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# Synthesis of First- and Second-Generation Poly(amide)-Dendronized Polymers via Ring-Opening Metathesis Polymerization

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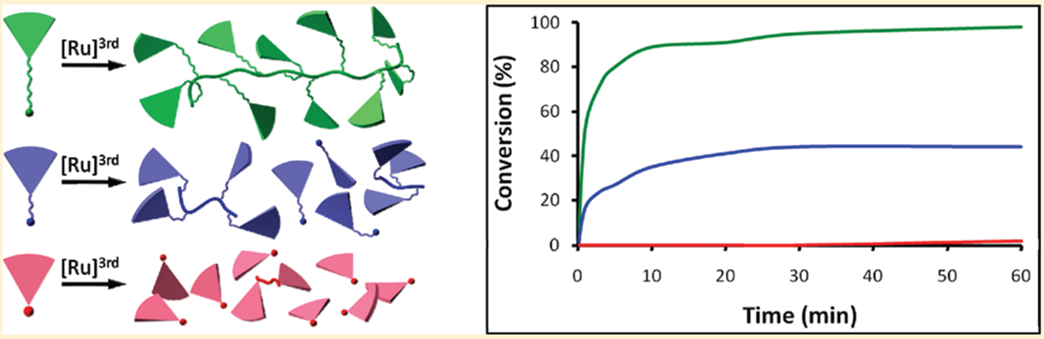
**ABSTRACT:**



First- and second-generation Newkome-type dendronized norbornene macromonomers were synthesized and polymerized by ring-opening metathesis polymerization (ROMP). In the case of the second-generation macromonomer, the rate of polymerization was highly dependent on the initial concentration of the macromonomer; quasi-quantitative polymerization was only achieved when the concentration was higher than 50 mM. Adding a linker between the polymerizable group and the dendron increased the rate of polymerization and it was possible to reach quantitative conversions at lower concentration. Doubling the length of the linker further improved the polymerization to a rate comparable with the polymerization of the first-generation dendronized macromonomer. The dendronized polymers presented herein consist of a poly(amide)-based dendron attached to the poly(norbornene) backbone. Because of the properties of these components such as biocompatibility, we foresee these polymers having possible applications in therapeutics.

## INTRODUCTION

Dendronized polymers are a subset of comb polymers in which perfectly branched dendrons are attached as pendant groups onto a linear polymer backbone, thus affording a structure where many active termini surround a single chain.[1−3] While many polymers exist as random coils in solution due to the high degree of conformational flexibility in the backbone, dendronized polymers can adopt a fully stretched linear structure due to the steric repulsion of neighboring dendrons.[4] The physical properties of these materials can be tailored by altering the dendron size/composition,[5,6] the polymer backbone composition, the degree of polymerization, and/or the length of the linker between the dendron and linear polymer.[7] Accordingly, dendronized polymers have received increasing attention due to their potential applications as responsive materials,[8,9] in molecular electronics,[10] as light-harvesting devices,[11−13] as nonaggregating polymer fluorophores,[14−16] and, of course, in the field of drug delivery.[17−20]

Dendronized polymers can be built via one of three synthetic approaches:[21] the graft-to route, the graft-from route, and the macromonomer route. In the graft-to route, a fully grown dendron is attached to a linear polymer with pendant active end groups at each repeat unit.[22−24] This route has the fewest linear synthetic steps, but shielding of the polymer's free termini by the random coil backbone and steric hindrance between dendrons may make full coverage of the polymer difficult or impossible.[1,21] In the graft-from route, first-generation dendrons are placed onto the polymer and the dendrons are grown larger from there.[25−27] Here, if a structural defect appears in the dendron, the defect is amplified as the dendron grows larger.[1,21] Finally, the macromonomer route describes the polymerization of a fully synthesized dendron containing a single polymerizable group.[7,28−30] This approach is attractive as all dendrons on the polymer chain will be incorporated perfectly, but a high degree of polymerization may be difficult to reach, possibly due to steric crowding of dendrons around the relatively smaller polymerizable group.[21,31,32] Previous reports have shown that the concentration of the macromonomer has a major influence on the degree of polymerization in the macromonomer route, allowing this problem to be mitigated.[28,30] The macromonomer route has been shown to be versatile—able to proceed under many different polymerization techniques, depending on the

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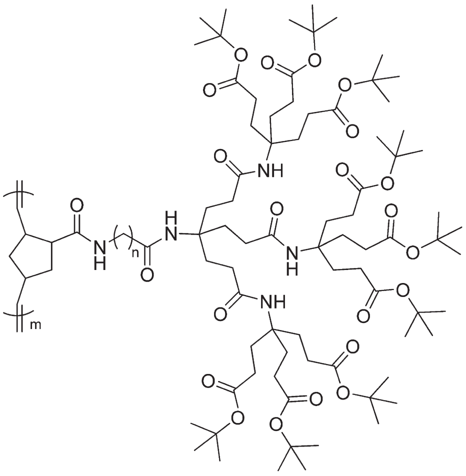


**Figure 1.** General structure of second-generation dendronized polymers synthesized for this study containing differing linker lengths ($n$ = 1, 10, 20).

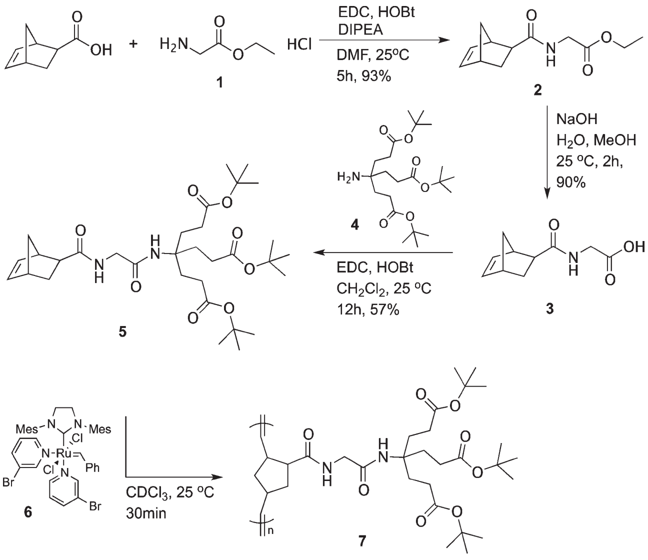
desired properties of the final polymer.[1,28] Many reports are based on the uncontrollable radical polymerization of vinyl groups.[5,30,33,34] For a number of applications, however, controlled polymerization techniques are necessary. Currently, controlled polymerization techniques used to polymerize dendronized macromonomers include atom-transfer radical polymerization (ATRP)[35,36] and ring-opening metathesis polymerization (ROMP).[37−39]

