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Synthesis of new unsymmetrical polyarylester dendrimers

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Abstract—Preparation of polyarylester dendrimers containing 2-(hydroxymethyl)-1,4-butanediol and 2,2-bis(hydroxymethyl)-1,4-butanediol cores is described. These polyarylester dendrimers are unsymmetrical with respect to chain lengths and function as model systems for studying in vitro controlled drug release systems. Reaction conditions for deprotection of trichloroethyl group of the dendritic wedges have been improved.

1. Introduction

Dendrimers are globular, highly branched, monodisperse macromolecules with a well-defined three-dimensional shape, size, and molecular weight. Although, dendrimer chemistry is more than two decades old, new synthetic strategies and experimental conditions get evolved, keeping in view their numerous applications; for instance, as slow drug releasing systems, catalysts, physiological and electrochemical devices, and liquid crystals.[1–7] In general, dendrimers consist of core, branching structure, and periphery. Physio-chemical properties, and hence applications depend on the nature of these basic constituents.

Polyester dendrimers were demonstrated as suitable candidates for drug delivery[8] applications; furthermore, with their chemistries well developed,[9–13] it was envisaged to prepare structures having functionalities that undergo hydrolytic cleavage at different rates. To enable this, polyester dendrimers built on unsymmetric cores were chosen; by virtue of their unequal chain lengths, these dendrimers may get hydrolyzed by the enzymes at different rates. It is hypothesized that the differential rates of hydrolysis would release the dendrimer bound/entrapped drugs gradually, thus sustaining the availability of the drug for longer periods. To study this phenomenon in vitro, herein, synthesis of some model systems is reported.

2. Results and discussion

The synthetic strategy presented in this paper describes the synthesis of new polyarylester dendrimers possessing unsymmetric aliphatic cores viz., 2-(hydroxymethyl)-1,4-butanediol (**2**) and 2,2-bis(hydroxymethyl)-1,4-butanediol (**3**). Consequently, ester dendrimers possessing these cores[14,15] are unsymmetrical with respect to chain lengths, and to the best of our knowledge triol (**2**) and tetrol (**3**) were hitherto not used for the preparation of dendrimers. Accordingly, G0-acid and G1-acid wedges were synthesized as shown in Scheme 1 and by adopting a fine combination of both convergent and divergent approaches; synthesis of the unsymmetrical dendrimers was accomplished.

2,2,2-Trichloroethyl-3,5-dihydroxy benzoate (**1**) was prepared in 60% yield by the reaction of 3,5-dihydroxybenzoic acid with a mixture of 2,2,2-trichloroethanol and concentrated H_2SO_4. However, isolation of ester (**1**) was done by slightly modifying the literature procedure.[9] Removal of H_2SO_4 through aqueous $NaHCO_3$ wash, prior to the removal of trichloroethanol solvent and recrystallization from 1:1 hexane/benzene gave trichloroethyl ester (**1**) as white solid having mp of 70 °C. On the contrary, the literature reports[9] indicated this compound to be a liquid. In the preparation of G1-acid, trichloroethyl group was selectively deprotected in presence of other ester groups using zinc and acetic acid. Deprotection following the literature procedure[9] resulted in an impure product. However, decreasing the mole ratio of Zn and acetic acid by three times solved this problem.

G0-acid was coupled to cores **2** and **3** using a combination of dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridinium *p*-toluenesulfonate (DPTS). Thus, first generation polyarylester dendrimers **4** and **5** were isolated in 95 and 93% yield respectively, as shown in Scheme 2.

