Amino-Functionalized, Second-Generation Dendritic Building Blocks

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The multi-gram scale synthesis of first- and second-generation dendrons with Boc- and Cbz-protected amino groups in the periphery and methyl/ethyl esters at the focal points is described. Saponification of the esters and deprotection of the amines are shown to be strictly orthogonal processes which makes these dendrons valuable building blocks for future constructions.

Introduction

The goal of a long-term project we are currently pursuing is to make available organic molecular objects with a defined and predetermined shape on a length scale of several nanometers.[1][2] An example are the recently synthesized molecular cylinders whose molecular structure can be described as dendrimers with polymeric core.[3] During this research some difficulties arose which made it desirable to have available a variety of dendritic building blocks which ought to differ not only in their main structure but, more importantly, in their functional group pattern at both focal point and periphery. This would siginificantly increase the synthetic flexibility and ensure structural perfection also in situations where, for example, a virtually 100% coverage of peripherial functional groups with new dendrons (dendritic fragments) is difficult to achieve. We describe here the synthesis of a series of orthogonally protected, second generation dendrons with amino functional groups at the periphery. Together with a recently published, hydroxy-functionalized dendron and related compounds,[4] these dendrons are the first members of a future dendrimer construction set consisting of dendritic building blocks.

Results and Discussion

Dendrons suitable as building blocks of a construction set should meet the following criteria:

a) a strictly orthogonal protective group pattern at the focal point and in the periphery,

b) complementarity of functional groups with the sets of other dendrons in order to allow any two building blocks to be combined to a larger dendron,

c) maximum efficiency in coupling reactions between any two dendrons,

d) convenient synthetic access on the multi-gram scale,

e) preferably be solids to make handling and purification facile, and

f) reasonable chemical and hydrolytic robustness of the basic skeleton and insensitivity to reactions performed at the functional groups.

This paper focuses on dendrons with amino groups in the periphery and carboxylic ester at the focal point. There are a number of *dendrimers* known with peripherial amino groups.[5] They are typically prepared by divergent procedures. Not much has been published, however, on *dendrons* with amino functions in the periphery and, at the same time, an orthogonal functional group at the focal point.[6] A prominent exception is the work of Roy,[7] who reported on dendrons with benzyl carbamate-(Cbz-)protected peripherial amino groups and a focal *tert*-butyl ester function. These dendrons meet all of the above criteria except for (f). Criterium (f) is not met because the branching units are tertiary amines, which make the skeleton susceptible towards electrophiles. They could therefore not be used for our purposes. For dendrons built from amino acids, see ref.[8].

Synthesis of Dendrons

The synthetic strategy is based on first-generation (G-1) dendrons **3** and **6** which carry identical functional and protecting group patterns, a feature which ought to make them fully compatible in growth reactions. The synthesis of dendron **3** starts from methyl resorcylate (**1**) which was easily obtained on the kilogram scale from commercially available resorcylic acid (Scheme 1). Reaction of **1** with acrylonitrile under base catalysis yielded a 2:1 mixture of the mono- and dicyanoethylated product. Crystalline dinitrile **2** was obtained in 100-g batches after a simple chromatographic separation. Hydrogenation in the presence of hydrochloric acid gave the diamine dihydrochloride **3a** in a yield of 80% due to some losses during work-up. According to TLC no by-product was formed. The amino groups of **3a** were easily Cbz- and Boc-protected by treating it with benzyl chloroformate and di-*tert*-butyl dicarbonate to furnish **3b** and **3d**, respectively. Saponification of the ester functions of **3b** and

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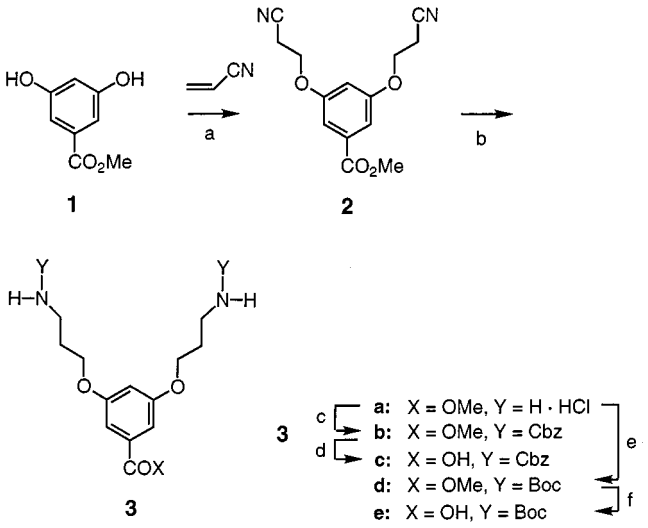
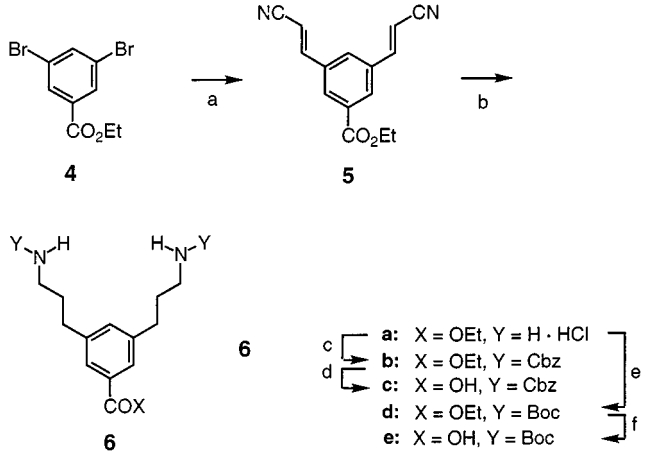
3d gave the corresponding carboxylic acids **3c** and **3e** in 85−95% yield. **3c** and **3e** crystallized from MeOH/H_2O, an important feature with respect to the purification of large quantities.

Scheme 1a. Reagents and conditions: a) acrylonitrile, sodium, benzyltriethylammonium chloride, 36 h, reflux (30%); b) H_2, PtO_2, methanol, 10 h, 45°C (80%); c) benzyl chloroformate, KOH, THF/H_2O, 2 h, 0°C (86%); d) KOH, methanol/H_2O, 2 h, reflux (85%); e) di-*tert*-butyl dicarbonate, KOH, THF/H_2O, 1 h, 0°C (65%); f) KOH, methanol/H_2O, 2 h, reflux (90%)



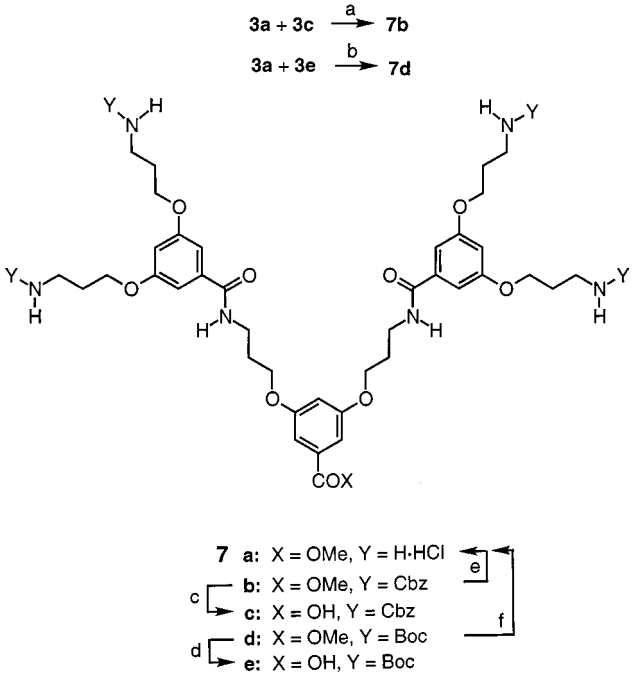
Scheme 1b. Reagents and conditions: a) Palladium(II) acetate, triphenylphosphane, NEt_3, acrylonitrile, 7 d, 120°C (56%); b) H_2, Pd/C, ethanol, 14 h, room temp. (96%); c) benzyl chloroformate, KOH, THF/H_2O, 2 h, 0°C (92%); d) KOH, methanol, 4 h, reflux (94%); e) di-*tert*-butyl dicarbonate, KOH, THF/H_2O, 1 h, 0°C (95%); f) KOH, methanol/H_2O, 4 h, reflux (88%)



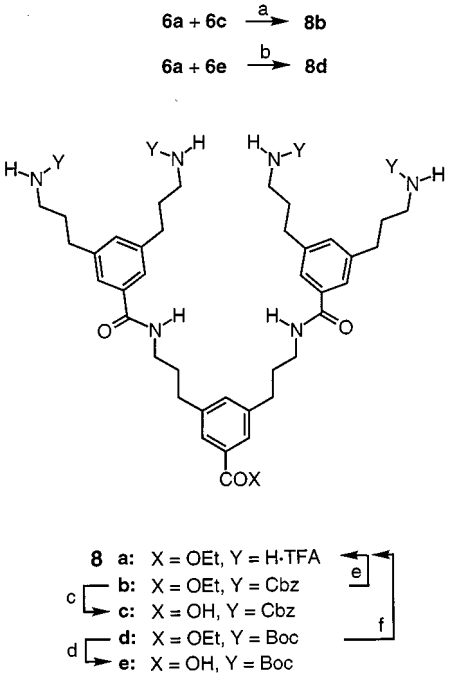
Dendron **6** was prepared by the Heck reaction between ethyl 3,5-dibromobenzoate (**4**) and acrylonitrile followed by hydrogenation of the intermediate **5**. Hydrogenation of **5** was carried out in the presence of hydrochloric acid using Pd/C and at a hydrogen pressure of $3 \cdot 10^5$ Pa[9] and gave the diamine **6a** as dihydrochloride in 80% yield. Protection of the amino functions with Cbz and Boc to give **6b** and **6d** and the saponification of their focal ethyl ester to give **6c** and **6e** was carried out analogously to the above described procedures. In contrast to dendrons **3c**, **3e**, and the Cbz-protected dendron **6c**, which are solids, the Boc-protected **6e** is an oil which could not be crystallized.

