DOI: 10.1002/chem.200401078

Synthesis of Water-Soluble, Multiple Functionalizable Dendrons for the Conversion of Large Dendrimers or Other Molecular Objects into Potential Drug Carriers

Stephan Müller and A. Dieter Schlüter*[a]

Abstract: The synthesis of dendrons and dendrimers which carry OEG chains and bidentate ligands and/or fluorescence tags is described. The orthogonally protected functional groups of the dendrons allow modification of the substitution pattern and attachment to larger entities. Both dendrons and dendrimers are highly water-soluble. The dendrons should have considerable potential to convert, for example, commercially available, high-generation dendrimers into water-soluble, versatile support materials for antitumor therapy.

Keywords: dendrimers · drug delivery · macromolecules

Introduction

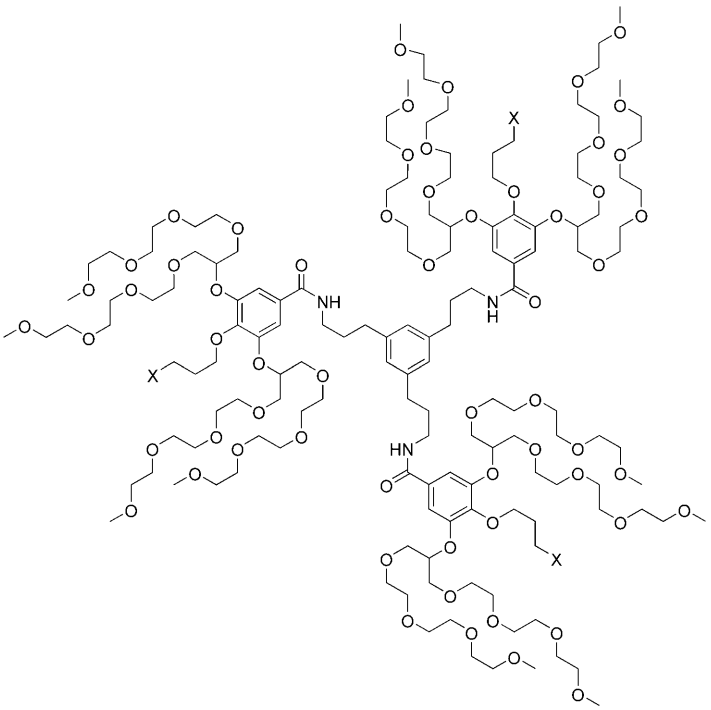
Dendrimers are versatile, monodisperse synthetic macromolecules with a near-perfect nanoscale structure and are synthesized step-by-step.[1] They can be selectively decorated with different motifs and the maximum (covalent) loading capacity towards a particular function is defined by the number of surface groups.[2] Dendrimers are a perfect example for macromolecular engineering.[3] Their solubilities and glass transition temperatures, for example, can be tailored in a wide range by simple chemical "surface" modification. It is thus to be expected that the coverage of a high-generation dendrimer with water-soluble small dendrons will render the whole dendrimer water-soluble. Water solubility is an important issue whenever biomedical applications like in drug delivery come into play.[4] It is normally achieved by the introduction of either charged groups[5] or decoration with polar oligomers of the ethylene glycol family (OEG).[6] Whereas especially positively charged compounds tend to be cytotoxic,[7,8] OEGs revealed low toxicity in in vivo applications.[9] Herein, we report on the synthesis of differently sized dendrons which carry OEG chains for water solubility, bidentate N- and O-based ligands for platinum complexation, and fluorescence tags to study cellular uptake and intracellular distribution. A selectively addressable functional group at the focal point allows the dendron's attachment to larger entities. The goal is to provide building blocks for the conversion of any larger and structurally defined molecular object, like a commercial high-generation dendrimer, into a water-soluble and versatile support material for antitumor therapy. Scheme 1 shows the simplest possible application of this concept in which three dendrons with branched OEG solubilizers and complexation sites X are attached to a 1,3,5-tris(aminopropyl)benzene through an hydrolytically stable amide bond to furnish a small dendrimer. A structure like this serves as proof of principle only and will not gain, of course, importance as a drug carrier itself.

[a] S. Müller, Prof. A. D. Schlüter[+]
Institut für Chemie/Organische Chemie
Freie Universität Berlin
Takustrasse 3, 14195 Berlin (Germany)
E-mail: dieter.schluter@mat.ethz.ch

[+] New address: Department of Materials
Institute of Polymers, Swiss Federal Institute of Technology
ETH Hönggerberg, HCI J 541, 8093 Zürich (Switzerland)
Fax: (+41) 44-633-1395

Results and Discussion

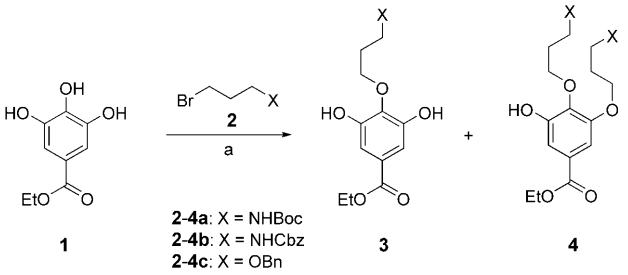
The synthetic procedures are compiled in Schemes 2–13. The main reactions used are etherifications, amido-coupling reactions (e.g., dendrimer assembly), and standard protection–deprotection protocols. The OEG chains used in this project are branched and were synthesized according to a known procedure. Commercially available OEGs were considered either too short to mediate sufficient water solublity or are polydisperse which was believed to be disadvantageous in regard to approval matters. The purification of all compounds was done by standard column chromatography. First the schemes will be described in general terms and then addressed in somewhat more detail. Scheme 2 and



Scheme 1. Structure of a small target dendrimer with branched oligoethyleneglycol (OEG) chains for water solubility and functional groups X which serve as ligands for metal complexation and as anchor sites for attaching fluorescence tags.

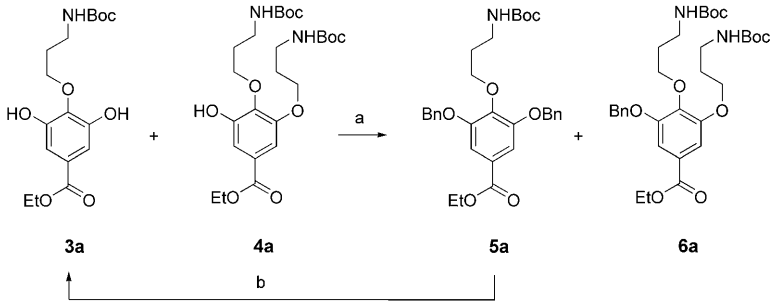
Scheme 3 show the monoalkylation of gallic acid (**1**) and the removal of undesired bis-alkylated by-product **4**. Scheme 4 and Scheme 5 depict the synthesis of the OEGylated dendron **8a** and its selective deprotection at both the amine (to **9**) and the focal point acid (to **10a**) for subsequent functionalization of **9** with an ethylene–diamine moiety to **12** and the fluorescence tag **14** to **15**, respectively. Scheme 6 illustrates the synthesis of the protected malonic acid derivatives **20a** and **20b** which have an additional carboxylic acid for attachment to the dendron. Scheme 7 and Scheme 8 contain the synthesis of the allyl-protected dendrons **21**, its modification to **22**, and the decoration of the latter with the malonic acid derivatives **20a** and **20b** to give dendrons **23** and **25**, respectively, as well as their deprotected counterparts **24** and **26**. Scheme 9 summarizes all the reactions leading to dendrimers **28**, **30**, **32**, **33**, and **35** as well as the subsequent deprotections, all of which serve as model reactions for the anticipated application to larger objects in the future. Scheme 10 shows the synthesis and selective deprotection of the orthogonally protected branching unit **40**, which is a key compound for the synthesis of the larger dendrons **49**–**54** and dendrimers **55**–**58** whose syntheses are shown in Scheme 11 and Scheme 12, respectively. Finally, Scheme 13 depicts the divergent synthesis of dendrimer **63** and its deprotection to **65**.

The synthesis of an OEGylated building block with two orthogonally protected anchor sites, an amine and a carboxylic acid, makes use of a selective alkylation of **1** in its 4-hydroxy position.[10] For this alkylation *tert*-butoxycarbonyl(*N*-Boc)- and benzyloxycarbonyl(*N*-Cbz)-protected 3-bromopropylamines **2a** and **2b**, respectively, and *O*-benzyl(*O*-Bn)-protected 3-bromopropanol **2c** were used in equimolar amounts to **1** (Scheme 2). The best results were obtained in



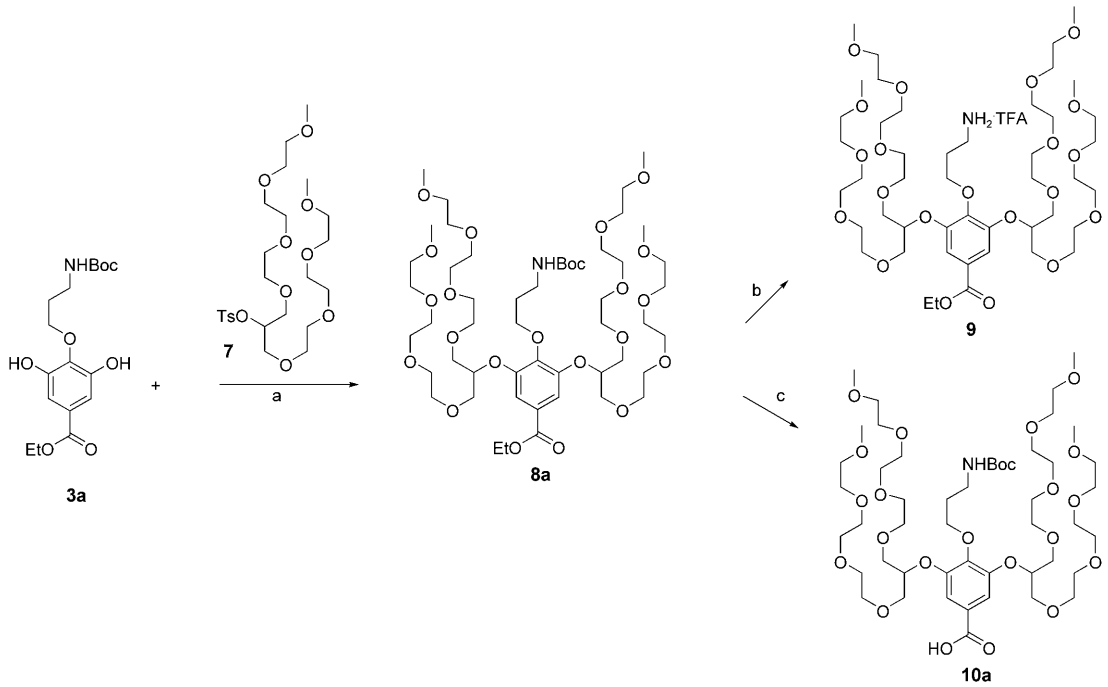
Scheme 2. Synthesis of mono-alkylated gallates. Reagents and conditions: a) DMF, $NaHCO_3$, KI, four days, room temperature.

DMF with excess of $NaHCO_3$ at room temperature, which gave the mono-alkylated products **3a**–**c**. Occasionally, some bis-alkylated by-product, for example, **4a**, was formed. In such a case, the resulting mixture could not easily be separated and was therefore exhaustively benzylated and then separated by standard column chromatography (Scheme 3). Catalytic hydrogenation of **5a** yielded pure **3a**.[11]



Scheme 3. Removal of bis-alkylated by-products. Reagents and conditions: a) K_2CO_3, DMF, benzyl bromide, 80 °C, one day; b) Pd/C, methanol, H_2.

In the next step **3a** was decorated with the symmetric OEGylated glycerol derivative **7**[12] to afford dendron **8a,** which has already a number of important features (Scheme 4). Not only is it fully water-soluble but also it carries a selectively addressable amine group and a focal point ester function for attachment to a larger object. The reactions of **7** with **3a**–**c** were carried out in DMF at 80 °C using

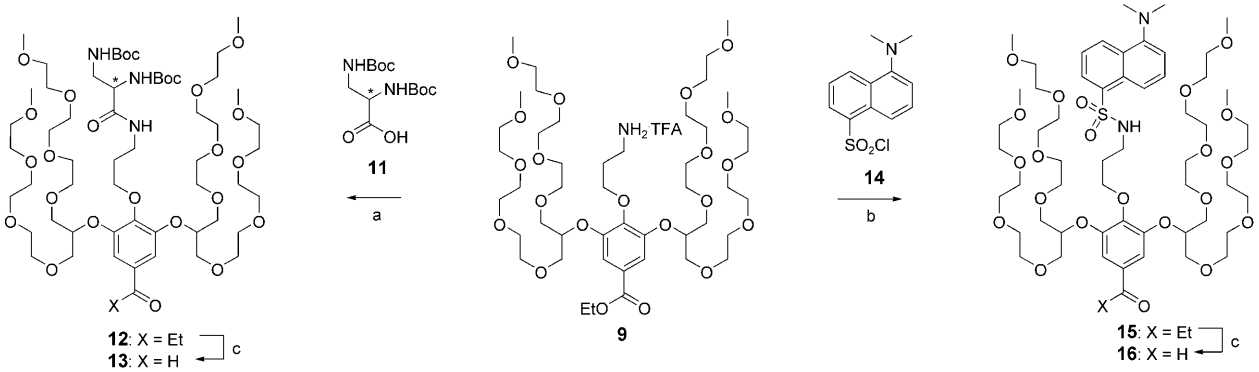


Scheme 4. Synthesis of water-soluble dendrons. Reagents and conditions: a) K_2CO_3, DMF, 80 °C, three days; b) TFA, CH_2Cl_2, room temperature, 12 h; c) 1 M KOH, ethanol, room temperature, 12 h.

K_2CO_3 as a base. The conversions of **3b** and **3c** are not shown in Scheme 4. Compounds **8a–c** were obtained in yields of 58–65 % indicating coupling efficiencies of 75–80 % per step. By keeping the temperature at 80 °C, base-induced elimination of toluenesulfonic acid from **7** (not shown) was kept at a minimum. Mitsunobu protocols were also applied, but did not prove superior due to tedious removal of triphenylphosphine oxide impurities.

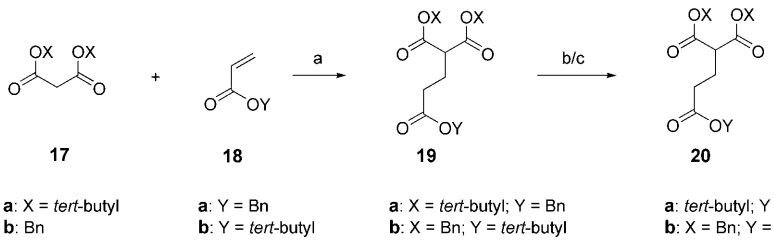
Starting from **8a** a variety of valuable compounds were synthesized. This first required selective deprotections at both the urea and the ester which was achieved by treating **8a** with trifluoroacetic acid (TFA) in CH_2Cl_2 (to give **9**) and KOH in ethanol (to give **10a**), respectively (Scheme 4). Both deprotections went smoothly and virtually quantitatively so that the products could be used as obtained in the further steps. The racemic *N*-Boc-protected diaminopropionoic acid **11** with its ethylenediamine moiety for Pt^{2+} complexation was then connected to **9** under standard amide coupling conditions to give **12** (Scheme 5). Interestingly, this coupling succeeded with *O*-(1*H*-benzotriazole-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) as active ester reagent, but failed with hydroxybenzotriazole hydrate/*N*-(3-dimethylaminopropyl)-N′-ethyl-carbodiimide hydrochloride (HOBt/EDC) and Hydroxysuccinimidyl/dicyclohexylcarbodiimide (HSu/DCC). The free benzoic acid **13** was generated from **12** in excellent yields with KOH at room temperature in ethanol.

Because of its high fluorescence intensity the 5-dimethylaminonaphthalene-1-sulfonyl (dansyl) group has often been used for biochemical applications and was also selected here



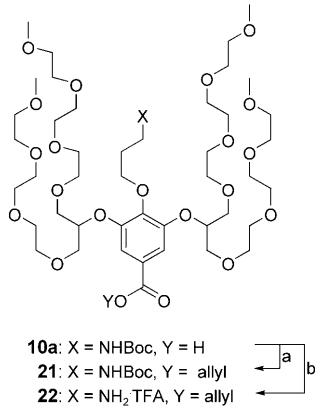
Scheme 5. Synthesis of dendrons with an ethylenediamine moiety or a fluorescent label. Reagents and conditions: a) DMF, TEA, TBTU; b) TEA, CH_2Cl_2, room temperature, 2 h; c) 1 M KOH, ethanol, room temperature, 12 h.

as fluorescence tag. The attachment went through its chloride (**14**) and gave **15** in virtually quantitative yields (Scheme 5). Saponification of the focal point ester of **15** cleanly furnished **16**.

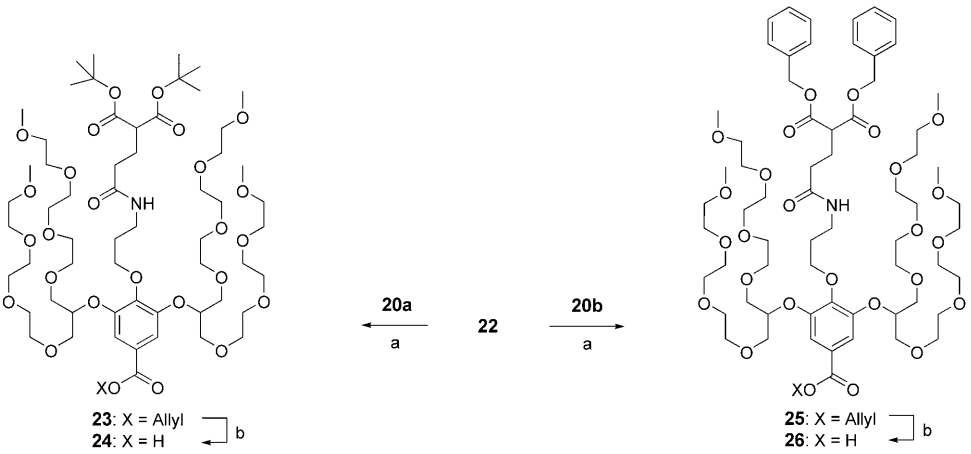


Scheme 6. Synthesis of protected malonic acid moieties. Reagents and conditions: a) K_2CO_3, Bu_4NI, benzene, reflux, one day; b) for **19a**: Pd/C, methanol, H_2; c) for **19b**: TFA, CH_2Cl_2, room temperature, 1–12 h.

Malonic acids are suitable bidentate ligands for structurally defined platinum(II) complexes. They may be superior to ethylenediamines in drug-carrier applications because platinated malonates can release Pt^{2+} at pH 4–5 by hydrolysis. To introduce malonic units to dendrons of the here described type a few aspects needed to be considered. First, the two carboxylic acid groups of the malonic part needed to be protected so that a linker for the attachment to the dendron could be introduced at the acidic carbon. The protecting groups chosen for this purpose needed to be removable at a later stage in the sequence without concomitant decarboxylation, which 1,3-dicarboxylic acids are prone to undergo. Second, the protecting groups had to be both stable under coupling conditions and orthogonal to the deprotection protocol at the focal point ester. The best candidates were *tert*-butyl and benzyl esters and, thus, compounds **20a** and **20b** were prepared through the tris-acid esters **19a** and **19b** (Scheme 6). They, in turn, were generated from the protected malonic acids **17a** and **17b** and orthogonally protected acrylic acids **18a** and **18b** under Michael conditions. This latter reaction always yielded a mixture of mono- and bis-alkylated malonates whose separation was tedious. Therefore, the raw mixture was directly deprotected at the linker's carboxylic acid and then separated by column chromatography. In this way pure **20a** and **20b** could be obtained in acceptable yields of 65% (for **20a**) and 67% (for **20b**), respectively. For the protection of the benzoic acid at the focal point, the propenyl ester with its known Pd-mediated deprotection protocol was chosen to avoid a detrimental interference with the other esters. Alkylation of the potassium salt of **10a** with an excess of allyl bromide gave the desired propenyl benzoate **21** (Scheme 7).



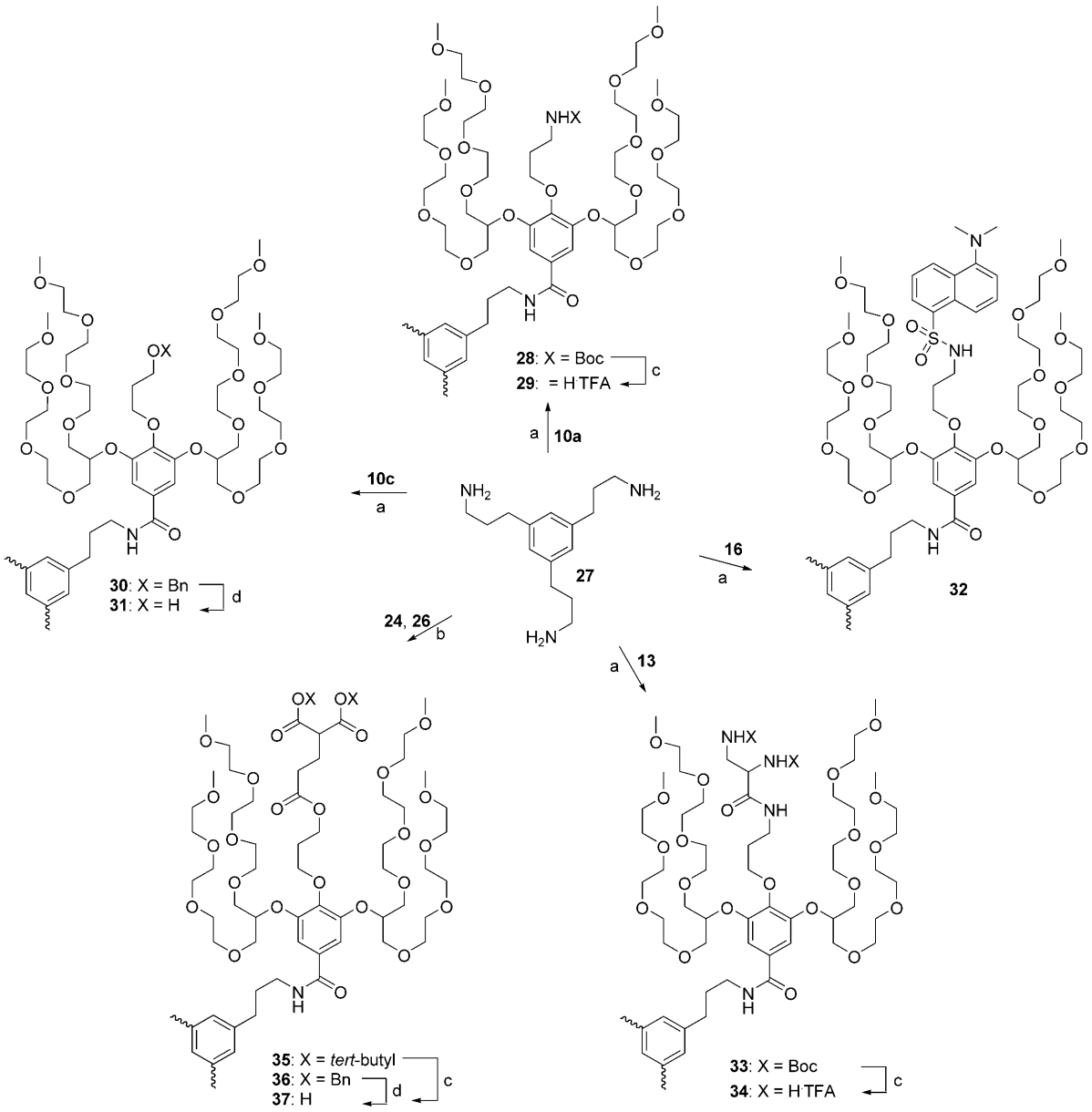
Scheme 7. Synthesis of a dendron for assembly with protected malonates. Reagents and conditions: a) allyl bromide, DMF, K_2CO_3, Bu_4NI, 12 days, room temperature; b) TFA, CH_2Cl_2, room temperature, 12 h.



Scheme 8. Synthesis of dendrons with a malonic acid moiety. Reagents and conditions: a) DMF, TEA, TBTU; b) $[Pd(PPh_3)_4]$, *p*-toluenesulfonic acid, CH_2Cl_2, methanol, room temperature, 0.5 h.

Removal of the *N*-Boc group in **21** was performed with TFA in CH_2Cl_2 and gave **22**. The protected malonic acid moieties **20a** and **20b** were then hooked on to **22** under standard amide coupling conditions to give **23** and **25**, respectively (Scheme 8). The best results for these couplings were obtained with TBTU, though the same products were also accessible with other active ester reagents (HOBt/EDC, HSu/DCC). The best results for the deprotection of the allyl benzoates were achieved by adding a solution of *p*-toluenesulfonic acid in methanol to a solution of the ester and $[Pd(PPh_3)_4]$ in CH_2Cl_2. Column chromatography gave the free benzoic acids **24** and **26** in high yields (**24**: 94%; **26**: 96%).

In the next step, the various small dendrons were attached to the trifunctional core molecule **27** (Scheme 9). This assembly served as a test for the concept's feasibility which is



Scheme 9. Synthesis of OEGylated dendrimers with different surface motifs. Reagents and conditions: a) HOBt, EDC, TEA, CH_2Cl_2, methanol; b) HOBt, EDC, TEA, CH_2Cl_2; c) TFA, CH_2Cl_2, room temperature, 1–12 h; d) Pd/C, methanol, H_2.

to convert large molecular objects into water-soluble drug-delivery systems by the attachment of appropriately designed dendrons. In all reactions the dendrons were used in 3.5 molar equivalents to **27**. In contrast to the amido-coupling protocol for alkanoic acids with primary alkylamines, the benzoic acids of **10a**, **10c**, **13**, **16**, **24**, and **26** reacted much more efficiently with HOBt/EDC than with TBTU. The active esters of **10a**, **10c**, **13**, and **16** were generated in situ by employing HOBt/EDC in CH_2Cl_2 at room temperature and adding them at −40 °C to solutions of **27** and triethylamine (TEA) in CH_2Cl_2 and methanol. The reaction temperature was slowly raised to room temperature and the mixtures stirred until conversions were complete (TLC). Column chromatography gave the dendrimers **28**, **29**, **32**, and **33** in high yields (**28**: 95%; **29**: 98%; **32**: 92%; **33**: 80%). The excess of respective active esters was recovered as the corresponding methyl esters which in turn were quantitatively reconverted into the free benzoic acids by saponification with aqueous 1 M KOH (not shown). The analogous recycling of the active esters of **24** and **26** did not give satisfactory results because the corresponding two ester functions (methyl benzoate and malonate) of the products could not be saponified with sufficiently high selectivity. Therefore, the amido-coupling procedure was carried out without methanol as solvent and quenched with aqueous 1 M $NaHCO_3$ which converted the excess active esters directly

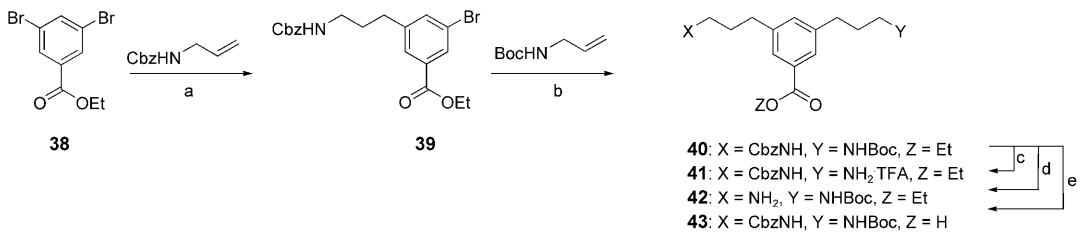
into the starting benzoic acids (**24** and **26**). All dendrimers were characterized by their fully assigned ^{1}H and ^{13}C NMR and MALDI-TOF mass spectra. The NMR assignment was achieved with the help of 2D homo- and heteronuclear correlated pulse sequences (COSY, HMBC, and HMQC). In the reflective mode, the MALDI-TOF mass spectra typically showed the monoisotopic peak of the potassium and sodium salts and the expected isotopic pattern.

