Macromolecules **2006,** *39,* 609−616

Synthesis of Generational Polyester Dendrimers Derived from Glycerol and Succinic or Adipic Acid

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Received August 21, 2005; Revised Manuscript Received November 5, 2005

ABSTRACT: The divergent syntheses of dendrimers composed of glycerol and varying layers of succinic and adipic acids are described. These alternating and bilayer generational copolymers are prepared in high yield using sequential esterification and hydrogenolysis reactions. The glass transition temperatures and solubilities are dependent on the composition of the outer generation layer.

Introduction

Dendrimers are monodisperse macromolecules consisting of a central core from which branched repeat units extend outward in a fractal-like pattern.[1−11] As the molecular weight of the dendrimer increases, the structure in solution adopts a globular conformation. The degree to which a dendrimer attains this globular shape is determined by the solvent it is dissolved in, the multiplicities of the core and branches, the orientation of the branching functionalities, the flexibility of the branching units, and the length of the repeat unit.[12−16] The dendritic structure possesses three distinct regions which include the central core, branching units, and end groups. The synthetic routes to dendrimers, whether divergent or convergent, allow for precise control within these three distinct regions of the macromolecule. Thus, dendrimers provide opportunities to fine-tune the composition and structure to afford macromolecules with specific properties for basic studies and applications in areas such as medicine, catalysis, photonics, and nanotechnology.[17−29]

Today, dendritic macromolecules are being explored within the medical field as carriers for MRI contrast agents, synthetic vectors for gene transfection, vehicles for drug delivery, and sealants for tissue repair.[23,30−38] These applications typically arise from utilizing the large number of functional groups on the periphery, the overall charge of the dendritic structure, or property differences between the interior and exterior of the dendrimer. For example, not only can a pharmaceutical be linked to the end groups,[35,39−43] but it can also be entrapped within the interior structure[38,44−49] or chemically linked to the core of the dendrimer.[50]

Recently, dendritic polymers composed of building blocks known to be biocompatible or degradable in vivo to natural metabolites have been synthesized.[51−56] These polyester and poly(ether−ester) macromolecules composed of glycerol, succinic acid, lactic acid, and/or poly(ethylene glycol) are being evaluated as hydrogel sealants to repair ophthalmic wounds,[37,57,58] as scaffolds for cartilage repair,[59] and as carriers for the delivery of hydrophobic anticancer drugs.[38,60] To further increase the diversity and resulting properties of aliphatic polyester dendrimers, we have expanded the system to include adipic acid, which is found in beet juice. This more hydrophobic dicarboxylic acid exhibits low acute toxicity.[61]

Herein we report the synthesis and physical properties of aliphatic dendrimers containing glycerol and various layers of succinic and adipic acid. The zero- through fourth-generation polymers described include poly(glycerol succinic−adipic acid) (**[G*n*]PGLSA-[G*n*]-PGLAA**), poly(glycerol adipic acid) [**[G*n*]-PGLAA**], and poly(glycerol succinic acid) [**[G*n*]-PGLSA**] dendrimers. Two new diblock succinic and adipic acid dendrimers were synthesized with varying amounts of adipic acid and succinic acid in either an alternating layered or single layered-block structural design (Figures 1−3). The numbers of reported layered or generational diblock dendrimers[62] are few and include examples of poly(aryl ester−ether) dendrimers by Fréchet,[63] poly(aryl ester−alkyne) dendrimers by Zimmerman,[64] and phosphorus-containing dendrimers by Majoral.[65] The polyester dendrimers described below are aliphatic macromolecules where the length of the dendritic backbone has been varied between four and six carbons. The single layered diblock dendrimer has a larger, more hydrophobic interior composed of adipic acid monomer units and an outer layer of succinic acid monomer units. The poly(glycerol−succinic acid) (PGLSA) dendrimers were prepared using an anhydride coupling approach as opposed to an earlier reported dicyclohexylcarbodiimide (DCC) coupling method.[52] The anhydride coupling approach afforded dendrimers that were more easily purified through straightforward aqueous washes and precipitation. Finally, we synthesized the dendrimer composed entirely of glycerol and adipic acid for comparisons with the other three dendritic structures.

Results and Discussion

The fourth generation of the four families of aliphatic dendrimers composed of glycerol, succinic acid, and/or adipic acid is shown in Figures 2 and 3. The AB_2 monomers used in the synthesis of all four types of dendrimers are shown in Scheme 1. All of the polyester dendrimers were synthesized using a divergent approach which entailed a coupling reaction to increase the generation number followed by a deprotection reaction to enable the subsequent coupling reactions. Specifically, the coupling reaction was an esterification reaction between an alcohol and a carboxylic acid or an anhydride. The deprotection step was a Pd-catalyzed hydrogenolysis reaction. The glycerol−succinate monomer, **3**, was synthesized in ∼95% yield as previously reported.[52] The anhydride, **4**, was prepared by treating the glycerol−succinate monomer, **3**, with 0.6 equiv of DCC in the presence of 4-(dimethylamino)pyridine (DMAP).

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10.1021/ma0518407 CCC: $33.50

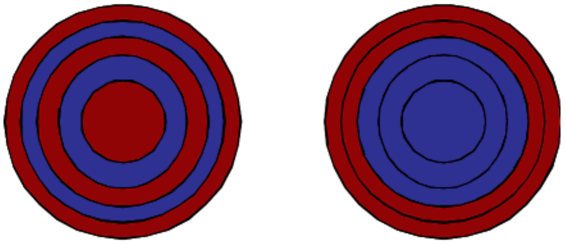


Figure 1. Schematic of an alternating layered-block dendrimer (left) and a single layered-block dendrimer (right).

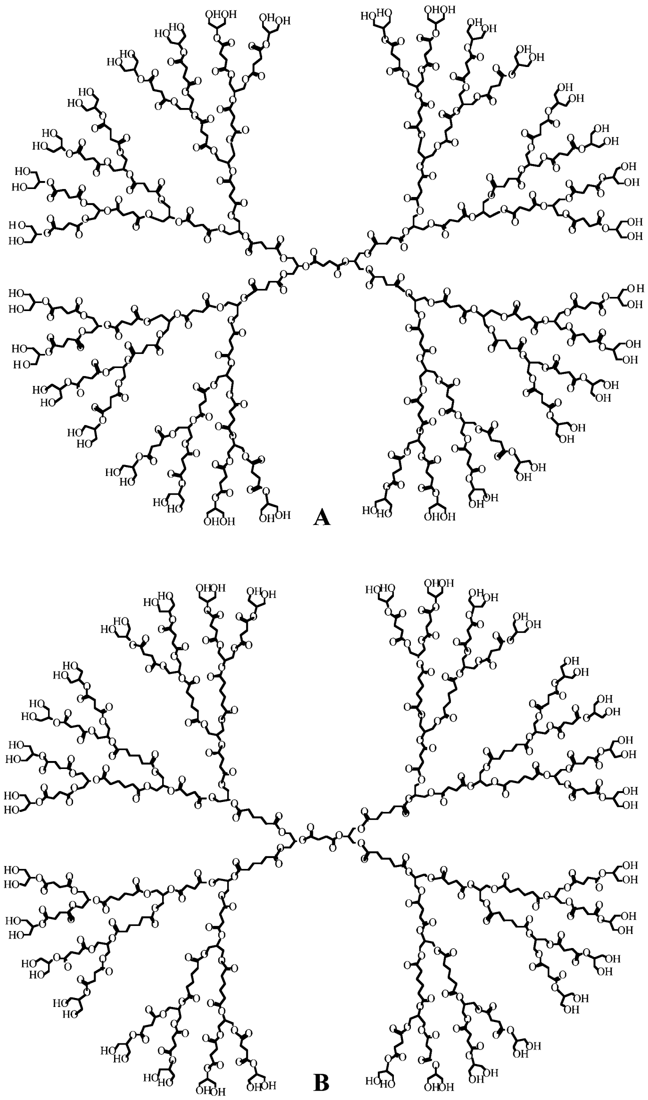


Figure 2. Structures of (A) **[G4]-PGLSA**-OH, **16**, and (B) **[G4,G2,-G0]-PGLSA-[G3,G1]-PGLAA**-OH, **34**, dendrimers.

