Chiral, Polyionic Dendrimers with Complementary Charges − Synthesis and Chiroptical Properties

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Chiral dendrimers up to the second generation have been prepared from enantiopure aromatic bis- and tris(amino acids) by peptide coupling techniques. The dendrimers could be deprotected to yield water-soluble polyamine and/or polycarboxylic acid macromolecules. Two complementary types, with respect to the charges carried in water at pH = 7, were synthesised. A chiroptical study of the protected dendrimers, which were soluble in THF and $CHCl_3$, was conducted. The results of that study indicate that the solution shapes of these dendrimers are rather decongested, with little steric interaction between different parts of the dendritic structure.

Introduction

Dendrimers, regularly branched polymers of well-defined size, have been very actively studied in recent years.[1−3] As synthetic techniques are now well-developed, the interest has shifted towards taking advantage of the properties of these unique macromolecules in various applications such as catalysis and molecular recognition.[4] In this context, chiral, enantiomerically enriched dendrimers are of special relevance, since they would potentially allow enantioselective catalysis and recognition.[5] To date, much less work has been devoted to chiral dendrimers than to their achiral counterparts, although a number of chiral structures have been reported.[6,7] In particular, chiral, polyionic dendrimers remain largely unexplored,[8−10] despite the fact that their achiral counterparts appear promising as catalysts,[11] solubilisation agents,[12] and ion-selective receptors.[13] Given the importance of making processes such as catalysis and molecular recognition enantioselective, chiral, polyionic dendrimers could have a major role to play.

We now wish to report the synthesis and chiroptical properties of a family of chiral dendrimers with protected amine and carboxylic acid groups. The protecting groups can be removed to reveal dendritic structures with ionisable groups that render the macromolecules water-soluble. Two complementary types of dendrimers, the A and B types, have been synthesised up to the second generation, see Scheme 1. For simplicity, we will refer to the A type of generation two, i.e. compound **1a** of Scheme 1, as G2A, while the B type of generation two, i.e. compound **2a** of Scheme 1, will be referred to as G2B. The A type features Boc-protected amines on the end groups and carboxylic acid methyl esters throughout the structure, while the B type has methyl esters on the end groups and Boc-protected amines throughout. By selective removal of protecting groups, either free carboxylic acids, free amines, or both can be unmasked in these structures, at the surface or throughout the dendrimers, see Scheme 1. The A and B types are complementary with respect to accessible functional groups, and if protecting groups are removed, they are also complementary with respect to their charge in water at neutral pH. Applications in chiral molecular or ionic recognition and enantioselective catalysis, including phase-transfer catalysis, can be imagined for these systems. A preliminary account of the synthesis of **1a** has been published.[14]

The dendrimers reported here were designed to be readily prepared in good yields. To this end, we decided to assemble the dendrimers through amide bond formation, to be able to take advantage of the efficient reagents available for peptide synthesis. To further facilitate the couplings, we avoided using amines and carboxylates directly attached to an aromatic ring in the amide bond couplings, since their aliphatic counterparts were expected to have higher reactivity. For this reason, methylene spacers were introduced at the focal points of the branches, between the aromatic rings and the amide linkages. These spacers also increase the flexibility of the structure. On the basis of these considerations, we synthesised monomers A (**9**) and B (**17**), see Schemes 2 and 3, to be used as building blocks in the dendrimer assembly.

Results and Discussion

Synthesis

Monomer A (**9**) was synthesised according to Scheme 2[14] Iodination of 4-aminophenylacetic acid **3** with ICl yielded diiodide **4** in agreement with the published procedure.[15] Diazotisation and reduction proved to be problematic, and the only conditions that afforded the desired product **5** involved addition of solid $NaNO_2$ to a refluxing solution of **4** in ethanol containing a catalytic amount of H_2SO_4. The diazotisation-reduction was accompanied by unwanted esterification, so a saponification of **5** to yield **6** followed by esterification with benzyl bromide was necessary before **7** could be obtained. Unfortunately, the diazo-

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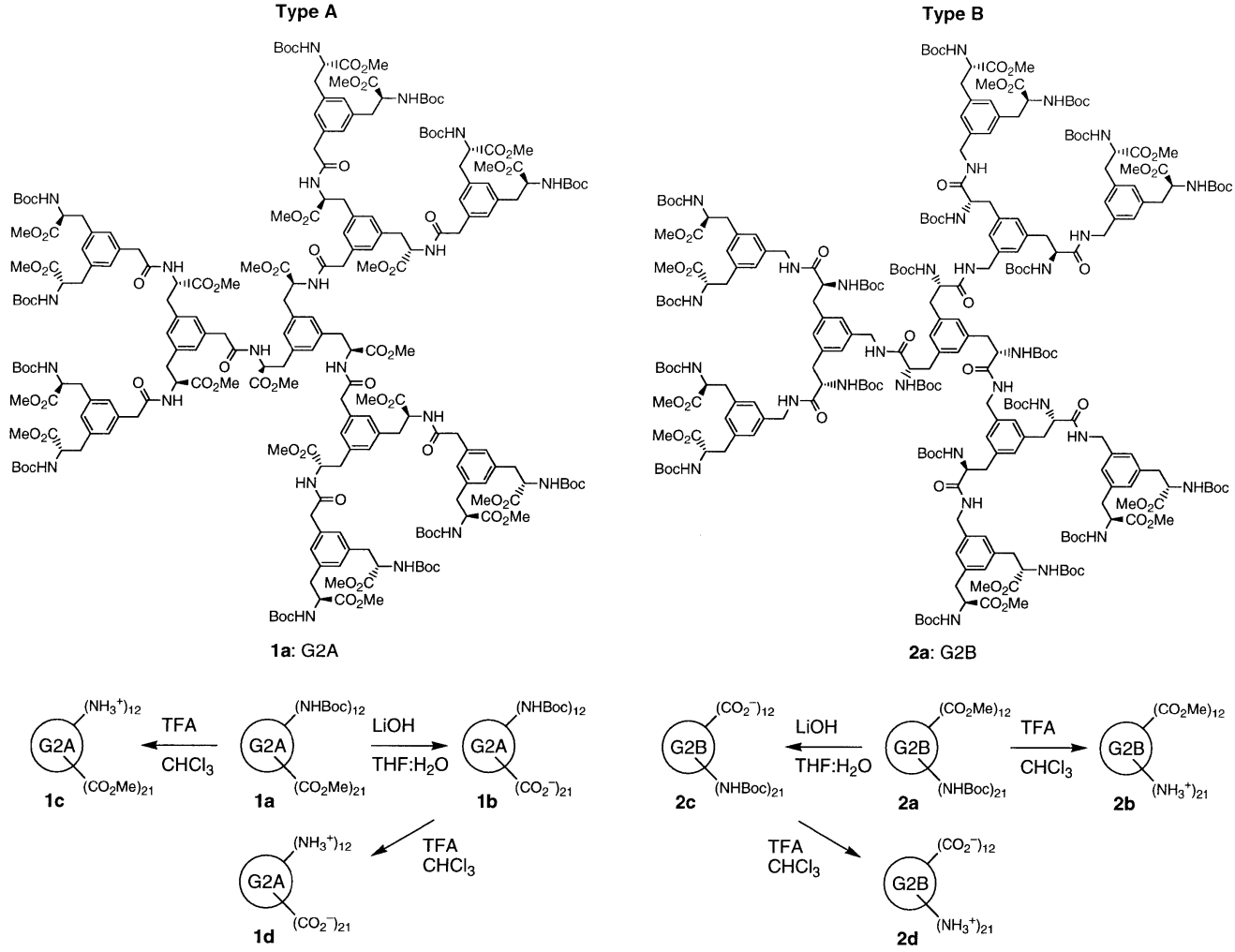
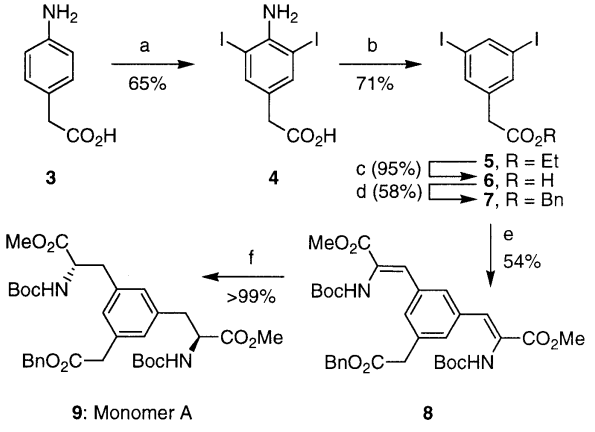


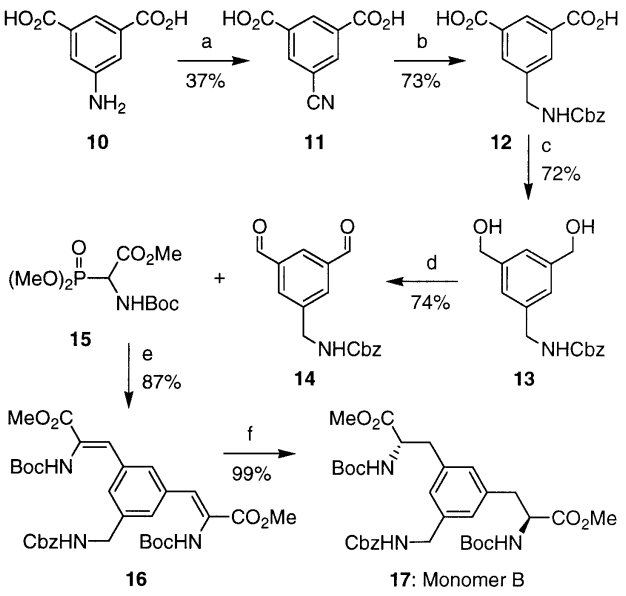
Scheme 1. Deprotection of the dendrimers G2A (**1a**) and G2B (**1b**)



Scheme 2. Reagents and conditions: (a) ICl, HCl (1 N), 18 h; (b) H_2SO_4, $NaNO_2$, EtOH, reflux, 1 h; (c) NaOH (2 N), reflux, 3 h, then HCl; (d) $KHCO_3$, BnBr, DMF, 60 °C, 2 h; (e) H_2C=C(NHBoc)CO_2Me, $Pd(OAc)_2$, $NaHCO_3$, Bu_4NCl, DMF, 80 °C, 8 h; (f) {Rh[(*S*,*S*)-Et-DuPHOS](COD)}OTf, H_2 (40 psi), MeOH, 6 h

tisation-reduction failed when benzyl alcohol was used instead of ethanol, because of extensive polymerisation of the former. It should be noted that a small amount, approximately 10−15%, of a by-product was formed in the diazotisation-reduction step, and this by-product could not be separated from **5**. The mixture was carried through to compound **7**, which fortunately could be obtained pure by recrystallisation. The identity of the by-product has not been firmly established, but it is probably an ethyl aryl ether formed from nucleophilic attack of ethoxide instead of hydride on the intermediate diazonium ion formed from **4**. It is known that such by-products can form in this type of reaction.[16] A double Heck coupling with methyl 2-[(*tert*-butoxycarbonyl)amino]acrylate[17] yielded the bis(didehydroamino acid) **8**, which could be asymmetrically hydrogenated to monomer A (**9**) in quantitative yield and with >98% *ee* and >99:1 *dr*, as analysed by ^{1}H NMR and chiral stationary phase HPLC. The hydrogenation catalyst employed here was a Rh^I-(*S*,*S*)-Et-DuPHOS (Et-DuPHOS = 1,2-bis(diethylphospholano)benzene, TFFH = *N*,*N*,*N*′,*N*′-tetramethyl-2-fluoroformamidinium hexafluorophosphate, DIEA = *N*,*N*-Diisopropylethylamine) complex known to produce amino acids of the (*S*) configuration with very high stereoselectivity.[18]

