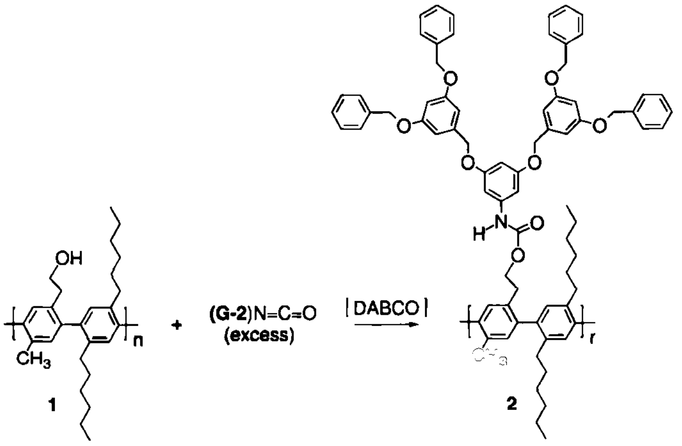
Repetitive Strategy for Exponential Growth of Hydroxy-Functionalized Dendrons

Abstract: The synthesis of dendrons with orthogonally protected functional groups, which allows the construction of dendrons in an exponential fashion, is described. The sequence has been carried out on a gram scale for the first, second, and fourth generation. The dendrons have a relatively loose and flexible structure, which should make further growth feasible. Owing to the dendrons' adjustable and broadly applicable substitution pattern, they are the first representatives of a future construction kit for the systematic synthesis of layered dendrimers. The coupling step involves urethane formation.

Keywords
dendrimers · exponential growth · repetitive syntheses

Introduction

The goal of a long-term project we are currently pursuing is to synthesize macromolecules that are hybrids of dendrimers and rigid-rod polymers.[1] These molecules are structurally characterized by a rigid backbone to which dendritic fragments (dendrons) have been attached through functional groups. If the density of dendrons on the backbone is high enough and the dendrons are large enough, these macromolecules should attain a cylindrical shape in solution. They are of interest not only because they complement conventional dendrimers,[2] for which spherical shapes have been postulated, but also because they could find application as new constituents of micelles, vesicles, and membranes, and in the wide field of biomedicine.[3] Recently, it was shown that the poly(*para*-phenylene) **1**, which carries hydroxyl functions at every other phenylene unit, can be completely substituted with first and second generation Fréchet-type dendrons with isocyanate focal points to give the dendrimer **2** (Scheme 1).[4] In order to be able to modify the "surface" of this and similar polymers, dendrons with functional groups in the periphery are required. They could then be used for growing a second and new dendritic layer on top of the first or for introducing charged groups. In the first case, cylinders with layered structures would be the target and in the second water-soluble cylinders. Here, we report the first steps of a multigram, repetitive synthesis of dendrons with acid azide functions at the focal point and protected hydroxyl functions on the periphery. The strategy used could potentially enable exponential growth, which is also shown.



Scheme 1. Substitution of a polymer backbone with dendrons

Results and Discussion

Repetitive strategies have gained increasing importance in synthetic organic chemistry, especially if large, monodisperse compounds are the targets. They use orthogonal protecting groups in each building block and reduce the synthetic effort to a minimum. The growth process can be linear, exponential, monodirectional or bidirectional. In the case of exponential growth, the total number of reaction steps is very small, even for compounds whose molecular weights are in the polymer range. Examples that come to mind are Whiting's polymethylene giganto cycles,[5] Moore's phenylacetylene macrocycles,[6] and Tour's phenylacetylene rods.[7] A similar approach has recently been applied to the synthesis of phenylacetylene dendrimers by Moore.[8, 9] Encouraged by these studies, we decided to apply this strategy to dendrons with hydroxyl functional groups on the periphery.[10] Scheme 2 outlines the functional and protecting groups used as well as the growth pattern, according to