Keywords: Dendrimers; Convergent-divergent approach; Dendritic wedge; Unsymmetrical; Polyaryl ester; Trichloroethyl protection.
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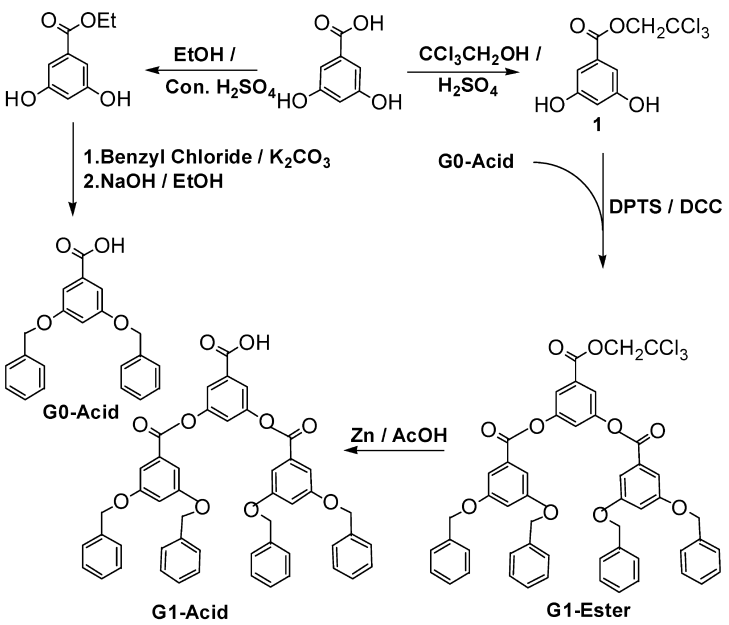
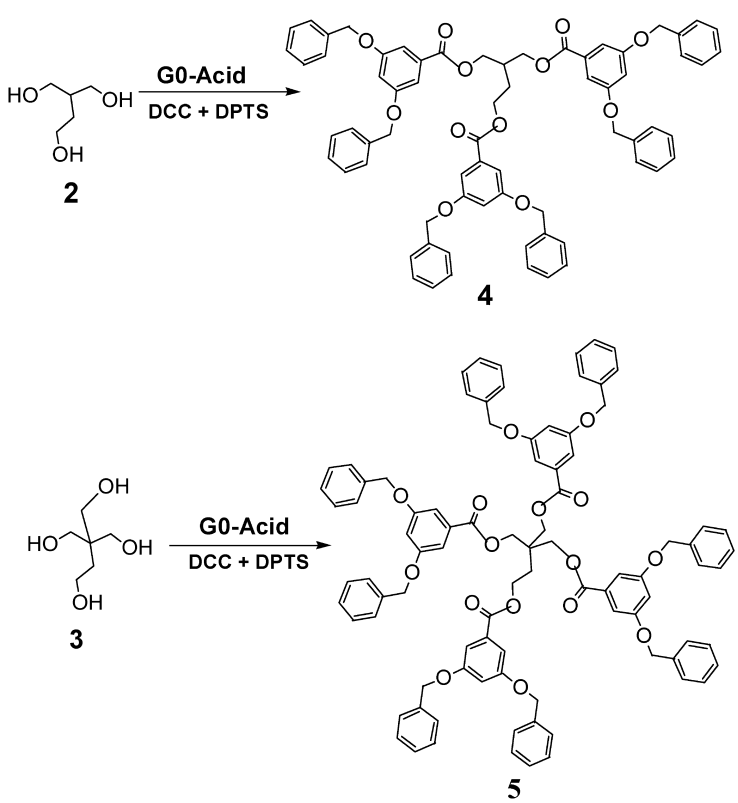


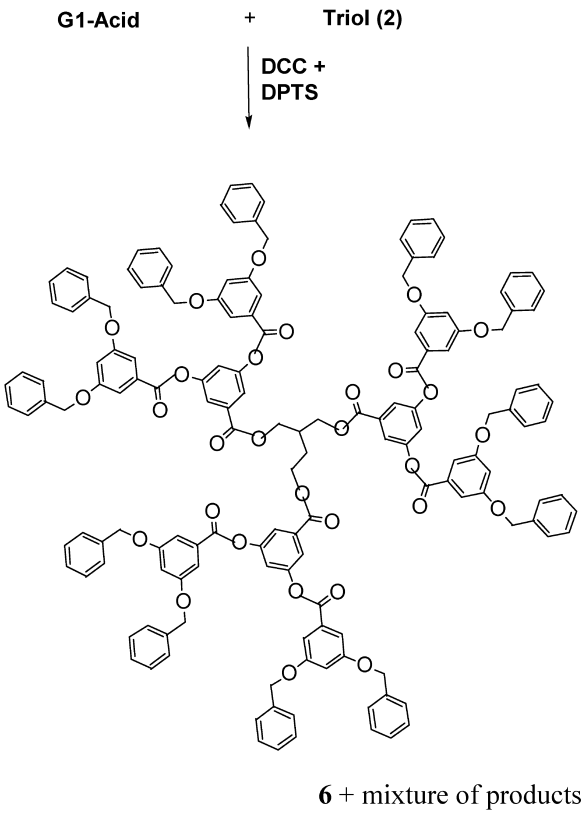
Scheme 1.

