Macromolecules

pubs.acs.org/Macromolecules

Article

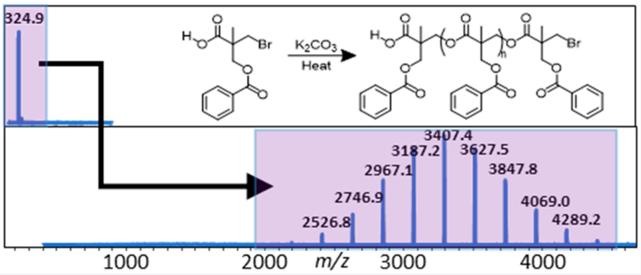
# Synthesis and Characterization of Linear, Homopolyester, Benzoyl-Protected Bis-MPA

Oluwapelumi O. Kareem, Samantha P. Daymon, Christopher B. Keller, Beibei Chen, Sergei Nazarenko, and Scott M. Grayson*

Cite This: https://dx.doi.org/10.1021/acs.macromol.0c01045

Read Online

**ABSTRACT:** Because of the growing interest in bis-MPA dendrimers and hyperbranched polymers, a linear, polyester equivalent is of great importance in understanding how this commercially viable family of branched polymers behaves when compared to their linear analogs. Herein, we describe the first synthesis and characterization of a novel, linear, chain-growth bis-MPA homopolyester that can be used for such an investigation. Linear benzoyl bis-MPA or poly(3-(benzoyloxy)-2-(bromomethyl)-2-methylpropanoic acid) (PBBM) was synthesized efficiently using a small molecule brominated bis-MPA derivative followed by a chain-addition polymerization using potassium carbonate ($K_2CO_3$). This polymerization can take place in a range of solvents with low dispersity values (<1.2). The polymerization mechanism and the postfunctionalization of PBBM are discussed. A preliminary solution size comparison using gel permeation chromatography (GPC) was also conducted with respect to benzylidene-protected bis-MPA dendrimers.



## ■ INTRODUCTION

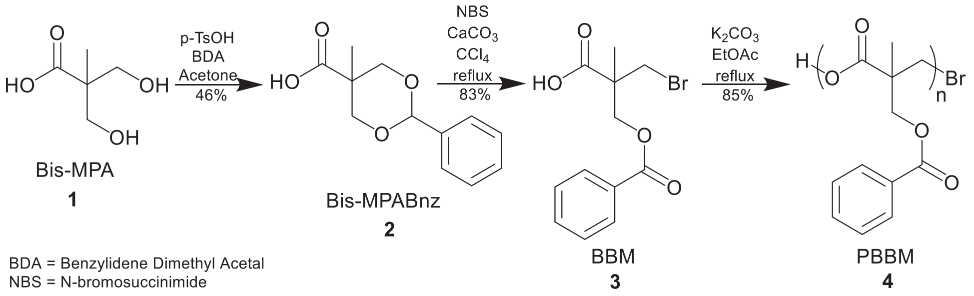
Dendrimers are monodisperse, polymeric materials that are composed of branched "arms" or "wedges" that emanate from a central "core". Their branched arms are made up of an $AB_x$-monomer that allows for growth of the dendrimer through successive iterative steps, which increases functionality exponentially. This growth strategy affords a polymer that is well-defined in nature and thus leads to a tighter correlation of structure−property relationships. Since their inception, various dendrimers have been synthesized with different properties and architectures expanding into numerous subcategories of dendritic materials.[1,2] This has led to the use of dendrimers as drug delivery vectors, as building blocks for three-dimensional networks, and as mass calibrants.[2−7] However, the potential for application of some of these dendrimers has often been limited due to their perceived synthetic difficulty and expensive reagents.[8] Therefore, a dendritic material that can be synthesized on a multigram scale while maintaining high purity and use of inexpensive, benign reagents has huge potential for commercial applications. Despite the perception of dendrimers being synthetically demanding, in recent years, there have been a few publications that have shown this synthetic reputation is no longer valid.[2,9−12] Bis-MPA-based dendrimers avoid many of the complications of some early dendrimers because they can be synthesized cleanly on the multigram scale using a fluoride activated divergent synthesis published by Malkoch and co-workers.[8]

Understanding how structure may influence the behavior of dendrimers is something that has been investigated in detail. Jean Fréchet found in his studies of aromatic polyesters and polyethers that the architecture of dendrimers, when compared to their hyperbranched and linear analogs, not only influenced physical properties like solubility and glass transition temperatures, but even the reactivity of their terminal hydroxyl groups.[13] Some have tried to relate these properties to the fact that the functional groups on dendrimers are localized at the periphery.[14−17] However, this assumption is highly debated, and there are multiple examples of studies that demonstrate that dendrimer arms may fold and extend depending on generation size, solvent quality, or distance between branch points.[18−20] It is unlikely that all dendritic materials follow one rule set, and for that reason it is important to understand how each dendritic system behaves.

In recent decades, the adoption of bis-MPA branched materials has greatly increased such that they can be purchased from commercial vendors such as Perstorp and Millipore-Sigma under trademarked names such as Boltorn and SpheriCal. As the use of these dendritic materials increases,

**Received:** May 1, 2020
**Revised:** July 3, 2020

**Scheme 1. Synthetic Scheme of Poly(3-(benzoyloxy)-2-(bromomethyl)-2-methylpropanoic acid) (PBBM)**



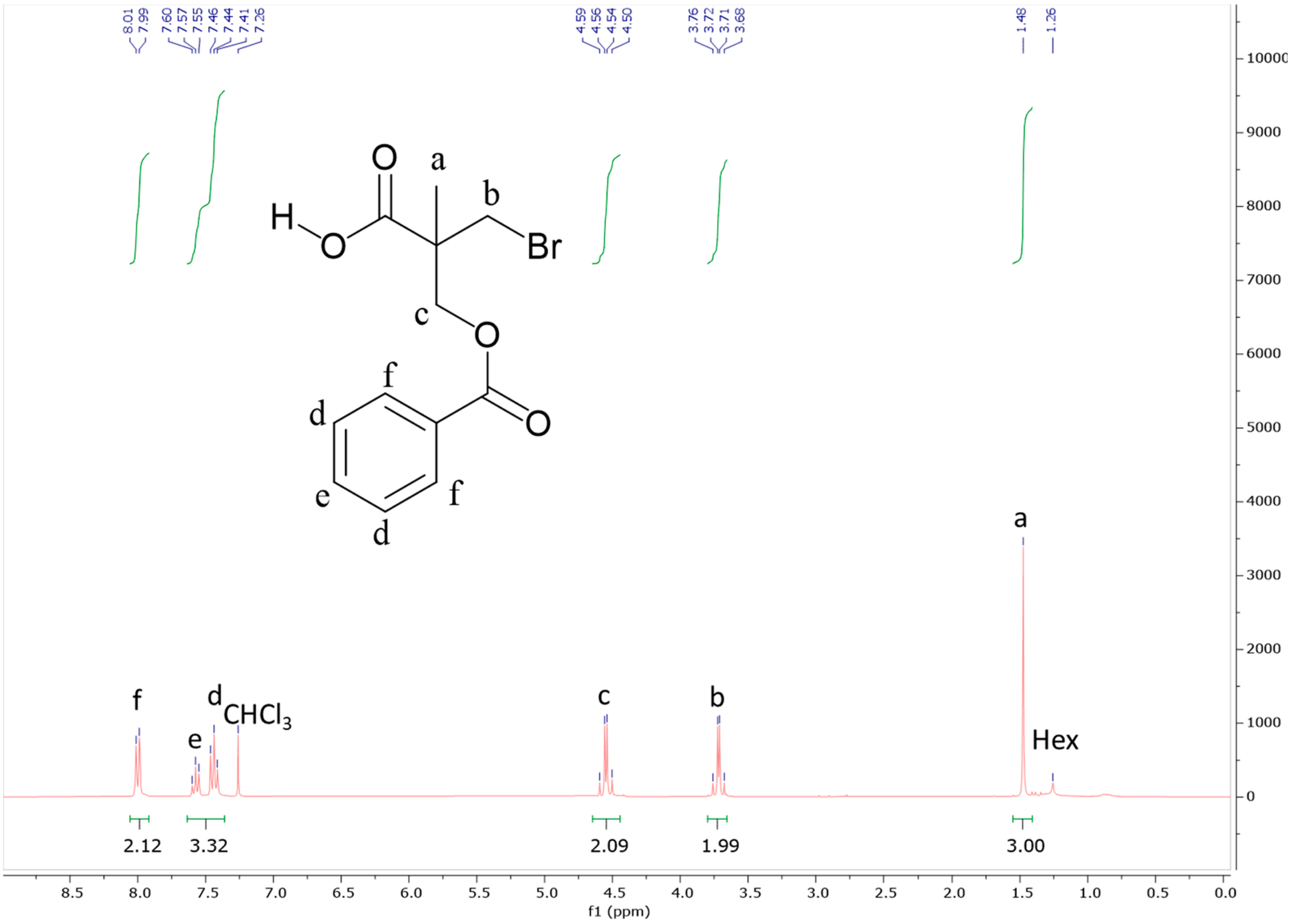


**Figure 1.** $^1$H NMR (300 MHz, $CDCl_3$) spectra of 3-(benzoyloxy)-2-(bromomethyl)-2-methylpropanoic acid (BBM).

there is a growing need to understand how their architecture may affect their behavior or reactivity. Although multiple branched architectures based on bis-MPA have been reported or are commercially available, a linear equivalent has remained elusive. A bis-MPA linear polycarbonate was first described by Bisht and co-worker synthesized through a ring-opening polymerization (ROP) of cyclic carbonate bis-MPA derivatives, "MBC" and "MCC".[21,22] However, this polycarbonate, and its derivatives, are not a good analog for bis-MPA dendritic materials. These linear polycarbonates contain carbonate linkages, which are not seen in either the dendrimer or the hyperbranched bis-MPA analogs. These polycarbonate examples contain a pendent carboxylic acid that can be later modified for biological applications. Some groups have even taken this initial synthesis and used these polycarbonates as scaffolds for several block copolymers or functionalized polycarbonate derivatives.[23−25] Even though these polycarbonates are biodegradable and can be synthesized to high mass ranges, a linear bis-MPA homopolyester analogous to the dendrimer or the hyperbranched polymer is more desirable for this type of comparison.

