Synthesis of small PAMAM-dendrimers with Well-defined Structural Diversity.

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ABSTRACT: PAMAM-dendrimers are the best investigated family of dendrimers, but methods for synthesizing PAMAM-dendrimers with well-defined heterogeneously substituted surfaces are lacking. In this paper, we present a general scalable, synthetic scheme that allows control over the position and number of different surface groups.

Dendrimers are synthetic macromolecules with a tree-like structure based on repetitive branching from a core. This type of growth leads to macromolecules rapidly increasing in size and molecular weight making them well-defined, covalently bound nanoparticles. Dendrimers are also an example of a class of compounds, where the potential applications always have been way ahead of the synthetic chemistry needed to make them. This is probably because they were born in industrial laboratories as potential products for commercialization[1]. There potential applications of dendrimer in a number of different areas ranging from diagnostics, nanomedicine, nanotechnology to cosmetics[2] due to their properties. The dendritic architecture provides a multivalent surface, which can be used for amplifying weak interactions between a ligand and a receptor as demonstrated with glycodendrimers[3, 4], for vaccines (MAPs)[5-8] or as artificial receptors[9-12]. The nanometer size of dendrimers allows targeting of cancer tumors using the enhanced permeation retention-effect (epr)[13-16]. Amino-terminated dendrimers form complexes with DNA or siRNA that can be used for transfection as well as siRNA-therapy[17-19] and the interior cavities can be used as molds for synthesizing well-defined nanoparticles[20-22].

Most dendrimers reported have simple structures with one type of branch cell and one type of surface group or a statistical distribution of surface groups, while well-defined dendrimers with a well-defined heterogenous surface are mainly limited to peptide dendrimers made by solid phase peptide synthesis (SPPS)[23-26] . For references

There are two different strategies that can be applied for synthesizing dendrimers with a well-defined surface chemistry; symmetry-breaking reactions on a preformed symmetrical dendrimer (which in essence is a protective group-free synthesis) or synthesis by convergent synthesis involving suitably protected building blocks. Symmetry-breaking reactions on preformed dendrimers such as amino-terminated dendrimers reflects the fact, that it is possible to achieve chemoselectivity in acylations on polyamines (see for example reference [27-29] and references therein. However due to the small differences in reactivity between the unmodified dendrimer and the partially acylated products mixtures are formed that require chromatographic separation of the products putting serious limitations to this approach[30].

In this paper we present a general synthetic methodology that allows synthesis of small generation, but well-defined structurally diverse PAMAM-dendrimers. Access to precisely functionalized dendrimers will make systematic studies of structure-activity relations between dendrimers and biological systems possible.

The only previous examples of well unsymmetrical PAMAM-dendrimers are Janus-dendrimers[31, 32] and partially acylated G0 PAMAMs[30].

The ideal synthesis of structurally diverse dendrimers should be robust and simple with respect to purification of the intermediates and final products and it should be scalable allowing preparation of multigram amounts if necessary.

A convergent synthesis of PAMAM-dendrimers based on the coupling of structurally diverse dendrons to a core requires a core having up to four orthogonally addressable groups (figure 1).

The present methodology is based on the previously reported convergent synthesis of all-symmetrical PAMAM-dendrimers.10 The methodology allows not only synthesis of PAMAM-dendrimers with a number of different surface groups but also analogs to the PAMAM-dendrimers built from different types of AB2-units (figure 2 & 3).

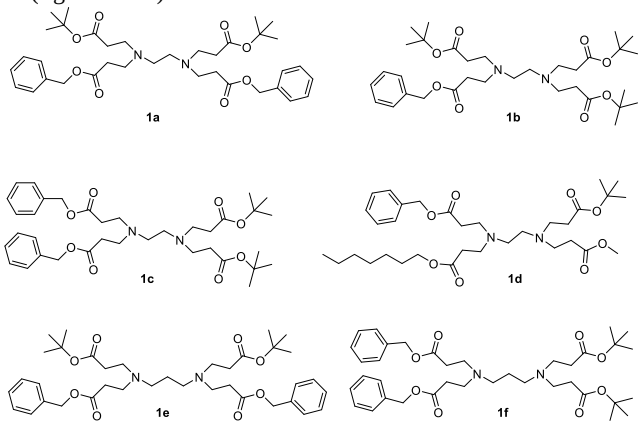


Figure 1: Cores synthesized. **1a** - **1d** are based on 1, 2-ethanediamine and **1e** and **1f** are based on 1,3-propanediamine.

The t-butyl esters are cleaved under acidic conditions, the benzyl esters by catalytic hydrogenation, the heptyl ester as an example of adding lipophilicity and potentially enzymatically cleavable and the methyl ester can be cleaved with nucleophiles or displaced by aminolysis. The cores were synthesized as shown in Schemes 1 - 4.

The ABAB-core **2a** was synthesized by a double Michael-addition between N,N'-dibenzyl-1,2-ethanediamine[33] and t-butyl acrylate to the N,N'-dibenzylamine **3a** in quantitative yield. Catalytic hydrogenation using Pearlman's catalyst removed the benzyl-groups in quantitative yield giving compound **4a**, which gave the ABAB-core 4a in 90% yield after a double Michael-addition with benzyl acrylate[34]. The AB3-core **2c** was synthesized in a similar manner starting from N-benzyl-1,2-ethanediamine[35] instead.

The A2B2- and ABCD-cores were synthesized from mono Z-protected 1,3-propanediamine and 1,2-ethanediamine respectively.11 Double Michael-addition with t-butyl acrylate gives the AB2-dendron **2b** in 95% yield, which after deprotection and a second Michael-addition with benzyl acrylate gives the A2B2-core **4b** in 99% yield.

We found that the Michael-additions between primary amines and acrylates proceed in a stepwise manner with very good selectivity for mono-addition. Furthermore, the mono- and the bis-adducts are very easily to separate by column chromatography. This was utilized in the synthesis of the ABCD-core **4d** as shown in Scheme 4.