Surprisingly, the above mentioned reaction conditions did not yield second-generation dendrimers **6** and **7** (Scheme 3). On the other hand, mixtures of inseparable products were obtained; despite running the reaction for longer times and at higher temperatures.

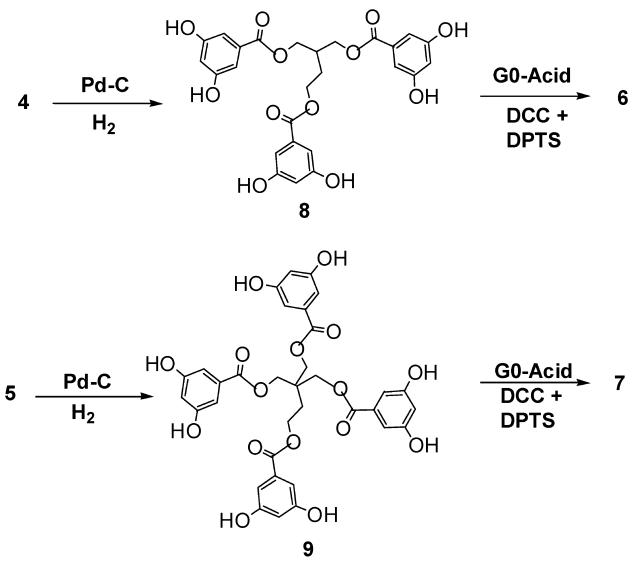
Failure of the reaction of G1-acid wedge with cores **2** and **3** is attributed, first, to crowding in the formation of dendrimers **6** and **7**. This is because the reacting aliphatic hydroxyl groups were very close to the center of the core. Second, the ester formation is considered relatively sluggish with aliphatic hydroxyl groups. However at this point, changing the strategy to a divergent approach solved these problems. The periphery of dendrimers **4** and **5** consist of six and eight benzyloxy groups respectively; accordingly, debenzylation of compounds **4** and **5** using Pd/C and H_2 resulted in hexahydroxy (**8**) and octahydroxy (**9**) intermediates (Scheme 4). With out further purification and



Scheme 2.



Scheme 3.



Scheme 4.

characterization, phenols **8** and **9** were reacted with G0-acid in presence of DCC/DPTS to give second-generation dendrimers **6** and **7** in 69 and 70% yields respectively (Scheme 5).

