148. Synthetic Analogues of Naturally Occurring Spider Toxins

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Naturally occurring spider toxins are potent inhibitors of glutamate receptors of the central nervous system and have the general structure (hetero)arylacyl→aminoacyl(I)→polyamine←aminoacyl(II) (the arrow indicates the direction of an amide linkage). In the present paper, the synthesis of the ten spider-toxin analogues **13**, **18**, **21**, **28**, **35**, **37**, **39**, **41**, **45**, and **53** are reported (*Schemes 1–12*). These compounds differ in their subunits and, in some cases, in the sequence of these moieties.

Introduction. – Glutamate receptors of the central nervous system of man and other mammalians are believed to be involved in higher neural functions such as memory and learning, and neurological disorders, *e.g.* hypoxemia, epilepsy, *Huntington*, *Alzheimer*, and *Parkinson* disease (for a survey of the different aspects of the topic, see, *e.g.*, [1]).

There are three major types of glutamate receptors: *N*-methyl D-aspartate (NMDA), quisqualate, and kainate, based on their response to agonists. While for NMDA antagonists became available in the last few years, inhibitors for quisqualate and kainate receptors are still missing [1]. Recently, the low molecular weight components of toxins isolated from the venom of spiders and wasps proved to be excellent inhibitors of glutamate receptors, including the quisqualate- and the kainate-sensitive ones, generating, therefore, much interest in this field [1]. The above-mentioned spider toxins are polyamine derivatives with the general structure (hetero)arylacyl→aminoacyl(I)→polyamine←aminoacyl(II), wherein the arrows indicate the direction of an amide linkage. As relatively little is known about the structure-activity relationship of these toxins [1a] [2], we have envisaged the synthesis of analogues in order to ascertain, or to exclude, which structural features are essential for the biological activity.

Results and Discussion. – We synthesized ten spider-toxin analogues of great structural similarity. For their heteroarylacyl moiety, fragments derived from (1*H*-indol-3-yl)acetic acid (= Iaa; **13**, **18**, **21**, **28**, **35**, **37**, **39**, **45**) or 3-(1*H*-indol-3-yl)propanoic acid (= Ipa; **41**) were chosen, some of them with a 5- or 4-OH substituent (**21**, **28**, **37**, **39**; these structural fragments are often present in natural spider toxins [1]). Amino acid (I), for simplicity, was L-alanine (= Ala; in natural spider toxins, it is often L-asparagine). For the polyamine, as simple models, hexane-1,6-diamine (= Dhx) and propane-1,3-diamine (= Dpr) were used. Amino acid (II) was represented either by acetic acid (**13**, **18**, **21**, **28**) or by L-lysine (Lys; **35**, **37**, **39**, **41**, **45**, **53**), to ascertain, whether a basic side chain is really

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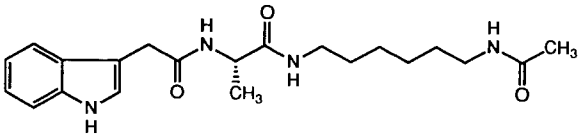
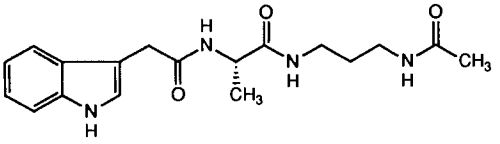
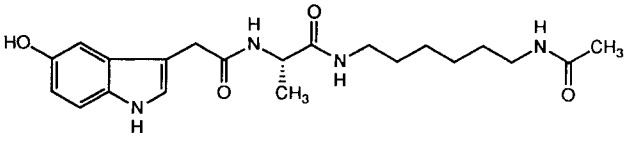


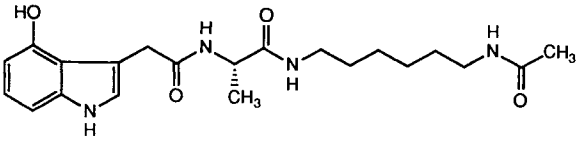
13 Iaa → Ala → Dhx ← Ac



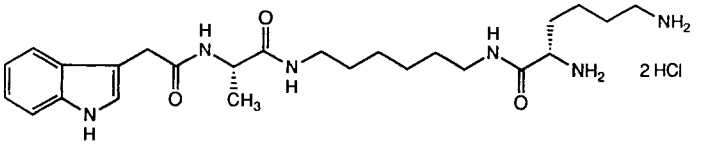
18 Laa → Ala → Dpr ← Ac



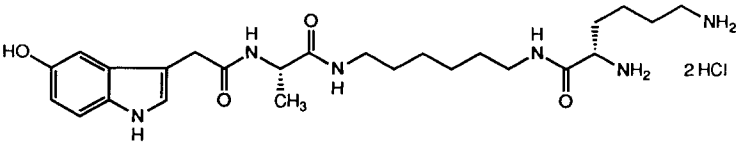
21 Iaa(5-OH) → Ala → Dhx ← Ac



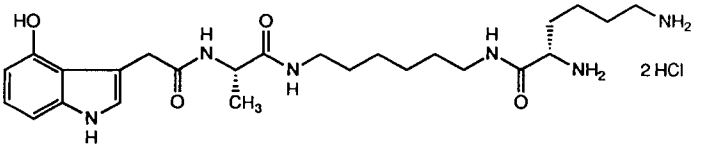
28 Iaa(4-OH) → Ala → Dhx ← Ac



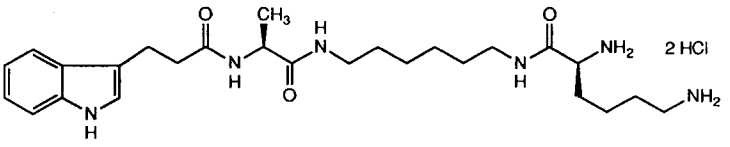
35 Iaa → Ala → Dhx ← $H^+LysH^+ \cdot 2\,Cl^-$



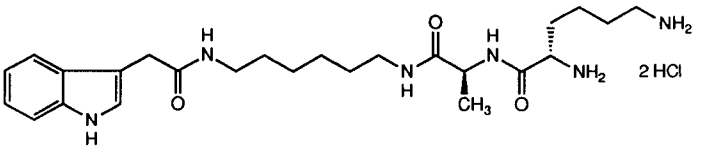
37 Iaa(5-OH) → Ala → Dhx ← $H^+LysH^+ \cdot 2\,Cl^-$



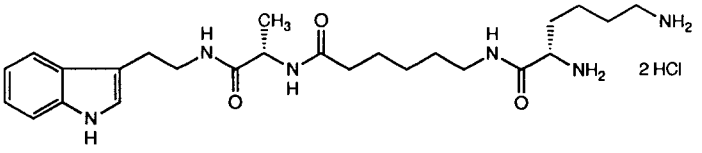
39 Iaa(4-OH) → Ala → Dhx ← $H^+LysH^+ \cdot 2\,Cl^-$



41 Ipa → Ala → Dhx ← $H^+LysH^+ \cdot 2Cl^-$



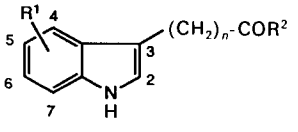
45 Iaa → Dhx ← Ala ← $H^+LysH^+ \cdot 2Cl^-$



53 Trm ← Ala ← ϵAhx ← $H^+LysH^+ \cdot 2Cl^-$

necessary for the biological activity (in natural spider toxins, this moiety is often L-arginine). Moreover, in compound **45**, the sequence aminoacyl(I)→polyamine was reversed. Finally, in compound **53**, the (1*H*-indol-3-yl)acyl moiety was replaced by tryptamine (Trm-H), and, consequently, the aminoacyl(I)→polyamine sequence was changed to ←aminoacyl(I)←ω-aminoacyl(I'). These structural variations may seem arbitrary but, as mentioned before, little is known about which part(s) is (are) responsible for the glutamate receptor blocking activity, hence, we had to consider changes in each regions of the toxins, including some reverse sequences as well.

The indole derivatives **1**–**7** were prepared according to literature procedures: 4-nitrophenyl (1*H*-indol-3-yl)acetate (**1**) was formed from the corresponding acid using 4-nitrophenol and *N*,*N*'-dicyclohexylcarbodiimide in anh. AcOEt [3]. Similarly, active esters **3**, **5**, and **7** were obtained from acids **2**, **4**, and **6**, respectively. The [5-(benzyloxy)-1*H*-indol-3-yl]acetic acid (**2**) was prepared in several steps from 5-(benzyloxy)-1*H*-indole [4] and [4-(benzyloxy)-1*H*-indol-3-yl]acetic acid (**4**) from a nitrotoluene derivative according to *Poon et al.* [5].



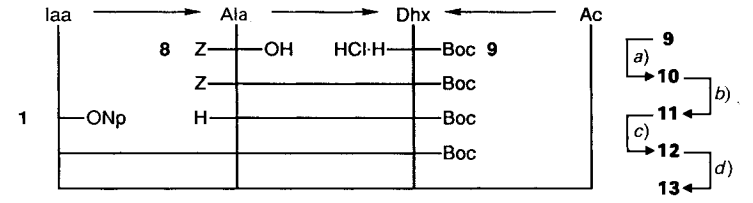
	R^1	R^2	*n*
1	H	NpO	1
2	5-BnO	OH	1
3	5-BnO	NpO	1
4	4-BnO	OH	1
5	4-BnO	NpO	1
6	H	OH	2
7	H	NpO	2

As an overwhelming part of the synthetic steps used in the preparation of spider-toxin analogues was amide-bond formation (the subunits are linked with peptide-like bonds),

an attempt was made to present clearly and shortly these sequences in the style of peptide-synthesis charts (*Schemes 1–12*[2])).

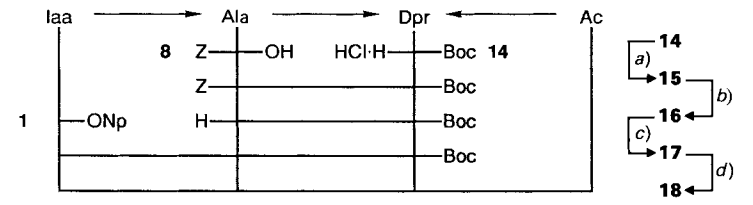
Schemes 1–3 show the synthesis of derivatives **13**, **18**, and **21** where amino acid (II) is represented by acetic acid, the indolylacetyl moiety is either hydroxylated or not, and the polyamine unit is hexane-1,6-diamine or propane-1,3-diamine. The synthesis started in each case with the preparation of the central unit. Thus *N*-[(benzyloxy)-carbonyl]-L-alanine (Z-Ala; **8**) was coupled in a mixed-anhydride procedure either with

Scheme 1[2])



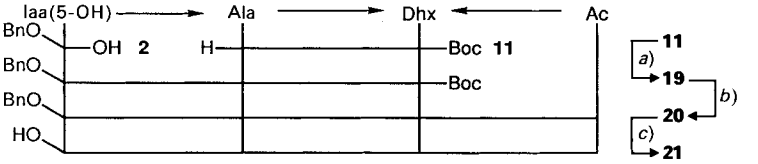
a) $ClCO_2Et$, Et_3N; 76.7%. *b*) H_2, Pd/C; 98.6%. *c*) 90.3%. *d*) HCl/dioxane, then Ac_2O/py; 23.8%.

Scheme 2[2])



a) $ClCO_2Et$, Et_3N; 68.5%. *b*) H_2, Pd/C; 97.7%. *c*) 88.4%. *d*) HCl/dioxane, then Ac_2O/py; 21.6%.

Scheme 3[2])



a) $ClCO_2Et$, Et_3N; 68.5%. *b*) HCl/dioxane, then Ac_2O/py; 29.5%. *c*) H_2, Pd/C; 66.3%.

