Synthesis of Discrete Mass Poly(butylene glutarate) Oligomers

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ABSTRACT: A series of discrete mass oligomers of the perfectly alternating copolymer poly(butylene glutarate) containing 2, 4, 8, 16, 32, and 64 structural units have been synthesized from glutaric anhydride and butanediol using an iterative divergent−convergent strategy. These materials were designed to serve as models for more complex polymer distributions. Orthogonal protection of difunctional starting material using 9-fluorenylmethoxycarbonyl chloride and *p*-methoxybenyl alcohol allowed control of chain growth during coupling with 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride and (*N*,*N*-dimethylamino)pyridine. Condensation products were monofunctionalized by removal of one protecting group using mild acidic or basic conditions that preserved the orthogonal protecting group. The fully unprotected target products were isolated in highly pure form and, with the exception of the 64-mer, in high yield (>70%). The synthetic oligomers were characterized using ^{1}H NMR, HPLC, GPC, EI-MS, CI-MS, LSI-MS, and MALDI-TOF-MS to confirm structure, molecular weight, and purity.

Introduction

Synthetic polymers of precisely defined degree of polymerization and structure may be utilized as models for their higher molecular weight, less well-defined polymeric homologues and have revealed important information related to the physical,[1] electronic,[2] and optical properties[3] of these materials. Although synthesis of uniform polymeric materials has been a target for over 35 years, the major synthetic obstacle is the isolation of the product in a pure form. Earlier efforts have focused on fractionation of oligomers produced by standard polymerization reactions with shortened reaction times and lower reaction temperatures to decrease molecular weight. Alternatively, discrete oligomers have been generated by degradation of polymers with higher degrees of polymerization. However, the yields were often very low and the preparative fractionations were inadequate for the isolation of pure products.[4]

Recent synthetic strategies have been focused on stepwise approaches. Most simply, a monofunctional monomer is added to a growing chain of the monomer, the product is purified, and the chain end refunctionalized for the addition of the next unit. An analogous approach is the addition of an oligomeric segment of a known degree of polymerization followed by purification and refunctionalization as above. Again, purification of the product in the presence of polymeric homologues can be problematic. Stepwise synthesis has been applied to the production of pure oligopeptides[5] and has yielded compounds containing up to 175 chain atoms.[6] Pure oligomers of polyurethanes,[7−10] poly(ethylene glycol),[11−13] and biodegradable oligo(ester amides)[14] have also been prepared in a similar manner. Linear oligomers of poly(hydroxy butyrate) (P(3-HB)) containing up to 96 3-HB units have been produced using an exponential segment-coupling strategy.[15]

The above synthesis technique can be enhanced by using insoluble polymeric supports, similar to those introduced by Merrifield,[16] to covalently anchor growing chains during synthesis. These supports allow addition of large excesses of monomer and coupling reagents to drive the desired process to near completion, thus increasing reaction efficiencies and providing higher yields. Excess reactants and byproducts can be conveniently removed by simple filtration and washing with appropriate solvents between steps. The product is isolated by selected cleavage of the support−polymer bond.

Similar synthesis can be performed on soluble supports such a poly(ethylene glycol) (PEG).[17,18] The utilization of homogeneous solution phase chemistry ensures accessibility of reactants to activated sites. Linear PEG distributions with $M_n \geq 5000$ amu have favorable physicochemical properties that allow separation of supported products from compounds not covalently bound to active chain ends. Soluble supports have been applied to the assembly of dendrimers of uniform purity.[19] However, improvements in reaction efficiencies and yields using supports, whether soluble or insoluble, are offset in long synthetic sequences by a decrease in the purity of the final product(s). These impurities stem from incomplete reactions, resulting in deletion of chain segments and formation of structurally similar compounds that are difficult to separate from the target product.

An increasingly important approach to providing control of macromolecular architecture is to utilize biological systems for the preparation of high-performance polymers.[20] The design, synthesis, and expression of an artificial gene encoding a poly(α,L-glutamic acid) (PLGA) derivative has been shown to produce materials having very low polydispersity indexes.[21] Biosynthesis of monodispersed derivatives of poly(γ-benzyl α,L-glutamate) has provided products that demonstrate smectic ordering in solutions and in films. The results of this study suggest that methods of preparing monodispersed polymers having these types of structures may provide access to new smectic phases having layer spacing that may be precisely controlled on the scale of tens of nanometers.[22]

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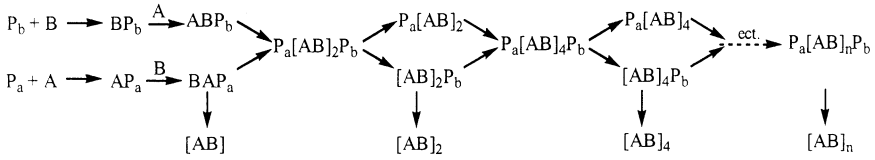
Scheme 1. Iterative Divergent−Convergent Synthesis of Butylene Glutarate Oligomers[a]



[a] P_a and P_b refer to the protecting groups on A and B, respectively.

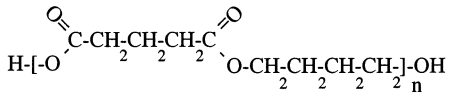
A practicable approach, based on an iterative divergent−convergent strategy, has been applied to the synthesis of long-chain linear aliphatic hydrocarbons.[23,24] Using this approach, the starting material, monomer M, with nonfunctional end groups X and Y, is divided into two portions. In one portion, the end group X is activated to form X′, and similarly, in the second fraction, Y is converted to activated Y′. The two functionalized fractions are then covalently linked to form XMMY with a loss of X′Y′. After purification of XMMY, the process can be repeated, resulting in "molecular doubling" of the X[M]$_n$Y chain. Purification is simplified since remaining reactant molecules are half the size of the product chains.

The above strategy has been applied to the synthesis of phenyl−alkyne oligomers[25−27] and oligo(thiophene−ethynylene)[2,27,28]—materials that may serve as molecular-scale electronic devices or molecular wires. The approach has also been used to isolate single linear oligomers of nylon-6, which were subsequently studied using time-of-flight secondary ion (TOF-SIMS),[29] electrospray ionization (ESI), matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF),[30] and MALDI collision-induced dissociation (CID) mass spectrometry.[31]

The purpose of this work was the synthesis of discrete mass oligomers of the perfectly alternating copolymer poly(butylene glutarate) using an iterative divergent−convergent synthetic strategy. These oligomers have application as standard reference materials for the mass calibration of analytical techniques such as mass spectrometry and gel permeation chromatography (GPC), which are commonly utilized to determine molecular weight averages of polymers. These materials may also serve as models of more complex distributions, thus simplifying the study of ion production, transmission, and detection efficiencies as well as fragmentation processes in mass spectrometry. Model oligomers of accurately known molecular weight provide the ability to study possible reasons for discrepancies[32] in polymer molecular weights averages obtained using various techniques.

Results and Discussion

Synthetic Strategy. The target products of this synthesis were discrete mass oligomers containing 2, 4, 8, 16, 32, and 64 structural units of the perfectly alternating copolymer poly(butylene glutarate). The X-mer denotation used in this report is defined as the combined number of glutaric acid and 1,4-butanediol residues within the given polymer chains having uniform structures. The applicability of these materials to the study of analytical phenomenon mandated that the final products be isolated in a highly pure form, i.e., free of significant amounts of oligomers having differing degrees of polymerization and/or other reaction byproducts.



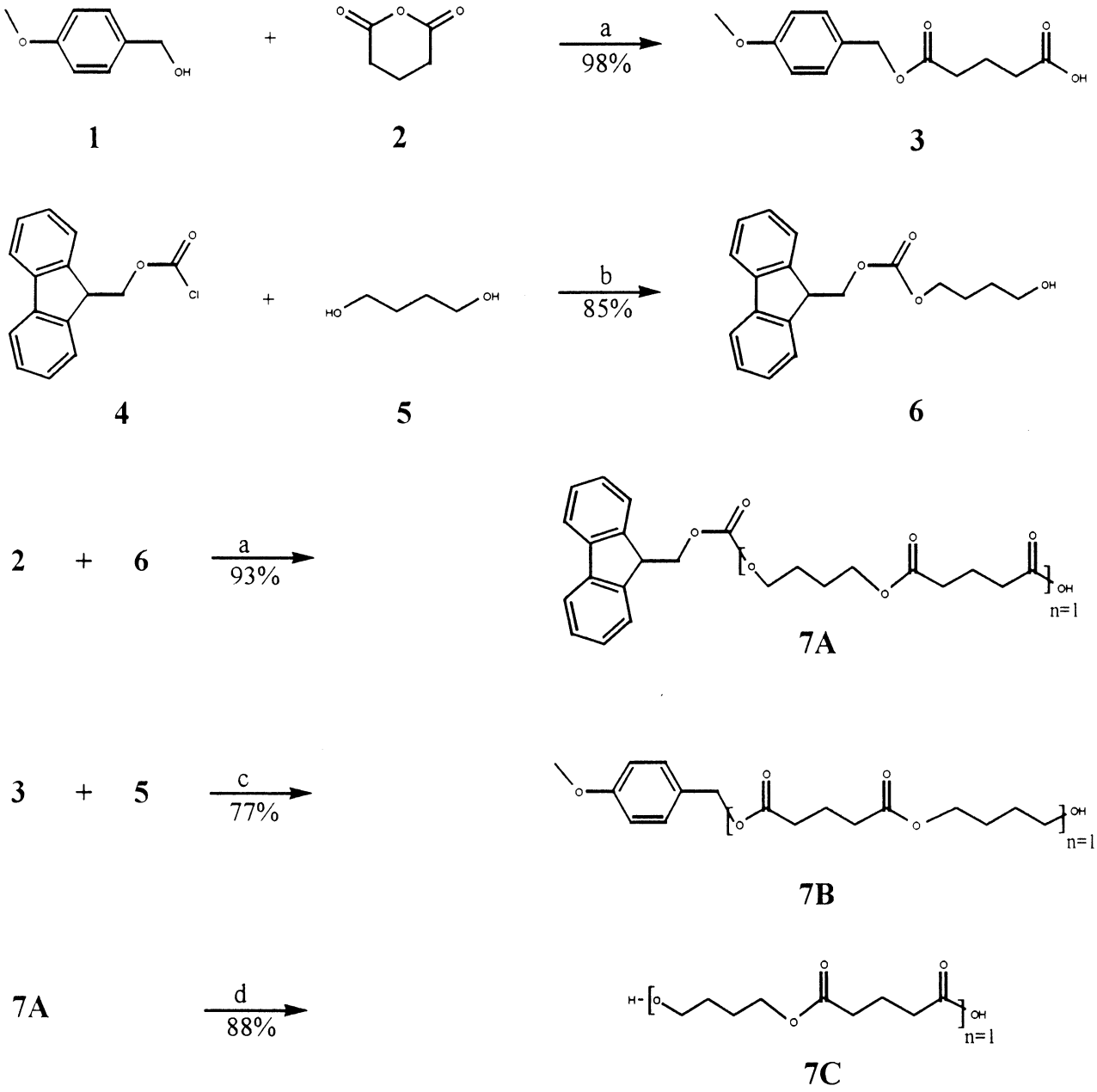
Synthetic control of the degree of polymerization was accomplished through monoprotection of the difunctional starting materials, glutaric anhydride (A) and butanediol (B), using protecting groups that are nonlabile under reaction conditions required for esterification or removal of an orthogonal protecting group. *p*-Methoxybenzyl ester[33] (P_a), which is labile under mildly acidic conditions but stable in basic solutions, was chosen for protection of the carboxylic acid moiety. Protection of the alcohol functionality was achieved using 9-fluorenylmethoxycarbonyl[34] (FMOC) (P_b), which is selectively removed in the presence of tertiary amines but is relatively inert in acidic solutions.

