Solution Synthesis and Characterization of Aza-β^3-peptides (N$^\alpha$-Substituted Hydrazino Acetic Acid Oligomers)

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Introduction

Pseudopeptidic oligomers, which can be conveniently considered as "biopolymer mimetics",[1e] are the object of great synthetic efforts. Several recent reviews reflect the increasing interest for such molecules.[1] Among other applications, they could be used as biomaterial surrogates,[2] peptidomimetics,[3] immunomodulators,[4] or genic therapy agents.[5] These potential properties mainly rely on both enhanced resistance to proteolysis and specific intramolecular or intermolecular three-dimensional arrangement such as turns, β-sheets, or helices. Peptoids,[6] azatides,[7] ureapeptoids,[8] and β-peptoids,[9] all described within the past decade, can be regarded as belonging to a particular family of pseudopeptides. For all of them, the side chains are connected to nitrogen atoms of the backbone.

Scheme 1

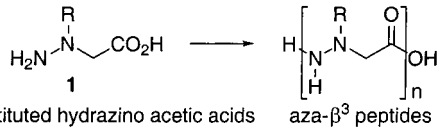

Table 1. Yields of Monomers 1 (%)

1x	1a NαhAla	1b NαhVal	1c NαhLeu	1d NαhPhe
Boc-**1x**-OMe		94	92	94
Boc-**1x**-OBn			66	
Boc-**1x**-OH		65	79	96
H-**1x**-OMe		68		
H-**1x**-OBn	84		78	76

Following our recent work on N$^\alpha$-substituted hydrazino acetic building blocks,[10] we have now showed that they can be used for the synthesis and characterization of new pseudopeptides, which share the same characteristics (Scheme 1). The first considerations on the ability of these oligomers to adopt specific secondary structure in solution are presented.

Results and Discussion

Monomers **1** were synthesized as N^β-Boc-protected benzyl or methyl esters, except for **1a,** which was directly prepared as free N^α-(Me)hydrazino acetic acid benzyl ester (Table 1). Boc deprotection was obtained by TFA/DCM (1/1) treatment for 15 min. Hydrogenolysis was performed using 5% Pd/C in 2-propanol under 1 atm (using methanol yields to partial transesterification). Saponifications were run in acetonitrile (Scheme 2). Free N$^\alpha$-substituted hydrazino acetic esters have to be freshly prepared (they can be stored several days in solution in DCM while they are unstable in the neat form).

These monomers can be very efficiently coupled under simple DCC/DMAP activation in dry DCM. Oligomers can be deprotected and elongated in the same way without any particular problems. A step by step approach and convergent procedure were combined to assemble a variety of oligomers from dimer to dodecamer as summarized in Scheme 3.

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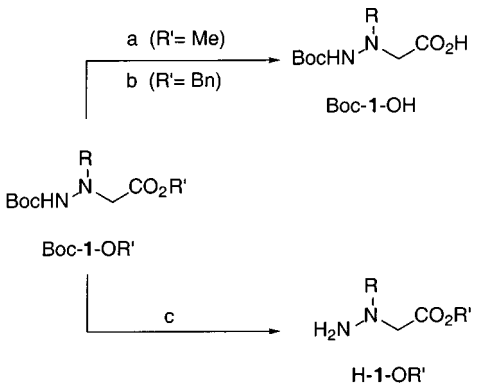
Scheme 2[a]



[a] Key: (a) NaOH, acetonitrile; (b) H_2 (1 atm), 5% Pd/C, 2-propanol; (c) TFA/DCM (1/1).

All the oligomers are oily products except the dodecamer **7**, which is an amorphous white powder. They show good solubility in most common organic solvents but are sparingly soluble in water. All the products were characterized by ^{1}H NMR; some ^{13}C NMR spectra were also recorded for the shortest members, but for the highest oligomers, in particular dodecamer **7**, the overlap of signals becomes very important. After column chromatography on silica gel, most of the compounds have reached an appreciable level of purity despite their polarity. Only compounds Boc-**2b**-OMe, H-**2b**-OMe, Boc-**3**-OH, Boc-**4**-OMe, and Boc-**5**-OMe, could not be purified over 85−90%. Some compounds were also characterized using electrospray mass spectrometry.

Due to the absence of a proton in the α and α′ positions relative to the NHs, no other ^3J coupling, except those present in the side chains, could be observed in the one-dimensional ^{1}H NMR spectra. On the other hand, fruitful information can be gained by using long-range COSY experiments.[11] It appears that each NH assumes ^4J couplings with the corresponding methylenes as illustrated in Figure 1.

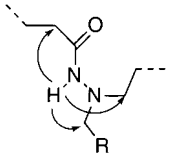


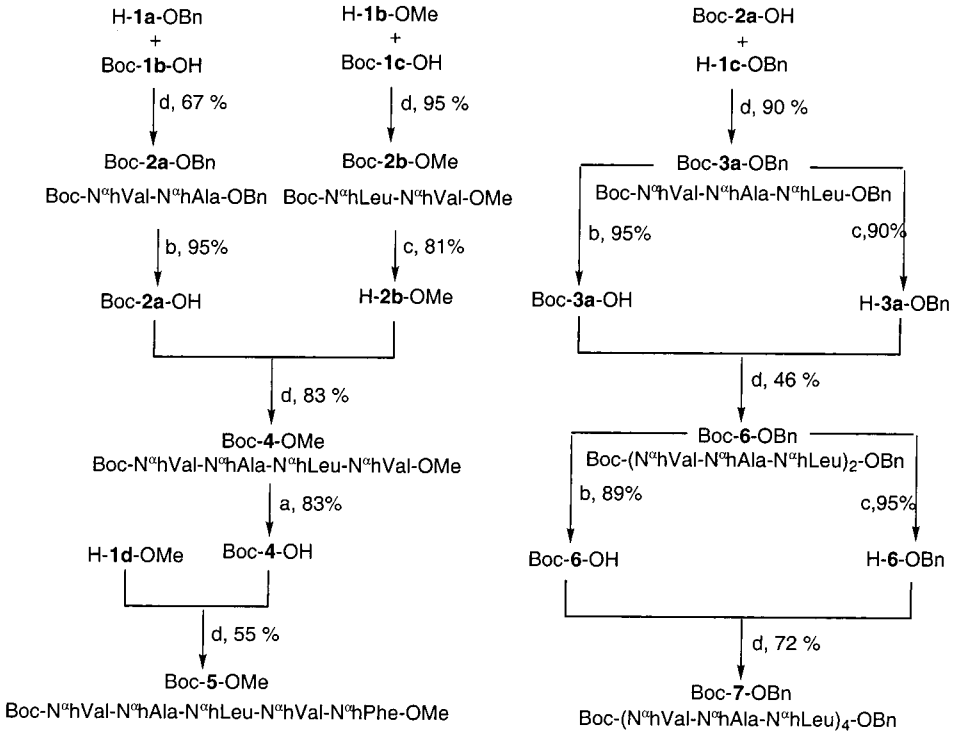
Figure 1. Schematic ^4J long-range COSY interactions involving NH protons.

