Building Units for N-Backbone Cyclic Peptides. 3. Synthesis of Protected N^{α}-(ω-Aminoalkyl)amino Acids and N^{α}-(ω-Carboxyalkyl)amino Acids

Dan Muller, Irena Zeltser, Gal Bitan, and Chaim Gilon*

Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem 91904, Israel

Received August 14, 1996[⊗]

An improved synthesis of a family of amino acids that contain ω-aminoalkyl groups and of a new family containing ω-carboxyalkyl groups linked to the α-amine is described. The synthesis was performed by alkylation of suitably monoprotected alkylenediamines and protected ω-amino acids with triflates of α-hydroxy acid esters. The reaction proceeded with inversion of configuration yielding optically pure products. The N^{α}-(ω-aminoalkyl)amino acids and N^{α}-(ω-carboxyalkyl)amino acids were orthogonally protected to allow their incorporation into peptides by solid-phase peptide synthesis (SPPS) methodology.

Introduction

Cyclization of linear peptides is used to restrict their conformational freedom, in order to confer metabolic stability, and to increase receptor affinity and selectivity.[1−3] Classical cyclization is normally achieved either by formation of a lactam ring through ω-amino (lysine, ornithine) and ω-carboxy (aspartic acid, glutamic acid) side chains, by formation of a disulfide bond between two ω-thio amino acids (cysteine, homocysteine), or by linking head-to-tail or side chains to terminal groups. If the linear peptide does not contain the appropriate ω-functional amino acids for cyclization, various amino acids in the native sequence are replaced by appropriate trifunctional amino acids.

Despite the impressive success achieved with cyclic peptides, these classical cyclization methods led in many cases to a strong decrease or even a loss of biological activity due to alteration of side chains and/or termini vital for the biological activity.[4,5] To overcome this problem, we have introduced the general concept of backbone cyclization, which does not necessarily alter either side chains or the carboxyl and amino termini.[5] Using backbone cyclization, ring closure is performed by linking ω-substituted alkyl chains replacing N^{α}-hydrogens in the peptidic backbone retaining the native sequence as well as the structure and chirality of the side chains and the terminal groups that are essential for biological activity.

Backbone cyclic peptides are prepared by incorporation of orthogonally protected building units, such as those shown in Figure 1, into the native peptide sequence.

The building unit is introduced into the peptide by replacement of the parent amino acid at the site of cyclization; thus, the side chains of the original amino acid is retained. We have shown that properties like

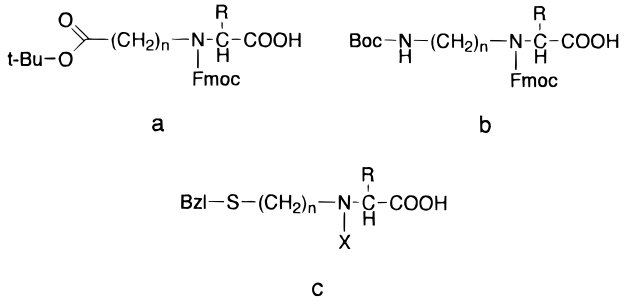

Figure 1. Building units for N-backbone cyclization: (a) ω-carboxyl, (b) ω-amine, (c) ω-thiol.

selectivity and metabolic stability could be achieved by backbone cyclization, in cases where the classical cyclization methods failed.[6,7]

We have previously presented the synthesis of some building units of the type N^{α}-(ω-aminoalkyl)amino acids (Figure 1b), which were prepared by a nucleophilic attack of monoprotected alkylene diamines on α-chloro or α-bromo carboxylic acids.[8] This method was efficient mostly for the preparation of N^{α}-(ω-aminoalkyl)glycine units. However, it has previously been shown by Effenberger et al.[9] that chloride and bromide give poor leaving groups when this reaction is tried with chiral amino acids with simple amines, giving mainly β-elimination or racemization products. This was also our observation when we tried to react α-halo carboxylic acids derived from alanine, phenylalanine, or leucine with mono-Boc-diamines.[8] Effenberger et al. have shown that the reaction is greatly improved if the leaving group is changed from a halogen to trifluoromethanesulfonate (triflate), giving high yield and high optical purity in much shorter times. In the second paper of this series, we implemented this method for the preparation of N^{α}-(ω-thio-substituted alkyl)amino

* To whom correspondence should be addressed. Phone: 972-2-6585276. Fax: 972-2-6586763. E-mail: gilon@vms.huji.ac.il.

[⊗] Abstract published in *Advance ACS Abstracts,* December 15, 1996.

(1) Hruby, V. J. *Life Sci.* **1982**, *31*, 189−199.
(2) Schiller, P. W. In *The Peptides*; Undenfriend, S., Meienhofer, J., Eds.; Academic Press: New York, 1984; Vol. 6, pp 254−268.
(3) Hruby, V. J.; Al-Obeidi, F.; Kazmierski, W. *Biochem. J.* **1990**, *268*, 249−262.
(4) Ovchinnikov, Y.; Chipens, G.; Ivanov, V. In *Peptides 1982*; Bláha, K., Malon, P., Eds.; Walter de Gruyter & Co.: Berlin, 1983; pp 1−18.
(5) Gilon, C.; Halle, D.; Chorev, M.; Selinger, Z.; Byk, G. *Biopolymeres* **1991**, *31*, 745−750.
(6) Gilon, C.; Halle, D.; Chorev, M.; Selinger, Z.; Byk, G. In *Peptides 1992*; Smith, J. A., Rivier, J., Eds.; ESCOM B. V.: Leiden, 1993; pp 476−478.
(7) Byk, G.; Zeltser, I.; Halle, D.; Bitan, G.; Selinger, Z.; Gilon, C. *J. Med. Chem.* **1996**, *39*, 3174−3178.
(8) Byk, G.; Gilon, C. *J. Org. Chem.* **1992**, *57*, 5687−5692.
(9) Effenberger, F.; Burkard, U.; Willfahrt, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 65−66.

S0022-3263(96)01580-0 CCC: $14.00

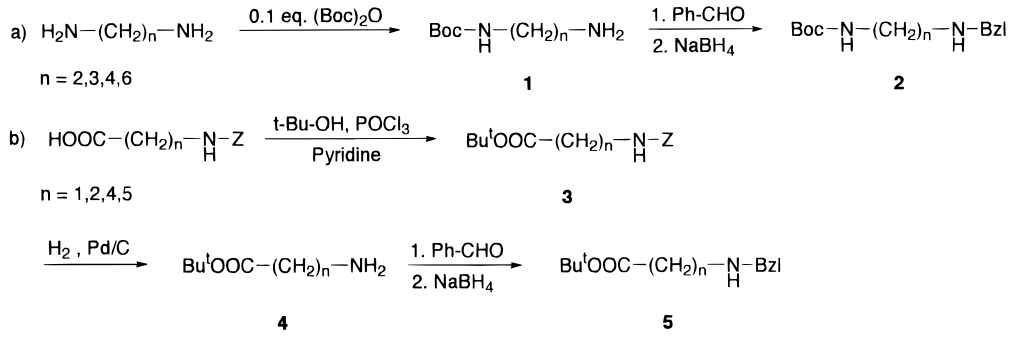

Figure 2. Synthesis of *N*-Boc-*N*′-benzylalkyldiamines and *ω*-(benzylamino) carboxylic acid *tert*-butyl esters.

acids.[10] It has been demonstrated that the α-triflates derived from leucine and phenylalanine readily reacted with suitably protected *ω*-thio-substituted alkylamines, to give the desirable building units, which were then protected and used for peptide synthesis. It was then only natural to extend the synthesis for preparation of other kinds of building units, namely, those that contain an *ω*-amino group on their *N*-alkyl chain. We also present here a new class of building units containing an *ω*-carboxyl group (Figure 1a), which were prepared by the same method.

