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Synthesis and Characterization of Poly(glycerol−succinic acid) Dendrimers

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ABSTRACT: The syntheses of novel dendrimers composed of glycerol and succinic acid are described. These "biodendrimers" are composed entirely of building blocks known to be biocompatible or degradable in vivo to natural metabolites and are prepared using a high yield divergent approach. Moreover, the synthetic strategy employed is amenable to the design and development of new materials as demonstrated by the attachment of a photopolymerizable group.

Introduction

Dendrimers are highly branched macromolecules possessing a large surface area-to-volume ratio with well-defined interior and exterior regions. In addition, a large number of terminal groups on the dendrimer are available for further functionalization, and these end groups influence the solubility and adhesive properties of the dendrimer. As the dendrimer generation increases, these monodisperse polymers adopt globular three-dimensional shapes.[1−20] These characteristics of dendrimers confer unique chemical and physical properties, which provide the impetus for further studies of this class of macromolecule. Dendrimers are currently being synthesized and investigated for applications in light harvesting,[21−29] catalysis,[30−40] molecular encapsulation,[41−50] and drug delivery.[51−59]

The wide range of applications being explored with dendrimers and dendrons is a reflection of the ability to control both the three-dimensional structure and material properties of the polymer through specific alterations at the molecular level. We are interested in polyester and polyether dendritic macromolecules as new surgical materials for orthopaedic and ophthalmic applications. Consequently, selection of the monomer is critical for both property optimization and biocompatibility. Suitable candidates for dendrimer synthesis and study include monomers currently used for preparation of medical-grade linear polymers and natural metabolites. For example, the naturally occurring α-hydroxy acids (e.g, lactic acid and glycolic acid) are components of conventional linear polyesters used in medical applications ranging from reconstructive surgery to drug delivery.[60−62] Metabolite candidates include, for example, glycerol, glucose, or succinic acid. Monomers from synthetic polymers such as poly(ethylene glycol) (PEG), poly(caproic acid) (PCL), or poly(trimethylene carbonate), which are known to be biocompatible, are also candidates. The naturally occurring amino acids represent another class of monomers suitable for use, and in 1988, Tam reported a poly(lysine) dendrimer for use as a multiple antigen peptide.[63−65] Incorporation of one or more of these building blocks in a dendritic structure[66] provides new opportunities to create well-defined, tailored polymers for tissue engineering applications.[67−73] Herein, we report the divergent synthesis and characterization of generation one (G1) through generation four (G4) dendrimers composed of glycerol and succinic acid and the preparation of photocross-linked dendritic gels.

Results and Discussion

Currently, both divergent (from core to surface)[13,18−20,74−76] and convergent (from surface to core)[17,77−80] synthetic approaches are used to prepare aromatic and aliphatic dendrons and dendrimers. A divergent route to poly(glycerol−succinic acid) dendrimers, **[Gn]-PGLSA**, is shown in Schemes 1 and 2. This synthetic strategy builds upon our recent success in preparing a polyether−ester dendrimer[66] using the benzylidene acetal (bzld) protecting group, which can be selectively removed under mild conditions.[76,81]

First, a tetrafunctional core, **3**, was synthesized in two steps. Succinic acid was coupled to 2 equiv of *cis*-1,3-*O*-benzylideneglycerol (**1**) in the presence of 3 equiv of *N*,*N*-dicyclohexylcarbodiimide (DCC) and 1 equiv of 4-(dimethylamino)pyridinium 4-toluenesulfonate (DPTS)[82] to afford **2** (90% yield). The benzylidene acetal group of the core was subsequently removed by hydrogenolysis (10% (w/w) of 10% Pd/C; 50 psi of H_2; in THF) to yield the tetrahydroxy core, **[G0]-PGLSA**-OH, **3** (97%). The branching ligand, **4** (2-(*cis*-1,3-*O*-benzylidene−glycerol)succinic acid mono ester), was prepared by treating **1** with succinic anhydride in pyridine and was isolated after recrystallization from cold (−20 °C) ethyl ether (95% yield). Next, compounds **3** and **4** were coupled in the presence of DCC and DPTS to afford the protected G1 dendrimer, **5**, in 97% yield. The **[G1]-PGLSA**-bzld was easily separated from the branching ligand by column chromatography. The G1 dendrimer was deprotected by hydrogenolysis in THF to yield the G1 dendrimer, **6** (**[G1]-PGLSA**-OH; 94% yield). Next, **4** was coupled to **6** in the presence of DCC and DPTS to produce **7** in 94% yield. Again, column chromatography was used to isolate the **[G2]-PGLSA**-bzld, and residual DCC was removed by precipitating the dendrimer in ethyl ether. Hydrogenolysis in THF afforded the G2 dendrimer **[G2]-PGLSA**-OH, **8** (95% yield). The **[G3]-PGLSA**-bzld dendrimer **10** was prepared by reacting **8** with **4**, followed by column chromatography and precipitation of the dendrimer from cold ethyl ether (90%