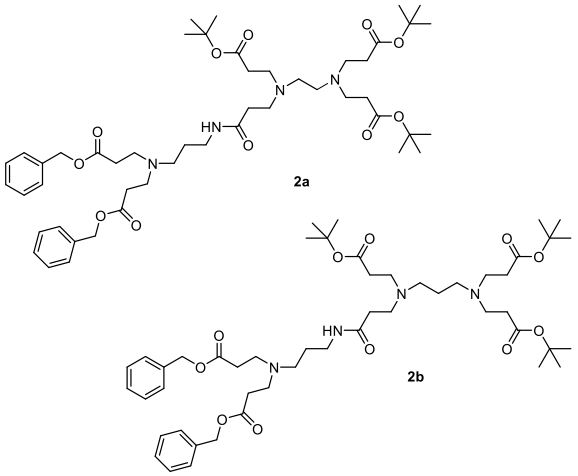


Figure 3: Unsymmetrical dendrimers with 5 surface groups.

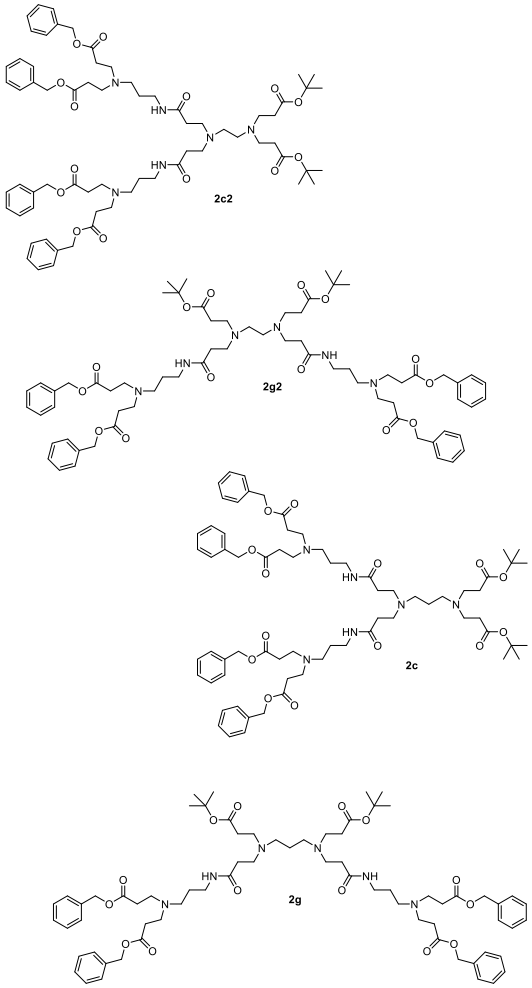


Figure 4: Unsymmetrical dendrimers with 6 surface groups.

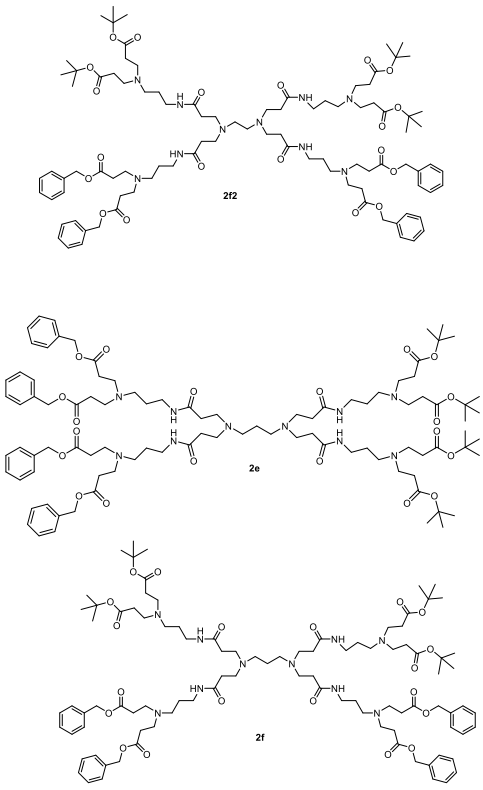


Figure 5: Unsymmetrical dendrimers with 8 surface groups and C2-symmetry.

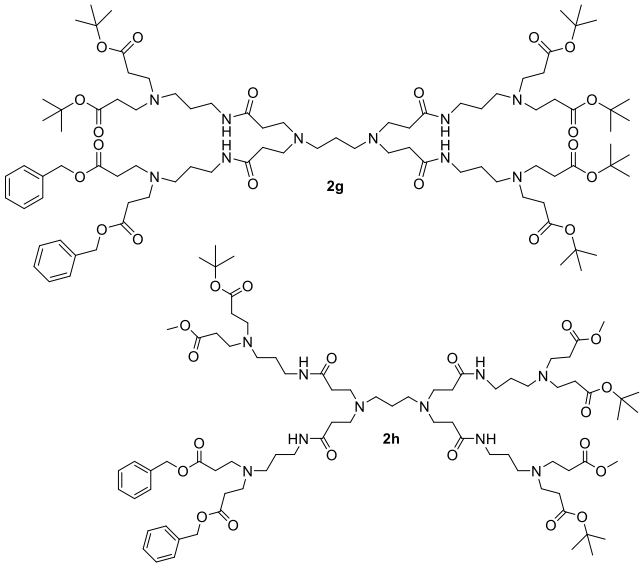


Figure 6: Unsymmetrical dendrimers with 8 surface groups.