Herein, we describe the first synthesis of a linear, benzoyl-protected, bis-MPA homopolyester (PBBM). This was accomplished using the Hanessian−Hullar[26] ring-opening procedure of benzylidene acetals using *N*-bromosuccinimide. Previously, this reaction was used predominantly in carbohydrate chemistry by providing an avenue for further functionalization of complex carbohydrates.[26,27] However, this procedure proved problematic because it utilized barium carbonate ($BaCO_3$), a toxic reagent, as an "acid scavenger". To avoid this, Chrétien et al.[27] described an alternative acid scavenger in calcium carbonate ($CaCO_3$) that still works as efficiently while avoiding issues of toxicity. The procedure described in this Article uses a synthetic methodology for ring-opening benzylidene acetals similar to that reported by Chrétien et al. (Scheme 1). This synthetic approach was used to synthesize BBM, which was subsequently used to produce a linear benzoyl-protected bis-MPA homopolyester (PBBM), both of these for the first time. PBBM is later compared to its dendritic analogs through a preliminary size comparison study.

## ■ EXPERIMENTAL SECTION

**Benzylidene-Protected Bis-MPA (5-Methyl-2-phenyl-1,3-dioxane-5-carboxylic Acid).**[28] A round-bottom flask was charged with a stir bar and acetone (1925 mL). While being stirred, bis-MPA (345.55 g, 258 mmol) was added slowly to prevent the stir bar from seizing because the solution is a suspension. Benzaldehyde dimethyl acetal (588.12 g, 386 mmol, 580 mL) then was added, followed by *para*-toluene sulfonic acid (*p*-TsOH, 4.19 g, 25 mmol). The reaction mixture was stirred for 16 h under inert atmosphere ($N_2$) as a suspension of white solid. The solution was then filtered to isolate the white solid, and the white solid was washed several times with cold acetone. The white solid was then dried under a high vacuum to remove residual acetone (266.168 g, 46.4%). $^1$H NMR (Figure S1) ($CDCl_3$, 300 MHz): $\delta$ 1.11 (s, 3H, $CH_3$), 3.70 (d, $J$ = 11.7 Hz, 2H, $CH_2$), 4.63 (d, $J$ = 11.7 Hz, 2H, $CH_2$), 5.49 (s, 1H, $CH_{acetal}$), 7.41 (m, 5H, ArH). $^{13}$C NMR (Figure S2) ($CD_3S(O)CD_3$, 75 MHz): $\delta$ 17.6 ($CH_3$), 41.5 ($C_{quaternary}$), 72.6 ($CH_2$), 100.3 ($CH_{acetal}$), 126.1 ($CH_{\textit{ortho}\ Ar-H}$), 128.0 ($CH_{\textit{meta}\ Ar-H}$), 128.7 ($CH_{\textit{para}\ Ar-H}$), 138.4 ($C_{quaternary\ Ar-H}$), 173.9 (C(O)).

**3-(Benzoyloxy)-2-(bromomethyl)-2-methylpropanoic Acid (BBM).** To a round-bottom flask were added benzylidene-protected bis-MPA (10.0 g, 45 mmol), *N*-bromosuccinimide (NBS, 8.81 g, 49 mmol), and $CaCO_3$ (5.45 g, 54 mmol). The flask was charged with a stir bar and placed under a reflux condenser. Carbon tetrachloride ($CCl_4$, 50 mL) was added to the flask, and the reaction was stirred at 85 °C for 3 h. The reaction mixture started as a white slurry and then turned to a red-orange slurry approximately 15 min after heating. After reacting, the red-orange slurry was then allowed to cool to room temperature and filtered to remove $CaCO_3$. The resulting red-orange translucent solution was then washed with sodium sulfite ($Na_2SO_3$), sodium hydrogen sulfate ($NaHSO_4$), and deionized $H_2O$. The red-orange solution turned orange after all of the washes and was then dried with magnesium sulfate ($MgSO_4$), filtered, and the solvent was removed via rotary evaporator. After concentration, the orange solution turned to a red viscous oil. The resulting red oil was dried under high vacuum and set aside for polymerization (11.2 g, 82.7%). MALDI-ToF MS (Figure S4): calcd $m/z$ + $Na^+$ [322.99 $m/z$], obs. $m/z$ + $Na^+$ [322.94 $m/z$]. $^1$H NMR (Figure 1) ($CDCl_3$, 300 MHz): $\delta$ 1.48 (s, 3H, $CH_3$), 3.69 (d, $J$ = 10.4 Hz, 1H, $CH_2$−Br), 3.74 (d, $J$ = 10.4 Hz, 1H, $CH_2$−Br), 4.52 (d, $J$ = 11.2 Hz, 1H, $CH_2$−OBz), 4.57 (d, $J$ = 11.2 Hz, 1H, $CH_2$−OBz), 7.43 (t, $J$ = 7.4 Hz, 2H, $CH_{\textit{meta}\ Ar-H}$), 7.57 (t, $J$ = 7.4, 1.6 Hz, 1H, $CH_{\textit{para}\ Ar-H}$), 8.00 (t, $J$ = 7.4, 1.6 Hz, 2H, $CCH_{\textit{ortho}\ Ar-H}$). $^{13}$C and $^{13}$C DEPT 135 NMR (Figure S3) ($CD_3S(O)CD_3$, 75 MHz): $\delta$ 19.85 ($CH_3$), 38.03 ($CH_2$−Br), 47.24 ($C_{quaternary}$), 67.37 ($CH_2$−O−C(O)), 129.32 ($CH_{\textit{ortho}\ Ar-H}$), 129.67 ($C_{quaternary\ Ar-H}$), 129.72 ($CH_{\textit{meta}\ Ar-H}$), 134.05 ($CH_{\textit{para}\ Ar-H}$), 165.69 (C(O)Bz), 173.89 ($C(O)_{backbone}$). Anal. Calcd for $C_{12}H_{13}BrO_4$: C, 47.9%; H, 4.4%. Found: C, 48.9%; H, 4.5%. IR stretches (Figure S5): 1650−1800 cm$^{-1}$ C═OBz and C═OOH, 2350−2800 cm$^{-1}$ C═OOH, 2800−3100 cm$^{-1}$ Ar−H, 3100−3700 cm$^{-1}$ O−H.

**Poly(3-(benzoyloxy)-2-(bromomethyl)-2-methylpropanoic acid) (PBBM).** A round-bottom flask was charged with a stir bar, BBM (8.00 g, 27 mmol), and $K_2CO_3$ (14.7 g, 106 mmol). Ethyl acetate (266 mL) was then added, and the reaction mixture was stirred under reflux for 16 h. The resulting mixture was then acidified with $NaHSO_4$ to quench the reaction. The product was extracted out with several washes of $CHCl_3$. This organic layer was then washed with DI water, dried with $MgSO_4$, and then excess solvent was removed using a rotary evaporator to produce a brown solid. This solid was then redissolved in $CHCl_3$ and precipitated into cold hexanes (1:10) to produce a white powder (4.91 g, 84.7%, $M_n$ 2200). MALDI-ToF MS (Figure 3): calcd $m/z$ + $Na^+$ [2085.92 $m/z$], obs. $m/z$ + $Na^+$ [2085.62 $m/z$]. $^1$H NMR (Figure 4) ($CDCl_3$, 300 MHz): $\delta$ 1.24 (m, $CH_{3\ backbone}$), 1.33 (s, $CH_{3\ end\ group}$), 3.62 (m, $CH_2$−Br), 4.35 (m, $CH_{2\ backbone}$), 7.37, (m, $CH_{\textit{meta}\ Ar-H,\ \textit{para}\ Ar-H}$), 7.85 (m, $CH_{\textit{ortho}\ Ar-H}$). $^{13}$C NMR (Figure 4) (75 MHz, $CDCl_3$): $\delta$ 17.7 ($CH_3$), 46.7 ($C_{quatenary}$), 65.70 ($CH_2$), 128.39 ($CH_{\textit{meta}\ Ar-C}$), 129.36 ($CH_{\textit{ortho}\ Ar-C}$), 129.54 ($C_{quaternary\ Ar-C}$), 133.15 ($CH_{\textit{para}\ Ar-C}$), 165.55 (C(O)Bz), 171.75 ($C(O)_{backbone}$). GPC (Figure 3) (THF, RI): $M_n$ ($Đ$) = 1800 g mol$^{-1}$ (1.02). Anal. Calcd for 10-mer $C_{120}H_{121}BrO_{40}$: C, 63.1%; H, 5.3%. Found: C, 63.5%; H, 5.4%. IR stretches (Figure S5): 1670−1820 cm$^{-1}$ C═OBz and C═O, 2800−3100 cm$^{-1}$ Ar−H, 3100−3700 cm$^{-1}$ O−H.

