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Synthesis of Segmented Polylactide Molecular Brushes and Their Transformation to Open-End Nanotubes

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ABSTRACT: Segmented polylactide (PLA) core−shell molecular brushes, where the shell layer was located only in the middle part of the bottlebrush, were synthesized and converted to organic nanotubes with controlled dimensions and open ends. Segmented bottlebrush copolymer precursors were prepared from a triblock copolymer backbone with orthogonally protected hydroxyl groups and consisted of a poly(solketal methacrylate) middle block and poly(2-(*p*-methoxybenzyloxy)ethyl methacrylate) end blocks. The use of two selective protecting groups allowed for the sequential grafting of the middle and end PLA brushes with different end-groups. The shell layer of poly(4-(3-butenyl)styrene) was added by RAFT polymerization from the middle PLA brushes. Nanotubes were obtained by cross-linking of the shell layer under dilute conditions and subsequent removal of the PLA core. Transmission electron microscopy characterization revealed the formation of nanotubes with uniform size and open pore structure. The cylindrical shape of the bottlebrush macromolecules was maintained by the inner PLA core, while the nanotube length was independently controlled by the width of the shell layer.

Introduction

Bottlebrush copolymers, or molecular brushes, are a unique class of densely grafted macromolecules with a comb-like architecture.[1−4] Steric repulsion between polymeric side chains causes the bottlebrush backbone to adopt an extended conformation. When the length of the backbone is larger than the length of the side chain branches, bottlebrush macromolecules take on a cylindrical shape in solution.[3,5,6] There is an increasing interest in the utilization of these polymers with a unique macromolecular architecture as templates to create nanoparticles,[7] nanowires,[8] and nanotubes,[9] as well as for the fabrication of advanced materials, such as supersoft elastomers[10,11] and photonic crystals.[12] Unique interactions of bottlebrush copolymers with surfaces have also led to the development of molecular tensile machines on their basis.[13]

Precise control over the dimensions and function of the nanomaterials generated from bottlebrush copolymers requires the use of well-defined, multicomponent polymer precursors. There are three general methods for the controlled synthesis of bottlebrush copolymers: grafting-onto,[14] grafting-through,[11,15−17] and grafting-from,[18−21] the latter two being the most common. In the grafting-through method, polymer branches with reactive chain ends, called macromonomers, are synthesized first. Subsequently, macromonomers are polymerized to provide molecular brushes. This method allows for the synthesis and characterization of well-defined branches, but the polymerization of macromonomers is sterically congested and often cannot be accomplished by controlled radical or ionic polymerization techniques.[11,16,17] Recently, several groups reported the use of ring-opening metathesis polymerization for the preparation of well-defined bottlebrushes by the grafting-through method.[15,22,23] Highly active ruthenium-based catalysts along with the formation of a five-carbon repeat unit allow for the successful polymerization of bulky macromonomers. On the other hand, in the grafting-from approach, a well-defined polymer backbone with latent initiating sites is synthesized first. Later, polymer branches are grafted from the backbone via ring-opening polymerization of lactones,[12,21,24] atom-transfer radical polymerization[18,19,25] or reversible addition−fragmentation chain transfer (RAFT) polymerization.[26,27] This method allows for the synthesis of well-defined backbones, but the density of branches along the backbone may be diminished due to reduced initiation efficiencies. Overall, the two methods are quite complementary and can provide well-defined bottlebrush copolymers with a better control over one structural characteristic than the other.

We recently reported a synthesis of multicomponent bottlebrush copolymers by a combination of the grafting-from and grafting-through methods and their transformation to well-defined tubular nanostructures.[9] This molecular templating technique enabled the fabrication of organic nanotubes with controlled dimensions (length and pore size) and functional composition in an unprecedented fashion. The synthesis of nanotubes with open pores, which are desired for drug delivery and other applications relying on encapsulation of guest molecules, remains a challenge. The previously used poly(ethylene oxide) bottlebrush stopper had limited versatility and did not provide nanotubes with easily identifiable open ends. To circumvent this limitation, we designed a new bottlebrush copolymer precursor that is composed of a degradable polylactide (PLA) bottlebrush with a cross-linkable poly(4-butenylstyrene) (PBS) shell located only in the middle of the molecule (Scheme 1). After cross-linking of the PBS layer and subsequent degradation of the PLA core, nanotubes with open pores are obtained. This new approach also allows for the independent control of the nanotube dimensions by the width of the PBS layer, while the cylindrical shape of the bottlebrush molecules is maintained by the core PLA brush. Herein, we report the synthesis of a core−shell bottlebrush copolymer with PLA stoppers at both ends and its transformation into organic nanotubes with open pores. The synthesis of the segmented PLA bottlebrush required the use of a triblock copolymer with orthogonally protected

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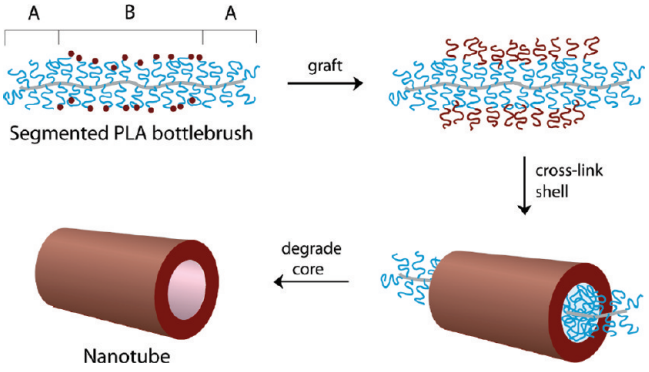
Scheme 1



hydroxyl groups. Toward this goal, we also describe the synthesis of a new protected 2-hydroxyethyl methacrylate (HEMA) monomer, which can be deprotected under mild conditions in the presence of hydrolytically unstable PLA. This new methodology exemplifies molecular engineering of the precursor macromolecules for the rational design of well-defined nanostructures.

