Synthesis of Novel Dendrimeric Systems Containing NLO Ligands

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The convergent synthesis of novel dendrimeric systems containing NLO-ligands is described. The poor solubility properties of dendrimers of type **A** containing NLO-ligands enticed us into developing novel dendrimers of type **B** leading to the convergent synthesis of third generation NLO-containing dendrimer **15** containing branches of unequal length. Furthermore, a strategy was developed for connection of dendrons leading to dendrimer-to-dendrimer systems of type **C**. For this a dendrimer was required of which selectively one branch could be deprotected i.e. dendrimer **22**. To the deprotected branch a next dendrimer moiety was attached leading to **23**, also containing a deprotectable branch, which was used for attachment of another dendrimer moiety, leading to dendrimer-to-dendrimer system **24**.

Introduction

As dendrimers possess – dependent on the generation – several branch-ends[1], we have been interested in using these macromolecular systems for organization and simultaneous presentation of several functional ligands. This has led among others to dendrimeric multivalent systems containing carbohydrate ligands, which can interact with carbohydrate binding proteins, showing significant enhancement of the binding affinity of these compounds as compared to the individual carbohydrate moieties.[2] As a result, multivalent dendrimeric systems containing carbohydrates capable of interacting with bacterial toxins, might be attractive for new approaches towards new antibiotics in which development of resistance by pathogens might be avoided. In addition to presenting several copies of a particular ligand, dendrimers might provide molecular scaffolds for spatially organizing ligands, so that binding properties or other individual molecular ligand-properties may be enhanced. However, we found that the "covalent organization" capacity of our amino acid based dendrimers[3] e.g. **A** (Figure 1) is fairly limited and Langmuir monolayer studies showed that the branches of these dendrimers tend to spread out.[4]

Next to biologically relevant ligands, dendrimers might be used for organization of ligands crucial in the determination of certain material properties.[1,5]

In this paper we have explored the possibilities of synthesizing dendrimers containing a relatively simple NLO[6] (nonlinear optical) moiety based on the earlier developed amino acid based dendrimers such as **A** (Figure 1), leading to novel dendrimer systems **B** and "dendrimer-to-dendrimer" systems **C**.

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Results and Discussion

Initially, we had planned to prepare NLO-group containing dendrimers based on monomer **4** since this can be prepared from building block **3** which on its turn can be easily synthesized on a large scale from 3,5-dihydroxybenzoic acid and Boc-2-bromoethylamine (Scheme 1). This building block has two identical "branches" and has been used in the preparation of the amino acid-based dendrimers[3] introduced by us. After removal of the Boc-groups in **3**, the 4-nitrophenyl group was introduced in a nucleophilic aromatic substitution reaction with 1-fluoro-4-nitrobenzene in DMSO and Et_3N as a base. Unfortunately, NLO monomer **4** was poorly soluble in common organic solvents, probably because of aromatic π-stacking. This poor solubility precluded synthesis of the second generation dendrimer based on monomers **3** and **4**. In order to improve the solubility – by preventing π-stacking of the aromatic rings –, it was decided to prepare a NLO monomer with "branches" of different lengths i.e. containing an ethyl and a propyl branch. The synthesis of this NLO-group containing monomer **8** started with mono-alkylation of 3,5-dihydroxybenzoic acid with 0.5 equiv. of Boc-2-bromoethylamine (**2**) in dimethylformamide. As expected the reaction afforded a mixture of mono-alkylated product **5**, di-alkylated product **3**, and unreacted 3,5-dihydroxybenzoic acid (**1**). After tedious purification, by four subsequent silica gel columns, the mono-alkylated product **5** was obtained in 26 % yield. The unreacted 3,5-dihydroxybenzoic acid could be re-used, and the di-alkylated product **3** was used in later steps of the synthesis of the NLO-group containing dendrimers (vide infra, Scheme 2). Alkylation of **5** with mesylate **6** in dimethylfor-

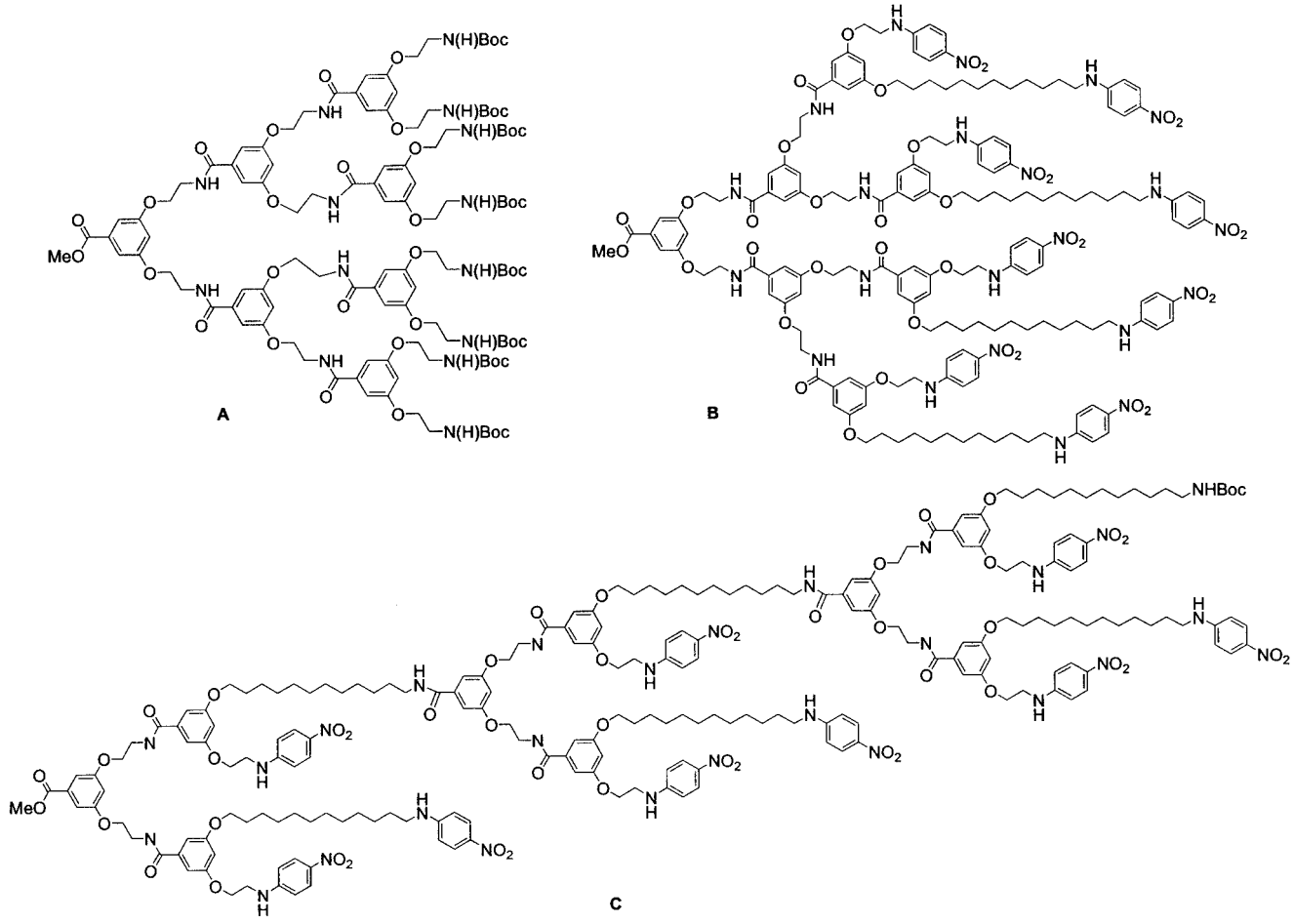
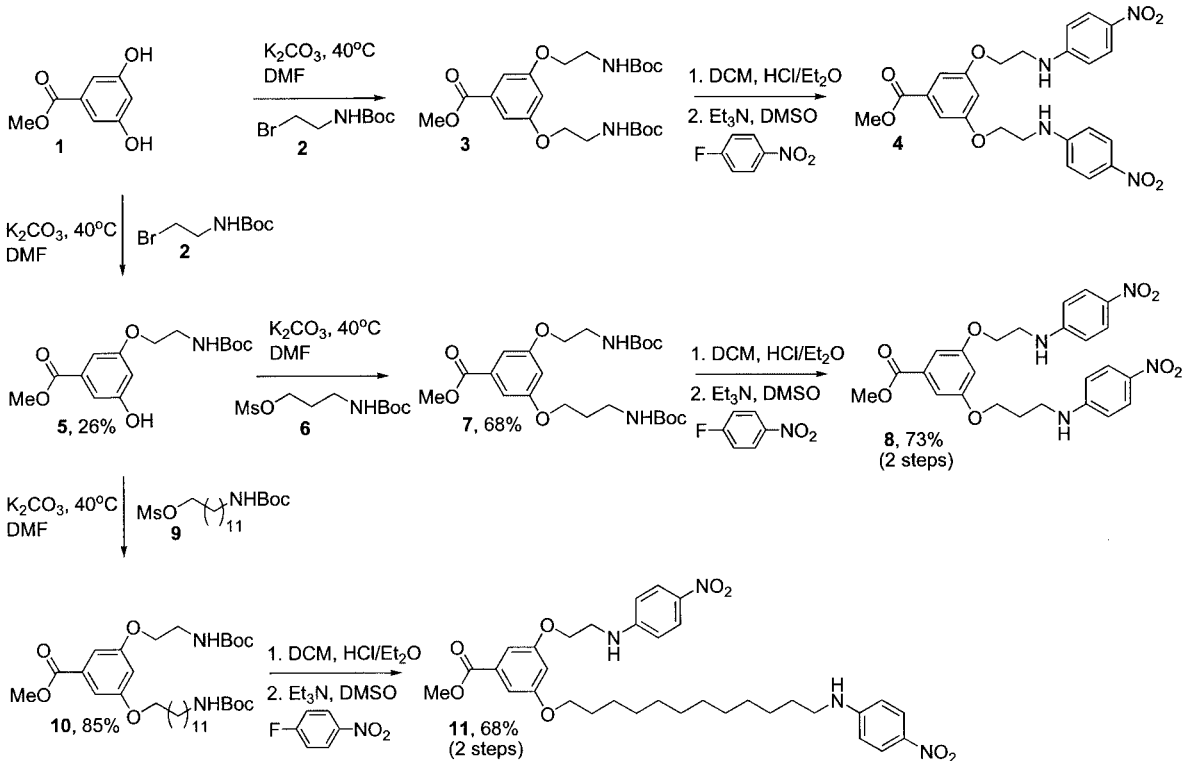


