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Synthesis and properties of chiral internally branched PAMAM-dendrimers

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ABSTRACT

Improved synthetic methodology for the synthesis of internally branched chiral poly(amidoamine) (PAMAM) dendrons and dendrimers has been developed and the compounds have been characterized by NMR spectroscopy, IR spectroscopy, and optical rotation measurements. The dendrons and dendrimers show increased degree of internal hydrogen bonding upon increasing generation and the presence of different types of amide-protons in the compounds is indicative of the existence of a tertiary structure in these PAMAM-dendrimers.

1. Introduction

Dendrimers and dendrons are highly branched synthetic macromolecules. They breach the gap between small-molecule organic chemistry and polymer chemistry in the sense that they can be similar in size to polymers and can be synthesized in a controlled manner to yield monodisperse materials. A dendrimer is a structure that consists of a core, an interior, and a surface with a large number of surface groups, which is a consequence of the highly branched structure. Dendrons are the branched wings of the dendrimers.[1–4] Large dendrimers have a diameter of nanometer-dimensions and can, if designed properly, compartmentalize small molecules through non-covalent interactions either to the surface groups (*exo*-complexation)[5–7] or the interior (*endo*-complexation).[5–7] This is a feature they share with some globular proteins.[8]

exo-Complexation provides the opportunity for using dendrimers as quantized nano-scale building blocks[9] for use in supramolecular chemistry and medicinal chemistry (e.g., in tectodendrimers)[10,11] and in the case of dendrimer–protein conjugation, where the stochiometries for the composition of the tectodendrimers or the conjugates are dependant on the size and nature of the surface of the dendrimers.[12] *endo*-Complexation provides an opportunity for using the dendrimer for drug-delivery purposes[13–15] or for using the interior of the dendrimer as a microenvironment to facilitate reactions to take place under mild conditions.[16,17]

A strong driving force for the development of the field of dendrimer science is the potential application of dendrimers in different areas of chemistry, nanotechnology, biology, and medicine.[13,14,18,19]

Although a large number of papers describing the synthesis of dendrons and dendrimers are available[1,20–22] surprisingly few describe structures beyond the lowest generations (sizes). Only a few families of dendrimers are commercially available with the PAMAM (poly(amidoamine))-,[23] PPI (poly(propyleneimine))-,[24,25] poly(lysine)-,[26,27] Majoral-Caminade phosphorous-,[28] and Hult polyester-dendrimers[29] as the best-known classes. This reflects the general challenge in the area of dendrimer synthesis: The synthesis of large well-defined synthetic macromolecules is difficult. It is difficult to achieve full conversions in coupling reactions in either divergent or convergent synthesis schemes, as the reactions can be very slow. The purification of the products is also difficult due to issues with compartmentalization of small molecules (and solvents) inside the macromolecules, structural similarities between different sizes of polymers/oligomers and solubility issues.

Dendrimers having *endo* amino-groups as part of their interior structure may form complexes with transition-metal ions, and these complexes can in many cases be reduced with suitable reducing reagents to form dendrimer-encapsulated metal nanoparticles (DENs).[5,30,31] DENs have been prepared with a number of different types of metals, and they have been shown to be efficient catalysts for a variety of reactions including catalytic hydrogenations,[32] oxidation reactions,[33,34] and Heck-,[35,36] Suzuki-,[37,38] and Stille-reactions.[39,40] Our own work on catalysis with DENs lead us

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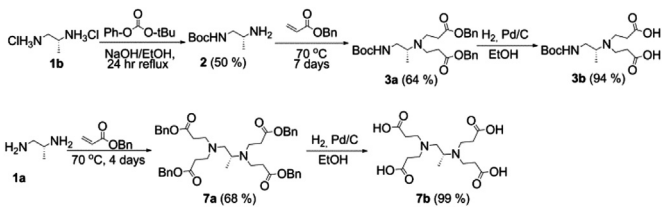
to consider the possibility of preparing chiral metal nanoparticles that might be used for catalyzing stereoselective reactions. We have previously reported a study on the convergent synthesis of internally branched PAMAM-dendrimers[41] and later a communication on chiral dendrimer-encapsulated metal nanoparticles of Pd and Rh.[42] Herein we describe our optimized synthetic protocols as well as the full characterization of a family of chiral PAMAM-dendrons and dendrimers based on chiral 1,2-diaminopropane.