Experimental Section

Materials. All reagents were used as received unless stated otherwise. $Yb(OTf)_3$ was purchased from Strem and used without further purification. Dichloromethane and *N*,*N*-dimethylformamide (DMF) were dried using a commercial solvent purification system (Innovative Inc.). Styrene (S) was purified by passing over basic alumina. 2,2.-Azoisobutyronitrile (AIBN) and D,L-lactide (LA) were purified by recrystallization from methanol and ethyl acetate, respectively. *S*-1-Dodecyl-*S*′-(α,α′-dimethyl-α′′-acetic acid)trithiocarbonate (TC),[28] 1,4-bis(2-(thiobenzoylthio)prop-2-yl)benzene (DT),[29] solketal methacrylate (SM),[30] and 4-(3-butenyl)styrene (BS)[31] were synthesized according to the reported procedures.

Synthesis of 2-(*p*-Methoxybenzyloxy)ethyl Methacrylate (BM). A solution of 2-hydroxyethyl methacrylate (1.8 mL, 15 mmol) and 4-methoxybenzyl alcohol (4.0 mL, 32 mmol) in dichloromethane (42 mL) was treated with $Yb(OTf)_3$ (0.9 mg, 1.5 mmol) and stirred at room temperature. After the completion of the reaction (TLC analysis), the mixture was diluted with water and the two layers were separated. The water layer was extracted with dichloromethane, and the combined organic layer was washed with water, dried (Na_2SO_4), and concentrated on a rotavap. Purification of the crude residue by column chromatography (silica gel, 7:1 hexane/ethyl acetate) provided the product as a colorless oil (1.9 g, 50%). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.3 (d, 2H), 6.9 (d, 2H), 6.1 (s, 1H), 5.6 (s, 1H), 4.5 (s, 2H), 4.3 (t, 2H), 3.8 (s, 3H), 3.7 (t, 2H), 1.9 (s, 3H). ^{13}C NMR ($CDCl_3$), δ (ppm): 167.9, 159.8, 136.7, 130.7, 129.8, 126.3, 114.3, 111.5, 78.0, 73.1, 68.1, 64.5, 55.8, 18.9. EI/HRMS: calculated for $C_{14}H_{18}O_4$, 273.1097; found, 273.1096.

Poly(SM) (1). SM (0.49 mL, 2.6 mmol), DT (6 mg, 1.3×10^{-2} mmol), AIBN (0.1 mL of 13 mM stock solution in toluene), and toluene (0.02 mL) were mixed in a reaction vessel and degassed by three freeze−pump−thaw cycles. The polymerization was conducted at 65 °C for 16 h. The reaction was stopped by cooling to room temperature and opening the vessel to air. The mixture was diluted with dichloromethane and precipitated in diethyl ether 3 times and dried under vacuum at 25 °C for 24 h. Yield = 0.29 g (77%). SEC (PS stds): M_n = 16 kg/mol, M_w/M_n = 1.32.

Triblock Copolymer Backbone Poly(BM-*b*-SM-*b*-BM) (2). Poly(SM) (70 mg, 5.0×10^{-3} mmol of RAFT groups), BM (160 mg, 0.64 mmol), AIBN (0.1 mL of 2.5 mM stock solution in toluene) and toluene (0.06 mL) were mixed in a reaction vessel and degassed by three freeze−pump−thaw cycles. The polymerization was conducted at 65 °C for 15 h. The reaction was then stopped by cooling to room temperature and opening the vessel to air. The mixture was diluted with dichloromethane and precipitated in methanol 3 times and dried under vacuum at 25 °C for 24 h. Yield = 0.19 g (77%). SEC (PS stds): M_n = 43 kg/mol, M_w/M_n = 1.39.

Hydrolysis of Poly(BM-*b*-SM-*b*-BM). Polymer **2** (50 mg), *p*-toluenesulfonic acid (13 mg) and 1 mL of THF were added into a 10 mL round-bottom flask. The reaction mixture was stirred at room temperature for 24 h. The resulting polymer was precipitated from THF into methanol 3 times and dried under vacuum at 25 °C for 24 h. Yield = 38 mg (92%).

Poly(BM-*b*-(SM-*g*-LA)-*b*-BM). Hydrolyzed polymer **2** (38 mg, 0.11 mmol of OH groups) and D,L-lactide (293 mg, 2.0 mmol) were added to a flame-dried 10 mL round-bottom flask in the glovebox. Dry DMF (1.8 mL) was then added under nitrogen, the flask was sealed and the mixture was stirred until all polymer dissolved. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 8.8 μL, 0.06 mmol) was then injected into the flask. After stirring at room temperature for 1.5 h, the reaction was quenched by adding 45 mg of benzoic acid. The resulting polymer was precipitated into methanol, redissolved in dichloromethane and precipitated in methanol 2 more times, and finally dried under vacuum at room temperature for 24 h. Yield = 0.25 g (87%). SEC (PS stds): $M_n = 1.5 \times 10^2$ kg/mol, M_w/M_n = 1.56.

