100. Template-Assembled Synthetic Proteins (TASP). Cyclic Templates with Incorporated Turn-Inducing Mimics

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The 8-amino-5,6,7,8-tetrahydronaphth-2-oic acid (**1**), 8-(aminomethyl)-5,6,7,8-tetrahydronaphth-2-oic acid (**2**), and 8-(aminomethyl)naphth-2-oic acid (**3**) were synthesized in their protected forms as turn-inducing dipeptide mimics. Two of them (**2** and **3**) were incorporated into a novel type of cyclic, peptide-based structures (see **21** and **34–36**) designed as templates for the synthesis of TASP molecules.

Introduction. – The introduction of the 'TASP' concept (*T*emplate-*A*ssembled *S*ynthetic *P*rotein) [1] has provided a novel, broadly applicable approach for the construction and study of novel proteins exhibiting a predetermined folding topology [2]. TASP molecules are built up by covalent attachment of several peptide sequences with a potential for amphiphilic secondary structure formation to a carrier molecule (template) resulting in a branched peptide chain architecture. As a key feature of this approach, the template is designed to direct and reinforce the folding of the attached secondary structure elements in the envisaged tertiary structures (see *Fig. 1* presenting a 4α-helical bundle

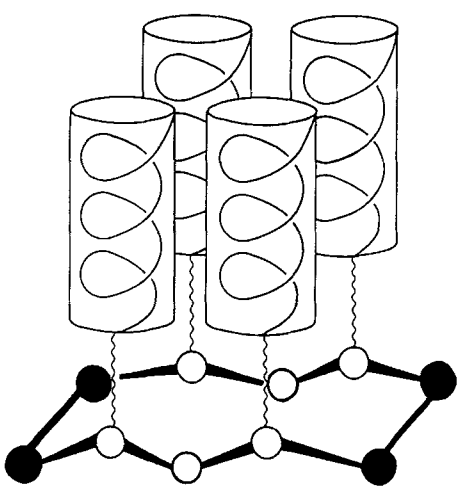


Fig. 1. *Schematic picture of a TASP molecule with a 4α-*helical bundle attached to a cyclic template

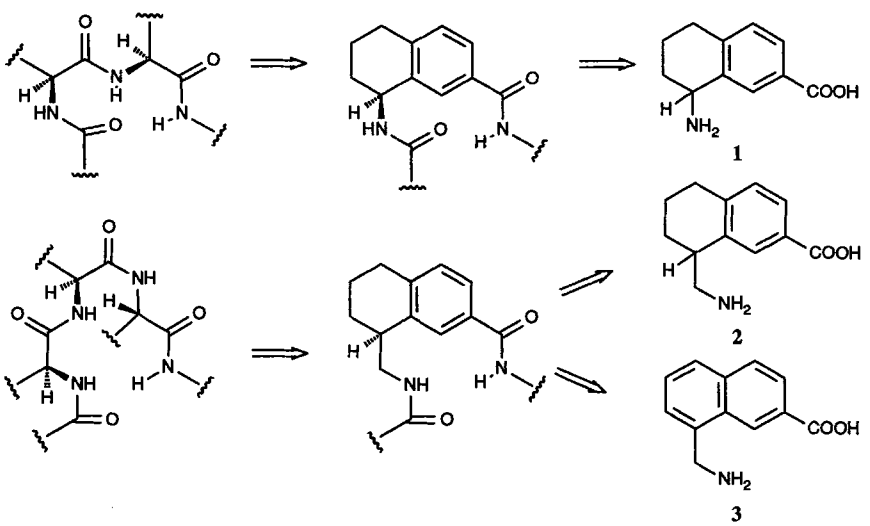
TASP). As a consequence, the critical hurdle in the *de novo* design of proteins, the well-known 'protein-folding problem' [3], can be circumvented. The usefulness of the TASP approach for a straightforward synthesis of protein models with sixty and more amino-acid residues and its positive effect on folding to defined tertiary structures in such branched molecules were demonstrated [4].

The templates so far applied in TASP syntheses were open-chain oligopeptides with a central Pro-Gly motive securing the desired U-form, or a cyclic version of the latter with both peptide ends connected by a disulfide bond [4].

In the process of a further development of the TASP concept, we considered the synthesis of tailor-made templates an important step toward the construction of TASP molecules exhibiting well-defined structural and functional properties. We now describe in full detail several examples of a novel type of cyclic templates with incorporated, newly developed, turn-inducing mimics [5].

Novel Turn-Inducing Mimics. – The major purpose of artificial turn-inducing mimics recently described in the literature [6] is to constrain, when incorporated at a proper place, the peptide chain into a semi-rigid, defined, spacial arrangement. With the aim to develop such constrained template molecules suitable for the construction of a variety of packing arrangements, *e.g.* a 4α-helix bundle (*Fig. 1*) or β-meander topology [2], we designed and synthesized three novel turn-inducing dipeptide mimics, *i.e.* compounds **1**–**3** (*Scheme 1*).

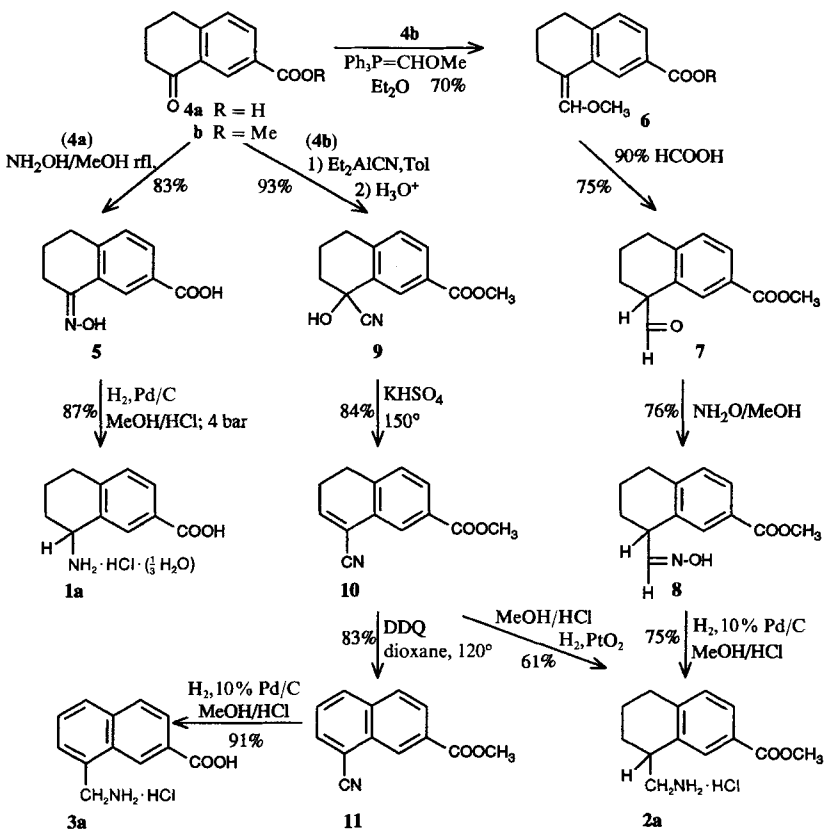
Scheme 1



One of the mimics, 8-amino-5,6,7,8-tetrahydronaphth-2-oic acid (Ahn; **1**) was designed as a substitute for the central dipeptide part of a β-turn (*Scheme 1*). The homologous 8-(aminomethyl)-5,6,7,8-tetrahydronaphth-2-oic acid (Amhn; **2**) – a modification of the preceding structure recommended by a CAMM analysis – rather corresponds to the central tripeptide unit of a reverse turn. Finally, the achiral 8-(aminomethyl)naphth-2-oic acid (Amn; **3**) represents a sterically acceptable simplification of **2**.

The common starting point for the synthesis of all three mimics was the known 5,6,7,8-tetrahydro-8-oxonaphth-2-oic acid (**4a**), easily prepared in five simple steps from the commercially available 4-phenylbutanoic acid [7] (*Scheme 2*). Hydrogenation of oxime **5** (5% Pd/C, HCl/MeOH) gave the crystalline hydrochloride **1a** of the racemic mimic **1** in high yield. For the synthesis of the homologous mimic **2**, methyl ester **4b** was first extended – in a two-step process involving the isomeric mixture of the enol ethers **6** as

Scheme 2



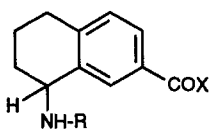
intermediate – to aldehyde **7**. In a similar way as in the case of **1**, the corresponding oxime **8** was hydrogenated to give the crystalline methyl ester hydrochloride **2a** in its racemic form. In an alternative synthesis of **2a**, methyl ester **4b** was transformed (Et_2AlCN in toluene; H_3O^+) into an isomeric mixture **9** of cyanohydrines which, on heating with $KHSO_4$ (150°), was dehydrated to methyl 8-cyano-5,6-dihydronaphth-2-oate (**10**). Hydrogenation of the latter, this time over Pt (PtO_2, H_2, HCl/MeOH), afforded **2a** in high overall yield.

The dihydronaphthalene derivative **10** served as a suitable intermediate also in the synthesis of the mimic **3**. Dehydrogenation of **10** (DDQ (= 2,3-dichloro-5,6-di-

cyanobenzo-1,4-quinone) in dioxane, 120°) afforded smoothly methyl 8-cyanonaphth-2-oate (**11**) which was hydrogenated over Pd (10% PdC, HCl/MeOH) to the crystalline methyl ester hydrochloride **3a**.

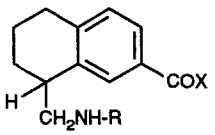
For their incorporation into peptide chains, the mimics were transformed to the *N*-Boc and *N*-Fmoc derivatives **1d**,**e**, **2g**,**h**, and **3f**–**h** (see *Exper. Part*). For the methyl

(RS)-Ahn Derivatives:



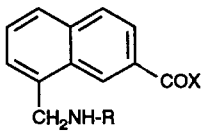
1a R = H(·HCl), X = OH
b R = Ac, X=OH
c R = Ac, X = NH(i-Pr)
d R = Fmoc, X = OH
e R = Boc, X = OH

(RS)-Amhn Derivatives:

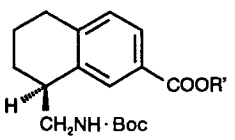


2a R = H(·HCl), X = MeO
b R = Ac, X = MeO
c R = Ac, X = OH
d R = Ac, X = NH(i-Pr)
e R = Z, X = MeO
f R = PhCO, X = MeO
g R = Boc, X = MeO
h R = Boc, X = OH

Amn Derivatives:



3a R = H(·HCl), X = MeO
b R = Ac, X = MeO
c R = Ac, X = OH
d R = Ac, X = NH(i-Pr)
e R = H(·HCl), X = OH
f R = Fmoc, X = OH
g R = Boc, X = MeO
h R = Boc, X = OH



(+)-(*S*)-**2g** R′ = Me
(*S*)-**2h** R′ = H

ester **2g** of racemic Boc-(*RS*)-Amhn, a preparative chromatographic resolution procedure [8a] on *m*-methylbenzoyl cellulose beads (MMBC) [8b] was elaborated allowing to isolate 10-g quantities of each enantiomer (+)- and (−)-**2g** in its optically pure form. The absolute configuration at their single chiral center C(8) was established by an X-ray analysis of the (+)-camphor-10-sulfonate **2i** (see *Formula* **2a**, with RSO_3H instead of HCl) of the dextrorotatory amino ester (obtained by treatment of (+)-**2g**) with CF_3COOH; it proved to be the (*S*)-enantiomer (*Fig. 2*).

The ability of the new mimics to induce a turn in a peptide chain was tested on their *N*-acetyl-*N*′-isopropylamides **1c**, **2d**, and **3d** as simple models of β-turn peptides (the Ac group simulating the *i*, the (i-Pr)NH grouping the $i + 3$ amino acid). X-Ray analysis of **1c** and **3d** (*Fig. 3*) showed lacking of the intramolecular H-bridge, thus confirming the results of their IR and NMR spectra. On the other hand, the ability of the two mimics to build up compounds with the general character of an open U-turn became evident. Similar conclusions, based on IR and NMR studies, could be made about the *N*-acetyl-*N*′-isopropylamide **2d**.

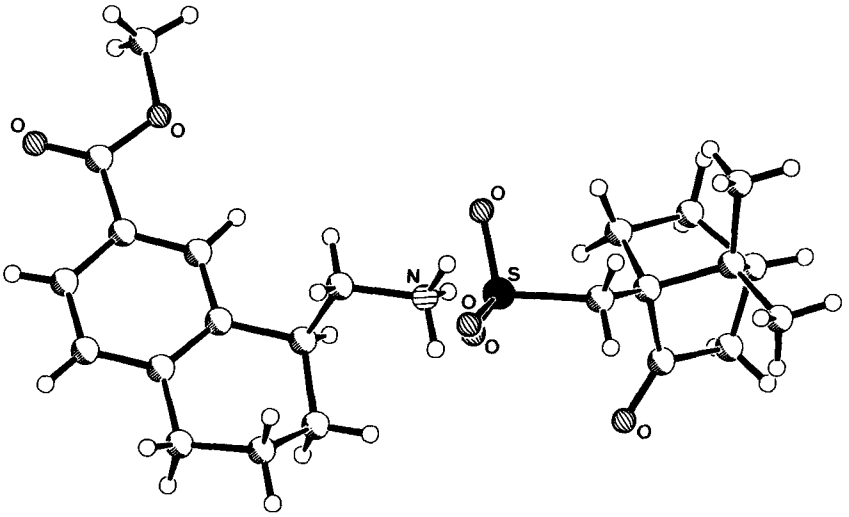


Fig. 2. *SCHAKAL drawing of the (+)-camphor-10-sulfonate (S)-***2i** *of methyl (8S)-8-(aminomethyl)-5,6,7,8-tetrahydronaphth-2-oate.* Crystal data and atomic parameters were submitted to the *Cambridge Crystallographic Data Center.*

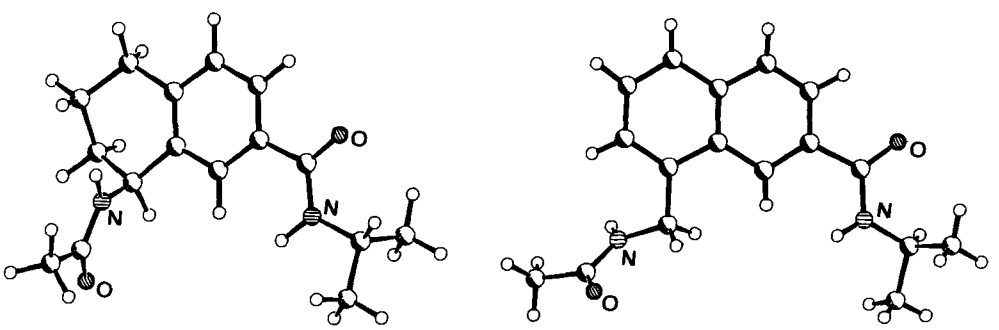
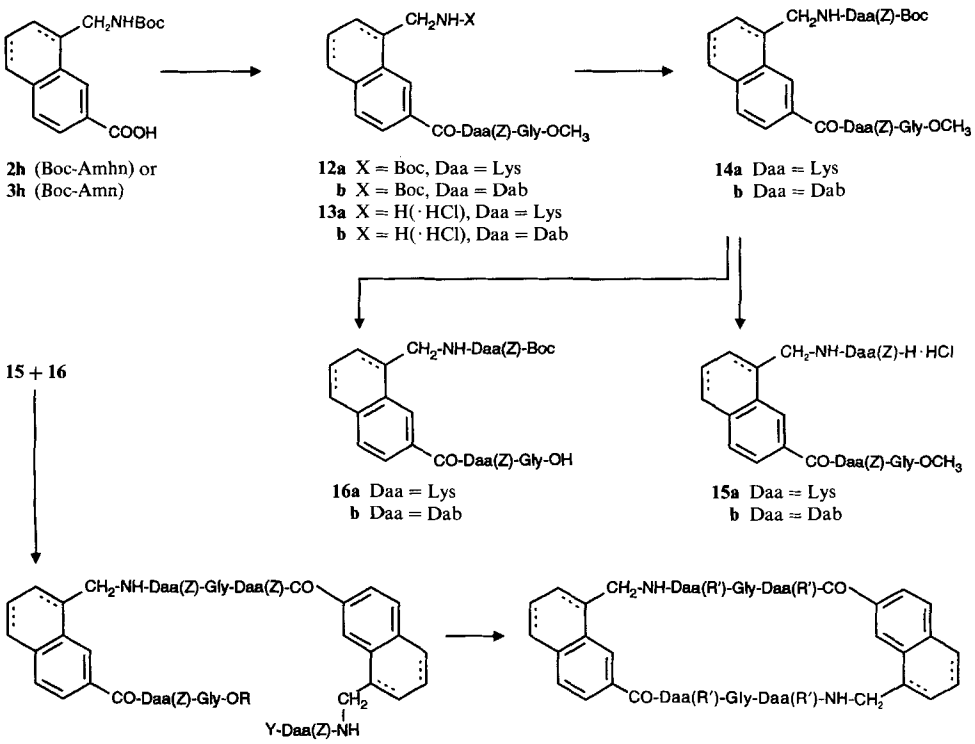


Fig. 3. *PLUTO drawings of mimic derivatives* **1c** (left) *and* **3d** (right). Crystal data and atomic parameters were submitted to the *Cambridge Crystallographic Data Center.*

Templates with Incorporated Turn-Inducing Mimics. – It seemed conceivable that an incorporation of the above described mimics into cyclic templates of the general type schematically shown in *Fig. 1*, in place of the dipeptide units involved in the turns (bold circles), might constrain the carriers to favorable conformations for the construction of TASP molecules. Computer simulations with energy minimalization of such template structures were supportive for this idea [9]. Based on these considerations, several examples of a novel type of cyclic templates were synthesized. Their general feature are two identical, antiparallel tripeptide motifs connected at each end through one of the above mentioned turn-inducing dipeptide mimics.

The tripeptide parts consist of two equal diamino-acid units (L-lysine (Lys) or L-2,4-diaminobutanoic acid (Dab)) linked by a glycine (Gly), thus forming templates suitable for a parallel attachment of four identical peptide fragments (see below, structure **21** in

Scheme 3



Scheme 3). In one case, orthogonally protected L-glutamic acid (Glu(OBzl)) and Dab flanking Gly in each tripeptide motif allow for an antiparallel attachment of peptide fragments to the template as, *e.g.*, needed for the construction of an antiparallel 4α-helical bundle (see below, structure **33** of the protected template in *Scheme 5*). Only templates with incorporated Amhn and Amn mimics **2** and **3**, respectively, are described in this paper. In the case of the former mimic, both enantiomers were used and all three possible diastereoisomers of the lysine-based template Amhn-**21a**[1]), *i.e.*, its (*S,S*)-, (*R,R*)-, and (*S,R*)-forms, were prepared[2]).

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[1]) The key numbers of the peptides (see also *Exper. Part*) are preceded by the amino-acid symbol of the incorporated mimic ('Amhn' or 'Amn') and, in the case of Amhn-containing peptides, by the configurational prefix(es) of the Amhn(s).

[2]) Starting from the racemic form of the mimic Boc-Amhn (**2h**), a mixture of all three diastereoisomeric templates Amhn-**21a** was also prepared *via* Amhn-**17a**. However, their HPLC separation proved difficult and gave little promise for securing the individual diastereoisomers in practical quantities. No good opportunity for a PC separation of any of the diastereoisomeric intermediates of this synthesis could be found, either (unpublished results).

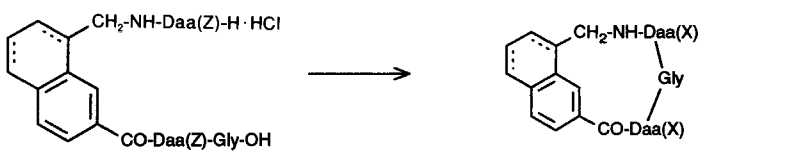
All templates were synthesized by classical methods in solution following a common synthetic pathway (*Scheme 3*). A characteristic feature is the construction of the open-chain octapeptide intermediates **17** from two molecules of the tetrapeptides **14** which, for that purpose, had been deblocked at their N-terminus (→ **15**) and at the C-terminus (→ **16**), respectively. In the synthesis of the octapeptide (*S,R*)-Amhn-**17a**, one molecule of (*S*)-Amhn-**15a** and of (*R*)-Amhn-**16a**, each, were used[1][2]).

Except for the tetrapeptide (*S*)-Amhn-**14a** which was prepared by a 2 + 2 condensation of Boc-Lys(Z)-(*S*)-Amhn-OH with HCl · H-Lys(Z)-Gly-OMe, the tetrapeptides **14** were obtained from the *N*-Boc-protected mimics **2h** or **3h** *via* the tripeptide intermediates **12** and **13**.

The synthetic strategy made use of N^{α}-Boc protection and dicyclohexylcarbodiimide/1*H*-benzotriazol-1-ol (DCC/HOBT) activation throughout[3]), except in the cyclization step where bis(phenyloxy)phosphoryl azide ($(PhO)_2P(O)N_3$) was successfully used as activating agent (**19** → **20**). Hydrogenolysis (Pd/C in HCl/AcOH) of the Z-protecting groups in **20** afforded the templates **21** as tetrahydrochlorides, ready for use in the TASP syntheses.

In an attempt to prepare the template Amn-**20a** by cyclodimerization with $(PhO)_2P(O)N_3$ from two molecules of the tetrapeptide Amn-**22a**, deprotected both on its N- and C-terminus, the cyclic 'monomer' Amn-**23a** was isolated as the only product in high yield (*Scheme 4*). No trace of Amn-**20a** could be detected even by performing the reaction at high concentration of Amn-**22a**[4]).

Scheme 4



22a Daa = Lys
b Daa = Dab

23a X = Z, Daa = Lys
b X = Z, Daa = Dab
24a X = H(· HCl), Daa = Lys
b X = H(· HCl), Daa = Dab

The synthesis of the template **33** with two different, orthogonal protecting groups (Boc and OBzL) required small changes in the general synthetic scheme (*cf. Scheme 4*) due to the introduction of additional orthogonal protecting groups (see *Scheme 5*). Thus, **27** (obtained *via* **25** and **26** from **3h**) was selectively deblocked (→ **28** and **29**; resp.) and, after condensation to yield octapeptide **30** and partial deprotection (→ **31** → **32**), cyclization gave **33** which was deprotected to **34**, **35**, or **36**.

