The Convergent Synthesis of Poly(glycerol-succinic acid) Dendritic Macromolecules

Nathanael R. Luman, Kimberly A. Smeds, and Mark W. Grinstaff*[a]

Abstract: The high-yield convergent synthesis of dendrons, dendrimers, and dendritic–linear hybrid macromolecules composed of succinic acid, glycerol, and poly(ethylene glycol) (PEG) is described. This convergent synthesis relies on two orthogonal protecting groups; namely, the benzylidene acetal (bzld) for the protection of the 1,3-hydroxyls of glycerol and the *tert*-butyldiphenylsilyl (TBDPS) ester for protection of the carboxylic acid of succinic acid. These novel polyester dendritic macromolecules are composed entirely of building blocks known to be biocompatible or degradable in vivo to give natural metabolites. Derivatization of the dendritic periphery with a methacrylate affords a polymer that can be subsequently photo-cross-linked. The three-dimensional cross-linked gels formed by ultraviolet irradiation are optically transparent, with mechanical properties dependent on the initial cross-linkable dendritic macromolecule.

Keywords: biomaterials · chemical biology · dendrimers · gels

Introduction

Dendrimers are three-dimensional, globular macromolecules possessing distinct concentric branching layers emanating from a focal point.[1–16] As a consequence of the multiple peripheral chain ends, globular shape, low viscosity, high solubility, and miscibility, dendritic macromolecules have increasingly attracted scientific attention.[13–16] Furthermore, the structural and derivatizational control afforded by dendrimers and dendrons provides synthetic opportunities to explore unique polymer architectures, to create larger supramolecular assemblies, or to prepare interfacial materials. We are investigating aliphatic dendrons, dendrimers, and dendritic–linear hybrid macromolecules composed of glycerol, succinic acid, and poly(ethylene glycol) (PEG) for potential use as temporary biodegradable scaffolds for wound healing.[17–20]

Polymeric biomaterials that supplement or replace damaged or diseased tissue with functional synthetic constructs are of widespread interest and represent an emerging industry sector that offers tremendous potential for advancing healthcare practices. These constructs provide a temporary scaffold for cells until the native tissue is remodeled. The function of the scaffold is multifaceted. Scaffolds should be biocompatible, degrade over time, promote cell growth and proliferation, and possess mechanical properties reminiscent of the original host native tissue.[21–27] Ideally, the formation of the natural extracellular matrix should be synchronized with loss of the scaffold. Polymers under investigation as scaffold materials include natural polymers such as collagen[28–30] and alginate,[31–33] as well as synthetic polymers such as poly(glycolic acid) and poly(lactic acid).[34–38] The synthetic polymers are advantageous for this application, since the degradation rate, hydrophobicity/hydrophilicity, and mechanical strength can be varied by controlling the polymer molecular weight, crystallinity, and composition. Of the scaffold formats being investigated, hydrogels resemble the physical characteristics of soft tissues, can be molded or shaped into specific objects, and can be prepared under physiological conditions.[39,40] Furthermore, these hydrogels are of interest for in situ applications whereby the photo-cross-linkable hydrogel precursors are injected in vivo and then subsequently cross-linked. In situ photopolymerization is being explored in the dental,[41–43] drug delivery,[44–46] cell transplantation,[47–49] biological adhesive,[50–52] and ophthalmology fields.[19,53,54]

Dendrimers may provide unique advantages where linear polymers have limitations due to the spatial orientation and high ligand density that are desired characteristics of good gelators.[18,19,55–59] Multiple interactions between individual building blocks are critical in the gel-formation process; with dendrimers the number of functional groups can be controlled by generation number and by the composition of the core and branching arms. Dendrimers are synthesized

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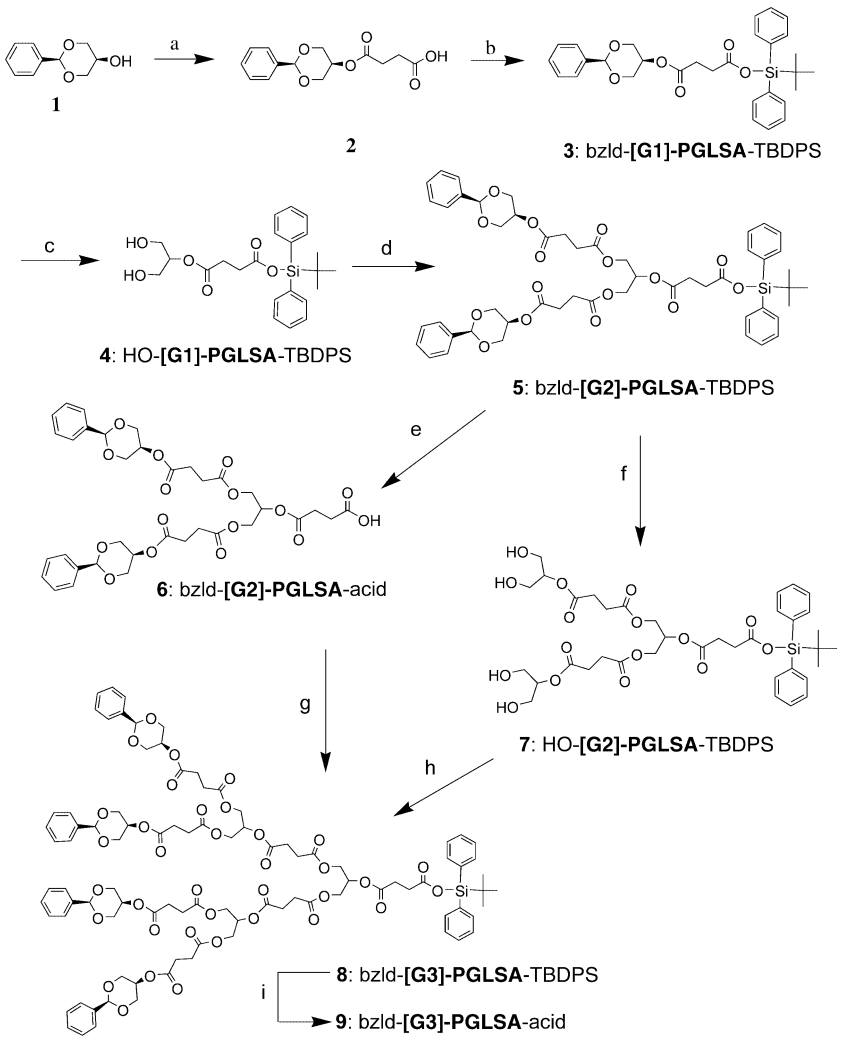
by means of either an iterative divergent[60–65] or convergent[66–73] approach. The convergent approach enables differentiated functionalities to be incorporated at the focal point and periphery of the macromolecule, as well as the preparation of more intricate multifunctionalized macromolecules, including segment-block and surface-block dendrimers, and dendritic–linear hybrids.[11,66] Moreover, the dendrons synthesized can be handled in a manner typical for the isolation, purification, and characterization of small molecules. The convergent synthesis described herein relies on two orthogonal protecting groups; namely, benzylidene acetal (bzld) for the protection of the 1,3-hydroxyl groups of glycerol and *tert*-butyldiphenylsilyl (TBDPS) ester for protection of the carboxylic acid of succinic acid. The bzld group can be selectively removed under hydrogenolysis conditions, while the TBDPS group can be selectively cleaved with tetrabutylammonium fluoride. By using this strategy we present the convergent synthesis of poly(glycerol–succinic acid) (PGLSA) dendrons, a PGLSA dendrimer, and a dendritic(PGLSA)-linear(poly(ethylene glycol)) hybrid macromolecule, the modification with methacrylate, and the formation of cross-linked dendritic gels.

