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Synthesis and reduction of endothiodipeptides containing malonic acid derivatives

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Abstract: Amides of malonic acid derivatives and protected dipeptides containing amino malonic acid have been synthesized and converted into the corresponding monothio analoga and endothiodipeptides. By reduction of the thioamides terminal protected β-carboxy amino derivatives were obtained. Reduction of endothiodipeptides containing amino malonic acid as the carboxy component resulted in protected Ψ[CH_2NH] pseudodipeptides for the use as dipeptide substitutes with proteolytic resistance.

Key words: Thioamides; thiopeptides; depsipeptides; amino acids and derivatives.

Introduction

In recent times the development of physiological active peptides, pseudopeptides and peptide mimetica as specific inhibitors of proteases [1] gained increasing importance for the design of pharmaceutically valuable compounds and for studies of structure activity relationships. For the synthesis and screening of high numbers of potential peptide based inhibitors the investigation of new building blocks is permanently required. While synthetic low molecular weight peptides generally could be synthesized in a large variety with small temporal, experimental and financial efforts, their use in vivo is often restricted by inadequate stability and oral availability. To overcome these disadvantages modification of effective peptides requires substitutions of side chains, addition or replacement of functionalized residues or change of their amide character. In this respect peptide backbone modifications of peptide lead structures are a logical step to obtain mimetica with comparable effectiveness and enhanced resistance against proteolytic cleavage as two of the manifold pretensions required for pharmaceutical purpose.

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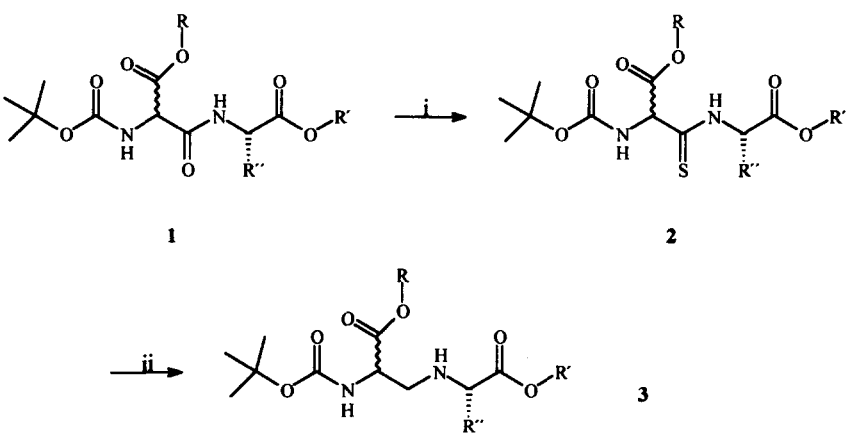
During our development of peptide inhibitors for metalloproteases a novel class of hydroxamic acid based inhibitors containing malonic acid derivatives was synthesized [2,3]. A relevant feature of these most effective substrate analogous peptide inhibitors designed was their amino malonic acid (Ama) residue carrying the hydroxamate function in position P_1[4]. Though the reactive site amide bond of these compounds showed resistance to hydrolysis by the target enzymes, a new P_1-P_1'-dipeptide analogous segment was required to ensure the following properties: Proteolytic resistance of the amide group in the reactive site, a protected carboxyl function in direct proximity of the former amide and topographical compatibility to the original dipeptide. This modification of the reactive site amide to a more stable isostere should be understood as an important step in conversion of these peptides to real peptide mimetica.

In this work the synthesis of $\Psi[CH_2NH]$ pseudodipeptides [5] or deoxodipeptides containing a protected carboxyl function in β-position to the nitrogen of the second amino acid or amine is described. Derived from dipeptides containing malonic acid derivatives (RMal) or amino malonic acid (**1**), the deoxopeptides were obtained from the corresponding endothiopeptides (**2**) by reductive desulfurization with Raney nickel [6,7]. In particular desoxy analoga of dipeptides containing amino malonic acid as carboxy components (**3**) with different terminal and Ama-side chain protecting group configurations were synthesized. Terminal deprotection led to reduced analoga of Ama(OR)-Xaa-building blocks which were applied to design various high potent peptide inhibitors of metalloproteases. Special precautions were taken in the reduction of those endothiodipeptides containing tyrosine with respect to the catalytically cleavable benzyl ether moiety at the phenolic hydroxyl function.



Scheme 1. Concept for the synthesis of terminal and side chain protected deoxodipeptides of the type Boc-D/L-Ama(OR)$\Psi[CH_2NH]$Xaa-OR′ (**3**). Reagents and conditions: i) Lawesson's reagent, toluene, Δ; ii) Raney nickel. R = Me or Et; R′= ^{t}Bu, Bzl, Me or Tmse (see table 1).

Results and Discussion

The synthesis of the endothiopeptides [8-10] occurred by thionation of the corresponding peptides with Lawesson's reagent [8], a current thionation agent commercially available. The reactions were carried out in toluene at about 80°C. The products were separated via silica gel column chromatography. The synthesized thiopeptides containing amino malonic acid and alkyl malonic acid derivatives, their yields and the yields of the reduced analoga are listed in table 1.

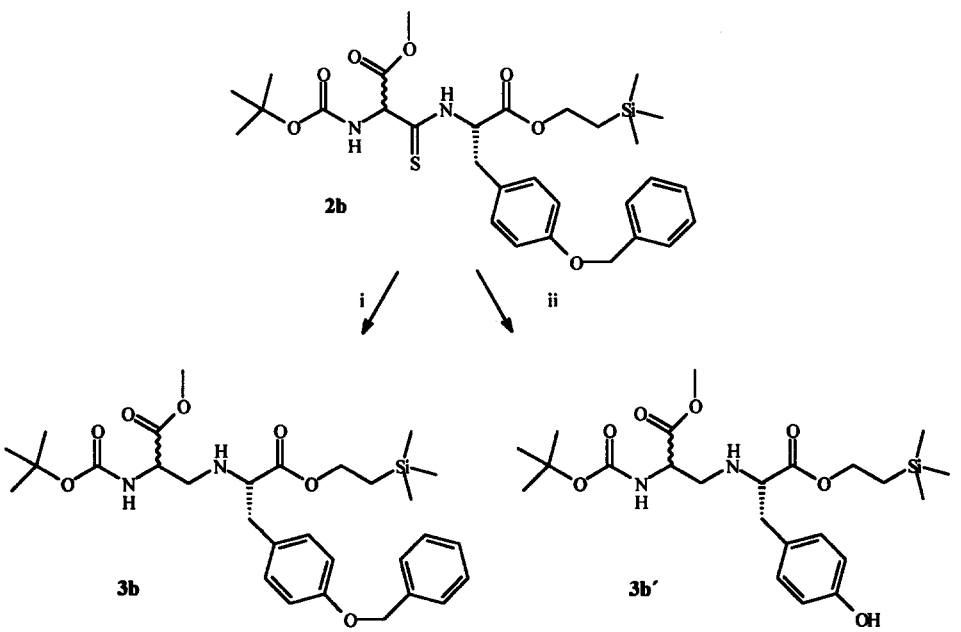
Table1. Yields of the synthesized endothiopeptides and thioamides and their reduced analoga.

