Convergent Synthesis and Diversity of Amino Acid Based Dendrimers

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The synthesis of amino acid based dendrimers **25** (fifth generation, 32 endgroups), **30** (fourth generation, 81 endgroups), chiral dendrimer **23** (third generation, 8 endgroups) as well as core-modified dendrimers **34** and **38** by the convergent method is described. The amino acid building blocks are derived from hydroxybenzoic acid derivatives and amino alcohol derivatives, and access to a considerable molecular diversity of these novel dendrimers can be achieved. The synthesis can be carried out on a relatively large scale, and this easy access of the dendrimers may lead to many potential applications.

Introduction

Peptides and many of the oligomeric peptidomimetics in which we are interested share the recurring central structural element of the (peptide) amide bond.[1] It is not surprising that this stable and often conveniently introduced moiety has been used in a considerable number of dendrimer types.[2] In our approach, we wanted to exploit the features of peptide synthesis (stepwise construction, high yields and clean synthesis) for the development of a reliable and efficient construction of a novel class of amino acid based dendrimers by the convergent method.[3] In addition, we wanted to be able to introduce a considerable degree of molecular diversity in the dendrimer synthetic strategy, so that it could be used for the synthesis of dendrimers[4] with a variety of branching patterns, interior cavity size, rigidity[2c,4] and surface functionality.[5] Therefore, we had three simple requirements for the building blocks of our dendrimers: (i) easy accessibility, (ii) to have at least two amino groups and one carboxylic group (or vice versa) and (iii) access to a diversity in monomer structure. The monomer which we envisioned as the building block of our prototype dendrimer was assembled from commercially available dihydroxybenzoic acid (**1**) and 2-bromoethylamine (**2**), and the first two requirements were therefore met. The third requirement, access to a diversity of other amino acid based dendrimers, is provided by the combination of various hydroxybenzoic acid derivatives and amino alcohol derivatives, which are either commercially available or synthetically easily accessible. From Figure 1 it follows that by combination of the depicted hydroxybenzoic acid derivatives and the shown amino alcohol derivatives twelve different (homo)-dendrimers are already accessible, that is, a significant molecular diversity can therefore be generated. The synthesis of illustrative examples starting from gallic acid (**3**) or chiral amino alcohol **9** of these dendrimers will be described here.

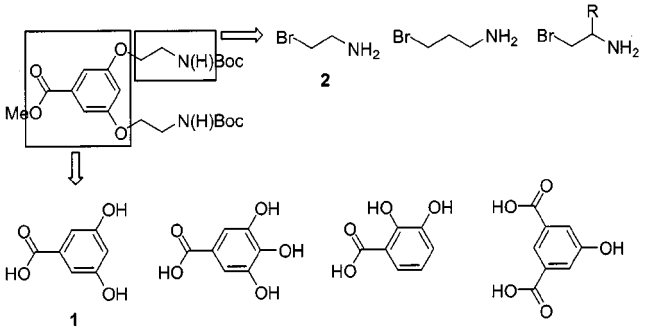

Figure 1. Molecular diversity of amino acid based dendrimer monomers

In addition, the diversity of the dendrimers is easily extended by a variation in the core and/or endgroups. These modifications provide access to a rapidly increasing number of applications in which dendrimers are used, for example, in catalysis[6] and as multivalent anti-adhesion compounds.[7] The synthesis of carbohydrate containing dendrimers will be described using our prototype dendrimer.[5] Replacement of the core methyl ester by other groups led to dendrimers with, for example, a fatty acid chain, and these were used in the preparation of Langmuir monolayers.[8]

Results and Discussion

The synthesis of the monomers used in the preparation of several dendrimers is shown in Scheme 1. From 3,5-dihydroxybenzoic acid (**1**) or gallic acid (**3**) the dendrimer monomers **12**−**15** were prepared by alkylation with a suitable bromide. 2-Bromoethylamine (**2**) and 3-bromopropylamine (**4**) are commercially available, 2-amino-3-phenylpropyl bromide (**11**) was derived from phenylalanine.

To synthesize monomers **12** and **15**, the best results for alkylation were obtained with potassium carbonate as a base in dimethylformamide (DMF). Monomers **12** and **15**

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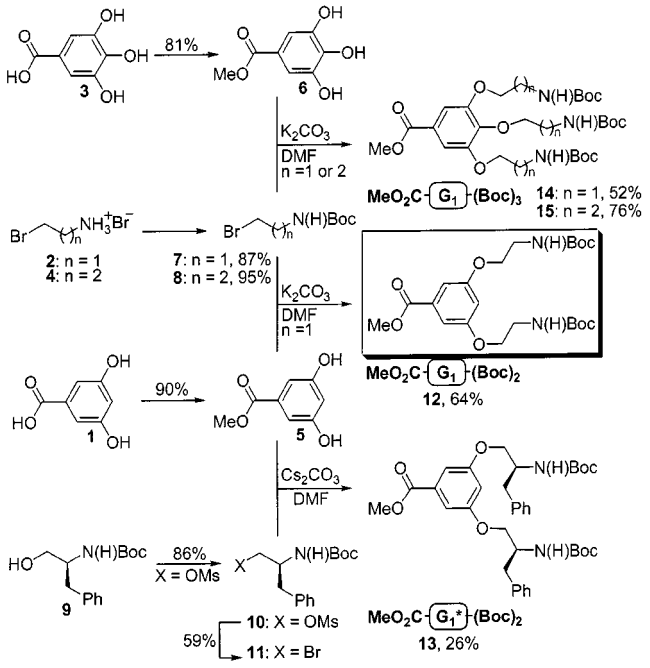


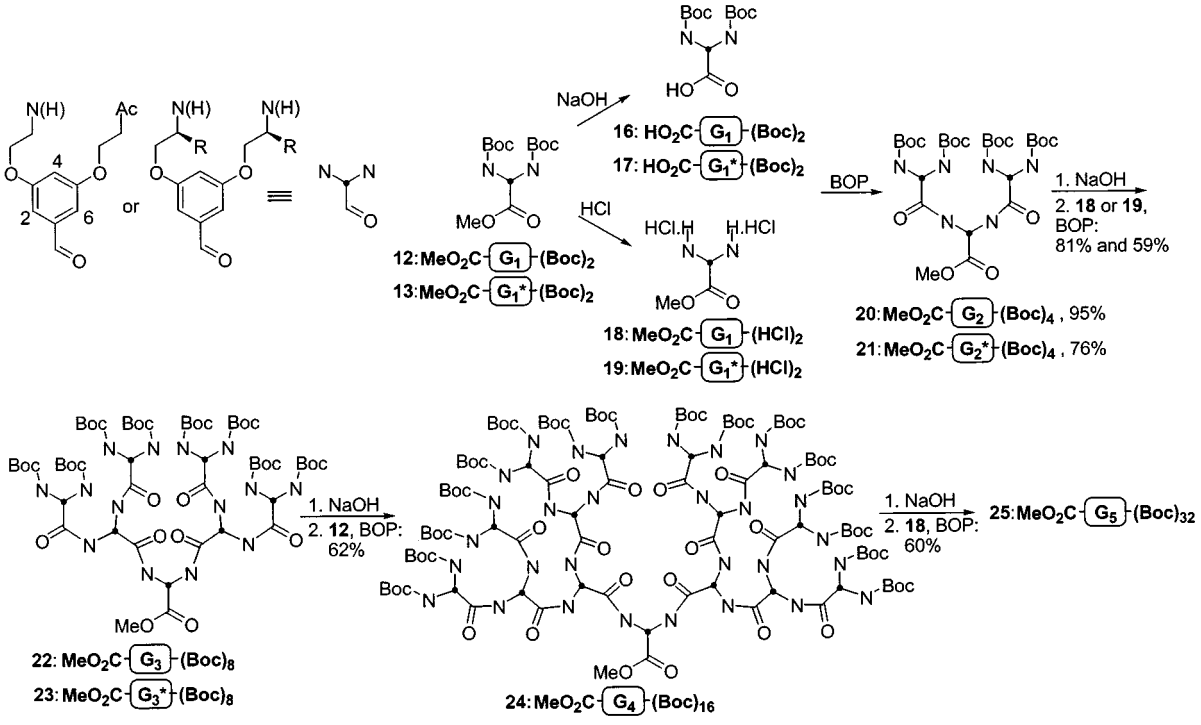
Scheme 1. Synthesis of dendrimer monomers **12**–**15**

were obtained in 64% and 76% yields, respectively. Under these conditions convenient large-scale syntheses of monomers **12** and **15** could be carried out. The synthesis of chiral monomer **13** under the same conditions gave low yields. Although several conditions were attempted to improve the yield, for example, different temperatures (40 or 60 °C), use of different bases (sodium carbonate, cesium carbonate or sodium hydride), and different solvents (DMF, THF or acetonitrile), the best results were obtained with cesium carbonate in acetonitrile at refluxing temperature, albeit with a low yield (26%) partly caused by a tedious purification.

With **12** as the first generation, amino acid based dendrimers up to the fifth generation were constructed by the convergent method as depicted in Scheme 2.

"Surface" monomer **16** was obtained by saponification of the methyl ester of **12** by slightly modified Tesser's base,[11] and removal of the Boc protective groups in **12** with HCl in diethyl ether gave the "branching" monomer **18**. Subsequently, second generation dendrimer **20** was synthesized in 95% yield by a peptide-amide coupling reaction, with (1*H*-benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) and 2 equiv. of the surface monomer **16** with 1 equiv. of the branching monomer **18**. Preparation of the third generation dendrimer **22** consisted of saponification of the methyl ester of the second generation dendrimer **20** followed by coupling to a branched monomer **18**. This coupling step was unsatisfactory when carried out in dichloromethane, but very good results (81% yield) were obtained when the reaction was performed in refluxing acetonitrile to ensure that the reaction mixture remained homogeneous. Fourth and fifth generation dendrimers **24** and **25** were synthesized accordingly and obtained in 62% and 60% yields, respectively. The structure of **25** is shown in Figure 2.

All dendrimers were obtained as white foams and characterized by ^{1}H and ^{13}C NMR spectroscopy, GPC, HPLC and mass spectrometry. ^{1}H and ^{13}C NMR spectra of the dendrimers are shown in Figure 3 and display the following



Scheme 2. Synthesis of up to 5th (**25**) generation of dendrimers based on monomers **16** and **18**; synthesis of up to 3rd (**23**) generation chiral dendrimers based on monomers **17** and **19**

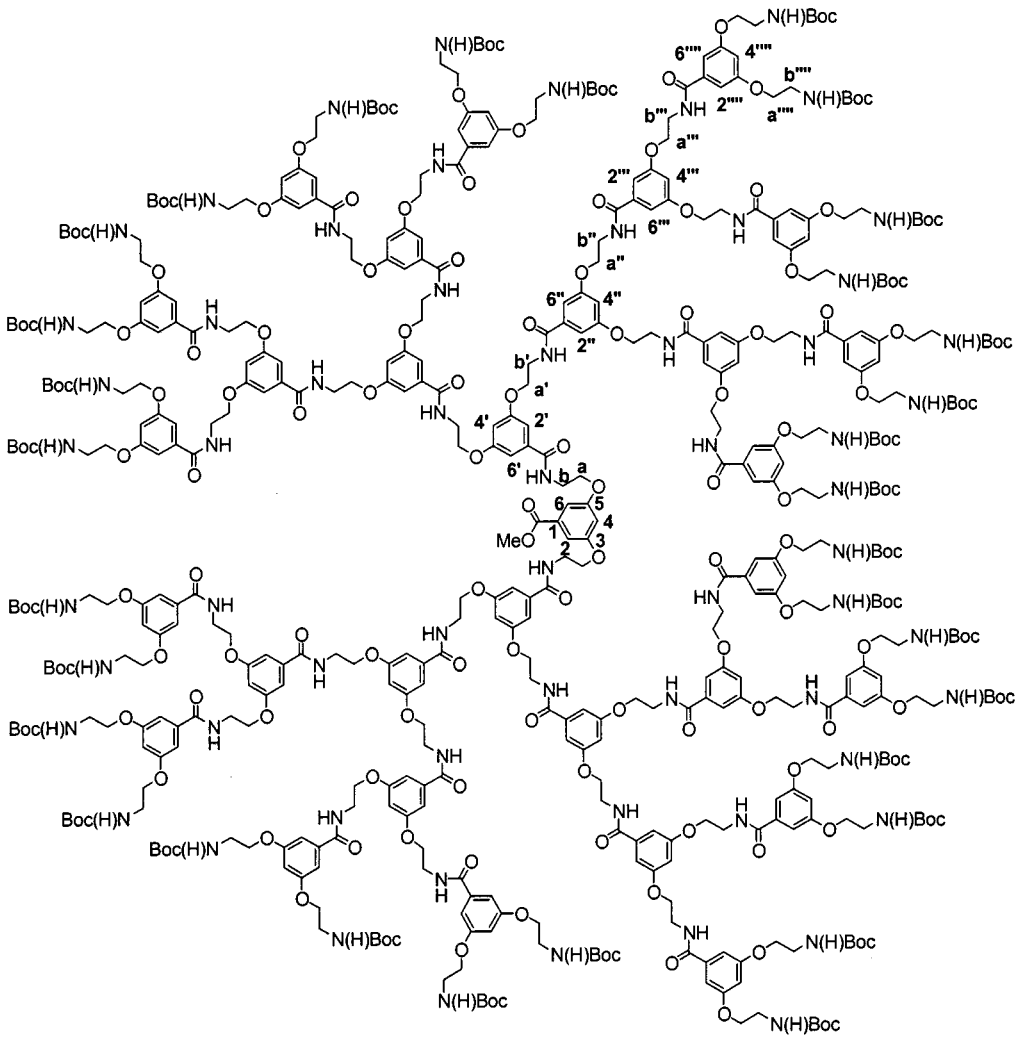


Figure 2. 5th generation amino acid based dendrimer (**25**) with 32 end groups (Boc)

