Synthetic Analogues of Naturally Occurring Spider Toxins: Synthesis of 2-(Hydroxyphenyl)propanamides of Spermidine and Spermine

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In a study on structure-activity relationships of spider toxins, six model compounds, namely the spermidine derivatives **6**, **8**, and **16** as well as the spermine derivatives **24**, **27**, and **32** were synthesized. The synthesis proceeds through stepwise construction of the polyamine backbone, including protection and deprotection of the amino functions. The differentiation of the derivatives by analytical and spectroscopic methods is discussed.

Introduction. – Naturally occurring spider toxins are potent inhibitors of glutamate receptors of the central nervous system. These receptors are believed to be involved in higher neural functions such as memory and learning, and neurological disorders, *e.g.*, hypoxemia, epilepsy, *Huntington*'s, *Alzheimer*'s and *Parkinson*'s diseases [1]. In recent years, there has been considerable interest in the isolation and identification of the constituents of spider toxins. These toxins are characterized as consisting of a variety of related compounds with a novel structure that contains one phenolic group in addition to a polyamine moiety [2]. The discovery of the bizarrely structured polyamine-containing toxins, which block glutamate receptors, led to the synthesis of a large variety of compounds [3–5]. As a continuation of our previously published results [6], it was of interest to carry out the synthesis of new model compounds of the spider toxins and to study their biological activity [7].

Synthesis and Discussion. – In one sequence of amide formation and removal of the protecting groups, we synthesized three spermidine and three spermine derivatives. For the synthesis of the target compounds, we chose the 3,4-dihydrocoumarin (**1**; *cf. Scheme 2*) or its protected and ring-opened equivalent 3-[2-(benzyloxy)phenyl]propanoic acid (**2**) as phenolic substrates, which were coupled with suitably protected spermidine or spermine derivatives **3** and **4**, respectively.

Synthesis of the Spermidine Derivatives. For amide formation, we followed the method of *Mukaiyama* and co-workers [8]. According to *Scheme 1*, the propanoic acid derivative **2** was treated with benzyl *N*-({8-[(benzyloxy)carbonyl]amino}-4-azaoctyl)-carbamate (**3**) [9] in the presence of 1-methyl-2-chloropyridinium iodide to give, in quantitative yield, the protected amide **5**. Removal of the benzyl (Bn) and (benzyloxy)-carbonyl (Z) protecting groups by hydrogenolysis (H_2/Pd) led to the deprotected amine **6**. For analytical purposes, **6** was converted to its *N*,*N*′′-diacetyl derivative **7**. Transamidation of the tertiary amide **6** was achieved with KH in propane-1,3-diamine according to [10–12]. The resulting secondary amide **8** and its *N*,*N*′′-diacetyl derivative **9** show different properties in comparison to the isomers **6** and **7**, respectively.

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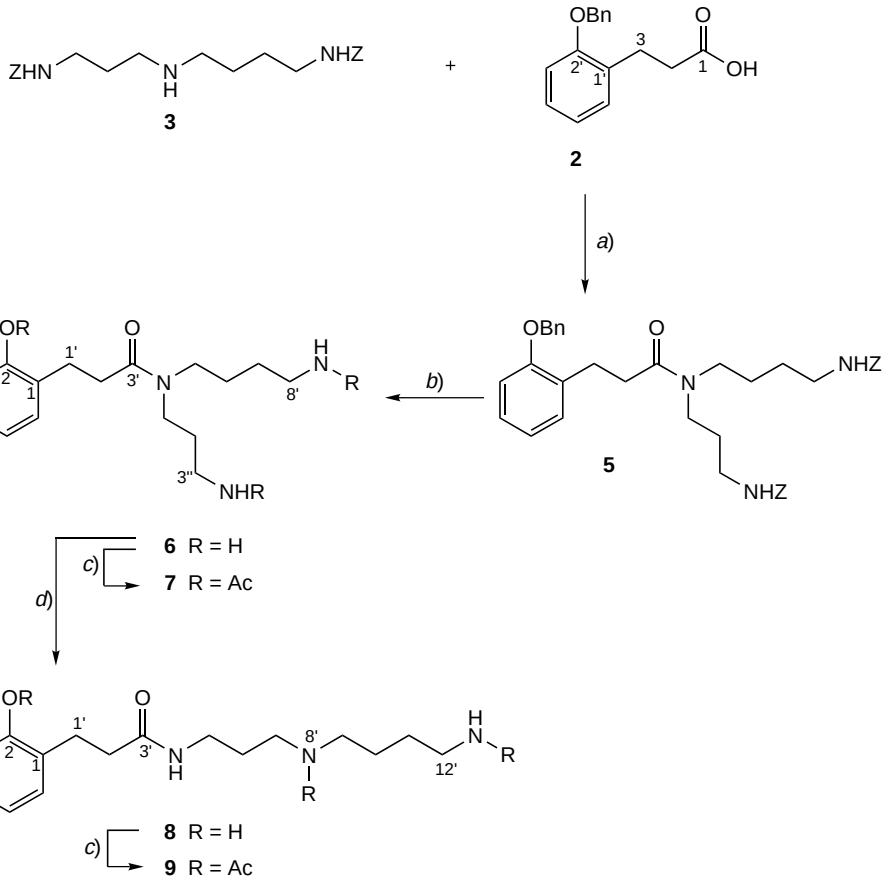
[1]) Part of the Ph.D. thesis of *K. P.*, Universität Zürich, 1999.

Scheme 1

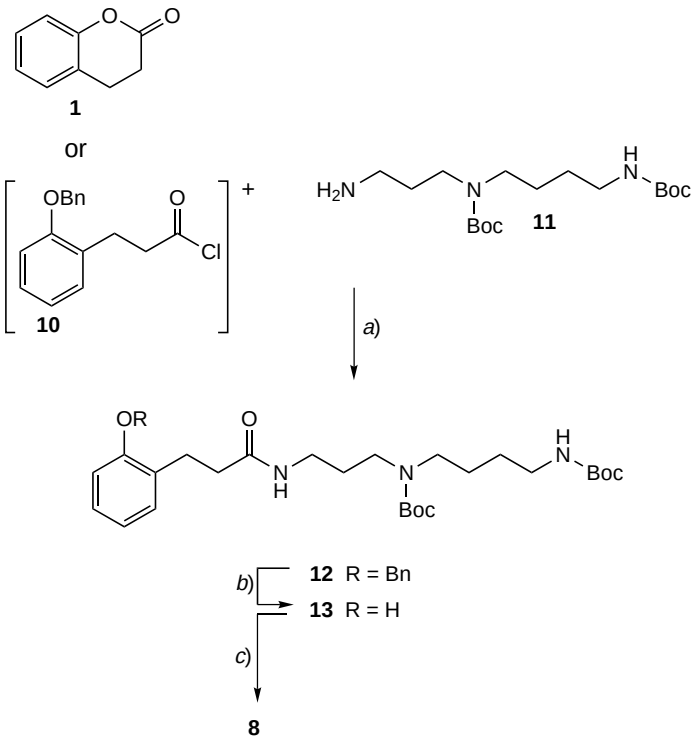


a) 1-Methyl-2-chloropyridinium iodide, Et_3N, CH_2Cl_2, r.t.; 98%. *b*) H_2/10% Pd/C, AcOH, r.t.; 95%. *c*) AcONa, Ac_2O, r.t., 80%. *d*) KH, propane-1,3-diamine, r.t.; 90%.

To confirm the isomerization of **6** to its counterpart **8**, the amine **8** was prepared by an independent procedure, which is outlined in *Scheme 2*. 3-[(2-Benzyloxy)phenyl]-propanoyl chloride (**10**) was converted to the *N*-acylspermidine derivative **12** by treatment with bis(Boc)-spermidine **11** [13] in AcOEt. Removal of the Bn groups in **12** by hydrogenolysis followed by treatment with CF_3COOH gave **8** in 65% yield. The synthesis of **8** was best accomplished by aminolysis of 3,4-dihydrocoumarin (**1**). The direct acylation of the primary amines with **1** proved to be more efficient for the preparation of amides. Therefore, treatment of the bis(Boc)-protected spermidine **11** with **1** led to the amide **13** in 96% yield, which, after removal of the Boc groups, gave the amine **8**.

The preparation of **16**, an isomer of **8**, was performed with the starting material *N*-(4-aminobutyl)-1,2,3,4,5,6-hexahydropyrimidine (**14**), obtained by reaction of HCOH with spermidine [14]. Treating **14** with **1** gave the aminal **15**. Deprotection with methanolic

Scheme 2



a) **1**, EtOH, r.t., 96%; **10**, EtOAc, Et_3N, 0°, 99%. *b*) H_2/10% Pd/C, AcOH, r.t. *c*) CF_3COOH, r.t., 95%.

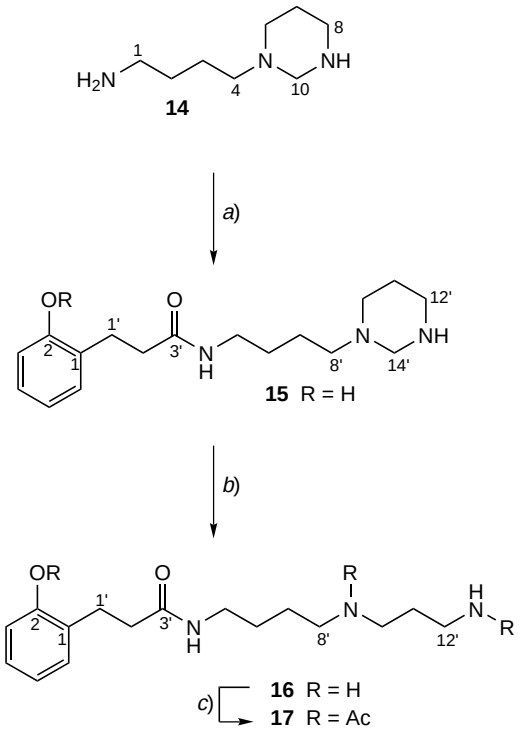
HCl led to the expected product, but in 60% yield only (*Scheme 3*). For analytical purposes, compound **16** was transformed to the corresponding *N*,*N*′-diacetyl derivative **17**.

The isomer **16** was also prepared by an alternative procedure starting from *N*-(4-aminobutyl)-3-(2-hydroxyphenyl)propanamide (**18**), formed in high yield by reaction of butane-1,4-diamine with **1**. The introduction of a third amino group in **18** by treatment with acrylonitrile gave a mixture of compounds, containing the mononitrile **19** as the main component and the dinitrile **20**. The mixture was subjected to catalytic reduction of the nitriles to give the amines **16** and **21** (ratio 84:16), which were then separated (*Scheme 4*).

Synthesis of the Spermine Derivatives. Spermine derivatives, like those of spermidine, were similarly synthesized. Following the strategy of aminolysis, we first prepared compound **24** (60% yield) by treating spermine with 1 equiv. of **1**. In this experiment, compound **23**, in which spermine had reacted with two molecules of **1**, was also obtained (*Scheme 5*). However, with spermine in excess, the reaction can be directed to form product **24** only. Compound **24** was transformed to its *N*,*N*′,*N*″-triacetyl derivative **25**.

In EtOH the aminolysis of **1** and the tris(Z)-protected spermine **4** in a 1:1 molar ratio gave none of the desired compound **26** even after prolongation of the reaction

Scheme 3



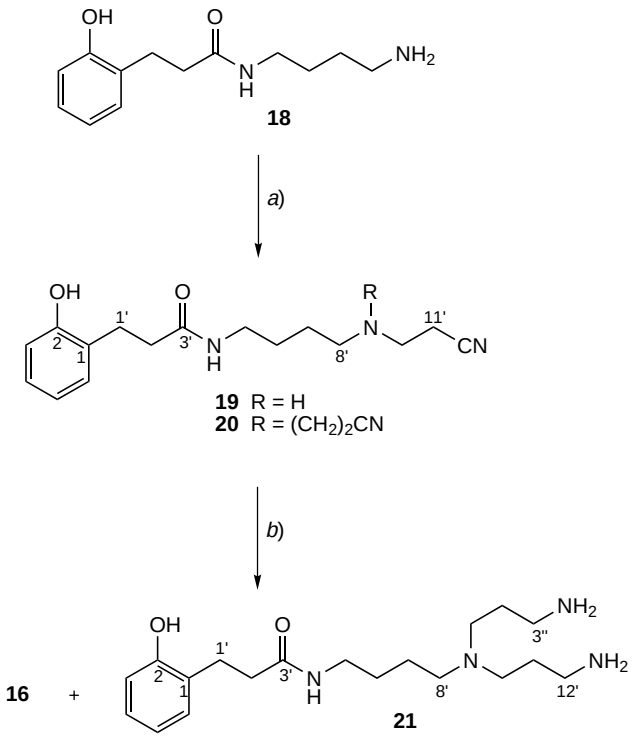
a) **1**, EtOH, r.t.; 92%. *b*) HCl, MeOH, r.t.; 60%. *c*) NaOAc, Ac_2O, r.t., 80%.

time to 30 h. Only when both components were allowed to react 7 d in toluene under reflux, 32% of compound **26** could be isolated. Cleavage of the Z-protecting groups by hydrogenolysis led to the amine **27** in an overall yield of 27% (*Scheme 6*). For analytical purposes **27** was converted into its *N*,*N*′,*N*″-triacetyl derivative **28**. As mentioned before, **1** seems to be a selective reagent for primary amines at room temperature, while secondary amines react only under drastic conditions.

An alternative route with higher yield was once more found in the method of *Mukaiyama* and co-workers for amide formation [8], which was used to prepare the target compound **27**. Thus, starting from the acid **2** and the spermine derivative **4**, the amide **29** was obtained in the presence of 1-methyl-2-chloropyridinium iodide. After removal of the protecting groups by hydrogenolysis (H_2/Pd), the desired product **27** was formed in 90% yield (*Scheme 7*). The overall yields from the two preparations of compound **27** (27% *vs.* 85%) were quite different. Finally, **27** was converted to its unbranched isomer **24** analogously to isomerization of **6** by treatment with KH in propane-1,3-diamine.