Monomer B (**17**) was synthesised in six steps starting from inexpensive 5-aminoisophthalic acid **10**, see Scheme 3. A Sandmeyer cyanation to **11**,[19] followed by reduction of the nitrile and protection of the resulting amine afforded **12**. Further reduction of the acid groups to the hydroxymethyl stage with BH_3·THF gave diol **13**, which was oxidised with PCC to dialdehyde **14**. All attempts to directly reduce both the acids and the nitrile functions of **11** failed, although a variety of reagents, such as BH_3·DMS, $LiAlH_4$ and sodium bis(methoxyethoxy)aluminium hydride, were tried. A possible explanation for this failure is the insolubility of the intermediate metal alkoxyamide that probably forms from **11** upon such reduction. Dialdehyde **14** was then coupled with phosphonate **15**[20] in a HWE olefination[20–22] and the resulting bis(didehydroamino acid) derivative was subjected to catalytic asymmetric hydrogenation as described for monomer A. This furnished monomer B (**17**) in quantitative yield and high stereoselectivity (*ee* >98%, *dr* >99:1).



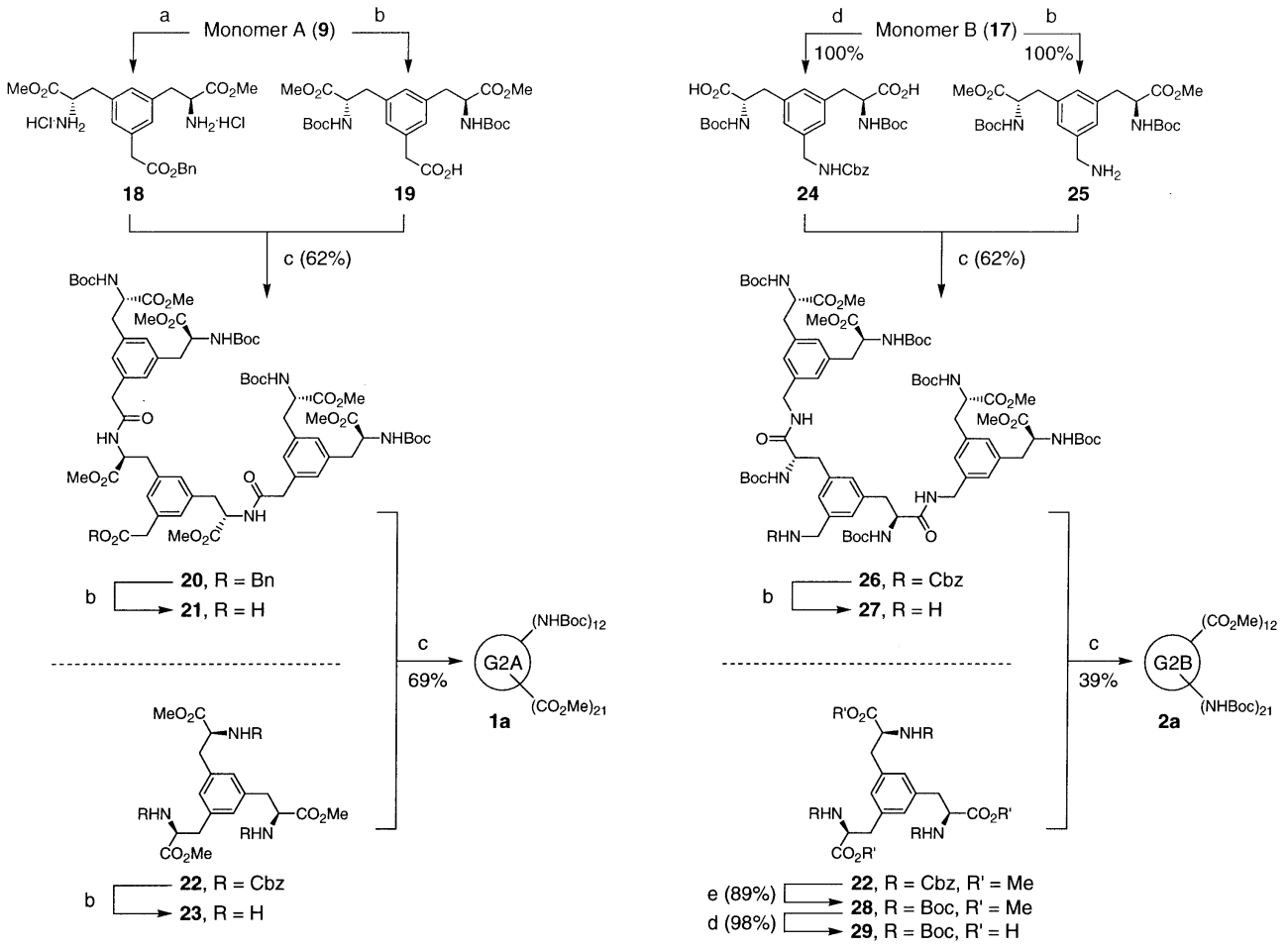
Scheme 3. Reagents and conditions: (a) 1. HCl, $NaNO_2$, 0 °C; 2. NaCN, CuCN, reflux, 40 min; (b) 1. Pd/C, H_2, HCl, MeOH, 24 h; 2. CbzCl, NaOH (2 N), 3 h; (c) BH_3·THF, THF, 6 h; (d) PCC, CH_2Cl_2, 3 h; (e) *N*,*N*,*N*′,*N*′-tetramethylguanidine, THF, overnight; (f) {Rh[(*S*,*S*)-Et-DuPHOS](COD)}OTf, H_2 (40 psi), MeOH, 15 h

The dendrimers were then assembled in a convergent, or outside-in, fashion, see Scheme 4. Deprotection of the appropriate groups of monomer A (**9**) yielded **18** and **19**. These derivatives were not isolated, but were subjected to coupling by means of TFFH.[23] This peptide coupling reagent was chosen because of its high reactivity, small size, and low tendency to cause epimerisation of the C-terminal residue which it activates by converting the carboxylic acid to an acyl fluoride. To ensure complete coupling, a double acylation of **18** with TFFH-activated **19** (2+2 equiv.) had to be carried out. This provided the dendritic wedge **20** in 62% yield. Hydrogenolytic removal of the focal-point protecting group yielded carboxylic acid **21**, while deprotection of the core phenyltrisalanine derivative **22**[24] gave triamine **23**. Coupling of **21** and **23** in a 4.5:1 ratio, without prior isolation of these fragments, finally furnished G2A dendrimer **1a** in 69% yield. The product could be purified by standard flash chromatography, or alternatively, using preparative size-exclusion chromatography on a BioBeads SX-1 cross-linked polystyrene stationary phase eluted with $CHCl_3$. The dendrimer **1a** was soluble in $CHCl_3$, sparingly soluble in THF, but insoluble in lower alcohols and most other solvents of medium and low polarity. Complete characterisation using ^1H and ^{13}C NMR, MALDI MS, and elemental analysis was possible. The NMR spectra had to be recorded at elevated temperature in [D_6]DMSO to avoid line broadening caused by the restricted rotations around the many amide and carbamate C–N bonds.

Dendrimer G2B was assembled analogously. Deprotection of monomer B (**16**) yielded derivatives **24** and **25**, which could be coupled in a 1:2.2 ratio to provide dendritic wedge **26** in 62% yield. A small amount of epimerisation of monomer B, approximately 2–3% per stereocentre, was detected after the basic hydrolysis of the methyl esters, despite the mild conditions employed (LiOH, water/THF 1:1 at 0 °C). This was deemed acceptable at this stage since the prospect of separating the diastereomers by chromatography was small owing to the very close similarity of the diastereomers. Deprotection of the focal-point amine gave wedge **27**, which was coupled in a 4:1 ratio with phenyltrisalanine derivative **29**, obtained from **22** by protecting group manipulations via **28**. The coupling furnished G2B in 39% yield after standard flash chromatography, again completely characterised by NMR spectroscopy, MALDI MS and elemental analysis.

We also synthesised the corresponding dendrimers of the first generation, G1A (**31**) and G1B (**32**), see Figure 1 (synthesis not shown). Using the same methodology as for the G2 dendrimers, **19** and **23** were coupled in a 4:1 ratio using TFFH to yield G1A (**31**). Similarly, **25** and **29** were coupled to yield G1B (**32**). Furthermore, we were interested in the possibility to selectively functionalise each layer of a dendrimer. In this case, different protecting groups must be installed in different layers. To demonstrate this concept, we synthesised the dendrimer **33**. This molecule can be selectively deprotected to reveal amines either in the interior or on the end groups, in addition to the carboxylic acids on the end groups. Dendrimer **33** was synthesised analogously to **32**, using a phenyltrisalanine derivative **30** (not shown) which carried Cbz groups instead of Boc groups but was otherwise identical to **29**.

To reveal the amines and carboxylic acids, the dendrimers were deprotected using the appropriate standard reagents (see Scheme 1). For the removal of the Boc groups, the dendrimers were treated with a 1:1 mixture of $CHCl_3$ and TFA for 30 min, followed by evaporation and washing with diethyl ether. For hydrolysis of the methyl esters, 0.5 M LiOH in water/THF 1:1 at 0 °C was used. In this way, we obtained all-carboxylic acid derivatives **1b** and **2c**, all-amine derivatives **1c** and **2b**, and mixed carboxylic acid/amine derivatives



Scheme 4. Reagents and conditions: (a) HCl (3 N in EtOAC), 30 min; (b) Pd/C, H_2; (c) TFFH, DIEA, DMF, 1−2 h; (d) LiOH (0.5 N in water/THF 1:1), 0 °C, 2 h; (e) 1. Pd/C, H_2, EtOH/EtOAc 1:1, 4 h; 2. Boc_2O, Et_3N, CH_2Cl_2, 2 h

1d and **2d**. It is worth noting that derivatives **1b** and **2b** carry complementary charges at neutral pH, as does **1c** and **2c**. All the deprotected derivatives could be characterised by ^1H NMR in 90:10 H_2O/D_2O and by ESI MS. Substantial line-broadening was observed in the ^1H NMR spectrum of dendrimers **1b** and **2c**, which still carried Boc groups, even at +50 °C. The other deprotected dendrimers gave sharp spectra at +25 °C. Very clean ESI mass spectra were obtained after deconvolution, and the dendrimers typically carried 3−6 charges per molecule. In contrast, MALDI-TOF mass spectra recorded using α-cyano-4-hydroxycinnamic acid or 2,5-dihydroxybenzoic acid as the matrix were very cluttered with many peaks, none of which corresponded to the dendrimer mass.