characteristics. The signals in the ^{1}H NMR spectra start to broaden significantly at the third generation dendrimer **22** and are broad in the spectrum of the fourth generation **24**. Although peaks were broad in the ^{1}H NMR spectrum of the third generation dendrimer **22**, the spin multiplicity was still visible. In the ^{1}H NMR spectrum of the fourth generation dendrimer **24** only broad singlets were observed. Interestingly, the signals of the aromatic protons viz., C^2H, C^4H and C^6H, of the first dendrimer layer are separate from those of the aromatic protons of the subsequent dendrimer layers and are still visible in the ^{1}H NMR spectrum of the fourth generation dendrimer **24** (C^2H and C^6H at $\delta = 7.04$; C^4H at $\delta = 6.61$) as well as the singlet of the methyl ester ($\delta = 3.82$). The signals in the ^{13}C NMR spectra of the dendrimers are still relatively sharp in the fifth generation dendrimer **25**. From the first to the fifth generation, the decrease and concomitant increase of the ^{13}C signals of CO_2Me ($\delta = 52.0$) and Boc-groups ($\delta = 29.7$), respectively, is clearly observed. The signals of CO_2Me, albeit weak, can still be distinguished in the ^{13}C NMR spectrum of the fifth generation dendrimer **25** and are clearly visible in the ^{13}C NMR spectrum of the fourth generation dendrimer **24** (Figure 3).

It was possible to measure satisfactory FAB mass spectra up to the fourth generation dendrimer (**24**). For the fifth generation dendrimer **25** it was possible to measure an electron spray mass spectrum with a distribution of pentapositive ions, and, for example, the presumed $[M + 5Na]^{5+}$ ion of $m/z = 2048.06$ corresponds to a molecular mass of 10,125.3.

It was possible to elute the dendrimers on an HPLC Econosphere C8 10 μm column with a standard gradient of water to acetonitrile containing trifluoroacetic acid (TFA). From the first to the fifth generation dendrimer, the elution time increased and both the fourth and fifth generation dendrimers show significant peak broadening. An Adsorbosphere C8 column, with more uniform sized pores, showed less peak broadening, but the separation of the fourth and fifth generation dendrimers was poorer. GPC analysis of the individual generations showed that each of the dendrimers eluted without significant peak broadening (Figure 6).

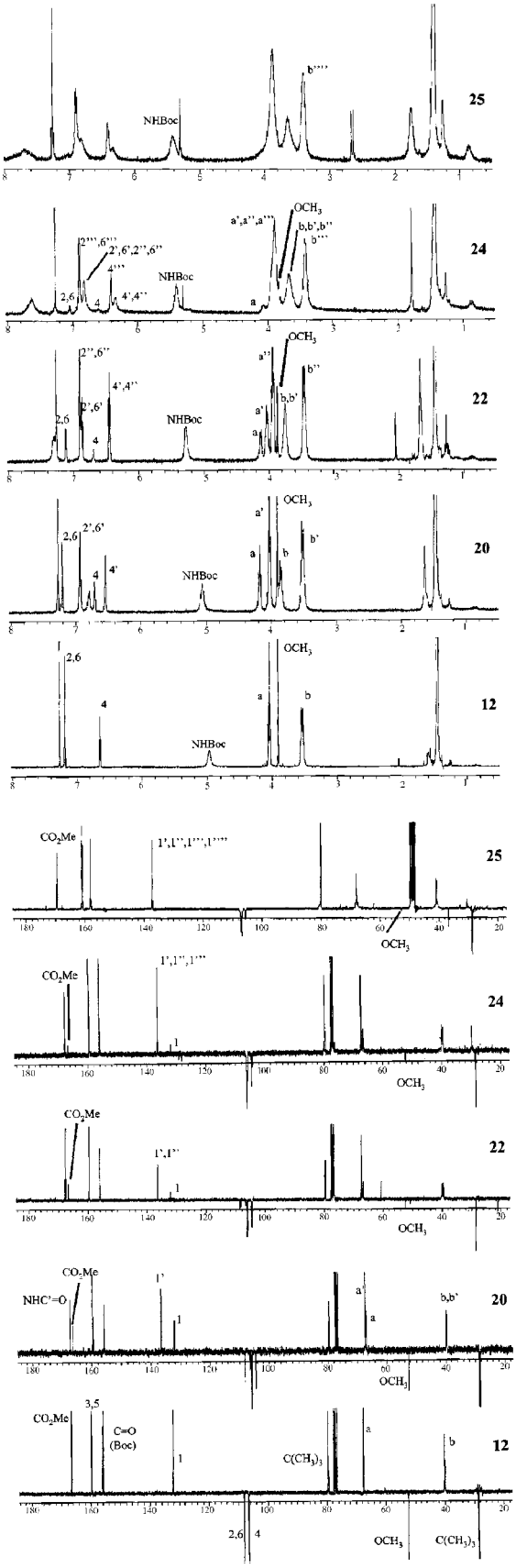


Figure 3. ^{1}H NMR and ^{13}C NMR spectra of dendrimers **12**, **20**, **22**, **24** and **25** (from bottom to top); see Figure 2 for structure numbering

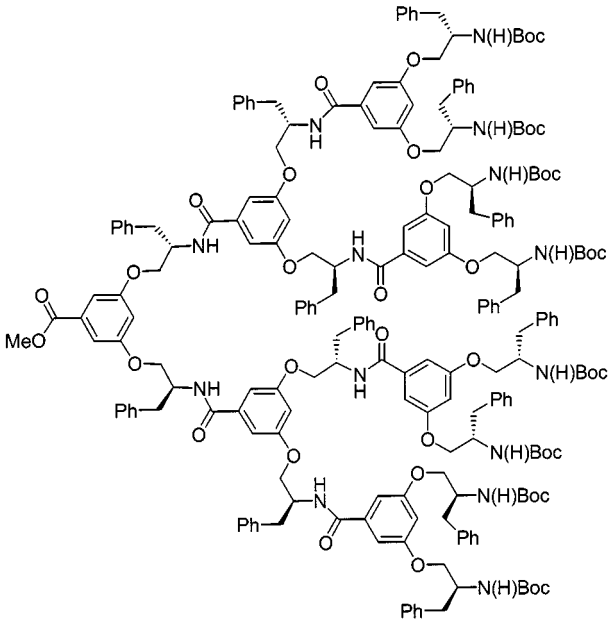
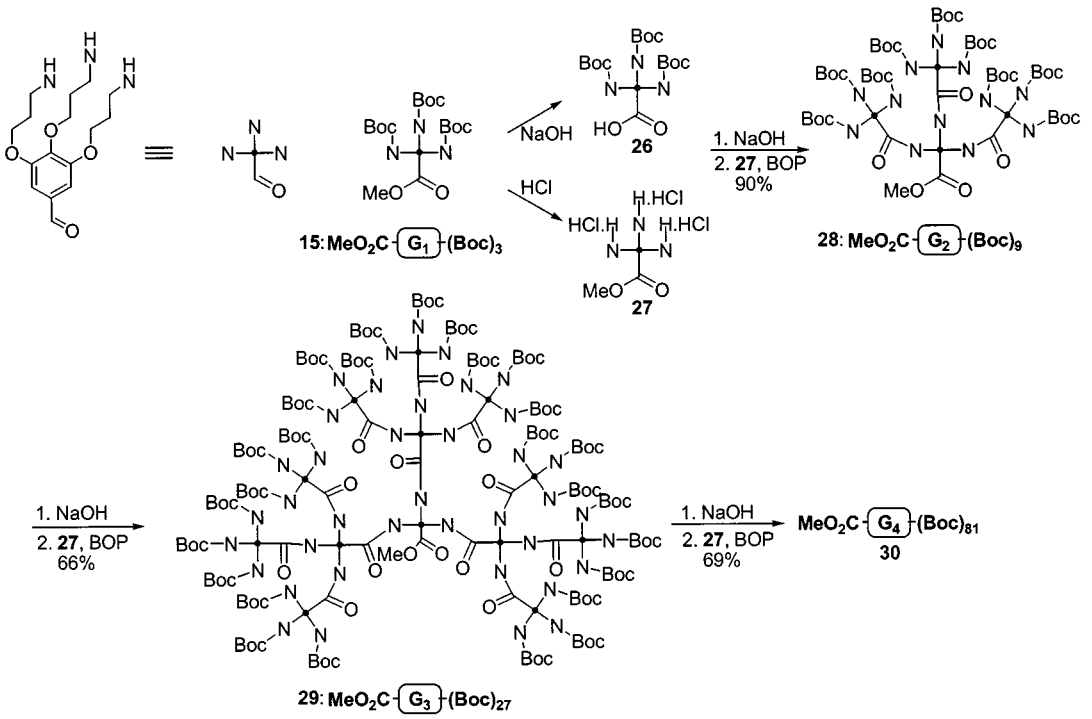


Figure 4. 3rd generation chiral amino acid based dendrimer (**23**)

The preparation of the "prototype" fifth generation dendrimer **25** set the stage for extension of this methodology to the preparation of even more sophisticated amino acid based dendrimers. To illustrate the possible diversity of the amino acid based dendrimers we embarked on the synthesis of a chiral dendrimer (Figure 4) and a dendrimer with a branching degree of three (Scheme 3).

As is schematically depicted in Scheme 2, the synthesis of the chiral dendrimers up to the third generation was completely analogous to the synthesis of dendrimers based on **12**, from monomers **17** and **19**.

The optical rotation of these chiral dendrimers was investigated and the results are summarized in Table 1. As a reference Boc-protected phenylalaninol was used. Interestingly, the specific rotation of the chiral dendrimer did not increase significantly from the first generation (−6.5°) to the second generation (−10.4°) and even decreased at the third generation (−5.0°). This is in agreement with data obtained for other chiral dendrimers, developed by Chow et al.[9] and McGrath et al.[10] Both groups showed that the molar rotation of the chiral dendrimers increased from the first to the second generation and subsequently decreased for the third generation dendrimer. However, Chow as well as McGrath and their co-workers found that the molar rotation per chiral residue remained approximately the same. In contrast to the results of Chow et al., the molar rotations of the three generations of dendrimers studied here (**13**, **21** and **23**) were not proportional to the number of residues, and this indicates that the chiral residues do not act as non-interacting moieties. In the third generation, the molar rotation per residue dropped, and this possibly indicates that the optical activity of the chiral residues are partly canceled out by each other. The GPC traces of the separate chiral dendrimers are shown in Figure 6.



Scheme 3. Synthesis of up to 4th (**30**) generation of dendrimers based on monomers **26** and **27** with a branching degree of three

Table 1. Optical rotations of dendrimers **13**, **21** and **23**

Compound	Generation	MW	$[\alpha]_D^{20}$	Molar rotation[a]	Rotation per residue
N-Boc-phenylalaninol (**9**)	–	251.3	−24.0	−60.3	−60.3
13	1	634.8	−6.5	−41.3	−20.6
21	2	1640.0	−10.4	−171	−28.5
23	3	3650.4	−5.0	−183	−13.1

[a] Molar rotation: $\Phi = [\alpha]MW/100$, see ref.[12]

In addition to the amino acid based dendrimers with a branching degree of two, dendrimers up to the fourth generation (**30**) (Figure 5) with a branching degree of three were synthesized. The monomer required for this type of dendrimer was assembled from gallic acid methyl ester and 2-(Boc-amino)ethyl bromide (**7**). However, the yield of **14** from the alkylation step with bromide **7** was moderate, 46% (Scheme 1). Fortunately, when 3-(Boc-amino)propyl bromide was used to afford **15** the yield improved to 76% (Scheme 1), and we decided to use this monomer for the construction of gallic acid derived dendrimers. The overall synthesis of dendrimers using this gallic acid derived monomer is schematically depicted in Scheme 3 and is performed analogously to the synthesis of the dendrimers from **12**, but with monomers **26** and **27**. The synthesis of the dendrimers up to the fourth generation proceeded smoothly (Scheme 3). However, the yield of the third (**29**) generation dendrimer was somewhat lower than that of corresponding prototype dendrimer (**22**) shown in Scheme 2 (66% compared to 81%). The low yield might be due to the increased steric hindrance caused by the higher degree of branching in each coupling step. However, the yield of the coupling to the fourth generation dendrimer with a branching degree of three was comparable to the yield of the corresponding prototype dendrimer **24** (69% compared to 62%).