	Thioamide	Yield (%)	reduced form, Yield (%)	
2a	Boc-D/L-Ama(OEt)Ψ[CSNH]Tyr(Bzl)-OMe	75	**3a**	80
2b	Boc-D/L-Ama(OMe)Ψ[CSNH]Tyr(Bzl)-OTmse	87	**3b**	75 (**3b'**: -Tyr-OTmse, 60%*)
2c	Boc-D/L-Ama(OMe)Ψ[CSNH]Tyr-O^{t}Bu	67	**3c**	69
2d	Boc-D/L-Ama(OMe)Ψ[CSNH]Tyr(Bzl)-OBzl	81	**3d**	23
2e	Boc-D/L-Ama(OMe)Ψ[CSNH]Phe-O^{t}Bu	74	**3e**	69
2f	Boc-D/L-Ama(OEt)Ψ[CSNH]Phe-O^{t}Bu	78	**3f**	81
2g	Boc-D/L-Ama(OEt)Ψ[CSNH]Phe-OMe	88	**3g**	87
2h	Boc-D/L-Ama(OMe)Ψ[CSNH]Leu-O^{t}Bu	82	**3h**	68
2i	D/L-EthylMal(OMe)Ψ[CSNH]Phe-OMe	72	**3i**	60
2j	D/L-AllylMal(OEt)Ψ[CSNH]N(L-1-phenyl)ethylamide	92	-	-

The yields of the reduced peptides referred to the applied thiopeptide. *) The pseudopeptide Boc-D/L-Ama(OMe)Ψ[CH_2NH]Tyr-OTmse (**3b'**) was also obtained by reduction of **2b** as described below.

The yields obtained by thionating of the peptides with Lawesson's reagent depended on the combination of the carboxyl protecting groups. Since methyl ester of malonic acids were more sensitive than those of most other carboxylic and amino acids the handling of these compounds required well controlled reaction conditions. The more stable malonic acid ethyl ester exhibited higher stability, thus the removal of this moiety from the reduced peptides demanded much more drastic measures. For C-terminal protection the trimethyl silyl ethyl ester appeared most suitable for the thionation and the following reactions. This carboxyl protecting group could selectively be cleaved by fluoride in organic solvents under mild conditions and its moderate acid stability allowed selective removal of the N-protecting Boc group by acid catalyzed hydrolysis.

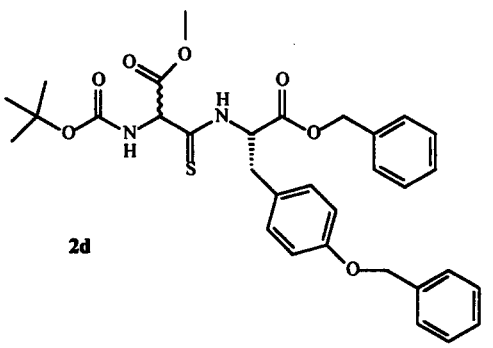
Reduction of the thioamides was performed by short time reactions with Raney nickel in an organic solvent by a permanent flow procedure. A small liquid chromatography column, about 6 x 70 mm depending on the molar amount of the thioamide derivatives, was filled with Raney nickel and washed first with water then thoroughly with the organic solvent by applying a pressure of about 0.5 to 1.5 bar to the solvent reservoir. Referred to the column dimensions given above, a solution of about 0.2 to 0.3 mmol of the thioamide in 1 to 1.5 ml solvent was injected into the flow system and the reduced product was obtained by fractionation. The reaction time respectively the time the reagent passed the nickel column was influenced by variation of the solvent reservoirs pressure. The conventional method of thioamide desulfurization with Raney nickel by stirring with the amide solution and subsequent filtration of the metal required about half a minute at least. In particular the elution of the peptide could be problematic due to adsorbance by the porous metal surface, requiring a number of washing steps and thus extending the reaction time up to minutes. The permanent flow method described allowed to achieve reaction times of about ten seconds or less with total reduction of the thioamide. In this way side reactions like transesterifications or cleavage of benzyl ether groups were reduced to a minimum.



Scheme 2. Reduction of Boc-D/L-Ama(OMe)Ψ[CSNH]Tyr(Bzl)-OTmse (**2b**). i) Raney nickel, acetone/methanol (50:1), 15 sec. ii) Raney nickel, dioxane/methanol (5:1), 10 min.

As an example Boc-D/L-Ama(OMe)Ψ[CSNH]Tyr(Bzl)-OTmse (**2b**) was dethionated by Raney nickel in the flow procedure to obtain the reduced anologon **3b** within 15 seconds in 75% yield and high purity. Longer reaction times caused partial loss of the benzyl ether moiety. Reduction in diluted solution by stirring with Raney nickel for a few minutes, filtration and washing of the metal gave a crude product, which required chromatographic purification to yield 60% of the derivative Boc-D/L-Ama(OMe)Ψ[CH_2NH]Tyr-OTmse (**3b'**, Scheme 2).

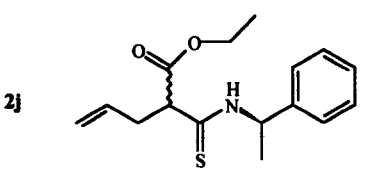
Whereas the tyrosine benzyl ether formation endured treatment with Raney nickel for many seconds, reduction of the benzyl ether protected derivative Boc-D/L-Ama(OMe)Ψ[CSNH]Tyr(Bzl)-OBzl (**2d**, Scheme 3) caused partial cleavage of the benzyl ester. Reaction times of about 15 seconds resulted in yields of approximative 25% containing 10% of the C-terminal unprotected deoxopeptide.



2d

Scheme 3. Boc-D/L-Ama(OMe)Ψ[CSNH]Tyr(Bzl)-OBzl

Trials in desulfurization of thionated derivatives of allyl malonic acid amides, like the given example (Scheme 4), to yield β-carboxy amino compounds with the reactive allyl function were not successful. Even very short reaction times required for complete reduction of the thioamide yielded mixtures of not specified products.



2j

Scheme 4. D/L-AllylMal(OEt)Ψ[CSNH](L-1-phenyl)ethylamide

As shown by the examples in the experimental section, the synthesis of protected dipeptides containing amino malonic acid on the N-terminal side, their conversion into the corresponding endothiopeptides and desulfurization is a convenient approach to pseudopeptides of the type Boc-D/L-Ama(OR)Ψ[CH_2NH]Xaa-OR′. While the stability of reduced peptide bonds against proteolytic cleavage in various pseudopeptides and inhibitors [10-16] and the conformational behaviour of reduced peptides [17-19] have been published, no deoxopeptides containing reduced amino malonic acid have been reported. This interesting dipeptide isostere with its protected carboxyl group direct proximity at the modified backbone offers various possibilities of combination and functionalisation in the synthesis of pseudopeptides and peptide based inhibitors with enhanced resistance towards proteolytic cleavage.

Experimental

Materials. Thin layer chromatography for analytical purpose was taken out with TLC-alu foil KG 60 F_{254} by Merck and solvent composition given below. Preparative column chromatography was performed with silica gel 60, 0.63-0.2 mm and 0.2-0.5 mm, by Merck. Used reagents were from Bachem, Merck or Fluka, solvents from Merck or Baker in p. a. quality. Toluene used for reactions with Lawesson's reagent and all solvents used in coupling reactions were dried over molecular sieve. Raney nickel was obtained as ready for use suspension in water from Fluka. MS measurements were performed with a Finnigan TSQ 700 Triple Quadrupol, ESI modus. NMR spectra were recorded with a Bruker AC 250 P (250 MHz, ^1H; 63 MHz, ^{13}C) and a Bruker DRX 500 (500 MHz, ^1H; 125 MHz, ^{13}C), data given below are δ in ppm, standard is TMS.