**Characterization.** Nuclear magnetic resonance (NMR) spectroscopy was performed on a Bruker AVANCE 300 MHz spectrometer (Figures 1, 4, S1−3, S15−22, S25−27, and S33). $^1$H NMR (300 MHz) experiments were performed at 298 K at a concentration of 3 mg/mL in chloroform-*d* ($CDCl_3$) or methanol-$d_4$ (MeOD), purchased from Cambridge Isotope Laboratories (Andover, MA). $^{13}$C and $^{13}$C DEPT 135 (75 MHz) experiments were performed at 298 K at a concentration of 10 mg/mL in chloroform-*d* ($CDCl_3$) or dimethyl sulfoxide-$d_6$ (DMSO). HSQC-NMR was performed at 298 K at a concentration of 20 mg/mL in dimethyl sulfoxide-$d_6$ (DMSO). Enough scans were collected to generate sufficient signal-to-noise with a relaxation delay of 3−6 s depending on the sample.

A Bruker Autoflex III MALDI-ToF mass spectrometer (Bruker Daltonics, Billerica, MA) was used to collect Figures 3, 5, 8, S4, S6−11, S13, S24, S28−29, and S31. Mass spectra data were collected in positive reflectron ion detection mode. Typical sample preparation for MALDI-ToF MS data was performed using two types of sample preparation. Stock solutions of matrix (20 mg/mL), polymer−analyte (1 mg/mL), and a cation source (1 mg/mL) in tetrahydrofuran (THF) (VWR) were made. The stock solutions were combined in a 5/1/1 $\mu$L ratio (v/v/v) (matrix/analyte/cation) and plated via the dried droplet method. Sodium trifluoroacetate was used as the cation source, and *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) (TCI) was used as the matrix in the first sample preparation method. The second method involved applying graphite from a #2 Ticonderoga pencil to the plate as the matrix, and then addition of 1 $\mu$L of polymer−analyte stock solution and 1 $\mu$L of cation stock solution via the dried droplet method. MALDI-ToF MS spectra were calibrated against SpheriCal dendritic calibrants (Polymer Factory, Sweden).

Gel permeation chromatography (GPC) was performed on a Waters model 1515 isocratic pump and a Waters model 2414 differential refractometer detector (Waters Corp., Milford, MA) with three PSS SDV analytical 500 Å (8 × 300 mm) columns in series (Polymer Laboratories Inc., Amherst, MA). Data (Figures 5, 8, S7, S12, S14, S30, and S32 and Table 1) were collected in THF at a flow rate of 1 mL/min at 30 °C. Samples for the size comparison study were collected by fractionation using a Waters model 1515 isocratic pump and a Waters model 2414 differential refractometer detector (Waters Corp., Milford, MA) with one PSS SDV Prep 1000 Å (40 × 250 mm) (Polymer Laboratories Inc., Amherst, MA). This was done in THF at a flow rate of 8 mL/min at 30 °C.

Attenuated total reflection Fourier-transform infrared (ATR-FTIR) measurements were performed on a Nicolet iS50R spectrometer. Data (Figures S5 and S23) were recorded at room temperature between 4000 and 400 cm$^{-1}$ at a resolution of 4 cm$^{-1}$, and 32 scans were averaged for each spectrum.

Thermogravimetric analysis (TGA) (Figure 6) was performed on a Q500 thermogravimetric analyzer (TA Instruments Inc.) at a 10 mg scale under a flowing nitrogen atmosphere at a heating rate of 10 °C/

**Table 1. Polymerization Trials of PBBM with Varying Initial Monomer Concentration and Types/Equivalents of Base in Ethyl Acetate at 70 °C under Reflux for 24 h**[a]

| base | equiv of base | int. [M] | obs. $M_{n\,\mathrm{MALDI}}$ | MALDI $Đ$ | obs. $M_{n\,\mathrm{GPC(PS)}}$ | GPC $Đ$ |
|---|---|---|---|---|---|---|
| $K_2CO_3$ | 2 | 1 | 3600 | 1.02 | 3300 | 1.21 |
| $K_2CO_3$ | 2 | 0.5 | 3800 | 1.02 | 3100 | 1.22 |
| $K_2CO_3$ | 2 | 0.1 | 7100 | 1.01 | 5970 | 1.11 |
| $K_2CO_3$ | 2 | 0.05 | 5200 | 1.01 | 4000 | 1.12 |
| $K_2CO_3$ | 2 | 0.01 | 4300 | 1.01 | 3400 | 1.07 |
| $K_2CO_3$ | 1 | 0.1 | 7100 | 1.01 | 6100 | 1.12 |
| $K_2CO_3$ | 4 | 0.1 | 7300 | 1.02 | 6400 | 1.11 |
| $K_2CO_3$ | 8 | 0.1 | 7000 | 1.01 | 5900 | 1.11 |
| TEA | 1 | 0.1 | 900 | 1.03 | 1000 | 1.03 |
| TEA | 2 | 0.1 | 900 | 1.03 | 1000 | 1.04 |
| TEA | 4 | 0.1 | 900 | 1.04 | 1000 | 1.03 |
| TEA | 8 | 0.1 | 800 | 1.04 | 1000 | 1.02 |

[a] MALDI-ToF $M_n$ and $Đ$ values were obtained using $Na^+$ as the counterion. GPC $M_n$ and $Đ$ (calibrated with polystyrene (PS)) values for each trial are also reported.

min from 25 to 600 °C. The temperature is reproducible to ±1 °C and mass to ±0.2%.

Thermal behavior was investigated by differential scanning calorimetry (DSC) using a TA Instruments DSC Q-100 (Figure 7). The calibration was carried out using indium and sapphire standards. All samples were first equilibrated at −60 °C and heated to 250 °C at a rate of 10 °C/min to erase thermal history, and then subjected to three cycles of cooling to −60 °C at 5 °C/min and heating back to 250 °C at a rate of 10 °C/min. All three cooling and heating scans are reported.

## ■ RESULTS AND DISCUSSION

**Synthesis of Monomer and Monomer Characterization.** Anders Hult and co-workers first reported the bis-MPA class of polyester dendrimer in 1993 and its related hyperbranched polymer at about the same time.[29−31] Although dendrimer and hyperbranched bis-MPA polymers have been studied and eventually commercialized, the exact linear bis-MPA polymer class has yet to be studied. Bisht and co-worker were the first to describe the use of related bis-MPA cyclic carbonates to synthesize linear bis-MPA polycarbonate materials.[21,22] These polycarbonates incorporate the diol of bis-MPA in their backbone and contain a pendent carboxylic acid moiety, which can be used as a vector for further functionality as demonstrated by Tempelaar et al., Olsson et al., and Sanders et al.[23−25] Although these linear bis-MPA polycarbonates are biodegradable and can be synthesized upward of ∼$M_n$ 13 000, they are not the best linear equivalent to bis-MPA-based dendrimers because they contain a carbonate linkage that is not seen in any dendrimer or hyperbranched bis-MPA material. As a result, a true linear analog for the purpose of comparison to bis-MPA dendrimers has remained elusive. Therefore, the work shown here is the first example of a linear, benzoyl-protected, bis-MPA polyester.

Annby et al.[32] were the first to use benzylidene-protected bis-MPA, and Trollsås et al.[28] used this bis-MPA derivative for a hyperbranched poly(caprolactone) system. Since then, it has been used in the synthesis of numerous benzylidene-protected bis-MPA dendritic materials.[7,9,33−35] Although typically used as a protecting group, the aforementioned benzylidene acetal can be transformed using the Hanessian−Hullar[27,36] reaction to yield 3-(benzoyloxy)-2-(bromomethyl)-2-methylpropanoic acid (BBM) (Scheme 1). This novel bis-MPA derivative (**3**) can be synthesized efficiently on a multigram scale (∼10 g) and contains a pendent benzoate ester and primary bromine, the latter of which provides a direct and efficient avenue for polymerization under basic conditions in a range of solvents.