By comparing this information, it becomes possible to assign all signals and to perform the full sequencing of the oligomers. A part of such spectra is shown in Figure 2. It was obtained for the tetramer Boc-**4**-OMe, and some chemical shifts are represented as illustrated below.

The title compounds are structurally related to hydrazinopeptides[12] and β^3-peptides.[13] These relationships are exemplified by comparing the structure of the corresponding building blocks with N$^\alpha$-substituted hydrazino acetic acid monomer **1,** which clearly shows the relationships (Figure 3).

Hydrazino acids **A** have the same backbone as monomers **1**. The difference relies on the position of the side chain, which has been formally shifted to the adjacent nitrogen. N$^\alpha$-Substituted hydrazino acetic acids can also be regarded as aza analogues of β^3-amino acids **B** (β^3-Haa). Therefore, a full satisfying nomenclature is not easy to adopt. The name N$^\alpha$-substituted hydrazinopeptides is ambiguous, as it does not clearly appear that the backbone is exclusively built up from hydrazino acetic acid units. N$^\alpha$-Substituted hydrazino acetic acid oligomers, although explicit, is quite a long name. Thus, even if it eclipses the relationship with hydrazino acids, aza-β^3-peptides seems the most attractive as a simple terminology relative to β^3-peptides.

Scheme 3[a]



[a] Key: (a) NaOH, acetonitrile; (b) H_2 (1 atm), 5% Pd/C, 2-propanol; (c) TFA/DCM (1/1); (d) DCC/DMAP, DCM.

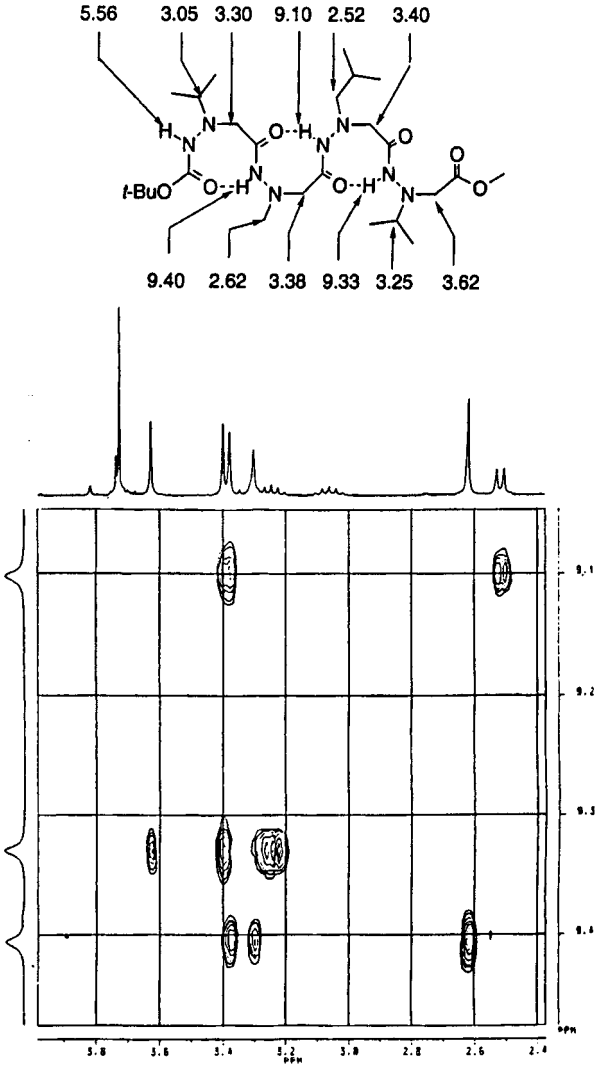


Figure 2. ^{1}H long-range COSY NMR spectrum of Boc-**4**-OMe.

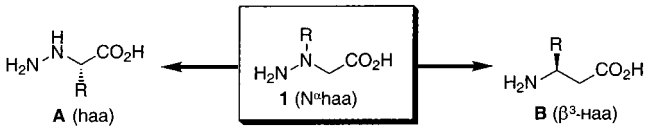
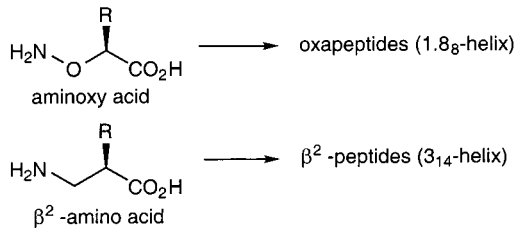


Figure 3. Structural comparisons between N$^\alpha$-substituted hydrazino acetic acid monomer **1** and related compounds.

Due to the rapid improvement of the synthesis of oligomeric pseudopeptides, it has become possible to investigate their ability to adopt defined secondary structure (a characteristic property of biopolymers). Some fascinating findings and perspectives have followed.[14]

Seebach[15] and Gellman have published important work on β-peptides.[16] Seebach worked on β^2-peptides and β^3-peptides and demonstrated that they could adopt specific helical secondary structure in organic solvents.

Scheme 4



As illustrated on Scheme 4, aminoxy acids are isosteric with β^2-amino acids. Recent studies on oxapeptides[17] revealed that they could also adopt helical secondary structure. Nevertheless, the characteristics of the latter differ from those of β^2-peptides (helix 1.8_8 versus helix 3_{14}) due to a preference for nearest neighbor interaction.

Some questions were then raised: as N$^\alpha$-substituted amino acetic acids are isosteric with β^3-amino acids, do aza-β^3-peptides behave as β^3-peptides or oxapeptides? Can they adopt secondary structure despite their lack of defined chirality?

An interesting starting point is the comparison of some NMR characteristics ($CDCl_3$) between monomers and oligomers. For this purpose, we prepared two new hydrazinoacetic esters Ac-**1b**-OMe and Ac-**1d**-OMe (Boc group is replaced by an acetyl) in order to have a reference with respect to hydrazidic bonds in the oligomers. In contrast to Boc-protected monomers, the corresponding acetyl compounds show two clearly distinct sets of resonances (relative intensities 60/40) in NMR spectra. This can be reasonably interpreted as reflecting the coexistence of both cis and trans conformations for the acethydrazide bond. This conformational equilibrium does not appear in the case of oligomers (except for the ester form of the dimer), although they contain several of these. Compounds seem constrained in a single state (Scheme 5).