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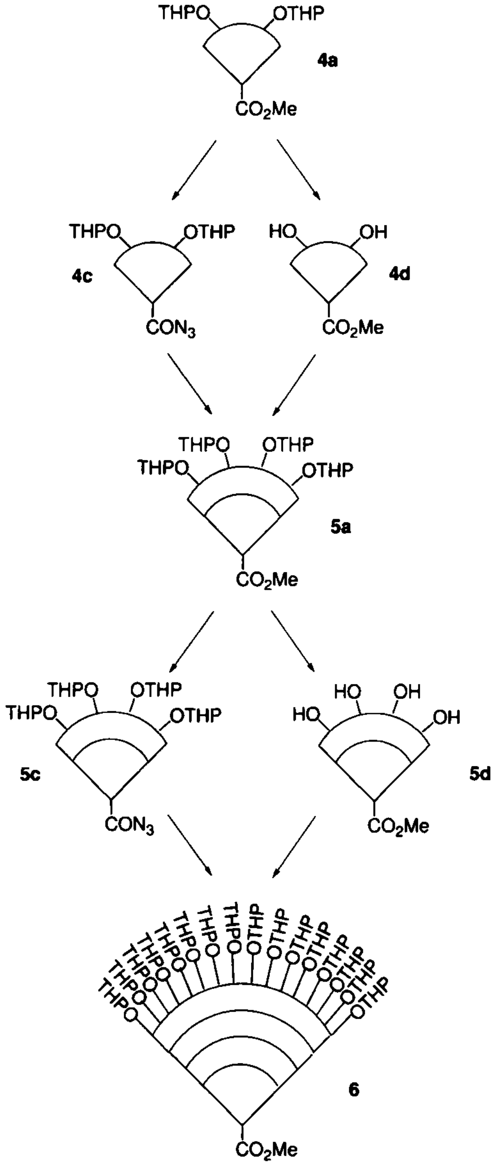
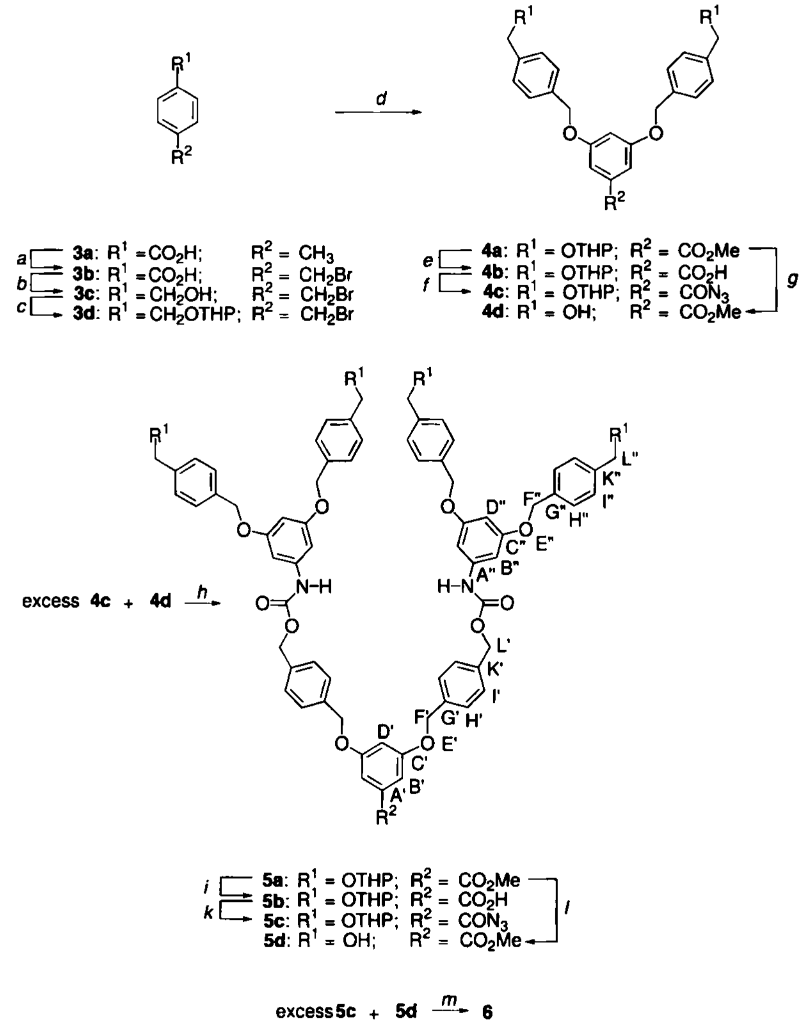


Scheme 2. Strategy for the synthesis of a fourth generation dendron functionalized with hydroxyl groups on the periphery.



Scheme 3. Reagents and conditions: a) NBS, hν, CH_2Cl_2, 2 h, reflux (80%); b) BH_3, THF, 1 h, reflux (80%); c) DHP, TsOH, CH_2Cl_2, 30 min, 0 °C (99%); d) methyl 2,4-dihydroxybenzoate, K_2CO_3, tetrabutylammonium iodide, acetone, reflux (95%); e) KOH, THF, 12 h, reflux (95%); f) 1. ClC(O)OEt, NEt_3, acetone, 30 min, 0 °C; 2. NaN_3/H_2O, acetone, 30 min, 0 °C (95%); g) HCl, DMF/MeOH (1:1), 12 h, RT (87%); h) DABCO, toluene, 2 h, reflux (ca. 60%); i) KOH, THF 12 h, reflux (93%); k) 1. ClC(O)OEt, NEt_3, acetone, 30 min, 0 °C; 2. NaN_3/H_2O, acetone, 2 h, 0 °C (85%); l) HCl, DMF/MeOH (1:1), 12 h, 20 °C (97%); m) DABCO, toluene, 2 h, reflux (89%).

which a fourth generation dendron was obtained after only two coupling steps. Scheme 3 provides the structural details of the dendrons synthesized as well as the actual chemistry involved.

