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Full Paper

Synthesis and Characterization of a Novel Biodegradable Amphiphilic Dendritic Polyether-ester

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A novel biodegradable amphiphilic dendritic polyether-ester composed of glycerol, glycolic acid oligomer and methoxy poly(ethylene glycol) is described. The monomer unit composed of glycerol and glycolic acid was protected by *tert*-butyl and benzyl groups. The amphiphilic dendritic polyether-ester was prepared in high yield using sequential deprotection reactions and esterification. The structure of all compounds was confirmed by ^{1}H NMR spectra, ^{13}C NMR spectra, GC-MS or matrix-assisted laser desorption–ionization time-of-flight mass spectrometry, and the amphiphilic dendritic macromolecule molecular weight and distribution were measured by gel permeation chromatography.

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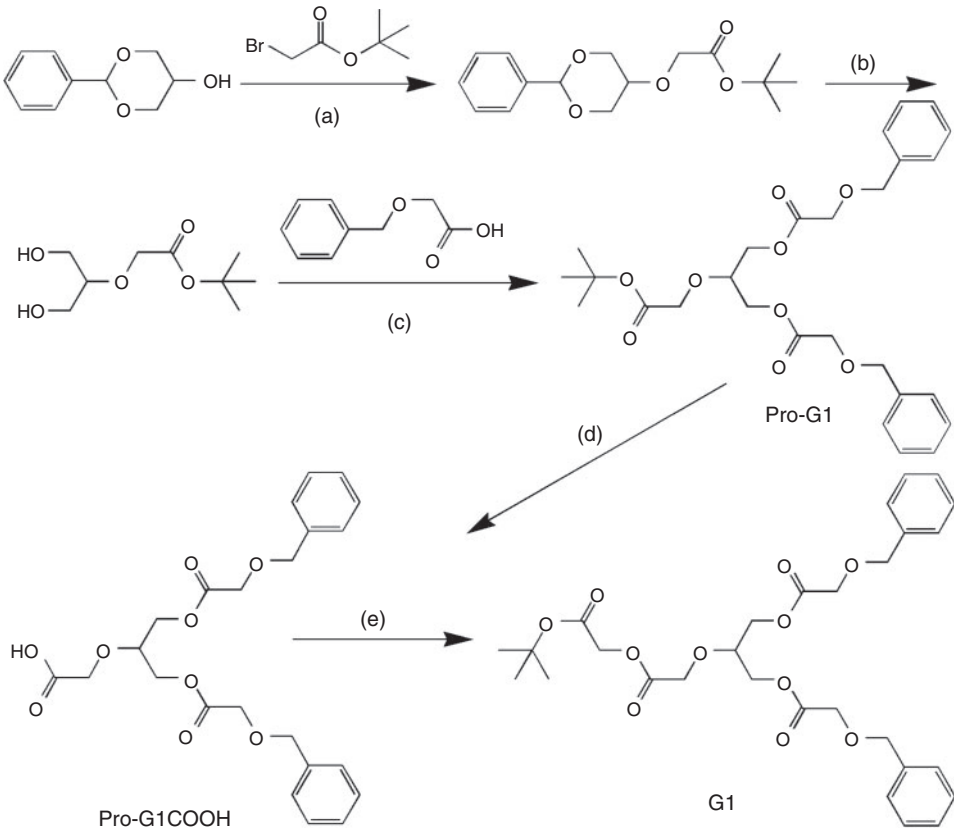
Introduction

Dendrimers are monodisperse synthetic macromolecules built from branched repeating units around a core. Dendrimers are synthesized stepwise, resulting in precisely controlled size and structure, and a well-defined number of surface end-groups.[1] Thus, dendrimers provide opportunities to fine-tune their composition and structure to afford macromolecules with specific properties for basic studies and applications in areas such as molecular encapsulation,[2] catalysis,[3] light-harvesting,[4] gene transfection[5] and drug delivery.[6] For example, polyamidoamine, polyethyleneimine and poly(propyleneimine) are some of the most widely used dendrimers in gene and drug delivery application[7–9] for increasing water solubility, biocompatibility and so on. However, these dendrimers also have some inherent drawbacks for biological use. Their polycationic surfaces lead to significant toxicity[7,9]; furthermore, these are all non-biodegradable.[9]

In recent years, much effort devoted to the preparation of dendrimers has explored polyesters as promising candidates for biological applications.[7,9] Owing to their intrinsic properties such as non-immunogenicity, good biocompatibility and biodegradability, they could be widely used in biomedical applications,[7,9–11] including sutures, scaffolds in tissue engineering and carriers in drug delivery. Several polyester dendrimers such as PMPA dendrimers[12] (based on 2,2-bis(hydroxymethyl) propanoic acid), PGLSA dendrimers[13] (based on glycerol and succinic acid) have been reported, and have demonstrated potential use in biological applications.[14]

Among the various dendritic macromolecules studied, linear dendritic block copolymers have emerged as an interesting class of dendrimer derivatives because of the interesting assemblies they can form in solution, on surfaces, or in the presence of other macromolecules. Linear dendritic block copolymers are usually composed of poly(ethylene glycol) and a hydrophobic dendritic block.[15] Furthermore, the size of dendrimers formed by these polymers tends to be uniform.[16] Some poorly water-soluble drugs and fluorescent probes have been physically encapsulated into these micelles.[2,15,16] Although many linear dendritic block copolymers have been explored, identification of new monomers and synthesis of novel biodegradable linear dendritic block copolymers remain an active area of research.