Chiroptical Study

Chiroptical properties, i.e. circular dichroism and optical rotation, are useful parameters for the determination of the gross solution structure of chiral dendrimers. If there is an additive relationship between the chiroptical parameters for the individual monomers and the whole dendritic structure, it can be inferred that the conformational equilibrium of the monomers is unperturbed in the dendrimer.[25] No chiral conformations or other organisation of the overall dendritic structure are then assumed to exist. Conversely, if there are deviations from this additivity, packing effects may be operative, and the monomer subunits of the dendrimer may exist in different conformations than the free monomers. One example has been reported by Meijer et al., where amino acid coated dendrimers showed decreasing optical rotation with increasing generation number.[26] In that study, packing effects could explain the trend, and in control experiments, where spacers were introduced between the amino acids and the dendrimer, the optical activity was restored owing to increased flexibility. However, the deviation from additivity can also be explained by constitutional differences, because the monomers are in different local environments in different parts of the dendrimer. A thorough investigation of such a case has been published by McGrath et al.[25]

Because of the structural similarity between monomers **9** and **17** and phenylalanine, it was appropriate at this point to consider the chiroptical properties of the latter substance. A detailed study of the circular dichroism of several phenylalanine derivatives has been reported by Smith.[27] From this investigation, it is known that phenylalanine derivatives exist mainly as two conformers, **35a** and **35b** (see Figure 2), with Cotton effects (CEs) of opposite sign in the

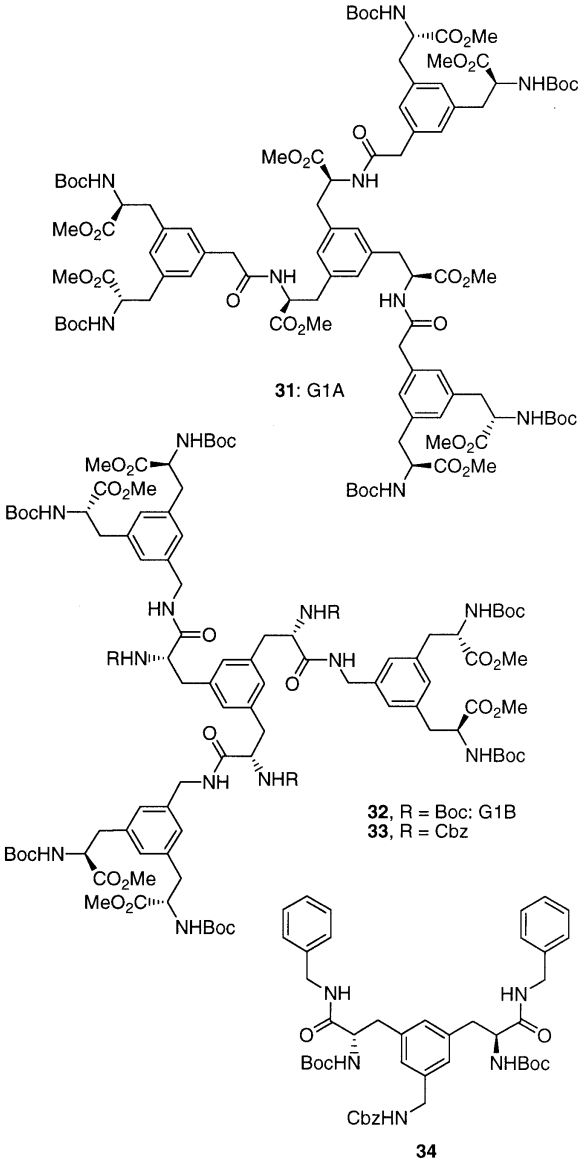


Figure 1. First generation dendrimers and model compound **34**

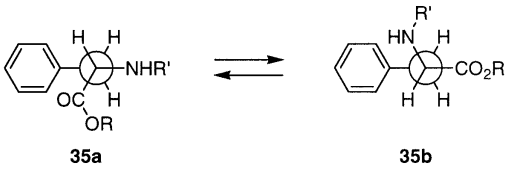


Figure 2. The dominant solution conformations of phenylalanine derivatives

240−270 nm region. Because of the large difference in the CD spectra of **35a** and **35b**, CD is a sensitive probe for measuring rotations around the $C_\alpha-C_\beta$ bond of phenylalanine derivatives.

The CD spectra of monomers A (**9**) and B (**17**) recorded in THF are shown in Figure 3. They are similar to those of phenylalanine derivatives,[26,27] but with larger molar ellipticities and less fine structure, and the CEs are bathochromically shifted approximately 7−8 nm. On the basis of this similarity, and the sensitivity of the CD spectra of phenylalanines as a measure of their conformation,[26,27] we assume that significant perturbations of the conformational equilibrium of our monomers will show as changes in the CD spectra. Since the dendrimers presented here are of low generation number, we did not expect to see steric packing effects, but hydrogen-bonding networks could potentially distort the dendritic structures, causing them to fold on themselves, and this would be expected to alter the CD spectra. To detect such effects, we recorded the CD spectra of the dendritic wedges **20** and **26**, along with those of the protected dendrimers G1A (**31**), G1B (**32**), G2A (**1a**), and G2B (**2a**). We then compared these spectra with corresponding sums of the CD spectra of monomers A (**9**) and B (**17**) and core phenyltrisalanine units **22** and **28**, following the precedent of Rosini et al.[28] All of the CD spectra were recorded in THF, and several were recorded in acetonitrile as well, but only very small solvent effects were seen.

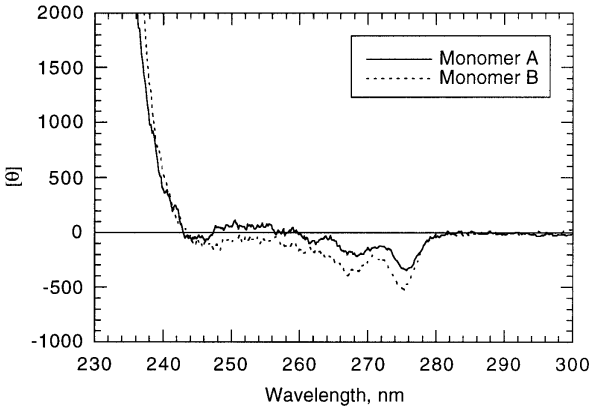


Figure 3. The CD spectra of monomers A and B

First we compared the CD spectrum of the dendritic wedge **20** with that of monomer A (**9**) multiplied by three, since three units of monomer A make up the wedge **20**. A good agreement between the two spectra was found (see Figure 4), but a slight negative CE at 245 nm was present in monomer A but absent in **20**. This small difference is most readily explained by constitutional differences, e.g. the replacement of carbamates with amides in one of the focal units of monomer A in compound **20**. The remaining CEs

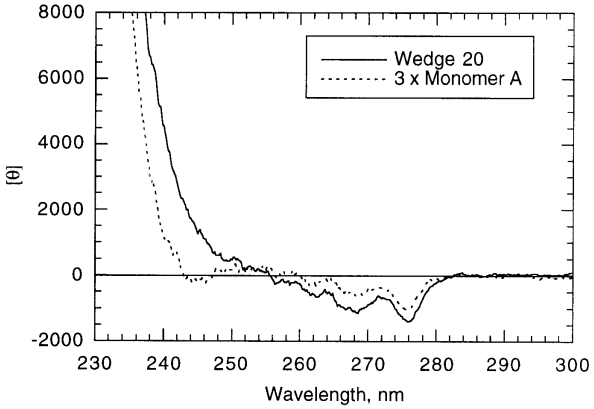


Figure 4. The CD spectrum of dendritic wedge **20** compared with that of monomer A (multiplied by three)

in the 250−280 nm region are of the same sign and of similar magnitude for both systems.

When a similar comparison was made for the B series compounds, the results were slightly different. The spectrum of dendritic wedge **26** displays a large negative CE at 244 nm, but this was absent in the spectrum of monomer B

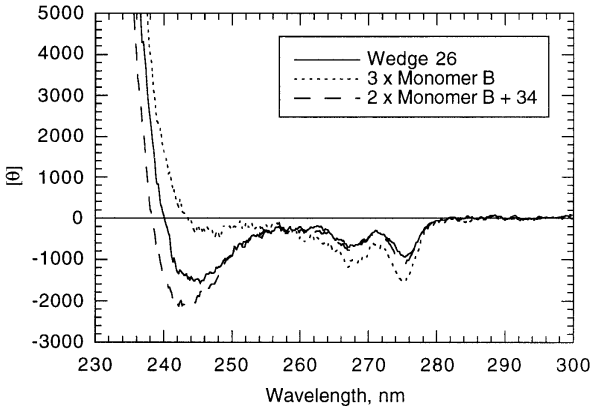


Figure 5. The CD spectrum of dendritic wedge **26** compared with those of monomer B (multiplied by three) and the sum of the CD spectra of monomer B (multiplied by two) and **34**

(**17**), again multiplied by three (see Figure 5). Since the CEs in the 260−280 nm region were similar in **26** and **17**, we suspected that constitutional effects, either through electronic or conformational mechanisms, could explain the discrepancy. To investigate this hypothesis, we synthesised compound **34** (see Figure 1), as a model compound for the focal-point monomer B in the wedge **26**. The CD spectrum of **26** does indeed display a large negative CE at 240 nm, and furthermore, the CEs at longer wavelengths are attenuated relative to those of monomer B. When the sum of two CD spectra of monomer B and the CD spectrum of **34** was compared with the CD spectrum of the wedge **26**, the agreement was very good. This result confirms that the discrepancy above stems from constitutional effects, rather than from packing effects or from hydrogen-bonding networks that perturb the conformational equilibrium of monomer B in the dendritic wedge **26**.

Next, we compared the CD spectrum of G2A (**1a**) with a predicted spectrum, calculated as the sum of the CD spectrum of **23** and three times the CD spectrum of **20** (see Figure 6). An excellent agreement between the observed and predicted spectra was found. These results indicate that only minor changes in conformations exist between monomer A and the monomer A subunits of G2A. This suggests that dendrimer G2A adopts a spread-out, flat shape in solution, with little or no steric packing of monomers. Similar results were obtained for the B series dendritic wedge **26** and dendrimer G2B (**2b**).