The acid-labile *N*-Boc-carbamates of **28** and **33** were quantitatively deprotected with a large excess of TFA in CH_2Cl_2 at room temperature and gave the corresponding free amines **29** and **34** (as hydrotrifluoroacetates), respectively. Completion of the procedure was monitored by ^{1}H NMR spectroscopy. The benzyl ether in **30** was cleaved by catalytic hydrogenation with Pd/C and gave the free alcohol **31**. The deprotected dendrimers were again characterized by their ^{1}H and ^{13}C NMR (assignment by 2D-correlated spectroscopy) and MALDI-TOF mass spectra. The *tert*-butyl malonates of **35** could be deprotected to **37** either with a large excess of TFA in CH_2Cl_2 or by catalytic hydrogenation of **36** with Pd/C in methanol (Scheme 9). Both procedures gave pure **37** directly. Irrespective of the method used the spectroscopic and spectrometric data of **37** were the same. Specifically there was no indication of decarboxylation. The MALDI-TOF mass spectrum of **37**, however, showed decarboxylated by-products. It seems therefore that this is caused by the MALDI process rather than by chemically induced undesired decarboxylation.

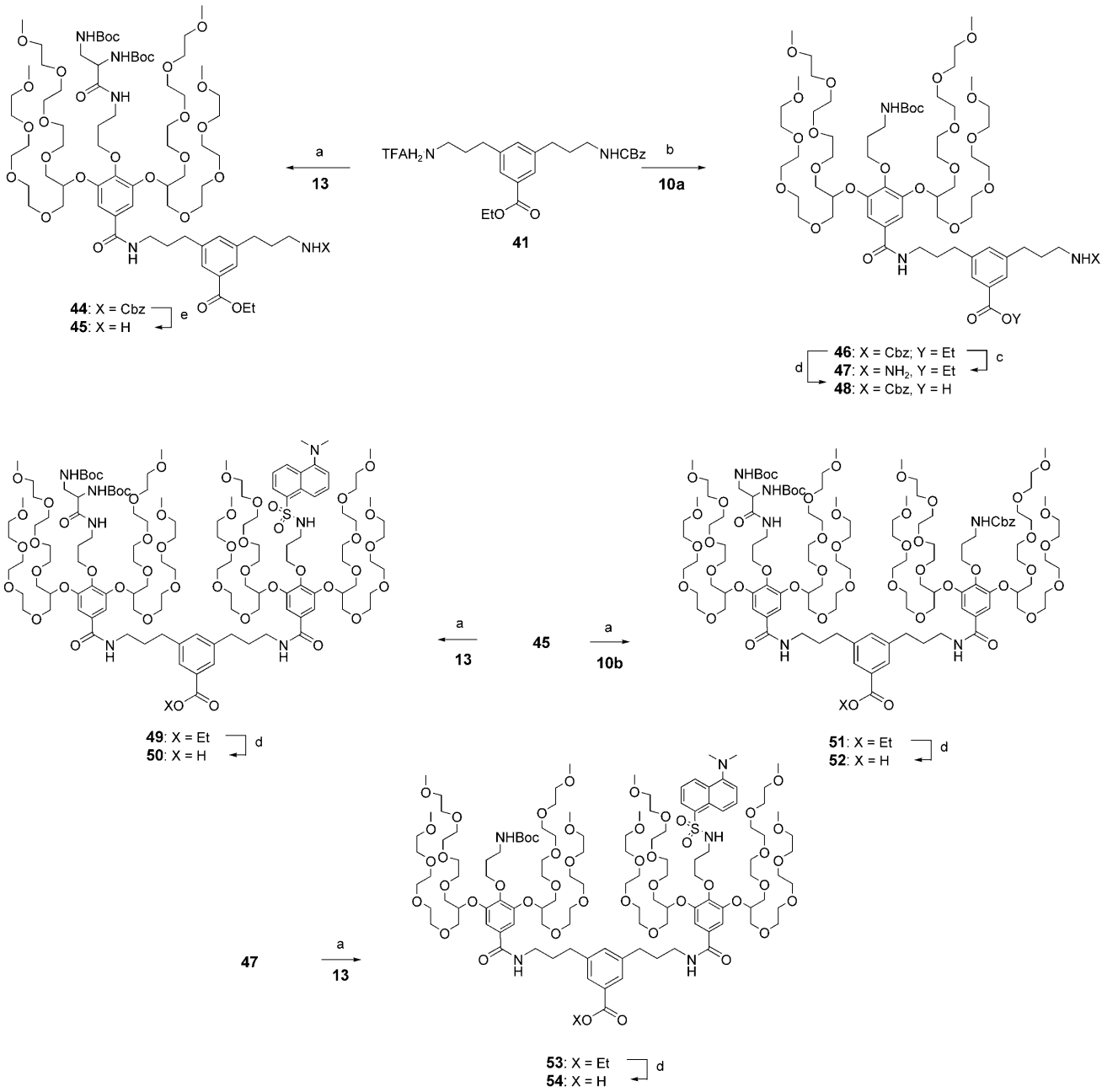
Another important goal of this work was to synthesize water-soluble dendrons with two different functional groups, for example, one for Pt-attachment and one for a fluorescence tag. For such an endeavor the (almost) orthogonally protected branching unit **40** was a key compound. Although known,[17] improvements of the procedure were necessary (Scheme 10). The sequence starts from **38** which was easily prepared on a 100-g scale.[18] Its subjection to Suzuki–Miyaura cross-coupling with Cbz-protected allylamine gave **39** on the 15-g scale in yields of 67%. Subsequent coupling with Boc-protected allylamine gave compound **40** in 92% yield. TFA deprotection of **40** gave **41**, whereby, however, also some of the Cbz was cleaved off. Compound **41** was purified by column chromatography. The Cbz group of **40** was removed by catalytic hydrogenation. The best solvents were ethanol/ethyl acetate mixtures and methanol. Both free amines, **41** and **42**, were stored under nitrogen. Saponification of the ester functionality of **40** was achieved cleanly with aqueous 1 M KOH in ethanol at room temperature and gave **43** virtually quantitatively.

Compound **41** was used to prepare the more complex dendrons **49**, **51**, and **53** as well as their deprotected counterparts **50**, **52**, and **54** which all carry different sets of anchor groups/fluorescence tags (Scheme 11). The reaction conditions resembled those already described and are therefore not given here. Yields were good to very high throughout and all compounds were fully characterized (except, of course, combustion analysis). The attachment of these dendrons to the trifunctional core molecule **27** (Scheme 12) gave dendrimers **55**, **57**, and **58**, respectively. The amide-coupling protocols applied were the same as the ones for the dendrimers assembled in Scheme 9 except that the reactions required longer times to reach completion. The resulting dendrimers were purified by column chromatography with very polar solvent mixtures and the excess of the dendrons were recycled after saponification. MALDI-TOF mass spectrometric measurements in the linear mode afforded the molecular peaks of the sodium salt. The NMR spectra showed broad lines and reliable assignments could therefore not be done. Additionally, the number of signals in the ^{13}C NMR spectra was usually too low because of superimpositions. Peripheral deprotections were so far only tried for dendrimer **55**. Extended exposure to TFA in CH_2Cl_2 led to a complete disappearence of the signal for the *tert*-butyl group in the ^{1}H NMR spectrum.

In a final sequence the known dendrimer **59**[8] was prepared from **43** and **27** (Scheme 13) to use it as starting material for dendrimers with peripheral malonates and fluorescence tags. The deprotection of the *N*-Cbz groups of **59** to **60** by catalytic hydrogenation proceeded cleanly without affecting the Boc groups. The free amines of **60** were then used to hook the dendron **13**, resulting in the formation of **61**. Deprotection of **61** and reaction of the corresponding free amine with both compounds **24** and **26** gave the corresponding dendrimers **63** and **64**, respectively, in good to excellent yields. The separation of these dendrimers from the excess of **24** and **26** by column chromatography was possible but too tedious. The excess of the respective active ester was therefore rather intercepted with methanol to give the corresponding methyl esters. Finally, dendrimer **65**, which provides free malonic acids with potential for platinum complexation, was obtained via deprotection of **63** with TFA in



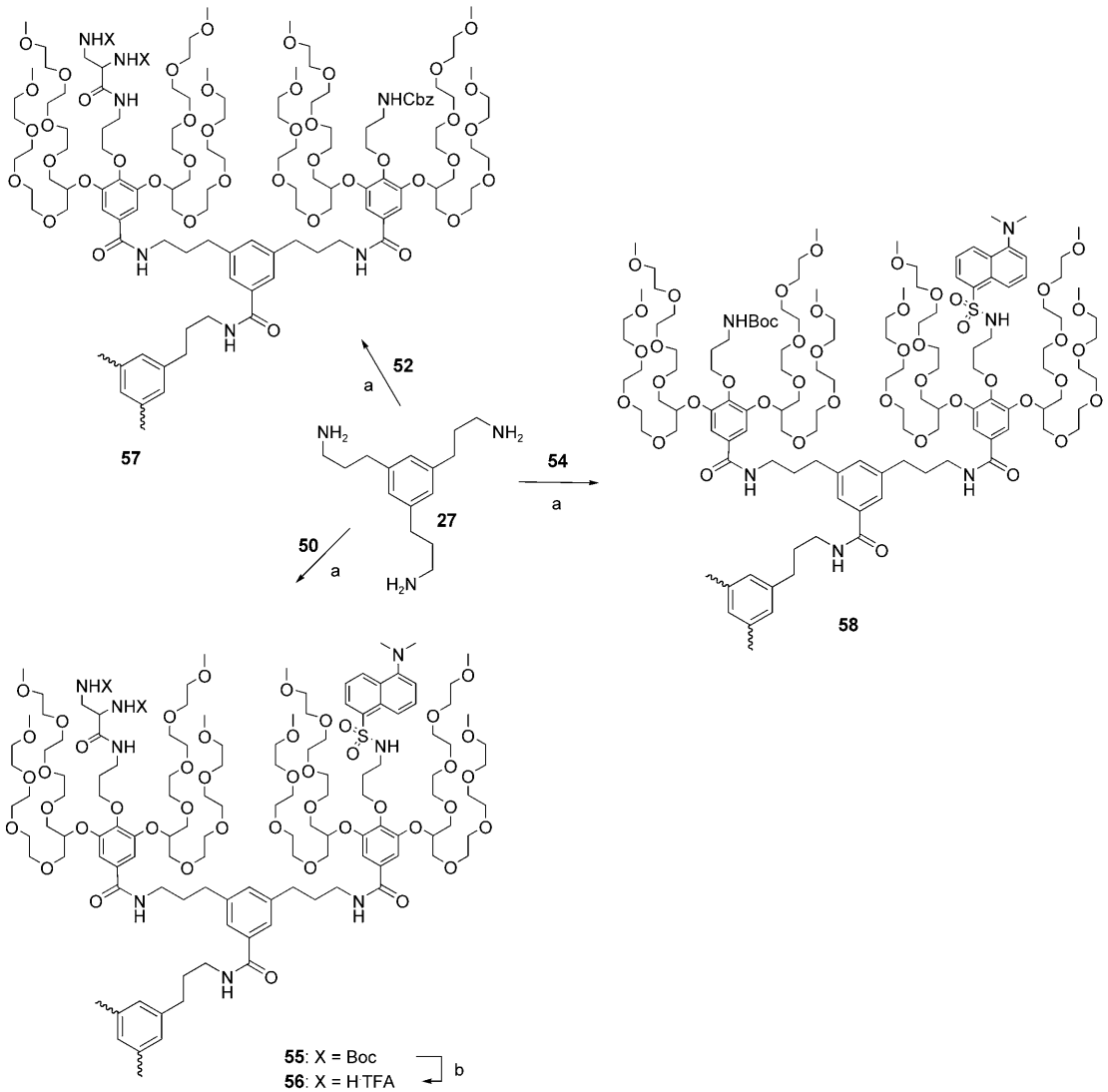
Scheme 10. Synthesis and selective deprotection of **40**. Reagents and conditions: a) 9-BBN, toluene, 0 °C, 12 h, then 1 M KOH, $[Pd(PPh_3)_4]$, 60 °C; b) 9-BBN, toluene, 0 °C, 12 h, then 1 M KOH, $[Pd(PPh_3)_4]$, reflux; c) CH_2Cl_2, TFA, 12 h, room temperature; d) ethyl acetate/ethanol, Pd/C, 1 h, H_2; e) 1 M KOH, ethanol, room temperature.



Scheme 11. Syntheses of dendrons. a) HOBt, EDC, CH_2Cl_2, TEA, MeOH; b) TBTU, CH_2Cl_2, DMF, TEA, MeOH; c) MeOH, Pd/C, 1 h, H_2; d) EtOH, 1 M KOH, room temperature, 12 h; e) ethyl acetate/MeOH, Pd/C, H_2, 1 h.

dichloromethane. The progress of the cleavage of the *tert*-butyl esters was conveniently monitored with ^{1}H NMR spectroscopy. In initial experiments it was not possible to deprotect the benzyl esters of **64** to gain **65**. The typical deprotection protocol with Pd/C in a hydrogen atmosphere failed.

In summary, a concept has been presented that should allow the conversion of molecular objects (e.g. large dendrimers) into non-ionic and yet water-soluble and surface addressable entities. Several dendrons of different sizes and complexity were prepared which not only carry either two or four branched OEG chains but also one or two mono- and bidendate anchor group(s) for complexation with pharmaceutically relevant metal complexes like Pt complexes. These anchor groups are either of the malonic (weak binding) or diaminopropionic acid type (strong binding). Some of the dendrons carry the dansyl substituent as fluorescence tag to enable cell distribution studies. All dendrons were attached to a trifunctional core which gave a variety of differently surface-decorated dendrimers combining several functions at the same time.



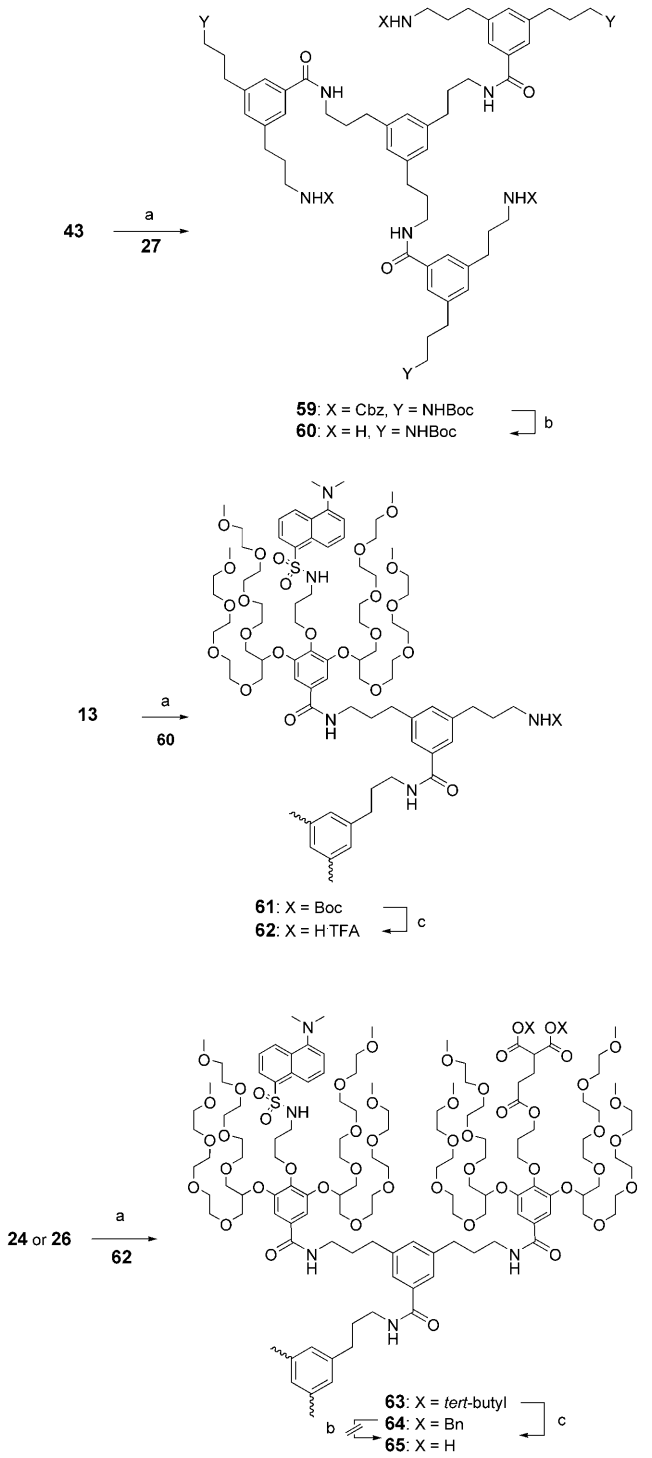
Scheme 12. Synthesis of dendrimers with different surface motifs. Reagents and conditions: a) CH_2Cl_2, HOBt, EDC, TEA, MeOH; b) CH_2Cl_2, TFA, room temperature.

Experimental Section

General: All starting materials were purchased from commercial sources and used without further purification. Solvents were dried under standard conditions. Compounds **1**, **14**, **17a**,**b**, and **18a**,**b** were commercially available. The following compounds were prepared according to literature procedures: **2a**,[13] **2b**,[14] **2c**,[15] **7**,[12] **11**,[16] **27**,[8] **38**,[18] **59**.[8] All dansyl-labeled compounds were stored and allowed to react in the dark to avoid oxidative degradation. Whenever possible, reactions were monitored by thin-layer chromatography (TLC) using TLC silica gel coated aluminum plates $60F_{254}$ (Merck). Compounds were detected by UV light (254 nm or 366 nm) and/or by treatment with a solution of ninhydrine in ethanol, anisaldehyde in H_2SO_4 followed by heating, or with iodine. Column chromatography was preformed using Merck silica gel 60, 0.040–0.063 mm (230–400 mesh).

^{1}H NMR spectra were recorded by using a Bruker AC 500 (500 MHz), an AM 270 spectrometer (270 MHz), or an AB 250 (250 MHz) instrument, and were referenced to the solvent signal: $CDCl_3$ at $\delta = 7.24$ ppm, CD_2Cl_2 at $\delta = 5.32$ ppm, CD_3OH at $\delta = 3.35$ or 4.78 ppm. ^{13}C NMR spectra were recorded by using a Bruker AC 500 (125 MHz), an AM 270 spectrometer (67.5 MHz), or an AB 250 (62.5 MHz) instrument, and were referenced to the solvent signal: $CDCl_3$ at $\delta = 77.0$ ppm, CD_2Cl_2 at $\delta = 53.5$ ppm, CH_3OH at $\delta = 49.0$ ppm. All spectra were recorded at 25 °C. Mass spectra were recorded on a Varian MAT 711 and CH6 (EI) or Type CH5DF (FAB), and a Bruker Reflex with delayed extraction source (MALDI-TOF). Elemental analyses were performed by using a Perkin-Elmer EA 240. Because of the polarity of the prepared compounds and their ability to complex metal ions, it was generally difficult to obtain correct data from elemental analysis. Analytical GPC was recorded on Waters Styragel HR 1 or HR 3 columns, Waters 2487 UV/VIS detector at 254 nm to demonstrate the purity of these compounds.

Ethyl 4-(3-*tert*-butoxycarbonylaminopropoxy)-3,5-dihydroxybenzoate (3a): Ethyl 3,4,5-trihydroxybenzoate (**1**; 7.49 g, 37.8 mmol), *tert*-butyl (3-bromopropyl)carbamate (**2a;** 9.00 g, 37.8 mmol), dry $KHCO_3$ (15.14 g, 151.2 mmol), and KI (0.11 g, 0.6 mmol) were suspended in dry DMF (40 mL). The mixture was degassed by three freeze–pump–thaw cycles, flushed with N_2, and stirred for four days at room temperature. After filtration, the organic phase was quenched with water (400 mL), neutralized, and extracted seven times with diethyl ether (60 mL). The combined organic phases were extracted three times with 1 M $NaHCO_3$ (100 mL), three times with water (100 mL), and once with brine (100 mL). The organic phase was dried over $MgSO_4$, filtered, and the solvent evaporated. The crude product was purified by column chromatog-



Scheme 13. Synthesis of a dendrimer with fluorescence tag and malonic acid moiety. Reagents and conditions: a) CH_2Cl_2, HOBt, EDC, TEA, MeOH; b) ethyl acetate/ethanol, Pd/C. c) CH_2Cl_2, TFA.

raphy (silica gel, hexane/ethyl acetate (3:1) as eluent). The colorless oil was dissolved in dioxane, filtered, and lyophilized. Yield: 8.73 g (65%) of a colorless solid. Alternatively, the same product was obtained by catalytic hydrogenation of **5a**. Compound **5a** (6.5 g, 12.1 mmol) was dissolved in methanol (10 mL), and Pd/C (0.65 g) was added. The mixture was stirred for 1 h in a hydrogen atmosphere. The reaction was monitored with TLC. After complete deprotection, the mixture was filtered and the solvent removed under reduced pressure. Further purification was not necessary. Yield: 4.28 g (quant) of a colorless solid.

$R_f = 0.23$ (silica gel, hexane/ethyl acetate 3:1); ^{1}H NMR ($CDCl_3$, [D$_4$]methanol, 270 MHz): $\delta = 1.29$ (t, ^3J(H,H) = 7.0 Hz, 3H; -CH_2CH_3), 1.39 (s, 9H; -$C(CH_3)_3$), 1.83 (m, 2H; β-CH_2), 3.36 (m, 2H; γ-CH_2), 4.02 (t, ^3J(H,H) = 5.2 Hz, 2H; α-CH_2), 4.25 (q, ^3J(H,H) = 7.0 Hz, 2H; -CH_2CH_3), 5.17 (br s, 1H; -NH), 7.09 ppm (2H; Ar-H); ^{13}C NMR ($CDCl_3$, [D$_4$]methanol, 68 MHz): $\delta = 13.85$, 28.05, 30.29, 36.65, 60.79, 69.38, 79.50, 109.17, 125.45, 138.05, 149.77, 157.08, 166.80 ppm; MS (EI, 80 eV, 160 °C): *m/z* (%): 354.9 (5) $[M]^+$, 310.0 (3) $[M-OEt]^+$, 255.9 (4), 254.9 (27) $[M-C_5H_9O_2]^+$, 101.9 (100) $[C_5H_9O_2]^+$; elemental analysis calcd (%) for $C_{17}H_{25}NO_7$ (355.16): C 57.45, H 7.09, N 3.94; found: C 57.21, H 7.07, N 3.83.

Ethyl 4-(3-benzyloxycarbonylaminopropoxy)-3,5-dihydroxybenzoate (3b): Ethyl 3,4,5-trihydroxybenzoate (**1**; 7.49 g, 37.8 mmol), benzyl (3-bromopropyl)carbamate (**2b;** 10.28 g, 37.8 mmol), dry $KHCO_3$ (15.14 g, 151.2 mmol), and KI (0.11 g, 0.6 mmol) were suspended in dry DMF (40 mL). The mixture was degassed by three freeze–pump–thaw cycles, flushed with N_2, and stirred for four days at room temperature. After filtration, the organic phase was quenched with water (400 mL), neutralized, and extracted seven times with diethyl ether (60 mL). The combined organic phases were extracted three times with 1 M $NaHCO_3$ (100 mL), three times with water (100 mL), and once with brine (100 mL). The organic phase was dried over $MgSO_4$, filtered, and the solvent evaporated. The crude product was purified by column chromatography (silica gel, hexane/ethyl acetate (3:1)). The colorless oil was dissolved in dioxane, filtered, and lyophilized. Yield: 8.54 g (58%) of a colorless solid.

$R_f = 0.20$ (silica gel, hexane/ethyl acetate (3:1)); ^{1}H NMR ($CDCl_3$, [D$_4$]methanol, 270 MHz): $\delta = 1.29$ (t, ^3J(H,H) = 7.1 Hz, 3H; -CH_2CH_3), 1.86 (m, 2H; β-CH_2), 3.42 (t, ^3J(H,H) = 5.8 Hz, 2H; γ-CH_2), 4.05 (t, ^3J(H,H) = 5.5 Hz, 2H; α-CH_2), 4.25 (q, ^3J(H,H) = 7.1 Hz, 2H; -CH_2CH_3), 5.06 (s, 2H; -OCH_2Ar), 5.66 (br s, 1H; -NH), 7.10 (2H; Ar-H: gallate), 7.26 ppm (m, 5H; -OCH_2Ar-*H*); ^{13}C NMR ($CDCl_3$, [D$_4$]methanol, 68 MHz): $\delta = 13.87$, 16.81, 29.93, 37.39, 60.86, 66.59, 69.54, 109.20, 125.47, 127.68, 127.81, 128.20, 136.20, 138.08, 149.71, 157.40, 166.80 ppm; MS (EI, 80 eV, 170 °C): *m/z* (%): 390.1 (1), 389.0 (4) $[M]^+$, 344.0 (1) $[M-OEt]^+$, 281.0 (3) $[M-C_7H_8O]^+$, 92.0 (8), 91.1 (100) $[C_7H_7]^+$; elemental analysis calcd (%) for $C_{20}H_{23}NO_7$ (389.15): C 61.69, H 5.95, N 3.60; found: C 61.52, H 5.94, N 3.66.

Ethyl 4-[3-(benzyloxy)propoxy]-3,5-dihydroxybenzoate (3c): Ethyl 3,4,5-trihydroxybenzoate (**1**; 11.01 g, 55.5 mmol), (3-bromopropoxymethyl)benzene (**2c**; 13.4 g, 58.5 mmol), dry $KHCO_3$ (22.25 g, 222.2 mmol), and KI (0.25 g, 1.4 mmol) were suspended in dry DMF (60 mL). The mixture was degassed by three freeze–pump–thaw cycles, flushed with N_2, and stirred for four days at room temperature. After filtration, the organic phase was quenched with water (400 mL), neutralized, and extracted seven times with diethyl ether (60 mL). The combined organic phases were extracted three times with 1 M $NaHCO_3$ (100 mL), three times with water (100 mL), and once with brine (100 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent evaporated. The crude product was purified by column chromatography. The colorless oil was dissolved in dioxane, filtered and lyophilized. Yield: 9.67 g (50%) of a colorless solid.

$R_f = 0.30$ (silica gel, hexane/ethyl acetate (3:1)); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.34$ (t, ^3J(H,H) = 7.1 Hz, 3H; -CH_2CH_3), 1.99 (m, 2H; β-CH_2), 3.76 (t, ^3J(H,H) = 5.5 Hz, 3H; γ-CH_2), 4.15 (t, ^3J(H,H) = 5.5 Hz, 2H; α-CH_2), 4.31 (q, ^3J(H,H) = 7.1 Hz, 2H; -CH_2CH_3), 4.64 (s, 2H; -OCH_2Ar), 7.07 (br s, 2H; -OH), 7.20 (s, 2H; Ar-H: gallate), 7.25–7.43 ppm (m, 5H; -OCH_2Ar-*H*); ^{13}C NMR ($CDCl_3$, 63 MHz): $\delta = 14.20$, 28.83, 60.99, 67.76, 71.64, 73.18, 109.47, 126.73, 128.05, 128.12, 128.49, 136.89, 137.61, 149.61, 166.43 ppm; MS (EI, 80 eV, 60 °C): *m/z* (%): 346.7 (8), 345.8 (41) $[M]^+$, 301.3 (11), 300.4 (8) $[M-OEt]^+$, 237.8 (8) $[M-C_7H_7O]^+$, 209.4 (4) $[M-C_9H_{11}O]^+$, 91.4 (100) $[C_7H_7]^+$; elemental analysis calcd (%) for $C_{19}H_{22}O_6$ (346.14): C 65.88, H 6.40; found: C 65.81, H 6.20.

Ethyl 4-(3-*tert*-butoxycarbonylamino-propoxy)-3,5-bis(benzyloxy)benzoate (5a): A mixture of **3a** and **4a** (5.0 g, <14 mmol), dry K_2CO_3

(7.74 g, 56.0 mmol), and benzyl bromide (5.78 g, 33.7 mmol) were suspended in dry DMF (30 mL) under an N_2 atmosphere and stirred for 1 h at 80 °C. The reaction was quenched by the addition of water (50 mL). The mixture was extracted with ethyl acetate. The combined organic phases were washed with brine and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, hexane/ethyl acetate (10:1)). Yield: 6.5 g of a colorless solid.

R_f = 0.27 (silica gel, hexane/ethyl acetate (10:1)); ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 1.35 (t, ^3J(H,H) = 6.9 Hz, 3H; -CH_2CH_3), 1.37 (s, 9H; -C-(CH_3)$_3$), 1.85 (m, 2H; β-CH_2), 3.27 (m, 2H; γ-CH_2), 4.09 (t, ^3J(H,H) = 5.8 Hz, 2H; α-CH_2), 4.32 (q, ^3J(H,H) = 6.9 Hz, 2H; -CH_2CH_3), 5.15 (s, 4H; -OCH_2Ar), 5.24 (br. s, 1H; -NH), 7.27–7.47 ppm (12H; Ar-H); ^{13}C NMR ($CDCl_3$, 68 MHz): δ = 14.28, 28.39, 29.92, 38.16, 61.02, 71.11, 71.77, 78.69, 108.85, 125.50, 127.50, 128.09, 128.58, 136.50, 142.20, 152.23, 156.00, 165.98 ppm; MS (EI, 130 °C): *m/z* (%): 536.1 (0.07), 535.0 (0.18) $[M]^+$, 491.0 (0.10), 490.0 (0.21) $[M-OEt]^+$, 462.9 (0.24), 462.0 (1.18) $[M-C_3H_5O_2]^+$, 92.2 (14.78), 91.1 (100.00) $[C_7H_7]^+$; elemental analysis calcd (%) for $C_{31}H_{37}NO_7$ (535.26): C 69.51, H 6.96, N 2.62; found: C 68.90, H 6.84, N 2.52.