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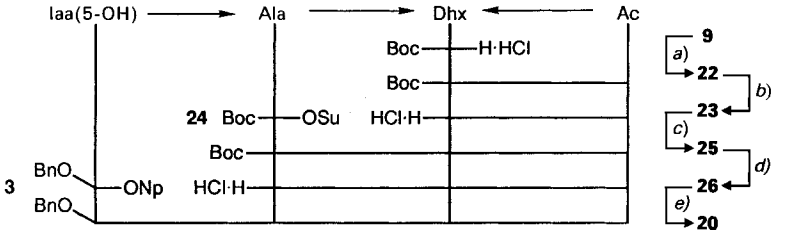
[2]) Peptide-type nomenclature [6] is used to ensure maximum clarity and transparency. Less common abbreviations and signs are: Iaa- = (1*H*-indol-3-yl)acetyl (3-$C_8H_6NCH_2CO$–) residue; Iaa(4- or 5-OH)- = 4- or 5-hydroxy-(1*H*-indol-3-yl)acetyl residue; Ipa- = 3-(1*H*-indol-3-yl)propanoyl (3-$C_8H_6NCH_2CH_2CO$–) residue; Trm- = N^{ω}-substituted tryptamine (3-$C_8H_6NCH_2CH_2NH$–) residue; Np- = 4-nitrophenyl (4-O_2N–C_6H_4–) residue; Su- = succinimido ($(CH_2)_2(CO)_2N$–) residue; εAhx- = 6-aminohexanoyl ($NH_2(CH_2)_5CO$–) residue [6a]; -Dhx- = 1,6-diiminohexane (–$HN(CH_2)_6NH$–) residue; -Dpr- = 1,3-diiminopropane (–$HN(CH_2)_3NH$–) residue. Arrows (→ and ←) are used to indicate the direction of the amide linkage. In this sense, the Ac group is considered to be an aminoacyl residue (Ac→ and ←Ac). Oblique hyphens denote side-chain substitution.

N-[(*tert*-butyloxy)carbonyl]hexane-1,6-diamine hydrochloride (Boc-Dhx·HCl; **9**) or with *N*-[(*tert*-butyloxy)carbonyl]propane-1,3-diamine hydrochloride (Boc-Dpr·HCl; **14**; *cf.* [7]) to give the corresponding derivative **10** and **15**, respectively. The N-protecting Z group was cleaved in a smooth reaction yielding derivatives **11** and **16**, respectively. Compound **11** was then allowed to react with active ester **1** to give **12**. Deblocking of the Boc group of **12** and direct acetylation afforded analogue **13**, however, in rather low yield. The same was experienced when the analogues **18** (from **17**) and **21** (from **11** *via* **19** and **20**) were prepared in a similar sequence. This suggested that it is advisable to introduce the acid- and base-sensitive indole moiety at the latest possible step during the synthesis.

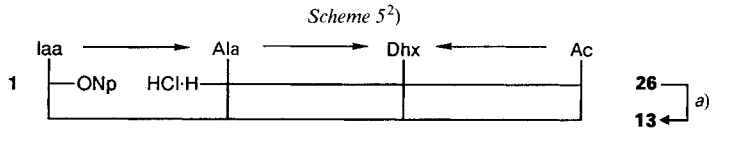
Therefore, acetyl derivative **21** was prepared by coupling first *N*-acetylhexane-1,6-diamine hydrochloride (**23**)[3]) with succinimido *N*-[(*tert*-butyloxy)carbonyl]-L-alaninate (**24**; *Scheme 4*). The resulting Boc derivative **25** was smoothly deprotected and hydrochloride **26** then allowed to react with active ester **3** to give benzyloxy derivative **20** in good yield (for the deprotection of **20**, *cf. Scheme 3*). Analogously, derivative **13** was obtained in good yield from ester **1** and hydrochloride **26** (*Scheme 5*). The same intermediate **26** was also used for the preparation of 4-hydroxyindole derivative **28** from active ester **5** *via* **27** (*Scheme 6*).

Scheme 4[2])



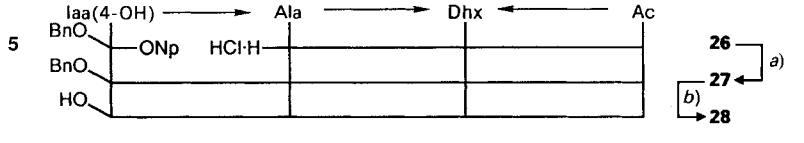
a) Ac_2O/py; 74.3%. *b*) HCl/dioxane; 93.6%. *c*) Et_3N; 57.7%. *d*) HCl/dioxane; 91.1%. *e*) Et_3N; 83.4%.

Scheme 5[2])



a) Et_3N; 88.1%.

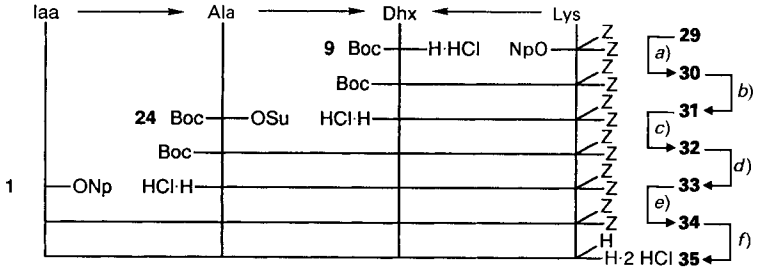
Scheme 6[2])



a) Et_3N; 94.3%. *b*) H_2, Pd/C; 90.7%.

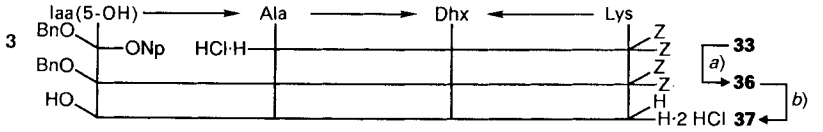
[3]) Compound **23** was obtained from *N*-acetyl-*N'*-[(*tert*-butyloxy)carbonyl]hexane-1,6-diamine (**22**); previously, it was synthesized by selective acetylation of hexane-1,6-diamine in a rather low yield [8].

Scheme 7[2])



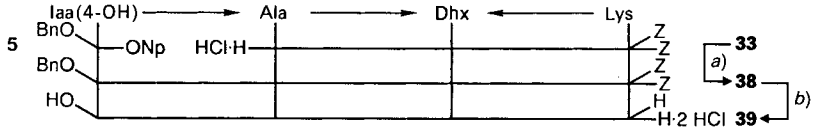
a) Et_3N; 94.9%. *b*) HCl/dioxane; 94.3%. *c*) Et_3N; 71.1%. *d*) HCl/dioxane; 95.8%. *e*) Et_3N; 49.4%. *f*) H_2, Pd/C, then HCl; 100%.

Scheme 8[2])



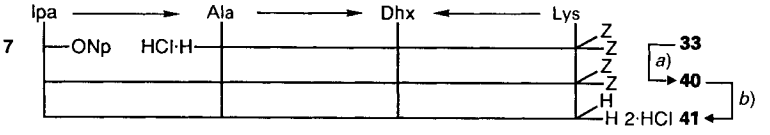
a) Et_3N; 40.7%. *b*) H_2, Pd/C, then HCl; 100%.

Scheme 9[2])



a) Et_3N; 49.2%. *b*) H_2, Pd/C, then HCl.

Scheme 10[2])



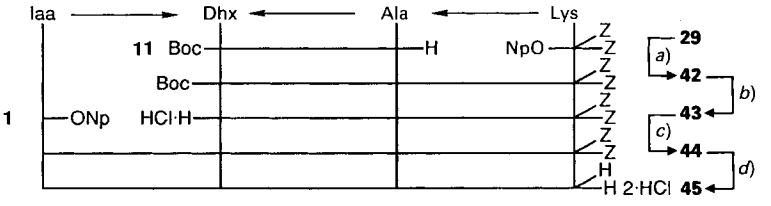
a) Et_3N; 41.3%. *b*) H_2, Pd/C, then HCl; 96.8%.

Next, we prepared the derivatives **35**, **37**, **39**, and **41** where amino acid (II) is L-lysine, the indole moiety is a (1*H*-indol-3-yl)acetyl, (5- or 4-hydroxy-1*H*-indol-3-yl)acetyl, or 3-(1*H*-indol-3-yl)propanoyl residue, and the polyamine unit is hexane-1,6-diamine (*Schemes 7–10*). All syntheses started from the 'right-hand side', coupling 4-nitrophenyl N^2,N^6-bis[(benzyloxy)carbonyl]-L-lysinate (**29**) with hydrochloride **9** (→ **30**; *Scheme 7*). Deprotection of the Boc group yielded hydrochloride **31** which was subsequently coupled with ester **24** (→ **32**). Repeated deblocking furnished the intermediate hydrochloride **33** as an extremely moisture-sensitive salt, which was then used in the preparation of further

derivatives. Thus, compound **35** was obtained from ester **1** and derivative **33** after coupling (→ **34**) and hydrogenation. Similarly, 5-hydroxyindole derivative **37** was prepared from ester **3** and **33** *via* **36** (*Scheme 8*). However, in synthesis of the isomeric 4-hydroxyindole derivative **39** from ester **5** and **33** (*Scheme 9*), the simultaneous removal of the *O*-benzyl and *N*-[(benzyloxy)carbonyl] protecting groups from intermediate **38** proved to be extremely sluggish. The deblocking was not complete, even not after 100 h when decomposition of the product already had started. In fact, the only indication for the formation of the expected product is the electronspray-ionization (ESI) mass spectrum of the corresponding dihydrochloride **39** which afforded the $[M + 1]^+$ ion. The synthesis of the 3-(1*H*-indol-3-yl)propanoyl derivative **41** from hydrochloride **33** and ester **7** *via* **40** was again straightforward (*Scheme 10*).

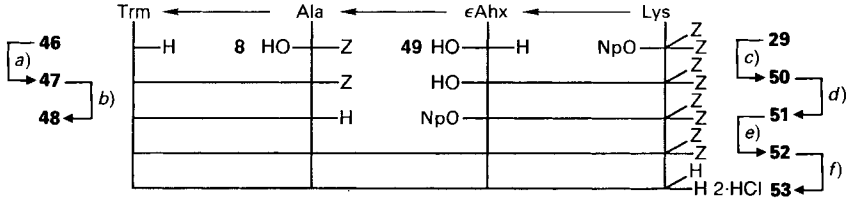
The central part of compound **45** (Iaa→Dhx←Ala←H^+Lys$H^+ \cdot 2Cl^-$) is reversed when compared to compound **35** (Iaa→Ala→Dhx←H^+Lys$H^+ \cdot 2Cl^-$). For its synthesis (*Scheme 11*), the previously obtained amine **11** (*Scheme 1*) was coupled with ester **29** (*Scheme 7*; → **42**). Deprotection of **42** (→ **43**), coupling with ester **1** (→ **44**), and deblocking gave the desired compound **45**.

Scheme 11[2])



a) 95.8%. *b*) HCl/dioxane; 98.5%. *c*) Et_3N; 74.9%. *d*) H_2, Pd/C, then HCl; 100%.

Scheme 12[2])



a) $ClCO_2Et$, Et_3N; 69.0%. *b*) H_2, Pd/C; 92.2%. *c*) *N,N,N',N'*-tetramethylguanidine; 52.6%. *d*) 4-nitrophenyl trifluoroacetate/py; 56.4%. *e*) 76.3%. *f*) H_2, Pd/C, then HCl, 100%.

For the synthesis of compound **53** (*Scheme 12*), tryptamine (**46**) was first coupled with L-alanine derivative **8** (→ **47**) to afford, after hydrogenation, N^{ω}-(L-alanyl)tryptamine (**48**). The latter was coupled with active ester **51** which was obtained from 6-aminohexanoic acid (**49**) and **29** (*Scheme 7*; → **50**) after transesterification with 4-nitrophenyl trifluoroacetate [9]. Deprotection of the resultant **52** afforded the analogue **53**.