The optical rotation for the monomers, dendritic wedges, and dendrimers in this study are summarised in Table 1. Molar rotations divided by the number of stereogenic centres appear to decrease with increasing size of the dendritic structures, different from the additivity observed for CD spectra. The reason for this difference is not clear, but can probably be traced to constitutional differences. It is

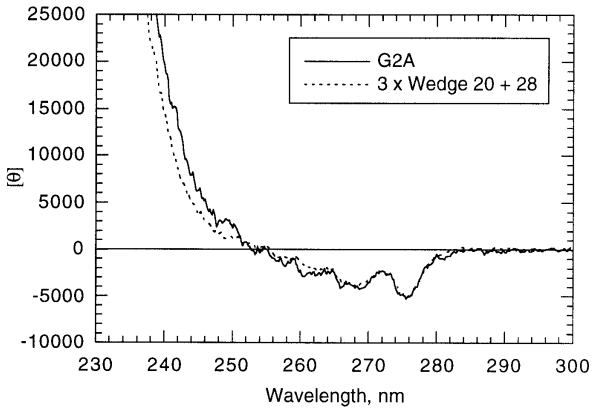


Figure 6. The CD spectrum of dendrimer G2A (**1a**) compared with the sum of the CD spectra of wedge **20** (multiplied by three) and phenyltrisalanine derivative **28**

Table 1. Optical rotations of the monomers and dendritic compounds

Compound	$[\alpha]_D$	$[\Phi]_D \times 10^{-2}$	$[\Phi]_D \times 10^{-2}$ per stereocentre
Monomer A (**9**)	52	3.3	1.64
Monomer B (**17**)	46	3.0	1.48
Wedge A (**20**)	43	6.3	1.05
Wedge B (**26**)	40	6.4	1.07
22	62	4.9	1.62
28	62	4.2	1.41
34	9	0.7	0.4
G2A (**1a**)	39	17.4	0.83
G2B (**2a**)	34	16.9	0.68

noteworthy that compound **34** possesses an abnormally low molar rotation relative to the other derivatives. This observation may correlate with the very weak CEs above 250 nm observed for this substance. Furthermore, optical rotations were recorded in $CHCl_3$ at concentrations of 10 mg/mL, while CD spectra were recorded in THF at 0.2−1 mg/mL. The solubility of the dendrimers in THF was too low to allow optical rotation measurements, while $CHCl_3$ absorbs too strongly below 250 nm to allow for recordings of CD spectra with the instrument available to us. As pointed out by a referee it is possible that the dendrimers form aggregates in nonpolar solutions, although no definite signs of such phenomena were seen. The line broadening observed by NMR spectroscopy is to a large extent certainly due to slow rotation of the amide and/or carbamate bonds and cannot be taken as clear evidence of aggregation. This question has to be investigated separately.

Conclusion

Chiral, ionic dendrimers up to the second generation have been prepared. Two types, complementary with respect to the charges carried at neutral pH, have been synthesised by a convergent strategy from aromatic bis- and tris(amino acids). The protected dendrimers are soluble in organic solvents, and a detailed chiroptical study indicates that they have flat, decongested overall shapes in THF solution. Ap-

plications in the fields of catalysis and molecular or ionic recognition are foreseen, and work in this area is in progress in our laboratory.

Experimental Section

General Remarks: NMR spectra were recorded on Bruker DRX400 or ARX300 NMR spectrometers in $CDCl_3$ at ambient temperature, unless otherwise noted. For the deprotected dendrimers **1b**−**d** and **2b**−**d**, NMR spectra were recorded in H_2O/D_2O 9:1 with a CW solvent presaturation pulse sequence. − MALDI-TOF mass spectra were recorded on a Bruker BIFLEX III instrument using 2,5-dihydroxybenzoic acid as the matrix. ESI mass spectra were recorded on a Micromass QuattroII tandem quadrupole mass spectrometer equipped with a pneumatically assisted electrospray source. The capillary voltage was 2.9 kV, the source temperature was 80 °C, and nitrogen was used as drying and nebulising gas. Samples were introduced by loop injections using acetonitrile/water 1:1. − CD spectra were recorded in THF at a concentration of 0.2−1 mg/mL on a Jasco J-500A spectropolarimeter. The molar ellipticity [θ] is given in degrees cm^{-2} $decimol^{-1}$ in Figure 3−6. − Optical rotations were measured on a Perkin−Elmer 241 polarimeter. − The Rh{[(*S*,*S*)-Et-DuPHOS](COD)}OTf catalyst was prepared[18] from (*S*,*S*)-Et-DuPHOS ligand and Rh[$(COD)_2$]OTf, both commercially available from Strem Chemicals. 5-Cyanoisophthalic acid **11**,[19] methyl 2-[(*tert*-butoxycarbonyl)amino]acrylate,[17] phosphonate **15**,[20] and phenyltrisalanine derivative **22**[24] were prepared by literature methods. We were unable to reproduce the reported yield (61.5%) of **11**. In our hands, the literature procedure afforded this compound in 37% yield. Flash chromatography was performed on Matrex (35−70 μm) silica gel using the indicated eluent.

4-Amino-3,5-diiodophenylacetic Acid (4): The procedure was adapted from the one reported by Barnett et al.[15] To a vigorously stirred solution of 4-aminophenylacetic acid (3.0 g, 20 mmol) in HCl (1 N, 60 mL) was added ICl (2.0 mL, 40 mmol). A brown suspension formed immediately, and the mixture was stirred for 18 h at room temp. after which the precipitate was collected by filtration. It was washed with water and recrystallised from a large volume of boiling acetone without prior drying. Two crops of light-brown crystals of 4-amino-3,5-diiodophenylacetic acid (5.2 g, 13 mmol, 65%) were obtained. M.p. 219−221 °C (dec). − ^{1}H NMR ([D_6]DMSO): δ = 3.39 (s, 2 H), 5.01 (s, 2 H), 7.53 (s, 2 H), 12.32 (s, 1 H). − ^{13}C NMR: δ = 37.98, 81.37, 127.25, 139.94, 145.64, 172.76. − HRMS (FAB+); *m*/*z* calcd. for $C_8H_7I_2NO_2$ (M) 402.8566; found 402.8574.

Ethyl 3,5-Diiodophenylacetate (5): The amine **4** (19.6 g, 48.6 mmol) was suspended in absolute ethanol (1.0 L), conc. H_2SO_4 (25 mL) was added, and the mixture was brought to reflux. Solid $NaNO_2$ was added in small portions (***Caution!*** Nitrogen evolution!) and the mixture was heated at reflux for 1 h. It was then cooled and most of the solvent was evaporated. The residue was neutralised with saturated $NaHCO_3$ (1 L) and extracted with diethyl ether (2 × 500 mL). The extracts were dried over $MgSO_4$, the solvent was evaporated and the residue was purified by flash chromatography (heptane/EtOAc, 9:1). The ester **5** was obtained as a pale yellow oil (14.4 g, 34.6 mmol, 71%), which was contaminated with *ca* 10% of a compound which is probably ethyl 3,5-diiodo-4-ethoxyphenyl acetate. − ^{1}H NMR: δ = 1.27 (t, *J* = 7.1 Hz, 3 H), 3.50 (s, 2 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 7.61 (d, *J* = 1.5 Hz, 2 H), 7.97 (t, *J* = 1.5 Hz, 1 H). − ^{13}C NMR: δ = 14.36, 40.36, 61.50, 94.94, 137.82, 138.11, 144.07, 170.53. − HRMS (FAB^+); *m*/*z* calcd. for $C_{10}H_{11}I_2O_2$ (M + H) 416.8849; found 416.8854.

3,5-Diiodophenylacetic Acid (6): The ethyl ester **5** (14.4 g, 34.6 mmol) was heated at reflux with NaOH (2 N, 650 mL) until a clear solution was obtained (ca. 3 h). The solution was cooled and diluted with water to dissolve a precipitate which appeared on cooling, and was then washed with diethyl ether (500 mL). The acid **6** was obtained as white crystals (12.8 g, 33.0 mmol, 95%) by acidification of the aqueous solution with HCl, followed by filtration, washing with water, and air-drying overnight. The crude product was contaminated with 10−15% of an impurity, probably of the same origin as that in the starting material (see the procedure for **5**). M.p. 193−196 °C (dec). − ^{1}H NMR ($CDCl_3$−[D_6]DMSO mixture): δ = 3.35 (s, 2 H), 7.49 (s, 2 H), 7.80 (s, 1 H). − ^{13}C NMR: δ = 40.04, 94.55, 137.58, 138.50, 143.36, 172.21. − HRMS (FAB^+); *m*/*z* calcd. for $C_8H_6I_2O_2$ (M) 387.8457; found 387.8454.

Benzyl 3,5-Diiodophenylacetate (7): The acid **6** (0.91 g, 2.3 mmol) and $KHCO_3$ (0.26 g, 2.6 mmol) were dissolved in water by gentle heating. The water was removed by evaporation, and the solid residue was suspended in DMF (30 mL). Benzyl bromide (0.31 mL, 2.6 mmol) was then added, and the mixture was stirred at +60 °C for 2 h. Most of the solvent was then evaporated, and the residue was partitioned between EtOAc (50 mL) and water (50 mL). The organic layer was washed with saturated $NaHCO_3$ (50 mL) and water (50 mL) and was dried over $MgSO_4$. The solvent was evaporated and the residue, a white solid, was recrystallised from heptane/EtOAc 10:1 (ca. 5 mL) after which benzyl ester **7** was obtained as white crystals (0.65 g, 1.4 mmol, 58%). Less than 5% of the impurity in the starting material (see the procedure for **6** above) remained, as judged from ^{1}H NMR. M.p. 91−92 °C. − ^{1}H NMR: δ = 3.56 (s, 2 H), 5.15 (s, 2 H), 7.32−7.40 (m, 5 H), 7.60−7.62 (m, 2 H), 7.97 (t, *J* = 1.5 Hz). − ^{13}C NMR: δ = 40.29, 67.24, 94.96, 128.47, 128.66, 128.88, 135.63, 137.82, 137.84, 144.14, 170.31. − HRMS (EI^+); *m*/*z* calcd. for $C_{15}H_{12}I_2O_2$ (M) 477.8927; found 477.8923.

Dimethyl 2,2′-Bis(*tert*-butyloxycarbonylamino)-3,3′-[(5-benzyloxycarbonylmethyl)-1,3-phenylene]bis(propenoate) (8): A mixture of diiodide **7** (4.5 g, 9.4 mmol), methyl 2-[(*tert*-butoxycarbonyl)amino]acrylate[17] (4.7 g, 24 mmol), $Pd(OAc)_2$ (0.21 g, 0.94 mmol), $NaHCO_3$ (4.0 g, 47 mmol), and Bu_4NCl (5.2 g, 19 mmol) in DMF (100 mL) was deoxygenated by N_2 bubbling for 5 min. The mixture was stirred and heated at 80 °C under N_2 in a sealed tube for 8 h. After this time, it was cooled and most of the solvent was evaporated. The dark brown residue was diluted with EtOAc (200 mL) and washed with half-saturated brine (4 × 200 mL). The organic phase was dried over Na_2SO_4, the solvent was evaporated, and the residue was purified by flash chromatography (heptane/EtOAc, 3:2). Further purification by recrystallisation from heptane/EtOAc was necessary to give the bis(didehydroamino acid) derivative **8** as white crystals (3.2 g, 5.1 mmol, 54%). M.p. 123−125 °C. − ^{1}H NMR: δ = 1.39 (s, 18 H), 3.65 (s, 2 H), 3.87 (s, 6 H), 5.14 (s, 2 H), 6.23 (br s, 2 H), 7.20 (s, 2 H), 7.32−7.37 (m, 5 H), 7.41 (s, 2 H), 7.59 (s, 1 H). − ^{13}C NMR: δ = 28.29, 41.23, 52.93, 67.00, 81.37, 125.31, 128.54, 128.56, 128.81, 128.98, 130.12, 131.19, 134.46, 134.92, 135.88, 152.72, 166.09, 170.89. − HRMS (FAB+); *m*/*z* calcd. for $C_{33}H_{41}N_2O_{10}$ (M + H) 625.2761; found 625.2755.