Condensation reagents and conditions were investigated to identify reactions that optimized yield, minimized byproducts, and preserved orthogonal protection. Dicyclohexylcarbodiimide (DCC) with catalytic (*N*,*N*-dimethylamino)pyridine (DMAP) was initially chosen, but this system produced progressively increasing amounts of the acylureas of the acid-functionalized starting materials with increase in reactant chain length, thus reducing both the reaction yields and the capability to adequately purify the oligomeric products. This problem was most likely the result of a decreasing probability of reactant chain-end encounters with increasing chain length, thus lowering the relative rates of reaction for ester vs acylurea formation. A complex of phenyl dichlorophosphate (PDP) with *N*,*N*-dimethylformamide (DMF) was successfully applied for condensation of butylene glutarate dimers but produced lower yields when coupling larger copolymer chains.

Consistent condensation results were achieved using 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride[35] (EDCI) catalyzed by (*N*,*N*-dimethylamino)-pyridine. This approach rendered reaction yields of 70−80% of chromatographically purified product for reactant chain lengths of 32 or fewer structural units, with little or no formation of adducts or oligomeric byproducts, thus facilitating simpler product purification.

The iterative divergent−convergent synthetic approach applied to the controlled synthesis of discrete mass butylene glutarate copolymer oligomers is illustrated in Scheme 1. Difunctional monomers A and B were monoprotected using orthogonal protecting groups P_a and P_b, which can each be selectively removed without perturbation of the other, yielding AP_a and BP_b. Coupling of the orthogonally protected copolymer monomers using condensation reagents yielded the fully protected tetramer $P_a[AB]_2P_b$, which was then divided into two molar equivalents. Protecting groups P_a and

Scheme 2. Synthesis of the Butylene Glutarate Dimer[a]



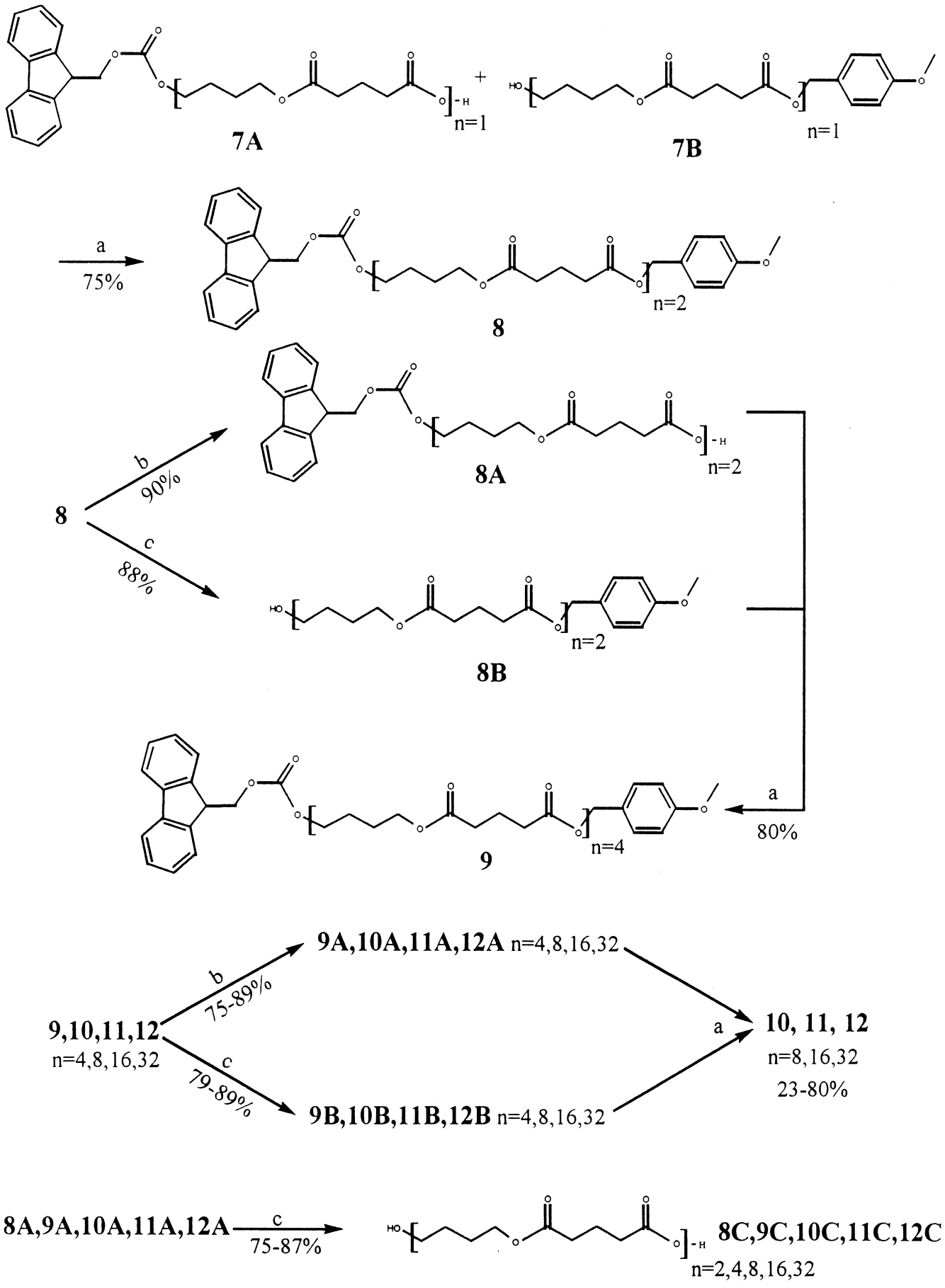
[a] Conditions: (a) 70° C, 4 h; (b) pyridine, 0 °C → RT, 18 h; (c) phenyl dichlorophosphate/*N*,*N*-dimethylformamide, 0 °C, 0.5 h/RT, 18 h; (d) 5.0% TEA/CH_2Cl_2, RT, 4 h.

P_b were then selectively removed to form monofunctionalized $P_a[AB]_2$ and $[AB]_2P_b$. Molecular doubling followed by selective or complete deprotection of products yielded a series of the discrete unprotected target oligomers $[AB]_n$ where $n = 1$, 2, 4, 8, 16, and 32.

Dimer Synthesis. Synthesis of the poly(butylene glutarate) (PBG) dimer is presented in Scheme 2. Glutaric acid mono-*p*-methoxybenzyl ester (**3**) was prepared by melt mixing (70 °C) of 1 equiv of 4-methoxybenzyl alcohol (**1**) with 2 equiv of glutaric anhydride (**2**). The mono-FMOC-protected butanediol (**6**) was synthesized by reaction of 9-fluorenylmethyl chloroformate (**4**) with 20 equiv of butanediol (**5**) using pyridine as a catalyst. Purified product (**6**) was subsequently melt mixed (70 °C) with 2 equiv of glutaric anhydride (**2**) to form the FMOC-protected butylene glutarate dimer (**7A**). Purified product (**3**) was then condensed with excess butanediol (**5**) (10 equiv), using a phenyl dichlorophosphate−*N*,*N*-dimethylformamide complex, to produce the *p*-methoxybenzyl-protected butylene glutarate dimer (**7B**). Product **7A** was subsequently fully deprotected by mixing with 5% TEA in CH_2Cl_2 for 4 h to yield the fully deprotected dimer (**7C**).