MALDI-ToF MS data (Figure S4) show the expected $m/z$ for **3** at 322.94 (theoretical: 322.99) with $Na^+$ counterion for the $^{79}Br$ product and at nearly the same peak intensity at [M +

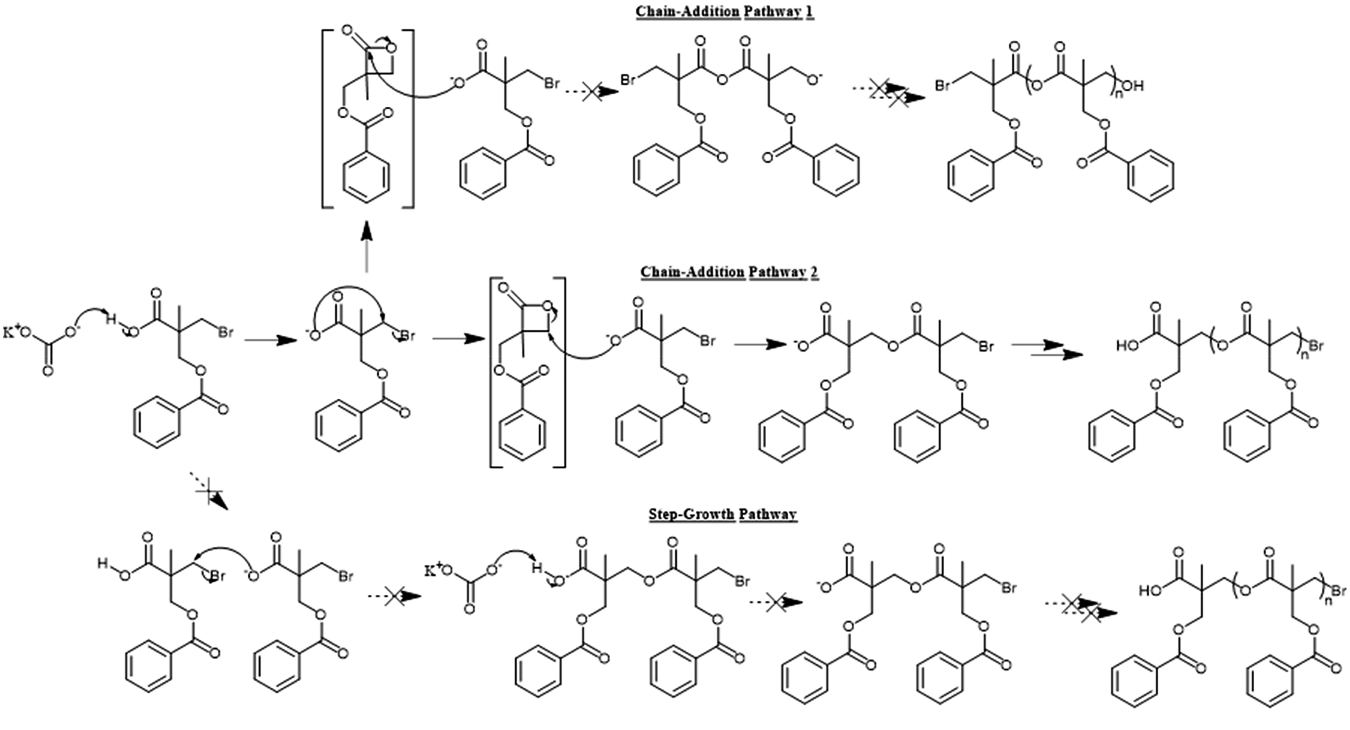


**Figure 2.** Possible polymerization mechanisms of PBBM.

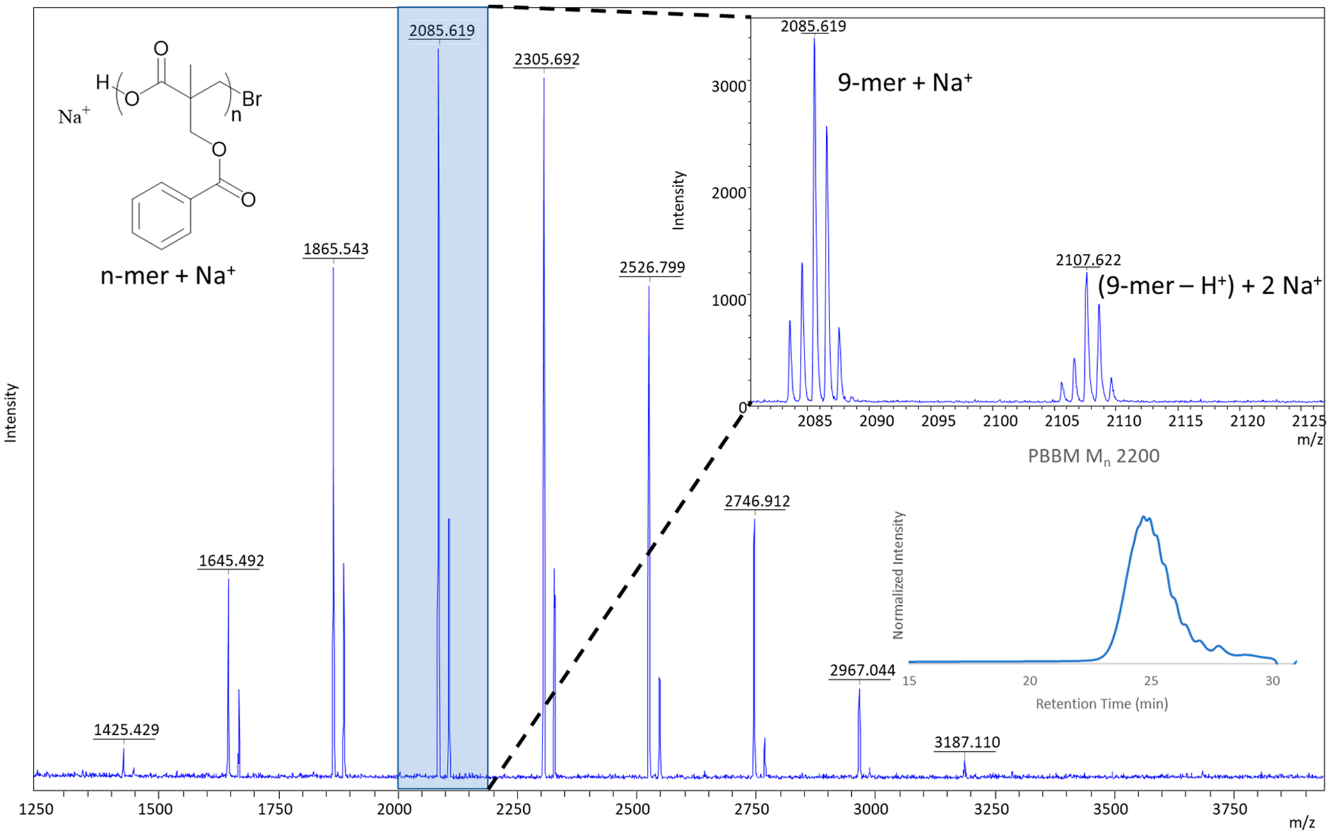


**Figure 3.** MALDI-ToF MS spectrum of $M_n$ 2200 PBBM in ethyl acetate. Spectrum was obtained using $Na^+$ as the counterion with DCTB as the matrix. GPC trace is of $M_n$ 2200 PBBM in THF.

$2]^+$ = 324.94 (theoretical: 324.99) for the $^{81}$Br product giving the expected isotopic distribution. This spectrum also shows the disodiated $^{79}$Br adduct at 344.93 *m*/*z* (theoretical: 344.97) and the disodiated $^{81}$Br adduct at 344.93 *m*/*z* (theoretical: 344.97), which is due to the proton of the carboxylic acid being exchanged for a sodium counterion. The $^1$H NMR spectrum (Figure 1) shows BBM has two sets of diastereotopic protons due to the chirality of the neighboring quaternary carbon. The first set is located on the brominated carbon shown at 3.71 ppm followed by the second set at 4.54 ppm, which is the **$CH_2$**−O−C(O) carbon. Additionally, the shift of the *ortho* protons on the benzoyl ring to 7.98 ppm in BBM (Figure 1) from 7.33 ppm in the starting material (Figure S1) confirms completion of the ring-opening reaction. $^{13}$C NMR shows the anticipated carbon signals, and $^{13}$C DEPT 135 (Figure S3) confirms the proper $CH_2$ peaks and disappearance of the quaternary carbonyl carbons at 165.6 and 173.8 ppm corresponding to the benzoyl and carboxylic acid carbons, respectively.

**Polymerization of PBBM and Mechanism.** The polymerization of BBM is accomplished via its carboxylic acid and bromine moieties using $K_2CO_3$. At the inception of the proposed synthetic scheme, the polymerization was expected to take place through a self-initiated, step-growth condensation polymerization. This would be due to deprotonation of the carboxylic acid to form the resulting carboxylate, which then attacks the brominated carbon of another BBM molecule (Figure 2). Initial trials showed polymerization occurs in several solvents (Figures S6), although ethyl acetate, which has poor miscibility with water, was selected due to low observed dispersity values and minimal formation of side products. Ethyl acetate may seem to be a poor choice of solvent due to possible transesterification. However, although PBBM is a polyester, its ester linkages are not formed by attack of a carboxylic acid by an alcohol or alkoxide, but rather attack of the *β*-carbon of a propiolactone (discussed later) by a carboxylate.