The choice of the solution methods throughout the syntheses made possible the preparation of up to gram quantities of the final templates and allowed for purification of

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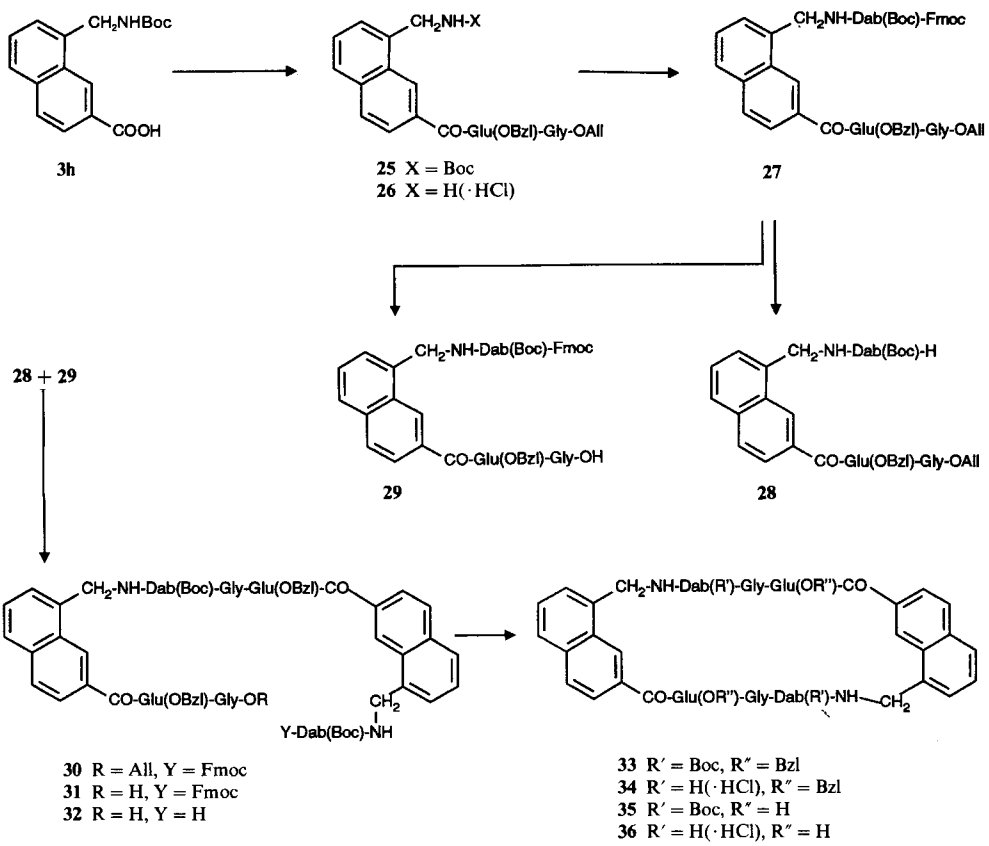
[3]) In few cases, TBTU(*O*-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate)/HOBT was used in place of DCC/HOBT for practical reasons.

[4]) Similarly, monomeric, cyclic products were obtained from **22b** and the corresponding (*S*)- and (*R*)-Amhn-**22** (unpublished results).

Scheme 5



intermediates (mostly by classical silica-gel chromatography) as well as of final products (reversed-phase HPLC, if necessary), thus ensuring the attainment of high-purity standards for all compounds.

In spite of their high purity, none of the protected templates **20a**, **b** and **33** or of their deprotected salts **21a**, **b** and **34**–**36** was, up to now, obtained in crystalline form (they were amorphous solids in our hands). On the other hand, valuable information about the conformational behavior of the novel templates in solution was obtained by detailed NMR studies (2D; (D_6)DMSO, H_2O/D_2O). Although these studies, which will be published separately [11], could confirm the centrosymmetrical geometry of both the protected templates **20a** and their *N*-deprotected salts **21a**, no clear indications for strong intramolecular H-bonds were found indicating that, in aqueous solutions, alternative low-energy conformations of the templates (without attached peptide blocks) may be attained. As shown, *e.g.*, in the case of the (*S*,*S*)-Amhn-**21a**, intramolecular hydrophobic interactions of the aromatic parts of the mimics in aqueous solution seem to constrain the molecule to a bent conformation with both mimic units in close proximity.

Computer simulations show the plausibility of the conformation of the cyclic octapeptide template sketched in *Fig. 1*. Molecular-dynamics calculations carried out for

the template Amhn-**21a** for 200 ps support the existence of a stable conformation in which the Lys-Gly-Lys portions form an antiparallel β-sheet and the Amhn units serve as β-turn mimic. During the simulation, two H-bonds between backbone atoms of both sheets are populated significantly. However, at 900 K, when the structures sampled during the simulations were subjected to energy minimisation, the structure with the two H-bonds was not preserved, but instead, the two hydrophobic turn mimics came together [9], thus supporting the NMR data. Nevertheless, both the molecular-dynamics and NMR studies place all four Lys side chains on the same (convex) side of the template structure in orientations ideal for the attachment of the peptide fragments [10]. It is important to note, that for the stabilization of 4α-helical bundle conformations, the ideal antiparallel β-sheet arrangement of the tripeptide elements X-G-X (X = Lys or Dab) in the template may not correspond to the preferred conformation of lowest conformational energy [9] [12]. Moreover, due to mutual interactions, the conformational properties of the template embedded in a TASP molecule may be fundamentally different from those of the isolated template as studied by NMR and molecular-dynamics calculations. The inherent propensity of the template molecules described here to induce and stabilize folding topologies encountered in natural proteins, *e.g.* as constituents of the 4α-bundle TASP molecules, will be the subject of a forthcoming publication [13].

We thank Messrs. *M. Kessler*, *Ch. Stürzinger*, and *P. Felber* (all Pharmaceutical Division, *Ciba-Geigy AG*, Basel) for their skillful technical assistance in the syntheses of the turn-inducing mimics, and the Kilo Laboratories, Pharmaceutical Division, *Ciba-Geigy AG*, Basel (Mr. *A. Schmidt* and coworkers), for large-scale preparation of the described mimics and several technical improvements of the synthetic procedures. We further thank the Analytical Services of *Ciba-Geigy AG*, Basel (Drs. *W. Padowetz* and *J. Pavel*), for the elemental analyses, Mr. *S. Moss* and Dr. *H. Fuhrer* (both Central Function Research, *Ciba-Geigy AG*, Basel) for the IR and some of the NMR spectra, respectively. *M. M.* thanks the *Swiss National Science Foundation* for financial support.

Experimental Part

General. TLC: Merck silica gel *60* F_{254} TLC plates. Prep. column chromatography (LC): *Merck 60* silica gel, particle size 0.063–0.200 mm. Chromatographic optical resolution (HPLC): anal. experiments with a modular liquid chromatograph *Shimadzu* (*Burckard Instrumente*, Zürich, Switzerland) composed of a *LC-6A* pump and a multiwavelength UV/VIS detector model *SPD-6AV* in series with a *Perkin-Elmer* polarimeter (model *241 LC*) equipped with a 80-µl cell (length 10 cm); both signals (UV absorption and optical rotation) were recorded and processed by an *IBM PC-AT3* microcomputer, *via* a *Dysc WD 24* analog interface module using the *Maxima 820* chromatographic software (*Carlo Erba*, Milan, Italy); prep. resolutions with a *Shimadzu* pump *LC-8A* and with a 1-ml flow-cell (polarimeter). M.p.: *Kofler*; uncorrected. IR Spectra: absorptions in cm^{-1}. ^{1}H-NMR Spectra: *Bruker-WM-400* and *Bruker-AM-360* spectrometers; some spectra on *Varian-Gemini-200* and *-Gemini-300* spectrometers; chemical shifts as δ values in ppm rel. to Me_4Si as internal ref. (= 0 ppm), coupling *constants J* in Hz. FAB-MS (fast-atom-bombardment ionization): *ZAB-HF* mass spectrometer/*11-250-J* data system (*Fisons Instruments*, Manchester, U.K.) equipped with a saddle-field atom gun (*Ion Tech Ltd.*, Teddington, U.K.); samples added to 1-thioglycerol as a liquid matrix and bombarded with a stream of Xe atoms of 10 keV kinetic energy; mass measurements recorded at 8 kV accelerating voltage and low instrumental resolution (of *ca.* 1000) in the multichannel analyzer mode by summation of slow, narrow scans (mass range 2000–800, scan time 200 s). PD-MS (plasma-desorption ionization): *BIO-ION-20* plasma desorption instrument (*Applied Biosystems AB*, Uppsala, Sweden) connected to a *PDP-11/73* data system; acceleration voltage 18 kV in the positive-ion mode; samples (1–10 µg) dissolved in 10 µl of H_2O/AcOH 1:1 were applied to a nitrocellulose matrix; unadsorbed material washed off by 5 drops of H_2O.

Abbreviations: Amn, 8-(aminomethyl)naphth-2-oic acid; Amhn, 8-(aminomethyl)-5,6,7,8-tetrahydronaphth-2-oic acid; Ahn, 8-amino-5,6,7,8-tetrahydronaphth-2-oic acid; Dab, L-2,4-diaminobutanoic acid; DCC, *N,N'*-dicyclohexylcarbodiimide; DCU, dicyclohexylurea; DMF, *N,N*-dimethylformamide; HOBT, 1*H*-benzotriazol-1-ol; MeMorph, *N*-methylmorpholine; TBTU, *O*-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate.

1. Syntheses of Turn-Inducing Mimics. – *8-(Hydroxyimino)-5,6,7,8-tetrahydronaphth-2-oic Acid* (**5**). To a soln. of 10.0 g (52.6 mmol) of 8-oxo-5,6,7,8-tetrahydronaphth-2-oic acid (**4a**) in 150 ml of MeOH, 158 ml of 0.5M NH_2OH/MeOH were added, and the resulting mixture was heated 2 h at 60°. After addition of 26.3 ml of 1N HCl, the brown mixture was concentrated *i.v.* to *ca.* 20 ml and diluted with H_2O and the oxime extracted with Et_2O. Drying (Na_2SO_4) and evaporation gave a brown solid (10.4 g) which on trituration with CH_2Cl_2 afforded 9.0 g (83.4%) of slightly beige crystals of **5**, pure by ^{1}H-NMR. For analysis, a sample was recrystallized from MeOH/H_2O. M.p. 235–237.5° (dec.). IR ((D$_6$)DMSO): 3160, 2940, 2870, 1700*s*, 1625, 1595, 1570, 1438, 1305, 1250*s*, 970*s*. ^{1}H-NMR (360 MHz, CD_3OD): 8.58 (*d*, 1 H); 7.86 (*dd*, 1 H); 7.26 (*d*, 1 H); 2.79 (*m*, 4 H); 1.85 (*m*, 2 H). Anal. calc. for $C_{11}H_{11}NO_3$ (205.21): C 64.38, H 5.41, N 6.83, O 23.39; found: C 64.35, H 5.45, N 6.72, O 23.52.

(RS)-8-Amino-5,6,7,8-tetrahydronaphth-2-oic Acid Hydrochloride (**1a**). A soln. of 10.26 g (50 mmol) of **5** in 200 ml of MeOH was hydrogenated over 3 g of 5% Pd/C at 25° and 4 bar H_2. The consumption of H_2 ceased after 5 h (95% of theor. amount). The crystalline product was dissolved by addition of 150 ml of 1N HCl, the catalyst filtered off, and the filtrate concentrated *i.v.* The crystalline **1a** was filtered off and the filtrate further concentrated: total 10.18 g (87.2%) of the pure **1a**. For analysis, a sample was recrystallized from MeOH/Et_2O. White needles. M.p. 293–295°. IR (KBr): 2919, 1693, 1598, 1574, 1519, 1402, 1333, 1239, 1205, 1181, 1130, 878, 767, 734, 629. ^{1}H-NMR (360 MHz, CD_3COOD): 8.23 (*d*, J = 1.85, 1 H); 7.98 (*dd*, J = 1.85, 8.37, 1 H); 7.32 (*d*, J = 8.37, 1 H); 4.75 (*t*, 1 H); 2.95 (*m*, 1 H); 2.85 (*m*, 1 H); 2.20 (*m*, 2 H); 2.05 (*m*, 1 H); 1.91 (*m*, 1 H). FAB-MS (pos.): 192 ([M + H]$^+$; M_{nom} for amino acid, 191). Anal. calc. for $C_{11}H_{13}NO_2 \cdot HCl \cdot {}^1/_3\, H_2O$ (233.69): C 56.61, H 6.32, Cl 15.19, N 6.00, O 15.87; found: C 56.54, H 6.35, Cl 15.23, N 5.97, O 16.03.

(RS)-8-(Acetylamino)-5,6,7,8-tetrahydronaphth-2-oic Acid (**1b**). A mixture of **1a** (500 mg, 2.14 mmol), pyridine (8.5 ml), and Ac_2O (8.5 ml) was stirred (Ar) at r.t. for 2.5 h and then evaporated. The residue was partitioned between AcOEt and 1M aq. Na_2CO_3, the aq. phase acidified with 2N HCl, and **1b** extracted into AcOEt. Drying (Na_2SO_4) and evaporation of the org. phase afforded a crystalline residue which on trituration with MeOH gave white crystals of **1b** (96.1%). For analysis, a sample was recrystallized from AcOEt. M.p. 260.7–262.7°. TLC (toluene/AcOH 10:3): R_f 0.20. IR ((D$_6$)DMSO): 3263, 2935, 1698*s*, 1664*s*, 1611, 1540*s*, 1434, 1373, 1261*s*, 1198, 1177, 984*s*, 771. ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 8.25 (*d*, J = 8.5, 1 H); 7.75 (*s*, 1 H); 7.70 (*dd*, J = 1.8, 8, 1 H); 7.20 (*d*, J = 8, 1 H); 4.97 (*ddd*, 1 H); 3.30 (*s*, 1 H); 2.78 (*m*, 2 H); 1.88 (*s*, 3 H); 1.87 (*m*, 2 H); 1.74 (*m*, 1 H); 1.65 (*m*, 1 H). Anal. calc. for $C_{13}H_{15}NO_3$ (233.27): C 66.94, H 6.48, N 6.01, O 20.58; found: C 66.97, H 6.56, N 5.90, O 20.64.

(RS)-8-(Acetylamino)-5,6,7,8-tetrahydro-N-isopropylnaphthalene-2-carboxamide (**1c**). A mixed anhydride, formed *in situ* in CH_2Cl_2 (8 ml) from **1b** (403 mg, 173 mmol) and an equivalent amount of isobutyl chloroformate (−15°, 40 min), was stirred at r.t. with 1.2 equiv. of (i-Pr)NH_2. After 3 h, another 0.4 equiv. of (i-Pr)NH_2 were added, and stirring was continued for 1 h. The resulting mixture was diluted with more CH_2Cl_2, washed with 1N HCl and 8% aq. $NaHCO_3$ soln., dried (Na_2SO_4), and evaporated: 423 mg (89.1%) of **1c**. Colorless crystals. M.p. 224–225.5° ($CHCl_3$/Et_2O). For X-ray analysis, well-developed crystals (white needles, m.p. 227.1–228.1°) were obtained by recrystallization from MeOH/H_2O. TLC (CH_2Cl_2/MeOH 9:1): R_f 0.54. IR (CH_2Cl_2): 3433, 2932, 1659*s*, 1518*s*, 1491*s*, 1457, 1370. IR ((D$_6$)DMSO): 3488, 3273, 2970, 2245, 1662*s*, 1646*s*, 1540*s*, 1495, 1458, 1372, 1283, 989; no significant signs of intramolecular H-bridge. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.58 (*s*, 1 H); 7.53 (*dd*, J = 1.5, 8, 1 H); 7.09 (*d*, J = 8, 1 H); 6.09 (*d*, J = 8, 1 H); 6.04 (*d*, J = 8, 1 H); 5.14 (*m*, 1 H); 4.23 (*dq*, 1 H); 2.78 (*m*, 2 H); 1.98 (*m*, 1 H); 2.03 (*s*, 3 H); 1.82 (*m*, 3 H); 1.23 (2*d*, J = 6.5, 6 H). ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 8.20 (*d*, J = 8.5, 1 H); 8.11 (*d*, J = 8, 1 H); 7.67 (*s*, 1 H); 7.64 (*dd*, J = 8, 1.5, 1 H); 7.14 (*d*, J = 8, 1 H); 4.97 (*m*, 1 H); 4.07 (*dq*, 1 H); 2.75 (*m*, 2 H); 1.86 (*s*, 3 H); 1.84 (*m*, 2 H); 1.68 (*m*, 2 H); 1.15 (2*d*, J = 7, 6 H). Anal. calc. for $C_{16}H_{22}N_2O_2$ (274.36): C 70.04, H 8.08, N 10.21 O 11.66; found: C 69.99, H 8.13, N 10.11, O 11.55.

(RS)-8-{[(Fluoren-9-yl)methoxycarbonyl]amino}-5,6,7,8-tetrahydronaphth-2-oic Acid (**1d**). To a suspension of 234 mg (1 mmol) of **1a** in 5 ml of CH_2Cl_2 and 1.7 ml of 1M Et_3N in CH_2Cl_2, 340 µl (2.7 mmol) of Me_3SiCl, followed by another 2 ml of 1M Et_3N in CH_2Cl_2 were added. The mixture was refluxed for 30 min. At r.t., a soln. of 354 mg (1.05 mmol) of *N*-{[(fluoren-9-yl)methyloxycarbonyl]oxy}succinimide in 2 ml of CH_2Cl_2 was dropwise added and the mixture stirred for 2.5 h. After evaporation, the solid residue was triturated with 5 ml of 0.5N aq. HCl and the white, crystalline **1d** filtered off, washed with more 0.5N HCl and with H_2O, and dried *i.v.*: 406 mg. M.p. 244–245° (dec.). For analysis, a sample was crystallized from hot toluene/AcOH 10:3. Very fine, white needles. M.p. 253.5–254.5° (dec.). TLC (toluene/AcOH 10:3, UV detection): R_f 0.52. IR (KBr): 3400 (br.), 3290, 2960, 1705 (sh), 1697*s*, 1683*s*, 1614, 1577, 1532 (br.), 1450, 1297, 1250 (br.), 1080, 760, 740. ^{1}H-NMR (400 MHz, (D$_6$)DMSO, 40°): 7.87 (*s*, 1 H); 7.85 (*s*, 2 H); 7.72 (*dd*, 3 H); 7.40 (*t*, J = 7.5, 2 H); 7.33 (*dd*, J = 7.5, 2 H); 7.20 (*d*, J = 7.5, 1 H); 4.73 (*m*, 1 H); 4.37 (*m*, 2 H); 4.26 (*m*, 2 H); 3.20 (HOD); 2.77 (*m*, 2 H); 1.92 (*m*, 2 H); 1.73 (*m*, 2 H). Anal. calc. for $C_{26}H_{23}NO_4$ (413.47): C 75.53, H 5.61, N 3.39, O 15.48; found: C 75.22, H 5.64, N 3.36, O 15.57.

(RS)-8-[(tert-Butoxy)carbonylamino]-5,6,7,8-tetrahydronaphth-2-oic Acid (**1e**). To a suspension of 234 mg (1 mmol) of **1a** in 2.0 ml of 1M Na_2CO_3 and 1 ml of dioxane, a soln. of 270 mg (1.25 mmol) of di(*tert*-butyl) dicarbonate (*Fluka*) in 1.5 ml of dioxane was dropwise added. The resulting mixture was mechanically shaken at r.t. overnight. An excess of 10% aq. citric acid was added and the suspension again shaken for another h. The white, crystalline product was filtered off and washed with H_2O: 243 mg (83.4%). M.p. 206–208° (dec.). For analysis, a sample was recrystallized from hot AcOEt. Fine, short needles. M.p. 213.0-213.5° (dec.). TLC (toluene/AcOH 10:3; UV and ninhydrine detection): R_f 0.52. IR (KBr): 3400 (br.), 3300, 2965, 2920, 1698 (sh), 1690*s*, 1681*s*, 1672*s*, 1607, 1570, 1512 (br.), 1358, 1290, 1241, 1178–1160, 1061. ^{1}H-NMR (400 MHz, CD_3COOD, 60°): 8.05 (*s*, 1 H); 7.84 (*dd*, *J* = 8, 1.8, 1 H); 7.18 (*d*, *J* = 8, 1 H); 4.84 (*m*, 1 H); 2.83 (*m*, 1 H); 2.07 (*m*, 1 H); 1.93 (*m*, 1 H); 1.83 (*m*, 2 H); 1.52 (*s*, 9 H). Anal. calc. for $C_{16}H_{21}NO_4$ (291.35): C 65.96, H 7.27, N 4.81, O 21.97; found: C 65.84, H 7.23, N 4.85, O 22.04.

Methyl 5,6,7,8-Tetrahydro-8-oxonaphth-2-oate (**4b**). a) At 0°, **4a**, [7] (20 g) was esterified in MeOH (150 ml) by adding 2.5% CH_2N_2/Et_2O, until a permanent, slight excess of the reagent was reached. Evaporation and flash chromatography (FC; 1 kg of *Merck 60* silica gel, toluene/AcOEt 9:1) followed by crystallization from CH_2Cl_2/Et_2O/pentane afforded 15.4 g (71.7%) of **4b**. Yellowish crystals. M.p. 74–75°. For analysis, a sample was recrystallized from hot cyclohexane. Yellowish, rhombic crystals. M.p. 75.8–76.5°. TLC (toluene/AcOEt 9:1): R_f 0.34. IR (CH_2Cl_2): 2870, 1680*s*, 1645*s*, 1570*s*, 1390, 1370 (sh), 1266*s*, 1202, 1180, 1153, 1140, 1090, 1070. ^{1}H-NMR (360 MHz, CD_3OD): 8.56 (*d*, *J* = 1.85, 1 H); 8.12 (*dd*, *J* = 1.85, 7.9, 1 H); 7.45 (*d*, *J* = 7.9, 1 H); 3.93 (*s*, 3 H); 3.07 (*t*, *J* = 6, 2 H); 2.68 (*t*, *J* = 6, 2 H); 2.15 (*q*, *J* = 6, 2 H). Anal. calc. for $C_{12}H_{12}O_3$ (204.23): C 70.57, H 5.92, O 23.50; found: C 70.64, H 5.98, O 23.48.

b) Oxo-acid **4a** (285 g) was esterified by refluxing its soln. in MeOH (2.8 l) containing conc. H_2SO_4 (50 g). Usual workup after 8 h afforded crude, partially solid, dark-colored ester which was decolorized in CH_2Cl/hexane on charcoal and further purified by crystallization and LC of the mother liquor (silica gel, CH_2Cl_2/hexane 1:1): 280.7 g (91.6%) of **4b**. M.p. 76–77°.

Methyl (E/Z)-8-(Methoxymethylidene)-5,6,7,8-tetrahydronaphth-2-oate (**6**). To a soln. of the phosphorane prepared *in situ* from 28.2 g (82 mmol) of (methoxymethyl)triphenylphosphonium chloride in 350 ml of abs. Et_2O and 47 ml (75.2 mmol) of 1.6M BuLi in hexane, a soln. of 7.0 g (34.27 mmol) of **4b** in 170 ml of abs. Et_2O was dropwise added at −30°. After another 30 min at −30°, the red mixture was stirred for 60 min at r.t. Washing with 8% aq. $NaHCO_3$ soln. and evaporation of the dried (Na_2CO_3) org. phase afforded an oily residue, which was submitted to FC (1.5 kg of *Merck 60* silica gel, toluene/AcOEt 9:1): oily **6** (5.6 g, 70.3%), (*E*)/(*Z*), 3:1 (by ^{1}H-NMR). TLC (toluene/AcOEt 9:1): R_f 0.53 (single spot). IR (CH_2Cl_2): 2940, 2865, 2840, 1722 (sh), 1712*s*, 1643, 1607, 1561, 1435, 1420 (sh), 1318, 1295, 1221*s*, 1130, 1112, 1070, 1041. ^{1}H-NMR (400 MHz, $CDCl_3$): (*E*)-**6**: 8.05 (*s*, 1 H); 7.68 (*dd*, *J* = 1.9, 8, 1 H); 7.11 (*d*, *J* = 8, 1 H); 6.74 ('*t*', partially overlapping with the *cis* signal, 1 H); 3.90 (*s*, 3 H); 3.77 (*s*, 3 H); 2.76 (*t*, *J* = 6.2, 2 H); 2.53 (*m*, 2 H); 1.78 (*q*, 2 H); (*Z*)-**6**: 8.05 (*s*, 1 H); 7.72 (*dd*, *J* = 2, 8, 1 H); 7.13 (*d*, *J* = 8, H); 6.75 ('*t*', partially overlapping with the *trans* signal, 1 H); 3.89 (*s*, 3 H); 3.77 (*s*, 3 H); 2.87 (*t*, *J* = 6.4, 2 H); 2.30 (*m*, 2 H); 1.86 (*q*, 2 H). Anal. calc. for $C_{14}H_{16}O_3$ (232.28): C 72.40, H 6.95, O 20.67; found: C 72.19, H 6.81, O 20.70.