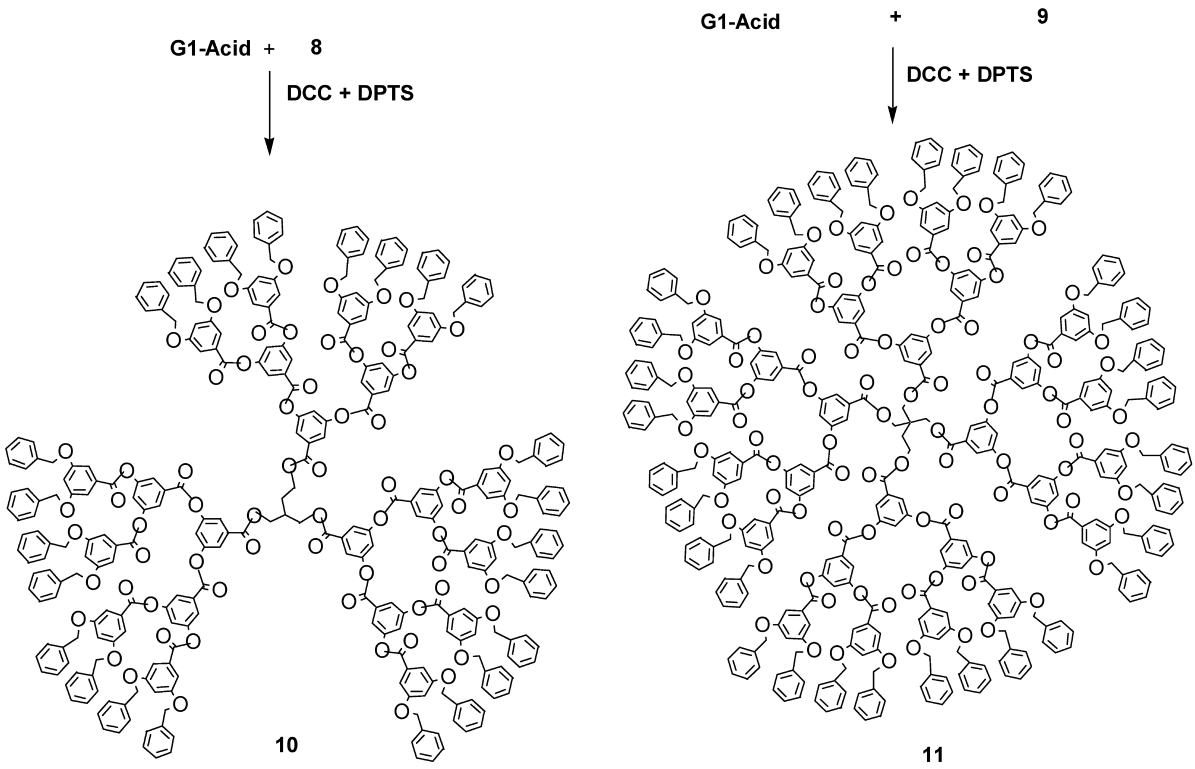
Similarly, following the above strategy, G1-acid wedge was reacted with intermediates **8** and **9** to produce third generation dendrimers **10** and **11** in 25 and 10% yields, respectively.

The divergent approach to synthesize the dendrimers **6**, **7** **10**, and **11** was successful because the reacting hydroxyl groups were phenolic and farther separated from the center of the core.

The values of the chemical shifts in the NMR spectra were in well agreement with those reported in the literature for similar dendritic polyarylesters.[9] To establish the extent of reaction and the generation number, the integration of ethereal hydrogens of the core (δ: 4.6) was compared with the peripheral benzylic hydrogens (δ: 4.9–5.0). MS techniques, FAB and MALDI were used to establish the molecular weight of the dendritic wedges and dendrimers. However, elemental analysis data of third generation dendrimers showed slight deviation from the calculated values. This discrepancy may be assumed originating from some kind of intramolecular transesterification reactions occurring when the reactions were performed for extended periods of time (72 and 96 h).

3. Conclusion

Synthesis of new unsymmetrical polyarylester dendrimers, by a combination of convergent and divergent approaches, was well demonstrated. Although the concept of differential hydrolytic cleavage for controlled drug delivery, as propounded in this paper, is new; its success depends greatly on the availability of new and diverse unsymmetrical dendrimers. To explore this phenomenon further,



Scheme 5.

synthesis of S-(+)-Naproxen based unsymmetrical polyarylester dendrimers[10] was also achieved. In vitro enzymatic hydrolysis of the ester dendrimers is under way and the findings at this stage are somewhat provisional.

4. Experimental

4.1. General directions

All the melting points reported are uncorrected and were determined using Buchi 525 instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian FT 200 MHz (Gemini) instrument, using tetramethyl silane (TMS) as the internal standard. The chemical shifts are expressed in δ scale. The abbreviations such as s, d, t, m, and b refer to singlet, doublet, triplet, multiplet, and broad respectively. The trisubstituted benzene is indicated as an aryl ring and is abbreviated as Ar and the monosubstituted benzene is indicated as a phenyl ring and is abbreviated as Ph. Mass spectra were recorded on VG Micromass 7070 H (EI and CI), Autospec (FAB), and Kratos Kompact SEQ (MALDI) instruments. Elemental analyses were recorded on a Perkin–Elmer 240C-CHN analyzer. Completion of the reaction and purity of the synthesised compounds were checked by TLC performed on silica gel (acmes) plates, using iodine and H_2SO_4 for visualizing the spots.