In 2001, the Grinstaff group first reported a novel polyester dendrimer that was synthesized using the divergent method with glycerol and lactic acid as the growth unit (PGLLA dendrimers),[17] and reported that PGLLA dendrimers degrade faster than PGLSA dendrimers.[10] They attribute this reactivity difference to the hydrophobicity and the inherent chemical reactivity present in the macromolecule (facile loss of monomer unit by an internal six-member cyclization reaction). The excellent degradation properties of polyether-ester dendrimers could help in achieving a desired degradation rate for specific in vivo applications. Despite these appealing advantages, no further study has been reported so far, mainly due to the difficult monomer synthesis and limited available synthetic methods (divergent method only).[17] The use of glycerol and glycolic acid to synthesize hyperbranched polymers has been reported recently.[18] However, that AB_2 monomer units synthesis was very difficult and tedious, and they were not suitable as dendrimer monomer units. Herein, we report a facile synthetic method of branching AB_2 monomer units composed of glycerol and glycolic acid. Two facile ways were used to introduce glycolic acid into this AB_2 monomer, and every glycolic acid could be replaced by other analogues,[19,20] such as lactic acid, glycolic acid oligomer and lactic acid oligomer. Those strategies



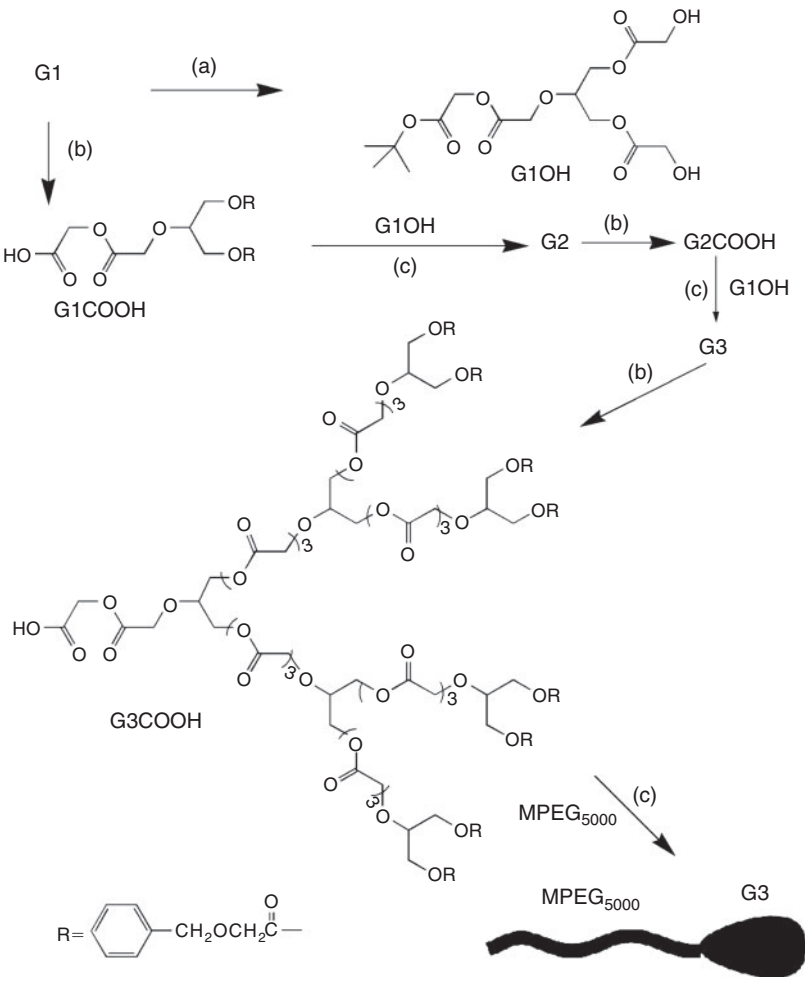
Scheme 1. Synthesis of AB_2 monomer unit (dendron G1): (a) *tert*-butyl bromoacetate, KOH, PEG_{6000}, K_2CO_3, room temp; (b) *p*-toluenesulfonic acid, ethanol, H_2O, 50°C; (c) DCC, DMAP, DCM, 0°C; (d) TFA, DCM, triethylsilane, 0°C; (e) *tert*-butyl bromoacetate, TBAB, acetone, 70°C.

would greatly increase the variability of dendrons, dendrimers and their derivatives, providing new opportunities to create tailored polymers that could regulate the degradation rate and other chemical and physical properties. Moreover, we used that AB_2 monomer unit and glycolic acid oligomer to synthesize a series of polyether-ester dendrons by the convergent method. Further, we used methoxy poly(ethylene glycol) (MPEG) conjunct dendrons as building block polymers. In addition, the MPEG-block-dendritic copolymer used benzyl protecting groups, which can be selectively removed in very high yields by catalytic hydrogenolysis without affecting the ester bonds of the polyester backbone, and the hydroxyl-terminated block polymer can be used in drug delivery[14] or photo-crosslinked dendritic gels.[13] These properties are likely to facilitate the design and development of new materials and provide new opportunities to create well-defined, tailored polymers for specific medical and tissue-engineering applications.

