Synthesis and Organocatalytic Ring-Opening Polymerization of Cyclic Esters Derived from L-Malic Acid

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The synthesis of 3-(*S*)-[(benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione (BMD) and 3,6-(*S*)-[di(benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione (malide) from commercially available L-malic acid is reported. Ring-opening polymerization (ROP) studies of BMD are reported showing that the controlled ROP of this monomer is possible in the absence of transesterification side reactions, despite the presence of side-chain esters, using 1-(3,5-bis(trifluoromethyl)phenyl)-3-cyclohexylthiourea and (−)-sparteine to catalyze the polymerization. The ROP of malide with this system was ineffective. Investigation of the effect of initiating species revealed that the electronic nature of the alcohol had a greater effect on the ultimate molecular weight and hence initiator efficiency than steric considerations. Deprotection of the resultant poly(BMD) using H_2 and Pd/C resulted in hydrophilic poly(glycolic-*co*-malic acid)s (PGMAs) that were able to undergo autocatalytic degradation in dilute H_2O solution such that complete degradation was observed within 6 days.

Introduction

Aliphatic poly(ester)s have received great interest over the past three decades primarily as a consequence of their biocompatibility and biodegradability.[1−3] Poly(lactide), PLA, has been an exemplar in this field and, in addition to being derived from renewable resources, has been utilized in a range of biomedical applications including controlled drug and gene delivery and degradable scaffolds for tissue growth.[1−7] For many applications, the ability to tune the physical properties of the PLAs is highly desirable. PLAs are commonly accessed by either polycondensation methods or by the ring-opening polymerization (ROP) of lactide. While polycondensation allows more ready access to a wider range of functional polymers, ROP enables greater levels of control over the molecular characteristics of the polymers to be attained and the ability to control molecular weight (including access to high molecular weight PLAs under milder conditions), tacticity, polydispersity (PDI), access to block copolymers, and end group fidelity.[5,8−10] Consequently, manipulation of the stereochemistry, crystallinity, and polymer architecture or copolymerization with glycolide,[11−15] ε-caprolactone,[16−20] or other monomers allows for tailoring of the polymer degradation rates, cross-linking, and physical properties. However, PLA and other aliphatic poly(ester)s including poly(glycolide) (PGA), poly(ε-caprolactone) (PCL), poly(δ-valerolactone) (PVL), and poly(β-propiolactone) (PPL) have limitations resulting from their hydrophobicity. The potential impact of functionality along the polymer backbone would enable careful tuning of the polymer properties including decreased hydrophobicity and the ability to covalently attach therapeutic molecules.

Several synthetic strategies have been considered for the introduction of functionality in poly(ester)s. Postpolymerization functionalization provides an attractive possibility, requiring a single prepolymer to provide many different characteristics; however, to date, the harsh conditions often applied result in some polymer degradation. The more commonly reported route is the ROP of functional cyclic ester monomers. ROP of these monomers can be complicated by reduced polymerization activity resulting from steric crowding of the esters and consequently reduced ring strain of the monomers. Furthermore, protection of pendant functional groups is also generally required to prevent side reactions during the polymerization. It is noteworthy that several studies have also focused on the synthesis and application in ROP of functional ε-caprolactones,[21−23] δ-valerolactones,[24−28] and β-propiolactones.[29−33]