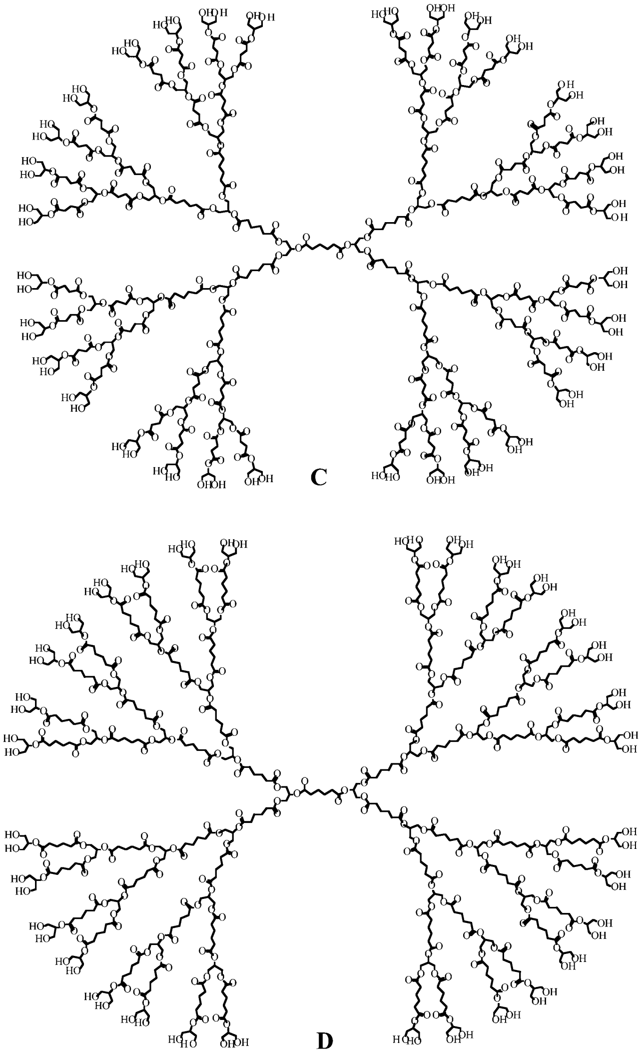
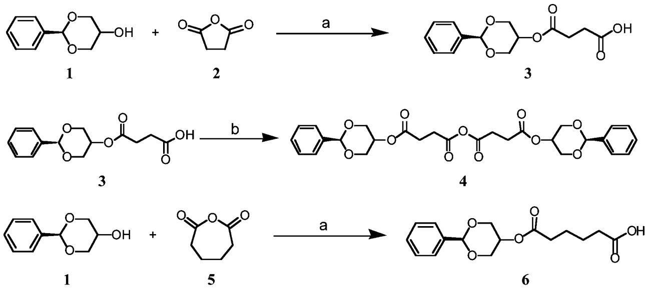


Figure 3. Structures of (C) **[G4-G3]-PGLSA-[G2-G0]-PGLAA**-OH, **38**, and (D) **[G4]-PGLAA**-OH, **26**, dendrimers.

Scheme 1. Synthesis of the Monomers for PGLSA and PGLAA Based Dendrimers[a]



[a] Reagents and conditions: (a) pyridine, 14 h, 25 °C; (b) DCC, DCM, 14 h, 25 °C.

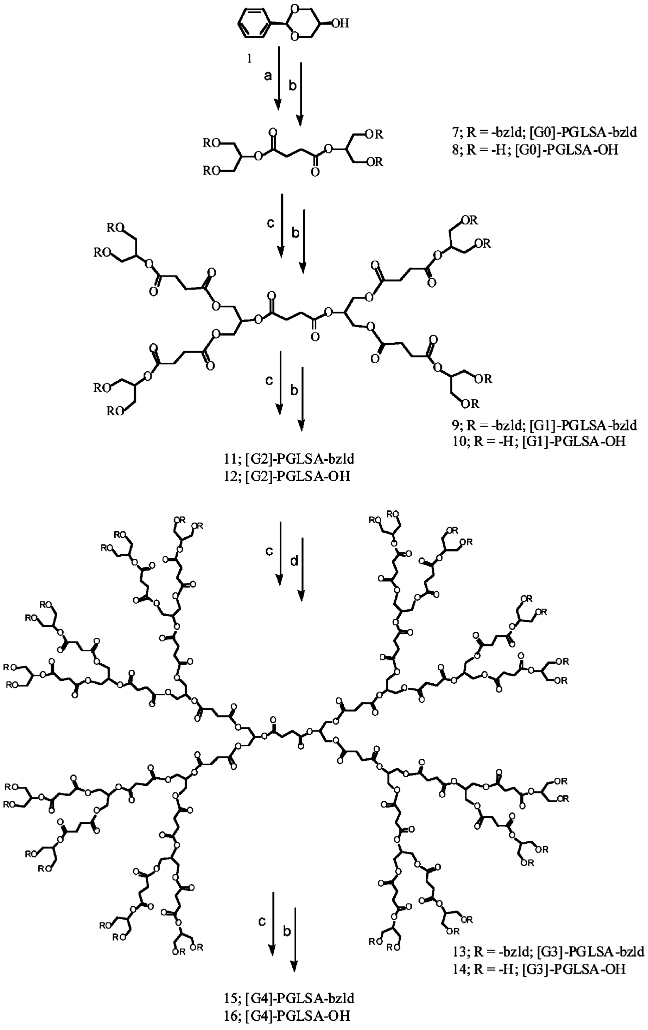
The glycerol–adipate monomer, **6**, was synthesized by treating *cis*-1,3-*O*-benzylidene glycerol, **1**, with adipic anhydride, **5**,[66] according to the literature. This reaction repeatedly proceeded in low yields ranging from 25% to 48%.

Because of the similarity in the synthetic steps to these four dendrimers, we will describe the synthesis of the **[G*n*]-PGLAA** and alternating layered **[G*n*]-PGLSA-[G*n*]-PGLAA** dendrimers in detail and will refer to the schemes and Supporting Information (SI) for the preparation of the **[G*n*]-PGLSA** and single-layered-block **[G*n*]-PGLSA-[G*n*]-PGLAA** dendrimers. The complete experimental details for all dendrimers (**7** to **38**) can be found in the SI.

The **[G*n*]-PGLSA** dendrimers have been synthesized previously using a DCC coupling reaction; however, this procedure required column chromatography to isolate the final product. The synthesis of the **[G1]-** to **[G4]-PGLSA** dendrimers is shown in Scheme 2. The esterification reactions using the anhydride, **6**, proceeded in high yield (88–97%) with an easier workup than the DCC/acid reaction.[37,67] Likewise, the hydrogenolysis reactions proceeded in high yield (>95%).