The skeleton of G-2 dendron **7** was prepared by treating either of the amino-protected G-1 carboxylic acids **3c** or **3e** with ester **3a** carrying unprotected amino functions (Scheme 2); the skeleton of **8** was obtained analogously from **6c**, **6e**, and **6a**. In order to achieve these coupling reactions the dihydrochlorides **3a** and **6a** were deprotonated with diazabicyclo[5.4.0]undecene (DBU) in CH_2Cl_2 which resulted in clear solutions within a few minutes to which the dendrons with activated carboxylic acid functions at the focal point were added. The use of triethylamine or ethyldiisopropylamine in the presence of some DMF instead of DBU gave comparable coupling yields. The DBU procedure, however, was preferentially used because removal of the last traces of DMF from the highly polar G-2 products was tedious. The carboxylic acids were activated by carbonyldiimidazole (CDI)[10] for **3c** and **3e** and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC)[11] for **6c** and **6e**. In both cases the yields for the Cbz-protected G-2 dendrons **7b** and **8b** were lower (52−78%) than for **7d** and **8d**, the Boc-protected ones (76−88%). These yields are not the highest possible because the carboxylic acids were only used in a slight excess of 1.1−1.2 equivalents.

Scheme 2a. Reagents and conditions: a) 1. CDI, acetonitrile, 12 h, room temp., 2. **3a**, NEt_3, acetonitrile, 12 h, 50°C (52%); b) 1. CDI, CH_2Cl_2, 12 h, room temp., 2. **3a**, NEt_3, acetonitrile/DMF, 48 h, room temp. (76%); c) KOH, THF/methanol/H_2O, 3 h, reflux (81%); d) KOH, THF/methanol/H_2O, 3 h, reflux (92%); e) H_2, Pd/C, ethanol, 5 h, 50°C (85%); f) HCl, THF/H_2O, 2 h, room temp. (99%)



Scheme 2b. Reagents and conditions: a) 1. EDC, hydroxybenzotriazole, CH_2Cl_2, 10 min, 0°C, 2. **6a**, iPr_2EtN, CH_2Cl_2, 14 h, room temp. (76%); b) EDC, hydroxybenzotriazole, CH_2Cl_2, 10 min, 0°C, 2. **6a**, iPr_2EtN, CH_2Cl_2, 14 h, room temp. (88%); c) KOH, THF/methanol/H_2O, 12 h, 60°C (84%); d) KOH, THF/methanol/H_2O, 12 h, 50°C (84%); e) H_2, Pd/C, ethanol, 14 h, room temp. (82%); f) TFA, CH_2Cl_2, 1 h, room. temp. (98%)

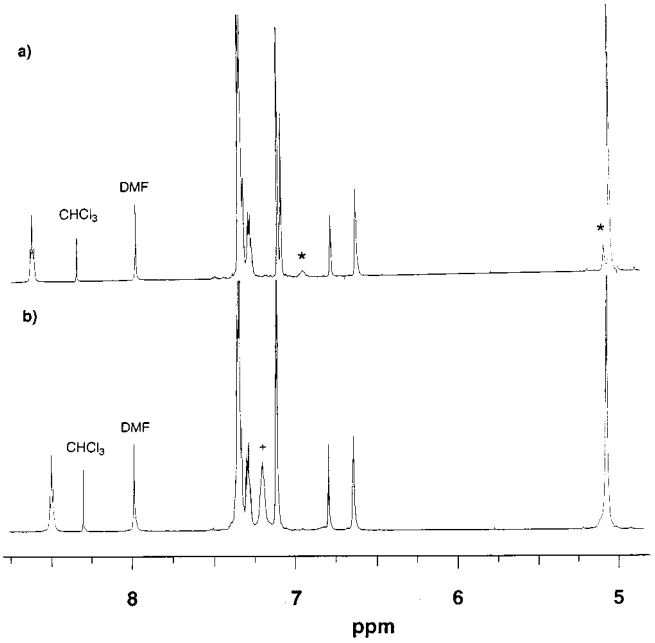


The [G-2] fragments differ in their solubility properties depending on the protecting group attached. The Cbz-protected dendron **7b** is soluble in DMSO and DMF, only poorly so in THF, and even insoluble in methanol. In contrast, the corresponding Boc-protected **7d** dissolves easily in all these solvents which may make it a more attractive candidate for further synthetic purposes. Similar solubility properties were found in the case of dendrons **8b** and **8d** where Cbz also leads to poorer general solubility behaviour than Boc. In accordance with this, Boc-dendron **8d** is an oily material very much like the corresponding [G-1] fragment **6d**.

Characterization, Purity, and Deprotection

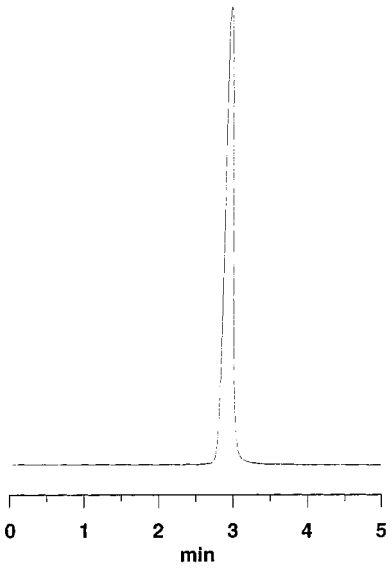
The described compounds are not yet in a high molecular weight range and their structure could therefore easily be established by NMR spectroscopy and the correct data from elemental analysis. All chemically inequivalent protons and carbon atoms of the [G-1] and [G-2] fragments are observed as individual signals. This fortunate feature ensured an unequivocal assignment to be made (see Experimental Section). The purity of all dendrons was investigated by high-field NMR (500 MHz) integration as well as HPLC. Dendritic compounds have a tendency to aggregate into larger clusters which gives rise to rather complex NMR spectra.[12] Most of the dendrons described here fortunately did not cause any problems and gave simple NMR spectra whose signals could be reliably integrated. In the case of dendron **7b**, however, the ^{1}H-NMR spectrum in [D_7]DMF shows small additional signals at δ = 5.1 and 6.9 (Figure 1a). To show that they do not belong to a side product but arise from aggregation, the NMR spectrum of the same sample was recorded at slightly elevated temperature (313 K, Figure 1b). This resulted in a disappearance of all additional signals which were also not observed when the spectrum was taken in a mixture of [D_4]methanol and [D_6]DMSO (1:1). According to NMR integration the purity of the dendrons exceeded 99% in all cases. This high degree of purity was also determined by HPLC. A typical HPLC trace of dendron **7b** is shown in Figure 2. Such a clean trace (peak area > 99.5%, UV detection) could only be obtained when the formation of aggregates was suppressed by addition of some MeOH to the solution of the dendron prior to injection. Otherwise, two peaks with retention times of 2.9 and 2.4 min were observed, whose intensity varied with concentration.

Figure 1. ^{1}H-NMR spectra (500 MHz) of G-2 dendron **7b** in [D_7]DMF at 293 K (a), 313 K (b); signals associated with aggregates are assigned (*); signals of the carbamate (+) are hidden in spectrum (a) under the signal at δ = 7.3



In the next step the extent was determined to which the G-2 dendrons **7** and **8** can be deprotected and the question investigated whether their skeletons decompose under the conditions of deprotection. Both matters were studied mostly by NMR spectroscopy. Figure 3 compares the ^{1}H-NMR spectra of Boc-protected **7d** (a) and its peripherially deprotected analogue **7a** (b). The intensity of the Boc signal at δ = 1.4 in spectrum (b) is reduced by more than 99.8% (NMR integration). At the same time, the ^{13}C-NMR spectrum of a representative sample of the deprotected dendron **7a** shows not even a trace of decomposition, thus establishing that the deprotection of Boc can be accomplished virtually quantitatively and leaving the skeleton untouched. Similar results were obtained for **8d** in the case of the Cbz-

Figure 2. HPLC elution curve of dendron **7b** dissolved in CH_2Cl_2/THF/MeOH (2.5:2.5:1) with CH_2Cl_2/THF (3:1) as eluent



protected dendrons **7b** and **8b**. The respective NMR spectra (not shown) do not give any indication of incomplete deprotection or decomposition of the skeleton. The degree of deprotection was also well above 99%.

Saponification of the ester groups of **7b**, **7d**, **8b**, and **8d** was investigated with the eventual hydrolytic instability of both the peripherial protecting groups and the amide function in mind. The reactions were run in MeOH/THF/H_2O (ratios see Experimental Section) at 50−90°C for 10−14 h using 2−4 equiv. of NaOH or KOH per functional group. Under these conditions TLC did not even show traces of side products. Isolated yields of carboxylic acids range between 80 and 95%, indicating clean reactions specifically considering losses during work-up caused by the difficult and incomplete extractions of carboxylic acids from aqueous phase.