Poly(BM-*b*-(SM-*g*-LA-TC)-*b*-BM) (3). Oxalyl chloride (1.45 mL, 2.9 mmol) and TC (0.1 g, 0.27 mmol) were mixed in dry dichloromethane (2.2 mL) under nitrogen atmosphere and stirred at room temperature until gas evolution stopped (~2 h). Excess reagents were then removed under high vacuum. Poly(BM-*b*-(SM-*g*-LA)-*b*-BM) (220 mg, 9.5×10^{-2} mmol of OH groups) in 5 mL of dry dichloromethane was then added to the reaction flask, and the reaction was allowed to proceed for 20 h at room temperature. The polymer was precipitated in methanol, redissolved in dichloromethane, precipitated in methanol two times, and dried in a vacuum oven overnight. Yield = 0.24 g (84%). ^{1}H NMR: End-group conversion >95%.

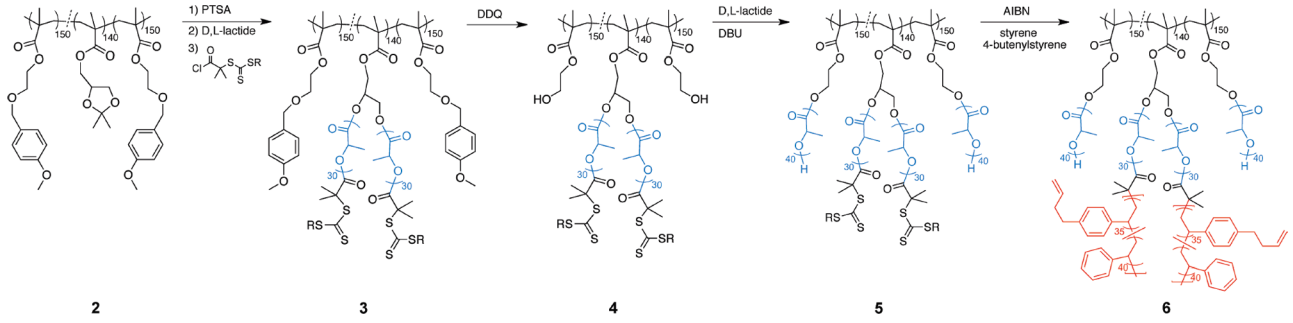
Debenzylation of Poly(BM-*b*-(SM-*g*-LA-TC)-*b*-BM) (4). Polymer **3** (104 mg, 3.4×10^{-2} mmol), 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ, 11 mg, 4.8×10^{-2}) and dichloromethane (2 mL) were added into a 10 mL round-bottom flask. The reaction mixture was stirred until all polymer dissolved. Deionized water (0.1 mL) was then added into the flask. After stirring at room temperature for 15 h, the resulting polymer **4** was precipitated in methanol three times and dried under vacuum at 25 °C for 24 h. Yield = 0.08 g (87%). ^{1}H NMR: Deprotection >95%.

Poly((BM-*g*-LA)-*b*-(SM-*g*-LA-TC)-*b*-(BM-*g*-LA)) (5). Polymer **4** (15 mg, 4.8×10^{-3} mmol of OH groups) and D,L-lactide (36 mg, 0.25 mmol) were added into a dried 10 mL round-bottom flask in the glovebox. Dry DMF (0.5 mL) was then added under nitrogen and the mixture was stirred until all polymer dissolved. The flask was sealed and removed from the glovebox, and DBU (1.1 μL, 7.5×10^{-3} mmol) was injected into the flask. After stirring at room temperature for 2 h, the reaction was quenched by adding benzoic acid (5 mg). The resulting polymer **5** was precipitated in methanol, redissolved in dichloromethane and precipitated in methanol 2 more times. The product was dried under vacuum at room temperature for 24 h. Yield = 26 mg (87%). SEC (PS stds): $M_n = 2.4 \times 10^2$ kg/mol, M_w/M_n = 1.40.

Poly((BM-*g*-LA)-*b*-(SM-*g*-LA-*g*-S/BS)-*b*-(BM-*g*-LA)) (6). Polymer **5** (10 mg, 1.6×10^{-3} mmol of RAFT groups), AIBN (0.1 mL of 1.6 mM stock solution in toluene), styrene (0.11 mL, 0.96 mmol), BS (0.16 mL, 0.96 mmol) and toluene (0.17 mL) were mixed in a reaction vessel and degassed by three freeze−pump−thaw cycles. The polymerization was then conducted at 55 °C for 23 h. The reaction was stopped by cooling down to room temperature and opening the flask to air. The resulting polymer **6** was then precipitated from dichloromethane into methanol 3 times and dried under vacuum at room temperature for 24 h. Yield = 26 mg (monomer conversion = 7%). SEC (PS stds): $M_n = 4.6 \times 10^2$ kg/mol, M_w/M_n = 1.36. ^{1}H NMR: Conversion = 10.5%.

Intramolecular Cross-Linking. Polymer **6** (10 mg) was dissolved in 20 mL of toluene under nitrogen. A solution of Grubbs'

Scheme 2



first generation catalyst (1 mg) in toluene (0.5 mL) was added into the reaction solution and then the mixture was stirred at room temperature under nitrogen for 24 h. Ethyl vinyl ether (0.4 mL) was added to the reaction mixture to quench the catalyst. The solvent was then evaporated and shell-cross-linked polymers were precipitated in methanol, redissolved in dichloromethane and precipitated in methanol.