Ethyl 4-(3-*tert*-butoxycarbonylaminopropoxy)-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoate (8a): Compound **3a** (4.40 g, 12.3 mmol), dry K_2CO_3 (6.91 g, 50.0 mmol), and tosylate **7** (16.00 g, 29.7 mmol) were suspended in dry DMF (30 mL) under an N_2 atmosphere. The mixture was stirred for three days at 80 °C. After filtration, the solvent was removed under reduced pressure. The crude product was purified by column chromatography. The slight yellowish oil was dissolved in benzene, filtered and lyophilized. Yield: 8.70 g (65 %) of a yellowish oil.

R_f = 0.22 (silica gel, CH_2Cl_2/methanol (30:1)); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.35 (t, ^3J(H,H) = 7.1 Hz, 3H; -CH_2CH_3), 1.41 (s, 9H; -C-(CH_3)$_3$), 1.85 (m, 2H; β-CH_2), 3.34 (hidden m, 2H; γ-CH_2), 3.34 (s, 12H; -OCH_3), 3.49–3.53 and 3.58–3.66 (2 m, 48H; -OCH_2CH_2O), 3.71 (m, 8H; -OCH(CH_2)$_2$), 4.03 (t, ^3J(H,H) = 5.5 Hz, 2H; α-CH_2), 4.31 (q, ^3J(H,H) = 7.2 Hz, 2H; -CH_2CH$_3$), 4.57 (quint, ^3J(H,H) = 4.9 Hz, 2H; -OCH(CH$_2$)$_2$), 5.60 (br. s, 1H; -NH), 7.36 ppm (s, 2H; Ar-H: gallate); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 14.18, 28.33, 29.75, 37.79, 58.73, 60.74, 70.05, 70.28, 70.36, 70.73, 70.92, 71.69, 77.44, 78.42, 110.54, 125.19, 143.52, 151.66, 155.91, 161.75, 165.69 ppm; MS (positive-ion mode FAB): *m/z* (%): 1128.0 (4), 1127.0 $[M+K]^+$, 1113.0 (6), 1112.0 (14), 1111.0 (24) $[M+Na]^+$, 1089.0 (4) $[M+H]^+$, 992.0 (10), 991.0 (12), 990.0 (53), 989.0 (100), 988.0 (15), 987.0 (30) $[M+H-C_5H_9O_2]^+$; elemental analysis calcd (%) for $C_{51}H_{93}NO_{23}$ (1087.61): C 56.29, H 8.61, N 1.29; found: C 56.62, H 8.18, N 0.71.

Ethyl 4-(3-benzyloxycarbonylaminopropoxy)-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoate (8b): Compound **3b** (2.00 g, 5.6 mmol), dry K_2CO_3 (3.10 g, 13.5 mmol) and tosylate **7** (7.27 g, 13.5 mmol) were suspended in dry DMF (15 mL) under an N_2 atmosphere. The mixture was stirred for three days at 80 °C. After filtration, the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/methanol 30:1). The slight yellowish oil was dissolved in benzene, filtered and lyophilized. Yield: 3.64 g (58 %) of a yellowish oil.

R_f = 0.21 (silica gel, CH_2Cl_2/methanol (25:1)); ^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 1.34 (t, ^3J(H,H) = 7.1 Hz, 3H; -CH_2CH_3), 1.89 (m, 2H; β-CH_2), 3.29 (s, 12H; -OCH_3), 3.42 (m, 2H; γ-CH_2), 3.48–3.64 (2 m, 48H; -OCH_2CH_2O), 3.66–3.76 (m, 8H; -OCH(CH_2)$_2$), 4.06 (t, ^3J(H,H) = 5.7 Hz, 2H; α-CH_2), 4.30 (q, ^3J(H,H) = 7.1 Hz, 2H; -CH_2CH$_3$), 4.60 (quint, ^3J(H,H) = 4.9 Hz, 2H; -OCH(CH$_2$)$_2$), 5.04 (s, 2H; -CO_2CH_2Ar), 6.04 (t, ^3J = 6.0 Hz, 1H; -NH), 7.25–7.35 (m, 5H; -CH_2Ar), 7.38 ppm (s, 2H; Ar-*H*: gallate); ^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 14.1, 29.8, 38.4, 58.5, 60.9, 66.0, 70.2, 70.3, 70.4, 70.5, 70.6, 70.9, 71.9, 77.6, 107.8, 110.4, 125.6, 127.8, 128.0, 128.4, 137.3, 143.5, 151.9, 156.4, 165.7 ppm; MS (positive-ion mode FAB): *m/z* (%): 1145.0 (41) $[M+Na]^+$, 1124.5 (2), 1124.1 (8), 1123.3 (29), 1122.3 (49), 1121.4 (8) $[M+H]^+$, 1079.4 (76), 1078.0 (100), 1076.2 (27) $[M+H-OEt]^+$; elemental analysis calcd (%) for $C_{54}H_{91}NO_{23}$ (1121.60): C 57.79, H 8.17, N 1.25; found: C 57.32, H 7.87, N 1.26.

Ethyl 4-[3-(benzyloxy)propoxy]-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoate (8c): Compound **3c** (1.50 g, 4.3 mmol), dry K_2CO_3 (2.21 g, 16.0 mmol), and tosylate **7** (5.60 g, 10.3 mmol) were suspended in dry DMF (15 mL) under an N_2 atmosphere. The mixture was stirred for three days at 80 °C. After filtration, the solvent was removed under reduced pressure. The crude product was purified by column chromatography. The colorless oil was dissolved in benzene, filtered and lyophilized. Yield: 2.83 g (61 %) of a colorless oil.

R_f = 0.22 (silica gel, CH_2Cl_2/methanol (30:1)); ^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 1.35 (t, ^3J(H,H) = 7.1 Hz, 3H; -CH_2CH_3), 2.02 (m, 2H; β-CH_2), 3.31 (s, 12H; -OCH_3), 3.44–3.65 (2 m, 48H; -OCH_2CH_2O), 3.69 (hidden m, 2H; γ-CH_2), 3.70 (m, 8H; -OCH(CH_2)$_2$), 4.15 (t, ^3J(H,H) = 6.3 Hz, 2H; α-CH_2), 4.31 (q, ^3J(H,H) = 7.1 Hz, 2H; -CH_2CH$_3$), 4.51 (s, 2H; -CH_2OBn), 4.58 (quint, ^3J(H,H) = 4.9 Hz, 2H; -OCH(CH$_2$)$_2$), 7.32 (m, 1H; Ar-*H*: Bn), 7.31 (s, 2H; Ar-*H*: Bn), 7.33 (s, 2H; Ar-*H*: Bn), 7.39 ppm (s, 2H; Ar-*H*: gallate); ^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 14.19, 30.69, 58.58, 60.89, 67.51, 70.31, 70.37, 70.42, 70.49, 70.57, 70.67, 70.99, 71.90, 72.78, 77.89, 111.03, 125.29, 127.34, 127.48, 128.24, 138.99, 144.13, 151.88, 165.78 ppm; MS (positive-ion mode FAB): *m/z* (%): 1102.6 (36) $[M+Na]^+$, 1082.9 (5), 1081.2 (51), 1079.7 (52) $[M+H]^+$, 1036.0 (32), 1034.7 (43) $[M+H-OEt]^+$; elemental analysis calcd (%) for $C_{53}H_{90}O_{22}$ (1078.59): C 58.98, H 8.41; found: C 58.64, H 8.05.

Ethyl 4-(trifluoroacetato-3-amoniumpropoxy)-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoate (9): Compound **8a** (2.96 g, 2.72 mmol) was dissolved in CH_2Cl_2 (30 mL) and TFA (4 mL) were added at room temperature. The mixture was stirred for 12 h. The solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/methanol (10:1)). The slight yellowish oil was dissolved in benzene, filtered and lyophilized. Yield: 2.79 g (91 %) of a yellowish oil.

R_f = 0.13 (silica gel, CH_2Cl_2/methanol (10:1)); ^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 1.34 (t, ^3J(H,H) = 7.1 Hz, 3H; -CH_2CH_3), 2.04–2.11 (m, 2H; β-CH_2), 3.25 (m, 2H; γ-CH_2), 3.31 (s, 12H; -OCH_3), 3.45–3.68 (2 m, 48H; -OCH_2CH_2O), 3.76 (m, 8H; -OCH(CH_2)$_2$), 4.22 (t, ^3J(H,H) = 5.1 Hz, 2H; α-CH_2), 4.31 (q, ^3J(H,H) = 7.1 Hz, 2H; -CH_2CH$_3$), 4.67 (quint, ^3J(H,H) = 4.6 Hz, 2H; -OCH(CH$_2$)$_2$), 7.41 (s, 2H; Ar-*H*: gallate), 7.52 ppm (s, 3H; -NH_3); ^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 14.15, 26.91, 40.16, 61.20, 69.89, 70.20, 70.30, 70.34, 70.46, 70.88, 71.83, 73.39, 77.18, 109.69, 126.48, 141.92, 151.31, 165.52 ppm; MS (positive-ion mode FAB): *m/z* (%): 991.6 (3), 990.6 (17), 989.5 (53), 988.5 (100), 987.6 (4), 986.5 (7) $[M-TFA]^+$, 944.6 (4) $[M-TFA-OEt]^+$; elemental analysis calcd (%) for $C_{48}H_{86}F_3NO_{23}$ (1101.55): C 52.31, H 7.86, N 1.27; found: C 52.27, H 7.63, N 1.11.

4-(3-*tert*-Butoxycarbonylaminopropoxy)-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoic acid (10a): Compound **8a** (2.60 g, 2.4 mmol) was dissolved in ethanol (80 mL) and 1 M aqueous KOH (10 mL) added at room temperature. The mixture was stirred for 12 h. The reaction was quenched by the addition of 1 M aqueous HCl (pH 5). The solvent was removed under reduced pressure. The crude product was diluted with CH_2Cl_2 and filtered. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/methanol). The yellow oil was dissolved in benzene, filtered, and lyophilized. Yield: 2.49 g (98 %) of a yellow oil.

R_f = 0.19 (silica gel, CH_2Cl_2/methanol 10:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.34 (s, 9H; -C(CH_3)$_3$), 1.79 (m, 2H; β-CH_2), 3.28 (hidden m, 2H; γ-CH_2), 3.28 (s, 12H; -OCH_3), 3.43–3.60 (2 m, 48H; -OCH_2CH_2O), 3.65 (m, 8H; -OCH(CH_2)$_2$), 3.98 (t, ^3J(H,H) = 5.6 Hz, 2H; α-CH_2), 4.51 (quint, ^3J(H,H) = 5.0 Hz, 2H; -OCH(CH$_2$)$_2$), 5.60 (t, ^3J(H,H) = 5.4 Hz, 1H; -NH), 7.38 ppm (s, 2H; Ar-*H*: gallate); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 28.34, 29.69, 37.72, 58.68, 58.69, 70.18, 70.29, 70,38, 70.76, 70.78, 71.01, 71.02, 71.70, 77.56, 78.44, 111.08, 124.80, 143.69, 151.72, 155.98, 168.43 ppm; MS (positive-ion mode FAB): *m/z* (%): 1100.5 (1.0), 1099.5 (3.2), 1098.5 (6.1) $[M+K]^+$, 1084.0 (0.1), 1083.0 (0.2) $[M+Na]^+$, 1061.0 (0.1) $[M+H]^+$, 59.0 (100) $[C_3H_7O]^+$; elemental analysis calcd (%) for $C_{49}H_{89}NO_{23}$ (1059.58): C 55.51, H 8.46, N 1.32; found: C 55.71, H 8.47, N 1.02.

4-(3-Benzyloxycarbonylaminopropoxy)-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoic acid (10b): Compound **8b**

(1.10 g, 1.9 mmol) was dissolved in ethanol (40 mL) and 1 M aqueous KOH (5 mL) added at room temperature. The mixture was stirred for 12 h. The reaction was quenched by the addition of 1 M aqueous HCl (pH 5). The solvent was removed under reduced pressure. The crude product was diluted with CH_2Cl_2 and filtered. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/methanol (10:1)). The yellow oil was dissolved in benzene, filtered and lyophilized. Yield: 1.05 g (96%) of a yellow oil.

R_f = 0.18 (silica gel, CH_2Cl_2/methanol 10:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.88 (m, 2H; β-CH_2), 3.35 (s, 12H; -OCH_3), 3.43 (m, 2H; γ-CH_2), 3.47–3.62 (2 m, 48H; -OCH_2CH_2O), 3.66 (d, ^3J(H,H) = 4.8 Hz, 8H; -OCH(CH_2)$_2$), 4.05 (t, ^3J(H,H) = 5.5 Hz, 2H; α-CH_2), 4.55 (quint, ^3J(H,H) = 4.8 Hz, 2H; -OC*H*(CH_2)$_2$), 5.04 (s, 2H; CH_2OBn), 6.07 (t, ^3J(H,H) = 5.8 Hz, 1H; -NH), 7.22–7.34 (m, 5H; Ar-*H*: Bn), 7.44 ppm (s, 2H; Ar-*H*: gallate); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 29.28, 30.00, 58.42, 67.87, 69.81, 69.92, 70.02, 70.09, 70.48, 70.69, 71.42, 77.23, 110.66, 124.63, 127.50, 127.73, 127.96, 136.43, 143.32, 151.43, 156.23, 168.09 ppm; MS (positive-ion mode FAB): *m/z* (%): 1118.6 (0.8), 1117.6 (2.4), 1116.6 (4.0) [*M*+Na]$^+$, 1051.4 (5.5), 1050.0 (8.8) [*M*−CO_2+H], 1048.1 [*M*−CO_2], 195.2 (1.1), 194.2 (1.0), 193.2 (6.4), 192.2 (46.9), 191.2 (1.2) [$C_{11}H_{14}NO_2$]$^+$, 148.9 (1.3), 147.9 (2.1), 146.9 (15.6) [$C_7H_{15}O_3$]$^+$, 92.2 (6.5), 91.2 (77.5), 90.2 (2.4) [C_7H_7]$^+$, 59.3 (3.5), 59.1 (100.0) [C_3H_7O]$^+$; elemental analysis calcd (%) for $C_{52}H_{87}NO_{23}$ (1093.57): C 57.08, H 8.01, N 1.28; found: C 56.78, H 7.98, N 1.25.

4-[3-(Benzyloxy)propoxy]-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]-ethoxy}propan-2-yloxy)benzoic acid (10c): Compound **8c** (2.00 g, 1.85 mmol) was dissolved in ethanol (80 mL) and 1 M aqueous KOH (8 mL) added at room temperature. The mixture was stirred for 12 h. The reaction was quenched by the addition of 1 M aqueous HCl (pH 5). The solvent was removed under reduced pressure. The crude product was diluted with CH_2Cl_2 and filtered. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/methanol (10:1)). The colorless oil was dissolved in benzene, filtered and lyophilized. Yield: 1.93 g (99%) of a colorless oil.

R_f = 0.25 (silica gel, CH_2Cl_2/methanol (10:1)); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.98 (m, 2H; β-CH_2), 3.34 (s, 12H; -OCH_3), 3.49–3.61 (2 m, 48H; -OCH_2CH_2O), 3.60 (m, 2H; γ-CH_2), 3.66 (m, 8H; -OCH-(CH_2)$_2$), 4.11 (t, ^3J(H,H) = 6.3 Hz, 2H; α-CH_2), 4.47 (s, 2H; -CH_2OBn), 4.51 (quint, ^3J(H,H) = 5.0 Hz, 2H; -OC*H*(CH_2)$_2$), 7.22 (m, 1H; Ar-*H*: Bn), 7.27 (br s, 1H; Ar-*H*: Bn), 7.28 (br s, 1H; Ar-*H*: Bn), 7.45 ppm (s, 2H; Ar-*H*: gallate); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 30.18, 58.37, 66.96, 69.88, 69.98, 70.05, 70.07, 70.49, 71.37, 72.38, 77.57, 111.46, 124.23, 126.93, 126.98, 127.79, 138.13, 144.05, 151.34, 168.29 ppm; MS (positive-ion mode FAB): *m/z* (%): 1129.2 (12), 1127.4 (34), 1126.4 (14) [*M*−H+2K]$^+$,1089.5 (50), 1088.5 (100), 1087.4 (7), 1086.3 (12), 1073.3 (18) [*M*−H+2K]$^+$, 1073.3 (18) [*M*+Na]$^+$; elemental analysis calcd (%) for $C_{51}H_{86}O_{22}$ (1050.56): C 58.27, H 8.25; found: C 58.00, H 8.28.

Ethyl 4-[3-(2,3-bis-*tert*-butoxycarbonylaminopropionylamido)propoxy]-3,5-bis (1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)-benzoate (12): Acid **11** (0.80 g, 2.62 mmol) was dissolved in dry DMF (5 mL), dry TEA (0.8 mL) was added, and the mixture was cooled to −20 °C. A solution of TBTU (0.93 g, 2.88 mmol) in dry DMF (6.5 mL) was added. The mixture was stirred for 2 h at −20 °C and then allowed to warm to room temperature. The esterification was monitored with TLC. After complete conversion, the mixture was cooled to −40 °C, and a solution of **9** (1.93 g, 1.74 mmol) and dry TEA (0.8 mL) in dry DMF (2 mL) was added. The reaction mixture was stirred for 1 h at −40 °C and then allowed to warm to room temperature. The solvents were evaporated. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/methanol 30:1 increasing to 10:1). The yellowish oil was dissolved in benzene, filtered and lyophilized. Yield: 2.08 g (94%) of a yellowish oil.

R_f = 0.21 (silica gel, CH_2Cl_2/methanol (20:1)); ^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 1.30 and 1.39 (2 s, 18H; -C(CH_3)$_3$), 1.35 (t, ^3J(H,H) = 7.1 Hz, 3H; -CH_2CH_3), 1.87 (m, 2H; β-CH_2), 3.31 (s, 12H; -OCH_3), 3.41 (m, 4H; α- and γ-CH_2), 3.45–3.49 and 3.53–3.67 (2 m, 48H; -OCH_2CH_2O), 3.74 (m, 8H; -OCH(CH_2)$_2$), 4.03 (m, 1H; -CH_2NHBoc), 4.11 (m, 2H; -CH_2NHBoc and -C*H*NHBoc), 4.31 (q, ^3J(H,H) = 7.1 Hz, 2H; -CH_2CH_3), 4.61 (quint, ^3J(H,H) = 4.9 Hz, 2H; -OC*H*(CH_2)$_2$), 5.44 (br s, 1H; -CH_2N*H*Boc), 5.93 (br s, 1H; -CHN*H*Boc), 7.30 (br s, 1H; -CH_2N*H*COAr), 7.39 ppm (s, 2H; Ar-*H*: gallate); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.13, 27.94, 28.08, 29.20, 37.20, 42.55, 54.55, 58.68, 60.73, 69.88, 70.02, 70.19, 70.20, 70.27, 70.29, 70.58, 70.61, 71.62, 78.90, 79.17, 110.37, 125.24, 143.39, 151.63, 155.55, 156.16, 165.59, 170.09 ppm; MS (positive-ion mode FAB): *m/z* (%): 1297.4 (0.5) [*M*+Na]$^+$, 1276.4 (0.3), 1275.7 (0.4), 1275.2 (0.6) [*M*+H]$^+$, 1176.8 (0.2), 1174.9 (14.3), 1173.2 (0.5), 1172.3 (1.3) [*M*−$C_5H_9O_2$]$^+$, 1076.4 (0.2), 1076.1 (0.4), 1074.4 (7.8), 1073.0 (1.1), 1072.1 (2.45) [*M*−2*$C_5H_9O_2$]$^+$, 102.9 (38.2) [$C_5H_{11}O_2$]$^+$, 57.1 (100) [C_4H_9]$^+$; elemental analysis calcd (%) for $C_{59}H_{107}N_3O_{26}$ (1273.71): C 55.60, H 8.46, N 3.30; found: C 55.82, H 8.33, N 3.58.

4-[3-(2,3-Bis-*tert*-butoxycarbonylaminopropionylamido)propoxy]-3,5-bis(1,3-bis {2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoic acid (13): Compound **12** (0.79 g, 0.62 mmol) was dissolved in ethanol (20 mL) and 1 M aqueous KOH (2.5 mL) was added at room temperature. The mixture was stirred for 12 h and quenched by the addition of 1 M aqueous HCl (pH 5). The solvent was removed under reduced pressure. The crude product was diluted with CH_2Cl_2 and filtered. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/methanol (10:1)). The yellowish oil was dissolved in benzene, filtered and lyophilized. Yield: 0.75 g (97%) of a yellowish oil.

R_f = 0.17 (silica gel, CH_2Cl_2/methanol (10:1)); ^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 1.30 and 1.39 (2 s, 18H; -C(CH_3)$_3$), 1.89 (m, 2H; β-CH_2), 3.33 (s, 12H; -OCH_3), 3.43 (m, 2H; α and γ-CH_2), 3.48–3.52 and 3.54–3.67 (2 m, 48H; -OCH_2CH_2O), 3.74 (m, 8H; -OCH(CH_2)$_2$), 4.05 (m, 2H; -CH_2NHBoc), 4.14 (m, 3H; -C*H*NHBoc and -CH_2NHBoc), 4.62 (quint, ^3J(H,H) = 4.9 Hz, 2H; -OC*H*(CH_2)$_2$), 5.46 (br s, 1H; -CH_2N*H*Boc), 5.98 (br s, 1H; -CHN*H*Boc), 7.37 (br s, 1H; -CH_2N*H*), 7.46 ppm (s, 2H; Ar-*H*: gallate); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 27.79, 27.94, 29.03, 37.15, 42.33, 54.62, 58.47, 69.77, 69.91, 69.96, 70.03, 70.12, 70.45, 70.49, 71.46, 77.12, 78.76, 78.99, 110.61, 124.96, 143.30, 151.50, 155.34, 156.05, 168.00, 170.25 ppm; MS (positive-ion mode FAB): *m/z* (%): 1271.7 (5), 1270.7 (12), 1269.7 (20) [*M*+Na]$^+$, 1248.4 (7), 1247.3 (11) [*M*+H]$^+$, 1147.3 (2), 1146.4 (9), 1145.4 (28), 1144.4 (44), 1143.3 (4), 1142.4 (7) [*M*−$C_5H_9O_2$]$^+$, 1046.4 (4), 1045.3 (13), 1044.3 (24), 1043.3 (6), 1042.3 (11) [*M*−2*$C_5H_9O_2$]$^+$, 344.3 (100) [$C_{16}H_{30}$ N_3O_5]$^+$; elemental analysis calcd (%) for $C_{57}H_{103}N_3O_{26}$ (1245.68): C 54.93, H 8.33, N 3.37; found: C 55.16, H 8.20, N 3.54.

Ethyl 4-[3-(5-dimethylamino-naphthalene-1-sulfonylamino)propoxy]-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benz-oate (15): Compound **9** (0.85 g, 0.77 mmol) and dry triethylamine (1.4 mL) were dissolved in CH_2Cl_2 (10 mL) and added dropwise at room temperature to a stirred solution of dansyl chloride **14** (0.30 g, 1.11 mmol) in dry CH_2Cl_2 (25 mL). The mixture was stirred for 2 h. The solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/methanol (10:1)). The green oil was dissolved in benzene, filtered and lyophilized. Yield: 0.93 g (99.3%) of a green oil.

R_f = 0.24 (silica gel, CH_2Cl_2/methanol (20:1)); ^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 1.36 (t, ^3J = 7.1 Hz, 3H; -CH_2CH_3), 1.79 (tt, ^3J(H,H) = 5.6 Hz, ^3J(H,H) = 5.8 Hz, 2H; β-CH_2), 2.86 (s, 6H; -N(CH_3)$_2$), 3.22 (dt, ^3J(H,H) = 5.6 Hz, ^3J(H,H) = 5.8 Hz, 2H; γ-CH_2), 3.31 (s, 12H; -OCH_3), 3.45–3.59 (2 m, 48H; -OCH_2CH_2O), 3.67 (d, ^3J(H,H) = 5.0 Hz, 8H; -OCH(CH_2)$_2$), 3.99 (t, ^3J(H,H) = 5.6 Hz, 2H; α-CH_2), 4.32 (q, ^3J = 7.1 Hz, 2H; -CH_2CH_3), 4.56 (quint, ^3J(H,H) = 5.0 Hz, 2H; -OC*H*(CH_2)$_2$), 6.23 (t, ^3J(H,H) = 5.6 Hz, 1H; -NH), 7.15 (d, ^3J(H,H) = 7.5 Hz, 1H; Ar-*H*: C6-dansyl), 7.38 (s, 2H; Ar-*H*: gallate), 7.49 (dd, ^3J(H,H) = 7.5 Hz, ^3J(H,H) = 8.5 Hz, 1H; Ar-*H*: C7-dansyl), 7.54 (dd, ^3J(H,H) = 7.3 Hz, ^3J(H,H) = 8.5 Hz, 1H; Ar-*H*: C3-dansyl), 8.22 (d, ^3J(H,H) = 7.3 Hz, 1H; Ar-*H*: C4-dansyl), 8.32 (d, ^3J(H,H) = 8.5 Hz, 1H; Ar-*H*: C8-dansyl), 8.52 ppm (d, ^3J(H,H) = 8.5 Hz, 1H; Ar-*H*: C2-dansyl); ^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 14.49, 30.49, 41.19, 45.50, 58.87, 61.26, 70.27, 70.38, 70.45, 70.50, 70.56, 70.92, 71.08, 71.93, 77.79, 110.61, 115.07, 119.30, 123.23, 125.60, 127.96, 129.01, 129.75, 129.95, 130.00, 136.04, 143.49, 151.83, 151.94, 165.78 ppm; MS (positive-ion mode FAB): *m/z* (%): 1224.0 (13), 1223.0 (46), 1221.7 (100), 1220.7 (53), 1219.8 (10) [*M*H]$^+$, 1175.4 (4) [*M*H−OEt]$^+$, 988.2 (1) [*M*H−$C_{12}H_{12}NO_2S$]$^+$, 294.3 (7), 293.3 (13), 292.3 (62), 291.3 (10), 290.4

(5) $[C_{15}H_{19}N_2O_2S+H]^{+\cdot}$; elemental analysis calcd (%) for $C_{58}H_{96}N_2O_{23}S$ (1220.61): C 57.03, H 7.92, N 2.29; found: C 56.78, H 7.63, N 2.26.

4-[3-(5-Dimethylamino-naphthalene-1-sulfonylamino)propoxy]-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoic acid (16): Compound **15** (0.74 g, 0.6 mmol) was dissolved in ethanol (20 mL) and 1 M aqueous KOH (2.5 mL) added at room temperature. The mixture was stirred for 12 h. The reaction was quenched by the addition of 1 M aqueous HCl (pH 5). The solvent was removed under reduced pressure. The crude product was diluted with CH_2Cl_2 and filtered. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/methanol (10:1)). The green oil was dissolved in benzene, filtered and lyophilized. Yield: 0.70 g (96.8%) of a green oil.

^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 1.79 (m, 2H; β-CH_2), 2.86 (s, 6H; -N-$(CH_3)_2$), 3.22 (m, 2H; γ-CH_2), 3.33 (s, 12H; -OCH_3), 3.49–3.59 (2 m, 48H; -OCH_2CH_2O), 3.68 (d, ^3J(H,C) = 5.0 Hz, 8H; -OCH(CH_2)$_2$), 4.01 (t, ^3J(H,H) = 5.0 Hz, 2H; α-CH_2), 4.57 (quint, ^3J(H,H) = 5.0 Hz, 2H; -OC*H*-$(CH_2)_2$), 6.28 (t, ^3J(H,H) = 6.0 Hz, 1H; -NH), 7.16 (d, ^3J(H,H) = 7.6 Hz, 1H; Ar-*H*: C6-dansyl), 7.45 (s, 2H; Ar-*H*: gallate), 7.49 (m, 1H; Ar-*H*: C7-dansyl), 7.54 (m, 1H; Ar-*H*: C3-dansyl), 8.22 (d, ^3J(H,H) = 7.3 Hz, 1H; Ar-*H*: C4-dansyl), 8.31 (d, ^3J(H,H) = 8.6 Hz, 1H; Ar-*H*: C8-dansyl), 8.52 ppm (d, ^3J(H,H) = 8.5 Hz 1H; Ar-*H*: C2-dansyl); ^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 30.20, 40.93, 45.24, 58.59, 70.28, 70.41, 70.42, 70.50, 70.55, 70.95, 71.92, 71.93, 77.94, 111.17, 115.08, 119.28, 123.23, 125.18, 127.96, 129.01, 129.74, 129.94, 130.01, 135.99, 143.57, 151.86, 151.92, 168.10 ppm; MS (positive-ion mode FAB): *m/z* (%): 1196.1 (7), 1194.7 (9), 1193.5 (10) $[M+H]^+$; elemental analysis calcd (%) for $C_{56}H_{92}N_2O_{23}S$ (1192.58): C 56.36, H 7.77, N 2.35; found: C 56.06, H 7.20, N 2.23.