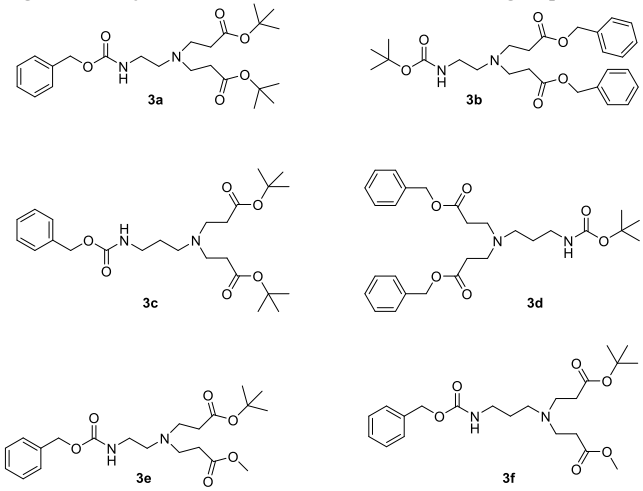
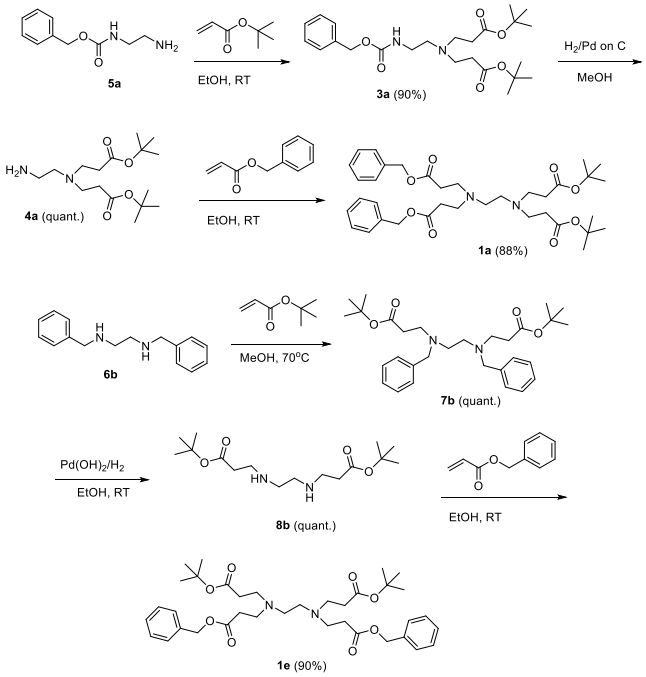
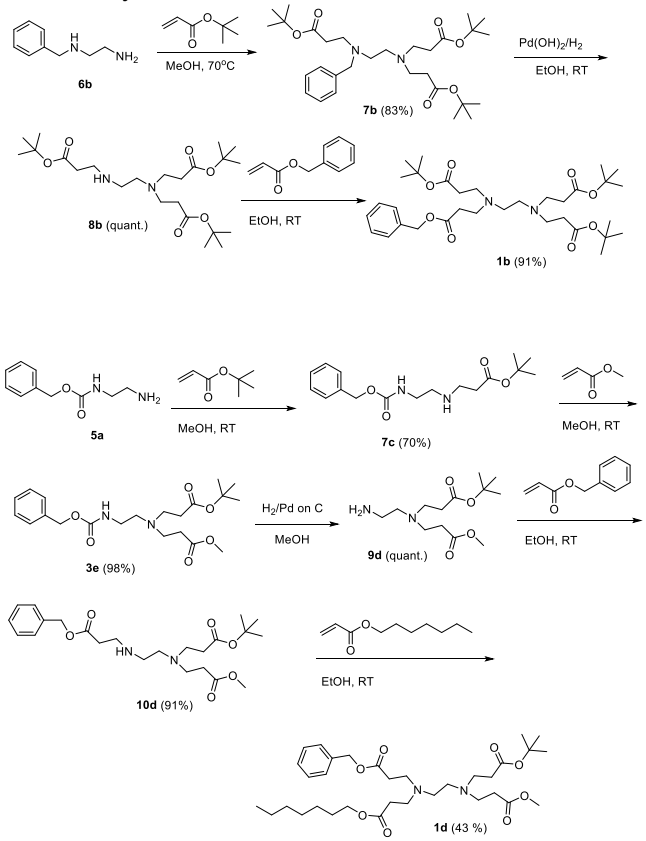


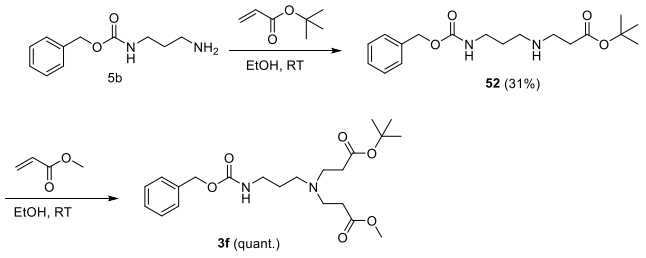
Figure 7: The protected dendron building blocks.



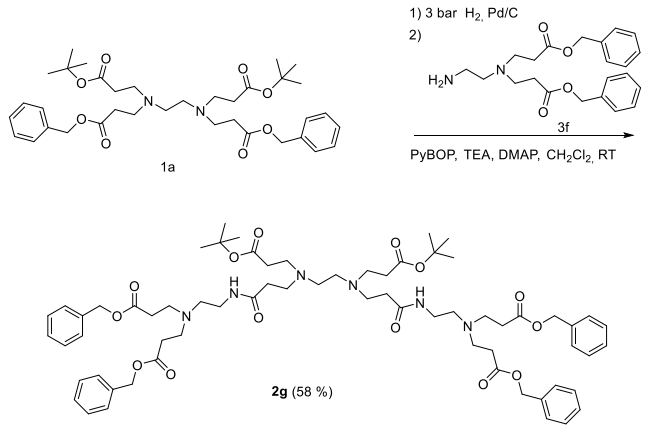
Scheme 1: Synthesis of the cores **1a** and **1e**.



Scheme 2: Synthesis of the cores **1b** and **1d**.



Scheme 4: Synthesis of dendron **3f**



Scheme 3: The principles of the synthetic scheme for dendrimer synthesis illustrated by the synthesis of compound **2g**.

Conclusion

We have developed a methodology for the synthesis of PAMAM-dendrimers and dendrons that allows synthesis of PAMAM-dendrimers carrying different wedges. This is expected to have huge impact on areas such as the biomedical applications of dendrimers, where the studies reported up to now either have been carried out with all-symmetrically functionalized compounds or with dendrimers that have been modified in a purely statistical manner. Access to precisely functionalized dendrimers opens completely new areas ranging from programmable self-assembly through systematic studies of structure-activity relations between PAMAM-dendrimers and biological systems to truly well-defined targeted drug delivery systems based on dendrimers.