Dimethyl 2,2′-Bis(*tert*-butyloxycarbonylamino)-3,3′-[(5-benzyloxycarbonylmethyl)-1,3-phenylene]bis(propanoate) (Monomer A) (9): Compound **8** (0.50 g, 0.80 mmol) was dissolved in absolute methanol (10 mL), and the solution was deoxygenated by N_2 bubbling for 30 min. To this solution was added Rh{[(*S*,*S*)-Et-

DuPHOS](COD)}OTf (5 mg), and the resulting yellow solution was hydrogenated for 6 h at 40 psi H_2. After this, the solvent was removed by evaporation and the residue was dissolved in EtOAc and passed through a short plug of silica to remove the catalyst. After evaporation of the solvent, monomer A (**9**) was obtained as a clear, colourless to pale-yellow syrup (0.52 g, >100%) that did not crystallize. A small amount of EtOAc (ca. 5% by weight according to ^{1}H NMR) was retained even after prolonged evaporation, hence the yield was greater than theory. A racemic, 1:1 diastereomeric mixture of monomer A was similarly obtained by using dppe as the ligand in the hydrogenation. HPLC on a 4.6 × 250 mm chiral (*R*,*R*)-Whelk-O1 column (Merck) eluted with *n*-hexane/2-propanol 85:15 produced two peaks (R_t = 19.4 and 21.2 min) with a 1:3 ratio for the racemically hydrogenated monomer A. The bigger peak must correspond to the *meso* form co-eluted with one of the enantiomers, while the smaller peak must correspond to the other enantiomer, since we have previously shown that each arm is hydrogenated independently of the other.[29] For the enantioselectively hydrogenated monomer A, only one peak was seen (R_t = 19.2 min). This peak co-eluted with the first peak of the racemically hydrogenated monomer A. If a 1% detection limit is assumed, monomer A was obtained in >98% *ee*. From the (*S*) selectivity of the catalyst,[18] the absolute configuration of monomer A was assigned as (*S*,*S*). The diastereomeric purity was best measured by ^{1}H NMR. In the racemically hydrogenated product, two peaks with a 1:1 ratio were seen at δ = 6.81 and 6.83. In the enantioselectively hydrogenated sample, only the peak at δ = 6.81 was seen, and no trace of the other peak at δ = 6.83 could be detected. If a 1% detection limit is again assumed, monomer A was obtained with a *dr* of >99:1. − $[\alpha]_D^{22}$ = +52 (*c* = 1.0, $CHCl_3$). − ^{1}H NMR: δ = 1.43 (s, 18 H), 3.01−3.05 (m, 4 H), 3.60 (s, 2 H), 3.69 (s, 6 H), 4.53−4.57 (m, 2 H), 5.00 (br d, *J* = 7.9 Hz, 2 H), 5.13 (s, 2 H), 6.81 (s, 1 H), 6.93 (s, 2 H), 7.31−7.37 (m, 5 H). − ^{13}C NMR: δ = 28.49, 38.26, 41.26, 52.46, 54.60, 66.88, 80.20, 128.45, 128.51, 128.78, 129.17, 129.50, 134.58, 135.96, 136.81, 155.26, 171.26, 172.37. − HRMS (FAB$^+$); *m*/*z* calcd. for $C_{33}H_{45}N_2O_{10}$ (M + H) 629.3074; found 629.3074.

5-[(Benzyloxycarbonyl)aminomethyl]isophthalic Acid (12): To a solution of 5-cyanoisophthalic acid (**11**)[19] (9.6 g, 50 mmol) in absolute ethanol (250 mL) was added conc. HCl (5.0 mL, 60 mmol) and Pd/C (10%, 1.0 g). The mixture was hydrogenated at atmospheric pressure for 24 h, after which a white precipitate formed. The precipitate was dissolved by dilution of the reaction mixture with water (250 mL). The catalyst was removed by filtration and the filtrate was concentrated to a volume of 100 mL, which was washed with diethyl ether (100 mL). The aqueous solution was evaporated to dryness and the residue was suspended in NaOH (2 N, 125 mL). The suspension was heated at reflux for 2 h and was then allowed to cool. It was washed with diethyl ether (100 mL) and EtOAc (100 mL), and partly evaporated to remove traces of the organic solvents. Benzyl chloroformate (7.1 mL, 50 mmol) was added and the mixture was stirred vigorously at room temp. After 1.5 h, the mixture had reached pH 6, and additional NaOH (2 N, 25 mL) and benzyl chloroformate (2 mL) were added. Stirring was continued for another 1.5 h and the reaction mixture was then washed with diethyl ether. It was evaporated briefly to remove dissolved diethyl ether, and was then acidified with conc. HCl to pH 1. The white precipitate that formed was filtered and dried over P_2O_5 in vacuo overnight to yield the diacid **12** as a white powder (12.1 g, 37 mmol, 73%). M.p. 245−247 °C (dec). − ^{1}H NMR ([D$_6$]DMSO): δ = 4.33 (d, *J* = 6.2 Hz, 2 H), 5.06 (s, 2 H), 7.29−7.39 (m, 5 H), 8.00 (t, *J* = 6.2 Hz, 1 H), 8.08 (s, 2 H), 8.36 (s, 1 H). − ^{13}C NMR: δ = 43.34, 65.53, 127.71, 127.87, 128.45, 128.65, 131.40, 132.02, 137.16, 141.24, 156.50, 166.64. − HRMS (EI$^+$); *m*/*z* calcd. for $C_{17}H_{15}NO_6$ (M) 329.0899; found 329.0896.

1,1′-{[(5-Benzyloxycarbonylamino)methyl]-1,3-phenylene}bis(methanol) (13): A solution of BH_3·THF (0.93 M, 64 mL, 60 mmol) was added dropwise to a stirred suspension of diacid **12** (7.6 g, 23 mmol) in dry THF (15 mL) at 0 °C. (***Caution!*** Hydrogen gas was evolved and the reaction was highly exothermic.) A thick, white precipitate formed, and hence the reaction mixture was diluted with THF (10 mL) to ensure efficient stirring. The mixture was stirred at room temp. for 6 h and the reaction was then quenched by careful addition of water/THF, 1:1 (15 mL). The water phase was saturated with K_2CO_3 (ca. 15 g) and the THF layer was separated. The aqueous layer was extracted with THF (3 × 25 mL) and the combined organic layers were dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by flash chromatography (neat EtOAc + MeOH as needed) after which the diol **13** was obtained as white crystals (5.0 g, 16 mmol, 72%). M.p. 112−114 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 4.19 (d, *J* = 6.3 Hz, 2 H), 4.70 (d, *J* = 5.6 Hz, 4 H), 5.05 (s, 1 H), 5.18 (t, *J* = 5.6 Hz, 2 H), 7.08 (s, 2 H), 7.14 (s, 1 H), 7.30−7.38 (m, 5 H), 7.83 (t, *J* = 6.2 Hz, 1 H). − ^{13}C NMR: δ = 43.93, 62.94, 65.35, 123.11, 123.49, 127.74, 127.82, 128.40, 137.26, 139.37, 142.36, 156.40. − HRMS (EI$^+$); *m*/*z* calcd. for $C_{17}H_{19}NO_4$ (M) 301.1314; found 301.1296.

5-[(Benzyloxycarbonylamino)methyl]isophthalaldehyde (14): Celite (13 g) and PCC (13 g, 60 mmol) were added to diol **13** (6.0 g, 20 mmol) suspended in CH_2Cl_2 (150 mL). The mixture was stirred for 3 h at room temp. and was then filtered. The filter cake was washed thoroughly with acetone (100 mL) and the combined filtrates were evaporated to dryness. The residue was partitioned between EtOAc (250 mL) and HCl (1 N, 250 mL), and the organic phase was washed with HCl (1 N, 250 mL) and saturated $NaHCO_3$ (2 × 250 mL), and was then dried over Na_2SO_4. The solvent was evaporated and the residue was purified by flash chromatography (heptane/EtOAc, 1:1) to give dialdehyde **14** (4.4 g, 15 mmol, 74%) as a clear oil, which crystallised in the refrigerator. M.p. 80−82 °C. − ^{1}H NMR: δ = 4.53 (d, *J* = 6.0 Hz, 2 H), 5.14 (s, 2 H), 5.51 (br s, 1 H), 7.30−7.40 (m, 5 H), 8.07 (s, 2 H), 8.26 (s, 1 H), 10.07 (s, 2 H). − ^{13}C NMR: δ = 44.33, 67.41, 128.38, 128.52, 128.77, 130.24, 133.40, 136.29, 137.48, 141.60, 156.74, 191.10. − HRMS (EI$^+$); *m*/*z* calcd. for $C_{17}H_{15}NO_4$ (M) 297.1001; found 297.0997.

Dimethyl 2,2′-Bis(*tert*-butyloxycarbonylamino)-3,3′-{[(5-benzyloxycarbonylamino)methyl]-1,3-phenylene}bis(propenoate) (16): Dialdehyde **14** (3.56 g, 12.0 mmol) and phosphonate **15**[20] (7.85 g, 26.4 mmol) were dissolved in dry THF (60 mL) followed by the addition of *N*,*N*,*N*′,*N*′-tetramethylguanidine (3.31 mL, 26.4 mmol). During the addition, the reaction flask was placed in a cold water bath since some heat was evolved. The resulting solution was stirred at room temp. overnight, and the solvent was then evaporated. The residue was dissolved in EtOAc (100 mL) and the solution was washed with half-saturated brine (2 × 100 mL) and was then dried over Na_2SO_4. Most of the solvent was removed by evaporation, and the residue was purified by flash chromatography (heptane/EtOAc, 1:2). It was advantageous not to evaporate the solvent completely before application to the column, because the crude product was sparsely soluble in the eluent. After chromatography, the product was recrystallised from EtOAc/heptane to yield pure **16** (6.67 g, 10.4 mmol, 87%) as white crystals. M.p. 136−138 °C. − ^{1}H NMR: δ = 1.39 (s, 18 H), 3.86 (s, 6 H), 4.36 (d, *J* = 5.9 Hz, 2 H), 5.11 (br s, 1 H), 5.14 (s, 2 H), 6.34 (br s, 2 H), 7.20 (s, 2 H), 7.31−7.39 (m, 7 H), 7.59 (s, 1 H). − ^{13}C NMR: δ = 28.28, 45.10, 52.93, 67.16, 81.36, 125.21, 128.38, 128.72, 128.87, 129.34, 130.37, 135.05, 136.59, 138.97, 152.64, 156.56, 166.05. −

HRMS (FAB$^+$); *m/z* calcd. for $C_{33}H_{42}N_3O_{10}$ (M + H) 640.2870; found 640.2868.