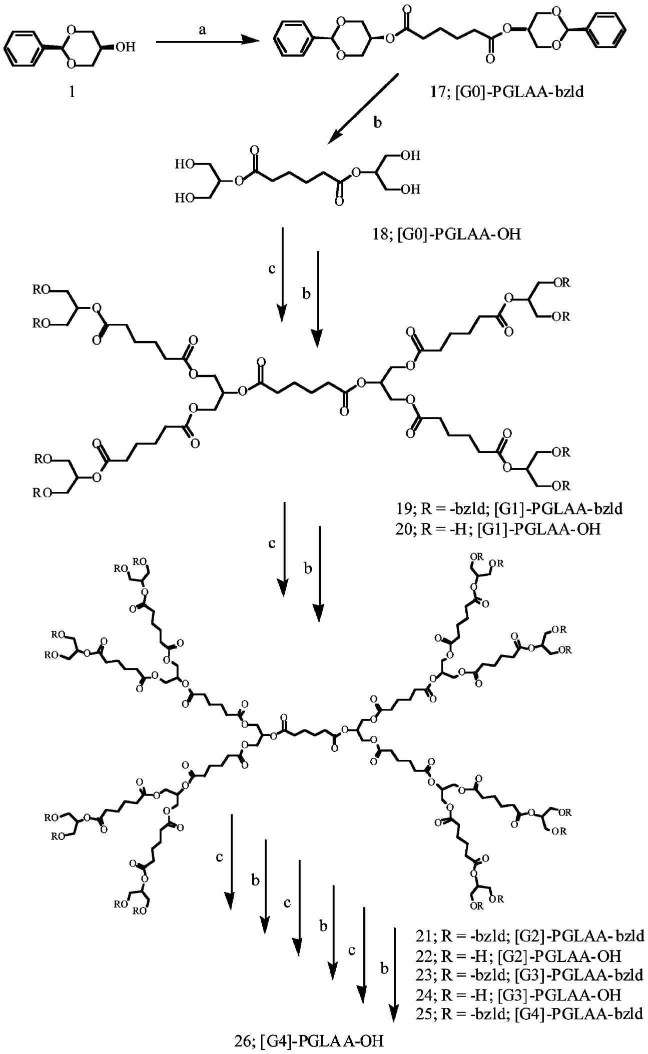
The fourth-generation poly(glycerol–adipic acid) dendrimer, **[G4]-PGLAA**, was synthesized as shown in Scheme 3. The **PGLAA** core, **[G0]-PGLAA**-OH, **18**, was synthesized in two steps by initially treating adipic acid with 2.5 equiv of **1** in the presence of DCC and DPTS in DCM to give **[G0]-PGLAA**-

Scheme 2. Synthesis of the [G1]- to [G4]-PGLSA Dendrimers[a]



[a] Reagents and conditions: (a) **4**, DMAP, DCM, 25 °C, 14 h; (b) 60 psi H_2, $Pd(OH)_2$/C, THF, 25 °C, 10 h; (c) **5**, DMAP, THF, 25 °C, 14 h; (d) 60 psi H_2, $Pd(OH)_2$/C, THF/MeOH (9:1), 25 °C, 10 h.

Scheme 3. Synthesis of G0 to G4 PGLAA Dendrimers[a]



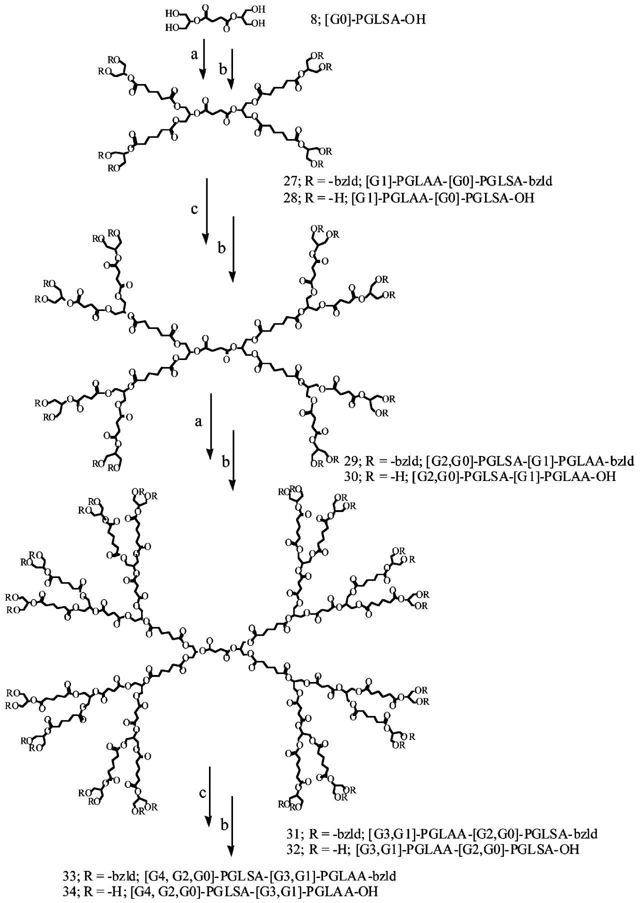
[a] Reagents and conditions: (a) **6**, DPTS, DCC, DCM, 25 °C, 14 h; (b) 60 psi H_2, $Pd(OH)_2$/C, THF, 25 °C, 10 h; (c) **2**, DPTS, DCC, THF, 25 °C, 14 h.

bzld, **17**, in 61% yield. Hydrogenolysis using 20% $Pd(OH)_2$/C in THF produced the product, **18**, in 96% yield. The first-generation dendrimer, **18**, was subsequently treated with **6** in the presence of DCC and DPTS to afford **19** in 99% yield. Another hydrogenolysis reaction provided the first generation dendrimer **[G1]-PGLAA**-OH **20**, in quantitative yield. Next, **20** was coupled to **6** in the presence of DCC and DPTS to produce **[G2]-PGLAA**-bzld, **21**, in 89% yield. Hydrogenolysis in THF afforded the G2 dendrimer **[G2]-PGLAA**-OH, **22**, in 99% yield. The **[G3]-PGLAA**-bzld dendrimer, **23**, was prepared by reacting **22** with **6** to afford the expected product in 86% yield. Hydrogenolysis of **23** in THF yielded **[G3]-PGLAA**-OH, **24**, in 98% yield. The **[G4]-PGLAA**-bzld, **25**, and **[G4]-PGLAA**-OH, **26**, dendrimers were prepared in an analogous stepwise procedure, whereby **24** was coupled to **6** (88% yield) followed by hydrogenolysis (96% yield). The protected **[G*n*]-PGLAA** dendrimers were soluble in most organic solvents except highly polar alcohols, and the deprotected dendrimers were soluble in polar organic solvents and THF but were not appreciably soluble in water.

The fourth-generation alternating layered diblock dendrimer (**[G4,G2,G0]-PGLSA-[G3,G1]-PGLAA**-OH, **34**), consisting of alternating generations of glycerol succinate and glycerol adipate, was synthesized as shown in Scheme 4. The compounds are named by first recording the composition of the outermost layer and its representative generations with the understanding that each generation alternates between succinic and adipic acid. These diblock dendrimers were synthesized by repeated esterifications reactions with **3** and **6**, and the benzylidene acetals of each generation were removed by hydrogenolysis reactions.