Experimental

Benzyl 3,3'-(2-(bis(3-tert-butoxy-3-oxopropyl)amino)ethylazanediyl)dipropanoate (1a)

A solution of **4f** (4.96 g, 15.67 mmol) and Benzyl Acrylate[34] (14.29 g, 88.09 mmol) in EtOH (abs., 50 mL) was stirred at RT for three days. 1,2-Ethanediamine (2.20 mL, 1.98 g, 32.94 mmol) was added and the reaction mixture stirred for additional two hours. This converts the excess of Benzyl Acrylate into mono- and bis-Michael adducts of 1,2-Ethanediamine that are retained on the column during purification. The solvent was removed *in vacuo* and the product purified on a dry column[36] (EtOAc/heptane, eluting 10% from heptane) to give the product **1a** as a light yellow oil. The yield for this reaction was 8.87 g (88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.27 (m, 10H), 5.10 (s, 4H), 2.79 (t, J = 7.2, 4H), 2.69 (t, J = 7.3, 4H), 2.47 (dt, J = 7.2, 8H), 2.31 (t, J = 7.3, 4H), 1.43 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.54, 172.15, 136.20, 128.74, 128.49, 128.40, 80.45, 66.42, 52.68, 52.38, 50.11, 49.99, 34.08, 33.06, 28.34.

MS (FAB) m/z (int. %): 641.7 $[MH]^+$ (18), 354.3 (66), 286.3 (57), 174.1 (99), 91.1 (100).

Anal. Calcd for $C_{36}H_{52}N_2O_8$: C, 67.48; H, 8.18; N, 4.37. Found: C, 67.69; H, 8.24; N, 4.25.

t-Butyl 3,3'-(2-((3-(benzyloxy)-3-oxopropyl)(3-tert-butoxy-3-oxopropyl)amino)-ethylazanediyl)dipropanoate (1b)

A solution of compound **8b** (3.61 g, 8.12 mmol) and benzyl acrylate (2.68 g, 16.52 mmol) in EtOH (abs., 15 mL) was stirred at RT for two days.1,2-Ethanediamine (EDA) (0.50 g, 8.40 mmol) was added and the mixture stirred for additional two hours followed by concentration *in vacuo* and purification by dry column chromatography[36] (EtOAc/heptane, eluting 10% from heptane) to give 4.45 g (91%) of the product as a yellowish to colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 - 7.11 (m, 5H), 5.11 (s, 2H), 2.74 (dt, J = 7.3, 16.9, 2H), 2.59 - 2.38 (m, 2H), 2.31 (t, J = 7.3, 2H), 1.43 (s, 27H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.61, 172.18, 172.13, 136.19, 128.75, 128.50, 128.41, 80.47, 66.43, 52.61, 52.46, 50.10, 49.95, 34.08, 34.03, 33.07, 28.35. MS (FAB) m/z (int. %): 607.8 $[MH]^+$ (36), 491.4 (13), 320.3 (58), 286.4 (90), 174.1 (100), 91.3 (41).

Anal. Calcd for $C_{33}H_{54}N_2O_8$: C, 65.32; H, 8.97; N, 4.62. Found: C, 65.48; H, 9.05; N, 4.52.

Benzyl 3,3'-(2-(bis(3-tert-butoxy-3-oxopropyl)amino)ethylazanediyl)dipropanoate (1c)

A solution of compound **3a** (4.96 g, 15.67 mmol) and benzyl acrylate (14.29 g, 88.09 mmol) in EtOH (abs., 50 mL) was stirred at RT for three days. 1,2-Ethanediamine (2.20 mL, 1.98 g, 32.94 mmol) was added and the mixture stirred for additional two hours. The solvent was removed *in vacuo* and the product purified by dry column chromatography[36] (EtOAc/heptane, eluting 10% from heptane) to give the product **1c** as a light yellow oil. The yield for this reaction was 8.87 g (88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.27 (m, 10H), 5.10 (s, 4H), 2.79 (t, *J* = 7.2, 4H), 2.69 (t, *J* = 7.3, 4H), 2.47 (dt, *J* = 7.2, 8H), 2.31 (t, *J* = 7.3, 4H), 1.43 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.54, 172.15, 136.20, 128.74, 128.49, 128.40, 80.45, 66.42, 52.68, 52.38, 50.11, 49.99, 34.08, 33.06, 28.34.

MS (FAB) *m/z* (int. %): 641.7 $[MH]^+$ (18), 354.3 (66), 286.3 (57), 174.1 (99), 91.1 (100).

Anal. Calcd for $C_{36}H_{52}N_2O_8$: C, 67.48; H, 8.18; N, 4.37. Found: C, 67.69; H, 8.24; N, 4.25.

Benzyl 3-((2-((3-tert-butoxy-3-oxopropyl)(3-methoxy-3-oxopropyl)amino)ethyl)(3-(heptyloxy)-3-oxopropyl)amino)propanoate (1d)

A solution of compound **10d** (3.55 g; 7.42 mmol) and heptyl acrylate (2.55 g; 15 mmol) in EtOH (abs., 50 mL) was stirred at RT for seven days. The volatile components were removed under reduced pressure and the product purified on a dry column (eluting from heptane with EtOAc) to give 4.5 g (43%) of **1d** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 5H), 5.11 (s, 2H), 4.04 (t, J = 6.8, 2H), 3.65 (s, 3H), 2.75 – 2.66 (m, 8H), 2.54 – 2.36 (m, 10H), 2.31 (t, J = 7.2, 2H), 1.66 – 1.56 (m, 2H), 1.43 (s, 9H), 1.39 – 1.22 (m, 8H), 0.93 – 0.79 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.23, 172.85, 172.60, 172.12, 136.16, 128.75, 128.50, 128.43, 80.50, 66.45, 64.83, 52.55, 52.43, 51.77, 50.15, 49.97, 49.92, 34.01, 33.02, 32.95, 32.84, 31.95, 29.17, 28.84, 28.33, 26.10, 22.82, 14.32. MS (FAB) m/z (int. %): 607.3 $[MH]^+$ (28), 605.2 (26), 362.2 (100), 188.1 (67), 91.0 (44).

Anal. calcd. for $C_{33}H_{54}N_2O_8$: C, 65.32; H, 8.97; N, 4.62. Found: C, 65.30; H, 8.53; N, 4.41.