Reduction of endothiopeptides. Except the synthesis of Boc-D/L-Ama(OMe)Ψ[CH_2NH]Tyr-OTmse (**3b′**), the preparation of the Ψ[CH_2NH] pseudodipeptides occured with a flow system descibed above. The Raney nickel (caution: toxic and spontaneously flammable in air!) in the column was first washed with water then with the organic solvent, in which the reaction was carried out. As solvent mixture either tetrahydrofuran/methanol (100:1) or acetone/methanol (50:1) was used. The flow of the solvent was regulated so that the peptide passed the Raney nickel within 30 seconds approx. The reaction times for compounds with tyrosine benzyl ether moieties should not exceed 15 to 20 seconds.

Boc-protection of amino malonic acid dialkylesters. Amino malonic acid dialkylester hydrochlorides (10 mmol) and $KHCO_3$ (1 g, 10 mmol) were dissolved in a mixture of water, THF and dioxane (20 ml, 9:7:3). At 0°C di-tert-butyl dicarbonate (2.4 g, 11 mmol) and after 15 minutes stirring another molar amount $KHCO_3$ was added. The mixture was stirred for two hours at 0°C and then at room temperature until the end of the reaction, which was monitored by TLC. The solvent was removed in vacuo for the most part, the residue dissolved in ethyl acetate, the solution extracted with 10% aqueous $NaHSO_4$ and dried with Na_2SO_4. After removal of the solvent in vacuo the product was obtained as a colorless oil in approx. 96% yield.

Boc-Ama(OEt)$_2$. NMR: ^1H (250 MHz, $CDCl_3$): 1.30 (t, 6 H); 1.45 (s, 9 H); 4.26 (m, 4 H); 4.94 (wd, 1 H); 5.54 (w, 1 H). ^{13}C (63 MHz, $CDCl_3$): 14.02; 28.26; 57.65; 62.45 (CH_2); 80.63 (C_q); 154.81; 166.89.

Boc-Ama(OMe)$_2$. DC: R_f 0.9 ($CHCl_3$, MeOH, 10:1). NMR: ^1H (250 MHz, $CDCl_3$): 1.45 (s, 9 H); 3.81 (s, 6 H); 5.0 (d, 1 H); 5.62 (wd, 1 H). ^{13}C (63 MHz, $CDCl_3$): 28.24; 53.28; 57.30; 80.86 (C_q); 154.81; 167.11.

Preparation of malonic acid monoalkylester derivatives. The dialkylmalonate (9 mmol) was dissolved in the corresponding anhydrous alcohol (here: methanol or ethanol, 15 ml). A solution of KOH (0.5 g, 9 mmol) in the alcohol (5 to 10 ml) was added dropwise at 0°C. After stirring overnight, the solvent was evaporated for about 90%, 10% $NaHCO_3$ (30 ml) was added, the solution extracted with ethyl acetate (TLC). The alkaline aqueous solution containing the product was acidified with $NaHSO_4$ added in small portions at 0°C. The solution was extracted with ethyl acetate several times. The combined organic extracts were dried with Na_2SO_4, evaporation at 25°C maximum yielded the free malonic acid derivative (about 80%).

Boc-D/L-Ama(OEt)OH. NMR: ^{1}H (250 MHz, $CDCl_3$): 1.32 (t, 3 H); 1.44 (s, 9 H); 4.28 (m, 2 H); 4.78 (d, 0.5 H); 5.0 (d, 0.5 H); 5.71 (d, 0.5 H); 7.59 (d, 0.5 H); 11.33 (s, 1 H). ^{13}C (63 MHz, $CDCl_3$): 14.05; 28.16; 57.41, 58.73; 62.39, 62.83 (CH_2); 81.21, 82.78 (C_q); 155.29, 156.62; 166.65; 168.34, 169.59.

Boc-D/L-Ama(OMe)OH. DC: R_f 0.55 ($CHCl_3$, MeOH, 32%HOAc, EtOAc, 5:3:1:4). NMR: ^{1}H (250 MHz, $CDCl_3$): 1.44 (s, 9 H); 3.83 (s, 3 H); 4.81 (d, 0.5 H); 5.02 (d, 0.5 H); 5.75 (d, 0.5 H); 7.59 (d, 0.5 H); 10.85 (s, 1 H). ^{13}C (63 MHz, $CDCl_3$): 28.13; 53.10, 53.41; 57.24, 58.55; 81.20, 82.88 (C_q); 155.29, 156.61; 167.20; 168.05; 168.93.

Boc-D/L-Ama(OEt)-Tyr(Bzl)-OMe (1a). Boc-D/L-Ama(OEt)OH (550 mg, 2.38 mmol) and HCl·H-Tyr(Bzl)-OMe (700 mg, 2.17 mmol) were suspended in a mixture of 70 ml dichloromethane and 30 ml DMF. DCC (450 mg, 2.17 mmol) and 4-methylmorpholine (285 µl, 2.6 mmol) were added at 0°C. The mixture was stirred at this temperature overnight, then the solvent was removed in vacuo and the residue dissolved in ethyl acetate. The solution was extracted with aqueous solutions of 0.5 N HCl in 10% NaCl for several times, 5% $NaHCO_3$ and then dried over Na_2SO_4. After removal of the solvent, the product was purified by precipitation of the remaining dicyclohexyl urea in dichloromethane. Yield 95% (relative to HCl·H-Tyr(Bzl)-OMe; 1.06 g, 2.06 mmol). DC: R_f 0.92 ($CHCl_3$, MeOH, 10:1). NMR: ^{1}H (250 MHz, $CDCl_3$): 1.16-1.26 (m, 3 H); 1.44, 1.45 (s, 9 H); 3.07 (m, 2 H); 3.70, 3.72 (s, 3 H); 4.08-4.28 (m, 2 H); 4.75-4.83 (m, 2 H); 5.02, 5.03 (s, 2 H); 5.73 (w, 1 H); 6.82-7.08 (m, 5 H); 7.27-7.43 (m, 5 H). ^{13}C (63 MHz, $CDCl_3$): 13.93; 28.25; 36.72, 36.91 (CH_2); 52.36, 52.44; 53.83, 53.88; 57.97; 62.49, 62.61 (CH_2); 70.04, 70.05 (CH_2); 80.58 (C_q); 115.03, 115.09; 127.44, 127.48; 127.73, 127.75 (C_q); 127.98; 128.59; 130.26, 130.30; 137.0 (C_q); 155.01; 158.06, 158.10; 164.51; 167.34, 167.45; 171.20, 171.28.