4.1.1. 2,2,2-Trichloroethyl-3,5-dihydroxybenzoate (1). To freshly distilled 2,2,2-trichloroethanol (25 ml) was added 3,5-dihydroxybenzoic acid (4.5 g, 29.2 mmol) followed by concentrated sulphuric acid (1.0 ml), and the mixture was stirred vigorously and heated at 90 °C for 48 h under nitrogen. The reaction mixture was cooled, poured into 10% aqueous $NaHCO_3$ solution (100 ml) and extracted with benzene (3×200 ml). The combined extracts were washed with distilled water, and evaporated to dryness under reduced pressure. The crude dark brown colored product was purified by recrystallization from 1:1 benzene/hexane to give 2,2,2-trichloroethyl-3,5-dihydroxybenzoate (**1**) (4.9 g) as a white crystalline solid. Yield: 60%; mp 70 °C. ^{1}H NMR ($CDCl_3$) δ: 4.90 (s, 2H, CH_2CCl$_3$), 5.1 (bs, 2H, D_2O exchangeable, 2×O*H*), 6.68 (t, 1H, *J*=3 Hz, Ar*H*), and 7.10 (d, 2H, *J*=3 Hz, Ar*H*); MS (EI) *m*/*z* (%): 284 (M^+, 10), 137 (100), 109 (30).

4.1.2. G1-ester dendritic wedge. To a solution of 3,5-dibenzyloxybenzoic acid (5.64 g, 16.8 mmol), 2,2,2-trichloroethyl-3,5-dihydroxybenzoate (2.0 g, 7.0 mmol) in dry dichloromethane (25 ml) was added 4-(dimethylamino)pyridinium *p*-toluenesulfonate (DPTS) (0.820 g, 2.7 mmol) and the mixture was stirred at room temperature under nitrogen atmosphere for 15 min. Dicyclohexylcarbodiimide (DCC) (3.40 g, 7.0 mmol) was then added and stirring continued at room temperature until the reaction had reached completion (16 h), a precipitate of dicyclohexylurea appeared during this time. The reaction mixture was filtered, and the filtrate was evaporated to dryness under reduced pressure. The crude product was then purified by column chromatography. Eluting with 1:1 $CHCl_3$/benzene and gradually increasing the polarity to $CHCl_3$ gave the G1-ester (5.9 g). Yield: 92%; mp 142–146 °C. ^{1}H NMR ($CDCl_3$) δ 5.00 (s, 2H, CH_2CCl$_3$), 5.12 (s, 8H, 4×PhCH_2O), 6.85 (t, 2H, *J*=3 Hz, 2×Ar*H*), 7.30–7.45 (m, 20H, 4×Ph*H*; 7H, 3×Ar*H*), and 7.88 (d, 2H, *J*=3 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 70.3, 74.6, 76.3, 108.2, 109.0, 120.8, 121.4, 127.5, 128.1, 128.6, 130.5, 130.8, 136.2, 151.4, 159.9, 163.2, and 164.1; MS (FAB) *m*-nitrobenzyl alcohol

(matrix) *m/z* (%): 919 [(M)$^+$, 22]. Anal. Calcd for $C_{51}H_{39}O_{10}Cl_3$: C, 66.71; H, 4.28. Found: C, 66.69; H, 4.30.

4.1.3. G1-acid dendritic wedge. To a solution of G1-ester (2.2 g, 2.4 mmol) in THF (15 ml) was added glacial acetic acid (5 ml) and the solution was stirred at room temperature under nitrogen atmosphere. Zinc dust (0.46 g, 7.2 mmol) was added and the reaction stirred vigorously at room temperature for 2.0 h. Then the reaction mixture was filtered and the filtrate poured into water (50 ml) and extracted with diethyl ether (3×50 ml). The combined extracts were washed with water, dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography. Eluting with CH_2Cl_2 and gradually increasing the polarity to 1:9 MeOH/CH_2Cl_2 gave G1-acid (1.52 g) as a white solid. Yield: 81%; mp 92–95 °C. ^{1}H NMR (acetone-D_6) δ 5.20 (s, 8H, 4×OCH_2Ph), 7.05 (m, 2H, Ar*H*), 7.30–7.60 (m, 20H, 4×Ph*H*; 5H, 3×Ar*H*), and 7.88 (d, 2H, *J*=3 Hz, *H*Ar-COOH); MS (FAB) benzyl alcohol (matrix) *m/z* (%): 809 [(M+23)$^+$, 10], 786 (M$^+$, 10). Anal. Calcd for $C_{49}H_{38}O_{10}$: C, 74.80; H, 4.87. Found: C, 74.68; H, 4.76.