Benzyl 3,3'-(2,2,16,16-tetramethyl-4,14-dioxo-3,15-dioxa-7,11-diazaheptadecane-7,11-diyl)dipropanoate (1e)

A solution of (**44**) (5.04 g, 15.27 mmol) and benzyl acrylate[34] (11.40 g, 68.97 mmol) in EtOH (abs., 60 mL) was stirred for six days, added EDA (2.00 mL, 1.50 g, 24.99 mmol) and stirred for additional 3 hours. The volatile compounds were removed under reduced pressure and the product purified on a dry column (eluting from heptane, 10% EtOAc) to give compound **1e** (9.81 g, 98%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.25 (m, 10H), 5.10 (s, 4H), 2.82 – 2.63 (m, 8H), 2.48 (t, J = 7.2, 4H), 2.43 – 2.24

(m, 8H), 1.53 (p, J = 7.5, 2H), 1.42 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.62, 172.13, 136.15, 128.66, 128.38, 128.31, 80.37, 66.32, 51.78, 49.44, 49.29, 33.76, 32.74, 28.26, 25.10. MS (FAB) m/z (int. %): $[MH]^+$ 655.4 (100), 347.1 (72), 264.1 (79), 91.0 (89).

Anal. Calcd for $C_{37}H_{54}N_2O_8$: C, 67.86; H, 8.31; N, 4.28. Found: C, 67.87; H, 8.55; N, 4.25.

Benzyl 3,3'-(3-(bis(3-tert-butoxy-3-oxopropyl)amino)propylazanediyl)dipropanoate (1f)

A solution of compound **4f** (8.79 g, 27.14 mmol) and benzyl acrylate (14.24 g, 87.86 mmol) in EtOH (abs., 100 mL) was stirred for four days and treated with EDA (2.00 mL, 1.50 g, 24.99 mmol) and stirred for additional two hours. The volatile components were removed in vacuo and the product purified on a dry column (eluting from heptane, 10% EtOAc) to yield 17.26 g (99 %) of the product as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.19 (m, 10H), 5.03 (s, 4H), 2.66 (dt, J = 7.3, 8H), 2.47 – 2.12 (m, 12H), 1.56 – 1.41 (m, 2H), 1.35 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.62, 172.24, 136.00, 128.67, 128.43, 128.34, 80.37, 66.35, 51.72, 51.60, 49.24, 49.16, 33.61, 32.58, 28.21, 24.91. MS (FAB) m/z (int. %): 655.3 $[MH]^+$ (26), 354.0 (67), 286.1 (64), 206.0 (31), 174.0 (100), 91.0 (74).

Anal. Calcd for $C_{37}H_{54}N_2O_8$: C, 67.86; H, 8.31; N, 4.28. Found: C, 67.39; H, 8.59; N, 4.16.

tert-Butyl 3,3'-(3-((3-(benzyloxy)-3-oxopropyl)(3-tert-butoxy-3-oxopropyl)amino)propylazanediyl)dipropanoate (1g)

A solution of (40) (6.27 g, 0.0137 mol) and benzyl acrylate[34] (4.25 g, 0.0262 mol) in EtOH (abs., 45 ml) was stirred for two days, added EDA (1.00 mL, 0.75 g, 12,50 mmol) and stirred for additional three hours. The volatile components were removed under reduced pressure and the product purified on a dry coloumn (eluting from heptane, 10% EtOAc) to give compound **1g** as a colorless oil (Yield: 8.45 g (quant.). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 5H), 5.11 (s, 2H), 2.77 (t, J = 7.3, 2H), 2.74 – 2.67 (m, 6H), 2.50 (t, J = 7.3, 2H), 2.43 – 2.30 (m, 10H), 1.59 – 1.46 (m, 2H), 1.46 (s, 27 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.67, 172.24, 172.17, 136.04, 128.67, 128.42, 128.34, 80.37, 66.34, 51.73, 51.68, 49.29, 49.17, 33.64, 33.61, 32.61, 28.23, 25.06. MS (FAB) m/z (int. %): 621.4 $[MH]^+$ (67), 453.2 (18), 264.1 (64), 174.0 (100), 91.1 (58).

Anal. Calcd for $C_{34}H_{56}N_2O_8$: C, 65.78; H, 9.09; N, 4.51. Found: C, 65.70; H, 9.25; N, 4.24.

Synthesis of the dendrimers:

Typically, there were used 1.25 equivalents of dendron per carboxylic acid moiety. The deprotection reactions were confirmed using ^{1}H-NMR and no further purification was done prior to coupling to the core unit.

The BOC groups and t-butyl esters were removed by dissolving the compound in CH_2Cl_2 (10 mL/g) followed by addition of Trifluoroacetic acid (5 mL/g). This was stirred for 2 – 3 hours followed by removal of the volatile compounds. The product was dried first in vacuo and then using a stream of N_2.

The Z groups and benzyl esters were removed using catalytic hydrogenation at 4 bar pressure (H_2) using Pd/C (10% on C, 0.10 g/g) and EtOH (96% or abs., about 15 mL/g) as solvent in a Parr shaker. The typical reaction time was about 15 h. The reaction mixture was filtered through a plug of celite on a glass filter funnel with suction and concentrated in vacuo. If the product was contaminated with residual Pd/C it was dissolved in CH_2Cl_2 (about 15 mL/g), filtered again using gravity filtration and concentrated in vacuo.

The PyBOP couplings were done by dissolving each of the deprotected compounds (dendron and core) in CH_2Cl_2 (10 mL/g) followed by adding Triethylamine to basic reaction on pH paper. The PyBOP (1.25 eq/acid moiety) was added the core followed by addition of the dendron solution. The resulting solution was added 4-N,N-Dimethylaminopyridine (10 mol%) and the reaction stirred for seven days. The volatile components were removed *in vacuo* and the product taken up in EtOAc (15 mL/g) and added water followed by vigorous stirring for several hours. The layers were separated and the organic phase washed with K_2CO_3 (aq) (10 %, 4 × 30 mL/g), $NaHCO_3$ (aq) (10%, 5 × 30 mL/g), water (5 × 30 mL/g) and finally brine (2 × 30 mL/g). The organic phase was dried (Na_2SO_4), filtered and the product concentrated in vacuo to give the product. The visual appearance of the product was light brown clear thick syrup.