In order to form a dendronized polymer that could potentially be useful as a drug-delivery system, a dendronized polymer scaffold that is biocompatible is required. In our research design, we chose a poly(amide)-based structure for the dendron. Previous cytotoxicity tests on poly(amide) dendrimers have shown them to be highly biocompatible.[40] Our dendrons consist of the $AB_3$ structure first described by Newkome et al.[41] We have recently reported that a multifunctional dendrimer based on this motif shows no toxicity toward human T98G cells,[42] making this an ideal dendron for our purposes. As for the polymer backbone, we chose poly(norbornene) (PNB), which can be synthesized via ROMP. Polymerization of norbornene using a ruthenium-based initiator is promising due to the high tolerance of ruthenium initiators toward various functional groups and the living character of ROMP.[43−47] Polymerization of norbornenes can be achieved with the ruthenium carbene complex $[(H_2IMes)(3\text{-Br-py})_2(Cl)_2Ru{=}CHPh]$, also known as Grubbs' third-generation initiator.[48] The PNB backbone also shows promise for biocompatibility.[49,50] Indeed, ROMP of norbornene has been used successfully in biological systems; notably, Kiessling and co-workers have reported the use of PNB in the investigation of various biological signaling pathways.[51−55] This contribution describes the syntheses of first- and second-generation Newkome-style dendronized polymers based on a poly(norbornene) backbone (Figure 1). We present results on the concentration dependence of the degree of polymerization and demonstrate the effects of spacer length on the degree of polymerization.

## RESULTS AND DISCUSSION

**Synthesis of First-Generation Dendronized Polymer.** The first-generation Newkome style dendronized macromonomer **5** was designed to contain a very short linker (one carbon) between the polymerizable group and the dendron. The synthesis is shown in Scheme 1. Isomerically pure *exo*-norbornene acid was coupled to glycine ethyl ester hydrochloride using *N*-(3-(dimethylamino)-propyl)-*N*′-ethylcarbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole hydrate (HOBt). After hydrolysis of the ethyl ester of **2** under basic conditions to give the free acid **3**, commercially available dendron **4** was coupled using EDC and HOBt to afford macromonomer **5**.

**Scheme 1. Schematic Representation of the Synthesis of the First-Generation Dendronized Macromonomer and Polymer**



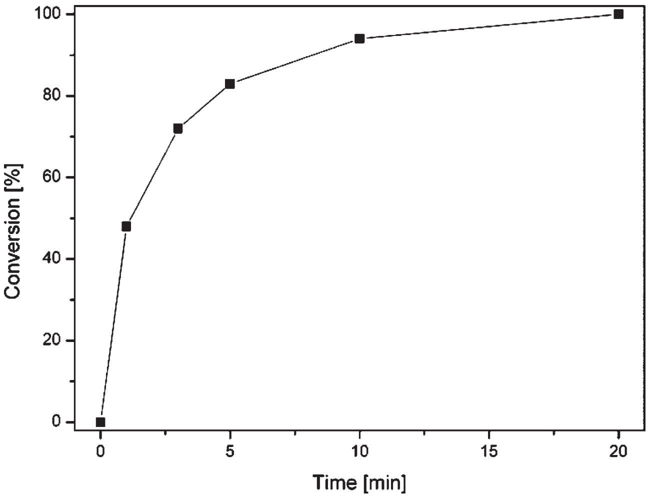
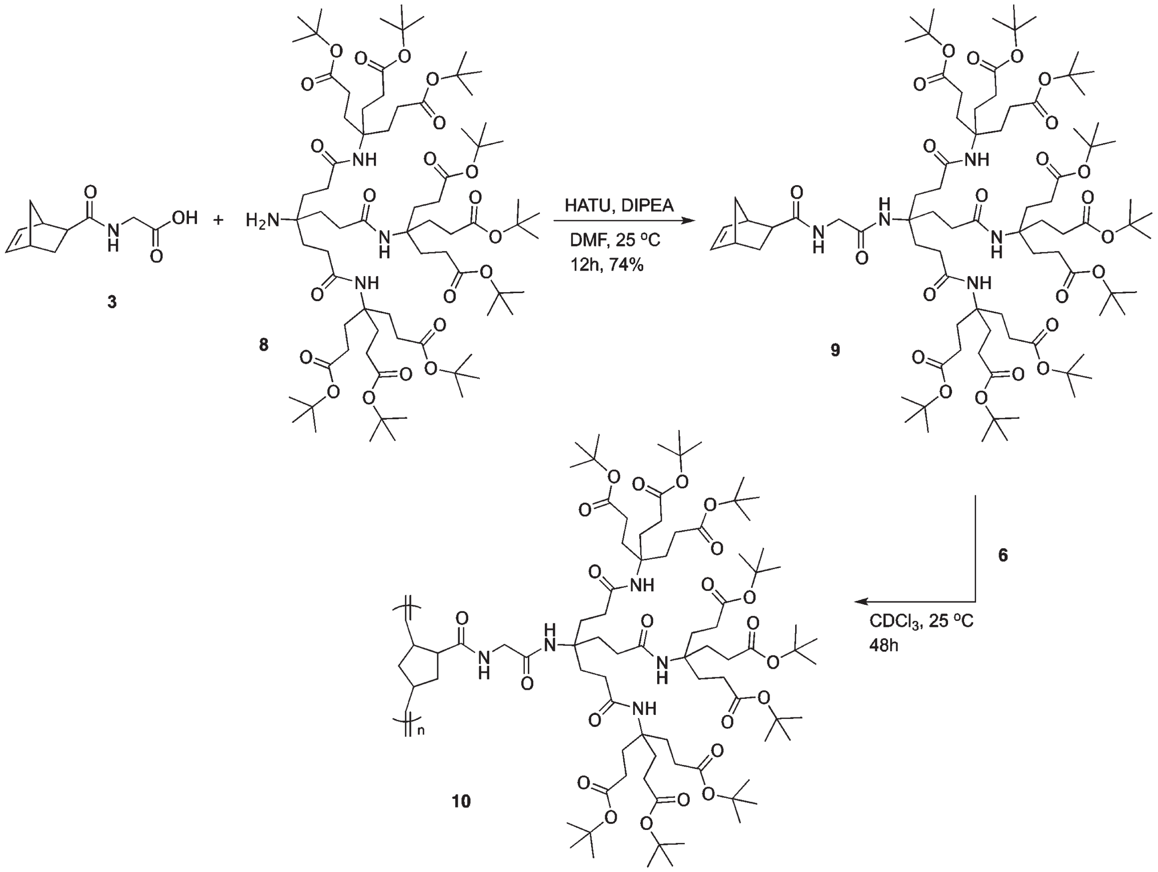


**Figure 2.** Kinetic study of the polymerization of **5** at a concentration of 10 mM chloroform.

Polymerization of **5** was carried out using Grubbs' third-generation initiator **6** in chloroform. The polymerization was followed by $^1H$ NMR spectroscopy. When activated, the olefinic protons of the monomer shift from 6.1 to 5.3 ppm and broaden significantly. At an initial macromonomer concentration of 10 mM, the polymerization reached greater than 98% completion within 30 min at 25 °C (Figure 2). The final structure **7** has a $M_n$ of 17 400 and a PDI of 1.33 as characterized

**Scheme 2. Schematic Representation of the Synthesis of the Second-Generation Dendronized Polymer Based on 9**



by gel-permeation chromatography (GPC) versus poly(styrene) standards.