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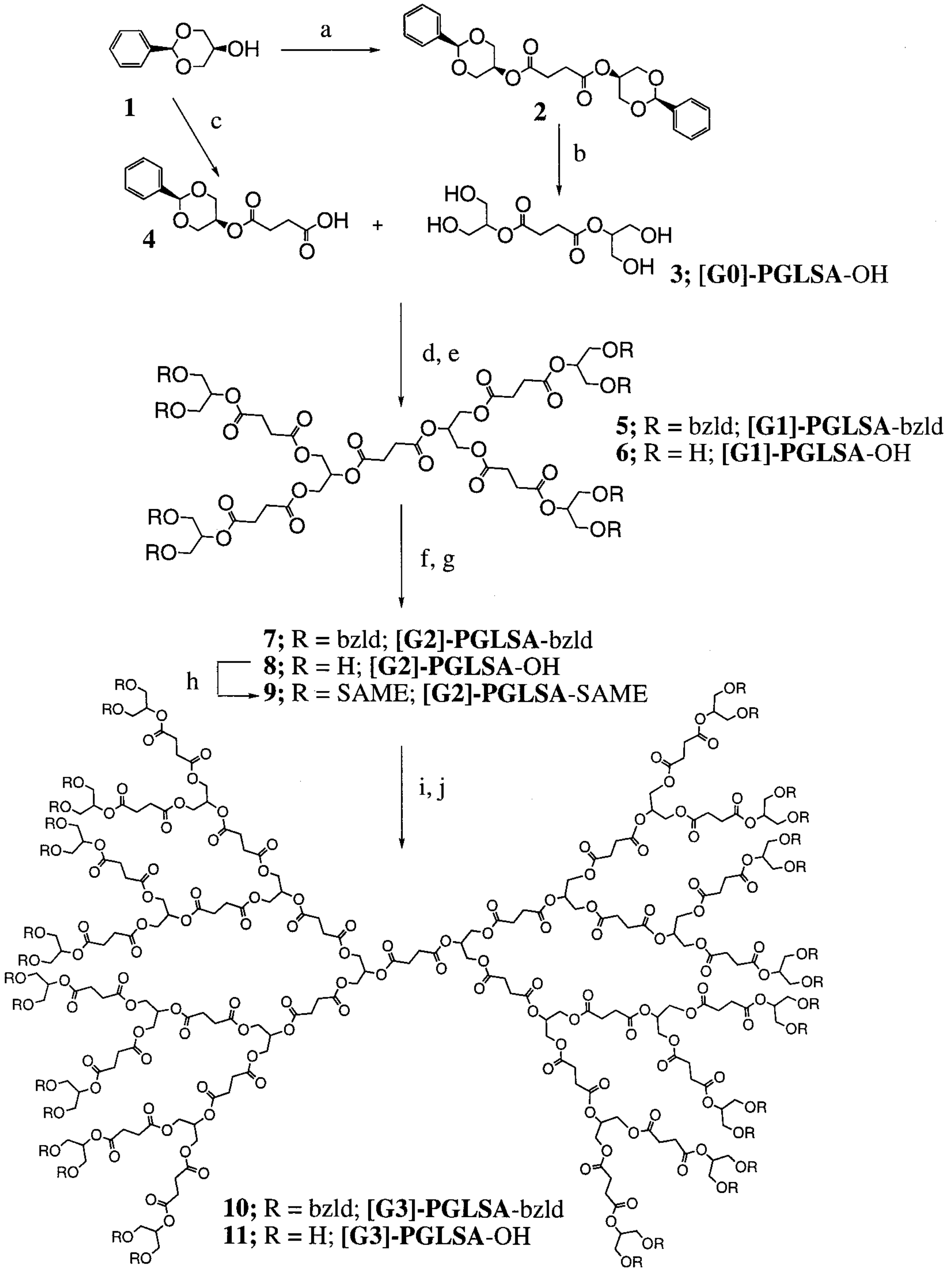
Scheme 1. Divergent Synthesis of G1, G2, and G3 Dendrimers Composed of Glycerol and Succinic Acid[a]

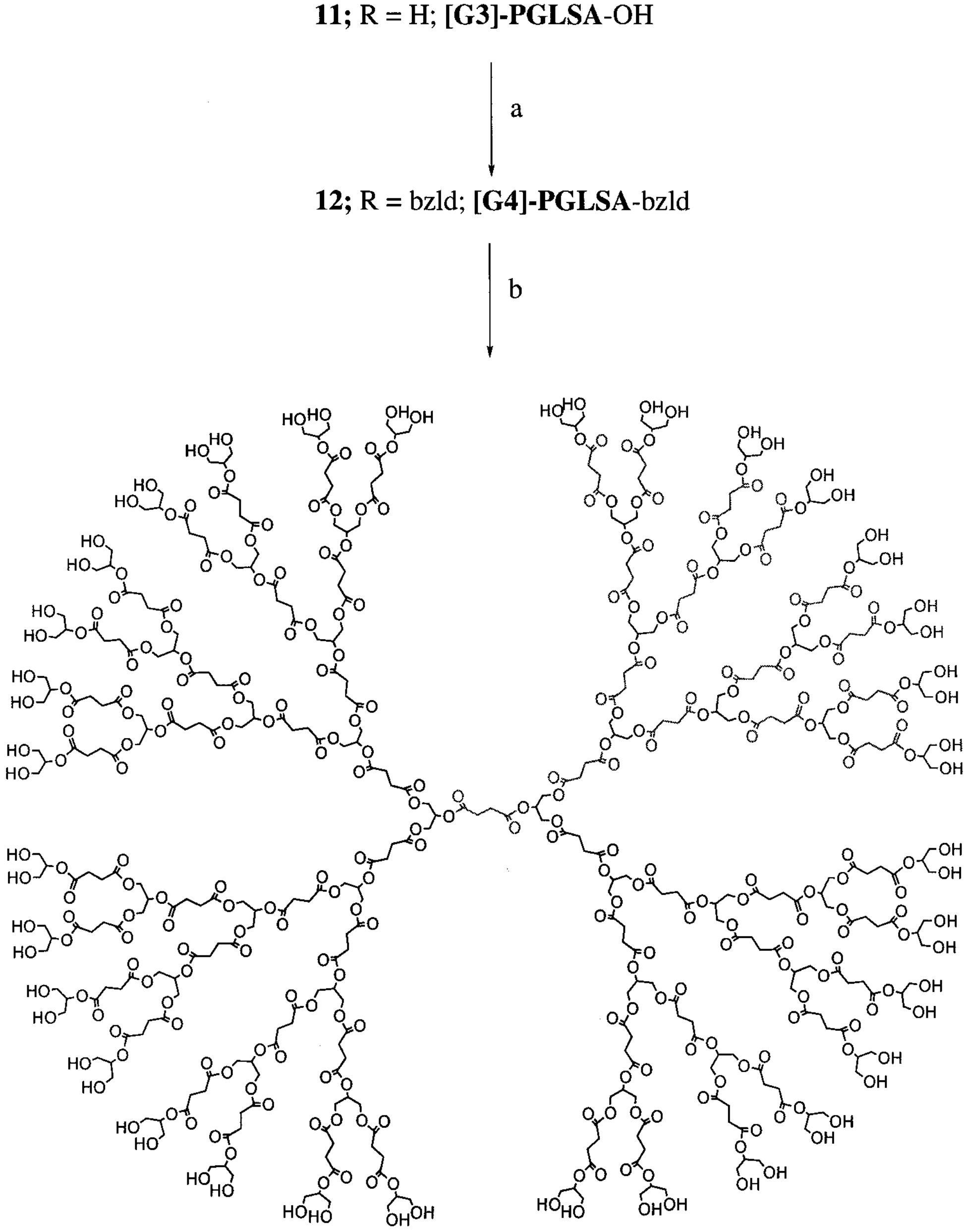


[a] Reagents and conditions: (a) succinic acid, DPTS, DCC, CH_2Cl_2, 25 °C, 14 h, 90% yield; (b) 50 psi H_2, Pd/C, THF, 25 °C, 10 h, 97% yield; (c) succinic anhydride, pyridine, 25 °C, 18 h, 95% yield; (d) DPTS, DCC, THF, 25 °C, 14 h, 97% yield; (e) 50 psi of H_2, Pd/C, THF, 25 °C, 10 h, 94% yield; (f) **4**, DPTS, DCC, THF, 25 °C, 14 h, 94% yield; (g) 50 psi of H_2, Pd/C, THF, 25 °C, 10 h, 95% yield; (h) succinic acid monomethallyl ester (SAME), DPTS, DCC, THF, 25 °C, 15 h, 68% yield; (i) **4**, DPTS, DCC, THF, 25 °C, 14 h, 90% yield; (j) 50 psi of H_2, Pd/C, THF:MeOH (9:1), 25 °C, 10 h, 95% yield.

yield). Hydrogenolysis in THF/methanol yielded the G3 dendrimer **[G3]-PGLSA**-OH, **11** (95% yield). The **[G4]-PGLSA**-bzld, **12**, and **[G4]-PGLSA**-OH, **13**, dendrimers were prepared in an analogous stepwise procedure, whereby **4** was coupled to **11** (73% yield) followed by hydrogenolysis (93% yield).