Results and Discussion

The previously described method for the preparation of building units containing an *ω*-amino alkyl group[8] suffered from three side reactions: (i) double alkylation of the nucleophilic amine, (ii) racemization, and (iii) *β*-elimination when applied to amino acids other than Gly. The first side reaction was avoided using a large excess (ca. 10 equiv) of the nucleophilic amine. However, purification of the product was consequently cumbersome and required extensive laborious workup. In the current work it has been found that temporary protection of the nucleophilic amine with a benzyl group overcame this problem. Thus, one of the amino groups in an alkylenediamine (Figure 2a) or the *ω*-carboxy group of an *ω*-amino acid (Figure 2b) was first protected by Boc[8,11] or by *tert*-butyl ester, respectively. Then, the nucleophilic amine was monobenzylated by reductive alkylation with benzaldehyde.[12] Compound **3c** was prepared via a route different from that of the other *N*-(carbobenzoxy)-*ω*-(*tert*-butylcarboxy)alkylamines since upon treatment of 4-[(carbobenzoxy)amino]butyric acid with 2-methyl-2-propanol in the presence of $POCl_3$ the *tert*-butyl ester produced underwent spontaneous cyclization (compare methods C and D).

The other two side reactions—racemization and *β*-elimination—were suppressed by changing the leaving group in the substrate of the nucleophilic substitution reaction. Except for the case of glycine derivatives, the substrates were changed from α-halo carboxylic acids to α-hydroxy carboxylic acid ester triflates. Glycine derivatives could still be prepared using commercial bromoacetate esters as substrates. In the first case, the methyl ester of the α-hydroxy carboxylic acids were used as substrates, following our previous procedure.[10] Then the ester was hydrolyzed by base after the alkylation step. In the following cases, however, it was found handy to use benzyl esters of the α-hydroxy carboxylic acid ester triflates, since the benzyl ester could be removed concurrently with the *N*-benzyl protecting group by catalytic hydrogenation, yielding the N^{α}-[*ω*-(Boc-amino)alkyl]-amino acids **(8)** and N^{α}-[*ω*-(*t*-Bu-carboxy)alkyl]amino acids **(11)** as zwitterions (Figure 3).

Table 1. Physical Data for Compounds 7 and 10

compd	*n*	R	R′	% yield	confign	$[\alpha]^{25}_D$ (*c* = 1, MeOH)
7a	2	H	Bzl	100		
7b	3	H	Bzl	100		
7c	4	H	Bzl	100		
7d	6	H	Bzl	100		
7e	3	Me	Me	69.5	*S*	−68.9
7f	3	Me	Me	71.0	*R*	nd
7g	6	Me	Me	81.4	*S*	−67.6
7h	3	Bzl	Me	67.7	*S*	−55.8
7i	3	Bzl	Me	51.5	*R*	+58.8
10a	1	H	Bzl	100		
10b	2	H	Bzl	91.1		
10c	3	H	Bzl	76.9		
10d	4	H	Bzl	86.5		
10e	5	H	Bzl	99.1		
10f	2	Bzl	Bzl	71.5	*S*	−62.7

Table 2. Physical Data for Compounds 6

	n	R	confign	% yield	$[\alpha]^{25}_D$ (*c* = 1, MeOH)	elem anal.
6a	3	Me	*S*	100	+4.2	calcd: C, 57.98; H, 7.84; N, 7.5 fnd: C, 58.04; H, 8.24; N, 6.47
6b	3	Me	*R*	100	−5.0	calcd: C, 57.98; H, 7.84; N, 7.5 fnd: C, 58.87; H, 8.25; N, 6.76
6c	6	Me	*S*	100	≈0	nd
6d	3	Bzl	*S*	100	−24	calcd: C, 64.20; H, 7.41; N, 6.24 fnd: C, 67.89; H, 7.97; N, 6.33
6e	3	Bzl	*R*	100	+15	nd

The α-hydroxy carboxylic ester triflates **(6)** were prepared as described elsewhere.[10] They were used for alkylation of the protected *ω*-functionalized alkylamines to give N^{α}-[*ω*-(Boc-amino)alkyl]- and N^{α}-[*ω*-(*t*-Bu-carboxy)alkyl]amino acids (**7** and **10**) as optically pure, fully protected products. After removal of the benzyl protection groups from the α-amine and the α-carboxyl groups, or hydrolysis of the methyl ester, the α-amine was protected by Fmoc (9-fluorenylmethyloxycarbonyl) in order to use the building units in solid-phase peptide synthesis.

In conclusion, we show here that the reaction of α-triflates derived from amino acid esters with *ω*-functionalized amines is a generally useful method for the preparation of building units, which are further incorporated in peptides and may be used for their derivatization and cyclization. The method provides an improvement for the previous preparation of *ω*-amine type building units from α-halo carboxylic acids. It also facilitates the preparation of a new subfamily of building units, containing an *ω*-carboxylic group on the *N*-alkyl.

(10) Bitan, G.; Gilon, C. *Tetrahedron* **1995**, *51*, 10513−10522.
(11) Dowd, M. M.; Baynes, J. W.; Thorpe, S. R. *Anal. Biochem*. **1992**, *205*, 369−371.
(12) Bergeron, R. J.; Garlich, J. R.; Stolowich, N. J. *J. Org. Chem*. **1984**, *49*, 2997−3001.

Table 3. Physical Data for Compounds 8 and 11

	n	R	confign	% yield	mp (°C)	elem anal.
8a	2	H		91.3	200−202	calcd: C, 49.52; H, 8.31; N, 12.84 fnd: C, 49.82; H, 8.18; N, 12.39
8b	3	H		74.0	214−216	calcd: C, 51.71; H, 8.68; N, 12.06 fnd: C, 50.47; H, 8.46; N, 10.52
8c	4	H		89.4	176−178	calcd: C, 53.63; H, 9.00; N, 11.37 fnd: C, 53.62; H, 8.37; N, 9.82
8d	6	H		80.0	172−174	calcd: C, 53.40; H, 9.65; N, 9.58 fnd: C, 54.34; H, 9.13; N, 9.58
8e	3	Me	*S*	74.8	213−215	calcd: C, 46.72; H, 8.20; N, 9.91 fnd: C, 49.67; H, 8.55; N, 10.34
8f	3	Me	*R*	79.1	213−215	calcd: C, 46.72; H, 8.20; N, 9.91 fnd: C, 48.82; H, 8.37; N, 10.44
8g	6	Me	*S*	64.5	134−136	calcd: C, 56.22; H, 10.07; N, 8.74 fnd: C, 56.03, H, 9.07; N, 8.46
8h	3	Bzl	*S*	86.1	208−212	nd
8i	3	Bzl	*R*	75.5	208−212	calcd: C, 61.00; H, 8.53; N, 7.90 fnd: C, 60.89; H, 7.76; N, 8.31
11a	1	H		55.4	139−141	nd
11b	2	H		89.2	164−166	nd
11c	3	H		75.7	semisolid	nd
11d	4	H		89.2	138−140	nd
11e	5	H		76.3	134−136	nd
11f	2	Bzl	*S*	48.2	semisolid	nd