Mass spectrometry is a powerful technique in the analysis of naturally occurring spider toxins [10]. Indeed, we found that ESI-MS provides excellent spectra for our

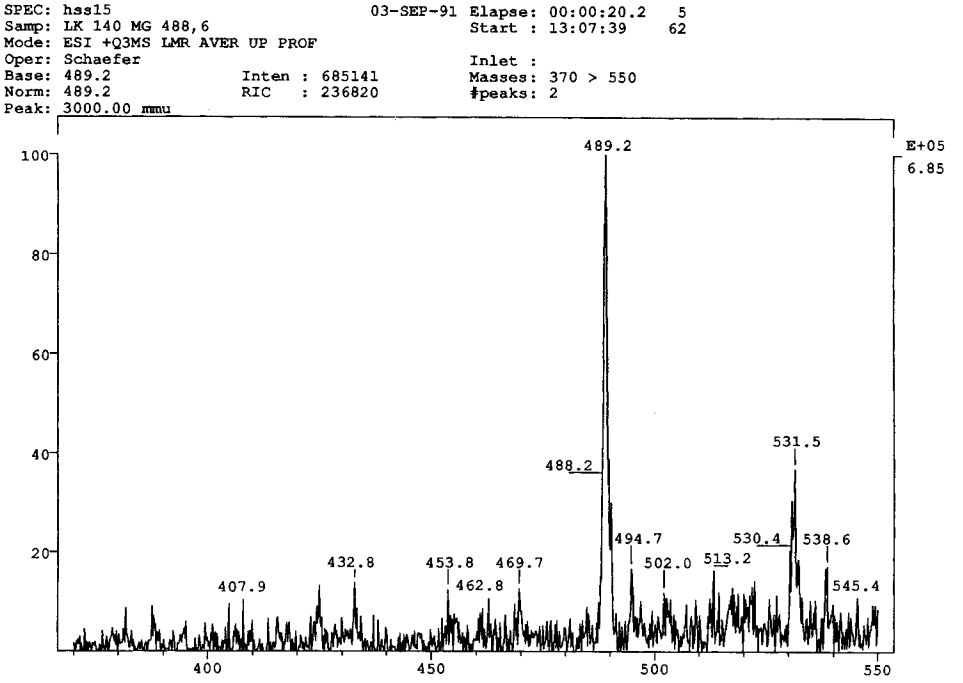


Figure. *Electrospray ionization mass spectrum (ESI-MS) of compound* N-{N-*[(5-hydroxy-1*H*-indol-3-yl)acetyl]*-L-*alanyl*}-N′-*(*L*-*lysyl)hexane-1,6-diamine dihydrochloride* (**37**). M^+ of the free base at 488.

spider-toxin analogues which are practically unanalysable under electron-impact, chemical-ionization, or fast-atom-bombardment conditions. An example is presented in the *Figure*.

The biological activity of the prepared analogues will be reported elsewhere.

We would like to express our sincere gratitude to Dr. *C. Werner* for the HPLC measurements, to Dipl.-chem. *H. Benz* for preparing compound **47** and for his assistance in the preparation of the manuscript, to Dr. *A. Schäfer* for recording the ESI mass spectra, and to the analytical department of our Institute for other spectral measurements. Last but not least, we thank the *Swiss National Foundation* for financial support and *F. Hoffmann-La Roche AG*, Basel, for the pharmacological testing.

Experimental Part

General. Potassium hydrogen phthalate buffer refers to a 0.05M soln. (pH 4.00). The [5-(benzyloxy)- and 4-(benzyloxy)-1*H*-indol-3-yl]acetic acids (**2** and **4**, resp.) were prepared according to [4] [5]. (1*H*-Indol-3-yl)acetic acid, 3-(1*H*-indol-3-yl)propanoic acid (**6**), dry AcOEt, dry dimethylformamide, dry dioxane, dry Et_2O, blue silica gel, *N*-[(benzyloxy)carbonyl]-L-alanine (**8**), *N*-[(*tert*-butyloxy)carbonyl]hexane-1,6-diamine hydrochloride (**9**) were purchased from *Fluka*. The 4-nitrophenyl N^2,N^6-bis[(benzyloxy)carbonyl]-L-lysinate (**29**), succinimido *N*-[(*tert*-butyloxy)carbonyl]-L-alaninate (**24**) were obtained from *Bachem AG*, Switzerland. *N*-[(*tert*-Butyloxy)-carbonyl]propane-1,3-diamine hydrochloride (**14**) was prepared according to *Geiger* [7]. All intermediate hydrochloride salts were stored in desiccators over KOH pellets and blue silica gel, characterized by ^{1}H-NMR, and directly used without further purification. The final toxine analogues were characterized by HPLC, ^{1}H-NMR, and

ESI-MS. Optical-rotation measurements were sometimes omitted due to the unstability and/or limited availability of some products. HPLC Separation: *Nucleosil C-8* column (5 m, 200 × 40 mm i.d.; *Macherey-Nagel*, Düren, Germany); flow rate 1 ml/min; two-step linear gradient: within 15 min from 30% solvent *B* in solvent *A* to 60% solvent *B* in *A* and subsequently within 20 min to 100% solvent *B*; solvent *A*, 1.5% H_3PO_4 in H_2O, solvent *B*, 1.5% H_3PO_4, 20% AcOH, and 25% MeCN in H_2O. TLC: silica gel *60 F_{254}*, *Merck*; detection of indole and Boc derivatives with a vanilline/H_2SO_4 reagent[4]). Prep. TLC: 'PSC-Fertigplatten Kieselgel *60 F_{254}*', *Merck*. Flash chromatography (FC): silica gel *60* (0.040–0.063 mm, *Merck*); eluents: hexane/AcOEt 8:2 (*A*1), 7:3 (*A*2), 4:6 (*A*3), 3:7 (*A*4), 2:8 (*A*5), and 1:9 (*A*6); CH_2Cl_2/MeOH 98:2 (*B*1), 97:3 (*B*2), 95:5 (*B*3), 9:1 (*B*4), 85:15 (*B*5), 8:2 (*B*6), and 7:3 (*B*7). M.p.: *Mettler-FP-5* instrument. Optical rotations: *Zeiss-LEP-A2* instrument. ^{1}H-NMR Spectra: *Bruker-AM-300* instrument (^{1}H: 300 MHz); δ in ppm, J in Hz; in $CDCl_3$, if not mentioned otherwise, as internal standard; deut. = exchanged upon addition of D_2O); superscripts * refer to interchangeable assignments. Mass Spectra: EI- and CI-MS, *Finnigan-SSQ-700* instrument, electrospray-ionization (ESI) MS, *Finnigan-TSQ-700* instrument (sample soln. in MeOH/5% AcOH 1:1). Microanalyses were obtained only for crystalline or distillable substances.

*4-Nitrophenyl [5-(Benzyloxy)-1*H*-indol-3-yl]acetate* (**3**; *Iaa(5-BnO)-ONp*). A mixture of **2** (1.888 g, 6.71 mmol) and 4-nitrophenol (0.933 g, 6.71 mmol) was dissolved under sonication in dry AcOEt (60 ml) and chilled in an ice-bath. *N,N'*-Dicyclohexylcarbodiimide (DCC; 1.384 g, 6.71 mmol) was added under stirring. After 1 h, the bath was removed and stirring continued for 18 h at r.t. The precipitate (*N,N'*-dicyclohexylurea) was filtered and washed with AcOEt and the filtrate evaporated. Chromatographic purification (*A*1, *A*2) provided an oil which solidified upon standing. Trituration under hexane afforded a yellow solid (1.695 g, 62.8%), m.p. 99.9–105.5°. An anal. sample was obtained by recrystallization from abs. EtOH. M.p. 105.0–106.3°. ^{1}H-NMR: 3.93 (*s*, indolyl-CH_2); 5.04 (*s*, PhCH_2); 6.90 (*dd*, J = 2.4, 8.8, H–C(6)); 7.10–7.40 (*m*, C_6H_5, H–C(2), H–C(4), H–C(7), H–C(2'), H–C(6')); 8.03 (br. *s*, deut., NH); 8.13 (*d*, J = 9.1, H–C(3'), H–C(5')). CI-MS (isobutane): 403 (94, $[M + 1]^+$), 373 (38, $[M + 1 - NO]^+$), 141 (10), 140 (100). Anal. calc. for $C_{23}H_{18}N_2O_5$ (402.410): C 68.65, H 4.51, N 6.96; found: C 68.55, H 4.55, N 7.03.

*4-Nitrophenyl [4-(Benzyloxy)-1*H*-indol-3-yl]acetate* (**5**; *Iaa(4-BnO)-ONp*). As described for **3**, from **4** (0.486 g, 1.73 mmol), 4-nitrophenol (0.240 g, 1.73 mmol), and DCC (0.357 g, 1.73 mmol) in dry AcOEt (40 ml): orange oil, which was ground under AcOEt to give a solid (0.526 g, 75.7%). M.p. 130.5–131.5°. ^{1}H-NMR: 4.14 (*s*, indolyl-CH_2); 5.11 (*s*, PhCH_2); 6.53 (*d*, J = 7.7, H–C(5)); 6.84–7.41 (*m*, C_6H_5, H–C(2), H–C(6), H–C(7), H–C(2'), H–C(6')); 8.05 (*m*, 3 H, upon deut. 2 H, H–C(3'), H–C(5'), NH). EI-MS: 402 (14, M^+), 236 (10), 173 (11), 145 (21), 139 (17), 117 (9), 91 (100), 65 (22). Anal. calc. for $C_{23}H_{18}N_2O_5$ (402.410): C 68.65, H 4.51, N 6.96; found: C 68.39, H 4.36, N 6.77.

*4-Nitrophenyl 3-(1*H*-Indol-3-yl)propanoate* (**7**; *Ipa-ONp*). As described for **3**, from **6** (9.461 g, 50.0 mmol), 4-nitrophenol (7.303 g, 52.5 mmol), and DCC (10.382 g, 52.5 mmol) in dry AcOEt (250 ml). After workup, the solid was recrystallized from AcOEt: 6.827 g, m.p. 108.6–110.8°. From the mother liquor, further crops were obtained. Overall: 7.839 g (50.5%). The remainder was highly contaminated (TLC), therefore, discarded. ^{1}H-NMR: 2.95, 3.18 (2*t*, CH_2CH_2); 7.01 (*s*, H–C(2)); 7.12 (*dd*, H–C(2'), H–C(6')); 7.14–7.19 (*m*, H–C(5), H–C(6)); 7.32 (*d*, J = 7.5, H–C(4)*); 7.58 (*d*, J = 7.5, H–C(7)*); 7.98 (br. *s*, deut., NH); 8.17 (*dd*, H–C(3'), H–C(5')). EI-MS: 310 (16, M^+), 178 (6), 139 (8), 130 (100), 71 (8), 57 (11), 43 (13). Anal. calc. for $C_{17}H_{14}N_2O_4$ (310.312): C 65.80, H 4.55, N 9.03; found: C 65.29, H 4.55, N 9.10.

N-{N-*[(Benzyloxy)carbonyl]*-L-*alanyl*}-N'-*[(*tert-*butyloxy)carbonyl]hexane-1,6-diamine* (**10**; *Z-Ala→Dhx-Boc*). To **8** (2.007 g, 8.99 mmol) in THF (10 ml), Et_3N (1.253 ml, 8.99 mmol) was added and the soln. chilled to −15 to −20°. Ethyl chloroformate (0.942 ml, 9.89 mmol) was added and the heterogeneous soln. stirred for 10 min at this temp. (soln. *A*). Meanwhile, **9** (2.50 g, 9.89 mmol) was suspended in THF (15 ml), then Et_3N (1.378 ml, 9.89 ml) and H_2O (1.5 ml) were added, and this soln. *B* was precooled to −15°. Soln. *B* was added in one portion to soln. *A*. After 10 min, the cooling bath was removed and the initially heterogeneous soln. stirred for 18 h at r.t. The bulk of THF was evaporated, and H_2O and AcOEt were added to dissolve the residue. The aq. phase was further extracted with AcOEt (2×), the combined org. layer washed with potassium hydrogen phthalate soln. and H_2O, dried, and evaporated, and the solid (3.339 g, 88.1%) recrystallized from CH_2Cl_2 (15 ml) and Et_2O (45 ml): 2.280 g, m.p. 112.5–112.7°. From the mother liquor, further crops were obtained. Overall: 2.906 g (76.7%). $[\alpha]_D^{24} = -11.5$ (c = 0.340, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO): 1.15–1.25 (*m*, CH_2CH_2, Me(Ala)); 1.37 (*m*, *t*-Bu, 2* CH_2); 2.88, 3.02 (2*m*, 2* CH_2N); 3.98 (*q*, upon deut. *q* with J = 7.1, (CH(Ala)); 5.00 (*AB*('*q*'), PhCH_2); 6.76 (*t*, J = 5.4, deut., NH); 7.35 (*m*, 6 H, upon deut. 5 H, C_6H_5, NH); 7.79 (*t*, J = 5.4, deut., NH). CI-MS (isobutane): 422 (8, $[M + 1]^+$), 348

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[4]) Detection reagents of similar composition were reported for indole derivatives [11].

(11), 322 (100), 258 (19), 240 (17), 214 (65), 91 (10). Anal. calc. for $C_{22}H_{35}N_3O_5$ (421.541): C 62.68, H 8.37, N 9.97; found: C 62.94, H 8.63, N 9.96.