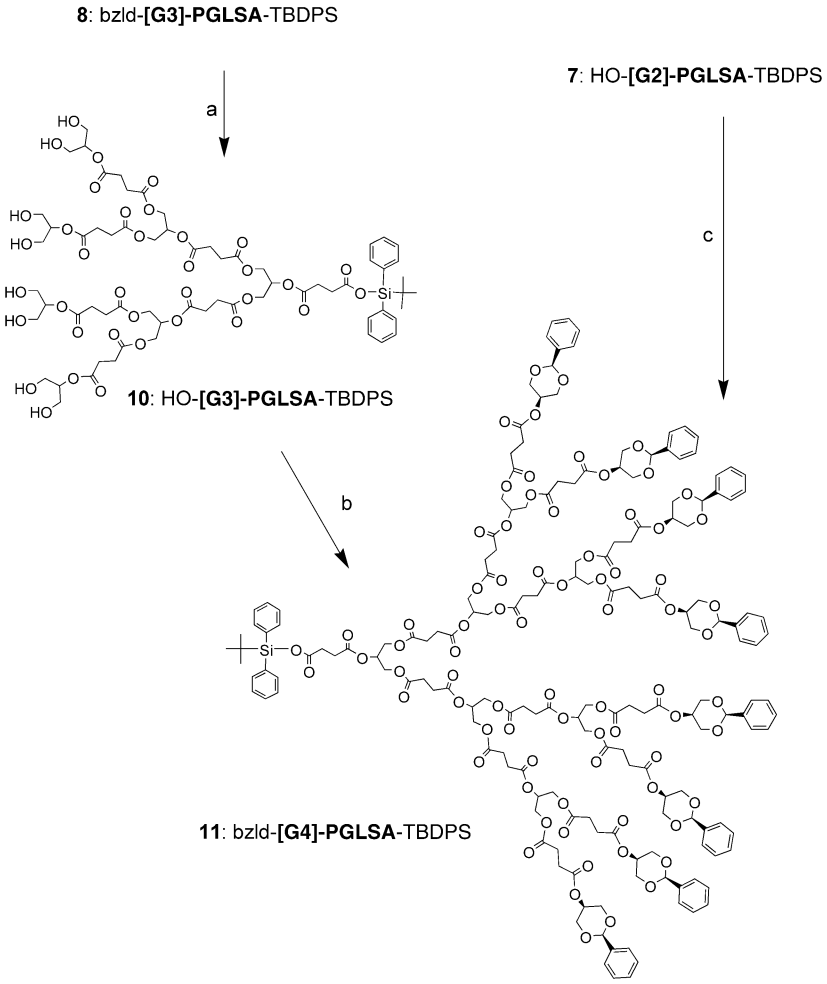


Scheme 1. Synthesis of the **[G3]-PGLSA** dendron. Reagents and conditions: a) succinic anhydride, pyridine, RT, 18 h, 95% yield; b) TBDPSi-Cl, imidazole, DMF, RT, 48 h, 86% yield; c) 20% $Pd(OH)_2$/C, 50 psi. H_2, THF, RT, 3 h, 95% yield; d) **2**, DCC, DPTS, DCM, RT, 18 h, 88% yield; e) TBAF, THF, 1 h, RT, 87% yield; f) 20% $Pd(OH)_2$/C, 50 psi. H_2, THF, RT, 3 h, 95% yield; g) **4**, DCC, DPTS, DCM, RT, 18 h, 83% yield; h) **2**, DCC, DPTS, DCM, RT, 18 h, 54% yield; i) TBAF, THF, 1 h, RT, 83% yield.

Results and Discussion

The polyester dendrons and dendrimers are composed of glycerol and succinic acid, whereas the polyester–ether dendritic–linear hybrid macromolecules are composed of glycerol, succinic acid, and polyethylene glycol. The generation one (G1) through four (G4) poly(glycerol–succinic acid) (PGLSA) dendrons are prepared as shown in Schemes 1 and 2. Both the divergent and convergent synthesis are shown for the dendrons. The convergent approach relies on the bzld protecting group for the 1,3-hydroxyl groups of glycerol and the TBDPS ester protecting group for the carboxylic acid of succinic acid. As mentioned above, the bzld and TBDPS group can be selectively removed by using hydrogen with a palladium catalyst and tetrabutylammonium fluoride, respectively. In comparison to the use of the *tert*-butyldiphenylsilyl ester protecting group in the synthesis of natural products and analogues, this group has been under utilized in macromolecular chemistry.

cis-1,3-*O*-Benzylidene glycerol (**1**) was synthesized from benzaldehyde and glycerol by using a catalytic amount of sulfuric acid.[74] The *cis* isomer was preferentially isolated by recrystallization in cold diethyl ether. The glycerol–succinic acid monoester **2** was synthesized by the addition of succinic anhydride to **1** in pyridine. The acid functionality of **2** was subsequently protected with *tert*-butyldiphenylsilyl chloride (TBDPS-Cl) to form the bi-protected bzld-**[G1]-PGLSA**-TBDPS dendron **3** in 86% yield. The bzld protecting group was removed by hydrogenolysis with a palladium catalyst (20% $Pd(OH)_2$/C or 10% Pd/C)[75] to yield a hydroxy terminated HO-**[G1]-PGLSA**-TBDPS dendron **4**. The silyl protecting group does not cleave under these mild conditions; however, it is selectively cleaved with tetrabutylammonium fluoride (TBAF). Compound **4** was then coupled to **2** with



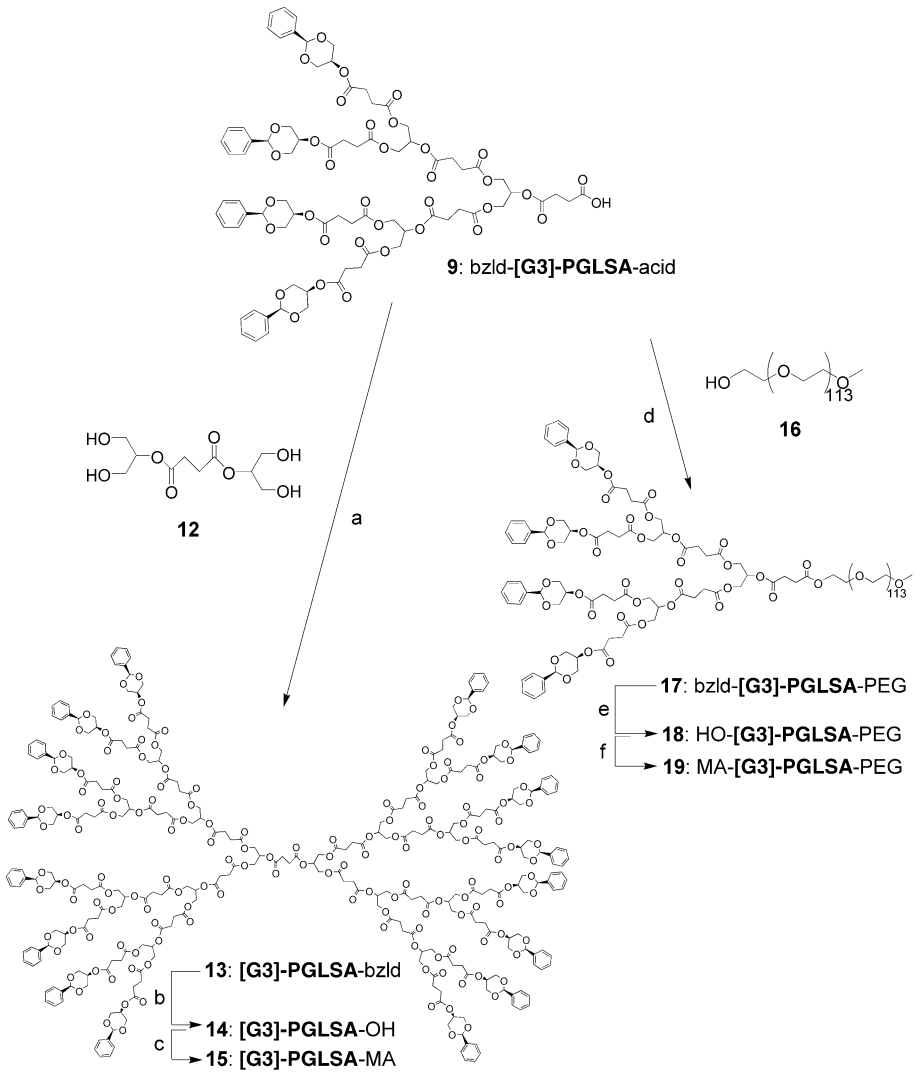
Scheme 2. Synthesis of the **[G4]-PGLSA** dendron. Reagents and conditions: a) 20% $Pd(OH)_2$/C, 50 psi. H_2, THF, RT, 3 h, 97% yield; b) **2**, DCC, DPTS, DCM, RT, 48 h, 60% yield; c) **6**, DCC, DPTS, DCM, RT, 72 h, 75% yield.

dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)-pyridinium *p*-toluenesulfonate (DPTS)[76] to afford a bi-protected G2 dendron (bzld-**[G2]-PGLSA**-TBDPS, **5**) in 88% yield. At this stage, either the carboxylic acid was deprotected to afford the bzld-**[G2]-PGLSA**-acid dendron **6** (87% yield), or the bzld groups were removed to yield a HO-**[G2]-PGLSA**-TBDPS dendron **7** (95% yield). The bzld-**[G3]-PGLSA**-TBDPS dendron **8** was synthesized convergently by coupling **6** to **4** (83% yield). Alternatively, in a divergent manner, **7** was coupled to **2** to give **8** (73% yield). As shown in Scheme 2, these iterative steps (benzylidene acetal deprotection followed by esterfication) were repeated to synthesize a bzld-**[G4]-PGLSA**-TBDPS **11**, from the HO-**[G3]-PGLSA**-TBDPS dendron **10** and **2** (60% yield). The dendron **11** was also synthesized in a convergent manner by coupling dendron **6** to **7** in the presence of DCC and DPTS (75% yield). The convergent pathway afforded the G4 dendron in seven reactions and a higher overall yield (42% vs 27%) as opposed to the divergent pathway, which involved eight reactions.