Molecular Doubling. The synthesis of PBG oligomers having higher degrees of polymerization is schematically outlined in Scheme 3. Orthogonally monoprotected dimers (**7A** and **7B**) were coupled using EDCI/DMAP to produce the fully protected PBG tetramer (**8**). Product **8** was then refunctionalized by dividing this product into 2 equimolar fractions followed by selective removal of one protection group. The *p*-methoxybenzyl group was removed by stirring product **8** in 5% trifluoroacetic acid (TFA) in CH_2Cl_2 for 2 h yielding (**8A**). The FMOC group was removed by stirring **8** in 5% triethylamine (TEA) in CH_2Cl_2 for 4 h, forming tetramer (**8B**). EDCI/DMAP coupling of **8A** and **8B** yielded the

Scheme 3. Molecular Doubling of Uniform Butylene Glutarate Oligomers[a]



[a] Conditions: (a) EDCI/DMAP, 0 °C, 2 h/RT, 18 h; (b) 5% TFA/CH_2Cl_2/RT, 2 h; (c) 5% TEA/CH_2Cl_2/RT, 4 h.

Table 1. Physical Properties, Synthetic, and Analytical Results from Discrete Mass Poly(butylene glutarate) Intermediates and Oligomers

entry	compound[a] no.	repeat units	molecular formula	mol wt[b]	mass spec	NMR ratio[c]	HPLC (min)	yield (%)
1	**3**	1	$C_{13}H_{16}O_5$	252.10	252[d]	1:1	2.60	98.7
2	**6**	1	$C_{19}H_{20}O_4$	312.14	312[d]	1:1	3.05	84.8
3	**7A**	2	$C_{24}H_{26}O_7$	426.17	426[d]	1:1	2.99	93.2
4	**7B**	2	$C_{17}H_{24}O_6$	324.16	324[d]	1:1	2.73	77.1
5	**7C**	2	$C_9H_{16}O_5$	204.10	205[e]	1:1	3.18	88.1
6	**8**	4	$C_{41}H_{48}O_{12}$	732.31	732[d]	3:1	2.91	74.5
7	**8A**	4	$C_{33}H_{40}O_{11}$	612.26	612[d]	3:1	2.77	90.1
8	**8B**	4	$C_{26}H_{38}O_{10}$	510.25	510[d]	3:1	2.84	88.3
9	**8C**	4	$C_{18}H_{30}O_9$	390.19	413[f−h]	3:1	3.12	86.9
10	**9**	8	$C_{59}H_{76}O_{20}$	1104.49	1127[h]	5:1	3.04	80.1
11	**9A**	8	$C_{51}H_{68}O_{19}$	984.44	1007[h]	5:1	2.78	75.1
12	**9B**	8	$C_{44}H_{66}O_{18}$	882.42	905[h]	6:1	3.06	79.1
13	**9C**	8	$C_{36}H_{58}O_{17}$	762.37	785[g,h]	5:1	3.60	85.3
14	**10**	16	$C_{95}H_{132}O_{36}$	1848.85	1872[h]	11:1	3.23	80.0
15	**10A**	16	$C_{87}H_{124}O_{35}$	1728.79	1752[h]	12:1	2.97	88.6
16	**10B**	16	$C_{80}H_{122}O_{34}$	1626.78	1650[h]	11:1	2.72	89.1
17	**10C**	16	$C_{72}H_{114}O_{33}$	1506.72	1530[g,h]	11:1	3.59	75.2
18	**11**	32	$C_{167}H_{244}O_{68}$	3337.56	3361[h]	23:1	3.36	70.9
19	**11A**	32	$C_{159}H_{236}O_{67}$	3217.51	3241[h]	24:1	3.34	87.1
20	**11B**	32	$C_{152}H_{234}O_{66}$	3115.51	3139[h]	23:1	3.06	88.2
21	**11C**	32	$C_{144}H_{226}O_{65}$	2995.44	3018[g,h]	23:1	3.59	82.2
22	**12**	64	$C_{311}H_{468}O_{132}$	6314.99	6340[h,i]	47:1	4.11	23.1
23	**12A**	64	$C_{303}H_{460}O_{131}$	6194.93	6221[h,i]	48:1	3.97	82.5
24	**12B**	64	$C_{296}H_{458}O_{130}$	6092.93	6120[h,i]	45:1	3.84	83.3
25	**12C**	64	$C_{288}H_{460}O_{129}$	5972.87	5999[h,i]	46:1	4.07	79.1

[a] From Schemes 2 and 3. [b] Nominal. [c] ^{1}H NMR ratio of main chain methylene to chain end or protecting group methylene. [d] EI-MS $(M)^+$. [e] CI-MS $(M + H)^+$. [f] LSI-MS $(M + Na)^+$. [g] ESI-MS $(M + Na)^+$. [h] MALDI-TOF-MS $(M + Na)^+$. [i] Apex of isotopic envelope.

fully protected PBG octamer (**9**). As shown in Scheme 3, orthogonal deprotection of fully protected oligomers (**9**, **10**, **11**, **12**) yielded the FMOC-protected (**9A**, **10A**, **11A**, **12A**) and the 4-methoxybenzyl-protected (**9B**, **10B**, **11B**, **12B**) oligomers. Subsequent molecular doubling using EDCI/DMAP coupling of copolymers of the same degree of polymerization yielded orthogonally protected products (**10**, **11**, **12**). Removal of FMOC with 5% TEA from fractions of the protected acids (**8A**, **9A**, **10A**, **11A**, **12A**) produced the unprotected synthetic target copolymers (**8C**, **9C**, **10C**, **11C**, and **12C**) with 4, 8, 16, 32, and 64 structural units, respectively.

Purification of PBA Oligomers. Products of the above coupling reactions and mono-deprotection steps were purified by gradient low-pressure liquid chromatography (LPLC) using silica gel as the stationary phase and hexanes or methylene chloride/ethyl acetate as the mobile phase. Column fractions of synthetic intermediates contaminated with components not resolved by LPLC were repurified using higher resolution flash liquid chromatography (FLC).[36] The fully functionalized oligomers were isolated by rotary evaporation to remove reaction solvents and TEA and then dried in a vacuum. The crude products were redissolved and then filtered, followed by recovery of the soluble materials using rotary evaporation. The waxy products were isolated in pure form by precipitation from a CH_2CH_2 solution using hexanes or diethyl ether. The 64-mer was recrystallized from hot ethanol.

Reaction Yields. The reaction yields from the synthesis of PBG oligomers and their intermediates, along with analytical results, are given in Table 1. It is seen that coupling reactions using PDP/DMF or EDCI/DMAP gave reaction yields of ca. 70−80% for starting materials having structural units ≤32. Reaction yields from deprotection steps were generally in the 80−90% range. High reaction yields were essential due to the number of synthetic steps (up to 25) required to obtain higher molecular weight products.

The synthesis of the fully protected 64-mer resulted in a low reaction yield (23.1%). The lower yield may have resulted from the reduced probability due to increased chain length of the hydroxyl-functionalized oligomers encountering an activated carboxyl terminus. In addition, ions from oligomeric byproducts, in the ca. 3000 Da range, were detected in the MALDI spectra of impure 64-mer reaction products, indicating the presence of competing reactions that further lowered product yield and inhibited efficient purification.

Analysis of PBG Oligomers. Progressive growth and purity of the products were monitored using thin-layer chromatography (TLC), high-performance liquid chromatography (HPLC), gel permeation chromatography (GPC), proton nuclear magnetic resonance spectroscopy (^{1}H NMR), electron impact ionization (EI), chemical ionization (CI), liquid secondary ion (LSI), electrospray ionization (ESI), and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) (Table 1). GPC traces and MALDI spectra of these discrete mass oligomers are included within a report detailing the analytical applications of these synthetic materials [*Anal. Chem.*, in press].

Figure 1 presents the ^{1}H NMR spectra of the fully protected PBG 32-mer. The ratios of main chain methylene (−[(O═C)$CH_2C\mathit{H}_2CH_2$(C═O)]−) (m) (2H) (1.95 ppm) to protecting group methylene (*p*-methoxybenzyl (s) (2H) (5.04 ppm) or FMOC methylene (d) (2H) (4.45 ppm)) of all protected products are included in Table 1. These ratios were calculated using peak areas from ^{1}H NMR spectra and were utilized to monitor progressive chain growth of fully and monoprotected intermediates.

Figure 2 displays a series of ^{1}H NMR spectra of the fully functionalized PBG oligomer products (compounds **7C**−**12C** of Table 1). NMR spectra support the absence of nonoligomeric impurities and illustrate the increase in the number of repeat units by monitoring the intensity ratio, calculated by integration of peak areas, of a repeat unit methylene (central methylene of the glutaric