2. Results and discussion

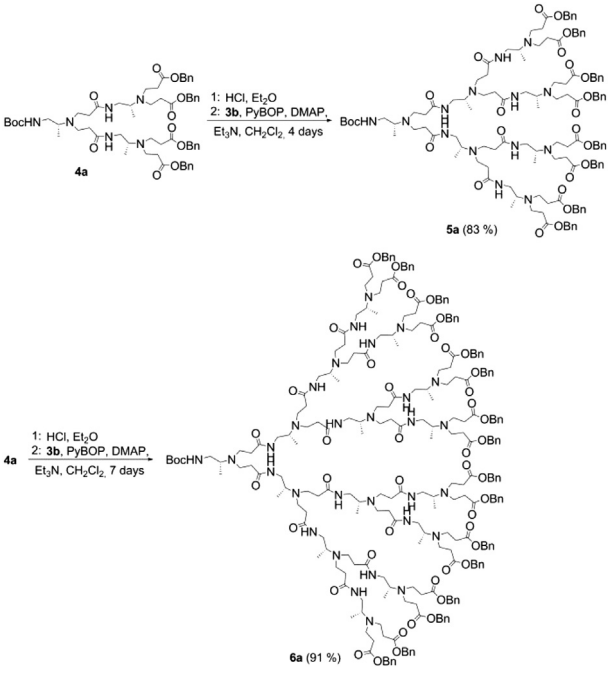
2.1. Synthesis

We chose to use 1,2-diaminopropane (**1a**) as the chiral element in the dendrons and dendrimers, because this keeps the PAMAM-skeleton of the dendrimers intact. 1,2-Diaminopropane (**1a**) is easily resolved on a large scale using classical resolution[43] with tartaric acid, and both enantiomers of the diamine were available. We have previously developed a methodology for the regiospecific carbamate monoprotection of polyamines[44] and in this case Boc-protection was chosen. We found it convenient to use the dihydrochloride of (2*R*)-1,2-diaminopropane (**1b**) instead of the free base for the synthesis of the mono Boc-protected amine (**2**). The hydrochloride was easily prepared by a simple ion-exchange reaction between the tartrate salt of the amine and KCl in water with formation of the poorly soluble potassium hydrogen tartrate as the driving force for the ion-exchange procedure. The mono Boc-protected diamine (**2**) was pure as seen by ^{1}H NMR spectroscopy with no signs of the opposite regioisomer. This regiochemistry was previously reported by our group in a study of the protection of diamines.[44] This material rearranges upon standing to give a mixture of the two regioisomers, and this was circumvented by performing the next step immediately after isolation of the mono protected diamine. The first step of the double Michael-addition in neat benzyl acrylate is a fast reaction giving the monoadduct. The second Michael-addition is slow, but can be driven to completion giving the building block (**3a**), which is stable and easily purified on large scale (>30 g) by dry column vacuum chromatography.[45] The Michael-additions proceed faster in hydroxylic solvents, but performing the reaction between the amine (**2**) and benzyl acrylate in either methanol or ethanol led to partial trans-esterification. Trans-esterification was not seen in 2-propanol, but in this case, the Michael-addition was slow. Deprotection of the Boc-group gives the primary amine (**3c**). This reaction may be performed using trifluoroacetic acid, but we found that using HCl in ether gave a cleaner product. Removal of the benzyl-esters was done by means of catalytic hydrogenation with Pd on C to give the di-carboxylic acid (**3b**) in 94% yield. Amide coupling of the two building blocks (**3c**) and (**3b**) with PyBOP as the coupling reagent gave the generation 0.5 dendron (**4a)** in 64% yield. The core was synthesized by quadruple Michael-addition between **1a** and benzyl acrylate (neat) to give the benzyl ester core (**7a**) in 68% yield. Removal of the benzyl-esters by catalytic hydrogenation using Pd/C gave the corresponding tetracarboxylic acid (**7b**) in 99% yield. The synthetic scheme is outlined in Scheme 1.



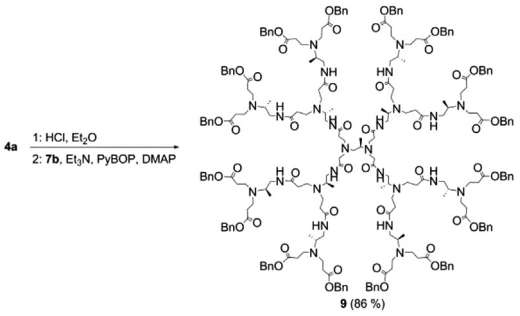
Scheme 1. The synthetic route to the building block for the dendrons (**3b**) and to the dendrimer core (**7b**).

Two strategies for synthesis of the higher generation dendrons were investigated; stepwise growth and accelerated growth as shown in Scheme 2. This is the first example of the use of accelerated growth in the synthesis of PAMAM-dendrons. Using accelerated growth gives access to higher generation dendrons more rapidly and the purification by size-exclusion chromatography turned out to be much easier than when using the stepwise growth process. It turned out that the coupling reaction was considerably slower requiring much longer reaction times (7 days vs 4 days) and we found that since the coupling reagent PyBOP slowly decomposes during the reaction, it was necessary to add additional amounts of fresh PyBOP to the reaction mixture during the coupling affording dendron **5a** in 83% and **6a** in 83% yield from dendron **4a**.



Scheme 2. Synthesis of dendrons **5a** and **6a**.

Coupling of the dendrons (**3a**, **4a**, **5**, **6**) to the core (**7b**) of the dendrimers was done as shown in Scheme 3. First the Boc-groups were deprotected with HCl in ether, then the carboxylic acid cores(**7b**)/dendrons (**3a**, **4a**, **5**, **6**) were added together with the amide coupling reagent and Et_3N. The dendrons and dendrimers synthesized are shown in Fig. 1.



Scheme 3. The synthesis of the final dendrimers was performed by coupling to the core **7b**. Here the coupling to form the G 2.5 dendrimer is illustrated.

2.2. Characterization

2.2.1. NMR spectroscopy. The full assignment of the ^{1}H and ^{13}C NMR spectra of **4**, **5**, **6**, **7**, and **8** was performed using different NMR

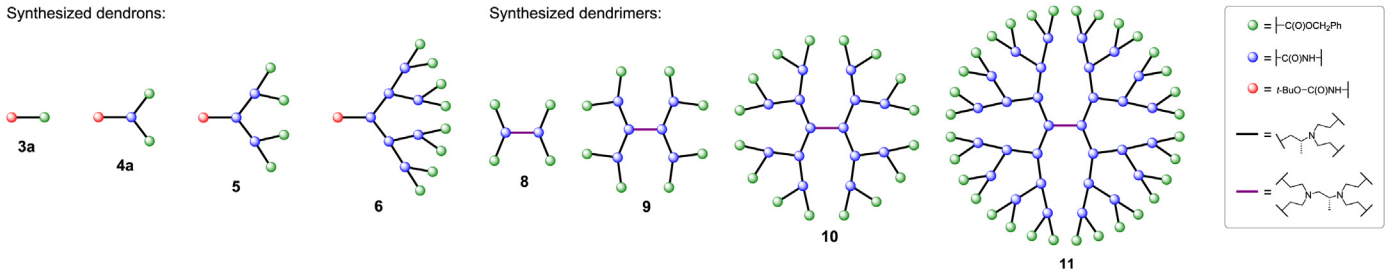


Fig. 1. Schematic representation of the synthesized dendrimers. One ball represents two connections to the specified functionality, except the red ball, which represents the BOC-protected amine moiety.

techniques. The numbered structures are shown in Fig. 2. The ^{1}H NMR spectrum of **3a** was assigned using HSQC-, 1D-TOCSY-, and HMBC-experiments. The 1D-TOCSY spectrum was used to confirm the directionality of the dendron. The HSQC experiment revealed that the 7-protons were diastereotropic. This can be seen by the coupling of the 7-carbon to two distinct proton signals in the HSQC-spectrum. The spectrum of the deprotected diacid, **3b**, was also assigned using HSQC experiments. The assignments of **3a** and **3b** can be seen in Tables 1 and 2.

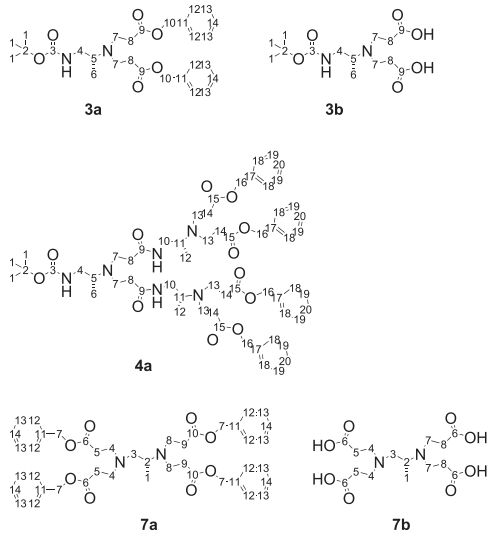


Fig. 2. Numbered structures of compounds **3a**, **3b**, **4a**, **7a**, **7b**.