**Synthesis of Second-Generation Dendronized Polymer.** The second-generation macromonomer **9** was synthesized following the same procedures as described above for **5**. Dendron **8** was coupled to **3** using 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) to form macromonomer **9** (Scheme 2). Polymerization of **9** under the same polymerization conditions as above resulted in less than 2% conversion. Increasing the initial monomer concentration, while holding the monomer/initiator ratio constant, did improve the polymerization, but even at an initial macromonomer concentration of 1 M, the polymerization stopped at about 50% conversion (Figure 3).

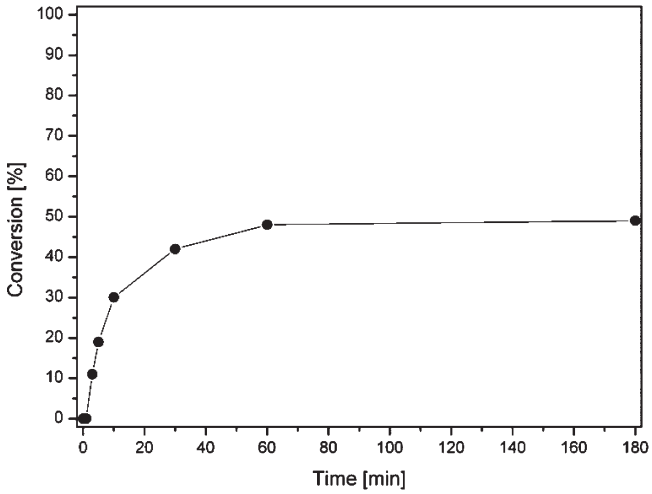
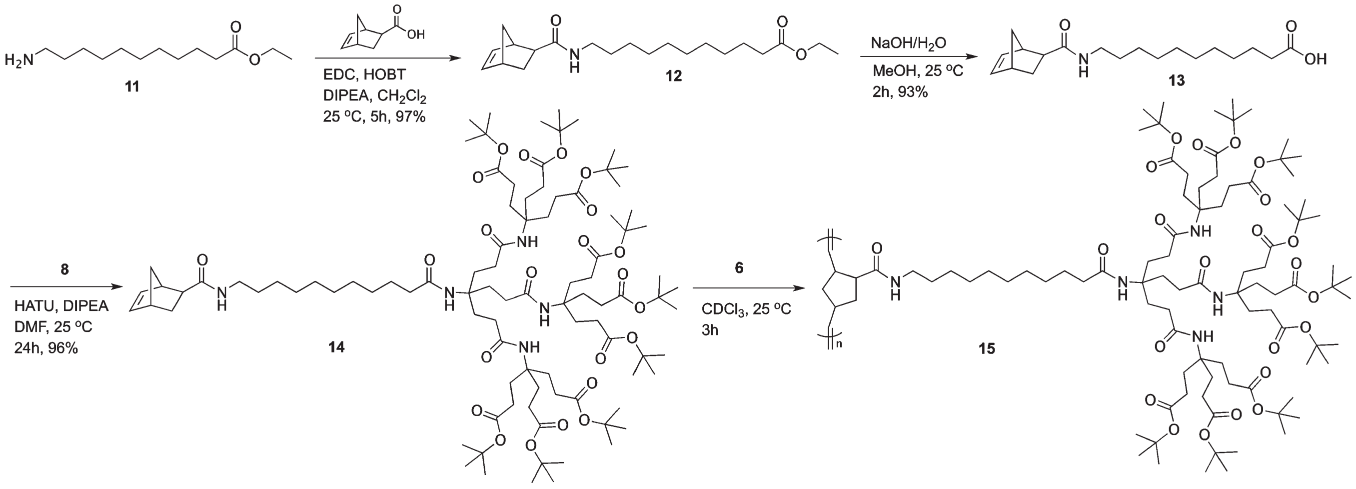


**Figure 3.** Kinetic study of the polymerization of **9** at an initial concentration of 1 M chloroform. Polymerization plateaus below 50% conversion under these conditions.

To investigate whether the ruthenium catalyst at the chain end of the polymer stays active during the polymerization or decomposes over time, we performed a block test using *exo*-norbornene acid octyl ester as a comonomer, which presents significantly less steric bulk.[56] We found that upon addition of the second monomer the polymerization did continue, and the second monomer was converted quantitatively according to $^1$H NMR spectroscopy, showing the disappearance of the new monomer olefin signal at 6.1 ppm. This suggests that the polymerization is not being inhibited due to catalyst decomposition. Upon GPC characterization, however, we did notice multiple signals, one eluting significantly faster, suggesting the formation of the block copolymer and one close to the elution time of the original dendronized polymer, suggesting that some polymer chains were terminated. The existence of the higher molecular weight species in the trace confirms that not all polymer chains have terminated and can actively incorporate new monomer.

Excluding complete decomposition of all terminal initiator groups at the chain ends of all polymers, we hypothesize that the

Scheme 3. Schematic Representation of the Synthesis of the Second-Generation Dendronized Polymer with a 10-Carbon Linker



homopolymerization of **9** is hindered due to the steric crowding of the large dendron around the polymerizable unit, forming a shell around the active chain end. This phenomenon has been reported before by Percec and co-workers.[57] Because no sterically bulky dendronized macromonomer can diffuse in, the initiator is forced to terminate prematurely or remain active without the opportunity to incorporate more sterically demanding monomer. In the case that a smaller, less sterically demanding monomer is added, it is able to diffuse into the area of the active chain end and continue polymerization.

**Effects of Linker Length on the Polymerization.** If shielding of the polymerizable group during the ROMP of **9** is hindering complete polymerization, we hypothesized that a longer linker between the dendron and the polymerizable group should alleviate this problem. Schlüter and co-workers have previously synthesized dendronized poly(methacrylate)s of varying spacer lengths to determine the effects a spacer has on the polymerization.[7] They presented two families of polymers: one, a dendronized methacrylate (linkerless), and the other, the same dendronized monomer containing an ethyleneoxycarbonyl group between the dendron and the polymerizable group (two-carbon linker). According to their experiments, neither polymerization time, yield, nor molar mass were affected by the spacer; thus, they proposed that no "spacer effect" can be observed.[28] Any differences which were traditionally postulated to be linked to spacer length may actually be due to any number of other factors, like monomer purity or concentration. Schlüter acknowledges that the results obtained are true only for the ethyleneoxy spacer used in these reports. We hypothesize that a change of only three bonds in length is very small compared to the size of the dendron and that there may still be an effect stemming from a linker which is comparable to the size of the dendron. Therefore, we decided to introduce a significantly longer linker between the norbornene and the dendron (Scheme 3). Linker **11** (10 carbons in length) was coupled to *exo*-norbornene acid, and the synthesis of macromonomer **14** proceeded as described above. ROMP of **14** with Grubbs' third-generation initiator at a starting concentration of 300 mM proceeded in 98% conversions within 10 min. GPC data for the resulting dendronized polymer **15** showed a $M_n$ of 13 900 and a PDI of 1.73 versus poly(styrene) standards.