4.1.4. First generation polyarylester dendrimer (4). To a solution of 3,5-dibenzyloxybenzoic acid (3.60 g, 10.7 mmol), 2-hydroxymethyl-1,4-butanediol (**2**) (0.430 g, 3.6 mmol) in dry dichloromethane (25 ml) was added DPTS (0.200 g, 0.72 mmol). The mixture was stirred at room temperature under nitrogen atmosphere for 15 min. DCC (2.20 g, 10.7 mmol) was then added and stirring continued at room temperature for 16 h, during this time a precipitate of dicyclohexylurea appeared. The reaction mixture was filtered and the filtrate was evaporated to dryness under reduced pressure, the crude product was then purified by column chromatography. Eluting with 1:1 benzene/$CHCl_3$ and gradually increasing the polarity to $CHCl_3$ gave the first generation ester dendrimer (**4**) (3.1 g) as a white solid. Yield: 95%; mp 108 °C. ^{1}H NMR ($CDCl_3$) δ: 2.05 (m, 2H, CH_2CH), 2.52 (m, 1H, C*H*CH$_2$), 4.42–4.55 (m, 6H, 3×OCH_2), 5.0 (s, 12H, 6×OCH_2Ph), 6.75 (m, 3H, 3×Ar*H*), 7.2 (d, 6H, 6×Ar*H*), and 7.3–7.4 (m, 30H, 6×Ph*H*). ^{13}C NMR ($CDCl_3$) δ: 27.9 35.2, 62.7, 64.7, 70.1, 107.3, 108.3, 127.4, 128.0, 128.5, 131.6, 131.9, 136.0, 159.7, 165.9, and 165.99; MS (FAB) *m*-nitrobenzyl alcohol (matrix) *m/z* (%): 1091 [(M+23)$^+$, 58]. Anal. Calcd for $C_{68}H_{26}O_{12}$: C, 78.92; H, 2.43. Found: C, 78.92; H, 2.28.

4.1.5. First generation polyarylester dendrimer (5). This compound was prepared from 3,5-dibenzyloxybenzoic acid (2.77 g, 8.3 mmol), 2,2-bis(hydroxymethyl)-1,4-butanediol (**3**) (0.250 g, 1.66 mmol), DPTS (0.100 g, 0.33 mmol).and DCC (1.70 g, 8.3 mmol) in dry dichloromethane (25 ml) following the procedure described for **4**. The reaction was carried out for 24 h. The crude product was then purified by column chromatography. Eluting with benzene gave the first generation polyarylester dendrimer (**5**) (2.20 g) as a white solid. Yield: 93%; mp 76–80 °C. ^{1}H NMR ($CDCl_3$) δ: 2.15 (m, 2H, CH_2C), 4.52 (s, 6H, 3×OCH_2C), 4.62 (m, 2H, OCH_2CH$_2$), 4.98 (s, 4H, 2×OCH_2Ph), 5.02 (s, 12H, 6×OCH_2Ph), 6.72 (t, 1H, *J*=2 Hz, Ar*H*), 6.80 (t, 3H, *J*=2 Hz 3×Ar*H*), 7.22 (d, 8H, *J*=2 Hz, 4×Ar*H*), and 7.32–7.45 (m, 40H, 8×Ph*H*); ^{13}C NMR ($CDCl_3$) δ 30.3, 41.3, 65.1, 70.1, 70.2, 107.7, 108.1, 108.3, 127.4, 128.0, 128.5, 131.3, 136.5, 159.8, and 165.6; MS (MALDI) *m/z* (%): 1415 (M$^+$, 28); 1439 [(M+23)$^+$, 100]; 1455 [(M+39)$^+$, 58]. Anal. Calcd for $C_{90}H_{78}O_{16}$: C, 76.36; H, 5.55. Found: C, 76.27; H, 5.44.

