# Synthetic Analogues to the Spermidine-Spermine Alkaloid Tenuilobine

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Naturally occurring spider and wasp toxins are potent inhibitors of glutamate receptors in the central nervous system. They consist of a polyamine backbone and carboxylic acids or amino acids linked by peptide bonds. In some respects, the plant alkaloid tenuilobine, a derivative of spermine and spermidine, shows structural similarities to these toxins. In the present paper, the synthesis of the five tenuilobine analogs **12**, **13**, **15**, **24**, and **25** is described. These derivatives differ in their aromatic carboxylic acid subunits and in the polyamine moiety.

**Introduction.** – The polyamines putrescine (= butane-1,4-diamine), spermidine (= *N*-(3-aminopropyl)butane-1,4-diamine), spermine (= *N*,*N*′-bis(3-aminopropyl)butane-1,4-diamine), and further biogenic amines, as well as their derivatives, are widely distributed throughout nature. Besides their presence in native form as free aliphatic bases, the common polyamines often occur conjugated [1] with sugars [2], steroids [3], phospholipids [4], and peptides [5], as well as as substructural units within numerous families of plant alkaloids [6][7]. Many natural products such as antibiotics, siderophores, and metabolites, have been found to be relatively complex conjugates of polyamines. By the mid-1970s, polyamines and their conjugates were beginning to emerge as wide-ranging biologically effective molecules with bright prospects for pharmaceutical development. Broad interest in such compounds developed since they were found to play an important role in many medicinal applications; *e.g.*, in cancer therapy.

Polyamines were found to be part of a group of naturally occurring compounds, the toxins of spiders and wasps [8–10], which are of great interest because of their neurotoxic properties. These toxins are comprised of a polyamine backbone and one or more carboxylic acids or amino acids linked by amide bonds. Recently, it has been found that components of the toxins are excellent inhibitors of glutamate receptors of the central nervous system of humans and other mammals. 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 [11]. Based on their response to antagonists, the glutamate receptors are devided into three major types; *N*-methyl-D-aspartate (NMDA), quisqualate, and kainate. There is considerable interest in developing agents that block glutamate receptors. While antagonists for NMDA have became available in the past few years, only relatively efficient inhibitors for the quisqualate and kainate receptors have been found [12]. In recent years, the synthesis of synthetic analogues of spider toxins has aroused considerable interest among biologists and chemists due to the potent and

[1]) Part of the Diploma thesis of *K. P.*, Universität Zürich, 1997.

selective pharmacological activity at glutamate receptors and certain voltage-sensitive calcium channels [13]. The discovery of polyamine-containing toxins that block glutamate receptors led to the synthesis of a large array of these compounds and variants [14][15]. To determine which structural features of the polyamine backbone are essential for the pharmacological activity, we carried out the synthesis of an analogue of tenuilobine. (= $N^1$-(4-aminobutyl)-$N^1$,$N^{16}$-bis(3-aminopropyl)-$N^{16}$-{4-[(3-aminopropyl)amino]butyl}hexadecanediamide). Tenuilobine, a cross-linked polyamine alkaloid, was isolated from the leaves of *Oncinotis tenuiloba* (Apocynaceae) [16]. It contains two polyamines, spermidine and spermine, coupled by an amide-bond linkage through an aliphatic chain. The idea was to prepare analogues of tenuilobine with two and three amide-bonded polyamines, in which the aliphatic chain is replaced by an hydroxylated aromatic core as anchor.

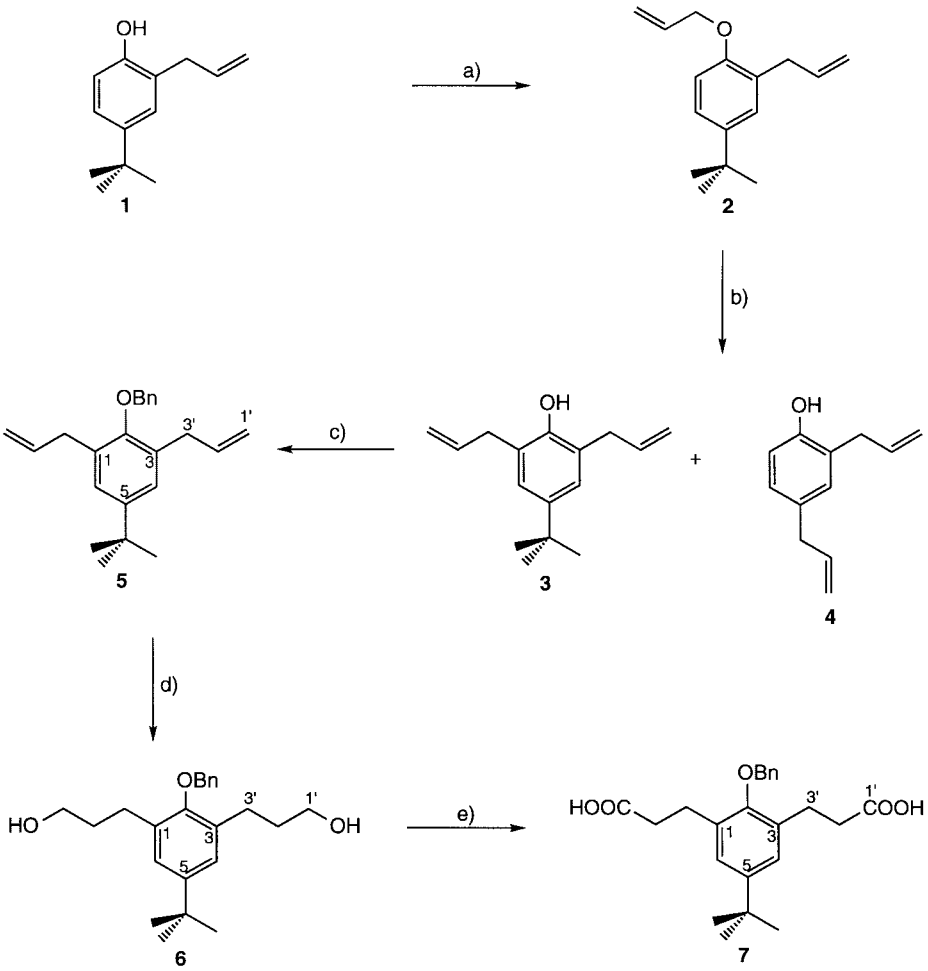
The results of the biological tests of synthetic compounds carried out with the 'ionotropic' glutamate receptors are still not complete and will be published elsewhere.

**Results and Discussion.** – We synthesized the five tenuilobine analogues, **12**, **13**, **15**, **24**, and **25**, the first three containing two, the last two three polyamine units. In all cases, the amines are coupled to the central part of the molecule by amide bonds. The corresponding acids, 2-(benzyloxy)-5-(*tert*-butyl)benzene-1,3-bis[propionic acid] (**7**) and 2-(benzyloxy)benzene-1,3,5-tris[propionic acid] (**21**) were synthesized from 4-(*tert*-butyl)-2-(prop-2-en-1-yl)phenol (**1**) [17][18] (*Scheme 1*). Using a sequence of repetitive allylation/*Claisen* rearrangement [18], we treated commercially available 4-(*tert*-butyl)phenol with allyl bromide to convert it *via* **1** and **2** to **3**. There was also obtained, in *ca*. 10% yield, a mixture of compound **4** and starting material **1**. The 1,6-diallylphenol **3** was treated with benzyl bromide (BnBr) to furnish the benzyl ether **5**. Hydroboration of the C=C bonds in the side chains of **5** by standard procedures [19], with an excess of 9-BBN, followed by treatment with basic $H_2O_2$ soln., yielded the diol **6**. Final oxidation of **6** with the *Jones* reagent according to [20] gave, after crystallization, the dicarboxylic acid **7**.

A mechanism for the formation of **4** is depicted in *Scheme 2*, probably the *t*-Bu group in **2** was cleaved by two [*3s*,*3s*] rearrangement of the allyl part, which gave the 1,4-diallylphenol **4**. Elimination of the *t*-Bu groups of substituted allylphenols are already observed during acid-catalyzed rearrangements [17].

*Synthesis of the Derivatives* **12**, **13**, *and* **15**. These polyamine derivatives were prepared by coupling suitably protected spermidine and spermine derivatives **8** and **9** with the diacid **7**. The di- and triprotected (benzyloxy)carbonyl (Z) spermidine and spermine derivatives, **8** and **9**, respectively, were prepared with benzyl cyanoformate (ZCN) according to [21][22]. For the amide formation we followed the method of *Mukaiyama* and co-workers, who employed 1-methyl-2-chloropyridinium iodide as the coupling reagent; thus, treatment of **7** with **8** in the presence of *Mukaiyama*'s reagent according to the procedure in [23] led to the amide **10** in 93% yield. Removal of the benzyl (Bn) and (benzyloxy)carbonyl (Z) groups by hydrogenolysis in the presence of Pd/C afforded the branched spermidine derivative **12** in 86% yield. By the same procedure, the spermine derivative **13**, was prepared through coupling of **7** with the corresponding spermine synthone **9**, followed by hydrogenolysis of the amide **11** so-formed (*Scheme 3*).