Figure 1. Earlier developed amino acid-based dendrimer **A**[3] and novel dendrimeric systems **B** and **C**

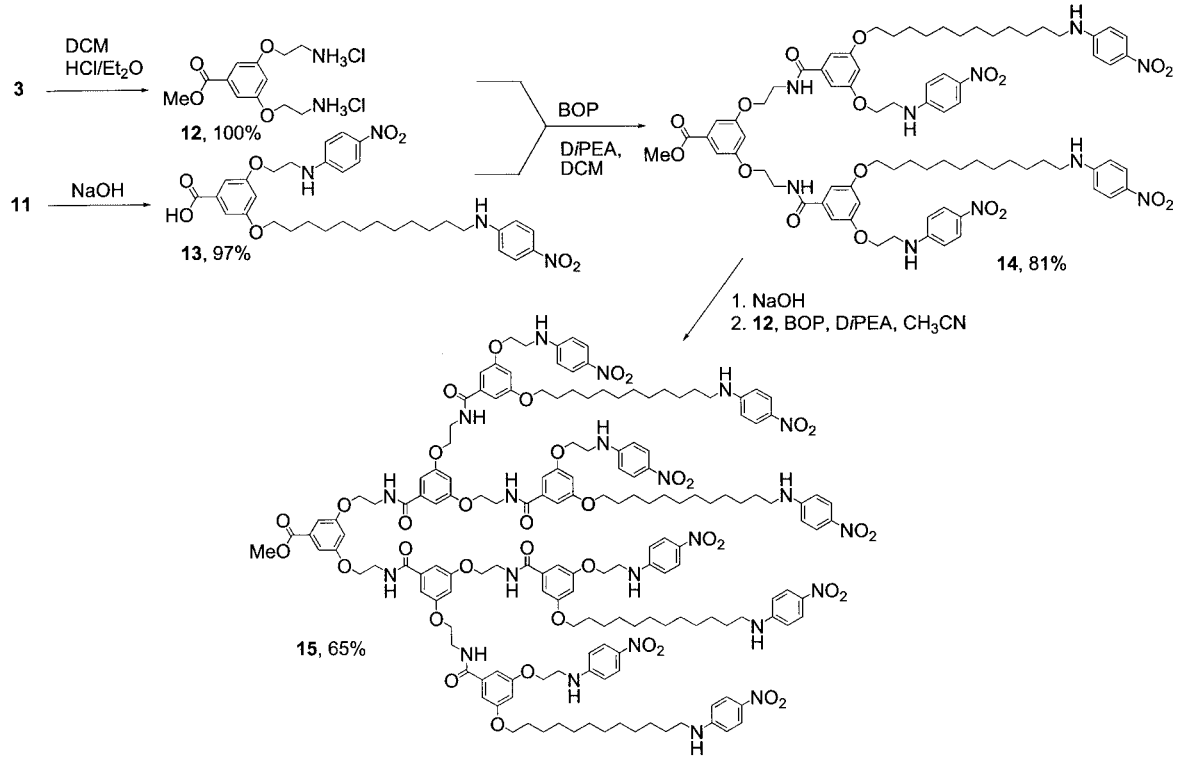
mamide afforded the Boc-protected monomer **7**. Boc-deprotection followed by reaction with 1-fluoro-4-nitrobenzene provided NLO monomer **8** in 73 % yield. As the solubility of **8** was only slightly better than the solubility of monomer **4**, it was decided to prepare a monomer with a much larger difference in the lengths of the "branches", and branches containing two and twelve carbon atoms were selected. To this end, **5** was alkylated with mesylate **9**, affording Boc-protected monomer **10** in 85 % yield. After deprotection of the amino groups, the substitution reaction with 1-fluoro-4-nitrobenzene, was cumbersome compared to other similar substitution reactions (to, **4** and **8**). Optimization, using dimethylacetamide as a solvent and D*i*PEA as a base instead of DMSO and Et_3N led to an improved procedure affording **11** in 68 % yield. Indeed, this NLO monomer had a much better solubility in most organic solvents than **4** or **8**.

This monomer was now suitable for the preparation of higher generations of NLO containing dendrimers (Scheme 2). Two types of monomers were needed: "surface" monomer **13**, which was obtained by saponification of methyl ester **11**, and "branching" monomer **12**,[3c] which was obtained by Boc-group removal of monomer **3**. Second generation dendrimer **14** was synthesized in 84 % yield by a peptide-amide coupling reaction, with BOP using two equivalents of "surface" monomer **13** and one equivalent of "branching" monomer **12**. Saponification of the methyl ester of the resulting second generation dendrimer **14**, followed by coupling to "branching" monomer **12**, afforded third generation dendrimer **15** in 65 % yield. The latter reaction was carried out using the higher boiling acetonitrile compared to dichloromethane, which also gave a more homogeneous reaction mixture. Although, third generation dendrimer **15** was very poorly soluble in most organic solvents, it still could be purified by column chromatography using methanol/dichloromethane mixtures. However, despite apparent formation of the fourth generation NLO-group containing dendrimer – according to TLC – attempts to obtain the pure compound failed due to now an almost insoluble crude product.

In order to obtain a "dendrimer-to-dendrimer" system as is schematically represented in Figure 1 (**C**), which might be also favorable for alignment of the NLO endgroups, dendrimers are called for containing one – protected – amino group, which could be used for connecting the next dendrimer system. For the preparation of such a dendrimer, a "surface" monomer was required viz. **19** having one 4-nitrophenyl-group and one Boc-protected amine, that was synthesized starting from methyl-3,5-dihydroxybenzoic acid (**1**, Scheme 3). Monoalkylation with Cbz-2-bromoethyl-

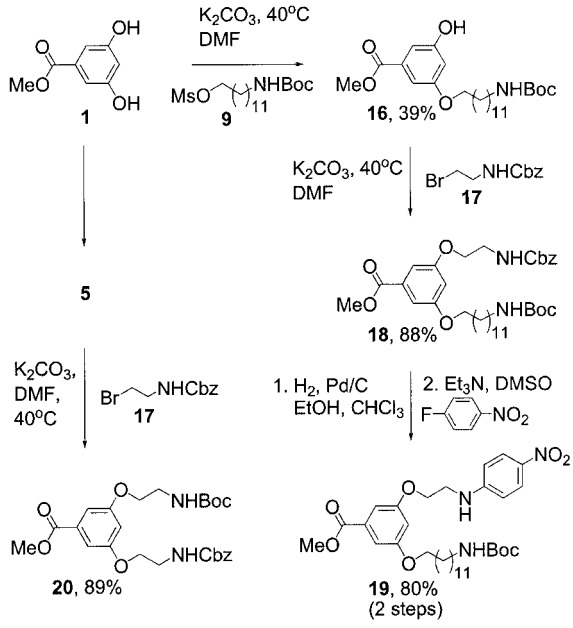


Scheme 1



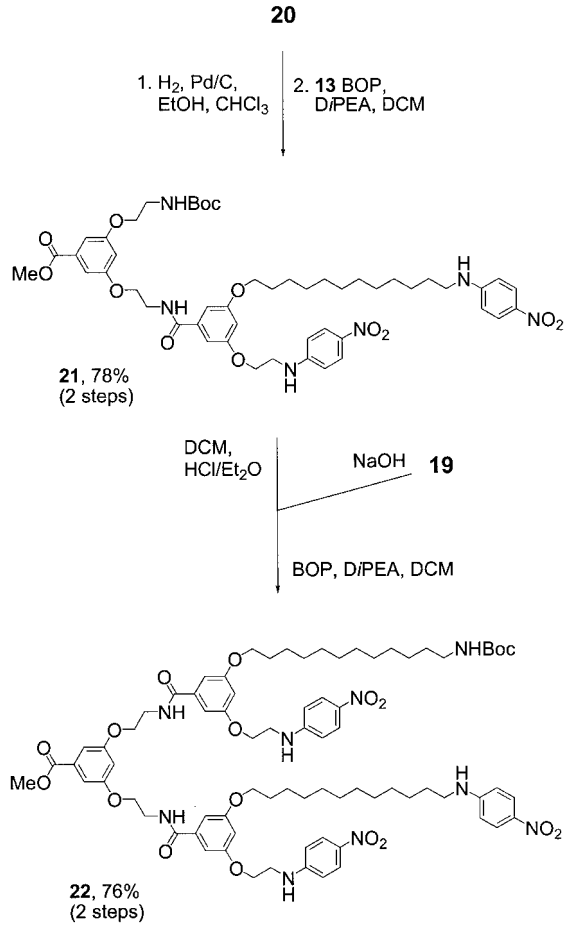
Scheme 2

amine (**17**), afforded the mono-alkylated product in only 14 % yield after a tedious purification. Fortunately, monoalkylation of **1** with mesylate **9** gave compound **16** in 39 % yield, which was clearly better than the monoalkylation reaction and subsequent purfication in the preparation of **5** (26 %), and therefore an attractive alternative for a future synthesis of **10** (Scheme 1). Next, alkylation with Cbz-2-bromoethylamine **17** gave monomer **18** (88 %), of which the Cbz-group was cleaved by hydrogenolysis in the presence of chloroform to give the hydrochloride salt, which was immediately converted into "surface" NLO monomer **19** in 82 % yield by a substitution reaction with 1-fluoro-4-nitrobenzene. In this monomer the Boc-group was deliberately attached to the amine functionality of the longest "branch" to prevent possible steric hindrance during coupling of the dendrimer systems to each other.