In order to investigate the potential for the synthesis of a versatile poly(ester) by ROP, we chose to examine the use of malic acid (MA, **1**). MA is a relatively inexpensive, commercially available α-hydroxy acid equivalent to aspartic acid, thus possessing a pendant carboxylic acid moiety that would potentially support a range of functional groups providing a high level of control over degradation times and physical properties of the resultant polymers. Previous studies to utilize MA in ROP include the synthesis of a range of β-lactones from ring closure between the hydroxyl group and β-carboxylic acid. These studies have resulted in a range of functional β-malolactones that through ROP result in a range of functional poly(hydroxyalkanoates)s including the highly desirable poly(β-malic acid) (PMA).[34,35] ROP of six-membered rings derived from MA has received relatively little attention despite being previously reported. Kimura et al. reported the synthesis and ROP of 3-(*S*)-[(benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione (BMD, Figure 1). ROP of BMD mediated by stannous(II) octanoate ($Sn(Oct)_2$) resulted in relatively poorly defined poly(ester)s (e.g., [M]/[I] = 100; M_n = 10 500 g·mol^{-1}; PDI = 2.0). Despite this poor control, BMD and its statistical copolymers with lactide have received some study, including micelle formation through self-assembly of an amphiphilic block copolymer with poly(ethylene oxide) (PEO).[36−39] Ouchi and co-workers also reported the synthesis of the cyclic diester of MA, 3,6-(*S*)-[di(benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione (malide, Figure 1). ROP of malide with different organotin catalysts between 130 and 220 °C led to polymers with low reactivities for ROP and unpredictable molecular parameters.[40] In both cases, the relatively poor control compared to that of less

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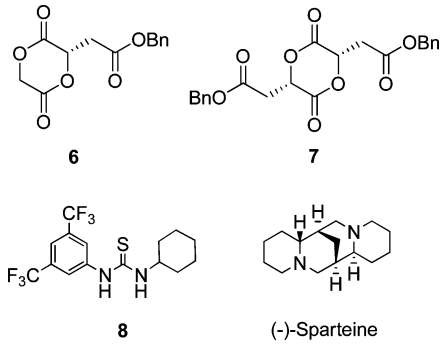


Figure 1. Cyclic diester monomers 3-(*S*)-[(benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione BMD (**6**) and 3,6-(*S*)-[di(benzyloxycarbonyl)-methyl]-1,4-dioxane-2,5-dione malide (**7**) synthesized from malic acid and 1-(3,5-bis(trifluoromethyl)phenyl)-3-cyclohexylthiourea (**8**)/(−)-sparteine organic catalysts.

hindered cyclic esters is thought to be a result of transesterification reactions. In all cases reported to date, ROP has been catalyzed by $Sn(Oct)_2$, while that being extensively applied in ROP is known to readily mediate transesterification reactions that may therefore limit control over the polymerization.

Several recent advances in ROP catalysis have resulted in greatly enhanced levels of selectivity for both ring opening of cyclic esters in preference to transesterification side reactions and selectivity for preferential ring opening based on the stereochemistry of the adjacent chiral center.[5,41] One of the most notable examples is the dual component thiourea/amine catalysts (Figure 1).[41,42] These organic molecules exhibit exceptional selectivity toward ring opening of lactide compared to transesterification of the polymer chain such that, even at very high monomer conversions and extended reaction times, polydispersities remain ≤ 1.07.[42,43] We hypothesized that selective and controlled ROP of malic-acid-based monomers would be possible using these highly selective catalysts to provide a potentially versatile platform for the synthesis of poly(ester)s with pendant ester functionality. Herein we report the improved synthesis of 3-(*S*)-[(benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione (BMD) and 3,6-(*S*)-[di(benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione (malide) from commercially available L-malic acid and describe the application of organic catalysts to mediate the controlled ROP of BMD to yield copolymers consisting of glycolic acid and benzyl α-L-malate units (PBMD).

Experimental Section

Materials. L-Lactide was purified by recrystallization from dry dichloromethane and sublimation (×2). Chloroform and (−)-sparteine were dried over CaH_2, distilled, degassed, and stored under a nitrogen atmosphere. All alcohol and amine initiators were dried over suitable dry agents and were distilled, degassed, and/or sublimed as required. Triethylamine, acetone, and benzylamine were dried and stored over 4 Å molecular sieves. 1-(3,5-Bis(trifluoromethyl)phenyl)-3-cyclohexylthiourea (**8**) was prepared as previously reported.[42] Compounds **2**−**7** and **9**−**16** were prepared using modified literature procedures.[43−51] All other chemicals and solvents were obtained from Aldrich and used as received.