In the preparation of the derivative **32**, we followed the strategy of polyamine chain elongation by the method of aminolysis. Starting from the spermidine derivative **15**, by a *Michael* reaction, **30** was prepared by treatment with equimolar amounts of

Scheme 4

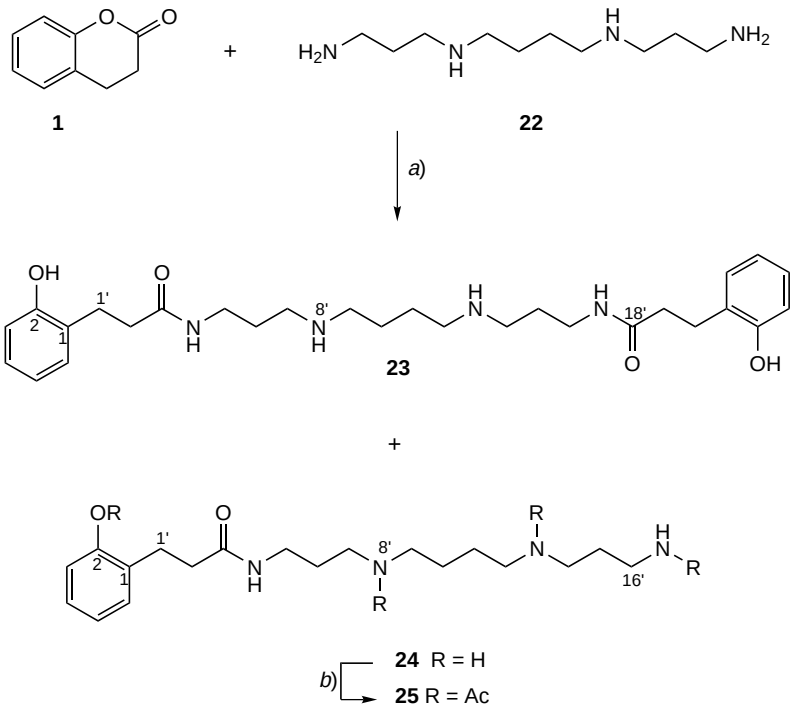


a) Acrylonitrile, MeOH, r.t.; 98%. *b*) H_2/*Raney*-Ni, 25% aq. NH_3 soln., EtOH, r.t.; **16**: 80%, **21**: 15%.

acrylonitrile. Reduction of the nitrile and chromatography of the reaction mixture afforded three products. The target compound **32** was obtained in 20% yield, while **31** in 36% yield and the monomethylated derivative of **32**, namely **34**, in 16% yield (*Scheme 8*). Compound **32** was acetylated to the *N*,*N*′,*N*″-triacetyl derivative **33**. Attempts to prepare **32** by hydrolysis of the aminal **31**, analogously to the transformation of **15** to **16** (*Scheme 3*) gave no positive results. The formation of **34** could be explained by reduced immonium species formed by opening of the aminal **30**.

Differentiation of the Spermidine Derivatives **6**, **8**, *and* **16**. The triamine spermidines contain three distinguishable amino groups. The three mono-substituted spermidine derivatives **6**, **8**, and **16** are different from each other. It was mentioned before that the *N*,*N*-disubstituted amide **6** can be converted to **8** by base or acid treatment or by gradual rearrangement without addition of reagents [12] (*Zip* reaction). Under the same conditions the isomers **8** and **16** are stable (*Scheme 9*). Unambiguous differentiation of all the three isomers by spectroscopic means seems to be possible, although, since the ^{1}H- and ^{13}C-NMR spectra of the isomers **8** and **16** are very similar, their differentiation by NMR is quite difficult. Also, due to their similar polarities, no striking differences in their R_f values were observed. Only the melting points of the hydrochlorides are different. Therefore, we investigated chemical reactions to differ-

Scheme 5

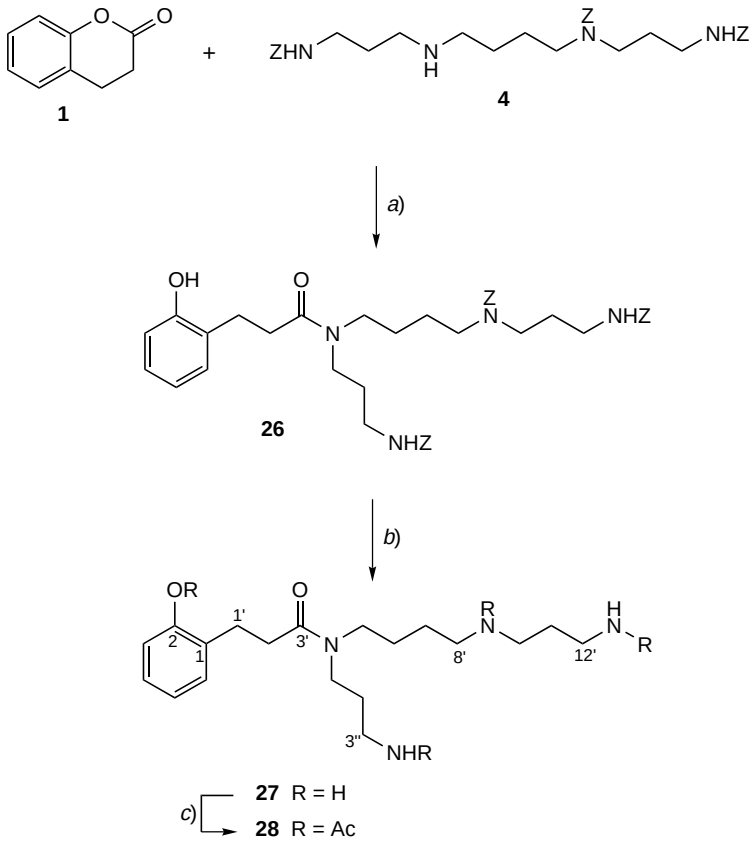


a) EtOH, r.t.; **23**: 39%, **24**: 60%. *b*) AcONa, Ac_2O, r.t.; 90%.

entiate the three isomers. As shown, the treatment of propane-1,3-diamine or some of its derivatives with HCOH led to the corresponding hexahydropyrimidines, butane-1,4-diamine does not react under these conditions. When the three isomers **6**, **8**, and **16** were treated with HCOH, compound **8** formed the hexahydropyrimidine derivative **35**, and **16** gave the isomer **15**, while **6** was recovered unchanged. On the other hand, we have shown that **1** reacts with primary amines only. Therefore, **6** could be converted to the triamide **36** by treatment with **1**, while the isomers **8** and **16** form the same diamide **37** (*Scheme 9*). The spectroscopic differentiation of the two reaction products is much easier (*e.g.*, in the IR spectrum ($CHCl_3$), amide absorption is at 1630 cm^{-1} for **35** and at 1640 and 1520 cm^{-1} for **15**). It should be mentioned that, during the derivatization reactions, no spontaneous isomerization occurred.

Mass-Spectral Differentiation of the Acetyl Derivatives of **6**, **8**, *and* **16**. In the course of the structural elucidation of polyamine alkaloids such as oncinotine [15] or verbascenine, the mass-spectral analysis (EI mode) of acylated, and of especially acetylated, degradation products has been proved to be a very valuable method. Therefore, the three isomers **6**, **8**, and **16** were converted to the corresponding *N*,*N*′,*O*′-triacetyl derivatives **7**, **9**, and **17**, respectively, by treatment with Ac_2O/NaOAc so that the same methodology could be applied to differentiate the three isomers. The EI mass spectra of the three compounds are shown in the *Figure*. It is known that *N*,*N*′,*N*″-

Scheme 6



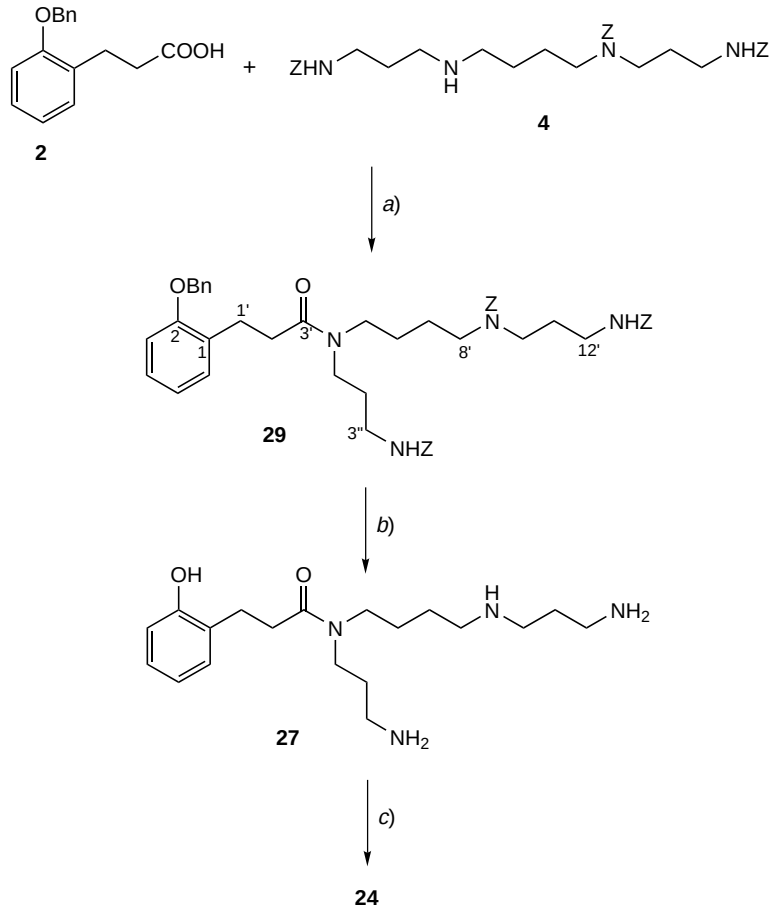
a) Toluene, reflux, 7 d; 32%. *b*) H_2/10% Pd/C, AcOH, r.t.; 87%. *c*) NaOAc, Ac_2O, r.t.; 77%.

triacetylspermidine derivatives under EI-MS conditions show a characteristic fragmentation pattern giving rise to the so-called *peak triade* [16].

Depending on the substitution of the spermidine unit with the 2-hydroxydihydrocoumaroyl residue at N(1), N(5), or N(10), different fragment ions are expected. During the formation of the ions of this peak triade the substituents of the propane-1,3-diamine part of the spermidine moiety at N(1) and N(5) are lost, only that at N(10) remains. Therefore, the triades formed from $\mathbf{7}^{+\cdot}$ and $\mathbf{9}^{+\cdot}$ are the same, while that of $\mathbf{17}^{+\cdot}$ is different (*Scheme 10*).

For differentiation of **7** and **9**, further fragmentation pathways had to be devised. By another reaction, the central *N*-substituent is omitted. As in compounds **9** and **17**, the same residue was placed at the N(5)-atom. The corresponding fragmentations appear in the case of **9** and **17** at the same mass, *m*/*z* 376; only **7** yielded a different result at *m*/*z* 228. In addition, by a set of other fragment ions, *m*/*z* 112 (**7** and **9**) and 260 (**17**), the three isomers **7**, **9**, and **17** can be differentiated (*Scheme 11*).

Scheme 7



a) 1-Methyl-2-chloropyridinium iodide, Et_3N, CH_2Cl_2, r.t.; 94%. *b*) H_2/10% Pd/C, AcOH, r.t.; 90%. *c*) KH, 1-propane-1,3-diamine, r.t., or gradual rearrangement without reagents [12].

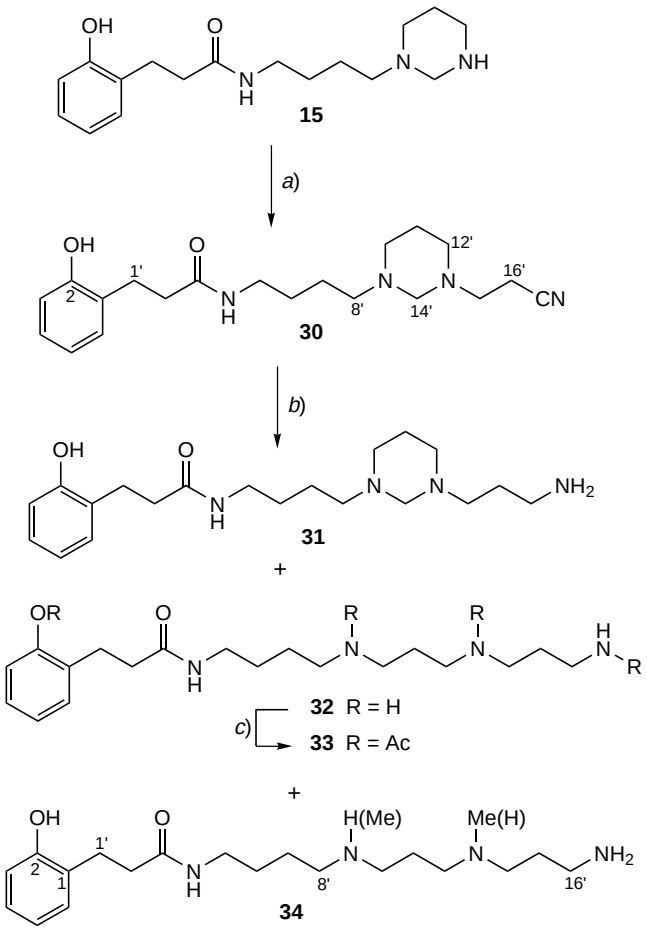
The mass-spectral analysis of the corresponding spermine derivatives will be published elsewhere.

We thank the analytical departments of our institute for measurements, especially Dr. *Laurent Bigler* for mass-spectral analysis, and the *Swiss National Science Foundation* for the financial support.