As shown in Scheme 4, the **[G0]-PGLSA**-OH, **8**, was treated with **6** in the presence of DCC and DPTS in THF to afford **[G1]-PGLAA-[G0]-PGLSA**-bzld, **27**, in 97% yield. Hydrogenolysis of **27** in the presence of 20% $Pd(OH)_2$/C in THF produced the deprotected dendrimer **[G1]-PGLAA-[G0]-PGLSA**-OH, **28**, in nearly quantitative yield (99%). The next esterification reaction was between **27** and **3** in the presence of DCC and DPTS in THF to afford **[G2,G0]-PGLSA-[G1]-PGLAA**-bzld, **29**, in 86% yield. Again, hydrogenolysis in the presence of 20% $Pd(OH)_2$/C in THF produced **[G2,G0]-PGLSA-[G1]-PGLAA**-OH, **30**, in 98% yield. The monomers **3** and **6** were once more incorporated in successive esterification reactions followed by hydrogenolysis reactions to afford **[G3,G1]-PGLAA-[G2,G0]-PGLSA**-bzld, **31** (yield 91%), **[G3,G1]-PGLAA-[G2,G0]-PGLSA**-OH, **32** (yield 98%), **[G4,G2,G0]-PGLSA-[G3,G1]-PGLAA**-bzld, **33** (yield 83%), and **[G4,G2,G0]-PGLSA-[G3,G1]-PGLAA**-OH, **34** (yield 99%). The protected alternating layered-block dendrimers were soluble in most organic solvents except highly polar alcohols whereas

Scheme 4. Synthesis of an Alternating G1 to G4 Layered-Block Dendrimer[a]



[a] Reagents and conditions: (a) **6**, DPTS, DCC, DCM, 25 °C, 14 h; (b) 60 psi H_2, $Pd(OH)_2/C$, THF, 25 °C, 10 h; (c) **3**, DPTS, DCC, THF, 25 °C, 14 h
.

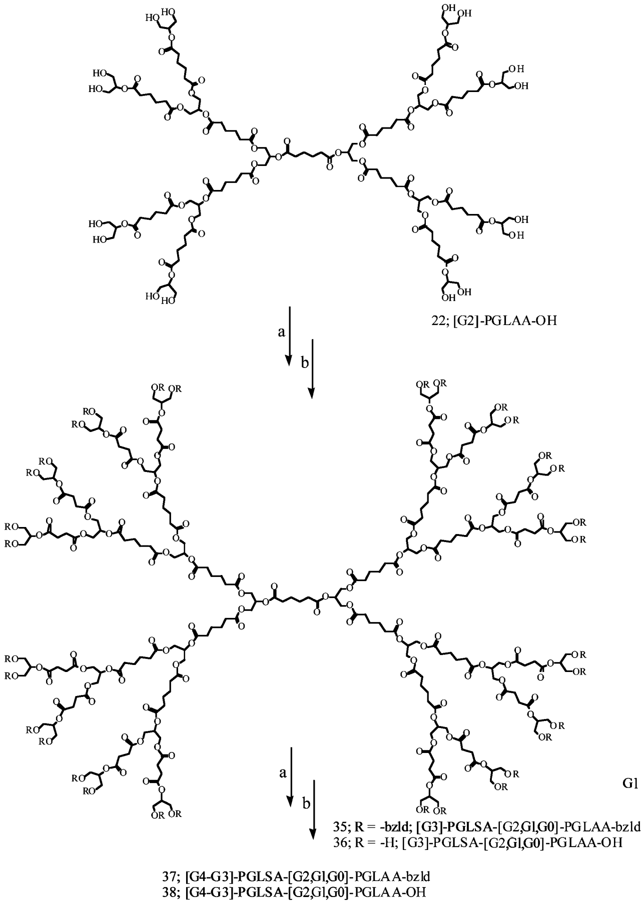
the hydroxyl-terminated dendrimers were soluble in polar organic solvents, THF, and water.

The fourth-generation single-layered diblock dendrimer, **[G4-G3]-PGLSA-[G2,G1,G0]-PGLAA**-OH, **38**, was synthesized as shown in Scheme 5. The composition of the outermost layer is named first followed by the inner layers. The dendrimer consists of adipic acid monomer units in the zero, first, and second generations and two succinic acid layers in the third and fourth generations. Starting with dendrimer **22**, sequential esterification and deprotection reactions were performed to give the final generation four dendrimers, **[G4,G3]-PGLSA-[G2,G1,G0]-PGLAA**-bzld, **37**, and **[G4,G3]-PGLSA-[G2,G1,G0]-PGLAA**-OH, **38**. As before, the esterification and deprotection reactions proceeded in high yield, 87 and 90%, and 95 and 95%, respectively. The protected single-layered diblock dendrimers were soluble in most organic solvents except highly polar alcohols, and the deprotected dendrimers were soluble in polar organic solvents, THF, and water.

The synthesis of the alternating layered-block dendrimers, **27**−**34** and **[G*n*]-PGLAA 17**−**26** dendrimers were attempted using the anhydrides of either the **PGLSA** or **PGLAA** monomer. However, when using the anhydride approach with adipic acid, nearly inseparable emulsions were produced. Therefore, DCC esterifications and workup involving column chromatography were necessary to obtain the alternating layer diblock dendrimers and the **[G*n*]-PGLAA** dendrimers.

Molecular weight data determined by either FAB MS or MALDI-TOF MS and size exclusion chromatography (SEC) for the protected and deprotected layered diblock, **PGLSA**, and **PGLAA** dendrimers are summarized in Table 1. The mass spectrometry data agree with the calculated molecular weights. Narrow polydispersity indices (PDIs) were measured for the G1 to G4 dendrimers by SEC.

Scheme 5. Synthesis of a G3 to G4 Single-Layered-Diblock Dendrimer with Two Layers[a]



[a] Reagents and conditions: (a) **4**, DMAP, 25 °C, 14 h; (b) 60 psi H_2, $Pd(OH)_2/C$, THF, 25 °C, 10 h.

The SEC determined number-average molecular weight (M_n) deviates from the mass spectrometry data as the generation number increases, which is consistent with the dendrimers adopting a more globular structure. When compared to the protected layered-block and **PGLAA** benzylidene protected dendrimers, the benzylidene protected **PGLSA** dendrimers tend to deviate sooner (second generation vs third generation) from the expected M_n, and the magnitude of this deviation is more pronounced in the third and fourth generation. This observation may suggest the benzylidene (bzld) protected **PGLSA** dendrimers adopt a more globular structure than any of the protected dendrimers containing adipic acid within the framework. Such generalizations are not observed with the hydroxyl-terminated dendrimers. The hydroxyl-terminated dendrimers appear larger than the polystyrene standards through three generations and then appear smaller at the fourth generation. However, the third-generation polymers with succinic acid monomer units on the outer layer, such as the **14** and **36** dendrimer, have an apparent number-average molecular weight closer to the standards than the two dendrimers with adipic acid on the peripheral layer. Upon examination of the hydroxyl-terminated fourth generation, the M_n of the layered dendrimer, **38**, is furthest from the polystyrene standards, while the M_n of the **PGLAA** dendrimer, **26**, and layered diblock dendrimer, **34,** are similarly lower than