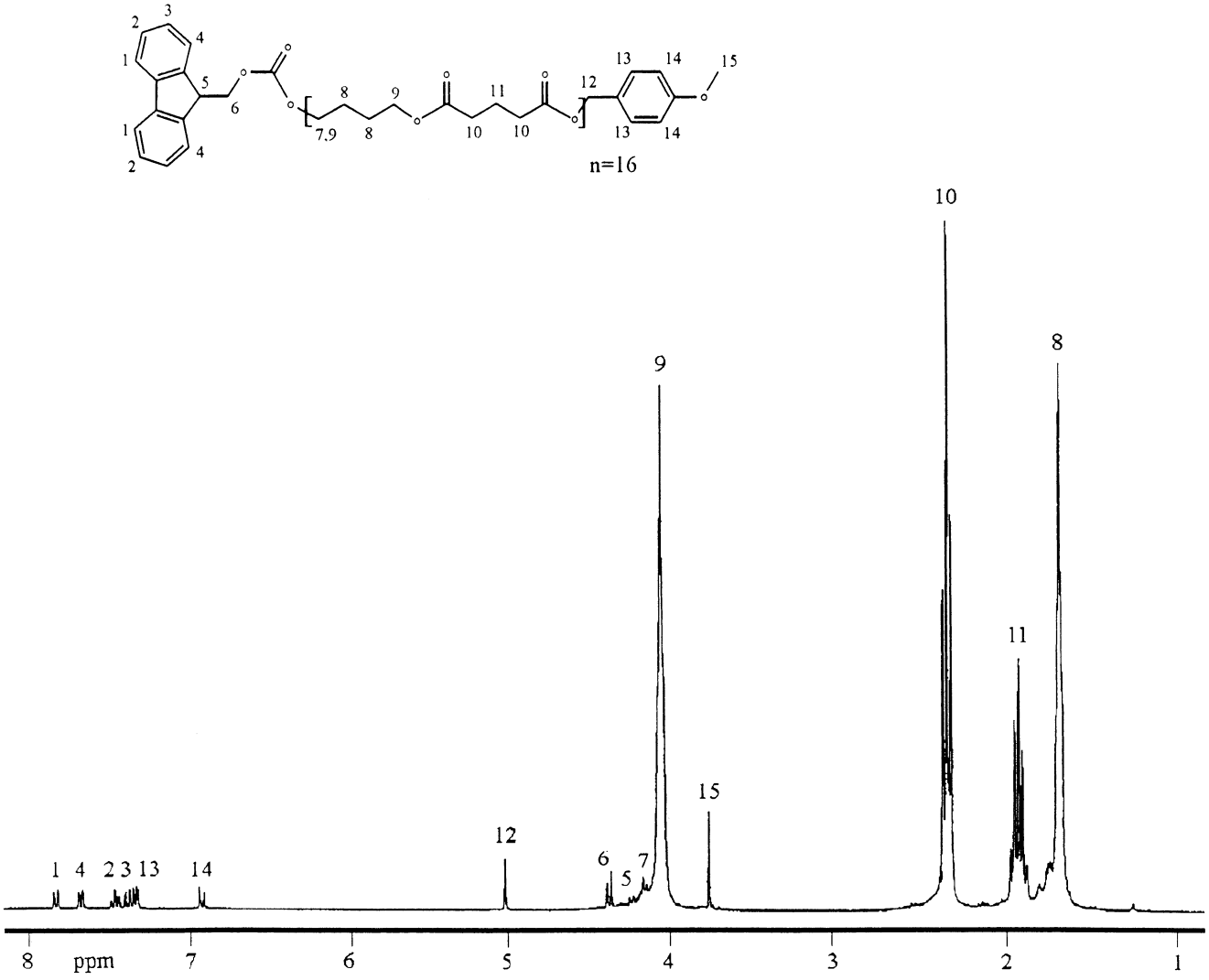


Figure 1. Proton nuclear magnetic resonance (^{1}H NMR) spectrum of the orthogonally protected butylene glutarate 32-mer. The proton peak assignments are shown in the inset.

acid comonomer) (−[(O═C)$CH_2C\mathit{H}_2CH_2$(C═O)]−) (m) (2H) (1.95 ppm) to the terminal group methylene (−$C\mathit{H}_2$OH) (t) (2H) (3.65 ppm).

In general, ^{1}H NMR ratios from poly(butylene glutarate) spectra tended to overestimate the relative number of main chain to end group methylene groups for copolymers with a degree of polymerization higher than 2. For example, the expected ratio for compound **11C**, composed of 16 glutaric acid monomer units, should be 16:1 as opposed to the measured value of 23:1. This discrepancy is probably due to loss of lower intensity end-group signals in spectral background noise. Thus, the application of these NMR ratios for molecular weight determination would result in erroneously high results.

Mass spectrometric analysis was successfully performed on all products listed in Table 1. EI-MS and CI-MS analysis of products having structural units ≥8 provided peaks from intact products M^+ and $(M + H)^+$, respectively, and indicated an absence of oligomeric impurities in these materials. CI-MS analysis of the unprotected dimer exhibited the $(M + H)^+$ peak at m/z = 205. LSI-MS analysis of the unprotected tetramer (**8C**) produced the $(M + Na)^+$ peak at m/z = 413. The MALDI-TOF-MS spectrum of the tetramer (**8C**) also provided the $(M + Na)^+$ peak (m/z = 413) but also indicated the presence of the PBG octamer (m/z = 785) having an intensity, relative to that of the product peak, of 10%. The presence of the PBG octamer was also observed (8%) in the ESI-MS spectra of this material.

MALDI-TOF-MS was utilized extensively for the evaluation of the purity of both protected and functionalized PBG oligomers having degrees of polymerizations ≥8. The MALDI spectrum of the fully functionalized PBG 64-mer (**12C**) is presented in Figure 3. The highest intensity peak seen in the MALDI spectrum results from the sodium cationized molecular ion $(M + Na)^+$ (5999 Da), which appears 23 amu higher than the predicted molecular weight of the oligomer. Additional weaker peaks (ca. 25% relative to the $(M + Na)^+$ intensity) are seen at 16 and 22 Da above the $(M + Na)^+$ peak and are identified as the potassium cationized molecular ion $(M + K)^+$ and the sodium cationized sodium salt of the carboxylic acid of the oligomer $(M + 2Na - H)^+$. The appearance of the latter ion probably results from the addition of NaCl to sample/matrix mixture during the preparation of MALDI sample targets. MALDI analysis of the fully deprotected 8-, 16-, and 32-mer also provided base peaks representative of the sodium cationized molecular ions at m/z = 785, 1530, and 3019 (**9C**−**11C**), respectively, as well as lower

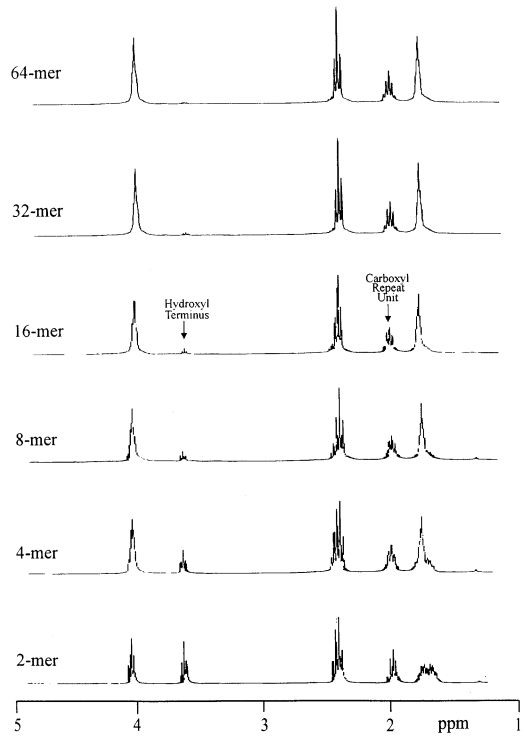


Figure 2. Progressive growth of butylene glutarate oligomers monitored by proton nuclear magnetic resonance (^{1}H NMR) spectroscopy. The peaks from the carboxyl repeat units (−(C═O)$CH_2CH_2CH_2$(C═O)−) and the hydroxyl termini (−CH_2OH) are identified.

intensity ions corresponding to $(M + K)^+$ and $(M + 2Na - H)^+$.

As seen in Figure 3, the MALDI mass spectrum of the 64-mer (**12C**) also indicated the presence of oligomeric impurities corresponding to addition (66-mer) (m/z = 6185) (4%) or subtraction (62-mer) (m/z = 5813) (5%) of one butylene glutarate unit, as well as peaks at m/z = 5885 (63-mer) (4%), corresponding to the subtraction of one glutaric acid unit ((C═O)−$(CH_2)_3$-(C═O)−O). Low levels of oligomeric impurities were also observed in the MALDI spectra of the fully functionalized PBG oligomer products **9C**−**11C**. The MALDI spectrum of the PBG octamer (**9C**) indicated the presence of the 16-mer (m/z = 1530) (3%). However, this impurity was not detected during ESI-MS analysis of this compound. MALDI analysis of the 16-mer (**10C**) produced peaks contributed to the loss by the product of one butylene glutarate unit (m/z = 1344) (3%), the loss of one glutaric acid unit (m/z = 1416) (1%), and the presence of the fully functionalized 8-mer (m/z = 785) (3%). The presence of the 8-mer (3%) was also observed in the ESI-MS spectra of the product 16-mer. MALDI spectra of the 32-mer (**11C**) provided peaks from impurities identified as the PBG 16-mer (m/z = 1530) (3%), 30-mer (m/z = 2832) (4%), 31-mer (m/z = 2904) (2%), and 34-mer (m/z = 3204) (2%).

The MALDI experiment was very sensitive to the presence of oligomeric impurities. Spectra of pure preparative column fractions of protected products indicated little or no contamination from materials differing from the product only in the degree of polymerization. However, spectra of the impure LPLC fractions of the products from the condensation and deprotection reactions revealed that larger amounts of impurities corresponding to product $n \pm 0.5$, 1, 2 were formed during synthesis.