General Considerations. All manipulations were performed under moisture- and oxygen-free conditions either in a nitrogen-filled glovebox or by standard Schlenk techniques. Gel-permeation chromatography (GPC) was used to determine the molecular weights and polydispersities of the synthesized polymers. GPC in THF was conducted on a system composed of a Varian 390-LC-Multi detector suite fitted with differential refractive index (DRI), light scattering (LS), and ultraviolet (UV) detectors equipped with a guard column (Varian Polymer Laboratories PLGel 5 μM, 50 × 7.5 mm) and two mixed D columns (Varian Polymer Laboratories PLGel 5 μM, 300 × 7.5 mm). The mobile phase was tetrahydrofuran with 5% triethylamine eluent at a flow rate of 1.0 mL min^{-1}, and samples were calibrated against Varian Polymer Laboratories Easi-Vials linear poly(styrene) standards (162-2.4 × 10^5 g mol^{-1}) using Cirrus v3.3. GPC in aqueous media was conducted on a system composed of a Varian 390-LC-Multi detector suite fitted with differential refractive index (DRI), viscometer (VIS), and ultraviolet (UV) detectors equipped with a guard column (Varian Polymer Laboratories PL-aquagel-OH Guard 8 μM, 50 × 7.5 mm), two Varian Polymer Laboratories PL-aquagel-OH 30 8 μM, 300 × 7.5 mm columns and one Varian Polymer Laboratories PL-aquagel-OH 40 8 μM, 300 × 7.5 mm column. The mobile phase was an aqueous solution containing 2 L of H_2O, 34 g of sodium nitrate, and 3.12 g of sodium phosphate monobasic dehydrate that was adjusted to pH 8.2 with a 1 M NaOH(aq) solution. The eluent flow rate was 1.0 mL min^{-1}, and samples were calibrated against Varian Polymer Laboratories Easi-Vials linear poly(ethylene glycol) standards (106-9.1 × 10^5 g mol^{-1}) using Cirrus v3.3. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-300, DPX-400, AC400, or DRX-500 spectrometer at 293 K unless stated otherwise. Chemical shifts are reported as δ in parts per million (ppm) and referenced to the chemical shift of the residual solvent resonances ($CDCl_3$: ^1H δ = 7.26 ppm; ^{13}C δ = 77.16 ppm). Mass spectra were acquired by MALDI-TOF (matrix-assisted laser desorption and ionization time-of-flight) mass spectrometry using a Bruker Daltonics Ultraflex II MALDI-TOF mass spectrometer, equipped with a nitrogen laser delivering 2 ns laser pulses at 337 nm with positive ion TOF detection performed using an accelerating voltage of 25 kV. Solutions of *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propylidene]malonitrile (DCTB) as matrix (0.3 μL of a 10 g L^{-1} acetone solution), sodium trifluoroacetate as cationization agent (0.3 μL of a 10 g L^{-1} acetone solution), and analyte (0.3 μL of a 1 g L^{-1} DCM solution) were applied sequentially to the target followed by solvent evaporation to prepare a thin matrix/analyte film. The samples were measured in reflectron ion mode and calibrated by comparison to 2 × 10^3 and 5 × 10^3 g mol^{-1} poly(ethylene glycol) standards. Elemental analyses were performed by Warwick Analytical Services. Phenolphthalein was used as the pH indicator to monitor the degradation of PBMA in H_2O.