Boc-D/L-Ama(OEt)Ψ[CSNH]Tyr(Bzl)-OMe (2a). 1a (770 mg, 1.5 mmol) and Lawesson's reagent (335 mg, 0.25 mmol) were stirred in dry toluene at 70°C for 3 h. After the solvent had been removed in vacuo, the most part of by-products were removed by flash chromatography with silica gel 60, 0.2-0.5 mm, eluent ethyl acetate. After further purification occured by two-fold fractionation over a silica gel 60 column in chloroform/ethyl acetate 15:1 afforded 75% of the endothiopeptide (597 mg, 1.125 mmol). DC: R_f 0.95 ($CHCl_3$, MeOH, 10:1). NMR: ^{1}H (250 MHz, $CDCl_3$): 1.16-1.31 (m, 3 H); 1.44, 1.45 (s, 9 H); 3.09-3.19 (m, 1 H); 3.28-3.38 (m, 1 H); 3.71, 3.72 (s, 3 H); 4.10-4.29 (m, 2 H); 5.02, 5.03 (s, 2 H); 5.05 (m, 1 H); 5.27 (m, 1 H); 6.05 (d, 1 H); 6.88 (m, 2 H); 7.01 (m, 2 H); 7.28-7.43 (m, 5 H); 8.55 (w, 1 H). ^{13}C (63 MHz, $CDCl_3$): 13.88, 13.91; 28.26; 35.23, 35.39 (CH_2); 52.50, 52.56; 59.05, 59.10; 62.54, 62.68 (CH_2); 63.19; 70.04 (CH_2); 80.71 (C_q); 115.07, 115.13; 127.44, 127.49; 127.98; 128.59; 130.30, 130.36; 136.97 (C_q); 154.99; 158.14, 158.18; 167.12, 167.22; 170.57, 170.61; 171.09; 195.22.

Boc-D/L-Ama(OEt)Ψ[CH_2NH]Tyr(Bzl)-OMe (3a). The preparation occurred in tetrahydrofuran/methanol (100:1). Reduction of 200 mg (0.389 mmol) thioamide yielded 165 mg (0.311 mmol, 80%). DC: R_f 0.9 ($CHCl_3$, MeOH, 10:1). NMR: ^{1}H (250 MHz, $CDCl_3$): 1.16-1.31 (m, 3 H); 1.44 (s, 9 H); 2.71-2.91 (m, 1.5 H); 2.96-3.11 (m, 2 H); 3.41 (m, 0.5 H); 3.66 (m, 3 H); 4.05-4.31 (m, 3 H); 5.01, 5.02 (s, 2 H); ca. 5.55 (w, 1 H); 6.86-6.90 (m, 3 H); 7.01-7.09 (m, 2 H); 7.27-7.42 (m, 5 H). ^{13}C (63 MHz, $CDCl_3$): 13.99, 14.01; 28.33; 38.63, 38.77 (CH_2); 39.32, 39.38 (CH_2); 49.05 (CH_2); 51.69, 52.31; 60.01 (CH_2); 61.34 (CH_2); 61.66; 62.41 (CH_2); 62.96, 63.06; 70.0 (CH_2); 80.12 (C_q); 114.82, 115.04; 127.43; 127.91, 127.94; 128.54, 128.56; 130.19, 130.53; 137.02, 137.11 (C_q); 155.51; 157.71, 158.05; 166.12; 171.54, 171.72; 174.58. MS: ESI (pos.): 501.2 $(M+H)^+$; 523.2 $(M+Na)^+$.

Boc-Tyr(Bzl)-OTmse. Boc-Tyr(Bzl)-OH (1 g, 2.69 mmol), 2-(trimethylsilyl)ethanol (0.384 ml, 2.69 mmol) and 4-dimethylaminopyridine (65 mg, 0.539 mmol) were dissolved in dichloromethane (10 ml). DCC (0.555 g, 2.69 mmol) was added at 0°C. The mixture was stirred one hour at this temperature and then kept at -25°C over night. After filtration the solvent was removed and the residue dissolved in ethyl acetate. The solution was extracted with aqueous solutions of 0.5 N HCl in 10 % NaCl and 10% NaCl, dried with Na_2SO_4 and evaporated. The crude product was purified by column chromatogaphy over silica gel 60 in chloroform, methanol (50:1, v:v). Yield 94% (1.2 g, 2.54 mmol). DC: R_f 0.88 ($CHCl_3$, MeOH, 50:1). NMR: ^{1}H (500 MHz, $CDCl_3$): -0.03 (s, 9 H); 0.96 (m, 2H); 1.41 (s, 9 H); 3.01 (m, 2 H); 4.17 (m, 2 H); 4.49 (m, 1 H); 4.96 (d, 1 H); 5.02 (s, 2 H); 6.88 (d, 2 H); 7.04 (d, 2 H); 7.24-7.42 (m, 5 H). ^{13}C (125 MHz, $CDCl_3$): -1.57; 17.29 (CH_2); 28.26; 37.45 (CH_2); 54.56; 63.60 (CH_2); 69.94 (CH_2); 79.69 (C_q); 114.78; 127.40; 127.90; 128.36 (C_q); 128.52; 130.34; 136.96 (C_q); 155.04; 157.82; 172.0.

H-Tyr(Bzl)-OTmse. Boc-Tyr(Bzl)-OTmse (1.1 g, 2.34 mmol) was dissolved in 2,2,2-trifluoroethanol (7 ml) and conc. HCl (0.7 ml) was added at room temperature. After 20 min the solution was poured into 5% aqueous Na_2CO_3 and the product extracted with ethyl acetate. The organic layer was dried with Na_2SO_4 and evaporated. The product, obtained as viscous oil, was stable for weeks at -20°C. For longer storage the amine preferably should be isolated as hydrochloride, obtainable through precipitation from etheric solution by adding a solution of anhydrous HCl in ether. DC: R_f 0.75 ($CHCl_3$, MeOH, 32%HOAc, EtOAc, 5:3:1:4). NMR: ^1H (500 MHz, $CDCl_3$): 0.04 (s, 9 H); 0.98 (t, 2H); ca. 1.85 (w, 2 H); 2.79, 3.01 (m, 2 H); 3.63 (m, 1 H); 4.19 (m, 2 H,); 5.02 (s, 2 H); 6.91 (d, 2 H); 7.10 (d, 2 H); 7.31-7.42 (m, 5 H). ^{13}C (125 MHz, $CDCl_3$): -1.58; 17.29 (CH_2); 40.04 (CH_2); 55.85; 63.19 (CH_2); 69.92 (CH_2); 114.85; 127.37; 127.86; 128.49; 129.38 (C_q); 130.24; 136.95 (C_q); 157.69 (C_q); 175.01.

Boc-D/L-Ama(OMe)-Tyr(Bzl)OTmse (1b). H-Tyr(Bzl)OTmse (665 mg, 1.79 mmol), Boc-D/L-Ama(OMe)OH (439 mg, 1.79 mmol) and diisopropyl ethyl amine (615 µl, 3.58 mmol) were dissolved in 10 ml dichloromethane. Chloro-tripyrrolidinophosphonium-hexafluorophosphate (760 mg, 1.8 mmol) was added at 0°C and the mixture stirred at this temperature for 18 h. After evaporation the residue was solved in ethyl acetate with 5% ether and the solution extracted with 5% aqueous $NaHCO_3$, 10% $NaHSO_4$, 10% NaCl and dried with Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by chromatography over silica gel 60 in chloroform/methanol 50:1. Yield 75% (790 mg, 1.35 mmol). DC: R_f 0.8 ($CHCl_3$, MeOH, 10:1). NMR: ^1H (500 MHz, $CDCl_3$): 0.02, 0.03 (s, 9 H); 0.93-0.99 (m, 2H); 1.42, 1.43 (s, 9 H); 3.01-3.09 (m, 2 H); 3.64, 3.74 (s, 3 H); 4.14-4.22 (m, 2 H); 4.72 (m, 1 H); 4.84 (d, 1 H); 5.0, 5.01 (s, 2 H); 5.72 (w, 1 H); 6.74, 6.85 (wd, 1 H); 6.85-6.89 (m, 2 H); 6.95-7.01 (m, 2 H); 7.30-7.41 (m, 5 H).