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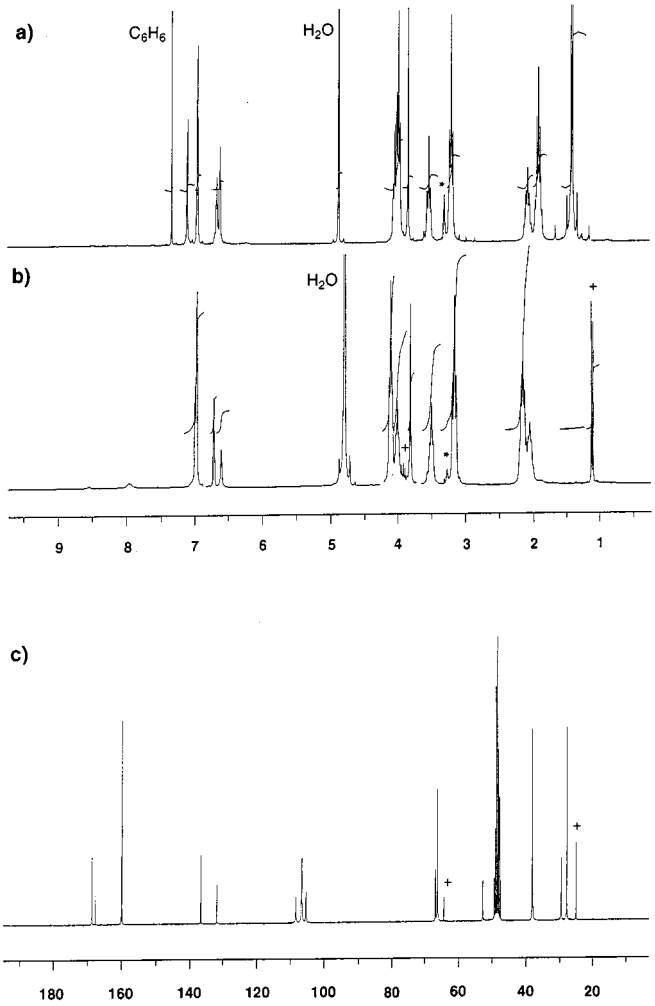
Experimental Section

All chemicals were purchased from Aldrich or Acros Chimica and used without further purification. Solvents: Dry THF was distilled from sodium using benzophenone as indicator for dryness. Dichloromethane was stored over sodium hydride and filtered before use. For some of the amide couplings dichloromethane was distilled from phosphorus pentoxide. Analytical equipment: NMR: AC 250, AM 270 and AMX 500. The NMR shifts of protecting groups are indicated by "pg". − MS: Varian MAT 112S, Varian MAT 711. − IR: FTIR-Interferometer-System 5SXC (Nicolet). − EA: EA 240 Perkin Elmer. Because of the polarity of the compounds prepared it was generally difficult to obtain correct data from elemental analysis. This was specificially so for all Boc-protected dendrons and some of the free carboxylic acids for which the carbon values obtained differed from the calculated ones by approx. 1%.

Figure 3. ^{1}H-NMR spectra (250 MHz) of **7d** (a) and the peripherically deprotected **7a** obtained from **7d** (b), as well as the ^{13}C-NMR spectrum (126 MHz) of **7a** (c); all spectra were recorded in [D_4]methanol whereby to the samples of **7a** a small portion of D_2O had been added to increase solubility; residual 2-propanol from work-up is assigned by + and in the ^{1}H-NMR spectra [D_4]methanol is assigned by *



Methyl 3,5-Bis(2-cyanoethyloxy)benzoate (**2**): Methyl resorcylate (200 g, 1.19 mol) is dissolved in methanol. To this solution sodium (5.47 g, 0.23 mol) is added. After the sodium has dissolved, the solvent is evaporated and the dry residue is refluxed with benzyltriethylammonium chloride (5 mol-%) in acrylonitrile (1 l) for 36 h. The reaction mixture is cooled to room temperature, acetic acid (90 g, 1.5 mol) is added and the acrylonitrile is evaporated under reduced pressure. The oily residue is further purified by column chromatography using dichloromethane as eluent. The obtained residue is pure but can be crystallized from methanol. Yield: 95 g (30%), m.p. 105°C. − IR (KBr): ν = 2949 (C−H), 2254 (CN), 1710 (C=O), 1608 (C=C), 1432 (C−H), 1245 cm^{-1} (C−O). − ^{1}H NMR (270 MHz, $CDCl_3$, 25°C): δ = 2.81 (t, 2 H, CH_2CN), 3.88 (s, 3 H, CH_3), 4.18 (t, 2 H, CH_2O), 6.64 (t, 1 H, arom.), 7.19 (d, 2 H, arom.). − ^{13}C NMR (68 MHz, $CDCl_3$, 25°C): δ = 18.5 (CH_2CN), 52.3 (CH_3), 62.9 (CH_2O), 107.0 (arom.), 108.5 (arom.), 117.0 (CN), 132.3 (CCO_2Me), 158.7 (arom.), 166.1 (C=O). − MS (70 eV, EI); *m/z* (%): 274 (100) [M^+]. − $C_{14}H_{14}N_2O_4$ (274.3): calcd. C 61.31, H 5.14, N 10.21; found C 61.13, H 5.07, N 9.89.

Methyl 3,5-Bis(3-aminopropyloxy)benzoate Dihydrochloride (**3a**): A solution of dinitrile **2** (22 g, 80 mmol) and hydrochloric acid (25%, 30 ml, 200 mmol) in methanol (200 ml) is hydrogenated at a hydrogen pressure of 4×10^5 Pa using platinum oxide (1.0 g, 4.4 mmol) as the hydrogenation catalyst. After 10 h, the reaction mixture is filtered to remove the catalyst and methanol is evaporated in vacuo. To the residual oily liquid 2-propanol (approx. 500 ml) is added under stirring until precipitation occurs. Stirring is then continued for 1 h. After this time, the mixture is filtered and the white precipitate is dried in vacuo at 50−60°C. Yield: 22.2 g (80%), m.p. 229°C. − IR (KBr): ν = 3390 (N−H), 3250 (N−H), 2935 (N−H), 2881 (N−H), 1723 (C=O), 1593 (C=C), 1243 cm^{-1} (C−O). − ^{1}H NMR (270 MHz, [D$_4$]MeOH/D$_2$O, 25°C): δ = 2.20 (quint, *J* = 7.4 Hz, 2 H, CC*H*$_2$C), 3.20 (t, *J* = 7.4 Hz, 2 H, CH$_2$N), 3.88 (s, 3 H, CH$_3$), 4.14 (t, *J* = 7.4 Hz, 2 H, CH$_2$O), 6.83 (t, *J* = 2.5 Hz, 1 H, arom.), 7.14 (d, *J* = 2.5 Hz, 2 H, arom.). − ^{13}C NMR (68 MHz, [D$_4$]MeOH/D$_2$O, 25°C): δ = 27.8 (CCH$_2$C), 38.4 (CH$_2$N), 53.3 (CH$_3$), 66.7 (CH$_2$O), 107.4 (arom.) 109.1 (arom.), 132.6 (*C*CO$_2$Me), 160.7 (arom.), 168.6 (C=O). − MS (FAB$^+$); *m/z* (%): 283 (100) [M$^+$+H]. − $C_{14}H_{24}Cl_2N_2O_4$ (355.3): calcd. C 47.33, H 6.81, N 7.89, Cl 19.96; found C 47.33, H 6.81, N 7.89.

Methyl 3,5-Bis[3-(benzyloxycarbonylamido)propyloxy]benzoate (**3b**): Dihydrochloride **3a** (20 g, 56 mmol) is suspended in a mixture of THF and water (5:1) to which potassium hydroxide (18.9 g, 337 mmol) and benzyl chloroformate (28.8 g, 169 mmol) is added at 0°C. After 2 h, the organic phase is separated and the aqueous phase is twice extracted with dichloromethane. The organic phases are combined and solvent is removed in vacuo. Recrystallization from toluene gives pure **3b**. Yield: 26.5 g (86%), m.p. 99−100°C. − IR (KBr): ν = 3311 (N−H), 3066 (C−H), 2949 (C−H), 2872 (C−H), 1725 (C=O), 1687 (amide I), 1598, 1536 (amide II), 1264 cm^{-1} (C−O). − ^{1}H NMR (270 MHz, CDCl3, 25°C): δ = 1.96 (quint, *J* = 6.5 Hz, 4 H; CC*H*$_2$C), 3.37 (dt, $J_{1=}J_{2=6}$.5 Hz, 4 H, C*H*$_2$NH), 3.86 (s, 3 H, CH$_3$), 3.99 (t, *J* = 6.5 Hz, 4 H, CH$_2$O), 5.07 (s, 4 H, CH$_2$-Ph), 6.58 (t, *J* = 2.4 Hz, 1 H, arom.), 7.14 (d, *J* = 2.4 Hz, 2 H, arom.), 7.25−7.35 (m, 10 H, Ph). − ^{13}C NMR (68 MHz, CDCl3, 25°C): δ = 29.2 (CCH$_2$C), 38.3 (CH$_2$N), 52.2 (CH$_3$), 65.8 (CH$_2$O), 66.6 (CH$_2$-Ph), 106.5 (arom.), 107.8 (arom.), 128.0 (arom.), 128.4 (arom.), 131.9 (*C*CO$_2$Me), 136.5 (arom.), 156.4 [NC(O)O], 159.6 (arom.), 166.6 (C=O). − MS (70eV, EI); *m/z* (%): 550 (0.14) [M$^+$]. − $C_{30}H_{34}N_2O_8$ (550.6): calcd. C 65.44, H 6.22, N 5.09; found C 65.46, H 6.04, N 4.74.