4,4-Di(*tert*-butoxycarbonyl)butanoic acid (20a): Di-*tert*-butyl malonate **17a** (4.00 g, 18.5 mmol), benzyl acrylate **18a** (3.00 g, 18.5 mmol), dry K_2CO_3 (2.56 g, 18.5 mmol), and Bu_4NI (0.01 g) were suspended in dry benzene (10 mL) under N_2. The mixture was refluxed for one day. After filtration, the organic phase was washed with water and brine. The organic phase was dried over $MgSO_4$, filtered and the solvent evaporated. The crude product was filtered through silica gel with hexane/ethyl acetate (5:1) to yield a mixture of mono- and bisalkylated malonate **19a** (6.60 g). The mixture was dissolved in methanol (20 mL), and Pd/C (0.7 g) was added. The mixture was stirred for 1 h in a hydrogen atmosphere. The reaction was monitored with TLC. After complete deprotection, the mixture was filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/methanol (20:1)). Yield: 3.47 g (65%) of a colorless solid.

R_f = 0.24 (silica gel, CH_2Cl_2/methanol (20:1)); ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 1.51 (s, 18H; -C(CH_3)$_3$), 2.07 (m, 2H; β-CH_2), 2.39 (t, ^3J(H,H) = 7.3 Hz, 2H; α-CH_2), 3.30 ppm (t, ^3J(H,H) = 7.6 Hz, 1H; -CH); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 24.94, 28.17, 32.09, 54.05, 82.82, 170.04, 176.22 ppm; MS (positive-ion mode FAB): *m/z* (%): 288.9 (13.16) $[M]^+$, 57.0 (69.67) $[C_4H_9]^+$; elemental analysis calcd (%) for $C_{14}H_{24}O_6$ (288.16): C 58.32, H 8.39; found: C 58.18, H 8.32.

4,4-Di(benzyloxycarbonyl)butanoic acid (20b): Dibenzyl malonate **17b** (14.20 g, 49.9 mmol), *tert*-butyl acrylate **18b** (6.39 g, 49.9 mmol), dry K_2CO_3 (6.91 g, 49.9 mmol), and Bu_4NI (0.03 g) were suspended in dry benzene (30 mL) under N_2. The mixture was refluxed for one day. After filtration, the organic phase was washed with water and brine. The organic phase was dried over $MgSO_4$, filtered, and the solvent evaporated. The crude product was filtered through silica gel with hexane/ethyl acetate (5:1) to yield a mixture of mono- and bisalkylated malonate **19b** (19.2 g). The mixture was dissolved in CH_2Cl_2 (100 mL) and TFA (10 mL) was added. The mixture was stirred at room temperature and was monitored by TLC. After complete deprotection, the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/methanol (20:1)). Yield: 11.9 g (67%) of a colorless solid.

R_f = 0.21 (silica gel, CH_2Cl_2/methanol 20:1); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.24 (m, 2H; β-CH_2), 2.44 (t, ^3J(H,H) = 7.4 Hz, 2H; α-CH_2), 3.58 (t, ^3J(H,H) = 7.4 Hz, 1H; -CH), 5.14 (s, 4H; -CH_2Ar), 7.30 (m, 10H; Ar-H), 11.04 ppm (br s, 1H; -COOH); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 23.38, 30.98, 50.63, 67.28, 128.16, 128.37, 128.55, 135.18, 168.52, 178.24 ppm; MS (EI): *m/z* (%): 357.9 (0.03), 356.9 (0.13) $[M+H]^+$, 266.9(0.17), 265.9 (1.11), 264.9 (8.34) $[M-C_7H_7]^+$, 108.0 (15.90), 107.1 (100.00) $[C_7H_7O]^+$; elemental analysis calcd (%) for $C_{20}H_{20}O_6$ (356.13): C 67.41, H 5.66; found: C 67.34, H 5.60.

Allyl-4-(3-*tert*-butoxycarbonylamino-propoxy)-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoate (21): Compound **10a** (2.50 g, 2.35 mmol), K_2CO_3 (0.33 g, 2.35 mmol), and tetrabutylammonium iodide (0.02 g) were suspended in dry DMF (20 mL) and stirred for 1 h at room temperature. 3-Bromopropene (0.86 g, 7 mmol) was added. The mixture was stirred for 12 h at room temperature. After filtration, the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/methanol (20:1)). The yellow oil was dissolved in benzene, filtered, and lyophilized. Yield: 2.55 g (98.5%) of a yellow oil.

R_f = 0.24 (silica gel; CH_2Cl_2/methanol (25:1)); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.43 (s, 9H; -C(CH_3)$_3$), 1.88 (m, 2H; β-CH_2), 3.36 (s, 12H; -OCH_3), 3.36 (m, 2H; γ-CH_2), 3.51–3.69 (2 m, 48H; -OCH_2CH_2O), 3.70–3.80 (m, 8H; -OCH(CH_2)$_2$), 4.07 (t, ^3J(H,H) = 5.6 Hz, 2H; α-CH_2), 4.61 (quint, ^3J(H,H) = 4.9 Hz, 2H; -OC*H*(CH_2)$_2$), 4.79 (ddd, ^3J(H,H) = 5.7 Hz, ^4J(H,H) = 1.5 Hz, ^4J(H,H) = 1.5 Hz, 2H; -CO_2CH_2CHCH$_2$), 5.29 (ddt, ^2J(H,H) = 1.5 Hz, Z-^3J(H,H) = 10.1 Hz, ^4J(H,H) = 1.5 Hz, 1H; -$CO_2CH_2CHCH(Z)$H), 5.39 (ddt, ^2J(H,H) = 1.5 Hz, E-^3J(H,H) = 16.9 Hz, ^4J(H,H) = 1.5 Hz, 1H; -$CO_2CH_2CHCH(E)$H), 5.70 (t, ^3J = 5.8 Hz, 1H; -NH), 6.03 (ddt, Z-^3J(H,H) = 10.1 Hz, E-^3J(H,H) = 16.9 Hz, ^3J(H,H) = 5.7 Hz, 1H; -$CO_2CH_2CHCH(E)$H), 7.42 ppm (s, 2H; Ar-*H*: gallate); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 28.3, 29.6, 37.6, 58.7, 65.3, 70.0, 70.2, 70.2, 70.3, 70.3, 70.7, 70.9, 71.6, 77.4, 78.3, 110.5, 117.9, 124.7, 132.0, 143.6, 151.6, 155.8, 165.2 ppm; MS (positive-ion mode FAB, 4 kV): *m/z* (%): 1123.3 (4), 1122.3 (5) $[M+Na]^+$, 1099.9 (3) $[M+H]^+$, 1002.8 (5), 1001.8 (18), 1000.8 (53), 999.8 (100), 998.8 (18), 997.9 (31) $[M-C_5H_{10}O_2]^+$; elemental analysis calcd (%) for $C_{52}H_{93}NO_{23}$ (1100.29): C 56.76, H 8.52, N 1.27; found: C 56.68, H 8.31, N 1.16.

Allyl 4-(3-trifluoroacetatoammoniumpropoxy)-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoate (22): Compound **21** (0.59 g, 0.54 mmol) was dissolved in CH_2Cl_2 (5 mL), and TFA (0.85 mL) was added at room temperature. The mixture was stirred for 12 h. The solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/methanol (10:1)). The slight yellowish oil was dissolved in benzene, filtered, and lyophilized. Yield: 0.60 g (98%) of a yellowish oil.

R_f = 0.15 (silica gel, CH_2Cl_2/methanol (10:1)); ^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 2.06 (m, 2H; β-CH_2), 3.27 (hidden m, 2H; γ-CH_2), 3.30 (s, 12H; -OCH_3), 3.46–3.48 and 3.53–3.65 (2 m, 48H; -OCH_2CH_2O), 3.75 (m, 8H; -OCH(CH_2)$_2$), 4.22 (t, ^3J(H,H) = 5.3 Hz, 2H; α-CH_2), 4.65 (quint, ^3J(H,H) = 4.6 Hz, 2H; -OC*H*(CH_2)$_2$), 4.76 (ddd, ^3J(H,H) = 5.5 Hz, ^4J(H,H) = 1.5 Hz, ^4J(H,H) = 1.5 Hz, 2H;-CO_2CH_2CHCH$_2$), 5.25 (ddt, ^2J(H,H) = 1.5 Hz, Z-^3J(H,H) = 10.4 Hz, ^4J(H,H) = 1.5 Hz, 1H; -$CO_2CH_2CHCH(Z)$H), 5.36 (ddt, ^2J(H,H) = 1.5 Hz, E-^3J(H,H) = 17.2 Hz, ^4J(H,H) = 1.5 Hz, 1H; -$CO_2CH_2CHCH(E)$H), 6.01 (ddt, Z-^3J(H,H) = 10.4 Hz, E-^3J(H,H) = 17.2 Hz, ^3J(H,H) = 5.5 Hz, 1H; -$CO_2CH_2CHCH(E)$H), 7.44 (s, 2H; Ar-*H*: gallate), 7.53 ppm (br s, 3H; -NH_3); ^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 26.92, 39.97, 58.46, 65.61, 69.98, 70.17, 70.27, 70.29, 70.42, 70.85, 71.79, 73.20, 77.34, 109.82, 117.86, 125.95, 132.40, 142.14, 151.39, 165.14 ppm; MS (positive-ion mode FAB): *m/z* (%): 1002.7 (23), 1001.5 (56), 1000.5 (100) $[M-TFA^-]^+$, 635.3 (2), 634.3 (7), 633.3 (8) $[M-TFA^-C_{17}H_{35}O_8]^+$.

Allyl 4-{3-[di-*tert*-butyl 2-(2-carbamoylethyl)malonyl]propoxy}-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoate (23): Compound **20a** (0.551 g, 1.73 mmol) was dissolved in dry DMF (3 mL). Dry TEA (0.6 mL) was added and the mixture was cooled to −20 °C. A solution of TBTU (0.640 g, 1.99 mmol) in dry DMF (5 mL) was added. The mixture was stirred for 2 h at −20 °C and then allowed to warm to room temperature. The esterification was monitored by TLC. After complete conversion, the mixture was cooled to −40 °C, and a solution of **22** (0.97 g, 0.87 mmol) and dry TEA (0.6 mL) in dry DMF (2 mL) was added. The reaction mixture was stirred for 1 h at −40 °C and then allowed to warm to room temperature. The solvents were evaporated. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/methanol 30:1 increasing to 10:1). The yellowish oil was dissolved

in benzene, filtered, and lyophilized. Yield: 0.94 g (85%) of a yellowish oil.

R_f = 0.27 (silica gel, CH_2Cl_2/methanol (20:1)); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.26 (s, 18H; -OC(CH_3)$_3$), 1.74 (m, 2H; β-CH_2), 1.93 (m, 2H; β′-CH_2), 2.05 (m, 2H; α′-CH_2), 3.03 (t, ^3J(H,H) = 7.4 Hz, 1H; γ′-CH), 3.19 (s, 12H; -OCH_3), 3.32 (m, 2H; γ-CH_2), 3.34–3.49 (2 m, 48H; -OCH_2CH_2O), 3.57 (m, 8H; -OCH(CH_2)$_2$), 3.92 (t, ^3J(H,H) = 5.6 Hz, 2H; α-CH_2), 4.43 (quint, ^3J(H,H) = 5.0 Hz, 2H; -OCH(CH_2)$_2$), 4.62 (br d, ^3J-(H,H) = 5.6 Hz, 2H; -CO_2CH_2CHCH_2), 5.11 (br d, Z-^3J(H,H) = 10.4 Hz, 1H; -$CO_2CH_2CHCH(Z)$H), 5.22 (br d, E-^3J(H,H) = 17.1 Hz, 1H; -$CO_2CH_2CHCH(E)$H), 5.85 (m, 1H; -$CO_2CH_2CHCH(E)$H), 6.65 (t, ^3J-(H,H) = 5.7 Hz, 1H; -NH), 7.26 ppm (s, 2H; Ar-H: gallate); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 24.05, 27.46, 29.16, 33.08, 36.72, 52.71, 58.52, 65.13, 69.86, 70.05, 70.09, 70.15, 70.16, 70.52, 71.22, 71.48, 77.37, 80.79, 110.61, 117.79, 124.63, 131.88, 143.53, 151.53, 165.06, 168.02, 171.37 ppm; MS (positive-ion mode FAB; CsI): *m/z* (%): 1403.8 (0.1), 1402.8 (0.2), 1402.4 (0.3) 1401.9 (0.1) $[M+Cs]^+$, 1292.9 (0.5), 1292.7 (0.8), 1291.4 (0.1) $[M+Cs]^+$, 1271.5 (0.5), 1270.6 (0.7), 1270.2 (0.3) $[M+H]^+$, 57.0 (100) $[C_4H_9]^+$.

4-{3-[Di-*tert*-butyl 2-(2-carbamoylethyl)malonyl]propoxy}-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoic acid (24): Compound **23** (840 mg, 0.66 mmol) was dissolved in CH_2Cl_2 (10 mL), and [Pd(PPh_3)$_4$] (40 mg, 4 mol%) was added. Then a solution of *p*-toluenesulfonic acid hydrate (130 mg, 0.72 mmol) in methanol (1 mL) was added. The reaction was monitored with TLC and stopped after 35 min. The solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/methanol (10:1)). The colorless oil was dissolved in benzene, filtered and lyophilized. Yield: 0.76 g (94%) of a colorless oil.

R_f = 0.24 (silica gel, CH_2Cl_2/methanol (10:1)); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.40 (s, 18H; -OC(CH_3)$_3$), 1.87 (m, 2H; β-CH_2), 2.07 (m, 2H; β′-CH_2), 2.19 (m, 2H; α′-CH_2), 3.17 (t, ^3J(H,H) = 7.4 Hz, 1H; γ′-CH), 3.36 (s, 12H; -OCH_3), 3.46 (m, 2H; γ-CH_2), 3.50–3.65 (2 m, 48H; -OCH_2CH_2O), 3.70 (m, 8H; -OCH(CH_2)$_2$), 4.05 (t, ^3J = 5.6 Hz, 2H; α-CH_2), 4.56 (quint, ^3J(H,H) = 4.9 Hz, 2H; -OCH(CH_2)$_2$), 6.74 (t, ^3J(H,H) = 5.8 Hz, 1H; -NH), 7.48 ppm (s, 2H; Ar-H: gallate); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 24.42, 27.80, 29.50, 33.48, 37.10, 53.08, 58.81, 70.28, 70.38, 70.41, 70.49, 70.50, 70.90, 71.56, 71.82, 77.77, 81.22, 111.37, 137.08, 143.62, 151.83, 168.40 (2), 171.84 ppm; MS (positive-ion mode FAB): *m/z* (%): 1269.4 (20.5), 1268.9 (17.1), 1268.2 (44.9), 1267.6 (23.5) $[M+K]^+$, 1254.0 (17.6), 1253.5 (61.1), 1252.7 (84.5), 1251.9 (100) $[M+Na]^+$, 1231.8 (7.4), 1231.5 (13.6), 1231.2 (22.6), 1230.8 (62.0), 1229.9 (31.5) $[M+H]^+$.

Allyl 4-{3-[dibenzyl 2-(2-carbamoylethyl)malonyl]propoxy}-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoate (25): Compound **20b** (0.619 g, 1.73 mmol) was dissolved in dry DMF (3 mL). Dry TEA (0.6 mL) was added and the mixture was cooled to −20 °C. A solution of TBTU (0.640 g, 1.99 mmol) in dry DMF (5 mL) was added. The mixture was stirred for 2 h at −20 °C and then allowed to warm to room temperature. The esterification was monitored with TLC. After complete conversion, the mixture was cooled to −40 °C, and a solution of **22** (0.97 g, 0.87 mmol) and dry TEA (0.6 mL) in dry DMF (2 mL) was added. The reaction mixture was stirred for 1 h at −40 °C and then allowed to warm to room temperature. The solvents were evaporated. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/methanol 30:1 increasing to 10:1). The yellowish oil was dissolved in benzene, filtered, and lyophilized. Yield: 1.00 g (86%) of a yellowish oil.

R_f = 0.23 (silica gel, CH_2Cl_2/methanol (20:1)); ^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 1.88 (m, 2H; β-CH_2), 2.21 (m, 4H; α′ and β′-CH_2), 3.31 (s, 12H; -OCH_3), 3.45 (m, 2H; γ-CH_2), 3.45–3.66 (2 m, 48H; -OCH_2CH_2O), 3.61 (m, 1H; γ′-CH), 3.74 (m, 8H; -OCH(CH_2)$_2$), 4.09 (t, ^3J(H,H) = 5.6 Hz, 2H; α-CH_2), 4.61 (quint, ^3J(H,H) = 4.9 Hz, 2H; -OCH(CH_2)$_2$), 4.78 (ddd, ^3J(H,H) = 5.6 Hz, ^4J(H,H) = 1.3 Hz, ^4J(H,H) = 1.3 Hz, 2H; -CO_2CH_2CHCH_2), 5.11 (m, 4H; -OCH_2Ar), 5.27 (dpq, $^{2/4}J$(H,H) = 1.3 Hz, Z-^3J(H,H) = 10.5 Hz, 1H; -$CO_2CH_2CHCH(Z)$H), 5.39 (dpq, $^{2/4}J$(H,H) = 1.6 Hz, E-^3J(H,H) = 17.2 Hz, 1H; -$CO_2CH_2CHCH(E)$H), 6.04 (m, 1H; -$CO_2CH_2CHCH(E)$H), 6.67 (t, ^3J(H,H) = 5.7 Hz, 1H; -NH), 7.25–7.35 (m, 10H; Ar-Bn), 7.44 ppm (s, 2H; Ar-H: gallate); ^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 24.50, 29.68, 33.01, 37.03, 51.06, 58.55, 65.48, 66.92, 70.24, 70.34, 70.40, 70.46, 70.53, 70.93, 71.67, 71.87, 77.72, 110.72, 117.74, 125.15, 127.98, 128.20, 128.47, 132.54, 135.63, 143.84, 151.98, 165.38, 168.80, 171.08 ppm; MS (positive-ion mode FAB): *m/z* (%): 1340.8 (4), 1339.8 (9), 1338.8 (12). 1337.8 (2), 1336.8 (2) $[M+H]^+$, 400.3 (1), 399.3(5), 398.3 (25), 397.3 (100), 396.3 (1), 395.3 (1) $[M-C_{20}H_{19}O_5+H]^+$; elemental analysis calcd (%) for $C_{67}H_{103}NO_{26}$ (1337.68): C 60.12, H 7.76, N 1.05; found: C 59.96, H 7.39, N 0.97.

4-{3-[Dibenzyl-2-(2-carbamoylethyl)malonyl]propoxy}-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoic acid (26): Compound **25** (434 mg, 0.32 mmol) was dissolved in CH_2Cl_2 (20 mL) and [Pd(PPh_3)$_4$] (19 mg, 5 mol%) was added. Then a solution of *p*-toluenesulfonic acid hydrate (64 mg, 0.35 mmol) in methanol (0.5 mL) was added. The reaction was monitored with TLC and stopped after 30 min. The solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/methanol 20:1 increasing to 10:1). The colorless oil was dissolved in benzene, filtered and lyophilized. Yield: 0.40 g (96%) of a colorless oil.

R_f = 0.19 (silica gel, CH_2Cl_2/methanol 10:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.86 (m, 2H; β-CH_2), 2.21 (m, 4H; α′ and β′-CH_2), 3.36 (s, 12H; -OCH_3), 3.45 (m, 2H; γ-CH_2), 3.47–3.64 (2 m, 48H; -OCH_2CH_2O), 3.57 (m, 1H; γ′-CH), 3.69 (m, 8H; -OCH(CH_2)$_2$), 4.04 (t, ^3J(H,H) = 5.7 Hz, 2H; α-CH_2), 4.56 (quint, ^3J(H,H) = 5.0 Hz, 2H; -OCH(CH_2)$_2$), 5.08 (m, 4H; -OCH_2Ar), 6.77 (t, ^3J(H,H) = 5.8 Hz, 1H; -NH), 7.21–7.29 (m, 10H; Ar-Bn), 7.49 ppm (s, 2H; Ar-H: gallate); ^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 24.28, 29.29, 30.92, 36.79, 50.87, 58.55, 66.95, 70.03, 70.05, 70.14, 70.19, 70.22, 70.61, 71.36, 71.56, 77.38, 110.88, 127.83, 128.09, 128.29, 135.03, 143.20, 151.52, 168.70 (2), 171.94 ppm; MS (positive-ion mode FAB): *m/z* (%): 1323.8 (10), 1322.7 (30), 1321.7 (65), 1320.6 (100) $[M+Na]^+$, 1302.6 (1), 1301.6 (5), 1300.6 (17), 1299.6 (43), 1298.7 (64), 1297.8 (6), 1296.8 (8) $[M+H]^+$.

1,3,5-Tris-{[4-(3-*tert*-butoxycarbonylamino)propoxy][3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzamidopropyl]}benzene (28): Compound **10a** (0.42 g, 0.40 mmol) was dissolved in dry CH_2Cl_2 (10 mL). The solution was cooled to −20 °C and HOBt (0.07 g, 0.48 mmol) and EDC (0.10 g, 0.52 mmol) were added. The mixture was stirred for 1 h at −20 °C and then allowed to warm to room temperature. The esterification was monitored with TLC. After complete conversion, the mixture was cooled to −40 °C, and a solution of core molecule **27** (0.04 g, 0.11 mmol) and dry TEA (1 mL) in absolute methanol (2 mL) was added. The reaction was stirred for 1 h at −40 °C and then allowed to warm to room temperature. The solvents were evaporated. The crude product was purified by column chromatography. The yellowish oil was dissolved in benzene, filtered and lyophilized. Yield: 0.37 g (95%) of a yellowish oil.

R_f = 0.24 (silica gel, CH_2Cl_2/methanol (10:1)); ^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 1.40 (s, 27H; -C(CH_3)$_3$), 1.84 (m, 6H; β′-CH_2), 1.89 (m, 6H; β-CH_2), 2.62 (t, ^3J(H,H) = 7.6 Hz, 6H; α-CH_2), 3.28 (s, 36H; -OCH_3), 3.30 (m, 6H; γ′-CH_2), 3.37 (m, 6H; γ-CH_2), 3.40–3.65 (2 m, 144H; -OCH_2CH_2O), 3.71 (m, 32H; -OCH(CH_2)$_2$), 4.01 (t, ^3J(H,H) = 5.7 Hz, 6H; α′-CH_2), 4.59 (quint, ^3J(H,H) = 4.9 Hz, 6H; -OCH(CH_2)$_2$), 5.60 (t, ^3J(H,H) = 5.4 Hz, 3H; -NH′), 6.89 (s, 3H; Ar-H: core), 6.95 (t, ^3J-(H,H) = 5.6 Hz, 3H; -NH), 7.21 ppm (s, 6H; Ar-H: gallate); ^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 28.26, 30.05, 31.23, 33.15, 37.88, 39.66, 58.53, 70.32, 70.33, 70.40, 70.83, 71.15, 71.85, 77.73, 78.21, 108.68, 126.11, 130.18, 141.87, 142.23, 151.93, 155.85, 166.42 ppm; MS (MALDI-TOF, dithranol): *m/z*: 3412.59 $[M+K]^+$ ($^{12}C_{162}{}^1H_{288}{}^{14}N_6{}^{16}O_{66}{}^{39}K$) calcd monoisotopic peak 3412.90; 3396.65 $[M+Na]^+$ calcd monoisotopic peak ($^{12}C_{162}{}^1H_{288}{}^{14}N_6{}^{16}O_{66}{}^{23}Na$) 3396.93.

1,3,5-Tris-{[4-(3-amoniopropoxy)]-[3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzamidopropyl]}benzene tris-hydrotrifluoroacetate (29): Compound **28** (0.36 g, 0.1 mmol) was dissolved in dry CH_2Cl_2 (20 mL) and TFA (5 mL) was added at room temperature. The deprotection was monitored by ^{1}H NMR spectroscopy. After complete conversion, the solvents were evaporated and dried in high vacuum. No further purification was necessary. Yield: 0.36 g (98%) of a yellowish oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.89 (m, 6H; β-CH_2), 1.93 (m, 6H; β′-CH_2), 2.48 (t, ^3J(H,H) = 7.6 Hz, 6H; α-CH_2), 3.11 (m, 6H; γ′-CH_2), 3.22

(s, 36H; -OCH_3), 3.26 (m, 6H; γ-CH_2), 3.30–3.56 (2 m, 144H; -OCH_2CH_2O), 3.63 (m, 32H; -$OCH(CH_2)_2$), 4.06 (t, ^3J(H,H) = 5.4 Hz, 6H; α′-CH_2), 4.58 (quint, ^3J(H,H) = 4.6 Hz, 6H; -$OCH(CH_2)_2$), 6.74 (s, 3H; Ar-H: core), 7.17 (s, 6H; Ar-H: gallate), 7.30 (br m, -NH_3), 8.04 ppm (t, ^3J(H,H) = 5.5 Hz, 3H; -NH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 26.09, 30.55, 32.77, 39.52, 39.64, 58.19, 69.37, 39.66, 69.76, 69.78, 69.80, 70.19, 71.23, 72.95, 76.32, 107.14, 125.55, 130.20, 139.78, 141.31, 150.68, 159.26, 156.56, 166.53 ppm; MS (MALDI-TOF, dithranol): *m/z*: 3096.72 $[M+Na]^+$ ($^{12}C_{147}{}^1H_{264}{}^{14}N_6{}^{16}O_{60}{}^{23}Na$) 3396.77, 3074.73 $[M+H]^+$ ($^{12}C_{147}{}^1H_{265}{}^{14}N_6{}^{16}O_{60}$) 3074.79.

1,3,5-Tris-{4-[3-(benzyloxy)propoxy][3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzamidopropyl]}benzene (30): Compound **10c** (0.73 g, 0.69 mmol) was dissolved in dry CH_2Cl_2 (15 mL). The solution was cooled to −20 °C and HOBt (0.12 g, 0.78 mmol) and EDC (0.16 g, 0.86 mmol) were added. The mixture was stirred for 1 h at −20 °C and then allowed to warm to room temperature. The esterification was monitored with TLC. After complete conversion, the mixture was cooled to −40 °C, and a solution of core molecule **27** (0.07 g, 0.19 mmol) and dry TEA (1 mL) in absolute methanol (2 mL) was added. The reaction mixture was stirred for 1 h at −40 °C and then allowed to warm to room temperature. The solvents were evaporated. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/methanol 30:1 increasing to 10:1). The yellowish oil was dissolved in benzene, filtered and lyophilized. Yield: 0.58 g (92 %) of a yellowish oil.

R_f = 0.27 (silica gel, CH_2Cl_2/methanol 10:1). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.81 (m, 6H; β-CH_2), 1.93 (m, 6H; β′-CH_2), 2.53 (t, ^3J(H,H) = 7.9 Hz, 6H; α-CH_2), 3.23 (s, 36H; -OCH_3), 3.32 (m, 6H; γ-CH_2), 3.35–3.56 (2 m, 144H; -OCH_2CH_2O), 3.59 (hidden m, 6H; γ′-CH_2), 3.60 (m, 32H; -$OCH(CH_2)_2$), 4.02 (t, ^3J(H,H) = 6.2 Hz, 2H; α′-CH_2), 4.42 (s, 6H; -CH_2OBn) 4.44 (quint, ^3J(H,H) = 4.9 Hz, 6H; -$OCH(CH_2)_2$), 6.78 (s, 3H; Ar-H: core), 6.90 (t, ^3J(H,H) = 5.8 Hz, 3H; -NH), 7.15 (m, 12H; Ar-H: Bn), 7.22 ppm (br s, 9H; Ar-H: Bn and gallate); ^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 30.29, 30.87, 32.91, 39.49 (2), 58.51, 67.16, 70.05, 70.07, 70.16, 70.43, 71.49, 72.51, 77.79, 109.44, 125.71, 127.04, 127.10, 127.09, 127.92, 129.29, 138.29, 141.40, 142.66, 151.51, 166.43 ppm; MS (MALDI-TOF, dithranol): *m/z*: 3385.69 $[M+K]^+$ ($^{12}C_{168}{}^1H_{279}{}^{14}N_6{}^{16}O_{66}{}^{39}K$) calcd monoisotopic peak 3385.84; 3396.79 $[M+Na]^+$ calcd monoisotopic peak ($^{12}C_{168}{}^1H_{279}{}^{14}N_6{}^{16}O_{66}{}^{23}Na$) 3396.86; 3347.73 $[M+K]^+$ ($^{12}C_{168}{}^1H_{280}{}^{14}N_6{}^{16}O_{66}$) calcd monoisotopic peak 3347.88.