Table 4. Physical Data for Building Units 9 and 12

	n	R	confign	mp (°C)	% yield	$[\alpha]^{25}_D$ (*c* = 1, MeOH)	elem anal.
9a	2	H		130−132	80.0		calcd: C, 65.43; H, 6.40; N, 6.36 fnd: C, 65.18; H, 6.11; N, 5.91
9b	3	H		125−127	85.0		calcd: C, 66.06; H, 6.65; N, 6.00 fnd: C, 66.05; H, 6.65; N, 6.16
9c	4	H		150−152	79.4		calcd: C, 66.65; H, 6.88; N, 5.98 fnd: C, 66.37; H, 6.84; N, 5.77
9d	6	H		78−80	81.5		calcd: C, 67.72; H, 7.31; N, 5.64 fnd: C, 68.02; H, 7.08; N, 5.37
9e	3	Me	*S*	70−72	75.1	−11.1	calcd: C, 66.65; H, 6.88; N, 5.98 fnd: C, 66.41; H, 6.78; N, 5.63
9f	3	Me	*R*	70−72	75.9	+9.9	calcd: C, 66.65; H, 6.88; N, 5.98 fnd: C, 66.03; H, 6.60; N, 5.93
9g	6	Me	*S*	58−60	72.8	−11.7	calcd: C, 68.21; H, 7.50; N, 5.49 fnd: C, 68.37; H, 7.40; N, 5.23
9h	3	Bzl	*S*	108−112	64.8	−87.0	calcd: C, 70.57; H, 6.66; N, 5.14 fnd: C, 69.12; H, 6.54; N, 4.99
9i	3	Bzl	*R*	108−112	61.6	+79.6	calcd: C, 70.57; H, 6.66; N, 5.14 fnd: C, 70.39; H, 6.83; N, 5.06
12a	1	H		54−56	70.9		calcd: C, 67.14; H, 6.12; N, 3.40 fnd: C, 66.91; H, 6.21; N, 3.01
12b	2	H		112−114	76.9		calcd: C, 67.75; H, 6.40; N, 3.29 fnd: C, 67.38; H, 6.34; N, 3.11
12c	3	H		80−82	64.1		calcd: C, 68.32; H, 6.65; N, 3.19 fnd: C, 68.29; H, 6.83; N, 3.88
12d	4	H		62−64	70.0		calcd: C, 68.85; H, 6.89; N, 3.09 fnd: C, 68.86; H, 7.17; N, 3.18
12e	5	H		88−90	81.0		calcd: C, 69.36; H, 7.11; N, 2.99 fnd: C, 69.59; H, 7.31; N, 2.95
12f	2	Bzl	*S*	69−71	37.5	nd	calcd: C, 72.21; H, 6.45; N, 2.72 fnd: C, 71.92; H, 6.39; N, 2.87

Experimental Section

Materials and Methods. Starting materials were purchased from Merck or Aldrich and were used without further purification. Elemental analyses were carried out at the Microanalytical Department of the Hebrew University, Jerusalem. ^{1}H NMR spectra were recorded on Brucker WP-200, AMX-300, and DRX 400 spectrometers at 298 K. COSY spectra of products were routinely recorded to assist with the proton assignment of ambiguous spectra. This was necessary since all of the urethane-protected building units existed as more than one isomer in solution.

Method A: Preparation of Boc-alkylenediamines (1). Di-*tert*-butyl bicarbonate (0.05 mol) dissolved in 250 mL of chloroform was added dropwise to a solution of 0.5 mol of alkylenediamine in 500 mL of chloroform during 3 h with stirring and cooling in an ice bath. The reaction mixture was stirred for additional 16 h at room temperature and was then washed with 8 × 250 mL of water. The organic phase was dried over Na_2SO_4, evaporated to dryness *in vacuo*, and obtained as colorless oils. For purification of product **1d** column chromatography was required (chloroform:methanol 2:1).

1a (*n* = 2). Yield: quantitative. NMR ($CDCl_3$): 5.12, broad s, 1H; 3.10, q, *J* = 7.0 Hz, 2H; 2.72, t, *J* = 6.4 Hz, 2H; 1.59, s, 2H; 1.37, s, 9H.

1b (*n* = 3). Yield: quantitative. NMR ($CDCl_3$): 5.02, broad, s, 1H; 3.14, q, *J* = 6.3 Hz, 2H; 2.70, t, *J* = 6.6 Hz, 2H; 1.69, s, 2H; 1.60−1.51, m, 2H; 1.38, s, 9H.

1c (*n* = 4). Yield: quantitative. NMR ($CDCl_3$): 5.16, broad, s, 1H; 3.08, q, *J* = 6.4 Hz, 2H; 2.65, t, *J* = 6.7 Hz, 2H; 1.56−1.44, m, 4H; 1.32, s, 11H.

1d (*n* = 6). Yield: 70%. NMR ($CDCl_3$): 4.54, broad s, 1H; 3.11, q, *J* = 7.2 Hz, 2H; 2.68, t, *J* = 7.0 Hz, 2H; 1.57 s, 2H; 1.44, s, 9H; 1.36−1.33, m, 8H.

For comparison see refs 13 and 14.

(13) Hansen, J. B.; Nielsen, M. C.; Ehrbar, U.; Buchardt, O. *Synthesis* **1982**, 404−405.

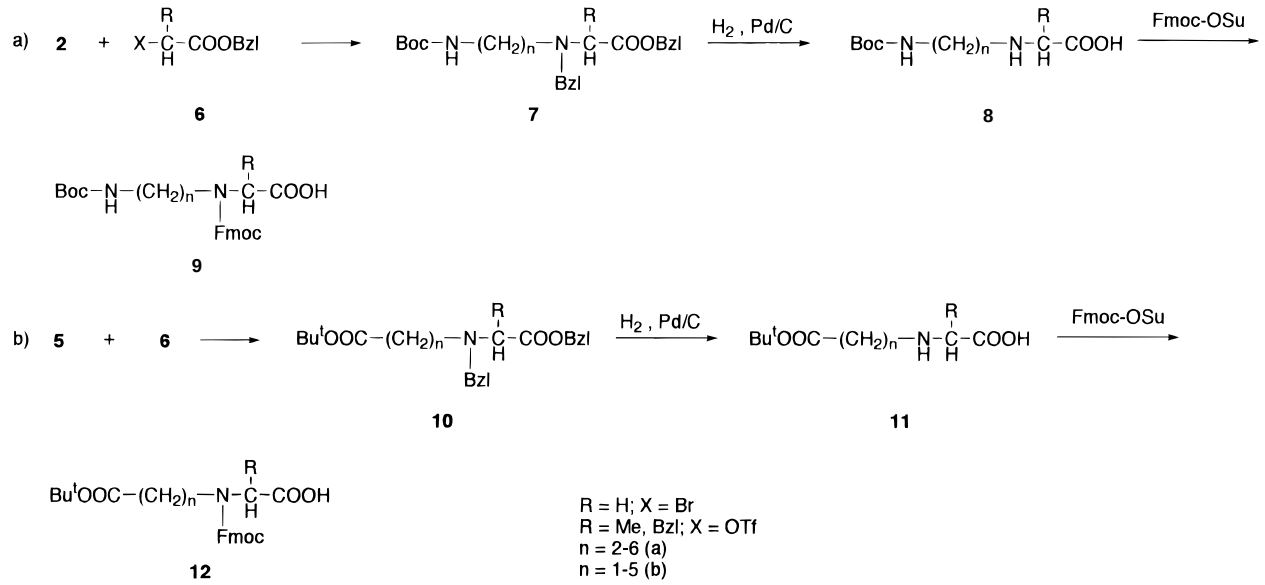

Figure 3. Synthesis and protection of building units.