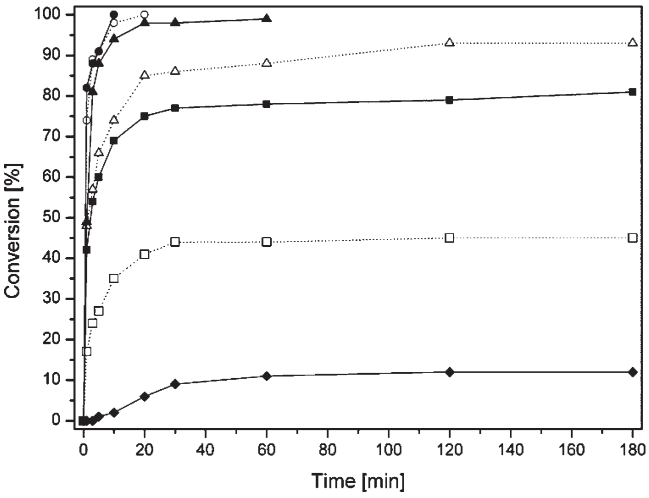
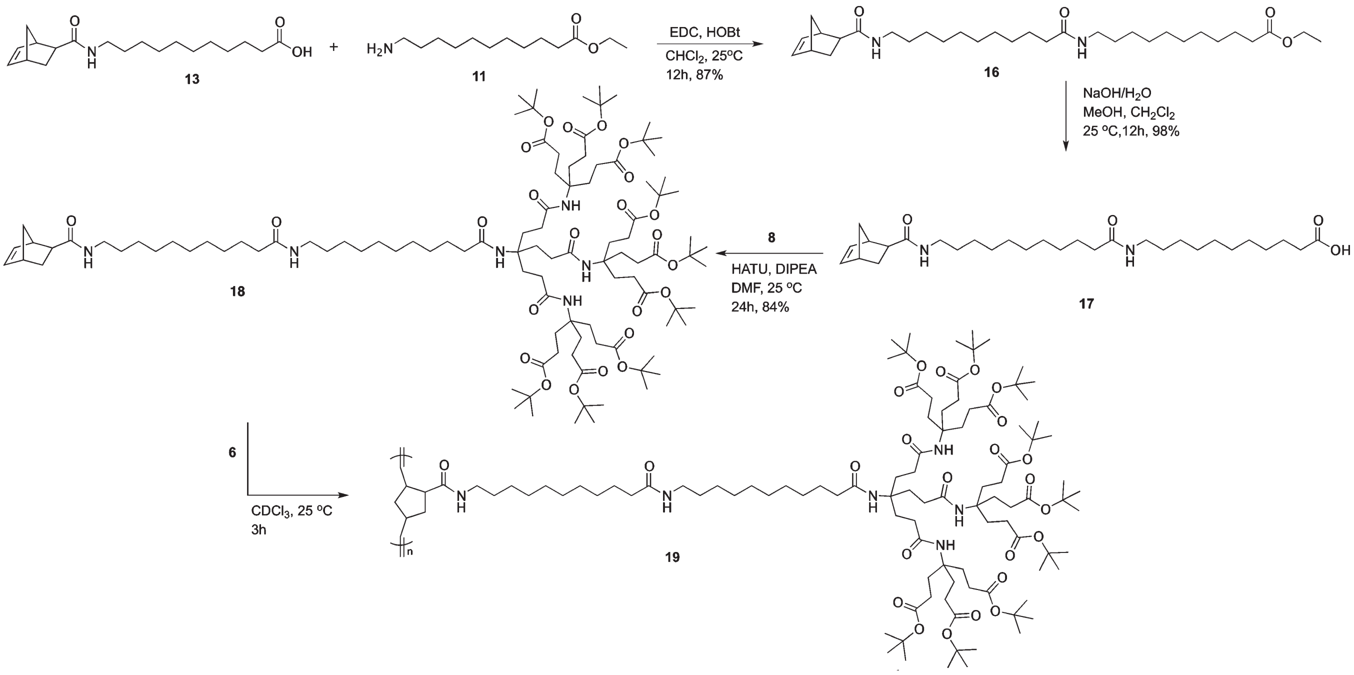


**Figure 4.** Concentration study of the polymerization of **14**. Each polymerization was carried out in DMF using Grubbs' third-generation initiator. Monomer concentrations are 300 mM (filled circles), 200 mM (empty circles), 100 mM (filled triangles), 50 mM (empty triangles), 30 mM (filled squares), 10 mM (empty squares), and 5 mM (diamonds).

The polymerization of **14** was performed in DMF-$d_7$ at varying initial concentrations, while holding the monomer/initiator ratio constant, to observe the effect of concentration on the polymerization (Figure 4). Greater than 99% conversions could be obtained at initial concentrations as low as 100 mM within 3 h. In very dilute solutions of 5 and 10 mM, polymerization reached only 10−40% conversion. We confirmed that higher initial concentrations of monomer lead to a more efficient polymerization.

A similar dependence on initial concentration for the degree of polymerization observed has also been reported by Schlüter and co-workers.[30] They report that the growing polymer forms a shell protecting the growing chain end, which forms a concentration gradient between the active terminus and the solution outside the shell. The diffusion of monomers across this barrier is hindered not only by the steric hindrance of the dendrons but also by the differences in concentration of dendron between the inside of the shell and the outside. At low initial concentrations, the shell contains few dendrons, but the exterior solution also contains few

**Scheme 4. Schematic Representation of the Synthesis of the Second-Generation Dendronized Polymer Containing a 20-Carbon Linker**



dendrons and the monomers have no impetus to cross the barrier. At a higher initial concentration, the concentration of the exterior solution greatly exceeds the concentration of dendron in the interior of the shell, and the monomers are driven to enter the shell and join the growing chain.

The same concentration effect on the polymerization behavior of dendron-containing monomers has also been reported by other groups. Percec[57] and Tsukahara[58] have reported independently of each other the concentration dependence of the polymerization of macromonomer via radical chemistry. In these cases, the radical polymerization of functionalized styrenes did not go to completion at low concentrations. Percec and co-workers suggest that this effect is due to steric crowding around the active chain end of the polymer. Taking into account the Schlüter, Percec, and Tsukahara reports as well as our observations, we suggest that a similar effect is hampering our polymerization efforts at low concentrations, explaining the concentration dependence of our monomer.

As with the linkerless macromonomer, we attempted to synthesize block copolymers from **14** and the octyl-substituted norbornene monomer. We found that the conditions used were able to successfully form a block copolymer, suggesting that the majority of polymer chains were still active. We also noticed that the initiator carbene signal in the $^1$H NMR spectrum did not disappear during the polymerization at an initial concentration of 100 mM, suggesting that the catalyst did not decompose under these conditions.