The purity of the fully functionalized target products was also evaluated using GPC. The GPC experiment is also sensitive to the presence of nontargeted oligomers having significantly differing degrees of polymerization from that of the product. The results support the mass spectrometric determination that the inclusion of significant quantities of these impurities in the products was not evident. The molecular weight averages and polydispersity estimates from GPC analysis of fully functionalized products, calibrated using poly(ethylene glycol) (PEG) standards, are presented in Table 2. While the molecular weight averages determined from these GPC traces generally agree with the calculated values and those measured by mass spectrometric methods,

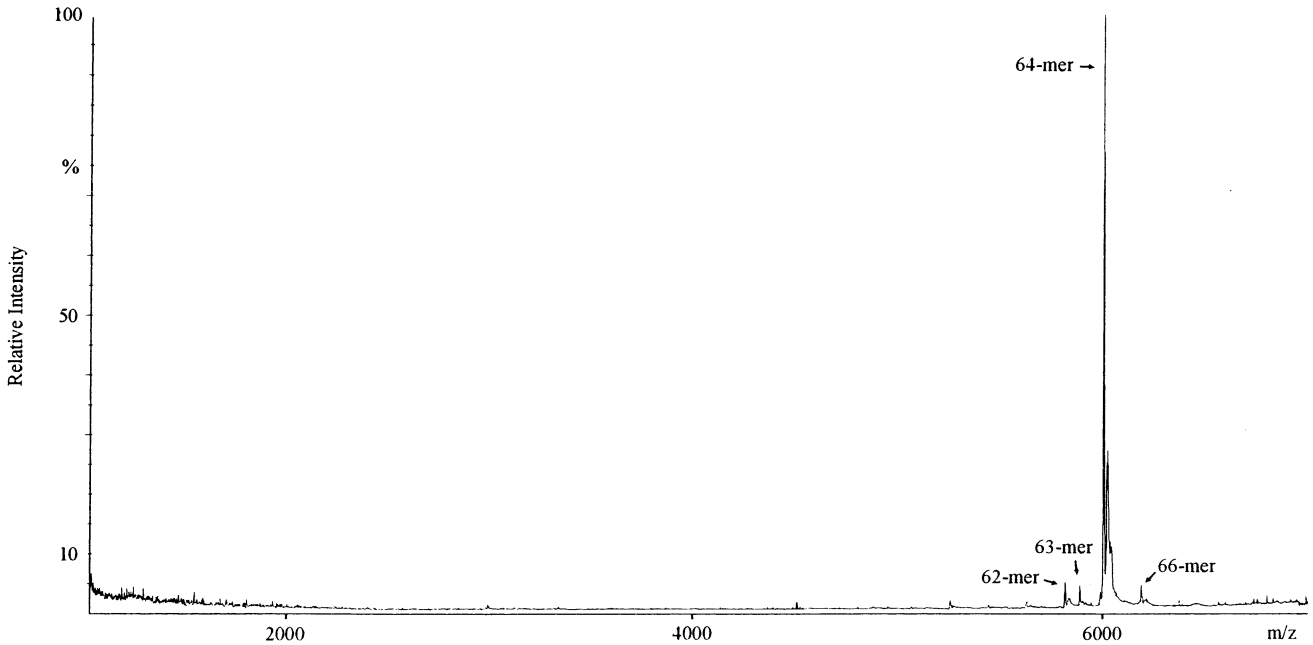


Figure 3. MALDI-TOF mass spectrum of the fully functionalized butylene glutarate 64-mer using *trans*-3-indole acrylic acid as the matrix. The molecular ions $(M + Na)^+$ of the product and oligomeric impurities are identified.

Table 2. GPC Molecular Weight Averages of Discrete Mass PBG Oligomers

entry	compd[a] no.	repeat units	mol wt[b]	M_n	M_w	M_w/M_n	M_p[c]
1	**7C**	2	204.10	190	200	1.04	200
2	**8C**	4	390.19	300	400	1.33	355
3	**9C**	8	762.37	860	870	1.01	890
4	**10C**	16	1506.72	1710	1940	1.14	1990
5	**11C**	32	2995.44	3460	3860	1.12	3550
6	**12C**	64	5972.87	5840	6180	1.06	5910

[a] From Schemes 2 and 3. [b] Nominal. [c] From peak apex.

some overestimation of molecular weight of products is observed. This probably results from relative differences in the hydrodynamic volume of the polyester analytes and PEG standards at similar masses.

Conclusions

The synthesis of a series of structurally uniform oligomers of the perfectly alternating copolymer of glutaric acid and butanediol has been made possible by orthogonal monoprotection of the respective difunctional monomers followed by effective coupling of monofunctional comonomers using EDCI/DMAP. An iterative divergent−convergent strategy consisting of orthogonal deprotection of equimolar fractions of fully protected PBA oligomers, followed by EDCI coupling, has produced poly(butylene glutarate) oligomers of high purity with 2, 4, 8, 16, 32, and 64 structural units. These materials have immediate application as models for development of analytical methodology for polymers, examination of disparities in molecular weight determinations of polymers using different methods, study of mass spectrometric processes, and utilization as calibration standards for relative methods of determination of polymer molecular weight averages.

Experimental Section

Synthesis. Butanediol, glutaric anhydride, 4-(*N*,*N*-dimethylamino)pyridine, *p*-methoxybenzyl alcohol, 9-fluorenylmethyl chloroformate, *N*,*N*-dimethylformamide, phenyl dichlorophosphate, pyridine, and 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (EDCI) were purchased from Aldrich Chemical Co. and dried prior to use. Triethylamine (TEA) and trifluoroacetic acid (TFA) were purchased from Avocado Research Chemical Limited. Methylene chloride, *N*,*N*-dimethylformamide, and tetrahydrofuran, employed for coupling reactions, were distilled and stored over molecular sieves until needed. All glassware was oven-dried and purged with dried nitrogen prior to use. All coupling reactions subsequently described were carried out under dry nitrogen. Solvents were removed using a water aspirated rotary evaporator heated with a water bath.

Low-pressure liquid chromatography (LPLC) was performed on a column of silica gel (Baker (60−200 mesh)) (weight silica gel:weight sample ≈ 30−100:1) using the cosolvents ethyl acetate and methylene chloride or hexanes as the mobile phase. Flash liquid chromatography (FLC) was performed on a column of silica gel (Merck, 230−400 mesh, 60 Å, Aldrich) with the cosolvents ethyl acetate and methylene chloride as the mobile phase. Thin-layer chromatography (TLC) was performed on Whitman 250 μM silica gel plates.

Glutaric Acid Mono-*p*-methoxybenzyl Ester Monomer (3). Glutaric anhydride (50.0 g, 440 mmol) was dissolved in 50 mL of CH_2Cl_2 and mixed with *p*-methoxybenzyl alcohol (30.4 g, 220 mmol) in a two-neck round-bottom flask with a condenser. The reaction mixture was stirred at 70 °C for 4 h and at RT overnight. This mixture was dissolved in 200 mL of diethyl ether and extracted with 6 × 200 mL of H_2O. The organic phase was rotary-evaporated and dried overnight in a vacuum providing a solid (mp = 66−68 °C) [yield: 54.7 g (98.7%)]. EI-MS: 252, 137, 121 *m*/*z*. ^{1}H NMR ($CDCl_3$) δ: 7.29 (d, 2H), 6.90 (d, 2H), 5.04 (s, 2H), 3.82 (s, 3H), 2.41 (t, 4H), 1.98 (m, 2H) (ratio 1:1) (theoretical ratio 1:1). HPLC (acetonitrile): 2.60 min; TLC R_f = 0.67 (80% CH_2Cl_2:ethyl acetate).

Mono-FMOC-Protected Butanediol Monomer (6). In a round-bottom flask, 49.0 g of butanediol (**5**) (540 mmol) was dissolved in 100 mL of THF and cooled to 0 °C. With stirring, 6.4 g of pyridine (81 mmol) was added followed by the dropwise addition (over 10 min) of 7.0 g of 9-fluorenylmethyl chloroformate (**4**) (27.1 mmol) in 50 mL of THF. The ice bath was removed, and the reaction was stirred for 18 h. The solvent was removed, and resulting mixture was placed in 250 mL of CH_2Cl_2 and extracted with 3 × 250 mL of water. The organic layer was evaporated and dried, and the crude product was purified using gradient LPLC with CH_2Cl_2:ethyl acetate (1:0−1:1) as the eluent [yield: 7.15 g (84.8%)]; oil. EI-MS: 312, 178, 165 *m*/*z*. ^{1}H NMR (d_6-acetone) δ: 7.78 (d, 2H), 7.63 (d, 2H), 7.44 (t, 2H), 7.33 (t, 2H), 4.46 (d, 2H), 4.29 (t, 1H), 4.23 (t, 2H), 3.69 (t, 2H), 1.82 (m, 2H), 1.68 (m, 2H) (ratio 1:1) (theoretical ratio 1:1). HPLC (acetonitrile) 3.05 min; TLC R_f = 0.41 (80% CH_2Cl_2:ethyl acetate).

FMOC-Protected Butylene Glutarate Dimer (7A). In a round-bottom flask equipped with a condenser, 7.15 g (22.4 mmol) of mono-FMOC-butanediol (**6**) was dissolved in 50 mL of CH_2Cl_2 followed by the addition of 5.2 g (46 mmol) of glutaric anhydride (**2**) with stirring. The reaction mixture was stirred at 70 °C for 4 h, then cooled and dissolved in 250 mL of diethyl ether, and extracted with 6 × 250 mL of H_2O. The organic phase was dried, and the product was purified using gradient LPLC on a column of silica gel with CH_2Cl_2:ethyl acetate (1:0−1:2) as the eluent [yield: 9.10 g (93.2%)]; oil. EI-MS: 426, 178, 165 *m*/*z*. ^{1}H NMR ($CDCl_3$) δ: 7.78 (d, 2H), 7.63 (d, 2H), 7.44 (t, 2H), 7.32 (t, 2H), 4.41 (d, 2H), 4.30 (t, 1H), 4.20 (t, 2H), 4.13 (t, 2H), 2.43 (t, 3H), 2.41 (t, 3H), 1.95 (t, 2H), 1.76 (m, 5H) (ratio 1:1) (theoretical ratio 1:1). HPLC (acetonitrile) 2.99 min; TLC R_f = 0.56 (80% CH_2Cl_2:ethyl acetate).