The dendrons were coupled to a multi-functional core (**12**) or linear poly(ethylene glycol) (PEG) macromolecule (**16**) to create a dendrimer or a dendritic–linear hybrid, respectively (Scheme 3). For example, a **[G3]-PGLSA**-bzld dendrimer (**13**) was synthesized by DCC coupling dendron **9** to the tetrafunctional core **12**. The tetrafunctional core was synthesized in two steps; succinic acid was first coupled to two equivalents of *cis*-1,3-*O*-benzylidene glycerol in the presence of DCC and DPTS (90% yield), followed by catalytic hydrogenolysis (97% yield). The dendritic–linear hybrid molecule bzld-**[G3]-PGLSA**-PEG-OMe (**17**) was prepared by DCC coupling of dendron **9** to a linear poly(ethylene glycol)-monomethyl ether (PEG-OMe) macromolecule (**16**) with a molecular weight of approximately 5000 $g\,mol^{-1}$.

The esterification and deprotection reactions were easily monitored by the appearance and disappearance of the benzylidene protons in the aromatic region, as well as the relative integrated areas of the benzylidene, glycerol, succinic acid, and TBDPS protons in the ^1H NMR spectra. The molecular weights of the synthesized macromolecules were determined by FAB- or MALDI-MS, and size exclusion chromatography (SEC). Data in Table 1 show that each increase in generation number corresponds to an approximate doubling of molecular weight. This trend is observed in both the FAB/MALDI-MS and SEC data. The synthesized dendrons, dendrimers, and dendritic–linear hybrids possess relatively low polydispersity indices, a characteristic of dendritic polymers.

This synthetic route provides access to a diverse set of structurally different dendritic macromolecules that possess a high number of surface end groups for further derivatization with cross-linking moieties, biological recognition ligands, or pharmaceuticals. As discussed earlier, we are interested in photo-cross-linkable macromolecules as temporary, resorable scaffolds that can fill irregular wounds or defects in vivo, and aid in wound healing. Ideally, these synthetic tissue scaffolds will perform a number of biological functions, including mimicking the physical and mechanical properties of native, healthy tissue. Swelling and mechanical studies on photo-cross-linked constructs of a methacrylated **[G3]-PGLSA** dendrimer (**15**) and a **[G3]-PGLSA**-PEG-OMe dendritic–linear hybrid macromolecule (**19**) show dramatically different properties. The cross-linkable methacrylated (MA) dendritic macromolecules were prepared by



Scheme 3. Synthesis of the **[G3]-PGLSA** dendrimer and dendritic–linear hybrid. Reagents and conditions. a) DCC, DPTS, DCM, RT, 72 h, 73% yield; b) 20% $Pd(OH)_2$/C, 50 psi. H_2, THF, RT, 3 h, 97% yield; c) methacrylic anhydride, DMAP, DCM, 4.5 h, RT, 64% yield; d) DCC, DPTS, DCM, RT, 168 h, 89% yield; e) 20% $Pd(OH)_2$/C, 50 psi. H_2, THF, RT, 3 h, 83% yield; f) methacrylic anhydride, DMAP, DCM, RT, 18 h, 96% yield. MA = methacrylate.

treating the hydroxylated terminated macromolecules (**14** or **18**) with methacrylic anhydride and DMAP as shown in Scheme 3. These cross-linkable derivatives were then irradiated with ultraviolet light to form gels (gels contained 2,2-dimethoxy-2-phenylacetophenone as the photoinititator). The photo-cross-linked construct composed of the methacrylated dendrimer (50% modified) **15** was hydrophobic (equilibrium water content; 2.6% w/w water) and possessed a low swelling ratio (q) in water ($q = 1.5$). The gel was relatively stiff, and possessed a dynamic shear modulus $|G^*|$ of 9.6×10^6 Pa (at 10 rad s^{-1}). However, the gel prepared from the dendritic–linear hybrid **19** (≈25% w/v) was hydrophilic (equilibrium water content; 91% w/w water) and swelled in water ($q = 11.4$). This gel was elastic and very soft to the touch. The $|G^*|$ was 180 Pa (at 10 rad s^{-1}) and approximately 10^4-fold less in magnitude than the construct composed of dendrimer **15**. Both the hydrophilicity and elasticity of the gels are significantly different between the dendrimer **15** and hybrid **19**. These data demonstrate that the properties of dendritic gels can be tuned. Our aim is to match the mechanical properties of the native host tissue through optimization of the polymer architecture, molecular weight, concentration in water, and cross-linking density of the dendritic macromolecule. For comparison with natural gel systems, the dynamic shear modulus of a 3.7% collagen solution is ≈150 Pa, the eye lens and nucleus pulposus are ≈15000 Pa, and the meniscus is ≈100000 Pa. A description and detailed analysis of the rheological properties of a series of dendritic gels will be described elsewhere.[77]

Conclusion

The synthesis and characterization of glycerol and succinic acid dendrons and dendrimers as well as dendritic–linear hybrid macromolecules composed of glycerol, succinic acid, and poly(ethylene glycol) are described. This synthesis capitalizes on the differential chemical reactivity of the benzylidene acetal and TBDPS protecting groups for the 1,3-hydroxyls of glycerol and the carboxylic acid of succinic acid, respectively. Since both the peripheral end groups and focal point are available for subsequent chemical reactions, this convergent synthetic approach is highly amenable to the preparation of a wide variety of dendritic macromolecules from biocompatible building blocks. Studies with the photo-cross-linked dendritic gels demonstrate that the mechanical properties of these constructs can be altered, and our current effort is aimed at synthesizing additional water-soluble dendritic macromolecules that upon photo-cross-linking afford a specific gel property. In summary, these biodendritic macromolecules are of interest for fundamental physiochemical studies and as new tailored materials for applications in drug delivery and tissue engineering.

Experimental Section

All solvents were dried and freshly distilled prior to use (DCM and pyridine with CaH, and THF with Na). All chemicals were purchased from Aldrich or Acros as highest purity grade and used without further purifi-

Table 1. FAB/MALDI MS and SEC data for dendrons, dendrimers, and dendritic–linear hybrid macromolecules.[a]

No.	Macromolecules	Calcd M_W	FAB/MALDI M_W	SEC M_w	SEC PDI
dendrons					
5	bzld-**[G2]-PGLSA**-TBDPS	955.08	955.3	940	1.01
6	bzld-**[G2]-PGLSA**-acid	716.68	715.2	810	1.01
7	HO-**[G2]-PGLSA**-TBDPS	779.5	778.3	800	1.01
8	bzld-**[G3]-PGLSA**-TBDPS	1827.9	1825.6	1830	1.01
9	bzld-**[G3]-PGLSA**-acid	1588.50	1587.5	1650	1.02
10	HO-**[G3]-PGLSA**-TBDPS	1475.47	1475.56	2101	1.05
11	bzld-**[G4]-PGLSA**-TBDPS	3573.54	3574.54	3420	1.02
dendrimers					
13	**[G3]-PGLSA**-bzld	6552.2	6553.4	4740	1.01
14	**[G3]-PGLSA**-OH	5142.5	5144.8	4764	1.01
15	**[G3]-PGLSA**-MA[b]	6231.6	6224.6	3525	1.30
dendritic–linear hybrids					
17	bzld-**[G3]-PGLSA**-PEG-OMe	6588	$M_n = 6628$ $M_w = 6671$ PDI = 1.01	6990	1.04
18	HO-**[G3]-PGLSA**-PEG-OMe	6136	$M_n = 6260$ $M_w = 6302$ PDI = 1.01	6660	1.03
19	MA-**[G3]-PGLSA**-PEG-OMe	6780	$M_n = 7008$ $M_w = 7080$ PDI = 1.01	6918	1.07

[a] Relative molecular weights by size exclusion chromatography were compared to polystyrene samples, with the exception of the PEG linear hybrids, which were compared to PEG standards. [b] 50% methacrylated.