Boc-D/L-Ama(OMe)Ψ[CSNH]Tyr(Bzl)-OTmse (2b). 1b (577 mg, 0.965 mmol) and Lawesson's reagent (390 mg, 0.483 mmol) were heated in 12 ml toluene at 80°C for three hours. The solvent was removed by destillation under reduced pressure, the residue taken up in 5 ml dichloromethane and fractionated over silica gel 60 first eluated with dichloromethane, then with ethyl acetate. After repeating this procedure, the analytically pure product was obtained in 87% yield (504 mg, 0.837 mmol). DC: R_f 0.2 (CH_2Cl_2), R_f 0.92 (EtOAc), DC: R_f 0.8 ($CHCl_3$, MeOH, 50:1). NMR: ^1H (500 MHz, $CDCl_3$): 0.02, 0.03 (s, 9 H); 0.97 (m, 2 H); 1.42, 1.44 (s, 9 H); 3.12, 3.34 (m, 2 H); 3.66, 3.74 (s, 3 H); 4.16-4.25 (m, 2 H); 5.01 (s, 2 H); 5.04 (w, 1 H); 5.14-5.21 (m, 1 H); 6.04 (wd, 1 H); 6.85-6.89 (m, 2 H); 6.97-7.01 (m, 2 H); 7.29-7.42 (m, 5 H); 8.45 (w, 1 H). ^{13}C (125 MHz, $CDCl_3$): -1.56; 17.42 (CH_2); 28.22; 35.02, 35.13 (CH_2); 53.16, 53.29; 59.08; 62.77, 63.03; 64.38, 64.43 (CH_2); 69.97 (CH_2); 80.77 (C_q); 114.95; 127.41; 127.47; 127.98; 128.57; 130.35; 130.41; 136.88 (C_q); 154.96; 158.02, 158.08; 167.68; 170.20; 194.68.

Boc-D/L-Ama(OMe)Ψ[CH$_2$NH]Tyr(Bzl)-OTmse (3b). 2b (252 mg, 0.43 mmol) was reduced in acetone/methanol (50:1). Yield 75% (185 mg, 0.323 mmol). NMR: ^1H (500 MHz, $CDCl_3$): 0.01 (s, 9 H); 0.87-0.96 (m, 2 H); 1.42, 1.45 (s, 9 H); 1.64 (w, 1 H); 2.67-3.08 (m, 3.5 H); 3.33 (m, 0.5 H); 3.60-3.68 (m, 3 H); 4.01-4.25 (m, 3 H); 5.0, 5.01 (s, 2 H); 5.36, ca. 5.75 (w, 1 H); 6.84-6.88 (m, 2 H); 7.01 (m, 1 H); 7.04-7.07 (m, 2 H); 7.29-7.41 (m, 5 H). ^{13}C (125 MHz, $CDCl_3$): -1.55; 17.34, 17.37 (CH_2); 28.23, 28.; 38.61 (CH_2); 38.76 (CH_2); 39.32 (CH_2); 48.97 (CH_2); 51.30; 52.27; 53.68, 53.86; 61.81; 63.10 (CH_2); 63.24; 63.96 (CH_2); 69.94 (CH_2); 79.83, 80.18 (C_q); 114.68, 114.91; 127.44; 127.92; 128.55; 129.63; 130.23; 130.56; 136.92, 137.01 (C_q); 157.59, 157.98; 166.53; 171.29; 172.11; 174.33. MS: ESI (pos.): 573.4 $(M+H)^+$; 595.3 $(M+Na)^+$.

Boc-D/L-Ama(OMe)Ψ[CH$_2$NH]Tyr-OTmse (3b'). Boc-D/L-Ama(OMe)Ψ[CSNH]Tyr(Bzl)-OTmse (**2b**; 105 mg, 0.179 mmol) was dissolved in 5 ml dioxane/methanol (5:1) and Raney nickel (about 1 ml, which was washed several times with dioxan) was added. The mixture was stirred until TLC indicated the reaction was completed. The filtered solution was evaporated and the product isolated by chromatographic separation over Sephadex LH 20 in methanol. Yield 60% (52 mg, 0.107 mmol). DC: R_f 0.7 ($CHCl_3$, MeOH, 10:1). NMR: ^1H (500 MHz, $CDCl_3$): -0.01, 0.0 (s, 9 H); 0.88-0.95 (m, 2 H); 1.40, 1.42 (s, 9 H); 2.68-3.03 (m, 3.5 H); 3.33 (m, 0.5 H); 3.58-3.65 (m, 3 H); 4.0-4.24 (m, 3 H); 5.45, 5.53 (m, 1 H); 6.68-6.70 (m, 2 H); 6.92-6.95 (m, 2 H). ^{13}C (125 MHz, $CDCl_3$): -1.62; 17.28 (CH_2); 28.13, 28.22; 38.42 (CH_2); 38.57 (CH_2); 39.18 (CH_2); 48.73, 48.82 (CH_2); 51.34; 52.33; 53.59, 53.72; 62.96; 63.11; 63.26 (CH_2); 64.08; 80.05, 80.43 (C_q); 115.29, 115.56; 128.12 (C_q); 130.16, 130.44; 155.17; 155.59; 166.92; 172.09; 174.50. MS: ESI (pos.): 483.2 $(M+H)^+$; 505.3 $(M+Na)^+$. ESI (neg.): 481.3 $(M-H)^-$.

Boc-D/L-Ama(OMe)-Tyr-O^{t}Bu (1c). To a solution of Boc-D/L-Ama(OMe)OH (238 mg, 1.02 mmol) and H-Tyr-O^{t}Bu (242 mg, 1.02 mmol) in 3 ml dichloromethane a solution of DCC (210 mg, 1.02 mmol) in 2 ml dichloromethane was added at 0°C and

stirred over night at this temperature. After filtration and evaporation the residue was dissolved in ethyl acetate and the product was purified by extraction with 10% $NaHSO_4$, 5% Na_2CO_3, and 5% $NaHCO_3$ solutions. After the solution was dried with Na_2SO_4 removal of the solvent yielded 94 % (433 mg, 0.959 mmol) of the dipeptide. DC: R_f 0.43 ($CHCl_3$, MeOH, 10:1). DC: R_f 0.87 ($CHCl_3$, MeOH, 32%HOAc, EtOAc, 5:3:1:4). NMR: ^1H (250 MHz, $CDCl_3$): 1.41-1.45 (m, 18 H); 3.02 (m, 2 H); 3.69, 3.74 (s, 3 H); 4.64 (m, 1 H); 4.87 (d, 1 H); 5.81 (wd, 1 H); 6.75 (m, 2 H); 6.87-6.98 (m, 3 H). ^{13}C (63 MHz, $CDCl_3$): 27.96; 27.98; 28.24; 36.75, 36.92 (CH_2); 53.20, 53.25; 54.25; 57.86; 80.87 (C_q); 82.66, 82.81 (C_q); 115.50; 126.73, 126.80 (C_q); 130.43, 130.51; 155.72; 163.65; 167.86; 167.91; 169.85, 170.06.