Methyl (RS)-8-Formyl-5,6,7,8-tetrahydronaphth-2-oate (**7**). To the soln. of **6** (3.0 g, 12.9 mmol) in 250 ml of 0.05M NaI in MeCN, Me_3SiCl (1.56 ml, 12.9 mmol) was added dropwise at r.t. within 5 min (Ar). After another 5 min of stirring at r.t., the mixture was diluted with Et_2O and washed with an 0.5N $Na_2S_2O_3$. The aq. phase was reextracted with Et_2O and the org. phase dried (Na_2SO_4) and evaporated: 2.8 g of crude oil. FC (160 g of *Merck 60* silica gel, toluene/AcOEt 97:3) gave 2.1 g (74.5%) of **7**. Yellowish oil. TLC (toluene/AcOEt 9:1) R_f 0.42. IR (CH_2Cl_2): 2950, 2861, 2840, 1722*s*, 1610, 1570, 1495, 1435, 1420 (sh), 1310, 1285–1250 (br.), 1205, 1197, 1140, 1129, 1110. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.71 (*d*, *J* = 1.5, 1 H); 7.87 (*dd*, *J* = 1.7, 8.5, 1 H); 7.86 ('*s*', 1 H); 7.22 (*d*, *J* = 8.5, 1 H); 3.90 (*s*, 3 H); 3.65 ('*t*', *J* = 5.5, 1 H); 2.82 (*t*, *J* = 6.4, 2 H); 2.29 (*m*, 1 H); 1.95 (*m*, 1 H); 1.84 (*m*, 1 H); 1.75 (*m*, 1 H).

Methyl (RS,E/Z)-5,6,7,8-Tetrahydro-8-[(hydroxyimino)methyl]naphth-2-oate (**8**). To a soln. of 6.4 g of **7** (29.32 mmol) in 150 ml of MeOH, 60 ml of 0.5M NH_2OH/MeOH was dropwise added at r.t. over 10 min. After another h at r.t., the mixture was evaporated, the residue dissolved in CH_2Cl_2, and the org. phase washed with H_2O and sat. NaCl soln., dried (Na_2SO_4), and evaporated: 6.93 g of slowly crystallizing oil. LC (250 g of silica gel, toluene/AcOEt 9:1): **8** (5.2 g, 76%), (*E*)/(*Z*) 65:35 (by ^{1}H-NMR). M.p. 84–87°. TLC (toluene/AcOEt 4:1): 2 spots, R_f 0.36 and 0.30. IR (CH_2Cl_2): 3560, 3300 (br.), 3025, 2955, 2862, 1720*s*, 1610, 1570, 1496, 1430 (br.), 1310, 1290–1250 (br.), 1200, 1170, 1130, 1109, 1082, 947, 915. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.82 (*s*, 1 H); 7.79 ('*d*', 1 H); 7.46 (*d*, *J* = 7.6, 1 H); 7.18 (*d*, *J* = 7.6, 1 H); 6.80 (br., 1 H); 4.56, 3.75 (2*q*, together 1 H); 3.89 (*s*, 3 H); 2.86 (*m*, 2 H); 2.1–1.7 (4*m*, 4 H). Anal. calc. for $C_{13}H_{15}NO_3$ (233.27): C 66.94, H 6.48, N 6.01, O 20.58; found: C 66.57, H 6.53, N 6.01, O 20.34.

Methyl (RS)-8-(Aminomethyl)-5,6,7,8-tetrahydronaphth-2-oate Hydrochloride (**2a**). a) *From* **8**. A soln. of **8** (1.50 g, 6.43 mmol) in MeOH (140 ml) containing excess HCl (added as 24% soln. in MeOH, 2.8 ml) was hydrogenated, after addition of 330 mg of 5% Pd/C, at 25° and at 1 atm. H_2. After 20 h, the H_2 consumption stopped (92.5% of theor. amount), the catalyst was filtered off, washed with MeOH, and the combined filtrates were evaporated: white crystals. Crystallization from MeOH/Et_2O afforded, in two crops, a total of 1.30 g (75.1%) of **2a**. White needles. M.p. 228–230°. TLC (AcOH/BuOH/H_2O 1:3:1): R_f 0.48. IR (KBr): 3437 (br.), 2952 (br.), 1724, 1610, 1595 (sh), 1570, 1495, 1437, 1317, 1284, 1270, 1240, 1201, 1167, 1126, 1105, 1007, 974, 909, 857, 811, 763. ^{1}H-NMR (400 MHz, CD_3OD): 7.92 (*d*, *J* = 1.7, 1 H); 7.79 (*dd*, *J* = 1.7, 8, 1 H); 7.24 (*d*, *J* = 8, 1 H); 4.83 (*s*, OH); 3.88 (*s*, 3 H); 3.27–3.22 (2*m*, 2 H); 3.12 (*m*, 1 H); 2.87 (*m*, 2 H); 2.05–1.78 (*m*, 4 H). Anal. calc. for $C_{13}H_{18}ClNO_2 \cdot {}^3/_4 H_2O$ (269.26): C 58.03, H 7.29, N 5.21, O 16.28, H_2O 4.93; found: C 58.38, H 7.37, N 5.20, O 16.08, H_2O 5.26.

b) *From* **10** (see below). Nitrile **10** (36.8 g, 172.6 mmol) was hydrogenated in MeOH (2 l) containing 4N HCl (44 ml), in the presence of PtO_2 (3.7 g; 22°, H_2 *ca.* 5 atm). The H_2 consumption ceased after 5 h (102% of theor. amount). Usual workup and repeated crystallization from MeOH/Et_2O gave 28.3 g (60.9%) of the pure **2a**. M.p. 229–230° (dec.).

Methyl (RS)-8-[(Acetylamino)methyl]-5,6,7,8-tetrahydronaphth-2-oate (**2b**). As described for **1b**, with **2a** (1.07 g, 4 mmol), Ac_2O (15 ml), and pyridine (15 ml; 4 h, r.t.). Washing with 0.5N HCl, 8% aq. NaHCO soln., and brine. The oily, slowly crystallizing residue was triturated with pentane and the crystalline product (1.0 g, white needles) recrystallized from MeOH/Et_2O/pentane: 890 mg (85.7%). Fine needles. M.p. 105.8–106.8°. TLC ($CHCl_3$/MeOH 9:1): R_f 0.52. IR (CH_2Cl_2): 3460, 2950, 1712*s*, 1680*s*, 1617, 1578, 1520 (br.), 1441, 1290–1255 (br.), 1202, 1130, 1110. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.88 (*d*, *J* = 1.5, 1 H); 7.78 (*dd*, *J* = 1.5, *ca.* 8, 1 H); 7.14 (*d*, *J* = 8, 1 H); 5.67 (br. *s*, 1 H); 3.88 (*s*, 3 H); 3.50 (*m*, 2 H); 3.03 (*m*, 1 H); 2.79 (*m*, 2 H); 1.99 (*s*, 3 H); 1.80 (*m*, 4 H). Anal. calc. for $C_{15}H_{19}NO_3$ (261.31): C 68.94, H 7.33, N 5.36, O 18.37; found: C 68.64, H 7.31, N 5.36, O 18.37.

(RS)-8-[(Acetylamino)methyl]-5,6,7,8-tetrahydronaphth-2-oic Acid (**2c**). At r.t., **2b** (650 mg, 2.49 mmol) was hydrolyzed in dioxane (20 ml) and H_2O (11 ml) with 2.7 ml of aq. 1N NaOH (18 h). The mixture was diluted with H_2O and extracted with CH_2Cl_2, the alkaline aq. phase acidified with 3 ml of 1N H_2SO_4, and **2c** extracted into AcOEt. Drying (Na_2SO_4) and evaporation afforded 610 mg (99%) of white needles. M.p. 222–222.5°. For analysis, a sample was recrystallized from MeOH/pentane. M.p. 224–225.5°. TLC ($CHCl_3$/MeOH 9:1, with 0.4% AcOH): R_f 0.27. IR (KBr): 3400 (sh), 3280 (br.), 3080, 2940, 2865, 1690 (sh), 1682*s*, 1640, 1610, 1572, 1432, 1421, 1375, 1289, 1276, 1232, 1202, 1194, 1131, 762. ^{1}H-NMR (200 MHz, (D_6)DMSO): 12.73 (*s*, 1 H); 8.08 (*t*, 1 H); 7.80 ('*s*', 1 H); 7.68 (*dd*, *J* ≈ 1.5, 8, 1 H); 7.18 (*d*, *J* ≈ 8, 1 H); 3.33 (*m*, 1 H); 3.07 (*m*, 1 H); 2.94 (*m*, 1 H); 2.77 (*m*, 2 H); 1.84 (*s*, 3 H); 1.75 (*m*, 4 H). Anal. calc. for $C_{14}H_{17}NO_3$ (247.29): C 68.00, H 6.93, N 5.66, O 19.41; found: C 67.87, H 6.88, N 5.69, O 19.42.

(RS)-8-[(Acetylamino)methyl]-5,6,7,8-tetrahydro-N-isopropylnaphth-2-amide (**2d**). To a suspension of **2c** (470 mg, 1.90 mmol) in CH_2Cl_2 (14 ml) containing MeMorph (250 µl, 1.2 equiv.), isobutyl chloroformate (95% pure; 275 µl, 1.05 equiv.) was added at −15°. After 20 min at −15°, (i-Pr)NH_2 (250 µl, 1.5 equiv.) was dropwise introduced. The resulting mixture was stirred at r.t. for 4 h. Then more CH_2Cl_2 was added, the org. phase washed with 1N HCl, 8% $NaHCO_3$ soln., and brine, dried (Na_2SO_4), and evaporated, and the oily residue triturated with Et_2O/pentane: 430 mg (78.5%) of white crystals. Recrystallization from CH_2Cl_2/Et_2O gave 320 mg of **2d**. Fine needles. M.p. 153.5–154.5°. TLC ($CHCl_3$/MeOH 9:1): R_f 0.44. IR (CH_2Cl_2): 3441, 3335, 2970, 2935, 1670 (sh), 1656*s*, 1610, 1570, 1519*s*, 1490, 1457, 1368, 1327, 1280–1255 (br.), 1197; no convincing evidence for an intramolecular H-bridge. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.64 (*d*, *J* ≈ 1.5, 1 H); 7.53 (*dd*, *J* ≈ 1.5, 8, 1 H); 7.13 (*d*, *J* ≈ 8,1 H); 6.16 (br. *d*, 1 H); 5.70 (br. *s*, 1 H); 4.27 (*m*, 1 H); 3.64 (*m*, 1 H); 3.48 (*m*, 1 H); 3.03 (*m*, 1 H); 2.79 (*m*, 2 H); 1.96 (*s*, 3 H); 1.87 (*m*, 2 H); 1.74 (*m*, 2 H); 1.26 (2*d*, 6 H); no convincing evidence for an intramolecular H-bridge on concentration or temp. changes. Anal. calc. for $C_{17}H_{24}N_2O_2$ (288.38): C 70.80, H 8.39, N 9.72, O 11.10; found: C 70.77, H 8.41, N 9.75, O 11.11.

Methyl (RS)-8-[(Benzyloxycarbonylamino)methyl]-5,6,7,8-tetrahydronaphth-2-oate (**2e**). To a soln. of 807 mg (3.0 mmol) of **2a** in 8 ml of dioxane and 4 ml of H_2O, 1.5 ml of 2N aq. NaOH were added, followed, at 5°, by 520 µl (*ca.* 3.3 mmol) of benzyl chloroformate (*Fluka*; 90%). The pH of the mixture was maintained at 8–9 by adding more 2N NaOH. After 80 min at 5°, the mixture was diluted with AcOEt and successively washed with 10% aq. citric acid soln., 8% aq. $NaHCO_3$ soln., and brine. Drying (Na_2SO_4) and evaporation gave 1.06 g of an oily, slowly crystallizing residue which was recrystallized from MeOH/Et_2O/pentane: 930 mg (87.7%) of **2e** (in 2 crops). Small, white needles. M.p. 95.1–95.6°. TLC (toluene/AcOEt 4:1): R_f 0.49. IR (CH_2Cl_2): 3445, 2942, 1720*s*, 1611, 1512*s*, 1452, 1435, 1282–1240 (br.), 1220, 1200, 1135, 1126, 1104. ^{1}H-NMR (60 MHz, $CDCl_3$): 7.78 ('*s*', 1 H); 7.70 (*dd*, *J* = 8, 1.7, 1 H); 7.26 ('*s*', 5 H); 7.05 (*d*, *J* = 8, 1 H); 5.03 (*s*, 2 H); 3.81 (*s*, 3 H); 3.42 (*m*, 2 H); 3.20–2.50 (2*m*,

3 H); 1.76 (*m*, 4 H). Anal. calc. for $C_{21}H_{23}NO_4$ (353.42): C 71.37, H 6.56, N 3.96, O 18.11; found: C 71.20, H 6.55, N 4.07, O 18.08.

*Methyl (*RS*)-8-[(Benzoylamino)methyl]-5,6,7,8-tetrahydronaphth-2-oate* (**2f**). As described for **2e**, with **2a** (803 mg, 3 mmol), dioxane/H_2O 2:1 (12 ml), benzoyl chloride (385 µl, 3.3 mmol), and NaOH (r.t., pH 8–9). Crystallization from MeOH/Et_2O afforded 590 mg (61.5%) of **2f**. Shiny needles. M.p. 139–140°. TLC (toluene/AcOEt 4:1): R_f 0.30. IR (CH_2Cl_2): 3450, 2940, 1715*s*, 1662*s*, 1610, 1602, 1580, 1520*s*, 1487, 1440, 1434, 1280–1200 (br.), 1195, 1136, 1126, 1104. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.95 (*d*, $J \approx 1.5$, 1 H); 7.80 (*dd*, $J \approx 1.5$, 8, 1 H); 7.76 (*m*, 2 H); 7.46 (*m*, 3 H); 7.18 (*d*, $J \approx 8$, 1 H); 6.3 ('*s*', 1 H); 3.86 (*s*, 3 H); 3.71 (*t*, $J = 6$, 2 H); 3.19 (*m*, 1 H); 2.82 (*m*, 2 H); 1.87 (*m*, 4 H). Anal. calc. for $C_{20}H_{21}NO_3$ (323.39): C 74.28, H 6.55, N 4.33, O 14.84; found: C 74.16, H 6.57, N 4.37, O 14.91.

*Methyl (*RS*)-8-{[(*tert*-Butoxy)carbonylamino]methyl}-5,6,7,8-tetrahydronaphth-2-oate* (**2g**). To a soln. of 25 g (95.5 mmol) of **2a** in 240 ml of dioxane and 120 ml of H_2O, 50 ml of 2N aq. NaOH were added at 5° followed by 23.1 (*ca.* 106 mmol) of di(*tert*-butyl)dicarbonate in 70 ml of dioxane. After several min of stirring at r.t., the crystalline **2g** started to separate. After a total of 2.5 h, it was extracted into Et_2O and the org. phase successively washed with 10% aq. citric acid soln., 8% aq. $NaHCO_3$ soln., and brine, dried, and concentrated. The separating crystals were filtered off and washed with hexane/i-PrOH 4:1. The filtrate was concentrated again and afforded, on treatment with hexane/i-PrOH 4:1, a second crop of pure **2g**; total 28.8 g (94.4%). White needles. M.p. 151.0–152.1°. For analysis, a sample was recrystallized from MeOH/Et_2O/pentane (no change of m.p.). TLC (toluene/AcOEt 4:1): R_f 0.48. IR (CH_2Cl_2): 3452, 2980, 2940, 1720 (sh), 1713*s*, 1610, 1573, 1508*s*, 1452, 1437, 1390, 1368, 1285–1250 (br.), 1195, 1170, 1127, 1107. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.88 ('*s*', 1 H); 7.78 (*dd*, $J = 8$, 1.7, 1 H); 7.15 (*d*, $J = 8$, 1 H); 4.62 (br. *s*, 1 H); 3.89 (*s*, 3 H); 3.46 (*m*, 1 H); 3.32 (*m*, 1 H); 2.80 (*m*, 2 H); 1.85 (*m*, 4 H); 1.47 (*s*, 9 H). Anal. calc. for $C_{18}H_{25}NO_4$ (319.40): C 67.69, H 7.89, N 4.39, O 20.04; found: C 67.61, H 7.82, N 4.45, O 19.94.

Chromatographic Resolution of Racemic **2g**. For the preparation of the chiral stationary phase (*m*-methylbenzoyl cellulose) and of the anal. HPLC columns, see [8b]. The prep. column (glass column 5 cm i.d. ×75 cm; *Büchi AG*, Flawil, Switzerland) was slurry-packed with a suspension of 550 g of *m*-methylbenzoyl-cellulose beads in hexane/i-PrOH 9:1. The glass column was topped with a column of the same dimension as a reservoir. After decantation of the material in the column, the reservoir was taken away and the stationary phase washed by pumping the eluent through the column equipped with an inlet plunger, at a flow rate of 60 ml/min until no more absorption was detected in UV at 254 nm. For anal. resolutions, a HPLC column (0.46 cm i.d. ×25 cm) was used with MeOH as mobile phase (separation and resolution factors, 1.49 and 2.06, resp.). For the prep. separation, a soln. of 1 g of racemate **2g** in 175 ml of hexane/i-PrOH 6:4 was injected repetitively and eluted with hexane/i-PrOH 8:2 (flow-rate 25 ml/min, run time *ca.* 6 h): (+)-(*S*)-**2g** followed by (−)-(*R*)-**2g**.

(+)-(*S*)-**2g**: M.p. 88.4–89.4° (Et_2O/pentane). $[\alpha]_D^{20} = +2.4 \pm 1$, $[\alpha]_{546} = +2.0 \pm 1$, $[\alpha]_{436} = -4.2$, $[\alpha]_{365} = -29.1$ ($c = 1$, $CHCl_3$). Anal. calc. for $C_{18}H_{25}NO_4$ (319.40): C 67.69, H 7.89, N 4.39; found: C 67.54, H 7.84, N 4.48.

(−)-(*R*)-**2g**: M.p. 87–88.9° (Et_2O/pentane). $[\alpha]_D^{20} = -2.8 \pm 1$, $[\alpha]_{546} = -2.2 \pm 1$; $[\alpha]_{436} = +4.8$, $[\alpha]_{365} = +29.2$ ($c = 1$, $CHCl_3$). Anal. calc. for $C_{18}H_{25}NO_4$ (319.40): C 67.69, H 7.89, N 4.39; found: C 67.83, H 7.73, N 4.38.

*(*R*)-8-{[(*tert*-Butoxy)carbonylamino]methyl}-5,6,7,8-tetrahydronaphth-2-oic Acid* ((*R*)-**2h**). A soln. of 2.50 g (7.83 mmol) of (*R*)-**2g** in 55 ml of dioxane, 8 ml of H_2O, and 4.0 ml of aq. 1N NaOH was stirred at r.t. for 15 min, whereafter another 8.0 ml of 1N NaOH were added (turbid→clear after 5 h). After 23 h, the mixture was diluted with 30 ml of H_2O, and dioxane was partially evaporated. Acidification with 1N H_2SO_4 liberated the title acid, which was extracted into AcOEt, and, after evaporation of the solvent, recrystallized from MeOH/Et_2O/pentane: 2.26 g (94.5%) of colorless, rhomboid crystals (in 2 crops). M.p. 163.5–165.0°. TLC ($CHCl_3$/MeOH/AcOH 90:10:0.4): R_f 0.45. ^{1}H-NMR (200 MHz, (D_6)DMSO): 12.75 (*s*, 1 H); 7.78 ('*s*', 1 H); 7.65 (*dd*, 1 H); 7.15 (*d*, 1 H); 7.08 (*t*, 1 H); 3.16 (*m*, 1 H); 2.98 (*m*, 2 H); 2.78 (*m*, 2 H); 1.74 (*m*, 4 H); 1.37 (*s*, 9 H). Anal. calc. for $C_{17}H_{23}NO_4$ (305.37): C 66.86, H 7.59, N 4.59, O 20.96; found: C 66.96, H 7.52, N 4.75, O 20.78.

*(+)-Camphor-10-sulfonate (*S*)-***2i*** *of Methyl (*S*)-8-(Aminomethyl)-5,6,7,8-tetrahydronaphth-2-oate.* Enantiomer (*S*)-**2g** (244 mg, 0.764 mmol) was stirred at r.t. in 25 ml of CF_3COOH. After 1 h, the soln. was evaporated, finally with added toluene, the residue dissolved in 1 ml of MeOH, and a soln. of dry HCl in Et_2O added at +5°. The precipitated hydrochloride was filtered off and washed with Et_2O. Its soln. in CH_2Cl_2 was shaken with 8% aq. $NaHCO_3$ soln., the free amino ester thus obtained (130 mg) dissolved in Et_2O (10 ml), and a soln. of 148 mg of (+)-camphor-10-sulfonic acid monohydrate in 1 ml of MeOH added. Another 10-ml portion of Et_2O was introduced to complete the separation of the crystalline salt. The latter was filtered off and recrystallized twice from acetone: 136 mg of (*S*)-**2i**. M.p. 147°. $[\alpha]_D^{20} = +24.4 \pm 0.9$ ($c = 1.023$, $CHCl_3$). Anal. calc. for $C_{23}H_{33}NO_6S \cdot 1H_2O$ (469.58): C 58.82, H 7.51, N 2.98, S 6.83; found: C 59.13, H 7.44, N 3.05, S 6.83.

The X-ray analysis showed this salt to be that of the (*S*)-enantiomer of **2**.