Table 1
Assigned chemical shifts for **3a** in $CDCl_3$, signals are given in ppm downfield from TMS, using the solvent residual peak as internal standard. Multiplicity is given in parentheses[a]

Position	δ (^{1}H)	δ (^{13}C)
1	1.38 (s)	28.49
2	—	78.82
3	—	156.13
4	3.20 (m); 2.80(m)	43.18
5	2.80 (m)	54.83
6	0.90 (d)	10.79
7	2.80 (m); 2.57 (m)	44.95
8	2.43 (m)	34.12
9	—	172.47
10	5.11 (s)	66.31
11	—	135.90
12, 13, 14	7.38–7.29 (m)	128.58; 128.41; 128.28
BocN*H*–	5.20 (br s)	—

[a] The multiplets are not reported as intervals but as the center of the multiplet. Intervals can be seen in Experimental section.

Table 2
Assigned chemical shifts for **3b** in DMSO-d_6, signals are given in ppm downfield from TMS, using the solvent residual peak as internal standard. Multiplicity is given in parentheses[a]

Position	δ (^{1}H)	δ (^{13}C)
1	1.38 (s)	28.20
2	—	77.48
3	—	155.59
4	2.92(m); 2.79 (m)	42.76
5	2.86 (m)	54.27
6	0.87 (d)	11.96
7	2.72 (m); 2.58 (m)	44.84
8	2.31	33.29
9	—	173.61
–COO*H*	12.30 (br s)	—
BocN*H*–	6.43 (br s)	—

[a] The multiplets are not reported as intervals but as the center of the multiplet. Intervals can be seen in Experimental section.

The ^{1}H NMR spectrum of **4a** was assigned by analysis of the HSQC-, DEPT-, and HMBC-spectra. The ^{1}H NMR spectrum was complicated due to the presence of the diastereotropic protons. Unambiguous assignment of the amide carbon and the ester carbon in the ^{13}C NMR spectrum was done by analyzing the HMBC spectrum for a ^{2}J-coupling to the amide proton. This was possible both in $CDCl_3$ and in DMSO-d_6. Through analysis of these data it was found that the amide carbon was located at 171.12 ppm and the ester carbon at 171.92 ppm in $CDCl_3$. The assignment of NMR chemical shift data of the ^{1}H and ^{13}C NMR spectra are shown in Table 3.

Table 3
Assigned chemical shifts for **4a** in $CDCl_3$, signals are given in ppm downfield from TMS, using the solvent residual peak as internal standard. Multiplicity is given in parentheses[a]

Position	δ (^{1}H)	δ (^{13}C)
1	1.34 (br s)	28.12
2	—	77.35
3	—	155.44
4	2.88 (m); 2.74 (m)	45.51
5	2.74 (m); 2.60 (m)	53.78
6	0.88–0.77 (m)	11.71
7	2.74 (m); 2.60 (m)	45.51
8	2.21–2.08 (m)	35.05
9	—	171.12
10	3.02 (m); 2.88 (m)	44.98
11	2.74 (m); 2.60 (m)	54.14
12	0.88–0.77 (m)	12.52
13	2.74 (m); 2.60 (m)	44.98
14	2.42 (t)	33.82
15	—	171.92
16	5.06	65.35
17	—	136.10
18, 19, 20	7.38–7.27 (m)	127.25; 127.92; 128.34
BocN*H*–	6.20	—
C(O)N*H*–	7.46	—

[a] The multiplets are not reported as intervals but as the center of the multiplet. Intervals can be seen in Experimental section.

The ^{13}C NMR spectrum of **7a** was especially informative since it showed the presence of two different carbonyl groups at 172.46 and 172.37 ppm, due to the asymmetric character of the molecule. These tightly separated signals are only 0.1 ppm apart in the ^{13}C NMR spectrum. The spectrum of **7b** was devoid of any splitting of the two different carbonyl groups, and only one signal could be observed at 182.37 ppm in DMSO-d_6. Assignment of the two carbonyl signals in the ^{13}C NMR spectrum of **7a** was accomplished through a COLOC experiment, the rest of the spectrum was assigned by analysis of the HMBC and HSQC spectra. A COLOC experiment is the carbon equivalent of an HMBC. Though this experiment has been largely superseded by the more sensitive HMBC it can provide insight when the resolution of the HMBC spectrum is not enough to assign separated carbon signals. Splitting of the benzylic- and phenylic carbons was not observed in the ^{13}C NMR spectrum of **7a**, under the applied conditions. The NMR spectrum of the deprotected core was also assigned by analysis of the HSQC and the DEPT spectra. The assignments are shown in Tables 4 and 5. The benzyl ester protected core (**7b**) has less splitting of the signals from the 4- and 7-protons in the ^{1}H NMR spectrum than the spectrum of the tetracarboxylic acid core (**7a**). The signals from these protons are still very complex and not simple triplets, perhaps due to the presence of zwitterionic structures.

Table 4
Assigned chemical shifts for **7a** in $CDCl_3$, signals are given in ppm downfield from TMS, using the solvent residual peak as internal standard. Multiplicity is given in parentheses[a]

Position	δ (^{1}H)	δ (^{13}C)
1	0.86 (d)	13.08
2	2.76 (m)	58.55
3	2.32 (dd); 2.18 (dd)	53.60
4	2.76 (m); 2.62(m)	49.99
5	2.41 (t)	32.80
6	—	172.46
7	2.76(m); 2.62 (m)	46.05
8	2.41 (t)	34.61
9	—	172.37
10	5.07 (s)	66.24
11	—	135.97
12, 13, 14	7.35–7.25 (m)	128.53; 128.33; 128.22

[a] The multiplets are not reported as intervals but as the center of the multiplet. Intervals can be seen in Experimental section.

Table 5
Assigned chemical shifts for **7b** in DMSO-d_6, signals are given in ppm downfield from TMS, using the solvent residual peak as internal standard. Multiplicity is given in parentheses[a]

Position	δ (^{1}H)	δ (^{13}C)
1	0.94 (d)	12.43
2	2.34 (m)	56.23
3	3.01 (dd); 2.56 (dd)	52.72
4	2.71 (m)	48.84
5	2.34 (m)	31.25
6	—	182.37
7	2.71 (m)	45.16
8	2.34 (m)	32.87

[a] The multiplets are not reported as intervals but as the center of the multiplet. Intervals can be seen in Experimental section.

2.2.2. Stability and internal structure. Dendrimers above and including generation 3.5 turned out to have low long-term stability undergoing retro-Michael addition. This could be due to increased steric crowding inside the dendrimers leading to a more rigid internal structure upon increasing generation, which could be further stabilized by internal hydrogen bonding between the secondary amides inside the dendrons and dendrimers.