Scheme 3

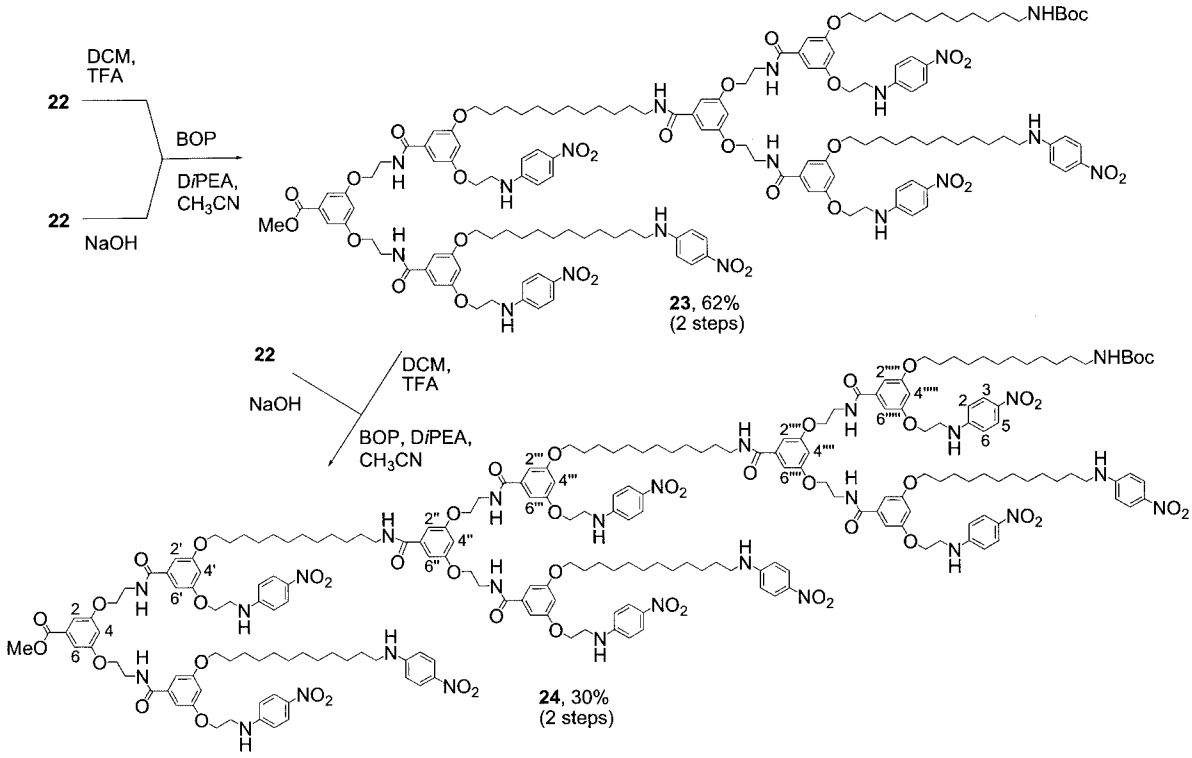
The other required monomer was "branching" monomer **20** (Scheme 3). This monomer was obtained after alkylation of mono-alkylated monomer **5** with Cbz-2-bromoethylamine **17** in 89 % yield. After removal of the Cbz-group in "branching" monomer **20**, monomer **13** was coupled in a BOP coupling, yielding dendrimer-half **21** (Scheme 4). Synthesis to give the "complete" second generation dendrimer system **22**, was achieved after Boc-cleavage and coupling with saponified "surface" monomer (**19**) in 76 % yield. Attempts to synthesize the third generation dendrimer containing seven *p*-nitrophenyl groups and one Boc-group were carried out by coupling of Cbz-deprotected **20** with saponified second generation NLO-group containing dendrimer **14**, followed by Boc-deprotection and coupling with saponified **22**. Unfortunately, a very poor solubility and inseparable impurities impeded with its purification. Therefore, it was decided to use only second generation dendrimer **22** for the construction of dendrimer-to-dendrimer systems. To this end, **22** was Boc-deprotected to afford the "core" dendrimer, and **22** was saponified affording the "surface" dendrimer (Scheme 5). Coupling of these dendrimers, using BOP, D*i*PEA and acetonitrile, afforded dendrimer-to-dendrimer **23** in 62 % yield. This dendrimer system was still very soluble in dichloromethane/methanol mixtures, and could be easily purified by column chromatography. Because of its solubility, it was also possible to couple a subsequent dendrimer to it. Therefore, the Boc-group was cleaved from dendrimer **23** and BOP-coupling of saponified dendrimer **22** gave dendrimer-to-dendrimer system **24** in 30 % yield. This dendrimer had still similar solubility properties as dendrimer **23**.



Scheme 4

Conclusions

We have synthesized dendrimers with "unequal" branches, thereby successfully coping with the insolubility of the earlier dendrimeric systems caused by the aromatic NLO ligands. Although, the dendrimers by themselves may organize the NLO ligands, which might be favorable for optical properties, we developed an alternative dendrimer-to-dendrimer system. This elongated system had good solubility properties and might provide additional organization of



Scheme 5

dendrimeric ligands. Studies of the optical properties of these novel dendrimeric systems, possibly reflecting their organization capacities, will be reported in due course.

Experimental Section

General Remarks: Unless stated otherwise, chemicals were obtained from commercial sources and used without further purification. Solvents were dried on molecular sieves (4 Å). Slightly modified Tesser's base used for saponifications was a mixture of dioxane, MeOH and 4 M NaOH (14:5:2, v/v/v).[7] TLC analysis was performed on Merck precoated 60 F-254 (0.25 mm) plates. Spots were visualized with UV light and ninhydrine. Solvents were evaporated under reduced pressure at 40 °C. Column chromatography was performed on Merck Kieselgel 60 (40–63 μm), all eluents are given in v/v. All dendrimers – except first generation dendrimers –, were purified by column chromatography, using a 18 cm silica column, with a diameter depending on the amount of crude dendrimer. For 1 g crude material a 3-cm diameter column was used. Elemental analyses were carried out at Kolbe Mikroanalytisches Laboratorium (Mülheim an der Ruhr, Germany). ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz) and COSY spectra were recorded with a Varian G-300 spectrometer. ^{1}H NMR (500 MHz), COSY and HMBC spectra of **24** were recorded with a Varian Inova-500 spectrometer. Chemical shifts are reported in ppm relative to TMS (δ = 0 ppm) or [D$_6$]DMSO (δ = 2.50 ppm) for the ^{1}H NMR, and $CDCl_3$ (δ = 77 ppm), [D$_6$]DMSO (δ = 39.5 ppm) or CD_3OD (δ = 49 ppm) for the ^{13}C NMR as internal standards. C^4-H: denotes a proton of the first generation; C$^{4'}$-H: denotes a proton of the second generation etc.; C$^{4',4''}$: denotes carbon atoms of the first and second generation. Ar denotes the *p*-nitroaromatic rings; Ph denotes the 3,5-dihydroxybenzoic acid based aromatic rings. MS (FAB) mass spectra were measured with a Jeol JMS SX/SX 102A four-sector mass spectrometer coupled with a HP-9000 data system. Electrospray mass spectra were recorded with a Shimadzu LCMS-QP-8000 spectrometer, or with a Fisons VG Platform II Single quadrupole mass spectrometer (Micromass, Manchester, UK).

Mono-Alkylated Monomer 5: A mixture of methyl 3,5-dihydroxybenzoate (**1**) (20.1 g, 120 mmol), K_2CO_3 (16.6 g, 120 mmol) and dry dimethylformamide (560 mL) was stirred at room temp. for 1h. A solution of 2-Boc-aminoethyl bromide (60 mmol) in dimethylformamide (40 mL) was added in four equal portions with 30 min of stirring after each addition. The temperature was raised to 40 °C and the mixture was stirred for two days. After filtration through Hyflo, the dimethylformamide was evaporated in vacuo. The residue was dissolved in ethyl acetate and washed with water (twice) and brine. The organic layer was dried with Na_2SO_4, and concentrated. After addition of dichloromethane (200 mL), the flask was rotated at 40 °C (waterbath) for 30 min, giving a precipitate, wich was removed by filtration. The solution was concentrated and purified by column chromatography (4 times, 4 % acetone/DCM). After the purification, wich was very tedious due to contaminations of non- and di-alkylated products, the product was obtained as a white solid (4.9 g, 26 %). R_f = 0.68 (EtOAc/hexanes, 1:1). M.p. 107 °C. ^{1}H NMR ($CDCl_3$): δ = 1.46 [s, 9 H, C(C*H*$_3$)$_3$], 3.52 (m, 2 H, NHC*H*$_2$), 3.89 (s, 3 H, OC*H*$_3$), 4.02 (t, 2 H, OC*H*$_2$, J = 5.1 Hz), 5.02 (br. s, 1 H, NHBoc), 6.28 (br. s, 1 H, OH), 6.61 (s, 1 H, Ph C^4-H), 7.14 (m, 2 H, Ph C^{2,6}-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.4 [C(*C*H$_3$)$_3$], 40.1 (NHCH$_2$), 52.3 (OCH$_3$), 67.3 (OCH$_2$), 80.1 [*C*(CH$_3$)$_3$], 106.9, 107.5, 109.7 (Ph C^{2,4,6}), 132.0 (Ph C^1), 156.3 [C=O (Boc)], 157.5, 159.7 (Ph C^{3,5}), 167.0 (CO_2Me) ppm. MS (ESI): m/z = 334.1 [M + Na]$^+$. $C_{15}H_{21}NO_6$ (311.33): calcd. C 57.87, H 6.80, N 4.50; found C 57.73, H 6.68, N 4.49.