cation (DCC 99%; DMAP 99%) except methacrylic anhydride, which was distilled prior to use, and poly(ethylene glycol) monomethyl ether (PEG-OMe) 5000 MW, which was purchased from Polysciences and dried under vacuum at 120 °C for 3 h. All polymer molecular weights are based on a PEG chain of 113 ethylene glycol units to calculate yields and molecular weights. All reactions were performed under nitrogen atmosphere at room temperature unless specified otherwise. NMR spectra were recorded on a Varian INOVA spectrometer (for ^{1}H and ^{13}C NMR, 400 MHz and 100.6 MHz, respectively) or a GE QE-300 (for HETCOR with APT) spectrometer. 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). Each polymer had an approximate 2000 molecular weight range. Elemental analysis was obtained from Atlantic Microlab. Size exclusion chromatography was performed with THF as the elutent on a Polymer Laboratories PLgel 3 μm MIXED-E column (3 μm bead size) and a Rainin HPLC system (temp = 25 °C; flow rate = 1.0 mL min^{-1}). Polystyrene standards (0.60 K, 1.00 K, 4.00 K, 20 K; PDI = 1.04–1.30; Polysciences) were used for calibration of compounds **5**–**11** and **13**–**15**; and polyethylene glycol standards (0.93 K, 4.45 K, and 12 K; PDI = 1.03–1.05; Polymer Standards Service-USA Inc.) were used for calibration of compounds **17**–**19**. Equilibrium water content was determined by TGA (TA TGA*Q*500). The swelling ratio was determined by weighing the cross-linked gels after formation and then after being suspended in 0.1 M HEPES buffer solution for 24 h. Acetylated derivatives were synthesized and characterized for compounds **4, 7**, and **10**, since these compounds were hydroscopic oils. Abbreviations: DCM = dichloromethane, THF = tetrahydrofuran, DCC = dicyclohexylcarbodiimide, DMAP = 4-(dimethylamino)pyridine, DCU = 1,3-dicyclohexylurea, $Pd(OH)_2/C = 20\%$ palladium hydroxide on activated carbon, Pd/C = 10% palladium on activated carbon, DPTS = 4-(dimethylamino)-pyridinium *p*-toluenesulfonate.

2(*cis*-1,3-*O*-Benzylidene glycerol)succinic acid monoester (2): *cis*-1,3-*O*-Benzylidene glycerol (**1**; 17.0 g, 0.094 mol) and succinic anhydride (14.42 g, 0.144 mol) were stirred in pyridine (150 mL) for 18 h. The pyridine was removed and the white powder was dissolved in H_2O. The pH of the water was adjusted to 7.0 with 1 N NaOH. The water layer was washed with CH_2Cl_2 to remove impurities. The water layer was then adjusted to pH 4.0 with 1 N HCl. The product was extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated to yield 25.02 g of pure product as a white powder (95% yield). ^{1}H NMR ($CDCl_3$): $\delta = 2.68$–2.72 (m, 4H; -CH_2-CH_2-), 4.11–4.14 (m, 2H; -CH_2-CH-CH_2-), 4.24–4.27 (m, 2H; -CH_2-CH-CH_2-), 4.71–4.72 (m, 1H; -CH$_2$-C*H*-CH$_2$-), 5.53 (s, 1H; C*H*), 7.34–7.36 (m, 3H; arom. C*H*), 7.48–7.50 ppm (m, 2H; arom. C*H*); ^{13}C NMR ($CDCl_3$): $\delta = 29.05$ (*C*H$_2$), 29.24 (*C*H$_2$), 66.57 (*C*H), 69.15 (*C*H$_2$), 101.43 (*C*H), 126.26 (*C*H), 128.51 (*C*H), 129.33 (*C*H), 137.95 (*C*H), 172.38 (*C*OOR), 178.07 ppm (*C*OOH); GC-MS: *m*/*z* calcd 280 $[M]^+$; found 281 $[M+H]^+$; elemental analysis calcd (%):C 59.99, H 5.75; found: C 60.07, H 5.80.

bzld-[G1]-PGLSA-TBDPS (3): Compound **2** (4.00 g, 0.014 mol) and imidazole (3.24 g, 0.048 mol) were stirred in DMF (150 mL). Next, diphenyl-*tert*-butyl silyl chloride (6.4 mL, 0.024 mol) was added, and the reaction was stirred for 48 h. The DMF was removed, the product was dissolved in CH_2Cl_2, washed with sat. $NaHCO_3$ and water, dried over Na_2SO_4, filtered, concentrated, and dried on the vacuum line. The product was purified by column chromatography (4:1 hexanes/EtOAc) affording 6.38 g of product as a viscous opaque oil (86% yield). $R_f = 0.13$ (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$): $\delta = 1.09$ (s, 9H; *t*Bu), 2.78–2.84 (m, 4H; -CH_2-CH_2), 4.11–4.15 (m, 2H; -CH_2-CH-CH_2-), 4.23–4.26 (m, 2H; -CH_2-CH-CH_2-), 4.70–4.71 (m, 1H; -CH$_2$-C*H*-CH$_2$-), 5.54 (s, 1H; C*H*), 7.33–7.42, 7.48–7.50, 7.67–7.68 ppm (m, 15H; arom. bzld and phenyl C*H*); ^{13}C NMR ($CDCl_3$): $\delta = 19.34$ (-*C*-(CH$_3$)$_3$), 27.07 (-C-(*C*H$_3$)$_3$), 29.72, 30.96 (succ. -*C*H$_2$-), 66.46, 69.18 (glycerol, 2C, -*C*H$_2$-), 101.39 (O-*C*H-O), 126.23, 127.94, 128.50, 129.28, 130.29, 131.93, 135.51 (arom. *C*H), 137.99 (arom. bzld -*C*-), 171.53, 172.52 ppm (succ. -C(=O)-); GC-MS: *m*/*z* calcd: 518.2 $[M]^+$; found: 519.2 $[M+H]^+$; HR-FAB: *m*/*z* calcd: 518.2125 $[M]^+$; found: 517.2028 $[M-H]^+$; elemental analysis calcd (%): C 69.47, H 6.61; found: C 69.18, H 6.69.

HO-[G1]-PGLSA-TBDPS (4): Compound **3** (2.41 g, 4.65 mmol) was dissolved in THF (45 mL), and 20% $Pd(OH)_2/C$ (1.0 g) was added. The solution was then placed in a Parr tube on a hydrogenator, evacuated, flushed with hydrogen, and shaken under 50 psi H_2 for 3 h. The solution was then filtered over wet Celite and the solvent removed by rotoevaporation. The product was purified by column chromatography (1:1 hexanes/EtOAc increasing to 1:4 hexanes/EtOAc) to yield 1.9 g of a clear oil (95% yield). $R_f = 0.24$ (1:4 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$): $\delta = 1.08$ (s, 9H; *t*Bu), 2.02 (br s, 2H; -O*H*), 2.64–2.85 (m, 4H; -CH_2-CH_2), 3.70–3.72, 4.07–4.14 (m, 4H; -CH_2-CH-CH_2-), 4.83–4.86 (m, 1H; -CH$_2$-C*H*-CH$_2$-), 7.33–7.44, 7.62–7.65 ppm (m, 10H; arom. phenyl C*H*); ^{13}C NMR ($CDCl_3$): $\delta = 19.30$ (-*C*-(CH$_3$)$_3$), 27.03 (-C-(*C*H$_3$)$_3$), 29.77, 31.37 (succ. -*C*H$_2$-), 62.45 (glycerol, -*C*H$_2$-), 75.86 (CH$_2$-*C*H-CH$_2$), 127.97, 130.36, 132.67, 135.49 (phenyl *C*H), 172.65, 178.24 ppm (succ. -C(=O)-); FAB-MS: *m*/*z* calcd: 430.57 $[M]^+$; found: 431 $[M-H]^+$.