The esterification and deprotection reactions are monitored by NMR spectroscopy since the relative integrated areas of the aromatic, glycerol, and succinic acid protons change with each successive generation. FTIR spectroscopy confirms the presence of free hydroxyls by the strong O−H stretch at ~3400 cm^{-1} (Figure 1). Molecular weight data determined by FAB/MALDI-TOF and size exclusion chromatography (SEC) for the protected (bzld) and deprotected **[Gn]-PGLSA** dendrimers are summarized in Table 1. The molecular weights of the dendrimer increase with each generation, and the mass spectrometry data agree with the calculated molecular weights. Narrow polydispersity indices (PDIs) are measured for the G1 to G4 dendrimers. The

Scheme 2. Divergent Synthesis of G4 Dendrimers Composed of Glycerol and Succinic Acid[a]



11; R = H; **[G3]-PGLSA**-OH

12; R = bzld; **[G4]-PGLSA**-bzld

13; [G4]-PGLSA-OH

[a] Reagents and conditions: (a) **4**, DPTS, DCC, THF:DMF (10:1), 25 °C, 14 h, 73% yield; (b) 50 psi of H_2, Pd/C, THF:MeOH (9:1), 25 °C, 10 h, 93% yield.

SEC determined molecular weight deviates from the mass spectrometry data as the generation number increases, consistent with the dendrimers adopting a more globular structure. The glass transition (T_g) temperature data for the protected and deprotected **[Gn]-PGLSA** dendrimers, determined by modulated differential scanning calorimetry (MDSC), are reported in Table 2. The T_g of the **PGLSA**-OH dendrimers increases from −20 to −14 °C as the generation number increases from G1 to G4. The protected **PGLSA** dendrimers are amorphous solids at room temperature, whereas the deprotected **PGLSA** dendrimers are viscous liquids. The protected **PGLSA** dendrimers are soluble in halogenated solvents, aromatic solvents, THF, and ethyl acetate. The deprotected **PGLSA** dendrimers are soluble in dimethylformamide, ethanol, methanol, and water.

Derivatization of the **[G2]-PGLSA**-OH with a functional group such as an olefin affords a polymer that can be subsequently photocross-linked (**[G2]-PGLSA-SAME**, **9**, SAME = succinic acid monomethallyl ester; Scheme 1). Three-dimensional cross-linked dendrimer gels are produced by ultraviolet irradiation ($\lambda_{max} = 375$ nm) of a 10% w/v solution of **[G2]-PGLSA-SAME** in CH_2Cl_2 containing 2,2-dimethoxy-2-phenylacetophenone as the photoinitiator. The photocross-linked dendrimer gels are optically transparent, pliable, soft, and adhesive to the touch. Contact angle experiments on dendrimer gels reveal a hydrophobic surface with a contact angle of 79 ± 2°. Atomic force microscopy (AFM) shows the film to be smooth and uniform with no appreciable defects observed at high magnification (50 nm resolution). The rms average of height deviation is ap-

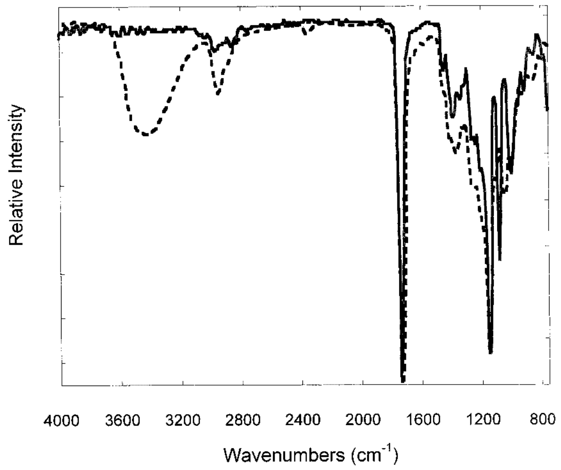


Figure 1. FTIR traces of **[G4]-PGLSA**-bzld (solid line) and **[G4]-PGLSA**-OH (dashed line).

Table 1. FAB/MALDI-TOF MS and SEC Data for Dendrimers[a]

no.	dendrimer	calcd MW	FAB/MALDI MW (MH$^+$)	SEC M_n	PDI
5	**[G1]-PGLSA**-bzld	1315.3	1315.6	1450	1.01
6	**[G1]-PGLSA**-OH	962.9	963.2	1500	1.01
7	**[G2]-PGLSA**-bzld	3060.9	3060.7	2990	1.01
8	**[G2]-PGLSA**-OH	2356.1	2357.3	3000	1.02
9	**[G2]-PGLSA**-SAME	4838.7	4840.9	5230	1.02
10	**[G3]-PGLSA**-bzld	6552.2	6553.4	5480	1.01
11	**[G3]-PGLSA**-OH	5142.5	5144.8	5370	1.01
12	**[G4]-PGLSA**-bzld	13534.7	13536.8	8900	1.01
13	**[G4]-PGLSA**-OH	10715.3	10715.6	8720	1.01

[a] SEC molecular weights relative to polystyrene standards.

Table 2. Glass Transition (T_g) Data for Dendrimers

	T_g (°C)	
dendrimer	bzld	OH
[G1]-PGLSA	37.7	−20.2
[G2]-PGLSA	45.9	−17.4
[G3]-PGLSA	47.1	−15.5
[G4]-PGLSA	47.2	−13.5

proximately 1.5 nm. This cross-linkable dendrimer is also amenable to standard photolithography processing methods, as demonstrated by preparation of a 100 μm line pattern as shown in Figure 2.

Conclusion

In summary, aliphatic polyester dendrimers composed of glycerol and succinic acid are synthesized in high yield using a divergent approach. These new biodendrimers expand the current repertoire of polymers available for medical studies that includes poly(ether glycol)s, poly(hydroxy acid)s, and polysaccharides. Importantly, dendrimers offer advantages over their linear polymer analogues such as possessing a single molecular weight with well-defined interior and exterior regions and displaying a large number of functional groups to the surroundings. The photocross-linkable dendrimers are of interest since complex patterns and structures may be formed using photolithography or multiphoton techniques. The flexibility of this synthetic approach combined with the selection of the appropriate biocompatible building blocks and functional peripheral groups is likely to facilitate the design and development of tailored biodendrimers for specific medical and biotechnological uses ranging from drug delivery vehicles to tissue engineering scaffolds.