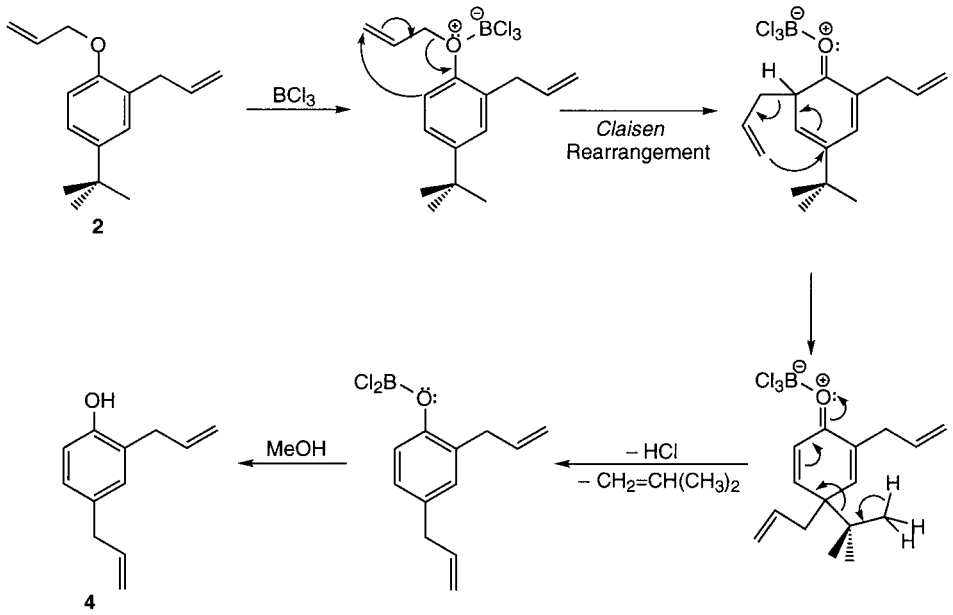
*Scheme 1*




a) 1. NaOEt, EtOH, 10°; 2. allyl bromide, 70°; 94%. b) 1. $BCl_3$, $Et_2O$, – 10°. 2. MeOH, 10°; 78%. c) 1. NaH, DMF, r.t.; 2. BnBr; 98%. d) 1. 9-Borabicyclo[3.3.1]nonane (9-BBN), THF, 65°. 2. 2N NaOH soln., 30% $H_2O_2$ soln., 0°; 95%. e) 0.54M $H_2CrO_4$ soln., acetone, r.t.; 96%.

The preparation of the unbranched spermidine isomer **15** was carried out by two different procedures. The isomerization of *N*-(3-aminopropyl) amides, which requires strongly basic or acidic conditions, is known as the *Zip* reaction [24][25]. In the first reaction, we decided to prepare **15** from its branched isomer **12** according to this method. Therefore, **12** was treated with KAPA (KH/propane-1,3-diamine) at room temperature to furnish, after workup, the unbranched isomer **15** in 80% yield. For spectroscopic characterization, **12** and **15** were converted to their diacetyl derivatives **14** and **16**, respectively, with $NaOAc/Ac_2O$ (*Scheme 4*).

*Scheme 2*



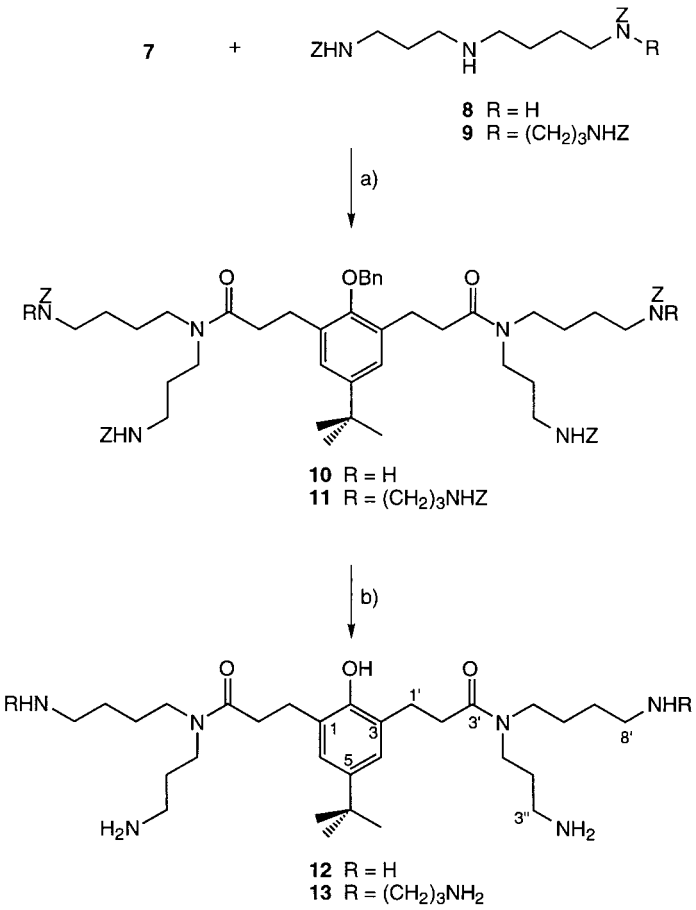

To confirm the isomerization of **12**, **15** was synthesized according to the *Mukaiyama*'s method of amide formation. Thus, **7** was treated with the spermidine derivative **17** [26] in the presence of 1-methyl-2-chloropyridinium iodide, to give the fully protected amide **18** in 30% yield. Deprotection of the Bn group of **18** by hydrogenolysis ($H_2$/Pd/C), followed by removal of the Boc groups with $CF_3COOH$, yielded **15**, which, on the basis of spectroscopic data, was found to be identical to the compound obtained by isomerization of **12** (*Scheme 5*).

*Synthesis of the Derivatives* **24** *and* **25**. The synthesis of the spermidine and spermine derivatives **24** and **25** was accomplished by the procedure depicted in *Scheme 6*. To carry out this synthesis, first the inseparable mixture of **1** and **4** was converted to the tricarboxylic acid **21**. This conversion was achieved under the same reaction conditions applied in the transformation of **3** to **6**. In this reaction step, it was possible to separate triol **20** from diol **6** by chromatography on silica gel. The oxidation of **20** by the *Jones* reagent furnished finally the tricarboxylic acid **21** in 70% yield (*Scheme 6*).

After preparation of **21**, the synthesis of the polyamine derivatives **24** and **25** was carried out in a way analogous to the preparation of **12**. Coupling of the acid **21** with the spermidine synthon **8** yielded the amide **22**, which, after hydrogenolysis ($H_2$/Pd/C), furnished the trisubstituted derivative **24** in 93% yield (*Scheme 7*). By the same procedure, the synthesis of the derivative **25** was accomplished, namely by coupling of **21** with the corresponding spermine synthon **9**, to give **23** followed by removal of the Bn and Z protecting groups, respectively (*Scheme 7*).

The extremely polar and strongly basic properties of the polyamines **24** and **25** hindered purification by column chromatography. Only for analytical purposes could

*Scheme 3*

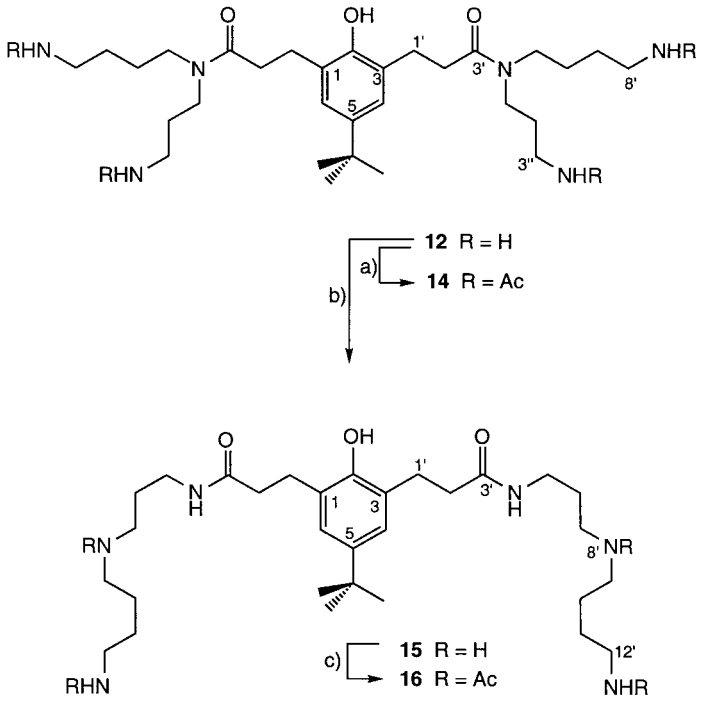



a) 1-Methyl-2-chloropyridinium iodide, $Et_3N$, $CH_2Cl_2$ r.t.; **10**: 93%, **11**: 95%. b) 10% $H_2$/Pd/C, AcOH (glacial), r.t.; **12**: 86%, **13**: 98%.

we purify small amounts on silica gel using 12% aq. NaCl soln./AcOH 100 : 2 as eluting solvent. Attempts to separate these compounds by other HPLC techniques, such as normal, reverse, or modified (by $NO_2$- or $NH_2$-) stationary phase, did not lead to positive results. Therefore, the planned transamidation reactions of **24** and **25** to their linear isomers (compare **12** → **15**) were not carried out. To avoid spontaneous transamidation reactions, the polyamines **24** and **25** were converted to their polyhydrochlorides immediately after preparation.

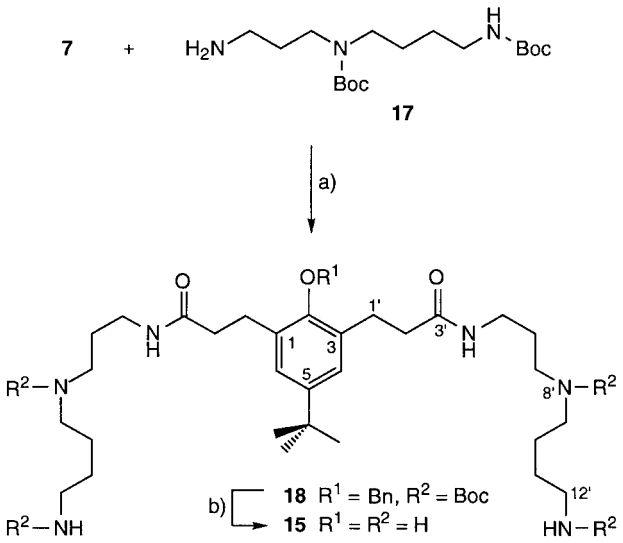
We thank PD Dr. *Stephan Bienz* for helpful discussions, the analytical departments of our institute for measurements, and the *Swiss National Science Foundation* for financial support.