GPC revealed that these four generations of dendrimers with a branching degree of three were pure (Figure 6). Unexpectedly, the fourth generation dendrimer **30** eluted later from the GPC column than the third generation **29** and the second generation **28**. A partial collapse of the structure or insufficient swelling in the eluent could explain the late elution of **30**. The purity was also assessed by HPLC, but unfortunately the fourth generation dendrimer **30** did not elute from the column. Interestingly, all dendrimers, including the higher generations, run on TLC in conventional organic solvents and can be purified by silica column chromatography.

It is possible, using the modular nature of these dendrimer building blocks, to introduce a considerable diversity in the "interior" of the dendrimers by a variation in the degree of branching as well as the length and nature of the branches. Obviously, the next important step, especially

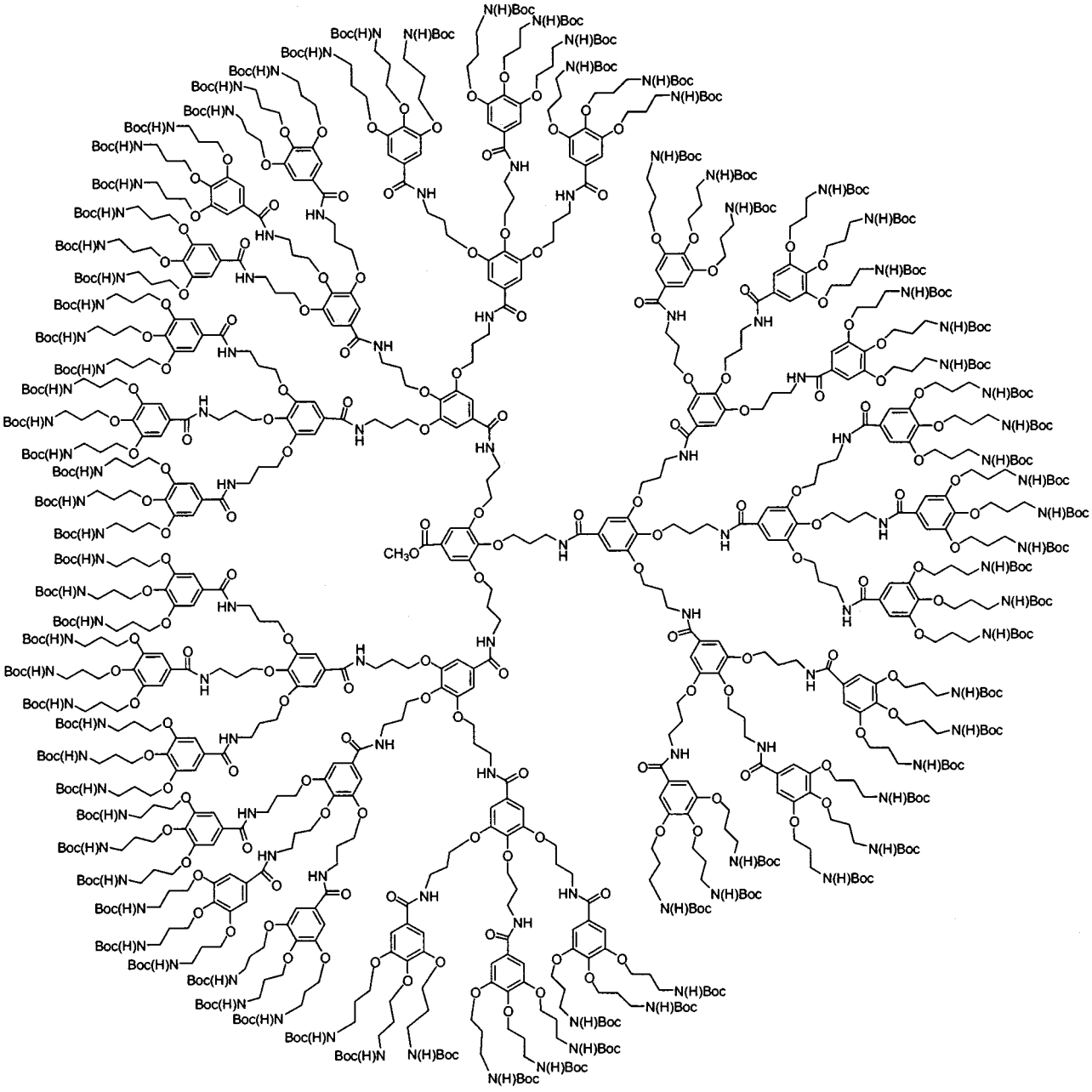


Figure 5. 4th generation amino acid based dendrimer (**30**) with 81 end groups (Boc)

with regard to application of dendrimers, is to vary the "core" and the "surface". At present, modification of the "surface" amino groups with carbohydrate residues is carried out for the development of anti-adhesion compounds. We have previously described the replacement of the "core" methyl ester with a long aliphatic amino acid for Langmuir studies.[8] Using this technique, it was possible to directly determine the size of these dendrimers. Other amines (**33, 37**) were used to synthesize dendrimers which may form monolayers on gold or micellar-like structures (Scheme 4). Thus, disulfide dendrimer **34** was assembled from disulfide **33** and the saponified third generation dendrimer **22**. The disulfide **33** was conveniently prepared from 12-aminododecanoic acid **31** via thioacetate **32**.

Dendrimer **38** with a triethylene glycol chain was prepared from **37** and saponified **22**. These two examples illustrate the versatility of transformation of the core of these dendrimers.

Conclusion

In summary, we have developed an efficient strategy for the synthesis of novel amino acid based dendrimers. The synthesis of these dendrimers can be conveniently carried out on a fairly large scale to provide accessible vehicles for a variety of applications. Variation of the aromatic residue and/or amino alcohol part of the dendrimer monomers,

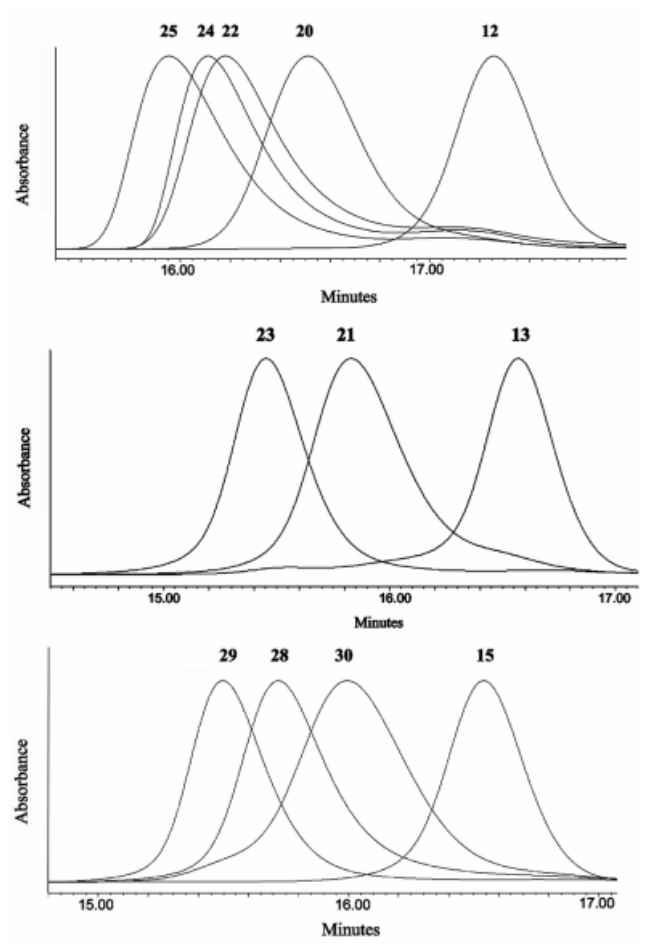
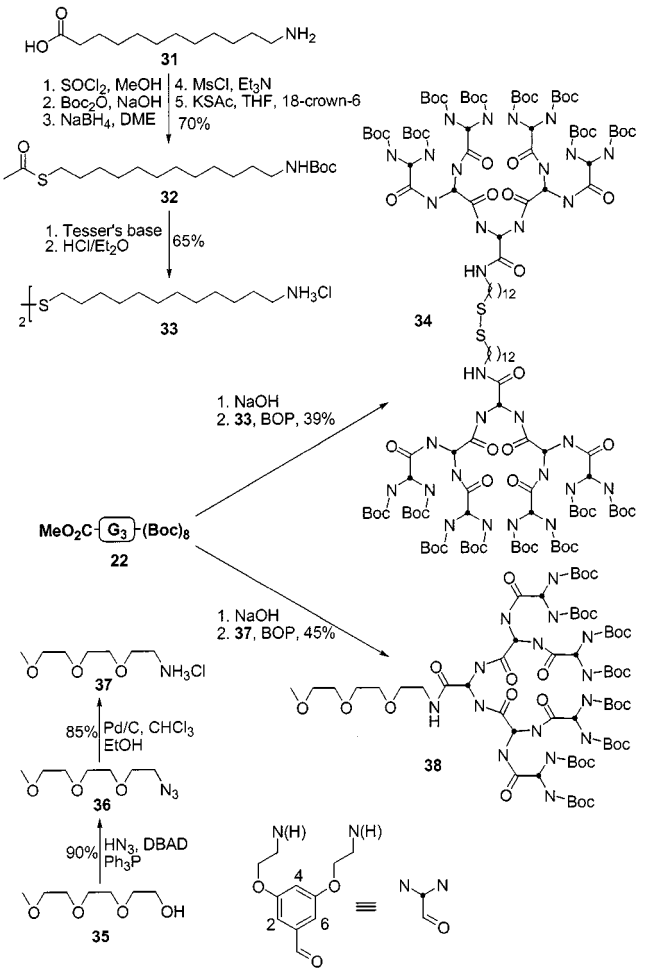


Figure 6. GPC traces of first to fifth generation dendrimers **12**, **20**, **22**, **24** and **25** (from right to left, top); first to third generation chiral dendrimers **13**, **21** and **23** (from right to left, middle); first to fourth generation dendrimers with a branching degree of three **15**, **30**, **28** and **29** (from right to left, bottom)



Scheme 4. Modification of the dendrimer "core"

leads to a considerable diversity in dendrimers, which can be easily extended to the synthesis of libraries using combinatorial approaches. Although the convergent method was used for the construction of dendrimers, the coupling results and purity of the dendrimers indicate that these dendrimers will also be accessible by the divergent method using, for example, solid phase synthesis.

The "core" methyl ester was easily replaced, this modification as well as modification of the "surface" groups will undoubtedly lead to interesting applications of these amino acid based dendrimers.

Experimental Section

General Remarks: Unless stated otherwise, chemicals were obtained from commercial sources and used without further purification. Solvents were dried with molecular sieves (4 Å), and 1,2-dimethoxyethane (DME) was distilled from $LiAlH_4$. Slightly modified Tesser's base used for saponifications was a mixture of dioxane, methanol (MeOH) and 4 M NaOH (14:5:2, v/v/v).[11] Saponification of the methyl ester in the higher generation dendrimers did not always go to completion after stirring overnight. If addition of Tesser's base did not lead to completion of the reaction, the mixture was worked up and the crude acid was purified by column chromatography [CH_3OH/CH_2Cl_2 (DCM) mixtures]. − Thin layer chromatography (TLC) was performed on Merck precoated 60 F-254 (0.25 mm) plates. Spots were visualized with UV light and ninhydrin. Solvents were evaporated under reduced pressure at 40 °C. − Column chromatography was performed on Merck Kieselgel 60 (40−63 μm), all eluents are given in v/v. All dendrimers, except first generation dendrimers, were purified by column chromatography, with an 18-cm silica column, and the diameter depends on the amount of crude dendrimer. For 20 g of crude material, an 8-cm diameter column was used. − Elemental analyses were carried out at Kolbe Mikroanalytisches Laboratorium (Mülheim an der Ruhr, Germany). − A Jasco Dip-4-Digital polarimeter was used for the measurement of specific optical rotation values. All optical rotations were measured in $CHCl_3$ (c = 1). − ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded with a Varian G-300 spectrometer. Chemical shifts are reported in ppm relative to TMS (δ = 0) for the ^1H NMR and to $CDCl_3$ (δ = 77) or CD_3OD (δ = 49) for the ^{13}C NMR as internal standards. C^4-H: denotes a proton of a first generation; $C^{4'}$-H: denotes a proton of a second generation etc.; $C^{4',4''}$: denotes carbon atoms of a second and third generation. − HPLC analysis was performed with a Gilson automated HPLC system 205 with a 233XL autosampler, a 119 UV/Vis detector, and an Adsorbospere XL Alltech column (C8 5 μm particle size, 90Å pore size). A gradient from water with 0.1% trifluo-

roacetic acid (TFA) to a mixture of acetonitrile/water (95:5) with 0.085% TFA was used. – GPC analysis was carried out with a Waters LCM1 apparatus, using a flow of 1 mL min^{-1} $CHCl_3$ at a column temperature of 35 °C and was monitored at 254 nm. – MS (FAB) mass spectra were measured with a JEOL JMS SX/SX 102A four-sector mass spectrometer coupled with an HP-9000 data system. A Fisions VG Platform II Single quadrupole mass spectrometer (Micromass, Manchester, UK) was used for measuring Electron-Spray mass spectra.