Experimental Part

General. All commercially available reagents were used without further purification. All reactions were followed by TLC (*Merck* silica gel *60* F_{254}). The detection was either by UV light or with $Ce(SO_4)_2$ and *Schlittler* reagent. Column chromatography (CC): *Merck* silica gel *60* (40–60 m). M.p.: *Mettler FP5*. Hydrogenation: *Parr Instruments Company, Inc.* IR [cm^{-1}]: *Perkin-Elmer 781*; measured as 2–3% soln. in $CHCl_3$ (*Fluka, for spectroscopy*), unless otherwise stated. ^{1}H-NMR ($CDCl_3$): *Bruker ARX-300* (300 MHz) or *Bruker AMX-600* (600 MHz), chemical shifts δ in ppm using Me_4Si (= 0 ppm) as internal standard, coupling constants J in Hz. ^{13}C-NMR ($CDCl_3$): *Bruker ARX-300* (75 MHz) or *Bruker AMX-600* (150 MHz); MS: *Finnigan SSQ-700*,

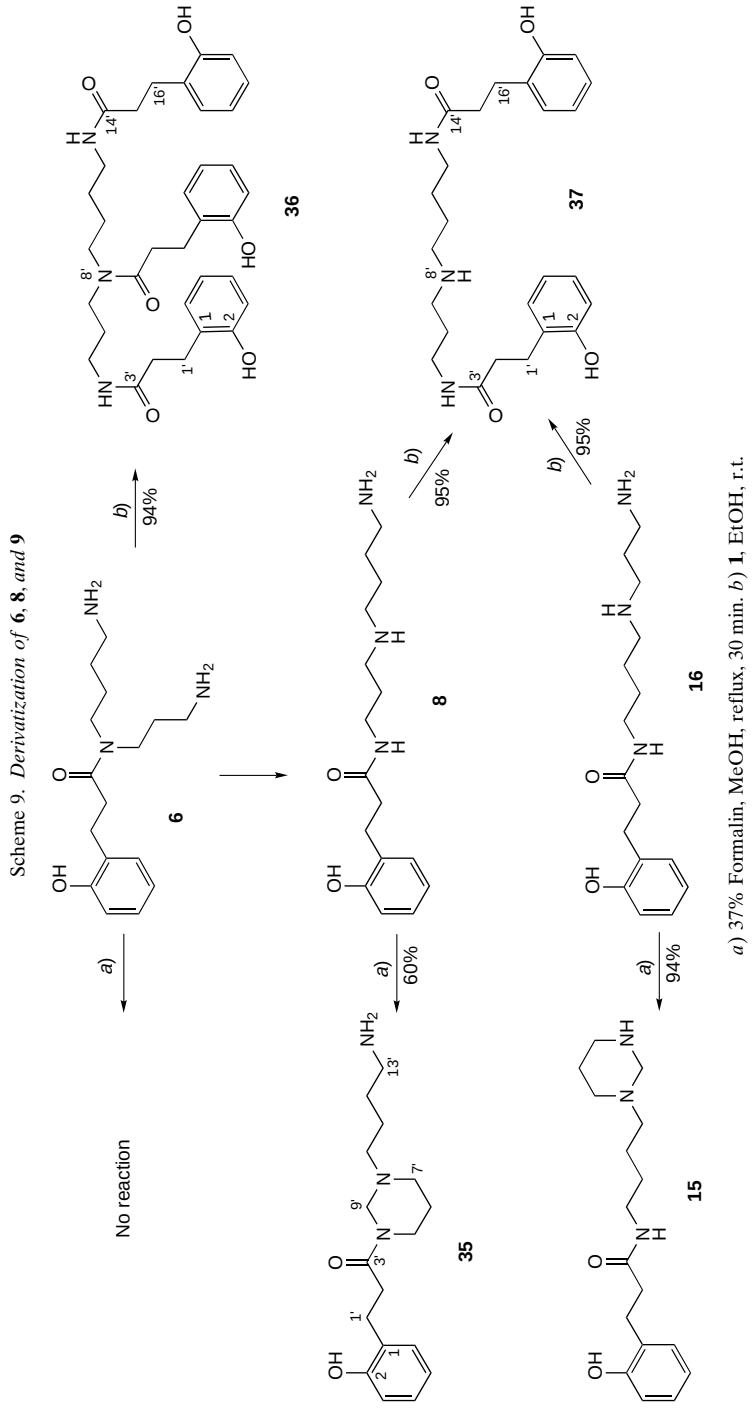
Scheme 8



a) Acrylonitrile, MeOH, r.t.; quant. *b*) H_2/*Raney*-Ni, 25% aq. NH_3 soln. EtOH, r.t., SiO_2; **31**: 36%, **32**: 20%, **34**: 16%. *c*) NaOAc, Ac_2O, r.t.; 82%.

chemical ionization (Cl) with NH_3, *Finnigan MAT 90*, electron impact (EI; 70 eV), and *Finnigan TSQ-700*, electrospray ionization (ESI). Compounds **25**, **28**, **33** were measured with a *Bruker ESQUIRE-LE* quadrupole ion-trap instrument (*Bruker-Franzen GmbH*, D-Bremen) connected to an orthogonal electrospray ion source (*Hewlett-Packard*, Palo Alto, CA 94304, USA). The MS detector was operated under the following conditions: N_2 nebulizer gas: 15 psi; dry N_2: 8 l/min; dry temp.: 250°; cap. voltage: 4200 V; end plate: 3700 V; capillary exit: 100 V; skimmer 1:25 V. The MS acquisitions were performed at normal resolution (0.6 u at the half-peak-height), under ion-charge-control (ICC) conditions (10000) in the mass range from *m*/*z* 100 to 800 and a 36 trap drive value; average of 8 scans were reported.

1. Synthesis of *N*-(4-Aminobutyl)-*N*-(3-aminopropyl)-3-(2-hydroxyphenyl)propanamide (6). *From 3-[2-(Benzyloxy)phenyl]propionic Acid* (**2**) and *Benzyl* N-*(8-{[(Benzyloxy)carbonyl]amino}-4-azaoctyl)carbamate* (**3**). N-*(4-{[(Benzyloxy)carbonyl]amino}butyl)*-N-*(3-{[(benzyloxy)carbonyl]amino}propyl)-3-[2-(benzyloxy)-phenyl]propanamide* (**5**). A suspension of **2** (512 mg, 2 mmol), 1-methyl-2-chloropyridinium iodide (613 mg, 2.4 mmol), and Et_3N (533 mg, 5.3 mmol) in CH_2Cl_2 (10 ml) were stirred 20 min at r.t. After addition of a soln. of **3** (826 mg, 2 mmol) in CH_2Cl_2 (10 ml), the mixture was stirred overnight at r.t. The solvent was evaporated, the



Scheme 9. *Derivatization of* **6**, **8**, *and* **9**

a) 37% Formalin, MeOH, reflux, 30 min. *b*) **1**, EtOH, r.t.

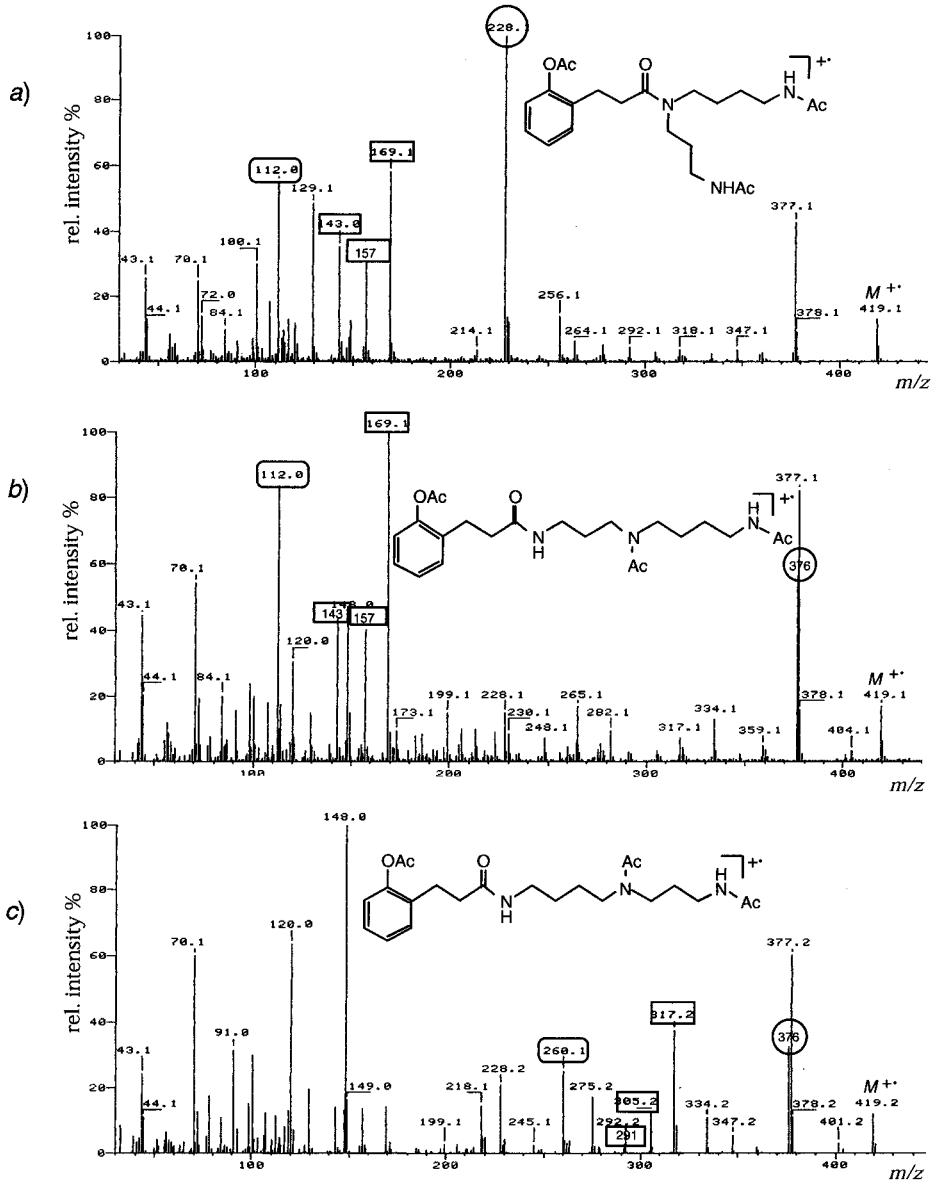
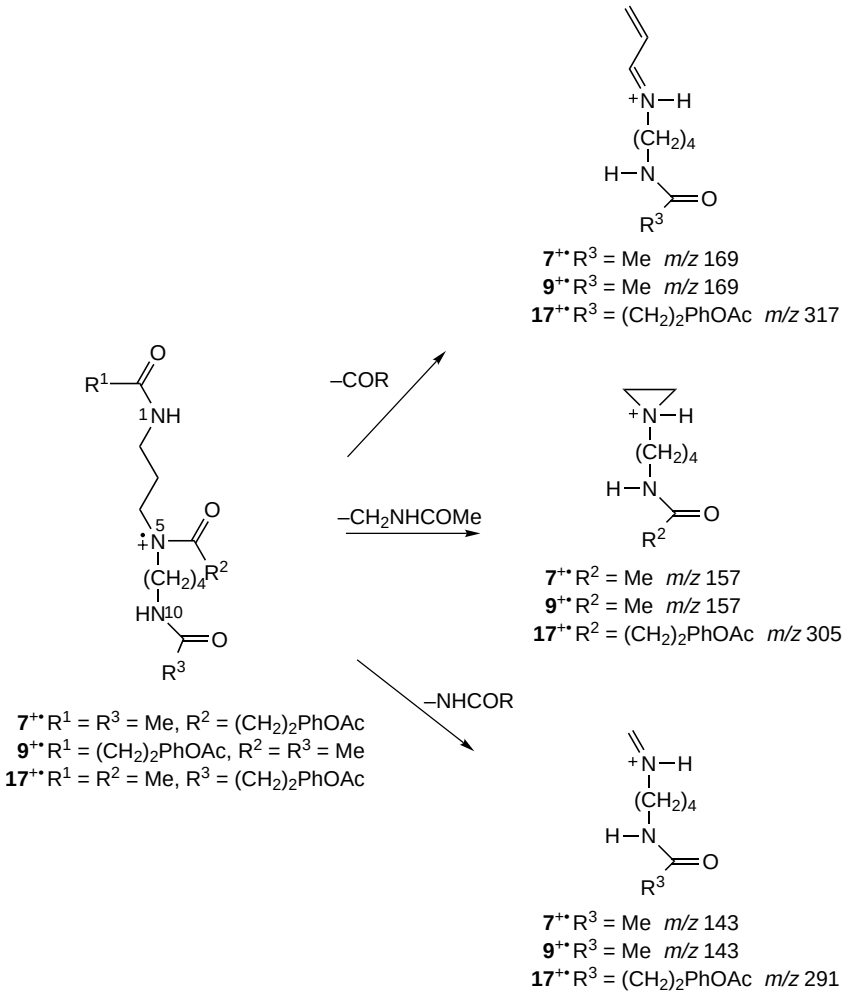


Figure. *Mass spectra* (EI mode, direct inlet, 70 eV): a) *3-(2-Acetoxyphenyl)*-N-*[4-(acetylamino)butyl]*-N-*[3-(acetylamino)propyl]propanamide* (**7**); b) *3-(2-acetoxyphenyl)*-N-*(3-{*N-*acetyl*-N-*[4-(acetylamino)butyl]amino}propyl)propanamide* (**9**); *and* c) *3-(2-acetoxyphenyl)*-N-*(4-{*N-*acetyl*-N-*[3-(acetylamino)propyl]amino}butyl)propanamide* (**17**)

residue was taken up in CH_2Cl_2 (100 ml), washed with 0.3N aq. HCl soln. and dried (Na_2SO_4). Removal of the solvent and purification of the residue by CC (SiO_2; CH_2Cl_2/MeOH 46 : 1) gave 1.25 g (96%) of **5**. Colorless oil. IR: 3445*m*, 3000*m*, 2935*m*, 1715*vs*, 1625*s*, 1505*s*, 1450*s*, 1375*m*, 1220*s*, 1135*m*, 1110*m*, 1080*m*, 1015*m*, 910*w*, 855*w*, 695*m*, 585*w*. ^{1}H-NMR: 7.41 – 7.27 (*m*, 15 arom. H); 7.19 – 7.13 (*m*, H–C(4), H–C(6)); 6.91 – 6.87 (*m*, H–C(3),