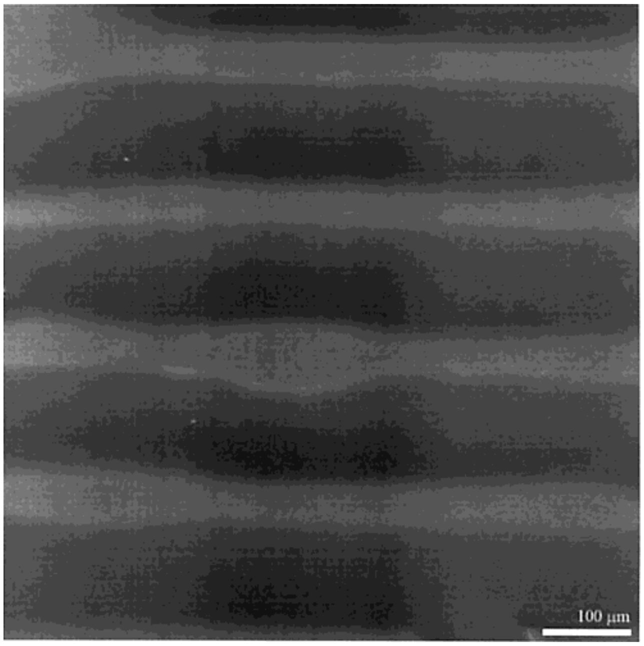


Figure 2. Scanning electron micrograph of 100 μm dendrimer-gel lines prepared using a photolithography technique.

Experimental Section

General Procedures. All solvents were dried and freshly distilled prior to use (CH_2Cl_2 with CaH; THF with Na; pyridine with CaH). All chemicals were purchased from Aldrich or Acros as highest purity grade and used without further purification (succinic acid, 99%; succinic anhydride, 99%; DCC, 99%). *cis*-1,3-*O*-Benzylideneglycerol was either purchased from Aldrich or prepared according to the literature.[83] All reactions were performed under nitrogen atmosphere. NMR spectra were recorded on a Varian INOVA spectrometer (for ^{1}H and ^{13}C at 400 and 100.6 MHz, respectively) or a GE QE-300 spectrometer (for HETCOR with APT). 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 DSC 2920 modulated DSC was used to collect T_g data (2 °C/min, ± 1 °C/40 s). Contact angle measurements were taken on a Ramé-Hart goniometer using 2 μL of H_2O. SEM images were obtained from a Philips 501 SEM. AFM images were obtained from a Digital Instruments Bioscope with a Nanoscope IIIa controller. Images were taken in TappingMode. DCC = dicyclohexylcarbodiimide, DPTS = 4-(dimethylamino)pyridinium 4-toluenesulfate, DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran, DCU = 1,3-dicyclohexylurea, EtOAc = ethyl acetate, Pd/C = 10% palladium on activated carbon, DMPA = 2,2-dimethoxy-2-phenylacetophenone, and VP = 1-vinyl-2-pyrrolidinone.

Synthesis of [G0]-PGLSA-bzld (2): Succinic acid (1.57 g, 13.3 mmol), *cis*-1,3-*O*-benzylideneglycerol (5.05 g, 28.0 mmol), and DPTS (4.07 g, 13.8 mmol) were dissolved in CH_2Cl_2 (60 mL). The reaction flask was flushed with nitrogen, and then DCC (8.19 g, 39.7 mmol) was added. Stirring at room temperature was continued for 14 h under a nitrogen atmosphere.

Upon reaction completion, the DCC−urea was filtered and washed with a small amount of $\mathrm{CH_2Cl_2}$ (20 mL). The crude product was purified by silica gel chromatography, eluting with 3:97 methanol:$\mathrm{CH_2Cl_2}$. The product was dissolved in $\mathrm{CH_2Cl_2}$, filtered (to remove any DCU), and precipitated in ethyl ether at −20 °C to remove the remaining DCC. Following vacuum filtration, 5.28 g of a white solid was collected (90% yield). ^{1}H NMR ($\mathrm{CDCl_3}$): δ 2.78 (s, 4, $-\mathrm{C}H_2-\mathrm{C}H_2-$), 4.08 (m, 4, $-\mathrm{C}H_2-\mathrm{CH}-\mathrm{C}H_2-$), 4.23 (m, 4, $-\mathrm{C}H_2-\mathrm{CH}-\mathrm{C}H_2-$), 4.69 (m, 2, $-\mathrm{CH_2}-\mathrm{C}H\text{-}\mathrm{CH_2}-$, $J = 1.54$ Hz, 1.71 Hz), 5.50 (s, 2, $\mathrm{C}H$), 7.34 (m, 6, arom $\mathrm{C}H$), 7.48 (m, 4, arom $\mathrm{C}H$). ^{13}C NMR ($\mathrm{CDCl_3}$): δ 172.32 ($C\mathrm{OOR}$), 138.03 ($C\mathrm{H}$), 129.23 ($C\mathrm{H}$), 128.48 ($C\mathrm{H}$), 126.24 ($C\mathrm{H}$), 101.33 ($C\mathrm{H}$), 69.16 ($C\mathrm{H_2}$), 66.50 ($C\mathrm{H}$), 29.57 ($C\mathrm{H_2}$). FTIR: ν ($\mathrm{cm^{-1}}$) 2992 (aliph C−H stretch), 1727 (C═O). GC-MS: 443 m/z ($\mathrm{MH^+}$) (theory: 442 m/z ($\mathrm{M^+}$)). HR FAB: 442.1635 m/z ($\mathrm{M^+}$) (theory: 442.1628 m/z ($\mathrm{M^+}$)). Elemental analysis: C, 65.25%; H, 5.85% (theory: C, 65.15%; H, 5.92%).

Synthesis of [G0]-PGLSA-OH (**3**): Pd/C (10% w/w) was added to a solution of benzylidene protected [G0]-PGLSA (2.04 g, 4.61 mmol) in THF (30 mL). The flask for catalytic hydrogenolysis was evacuated and filled with 50 psi of $\mathrm{H_2}$ before shaking for 10 h. The catalyst was filtered and washed with THF (20 mL). The filtrate was evaporated to give 1.18 g of a clear viscous oil (97% yield). ^{1}H NMR ($\mathrm{CD_3OD}$): δ 2.67 (s, 4, $-\mathrm{C}H_2-\mathrm{C}H_2-$), 3.64 (m, 8, $-\mathrm{C}H_2-\mathrm{CH}-\mathrm{C}H_2-$), 4.87 (m, 2, $-\mathrm{CH_2}-\mathrm{C}H-\mathrm{CH_2}-$). ^{13}C NMR ($\mathrm{CD_3OD}$): δ 172.77 ($C\mathrm{OOR}$), 75.84 ($C\mathrm{H_2}$), 60.41 ($C\mathrm{H}$), 28.96 ($C\mathrm{H_2}$). FTIR: ν ($\mathrm{cm^{-1}}$) 3299 (OH), 1728 (C═O). GC-MS 284 m/z ($\mathrm{M + NH_4^+}$) (theory: 266 m/z ($\mathrm{M^+}$)). Elemental analysis: C, 44.94%; H, 6.87% (theory: C, 45.11%; H, 6.81%).