3,5-Bis[3-(benzyloxycarbonylamido)propyloxy]benzoic Acid (**3c**): A solution of ester **3b** (5.14 g, 9.34 mmol) and potassium hydroxide (0.79 g, 14 mmol) in methanol (50 ml) is refluxed for 2 h (TLC). After cooling to room temperature, acetic acid is added and the solvent is evaporated in vacuo. The obtained raw material is recrystallized from methanol/water. Yield: 4.26 g (85%), m.p. 124−127°C. − IR (KBr): ν = 3338 (N−H), 3029 (C−H), 2951 (C−H), 2874 (C−H), 1691 (C=O, amide I), 1527 (amide II), 1250 cm^{-1} (C−O). − ^{1}H NMR (270 MHz, [D$_7$]DMF, 25°C): δ = 1.58 (quint, *J* = 6.2 Hz, 4 H, CC*H*$_2$C), 2.94 (dt, *J* = 6.2 Hz, 4 H, CH$_2$N), 3.69 (t, *J* = 6.2 Hz, 4 H, CH$_2$O), 6.35 (t, *J* = 2.4 Hz, 1 H, arom.), 6.77 (d, *J* = 2.4 Hz, 2 H, arom.), 6.87−7.08 (m, 12 H, arom. + NH). − ^{13}C NMR (68 MHz, [D$_7$]DMF, 25°C): δ = 30.1 (CCH$_2$C), 38.2 (CH$_2$N), 66.0 (CH$_2$O), 66.2 (CH$_2$-Ph), 106.0 (arom.), 108.3 (arom.), 128.3 (arom.), 128.9 (arom.), 134.1 (CCO$_2$H), 138.2 (arom.), 157.1 [NC(O)O], 160.6 (C=O). − MS (FAB$^-$); *m/z* (%): 535 (72.29) [M$^-$ − H].

Methyl 3,5-Bis[3-(tert-butyloxycarbonylamido)propyloxy]benzoate (**3d**): Dihydrochloride **3a** (22.7 g, 64 mmol) is suspended in a mixture of THF and water (5:1, 600 ml) to which potassium hydroxide (17.9 g, 320 mmol) and di-*tert*-butyl dicarbonate (35 g, 160 mmol) are added under stirring at 0°C. After 1 h, the aqueous phase is separated and extracted twice with dichloromethane. The organic layers are combined, dried with MgSO$_4$, and the solvent is evaporated in vacuo. The remaining residue is further purified by column chromatography using dichloromethane/methanol (2%) as the eluent. Yield: 18.6 g (66%), m.p. 122−124°C. − IR (KBr): ν = 3388 (N−H), 3373 (N−H), 2977 (C−H arom.), 2951 (C−H arom.), 2874 (C−H arom), 1720 (C=O), 1688 (amide I), 1528 (amide II), 1244 cm^{-1} (C−O). − ^{1}H NMR (270 MHz, CDCl$_3$, 25°C): δ = 1.40 (s, 18 H, C*Me*$_3$), 1.93 (quint, *J* = 6.2 Hz, 4 H, CH$_2$C*H*$_2$CH$_2$), 3.26 (q, *J* = 6.2 Hz, 4 H, CH$_2$N), 3.84 (s, 3 H, CH$_3$), 3.98 (t, *J* = 6.2 Hz, 4 H, CH$_2$O), 4.82 (t, *J* = 6.2 Hz, 2 H, NH), 6.58 (t, *J* = 2.4 Hz, 1 H, arom.), 7.11 (d, *J* = 2.4 Hz, 2 H, arom.). − ^{13}C NMR (68 MHz, CDCl$_3$, 25°C): δ = 28.3 (C*Me*$_3$), 29.4 (CH$_2$CH$_2$CH$_2$), 37.7 (CH$_2$N), 52.1 (CH$_3$), 65.9 (CH$_2$O), 79.1 (CMe$_3$), 106.5 (arom.), 107.7 (arom.), 131.8 (C_{Ar}CO$_2$Me), 159.7 (C_{Ar}O), 166.6 (*C*OOMe). − MS (70eV, EI); *m/z* (%): 482 (6.69) [M$^+$].

3,5-Bis[3-(tert-butyloxycarbonylamido)propyloxy]benzoic Acid (**3e**): A solution of ester **3d** (18.6 g, 41.9 mmol) and potassium hydroxide (3.37 g, 60 mmol) in a mixture of methanol and water (3:1, 300 ml) is refluxed for 2 h. After cooling to room temperature, acetic acid (pH = 5) is added and standard work-up using dichloromethane yields a raw material which is further purified by crystallization from methanol/water (3:1). Yield: 16.2 g (90%), m.p. 127−129°C. − IR (KBr): ν = 3367 (N−H), 2972 (C−H arom.), 2936 (C−H arom.), 2884 (C−H arom.), 1687 (C=O, amide I), 1598, 1526 (amide II), 1252 cm^{-1} (C−O). − ^{1}H NMR (270 MHz, [D$_4$]MeOH, 25°C): δ = 1.42 (s, 9 H, C*Me*$_3$), 1.94 (quint, 4 H, CH$_2$C*H*$_2$CH$_2$), 3.22 (t, 4 H, CH$_2$N), 4.01 (t, 4 H, CH$_2$O), 6.70 (t, 1 H, arom.), 7.13 (d, 2 H, arom.). − ^{13}C NMR (68 MHz, [D$_4$]MeOH, 25°C): δ = 28.8 (C*Me*$_3$), 30.6 (CH$_2$CH$_2$CH$_2$), 38.4 (CH$_2$N), 66.9 (CH$_2$O), 80.0 (CMe$_3$), 107.2 (arom.), 109.0 (arom.), 134.0 (*C*CO$_2$H), 158.5 [NC(O)O], 161.4 (C_{Ar}O), 169.7 (*C*OOH). − MS (FAB$^-$); *m/z* (%): 467 (64.05) [M$^-$ − H].

Ethyl 3,5-Bis(2-cyanoethenyl)benzoate (**5**): A solution of 78 g of ethyl 3,5-dibromobenzoate (0.25 mol), 82 ml of acrylonitrile (66.25 mg, 5 equiv.) and 2.62 g of triphenylphosphane (0.01 mol, 0.04 equiv.) in 120 ml of triethylamine is degassed. After degassing the reaction mixture, 1.12 g of palladium(II) acetate (5 mmol, 0.02 equiv.) is added under nitrogen. The solution is heated to 120°C for 7 d. After complete reaction (TLC-monitored), the participating solid is collected by filtration of the hot solution. The catalyst is removed by dissolving the colourless solid in CH_2Cl_2 and filtration through Celite. After the CH_2Cl_2 is removed in vacuo, the solid is washed with hot ethanol three times to yield 35.3 g (56.0%) of the product **5** as colourless solid, m.p. 227−228°C. − IR (KBr): ν = 3049.1 (NH), 2924.4 (CH-arom), 2215.8 (CH-arom), 1623.1 cm^{-1} (C=O). − ^{1}H NMR (270 MHz, CDCl$_3$, 25°C): δ = 1.41 (t, *J* = 7.2 Hz, 3 H, CH$_3$), 4.41 (q, *J* = 7.2 Hz, 2 H, CH$_2$), 6.02 (d, *J* = 16 Hz, 2 H, C=C), 7.45 (d, *J* = 16 Hz, 2 H, C=C), 7,62 (m, 1 H, H-ar), 8.16 (m, 2 H, H-ar). − ^{13}C NMR (63 MHz, [D$_6$]DMSO, 25°C): δ = 13.96 (s, CH$_3$), 61.18 (s, CH$_2$), 99.29 (s, C=C), 129.38 (s, C=C), 130.31 (s, C-ar), 131.41 (s, C-ar), 134.89 (s, C-ar), 148.58 (s, C-ar), 164.49 (s, C=O). − MS (EI, 180°C); *m/z* (%): 252 (39.95) [M$^+$]. − $C_{15}H_{12}N_2O_2$ (252.2): calcd. C 71.42, H 4.79, N 11.10; found C 71.27, H 4.88, N 10.89.

Ethyl 3,5-Bis(3-aminopropyl)benzoate Dihydrochloride (**6a**): 10 g of dinitrile **5** (39.7 mmol) is hydrogenated in ethanol with 28 ml of hydrochloric acid (25% HCl, 198 mmol, 5 equiv.) at 3.6 bar over palladium/C (2 g, 20%) for 14 h. After removal of the catalyst by

filtration, the solvent is removed in vacuo and 12.9 g of the dihydrochloride **6a** (96.5%) is obtained by precipitation with diethyl ether as a colourless solid, m.p. 241°C. – IR (KBr): ν = 3393.3 (NH), 3136.8 (CH-arom), 3046.4 (CH-arom), 1606.1 cm^{-1} (C=O). – ^1H NMR (270 MHz, [D$_4$]MeOH, 25°C): δ = 1.37 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.99 (m, 4 H, CH_2-), 2.77 (t, *J* = 8 Hz, 4 H, CH_2C_{arom}), 2.96 (t, *J* = 7.8 Hz, 4 H, CH_2C_{amine}), 4.35 (q, *J* = 7.1 Hz, 4 H, CH_2/ester), 7.42 (m, 1 H, H-ar), 7.76 (m, 2 H, H-ar). – ^{13}C NMR (63 MHz, [D$_4$]MeOH, 25°C): δ = 14.63 (s, CH_3), 30.01 (s, CH_2), 33.14 (s, CH_2), 40.27 (s, CH_2), 62.13 (s, CH_2/ester), 128.31 (s, C-ar), 132.01 (s, C-ar), 134.44 (s, C-ar), 142.77 (s, C-ar), 167.95 (s, C=O). – MS (EI, 200°C); *m/z* (%): 264 (amine, 7.7) [M^+].