Method B: Preparation of N^{α}-Benzyl-N^{ω}-Boc-alkylenediamines (2). Triethylamine (20 mmol, 2.8 mL), 75 mmol (9 g) of $MgSO_4$, and 55 mmol (5.6 mL) of freshly distilled benzaldehyde were added to a solution of 50 mmol of **1** in 60 mL of methanol. The reaction was mixture was stirred at room temperature for 1.5 h and was then cooled to −5 °C. $NaBH_4$ (0.3 mol, 11.34 g) was added in small portions during 30 min. The reaction mixture was stirred for 1 h at −5 °C and for an additional 1 h at 0 °C. The reaction was quenched by addition of 200 mL of water. The product was extracted into ethyl acetate (3 × 200 mL), and the combined ethyl acetate extracts were washed with water (4 × 100 mL). Compounds **2a**−**c** were extracted as hydrochlorides from the ethyl acetate with a solution of 0.5 N HCl (4 × 100 mL), and the aqueous solution was cooled to 0 °C and was neutralized with 25 mL of 25% NH_4OH. The products were extracted again with chloroform (3 × 100 mL), and the combined extracts were washed with water (3 × 80 mL), dried over Na_2SO_4, evaporated to dryness *in vacuo*, and obtained as colorless oils.

The ethyl acetate extracts containing compound **2d** were dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was dissolved in 400 mL of chloroform, washed with 3 × 50 mL of 0.5 N HCl and 2 × 100 mL of water, dried over Na_2SO_4, and evaporated to dryness. Two hundred mL of ether was added. The precipitated product was collected by filtration, washed with ether (3 × 50 mL), and dried *in vacuo*.

2a. Yield: 65%. NMR ($CDCl_3$): 7.31−7.12, m, 5H; 4.98, broad s, 1H; 3.71 s, 2H; 3.15, q, J = 6.0 Hz, 2H; 2.66, t, J = 6.0 Hz, 2H; 1.54, s, 1H; 1.38, s, 9H.

2b. Yield: 75%. NMR ($CDCl_3$): 7.41−7.21, m, 5H; 5.50, broad s, 1H; 3.62, s, 2H; 3.22, q, J = 7.6 Hz, 2H; 2.69, t, J = 6.0 Hz, 2H; 1.75−1.60, m, 2H; 1.43, s, 9H; 1.40, s, 1H.

2c. Yield: 63%. NMR ($CDCl_3$): 7.31−7.13, m, 5H; 4.70, broad s, 1H; 3.69, s, 2H; 3.11, q, J = 7.7 Hz, 2H; 2.65, t, J = 7.6 Hz, 2H; 1.56−1.49, m, 4H; 1.44, s, 10H.

2d. Yield: 70%. NMR ($CDCl_3$): 7.41−7.34, m, 5H; 4.53, broad s, 1H; 3.78, s, 2H; 3.09, q, J = 6.8 Hz, 2H; 2.63, t, J = 7.0 Hz, 2H; 1.68−1.27, m, 18H.

For comparison see ref 11.

Method C: Preparation of *N*-(Carbobenzoxy)-ω-(*tert*-butylcarboxy)alkylamines (3a,b,d,e). $POCl_3$ (47 mmol, 4.4 mL) was added to a solution of 23.5 mmol of ω-(*N*-carbobenzoxy)amino acids ($ZNH(CH_2)_nCOOH$), 47 mmol (3.8 mL) of pyridine, and 120 mmol (9.5 g) of 2-methyl-2-propanol in 80 mL of dry DCM (dichloromethane). The reaction mixture was stirred for 18 h at room temperature. Then, 150 mL of chloroform was added, and the mixture was washed with 3 × 100 mL of water, 3 × 100 mL of 3% $NaHCO_3$ solution, and again with 3 × 100 mL of water. The organic phase was dried over Na_2SO_4 and evaporated to dryness *in vacuo* to give the products as colorless oils.

Method D: Preparation of *N*-Carbobenzoxy-ω-(*tert*-butylcarboxy)propylamine (3c). DCC (34.5 mmol, 7.1 g) was added to a solution of 30 mmol (7.1 g) of 4-[*N*-(carbobenzoxy)amino]butyric acid, 90 mmol (6.7 g) of 2-methyl-2-propanol and 3 mmol (0.4 g) of DMAP in 60 mL of dry DCM. The reaction mixture was stirred for 18 h at room temperature, and then the dicyclohexylurea was filtrated and washed with 3 × 30 mL of DCM. The combined DCM filtrates were added to the rest of the solvent, which was then washed with 2 × 100 mL of water, 2 × 100 mL of 1 N HCl, 2 × 100 mL of water, 5 × 100 mL of 5% $NaHCO_3$ solution, and 2 × 100 mL of water. The organic phase was dried over Na_2SO_4, the solvent was evaporated *in vacuo*, and then 100 mL of ether was added and the white precipitate collected by filtration. The filtrate was evaporated to dryness *in vacuo*, and additional product was obtained as a white powder (mp 161−162 °C).

3a (n = 1). Yield: 61%. NMR ($CDCl_3$): 7.25, s, 5H; 5.23, broad s, 1H; 5.01, s, 2H; 3.78, s, 2H; 1.39, s, 9H.

3b (n = 2). Yield: 64%. NMR ($CDCl_3$): 7.22, s, 5H; 5.15, broad s, 1H; 5.04, s, 2H; 3.36, t, J = 6.5 Hz, 2H; 2.38, t, J = 7.0 Hz, 2H; 1.38, s, 9H.

3c (n = 3). Yield: 96%.

3d (n = 4). Yield: 80%. NMR ($CDCl_3$): 7.29, s, 5H; 5.04, s, 2H; 4.83, broad, s, 1H; 3.21−3.08, m, 2H; 2.19, t, J = 7.0 Hz, 2H; 1.92−1.05, m, 13H.

3e (n = 5). Yield: 66%. NMR ($CDCl_3$): 7.28−7.24, m, 5H; s, 3H; 4.72, broad s, 1H; 3.10, q, J = 5.9 Hz, 2H; 2.11, t, J = 7.3 Hz, 2H; 1.58−1.18, m, 15H.

Method E: Preparation of ω-(*tert*-Butylcarboxy)alkylamines (4). Fifteen percent w/w of 10% Pd/C was added to a solution of 20 mmol of **3** in 60 mL of methanol and 5 mL of glacial acetic acid. The reaction mixture was hydrogenated for 4 h with 60 psi H_2 at room temperature. The catalyst was filtrated and washed with 2 × 40 mL of methanol, and the combined fractions was evaporated to dryness *in vacuo*. One hundred mL of 0.5 N HCl was added to the residue, and the solution was washed with a mixture of petroluem ether:ether 1:1 (2 × 80 mL), cooled to 0 °C, and set to pH 10 with aqueus 25% ammonia. The product was then extracted with a mixture of 2-propanol:chloroform 1:3 (3 × 80 mL), and the organic phase was dried over Na_2SO_4 and evaporated *in vacuo*. The product was clean enough to be used without further purification.