*Scheme 4*



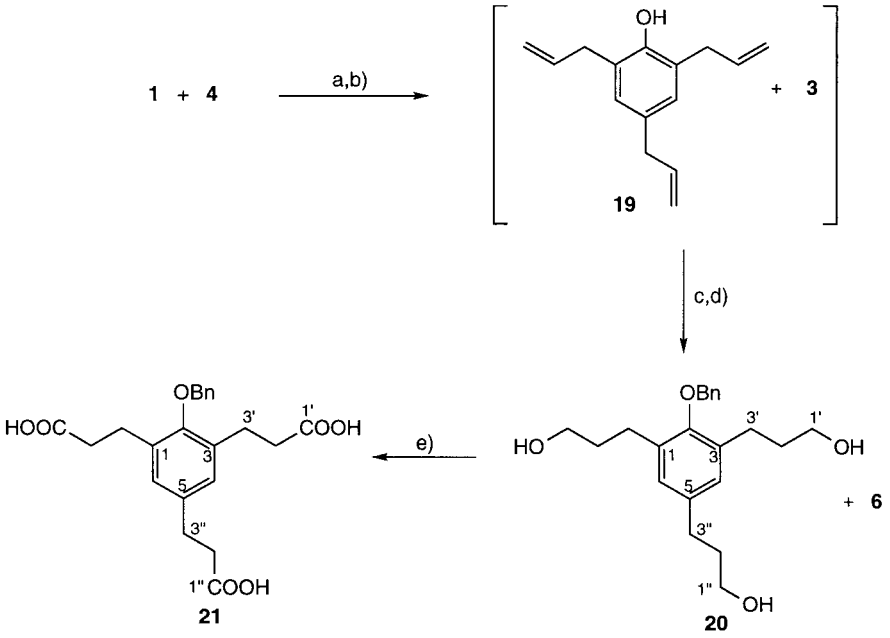

a) NaOAc, $Ac_2O$, r.t.; 83%. b) KH, Propane-1,3-diamine, r.t.; 80%. c) NaOAc, $Ac_2O$, r.t.; 76%.

*Scheme 5*




a) 1-Methyl-2-chloropyridinium iodide, $Et_3N$, $CH_2Cl_2$, r.t.; 30%. b) $H_2$/10% Pd/C, AcOH (glacial), r.t.; 2. $CF_3COOH$, r.t.; 40%.

*Scheme 6*




a) 1. NaOEt, EtOH, 10°; 2. allyl bromide, 70°. b) 1. $BCl_3$, $Et_2O$, – 10°; 2. MeOH, 10°. c) NaH, DMF, r.t.; 2. BnBr, r.t. d) 9-BBN, THF, 65°; 2. 3M aq. NaOH soln., 30% aq. $H_2O_2$ soln., 0°; 45%. e) 0.54M aq. $H_2CrO_4$ soln. r.t.; 70%.

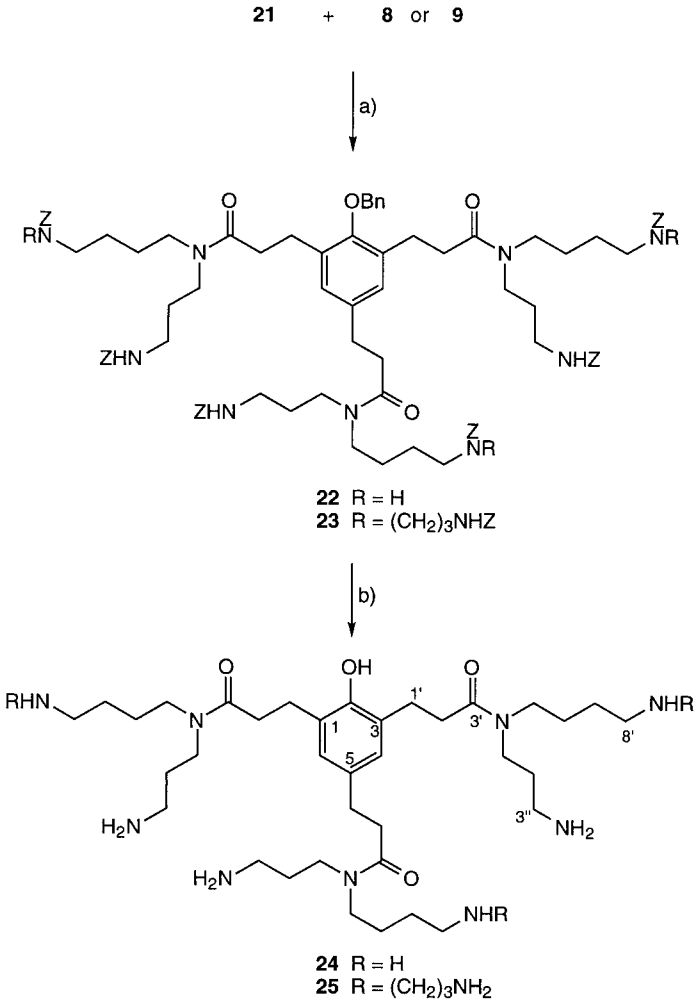
## Experimental Part

*General*. All commercially available reagents were used without further purification. All reactions were followed by TLC (*Merck* silica gel *60F*$_{254}$). The detection was performed either with UV light or with the following reagents: cerium(IV) sulfate reagent (10 g of $Ce(SO_4)_2$ in 55 ml of conc. $H_2SO_4$ diluted to 1000 ml $H_2O$); *Schlittler* reagent (1 g of $H_2PtCl_6$ in 6 ml of $H_2O$, 20 ml of 1N HCl, and 25.5 g of KI in 225 ml of $H_2O$ diluted to 1000 ml). Column chromatography (CC): *Merck* silica gel *60* (40–60 mesh). 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: *Bruker ARX-300* (300 MHz) or *Bruker AMX-600* (600 MHz); chemical shifts $\delta$ in ppm using $Me_4Si$ (=0 ppm) as internal standard, *J* values in Hz. $^{13}$C-NMR: *Bruker ARX-300* (75 MHz) or *Bruker AMX-600* (150 MHz). MS: *Finnigan SSQ-700* (chemical ionization (Cl) with $NH_3$), *Finnigan MAT 90* (electron impact (EI; 70 eV)), and *Finnigan TSQ-700* (electrospray ionization (ESI)).

*2-(Benzyloxy)-5-(*tert*-butyl)-1,3-di(prop-2-en-1-yl)benzene* (**5**). To a suspension of NaH (7.42 g, 309 mmol) in DMF (60 ml), a soln. of *4-(*tert*-butyl)-2,6-di(prop-2-en-1-yl)phenol* (**3**) (32.38 g, 140 mmol) in DMF (80 ml) was added dropwise. After 90 min stirring at r.t., BnBr (26.34 g, 154 mmol) was added dropwise, and the stirring was continued for 30 min. The solvent was evaporated, the residue was taken up in $H_2O$ (300 ml) and extracted with $Et_2O$. The combined org. layer was treated with 1.5M aq. NaOH soln., washed with $H_2O$, and dried ($Na_2SO_4$). Evaporation of the solvent yielded 44.3 g (98%) of **5** as a yellow oil, which was used in the next step without further purification. For anal. purposes, 800 mg of **5** were distilled at 175°/6 mbar to furnish 710 mg (88%) as colorless oil. IR (Film): 3530*w*, 3070*m*, 2960v*s*, 2900*s*, 2865*s*, 1705*w*, 1640*m*, 1605*w*, 1495*m*, 1480v*s*, 1455*s*, 1430*m*, 1390*m*, 1375*m*, 1355*s*, 1280*s*, 1240*m*, 1190v*s*, 1120*m*, 1080*m*, 1020*s*, 995*s*, 915*s*, 875*m*, 850*w*, 815*w*, 730*s*, 695*s*, 600*m*. $^1$H-NMR ($CDCl_3$)[2]: 7.48–7.30 (*m*, 5 arom. H); 7.09 (*s*, H–C(4), H–C(6)); 6.00 (*ddt*, *J* = 17.6,

[2]) The numbering of the C-atoms in the *Schemes* serves exclusively for assignments of the $^1$H- and $^{13}$C-NMR chemical shifts. It is irrelevant for the systematic nomenclature.

*Scheme 7*




a) 1-Methyl-2-chloropyridinium iodide, $Et_3N$, $CH_2Cl_2$, r.t.; **22**: 93%, **23**: 98%. b) 10% $H_2$/Pd/C, AcOH (glacial), r.t.; **24**: 99%, **25**: 94%.

9.6, 6.5, 2 H–C(2′)); 5.07 (*ddt*, *J* = 17.6, 9.6, 1.6, 2 $H_a$–C(1′), 2 $H_b$–C(1′)); 4.80 (*s*, PhC$H_2$); 3.46 (*ddd*, *J* = 6.5, 1.6, 2 $CH_2$(3′)); 1.29 (*s*, $Me_3$C(1″)). $^{13}$C-NMR ($CDCl_3$): 152.6 (*s*, C(2)); 146.8 (*s*, C(5)); 137.7 (*s*, arom. C); 137.6 (*d*, 2 C(2′)); 132.3 (*s*, C(1), C(3)); 128.4, 127.8, 127.5 (3*d*, 5 arom. C); 125.5 (*d*, C(4), C(6)); 115.6 (*t*, 2 C(1′)); 75.3 (*t*, PhC$H_2$); 35.7 (*s*, $Me_3C$); 34.4 (*t*, 2 C(3′)); 31.4 (*q*, $Me_3$C). EI-MS: 320 (48, $M^{+\cdot}$), 306 (24), 305 (100, $[M - CH_3]^+$), 229 (20, $[M - Bn]^+$), 215 (42), 230 (10), 173 (16), 91 (59), 57 (15).