Ethyl 3,5-Bis[3-(benzyloxycarbonylamino)propyl]benzoate (**6b**): 6.1 g (18.1 mmol) of the dihydrochloride **6a** is suspended with 6 g of KOH in 100 ml of THF and 20 ml of water at 0°C. 6.64 ml (7.7 g, 45.3 mmol, 2.5 equiv.) of benzyl chloroformate is slowly added, the reaction mixture is stirred for one more hour. After complete reaction (TLC), the layers are separated, the organic layer is washed once with brine and the inorganic layer extracted with diethyl ether. The combined organic layers are dried with $MgSO_4$, the solvent is removed in vacuo. Crystallization in ethanol/methanol (1:1) furnishes 8.9 g (92.4%) of **6b** as colourless solid, m.p. 78–80°C. – IR (KBr): ν = 3323.4 (NH), 2940.6 (CH-arom), 2863.0 (CH-arom), 1687.6 cm^{-1} (C=O). – ^1H NMR (270 MHz, $CDCl_3$, 25°C): δ = 1.38 (t, *J* = 7 Hz, 3 H, CH_3), 1.82 (m, 4 H, CH_2), 2.64 (t, *J* = 7.5 Hz, 4 H, CH_2C_{arom}), 3.17 (q, *J* = 7 Hz, 4 H, CH_2C_{amine}), 4.33 (q, *J* = 7 Hz, 2 H, CH_2/ester), 5.07 (s, 4 H, CH_2/benzyl), 7.16 (s, 1 H, H-ar), 7.29 (m, 10 H, H-ar-pg), 7.66 (d, *J* = 1 Hz, 2 H, H-ar). – ^{13}C NMR (63 MHz, CDCl3, 25°C): δ = 14.29 (s, CH_3), 31.32 (s, CH_2), 32.54 (s, CH_2), 40.34 (s, CH_2), 60.87 (s, CH_2/ester), 66.57 (s, CH_2/benzyl), 127.12 (s, C-ar), 128.01 (s, C-ar/pg), 128.43 (s, C-ar/pg), 130.74 (s, C-ar), 133.11 (s, C-ar), 136.54 (s, C-ar/pg), 141.72 (s, C-ar), 156.40 (s, C=O/pg), 166.67 (s, C=O/ester). – MS (EI, 180°C); *m/z* (%): 532 (16.15) [M^+]. – $C_{31}H_{36}N_2O_6$ (532.6): calcd. C 69.91, H 6.81, N 5.26; found C 69.59, H 6.52, N 5.10.

3,5-Bis[3-(benzyloxycarbonylamino)propyl]benzoic Acid (**6c**): 1.2 g (2.25 mmol) of the G1 ester **6b** is heated with 504 mg of potassium hydroxide (9 mmol, 4 equiv.) in methanol to 60°C for 4 h. When the reaction is finished (TLC), acetic acid is added to give a pH = 5. The G1 acid **6c** is extracted with CH_2Cl_2. The organic layer is dried with $MgSO_4$. After evaporation of the solvent, 1.06 g (93.8%) of the G1 acid **6c** is obtained as a colourless solid, m.p. 96°C. – IR (KBr): ν = 3328.8 (NH), 2946.2 (CH-arom), 1689.6 cm^{-1} (C=O). – ^1H NMR (270 MHz, $CDCl_3$, 25°C): δ = 1.81 (m, 4 H, CH_2), 2.62 (m, 4 H, CH_2C_{arom}), 3.19 (m, 4 H, CH_2C_{amine}), 4.90 (s, br, 2 H, NH), 5.08 (s, 4 H, CH_2/benzyl), 7.18 (s, 1 H, H-ar), 7.34 (m, 10 H, H-ar/pg), 7.93 (s, 2 H, H-ar). – ^{13}C NMR (63 MHz, $CDCl_3$, 25°C): δ = 31.22 (s, CH_2), 32.47 (s, CH_2), 40.35 (s, CH_2), 66.6 (s, CH_2/benzyl), 127.63 (s, C-ar), 127.99 (s, C-ar/pg), 128.40 (s, C-ar/pg), 130.02 (s, C-ar), 133.69 (s, C-ar), 136.44 (s, C-ar/pg), 141.83 (s, C-ar), 156.52 (s, C=O/pg), 170.52 (s, C=O/acid). – MS (EI, 300°C); *m/z* (%): 504 (0.1) [M^+]. – $C_{29}H_{32}N_2O_6$ (504.6): calcd. C 69.03, H 6.39, N 5.55; found C 69.32, H 6.69, N 5.26.

Ethyl 3,5-Bis[3-(tert-butyloxycarbonylamino)propyl]benzoate (**6d**): 9.0 g (26.7 mmol) of the hydrochloride **6a** is suspended with 9 g of KOH in 100 ml of THF and 20 ml of water at 0°C. 13.97 g (64.1 mmol, 2.4 equiv.) of di-*tert*-butyl dicarbonate is added slowly, the reaction mixture is stirred for one more hour. After complete reaction (TLC), the layers are separated, the organic layer is washed once with brine, the inorganic layer extracted with diethyl ether. The combined organic layers are dried with $MgSO_4$, the solvent is removed in vacuo. 11.7 g (94.6%) of **6d** is obtained as a colourless oil which slowly turns into an amorphous solid, m.p. 47°C. – IR (KBr): ν = 3366.1 (NH), 2978.2 (CH-arom), 2934.2 (CH-arom), 1712.3 cm^{-1} (C=O). – ^1H NMR (270 MHz, $CDCl_3$, 25°C): δ = 1.34 (t, *J* = 7 Hz, 3 H, CH_3/ester), 1.39 (s, 18 H, CH_3/Boc), 1.77 (m, 4 H, CH_2), 2.61 (t, *J* = 7.5 Hz, 4 H, CH_2C_{arom}), 3.08 (m, 4 H, CH_2C_{amine}), 4.31 (q, *J* = 7 Hz, 2 H, CH_2/ester), 4.78 (s, br, 2 H, NH), 7.14 (m, 1 H, H-ar), 7.63 (m, 2 H, H-ar). – ^{13}C NMR (63 MHz, $CDCl_3$, 25°C): δ = 14.24 (s, CH_3/ester), 28.32 (s, CH_3-Boc), 31.51 (s, CH_2), 32.66 (s, CH_2), 39.94 (s, CH_2), 60.79 (s, CH_2/ester), 78.99 [s, $C(CH_3)_3$], 127.05 (s, C-ar), 130.64 (s, C-ar), 133.05 (s, C-ar), 141.84 (s, C-ar), 155.91 (s, C=O/amid), 166.67 (s, C=O/ester). – MS (EI, 160°C); *m/z* (%): 464 (0.52) [M^+].

3,5-Bis[3-(tert-butyloxycarbonylamino)propyl]benzoic Acid (**6e**): 1.37 g (2.97 mmol) of the G1 ester **6d** is heated with 663 mg of potassium hydroxide (11.8 mmol, 4 equiv.) in methanol/water (4:1) to 50°C for 6 h. The reaction is monitored by TLC. When the reaction is finished, acetic acid is added until pH = 5 is reached. The G1 acid **6e** is extracted with CH_2Cl_2. The organic layer is dried with $MgSO_4$. After evaporation of the solvent, 1.14 g (88.2%) of **6e** is obtained as a colourless foam. – IR (KBr): ν = 3393.6 (NH), 2976.8 (CH-arom), 2932.6 (CH-arom), 1688.5 cm^{-1} (C=O). – ^1H NMR (270 MHz, $CDCl_3$, 25°C): δ = 1.41 (s, 18 H, CH_3-pg), 1.78 (m, 4 H, CH_2), 2.62 (t, *J* = 6.5 Hz, 4 H, CH_2C_{arom}), 3.09 (q, *J* = 6.5 Hz, 4 H, CH_2C_{amine}), 4.64 (s, br., 2 H, NH), 7.16 (m, 1 H, H-ar), 7.64 (m, 2 H, H-ar). – ^{13}C NMR (63 MHz, $CDCl_3$, 25°C): δ = 28.37 (s, CH_3), 31.54 (s, CH_2), 32.71 (s, CH_2), 39.95 (s, CH_2), 52.90 [s, $C(CH_3)_3$], 127.15 (s, C-ar), 132.11 (s, C-ar), 134.21 (s, C-ar), 141.95 (s, C-ar), 155.96 (s, C=O/pg), 167.43 (s, C=O/acid). – MS (EI, 220°C); *m/z* (%): 436 (3.15) [M^+].

Methyl 3,5-Bis{3-[3,5-bis(3-aminopropyloxy)benzoylamino]propyloxy}benzoate Tetrahydrochloride (**7a**): Tetraamine **7a** is obtained from **7b** (a) and **7d** (b)

a) Ester **7b** (2.0 g, 1.52 mmol) is suspended in ethanol (10 ml). To this suspension hydrochloric acid (25%, 1.3 ml) and Pd/C (0.2 g) are added. Hydrogenation is done at a hydrogen pressure of 4 × 10^5 Pa for 5 h after which time the reaction mixture is filtered to remove the catalyst. Evaporation of most of the ethanol gives an oily liquid to which 2-propanol is added until precipitation occurs. The precipitate is recovered by filtration and dried at 50°C in vacuo to give pure **7a**. Yield: 1.19 g (85%).

b) Ester **7d** (1.03 g, 0.87 mmol) is dissolved in THF (10 ml) and hydrochloric acid (25%, 7–8 ml) is added. After stirring for 2 h, the solution is added to acetone by which **7a** precipitates. Evaporation of the solvent at reduced pressure at 50°C gives pure **7a**. Yield: 0.81 g (99%), m.p. 236–237°C. – IR (KBr): ν = 3390 (N–H), 3250 (N–H), 2956 (N–H), 2881 (N–H), 1723 (C=O, amide I), 1544 (amide II), 1243 cm^{-1} (C–O). – ^1H NMR (500 MHz, [D$_4$]MeOH, 25°C): δ = 2.08 (quint, *J* = 6.4 Hz, 4 H, CCH_2C), 2.17 (quint, *J* = 6.4 Hz, 8 H, CCH_2C), 3.18 (t, *J* = 7.5 Hz, 8 H, CH_2N), 3.54 (t, *J* = 7.5 Hz, 4 H, CH_2N), 3.85 (s, 3 H, CH_3), 4.04 (t, *J* = 5.8 Hz, 4 H, CH_2O), 4.13 (t, *J* = 5.8 Hz, 8 H, CH_2O), 6.65 (t, *J* = 2.5 Hz, 1 H, arom.), 6.73 (t, *J* = 2.5 Hz, 2 H, arom.), 7.01 (d, *J* = 2.5 Hz, 4 H, arom.), 7.05 (d, *J* = 2.5 Hz, 2 H, arom.), 7.97–8.08 (br., 0.7 H, aggregate), 8.61 (t, 0.1 H, aggregate). – ^{13}C NMR (68 MHz, [D$_4$]MeOH, 25°C): δ = 28.1 (CCH_2C), 29.8 (CCH_2C), 38.3 (CH_2N), 38.5 (CH_2N), 53.2 (CH_3), 66.7 (CH_2O), 67.4 (CH_2O), 105.9 (arom.), 107.2 (arom.), 107.3 (arom.), 108.9 (arom.), 132.7 ($C_{Ar}CO_2Me$), 137.4 ($C_{Ar}CONHR$), 160.9 ($C_{Ar}O$), 161.2 ($C_{Ar}O$), 168.6 (C=O), 169.7 [NHC(O)R]. – MS (FAB$^+$); *m/z* (%): 783 (2.28) [M^+ + H] (tetraamine).