N-(L-*Alanyl*)-N′-[(tert-*butyloxy*)*carbonyl*]*hexane-1,6-diamine* (**11**; *Ala*→*Dhx-Boc*). A soln. of **10** (2.000 g, 4.75 mmol) in MeOH (12 ml) was dropped into a flask containing 10% Pd/C (0.1 g) under Ar. The flask was purged several times with H_2 and the mixture hydrogenated under vigorous stirring for 20 h, then filtered through a *Celite* pad, and washed several times with MeOH. Evaporation gave a colourless, homogeneous (TLC) liquid (1.345 g, 98.6%). An anal. sample was obtained by prep. TLC (*B*7). $[\alpha]_D^{20} = +0.8$ ($c = 0.893$, MeOH). ^{1}H-NMR ((D$_6$)DMSO): 1.09 (*d*, $J = 6.9$, Me(Ala)); 1.22 (*m*, CH_2CH_2); 1.35 (*m*, *t*-Bu, 2 CH_2); 1.86 (br. *s*, deut., NH_2); 2.88 (*m*, CH_2); 3.03 (*m*, CH_2); 3.21 (*q*, $J = 6.9$, CH(Ala)); 6.75 (*m*, deut., NH); 7.73 (*m*, deut., NH). CI-MS (NH_3): 288 (48, $[M + 1]^+$), 232 (100), 214 (12), 188 (31).

N-[(tert-*Butyloxy*)*carbonyl*]-N′-{N-[(1H-*indol-3-yl*)*acetyl*]-L-*alanyl*}*hexane-1,6-diamine* (**12**; *Iaa*→*Ala*→*Dhx-Boc*). To a soln. of **11** (0.457 g, 1.59 mmol) in THF (10 ml) was added 4-nitrophenyl (1*H*-indol-3-yl)acetate (**1**; 0.428 g, 1.45 mmol) in one portion. The homogeneous soln. was stirred for 21 h at r.t., then evaporated and chromatographed (*B*2, *B*3): amorphous, waxy solid (0.580 g, 90.3%). $[\alpha]_D^{22} = -13.1$ ($c = 0.510$, MeOH). ^{1}H-NMR: 1.15–1.45 (*m*, 4 CH_2); 1.48 (*s*, *t*-Bu); 2.98–3.20 (*m*, 2 CH_2N); 3.72 (*s*, indolyl-CH_2); 4.50 (*dq*, $J = 7.0$, 7.6, CH(Ala)); 4.65 (br. *s*, deut., NH); 6.79 (*d*, $J = 7.6$, deut., NH(Ala)); 6.88 (br. *s*, deut., NH); 7.09–7.23 (*m*, H–C(2), H–C(5), H–C(6)); 7.40 (*d*, $J = 7.2$, H–C(4)*); 7.55 (*d*, $J = 7.9$, H–C(7)*); 8.90 (br. *s*, deut., NH). CI-MS (isobutane): 455 (20, $[M + 1]^+$), 346 (22), 345 (100).

N-*Acetyl*-N′-{N-[(1H-*indol-3-yl*)*acetyl*]-L-*alanyl*}*hexane-1,6-diamine* (**13**; *Iaa*→*Ala*→*Dhx*←*Ac*). The soln. of **12** (0.556 g, 1.25 mmol) in dry dioxane (10 ml) was added with a syringe within 2 min to a sat. HCl/dioxane soln. (50 ml) stirred under Ar. After 1 min, the homogeneous soln. became cloudy, and soon an oil was separated from the mixture. After 40 min stirring, the soln. was evaporated and the residual semisolid ground under dry Et_2O to yield a hygroscopic powder which was directly acetylated in the following way: a soln. of the salt in dry DMF (10 ml) and pyridine (0.504 ml, 6.25 mmol) was stirred under Ar and cooled to 0°, then Ac_2O (0.414 ml, 4.38 mmol) was introduced and the mixture stirred at 0° for 1 h then at r.t. for 18 h. DMF was evaporated, the residue co-evaporated with toluene (2×), then dissolved in CH_2Cl_2, the soln. washed with potassium hydrogen phthalate buffer (2×), H_2O (1×), sat. $NaHCO_3$ soln. (2×), and brine (1×), dried, evaporated, and the residue chromatographed (*B*3): 115.0 mg (23.8%) of amorphous powder. $[\alpha]_D^{23} = -11.7$ ($c = 0.300$, MeOH). ^{1}H-NMR: 1.08–1.39 (*m*, 4 CH_2, Me(Ala)); 1.89 (*s*, Ac); 3.13 (*m*, 2 CH_2N); 3.66 (*s*, indolyl-CH_2); 4.41 (*dq*, $J = 7.0$, 7.8, upon deut. *q*, CH(Ala)); 5.83 (br. *s*, deut., NH); 6.31 (*d*, $J = 7.8$, deut., NH(Ala)); 6.39 (*t*, $J = 5.7$, NH); 7.02–7.16 (*m*, H–C(2), H–C(5), H–C(6)); 7.32 (*d*, $J = 8.1$, H–C(4)*); 7.47 (*d*, $J = 7.9$, H–C(7)*); 8.94 (br. *s*, deut., H–N(1)). CI-MS (isobutane): 387 (100, $[M + 1]^+$), 369 (13), 159 (6).

N-{N-[(*Benzyloxy*)*carbonyl*]-L-*alanyl*}-N′-[(tert-*butyloxy*)*carbonyl*]*propane-1,3-diamine* (**15**; *Z-Ala*→*Dpr-Boc*). As described for **10**, a mixed anhydride was prepared from **8** (2.232 g, 10.0 mmol), Et_3N (1.394 ml, 10.0 mmol), ethyl chloroformate (1.048 ml, 11.0 mmol), and THF (10 ml). This was *in situ* transformed using **14** (2.236 g, 10.61 mmol) and Et_3N (1.48 ml, 10.61 mmol) in THF (15 ml) and H_2O (1.5 ml). The crude product was recrystallized from CH_2Cl_2 (20 ml) and Et_2O (75 ml): 1.894 g, m.p. 100.8–105.0°. The mother liquor was chromatographed (*A*3, *A*4): 0.706 g, m.p. 103.9–105.7°. Overall: 2.600 g (68.5%). $[\alpha]_D^{24} = -10.7$ ($c = 0.580$, $CHCl_3$). ^{1}H-NMR: 1.40 (*d*, $J = 7.0$, Me(Ala)); 1.42 (*s*, *t*-Bu); 1.59 (*m*, CH_2); 3.12 (*m*, CH_2N); 3.28 (*m*, CH_2N); 4.22 (*m*, CH(Ala)); 4.93 (br. *s*, deut., NH); 5.10 (*s*,. PhCH_2); 5.49 (*d*, $J = 6.3$, deut., NH(Ala)); 6.83 (br. *s*, deut., NH); 7.35 (*m*, C_6H_5). CI-MS (isobutane): 380 (1, $[M + 1]^+$), 272 (17, $[M + 1 - C_6H_5CH_2OH]^+$), 216 (100), 172 (1), 147 (6), 91 (1). Anal. calc. for $C_{19}H_{29}N_3O_5$ (379.460): C 60.14, H 7.70, N 11.07; found: C 59.98, H 7.65, N 11.09.

N-(L-*Alanyl*)-N′-[(tert-*butyloxy*)*carbonyl*]*propane-1,3-diamine* (**16**; *Ala*→*Dpr-Boc*). Compound **15** (1.400 g, 3.69 mmol) in MeOH (5 ml) was hydrogenated in the presence of 10% Pd/C (70 mg) for 16 h under vigorous stirring. Workup (see **11**) provided an oil which slowly crystallized on standing. Trituration under hexane gave a solid (0.884 g, 97.7%), m.p. 75.3–76.5°. An anal. sample was obtained by recrystallization from Et_2O. M.p. 75.5–77.0°. $[\alpha]_D^{22} = -1.0$ ($c = 1.033$, MeOH). ^{1}H-NMR ((D$_6$)DMSO): 1.13 (*d*, $J = 6.9$, Me(Ala)); 1.41 (*s*, *t*-Bu); 1.52 (*m*, CH_2); 1.90 (very br. *s*, deut., NH_2); 2.93 (*m*, CH_2N); 3.07 (*m*, CH_2N); 3.23 (*q*, $J = 6.9$, CH(Ala)); 6.80 (unresolved *t*, deut., NH); 7.82 (unresolved *t*, deut., NH). CI-MS (isobutane): 491 (32, $[2M + 1]^+$), 435 (7), 246 (79, $[M + 1]^+$), 190 (100), 146 (3). Anal. calc. for $C_{11}H_{23}N_3O_3$ (245.324): C 53.85, H 9.45, N 17.13; found: C 53.99, H 9.61, N 17.17.

N-[(tert-*Butyloxy*)*carbonyl*]-N′-{N-[(1H-*indol-3-yl*)*acetyl*]-L-*alanyl*}*propane-1,3-diamine* (**17**; *Iaa*→*Ala*→*Dpr-Boc*). Compound **16** (1.397 g, 5.69 mmol) and **1** (1.606 g, 5.42 mmol) in THF (15 ml) were allowed to react at r.t. for 18 h under continuous stirring. Chromatography of the evaporated mixture (*B*2) afforded an amorphous foam (1.929 g, 88.4%). $[\alpha]_D^{23} = -20.4$ ($c = 1.000$, MeOH). ^{1}H-NMR: 1.08 (*d*, $J = 7.0$, Me(Ala)); 1.35 (*m*, *t*-Bu, CH_2); 2.95 (*m*, CH_2); 3.08 (*m*, CH_2N); 3.68 (*s*, indolyl-CH_2); 4.41 (*dq*, $J = 7.0$, 7.2, CH(Ala)); 4.85 (br. *s*, deut.,

NH); 6.28 (br. *s*, deut., NH); 6.72 (br. *s*, deut., NH); 7.03–7.17 (*m*, H–C(2), H–C(5), H–C(6)); 7.30 (*d*, J = 8.6, H–C(4)*); 7.49 (*d*, J = 7.8, H–C(7)*); 8.52 (br. *s*, deut., NH). ESI-MS: 402 ($[M + 1]^+$).

N-*Acetyl*-N′-{N-*[(1*H*-indol-3-yl)acetyl]*-L-*alanyl*}*propane-1,3-diamine* (**18**; *Iaa→Ala→Dpr←Ac*). As described for **13**, **17** (0.600 g, 1.49 mmol) in dry dioxane (10 ml) was treated with sat. HCl/dioxane (50 ml) and then immediately with pyridine (0.524 ml, 6.5 mmol) and Ac_2O (0.425 ml, 4.5 mmol) in dry DMF (12 ml). Chromatography (*B*3) of the crude product provided an oil which was further purified by prep. TLC (*B*4): 109.0 mg (21.6%) of amorphous **18**. $[\alpha]_D^{24} = -19.3$ (c = 0.503, MeOH). ^{1}H-NMR: 1.17 (*d*, J = 7.0, Me(Ala)); 1.42 (*m*, CH_2); 1.88 (*s*, Ac); 3.00–3.11 (*m*, 2 CH_2N); 3.68 (*s*, indolyl-CH_2); 4.38 (*dq*, upon deut. *q* with J = 7.0, CH(Ala)); 6.16–6.22 (*m*, deut., 2 NH); 6.75 (br. *s*, deut., NH); 7.03–7.17 (*m*, H–C(2), H–C(5), H–C(6)); 7.32 (*d*, J = 8.1, H–C(4)*); 7.48 (*d*, J = 7.9, H–C(7)*); 8.52 (br. *s*, deut., H–N(1)). CI-MS (isobutane): 345 (100, $[M + 1]^+$), 214 (47), 198 (19), 188 (24), 174 (10), 159 (7), 117 (12).

N-{N-{*[5-(Benzyloxy)-1*H*-indol-3-yl]acetyl*}-L-*alanyl*}-N′-*[(*tert*-*butyloxy)carbonyl]hexane-1,6-diamine* (**19**; *Iaa(5-BnO)→Ala→Dhx-Boc*). As described for **10**, from **2** (1.119 g, 3.98 mmol), Et_3N (0.585 ml, 4.18 mmol), and ethyl chloroformate (0.40 ml, 4.18 mmol) in THF (15 ml) (soln. *A*) and **11** (1.201 g, 4.18 mmol) in THF (10 ml) (soln. *B*). The evaporated reaction mixture was subjected directly to chromatography (*B*2): 1.502 g (68.5%), amorphous foam. An anal. sample was obtained using prep. TLC (*B*3). $[\alpha]_D^{22} = -9.1$ (c = 0.473, MeOH). ^{1}H-NMR: 1.07–1.38 (*m*, 4 CH_2, Me(Ala)); 1.40 (*s*, *t*-Bu); 2.88–3.10 (*m*, 2 CH_2N); 3.62 (*s*, indolyl-CH_2); 4.40 (*dq*, upon deut. *q* with J = 6.8, CH(Ala)); 4.55 (br. *s*, deut., NH); 5.01 (*s*, PhCH_2); 6.18 (br. *s*, deut., 2 NH); 6.89 (*d*, J = 8.8, H–C(7)*); 7.02 (*m*, H–C(4)*, H–C(6)*); 7.23–7.45 (*m*, C_6H_5, H–C(2)); 8.67 (br. *s*, deut., H–N(1)). EI-MS: 551 (17, $[M + 1]^+$), 451 (89), 361 (35), 288 (26), 277 (53), 249 (50), 247 (100), 236 (57), 217 (74).