*2-(Benzyloxy)-5-(*tert*-butyl)benzene-1,3-bis[propanol]* (**6**). To a suspension of 9-borabicyclo[3.3.1]nonane (9-BBN) in THF (90 ml), a soln. of **5** (16 g, 50 ml) in THF (50 ml) was added dropwise under Ar, the mixture was heated 3.5 h at 65°, and afterwards stirred overnight at r.t. Under strong stirring at −2–0°, a 3M aq. NaOH soln. (90 ml) was added. Then, after cooling to −50°, 30% aq. $H_2O_2$ soln. (94 ml) was added carefully. The mixture was warmed to r.t. and stirred for 1.5 h at r.t. The white suspension was washed with sat. aq. NaCl soln., and the solvent was evaporated. Purification of the residue by CC ($SiO_2$, $CH_2Cl_2$/MeOH 12:1) gave 16.9 g

(95%) of **6** as colorless solid. Crystalliztion from hexane/$Et_2O$ 4:1 yielded 14.6 g (86%) of **6**. White needles. M.p. 68–70° (hexane/$Et_2O$ 4:1). IR (KBr): 3500–3100v*s* (br. OH), 2940v*s*, 2860v*s*, 1610*m*, 1590*m*, 1500*s*, 1455v*s*, 1375*s*, 1295*m*, 1240v*s*, 1195v*s*, 1115v*s*, 1065v*s*, 1020*s*, 990*m*, 885*m*, 845*m*, 765*m*, 735v*s*, 695v*s*, 660*m*, 615*m*. $^1$H-NMR ($CDCl_3$): 7.50–7.32 (*m*, 5 arom. H); 7.07 (*s*, H–C(4), H–C(6)); 4.83 (*s*, PhC$H_2$); 3.54 (*t*, *J* = 6.2, 2 $CH_2$(1′)); 2.76 (*t*, *J* = 7.4, 2 $CH_2$(3′)); 1.98 (*s*, OH); 1.85 (*quint.*, *J* = 7.4, 2 $CH_2$(2′)); 1.30 (*s*, *Me*$_3$C(1″)). $^{13}$C-NMR ($CDCl_3$): 152.0 (*s*, C(2)); 146.5 (*s*, C(5)); 136.13 (*s*, arom. C); 132.3 (*s*, C(1), C(3)); 127.7, 127.2, 126.7 (3*d*, 5 arom. C); 124.3 (*d*, C(4), C(6)); 75.9 (*t*, Ph*C*H$_2$); 61.6 (*t*, 2 C(1′)); 34.2 (*s*, Me$_3$*C*); 33.7 (*t*, 2 C(2′)); 31.4 (*q*, *Me*$_3$C); 26.3 (*t*, 2 C(3′)). CI-MS ($NH_3$): 375 (24, $[M+H+NH_4]^+$), 374 (100, $[M+NH_4]^+$), 357 (33, $[M+H]^+$), 318 (15), 282 (28), 265 (13, $[M-Bn]^+$). Anal. calc. for $C_{23}H_{32}O_3$ (356.45): C 77.49, H 9.04; found: C 77.39, H 9.03.

*2-(Benzyloxy)-5-(*tert*-butyl)benzene-1,3-bis[propionic acid]* (**7**). To a soln. of **6** (1.53 g, 4.3 mmol) in acetone (40 ml) was added a 0.5M aq. $H_2CrO_4$ soln. (30 ml) during 30 min. The mixture was stirred 3 h at r.t., evaporated, the residue was taken up in $H_2O$ (100 ml) and extracted with $Et_2O$. The org. layer was acidified with 2N aq. HCl soln. to pH 1, extracted with $Et_2O$, dried ($Na_2SO_4$), and evaporated. Crystallization of the residue from $Et_2O$/hexane yielded 1.51 g (91%) of **7**. Colorless needles. M.p. 155–158° (hexane/$Et_2O$ 2:1). IR (KBr): 3015*m*, 2960*s*, 2760*m*, 1710v*s*, 1485*m*, 1455*m*, 1430*m*, 1410*m*, 1360*m*, 1330*m*, 1290*m*, 1215*s*, 1110*m*, 1080*w*, 995*m*, 940*m*, 880*m*, 850*m*, 770*m*. $^1$H-NMR ($CDCl_3$): 10.30 (br. *s*, OH); 7.49–7.29 (*m*, 5 arom. H); 7.10 (*s*, H–C(4), H–C(6)); 4.84 (*s*, PhC$H_2$); 2.99 (*t*, *J* = 7.4, 2 $CH_2$(3′)); 2.69 (*t*, *J* = 7.4, 2 $CH_2$(2′)); 1.28 (*s*, *Me*$_3$C(1″)). $^{13}$C-NMR ($CDCl_3$): 179.3 (*s*, C(1′)); 153.0 (*s*, C(2)); 147.3 (*s*, C(5)); 137.3 (*s*, arom. C); 132.8 (*s*, C(1), C(3)); 128.6, 128.0, 127.6 (3*d*, 5 arom. C); 125.5 (*d*, C(4), C(6)); 75.5 (*t*, Ph*C*H$_2$); 34.8 (*t*, 2 C(2′)); 34.3 (*s*, Me$_3$*C*); 31.4 (*q*, *Me*$_3$C); 25.9 (*t*, 2 C(3′)). CI-MS ($NH_3$): 403 (25, $[M+H+NH_4]^+$), 402 (100, $[M+NH_4]^+$), 386 (12, $[M+2H]^+$), 384 (9, $[M+NH_4-H_2O]^+$), 346 (15), 328 (5), 295 (<5, $[M-Bn]^+$). Anal. calc. for $C_{23}H_{28}O_5$ (384.45): C 71.86, H 7.34; found: C 71.90, H 7.46.

*2-(Benzyloxy)benzene-1,3,5-tris[propanol]* (**20**). To a soln. of Na (2.8 g, 122 mmol) in EtOH (90 ml) was added the soln. of the mixture of *4-(*tert*-butyl)-2-(prop-2-en-1-yl)phenol* (**1**) [17][18] and *2,4-di(prop-2-en-1-yl)phenol* (**4**) (9.2 g, 48 mmol) in EtOH (20 ml)[3]. After 1 h stirring at r.t., allyl bromide (11.3 g, 93 mmol) was added, and the mixture was heated overnight at 70°. The solvent was evaporated, the residue taken up in $H_2O$ (150 ml), extracted with $Et_2O$ and evaporated. To a soln. of the residue (10.6 g) in $CH_2Cl_2$ (10 ml) at 10°, a 1M $BCl_3$ soln. in THF (46 ml) was added dropwise. After 2 h stirring at r.t., the reaction was quenched with MeOH, the mixture was stirred overnight at r.t. and evaporated. The residue was distilled over a 10-cm *Vigreux* column to give 6.6 g of a pale yellow product, which consisted of **3** ($M_r$ 230) and **19** ($M_r$ 214), and which could not be separated by CC. Therefore, the product mixture (6.3 g, 27 mmol) was dissolved in DMF (60 ml), added dropwise to a suspension of NaH (1.2 g, 50 mmol) in DMF (20 ml), and the mixture was stirred 2 h at r.t. The solvent was removed *in vacuo*, the residue was taken up in $H_2O$, and extracted with $Et_2O$. The oily residue (6.1 g) was reacted in the next step without further purification. This mixture (5.8 g, 18 mmol) in THF (20 ml) was added to a suspension of 9-BBN (11.5 g, 94 mmol) in THF (30 ml). The mixture was heated for 3 h under reflux and stirred overnight at r.t. To this mixture at −2°, a 3M aq. NaOH soln. (34 ml) was added, followed by 30% aq. $H_2O_2$ soln. (34 ml). The white suspension was washed with sat. aq. NaCl soln., extracted with $Et_2O$, and the org. layer was dried ($Na_2SO_4$). Evaporation of the solvent and purification of the residue by CC ($SiO_2$; $CH_2Cl_2$/MeOH 12:1) yielded 1.8 g (28%) of **6** and 3.1 g (45%) of **20**.

*Data of* **20**: IR ($CHCl_3$): 3550–3350v*s* (br., OH), 3000*m*, 2940*m*, 2880*m*, 1495*w*, 1470*m*, 1450*m*, 1375*w*, 1335*w*, 1260*w*, 1190*w*, 1135*w*, 1050*m*, 1010*m*, 980*w*, 910*w*, 880*w*, 860*w*, 690*w*. $^1$H-NMR ($CDCl_3$): 7.47–7.32 (*m*, 5 arom. H); 6.89 (*s*, H–C(4), H–C(6)); 4.80 (*s*, PhC$H_2$); 3.61 (*t*, *J* = 6.4, $CH_2$(1″)); 3.51 (*t*, *J* = 6.3, 2 $CH_2$(1′)); 2.71 (*t*, *J* = 7.2, 2 $CH_2$(3′)); 2.61 (*t*, *J* = 7.2, $CH_2$(3″)); 2.40 (*s*, OH); 1.88–1.80 (*m*, 2$CH_2$(2′), $CH_2$(2″)). $^{13}$C-NMR ($CDCl_3$): 153.3 (*s*, C(2)); 138.1 (*s*, C(5)); 137.3 (*s*, arom. C); 134.4 (*s*, C(1), C(3)); 128.6, 128.2, 128.1 (3*d*, 5 arom. C); 127.6 (*d*, C(4), C(6)); 75.6 (*t*, Ph*C*H$_2$); 61.8 (*t*, C(1″)); 61.4 (*t*, 2 C(1′)); 34.1 (*t*, C(2″)); 33.5 (*t*, 2 C(2′)); 31.3 (*t*, C(3″)); 26.0 (*t*, 2 C(3′)). CI-MS ($NH_3$): 377 (22, $[M+H+NH_4]^+$), 376 (100, $[M+NH_4]^+$), 359 (84, $[M+H]^+$), 341 (18), 284 (16), 265 (33, $[M-Bn]^+$), 162 (10), 145 (16).

*2-(Benzyloxy)benzene-1,3,5-tris[propionic acid]* (**21**). From a reaction analogous to the preparation of **7**, with **20** (1.48 g, 4.2 mmol) and 0.5M aq. $H_2CrO_4$ soln. in acetone (30 ml), 1.2 g (70%) of **21** were obtained after workup. M.p. 153–155° ($Et_2O$/hexane 2:1). IR (KBr): 3010*s*, 2920*s*, 1700v*s*, 1470*m*, 1450*m*, 1430*m*, 1410*m*, 1370*w*, 1305*m*, 1225*s*, 1205*m*, 1175*w*, 1145*m*, 1130*m*, 995*m*, 920*m*, 880*w*, 730*m*, 695*w*, 605*w*. $^1$H-NMR ($CDCl_3$):

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[3]) This mixture was obtained when **1** was converted to **3** according to [17][18] in *ca.* 10% yield as a side-product.