Methyl 3,5-Bis(3-{3,5-bis[3-(benzyloxycarbonylamino)propyloxy]benzoylamino}propyloxy)benzoate (**7b**): Dry **3c** (19.78 g, 36.9

mmol) is heated to 60°C in high vacuo for 5 h. The obtained material is now suspended in acetonitrile under nitrogen and CDI (6.04 g, 37.2 mmol) is added under stirring in one portion. Acid **3c** dissolves with evolution of carbon dioxide and stirring is continued for 12 h. Triethylamine (7.7 ml, 55.3 mmol) and dihydrochloride **3a** (6.55 g, 18.4 mmol) are added and stirring is continued for further 12 h. After completion of the reaction, the solvent is evaporated in vacuo and the residue is purified by column chromatography using dichloromethane with 5% methanol as eluent. Yield: 13 g (52%), m.p. 94−102°C. − IR (KBr) ν = 3336 (N−H), 3296 (N−H), 3063 (C−H arom.), 3032 (C−H arom.), 2936 (C−H arom.), 2875 (C−H arom.), 1720 (C=O), 1693 (amide I), 1532 (amide II), 1244 cm^{-1} (C−O). − ^1H NMR {500 MHz, [D$_4$]MeOH/[D$_6$]DMSO(2:1), 25°C}: δ = 1.83 (quint, *J* = 6.5 Hz, 8 H, $CH_2CH_2CH_2$), 1.96 (quint, *J* = 6.5 Hz, 4 H, $CH_2CH_2CH_2$), 3.18 (t, *J* = 6.5 Hz, 8 H, CH_2N), 3.42 (t, *J* = 6.5 Hz, 4 H, CH_2N), 3.74 (s, 3 H, CH_3), 3.91 (t, *J* = 6.5 Hz, 8 H, CH_2O), 3.96 (t, *J* = 6.5 Hz, 4 H, CH_2O), 4.96 (s, 8 H, CH_2-Ph), 6.53 (t, *J* = 2.1 Hz, 2 H, arom.), 6.63 (t, *J* = 2.1 Hz, 1 H, arom.), 6.92 (d, *J* = 2.1 Hz, 4 H, arom.), 7.02 (d, *J* = 2.1 Hz, 2 H, arom.), 7.13−7.30 (m, 20 H, CH_2-Ph). − ^{13}C NMR {63 MHz, [D$_4$]MeOH/[D$_6$]DMSO (2:1), 25°C}: δ = 29.7 ($CH_2CH_2CH_2$), 30.1 ($CH_2CH_2CH_2$), 37.6 (CH_2N), 38.3 (CH_2N), 52.7 (CH_3), 66.3 (CH_2O), 66.5 (CH_2-Ph), 66.8 (CH_2O), 104.9 (arom.), 106.6 (arom.), 106.9 (arom.),108.4 (arom.) 128,5 (arom.), 128.6 (arom.), 129.2 (arom.), 132.7 (C_{Ar}COOMe), 137.4 (arom.), 138.2 (C_{Ar}CONHR), 157.8 [NC(O)O], 160.9 ($C_{Ar}O$), 167.3 (COOMe), 168.3 (CONHR). − MS (FAB$^+$); *m/z* (%): 1319 (1.63) [M$^+$ + H]. − $C_{72}H_{82}N_6O_{18}$ (1319.5): calcd. C 65.54, H 6.26, N 6.37; found C 65.07, H 6.05, N 6.16.

3,5-Bis(3-{3,5-bis[3-(benzyloxycarbonylamino)propyloxy]-benzoylamino}propyloxy)benzoic Acid (**7c**): A solution of ester **7b** (23.0 g, 41.8 mmol) and potassium hydroxide (5.61 g, 100 mmol) in a mixture of THF, methanol and water (250 ml, 1:3:1) is refluxed several hours until the reaction is complete (TLC). The mixture is cooled to room temperature and acetic acid is added. After standard work-up with dichloromethane and evaporation of the solvent, the raw material is recrystallized from methanol/water. Yield: 18.3 g (81.6%), m.p. 70−85°C. − IR (KBr): ν = 3337 (N−H), 3065 (C−H arom.), 3033 (C−H arom.), 2936 (C−H arom.), 2877 (C−H arom.), 1695 (C=O, amide I), 1535 cm^{-1} (amide II). − ^1H NMR {250 MHz, [D$_4$]MeOH/[D$_6$]DMSO (2:1), 25°C}: δ = 1.82 (quint, *J* = 6.5 Hz, 8 H, $CH_2CH_2CH_2$), 1.95 (quint, *J* = 6.5 Hz, 4 H, $CH_2CH_2CH_2$), 3.16 (m, 8 H, CH_2N), 3.41 (t, *J* = 6.5 Hz, 4 H, CH_2N), 3.92 (m, 12 H, CH_2O), 4.94 (s, 8 H, CH_2-Ph), 6.52 (t, *J* = 2.1 Hz, 2 H, arom.), 6.59 (t, *J* = 2.1 Hz, 1 H, arom.), 6.89 (d, *J* = 2.1 Hz, 4 H, arom.), 7.03 (d, *J* = 2.1 Hz, 2 H, arom.), 7.13−7.31 (m, 20 H, CH_2-Ph). − ^{13}C NMR {63 MHz, [D$_4$]MeOH/[D$_6$]DMSO (2:1), 25°C}: δ = 30.2 ($CH_2CH_2CH_2$), 30.6 ($CH_2CH_2CH_2$), 38.0 (CH_2N), 66.9 (CH_2O), 67.0 (CH_2-Ph), 67.3 (CH_2O), 105.5 (arom.), 107.1 (arom.), 109.1 (arom.), 128,9 (arom.), 129.0 (arom.), 129.6 (arom.), 134.0 (C_{Ar}COOH), 137.9 (arom.), 138.6 (C_{Ar}CONHR), 158.3 [NC(O)O], 161.3 ($C_{Ar}O$), 161.4 ($C_{Ar}O$), 169.0 (CONHR), 169.2 (COOH). − MS (FAB$^+$); *m/z* (%): 1305 (0.91) [M$^+$ + H]. − $C_{71}H_{80}N_6O_{18}$ (1305.4): calcd. C 65.33, H 6.18, N 6.44; found C 64.85, H 6.16, N 6.30.

Methyl 3,5-Bis(3-{3,5-bis[3-(tert-butyloxycarbonylamino)propyloxy]benzoylamino}propyloxy)benzoate (**7d**): Dry **3e** (20.0 g, 42.7 mmol) is heated to 60°C in high vacuo for 5 h. The obtained material is suspended in dichloromethane under nitrogen and CDI (6.92 g, 42.7 mmol) is added under stirring in one portion. Acid **3c** dissolves under evolution of carbon dioxide and stirring is continued for 12 h. In a separate flask dihydrochloride **3a** (7.58 g, 21 mmol) is also suspended in dichloromethane which dissolves upon addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (3.2 g, 43 mmol). The solution of the imidazolide is added to the dissolved dihydrochloride **3a** and stirring is continued for 12 h. After completion of the reaction, the solvent is evaporated in vacuo and the residue is purified by column chromatography using dichloromethane with 5% methanol as eluent. Yield: 15 g (60%), m.p. 74−80°C. − IR (KBr) ν = 3347 (N−H), 2975 (C−H arom.), 2933 (C−H arom.), 2879 (C−H arom.), 1694 (C=O, amide I), 1534 (amide II), 1252 cm^{-1} (C−O). − ^1H NMR (500 MHz, [D$_4$]MeOH, 25°C): δ = 1.40 [s, 36 H, C(CH_3)], 1.89 (quint, *J* = 6.4 Hz, 8 H, $CH_2CH_2CH_2$), 2.05 (quint, *J* = 6.3 Hz, 4 H, $CH_2CH_2CH_2$), 3.19 (t, *J* = 6.4 Hz, 8 H, CH_2N), 3.53 (t, *J* = 6.3 Hz, 4 H, CH_2N), 3.83 (s, 3 H, CH_3), 3.96 (t, *J* = 6.4 Hz, 8 H, CH_2O), 4.01 (t, *J* = 6.3 Hz, 4 H, CH_2O), 6.58 (t, *J* = 2.5 Hz, 2 H, arom.), 6.63 (t, *J* = 2.5 Hz, 1 H, arom.), 6.94 (d, *J* = 2.5 Hz, 4 H, arom.), 7.07 (d, *J* = 2.5 Hz, 2 H, arom.). − ^{13}C NMR (126 MHz, [D$_4$]MeOH, 25°C): δ = 28.8 [C(CH_3)], 30.1 ($CH_2CH_2CH_2$), 30.6 ($CH_2CH_2CH_2$), 38.3 (CH_2N), 38.4 (CH_2N), 52.8 (CH_3), 66.8 (CH_2O), 67.1 (CH_2O), 79.9 [$C(CH_3)$], 105.5 (arom.), 106.8 (arom.), 107.3 (arom.), 108.8 (arom.), 129.3 (C_{Ar}-COOH), 137.5 (C_{Ar}CONHR), 158.4 [NC(O)O], 161.3 ($C_{Ar}O$), 161.5 ($C_{Ar}O$), 168.1 (*C*OOMe), 169.8 (CONHR). − MS (FAB$^+$); *m/z* (%): 1206 (0.08) [M$^+$ + Na].