Dimethyl 2,2′-Bis(*tert*-butyloxycarbonylamino)-3,3′-{[(5-benzyloxycarbonylamino)methyl]-1,3-phenylene}bis(propanoate) (Monomer B) (17): Bis(didehydroamino acid) **16** (2.00 g, 3.13 mmol) was dissolved in absolute methanol (40 mL), and the solution was deoxygenated by N_2 bubbling for 30 min. To this solution was added Rh{[(*S*,*S*)-Et-DuPHOS](COD)}OTf (10 mg), and the resulting yellow solution was hydrogenated for 15 h at 40 psi H_2. After this, the solvent was removed by evaporation and the residue was dissolved in EtOAc and passed through a short plug of silica to remove the catalyst. After evaporation of the solvent a clear, colourless syrup was obtained, which was crystallised from EtOAc/heptane (refrigerator) to yield pure monomer B (1.99 g, 3.09 mmol, 99%) as white crystals. The stereochemical composition was found to be >99:1 *dr* and >98% *ee*, after analysis as for monomer A (**9**), but using a racemically hydrogenated sample of monomer B as reference. M.p. 70−75 °C. − $[\alpha]_D^{22}$ = +46 (*c* = 1.0, $CHCl_3$). − ^{1}H NMR: δ = 1.40 (s, 18 H), 2.94−3.06 (m, 4 H), 3.67 (s, 6 H), 4.30 (br d, *J* = 5.6 Hz, 2 H), 4.50−4.55 (m, 2 H), 5.04 (br d, *J* = 7.3 Hz, 2 H), 5.12 (s, 2 H), 5.21 (br s, 1 H), 6.78 (s, 1 H), 6.91 (s, 2 H), 7.29−7.36 (m, 5 H). − ^{13}C NMR: δ = 28.38, 38.15, 44.96, 52.35, 54.50, 66.93, 80.09, 127.16, 128.25, 128.62, 129.74, 136.56, 136.87, 139.10, 155.18, 156.49, 172.30. − HRMS (FAB$^+$); *m/z* calcd. for $C_{33}H_{46}N_3O_{10}$ (M + H) 644.3183; found 644.3196.

General Procedure for Amide Bond Formation Using TFFH: TFFH (1 equiv.) and DIEA (2 equiv.) were added to the carboxylic acid component dissolved in DMF (5−10 mL/g). The mixture was kept at room temp. for 5 min and then a solution of the primary amine component in DMF (5−10 mL/g) was added. (If the amine component was available as an ammonium salt, it was neutralised with DIEA prior to the addition.) The reaction was allowed to proceed for 1−2 h at room temp. whereafter the solvent was evaporated and the residue was dissolved in $CHCl_3$. The resulting solution was washed twice with 0.5% $KHSO_4$, twice with saturated Na_2CO_3, and once with brine, and was then dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by flash chromatography ($CHCl_3$/MeOH or heptane/EtOAc/acetone) to yield the coupled product.

Dendritic Wedge, Type A (20): Monomer A (**9**) (0.48 g, 0.77 mmol) was dissolved in HCl in EtOAc (3 N, prepared by bubbling HCl gas through EtOAc) and kept at room temp. for 30 min. After evaporation of the solvent, the bis(hydrochloride) **18** was obtained as a white powder which was used immediately in the coupling. Another portion of monomer A (2.0 g, 3.2 mmol) was dissolved in absolute ethanol (100 mL) and Pd/C (5%, 0.20 g) was added. The mixture was hydrogenated for 12 h and then filtered. After evaporation of the solvent, the carboxylic acid **19** was obtained as a white powder (1.57 g, 2.9 mmol, 92%) which was used without further purification. Acylation of **18** with **19** according to the general procedure above had to be performed twice to ensure complete conversion. The first coupling was performed with **19** (0.83 g, 1.5 mmol) and the second one with 0.74 g (1.4 mmol). After flash chromatography (heptane/EtOAc/acetone, 3:6:1), the wedge **20** was obtained as a white solid (0.70 g, 0.48 mmol, 62%). M.p. 97−100 °C. − $[\alpha]_D^{22}$ = +43 (*c* = 0.89, $CHCl_3$). − ^{1}H NMR (+50 °C): δ = 1.40 (s, 36 H), 2.92−3.08 (m, 12 H), 3.45 (s, 4 H), 3.56 (s, 2 H), 3.63 (s, 6 H), 3.67 (s, 12 H), 4.49 (br s, 4 H), 4.74−4.80 (m, 2 H), 5.06 (br s, 4 H), 5.13 (s, 2 H), 6.04 (d, *J* = 7.8 Hz, 2 H), 6.78 (s, 1 H), 6.83 (s, 2 H), 6.88 (s, 2 H), 6.91 (s, 4 H), 7.28−7.34 (m, 5 H). − ^{13}C NMR: δ = 28.50, 37.35, 38.55, 41.13, 43.28, 52.34, 52.39, 53.70, 54.91, 66.87, 80.14, 128.34, 128.49, 128.79, 128.98, 129.18, 129.27, 129.55, 134.55, 135.35, 136.11, 137.16, 137.33, 155.21, 170.49, 171.24, 172.00, 172.34. − HRMS (FAB$^+$); *m/z* calcd. for $C_{75}H_{100}N_6O_{24}Na$ (M + Na) 1491.6687; found 1491.6636.

Dendrimer G2A (1a): The dendritic wedge **20** (0.66 g, 0.45 mmol) was dissolved in EtOH/EtOAc (2:1, 30 mL) and Pd/C (5%, 66 mg) was added. After hydrogenation overnight at atmospheric pressure, the reaction mixture was filtered and the solvents were removed by evaporation to yield **21**, which was used immediately. Phenyltrisalanine derivative **22**[24] (78 mg, 0.10 mmol) was hydrogenated in the same way, with EtOH/EtOAc (1:1, 5 mL) as solvent and with catalyst (10 mg), to afford the triamine **23**. Coupling of **21** and **23** using the general procedure above afforded the dendrimer G2A (**1b**) as a white solid (0.31 g, 69 μmol, 69%) after flash chromatography ($CHCl_3$/MeOH, 30:1). Preparative size exclusion chromatography using a BioBeads SX-1 cross-linked polystyrene stationary phase eluted with $CHCl_3$ was found to be an alternative purification technique. A 25 × 500 mm column was used, but the capacity was low, so only 25−50 mg could be purified at a time. M.p. 98−102 °C. − $[\alpha]_D^{22}$ = +39 (*c* = 0.72, $CHCl_3$). − ^{1}H NMR ([D$_6$]DMSO, +80 °C): δ = 1.34 (s, 108 H), 2.82−2.99 (m, 42 H), 3.35−3.48 (m, 18 H), 3.53 (s, 9 H), 3.55 (s, 18 H), 3.59 (s, 36 H), 4.16−4.22 (m, 12 H), 4.45−4.51 (m, 9 H), 6.70 (m, 12 H), 6.90−6.93 (m, 30 H), 8.09 (d, *J* = 7.6 Hz, 6 H), 8.13 (d, *J* = 7.7 Hz, 3 H). − ^{13}C NMR: δ = 27.73, 36.54, 36.81, 41.29, 51.13, 53.46, 54.98, 78.12, 127.42, 127.66, 127.72, 135.42, 135.51, 136.56, 136.71, 136.81, 154.65, 169.59, 171.36, 171.88. − MS (MALDI); *m/z* calcd. for $C_{222}H_{303}N_{21}O_{75}Na$ (M + Na) 4488.9; found 4488.7. − $C_{222}H_{303}N_{21}O_{75}$: calcd. C 59.71, H 6.84, N 6.59; found C 59.55, H 7.05, N 6.6.

(2*S*, 2′*S*)-2,2′-Bis(*tert*-butyloxycarbonylamino)-3,3′-{[(5-benzyloxycarbonylamino)methyl]-1,3-phenylene}bis(propanoic Acid) (24): A pre-cooled solution (ca. 0 °C) of LiOH·H_2O (0.21 g, 5.0 mmol) in water (5 mL) was added to a solution of monomer B (**17**) (0.64 g, 1.0 mmol) in THF (5 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C. A clear solution was obtained, which was concentrated by evaporation of THF. The remaining solution was acidified with HCl (1 N, 55 mL) to pH 2 to produce a white precipitate. The entire mixture was extracted with EtOAc (2 × 25 mL), the precipitate dissolved and the organic extracts were combined and dried over Na_2SO_4. After evaporation of the solvent, the diacid **24** was obtained as a white solid (0.69 g, >100%), that retained a small amount of solvent, hence the yield was greater than theoretically expected. This material was used without further purification. M.p. 86−91 °C (dec). $[\alpha]_D^{21}$ +96 (*c* 1.0, $CHCl_3$). ^{1}H NMR:([D$_6$]DMSO, +60 °C): δ = 1.35 (s, 18 H), 2.83 (dd, J_1 = 14 Hz, J_2 = 9.4 Hz, 2 H), 2.98 (dd, J_1 = 14 Hz, J_2 = 4.9 Hz, 2 H), 4.11−4.14 (br m, 2 H), 4.17 (d, *J* = 6.0 Hz, 2 H), 5.07 (s, 2 H), 6.76 (br s, 2 H), 7.00 (s, 3 H), 7.27−7.37 (m, 5 H), 7.51 (br s, 1 H). − ^{13}C NMR: δ = 27.89, 36.44, 54.73, 65.10, 77.60, 125.66, 127.29, 127.39, 128.02, 128.14, 137.01, 137.58, 138.99, 154.97, 156.00, 173.03. − HRMS (FAB$^+$); *m/z* calcd. for $C_{31}H_{42}N_3O_{10}$ (M + H) 616.2870; found 616.2885.

To test for epimerisation, a racemic sample of monomer B was treated in the same way. Since the ^{1}H NMR:spectra of the racemate and of the optically active sample were identical, determination of *dr* was not possible. To solve this problem, the diacid samples were re-esterified using TFFH and MeOH to yield monomer B, and the esters were then analysed by ^{1}H NMR. In the optically active sample, the *dr* was found to be ca 95:5, corresponding to 2−3% epimerisation per stereocenter.