1,3,5-Tris-{4-(3-hydroxypropoxy)[3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzamidopropyl]}benzene (31): Compound **30** (0.34 g, 0.1 mmol) was dissolved in methanol (8 mL) and Pd/C (40 mg) was added. The reaction mixture was stirred for 24 h under a H_2 atmosphere at room temperature. The deprotection was monitored by ^{1}H NMR spectroscopy. After filtration, the solvent was evaporated and dried under high vacuum. No further purification was carried out. Yield: 0.30 g (97 %) of a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.82 (m, 12H; β/β′-CH_2), 2.53 (t, ^3J(H,H) = 7.5 Hz, 6H; α-CH_2), 3.20 (m, 3H; -OH), 3.25 (s, 36H; -OCH_3), 3.32 (m, 6H; γ-CH_2), 3.36–3.59 (2 m, 144H; -OCH_2CH_2O), 3.63 (m, 32H; -$OCH(CH_2)_2$), 3.77 (m, 6H; γ′-CH_2), 4.04 (t, ^3J(H,H) = 5.3 Hz, 2H; α′-CH_2), 4.49 (quint, ^3J(H,H) = 4.7 Hz, 6H; -$OCH(CH_2)_2$), 6.78 (s, 3H; Ar-H: core), 6.87 (t, ^3J(H,H) = 5.2 Hz, 3H; -NH), 7.14 ppm (s, 6H; Ar-H: gallate); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 30.77, 32.39, 38.82, 39.41, 58.51, 59.45, 69.91, 70.03, 70.13, 70.40, 70.67, 71.46, 77.20, 77.34, 108.63, 125.72, 129.50, 141.34, 142.07, 151.41, 166.39 ppm; MS (MALDI-TOF, α-cyano-4-hydroxycinnamonic acid (CCA)): *m/z*: 3115.42 $[M+K]^+$ ($^{12}C_{147}{}^1H_{261}{}^{14}N_3{}^{16}O_{63}{}^{39}K$) calcd monoisotopic peak 3115.69; 3099.47 $[M+Na]^+$ calcd monoisotopic peak ($^{12}C_{147}{}^1H_{261}{}^{14}N_3{}^{16}O_{63}{}^{23}Na$) 3099.72; 3077.51 $[M+H]^+$ ($^{12}C_{147}{}^1H_{262}{}^{14}N_3{}^{16}O_{63}$) calcd monoisotopic peak 3077.74.

1,3,5-Tris-{[3-(5-dimethylaminonaphthalene-1-sulfonylamino)propoxy][3,5-bis (1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)-benzamidopropyl]}benzene (32): Compound **16** (0.39 g, 0.33 mmol) was dissolved in dry CH_2Cl_2 (15 mL). The solution was cooled to −20 °C and HOBt (0.06 g, 0.42 mmol) and EDC (0.09 g, 0.47 mmol) were added. The mixture was stirred for 1 h at −20 °C and then the temperature was increased slowly to room temperature. The esterification was monitored with TLC. After complete conversion, the mixture was cooled to −40 °C, and a solution of core molecule **27** (0.03 g, 0.09 mmol) and dry TEA (0.85 mL) in absolute methanol (1 mL) was added. The reaction mixture was stirred for 1 h at −40 °C and then the temperature was increased very slowly to room temperature. The solvents were evaporated. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/methanol 30:1 increasing to 10:1). The green oil was dissolved in benzene, filtered, and lyophilized. Yield: 0.58 g (92 %) of a green oil.

R_f = 0.31 (silica gel, CH_2Cl_2/methanol (10:1)); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.63 (m, 6H; β′-CH_2), 1.76 (m, 6H; β-CH_2), 2.47 (t, ^3J(H,H) = 6.8 Hz, 6H; α-CH_2), 2.68 (s, 18H; -$N(CH_3)_3$), 3.07 (m, 6H; γ′-CH_2), 3.15 (s, 36H; -OCH_3), 3.26 (m, 6H; γ-CH_2), 3.30–3.45 (2 m, 144H; -OCH_2CH_2O), 3.50 (d, ^3J(H,H) = 4.8 Hz, 32H; -$OCH(CH_2)_2$), 4.82 (t, ^3J(H,H) = 5.3 Hz, 6H; α′-CH_2), 4.38 (quint, ^3J(H,H) = 4.8 Hz, 6H; -$OCH(CH_2)_2$), 6.22 (t, ^3J(H,H) = 6.0 Hz, 3H;-NH′), 6.72 (s, 3H; Ar-H: Core), 6.96 (d, ^3J(H,H) = 7.6 Hz, 3H; Ar-H: C6-dansyl), 7.10 (s, 6H; Ar-H: gallate), 7.14 (t, ^3J(H,H) = 5.3 Hz, 3H; -NH), 7.30 (dd, ^3J(H,H) = 7.6 Hz, ^3J(H,H) = 8.6 Hz, 3H; Ar-H: C7-dansyl), 7.34 (dd, ^3J(H,H) = 7.2 Hz, ^3J(H,H) = 8.4 Hz, 3H; Ar-H: C3-dansyl), 8.07 (d, ^3J(H,H) = 7.2 Hz, 3H; Ar-H: C4-dansyl), 8.19 (d, ^3J(H,H) = 8.4 Hz, 3H; Ar-H: C8-dansyl), 8.33 ppm (d, ^3J(H,H) = 8.4 Hz, 3H; Ar-H: C2-dansyl); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 29.54, 30.66, 32.73, 39.30, 40.30, 44.84, 58.30, 69.83, 69.85, 69.87, 69.95, 70.17, 70.35, 71.30, 77.19, 77.39, 108.54, 114.52, 118.92, 122.62, 125.57, 127.37, 128.37, 129.21, 129.32, 129.37, 129.39, 135.45, 141.24, 141.64, 151.16, 151.27, 166.19 ppm; MS (MALDI-TOF, dithranol): *m/z*: 3811.70 $[M+K]^+$ ($^{12}C_{183}{}^1H_{297}{}^{14}N_9{}^{16}O_{66}{}^{32}S_3{}^{39}K$) calcd monoisotopic peak 3811.90; 3795.83 $[M+Na]^+$ calcd monoisotopic peak ($^{12}C_{183}{}^1H_{297}{}^{14}N_9{}^{16}O_{66}{}^{32}S_3{}^{23}Na$) 3795.92; 3773.78 $[M+H]^+$ ($^{12}C_{183}{}^1H_{298}{}^{14}N_9{}^{16}O_{66}{}^{32}S_3$) calcd monoisotopic peak 3773.94.

1,3,5-Tris-{[3-(2,3-bis-*tert*-butoxycarbonylamino-propionylamido)propoxy][3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzamidopropyl]}benzene (33): Compound **13** (0.25 g, 0.20 mmol) was dissolved in dry CH_2Cl_2 (5 mL). The solution was cooled to −20 °C and HOBt (0.04 g, 0.22 mmol) and EDC (0.06 g, 0.24 mmol) were added. The mixture was stirred for 1 h at −20 °C and then allowed to warm to room temperature. The esterification was monitored with TLC. After complete conversion, the mixture was cooled to −40 °C, and a solution of core molecule **27** (0.02 g, 0.06 mmol) and dry TEA (0.5 mL) in absolute methanol (1 mL) was added. The reaction mixture was stirred for 1 h at −40 °C and then allowed to warm to room temperature. The solvents were evaporated. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/methanol 20:1 increasing to 10:1). The yellowish oil was dissolved in benzene, filtered, and lyophilized. Yield: 0.18 g (80 %) of a yellowish oil.

R_f = 0.15 (silica gel, CH_2Cl_2/methanol (10:1)); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.22 and 1.29 (2 s, 54H; -$C(CH_3)_3$), 1.79 (m, 12H; β/β′-CH_2), 2.51 (t, ^3J(H,H) = 7.4 Hz, 6H; α-CH_2), 3.22 (s, 36H; -OCH_3), 3.32 (m, 18H; α′-, γ- and γ′-CH_2), 3.37–3.57 (2 m, 144H; -OCH_2CH_2O), 3.62 (m, 24H; -$OCH(CH_2)_2$), 3.91 (m, 3H; -CH_2NHBoc), 3.98 (m, 3H; -CH_2NHBoc), 4.09 (m, 3H; -*CH*NHBoc), 4.48 (m, 6H; -$OCH(CH_2)_2$), 5.29 (m, 3H; -CH_2N*H*Boc), 5.78 (d, ^3J(H,H) = 7.7 Hz, 3H; -CHN*H*Boc), 6.78 (s, 3H; Ar-H: core), 7.04 (m, 3H; -CH_2N*H*COAr), 7.15 (s, 6H; Ar-H: gallate), 7.27 ppm (m, 3H; -CH_2N*H*′); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 27.88, 27.99, 29.17, 30.92, 32.96, 37.09, 39.57, 42.49, 54.45, 58.52, 69.95, 70.04, 70.05, 70.15, 70.35, 70.38, 71.41, 71.50, 77.39, 78.82, 79.08, 108.74, 125.73, 129.61, 141.42, 142.04, 151.55, 155.37, 156.10, 166.37, 169.99 ppm; MS (MALDI-TOF, dithranol): *m/z*: 3955.12 $[M+Na]^+$ calcd monoisotopic peak ($^{12}C_{186}{}^1H_{330}{}^{14}N_{12}{}^{16}O_{75}{}^{23}Na$) 3955.23.

1,3,5-Tris-{[3-(2,3-diaminopropionylamido)propoxy][3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzamidopropyl]}benzene hexakis-trifluoroacetato (34): Compound **33** (0.18 g, 0.045 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and TFA (1 mL) was added at room temperature. The deprotection was monitored by ^{1}H NMR spectroscopy. The solvent was evaporated and dried in high vacuum. No further purification was carried out. Yield: 0.18 g (79 %) of a yellowish oil.

^{1}H NMR (CD_3OD, 500 MHz): δ = 1.78 (m, 6H; β-CH_2), 1.84 (m, 6H; β′-CH_2), 2.50 (t, ^3J(H,H) = 7.6 Hz, 6H; α-CH_2), 3.17 (s, 36H; -OCH_3), 3.24 (t, ^3J(H,H) = 7.1 Hz, 6H; γ-CH_2), 3.31–3.54 (2 m, 144H; -OCH_2CH_2O),

3.43 and 3.49 (2 m, 12 H; α′- and γ′-CH_2), 3.63 (m, 24 H; -OCH(CH_2)$_2$), 3.98; 4.04 and 4.17 (3 m, 9 H; -CHNH$_3$ and -CH_2NH$_3$), 4.58 (quint, ^3J(H,H) = 4.9 Hz, 6 H; -OCH(CH_2)$_2$), 6.78 (s, 3 H; Ar-H: core), 7.16 ppm (s, 6 H; Ar-H: gallate); ^{13}C NMR (CD_3OD/$CDCl_3$, 125 MHz): δ = 28.25, 30.14, 32.16, 37.29, 38.80, 38.94, 50.00, 52.62, 57.04, 69.01, 69.04, 69.11, 69.20, 69.55, 69.60, 71.31, 76.31, 107.56, 125.08, 128.94, 140.97, 150.89, 164.24, 166.64 ppm; MS (MALDI-TOF, CCA): *m/z*: 3370.46 [*M*+K]$^+$ calcd monoisotopic peak ($^{12}C_{156}{}^1H_{282}{}^{14}N_{12}{}^{16}O_{63}{}^{39}K$) 3370.89; 3354.47 [*M*+Na]$^+$ calcd monoisotopic peak ($^{12}C_{156}{}^1H_{282}{}^{14}N_{12}{}^{16}O_{63}{}^{23}Na$) 3354.91; 3332.51 [*M*+H]$^+$ calcd monoisotopic peak ($^{12}C_{156}{}^1H_{283}{}^{14}N_{12}{}^{16}O_{63}$) 3332.93.

1,3,5-Tris-({3-[di-*tert*-butyl-2-(2-Carbamoylethyl)malonyl]propoxy}[3,5-bis(1,3-bis {2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzamidopropyl])benzene (35): Compound **24** (0.20 g, 0.16 mmol) was dissolved in dry CH_2Cl_2 (8 mL). The solution was cooled to −20 °C and HOBt (0.04 g, 0.22 mmol) and EDC (0.06 g, 0.24 mmol) were added. The mixture was stirred for 1 h at −20 °C and then allowed to warm to room temperature. The esterification was monitored with TLC. After complete conversion, the mixture was cooled to −40 °C, and transferred to a solution of core molecule **27** (15 mg, 0.04 mmol) and dry TEA (0.5 mL) in dry CH_2Cl_2 (5 mL). The reaction mixture was stirred for 1 h at −40 °C and then allowed to warm to room temperature. The reaction was quenched by the addition of 1 M $NaHCO_3$ (5 mL). The organic phase was washed once with brine and dried. The solvents were evaporated. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/methanol 20:1 increasing to 10:1). The yellowish oil was dissolved in benzene, filtered, and lyophilized. Yield: 0.15 g (96 %) of a yellowish oil.

R_f = 0.18 (silica gel, CH_2Cl_2/methanol 10:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.33 (s, 54 H; -C(CH_3)$_3$), 1.80 (m, 12 H; β/β′-CH_2), 1.98 (m, 6 H; β″-CH_2), 2.11 (m, 6 H; α″-CH_2), 2.52 (t, ^3J(H,H) = 7.6 Hz, 6 H; α-CH_2), 3.10 (t, ^3J(H,H) = 7.4 Hz, 3 H; γ″-CH_2), 3.23 (s, 36 H; -OCH_3), 3.32 (m, 6 H; γ′-CH_2), 3.37 (m, 6 H; γ-CH_2), 3.39–3.56 (2 m, 144 H; -OCH_2CH_2O), 3.62 (m, 24 H; -OCH(CH_2)$_2$), 3.95 (t, ^3J(H,H) = 5.4 Hz, 6 H; α′-CH_2), 4.49 (quint, ^3J(H,H) = 4.5 Hz, 6 H; -OCH(CH_2)$_2$), 6.69 (t, ^3J(H,H) = 5.8 Hz, 6 H; -NH′), 6.77 (s, 3 H; Ar-H: core), 7.06 (m, 3 H; -NH), 7.16 ppm (s, 6 H; Ar-H: gallate); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 24.22, 27.63, 29.38, 31.03, 33.09, 33.25, 36.84, 39.71, 52.91, 58.63, 70.12, 70.14, 70.16, 70.17, 70.26, 70.51, 71.28, 71.60, 77.55, 81.02, 108.90, 125.82, 129.69, 141.53, 142.14, 151.61, 166.50, 168.22, 171.60 ppm; MS (MALDI-TOF, dithranol): *m/z*: 3923.04 [*M*+K]$^+$ calcd monoisotopic peak ($^{12}C_{189}{}^1H_{330}{}^{14}N_6{}^{16}O_{75}{}^{39}K$) 3923.18; 3907.07 [*M*+Na]$^+$ calcd monoisotopic peak ($^{12}C_{189}{}^1H_{330}{}^{14}N_6{}^{16}O_{75}{}^{23}Na$) 3907.21.

1,3,5-Tris-({3-[dibenzyl-2-(2-carbamoylethyl)malonyl]propoxy}[3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzamidopropyl])benzene (36): Compound **25** (0.35 g, 0.27 mmol) was dissolved in dry CH_2Cl_2 (15 mL). The solution was cooled to −20 °C and HOBt (0.05 g, 0.29 mmol) and EDC (0.07 g, 0.29 mmol) were added. The mixture was stirred for 1 h at −20 °C and then allowed to warm to room temperature. The esterification was monitored with TLC. After complete conversion, the mixture was cooled to −40 °C, and transferred to a cooled solution of core molecule **27** (0.03 g, 0.07 mmol) and dry TEA (0.7 mL) in dry CH_2Cl_2 (5 mL). The reaction mixture was stirred for 1 h at −40 °C and then allowed to warm to room temperature. The reaction was quenched by the addition of 1 M $NaHCO_3$ (5 mL). The organic phase was washed once with brine and dried. The solvents were evaporated. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/methanol 20:1 increasing to 10:1). The yellowish oil was dissolved in benzene, filtered, and lyophilized. Yield: 0.28 g (93 %) of a yellowish oil.

R_f = 0.13 (silica gel, CH_2Cl_2/methanol (10:1)); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.87 (m, 6 H; β′-CH_2), 1.91 (m, 6 H; β-CH_2), 1.98 (m, 6 H; β″-CH_2), 2.20 (m, 15 H; α″, β″, γ″-CH_2), 2.64 (t, ^3J(H,H) = 7.8 Hz, 6 H; α-CH_2), 3.30 (s, 36 H; -OCH_3), 3.40 (m, 6 H; γ-CH_2), 3.44 (m, 6 H; γ′-CH_2), 3.45–3.65 (2 m, 144 H; -OCH_2CH_2O), 3.72 (m, 24 H; -OCH(CH_2)$_2$), 4.04 (t, ^3J(H,H) = 5.7 Hz, 6 H; α′-CH_2), 4.61 (quint, ^3J(H,H) = 4.7 Hz, 6 H; -OCH(CH_2)$_2$), 5.12 (m, 12 H; -OCH_2Ar), 6.68 (t, ^3J(H,H) = 5.4 Hz, 6 H; -NH′), 6.91 (s, 3 H; Ar-H: core), 7.09 (t, ^3J(H,H) = 5.6 Hz, 6 H; -NH), 7.24–7.39 ppm (m, 36 H; Ar-H: gallate and benzyl); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 24.55, 29.75, 31.39, 33.07, 33.32, 37.09, 39.87, 51.14, 58.59, 66.99, 70.36, 70.38, 70.42, 70.48, 70.86, 70.88, 71.62, 71.89, 77.78, 108.83, 126.14, 128.04, 128.25, 128.52, 130.23, 135.66, 141.98, 142.30, 151.97, 166.45, 168.87, 171.17 ppm; MS (MALDI-TOF, dithranol): *m/z*: 4126.95 [*M*+K]$^+$ calcd monoisotopic peak ($^{12}C_{207}{}^1H_{318}{}^{14}N_{06}{}^{16}O_{75}{}^{39}Na$) 4127.09; 4111.01 [*M*+Na]$^+$ calcd monoisotopic peak ($^{12}C_{207}{}^1H_{318}{}^{14}N_{06}{}^{16}O_{75}{}^{23}Na$) 4111.11.

1,3,5-Tris-({3-[2-(2-Carbamoylethyl)malonato]propoxy}[3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzamidopropyl])-benzene (37): Method A: **35** (0.15 g, 0.04 mmol) was dissolved in CH_2Cl_2 (5 mL). TFA (3 mL) was added. The reaction was monitored with ^{1}H NMR. After complete deprotection, the solvent was removed under reduced pressure at room temperature. The remaining oil was coevaporated 5 times with CH_2Cl_2 (5 mL) to remove the remaining TFA. No further purification. Yield: 0.13 g (96 %) of a colorless oil. Method B: **36** (0.32 g, 0.08 mmol) was dissolved in methanol (10 mL) and Pd/C (0.03 g) was added. The reaction mixture was stirred for 24 h under a H_2 atmosphere at room temperature. The deprotection was monitored by ^{1}H NMR spectroscopy. After filtration, the solvent was evaporated at room temperature. No further purification. Yield: 0.25 g (91 %) of a colorless oil. Both compounds had the same spectroscopic and spectrometric parameters.

^{1}H NMR (CD_3OD, 500 MHz): δ = 1.88 (m, 12 H; β/β′-CH_2), 2.10 (t, ^3J(H,H) = 7.2 Hz, 6 H; β″-CH_2), 2.26 (t, ^3J(H,H) = 7.4 Hz, 6 H; α″-CH_2), 2.61 (t, ^3J(H,H) = 7.1 Hz, 6 H; α-CH_2), 3.28 (br s, 39 H; -OCH_3 and γ″-CH), 3.35 (t, ^3J(H,H) = 6.9 Hz, 6 H; γ-CH_2), 3.41 (t, ^3J(H,H) = 6.6 Hz, 6 H; γ′-CH_2), 3.41–3.64 (2 m, 144 H; -OCH_2CH_2O), 3.72 (m, 24 H; -OCH(CH_2)$_2$), 4.05 (t, ^3J(H,H) = 5.7 Hz, 6 H; α′-CH_2), 4.60 (quint, ^3J(H,H) = 4.8 Hz, 6 H; -OCH(CH_2)$_2$), 6.89 (s, 3 H; Ar-H: core), 7.23 ppm (s, 6 H; Ar-H: gallate); ^{13}C NMR (CD_3OD, 125 MHz): δ = 25.77, 30.71, 32.19, 34.19, 34.35, 38.04, 40.79, 59.11, 71.16, 71.29, 71.35, 71.79, 72.39, 72.76, 78.86, 109.85, 127.13, 130.61, 143.00, 143.52, 153.10, 168.87, 172.17, 174.25 ppm; MS (MALDI-TOF, CCA): *m/z*: 3572.71 [*M*+Na]$^+$ calcd molecular weight peak ($C_{165}H_{282}N_6O_{75}Na$) 3572.99.

Ethyl 3-(3-benzyloxycarbonylamino-propyl)-5-bromobenzoate (39): Compound **2b** (0.46 g, 2.37 mmol) and 9-BBN (0.32 g 2.61 mmol) were dissolved in dry toluene (10 mL) in a N_2 atmosphere at 0 °C. The reaction mixture was stirred for 12 h. Then **38** (0.84 g, 2.37 mmol), 1 M aqueous KOH (5 mL) and toluene (5 mL) were added. The reaction mixture was degassed by three freeze-pump-thaw-cycles. [Pd(PPh_3)$_4$] (0.11 g, 0.1 mmol) added and another freeze-pump-thaw-cycle was applied. The reaction mixture was vigorously stirred at 60 °C for two days. The compound was purified by column chromatography through silica gel using as solvent hexane/ethyl acetate to give **39** (0.95 g) as colorless plates in 95 % yield.

R_f = 0.19 (hexane/ethyl acetate 3:1); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.31 (t, ^3J(H,H) = 7.0 Hz, 3 H; -CH_2CH_3), 1.75 (m, 2 H; β-CH_2), 2.57 (t, ^3J(H,H) = 7.7 Hz, 2 H; α-CH_2), 3.14 (m, 2 H; γ -CH_2), 4.29 (q, ^3J(H,H) = 7.0 Hz, 2 H; -CH_2CH_3), 4.91 (br s, 1 H; -NH), 5.03 (s, 2 H; -OCH_2Ar), 7.27 (m, 5 H; -OCH_2Ar-*H*), 7.42 (s, 1 H; Ar-H), 7.70 (s, 1 H; Ar-H), 7.92 ppm (s, 1 H; Ar-H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 14.20, 31.27, 32.44, 61.29, 66.62, 122.30, 128.04, 128.43, 130.12, 132.34, 135.54, 136.49, 143.86, 156.36, 165.23 ppm; MS (EI, 80 eV, 140 °C): *m/z* (%): 421.0 (1.3), 419.0 (1.3) [*M*]$^+$, 91.0 (100) [C_7H_7]$^+$; elemental analysis calcd for $C_{20}H_{22}BrNO_4$ (419.07): C 57.15, H 5.28, N 3.33; found: C 57.10, H 5.04, N 3.29.

Ethyl 3-(3-benzyloxycarbonylaminopropyl)-5-(3-*tert*-butoxycarbonylaminopropyl)benzoate (40): Compound **2a** (0.50 g, 3.20 mmol) and 9-BBN (0.43 g, 3.50 mmol) were dissolved in dry toluene (10 mL) in a N_2 atmosphere at 0 °C. The reaction mixture was stirred for 12 h. Then **39** (1.26 g, 3.00 mmol), 1 M aqueous KOH (5 mL), and toluene (5 mL) were added. The reaction mixture was degassed by three freeze-pump-thaw-cycles. [Pd(PPh_3)$_4$] (0.11 g, 0.1 mmol) was added and another cycle was applied. The reaction mixture was refluxed for two days. The phases were separated, the organic layer washed three times with brine, and dried. The solvent was removed under reduced pressure. Chromatographic separation through silica gel with hexane/ethyl acetate and then with dichlorome-

thane gave **40** (1.38 g; 92%) as a colorless oil. $R_f = 0.17$ (silica gel; hexane/ethyl acetate (3:1)).

Ethyl 3-[3-(benzyloxycarbonylamino)propyl]-5-(trifluoroacetato-3-ammoniumpropyl)benzoate (41): Compound **40** (0.52 g, 1.0 mmol) was dissolved in dichloromethane (5 mL) and TFA (3 mL) was added. The mixture was stirred for 12 h at room temperature. The reaction was monitored with TLC. After complete deprotection the solvent removed under reduced pressure. Chromatographic separation through silica gel with dichloromethane/methanol to give 0.47 g of **41** (95%) as a yellowish solid. $R_f = 0.11$ (silica gel; dichloromethane/methanol 10:1).

Ethyl 3-[3-(*tert*-butoxycarbonylamino)propyl]-5-(3-aminopropyl)benzoate (42): Compound **40** (1.28 g, 0.25 mmol) was dissolved in ethyl acetate/ethanol (1:1) (10 mL) and then Pd/C (0.012 g) was added. The mixture was stirred for 1 h in a H_2 atmosphere. The reaction was monitored with TLC. After complete deprotection the mixture was filtered and the solvent removed under reduced pressure. Further purification was not necessary. Yield: 0.9 g (quant.) of a yellowish oil.

^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.33$ (t, $^3J(H,H) = 7.2$ Hz, 3H; -CH_2-CH_3), 1.38 (s, 9H; -C(CH_3)$_3$), 1.76 (m, 4H; β/β′-CH_2), 2.61 (m, 6H; γ/γ′-CH_2 and NH_2), 2.70 (m, 2H; α-CH_2), 3.08 (m, 2H; α′-CH_2), 4.30 (q, $^3J(H,H) = 7.1$ Hz, 2H; -CH_2CH_3), 4.67 (br s, 1H; -NH), 7.14 (s, 1H; Ar-H), 7.62 (s, 1H; Ar-H), 7.63 ppm (s, 1H; Ar-H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 14.24$, 28.32, 31.57, 32.76, 32.79, 34.35, 40.06, 41.23, 60.78, 79.00, 126.95, 127.05, 130.61, 133.01, 141.86, 142.16, 155.91, 166.71 ppm.

Ethyl 3-(3-benzyloxycarbonylamino-propyl)-5-(3-{4-[3-(2,3-bis-*tert*-butoxycarbonylamino-propionylamido)propoxy]-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoylamino}propyl)benzoate (44): Compound **13** (1.12 g, 0.89 mmol) was dissolved in dry dichloromethane (10 mL). The solution was cooled to −20 °C and HOBt (0.15 g, 1.00 mmol) and EDC (0.17 g, 1.07 mmol) were added. The mixture was stirred for 1 h at −20 °C and then allowed to warm to room temperature. The esterification was monitored with TLC. After complete conversion, the mixture was cooled to −40 °C, and a solution of **41** (0.55 g, 1.07 mmol) and dry TEA (0.5 mL) in absolute methanol was added. The reaction was stirred for 1 h at −40 °C and then allowed to warm to room temperature. The solvents were evaporated. The crude product was purified by column chromatography (silica gel; dichloromethane/methanol 30:1 increasing to 10:1). The yellowish oil was dissolved in benzene, filtered and lyophilized to give a yellowish oil (1.18 g; 80%).