Synthesis of 2-[2,2-Dimethyl-5-oxo-1,3-dioxolan-4-yl]acetic Acid (2).[44] To a mixture of L-malic acid (20 g, 0.15 mol) and 2,2-dimethoxypropane (74 mL, 0.60 mol) in a Schlenk tube under nitrogen was added *p*-toluenesulfonic acid monohydrate (0.29 g, 1.5 mmol), and the solution was stirred at room temperature for 3.5 h. H_2O (100 mL) containing $NaHCO_3$ (0.13 g, 1.5 mmol) was added to the solution before the aqueous layer was separated and extracted with DCM (5 × 100 mL). The combined organic layers were dried with $NaSO_4$ and filtered, and the solvent was removed under reduced pressure. The resulting solid was recrystallized from Et_2O, yielding a white solid (16.89 g, 97 mmol, 65%). Data were in accordance with that previously reported. ^1H NMR ($CDCl_3$, 400.0 MHz): δ = 11.02 (1H, s, −COO*H*), 4.71 (1H, dd, $^3J_{H-H}$ = 6.53 Hz, $^3J_{H-H}$ = 3.76 Hz, −C*H*CO−), 3.00 (1H, dd, $^2J_{H-H}$ = 17.32 Hz, $^3J_{H-H}$ = 3.76 Hz, −C*H*$_2$COOH), 2.86 (1H, dd, $^2J_{H-H}$ = 17.31 Hz, $^3J_{H-H}$ = 6.53 Hz, −C*H*$_2$COOH), 1.62 (3H, s, −C*H*$_3$), 1.57 (3H, s, −C*H*$_3$). ^{13}C NMR ($CDCl_3$, 100.0 MHz): δ = 175.1 (−*C*OOH), 171.9 (−*C*OO−), 111.4 (−*C*(CH$_3$)$_2$), 70.4 (−*C*HCOO−), 36.0 (−*C*H$_2$COOH), 26.8 (−*C*H$_3$), 25.8 (−*C*H$_3$).

Synthesis of 2-[2,2-Dimethyl-5-oxo-1,3-dioxolan-4-yl]acetic Acid Benzyl Ester (3).[45] To a solution of **2** (10 g, 61 mmol) in dry acetone under nitrogen was added dry NEt_3 (10.2 mL, 73 mmol) followed by benzyl bromide (8.9 mL, 75 mmol). The solution was refluxed for 60 h at 50 °C before being cooled to room temperature. The solids were removed by filtration and washed with acetone before the volatile organic solvents were removed under reduced pressure. The resulting residue was dissolved in EtOAc (300 mL) and H_2O (150 mL). The aqueous layer was further extracted with EtOAc (2 × 100 mL) before the combined organic layers were dried with $MgSO_4$, filtered, and reduced in vacuo. The resultant solid was recrystallized from Et_2O to

yield white crystals (12.14 g, 46 mmol, 80%). Data were in accordance with that previously reported. ^{1}H NMR ($CDCl_3$, 400.0 MHz): $\delta = 7.36$ (5H, m, $-CH_{aromatic}$), 5.18 (2H, d, $^3J_{H-H} = 2.01$ Hz, $-CH_2Ar$), 4.74 (1H, dd, $^3J_{H-H} = 6.53$ Hz, $^3J_{H-H} = 3.77$ Hz, $-CHCOO-$), 2.98 (1H, dd, $^2J_{H-H} = 16.94$ Hz, $^3J_{H-H} = 3.77$ Hz, $-CH_2COOCH_2Ar$), 2.84 (1H, dd, $^2J_{H-H} = 16.81$ Hz, $^3J_{H-H} = 6.52$ Hz, $-CH_2COOCH_2Ar$), 1.58 (3H, s, $-CH_3$), 1.56 (3H, s, $-CH_3$). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.0 MHz): $\delta = 169.1$ ($-COO-$), 135.3 ($-C_{ipso\text{-}aromatic}$), 128.6 ($-CH_{meta\text{-}aromatic}$), 128.5 ($-CH_{para\text{-}aromatic}$), 128.4 ($-CH_{ortho\text{-}aromatic}$), 111.2 ($-C(CH_3)_2$), 70.7 ($-CHCOO-$), 67.0 ($-CH_2Ar$), 36.3 ($-CH_2COOCH_2Ar$), 26.7 ($-CH_3$), 25.9 ($-CH_3$).