Results and Discussion

The strategy for the preparation of the monomer unit is outlined in Scheme 1. Transformation of 5-phenyl-1,4-dioxan-2-ol into *tert*-butyl-2-(1,3-dihydroxypropan-2-yloxy)acetate was easily carried out in a yield of 80 % by KBr exchange under mild conditions. In this reaction, KOH was used as base rather than Na or NaH, which need anhydrous, anaerobic and low-temperature conditions. The benzylidene acetal group of the *tert*-butyl-2-(1,3-dihydroxypropan-2-yloxy)acetate was subsequently removed by hydrogenolysis (with *p*-toluenesulfonic acid as a catalyst) to yield the 2-(1,3-dihydroxypropan-2-yloxy)acetate. The hydroxyl groups were then protected with benzyloxyacetic acid using dicyclohexylcarbodiimide (DCC) chemistry. The *tert*-butyl of the protected dendron pro-Generation 1 (pro-G1) was deprotected by CF_3COOH and yielded the carboxylic acid-terminated dendron pro-G1COOH. The pro-G1COOH reacted with *tert*-butyl bromoacetate by KBr exchange with K_2CO_3 as base and produced a novel bi-protected AB_2 monomer unit (dendron Generation 1) protected by *tert*-butyl and benzyl groups. As mentioned above, the benzyl and *tert*-butyl groups can be selectively removed by using hydrogen with a palladium catalyst and CF_3COOH respectively.

The strategy for the synthesis of dendrons Generation 1 (G1) to Generation 3 (G3) is outlined in Scheme 2. The protected G1 was deprotected by CF_3COOH to yield the carboxylic acid-terminated dendron G1COOH. The benzyl group of G1 was subsequently removed by hydrogenolysis (10 % (w/w) of 10 % Pd/C, 2.9 MPa H_2, in CH_3OH) to produce a hydroxyl-terminated G1OH. Next, dendrons G1OH and G1COOH were coupled in the presence of DCC and dimethylaminopyridine (DMAP) to afford the protected G2 dendron; the G2 dendron was deprotected in CF_3COOH/CH_2Cl_2 (1 : 1) to yield the carboxylic acid-terminated dendron G2COOH. The dendron G3 was prepared by reacting dendron G1OH with G2COOH. The *tert*-butyls of dendron G3 were subsequently removed by CF_3COOH to yield the carboxylic acid-terminated dendron G3COOH. All reactions were conducted under mild conditions and had excellent yields. The esterification and deprotection reactions were monitored by NMR spectroscopy as the relative integrated areas of the aromatic, glycerol and *tert*-butyl protons change with each successive generation. The phenyl, methylene and *tert*-butyl groups could serve as diagnostic NMR tags to monitor the



Scheme 2. Synthesis of dendron G1 to MPEG-(polyether-ester) dendritic (a) Pd/C, H_2, CH_3OH, room temp; (b) TFA, DCM, triethylsilane, room temp; (c) DCC, DMAP, CH_2Cl_2, 0°C.

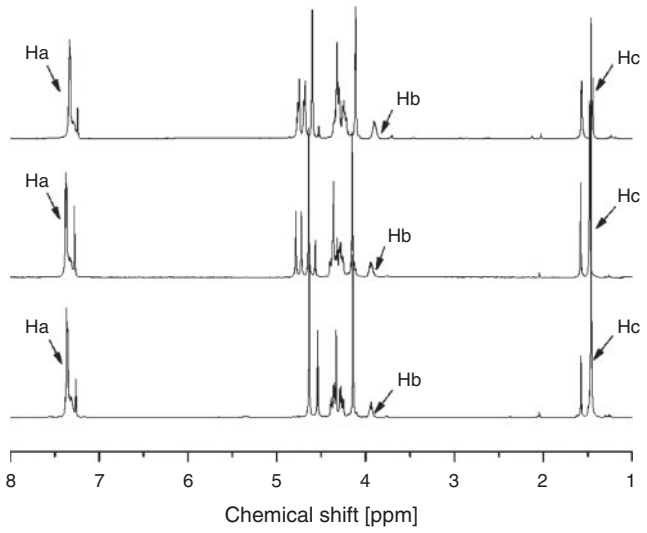


Fig. 1. ^{1}H NMR spectrum of G1 to G3 dendrons.

increase of dendron generation, as they are recognizable in every dendron molecule from G1 to G3, and we could use the integration ratio (phenyl/methylene/*tert*-butyl = 10 : 1 : 9, 20 : 3 : 9, 40 : 7 : 9 for G1, G2 and G3 respectively) to judge whether the generation increase was successful or not.

The ^{1}H NMR spectra of dendrons G1 to G3 are compared in Fig. 1. Peaks at 7.35 ppm were attributed to the phenyl protons (Ha) of the benzyl group; the single peak at 1.47 ppm belongs to the *tert*-butyl (Hc) group. The ^{1}H NMR spectra of dendrons G1COOH to G3COOH are shown in Fig. 2. The disappearance of peaks at 1.47 ppm indicates the complete removal of the *tert*-butyl group. In addition, the dendrons' purity and molecular weight could be determined by MALDI-TOF (matrix-assisted laser desorption–ionization time-of-flight) mass spectrometry. The MALDI-TOF spectra of protected dendrons is shown in Fig. 3. In all cases, a strong signal for the molecular ion is observed at the expected molecular weight (G1 599.3 (M + K), G2 1391.3 (M + K) and G3 2976.0 (M + K)) and there is no sign of incomplete branches. A abnormal feature was observed in the spectra of every dendron, which showed the presence of strong peaks of lower mass by ~56 from the mass ions corresponding to the desired products, ascribed to the *tert*-butyl group of the dendrons being easily lost in laser excitation.[21] The MALDI-TOF MS spectra of deprotected dendrons are shown in Fig. 4. In this case, two strong peaks (M + 39, M + 77) were observed in the spectra, which correspond to the K^+ adduct and $2K^+$ adduct (the hydrogen ion of the carboxyl was replaced by a K ion).