$R_f = 0.40$ (silica gel; dichloromethane/methanol 10:1); ^{1}H NMR (CD_2Cl_2, 500 MHz): $\delta = 1.32$ and 1.40 (2 s, 18H; -C(CH_3)$_3$), 1.36 (t, $^3J(H,H) = 7.2$ Hz, 3H; -CH_2CH_3), 1.83 (m, 4H; β′-CH_2 and β″-CH_2), 1.92 (m, 2H; β-CH_2), 2.66 (t, $^3J(H,H) = 7.8$ Hz, 2H; α′-CH_2), 2.71 (t, $^3J(H,H) = 7.5$ Hz, 2H; α-CH_2), 3.18 (m, 2H; γ′-CH_2), 3.30 (s, 12H; -OCH_3), 3.41 (m, 4H; γ-CH_2 and γ″-CH_2), 3.44–3.66 (2 m, 48H; -OCH_2CH_2O), 3.73 (m, 8H; -OCH(CH_2)$_2$), 4.02 (m, 2H; -CH_2NHBoc), 4.12 (m, 3H;-CHNHBoc and α″-CH_2), 4.32 (q, $^3J(H,H) = 7.2$ Hz, 2H; -CH_2CH$_3$), 4.62 (quint, $^3J(H,H) = 4.9$ Hz, 2H; -OCH(CH_2)$_2$), 5.05 (s, 2H; benzyl CH_2), 5.30 (br s, 1H; -NH′), 5.57 (br s, 2H; -NH and -NH″), 7.02 (t, $^3J(H,H) = 5.7$ Hz, 1H; -NH), 7.25 (s, 2H; Ar-H gallate), 7.26 (br s, 1H; Ar-H), 7.27–7.35 (br m, 5H; benzyl Ar-H), 7.68 (br s, 1H; Ar-H), 7.71 (br s, 1H; Ar-H); ^{13}C NMR (CD_2Cl_2, 125 MHz): $\delta = 14.18$, 28.04, 28.14, 29.15, 29.66, 31.25, 31.51, 32.71, 33.01, 37.49, 39.56, 40.52, 58.58, 60.84, 66.27, 70.35, 70.40, 70.44, 70.45, 70.46, 70.49, 70.78, 70.82, 71.89, 77.67, 79.07, 79.29, 108.70, 127.02, 127.05, 127.84, 127.91, 128.42, 130.24, 130.83, 133.21, 137.16, 142.12, 142.26, 142.32, 152.01, 156.38, 156.41, 166.55, 166.58, 170.25 ppm; MS (MALDI-TOF, dithranol): *m/z*: 1664.82 $[M+K]^+$ ($^{12}C_{80}{}^1H_{131}{}^{14}N_5{}^{16}O_{29}{}^{39}K$) calcdmonoisotopic peak 1664.86; 1648.84 $[M+Na]^+$ ($^{12}C_{80}{}^1H_{131}{}^{14}N_5{}^{16}O_{29}{}^{23}Na$) calcd monoisotopic peak 1648.88.

Ethyl 3-(3-aminopropyl)-5-(3-{4-[3-(2,3-bis-*tert*-butoxycarbonylaminopropionylamido)propoxy]-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]-ethoxy}propan-2-yloxy)benzoylamino}propyl)benzoate (45): Compound **44** (1.00 g, 0.7 mmol) was dissolved in ethyl acetate/ethanol (1:1) (20 mL) and Pd/C 0.13 g was added. The mixture was stirred for 1 h in a H_2 atmosphere. The reaction was monitored with TLC. After complete deprotection, the mixture was filtered and the solvent removed under reduced pressure. The compound was obtained as a yellowish oil (0.67 g, 73%) and did not need additional purifications (losses during workup).

$R_f = 0.11$ (silica gel; CH_2Cl_2/methanol (10:1)); ^{1}H NMR (CD_3OD, 500 MHz): $\delta = 1.38$ and 1.45 (2 s, 18H; -C(CH_3)$_3$), 1.39 (t, $^3J(H,H) = 7.1$ Hz, 3H; -CH_2CH_3), 1.94 (2 m, 2H; β′-CH_2), 2.01 (m, 4H; β-CH_2), 2.75 (t, 2H; $^3J(H,H) = 7.4$ Hz, α-CH_2), 3.00 (m, 2H; γ-CH_2), 3.34 (s, 12H; -OCH_3), 3.43 (m, 4H; γ-CH_2 and γ′-CH_2), 3.50–3.72 (2 m, 48H; -OCH_2CH_2O), 3.81 (m, 8H; -OCH(CH_2)$_2$), 4.11 (br s, 2H; α′-CH_2), 4.17 and 4.21 (2 m, 3H; -CH_2NHBoc and -CHNHBoc), 4.36 (q, $^3J(H,H) = 7.1$ Hz, 2H; -CH_2CH_3), 4.78 (m, 2H; -OCH(CH_2)$_2$), 6.51 (br s, 1H; -NH), 6.55 (s, 1H; -NH), 7.37 (s, 1H; Ar-H), 7.39 (s, 2H; Ar-H gallate), 7.72 (s, 1H; Ar-H), 7.75 (s, 1H; Ar-H), 7.99 (s, 1H; -NH), 8.49 ppm (s, 1H; -NH); ^{13}C NMR (CD_2Cl_2, 125 MHz): $\delta = 14.70$, 28.64, 29.79, 30.60, 31.82, 32.98, 33.77, 38.18, 40.23, 40.43, 42.99, 56.42, 59.01, 61.82, 71.00, 71.09, 71.19, 71.60, 71.66, 72.62, 78.40, 79.96, 80.22, 109.34, 127.78, 128.22, 130.50, 131.72, 134.19, 142.17, 143.09, 143.72, 152.99, 157.06, 157.97, 167.56, 166.36, 172.21 ppm; MS (MALDI-TOF, dithranol): *m/z*: 1530.86 $[M+K]^+$ ($^{12}C_{72}{}^1H_{125}{}^{14}N_5{}^{16}O_{27}{}^{39}K$) calcd monoisotopic peak 1530.82; 1514.85 $[M+Na]^+$ calcd monoisotopic peak ($^{12}C_{80}{}^1H_{131}{}^{14}N_5{}^{16}O_{29}{}^{23}Na$) 1514.85; 1492.88 $[M+H]^+$ calcd monoisotopic peak ($^{12}C_{80}{}^1H_{132}{}^{14}N_5{}^{16}O_{29}$) 1492.86.

Ethyl 3-(3-benzyloxycarbonylamino-propyl)-5-(3-{4-(3-*tert*-butoxycarbonylaminopropoxy)-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}-propan-2-yloxy)benzoylamino}propyl)benzoate (46): Compound **10a** (0.80 g, 0.75 mmol) was dissolved in dry dichloromethane (7 mL). Dry triethylamine (0.1 mL) was added and the mixture was cooled to −20 °C. A solution of TBTU (0.27 g, 0.83 mmol) in dry DMF was added. The mixture was stirred for 2 h at −20 °C and then allowed to warm to room temperature. The esterification was monitored with TLC. After complete conversion, the mixture was cooled to −40 °C, and a solution of **41** (0.25 g, 0.57 mmol) and dry triethylamine (0.2 mL) in absolute methanol was added. The reaction mixture was stirred for 1 h at −40 °C and then allowed to warm to room temperature. The solvents were evaporated. The crude product was purified by column chromatography (silica gel; dichloromethane/methanol 30:1 increasing to 10:1). The yellowish oil was dissolved in benzene, filtered and lyophilized to give **46** (0.7 g, 64%) as a yellowish oil.

$R_f = 0.27$ (silica gel; dichloromethane/methanol (20:1)); ^{1}H NMR (CD_2Cl_2, 500 MHz): $\delta = 1.35$ (t, $^3J(H,H) = 7.1$ Hz, 3H; -CH_2CH_3), 1.40 (s, 9H; -C(CH_3)$_3$), 1.82 (m, 2H; β′-CH_2), 1.84 (m, 2H; β″-CH_2), 1.91 (m, 2H; β-CH_2), 2.65 (t, $^3J(H,H) = 7.7$ Hz, 2H; α′-CH_2), 2.70 (t, $^3J(H,H) = 7.7$ Hz, 2H; α-CH_2), 3.17 (m, 2H; γ″-CH_2), 3.28 (s, 12H; -OCH_3), 3.28 (hidden m, 2H; γ-CH_2), 3.38 (m, 2H; γ″-CH_2), 3.44–3.65 (2 m, 48H; -OCH_2CH_2O), 3.72 (m, 8H; -OCH(CH_2)$_2$), 4.02 (t, $^3J(H,H) = 5.7$ Hz, 2H; α″-CH_2), 4.31 (q, $^3J(H,H) = 7.1$ Hz, 2H; -CH_2CH_3), 4.60 (quint, $^3J(H,H) = 4.9$ Hz, 2H; -OCH(CH_2)$_2$), 5.03 (s, 2H; benzyl CH_2), 5.17 (br s, 1H; -NH′), 5.57 (br s, 1H; -NH″), 6.96 (br s, 1H; -NH), 7.22 (s, 2H; Ar-H gallate), 7.25 (br s, 1H; Ar-H), 7.30–7.35 (br m, 5H; benzyl Ar-H), 7.67 (br s, 1H; Ar-H), 7.70 ppm (br s, 1H; Ar-H); ^{13}C NMR (CD_2Cl_2, 125 MHz): $\delta = 14.21$, 28.34, 30.13, 31.27, 31.55, 32.75, 33.05, 38.01, 39.58, 40.57, 58.63, 60.88, 66.33, 70.40, 70.41, 70.47, 70.51, 70.53, 70.93, 71.31, 71.94, 77.88, 78.39, 108.77, 127.05, 127.10, 127.88, 127.94, 128.46, 130.21, 130.88, 133.24, 137.20, 142.14, 142.31, 142.38, 152.06, 156.00, 156.39, 166.60, 166.63 ppm; MS (positive-ion mode FAB): *m/z* (%): 1480.1 (3) $[M+H+K]^+$; 1479.2 (2) $[M+K]^+$; 1464.0 (20), 1463.1 (22) $[M+Na]^+$; 1440.9 (4) $[M+H]^+$; 1352.2 (2), 1351.1 (4), 1349.8 (4), $[M-C_7H_7+H]^+$; 1336.9 (40), 1335.8 (69), 1334.8 (100), $[M-C_7H_7O+H]^+$; 1333.9 (14), 1333.5 (11), 1332.7 (31) $[M-C_7H_7O+H]^+$; elemental analysis calcd for $C_{72}H_{117}N_3O_{26}$ (1439.79): C 60.02, H 8.19, N 2.92; found: C 59.95, H 7.79, N 2.78.

Ethyl 3-(3-aminopropyl)-5-(3-{4-(3-*tert*-butoxycarbonylaminopropoxy)-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoylamino}propyl)benzoate (47): Compound **46** (0.50 g, 0.35 mmol) was dissolved in methanol (10 mL) and then Pd/C (0.05 g) was added. The mixture was stirred for 1 h in a H_2 atmosphere. The reaction was monitored with TLC. After complete deprotection, the mixture was filtered and the solvent removed under reduced pressure. Further purification was not necessary. Yield: 0.40 g (89%) of a yellowish oil (losses during work up).

$R_f = 0.14$ (silica gel; dichloromethane/methanol (10:1)); ^{1}H NMR (CD_2Cl_2, 500 MHz): $\delta = 1.35$ (t, $^3J(H,H) = 7.2$ Hz, 3H; -CH_2CH_3), 1.41 (s,

9H; -C(CH_3)$_3$), 1.85 (m, 2H; β″-CH_2), 1.90 (m, 2H; β′-CH_2), 1.95 (m, 2H; β-CH_2), 2.61 (t, ^3J(H,H) = 7.2 Hz, 2H; α′-CH_2), 2.70 (t, ^3J(H,H) = 7.2 Hz, 2H; α-CH_2), 2.87 (m, 2H; γ′-CH_2), 3.28 (s, 12H; -OCH_3), 3.32 (m, 2H; γ″-CH_2), 3.36 (m, 2H; γ-CH_2), 3.43–3.67 (2 m, 48H; -OCH_2CH_2O), 3.74 (m, 8H; -OCH(CH_2)$_2$), 4.05 (t, ^3J(H,H) = 5.4 Hz, 2H; α″-CH_2), 4.31 (q, ^3J(H,H) = 7.2 Hz, 2H; -CH_2CH$_3$), 4.68 (quint, ^3J(H,H) = 4.4 Hz, 2H; -OC*H*(CH$_2$)$_2$), 5.57 (m, 1H; -NHBoc), 7.04 (br s, 2H; -NH_2), 7.20 (br s, 1H; Ar-H), 7.24 (s, 2H; Ar-H gallate), 7.36 (m, 1H; -NH), 7.60 (br s, 1H; Ar-H), 7.70 ppm (br s, 1H; Ar-H); ^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 14.15, 28.28, 28.34, 30.22, 30.31, 31.90, 32.70, 37.89, 39.30, 39.81, 58.53, 60.87, 70.18, 70.23, 70.30, 70.33, 70.39, 70.80, 71.36, 71.75, 77.45, 78.47, 108.23, 126.94, 127.56, 129.81, 130.87, 133.03, 140.43, 141.78, 142.66, 151.82, 156.08, 166.43, 166.55 ppm; MS (positive-ion mode FAB): *m/z* (%): 1440.7 (5), 1439.8 (15), 1438.7 (23) [*M*+CsI]$^+$, 1330.6 (4), 1329.7 (8), 1328.7 (10) [*M*+Na]$^+$, 1309.3 (4), 1308.6 (9), 1308.1 (32), 1307.4 (74), 1306.7 (100), 1305.0 (11) [*M*+H]$^+$.

3-(3-Benzyloxycarbonylaminopropyl)-5-(3-{4-(3-*tert*-butoxycarbonylamino-propoxy)-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoylamino}propyl)benzoic acid (48): Compound **46** (0.24 g, 0.17 mmol) was dissolved in ethanol (10 mL) and 1 M aqueous KOH (1 mL) added at room temperature. The mixture was stirred for 12 h. The reaction was quenched by the addition of 1 M aqueous HCl (pH 5). The solvent was removed under reduced pressure. The crude product was diluted with dichloromethane and filtered. No further purification was carried out. The yellowish oil was dissolved in benzene, filtered, and lyophilized. Yield: 0.23 g (98%) of a colorless oil.

R_f = 0.23 (silica gel; dichloromethane/methanol (15:1)); ^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 1.40 (s, 9H; -C(CH_3)$_3$), 1.83 (m, 4H; β- and β″-CH_2), 1.93 (m, 2H; β′-CH_2), 2.56 (m, 2H; α-CH_2), 2.67 (m, 2H; α′-CH_2), 3.11 (m, 2H; γ-CH_2), 3.32 (s, 12H; -OCH_3), 3.35 (m, 2H; γ″-CH_2), 3.40 (m, 2H; γ′-CH_2), 3.42–3.64 (2 m, 48H; -OCH_2CH_2O), 3.70 (m, 8H; -OCH(CH_2)$_2$), 4.00 (t, ^3J(H,H) = 5.3 Hz, 2H; α″-CH_2), 4.57 (br s, 2H; -OC*H*(CH$_2$)$_2$), 4.98 (br s, 1H; -NH), 5.04 (s, 2H; benzyl CH_2), 5.21 (br s, 1H; -NH), 5.62 (br s, 1H; -NH), 7.22 (s, 2H; Ar-H gallate), 7.25 (br s, 1H; Ar-H), 7.30–7.35 (br m, 5H; benzyl Ar-H), 7.67 (br s, 1H; Ar-H), 7.70 ppm (br s, 1H; Ar-H); ^{13}C NMR (CD_3OD, 125 MHz): δ = 28.71, 30.21, 31.31, 31.62, 32.75, 33.17, 33.43, 38.09, 40.10, 40.68, 59.02, 66.77, 70.24, 70.41, 70.51, 70.56, 70.93, 71.31, 71.94, 77.86, 78.11, 109.08, 127.88, 128.11, 128.29, 128.76, 130.05, 132.66, 137.13, 142.06, 142.61, 142.38, 152.23, 157.04, 157.55, 167.85 ppm; MS (MALDI-TOF, dithranol): *m/z*: 1434.94 [*M*+Na]$^+$ ($^{12}C_{70}{}^1H_{113}{}^{14}N_3{}^{16}O_{26}{}^{23}$Na) calcd monoisotopic peak 1434.75; 1450.89 [*M*+K]$^+$ ($^{12}C_{70}{}^1H_{113}{}^{14}N_3{}^{16}O_{26}{}^{39}$K) calcd monoisotopic peak 1450.72; 1456.90 [M−H+2Na]$^+$ ($^{12}C_{70}{}^1H_{112}{}^{14}N_3{}^{16}O_{26}{}^{23}Na_2$) calcd monoisotopic peak 1456.73.

Ethyl 3-(3-{4-[3-(2,3-bis-*tert*-butoxycarbonylamino-propionylamido)-propoxy]-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoylamino}propyl)-5-[3-(5-dimethylaminonaphthalene-1-sulfonylamino)propoxy][3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoylamino]propyl)]benzoate (49): Compound **13** (0.44 g, 0.37 mmol) was dissolved in dry dichloromethane (5 mL). The solution was cooled to −20 °C and HOBt (0.06 g, 0.41 mmol) and EDC (0.09 g, 0.45 mmol) were added. The mixture was stirred for 1 h at −20 °C and then allowed to warm to room temperature. The esterification was monitored with TLC. After complete conversion, the mixture was cooled to −40 °C, and a solution of **45** (0.35 g, 0.23 mmol) and dry triethylamine (0.2 mL) in absolute methanol (3 mL) was added. The reaction mixture was stirred for 1 h at −40 °C, allowed to warm to room temperature, and monitored with TLC. The solvents were evaporated. The crude product was purified by column chromatography (silica gel; dichloromethane/methanol 20:1 increasing to 10:1). The yellowish oil was dissolved in benzene, filtered, and lyophilized. Yield: 0.54 g (90%) of a yellowish oil.

R_f = 0.23 (silica gel; dichloromethane/methanol (15:1)); ^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 1.32 and 1.40 (2 s, 18H; -C(CH_3)$_3$), 1.36 (t, ^3J(H,H) = 7.2 Hz, 3H; -CH_2CH_3), 1.78 (m, 4H; β″-CH_2), 1.88 (m, 2H; β′-CH_2), 1.93 (m, 4H; β-CH_2), 2.72 (t, ^3J(H,H) = 7.6 Hz, 4H; α-CH_2), 2.88 (s, 6H; -N(CH_3)$_2$), 3.22 (m, 2H; γ″-CH_2), 3.29 and 3.30 (2 s, 24H; -OCH_3), 3.41 (m, 6H; γ-CH_2 and γ′-CH_2), 3.44–3.62 (2 m, 96H; -OCH_2CH_2O), 3.63 (m, 2H; α′-CH_2), 3.67 (d, 8H; ^3J(H,H) = 5.0 Hz, -OCH(CH_2)$_2$), 3.72 (d, ^3J(H,H) = 4.9 Hz, 4H; -OCH(CH_2)$_2$), 3.75 (d, ^3J(H,H) = 4.9 Hz, 4H; -OCH(CH_2)$_2$), 3.97 (t, ^3J(H,H) = 5.6 Hz, 2H; α″-CH_2), 4.02 and 4.09 and 4.12 (m, 3H; -CH_2NHBoc and -C*H*NHBoc), 4.32 (q, ^3J(H,H) = 7.2 Hz, 2H; -CH_2CH$_3$), 4.57 (quint, ^3J(H,H) = 5.0 Hz, 2H; -OC*H*(CH$_2$)$_2$), 4.63 (quint, ^3J(H,H) = 4.9 Hz, 2H; -OC*H*(CH$_2$)$_2$), 5.45 (br s, 1H; -CH$_2$N*H*Boc), 5.93 (br s, 1H; -CHN*H*Boc), 6.26 (t, ^3J(H,H) = 6.1 Hz, 2H; -NH″), 7.12 (m, 2H; -NHAr), 7.18 (d, ^3J(H,H) = 7.6 Hz, 1H; Ar-H dansyl), 7.23 and 7.25 (2 s, 4H; Ar-H gallate), 7.29 (t, ^4J(H,H) = 1.5 Hz, 1H; Ar-H dendron), 7.32 (br s, 1H; -NH′), 7.50 (dd, ^3J(H,H) = 8.7 Hz, ^3J(H,H) = 7.6 Hz, 1H; Ar-H dansyl), 7.54 (dd, ^3J(H,H) = 8.5 Hz, ^3J(H,H) = 7.3 Hz, 1H; Ar-H dansyl), 7.71 (d, ^4J(H,H) = 1.5 Hz, 2H; Ar-H dendron), 8.22 (dd, ^3J(H,H) = 7.3 Hz, ^4J(H,H) = 1.2 Hz, 1H; Ar-H dansyl), 8.33 (d, ^3J(H,H) = 8.7 Hz, 1H; Ar-H dansyl), 8.52 ppm (d, ^3J(H,H) = 8.5 Hz, 1H; Ar-H dansyl); ^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 14.19, 28.02, 28.13, 29.62, 30.16, 31.31, 33.12, 37.47, 39.71, 40.95, 42.73, 45.22, 45.25, 55.08, 58.57, 60.82, 70.33, 70.37, 70.38, 70.40, 70.42, 70.44, 70.45, 70.78, 70.81, 71.02, 71.87, 77.61, 77.87, 79.06, 79.31, 108.62, 108.75, 115.15, 119.49, 123.30, 126.95, 127.91, 129.00, 129.72, 129.84, 129.89, 130.10, 130.15, 130.78, 133.25, 136.03, 142.02, 142.19, 142.37, 151.59, 151.86, 151.97, 155.70, 156.44, 166.50, 166.52, 166.58, 170.28 ppm; MS (MALDI-TOF, dithranol): *m/z*: 2689.42 [*M*+Na]$^+$ ($^{12}C_{128}{}^1H_{215}{}^{14}N_7{}^{16}O_{49}{}^{23}$Na) calcd monoisotopic peak 2689.42.

3-(3-{4-[3-(2,3-bis-*tert*-Butoxycarbonylaminopropionylamido)propoxy]-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoylamino}propyl)-5-[3-(5-dimethylamino-naphthalene-1-sulfonylamino)-propoxy][3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoylamino]propyl)]benzoic acid (50): Compound **49** (0.52 g, 0.20 mmol) was dissolved in ethanol (10 mL) and 1 M aqueous KOH (1 mL) added at room temperature. The mixture was stirred for 12 h in the dark. The reaction was quenched by the addition of 1 M aqueous HCl (pH 5). The solvent was removed under reduced pressure. The crude product was diluted with dichloromethaneand filtered. No further purification was carried out. The yellowish oil was dissolved in benzene, filtered, and lyophilized. Yield: 0.48 g (93%) of a yellowish oil.

R_f = 0.14 (silica gel; dichloromethane/methanol (15:1)); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.28 and 1.37 (2 s, 18H; -C(CH_3)$_3$), 1.76 (m, 4H; β″-CH_2), 1.87 (m, 2H; β′-CH_2), 1.92 (m, 4H; β-CH_2), 2.67 (m, 4H; α-CH_2), 2.82 (s, 6H; -N(CH_3)$_2$), 3.21 (m, 2H; γ″-CH_2), 3.28 and 3.29 (2 s, 24H; -OCH_3), 3.40 (m, 6H; γ-CH_2 and γ′-CH_2), 3.44–3.62 (2 m, 96H; -OCH_2CH_2O), 3.61 (m, 2H; α′-CH_2), 3.64 (m, 8H; -OCH(CH_2)$_2$), 3.68 (m, 4H; -OCH(CH_2)$_2$), 3.72 (m, 4H; -OCH(CH_2)$_2$), 3.95 (t, ^3J(H,H) = 5.2 Hz, 2H; α″-CH_2), 4.00, 4.08, and 4.20 (m, 3H; -CH_2NHBoc and -C*H*NHBoc), 4.53 (m, 2H; -OC*H*(CH$_2$)$_2$), 4.59 (m, 2H; -OC*H*(CH$_2$)$_2$), 5.56 (br s, 1H; -CH$_2$N*H*Boc), 6.00 (br s, 1H; -CHN*H*Boc), 6.41 (t, ^3J(H,H) = 6.2 Hz, 2H; -NH″), 7.10 (d, ^3J(H,H) = 7.4 Hz, 1H; Ar-H dansyl), 7.23 (s, 1H; Ar-H dendron), 7.25 and 7.26 (2 s, 4H; Ar-H gallate), 7.43 (m, 1H; Ar-H dansyl), 7.48 (m, 1H; Ar-H dansyl), 7.69 (s, 2H; Ar-H dendron), 8.20 (d, ^3J(H,H) = 7.3 Hz, 1H; Ar-H dansyl), 8.32 (d, ^3J(H,H) = 8.7 Hz, 1H; Ar-H dansyl), 8.57 ppm (d, ^3J(H,H) = 8.5 Hz, 1H; Ar-H dansyl); ^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 27.55, 27.69, 28.82, 29.43, 30.29, 32.42, 36.82, 38.98, 39.05, 40.15, 42.05, 44.70, 54.34, 58.14, 69.65, 69.69, 69.71, 69.79, 70.02, 70.05, 70.20, 71.14, 76.87, 77.13, 78.41, 78.66, 108.14, 108.30, 114.40, 118.78, 122.51, 126.72, 127.25, 128.23, 129.05, 129.12, 129.16, 129.23, 130.09, 132.51, 135.31, 141.41, 141.45, 141.55, 151.02, 151.09, 151.20, 155.06, 155.82, 166.09, 166.15, 167.76, 169.88 ppm; MS (MALDI-TOF, dithranol): *m/z*: 2683.38 [*M*−H+2Na]$^+$ ($^{12}C_{126}{}^1H_{210}{}^{14}N_7{}^{16}O_{49}{}^{23}Na_2$) calcd monoisotopic peak 2683.37; 2677.38 [*M*+K]$^+$ ($^{12}C_{126}{}^1H_{211}{}^{14}N_7{}^{16}O_{49}{}^{39}$K) calcd monoisotopic peak 2677.36; 2661.42 [*M*+Na]$^+$ ($^{12}C_{126}{}^1H_{211}{}^{14}N_7{}^{16}O_{49}{}^{23}$Na) calcd monoisotopic peak 2661.38.

Ethyl 3-(3-{4-(3-benzyloxycarbonylaminopropoxy)-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoylamino}propyl)-5-(3-{4-[3-(2,3-bis-*tert*-butoxycarbonylaminopropionylamido)propoxy]-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoylamino}propyl)benzoate (51): Compound **10b** (0.40 g, 0.36 mmol) was dissolved in dry dichloromethane (7 mL). The solution was cooled to −20 °C and HOBt (0.06 g, 0.40 mmol) and EDC (85 mg, 0.44 mmol) were added. The mixture was stirred for 1 h at −20 °C and then allowed to

warm to room temperature. The esterification was monitored with TLC. After complete conversion, the mixture was cooled to −40 °C, and a solution of **45** (0.35 g, 0.23 mmol) and dry triethylamine (0.2 mL) in absolute methanol was added. The reaction mixture was stirred for 1 h at −40 °C and then allowed to warm to room temperature. The solvents were evaporated. The crude product was purified by column chromatography (silica gel; dichloromethane/methanol 30:1 increasing to 15:1). The yellowish oil was dissolved in benzene, filtered, and lyophilized. Yield: 0.49 g (77 %) of a yellowish oil.

R_f = 0.21 (silica gel; dichloromethane/methanol 20:1); ^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 1.31 and 1.39 (2 s, 18 H; -C(CH_3)$_3$), 1.36 (t, ^3J(H,H) = 7.1 Hz, 3 H; -CH_2CH_3), 1.89 (m, 4 H; β′-CH_2), 1.92 (m, 4 H; β-CH_2), 2.71 (t, ^3J(H,H) = 7.9 Hz, 4 H; α-CH_2), 3.28 and 3.29 (2 s, 24 H; -OCH_3), 3.42 (m, 8 H; γ-CH_2 and γ′-CH_2), 3.43–3.65 (2 m, 96 H; -OCH_2CH_2O), 3.72 (m, 16 H; -OCH(CH_2)$_2$), 4.05 (t, ^3J(H,H) = 5.6 Hz, 4 H; α′-CH_2), 4.02, 4.09 and 4.12 (m, 3 H; -CH_2NHBoc and -CHNHBoc), 4.32 (q, ^3J(H,H) = 7.1 Hz, 2 H; -CH_2CH_3), 4.61 (m, 4 H; -OCH(CH_2)$_2$), 5.05 (s, 2 H; benzyl CH_2), 5.47 (m, 1 H; -NH), 5.93 (m, 1 H; -NH), 6.04 (t, ^3J(H,H) = 5.4 Hz, 2 H; -NH), 7.03 (t, ^3J(H,H) = 5.6 Hz, 2 H; -NH), 7.05 (t, ^3J(H,H) = 5.6 Hz, 2 H; -NH), 7.22 (s, 2 H; Ar-H), 7.24 (s, 2 H; Ar-H gallate), 7.26–7.36 (m, 5 H; benzyl Ar-H), 7.71 ppm (s, 1 H; Ar-H); ^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 14.18, 28.00, 28.12, 29.62, 29.87, 31.27, 33.07, 37.47, 38.49, 39.66, 42.73, 55.06, 58.55, 60.78, 66.07, 70.32, 70.33, 70.37, 70.39, 70.41, 70.42, 70.43, 70.44, 70.75, 70.80, 70.82, 71.86, 77.65, 77.79, 79.01, 79.26, 108.66, 126.94, 127.83, 127.99, 128.37, 130.13, 130.16, 130.78, 133.21, 137.31, 142.17, 142.31, 142.32, 151.96, 151.97, 156.42, 166.52, 166.55, 170.23 ppm; MS (MALDI-TOF, dithranol): *m/z*: 2606.33 $[M+K]^+$ ($^{12}C_{124}{}^1H_{210}{}^{14}N_6{}^{16}O_{49}{}^{39}K$) calcd monoisotopic peak 2606.38; 2590.36 $[M+Na]^+$ calcd monoisotopic peak ($^{12}C_{124}{}^1H_{210}{}^{14}N_6{}^{16}O_{49}{}^{23}Na$) 2590.40.