Synthesis of 2-(*cis*-1,3-*O*-Benzylidene glycerol)succinic Acid Monoester (**4**): *cis*-1,3-*O*-Benzylideneglycerol (9.90 g, 54.9 mmol) was dissolved in pyridine (100 mL) followed by the addition of succinic anhydride (8.35 g, 83.4 mmol). The reaction mixture was stirred at room temperature for 18 h before the pyridine was removed under vacuum at 40 °C. The remaining solid was dissolved in $\mathrm{CH_2Cl_2}$ (100 mL) and washed three times with cold 0.2 N HCl (100 mL) or until the aqueous phase remained at pH 1. The organic phase was evaporated, and the solid was dissolved in deionized water (300 mL). 1 N NaOH was added until pH 7 was obtained, and the product was dissolved in solution. The aqueous phase was extracted with $\mathrm{CH_2Cl_2}$ (200 mL) and then readjusted to pH 4. The aqueous phase was subsequently extracted twice with $\mathrm{CH_2Cl_2}$ (200 mL), dried with $\mathrm{Na_2SO_4}$, filtered, and evaporated. The solid was stirred in ethyl ether (50 mL) and cooled to −25 °C for 3 h before collecting 14.6 g of a white powder (95% yield). ^{1}H NMR ($\mathrm{CDCl_3}$): δ 2.68 (m, 4, $-\mathrm{C}H_2-\mathrm{C}H_2-$), 4.13 (m, 2, $-\mathrm{C}H_2-\mathrm{CH}-\mathrm{C}H_2-$), 4.33 (m, 2, $-\mathrm{C}H_2-\mathrm{CH}-\mathrm{C}H_2-$), 4.70 (m, 1, $-\mathrm{CH_2}-\mathrm{C}H\text{-}\mathrm{CH_2}-$), 5.51 (s, 1, $\mathrm{C}H$), 7.34 (m, 3, arom $\mathrm{C}H$), 7.47 (m, 2, arom $\mathrm{C}H$). ^{13}C NMR ($\mathrm{CDCl_3}$): δ 178.07 ($C\mathrm{OOH}$), 172.38 ($C\mathrm{OOR}$), 137.95 ($C\mathrm{H}$), 129.33 ($C\mathrm{H}$), 128.51 ($C\mathrm{H}$), 126.26 ($C\mathrm{H}$), 101.43 ($C\mathrm{H}$), 69.15 ($C\mathrm{H_2}$), 66.57 ($C\mathrm{H}$), 29.24 ($C\mathrm{H_2}$), 29.05 ($C\mathrm{H_2}$). FTIR: ν ($\mathrm{cm^{-1}}$) 2931 (aliph C−H stretch), 1713 (C═O). GC-MS: 281 m/z ($\mathrm{MH^+}$) (theory: 280 m/z ($\mathrm{M^+}$)). Elemental analysis: C, 60.07%; H, 5.80% (theory: C, 59.99%; H, 5.75%).

Synthesis of [G1]-PGLSA-bzld (**5**): 2-(*cis*-1,3-*O*-Benzylidene glycerol)succinic acid mono ester (6.33 g, 22.6 mmol), [G0]-PGLSA (1.07 g, 4.02 mmol), and DPTS (2.51 g, 8.53 mmol) were dissolved in THF (60 mL). The reaction flask was flushed with nitrogen, and then DCC (7.04 g, 34.1 mmol) was added. 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 (20 mL), and the solvent was evaporated. The crude product was purified by silica gel chromatography, eluting with 3:97 to 5:95 methanol:$\mathrm{CH_2Cl_2}$. The product was dissolved in $\mathrm{CH_2Cl_2}$, filtered (to remove any DCU), and precipitated in ethyl ether at −20 °C to remove remaining DCC. The ethyl ether was decanted, and the precipitate was isolated to yield 5.11 g of a white powder (97% yield). ^{1}H NMR ($\mathrm{CDCl_3}$): δ 2.58 (m, 4, $-\mathrm{C}H_2-\mathrm{C}H_2-$), 2.63 (m, 8, $-\mathrm{C}H_2-\mathrm{C}H_2-$), 2.71 (m, 8, $-\mathrm{C}H_2-\mathrm{C}H_2-$), 4.12 (m, 12, $-\mathrm{C}H_2-\mathrm{CH}-\mathrm{C}H_2-$), 4.23 (m, 12, $-\mathrm{C}H_2-\mathrm{CH}-\mathrm{C}H_2-$), 4.69 (m, 4, $-\mathrm{CH_2}-\mathrm{C}H-\mathrm{CH_2}-$), 5.20 (m, 2, $-\mathrm{CH_2}-\mathrm{C}H-\mathrm{CH_2}-$), 5.51 (m, 4, $\mathrm{C}H$), 7.33 (m, 12, arom $\mathrm{C}H$), 7.46 (m, 8, arom $\mathrm{C}H$). ^{13}C NMR ($\mathrm{CDCl_3}$): δ 172.28 ($C\mathrm{OOR}$), 171.91 ($C\mathrm{OOR}$), 171.53 ($C\mathrm{OOR}$), 138.03 ($C\mathrm{H}$), 129.26 ($C\mathrm{H}$), 128.48 ($C\mathrm{H}$), 126.22 ($C\mathrm{H}$), 101.32 ($C\mathrm{H}$), 69.50 ($C\mathrm{H}$), 69.16 ($C\mathrm{H_2}$), 66.54 ($C\mathrm{H}$), 62.49 ($C\mathrm{H_2}$), 29.36 ($C\mathrm{H_2}$), 29.03 ($C\mathrm{H_2}$). FTIR: ν ($\mathrm{cm^{-1}}$) 2858 (aliph C−H stretch), 1731 (C═O). FAB MS: 1315.6 m/z ($\mathrm{MH^+}$) (theory: 1315.3 m/z ($\mathrm{M^+}$)). Elemental analysis: C, 60.13%; H, 5.82% (theory: C, 60.27%; H, 5.67%). SEC M_w: 1460; M_n: 1450; PDI: 1.01.