Since lengthening the linker from 1 carbon to 10 carbons improved the polymerization significantly, we postulated that the polymerization could be further improved by doubling the linker length (Scheme 4). Norbornene derivative **13** was coupled to linker **11** to form the norbornene-functionalized 20-carbon linker **16**, which was then hydrolyzed to afford the free acid **17**.

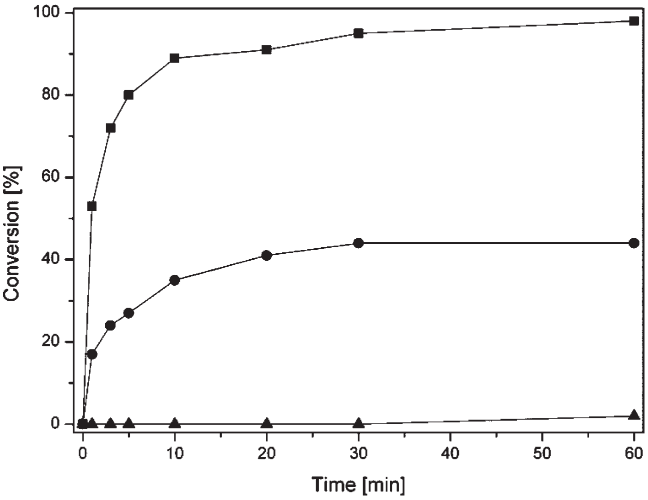


**Figure 5.** Kinetic data comparing the polymerization of **9** (triangles), **14** (circles), and **18** (squares) at the same initial concentration of 10 mM in chloroform. As linker length increases, the polymerization approaches completion. This implies that for longer linkers the linker length does play a role in the polymerization.

Second-generation dendron **8** was subsequently coupled to the linker to afford macromonomer **18**.

Polymerization of **18** proceeded under the same conditions as polymerization of the first-generation macromonomer to afford **19** with an $M_n$ of 20 800 and a PDI of 1.25 versus poly(styrene) standards. Dynamic light scattering calculations show the resulting polymer has an average hydrodynamic radius of 4.26 nm. The polymerization reached greater than 98% conversion at an initial monomer concentration of 10 mM within 1 h, in comparison to the polymerization of **14** at the same concentration stopped at

~50% completion, demonstrating the effect of the longer linker (Figure 5). We also noticed the carbene signal of the catalyst persisted for 100 min in the NMR (40 min after complete polymerization of **18**) at a concentration of 100 mM. As before, a simple block test using the norbornene octyl ester resulted in the formation of block copolymers. In comparison to the shell effect previously described, we suggest that the polymerization of **18** has too long of a linker to form a complete shell, and thus diffusion of monomer into the area of the active chain end is not hindered and polymerization can proceed normally.

## CONCLUSION

We have prepared first- and second-generation Newkome style dendronized poly(norbornene)s using Grubbs' third-generation initiator. Polymerization of the first-generation dendronized polymer proceeded without problem, but larger generation dendrons did not polymerize completely. By increasing the length of the linker connecting the dendron to the norbornene, the polymerization behavior of all second-generation dendron-containing monomers was improved. We therefore confirmed that the polymerization of macromonomers was highly dependent on both the monomer concentration and linker length, and we demonstrated that the rate of polymerization is directly affected by changing the length of the linker. We foresee these materials being potentially useful as drug delivery agents due to the peptide-like poly(amide)-based dendrons attached to a robust poly(norbornene) backbone. Further studies on polyfunctionalization and applications of these materials are in progress.

## EXPERIMENTAL SECTION

All chemicals were purchased either from Acros Organics, Cambridge Isotope Laboratories, or Sigma-Aldrich and used without further purification unless otherwise noted. Dendron **4** was purchased from Frontier Scientific. Metal scavenger SiliaBond DMT was purchased from SiliCycle. Polymerization solvents were degassed by the freeze−pump−thaw method. Ultrafiltration membranes were purchased from Millipore and used as received. *exo*-Norbornene acid,[51] initiator **6**,[48] second-generation dendron **8**,[59,60] linker **11**,[61] and *exo*-norbornene acid octyl ester[56] were synthesized according to literature reports. NMR spectra were recorded on a Bruker AV-400 ($^1$H: 400.1 MHz; $^{13}$C: 100.6 MHz) spectrometer. Chemical shifts are reported in ppm and referenced to the corresponding residual nuclei in deuterated solvents. Gel-permeation chromatography (GPC) analyses were carried out using a Shimadzu pump coupled to a Shimadzu UV detector with tetrahydrofuran (THF) as the eluent and a flow rate of 1 mL/min on American Polymer Standards column set (100, 1000, 100 000 Å, linear mixed bed). All GPCs were calibrated using linear poly(styrene) standards and carried out at 25 °C. $M_w$, $M_n$, and PDI represent the weight-average molecular weight, number-average molecular weight, and polydispersity index, respectively. It should be noted that dendronized polymers, due to their structure, will have a lower hydrodynamic volume compared to strictly linear analogues, and thus GPC can greatly underestimate the final size of dendronized polymers.[38,62,63] Dynamic light scattering (DLS) was performed at room temperature on a DynaPro Protein Solutions DLS in dichloromethane solutions.

**Kinetic Studies.** Solutions of monomers **5**, **9**, and **18** at given concentrations in $CDCl_3$ were formulated in a scintillation vial. To this was added Grubbs' third-generation initiator. At specified times during the reaction, small aliquots were removed, quenched with ethyl vinyl ether, concentrated, and analyzed by $^1$H NMR spectroscopy. Polymerizations were followed by integrating the olefinic signals (multiplets at 6.2−6.0 [monomer] and 5.5−5.1 [polymer]) to determine conversions. Studies on the polymerization of **14** with varying concentrations were carried out in DMF-$d_7$ in a sealed NMR tube.

**Block Tests.** Solutions of monomers **9**, **14**, and **18** were made and polymerized as stated below with monomer/initiator ratio of 20 and at an initial monomer concentration of 100 mM in $CDCl_3$. After 100 min, *exo*-norbornene acid octyl ester (0.75 mmol, 500 equiv) in a 100 mM solution was added, and the polymerization was left to run overnight. Complete polymerizations were characterized by $^1$H NMR spectroscopy followed by termination. GPC analysis of the resulting polymer showed bimodal graphs: one peak overlapping with the weight of the dendronized homopolymer and the other much higher in weight. Results from these tests were as follows: poly(**9**)-*b*-poly(norbornene acid octyl ester): $M_w$ = 2000 kDa, $M_n$ = 1350 kDa; poly(**14**)-*b*-poly(norbornene acid octyl ester): $M_w$ = 900 kDa, $M_n$ = 400 kDa; poly(**18**)-*b*-poly(norbornene acid octyl ester): $M_w$ = 1750 kDa, $M_n$ = 900 kDa. During the run of poly(**9**)-*b*-poly(norbornene acid octyl ester), a third peak was observed corresponding to the mass of **5** due to the incomplete polymerization of **5**.