3-(3-{4-(3-Benzyloxycarbonylaminopropoxy)-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy) ethoxy]ethoxy}propan-2-yloxy)benzoylamino}propyl)-5-(3-{4-[3-(2,3-bis-*tert*-butoxycarbonylaminopropionylamido)propoxy]-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoylamino}propyl)benzoic acid (52): Compound **51** (0.47 g, 0.18 mmol) was dissolved in ethanol (10 mL) and 1 M aqueous KOH (1 mL) added at room temperature. The mixture was stirred for 12 h. The reaction was quenched by the addition of 1 M aqueous HCl (pH 5). The solvent was removed under reduced pressure. The crude product was diluted with dichloromethaneand filtered. No further purification was carried out. The yellowish oil was dissolved in benzene, filtered, and lyophilized. Yield: 0.46 g (99 %) of a yellowish oil.

R_f = 0.17 (silica gel; dichloromethane/methanol (20:1)); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.20 and 1.28 (2 s, 18 H; -C(CH_3)$_3$), 1.78 (m, 4 H; β′-CH_2), 1.84 (m, 4 H; β-CH_2), 2.59 (t, ^3J(H,H) = 7.4 Hz, 4 H; α-CH_2), 3.21 and 3.22 (2 s, 24 H; -OCH_3), 3.32 (m, 8 H; γ-CH_2 and γ′-CH_2), 3.37–3.55 (2 m, 96 H; -OCH_2CH_2O), 3.60 (m, 16 H; -OCH(CH_2)$_2$), 3.93 (t, ^3J(H,H) = 5.8 Hz, 4 H; α′-CH_2), 3.91, 3.98 and 4.10 (m, 3 H; -CH_2NHBoc and -CHNHBoc), 4.49 (m, 4 H; -OCH(CH_2)$_2$), 4.96 (s, 2 H; benzyl CH_2), 5.33 (m, 1 H; -NH), 5.82 (t, ^3J(H,H) = 7.4 Hz, 1 H; -CHNHBoc), 6.05 (t, ^3J(H,H) = 5.6 Hz, 2 H; -NH), 7.13 (s, 2 H; Ar-H), 7.14 (s, 2 H; Ar-H gallate), 7.16 (m, 2 H; NH), 7.17–7.24 (m, 5 H; benzyl Ar-H), 7.59 ppm (s, 1 H; Ar-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 27.81, 27.93, 29.08, 29.31, 30.51, 32.66, 37.06, 38.03, 39.27, 42.38, 54.48, 58.43, 58.44, 65.87, 69.96, 69.96, 69.98, 70.07, 70.27, 70.30, 70.32, 70.66, 71.42, 71.45, 77.19, 78.78, 79.02, 108.36, 127.01, 127.51, 127.72, 127.98, 129.46, 130.09, 132.83, 136.48, 141.67, 141.74, 141.82, 151.44, 155.34, 156.08, 156.23, 166.35, 166.42, 167.95, 170.08 ppm; MS (MALDI-TOF, dithranol): *m/z*: 2578.42 $[M+K]^+$ ($^{12}C_{122}{}^1H_{206}{}^{14}N_6{}^{16}O_{49}{}^{39}K$) calcd monoisotopic peak 2578.34; 2562.44 $[M+Na]^+$ calcd monoisotopic peak ($^{12}C_{122}{}^1H_{206}{}^{14}N_6{}^{16}O_{49}{}^{23}Na$) 2562.37.

Ethyl 3-(3-{4-(3-*tert*-butoxycarbonylamino-propoxy)-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoylamino}propyl){5-[3-(5-dimethylamino-naphthalene-1-sulfonylamino)propoxy][3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoylamino]propyl)}benzoate (53): Compound **13** (0.24 g, 0.20 mmol) was dissolved in dry dichloromethane (5 mL). The solution was cooled to −20 °C and HOBt (34 mg, 0.22 mmol) and EDC (46 mg, 0.24 mmol) were added. The mixture was stirred for 1 h at −20 °C and then allowed to warm to room temperature. The esterification was monitored with TLC. After complete conversion, the mixture was cooled to −40 °C, and a solution of **47** (0.19 g, 0.14 mmol) and dry triethylamine (0.3 mL) in absolute methanol (1 mL) was added. The reaction mixture was stirred for 1 h at −40 °C, allowed to warm to room temperature, and monitored with TLC. The solvents were evaporated. The crude product was purified by column chromatography (silica gel; dichloromethane/methanol 20:1 increasing to 10:1). The yellowish oil was dissolved in benzene, filtered, and lyophilized. Yield: 0.340 g (95 %) of a yellowish oil.

R_f = 0.28 (silica gel; dichloromethane/methanol (15:1)); ^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 1.36 (t, ^3J(H,H) = 7.1 Hz, 3 H; -CH_2CH_3), 1.41 (s, 9 H; -C(CH_3)$_3$), 1.78 (m, 2 H; β′-CH_2), 1.86 (m, 2 H; β″-CH_2), 1.93 (m, 4 H; β-CH_2), 2.71 (t, ^3J(H,H) = 7.6 Hz, 4 H; α-CH_2), 2.86 (s, 6 H; -N-(CH_3)$_2$), 3.22 (m, 2 H; γ′-CH_2), 3.29 (2 s, 24 H; -OCH_3), 3.33 (m, 2 H; γ″-CH_2), 3.40 (m, 4 H; γ-CH_2), 3.43–3.60 (2 m, 96 H; -OCH_2CH_2O), 3.60–3.76 (3 m, 16 H; -OCH(CH_2)$_2$), 3.97 (t, ^3J(H,H) = 5.4 Hz, 2 H; α′-CH_2), 4.04 (t, ^3J(H,H) = 5.4 Hz, 2 H; α″-CH_2), 4.32 (q, ^3J(H,H) = 7.1 Hz, 2 H; -CH_2CH_3), 4.48, 4.56 and 4.62 (3 m, 4 H; -OCH(CH_2)$_2$), 5.62 (br s, 1 H; -NH″), 6.25 (t, ^3J(H,H) = 6.1 Hz, 1 H; -NH′), 7.03 (br s, 2 H; -NH), 7.16 (m, 1 H; Ar-H dansyl), 7.22 and 7.24 (2 s, 4 H; Ar-H gallate), 7.29 (s, 1 H; Ar-H dendron), 7.48 (m, 1 H; Ar-H dansyl), 7.53 (m, 1 H; Ar-H dansyl), 7.71 (m, 1 H; Ar-H dendron), 8.22 (d, ^3J(H,H) = 7.3 Hz, 1 H; Ar-H dansyl), 8.31 (d, ^3J(H,H) = 8.7 Hz, 1 H; Ar-H *d*ansyl), 8.51 ppm (d, ^3J-(H,H) = 8.5 Hz, 1 H; Ar-H dansyl); ^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 14.17, 28.28, 29.62, 30.15, 31.26, 33.08, 37.91, 39.63, 40.90, 45.18, 58.53, 58.54, 60.77, 70.28, 70.30, 70.33, 70.35, 70.38, 70.39, 70.41, 70.43, 70.44, 70.47, 70.74, 70.84, 71.83, 71.84, 71.86, 77.71, 77.81, 78.26, 108.63, 108.70, 115.02, 119.27, 123.18, 126.94, 127.89, 128.93, 129.70, 129.89, 129.92, 130.07, 130.09, 130.73, 133.23, 136.01, 142.35, 151.82, 151.87, 151.95, 155.91, 166.48, 166.54 ppm; MS (MALDI-TOF, dithranol): *m/z*: 2519.24 $[M+K]^+$ ($^{12}C_{120}{}^1H_{201}{}^{14}N_5{}^{16}O_{46}{}^{39}K$) calcd monoisotopic peak 2519.29; 2503.45 $[M+Na]^+$ ($^{12}C_{120}{}^1H_{201}{}^{14}N_5{}^{16}O_{46}{}^{23}Na$) calcd monoisotopic peak 2503.32.

3-(3-{4-(3-*tert*-Butoxycarbonylamino-propoxy)-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoylamino}propyl){5-[3-(5-dimethylaminonaphthalene-1-sulfonylamino)propoxy][3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoylamino]-propyl)}benzoic acid (54): Compound **53** (0.33 g, 0.13 mmol) was dissolved in ethanol (5 mL) and 1 M aqueous KOH (1 mL) added at room temperature. The mixture was stirred for 12 h in the dark. The reaction was quenched by the addition of 1 M aqueous HCl (pH 5). The solvent was removed under reduced pressure. The crude product was diluted with dichloromethaneand filtered. No further purification was carried out. The yellowish oil was dissolved in benzene, filtered, and lyophilized. Yield: 0.24 g (73 %) of a yellowish oil.

R_f = 0.24 (silica gel; dichloromethane/methanol (10:1)); ^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 1.41 (s, 9 H; -C(CH_3)$_3$), 1.78 (m, 2 H; β″-CH_2), 1.85 (m, 2 H; β′-CH_2), 1.94 (m, 4 H; β-CH_2), 2.70 (t, ^3J(H,H) = 6.9 Hz, 4 H;α-CH_2), 2.85 (s, 6 H; -N(CH_3)$_2$), 3.22 (m, 2 H; γ″-CH_2), 3.29 (m, 24 H; -OCH_3), 3.33 (m, 2 H; γ′-CH_2), 3.40 (m, 4 H; γ-CH_2), 3.43–3.60 (2 m, 96 H; -OCH_2CH_2O), 3.60–3.77 (3 m, 16 H; -OCH(CH_2)$_2$), 3.97 (t, ^3J-(H,H) = 6.1 Hz, 2 H; α″-CH_2), 4.04 (t, ^3J(H,H) = 5.6 Hz, 2 H; α″-CH_2), 4.48, 4.57 and 4.63 (3 m, 4 H; -OCH(CH_2)$_2$), 5.65 (br s, 1 H; -NH′), 6.32 (m, 1 H; -NH″), 7.16 (m, 1 H; Ar-H dansyl), 7.20 (br s, 2 H; -NH), 7.22 and 7.24 (2 s, 4 H; Ar-H gallate), 7.26 (s, 1 H; Ar-H dendron), 7.48 (m, 1 H; Ar-H dansyl), 7.53 (m, 1 H; Ar-H dansyl), 7.70 (m, 1 H; Ar-H dendron), 8.21 (d, ^3J(H,H) = 7.2 Hz, 1 H; Ar-H dansyl), 8.32 (d, ^3J(H,H) = 8.7 Hz, 1 H; Ar-H dansyl), 8.51 ppm (d, ^3J(H,H) = 8.7 Hz, 1 H; Ar-H dansyl); ^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 28.26, 30.03, 30.14, 30.89, 32.99, 37.91, 39.58, 40.87, 45.18, 58.51, 70.24, 70.26, 70.31, 70.35, 70.37, 70.38, 70.40, 70.41, 70.72, 70.81, 70.95, 71.19, 71.81, 71.82, 77.56, 77.66, 108.09, 108.55, 115.03, 119.30, 123.19, 127.31, 127.89, 128.91, 129.68, 129.86, 129.91, 130.02, 135.98, 142.24, 151.75, 151.88, 155.96, 166.59 ppm; MS (MALDI-TOF, dithranol): *m/z*: 2475.28 $[M+Na]^+$ ($^{12}C_{118}{}^1H_{197}{}^{14}N_5{}^{16}O_{46}{}^{23}Na$) calcd monoisotopic peak 2475.28; 2491.24 $[M+K]^+$ ($^{12}C_{118}{}^1H_{197}{}^{14}N_5{}^{16}O_{46}{}^{39}K$) calcd monoisotopic peak 2491.26.

1,3,5-Tris-[3-(3-{4-[3-(2,3-bis-*tert*-butoxycarbonylaminopropionylamido)-propoxy]-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoylamino}propyl)-5-[3-(5-dimethylamino-naphthalene-1-sulfo-

nylamino)propoxy][3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoylamino]propyl)]benzamidopropyl]benzene (55): Compound **50** (0.44 g, 0.165 mmol) was dissolved in dry dichloromethane (10 mL). The solution was cooled to −20 °C and HOBt (0.03 g, 0.196 mmol) and EDC (0.04 g, 0.21 mmol) were added. The mixture was stirred for 1 h at −20 °C and then allowed to warm to room temperature. The esterification was monitored with TLC. After complete conversion, the mixture was cooled to −40 °C, and a solution of **27** (17 mg, 0.05 mmol) and dry TEA (0.5 mL) in absolute methanol (2 mL) was added. The reaction mixture was stirred for 1 h at −40 °C and then allowed to warm to room temperature. The solvent was evaporated. The crude product was extracted twice with 1 M aqueous $NaHCO_3$ and once with brine, and purified by column chromatography. The greenish oil was dissolved in benzene, filtered, and lyophilized. Yield: 0.334 g (84 %) of a yellowish oil.

R_f = 0.10 (silica gel; dichloromethane/methanol (10:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.24 and 1.30 (2 s, 18 H; -C(CH_3)$_3$), 1.69 (m, 6 H; β′-CH_2), 1.79 (m, 6 H; β″-CH_2), 1.82 (m, 18 H; β-CH_2), 2.53 (m, 6 H; α-CH_2), 2.56 (m, 12 H; α*-CH_2), 2.77 (s, 18 H; -N(CH_3)$_2$), 3.13 (m, 6 H; γ′-CH_2), 3.21 and 3.23 (2 s, 72 H; -OCH_3), 3.31 (m, 18 H; γ-CH_2), 3.35 (m, 6 H; γ-″CH_2), 3.37–3.55 (2 m, 288 H; -OCH_2CH_2O), 3.57, 3.60 and 3.66 (3 m, 48 H; -OCH(CH_2)$_2$), 3.89 (t, ^3J(H,H) = 5.4 Hz, 6 H; α′-CH_2), 3.97 (t, ^3J(H,H) = 5.6 Hz, 6 H; α″-CH_2), 3.93, 3.99 and 4.10 (m, 9 H; -CH_2NHBoc and -C*H*NHBoc), 4.44 and 4.49 (2 m, 12 H; -OC*H*(CH_2)$_2$), 5.30 (br s, 3 H; -CH_2N*H*Boc), 5.77 (d, ^3J(H,H) = 7.2 Hz, 3 H; -CHN*H*Boc), 6.26 (t, ^3J(H,H) = 5.9 Hz, 3 H; -NH″), 6.78 (s, 3 H; Ar-H core), 7.04 (d, ^3J(H,H) = 7.6 Hz, 1 H; Ar-H dansyl), 7.06 (s, 3 H; Ar-H dendron), 7.08 (m, 3 H; -NH), 7.16 and 7.18 (2 s, 12 H; Ar-H gallate), 7.22 (m, 6 H; -NH), 7.27 (m, 1 H; -NH′), 7.36 (m, 3 H; Ar-H dansyl), 7.39 (s, 6 H; Ar-H dendron), 7.41 (m, 3 H; Ar-H dansyl), 8.13 (d, ^3J(H,H) = 7.3 Hz, 1 H; Ar-H dansyl), 8.25 (d, ^3J(H,H) = 8.7 Hz, 1 H; Ar-H dansyl), 8.41 ppm (d, ^3J(H,H) = 8.5 Hz, 1 H; Ar-H dansyl); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 27.96, 28.07, 29.27, 30.67, 30.71, 32.75, 32.92, 37.16, 39.29, 39.33, 39.49, 40.54, 42.59, 45.12, 58.59, 70.01, 70.10, 70.21, 70.41, 70.45, 70.54, 70.64, 71.56, 77.20, 77.42, 77.66, 78.93, 79.18, 108.77, 108.84, 114.80, 119.22, 122.90, 124.50, 124.59, 125.93, 127.62, 128.65, 129.47, 129.56, 129.60, 131.15, 131.21, 131.23, 134.71, 135.65, 141.44, 141.65, 141.70, 141.97, 142.11, 151.35, 151.53, 151.62, 155.43, 156.16, 166.48, 166.53, 167.54, 170.06 ppm; MS (MALDI-TOF, dithranol): *m/z*: 8137.30 $[M+Na]^+$ ($C_{393}H_{654}N_{24}O_{144}S_3Na$) calcd molecular weight peak 8138.61.

1,3,5-Tris-[3-(3-{4-[3-(2,3-diaminopropionylamido)propoxy]-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoylamino}-propyl)-5-[3-(5-dimethylaminonaphthalene-1-sulfonylamino)propoxy][3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)-benzoylamino]propyl)]benzamidopropyl]benzene hexakis-trifluoroacetato (56): Compound **55** (0.30 g, 0.165 mmol) was dissolved in dichloromethane (10 mL) and TFA (5 mL) was added at room temperature. The deprotection was monitored with ^{1}H NMR. The solvent was evaporated and remaining TFA was removed by co-evaporation with methylene chloride. The sample was dried in high vacuum. No further purification was carried out. Yield: 0.297 g (98 %) of a yellowish oil.

^{1}H NMR (CD_3OD, 500 MHz): δ = 1.72 (m, 12 H; β′-CH_2), 1.86 (m, 12 H; β-CH_2), 1.91 (m, 6 H; β-CH_2), 2.55 (t, ^3J(H,H) = 7.1 Hz, 6 H; α-CH_2), 2.63 (m, ^3J(H,H) = 7.1 Hz, 12 H; α*-CH_2), 2.97 (s, 18 H; -N(CH_3)$_2$), 3.10 (t, ^3J(H,H) = 6.9 Hz, 12 H; γ′-CH_2), 3.21 and 3.24 (2 s, 72 H; -OCH_3), 3.31 (m, 18 H; γ-CH_2), 3.37–3.50 (2 m, 288 H; -OCH_2CH_2O), 3.51 and 3.56 (2 m, 48 H; -OCH(CH_2)$_2$), 3.91 (t, ^3J(H,H) = 5.7 Hz, 12 H; α′-CH_2), 4.05, 4.13 and 4.21 (m, 9 H; -CH_2NHBoc and -C*H*NHBoc), 4.48 and 4.65 (2 m, 12 H; -OC*H*(CH_2)$_2$), 6.84 (s, 3 H; Ar-H core), 7.17 (s, 6 H; Ar-H gallate), 7.19 (s, 3 H; Ar-H dendron), 7.23 (s, 6 H; Ar-H gallate), 7.40 (d, ^3J(H,H) = 7.8 Hz, 1 H; Ar-H dansyl), 7.43 (m, 6 H; Ar-H dendron), 7.55 (m, 3 H; Ar-H dansyl), 7.60 (m, 3 H; Ar-H dansyl), 8.19 (d, ^3J(H,H) = 7.3 Hz, 3 H; Ar-H dansyl), 8.45 ppm (m, 6 H; Ar-H dansyl); ^{13}C NMR (CD_3OD, 125 MHz): δ = 30.41, 30.67, 31.58, 32.13, 32.17, 34.09, 34.32, 39.56, 40.68, 40.78, 41.04, 41.82, 46.04, 52.14, 59.05, 59.10, 71.18, 71.26, 71.37, 71.45, 71.71, 71.76, 71.88, 71.97, 72.80, 72.88, 73.62, 78.47, 79.03, 109.61, 109.83, 116.78, 121.29, 124.81, 126.02, 126.11, 127.34, 129.11, 130.22, 130.66, 130.96, 131.10, 132.85, 136.03, 137.44, 153.16, 153.25, 166.38, 168.87, 168.99, 169.99 ppm; MS (MALDI-TOF, CCA): *m/z*: 7926.26 $[M+3\,CCA-6\,H_2O]^+$ ($C_{393}H_{615}N_{27}O_{132}S_3$) calcd molecular weight peak 7926.48.

1,3,5-Tris-[3-(3-{4-(3-Benzyloxycarbonylaminopropoxy)-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoylamino}propyl)-5-(3-{4-[3-(2,3-bis-*tert*-butoxycarbonylaminopropionylamido)propoxy]-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoylamino}propyl)]benzamidopropyl]benzene (57): Compound **52** (0.27 g, 0.10 mmol) was dissolved in dry dichloromethane (4 mL). The solution was cooled to −20 °C and HOBt (0.02 g, 0.14 mmol) and EDC (0.03 g, 0.144 mmol) were added. The mixture was stirred for 1 h at −20 °C and then allowed to warm to room temperature. The esterification was monitored with TLC. After complete conversion, the mixture was cooled to −40 °C, and a solution of **27** (0.01 g, 0.03 mmol) and dry TEA (0.3 mL) in absolute methanol (0.5 mL) was added. The reaction mixture was stirred for 1 h at −40 °C and then allowed to warm to room temperature. The solution was extracted twice with 1 M aqueous $NaHCO_3$ and once with brine, and purified by column chromatography. The colorless oil was dissolved in benzene, filtered, and lyophilized. Yield: 0.20 g (91 %) of a colorless oil. R_f = 0.12 (silica gel; dichloromethane/methanol (10:1)); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.26 and 1.32 (2 s, 54 H; -C(CH_3)$_3$), 1.82 (m, 30 H; β-CH_2), 2.55 (m, 6 H; α-CH_2), 2.58 (m, 12 H; α*-CH_2), 3.13 (m, 6 H; γ′-CH_2), 3.24 and 3.25 (2 s, 72 H; -OCH_3), 3.34 (m, 18 H; γ-CH_2), 3.38 (m, 12 H; γ′-CH_2), 3.39–3.59 (2 m, 288 H; -OCH_2CH_2O), 3.62 and 3.66 (2 m, 48 H; -OCH(CH_2)$_2$), 3.96 (t, ^3J(H,H) = 5.6 Hz, 12 H; α′-CH_2), 3.94, 4.01 and 4.12 (m, 9 H; -CH_2NHBoc and -C*H*NHBoc), 4.50 (m, 12 H; -OC*H*(CH_2)$_2$), 4.99 (s, 6 H; benzyl CH_2), 5.30 (br s, 3 H; -CH_2N*H*Boc), 5.80 (d, ^3J(H,H) = 7.3 Hz, 3 H; -CHN*H*Boc), 6.05 (t, ^3J(H,H) = 5.8 Hz, 3 H; -NH′), 6.80 (s, 3 H; Ar-H core), 7.05 (m, 3 H; NH), 7.08 (s, 3 H; Ar-H dendron), 7.13–7.33 (br m, 33 H; Ar-H gallate, benzyl Ar-H, -NH), 7.40 ppm (s, 6 H; Ar-H dendron); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 28.06, 28.16, 29.38, 29.58, 30.82, 30.92, 32.83, 33.03, 37.26, 38.23, 39.42, 39.45, 39.60, 42.71, 54.57, 58.70, 58.71, 66.10, 70.16, 70.22, 70.23, 70.32, 70.33, 70.52, 70.55, 70.57, 71.67, 77.20, 77.58, 77.63, 79.06, 79.32, 108.82, 108.94, 124.60, 124.66, 126.02, 127.74, 127.96, 128.22, 129.70, 131.25, 134.84, 136.74, 141.52, 141.77, 141.79, 142.18, 142.27, 151.74, 155.52, 156.26, 156.43, 166.60, 166.67, 167.63, 170.16 ppm; MS (MALDI-TOF, dithranol): *m/z*: 7841.79 $[M+Na]^+$ ($C_{381}H_{639}N_{21}O_{144}Na$) calcd molecular weight peak 7841.19.

1,3,5-Tris-[3-(3-{4-(3-*tert*-butoxycarbonylaminopropoxy)-3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoylamino}propyl){5-[3-(5-dimethylaminonaphthalene-1-sulfonylamino)propoxy][3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)benzoylamino]propyl)}benzamidopropyl]benzene (58): Compound **54** (0.225 g, 0.095 mmol) was dissolved in dry dichloromethane (6 mL). The solution was cooled to −20 °C and HOBt (16 mg, 0.10 mmol) and EDC (22 mg, 0.15 mmol) were added. The mixture was stirred for 1 h at −20 °C and then allowed to warm to room temperature. The esterification was monitored with TLC. After complete conversion, the mixture was cooled to −40 °C, and a solution of **27** (0.01 g, 0.03 mmol) and dry TEA (0.5 mL) in absolute methanol (2 mL) was added. The reaction mixture was stirred for 1 h at −40 °C and then allowed to warm to room temperature. The solvent was evaporated. The crude product was redissolved in dichloromethane, extracted twice with 1 M aqueous $NaHCO_3$ and once with brine, and purified by column chromatography. The greenish oil was dissolved in benzene, filtered, and lyophilized. Yield: 0.18 g (82 %) of a yellowish oil.

Alternatively, the same compound was synthesized as follows: Compound **10a** (0.20 g, 0.19 mmol) was dissolved in dry dichloromethane (10 mL). The solution was cooled to −20 °C and HOBt (0.03 g, 0.21 mmol) and EDC (44 mg, 0.30 mmol) were added. The mixture was stirred for 1 h at −20 °C and then allowed to warm to room temperature. The esterification was monitored with TLC. After complete conversion, the mixture was cooled to −40 °C, and a solution of **62** (0.25 g, 0.05 mmol) and dry triethylamine (0.5 mL) in absolute methanol (2 mL) was added. The reaction mixture was stirred for 1 h at −40 °C and then allowed to warm to room temperature. The crude product was extracted twice with 1 M aqueous $NaHCO_3$, once with brine, and purified by

column chromatography. The greenish oil was dissolved in benzene, filtered, and lyophilized. Yield: 0.35 g (89%) of a yellowish oil.

R_f = 0.19 (silica gel; dichloromethane/methanol (10:1)); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.36 (s, 27H; -C(CH_3)$_3$), 1.72 (m, 6H; β′-CH_2), 1.80 (m, 6H; β″-CH_2), 1.86 (m, 18H; β-CH_2), 2.56 (m, 6H; α-CH_2), 2.60 (m, 12H; α*-CH_2), 2.81 (s, 18H; -N(CH_3)$_2$), 3.18 (m, 6H; γ′-CH_2), 3.25 and 3.26 (2 s, 72H; -OCH_3), 3.30 (m, 6H; γ″-CH_2), 3.35 (m, 18H; γ-CH_2), 3.40–3.58 (2 m, 288H; -OCH_2CH_2O), 3.61 and 3.66 (2 m, 48H; -OCH(CH_2)$_2$), 3.92 (t, ^3J(H,H) = 5.4 Hz, 6H; α′-CH_2), 3.97 (t, ^3J(H,H) = 5.6 Hz, 6H; α″-CH_2), 4.39, 4.47, and 4.52 (3 m, 12H; -OC*H*(CH_2)$_2$), 5.60 (br s, 3H; -NH′), 6.26 (m, 3H; -NH″), 6.81 (s, 3H; Ar-H core), 7.10 (m, 3H; Ar-H dansyl), 7.15 (m, 6H; -NH), 7.18 and 7.19 (2 s, 12H; Ar-H gallate), 7.20 (s, 3H; Ar-H dendron), 7.42 (m, 9H; Ar-H dansyl), 8.16 (d, ^3J(H,H) = 7.2 Hz, 1H; Ar-H dansyl), 8.29 (d, ^3J(H,H) = 8.7 Hz, 1H; Ar-H dansyl), 8.45 ppm (d, ^3J(H,H) = 7.8 Hz, 1H; Ar-H dansyl); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 28.40, 29.48, 29.79, 29.90, 30.84, 30.86, 30.95, 32.88, 33.07, 37.73, 39.47, 39.66, 40.67, 40.72, 45.28, 58.75, 70.05, 70.23, 70.24, 70.25, 70.27, 70.29, 70.33, 70.35, 70.38, 70.54, 70.63, 70.68, 70.76, 70.97, 71.70, 71.71, 71.72, 77.20, 77.68, 77.81, 78.45, 108.93, 108.99, 114.96, 119.43, 123.07, 124.68, 126.04, 127.73, 128.79, 129.60, 129.61, 129.67, 129.70, 131.28, 132.08, 134.86, 135.80, 140.28, 141.55, 141.81, 141.83, 141.85, 142.12, 142.32, 142.35, 151.67, 151.80, 151.90, 155.99, 166.66, 166.70, 167.66, 170.66 ppm; MS (MALDI-TOF, dithranol): *m/z*: 7580.60 $[M+Na]^+$ ($C_{396}H_{612}N_{18}O_{135}S_3Na$) calcd molecular weight peak 7580.03.

1,3,5-Tris-[3-(3-benzyloxycarbonylaminopropyl)-5-(3-*tert*-butoxycarbonylamidopropyl)benzoylamidopropyl]benzene (59): Compound **43** (2.00 g, 4.25 mmol) was dissolved in dry dichloromethane (20 mL). The solution was cooled to −20 °C and HOBt (0.72 g, 4.67 mmol) and EDC (0.98 g, 5.14 mmol) were added. The mixture was stirred for one hour at −20 °C and then allowed to warm to room temperature. The esterification was monitored with TLC. After complete conversion, the mixture was cooled to −40 °C, and a solution of **27** (0.425 g, 1.18 mmol) and dry TEA (1 mL) in absolute methanol (5 mL) was added. The reaction mixture was stirred for 1 h at −40 °C and then allowed to warm to room temperature. The organic phase was extracted twice with 1 M $NaHCO_3$, once with brine, and dried. The solvents were evaporated. The crude product was purified by column chromatography (silica gel; dichloromethane/methanol (30:1)). Yield: 1.69 g (89%) of a colorless solid.