Boc-D/L-Ama(OMe)Ψ[CSNH]Tyr-O^{t}Bu (2c). Boc-D/L-Ama(OMe)-Tyr-O^{t}Bu (**1c**; 360 mg, 0.796 mmol) and Lawesson's reagent (640 mg, 1.58 mmol) were suspended in 25 ml toluene and stirred at 70-80°C until the educt was vanished (TLC control). The product was isolated by the chromatographic procedure described in the preparation of **2b** and supplemental fractionation over silica gel 60 with ethyl acetate. Yield 67% (250 mg, 0.534 mmol). DC: R_f 0.57 ($CHCl_3$, MeOH, 10:1).

Boc-D/L-Ama(OMe)Ψ[CH_2NH]Tyr-O^{t}Bu (3c). Reduction of the corresponding thioamide (88 mg, 0.188 mmol) in acetone/ methanol (50:1) yielded 69% (57 mg, 0.13 mmol) of the deoxopeptide. DC: R_f 0.55 ($CHCl_3$, MeOH, 10:1). NMR: ^1H (250 MHz, $CDCl_3$): 1.38-1.46 (m, 18 H,; 2.68-3.10 (m, 3.5 H); 3.23-3.28 (m, 0.5 H); 3.65-3.70 (m, 3 H); 3.81-4.27 (m, 1 H); ca. 5.5 (w, 1 H); 6.73 (d, 2 H); 7.0 (dd, 2 H). ^{13}C (63 MHz, $CDCl_3$): 27.99; 28.06; 28.27; 28.35; 38.64, 38.81, 39.43 (CH_2); 48.92, 49.54 (CH_2); 51.34; 52.33; 53.85; 62.16; 63.54; 63.70; 81.49, 81.54 (C_q); 82.52, 82.64 (C_q); 115.28, 115.56; 126.99, 127.18 (C_q); 130.39, 130.64; 155.09; 155.55; 166.92; 170.41; 172.20; 173.68. MS: ESI (pos.): 439.3 $(M+H)^+$.

Boc-D/L-Ama(OMe)-Phe-O^{t}Bu (1e). Boc-D/L-Ama(OMe)OH (480 mg, 2.05 mmol), HCl·H-Phe-O^{t}Bu (528 mg, 2.05 mmol), 1-hydroxybenzotriazole (305 mg) and 4-methylmorpholine (225 µl) were disolved in 20 ml tetrahydrofuran. DCC (423 mg, 2.05 mmol) in 5 ml tetrahydrofuran was added at 0°C. The mixture was stirred over night at 4°C. The product was purified by extraction of its solution in ethyl acetate comparable to the separation of **1c**. Yield 86% (770 mg, 1.76 mmol). DC: R_f 0.92 ($CHCl_3$, MeOH, 10:1). NMR: ^1H (250 MHz, $CDCl_3$): 1.39, 1.42, 1.43, 1.44 (s, 18 H); 3.10 (m, 2 H); 3.70, 3.77 (s, 3 H); 4.69 (m, 1 H); 4.84 (w, 1 H); 5.72 (wd, 1 H); 6.79, 6.86 (w, 1 H); 7.08-7.16 (m, 2 H); 7.19-7.32 (m, 3 H). ^{13}C (63 MHz, $CDCl_3$): 27.93; 27.97; 28.25; 37.63, 37.83 (CH_2); 53.08, 53.17; 54.10, 54.17; 57.86; 80.06 (C_q); 82.63, 82.77 (C_q); 127.05, 127.09; 128.44, 128.47; 129.45, 129.50; 135.77, 135.84 (C_q); 155.11; 163.79; 167.99; 169.66, 169.78.

Boc-D/L-Ama(OMe)Ψ[CSNH]Phe-O^{t}Bu (2e). The synthesis and chromatographic purification was analogous to the preparation of **2c** with a yield of 74%. DC: R_f 0.95 ($CHCl_3$, MeOH, 10:1). NMR: ^1H (250 MHz, $CDCl_3$): 1.39, 1.41, 1.44, 1.45 (s, 18 H); 3.28 (m, 2 H); 3.71, 3.77 (s, 3 H); 5.04-5.17 (m, 2 H); 6.04 (w, 1 H); 7.11-7.17 (m, 2 H); 7.20-7.32 (m, 3 H); 8.54 (w, 1 H). ^{13}C (63 MHz, $CDCl_3$): 27.93; 28.26; 35.88, 36.08 (CH_2); 53.16, 53.26; 54.10, 54.17; 59.29; 80.80 (C_q); 83.21, 83.31 (C_q); 127.14, 127.20; 128.48, 128.50; 129.48, 129.55; 135.55 (C_q); 155.0; 167.75; 169.02, 169.13; 194.43.

Boc-D/L-Ama(OMe)Ψ[CH_2NH]Phe-O^{t}Bu (3e). Reduction of **2e** (79 mg, 0.175 mmol) in acetone/methanol (50:1) yielded 69% (53 mg, 0.121 mmol). DC: R_f 0.9 ($CHCl_3$, MeOH, 10:1). NMR: ^1H (250 MHz, $CDCl_3$): 1.37-1.46 (m, 18 H); ca. 1.65 (w, 1 H); 2.62-3.13 (m, 3.5 H); 3.30 (m, 0.5 H); 3.64-3.71 (m, 3 H); 4.0 (m, 0.5 H); 4.26 (w, 0.5 H); 5.37, 5.72 (w, 1 H); 7.17-7.30 (m, 5 H). ^{13}C (63 MHz, $CDCl_3$): 27.95; 28.04; 28.27; 28.35; 39.57, 39.74, 40.34 (CH_2); 48.87, 48.95, 49.76 (CH_2); 51.24; 52.23; 52.28; 62.11; 63.37, 63.58; 80.12 (C_q); 81.34 (C_q); 81.39 (C_q); 82.50 (C_q); 126.59, 127.04; 128.25, 128.55; 129.37, 129.64; 135.83, 137.62 (C_q); 166.58; 170.13; 172.14; 173.42. MS: ESI (pos.): 423.2 $(M+H)^+$.

Boc-D/L-Ama(OEt)-Phe-O^{t}Bu (1f). Relative to quantities and procedure the preparation was analogous to the synthesis and separation of **1e**. Yield 92% (850 mg, 1.88 mmol). DC: R_f 0.93 ($CHCl_3$, MeOH, 10:1). NMR: ^1H (250 MHz, $CDCl_3$): 1.17-1.30 (m, 3 H); 1.39, 1.42, 1.44, 1.45 (s, 18 H); 3.10 (m, 2 H); 4.07-4.29 (m, 2 H); 4.69 (m, 1 H); 4.84 (wd, 1 H); 5.74 (w, 1 H); 6.90 (w, 1 H); 7.08-7.18 (m, 2 H.); 7.20-7.32 (m, 3 H). ^{13}C (63 MHz, $CDCl_3$): 13.93; 27.90, 27.95; 28.25; 37.61, 37.88 (CH_2); 54.16; 57.98; 62.41, 62.52 (CH_2); 80.45 (C_q); 82.53, 82.70 (C_q); 127.0, 127.06; 128.40, 128.45; 129.45, 129.50; 135.83, 135.87 (C_q); 155.08; 163.97, 164.29; 167.44, 167.49; 169.68, 169.78.

Boc-D/L-Ama(OEt)Ψ[CSNH]Phe-O^{t}Bu (2f). The preparation was analogous to that of the corresponding methylester derivative. Yield 78%. DC: R_f 0.96 ($CHCl_3$, MeOH, 10:1).