Methyl 3,5-Dihydroxybenzoate (5): To a solution of 3,5-dihydroxybenzoic acid (**1**) (5.0 g; 32 mmol) in methanol (170 mL) was added a catalytic amount of sulfuric acid (0.3 mL). After stirring at refluxing temperature overnight, the mixture was cooled to room temp. and neutralized with 2 M NaOH. After concentration, the residue was dissolved in ethyl acetate. The solution was washed with water and brine, dried (Na_2SO_4) and concentrated to dryness. Methyl ester **5** (5.45 g, 90%) was obtained as a white solid. – R_f = 0.63 (EtOAc). – ^{1}H NMR (CD_3OD): δ = 3.83 (s, 1 H, OCH_3), 4.88 (br. s, 2 H, 2 × OH), 6.48 (t, 1 H, Ph-C^4-H), 6.92 (t, 2 H, Ph-$C^{2,6}$-H). – ^{13}C NMR (CD_3OD): δ = 51.0 (OCH_3), 106.5 (Ph-C^4), 107.1 (Ph-$C^{2,6}$), 130.6 (Ph-C^1), 156.9 (Ph-$C^{3,5}$), 166.7 (CO_2CH_3).

Methyl Gallate (6): The synthesis of methyl gallate was performed under the same conditions as were employed for the synthesis of **5**, using gallic acid (**3**) (5.0 g; 29 mmol), methanol (150 mL) and a catalytic amount of sulfuric acid (0.3 mL). Methyl gallate (4.39 g, 81%) was obtained as a white solid. – R_f = 0.51 (diethyl ether). – ^{1}H NMR ($CDCl_3$): δ = 3.83 (s, 3 H, OCH_3), 4.99 (br. s, 3 H, 3 × OH), 7.09 (s, 2 H, Ph-$C^{2,6}$-H). – ^{13}C NMR ($CDCl_3/CD_3OD$): δ = 52.5 (OCH_3), 110.3 (Ph-$C^{2,6}$), 121.6 (Ph-C^1), 139.8 (Ph-C^4), 146.5 (Ph-$C^{3,5}$), 169.2 (CO_2CH_3).

2-(Boc-amino)ethyl Bromide (7): To a cooled (ice bath) and stirred suspension of (2-bromoethyl)amine (**2**) (512 g; 2.50 mol), di-*tert*-butyl dicarbonate (546 g; 2.50 mol) and dichloromethane (1.25 L), triethylamine (417 mL, 3.00 mol) was added dropwise over 3 h. After stirring for 1 d with a mechanical stirrer, dichloromethane was added and the solution was washed with 1 M $KHSO_4$, water and brine, the mixture was dried (Na_2SO_4) and concentrated in vacuo. Compound **7** was isolated as a clear light-yellow oil (585 g, 87%). The product contained some unchanged Boc_2O (5%), which was easily removed after alkylation to monomer **12**. – R_f = 0.72 (diethyl ether). – ^{1}H NMR ($CDCl_3$): δ = 1.46 [s, 9 H, $C(CH_3)_3$], 3.44–3.55 (m, 4 H, $BrCH_2$, CH_2NH), 4.94 (br. s, 1 H, NH). – ^{13}C NMR ($CDCl_3$): δ = 28.2 [$C(CH_3)_3$], 32.5 ($BrCH_2$), 42.3 (CH_2NH), 79.6 [$C(CH_3)_3$], 155.5 [C=O (Boc)].

3-(Boc-amino)propyl Bromide (8): Bromide **8** was prepared following the same procedure used for **7**, with (3-bromopropyl)amine (21.9 g, 0.10 mol), di-*tert*-butyl dicarbonate (21.8 g, 0.10 mol), dichloromethane (100 mL) and triethylamine (16.7 mL, 0.12 mol). The bromide (22.5 g, 95%) was obtained as a clear colorless oil which solidified at 4 °C. The product contained some unchanged Boc_2O (4.5%), which was easily removed after alkylation to monomer **15**. – R_f = 0.87 (EtOAc/hexanes, 1:1). – ^{1}H NMR ($CDCl_3$): δ = 1.45 [s, 9 H, $C(CH_3)_3$], 2.06 (m, 2 H, $CH_2CH_2CH_2$), 3.28 (m, 2 H, CH_2NH), 3.45 (t, 2 H, $BrCH_2$, J = 6.6 Hz), 4.64 (br. s, 1 H, NH). – ^{13}C NMR ($CDCl_3$): δ = 28.2 [$C(CH_3)_3$], 30.6 ($BrCH_2$), 32.6 ($CH_2CH_2CH_2$), 38.9 (CH_2NH), 79.2 [$C(CH_3)_3$], 155.9 (C=O (Boc)].

***N*-Boc-phenylalaninol (9):** After dropwise addition of thionyl chloride (7.5 mL; 103 mmol) to cooled (–20 °C) methanol (150 mL), phenylalanine (8.32 g; 50.4 mmol) was added in one portion. The temperature was raised to reflux temperature, and the mixture was stirred overnight. Concentration in vacuo, followed by crystallization from methanol/diethyl ether, afforded the methyl ester of phenylalanine as a white solid (10.3 g, 95%). To a cooled solution (0 °C) of this methyl ester (43.1 g; 200 mmol) in dioxane (300 mL) and 1 M NaOH (200 mL, 200 mmol), was slowly added di-*tert*-butyl dicarbonate (43.6 g; 200 mmol) in dioxane (40 mL). The pH of the mixture was kept at ca. 8, by the addition of 1 M NaOH. After stirring for 6 h, the pH of the reaction mixture was adjusted to 7 with 1 M $KHSO_4$. The mixture was concentrated, and the residue was dissolved in ethyl acetate and water. The organic layer was washed with 1 M $KHSO_4$, water and brine, the mixture was dried (Na_2SO_4) and concentrated in vacuo. Boc-Phe-OMe was obtained as a light-yellow oil (51.4 g, 92%). A mixture of sodium borohydride (1.82 g; 48.1 mmol), dry lithium iodide (6.42 g; 48.0 mmol) and dry DME (20 mL) was stirred at room temp. for 15 min. Boc-Phe-OMe (11.2 g; 40.1 mmol) in DME (10 mL) was added dropwise. After stirring for 2.5 h at 40 °C, the excess hydride was destroyed by the slow addition of 1 M $KHSO_4$. The reaction mixture was filtered and concentrated in vacuo. The residue was dissolved in ethyl acetate and washed with 1 M $KHSO_4$, 5% $Na_2S_2O_3$, 5% $NaHCO_3$ and brine. Drying (Na_2SO_4) and concentration in vacuo afforded alcohol **9** as a white solid (7.26 g, 72%). – R_f = 0.85 (EtOAc). – $[\alpha]_D^{20}$ = –24.0. – ^{1}H NMR ($CDCl_3$): δ = 1.42 [s, 9 H, $C(CH_3)_3$], 2.85 (d, 2 H, $PhCH_2$, J = 6.9 Hz), 3.58–3.66 (m, 2 H, OCH_2), 3.86 (br. s, 1 H, CH), 4.69 (br. s, 1 H, NH), 7.20–7.33 (m, 5 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 28.3 [$C(CH_3)_3$], 37.4 (CH_2Ph), 53.7 (CH), 63.9 (OCH_2), 79.6 [$C(CH_3)_3$], 126.4, 128.4, 129.3, 137.9 (Ph), 156.1 [C=O (Boc)].

Mesylate 10: To a cooled solution (ice bath) of *N*-Boc-phenylalaninol (**9**) (1.43 g; 5.7 mmol) and triethylamine (0.80 mL; 5.8 mmol) in dry dichloromethane (20 mL), was added methanesulfonyl chloride (0.43 mL; 5.5 mmol) in dry dichloromethane (10 mL) over 40 min. After stirring overnight, an additional portion of triethylamine (0.20 mL; 1.44 mmol) and methanesulfonyl chloride (0.11 mL; 1.42 mmol) was added. After stirring for 2 h, the reaction mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate and washed with water, 1 M $KHSO_4$, and brine, the mixture was dried (Na_2SO_4) and concentrated to dryness. Crystallization (EtOAc/hexanes) afforded mesylate **10** as white crystals (1.57 g, 86%). – R_f = 0.66 (EtOAC/hexanes, 1:1). – ^{1}H NMR ($CDCl_3$): δ = 1.42 [s, 9 H, $C(CH_3)_3$], 2.84–2.92 (m, 2 H, $PhCH_2$), 3.02 (s, 3 H, CH_3), 4.14 (m, 2 H, $MsOCH_2$), 4.25 (m, 1 H, CH), 4.73 (br. s, 1 H, NH), 7.21–7.36 (m, 5 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 28.2 [$C(CH_3)_3$], 37.2 (CH_3), 41.4 (CH_2Ph), 53.7 (CH), 69.8 ($MsOCH_2$), 79.9 [$C(CH_3)_3$], 126.9, 127.2, 128.7, 128.9, 129.2, 136.6 (Ph), 155.1 [C=O (Boc)].

Bromide 11: A mixture of mesylate **10** (3.32 g; 10.1 mmol) and lithium bromide (2.43 g; 28.0 mmol) in acetone (20 mL) was stirred at 30 °C overnight. The reaction mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (50 mL) and water. The organic layer was washed with water, 5% $NaHCO_3$ and brine, and the mixture was dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (EtOAc/hexanes; 1:9) afforded bromide **11** (1.85 g, 59%) as a white solid. – R_f = 0.85 (EtOAc/hexanes, 1:1). – ^{1}H NMR ($CDCl_3$): δ = 1.44 [s, 9 H, $C(CH_3)_3$], 2.86 (dd, 1 H, $PhCH^a$, J_{gem} = 13.5 Hz, J_{vic} = 8.1 Hz), 2.95 (dd, 1 H, $PhCH^b$, J_{vic} = 6.2 Hz), 3.37 (dd, 1 H, $BrCH^a$, J_{gem} = 10.2 Hz, J_{vic} = 3.3 Hz), 3.53 (dd, 1 H, $BrCH^b$, J_{vic} = 4.1 Hz), 4.05 (br. s, 1 H, CH), 4.84 (br. s, 1 H, NH), 7.21–7.35 (m, 5 H, Ph); – ^{13}C NMR ($CDCl_3$): δ = 28.3 [$C(CH_3)_3$], 37.2 ($PhCH_2$), 38.8 ($BrCH_2$), 51.4 (CH), 79.7 [$C(CH_3)_3$], 126.8, 128.6, 129.2, 137.1 (Ph), 154.9 [C=O (Boc)].