R_f = 0.30 (silica gel; dichloromethane/methanol (30:1)); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.39 (s, 27H; -C(CH_3)$_3$), 1.69 (m, 6H; β″-CH_2), 1.73 (m, 6H; β′-CH_2), 1.87 (m, 6H; β-CH_2), 2.52 (m, 6H; α″-CH_2), 2.53 (m, 6H; α′-CH_2), 2.56 (m, 6H; α-CH_2), 3.01 (m, 6H; γ″-CH_2), 3.10 (m, 6H; γ′-CH_2), 3.37 (m, 6H; γ-CH_2), 4.77 (br s, 3H; -NH″), 5.03 (s, 6H; -CH_2Ar), 5.20 (br s, 3H; -NH′), 6.81 (s, 3H; Ar-H core), 7.02 (s, 3H; Ar-H dendron), 7.04 (br s, 3H; -NH), 7.22–7.30 (m, 15H; benzyl Ar-H), 7.36 (s, 3H; Ar-H dendron), 7.38 ppm (s, 3H; Ar-H dendron); ^{13}C NMR (CD_3OD, 125 MHz): δ = 28.18, 30.64, 30.85, 31.03, 32.22, 32.89, 39.43, 39.93, 66.17, 78.75, 124.62, 124.68, 125.89, 127.65, 127.71, 128.16, 131.25, 134.60, 136.42, 141.44, 141.48, 141.56, 155.94, 156.42, 167.63 ppm; MS (MALDI-TOF, dithranol): *m/z*: 1645.99 $[M+Na]^+$ ($^{12}C_{93}{}^1H_{123}{}^{14}N_9{}^{16}O_{15}{}^{23}Na$) calcd monoisotopic peak 1629.99.

1,3,5-Tris-[3-(3-*tert*-butoxycarbonylamino-propyl)-5-({4-[3-(5-dimethylaminonaphthalene-1-sulfonylamido)propoxy]}[3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)]benzoylamidopropyl)benzoylamidopropyl]benzene (61): Compound **13** (0.97 g, 0.81 mmol) was dissolved in dry dichloromethane (30 mL). The solution was cooled to −20 °C and HOBt (0.14 g, 0.94 mmol) and EDC (0.19 g, 1.01 mmol) were added. The mixture was stirred for 1 h at −20 °C and then allowed to warm to room temperature. The esterification was monitored with TLC. After complete conversion, the mixture was cooled to −40 °C, and a solution of **60** (0.25 g, 0.21 mmol) and dry TEA (0.3 mL) in absolute methanol (3 mL) was added. The reaction mixture was stirred for 1 h at −40 °C and then allowed to warm to room temperature. The solvents were evaporated. The crude product was purified by column chromatography (silica gel; dichloromethane/methanol (25:1)). The greenish oil was dissolved in benzene, filtered and lyophilized. Yield: 0.950 g (97%) of a yellowish oil.

R_f = 0.29 (silica gel; dichloromethane/methanol (25:1)); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.32 (s, 27H; -C(CH_3)$_3$), 1.64 (m, 6H; β′-CH_2), 1.70 (m, 6H; β″-CH_2), 1.83 (m, 12H; β-CH_2), 2.47 (t, ^3J(H,H) = 7.4 Hz, 6H; α′-CH_2), 2.54 (m, 12H; α-CH_2), 2.77 (s, 18H; -N(CH_3)$_2$), 2.96 (m, 6H; γ′-CH_2), 3.15 (m, 6H; γ″-CH_2), 3.23 (s, 36H; -OCH_3), 3.32 (m, 12H; γ-CH_2), 3.37–3.52 (2 m, 144H; -OCH_2CH_2O), 3.58 (d, ^3J(H,H) = 5.0 Hz, 24H; -OCH(CH_2)$_2$), 3.89 (t, ^3J(H,H) = 5.4 Hz, 6H; α″-CH_2), 4.46 (quint, ^3J(H,H) = 5.0 Hz, 6H; -OC*H*(CH_2)$_2$), 4.91 (t, ^3J(H,H) = 5.6 Hz, 3H; -NH′), 6.28 (t, ^3J(H,H) = 6.3 Hz, 3H; -NH″), 6.79 (s, 3H; Ar-H core), 7.01 (s, 3H; Ar-H dendron), 7.04 (d, ^3J(H,H) = 7.6 Hz, 3H; Ar-H dansyl), 7.09 (t, ^3J(H,H) = 5.5 Hz, 3H; -NH), 7.17 (s, 6H; Ar-H gallate), 7.23 (t, ^3J(H,H) = 5.6 Hz, 3H; -NH), 7.32 (s, 3H; Ar-H dendron), 7.36 (m, 3H; Ar-H dansyl), 7.36 (s, 3H; Ar-H dendron), 7.41 (dd, ^3J(H,H) = 8.5 Hz, ^3J-(H,H) = 7.4 Hz, 3H; Ar-H dansyl), 8.14 (dd, ^3J(H,H) = 7.3 Hz, ^4J(H,H) = 1.1 Hz, 3H; Ar-H dansyl), 8.25 (d, ^3J(H,H) = 8.7 Hz, 3H; Ar-H dansyl), 8.41 ppm (d, ^3J(H,H) = 8.4 Hz, 3H; Ar-H dansyl); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 27.81, 29.50, 30.25, 30.70, 31.92, 32.30, 32.56, 38.92, 39.02, 39.09, 40.20, 44.71, 58.15, 69.66, 69.70, 69.72, 69.75, 69.82, 70.04, 70.22, 71.17, 77.19, 78.03, 108.43, 114.42, 118.80, 122.52, 124.24, 125.55, 127.26, 128.24, 129.08, 129.19, 129.26, 130.72, 134.22, 135.35, 141.15, 141.23, 141.58, 151.06, 151.16, 155.55, 166.17, 167.11 ppm; MS (MALDI-TOF, dithranol): *m/z*: 4754.01 $[M+Na]^+$ ($C_{237}H_{375}N_{15}O_{75}S_3Na$) calcd molecular weight peak 4754.01; 4428.57 $[M+H]^+$ ($^{12}C_{222}{}^1H_{352}{}^{14}N_{15}{}^{16}O_{69}{}^{32}S_3$) calcd monoisotopic peak 4428.37.

1,3,5-Tris-[3-(3-amino-propyl)-5-({4-[3-(5-dimethylaminonaphthalene-1-sulfonylamido)propoxy]}[3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)]benzoylamidopropyl)benzoylamidopropyl]benzenetris-hydrotrifluoro acetate (62): Compound **61** (0.66 g, 0.14 mmol) was dissolved in dry dichloromethane (10 mL) and TFA (5 mL) was added at room temperature. The deprotection was monitored by ^{1}H NMR spectroscopy. After complete conversion, the solvents were evaporated and the remainder dried in high vacuum. No further purification was carried out. Yield: 0.658 g (99%) of a yellowish oil.

^{1}H NMR (CD_3OD, 500 MHz): δ = 1.75 (m, 6H; β″-CH_2), 1.87 (m, 18H; β-CH_2), 2.57 (m, 6H; α-CH_2), 2.61 (m, 6H; α′-CH_2), 2.65 (t, ^3J(H,H) = 7.6 Hz, 6H; α-CH_2), 2.85 (m, 6H; γ-CH_2), 2.88 (s, 18H; -N(CH_3)$_2$), 3.12 (t, ^3J(H,H) = 7.1 Hz, 6H; γ″-CH), 3.24 (s, 36H; -OCH_3), 3.26 (sept, ^4J-(H,H) = 1.7 Hz, 3H; -N*H*(CH_3)$_2$), 3.33 (t, ^3J(H,H) = 6.4 Hz, 12H; γ-CH_2), 3.39–3.52 (2 m, 144H; -OCH_2CH_2O), 3.59 (m, 24H; -OCH(CH_2)$_2$), 3.96 (t, ^3J(H,H) = 5.7 Hz, 6H; α″-CH_2), 4.52 (quint, ^3J(H,H) = 4.8 Hz, 6H; -OC*H*(CH_2)$_2$), 6.86 (s, 3H; Ar-H core), 7.16 (s, 3H; Ar-H dendron), 7.17 (s, 6H; Ar-H gallate), 7.28 (d, ^3J(H,H) = 7.6 Hz 3H; Ar-H dansyl), 7.43 (m, 6H; Ar-H dendron), 7.53 (dd, ^3J(H,H) = 8.7 Hz, ^3J(H,H) = 7.7 Hz, 3H; Ar-H dansyl), 7.57 (dd, ^3J(H,H) = 8.5 Hz, ^3J(H,H) = 7.4 Hz, 3H; Ar-H dansyl), 8.18 (dd, ^3J(H,H) = 7.3 Hz, ^4J(H,H) = 1.1 Hz, 3H; Ar-H dansyl), 8.36 (d, ^3J(H,H) = 8.7 Hz, 3H; Ar-H dansyl), 8.50 ppm (d, ^3J-(H,H) = 8.5 Hz, 3H; Ar-H dansyl); ^{13}C NMR (CD_3OD, 125 MHz): δ = 29.92, 31.57, 31.89, 31.92, 32.12, 33.20, 33.99, 34.28, 40.29, 40.58, 40.79, 41.79, 46.17, 59.07, 71.19, 71.38, 71.84, 71.99, 72.82, 78.97, 109.68, 117.12, 121.91, 125.05, 126.06, 126.26, 126.28, 127.28, 129.06, 130.22, 130.37, 130.50, 130.65, 130.91, 132.71, 136.18, 137.55, 142.30, 143.18, 143.34, 143.76, 151.08, 153.21, 168.92, 169.88 ppm; MS (MALDI-TOF, CCA): *m/z*: 4450.63 $[M+Na]^+$ ($^{12}C_{222}{}^1H_{351}{}^{14}N_{15}{}^{16}O_{69}{}^{32}S_3{}^{23}Na$) calcd monoisotopic peak 4450.35; 4428.57 $[M+H]^+$ ($^{12}C_{222}{}^1H_{352}{}^{14}N_{15}{}^{16}O_{69}{}^{32}S_3$) calcd monoisotopic peak 4428.37.

1,3,5-Tris-[3-({4-[3-(5-dimethylaminonaphthalene-1-sulfonylamido)propoxy]}[3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)]amidopropyl)-5-{[4-{3-[di-*tert*-butyl-2-(2-carbamoylethyl)malonyl]-propoxy}][3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)]benzoylamidopropyl}benzoylamidopropyl]benzene (63): Compound **24** (0.14 g, 0.11 mmol) was dissolved in dry dichloromethane (7 mL). The solution was cooled to −20 °C and HOBt (19 mg, 0.12 mmol) and EDC (26 mg, 0.14 mmol) were added. The mixture was stirred for 1 h at −20 °C and then allowed to warm to room temperature. The esterification was monitored with TLC. After complete conversion, the mixture was cooled to −40 °C, and a solution of **62** (0.15 g, 0.03 mmol) and dry TEA (1 mL) in absolute methanol (1 mL) was added. The reaction mixture was stirred for 1 h at −40 °C and then al-

lowed to warm to room temperature. The solvents were evaporated. The crude product was purified by column chromatography (silica gel; dichloromethane/methanol 30:1 increasing to 10:1). The greenish oil was dissolved in benzene, filtered, and lyophilized. Yield: 0.24 g (94%) of a greenish oil.

$R_f = 0.27$ (silica gel; dichloromethane/methanol (15:1)); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.31$ (s, 54H; -C(CH_3)$_3$), 1.67 (m, 6H; β″-CH_2), 1.77 (m, 6H; β′-CH_2), 1.80 (m, 18H; β-CH_2), 1.97 (m, 6H; β‴-CH_2), 2.09 (m, 6H; α‴-CH_2), 2.52 (m, 18H; α-CH_2), 2.74 (s, 18H; -N(CH_3)$_2$), 3.08 (t, ^3J(H,H) = 4.9 Hz, 3H; γ‴-CH), 3.11 (m, 6H; γ″-CH_2), 3.19 and 3.20 (2 s, 72H; -OCH_3), 3.28 (m, 18H; γ-CH_2), 3.33–3.52 (2 m, 288H; -OCH_2CH_2O), 3.36 (m, 6H; γ′-CH_2), 3.54 and 3.59 (2 m, 48H; -OCH(CH_2)$_2$), 3.87 (t, ^3J(H,H) = 5.4 Hz, 6H; α″-CH_2), 3.93 (t, ^3J(H,H) = 5.6 Hz, 6H; α′-CH_2), 4.41 (quint, ^3J(H,H) = 5.0 Hz, 6H; -OCH(CH_2)$_2$), 4.45 (quint, ^3J(H,H) = 4.9 Hz, 6H; -OCH(CH_2)$_2$), 6.22 (t, ^3J(H,H) = 6.1 Hz, 3H; -NH″), 6.67 (t, ^3J(H,H) = 5.7 Hz, 3H; -NH′), 6.76 (s, 3H; Ar-H core), 7.01 (s, ^3J(H,H) = 7.4 Hz, 3H; Ar-H dansyl), 7.04 (s, 3H; Ar-H dendron), 7.08 (m, 3H; -NH), 7.12 (m, 6H; -NH), 7.14 and 7.15 (2 s, 12H; Ar-H gallate), 7.33 (m, 3H; Ar-H dansyl), 7.35 (m, 6H; Ar-H dendron), 7.39 (m, 3H; Ar-H dansyl), 8.11 (d, ^3J(H,H) = 7.4 Hz, 3H; Ar-H dansyl), 8.23 (d, ^3J(H,H) = 8.8 Hz, 3H; Ar-H dansyl), 8.38 ppm (d, ^3J(H,H) = 8.5 Hz, 3H; Ar-H dansyl); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 24.10, 27.51, 29.27, 29.69, 30.57, 32.59, 32.78, 33.10, 36.74, 39.18, 39.32, 40.44, 45.01, 52.77, 70.00, 70.02, 70.12, 70.32, 70.38, 70.53, 71.15, 71.46, 77.43, 77.54, 80.87, 108.73, 108.80, 114.69, 119.09, 122.79, 124.42, 124.50, 125.86, 127.52, 128.53, 129.36, 129.46, 129.52, 131.05, 134.60, 135.57, 141.35, 141.54, 141.86, 142.08, 151.30, 151.43, 151.51, 166.42, 167.43, 168.09, 171.44 ppm; MS (MALDI-TOF, CCA): m/z: 8088.55 [M+K]$^+$ ($^{12}C_{395}{}^1H_{654}{}^{14}N_{18}{}^{16}O_{144}{}^{32}S_3{}^{39}K$) calcd monoisotopic peak 8089.32.

1,3,5-Tris-[3-({4-[3-(5-dimethylaminonaphthalene-1-sulfonylamido)propoxy]}[3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)]benzoylamidopropyl)-5-{[4-{3-[dibenzyl-2-(2-carbamoylethyl)malonyl]propoxy}]}[3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)]benzoylamidopropyl}benzoylamidopropyl]benzene (64): Compound **26** (0.14 g, 0.11 mmol) was dissolved in dry dichloromethane (7 mL). The solution was cooled to −20 °C and HOBt (0.02 g, 0.12 mmol) and EDC (26 mg, 0.14 mmol) were added. The mixture was stirred for 1 h at −20 °C and then allowed to warm to room temperature. The esterification was monitored with TLC. After complete conversion, the mixture was cooled to −40 °C, and a solution of **62** (0.150 g, 0.031 mmol) and dry TEA (1 mL) in absolute methanol (1 mL) was added. The reaction mixture was stirred for 1 h at −40 °C and then allowed to warm to room temperature. The solvents were evaporated. The crude product was purified by column chromatography (silica gel; dichloromethane/methanol 30:1 increasing to 15:1). The greenish oil was dissolved in benzene, filtered, and lyophilized. Yield: 0.190 g (74%) of a greenish oil.

$R_f = 0.24$ (silica gel; dichloromethane/methanol (15:1)); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.77$ (m, 6H; β″-CH_2), 1.85 (m, 6H; β′-CH_2), 1.91 (m, 12H; β-CH_2), 2.24 (m, 12H; α‴-CH_2 and β‴-CH_2), 2.61 (m, 6H; α-CH_2), 2.65 (m, 6H; α*-CH_2), 3.22 (m, 6H; γ″-CH_2), 3.30 (s, 90H; -OCH_3 and -N(CH_3)$_2$), 3.42 (m, 18H; γ-CH_2), 3.45–3.61 (2 m, 288H; -OCH_2CH_2O), 3.62 (m, 3H; γ‴-CH_2), 3.66 and 3.69 (2 m, 48H; -OCH(CH_2)$_2$), 3.96 (t, ^3J(H,H) = 5.4 Hz, 6H; α″-CH_2), 4.01 (t, ^3J(H,H) = 5.6 Hz, 6H; α′-CH_2), 4.54 (q, ^3J(H,H) = 4.9 Hz, 6H; -OCH(CH_2)$_2$),4.57 (q, ^3J(H,H) = 5.0 Hz, 6H; -OCH(CH_2)$_2$), 5.09 (m, 12H; -OCH_2Ar), 6.42 (br s, 3H; -NH″), 6.82 (t, ^3J(H,H) = 5.6 Hz, 3H; -NH′), 6.86 (s, 3H; Ar-H core), 7.13 (m, 3H; -NH), 7.15 (s, 3H; Ar-H dendron), 7.25 (s, 12H; Ar-H gallate), 7.22–7.28 (m, 39H; Ar-H dansyl, benzyl Ar-H, -NH), 7.47 (m, 6H; Ar-H dendron), 7.49 (m, 6H; Ar-H dansyl), 8.22 (d, ^3J(H,H) = 7.4 Hz, 3H; Ar-H dansyl), 8.38 (m, 3H; Ar-H dansyl), 8.56 ppm (m, 3H; Ar-H dansyl); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 24.18, 29.29, 29.78, 30.66, 30.70, 30.75, 32.69, 32.81, 32.89, 36.86, 39.27, 39.32, 39.46, 40.54, 45.12, 50.76, 58.58, 66.66, 70.09, 70.10, 70.11, 70.12, 70.22, 70.40, 70.45, 70.62, 71.28, 71.56, 77.20, 77.56, 77.69, 108.88, 108.96, 114.82, 119.23, 122.92, 124.49, 124.58, 125.92, 127.59, 127.70, 127.93, 128.19, 128.64, 129.46, 129.56, 129.58, 131.13, 134.73, 135.08, 135.66, 141.42, 141.61, 141.65, 142.02, 142.21, 151.54, 151.61, 166.51, 166.53, 167.48, 168.50, 171.14 ppm; MS (MALDI-TOF, CCA): m/z: 8305.72 [M+K]$^+$ ($^{12}C_{414}{}^1H_{642}{}^{14}N_{18}{}^{16}O_{144}{}^{32}S_3{}^{39}K$) calcd monoisotopic peak 8305.23; 8289.92 [M+Na]$^+$ ($^{12}C_{414}{}^1H_{642}{}^{14}N_{18}{}^{16}O_{144}{}^{32}S_3{}^{23}Na$) calcd monoisotopic peak 8289.25.

1,3,5-Tris-[3-({4-[3-(5-dimethylaminonaphthalene-1-sulfonylamido)propoxy]}[3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)]benzoylamidopropyl)-5-{[4-{3-[2-(2-carbamoylethyl)malonato]propoxy}][3,5-bis(1,3-bis{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propan-2-yloxy)]benzoylamidopropyl]benzoylamidopropyl]benzene (65): Compound **63** (0.20 g, 0.025 mmol) was dissolved in dichloromethane (7 mL) and TFA (4 mL) was added at room temperature. The deprotection was monitored with ^{1}H NMR. The solvent was evaporated. Remaining TFA was removed by coevaporation with dichloromethane. The sample was dried in high vacuum. No further purification was carried out. Yield: 0.19 g (97%) of a colorless oil.

^{1}H NMR (CD_3OD, 500 MHz): $\delta = 1.61$ (m, 6H; β″-CH_2), 1.74 (m, 24H; β-CH_2 and β′-CH_2), 1.96 (m, 6H; β‴-CH_2), 2.13 (m, 6H; α‴-CH_2), 2.45 (t, ^3J(H,H) = 7.2 Hz, 6H; α-CH_2), 2.52 (m, ^3J(H,H) = 6.8 Hz, 12H; α*-CH_2), 3.03 (t, ^3J(H,H) = 6.9 Hz, 6H; γ″-CH_2), 3.11 (s, 18H; -N(CH_3)$_2$), 3.12 (2 s, 72H; -OCH_3), 3.21 (m, 21H; γ‴-CH and γ-CH_2), 3.26 (m, 6H; γ′-CH_2), 3.27–3.42 (2 m, 288H; -OCH_2CH_2O), 3.45 and 3.56 (2 m, 48H; -OCH(CH_2)$_2$), 3.80 (t, ^3J(H,H) = 5.6 Hz, 6H; α″-CH_2), 3.92 (t, ^3J(H,H) = 5.6 Hz, 6H; α′-CH_2), 4.37 (q, ^3J(H,H) = 5.0 Hz, 6H; -OCH(CH_2)$_2$), 4.45 (q, ^3J(H,H) = 4.9 Hz, 6H; -OCH(CH_2)$_2$), 6.74 (s, 3H; Ar-H core), 7.05 (s, 6H; Ar-H gallate), 7.09 (s, 3H; Ar-H dendron), 7.11 (s, 6H; Ar-H gallate), 7.33 (m, 6H; Ar-H dendron), 7.55 (m, 3H; Ar-H dansyl), 7.63 (m, 6H; Ar-H dansyl), 8.18 (d, ^3J(H,H) = 7.3 Hz, 3H; Ar-H dansyl), 8.32 (d, ^3J(H,H) = 8.8 Hz, 6H; Ar-H dansyl), 8.87 (d, ^3J(H,H) = 8.5 Hz, 6H; Ar-H dansyl); ^{13}C NMR (CD_3OD, 125 MHz): δ = 25.93, 30.83, 31.43, 32.07, 34.04, 34.27, 34.38, 38.19, 40.70, 40.79, 41.86, 47.52, 59.04, 71.19, 71.31, 71.38, 71.41, 71.80, 71.85, 72.49, 72.80, 78.90, 78.94, 109.83, 119.84, 126.04, 127.29, 127.82, 128.75, 130.62, 130.66, 130.98, 132.86, 135.90, 138.68, 143.16, 143.38, 143.56, 143.58, 153.13, 153.28, 160.00, 160.01, 160.30, 169.02, 169.05, 170.01, 172.33, 174.51 ppm; MS (MALDI-TOF, dithranol): m/z: 7753.58 [M+Na]$^+$ ($C_{372}H_{605}N_{18}O_{144}S_3Na$) calcd molecular weight peak 7753.00.

Acknowledgements

We thank C. Winterboer and G. Hertel for their skillful help with some of the experiments, and Dr. A. Schäfer and his crew for recording all 2D NMR spectra. We also thank Dr. P. Franke for measuring the MALDI-TOF mass spectra, Dr. S. Hecht, Dr. F. Kutzner, and Dr. S. Fuchs for helpful advice and fruitful discussions, and Dr. D. Opris for help with the manuscript.

[1] a) G. R. Newkome, C. N. Moorefield, F. Vögtle, *Dendrimers and Dendrons: Concepts, Synthesis, Applications*, Wiley-VCH, Weinheim, Germany, **2001**; b) J. M. J. Fréchet, D. A. Tomalia, *Dendrimers and other dendritic polymers*, Wiley, New York, **2001**.

[2] a) D. A. Tomalia, H. Baker, J. Dewald, M. Hall, G. Kallos, S. Martin, J. Roeck, J. Ryder, P. Smith, *Polym. J.* **1985**, 117–132; b) G. R. Newkome, Z. Yao, G. R. Baker, V.K. Gupta, *J. Org. Chem.* **1985**, *50*, 2003–2004; c) C. J. Hawker, J. M. J. Fréchet, *J. Am. Chem. Soc.* **1990**, *112*, 7638–7647.

[3] for some recent reviews, see: a) S. Hecht, *J. Polym. Sci. Part A-Polym. Chem.* **2003**, *41*, 1047–1058; b) D. A. Tomalia, J. M. J. Fréchet, *J. Polym. Sci. Part A-Polym. Chem.* **2002**, *40*, 2719–2728; c) M. J. Cloninger, *Curr. Opin. Chem. Biol.* **2002**, *6*, 742–748; d) S. Hecht, J. M. J. Fréchet, *Angew. Chem.* **2001**, *113*, 74–94; *Angew. Chem. Int. Ed.* **2001**, *40*, 74–91; e) S.K. Grayson, J. M. J. Fréchet, *Chem. Rev.* **2001**, *101*, 3819–3867.

[4] a) R. Esfand, D. A. Tomalia, *Drug Discovery Today* **2001**, *6*, 427–436; b) A.K. Patri, I. J. Majoros, J. R. Baker, *Curr. Opin. Chem. Biol.* **2002**, *6*, 466–471.

[5] a) G. R. Newkome, C. N. Moorefield, G. R. Baker, M. J. Saunders, S. H. Grossman, **1991**, *103*, 1207–1209; *Angew. Chem. Int. Ed.*

Engl. **1991**, *30*, 1178–1180; b) P. R. Ashton, S. E. Boyd, C. L. Brown, N. Jayaraman, S. A. Nepogodiev, J. F. Stoddart, *Chem. Eur. J.* **1996**, *2*, 1115–1128.

[6] a) O. L. Padilla De Jesus, H. R. Ihre, L. Gagne, J. M. J. Fréchet, F. C. Szoka, Jr., *Bioconj. Chem.* **2002**, *13*, 453–461; b) M. Liu, K. Kono, J. M. J. Fréchet, *J. Controlled Release* **2000**, *65*, 121–131; c) M. Liu, K. Kono, J. M. J. Fréchet, *J. Polym. Sci. Part A: Polym. Chem.* **1999**, *37*, 3492–3503; d) E. R. Gillies, J. M. J. Fréchet, *J. Am. Chem. Soc.* **2002**, *124*, 14137–14146; e) S. M. Grayson, M. Jayaraman, J. M. J. Fréchet, *Chem. Commun.* **1999**, 1329–1330.

[7] N. Malik, R. Wiwattanapatapee, R. Klopsch, K. Lorenz, H. Frey, J. W. Weener, E. W. Meijer, W. Paulus, R. Duncan, *J. Controlled Release* **2000**, *65*, 133–148.

[8] S. Fuchs, T. Kapp, H. Otto, T. Schöneberg, P. Franke, R. Gust, A. D. Schlüter, *Chem. Eur. J.* **2004**, *10*, 1167–1192.

[9] O. L. P. De Jesus, H. R. Ihre, L. Gagne, J. M. J. Fréchet, F. C. Szoka, *Bioconjugate Chem.* **2002**, *13*, 453–461.

[10] A. W. Freeman, L. A. J. Chrisstoffels, J. M. J. Fréchet, *J. Org. Chem.* **2000**, *65*, 7612–7617.

[11] Consequently, **1** was used in slight excess (1.2 equiv) to avoid the extra steps. This improved protocol did not lead to any by-products **4**.

[12] Compound **7** was prepared in two steps according to literature procedures. First, the ring-opening of epi-chlorohydrine was initiated with the sodium salt of tri-ethylene glycol monomethyl ether and gave the corresponding pegylated alcohol. The tosylate **7** was obtained from the reaction with pyridinium tosylate: U. Lauter, W. H. Meyer, V. Enkelmann, G. Wegner, *Macromol. Chem. Phys.* **1998**, *199*, 2129–2140.

[13] N. Stuhr-Hansen, B. Ebert, P. Kroqsqaard-Larsen, J. Kehler, *Org. Lett.* **2000**, *2*, 6–10.

[14] W. Wei, T. Tomohiro, M. Kodaka, H. Okuno, *J. Org. Chem.* **2000**, *65*, 8979–8987.

[15] J. Hasserodt, K. D. Janda, R. Lerner, *J. Am. Chem. Soc.* **1997**, *119*, 5993–5998.

[16] C. Sergheraert, P. Maes, A. Tartar, *J. Chem. Soc. Perkin Trans. 1* **1986**, 1061–1064.

[17] a) S. Vetter, S. Koch, A. D. Schlüter, *J. Polym. Sci. Part A: Polym. Chem.* **2001**, *39*, 1940–1954; b) S. Koch, PhD Dissertation, Freie Universität Berlin, Germany, **2000**.

[18] O. Henze, PhD Dissertation, Freie Universität Berlin. Germany, **2000**.

Received: October 22, 2004
Revised: February 21, 2005
Published online: July 15, 2005