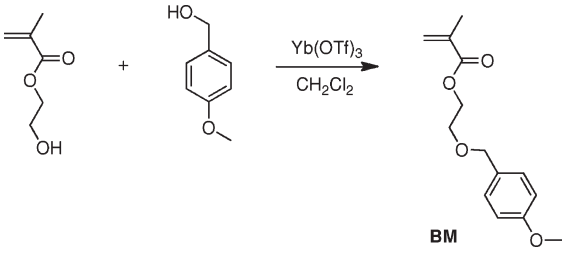
Core etching. Intramolecularly cross-linked polymer **6** (8 mg) was dissolved in 1,4-dioxane (16 mL). Hydrochloric acid (5 M, 2 mL) was then added to the above solution dropwise under stirring. The mixture was placed in an oil bath at 90 °C and stirred for 1 day. The solvent was removed on a rotary evaporator. The isolated polymer was precipitated in methanol, redissolved in tetrahydrofuran, and precipitated in methanol again.

Measurements. All ^{1}H NMR spectra were recorded on a Varian Inova-500 spectrometer (500 MHz) by using $CDCl_3$ or DMSO-d_6 as a solvent. Size exclusion chromatography (SEC) data was obtained using a Viscotek's GPCmax and TDA302 Tetradetector Array system equipped with three Olexis columns (Polymer Laboratories, Varian Inc.). The detector unit contained a refractive index, UV, viscosity, low (7°) and right angle light scattering modules. Tetrahydrofuran (30 °C, 1 mL/min) was used as a mobile phase. The system was calibrated with 10 polystyrene standards from 1.2×10^6 to 500 g/mol. The refractive index increment (dn/dc) for poly(SM) was measured to be 0.067 mL/g in THF (T = 30 °C, λ = 630 nm), and was used to determine absolute molecular weights of the homopolymer. The dried nanotube aggregates were examined using the FTIR (Perkin-Elmer 1760X). TEM images were obtained using a JEOL 2010 TEM instrument. Samples were prepared by dip-coating a 400 mesh carbon-coated copper grid (Ted Pella Inc.) from a dilute sample solution in toluene. High-resolution mass spectrometry (HRMS) data was recorded on a VG 70-SE mass spectrometer with electron ionization mode. Dynamic light scattering measurements were carried out using a Zetasizer Nano ZS (Malvern Instruments, Malvern, UK) equipped with a He−Ne laser (λ = 633 nm) as the incident beam.

Results and Discussion

Synthetic Strategy. According to our molecular design depicted in Scheme 1, we targeted the synthesis of a core−shell bottlebrush copolymer with the outer shell layer located only in the middle of the bottlebrush. The synthetic route to such molecular brushes via the grafting-from approach is outlined in Scheme 2. First, a triblock copolymer backbone is synthesized to contain ketal groups in the middle block and *p*-methoxybenzyl (PMB) protected hydroxyls in the end blocks (polymer **2**). The ketal groups are then hydrolyzed to expose diol initiators, which are subsequently used to install polylactide branches located only in the middle block and end-capped with trithiocarbonate groups (polymer **3**). In the following step, *p*-methoxybenzyl groups are deprotected to provide hydroxyl groups located in the end block of the triblock copolymer backbone (polymer **4**). The hydroxyl initiators are then used to grow PLA branches from the end blocks to provide a segmented PLA bottlebrush containing trithiocarbonate RAFT chain transfer groups only within the middle segment (polymer **5**). Lastly, a random copolymer of styrene and 4-(3-butenyl)styrene is added as a cross-linkable shell layer via RAFT polymerization (polymer **6**).

Scheme 3



Synthesis of *p*-Methoxybenzyl-Protected HEMA. The choice of *p*-methoxybenzyl as one of the protecting groups in the triblock copolymer **2** backbone stemmed from the stringent requirements on the stability of this group under acidic conditions as well as on the mild conditions necessary for its removal. According to our synthetic strategy illustrated in Scheme 2, this functional group has to survive conditions of ketal hydrolysis, lactide polymerization and RAFT chain transfer agent end-capping, as well as be deprotected in the presence of hydrolytically unstable PLA. It has been documented before that PMB groups can be efficiently removed by oxidative debenzylation.[32,33] This process proceeds under mild conditions with DDQ as the oxidizing agent in dichloromethane in the presence of trace amounts of water and thus should be compatible with PLA.

PMB-protected 2-hydoxyethyl methacrylate (BM) was synthesized in one step from commercially available reagents (Scheme 3). The reaction of HEMA with PMB alcohol (2 equiv) in the presence of $Yb(OTf)_3$ (10 mol %)[34] was carried out in dichloromethane at room temperature to give the product in 50% yield. The formation of PMB alcohol dimer was a major side reaction, but a clean BM monomer could be obtained after column chromatography purification. The structure of the obtained PMB protected monomer was confirmed by NMR and MS analyses (Supporting Information, Figure S1).

