H); 4.21–4.32 (*m*, 4 H); 5.02 (*s*, 2 H); 7.26–7.35 (*m*, 7 H); 7.78 (*d*, *J* = 7.7, 1 H); 7.93 (*d*, *J* = 7.4, 1 H); 8.09 (*d*, *J* = 8.0, 1 H). ^{13}C-NMR (100 MHz, CD_3OD): 9.85 (Me); 11.06 (Me); 15.33 (Me); 18.08 (Me); 19.15 (Me); 21.57 (Me); 22.93 (Me); 24.01 (CH); 24.69 (CH_2); 25.34 (CH_2); 25.96 (CH_2); 29.69 (Me); 30.23 (CH); 36.17 (CH); 38.81 (CH_2); 40.59 (CH_2); 50.90 (CH); 51.52 (Me); 53.32 (CH); 56.15 (CH); 56.24 (CH); 60.15 (CH); 65.31 (CH_2); 127.56 (CH); 127.70 (CH); 128.27 (CH); 137.04 (C); 156.06 (C); 170.73 (C); 170.97 (C); 171.54 (C); 171.77 (C); 207.56 (C). FAB-MS: 1408 (10, $[2M+1]^+$), 704 (100, $[M+1]^+$), 559 (36), 474 (21), 347 (10).

7. *Decyanation of an Aca-Containing Peptide. Boc-Leu-(4,5-didehydro)Nva-Leu-NH$_2$* (**116a/b**). At −75° (dry ice/aceton), Na (0.160 g, 7.2 mmol) was dissolved in NH_3 (*ca.* 30 ml). Then, **97a** (0.10 g, 0.2 mmol) in THF (10 ml) was added dropwise to the blue soln. After 1.5 h, solid NH_4Cl was added, until the blue color disappeard. The mixture was warmed up to r.t. After complete evaporation of the NH_3, the residue was taken up in AcOEt and H_2O. The aq. phase was extracted twice with AcOEt. The combined org. phases were washed with aq. sat. NaCl soln., dried ($MgSO_4$), and evaporated. FC (hexane/AcOEt 1 : 1): 57 mg (64%) of **116a/b** as a 1 : 1 mixture of epimers (not separated). ^{1}H-NMR (200 MHz, CD_3OD): 0.87–0.98 (*m*, 12 H); 1.30–1.70 (*m*, 6 H); 1.44, *1.47* (2*s*, 9 H); 2.84–2.88 (*m*, 2 H); 3.43–3.55 (*m*, 2 H); 3.96–4.04 (*m*, 2 H); 5.23–5.34 (*m*, 2 H); 5.70–5.82 (*m*, 1 H). ^{13}C-NMR (50 MHz, CD_3OD): 21.92; 22.05; 22.21; 23.16; 23.35; 23.76; 25.73; 28.71; 37.47; 40.71; 41.00; 41.66; 49.73; 50.80; 51.03; 51.88; 55.38; 59.72; 65.41; 81.28; 118.32; 118.83; 122.29; 130.54; 158.66; 167.01; 176.06. FAB-MS: 570 (21), 475 (28), 453 (33, $[M+23]^+$), 430 (15, M^+), 397 (100), 388 (35), 372 (19), 354 (17), 332 (25).

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