$(Boc)_2$-[G1]-CO_2Me, Monomer (12): A mixture of methyl 3,5-dihydroxybenzoate (**5**) (135 g; 0.80 mol), 2-Boc-aminoethyl bromide (**7**) (536 g (87% pure); 2.10 mol), potassium carbonate (498 g; 3.60 mol) and dry dimethylformamide (1.2 L) was mechanically stirred at 40 °C. After 16 h, the mixture was filtered through Hyflo and the solvent was evaporated. The residue was dissolved in ethyl acetate and washed with water (twice), and brine, the mixture was dried (Na_2SO_4) and concentrated in vacuo. Crystallization (EtOAc/hexanes) afforded **12** as a white solid (234 g, 64%). − R_f = 0.73 (MeOH/DCM, 1:9). − ^{1}H NMR ($CDCl_3$): δ = 1.45 [s, 18 H, 2 × $C(CH_3)_3$], 3.54 (m, 4 H, 2 × CH_2NH), 3.90 (s, 3 H, OCH_3), 4.04 (t, 4 H, 2 × OCH_2, J = 5.0 Hz), 4.98 (br. s, 2 H, 2 × NH), 6.63 (dd, 1 H, Ph-C^4-H, J = 2.2 Hz, J = 2.2 Hz), 7.18 (d, 2 H, Ph-C^{2,6}-H, J = 2.2 Hz). − ^{13}C NMR ($CDCl_3$): δ = 28.3 [C(CH_3)$_3$], 40.0 (CH_2NH), 52.1 (OCH_3), 67.5 (OCH_2), 79.5 [C(CH_3)$_3$], 106.4 (Ph-C^4), 108.1 (Ph-C^{2,6}), 132.1 (Ph-C^1), 155.8 [C=O (Boc)], 159.6 (Ph-C^{3,5}), 166.5 (CO_2CH_3). − MS (FAB): m/z = 455.1 [M + H]$^+$, 477.1 [M + Na]$^+$. − $C_{22}H_{34}N_2O_8$: calcd. C 58.14, H 7.54, N 6.16; found C 58.20, H 7.59, N 6.12.

$(Boc)_2$-[G1*]-CO_2Me, Monomer (13): A mixture of **5** (336 mg; 2.00 mmol), bromide **11** (1.63 g; 5.20 mmol), cesium carbonate (2.93 g; 9.00 mmol) and dry acetonitrile (20 mL) was refluxed for 3 d. The mixture was cooled to room temp., filtered through Hyflo and concentrated in vacuo. The residue was dissolved in ethyl acetate and water. The organic layer was washed with water, 5% $NaHCO_3$ and brine, and the mixture was dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (Silica 60H; DCM) followed by crystallization (EtOAc/hexanes) afforded monomer **13** as a white solid (318 mg, 26%). − R_f = 0.57 (EtOAc/hexane, 3:7). − $[\alpha]_D^{20}$ = −6.5. − ^{1}H NMR ($CDCl_3$): δ = 1.44 [s, 18 H, 2 × $C(CH_3)_3$], 2.96 (m, 4 H, 2 × C_6H_5−CH_2), 3.91 (m, 7 H, OCH_3, 2 × OCH_2), 4.16 (m, 2 H, 2 × CH), 4.89 (br. d, 2 H, 2 × NH), 6.64 (m, 1 H, Ph-C^4-H), 7.17−7.31 (m, 12 H, 2 × C_6H_5, Ph-C^{2,6}-H). − ^{13}C NMR ($CDCl_3$): δ = 28.4 [C(CH_3)$_3$], 37.7 ($C_6H_5CH_2$), 51.2 (CH), 52.2 (OCH_3), 68.2 (OCH_2), 79.6 [C(CH_3)$_3$], 106.4 (Ph-C^4), 108.3 (Ph-C^{2,6}), 126.6, 128.6, 129.4 (C_6H_5-C^{2,3,4}), 132.2 (Ph-C^1), 137.6 (C_6H_5-C^1), 155.2 [C=O (Boc)], 159.6 (Ph-C^{3,5}), 166.5 (CO_2CH_3). − MS (FAB): m/z = 635.4 [M + H]$^+$, 657.4 [M + Na]$^+$. − $C_{36}H_{46}N_2O_8$: calcd. C 68.12, H 7.30, N 4.41; found C 68.28, H 7.39, N 4.40.

$(Boc)_3$-[G1]-CO_2Me, Monomer (15): A mixture of methyl gallate **6** (14.7 g; 80.0 mmol), 3-(Boc-amino)propyl bromide (**8**) (74.3 g; 312 mmol), potassium carbonate (49.8 g; 360 mmol) and dry dimethylformamide (300 mL) was stirred at 40 °C for 3 d. The reaction mixture was filtered through Hyflo, and concentrated in vacuo. The residue was dissolved in ethyl acetate and water. The organic layer was washed with water, 5% $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated. Most contaminants were removed by column chromatography (EtOAc/hexanes gradient, 1:9−1:1). The product was completely purified by crystallization from EtOAc/hexanes, to afford monomer **15** (39.7 g, 76%) as a white solid. − R_f = 0.71 (MeOH/DCM, 1:9). − ^{1}H NMR ($CDCl_3$): δ = 1.44 [s, 27 H, $C(CH_3)_3$], 1.94 (m, 2 H, Ph-C^4−OCH_2CH_2), 2.03 (m, 4 H, Ph-C^{3,5}−OCH_2CH_2), 3.31−3.41 (m, 6 H, $NHCH_2$), 3.90 (s, 3 H, OCH_3), 4.10, 4.11 (2t, 6 H, OCH_2, J = 5.5 Hz), 5.06 [br. s, 2 H, Ph-C^{3,5}−$O(CH_2)_3NH$], 5.34 [br. s, 1 H, Ph-C^4−$O(CH_2)_3NH$], 7.27 (s, 2 H, Ph-C^{2,6}-H). − ^{13}C NMR ($CDCl_3$): δ = 28.4 [C(CH_3)$_3$], 29.6 (G1−3,5−OCH_2CH_2), 30.0 (G1-4-OCH_2CH_2), 38.0, 38.3 ($NHCH_2$), 52.1 (OCH_3), 67.1, 71.6 (OCH_2), 79.1 [C(CH_3)$_3$], 107.8 (Ph-C^{2,6}), 125.2 (Ph-C^1), 141.4 (Ph-C^4), 152.2 (Ph-C^{3,5}), 156.0, 156.1 (C=O Boc), 166.5 (CO_2CH_3). − MS (FAB): m/z = 656.5 [M + H]$^+$, 678.5 [M + Na]$^+$. − $C_{32}H_{53}N_3O_{11}$: calcd. C 58.61, H 8.15, N 6.41; found C 58.72, H 8.12, N 6.33.

Hydrochloride 18: To a solution of **12** (45.4 g; 0.10 mol) in dry dichloromethane (180 mL), was added diethyl ether (180 mL), saturated with HCl. After stirring for 1.5 h at room temp., the mixture was concentrated in vacuo, and the residue was dried with KOH overnight. The hydrochloride salt was obtained as a white solid in quantitative yield (32.6 g). − ^{1}H NMR (D_2O): δ = 3.50 (t, 4 H, 2 × CH_2NH, J = 5.0 Hz), 3.97 (s, 3 H, OCH_3), 4.38 (t, 4 H, 2 × OCH_2, J = 5.0 Hz), 4.80 (br. s, 2 H, 2 × NH), 6.95 (dd, 1 H, Ph-C^4-H, J = 2.2 Hz, J = 2.2 Hz), 7.35 (d, 2 H, Ph-C^{2,6}-H, J = 2.2 Hz). − ^{13}C NMR (D_2O): δ = 38.2 (CH_2NH), 52.1 (OCH_3), 63.6 (OCH_2), 106.2 (Ph-C^4), 107.9 (Ph-C^{2,6}), 130.9 (Ph-C^1), 157.9 (Ph-C^{3,5}), 167.5 (CO_2CH_3).

Hydrochloride 19: Boc deprotection of monomer **13** (385 mg; 0.63 mmol), was performed using the procedure described for **18** to afford **19** as a white solid (320 mg) in a quantitative yield. − ^{1}H NMR (D_2O): δ = 3.18 (d, 4 H, 2 × $C_6H_5CH_2$, J = 7.0 Hz), 3.94 (s, 3 H, OCH_3), 3.99, 4.09 (2 m, 4 H, 2 × OCH_2), 4.26 (d, 2 H, 2 × CH), 6.80 (s, 1 H, Ph-C^4-H), 7.24 (s, 2 H, Ph-C^{2,6}-H), 7.34−7.43 (m, 10 H, 2 × C_6H_5). − ^{13}C NMR (D_2O): δ = 34.0 ($C_6H_5CH_2$), 51.2 (OCH_3), 52.1 (CH), 65.7 (OCH_2), 105.9 (Ph-C^4), 107.9 (Ph-C^{2,6}), 126.8, 128.3, 128.6 (C_6H_5-C^2,C^3,C^4), 131.1 (Ph-C^1), 134.4 (C_6H_5-C^1), 157.9 (Ph-C^{3,5}), 167.6 (CO_2CH_3).

$(Boc)_4$-[G2]-CO_2Me (20): Monomer **12** (20.5 g; 45.1 mmol) was dissolved in slightly modified Tesser's base (508 mL) and stirred at room temp. After 4.5 h, the pH of the mixture was adjusted to approximately 2 with 1 M $KHSO_4$ and the mixture was concentrated in vacuo. The residue was dissolved in dichloromethane and water. The organic layer was washed with water and brine, and the mixture was dried (Na_2SO_4) and concentrated in vacuo. Acid **16** (19.9 g, 95%) was obtained as a white solid. To a suspension of acid **16** (17.6 g; 40 mmol), hydrochloride salt **18** (6.54 g; 20 mmol) and BOP (19.4 g; 44 mmol) in dry dichloromethane (200 mL), *N*,*N*-diisopropylethylamine (DiPEA) (22.6 mL; 130 mmol) was slowly added. The mixture was stirred at room temp. for 1.5 h, and concentrated in vacuo. The residue was dissolved in ethyl acetate and washed with 1 M $KHSO_4$ (twice), 1 M NaOH (twice) and brine, the mixture was dried (Na_2SO_4) and concentrated to dryness. Column chromatography (MeOH/DCM, 4:96) afforded the second generation dendrimer **20** as a white solid (20.8 g, 95%). − R_f = 0.45 (MeOH/DCM, 1:9). − ^{1}H NMR ($CDCl_3$): δ = 1.45 [s, 36 H, 4 × $C(CH_3)_3$], 3.50 (m, 8 H, 4 × C′H_2N′H), 3.84 (m, 4 H, 2 × CH_2NH), 3.89 (s, 3 H, OCH_3), 4.02 (m, 8 H, 4 × OC′H_2), 4.18 (m, 4 H, 2 × OCH_2), 5.05 (br. s, 4 H, 4 × N′H), 6.55 (dd, 2 H, 2 × Ph-C$^{4'}$-H, J = 2.2 Hz, J = 2.2 Hz), 6.70 (dd, 1 H, Ph-C^4-H, J = 2.2 Hz, J = 2.2 Hz), 6.79 (br. s, 2 H, 2 × NH), 6.93 (br. s, 4 H, 2 × Ph-C$^{2',6'}$-H); 7.20 (d, 2 H, Ph-C^{2,6}-H, J = 2.2 Hz). − ^{13}C NMR ($CDCl_3$): δ = 28.3 [C(CH_3)$_3$], 39.5 (C′H_2N′H), 39.8 (CH_2NH), 52.2 (OCH_3), 67.0 (OC′H_2), 67.3 (OCH_2), 79.6 [C(CH_3)$_3$], 104.5, 105.9, 108.3 (Ph-C$^{4,4'}$, Ph-C$^{2,6,2',6'}$), 132.1 (Ph-C^1), 136.4 (Ph-C$^{1'}$), 155.9 [C=O (Boc)], 159.5, 159.7 (Ph-C^{3,5}, Ph-C$^{3',5'}$), 166.5 (CO_2CH_3), 167.3 (N′HC′=O). − MS (FAB): m/z = 1121.3 [M + Na]$^+$ − $C_{54}H_{78}N_6O_{18}$: calcd. C 59.00, H 7.15, N 7.65; found C 58.88, H 7.17, N 7.58.

$(Boc)_4$-[G2*]-CO_2Me (21): $(Boc)_2$-[G1*]-CO_2Me (**13**) (9.89 g; 9.00 mmol) was saponified following the same procedure as described in the synthesis of **20**, using slightly modified Tesser's base (15 mL). After stirring overnight, $(Boc)_2$-[G1*]-CO_2H (**17**) (816 mg; 97%) was obtained as a white solid. The coupling step was performed according to the procedure described in **20**, using acid **17** (649 mg; 1.09 mmol), hydrochloride salt **19** (268 mg; 0.53 mmol), BOP (550 mg; 1.25 mmol), dichloromethane (6 mL) and DiPEA (0.87 mL; 4.99 mmol). The reaction mixture was stirred for 1 h.