Table 1. FAB or MALDI MS and SEC[a] Data for PGLSA, PGLAA, Mixed, and Layered Dendrimers

no.	dendrimer	calcd M_w	FAB or MALDI-TOF M_w	SEC[a] M_n	PDI
9	**[G1]-PGLSA**-bzld	1315	1315	1450	1.01
10	**[G1]-PGLSA**-OH	963	962	1500	1.01
11	**[G2]-PGLSA**-bzld	3061	3060	2990	1.01
12	**[G2]-PGLSA**-OH	2356	2356	3000	1.02
13	**[G3]-PGLSA**-bzld	6552	6552	5480	1.01
14	**[G3]-PGLSA**-OH	5143	5144	5370	1.01
15	**[G4]-PGLSA**-bzld	13535	13536	8900	1.01
16	**[G4]-PGLSA**-OH	10715	10715	8720	1.01
19	**[G1]-PGLAA**-bzld	1456	1455	1530	1.02
20	**[G1]-PGLAA**-OH	1103	1103	1630	1.01
21	**[G2]-PGLAA**-bzld	3426	3426	3760	1.01
22	**[G2]-PGLAA**-OH	2721	2721	3630	1.01
23	**[G3]-PGLAA**-bzld	7366	7367	7130	1.02
24	**[G3]-PGLAA**-OH	5956	5952	6780	1.01
25	**[G4]-PGLAA**-bzld	15246	15241	11090	1.01
26	**[G4]-PGLAA**-OH	12427	12423	10770	1.01
27	**[G1]-PGLAA-[G0]-PGLSA**-bzld	1428	1425	1650	1.01
28	**[G1]-PGLAA-[G0]-PGLSA**-OH	1075	1075	1660	1.01
29	**[G2,G0]-PGLSA-[G1]-PGLAA**-bzld	3173	3172	3540	1.02
30	**[G2,G0]-PGLSA-[G1]-PGLAA**-OH	2468	2469	3340	1.02
31	**[G3,G1]-PGLAA-[G2,G0]-PGLSA**-bzld	7113	7114	7060	1.01
32	**[G3,G1]-PGLAA-[G2,G0]-PGLSA**-OH	5707	5707	6490	1.01
33	**[G4,G2,G0]-PGLSA-[G3,G1]-PGLAA**-bzld	14096	14081	10290	1.02
34	**[G4,G2,G0]-PGLSA-[G3,G1]-PGLAA**-OH	11276	11276	9000	1.02
35	**[G3]-PGLSA-[G2,G1,G0]-PGLAA**-bzld	6917	6919	6500	1.01
36	**[G3]-PGLSA-[G2,G1,G0]-PGLAA**-OH	5507	5506	5820	1.01
37	**[G4-G3]-PGLSA-[G2,G1,G0]-PGLAA**-bzld	13899	13902	10310	1.02
38	**[G4,G3]-PGLSA-[G2,G1,G0]-PGLAA**-OH	11080	11084	8160	1.02

[a] SEC molecular weights relative to polystyrene standards.

Table 2. Hydrodynamic Radius (R_h) Measurements for PGLSA, Layered, and PGLAA Dendrimers in Methanol

	R_h (nm)	
dendrimer	G4	G3
PGLSA-OH	5.6 ± 0.1	3.6 ± 0.1
layered dendrimer **34** or **32**	6.8 ± 0.1	2.8 ± 0.5
layered dendrimer **38** or **36**	6.4 ± 0.3	2.7 ± 0.4
PGLAA-OH	5.3 ± 0.1	2.8 ± 0.4

Table 3. Glass Transition (T_g) Data for PGLSA, PGLAA, and Layered Dendrimers

	T_g (°C)	
dendrimer	-bzld	-OH
[G1]-PGLSA	39.5	−20.2
[G2]-PGLSA	42.3	−17.4
[G3]-PGLSA	45.7	−15.5
[G4]-PGLSA	47.0	−13.5
[G1]-PGLAA	−0.6	−35.2
[G2]-PGLAA	4.4	−30.8
[G3]-PGLAA	2.5	−27.6
[G4]-PGLAA	8.8	−30.7
[G1]-PGLAA-[G0]-PGLSA	6.3	−40.5
[G2,G0]-PGLSA-[G1]-PGLAA	32.3	−22.1
[G3,G1]-PGLAA-[G2,G0]-PGLSA	13.4	−23.8
[G4,G2,G0]-PGLSA-[G3,G1]-PGLAA	32.7	−21.6
[G3]-PGLSA-[G2,G1,G0]-PGLAA	28.0	−24.1
[G4-G3]-PGLSA-[G2,G1,G0]-PGLAA	36.2	−21.2

the expected M_n, and the **PGLAA** dendrimer deviates the least from the expected M_n.

Light scattering (QELS) experiments were performed to determine the hydrodynamic radius (R_h) of the third- and fourth-generation dendrimers in dry methanol (Table 2). Water was not used in these studies since aggregation occurred with the dendrimers. The fourth-generation dendrimers ranged in size from 5.3 ± 0.1 nm for the **PGLAA** dendrimer, **26**, to 6.8 ± 0.1 nm for the layered dendrimer, **34**. Notably, the fourth-generation **PGLSA** and **PGLAA** have similar hydrodynamic radii, while the layered dendrimers both have a larger hydrodynamic radii ~1 nm larger. The third generation of the **PGLSA** dendrimer adopts a structure with an R_h of 3.6 ± 0.1 nm, whereas the **PGLAA** dendrimer has an R_h of 2.8 ± 0.4 nm.

The glass transition temperature (T_g) data for the protected and deprotected **[G*n*]-PGLSA**, [G*n*] alternating- and single-layer diblock, and **[G*n*]-PGLAA** dendrimers, determined by modulated differential scanning calorimetry (MDSC), are reported in Table 3. The values are the average of the half-heights recorded on the third heating and cooling cycle. The T_g of the **PGLSA**-bzld dendrimers increases from 39.5 to 47.0 °C, and the T_g of the **PGLSA**-OH dendrimers increases from −20.2 to −13.5 °C as the generation number increases from G1 to G4. The T_g of the **PGLAA**-bzld dendrimers increases from −0.6 to 8.8 °C, and the T_g of the **PGLAA**-OH dendrimers vary from −35.2 to −30.7 °C as the generation number increases from G1 to G4. Interestingly, the T_g of the protected and deprotected layered-block dendrimers increased or decreased noticeably depending on the composition of the branching unit on the periphery. The presence of either adipate or succinate based branching units on the periphery highly influences the glass transition temperature of the dendrimer. Accordingly, the dendrimer possessing an outer succinic acid or adapic acid has a T_g similar to the that of **PGLAA** or **PGLSA** dendrimer of the corresponding generation, respectively.

Conclusions

In summary, four different polyester dendrimers were synthesized using highly efficient esterification and hydrogenolysis reactions. The two aliphatic monomers composed of glycerol and either succinic or adipic acid were synthesized through the nucleophilic addition of *cis*-1,3-*O*-benzylidene glycerol to the respective anhydride. The properties of the dendrimer rely heavily on the composition of the outer generation layer. Given the opportunity with dendrimers to precisely tailor the composition, structure, and resulting properties, these well-defined macromolecules are finding ever-increasing uses in the areas of photonics, catalysis, separations, and medicine. As a result, new synthetic methods, monomer units, and dendritic structures are highly sought after to meet the varied demands of research.