**Synthesis of 2.** *exo*-Norbornene acid (200 mg, 1.45 mmol), glycine ethyl ester hydrochloride (242 mg, 1.74 mmol), EDC (389 mg, 2.03 mmol), and HOBt hydrate (235 mg, 1.74 mmol) were dissolved in anhydrous DMF (5 mL). To this solution, DIPEA (0.3 mL, 1.88 mmol) was added. The reaction was stirred at room temperature for 5 h. The DMF was removed *in vacuo*; the mixture dissolved in dichloromethane and extracted with water (2 × 30 mL). The organic layer was washed with water (30 mL), dried ($MgSO_4$), and concentrated. Purification was carried out by column chromatography (3:1 hexane:EtOAc) to afford **2** (300 mg, 93%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.12 (dq, $J$ = 7.62 Hz, 2.92 Hz, 2H), 6.01 (br s, 1H), 4.21 (q, $J$ = 7.15, 2H), 4.03 (t, $J$ = 5.12, 2H), 2.97 (br s, 1H), 2.91 (br s, 1H), 2.11−2.06 (m, 1H), 1.96−1.91 (m, 1H), 1.68 (br d, $J$ = 8.22 Hz, 1H), 1.35 (br d, $J$ = 9.32 Hz, 2H), 1.28 (t, $J$ = 7.15, 3H). $^{13}$C NMR (400 MHz, $CDCl_3$): $\delta$ 176.0, 170.4, 138.4, 136.0, 61.6, 47.2, 46.4, 44.6, 41.7, 41.6, 30.5, 14.2. MS-ESI $(M + Na)^+$ $m/z$ calcd for $C_{12}H_{17}NO_3Na$: 246.11; found: 246.0.

**Synthesis of 3.** To a solution of **2** (1.00 g, 4.48 mmol) in water/methanol (1 mL:10 mL) was added NaOH (358 mg, 8.96 mmol). The mixture was stirred for 2 h at room temperature, after which the methanol was evaporated. Water (10 mL) was added, and the mixture was neutralized with HCl. The mixture was separated with ethyl acetate, and the combined organic layers were dried ($MgSO_4$) and concentrated to afford **3** (784 mg, 90%). $^1$H NMR (400 MHz, MeOD): $\delta$ 6.15 (s, 2H), 3.90 (d, $J$ = 2.80 Hz, 2H), 2.94 (br s, 1H), 2.88 (br s, 1H), 2.20−2.16 (m, 1H), 1.91−1.86 (m, 1H), 1.66 (br d, $J$ = 8.00 Hz, 1H), 1.35−1.30 (m, 2H). $^{13}$C NMR (400 MHz, MeOD): $\delta$ 178.9, 173.2, 139.1, 137.3, 48.4, 47.1, 45.1, 42.8, 41.9, 31.2. MS-ESI $(M - H)^-$ $m/z$ calcd for $C_{10}H_{12}NO_3$: 194.08; found: 194.1. Anal. Calcd for $C_{10}H_{13}NO_3$: C 61.53, H 6.71, N 7.18. Found: C 61.66, H 6.97, N 7.14.

**First-Generation Macromonomer (5).** Compound **3** (517 mg, 2.65 mmol) and the first-generation dendron **4** (1.32 g, 3.18 mmol) were dissolved along with EDC (710 mg, 3.71 mmol) and HOBt hydrate (501 mg, 3.71 mmol) in dry $CH_2Cl_2$ (40 mL). The reaction was left to stir at room temperature for 12 h. Water (30 mL) was added, and the product was extracted with dichloromethane (2 × 30 mL). The organic layers were combined, washed with water (30 mL), dried over magnesium sulfate, and concentrated. Compound **5** was purified by column chromatography (3:2; hexane:EtOAc) (865 mg, 57%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.60 (s, 1H), 6.40 (br s, 1H), 6.13−6.10 (m, 2H), 3.84 (t, $J$ = 5.2 Hz, 2H), 2.95 (br s, 1H) 2.91 (br s, 1H) 2.20 (t, $J$ = 7.2 Hz, 6H), 2.10−2.07 (m, 1H), 1.98−1.89 (m, 7H), 1.67 (d, $J$ = 8.4 Hz, 1H), 1.42 (s, 27H), 1.34 (d, $J$ = 8.8 Hz, 2H). $^{13}$C NMR (400 MHz, $CDCl_3$): $\delta$ 176.4, 172.9, 168.5, 138.4, 136.2, 80.9, 57.9, 47.4, 46.5, 44.6, 44.2, 41.8, 30.7, 30.2, 29.9, 28.3. MS-ESI $(M + Na)^+$ $m/z$ calcd for $C_{32}H_{52}N_2O_8Na$: 615.36; found: 615.5. Anal. Calcd for $C_{32}H_{52}N_2O_8$: C 64.84, H 8.84, N 4.73. Found: C 64.76, H 8.87, N 4.76.

**First-Generation Dendronized Polymer (7).** To a solution of **5** (118.4 mg, 200 μmol) in degassed $CDCl_3$ (19 mL) was added a solution of Grubbs' third-generation initiator (8.8 mg 10 μmol) in degassed $CDCl_3$ (1 mL), and the reaction was stirred for 3 h at room temperature. Afterward, excess ethyl vinyl ether (1 mL) was added to quench the polymerization. After removal of the catalyst with the metal scavenger, the mixture was filtered. After concentration, polymer **7** was purified by ultrafiltration against methanol (3000 NMWL) (87 mg, 74%). $^1H$ NMR (400 MHz, MeOD): δ 7.04−7.43 (br m, 0.5H, NH protons exchanging with solvent), 5.03−5.45 (br m, 2H), 3.32−3.93 (br m, 2H), 2.80−3.11 (br m, 1H), 2.31−2.73 (br m, 2H), 1.68−2.24 (br m, 14H), 1.46−1.70 (br m, 1H), 1.21−1.45 (br s, 27H), 0.95−1.21 (br m, 2H). $^{13}C$ NMR (400 MHz, MeOD): δ 176.4, 172.9, 169.3, 132.9, 130.1, 80.2, 57.4, 52.0, 51.6, 42.9, 41.9, 37.1, 36.7, 36.4, 29.3, 27.0. GPC: $M_w$ = 23.3 kDa, $M_n$ = 17.4 kDa, PDI = 1.3.

**Second-Generation Macromonomer, 1C Linker (9).** Compound **3** (150 mg, 0.26 mmol) and dendron **8** (405 mg, 0.30 mmol) were placed in a Schlenk flask with HATU (126 mg, 0.33 mmol) and then placed under a nitrogen atmosphere. Anhydrous DMF (5 mL) and DIPEA (0.08 mL, 0.51 mmol) were added, and the reaction was left to stir for 12 h at room temperature. The reaction was concentrated, and the product was purified by column chromatography (3:4; hexane:EtOAc) to afford **9** (306 mg, 74%). $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.31 (t, *J* = 5.52 Hz, 2H), 6.21 (s, 3H), 6.13−6.11 (m, 2H), 3.66 (t, *J* = 6.00 Hz, 2H), 3.15 (s, 1H), 2.92 (s, 1H), 2.31−2.25 (m, 1H), 2.25−2.13 (m, 24H), 2.08−1.90 (m, 25H), 1.73 (d, *J* = 7.84, 1H), 1.43 (s, 81H), 1.38−1.31 (m, 2H). $^{13}C$ NMR (400 MHz, $CDCl_3$): δ 177.6, 173.2, 173.0, 169.9, 138.2, 136.5, 81.0, 80.7, 76.9, 58.3, 57.4, 47.0, 46.4, 45.1, 44.4, 41.7, 31.5, 30.8, 30.7, 30.2, 29.9, 28.2. MS-ESI $(M + Na)^+$ *m/z* calcd for $C_{86}H_{145}N_5O_{23}Na$: 1639.02; found: 1639.3. Anal. Calcd for $C_{86}H_{145}N_5O_{23}$: C 63.88, H 9.04, N 4.33. Found: C 63.59, H 9.23, N 4.19.