The strategy for the synthesis of dendritic MPEG-(polyether-ester) is outlined in Scheme 2. $MPEG_{5000}$ and dendron G3COOH were coupled in the presence of DCC and DMAP to afford the MPEG-(polyether-ester) dendritic copolymer.

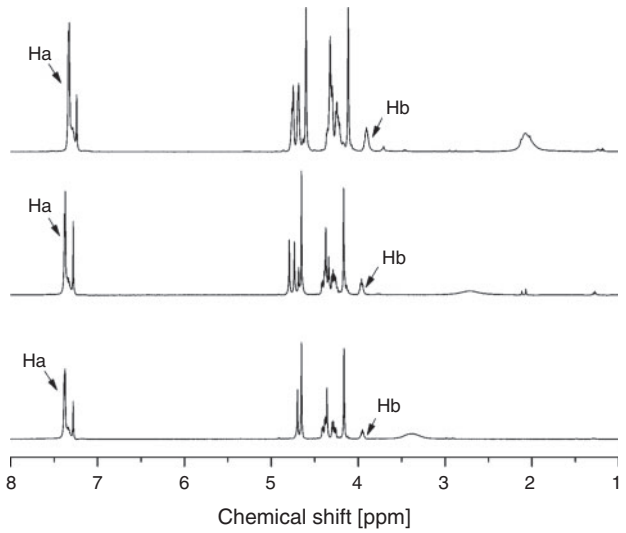


Fig. 2. ^{1}H NMR spectrum of G1COOH to G3COOH dendrons.

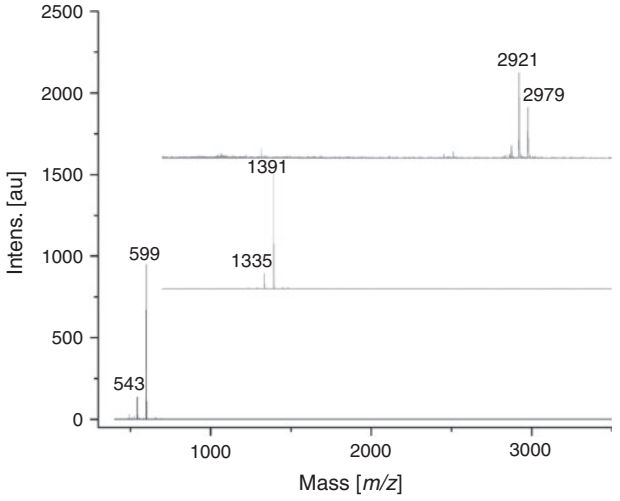


Fig. 3. MALDI-TOF (matrix-assisted laser desorption–ionization time-of-flight) mass spectra of G1 to G3 dendrons.

The molecular weights of the dendrons and the linear-MALDI-TOF mass spectrum are summarized in Fig. 5. The spectrum now consists of a series of peaks centred at a mass of 7791, exhibits the expected mass difference of 44 between individual components, and shows no signs of unreacted $MPEG_{5000}$. The linear dendritic copolymer gel permeation chromatography (GPC) curves (polystyrene standard and DMF as eluent) show a unimodal peak (Fig. 6); compared with $MPEG_{5000}$ and G3COOH, it can be seen that the molecular weight distribution of the copolymers was controlled to a very narrow range. The molecular weight and molecular weight distribution are 16819 and 1.04 respectively. These data all imply that the dendritic copolymers were obtained successfully.

Conclusion

The synthesis and characterization of glycerol and glycolic acid oligomer dendrons as well as linear dendritic copolymers composed of glycerol, glycolic acid oligomer and methoxy poly (ethylene glycol) are described. This synthesis yields a novel AB_2 monomer unit protected by *tert*-butyl and benzyl groups. Dendrons were prepared in high yield using sequential deprotection reactions and esterification. The oligomers were introduced successfully into the dendritic polymers and could increase its variability and keep biocompatibility and biodegradability. This biocompatible, biodegradable amphiphilic dendritic polyether-ester expands the repertoire of polymers available for study, and is believed to have potential applications

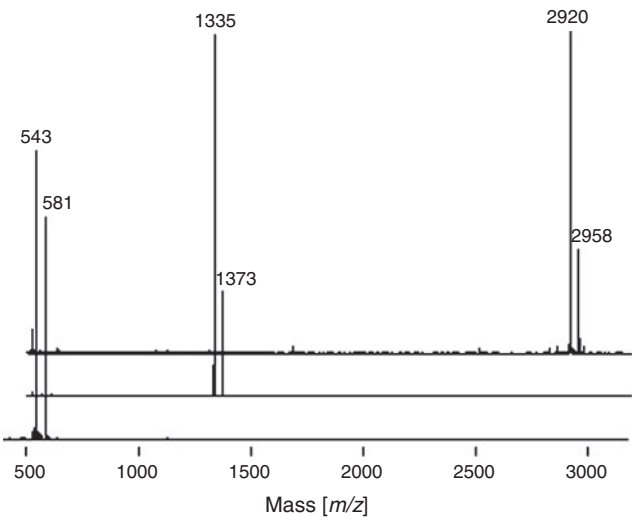


Fig. 4. MALDI-TOF (matrix-assisted laser desorption–ionization time-of-flight) mass spectra of G1COOH to G3COOH deprotected dendrons.