Experimental Section

All solvents were dried and freshly distilled prior to use (CH_2Cl_2 with CaH_2; THF with Na; pyridine with CaH_2). All chemicals were purchased from Aldrich or Acros as highest purity grade and used without further purification (succinic acid, 99%; succinic anhydride, 99%; adipic acid, 99%; DCC, 99%; DMAP, 99%). All reactions were performed under a nitrogen atmosphere. NMR spectra were recorded on a Varian INOVA 400 or a GE QE-300 (for HETCOR with APT) spectrometer. FT-IR spectra were recorded on a Nicolet Smart MIRacle Avatar 360 using a zinc selenide crystal. Chemical ionization mass spectra were obtained on a Hewlett-Packard HP 5988A spectrometer using NH_3. Fast atom bombardment mass spectra (FABMS) were obtained on a JEOL JMS-SX102A spectrometer using a 3-nitrobenzyl alcohol matrix. MALDI-TOF mass spectra were obtained using a PerSpective Biosystems Voyager-DE Biospectrometry workstation operating in the positive ion mode using 2-(4-hydroxyphenylazo)benzoic acid (HABA). Elemental analysis was obtained from Atlantic Microlab, Inc. Size exclusion chromatography was performed using THF as the eluent on a Polymer Laboratories PLgel 3 μm MIXED-E column (3 μm bead size) and a Rainin HPLC system (temperature = 25 °C; flow rate = 1.0 mL/min). Polystyrene standards (1K, 4K, and 23K) were used for calibration. A TA Instruments Q1000 modulated DSC was used to collect T_m and T_g data (3 °C/min, ±1 °C/40 s). The T_g values are reported as the average temperature of the thermal peak upon heating and cooling on the third cycle. Hydrodynamic radii were measured at 25 °C using a Wyatt Mini-Dawn quasi-elastic light scattering (QELS) instrument using a microcuvette measurement accessory. All solvents were filtered through 0.02 μm membrane syringe-tip filters.

As a representative example, we will describe the synthesis of the alternating layered diblock dendrimers from generation one to four. The complete experimental details for all dendrimers (**7** to **38**) can be found in the SI.

Synthesis of [G1]-PGLAA-[G0]-PGLSA-bzld (27). 2-(*cis*-1,3-*O*-Benzylidene glycerol)adipic acid mono ester, **6** (11.79 g, 38.25 mmol), **[G0]-PGLSA**-OH (1.18 g, 4.45 mmol), and DPTS (2.85 g, 9.70 mmol) were dissolved in THF (50 mL) followed by the addition of DCC (7.22 g, 34.97 mmol). The reaction was stirred at room temperature for 14 h under a nitrogen atmosphere. Upon completion, the DCU was filtered and washed with a small amount of THF (50 mL), and the solvent was evaporated. The crude product was purified by silica gel chromatography, eluting with 1:1 to 4:1 EtOAc:hexanes. The appropriate isolated fractions were concentrated, filtered (to remove any remaining DCU), and directly precipitated in hexanes and cooled to −20 °C overnight. The hexanes were decanted, and the precipitate was isolated to yield 7.173 g of a sticky solid (97% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 1.65 (m, 16, $-CH_2-CH_2-CH_2-CH_2-$), 2.33 (m, 8, $-CH_2-CH_2-CH_2-CH_2-$), 2.42 (m, 8, $-CH_2-CH_2-CH_2-CH_2-$), 2.59 (m, 4, $-CH_2-CH_2-$), 4.11 (m, 12, $-CH_2-CH-CH_2-$), 4.24 (m, 12, $-CH_2-CH-CH_2-$), 4.67 (m, 4, $-CH_2-CH-CH_2-$), 5.20 (m, 2, $-CH_2-CH-CH_2-$), 5.51 (s, 4, C*H*), 7.33 (m, 12, arom C*H*), 7.47 (m, 8, arom C*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 173.41 (*C*OOR), 172.92 (*C*OOR), 171.48 (*C*OOR), 138.02 (*C*H), 129.28 (*C*H), 128.49 (*C*H), 126.21 (*C*H), 101.38 (*C*H), 69.65 (*C*H), 69.27 (CH_2), 66.11 (*C*H), 62.19 (CH_2), 34.09 (CH_2), 33.73 (CH_2), 28.97 (CH_2), 24.44 (CH_2), 24.36 (CH_2). FTIR: ν (cm^{-1}) 2948 and 2862 (aliph C−H stretch), 1730 (C═O). FAB MS 1425.5 *m*/*z* $[M + H]^+$ (theory: 1427.49 *m*/*z* $[M]^+$). Elemental analysis C: 61.91%; H 6.30% (theory C: 62.26%; H 6.35%). SEC M_w: 1670, M_n: 1650, PDI: 1.01. T_g (°C): 6.3.

Synthesis of [G1]-PGLAA-[G0]-PGLSA-OH (28). $Pd(OH)_2/C$ (20% w/w) was added to a solution of **[G1]-PGLAA-[G0]-PGLSA**-bzld (5.90 g, 4.13 mmol) in THF (50 mL). The flask for catalytic hydrogenolysis was evacuated and filled with 60 psi of H_2 before shaking for 10 h. The catalyst was filtered and washed with THF (50 mL). The filtrate was evaporated to give 4.41 g of a colorless, viscous oil (99% yield). ^1H NMR (400 MHz, CD_3OD): δ 1.63 (m, 16, $-CH_2-CH_2-CH_2-CH_2-$), 2.36 (m, 16, $-CH_2-CH_2-CH_2-CH_2-$), 2.61 (m, 4, $-CH_2-CH_2-$), 3.52 (m, 3, $-CH_2-CH-CH_2-$), 3.59−3.65 (broad m, 9, $-CH_2-CH-CH_2-$), 3.69 (m, 2, $-CH_2-CH-CH_2-$), 3.79 (m, 2, $-CH_2-CH-CH_2-$), 4.03 (m, 2, $-CH_2-CH-CH_2-$), 4.15 (m, 5, $-CH_2-CH-CH_2-$), 4.30 (m, 4, $-CH_2-CH-CH_2-$), 5.25 (m, 2, $-CH_2-CH-CH_2-$). ^{13}C NMR (100.6 MHz, CD_3OD): δ 173.85 (*C*OOR), 173.67 (*C*OOR), 173.41 (*C*OOR), 171.95 (*C*OOR), 75.42 (*C*H), 69.93 (*C*H), 69.78 (*C*H), 65.36 (CH_2), 62.87 (CH_2), 62.04 (CH_2), 60.50 (CH_2), 33.50 (CH_2), 33.29 (CH_2), 33.19 (CH_2), 28.61 (CH_2), 24.12 (CH_2). FTIR: ν (cm^{-1}) 3436 (OH), 2947 (aliph C−H stretch), 1727 (C═O). MALDI-TOF MS 1098 *m*/*z* $[M + Na]^+$ (theory: 1075 *m*/*z* $[M]^+$). Elemental analysis C: 50.96%; H 6.79% (theory C: 51.39%; H 6.94%). SEC M_w: 1680, M_n: 1660, PDI: 1.01. T_g (°C): −40.5.