The sequence starts with the first generation dendron **4a**, which contains two tetrahydropyran(THP)-protected hydroxyl functions on the "periphery" and an ester function at the focal point. If a repetitive strategy is to be brought about, then both the conversion of the ester into an azide to give **4c** and the selective deprotection of the hydroxides to give **4d** ought to proceed without mutual interference. Reaction of two equivalents of **4c** with **4d** should then furnish the second generation dendron **5a** which has the same substitution pattern as **4a**. Repetition of the two steps, azide formation and deprotection, should give **5c** and **5d**, which can then be used to synthesize higher generation dendrons as well as to modify polymers with dendritic fragments. Dendrons **4a** and **5a** play a key-role and were therefore synthesized on a multi-gram scale. Their selective deprotection and trans-functionalization were carefully studied.

Dendron **4a** was prepared in high yield from methyl 2,4-dihydroxybenzoate and benzyl bromide (**3d**) by standard chemistry and was obtained in 150 g batches. Basic hydrolysis of **4a** gave **4b**, which was esterified with ethyl chloroformate and then converted into the azide **4c** with sodium azide. The THP protective groups on **4a** were cleaved in dimethylformamide/methanol (1:1) with traces of HCl.[11] Dendrons **4c** and **4d** were obtained in yields of 88% (two steps, purified by column chromatography) and 74% (purified by crystallization), respectively. According to an NMR analysis of purified samples, both deprotection and azide formation can be driven beyond 98%. How this was determined will be explained for the next generation dendron **5a** (see below). Since azide **4c** is an oil and cannot be lyophilized, some effort was expended to make sure it was dry before converting it into the isocyanate. The best results were obtained with barium oxide. Treatment of a concentrated toluene slurry of **4c** with approximately 100 wt% of this drying agent after filtration afforded a material which still contained some water, but was dry enough for further use. Dendron **4c** was attached to **4d** by adding a solution of the isocyanate precursor (slight excess) to a refluxing toluene solution of **4d** in the presence of catalytic amounts of diazabicyclo[2.2.2]octane (DABCO).[12] The progress of the reaction was monitored by

TLC. Standard workup gave **5a** as an analytically pure material in an overall yield of 60% (based on **4a**) on a 20 g scale. Figure 1a shows the ^{1}H NMR spectrum of material prepared in a 10 g batch to illustrate the purity, which is estimated to be 96–97%. A product with a higher purity can be obtained, but only by repeated column chromatrography, which is associated with loss of material.

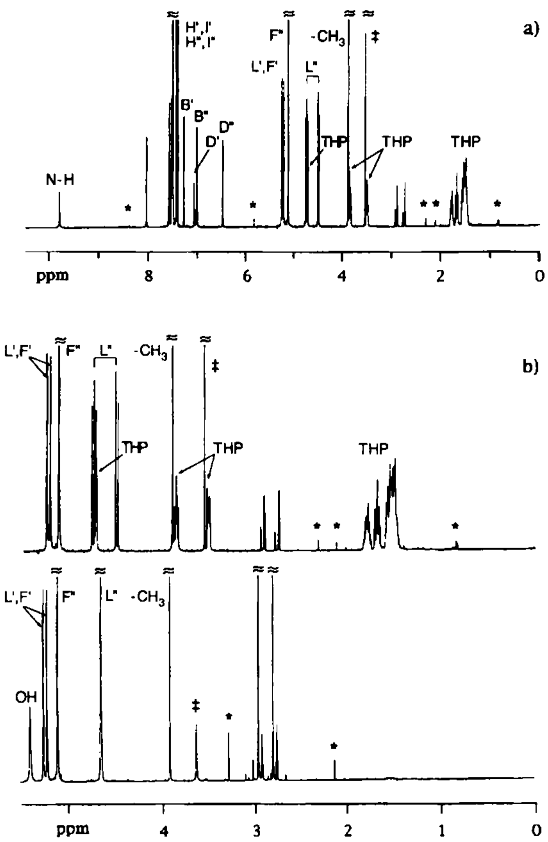


Fig. 1. a) ^{1}H NMR spectrum (500 MHz, [D$_7$]DMF, 20 °C) of **5a**; b) comparison of the ^{1}H NMR spectra of **5a** and **5d** (expansions) showing the disappearance of the signals of the THP protecting groups. Unidentified signals are indicated by *; water is indicated by ‡. The lettering used for the assignment is explained in Scheme 3. Signals from residual DMF appear at δ = 2.7 and 2.9.