3,5-Bis(3-{3,5-bis[3-(tert-butyloxycarbonylamino)propyloxy]-benzoylamino}propyloxy)benzoic Acid (**7e**): A solution of ester **7d** (6.5 g, 5.86 mmol) and potassium hydroxide (1.0 g, 17.6 mmol) in a mixture of THF, methanol and water (2:3:1) is refluxed for 3 h. After cooling to room temperature, acetic acid is added and standard work-up using dichloromethane furnishes a raw material which is further purified by column chromatography using dichloromethane/methanol (10%) as eluent. Yield: 6.3 g (92%), m.p. 80−95°C. − IR (KBr): ν = 3361 (N−H), 2975 (C−H arom.), 2933 (C−H arom.), 2878 (C−H arom.), 1687 (C=O, amide I), 1530 (amide II), 1251 cm^{-1} (C−O). − ^1H NMR (500 MHz, [D$_4$]MeOH, 25°C): δ = 1.40 [s, 36 H, C(CH_3)], 1.90 (quint, *J* = 6.7 Hz, 8 H, $CH_2CH_2CH_2$), 2.07 (quint, *J* = 6.7 Hz, 4 H, $CH_2CH_2CH_2$), 3.20 (t, *J* = 6.7 Hz, 8 H, CH_2NH-Boc), 3.54 (t, *J* = 6.7 Hz, 4 H, CH_2N), 3.98 (t, *J* = 6.7 Hz, 8 H, CH_2O), 4.04 (t, *J* = 6.7 Hz, 4 H, CH_2O), 6.61 (m, 3 H, arom.), 6.94 (s, 4 H, arom.), 7.13 (d, *J* = 2.0 Hz, 2 H, arom.). − ^{13}C NMR (126 MHz, [D$_4$]MeOH, 25°C): δ = 28.8 [C(CH_3)], 30.1 ($CH_2CH_2CH_2$), 30.6 ($CH_2CH_2CH_2$), 38.3 (CH_2N), 38.3 (CH_2N), 66.8 (CH_2O), 67.0 (CH_2O), 79.9 [$C(CH_3)$], 105.6 (arom.), 106.7 (arom.), 106.8 (arom.), 108.9 (arom.), 129.3 (C_{Ar}COOH), 137.5 (C_{Ar}CONHR), 158.5 [NC(O)O], 161.2 ($C_{Ar}O$), 161.5 ($C_{Ar}O$), 169.9 (CONHR), 170.6 (COOH). − MS (FAB$^+$); *m/z* (%): 1170 (0.39) [M$^+$ + H].

Ethyl 3,5-Bis{3-[3,5-bis(3-aminopropyl)benzoylamino]propyl}-benzoate Tetratrifluoroacetate (**8a**): 75 mg (0.07 mmol) of the protected G2 fragment **8d** is dissolved in CH_2Cl_2 (1.5 ml) and the same amount of trifluoroacetic acid. After stirring for 1 h, the solvent is removed completely in vacuo to give 80 mg (98.5%) of **8a** as yellowish oil. − IR (KBr): ν = 3054.9 (NH), 1677.0 cm^{-1} (C=O). − ^1H NMR (270 MHz, [D$_4$]MeOH, 25°C): δ = 1.35 (t, *J* = 7 Hz, 3 H, CH_3/ester), 1.98 (m, 12 H, CH_2), 2.73 (m, 12 H, CH_2C_{arom}), 2.92 (m, 8 H, CH_2C_{amine}), 3.40 (m, 4 H, CH_2C_{amine}), 4.31 (q, *J* = 7 Hz, 2 H, CH_2/ester), 7.27 (s, 2 H, H-ar), 7.34 (s, 1 H, H-ar), 7.51 (s, 4 H, H-ar), 7.69 (s, 2 H, H-ar). − ^{13}C NMR (63 MHz, [D$_4$]MeOH, 25°C): δ = 14.59 (s, CH_3/ester), 30.02 (s, CH_2), 31.92 (s, CH_2), 33.22 (s, CH_2), 34.05 (s, CH_2), 40.18 (s, CH_2), 40.69 (s, CH_2), 62.10 (s, CH_2/ester), 117.77 (q, CF_3), 126.27 (s, C-ar), 128.05 (s, C-ar), 131.76 (s, C-ar), 132.69 (s, C-ar), 134.55 (s, C-ar), 136.35 (s, C-ar), 142.66 (s, C-ar), 143.74 (C-ar), 162.27 (q, C=O/TFA), 168.40 (s, C=O/ester), 170.20 (s, C=O/amide). − MS (FAB$^+$); *m/z* (%): 701 (37.63) [M$^+$ + H].

Ethyl 3,5-Bis(3-{3,5-bis[3-(benzyloxycarbonylamino)propyl]-benzoylamino}propyl)benzoate (**8b**): 4.4 g (8.7 mmol) of the G1 acid **6c** is dissolved under nitrogen in dry CH_2Cl_2 at 0°C. 1.336 g (8.7 mmol, 1 equiv.) of hydroxybenzotriazole is added. After 10 min, 1.84 g (9.6 mmol, 1.1 equiv.) of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride is added and the reaction mixture is stirred until the hydrochloride is dissolved completely. Then 3.03 ml (2.25 mg, 12.4 mmol, 2 equiv.) of ethyldiisopropylamine and 1.47 g (4.35 mmol, 0.5 equiv.) of the G1 hydrochloride **6a** are added. The reaction mixture is stirred for 14 h at room temperature. It is then washed with a saturated solution of $NaHCO_3$, citric acid (20%) and brine and the aqueous solutions are extracted with CH_2Cl_2. The combined organic layers are dried with $MgSO_4$, the solvent is removed in vacuo. Treatment of the crude reaction mixture with methanol under ultrasound furnishes 4.1 g (76.4%) of **8b** as a colourless solid, m.p. 76°C. − IR (KBr): ν = 3328 (NH), 2939 (CH-arom.), 2862 (CH-arom.), 1689 cm^{-1} (C=O). − ^1H NMR (270 MHz, $CDCl_3$, 25°C): δ = 1.31 (t, *J* = 7 Hz, 3 H, CH_3/ester), 1.72 (m, 8 H, CH_2), 1.91 (m, 4 H, CH_2), 2.51 (t, *J* = 7 Hz, 8 H, CH_2C_{arom}), 2.66 (t, *J* = 7 Hz, 4 H, CH_2C_{arom}), 3.08 (q, *J* = 6 Hz, 8 H, CH_2C_{amine}), 3.38 (q, *J* = 6, 4 H, CH_2C_{amine}), 4.32 (q, *J* = 7 Hz, 2 H, CH_2/ester), 5.02 (s, 8 H, CH_2-benzyl-pg), 5.12 (s, br., 4 H, NH-pg), 7.02 (s, br., 2 H, H-ar), 7.18 (s, 1 H, H-ar), 7.35 (s, 22 H, H-ar-pg + NH), 7.38 (s, 4 H, H-ar), 7.66 (s, H-ar). − ^{13}C NMR (63 MHz, CDCl3, 25°C): δ = 14.15 (s, CH_3/ester), 30.56 (s, CH_2), 30.85 (s, CH_2), 32.17 (s, CH_2), 32.74 (s, CH_2), 39.29 (s, CH_2), 39.87 (s, CH_2), 60.79 (s, CH_2/ester), 66.34 (s, CH_2-pg), 124.70 (s, C-ar), 127.01 (s, C-ar), 127.55 (s, C-ar-pg), 127.84 (s, C-ar-pg), 128.28 (s, C-ar-pg), 130.46 (s, C-ar), 131.42 (s, C-ar), 133.08 (s, C-ar), 134.65 (s, C-ar), 136.41 (s, C-ar-pg), 141.52 (s, C-ar), 141.83 (s, C-ar), 156.46 (s, C=O/pg), 166.65 (s, C=O/ester), 167.77 (s, C=O/amide). − MS (FAB^+); *m/z* (%): 1237 (0.44) [M^+ + H]. − $C_{73}H_{84}N_6O_{12}$ (1236.6): calcd. C 70.84, H 6.85, N 6.79; found C 70.44, H 6.63, N 6.70.