Boc-D/L-Ama(OEt)Ψ[CH_2NH]Phe-O^{t}Bu (3f). Reduction of corresponding thioamide (82 mg, 0.176 mmol) in acetone/methanol (50:1) yielded 81% (62 mg, 0.142 mmol). DC: R_f 0.9 ($CHCl_3$, MeOH, 10:1). NMR: ^1H (250 MHz, $CDCl_3$): 1.17-1.31 (m, 3 H); 1.36-1.46 (m, 18 H); ca. 1.7 (w, 1 H); 2.62-3.14 (m, 3.5 H); 3.31 (m, 0.5 H); 3.99-4.25 (m, 4 H); ca. 5.35, 5.74 (w, 1 H); 7.16-7.32 (m, 5 H). ^{13}C (63 MHz, $CDCl_3$): 14.13, 14.17, 14.53; 27.96; 28.02; 28.28; 39.60, 39.76, 40.41 (CH_2); 48.92, 48.98, 49.76 (CH_2); 53.93; 59.96, 61.32 (CH_2); 62.18; 63.44, 63.55; 80.06 (C_q); 81.33 (C_q); 81.36 (C_q); 82.47 (C_q); 126.59, 127.05; 128.27, 128.53; 129.36, 129.66; 136.06, 137.61 (C_q); 166.18; 170.17; 171.63; 173.44.

Boc-D/L-Ama(OEt)-Phe-OMe (1g). The preparation occured by DCC coupling of Boc-D/L-Ama(OEt)OH (630mg, 2.55 mmol) with H-Phe-OMe (500 mg, 2.32 mmol of the hydrochloride neutralized with triethylamine) in dichloromethane/methanol (7:1) comparable to the synthesis and isolation of **1a**. Yield 90% (852 mg, 2.09 mmol). DC: R_f 0.93 ($CHCl_3$, MeOH, 32%HOAc, EtOAc, 5:3:1:4). NMR: ^1H (250 MHz, $CDCl_3$): 1.17-1.32 (m, 3 H); 1.45 (s, 9 H); 3.14 (m, 2 H); 3.71, 3.74 (s, 3 H); 4.08-4.31 (m, 2 H); 4.83 (m, 1 H); 4.97 (wd, 0.5 H); 5.56 (w, 0.5 H); 5.71 (w, 1 H); 6.86 (w, 1 H); 7.04-7.18 (m, 2 H); 7.23-7.33 (m, 3 H). ^{13}C (63 MHz, $CDCl_3$): 13.92, 13.99; 28.25; 37.55, 37.76 (CH_2); 52.40, 52.49; 53.21; 53.73; 62.51, 62.57 (CH_2); 80.06 (C_q); 127.21, 127.28; 128.63, 128.69; 129.20, 129.25; 135.49 (C_q); 155.26; 167.32; 171.12; 171.20.

Boc-D/L-Ama(OEt)Ψ[CSNH]Phe-OMe (2g). The synthesis and chromatographic purification was analogous to the preparation of **2c**. Yield 88%. DC: R_f 0.94 ($CHCl_3$, MeOH, 32%HOAc, EtOAc, 5:3:1:4). NMR: ^1H (250 MHz, $CDCl_3$): 1.18-1.32 (m, 3 H); 1.45 (s, 9 H); 3.21, 3.40 (m, 2 H); 3.73, 3.74 (s, 3 H); 4.10-4.30 (m, 2 H); 5.04 (m, 1 H); ca. 5.6 (w, 1 H); 6.04 (w, 1 H); 7.08-7.12 (m, 2 H); 7.24-7.33 (m, 3 H); 8.54 (w, 1 H). ^{13}C (63 MHz, $CDCl_3$): 13.91, 13.99; 28.26; 36.04, 36.21 (CH_2); 52.52, 52.59; 53.21; 58.88, 58.94; 62.57, 62.71 (CH_2); 80.74 (C_q); 127.33, 127.39; 128.67, 128.73; 129.24, 129.29; 135.20, 135.25 (C_q); 154.74; 167.12, 167.20; 195.29.

Boc-D/L-Ama(OEt)Ψ[CH_2NH]Phe-OMe (3g). Reduction of corresponding thioamide (90 mg, 0.249 mmol) in tetrahydrofuran /methanol (100:1) yielded 87% (72 mg, 0.217 mmol). DC: R_f 0.84 ($CHCl_3$, MeOH, 10:1). NMR: ^1H (250 MHz, $CDCl_3$): 1.16-1.32 (m, 3 H); 1.45 (m, 9 H); 1.78 (w, 1 H); 2.63-3.18 (m, 3.5 H); 3.45 (m, 0.5 H); 3.65, 3.66, 3.71 (s, 3 H); 4.05-4.30 (m, 2 H); ca. 4.9 (w, 1 H); ca. 5.3 (w, 1 H); 5.55 (w, 1 H); 7.14-7.31 (m, 5 H). ^{13}C (63 MHz, $CDCl_3$): 13.99, 14.10, 14.15; 28.25, 28.35; 39.53, 39.68, 40.24 (CH_2); 49.05 (CH_2); 51.75; 52.36; 53.20; 57.49; 61.36, 62.56 (CH_2); 62.86; 63.03; 79,77, 80.18, 80.73 (C_q); 126.73, 126.77; 128.41, 128.43; 129.19, 129.47; 135.63, 137.28 (C_q); 166.54; 167.25; 171.54; 174.60.

Boc-D/L-Ama(OMe)-Leu-O^{t}Bu (1h). The preparation was analogous to that of **1c** by DCC coupling of Boc-D/L-Ama(OMe)OH with H-Leu-O^{t}Bu. Yield 75 %. DC: R_f 0.89 ($CHCl_3$, MeOH, 10:1). NMR: ^1H (250 MHz, $CDCl_3$): 0.93 (m, 6 H); 1.45, 1.46 (s, 18 H); 1.49-1.72 (m, 3 H); 3.80, 3.83 (s, 3 H); 4.48 (m, 1 H); 4.89 (m, 1 H); 5.79 (w, 1 H, NH); 6.78, 6.85 (wd, 1 H). ^{13}C (63 MHz, $CDCl_3$): 22.06; 22.79, 22.82; 24.91, 24.93; 27.97, 27.99; 28.25; 41.53, 41.74 (CH_2); 51.97, 52.0; 53.09, 53.18; 57.94; 80.65 (C_q); 82.07, 82.17 (C_q); 164.56; 168.17, 168.25; 171.19, 171.30.

Boc-D/L-Ama(OMe)Ψ[CSNH]Leu-O^{t}Bu (2h). The preparation and purification was analogous to the synthesis of **2c**. Yield 82%. DC: R_f 0.93 ($CHCl_3$, MeOH, 10:1). NMR: ^1H (250 MHz, $CDCl_3$): 0.91-0.98 (m, 6 H); 1.45, 1.47 (s, 18 H); 1.61-1.83 (m, 3 H); 3.79, 3.81 (s, 3 H); 4.94 (m, 1 H); 5.10 (m, 1 H); 6.07 (wd, 1 H); ca. 8.5 (w, 1 H).