Method F: Preparation of *N*-Benzyl-ω-(*tert*-butylcarboxy)alkylamine (5). These products were prepared from **4** by method B.

5a. Yield: 54%. NMR ($CDCl_3$): 7.29−7.19, m, 5H; 3.74, s, 2H; 3.25, s, 2H; 1.40, s, 9H; 1.16, s, 1H.

(14) Krapcho, A. P.; Kuell, C. S. *Synth. Commun.* **1990**, *20*, 2559−2564.

5b. Yield: 54%. NMR ($CDCl_3$): 7.28−7.17, m, 5H; 3.74, s, 2H; 2.81, t, J = 6.5 Hz, 2H; 2.41, t, J = 6.6 Hz, 2H; 1.91, s, 1H; 1.38, s, 9H.

5c. Yield: 31%. NMR ($CDCl_3$): 7.23−7.16, m, 5H; 3.72, s, 2H; 2.58, t, J = 7.4 Hz, 2H; 2.21, t, J = 7.8 Hz, 2H; 1.81−1.68, m, 3H; 1.38, s, 9H.

5d. Yield: 33%. NMR ($CDCl_3$): 7.25−7.18, m, 5H; 3.73, s, 2H; 2.60, t, J = 6.9 Hz, 2H; 2.15, t, J = 7.7 Hz, 2H; 1.91−1.50, m, 4H; 1.39, s, 9H; 1.22, s, 1H.

5e. Yield: 30%. NMR ($CDCl_3$): 7.60−7.30, m, 5H; 4.00, s, 2H; 2.81−2.65, m, 2H; 2.18, t, J = 7.0 Hz, 2H; 1.83−1.25, m, 16H.

Method G: Preparation of *(R)*-α-Hydroxy3-phenylpropionic Acid Benzyl Ester [HOCH(Bzl)COOBzl]. Cs_2CO_3 (4.9 g, 15 mmol) in 20 mL of water was added to a solution of 30 mmol (5 g) of *(R)*-α-hydroxy-3-phenylpropionic acid (prepared as described in ref 10) in 60 mL of methanol. The solvent was evaporated to dryness *in vacuo*, 20 mL of DMF was added, and the solvent was evaporated again. This was repeated twice. The dry salt was dissolved in 20 mL of DMF and cooled to 0 °C, and 30 mmol (3.6 mL) of benzyl bromide was added. After 2 h the temperature was raised to room temperature and the mixture was stirred for additional 22 h. Then the solvent was evaporated *in vacuo*, and 100 mL of water was added. The product was extracted into 3 × 100 mL of ether, and the combined ether extracts were washed with 2 × 60 mL of a solution of 10% $KHCO_3$ and 2 × 100 mL of water. The crude product was adsorbed on 50 g of silica gel, which was placed in a Buchner funnel and washed with 400 mL of petroleum ether. The product was eluted with 400 mL of a mixture of petroleum ether:ethyl acetate 4:1. The solvent was evaporated *in vacuo* to give a light yellow oil. Yield: 70.2%. R_f = 0.81 (silica; petroleum ether:ethyl acetate 1:1). $[\alpha]^{25}_D$ = +13.6 (c = 1, MeOH). NMR ($CDCl_3$): 7.38−6.97, m, 10 H; 5.16, s, 2H; 4.67, s, 1H; 4.48−4.43, m, 1H; 3.16−3.08, m, 1H; 2.99−2.92, m, 1H.

Method H: Preparation of N^{α}-Benzyl-N^{α}-[ω-(Boc-amino)alkyl]glycine Benzyl Esters 7a−d and N^{α}-Benzyl-N^{α}-[ω-*tert*-butylcarboxy)alkyl]glycine Benzyl Esters 11a−e. A solution of 32.5 mol of **2** or **5** in 10 mL DMF was cooled in an ice bath. Then 5.66 mL (32.5 mol) of DIEA (diisopropylethylamine) followed by 5.15 mL (32.5 mol) of benzyl bromoacetate were added. The reaction mixture was stirred for 30 min at 0 °C, and then the temperature was allowed to rise to ambient temperature. The mixture was stirred for an additional 3 h. Two hundred mL of ether was added, and the white precipitate that formed was removed by filtration. The ether filtrate was washed with water (3 × 100 mL), 1 N HCl (2 × 100 mL), and water again (3 × 100 mL), dried over Na_2SO_4, and evaporated *in vacuo*.

7a. NMR ($CDCl_3$): 7.36−7.18, m, 10H; 5.22, broad s, 1H; 5.16, s, 2H; 3.76, s, 2H;, 3.35, s, 2H; 3.18, q, J = 6.5 Hz, 2H; 2.77, t, J = 7.3 Hz, 2H; 1.42, s, 9H.

7c. NMR ($CDCl_3$): 7.40−7.28, m, 10H; 5.14, s, 2H; 4.59, broad s, 1H; 3.77, s, 2H; 3.35, s, 2H; 3.09, m, 2H; 2.65 m, 2H; 1.68−1.42, s, 13H.

7d. NMR ($CDCl_3$): 7.58−7.29, m, 10H; 5.16, s, 2H; 4.51, broad s, 1H; 3.82, s, 2H; 3.38, s, 2H; 3.08, q, J = 6.8 Hz, 2H; 2.66, t, J = 7.3 Hz, 2H; 1.54−1.21, m, 17H.

10a NMR ($CDCl_3$): 7.37−7.28, m, 10H; 5.13, s, 2H; 3.89, s, 2H; 3.58, s, 2H; 3.44, s, 2H; 1.42, s, 9H.

10b NMR ($CDCl_3$): 7.29−7.16, m, 10H; 5.05, s, 2H; 3.74, s, 2H; 3.29, s, 2H; 2.95, t, J = 7.1 Hz, 2H; 2.34, t, J = 7.0 Hz, 2H; 1.35, s, 9H.

10c NMR ($CDCl_3$): 7.38−7.22, m, 10H; 5.14, s, 2H; 3.80, s, 2H; 3.36, s, 2H; 2.68, t, J = 7.3 Hz, 2H; 2.28, t, J = 7.6 Hz, 2H; 1.87−1.70, m, 2H; 1.41, s, 9H.

10d NMR ($CDCl_3$): 7.47−7.19, m, 10H; 5.08, s, 2H; 3.91, s, 2H; 3.40, s, 2H; 2.79, t, J = 6.8 Hz, 2H; 2.12, t, J = 5.9 Hz, 2H; 1.67−1.51, m, 4H; 1.36, s, 9H.

10e NMR ($CDCl_3$): 7.47−7.18, m, 10H; 5.09, s, 2H; 4.01, s, 2H; 3.46, s, 2H; 2.82, t, J = 7.6 Hz, 2H; 2.21−2.04, m, 2H; 1.92−1.04, m, 15H.