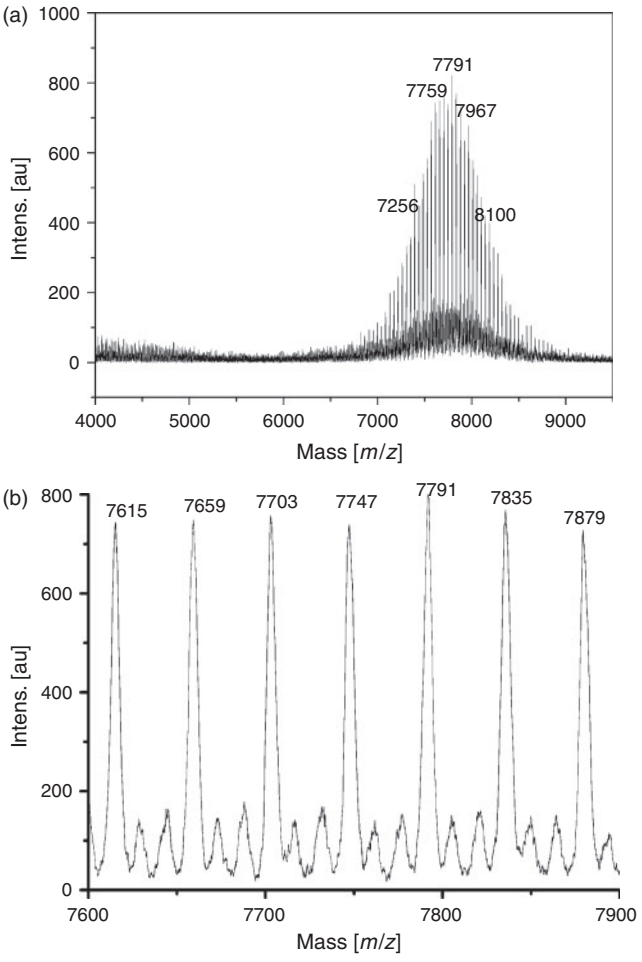


Fig. 5. MALDI-TOF (matrix-assisted laser desorption–ionization time-of-flight) mass spectra of dendritic.

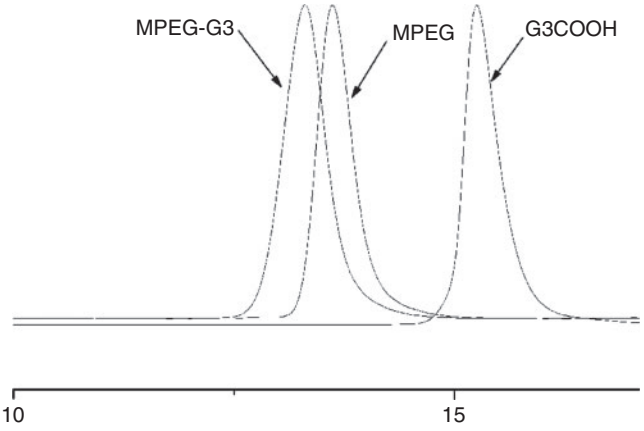


Fig. 6. Gel permeation chromatography curves of dendritic copolymers.

in controlled drug release in the biomedical and tissue engineering field.

Experimental

General Procedures and Requirements

^{1}H NMR spectra were recorded on a Bruker AV-400 M in $CDCl_3$. Chemical shifts are given in parts per million with respect to tetramethylsilane as an internal reference. ^{13}C NMR spectra were recorded on a Bruker AV-400 M in $CDCl_3$; GPC measurements were conducted with a PL-GPC120 (DMF as eluent, polystyrene standard). Mass spectrometry measurements were carried out using GC-MS (Agilent 7890–5975C GC-MSD, ethyl acetate as solvent) or MALDI-TOF (BrukerSaxonia Reflex IV apparatus equipped with a 337-nm nitrogen laser, 2,5-dihydroxy benzoic acid and 2-hydroxy-5-methoxybenzoic acid (9 : 1 w/w) as the matrix and CF_3COOK as cationic reagent).

Synthetic Procedures and Physical Data for All New Compounds

Benzyloxyacetic acid and 5-phenyl-1,4-dioxan-2-ol were synthesized according to literature procedures.[19,22]

Synthesis of tert*-Butyl-2-(2-phenyl-1,3-dioxan-5-yloxy) acetate*

To a one-necked flask equipped with a magnetic stirrer was added 5-phenyl-1,4-di-oxan-2-ol (10.0 g, 55.5 mmol), followed by dichloromethane (100 mL), 5.1 g (90 mmol) KOH and a catalytic amount of poly(ethylene glycol) (Mn = 2000). The mixture was stirred for 24 h at room temperature. Reaction progress was monitored by TLC. After the disappearance of the 5-phenyl-1,4-dioxan-2-ol, the reaction mixture was filtered, and the filtrate was evaporated to dryness. The product was purified by recrystallization in cold (−21°C) hexane to get a white solid (90 % yield). δ_H (400 MHz, $CDCl_3$) 7.35–7.53 (5H, C_6H_5), 5.57 (1H, C_6H_5CH), 4.1–4.44 (6H, CH_2CHCH_2CO), 3.54 (1H, CH_2CH), 1.49 (9H, $C(CH_3)_3$). δ_C (100 MHz, $CDCl_3$) 28.1, 66.3, 69.0, 70.6, 81.6, 101.2, 126.1, 128.1, 128.8, 138.1, 169.8. *m*/*z* (GC-MS) Calc. for $C_{16}H_{22}O_5$: 294. Found: 293 (M − H).