Synthesis of [G1]-PGLSA-OH (**6**): Pd/C (10% w/w) was added to a solution of benzylidene protected [G1]-PGLSA (0.270 g, 0.230 mmol) in THF (20 mL). The flask for catalytic hydrogenolysis was evacuated and filled with 50 psi of $\mathrm{H_2}$ before shaking for 10 h. The catalyst was filtered and washed with THF (20 mL). The filtrate was evaporated to give 0.178 g of a colorless, viscous oil (94% yield). ^{1}H NMR ($\mathrm{CD_3OD}$): δ 2.63 (m, 20, $-\mathrm{C}H_2-\mathrm{C}H_2-$), 3.52 (m, 4, $-\mathrm{C}H_2-\mathrm{CH}-\mathrm{C}H_2-$), 3.64 (m, 8, $-\mathrm{C}H_2-\mathrm{CH}-\mathrm{C}H_2-$), 3.80 (m, 2, $-\mathrm{CH_2}-\mathrm{C}H-\mathrm{CH_2}-$), 4.05 (m, 2, $-\mathrm{C}H_2-\mathrm{CH}-\mathrm{C}H_2-$), 4.14 (m, 2, $-\mathrm{C}H_2-\mathrm{CH}-\mathrm{C}H_2-$), 4.21 (m, 4, $-\mathrm{C}H_2-\mathrm{CH}-\mathrm{C}H_2-$), 4.30 (m, 4, $-\mathrm{C}H_2-\mathrm{CH}-\mathrm{C}H_2-$), 4.85 (m, 2, $-\mathrm{CH_2}-\mathrm{C}H-\mathrm{CH_2}-$), 5.25 (m, 2, $-\mathrm{CH_2}-\mathrm{C}H-\mathrm{CH_2}-$). ^{13}C NMR ($\mathrm{CD_3OD}$): δ 172.82 ($C\mathrm{OOR}$), 172.58 ($C\mathrm{OOR}$), 172.48 ($C\mathrm{OOR}$), 172.08 ($C\mathrm{OOR}$), 75.82 ($C\mathrm{H}$), 69.90 ($C\mathrm{H}$), 69.68 ($C\mathrm{H}$), 65.66 ($C\mathrm{H_2}$), 62.85 ($C\mathrm{H_2}$), 62.30 ($C\mathrm{H_2}$), 60.43 ($C\mathrm{H_2}$), 28.83 ($C\mathrm{H_2}$), 28.61 ($C\mathrm{H_2}$). FTIR: ν ($\mathrm{cm^{-1}}$) 3405 (OH), 2943 (aliph C−H stretch), 1726 (C═O). FAB MS: 963.2 m/z ($\mathrm{MH^+}$) (theory: 962.9 m/z ($\mathrm{M^+}$)). Elemental analysis: C, 47.13%; H, 6.11% (theory: C, 47.40%; H, 6.07%). SEC M_w: 1510; M_n: 1500; PDI: 1.01.

Synthesis of [G2]-PGLSA-bzld (**7**): 2-(*cis*-1,3-*O*-Benzylidene glycerol)succinic acid mono ester (4.72 g, 16.84 mmol), [G1]-PGLSA (1.34 g, 1.39 mmol), and DPTS (1.77 g, 6.02 mmol) were dissolved in THF (50 mL). The reaction flask was flushed with nitrogen, and then DCC (4.62 g, 22.4 mmol) was added. 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 (20 mL), and the solvent was evaporated. The crude product was purified by silica gel chromatography, eluting with 3:97 to 5:95 methanol:$\mathrm{CH_2Cl_2}$. The product was dissolved in $\mathrm{CH_2Cl_2}$, filtered (to remove any DCU), and precipitated in ethyl ether at −20 °C to remove remaining DCC. The ethyl ether was decanted, and the precipitate was isolated to yield 4.00 g of a white powder (94% yield). ^{1}H NMR ($\mathrm{CDCl_3}$): δ 2.59 (broad m, 26, $-\mathrm{C}H_2-\mathrm{C}H_2-$), 2.69 (broad m, 52, $-\mathrm{C}H_2-\mathrm{C}H_2-$), 4.13 (m, 28, $-\mathrm{C}H_2-\mathrm{CH}-\mathrm{C}H_2-$), 4.13 (m, 28, $-\mathrm{C}H_2-\mathrm{CH}-\mathrm{C}H_2-$), 4.69 (m, 8, $-\mathrm{CH_2}-\mathrm{C}H-\mathrm{CH_2}-$), 5.22 (m, 6, $-\mathrm{CH_2}-\mathrm{C}H-\mathrm{CH_2}-$), 5.50 (s, 8, $\mathrm{C}H$), 7.32 (m, 24, arom. $\mathrm{C}H$), 7.47 (m, 16, arom $\mathrm{C}H$). ^{13}C NMR ($\mathrm{CDCl_3}$): δ 172.27 ($C\mathrm{OOR}$), 171.88 ($C\mathrm{OOR}$), 171.60 ($C\mathrm{OOR}$), 138.04 ($C\mathrm{H}$), 129.25 ($C\mathrm{H}$), 128.47 ($C\mathrm{H}$), 126.21 ($C\mathrm{H}$), 101.30 ($C\mathrm{H}$), 69.48 ($C\mathrm{H}$), 69.15 ($C\mathrm{H_2}$), 66.54 ($C\mathrm{H}$), 62.57 ($C\mathrm{H_2}$), 29.35 ($C\mathrm{H_2}$), 29.18 ($C\mathrm{H_2}$) 29.03 ($C\mathrm{H_2}$), 28.84 ($C\mathrm{H_2}$). FTIR: ν ($\mathrm{cm^{-1}}$) 2969 (aliph C−H stretch), 1733 (C═O). FAB MS: 3060.7 m/z ($\mathrm{MH^+}$) (theory: 3060.9 m/z ($\mathrm{M^+}$)). Elemental analysis: C, 59.20%; H, 5.64% (theory: C, 58.86%; H, 5.60%). SEC M_w: 3030; M_n: 2990; PDI: 1.01.

Synthesis of [G2]-PGLSA-OH (**8**): Pd/C (10% w/w) was added to a solution of benzylidene protected [G2]-PGLSA (2.04 g, 0.667 mmol) in THF (20 mL). The flask for catalytic hydrogenolysis was evacuated and filled with 50 psi of $\mathrm{H_2}$ before shaking for 10 h. The catalyst was filtered and washed with THF (20 mL). The filtrate was evaporated to give 1.49 g of a colorless, viscous oil (95% yield). ^{1}H NMR ($\mathrm{CD_3OD}$): δ 2.64 (m, 52, $-\mathrm{C}H_2-\mathrm{C}H_2-$), 3.53 (m, 16, $-\mathrm{C}H_2-\mathrm{CH}-\mathrm{C}H_2-$), 3.64 (m, 4, $-\mathrm{C}H_2-\mathrm{CH}-\mathrm{C}H_2-$), 3.80 (m, 8, $-\mathrm{CH_2}-\mathrm{C}H-\mathrm{CH_2}-$), 4.06 (m, 8, $-\mathrm{C}H_2-\mathrm{CH}-\mathrm{C}H_2-$), 4.14 (m, 6, $-\mathrm{C}H_2-\mathrm{CH}-\mathrm{C}H_2-$), 4.21 (m, 11, $-\mathrm{C}H_2-\mathrm{CH}-\mathrm{C}H_2-$), 4.30 (m, 11, $-\mathrm{C}H_2-\mathrm{CH}-\mathrm{C}H_2-$), 5.25 (m, 6, $-\mathrm{CH_2}-\mathrm{C}H-\mathrm{CH_2}-$). ^{13}C NMR ($\mathrm{CD_3OD}$): δ 172.83 ($C\mathrm{OOR}$), 172.59 ($C\mathrm{OOR}$), 172.49 ($C\mathrm{OOR}$), 69.91 ($C\mathrm{H}$), 69.69 ($C\mathrm{H}$), 65.68 ($C\mathrm{H_2}$), 62.88 ($C\mathrm{H_2}$), 62.37 ($C\mathrm{H_2}$), 28.61 ($C\mathrm{H_2}$). FTIR: ν ($\mathrm{cm^{-1}}$) 3429 (OH), 2952 (aliph C−H stretch), 1728 (C═O). MALDI MS: 2357.3 m/z ($\mathrm{MH^+}$) (theory: 2356.1 m/z ($\mathrm{M^+}$)). Elemental analysis: C, 48.32%; H, 5.97% (theory: C, 47.92%; H, 5.90%). SEC M_w: 3060; M_n: 3000; PDI: 1.02.