3-Boc-aminopropylmesylate (6): 3-Aminopropanol (22.9 mL, 300 mmol) was dissolved in dichloromethane (175 mL). After cooling to 0 °C di-*tert*-butyl dicarbonate (65.5 g, 300 mmol) in dichlo-

romethane (50 mL) was added dropwise. The reaction was stirred at room temp. for 5.5 h. After addition of more dichloromethane, the mixture was washed with water and brine, dried (Na_2SO_4) and concentrated in vacuo. 3-Boc-aminopropanol was obtained as a colorless oil (49.4 g, 94 %). R_f = 0.47 (diethylether). ^{1}H NMR ($CDCl_3$): δ = 1.44 [s, 9 H, C(CH_3)$_3$], 1.67 (m, 2 H, $CH_2CH_2CH_2$), 2.97 (br. s, 1 H, OH), 3.28 (m, 2 H, CH_2NH), 3.66 (br. s, 2 H, OCH_2), 4.78 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.3 [C(CH_3)$_3$], 32.6 ($CH_2CH_2CH_2$), 37.0 (CH_2NH), 59.3 (OCH_2), 79.4 [C(CH_3)$_3$], 157.0 [C=O (Boc)] ppm.

To a cooled solution (ice-bath) of 3-Boc-aminopropanol (2.60 g, 14.8 mmol) and methanesulfonyl chloride (1.28 mL, 16.5 mmol) in dichloromethane (13 mL) was slowly added triethylamine (2.3 mL, 16.5 mmol). After stirring for 1 h, the reaction mixture was concentrated and dissolved in ethyl acetate. The solution was washed with 1 M $KHSO_4$, water (twice) and brine, dried (Na_2SO_4) and concentrated in vacuo. The mesylate was obtained as a yellow solid (3.41 g, 91 %), and was directly used without further purification in the synthesis of monomer **7**. R_f = 0.62 (EtOAc/hexanes, 1:1).

Monomer 7: A mixture of **5** (2.02 g, 6.5 mmol), potassium carbonate (2.02 g, 14.6 mmol), mesylate **6** (2.14 g, 8.45 mmol) and dimethylformamide (13 mL) was stirred for three days at 40 °C. The reaction mixture was cooled to room temp. and filtered over Hyflo. After evaporation of the solvent in vacuo, the residue was dissolved in ethyl acetate and water. The organic layer was washed with water and brine, dried (Na_2SO_4) and concentrated. Column chromatography (EtOAc/hexanes, 3:7) afforded the product as a white foam (2.07 g, 68 %). R_f = 0.18 (EtOAc/hexanes, 3:7). ^{1}H NMR ($CDCl_3$): δ = 1.45 (s, 18 H, 2 × C(CH_3)$_3$), 2.00 (m, 2 H, $OCH_2CH_2CH_2$), 3.32 (m, 2 H, $NHCH_2CH_2CH_2$), 3.54 (m, 2 H, $NHCH_2CH_2O$), 3.90 (s, 3 H, OCH_3), 4.04 (m, 4 H, 2 × OCH_2), 4.72 [br. s, 1 H, NH(CH_2)$_3$O], 4.96 [br. s, 1 H, NH(CH_2)$_2$O], 6.64 (m, 1 H, Ph C^4-H), 7.18 (m, 2 H, Ph C^{2,6}-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.4 [C(CH_3)$_3$], 29.5 ($OCH_2CH_2CH_2$), 37.9 ($NHCH_2CH_2CH_2$), 40.1 ($NHCH_2CH_2O$), 52.2 (OCH_3), 66.1 [OCH_2(CH_2)$_2$], 67.5 (OCH_2CH_2NH), 79.2, 79.6 [C(CH_3)$_3$], 106.6, 107.9, 108.1 (Ph C^{2,4,6}), 132.1 (Ph C^1), 155.8, 156.0 [C=O (Boc)], 159.6, 159.8 (Ph C^{3,5}-H), 166.6 (CO_2Me) ppm.

NLO Monomer 8: To a solution of **7** (1.98 g, 4.23 mmol) in dry dichloromethane (10 mL), was added diethylether (20 mL), saturated with HCl. After stirring for 35 min, the mixture was concentrated in vacuo, and the residue was dried with KOH overnight. The hydrochloride salt was obtained as a white solid (1.42 g, 99 %). A mixture of the hydrochloride salt (171 mg, 0.50 mmol), 1-fluoro-4-nitrobenzene (117 μL, 1.1 mmol), dimethyl sulfoxide (2.5 mL) and triethylamine (313 μL, 2.25 mmol) was refluxed overnight. After cooling to room temp., ethyl acetate (15 mL) was added and the mixture was washed with 1M $KHSO_4$, water (twice) and brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Crystallization (DMSO/MeOH) afforded the product as a yellow solid (188 mg, 74 %). R_f = 0.47 (EtOAc/hexanes, 3:7). M.p. 152 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 1.95 (m, 2 H, $OCH_2CH_2CH_2$), 3.25 (m, 2 H, $NHCH_2CH_2CH_2$), 3.50 (m, 2 H, $NHCH_2CH_2O$), 3.76 (s, 3 H, OCH_3), 4.03, 4.13 (2 m, 4 H, 2 × OCH_2), 6.58, 6.66 (2d, J = 9.5, J = 9.5 Hz, 4 H, 2 × Ar C^{2,6}-H), 6.73 (s, 1 H, Ph C^4-H), 7.01 (m, 2 H, Ph C^{2,6}-H), 7.25, 7.37 (2br. s, 2 H, 2 × NH), 7.92 (m, 4 H, 2 × Ar C^{3,5}-H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 28.0 ($OCH_2CH_2CH_2$), 40.4, 41.9 ($NHCH_2$), 52.3 (OCH_3), 65.6, 66.7 (OCH_2), 106.4, 107.6, 107.7 (Ph C^{2,4,6}), 111.0 (Ar C^{2,6}), 126.2, 126.3 (Ar C^{3,5}), 131.7 (Ph C^1), 135.8, 136.0 (Ar C^1), 154.5, 154.6 (Ar C^4), 159.6, 159.8 (Ph C^{3,5}-H), 166.0 (CO_2Me) ppm. MS (ESI): m/z = 511.4 [M + H]$^+$, 533.9 [M + Na]$^+$. $C_{25}H_{26}N_4O_8$ (510.50): calcd. C 58.82, H 5.13, N 10.98; found C 58.88, H 5.19, N 10.85.

Mesylate 9: Mesylate **9** was prepared from 12-aminododecanoic acid by esterification, Boc-protection, reduction and mesylation, affording a white solid (87 %, 4 steps)[3c]. R_f = 0.77 (EtOAc/hexanes, 1:1). M.p. 47 °C. ^{1}H NMR ($CDCl_3$): δ = 1.27–1.44 [m, 27 H, C(CH_3)$_3$, $NHCH_2$(CH_2)$_9$], 1.74 (m, 2 H, OCH_2CH_2), 3.00 (s, 3 H, CH_3SO_3), 3.10 (m, 2 H, $NHCH_2$), 4.22 (t, 2 H, OCH_2, J = 6.6 Hz), 4.48 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.3, 26.7, 28.9, 29.0, 29.2, 29.3 (2 ×), 29.4, 30.0 [$NHCH_2$(CH_2)$_{10}$], 28.3 [C(CH_3)$_3$], 37.3 (OCH_3), 40.5 ($NHCH_2$), 70.1 (OCH_2), 78.9 [C(CH_3)$_3$], 155.9 [C=O (Boc)] ppm. MS (ESI): m/z = 402.3 [M + Na]$^+$. $C_{18}H_{37}NO_5S$ (379.56): calcd. C 56.96, H 9.83, N 3.69; found C 56.83, H 9.75, N 3.73.

Monomer 10: A mixture of **5** (1.12 g, 3.6 mmol), K_2CO_3 (2.24 g, 16.2 mmol), mesylate **9** (1.38 g, 3.96 mmol) and dimethylformamide (7.2 mL) was stirred at 40 °C for 6 days. The mixture was filtered over Hyflo, and the solvent was removed in vacuo. After adding ethyl acetate, the mixture was washed with water (twice) and brine, dried and concentrated. Column chromatography (EtOAc/hexanes, 3:7) afforded monomer **10** as a clear colorless oil (1.8 g, 85 %). R_f = 0.26 (EtOAc/hexanes, 3:7). ^{1}H NMR ($CDCl_3$): δ = 1.26–1.44 [m, 36 H, 2 × C(CH_3)$_3$, 2 × $NHCH_2$(CH_2)$_9$], 1.75 [m, 2 H, OCH_2CH_2(CH_2)$_{10}$], 3.09 [m, 2 H, $NHCH_2$(CH_2)$_{11}$], 3.52 (m, 2 H, $NHCH_2CH_2O$), 3.89 (s, 3 H, OCH_3), 3.96 [t, J = 6.6 Hz, 2 H, OCH_2(CH_2)$_{11}$], 4.03 (t, J = 5.0 Hz, 2 H, OCH_2CH_2NH), 4.51 [br. s, 1 H, NH(CH_2)$_{12}$], 4.99 [br. s, 1 H, NH(CH_2)$_2$O], 6.63 (m, 1 H, Ph C^4-H), 7.16 (m, 2 H, Ph C^{2,6}-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.8, 26.6, 29.0, 29.1 (2 ×), 29.3, 29.9 [$NHCH_2$(CH_2)$_{10}$], 8.2, 28.3 [C(CH_3)$_3$], 39.9 ($NHCH_2CH_2O$), 40.5 [$NHCH_2$(CH_2)$_{11}$], 52.0 (OCH_3), 67.3 (OCH_2CH_2NH), 68.2 [OCH_2(CH_2)$_{11}$], 78.7, 79.2 [C(CH_3)$_3$], 106.4, 107.5, 108.0 (Ph C^{2,4,6}), 131.8 (Ph C^1), 155.7, 155.9 [C=O (Boc)], 159.4, 160.0 (Ph C^{3,5}), 166.5 (CO_2Me) ppm. MS (ESI): m/z = 595.4 [M + H]$^+$, 617.6 [M + Na]$^+$. $C_{32}H_{54}N_2O_8$ (594.78): calcd. C 64.62, H 9.15, N 4.71; found C 64.75, H 9.22, N 4.59.