Methyl 8-Cyano-5,6-dihydronaphth-2-oate (**10**). To a soln. of 20.4 g (100 mmol) of **4b** in 160 ml of toluene, 182 ml (200 mmol) of 1.1M diethylaluminium cyanide in toluene (*Aldrich*), diluted with 40 ml of toluene, was dropwise added under Ar while keeping the temp. at −25 to −20°. After 1.5 h at −15°, the resulting suspension was slowly transferred by Ar pressure into a mixture of 750 ml of MeOH and 450 ml of conc. HCl soln. stirred at −70° (strongly exothermic reaction). After another h of stirring at −70°, the suspension was poured onto 1.8 l of ice-water and 600 ml of conc. HCl soln. and the product extracted into CH_2Cl_2. After washing the extract with H_2O and drying (Na_2SO_4), the solvent was evaporated (160 mg of TsOH was added to suppress dec.): 21.6 g (93.4%) of cyanohydrine **9**. IR (CH_2Cl_2): 3560, 3400, 2940, 2225*w*, 1715*s*, 1608, 1570, 1429, 1280, 1245 (sh), 1190, 1160, 1130, 1117, 1101, 1085, 1015, 980, 960, 910, 860. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.41 (*d*, $J \approx 1.5$, 1 H); 7.96 (*dd*, $J \approx 1.5$, 8, 1 H); 7.25 (*d*, $J \approx 8$, 1 H); 3.92 (*s*, 3 H); 3.13 (*s*, 1 H); 2.89 (*m*, 2 H); 2.34 (*m*, 2 H); 2.04 (*m*, 2 H).

Cyanohydrine **9** (21.31 g, 92.1 mmol) was thoroughly mixed with $KHSO_4$ (10.65 g) and the mixture heated, with stirring, 1 h at 150° (bath). The cooled mixture was partitioned between CH_2Cl_2 and H_2O, the org. phase dried (Na_2SO_4) and evaporated, and the crystalline residue submitted to FC (650 g of silica gel, toluene/AcOEt 4:1). Some **4b** (*ca.* 2 g) was isolated from the last chromatographic fractions. The collected **10** was crystallized from CH_2Cl_2/EtO in several crops: 16.55 g (84.2%). Colorless crystals. M.p. 88.2–88.7°. TLC ($CHCl_3$ with 1% EtOH): R_f 0.50. IR (CH_2Cl_2): 2940, 2880, 2810, 2208, 1710*s*, 1615, 1598, 1430, 1361, 1322, 1292, 1280, 1235 (sh), 1220, 1183, 1100, 1010, 911, 830. ^{1}H-NMR (360 MHz, $CDCl_3$): 8.08 (*d*, 1 H); 7.95 (*dd*, 1 H); 7.22 (*d*, 1 H); 6.96 (*t*, 1 H); 3.93 (*s*, 3 H); 2.92 (*t*, 2 H); 2.55 (*m*, 2 H). Anal. calc. for $C_{13}H_{11}NO_2$ (213.24): C 73.23, H 5.20, N 6.57; found: C 73.27, H 5.28, N 6.61.

Methyl 8-Cyanonaphth-2-oate (**11**). A soln. of **10** (1.066 g, 5 mmol) and DDQ (3.4 g, 15 mmol) in dioxane (50 ml) was heated under Ar in a pressure bottle at 120° (bath temp.). After 14 h, the brown mixture was filtered through a cake of *Merck* silica gel which was washed with CH_2Cl_2. The material obtained by evaporation of the combined filtrates was chromatographed (silica gel (200 g), CH_2Cl_2) to give 990 mg (93.7%) of **11**. Crystallization from CH_2Cl_2/Et_2O/pentane yielded 875 mg (83%) of fine, off-white needles. M.p. 136.1–136.3°. TLC ($CHCl_3$ with 1% EtOH): R_f 0.55. ^{1}H-NMR (360 MHz, $CDCl_3$): 8.97 (*d*, 1 H); 8.22 (*dd*, 1 H); 8.11 (*d*, 1 H); 7.99 (2 *d*, 2 H); 7.65 (*t*, 1 H); 4.03 (*s*, 3 H). Anal. calc. for $C_{13}H_9NO_2$ (211.21): C 73.92, H 4.29, N 6.63, O 15.15; found: C 73.58, H 4.34, N 6.74, O 15.15.

Methyl 8-(Aminomethyl)naphth-2-oate Hydrochloride (**3a**). Nitrile **11** (100.6 g, 476 mmol) was hydrogenated in MeOH (6 l) in the presence of 4N HCl (120 ml) and of 10% Pd/C catalyst (20 g; 23°, 5 atm H_2). In 18 h, 97.2% of the theor. amount of H_2 was consumed. The usual workup and crystallization from MeOH/Et_2O gave 109 g (91%) of **3a**. White, fine needles. M.p. 254–256°. TLC (AcOH/BuOH/H_2O 1:3:1): R_f 0.65. IR (KBr): 3400, 2945 (br.), 2680, 2640, 1715, 1627, 1595, 1570, 1535, 1470, 1458, 1385, 1337, 1285, 1185, 1120, 1050, 1010, 880, 840, 791, 762. ^{1}H-NMR (360 MHz, CD_3OD): 8.82 ('*s*', 1 H); 8.12 (*dd*, 1 H); 8.06 (*d*, 1 H); 8.04 (*d*, 1 H); 7.75 (*d*, 1 H); 7.69 (*t*, 1 H); 4.80 (*s*, 3 H); 4.70 (*s*, 2 H); 4.00 (*s*, 3 H). Anal. calc. for $C_{13}H_{14}ClNO_2$ (251.71): C 62.03, H 5.61, N 5.57, O 12.71; found: C 62.08, H 5.57, N 5.57, O 12.75.

Methyl 8-[(Acetylamino)methyl]naphth-2-oate (**3b**). As described for **1b**, with **3a** (1.007 g, 4 mmol), Ac_2O (15 ml), and pyridine (15 ml; 3.5 h, r.t.). Evaporation at 40° (bath) and washing with 10% aq. citric acid soln., 8% aq. $NaHCO_3$ soln., and brine. The slowly crystallizing residue gave, on treatment with Et_2O/pentane, 980 mg (95.2%) of fine, white needles, m.p. 145.5–146.5°. It was recrystallized from CH_2Cl_2/Et_2O/pentane: 830 mg of **3b**. Long, fine needles. M.p. unchanged. TLC ($CHCl_3$/MeOH 9:1): R_f 0.53. IR (CH_2Cl_2): 3435, 3040, 2940, 1715*s*, 1670*s*, 1510*s*, 1450, 1430, 1365, 1280–1245 (br.), 1225, 1110, 845. ^{1}H-NMR (360 MHz, $CDCl_3$): 8.74 ('*s*', 1 H); 8.07 (*d*, 1 H); 7.89 (*d*, 1 H); 7.81 (*dd*, 1 H); *ca.* 7.52 (overlapping *d* + *t*, 2 H); 6.00 (br. *s*, 1 H); 4.91 (*d*, 2 H); 3.97 (*s*, 3 H); 2.02 (*s*, 3 H). Anal. calc. for $C_{15}H_{15}NO_3$ (257.28): C 70.02, H 5.88, N 5.45, O 18.66; found: C 69.66, H 6.00, N 5.71, O 18.57.

8-[(Acetylamino)methyl]naphth-2-oic Acid (**3c**). At r.t. **3b** (780 mg, 3.03 mmol) was hydrolyzed with 1N NaOH (3.3 ml) in dioxane/H_2O 2:1 (30 ml). After 20 h at r.t., H_2O (20 ml) was added and most dioxane evaporated. The residual aq. soln. was extracted with CH_2Cl and then acidified (3.7 ml of 1N H_2SO_4) and the precipitated **3c** extracted into $CHCl_3$. The crude product thus obtained was recrystallized from $CHCl_3$/MeOH/pentane: 545 mg (74%). Fine colorless needles. M.p. 281–282.5°. TLC ($CHCl_3$/MeOH 9:1, +0.4% AcOH): R_f 0.23. IR ((D_6)DMSO): 3269, 2881, 2484, 1700*s*, 1668*s*, 1656, 1546, 1458, 1372, 1278*s*, 1226. ^{1}H-NMR (360 MHz, (D_6)DMSO): 13.15 (br. *s*, 1 H); 8.70 ('*s*', 1 H); 8.37 (*t*, 1 H); 8.02 (*d*, 1 H); 7.98 (*dd*, 1 H); 7.90 (*d*, 1 H); 7.58 (*t*, 1 H); 7.50 (*d*, 1 H); 4.74 (*d*, 2 H); 3.30 (br. *s*, HOD); 1.87 (*s*, 3 H). Anal. calc. for $C_{14}H_{13}NO_3$ (243.25): C 69.12, H 5.39, N 5.76, O 19.73; found: C 68.85, H 5.45, N 5.82, O 19.64.

8-[(Acetylamino)methyl]-N-isopropylnaphth-2-amide (**3d**). To a soln. of **3c** (330 mg, 1.357 mmol) in DMF (8 ml), MeMorph (180 µl, 1.2 equiv.) was added, followed, at −15°, by isobutyl chloroformate (95% pure; 200 µl, 1.05 equiv.). After 20 min at −15°, (i-Pr)NH_2 (180 µl, 1.5 equiv.) was dropwise introduced. The clear soln. was stirred at

r.t. (Ar) for 4 h. After evaporation, the residue was dissolved in AcOEt, the soln. washed with 10% citric acid soln., 8% aq. $NaHCO_3$ soln., and brine, dried (Na_2SO_4), and evaporated and the residue triturated with Et_2O: 310 mg (80.4%) of white needles, m.p. 217.0–217.2°. Recrystallization from CH_2Cl_2/Et_2O/pentane gave colorless, rhomboid rods, changing at *ca.* 200° into long, fine needles. M.p. 217.0–217.2°. TLC ($CHCl_3$/MeOH 9:1): R_f 0.44. IR (CH_2Cl_2): 3439, 3065, 2974, 1658*s*, 1628 (sh), 1532, 1502, 1457, 1387, 1371, 1279 (br.), 1189, 1070, 1030, 881. ^{1}H-NMR (360 MHz, (D_6)DMSO): 8.56 (*s*, 1 H); 8.45 (*t*, 1 H); 8.32 (*d*, 1 H); 8.00 (*d*, 1 H); 7.95 (*d*, 1 H); 7.87 (*d*, 1 H); 7.54 (*t*, 1 H); 7.45 (*d*, 1 H); 4.81 (*d*, 2 H); 4.16 (*m*, 1 H); 1.92 (*s*, 3 H); 1.20 (*d*, 6 H). Anal. calc. for $C_{17}H_{20}N_2O_2$ (284.35): C 71.80, H 7.09, N 9.85, O 11.25; found: C 71.77, H 7.02, N 9.92, O 11.08.

8-(Aminomethyl)naphth-2-oic Acid Hydrochloride (**3e**). For 5 h, **3a** (10.0 g, 39.7 mmol) was hydrolyzed in boiling 18% HCl soln. (500 ml). Then, the mixture was cooled to r.t. and the precipitate sucked off (8.45 g). Another small crop (0.45 g) of crystals was obtained on concentration of the filtrate. Total yield 94.3% of **3e**. The product was dried at 50°/high vacuum and recrystallized from MeOH/Et_2O. Tiny, white needles. M.p. 274–276° (dec.). TLC (AcOH/BuOH/H_2O 1:3:1): R_f 0.62. IR ((D_6)DMSO): 2890, 2750, 2600, 1698, 1626, 1537, 1464, 1276, 1238, 1116, 850, 737. ^{1}H-NMR (360 MHz, (D_6)DMSO): 13.3 (br. *s*, 1 H); 8.72 (*s*, 1 H); 8.70 (br. *s*, 3 H); 8.08 (*m*, 3 H); 7.77 (*d*, 1 H); 7.70 (*t*, 1 H); 4.59 (*s*, 2 H). Anal. calc. for $C_{12}H_{12}ClNO_2$ (237.69): C 60.63, H 5.09, Cl 14.92, N 5.89, O 13.46; found: C 60.32, H 5.05, Cl 14.78, N 5.98, O 13.51.

8-{{[(Fluor-9-enyl)methoxycarbonyl]amino}methyl}naphth-2-oic Acid (**3f**). A soln. of 1.19 g (5 mmol) of **3e** in 7 ml of H_2O and 7 ml of acetone was neutralized with 0.84 g (10 mmol) of $NaHCO_3$. Then *N*-{[(fluoren-9-yl)methyloxycarbonyl]oxy}succinimide (1.69 g, 5 mmol) was added and the mixture stirred at r.t. for 18 h. The resulting thick, crystalline pulp was adjusted to pH 2 by adding 2N HCl, the product separated by suction, washed with H_2O, and recrystallized from DMF/H_2O: white, tiny needles (1.88 g, 88.8%). M.p. 268–269°. TLC (toluene/AcOH 10:3): R_f 0.53. IR ((D_6)DMSO): 3245, 3040, 1712*s*, 1600, 1540, 1452, 1254, 1140. ^{1}H-NMR (360 MHz, (D_6)DMSO): 8.75 (*s*, 1 H); 8.04 (*m*, 2 H); 7.93 (*d*, 1 H); 7.89 (*d*, 2 H); 7.70 (*d*, 2 H); 7.63 (*t*, 1 H); 7.47 (*d*, 1 H); 7.41 (*t*, 2 H): 7.32 (*t*, 2 H); 4.73 (*d*, 2 H); 4.36 (*d*, 2 H); 4.25 (*t*, 1 H). Anal. calc. for $C_{27}H_{21}NO_4$ (423.47): C 76.58, H 5.00, N 3.31; found: C 76.39, H 5.03, N 3.50.

*Methyl 8-{[(*tert*-Butoxy)carbonylamino]methyl}naphth-2-oate* (**3g**). Di(*tert*-butyl) dicarbonate (5.73 g, 26.2 mmol) was added at r.t. to a soln. of methyl 8-(aminomethyl)naphth-2-oate, liberated from its hydrochloride **3a** (6.0 g, 23.8 mmol) in dioxane/H_2O 2:1 (100 ml) by 12.5 ml of aq. 2N NaOH. On stirring at r.t., the oily product separated and later solidified. After 3 h, most dioxane was evaporated, the product dissolved in AcOEt, and the soln. washed with 5% aq. citric acid soln., 8% aq. $NaHCO_3$ soln., and brine, dried (Na_2SO_4), and evaporated: 7.50 g of **3g**. Colorless, tiny crystals. M.p. 110.2–111.0°. TLC (toluene/AcOEt 4:1): R_f 0.49. IR (CH_2Cl_2): 3445, 2980, 1718*s* (br.), 1510 (sh), 1502*s*, 1455, 1431, 1390, 1367, 1280–1198 (br.), 1224, 1163, 1110, 840. ^{1}H-NMR (360 MHz, $CDCl_3$): 8.79 ('*s*', 1 H); 8.09 (*dd*, 1 H); 7.90 (*d*, 1 H); 7.81 (*dd*, 1 H); 7.51 (*m*, 2 H); 4.91 (br. *s*, 1 H); 4.84 ('*d*', 2 H); 3.97 (*s*, 3 H); 1.48 (*s*, 9 H). Anal. calc. for $C_{18}H_{21}NO_4$ (315.37): C 68.55, H 6.71, N 4.44, O 20.29; found: C 68.55, H 6.47, N 4.58, O 20.23.

*8-{[(*tert*-Butoxy)carbonylamino]methyl}naphth-2-oic Acid* (**3h**). To a soln. of 11.56 g (36.65 mmol) of **3g** in 80 ml of dioxane, 55 ml of 1N aq. NaOH and 25 ml of H_2O were added at r.t. A small part of **3g** precipitated, but dissolved again on stirring at r.t. for 2 h. After a total of 3 h, most dioxane was evaporated, the mixture diluted with 40 ml of H_2O and extracted with CH_2Cl_2, the aq. phase acidified with 28 ml of 2N HCl, and the precipitated product extracted into $CHCl_3$: 10.94 g (99.0%) of **3h**. White crystalline powder. M.p. 196–197° (dec.). For analysis, a sample was recrystallized from MeOH/Et_2O/pentane. M.p. 199° (dec.). TLC ($CHCl_3$/MeOH 9:1, +0.4% AcOH): R_f 0.40. IR ((D_6)DMSO): 3253, 2976, 2500, 1703*s*, 1657, 1531*s*, 1456, 1365, 1270, 1250, 1226, 1170. ^{1}H-NMR (360 MHz, (D_6)DMSO): 13.10 (*s*, 1 H); 8.76 (*s*, 1 H); 8.03 (*d*, 1 H); 8.00 (*d*, 1 H); 7.91 (*d*, 1 H); 7.61 (*t*, 1 H); 7.50 (*d*, 1 H); 7.46 (br. *s*, 1 H); 4.65 ('*d*', 2 H); 1.39 (*s*, 9 H). Anal. calc. for $C_{17}H_{19}NO_4$ (301.34): C 67.76, H 6.36, N 4.65, O 21.24; found: C 67.62, H 6.26, N 4.72, O 21.10.

2. Synthesis of Templates. – 2.1. *Dipeptide Intermediates. Boc-Lys(Z)-Gly-OMe.* Prepared from methyl glycinate hydrochloride (*Bachem*; 6.3 g, 50 mmol) and N^2-Boc-N^6-Z-L-lysine (*Bachem*; 19.0 g, 50 mmol) in THF (450 ml) using DCC (10.45 g, 1 equiv.) and HOBT (8.45 g, 1 equiv.) as condensing agents and MeMorph (5.5 ml, 1 equiv.) as base. Usual workup after 20 h at r.t. and crystallization from AcOEt/Et_2O gave 18.4 g (81.5%) of fine, white needles. M.p. 82.5–84.0°. TLC ($CHCl_3$/MeOH 9:1): R_f 0.60.

HCl·H-Lys(Z)-Gly-OMe. Boc-Lys(Z)-Gly-OMe (17.0, 37.65 mmol) was stirred at r.t. for 10 min in 1.2N HCl/AcOH (90 ml). The hydrochloride was precipitated with Et_2O (700 ml), filtered off, and washed with fresh Et_2O: white, crystalline powder (14.1 g, 96.6%). M.p. 162.0–165.5°. TLC (AcOH/BuOH/H_2O 1:3:1): R_f 0.58.

HCl·H-Dab(Z)-Gly-OMe. N^2-Boc-N^4-Z-L-2,4-diaminobutanoic acid (4.9 g, 14.03 mmol) and methyl glycinate hydrochloride (1.77 g, 1 equiv.; both *Bachem*) were condensed with DCC (2.91 g, 1 equiv.) and HOBT (2.37 g, 1 equiv.) in THF (70 ml) in the presence of MeMorph (2.0 ml, 1.5 equiv.; r.t., 22 h): amorphous solid (5.61 g, 89.0%). TLC ($CHCl_3$/MeOH 19:1): R_f 0.43.

Removal of the Boc group in 1.2N HCl/AcOH (3.94 g of the Boc derivative in 30 ml). Precipitation, after 10 min at r.t., with Et_2O afforded the hydrochloride (2.95 g, 88.1%) as a white, hygroscopic powder. M.p. 72–74.5°. TLC (AcOH/BuOH/H_2O 1:3:1): R_f 0.52.

HCl·H-Gly-OAll (All = allyl). A soln. of 17.51 g (0.10 mol) of *N*-Boc-glycine in 150 ml of CH_2Cl_2 was stirred at r.t. with 13.0 ml (1.54 equiv.) of allyl bromide in the presence of 20.5 ml (1.2 equiv.) of $(i\text{-}Pr)_2EtN$. After 18 h, another portion of 4.0 ml of allyl bromide was added and the soln. heated under reflux for 6 h. Evaporation and washing of the residue, redissolved in CH_2Cl_2, with 0.5N HCl, 8% aq. $NaHCO_3$ soln., and brine, afforded, after evaporation, 21.5 (*ca.* quant.) of pure (by TLC) *allyl* N-*Boc-glycinate*. Mobile liquid. TLC ($CHCl_3$/MeOH 9:1): R_f 0.75.

Allyl *N*-Boc-glycinate (21.2 g) was stirred at r.t. in 120 ml of 1.2N HCl/AcOH. After 10 min, the soln. was concentrated *in vacuo* (30° bath), and HCl·H-Gly-OAll precipitated with Et_2O (250 ml). The oily product crystallized on trituration with fresh Et_2O (6.8 g, off-white crystals). The combined Et_2O parts were evaporated, and the residue – mainly unchanged Boc-Gly-OAll – was treated with 1.2N HCl/AcOH as described above. Another crop of crystalline HCl·H-Gly-OAll was obtained. Both crops were recrystallized from $CHCl_3/Et_2O$ giving 14.1 (94.4%) of white crystals. M.p. 79.1–79.6°. ^{1}H-NMR (360 MHz, CD_3OD): 5.92 (*dq*, 1 H); 5.32 (*dd*, 1 H); 5.24 (*dd*, 1 H); 4.69 (*dd*, 2 H); *ca.* 4.5 (br. signal, 3 H); 3.79 (*s*, 2 H). Anal. calc. for $C_5H_{10}ClNO_2$ (151.60): C 39.61, H 6.65, Cl 23.39, N 9.24, O 21.11; found: C 39.63, H 6.65, Cl 23.26, N 9.26, O 20.80.

Boc-Glu(OBzl)-Gly-OAll. To a soln. of 2.275 g (15 mmol) of allyl glycinate hydrochloride, 5.06 g (15 mmol) of 5-benzyl 1-hydrogen N^2-Boc-glutamate (*Nova Biochem*), 2.53 g (15 mmol) of HOBT, and 5.1 ml (*ca.* 30 mmol) of $(i\text{-}Pr)_2EtN$ in 50 ml of abs. CH_2Cl_2, a soln. of 3.3 g (*ca.* 16 mmol) of DCC in 15 ml of CH_2Cl_2 was added at r.t. After 18 h of stirring at r.t., DCU was filtered off, the filtrate evaporated, the residue dissolved in AcOEt, and the soln. washed with H_2O, 0.5N aq. HCl, 8% aq. $NaHCO_3$ soln., and brine, dried (Na_2SO_4), and evaporated: 6.48 g (*ca.* 100%) of oil which soon solidified to a hard, crystalline, block. For analysis, a sample was crystallized from Et_2O/pentane. M.p. 65.1–66.5°. TLC ($CHCl_3$/MeOH 19:1): R_f 0.66. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.35 (*m*, 5 H); 6.81 (br. signal, 1 H); 5.89 (*dq*, 1 H); 5.32 (*dd*, 1 H); *ca.* 5.30 (br., 1 H); 5.26 (*dd*, 1 H); 5.12 (*s*, 2 H); 4.63 (*dd*, 2 H); 4.25 (br. signal, 1 H); 4.05 (*ddd*, 2 H); 2.54 (*m*, 2 H); 2.19 (*m*, 1 H); 1.97 (*m*, 1 H); 1.40 (*s*, 9 H). Anal. calc. for $C_{22}H_{30}N_2O_7$ (434.48): C 60.81, H 6.96, N 6.45, O 25.78; found: C 60.78, H 6.98, N 6.50, O 25.40.

HCl·H-Glu(OBzl)-Gly-OAll. A soln. of 8.0 g (18.4 mmol) of Boc-Glu(OBzl)-Gly-OAll in 60 ml of 1.2N HCl/AcOH was stirred at r.t. for 10 min and introduced into Et_2O/pentane 2:5 (700 ml). The oily precipitate was separated by decantation and washed with more Et_2O/pentane. The oily product was dissolved in H_2O and lyophilized: 6.50 g (95.2%) of HCl·H-Glu(OBzl)-Gly-OAll. Amorphous, sticky material. TLC (AcOH/BuOH/H_2O 1:3:1): R_f 0.64. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.74 (*m*, 1 H); 8.27 (br. signal, 3 H); 7.29 (*m*, 5 H); *ca.* 5.80 (*m*, 1 H); 5.26 ('*d*', 1 H); 5.15 ('*d*', 1 H); 5.06 (*s*, 2 H); 4.55 (br. signal, 1 H); 4.54 ('*d*', 2 H); 4.03 (*ddd*, 2 H); 2.70 (*ddd*, 2 H); 2.41 (*m*, 1 H); 2.29 (*m*, 1 H).