Column chromatography (MeOH/DCM gradient, 1:99−2:98) afforded the chiral second generation dendrimer **21** as a white solid (660 mg, 76%). − R_f = 0.63 (MeOH/DCM, 1:9). − $[\alpha]_D^{20}$ = −10.4. − ^{1}H NMR ($CDCl_3$): δ = 1.43 [s, 36 H, 4 × $C(CH_3)_3$], 2.97 (br. d, 8 H, 4 × C′$_6$H$_5$-C′H_2), 3.13 (br. d, 4 H, 2 × C_6H_5-CH_2), 3.88 (m, 11 H, OCH_3, 4 × OC′H_2), 4.05 (m, 4 H, 2 × OCH_2), 4.17 (m, 4 H, 4 × C′H), 4.67 (m, 2 H, 2 × CH), 4.88 (br. d, 4 H, 4 × N′H), 6.44 (br. d, 2 H, 2 × NH), 6.53 (br. s, 2 H, 2 × Ph-C$^{4′}$-H), 6.71 (br. s, 1 H, Ph-C^4-H), 6.86 (br. s, 4 H, 2 × Ph-C$^{2′,6′}$-H), 7.18−7.30 (m, 32 H, Ph-C^{2,6}-H, 2 × C_6H_5, 4 × C′$_6$H$_5$). − ^{13}C NMR ($CDCl_3$): δ = 28.3 [C(CH_3)$_3$], 37.2, 37.6 (CH_2−C_6H_5, $C′H_2$−C′$_6$H$_5$), 50.4, 50.9 (CH, C′H), 52.2 (OCH_3), 68.0, 68.2 (OCH_2, OC′H_2), 79.6 [C(CH_3)$_3$], 104.6 (Ph-C$^{4′}$), 105.9 (Ph-C$^{2′,6′}$), 106.3 (Ph-C^4), 108.6 (Ph-C^{2,6}), 126.6, 126.8, 128.6, 128.7, 129.3 (C_6H_5-C$^{2′,3′,4′}$), 132.3 (Ph-C^1), 136.7, 137.3, 137.5 (Ph-C$^{1′}$, C_6H_5-C^1, C′$_6$H$_5$-C$^{1′}$), 155.2 [C=O (Boc)], 159.6, 159.8 (Ph-C^{3,5}, Ph-C$^{3′,5′}$), 166.4, 166.6 (C′=O, CO_2CH_3). − MS (FAB): m/z = 1639.8 [M + H]$^+$, 1661.8 [M + Na]$^+$. − $C_{96}H_{114}N_6O_{18}$: calcd. C 70.31, H 7.01, N 5.12; found C 70.19, H 6.92, N 5.19.

(Boc)$_8$-[G3]-CO$_2$Me (22): (Boc)$_4$-[G2]-CO_2Me (**20**) (19.8 g; 18.0 mmol) was saponified following the same procedure as described in the synthesis of **20**, using slightly modified Tesser's base (203 mL). After stirring overnight, (Boc)$_4$-[G2]-CO_2H (18.5 g, 94%) was obtained as a white solid. To a mixture of hydrochloride salt **18** (2.78 g; 8.5 mmol), (Boc)$_4$-[G2]-CO_2H (18.5 g; 17.0 mmol) and BOP (8.23 g; 18.7 mmol) in dry acetonitrile (138 mL), DiPEA (9.6 mL; 55.3 mmol) was slowly added at room temp. After refluxing for one night, the mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate. The solution was washed with 1 M $KHSO_4$ (twice), 1 M NaOH (twice), and brine, and the mixture was dried (Na_2SO_4) and concentrated. Column chromatography (MeOH/DCM, 4:96) afforded the third generation dendrimer **22** as a white foam (16.5 g, 81%). − R_f = 0.40 (MeOH/DCM, 1:9). − ^{1}H NMR ($CDCl_3$): δ = 1.43 [s, 72 H, 8 × $C(CH_3)_3$], 3.44 (m, 16 H, 8 × C"H_2N′′H), 3.73 (m, 12 H, 2 × CH_2NH, 4 × C′H_2N′H), 3.85 (s, 3 H, OCH_3), 3.92 (br. t, 16 H, 8 × OC′′H_2), 4.01 (br. t, 8 H, 4 × OC′H_2), 4.11 (br. t, 4 H, 2 × OCH_2), 5.30 (br. s, 8 H, 8 × N′′H), 6.43 (br. s, 6 H, 2 × Ph-C$^{4′}$-H, 4 × Ph-C$^{4′′}$-H), 6.66 (br. s, 1 H, Ph-C^4-H), 6.87 (s, 4 H, 2 × Ph-C$^{2′,6′}$-H), 6.89 (s, 8 H, 4 × Ph-C$^{2′′,6′′}$-H), 7.09 (s, 2 H, Ph-C^{2,6}-H), 7.36 (br. s, 6 H, 2 × NH, 4 × N′H). − ^{13}C NMR ($CDCl_3$): δ = 28.3 [C(CH_3)$_3$], 39.4, 39.8 (CH_2NH, C′H_2N′H, C′′H_2N′′H), 52.1 (OCH_3), 66.6, 66.7, 67.1 (OCH_2, OC′H_2, OC′′H_2), 79.5 [C(CH_3)$_3$], 104.4, 105.8, 106.0, 108.3 (Ph-C$^{4,4′,4′′}$, Ph-C$^{2,6,2′,6′,2′′,6′′}$), 131.9 (Ph-C^1), 136.2 (Ph-C$^{1′′}$), 136.3 (Ph-C$^{1′}$), 155.9 [C=O (Boc)], 159.5 (Ph-C$^{3,5,3′,5′,3′′,5′′}$), 166.4 (CO_2CH_3), 167.4 (N′HC′=O, N′′HC′′=O). − MS (FAB): m/z = 2388.3 [M + H]$^+$, 2409.7 [M + Na]$^+$. − $C_{118}H_{166}N_{14}O_{38}$: calcd. C 59.33, H 7.00, N 8.21; found C 59.26, H 7.08, N 8.27.

Boc)$_8$-[G3*]-CO$_2$Me (23): (Boc)$_4$-[G2*]-CO_2Me (**21**) (287 mg; 0.175 mmol) was saponified following the same procedure as described in the synthesis of **20**, using slightly modified Tesser's base (1.9 mL). After stirring overnight, (Boc)$_4$-[G2*]-CO_2H (273 mg, 96%) was obtained as a white solid. The coupling step was performed according to the procedure described in **20**, using hydrochloride salt **19** (31.3 mg; 61.7 μmol), (Boc)$_4$-[G2*]-CO_2H (190 mg; 0.122 mmol), BOP (57 mg; 0.129 mmol), dichloromethane (0.6 mL) and DiPEA (0.66 mL; 0.381 mmol). Column chromatography (MeOH/DCM, 3:97) afforded the chiral third generation dendrimer **23** as a white solid (104 mg, 59%). − R_f = 0.67 (EtOAc). − $[\alpha]_D^{20}$ = −5.0. − ^{1}H NMR ($CDCl_3$): δ = 1.40 [s, 72 H, 8 × $C(CH_3)_3$], 2.93 (br. d, 16 H, 8 × C′′$_6$H$_5$−C′′H_2), 3.09 (br. d, 12 H, 12 × C_6H_5-CH_2, 4 × C′$_6$H$_5$-C′H_2), 3.84 (m, 19 H, OCH_3, 8 × OC′′H_2), 4.02 (m, 12 H, 2 × OCH_2, 4 × OC′H_2), 4.13 (m, 8 H, 8 × C′′H), 4.67 (m, 6 H, 2 × CH, 4 × C′H), 4.92 (br. s, 8 H, 8 × N′′H), 6.50 (br. s, 8 H, 4 × Ph-C$^{4′′}$-H, 4 × N′H), 6.59 (br. s, 2 H, 2 × Ph-C$^{4′}$-H), 6.66 (br. s, 1 H, Ph-C^4-H), 6.78 (br. s, 2 H, 2 × NH), 6.86 (br. s, 8 H, 4 × Ph-C$^{2′′,6′′}$-H), 7.02 (s, 2 H, Ph-C^{2,6}-H), 7.17−7.26 (m, 74 H, 2 × C_6H_5, 4 × C′$_6$H$_5$, 8 × C′′$_6$H$_5$, 2 × Ph-C$^{2′,6′}$-H). − ^{13}C NMR ($CDCl_3$): δ = 28.1 [C(CH_3)$_3$], 36.9, 37.4 (C_6H_5-CH_2, C′$_6$H$_5$-$C′H_2$, C′′$_6$H$_5$-$C′′H_2$), 50.1, 50.4, 50.8 (CH, C′H, C′′H), 52.1 (OCH_3), 68.2 (OCH_2, OC′H_2, OC′′H_2), 79.6 [C(CH_3)$_3$], 104.5, 105.9, 106.1, 106.3, 108.3 (Ph-C$^{4,4′,4′′}$, Ph-C$^{2,6,2′,6′,2′′,6′′}$), 126.4, 126.5, 128.4, 128.5, 128.7, 128.8, 129.2 (C_6H_5-C^{2,3,4}, C′$_6$H$_5$-C$^{2′,3′,4′}$, C′′$_6$H$_5$-C$^{2′′,3′′,4′′}$), 131.9, 136.3, 137.0, 137.3, 137.4 (Ph-C$^{-1,1′,1′′}$, C_6H_5-C^1, C′$_6$H$_5$-C$^{1′}$, C′′$_6$H$_5$-C$^{1′′}$), 155.4, 155.5 [C=O (Boc)], 159.0, 159.6 (Ph-C$^{3,5,3′,5′,3′′,5′′}$), 166.6, 167.0, 167.1 (CO_2CH_3, N′HC′=O, N′′HC′′=O). − MS (FAB): m/z [M + H]$^+$ = 3650, [M + Na]$^+$ = 3671 (isotope peaks are not visible, peaks are very broad). − $C_{216}H_{250}N_{14}O_{38}$: calcd. C 71.07, H 6.90, N 5.35; found C 71.17, H 6.99, N 5.29.

(Boc)$_{16}$-[G4]-CO$_2$Me (24): Following the same procedure as described in the synthesis of **20**, (Boc)$_4$-[G3]-CO_2Me (**22**) (11.9 g; 5.0 mmol) was saponified using slightly modified Tesser's base (65.3 mL). However, the reaction was performed at 40 °C overnight. The resulting (Boc)$_8$-[G3]-CO_2H (11.9 g, 92%) was isolated as a white solid. The coupling reaction to **24** was performed under the same conditions as were employed for **22**, using hydrochloride salt **18** (1.23 g; 3.75 mmol), (Boc)$_8$-[G3]-CO_2H (17.8 g; 7.5 mmol), BOP (3.63 g; 8.25 mmol), dry acetonitrile (56 mL) and DiPEA (4.24 mL; 24.4 mmol). Column chromatography (MeOH/DCM, 5:95) afforded the fourth generation dendrimer **24** (11.5 g, 62%) as a white foam. − R_f = 0.39 (MeOH/DCM, 1:9). − ^{1}H NMR ($CDCl_3$): δ = 1.42 [s, 144 H, 16 × $C(CH_3)_3$], 3.42 (br. s, 32 H, 16 × C′′′H_2N′′′H), 3.66 (br. s, 28 H, 2 × CH_2NH, 4 × C′H_2N′H, 8 × C′′H_2N′′H), 3.82 (s, 3 H, OCH_3), 3.89 (br. s, 56 H, 4 × OC′H_2, 8 × OC′′H_2, 16 × OC′′′H_2), 4.07 (br. s, 4 H, 2 × OCH_2), 5.37 (br. s, 16 H, 16 × N′′′H), 6.34 (br. s, 6 H, 2 × Ph-C$^{4′}$-H, 4 × Ph-C$^{4′′}$-H), 6.41 (br. s, 8 H, 8 × Ph-C$^{4′′′}$-H), 6.62 (br. s, 1 H, Ph-C^4-H), 6.81 (br. s, 12 H, 2 × Ph-C$^{2′,6′}$-H, 4 × Ph-C$^{2′′,6′′}$-H), 6.89 (br. s, 16 H, 8 × Ph-C$^{2′′′,6′′′}$-H), 7.05 (br. s, 2 H, Ph-C^{2,6}-H), 7.61 (br. s, 14 H, 2 × NHCO, 4 × N′HCO, 8 × N′′HCO). − ^{13}C NMR ($CDCl_3$): δ = 28.4 [C(CH_3)$_3$], 39.6, 39.9 (CH_2NH, C′H_2N′H, C′′H_2N′′H, C′′′H_2N′′′H), 52.2 (OCH_3), 66.5, 67.2 (OC′H_2, OCH_2, OC′′H_2, OC′′′H_2), 79.5 [C(CH_3)$_3$], 104.4, 106.0 (Ph-C$^{4,4′,4′′,4′′′}$, Ph-C$^{2,6,2′,6′,2′′,6′′,2′′′,6′′′}$), 131.8 (Ph-C^1), 136.2 (Ph-C$^{1′,1′′,1′′′}$), 156.0 [C=O (Boc)], 159.5, 159.6 (Ph-C$^{3,5,3′,5′,3′′,5′′,3′′′,5′′′}$), 166.6 ($CO_2CH_3$), 167.6, 167.7 (C′=O, C′′=O, C′′′=O). − MS (FAB): m/z = 4990 (average mass) [M + Na]$^+$. − $C_{2246}H_{342}N_{30}O_{78}$: calcd. C 59.48, H 6.94, N 8.46; found C 59.55, H 6.99, N 8.38.