7.49–7.31 (*m*, 5 arom. H); 6.98 (*s*, H–C(4), H–C(6)); 4.82 (*s*, PhC*H*$_2$); 2.93 (*t*, *J* = 7.4, 2 CH$_2$(3′)); 2.83 (*t*, *J* = 7.5, CH$_2$(3″)); 2.58 (*t*, *J* = 8.2, 2 CH$_2$(2′), CH$_2$(2″)). $^{13}$C-NMR (CDCl$_3$): 176.8 (*s*, 2 C(1′)); 176.7 (*s*, C(1″)); 154.9 (*s*, C(2)); 138.8 (*s*, C(5)); 138.3 (*s*, arom. C); 135.3 (*s*, C(1), C(3)); 129.5, 129.3, 129.2 (3*d*, 5 arom. C); 129.1 (*d*, C(4), C(6)); 76.6 (*t*, PhCH$_2$); 36.8 (*t*, C(2″)); 35.6 (*t*, 2 C(2′)); 31.5 (*t*, C(3″)); 26.8 (*t*, 2 C(3′)). CI-MS: 418 (100, $[M+NH_4]^+$), 401 (< 5, $[M+1]^+$), 400 (13, $[M+NH_4-H_2O]^+$), 318 (18, $[M-Bn]^+$).

*2-(Benzyloxy)*-N,N′-*bis(4-{[(benzyloxy)carbonyl]amino}butyl)*-N,N′-*bis(3-{[(benzyloxy)carbonyl]amino}propyl)-5-(*tert-*butyl)benzene-1,3-bis[propanamide]* (**10**). A suspension of **7** (769 mg, 2 mmol), 1-methyl-2-chloropyridinium iodide (1.23 g, 4.8 mmol), and Et$_3$N (972 mg, 9.6 mmol) in CH$_2$Cl$_2$ (40 ml) was stirred 30 min at r.t. After addition of a soln. of *benzyl {4-[(3-{[(benzyloxy)carbonyl]amino}propyl)amino]butyl}carbamate* (**8**) [21][22] (1.48 g, 3.6 mmol) in CH$_2$Cl$_2$ (18 ml), the mixture was stirred overnight at r.t. The solvent was evaporated, the residue was taken up in CH$_2$Cl$_2$ (150 ml), washed with 0.3N aq. HCl soln., and dried (Na$_2$SO$_4$). Removal of the solvent and purification of the residue by CC (SiO$_2$; CH$_2$Cl$_2$/MeOH 49 : 1) gave 2.17 g (93%) of **10**. Pale yellow oil. IR (CHCl$_3$): 3445*m*, 3400–3300*m* (br., NH), 3000*m*, 2960*m*, 1710v*s*, 1630*m*, 1455*m*, 1330*m*, 1260–1200*s* (br.), 1140*m*, 1100*m*, 1020*m*, 910*s*, 810*m*, 690*m*, 620*m*. $^1$H-NMR (CDCl$_3$): 7.45–7.27 (*m*, 25 arom. H); 7.09 (*s*, H–C(4), H–C(6)); 5.81 (br., *s*, 2 NHCO); 5.08, 5.03, 5.00 (3*s*, 4 PhC*H*$_2$); 4.81 (*s*, PhC*H*$_2$); 3.33–3.18 (*m*, 2 CH$_2$(1″), 2 CH$_2$(5′)); 3.05–3.03 (*m*, 2 CH$_2$(3″), 2 CH$_2$(8′)); 2.97–2.83 (*m*, 2 CH$_2$(1′)); 2.57 (*t*, *J* = 7.0, CH$_2$(2′)); 1.76 (br., *s*, 2 NHCO); 1.59–1.47 (*t*-like *m*, *J* = 5.7, 2 CH$_2$(2″)); 1.40–1.32 (*m*, 2 CH$_2$(6′), 2 CH$_2$(7′)); 1.27 (*s*, *Me*$_3$C). $^{13}$C-NMR (CDCl$_3$): 172.8 (*s*, 2 C(3′)); 156.5, 156.5 (2*s*, 4 CO); 153.1 (*s*, C(2)); 147.4 (*s*, C(5)); 137.3, 136.8, 136.5 (3*s*, 5 arom. C); 133.6 (*s*, C(1), C(3)); 128.6, 128.4, 128.4, 128.2, 128.1, 128.0, 128.0, 127.9 (8*d*, 25 arom. C); 75.6 (*t*, PhCH$_2$); 66.5, 66.3 (2*t*, 4 PhCH$_2$); 47.1 (*t*, 2 C(1″)); 45.4 (*t*, 2 C(1″)), 2 CH$_2$(5′); 42.1 (*t*, 2 C(8′)); 40.3 (*t*, 2 C(3″)); 37.5 (*t*, 2 C(2′)); 34.3 (*s*, Me$_3$*C*); 33.9 (*t*, 2 C(2″)); 31.4 (*q*, *Me*$_3$C); 27.8 (*t*, 2 C(1′)); 27.2 (*t*, 2 C(7′)); 25.9 (*t*, 2 C(6′)). ESI-MS: 1197 (100, $[M+Na]^+$), 1175 (< 5, $[M+H]^+$), 857 (10), 610 (100, $[M+2\,Na]^{2+}$).

N,N′-*Bis(4-aminobutyl)*-N,N′-*bis(3-aminopropyl)-5-(*tert-*butyl)-2-hydroxybenzene-1,3-bis[propanamide]* (**12**). To a suspension of 10% Pd/C (300 mg) in AcOH (glacial, 110 ml) was added a soln. of **10** (710 mg, 0.6 mmol), and the mixture was hydrogenated overnight in a *Parr* apparatus (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. 6 : 3 : 1) to give 280 mg (86%) of **12** as colorless oil, which was converted to its hydrochloride. The oily product (251 mg, 0.45 mmol) was taken up in EtOH (10 ml), treated with 0.3N aq. HCl soln. (pH 1), and the solvent was evaporated. Drying of the residue at $10^{-3}$ bar yielded 210 mg (65%) of **12** · 4 HCl. Colorless foam. IR (CHCl$_3$): 3600–3450*m* (br. OH), 3350–3100*w* (br. NH$_2$), 2960*m*, 2860*m*, 1620*m*, 1485*m*, 1450*m*, 1370*w*, 1300*w*, 1260*m*, 1200*m*, 1150*w*, 1090*m*, 1010*m*, 880*m*, 660*w*. $^1$H-NMR (CD$_3$OD): 7.30 (br., 4 NH$_2$); 7.00 (*s*, H–C(4), H–C(6)); 5.03 (*s*, OH); 3.47–3.35 (*m*, 2 CH$_2$(1″), 2 CH$_2$(5′)); 2.92–2.85 (*m*, 2 CH$_2$(3″), 2 CH$_2$(8′), 2 CH$_2$(1′)); 2.72 (*t*, *J* = 6.5, CH$_2$(2′)); 1.90–1.87 (*m*, 2 CH$_2$(2″)); 1.62 (br. *m*, CH$_2$(6′), CH$_2$(7′)); 1.27 (*s*, *Me*$_3$C). $^{13}$C-NMR (CD$_3$OD): 176.4, 175.6 (2*s*, 2 C(3′)); 151.7 (*s*, C(2)); 146.1 (*s*, C(5)); 129.2 (*s*, C(1), C(3)); 126.6 (*d*, C(4), C(6)); 48.7, 48.4 (2*t*, 2 C(1″)); 46.4, 46.3 (2*t*, 2 C(5′)); 43.8, 43.8 (2*t*, 2 C(8′)); 38.3, 38.1 (2*t*, 2 C(3″)); 35.0 (*t*, 2 C(2′)); 34.8 (*s*, Me$_3$*C*); 31.1 (*q*, *Me*$_3$C); 27.7 (2*t*, 2 C(2″)); 26.9 (*t*, 2 C(2″)); 26.8 (*t*, 2 C(1′)); 25.9 (*t*, 2 C(7′)); 25.6 (*t*, 2 C(6′)). ESI-MS: 571 (6, $[M+Na]^+$), 549 (30, $[M+H]^+$), 275 (100, $[M+2\,H]^{2+}$).

N,N′-*Bis[4-(acetylamino)butyl]*-N,N′-*bis[3-(acetylamino)propyl]-5-(*tert-*butyl)-2-hydroxybenzene-1,3-bis-[propanamide]* (**14**). A suspension of **12** (53 mg, 0.96 mmol) and NaOAc (150 mg, 1.8 mmol) in Ac$_2$O (10 ml) was stirred overnight at r.t., and the mixture was evaporated. The residue was taken up in sat. aq. K$_2$CO$_3$ soln., extracted with CHCl$_3$, and dried (Na$_2$SO$_4$). After evaporation of the solvent and chromatography of the residue (SiO$_2$; CHCl$_3$/MeOH 19 : 1), 60 mg (88%) of **14** were obtained. Colorless oil. IR (CHCl$_3$): 3600*w*, 3380–3320*w* (br. OH), 3000*m*, 2960*m*, 2960*m*, 1660*m*, 1520*m*, 1485*m*, 1435*m*, 1365*m*, 1260*m*, 1095*m*, 1010*m*, 880*w*, 820*w*, 660*w*. $^1$H-NMR (CDCl$_3$): 7.18–6.82 (br., *m*, 4 NHAc); 7.00 (*s*, H–C(4), H–C(6)); 5.04 (*s*, OH); 3.38–3.36 (*m*, 2 CH$_2$(3″), 2 CH$_2$(8′)); 3.28–3.24 (*m*, 2 CH$_2$(1″)); 3.13–3.12 (*m*, 2 CH$_2$(5′)); 2.91 (*m*, 2 CH$_2$(1′)); 2.67 (*t*, *J* = 6.5, 2 CH$_2$(2′)); 2.00, 1.99 (2*s*, 4 *Me*CO); 1.69–1.65 (*m*, 2 CH$_2$(2″)); 1.53–1.51 (*m*, 2 CH$_2$(6′), 2 CH$_2$(7′)); 1.27 (*s*, *Me*$_3$C). $^{13}$C-NMR (CDCl$_3$): 174.1, 174.6 (2*s*, 2 C(3′)); 170.9, 170.7 (2*s*, 4 Me*C*O); 150.8 (*s*, C(2)); 142.5 (*s*, C(5)); 127.7 (*s*, C(1), C(3)); 125.8 (*d*, C(4), C(6)); 47.6 (*t*, 2 C(1″)); 45.8 (*t*, 2 C(5′)); 43.1 (*t*, 2 C(8′)); 38.7 (*t*, 2 C(3″)); 36.9 (*t*, 2 C(2′)); 34.2 (*t*, 2 C(2″)); 33.8 (*s*, Me$_3$*C*); 31.5 (*q*, *Me*$_3$C); 27.3 (*t*, 2 C(1′)); 26.7 (*t*, 2 C(7′)); 25.8 (*t*, 2 C(6′)); 22.5 (*q*, Me*C*O). ESI-MS: 739 (65, $[M+Na]^+$), 717 (< 5, $[M+H]^+$), 485 (7), 397 (5, $[M+2\,Na+2\,MeOH]^{2+}$), 381 (100, $[M+2\,Na]^{2+}$).