Synthesis of poly(BM-*b*-SM-*b*-BM) Triblock Copolymer. A difunctional RAFT agent DTB was synthesized according to the reported procedure[29] and was used in the AIBN initiated RAFT polymerization of solketal methacrylate (SM) (Scheme 4, Supporting Information Figure S2). DTB-mediated polymerization of SM provided telechelic polymers with a relatively narrow molecular weight distribution (Table 1). The absolute degree of polymerization of poly(SM) (**1**) was measured by SEC-light scattering analysis to be 140 units. Subsequently, poly(SM) macro-chain-transfer

Scheme 4

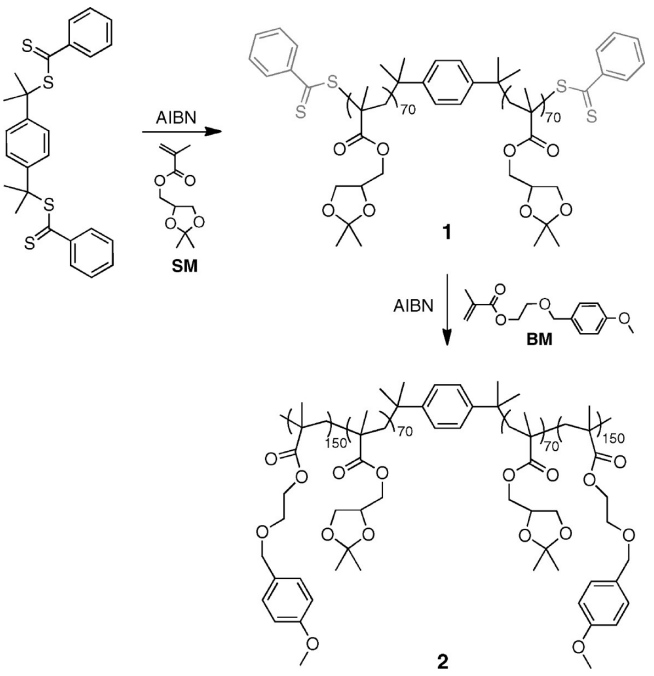


Table 1. Molecular Weights and Polydispersities of the Synthesized Copolymers

polymer	$M_{n,\,NMR}$[a] (kg/mol)	$M_{n,\,SEC}$[b] (kg/mol)	M_w/M_n[b]
1	29	16	1.32
2	105	43	1.39
3	870	145	1.43
5	1790	240	1.40
6	4600	460	1.42

[a] Calculated by NMR analysis knowing molecular weights of the precursors. [b] From SEC analysis using PS calibration.

agent was utilized to prepare an ABA triblock copolymer **2** by polymerizing BM. The SEC analysis corroborated the formation of a well-defined block copolymer without an increase in polydispersity values (Table 1 and Figure 1). A complete shift of the polymer molecular weight distribution peak in SEC confirmed efficient initiation from the poly(SM) macro-chain-transfer agent. The copolymer composition was calculated from ^{1}H NMR analysis by comparing the integral ratio of the aromatic peak (6.9 ppm) of poly(BM) and methyl signals (1.28 and 1.34 ppm) from poly(SM) (Figure 2). Triblock copolymer **2** was measured to contain 150 units of poly(BM) in each of the end blocks. The obtained molecular weight characteristics of the copolymers are summarized in Table 1. The structure of the triblock copolymer **2** in Scheme 2 was drawn to omit the middle benzene ring from the backbone for simplicity.

Synthesis of Segmented PLA Bottlebrush Copolymers. Triblock copolymer **2** contained orthogonally protected hydroxyls, by ketal groups in the middle block and by PMB groups in the end blocks. In the first step toward the synthesis of segmented PLA bottlebrushes, ketal groups were removed to expose hydroxyl initiators in the middle block only. Previously reported conditions for ketal hydrolysis (1 N HCl−tetrahydrofuran mixture)[12] resulted in a concurrent partial deprotection of PMB groups. However, under milder conditions, in the presence of *p*-toluenesulfonic acid, we were able to selectively remove ketal groups, while leaving PMB functionalities intact. Complete deprotection of diols was verified by ^{1}H NMR spectroscopy (Figure 2), as methyl proton

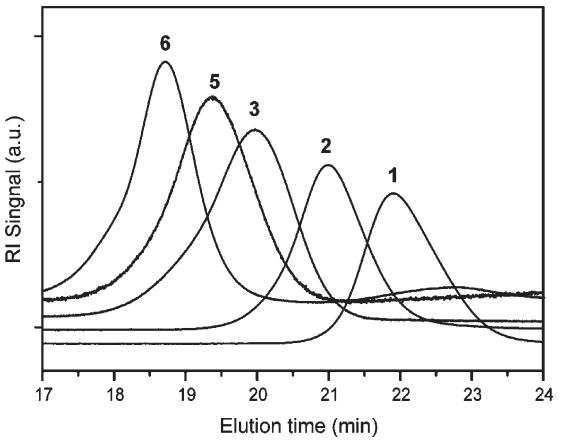


Figure 1. SEC characterization of the synthesized copolymers.