The transformation of **5a** into **5c** and **5d** was carried out in a virtually identical fashion as for **4a**, and gave these materials on a 3 and 5 g scale. The degree of conversion in the transformation of **5a** to **5d** was investigated in some detail because of its importance for the project outlined. The best results were obtained when **5a** was treated with hydrochloric acid (0.13%) in DMF/MeOH (1:1) in two consecutive steps each lasting 10 h. After the first run the degree of deprotection was 96.0–97.5% and after the second run over 99.6%. These values were determined by integration of reliable signals in the ^{1}H NMR spectra of crude **5a**.[13] Figure 1b compares the spectra of **5a** (top) and **5d** (bottom) obtained after the first exposure to hydrochloric acid. The THP signals of **5a** have virtually disappeared in the spectrum of **5d**. For a quantitative analysis the weighted intensities of the benzylic signals L" (Scheme 3) of **5d** were compared with the averaged residual intensities of THP at both δ = 1.4–1.9 and δ = 4.7–4.8. It should be noted that neither the NMR spectra nor TLC investigations gave any indication of dendron decomposition, even after ten times the reaction times and concentrations of acid (1.3%), and higher temperatures (70 °C). This is an important issue with regard to the polymer-related goal of this research. Once dendrons are attached to a polymer, even partial decomposition is detrimental, because purification or healing is inherently impossible.

Encouraged by the clean deprotection of **5d**, we then aimed to demonstrate that this strategy can be used to realize exponential growth patterns in hydroxyl-functionalized dendrons on a gram scale. All that was required was the synthesis of the corresponding fourth generation dendron **6**. This was achieved by attaching isocyanates derived from **5c** to each of the four hydroxyl groups of **5d**. Both **5c** and **5d** were carefully dried prior to use: **5d** was heated to 100 °C under a high vacuum for 2 h; **5c** was first lyophilized (benzene) and then warmed to 50 °C under high vacuum for 5 h, whereby the initially very light and voluminous material solidified into a fully transparent, colorless glass which was used as obtained. The growth reaction was achieved by treating a solution of **5d** in dimethylformamide with five equivalents of **5c** (only 1 equiv excess!) in toluene at 110 °C. Column chromatography afforded the expected dendron **6** on a 3 g scale in yields of 85–90%. The extent of substitution of the hydroxyl groups of **5d** in **6** was investigated by NMR. As a reference, a sample of **6** was synthesized with an average coverage of only 72%. With incomplete coverage of **5d** with **5c** dendrons, free hydroxymethylene groups (L") are present, which resonate at δ = 4.59. The ^{1}H NMR spectrum of **6** prepared as described above shows this signal, but with a very low intensity. The integrals point to an average coverage significantly higher than 96%. Dendron **6** was further characterized by MALDI-TOF mass spectrometry with *trans*-3-(3-indolylic)acrylic acid as the matrix material (Fig. 2). The spectrum shows the peak of highest intensity at 7.257 kDa (width at half height: 22 Da), which resembles the sodium adduct (molecular mass of **6**: 7.234 kDa), and a smaller peak of comparable width at 7.172 kDa. Since the mass difference between these peaks is that of THP (85 Da), the signal at lower mass indicates some fragmentation with loss of one THP protecting group or, alternatively, partial deprotection initiated by the acidic conditions.[14] It is worth noting that there are no signals with smaller molar masses, which would be expected for incomplete coverage. The small signals at molar masses 14.402 kDa and 14.482 kDa stem from noncovalently bonded dimeric aggregates. Gel permeation chromatography shows a monomodal elution curve at 8.830 kDa (peak maximum) relative to polystyrene with a polydispersity of 1.05 and gives no indication of a dimeric species.[15]

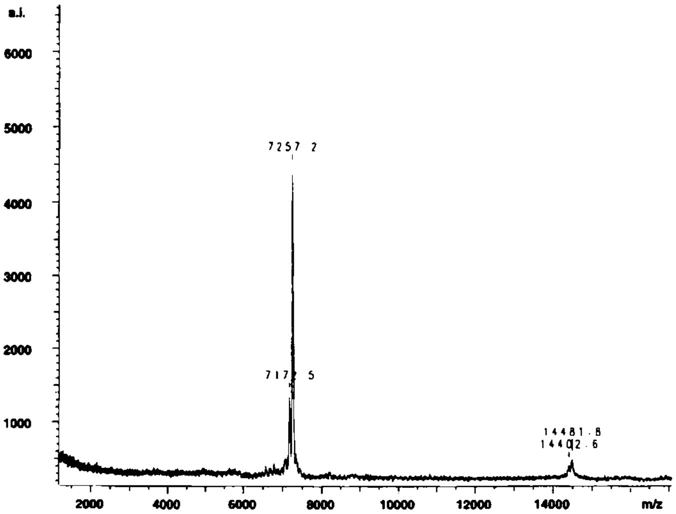


Fig. 2. MALDI-TOF spectrum of (THPO)$_{16}$[G-4]CO$_2$Me (**6**).