*2-(Benzyloxy)*-N,N′-*bis(4-{[(benzyloxy)carbonyl](3-{[(benzyloxy)carbonyl]amino}propyl)amino}butyl)*-N,N′-*bis(3-{[(benzyloxy)carbonyl]amino}propyl)-5-(*tert-*butyl)benzene-1,3-bis[propanamide]* (**11**). In a reaction analogous to the preparation of **10**, from compound **7** (288 mg, 0.75 mmol), 1-methyl-2-chloropyridinium iodide (460 mg, 1.8 mmol), Et$_3$N (585 mg, 4.8 mmol), and *(3-{[(benzyloxy)carbonyl]amino}propyl){4-[(3-*

*{[(benzyloxy)carbonyl]amino}propyl)amino]butyl}carbamate* (**9**) [21][22] (905 mg, 1.5 mmol) in $CH_2Cl_2$ (25 ml), 1.12 g (95%) of **11** were obtained. Slightly yellowish oil. IR ($CHCl_3$): 3650*w*, 3440*w*, 2930*m*, 1705*s*, 1625*m*, 1510*s*, 1475*m*, 1415*m*, 1365*m*, 1215*m*, 1130*m*, 1075*m*, 1015*m*, 905*w*, 855*w*, 820*w*, 595*w*. $^1$H-NMR ($CDCl_3$): 7.44–7.25 (*m*, 35 arom. H); 7.11 (*s*, H–C(4), H–C(6)); 5.08, 5.05, 5.00 (3*s*, 6 PhC$H_2$); 4.80 (*s*, PhC$H_2$); 3.34–3.22 (*m*, 2 $CH_2$(1″), 2 $CH_2$(5′)); 3.11 (*m*, 2 $CH_2$(3″), 2 $CH_2$(12′)); 3.09–3.02 (*m*, 2 $CH_2$(8′), 2 $CH_2$(10′)); 3.00 (br., 2 $CH_2$(1′)); 2.54 (br., 2 $CH_2$(2′)); 1.70–1.48 (*m*, 2 $CH_2$(2″), 2 $CH_2$(11′)); 1.39–1.34 (*m*, 2 $CH_2$(6′), 2 $CH_2$(7′)); 1.27 (*s*, $Me_3$C). $^{13}$C-NMR ($CDCl_3$): 172.7 (*s*, 2 C(3′)); 156.4 (*s*, 6 CO); 153.1 (*s*, C(2)); 147.4 (*s*, C(5)); 137.2, 136.7 (2*s*, 6 arom. C); 133.6 (*s*, C(1), C(3)); 128.5, 128.3, 128.1, 127.9, 127.8 (5*d*, 35 arom. C); 125.5 (*d*, C(4), C(6)); 75.5 (*t*, PhC$H_2$); 67.1, 66.3 (2*t*, 6 PhC$H_2$); 47.0 (*t*, 2 C(1″)); 46.3 (*t*, 2 C(5′)); 45.1 (*t*, 2 C(8′)); 44.0 (*t*, 2 C(10′)); 42.0 (*t*, 2 C(12′)); 38.3 (*t*, 2 C(3″)); 34.2 (*s*, $Me_3C$); 33.8 (*t*, 2 C(2′)); 31.4 (*q*, $Me_3$C); 28.8 (*t*, 2 C(1′)); 27.6 (*t*, 2 C(2″)); 26.8 (*t*, 2 C(11′)); 25.7 (*t*, 2 C(7′)); 25.1 (*t*, 2 C(6′)). ESI-MS: 1580 (100, $[M+Na]^+$), 801 (75, $[M+2\,Na]^{2+}$).

N,N′-*Bis(3-aminopropyl)*-N,N′-*bis[4-(3-aminopropyl)butyl]-5-(*tert-*butyl)-2-hydroxybenzene-1,3-bis[propanamide]* (**13**). Analogous to the preparation of **12**, reaction of **11** (780 mg, 0.5 mmol) and 10% Pd/C (350 mg) in AcOH (glacial, 110 ml) in a *Parr* apparatus (3.5 bar $H_2$ pressure) afforded 430 mg (98%) of **13**. Colorless oil. IR (KBr): 3415*m*, 2957v*s*, 1607*s*, 1484*s*, 1392*m*, 1294*w*, 1199*m*, 1153*w*, 1112*w*, 1061*w*, 1005*w*, 879*w*, 822*w*, 754*w*, 531*w*. $^1$H-NMR ($CD_3OD$): 8.78, 8.09, 7.96 (br., 3*s*, 2 $^+NH_2$, 4 $^+NH_3$); 7.01 (*s*, H–C(4), H–C(6)); 3.49–3.40 (*m*, 2 $CH_2$(3″), 2 $CH_2$(12′)); 3.16–3.10 (*m*, 2 $CH_2$(1″), 2 $CH_2$(5′)); 3.00–2.98 (*m*, 2 $CH_2$(8′), 2 $CH_2$(10′)); 2.90 (br., 2 $CH_2$(1′)); 2.74 (br., 2 $CH_2$(2′)); 2.16–1.94 (*m*, 2 $CH_2$(2″), 2 $CH_2$(11′)); 1.70 (br., 2 $CH_2$(6′), 2 $CH_2$(7′)); 1.27 (*s*, $Me_3$C). $^{13}$C-NMR ($CD_3OD$): 170.5 (*s*, 2 C(3′)); 151.5 (*s*, C(2)); 144.2 (*s*, C(5)); 129.0 (*s*, C(1), C(3)); 126.6 (*d*, C(4), C(6)); 46.3 (*t*, 2 C(8′)); 45.9 (*t*, 2 C(10′)); 43.8 (*t*, 2 C(1″)); 38.2 (*t*, 2 C(5′)); 37.9 (*t*, 2 C(3″)); 35.3 (*s*, $Me_3C$); 35.0 (*t*, 2 C(2′)); 34.7 (*t*, 2 C(12′)); 32.0 (*q*, $Me_3$C); 27.8 (*t*, 2 C(2″)); 26.8 (*t*, 2 C(11′)); 25.6 (*t*, 2 C(1′)); 25.2 (*t*, 2 C(7′)); 24.4 (*t*, 2 C(6′)). ESI-MS: 664 (7, $[M+H]^+$), 332 (100, $[M+2H]^{2+}$), 222 (82, $[M+3H]^{3+}$).

*2-(Benzyloxy)*-N,N′-*bis(3-{[(*tert-*butoxy)carbonyl](4-{[(*tert-*butoxy)carbonyl]amino}butyl)amino}propyl)-5-(*tert-*butyl)benzene-1,3-bis[propanamide* (**18**). Analogous to the preparation of **10**, reaction of **7** (373.7 mg, 0.97 mmol), 1-methyl-2-chloropyridinium iodide (594 mg, 2.3 mmol), $Et_3N$ (471 mg, 4.65 mmol), and *di(*tert-*butyl)* N-*(3-aminopropyl)*-N,N′-*(butan-1,4-diyl)bis[carbamate]* (**17**) (634 mg, 1.83 mmol) in $CH_2Cl_2$ (20 ml): 303 mg (30%) of **18** as colorless oil. IR ($CHCl_3$): 3870*w*, 3450*m*, 3000v*s*, 2870*m*, 1660v*s*, 1585v*s*, 1540v*s*, 1515v*s*, 1480*s*, 1455*s*, 1420*s*, 1390*m*, 1365*s*, 1320*m*, 1245*s*, 1200*s*, 1170v*s*, 1050*m*, 1005*m*, 925*w*, 875*m*, 860*w*, 845*w*, 690*w*, 655*w*, 620*w*. $^1$H-NMR ($CDCl_3$): 7.52–7.34 (*m*, 5 arom. H); 7.08 (*s*, H–C(4), H–C(6)); 6.60 (br. *s*, NHBoc); 4.86 (*s*, PhC$H_2$); 3.14–3.12 (*m*, 2 $CH_2$(5′), 2 $CH_2$(7′), $CH_2$(9′), 2 $CH_2$(12′)); 2.99 (*t*, *J* = 7.4, 2 $CH_2$(1′)); 2.49 (*t*, *J* = 7.4, 2 $CH_2$(2′)); 1.59–1.47 (*m*, 2 $CH_2$(10′), 2 $CH_2$(11′)); 1.42 (*s*, 4 $Me_3$CO); 1.28–1.22 (*m*, $CH_2$(6′)); 1.27 (*s*, $Me_3$C). $^{13}$C-NMR ($CDCl_3$): 172.2 (*s*, 2 C(3′)); 156.0 (*s*, 4 CO); 152.8 (*s*, C(2)); 149.4 (*s*, C(5)); 137.6 (*s*, arom. C); 133.4 (*s*, C(1), C(3)); 128.5, 127.9, 127.8 (3*d*, 5 arom. C); 125.4 (*d*, C(4), C(6)); 79.6, 79.1 (2*s*, 4 $Me_3CO$); 75.6 (*t*, PhC$H_2$); 46.7 (*t*, 2 C(12′)); 43.4 (*t*, 2 C(7′)); 40.1 (*t*, 2 C(9′)); 37.7 (*t*, 2 C(5′)); 35.8 (*s*, $Me_3C$); 35.8 (*t*, 2 C(2′)); 31.4 (*q*, $Me_3$C); 29.6 (*t*, 2 C(1′)); 27.4 (*t*, 2 C(6′)); 28.4 (*q*, 4 $Me_3$CO); 26.8 (*t*, 2 C(11′)); 25.7 (*t*, 2 C(10′)). ESI-MS: 1061 (70, $[M+Na]^+$), 542 (100, $[M+2\,Na]^{2+}$). Anal. calc. for $C_{57}H_{94}N_6O_{11}$ (1039.50): C 65.86, H 9.11, N 8.08; found: C 65.64, H 8.87, N 8.51.