NLO Monomer 11: Monomer **10** was Boc-deprotected following the procedure as described in the synthesis of **8**, affording the hydrochloride salt as a white solid (1.33 g, 95 %). A mixture of the hydrochloride salt (1.28 g, 2.75 mmol), 1-fluoro-4-nitrobenzene (642 μL, 6.05 mmol), dimethylacetamide (14 mL) and diisopropylethylamine (1.91 mL, 11.0 mmol) was stirred at 100 °C overnight. After cooling to room temp., ethyl acetate (90 mL) was added and the mixture was washed with 1 M $KHSO_4$, water and brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (hexanes/DCM, 6:94) followed by crystallization (EtOAc/hexanes) afforded the product as a yellow solid (1.26 g, 72 %). R_f = 0.54 (EtOAc/hexanes, 1:1). M.p. 93 °C. ^{1}H NMR ($CDCl_3$): δ = 1.30 [m, 16 H, $NHCH_2CH_2$(CH_2)$_8$], 1.64 [m, 2 H, $NHCH_2CH_2$(CH_2)$_{10}$], 1.77 [m, 2 H, OCH_2CH_2(CH_2)$_{10}$], 3.21 [m, 2 H, $NHCH_2$(CH_2)$_{11}$], 3.65 (m, 2 H, $NHCH_2CH_2O$), 3.91 (s, 3 H, OCH_3), 3.97 [t, J = 6.2 Hz, 2 H, OCH_2(CH_2)$_{11}$], 4.22 (t, J = 5.0 Hz, 2 H, OCH_2CH_2NH), 4.47 [br. s, 1 H, NH(CH_2)$_{12}$], 4.86 [br. s, 1 H, NH(CH_2)$_2$O], 6.52, 6.62 (2d, J = 9.2, J = 9.1 Hz, 4 H, 2 × Ar C^{2,6}-H), 6.65 (m, 1 H, Ph C^4-H), 7.22, 7.26 (2br. s, 2 H, Ph C^{2,6}-H), 8.10 (m, 4 H, Ar C^{3,5}-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.9, 26.9, 29.1, 29.2, 29.3, 29.5, 29.7 [$NHCH_2$(CH_2)$_{10}$], 42.6 ($NHCH_2CH_2O$), 43.4 [$NHCH_2$(CH_2)$_{11}$], 52.3 (OCH_3), 66.3 (OCH_2CH_2NH), 68.4 [OCH_2(CH_2)$_{11}$], 106.7 (Ph C^4), 107.4, 108.5 (Ph C^{2,6}) 110.9, 111.3 (Ar C^{2,6}), 126.3, 126.4 (Ar C^{3,5}), 132.1 (Ph C^1), 137.7, 138.4 (Ar C^1), 153.0, 153.5 (Ar C^4), 159.2, 160.3 (Ph C^{3,5}), 166.7 (CO_2Me) ppm. MS (FAB): m/z = 637.5 [M + H]$^+$. $C_{34}H_{44}N_4O_8$ (636.74): calcd. C 64.13, H 6.97, N 8.80; found C 64.20, H 6.92, N 8.71.

Dendrimer 14: A solution of monomer **11** (1.02 g, 1.60 mmol) in slightly modified Tesser's base (18 mL), was stirred for 2 h at room temp. The pH was adjusted to approximately 2 with 1 M $KHSO_4$ and the mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate and water. The organic layer was washed with water and brine, dried (Na_2SO_4) and concentrated in vacuo. The acid was obtained as a yellow solid (966 mg, 97 %). To a suspension of the acid (810 mg, 1.30 mmol), hydrochloride salt **12**[3c] (213 mg, 0.65 mmol) and BOP (630 mg, 1.43 mmol) in dry dichloromethane (6.5 mL) was slowly added D*i*PEA (736 μL, 4.23 mmol). The mixture was stirred at room temp. for 4 h, and concentrated in vacuo. The residue was dissolved in dichloromethane and washed with water and brine, dried (Na_2SO_4) and concentrated to dryness. Column chromatography (MeOH/DCM, 2:98) afforded second generation dendrimer **14** as a yellow foam (801 mg, 84 %). R_f = 0.67 (MeOH/DCM, 1:9). M.p. 46 °C. ^{1}H NMR ($CDCl_3$): δ = 1.27–1.37 [m, 32 H, 2 × $NHCH_2CH_2(CH_2)_8$], 1.58–1.68 [m, 4 H, 2 × $NHCH_2CH_2(CH_2)_{10}$], 1.71–1.76 [m, 4 H, 2 × $OCH_2CH_2(CH_2)_{10}$], 3.18 [m, 4 H, 2 × $NHCH_2(CH_2)_{11}$], 3.59 (m, 4 H, 2 × $ArNHCH_2CH_2O$), 3.81 [m, 4 H, 2 × $PhC(O)NHCH_2CH_2O$], 3.87 (s, 3 H, OCH_3), 3.91 (t, J = 6.5 Hz, 4 H, 2 × $OCH_2(CH_2)_{11}$), 4.10 (t, J = 5.0 Hz, 4 H, 2 × $OCH_2CH_2NHC{=}O$), 4.15 (t, J = 5.2 Hz, 4 H, 2 × OCH_2CH_2NHAr), 4.65 [bt, 2 H, 2 × $NH(CH_2)_{12}$], 5.12 [m, 2 H, 2 × $ArNH(CH_2)_2O$], 6.47–6.60 (m, 11 H, 4 × Ar C^{2,6}-H, Ph C^4-H, 2 × Ph C$^{4'}$-H), 6.75 (bt, 2 H, 2 × NHC=O), 6.88, 6.93 (2 m, 4 H, 2 × Ph C$^{2',6'}$-H), 7.14 (d, 2 H, Ph C^{2,6}-H), 8.04 (m, 8 H, 4 × Ar C^{3,5}-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.9, 26.9, 29.0, 29.1, 29.2, 29.4, 29.7, [$NHCH_2(CH_2)_{10}$], 39.6 [$PhC(O)NHCH_2$] 42.6 ($ArNHCH_2CH_2O$), 43.4 [$NHCH_2(CH_2)_{11}$], 52.3 (OCH_3), 66.3 (OCH_2CH_2NHAr), 67.0 ($OCH_2CH_2NHC{=}O$), 68.4 [$OCH_2(CH_2)_{11}$], 104.7, 105.2, 106.3, 108.3 (Ph C$^{2,4,6,2',4',6'}$), 110.9, 111.3 (Ar C^{2,6}), 126.3, 126.4 (Ar C^{3,5}), 132.2 (Ph C^1), 136.4 (Ph C$^{1'}$), 137.6, 138.2 (Ar C^1), 153.1, 153.6 (Ar C^4), 159.5, 160.5 (Ph C$^{3,5,3',5'}$), 166.5 (CO_2Me), 167.5 (NHC=O) ppm. MS (FAB): m/z = 1463.9 [M + H]$^+$. $C_{78}H_{98}N_{10}O_{18}$ (1463.67): calcd. C 64.01, H 6.75, N 9.57; found C 64.24, H 6.41, N 9.36.

Dendrimer 15: Second generation dendrimer **14** (110 mg, 75.0 μmol) was saponified following the procedure described in the synthesis of **14**, affording the acid as a yellow foam (108 mg, 99 %). To a mixture of the acid (116 mg, 79.8 μmol), hydrochloride salt **12** (13.1 mg, 40.0 μmol), BOP (38.7 mg, 87.9 μmol) and acetonitrile (0.4 mL) was added D*i*PEA (45.2 μL, 0.259 mmol) at room temp. The mixture was refluxed for 4 h, cooled to room temp. and concentrated in vacuo. The residue was dissolved in dichloromethane and washed with 1 M $KHSO_4$ (twice), 1 M NaOH (twice) and brine. Crystallization out of the organic layer afforded yellow needles (40.3 mg). Column chromatography (MeOH/DCM, 3:97) from the mother liquor afforded the product as a yellow foam (41.6 mg), giving a total yield of 66 % (81.9 mg). R_f = 0.61 (MeOH/DCM, 1:9). M.p. 75 °C. ^{1}H NMR ($CDCl_3$/CD_3OD): δ = 1.27 [m, 64 H, 4 × $NHCH_2CH_2(CH_2)_8$], 1.63 [m, 8 H, 4 × $NHCH_2CH_2(CH_2)_{10}$], 1.73 [m, 8 H, 4 × $OCH_2CH_2(CH_2)_{10}$], 3.17 [t, 8 H, 4 × $NHCH_2(CH_2)_{11}$], 3.57 (t, 8 H, 4 × $ArNHCH_2CH_2O$), 3.74 [m, 12 H, 6 × $PhC(O)NHCH_2CH_2O$], 3.85 (s, 3 H, OCH_3), 3.91 [t, 8 H, 4 × $OCH_2(CH_2)_{11}$], 4.09–4.16 (m, 20 H, 6 × $OCH_2CH_2NHC{=}O$, 4 × OCH_2CH_2NHAr), 6.54 (4 lines, 22 H, 8 × Ar C^{2,6}-H, Ph C$^{4',4''}$-H), 6.70 (br. s, 1 H, Ph C^4-H), 6.91 (br. s, 8 H, Ph C$^{2'',6''}$-H), 6.97 (br. s, 4 H, Ph C$^{2',6'}$-H), 7.13 (br. s, 2 H, Ph C^{2,6}-H), 8.01 (2d, 16 H, 8 × Ar C^{3,5}-H) ppm. ^{13}C NMR (DMSO): δ = 25.5, 26.5, 28.3, 28.6, 28.8, 29.0 [$NHCH_2(CH_2)_{10}$], 38.9 [$PhC(O)NHCH_2$] 41.9, 42.3 ($ArNHCH_2$), 52.1 (OCH_3), 66.4, 67.7 [OCH_2CH_2NHAr, $OCH_2CH_2NHC{=}O$, $OCH_2(CH_2)_{11}$], 104.0, 105.7, 106.1, 107.7 (Ph C$^{2,4,6,2',4',6',2'',4'',6''}$), 110.5, 110.8 (Ar C^{2,6}), 126.1, 126.2 (Ar C^{3,5}), 131.6 (Ph C^1), 135.4, 135.9, 136.2, 136.3 (Ph C$^{1',1''}$, Ar C^1), 154.4, 154.5 (Ar C^4), 159.3, 159.4, 159.6, 159.7 (Ph C$^{3,5,3',5',3'',5''}$), 165.7, 165.9, 166.0 (CO_2CH_3, NHC=O, N′HC=O) ppm. MS (FAB): m/z = 3115.6 [M]$^+$. $C_{166}H_{206}N_{22}O_{38}$ (3117.54): calcd. C 63.95, H 6.66, N 9.88; found C 64.08, H 6.60, N 9.75.