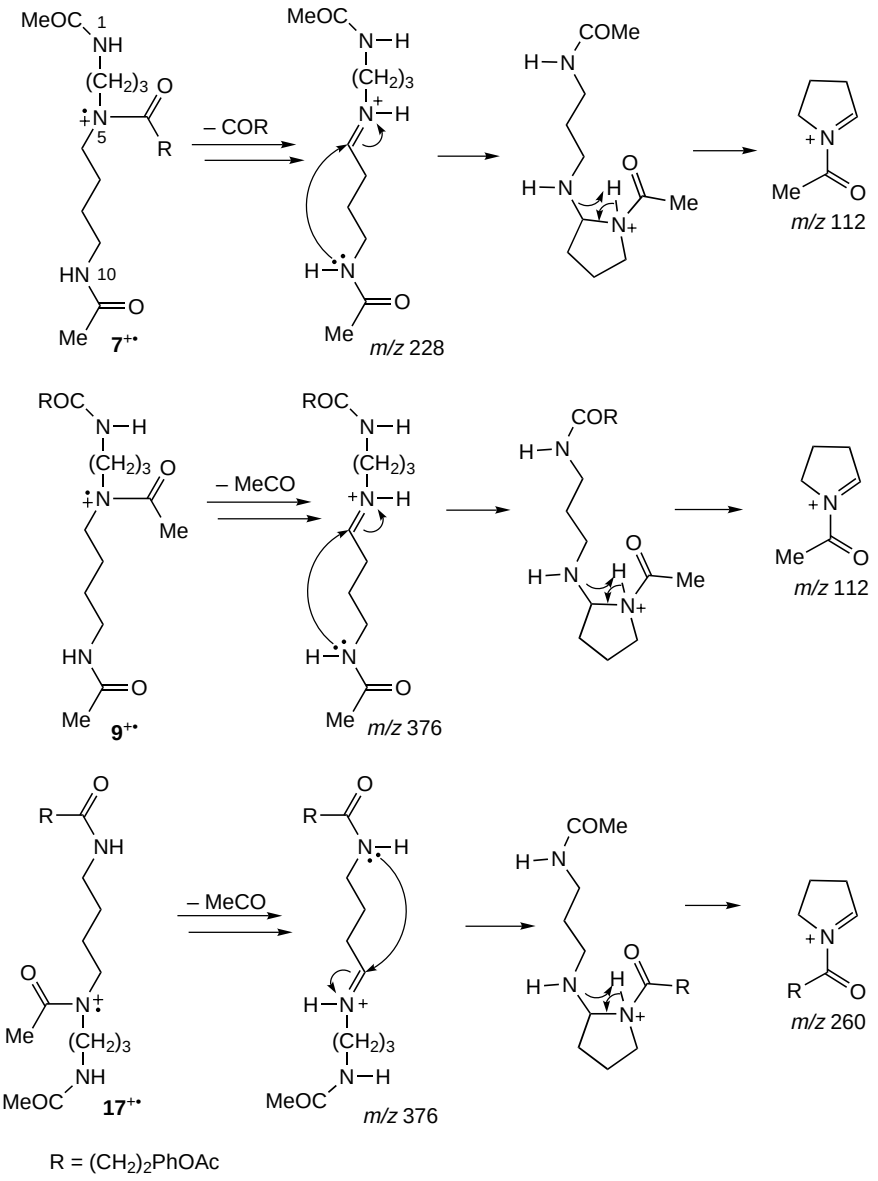
Scheme 10. *Peak Triade of Compounds* **7**, **9**, *and* **17**



H–C(5)); 5.82, 4.79 (2 br. *s*, 2 NHCO); 5.08 (*s*, PhCH_2); 5.05, 5.02 (2*s*, 2 PhCH_2); 3.16–3.11 (*m*, CH_2(1″), CH_2(5′)); 3.01–2.95 (*m*, CH_2(3″), CH_2(8′)); 2.96 (*t*, *J* = 7.1, CH_2(1′)); 2.57 (*t*, *J* = 7.2, CH_2(2′)); 1.60–1.65 (*m*, CH_2(2″)); 1.49–1.22 (*m*, CH_2(6′), CH_2(7′)). ^{13}C-NMR: 173.1 (*s*, C(3′)); 156.5, 156.3 (2*s*, 2 CO); 137.1 (*s*, C(2)); 136.8, 136.4 (2*s*, 2 arom. C); 130.4 (*d*, C(4)); 128.1 (*d*, C(6)); 128.0 (*s*, C(1)); 120.9 (*d*, C(5)); 111.6 (*d*, C(3)); 128.3, 127.9, 127.5 (3*d*, 15 arom. C); 69.7 (*t*, PhCH_2); 66.6, 66.3 (2*t*, 2 PhCH_2); 47.0 (*t*, C(1″)); 45.2 (*t*, C(5′)); 42.1 (*t*, C(8′)); 40.3 (*t*, C(3″)); 37.4 (*t*, C(2′)); 33.1 (*t*, C(2″)); 27.3 (*t*, C(1′)); 27.1 (*t*, C(7′)); 25.8 (*t*, C(6′)). CI-MS: 652 (< 5, $[M+1]^+$), 544 (63), 436 (100, $[M$ of **3** + Na$]^+$).

Compound **6**. To a suspension of 10% Pd/C (600 mg) in conc. AcOH (110 ml) was added a soln. of **5** (1.98 g, 3 mmol), and the mixture was hydrogenated overnight in a *Parr* apparatus at 3.5 bar H_2 pressure. The mixture was filtered over *Celite*, the filtrate evaporated, and the residue was purified by CC (SiO_2; $CHCl_3$/MeOH/25% aq. NH_3 soln. 10:4:1) to give 880 mg (99%) of **6** (colorless oil), which were taken up in EtOH (8 ml) and treated dropwise with 0.3N aq. HCl soln. (pH 1). Removal of the solvent *in vacuo* and crystallization of the residue from EtOH yielded 1.05 g (96%) **6**·2 HCl. Colorless crystals. M.p. 204–205°. IR: 3150*m*, 2930*s*, 1620*s*,

Scheme 11



1455*m*, 1375*m*, 1305*m*, 1245*m*, 1150*m*, 1095*m*, 945*w*, 885*w*, 840*m*, 655*w*. ^{1}H-NMR: 7.07–7.03 (*m*, H–C(4), H–C(6)); 6.84–6.74 (*m*, H–C(3), H–C(5)); 3.59 (br., 2 NH_2); 3.38 (*t*, $J = 6.8$, $CH_2(1'')$); 3.18 (*t*, $J = 7.2$, $CH_2(5')$); 2.92 (*t*, $J = 6.6$, $CH_2(1')$); 2.66 (*t*, $J = 6.8$, $CH_2(3'')$, $CH_2(8')$); 2.59 (*t*, $J = 7.0$, $CH_2(2')$); 1.62 (*quint.*, $J = 6.6$, $CH_2(2'')$); 1.60–1.35 (*m*, $CH_2(6')$, $CH_2(7')$). ^{13}C-NMR: 173.6 (*s*, C(3′)); 155.4 (*s*, C(2)); 130.5 (*d*, C(4)); 128.0 (*s*, C(1)); 127.6 (*d*, C(6)); 119.6 (*d*, C(5)); 116.5 (*d*, C(3)); 47.6 (*t*, C(1″)); 45.9, 45.5 (2*t*, C(5′)); 43.0, 41.2 (2*t*, C(8′)); 38.9, 38.5 (2*t*, C(3″)); 34.2 (*t*, C(2′)); 30.7, 30.2 (2*t*, C(2″)); 26.1 (*t*, C(1′)); 25.9 (*t*, C(7′)); 24.8 (*t*, C(6′)). ESI-MS: 294 ($[M+1]^+$). ESI-MS/MS (of *m*/*z* 294.2, – 15 eV): 294 (100, $[M+1]^+$), 277 (45), 259 (10), 223 (10),

206 (46, $[M-87]^+$), 146 (28, [*M* of spermidine + 1]$^+$), 129 (< 10), 72 (12). ESI-MS/MS (of *m*/*z* 294.2, − 20 eV): 294 (10, $[M+1]^+$), 277 (17), 259 (< 10), 206 (100, $[M-87u]^+$), 146 (10, [*M* of spermidine + H]$^+$), 129 (< 10), 112 (11), 72 (26).

3-(2-Acetoxyphenyl)-N-*[4-(acetylamino)butyl]*-N-*[3-(acetylamino)propyl]propanamide* (**7**). A suspension of **6** (9 mg, 0.03 mmol) and AcONa (50 mg, 0.6 mmol) in Ac_2O (5 ml) was stirred overnight at r.t.; then, the mixture was evaporated. The residue was taken up in sat. aq. K_2CO_3 soln., extracted with $CHCl_3$, and dried (Na_2SO_4). Evaporation of the solvent and chromatography of the residue (SiO_2; $CHCl_3$/MeOH 19 : 1) gave 10 mg (80%) of **7**. Pale-yellow oil. ^{1}H-NMR: 7.23 – 7.14 (*m*, H−C(4), H−C(6)); 7.02 – 6.99 (*m*, H−C(3), H−C(5)); 6.78, 6.08 (2 br. *s*, 2 NHAc); 3.39 (*t*, *J* = 8.4, CH_2(3″)); 3.29 (*t*, *J* = 6.1, CH_2(8′)); 3.19 – 3.11 (*m*, CH_2(1″), CH_2(5′)); 2.90 (*t*, *J* = 7.4, CH_2(1′)); 2.54 (*t*, *J* = 7.5, CH_2(2′)); 2.00, 1.92 (2*s*, 3 *Me*CO); 1.65 (*quint.*, *J* = 6.4, CH_2(2″)); 1.56 – 1.41 (*m*, CH_2(6′), CH_2(7′)). ESI-MS: 458 (25, $[M+K]^+$), 442 (80, $[M+Na]^+$), 420 (100, $[M+1]^+$), 378 (18). ESI-MS/MS (of *m*/*z* 420.3, − 15 eV): 420 (70, $[M+1]^+$), 378 (100), 360 (10), 319 (12), 230 (40), 212 (16). ESI-MS/MS (of *m*/*z* 420.3, − 20 eV): 420 (< 10, $[M+1]^+$), 378 (65), 360 (< 10), 319 (12), 230 (100), 212 (28), 171 (17), 100 (14). ESI-MS/MS/MS (of *m*/*z* 230.3, − 40 eV): 230 (48), 213 (< 10), 171 (< 10), 114 (< 10), 100 (100), 72 (< 10). ESI-MS/MS/MS (of *m*/*z* 230.3, − 42 eV): 230 (34), 213 (< 10), 171 (< 10), 114 (< 10), 100 (100), 72 (< 10). EI-MS: See *Fig. 1, a*.

3-(2-Hydroxyphenyl)-N-*[3-([4-[3-(2-hydroxyphenyl)propanamido]butyl][3-(2-hydroxyphenyl)propanoyl]-amino)propyl]propanamide* (**36**). To a soln. of **6** · 2 HCl (60 mg, 0.2 mmol) in EtOH (7 ml) was added MeONa (33 mg, 0.6 mmol), and the mixture was stirred 30 min at r.t. The solvent was removed *in vacuo*, the residue was dissolved in EtOH (10 ml) and treated with a soln. of *3,4-dihydrocoumarin* (**1**, 101 mg, 2.2 mmol). After 1 h stirring at r.t., the mixture was evaporated and purified by CC (SiO_2; $CHCl_3$/MeOH 19 : 1) to yield 91 mg (94%) of **36**. Colorless oil. IR: 3000*m*, 1640*m*, 1520*m*, 1485*m*, 1410*w*, 1305*w*, 1220*m*, 1095*w*, 1035*w*, 925*w*, 840*w*, 665*m*, 620*w*. ^{1}H-NMR: 9.20, 9.06, 8.95 (3*s*, 3 OH); 7.08 – 7.00 (*m*, 3 H−C(4), 3 H−C(6)); 6.84 – 6.73 (*m*, 3 H−C(3), 3 H−C(5)); 3.12 – 3.10 (*m*, CH_2(9′), CH_2(12′)); 3.05 (*t*, *J* = 7.1, CH_2(5′), CH_2(7′)); 2.90 (*t*, *J* = 6.6, CH_2(1′), CH_2(1″), CH_2(16′)); 2.55 (*t*, *J* = 7.0, CH_2(2′), CH_2(2″), CH_2(15′)); 1.50 (*quint.*, CH_2(6′)); 1.31 – 1.30 (*m*, CH_2(10′), CH_2(11′)). ^{13}C-NMR: 174.4, 174.3, 173.2 (3*s*, C(3′), C(3″), C(14′)); 154.7, 154.5, 154.4 (3*s*, 3 C(2)); 130.4, 130.3 (2*d*, 3 C(4)); 127.8, 127.7 (2*d*, 3 C(6)); 127.4, 127.2 (2*s*, 3 C(1)); 120.1, 120.0 (2*d*, 3 C(5)); 116.4, 116.3 (2*d*, 3 C(3)); 47.5 (*t*, C(7′)); 45.6 (*t*, C(9′)); 43.2 (*t*, C(5′)); 38.8 (*t*, C(12′)); 36.9, 36.7, 36.6 (3*t*, C(2′), C(2″), C(15′)); 33.8 (*t*, C(6′)); 28.4, 26.8, 26.4 (3*t*, C(1′), C(1″), C(16′)); 26.1 (*t*, C(11′)); 25.6 (*t*, C(10′)). EI-MS: 612 (100, $[M+Na]^+$), 590 (15, $[M+1]^+$).

2. Synthesis of *N*-{3-[(4-Aminobutyl)amino]propyl}-3-(2-hydroxyphenyl)propanamide (8). 2.1. *From* **6**. A suspension of KH (500 mg, 12 mmol) in propane-1,3-diamine (5 ml) was stirred at r.t. 30 min under Ar. A soln. of **6** (110 mg, 0.38 mmol) in propane-1,3-diamine (5 ml) was added dropwise and stirring was continued for 1.5 h. The mixture was treated carefully with 0.3N aq. HCl soln. and the solvents were removed *in vacuo*. The residue was taken up in sat. aq. K_2CO_3 soln. (5 ml), extracted with $CHCl_3$, and the org. layer was dried (Na_2SO_4). Evaporation of the solvent and purification of the residue by CC (SiO_2; $CHCl_3$/MeOH/25 aq. NH_3 soln. 10 : 4 : 1) yielded 100 mg (90%) of **8** as slightly yellow-colored oil, which was crystallized as hydrochloride **8** · 2 HCl. M.p. 116 – 118° (EtOH). IR: 3300*w* (br.), 2930*m*, 1640*s*, 1520*m*, 1455*m*, 1370*w*, 1240*w*, 1175*w*, 1135*m*, 1010*w*, 900*w*, 835*w*, 650*w*. ^{1}H-NMR: 7.58 (br., NHCO); 7.08 – 7.03 (*m*, H−C(4), H−C(6)); 6.84 – 6.76 (*m*, H−C(3), H−C(5)); 3.21 (*t*, *J* = 6.2, CH_2(5′)); 2.89 (*t*, *J* = 7.0, CH_2(1′)); 2.76 (*t*, *J* = 6.4, CH_2(12′)); 2.63 (*t*, *J* = 6.4, CH_2(7′), CH_2(9′)); 2.56 (*t*, *J* = 7.0, CH_2(2′)); 1.66 (*quint.*, *J* = 6.5, CH_2(6′)); 1.64 – 1.58 (*m*, CH_2(10′), CH_2(11′)). ^{13}C-NMR: 174.6 (*s*, C(3′)); 154.6 (*s*, C(2)); 130.2 (*d*, C(4)); 127.5 (*d*, C(6)); 127.2 (*s*, C(1)); 119.8 (*d*, C(5)); 116.0 (*d*, C(3)); 48.9 (*t*, C(7′)); 46.6 (*t*, C(9′)); 41.0 (*t*, C(5′)); 37.3 (*t*, C(12′)); 36.5 (*t*, C(2′)); 30.0 (*t*, C(1′)); 28.2 (*t*, C(6′)); 26.5 (*t*, C(11′)); 25.8 (*t*, C(10′)). ESI-MS: 294 ($[M+1]^+$). ESI-MS/MS (of *m*/*z* 294.2, − 15 eV): 294 (100, $[M+1]^+$), 277 (25), 259 (< 10), 223 (< 10), 206 (26, $[M-87u]^+$), 146 (10), 129 (< 10), 75 (< 10), 72 (10). ESI-MS/MS (of *m*/*z* 294.2, − 20 eV): 294 (16, $[M+1]^+$), 277 (20), 259 (11), 206 (100, $[M-87]^+$), 146 (< 10), 129 (< 10), 112 (< 10), 75 (10), 72 (27).