Method I: Preparation of N^{α}-Benzyl-N^{α}-[ω-(Boc-amino)alkyl]amino Acid Esters Other than Glycine 7e−i and 10f. A solution of 22 mmol of **6** (prepared as described in ref 10) in 20 mL of dry DCM was added dropwise to a cooled stirred solution of 20 mmol of **2** or **5** in 25 mL of dry DCM containing 22 mmol of triethylamine. After 30 min, the temperature was allowed to rise to ambient temperature and the mixture was stirred for an additional 18 h. Then 150 mL of chloroform was added, and the yellow solution was washed with water (3 × 80 mL). The organic phase was dried over Na_2SO_4. The crude product was adsorbed on 50 g of silica gel, which was placed in a Buchner funnel and was washed with 1 L of petroleum ether. Then the product was eluted from silica gel with 0.5 L of a mixture of petroleum ether:ethyl acetate 4:1, and the solvent was evaporated *in vacuo*. **7h−k** and **8f** needed purification by column chromatography. First impurities were eluted with 0.8 L of hexane, and then the products were eluted with 1.5 L of a mixture of petroleum ether:ethyl acetate 4:1.

7e,f. NMR ($CDCl_3$): 7.35−7.22, m, 5H; 5.20, broad s, 1H; 3.73, d, J = 11.9 Hz, 1H; 3.71, s, 3H; 3.61, d, J = 13.9 Hz, 1H; 3.53, q, J = 7.1 Hz, 1H; 3.20−3.06, m, 2H; 2.67−2.54, m, 2H; 1.64−1.55, m, 2H; 1.43, s, 9H; 1.28, d, J = 7.1 Hz, 3H.

7g. NMR ($CDCl_3$): 7.25−7.15, m, 5H; 4.42, broad s, 1H; 3.75, d, J = 14.4 Hz, 1H; 3.63, s, 3H; 3.53, d, J = 14.3 Hz, 1H; 3.44, q, J = 7.1 Hz, 1H; 3.00, q, J = 6.4 Hz, 2H; 2.54−2.39, m, 2H; 1.40−1.34, m, 4H; 1.37, s, 9H; 1.24−1.15, m, 4H; 1.20, d, J = 7.1 Hz, 3H.

7h,i. NMR ($CDCl_3$): 7.33−7.10, m, 10H; 4.71, broad s, 1H; 3.92, d, J = 18.4 Hz, 1H; 3.70−3.67, m, 4H; 3.59, d, J = 20.0 Hz, 1H; 3.17−2.88 m, 4H; 2.76−2.53, m, 2H; 1.63−1.55, m, 2H; 1.42, s, 9H.

Method J: Preparation of N^{α}-Benzyl-N^{α}-[ω-(Boc-amino)alkyl]amino Acids (8) by Hydrolysis of Methyl Esters. A solution of 0.015 mol of **7e−i** in 40 mL of methanol was cooled in an ice−water bath. Then 10 mL of 7.5 N NaOH was added, and the mixture was stirred at room temperature for approximately 24 h. One hundred mL of water was added, and the reaction mixture was washed with petroleum ether (3 × 80 mL). The aqueous solution was cooled to 0 °C and then acidified with 40 mL of 2 N HCl. The product was extracted with a mixture of chloroform: 2-propanol 3:1 (3 × 80 mL) and dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. White foams were obtained in quantitative yields.

8a,b NMR (D_2O as sodium salts): 7.42−7.35, m, 5H; 3.88, d, J = 13.6 Hz, 1H; 3.62, d, J = 13.2 Hz, 1H; 3.47, q, J = 7.1 Hz, 1H; 2.99, t, J = 6.4 Hz, 2H; 2.77−2.62, m, 2H; 1.69−1.49, m, 2H; 1.41, s, 9H; 1.30, d, J = 7.0 Hz, 3H.

8c. (DMSO-d_6): 7.35−7.23, m, 5H; 6.73, broad, s, 1H; 3.79, d, J = 14.3 Hz, 1H; 3.49, d, J = 14.3 Hz, 1H; 2.84, q, J = 6.7 Hz, 2H; 2.51−2.49, m, 2H; 1.36, s, 9H; 1.31−1.27, m, 4H; 1.19, d, J = 7.0 Hz, 3H; 1.17−1.11, m, 4H.

8d,e. NMR (DMSO-d_6): 7.29−6.66, m, 10H; 6.31, broad s, 1H; 3.87, d, J = 14 Hz, 1H; 3.55, d, J = 14.4 Hz, 1H; 3.48, q, J = 7.5 Hz, 1H; 3.0, q, J = 7.8 Hz, 1H; 2.86−2.81, m, 3H; 2.66−2.59, m, 1H; 2.50−2.43, m 1H; 1.50−1.41, m, 2H; 1.35, s, 9H.

Method K: Preparation of N^{α}-[ω-(Boc-amino)alkyl]-amino Acids 8 and N^{α}-[ω-(*tert*-Butylcarboxyl)alkyl]-amino Acids (11). 1. Preparation of 9a−d and 12 hydrogenation. One g of 15% w/w of 10% Pd/C was added to a solution of **7a−d** or **10** in 60 mL of methanol. The reaction mixture was hydrogenated for 4 h with 60 psi H_2 at room temperature. The catalyst was removed by filtration and washed with 2 × 40 mL of methanol. The solvent was evaporated to dryness *in vacuo*. Two hunderd mL of ether was added to the residual oil, and the formed precipitate was collected by filtration, washed with 2 × 30 mL of ether, and dried *in vacuo*.

2. Preparation of 8e−i (Hydrogenation). Pd/C (10%, 0.5 G) was added to a solution of 0.012 mol of **8** in 60 mL of MeOH:DMF 11:1. The solution was hydrogenated for 4 h with 50 psi H_2 at room temperature. Then 200 mL of a mixture of DMF:MeOH:H_2O: glacial AcOH 1:3:5:1 was added. The catalyst was removed by filtration and washed with water (2 × 15 mL). The filtrates were washed with petroleum ether (2 × 100 mL) and evaporated to dryness, and the product was recrystallized from methanol:ether 1:16.

8a. NMR (D_2O): 3.69, s, 2H; 3.47, t, J = 5.9 Hz, 2H; 3.23, t, J = 6.5 Hz, 2H; 1.48 s, 9H.

8b. NMR (D_2O): 3.65, s, 2H; 3.22, t, J = 6.8 Hz, 2H; 3.11, t, J = 8.2 Hz, 2H; 2.00, m, 2H; 1.46, s, 9 H.

8c. NMR (D_2O): 3.68, s, 2H; 3.18−3.08, m, 4H; 1.85−1.56, m, 4H; 1.47, s, 9H.

8d. NMR (D_2O): 3.67, s, 2H; 3.16−3.04, m, 4H; 1.82−1.67, m, 2H; 1.60−1.32, m, 15H.

8e,f (Ca Salt). NMR (D_2O): 3.76, q, J = 7.1 Hz, 1H; 3.18, t, J = 6.6 Hz, 2H; 3.07, t, J = 7.8 Hz, 2H; 1.92−1.85, m, 2H; 1.51, d, J = 7.2 Hz, 3H; 1.43, s, 9H.

8g (Ca Salt). NMR (D_2O): 3.26, q, J = 7.0 Hz, 1H; 3.00, t, J = 6.7 Hz, 2H; 2.68−2.59, m, 2H; 1.54−1.42, m, 4H; 1.42, s, 9H; 1.36−1.29, m, 4H; 1.27, d, J = 7.0 Hz, 3H.

8h,i (Ca Salt). NMR (D_2O): 7.34−7.22, m, 5H; 3.29, t, J = 7.3 Hz, 1H; 3.08−2.97, m, 2H; 2.90, dd, $J_{\alpha\beta}$ = 13.3 Hz, $J_{\beta\beta}$ = 6.7 Hz, 2H; 2.59−2.48, m, 0.9H; 2.46−2.39, m, 1, 1H; 1.70−1.49, m, 2H; 1.39, s, 9H.