3,5-Bis(3-{3,5-bis[3-(benzyloxycarbonylamino)propyl]benzoylamino}propyl)benzoic Acid (**8c**): 6.9 g (5.58 mmol) of the G2 ester **8b** is stirred in 500 ml of a methanol/water/THF mixture (3:1:1) with 1.25 g of potassium hydroxide (22.3 mmol, 4 equiv.) for 12 h at 60°C. After the reaction mixture has cooled, acetic acid is added until pH = 5 is reached.The acid is extracted with CH_2Cl_2. The organic layer is dried with $MgSO_4$ and then concentrated to approx. 25%. Upon cooling, acid **8c** crystallizes as colourless solid. Yield: 5.66 g (84.1%), m.p. 91°C. − IR (KBr): ν = 3328.4 (NH), 2941.2 (CH-arom), 2863.1 (CH-arom), 1692.7 cm^{-1} (C=O). − ^1H NMR (270 MHz, $CDCl_3$, 25°C): δ = 1.79 (m, 12 H, CH_2), 2.50 (m, 8 H, CH_2C_{arom}), 2.59 (m, 4 H, CH_2C_{arom}), 3.03 (m, 8 H, CH_2C_{amine}), 3.25 (m, 4 H, CH_2C_{amine}), 5.09 (s, 8 H, CH_2-benzyl), 5.34 (s, br, 4 H, NH-pg), 6.99 (s, 2 H, H-ar), 7.25 (s, 20 H, H-ar-pg), 7.34 (s, 2 H, H-ar), 7.39 (s, 4 H, H-ar), 7.64 (s, 1 H, H-ar). − ^{13}C NMR (63 MHz, $CDCl_3$, 25°C): δ = 30.46 (s, CH_2), 30.98 (s, CH_2), 32.32 (s, CH_2), 32.68 (s, CH_2), 39.17 (s, CH_2), 40.02 (s, CH_2), 66.43 (s, CH_2-benzyl), 124.83 (s, C-ar), 125.87 (s, C-ar), 127.85 (s, C-ar-pg), 128.37 (s, C-ar-pg), 131.57 (s, br., C-ar), 132.12 (s, C-ar), 134.66 (s, C-ar), 136.52 (s, C-ar-pg), 141.68 (s, C-ar), 142.11 (s, C-ar), 156.57 (s, C=O/amide-pg), 165.5 (s, C=O/acid), 167.90 (s, C=O/amide). − MS (FAB^+); *m/z* (%): 1231 (0.25) [M + Na], 1209 (0.59) [M + H]. − $C_{71}H_{80}N_6O_{12}$ (1208.6): calcd. C 70.50, H 6.67, N 6.95; found C 70.00, H 6.78, N 6.78.

Ethyl 3,5-Bis(3-{3,5-bis[3-(tert-butyloxycarbonylamino)propyl]-benzoylamino}propyl)benzoate (**8d**): 1.305 g (3.0 mmol) of the G1 acid **6e** is dissolved under nitrogen in dry CH_2Cl_2 at 0°C. 459 mg (3.0 mmol, 1 equiv.) hydroxybenzotriazole is added. After 10 min, 633 mg (3.3 mmol, 1.1 equiv.) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride is added, the reaction mixture is stirred until the hydrochloride is dissolved completely. Then 1.044 ml (775 mg, 6 mmol, 2 equiv.) of ethyldiisopropylamine and 506 mg (1.5 mmol, 0.5 equiv.) of the G1 hydrochloride **6a** are added. The reaction mixture is stirred for 14 h at room temperature. It is then washed with a saturated solution of $NaHCO_3$, citric acid (20%) and brine, the aqueous solutions are extracted with CH_2Cl_2. The combined organic layers are dried with $MgSO_4$, the solvent is removed in vacuo. Column chromatography (silica gel/CH_2Cl_2 with 2% methanol) gives 1.45 g (88%) of the G2 **8d** as colourless foam. − IR (KBr): ν = 3339.3 (NH), 2976.2 (CH-arom), 2932.3 (CH-arom), 1713.3 (C=O), 1692.7 cm^{-1} (C=O). − ^1H NMR (270 MHz, $CDCl_3$, 25°C): δ = 1.24 (t, *J* = 7 Hz, 3 H, CH_3-ester), 1.39 (s, 18 H, CH_3-pg), 1.72 (m, 8 H, CH_2), 1.95 (m, 4 H, CH_2), 2.56 (m, 8 H, CH_2C_{arom}), 2.69 (m, 4 H, CH_2C_{arom}), 3.04 (m, 8 H, CH_2C_{amine}), 3.40 (m, 4 H, CH_2C_{amine}), 4.31 (q, *J* = 7 Hz, 2 H, CH_2-ester), 4.73 (s, br., 4 H, NH-pg), 7.04 (s, br., 5 H, H-ar + NH), 7.39 (s, 4 H, H-ar), 7.67 (s, 2 H, H-ar). − ^{13}C NMR (63 MHz, $CDCl_3$, 25°C): δ = 14.32 (s, CH_3/ester), 28.39 (s, CH_3-pg), 30.88 (s, CH_2), 31.28 (s, CH_2), 32.38 (s, CH_2), 32.97 (s, CH_2), 39.46 (s, br, CH_2), 60.88 (s, CH_2/ester), 79.14 [s, $C(CH_3)_3$], 124.81 (s, C-ar), 127.19 (s, C-ar), 130.66 (s, C-ar), 131.56 (s, C-ar), 133.28 (s, C-ar), 134.77 (s, C-ar), 141.74 (s, C-ar), 141.96 (s, C-ar), 156.09 (s, C=O/pg), 166.78 (s, C=O/ester), 167.86 (s, C=O/amide). − MS (FAB^+); *m/z* (%) = 1124 (0.12) [M + Na].

3,5-Bis(3-{3,5-bis[3-(tert-butyloxycarbonylamino)propyl]benzoylamino}propyl)benzoic Acid (**8e**): 1.18 g (1.07 mmol) of the G2 ester **8d** is stirred in 100 ml of a methanol/water/THF mixture (3:1:1) with 240 mg of potassium hydroxide (4.28 mmol, 4 equiv.) for 12 h at 50°C. After the reaction mixture has cooled, acetic acid is added until pH = 5 is reached. The acid is extracted with CH_2Cl_2. The organic layer is dried with $MgSO_4$. After purification by column chromatography (silica gel/CH_2Cl_2 with 5% MeOH), 963 mg of the acid **8e** (84.3%) is obtained as colourless oil. − IR (KBr): ν = 3346.2 (NH), 2976.4 (CH-arom), 2932.3 (CH-arom), 1693.1 cm^{-1} (C=O). − ^1H NMR (270 MHz, $CDCl_3$, 25°C): δ = 1.38 (s, 18 H, CH_3-pg), 1.71 (m, 8 H, CH_2), 1.91 (m, 4 H, CH_2), 2.54 (m, 8 H, CH_2C_{arom}), 2.65 (m, 4 H, CH_2C_{arom}), 3.02 (m, 8 H, CH_2C_{amine}), 3.35 (m, 4 H, CH_2C_{amine}), 4.82 (s, br., 4 H, NH-pg), 7.02 (s, br., 4 H, H-ar+NH), 7.19 (s, 1 H, H-ar), 7.36 (s, 4 H, H-ar), 7.69 (s, 2 H, H-ar). − ^{13}C NMR (63 MHz, $CDCl_3$, 25°C): δ = 28.35 (s, CH_3/Boc), 30.89 (s, CH_2), 31.29 (s, CH_2), 32.45 (s, CH_2), 33.03 (s, CH_2), 39.62 (s, br, CH_2), 79.10 [s, $C(CH_3)_3$], 124.78 (s, C-ar), 127.53 (s, C-ar), 130.60 (s, C-ar), 131.49 (s, C-ar), 133.19 (s, C-ar), 134.65 (s, C-ar), 141.74 (s, br., C-ar), 156.15 (s, C=O/pg), 166.78 (s, C=O/acid), 167.86 (s, C=O/amide). − MS (FAB^+); *m/z* (%): 1072 (42.74) [M^+].

Note added in proof (April 29, 1998): We thank one of the referees for drawing our attention to a suggested dendron nomenclature according to which the G-2 dendrons reported here are G-1 dendrons. Since the nomenclature of these compounds is still under debate we prefer to wait until IUPAC recommendations are available.

[1] A.-D. Schlüter, *Towards Nanocylinders: Dendrimers with Polymeric Core* in *Top. Curr. Chem.*, vol. "Dendrimers" (Ed.: F. Vögtle), Springer, Heidelberg, to appear **1998**.
[2] S. I. Stupp, S. Son, L. S. Li, H. C. Lin, M. Keser, *J. Am. Chem. Soc.* **1995**, *117*, 5212.
[3] B. Karakaya, W. Claussen, K. Gessler, W. Saenger, A.-D. Schlüter, *J. Am. Chem. Soc.* **1997**, *119*, 3296; W. Stocker, B. L. Schürmann, J. P. Rabe, S. Förster, P. Lindner, I. Neubert, A.-D. Schlüter, *Adv. Mater.*, in press; W. Stocker, B. Karakaya, B. L. Schürmann, J. P. Rabe, A.-D. Schlüter, *J. Am. Chem. Soc.*, submitted.

[4] R. Klopsch, P. Franke, A.-D. Schlüter, *Chem. Eur. J.* **1996, 2**, 1330−1334.
[5] For references, see: G. R. Newkome, C. N. Moorefield, F. Vögtle, *Dendritic Molecules − Concepts, Syntheses, Perspectives*, VCH, Weinheim, **1996**.
[6] After we had started this work, a different but related synthesis to amino-functionalized dendrons appeared in the literature: S. J. E. Mulders, A. J. Brouwer, P. G. J. van der Meer, R. M. J. Liskamp, *Tetrahedron Lett.* **1997**, *38*, 631; S. J. E. Mulders, A. J. Brouwer, R. M. J. Liskamp, *Tetrahedron Lett.* **1997**, *38*, 3085.
[7] D. Zanini, R. Roy, *J. Org. Chem.* **1996**, *61*, 7348−7354.
[8] G. Denkewalter, J. Kolc, W.J . Lucasavage, *U.S. Pat. 4,289,872* (Sept. 15, **1981**).
[9] Lower hydrogen pressure ($1 \cdot 10^{+5}$ Pa) leads to hydrogenation of the olefins only.
[10] H. A. Staab, *Justus Liebigs Ann. Chem.* **1957**, *609*, 75.
[11] J. C. Sheehan, J. Preston, P. A. Cruickshank, *J. Am. Chem. Soc.* **1965**, *87*, 2492; J. C. Sheehan, S. L. Ledis *J. Am. Chem. Soc.* **1973**, *95*, 875; W. König, R. Geiger, *Chem. Ber.* **1970**, *103*, 788.
[12] A. Kraft, *J. Chem. Soc., Chem. Commun*. **1996**, 77.

[98033]