N-*Acetyl*-N′-{N-{*[5-(benzyloxy)-1*H*-indol-3-yl]acetyl*}-L-*alanyl*}*hexane-1,6-diamine* (**20**; *Iaa(5-BnO)→Ala→Dhx←Ac*). As described for **13**, **19** (0.583 g, 1.06 mmol) in dry dioxane (10 ml) was treated with sat. HCl/dioxane soln. (50 ml) and then immediately acetylated using pyridine (0.504 ml, 6.25 mmol) and Ac_2O (0.414 ml, 4.38 mmol). The crude product was subjected to chromatography (*B*3), then further purified by prep. TLC (*B*4): 154.0 mg (29.5%), which was triturated under hexane to give a solid. M.p. 147.0–149.3°. $[\alpha]_D^{25} = -9.2$ (c = 0.510, MeOH). ^{1}H-NMR: 1.05–1.36 (*m*, 3 CH_2, Me(Ala)); 1.58 (*q*, CH_2); 1.88 (*s*, Ac); 2.89–3.10 (*m*, 2 CH_2N); 3.60 (*s*, indolyl-CH_2); 4.40 (*dq*, J = 7.0, 7.9, CH(Ala)); 5.00 (*s*, PhCH_2); 5.93 (br. *s*, deut., NH); 6.41 (*d*, J = 7.9, deut., NH(Ala)); 6.49 (*t*, J = 5.7, deut., NH); 6.86 (*dd*, J = 8.8, 2.4, H–C(6)); 7.00 (*s*, H–C(2), H–C(7)); 7.19–7.41 (*m*, C_6H_5, H–C(4)); 8.98 (br. *s*, deut., H–N(1)). CI-MS (NH_3): 493 (100, $[M + 1]^+$), 334 (3), 263 (10), 230 (3), 159 (7). Anal. calc. for $C_{28}H_{36}N_4O_4$ (492.624): C 68.26, H 7.37, N 11.37; found: C 68.11, H 7.39, N 11.48.

N-*Acetyl*-N′-{N-*[(5-hydroxy-1*H*-indol-3-yl)acetyl]*-L-*alanyl*}*hexane-1,6-diamine* (**21**; *Iaa(5-OH)→Ala→Dhx←Ac*). A soln. of **20** (113.8 mg, 0.231 mmol) in MeOH (2 ml) was hydrogenated in the presence of 10% Pd/C (7 mg) for 18 h. Chromatographic purification (*B*5) of the filtered and evaporated mixture afforded an oil (61.6 mg, 66.3%). ^{1}H-NMR ((D_6)DMSO): 1.16–1.38 (*m*, 4 CH_2, Me(Ala)); 1.78 (*s*, Ac); 2.98 (*m*, 2 CH_2N); 3.45 (*s*, indolyl-CH_2); 4.22 ('*quint.*', upon deut. *q* with J = 7.0, CH(Ala)); 6.58 (*dd*, J = 8.6, 2.3, H–C(6)); 6.82 (*d*, J = 2.1, H–C(2)); 7.10 (*m*, H–C(4), H–C(7)); 7.75 (*m*, deut., 2 NH); 7.88 (*d*, J = 7.6, deut., NH(Ala)); 8.57 (br. *s*, deut., H–N(1)); 10.55 (br. *s*, deut., OH). EI-MS: 402 (6, M^+), 384 (13), 230 (22), 173 (58), 146 (100), 133 (58), 44 (63).

N-*Acetyl*-N′-*[(*tert*-*butyloxy)carbonyl]hexane-1,6-diamine* (**22**; *Boc-Dhx←Ac*). To a suspension of **9** (2.528 g, 10.0 mmol) in CH_2Cl_2 (20 ml), pyridine (3.23 ml, 40.0 mmol) was added under stirring. The mixture was chilled to 0° and Ac_2O (2.36 ml, 25.0 mmol) added in one portion. Stirring was continued at 0° for 1 h, then at r.t. for 24 h. The homogeneous soln. was diluted with CH_2Cl_2 and worked up as described for **13**. Chromatography (*B*2) followed by trituration under hexane gave a solid (1.92 g, 74.3%). An anal. sample was obtained by recrystallization from Et_2O. M.p. 66.2–67.4°. ^{1}H-NMR: 1.26 (*m*, 2 CH_2); 1.37–1.45 (*m*, *t*-Bu, 2 CH_2); 1.91 (*s*, Ac); 3.04 (*m*, CH_2N); 3.16 (*m*, CH_2N); 4.47 (br. *s*, deut., NH); 5.60 (br. *s*, deut., NH). Anal. calc. for $C_{13}H_{26}N_2O_3$ (258.364): C 60.43, H 10.14, N 10.84; found: C 60.19, H 9.98, N 10.63.

N-*Acetylhexane-1,6-diamine Hydrochloride* (**23**; *HCl·H-Dhx←Ac*). As described for **13**, **22** (1.853 g, 7.17 mmol) in dry dioxane (20 ml) was treated with sat. HCl/dioxane (50 ml; reaction time 1 h). Dioxane was evaporated and the residue co-evaporated twice with MeOH and then crystallized from i-PrOH (8.5 ml) and Et_2O (4.5 ml) at –30° for several days: 0.935 g, m.p. 129.0–130.0° ([8]: 130–131°). From the mother liquor, an additional crop was obtained. Overall: 1.307 g (93.6%). ^{1}H-NMR ((D_6)DMSO): 1.32–1.42 (*m*, 6 H) and 1.53 (*t*, 4 CH_2); 1.78 (*s*, Ac); 2.73 ('*q*', upon deut. *t* with J = 7.5, CH_2N); 3.01 ('*quint.*', upon deut. *t* with J = 6.9, CH_2N); 7.86–8.01 (br. *m*, deut., NH, NH_3^+).

N-*Acetyl*-N′-{N-*[(*tert*-*butyloxy)carbonyl]*-L-*alanyl*}*hexane-1,6-diamine* (**25**; *Boc-Ala→Dhx←Ac*). To a suspension of **23** (0.680 g, 3.49 mmol) in THF (40 ml), Et_3N (0.487 ml, 3.49 mmol) was added under sonication, then **24** (1.00 g, 3.49 mmol), in one portion. The mixture was stirred for 18 h at r.t., $Et_3N·HCl$ was filtered off, the

soln. evaporated, the residue dissolved in CH_2Cl_2, the soln. washed with H_2O (3×) and brine (1×), dried, and evaporated. The solid residue was triturated under AcOEt and filtered: 0.664 g (57.7%), m.p. 98.0–100.5°. $[\alpha]_D^{24} = -30.7$ ($c = 0.537$, MeOH). ^{1}H-NMR: 1.30–1.57 (*m*, 4 CH_2, *t*-Bu, Me(Ala)); 2.00 (*s*, Ac); 3.25 (*m*, 2 CH_2N); 4.14 (*m*, upon deut. *q* with $J = 6.8$, CH(Ala)); 5.08 (br. *s*, deut., NH); 5.68 (br. *s*, deut., NH); 6.78 (br. *s*, deut., NH). CI-MS (NH_3): 330 (100, $[M + 1]^+$), 273 (11), 256 (24), 230 (49). Anal. calc. for $C_{16}H_{31}N_3O_4$ (329.443): C 58.34, H 9.49, N 12.76; found: C 58.47, H 9.30, N 12.58.

N-*Acetyl*-N′-(L-*alanyl*)*hexane-1,6-diamine Hydrochloride* (**26**; *HCl·Ala→Dhx←Ac*). As described for **13**, **25** (0.656 g, 1.99 mmol) in dry dioxane (20 ml) was treated with a sat. HCl/dioxane soln. (50 ml). The evaporated reaction mixture was co-evaporated with abs. EtOH (2×) and the sticky residue triturated under Et_2O to give the hygroscopic salt: 0.482 g (91.1%). M.p. 126–138°. ^{1}H-NMR ((D_6)DMSO): 1.25–1.40 (*m*, 4 CH_2, Me(Ala)); 1.78 (*s*, Ac); 2.99 (*m*, CH_2N); 3.08 (*m*, CH_2N); 3.78 (*m*, upon deut. *q* with $J = 7.0$, CH(Ala)); 7.86 (br. *s*, deut., NH); 8.20 (br. *s*, deut., NH_3^+); 8.45 (br. *s*, deut., NH).

Iaa(*5-BnO*)*→Ala→Dhx←Ac* (**20**) *from* **26**. A soln. of **3** (0.151 g, 0.376 mmol) in THF (10 ml) was allowed to react with **26** (0.100 g, 0.376 mmol) in the presence of Et_3N (0.052 ml, 0.376 mmol). After 18 h, there was still unreacted **3** (TLC). The mixture was evaporated and the residue purified by prep. TLC (*B*4): 45.8 mg of **3** and 108.0 mg (83.4%; 69.5% conversion) of **20** were obtained as an oil. The latter was seeded with **20** (from **19**) and triturated under hexane/AcOEt 1:1 to give crystals. M.p. 146.7–147.8°. ^{1}H-NMR, TLC: identical with a sample obtained in an earlier experiment. Deprotection of **20** to **21** was achieved as described above.

Iaa→Ala→Dhx←Ac (**13**) *from* **26**. A soln. of **1** (0.123 g, 0.414 mmol) in THF (10 ml) was allowed to react with **26** (0.110 g, 0.414 mmol) and with excess Et_3N (0.200 ml, 1.60 mmol). The mixture war stirred for 40 h, then the salts were filtered off, the filtrate was evaporated and the residue submitted to prep. TLC (*B*3) to give an oily product (141.0 mg, 88.1%), identical (^{1}H-NMR, TLC) with the previously prepared sample.

N-*Acetyl*-N′-{N-{[*4-(benzyloxy)-1*H-*indol-3-yl*]*acetyl*}-L-*alanyl*}*hexane-1,6-diamine* (**27**; *Iaa*(*4-BnO*)*→Ala→Dhx←Ac*). A soln. of **5** (0.151 g, 0.376 mmol) in THF (10 ml) was allowed to react with **26** (0.100 g, 0.376 mmol) in the presence of Et_3N (0.052 ml, 0.376 mmol). After 18 h, the precipitated solid was filtered off and washed several times with CH_2Cl_2. These washings were evaporated, and the residue was triturated under AcOEt/hexane to give a solid (92.0 mg), m.p. 129.2–132.2°. The filtrate from the reaction mixture was evaporated and the residue submitted to prep. TLC (*B*4): 82.8 mg, m.p. 126.0–128.0°. Overall: 174.8 mg (94.3%). $[\alpha]_D^{19} = +6.4$ ($c = 0.497$, MeOH). ^{1}H-NMR: 0.9 (*d*, $J = 7.2$, Me(Ala)); 1.25–1.40 (*m*, 4 CH_2); 1.97 (*s*, Ac); 3.00–3.10 (*m*, 2 CH_2N); 3.55 (*s*, indolyl-CH_2); 4.20 (*dq*, CH(Ala)); 5.15 (*AB*('*q*'), PhCH_2); 5.90 (br. *s*; deut., NH); 5.98 (br. *s*, deut., NH); 7.04 (*d*, $J = 2.0$, H–C(2)); 7.30–7.45 (*m*, 9 H, upon deut. 8 H, C_6H_5, NH, H–C(5), H–C(6), H–C(7)); 9.40 (br. *s*, deut., NH). EI-MS: 492 (6, $M^{+\cdot}$), 402 (3), 263 (36), 172 (38), 146 (59), 91 (100), 44 (75). Anal. calc. for $C_{28}H_{36}N_4O_4$ (492.624): C 68.26, H 7.37, N 11.37; found: C 68.08, H 7.48, N 11.20.