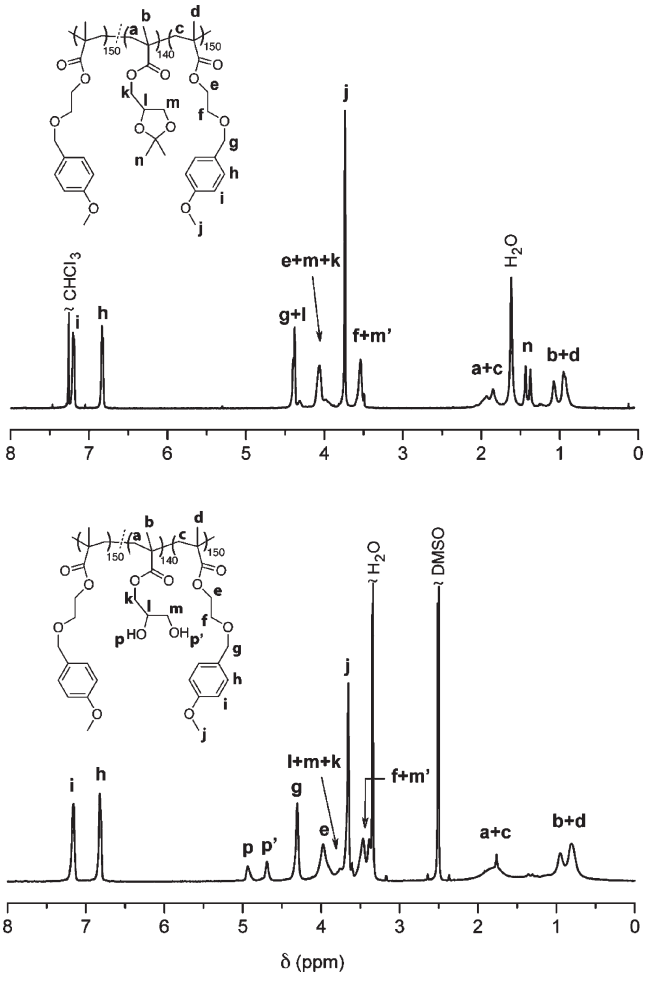


Figure 2. ^{1}H NMR spectra of the pristine triblock copolymer **2** (top, $CDCl_3$) and selectively hydrolyzed copolymer **2** (bottom, DMSO-d_6).

signals of the solketal group (1.28 and 1.34 ppm) completely disappeared after hydrolysis. At the same time, two new peaks originating from the diol hydroxyl protons could be clearly distinguished at 4.6 and 4.8 ppm in deuterated DMSO. Importantly, aromatic signals (7.2 and 6.9 ppm) from PMB groups remained unchanged, indicating that no deprotection of the PMB groups had taken place during the process of ketal hydrolysis.

The produced diol groups were then utilized as initiators for the ring-opening polymerization of D,L-lactide (LA),

which was carried out under mild conditions in the presence of DBU as the catalyst at room temperature.[35] SEC analysis showed a new monomodal elution peak with a relatively low polydispersity, cleanly shifted from the triblock macroinitiator peak (Figure 1 and Table 1). The length of the obtained PLA branches was calculated to be 30 repeat units per branch from the NMR end-group analysis by comparing the main chain PLA methine signal at 5.2 ppm to the end-group methine signal at 4.4 ppm (Supporting Information, Figure S3). The number of PLA branches per backbone was calculated by comparing ^{1}H NMR signal intensities of the PLA methine end-group peak at 4.4 ppm to the PMB aromatic protons at 6.9 ppm. The obtained number was approximately twice as large as the number of SM repeat units in the backbone, indicating the formation of 2 PLA branches for every diol group, and thus, quantitative initiation. This result is in agreement with our previous reports of quantitative initiation of PLA from polyol initiators[9] and demonstrates the formation of remarkably densely grafted molecular brushes.

The hydroxyl end-groups of PLA grafts were then capped with trithiocarbonate RAFT agents. Using previously reported conditions,[9] oxalyl chloride mediated coupling of acid-functionalized trithiocarbonate chain transfer agent (TC) with PLA chain ends proceeded to complete conversion. The successful outcome of the reaction was corroborated by ^{1}H NMR analysis (Figure 3) with complete disappearance of the PLA methine end-group signal at 4.4 ppm and the appearance of a new characteristic signal at 3.3 ppm, corresponding to methylene protons adjacent to the trithiocarbonate group.

In the following step, *p*-methoxybenzyl protecting groups at the end blocks of the backbone were cleaved by oxidative debenzylation with DDQ. ^{1}H NMR analysis (Figure 3) confirmed a complete removal of the PMB groups. Signals at 6.9 and 7.2 ppm, corresponding to the PMB aromatic protons, disappeared, while a new peak at 4.9 ppm was attributed to the hydroxyl proton of the deprotected alcohol. To confirm that no PLA degradation had taken place during deprotection, we compared peak integral ratios of the PLA backbone methine signal at 5.2 ppm to the methylene protons of the PMB groups before (4.1 ppm) and after (3.9 ppm) debenzylation (Figure 3). Both ratios were close to 15, suggesting good chemical stability of PLA under the deprotection conditions. In addition, no PLA methine end-group peak at 4.4 ppm (which would result from a random PLA backbone cleavage) was detected after deprotection with DDQ, confirming the absence of PLA degradation under these conditions.

The obtained hydroxyl groups at the end blocks were then used to initiate a ring-opening polymerization of D,L-lactide in the presence of DBU to provide a triblock PLA bottlebrush copolymer with RAFT agent groups located only in the middle segment (polymer **5**). A clean shift of the SEC elution curve for the polymer after second PLA grafting suggested efficient initiation and the absence of major side reactions (Figure 1 and Table 1). Characteristic PLA end group signals at 4.4 ppm (methine) and at 2.8 ppm (hydroxyl protons) could be observed in the ^{1}H NMR spectrum of the product, while main chain PLA peaks overlapped with those of the middle PLA brush (Figure 4). The length of end-block PLA branches was calculated to be 40 repeat units per branch from the NMR end-group analysis (vide supra).