Acetyl derivative of compound 4: Compound **4** was a hydroscopic oil and repeated attempts to obtain satisfactory elemental analysis failed. Thus, we decided to prepare the acetyl analogue for elemental analysis. Compound **4** (0.44 g, 1.02 mmol) was stirred in CH_2Cl_2 (30 mL) with DPTS (0.30 g, 1.02 mmol), freshly distilled acetic acid (0.15 mL, 2.66 mmol), and DCC (0.63 g, 3.07 mmol). The solution was stirred for 18 h. The DCU precipitate was filtered and the solvent was evaporated. A solution of 1:1 hexanes/EtOAc was added and impurities precipitated. The solution was filtered, concentrated and further purified by column chromatography (3:1 hexanes/EtOAc), to afford 0.44 g of product (83% yield). $R_f = 0.19$ (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$): $\delta = 1.08$ (s, 9H; *t*Bu), 1.87–1.93 (m, 6H; -CH_3), 2.50–2.71 (m, 4H; -CH_2-CH_2), 3.96–4.19 (m, 4H; -CH_2-CH-CH_2-), 5.06–5.18 (m, 1H; -CH$_2$-C*H*-CH$_2$-), 7.22–7.33, 7.51–7.56 ppm (m, 10H; phenyl C*H*); ^{13}C NMR ($CDCl_3$): $\delta = 19.10$ (-*C*-(CH$_3$)$_3$), 20.61

(OC-*C*H$_3$), 26.82 (-C-(*C*H$_3$)$_3$), 29.14, 30.62 (succ. -*C*H$_2$-), 62.12, 69.28 (glycerol, -*C*H$_2$-), 127.71, 130.09, 131.65, 135.27 (arom. *C*H), 170.52, 171.19, 171.58 ppm (-*C*(=O)-); FAB-MS: *m*/*z* calcd: 514.6 $[M]^+$; found: 515.4 $[M+H]^+$; elemental analysis calcd (%): C 63.01, H 6.66; found: C 62.76, H 6.69; SEC: $M_w = 547$, $M_n = 528$, PDI = 1.04.

bzld-[G2]-PGLSA-TBDPS (5): Compound **4** (1.90 g, 4.41 mmol) was stirred in CH_2Cl_2 (100 mL) with DPTS (1.30 g, 4.41 mmol), compound **2** (2.72 g, 9.70 mmol), and DCC (2.00 g, 9.70 mmol). The solution was stirred for 18 h. The DCU precipitate was filtered and the solvent was evaporated. A solution of 1:1 hexanes/EtOAc was added and impurities precipitated. The solution was filtered, concentrated and further purified by column chromatography (1:1 hexanes/EtOAc) to afford 3.70 g of product (88% yield). $R_f = 0.22$ (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$): $\delta = 1.08$ (s, 9H; *t*Bu), 2.57–2.79 (m, 12H; -C*H*$_2$-C*H*$_2$), 4.08–4.14, 4.16–4.22 (m, 12H; -C*H*$_2$-CH-C*H*$_2$-), 4.70–4.71 (m, 2H; -CH$_2$-C*H*-CH$_2$-), 5.21 (m, 1H; C*H*), 5.49–5.54 (m, 1H; C*H*), 7.32–7.41, 7.47–7.49, 7.62–7.67 ppm (m, 20H; arom. bzld and phenyl C*H*); ^{13}C NMR ($CDCl_3$): $\delta = 19.31$ (-*C*-(CH$_3$)$_3$), 27.04 (-C-(*C*H$_3$)$_3$), 28.98, 29.33, 30.81 (succ. -*C*H$_2$-), 62.48, 66.50, 69.16, 69.43 (glycerol, -*C*H$_2$-), 101.33 (O-*C*H-O), 126.22, 127.95, 128.49, 129.26, 130.32, 131.92, 135.49 (arom. *C*H), 138.02 (arom. bzld -*C*-), 171.93, 172.28 ppm (succ. -C(=O)-); GC-MS: *m*/*z* calcd: 954.4 $[M]^+$; found: 955.3 $[M+H]^+$; elemental analysis calcd (%): C 64.14, H 6.12; found: C 64.35, H 6.29; SEC: $M_w = 940$, $M_n = 930$, PDI = 1.01.

bzld-[G2]-PGLSA-acid (6): Compound **5** (1.00 g, 1.04 mmol) was dissolved in THF (75 mL). Next, tetrabutylammonium fluoride trihydrate (1.25 g, 3.96 mmol) was added to the solution and it was stirred for 1 hour, after which the reaction was complete as indicated by TLC. The solution was diluted with H_2O (25 mL) and acidified with 1 N HCl to pH 3. The product was extracted into CH_2Cl_2, dried over Na_2SO_4, concentrated, and dried on the vacuum line. The product was purified by column chromatography (0–5% MeOH in CH_2Cl_2) for 0.65 g of product (87% yield). $R_f = 0.24$ (5% MeOH in CH_2Cl_2). ^{1}H NMR ($CDCl_3$): $\delta = 2.55$–2.77 (m, 12H; -C*H*$_2$-C*H*$_2$), 4.10–4.17, 4.24–4.31 (m, 12H; -C*H*$_2$-CH-C*H*$_2$-), 4.74–4.75 (m, 2H; -CH$_2$-C*H*-CH$_2$-), 5.28–5.31 (m, 1H; C*H*), 5.52–5.54 (m, 2H; C*H*), 7.33–7.38, 7.47–7.49 ppm (m, 10H; arom. bzld C*H*); ^{13}C NMR ($CDCl_3$): $\delta = 28.72$, 29.03, 29.38 (succ. -*C*H$_2$-), 62.68, 66.56, 69.16 (glycerol, -*C*H$_2$-), 101.44 (O-*C*H-O), 126.23, 128.50, 129.33 (arom. *C*H), 137.75 (arom. bzld -*C*-), 172.67, 175.16 (succ. -C(=O)-); GC-MS: *m*/*z* calcd: 716.2 $[M]^+$; found: 715.2 $[M-H]^-$; elemental analysis calcd (%):C 58.66, H 5.63; found: C 58.71, H 5.82; SEC: $M_w = 810$, $M_n = 800$, PDI = 1.01.

HO-[G2]-PGLSA-TBDPS (7): Compound **5** (1.55 g, 1.62 mmol) was dissolved in THF (40 mL) and 20% $Pd(OH)_2$/C (1.0 g) was added. The solution was then placed in a Parr tube on a hydrogenator and shaken under 50 psi H_2 for 4 h. The solution was then filtered over wet Celite, concentrated, and purified by column chromatography (0–25% acetone in EtOAc) to yield 1.12 g of product (95% yield). $R_f = 0.25$ (1:3 acetone/EtOAc). ^{1}H NMR ($CDCl_3$): $\delta = 1.07$ (s, 9H; *t*Bu), 2.25 (br s, 4H; -O*H*), 2.58–2.82 (m, 12H; -C*H*$_2$-C*H*$_2$), 3.71–3.74, 4.09–4.26 (m, 12H; -C*H*$_2$-CH-C*H*$_2$-), 4.87–4.99, 5.24–5.25 (m, 3H; -CH$_2$-C*H*-CH$_2$-), 7.34–7.43, 7.63–7.68 ppm (m, 10H; phenyl C*H*); ^{13}C NMR ($CDCl_3$): $\delta = 14.52$ (-*C*-(CH$_3$)$_3$), 25.78 (-C-(*C*H$_3$)$_3$), 26.99, 29.30, 30.51, 30.81 (succ. -*C*H$_2$-), 62.08, 63.44, 68.17, 70.23 (glycerol, -*C*H$_2$-), 125.71, 127.96, 130.35, 135.45 (phenyl), 171.94, 172.40 (succ. -C(=O)-); GC-MS: *m*/*z* calcd: 778.3 $[M]^+$; found 779.5 $[M+H]^+$; SEC: $M_w = 800$, $M_n = 792$, PDI = 1.01

Acetyl derivative of compound 7: Compound **7** was a hydroscopic oil and repeated attempts to obtain satisfactory elemental analysis failed. Thus, we decided to prepare the acetyl analogue. Compound **7** (0.55 g, 0.70 mmol) was stirred in CH_2Cl_2 (40 mL) with DPTS (0.39 g, 1.34 mmol), freshly distilled acetic acid (0.19 mL, 3.36 mmol), and DCC (0.87 g, 4.20 mmol). The solution was stirred for 18 h. The DCU precipitate was filtered and the solvent was evaporated. The residue was resuspended in a minimum of CH_2Cl_2, cooled to 10 °C and filtered. The resulting solution was concentrated and further purified by column chromatography (0–5% acetone in CH_2Cl_2) to afford 0.49 g of product (66% yield). $R_f = 0.17$ (5% acetone in CH_2Cl_2); ^{1}H NMR ($CDCl_3$): $\delta = 1.07$ (s, 9H; *t*Bu), 2.04 (s, 12H; -C*H*$_3$), 2.55–2.83 (m, 12H; -C*H*$_2$-C*H*$_2$), 4.09–4.32 (m, 12H; -C*H*$_2$-CH-C*H*$_2$-), 5.20–5.29 (m, 3H; -CH$_2$-C*H*-CH$_2$-), 7.32–7.44, 7.61–7.67 ppm (m, 10H; phenyl C*H*); ^{13}C NMR ($CDCl_3$): $\delta = 19.10$ (-*C*-(CH$_3$)$_3$), 20.67 (OC-*C*H$_3$), 26.82 (-C-(*C*H$_3$)$_3$), 28.60, 28.80, 29.10, 30.59 (succ. -*C*H$_2$-), 62.11, 62.31, 69.39 (glycerol, -*C*H$_2$-), 127.72, 130.09, 131.67, 135.27 (arom. *C*H), 170.50, 171.33, 171.61 ppm (-*C*(=O)-); FAB-MS: *m*/*z* calcd: 947.0 $[M]^+$; found: 947.9 $[M+H]^+$; elemental analysis calcd (%):C 57.07, H 6.17; found: C 57.15, H 6.26; SEC: $M_w = 1075$, $M_n = 1041$, PDI = 1.03.

bzld-[G3]-PGLSA-TBDPS (8): Dendron **8** was synthesized by two methods, first by coupling dendron **6** to dendron **4** convergently, and second by coupling compound **2** to dendron **7** divergently.