N-*Acetyl*-N′-{N-[*(4-hydroxy-1*H-*indol-3-yl)acetyl*]-L-*alanyl*}*hexane-1,6-diamine* (**28**; *Iaa*(*4-OH*)*→Ala→Dhx←Ac*). As described for **11**, **27** (140.4 mg, 0.285 mmol) in MeOH (2 ml) was hydrogenated in the presence of 10% Pd/C (8 mg). Prep. TLC (*B*5) gave an oil (104.0 mg, 90.7%). ^{1}H-NMR ((D_6)DMSO): 1.15–1.31 (*m*, 4 CH_2, Me(Ala)); 1.78 (*s*, Ac); 2.98 (*m*, CH_2N); 3.67 (*s*, indolyl-CH_2); 4.23 ('*quint.*', upon deut. *q*, with $J = 7.1$, CH(Ala)); 6.72 (*dd*, $J = 6.4, 1.9$, H–C(5)*); 6.83 (*m*, H–C(6), H–C(7)*); 6.98 (*s*, H–C(2)); 7.78 (br. *s*, deut., NH); 7.87 (br. *s*, deut., NH); 8.32 (*d*, $J = 7.3$, deut., NH(Ala)); 10.25 (br. *s*, deut., NH); 10.78 (br. *s*, deut., OH). EI-MS: 402 (1, $M^{+\cdot}$), 384 (30, $[M - H_2O]^+$), 171 (15), 146 (85), 130 (100), 44 (63).

N-{N^2,N^6-*Bis*[*(benzyloxy)carbonyl*]-L-*lysyl*}-N′-[*(* tert-*butyloxy)carbonyl*]*hexane-1,6-diamine* (**30**; *Boc-Dhx←[Z-Lys(Z)]*). To a suspension of **9** (1.327 g, 5.25 mmol) in THF (40 ml), Et_3N (0.732 ml, 5.25 mmol) was added under stirring. Then, **29** (2.678 g, 5.00 mmol) was added in one portion and stirring continued for 40 h. The salts were filtered off and the filtrate was evaporated. The slow solidification of the oily residue was completed by trituration with hexane/AcOEt 1:1: 2.473 g, m.p. 112.3–114.8°. From the mother liquor, a further 4-nitrophenol-free crop was obtained. Overall: 2.909 g (94.9%). $[\alpha]_D^{21} = -6.1$ ($c = 1.067$, MeOH). ^{1}H-NMR: 1.33–1.68 (*m*, 7 CH_2, *t*-Bu); 3.08–3.28 (*m*, 3 CH_2); 4.11 ('*quint.*', upon deut. *t*, CH(Lys)); 4.60 (br. *s*, deut., NH); 4.91 (br. *s*, deut., NH); 5.10 (*m*, 2 PhCH_2); 5.58 (br. *s*, deut., NH); 6.23 (br. *s*, deut., NH); 7.84 (br. *s*, 2 C_6H_5). CI-MS (isobutane): 613 (1, $[M + 1]^+$), 539 (1), 405 (4), 323 (8), 297 (15), 237 (36), 147 (100). Anal. calc. for $C_{33}H_{48}N_4O_7$ (612.773): C 64.68, H 7.90, N 9.14; found: C 64.74, H 7.80, N 9.19.

N-{N^2,N^6-*Bis*[*(benzyloxy)carbonyl*]-L-*lysyl*}*hexane-1,6-diamine Hydrochloride* (**31**, *HCl·H-Dhx←[Z-Lys(Z)]*). As described for **13**, **30** (2.901 g; 4.73 mmol) in dry dioxane (30 ml) was treated with sat. HCl/dioxane (100 ml): 2.453 g (94.3%). ^{1}H-NMR ((D_6)DMSO): 1.22–1.59 (*m*, 7 CH_2); 2.72 (*m*, CH_2N); 2.91–3.08 (*m*, 2 CH_2N); 3.88 ('*q*', CH(Lys)); 4.99 (*s*, PhCH_2); 5.01 (*s*, PhCH_2); 7.25–7.38 (*m*, 12 H, upon deut. 10 H, 2 C_6H_5, 2 NH); 7.86–7.98 (*m*, deut., NH, NH_3^+).

N-{N^2,N^6-*Bis[(benzyloxy)carbonyl]*-L-*lysyl*}-N'-{N-[(tert-*butyloxy)carbonyl]*-L-*alanyl*}*hexane-1,6-diamine* (**32**; *Boc-Ala→Dhx←[Z-Lys(Z)]*). To a suspension of **31** (2.453 g, 4.47 mmol) in THF (100 ml), Et_3N (0.923 ml, 6.60 mmol) was added under sonication. Then, **24** (1.279 g, 4.47 mmol) in THF (15 ml) was added in one portion to the intensively stirred suspension. After 18 h stirring, the salts were filtered off, the filtrate was evaporated, and the residue taken up in AcOEt. This soln. was extracted with H_2O (3×) and brine (1×), dried, evaporated, and the residue chromatographed (*A*5, *A*6, finally neat AcOEt): amorphous foam (2.172 g, 71.1%). $[\alpha]_D^{24} = -13.9$ (c = 1.087, MeOH). ^{1}H-NMR: 1.20–1.80 (*m*, 7 CH_2, *t*-Bu, Me(Ala)); 3.05–3.25 (*m*, 3 CH_2N); 4.10 (*m*, CH(Ala), CH(Lys)); 5.00 (br. *s*, 5 H, upon deut. 4 H, 2 PhCH_2, NH); 5.73 (br. *s*, deut., NH); 5.85 (br. *s*, deut., NH); 6.52 (br. *s*, deut., NH); 7.25 (*m*, 2 C_6H_5). CI-MS (NH_3): 684 (100, $[M + 1]^+$), 610 (5), 584 (13), 576 (32), 502 (32), 476 (100), 394 (28), 368 (40), 108 (12), 91 (100).

N-(L-*Alanyl*)-N'-{N^2,N^6-*bis[(benzyloxy)carbonyl]*-L-*lysyl*}*hexane-1,6-diamine Hydrochloride* (**33**, *HCl·Ala→Dhx←[Z-Lys(Z)]*). As described for **13**, **32** (2.276 g, 3.33 mmol) in dry dioxane (30 ml) was treated with sat. HCl/dioxane (100 ml): 1.977 g (95.8%) of extremely moisture-sensitive, electrostatic white powder. ^{1}H-NMR ((D_6)DMSO): 1.21–1.58 (*m*, 7 CH_2, Me(Ala)); 2.94–3.15 (*m*, 3 CH_2N); 3.78 (*m*, CH(Lys)); 3.88 (*m*, CH(Ala)); 5.00 (*s*, 2 PhCH_2); 7.22 (*t*, deut., NH); 7.30–7.38 (*m*, 2 C_6H_5); 7.86 (*t*, deut., NH); 7.92 (*t*, deut., NH); 8.13 (br. *s*, deut., NH_3^+); 8.38 (*t*, deut., NH).

N-{N^2,N^6-*Bis[(benzyloxy)carbonyl]*-L-*lysyl*}-N'-{N-[(1H-*indol-3-yl)acetyl]*-L-*alanyl*}*hexane-1,6-diamine* (**34**; *Iaa→Ala→Dhx←[Z-Lys(Z)]*). To a suspension of **33** (0.310 g, 0.50 mmol) in THF (20 ml) and MeOH (20 ml), excess Et_3N (0.348 ml, 2.50 mmol) was added, then in one portion **1** (0.148 g, 0.50 mmol). After 18 h stirring, the salts were filtered off, the filtrate was evaporated, and the residue chromatographed (*B*2, *B*3): amorphous solid (0.183 g, 49.4%). $[\alpha]_D^{25} = -11.7$ (c = 0.480, MeOH). ^{1}H-NMR: 1.10–1.72 (*m*, 7 CH_2, Me(Ala)); 2.90–3.28 (*m*, 3 CH_2N); 3.67 (*s*, indolyl-CH_2); 4.15 (*m*, upon deut. *t* with J = 6.8, CH(Lys)); 4.50 ('*q*', upon deut. *q* with J = 7.0, CH(Ala)); 5.09 (*s*, 5 H, upon deut. 4 H, 2 PhCH_2, NH); 5.92 (*d*, J = 5.6, deut., NH); 6.49 (br. *s*, deut., NH); 6.62 (br. *s*, deut., NH); 6.70 (br. *s*, deut., NH); 7.07–7.34 (*m*, 2 C_6H_5, H–C(2), H–C(5), H–C(6), H–C(7)*); 7.54 (*d*, J = 7.8, H–C(4)*); 8.70 (br. *s*, deut., NH). EI-MS: 632 (8, $[M - C_7H_7O]^+$), 575 (20), 338 (8), 157 (17), 130 (28), 91 (100), 43 (41).

N-{N-[(1H-*Indol-3-yl)acetyl]*-L-*alanyl*}-N'-(L-*lysyl)hexane-1,6-diamine Dihydrochloride* (**35**; *Iaa→Ala→Dhx←H^+LysH^+·2Cl^-*). A soln. of **34** (139.4 mg, 0.188 mmol) in MeOH (3 ml) was hydrogenated for 30 h in the presence of 10% Pd/C (20 mg) under vigorous stirring. Filtration and evaporation gave a homogeneous oil (TLC) which was transformed into dihydrochloride salt using sat. HCl/dioxane soln. (10 ml). The precipitated gum was redissolved in MeOH (5 ml), then the soln. evaporated immediately, and the residue triturated with dry Et_2O to yield the solid, hygroscopic dihydrochloride (110 mg, quant.). HPLC: t_R 6.72 min. ^{1}H-NMR ((D_6)DMSO): 1.18–1.45 (*m*, 5 CH_2, Me(Ala)); 1.58 (*m*, CH_2); 1.72 (*m*, CH_2); 2.72 (*m*, CH_2N); 3.00 (*m*, CH_2N); 3.10 (*m*, CH_2N); 3.55 (overlapping with the H_2O signal, indolyl-CH_2); 3.72 (*m*, upon deut. *t* with J = 6.5, CH(Lys)); 4.23 ('*q*', upon deut. *q* with J = 7.1, CH(Ala)); 6.96 (*dd*, H–C(5)*); 7.07 (*dd*, H–C(7)*); 7.20 (*d*, J = 2.0, upon deut. *s*, H–C(2)); 7.35 (*d*, J = 8.0, H–C(4)); 7.55 (*d*, J = 7.8, H–C(6)); 7.84 (*t*, deut., NH); 7.98 (br. *s*, deut., NH_3^+); 8.05 (*d*, J = 7.0, NH(Ala)); 8.25 (br. *s*, deut., NH_3^+); 8.57 (br. *s*, deut., NH); 10.80 (br. *s*, deut., H–N(1)). ESI-MS: 473 ($[M + 1]^+$).

N-{N^2,N^6-*Bis[(benzyloxy)carbonyl]*-L-*lysyl*}-N'-{N-{[5-(*benzyloxy)-1*H-*indol-3-yl]acetyl*}-L-*alanyl*}*hexane-1,6-diamine* (**36**; *Iaa(5-BnO)→Ala→Dhx←[Z-Lys(Z)]*). Ester **3** (0.500 g, 0.806 mmol) and **33** (0.324 g, 0.806 mmol) were coupled in the usual way in the presence of Et_3N (0.167 ml, 1.20 mmol), in THF (20 ml), MeOH (1 ml), and DMF (0.5 ml). After 18 h stirring, the mixture was evaporated, the residue taken up in H_2O and extracted with CH_2Cl_2, and the combined org. phase washed with brine, dried, and evaporated. The residue was subjected to column chromatography (*B*2, *B*3): amorphous solid (0.278 g, 40.7%). $[\alpha]_D^{22} = -9.1$ (c = 1.020, MeOH). ^{1}H-NMR: 1.08–1.72 (*m*, 7 CH_2, Me(Ala)); 2.85–3.20 (*m*, 3 CH_2N); 3.57 (*s*, indolyl-CH_2); 4.08 (*m*, CH(Lys)); 4.43 ('*quint.*', upon deut. *q* with J = 7.0, CH(Ala)); 5.00 (br. *s*, 7 H, upon deut. 6 H, 3 PhCH_2, NH); 5.84 (br. *s*, deut., NH); 6.54 (br. *s*, deut., NH); 6.63 (br. *s*, deut., NH); 6.85 (*dd*, J = 8.8, 2.3, H–C(6)); 7.00 (*m*, H–C(2), H–C(4)); 7.17–7.40 (*m*, 3 C_6H_5, H–C(7)); 8.62 (br. *s*, deut., H–N(1)). ESI-MS: 847 ($[M + 1]^+$).