Experimental Section

Materials and general methods: All chemicals were purchased from Aldrich or Merck and used without further purification. Toluene was dried with sodium metal and benzophenone as indicator. DMF was dried by heating to 100 °C over BaO for 5 h under reduced pressure. Because of their high reactivity, isocyanates were not normally isolated, but generated in situ from the corresponding azides by a clean thermal rearrangement at 110 °C. The azides were purified by column chromatography on silica gel. Owing to the thermal instability of azides, the microanalytical data were obtained from the isocyanates. Most NMR spectra were recorded in $CDCl_3$ (Tables 1 and 2). Some spectra were recorded in $[D_7]$DMF for solubility as well as assignment reasons. These data are given below.

Table 1. Selected ^{13}C NMR data of compounds **4a**–**6** (spectra were obtained in $CDCl_3$ at 20 °C).

	Gen. [e]	A	B	C	D	F [a]	G [b]	H [c]	I [c]	K [b]	L [a]
4a	1	132.0	108.3	159.7	107.3	70.1	135.7	127.6	128.0	138.3	68.4
4b	1	131.3	108.8	159.7	108.0	70.0	135.6	127.6	128.1	138.2	68.4
4c	1	132.3	107.0	159.8	108.5	70.0	135.4	127.5	127.9	138.3	68.3
4d	1	132.0	108.4	159.7	107.3	70.0	135.8	127.2	127.7	140.8	64.9
5a	1	131.8	107.0	159.4	108.2	69.5	135.8	127.4	128.2	136.3	66.3
	2	139.7	97.9	160.0	97.3	69.5	135.8	127.3	127.7	137.8	68.2
5b [d]	1	134.0	108.9	160.5	107.1	70.2	137.4	128.4	129.0	137.6	66.4
	2	142.0	98.3	160.9	96.7	70.0	137.1	128.6	128.9	139.1	68.8
5c	1	132.4	108.1	159.7	108.5	69.8	135.9	127.6	128.4	136.3	66.5
	2	139.6	98.0	160.2	97.5	69.8	135.9	127.5	127.9	138.0	68.4
5d [d]	1	132.7	108.7	160.6	107.4	70.2	137.6	128.6	128.9	137.5	66.3
	2	142.0	98.4	160.9	96.7	70.1	136.4	127.2	128.3	143.3	64.0
6	1	132.0	108.4	159.5	107.1	69.4	135.7	127.5–128.4		136.5	66.5
	2	139.6	97.8	160.0	97.8	69.7	135.2	127.5–128.4		136.8	66.5
	3	139.6	97.6	160.1	97.3	69.7	135.9	127.5–128.4		137.9	68.4

[a] The assignment of shifts to positions F and L is uncertain, except for **4a**–**4d**. [b] The assignment of shifts to positions G and K is uncertain. [c] The assignment of shifts to positions H and I is uncertain. [d] Recorded in $[D_7]$DMF. [e] Generations were assigned by comparing intensities.

Table 2. Selected ^1H NMR ($CDCl_3$) chemical shift data of compounds **4a**–**6**.

	Gen.	B	D	F	H/I	L [a]
4a		7.28	6.78	5.02	7.40	4.50/4.78
4b		7.35	6.82	5.06	7.40	4.52/4.80
4c		7.26	6.83	5.04	7.40	4.52/4.81
4d		7.25	6.74	5.02	7.35 [b]	4.65
5a	1	7.28	6.76	5.01	7.00	5.16
	2	6.74	6.32	4.96	7.44	4.49/4.78
5b [c]	1	7.28	7.01	5.20	7.53 [b]	5.24
	2	6.98	6.45	5.11	7.45 [b]	4.49/4.75
5c	1	7.24	6.79	5.04	7.39	5.18
	2	6.69	6.32	4.98	7.26 [b]	4.69/4.78
5d [c]	1	7.29	7.07	5.23	7.55 [b]	5.26
	2	7.01	6.46	5.10	7.44 [b]	4.65
6	1	7.16	6.63	4.89	7.23	5.02
	2	6.61	6.18	4.81	7.22	5.02
	3	6.63	6.21	4.84	7.25	4.39/4.68

[a] Diastereotopic protons in the periphery except for **4d** and **5d**. [b] AA'BB' centered at this chemical shift. [c] Recorded in $[D_7]$DMF.