Synthesis of [G2,G0]-PGLSA-[G1]-PGLAA-bzld (29). 2-(*cis*-1,3-*O*-Benzylidene glycerol)succinic acid mono ester, **6** (12.76 g, 45.52 mmol), **[G1]-PGLAA-[G0]-PGLSA**-OH (4.28 g, 3.98 mmol), and DPTS (5.11 g, 17.38 mmol) were dissolved in THF (100 mL) followed by the addition of DCC (13.91 g, 67.44 mmol). The reaction was stirred at room temperature for 14 h under a nitrogen atmosphere. Upon completion, the DCU was filtered and washed with a small amount of THF (50 mL), and the solvent was evaporated. The crude product was purified by silica gel chromatography, eluting with 2 % MeOH in DCM. The appropriate isolated fractions were concentrated, filtered (to remove any remaining DCU), and directly precipitated in hexanes and cooled to −20 °C overnight. The hexanes were decanted, and the precipitate was isolated to yield 10.84 g of a white solid (85.7% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 1.60 (m, 17, $-CH_2-CH_2-CH_2-CH_2-$), 2.30 (m, 17, $-CH_2-CH_2-CH_2-CH_2-$), 2.63 (m, 20, $-CH_2-CH_2-$), 2.72 (m, 16, $-CH_2-CH_2-$), 4.11 (m, 29, $-CH_2-CH-CH_2-$), 4.23 (m, 29, $-CH_2-CH-CH_2-$), 4.70 (m, 8, $-CH_2-CH-CH_2-$), 5.20 (m, 6, $-CH_2-CH-CH_2-$), 5.51 (s, 8, C*H*), 7.34 (m, 12, arom C*H*), 7.46 (m, 8, arom C*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 173.41 (*C*OOR), 172.92 (*C*OOR), 171.48 (*C*OOR), 138.02 (*C*H), 129.28 (*C*H), 128.49 (*C*H), 126.21 (*C*H), 101.38 (*C*H), 69.65 (*C*H), 69.27 (CH_2), 66.11 (*C*H), 62.19 (CH_2), 34.09 (CH_2), 33.73 (CH_2), 28.97 (CH_2), 24.44 (CH_2), 24.36 (CH_2). FTIR: ν (cm^{-1}) 2950 (aliph C−H stretch), 1732 (C═O). FAB MS 3172.7 *m*/*z* $[M + H]^+$ (theory: 3173.1 *m*/*z* $[M]^+$). Elemental analysis C: 59.61%; H 5.84% (theory C: 59.81%; H 5.91%). SEC M_w: 3600, M_n: 3540, PDI: 1.02. T_g (°C): 32.3.

Synthesis of [G2,G0]-PGLSA-[G1]-PGLAA-OH (30). $Pd(OH)_2/C$ (20% w/w) was added to a solution of **[G2,G0]-PGLSA-[G1]-PGLAA**-bzld (5.25 g, 1.65 mmol) in THF (100 mL). The flask for catalytic hydrogenolysis was evacuated and filled with 60 psi of H_2 before shaking for 10 h. The catalyst was filtered and washed with THF (50 mL). The filtrate was evaporated to give 4.01 g of a colorless, viscous oil (98.2% yield). ^1H NMR (400 MHz, CD_3OD): δ 1.62 (m, 17, $-CH_2-CH_2-CH_2-CH_2-$), 2.36 (m, 17, $-CH_2-CH_2-CH_2-CH_2-$), 2.64 (m, 36, $-CH_2-CH_2-$), 3.52 (m, 2, $-CH_2-CH-CH_2-$), 3.60−3.66 (broad m, 26, $-CH_2-CH-CH_2-$), 3.69 (m, 9, $-CH_2-CH-CH_2-$), 3.80 (m, 1, $-CH_2-CH-CH_2-$), 4.18 (m, 14, $-CH_2-CH-CH_2-$), 4.32 (m, 12, $-CH_2-CH-CH_2-$), 5.25 (m, 6, $-CH_2-CH-CH_2-$). ^{13}C NMR (100.6 MHz, CD_3OD): δ 173.38 (*C*OOR), 173.05 (*C*OOR), 172.56 (*C*OOR), 172.24 (*C*OOR), 172.00 (*C*OOR), 75.81 (*C*H), 69.80 (*C*H), 69.35 (*C*H), 67.65 (CH_2), 65.68 (CH_2), 62.87 (CH_2), 62.42 (CH_2), 62.11 (CH_2), 60.43 (CH_2), 33.49 (CH_2), 33.20 (CH_2), 28.83 (CH_2), 28.64 (CH_2), 25.28 (CH_2), 24.09 (CH_2). FTIR: ν (cm^{-1}) 3468 (OH), 2951 (aliph C−H stretch), 1728 (C═O). MALDI−TOF MS 2492 *m*/*z* $[M + Na]^+$ (theory: 2468 *m*/*z* $[M]^+$). Elemental analysis C: 50.00%; H 6.40% (theory C: 49.63%; H 6.29%). SEC M_w: 3390, M_n: 3340, PDI: 1.02. T_g (°C): −22.1.

Synthesis of [G3,G1]-PGLAA-[G2,G0]-PGLSA-bzld (31). 2-(*cis*-1,3-*O*-Benzylidene glycerol)adipic acid mono ester, **6** (10.75 g, 34.87 mmol), **[G2,G0]-PGLSA-[G1]-PGLAA**-OH (3.77 g, 1.53 mmol), and DPTS (1.46 g, 4.97 mmol) were dissolved in THF (120 mL) followed by the addition of DCC (10.60 g, 51.38 mmol). The reaction was stirred at room temperature for 14 h under a nitrogen atmosphere. Upon completion, the DCC−urea was filtered and washed with a small amount of THF (50 mL), and the solvent was evaporated. The crude product was purified by silica gel chromatography, eluting with 1.5 % MeOH in DCM. The appropriate isolated fractions were concentrated, filtered (to remove any remaining DCU), and directly precipitated in hexanes and cooled to −20 °C overnight. The hexanes were decanted, and the precipitate was isolated to yield 9.88 g of a sticky solid (90.9% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.65 (m, 81, $-CH_2-CH_2-CH_2-CH_2-$), 2.31 (m, 52, $-CH_2-CH_2-CH_2-CH_2-$), 2.42 (m, 32, $-CH_2-CH_2-CH_2-CH_2-$), 2.58 (m, 36 $-CH_2-CH_2-$), 4.10 (m, 62, $-CH_2-CH-CH_2-$), 4.23 (m, 62, $-CH_2-CH-CH_2-$), 4.66 (m, 16, $-CH_2-CH-CH_2-$), 5.19 (m, 14, $-CH_2-CH-CH_2-$), 5.51 (s, 16, C*H*), 7.33 (m, 47, arom C*H*), 7.46 (m, 32, arom C*H*). ^{13}C NMR (100.6 MHz, CDCl$_3$): δ 173.39 (*C*OOR), 172.90 (*C*OOR), 171.82 (*C*OOR), 171.53 (*C*OOR), 138.04 (*C*H), 129.26 (*C*H), 128.49 (*C*H), 126.22 (*C*H), 101.36 (*C*H), 69.65 (*C*H), 69.26 (*C*H$_2$), 66.11 (*C*H), 62.64 (*C*H$_2$), 62.15 (*C*H$_2$), 34.07 (*C*H$_2$), 33.73 (*C*H$_2$), 28.96 (*C*H$_2$), 28.80 (*C*H$_2$), 24.43 (*C*H$_2$), 24.35 (*C*H$_2$). FTIR: ν (cm^{-1}) 2948 and 2862 (aliph C−H stretch), 1731 (C═O). MALDI−TOF MS 7137 *m*/*z* [M + Na]$^+$ (theory: 7113 *m*/*z* [M]$^+$). Elemental analysis C: 60.27%; H 6.21% (theory C: 60.45%; H 6.26%). SEC M_w: 7160, M_n: 7060, PDI: 1.01. T_g (°C):13.4.