***p*-Methoxybenzyl Butylene Glutarate Dimer (7B).** Into a dry round-bottom flask containing 7.0 g of *N*,*N*-dimethylformamide (96 mmol) at 0 °C, 12.7 g of phenyl dichlorophosphate (60 mmol) was added with mechanical stirring. The resulting complex was allowed to stand under dry N_2 at 0 °C for 10 min followed by mixing with 0 °C anhydrous THF. To the resulting suspension, 10.0 g (39.7 mmol) of glutaric acid mono-*p*-methoxybenzyl ester (**3**) was added and stirred until the solution was homogeneous (10 min), followed by 35.7 g (397 mmol) of butanediol (**5**). After 10 min, 12.6 g of pyridine (160 mmol) was added, and the reaction mixture was stirred at RT for 18 h. The solvent was removed, the mixture was placed in 200 mL of CH_2Cl_2 and extracted with 3 × 250 mL of water. The organic fraction was dried and the product was purified by gradient LPLC with hexane:ethyl acetate (5:1−1:3) as the eluent [yield: 9.92 g, (77.1%)]; oil. EI-MS: 324, 137, 121 *m*/*z*. ^{1}H NMR ($CDCl_3$) δ: 7.29 (d, 2H), 6.90 (d, 2H), 5.04 (s, 2H), 4.10 (t, 2H), 3.80 (s, 3H), 3.65 (t, 2H), 2.40 (t, 2H), 2.36 (t, 2H), 1.93 (t, 2H), 1.71 (t, 2H), 1.66 (t, 2H) (ratio 1:1) (theoretical ratio 1:1). HPLC (acetonitrile) 2.73 min; TLC R_f = 0.31 (80% CH_2Cl_2:ethyl acetate).

Butylene Glutarate Dimer (7C). In an 50 mL Erlenmeyer flask, 100 mg (0.23 mmol) of FMOC-protected butylene glutarate (**7A**) was stirred with 1.2 g (11.7 mmol, 50 equiv) of TEA in 30 mL of CH_2Cl_2 for 4 h. After removal of the solvent and TEA by rotary evaporation and vacuum-drying, the product was isolated by filtration of a CH_2Cl_2 solution followed by washing with hexanes [yield: 42.2 mg (88.1%)]; oil. CI-MS: 205, 115. ESI-MS: 227, 150, 102 *m*/*z*. ^{1}H NMR ($CDCl_3$) δ: 4.13 (t, 2H), 3.69 (t, 2H), 2.38 (p, 4H), 1.95 (m, 2H), 1.76 (t, 2H), 1.70 (t, 2H) (ratio 1:1) (theoretical ratio 1:1). HPLC (acetonitrile) 3.18 min.

Orthogonally Protected Butylene Glutarate Tetramer (8). In a round-bottom flask at 0 °C, 3.2 g (9.9 mmol) of *p*-methoxybenzyl butylene glutarate (**7B**), 4.2 g (9.9 mmol) of FMOC-butylene glutarate (**7A**), and 0.25 g of DMAP (2.0 mmol) were mixed with stirring in 75 mL of CH_2Cl_2. EDCI (1.6 g) (10.9 mmol) was added, and the mixture was stirred at

0 °C for 2 h and at RT for 18 h. After concentration, the product was purified by gradient LPLC with CH_2Cl_2:ethyl acetate (1:0−1:1) as the eluent [yield: 5.40 g, (74.5%)]; oil. EI-MS: 732, 554, 510, 178, 121 *m*/*z*. ^{1}H NMR ($CDCl_3$) δ: 7.78 (d, 2H), 7.63 (d, 2H), 7.44 (t, 2H), 7.33 (t, 2H), 7.29 (d, 2H), 6.90 (d, 2H), 5.05 (s, 2H), 4.41 (t, 2H), 4.29 (t, 1H), 4.23 (t, 2H), 4.10 (t, 4H), 3.80 (s, 3H), 2.39 (m, 9H), 1.91 (m, 5H), 1.78 (t, 5H), 1.70 (t, 5H) (ratio 2.5:1) (theoretical ratio 2:1). HPLC (acetonitrile) 2.91 min; TLC R_f = 0.78 (80% CH_2Cl_2:ethyl acetate).

FMOC-Protected Butylene Glutarate Tetramer (8A). In a round-bottom flask, 5.2 g (7.10 mmol) of orthogonally protected butylene glutarate tetramer[37] (**8**) was stirred in a 200 mL solution of 5% TFA in CH_2Cl_2 for 2 h. The reaction mixture was extracted 3 × 200 mL of water, and the organic fraction was rotary evaporated and dried overnight. The crude product was purified by gradient LPLC with CH_2Cl_2:ethyl acetate (1:0−0:1) as the eluent [yield: 3.92 g, (90.1%)]; oil. EI-MS: 612, 178, 165 *m*/*z*. ^{1}H NMR ($CDCl_3$) δ: 7.78 (d, 2H), 7.63 (d, 2H), 7.44 (t, 2H), 7.33 (t, 2H), 4.41 (t, 2H), 4.28 (t, 1H), 4.23 (t, 2H), 4.10 (t, 6H), 2.39 (m, 9H), 1.93 (m, 6H), 1.78 (t, 5H), 1.70 (t, 6H) ppm (ratio 3:1) (theoretical ratio 2:1). HPLC (acetonitrile) 2.77 min; TLC R_f = 0.26 (80% CH_2Cl_2:ethyl acetate).

***p*-Methoxybenzyl-Protected Butylene Glutarate Tetramer (8B).** In a round-bottom flask, 4.30 g (5.90 mmol) of orthogonally protected butylene glutarate tetramer[37] (**8**) was stirred in a 100 mL 5% w/w solution of TEA in CH_2Cl_2 at RT for 4 h. The volatile components were removed using rotary evaporation, and the crude product was dried overnight, then dissolved in CH_2Cl_2, and filtered, followed by purification by gradient LPLC with CH_2Cl_2:ethyl acetate (1:0−0:1) as the eluent [yield: 2.65 g (88.3%)]; oil. EI-MS: 510, 373, 121 *m*/*z*. ^{1}H NMR ($CDCl_3$) δ: 7.29 (d, 2H), 6.90 (d, 2H), 5.06 (s, 2H), 4.13 (t, 5H), 3.82 (s, 3H), 3.69 (t, 2H), 2.39 (m, 9H), 1.96 (m, 5H), 1.69 (t, 11H) (ratio 2.5:1) (theoretical ratio 2:1). HPLC (acetonitrile) 2.84; TLC R_f = 0.18 (80% CH_2Cl_2:ethyl acetate).

Butylene Glutarate Tetramer (8C). In an 50 mL Erlenmeyer flask, 50 mg (0.082 mmol) of FMOC-protected butylene glutarate tetramer (**8A**) was stirred with 410 mg (4.1 mmol, 50 equiv) of TEA in 30 mL of CH_2Cl_2 for 4 h. The solvent and TEA were removed by rotary evaporation followed by vacuum-drying, and the pure product was isolated by filtration of a CH_2Cl_2 solution and washing with hexanes [yield: 27.7 mg (86.9%)]; oil. CI-MS 391. ESI-MS, LSI-MS, and MALDI−TOF-MS 413 *m*/*z*. ^{1}H NMR ($CDCl_3$) δ: 4.13 (t, 6H), 3.69 (t, 2H), 2.38 (m, 8H), 1.95 (m, 6H), 1.70 (s, 11H) (ratio 3:1) (theoretical ratio 2:1). HPLC (acetonitrile) 3.12 min.

Orthogonally Protected Butylene Glutarate Octamer (9). In a round-bottom flask, 3.20 g (5.20 mmol) of FMOC-protected butylene glutarate tetramer (**8A**), 2.65 g (5.20 mmol) of *p*-methoxybenzyl-protected butylene glutarate tetramer (**8B**), and 0.13 g (1.0 mmol) of DMAP were stirred at 0 °C. 1.10 g of EDCI (5.72 mmol) was added, and the reaction mixture was stirred at 0 °C for 2 h and at RT for 18 h. The solvent was reduced, and the crude product was purified by gradient LPLC using CH_2Cl_2:ethyl acetate (1:0−1:1) [yield: 4.60 g (80.1%)]; oil. MALDI−TOF-MS: 1143, 1127 *m*/*z*. ^{1}H NMR ($CDCl_3$) δ: 7.78 (d, 2H), 7.61 (d, 2H), 7.40 (t, 2H), 7.33 (d, 2H), 7.29 (d, 2H), 6.88 (d, 2H), 5.04 (s, 2H), 4.40 (t, 2H), 4.23 (t, 1H), 4.17 (t,2H), 4.11 (t, 11H), 3.79 (s, 3H), 2.36 (m, 17H), 1.93 (t, 10H), 1.78 (t, 8H), 1.67 (t, 7H) (ratio 5:1) (theoretical ratio 4:1). HPLC (acetonitrile) 3.04 min; TLC R_f = 0.54 (80% CH_2Cl_2:ethyl acetate).

FMOC-Protected Butylene Glutarate Octamer (9A). In a round-bottom flask, 4.05 g (3.75 mmol) of orthogonally protected butylene glutarate octamer[37] (**9**) was stirred for 2 h in 100 mL of 5% w/w TFA in CH_2Cl_2. The reaction mixture was extracted with 3 × 100 mL of water and the organic fraction rotary-evaporated and vacuum-dried. The crude product was purified by gradient LPLC with CH_2Cl_2:ethyl acetate (1:0−0:1) as the eluent. Impure LPLC column fractions were repurified using FLC (80% CH_2Cl_2:ethyl acetate) [yield: 2.72 g (75.1%)]; oil. MALDI−TOF-MS: 1023, 1007 *m*/*z*. ^{1}H NMR ($CDCl_3$) δ: 7.76 (d, 2H), 7.61 (d, 2H), 7.46 (t, 2H), 7.32 (t, 2H), 4.40 (d, 2H), 4.28 (t, 1H), 4.22 (t, 2H), 4.09 (t, 14H), 2.37 (p, 17H), 1.94 (m, 10H), 1.75 (m, 13H) (ratio 5:1) (theoretical ratio 4:1). HPLC (acetonitrile) 2.78 min; TLC R_f = 0.48 (60% CH_2Cl_2:ethyl acetate).