3-(2-Acetoxyphenyl)-N-*(3-{(acetyl)[4-(acetylamino)butyl]amino}propyl)propanamide* (**9**). Analogously to the preparation of **7**, from **8** (9 mg, 0.03 mmol) and AcONa (50 mg, 0.6 mmol) in Ac_2O (5 ml), 10.5 mg (84%) of **9** were obtained after workup. ^{1}H-NMR: 7.23 – 7.12 (*m*, H−C(4), H−C(6)); 7.02 – 6.98 (*m*, H−C(3), H−C(5)); 6.71, 5.70 (br., NHAc); 3.30 – 3.28 (*m*, CH_2(12′)); 3.25 – 3.19 (*m*, CH_2(5′)); 3.14 – 3.10 (*m*, CH_2(7′), CH_2 (9′)); 2.88 (*t*, *J* = 7.2, CH_2(1′)); 2.43 (*t*, *J* = 7.2, CH_2(2′)); 2.07, 2.01 (2*s*, 3 *Me*CO); 1.59 (*quint.*, *J* = 6.6, CH_2(6′)); 1.54 – 1.50 (*m*, CH_2(10′), CH_2(11′)). ^{13}C-NMR[2]): 171.8 (*s*, C(3′)); 170.2 (*s*, 3 CO); 148.8 (*s*, C(2)); 130.2 (*d*, C(4)),

[2]) The ^{13}C-NMR signal of C(2) in the spectrum of **9** is not observed.

C(6)); 126.0 (*d*, C(5)); 122.2 (*d*, C(3)); 48.1 (*t*, C(12′)); 42.1 (*t*, C(7′)); 38.7 (*t*, C(9′)); 36.7 (*t*, C(5′)); 35.7 (*t*, C(2′)); 27.3 (*t*, C(1′)); 27.0 (*t*, C(6′)); 26.1 (*t*, C(11′)); 25.9 (*t*, C(10′)); 23.1, 21.2, 20.9 (3*q*, 3 *Me*CO). ESI-MS: 458 (10, $[M+K]^+$), 442 (26, $[M+Na]^+$), 420 (100, $[M+1]^+$), 378 (34). ESI-MS/MS (of *m*/*z* 420.3, −20 eV): 378 (11, $[M+2-Ac]^{2+}$), 318 (26), 230 (100), 213 (50), 206 (20), 112 (<10), 100 (17). ESI-MS/MS (of *m*/*z* 420.3, −30 eV): 318 (20), 248 (12), 230 (14), 213 (76), 206 (100), 171 (17), 143 (16), 114 (52), 100 (80), 72 (22). ESI-MS/MS/MS (of *m*/*z* 230.3, −40 eV): 230 (20), 213 (22), 114 (14), 100 (100), 72 (10). ESI-MS/MS/MS (of *m*/*z* 230.3, −42 eV): 230 (<10), 213 (15), 114 (15), 100 (100), 72 (16). ESI-MS: See the *Figure*, *b*.

1-[3-(4-Aminobutyl)-1,2,3,4,5,6-hexahydropyrimidin-1-yl]-3-(2-hydroxyphenyl)propan-1-one (**35**). Analogously to the treatment of **6**·2 HCl, from **8**·2 HCl (30 mg, 0.082 mmol) and 37% formaline (3 drops) in MeOH (5 ml), 15 mg (60%) of **35** were obtained after workup. IR: 2940*m*, 1630*s*, 1450*m*, 1305*w*, 1230*m*, 1135*w*, 1095*m*, 1005*w*, 905*w*, 655*w*. ^{1}H-NMR: 7.12–7.04 (*m*, H−C(4), H−C(6)); 6.93–6.76 (*m*, H−C(3), H−C(5)); 4.50 (br. *s*, NH_2); 4.17, 4.06 (2*s*, CH_2(9′)); 3.59 (*t*, *J* = 5.7, H_a−C(5′)); 3.43 (*t*, *J* = 5.7, H_b−C(5′)); 2.91 (*t*, *J* = 8.0, CH_2(1′)); 2.83 (*t*, *J* = 6.2, CH_2(13′)); 2.72 (*t*, *J* = 7.0, CH_2(7′)); 2.69 (*t*, *J* = 7.6, CH_2(2′)); 2.37 (*t*, *J* = 6.6, CH_2(10′)); 1.63–1.51 (*m*, CH_2(6′)); 1.59–1.53 (*m*, CH_2(11′), CH_2(12′)). ^{13}C-NMR: 173.3 (*s*, C(3′)); 154.8 (*s*, C(2)); 130.2 (*d*, C(4)); 127.8 (*d*, C(6)); 127.4 (*s*, C(1)); 120.0 (*d*, C(5)); 116.9 (*d*, C(3)); 66.5, 62.5 (2*t*, C(9′)); 53.2 (*t*, C(5′)); 45.5 (*t*, C(7′)); 40.3 (*t*, C(10′)); 39.9 (*t*, C(13′)); 34.0 (*t*, C(2′)); 27.5 (*t*, C(1′)); 25.1 (*t*, C(12′)); 24.6 (*t*, C(11′)). EI-MS: 306 ($[M+1]^+$).

3,3′-Bis(2-hydroxyphenyl)-N,N′*-(4-azaoctane-1,8-diyl)bis[propanamide]* (**37**). Analogously to the preparation of **36**, from **8**·2 HCl (55 mg, 0.15 mmol), MeONa (100 mg) and **1** (66 mg, 0.45 mmol) in MeOH (10 ml), 63 mg (94%) of **37** were obtained after workup. IR: 2960*m*, 1640*m*, 1520*m*, 1485*m*, 1410*m*, 1380*w*, 1220*m*, 1105*m*, 1025*w*, 925*w*, 840*w*, 800*m*, 665*m*, 620*w*. ^{1}H-NMR: 7.08–7.03 (*m*, 2 H−C(4), 2 H−C(6)); 6.84–6.76 (*m*, 2 H−C(3), 2 H−C(5)); 3.22 (*t*, *J* = 6.5, CH_2(5′)); 3.15 (*t*, *J* = 6.5, CH_2(12′)); 2.88 (*t*, *J* = 7.0, CH_2(1′), CH_2(16′)); 2.56–2.53 (*m*, CH_2(7′), CH_2(9′)); 2.51 (*t*, *J* = 7.2, CH_2(2′), CH_2(15′)); 1.59 (*quint.*, *J* = 6.4, CH_2(6′)); 1.42–1.38 (*m*, CH_2(10′), CH_2(11′)). ^{13}C-NMR: 174.3, 174.1 (2*s*, C(3′), C(14′)); 154.6 (*s*, 2 C(2)); 130.1 (*d*, 2 C(4)); 127.6 (*d*, 2 C(6)); 127.4 (*s*, 2 C(1)); 120.0 (*d*, 2 C(5)); 116.3 (*d*, 2 C(3)); 48.5 (*t*, C(7′)); 46.4 (*t*, C(9′)); 38.9 (*t*, C(5′)); 37.2 (*t*, C(12′)); 36.8 (*t*, C(2′)); 36.7 (*t*, C(15′)); 28.1 (*t*, C(6′)); 26.4 (*t*, C(1′)); 25.9 (*t*, C(16′)); 25.4 (*t*, C(11′)); 25.3 (*t*, C(10′)). ESI-MS: 442 ($[M+1]^+$).

2.2. *From* **2** *and Di*(tert-*butyl)* N-*(1-Aminopropyl)*-N,N′*-(butane-5,8-diyl)bis[carbamate]* (**11**). *3-[(2-Benzyloxy)phenyl]*-N-*(3-{[*(tert-*butoxy)carbonyl](4-{[*(tert-*butoxy)carbonyl]amino}butyl)amino}propyl]propanamide* (**12**). A mixture of **2** (512 mg, 2 mmol), DMF (2 drops) and $SOCl_2$ (713 mg, 6 mmol) in toluene (20 ml) was heated at 100°. After 2 h, the mixture was cooled to r.t., the solvent was evaporated, and the residue was dried at 10^{-3} bar. To the soln. of crude *3-(2-hydroxyphenyl)propanoyl chloride* (**10**; 545 mg, 2 mmol) and Et_3N (606 mg, 6 mmol) in AcOEt (20 ml) was added at 0° the soln. of **11** (690 mg, 2 mmol) in EtOAc (10 ml). The mixture was stirred for 1 h at r.t., the solvent was evaporated, and the residue purified by CC (SiO_2; $CHCl_3$/MeOH 19:1) to give 1.16 g (99%) of **12**. Colorless oil. IR: 3445*m*, 2960*m*, 1645v*s*, 1600*m*, 1490*s*, 1450*s*, 1415*s*, 1365*s*, 1290*m*, 1220*s*, 1165v*s*, 1110*m*, 1015*w*, 900*w*, 860*m*, 690*w*, 655*w*. ^{1}H-NMR: 7.46–7.31 (*m*, 5 arom. H); 7.19–7.15 (*m*, H−C(4), H−C(6)); 6.91–6.87 (*m*, H−C(3), H−C(5)); 6.62 (br., NHBoc); 5.09 (*s*, PhCH_2); 4.68 (br., NHCO); 3.15–3.13 (*m*, CH_2(5′)); 3.11–3.09 (*m*, CH_2(12′)); 3.07–3.05 (*m*, CH_2(7′), CH_2(9′)); 3.01 (*t*, *J* = 7.3, CH_2(1′)); 2.49 (*t*, *J* = 7.2, CH_2(2′)); 1.53–1.52 (*m*, CH_2(6′)); 1.50–1.46 (*m*, CH_2(10′), CH_2(11′)); 1.43, 1.42 (2*s*, 2 Me_3C). ^{13}C-NMR: 172.6 (*s*, C(3′)); 156.5, 156.0 (2*s*, 2 CO); 153.1 (*s*, C(2)); 137.3 (*s*, arom. C); 130.2 (*d*, C(4)); 129.5 (*s*, C(1)); 128.5 (*d*, C(6)); 127.4, 127.2, 127.0 (3*d*, 5 arom. C); 120.7 (*d*, C(5)); 111.6 (*d*, C(3)); 79.6, 79.1 (2*s*, 2 Me$_3$*C*); 69.9 (*t*, Ph*C*H$_2$); 46.4 (*t*, C(12′)); 43.1 (*t*, C(7′)); 40.0 (*t*, C(9′)); 36.6 (*t*, C(5′)); 35.4 (*t*, C(2′)); 28.3 (*q*, 2 Me_3C); 27.3 (*t*, C(1′)); 27.0 (*t*, C(6′)); 26.8 (*t*, C(11′)); 25.6 (*t*, C(10′)). ESI-MS: 606 ($[M+Na]^+$).

N-*[3-({*(tert-*Butoxy)carbonyl](4-{[*(tert-*butoxy)carbonyl]amino}butyl]amino)propyl]-3-(2-hydroxyphenyl)propanamide* (**13**). To a soln. of **12** (1.05 g, 1.8 mmol) in AcOH (110 ml) was added 10% Pd−C (500 mg), and the mixture was hydrogenated overnight in a *Parr* apparatus at 3.5 bar H_2 pressure. Filtration, evaporation, and purification of the residue by CC (SiO_2; $CHCl_3$/MeOH/25% aq. NH_3 soln. 10:4:1) gave 805 mg (90%) of **13**. Colorless oil. IR: 3445*m*, 2460*m*, 1615v*s*, 1580*m*, 1490*s*, 1450*s*, 1415*s*, 1365*s*, 1305*m*, 1230*s*, 1160v*s*, 1100*w*, 1035*w*, 1005*w*, 945*w*, 905*s*, 855*m*, 645*w*. ^{1}H-NMR: 7.11–7.03 (*m*, H−C(4), H−C(6)); 6.90–6.78 (*m*, H−C(3), H−C(5)); 4.68 (br., NHBoc); 3.18–3.16 (*m*, CH_2(5′)); 3.13–3.11 (*m*, CH_2(12′)); 3.09–3.07 (*m*, CH_2(7′), CH_2(9′)); 2.90 (*t*, *J* = 6.5, CH_2(1′)); 2.61 (*t*, *J* = 6.3, CH_2(2′)); 1.61–1.57 (*m*, CH_2(6′)); 1.50–1.47 (*m*, CH_2(10′), CH_2(11′)); 1.44, 1.43 (2*s*, 2 Me_3C). ^{13}C-NMR: 174.0 (*s*, C(3′)); 156.0 (*s*, 2 CO); 154.9 (*s*, C(2)); 130.4 (*d*, C(4)); 127.9 (*s*, C(1)); 127.7 (*d*, C(6)); 120.0 (*d*, C(5)); 117.3 (*d*, C(3)); 79.9, 78.5 (2*s*, 2 Me$_3$*C*); 46.6 (*t*, C(12′)); 43.5 (*t*, C(7′)); 39.9 (*t*, C(9′)); 37.0 (*t*, C(5′)); 36.0 (*t*, C(2′)); 28.3 (*q*, 2 Me_3C); 27.3 (*t*, C(1′)); 26.8 (*t*, C(6′)); 25.5 (*t*, C(11′)); 24.6 (*t*, C(10′)).

Compound **8**. A soln. of **13** (805 mg, 1.63 mmol) in CF_3COOH (TFA) (10 ml) was stirred overnight at r.t. The removal of the solvent and chromatography of the residue (SiO_2; $CHCl_3$/MeOH/25% aq. NH_3 soln. 5 : 3 : 1) gave 300 mg (65%) of **8**, which was crystallized as its hydrochloride, which was identical (TLC, IR, ^{1}H-NMR, ^{13}C-NMR, and MS analysis) to the compound described under *2.1*.

2.3. *From* **1** *and* **11**. *Compound* **13**. A soln. of **1** (148 mg, 1 mmol) and **11** (545 mg, 1 mmol) in EtOH (5 ml) was stirred 1 h at r.t. The mixture was evaporated and the residue purified by CC (SiO_2; $CHCl_3$/MeOH 19 : 1): 473 mg (96%) of **13**. Slightly yellow-colored oil. Compound **13** was found to be identical (TLC, IR, ^{1}H-NMR, ^{13}C-NMR, and MS analysis) with the compound described under *2.2*.