(Boc)$_{32}$-[G5]-CO$_2$Me (25): Following the same procedure as described in the synthesis of **20**, (Boc)$_8$-[G4]-CO_2Me (**24**) (3.97 g; 0.80 mmol) was saponified using slightly modified Tesser's base (18.3 mL). However, the reaction was performed at 40 °C overnight. (Boc)$_{16}$-[G4]-CO_2H (3.96 g, 99%) was afforded as a white solid. The coupling reaction to **25** was performed under the same conditions as were employed for **22**, using hydrochloride salt **18** (0.035 g; 0.11 mmol), (Boc)$_{16}$-[G4]-CO_2H (0.99 g; 0.20 mmol), BOP (0.10 g; 0.23 mmol), acetonitrile (4 mL) and DiPEA (0.12 mL; 0.69 mmol). After column chromatography (MeOH/DCM, 5:95) the fifth generation dendrimer **25** (644 mg, 60%) was isolated as a white foam. − R_f = 0.39 (MeOH/DCM, 1:9). − ^{1}H NMR ($CDCl_3$): δ = 1.40 [s, 288 H, 32 × $C(CH_3)_3$], 3.40 (br. s, 64 H, 32

× C′′′′H_2N′′′′H), 3.65 (br. s, 60 H, 2 × CH_2NH, 4 × C′H_2N′H, 8 × C′′H_2N′′H, 16 × C′′′H_2N′′′H), 3.87 (br. s, 124 H, 2 × OCH_2, 4 × OC′H_2, 8 × OC′′H_2, 16 × OC′′′H_2, 32 × OC′′′′H_2), 5.41 (br. s, 32 H, 32 × N′′′′H), 6.32, 6.40 (2br. s., 31 H, Ph-C^4-H, 2 × Ph-C$^{4'}$-H, 4 × Ph-C$^{4''}$-H, 8 × Ph-C$^{4'''}$-H, 16 × Ph-C$^{4''''}$-H), 6.81, 6.89 (2br. s., 62 H, Ph-C^{2,6}-H, 2 × Ph-C$^{2',6'}$-H, 4 × Ph-C$^{2'',6''}$-H, 8 × Ph-C$^{2''',6'''}$-H, 16 × Ph-C$^{2'''',6''''}$-H), 7.68 (br. s, 30 H, 2 × NH, 4 × N′H, 8 × N′′H, 16 × NH′′′); ^{13}C NMR ($CDCl_3$): δ = 27.9 [C(CH_3)$_3$], 40.0 (CH_2NH, C′H_2N′H, C′′H_2N′′H, C′′′H_2N′′′H, C′′′′H_2N′′′′H), 52.0 (OCH_3), 66.7, 67.3 (OC′H_2, OCH_2, OC′′H_2, OC′′′H_2, OC′′′′H_2), 79.3 [C(CH_3)$_3$], 104.9, 106.3 (Ph-C$^{4,4',4'',4''',4''''}$, Ph-C$^{2,6,2',6',2'',6'',2''',6''',2'''',6''''}$), 132.0 (Ph-C^1), 136.4 (Ph-C$^{1',1'',1''',1''''}$), 157.3 [C=O (Boc)], 160.2 (Ph-C$^{3,5,3',5',3'',5'',3''',5''',3'''',5''''}$), 167.1 ($CO_2CH_3$), 168.8 (C′=O, C′′=O, C′′′=O, C′′′′=O). − MS (ESI): m/z = 2026 [M + 5 H]$^{5+}$, 2030 [M + 4 H + Na]$^{5+}$, 2035 [M + 3 H + 2 Na]$^{5+}$, 2039 [M + 2 H + 3 Na]$^{5+}$, 2047 [M + 1 H + 4 Na]$^{5+}$, 2048 [M + 5 Na]$^{5+}$. − $C_{502}H_{694}N_{262}O_{158}$: calcd. C 59.55, H 6.91, N 8.58; found C 59.43, H 7.01, N 8.46.

Hydrochloride Salt 27: Boc deprotection of monomer **15** (7.87 g; 12.0 mmol), was performed using the procedure described for **18**, affording a white solid (5.70 g) in a quantitative yield. − R_f = 0.22 ($CHCl_3$/MeOH/25% NH_4OH, 60:45:20). − ^{1}H NMR (D_2O): δ = 2.14 (m, 2 H, Ph-C^4-OCH_2CH_2), 2.26 (m, 4 H, Ph-C^{3,5}-OCH_2CH_2), 3.26 (m, 6 H, 3 × NHCH_2), 3.95 (s, 3 H, OCH_3), 4.27 (m, 6 H, 3 × OCH_2), 7.44 (s, 2 H, Ph-C^{2,6}-H). − ^{13}C NMR (D_2O): δ = 25.9 (Ph-C^{3,5}-OCH_2CH_2), 26.6 (Ph-C^4-OCH_2CH_2), 36.5, 37.0 ($NHCH_2$), 52.1 (OCH_3), 65.6, 70.7 (OCH_2), 107.5 (Ph-C^{2,6}), 124.7 (Ph-C^1), 139.5 (Ph-C^4), 150.7 (Ph-C^{3,5}), 167.3 (CO_2CH_3).

(Boc)$_9$-[G2]-CO_2Me (28): (Boc)$_3$-[G1]-CO_2Me (**15**) (9.8 g; 15.0 mmol) was saponified following the same procedure as described in the synthesis of **20**, using slightly modified Tesser's base (170 mL). After stirring overnight, acid **26** (9.0 g, 94%) was obtained as a white foam. The coupling step was performed according to the procedure described for **20**, using acid **26** (8.7 g; 13.5 mmol), hydrochloride salt **27** (2.1 g; 4.5 mmol) and BOP (7.4 g; 16.9 mmol), dichloromethane (60 mL) and DiPEA (7.6 mL; 43.9 mmol). The mixture was stirred for 4 h. Column chromatography (MeOH/DCM, 4:96) afforded the second generation dendrimer **28** as a white solid (9.0 g, 90%). − R_f = 0.67 (MeOH/DCM, 1:9). − ^{1}H NMR ($CDCl_3$): δ = 1.42, 1.42, 1.44 [3s, 81 H, 9 × C(CH_3)$_3$], 1.88−1.99 (m, 18 H, 9 × OC′H_2C′H_2), 2.10 (m, 6 H, 3 × OCH_2CH_2), 3.19−3.39 (m, 18 H, 9 × N′HC′H_2), 3.64 (m, 6 H, 3 × NHCH_2), 3.82, 4.06 (2 m, 18 H, 9 × OC′H_2), 3.89 (s, 3 H, OCH_3), 4.13 (m, 6 H, 3 × OCH_2), 5.21, 5.36 (2br. s., 9 H, 9 × N′H), 6.98 [s, 2 H, Ph(B)-C$^{2',6'}$-H], 7.11 [s, 4 H, Ph(AA)-C$^{2',6'}$-H], 7.28 (s, 2 H, Ph-C^{2,6}-H), 7.30 (br. s, 2 H, Ph-C^{3,5}-$OCH_2CH_2CH_2NH$), 7.54 (br. s, 1 H, Ph-C^4-$OCH_2CH_2CH_2NH$). − ^{13}C NMR ($CDCl_3$): δ = 28.4, 28.4 [C(CH_3)$_3$], 29.2, 29.6, 30.0 (OCH_2CH_2, OC′H_2C′H_2), 37.6, 38.0, 38.3, 38.7 ($NHCH_2$, N′H_2C′H_2), 52.2 (OCH_3), 66.9, 67.1, 71.5, 72.8 (OCH_2, OC′H_2), 79.0 [C(CH_3)$_3$], 105.7, 105.9 (Ph-C$^{2',6'}$), 107.9 (Ph-C^{2,6}), 125.5 (Ph-C^1), 129.8 (Ph-C$^{1'}$), 140.1 (Ph-C$^{4'}$), 141.4 (Ph-C^4), 152.3, 152.3, 152.3 (Ph-C^{3,5}, Ph-C$^{3',5'}$), 156.1 [C=O (Boc)], 166.3 (CO_2CH_3), 167.1, 167.4 (N′HC′=O). − MS (FAB): m/z = 2249.6 (average mass) [M + Na]$^+$. − $C_{110}H_{176}N_{12}O_{35}$: calcd. C 59.34, H 7.97, N 7.55; found C 59.26, H 7.92, N 7.48.

(Boc)$_{27}$-[G3]-CO_2Me (29): (Boc)$_9$-[G2]-CO_2Me (**28**) (4.45 g; 2.00 mmol) was saponified following the same procedure as described in the synthesis of **20**, using slightly modified Tesser's base (15 mL). After stirring overnight, (Boc)$_9$-[G2]-CO_2H (4.34 g, 98%) was obtained as a white solid. The coupling step was performed according to the procedure described in **22**, using hydrochloride salt **27** (232 mg; 0.50 mmol), (Boc)$_9$-[G2]-CO_2H (3.32 g; 1.50 mmol), BOP (828 mg; 1.88 mmol), acetonitrile (5 mL) and DiPEA (0.85 ml; 4.88 mmol). Column chromatography (MeOH/DCM, 4:96) afforded the third generation dendrimer **29** as a white solid (2.29 g, 66%). − R_f = 0.57 (MeOH/DCM, 1:9). − ^{1}H NMR ($CDCl_3$): δ = 1.40, 1.42, 1.43 [3 s, 243 H, 27 × C(CH_3)$_3$], 1.79−2.11 (m, 78 H, 3 × OCH_2CH_2, 9 × OC′H_2C′H_2, 27 × OC′′H_2C′′H_2), 3.17−3.60 (m, 78 H, 3 × NHCH_2, 9 × N′HC′H_2, 27 × N′′HC′′H_2), 3.80, 4.00−4.10 (2 m, 78 H, 3 × OCH_2, 9 × OC′H_2, 27 × OC′′H_2), 3.86 (s, 3 H, OCH_3), 5.40 (br. s, 27 H, 27 × N′′H), 7.00, 7.13, 7.27 (3 br. s., 26 H, Ph-C^{2,6}-H, 3 × Ph-C$^{2',6'}$-H, 9 × Ph-C$^{2'',6''}$-H), 7.78, 7.93, 8.03 (3 br. s., 12 H, 3 × NH, 9 × N′H). − ^{13}C NMR ($CDCl_3$): δ = 28.2 [C(CH_3)$_3$], 29.0, 29.4, 29.9 (OCH_2CH_2, OC′H_2C′H_2, OC′′H_2C′′H_2), 37.2, 37.8, 38.1, 38.7 ($NHCH_2$, N′HC′H_2, N′′HC′′H_2), 52.0 (OCH_3), 66.8, 71.3, 72.5 (OCH_2, OC′H_2, OC′′H_2), 78.7 [C(CH_3)$_3$], 105.6 (Ph-C$^{2',6'}$, Ph-C$^{2'',6''}$), 107.5 (Ph-C^{2,6}), 125.0 (Ph-C^1), 129.3, 129.4, 129.5, 130.0, 130.2 (Ph-C$^{1'}$, Ph-C$^{1''}$), 139.6, 139.7, 139.9 (Ph-C$^{4'}$, Ph-C$^{4''}$), 141.4 (Ph-C^4), 152.0, 152.2 (Ph-C^{3,5}, Ph-C$^{3',5'}$, Ph-C$^{3'',5''}$), 155.9 [C=O (Boc)], 166.3 (CO_2CH_3), 167.0, 167.1, 167.1, 167.3 (N′HC′=O, N′′HC′′=O). − MS (ESI): m/z = 1389 [M + 5 H]$^{5+}$, 1736 [M + 4 H]$^{4+}$, 2336 [M + H + 2 Na]$^{3+}$. − $C_{344}H_{545}N_{39}O_{107}$: calcd. C 59.54, H 7.92, N 7.87; found C 59.68, H 7.88, N 7.91.