***p*-Methoxybenzyl-Protected Butylene Glutarate Octamer (9B).** In a round-bottom flask, 3.15 g (2.93 mmol) of orthogonally protected butylene glutarate octamer[37] (**9**) was stirred in a solution of 5.0% TEA in 50 mL of CH_2Cl_2 at RT for 4 h. The volatile components were removed by rotary evaporation and dried overnight. The crude product was redissolved in CH_2Cl_2, filtered, and then purified by gradient LPLC with CH_2Cl_2:ethyl acetate (9:1−0:1) as the eluent. Impure LPLC column fractions were repurified using FLC (80% CH_2Cl_2:ethyl acetate) [yield: 2.04 g (79.1%)]; oil. MALDI−TOF-MS: 921, 905 *m*/*z*. ^{1}H NMR ($CDCl_3$) δ: 7.28 (d, 2H), 6.88 (d, 2H), 5.04 (s, 2H), 4.10 (t, 16H), 3.80 (s, 3H), 2.37 (m, 18H), 1.94 (t, 12H), 1.68 (m, 15H) (ratio 6:1) (theoretical ratio 4:1). HPLC (acetonitrile) 3.06 min; TLC R_f = 0.46 (60% CH_2Cl_2:ethyl acetate).

Butylene Glutarate Octamer (9C). In an 50 mL Erlenmeyer flask, 75 mg (0.085 mmol) of FMOC-protected butylene glutarate octamer (**9A**) was stirred with 30 mL of 5% TEA in CH_2Cl_2 at RT for 4 h and then extracted with 3 × 30 mL of H_2O. The organic solvent was removed by rotary evaporation, and the crude product was then vacuum-dried (48 h) and isolated by filtration of a CH_2Cl_2 solution followed by precipitation with hexanes [yield: 55.3 mg (85.3%)]; waxy solid. MALDI−TOF-MS 807, 785 *m*/*z*. ^{1}H NMR ($CDCl_3$) δ: 4.13 (t, 16H), 3.69 (t, 2H), 2.38 (m, 17H), 1.95 (m, 10H), 1.70 (s, 17H) (ratio 5:1) (theoretical ratio 4:1); HPLC (acetonitrile) 3.60 min.

Orthogonally Protected Butylene Glutarate 16-mer (10). In a round-bottom flask, 2.27 g (2.31 mmol) of FMOC-protected butylene glutarate octamer (**9A**), 2.04 g (2.31 mmol) of *p*-methoxybenzyl-protected butylene glutarate octamer (**9B**), and 0.06 g (0.47 mmol) of DMAP were mixed in 100 mL of CH_2Cl_2 at 0 °C. EDCI (0.45 g) (2.55 mmol) was added, and the reaction mixture was stirred at 0 °C for 2 h and at RT for 18 h. The mixture was then reduced to 10 mL, and the crude product was purified by gradient LPLC with CH_2Cl_2:ethyl acetate (8:1−5:1) as the eluent. Impure fractions were repurified by FLC with CH_2Cl_2:ethyl acetate (7.5:1) as the eluent [yield: 3.42 g (80.0%)]; oil. MALDI−TOF-MS: 1888, 1872 *m*/*z*. ^{1}H NMR ($CDCl_3$) δ: 7.77 (d, 2H), 7.61 (d, 2H), 7.39 (t, 2H), 7.33 (t, 2H), 7.28 (d,2H), 6.88 (d, 2H), 5.04 (s, 2H), 4.34 (d, 2H), 4.23 (t,1H), 4.18 (t, 2H), 4.09 (t, 38H), 3.78 (s, 3H), 2.35 (m,40H), 1.91 (t, 22H), 1.76 (s, 6H), 1.66 (s, 30H) (ratio 11:1) (theoretical ratio 8:1). HPLC (acetonitrile) 3.23 min; TLC R_f = 0.73 (60% CH_2Cl_2:ethyl acetate).

FMOC-Protected Butylene Glutarate 16-mer (10A). In a round-bottom flask, 1.50 g (0.811 mmol) of orthogonally protected butylene glutarate 16-mer (**10**) was stirred with 50 mL of 5% w/w TFA in CH_2Cl_2 at RT for 2 h. The reaction mixture was extracted 3 × 50 mL of water and the organic fraction was dried prior to purification of the crude product by gradient LPLC with CH_2Cl_2:ethyl acetate (7:1−0:1) as the eluent [yield: 1.24 g (88.6%)]; oil. MALDI−TOF-MS: 1768, 1752 *m*/*z*. ^{1}H NMR ($CDCl_3$) δ: 7.78 (d, 2H), 7.62 (d, 2H), 7.40 (t, 2H), 7.33 (t, 2H), 4.40 (d, 2H), 4.23 (t, 1H), 4.19(t), 4.10 (t, 38H), 2.35 (m, 42H), 1.92 (m, 24H), 1.78 (t, 7H), 1.73 (t, 29H) (ratio 12:1) (theoretical ratio 8:1). HPLC (acetonitrile) 2.97 min; TLC R_f = 0.42 (60% CH_2Cl_2:ethyl acetate).

***p*-Methoxybenzyl-Protected Butylene Glutarate 16-mer (10B).** In a round-bottom flask, 1.45 g (0.785 mmol) of orthogonally protected butylene glutarate 16-mer[37] (**10**) was stirred with 4.0 g of TEA (50 equiv) in 50 mL of CH_2Cl_2 at RT for 4 h. The reaction mixture was rotary-evaporated and dried overnight to remove volatile components. The crude product was dissolved in CH_2Cl_2, filtered, and then purified by gradient LPLC with CH_2Cl_2:ethyl acetate (8:1−5:1) as the eluent. Impure fractions were repurified by FLC with CH_2Cl_2 (6:1) as the eluent [yield: 1.14 g 89.1%)]; oil. MALDI−TOF-MS: 1666, 1650 *m*/*z*. ^{1}H NMR ($CDCl_3$) δ: 7.28 (d, 2H), 6.87 (d, 2H), 5.04 (s, 2H), 4.09 (t, 39H), 3.79 (s, 3H), 3.65 (t, 2H), 2.35 (m, 42H), 1.92 (m, 22H), 1.64 (s, 36H) (ratio 11:1) (theoretical ratio 8:1); HPLC (acetonitrile) 2.72 min; TLC R_f = 0.48 (60% CH_2Cl_2:ethyl acetate).

Butylene Glutarate 16-mer (10C). In an 50 mL Erlenmeyer flask, 50 mg (0.029 mmol) of FMOC-protected butylene glutarate octamer (**10B**) was stirred with 146 mg (1.5 mmol, 50 equiv) of TEA in 30 mL of CH_2Cl_2 for 4 h. The solvent and TEA were removed by rotary evaporation and vacuum-drying overnight. The product was isolated by filtration of a CH_2Cl_2 solution followed by precipitation with hexanes [yield: 32.8 mg (75.2%)]; waxy solid. MALDI-TOF-MS 1552, 1530 *m*/*z*. ^{1}H NMR ($CDCl_3$) δ: 4.13 (t, 37H), 3.69 (t, 2H), 2.38 (m, 40H), 1.95 (m, 22H), 1.70 (s, 36H) (ratio 11:1) (theoretical ratio 8:1); HPLC (acetonitrile) 3.59 min.

Orthogonally Protected Butylene Glutarate 32-mer (11). In a round-bottom flask 0.89 g (0.515 mmol) of FMOC-protected butylene glutarate 16-mer (**10A**), 0.84 g (0.515 mmol) of *p*-methoxybenzyl-protected butylene glutarate 16-mer (**10B**), and 13 mg of DMAP (0.10 mmol) were stirred at 0 °C in 50 mL of CH_2Cl_2. EDCI (0.11 g) (0.567 mmol) was added, and the reaction mixture was stirred at 0 °C for 2 h and at RT for 20 h. The mixture was concentrated to 10 mL, and the crude product was purified by LPLC with CH_2Cl_2 (3:2) as the eluent [yield: 1.22 g (70.9%)]; waxy solid. MALDI−TOF-MS: 3377, 3361 *m*/*z*. ^{1}H NMR ($CDCl_3$) δ: 7.78 (d, 2H), 7.63 (d, 2H), 7.44 (t, 2H), 7.31 (t, 2H),7.29 (d, 2H), 6.90 (d, 2H), 5.04 (s, 2H), 4.40 (d, 2H), 4.28 (t, 1H), 4.22 (t, 2H), 4.09 (t, 94H), 3.80 (s, 3H), 2.37 (m, 104H), 1.92 (t, 50H), 1.69 (s, 96H) (ratio 23:1) (theoretical ratio 16:1). HPLC (acetonitrile) 3.36 min; TLC R_f = 0.53 (60% CH_2Cl_2:ethyl acetate).

FMOC-Protected Butylene Glutarate 32-mer (11A). In an 50 mL Erlenmeyer flask, 100.0 mg (0.030 mmol) of fully protected butylene glutarate 32-mer (**11**) was stirred in a 5% TFA in 25 mL of CH_2Cl_2 for 2 h. The reaction mixture was extracted 3 × 25 mL of H_2O, and the organic phase was dried by rotary evaporation and vacuum-drying. The pure product was isolated by precipitation with hexanes from CH_2Cl_2 [yield: 84.0 mg (87.1%)]; waxy solid. MALDI−TOF-MS: 3257, 3241 *m*/*z*. ^{1}H NMR ($CDCl_3$) δ: 7.78 (d, 2H), 7.62 (d, 2H), 7.41 (t, 2H), 7.32 (t, 2H), 4.41 (d, 2H), 4.28 (t, 1H), 4.10 (s, 91H), 2.38 (t, 92H), 1.96 (m, 48H), 1.70 (s, 99H) (ratio 24:1) (theoretical ratio 16:1). HPLC (acetonitrile) 3.34 min; TLC R_f = 0.44 (50% CH_2Cl_2:ethyl acetate).