Mono-Alkylated Monomer 16: The preparation of monomer **16** was performed following the procedure described for the synthesis of **5**, on a 1.0 mmol scale. The reaction mixture was stirred for three days at 40 °C, and cooled to room temp. After workup, the residue was purified by column chromatography (EtOAc/hexanes, 2:8) affording white crystalline discs (87.5 mg, 39 %). R_f = 0.46 (EtOAc/hexanes, 3:7). M.p. 51 °C. ^{1}H NMR ($CDCl_3$): δ = 1.18–1.45 [m, 27 H, $OCH_2CH_2(CH_2)_9$, $C(CH_3)_3$], 1.74 (m, 2 H, OCH_2CH_2, 3.10 (m, 2 H, $NHCH_2$), 3.88 (s, 3 H, OCH_3), 3.95 (t, J = 6.4 Hz, 2 H, OCH_2), 4.63 (br. s, 1 H, NH), 6.64 (m, 1 H, Ph C^4-H), 7.14 (m, 2 H, Ph C^{2,6}-H), 7.19 (br. s, 1 H, OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.9, 26.7, 29.0, 29.1, 29.2, 29.3, 29.4, 29.5, 30.0 [$OCH_2(CH_2)_{10}$], 28.4 [$C(CH_3)_3$], 40.7 ($NHCH_2$), 52.1 (CH_3), 68.3 (OCH_2), 79.5 [$C(CH_3)_3$], 107.2, 107.4, 109.2 (Ph C^{2,4,6}), 131.9 (Ph C^1), 156.4 [C=O (Boc)], 157.5, 160.4 (Ph C^{3,5}), 167.1 (CO_2Me) ppm. MS (ESI): m/z = 352.3 [M – Boc + H]$^+$, 474.5 [M + Na]$^+$. $C_{25}H_{41}NO_6$ (451.60): calcd. C 66.49, H 9.15, N 3.10; found C 66.57, H 9.22, N 3.06.

2-Cbz-aminoethyl Bromide (17): To a cooled (ice-bath) solution of aminoethyl bromide·HBr (20.5 g, 100 mmol) and 2 M NaOH (100 mL, 200 mmol) in dioxane (100 mL), was added Cbz-chloride (14.3 mL, 100 mmol) dropwise. The temperature was raised to room temp. and the mixture was stirred overnight. The mixture was concentrated to dryness and dissolved in ethyl acetate and 1 M $KHSO_4$. The organic layer was washed with water (twice) and brine, dried and concentrated. A silica gel plug (EtOAc/hexanes, 1:9) afforded the bromide as a white crystalline solid (23.1 g, 90 %). R_f = 0.37 (EtOAc/hexanes, 2:8). ^{1}H NMR ($CDCl_3$): δ = 3.48 (t, 2 H, $BrCH_2$), 3.61 (m, 2 H, $NHCH_2$), 5.13 (s, 2 H, $ArCH_2$), 5.18 (br. s, 1 H, NH), 7.37 (m, 5 H, C_6H_5) ppm. ^{13}C NMR ($CDCl_3$): δ = 32.3 ($BrCH_2$), 42.7 ($NHCH_2$), 66.9 ($ArCH_2$), 128.1, 128.2, 128.5 (Ar C$^{2-6}$), 136.2 (Ar C^1), 155.2 (C=O (Cbz) ppm.

Monomer 18: A mixture of **16** (497 mg, 1.10 mmol), bromide **17** (369 mg, 1.43 mmol), K_2CO_3 (342 mg, 2.47 mmol) and dimethylformamide (2.2 mL) was stirred overnight at 40 °C. After cooling to room temp., ethyl acetate (20 mL) was added and the organic layer was washed with water (twice, 10 mL) and brine. Drying (Na_2SO_4), concentration and column chromatography (EtOAc, hexanes, 2:8) afforded the monomer as a clear colorless oil, which slowly solidified (607 mg, 88 %). R_f = 0.18 (EtOAc/hexanes, 2:8). ^{1}H NMR ($CDCl_3$): δ = 1.26–1.44 [m, 27 H, $OCH_2CH_2(CH_2)_9$, $C(CH_3)_3$], 1.77 (m, 2 H, $OCH_2CH_2CH_2$), 3.10 [m, 2 H, $NHCH_2(CH_2)_{11}$], 3.61 (m, 2 H, $NHCH_2CH_2O$), 3.90 (s, 3 H, OCH_3), 3.96 [t, 2 H, $OCH_2(CH_2)_{11}$], 4.06 (t, 2 H, OCH_2CH_2NH), 4.51 [br. s, 1 H, $NH(CH_2)_{12}$], 5.12 [s, 2 H, $ArCH_2$ (Cbz)], 5.23 [br. s, 1 H, $NH(CH_2)_2O$], 6.62 (t, J = 2.2 Hz, 1 H, Ph C^4-H), 7.17 (m, 2 H, Ph C^{2,6}-H), 7.28–7.37 [m, 5 H, C_6H_5 (Cbz)] ppm. ^{13}C NMR: δ = 25.7, 26.5, 28.2, 28.9, 29.0, 29.1, 29.3, 29.8 [$OCH_2(CH_2)_{10}$], 28.2 [$C(CH_3)_3$], 40.3 ($NHCH_2$), 51.8 (OCH_3), 66.5, 66.9 [$ArCH_2$ (Cbz), OCH_2CH_2NH], 68.0 [$OCH_2(CH_2)_{11}$], 78.5 [$C(CH_3)_3$], 106.3, 107.3, 108.0 (Ph C^{2,4,6}), 127.8, 128.2 [Ar C$^{2-6}$ (Cbz)], 131.7 (Ph C^1), 136.3 [Ar C^1 (Cbz)], 155.8, 156.2 [C=O (Boc, Cbz)], 159.3, 160.0 (Ph C^{3,5}), 166.4 (CO_2Me) ppm.

Monomer 19: To a solution of monomer **18** (277 mg, 0.40 mmol) in ethanol (15 mL) was added chloroform (0.3 mL) and 10 % Pd/C (app. 10 mg). The mixture was shaken under hydrogen (3 bar) in a Parr apparatus overnight. After the catalyst was removed by fil-

tration through Hyflo, the mixture was concentrated and coevaporated with chloroform. The hydrochloride salt was obtained as a yellow oil (206 mg, 97 %). The hydrochloride salt (187 mg, 0.315 mmol) was used in a substitution reaction with 1-fluoro-4-nitrobenzene (41.1 μL, 0.387 mmol), following the procedure described in the synthesis of **11**. Column chromatography (DCM) afforded the product as a yellow oil (160 mg, 82 %). R_f = 0.88 (MeOH/DCM, 1:9). ^{1}H NMR ($CDCl_3$): δ = 1.23–1.40 [m, 27 H, $OCH_2CH_2(CH_2)_{10}$, $C(CH_3)_3$], 1.73 [m, 2 H, $OCH_2CH_2(CH_2)_{10}$], 3.04 [m, 2 H, $NHCH_2(CH_2)_{11}$], 3.58 (m, 2 H, $NHCH_2CH_2O$), 3.85 (s, 3 H, OCH_3), 3.91 [t, J = 6.5 Hz, 2 H, $OCH_2(CH_2)_{11}$], 4.16 (m, 2 H, OCH_2CH_2NH), 4.62 [br. s, 1 H, $NH(CH_2)_{12}$], 5.27 [bt, 1 H, $NH(CH)_2O$], 6.59 (m, 3 H, Ar $C^{3,5}$-H, Ph C^4-H), 7.11, 7.15 (2s, 2 H, Ph $C^{2,6}$-H), 8.02 (d, 2 H, Ar $C^{2,6}$-H, J = 9.2 Hz) ppm. ^{13}C NMR: δ = 25.8, 26.6, 29.0, 29.1, 29.2, 29.4, 29.9 [$OCH_2(CH_2)_{10}$], 28.3 [$C(CH_3)_3$], 40.5 [$NHCH_2(CH_2)_{11}$], 42.4 ($NHCH_2CH_2O$), 52.1 (OCH_3), 66.2 (OCH_2CH_2NH), 68.3 [$OCH_2(CH_2)_{11}$], 78.8 [$C(CH_3)_3$], 106.5, 107.3, 108.3 (Ph $C^{2,4,6}$), 111.1 (Ar C^2), 126.2 (Ar C^3), 131.9 (Ph C^1), 138.1 (Ar C^1), 153.1 (Ar C^4), 155.9 [C=O (Boc)], 159.2, 160.2 (Ph $C^{3,5}$), 166.6 (CO_2Me) ppm.