Dimethyl (2*S*,2′*S*)-2,2′-Bis(*tert*-butyloxycarbonylamino)-3,3′-[(5-aminomethyl)-1,3-phenylene]bis(propanoate) (25): Monomer B (**17**)

(1.29 g, 2.00 mmol) was dissolved in EtOH/HOAc (1:1, 20 mL), and Pd/C (10%, 0.13 g) was added. Mild acidic conditions were necessary in order to avoid cleavage of the benzylic C−N bond. The mixture was hydrogenated for 2 h and then filtered. The solvents were removed by evaporation, and the residue was dissolved in $CHCl_3$ (20 mL). The solution was washed with saturated Na_2CO_3 and was then dried over Na_2SO_4. After evaporation of the solvent, the free amine **25** was obtained as a white powder (1.02 g, 2.00 mmol, 100%) which was used without further purification. M.p. 45−47 °C. − $[\alpha]_D^{21}$ = +53 (*c* = 1.0, $CHCl_3$). − ^{1}H NMR:(+40 °C): δ = 1.41 (s, 18 H), 2.98−3.09 (m, 4 H), 3.70 (s, 6 H), 3.80 (s, 2 H), 4.53 (br s, 2 H), 5.00 (br s, 2 H), 6.76 (s, 1 H), 6.96 (s, 2 H). − ^{13}C NMR: δ = 28.44, 38.26, 46.30, 52.40, 54.59, 80.10, 126.89, 129.00, 136.69, 143.84, 155.23, 172.45. − HRMS (FAB^+); *m/z* calcd. for $C_{25}H_{40}N_3O_8$ (M + H) 510.2815; found 510.2821.

Dendritic Wedge, Type B (26): The diacid **24** (185 mg, 300 μmol) and the amine **25** (336 mg, 660 μmol) were coupled using TFFH (174 mg, 660 μmol) and DIEA (226 μL, 1.32 mmol) according to the general procedure. After flash chromatography (heptane/EtOAc/acetone 3:6:1), the wedge **26** was obtained as a white solid (296 mg, 185 μmol, 62%). M.p. 143−146 °C. − $[\alpha]_D^{21}$ = +40 (*c* = 1.0, $CHCl_3$). − ^{1}H NMR ([D$_6$]DMSO, +80 °C): δ = 1.32 (s, 18 H), 1.36 (s, 36 H), 2.75−3.02 (m, 12 H), 3.61 (s, 12 H), 4.16−4.33 (m, 12 H), 5.07 (s, 2 H), 6.34 (br s, 2 H), 6.73 (br s, 4 H), 6.95 (s, 2 H), 6.97 (s, 4 H), 7.01 (s, 3 H), 7.24 (br s, 1 H), 7.26−7.36 (m, 5 H), 7.95 (br t, *J* = 5.8 Hz, 2 H). − ^{13}C NMR: δ = 27.68, 36.46, 37.45, 41.89, 43.89, 51.06, 54.87, 55.60, 65.02, 77.84, 78.02, 125.58, 125.90, 127.08, 127.15, 127.78, 128.28, 136.81, 136.95, 137.37, 138.50, 138.69, 154.52, 155.72, 170.92, 171.78. − HRMS (FAB^+); *m/z* calcd. for $C_{81}H_{116}N_9O_{24}$ (M + H) 1598.8133; found 1598.8144.

Dimethyl (*S*,*S*,*S*)-2,2′-Bis(*tert*-butyloxycarbonylamino)-3,3′-{5-[(2-*tert*-butyloxycarbonylamino)-2-(methoxycarbonyl)ethyl]-1,3-phenylene}bis(propanoate) (28): The Cbz-protected phenyltrisalanine derivative **22**[24] (0.39 g, 0.50 mmol) was dissolved in EtOH/EtOAc (1:1, 20 mL) and Pd/C (10%, 40 mg) was added. The mixture was hydrogenated for 4 h and then filtered. After evaporation of the solvents, the residue was dissolved in CH_2Cl_2 (10 mL), and di-*tert*-butyldicarbonate (0.44 g, 2.0 mmol) and triethylamine (0.28 mL, 2.0 mmol) were added. (***Caution!*** A pressure-equalised reaction flask should be used due to CO_2 gas evolution.) The solution was stirred at room temp. for 2 h and then the solvent was evaporated. The residue was purified by flash chromatography (heptane/EtOAc 1:1) to yield the phenyltrisalanine derivative **28** as white crystals (0.30 g, 0.44 mmol, 89%). M.p. 127−129 °C. − $[\alpha]_D^{21}$ = +62 (*c* = 1.0, $CHCl_3$). − ^{1}H NMR: δ = 1.43 (s, 27 H), 2.99−3.04 (m, 6 H), 3.72 (s, 9 H), 4.51−4.58 (m, 3 H), 5.02 (br d, *J* = 7.0 Hz, 3 H), 6.76 (s, 3 H). − ^{13}C NMR: δ = 28.49, 38.31, 52.48, 54.64, 80.26, 129.29, 136.75, 155.27, 172.36. − HRMS (FAB^+); *m/z* calcd. for $C_{33}H_{52}N_3O_{12}$ (M + H) 682.3551; found 682.3555.

(*S*,*S*,*S*)-2,2′-Bis(*tert*-butyloxycarbonylamino)-3,3′-{5-[(2-*tert*-butyloxycarbonylamino)-2-(methoxycarbonyl)ethyl)]-1,3-phenylene}bis-(propanoic acid) (29): Compound **28** (0.27 g, 0.40 mmol) in THF (3 mL) was treated as for **24** using a pre-cooled solution (0 °C) of $LiOH·H_2O$ (0.13 g, 3.0 mmol) in water (3 mL). The triacid **29** was obtained as a white solid (0.25 g, 0.39 mmol, 98%). This material was used without further purification. M.p. >300 °C (dec). − $[\alpha]_D^{21}$ = +103 (*c* = 1.0, $CHCl_3$). − ^{1}H NMR ([D$_6$]DMSO, +60 °C): δ = 1.35 (s, 27 H), 2.78−3.00 (m, 6 H), 4.10−4.14 (m, 3 H), 6.70 (br s, 3 H), 6.96 (s, 3 H), 12.30 (br s, 3 H). − ^{13}C NMR: δ = 27.87, 36.41, 54.66, 77.80, 127.58, 137.30, 154.94, 172.99. − HRMS (FAB^+); *m/z* calcd. for $C_{30}H_{46}N_3O_{12}$ (M + H) 640.3082; found 640.3090.

Dendrimer G2B (2a): A mixture of wedge **26** (0.48 g, 0.30 mmol) in EtOH/HOAc (1:1, 7 mL) and Pd/C (10%, 70 mg) was hydrogenated for 3 h at atmospheric pressure and then filtered. The solvents were evaporated, and the residue was dissolved in $CHCl_3$ (20 mL). This solution was washed with saturated Na_2CO_3 (20 mL) and then dried over Na_2SO_4. After evaporation of the solvent, dendritic wedge **27** was obtained as a white solid (0.47 g, >100%), which retained a small amount of solvent. Part of this material (0.19 g, 0.13 mmol) was immediately used in the coupling reaction with the triacid **29** (18 mg, 28 μmol), using TFFH (34 mg, 0.13 mmol) and DIEA (44 μL, 0.26 mmol) according to the general procedure above. After flash chromatography (heptane/EtOAc/acetone, 2:7:1), the dendrimer G2B (**2a**) was obtained as a white solid (55 mg, 11 μmol, 39%). M.p. 120−124 °C. − $[\alpha]_D^{21}$ = +34 (*c* = 1.0, $CHCl_3$). − ^{1}H NMR ([D$_6$]DMSO, +100 °C): δ = 1.30 (s, 27 H), 1.32 (s, 54 H), 1.36 (s, 108 H), 2.75−3.06 (m, 42 H), 3.61 (s, 36 H), 4.16−4.36 (m, 39 H), 6.17 (br d, 3 H), 6.20 (br d, 6 H), 6.57 (br d, *J* = 7.5 Hz, 12 H), 6.94 (s, 6 H), 6.97 (s, 15 H), 7.00−7.03 (m, 9 H), 7.75 (br t, 3 H), 7.84 (br t, *J* = 5.6 Hz, 6 H). − ^{13}C NMR ([D$_6$]DMSO, +80 °C): δ = 27.69, 36.48, 37.42, 41.92, 42.20, 51.07, 54.89, 55.64, 77.87, 77.89, 78.02, 125.91, 126.01, 127.59, 127.80, 128.10, 136.95, 137.17, 137.49, 138.11, 138.70, 154.55, 170.94, 170.97, 171.78. − MS (MALDI-TOF); *m/z* calcd. for $C_{249}H_{366}N_{30}O_{75}Na$ (M + Na) 4999.6; found 4998.7. − $C_{249}H_{366}N_{30}O_{75}$: calcd. C 60.06, H 7.41, N 8.44; found C 60.1, H 7.6, N 8.35.

Dendrimer G1A (31): Monomer A (**9**) (0.57 g, 0.90 mmol) was dissolved in EtOH (10 mL) and Pd/C (10%, 30 mg) was added. After hydrogenation overnight at atmospheric pressure, the reaction mixture was filtered and the solvents were removed by evaporation to yield the carboxylic acid **19**, which was used directly in the coupling step. Phenyltrisalanine derivative **22**[24] (0.16 g, 0.20 mmol) was hydrogenated in the same way, with EtOH/EtOAc (1:1, 10 mL) as solvent and with catalyst (10 mg), to afford the triamine **23**. Coupling of **19** and **23** using the general procedure above afforded the dendrimer G1A (**31**) as a white solid (0.33 g, 0.17 mmol, 84%) after flash chromatography ($CHCl_3$/MeOH, 30:1). M.p. 130−133 °C. − $[\alpha]_D^{21}$ = +40 (*c* = 1.0, $CHCl_3$). − ^{1}H NMR (+50 °C): δ = 1.41 (s, 54 H), 2.94−3.09 (m, 18 H), 3.50 (s, 6 H), 3.66 (s, 9 H), 3.70 (s, 18 H) 4.50 (br s, 6 H), 4.73−4.79 (m, 3 H), 5.12 (br s, 6 H), 6.18 (br d, *J* = 6.8 Hz, 3 H), 6.76 (s, 3 H), 6.85 (s, 3 H), 6.93 (s, 6 H). − ^{13}C NMR: δ = 28.55, 37.94, 38.57, 43.27, 52.40, 52.47, 53.87, 55.00, 80.19, 129.01, 129.32, 129.55, 135.41, 137.15, 137.37, 155.27, 170.65, 172.09, 172.43. − MS (ESI^+); *m/z* calcd. for $C_{96}H_{136}N_9O_{33}$ (M + H) 1942.9; found 1943.7. − $C_{96}H_{135}N_9O_{33}$: calcd. C 59.34, H 7.00, N 6.49; found C 59.25, H 7.25, N 6.55.

Dendrimer G1B (32): The free amine **25** (0.92 g, 1.8 mmol) and the triacid **29** (0.26 g, 0.40 mmol) were coupled according to the general procedure above. After flash chromatography (heptane/EtOAc/acetone 3:6:1), the dendrimer G1B (**32**) was obtained as a white solid (0.64 g, 0.30 mmol, 76%). M.p. 107−109 °C. − $[\alpha]_D^{21}$ = +44 (*c* = 1.0, $CHCl_3$). − ^{1}H NMR ([D$_6$]DMSO, +70 °C): δ = 1.32 (s, 27 H), 1.35 (s, 54 H), 2.72−3.00 (m, 18 H), 3.60 (s, 18 H), 4.15−4.34 (m, 15 H), 6.38 (br s, 3 H), 6.83 (br s, 6 H), 6.95 (s, 3 H), 6.96−6.98 (m, 9 H), 7.98 (br t, *J* = 5.8 Hz, 3 H). − ^{13}C NMR: δ = 27.75, 36.48, 37.49, 41.92, 51.17, 54.94, 55.76, 77.89, 78.06, 125.95, 127.63, 127.85, 137.02, 137.18, 138.81, 154.61, 171.08, 171.91. − MS (MALDI-TOF); *m/z* calcd. for $C_{105}H_{156}N_{12}O_{33}Na$ (M + Na) 2136.1; found 2137.4. − $C_{105}H_{156}N_{12}O_{33}$: calcd. C 59.64, H 7.44, N 7.95; found C 59.8, H 7.7, N 7.9.