3,5-Bis[4-(tetrahydropyran-2-yloxymethyl)benzyloxy]benzoic acid methylester (4a): Benzyl bromide **3d** (124 g, 435 mmol), methyl 2,4-dihydroxybenzoate (34.7 g, 206 mmol), potassium carbonate (90 g, 651 mmol), and tetrabutylammonium iodide (1 g, 3 mmol) were placed in a three-necked flask and refluxed with dry acetone (1200 mL) for 12 h. After the mixture had cooled to RT, precipitated potassium bromide was filtered off and the solvent evaporated in vacuo. **4a** was obtained as a pale, yellowish oil (112.9 g, 95%) and used without further purification. IR (KBr film): $\tilde{\nu}$ = 3055, 3023 (C–H arom.), 2944, 2870 (C–H aliph.), 1723 (C=O), 1595, 1517 (C=C), 1446, 1375, 1349, 1323, 1300, 1235, 1201, 1182, 1158 (C–O), 1135, 1120, 1077, 1058, 1035, 1020, 976, 906, 888, 870, 859, 845, 815, 782, 768, 736, 677, 429 cm^{-1}; MS (70 eV, EI) *m/z* (%): 576 (1.2) $[M^+]$; $C_{34}H_{40}O_8$ (576.7): calcd C 70.81, H 6.99, found C 70.73, H 6.90.

3,5-Bis[4-(tetrahydropyran-2-yloxymethyl)benzyloxy]benzoic acid (4b): The ester **4a** (18.2 g, 31.5 mmol) was dissolved in THF (250 mL). To this solution was added water (25 mL) and potassium hydroxide (8.4 g, 150 mmol). The reaction mixture was heated under reflux for 14 h, allowed to cool to RT, and added to 5% acetic acid. Standard workup with diethyl ether as extracting solvent gave 16.8 g of **4b** (95%) after silica gel chromatography with CH_2Cl_2/10% methanol as eluent. M.p. 111–118 °C; IR (KBr): $\tilde{\nu}$ = 3059, 3021 (C–H arom.), 2942, 2893, 2869 (C–H aliph.), 2703, 2640, 2563, 2529 (OH), 1694 (C=O), 1596, 1519 (C=C), 1465, 1449, 1420, 1379, 1348, 1301, 1272, 1219, 1201, 1168 (C–O), 1122, 1060, 1034, 974, 906, 869, 845, 814, 769, 732, 493 cm^{-1}; MS (FAB^-): *m/z* (%): 561 (100) $[M^- - H]$; $C_{33}H_{38}O_8$ (562.7): calcd C 70.44, H 6.81, found C 70.3, H 6.80.

3,5-Bis[4-(tetrahydropyran-2-yloxymethyl)benzyloxy]benzoic acid azide (4c): Triethylamine (1.1 mL, 7.91 mmol) and ethyl chloroformate (0.83 mL, 8.63 mmol) were added to a stirred solution of **4b** (4.05 g, 7.2 mmol) in dry acetone (50 mL) under nitrogen at 0 °C . After 0.5 h the mixed anhydride was further treated with a solution of sodium azide (0.94 g, 14.4 mmol) in 1–2 mL of water. Azide formation was complete within 0.5 h as indicated by TLC. Standard workup with ice-water as the aqueous phase and ether yielded 3.95 g of **4c** (93%) as a yellowish oil after silica gel chromatography (CH_2Cl_2/1% methanol). IR (KBr film): $\tilde{\nu}$ = 3096, 3057, 3026 (C–H arom.), 2740, 2653 (OH), 2263 (N=C=O, w), 2143 (N=N=N, s), 1695 (C=O), 1594, 1518 (C=C), 1445, 1422, 1375, 1349, 1321, 1297, 1261, 1201, 1159 (C–O), 1134, 1122, 1057, 1034, 1018, 976, 905, 870, 846, 789, 742, 673, 568, 528, 484, 458, 429 cm^{-1}; MS (FAB^+): *m/z* (%): 587 (0.34) $[M^+]$; $C_{33}H_{37}NO_7$ (559.7): calcd C 70.82, H 6.66, N 2.50, found C 70.78, H 6.65, N 2.45 (values for isocyanate).

Methyl 3,5-bis[4-(hydroxymethylbenzyloxy)]benzoate (4d): Compound **4a** (52.0 g, 90.2 mmol) was dissolved in dry DMF (200 mL). Methanol (100 mL) containing 2.5% hydrochloric acid was added dropwise to this solution. After 12 h the reaction was quenched by neutralization with potassium carbonate (5.0 g, 36 mmol). The solvent was evaporated in vacuo, and the remaining residue recrystalized from chloroform to yield 27.4 g (74.4%) of pure **4d**. M.p. 116–118 °C; IR (KBr): $\tilde{\nu}$ = 3278 (OH), 3099, 3063, 3027 (C–H arom.), 2995, 2950, 2917, 2900, 2867 (C–H aliph.), 1725 (C=O), 1597, 1517 (C=C), 1499, 1445, 1434, 1376, 1352, 1300, 1255, 1238, 1217, 1164 (C–O), 1107, 1063, 1035, 1020, 1002, 962, 938, 898, 866, 856, 837, 818, 764, 671, 652, 625, 593, 481 cm^{-1}; MS (70 eV, EI): *m/z* (%): 408 (6.6) $[M^+]$; $C_{24}H_{24}O_6$ (408.5): calcd C 70.58, H 5.92, found C 70.73, H 5.87.