Synthesis of 2-Hydroxysuccinic Acid 4-Benzyl Ester (4).[46] A solution of **3** (20.47 g, 77 mmol) was dissolved in AcOH/THF/H_2O (1:1:1) (300 mL) and heated for 24 h at 40 °C. The solvent was removed under reduced pressure, and the resulting colorless oil was freeze-dried to yield a white solid (16.02 g, 72 mmol, 92%). Data were in accordance with that previously reported. ^{1}H NMR ($CDCl_3$, 400.0 MHz): $\delta = 7.35$ (5H, m, $-CH_{aromatic}$), 5.18 (2H, d, $^3J_{H-H} = 2.01$ Hz, $-CH_2Ar$), 4.58 (1H, dd, $^3J_{H-H} = 4.52$ Hz, $^3J_{H-H} = 3.14$ Hz, $-CHCOO-$), 2.99 (1H, dd, $^2J_{H-H} = 16.94$ Hz, $^3J_{H-H} = 4.52$ Hz, $-CH_2COOCH_2Ar$), 2.90 (1H, dd, $^2J_{H-H} = 16.69$ Hz, $^3J_{H-H} = 6.27$ Hz, $-CH_2COOCH_2Ar$). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.0 MHz): $\delta = 176.8$ ($-COOH$), 171.0 ($-COO-$), 135.1 ($-C_{ipso\text{-}aromatic}$), 128.7 ($-CH_{meta\text{-}aromatic}$), 128.5 ($-CH_{para\text{-}aromatic}$), 128.4 ($-CH_{ortho\text{-}aromatic}$), 67.2 ($-CH_2Ar$), 67.0 ($-CHCOO-$), 38.2 ($-CH_2COOCH_2Ar$).

Synthesis of 2-(2-Bromoacetoxy)succinic Acid 4-Benzyl Ester (5).[47] A solution of α-hydroxy acid, **4** (6.6 g, 0.029 mol), and NEt_3 (4.1 mL, 29 mmol) in CH_2Cl_2 (200 mL) was added to a solution of bromoacetyl bromide (2.56 mL, 29 mmol) and DMAP (0.36 g, 29 mmol) in CH_2Cl_2 (125 mL) at 0 °C. The resulting solution was stirred at room temperature for 16 h under a nitrogen atmosphere. The reaction was then concentrated in vacuo, and the salts were precipitated out with the addition of Et_2O (150 mL). After filtration, the solvent was evaporated, yielding the product as an orange oil that was used as obtained without further purification (9.87 g, 29 mmol, 97%). Data were in accordance with that previously reported. ^{1}H NMR ($CDCl_3$, 400.0 MHz): $\delta = 7.30-7.19$ (5H, m, $-CH_{aromatic}$), 5.48 (1H, dd, $^3J_{H-H} = 6.53$ Hz, $^3J_{H-H} = 3.77$ Hz, $-HOOCCHOCO-$), 5.05 (2H, d, $^3J_{H-H} = 2.01$ Hz, $-CH_2Ar$), 3.75 (2H, m, $-COCH_2Br$), 2.94 (2H, dd, $^2J_{H-H} = 16.54$ Hz, $^3J_{H-H} = 4.52$ Hz, $-CH_2COOCH_2Ar$). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.0 MHz): $\delta = 173.3$ ($-COOH$), 168.5 ($-CH_2COOCH_2Ar$), 166.2 ($-COOCH_2Br$), 135.0 ($-C_{ipso\text{-}aromatic}$), 128.6 ($-CH_{meta\text{-}aromatic}$), 128.5 ($-CH_{para\text{-}aromatic}$), 128.4 ($-CH_{ortho\text{-}aromatic}$), 69.0 ($-CHCOO-$), 66.9 ($-CH_2Ar$), 35.5 ($-CH_2COOCH_2Ar$), 24.8 ($-COOCH_2Br$).