Convergent synthesis: Compound **6** (1.05 g, 1.47 mmol) was stirred in CH_2Cl_2 (75 mL), and compound **4** (0.29 g, 0.67 mmol), DPTS (0.20 g, 0.67 mmol), and DCC (0.41 g, 2.00 mmol) were added. The solution was stirred for 48 h. The DCU precipitate was filtered and the solvent was evaporated. The product was purified by column chromatography (3:7 hexanes/EtOAc) to afford 0.99 g of product (82% yield).

Divergent synthesis: Compound **7** (0.55 g, 0.71 mmol) was stirred in CH_2Cl_2 (50 mL), and DPTS (0.42 g, 1.41 mmol), compound **2** (0.87 g, 3.11 mmol), and DCC (0.64 g, 3.12 mmol) were added. The solution was stirred for 18 h. The DCU precipitate was filtered and the solvent was evaporated. The product was purified by column chromatography (3:7 hexanes/EtOAc) to afford 0.71 g of product (54% yield). $R_f = 0.08$ (3:7 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$): $\delta = 1.08$ (s, 9H; *t*Bu), 2.54–2.92 (m, 28H; -C*H*$_2$-C*H*$_2$), 4.08–4.15, 4.22–4.27 (m, 28H; -C*H*$_2$-CH-C*H*$_2$-), 4.71 (s, 4H; -CH$_2$-C*H*-CH$_2$-), 5.21–5.24 (m, 3H; C*H*), 5.52 (s, 4H; C*H*), 7.31–7.42, 7.45–7.49, 7.65–7.67 ppm (m, 30H; arom. bzld and phenyl C*H*); ^{13}C NMR ($CDCl_3$): $\delta = 19.31$ (-*C*-(CH$_3$)$_3$), 27.04 (-C-(*C*H$_3$)$_3$), 29.35, 30.81 (succ. -*C*H$_2$-), 62.49, 66.53, 69.16, 69.47 (glycerol, -*C*H$_2$-), 101.33 (O-*C*H-O), 126.21, 127.94, 128.48, 129.26, 130.32, 135.47 (arom. *C*H), 138.02 (arom. bzld -*C*-), 171.90, 172.28 ppm (succ. -C(=O)-); GC-MS: *m*/*z* calcd: 1827.9 $[M]^+$; found: 1825.6 $[M-H]^+$; HR-FAB: *m*/*z* calcd: 1826.6233 $[M]^+$; found: 1825.6124 $[M-H]^+$; elemental analysis calcd (%):C 61.11, H 5.85; found: C 60.66, H 5.85; SEC: $M_w = 1830$, $M_n = 1810$, PDI = 1.01.

bzld-[G3]-PGLSA-acid (9): Compound **8** (2.00 g, 1.09 mmol) was dissolved in THF (125 mL). Next, tetrabutylammonium fluoride trihydrate (1.3 g, 4.1 mmol) was added to the solution. The mixture was stirred for 1 hour, after which the reaction was complete as indicated by TLC. The solution was diluted with H_2O (25 mL) and acidified with 1 N HCl to pH 3. The product was extracted into CH_2Cl_2, dried over Na_2SO_4, concentrated, and dried on the vacuum line. The product was purified by column chromatography (0–5% MeOH in CH_2Cl_2) to afford 1.44 g of product (83% yield). $R_f = 0.21$ (5% MeOH in CH_2Cl_2); ^{1}H NMR ($CDCl_3$): $\delta =$ 2.58–2.75 (m, 28H; -C*H*$_2$-C*H*$_2$), 4.11–4.16, 4.19–4.27 (m, 28H; -C*H*$_2$-CH-C*H*$_2$-), 4.71–4.72 (m, 4H; -CH$_2$-C*H*-CH$_2$-), 5.21–5.28 (m, 3H; C*H*), 5.52–5.53 (m, 4H; C*H*), 7.32–7.37, 7.46–7.49 ppm (m, 20H; arom. bzld C*H*); ^{13}C NMR ($CDCl_3$): $\delta = 29.05$, 29.36 (succ. -*C*H$_2$-), 62.51, 66.58, 69.16 (glycerol, -*C*H$_2$-), 101.36 (O-*C*H-O), 126.21, 128.49, 129.29 (arom. *C*H), 137.95 (arom. bzld -*C*-), 171.83, 173.01 ppm (succ. -C(=O)-); GC-MS: *m*/*z* calcd: 1588.5 $[M]^+$; found: 1587.5 $[M-H]^+$; elemental analysis calcd (%):C 58.18, H 5.58; found: C 58.02, H 5.60; SEC: $M_w = 1650$, $M_n = 1620$, PDI = 1.02.

HO-[G3]-PGLSA-TBDPS (10): Compound **8** (0.53 g, 0.29 mmol) was dissolved in THF (50 mL) in a Parr tube. 20% $Pd(OH)_2$/C (0.4 g) was added and the flask was evacuated and filled with 50 psi of H_2. The mixture was shaken for 8 h, then filtered over wet Celite. The filtrate was dried to produce a clear oil, which was purified by column chromatography (0–50% acetone in EtOAc) to afford 0.38 g of product (88% yield). $R_f = 0.23$ (1:1 acetone/EtOAc); ^{1}H NMR ($CDCl_3$): $\delta = 1.3$ (s, 9H; *t*Bu), 2.52–2.86 (m, 28H; -C*H*$_2$-C*H*$_2$), 3.44–3.94 (m, 24, -C*H*$_2$-CH-C*H*$_2$- and -O*H*), 4.10–4.38, (m, 12H; -C*H*$_2$-CH-C*H*$_2$-), 4.82–4.92 (m, 4H; C*H*), 5.18–5.30 (m, 3H; C*H*), 7.28–7.43, 7.50–7.54, 7.60–7.66 ppm (m, 10H; phenyl C*H*); ^{13}C NMR ($CDCl_3$): $\delta = 19.04$ (-*C*-(CH$_3$)$_3$), 24.44 (-C-(*C*H$_3$)$_3$), 26.76, 27.12, 28.82, 28.97, 29.10, 30.57 (succ. -*C*H$_2$-), 61.17, 62.33, 63.21, 69.30, 75.52 (glycerol, -*C*H$_2$-), 127.72, 130.11, 131.57, 134.36, 135.20 (arom. *C*H), 171.66, 171.72, 171.99, 172.27, 172.38, 172.46 ppm (succ. -C(=O)-); MALDI-MS: *m*/*z* calcd: 1475.5 $[M]^+$; found: 1475.56 $[M+H]^+$; SEC: $M_w = 2101$, $M_n = 1994$, PDI = 1.05.

Acetyl derivative of compound 10: Compound **10** was a hydroscopic oil and repeated attempts to obtain satisfactory elemental analysis failed. Thus, we decided to prepare the acetyl analogue. Compound **10** (0.24 g, 0.16 mmol) was stirred in CH_2Cl_2 (40 mL) with DPTS (0.19 g, 0.65 mmol), freshly distilled acetic acid (0.09 mL, 1.55 mmol), and DCC (0.40 g, 1.94 mmol). The solution was stirred for 18 h. The DCU precipitate was filtered and the solvent was evaporated. The residue was resuspended in a minimum of CH_2Cl_2, cooled to 10 °C and filtered. The resulting

solution was concentrated and further purified by column chromatography (4:1 hexanes/EtOAc increasing to 3:7 hexanes/EtOAc) to afford 0.18 g of product (63% yield). $R_f = 0.15$ (3:7 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$): $\delta = 1.10$ (s, 9H; *t*Bu), 1.99 (s, 24H; -CH_3), 2.48–2.78 (m, 28H; -CH_2-CH_2), 4.02–4.30 (m, 28H; -CH_2-CH-CH_2-), 5.12–5.26 (m, 7H; -CH$_2$-C*H*-CH$_2$-), 7.25–7.38, 7.55–7.61 ppm (m, 10H; phenyl C*H*); ^{13}C NMR ($CDCl_3$): $\delta = 18.87$ (-*C*-(CH$_3$)$_3$), 20.46 (OC-*C*H$_3$), 26.61 (-C-(*C*H$_3$)$_3$), 26.95, 28.47, 28.55, 28.64, 28.90, 30.39 (succ. -*C*H$_2$-), 61.90, 62.10, 69.02, 69.22 (glycerol, -*C*H$_2$-), 127.52, 129.90, 131.48, 135.05 (arom. *C*H), 170.26, 171.14, 171.40, 171.46 ppm (-*C*(=O)-); FAB-MS: *m*/*z* calcd: 1811.8 $[M]^+$; found: 1812.2 $[M+H]^+$; elemental analysis calcd (%):C 53.70, H 5.90; found: C 53.95, H 6.12; SEC: $M_w = 1943$, $M_n = 1882$, PDI = 1.03.

bzld-[G4]-PGLSA-TBDPS (11): Dendron **11** was synthesized by two methods, first by coupling dendron **6** to dendron **7** convergently, and secondly by coupling the monoester **2** to dendron **10** divergently.