Monomer 20: A mixture of **5** (1.09 g, 3.50 mmol), **17** (1.17 g, 4.55 mmol), K_2CO_3 (1.09 g, 7.88 mmol) and dimethylformamide (10 mL) was stirred overnight at 40 °C. After cooling to room temp., the mixture was filtered over Hyflo and concentrated in vacuo. Ethyl acetate was added, and the organic layer was washed with water (twice) and brine. Drying and concentration in vacuo, followed by column chromatography (EtOAc/hexanes, 3:7) afforded the monomer as a clear colorless oil (1.53 g, 89 %). R_f = 0.18 (EtOAc/hexanes, 3:7). M.p. 58 °C. ^{1}H NMR ($CDCl_3$): δ = 1.45 [s, 9 H, $C(CH_3)_3$], 3.52, 3.60 (2 m, 4 H, 2 × $NHCH_2$), 3.89 (s, 3 H, OCH_3), 4.01 (m, 4 H, 2 × OCH_2), 5.02 (br. s, 1 H, NHBoc), 5.11 (s, 2 H, $ArCH_2$), 5.29 (br. s, 1 H, NHCbz), 6.61 (s, 1 H, Ph C^4-H), 7.16 (s, 2 H, Ph $C^{2,6}$-H), 7.34 (m, 5 H, C_6H_5) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.3 [$C(CH_3)_3$], 39.9, 40.4 ($NHCH_2$), 52.2 (OCH_3), 66.8, 67.2, 67.5 ($ArCH_2$, OCH_2), 79.5 [$C(CH_3)_3$], 106.5, 108.0, 108.2 (Ph $C^{2,4,6}$), 128.0, 128.1, 128.5 (Ar C^{2-6}), 132.1 (Ph C^1), 136.3 (Ar C^1), 155.8, 156.3 [C=O (Boc, Cbz)], 159.5, 159.6 (Ph $C^{3,5}$), 166.5 (CO_2Me) ppm. MS (ESI): m/z = 389.3 [M – Boc + H]$^+$, 511.4 [M + Na]$^+$. $C_{25}H_{32}N_2O_8$ (488.53): calcd. C 61.46, H 6.60, N 5.73; found C 61.48, H 6.64, N 5.71.

Half Coupled Dendrimer 21: Monomer **20** was Cbz-deprotected following the procedure described in the synthesis of **19**, affording the hydrochloride salt in a quantitative yield. To a mixture of the hydrochloride salt (0.45 mmol), **13** (280 mg, 0.45 mmol), BOP (218 mg, 0.495 mmol) and dry dichloromethane, was added D*i*PEA (255 μL, 1.46 mmol). The mixture was stirred at room temp. for 1 h. After concentration, the residue was dissolved in ethyl acetate and washed with 1 M $KHSO_4$ (twice), 1 M NaOH (twice) and brine. The organic layer was dried (Na_2SO_4) and the solvents evaporated in vacuo. Column chromatography (MeOH/DCM, 2:98) afforded the product as a yellow foam (333 mg, 78 %). R_f = 0.74 (MeOH/DCM, 1:9). ^{1}H NMR ($CDCl_3$): δ = 1.21–1.42 [m, 25 H, $OCH_2CH_2(CH_2)_8$, $C(CH_3)_3$], 1.61 [m, 2 H, $NHCH_2CH_2(CH_2)_{10}$], 1.71 [m, 2 H, $OCH_2CH_2(CH_2)_{10}$], 3.16 [m, 2 H, $ArNHCH_2$-$(CH_2)_{11}$], 3.47 (m, 2 H, $BocNHCH_2$), 3.57 (m, 2 H, $ArNHCH_2$-CH_2O), 3.80 [m, 2 H, $PhC(O)NHCH_2$], 3.85 (s, 3 H, OCH_3), 3.89 [m, 2 H, $OCH_2(CH_2)_{11}$], 3.95 (m, 2 H, OCH_2CH_2NHBoc), 4.13 [m, 4 H, OCH_2CH_2NHAr, $OCH_2CH_2NHC(O)Ph$], 4.87 [bt, 1 H, $ArNH(CH_2)_{12}$], 5.10 (br. s, 1 H, NHBoc), 5.28 [m, 1 H, $ArNH(CH_2)_2O$], 6.47 (m, 2 H, Ph $C^{4,4'}$-H), 6.54 (m, 4 H, 2 × Ar $C^{2,6}$-H), 6.93 [m, 3 H, Ph $C^{2',6'}$-H, NHC(O)Ph], 7.10 (m, 2 H, Ph $C^{2,6}$-H), 8.00 (m, 4 H, 2 × Ar $C^{3,5}$-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.8, 26.8, 28.9, 29.0, 29.1, 29.2, 29.3 [$OCH_2(CH_2)_{10}$], 28.3 [$C(CH_3)_3$], 39.5, 39.9 [CH_2NHBoc, $CH_2NHC(O)Ph$], 42.4 ($ArNHCH_2$), 43.2 [$NHCH_2(CH_2)_{11}$], 52.1 (OCH_3), 66.2 (OCH_2CH_2NHAr), 66.9 [$OCH_2CH_2NHC(O)Ph$], 67.3 (OCH_2CH_2NHBoc), 68.3 [$OCH_2(CH_2)_{11}$], 79.5 [$C(CH_3)_3$], 104.6, 105.1, 106.2, 108.0 (Ph $C^{2,4,6,2',4',6'}$), 110.7, 111.1 (Ar $C^{2,6}$), 126.2, 126.3 (Ar $C^{3,5}$), 131.9 (Ph C^1), 136.4 (Ph $C^{1'}$), 137.3, 137.9 (Ar C^1), 153.1, 153.6 (Ar C^4), 155.8 (C=O (Boc)], 159.4, 159.5, 160.4 (Ph $C^{3,5,3',5'}$), 166.4 (CO_2Me), 167.4 [NHC(O)Ph] ppm. MS (FAB); m/z [M + H]$^+$ = 959.5.

Dendrimer 22: To a solution of **21** (329 mg, 0.347 mmol) in dichloromethane (4 mL) was added diethylether (4 mL), saturated with HCl. The mixture was concentrated in vacuo and dried with KOH overnight, giving the hydrochloride salt as a yellow foam (301 mg, 98 %). Monomer **19** (160 mg, 0.260 mmol) was saponified usingthe procedure described in the synthesis of **14** affording a yellow solid (152 mg, 97 %). To this carboxylic acid was added the hydrochloride salt (223 mg, 0.253 mmol), BOP (122 mg, 0.277 mmol), dichloromethane (2.5 mL) and D*i*PEA (143 μL, 0.821 mmol). After stirring the mixture for 75 min at room temp., the solvent was evaporated and ethyl acetate was added. The organic layer was washed with 1 M $KHSO_4$ (twice), 1 M NaOH (twice) and brine, dried (Na_2SO_4) and concentrated. Column chromatography (MeOH/DCM, 2:98) afforded the dendrimer as a yellow foam (275 mg, 76 %). R_f = 0.68 (MeOH/DCM, 1:9). M.p. 50 °C. ^{1}H NMR ($CDCl_3$): δ = 1.24–1.43 [m, 43 H, $C(CH_3)_3$, $BocNHCH_2(CH_2)_9$, $ArNHCH_2CH_2(CH_2)_8$], 1.61 [m, 2 H, $ArNHCH_2CH_2(CH_2)_{10}$], 1.69 [m, 4 H, 2 × $OCH_2CH_2(CH_2)_{10}$], 3.07 [m, 2 H, $BocNHCH_2(CH_2)_{12}$], 3.16 [m, 2 H, $ArNHCH_2(CH_2)_{11}$], 3.54 (m, 4 H, 2 × $ArNHCH_2CH_2O$), 3.77 [m, 4 H, 2 × $PhC(O)NHCH_2$], 3.81 (s, 3 H, OCH_3), 3.86 [m, 4 H, 2 × $OCH_2(CH_2)_{11}$], 4.03 (m, 4 H, 2 × $OCH_2CH_2NHC{=}O$), 4.11 (m, 4 H, 2 × OCH_2CH_2NHAr), 4.65 (br. s, 1 H, NHBoc), 5.02 [m, 1 H, $ArNH(CH_2)_{12}$], 5.45 [m, 2 H, 2 × $ArNH(CH_2)_2O$], 6.51 (m, 9 H, Ph C^4-H, 2 × Ph $C^{4'}$-H, 3 × Ar $C^{2,6}$-H), 6.93, 6.98, 7.03 (3s, 6 H, Ph $C^{2,6}$-H, 2 × Ph $C^{2',6'}$-H), 7.19 [br. s, 2 H, 2 × NHC(O)Ph], 7.98 (m, 6 H, 3 × Ar $C^{3,5}$-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.8, 26.6, 26.8, 28.8, 29.0, 29.1, 29.2, 29.3, 29.4 [$OCH_2(CH_2)_{10}$], 28.3 [$C(CH_3)_3$], 39.5 ($NHCH_2$) 40.5 ($BocN'HCH_2$), 42.4 ($ArN'HCH_2CH_2O$), 43.2 [$ArN'HCH_2(CH_2)_{11}$], 52.1 (OCH_3), 66.2 ($OC'H_2CH_2NH$), 66.7 (OCH_2CH_2NH), 68.2 [$OC'H_2(CH_2)_{11}$], 78.9 [$C(CH_3)_3$], 104.6, 105.1, 106.1, 106.2, 108.1 (Ph $C^{2,4,6,2',4',6'}$), 110.7, 111.0 (Ar $C^{2,6}$), 126.2, 126.3 (Ar $C^{3,5}$), 131.8 (Ph C^1), 136.2, 137.1, 137.7, 136.3 (Ph $C^{1'}$, Ar C^1), 153.3, 153.7 (Ar C^4), 155.9 [C=O (Boc)], 159.3, 159.4, 160.3 (Ph $C^{3,5,3',5'}$), 166.4, 167.5 (CO_2Me, NHC=O) ppm. MS (FAB): m/z = 1443.1 [M + H]$^+$. $C_{77}H_{103}N_9O_{18}$ (1442.69): calcd. C 64.10, H 7.20, N 8.74; found C 63.92, H 7.18, N 8.70.