Boc-Dab(Z)-Amn-OMe was prepared by a DCC/HOBT condensation of 1.26 g (5 mmol) of HCl·H-Amn-OMe (**3a**) and of Boc-Dab(Z)-OH (liberated from its dicyclohexyl ammonium salt, *Bachem*; 5 mmol) in 15 ml of $MeCONMe_2$ containing 720 µl of MeMorph. After 24 h at r.t. $MeCONMe_2$ was evaporated, the residue dissolved in $CHCl_3$/AcOEt, and the soln. washed with 10% aq. citric acid soln., 8% aq. $NaHCO_3$ soln., and brine, dried (Na_2SO_4), and evaporated; 2.7 g of white powder, pure by TLC standards. TLC ($CHCl_3$/MeOH 9:1): R_f 0.71.

Boc-Dab(Z)-Amn-OH. To a soln. of Boc-Dab(Z)-Amn-OMe (2.02 g, 3.65 mmol) in dioxane (40 ml) and H_2O (5 ml), 1N NaOH (85.0 ml) was added followed by 5 ml of H_2O. After 30 min of stirring at r.t., more H_2O was gradually added in a way to keep a clear soln. (after 3 h, dioxane/H_2O was *ca.* 4:3). After 4 h, the acid was liberated by adding 7 ml of 1N H_2SO_4 and extracted into AcOEt; 1.88 g (95.5%) of white, amorphous powder. TLC ($CHCl_3$/MeOH 9:1): R_f 0.31.

Boc-Lys(Z)-(S)-Amhn-OMe was prepared from 1.79 g (7.0 mmol) of (*S*)-HCl·H-Amhn-OMe ((*S*)-**2a**), as obtained from the Boc-Amhn-OMe ((*S*)-**2g**) by the HCl/AcOH method, and from 2.66 g (7.0 mmol) of Boc-Lys(Z)-OH (*Bachem*) in 30 ml of $MeCONMe_2$ using 1.45 g of DCC (7.0 mmol) and 1.18 g (7.0 mmol) of HOBT as condensing agents and 1.0 ml (*ca.* 9.1 mmol) of MeMorph as base. After 23 h at r.t., DCU was filtered off, the filtrate evaporated, the residue dissolved in $CHCl_3$, the soln. washed with 10% aq. citric acid soln. 8% aq. $NaHCO_3$ soln., and brine and evaporated, and the crude product chromatographed (250 g of silica gel, $CHCl_3$/MeOH 95:5): 4.09 g (*ca.* 100%) of white microcrystalline (?) powder. M.p. 153–155°. TLC ($CHCl_3$/MeOH 9:1): R_f 0.72. TLC ($CHCl_3$/MeOH 19:1): R_f 0.63. ^{1}H-NMR (360 MHz, (D_6)DMSO): 7.88 (*t*, 1 H); 7.77 ('*s*', 1 H); 7.64 (*dd*,

1 H); *ca.* 7.28 (*m*, 5 H); 7.15 (*d*, 1 H); *ca.* 7.14 (*d*, 1 H); 6.72 (*d*, 1 H); 4.95 (*s*, 2 H); *ca.* 3.82 (*m*, 1 H); 3.77 (*s*, 3 H); *ca.* 3.18 (*m*, 2 H); 2.91 (*m*, 3 H); *ca.* 2.70 (*m*, 2 H); 1.77–1.40 (3*m*, 8 H); 1.33 (*s*, 9 H); *ca.* 1.20 (*m*, 3 H). Anal. calc. for $C_{32}H_{43}N_3O_7$ (581.69): C 66.07, H 7.45, N 7.22, O 19.25; found: C 66.04, H 7.47, N 7.61, O 19.05.

Boc-Lys(Z)-(S)-Amhn-OH. A soln. of 3.80 g (6.53 mmol) of Boc-Lys(Z)-(*S*)-Amhn-OMe in 90 ml of dioxane, 10 ml of H_2O, and 7.0 ml of 1N aq. NaOH was stirred at r.t. Another 30 ml of H_2O were added in 3 portions after 20, 40, and 60 min. After a total of 5 h, the soln. was slightly diluted with H_2O, the remaining ester extracted with AcOEt (0.84 g of the latter was recovered), the alkaline, aq. phase acidified with 1N H_2SO_4, and the product taken into AcOEt. Drying (Na_2SO_4) and evaporation afforded 2.66 g of white, amorphous (?) powder. Hydrolysis of the recovered educt under the same conditions gave another 0.67 g of Boc-Lys(Z)-(*S*)-Amhn-OH (and still 0.30 g of ester). Total yield: 3.33 g (89.0%). TLC ($CHCl_3$/MeOH 9:1): R_f 0.38. Anal. calc. for $C_{31}H_{41}N_3O_7 \cdot \frac{1}{2}H_2O$ (576.68): C 64.58, H 7.34, N 7.29; found: C 64.83, H 7.24, N 7.48.

2.2. *Tripeptide Intermediates. Boc-Amn-Lys(Z)-Gly-OMe* (Amn-**12a**). To a soln. of 13.58 g (35 mmol) of HCl·H-Lys(Z)-Gly-OMe, 10.55 g (35 mmol) of Boc-Amn (**3h**), 3.85 ml of MeMorph, and 5.90 g (80%; 35 mmol) of HOBT in 230 ml of abs. THF, a soln. of 7.22 g (35 mmol) of DCC in 60 ml of THF was added at 0–5°. After 30 min at 0–5°, stirring was continued at r.t. for 22 h. DCU was filtered off, the filtrate evaporated, the residue dissolved in AcOEt, the soln. washed with 10% aq. citric acid soln., H_2O, 8% aq. $NaHCO_3$ soln., and brine, dried (Na_2SO_4), and evaporated, and the crude product (*ca.* 23 g) chromatographed (600 g of silica gel, $CHCl_3$ with increasing amounts of MeOH). The product was eluted with $CHCl_3$ containing 2% MeOH. Rechromatography of some less pure fractions under similar conditions yielded a total of 19.7 g (88.7%) of pure Amn-**12a**. Colorless, solid, amorphous foam. TLC ($CHCl_3$/MeOH 19:1): R_f 0.43 TLC (toluene/AcOH 10:3): R_f 0.29. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.72 (*s*, 1 H); 7.92 (*d*, 1 H); 7.81 (*d*, 1 H); 7.74 (*d*, 1 H); 7.46 (*t*, 1 H); 7.45 (br., 1 H);): 7.39 (*d*, 1 H); 7.26 (*m*, 5 H); 7.20 (br., 1 H); 5.42 (br., 1 H); 5.18 (br., 1 H); 4.92 (*dd*, 2 H); 4.80 (*m*, 1 H); 4.70 (*m*, 1 H); 4.51 (*m*, 1 H); 4.51 (*m*, 1 H); 4.06 (*dd*, 1 H); 3.96 (*dd*, 1 H); 3.66 (*s*, 3 H); 3.21 (*m*, 2 H); 2.02 (*m*, 1 H); 1.91 (*m*, 1 H); 1.60–1.52 (*m*, 2 H); 1.53 (*m*, 2 H); 1.40 (*s*, 9 H). Anal. calc. for $C_{34}H_{42}N_4O_8$ (634.73): C 64.34, H 6.67, N 8.83, O 20.16; found: C 63.84, H 6.78, N 8.63, O 19.97.

HCl·H-Amn-Lys(Z)-Gly-OMe (Amn-**13a**). To 15.0 g (23.6 mmol) of Amn-**12a**, 120 ml of 1.2N dry HCl/AcOH were added. The mixture was stirred at r.t. for 14 min, the clear soln. cooled in an ice-water bath, and the product precipitated by adding 750 ml of Et_2O. After stirring for 30 min in the cooling bath, the amorphous precipitate was sucked off and triturated – on the filter – with more Et_2O. A white, amorphous (?) powder of Amn-**13a** was thus obtained which was dried under high vacuum (12.05 g, 89.4%). TLC (AcOH/BuOH/H_2O 1:3:1): R_f 0.67. Anal. calc. for $C_{29}H_{35}ClN_4O_6 \cdot \frac{1}{4}H_2O$ (575.57): C 60.52, H 6.22, Cl 6.17, N 9.74, O 17.36; found: C 60.46, H 6.13, Cl 6.18, N 9.82, O 17.54.

Boc-Amn-Dab(Z)-Gly-OMe (Amn-**12b**). Prepared similarly to Amn-**12a**, from 3.49 g (9.7 mmol) of HCl. H-Dab(Z)-Gly-OMe, 2.93 g (9.7 mmol) of **3h**, 60 ml of THF, 2.10 g (10.2 mmol) of DCC, 1.64 g (9.7 mmol, calc. as 80%) of HOBT, and 1.3 ml (11.8 mmol) of MeMorph as base. Isolation of the crude product after 24 h at r.t. and LC (silica gel, $CHCl_3$/MeOH) afforded 6.04 g of a colorless, solid foam retaining some $CHCl_3$, even after prolonged drying under high vacuum TLC ($CHCl_3$/MeOH 97:3): R_f 0.27. Anal. calc. for $C_{32}H_{38}N_4O_8$ (606.68) +2.67% $CHCl_3$: C 61.93, H 6.16, Cl 2.38, N 8.99, O 20.54; found: C 61.60, H 6.15, Cl 2.38, N 8.94, O 20.91.

HCl·H-Amn-Dab(Z)-Gly-OMe (Amn-**13b**). As described for Amn-**13a**, from 4.85 g (7.99 mmol) of Amn-**12b**: white, amorphous powder (3.8 g, 88.5%). TLC (AcOH/BuOH/H_2O 1:3:1): R_f 0.60.

Boc-(R)-Amhn-Lys(Z)-Gly-OMe ((*R*)-Amhn-**12a**). As described for Amn-**12a**, with 2.30 g (7.53 mmol) of Boc-(*R*)-Amhn ((*R*)-**2h**), 2.92 g (7.53 mmol) of HCl·H-Lys(Z)-Gly-OMe, 50 ml of abs. THF, 1.27 g (7.53 mmol) of HOBT, 1.0 ml (*ca.* 1.2 equiv.) of MeMorph as base, 1.63 g (1.05 equiv.) of DCC, and 10 ml of THF (25 min, at 0–5°, 22 h at r.t.). Washing first with H_2O, then as for Amn-**12a**. On evaporation, the product separated as a white solid, the amount of the precipitate increasing on addition of Et_2O: 4.54 g (94.4%) of TLC-pure (*R*)-Amhn-**12a**. White, amorphous (?) powder. TLC ($CHCl_3$/MeOH 9:1): R_f 0.55. ^{1}H-NMR (200 MHz, (D_6)DMSO): 8.39 (*m*, 2 H); 7.71 ('*s*', 1 H); 7.65 (*dd*, 1 H); 7.33 (*m*, 5 H); 7.26 (*t*, 1 H); 7.14 (*d*, 1 H); 7.07 (*t*, 1 H); 4.99 (*s*, 2 H); 4.47 (*m*, 1 H); 3.86 (*dd*, 2 H); 3.63 (*s*, 3 H); *ca.* 3.30 (*m*, 1 H); *ca.* 2.96 (*m*, 4 H); 2.75 (*m*, 2 H); *ca.* 1.72 (*m*, 8 H); 1.38 (*s*, 9 H); *ca.* 1.35 (*m*, 2 H).

HCl-H-(R)-Amhn-Lys(Z)-Gly-OMe ((*R*)-Amhn-**13a**). As described for Amn-**13a**, with 4.34 g (6.79 mmol) of (*R*)-Amhn-**12a** in 35 ml of 1.2N HCl/AcOH (10 min at r.t.), and 350 ml of Et_2O: 3.67 g (93.3%) of (*R*)-Amhn-**13a**. M.p. 96.5–98° (however, crystallinity uncertain). TLC (AcOH/BuOH/H_2O 1:3:1): R_f 0.58. ^{1}H-NMR (200 MHz, (D_6)DMSO): 8.46 (*m*, 2 H); 8.14 (br. *s*, 2 H); 7.80 ('*s*', 1 H); 7.70 (*dd*, 1 H); 7.33 (*m*, 5 H); 7.29 (*t*, 1 H); 7.20 (*d*, 1 H); 5.00 (*s*, 2 H); 4.48 (*m*, 1 H); 3.87 (*m*, 2 H); 3.62 (*s*, 3 H); 3.40 (br. *s*, *ca.* 3 H); 3.18 (*m*, 2 H); 2.98 (*m*, 3 H); 2.76 (*m*, 2 H); *ca.* 1.8 (*m*, 6 H); 1.40 (*m*, 4 H).

Boc-Amn-Glu(OBzl)-Gly-OAll (**25**). As described for Amn-**12a**, with 6.44 g (17.53 mmol) of HCl·H-Glu-(OBzl)-Gly-OAll, 5.23 g (17.53 mmol) of **3h**, CH_2Cl_2 (150 ml) instead of THF, DCC (3.60 g, 1 equiv.), HOBT (2.93 g, 1 equiv.), and $(i\text{-Pr})_2EtN$ (3.6 ml, 1.2 equiv.) as base (22 h at r.t.): 10.8 g of a crude product which was chromatographed (500 g of silica gel, $CHCl_3$ (stabilized with 1% EtOH) and $CHCl_3$/MeOH 97.5:2.5): 9.98 g (92.15%) of **25**. Amorphous solid. TLC ($CHCl_3$/MeOH 9:1): R_f 0.72. ^{1}H-NMR (360 MHz, $CDCl_3$): 8.70 (br., 1 H); 7.95–7.73 (*m*, *s*, 4 H); 7.50 (*m*, 2 H); 7.29 (*m*, 7 H); 5.85 (*dq*, 1 H); 5.29 (*dd*, 1 H); 5.21 (*dd*, 1 H); 5.12 (*s*, 2 H); *ca.* 4.79 (*m*, 3 H); 4.60 (*dd*, 2 H); 4.05 (*ddd*, 2 H); 2.74 (*dt*, 1 H); 2.63 (*dt*, 1 H); 2.35 (*m*, 1 H); 2.28 (*m*, 1 H); 1.40 (*s*, 9 H). Anal. calc. for $C_{34}H_{39}N_3O_8$ (617.68): C 66.11, H 6.36, N 6.80, O 20.72; found: C 66.21, H 6.42, N 6.89, O 20.29.

HCl·H-Amn-Glu(OBzl)-Gly-OAll (**26**). As described for Amn-**13a**, with 6.30 g (10.2 mmol) of **25**, 40 ml of 1.2N HCl/AcOH (10 min at r.t.), and 400 ml of Et_2O. After decantation, the solid was triturated with fresh Et_2O, finally also on the filter, and recrystallized from MeOH/Et_2O: white, fine needles. M.p. 152.4–153.5°. TLC (AcOH/BuOH/H_2O 1:3:1): R_f 0.67. Anal. calc. for $C_{29}H_{32}ClN_3O_6$ (554.04): C 62.87, H 5.82, Cl 6.40, N 7.58, O 17.33; found: C 62.50, H 5.76, Cl 6.40, N 7.73, O 17.20.

2.3. *Tetrapeptide Intermediates. Boc-Lys(Z)-Amn-Lys(Z)-Gly-OMe* (Amn-**14a**). To a soln. of Amn-**13a** (12.67 g) in 80 ml of DMF and 160 ml of THF, 2.7 ml of MeMorph, 8.46 g of Boc-Lys(Z)-OH in 60 ml of THF, and 3.75 g of HOBT in 60 ml of THF were added. The clear soln. was cooled to 0–5° and a soln. of 4.60 g of DCC in 60 ml of THF was slowly introduced. After 30 min at 0–5°, stirring (Ar) was continued for 22 h at r.t. Workup as described for Amn-**12a** (evaporation finally under high vacuum). The solid foam was chromatographed (650 g of silica gel, $CHCl_3$ with increasing amounts of MeOH), the product being eluted with 2 and 2.5% of MeOH/$CHCl_3$: 18.0 g (90.4%) of pure Amn-**14a**. Colorless, solid foam (dried under high vacuum) TLC ($CHCl_3$/MeOH 9:1): R_f 0.57. TLC ($CHCl_3$/MeOH 19:1): R_f 0.34. ^{1}H-NMR (400 MHz, (D_6)DMSO): 8.68 (*d*, 1 H); 8.63 (*s*, 1 H); *ca.* 8.45 (*m*, 2 H); 7.98 ('*s*', 2 H); 7.84 (*d*, 1 H); 7.52 (*t*, 1 H); 7.48 (*d*, 1 H); 7.30 (*m*, 10 H); 7.21 (*t*, 2 H); 6.92 (*d*, 1 H); 5.00 (*s*, 2 H); 4.97 (*s*, 2 H); 4.85 (*t*, 2 H); 4.55 (*m*, 1 H); 3.98 (*m*, 1 H); 3.92–3.83 (*m*, 2 H); 3.60 (*s*, 3 H); 2.98 (*m*, 4 H); 1.85–1.77 (*m*, 2 H); 1.63–1.58 (*m*, 2 H); *ca.* 1.4 (*m*, 8 H); 1.36 (*s*, 9 H). Anal. calc. for $C_{48}H_{60}N_6O_{11}$ (897.04): C 64.27, H 6.74, N 9.22, O 19.62; found: C 64.13, H 6.89, N 9.22, O 19.58.

HCl·H-Lys(Z)-Amn-Lys(Z)-Gly-OMe (Amn-**15a**). As described for Amn-**13a**, with Amn-**14a** (7.70 g), 70 ml of 1.2N HCl/AcOH (9 min at r.t.), and 600 ml of Et_2O. After decantation, the semisolid, amorphous precipitate was triturated twice with Et_2O. The white powder was then dried under high vacuum (6.75 g, 94.3%). TLC (AcOH/BuOH/H_2O 1:3:1): R_f 0.71. ^{1}H-NMR (400 MHz, (D_6)DMSO): 9.32 (*t*, 1 H); 8.82 (*d*, 1 H); 8.68 ('*s*', 1 H); 8.52 (*t*, 1 H); *ca.* 8.30 (br. *s*, 3 H); 8.01 (*s*, 2 H); 7.89 (*dd*, 1 H); 7.55 (*m*, 2 H); 7.35–7.20 (*m*, 10 H); *ca.* 7.3 (*m*, 2 H); 5.00 (*s*, 2 H); 4.98 (*s*, 2 H); 4.90 (*ddd*, 2 H); 4.56 (*m*, 1 H); *ca.* 3.88 (*m*, 1 H); *ca.* 3.86 (*ddd*, 2 H); 3.61 (*s*, 3 H); 3.01 (*m*, 2 H); 2.91 (*m*, 2 H); 1.84 (*m*, 2 H); 1.78 (*m*, 2 H); *ca.* 1.45 (*m*, 2 H); *ca.* 1.40 (*m*, 4 H); *ca.* 1.30 (*m*, 2 H). Anal. calc. for $C_{43}H_{53}ClN_6O_9$ (833.38): C 61.97, H 6.41, Cl 4.25, N 10.09; found: C 61.60, H 6.49, Cl 4.30, N 10.03.

Boc-Lys(Z)-Amn-Lys(Z)-Gly-OH (Amn-**16a**). To a soln. of Amn-**14a** (7.92 g, 8.84 mmol) in 70 ml of dioxane, 14.0 ml of aq. 1N NaOH were added at r.t. followed by 56 ml of H_2O. The soln. was stirred at r.t. for 90 min, then most dioxane removed *i.v.*, and 1N H_2SO_4 (14.7 ml) added. The somewhat glutinous precipitate changed to a white powder on stirring in the supernatant, and later, after its decantation, in H_2O. It was sucked off and dissolved in $CHCl_3$/MeOH and the soln. dried (Na_2SO_4) and evaporated: 7.71 g (98.8%) of Amn-**16a**. Solid foam. TLC (AcOH/BuOH/H_2O 1:3:1): R_f 0.88. ^{1}H-NMR (400 MHz, (D_6)DMSO): 8.72 (*d*, 1 H); 8.68 ('*s*', 1 H); 8.64 (*t*, 1 H); 8.20 (*t*, 1 H); 7.98 (*m*, 2 H); 7.84 (*dd*, 1 H); 7.52 (*dd*, 1 H); 7.49 (*d*, 1 H); *ca.* 7.30 (*m*, 10 H); 7.22 (*m*, 2 H); 7.05 (*d*, 1 H); 5.00 (*s*, 2 H); 4.97 (*s*, 2 H); 4.85 (*ddd*, 2 H); 4.55 (*m*, 1 H); 3.94 (*m*, 1 H); *ca.* 1.6 (*m*, 2 H); 3.71 (*ddd*, 2 H); 2.98 (*m*, 4 H); 1.86 (*m*, 1 H); 1.74 (*m*, 1 H); *ca.* 1.6 (*m*, 1 H); *ca.* 1.4 (*m*, 8 H); 1.32 (*s*, 9 H). Anal. calc. for $C_{47}H_{58}N_6O_{11}$ (883.01): C 63.93, H 6.62, N 9.52; found: C 63.78, H 6.67, N 9.46.

HCl·H-Lys(Z)-Amn-Lys(Z)-Gly-OH (Amn-**22a**). As described for Amn-**13a**, with Amn-**16a** (1.6 g, 1.81 mmol), 20 ml of 1.2N HCl/AcOH (8 min at r.t.), and 200 ml of Et_2O: 1.44 g (97%) of white powder, after drying under high vacuum TLC (AcOH/BuOH/H_2O 1:3:1): R_f 0.70. Anal. calc. for $C_{42}H_{51}ClN_6O_9$ (819.36): N 10.26, Cl 4.33; found: N 10.27, Cl 4.63. FAB-MS (pos.): 783 ($[M + H]^+$; calc. for $C_{42}H_{50}N_6O_9$, M_{nom} 782).

Boc-Dab(Z)-Amn-Dab(Z)-Gly-OMe (Amn-**14b**). a) From Amn-**13b** (4.0 g, 7.54-mmol) and Boc-Dab(Z)-OH (*Bachem*) as described for Amn-**14a**: 5.81 g (91.8%) of Amn-**14b**, after LC (silica gel, $CHCl_3$ with 5% of MeOH). Colorless, solid foam. TLC ($CHCl_3$/MeOH 9:1): R_f 0.60.

b) By 2 + 2 fragment condensation of Boc-Dab(Z)-Amn-OH (2.05 g, 3.8 mmol) and of HCl·H-Dab(Z)-Gly-OMe (1.35 g, *ca.* 3.8 mmol) in $MeCONMe_2$ (20 ml) using TBTU (1.40 g, 4.37 mmol) and HOBT (0.32 g) as condensing agents and $(i\text{-Pr})_2EtN$ (1.52 ml, *ca.* 8.9 mmol) as base. After 4 h at r.t., $MeCONMe_2$ was evaporated under high vacuum and the residue, dissolved in AcOEt, was successively washed with 10% citric acid, soln. 2% $NaHCO_3$ soln., and brine. The crude product was chromatographed (180 g of silica gel, $CHCl_3$/MeOH 95:5): 3.0 g

(93.9%) of Amn-**14b**. Solid, TLC-pure foam. ^{1}H-NMR (360 MHz, (D_6)DMSO): 8.76 (*d*, 1 H); 8.66 (*s*, 1 H); 8.43 (*m*, 2 H); 8.00 (*t*, 2 H); 7.87 (*d*, 1 H); 7.50 (*m*, 2 H); 7.31 (*m*, 10 H); 7.28 (*d*,(?), 1 H); 7.18 (*t*, 1 H); 7.04 (*d*, 1 H); 5.01 (*s*, 4 H); 4.89 (*d*, 2 H); 4.62 (*dd*, 1 H); 4.07 (*dd*, 1 H); 3.93 (*dd*, 1 H); 3.86 (*dd*, 1 H); 3.63 (*s*, 3 H); 3.19 (*m*, 2 H); 3.09 (*m*, 2 H); 2.07 (*m*, 1 H); 1.88 (*m*, 2 H); 1.73 (*m*, 1 H); 1.37 (*s*, 9 H). Anal. calc. for $C_{44}H_{52}N_6O_{11} \cdot 1H_2O$ (858.94): C 61.52, H 6.34, N 9.79; found: C 61.48, H 6.27, N 10.14.