Shell Grafting. The shell layer, composed of a random copolymer of styrene and 4-(3-butenyl)styrene, was grafted from the segmented PLA bottlebrush by RAFT polymerization (polymer **6**). The polymerization was stopped at low conversions in order to prevent bimolecular coupling of polystyrene radicals leading to cross-linking. No broadening of the polymer molecular weight distribution was observed

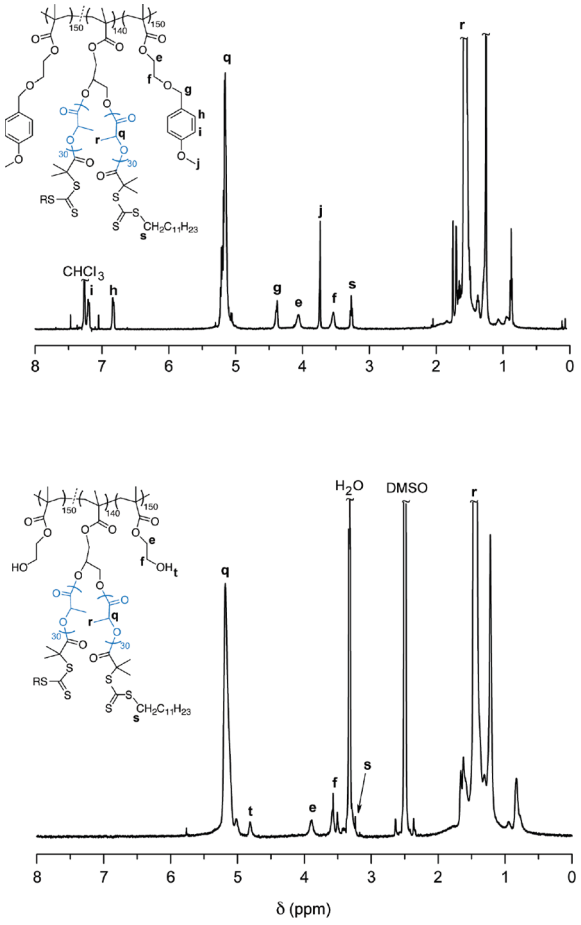


Figure 3. ^{1}H NMR spectra of PLA bottlebrush copolymer **3** (top, $CDCl_3$) and DDQ-deprotected copolymer **4** (bottom, DMSO-d_6).

after RAFT grafting, confirming the absence of major side reactions. The presence of pendant terminal alkenes in the shell layer was confirmed by NMR analysis, where peaks at 5.0 and 5.8 ppm were clearly distinguished. Copolymer chains obtained by RAFT were calculated to contain 40 units of styrene and 35 units of BS from the NMR spectrum by comparing integral areas of the aromatic and olefinic signals to the PLA signal at 5.2 ppm. SEC traces of the final bottlebrush copolymer exhibited a monomodal molecular weight distribution with only a slight high molecular weight shoulder (Figure 1), which was attributed to the bimolecular recombination of propagating polystyrene radicals.

Synthesis of Open-Ended Nanotubes. The synthesized core−shell bottlebrush copolymers with a long PLA core and a shorter cross-linkable shell were then converted to standalone organic nanotubes. In the first step, intramolecular cross-linking of the bottlebrush copolymers with the Grubbs' catalyst under dilute conditions produced cylindrical nanoparticles. Terminal olefins of the BS units were linked together by the cross-metathesis reaction with concurrent release of ethylene. FTIR analysis was used to confirm the progress of the cross-linking reaction with complete disappearance of the terminal double bond vibration at 1640 cm^{-1} (Supporting Information Figure S4). In the ^{1}H NMR spectrum of the cross-linked bottlebrush copolymers, no peaks corresponding to the shell layer could be observed due to the formation of a rigid shell (Supporting Information Figure S5). Only weak signals at 5.2 and 1.6 ppm corresponding to the PLA core were detected. Transmission electron microscopy (TEM) analysis revealed the formation

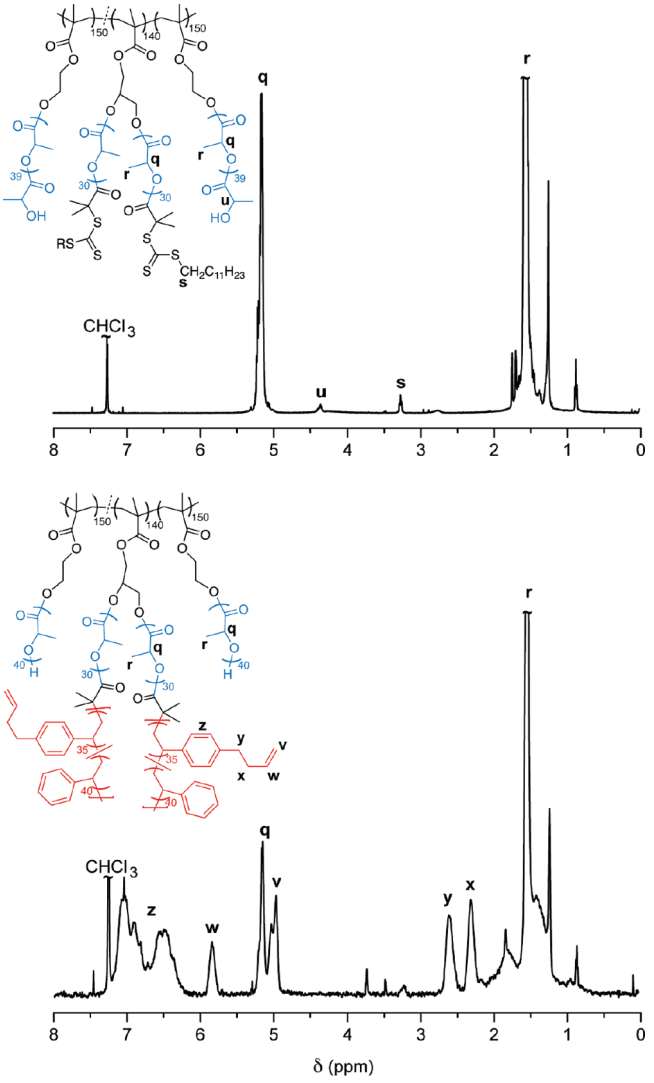


Figure 4. ^{1}H NMR ($CDCl_3$) spectra of the segmented PLA bottlebrush copolymer **5** (top) and the core−shell bottlebrush copolymer **6** (bottom).