**Second-Generation Dendronized Polymer, 1C Linker (10).** Grubbs' third-generation initiator (22 mg, 25 μmol) was added to a stirred solution of **9** (808 mg, 0.5 mmol) in $CDCl_3$ (0.5 mL). After 3 h, excess ethyl vinyl ether was added to quench the polymerization. The metal scavenger was added, and the reaction was filtered. This polymer could not be purified but was detected by GPC. GPC: $M_w$ = 18.0 kDa, $M_n$ = 11.2 kDa, PDI = 1.6.

**Synthesis of 12.** *exo*-Norbornene acid (528 mg, 3.82 mmol), linker **11** (1.051 g, 4.58 mmol), EDC (1.025 g, 5.35 mmol), and HOBt (722 mg, 5.35 mmol) were dissolved in anhydrous $CH_2Cl_2$ (10 mL). After stirring for 5 h at room temperature, the mixture was diluted with dichloromethane and extracted with water (30 mL). The organic layer was dried ($MgSO_4$) and purified by column chromatography (4:1 hexane:EtOAc) to afford **12** (1.29 g, 97%). $^1H$ NMR (400 MHz, $CDCl_3$): δ 6.12 (m, 2H), 5.46 (br s, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 2.91 (m, 2H), 2.28 (t, *J* = 7.6 Hz, 2H), 2.04−1.89 (m, 2H) 1.74−1.72 (m, 1H), 1.63−1.57 (m, 2H), 1.51−1.45 (m, 2H), 1.28−1.25 (m, 17H). $^{13}C$ NMR (400 MHz, $CDCl_3$): δ = 175.6, 174.1, 138.4, 136.2, 60.3, 47.4, 46.5, 44.9, 41.7, 39.8, 34.5, 30.7, 29.9, 29.6, 29.5, 29.4, 29.3, 29.2, 27.1, 25.1, 14.4. MS-ESI $(M + Na)^+$ *m/z* calcd for $C_{21}H_{35}NO_3Na$: 372.25; found: 372.3. Anal. Calcd for $C_{21}H_{35}NO_3$: C 72.17, H 10.09, N 4.01. Found: C 72.52, H 10.27, N 4.04.

**Synthesis of 13.** Linker **12** (1.335 g, 3.82 mmol) was dissolved in a mixture of NaOH (305 mg, 7.64 mmol), water (5 mL), and MeOH (5 mL). The mixture was stirred at room temperature for 2 h, after which the methanol was evaporated. The reaction was extracted with ethyl acetate (2 × 20 mL), and the organic layer washed with water (20 mL), dried ($MgSO_4$), and concentrated to afford **13** (2.28 g, 93%). $^1H$ NMR (400 MHz, MeOD): δ 6.12 (m, 2H), 5.46 (br s, 1H), 2.91 (m, 2H), 2.28 (t, *J* = 7.6 Hz, 2H), 2.04−1.89 (m, 2H) 1.74−1.72 (m, 1H), 1.63−1.57 (m, 2H), 1.51−1.45 (m, 2H), 1.28−1.25 (m, 14H). $^{13}C$ NMR (400 MHz, MeOD): δ 178.4, 177.8, 139.1, 137.5, 47.2, 45.4, 42.9, 40.8, 40.6, 35.1, 31.4, 30.7, 30.6, 30.5, 30.4, 28.1, 26.2. MS-ESI $(M + Na)^+$ *m/z* calcd for $C_{19}H_{31}NO_3Na$: 344.22; found: 344.3. Anal. Calcd for $C_{19}H_{31}NO_3$: C 70.99, H 9.72, N 4.36. Found: C 71.11, H 9.90, N 4.33.

**Second-Generation Macromonomer, 10C Linker (14).** Dendron **8** (1.60 g, 1.12 mmol), norbornene derivative **13** (300 mg, 0.93 mmol), and HATU (496 mg, 1.31 mmol) were placed under nitrogen. Anhydrous DMF (10 mL) and DIPEA (0.3 mL, 1.86 mmol) were added, and the reaction was left to stir for 24 h at room temperature. The reaction was concentrated and purified by column chromatography (1:1; hexane:EtOAc) to afford **14** (1.56 g, 96%). $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.36 (br s, 1H), 6.14−6.08 (m, 5H), 5.64 (br s, 1H), 3.24 (q, *J* = 6.4 Hz, 2H), 2.91 (br s, 2H), 2.21−2.11 (m, 27H), 1.96−1.90 (m, 24H), 1.72 (d, *J* = 8.4 Hz, 1H), 1.71 (br s, 3H), 1.43 (s, 81H), 1.28 (br s, 17H). $^{13}C$ NMR (400 MHz, $CDCl_3$): δ 175.6, 173.8, 173.0, 172.8, 138.3, 136.2, 80.7, 57.5, 47.3, 46.4, 44.8, 41.6, 39.7, 37.5, 32.2, 31.9, 30.6, 30.0, 29.9, 29.8, 29.5, 29.4, 28.2, 27.0, 25.8. MS-ESI $(M + Na)^+$ *m/z* calcd for $C_{95}H_{163}N_5O_{23}Na$: 1765.16; found: 1765.3.

**Second-Generation Dendronized Polymer, 10C Linker (15).** Monomer **14** (261 mg, 0.15 mmol) was dissolved in $CDCl_3$ (0.4 mL) in a screw-top vial. A solution of Grubbs' third-generation initiator (6.6 mg, 7.5 μmol) in $CDCl_3$ (0.1 mL) was added, and the reaction was allowed to stir at room temperature for 3 h. After the reaction was complete, excess ethyl vinyl ether was added to quench the polymerization. After addition and filtration of the metal scavenger, the solution was concentrated, followed by purification using ultrafiltration against methanol (3000 NMWL) to afford polymer **15** (180 mg, 69%). $^1H$ NMR (400 MHz, MeOD): δ 7.32−7.88 (br m, 5H), 5.10−5.49 (br m, 2H), 2.97−3.30 (br m, 3H), 2.61−2.85 (br m, 1H), 2.10−2.50 (br m, 27H), 1.86−2.10 (br m, 24H), 1.58−1.74 (br s, 4H), 1.39−1.59 (s, 81H), 1.24−1.44 (br s, 16H). $^{13}C$ NMR (400 MHz, MeOD): δ 174.6, 174.1, 172.9, 132.9, 131.0, 80.2, 57.4, 36.6, 31.0, 30.8, 29.3, 29.2, 27.2, 27.0, 25.8. GPC: $M_w$ = 24.1 kDa, $M_n$ = 13.9 kDa, PDI = 1.7.