Compound **8**. A soln. of **13** (470 mg, 0.95 mmol) in CF_3COOH (7 ml) was stirred overnight at r.t., and the mixture was evaporated. Chromatography of the residue (SiO_2; $CHCl_3$/MeOH/25% aq. NH_3 soln. 5 : 3 : 1) yielded 280 mg (95%) of **8**, which was crystallized as its hydrochloride. Compound **8** was found to be identical (TLC, IR, ^{1}H-NMR, ^{13}C-NMR, and MS analysis) with the compound described under *2.2*.

3. Synthesis of *N*-{4-[*N*-(3-Aminopropyl)amino]butyl}-3-(2-hydroxyphenyl)propanamide (16). 3.1 *From 1-(4-Aminobutyl)-1,2,3,4,5,6-hexahydropyrimidine* (**14**) *and* **1**. N-*[4-(1,2,3,4,5,6-Hexahydropyrimidin-1-yl)butyl]-3-(2-hydroxyphenyl)propanamide* (**15**). To a soln. of **14** (50 mg, 0.31 mmol) in EtOH (5 ml) was added dropwise a soln. of **1** (51 mg, 0.51 mmol) in EtOH (5 ml). The mixture was stirred 1 h at r.t. and then evaporated. The residue was purified by CC (SiO_2; $CHCl_3$/MeOH/25% aq. NH_3 soln. 85 : 14 : 1) to give 90 mg (92%) of **15**. Amorphous solid. IR: 3250*m* (br.), 2940v*s*, 2710*s*, 1640v*s*, 1520*s*, 1485*s*, 1450*s*, 1320*m*, 1300*m*, 1220*s*, 1165*m*, 1100*m*, 1035*w*, 1010*w*, 975*w*, 885*w*, 835*m*, 655*m*, 620*w*. ^{1}H-NMR: 7.09–7.03 (*m*, H–C(4), H–C(6)); 6.85–6.75 (*m*, H–C(3), H–C(5)); 6.68 (br., NHCO); 5.59 (br., NH); 3.40 (*s*, CH_2(14′)); 3.20–3.14 (*m*, CH_2(5′)); 2.92 (*t*, J = 6.8, CH_2(1′)); 2.83 (*t*, J = 5.5, CH_2(12′)); 2.57 (*t*, J = 6.5, CH_2(8′)); 2.55 (*t*, J = 6.3, CH_2(2′)); 2.24 (*t*, J = 6.7, CH_2(10′)); 1.64 (*quint.*, J = 5.4, CH_2(11′)); 1.54–1.45 (*m*, CH_2(6′), CH_2(7′)). ^{13}C-NMR: 173.7 (*s*, C(3′)); 155.0 (*s*, C(2)); 130.3 (*d*, C(4)); 127.8 (*s*, C(1)); 127.6 (*d*, C(6)); 119.9 (*d*, C(5)); 116.9 (*d*, C(3)); 69.4 (*t*, C(14′)); 54.3 (*t*, C(8′)); 52.7 (*t*, C(10′)); 44.7 (*t*, C(12′)); 39.2 (*t*, C(5′)); 37.0 (*t*, C(2′)); 27.0 (*t*, C(1′)); 26.3 (*t*, C(11′)); 25.2 (*t*, C(6′)); 23.7 (*t*, C(7′)). CI-MS: 306 (100, $[M+1]^+$), 166 (17), 158 (25), 101 (13).

Compound **16**. Through a soln. of **15** (250 mg, 0.8 mmol) in MeOH (7 ml) was bubbled a stream of HCl gas for 3 min. The mixture was evaporated, and the residue was washed with EtOH and purified by CC (SiO_2; $CHCl_3$/EtOH/25% aq. NH_3 soln. 5 : 3 : 1) to give 140 mg (60%) of **16** as colorless oil, which was crystallized as its hydrochloride **16** · 2 HCl. M.p. 133–135° (EtOH). IR (KBr): 2965v*s*, 1637v*s*, 1593*s*, 1551*s*, 1503*m*, 1489*m*, 1455*s*, 1383*m*, 1241*m*, 1157*w*, 1102*w*, 1042*w*, 757*m*, 589*w*. ^{1}H-NMR: 7.39 (br., NHCO); 7.07–7.01 (*m*, H–C(4), H–C(6)); 6.85–6.74 (*m*, H–C(3), H–C(5)); 3.20–3.15 (*m*, CH_2(5′)); 2.88 (*t*, J = 7.1, CH_2(1′)); 2.83 (*t*, J = 6.5, CH_2(12′)); 2.74 (*t*, J = 6.8, CH_2(10′)); 2.61 (*t*, J = 6.6, CH_2(8′)); 2.54 (*t*, J = 7.1, CH_2(2′)); 1.73 (*quint.*, J = 6.7, CH_2(11′)); 1.47–1.41 (*m*, CH_2(6′), CH_2(7′)). ^{13}C-NMR: 174.1 (*s*, C(3′)); 154.7 (*s*, C(2)); 130.1 (*d*, C(4)); 127.5 (*s*, C(1)); 127.4 (*d*, C(6)); 119.7 (*d*, C(5)); 116.0 (*d*, C(3)); 48.8 (*t*, C(7′)); 47.2 (*t*, C(9′)); 39.7 (*t*, C(5′)); 39.0 (*t*, C(12′)); 36.7 (*t*, C(2′)); 32.1 (*t*, C(11′)); 26.6 (*t*, C(1′)); 26.5 (*t*, C(6′)); 25.9 (*t*, C(7′)). ESI-MS: 294 ($[M+1]^+$). ESI-MS/MS (of *m*/*z* 294.4, −20 eV): 294 (100, $[M+1]^+$), 277 (24), 220 (52, $[M-73]^+$), 202 (16), 146 (36), 129 (26), 112 (43), 75 (<10), 72 (30). ESI-MS/MS (of *m*/*z* 294.4, −22 eV): 294 (42, $[M+1]^+$), 277 (32), 220 (100, $[M-73u]^+$), 202 (27), 148 (20), 146 (27), 129 (38), 112 (100), 84 (11), 72 (56).

3-(2-Acetoxyphenyl)-N-*(4-{(acetyl)[3-(acetylamino)propyl]amino}butyl)propanamide* (**17**). Analogously to the preparation of **7**, from **16** (40 mg, 0.136 mmol) and AcONa (60 mg, 0.7 mmol) in Ac_2O (5 ml), 45 mg (80%) of **17** was obtained after workup. ^{1}H-NMR: 7.25–7.12 (*m*, H–C(4), H–C(6)); 7.01–6.97 (*m*, H–C(3), H–C(5)); 6.87 (br., NHCO); 6.42, 5.83 (2 br., *s*, N*H*Ac); 3.35 (*t*, J = 6.3, CH_2(12′)); 3.25 (*t*, J = 6.1, CH_2(5′)); 3.21–3.11 (*m*, CH_2(8′), CH_2(10′)); 2.88 (*t*, J = 7.4, CH_2(1′)); 2.39 (*t*, J = 7.4, CH_2(2′)); 2.07, 1.96 (2*s*, 3 *Me*CO); 1.63 (*quint.*, J = 6.0, CH_2(11′)); 1.48–1.33 (*m*, CH_2(6′), CH_2(7′)). ^{13}C-NMR: 171.8 (*s*, C(3′)); 171.0, 170.2 (2*s*, 3 CO); 148.8 (*s*, C(2)); 132.3 (*s*, C(1)); 130.4 (*d*, C(4)); 127.5 (*d*, C(6)); 126.1 (*d*, C(5)); 122.4 (*d*, C(3)); 48.1 (*t*, C(12′)); 42.0 (*t*, C(8′)); 38.5 (*t*, C(10′)); 36.3 (*t*, C(5′)); 35.7 (*t*, C(2′)); 27.2 (*t*, C(1′)); 26.7 (*t*, C(11′)); 26.1 (*t*, C(7′)); 25.7 (*t*, C(6′)); 23.2, 21.1, 20.8 (3*q*, 3 *Me*CO). ESI-MS: 458 (20, $[M+K]^+$), 442 (100, $[M+Na]^+$), 420 (49, $[M+1]^+$), 378 (16). ESI-MS/MS (of *m*/*z* 420.3, −15 eV): 420 (89, $[M+1]^+$), 378 (100), 360 (36), 319 (11), 230 (40), 171 (<10), 100 (<10). ESI-MS/MS (of *m*/*z* 420.3, −20 eV): 378 (100), 360 (48), 318 (27), 230 (92), 213 (16), 171 (18), 100 (10). ESI-MS/MS/MS (of *m*/*z* 230.3, −40 eV): 230 (74), 213 (31), 114 (12), 100 (100), 72 (24). ESI-MS/MS/MS (of *m*/*z* 230.3, −42 eV): 230 (12), 213 (17), 114 (11), 100 (100), 72 (33). ESI-MS: See *Fig. 1, c*.

3.2. *From* **1** *and Butane-1,4-diamine.* N-*(4-Aminobutyl)-3-(2-hydroxyphenyl)propanamide* (**18**). A mixture of butane-1,4-diamine (1.79 g, 20 mmol) and **1** (1 g, 6.8 mmol) in EtOH (25 ml) was stirred 1 h at r.t. Evaporation of the solvent and chromatography of the residue (SiO_2; $CHCl_3$/MeOH/25% aq. NH_3 soln. 12 : 4 : 1) yielded 1.4 g (90%) of **18**. Colorless oil. ^{1}H-NMR: 7.08–7.01 (*m*, H–C(4), H–C(6)); 6.89 (br., NHCO); 6.84–6.75 (*m*, H–C(3), H–C(5)); 3.15 (*t*, J = 6.4, CH_2(5′)); 2.88 (*t*, J = 7.1, CH_2(1′)); 2.64 (*t*, J = 6.0, CH_2(8′)); 2.53 (*t*,

$J = 6.9$, $CH_2(2')$); 1.56–1.39 (*m*, $CH_2(6')$, $CH_2(7')$). ^{13}C-NMR: 173.9 (*s*, C(3′)); 154.7 (*s*, C(2)); 130.3 (*d*, C(4)); 127.6 (*s*, C(1)); 127.5 (*d*, C(6)); 119.8 (*d*, C(5)); 116.4 (*d*, C(3)); 40.7 (*t*, C(5′)); 39.1 (*t*, C(8′)); 36.9 (*t*, C(2′)); 29.1 (*t*, C(7′)); 26.2 (*t*, C(1′)); 25.3 (*t*, C(6′)). ESI-MS: 237 ($[M+1]^+$).

N-*{4-[(2-Cyanoethyl)amino]butyl}-3-(2-hydroxyphenyl)propanamide* (**19**). To a stirred soln. of **18** (1.38 g, 5.58 mmol) in MeOH was added dropwise acrylonitrile (372 mg, 7.02 mmol), and the stirring was continued at r.t. for 24 h. After evaporation and purification by CC (SiO_2; $CHCl_3$/MeOH/25% aq. NH_3 soln. 85 : 14 : 1), 1.68 g (99%) of **19** and N-*{4-[bis(2-cyanoethyl)amino]butyl}-3-(2-hydroxyphenyl)propanamide* (**20**) were obtained. ^{1}H-NMR: 7.13–7.04 (*m*, H–C(4), H–C(6)); 6.90–6.80 (*m*, H–C(3), H–C(5)); 6.09 (br., NHCO); 3.22 (*t*, $J =$ 6.6, $CH_2(5')$); 2.94 (*t*, $J = 6.8$, $CH_2(1')$); 2.72 (*t*, $J = 6.5$, $CH_2(10')$); 2.66 (*t*, $J = 6.6$, $CH_2(8')$); 2.60 (*t*, $J = 7.1$, $CH_2(2')$); 2.42 (*t*, $J = 6.6$, $CH_2(11')$); 1.58–1.44 (*m*, $CH_2(6')$, $CH_2(7')$). ^{13}C-NMR: 173.1 (*s*, C(3′)); 153.3 (*s*, C(2)); 130.7 (*d*, C(4)); 128.0 (*d*, C(6)); 127.7 (*s*, C(1)); 120.2 (*d*, C(5)); 117.4 (*d*, C(3)); 99.7 (*s*, CN); 49.8 (*t*, C(8′)); 45.11 (*t*, C(10′)); 37.3 (*t*, C(5′)); 37.0 (*t*, C(2′)); 31.2 (*t*, C(7′)); 26.1 (*t*, C(1′)); 24.6 (*t*, C(6′)). ESI-MS: 312 (5, $[M+Na]^+$), 290 (100, $[M+1]^+$).

Compound **16** *and* N-*{4-Bis(3-aminopropyl)amino]butyl}-3-(2-hydroxyphenyl)propanamide* (**21**). To a soln. of **19** (1.65 g, 5.7 mmol) in EtOH (90 ml) and 25% aq. NH_3 soln. (25 ml) was added *Raney*-Ni (700 mg), and the mixture was hydrogenated over night in a *Parr* apparatus at 3.5 bar H_2 pressure. The mixture was filtered over *Celite*, the filtrate was evaporated, and the residue was chromatographed (SiO_2; $CHCl_3$/MeOH/25% aq. NH_3 soln. 5 : 3 : 1): 1.35 g (80%), 1st fraction) of **16** and 260 mg (15%, 2nd fraction) of **21** were obtained. Both products were converted to their hydrochlorides by treatment with 0.3N aq. HCl soln.

Data of **16**: Compound **16** was found to be identical (TLC, IR, ^{1}H-NMR, ^{13}C-NMR, and MS analysis) to the compound described under *3.1*.

Data of **21**: ^{1}H-NMR: 7.37 (br., NHCO); 7.07–7.01 (*m*, H–C(4), H–C(6)); 6.85–6.74 (*m*, H–C(3), H–C(5)); 3.17–3.15 (*m*, $CH_2(5')$); 2.89 (*t*, $J = 7.0$, $CH_2(1')$); 2.81 (*t*, $J = 6.5$, $CH_2(12')$, $CH_2(3'')$); 2.55 (*t*, $J = 6.9$, $CH_2(2')$); 2.45 (*t*, $J = 6.8$, $CH_2(10')$, $CH_2(1'')$); 2.34 (*t*, $J = 6.5$, $CH_2(8')$); 1.95 (br., 2 NH_2); 1.65 (*quint.*, $J = 6.6$, $CH_2(11')$, $CH_2(2'')$); 1.39–1.35 (*m*, $CH_2(6')$, $CH_2(7')$). ^{13}C-NMR: 174.0 (*s*, C(3′)); 154.9 (*s*, C(2)); 130.2 (*d*, C(4)); 127.5 (*s*, C(1)); 127.4 (*d*, C(6)); 119.6 (*d*, C(5)); 116.1 (*d*, C(3)); 53.2, 52.3 (2*t*, C(10′), C(1″)); 49.1 (*t*, C(8′)); 39.8 (*t*, C(5′)); 38.8, 38.7 (2*t*, C(12′), C(3″)); 36.7 (*t*, C(2′)); 27.1 (*t*, C(11′), C(2″)); 26.8 (*t*, C(1′)); 25.7 (*t*, C(7′)); 24.0 (*t*, C(6′)). ESI-MS: 351 ($[M+1]^+$).