Synthesis of Succinic Acid Monomethallyl Ester (SAME). 2-Methyl-2-propen-1-ol (4.90 mL, 58.2 mmol) was dissolved in pyridine (20 mL) followed by the addition of succinic anhydride (7.15 g, 71.4 mmol). The reaction mixture was stirred at room temperature for 15 h before the pyridine was removed under vacuum at 30 °C. The remaining liquid was dissolved in CH_2Cl_2 (100 mL) and washed two times with cold 0.2 N HCl (100 mL). The organic phase was dried with Na_2SO_4, gravity filtered, and evaporated to give 9.25 g of a clear liquid (92% yield). ^{1}H NMR ($CDCl_3$): δ 1.70 (s, 3, CH_3), 2.64 (m, 4, $-CH_2-CH_2-$), 4.48 (s, 2, $-CH_2-$), 4.88 (m, 1, vinyl CH_2), 4.93 (m, 1, vinyl CH_2). ^{13}C NMR ($CDCl_3$): δ 178.58 (COOH), 172.05 (COOR), 139.88 (CH), 113.31 (CH_2), 68.31 (CH_2), 29.11 (CH_2), 28.99 (CH_2), 19.59 (CH_3). FTIR: ν (cm^{-1}) 2939 (aliph C−H stretch), 1711 (C═O). GC-MS 173 m/z (MH$^+$) (theory: 172 m/z (M$^+$)). Elemental analysis: C, 55.51%; H, 7.09% (theory: C, 55.81%; H, 7.02%).

Synthesis of [G2]-PGLSA-SAME (9): Succinic acid monomethallyl ester (0.826 g, 4.80 mmol), [G2]-PGLSA (0.401 g, 0.170 mmol), and DPTS (0.712 g, 2.42 mmol) were dissolved in THF (50 mL). The reaction flask was flushed with nitrogen, and then DCC (1.52 g, 7.37 mmol) was added. Stirring at room temperature was continued for 14 h under nitrogen atmosphere. Upon completion, the DCC−urea was filtered and washed with a small amount of CH_2Cl_2 (20 mL), and the solvent was evaporated. The crude product was purified by silica gel chromatography, eluting with 3:97 to 5:95 methanol: CH_2Cl_2. The product was dissolved in CH_2Cl_2, filtered (to remove any DCU), and precipitated in ethyl ether at −20 °C to remove remaining DCC. The ethyl ether was decanted, and the precipitate was isolated to yield 0.558 g of a clear colorless oil (68.2% yield). ^{1}H NMR ($CDCl_3$): δ 1.72 (s, 48, CH_3), 2.63 (m, 116, $-CH_2-CH_2-$), 4.16 (m, 23, $-CH_2-CH-CH_2-$), 4.27 (m, 23, $-CH_2-CH-CH_2-$), 4.48 (s, 32, $-CH_2-$), 4.89 (s, 16, vinyl CH_2), 4.94 (s, 16, vinyl CH_2), 5.24 (m, 14, $-CH_2-CH-CH_2-$). ^{13}C NMR ($CDCl_3$): δ 171.91 (COOR), 171.67 (COOR), 139.98 (CH), 113.22 (CH_2), 69.43 (CH), 68.31 (CH_2), 62.56 (CH_2), 29.10 (CH_2), 29.02 (CH_2) 28.83 (CH_2), 19.66 (CH_3). FTIR: ν (cm^{-1}) 2969 (aliph C−H stretch), 1734 (C═O). MALDI MS: 4840.9 m/z (MH$^+$) (theory: 4838.7 m/z (M$^+$)). Elemental analysis: C, 55.37%; H, 6.22% (theory: C, 55.35%; H, 6.29%). SEC M_w: 5310; M_n: 5230; PDI: 1.02.

Synthesis of [G3]-PGLSA-bzld (10): 2-(*cis*-1,3-*O*-Benzylidene glycerol)succinic acid mono ester (2.77 g, 9.89 mmol), [G2]-PGLSA (1.00 g, 0.425 mmol), and DPTS (1.30 g, 4.42 mmol) were dissolved in THF (40 mL). The reaction flask was flushed with nitrogen, and then DCC (2.67 g, 12.9 mmol) was added. 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 (20 mL), and the solvent was evaporated. The crude product was purified by silica gel chromatography, eluting with 3:97 to 5:95 methanol:CH_2Cl_2. The product was dissolved in CH_2Cl_2, filtered (to remove any DCU), and precipitated in ethyl ether at −20 °C to remove remaining DCC. The ethyl ether was decanted, and the precipitate was isolated to yield 3.51 g of a white powder (90% yield). ^{1}H NMR ($CDCl_3$): δ 2.57−2.72 (broad m, 116, $-CH_2-CH_2-$), 4.12 (m, 60, $-CH_2-CH-CH_2-$), 4.23 (m, 60, $-CH_2-CH-CH_2-$), 4.68 (m, 16, $-CH_2-CH-CH_2-$), 5.22 (m, 14, $-CH_2-CH-CH_2-$), 5.49 (s, 16, CH), 7.33 (m, 48, arom CH), 7.46 (m, 32, arom CH). ^{13}C NMR ($CDCl_3$): δ 172.31 (COOR), 171.97 (COOR), 171.65 (COOR), 138.01 (CH), 129.28 (CH), 128.49 (CH), 126.21 (CH), 101.28 (CH), 69.45 (CH), 69.16 (CH_2), 66.53 (CH), 62.59 (CH_2), 29.32 (CH_2), 29.16 (CH_2) 29.01 (CH_2), 28.81 (CH_2). FTIR: ν (cm^{-1}) 2984 (aliph C−H stretch), 1733 (C═O). MALDI MS: 6553.4 m/z (MH$^+$) (theory: 6552.2 m/z (M$^+$)). Elemental analysis: C, 58.50%; H, 5.66% (theory: C, 58.29%; H, 5.57%). SEC M_w: 5550; M_n: 5480; PDI: 1.01.