The chemical shift of a carbazic NH in a monomer is around 5.6 ppm, whereas the hydrazidic one is around 7.3 ppm. The corresponding values in an oligomer show that the former is almost unaffected (average variation of 0.2 ppm) while the latter undergoes a drastic shifting to lower fields ranging from 2 to 2.7 ppm. This is a strong indication that they are engaged in hydrogen bond interaction. No significant differences were observed

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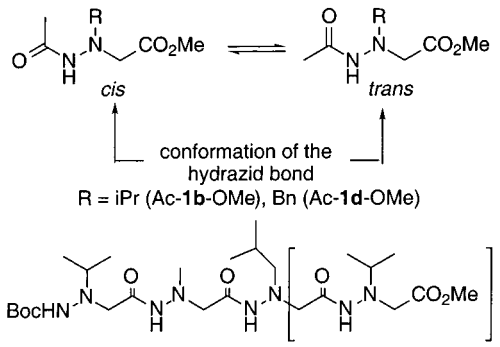
Scheme 5



between the spectra that were obtained for different concentrations (from 10^{-1} to 10^{-3} M) of oligomers, which indicate that the molecules exhibit no tendency toward aggregation.

Nearest neighbor hydrogen bond interactions can only explain the "high" chemical shift of *all the hydrazidic NH* of an oligomer. Two cases have to be considered; one relying on repetitive six-membered hydrogen-bonded pseudocycles, the other one on eight-membered rings in an opposite direction (Figure 4a,b).

In the first hypothesis, it must be assumed that the carbazic NH does not participate to the structuration as its chemical shift is the same in the monomer as well as in the oligomer as previously mentioned (this was confirmed by the addition of small amounts of DMSO, which displaces the carbazic NH to around 8.2 ppm while the hydrazidic NHs remain unaffected). In the second hypothesis, this is more easily explained as the carbazic NH has no bonding partner. Moreover, since the deprotection of the C-terminus induces only small variations of NH chemical shifts (around 0.2 ppm increment), the N-terminus deprotection leads to an upfield shielding of one hydrazidic NH to 8 ppm (Figure 4c). This can be best rationalized once more with the second model, as the N-terminal hydrazidic NH has simply no more carbonyl partner.

Recently, we grew racemic crystals from small model compounds that incorporate one hydrazino acetic unit. We observed that they are structured by the formation of a bifidic intramolecular eight-membered hydrogen-bonded interaction very similar to "hydrazinoturn" and "N−O" turn already described. The N^{β}-Boc-N^{α}-benzylhydrazinoacetic monomer Boc-**1d**-OH also shows an interaction involving the acidic proton and the carbonyl of the carbazate as illustrated in Figure 5. The O4−H1 distance (2.15 Å) is typical of a strong hydrogen bond, and the N1−H1 distance (2.17 Å) unambiguously indicates the participation of this atom to further stabilization.

All the available data demonstrate the ability of aza-β^3-peptides to fold in $CDCl_3$ solution. Our favorite hypothesis for the moment is the existence of a hydrogen bond network relying on the formation of successive eight-membered pseudocycles. In this model, the driving force seems to be the reinforcement of the structure by participation of the lone pair of electron of each N^{α} atom. In the proposed model, all the hydrazidic bonds have the trans conformation as illustrated in Figure 6.

Conclusion

Using standard protective groups and a very simple coupling procedure, N^{α}-hydrazino acetic derivative can be assembled into a new class of pseudopeptidic compounds. The procedure should be reasonably implemented on solid support. The resulting aza-β^3-peptides attract attention by the presence of pyramidal nitrogen atoms, which are as much chiral centers with free configuration. Despite the resulting degenerated chirality, aza-β^3-peptides show NMR characteristics that

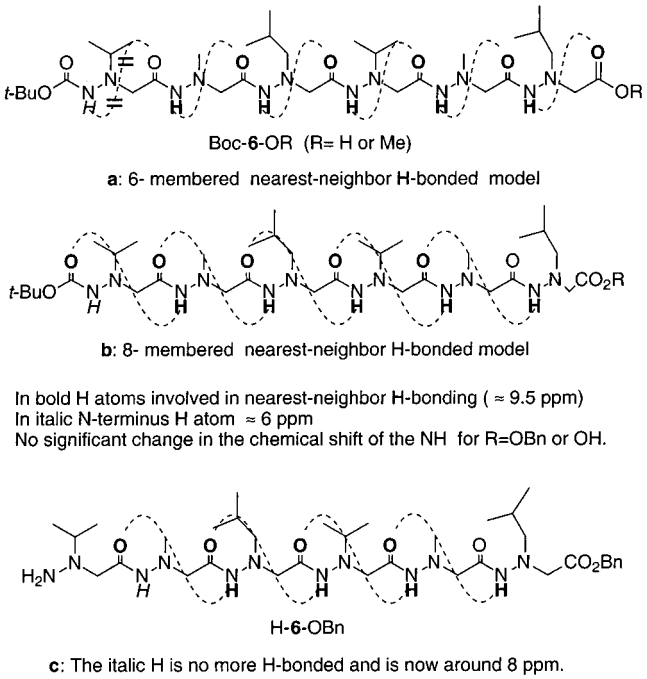


Figure 4. Nearest-neighbor hydrogen-bonding models for hexamers **6**.

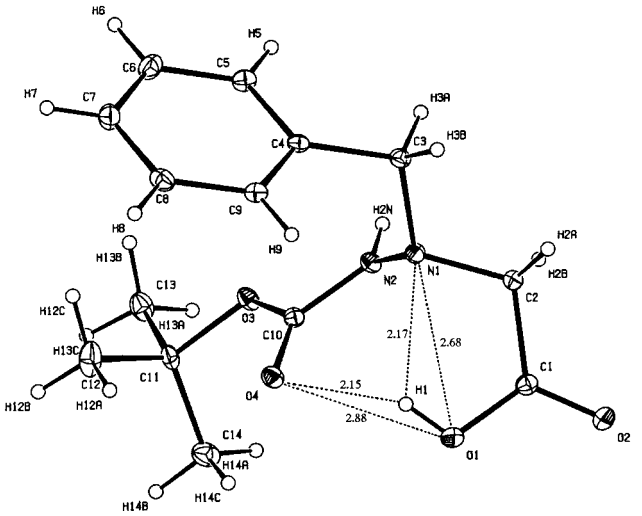


Figure 5. X-ray crystal structure of Boc-**1d**-OH. Distances are given in angstroms.

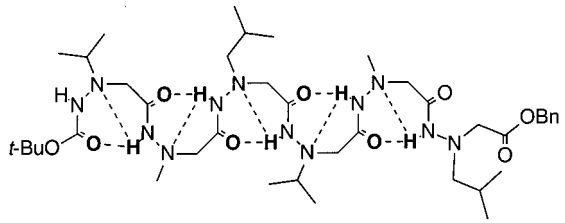


Figure 6. Schematic two-dimensional representation of possible H-bond network for hexamer **6**.

strongly suggest their ability to self-organize through intramolecular hydrogen bond network in solution. Confirmation of these preliminary results is in progress. These easily and inexpensively obtainable oligomers could be useful as "foldamer" models. Questions in connection with the relative configuration of nitrogen centers are particularly intriguing. It is interesting to point out that the formation of a hydrogen bond network is likely to reduce the distance between successive side chains. Such kinds of molecular contraction could balance the elongated backbone of aza-β^3-peptides, making them attractive surrogates with respect to their parent peptides. From this point of view, some interesting questions still need to be answered concerning their biochemical stability in comparison with the excellent resistance of the closely related β^3-peptides to peptidolysis.