11b. NMR (D_2O): 3.77, s, 2H; 3.36, t, J = 6.6 Hz, 2H; 2.80, t, J = 6.6 Hz, 2H; 1.48, s, 9H.

11c. NMR (D_2O): 4.09, s, 0.4 H; 3.75, s, 1.6H; 3.56, t, J = 7.2 Hz, 0.4H; 3.12, t, J = 7.8 Hz, 1.6H; 2.54, t, J = 7.1 Hz, 0.4H; 2.45, t, J = 7.1 Hz, 1.6H; 2.12−2.09, m, 0.4H; 2.03−1.94, m, 1.6H; 1.47, s, 9H.

11d (Ca Salt). NMR (D_2O): 3.57, s, 0.7H; 3.46, s, 1.3H; 3.02, t, J = 7.6 Hz, 0.7H; 2.95, t, J = 6 Hz, 1.3H; 2.36, t, J = 7.0 Hz, 0.7H; 2.31, t, J = 7.2 Hz, 1.3H; 1.72−1.64, m, 2.7H ($^2CH_2$ and $^3CH_2$ [E]); 1.64−1.58, m, 1.3H; 1.47, s, 3.2H; 1.46, s, 5.8H.

11e (Ca Salt). NMR (D_2O): 3.45s, 0.4H; 3.39, s, 1.6H; 2.88, t, J = 7.5 Hz, 0.4H, 2.81, t, J = 7.6 Hz, 1.6H; 2.39, t, J = 7.3 Hz, 0.4H; 2.31, t, J = 7.3 Hz, 1.6H; 1.66−1.57, m, 2H; 1.46, s, 9H; 1.38−1.25, m, 4H.

Method L: Preparation of N^{α}-Fmoc-N^{α}-[ω-(Boc-amino)-alkyl]amino Acids 9 and N^{α}-Fmoc-N^{α}-[ω-(*tert*-Butylcarboxy)alkyl]amino Acids 12. Twenty mmol of triethylamine was added to a solution of 10 mmol of **8** or **11** in 40 mL of water. The mixture was stirred until a clear solution was obtained. Then a solution of 20 mmol of Fmoc-OSu in 80 mL of acetonitrile was added. The reaction mixture was stirred at room temperature for 4 h. Water (150 mL) was added, and the mixture was washed with petroleum ether (3 × 100 mL) and with a mixture of ether:petroleum ether 3:7 (2 × 100 mL). The aqueous solution was cooled to 0 °C and acidified with 40 mL of 1 N HCl, and the product was extracted with ethyl acetate (4 × 100 mL). The organic solution was washed with water (4 × 100 mL) and dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. The product was recrystallized from ether:petroleum-ether 1:10.

9a. NMR (MeOD): 7.71−7.67, m, 2H; 7.53, d, J = 7.4H, 0.95H; 7.49, d, J = 7.4H, 1.05H; 7.29, q, J = 7.0, 2H; 7.25−7.18, m, 2H; 4.33, d, J = 6.3 Hz, 0.95 H; 4.25, d, J = 6.3 Hz, 1.05H; 4.19, t, J = 6.2 Hz, 0.45H; 4.10, t, J = 6.6 Hz, 0.55H; 3.895, s, 0.45H; 3.887, s, 0.55H; 3.30, t, J = 6.2 Hz, 1.05H; 3.21, m, 0.95H; 3.09, t, J = 6.1 Hz, 1.05H; 2.91, t, J = 6.0 Hz, 0.95H; 1.31, s, 4.3H; 1.30, s, 4.7H.

9b. NMR ($CDCl_3$; 305 K): 7.76−7.72, m, 2H; 7.57−7.53, m, 2H; 7.38, q, J = 8.0 Hz, 2H; 7.33−7.28, m, 2H; 6.06, broad s, 0.8H; 5.18, broad s, 0.2H; 4.59, m, 0.8H; 4.44, m, 1.2H; 4.23, m, 0.4H; 4.19, m, 0.6H; 3.96, s, 1.2H; 3.88, s, 0.8H; 3.49, t, J = 7.0 Hz, 1.1H; 3.10, m, 2H; 2.87, m, 0.9H; 1.65, m, 0.95H; 1.43, m, 10.05H.

9c. NMR ($CDCl_3$): 7.77−7.71, m, 2H; 7.55, t, J = 7.55, t, J = 7.5 Hz, 2H; 7.35, q, J = 8.0 Hz, 2H; 7.30−7.27, m, 2H; 5.9, broad s, 0.5H; 5.7, broad s, 0.5H; 4.56, d, J = 5.5 Hz, 1.1H; 4.42, d, J = 6.4 Hz, 0.90H; 4.24−4.17, m, 1H; 3.96, s, 1.1H; 3.90, s, 0.9H; 3.35, t, J = 7.0 Hz, 0.9H; 3.08, t, J = 7.0 Hz, 2H; 2.98, m, 1.1H; 1.60−1.44, m, 10H; 1.29−1.26, m, 0.9H; 1.23−1.18, m, 1.1H.

9d. NMR ($CDCl_3$): 7.73t, J = 8.0 Hz, 2H; 7.54, t, J = 6.9 Hz, 2H; 7.39−7.34, m, 2H; 7.33−7.24, m, 2H; 5.9, broad s, 0.3H; 4.57, broad s, 0.7H; 4.48, d, J = 6.1 Hz, 1.3H; 4.38, d, J = 6.5 Hz, 0.7H; 4.22−4.17, m, 1H; 3.93, s, 1.3H; 3.9, s, 0.7H; 3.50−3.48, m, 1.1H; 3.12−3.08, m, 2.9H; 1.44, s, 9H; 1.29, m, 2H; 1.20, m, 2H; 1.10, m, 2H.

9e,f. NMR ($CDCl_3$): 7.75, m, 2H; 7.55, d, J = 7.2 Hz, 2H; 7.39−7.36, m, 2H; 7.30, m, 2H; 6.51, broad s, 0.2 H; 6.36, broad s, 0.3H; 5.26, broad s, 0.5H; 4.61, m, 0.95H; 4.48, m, 0.6H; 4.36, m, 0.4H; 4.21, m, 1.05H; 3.64, m, 0.3H; 3.43, m. 0.6H; 3.14−3.02, m, 2H; 2.87−2.84, m, 1.9H; 2.65, m, 0.3H; 1.64, m, 0.5H; 1.45, s, 4H; 1.42, s, 5H; 1.36−1.29, m, 3.4H; 1.54−1.40, m, 0.1H; 0.88−0.82, m, 0.5H.

9g. NMR ($CDCl_3$): 7.77−7.72, m, 2H; 7.56, d, J = 7.4 Hz, 2H; 7.40−7.36, m, 2H; 7.31−7.28, m, 2H; 5.92, broad s, 0.8H; 5.41, broad s, 0.2H; 4.63, m, 0.38H; 4.57−4.48m, 1.6H; 4.42−4.39, m, 0.65H; 4.32−4.28, m, 0.20H; 4.23−4.20, m, 1.17H; 4.04, d, J = 6.1 Hz, 0.1H; 3.48−3.43, m, 0.12H; 3.37−3.30, m, 0.3H; 3.11−2.88, m, 2.9; 2.94−2.88, m, 0.5H; 1.55−1.53, m, 0.5H; 1.51, d, J = 6.6 Hz, 0.2H; 1.44−1.41, m, 11H; 1.40, d, J = 7.2 Hz, 1.8H; 1.32, d, b of abx, J = 7.0 Hz, 1H; 1.29, m, 2H; 1.18, m, 0.8H; 1.05, m, 1.2H.