HCl·H-Dab(Z)-Amn-Dab(Z)-Gly-OMe (Amn-**15b**). As described for Amn-**13a**, with Amn-**14b** (1.97 g, 2.30 mmol), 11 ml of 1.2N HCl/AcOH (10 min at r.t.), and 120 ml of Et_2O: 1.64 g (91.9%) of white powder. TLC (AcOH/BuOH/H_2O 1:3:1): R_f 0.64.

Boc-Dab(Z)-Amn-Dab(Z)-Gly-OH (Amn-**16b**). Hydrolysis of Amn-**14b** (2.31 g, 2.75 mmol) in 25 ml of dioxane and 20 ml of H_2O by 4.2 ml of 1N NaOH gave, after 1 h at r.t. and similar workup as for Amn-**16a**, 2.16 g (95.2%) of Amn-**16b**. Colorless, solid foam. TLC (AcOH/BuOH/H_2O 1:3:1): R_f 0.85.

Fmoc-Dab(Boc)-Amn-Glu(OBzl)-Gly-OAll (**27**). To a soln. of 3.60 g (6.5 mmol) of **26**, 2.86 g (6.5 mmol) of N^2-Fmoc-N^4-Boc-L-2,4-diaminobutanoic acid (*Bachem*), 520 mg of HOBT and 1.68 ml of (i-Pr)$_2$EtN in 25 ml of $MeCONMe_2$, a soln. of 2.3 g (1.1 equiv.) of TBTU in 7 ml of $MeCONMe_2$ was added at r.t. After 3 h of stirring at r.t., another 0.5 ml of (i-Pr)$_2$EtN were added and stirring continued for another 3 h. The mixture was evaporated under high vacuum and the residue, dissolved in AcOEt/$CHCl_3$, was washed with H_2O, 10% aq. citric acid soln., 8% aq. $NaHCO_3$ soln., and brine. The crude, solid product was chromatographed (500 g of silica gel, $CHCl_3$/MeOH 97:3): 5.83 g (95.4%) of white, probably amorphous powder. TLC ($CHCl_3$/MeOH 9:1): R_f 0.74. ^{1}H-NMR (400 MHz, (D_6)DMSO): 8.78 (*d*, 1 H); 8.67 (br. *s*, 1 H); *ca.* 8.52 (*m*, 2 H); 7.99 (*s*, 2 H); 7.89 (*d*, 2 H); 7.86 (*d*, 1 H); 7.73 (*dd*, 2 H); 7.65 (*d*, 1 H); 7.53 (*t*, 1 H); 7.48 (*d*, 1 H); 7.41 (*dt*, 2 H); 7.33 (*m*, 5 H); *ca.* 7.30 (*m*, 2 H); 6.76 ('*t*', 1 H); 5.88 (*m*, 1 H); 5.29 (*dq*, 1 H); 5.17 (*dq*, 1 H);); 5.08 (*dd*, 2 H); 4.89 (*m*, 2 H); 4.63 (*m*, 1 H); 4.56 (*dt*, 2 H); 4.30–4.18 (*m*, 3 H); 4.14 (*m*, 1 H); 3.97 (*dd*, 1 H); 3.87 (*dd*, 1 H); 3.03 (*m*, 2 H); 2.56 (*t*, 2 H); 2.18 (*m*, 1 H); 2.07 (*m*, 1 H); 1.88 (*m*, 1 H); 1.76 (*m*, 1 H); 1.37 (*s*, 9H). Anal. calc. for $C_{53}H_{57}N_5O_{11}$ (940.06): C 67.72, H 6.11, N 7.45, O 18.72; found: C 67.51, H 6.18, N 7.44, O 18.87.

H-Dab(Boc)-Amn-Glu(OBzl)-Gly-OAll (**28**). At r.t., **27** (1.55 g, 1.65 mmol) was stirred in DMF/piperidine 4:1 (30 ml) for 30 min. The resulting, colorless soln. was diluted with Et_2O (100 ml) and introduced into pentane (200 ml). The oily precipitate was separated by decantation and washed with Et_2O/pentane and pentane alone. Drying under high vacuum gave 1.12 g (94.6%) of **28**. Colorless, solid foam (pure by TLC). TLC ($CHCl_3$/MeOH 9:1): R_f 0.32. ^{1}H-MNR (360 MHz, (D_6)DMSO): 8.72 (*d*, 1 H); 8.69 (*s*, 1 H); 8.47 (*m*, 2 H); 8.01 (*m*, 2 H); 7.88 (*d*, 1 H); 7.59 (*t*, 1 H); 7.51 (*d*, 1 H); 7.32 (*m*, 5 H); 6.74 (br. signal, 1 H); 5.88 (*ddd*, 1 H); 5.31 (*dd*, 1 H); 5.18 (*dd*, 1 H); 5.09 (*s*, 2 H); 4.88 (*ddd*, 2 H); 4.63 (*m*, 1 H); 4.59 (*d*, 2 H); 3.93 (*ddd*, 2 H); *ca.* 3.4–3.2 (*m*, 3 H); 3.05 (br. signal, 2 H); 2.58 (*t*, 2 H); 2.19 (*m*, 1 H); 2.08 (*m*, 1 H); 1.80 (*m*, 1 H); 1.37 (*s*, 9 H).

Fmoc-Dab(Boc)-Amn-Glu(OBzl)-Gly-OH (**29**). A soln. of 1.50 g (1.6 mmol) of **27**, 0.50 g (3.2 mmol) of *N,N'*-dimethylbarbituric acid (= 1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione), 190 mg (0.164 mmol) of $[Pd(PPh_3)_4]$, and of 210 mg (0.80 mmol) of PPh_3 in 32 ml of freshly *Alox*-filtered and degassed (Ar) THF was stirred at r.t. under Ar and in the dark for 30 min. The resulting, yellow mixture was introduced into 350 ml of Et_2O (also degassed). After 2 h standing in a refrigerator, the precipitate was sucked off and washed with several portions of Et_2O. Drying under high vacuum afforded 1.40 g (97.5%) of **29**. Amorphous, yellowish powder. TLC ($CHCl_3$/MeOH 4:1): R_f 0.26. ^{1}H-MNR (400 MHz, (D_6)DMSO): 12.52 (br. signal, 1 H); 8.77 (*d*, 1 H); 8.68 (br. *s*, 1 H); 8.63 (br. signal, 1 H); 8.32 (*t*, 1 H); 7.99 (*m*, 2 H); 7.87 (2 *d*, 2 H); 7.73 (*m*, 3 H); 7.55–7.44 (*m*, 2 H); 7.40 (*t*, 2 H); ; 7.33 (*m*, 5 H); *ca.* 7.30 (*m*, 2 H); 6.76 (*t*, 1 H); 5.08 (*dd*, 2 H); 4.90 (*m*, 2 H); 4.63 (*m*, 1 H); 4.30–4.18 (*m*, 3 H); 4.14 (*m*, 1 H); 3.82 (*dd*, 1 H); 3.73 (*dd*, 1 H); 3.03 (*m*, 2 H); 2.55 (*t*, 2 H); 2.18 (*m*, 1 H); 2.06 (*m*, 1 H); 1.88 (*m*, 1 H); 1.76 (*m*, 1 H); 1.37 (*s*, 9 H).

Boc-Lys(Z)-(S)-Amhn-Lys(Z)-Gly-OMe ((*S*)-Amhn-**14a**). A soln. of 3.0 g (5.28 mmol) of Boc-Lys(Z)-(*S*)-Amhn-OH, 2.15 g (1.05 equiv.) of HCl·H-Lys(Z)-Gly-OMe, 1.87 g (1.1 equiv.) of TBTU, 450 mg (0.5 equiv.) of HOBT, and 2.0 ml (2.2 equiv.) of (i-Pr)$_2$EtN in 30 ml of $MeCONMe_2$ was stirred at r.t. for 3.5 h. The soln. was evaporated under high vacuum and the residue, dissolved in AcOEt washed with 10% aq. citric acid soln., 8% aq. $NaHCO_3$ soln., and brine. After evaporation, the residue was chromatographed (250 g of silica gel, 3% MeOH/$CHCl_3$): 4.48 g (94.2%) of (*S*)-Amhn-**14a**. Colorless, solid foam. TLC ($CHCl_3$/MeOH 9:1): R_f 0.63. ^{1}H-MNR (360 MHz, $CDCl_3$): 7.76 (br. *s*, 1 H); 7.56 ('*s*', 1 H); 7.50 ('*d*', 1 H); 7.45 (br. *s*, 1 H); *ca.* 7.24 (*m*, 12 H); 6.98 (*d*, 1 H); 6.78 (br. *s*, 1 H); 5.43 (*m*, 1 H); 5.19 (*m*, 1 H); 5.12 (*m*, 1 H); 5.00 (*s*, 2 H); 4.93 (*s*, 2 H); 4.70 (*m*, 1 H); 3.98 (*dd*, 1 H); *ca.* 3.92 (*m*, 1 H); 3.82 (*dd*, 1 H); *ca.* 3.6 (*m*, 1 H); 3.59 (*s*, 3 H); 3.12 (*m*, 4 H); 2.7–2.5 (*m*, 2 H); 1.89 (*m*, 2 H); *ca.* 1.65 (*m*, 6 H); *ca.* 1.45 (*m*, 8 H); 1.33 (*s*, 9 H). FAB-MS (pos.): 901 ($[M + H]^+$; calc. for $C_{48}H_{64}N_6O_{11}$, M_{nom} 900). Anal. calc. for $C_{48}H_{64}N_6O_{11}$ (901.05): C 63.98, H 7.16, N 9.33, O 19.53; found: C 63.62, H 7.19, N 9.55, O 19.88.

HCl·H-Lys(Z)-(S)-Amhn-Lys(Z)-Gly-OMe ((*S*)-Amhn-**15a**). From 1.72 g (1.91 mmol) of (*S*)-Amhn-**14a**, as described for Amn-**13a**, with 17 ml of 1.2NHCl/AcOH (10 min at r.t.): 1.44 g (90.0%) of (*S*)-Amhn-**15a**. White

powder. TLC (AcOH/BuOH/H_2O 1:3:1): R_f 0.69. ^{1}H-MNR (300 MHz, (D_6)DMSO): 8.84 (*s*, 1 H); *ca.* 8.50 (*m*, 2 H); 8.29 (br. *s*, 2 H); ; 7.82 (*s*, 1 H); 7.76 (*d*, 1 H); *ca.* 7.4 (*m*, 12 (?) H); 7.21 (*d*, 1 H); 5.08 (*s*, 4 H); 4.55 (*m*, 1 H); 3.91 (*m*, 2 H); 3.84 (*m*, 1 H); 3.69 (*s*, 3 H); 3.40 (*m*, 2 H); *ca.* 3.4 (*s*, HOD); 3.07 (*m*, 6 H); 2.80 (*m*, 2 H); *ca.* 1.8 (*m*, 8 (?) H); *ca.* 1.4 (*m*, 8 (?) H).

*Boc-Lys(Z)-(*S*)-Amhn-Lys(Z)-Gly-OH* ((*S*)-Amhn-**16a**). At r.t., (*S*)-Amhn-**14a** (1.72 g, 1.91 mmol) was hydrolyzed in 17 ml of dioxane and 17 ml of H_2O containing 2.9 mmol of NaOH. After 1 h, the soln. was diluted with H_2O (20 ml), the acid liberated with 1N H_2SO_4 and extracted into AcOEt. Washing with brine, drying (Na_2SO_4), and evaporation afforded 1.70 g (quant.) of (*S*)-Amhn-**16a**. Solid foam. TLC (AcOH/BuOH/H_2O 1:3:1): R_f 0.85. ^{1}H-MNR (300 MHz, (D_6)DMSO): 8.41 (*d*, 1 H); 8.30 (*t*, 1 H); 8.04 (*m*, 1 H); 7.81 ('*s*', 1 H); 7.72 (*dd*, 1 H); *ca.* 7.4 (*m*, 10 H); 7.31 (*m*, 2 H); 7.21 (*d*, 1 H); 6.88 (*d*, 1 H); 5.08 (2 *s*, 4 H); 4.55 (*m*, 1 H); 3.93 (*dd*, 1 H); 3.83 (*dd*, 1 H); 3.68 (*m*, 1 H ?); 3.41 (*m*, 2 H); *ca.* 3.30 (*m*, 1 H); 3.06 (*m*, 6 H); *ca.* 2.8 (*m*, 2 H); *ca.* 1.8 (*m*, 10 H); 1.47 (*s*, 9 H); *ca.* 1.45 (*m*, 6 H?).

*Boc-Lys(Z)-(*R*)-Amhn-Lys(Z)-Gly-OMe* ((*R*)-Amhn-**14a**). Condensation of 3.38 g (5.88 mmol) of (*R*)-Amhn-**13a** with 2.23 g (5.88 mmol) of Boc-Lys(Z)-OH in 15 ml of $MeCONMe_2$ and 25 ml of THF using 1.3 g of DCC, 780 µl of MeMorph, and 1.0 g of HOBT afforded, after 20 h at r.t. and usual workup, an amorphous, white solid. LC (250 g of silica gel, $CHCl_3$/MeOH 97:3) gave 4.82 g (91.0%) of (*R*)-Amhn-**14a**. Colorless, solid foam. TLC ($CHCl_3$/MeOH 9:1): R_f 0.63. ^{1}H-MNR (200 MHz, (D_6)DMSO): 8.38 (*m*, 2 H); 8.00 (*t*, 1 H); 7.77 (*d*, 1 H); 7.65 (*dd*, 1 H); 7.33 (*m*, 10 H); 7.28 (*m*, 2 H); 7.15 (*d*, 1 H); 6.85 (*d*, 1 H); 5.01 (*s*, 2 H); 4.99 (*s*, 2 H); 4.49 (*m*, 1 H); 3.87 (*ddd*, 2 H); 3.62 (*s*, 3 H); *ca.* 3.42 (*m*, 1 H); *ca.* 3.15 (*m*, 1 H); 2.97 (*m*, 6 H); 2.73 (*m*, 2 H); 1.8–1.2 (*m*'s, 16 H); 1.36 (*s*, 9 H). FAB-MS: (pos.): 902 ($[M + H]^+$; calc. for $C_{48}H_{64}N_6O_{11}$, M_r 901.05).

*HCl·H-Lys(Z)-(*R*)-Amhn-Lys(Z)-Gly-OMe* ((*R*)-Amhn-**15a**). As described for (*S*)-Amhn-**15a**, from 1.80 g (2 mmol) of (*R*)-Amhn-**14a**. White powder (1.495 g, 89.0%). TLC (AcOH/BuOH/H_2O): R_f 0.72. ^{1}H-MNR (200 MHz, (D_6)DMSO): 8.79 (*t*, 1 H); 8.46 (*m*, 2 H); 8.28 (br. 3 H); 7.80 ('*s*', 1 H); 7.70 (*dd*, 1 H); *ca.* 7.34 (*m*, 10 H); 7.28 (*t* (?), 1 H); 4.99 (*s*, 4 H); 4.48 (*m*, 1 H); 3.83 (*m*, 3 H); 3.62 (*s*, 3 H); *ca.* 3.45 (*m*, 1 H); *ca.* 3.25 (*m*, 1 H); 2.98 (*m*, 6 H); 2.75 (*m*, 2 H); 1.78 (*m*, 8 H); *ca.* 1.40 (*m*, 8 H).

*Boc-Lys(Z)-(*R*)-Amhn-Lys(Z)-Gly-OH* ((*R*)-Amhn-**16a**). As described for (*S*)-Amhn-**16a**, from (*R*)-Amhn-**14a** (2.57 g, 2.85 mmol), 35 ml of dioxane, 25 ml of H_2O, and 4.2 ml of 1N NaOH (2 h at r.t.): solid, colorless foam (2.52 g, *ca.* 100%). TLC ($CHCl_3$/MeOH 4:1): R_f 0.19. ^{1}H-NMR (200 MHz, (D_6)DMSO): 12.50 (br. *s*, 1 H); 8.39 (*d*, 1 H); 8.26 (*t*, 1 H); 8.03 (br. *t*, 1 H); 7.76 ('*s*', 1 H); 7.65 (*dd*, 1 H); *ca.* 7.30 (*m*, 10 H); 7.26 (*t*, 1 H); 7.16 (*d*, 1 H); 6.85 (*dd*, 1 H); 5.00 (*s*, 2 H); 4.98 (*s*, 2 H); 4.49 (*m*, 1 H); 3.88 (*m*, 1 H); 3.78 (*t*, 2 H); *ca.* 3.40 (*m*, 1 H); *ca.* 3.40 (*m*, 1 H); *ca.* 3.18 (*m*, 1 H); 2.98 (*m*, 6 H); 2.75 (*m*, 2 H); 1.75 (*m*, 8 H); *ca.* 1.40 (*m*, 8 H); 1.38 (*s*, 9 H).

2.4. *Open-Chain Octapeptide Intermediates. Boc-Lys(Z)-Amn-Lys(Z)-Gly-Lys(Z)-Amn-Lys(Z)-Gly-OMe* (Amn-**17a**). To a soln. of 6.32 g (7.58 mmol) of Amn-**15a**, 6.70 g (7.58 mmol) of Amn-**16a**, 1.37 g (1.07 equiv.) of HOBT, and 0.96 ml (1.15 equiv.) of MeMorph in 120 ml of DMF, a soln. of 1.57 g (*ca.* 1 equiv.) of DCC in 40 ml of DMF was slowly added, while stirring under Ar at +5°. After 30 min at +5°, stirring was continued at r.t. After a total of 22 h, the mixture was concentrated under high vacuum to *ca.* 40 ml, DCU filtered off and washed with DMF, and the combined filtrate (*ca.* 50 ml) diluted with H_2O whereupon the product separated as a sticky amorphous material. Decantation of the supernatant and stirring the precipitate with more H_2O afforded a white powder which was sucked off and dried *i.v.* For purification, it was reprecipitated from DMF with Et_2O: 10.9 g (86.5%) of pure Amn-**17a**. White, amorphous powder. TLC ($CHCl_3$/MeOH 9:1): R_f 0.47. ^{1}H-NMR (400 MHz, (D_6)DMSO): 8.75 (*d*, 1 H); 8.70 (*d*, 1 H); 8.66 (br. *s*, 2 H); 8.55 (*t*, 1 H); 8.45 (*m*, 2 H); 8.34 (*t*, 1 H); 8.02 (*d*, 1 H); 7.97 (br. *s* + *m*, 4 H); 7.84 (*d*, 1 H); 7.82 (*d*, 1 H); 7.49 (*m*, 4 H); *ca.* 7.30 (*m*, 20 H); 7.22 (*t*, 3 H); 7.17 (*t*, 1 H); 6.94 (*d*, 1 H); 5.00–4.95 (3*s*, 8 H); *ca.* 4.87 (*m*, 4 H); 4.56 (*m*, 1 H); 4.46 (*m*, 1 H); 4.33 (*m*, 1 H); 3.98 (*m*, 1 H); 3.95–3.75 (*m*, 4 H); 3.61 (*s*, 3 H); 2.95 (*m*, 8 H); *ca.* 1.80 (*m*, 4 H); *ca.* 1.62 (*m*, 4 H); *ca.* 1.45 (*m*, 8 H); *ca.* 1.40 (*m*, 8 H); 1.38 (*s*, 9 H). Anal. calc. for $C_{90}H_{108}N_{12}O_{19}$ (1661.88): C 65.04, H 6.55, N 10.12, O 18.29; found: C 64.71, H 6.62, N 10.13, O 18.51.

Boc-Lys(Z)-Amn-Lys(Z)-Gly-Lys(Z)-Amn-Lys(Z)-Gly-OH (Amn-**18a**). To a soln. of 3.32 g (2.0 mmol) of Amn-**17a** in 210 ml of dioxane and 90 ml of MeOH, 30 ml of 0.1N NaOH was added at 30° followed by 150 ml of H_2O. After 2.5 h stirring at r.t., the pH was adjusted to *ca.* 7.5 and the somewhat turbid mixture filtered. Most MeOH and dioxane were then evaporated from the filtrate. Addition of 0.1N HCl to the residual, aq. soln. liberated a sticky, amorphous precipitate which slowly solidified on further stirring in the supernatant. It was sucked off, washed with H_2O, dried in a stream of Ar, and triturated with Et_2O: 2.94 g (89.2%) of Amn-**18a**. White powder. TLC ($CHCl_3$/MeOH 4:1): R_f 0.41. Anal. calc. for $C_{89}H_{106}N_{12}O_{19}\cdot H_2O$ (1665.87): C 64.16, H 6.53, N 10.09, O 19.21; found: C 64.17, H 6.54, N 10.01, O 18.90.

HCl·H-Lys(Z)-Amn-Lys(Z)-Gly-Lys(Z)-Amn-Lys(Z)-Gly-OH (Amn-**19a**). As described for Amn-**13a**, with Amn-**18a** (2.90 g, 1.74 mmol), 120 ml of 1.2N HCl/AcOH (10 min at r.t.) and 600 ml of Et_2O: 2.61 g (94.7%) of Amn-**19a**. White, amorphous powder. TLC (AcOH/BuOH/H_2O 1:3:1): R_f 0.78. ^{1}H-NMR (400 MHz,

(D_6)DMSO): 9.20 (*t*, 1 H); 8.84 (*d*, 1 H); 8.71 (*d*, 1 H); 8.68 (*s*, 1 H); 8.66 (*s*, 1 H); 8.59 (*t*, 1 H); 8.39 (*t*, 1 H); 8.32 (*t*, 1 H); 8.22 (*m*, 3 H); 8.03 (*d*, 1 H); 8.00–7.97 (*m*, 4 H); 7.89 (*d*, 1 H); 7.81 (*d*, 1 H); 7.53 (*m*, 3 H); 7.44 (*d*, 1 H); 7.35–7.15 (*m*, 24 H); 5.1–4.8 (3*s*, *m*, 12 H); 4.56 (*m*, 1 H); 4.48 (*m*, 1 H); 4.32 (*m*, 1 H); 3.9–3.7 (*m*, 5 H); 3.0–2.9 (*m*, 8 H); 1.9–1.2 (*m*, 24 H). Anal. calc. for $C_{84}H_{99}ClN_{12}O_{17} \cdot 3H_2O$ (1638.26): C 61.58, H 6.46, Cl 2.16, N 10.26, O 19.53; found: C 61.32, H 6.51, Cl, 2.22, N 10.44, O 19.10.