N,N′-*Bis{3-[(4-aminobutyl)amino]propyl}-5-(*tert-*butyl)-2-hydroxybenzene-1,3-bis[propanamide]* (**15**). To a soln. of **18** (120 mg, 0.11 mmol) in AcOH (glacial, 110 ml) was added 10% Pd/C (200 mg), and the mixture was hydrogenated overnight in a *Parr* apparatus (3.5 bar $H_2$ pressure). The mixture was filtered over *Celite*, and the filtrate was evaporated. The crude product was dissolved in $CF_3COOH$ (5 ml) and stirred overnight at r.t. Removal of the solvent *in vacuo* and purification of the residue by CC ($SiO_2$; $CHCl_3$/MeOH/25% aq. $NH_3$ soln. 6:3:1) gave 25 mg (40%) of **15**, which was converted to **15**·4 HCl. IR ($CHCl_3$): 3440*w*, 3240*w*, 2990*m*, 2960*m*, 2930*m*, 2860*m*, 1650*m*, 1600*w*, 1530*m*, 1490*m*, 1450*w*, 1410*w*, 1360*w*, 1300*w*, 1260*m*, 1200*w*, 1155*w*, 1115*w*, 1095*w*, 1050*w*, 1010*w*, 880*w*, 860*w*, 815*w*, 710*w*, 665*w*. $^1$H-NMR ($CD_3OD$): 8.13–7.96 (br., $NH_2$); 6.97 (*s*, H–C(4), H–C(6)); 5.03 (*s*, OH); 3.19 (*t*, *J* = 7.3, 2 $CH_2$(5′)); 2.87 (*t*, *J* = 6.8, 2 $CH_2$(1′)); 2.65 (*t*, *J* = 6.8, 2 $CH_2$(12′)); 2.54 (*t*, *J* = 7.0, 2 $CH_2$(2′)); 2.49–2.48 (*m*, 2 $CH_2$(7′), 2 $CH_2$(9′)); 1.64 (*quint.*, *J* = 7.1, 2 $CH_2$(6′)); 1.52–1.51 (*m*, 2 $CH_2$(10′), 2 $CH_2$(11′)); 1.26 (*s*, $Me_3$C). $^{13}$C-NMR ($CD_3OD$): 176.0 (*s*, 2 C(3′); 151.4 (*s*, C(2)); 143.6 (*s*, C(5)); 128.9 (*s*, C(1), C(3)); 126.2 (*d*, CH(4), CH(6)); 50.2 (*t*, 2 C(7′)); 47.6 (*t*, 2 C(9′)); 42.2 (*t*, 2 C(5′)); 38.1 (*t*, 2 C(12′)); 37.6 (*t*, 2 C(2′)); 34.7 (*s*, $Me_3C$); 32.0 (*q*, $Me_3$C); 31.1 (*t*, 2 C(1′)); 30.0 (*t*, 2 C(6′)); 27.8 (*t*, 2 C(11′)); 27.7 (*t*, 2 C(10′)). ESI-MS: 571 (6, $[M+Na]^+$), 549 (100, $[M+H]^+$), 478 (5, $[M-(CH_2)_4NH_2]^+$), 275 (88, $[M+2\,H]^{2+}$). ESI-MS/MS (of *m/z* 549.3, −35 eV): 531 (<5), 404 (11, $[M-146u+2\,H]^+$), 387 (23), 333 (9), 316 (100, $[M-146u-88u+2\,H]^+$), 146 (12, [*M* of spermidine $-H]^+$), 129 (11), 112 (5), 72 (11). ESI-MS/MS (of *m/z* 549.3, −30 eV): 549 (12, $[M+H]^+$), 404 (63, $[M-146u+2\,H]^+$), 387 (52), 333 (22), 316 (100, $[M-146u-88u+2\,H]^+$), 146 (30, [*M* of spermidine $-H]^+$), 129 (115), 72 (11).

N,N′-*Bis(3-{(acetyl)[4-(acetylamino)butyl]amino}propyl)-5-(*tert-*butyl)-2-hydroxybenzene-1,3-bis[propanamide]* (**16**). Analogous to the preparation of **14**, reaction of **15** (20 mg, 0.037 mmol) with NaOAc (200 mg, 2.43 mmol) in $Ac_2O$ (10 ml) afforded 20 mg (76%) of **16**. Colorless foam. IR ($CHCl_3$): 3450*w*, 3380–3320*w* (br. OH), 3000*m*, 2960*m*, 2915*m*, 1660*m*, 1525*s*, 1485*m*, 1435*m*, 1365*m*, 1300*w*, 1260*m*, 1200*w*, 1170*w*, 1090*m*, 1010*w*, 880*w*, 820*w*, 660*w*. $^1$H-NMR ($CDCl_3$): 6.95 (*s*, H–C(4), H–C(6)); 5.04 (*s*, OH); 3.56–3.54 (*m*, 2 $CH_2$(12′)); 3.28–3.26 (*m*, 2 $CH_2$(5′)); 3.19–3.15 (*m*, 2 $CH_2$(7′), 2 $CH_2$(9′)); 2.90 (*t*, *J* = 6.4, 2 $CH_2$(1′)); 2.58 (*t*, *J* = 6.5, 2 $CH_2$(2′)); 2.00, 1.99 (2*s*, 4 *Me*CO); 1.65–1.63 (*m*, 2 $CH_2$(6′)); 1.61–1.51 (*m*, 2 $CH_2$(10′), 2 $CH_2$(11′)); 1.27 (*s*, $Me_3$C). $^{13}$C-NMR ($CDCl_3$): 171.0 (*s*, C(3′)); 170.4 (*s*, MeCO); 146.3 (*s*, C(2)); 138.7 (*s*, C(5)); 127.4 (*s*, C(1), C(3)); 125.4 (*d*, C(4), C(6)); 48.2 (*t*, 2 C(12′)); 42.5 (*t*, 2 C(7′)); 38.7 (*t*, 2 C(9′)); 37.0 (*t*, 2 C(2′)); 33.8 (*s*, $Me_3C$); 31.5 (*q*, $Me_3$C); 29.6 (*t*, 2 C(5′)); 29.5 (*t*, 2 C(6′)); 27.3 (*t*, 2 C(1′)); 26.9 (*t*, 2 C(11′)); 26.2 (*t*, 2 C(10′)); 21.2 (*q*, *Me*CO). ESI-MS: 740 (100, $[M+H+Na]^+$), 717 (9, $[M+H]^+$), 485 (6), 397 (24, $[M+2\,Na+2\,MeOH]^{2+}$), 381 (24, $[M+2\,Na]^{2+}$).

N,N′-*Bis{3-[(4-aminobutyl)amino]propyl}-5-(*tert-*butyl)-2-hydroxybenzene-1,3-bis[propanamide]* (**15**). A suspension of KH (600 mg, 15 mmol) in propane-1,3-diamine (5 ml) was stirred under Ar 30 min at r.t. A soln. of **12** (200 mg, 0.36 mmol) in propane-1,3-diamine (3 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. (3 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. 6:3:1) yielded 142 mg (80%) of **15** as slightly yellow colored oil, which was crystallized as **15**·4 HCl. Compound **15** was identical (TLC, IR, $^1$H-NMR, $^{13}$C-NMR and MS) to the sample prepared from **7** and **17**.