IR-spectroscopy has previously been used for probing hydrogen bonding in dendrimers in solution,[46] and IR spectra of the dendrons and dendrimers in acetonitrile solution were recorded. Representative spectra are shown in Figs. 3 and 4, the small changes in the NH-stretching regions of the IR-spectra (Amide I/II bands) indicates that the smaller generation of dendrons and dendrimers are already held together by hydrogen bonding, however, no difference between these internally branched dendrimers and the similar series of ester-terminated PAMAM-dendrimers could be seen (The IR-spectra of G 0.5–G 3.5 methyl-ester-terminated PAMAM-dendrimers are in Supplementary data.). ^{1}H NMR spectroscopy is another method that has been used for studying hydrogen bonding in dendrimers.[1] The chemical shift values for the amide-protons for the dendrons (**3**–**6**) and the dendrimers (**8**–**11**) are shown in Table 6. Common for all the dendrons (with the G2-dendron as an exception) was that the different types of amide-protons showed different degrees of hydrogen bonding. The dendrimers from G1.5 to G3.5 have an increasing degree of hydrogen bonding as evidenced from the observed downfield shifts for the amide-protons.

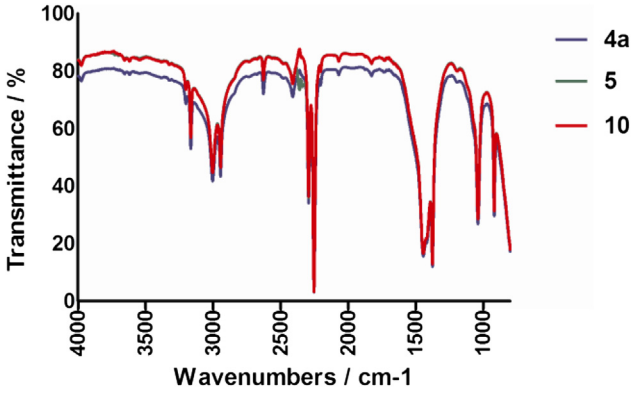


Fig. 3. IR-spectra of **4a**, **5**, and **10**.

Table 6
The chemical shift values for the amide-protons in the synthesized dendrons and dendrimers. Signals reported in ppm, downfield from TMS using the solvent residual peak as internal standard ($CDCl_3$)

Dendron	C(O)N*H*	Dendrimer	C(O)N*H*
3a	5.23	**8**	6.94
			6.87
4a	6.79	**9**	7.08
	5.34		7.03
5	7.09	**10**	7.09
	7.03		7.03
6	7.16	**11**	6.92; 6.87
	7.06		6.67

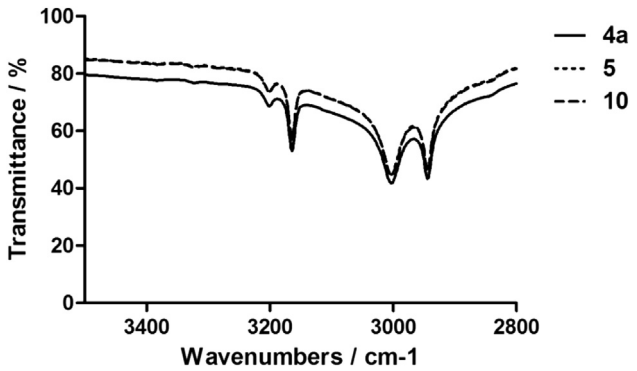


Fig. 4. Zoom of the Amide–I/II bands in the IR spectra.

2.2.3. Optical rotation. The optical rotation of the dendrons and dendrimers was measured in CH_3CN. The molar optical rotation per chiral center ($[\Phi]/n$) is shown in Fig. 5 for the dendrimers and the dendrons, and it is interesting that while $[\Phi]/n$ levels off asymptotically for the dendrimers upon increasing generation, the dendrons seem to undergo a conformational change affecting $[\Phi]/n$.

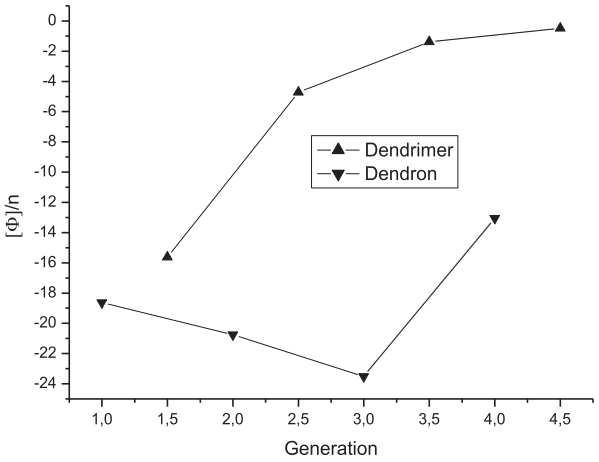


Fig. 5. Plot showing the generational dependency between the dendrons and the $[\Phi]/n$ levels.

3. Conclusion

Improved synthetic methodology for the synthesis of internally branched chiral PAMAM-dendrons and dendrimers has been developed and the compounds have been characterized by NMR, IR, and optical rotation. The dendrons and dendrimers show an increased degree of internal hydrogen bonding upon increasing generation and the presence of different types of amide-protons in the compounds is indicative of the existence of a tertiary structure in these PAMAM-dendrimers, which could affect their biological properties. It has also been shown that these dendrons and dendrimers become unstable toward retro-Michael addition at large generations indicative of a highly compact and strained structure.

4. Experimental section

4.1. General

Solvents and chemicals were obtained from commercial sources and were used without further purification. Chromatographic purification was done using dry column vacuum chromatography on Silicagel 60 (400–800 mesh). NMR was recorded at either 300 MHz or 500 MHz (equipped with a cryoprobe). For ^{1}H NMR chemical shifts for proton are reported in parts per million downfield from tetramethylsilane and are referenced to residual hydrogen in the NMR solvent ($CDCl_3$, δ 7.26 ppm). For ^{13}C NMR, chemical shifts were reported in the scale relative to NMR solvent ($CDCl_3$, δ 77.0 ppm) as an internal reference. NMR data are reported as follows: chemical shifts, multiplicity (s: singlet, d: doublet, dd: doublet of doublets, t: triplet, m: multiplet), coupling constant (Hz), and integration. Optical rotation was measured using a 5 ml cell with a 1.0 dm path length on a polarimeter. Mass spectra were measured by MALDI-TOF, FABMS or electrospray as specified. Dithranol was used as the matrix for MALDI-TOF and *m*-NBA was used as the matrix for FABMS.

Elemental analysis was performed by Ms Birgitta Kegel, Department of Chemistry, University of Copenhagen.