4.1.6. Hexahydroxy intermediate (8). Dendrimer (**4**) (0.400 g, 0.36 mmol) was dissolved in ethyl acetate (3 ml) and Pd/C (0.100 g) was then added. The reaction mixture was stirred in presence of H_2 for 16 h. Pd–C was filtered off, the filtrate concentrated to dryness under reduced pressure to give **8** (0.180 g) as a white solid.

4.1.7. Octahydroxy intermediate (9). This compound was prepared from polyarylester dendrimer (**5**) (0.200 g, 0.14 mmol) in ethylacetate (5 ml) and Pd/C (0.100 g) was then added. The reaction mixture was stirred in presence of H_2 for 24 h to give **9** (0.096 g) as a white solid.

4.1.8. Second generation polyarylester dendrimer (6). This compound was prepared from 3,5-dibenzyloxybenzoic acid (0.507 g, 1.52 mmol), the hexahydroxy intermediate (**8**) (0.100 g, 0.189 mmol), DPTS (0.090 g, 0.30 mmol) and DCC (0.313 g, 1.52 mmol) by following the procedure as described for **4**. The reaction was carried out for 72 h and the crude product was purified by column chromatography. Eluting with benzene and gradually increasing the polarity to 1:1 $CHCl_3$/benzene gave the second generation ester dendrimer (**6**) (0.250 g) as a white solid. Yield 69%; mp 58–64 °C. ^{1}H NMR ($CDCl_3$) δ: 2.1 (b, 2H, CH_2CH), 2.6 (m, 1H, C*H*CH$_2$), 4.50–4.59 (m, 6H, 3×OCH_2), 5.0 (s, 24H, 12×OCH_2Ph), 6.75 (d, 6H, *J*=2 Hz, 6×Ar*H*), 7.35–7.50 (m: 60H, 12×Ph*H*; 15H, 9×Ar*H*), and 7.72–7.78 (two d, 6H, (ArH)$_3$core); ^{13}C NMR ($CDCl_3$) δ 27.8, 35.1, 63.1, 65.2, 70.3, 108.2, 108.9, 120.4, 127.5, 128.0 128.5, 130.6, 131.9, 136.2, 151.2, 159.8, 164.1, and 164.6; MS (MALDI) *m/z* (%): 2449 [(M+23)$^+$, 100], 2465 [(M+39)$^+$, 5]. Anal. Calcd for $C_{152}H_{120}O_{30}$: C, 75.24; H, 4.98. Found: C, 75.14, H, 4.87.

4.1.9. Second generation polyarylester dendrimer (7). This compound was prepared from 3,5-dibenzyloxybenzoic acid (0.481 g, 1.44 mmol), the octahydroxy intermediate (**9**) (0.100 g, 0.144 mmol), DPTS(0.100 g, 0.028 mmol) and DCC (0.296 g, 1.44 mmol) by following the procedure as described for **4**. The reaction was carried out for 72 h and the crude product was purified by column chromatography. Eluting with benzene and gradually increasing the polarity to 1:1 chloroform/benzene gave the second generation polyarylester dendrimer (**7**) (0.320 g) as a white solid. Yield 70%; mp 88–92 °C. ^{1}H NMR ($CDCl_3$) δ 2.29 (b, 2H, CH_2C), 4.60–4.69 (b, 8H, 4×CH_2O), 4.92 (s, 8H, 4×OCH_2Ph), 4.98 (s, 24H, 12×OCH_2Ph), 6.69–6.76 (m, 8H, 8×Ar*H*), 7.30–7.42 (m, 80H, 16×Ph*H*; 20H, 12×Ar*H*), and 7.70–7.75 (d, 8H, *J*=2 Hz, (Ar*H*)$_4$ core); ^{13}C NMR ($CDCl_3$) δ 30.2, 41.2, 65.2, 70.3, 108.3, 109.0, 120.4, 127.5, 128.1, 128.6, 130.7, 131.6, 136.40, 151.3, 151.3, 159.9 164.0, and 164.1; MS (MALDI) *m/z* (%): 3248 [(M+23)$^+$, 23], 3264 [(M+39)$^+$, 06]. Anal. Calcd for $C_{202}H_{158}O_{40}$: C, 75.22; H, 4.94. Found: C, 75.02, H, 4.82.