*2-(Benzyloxy)*-N,N′,N″-*tris(4-{[(benzyloxy)carbonyl]amino}butyl)*-N,N′,N″-*tris(3-{[(benzyloxy)carbonyl]amino}propyl)benzene-1,3,5-tris[propanamide]* (**22**). A mixture of **21** (200 mg, 0.5 mmol), 1-methyl-2-chloropyridinium iodide (460 mg, 1.8 mmol), and $Et_3N$ (545 mg, 5.4 mmol) in $CH_2Cl_2$ (15 ml) was stirred 20 min at r.t. After addition of a soln. of **8** (620 mg, 1.5 mmol) in $CH_2Cl_2$ (10 ml), the mixture was stirred overnight at r.t. and evaporated. The 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 97:3) gave 700 mg (93%) **22**. Slightly yellow oil. IR ($CHCl_3$): 3445*m*, 3350*w* (br.), 2935*m*, 1710v*s*, 1625*m*, 1505*m*, 1450*m*, 1375*m*, 1255*s*, 1100*m*, 1135*m*, 1080*m*, 1010*m*, 910*w*, 860*w*, 810*m*, 690*m*. $^1$H-NMR ($CDCl_3$): 7.44–7.25 (*m*, 35 arom. H); 6.87 (*s*, H–C(4), H–C(6)); 5.85, 5.48, 5.29 (3 br. *s*, 6 NHCO); 5.06, 5.04, 5.00 (3*s*, 6 PhC$H_2$); 4.78 (*s*, PhC$H_2$); 3.29 (*t*, *J* = 5.3, 3 $CH_2$(3″)); 3.14 (*t*, *J* = 5.2, 3 $CH_2$(8′)); 3.03–3.02 (*m*, 3 $CH_2$(1″), 3 $CH_2$(5′)); 2.97 (*t*, *J* = 6.0, 3 $CH_2$(1′)); 2.55–2.53 (*m*, 3 $CH_2$(2′)); 1.56 (br. *m*, 3 $CH_2$(2″)); 1.45–1.43 (*m*, 3 $CH_2$(6′), 3 $CH_2$(7′)). $^{13}$C-NMR ($CDCl_3$): 172.6 (*s*, 3 C(3′)); 156.5 (*s*, 6 CO); 153.5 (*s*, C(2)); 137.1 (*s*, C(5)); 136.7, 136.5 (2*s*, 7 arom. C); 134.2 (*s*, C(1), C(3)); 128.9, 128.5, 128.3, 128.1, 127.9 (5*d*, 35 arom. C); 75.5 (*t*, Ph$CH_2$); 66.4, 66.3 (2*t*, 6 Ph$CH_2$); 47.3, 47.1 (2*t*, 3 C(5′)); 45.4 (*t*, 3 C(1″)); 42.4, 42.1 (2*t*, 3 C(8′)); 40.3, 38.3 (2*t*, 3 C(3″)); 33.3 (*t*, 3 C(2′)); 29.4 (*t*, 3 C(2″)); 27.7, 27.3, 27.1 (3*t*, 3 C(6′)); 26.4 (*t*, 3 C(1′)); 26.0, 25.9, 24.7 (3*t*, 3 C(7′)). ESI-MS: 1625 (12, $[M+K]^+$), 1609 (100, $[M+Na]^+$), 1587 (15, $[M+H]^+$), 816 (30, $[M+2\,Na]^{2+}$).

N,N′,N″-*Tris(4-aminobutyl)*-N,N′,N″-*tris(3-aminopropyl)-2-hydroxybenzene-1,3,5-tris[propanamide]* (**24**). To a suspension of 10% Pd/C (250 mg) in AcOH (110 ml) was added a soln. of **22** (470 mg, 0.3 mmol), and the mixture was hydrogenated overnight in a *Parr* apparatus (3.5 bar $H_2$ pressure). The mixture was filtered over *Celite*, and the filtrate was evaporated. The residue was taken up in EtOH (7 ml) and treated dropwise with 0.3N aq. HCl soln. (pH 1). Removal of the solvent *in vacuo* and drying of the residue at $10^{-3}$ bar yielded 267 mg (99%) of **24**·4 HCl. Yellow foam. IR (KBr): 3411*s*, 2967v*s*, 1996*w*, 1604v*s*, 1481*s*, 1394*m*, 1270*m*, 1145*m*, 1010*w*, 740*w*, 547*w*. $^1$H-NMR ($CD_3OD$): 7.92, 7.85, 7.65 (3br., *s*, 6 $^+NH_3$); 6.93 (*s*, H–C(4), H–C(6)); 3.62–3.31 (*m*, 3 $CH_2$(1″), 3 $CH_2$(5′)); 2.92 (br., 3 $CH_2$(1′)); 2.86–2.84 (*m*, 3 $CH_2$(3″), 3 $CH_2$(8′)); 2.40 (br., 3 $CH_2$(2′)); 1.97 (br., 3 $CH_2$(2″)); 1.70 (br., 3 $CH_2$(6′), 3 $CH_2$(7′)). $^{13}$C-NMR ($CD_3OD$): 174.9 (2*s*, 3 C(3′)); 151.0 (*s*, C(2)); 132.4 (*s*, C(5)); 130.9 (*s*, C(1), C(3)); 128.5 (*d*, C(4), C(6)); 45.0 (*t*, 3 C(1″)); 42.4 (*t*, 3 C(5′)); 39.3 (*t*, 3 C(8′)); 37.1 (*t*, 3 C(3″)); 34.7 (*t*, 3 C(2′)); 29.2 (*t*, 3 C(1′)); 26.1 (*t*, 3 C(2″)); 25.5 (*t*, 3 C(7′)); 24.4 (*t*, 3 C(6′)). ESI-MS: 692 (8, $[M+H]^+$), 347 (100, $[M+2\,H]^{2+}$).

*2-(Benzyloxy)*-N,N′,N″-*tris(3-{[(benzyloxy)carbonyl]amino}propyl)*-N,N′,N″-*tris(4-{[(benzyloxy)carbonyl](3-{[(benzyloxy)carbonyl]amino}propyl)amino}butyl)benzene-1,3,5-tris[propanamide]* (**23**). Analogous to the preparation of **22**, reaction of **21** (200 mg, 0.5 mmol), 1-methyl-2-chloropyridinium iodide (460 mg, 1.8 mmol), $Et_3N$ (545 mg, 5.4 mmol), and **9** (876 mg, 1.45 mmol) in $CH_2Cl_2$ (20 ml) afforded 1.06 g (98%) **23**. IR ($CHCl_3$): 3435*m*, 2925*m*, 1700v*s*, 1630*s*, 1510v*s*, 1450*s*, 1370*m*, 1215*s*, 1135*s*, 1080*m*, 1025*m*, 910*w*, 820*w*, 610*m*. $^1$H-NMR ($CDCl_3$): 7.43–7.28 (*m*, 50 arom. H); 6.90 (*s*, H–C(4), H–C(6)); 5.07, 5.05, 5.00 (3*s*, 9 PhC$H_2$); 4.76 (*s*, PhC$H_2$); 3.27–3.21 (*m*, 3 $CH_2$(1″), 3 $CH_2$(5′)); 3.11 (*m*, 3 $CH_2$(3″), 3 $CH_2$(12′)); 2.99–2.94 (*m*, 3 $CH_2$(8′), 3 $CH_2$(10′)); 2.84 (*t*, *J* = 7.1, 3 $CH_2$(1′)); 2.52 (br., 3 $CH_2$(2′)); 1.98 (br., 6 NHCO); 1.67–1.56 (*m*, 3 $CH_2$(2″),

3 $CH_2$(11′)); 1.44–1.33 (*m*, 33 $CH_2$(6′), 33 $CH_2$(7′)). $^{13}$C-NMR ($CDCl_3$)[4]): 170.4 (*s*, 3 C(3′)); 156.4 (*s*, 9 CO); 136.7 (*s*, 9 arom. C); 133.8 (*s*, C(1), C(3), C(5)); 128.4 (*d*, C(4), C(6)); 128.3, 127.9 (2*d*, 50 arom. C); 75.6 (*t*, Ph*C*$H_2$)); 67.1, 66.3 (2*t*, 9 Ph*C*$H_2$); 47.0 (*t*, 3 C(1″)); 46.3 (*t*, 3 C(5′)); 45.2 (*t*, 3 C(8′)); 44.1 (*t*, 3 C(10′)); 42.1 (*t*, 3 C(3″)); 37.6 (*t*, 3 C(2′)); 39.2 (*t*, 3 C(2″)); 28.8 (*t*, 3 C(11′)); 27.6 (*t*, 3 C(1′)); 26.3 (*t*, 3 C(7′)); 25.7 (*t*, 3 C(6′)); 23.1 (*t*, 3 C(12′)). ESI-MS: 2184 (48, $[M+Na]^+$), 2162 (7, $[M+1]^+$), 1103 (100, $[M+2\,Na]^{2+}$).

N,N′,N″-*Tris{4-[(3-aminopropyl)amino]butyl}*-N,N′,N″-*tris(3-aminopropyl)-2-hydroxybenzene-1,3,5-tris-[propanamide]* (**25**). Analogous to the preparation of **24**, reaction of **23** (640 mg, 0.29 mmol) and 10% Pd/C (300 mg) in AcOH (glacial, 110 ml) in a *Parr* apparatus (3.5 bar $H_2$ pressure) yielded 239 mg (94%) of **25** as a colorless oil, which was converted to the polyhydrochloride as it was described for **24**. IR (KBr): 3419*m*, 2959v*s*, 1606v*s*, 1471v*s*, 1267*w*, 1150*m*, 1063*w*, 1009*w*, 753*w*, 479*w*. $^1$H-NMR ($CD_3OD$): 8.80, 8.16, 8.00 (3br. *s*, 3 $^+NH_2$, 6 $^+NH_3$); 6.93 (*s*, H–C(4), H–C(6)); 3.56–3.51 (*m*, 3 $CH_2$(3″), 3 $CH_2$(12′)); 3.50–3.43 (*m*, 3 $CH_2$(8′), 3 $CH_2$(10′)); 3.32–3.14 (*m*, 3 $CH_2$(1″), 3 $CH_2$(5′)); 2.92 (br., 3 $CH_2$(1′)); 2.60 (br., 3 $CH_2$(2′)); 2.21–2.20 (*m*, 3 $CH_2$(2″)); 1.99–1.98 (*m*, 3 $CH_2$(11′)); 1.75 (br., 3 $CH_2$(6′), 3 $CH_2$(7′)). $^{13}$C-NMR ($CD_3OD$): 170.4 (*s*, 3 C(3′)); 152.3 (*s*, C(2)); 133.8 (*s*, C(1), C(3), C(5)); 129.8 (*d*, C(4), C(6)); 48.8 (*t*, 3 C(8′)); 46.3 (*t*, 3 C(10′)); 46.1 (*t*, 3 C(1″)); 43.9 (*t*, 3 C(5′)); 38.4 (*t*, 3 C(3″)); 38.0 (*t*, 3 C(12′)); 34.9 (*t*, 3 C(2′)); 27.8 (*t*, 3 C(2″)); 26.8 (*t*, 3 C(11′)); 25.7 (*t*, 3 C(1′)); 25.2 (*t*, 3 C(7′)); 24.5 (*t*, 3 C(6′)). ESI-MS: 863 (< 5, $[M+H]^+$), 606 (18), 432 (100, $[M+2\,H]^{2+}$), 288 (73, $[M+3\,H]^{3+}$).

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[4]) The signal of C(2) of **23** was not observed.

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