4.2. (*R*)-1,2-Diaminopropane dihydrochloride (1a)

Racemic 1,2-diaminopropane was resolved with L-tartaric acid according to the previously reported procedure.[43] We found that the use of a basket centrifuge for the filtration of the diastereomeric salt was highly convenient in order to reduce the number of recrystallization necessary. The diastereomeric tartrate was finally converted to the dihydrochloride (**1b**) by reaction with KCl in water as described.[43] $[\alpha]_D^{20}$ +3.97 (*c* 0.123, H_2O) (lit. $[\alpha]_D^{20}$ +3.99 to +4.10).[47]

4.3. Synthesis of (*R*)-*tert*-butyl 2-aminopropylcarbamate (2)

To a mixture of NaOH (8.82 g; 0.2205 mol) and 96% ethanol (150 ml) was added compound **1b** (16.36 g; 0.11 mol), under vigorous stirring. After 2 h the white precipitate was filtered of and to the filtrate was added *tert*-butyl phenylcarbonate (39.37 g; 0.203 mol). The mixture was refluxed for 24 h and then concentrated in vacuo to a colorless oil. Water (175 ml) was added to the oil and the pH was adjusted to 3 using 2 M H_2SO_4. The aqueous phase was washed with CH_2Cl_2 (3×200 ml) and then the pH was adjusted to 12 with 2 M NaOH. The aqueous phase was then extracted with CH_2Cl_2 (4×200 ml), the organic phases were collected, dried over Na_2SO_4, and concentrated to yield compound **2** as a colorless oil (9.58 g; 50% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ=4.94 (s, 1H, BocHN–C*H*$_2$–CH(CH_3)–NH_2), 3.17–3.07 (m, 1H, BocHN–C*H*$_2$–CH(CH_3)–NH_2), 3.05–2.92 (m, 1H, BocHN–CH_2–C*H*(CH_3)–NH_2), 1.42 (s, 9H, (C*H*$_3$)$_3$C–C(O)–NH–), 1.04 (d, 3H, BocHN–CH_2–CH(C*H*$_3$)–NH_2, ^{2}J=6.3). ^{13}C NMR (126 MHz, $CDCl_3$) δ=156.24, 79.12, 48.53, 46.87, 28.39, 21.54. MS (FAB) *m*/*z*=175 $[M+H]^+$.

4.4. Synthesis of (*R*)-benzyl 3,3′-(1-(*tert*-butoxycarbonylamino)propan-2-ylazanediyl)dipropanoate (3a)

Compound **2** (19.71 g; 0.1131 mol) was dissolved in benzyl acrylate (150 ml) containing hydroquinone (0.25 g). The resulting solution was stirred at 70 °C for 7 days. Excess benzyl acrylate was removed by distillation (61–63 °C; 0.1 mmHg) resulting in the crude product as a brown oil. The product was purified by dry column vacuum chromatography, eluting from heptane to EtOAc with 5% increments, yielding compound **3** as a colorless oil (36.42 g; 64% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ=7.38–7.27 (m, 10H), 5.20 (br s, 1H, BocN*H*–CH_2–CH(CH_3)–N–), 5.11 (s, 4H, Ph–C*H*$_2$–O–C(O)–), 3.20 (dd, 1H, BocHN–C*H*$_2$–CH(CH_3)–N–), 2.88–2.76 (m, 4H, BocHN–C*H*$_2$–C*H*(CH_3)–N–; –NC*H*$_2$–CH_2C(O)–O–), 2.61–2.53 (m, 2H, –NC*H*$_2$–CH_2C(O)–O–), 2.49–2.36 (m, 4H, –NCH_2–C*H*$_2$C(O)–O–), 1.43 (s, 9H, (C*H*$_3$)$_3$C–C(O)–NH–), 0.90 (d, 3H, BocHN–CH_2–CH(C*H*$_3$)–N–, ^3J=6.2). ^{13}C NMR (126 MHz, $CDCl_3$) δ=172.47 (Ph–CH_2–O–*C*(O)–CH_2–CH_2–), 156.13, 135.90 (*Ph*–CH_2–O–C(O)–CH_2–CH_2–), 128.58 (*Ph*–CH_2–O–C(O)–CH_2–CH_2–), 128.41 (*Ph*–CH_2–O–C(O)–CH_2–CH_2–), 128.28 (*Ph*–CH_2–O–C(O)–CH_2–CH_2–), 78.82 ((CH_3)$_3$C–C(O)–NH–), 66.31 (Ph–CH_2–O–C(O)–CH_2–CH_2–), 54.83 (BocHN–CH_2–C*H*(CH_3)–N–), 44.95 (–O–C(O)–CH_2–C*H*$_2$–N–), 43.18 (BocHN–C*H*$_2$–CH(CH_3)–N–), 34.12 (–O–C(O)–C*H*$_2$–CH_2–N–), 28.49 ((C*H*$_3$)$_3$C–C(O)–NH–), 10.79 (BocHN–CH_2–CH(C*H*$_3$)–N–). MS (FAB) *m*/*z*=499 $[M+H]^+$. Elemental analysis: calculated (%): C: 67.45; H: 7.68; N: 5.62. Found (%): C: 67.68; H: 7.66; N: 5.49. $[\alpha]_D^{20}$ −39.1 (*c* 1.03, CH_3CN).

4.5. (*R*)-3,3′-(1-(*tert*-Butoxycarbonylamino)propan-2-ylazanediyl)dipropanoic acid (3b)

Compound **3a** (1.7865 g; 3.583 mol) was dissolved in 96% ethanol (100 ml) and hydrogenated over 10% Pd/C (50 mg) under a 3 bar H_2 atmosphere for 16 h. The solution was filtered through a plug of Celite and evaporated to a colorless oil. CH_2Cl_2 (45 ml) was added to the oil and evaporated, yielding compound **3b** as a white

solid (1.07 g; 94% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ=12.30 (br s, 2H, *H*O–C(O)–CH_2–), 6.43 (m, 1H, BocN*H*–CH_2–CH(CH_3)–N–), 2.92 (m, 1H, BocHN–C*H*$_2$–CH(CH_3)–N–), 2.86 (m, 1H, BocHN–CH_2–C*H*(CH_3)–N–), 2.79 (m, 1H, BocHN–C*H*$_2$–CH(CH_3)–N–), 2.72 (m, 2H, –NC*H*$_2$–CH_2C(O)–OH), 2.58 (m, 2H, –NC*H*$_2$–CH_2C(O)–OH), 2.31 (t, 4H, –NC*H*$_2$–C*H*$_2$C(O)–OH, ^3J=7.0), 1.38 (s, 9H, (C*H*$_3$)$_3$C–C(O)–NH–), 0.87 (d, 3H, BocHN–CH_2–CH(C*H*$_3$)–N–, ^2J=6.3). ^{13}C NMR (126 MHz, DMSO-d_6) δ=173.61 (HO–*C*(O)–CH_2–CH_2–), 155.59 ((CH_3)$_3$C–*C*(O)–NH–), 77.48 ((CH_3)$_3$*C*–C(O)–NH–), 54.27 (BocHN–CH_2–*C*H(CH_3)–N–), 44.84 (HO–C(O)–CH_2–*C*H$_2$–N–), 42.76 (BocHN–*C*H$_2$–CH(CH_3)–N–), 33.29 (HO–C(O)–*C*H$_2$–CH_2–N–), 28.20 ((CH_3)$_3$*C*–C(O)–NH–), 11.96 (BocHN–CH_2–CH(*C*H$_3$)–N–). Mp (°C)=66–68. MS (ESP) m/z=319 $[M+H]^+$.