Dendrimer 33: The methyl esters of the phenyltrisalanine derivative **22** were removed by basic hydrolysis using the procedure described

for **29**. From **22** (78 mg, 0.10 mmol) and $LiOH·H_2O$ (31 mg, 0.75 mmol), the triacid **30** was obtained as a white solid, which was used without purification. The free amine **25** (0.18 g, 0.34 mmol) and the triacid **30** were coupled according to the general procedure. After flash chromatography (heptane/EtOAc/acetone, 3:6:1), the dendrimer **32** was obtained as a white solid (0.11 g, 48 μmol, 63%). M.p. 134−137 °C. − $[\alpha]_D^{21}$ = +40 (*c* = 1.0, $CHCl_3$). − ^{1}H NMR ([D$_6$]DMSO, +90 °C): δ = 1.35 (s, 54 H), 2.77−3.04 (m, 18 H), 3.60 (s, 18 H), 4.14−4.25 (m, 9 H), 4.28−4.35 (m, 6 H), 4.97 (s, 6 H), 6.64 (br d, *J* = 6.2 Hz, 6 H), 6.83 (br s, 3 H), 6.95 (s, 3 H), 6.97 (s, 6 H), 7.02 (s, 3 H), 7.22−7.32 (m, 15 H), 7.93 (br t, *J* = 5.8 Hz, 3 H). − ^{13}C NMR: δ = 27.63, 36.48, 37.40, 41.87, 50.97, 54.83, 56.01, 65.11, 78.01, 125.81, 126.89, 127.02, 127.56, 127.64, 127.69, 136.49, 136.89, 137.04, 138.61, 154.49, 155.14, 170.67, 171.68. − MS (MALDI-TOF); *m*/*z* calcd. for $C_{114}H_{150}N_{12}O_{33}Na$ (M + Na) 2238.0; found 2239.4. − $C_{114}H_{150}N_{12}O_{33}$: calcd. C 61.77, H 6.82, N 7.58; found C 61.75, H 7.15, N 7.6.

***N*,*N*′-Dibenzyl (2*S*, 2′*S*)-2,2′-Bis(*tert*-butyloxycarbonylamino)-3,3′-{[(5-benzyloxycarbonylamino)methyl]-1,3-phenylene}bis(propanamide) (34):** The dicarboxylic acid **24** (31 mg, 50 μmol) and benzylamine (22 μL, 0.20 mmol) were coupled by the general procedure above, using TFFH (40 mg, 0.15 mmol) and DIEA (51 μL, 0.30 mmol). After flash chromatography (heptane/EtOAc, 1:2), compound **34** was obtained as a white solid (8 mg, 10 μmol, 20%). − $[\alpha]_D^{21}$ = +9 (*c* = 1.0, $CHCl_3$). − ^{1}H NMR (+50 °C): δ = 1.40 (s, 18 H), 2.95−3.04 (m, 4 H), 4.23−4.41 (m, 8 H), 4.89 (br s, 1 H), 5.02 (br s, 2 H), 5.12 (s, 2 H), 6.21 (br s, 2 H), 6.98 (s, 3 H), 7.10−7.13 (m, 4 H), 7.20−7.36 (m, 11 H). − ^{13}C NMR: δ = 28.54, 38.78, 43.74, 56.52, 67.17, 80.60, 127.28, 127.71, 127.86, 127.95, 128.36, 128.76, 128.88, 129.77, 136.84, 138.08, 138.20, 139.58, 155.55, 156.56, 171.02. − HRMS (FAB$^+$); *m*/*z* calcd. for $C_{45}H_{56}N_5O_8$ (M + H) 794.4129; found 794.4128.

Free Acid Dendrimer G2A (1b): The G2A dendrimer **1a** (60 mg, 13 μmol) was suspended in THF (1 mL) at 0 °C, and a pre-cooled solution of $LiOH·H_2O$ (42 mg, 1.0 mmol) in water (1 mL) was added. The mixture was stirred at 0 °C for 8 h. After this time, it still contained undissolved material. The THF was evaporated and the volume adjusted to 3 mL by addition of water. Stirring at 0 °C was continued for 1 h, after which THF (3 mL) was added. After a further 3.5 h of stirring at 0 °C, a clear solution was obtained. The solution was acidified with conc. HCl (ca. 100 μL) and extracted several times with hot $CHCl_3$ (50 mL total). The extracts were combined and dried briefly over Na_2SO_4. After evaporation of the solvent, the free acid dendrimer **1b** was obtained as a white solid (50 mg, 12 μmol, 89%), which could be dissolved in water by the addition of NaOH solution (1 N) to pH 6. − ^{1}H NMR (H_2O/D_2O 9:1, +50 °C, pH 6): δ = 1.56 (s, 108 H), 3.00−3.41 (m, 42 H), 3.72−3.86 (m, 18 H), 7.21−7.32 (m, 30 H), 7.92 (br s, 6 H), 8.11 (br s, 3 H). Some peaks were obscured by the residual H_2O signal at: δ = 4.8. − MS (ESI$^-$); *m*/*z* calcd. for $C_{201}H_{262}N_{21}O_{75}$ (M + H) 4169.7; found 4169.7.

Free-Acid Dendrimer G2B (2c): The G2B dendrimer **2a** (30 mg, 6.0 μmol) was suspended in THF (0.5 mL) at 0 °C, and a pre-cooled solution of $LiOH·H_2O$ (21 mg, 0.50 mmol) in water (0.5 mL) was added. The mixture was stirred at 0 °C for 2 h, after which a clear solution was obtained. The THF was evaporated and the remaining solution was diluted with water (2 mL) and was then acidified with conc. HCl (ca. 50 μL) to pH 1. A white precipitate formed, and the mixture was extracted with $CHCl_3$ (2 × 2 mL) to dissolve the precipitate. The extracts were dried over Na_2SO_4 and the solvent was then evaporated to yield the free acid dendrimer **2c** as a white solid (25 mg, 5.2 μmol, 86%), which could be dissolved in water by the addition of NaOH (1 N) solution to pH 7. − ^{1}H NMR (H_2O/D_2O, 9:1, +50 °C, pH 7): δ = 1.57 (s, 189 H), 3.00−3.40 (m, 42 H), 7.29 (br s, 30 H), 8.45 (br s, 9 H). Some peaks were obscured by the residual H_2O signal at δ = 4.8. At +25 °C, several broad peaks (N*H*Boc) were seen in the δ = 5.7−7 ppm region. − MS (ESI$^-$); *m*/*z* calcd. for $C_{237}H_{343}N_{30}O_{75}$ (M + H) 4809.4; found 4809.6.

General Procedure for Removal of Boc-Protecting Groups: The Boc-protected dendrimer (ca. 30 mg) was dissolved in $CHCl_3$/TFA 1:1 (1 mL) and the solution was kept at room temp. for 30 min after which it was evaporated to dryness. The residue was triturated with diethyl ether (2 × 5 mL) and vacuum-dried to yield the deprotected dendrimer-TFA salt as a white solid which was readily soluble in water.

Free-Amine Dendrimer G2A (1c): Yield 96%. − ^{1}H NMR (H_2O/D_2O 9:1, pH 3): δ = 2.84−3.06 (m, 18 H), 3.14−3.31 (m, 24 H), 3.40−3.60 (m, 18 H), 3.66 (s, 18 H), 3.69 (s, 9 H), 3.80 (s, 36 H), 4.38 (t, *J* = 6.7 Hz, 12 H), 6.83 (s, 9 H), 6.93 (s, 3 H), 7.02 (s, 12 H), 7.07 (s, 6 H), 8.26 (br d, *J* = 7.6 Hz, 3 H), 8.52 (br d, *J* = 7.5 Hz, 6 H). Some peaks were obscured by the residual H_2O signal at δ = 4.8. − MS (ESI$^+$); *m*/*z* calcd. for $C_{162}H_{208}N_{21}O_{51}$ (M + H) 3263.4; found 3263.8.

Completely Deprotected Dendrimer G2A (1d): Yield 77%. − ^{1}H NMR (H_2O/D_2O 9:1, pH 6): δ = 2.72−3.21 (m, 42 H), 3.33−3.51 (m, 18 H), 3.94 (t, *J* = 7.2 Hz, 12 H), 4.34 (br s, 9 H), 6.83 (s, 6 H), 6.94 (s, 18 H), 7.04 (s, 6 H), 7.84 (br d, *J* = 7.8 Hz, 3 H), 7.93 (br d, *J* = 7.8 Hz, 6 H). At pH 2, the spectrum was similar, but the amide N*H* protons at δ = 7.84 and 7.93 and the C$_\alpha$*H* protons at δ = 3.94 and 4.34 were shifted ca. 0.15 ppm downfield. − MS (ESI$^+$); *m*/*z* calcd. for $C_{141}H_{165}N_{21}O_{51}$ (M) 2968.1; found 2968.0.

Free Amine Dendrimer G2B (2b): Yield 99%. − ^{1}H NMR (H_2O/D_2O 9:1, pH 4): δ = 3.00−3.35 (m, 42 H), 3.81 (s, 36 H), 4.21−4.32 (m, 18 H), 4.37 (t, *J* = 7.0 Hz, 12 H), 7.05 (s, 3 H), 7.09 (s, 18 H), 7.14 (s, 6 H), 7.21 (s, 3 H), 8.85 (br t, 6 H), 8.97 (br t, 3 H). Some peaks were obscured by the residual H_2O signal at δ = 4.8. − MS (ESI$^+$); *m*/*z* calcd. for $C_{144}H_{199}N_{30}O_{33}$ (M + H) 2876.5; found 2876.5.

Completely Deprotected Dendrimer G2B (2d): Yield 99%. − ^{1}H NMR (H_2O/D_2O 9:1, pH 5): δ = 3.00−3.16 (m, 42 H), 3.95 (t, *J* = 6.1 Hz, 12 H), 4.13−4.33 (m, 27 H), 6.94 (s, 15 H), 7.01 (s, 6 H), 7.07 (s, 6 H), 7.11 (s, 3 H). The amide N*H* protons were invisible, probably because of rapid chemical exchange. At pH 2, they were visible at δ = 8.75 (br t, *J* = 5.6, 6 H) and 8.98 (br t, 3 H), and at this pH, the C$_\alpha$*H* protons at δ = 3.95 and 4.13−4.33 were shifted ca. 0.2 ppm downfield, as they were for **1d**. − MS (ESI$^+$); *m*/*z* calcd. for $C_{132}H_{174}N_{30}O_{33}$ (M + H) 2708.3; found 2708.7.

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