Experimental Section

NMR spectra were run at 200, 300 (^{1}H), or 75.5 MHz (^{13}C). HR-MS were obtained from the Centre Régional de Mesures Physiques de l'Ouest, using MS/MS mass spectrometer ZAB Spec TOF. Infrared spectra were recorded on an FT-IR spectrometer as suspensions in KBr. Elemental analyses were performed by the analytical laboratory, CNRS (Lyon). X-ray structure was performed from the Centre de Cristallographie de Rennes.

The following were prepared according to literature procedures: substituted hydrazines,[18] H-N$^\alpha$hAla-OBn, H-**1a**-OBn.[19]

General Procedure for the Preparation of N$^\alpha$-Substituted *N*$^\beta$-Boc-hydrazinoglycine Ester 1. Boc-*N*$^\alpha$-Val-OMe (Boc-1b-OMe). To a solution of *N*$^\alpha$-isopropyl-*N*$^\beta$-Boc-hydrazine (5.76 g, 33.10 mmol) and methyl 2-bromoacetate (13 g, 85 mmol) in toluene (30 mL) was added dry K_2CO_3 (4.56 g, 33.10 mmol). The mixture was refluxed under stirring for 12 h. After filtration, the organic layer was concentrated in vacuo. The excess of methyl 2-bromoacetate was conveniently eliminated by coevaporation with fresh toluene. The residue was purified by chromatography on silica gel (ether/petroleum ether) (3/1) to give (4.97 g, 61%) of Boc-**1b**-OMe as an oil: IR (KBr) 3695−3140, 1740, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (d, J = 6.3 Hz, 6H), 1.63 (s, 9H), 3.42 (m, 1H), 3.91 (s, 3H), 3.94 (s, 2H), 6.72 (s br, 1H); ^{13}C NMR ($CDCl_3$) δ 20.4 (q, J = 126.3 Hz), 28.3 (q, J = 126.7 Hz), 51.6 (q, J = 147.5 Hz), 54.6 (t, J = 136.7 Hz), 54.7 (d, J = 133.7 Hz), 79.7 (s), 155.3 (s), 171.7 (s); HR-MS m/z for $C_{11}H_{22}N_2O_4$ calcd 246.15796 (M), obsd 246.15838.

Boc-*N*$^\alpha$-Phe-OMe (Boc-1d-OMe). The reaction was carried out according to the general procedure using *N*$^\alpha$-benzyl-*N*$^\beta$-Boc-hydrazine (1.73 g, 7.8 mmol), methyl 2-bromoacetate (3 g, 19.5 mmol), and K_2CO_3 (1.1 g, 7.8 mmol). The residue was purified by chromatography on silica gel (ethyl acetate/hexanes) (1/9) to give Boc-**1d**-OMe (2.15 g, 94%) as an oil: IR (KBr) 3370, 2946, 1752, 1719 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 9H), 3.60 (s, 2H), 3.66 (s, 3H), 4.04 (s, 2H), 6.57 (br s, 1H), 7.16−7.37 (m, 5H).

Boc-N$^\alpha$-Leu-OBn (Boc-1c-OBn). The reaction was carried out according to the general procedure using *N*$^\alpha$-isobutyl-*N*$^\beta$-Boc-hydrazine (4.50 g, 23.94 mmol), benzyl 2-bromoacetate (14.14 g, 61.48 mmol), and K_2CO_3 (3.29 g, 23.94 mmol). The residue was purified by chromatography on silica gel (ethyl acetate/hexanes) (1/9) to give Boc-**1c**-OBn (5.25 g, 66%) as an oil: IR (KBr) 3440−3220, 3080−3020, 1725, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (d, J = 6.25 Hz, 6H), 1.46 (s, 9H), 1.73 (m, 1H), 2.67 (d, J = 7.25 Hz, 2H), 3.75 (s, 2H), 5.17 (s, 2H), 6.56 (br s, 1H), 7.37 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 20.6 (q, J = 125.1 Hz), 26.6 (d, J = 122.1 Hz), 28.3 (q, J = 126.5 Hz), 56.0 (t, J = 137.9 Hz), 64.9 (t, J = 132.5 Hz), 66.4 (t, J = 147.8 Hz), 79.8 (s), 128.4 (d, J = 157.5 Hz), 128.5 (d, J = 155.7 Hz), 128.7 (d, J = 159.8 Hz), 135.4 (s), 154.9 (s), 170.9 (s); HR-MS m/z for $C_{11}H_{22}N_2O_4$ calcd 336.2049 (M$^+$), obsd 336.2047.

Boc-*N*$^\alpha$-Leu-OMe (Boc-1c-OMe). The reaction was carried out according to the general procedure using *N*$^\alpha$-isobutyl-*N*$^\beta$-Boc-hydrazine (7 g, 37.23 mmol), methyl 2-bromoacetate (15 g, 98 mmol), and K_2CO_3 (5.4 g, 39 mmol). The residue was purified by chromatography on silica gel (ethyl acetate/hexanes) (1/9) to give (Boc-**1c**-OMe) (9.58 g, 99%) as an oil: ^{1}H NMR ($CDCl_3$) δ 0.87 (d, J = 6.6 Hz, 6H), 1.37 (s, 9H), 1.63 (m, 1H), 2.57 (d, J = 7.3 Hz, 2H), 3.62 (s, 2H), 3.65 (s, 3H), 6.48 (br s, 1H).

General Procedure for Saponification. Boc-*N*$^\alpha$-Val-OH (Boc-1b-OH). To a solution of *N*$^\alpha$-isopropyl-*N*$^\beta$-Boc-hydrazinoglycine methyl ester Boc-**1b**-OMe (2.93 g, 11.91 mmol) in acetonitrile (30 mL) was added NaOH 2 N (6 mL). The mixture was stirred for 1 h 30 min at room temperature. After evaporation of acetonitrile, the residue was diluted with 30 mL of water, washed twice with ether (2 × 30 mL), acidified by addition of HCl 2 N, and extracted with CH_2Cl_2 (2 × 50 mL), and the combined extracts were dried over Na_2SO_4. Filtration and evaporation of the solvent afforded 1.80 g of Boc-**1b**-OH (65%) as a viscous oil that crystallized by addition of ether: mp 73−75 °C; IR (KBr) 3500−2500, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.03 (d, J = 6.5 Hz, 6H), 1.39 (s, 9H), 3.09 (m, 1H), 3.47 (s, 2H), 6.29 (br s, 1H), 8.97 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.8 (q, J = 126 Hz), 28.6 (q, J = 127 Hz), 56.9 (d, J = 138 Hz), 57.7 (t, J = 137 Hz), 65.2 (t, J = 132 Hz), 82.1 (s), 157.8 (s), 172.6 (s); HR-MS m/z for $C_{11}H_{22}N_2O_4$ calcd 232.1423 (M$^+$), obsd 232.1434.