If the product was contaminated with amino-terminated Dendron (checked with 1 % Ninhydrine in EtOH), it was dissolved in CH_2Cl_2 and treated with polystyrene carboxylic acid chloride (take a carboxylic acid ion exchange resin, dry and convert into the acid chloride by treatment with thionyl chloride) followed by filtration and evaporation.

Compound 2c ($Bn_2Bu^t_2$-C2-Bu^t)

This compound was synthesized as described for the general procedure from the core **1b** and the dendron **3a**. Yield 58%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 10H), 7.09 (t, J = 5.2, 1H), 5.10 (s, 4H), 3.17 (td, J = 3.5, 6.6, 2H), 2.90 – 2.64 (m, 12H), 2.62 – 2.23 (m, 18H), 1.43 and 1.42 (s,s, 27H). 13C NMR (126 MHz, $CDCl_3$) δ 172.48, 172.33, 172.05, 135.98, 128.71, 128.47, 128.42, 80.43, 66.49, 53.13, 52.07, 52.02, 50.54, 49.96, 49.78, 49.40, 46.45, 37.34, 34.04, 33.93, 33.52, 32.88, 28.26, 26.60. MS (FAB) m/z (int. %): 884.9 $[MH]^+$ (33).

Compound 2c2 (Bn_2Bu^t-C2-Bn_2Bu^t)

This compound was synthesized as described for the general procedure from core **1c** and dendron **3b**. Yield: 47%.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.17 (m, 20H), 6.98 (t, J = 5.3, 2H), 5.02 (s, 8H), 3.18 (q, J = 5.9, 4H), 2.78 – 2.57 (m, 16H), 2.52 – 2.33 (m, 16H), 2.33 – 2.14 (m, 8H), 1.33 (s, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.49, 172.30, 172.03, 135.97, 128.70, 128.45, 128.41, 80.47, 66.49, 53.09, 51.73, 50.46, 49.82, 49.40, 37.37, 34.07, 33.55, 32.90, 28.25. MS (FAB) m/z (int. %): 1193.9 $[MH]^+$ (56), 755.4 (23).

Compound 2g2 (Bn_2Bu^t-C2-Bn_2Bu^t)

This compound was synthesized as described for the general procedure from the core **1a** and the dendron **3b**. Yield: 47 %.

This compound was synthesized as described for the general procedure. Yield 47%.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.17 (m, 20H), 6.98 (t, J = 5.3, 2H), 5.02 (s, 8H), 3.18 (q, J = 5.9, 4H), 2.78 – 2.57 (m, 16H), 2.52 – 2.33 (m, 16H), 2.33 – 2.14 (m, 8H), 1.33 (s, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.49, 172.30, 172.03, 135.97, 128.70, 128.45, 128.41, 80.47, 66.49, 53.09, 51.73, 50.46, 49.82, 49.40, 37.37, 34.07, 33.55, 32.90, 28.25.

MS (FAB) m/z (int. %): 1193.9 $[MH]^+$ (56), 755.4 (23).

Compound 2c (Bn_4-C3-Bu^t_2)

This compound was synthesized as described for the general procedure from the core **1c** and the dendron **3a**. Yield: 66%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 20H), 5.08 (s, 8H), 3.20 – 3.10 (m, 4H), 2.81 – 2.64 (m, 16H), 2.53 – 2.26 (m, 24H), 1.71 – 1.54 (m, 6H), 1.43 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.59, 172.39, 172.27, 135.99, 128.69, 128.44, 128.39,

80.47, 66.44, 51.97, 51.30, 51.00, 49.98, 49.29, 37.29, 33.81, 33.77, 32.73, 28.26, 26.94, 24.52.

MS (FAB) m/z (int. %): [MH]+ 1235.55 (7).

Compound 2e (Bn_4-C3-Bu^t_4)

This compound was synthesized as described for the general procedure from core **1c** and dendron **3a**. Yield: 51%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.22 (m, 20H), 5.09 (s, 8H), 3.29 – 3.07 (m, 8H), 2.81 – 2.61 (m, 24H), 2.55 – 2.17 (m, 36H), 1.76 – 1.49 (m, 10H), 1.43 (s, 36H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.63, 172.35, 172.12, 135.99, 128.68, 128.42, 128.38, 80.59, 66.43, 52.48, 51.06, 50.68, 50.14, 50.02, 49.43, 49.27, 46.43, 46.40, 37.33, 34.01, 33.78, 33.57, 32.71, 28.24, 26.88, 26.59, 26.52, 25.77.

MS (FAB) m/z (int. %): 1748.52 [MH]+ (3).

Compound 2g (Bn_2Bu^t-C3-Bn_2Bu^t)

This compound was synthesized as described for the general procedure from core **1e** and dendron **4a**. The yield was 78%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 20H), 7.19 (t, J = 5.6, 2H), 5.09 (s, 8H), 3.22 – 3.10 (m, 4H), 2.80 – 2.63 (m, 16H), 2.51 – 2.22 (m, 24H), 1.66 – 1.50 (m, 6H), 1.42 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.58, 172.38, 172.09, 136.01, 128.70, 128.46, 128.40, 80.52, 66.45, 51.52, 50.98, 50.11, 49.31, 37.30, 34.00, 33.34, 32.74, 28.26, 26.92, 24.19.

MS (FAB) m/z (int. %): $[MH]^+$ 1235.8 (9).

Compound 2f (($Bn_2Bu^t_2$-C3-$Bn_2Bu^t_2$)

This compound was synthesized as described for the general procedure from core **1e**, dendron **3c** and dendron **3a**. Yield: 61%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 20H), 5.09 (s, 8H), 3.24 – 3.09 (m, 8H), 2.80 – 2.61 (m, 24H), 2.52 – 2.25 (m, 36H), 1.73 – 1.50 (m, 10H), 1.46 (s, 36H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.59, 172.31, 172.11, 136.00, 128.69, 128.43, 128.39, 80.56, 66.43, 52.49, 51.63, 51.06, 50.72, 50.03, 49.43, 49.28, 37.32, 34.03, 33.78, 33.57, 32.72, 28.25, 26.93, 25.77.

MS (FAB) m/z (int. %): $[MH]^+$ 1748.00 (2).