Boc-Dab(Z)-Amn-Dab(Z)-Gly-Dab(Z)-Amn-Dab(Z)-Gly-OMe (Amn-**17b**). A soln. of 1.87 g (2.4 mmol) of Amn-**15b**, 2.09 g (2.4 mmol) of Amn-**16b**, 850 mg (1.1 equiv.) of TBTU, and of 100 mg of HOBT in 45 ml of $MeCONMe_2$, containing 1.1 ml of $(i\text{-}Pr)_2EtN$, was stirred at r.t. for 3.5 h. The resulting mixture was concentrated under high vacuum to *ca.* 20 ml and introduced into 250 ml of Et_2O. The amorphous, sticky precipitate was separated by decantation and stirred with fresh Et_2O until it solidified. It was sucked off and washed on the filter with more Et_2O. After drying under high vacuum, 3.69 g (99%) of Amn-**17b** were obtained. The white, amorphous powder was only poorly soluble in various $CHCl_3$/MeOH mixtures tending to form gelatinous suspensions. TLC ($CHCl_3$/MeOH/AcOH 87:8:5): R_f 0.47. ^{1}H-NMR (400 MHz, (D_6)DMSO): 8.86 (*d*, 1 H); 8.80 (*d*, 1 H); 8.67 (br. *s*, 2 H); 8.57 (*t*, 1 H); 8.46 (*m*, 2 H); 8.34 (*t*, 1 H); 8.18 (*d*, 1 H); 7.99 (*s*, 4 H); 7.86 (*d*, 1 H); 7.82 (*d*, 1 H); *ca.* 7.5 (*m*, 4 H); *ca.* 7.3 (*m*, 20 H); 7.20 (*m*, 2 H); 7.08 (*d*, 1 H); *ca.* 5.0 (*s*, 8 H); 4.87 (*m*, 4 H); 4.62–4.55 (*m*, 2 H); 4.42 (*dd*, 1 H); 4.07 (*dd*, 1 H); 3.91–3.83 (*m*, 4 H); 3.63 (*s*, 3 H); 3.18 (*m*, 4 H); 3.08 (*m*, 5 (?) H); 2.04 (*m*, 2 H); *ca.* 1.9–1.7 (*m*, 4 H); 1.37 (*s*, 9 H). FAB-MS (pos): 1571.6 ($[M + Na]^+$; calc. for $C_{82}H_{92}N_{12}O_{19}$, M_{nom} 1548, M_r 1549.7).

Boc-Dab(Z)-Amn-Dab(Z)-Gly-Dab(Z)-Amn-Dab(Z)-Gly-OH (Amn-**18b**). To a soln. of 3.26 g (2.1 mmol) of Amn-**17b** in 40 ml of $MeCONMe_2$, 32 ml of 1N aq. NaOH were added at r.t. followed by 10 ml of H_2O. On stirring at r.t., the gelatinous Na-salt of Amn-**18b** soon started to precipitate and, after 30 min, made vigorous shaking necessary. After a total of 70 min, 40 ml of 1N H_2SO_4 and 100 ml H_2O were added to the suspension, and the resulting mixture was stirred in an ice-water bath for several min. Amn-**18b** was sucked off and washed with H_2O: white, amorphous powder (2.97 g, 91.3%). TLC ($CHCl_3$/MeOH 4:1): R_f 0.28.

HCl·H-Dab(Z)-Amn-Dab(Z)-Gly-Dab(Z)-Amn-Dab(Z)-Gly-OH (Amn-**19b**). As described for Amn-**13a**, with Amn-**18b** (2.89 g, 1.88 mmol), 40 ml of 1.2N HCl/AcOH (10 min at r.t.), and 400 ml of Et_2O: white, amorphous powder (2.68 g, 96.8%). TLC ($CHCl_3$/MeOH 4:1): R_f 0.23.

Fmoc-Dab(Boc)-Amn-Glu(OBzl)-Gly-Dab(Boc)-Amn-Glu(OBzl)-Gly-OAll (**30**). A soln. of 1.40 g (1.56 mmol) of **29**, 1.12 g (1.56 mmol) of **28**, 600 mg (1.87 mmol) of TBTU, 60 mg of HOBT, and 480 µl (*ca.* 1.8 equiv.) of $(i\text{-}Pr)_2EtN$ in 12 ml of $MeCONMe_2$ was stirred under Ar at r.t. overnight. A gum was precipitated with 250 ml of Et_2O, which solidified by trituration with fresh Et_2O (2.72 g). LC (20 g of silica gel, $CHCl_3$/MeOH 4:1) gave 2.09 g (83.7%) of **30**. Off-white, amorphous solid. TLC ($CHCl_3$/MeOH 9:1): R_f 0.73, TLC ($CHCl_3$/MeOH 19:1): R_f 0.46. ^{1}H-NMR (400 MHz, (D_6)DMSO): 8.83 (*d*, 1 H); 8.77 (*d*, 1 H); 8.67 (*s*, 1 H); 8.65 (*s*, 1 H); 8.55–8.47 (*m*, 3 H); 8.33 (*t*, 1 H); 8.13 (*d*, 1 H); 7.98 (*s*, 4 H); 7.87 (*d*, 2 H); 7.85 (*d*, 1 H); 7.82 (*d*, 1 H); 7.73 (*d*, 2 H); 7.64 (*d*, 1 H); 7.55–7.44 (*m*, 4 H); 7.40 ('*t*', 2 H); *ca.* 7.30 (*m*, 12 H); 6.75 (*t*, 1 H); 6.70 (*t*, 1 H); 5.87 (*m*, 1 H); 5.29 (*dq*, 1 H); 5.17 (*dq*, 1 H); 5.07 (*m*, 4 H); 4.95–4.80 (*m*, 4 H); 4.62 (*m*, 1 H); 4.56 (*dt*, 2 H); *ca.* 4.55 (*m*, 1 H); 4.37 (*m*, 1 H); 4.3–4.2 (*m*, 3 H); 4.14 (*m*, 1 H); 3.95 (*dd*, 1 H); 3.87 (*dd*, 1 H); 3.82 (br. *d*, 2 H); 3.01 (*m*, 4 H); 2.55 (*t*, 4 H); 2.17 (*m*, 2 H); 2.06 (*m*, 2 H); 1.90 (*m*, 2 H); 1.74 (*m*, 2 H); 1.37 (*s*, 9 H); 1.34 (*s*, 9 H). FAB-MS (pos.): 1622.3 ($[M + Na]^+$; calc. for $C_{88}H_{98}N_{10}O_{19}$, M_{nom} 1598, M_r 1599.8).

Fmoc-Dab(Boc)-Amn-Glu(OBzl)-Gly-Dab(Boc)-Amn-Glu(OBzl)-Gly-OH (**31**). As described for **29**, with **30** (2.90 g, 1.81 mmol), *N,N'*-dimethylbarbituric acid (1.79 g, 11.47 mmol), $[Pd(PPh_3)_4]$ (550 mg, 0.48 mmol), PPh_3 (254 mg, 0.97 mmol), $MeCONMe_2$ (18 ml)/THF (27 ml; both solvents degassed in a stream of Ar; 45 min at r.t. (Ar)), and Et_2O (600 ml, degassed): 2.80 g (*ca.* 100%) of **31**. Slightly orange, amorphous powder. TLC ($CHCl_3$/MeOH 9:1): R_f 0.37.

H-Dab(Boc)-Amn-Glu(OBzl)-Gly-Dab(Boc)-Amn-Glu(OBzl)-Gly-OH (**32**). A soln. of **31** (2.55 g) in 40 ml of DMF/piperidine 4:1 was stirred at r.t. for 30 min. The resulting mixture was concentrated at 30° (bath)/high vacuum to *ca.* 10 ml, 5 ml of DMF and 3 ml of $(i\text{-}Pr)_2EtN$ were added, and the soln. was concentrated again; the latter procedure was repeated once more. Finally, the concentrate was introduced into 250 ml of Et_2O, the precipitate separated by suction and washed with fresh Et_2O. The crude, orange product was chromatographed (100 g of silica gel, $CHCl_3$/MeOH 4:1): 1.03 g (47% over 2 steps) of **32**. Yellowish, amorphous powder. TLC (AcOH/BuOH/H_2O 1:3:1): R_f 0.77. TLC ($CHCl_3$/MeOH 4:1): R_f 0.32. FAB-MS (pos.): 1338.2 ($[M + H]^+$; calc. for $C_{70}H_{84}N_{10}O_{17}$, M_r 1337.5).

Boc-Lys(Z)-(S)-Amhn-Lys(Z)-Gly-Lys(Z)-(S)-Amhn-Lys(Z)-Gly-OMe ((*S,S*)-Amhn-**17a**). A soln. of 1.05 g (1.25 mmol) of (*S*)-Amhn-**15a**, 1.11 g (1.25 mmol) of (*S*)-Amhn-**16a**, 0.46 g (*ca.* 1.13 equiv.) of TBTU, 90 mg of HOBT and of 0.51 ml (2.4 equiv.) of $(i\text{-}Pr)_2EtN$ in 18 ml of $MeCONMe_2$ was stirred at r.t. for 3 h. The resulting soln. was introduced into 200 ml of Et_2O, the oily precipitate separated by decantation, triturated with several portions of Et_2O, and dissolved in $CHCl_3$/MeOH 4:1, and the soln. evaporated. The solid foam was chro-

matographed (200 g of silica gel, $CHCl_3$/MeOH 9:1): 2.06 g (98.7%) of (*S,S*)-Amhn-**17a**. Colorless, solid foam. TLC ($CHCl_3$/MeOH 9:1): R_f 0.36. ^{1}H-NMR (360 MHz, (D_6)DMSO): 8.35 (*m*, 3 H); 8.24 ('*t*', 1 H); 8.02 ('*t*', 1 H); 7.90 (br. signal, 1 H); 7.86 (*d*, 1 H); 7.76 ('*s*', 1 H); 7.64 (*t*, 2 H); 7.32 (*m*, 20 H); 7.18, 7.12 (2 *m*, 6 H); 6.74 (*d*, 1 H); 4.99 (*m*, 8 H); 4.49 (*m*, 1 H); 4.39 (*m*, 1 H); 4.22 (*m*, 1 H); 3.87 (*ddd*, 2 H); *ca.* 3.85 (*m*, 1 H); 3.76 (*m*, 2 H); 3.62 (*s*, 3 H); *ca.* 3.20 (*m*, 2 H); 2.95 (*m*, 12 H); *ca.* 2.72 (*m*, 4 H); 1.8–1.2 (*m*'s, 32 H); 1.37 (*s*, 9 H). FAB-MS (pos.): 1691 ($[M + Na]^+$; calc. for $C_{90}H_{116}N_{12}O_{19}$, M_{nom} 1668).

*HCl·H-Lys(Z)-(*S*)-Amhn-Lys(Z)-Gly-Lys(Z)-(*S*)-Amhn-Lys(Z)-Gly-OH* ((*S,S*)-Amhn-**19a**). (*S,S*)-Amhn-**17a** (1.84 g, 1.10 mmol) was first hydrolyzed in dioxane (75 ml) and MeOH (37.5 ml) with aq. 1N NaOH (16.5 ml). H_2O (60 ml) was slowly added to the mixture while stirring at r.t. *Boc-Lys(Z)-(*S*)-Amhn-Lys(Z)-Gly-Lys(Z)-(*S*)-Amhn-Lys(Z)-Gly-OH* ((*S,S*)-Amhn-**18a**) was liberated after 1.5 h with 1N H_2SO_4 and washed in AcOEt with H_2O and brine. Evaporation afforded 1.78 g (97.7%) of a colorless, solid foam. TLC ($CHCl_3$/MeOH 4:1): R_f 0.38.

Treatment of (*S,S*)-Amhn-**18a** (1.73 g, 1.045 mmol) with 1.2N HCl/AcOH (50 ml, r.t., 10 min) and precipitation with Et_2O gave, after the usual trituration of the precipitate with Et_2O and drying, 1.46 g (87.8%) of (*S,S*)-Amhn-**19a**. White, amorphous powder. TLC (AcOH/BuOH/H_2O 1:3:1): R_f 0.79. FAB-MS (pos.): 1557 ($[M + H]^+$; calc. for $C_{84}H_{106}N_{12}O_{17}$ (base), M_r 1555.8).

*Boc-Lys(Z)-(*R*)-Amhn-Lys(Z)-Gly-Lys(Z)-(*R*)-Amhn-Lys(Z)-Gly-OMe* ((*R,R*)-Amhn-**17a**). As described for (*S,S*)-Amhn-**17a**, with 1.44 g (1.72 mmol) of (*R*)-Amhn-**15a** and 1.52 g (1.72 mmol) of (*R*)-Amhn-**16a**, TBTU (620 mg), HOBT (110 mg), and $(i\text{-}Pr)_2EtN$ (750 µl) in $MeCONMe_2$ (20 ml). LC (silica gel (250 g), $CHCl_3$/MeOH 19:1) gave 2.41 g (83.9%) of (*R,R*)-Amhn-**17a**. White, fluffy powder. TLC ($CHCl_3$/MeOH 9:1): R_f 0.42. FAB-MS (pos.): 1692 ($[M + Na]^+$; calc. for $C_{90}H_{116}N_{12}O_{19}$, M_r 1669.95, M_{nom} 1668).

*HCl·H-Lys(Z)-(*R*)-Amhn-Lys(Z)-Gly-Lys(Z)-(*R*)-Amhn-Lys(Z)-Gly-OH* ((*R,R*)-Amhn-**19a**). Hydrolysis of 2.25 g (1.347 mmol) of (*R,R*)-Amhn-**17a** (20 ml of 0.1N NaOH in 90 ml of dioxane, 45 ml of MeOH, and 75 ml of H_2O, 2 h at r.t.) afforded, after acidification with 0.1N H_2SO_4 and extraction with AcOEt/$CHCl_3$, 2.2 g (100%) of *Boc-Lys(Z)-(*R*)-Amhn-Lys(Z)-Gly(*R*)-Amnh-Lys(Z)-Gly-OH* ((*R,R*)-Amhn-**18a**), less soluble than (*S,S*)-Amhn-**18a** in AcOEt and $CHCl_3$/MeOH mixtures. TLC ($CHCl_3$/MeOH 4:1): R_f 0.35. Treatment of (*R,R*)-Amhn-**18a** (2.31 g) with 1.2N HCl/AcOH (70 ml; at r.t., 10 min) and Et_2O (750 ml) as described for (*S,S*)-Amhn-**19a** gave (*R,R*)-Amhn-**19a** (1.87 g, 84.2%). White, amorphous powder. TLC (AcOH/BuOH/H_2O 1:3:1): R_f 0.73.

*Boc-Lys(Z)-(*R*)-Amhn-Lys(Z)-Gly-Lys(Z)-(*S*)-Amhn-Lys(Z)-Gly-OMe* ((*R,S*)-Amhn-**17a**). As described for (*S,S*)-Amhn-**17a**, with (*S*)-Amhn-**15a** (370 mg, 0.44 mmol), (*R*)-Amhn-**16a** (390 mg, 0.44 mmol), $MeCONMe_2$ (7 ml), TBTU (160 mg, 1.13 equiv.), HOBT (30 mg, 0.4 equiv.) and $(i\text{-}Pr)_2EtN$ (190 µl, *ca.* 2.5 equiv.; 4 h at r.t.). LC (75 g of silica gel, $CHCl_3$/MeOH 9:1) afforded (*R,S*)-Amhn-**17a** (660 mg, 89.8%). Colorless, solid foam. TLC ($CHCl_3$/MeOH 9:1): R_f 0.37. ^{1}H-NMR (360 MHz, (D_6)DMSO): 8.46 (*d*, 1 H); 8.38 (*m*, 1 H); 8.28 (*t*, 1 H); 8.05 (br. *t*, 1 H); 7.98 (br. *t*, 1 H); 7.90 (*d*, 1 H); 7.75 (*s*, 1 H); 7.73 (*s*, 1 H); 7.66 (*d*, 1 H); 7.63 (*d*, 1 H); 7.32 (*m*, 21 H); 7.25 (*m*, 4 H); 7.12 (*m*, 2 H); 6.82 (*d*, 1 H); 5.02 (br., 1 H); 4.98 (4 *s*, 8 H); 4.48 (*m*, 1 H); 4.38 (*m*, 1 H); 4.20 (*m*, 1 H); 3.85 (*ddd*, 2 H); 3.75 (*m*, 2 H); 3.60 (*s*, 3 H); 3.38 (*m*, 1 H); 3.16 (*m*, 2 H); 2.96 (*m*, 12 H); *ca.* 2.70 (*m*, 4 H); 1.80–1.50 (*m*'s, 16 H); *ca.* 1.40–1.25 (*m*'s, 16 H); 1.37 (*s*, 9 H). FAB-MS (pos.): 1691.5 ($[M + Na]^+$; calc. for $C_{90}H_{116}N_{12}O_{19}$, M_{nom} 1668, M_r 1669.95).

*HCl·H-Lys(Z)-(*R*)-Amhn-Lys(Z)-Gly-Lys(Z)-(*S*)-Amhn-Lys(Z)-Gly-OH* ((*R,S*)-Amhn-**19a**). Hydrolysis of 590 mg (0.393 mmol) of (*R,S*)-Amhn-**17a** in dioxane (25 ml), MeOH (10 ml), and H_2O (25 ml), containing 1.5 equiv. of NaOH, acidification with 1N H_2SO_4 after 2 h, and extraction with AcOEt, afforded *ca.* 580 mg of *Boc-Lys(Z)-(*R*)-Amhn-Lys(Z)-Gly-Lys(Z)-(*S*)-Amhn-Lys(Z)-Gly-OH* ((*R,S*)-Amhn-**18a**) as a solid, colorless foam. TLC ($CHCl_3$/MeOH 4:1): R_f 0.32. The latter was treated with 25 ml of 1.2N HCl/AcOH (10 min, r.t.) and Et_2O (250 ml) as described for (*S,S*)-Amhn-**19a**: 460 mg (85.4% over 2 steps) of (*R,S*)-Amhn-**19a**. White, amorphous powder. TLC (AcOH/BuOH/H_2O 1:3:1): R_f 0.81.

2.5. *Cyclic Octapeptides (Templates). Cyclo[-Amn-Lys(Z)-Gly-Lys(Z)-Amn-Lys(Z)-Gly-Lys(Z)-]* (Amn-**20a**). To a soln. of 2.27 g (1.43 mmol) of Amn-**19a** in 400 ml of DMF, 420 µl (*ca.* 2.1 equiv.) of Et_3N were added, followed, at +5°, by 310 µl (1 equiv.) of bis(phenyloxy)-phosphoryl azide ($(PhO)_2P(O)N_3$) diluted with 4 ml of DMF. The soln. was stirred under Ar at r.t. Three 100 µl portions of $(PhO)_2P(O)N_3$ were added after 5, 23, and 27 h, resp., the last portion along with 20 µl of Et_3N. After a total of 48 h, the mixture was concentrated under high vacuum to *ca.* 30 ml and the product precipitated by pouring the concentrate into 350 ml of Et_2O. The amorphous precipitate was separated by decantation, washed twice with Et_2O, and dissolved in $CHCl_3$/MeOH 9:1, the soln. dried (Na_2SO_4) and evaporated, and the crude solid, colorless foam chromatographed (200 g of silica gel, 5% MeOH/$CHCl_3$): 1.92 g (86.75%), of Amn-**20a**·H_2O. Solid foam. TLC ($CHCl_3$/MeOH 9:1): R_f 0.56. TLC ($CHCl_3$/MeOH/AcOH 92:5:3): R_f 0.46. ^{1}H-NMR (400 MHz, (D_6)DMSO): 8.72 (*d*, 2 H); 8.57 (*s*, *m*, 4 H); 8.48 (*t*, 2 H); 8.13 (*d*, 2 H); 7.88 (*d*, 2 H); 7.84 (*d*, 2 H); 7.73 (*d*, 2 H); 7.45 (*t*, 2 H); 7.30 (*m*, 22 H); 7.21–7.18 (*m*, 4 H); 5.0–4.9 (2 *s*, *m*,

10 H); 4.69 (*dd*, 2 H); 4.47 (*m*, 2 H); *ca.* 4.30 (*m*, 2 H); 3.94 (*dd*, 2 H); 3.62 (*dd*, 2 H); 2.97–2.92 (*m*, 8 H); 1.9–1.2 (*m*, 24 H). Anal. calc. for $C_{84}H_{96}N_{12}O_{16} \cdot H_2O$ (1529.76 + 18.02): C 65.18, H 6.38, N 10.86, O 17.57; found: C 65.10, H 6.35, N 10.75, O 17.52. FAB-MS (pos.): 1529.7 ($[M + H]^+$), 1551.7 ($[M + Na]^+$).

Cyclo(-Amn-Lys-Gly-Lys-Amn-Lys-Gly-Lys-)·4 HCl (Amn-**21a**). Amn-**20a** (2.76 g, 1.78 mmol) was dissolved in 250 ml of 90% AcOH and 10.8 ml of 1N HCl and hydrogenated at r.t. and 1 atm H_2 over 2.8 g of 10% Pd/C. After 4.5 h, the catalyst was filtered off and washed with 90% AcOH. The combined filtrates were evaporated. The amorphous, glassy residue was dissolved in H_2O (*ca.* 80 ml) containing 1 ml of 1N HCl and the soln. evaporated. After drying under high vacuum, 1.82 g (87.0%) of Amn-**21a**·$2H_2O$ were obtained. Colorless, glassy solid. TLC (AcOH/BuOH/H_2O/pyridine 1:4:2:1): R_f 0.20. HPLC (*Nucleosil C18*; eluant *A*, H_2O + 0.1% CF_3COOH; eluant *B*, MeCN + 0.1% CF_3COOH; gradient *A* + 10% *B* (30 min)→*A* + *30% B*; 1.0 ml/min, r.t., UV detection at 215 nm): t_R 24.70 min (96.6%). ^{1}H-NMR (400 MHz, (D_6)DMSO): 9.30 (*d*, 2 H); 8.80 (*s*, 2 H); 8.74 (*t*, 2 H); 8.49 (*t*, 2 H); 8.26 (*d*, 2 H); 8.0–7.9 (*m*, 16 H); 7.73 (*d*, 2 H); 7.44 (*t*, 2 H); 7.32 (*d*, 2 H); 5.00 (*dd*, 2 H); 4.76 (*dd*, 2 H); 4.44 (*q*, 2 H); 4.32 (*q*, 2 H); 4.02 (*dd*, 2 H); 3.63 (*dd*, 2 H); 2.72 (*m*, 8 H); 2.0–1.3 (*m*, 24 H). Anal. calc. for $C_{52}H_{72}N_{12}O_8 \cdot 4HCl \cdot 2H_2O$ (1175.12): C 53.14, H 6.86, Cl 12.07, N 14.30; found: C 52.99, H 6.72, Cl 11.91, N 14.34. FAB-MS (pos.): 993.6 ($[M + H]^+$), 1015.6 ($[M + Na]^+$); calc. for $C_{52}H_{72}N_{12}O_8$ (base), M_{nom} 992.