Synthesis of tert*-Butyl-2-(1,3-dihydroxypropan-2-yloxy) acetate*

Compound **6** (5 g, 18.52 mmol) was added to a one-necked flask equipped with a magnetic stirrer, followed by 30 mL of ethanol. When the solid had dissolved, *p*-toluenesulfonic acid (0.5 g) and an additional of 5 mL distilled water were added. The reaction mixture was stirred for 30 min at 50°C. The reaction progress was monitored by TLC. After reaction, the mixture was evaporated and dissolved into dichloromethane (20 mL). The solution was washed with saturated aqueous sodium bicarbonate, and dried with $MgSO_4$, and then evaporated. Yield 2.90 g (86 %) of *tert*-butyl-2-(1,3-dihydroxypropan-2-yloxy)acetate as a colourless liquid. δ_H (400 MHz, $CDCl_3$) 1.49 (9H, $C(CH_3)_3$), 3.51–3.54 (1H, CH), 3.70–3.71 (4H, CH_2–CH), 4.17 (CH_2CO). δ_C (100 MHz, $CDCl_3$) 171.6, 83.5, 82.7, 68.1, 62.4, 28.0. *m*/*z* (GC-MS) Calc. for $C_9H_{18}O_5$: 206. Found: 207 (M + H).

Synthesis of Dendron Pro-G1

In a flask equipped with a magnetic stirrer, *tert*-butyl-2-(1,3-dihydroxypropan-2-yloxy)acetate (4 g, 20.0 mmol) and benzyloxyacetic acid (6.64 g, 40.04 mmol) were dissolved in dichloromethane (100 mL), and then DMAP (catalytic amount) and DCC (4.13 g, 40.04 mmol) were added. Stirring at 0°C was continued for 14 h. The DCC-urea was filtered and washed with a small amount of dichloromethane (10 mL), and the filtrate was evaporated. The crude product was purified by silica gel chromatography (ethyl acetate/hexane 1 : 5) to yield 4.65 g of a colourless liquid (95 % yield). δ_H (400 MHz, $CDCl_3$) 7.30–7.37 (10H, C_6H_5), 4.63 (4H, $CH_2C_6H_5$), 4.24–4.38 (4H, CH_2CH), 4.08–4.19 (4H, CH_2CO), 3.87–3.90 (1H, CH), 1.45 (9H, $C(CH_3)_3$). δ_C (100 MHz, $CDCl_3$) 170.0, 169.0, 137.1, 128.4, 128.2, 128.1, 128.0, 127.8, 81.9, 75.5, 73.4, 67.9, 67.0, 63.2, 28.0. *m*/*z* (MALDI-TOF) Calc. for $C_{27}H_{34}O_9$: 502. Found: 541 $(M + K)^+$.

Synthesis of Dendron Pro-G1COOH

In a flask equipped with a magnetic stirrer, dendron pro-G1 (10 g, 22.42 mmol) was dissolved in anhydrous CH_2Cl_2 (30 mL). The solution was chilled to room temperature and treated with trifluoroacetic acid (TFA, 15 mL) and triethylsilane (1 mL). After stirring for 2 h, TFA and CH_2Cl_2 were removed under reduced pressure. The residue was dissolved in saturated aqueous sodium bicarbonate, and extracted with dichloromethane twice. Removing the organic extract, the aqueous layer (adjusted to pH 3.0 with 1 M HCl) was extracted with dichloromethane three times and the extracts were dried over $MgSO_4$. The product was obtained by removal of the solvent from the dried extract. δ_H (400 MHz, $CDCl_3$) 7.30–7.37 (10H, C_6H_5), 4.63 (4H, $CH_2C_6H_5$), 4.13–4.40 (6H, CH_2CHCH_2CO), 4.06 (4H, CH_2CO), 3.88–3.90 (1H, CH). δ_C (100 MHz, $CDCl_3$) 173.1, 170.0, 136.9, 128.5, 128.3, 128.1, 128.0, 76.3, 73.4, 67.2, 67.0, 63.2. *m*/*z* (MALDI-TOF) Calc. for $C_{23}H_{26}O_9$: 446. Found: 485 $(M + K)^+$, 523 $(M + K^+ + K^+ - H)$.