9h,i. NMR (MeOD): 7.71−7.65, m, 2H; 7.57−7.46, m, 2H; 7.31−7.19, m, 4H, 7.16−6.96, m, 4H; 6.66−6.64, m, 1H; 4.49, dd, J_1 = 10.3 Hz, J_2 = 5.6 Hz, 0.54H; 4.39−4.32, m, 1.1H; 4.14−4.10, m, 1.96H; 3.99−3.97, m, 0.40H; 3.14, dd, $J_{\alpha\beta}$ = 14.1 Hz, $J_{\beta\beta}$ = 4.7 Hz, 0.7H; 3.08−3.01m, 0.7H; 2.98−2.90, m, 0.5H; 2.83, dd, $J_{\alpha\beta}$ = 14.8 Hz, $J_{\beta\beta}$ = 4.6 Hz, 0.6H; 2.82−2.75, m, 0.5H; 2.68, t, J = 6.2 Hz, 0.9H; 2.58−2.49, m, 1.4H; 2.46−2.37, m, 0.9H; 1.30−0.97, 11H.

12a. NMR ($CDCl_3$): 7.76, t, J = 7.1 Hz, 2H; 7.57−7.55, m, 2H; 7.42−7.37, q, J = 7.0 Hz, 2H; 7.33−7.28, m, 2H; 4.45, d, J = 5.1 Hz, 0.4H; 4.43, d, J = 5.0 Hz, 0.6H; 4.26−4.22, t, J = 6.9 Hz, 2H; 4.16, s, 1.2H; 4.07, s, 0.8H; 4.06, s, 1.2H; 4.01, s, 0.8H; 1.50, s, 4.5H; 1.48, s, 4.5H.

12b. NMR ($CDCl_3$): 7.75, d, J = 15.0 Hz, 1.05H; 7.74, d, J = 15.0 Hz, 0.95H; 7.58, d, J = 7.3 Hz, 1.05H; 7.52, d, J = 7.2 Hz, 0.95H; 7.39, q, J = 7.0 Hz, 2H; 7.33−7.28, m, 2H; 4.53, d, J = 6.1 Hz, 1.05H; 4.44, d, J = 6.2 Hz, 0.95H; 4.27, t, J = 5.9 Hz, 0.53 H; 4.19, t, J = 5.9 Hz, 0.47H; 4.11, s, 1.05H; 4.02, s, 0.95H; 3.55, t, J = 6.1 Hz, 0.95H; 3.43, t, J = 6.6 Hz, 1.05H; 2.55, t, J = 6.2 Hz, 0.95H; 2.30, t, J = 6.54 Hz, 1.05H; 1.44, s, 5.6H; 1.42, s, 3.4H.

12c. NMR ($CDCl_3$): 7.77−7.71, m, 2H; 7.57, d, J = 7.3 Hz, 1.2H; 7.52, d, J = 7.4 Hz, 0.8H, 7.41−7.36, m, 2H; 7.34−7.28, m, 2H; 4.53, d, J = 5.9 Hz, 1.2H; 4.45, d, J = 6.2 Hz, 0.8H; 4.26, t, J = 5.7 Hz, 0.6H; 4.19, t, J = 5.9 Hz, 0.4H; 4.00, s, 1.2H; 3.88, s, 0.8H; 3.48, t, J = 6.9 Hz, 0.8H; 3.17, t, J = 6.9 Hz, 1.2H; 2.24, t, J = 7.2 Hz, 0.8H; 2.04, t, J = 7.2 Hz, 1.2H; 1.79, t, J = 7.1 Hz, 0.8H; 1.60, t, J = 7.1 Hz, 1.2H; 1.43, s, 5.6H.

12d. NMR ($CDCl_3$): 7.77−7.71, m, 2H; 7.57, d, J = 7.4 Hz, 1.2H; 7.52, d, J = 7.4 Hz, 0.8H; 7.38, q, J = 7.0 Hz, 2H; 7.30, q, J = 8.0 Hz, 2H; 4.54, d, J = 5.9 Hz, 1.2H; 4.44, d, J = 6.3 Hz, 0.8H; 4.25, t, J = 5.8 Hz, 0.6H; 4.19, t, J = 6.2 Hz, 0.4H; 3.98, s, 1.2H; 3.88, s, 0.8H; 3.32, t, J = 6.2 Hz, 0.8H; 3.11, t, J = 7.1 Hz, 1.2H; 2.22, t, J = 6.6 Hz, 0.8H; 2.12, t, J = 7.1 Hz, 1.2H; 1.67−1.54, m, 1.4H; 1.43, s, 9H; 1.40−1.27, m, 2.1H; 1.21−1.13, m, 0.5H.

12e. NMR ($CDCl_3$): 7.77−7.72, m, 2H; 7.58−7.52, m, 2H; 7.41−7.34, m, 2H; 7.33−7.28, m, 2H; 4.54, d, J = 5.9 Hz, 1.2H; 4.45, d, J = 5.9 Hz, 0.8H; 4.25, t, J = 5.6 Hz, 0.6H; 4.19, t, J = 5.6 Hz, 0.4H; 3.99, s, 1.2H; 3.86, s, 0.8H; 3.30, t, J = 7.0 Hz, 0.8H; 3.13, t, J = 7.3 Hz, 1.2H; 2.19−2.16, m, 2H; 1.48−1.49, m, 2.9H; 1.44, s, 9H; 1.37−1.29, m, 1.6H; 1.16−1.12, m, 1.2H; 1.21−1.13, m, 0.3H.

12f. NMR ($CDCl_3$): 7.77−7.75, m, 2H; 7.71−7.52, m, 2H; 7.40−7.10, m, 8.5H; 6.76−6.80, m, 0.5H; 4.84, dd, J_1 = 10.7 Hz, J_2 = 4.5 Hz, 0.5H; 4.66, dd, J_1 = 10.6 Hz, J_2 = 5.7 Hz, 0.6H; 4.57, dd, J_1 = 11.1 Hz, J_2 = 4.2 Hz, 0.6H; 4.43, dd, J_1 = 10.8 Hz, J_2 = 6.2 Hz, 0.9H; 4.27−4.24, m, 0.5H; 4.21−4.19, m, 0.5H; 4.03, dd, J_1 = 10.3 Hz, J_2 = 4.2, 0.5H; 3.35−3.26, m, 1.3H; 3.24−3.10, m, 0.7H; 2.97−2.90, dd, J_1 = 12.6 Hz, J_2 = 4.1 Hz, 0.5H; 2.70−2.51, m, 1.3H; 2.48−2.40, m, 0.7H; 2.19−2.09, m, 0.9H; 2.03−1.95, m, 0.6H; 1.40, s, 5.6H; 1.37, s, 3.4H.

Acknowledgment. This research was financed by Peptor Co. Ltd. Rehovot, Israel, and by the GIF Foundation.

Supporting Information Available: A listing of NMR spectra including detailed assignment of proton chemical shifts (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO961580E