Cyclo[-Amn-Dab(Z)-Gly-Dab(Z)-Amn-Dab(Z)-Gly-Dab(Z)-] (Amn-**20b**). Amn-**19b** (2.42 g, 1.64 mmol) was cyclized in 250 ml of DMF with $(PhO)_2P(O)N_3$ (355 µl, 1 equiv.) in the presence of $(i\text{-}Pr)_2EtN$ (710 µl, 2.5 equiv.). After 24 h stirring at r.t. (Ar), another 180 µl of $(PhO)_2P(O)N_3$, and, after another 6 h, a 3rd portion of 160 µl of $(PhO)_2P(O)N_3$ were added along with 280 µl (1 equiv.) of $(i\text{-}Pr)_2EtN$. After a total of 48 h, the mixture was concentrated under high vacuum to *ca.* 25 ml and introduced into 250 ml of Et_2O. The sticky precipitate was separated by decantation, triturated with fresh Et_2O whereupon it solidified, sucked off, washed with more Et_2O, and purified by LC (silica gel $CHCl_3/CF_3CH_2OH$ 4:1): 1.55 g (66.5%) of pure Amn-**20b**. White, amorphous powder, only poorly soluble in $CHCl_3$/MeOH systems (aggregation). TLC ($CHCl_3/CF_3CH_2OH$ 4:1): R_f 0.32. ^{1}H-NMR (400 MHz, (D_6)DMSO): 8.77 (*d*, 2 H); 8.59 (*s*, 2 H); 8.56 (*t*, 2 H); 8.45 (*t*, 2 H); 8.23 (*d*, 2 H); 7.87 (*s*, 4 H); 7.76 (*d*, 2 H); 7.45 (*t*, 2 H); 7.35 (*d*, 2 H); *ca.* 7.3 (*m*, 20 H); *ca.* 7.25 (*m*, 4 H); 4.98 (2 *s*, 8 H); 4.92 (*dd*, 2 H); 4.73 (*dd*, 2 H); 4.54 (*dd*, 2 H); 4.37 (*dd*, 2 H); 3.98 (*dd*, 2 H); 3.66 (*dd*, 2 H); 3.09 (*m*, 8 H); 2.05–1.89 (*m*, 8 H). FAB-MS (pos.): 1418.5 ($[M + H]^+$), 1440.6 ($[M + Na]^+$); calc. for $C_{76}H_{80}N_{12}O_{16}$, M_r 1417.52.

Cyclo(-Amn-Dab-Gly-Dab-Amn-Dab-Gly-Dab-)·4 HCl (Amn-**21b**). Amn-**20b** (1.0 g, 0.71 mmol) was hydrogenated in 45 ml of $MeCONMe_2$, 10 ml of 90% AcOH/HO_2, and 4.2 ml of 1N HCl over 1.0 g of 10% Pd/C (1 atm H_2, r.t.). After 22 h, the catalyst was filtered off and washed with 90% AcOH/H_2O. The combined filtrates were concentrated first *in vacuo*, later under high vacuum. At *ca.* 20 ml, a white solid separated. The suspension was slowly diluted with Et_2O and the product sucked off, washed with $MeCONMe_2/Et_2O$ and then Et_2O, and dried under high vacuum: 701 mg (96.8%) of Amn-**21b**. White, hygroscopic, probably amorphous powder. TLC (AcOH/BuOH/H_2O/pyridine 1:4:2:1): R_f 0.10. HPLC (*Nucleosil 5C18*, 300 Å; *A*, H_2O + 0.1% CF_3COOH; *B*, MeCN + 0–1% CF_3COOH; gradient 4→ 24% *B* within 30 min, then 15 min 24% *B*; UV detection at 215 nm): t_R 30.11 min. FAB-MS (pos.): 881 ($[M + H]^+$; calc. for $C_{44}H_{56}N_{12}O_8$ (base), M_{nom} 880).

Cyclo[-Amn-Glu(OBzl)-Gly-Dab(Boc)-Amn-Glu(OBzl)-Gly-Dab(Boc)-] (**33**). A soln. of 980 mg (0.733 mmol) of **32** in 100 ml of $MeCONMe_2$, containing 200 µl (1.2 equiv.) of $(PhO)_2P(O)N_3$ and 300 µl (2.4 equiv.) of $(i\text{-}Pr)_2EtN$, was stirred under Ar at r.t. After 5 h, another 70 µl (0.4 equiv.) of $(i\text{-}Pr)_2EtN$ was added and stirring continued for another 18 h. The resulting soln. was concentrated under high vacuum and the concentrate transferred into 220 ml of Et_2O. The precipitate was sucked off and washed with fresh Et_2O. The crude product (*ca.* 950 mg) was chromatographed (100 g of silica gel, $CHCl_3$/MeOH 19:1): **33** (630 mg, 65.2%). Slightly yellowish glass. TLC ($CHCl_3$/MeOH 9:1): R_f 0.69. ^{1}H-NMR (400 MHz, (D_6)DMSO): 8.80 (*d*, 2 H); 8.59 (*s*, 2 H); 8.55 (*t*, 2 H); 8.46 (*t*, 2 H); 8.20 (*d*, 2 H); 7.88 (*s*, 4 H); 7.75 (*d*, 2 H); 7.45 (*t*, 2 H); 7.35–7.25 (*m*, 12 H); 6.72 (*t*, 2 H); 5.06 (*dd*, 4 H); 4.92 (*m*, 2 H); 4.71 (*m*, 2 H); 4.51 (*m*, 2 H); 4.31 (*m*, 2 H); 3.96 (*dd*, 2 H); 3.65 (*dd*, 2 H); 2.99 (*t*, 4 H); 2.47 (*t*, 4 H); 2.19 (*m*, 2 H); 2.03 (*m*, 2 H); 1.92 (*m*, 2 H); 1.76 (*m*, 2 H); 1.35 (*s*, 18 H). FAB-MS (pos.): 1341 ($[M + Na]^+$; calc. for $C_{70}H_{82}N_{10}O_{16}$, M_{nom} 1318).

Cyclo[-Amn-Glu(OBzl)-Gly-Dab-Amn-Glu(OBzl)-Gly-Dab-]·2HCl (**34**). For 6 min, **33** (70 mg) was stirred in 2 ml of 1.2N HCl/AcOH and the product precipitated with 25 ml of Et_2O. The gelatinous precipitate was filtered off, washed with Et_2O, and dried under high vacuum: 49 mg (77.5%) of **34**. White, amorphous powder. TLC (AcOH/BuOH/H_2O/pyridine 1:4:2:1): R_f 0.62. FAB-MS (pos.): 1119.8 ($[M + H]^+$; calc. for $C_{60}H_{66}N_{10}O_{12}$ (base), M_{nom} = 1118, M_r = 1119.2).

Cyclo[-Amn-Glu-Gly-Dab(Boc)-Amn-Glu-Gly-Dab(Boc)-] (**35**). A soln. of 39 mg of **33** in 2 ml of 90% AcOH/H_2O was stirred under H_2 at r.t. in the presence of 40 mg of 10% Pd/C. Filtration after 3 h and evaporation of the filtrate afforded 32.9 mg of **35**. Colorless glass. TLC (AcOH/BuOH/H_2O/pyridine 1:4:2:1): R_f 0.72. FAB-MS (pos.): 1161.8 ($[M + Na]^+$; calc. for $C_{56}H_{70}N_{10}O_{16}$, M_{nom} 1138, M_r 1139.2).

Cyclo(-Amn-Glu-Gly-Dab-Amn-Glu-Gly-Dab-)·2HCl (**36**). For 15 min, **33** (38 mg) was treated with 2.5 ml of 1.2N HCl/AcOH. After evaporation, the residue was hydrogenated in 3 ml of 90% AcOH/H_2O over 40 mg of 10% Pd/C. Filtration after 4 h and evaporation gave 32.5 mg of **36**. Colorless glass. TLC (AcOH/BuOH/H_2O/pyridine 1:4:2:1): R_f 0.28. FAB-MS (pos.): 939 ($[M + H]^+$; calc. for $C_{46}H_{54}N_{10}O_{12}$ (base), M_{nom} 938).

Cyclo[-(S)-Amhn-Lys(Z)-Gly-Lys(Z)-(S)-Amhn-Lys(Z)-Gly-Lys(Z)-] ((*S,S*)-Amhn-**20a**). A soln. of (*S,S*)-Amhn-**19a** (1.40 g, 0.879 mmol) in $MeCONMe_2$ (120 ml) containing $(i\text{-}Pr)_2EtN$ (350 µl, 2.3 equiv.) and $(PhO)_2P(O)N_3$ (210 µl, 1.1 equiv.) was stirred at r.t. After 4.5 h, another portion of $(PhO)_2P(O)N_3$ (110 µl) and of $(i\text{-}Pr)_2EtN$ (90 µl) were added, and stirring was continued for a total of 24 h. Evaporation under high vacuum, trituration with Et_2O, and LC (200 g of silica gel, $CHCl_3$/MeOH 4:1) gave (*S,S*)-Amhn-**20** (1.03 g, 76.2%). Colorless, solid foam. TLC ($CHCl_3$/MeOH 9:1): R_f 0.38. TLC ($CHCl_3$/MeOH 4:1): R_f 0.72. FAB-MS (pos.): 1536 ($[M + H]^+$). PD-MS (pos.): 1561 ($[M + Na]^+$; calc. for $C_{84}H_{104}N_{12}O_{16}$, M_{nom} 1536, M_r 1537.8).

Cyclo[-(S)-Amhn-Lys-Gly-Lys-(S)-Amhn-Lys-Gly-Lys-]·4 HCl ((*S,S*)-Amhn-**21a**). (*S,S*)-Amhn-**20a** (900 mg, 0.585 mmol) was hydrogenated in 90% AcOH/H_2O (77 ml) containing aq. 1N HCl (3.5 ml), over 0.9 g of 10% Pd/C (1 atm H_2, r.t.). Usual workup after 4.5 h and final evaporation of the product soln. in 0.1N HCl (10 ml, repeated twice) afforded (*S,S*)-Amhn-**21a** (610 mg, 90.9%). Colorless, glassy solid. HPLC (*Nucleosil 5C18*, 1 ml/min, 200 bar; *A*: H_2O + 0.1% CF_3COOH; *B*: MeCN + 0.1% CF_3COOH; gradient 4→24% *B* within 30 min, then 15 min 24% *B*; UV detection at 215 nm): t_R 35.83 min (95.3%). ^{1}H-NMR (500 MHz, D_2O, 290 K): 7.53 (*d*, 2 H); 7.43 (*s*, 2 H); 7.04 (*s*, 2H); 4.66 (*t*, 2 H); 4.24 (*q*, 2 H); 4.02 (*d*, 2 H); 3.80 (*d*, 2 H); 3.30 (*t*, 2 H); 3.05–2.95 (*m*, 10 H); *ca.* 2.63 (*m*, 4 H); 2.46 (*m*, 2 H); 1.98–1.88 (*m*, 6 H); 1.76–1.55 (*m*, 16 H); 1.52–1.40 (*m*, 8 H); 1.31 (*m*, 2 H). PD-MS (pos.): 1002.1 ($[M + H]^+$; calc. for $C_{52}H_{80}N_{12}O_8$ (base), M_r 1001.25).

Cyclo[-(R)-Amhn-Lys(Z)-Gly-Lys(Z)-(R)-Amhn-Lys(Z)-Gly-Lys(Z)-] ((*R,R*)-Amhn-**20a**). Cyclization of 1.76 g (1.1 mmol) of (*R,R*)-Amhn-**19a** in 150 ml of $MeCONMe_2$ with $(PhO)_2P(O)N_3$ (390 µl, 1.63 equiv., added in 2 portions) in the presence of $(i\text{-}Pr)_2EtN$ (540 µl, 2.9 equiv.) and similar workup as described for (*S,S*)-Amhn-**20a** afforded, after LC (silica gel (180 g), $CHCl_3$/MeOH 9:1), 1.40 g of solid, amorphous material. Although seemingly pure by TLC ($CHCl_3$/MeOH 9:1), it was a mixture of (*R,R*)-Amhn-**20a** and of its complex with K and/or Ca salts of diphenyl hydrogen phosphate (FAB-MS (pos.) and K, Ca, and P evidence by anal.). The complex was destroyed by repeated dissolution in $MeCONMe_2$ and precipitation of the peptide with a tenfold volume of H_2O: 1.065 g (62.7%) of pure (*R,R*)-Amhn-**20a**. Colorless, solid foam. TLC ($CHCl_3$/MeOH 9:1): R_f 0.34. ^{1}H-NMR (360 MHz, (D_6)DMSO): 8.62 (br. *d*, 2 H); 8.47 (br., 2 H); 7.95 (br. *d*, 2 H); 7.85 (br., 2 H);); 7.66 (*d*, 2 H); 7.51 (br., 2 H); *ca.* 7.32 (*m*, 20 H); 7.23 (*m*, 2 H); 7.08 (*d*, 2 H); 5.00 (*s*, 4 H); 4.98 (*s*, 4 H); 4.37 (*m*, 2 H); 4.16 (*m*, 2 H); 3.94 (*dd*, 2 H); 3.58 (*dd*, 2 H); *ca.* 3.34 (*m*, 2 H(?)); *ca.* 3.05–2.80 (*m*'s, 14 H); *ca.* 2.69 (*m*, 2 H); *ca.* 2.58 (*m*, 2 H); 1.85–1.50 (*m*, 16 H); 1.45–1.25 (*m*, 16 H). FAB-MS (pos.): 1538.8 ($[M + H]^+$), 1560.7 ($[M + Na]^+$; calc. for $C_{84}H_{104}N_{12}O_{16}$, M_r 1537.79.

Cyclo[-(R)-Amhn-Lys-Gly-Lys-(R)-Amhn-Lys-Gly-Lys-]·4 HCl ((*R,R*)-Amhn-**21a**). As described for (*S,S*)-Amhn-**21a**, with (*R,R*)-Amhn-**20a** (800 mg), 90% AcOH/H_2O (62 ml), 3.2 ml of 1N HCl, and 10% Pd/C (800 mg): (*R,R*)-Amhn-**21a** (600 mg). Colorless glass. HPLC (*Nucleosil 5C18*, 1 ml/min, 160 bar; *A*: H_2O + 0.1% CF_3COOH; *B*: MeCN + 0.1% CF_3COOH; gradient 4→24% *B* within 30 min, then 15 min 24% *B*; detection at 215 nm): t_R 36.84 min (95.4%). ^{1}H-NMR (500 MHz, D_2O, 290 K): 7.57 (*d*, 2 H); 7.16 (*d*, 2 H); 7.15 (*s*, 2 H); 4.44 (*q*, 2 H); 4.29 (*q*, 2 H); 4.14 (*d*, 2 H); 3.80 (*d*, 2 H); 3.25 (*q*, 2 H); 3.15 (*q*, 2 H); 2.98 (*m*, 8 H); 2.68 (*m*, 2 H); 2.58 (*m*, 2 H); 2.49 (*m*, 2 H); 2.02–1.89 (*m*, 6 H); 1.80–1.35 (*m*, 26 H). FAB-MS (pos.): 1001.7 ($[M + H]^+$; calc. for $C_{52}H_{80}N_{12}O_8$ (base), M_{nom} 1000, M_r 1001.3).

Cyclo[-(R)-Amhn-Lys(Z)-Gly-Lys(Z)-(S)-Amhn-Lys(Z)-Gly-Lys(Z)-] ((*R,S*)-Amhn-**20a**). Cyclization of 430 mg (0.27 mmol) of (*R,S*)-Amhn-**19a** in 40 ml of $MeCONMe_2$ with 150 µl (*ca.* 1.9 equiv.) of $(PhO)_2P(O)N_3$ in the presence of 140 µl (*ca.* 3 equiv.) of $(i\text{-}Pr)_2EtN$ (r.t., 24 h) afforded, after the usual workup and chromatography (40 g of silica gel, $CHCl_3$/MeOH 9:1), 338 mg (84.6%) of (*R,S*)-Amhn-**20a**. Colorless glass. TLC ($CHCl_3$/MeOH 9:1): R_f 0.35. ^{1}H-NMR (360 MHz, (D_6)DMSO): 8.52 (*d*, 2 H); 8.37 (br., 1 H); 8.29 (br. 1 H); 8.03 (br., 2 H); 7.87 (*t*, 2 H); 7.70 ('*d*', 2 H); 7.64 ('*t*', 2 H); *ca.* 7.33 (*m*, 20 H); 7.24 (*m*, 2 H); 7.18 (*m*, 2 H); 7.09 (*dd*, 2 H); 4.99 (*s*, 4 H); 4.97 (*s*, 4 H); *ca.* 4.42 (*m*, 1 H); 4.35 (*m*, 1 H); 4.20 (*m*, 2 H); 3.92 (*dd*, 2 H); 3.58 (*m*, 2 H); 3.42–3.27 (*m*, 2 H); *ca.* 3.14 (br., 2 H); 2.97, 2.89 (2*m*, together 10 H); 2.67 (*m*, 4 H); *ca.* 1.75, *ca.* 1.64 (2*m*, together 16 H); 1.43–1.15 (*m*, 16 H). FAB-MS (pos.): 1537 ($[M + H]^+$; calc. for $C_{84}H_{104}N_{12}O_{16}$, M_{nom} 1536).

Cyclo[-(R)-Amhn-Lys-Gly-Lys-(S)-Amhn-Lys-Gly-Lys-]·4 HCl ((*R,S*(-Amhn-**21a**). As described for (*S,S*)-Amhn-**21a**, with (*R,S*)-Amhn-**20a** (270 mg), 22 ml of 90% AcOH/H_2O, 1.1 ml of 1N HCl, and 10% Pd/C: 200 mg of (*R,S*)-Amhn-**21a**. Colorless glass. HPLC (for conditions, see (*S,S*)-Amhn-**21a**): t_R 36.10 min. ^{1}H-NMR (500 MHz, D_2O, 290 K): 7.59 (*s*, 1 H); 7.53 (*s*, 1 H); 7.56 (*d*, 1 H); 7.52 (*d*, 1 H); 7.16 (*d*, 1 H); 7.15 (*d*, 1 H); 4.46 (*q*, 1 H); 4.41 (*q*, 1 H); 4.31 (*q*, 1 H); 4.27 (*d*, 1 H); 4.17 (*d*, 1 H); 4.11 (*d*, 1 H); 3.82 (*d*, 2 H); 3.30 (*q*, 1 H); 3.21 (*q*, 1 H); 3.15 (*q*, 1 H); 3.01–2.98 (*m*, 5 H); 2.96–2.90 (*m*, 4 H); 2.83 (*m*, 2 H); 2.70 (*m*, 1 H); 2.65 (*m*, 1 H); 2.56 (*m*, 1 H); 2.47 (*m*,

1 H); 2.00–1.82 (*m*, 6 H); 1.77–1.32 (*m*, 26 H). FAB-MS (pos.): 1001 ($[M + H]^+$; calc. for $C_{52}H_{80}N_{12}O_8$ (base), M_{nom} = 1000).

Cyclo[-Amn-Lys(Z)-Gly-Lys(Z)-] (Amn-**23a**). To a soln. of 1.44 g (1.76 mmol) of Amn-**22a** in 150 ml of DMF, containing 540 µl (*ca.* 2.2 equiv.) of Et_3N, a soln. of 420 µl (*ca.* 1.1 equiv.) of $(PhO)_2P(O)N_3$ in 50 ml of DMF was added and the mixture stirred under Ar at r.t. After 5 h, 210 µl of $(PhO)_2P(O)N_3$ were added, and stirring was continued for another 17 h. After concentration of the soln. under high vacuum to *ca.* 20 ml, an amorphous, fluffy product was precipitated by introducing the concentrate into 100 ml of Et_2O. It was isolated by suction, and washed with Et_2O and then with several portions of H_2O, and dried under high vacuum: 1.10 g (72.4%) of Amn-**23a**. White, amorphous powder, poorly soluble in many solvents, forming, *e.g.*, in various $CHCl_3$/MeOH mixtures, gelatinous suspensions by aggregation. TLC ($CHCl_3$/MeOH 9:1): R_f 0.50; no Amn-**20a**. ^{1}H-NMR (400 MHz, (D_6)DMSO): 8.57 (*d*, 1 H); 8.51 (*dd*, 1 H); 8.34 ('*s*', 1 H); 8.02 (*m*, 1 H); 7.99 (*d*, 1 H); *ca.* 7.92 (*m*, 2 H); 7.83 (*dd*, 1 H); 7.57 (*d*, 1 H); 7.53 (*t*, 1 H); *ca.* 7.3 (*m*, 10 H); *ca.* 7.22 (*m*, 2 H); 5.30 (*dd*, 1 H); 4.97 (2*s*, 4 H); 4.50 (*m*, 1 H); 4.23 (*m*, 2 H); 4.09 (*m*, 1 H); 3.20 (*dd*, 1 H); 3.00 (*m*, 2 H); 2.95 (*m*, 2 H); 1.89 (*m*, 1 H); 1.67 (*m*, 2 H); 1.51–1.12 (*m*, 9 H). Anal. calc. for $C_{42}H_{48}N_6O_8$ (764.88): C 65.95, H 6.33, N 10.99, O 16.73; found: C 65.93, H 6.30, N 10.87, O 16.68. FAB-MS (pos.): 765 ($[M + H]^+$), 787 ($[M + Na]^+$; calc. for $C_{42}H_{48}N_6O_8$, M_{nom} 764).

Cyclo(-Amn-Lys-Gly-Lys-)·2 HCl (Amn-**24a**). Amn-**23a** (1.0 g, 1.31 mmol) was hydrogenated in 100 ml of 90% AcOH/H_2O over 1.0 g of 10% Pd/C (1 atm H_2, r.t.). After 3.5 h, the catalyst was filtered off and washed with 90% AcOH/H_2O, the combined filtrate evaporated after addition of 3 ml of 1N HCl, the glassy residue dissolved in 125 ml of H_2O, and the soln. filtered and lyophilized: 710 mg (95.3%) of Amn-**24a**. White, fluffy powder. TLC (AcOH/BuOH/H_2O/pyridine 1:4:2:1): R_f 0.36. ^{1}H-NMR (400 MHz, (D_6)DMSO, 298 K): 8.85 (*d*, 1 H); 8.74 (*dd*, 1 H); 8.61 (br. *s*, 1 H); 8.36 (*t*, 1 H); 8.17 (*d*, 1 H); 7.99 (*d*, 1 H); 7.9–7.82 (*m*, 8 H); 7.58 (*d*, 1 H); 7.51 (*t*, 1 H); 5.17 (*dd*, 1 H); 4.53 (*q*, 1 H); 4.32 (*dd*, 1 H); 4.08 (*m*, 2 H); 3.38 (*dd*, 1 H); 2.74 (*m*, 4 H); 2.0–1.2 (*m*, 12 H). FAB-MS (pos.): 497 ($[M + H]^+$), 519 ($[M + Na]^+$; calc. for $C_{26}H_{36}N_6O_4$ (base), M_{nom} 496). Anal. calc. for $C_{26}H_{38}Cl_2N_6O_4 \cdot 1\,H_2O$ (587.56): C 53.14, H 6.86, Cl 12.07, N 14.31; found: C 52.94, H 7.02, Cl 12.50, N 14.16.

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