Synthesis of Dendron G1

In a flask equipped with a magnetic stirrer, glycolic acid (4.46 g, 0.010 mol) was dissolved in 150 mL of acetone and $KHCO_3$ (15.2 g, 0.152 mol) was added. The mixture was stirred for ~2 h. *tert*-Butyl bromoacetate (2.14 g, 0.011 mol) and tetrabutylammonium bromide (cat.) were added. The reaction mixture was stirred for 48 h at 70°C and then filtered; the solvent was removed under reduced pressure. Column chromatography (silica gel, ethyl acetate/hexane) yielded 5.21 g (93 %) of dendron G1. δ_H (400 MHz, $CDCl_3$) 7.30–7.37 (10H, C_6H_5), 4.63 (4H, $CH_2C_6H_5$), 4.53 (2H, $COCH_2CO$) 4.24–4.39 (6H, CH_2CHOCH_2CO), 4.08–4.14 (4H, $C_6H_5CH_2OCH_2$), 3.92–3.95 (1H, CH), 1.49 (9H, $C(CH_3)_3$). δ_C (100 MHz, $CDCl_3$) 170.0, 169.3, 166.2 137.0, 128.5, 128.3, 128.02, 128.0, 82.7,

75.9, 73.4, 67.2, 67.0, 66.9, 63.2, 61.3, 28.0. *m/z* (MALDI-TOF) Calc. for $C_{29}H_{36}O_{11}$: 560. Found: 599 $(M + K)^+$.

Synthesis of Dendron G1COOH

Dendron G1 (5 g, 8.93 mmol) was dissolved in 20 mL anhydrous CH_2Cl_2. The solution was chilled to room temperature and treated with TFA (15 mL) and triethylsilane (1 mL). After stirring for 2 h, TFA and CH_2Cl_2 were removed under reduced pressure. The residue was dissolved in saturated aqueous sodium bicarbonate, and extracted with dichloromethane two times. Removing the organic extract, the aqueous layer (adjusted to pH 3.0 with 1 M HCl) was extracted with dichloromethane three times and the extracts were dried over $MgSO_4$. The product was obtained by removal of the solvent from the dried extract. δ_H (400 MHz, $CDCl_3$) 7.32–7.38 (10H, C_6H_5), 4.65–4.69 (4H, $CH_2C_6H_5CH_2COOH$), 4.16–4.41 (6H, CH_2CHOCH_2CO), 4.16 (4H, $C_6H_5CH_2OCH_2CO$), 3.93–3.96 (1H, CH). δ_C (100 MHz, $CDCl_3$) 170.4, 170.1, 169.4, 136.9, 128.5, 128.0, 75.9, 73.4, 67.1, 63.2, 60.3. *m/z* (MALDI-TOF) Calc. for $C_{133}H_{148}O_{71}$: 502. Found: 543 $(M + K)^+$, 581 $(M + K^+ + K^+ - H)$.

Synthesis of Dendron G1OH

In a flask equipped with a magnetic stirrer, Pd/C (10 % w/w) was added to a solution of dendron G1 (2 g, 3.57 mmol) in EtOAc/MeOH (3 : 1, 40 mL). The flask was evacuated and filled with 2.9 MPa of H_2 before shaking for 20 min. The catalyst was filtered off and washed with EtOAc (10 mL). The filtrate was then evaporated to give 1.22 g of a colourless viscous oil. δ_H (400 MHz, $CDCl_3$) 4.59 (2H, $COCH_2CO$), 4.24–4.39 (6H, CH_2CHOCH_2CO), 4.08–4.14 (4H, $HOCH_2CO$), 3.92–3.95 (1H, CH), 1.49 (9H, $C(CH_3)_3$). δ_C (100 MHz, $CDCl_3$) 172.8, 169.5, 166.3, 83.0, 75.9, 67.2, 63.7, 61.3, 60.6, 60.3, 28.0. *m/z* (MALDI-TOF) Calc. for $C_{25}H_{28}O_{11}$: 380. Found: 419 $(M + K)^+$.

Synthesis of Dendron G2

In a flask equipped with a magnetic stirrer were placed dendrons G1OH (1.0 g, 2.63 mmol), G1COOH (2.92 g, 5.79 mmol) and 30 mL dichloromethane; DMAP (cat.) and DCC (1.19 g, 5.79 mmol) were added. Stirring was continued for 24 h at room temperature. The DCC-urea was filtered off and washed with a small amount of dichloromethane and the filtrate was evaporated. The crude product was purified by silica gel chromatography to yield 3.2 g of a colourless liquid (90 % yield). δ_H (400 MHz, $CDCl_3$) 7.31–7.37 (20H, C_6H_5), 4.56–4.78 (18H, $CH_2C_6H_5COCH_2CO$), 4.19–4.38 (18H, CH_2CHOCH_2CO), 4.09–4.13 (16H, $C_6H_5CH_2OCH_2$), 3.92 (3H, CH). δ_C (100 MHz, $CDCl_3$) 170.0, 169.4, 166.7, 166.6, 166.2, 137.1, 128.5, 128.3, 82.8, 75.9, 75.6, 73.4, 67.2, 67.1, 67.0, 63.7, 63.1, 61.03, 60.4, 28.0. *m/z* (MALDI-TOF) Calc. for $C_{65}H_{76}O_{13}$: 1352. Found: 1391 $(M + K)^+$.