Synthesis of 3-(*S*)-[(Benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione (6).[48] To a vigorously stirred solution of $NaHCO_3$ (0.73 g, 8.7 mmol) in DMF (200 mL) at room temperature was added **5** (2.0 g, 5.8 mmol) in DMF (40 mL) via a syringe pump over 28 h. The solution was then filtered and the DMF removed in vacuo. The residual salts were precipitated by addition of EtOAc and filtered before the solution was concentrated in vacuo. The resulting brown solid was washed with hexane (200 mL) followed by MeOH (100 mL) before being recrystallized from 2-propanol to yield white needles that were dried over 4 Å molecular sieves in CH_2Cl_2 solution (0.84 g, 3.2 mmol, 55%). Data were in accordance with that previously reported. ^{1}H NMR ($CDCl_3$, 400.0 MHz): $\delta = 7.32-7.19$ (5H, m, $-CH_{aromatic}$), 5.22 (1H, t, $^3J_{H-H} = 4.68$ Hz, $-CHCH_2COOCH_2Ar$), 5.11 (2H, s, $-CH_2Ar$), 5.02−4.88 (2H, dd, $^2J_{H-H} = 16.83$ Hz, $^2J_{H-H} = 29.92$ Hz, $-COOCH_2COO-$), 3.12 (2H, d, $^3J_{H-H} = 4.68$ Hz, $-CHCH_2COOCH_2Ar$). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.0 MHz): $\delta = 169.0$ ($-CHCOOCH_2-$), 164.7 ($-CH_2COOCH_2Ar$), 162.8 ($-CH_2COOCH-$), 134.6 ($-C_{ipso\text{-}aromatic}$), 128.8 ($-CH_{meta\text{-}aromatic}$), 128.7 ($-CH_{para\text{-}aromatic}$), 128.4 ($-CH_{ortho\text{-}aromatic}$), 72.0 ($-CHCOO-$), 67.6 ($-CH_2Ar$), 65.5 ($-COOCH_2COO-$), 36.4 ($-CH_2COOCH_2Ar$).

Synthesis of 3,6-(*S*)-[Di(benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione (7).[49] A solution of **4** (5.6 g, 25 mmol) and *p*-toluenesulfonic acid monohydrate (0.48 g, 2.5 mmol) in toluene (500 mL) was heated to reflux for 50 h, with the resulting water formed continuously removed via Dean−Stark apparatus. The solution was then concentrated in vacuo and the resulting crude solid purified by column chromatography (3:1 hexane/EtOAc) followed by washing with diethyl ether to yield a white solid (1.57 g, 3.8 mmol, 30%). Data were in accordance with that previously reported. ^{1}H NMR ($CDCl_3$, 400.0 MHz): $\delta = 7.37$ (5H, m, $-CH_{aromatic}$), 5.45 (1H, dd, $^3J_{H-H} = 4.86$ Hz, $^3J_{H-H} = 3.27$ Hz, $-CHCOO-$), 5.19 (2H, d, $^3J_{H-H} = 2.00$ Hz, $-CH_2Ar$), 3.23 (1H, dd, $^2J_{H-H} = 17.48$ Hz, $^3J_{H-H} = 4.86$ Hz, $-CH_2COOCH_2Ar$), 3.07 (1H, dd, $^2J_{H-H} = 17.57$ Hz, $^3J_{H-H} = 6.73$ Hz, $-CH_2COOCH_2Ar$). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.0 MHz): $\delta = 168.5$ ($-CHCOOCH-$), 164.9 ($-CH_2COOCH_2Ar$), 135.0 ($-C_{ipso\text{-}aromatic}$), 128.7 ($-CH_{meta\text{-}aromatic}$), 128.6 ($-CH_{para\text{-}aromatic}$), 128.4 ($-CH_{ortho\text{-}aromatic}$), 72.6 ($-CHCOO-$), 67.5 ($-CH_2Ar$), 35.7 ($-CH_2COOCH_2Ar$).