4. Synthesis of *N*-[3-({4-[(3-Aminopropyl)amino]butyl}amino)propyl]-3-(2-hydroxyphenyl)propanamide (24). 4.1. *From* **1** *and Spermine* (**22**). *3,3′-Bis[3-(2-hydroxyphenyl)]*-N,N′*-(4,9-diazadodecane-1,12-diyl)bis-[propanamide]* (**23**) *and* **24**. To a stirred soln. of spermine (242 mg, 1.2 mmol) in EtOH (150 ml) was added dropwise the soln. of **1** (177 mg, 1.2 mmol) in EtOH (60 ml), and the stirring was continued for 1 h at r.t. The solvent was removed, and the residue was purified by CC (SiO_2; CH_2Cl_2/EtOH/25% aq. NH_3 soln. 6 : 3 : 1): 233 mg (39%) of **23** (1st fraction) and 252 mg (60%) of **24** (2nd fraction) were obtained, which were crystallized as hydrochlorides.

Data of **23**: M.p. 198–200° (EtOH). IR: 3300*s* (br.), 2940*s*, 2825*m*, 1640v*s*, 1520*s*, 1450*s*, 1370*m*, 1300*m*, 1230*s*, 1150*w*, 1100*m*, 1015*s*, 945*w*, 835*w*, 650*w*. ^{1}H-NMR: 7.32 (br., 2 NHCO); 7.06–7.01 (*m*, 2 H–C(4), 2 H–C(6)); 6.82–6.74 (*m*, 2 H–C(3), 2 H–C(5)); 3.20 (*t*, $J = 6.0$, $CH_2(5')$, $CH_2(16')$); 2.88 (*t*, $J = 6.6$, $CH_2(1')$, $CH_2(20')$); 2.76 (*t*, $J = 7.0$, $CH_2(7')$, $CH_2(14')$); 2.54 (*t*, $J = 6.7$, $CH_2(2')$, $CH_2(19')$); 2.52–2.49 (*m*, $CH_2(9')$, $CH_2(12')$); 1.57 (*quint.*, $J = 6.4$, $CH_2(6')$, $CH_2(15')$); 1.52–1.51 (*m*, $CH_2(10')$, $CH_2(11')$). ^{13}C-NMR: 174.1 (*s*, C(3′), C(18′)); 154.8, (*s*, 2 C(2)); 130.3 (*d*, 2 C(4)); 127.5 (*d*, 2 C(6)); 127.4 (*s*, 2 C(1)); 119.7 (*d*, 2 C(5)); 116.2 (*d*, 2 C(3)); 48.7 (*t*, C(9′), C(12′)); 46.5 (*t*, C(7′), C(14′)); 37.6 (*t*, C(5′), C(16′)); 36.7 (*t*, C(2′)); 27.9 (*t*, C(1′), C(20′)); 26.9 (*t*, C(6′), C(15′)); 25.7 (*t*, C(10′), C(11′)). ESI-MS: 499 ($[M+1]^+$).

Data of **24**: M.p. 294–296° (EtOH). IR ($CHCl_3$): 3300*w*, 2930*s*, 2840*m*, 1640*s*, 1520*m*, 1455*m*, 1370*w*, 1300*w*, 1235*m*, 1110*m*, 1005*w*, 940*w*, 885*w*, 835*w*, 655*w*. ^{1}H-NMR: 7.45 (br., NHCO); 7.08–7.02 (*m*, H–C(4), H–C(6)); 6.81–6.75 (*m*, H–C(3), H–C(5)); 3.22 (*t*, $J = 6.5$, $CH_2(5')$); 2.89 (*t*, $J = 7.0$, $CH_2(1')$); 2.76 (*t*, $J = 7.0$, $CH_2(16')$); 2.66 (*t*, $J = 7.1$, $CH_2(7')$, $CH_2(14')$); 2.54 (*t*, $J = 6.7$, $CH_2(2')$); 2.52–2.50 (*m*, $CH_2(9')$, $CH_2(12')$); 1.66 (*quint.*, $J =$ 7.2, $CH_2(6')$); 1.59 (*quint.*, $J = 6.5$, $CH_2(15')$); 1.54–1.50 (*m*, $CH_2(10')$, $CH_2(11')$). ^{13}C-NMR: 175.5 (*s*, C(3′)); 154.9 (*s*, C(2)); 130.5 (*d*, C(4)); 127.6 (*d*, C(6)); 127.5 (*s*, C(1)); 119.9 (*d*, C(5)); 116.1 (*d*, C(3)); 53.1 (*t*, C(9′)); 53.0 (*t*, C(12′)); 51.0 (*t*, C(7′)); 50.9 (*t*, C(14′)); 43.6 (*t*, C(5′)); 41.6 (*t*, C(16′)); 40.6 (*t*, C(2′)); 36.0 (*t*, C(6′)); 32.1 (*t*, C(15′)); 31.0 (*t*, C(1′)); 30.9 (*t*, C(11′)); 29.8 (*t*, C(10′)). ESI-MS: 351 ($[M+1]^+$). ESI-MS/MS (of *m*/*z* 351.3, −20 eV): 351 (39, $[M+1]^+$), 277 (75), 259 (21), 206 (53, $[M-144u]^+$), 203 (10), 129 (100), 72 (30). ESI-MS/MS (of *m*/*z* 351.3, −25 eV): 277 (19), 259 (11), 206 (100, $[M-144u]^+$), 129 (67), 112 (63).

3-(2-Acetoxyphenyl)-N-*{3-[(acetyl)(4-{(acetyl)[3-(acetylamino)propyl]amino}butyl)amino]propyl}propanamide* (**25**). Analogously to the preparation of **7**, from **24**·3 HCl (6 mg), AcONa (50 mg) in Ac_2O (5 ml), 5.6 mg (90%) of **25** were obtained after workup. ESI-MS: 499 (15 $[M+Na]^+$), 477 (100, $[M+1]^+$), 371 (20),

329 (17), 312 (5). ESI-MS/MS (of 477.3, fragmentation amplification (FA) 1.0 V): 459 (12), 417 (9), 329 (100), 312 (10), 287 (3), 213 (4), 171 (4). ESI-MS/MS/MS (of *m/z* 477.3/329.3, FA 1.0 V): 329 (30), 312 (45), 287 (27), 269 (17), 230 (62), 213 (60), 171 (100), 114 (14), 100 (70). ESI-MS/MS/MS (of *m/z* 477.3/417.1, FA 1.0 V): 399 (11), 319 (11), 269 (25), 213 (12), 206 (100), 171 (43).

5. Synthesis of *N*-{4-[(3-Aminopropyl)amino]butyl}-*N*-(3-aminopropyl)-3-(2-hydroxyphenyl)propanamide (27). 5.1. *From* **1** *and Dibenzyl N,N′-[4-(Benzyloxycarbonyl)-4,9-diazadodecane-1,12-diyl]bis[carbamate]* (**4**). N-*(3-[[(Benzyloxy)carbonyl]amino]propyl)*-N-*[4-[(3-[[(benzyloxy)carbonyl]amino]propyl)amino]butyl]- 3-(2-hydroxyphenyl)propanamide* (**26**). A mixture of **4** (605 mg, 1 mmol) and **1** (148 mg, 1 mmol) in toluene (20 ml) was stirred under reflux for 7 d. After cooling to r.t., the solvent was removed *in vacuo*, and the residue was purified by CC (SiO_2; $CHCl_3$/MeOH 49:1) to give 250 mg (33%) of **26**. Slightly yellow oil. IR: 3440*m*, 2940*m*, 1710v*s*, 1610*s*, 1505*s*, 1440*s*, 1365*m*, 1235*s*, 1135*m*, 1080*m*, 1010*m*, 905*w*, 840*w*, 690*w*. ^{1}H-NMR: 9.05 (br. *s*, OH); 7.35–7.30 (*m*, 15 arom. H); 7.10–7.00 (*m*, H–C(4), H–C(6)); 6.88–6.80 (*m*, H–C(3), H–C(5)); 5.58 (br., 2 NHCO); 5.08 (*s*, 3 PhCH_2); 3.36–3.33 (*m*, CH_2(3″), CH_2(12′)); 3.26–3.13 (*m*, CH_2(1″), CH_2(5′)); 3.04–3.02 (*m*, CH_2(8′), CH_2(10′)); 2.90 (*t, J* = 6.5, CH_2(1′)); 2.60 (br., CH_2(2′)); 1.70–1.68 (*m*, CH_2(2″), CH_2(11′)); 1.66–1.42 (*m*, CH_2(6′), CH_2(7′)). ^{13}C-NMR: 174.0 (*s*, C(3′)); 156.4 (*s*, 3 CO); 154.9 (*s*, C(2)); 136.6 (*s*, 3 arom. C); 130.4 (*d*, C(4)); 128.4 (*s*, C(1)); 128.3 (*d*, C(6)); 128.1, 127.9, 127.7 (3*d*, 15 arom. C), 120.0 (*d*, C(5)); 117.5 (*d*, C(3)); 67.3, 66.4 (2*t*, 3 PhCH_2)); 47.3 (*t*, C(8′)); 46.3 (*t*, C(10′)); 46.1 (*t*, C(3″)); 43.9 (*t*, C(12′)); 42.9 (*t*, C(1″)); 37.7 (*t*, C(5′)); 34.4 (*t*, C(2′)); 27.6 (*t*, C(2″)); 25.6 (*t*, C(1′)); 25.2 (*t*, C(11′)); 24.9 (*t*, C(7′)); 24.6 (*t*, C(6′)). ESI-MS: 775 ([M + Na]$^+$).

Compound **27**. A suspension of 10% Pd/C (120 mg) and **26** (245 mg, 0.31 mmol) in AcOH (110 ml) was hydrogenated overnight in a *Parr* apparatus at 3.5 bar H_2 pressure. The catalyst was filtered off, the filtrate was evaporated, and the residue was purified by CC (SiO_2; CH_2Cl_2/EtOH/25% aq. NH_3 soln. 5:3:1): 110 mg (100%) of **27**, which was crystallized as hydrochloride **27** · 3 HCl (colorless foam). IR: 3380*w*, 2930*s*, 1610*s*, 1455*m*, 1375*m*, 1305*w*, 1235*m*, 1115*w*, 1095*w*, 945*w*, 885*w*, 840*m*, 700*w*, 655*w*. ^{1}H-NMR (CD_3OD): 8.09 (br., $^+NH_2$, 2 $^+NH_3$); 7.10–7.01 (*m*, H–C(4), H–C(6)); 6.83–6.72 (*m*, H–C(3), H–C(5)); 3.47 (*t, J* = 6.6, CH_2(3″)); 3.36 (*t, J* = 6.8, CH_2(12′)); 3.17–3.11 (*m*, CH_2(1″), CH_2(5′)); 3.06 (*t, J* = 7.5, CH_2(1′)); 2.87 (*t, J* = 7.3, CH_2(10′)); 2.82 (*t, J* = 7.3, CH_2(8′)); 2.72 (*t, J* = 7.6, CH_2(2′)); 2.13 (*quint., J* = 7.5, CH_2(2″)); 1.88 (*quint., J* = 6.8, CH_2(11′)); 1.73–1.68 (*m*, CH_2(6′), CH_2(7′)). ^{13}C-NMR (CD_3OD): 176.4 (*s*, C(3′)); 156.4 (*s*, C(2)); 131.3 (*d*, C(4)); 128.7 (*d*, C(6)); 128.1 (*s*, C(1)); 120.6 (*d*, C(5)), 116.1 (*d*, C(3)); 48.6 (*t*, (C(8′)); 46.1 (*t*, C(10′)); 45.8 (*t*, C(3″)); 43.5 (*t*, C(12′)); 38.1 (*t*, C(1″)); 37.8 (*t*, C(5′)); 33.9 (*t*, C(2′)); 28.1 (*t*, C(1″)); 27.8 (*t*, C(1′)); 26.8 (*t*, C(11′)); 25.2 (*t*, C(7′)); 24.4 (*t*, C(6′)). ESI-MS: 351 (15, [M + 1]$^+$), 206 (58), 129 (90), 112 (100). ESI-MS/MS (of *m/z* 351.3, −20 eV): 351 (100, [M + 1]$^+$), 331 (10), 277 (19), 206 (33, [M − 144u]$^+$), 203 (44), 129 (100), 72 (40). ESI-MS/MS (of *m/z* 351.3, −25 eV): 351 (10, [M + 1]$^+$), 277 (<10), 206 (59, [M − 144]$^+$), 203 (11), 129 (92), 112 (100).

5.2. *From* **2** *and* **4**. N-*(3-[[Benzyloxy)carbonyl]amino]propyl)*-N-*[4-[(3-[[(benzyloxy)carbonyl]amino]-propyl)amino]butyl]-3-[2-(benzyloxy)phenyl]propanamide* (**29**). To a mixture of 1-methyl-2-chloropyridinium iodide (460 mg, 1.8 mmol), Et_3N (363 mg, 3.6 mmol), and **2** (384 mg, 1.5 mmol) in CH_2Cl_2 (25 ml) was added a soln. of **4** (907 mg, 1.5 mmol) in CH_2Cl_2 (10 ml). The mixture was stirred overnight at r.t., and the solvent was evaporated. The residue was dissolved in $CHCl_3$ (80 ml), washed with 0.3N aq. HCl soln., and dried (Na_2SO_4). Evaporation of the solvent and chromatography of the residue (SiO_2; $CHCl_3$/MeOH 49:1) furnished 1.22 g (94%) **29**. Colorless oil. IR: 3440*w*, 2930*w*, 1700*s*, 1630*s*, 1510*s*, 1450*m*, 1370*w*, 1300*m*, 1215*s*, 1130*m*, 1110*m*, 1075*m*, 1020*m*, 910*w*, 855*w*, 620*w*. ^{1}H-NMR: 7.41–7.27 (*m*, 20 arom. H); 7.19–7.14 (*m*, H–C(4), H–C(6)); 6.90–6.85 (*m*, H–C(3), H–C(5)); 5.82, 5.58 (2 br. *s*, 2 NHCO); 5.26 (*s*, PhCH_2); 5.06, 5.04, 5.03 (3*s*, 3 PhCH_2); 3.29–3.21 (*m*, CH_2(1″), CH_2(5′)); 3.10–3.02 (*m*, CH_2(3″), CH_2(12′)); 3.01–2.99 (*m*, CH_2(8′), CH_2(10′)); 2.96 (*t, J* = 8.1, CH_2(1′)); 2.55–2.50 (*m*, CH_2(2′)); 1.62 (*quint., J* = 6.5, CH_2(2″), CH_2(11′)); 1.57–1.44 (*m*, CH_2(6′), CH_2(7′)). ^{13}C-NMR: 173.1 (*s*, C(3′)); 156.5, 156.4 (2*s*, 3 CO); 137.1 (*s*, C(2)); 136.8 (*s*, 3 arom. C); 130.4 (*d*, C(4)); 128.5 (*d*, C(6)); 127.8 (*s*, C(1)); 128.4, 128.1, 127.5 (3*d*, 20 arom. C); 120.9 (*d*, C(5)); 111.6 (*d*, C(3)); 69.8 (*t*, PhCH_2)); 67.1, 66.3 (2*t*, 3 PhCH_2)); 47.0 (*t*, C(8′)); 46.2 (*t*, C(10′)); 45.0 (*t*, C(3″)); 43.9 (*t*, C(12′)); 41.9 (*t*, C(1″)); 37.4 (*t*, C(5′)); 33.2 (*t*, C(2′)); 29.3 (*t*, C(2″)); 27.6 (*t*, C(1′)); 27.2 (*t*, C(11′)); 25.5 (*t*, C(7′)); 24.9 (*t*, C(6′)). ESI-MS: 865 ([M + Na]$^+$).