**Synthesis of 16.** Compounds **11** (893 mg, 3.36 mmol) and **13** (900 mg, 2.80 mmol) were added to EDC (805 mg, 4.20 mmol) and HOBt (567 mg, 4.20 mmol), and the mixture was dissolved in $CH_2Cl_2$ (30 mL). Then, DIPEA (1.1 mL, 6.72 mmol) was added. The mixture was allowed to stir at room temperature for 12 h. The reaction was extracted with water (30 mL), and the organic layer was dried ($MgSO_4$) and purified by column chromatography (1:1; hexane:EtOAc) to afford **16** (1.30 g, 87%). $^1H$ NMR (400 MHz, $CDCl_3$): δ 6.11 (dq, *J* = 5.64 Hz, 3.2 Hz, 2H), 5.50 (br s, 1H), 5.43 (br s, 1H), 4.11 (q, *J* = 7.24 Hz, 2H), 3.28−3.19 (m, 4H), 2.92−2.88 (m, 2H), 2.28 (t, *J* = 7.24 Hz, 2H), 2.14 (t, *J* = 7.64, 2H), 1.99−1.87 (m, 2H), 1.72 (br d, *J* = 8.04, 1H), 1.65−1.56 (m, 4H), 1.53−1.43 (m, 4H), 1.36−1.1.22 (m, 29H). $^{13}C$ NMR (400 MHz, $CDCl_3$): δ 175.6, 174.1, 173.2, 138.4, 136.2, 60.3, 47.4, 46.5, 44.9, 41.7, 39.8, 39.6, 37.1, 34.5, 30.7, 29.9, 29.8, 29.6, 29.5, 29.4, 29.4, 29.4, 29.3, 29.2, 27.1, 27.0, 25.9, 25.1, 14.4. MS-ESI $(M + Na)^+$ *m/z* calcd for $C_{35}H_{56}N_2O_4Na$: 555.41; found: 555.5.

**Synthesis of 17.** Compound **16** (1.00 g, 1.88 mmol) and NaOH (150 mg, 3.75 mmol) were dissolved in a mixture of water (2 mL), dichloromethane (20 mL), and MeOH (30 mL). After stirring for 12 h at room temperature, the solvent was evaporated and water (20 mL) was added. The solution was neutralized with HCl, and the product was collected by vacuum filtration (928 mg, 98%). $^1H$ NMR (400 MHz, DMF-$d_7$): δ 12.19 (s, 1H), 7.77 (br s, 1H), 7.70 (br s, 1H), 6.15−6.09 (m, 2H), 3.25−3.11 (m, 4H), 2.84 (s, 2H), 2.29 (t, *J* = 7.4 Hz, 2H), 2.14 (t, *J* = 6.44 Hz, 2H), 1.93−1.86 (m, 2H), 1.76−1.11 (m, 35H). $^{13}C$ NMR (400 MHz, DMSO-$d_6$): δ 174.5, 174.3, 171.8, 137.7, 136.3, 46.9, 45.6, 43.0, 41.0, 38.5, 38.3, 35.4, 33.7, 29.8, 29.1, 29.0, 28.9, 28.8, 28.7, 28.6, 28.5, 26.4, 25.3, 24.5. MS-ESI $(M-H)^-$ *m/z* calcd for $C_{30}H_{51}N_2O_4$: 503.38; found: 503.3. Anal. Calcd for $C_{30}H_{52}N_2O_4$: C 71.39, H 10.38, N 5.55. Found: C 71.27, H 10.50, N 5.54.

**Second-Generation Macromonomer, 20C Linker (18).** Dendron **8** (1.90 g, 0.750 mmol), **17** (347 mg, 0.687 mmol), and

HATU (365 mg, 0.960 mmol) were dissolved in anhydrous DMF (10 mL) under an inert atmosphere. DIPEA (0.24 mL, 1.37 mmol) was added, and the reaction was allowed to stir for 24 h at room temperature. Column chromatography (1:2; hexane:EtOAc) afforded **18** (1.11 g, 84%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.46 (s, 1H), 6.19 (br s, 3H), 6.15−6.07 (m, 2H), 5.65 (br s, 1H), 5.58 (br s, 1H), 3.23 (p, $J$ = 5.48 Hz, 4H), 2.91 (br s, 2H), 2.24−2.09 (m, 26H), 2.06−1.83 (m, 28H), 1.72 (br d, $J$ = 8.52 Hz, 1H), 1.66−1.54 (m, 4H), 1.52−1.38 (m, 85H), 1.36−1.25 (m, 26H). $^{13}$C NMR (400 MHz, $CDCl_3$): $\delta$ 175.6, 173.8, 173.2, 173.0, 172.8, 138.3, 136.2, 80.7, 57.6, 57.5, 47.3, 46.4, 44.8, 41.6, 39.7, 39.6, 37.5, 36.9, 32.2, 31.9, 30.6, 30.0, 29.9, 29.8, 29.7, 29.5, 29.4, 29.3, 29.3, 28.2, 27.0, 26.9, 25.9. MS-ESI $(M + Na)^+$ $m/z$ calcd for $C_{106}H_{184}N_6O_{24}Na$: 1948.33; found: 1948.3.

**Second-Generation Dendronized Polymer, 20C Linker (19).** Monomer **18** (96.3 mg, 50 $\mu$mol) was dissolved in $CDCl_3$ (4.8 mL) in a screw-top vial. A solution of Grubbs' third-generation initiator (2.2 mg, 2.5 $\mu$mol) in $CDCl_3$ (0.2 mL) was added, and the reaction was allowed to stir at room temperature for 3 h. Then, excess ethyl vinyl ether was added to quench the polymerization. After addition and filtration of the metal scavenger, the mixture was concentrated. The polymer was purified by ultrafiltration against methanol (3000 NMWL) and concentrated to afford polymer **15** (82 mg, 85%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.19−7.92 (br m, 4H), 4.96−5.38 (br m, 2H), 2.87−3.17 (br m, 5H), 2.02−2.32 (br m, 28H), 1.73−2.01 (br m, 26H), 1.45−1.60 (br m, 5H), 1.29−1.45 (br s, 85H), 1.11−1.29 (br m, 26H). $^{13}$C NMR (400 MHz, $CDCl_3$): $\delta$ 174.6, 174.1, 174.0, 172.9, 133.0, 130.8, 80.2, 57.4, 57.3, 39.2, 39.1, 36.5, 35.9, 30.9, 30.7, 29.3, 29.2, 29.1, 27.2, 26.8, 25.8, 25.7. GPC: $M_w$ = 24.1 kDa, $M_n$ = 13.9 kDa, PDI = 1.7.

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