Synthesis of [G3,G1]-PGLAA-[G2,G0]-PGLSA-OH (32). Pd(OH)$_2$/C (20% w/w) was added to a solution of **[G3,G1]-PGLAA-[G2,G0]-PGLSA**-bzld (9.17 g, 1.29 mmol) in THF (100 mL). The flask for catalytic hydrogenolysis was evacuated and filled with 60 psi of H$_2$ before shaking for 10 h. The catalyst was filtered and washed with THF (50 mL). The filtrate was evaporated to give 7.22 g of a colorless, viscous oil (98.1% yield). ^{1}H NMR (400 MHz, CD$_3$OD): δ 1.63 (m, 83, $-CH_2-CH_2-CH_2-CH_2-$), 2.37 (m, 83, $-CH_2-CH_2-CH_2-CH_2-$), 2.61 (m, 36, $-CH_2-CH_2-$), 3.52 (m, 8, $-CH_2-CH-CH_2-$), 3.60−3.71 (broad m, 57, $-CH_2-CH-CH_2-$), 3.80 (m, 4, $-CH_2-CH-CH_2-$), 4.03 (m, 5, $-CH_2-CH-CH_2-$), 4.11−4.23 (m, 34, $-CH_2-CH-CH_2-$), 4.30 (m, 29, $-CH_2-CH-CH_2-$), 5.25 (m, 14, $-CH_2-CH-CH_2-$). ^{13}C NMR (100.6 MHz, CD$_3$OD): δ 173.85 (*C*OOR), 173.67 (*C*OOR), 173.41 (*C*OOR), 171.95 (*C*OOR), 75.42 (*C*H), 69.93 (*C*H), 69.78 (*C*H), 65.36 (*C*H$_2$), 62.87 (*C*H$_2$), 62.04 (*C*H$_2$), 60.50 (*C*H$_2$), 33.50 (*C*H$_2$), 33.29 (*C*H$_2$), 33.19 (*C*H$_2$), 28.61 (*C*H$_2$), 24.12 (*C*H$_2$). FTIR: ν (cm^{-1}) 3463 (OH), 2947 (aliph C−H stretch), 1729 (C═O). MALDI−TOF MS 5730 *m*/*z* [M + Na]$^+$ (theory: 5703 *m*/*z* [M]$^+$). Elemental analysis C: 51.91%; H 6.93% (theory C: 51.80%; H 6.68%). SEC M_w: 6570, M_n: 6490, PDI: 1.01. T_g (°C): −23.8.

Synthesis of [G4,G2,G0]-PGLSA-[G3,G1]-PGLAA-bzld (33). 2-(*cis*-1,3-*O*-Benzylidene glycerol)succinic acid mono ester, **6** (11.57 g, 41.28 mmol), **[G3,G1]-PGLAA-[G2,G0]-PGLSA**-OH (5.59 g, 0.98 mmol), and DPTS (4.09 g, 13.92 mmol) were dissolved in THF (80 mL) followed by the addition of DCC (12.60 g, 61.05 mmol). The reaction was stirred at room temperature for 14 h under nitrogen atmosphere. Upon completion, the DCC−urea was filtered and washed with a small amount of THF (50 mL), and the solvent was evaporated. The crude product was purified by silica gel chromatography, eluting with 1.5% to 5.0 % MeOH in DCM. The appropriate isolated fractions were concentrated, filtered (to remove any remaining DCU), and directly precipitated in hexanes and cooled to −20 °C over 48 h. The hexanes were decanted, and the precipitate was isolated to yield 11.50 g of a white solid (83.2% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.59 (m, 83, $-CH_2-CH_2-CH_2-CH_2-$), 2.30 (m, 83, $-CH_2-CH_2-CH_2-CH_2-$), 2.62 (m, 104, $-CH_2-CH_2-$), 2.70 (m, 63, $-CH_2-CH_2-$), 4.12 (m, 130, $-CH_2-CH-CH_2-$), 4.22 (m, 130, $-CH_2-CH-CH_2-$), 4.68 (m, 32, $-CH_2-CH-CH_2-$), 5.18 (m, 30, $-CH_2-CH-CH_2-$), 5.50 (s, 32, C*H*), 7.33 (m, 97, arom C*H*), 7.46 (m, 66, arom C*H*). ^{13}C NMR (100.6 MHz, CDCl$_3$): δ 172.88 (*C*OOR), 172.53 (*C*OOR), 172.25 (*C*OOR), 171.89 (*C*OOR), 138.04 (*C*H), 129.26 (*C*H), 128.48 (*C*H), 126.22 (*C*H), 101.28 (*C*H), 69.14 (*C*H$_2$), 66.54 (*C*H), 62.60 (*C*H$_2$), 33.81 (*C*H$_2$), 33.66 (*C*H$_2$), 29.35 (*C*H$_2$), 29.03 (*C*H$_2$), 24.30 (*C*H$_2$). FTIR: ν (cm^{-1}) 2959 (aliph C−H stretch), 1732 (C═O). MALDI-TOF MS 14082 *m*/*z* [M + H]$^+$ (theory: 14096 *m*/*z* [M]$^+$). Elemental analysis C: 59.17%; H 6.07% (theory C: 59.13%; H 5.916%). SEC M_w: 10440, M_n: 10290, PDI: 1.02. T_g (°C): 32.7.

Synthesis of [G4,G2,G0]-PGLSA-[G3,G1]-PGLAA-OH (34). Pd(OH)$_2$/C (20% w/w) was added to a solution of **[G4,G2,G0]-PGLSA-[G3,G1]-PGLAA**-bzld (2.08 g, 0.15 mmol) in THF (80 mL). The flask for catalytic hydrogenolysis was evacuated and filled with 60 psi of H$_2$ before shaking for 10 h. The catalyst was filtered and washed with THF (75 mL). The filtrate was evaporated to give 1.65 g of a colorless, viscous oil (99.1% yield). ^{1}H NMR (400 MHz, CD$_3$OD): δ 1.62 (m, 80, $-CH_2-CH_2-CH_2-CH_2-$), 2.37 (m, 80, $-CH_2-CH_2-CH_2-CH_2-$), 2.64 (m, 164, $-CH_2-CH_2-$), 3.52 (m, 12, $-CH_2-CH-CH_2-$), 3.63−3.71 (broad m, 160, $-CH_2-CH-CH_2-$), 3.80 (m, 6, $-CH_2-CH-CH_2-$), 4.06 (m, 14, $-CH_2-CH-CH_2-$), 4.20 (m, 62, $-CH_2-CH-CH_2-$), 4.30 (m, 60, $-CH_2-CH-CH_2-$), 5.25 (m, 30, $-CH_2-CH-CH_2-$). ^{13}C NMR (100.6 MHz, CD$_3$OD): δ 173.40 (*C*OOR), 173.06 (*C*OOR), 172.58 (*C*OOR), 75.82 (*C*H), 69.90 (*C*H), 69.34 (*C*H), 67.64 (*C*H$_2$), 62.45 (*C*H$_2$), 62.15 (*C*H$_2$), 60.46 (*C*H$_2$), 33.25 (*C*H$_2$), 28.87 (*C*H$_2$), 28.67 (*C*H$_2$), 25.27 (*C*H$_2$), 24.12 (*C*H$_2$). FTIR: ν (cm^{-1}) 3441 (OH), 2948 (aliph C−H stretch), 1728 (C═O). MALDI-TOF MS 11299 *m*/*z* [M + Na]$^+$ (theory: 11276 *m*/*z* [M]$^+$). Elemental analysis C: 50.49%; H 6.41% (theory C: 50.06%; H 6.24%). SEC M_w: 9150, M_n: 9000, PDI: 1.02. T_g (°C): −21.6.

Acknowledgment. This research was supported by the NIH (R01-EY13881) and Johnson & Johnson. M.W.G. also thanks the Dreyfus Foundation for a Camille Dreyfus Teacher-Scholar and the Alfred P. Sloan Foundation for a Research Fellowship.

Supporting Information Available: Experimental details for dendrimers **7**−**38**. This material is available free of charge via the Internet at http://pubs.acs.org.

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MA0518407