MALDI-ToF MS data (Figure 3) show that the initial MALDI-ToF MS and GPC analysis reported very narrow dispersity values of less than 1.2. This was unexpected on the basis of the proposed synthetic scheme (Scheme 1), which would suggest a step-growth polymerization mechanism (Figure 2). This step-growth mechanism should result in a dispersity closer to 2.0, which is not what is observed. To test the initial step-growth hypothesis, poly(3-(benzoyloxy)-2-(bromomethyl)-2-methylpropanoic acid (PBBM) ($M_n$ 2200) was allowed to react for 96 h under basic conditions, and no significant $M_n$ increase was observed (Figure S7). In other polymerization trials, additional potassium carbonate without additional monomer was added, and little polymer growth was observed. Subsequent polymerization trials where the types of base, the equivalents of base, and the initial monomer concentration were varied (Table 1) showed the limit of achieved molecular weight. It was always under ∼7 kDa using the same starting amount of monomer. Because of this behavior and low dispersity values, it is suspected this monomer may polymerize using a chain-reaction polymerization, possibly through a fleeting propiolactone intermediate (Figures 2 and S28). This suggests that polymerization requires more available monomer, or monomer intermediate, rather than the polymer for the carboxylate nucleophile to attack. This supports the idea of polymerization being limited

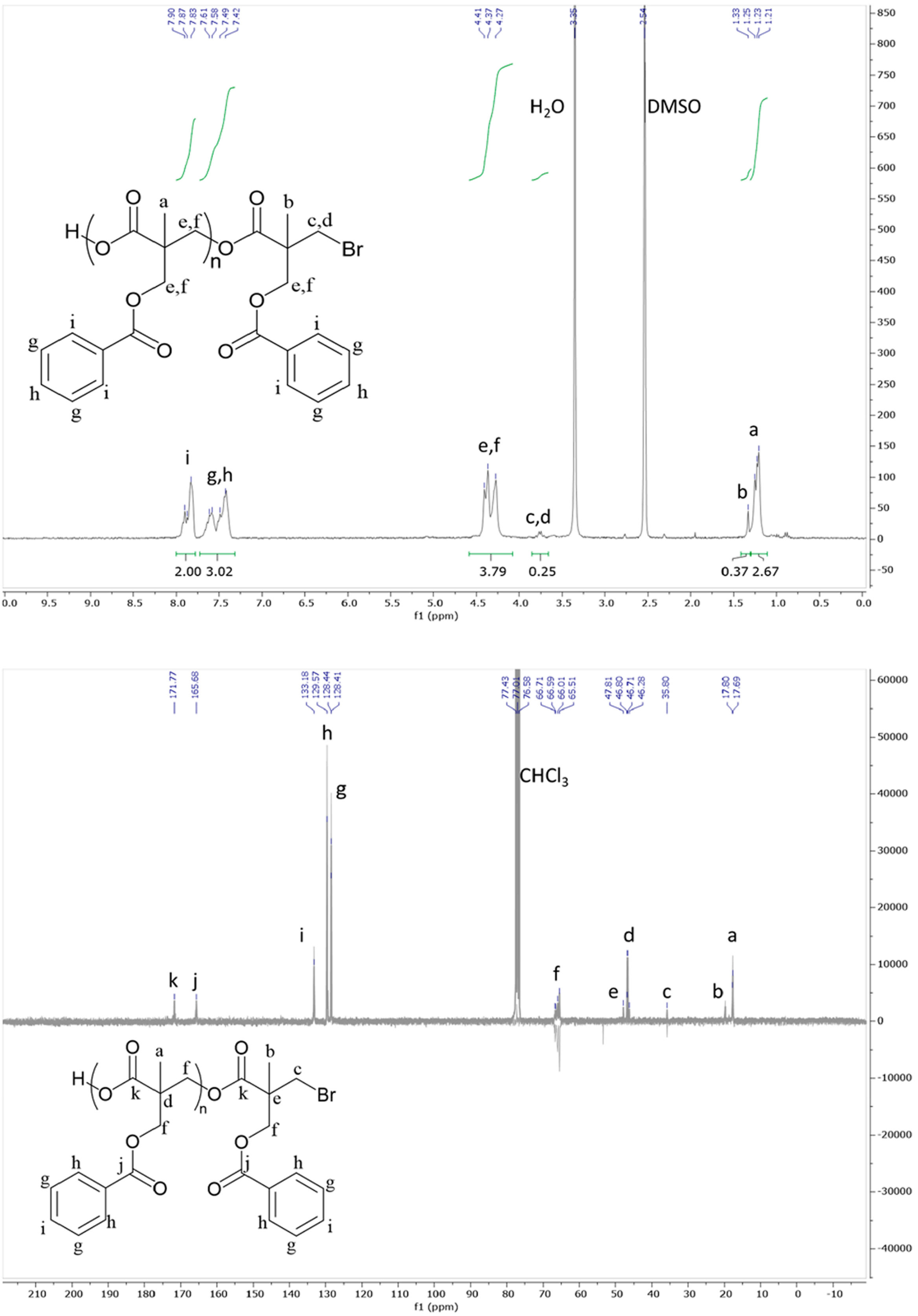


**Figure 4.** $^1$H NMR spectra of poly(3-(benzoyloxy)-2-(bromomethyl)-2-methylpropanoic acid) (PBBM) in DMSO at 3 mg/mL. $^{13}$C NMR and $^{13}$C DEPT 135 NMR spectra of poly(3-(benzoyloxy)-2-(bromomethyl)-2-methylpropanoic acid) (PBBM) in CDCl$_3$ at 10 mg/mL.

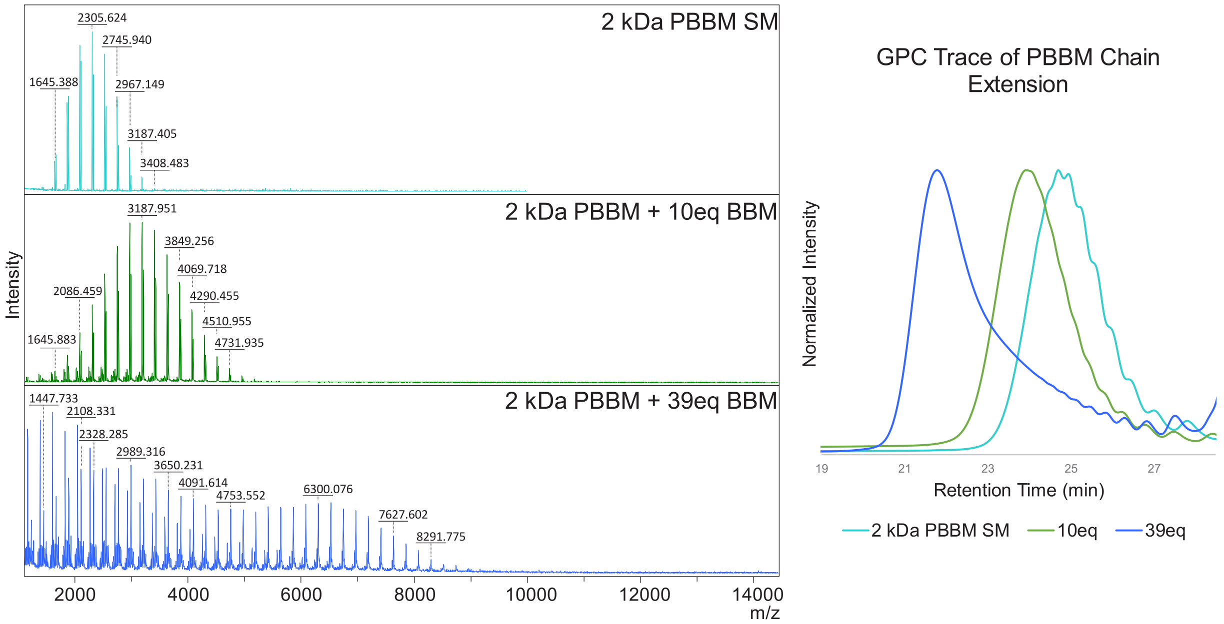


**Figure 5.** MALDI-ToF MS and GPC of PBBM chain extension trials. Starting with $M_n$ 2200 PBBM, 10 equiv followed by an additional 39 equiv of 0.1 M BBM was added to the reaction flask at 1 mL/min.

by a low concentration of the proposed lactone intermediate or increasing steric bulk around the brominated carbon hindering the step-growth pathway.

Mechanistically, a lactone pathway (Figure 2) could result in either a hydroxyl-terminated polyester with a hydroxyl on one end and a bromine on the other or a carboxylic acid on one end and a bromine on the other. Although both lactone mechanisms are plausible, there is previous work that shows attack at the $\beta$-position is preferred in the case of carboxylate nucleophiles.[37] On the basis of chain-addition pathway 1, the expected resulting polymer is not observed according to MALDI-ToF MS due to the existence of the disodiated adduct (Figure 3) of the carboxylic acid and lack of a carbonate signal in the $^{13}$C NMR spectrum (Figure 4). Although a cyclic structure would also lack a carbonate signal, a cyclic structure would have both a different $m/z$ than what is observed, due to the loss of the bromine end group, and a disodiated adduct that would not be observed by MALDI-ToF-MS. Not only does the MALDI-ToF MS $m/z$ match what is expected (Figure 3), but the isotopic distribution also matches the expected pattern for a bromine-containing product for both the monosodiated and the disodiated adducts (Figure S24).

It is possible that the step-growth pathway is inhibited due to use of a weak nucleophile in the carboxylate and increasing steric bulk around the terminal bromine. To test this notion of accessibility, PBBM was reacted with BnBr and 1-bromododecane under the same conditions after the polymerization, and both were added to the polymer end group (Figures S8, S26, and S27). Although the reaction is slow (16−48 h), it demonstrates the nucleophilicity of the carboxylic acid at the end of the polymer chain. Additionally, $NaN_3$ can also replace the bromine at the end of the polymer chain (Figures S9 and S25). This further supports the assertion of the mechanism proceeding through a monomer intermediate because both the carboxylic acid appears to be a sufficient nucleophile and the bromine appears to be accessible. These observations, as well as no growth observed after 96 h, support the unlikelihood of a step-growth polymerization. Therefore, earlier polymerization trials were likely stunted due to a low concentration of available monomer. Finally, isopropoxy-BBM (2-(bromomethyl)-3-isopropoxy-2-methyl-3-oxopropyl benzoate) was added to the polymerization of BBM at a 10% molar ratio, yet no incorporation of this monomer derivative was observed according to MALDI-ToF MS data. This lack of isopropoxy-BBM monomer incorporation is expected in a chain-growth polymerzaton, but not a step-growth polymerization (Figure S10). The isopropoxy group would prevent the formation of the lactone, which may be the reason it is not incorporated in the polymer chain.