Compound **27**. Analogously to the preparation of **6**, from **29** (930 mg, 1.1 mmol) and 10% Pd/C (500 mg) in conc. AcOH (110 ml), 340 mg (90%) of **27** were obtained after workup. Compound **27** was found to be identical (TLC, IR, ^{1}H-NMR, ^{13}C-NMR, and MS analysis) with the compound described under *5.1*.

3-(2-Acetoxyphenyl)-N-*[3-(acetylamino)propyl]*-N-*(4-{[3-(acetylamino)propyl]amino}butyl)propanamide* (**28**). Analogously to the preparation of **7**, from **27** · HCl (5 mg), AcONa (50 mg) in Ac_2O (5 ml), 4 mg (77%) of **28** were obtained after workup. ESI-MS: 499 (3, [M + Na]$^+$), 477 (100, [M + 1]$^+$), 371 (3), 329 (15). ESI-MS/MS (of 477.3, FA 1.0 V): 459 (7), 417 (17), 329 (100), 312 (6); 311 (9), 213 (5), 171 (9). ESI-MS/MS/MS (of *m/z*

477.3/329.3, FA 1.0 V): 329 (25), 312 (48), 287 (33), 269 (13), 230 (58), 213 (85), 171 (100), 114 (14), 100 (78). ESI-MS/MS/MS (of *m/z* 477.3/329.3, FA 1.0 V): 329 (25), 312 (48), 311 (15), 287 (33), 269 (13), 230 (58), 213 (85), 171 (100), 114 (14), 100 (78). ESI-MS/MS/MS (of *m/z* 477.3/417.3, FA 1.0 V): 269 (26), 220 (43), 213 (26), 171 (100).

6. Synthesis of *N*-(12-Amino-5,9-diazadodecyl)-3-(2-hydroxyphenyl)propanamide (32). N-*{4-[2-(Cyanoethyl)-1,2,3,4,5,6-hexahydropyrimidin-1-yl]butyl}-3-(2-hydroxyphenyl)propanamide* (**30**). To a soln. of **15** (715 mg, 2.34 mmol) in MeOH (30 ml) was added dropwise acrylonitrile (161 mg, 3 mmol) in MeOH (5 ml), and the mixture was stirred overnight at r.t. Removal of the solvent *in vacuo* and chromatography of the residue (SiO_2; $CHCl_3$/MeOH/25% aq. NH_3 soln. 90:10:1) gave 837 mg (100%) of **30**. Colorless oil. IR: 2940*m*, 2800*w*, 1640v*s*, 1520*m*, 1485*m*, 1415*m*, 1365*w*, 1220*s*, 1105*m*, 1035*w*, 970*w*, 925*w*, 800*m*, 655*m*, 620*w*. ^{1}H-NMR: 7.11–7.03 (*m*, H–C(4), H–C(6)); 6.90–6.77 (*m*, H–C(3), H–C(5)); 6.73 (br., NHCO); 3.22 (*t*, *J* = 6.2, CH_2(5′)); 3.17 (*s*, CH_2(14′)); 2.90 (*t*, *J* = 6.2, CH_2(1′)); 2.70 (*t*, *J* = 7.2, CH_2(15′)); 2.59 (*t*, *J* = 6.2, CH_2(8′)); 2.57 (*t*, *J* = 6.3, CH_2(2′)); 2.46 (*t*, *J* = 6.6, CH_2(10′), CH_2(12′)); 2.32 (*t*, *J* = 6.7, CH_2(16′)); 1.67 (*quint.*, *J* = 5.5, CH_2(11′)); 1.51–1.42 (*m*, CH_2(6′), CH_2(7′)). ^{13}C-NMR: 174.0 (*s*, C(3′)); 155.0 (*s*, C(2)); 130.4 (*d*, C(4)); 128.0 (*s*, C(1)); 127.7 (*d*, C(6)); 120.0 (*d*, C(5)); 118.7 (*s*, CN); 117.4 (*d*, C(3)); 75.1 (*t*, C(14′)); 54.0 (*t*, C(8′)); 52.0 (*t*, C(15′)); 51.8 (*t*, C(12′)); 50.2 (*t*, C(10′)); 39.4 (*t*, C(5′)); 37.0 (*t*, C(2′)); 27.0 (*t*, C(1′)); 24.7 (*t*, C(11′)); 24.2 (*t*, C(7′)); 22.9 (*t*, C(6′)); 16.5 (*t*, C(16′)). ESI-MS: 359 (100, $[M+1]^+$), 263 (18).

1-[2-(4-Aminobutyl)-1,2,3,4,5,6-hexahydropyrimidin-1-yl]-3-(2-hydroxyphenyl)propan-1-one (**35**), N-*(12-Amino-5-methyl-5,9-diazadodecyl)-3-(2-hydroxyphenyl)propanamide* (**34**), *and* N-*(12-Amino-5,9-diazadodecyl)-3-(2-hydroxyphenyl)propanamide* (**32**). A suspension of *Raney*-Ni (200 mg) and **30** (830 mg, 2.23 mmol) in EtOH (90 ml) and 25% aq. NH_3 soln. (25 ml) was hydrogenated overnight in a *Parr* apparatus at 3.5 bar H_2 pressure. The mixture was filtered, and the filtrate was evaporated. Purification of the residue by CC (SiO_2; $CHCl_3$/EtOH/25% aq. NH_3 soln. 6:3:1) yielded 310 mg (36%, 1st fraction) of **31**, 140 mg (16% 2nd fraction) of **34**, and 170 mg (20%, 3rd fraction) of **32**, which was crystallized as its hydrochloride **32** · 3 HCl.

Data of **31**: IR: 2930*s*, 1640*s*, 1520*m*, 1485*m*, 1450*m*, 1370*m*, 1305*w*, 1220*m*, 1100*m*, 1035*m*, 975*w*, 925*w*, 875*w*, 800*w*, 655*m*, 620*w*. ^{1}H-NMR: 7.22 (br., NHCO); 7.06–7.01 (*m*, H–C(4), H–C(6)); 6.88–6.74 (*m*, H–C(3), H–C(5)); 3.38, 3.04 (2*s*, CH_2(14′)); 3.19–3.17 (*m*, CH_2(5′)); 2.89 (*t*, *J* = 6.7, CH_2(1′)); 2.77 (*t*, *J* = 5.8, CH_2(17′)); 2.55 (*t*, *J* = 6.8, CH_2(2′)); 2.38 (*t*, *J* = 7.0, CH_2(10′), CH_2(12′)); 2.30–2.26 (*m*, CH_2(8′), CH_2(14′)); 1.64 (*quint.*, *J* = 6.4, CH_2(11′), CH_2(16′)); 1.55–1.38 (*m*, CH_2(6′), CH_2(7′)). ^{13}C-NMR: 173.6 (*s*, C(3′)); 155.1 (*s*, C(2)); 130.3 (*d*, C(4)); 128.0 (*s*, C(1)); 127.4 (*d*, C(6)); 119.6 (*d*, (C(5)); 116.4 (*d*, C(3)); 75.8 (*t*, C(14′)); 54.3 (*t*, C(8′)); 53.0 (*t*, C(15′)); 52.4 (*t*, C(12′)); 52.2 (*t*, C(10′)); 40.4 (*t*, C(5′)); 39.2 (*t*, C(17′)); 36.9 (*t*, C(2′)); 29.3 (*t*, C(16′)); 28.8 (*t*, C(1′)); 25.7 (*t*, C(11′)); 24.2 (*t*, C(7′)); 23.6 (*t*, C(6′)). ESI-MS: 385 (16, $[M+Na]^+$), 363 (100, $[M+1]^+$).

Data of **34**: ^{1}H-NMR: 7.38 (br., NHCO); 7.06–7.00 (*m*, H–C(4), H–C(6)); 6.79–6.72 (*m*, H–C(3), H–C(5)); 3.20–3.16 (*m*, CH_2(5′)); 2.88 (*t*, *J* = 7.1, CH_2(1′)); 2.78 (*t*, *J* = 6.7, CH_2(16′)); 2.73–2.67 (*m*, CH_2(8′), CH_2(10′)); 2.53 (*t*, *J* = 7.0, CH_2(2′)); 2.37 (*t*, *J* = 5.0, CH_2(12′), CH_2(14′)); 2.19, 2.17 (2*s*, Me); 1.67 (*quint.*, *J* = 6.1, CH_2(11′), CH_2(15′)); 1.59–1.45 (*m*, CH_2(6′), CH_2(7′)). ^{13}C-NMR: 173.5 (*s*, C(3′)); 155.2 (*s*, C(2)); 130.2 (*d*, C(4)); 127.9 (*s*, C(1)); 127.3 (*d*, C(6)); 119.4 (*d*, (C(5)); 116.2 (*d*, C(3)); 56.1 (*t*, C(10′) or C(8′)); 55.5 (*t*, C(12′) or C(14′)); 48.8 (*t*, C(8′) or C(10′)); 48.2 (*t*, C(14′) or C(12′)); 41.9 (*q*, Me); 40.2 (*t*, C(5′)); 39.2 (*t*, C(16′)); 36.9 (*t*, C(2′)); 31.6 (*t*, C(11′)); 29.5 (*t*, C(15′)); 26.7 (*t*, C(1′)); 26.0 (*t*, C(7′)); 24.5 (*t*, (6′)). ESI-MS: 365 (100, $[M+1]^+$), 183 (17, $[M+2]^{2+}$).

Data of **32**: M.p. 243–245° (EtOH). IR (KBr): 3290*s*, 2943v*s*, 2772v*s*, 2505*m*, 1633*s*, 1548*m*, 1489*m*, 1455*s*, 1406*m*, 1357*w*, 1247*m*, 1169*w*, 1102*w*, 1044*w*, 1006*w*, 720*m*. ^{1}H-NMR (D_2O): 7.11–7.05 (*m*, H–C(4), H–C(6)); 6.89–6.80 (*m*, H–C(3), H–C(5)); 3.13–3.10 (*m*, CH_2(5′)); 3.09–3.06 (*m*, CH_2(8′)); 3.03 (*t*, *J* = 7.0, CH_2(10′), CH_2(12′), CH_2(14′)); 2.91 (*t*, *J* = 7.2, CH_2(16′)); 2.80 (*t*, *J* = 7.1, CH_2(1′)); 2.44 (*t*, *J* = 7.0, CH_2(2′)); 2.08 (*quint.*, *J* = 5.6, CH_2(11′)); 2.03 (*quint.*, *J* = 5.6, CH_2(15′)); 1.48–1.30 (*m*, CH_2(6′), CH_2(7′)). ^{13}C-NMR (D_2O): 175.8 (*s*, C(3′)); 153.5 (*s*, C(2)); 130.5 (*d*, C(4)); 127.9 (*d*, C(6)); 126.8 (*s*, C(1)); 120.5 (*d*, (C(5)); 115.4 (*d*, C(3)); 47.2 (*t*, C(10′)); 44.6 (*t*, C(12′)); 44.5 (*t*, C(8′)); 44.2 (*t*, C(14′)); 38.3 (*t*, C(5′)); 35.6 (*t*, C(2′)); 26.0 (*t*, C(1′)); 25.3 (*t*, C(11′)); 23.6 (*t*, C(15′)); 22.6 (*t*, C(7′)); 22.5 (*t*, C(6′)). ESI-MS: 351 (100, $[M+1]^+$), 176 (65, $[M+2]^{2+}$). ESI-MS/MS (of *m/z* 351.4, −24 eV): 351 (100, $[M+1]^+$), 277 (52), 259 (10), 220 (18, $[M-130]^+$), 203 (46), 129 (10), 115 (64), 112 (34), 98 (28). ESI-MS/MS (of *m/z* 351.4, −26 eV): 351 (100, $[M+1]^+$), 277 (58), 259 (20), 220 (39, $[M-130]^+$), 203 (27), 129 (19), 115 (100), 112 (96), 98 (82), 72 (18).

3-(2-Acetoxyphenyl)-N-*(4-{(acetyl)[3-({(acetyl)[3-(acetylamino)propyl]}amino)propyl]amino}butyl)propanamide* (**33**). Analogously to the preparation of **7**, from **32** · 3 HCl (6 mg), AcONa (50 mg) in Ac_2O (5 ml); 5.1 mg (82%) of **33** were obtained after workup. ESI-MS: 515 (3, $[M+K]^+$), 499 (9, $[M+Na]^+$), 477 (100, $[M+1]^+$), 371 (10), 329 (10), 287 (4). ESI-MS/MS (of *m/z* 477.3, FA 1.0 V): 459 (23), 417 (46), 329 (100), 319

(23), 269 (7), 220 (7), 213 (16), 199 (11), 171 (2). ESI-MS/MS/MS (of *m/z* 477.3/329.3, FA 1.0 V): 329 (2), 312 (3), 311 (4), 287 (4), 269 (17), 213 (100), 199 (38), 171 (2), 114 (10). ESI-MS/MS/MS (of *m/z* 477.3/417.3, FA 1.0 V): 399 (5), 376 (2), 319 (85), 318 (100), 270 (5), 269 (5), 220 (44), 202 (14).

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