Convergent synthesis: Compound **7** (0.14 g, 0.18 mmol) was dissolved in CH_2Cl_2 (30 mL). Next, DPTS (0.05 g, 0.18 mmol), compound **6** (0.82 g, 1.10 mmol), and DCC (0.22 g, 1.10 mmol) were added. The solution was stirred for 72 h. The DCU was filtered, the filtrate was concentrated to dryness, and the residue was resuspended in a minimum of cold THF. The solution was filtered, concentrated, and purified by column chromatography (1:1 hexanes/EtOAc increasing to 1:4 hexanes/EtOAc) to afford 0.48 g of product (75% yield).

Divergent synthesis: Compound **10** (0.38 g, 0.26 mmol) was dissolved in CH_2Cl_2 (50 mL). Next, compound **2** (1.00 g, 3.57 mmol), DPTS (0.10 g, 0.34 mmol), and DCC (0.66 g, 3.57 mmol) were added to the mixture. The solution was stirred for 48 h. The solution was filtered to remove the DCU precipitate, concentrated, and then purified by column chromatography (1:1 hexanes/EtOAc increasing to 1:4 hexanes/EtOAc) to afford 0.57 g of product (60% yield). $R_f = 0.14$ (1:4 hexanes/EtOAc). ^{1}H NMR ($CDCl_3$): $\delta = 1.07$ (s, 9H; *t*Bu), 2.55–2.77 (m, 60H; -CH_2-CH_2), 4.07–4.15, 4.22–4.25 (m, 60H; -CH_2-CH-CH_2-), 4.70 (s, 8H; -CH$_2$-C*H*-CH$_2$-), 5.19–5.21 (m, 7H; C*H*), 5.51 (s, 8H; C*H*), 7.30–7.40, 7.46–7.48, 7.63–7.65 ppm (m, 50H; arom. bzld and phenyl C*H*); ^{13}C NMR ($CDCl_3$): $\delta = 14.40$ (-*C*-(CH$_3$)$_3$), 27.03 (-C-(*C*H$_3$)$_3$), 29.02, 29.35 (succ. -*C*H$_2$-), 62.47, 66.53, 69.16, 69.49 (glycerol, -*C*H$_2$-), 101.31 (O-*C*H-O), 126.21, 127.94, 128.48, 129.26, 135.47 (arom. *C*H), 138.03 (arom. bzld -*C*-), 171.50, 171.90, 172.27 ppm (succ. -C(=O)-); MALDI-MS: *m*/*z* calcd: 3573.54 $[M]^+$; found: 3574.54 $[M+H]^+$; elemental analysis calcd (%):C 59.19, H 5.74; found: C 59.49, H 5.70; SEC: $M_w = 3420$, $M_n = 3350$, PDI = 1.02.

Tetrafunctional G0 Core ([G0]-PGLSA-bzld): Succinic acid (1.57 g, 13.3 mmol), compound **1** (5.05 g, 28.0 mmol), and DPTS (4.07 g, 13.8 mmol) were dissolved in CH_2Cl_2 (100 mL). Next, DCC (8.19 g, 39.7 mmol) was added and the reaction was stirred for 18 h. The DCU was filtered and the filtrate was concentrated and purified by column chromatography (0–3% MeOH in CH_2Cl_2) to afford 5.28 g of product (90% yield). $R_f = 0.69$ (3% MeOH in CH_2Cl_2); ^{1}H NMR ($CDCl_3$): $\delta = 2.78$ (s, 4H; -CH_2-CH_2-), 4.07–4.11 (m, 2H; -CH_2-CH$_2$-CH_2-), 4.23–4.26 (m, 2H; -CH_2-CH$_2$-CH_2-), 4.70 (s, 2H; -CH$_2$-CH_2-CH$_2$-), 5.51 (s, 2H; C*H*), 7.31–7.37 (m, 6H; arom. C*H*), 7.47–7.49 ppm (m, 4H; arom. C*H*); ^{13}C NMR ($CDCl_3$): $\delta = 29.57$ (*C*H$_2$), 66.49 (*C*H), 69.17 (*C*H$_2$), 101.35 (*C*H), 126.23 (*C*H), 128.48 (*C*H), 129.25 (*C*H), 138.05 (*C*H), 172.35 ppm (*C*OOR); GC-MS: *m*/*z* calcd: 442 $[M]^+$; found: 443 $[M+H]^+$; HR-FAB: *m*/*z* calcd: 442.1628 $[M]^+$; found: 442.1635 $[M]^+$; elemental analysis calcd (%): C 65.15, H 5.92; found: C 65.25, H 5.85.

[G0]-PGLSA-OH (12): **[G0]-PGLSA**-bzld (1.00 g, 0.0023 mol) was dissolved in THF (40 mL) in a Parr tube. Next, 20% Pd(OH)$_2$/C (0.50 g) was added. The Parr tube was evacuated, and filled with 50 psi of H_2. The solution was shaken for 3 h. The catalyst was filtered through wet Celite and washed with THF. The filtrate was evaporated to give 0.57 g of a clear oil (95% yield). ^{1}H NMR ($CDCl_3$): $\delta = 2.67$ (s, 4H; -CH_2-CH_2-), 3.64 (m, 8, -CH_2-CH$_2$-CH_2-), 4.87 ppm (m, 2H; -CH$_2$-CH_2-CH$_2$-); ^{13}C NMR ($CDCl_3$): $\delta = 28.96$ (*C*H$_2$), 60.41 (*C*H), 75.85 (*C*H$_2$), 172.78 ppm (*C*OOR); GC-MS: *m*/*z* calcd: 266 $[M]^+$; found: 284 $[M+NH_4]^+$; elemental analysis calcd (%):C 45.11, H 6.81; found: C 44.94, H 6.87.

[G3]-PGLSA-bzld dendrimer (13): Compound **12** (0.019 g, 0.084 mmol) was dissolved in CH_2Cl_2 (50 mL). Next, compound **9** (0.64 g, 0.40 mmol), DPTS (0.074 g, 0.25 mmol), and DCC (0.10 g, 0.50 mmol) were added. The solution was stirred for 72 h. The DCU was filtered and the filtrate was concentrated. The additional DCU was precipitated in cold THF and filtered. The product was purified by column chromatography (0–5% MeOH in CH_2Cl_2) to yield 0.40 g of product (73% yield). ^{1}H NMR ($CDCl_3$): $\delta = 2.60$–2.74 (m, 116H; -CH_2-CH_2), 4.08–4.17 (m, 60H; -CH_2-CH-CH_2-), 4.22–4.26 (m, 60H; -CH_2-CH-CH_2-), 4.70 (s, 16H; -CH$_2$-C*H*-CH$_2$-), 5.20–5.23 (m, 14H; C*H*), 5.51 (s, 16H; C*H*), 7.32–7.36, 7.46–7.48 ppm (m, 80H; arom. bzld C*H*); ^{13}C NMR ($CDCl_3$): $\delta = 29.02$, 29.35 (succ. -*C*H$_2$-), 62.47, 66.54, 69.16 (glycerol, -*C*H$_2$-), 101.31 (O-*C*H-O), 126.21, 128.48, 129.26 (arom. *C*H), 138.01 (arom. bzld -*C*-), 171.83, 172.29 ppm (succ. -C(=O)-); MALDI: *m*/*z* calcd: 6552.2 $[M]^+$; found: 6553.4 $[M+H]^+$; elemental analysis calcd (%):C 58.29, H 5.57; found: C 58.50, H 5.48; SEC: $M_w = 4740$, $M_n = 4590$, PDI = 1.01.