Synthesis of [G3]-PGLSA-OH (11): Pd/C (10% w/w) was added to a solution of benzylidene protected [G3]-PGLSA (1.23 g, 0.188 mmol) in 9:1 THF/MeOH (20 mL). The flask for catalytic hydrogenolysis was evacuated and filled with 50 psi of H_2 before shaking for 10 h. The catalyst was filtered and washed with 9:1 THF/MeOH (20 mL). The filtrate was evaporated to give 0.923 g of a colorless, viscous oil (95% yield). ^{1}H NMR (CD_3OD): δ 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, $-CH_2-CH\text{-}CH_2-$), 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 (m, 14, $-CH_2-CH-CH_2$). ^{13}C NMR (CD_3OD): δ 172.86 (COOR), 69.91 (CH), 67.64 (CH), 65.67 (CH_2), 62.87 (CH_2), 62.41 (CH_2), 28.61 (CH_2). FTIR: ν (cm^{-1}) 3442 (OH), 2959 (aliph C−H stretch), 1731 (C═O). MALDI MS: 5144.8 m/z (MH$^+$) (theory: 5142.5 m/z (M$^+$)). Elemental analysis: C, 48.07%; H, 5.84% (theory: C, 48.11%; H, 5.84%). SEC M_w: 5440; M_n: 5370; PDI: 1.01.

Synthesis of [G4]-PGLSA-bzld (12): 2-(*cis*-1,3-*O*-Benzylidene glycerol)succinic acid mono ester (2.43 g, 8.67 mmol), [G3]-PGLSA (0.787 g, 0.153 mmol), and DPTS (1.30 g, 4.42 mmol) were dissolved in 10:1 THF/DMF (40 mL). The reaction flask was flushed with nitrogen, and then DCC (2.63 g, 12.7 mmol) was added. The reaction was stirred at room temperature for 14 h under nitrogen atmosphere. Upon completion, solvents were removed under vacuum, and the remaining solids were redissolved CH_2Cl_2. The DCC−urea was filtered and washed with a small amount of CH_2Cl_2 (20 mL), and the solvent was evaporated. The crude product was purified by silica gel chromatography, eluting with 3:97 to 5:95 methanol: CH_2Cl_2. The product was dissolved in CH_2Cl_2, filtered (to remove any DCU), and precipitated in ethyl ether at −20 °C to remove remaining DCC. The ethyl ether was decanted, and the precipitate was isolated to yield 1.50 g of a white powder (73% yield). ^{1}H NMR ($CDCl_3$): δ 2.63 (m, 70, $-CH_2-CH_2-$), 2.72 (m, 146, $-CH_2-CH_2-$), 2.90 (m, 32, $-CH_2-CH_2-$), 4.14 (m, 100, $-CH_2-CH-CH_2-$), 4.25 (m, 100, $-CH_2-CH-CH_2-$), 4.70 (m, 32, $-CH_2-CH-CH_2-$), 5.25 (m, 16, $-CH_2-CH-CH_2-$), 5.52 (s, 32, CH), 7.33 (m, 96, arom. CH), 7.47 (m, 64, arom. CH). ^{13}C NMR ($CDCl_3$): δ 172.27 (COOR), 171.90 (COOR), 171.57 (COOR), 138.08 (CH), 129.25 (CH), 128.47 (CH), 126.23 (CH), 101.27 (CH), 69.49 (CH), 69.13 (CH_2), 66.54 (CH), 62.45 (CH_2), 29.34 (CH_2), 29.02 (CH_2), 28.83 (CH_2). FTIR: ν (cm^{-1}) 2978 (aliph C−H stretch), 1733 (C═O). MALDI MS: 13536.8 m/z (MH$^+$) (theory: 13 534.7 m/z (M$^+$)). Elemental analysis: C, 58.20%; H, 5.56% (theory: C, 58.04%; H, 5.56%). SEC M_w: 9000; M_n: 8900; PDI: 1.01.

Synthesis of [G4]-PGLSA-OH (13): Pd/C (10% w/w) was added to a solution of benzylidene protected [G4]-PGLSA (0.477 g, 0.0352 mmol) in 9:1 THF/MeOH (20 mL). The flask for catalytic hydrogenolysis was evacuated and filled with 50 psi of H_2 before shaking for 10 h. The catalyst was filtered and washed with 9:1 THF/MeOH (20 mL). The filtrate was evaporated to give 0.351 g of a colorless, viscous oil (93% yield). ^{1}H NMR (CD_3OD): δ 2.65 (m, 244, $-CH_2-CH_2-$), 3.53 (m, 50, $-CH_2-CH-CH_2$), 3.65 (m, 22, $-CH_2-CH-CH_2-$), 3.81 (m, 28, $-CH_2-CH-CH_2-$), 4.05 (m, 32, $-CH_2-CH-CH_2-$), 4.14 (m, 32, $-CH_2-CH-CH_2-$), 4.24 (m, 60, $-CH_2-CH-CH_2-$), 4.30 (m, 60, $-CH_2-CH-CH_2-$), 5.26 (m, 32, $-CH_2-CH-CH_2-$). ^{13}C NMR (CD_3OD): δ 172.94 (COOR), 69.92 (CH), 65.72 (CH_2), 62.91 (CH_2), 28.67 (CH_2). FTIR: ν (cm^{-1}) 3444 (OH), 2931 (aliph C−H stretch), 1729 (C═O). MALDI MS: 10715.6 m/z (MH$^+$) (theory: 10715.3 m/z (M$^+$)). Elemental analysis: C, 48.50%; H, 5.83% (theory: C, 48.20%; H, 5.81%). SEC M_w: 8800; M_n: 8720; PDI: 1.01.

Polymerization of [G2]-PGLSA-SAME: Gels were prepared by dissolving [G2]-PGLSA-SAME and DMPA (0.1% w/w) in CH_2Cl_2 to make 10% w/w solutions. One drop of solution was applied from a pipet tip onto a fresh mica surface and immediately exposed to UV light from a UVP BLAK-RAY long wave ultraviolet lamp for 15 min. The surface was washed with 1.0 mL of hexane and allowed to dry overnight.

Photomask Polymerization of [G2]-PGLSA-SAME. Gels were prepared by dissolving [G2]-PGLSA-SAME, DMPA, and VP (1000:10:1, respectively) in CH_2Cl_2, and the solution was concentrated. Next, a small amount of the polymer (with initiator and accelerator) was dissolved in a minimal amount of CH_2Cl_2 to allow spin-coating of a glass coverslip. A photomask was placed on top of this coverslip and exposed to UV light from a UVP BLAK-RAY long wave ultraviolet lamp for

15 min. The surface was washed with 1.0 mL of hexane and allowed to air-dry overnight.

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