Dendrimer-to-Dendrimer System 23: Dendrimer **22** (161 mg, 0.113 mmol) was saponified using the procedure described in the synthesis of **14** affording the acid as a yellow foam (156 mg, 98 %). To a solution of dendrimer **22** (54.9 mg, 21.7 μmol) was added dichloromethane (1.5 mL) and trifluoroacetic acid (1.5 mL). After stirring at room temp. for 15 min, the mixture was concentrated and co-evaporated with chloroform (three times). The acid (30.7 mg, 21.5 μmol), BOP (10.5 mg, 23.9 μmol), dry acetonitrile (0.5 mL) and D*i*PEA (12 μL, 70 μmol) were added, and the mixture was refluxed for 3 h. The solvent was evaporated and dichloromethane (20 mL) was added, after which the product slowly solidified. Filtration followed by column chromatography (MeOH/DCM, 4:96) afforded dendrimer-to-dendrimer system **23** as a yellow foam (37 mg, 62 %). R_f = 0.32 (MeOH/DCM, 5:95). M.p. 64 °C. ^{1}H NMR ($CDCl_3$/CD_3OD): δ = 1.21–1.43 [m, 75 H, $C(CH_3)_3$, $BocNHCH_2(CH_2)_9$, $NHCH_2CH_2(CH_2)_8$], 1.57–1.71 [m, 14 H, 2 × $ArNHCH_2CH_2(CH_2)_{10}$, $PhC(O)NHCH_2CH_2(CH_2)_{10}$,

4 × $OCH_2CH_2(CH_2)_{10}$], 3.06 (m, 2 H, $BocNHCH_2$), 3.16 [m, 4 H, 2 × $ArNHCH_2(CH_2)_{11}$], 3.35 [m, 2 H, $PhC(O)NHCH_2(CH_2)_{11}$], 3.55 (m, 8 H, 4 × $ArNHCH_2CH_2O$), 3.74 [m, 8 H, 4 × $PhC(O)NHCH_2CH_2O$], 3.85 (s, 3 H, OCH_3), 3.89 [m, 8 H, 4 × $OCH_2(CH_2)_{11}$], 4.02 [m, 8 H, 4 × $OCH_2CH_2NHC(O)Ph$], 4.12 (m, 8 H, 4 × OCH_2CH_2NHAr), 4.70 (br. s, 1 H, NHBoc), 5.03 [br. s, 2 H, 2 × $ArNH(CH_2)_{12}O$], 5.57 [br. s, 4 H, 4 × $ArNH(CH_2)_2O$], 6.39–6.56 (m, 18 H, 6 × Ar $C^{2,6}$-H, Ph $C^{4,4''}$-H, 2 × Ph $C^{4',4'''}$-H), 6.85–7.05 (m, 12 H, Ph $C^{2,6,2'',6''}$-H, 2 × Ph $C^{2',6',2''',6'''}$-H), 7.36 [br. s, 5 H, 5 × NHC(O)Ph], 8.00 (m, 12 H, 6 × Ar $C^{3,5}$-H) ppm. ^{13}C NMR ($CDCl_3/CD_3OD$): δ = 25.6, 25.7, 26.2, 26.7, 28.7, 28.9, 29.0 (2 ×), 29.2 (2 ×), 29.3, 29.5, 29.7 [$OCH_2(CH_2)_{10}$], 28.1 [$C(CH_3)_3$], 39.2, 39.3 [$PhC(O)NHCH_2$], 40.3 ($BocNHCH_2$), 42.2 ($ArNHCH_2CH_2O$), 43.0 [$ArNHCH_2(CH_2)_{11}$], 52.1 (OCH_3), 66.3, 66.5, 66.7 (OCH_2CH_2NH), 68.3 [$OCH_2(CH_2)_{11}$], 104.5, 104.7, 105.2, 106.2, 108.2 (Ph $C^{2,4,6}$), 110.6, 110.9 (Ar $C^{2,6}$), 126.2, 126.3 (Ar $C^{3,5}$), 131.8 (Ph C^1), 136.1, 136.6, 136.9, 137.5 (Ar C^1, Ph $C^{1,1',1'',1'''}$), 153.5, 153.6, 153.9 (Ar C^4), 159,6, 160.3 (Ph $C^{3,5}$), 166.7 (CO_2Me), 167.5, 168.0 [PhC(O)NH] ppm. The signals of $C(CH_3)_3$ and C=O (Boc) were not visible in the ^{13}C NMR. MS (FAB): *m/z* = 2651.3 $[M - Boc]^+$. $C_{148}H_{194}N_{18}O_{33}$ (2753.23): calcd. C 64.56, H 7.10, N 9.16; found C 64.70, H 7.18, N 9.19.

Dendrimer-to-Dendrimer System 24: To a solution of dendrimer **23** (13.0 mg, 4.72 μmol) was added dichloromethane (0.5 mL) and trifluoroacetic acid (0.5 mL). After 30 min stirring at room temp., the mixture was concentrated and coevaporated with chloroform (three times). Saponified **22** (6.6 mg, 4.62 μmol), BOP (2.3 mg, 5.22 μmol), dry acetonitrile (0.25 mL) and a D*i*PEA solution in dichloromethane (10 % v/v, 48 μL, 27.7 μmol) were added. The mixture was refluxed for 3 h, followed by evaporation of the solvent. Purification by column chromatography (MeOH/DCM, 3:97) and preparative TLC (MeOH/DCM, 5:95), afforded dendrimer-to-dendrimer system **24** as a yellow film (5.7 mg, 30 %). R_f = 0.30 (MeOH/DCM, 5:95). ^1H NMR ($CDCl_3/CD_3OD$): δ = 1.21–1.56 [m, 107 H, $C(CH_3)_3$, $BocNHCH_2(CH_2)_9$, 5 × $NHCH_2CH_2(CH_2)_8$], 1.59–1.72 [m, 22 H, 3 × $ArNHCH_2CH_2(CH_2)_{10}$, 2 × $PhC(O)NHCH_2CH_2(CH_2)_{10}$, 6 × $OCH_2CH_2(CH_2)_{10}$], 3.07 (m, 2 H, $BocNHCH_2$), 3.15 [m, 6 H, 3 × $ArNHCH_2(CH_2)_{11}$], 3.35 [m, 4 H, $PhC(O)NHCH_2(CH_2)_{11}$], 3.57 (m, 12 H, 6 × $ArNHCH_2CH_2O$), 3.70 [m, 12 H, 6 × $PhC(O)NHCH_2CH_2O$], 3.86 (s, 3 H, OCH_3), 3.89 [m, 12 H, 6 × $OCH_2(CH_2)_{11}$], 4.02 [m, 12 H, 6 × $OCH_2CH_2NHC(O)Ph$], 4.13 (m, 12 H, 6 × OCH_2CH_2NHAr), 4.76 (br. s, 1 H, NHBoc), 5.12 [br. s, 3 H, 3 × $ArNH(CH_2)_{12}O$], 5.67 [br. s, 6 H, 6 × $ArNH(CH_2)_2O$], 6.37–6.56 (m, 27 H, 9 × Ar $C^{2,6}$-H, Ph $C^{4,4'',4'''',}$-H, 2 × Ph $C^{4',4''',4''''',}$-H), 6.83–7.07 (m, 18 H, Ph $C^{2,6,2'',6'',2'''',6''''}$-H, 2 × Ph $C^{2',6',2''',6''',2''''',6'''''}$-H), 7.56 (br. m, 8 H, 8 × NHC(O]Ph), 8.01 (m, 18 H, 9 × Ar $C^{3,5}$-H) ppm. ^{13}C NMR ($CDCl_3/CD_3OD$): δ = 25.8, 26.8, 28.2, 28.8, 29.0, 29.1, 29.3, 29.4, 29.5 [$OCH_2(CH_2)_{10}$, $C(CH_3)_3$], 39.3, 42.2, 43.0 [$PhC(O)NHCH_2$, $BocNHCH_2$, $ArNHCH_2$, $ArNHCH_2(CH_2)_{11}$], 52.2 (OCH_3), 63.8, 66.1, 66.4, 68.2 [OCH_2CH_2NH, $OCH_2(CH_2)_{11}$], 103.9, 104.6, 105.1, 105.7, 106.2, 108.0, 110.6, 110.9 (Ph $C^{2,6}$), 110.6, 110.9 (Ar $C^{2,6}$), 126.3, 126.4 (Ar $C^{3,5}$), 131.9 (Ph C^1), 136.0, 136.5, 137.4 (Ar C^1, Ph $C^{1–1'''''}$), 153.5, 153.8 (Ar C^4), 159.4, 159.5.3, 160.2 (Ph $C^{3,5}$), 166.7 (CO_2Me), 167.5, 168.0 [PhC(O)NH] ppm. The signals of $C(CH_3)_3$ and C=O (Boc) were not visible in the ^{13}C NMR. MS (ESI): *m/z* = 1993.7 $[M - Boc + Na + H]^{2+}$, 2054.7 $[M + 2Na]^{2+}$, 2732.2 $[2M + 3Na]^{3+}$, 4086.8 $[M + Na]^+$. $C_{219}H_{285}N_{27}O_{48}$ (4063.76): calcd. C 64.73, H 7.07, N 9.31; found C 64.80, H 6.97, N 9.12.

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