Finally, if the polymerization proceeded through a chain-addition mechanism, then it should be possible to perform a chain extension on this polymer. A 0.1 M solution of BBM was added at 1 mL/h to a flask of 0.1 M PBBM ($M_n$ 2200) and $K_2CO_3$ at 70 °C. This resulted in an increase in polymer molecular weight, but it also increased the dispersity (Figure 5). Increased dispersity is likely due to the addition of monomer diluting the solution to a level where the formation of new chains was faster than addition to previously formed chains. To avoid this, another polymerization with a highly pure batch of BBM was done where BBM would be added neat. This BBM was added dropwise in 100 mg fractions every hour over a 6 h period. Even in this polymerization trial, where dispersity would be artificially broadened due to monomer being added as the polymerization proceeded, dispersity never exceeded 1.3 by GPC or MALDI-ToF MS (Figures S29 and S30). However, measurement of early time points in the reaction was needed to see if the low observed dispersity values (<1.2) were a product of reaction times being too long in earlier trials such as in Table 1. To investigate this, a 300 mg scale polymerization of this highly pure BBM was analyzed using crude time aliquots from 0 to 18 h. These time aliquots were analyzed using MALDI-ToF MS and GPC (Figures S31 and S32) to determine if a dispersity of 2 (characteristic of step-growth polymerizations) would be observed earlier in the reaction. According to these data, dispersity remains below 1.04 by MALDI-ToF MS and 1.10 by GPC throughout the

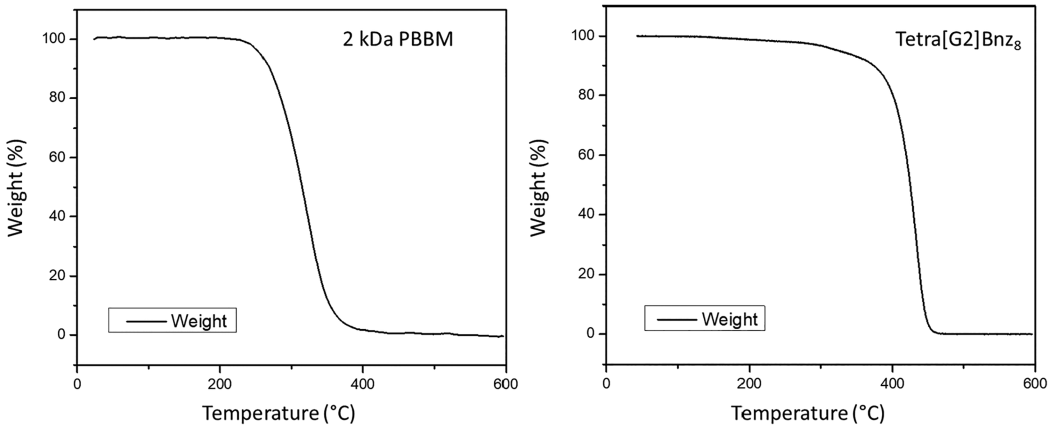


**Figure 6.** TGA analysis of 2 kDa PBBM and Tetra[G2]$Bnz_8$.

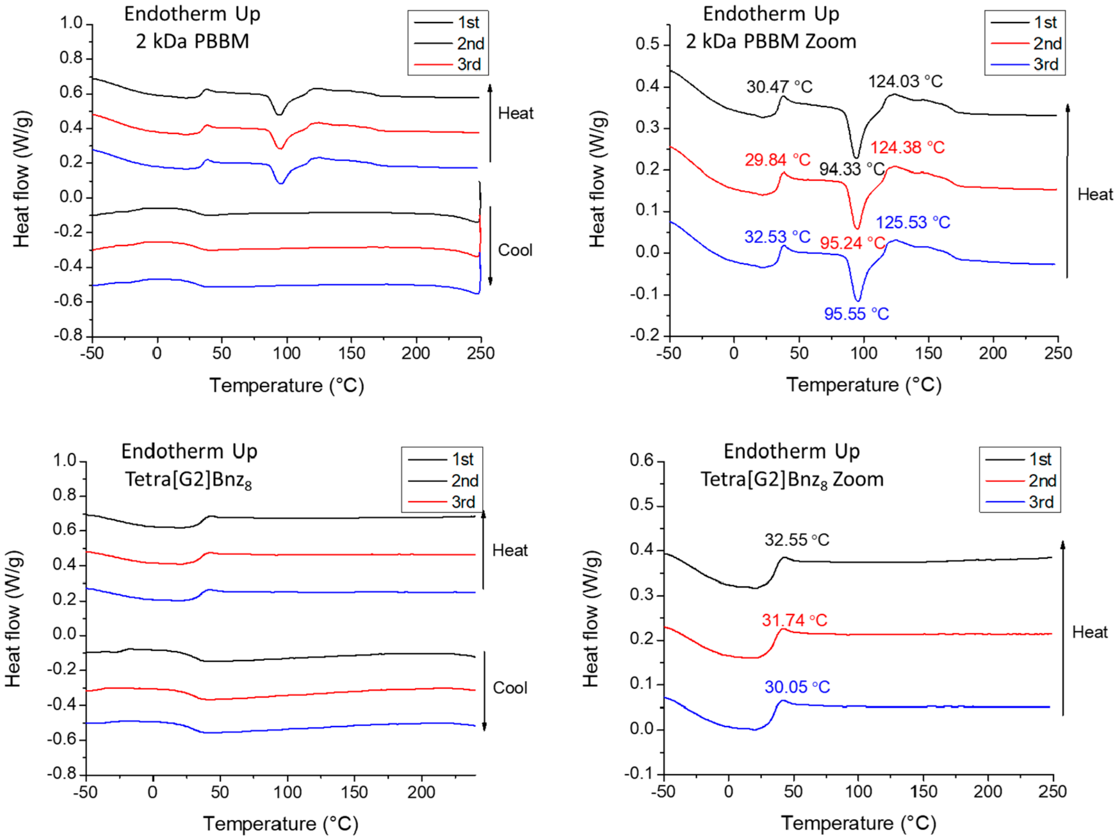


**Figure 7.** DSC analysis of 2 kDa PBBM and Tetra[G2]$Bnz_8$. A zoom-in of the three heat cycles of each material is provided to better show thermal transitions.

reaction. As a result of all of these observations, we believe this polymer is synthesized through a self-initiated, chain-addition polymerization.

**Thermal Properties of BBM and PBBM.** The BBM was isolated as an oil. This has a substantially lower melting point than those of unprotected bis-MPA (181−190 °C)[38] and bis-MPABnz (197−198 °C).[28] TGA analysis of 2 kDa PBBM and Tetra[G2]$Bnz_8$ demonstrates the increased stability of the branched architecture within a dendrimer (Figure 6). The midpoint of thermal degradation of PBBM is ∼316 °C, while that of Tetra[G2]$Bnz_8$ is ∼405 °C according to TGA analysis. Because the polyester linkages in 2 kDa PBBM and Tetra[G2]$Bnz_8$ should be similar and they are of similar molecular weight, the differences in thermal degradation are likely due to architecture. The increased stability of Tetra[G2]$Bnz_8$ is due to degradation of the dendrimer subunits involving scission of three bonds versus two bond scissions in PBBM. The TGA spectrum of PBBM exhibits one degradation event, which shows homogeneity among its backbone esters. This lends credence to the structure uniformity of PBBM. Tetra[G2]$Bnz_8$ also exhibits one thermal degradation event. Because this molecule is made up of largely the same bis-MPA ester linkages, this thermal event corresponds to the degradation of these esters.

Tetra[G2]$Bnz_8$ and 2 kDa PBBM were also analyzed by DSC (Figure 7). Both samples were analyzed using three heat