4.6. Synthesis of dendron 4a

Compound **3a** (1.2591 g; 2.525 mmol) was dissolved in ether (25 ml) and a 6 M solution of HCl in ether (9 ml) was added to this solution. After 2 h the solution was evaporated resulting in a white solid. The white solid was dissolved in CH_2Cl_2 then compound **3b** (0.3962 g; 1.244 mmol), Et_3N (1.38 ml; 1 g; 9.956 mmol), and PyBOP (1.7168 g; 3.299 mmol) were added to the solution in that order. After 24 h stirring, the solution was washed with an aqueous 10% Na_2CO_3 solution (2×15 ml) and water (2×15 ml). Then the product was isolated by dry column vacuum chromatography, eluting from heptane to EtOAc with 20% increments and 1% Et_3N added to all phases. Compound **4a** was isolated as a yellow oil (1.142 g; 85% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ=7.31–7.16 (m, 20H, *Ph*–CH_2–O–C(O)–), 6.79 (br s, 2H, –N–CH(CH_3)–CH_2–N*H*–C(O)–), 5.37 (br s, 1H, Boc–N*H*–CH_2–CH(CH_3)–N–), 5.01 (s, 8H, Ph–C*H*$_2$–O–C(O)–), 3.41 (t, 2H, –C(O)–NH–C*H*$_2$–CH(CH_3)–N–, ^3J=8.6), 3.11 (m, 1H, Boc–NH–C*H*$_2$–CH(CH_3)–N–), 2.85–2.67 (m, 12H, –C(O)–NH–C*H*$_2$–CH(CH_3)–N–, Boc–NH–C*H*$_2$–CH(CH_3)–N–, –C(O)–NH–CH_2–*C*H(CH_3)–N–, Boc–NH–CH_2–C*H*(CH_3)–N–, –N–C*H*$_2$–CH_2–C(O)–NH–, -N–C*H*$_2$–CH_2–C(O)–O–Bn), 2.56–2.44 (m, 4H, –N–C*H*$_2$–CH_2–C(O)–O–Bn), 2.44–2.27 (m, 10H, –N–CH_2–C*H*$_2$–C(O)–O–Bn, –N–C*H*$_2$–CH_2–C(O)–NH–), 2.27–2.08 (m, 4H, –N–CH_2–C*H*$_2$–C(O)–NH–), 1.32 (s, 9H, (C*H*$_3$)$_3$C–C(O)–NH–), 0.82 (d, 6H, –C(O)–NH–CH_2–CH(C*H*$_3$)–N–, ^2J=5.9), 0.77 (d, 3H, BocHN–CH_2–CH(C*H*$_3$)–N–, ^2J=5.4). ^{13}C NMR (126 MHz, $CDCl_3$) δ=172.49 (Bn–O–*C*(O)–CH_2), 172.21 (–NH–*C*(O)–CH_2), 156.10 ((CH_3)$_3$–C–O–*C*(O)–NH–), 135.83 (*Ph*–CH_2–O–C(O)–), 128.57 (*Ph*–CH_2–O–C(O)–), 128.32 (*Ph*–CH_2–O–C(O)–), 128.27 (*Ph*–CH_2–O–C(O)–), 78.42 ((CH_3)$_3$–*C*–O–C(O)–NH–), 66.34 (Ph–C*H*$_2$–O–C(O)–), 54.68 (–C(O)–NH–CH_2–*C*H(CH_3)–N–), 53.90 (BocHN–CH_2–*C*H(CH_3)–N–), 45.38, 44.78 (–O–C(O)–CH_2–*C*H$_2$–N–), 43.31 (–NH–C(O)–CH_2–*C*H$_2$–N–), 41.82 (BocHN–*C*H$_2$–CH(CH_3)–N–), 35.39 (–O–C(O)–*C*H$_2$–CH_2–N–), 34.06 (–NH–C(O)–*C*H$_2$–CH_2–N–), 28.54 ((CH_3)$_3$C–C(O)–NH–), 11.18 (–C(O)–HN–CH_2–CH(*C*H$_3$)–N–), 10.50 (BocHN–CH_2–CH(*C*H$_3$)–N–). MS (FAB) m/z=1079 $[M+H]^+$. $[\alpha]_D^{20}$ –77.9 (*c* 1.344, CH_3CN).

4.7. Synthesis of dendron 5a

Compound **3a** (0.1999 g; 0.18521 mmol) was dissolved in CH_2Cl_2 (20 ml) and a 6 M solution of HCl in ether (6 ml) was added to the solution. After 3 h the solution was evaporated resulting in a white sticky solid. The solid was dissolved in CH_2Cl_2 (20 ml) then compound **3b** (0.0290 g; 0.0911 mmol), Et_3N (0.11 ml; 0.07997 g; 0.7903 mmol), PyBOP (0.1137 g; 0.21849 mmol), and DMAP were added to the solution in that order. After 4 days stirring, the reaction mixture was concentrated in vacuo, redissolved in CH_2Cl_2 (6 ml), and the product purified on BioBeads SX-1. Dendron **5a** was isolated as a yellow sticky oil (0.1761 g; 86% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ=7.30–7.16 (m, 40H, *Ph*–CH_2–O–C(O)–), 7.11–7.00 (m, 4H, –C(O)–N*H*–CH_2–), 6.68–6.64 (m, 2H, –C(O)–N*H*–CH_2–), 5.84–5.74 (m, 1H, –C(O)–N*H*–CH_2–), 5.00 (s, 16H, Ph–C*H*$_2$–O–C(O)–), 3.45–3.29 (m, 8H), 3.06–3.00 (m, 3H), 2.74 (br s, 16H), 2.32 (br s, 34H), 1.34 (br s, 9H, (C*H*$_3$)$_3$C–C(O)–NH–), 1.18 (br s, 7H), 0.83 (br s, 11H). ^{13}C NMR (126 MHz, $CDCl_3$) δ=172.26, 156.11, 135.85, 128.61, 128.59, 128.30, 128.24, 78.42, 66.32, 54.01, 45.56, 44.95, 44.35, 41.62, 39.97, 33.56, 28.18, 10.58, 10.35. MS (MALDI-TOF) m/z=2241 $[M+H]^+$; matrix: dithranol. $[\alpha]_D^{20}$ –79.9 (*c* 1.086, CH_3CN).