Boc-*N*$^\alpha$-Leu-OH (Boc-1c-OH). The reaction was carried out according to the general procedure using *N*$^\alpha$-isobutyl-*N*$^\beta$-Boc-hydrazinoglycine methyl ester Boc-**1c**-OMe (4 g, 15.38 mmol) to afford Boc-**1c**-OH (2.97 g, 79%) as a viscous oil: IR (KBr) 3457−3189, 1738, 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (d, J = 6.8 Hz, 6H), 1.46 (s, 9H), 1.70 (m, 1H), 2.64 (d, J = 7.1 Hz, 2H), 3.57 (s, 2H), 5.97 (br s, 1H), 9.35 (br s, 1H).

Boc-*N*$^\alpha$-Phe-OH (Boc-1d-OH). The reaction was carried out according to the general procedure using *N*$^\alpha$-benzyl-*N*$^\beta$-Boc-hydrazinoglycine methylester Boc-**1d**-OMe (6 g, 20.41 mmol) to afford Boc-**1d**-OH (5.48 g, 96%) as white crystals: mp 125 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9H), 3.64 (s, 2H), 4.08 (s, 2H), 5.98 (br s, 1H), 7.39 (s, 5H), 7.65 (br s, 1H). X-ray crystal data of Boc-**1d**-OH: $C_{14}H_{20}N_2O_4$, M = 280.32 g·mol^{-1}crystallizes in space group $P2_1/c$ with lattice parameters a = 16.5786(3) Å, b = 9.3781(2) Å, c = 20.6580(4) Å, β = 112.4555(8)°, V = 2968.29 Å^3 , Z = 8, D_c = 1.255 g·cm^{-3}. From a crystal with dimensions 0.47 × 0.19 × 0.055 mm^3 7482 unique reflections were collected at T = 95(1) K over a 2θ range (2−55.8°) with a Nonius KappaCCD diffractometer equipped with a graphite-monochromatized Mo Kα (λ = 0.710 t73 Å) radiation. The crystal structure was solved by direct method using SIR97 program. All hydrogen atoms were included at calculated positions excepted for H2N located by difference Fourier syntheses and full-matrix least-squares refinement using 4804 reflections with $I > 2\sigma(I)$ were performed with SHELXL97 and converged to final agreement factors R = 0.0489 (R = 0.0908 for all reflections), GOF = 1.038.

Boc-*N*$^\alpha$-Val-*N*$^\alpha$-Ala-*N*$^\alpha$-Leu-*N*$^\alpha$-Val-OH (Boc-4-OH). The reaction was carried out according to the general procedure using Boc-**4**-OMe (0.5 g, 0.87 mmol) to give Boc-**4**-OH (0.31 g, 64%) as a viscous oil: IR (KBr) 3457−3189, 1738, 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (d, J = 6.5 Hz, 6H), 0.98 (d, J = 6.4 Hz, 6H), 1.05 (d, J = 6.5 Hz, 6H), 1.38 (s, 9H), 1.39 (m, 1H), 2.50 (d, J = 7.1 Hz, 2H), 2.58 (s, 3H), 3.07 (m, 2H), 3.23 (s, 2H), 3.34 (s, 2H), 3.41 (s, 2H), 3.44 (s, 2H), 5.90 (br s, 1H), 6.20 (br s, 1H), 9.29 (br s, 1H), 9.48 (br s, 1H), 9.90 (br s, 1H).

General Procedure for Boc Deprotection. H-*N*$^\alpha$-Leu-OBn (H-1c-OBn). A solution of Boc-**1c**-OBn (2.08 g, 6.19 mmol) in CH_2Cl_2 (10 mL) and TFA (10 mL) was stirred for 2 h at room temperature. After evaporation of the solvent, the residue was diluted with water (20 mL) and washed with ether (2 × 25 mL). The aqueous phase was treated with $NaHCO_3$ 1 N until pH 7−8 and extracted by CH_2Cl_2 (3 × 30 mL). The organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo to afford H-**1c**-OBn (1.14 g, 78%) as an oil: IR (KBr) 3340, 3080−3020, 1750−1700, 1580 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 6.6 Hz, 6H), 1.78 (m, 1H), 2.49 (d, J = 7.4 Hz, 2H), 3.29 (br s, 2H), 3.52 (s, 2H), 5.14 (s, 2H), 7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.6 (q, J = 125.1 Hz), 26.4 (d, J = 125.7 Hz), 61.1 (t, J = 136.4 Hz), 66.2 (t, J = 149.5 Hz), 68.3 (t, J = 131.2 Hz), 128.3 (d, J = 158.7 Hz), 128.4 (d, J = 163 Hz), 128.6 (d, J = 161.1 Hz), 135.7 (s), 170.7 (s).

(18) Cheguillaume, A.; Lehardy, F.; Bouget, K.; Baudy-Floc'h, M.; Le Grel, P. *J. Org. Chem* **1999**, *64*, 2924−2927.

(19) Masters, J. J.; Hegedus, L. S. *J. Org. Chem*. **1993**, *58*, 4547−4554.

H-*N*$^{\alpha}$-Val-OMe (H-1b-OMe). The reaction was carried out according to the general procedure using Boc-**1b**-OMe (5 g, 20.33 mmol) to give H-**1b**-OMe (2.01 g, 68%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.07 (d, J = 6.5 Hz, 6H), 2.97 (m, 1H), 3.25 (br s, 2H), 3.71 (s, 2H), 3.72 (s, 3H).

H-*N*$^{\alpha}$-Phe-OMe (H-1d-OMe). The reaction was carried out according to the general procedure using Boc-*N*$^{\alpha}$-Phe-OMe Boc-**1d**-OMe (5 g, 17.01 mmol) to give H-**1d**-OMe (2.5 g, 76%) as an oil: ^{1}H NMR ($CDCl_3$) δ 3.39 (br s, 2H), 3.56 (s, 2H), 3.74 (s, 3H), 3.97 (s, 2H), 7.35 (m, 5H).

H-*N*$^{\alpha}$-Leu-*N*$^{\alpha}$-Val-OMe (H-2b-OMe). The reaction was carried out according to the general procedure using Boc-**2b**-OMe (2.5 g, 6.68 mmol) to give H-**2b**-OMe (1.51 g, 83%) as an oil: ^{1}H NMR ($CDCl_3$) δ 0.85 (d, J = 6.6 Hz, 6H), 1.02 (d, J = 6.4 Hz, 6H), 1.72 (m, 1H), 2.25 (d, J = 7.4 Hz, 2H), 2.30 (br s, 2H), 3.10 (s, 2H), 3.21 (m, 1H), 3.62 (s, 3H), 3.69 (s, 2H), 8.57 (br s, 1H).