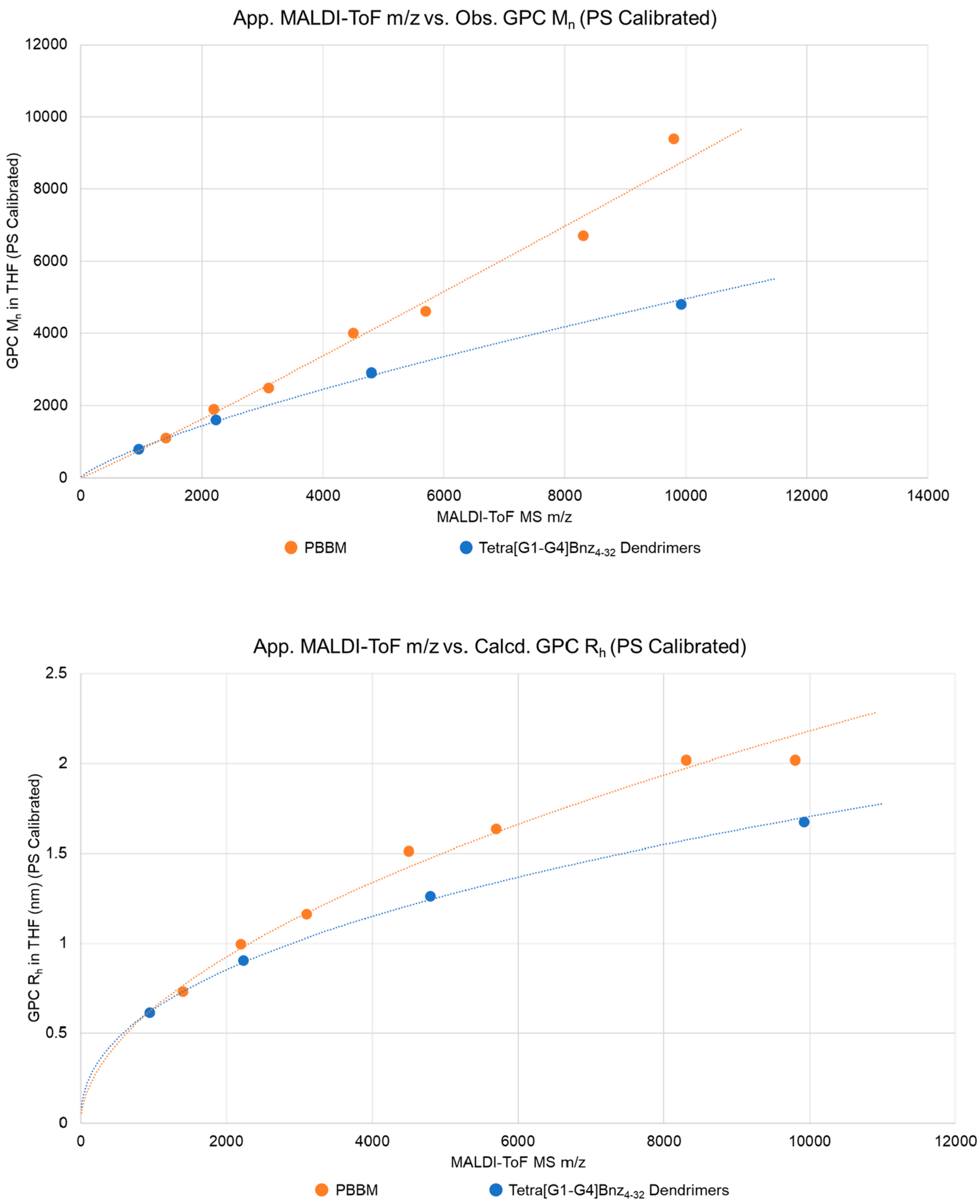


**Figure 8.** PBBM versus Tetra[G1−G4] dendrimer $M_n$ values acquired by MALDI-ToF MS and GPC in THF. GPC $M_n$ values were used to calculate hydrodynamic radius values using an equation for polystyrene (PS) in THF from Mays and co-workers.[42]

and cool cycles to ensure repeatability of thermal transitions. According to DSC, 2 kDa PBBM exhibits three thermal transitions: a glass transition temperature ($T_g$), a crystallization temperature ($T_c$), and a melting temperature ($T_m$). The existence of these transitions suggests that PBBM is at least semicrystalline most likely due to the aromatic rings of the pendent benzoate group. The $T_g$, $T_c$, and $T_m$ values are observed in the heating cycles of PBBM with transitions at ~30, ~95, and ~124 °C, respectively. The 2 kDa PBBM and Tetra[G2]$Bnz_8$ appear to have similar glass transition temperatures as can be seen in the zoom-in of each set of curves. This may be attributed to the 2 kDa molecular weight or the difference in functional groups between the benzylidene acetal terminated dendrimer and the pendent benzoate ester of PBBM.[39−41] Also, there is no observed $T_c$ of Tetra[G2]$Bnz_8$,

https://dx.doi.org/10.1021/acs.macromol.0c01045

which supports the expected amorphous nature of the dendritic materials.

**Preliminary Apparent Size Comparison.** A linear equivalent to bis-MPA-based dendrimers helps to increase the understanding of how architecture affects polymer physical properties within the bis-MPA family. A preliminary investigation into the effect of architecture on the apparent solution size of PBBM and its dendrimer analog was conducted using gel permeation chromatography (GPC) and MALDI-ToF MS analysis (Figure 8). PBBM was fractionated using preparative GPC to separate different molecular weight distributions within the same sample (Figures S13 and S14). All fractions were analyzed by MALDI-ToF MS, and fractions within a 10% mass range of the corresponding [G1−G4] pentaerythritol-core dendrimers were selected for size comparison (Figures S11 and S12). Additional molecular weight fractions of PBBM were also examined to allow for a better trendline fit.

As expected, the dendrimers appear to be "smaller" in hydrodynamic radius than their corresponding PBBM analog despite similar molecular weights above ~$M_n$ 2000. This is due to the branched nature of the dendrimer, which means its molecular weight is spread out radially and not in a linear fashion as in the case of PBBM. At lower molecular weights, PBBM and the dendrimers appear to be similar in terms of apparent hydrodynamic volume, but as the molecular weight increases the difference between them is as expected with the dendrimer appearing increasingly smaller by comparison despite similar $M_n$. Although this size analysis is preliminary, PBBM does appear to behave as we would expect a linear bis-MPA analog would.

## CONCLUSION

The synthesis of a linear, benzoyl-protected bis-MPA homopolyester, PBBM, is reported. This polymer can be synthesized on the multigram scale in a range of solvents under basic conditions. Postfunctionalization of this polymer has also been demonstrated on both the carboxylic acid and the bromine ends. This novel polyester undergoes a chain-growth polymerization, possibly through a ring-opening mechanism involving a propiolactone. Thermal analysis showed BBM has a lower melting point than does its benzylidene-protected precursor. The glass transition temperature of 2 kDa PBBM was found to be about the same as the $T_g$ of the corresponding Tetra[G2]Bnz$_8$ but has a lower degradation temperature according to TGA. Investigation of higher molecular weight analogs is necessary to confirm these thermal observations. Finally, preliminary size analysis shows PBBM is consistently larger than the pentaerythritol-core dendrimers in THF above ~$M_n$ 2000 despite similar molecular weights.

PBBM has been shown to be a good analog for benzylidene-protected bis-MPA dendrimers due to its atom economy being similar to that of the dendrimer benzylidene end group. Initial size data show that high generation dendrimers have a lower size than their linear analogs, but a deeper investigation into how solvent may affect these results is required. In the future, we would like to look at how solvent affects the apparent size of PBBM when compared to the pentaerythritol-core dendrimers.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.macromol.0c01045.

Synthetic procedures for benzylidene bis-MPA and the synthesis of BBM; FTIR data for PBBM and MALDI-ToF MS data for PBBM; MALDI-ToF MS and $^1$H NMR spectra of the end group functionalizations for PBBM with azide terminal end group and the dodecanoxy and benzyl ester end groups; the benzylidene-protected bis-MPA dendrimers; the isolated fractions of PBBM; the bromine isotopic ratio of PBBM; additional PBBM characterizations; and the HSQC NMR of the end groups (PDF)

## AUTHOR INFORMATION

### Corresponding Author

**Scott M. Grayson** − *Department of Chemistry, Percival Stern Hall, Tulane University, New Orleans, Louisiana 70118, United States*; orcid.org/0000-0001-6345-8762; Email: sgrayson@tulane.edu

### Authors

**Oluwapelumi O. Kareem** − *Department of Chemistry, Percival Stern Hall, Tulane University, New Orleans, Louisiana 70118, United States*

**Samantha P. Daymon** − *Department of Polymer Science and Engineering, Shelby F. Thames Polymer Science Research Center, University of Southern Mississippi, Hattiesburg, Mississippi 39406, United States*

**Christopher B. Keller** − *Department of Chemistry, Percival Stern Hall, Tulane University, New Orleans, Louisiana 70118, United States*

**Beibei Chen** − *Department of Polymer Science and Engineering, Shelby F. Thames Polymer Science Research Center, University of Southern Mississippi, Hattiesburg, Mississippi 39406, United States*

**Sergei Nazarenko** − *Department of Polymer Science and Engineering, Shelby F. Thames Polymer Science Research Center, University of Southern Mississippi, Hattiesburg, Mississippi 39406, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.macromol.0c01045

### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

We are thankful for the support of the American Chemical Society-Petroleum Research Fund (53980-ND7), the National Science Foundation-MSN (1807358), and to the National Science Foundation-MRI for the MALDI-ToF MS (0619770). O.O.K. thanks the Louisiana Board of Regents and Southern Regional Education Board for his graduate fellowship.

## REFERENCES

(1) García-Gallego, S.; Nyström, A. M.; Malkoch, M. Chemistry of Multifunctional Polymers Based on Bis-MPA and Their Cutting-Edge Applications. *Prog. Polym. Sci.* **2015**, *48*, 85−110.

(2) Sowinska, M.; Urbanczyk-Lipkowska, Z. Advances in the Chemistry of Dendrimers. *New J. Chem.* **2014**, *38*, 2168−2203.

(3) Mendes, L. P.; Pan, J.; Torchilin, V. P. Dendrimers as Nanocarriers for Nucleic Acid and Drug Delivery in Cancer Therapy. *Molecules* **2017**, *22*, 1−21.

(4) Jansen, J. F. G. A.; de Brabander-van den Berg, E. M. M.; Meijer, E. W. Encapsulation of Guest Molecules into a Dendritic Box. *Science* **1994**, *266*, 1226−1229.

(5) Calderón, M.; Quadir, M. A.; Strumia, M.; Haag, R. Functional Dendritic Polymer Architectures as Stimuli-Responsive Nanocarriers. *Biochimie*; Elsevier Masson SAS: France, 2010; pp 1242−1251.