Boc-D/L-Ama(OMe)Ψ[CH_2NH]Leu-O^{t}Bu (3h). Reduction of corresponding thioamide in acetone/methanol (50:1) yielded 68%. NMR: ^1H (250 MHz, $CDCl_3$): 0.85-0.97 (m, 6 H); ca. 1.4 (m, 2 H); 1.45, 1.46 (s, 18 H); 1.52-1.78 (m, 2 H); 2.67-2.86, 3.01-3.11 (m, 2 H); 3.69-3.75 (m, 3 H); 4.30 (w, 1 H); 5.43 (w, 1 H). ^{13}C (63 MHz, $CDCl_3$): 22.04; 22.20; 22.77; 22.81; 24.57, 24.84, 24.88; 28.01; 28.13; 28.26; 28.35; 42.60, 42.74 (CH_2); 48.80, 49.08 (CH_2); 51.28; 52.26, 52.31; 59.82; 60.81; 80.14 (C_q); 81.02 (C_q); 81.09 (C_q); 82.13 (C_q); 171.57; 172.27; 174.81, 174.88. MS: ESI (pos.): 489.2 $(M+H)^+$.

Ethyl malonic acid monomethylester. NMR: ^1H (500 MHz, $CDCl_3$): 0.92 (t, 3 H); 1.87 (m, 2 H); 3.27 (t, 1 H); 3.66, 3.69 (s, 3 H); 11.11 (w, 1 H). ^{13}C (125 MHz, $CDCl_3$): 11.61; 22.13 (CH_2); 52.46; 52.93; 169.59; 174.96.

D/L-EthylMal(OMe)-Phe-OMe (1i). The preparation was analogous to the synthesis of **1g** with a yield of 76%. DC: R_f 0.91 ($CHCl_3$, MeOH, 10:1). NMR: ^1H (250 MHz, $CDCl_3$): 0.83-0.99 (m, 3 H); 1.80-2.03 (m, 2 H); 3.02-3.23 (m, 3 H); 3.69, 3.70, 3.72, 3.73 (s, 6 H); 4.86 (m, 1 H); 6.92 (wt, 1 H); 7.09-7.14 (m, 2 H); 7.20-7.32 (m, 3 H). ^{13}C (63 MHz, $CDCl_3$): 11.66, 11.84;

24.02, 24.20 (CH_2); 37.80, 37.86 (CH_2); 52.31; 52.34; 52.37; 53.25; 53.25, 53.36; 54.19, 54.31; 127.13, 127.15; 128.57; 129.25, 129.27; 135.88 (C_q); 167.86, 167.92; 171.69; 171.76; 171.86.

D/L-EthylMal(OMe)Ψ[CSNH]Phe-OMe (2i). The preparation was analogous to that of **2b**. Yield 72%. DC: R_f 0.92 ($CHCl_3$, MeOH, 10:1). NMR: ^1H (250 MHz, $CDCl_3$): 0.84-0.99 (m, 3 H); 1.85-2.06 (m, 2 H); 3.15-3.46 (m, 2 H); 3.68-3.80 (m, 7 H); 5.29-5.40 (m, 1 H); 7.08-7.15 (m, 2 H); 7.21-7.33 (m, 3 H); 8.87, 8.97 (w, 1 H). ^{13}C (63 MHz, $CDCl_3$): 11.45, 11.52 (CH_3); 28.34 (CH_2); 36.40, 36.42 (CH_2); 52.38; 52.46; 52.51; 58.83, 58.92; 61.81, 61.86; 127.30; 128.62; 129.25; 135.40, 135.50 (C_q); 170.77, 170.92; 172.64, 172.76; 199.0, 199.19.

D/L-EthylMal(OMe)Ψ[CH_2NH]Phe-OMe (3i). Reduction of corresponding thioamide occured in tetrahydrofuran/methanol (100:1) with a yield of 60%. DC: R_f 0.92 ($CHCl_3$, MeOH, 10:1). NMR: ^1H (250 MHz, $CDCl_3$): 0.86 (m, 3 H); 1.54 (m, 2 H); 1.67 (ws, 1 H); 2.27-2.77 (m, 3 H); 2.82-2.97 (m, 2 H); 3.43-3.53 (m, 1 H); 3.60, 3.61, 3.64 (s, 6 H); 7.14-7.30 (m, 5 H). ^{13}C (63 MHz, $CDCl_3$): 11.64, 11.67; 23.19, 23.24 (CH_2); 39.63, 39.70 (CH_2); 47.50; 48.07; 49.18, 49.60 (CH_2); 51.39; 51.43; 51.63; 62.87, 63.21; 126.63, 126.64; 128.33, 128.35; 129.21; 137.42, 137.46 (C_q); 174.80, 174.94; 175.43, 175.62.

Allyl malonic acid monoethylester. NMR: ^1H (500 MHz, $CDCl_3$): 1.24 (t, 3 H); 2.62 (m, 2 H); 3.44 (t, 1 H); 4.10-4.20 (m, 2 H); 5.0-5.12 (m, 2 H); 5.74 (m, 1 H); ca. 9.1 (w, 1 H). ^{13}C (125 MHz, $CDCl_3$): 13.96; 32.72 (CH_2); 51.34; 61.77 (CH_2); 117.87 (CH_2); 133.52; 168.74; 174.33.

D/L-AllylMal(OEt)-N(L-1-phenyl)ethylamide (1j). Allyl malonic acid monoethylester (500 mg, 2.91 mmol) and L-(-)-1-phenyl ethylamine (353 mg, 2.91 mmol) were dissolved in 20 ml dichloromethane. N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide-hydrochloride (558 mg, 2.91 mmol) was added at 0°C. The solution was stirred 2 h at 0°C, then 4 h at room temperature. The solvent was removed, the residue taken up in ethyl acetate and the prduct was purified by extraction. Yield 70% (532 mg, 2.04 mmol). DC: R_f 0.8 ($CHCl_3$, MeOH, 32%HOAc, EtOAc, 5:3:1:4). NMR: ^1H (250 MHz, $CDCl_3$): 1.25 (m, 3 H); 1.48 (dd, 3 H); 2.65 (m, 2 H); 3.28 (m, 1 H); 4.12-4.23 (m, 2 H); 5.0-5.17 (m, 3 H); 5.73 (m, 1 H); 6.87 (w, 1 H); 7.21-7.36 (m, 5 H). ^{13}C (63 MHz, $CDCl_3$): 14.09, 14.11; 21.87, 21.90; 34.59, 34.72 (CH_2); 48.91, 48.98; 52.51, 52.58; 61.48 (CH_2); 117.68, 117.72 (CH_2); 126.04, 126.09; 127.32, 127.37; 128.63, 128.67; 133.99, 134.03; 143.0, 143.10 (C_q); 166.79; 171.42, 171.48.

D/L-AllylMal(OEt)Ψ[CSNH]N(L-1-phenyl)ethylamide (2j). The preparation was analogous to the synthesis of **2b**. Yield 92%. DC: R_f 0.9 ($CHCl_3$, MeOH, 10:1). NMR: ^1H (250 MHz, $CDCl_3$): 1.25 (m, 3 H); 1.58 (dd, 3 H); 2.60-2.86 (m, 2 H); 3.89 (m, 1 H); 4.16 (m, 2 H); 4.99-5.16 (m, 2 H); 5.69 (m, 2 H); 7.23-7.39 (m, 5 H); 9.04 (w, 1 H). ^{13}C (63 MHz, $CDCl_3$): 14.07; 20.40, 20.63; 39.11, 39.20 (CH_2); 54.69, 54.76; 59.65, 59.79; 61.69 (CH_2); 118.27, 118.35 (CH_2); 126.34, 126.42; 127.70; 128.76, 128.80; 133.15, 133.19; 141.36, 141.43 (C_q); 172.52, 172.58; 196.77, 196.86.

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References and Notes

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