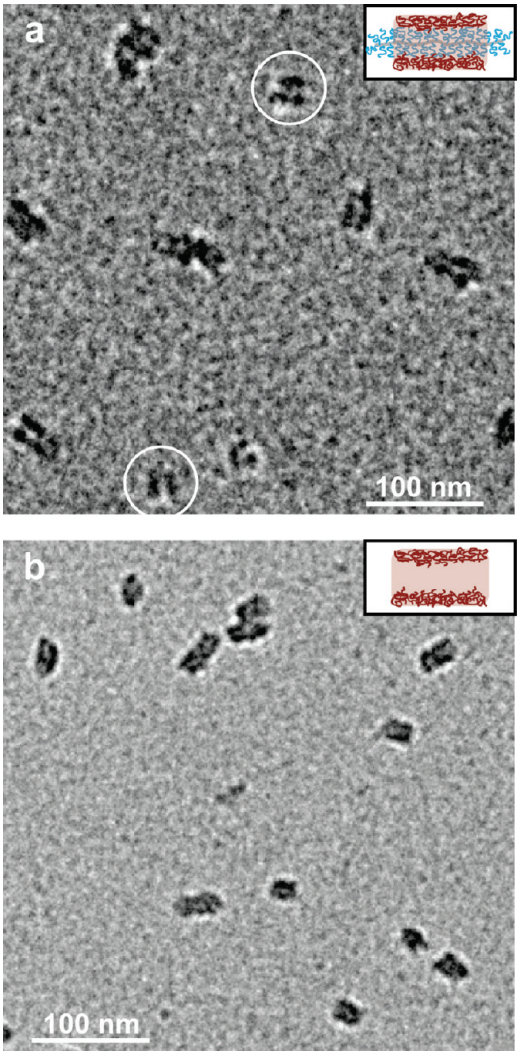


Figure 5. TEM analysis (no staining) of the cross-linked bottlebrush copolymer **6** (a) and organic nanotubes prepared on its basis (b).

of cylindrical core−shell nanoparticles with a darker shell and a lighter core (Figure 5a and Supporting Information Figure S6). The images were obtained without prior staining, and the contrast is presumably coming from the residual ruthenium catalyst trapped in the shell layer. Upon closer inspection, TEM images provide clear evidence for the formation of core−shell nanoparticles with open ends (Figure 5a). It appears that the presence of PLA bottlebrush stoppers at both ends is preventing the shell layer from creating closed capsules by curving around the ends of the cylindrical nanoparticles. The effect of the long core layer is even more evident for shorter nanoparticles (highlighted in circles in Figure 5a). For these nanostructures, the aspect ratio is almost 1, with the diameter being equal to the length of the shell layer. The nonspherical shape of these nanoparticles is maintained by the long PLA core layer. This demonstrates the feasibility to synthesize short nanotubes from segmented core−shell bottlebrush copolymers where the shell layer is located only in the middle of the molecule, while the core layer is forcing the molecule to take on a cylindrical shape.

After cross-linking, the PLA core was removed by acidic hydrolysis. The complete degradation of PLA was confirmed by the disappearance of the characteristic PLA carbonyl stretch peak (1759 cm^{-1}) in the FTIR spectrum (Supporting Information Figure S4). Dynamic light scattering analysis in dichloromethane solution revealed the formation of nanoparticles with an average hydrodynamic diameter of 62 nm. (Supporting Information Figure S7). TEM analysis confirmed that the size and the shape of nanoparticles after core removal remained unchanged (Figure 5b). In particular, cylindrical nanoparticles with flat, noncurved ends could be distinguished, suggesting the formation of open-end nanotubes. The average pore diameter of the nanotubes was around 3−5 nm, while their length was measured to be 30 ± 6 nm. The length of the prepared tubular nanostructures agreed very well with the length of a fully stretched middle segment backbone (140 repeat units, ~35 nm). Cross-linking of the shell layer was necessary to maintain the overall nanoparticle structure. PLA degradation without prior cross-linking of the shell led to the disintegration of the bottlebrush copolymer to small molecular weight chains.

Conclusions

Segmented PLA bottlebrushes were synthesized from a triblock copolymer backbone with orthogonally protected hydroxyl groups. The use of ketal groups and *p*-methoxybenzyl protecting groups, which can be cleaved under very mild conditions in the presence of hydrolytically unstable PLA, allowed for the sequential double grafting of PLA branches to provide a polylactide molecular brush with RAFT agent end-groups located only along the middle

segment. The core−shell bottlebrush copolymers prepared from these segmented PLA molecular brushes were successfully converted to standalone organic nanotubes, whose dimensions closely resembled those of the precursor copolymers. The presence of PLA brush stoppers at both ends prevented the formation of closed capsules during shell cross-linking and resulted in the fabrication of nanotubes with open pores. These results demonstrate a high degree of nanomaterial structural control that can be achieved by rational molecular design of the precursor copolymers.

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Supporting Information Available: Figures S1−S4, showing NMR and FTIR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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