Methyl 3,5-bis{4-[*N*-(3,5-bis{4-(tetrahydropyran-2-yloxymethyl)benzyloxy}phenyl)-aminocarbonyloxymethyl]benzyloxy}benzoate (5a): A dry solution of **4c** (1.51 g, 2.57 mmol) in toluene was added dropwise at 110 °C to a suspension of **4d** (0.5 g, 1.22 mmol) in dry toluene containing DABCO (22 mg, 0.2 mmol). After complete addition the reaction mixture was kept at 80 °C for a further hour and then allowed to cool to RT. Toluene was removed in vacuo at RT and the remaining residue was purified by silica gel chromatography with CH_2Cl_2/1% methanol as eluent. Yield 1.39 g (72%) of **5a**. M.p. 67–73 °C; IR (KBr): $\tilde{\nu}$ = 3400, 3327, (N–H), 2941, 2869 (C–H aliph.), 1732, 1726 (C=O), 1602 (C=C), 1549 (C=O), 1518 (C=C), 1442, 1423, 1373, 1345, 1300, 1258, 1216, 1155 (C–O), 1119, 1077, 1060, 1034, 1019, 994, 975, 905, 889, 869, 814, 767, 681 cm^{-1}; MS (FAB^-): *m/z* (%): 1527 (0.4) $[M^- - H]$, 1680 (0.57) $[M^- + \text{matrix (153)}]$; $C_{90}H_{98}N_2O_{20}$ (1527.8): calcd C 70.76, H 6.47, N 1.83; found C 70.61, H 6.50, N 1.78.

3,5-Bis{4-[*N*-(3,5-bis{4-(tetrahydropyran-2-yloxymethyl)benzyloxy}phenyl)aminocarbonyloxymethyl]benzyloxy}benzoic acid (5b): The reaction was carried out as described for **4b** except for the use of 5 equiv of KOH. Yield: 93%. M.p. 101–110 °C ; IR (KBr): $\tilde{\nu}$ = 3397, 3318 (N–H), 3027 (C–H arom.), 2941, 2869 (C–H aliph.), 1735 (C=O), 1603 (C=C), 1550 (C=O), 1464, 1440, 1420, 1374, 1343, 1322, 1269, 1259, 1216, 1154 (C–O), 1120, 1077, 1060, 1035, 1019, 994, 975, 905, 888, 868, 813, 681, 543 cm^{-1}; MS (FAB^-): *m/z* (%): 1513 (0.88) $[M^- - H]$; $C_{89}H_{96}N_2O_{20}$ (1513.7): calcd C 70.62, H 6.39, N 1.85; found C 70.40 , H 6.40 , N 1.75.

3,5-Bis{4-[*N*-(3,5-bis-{4-(tetrahydropyran-2-yloxymethyl)benzyloxy}phenyl)aminocarbonyloxymethyl]benzyloxy}benzoyl azide (5c): The reaction was carried out as described for the first generation fragment by using 5 equiv of sodium azide and a reaction time of 2 h. Yield: 85%. M.p. 67–75 °C ; IR (KBr): $\tilde{\nu}$ = 3318 (N–H), 3097, 3056, 3027 (C–H arom.), 2941, 2869 (C–H aliph.), 2261 (N=C=O, w), 2143 (N=N=N, s), 1735 (C=O), 1603 (C=C), 1549 (C=O), 1519 (C=C), 1442, 1422, 1374, 1346, 1321, 1297, 1258, 1213, 1155 (C–O), 1120, 1077, 1059, 1034, 1019, 975, 905, 868, 813, 768, 742, 681, 619, 566 cm^{-1}; MS (FAB^+): *m/z* (%): 1539 (0.01) $[M^+ + H]$; $C_{89}H_{95}N_3O_{19}$ (1524.8): calcd C 70.76, H 6.34, N 2.78; found C 70.68, H 6.36, N 2.89 (values for isocyanate).

Methyl 3,5-bis{4-[*N*-(3,5-bis{4-hydroxymethylbenzyloxy}phenyl)aminocarbonyloxymethyl]benzyloxy}benzoate (5d): Methanol (5 mL) containing 0.25% hydrochloric acid was added to a solution of **5a** (260 mg, 0.17 mmol) in dry DMF (5 mL) with stirring . The mixture was allowed to react for 10 h, and then triethylamine (0.1 mL) was added. After evaporation of the solvent under high vacuum at RT, this procedure was repeated. The solvent was evaporated again, and the crude material was filtered through silica gel with acetone as eluent to remove triethylamine hydrochloride. Pure **5d** was obtained in 80% yield. M.p. 125–129 °C ; IR (KBr): $\tilde{\nu}$ = 3311 (N–H, O–H), 3098, 3056, 3027 (C–H arom.), 2928, 2873 (C–H aliph.), 1717 (C=O), 1602 (C=C), 1552 (C=O), 1518 (C=C), 1445, 1422, 1374, 1339, 1327, 1301, 1261, 1221, 1155 (C–O), 1084, 1037, 1018, 820, 767, 680, 543, 482 cm^{-1}; MS (FAB^+): *m/z* (%): 1229 (0.22) $[M^+ + K]$; Tetraacetate: $C_{78}H_{74}N_2O_{20}$ (1359.4): calcd C 68.92, H 5.49, N 2.06; found C 68.79, H 5.32, N 1.93.