[G3]-PGLSA-OH dendrimer (14): Compound **13** (0.33 g, 0.051 mmol) was dissolved in a 9:1 solution of THF and MeOH (50 mL) in a Parr tube. Next, 20% Pd(OH)$_2$/C (0.50 g) was added, and the flask was evacuated and filled with 50 psi of H_2. The mixture was shaken for 7 h, then filtered over wet Celite. The filtrate was dried to produce 0.25 g of a clear oil (0.049 mmol, 97% yield). ^{1}H NMR (CD_3OD): $\delta = 2.64$ (m, 116, -CH_2-CH_2-), 3.51 (m, 26, -CH_2-CH-CH_2-), 3.67 (m, 28, -CH_2-CH-CH_2-), 3.80 (m, 12, -CH$_2$-C*H*-CH$_2$-), 4.05 (m, 14, -CH_2-CH-CH_2-), 4.14 (m, 14, -CH_2-CH-CH_2-), 4.22 (m, 22, -CH_2-CH-CH_2-), 4.30 (m, 22, -CH_2-CH-CH_2-), 5.26 ppm (m, 14, -CH$_2$-C*H*-CH$_2$); ^{13}C NMR (CD_3OD): $\delta = 28.61$ (*C*H$_2$), 62.41 (*C*H$_2$), 62.87 (*C*H$_2$), 65.67 (*C*H$_2$), 67.64 (*C*H), 69.91 (*C*H), 172.86 ppm (*C*OOR); MALDI-MS: *m*/*z* calcd: 5142.5 $[M]^+$; found: 5144.8 $[M+H]^+$; elemental analysis calcd (%):C 48.11, H 5.84; found: C 48.07, H 5.84; SEC M_w: 5440; M_n: 5370; PDI: 1.01.

[G3]-PGLSA-MA dendrimer (50% derivatized) (15): Compound **14** (0.22 g, 0.041 mmol) was dissolved in DMF (5 mL). Next, DMAP (0.20 g, 1.66 mmol) was added followed by methacrylic anhydride (0.10 mL, 0.67 mmol, 0.5 equiv of the peripheral hydroxyl groups on **14**). After 4.5 h the reaction was complete as indicated by TLC. MeOH (0.03 mL, 0.67 mmol) was added to the reaction, and the mixture was stirred for an additional 20 minutes. The solution was precipitated into cold diethyl ether (300 mL). The diethyl ether was decanted and the remaining oily residue was diluted with CH_2Cl_2 (20 mL). The organic phase was washed with 1 N HCl and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated to approximately 2 mL. This concentrated solution was precipitated in cold diethyl ether (300 mL). The diethyl ether was decanted and the resulting oily residue was dried under reduced pressure to yield 0.20 g of product (78% yield). ^{1}H NMR ($CDCl_3$): $\delta = 1.90$ (s, 42H; -CH_3), 2.55–2.77 (m, 116H; -CH_2-CH_2), 3.61–3.78 (m, 30H; -CH$_2$-C*H*-CH$_2$-), 4.07–4.30 (m, 120H; -CH_2-CH-CH_2-), 5.58–5.62 (m, 16H; =C*H*), 6.03–6.16 ppm (m, 16H; =C*H*); ^{13}C NMR ($CDCl_3$): $\delta = 18.24$ (-*C*H$_3$), 29.56, 29.75 (succ. -*C*H$_2$-), 61.52, 62.09, 62.14, 65.17, 65.83, 69.39, 69.56, 70.04, 73.23, 75.89 (glycerol -*C*H$_2$-), 171.04, 171.25, 171.37, 171.58, 171.79, 172.14, 172.51 ppm; MALDI-MS: *m*/*z* calcd: 6231.6 $[M]^+$; found: 6224.6 $[M+H]^+$; SEC: $M_w = 3525$, $M_n = 2708$, PDI = 1.30.

bzld-[G3]-PGLSA-PEG-OMe (17): Compound **9** (0.29 g, 0.18 mmol) was dissolved in CH_2Cl_2 (75 mL). Next, 5000 MW poly(ethylene glycol) mono-methyl ether (PEG-OMe; 0.45 g, 0.09 mmol; MALDI-MS: $M_w = 5147$, $M_n = 5074$, PDI = 1.01), DCC (0.037 g, 0.18 mmol), and DPTS (0.026 g, 0.09 mmol) were added to the solution. The solution was stirred for 168 h. The DCU was filtered and the filtrate was concentrated to dryness. The resulting residue was resuspended in THF and cooled, and the DCU was filtered. The resulting solution was precipitated in diethyl ether. The solid was dissolved in THF, stirred with Amberlyst A-21 ion-exchange resin (Aldrich) (weakly basic resin) to eliminate excess **9**. The solution was filtered and the filtrate was dried over Na_2SO_4, dissolved in CH_2Cl_2, washed with 0.1 N HCl, dried over Na_2SO_4, and concentrated to dryness to yield 0.53 g of a solid white product (89% yield). ^{1}H NMR ($CDCl_3$): $\delta = 2.60$–2.73 (m, 28H; -CH_2-CH_2), 3.36 (s, MME CH_3), 3.57–3.64 (m, 406H; PEG CH_2), 4.11–4.26 (m, 28H; -CH_2-CH-CH_2-), 4.71 (m, 4H; -CH$_2$-C*H*-CH$_2$-), 5.21–5.23 (m, 3H; C*H*), 5.52–5.54 (m, 4H; C*H*), 7.32–7.37, 7.46–7.49 ppm (m, 20H; arom. bzld C*H*); ^{13}C NMR ($CDCl_3$): $\delta = 29.36$, 29.90 (succ. -*C*H$_2$-), 62.48, 66.53, 69.17 (glycerol, -*C*H$_2$-), 70.77 (PEG, -*C*H$_2$-), 101.33 (O-*C*H-O), 126.21, 128.48, 129.26 (arom. *C*H), 137.80 (arom. bzld -*C*-), 171.90 ppm (succ. -C(=O)-); MALDI-MS: $M_w = 6671$, $M_n = 6628$, PDI = 1.01 (theoretical $M_W = 6588$); SEC: $M_w = 6990$, $M_n = 6670$, PDI = 1.04.

HO-[G3]-PGLSA-PEG-OMe (18): Compound **17** (0.52 g) was dissolved in THF (40 mL). Next, 20% Pd(OH)$_2$/C (0.10 g) was added. The reaction vessel was evacuated and flushed with hydrogen. The solution was

shaken for 3 h under 50 psi H_2. The $Pd(OH)_2$/C was removed by filtering over wet Celite. The filtrate was dried and precipitated in diethyl ether to yield 0.40 g of an opaque hydroscopic solid (83% yield). ^{1}H NMR ($CDCl_3$): $\delta = 2.60$–2.70 (m, 28H; -CH_2-CH_2), 3.36 (s, MME CH_3) 3.53–3.78 (br m, 422H; PEG CH_2 and -CH_2-CH-CH_2-), 4.17–4.27 (m, 12H; -CH_2-CH-CH_2-), 4.92 (m, 4H; -CH_2-CH-CH_2-), 5.21–5.23 ppm (m, 3H; CH); ^{13}C NMR (DMSO): $\delta = 29.14$, 29.36 (succ. -CH_2-), 60.25 (-CH_3 OMe), 63.22, 66.54, 69.87 (glycerol, -CH_2-), 70.43 (PEG, -CH_2-), 172.35, 172.57 ppm (succ. -C(=O)-); MALDI-MS: $M_w = 6302$, $M_n = 6260$, PDI = 1.01 (theoretical $M_W = 6136$); SEC: $M_w = 6660$, $M_n = 6460$, PDI = 1.03.

MA-[G3]-PGLSA-PEG-OMe (19): Compound **18** (0.39 g, 0.064 mmol) was dissolved in CH_2Cl_2 (30 mL). Next, DMAP (10 mg, 0.08 mmol) and methacrylic anhydride (0.15 mL, 1.0 mmol) were added, and the solution was stirred for 18 h. The solution was then washed with 0.1 N HCl, dried over Na_2SO_4, concentrated, and precipitated in diethyl ether to afford 0.41 g of product (96% yield). ^{1}H NMR ($CDCl_3$): $\delta = 1.92$ (s, 24H; -CH_3-methacrylate), 2.63 (m, 28H; -CH_2-CH_2), 3.36 (s, MME CH_3) 3.59–3.67 (m, 406H; PEG CH_2), 4.19–4.39 (m, 28H; -CH_2-CH-CH_2-), 5.24 (m, 4H; -CH_2-CH-CH_2), 5.35 (m, 3H; CH), 5.59 (s, 8H; -CH_2- methacrylate), 6.10 ppm (s, 8H; -CH_2- methacrylate); MALDI-MS: $M_w = 7080$, $M_n = 7008$, PDI = 1.01 (theoretical $M_W = 6780$); SEC: $M_w = 6918$, $M_n = 6465$, PDI = 1.07.

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