H-*N*$^{\alpha}$-Val-*N*$^{\alpha}$-Ala-*N*$^{\alpha}$-Leu-OBn (H-3-OBn). The reaction was carried out according to the general procedure using Boc-**3**-OBn (0.94 g, 1.75 mmol) to give H-**3**-OBn (0.68 g, 90%) as an oil: ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J = 6.1 Hz, 6H), 1.01 (d, J = 6.4 Hz, 6H), 1.63 (m, 1H), 2.72 (m, 6H), 3.10 (s, 2H), 3.41 (s, 2H), 3.72 (s, 2H), 5.19 (s, 2H), 7.36 (s, 5H), 8.19 (br s, 1H), 8.80 (s, 1H).

H-(*N*$^{\alpha}$-Val-*N*$^{\alpha}$-Ala-*N*$^{\alpha}$-Leu)$_2$-OBn (H-6-OBn). The reaction was carried out according to the general procedure using Boc-**6**-OBn (190 mg, 0.22 mmol) to give H-**6**-OBn (160 mg, 95%) as an oil: ^{1}H NMR ($CDCl_3$) δ 0.87 (m, 12H), 1.00 (m, 12H), 1.51 (m, 2H), 2.51 (m, 5H), 2.64 (m, 5H), 2.76 (m, 1H), 2.99 (m, 1H), 3.05 (s, 2H), 3.28 (s, 2H), 3.31 (s, 2H), 3.37 (br s, 4H), 3.65 (s, 2H), 5.12 (s, 2H), 7.31 (s, 5H), 8.15 (br s, 1H), 9.09 (s, 1H), 9.24 (s, 1H), 9.40 (s br, 1H), 9.52 (s, 1H).

General Procedure for Acetylation. Ac-*N*$^{\alpha}$-Val-OMe (Ac-1b-OMe). To a solution of H-**1b**-OMe (1 g, 6.85 mmol) in CH_2Cl_2 (10 mL) was added NEt_3 (0.7 g, 6.9 mmol). The mixture was cooled to 0 °C, and acetyl chloride (0.55 g, 6.9 mmol) was added dropwise. The mixture was allowed to warm to room temperature and was stirred for 4 h. The solvent was removed in vacuo. The residue was dissolved in water and extracted with several portions of ether. Drying of combined extracts with Na_2SO_4, evaporation of the solvent in vacuo, and purification of the residue by silica gel chromatography (ether/petroleum ether: 50/50) gave (50%) of Ac-**1b**-OMe as a mixture of two isomers cis and trans: ^{1}H NMR ($CDCl_3$) δ (major isomer) 1.12 (m, 6H), 2.16 (s, 3H), 3.28 (m, 1H), 3.75 (s, 3H), 3.82 (s, 2H), 6.95 (br s, 1H).

Ac-*N*$^{\alpha}$-Phe-OMe (Ac-1d-OMe). The reaction was carried out according to general procedure using H-**1d**-OMe (1 g, 5.23 mmol) to give Ac-**1b**-OMe as a viscous oil: ^{1}H NMR ($CDCl_3$) δ (major isomer) 1.95 (s, 3H), 3.78 (s, 3H), 3.80 (s, 2H), 4.09 (s, 2H), 7.36 (m, 6H).

General Procedure for Hydrogenolysis. Boc-*N*$^{\alpha}$-Val-*N*$^{\alpha}$-Ala-OH (Boc-2a-OH). To a solution of Boc-**2a**-OBn (0.65 g, 1.59 mmol) in 2-propanol (15 mL) was added Pd/C 10% (60 mg per mmol, 93 mg). After 18 h of stirring under H_2 atmosphere, the solution was filtered on Celite and the solvent was evaporated to afford Boc-**2a**-OH (0.48 g, 95%) as a viscous oil: IR (KBr) 3400−3100, 1800, 1740, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.98 (d, J = 4.77 Hz, 6H), 1.35 (s, 9H), 2.67 (s, 3H), 2.99 (m, 1H), 3.34 (s, 2H), 3.49 (s, 2H), 6.18 (br s, 1H), 8.57 (br s, 1H), 9.76 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 17.9 (q, J = 125.5 Hz), 28.2 (q, J = 126.9 Hz), 45.7 (q, J = 136.4 Hz), 57.2 (t, J = 136.7 Hz), 57.8 (d, J = 137.9 Hz), 61.0 (t, J = 138.8 Hz), 81.1 (s), 156.9 (s), 170.1 (s), 171.3 (s); HR-MS m/z for $C_{13}H_{26}N_4O_5$ calcd 318.1903 (M^+), obsd 318.1901.

Boc-*N*$^{\alpha}$-Val-*N*$^{\alpha}$-Ala-*N*$^{\alpha}$-Leu-OH (Boc-3-OH). The reaction was carried out according to the general procedure for hydrogenolysis using Boc-**3**-OBn (0.71 g, 1.33 mmol) to give Boc-**3**-OH (0.56 g, 95%) as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 0.93 (d, J = 6.61 Hz, 6H), 1.03 (d, J = 6.51 Hz, 6H), 1.42 (s, 9H), 1.55 (m, 1H), 2.63 (d, J = 6.96 Hz, 2H), 2.66 (s, 3H), 3.02 (m, 1H), 3.31 (s, 2H), 3.47 (s, 2H), 3.50 (s, 2H), 5.69 (br s, 1H), 9.45 (br s, 1H), 9.58 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 17.6 (q, J = 124.5 Hz), 20.5 (q, J = 126.0 Hz), 26.4 (d, J = 131.2 Hz), 28.2 (q, J = 126.6 Hz), 46.9 (q, J = 136.6 Hz), 57.3 (d, J = 138.5 Hz), 58.0 (t, J = 134.9 Hz), 61.1 (t, J = 137.0 Hz), 61.5 (t, J = 138.9 Hz), 66.3 (t, J = 134.9 Hz), 81.4 (s), 157.0 (s), 169.4 (s), 169.4 (s), 171.7 (s).

Boc-(*N*$^{\alpha}$-Val-*N*$^{\alpha}$-Ala-*N*$^{\alpha}$-Leu)$_2$-OH (Boc-6-OH). The reaction was carried out according to the general procedure for hydrogenolysis using Boc-**6**-OBn (190 mg, 0.22 mmol) to give Boc-**6**-OH (150 mg, 89%) as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 0.93 (m, 12H), 1.07 (m, 12H), 1.45 (s, 9H), 1.46 (m, 2H), 2.52 (d, J = 6.2 Hz, 2H), 2.62 (s, 3H), 2.67 (m, 5H), 3.05 (m, 2H), 3.22 (s, 2H), 3.33 (s, 2H), 3.42 (s, 2H), 3.44 (s, 2H), 3.47 (s, 2H), 3.52 (s, 2H), 9.32 (br s, 1H), 9.53 (s, 2H), 9.60 (s, 1H), 9.79 (br s, 1H).