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Methyl 3,5-Bis{4-[N^1-(3,5-bis{4-[N^2-(3,5-bis{4-[N^3-(3,5-bis{4-(tetrahydropyran-2-yloxymethyl)benzyloxy}phenyl)aminocarbonyloxymethyl]benzyloxy}phenyl)aminocarbonyloxymethyl]benzyloxy}phenyl)aminocarbonyloxymethyl]benzyloxy}benzoate (6): The reaction was carried out in analogy to the method use for the synthesis of **5a**. The azide **5c** (3.24 g, 2.10 mmol) was dried at 50 °C in a high vacuum for 5 h, during which time the material became glassy. It was dissolved in dry toluene (10 mL) and added to a solution of carefully dried **5d** (0.501 g, 0.42 mmol) and DABCO (1–2 mg) in dry DMF (1 mL) at 110 °C. After 3 h dry isobutanol (0.3 mL) was added, and heating continued for 2 h. The solvent was then evaporated in vacuo, and the remaining residue purified by column chromatography with CH_2Cl_2/1.5% MeOH as eluent. The oil obtained was freeze-dried to give **6** as a white powder (2.705 g, 89%). M.p. 79–95 °C; IR (KBr): $\tilde{\nu}$ = 3390, 3314 (N–H), 3056, 3027 (C–H arom.), 2941, 2869 (C–H aliph.), 1734 (C=O), 1603 (C=C), 1547 (C=O), 1477, 1464, 1441, 1422, 1373, 1342, 1321, 1299, 1256, 1214, 1179, 1153 (C–O), 1120, 1077, 1060, 1035, 1019, 994, 975, 906, 889, 868, 814, 767, 681, 544 cm^{-1}; ^1H NMR (500 MHz, $[D_7]$DMF, 25 °C): $\delta = 1.43-1.84$ (m, 96H, $-(CH_2)_3-$ (THP)), 3.47–3.53 (m, 16H, $-CH_2O-$ (THP)), 3.81–3.87 (m, 16H, $-CH_2O-$ (THP)), 3.88 (s, 3H, $-CH_3$), 4.41 (d, 16H, L""), 4.70 (t, 16H, $-O-CH_2-O-$), 4.74 (d, 16H, L""), 5.10 (s, 32H, F""), 5.12 (s, 24H, L", L'''), 5.18 (s, 28H, F", F''', L'), 5.23 (s, 4H, F'), 6.45 (s, 14H, D"–D""), 6.98 (s, 28H, B"–B""), 7.05 (t, 1H, B'), 7.25 (d, 2H, D'), 7.37–7.59 (m, 120H, H'–H"", I'–I""), 9.79–9.81 (m, 14H, -NHC(O)); ^{13}C NMR (126 MHz, $[d_7]$DMF, 25 °C): $\delta = 19.9$ (THP), 25.6 (THP), 31.1 (THP), 52.6 ($-CH_3$), 62.2 (THP), 66.4, 67.9, 68.8, 69.9, 70.0 (F'–F"", L'–L""), 96.7 (D"–D""), 98.4 (THP, B"–B""), 107.4 (D'), 108.7 (B'), 128.1, 128.2, 128.4, 128.6, 128.7, 128.8, 129.0 (H'–H"", I'–I""), 132.7 (A'), 137.1, 137.3, 137.4, 137.5 137.9, 139.1 (G'–G"", K–K""), 142.0 (A"–A""), 154.2 (NHC(O)), 160.6 (C'), 160.8 (C"–C""), 166.8 ($-CO_2Me$); MS (MALDI-TOF): m/z: 7257.8 $[M + Na^+]$; $C_{426}H_{446}N_{14}O_{92}$ (7234.3): calcd C 70.73, H 6.21, N 2.71; found C 70.60, H 6.23, N 2.42.

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[13] Repetition rate 13 s (relaxation delay: 10 s, acquisition time 3 s); sweep width: 20 ppm; data points 64 K.

[14] The spectrum was taken from material which was not fully purified and therefore also contains signals from a urea-type impurity.

[15] The elution curve shows a slight shoulder at the low molecular weight onset, which may be attributed to a urea-type impurity.