N-{N-[(5-*Hydroxy-1*H-*indol-3-yl)acetyl]*-L-*alanyl*}-N'-(L-*lysyl)hexane-1,6-diamine Dihydrochloride* (**37**; *Iaa(5-OH)→Ala→Dhx←H^+LysH^+·2Cl^-*). A soln. of **36** (225.6 mg, 0.266 mmol) in MeOH (5 ml) and DMF (3 ml) was hydrogenated for 60 h in the presence of 10% Pd/C (42 mg). The mixture was filtered, the filtrate evaporated, and its residue co-evaporated with toluene (2×) and dissolved in MeOH (5 ml). Sat. HCl/Et_2O soln. was added (5 ml) and the soln. evaporated and triturated under Et_2O: solid dihydrochloride (150.0 mg, 100%). HPLC: t_R 3.73 min. ^{1}H-NMR ((D_6)DMSO): 1.15–1.46 (*m*, 5 CH_2, Me(Ala)); 1.58 (*m*, CH_2); 1.72 (*m*, CH_2); 2.75 (*m*, CH_2N); 3.00 (*m*, CH_2N); 3.09 (*m*, CH_2N); 3.45 (*s*, indolyl-CH_2); 3.70 (overlapping with the H_2O signal, CH(Lys)); 4.22 ('*quint.*', CH(Ala)); 6.58 (*dd*, J = 8.6, 2.3, H–C(6)); 6.83 (*d*, J = 2.1, H–C(2)); 7.12 (*m*, H–C(4),

H–C(7)); 7.82 (*t*, deut., NH); 7.96 (br. *m*, deut., NH_3^+, NH); 8.23 (br. *s*, deut., NH_3^+); 8.58 (br. *s*, deut., NH); 8.66 (br. *s*, deut., NH); 10.58 (br. *s*, deut., H–N(1)). ESI-MS: 489 ($[M + 1]^+$); *Figure*.

N-{N-{*[4-(Benzyloxy)-1*H*-indol-3-yl]acetyl*}-L-*alanyl*}-N′-{N^2,N^6-*bis[(benzyloxy)carbonyl]*-L-*lysyl*}-*hexane-1,6-diamine* (**38**; *Iaa(4-BnO)→Ala→Dhx←[Z-Lys(Z)]*). Ester **5** (0.140 g, 0.348 mmol) and **33** (0.259 g, 0.418 mmol) were coupled in the usual way in the presence of Et_3N (0.070 ml, 0.50 mmol), in THF/DMF 5:1. After 18 h stirring, the salts were filtered off, the filtrate was evaporated and the residue co-evaporated with toluene (2×) and chromatographed (*B*2, *B*3): amorphous powder (145.0 mg, 49.2%). $[\alpha]_D^{25} = +6.3$ ($c = 0.540$, MeOH). ^{1}H-NMR: 0.77–1.00 (*m*, 3 CH_2, Me(Ala)); 1.18–1.42 (*m*, 3 CH_2); 1.54–1.80 (*m*, CH_2); 2.75–3.14 (*m*, 3 CH_2); 3.59, 3.83 (2*d*, each $J = 15.0$, CH_2); 4.05–4.23 (*m*, CH(Ala), CH(Lys)); 5.01 (*s*, 2 PhCH_2); 5.15 (*AB*('*q*'), CH_2); 5.83 (br. *s*, deut., NH); 6.67 (br. *s*, deut., NH); 6.58 (*m*, deut., 2 NH); 6.73 (br. *s*, deut., NH); 7.00 (*m*, H–C(5), H–C(6), H–C(7)); 7.21–7.49 (*m*, 3 C_6H_5, H–C(2)); 9.12 (br. *s*, deut., H–N(1)). ESI-MS: 848 ($[M + 1]^+$).

N{N-*[(4-Hydroxy-1*H*-indol-3-yl)acetyl]*-L-*alanyl*}-N′-*(L-lysyl)hexane-1,6-diamine Dihydrochloride* (**39**; *Iaa(4-OH)→Ala→Dhx←H^+LysH$^+ \cdot 2Cl^-$*). A soln. of **38** (145.0 mg, 0.171 mmol) in MeOH (2 ml) and DMF (1 ml) was hydrogenated in the presence of 10% Pd/C (10 mg). The sluggish reaction was not complete, even not after 100 h (fresh catalyst and H_2 being added from time to time); however, decomposition of the product already started. Therefore, the mixture was worked up and the dihydrochloride formed as described for **37**. TLC, HPLC, and ^{1}H-NMR: mixture of **38**, **39**, and decomposition products. HPLC: t_R (**39**) 4.82 min. ESI-MS: 489 ($[M + 1]^+$).

N-{N^2,N^6-*Bis[(benzyloxy)carbonyl]*-L-*lysyl*}-N′-{N-*[3-(1*H*-indol-3-yl)propanoyl]*-L-*alanyl*}*hexane-1,6-diamine* (**40**; *Ipa→Ala→Dhx←[Z-Lys(Z)]*). Ester **7** (0.350 g, 1.13 mmol) and **33** (0.700 g, 1.13 mmol) were coupled in the usual way in the presence of Et_3N (0.236 ml, 1.70 mmol), in THF (20 ml) and DMF (2.5 ml), by stirring for 18 h. The salts were filtered off, the filtrate was evaporated and the residue then worked up and chromatographed as described for **36**: amorphous foam (0.352 g, 41.3%). $[\alpha]_D^{20} = -15.4$ ($c = 0.583$, MeOH). ^{1}H-NMR: 1.13–1.46 (*m*, 7 CH_2, Me(Ala)); 1.58 (*m*, CH_2); 1.72 (*m*, CH_2); 2.95–3.23 (*m*, 4 CH_2); 4.10 (*m*, CH(Lys)); 4.40 ('*quint.*', 1 H, upon deut. *q*, $J = 7.0$, CH(Ala)); 5.00 (br. *s*, 5 H, upon deut. 4 H, 2 PhCH_2, NH); 5.84 (br. *s*, deut., NH); 6.45 (br. *s*, deut., NH); 6.63 (br. *m*, deut., 2 NH); 6.98–7.30 (*m*, 2 C_6H_5, H–C(2), H–C(5), H–C(6), H–C(7)*); 7.49 (*d*, $J = 7.5$, H–C(4)*); 8.35 (br. *s*, deut., H–N(1)). ESI-MS: 755 ($[M + 1]^+$).

N-{N-*[3-(1*H*-Indol-3-yl)propanoyl]*-L-*alanyl*}-N′-*(L-lysyl)hexane-1,6-diamine Dihydrochloride* (**41**; *Ipa→Ala→Dhx←H^2LysH$^+ \cdot 2Cl^-$*). A soln. of **40** (0.292 g, 0.388 mmol) in DMF (2.5 ml) and MeOH (4 ml) was hydrogenated in the presence of 10% Pd/C (15 mg) for 14 h. Then, fresh catalyst (15 mg) was added and hydrogenation continued for additional 23 h. The mixture was worked up and the dihydrochloride formed as described for **37**: 210.0 mg (96.8%). HPLC: t_R 7.83 min. ^{1}H-NMR ((D_6)DMSO): 1.17 (*d*, $J = 7.00$, Me(Ala)); 1.23–1.42 (*m*, 5 CH_2); 1.57 (*m*, CH_2); 1.72 (*m*, CH_2); 2.45 (overlapping with DMSO signal, CH_2); 2.72 (*m*, CH_2); 2.90 (*m*, CH_2); 3.02 (*m*, CH_2); 3.11 (*m*, CH_2); 3.72 (overlapping with H_2O signal, upon deut. *t*, CH(Lys)); 4.24 ('*quint.*', upon deut. *q*, $J = 7.0$, CH(Ala)); 6.96 (*dd*, H–C(5)*); 7.06 (*dd*, H–C(6)*); 7.10 (*d*, $J = 2.0$, H–C(2)); 7.32 (*d*, $J = 8.0$, H–C(4)); 7.52 (*d*, $J = 8.0$, H–C(7)); 7.78 (br. *s*, deut., NH); 7.93 (br. *s*, deut., NH_3^+); 8.04 (*d*, deut., NH(Ala)); 8.20 (br. *s*, deut., NH_3^+); 8.54 (br. *s*, deut., NH); 10.79 (br. *s*, deut., OH). ESI-MS: 487 ($[M + 1]^+$).

N-{N-{N^2,N^6-*Bis[(benzyloxy)carbonyl]*-L-*lysyl*}-L-*alanyl*}-N′-*[(*tert*-butyloxy)carbonyl]hexane-1,6-diamine* (**42**; *Boc-Dhx←Ala←[Z-Lys(Z)]*). A mixture of **11** (1.080 g, 3.76 mmol) in THF (15 ml) and **29** (2.012 g, 3.76 mmol) in THF (12 ml) was stirred for 18 h. The formed precipitate was filtered and washed with Et_2O to give the product (1.746 g), m.p. 131.7–136.0°. From the mother liquor, an additional crop was obtained by chromatography (*B*1, *B*3). Overall: 2.460 g (95.8%). An anal. sample was prepared by recrystallization from MeOH/Et_2O. M.p. 134.0–136.0°. $[\alpha]_D^{24} = -18.6$ ($c = 0.533$, MeOH). ^{1}H-NMR: 1.22–1.80 (*m*, 7 CH_2, *t*-Bu, Me(Ala)); 3.00–3.20 (*m*, 3 CH_2); 4.03 (*m*, CH(Lys)); 4.33 (*m*, upon deut. *q* with $J = 7.0$, CH(Ala)); 4.57 (br. *s*, deut., NH); 5.00 (*m*, 5 H, upon deut., 4 H, 2 PhCH_2, NH); 5.73 (br. *s*, deut., NH); 6.35 (br. *s*, deut., NH); 6.50 (*d*, deut., NH(Ala)); 7.25 (*m*, 2 C_6H_5). ESI-MS: 684 ($[M + 1]^+$). Anal. calc. for $C_{36}H_{53}N_5O_8$ (683.853): C 63.23, H 7.81, N 10.24; found: C 63.48, H 7.51, N 10.13.

N-{N-{N^2,N^6-*Bis[(benzyloxy)carbonyl]*-L-*lysyl*}-L-*alanyl*}*hexane-1,6-diamine Hydrochloride* (**43**; *HCl·H-Dhx←Ala←[Z-Lys(Z)]*). A soln. of **42** (2.324 g, 3.40 mmol) in dry dioxane (60 ml) was treated in the usual way (100 ml sat. HCl/dioxane, 1 h): white hygroscopic powder (2.077 g, 98.5%). ^{1}H-NMR ((D_6)DMSO): 1.20–1.63 (*m*, 7 CH_2, Me(Ala)); 2.72 (*m*, CH_2); 2.95–3.12 (*m* 2 CH_2); 3.96 (*m*, CH(Lys)); 4.22 ('*quint.*', CH(Ala)); 5.00 (*s*, PhCH_2); 5.03 (*s*, PhCH_2); 7.24 (*m*, deut., NH); 7.35 (*m*, 2 C_6H_5); 7.82–8.03 (*m*, deut., NH_3^+, 3 NH).

N-{N-{N^2,N^6-*Bis[(benzyloxy)carbonyl]*-L-*lysyl*}-L-*alanyl*}-N′-*[(1*H*-indol-3-yl)acetyl]hexane-1,6-diamine* (**44**; *Iaa→Dhx←Ala←[Z-Lys(Z)]*). A mixture of **43** (0.800 g, 1.29 mmol), Et_3N (0.250 ml, 1.80 mmol), and **1** (0.382 g, 1.29 mmol) in THF (20 ml) and DMF (3 ml) was stirred for 18 h. Workup and chromatography as

described for **38** gave an amorphous powder (0.716 g, 74.9%). $[\alpha]_D^{23} = -16.9$ ($c = 0.557$, MeOH). ^{1}H-NMR ((D$_6$)DMSO/CDCl$_3$): 1.03–1.75 (*m*, 7 CH$_2$, Me(Ala)); 2.95–3.10 (*m*, 3 CH$_2$); 3.64 (*s*, indolyl-CH$_2$); 4.03 (*m*, CH(Lys)); 4.32 ('*quint.*', upon deut. *q* with $J = 7.0$, CH(Ala)); 4.99 (*s*, PhCH$_2$); 5.02 (*s*, PhCH$_2$); 5.98 (br. *s*, deut., NH); 6.29 (br. *s*, deut., NH); 6.50 (br. *s*, deut., NH); 6.93 (br. *s*, deut., NH); 7.02 (*dd*, H–C(5)*); 7.09 (*m*, 2 H, upon deut. 1 H, H–C(6)*, NH); 7.21–7.35 (*m*, 2 C$_6$H$_5$, H–C(2), H–C(4)); 7.47 (*d*, $J = 7.7$, H–C(7)); 9.96 (br. *s*, deut., NH). ESI-MS: 741 ($[M + 1]^+$).