General Procedure for Coupling. Boc-*N*$^{\alpha}$-Val-*N*$^{\alpha}$-Ala-OBn (Boc-2a-OBn). To a solution of Boc-*N*$^{\alpha}$-Val-OH (Boc-**1b**-OH) (0.7 g, 3.02 mmol), H-*N*$^{\alpha}$-Ala-OBn (H-**1a**-OBn) (0.59 g, 3.02 mmol), and DMAP (14 mg, 0.11 mmol) in CH_2Cl_2 (50 mL) cooled at 0 °C was added DCC (0.93 g, 4.53 mmol). After 5 min, the mixture was stirred at room temperature for 12 h. The DCU was filtered on Celite, and the solvent was evaporated. The residue was purified by column chromatography on silica gel using ether and then methanol. The crude product eluted by MeOH was washed with HCl 2 N, dried over Na_2SO_4, and evaporated to afford Boc-**2a**-OBn (0.82 g, 67%) as a viscous oil: IR (KBr) 3370−3120, 1710, 1705, 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.02 (d, J = 6.5 Hz, 6H), 1.43 (s, 9H), 2.77 (s, 3H), 3.04 (m, 1H), 3.28 (s, 2H), 3.68 (s, 2H), 5.22 (s, 2H), 5.59 (br s, 1H), 7.3−7.5 (m, 5H), 9.52 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.2 (q, J = 126 Hz), 28.6 (q, J = 126.7 Hz), 44.8 (q, J = 135.1 Hz), 57.3 (d, J = 136.4 Hz), 58.6 (t, J = 136.1 Hz), 59.2 (t, J = 136.4 Hz), 66.8 (t, J = 148.2 Hz), 80.8 (s), 128.7 (d, J = 160.5 Hz); 128.9 (d, J = 158.1 Hz), 128.9 (d, J = 158.9 Hz); 136.0 (s); 156.3 (s); 168.1 (s), 169.8 (s). HR-MS FAB m/z for $C_{20}H_{32}N_4O_5$ calcd 431.2270 [M + Na]$^+$, obsd 431.2270.

Boc-*N*$^{\alpha}$-Leu-*N*$^{\alpha}$-Val-OMe (Boc-2b-OMe). The reaction was carried out according to the general procedure for coupling using Boc-*N*$^{\alpha}$-Leu-OH Boc-**1c**-OH (2.75 g, 11.18 mmol), H-*N*$^{\alpha}$-Val-OMe H-**1b**-OMe (1.63 g, 11.18 mmol), DMAP (56 mg, 0.42 mmol), DCC (3.46 g, 16.76 mmol), and CH_2Cl_2 (40 mL) to give Boc-**2b**-OMe (3.56 g, 85%) as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 0.97 (d, J = 6.6 Hz, 6H), 1.09 (d, J = 6.4 Hz, 6H), 1.42 (s, 9H), 1.67 (m, 1H), 2.52 (d, J = 7.2 Hz, 2H), 3.29 (m, 1H), 3.35 (s, 2H), 3.68 (s, 2H), 3.71 (s, 3H), 5.58 (s br, 1H), 9.16 (s br, 1H); ^{13}C NMR ($CDCl_3$) δ 20.1 (q, J = 123.6 Hz), 20.9 (q, J = 124.7 Hz), 26.8 (d, J = 126.3 Hz), 28.6 (q, J = 126.5 Hz), 52.1 (q, J = 147.3 Hz), 55.2 (t, J = 138.6 Hz), 55.4 (d, J = 138.3 Hz), 62.2 (t, J = 136.2 Hz), 68.3 (t, J = 132.8 Hz), 80.7 (s), 155.85 (s), 168.5 (s), 171.1 (s); HR-MS FAB m/z for $C_{17}H_{34}N_4O_5$ calcd 397.2427 [M + Na]$^+$, obsd 397.2428.

Boc-*N*$^{\alpha}$-Val-*N*$^{\alpha}$-Ala-*N*$^{\alpha}$-Leu-OBn (Boc-3-OBn). The reaction was carried out according to the general procedure for coupling using Boc-*N*$^{\alpha}$-Val-*N*$^{\alpha}$-Ala-OH Boc-**2a**-OH (1.37 g, 4.31 mmol), H-*N*$^{\alpha}$-Leu-OBn H-**1c**-OBn (1 g, 4.3 mmol), DMAP (20 mg, 0.14 mmol), DCC (1.34 g, 6.46 mmol), and CH_2Cl_2 (85 mL) to give Boc-**3**-OBn (2.10 g, 93%) as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 6.63 Hz, 6H), 1.02 (d, J = 6.49 Hz, 6H), 1.42 (s, 9H), 1.57 (m, 1H), 2.60 (s, 3H), 2.69 (d, J = 7.01 Hz, 2H), 3.00 (m, 1H), 3.26 (s, 2H), 3.38 (s, 2H), 3.69 (s, 2H), 5.18 (s, 2H), 5.55 (br s, 1H), 7.3−7.37 (m, 5H); 9.15 (br s, 1H); 9.34 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 17.7 (q, J = 123.3 Hz), 20.7 (q, J = 124.9 Hz), 26.45 (d, J = 131.2 Hz), 28.3 (q, J = 126.9 Hz), 46.7 (q, J = 136.5 Hz), 57.2 (d, J = 137.9 Hz), 58.2 (t, J = 134.9 Hz), 58.4 (t, J = 138.5 Hz), 62.4 (t, J = 140.4 Hz), 64.3 (t, J = 147.7 Hz, CH_2), 66.3 (t, J = 148.3 Hz), 81.1 (s), 128.3 (d), 128.4 (d), 128.5 (d), 135.8 (s), 156.6 (s), 167.1 (s), 168.3 (s), 169.9 (s); HR-MS FAB m/z for $C_{26}H_{44}N_6O_6$ calcd 559.3220 [M + Na]$^+$, obsd 559.3223.