4.1.10. Third generation polyarylester dendrimer (10). This compound was prepared from G1-acid (1.2 g, 1.52 mmol), the hexahydroxy intermediate (**8**) (0.102 g,

0.193 mmol), DPTS (0.100 g, 0.308 mmol) and DCC (0.318 g, 1.54 mmol) by following the procedure as described for **4**. The reaction was carried out for 72 h and the crude product was purified by column chromatography. Eluting with benzene and gradually increasing the polarity to 3:7 benzene/chloroform gave the third generation ester dendrimer (**10**) (0.196 g) as a white solid. Yield: 25%; mp 94–100 °C. ^{1}H NMR ($CDCl_3$) δ 2.25 (bm, 2H, CH_2CH), 2.60 (bm, 1H, CHCH$_2$), 4.55 (bm, 6H, 3×CH_2O), 4.95 (bs, 48H, 24×PhCH_2O), 6.70 (t, 12H, 12×PhCH$_2$OArH), 7.20–7.40 (m: 120H, 24×PhH; 24H 12×ArH; 6H, 6×ArH; 3H, 3×ArH), 7.75 (d, 4H, J=2.5 Hz; 2×ester-ArH), 7.80 (d, 2H, ester-ArH), and 7.88 (m, 12H, ester-ArH). ^{13}C NMR ($CDCl_3$) δ 27.7, 35.2, 63.2, 65.5, 70.2, 108.2, 108.8, 120.5, 121.0, 121.3, 127.5, 128.0, 128.5, 130.4, 130.9, 131.0, 132.1, 132.2, 136.2, 150.9, 151.3, 159.8, 162.7, 164.0, and 164.40. MS (MALDI) m/z: 5164 [(M+23)$^+$]. Anal. Calcd for $C_{320}H_{240}O_{66}$: C, 74.76; H, 4.71. Found: C, 74.34: H, 4.57.

4.1.11. Third generation polyarylester dendrimer (11). This compound was prepared from G1-acid (1.13 g, 1.44 mmol), the octahydroxy intermediate (**9**) (0.100 g, 0.144 mmol), DPTS (0.084 g, 0.028 mmol) and DCC (0.296 g, 1.44 mmol) by following the procedure as described for **4**. The reaction was carried out for 96 h and the crude product was purified by column chromatography. Eluting with benzene and gradually increasing the polarity to 3:7 benzene/$CHCl_3$ gave the third generation ester dendrimer (**11**) (0.098 g) as a white solid. Yield: 10%; mp 92–94 °C. ^{1}H NMR ($CDCl_3$) δ 2.30 (b, 2H, CH_2C), 4.68 (b, 8H, 4×CH_2O), 4.95 (s, 64H, 32×OCH_2Ph), 6.72 (m, 16H, 16×ArH), 7.20–7.42 (m, 160H, 32×PhH; 32H, 16×ArH; 8H, 8×ArH; 4H, 4×ArH), 7.75 (d, 6H, J=2 Hz; 3×ester ArH), 7.79 (d, 2H, J=2 Hz; ester ArH), and 7.90 (m, 16H, 8×ester ArH).^{13}C NMR ($CDCl_3$) δ: 29.6, 41.3, 65.2, 70.2, 108.2, 108.9, 120.5, 121.0, 121.2, 127.5, 128.0, 128.5, 130.5, 131.0, 131.1, 131.6, 136.3, 151.0, 151.3, 159.8, 162.6, 164.0, and 164.2; MS (MALDI) m/z (%): 6883 [(M+39)$^+$, 100]. Anal. Calcd for $C_{426}H_{318}O_{88}$: C, 74.74; H, 4.69. Found: C, 75.12; H, 4.11.

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