N-*[(1H-Indol-3-yl)acetyl]*-N′-*[*N-*(*L-*lysyl)*-L-*alanyl]hexane-1,6-diamine Dihydrochloride* (**45**; *Iaa→Dhx←Ala←H$^+$LysH$^+$·2Cl$^-$*). A soln. of **44** (303.2 mg, 0.409 mmol) in MeOH (3 ml) and DMF (1 ml) in the presence of 10% Pd/C (17 mg) was hydrogenated for 48 h. The mixture was worked up and the residue transformed into its dihydrochloride as described for **37**: 230.0 mg (quant.). HPLC: t_R 7.56 min. ^{1}H-NMR ((D$_6$)DMSO): 1.18–1.42 (*m*, 5 CH$_2$, Me(Ala)); 1.57 (*m*, CH$_2$); 1.72 (*m*, CH$_2$); 2.72 (*m*, CH$_2$); 3.03 (*m*, 2 CH$_2$); 3.48 (*s*, indolyl-CH$_2$); 3.74 (overlapping with the H$_2$O signal, detected upon deut., *t*, 1 H, CH(Lys)); 4.29 ('*quint.*', upon deut. *q*, with $J = 7.0$, CH(Ala)); 6.96 (*dd*, H–C(5)*); 7.03 (*dd*, H–C(6)*); 7.18 (*d*, upon deut. *s*, $J = 2.2$, H–C(2)); 7.34 (*d*, $J = 8.0$, H–C(4)); 7.54 (*d*, $J = 7.8$, H–C(7)); 7.95–8.05 (*m*, deut., NH$_3^+$, 2 NH); 8.69 (br. *s*, deut., NH); 10.89 (br. *s*, deut., NH). ESI-MS: 473 ($[M + 1]^+$).

N$^\omega$-{N-*[(Benzyloxy)carbonyl]*-L-*alanyl*}*tryptamine* (**47**; *Trm←(Z-Ala)*). As described for **10** from **8** (2.33 g, 10.0 mmol), tryptamine (**46**; 1.06, 10 mmol), ethyl chloroformate (1.08 g, 10.0 mmol), and Et$_3$N (1.01 g, 10.0 mmol) in THF (80 ml): 2.51 (69.0%). White solid. M.p. 121.5–122.0° (AcOEt/MeOH/hexane). $[\alpha]_D^{23} = -20.8$ ($c = 0.749$, MeOH). ^{1}H-NMR (CD$_3$OD): 1.27 (*d*, $J = 7.2$, Me(Ala)); 2.93 (*m*, $J = 7.0$), 3.39–3.49 (*m*, 2 CH$_2$); 4.08 (*q*, $J = 7.2$, CH(Ala)); 5.07 (*s*, PhCH$_2$); 6.96–7.34 (*m*, H–C(4), H–C(5), H–C(6), H–C(7), C$_6$H$_5$); 7.55 (*d*, $J = 7.8$, H–C(2)). CI-MS (isobutane): 366 (100, $[M + 1]^+$). Anal. calc. for C$_{21}$H$_{23}$N$_3$O$_3$ (365.436): C 69.02, H 6.34, N 11.50; found: C 69.00, H 6.25, N 11.59.

N$^\omega$-*(*L-*Alanyl)tryptamine* (**48**; *Trm←Ala*). A soln. of **47** (1.853 g, 5.07 mmol) in MeOH (18 ml) was hydrogenated in the presence of 10% Pd/C (95 mg) for 20 h. The crude product was chromatographed (*B*4, *B*6) to yield an oil (1.081 g, 92.2%). An anal. sample was obtained by prep. TLC (*B*6): oil. $[\alpha]_D^{25} = -4.1$ ($c = 0.927$, MeOH). ^{1}H-NMR ((D$_6$)DMSO): 1.10 (*d*, $J = 6.9$, Me(Ala)); 1.97 (br. *s*, deut., NH$_2$); 2.81 (*t*, $J = 7.4$, CH$_2$); 3.22 (*q*, $J = 6.9$, CH(Ala)); 3.35 (overlapping with the H$_2$O signal, CH$_2$); 6.98 (*m*, H–C(5)); 7.05 (*m*, H–C(6)); 7.14 (*d*, $J = 2.2$, H–C(2)); 7.32 (*d*, $J = 8.0$, H–C(4)); 7.54 (*d*, $J = 8.0$, H–C(7)); 7.90 (br. *s*, deut., NH). CI-MS (NH$_3$): 232 (100, $[M + 1]^+$), 143 (5).

6-{{N^2,N^6-*Bis[(benzyloxy)carbonyl]*-L-*lysyl*}*amino*}*hexanoic Acid* (**50**; *εAhx←[Z-Lys(Z)]*). A mixture of 6-aminohexanoic acid (**49**; 0.344 g, 2.63 mmol), *N,N,N′,N′*-tetramethylguanidine (0.330 ml, 2.63 mmol), and **29** (1.339 g, 2.63 mmol) in MeOH (20 ml) was intensively stirred for 18 h. The mixture was evaporated, the residue taken up in H$_2$O and acidified with AcOH (0.172 ml; 3.0 mmol), and the emulsion extracted with AcOEt. The org. extracts were washed with H$_2$O and brine, dried, and evaporated. The residue was chromatographically purified (*A*4, then *B*4, *B*6). The obtained oil was made crystalline by addition of hexane/AcOEt 1:1 and sonication, then storage in a refrigerator: 0.694 g (52.6%). An anal. sample was obtained by recrystallization from MeOH, AcOEt, and hexane. M.p. 114.0–117.0°. $[\alpha]_D^{20} = -7.5$ ($c = 0.927$, MeOH). ^{1}H-NMR: 1.21–1.79 (*m*, 6 CH$_2$); 2.25 (*m*, CH$_2$); 3.12 (*m*, CH$_2$N, CH$_2$CO); 3.30 (br. *s*, deut., NH); 4.06 (*m*, CH(Lys)); 5.00 (*s*, 2 PhCH$_2$); 5.08 (br. *s*, deut., NH); 5.75 (br. *s*, deut., NH*); 6.45 (br. *s*, deut., OH*); 7.25 (*m*, 2 C$_6$H$_5$). CI-MS (NH$_3$): 528 (100, $[M + 1]^+$), 484 (10), 437 (31), 420 (18), 394 (18), 391 (38), 376 (12), 218 (7), 108 (19), 102 (60). Anal. calc. for C$_{28}$H$_{37}$N$_3$O$_7$ (527.623): C 63.74, H 7.07, N 7.96; found: C 63.76, H 7.08, N 8.11.

4-Nitrophenyl 6-{{N^2,N^6-*Bis[(benzyloxy)carbonyl]*-L-*lysyl*}*amino*}*hexanoate* (**51**; *(εAhx-NpO)←[Z-Lys(Z)]*). To a soln. **50** (0.420 g, 0.796 mmol) in dry pyridine (1 ml, 12.4 mmol), 4-nitrophenyl trifluoroacetate (0.225 g, 0.955 mmol) was added in one portion and the mixture stirred for 1.5 h. The soln. was poured into H$_2$O. The precipitated oil was sonicated to give a crystalline solid which contained (TLC) some unreacted **50**. Chromatographic purification (*A*4, *A*5, *A*6) yielded pure **51** (0.291 g, 56.4%). M.p. 116.3–118.6°. $[\alpha]_D^{20} = -4.3$ ($c = 1.224$, MeOH). ^{1}H-NMR: 1.20–1.72 (*m*, 6 CH$_2$); 2.53 (*t*, CH$_2$); 3.08–3.24 (*m*, CH$_2$N, CH$_2$CO); 4.00 ('*quint.*', CH(Lys)); 4.76 (br. *s*, deut., NH); 5.00 (*s*, 2 PhCH$_2$); 5.92 (br. *s*, deut., NH); 6.09 (br. *s*, deut., NH); 7.24 (*m*, 2 C$_6$H$_5$, H–C(2), H–C(6)); 8.19 (*d*, $J = 9.1$, H–C(3), H–C(5)). CI-MS (NH$_3$): 649 (100, $[M + 1]^+$), 619 (10), 541 (13), 511 (20), 403 (9), 311 (3), 110 (7) 96 (78), 79 (100). Anal. calc. for C$_{34}$H$_{40}$N$_4$O$_9$ (648.719): C 62.95, H 6.22, N 8.64; found: C 62.79, H 6.30, N 8.50.

N$^\omega$-{6-{{N-{N^2,N^6-*Bis[(benzyloxy)carbonyl]*-L-*lysyl*}*amino*}*hexanoyl*}-L-*alanyl*}*tryptamine* (**52**; *Trm←Ala←εAhx←[Z-Lys(Z)]*). To a soln. of **51** (0.185 g, 0.285 mmol) in THF (5 ml), **48** (0.0659 g; 0.285 mmol) in THF (5 ml) was added in one portion. The mixture was stirred for 18 h. The precipitate was filtered and washed with Et$_2$O: **52** (0.1394 g, 66.0%), m.p. 171.3–173.5°. A further crop was obtained from the evaporated mother liquor by prep. TLC (*B*4). Overall: 0.1611 g (76.3%). An anal. sample was obtained by repeated prep. TLC (*B*4).

M.p. 173.0–174.0°. $[\alpha]_D^{20} = -21.7$ ($c = 0.557$, MeOH). ^{1}H-NMR ((D$_6$)DMSO): 1.13–1.56 (*m*, 6 CH$_2$, Me(Ala)); 2.10 (*m*, CH$_2$); 2.80 (*t*, CH$_2$); 2.98 (*m*, 2 CH$_2$); 3.30 (overlapping with the H$_2$O signal, CH$_2$); 3.89 ('*quint.*', CH(Lys)); 4.24 ('*quint.*', CH(Ala)); 6.95 (*dd*, H–C(5)); 7.05 (*dd*, H–C(6)); 7.12 (*d*, $J = 2.0$, H–C(2)); 7.23 (br. *s*, deut., NH); 7.35 (*m*, 12 H, upon deut. 11 H, 2 C$_6$H$_5$, H–C(7), NH); 7.53 (*d*, $J = 7.7$, H–C(4)); 7.83 (*t*, deut., NH); 7.90 (*m*, deut., 2 NH); 10.80 (br. *s*, deut., H–N(1)). CI-MS (NH$_3$): 525 (18), 391 (1), 365 (2), 258 (14), 187 (6), 143 (5), 79 (100). Anal. calc. for C$_{41}$H$_{52}$N$_6$O$_7$ (740.908): C 66.47, H 7.07, N 11.34; found: C 66.31, H 7.19, N 11.51.

N$^{\omega}$-{N-{6-[(L-*Lysyl*)*amino*]*hexanoyl*}-L-*alanyl*}*tryptamine Dihydrochloride* (**53**; *Trm*←*Ala*←*εAhx*←*H*$^+$*LysH*$^+\cdot$*2Cl*$^-$). A soln. of **52** (0.120 g, 0.162 mmol) in MeOH (3 ml) and DMF (2 ml) was hydrogenated for 20 h in the presence of 10% Pd/C (7 mg). The mixture was worked up and transformed into its dihydrochloride as described for **37**: 109.0 mg (quant.). HPLC: t_R 6.70 min. ^{1}H-NMR ((D$_6$)DMSO): 1.15–1.74 (*m*, 6 CH$_2$, Me(Ala)); 2.10 (*m*, CH$_2$); 2.77 (*m*, CH$_2$); 3.10 (*m*, CH$_2$); 3.32 (*m*, CH$_2$); 3.73 (*m*, CH(Lys)); 4.25 ('*quint.*', CH(Ala)); 6.96 (*dd*, H–C(5)); 7.05 (*dd*, H–C(6)); 7.12 (*d*, $J = 2.0$, H–C(2)); 7.33 (*d*, $J = 7.9$, H–C(4)); 7.53 (*d*, $J = 7.8$, H–C(7)); 7.97 (*m*, deut., NH$_3^+$, 2 NH); 8.25 (*m*, deut., NH$_3^+$); 8.59 (*t*, deut., NH); 10.85 (br. *s*, deut., H–N(1)). ESI-MS: 473 ([*M* + 1]$^+$).

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