4.8. Synthesis of dendron 4b

Dendron **4a** (112 mg, 410 μmol) was dissolved in 96% ethanol (75 ml) and hydrogenated over 10% Pd/C (25 mg) under a 3 bar H_2 atmosphere for 16 h. The solution was filtered through a plug of Celite, removal of the volatiles yielded dendron **4b** as a hygroscopic pale solid (72 mg; 96% yield). ^{1}H NMR (500 MHz, $CDCl_3$, DMSO-d_6 added) δ=8.32 (br s, 2H, -C(O)–N*H*–CH_2–CH(CH_3)–N–), 6.04 (br s, 1H, BocN*H*–CH_2–CH(CH_3)–N–), 3.67 (br s, 1H), 3.35 (br s, 15H), 2.67 (br s, 16H), 1.35 (s, 9H, (C*H*$_3$)$_3$C–O–C(O)–NH–), 1.18 (br s, 3H, BocNH–CH_2–CH(C*H*$_3$)–N–), 1.07 (br s, 6H, –C(O)–NH–CH_2–CH(C*H*$_3$)–N–). ^{13}C NMR (126 MHz, $CDCl_3$, DMSO-d_6 added) δ=175.18, 156.21, 79.04, 46.15, 41.08, 40.18, 32.18, 31.47, 29.45, 28.33, 12.89, 10.71, 10.03. MS (FAB) m/z=719 $[M+H]^+$.

4.9. Synthesis of dendron 6a

Dendron **4a** (46.1 mg; 43 μmol) was dissolved in ether (15 ml) and a 6 M solution of HCl in ether (3 ml) was added to the solution. After 3 h the solution was evaporated resulting in a white sticky solid. The solid was dissolved in CH_2Cl_2 (15 ml) and dendron **4b** (7.68 mg; 10.7 μmol), Et_3N (0.03 ml; 21.81 mg; 0.22 mmol), PyBOP (28 mg; 54 μmol), and DMAP (130 mg; 1 μmol) were added to the solution in that order. Additional PyBOP was added in portions of 20 mg every second day. After stirring the solution for 7 days, the solvent was removed and the remaining mixture was dissolved in CH_2Cl_2 (6 ml). The product was purified on BioBeads SX-1, yielding dendron **6a** as a yellow sticky oil (44 mg; 91% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ=7.38–7.25 (m, 80H, *Ph*–CH_2–O–C(O)–), 5.63 (s, 18H, –C(O)–N*H*–CH_2–CH(CH_3)–N–), 5.13–5.02 (m, 40H, Ph–C*H*$_2$–O–C(O)–), 3.72–3.66 (m, 4H), 3.38 (br s, 30H), 3.20–3.14 (m, 16H), 2.98 (br s, 25H), 2.80 (br s, 61H), 2.57 (br s, 33H), 2.40 (br s, 83H), 1.82 (t, 14H, ^3J=6.6) 1.38 (br s, 9H, (C*H*$_3$)$_3$C–O–C(O)–NH–), 0.90 (br s, 59H). ^{13}C NMR (126 MHz, $CDCl_3$) δ=172.48, 156.26, 135.77, 128.58, 128.30, 82.44, 66.34, 63.39, 57.97, 54.51, 53.00, 46.27, 45.80, 44.89, 42.23, 41.92, 34.09, 29.70, 28.53, 26.45, 11.45, 11.23, 8.66, 8.13. MS (MALDI-TOF) m/z=4564 $[M+H]^+$. $[\alpha]_D^{20}$ –54.0 (*c* 1.256, CH_3CN).

4.10. Synthesis of (*R*)-Benzyl 3,3′,3″,3‴-(propane-1,2-diylbis(azanetriyl))tetrapropanoate (7a)

(2*R*)-1,2-Diaminopropane dihydrochloride (4.5 g, 0.0306 mol), KOH (85%; 5 g, 0.0893 mol), and NaOH (2.5 g, 0.0625 mol) were stirred with a mechanical stirrer and after 2 h the liquid layer was decanted. The diamine was further purified by distillation to give 2.622 g; 51% yield. To benzyl acrylate (75 ml) was added hydroquinone (25 mg) and the resulting diamine (2.622 g; 0.03538 mol). This mixture was stirred at 70 °C for 4 days. Excess benzyl acrylate was removed by distillation (61–63 °C at 0.1 mmHg) and the product purified by dry column vacuum chromatography, eluting from heptane to EtOAc with 5% increments. This yielded compound **6a** as a colorless oil (17.51 g; 68% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ=7.35–7.25 (m, 20H, *Ph*–CH_2–O–C(O)–), 5.07 (s, 8H, Ph–C*H*$_2$–O–C(O)–), 2.84–2.68 (m, 5H, –N–CH_2–C*H*(CH_3)–N–, –N–C*H*$_2$–CH_2–C(O)–O–), 2.68–2.56 (m, 4H, –N–C*H*$_2$–CH_2–C(O)–O–), 2.41 (t, 8H, –N–CH_2–C*H*$_2$–C(O)–O–, ^3J=7.1), 2.32 (dd, 1H,

–N–CH_2–CH(CH_3)–N–, ^2J=4.2, 12.8), 2.18 (dd, 1H, –N–CH_2–CH(CH_3)–N–, ^2J=9.3, 12.8), 0.86 (d, 3H, –N–CH_2–CH(CH_3)–N–, ^2J=6.5). ^{13}C NMR (126 MHz, $CDCl_3$) δ=172.46 (Bn–O–*C*(O)–CH_2–), 172.37 (Bn–O–*C*(O)–CH_2–), 136.05 (*Ph*–CH_2–O–C(O)–CH_2–), 135.97 (*Ph*–CH_2–O–C(O)–CH_2–), 128.55 (*Ph*–CH_2–O–C(O)–CH_2–), 128.53 (*Ph*–CH_2–O–C(O)–CH_2–), 128.33 (*Ph*–CH_2–O–C(O)–CH_2–), 128.22 (*Ph*–CH_2–O–C(O)–CH_2–), 128.18 (*Ph*–CH_2–O–C(O)–CH_2–), 66.24 (Ph–*C*H_2–O–C(O)–CH_2–), 66.14 (Ph–*C*H_2–O–C(O)–CH_2–), 58.55 (–N–CH_2–*C*H(CH_3)–N–), 53.60 (–N–*C*H_2–CH(CH_3)–N–), 49.99 (–N–*C*H_2–CH_2–C(O)–O–), 46.05 (–N–*C*H_2–CH_2–C(O)–O–), 34.61 (–N–CH_2–*C*H_2–C(O)–O–), 32.80 (–N–CH_2–*C*H_2–C(O)–O–), 13.08 (–N–CH_2–CH(*C*H_3)–N–). MS (FAB)=*m*/*z*=723 $[M+H]^+$. Elemental analysis: calculated (%): C: 71.45; H: 6.97; N: 3.88. Found (%): C: 71.68; H: 7.04; N: 3.85.