***p*-Methoxybenzyl-Protected Butylene Glutarate 32-mer (11B).** In an 50 mL Erlenmeyer flask, 60 mg (18 μmol) of fully protected butylene glutarate 32-mer (**11**) was stirred with 75 mg (0.75 mmol, 50 equiv) of TEA in 30 mL of CH_2Cl_2 for 4 h. The solvent and TEA were removed by rotary evaporation and vacuum-drying, and the product was isolated by filtration of a CH_2Cl_2 solution and washing with hexanes [yield: 49.4 mg (88.2%)]; waxy solid. MALDI-TOF-MS: 3155, 3139 *m*/*z*. ^{1}H NMR ($CDCl_3$) δ: 7.28 (d, 2H), 6.86 (d, 2H), 5.04 (s, 2H), 4.19 (s, 89H), 3.80 (s, 3H), 3.64 (t, 2H), 2.38 (t, 92H), 1.92 (m, 50H), 1.71 (s, 94H) (ratio 23:1) (theoretical ratio 16:1). HPLC (acetonitrile) 3.06 min; TLC R_f = 0.52 (50% CH_2Cl_2:ethyl acetate).

Butylene Glutarate 32-mer (11C). In an 50 mL Erlenmeyer flask, 50 mg (16 μmol) of FMOC-protected butylene glutarate 32-mer (**11B**) was stirred with 78 mg (0.78 mmol, 50 equiv) of TEA in 30 mL of CH_2Cl_2 for 4 h. The solvent and TEA were removed by rotary evaporation and vacuum-drying, and the product was isolated by filtration of a CH_2Cl_2 solution and washing with hexanes [yield: 39.5 mg (82.2%)]; waxy solid. MALDI−TOF-MS: 3040, 3018 *m*/*z*. ^{1}H NMR ($CDCl_3$) δ: 4.12 (s, 81H), 3.69 (t, 2H), 2.39 (t, 90H), 1.93 (m, 46H), 1.70 (s, 89H) (ratio 23:1) (theoretical ratio 16:1). HPLC (acetonitrile) 3.59 min.

Orthogonally Protected Butylene Glutarate 64-mer (12). In a round-bottom flask 31.0 mg (1.0 μmol) of FMOC-protected butylene glutarate 32-mer (**11A**), 30.0 mg (1.0 μmol) of *p*-methoxybenzyl-protected butylene glutarate 32-mer (**11B**), and 0.24 mg of DMAP (1.9 μmol) were stirred at 0 °C in 15 mL of CH_2Cl_2. EDI (2.03 mg) (10.6 μmol) was added, and the reaction mixture was stirred at 0 °C for 4 h and at RT for 16 h. The mixture was extracted 4 × 30 mL of H_2O, and the organic fraction was evaporated and dried. The crude product was dissolved in 5 mL of CH_2Cl_2 and precipitated using 50 mL of ether and then filtered and washed with ether. The precipitation product mixture was removed from the frit using acetone, then dried and recrystallized three times from 50 mL of hot ethanol, filtered, washed with ethanol, removed from the frit using acetone, and dried after each recrystallization. The recrystallized product was purified by gradient FLC with CH_2Cl_2:ethyl acetate (7:3−1:1) as the eluent. Product fractions were combined and recrystallized five times from 50 mL of ethanol, washed, and dried [yield: 14.0 mg (23.1%)]; waxy solid. MALDI−TOF-MS: 6356, 6340 *m*/*z*. ^{1}H NMR ($CDCl_3$) δ: 7.78 (d, 2H), 7.63 (d, 2H), 7.44 (t, 2H), 7.31 (t, 2H),7.29 (d, 1H), 6.90 (d, 2H), 5.04 (s, 2H), 4.40 (d, 2H), 4.09 (s, 160H), 3.80 (s, 2H), 2.37 (s, 176H), 1.92 (t, 94H), 1.69 (s,164H) (ratio 47:1) (theoretical ratio 32:1). HPLC (acetonitrile) 4.11 min; TLC R_f = 0.42 (60% CH_2Cl_2:ethyl acetate).

FMOC-Protected Butylene Glutarate 64-mer (12A). In an 25 mL Erlenmeyer flask, 12.0 mg (2.0 μmol) of fully protected butylene glutarate 64-mer (**12**) was stirred in a 5% TFA in 15 mL of CH_2Cl_2 for 2 h. The reaction mixture was extracted 3 × 25 mL of H_2O, and the organic phase was dried by rotary evaporation and vacuum-drying overnight. The pure product was isolated by precipitation with 50 mL of ether from 2 mL of CH_2Cl_2 and recrystallization using 50 mL of ethanol [yield: 9.8 mg (82.5%)]; waxy solid. MALDI−TOF-MS: 6237, 6221 *m*/*z*. ^{1}H NMR ($CDCl_3$) δ: 7.78 (d, 2H), 7.62 (d, 2H), 7.41 (t, 2H), 7.32 (t, 2H), 4.41 (d, 2H), 4.10 (s, 166H), 2.38 (s, 171H), 1.96 (t, 96H), 1.70 (s, 153H) (ratio 48:1) (theoretical ratio 32:1). HPLC (acetonitrile) 3.97 min; TLC R_f = 0.31 (50% CH_2Cl_2:ethyl acetate).

***p*-Methoxybenzyl-Protected Butylene Glutarate 64-mer (12B).** In a round-bottom flask, 3.0 mg (0.5 μmol) of orthogonally protected butylene glutarate 64-mer (**12**) was stirred with 50 mg of TEA in 5 mL of CH_2Cl_2 at RT for 4 h. The reaction mixture was rotary-evaporated and dried overnight to remove volatile components. The crude product was dissolved in CH_2Cl_2 and filtered, then precipitated with 50 mL of ether from 2 mL of CH_2Cl_2, filtered, and washed with ether. The isolated precipitate was recrystallized using 50 mL of ethanol, filtered, washed, and dried [yield: 2.5 mg (83.3%)]; wax. MALDI−TOF-MS: 6136, 6120 *m*/*z*. ^{1}H NMR ($CDCl_3$) δ: 7.28 (d, 1H), 6.87 (d, 2H), 5.04 (s, 2H), 4.09 (s, 158H), 3.79 (s, 3H), 3.65 (t, 2H), 2.35 (s, 182H), 1.92 (t, 90H), 1.64 (s, 161H) (ratio 45:1) (theoretical ratio 32:1). HPLC (acetonitrile) 3.84 min.

Butylene Glutarate 64-mer (12C). In an 50 mL Erlenmeyer flask, 7.5 mg (1.0 μmol) of FMOC-protected butylene glutarate 64-mer (**12A**) was stirred in 2 mL of 5% TEA:CH_2Cl_2 for 4 h. TEA and CH_2Cl_2 were then removed by rotary evaporation followed by vacuum-drying for 48 h. The crude product was redissolved in 2 mL of CH_2Cl_2, filtered, and precipitated with 50 mL of ether and then filtered and washed. The precipitate was recrystallized from hot ethanol, filtered, washed with ethanol, captured with acetone, and dried [yield: 5.9 mg (79.1%)]; waxy solid. MALDI-TOF-MS: 6021, 6015, 5999 *m*/*z*. ^{1}H NMR ($CDCl_3$) δ: 4.12 (s, 179H), 3.69 (t, 2H), 2.39 (t, 187 H), 1.93 (t, 93H), 1.70 (s, 179H) (ratio 46:1) (theoretical ratio 32:1). HPLC (acetonitrile) 4.07 min.

Analysis. ^{1}H nuclear magnetic resonance (NMR) spectra were acquired using a Bruker Aspect-3000, AM-500 spectrometer (500 MHz) without nuclear Overhauser enhancement (NOE) using $CDCl_3$ or d_6-acetone as the solvent. Relative NMR intensity values were obtained by integration to provide peak areas. Electron impact (EI-MS), chemical ionization (CI-MS), and liquid secondary ionization (LSI-MS) mass spectrometry were performed on a VG Autospec 3 sector mass spectrometer in the positive ion mode. MALDI-TOF-MS was performed on a PE Biosystem Voyager System STR 4087 time-of-flight mass spectrometer (Carnegie Mellon University) and a Voyager-DE STR, PE Biosystems time-of-flight mass spectrometer (Vanderbilt University) using *trans*-3-indoleacrylic acid (Aldrich) as the matrix. Electrospray ionization mass spectrometry (ESI-MS) was carried out using a Mariner (PE Biosystem) mass spectrometer having a TOF analyzer. Relative peak intensities from mass spectrometric techniques were estimated using peak heights.

High-performance liquid chromatography was performed on a Hewlett-Packard 1100 series LC/MSD system equipped with a C-18 column, UV (200−400 nm), and AP-ESI-MS detection (100−2000 Da), using acetonitrile with a flow of 0.400 mL/min as the mobile phase. Gel permeation chromatography (GPC) was performed at 35 °C at a flow rate of 0.40 mL/min maintained by a Waters 510 HPLC pump using a Phenomenex Phenogel 5 μM, 500 Å column with tetrahydrofuran as the mobile phase. The instrument was equipped with a Waters 410 refractive index detector and a Waters 745 data module. Polyester samples and poly(ethylene glycol) (Polyscience) calibration standards of molecular weights 200, 900, 1500, 5000, and 9000 were prepared at a concentration of 1 mg/mL.

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References and Notes

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(37) The quantities of reactant(s) for this synthetic step reflect the addition of supplemental material(s) produced in a separate but similar reaction.

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