Synthesis of Dendron G2COOH

In a flask equipped with a magnetic stirrer, dendron G2 (3 g, 2.22 mmol) was dissolved in 20 mL anhydrous dichloromethane. The solution was chilled to room temperature and treated with TFA (15 mL) and triethylsilane (1 mL). After stirring for 2 h, TFA and dichloromethane were removed under reduced pressure. The crude product was purified by silica gel chromatography (ethyl acetate/hexane 2 : 1) to yield 2.59 g of colourless liquid (90 % yield). δ_H (400 MHz, $CDCl_3$) 7.33–7.38 (20H, C_6H_5), 4.65–4.79 (18H, $CH_2C_6H_5COCH_2CO$), 4.25–4.41 (18H, CH_2CHOCH_2CO), 4.16 (8H, $C_6H_5CH_2OCH_2$), 3.92–3.96 (3H, CH). δ_C (100 MHz, $CDCl_3$) 170.2, 170.1, 169.5, 168.8, 166.9, 166.7, 137.0, 129.0, 128.9, 128.8, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 77.4, 77.2, 77.0 76.7, 76.0, 75.8, 73.6, 73.4, 69.1, 67.3, 67.2, 67.1, 66.7, 65.4, 65.3, 64.0, 63.7, 63.2, 61.2, 60.5. *m/z* (MALDI-TOF) Calc. for $C_{61}H_{68}O_{31}$: 1296. Found: 1335 $(M + K)^+$, 1373 $(M + K^+ + K^+ - H)$.

Synthesis of Dendron G3

In a flask equipped with a magnetic stirrer were placed dendrons G1OH (0.4 g, 1.05 mmol), G2COOH (3.0 g, 2.31 mmol) and 10 mL dichloromethane; DMAP (cat.) and DCC (0.46 g, 2.31 mmol) were added. Stirring at 0°C was continued for 24 h. The DCC-urea was filtered off and washed with a small amount of dichloromethane and the filtrate was evaporated. The crude product was purified by silica gel chromatography (ethyl acetate/hexane 3 : 1) to yield 3.49 g of a colourless liquid (90 % yield). δ_H (400 MHz, $CDCl_3$) 7.26–7.35 (40H, C_6H_5), 4.54–4.78 (42H, $CH_2C_6H_5COCH_2CO$), 4.24–4.38 (42H, CH_2CHOCH_2CO), 4.09–4.19 (16H, $C_6H_5CH_2OCH_2$), 3.91–3.92 (7H, CH), 1.46 (9H, $C(CH_3)_3$). δ_C (100 MHz, $CDCl_3$) 170.0, 169.4, 166.7, 166.6, 166.2, 137.2, 129.8, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 82.6, 75.9, 75.6, 73.3, 67.2, 67.1, 67.0, 63.7, 63.5, 63.1, 61.3, 61.0, 60.6, 60.4, 28.0. *m/z* (MALDI-TOF) Calc. for $C_{137}H_{156}O_{71}$: 2936. Found: 2979 $(M + K)^+$.

Synthesis of Dendron G3COOH

In a flask equipped with a magnetic stirrer, dendron G3 (1 g, 0.35 mmol) was dissolved in 10 mL anhydrous CH_2Cl_2. The solution was chilled to room temperature and treated with TFA (10 mL) and triethylsilane (0.5 mL). After stirring for 2 h, TFA and dichloromethane were removed under reduced pressure. The crude product was purified by silica gel chromatography (ethyl acetate/hexane 3 : 1) to yield 0.9 g of a colourless liquid (95 % yield). δ_H (400 MHz, $CDCl_3$) 7.26–7.34 (40H, C_6H_5), 4.62–4.78 (42H, $CH_2C_6H_5COCH_2CO$), 4.24–4.56 (42H, CH_2CHOCH_2CO), 4.12–4.15 (16H, $C_6H_5CH_2OCH_2$), 3.95 (7H, CH). δ_C (100 MHz, $CDCl_3$) 171.2, 170.1, 169.4, 169.2, 166.8, 166.7, 137.0, 129.9, 128.5, 128.3, 127.7, 127.4, 76.7, 75.8, 75.7, 73.6, 73.4, 67.2, 67.1, 67.0, 63.8, 63.4, 63.2, 61.1, 60.8, 60.4, 60.4. *m/z* (MALDI-TOF) Calc. for $C_{133}H_{148}O_{71}$: 2882.6. Found: 2919 $(M + K)^+$, 2958 $(M + K^+ + K^+ - H)$.

Synthesis of Dendrons MPEG-G3 Dendritic

In a flask equipped with a magnetic stirrer were placed $MPEG_{5000}$ (0.70 g, 0.14 mmol), dendron G3COOH (0.8 g, 0.28 mmol) and 5 mL dichloromethane; DMAP (cat.) and DCC (0.058 g, 0.28 mmol) were added. Stirring at 0°C was continued for 24 h. The DCC-urea was filtered off and washed with a small amount of dichloromethane and the filtrate was evaporated. Anhydrous ether was added dropwise to the crude product to precipitate the products; this was repeated twice, and the precipitate was filtered off and vacuum-dried to yield 0.99 g of a white powder (81 % yield). δ_H (400 MHz, $CDCl_3$) 7.26–7.35 (40H, C_6H_5), 4.62–4.76 (42H, $CH_2C_6H_5COCH_2CO$), 4.24–4.34 (42H, CH_2CHOCH_2CO), 4.13 (16H, $C_6H_5CH_2OCH_2$), 3.92 (7H, CH), 3.64 (CH_2CH_2O), 3.38 (3H, CH_3O). δ_C (100 MHz, $CDCl_3$) 170.0, 69.4, 137.1, 128.5, 128.0, 75.8, 75.7, 73.4, 70.6, 67.32, 67.1, 63.7, 63.1. *m/z* (MALDI-TOF) Calc. for: 7925. Found: 7791 $(M + K)^+$.

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