4.11. (*R*)-3,3′,3″,3‴-(Propane-1,2-diylbis(azanetriyl))tetrapropanoic acid (7b)

Compound **6a** (6.61 g; 9.144 mmol) was dissolved in 96% ethanol (120 ml) and hydrogenated over 10% Pd/C (50 mg) under a 3 bar H_2 atmosphere for 16 h. The slurry was filtered through a plug of Celite, which was thoroughly washed with 96% ethanol. Removal of the volatiles resulted in compound **6b** as a white solid (3.29 g; 99% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ=3.01 (dd, 1H, –N–*C*H_2–CH(CH_3)–N–, ^2J=6.4, 13.2), 2.83–2.60 (m, 8H, –N–*C*H_2–CH_2–C(O)–OH), 2.56 (dd, 1H, –N–*C*H_2–CH(CH_3)–N–, ^2J=6.4, 13.2), 2.41–2.26 (m, 9H, –N–CH_2–*C*H_2–C(O)–OH, –N–CH_2–*C*H(CH_3)–N–), 0.94 (d, 3H, –N–CH_2–CH(*C*H_3)–N–, ^2J=6.5). ^{13}C NMR (126 MHz, DMSO-d_6) δ=182.37 (–N–CH_2–CH_2–*C*(O)–OH), 56.23 (–N–CH_2–*C*H(CH_3)–N–), 52.72 (–N–CH_2–CH(CH_3)–N–), 48.84 (–N–*C*H_2–CH_2–C(O)–OH), 45.16 (–N–CH_2–CH_2–C(O)–OH), 32.87 (–N–CH_2–*C*H_2–C(O)–OH), 31.25 (–N–CH_2–*C*H_2–C(O)–OH), 12.43 (–N–CH_2–CH(*C*H_3)–N–). MS (FAB) *m*/*z*=363 $[M+H]^+$.

4.12. General procedure for amide bond formation in the dendrimers

Boc-protected dendron was dissolved in CH_2Cl_2 and a 6 M solution of HCl in ether (6 ml) was added to the solution. When the deprotection was complete the solvent was removed in vacuo. The resulting solid was dissolved in CH_2Cl_2 and compound **7b** (0.245 equiv), Et_3N (4 equiv per carboxylic acid moiety), PyBOP (1.40 equiv per carboxylic acid moiety), and DMAP (0.1 equiv per carboxylic acid moeity) were added. When the coupling was judged complete, removal of the solvent, redissolution in CH_2Cl_2, and purification on BioBeads SX-1 using CH_2Cl_2 as the eluant yielded the dendrimers.

4.12.1. Synthesis of dendrimer ***8a***. This compound was prepared according to the general procedure for amide bond formation using compound **3a** as the dendron (661.9 mg; 1.327 mmol). The dendrimer was isolated as a brown sticky oil (527.7 mg; 86% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ=7.28–7.20 (m, 40H, *Ph*–CH_2–O–C(O)–), 5.00 (s, 16H, Ph–*C*H_2–O–C(O)–), 3.42–3.22 (m, 4H), 3.22–3.12 (m, 2H), 3.02–2.70 (m, 18H), 2.70–2.30 (m, 32H), 0.91 (br s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ=172.16, 152.66, 148.46, 136.62, 128.61, 66.65, 46.28, 45.62, 45.20, 41.24, 32.45, 30.47, 11.15, 9.95. MS (MALDI-TOF) *m*/*z*=1885 $[M+H]^+$. $[\alpha]_D^{20}$ –78.10 (*c* 0.908, CH_3CN).

4.12.2. Synthesis of dendrimer ***9a***. This compound was prepared according to the general procedure for amide bond formation using compound **4a** as the dendron (0.29 g; 0.27 mmol). The dendrimer was isolated as a light brown sticky oil (234 mg; 86% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ=7.28–7.17 (m, 80H, *Ph*–CH_2–O–C(O)–), 7.05 (br s, 7H, –C(O)–N*H*–CH_2–CH(CH_3)–), 6.80 (br s, 1H, –C(O)–N*H*–CH_2–CH(CH_3)–) 5.05–4.93 (m, 32H, Ph–*C*H_2–O–C(O)–), 3.33 (d, 18H, ^2J=7.3), 3.12–3.06 (m, 4H), 2.73 (br s, 37H), 2.53–2.22 (m, 65H), 1.37–1.24 (m, 13H), 0.82 (br s, 28H). ^{13}C NMR (126 MHz, $CDCl_3$) δ=172.71, 135.80, 128.60, 128.38, 128.30, 66.44, 54.12, 53.43, 52.58, 45.96, 44.55, 51.83, 33.80, 26.40, 10.66, 10.42, 8.68. MS (MALDI-TOF) *m*/*z*: 4208 $[M+H]^+$. $[\alpha]_D^{20}$ –61.28 (*c* 1.076, CH_3CN).

4.12.3. Synthesis of dendrimer ***10a***. This compound was prepared according to the general procedure for amide bond formation using compound **5a** as the dendron (52.2 mg; 23.3 μmol). The dendrimer was isolated as a colorless sticky oil (39.98 mg; 78% yield). Turns brown upon storage. ^{1}H NMR (500 MHz, $CDCl_3$) δ=7.29–7.23 (m, 160H, *Ph*–CH_2–O–C(O)–), 7.20–6.90 (m, 25H, –C(O)–N*H*–CH_2–CH(CH_3)–N–), 5.30 (br s, 9H, –C(O)–N*H*–CH_2–CH(CH_3)–N–), 5.07 (br s, 64H, Ph–*C*H_2–O–C(O)–), 3.56–3.33 (m, 40H), 2.82 (br s, 65H), 2.56 (br s, 48H), 2.41 (br s, 66H), 1.25 (br s, 19H), 0.91 (br s, 41H). ^{13}C NMR (126 MHz, $CDCl_3$) δ=172.57, 159.20, 135.79, 128.59, 128.32, 77.28, 77.02, 76.77, 66.42, 54.35, 52.80, 45.77, 44.77, 41.91, 33.95, 29.71, 24.10, 23.87, 8.63, 7.72, 6.63. $[\alpha]_D^{20}$ –39.96 (*c* 1.506, CH_3CN).

4.12.4. Synthesis of dendrimer ***11a***. This compound was prepared according to the general procedure for amide bond formation, with the following modification: the PyBOP was split into four portions and added with an interval of 2 days. Compound **6a** was used as the dendron (25.4 mg; 5.57 μmol). The dendrimer was isolated as a colorless sticky solid (20.2 mg; 79% yield). The solid turns dark brown overnight, even when stored cold. ^{1}H NMR (500 MHz, $CDCl_3$) δ=7.32 (br s, 319H, *Ph*–CH_2–O–C(O)–), 5.07 (s, 128H, Ph–*C*H_2–O–C(O)–), 3.39 (br s, 121H), 2.81 (br s, *J*=6.2 Hz, 297H), 2.68–2.10 (m, 497H), 1.98–1.53 (m, 249H), 1.39–1.02 (m, 750H), 1.00–0.78 (m, 335H). ^{13}C NMR (126 MHz, $CDCl_3$) δ=172.48, 135.86, 130.18, 128.58, 128.33, 66.35, 54.57, 44.79, 41.92, 34.10, 31.94, 29.71, 29.67, 29.38, 22.71, 14.34, 14.13, 11.19. $[\alpha]_D^{20}$ –29.49 (*c* 1.288, CH_3CN).

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.12.080.

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