Compound 2h (Bn_2Bu^tMe-C3-Bu^tMeBu^{t}Me)

This compound was synthesized as described for the general procedure from dendrimer **2b** and dendron **3f**. Yield: 42 %

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 10H), 5.02 (s, 4H), 3.63 (s, 9H), 3.25 – 3.12 (m, 8H), 2.80 – 2.64 (m, 24H), 2.50 – 2.27 (m, 36H), 1.70 – 1.55 (m, 10H), 1.44 (s, 27H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.30, 172.65, 172.61, 172.25, 136.00, 129.10, 128.71, 128.44, 128.40, 80.61, 66.46, 51.77, 51.67, 51.03, 50.06, 49.49, 49.28, 37.42, 34.08, 33.82, 32.72, 32.52, 28.24, 26.93. MS (FAB) m/z (int. %): $[MH]^+$ 1554.1 (18).

Compound 2b (Bn_2Bu^t-C3-Bu^t_2)

This compound was synthesized as described for the general procedure from core **1b** and dendron **3b**. Yield was 71%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 10H), 5.09 (s, 4H), 3.17 (q, J = 6.3, 2H), 2.80 - 2.66 (m, 12H), 2.52 – 2.27 (m, 18H), 1.65 – 1.52 (m, 4H), 1.43 (s,s, 27H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.55, 172.48, 172.16, 136.03, 128.69, 128.46, 128.38, 80.40, 66.43, 51.89, 51.41, 51.05, 50.24, 49.38, 49.32, 49.17, 37.24, 33.86, 33.78, 33.23, 32.76, 28.27, 27.04, 24.67.

MS (FAB) m/z (int. %): $[MH]^+$ 911.6 (100), 849.4 (36).

Compound 2g ($Bn_2Bu^t_2$-C3-Bu^t_4)

This compound was synthesized as described for the general procedure from dendrimer **2b** and dendron **3c**. Yield: 58%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 10H), 5.07 (s, 4H), 3.25 – 3.11 (m, 8H), 2.80 – 2.65 (m, 24H), 2.53 – 2.25 (m, 36H), 1.69 – 1.57 (m, 10H), 1.45 (s, 54H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.61, 172.33, 172.12, 136.02, 128.70, 128.44, 128.39, 80.57, 66.44, 52.49, 50.75, 50.04, 49.44, 49.29, 46.41, 37.33, 34.03, 33.80, 33.58, 32.74, 28.26, 26.97, 26.60, 26.54, 25.78.

MS(FAB) m/z (int. %): [MH]+ 1680.25 (7).

Synthesis of the protected dendrons:

Starting materials tert-butyl (2-aminoethyl)carbamate, tert-butyl (3-aminopropyl)carbamate, benzyl (2-aminoethyl)carbamate and benzyl (3-aminopropyl)carbamate were synthesized as previously described[28, 29].

Di-tert-butyl 3,3'-((2-(((benzyloxy)carbonyl)amino) ethyl) azanediyl) dipropionate (3a)[37]

A solution of Benzyl (2-aminoethyl)carbamate (13.57 g, 70.00 mmol) and tert-Butyl acrylate (45.67 g, 356.31 mmol) in MeOH (100 mL) was stirred for six days followed by removal of the volatile component in vacuo. The product was purified on a dry column (eluting from heptane, with EtOAc, 10% fractions). The product was isolated as light yellow oil. Yield: 28.34 g (90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 5.48 (s, 1H), 5.09 (s, 2H), 3.33 – 3.17 (m, 2H), 2.71 (t, J = 6.9, 4H), 2.59 – 2.46 (m, 2H), 2.33 (t, J = 6.9, 4H), 1.42 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.13, 156.65, 136.98, 128.50, 128.08, 127.99, 80.72, 66.52, 53.09, 49.19, 38.69, 33.77, 28.22. MS (FAB) m/z (int. %): 451.2 $[MH]^+$ (5), 339.0 (15), 286.1 (13), 174.0 (32), 57.0 (100).

Dibenzyl 3,3'-((2-((tert-butoxycarbonyl)amino)ethyl)azanediyl)dipropionate (3b)[38]

A solution of Benzyl (2-aminoethyl)carbamate (11.36 g, 70.91 mmol) and benzyl acrylate (50.14 g, 309.15 mmol) in EtOH (100 mL) was stirred for five days. The mixture was added EDA (3 mL) and the reaction was stirred for additional three hours. The solvent was removed in vacuo and the product purified on a dry column (eluting from heptane with EtOAc, 10%) to give 30.45 g (89%) of compound **3b** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 10H), 5.11 and 5.05 (s, bs, 5H), 3.15 (bs, 2H), 2.76 (t, 4H), 2.47 (dt, 6H), 1.43 (s, 9H). MS (FAB) m/z (int. %): 485.1 $[MH]^+$ (36), 354.2 (100), 279.1 (10), 91.2 (77). Data are consistent with literature except for the signal in the ^{1}H-NMR at 1.43 (tert-butyl), which is not reported in the patent application.

Di-tert-butyl 3,3'-((3-(((benzyloxy)carbonyl)amino)propyl) azanediyl)dipropionate (3c)

A solution of (34) (32.53 g, 156.20 mmol) and tert-butyl acrylate (80.73 g, 629.87 mmol) in MeOH (150 mL) was stirred for six days and added EDA (15.00 mL, 11.27 g, 187.44 mmol) and stirred for additional 3 hours. The volatile components were removed in vacuo and the product purified on a dry column (eluting from heptane with EtOAc, 10%) to give 69.11 g (95%) of the product as a slightly yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.19 (m, 5H), 5.55 (s, 1H), 5.03 (s, 2H), 3.15 (q, J = 6.2, 2H), 2.62 (t, J = 7.0, 4H), 2.38 (t, J = 6.2, 2H), 2.27 (t, J = 7.0, 4H), 1.66 – 1.50 (m, 2H), 1.36 (s, 18H). ^{13}C NMR (75 MHz, CDCl3) δ 172.20, 156.68, 137.09, 128.57, 128.11, 128.03, 80.65,

66.49, 51.00, 49.55, 39.37, 33.79, 28.24, 26.85. MS (FAB) m/z (int. %): 465.1 $[MH]^+$ (93), 286.2 (100), 174.0 (87), 91.2 (82). Anal. Calcd for $C_{25}H_{40}N_2O_6$: C, 64.63; H, 8.68; N, 6.03. Found: C, 65.08; H, 8.78; N, 5.95.