(Boc)$_{81}$-[G4]-CO_2Me (30): (Boc)$_{27}$-[G3]-CO_2Me (**29**) (2.30 g; 0.33 mmol) was saponified following the same procedure as described in the synthesis of **20**, using slightly modified Tesser's base (2.5 mL). After stirring overnight at 40 °C, (Boc)$_{27}$-[G3]-CO_2H (1.55 g; 68%) was obtained as a white solid. The coupling step was performed similar to the procedure described in **22**, using hydrochloride salt **27** (30 mg; 0.064 mmol), (Boc)$_{27}$-[G3]-CO_2H (1.32 g; 0.19 mmol), BOP (105 mg; 0.24 mmol), acetonitrile (0.85 mL) and DiPEA (0.11 ml; 0.62 mmol). Column chromatography (MeOH/DCM, 6:94) afforded the fourth generation dendrimer **30** as a white solid (922 mg, 69%). − R_f = 0.55 (MeOH/DCM, 1:9). − ^{1}H NMR ($CDCl_3$): δ = 1.39, 1.41 [2 br. s, 729 H, C(CH_3)$_3$], 1.88 (br. s, 240 H, OCH_2CH_2, OC′H_2C′H_2, OC′′H_2C′′H_2, OC′′′H_2C′′′H_2), 3.20−3.59 (m, 240 H, CH_2NH, C′H_2N′H, C′′H_2N′′H, C′′′H_2N′′′H), 3.78, 3.92−4.00 (2 m, 240 H, OCH2, OC′H2, OC′′H2, OC′′′H2), 3.82 (s, 3 H, OCH_3), 5.46 (br. s, 81 H, N′′′H), 6.99, 7.13, 7.26 (3br. s., 80 H, Ph-C^{2,6}-H, Ph-C$^{2',6'}$-H, Ph-C$^{2'',6''}$-H, Ph-C$^{2''',6'''}$-H), 7.83, 8.08, 8.14 (3br. s., 39 H, NH, N′H, N′′H). − ^{13}C NMR ($CDCl_3$): δ = 28.4 [C(CH_3)$_3$], 29.6, 30.1 (OCH_2CH_2, OC′H_2C′H_2, OC′′H_2C′′H_2, OC′′′H_2C′′′H_2), 37.5, 38.0, 38.2 (CH_2NH, C′H_2N′H, C′′H_2N′′H, C′′′H_2N′′′H), 67.0, 71.5, 72.3(OCH_2, OC′H_2, OC′′H_2, OC′′′H_2), 78.9 [C(CH_3)$_3$], 105.8 (Ph-C$^{2',6'}$, Ph-C$^{2'',6''}$, Ph-C$^{2''',6'''}$), 129.5, 129.6, 129.7, 130.1 (Ph-C$^{1'}$, Ph-C$^{1''}$, Ph-C$^{1'''}$), 140.0 (Ph-C$^{4'}$, Ph-C$^{4''}$, Ph-C$^{4'''}$), 152.3, 152.4 (Ph-C^{3,5}, Ph-C$^{3',5'}$, Ph-C$^{3'',5''}$, Ph-C$^{3''',5'''}$), 156.1 (C=O Boc), 167.3, 167.3, 167.4, 167.5 (C′=O, C′′=O, C′′′=O). The signals of Ph-C^1, Ph-C^4 and CO_2CH_3 are not visible. − MS (ESI): m/z = 2343.8 [M + 9 H]$^{9+}$, 2636.4 [M + 8 H]$^{8+}$. − $C_{1046}H_{1652}N_{120}O_{323}$: calcd. C 59.61, H 7.90, N 7.97; found C 59.79, H 7.85, N 7.87.

Thioacetate 32: 12-Aminododecanoic acid (**31**) was esterified, Boc-protected, reduced and mesylated following the procedures described in the synthesis of **9** and **10**, to afford Boc(H)N(CH_2)$_{12}$OMs as a white solid (87%, 4 steps). A suspension of Boc(H)(CH_2)$_{12}$-OMs (174 mg, 0.5 mmol), potassium thioacetate (63 mg, 0.55 mmol) and a catalytic amount of 18-crown-6 in THF (1 mL) was stirred at room temp. overnight. The mixture was concentrated and dissolved in ethyl acetate and water. The organic layer was washed with 5% $NaHCO_3$, water and brine, dried (Na_2SO_4) and

concentrated in vacuo. Column chromatography (EtOAc/hexanes, 1:15) afforded the thioacetate as an off-white solid (144 mg, 81%). − R_f = 0.3 (EtOAc/hexanes, 1:9). − ^{1}H NMR ($CDCl_3$): δ = 1.20−1.58 [m, 29 H, SCH_2-(CH_2)$_{10}$, $C(CH_3)_3$], 2.29 (s, 3 H, OCH_3), 2.83 (t, 2 H, SCH_2, J = 7.4 Hz), 3.06 (m, 2 H, $NHCH_2$), 4.55 (br. s, 1 H, NH). − ^{13}C NMR ($CDCl_3$): δ = 26.7, 29.0, 29.1, 29.2, 29.3, 29.4, 30.0 [$S(CH_2)_{11}$], 28.4 [$C(CH_3)_3$], 30.5 (CH_3C=O), 40.6 ($NHCH_2$), 78.8 [$C(CH_3)_3$], 155.9 [C=O (Boc)], 195.8 (CH_3C=O).

(Boc)$_8$-[G3]-C(O)NH-(CH$_2$)$_{12}$-S-]$_2$ (34): A solution of thioacetate **32** (143 mg, 0.40 mmol) in slightly modified Tesser's base (4.0 mL) was stirred overnight at room temp. The mixture was concentrated and dissolved in ethyl acetate and water. The organic layer was washed with water and brine, dried (Na_2SO_4) and concentrated to dryness. The disulfide (81 mg, 65%) was obtained as a white solid. To a solution of the disulfide (80 mg, 0.127 mmol) in dichloromethane (1 mL), was added diethyl ether (1 mL), saturated with HCl. After stirring for 30 min at room temp., the mixture was concentrated to dryness, and dried with KOH overnight. Hydrochloride salt **33** (64 mg) was obtained in a quantitative yield as a white solid. To a mixture of the hydrochloride salt (18 mg, 0.035 mmol), (Boc)$_8$-[G3]-CO_2H (see synthesis of **24**) (166 mg, 0.070 mmol), BOP (34 mg, 0.077 mmol) and dry acetonitrile (0.53 mL), DiPEA (40 μL, 0.228 mmol) was added at room temp. After refluxing for 3 h, the reaction mixture was worked up similarly to **24**. The purification was tedious with column chromatography (MeOH/DCM, 6:94) and HPLC, owing to bad separation. A 1.5-m LH-20 column (MeOH/DCM, 1:1), followed by a normal silica column (MeOH/DCM, 6:94) afforded the pure disulfide dendrimer **34** as a white foam (71 mg, 39%). − R_f = 0.25 (MeOH/DCM, 7:93). − ^{1}H NMR ($CDCl_3$): δ = 1.26−1.78 [m, 184 H, 16 × $C(CH_3)_3$, 2 × $SCH_2(CH_2)_{10}$], 2.68 (t, 4 H, 2 × SCH_2, J = 7.3 Hz), 3.44 [m, 36 H, 2 × $NHCH_2(CH_2)_{11}$, 16 × N′′HC′′H_2], 3.68 (m, 24 H, 4 × $NHCH_2$, 8 × N′HC′H_2), 3.90 (m, 56 H, 4 × OCH_2, 8 × O′C′H_2, 16 × O′′C′′H_2), 5.30 (br. s, 16 H, 16 × N′′H), 6.22 (br. s, 2 H, 2 × Ph-C^4-H), 6.36 (br. s, 4 H, 4 × Ph-C$^{4'}$-H), 6.43 (br. s, 8 H, 8 × Ph-$^{C4''}$-H), 6.78 (br. s, 4 H, 2 × Ph-C^{2,6}-H), 6.83 (br. s, 8 H, 4 × Ph-C$^{2',6'}$-H), 6.91 (br. s, 16 H, 8 × Ph-C$^{2'',6''}$-H), 7.52 (br. s, 14 H, 2 × N$H(CH_2)_{12}$, 4 × NHC=O, 8 × N′HC=O). − ^{13}C NMR ($CDCl_3$): δ = 27.1, 29.1, 29.2, 29.4, 29.5, 29.6 [$SCH_2(CH_2)_{10}$], 28.4 [C(*C*H3)3], 39.4, 39.6, 39.9 [$NHCH_2$, N′HC′H_2, N′′HC′′H_2, $NHCH_2(CH_2)_{11}$, SCH_2], 66.4, 67.3 (OCH_2, OC′H_2, O′′C′′H_2), 79.6 [$C(CH_3)_3$], 104.6 (Ph-C$^{4,4',4''}$), 106.0 (Ph-C$^{2,6,2',6',2'',6''}$), 136.3, 137.1 (Ph-C$^{1,1',1''}$), 156.0 [C=O (Boc)], 159.6, 159.7 (Ph-C$^{3,5,3',5',3'',5''}$), 167.4, 167.6, 167.7 [$(CH_2)_{12}NHC$=O, NHC=O, N′HC=O].

Hydrochloride 37: To a cooled solution (ice bath) of Ph_3P (525 mg, 2.0 mmol) in dry THF (5.4 mL) di-*tert*-butylazodicarboxylate (DBAD) (461 mg, 2.0 mmol) and an HN_3 solution in benzene (1.4 mL, 2.0 mmol, 1.45 M) (dropwise) were added consecutively. Triethylene glycol monomethyl ether (**35**) (0.31 mL, 2.0 mmol) was added at once, and the mixture was stirred at room temp. for 1.5 h. Concentration in vacuo followed by column chromatography (EtOAc/hexanes, 2:8) afforded azide **36** as a clear colorless oil (339 mg, 90%). A mixture of azide **36** (338 mg, 1.79 mmol), chloroform (0.5 mL), Pd/C (catalytic amount) and ethanol (20 mL), under hydrogen (4 atm), was shaken overnight. The reaction mixture was filtered through Hyflo, concentrated and coevaporated with chloroform. Hydrochloride salt **37** was obtained as a light-yellow oil (303 mg, 85%). − ^{1}H NMR (CD_3OD): δ = 3.14 (br. t, 2 H, NCH_2), 3.37 (s, 3 H, OCH_3), 3.55−3.76 (m, 10 H, 5 × OCH_2), 4.94 (br. s, 2 H, NH_2). − ^{13}C NMR (CD_3OD): δ = 40.9 (NCH_2), 59.4 (OCH_3), 66.0, 71.3, 71.4, 71.6, 73.0 (OCH_2),.

(Boc)$_8$-[G3]-C(O)NH-(CH$_2$CH$_2$O)$_3$-OMe (38): To a mixture of hydrochloride salt **37** (45 mg, 0.25 mmol), (Boc)$_8$-[G3]-CO_2H (see synthesis of **24**), BOP (121 mg, 0.275 mmol) and acetonitrile (2.5 mL), was added DiPEA (141 μL, 0.81 mmol). The mixture was refluxed for 4.5 h, cooled to room temp. and concentrated. The residue was dissolved in ethyl acetate and washed with 1 M $KHSO_4$ (twice), 1 M NaOH (twice) and brine, dried (Na_2SO_4) and concentrated to dryness. Column chromatography (MeOH/DCM, 5:95), afforded dendrimer **38** as a white foam (283 mg, 45%). − R_f = 0.19 (MeOH/DCM, 7:93). − ^{1}H NMR ($CDCl_3$): δ = 1.42 [br. s, 72 H, 8 × $C(CH_3)_3$], 3.28 (s, 3 H, OCH_3), 3.42−3.68 (m, 40 H, 6 × CH_2 (glycol core), 2 × $NHCH_2$, 4 × N′HC′H_2, 8 × N′′HC′′H_2), 3.93 (m, 28 H, 2 × OCH_2, 4 × O′C′H_2, 8 × O′′C′′H_2), 5.40 (br. s, 8 H, 8 × N′′H), 6.39 (br. s, 1 H, Ph-C^4-H), 6.42 (br. s, 6 H, 2 × Ph-C$^{4''}$-H, 4 × Ph-C$^{4''}$-H), 6.82 (br. s, 2 H, Ph-C^{2,6}-H), 6.85 (br. s, 4 H, 2 × Ph-C$^{2',6'}$-H), 6.91 (2s, 4 × Ph-C$^{2'',6''}$-H), 7.28 (br. s, 7 H, NHC=O (glycol core), 2 × NHC=O, 4 × N′HC=O). − ^{13}C NMR ($CDCl_3$): δ = 27.2, 27.9 [$C(CH_3)_3$], 36.7, 39.5, 39.8 [$NHCH_2$, N′HC′H_2, N′′HC′′H_2, $NHCH_2$ (glycol core)], 58.7 (OCH_3), 66.6 (OCH_2), 67.2 (O′C′H_2, O′′C′′H_2), 69.6, 70.1, 70.3, 70.4, 71.7, 75.3, 76.0, 76.6 [OCH_2 (glycol core)], 79.5 [$C(CH_3)_3$], 104.5 (Ph-C$^{4,4',4''}$), 106.0, 106.4 (Ph-C$^{2,6,2',6',2'',6''}$), 136.2, 136.4, 136.7 (Ph-C$^{1,1',1''}$), 156.0, 156.2 [C=O (Boc)], 159.6, 159.7, 159.8 (Ph-C$^{3,5,3',5',3'',5''}$), 167.4, 167.5, 167.7, 167.8 (NHC=O (glycol core), NHC=O, N′HC=O).

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