(6) Giles, M. D.; Liu, S.; Emanuel, R. L.; Gibb, B. C.; Grayson, S. M. Dendronized Supramolecular Nanocapsules: pH Independent, Water-Soluble, Deep-Cavity Cavitands Assemble via the Hydrophobic Effect. *J. Am. Chem. Soc.* **2008**, *130*, 14430−14431.

(7) Carlmark, A.; Malmström, E.; Malkoch, M. Dendritic Architectures Based on Bis-MPA: Functional Polymeric Scaffolds for Application-Driven Research. *Chem. Soc. Rev.* **2013**, *42*, 5858.

(8) Stenström, P.; Andrén, O. C. J.; Malkoch, M. Fluoride-Promoted Esterification (FPE) Chemistry: A Robust Route to Bis-MPA Dendrons and Their Postfunctionalization. *Molecules* **2016**, *21*, 366.

(9) Stenström, P.; Andrén, O.; Malkoch, M. Fluoride-Promoted Esterification (FPE) Chemistry: A Robust Route to Bis-MPA Dendrons and Their Postfunctionalization. *Molecules* **2016**, *21*, 366.

(10) García-Gallego, S.; Hult, D.; Olsson, J. V.; Malkoch, M. Fluoride-Promoted Esterification with Imidazolide-Activated Compounds: A Modular and Sustainable Approach to Dendrimers. *Angew. Chem., Int. Ed.* **2015**, *54*, 2416−2419.

(11) Bosman, A. W.; Janssen, H. M.; Meijer, E. W. About Dendrimers: Structure, Physical Properties, and Applications. *Chem. Rev.* **1999**, *99*, 1665−1688.

(12) Astruc, D.; Boisselier, E.; Ornelas, C. Dendrimers Designed for Functions: From Physical, Photophysical, and Supramolecular Properties to Applications in Sensing, Catalysis, Molecular Electronics, Photonics, and Nanomedicine. *Chem. Rev.* **2010**, *110*, 1857−1959.

(13) Fréchet, J. M. J. Functional Polymers and Dendrimers: Reactivity, Molecular Architecture, and Interfacial Energy. *Science (Washington, DC, U. S.)* **1994**, *263*, 1710−1715.

(14) Lescanec, R. L.; Muthukumar, M. Configurational Characteristics and Scaling Behavior of Starburst Molecules: A Computational Study. *Macromolecules* **1990**, *23*, 2280−2288.

(15) Ihre, H.; Hult, A.; Söderlind, E. Synthesis, Characterization, and 1 H NMR Self-Diffusion Studies of Dendritic Aliphatic Polyesters Based on 2,2-Bis(Hydroxymethyl)Propionic Acid and 1,1,1-Tris-(Hydroxyphenyl)Ethane. *J. Am. Chem. Soc.* **1996**, *118*, 6388−6395.

(16) Chai, M.; Niu, Y.; Youngs, W. J.; Rinaldi, P. L. Structure and Conformation of DAB Dendrimers in Solution via Multidimensional NMR Techniques. *J. Am. Chem. Soc.* **2001**, *123*, 4670−4678.

(17) Jeong, M.; Mackay, M. E.; Vestberg, R.; Hawker, C. J. Intrinsic Viscosity Variation in Different Solvents for Dendrimers and Their Hybrid Copolymers with Linear Polymers. *Macromolecules* **2001**, *34*, 4927−4936.

(18) Lyulin, S. V.; Evers, L. J.; Van Der Schoot, P.; Darinskii, A. A.; Lyulin, A. V.; Michels, M. A. J. Effect of Solvent Quality and Electrostatic Interactions on Size and Structure of Dendrimers. Brownian Dynamics Simulation and Mean-Field Theory. *Macromolecules* **2004**, *37*, 3049−3063.

(19) Rubio, A. M.; McBride, C.; Freire, J. J. Binary Interactions between Dendrimer Molecules. A Simulation Study. *Macromolecules* **2014**, *47*, 5379−5387.

(20) de Gennes, P. G.; Hervet, H. Statistics of "Starburst" Polymers. *J. Phys., Lett.* **1983**, *44*, 351−360.

(21) Al-Azemi, T. F.; Bisht, K. S. Novel Functional Polycarbonate by Lipase-Catalyzed Ring-Opening Polymerization of 5-Methyl-5-Benzyloxycarbonyl-1,3-Dioxan-2-One. *Macromolecules* **1999**, *32*, 6536−6540.

(22) Al-Azemi, T. F.; Bisht, K. S. One-Step Synthesis of Polycarbonates Bearing Pendant Carboxyl Groups by Lipase-Catalyzed Ring-Opening Polymerization. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 1267−1274.

(23) Tempelaar, S.; Mespouille, L.; Dubois, P.; Dove, A. P. Organocatalytic Synthesis and Postpolymerization Functionalization of Allyl-Functional Poly(Carbonate)s. *Macromolecules* **2011**, *44*, 2084−2091.

(24) Olsson, J. V.; Hult, D.; Cai, Y.; Garcia-Gallego, S.; Malkoch, M. Reactive Imidazole Intermediates: Simplified Synthetic Approach to Functional Aliphatic Cyclic Carbonates. *Polym. Chem.* **2014**, *5*, 6651−6655.

(25) Sanders, D. P.; Fukushima, K.; Coady, D. J.; Nelson, A.; Fujiwara, M.; Yasumoto, M.; Hedrick, J. L. A Simple and Efficient Synthesis of Functionalized Cyclic Carbonate Monomers Using a Versatile Pentafluorophenyl Ester Intermediate. *J. Am. Chem. Soc.* **2010**, *132*, 14724−14726.

(26) Hanessian, S.; Plessas, N. R. The Reaction of O-Benzylidene Sugars with N-Bromosuccinimide. III. Applications to the Synthesis of Aminodeoxy and Deoxy Sugars of Biological Importance. *J. Org. Chem.* **1969**, *34*, 1045−1053.

(27) Chrétien, F.; Khaldi, M.; Chapleur, Y. An Improved Procedure for the Ring Opening of Benzylidene Acetals with N - Bromosuccinimide. *Synth. Commun.* **1990**, *20*, 1589−1596.

(28) Trollsås, M.; Atthoff, B.; Claesson, H.; Hedrick, J. L. Hyperbranched Poly(ε;-Caprolactone)s. *Macromolecules* **1998**, *31*, 3439−3445.

(29) Malmström, E.; Johansson, M.; Hult, A. Hyperbranched Aliphatic Polyesters. *Macromolecules* **1995**, *28*, 1698−1703.

(30) Hult, A.; Malmström, E.; Sörensen, K. Dendritic Macromolecule, Process for Preparation Thereof and Use Thereof. WO 93/17060, 1993.

(31) Hult, A.; Malmström, E.; Sörensen, K. Dendritic Macromolecule And Processs for Preparation Thereof. 5418301, 1995.

(32) Annby, U.; Malmberg, M.; Pettersson, B.; Rehnberg, N. Benzylidene Protected Bis-MPA a Convenient Dendrimer Building Block. *Tetrahedron Lett.* **1998**, *39*, 3217−3220.

(33) Malkoch, M.; Malmström, E.; Hult, A. Rapid and Efficient Synthesis of Aliphatic Ester Dendrons and Dendrimers. *Macromolecules* **2002**, *35*, 8307−8314.

(34) van der Poll, D. G.; Kieler-Ferguson, H. M.; Floyd, W. C.; Guillaudeu, S. J.; Jerger, K.; Szoka, F. C.; Fréchet, J. M. Design, Synthesis, and Biological Evaluation of a Robust, Biodegradable Dendrimer. *Bioconjugate Chem.* **2010**, *21*, 764−773.

(35) Grayson, S. M.; Fréchet, J. M. J. A New Approach to Heterofunctionalized Dendrimers: A Versatile Triallyl Chloride Core. *Org. Lett.* **2002**, *4*, 3171−3174.

(36) Hanessian, S. The Reaction Products Are Versatile Intermediates for Further Synthetic Work in the Carbohydrate Series since They Possess the Combined Advantages of a Good Leaving-Group At. *Carbohydr. Res.* **1966**, *2*, 86−88.

(37) Jaffredo, C. G.; Guillaume, S. M. Benzyl β-Malolactonate Polymers: A Long Story with Recent Advances. *Polym. Chem.* **2014**, *5*, 4168−4194.

(38) Magnusson, H.; Malmström, E.; Hult, A. Structure Buildup in Hyperbranched Polymers from 2,2-Bis(Hydroxymethyl)Propionic Acid. *Macromolecules* **2000**, *33*, 3099−3104.

(39) Farrington, P. J.; Hawker, C. J.; Fréchet, J. M. J.; Mackay, M. E. The Melt Viscosity of Dendritic Poly(Benzyl Ether) Macromolecules. *Macromolecules* **1998**, *31*, 5043−5050.

(40) Morikawa, A. Comparison of Properties among Dendritic and Hyperbranched Poly(Ether Ether Ketone)s and Linear Poly(Ether Ketone)s. *Molecules* **2016**, *21*, 219.

(41) Hay, G.; Mackay, M. E.; Hawker, C. J. Thermodynamic Properties of Dendrimers Compared with Linear Polymers: General Observations. *J. Polym. Sci., Part B: Polym. Phys.* **2001**, *39*, 1766−1777.

(42) Fetters, L. J.; Hadjichristidis, N.; Lindner, J. S.; Mays, J. W. Molecular Weight Dependence of Hydrodynamic and Thermodynamic Properties for Well-Defined Linear Polymers in Solution. *J. Phys. Chem. Ref. Data* **1994**, *23*, 619−640.