Dibenzyl 3,3'-((3-((tert-butoxycarbonyl)amino)propyl) azanediyl)dipropionate (3d)

A solution of t-Butyl (3-aminopropyl)carbamate (14.03 g, 80.52 mmol) and benzyl acrylate[34] (33.42 g, 206.05 mmol) in EtOH (abs., 100 mL) was stirred for five days and the solvent removed in vacuo. The product was purified on a dry column (eluting from heptane with EtOAc, 10%) to give compound **3d** (38.13 g (95%)) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.16 (m, 10H), 5.04 (s, 4H), 3.14 – 2.88 (m, *2H), 2*.67 (t, J = 7.0, 4H), 2.50 – 2.27 (m, 6H), 1.62 – 1.46 (m, 4H), 1.35 (s, 9H). MS (FAB) m/z (int. %): 499.2 $[MH]^+$ (49), 354.1 (73), 292.1 (36), 91.1 (100).

t-Butyl 3-((2-(((benzyloxy)carbonyl)amino)ethyl)(3-methoxy-3-oxopropyl)amino)propanoate (3e)

A solution of compound **7c** (2.52 g, 7.82 mmol) and methyl acrylate (2.29 g, 26.58 mmol) in MeOH (20 mL) was stirred for two days and the volatile components removed under reduced pressure. The product was purified on a dry column (eluting from heptane, EtOAc, 10% increase) to compound **3e** as a light yellow oil. Yield: 2.89 g (91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 - 7.28 (m, 5H), 5.47 (br s, 1H), 5.10 (s, 2H), 3.62 (s, 3H), 3.27 (m, 2H), 2.72 (dt, J = 6.8, 4H), 2.58 – 2.47 (m, 2H), 2.42 (t, J = 6.8, 2H), 2.32 (t, J = 6.7, 2H), 1.41 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.13, 172.04, 156.63, 137.00, 128.51, 128.07, 128.00, 80.72, 66.52, 53.18, 51.72, 49.24, 49.20, 38.69, 33.80, 32.65, 28.18. MS (FAB) m/z (int. %): 409.0 $[MH]^+$ (18), 352.9 (32), 243.9 (47), 188.0 (100), 91.0 (98).

t-Butyl 3-((3-(((benzyloxy)carbonyl)amino)propyl)(3-methoxy-3-oxopropyl)amino)propanoate (3f)

A solution of (**52**) (3.40 g, 10.11 mmol) and methyl acrylate (2.02 g, 23.46 mmol) in EtOH (abs., 5 mL) was stirred at RT for 28 hours. The volatile components were removed *in vacuo* and the product purified on a dry column (eluting from heptane, 10% EtOAc) and dried *in vacuo* to give 4.26 g (quant.) of the product as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H), 5.57 (s, 1H), 5.09 (s, 2H), 3.64 (s, 3H), 3.30 – 3.11 (m, 2H), 2.70 (dt, J = 7.0, 4H), 2.49 – 2.41 (m, 4H), 2.33 (t, J = 7.0, 2H), 1.70 – 1.59 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.22, 172.12, 156.64, 137.06, 128.57, 128.14, 128.05, 80.67, 66.49, 51.77, 51.26, 49.56, 49.42, 39.44, 33.81, 32.54, 28.22, 26.79.
MS (FAB) m/z (int. %): $[MH]^+$ 423.3 (100), 367.2 (49), 244.2 (47), 188.1 (48), 91.3 (59).
Anal. Calcd for $C_{22}H_{34}N_2O_6$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.30; H, 7.84; N, 6.36.

t-Butyl 3-((2-(((benzyloxy)carbonyl)amino)ethyl)amino) propanoate (7c)

A solution of Benzyl (2-aminoethyl)carbamate (3.00 g, 15.45 mmol) and tert-butyl acrylate (1.98 g, 15.45 mmol) in MeOH (20 mL) was stirred overnight, the volatile components removed under reduced pressure and the product purified on a dry column (eluting from heptane with EtOAc, 10%) to give compound **7c** as an oil. Yield: 3.50 g (70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 5H), 5.26 (bs, 1H), 5.10 (s, 2H), 3.28 (q, J = 6.0, 2H), 2.82 and 2.74 (dt, J = 6.0, 6.3, 4H), 2.39 (t, J = 6.3, 2H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.27, 156.61, 136.78, 128.60, 128.20, 128.15, 80.74, 66.70, 48.65, 44.81, 40.67, 36.01, 28.24. MS (FAB) m/z (int. %): 323.1 $[MH]^+$ (62), 267.1 (100), 91.0 (64). Anal. Calcd. for $C_{17}H_{26}N_2O_4$: C, 63.33; H, 8.13; N, 8.69. Found: C, 63.02; H, 8.27; N, 8.69.

t-Butyl 3-(3-(benzyloxycarbonylamino)propylamino)propanoate (52)

A solution of benzyl (3-aminopropyl)carbamate (7.57 g, mmol) and *tert*-butyl acrylate (4.66 g, mmol) in EtOH (abs, 100 mL) was stirred overnight and the solvent was removed *in vacuo*. The product was purified on a dry column (eluting from heptane, 10% EtOAc) to give 3.82 g (31%) of the product as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 5H), 7.31 – 7.28 (m, 1H), 5.09 (s, 2H), 3.35 – 3.20 (m, 2H), 2.81 (t, J = 6.4, 2H), 2.69 (t, J = 6.5, 2H), 2.40 (t, J = 6.5, 2H), 1.72 – 1.59 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.33, 156.61, 136.94, 128.63, 128.23, 128.15, 80.70, 66.62, 47.83, 45.35, 40.16, 35.94, 29.71, 28.26. MS (FAB) m/z (int. %): $[MH]^+$ 337.1 (100), 281.1 (44), 91.2 (27).
Anal. Calcd for $C_{18}H_{28}N_2O_4$: C, 64.26; H, 8.39; N, 8.33. Found: C, 64.27; H, 8.32; N, 8.18.

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