Boc-*N*$^{\alpha}$-Val-*N*$^{\alpha}$-Ala-*N*$^{\alpha}$-Leu-*N*$^{\alpha}$-Val-OMe (Boc-4-OMe). The reaction was carried out according to the general procedure for coupling using Boc-*N*$^{\alpha}$-Val-*N*$^{\alpha}$-Ala-OH Boc-**2a**-OH (1.07 g, 3.37 mmol), H-*N*$^{\alpha}$-Leu-*N*$^{\alpha}$-Val-OMe H-**2b**-OMe (0.93 g, 3.39 mmol), DMAP (16 mg, 0.13 mmol), DCC (1.05 g, 5.09 mmol), and CH_2Cl_2 (50 mL) to give Boc-**4**-OMe (1.60 g, 83%) as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 0.96 (d, J = 6.5 Hz, 6H), 1.03 (d, J = 6.5 Hz, 6H), 1.07 (d, J = 6.4 Hz, 6H), 1.44 (s, 9H), 1.49 (m, 1H), 2.53 (d, J = 7.1 Hz, 2H), 2.63 (s, 3H), 3.08 (m, 1H), 3.28 (m, 1H), 3.31 (s, 2H), 3.39 (s, 2H), 3.41 (s, 2H), 3.64 (s, 2H), 3.74 (s, 3H), 5.72 (s br, 1H), 9.06 (s br, 1H), 9.29 (s br, 1H), 9.38 (s br, 1H); ^{13}C NMR ($CDCl_3$) δ 17.8 (q, J = 126.1 Hz), 19.7 (q, J = 128.1 Hz), 20.9 (q, J = 134.6 Hz), 26.7 (d, J = 121.5 Hz), 28.6 (q, J = 126.9 Hz), 47.1 (q, J = 136.6 Hz); 52.1 (q, J = 147.2 Hz), 55.3 (d, J = 137.8 Hz), 55.6 (t, J = 137.0 Hz), 57.5 (d, J = 124.8 Hz), 58.9 (t, J = 135.3 Hz), 62.2 (t, J = 134.7 Hz), 62.5 (t, J = 135.1 Hz), 67.4 (t, J = 133.1 Hz), 81.5 (s), 157.1 (s), 168.0 (s), 168.4 (s), 169.5 (s);

171.0 (s); HR-MS FAB *m*/*z* for $C_{25}H_{50}N_8O_7$ calcd 597.3700 $[M + Na]^+$, obsd 597.3705.

Boc-*N*$^\alpha$-Val-*N*$^\alpha$-Ala-*N*$^\alpha$-Leu-*N*$^\alpha$-Val-*N*$^\alpha$-Phe-OMe (Boc-5-OMe). The reaction was carried out according to the general procedure for coupling using Boc-*N*$^\alpha$-Val-*N*$^\alpha$-Ala-*N*$^\alpha$-Leu-*N*$^\alpha$-Val-OH Boc-**4**-OH (500 mg, 0.89 mmol), H-N$^\alpha$-Phe-OMe H-**1d**-OMe (170 mg, 0.89 mmol), DMAP (4 mg, 0.03 mmol), DCC (280 mg, 1.33 mmol), and CH_2Cl_2 (10 mL) to give Boc-**5**-OMe (0.36 g, 55%) as a viscous oil: ^{1}H NMR ($CDCl_3$) 0.93 (d, J = 6.24 Hz, 6H), 1.06 (d, J = 6.38 Hz, 6H), 1.08 (d, J = 6.38 Hz, 6H), 1.43 (s, 19H), 2.41 (d, J = 7.0 Hz, 2H), 2.63 (s, 3H), 2.95 (m, 1H), 3.36 (s, 2H), 3.38 (s, 2H), 3.48 (s, 2H), 3.64 (s, 2H), 3.74 (s, 2H), 4.13 (s, 2H), 5.88 (br s, 1H), 7.31 (m, 5H), 9.10 (br s, 1H), 9.42 (br s, 1H), 9.46 (br s, 1H), 9.66 (br s, 1H).

Boc-(*N*$^\alpha$-Val-*N*$^\alpha$-Ala-*N*$^\alpha$-Leu)$_2$-OBn (Boc-6-Bn). The reaction was carried out according to the general procedure for coupling using Boc-*N*$^\alpha$-Val-*N*$^\alpha$-Ala-*N*$^\alpha$-Leu-OH Boc-**3**-OH (420 mg, 0.94 mmol), H-*N*$^\alpha$-Val-*N*$^\alpha$-Ala-*N*$^\alpha$-Leu-OBn **3c** (490 mg, 0.94 mmol), DMAP (4 mg, 0.03 mmol), DCC (290 mg, 1.41 mmol), and CH_2Cl_2 (25 mL) to give Boc-**6**-OBn (0.37 g, 46%) as a viscous oil: ^{1}H NMR ($CDCl_3$) 0.90 (d, J = 6.45 Hz, 6H), 0.92 (d, J = 6.45 Hz, 6H), 1.04 (d, J = 6.38 Hz, 6H), 1.05 (d, J = 6.38 Hz, 6H), 1.44 (s, 9H), 1.52 (m, 2H), 2.45 (d, J = 7.0 Hz, 2H), 2.56 (s, 3H), 2.66 (s, 3H), 2.68 (d, 2H, J = 7.0 Hz, CH_2), 2.95 (m, 2H), 3.26 (s, 2H), 3.31 (s, 2H), 3.37 (s, 2H), 3.41(br s, 4H), 3.70 (s, 2H), 5.17 (s, 2H), 5.83 (br s, 1H), 7.36 (br s, 5H), 9.13 (br s, 1H), 9.26 (br s, 1H), 9.49 (br s, 3H); HR-MS FAB *m*/*z* for $C_{40}H_{72}N_{12}O_9$ calcd 887.5443 $[M + Na]^+$, obsd 887.5434.

Boc-(*N*$^\alpha$-Val-*N*$^\alpha$-Ala-*N*$^\alpha$-Leu)$_4$-OBn (Boc-7-OBn). The reaction was carried out according to the general procedure for coupling using Boc-(*N*$^\alpha$-Val-*N*$^\alpha$-Ala-*N*$^\alpha$-Leu)$_2$-OH Boc-**6**-OH (150 mg, 0.19 mmol), H-(*N*$^\alpha$-Val-*N*$^\alpha$-Ala-N$^\alpha$-Leu)$_2$-OBn H-**6**-OBn (150 mg, 0.19 mmol), DMAP (1 mg, 0.01 mmol), DCC (60 mg, 0.29 mmol), and CH_2Cl_2 (10 mL) to give Boc-**7**-OBn (0.21 g, 72%) as a white powder: mp 118−121 °C; HR-MS FAB *m*/*z* for $C_{68}H_{128}N_{24}O_{15}$ calcd 1543.9889 $[M + Na]^+$, obsd 1543.9835.

Supporting Information Available: Tables of X-ray structural data for Boc-**1d**-OH. Copies of ^{1}H NMR spectra for compounds Boc-**1b**-OMe, Boc-**1b**-OH, H-**1b**-OMe, Boc-**1c**-OMe, Boc-**1c**-OH, Boc-**1c**-OBn, H-**1c**-OBn, Boc-**1d**-OMe, H-**1d**-OMe, Boc-**1d**-OH, Ac-**1b**-OMe, Ac-**1d**-OMe, Boc-**2a**-OBn, Boc-**2a**-OH, Boc-**2b**-OMe, H-**2b**-OMe, Boc-**3**-OBn, Boc-**3**-OH, Boc-**4**-OMe, Boc-**4**-OH, Boc-**5**-OMe, Boc-**6**-OBn, Boc-**6**-OH, H-**6**-OBn, Boc-**7**-OBn. This material is available free of charge via the Internet at http://pubs.acs.org.

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