General Procedure for Polymerization of 6 ([M]/[I] = 20). A solution of **8** (0.01 g, 0.027 mmol, 25 mol %), (−)-sparteine (0.99 μL, 0.004 mmol, 5 mol %), and initiator (0.0044 mmol, 1 equiv) was added to **6** (23 mg, 0.087 mmol, 20 equiv) in $CHCl_3$ (0.3 mL). The solution was left to stir at room temperature for the allotted time period before being diluted with DCM (4 mL), washed with cold 2 M $HCl_{(aq)}$ (2 × 5 mL), and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The excess thiourea was then removed by washing with Et_2O, and the PBMD was precipitated into ice-cold petroleum ether (b.p. 40−60 °C) to yield pure PBMD as a white solid (0.022 g, 0.0042 mmol, 96%). ^{1}H NMR ($CDCl_3$, 400.0 MHz): $\delta = 7.40-7.25$ (100H, m, $-CH_{aromatic}$), 5.65−5.54 (20H, m, $-CHCOO-$), 5.15−5.11 (40H, m, $-CH_2Ar$), 4.82−4.49 (40H, m, $-COCH_2OCOCH-$), 3.83−3.80 (2H, m, $-CH_2(CH_3)_3$), 3.08−2.85 (40H, m, $-CH_2COOCH_2Ar$), 0.92 and 0.89 (9H, s, $-CH_2(CH_3)_3$). GPC (THF, RI): M_n (PDI) = 6750 g mol^{-1} (1.17) (initiation from 2,2-dimethyl-1-propanol).

General Procedure for the Deprotection of PBMD ([M]/[I] = 20). A balloon of H_2 was bubbled through a suspension of PBMD (0.05 g, 0.0095 mmol) and Pd/C (0.01 g, 10 wt % loading) in THF (20 mL). The solution was maintained under a H_2 atmosphere at 30 °C for 4 h before being filtered to remove Pd/C and concentrated in vacuo. The PGMA was extracted into MeOH and concentrated in vacuo to yield the desired product as a colorless oil (0.024 g, 0.006 mmol, 73%). ^{1}H NMR (THF-d_8, 400.0 MHz): $\delta = 5.60-5.55$ (20H, m, $-CHCOO-$), 4.44 (20H, br s, $-COOH$), 4.86−4.64 (40H, m, $-COCH_2OCOCH-$), 3.03−2.70 (40H, m, $-CH_2COOCH_2Ar$), 0.9 (9H, s, $-CH_2(CH_3)_3$). ^{13}C{^{1}H} NMR (THF-d_8, 100.0 MHz): $\delta = 170.6$ ($-COOCH_2C(CH_3)_3$), 168.7 ($-CHCOOCH_2-$), 167.2 ($-CH_2COOH$), 70.3 ($-CH_2COOCHCOO-$), 61.5 ($-CH_2COOCHCOO-$), 36.2 ($-CH_2COOCH_2Ar$). GPC (H_2O, RI): M_n (PDI) = 2410 g mol^{-1} (1.08).

General Procedure for the Degradation of PGMA ([M]/[I] = 20). PGMA (14.5 mg, 0.0042 mmol) was dissolved in H_2O (7.5 mL) and monitored via acid−base titration of a sample (0.2 mL) with an aqueous NaOH solution (18.36 mg L^{-1}) using phenolphthalein as a pH indicator, ^{1}H NMR spectroscopy in D_2O, and GPC analysis.

Synthesis of Isopropyl 2-hydroxyacetate (9).[50] Glycolic acid (12.5 g, 164 mmol) was dissolved in 2-propanol (50 mL) containing *p*-toluenesulfonic acid (0.125 g, 0.657 mmol). The solution was refluxed overnight in a Soxhlet extractor containing 4 Å molecular sieves. After cooling, the reaction was poured into 10% Na_2CO_3 and extracted into CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$. The solution was concentrated in vacuo to yield the desired product as a colorless oil which was further purified by distillation (60 °C, 0.025 mmHg) (11.3 g, 95.2 mmol, 58%). ^{1}H NMR ($CDCl_3$, 400.0 MHz): $\delta = 5.12$ (1H, sept, $^3J_{H-H} = 6.27$ Hz, $-COOCH(CH_3)_2$), 4.10 (2H, s, $-COOCH_2OH$), 1.27 (6H, d, $^3J_{H-H} = 6.27$ Hz, $-COOCH(CH_3)_2$). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.0 MHz): $\delta = 172.9$ ($-COOCH(CH_3)_2$), 69.5 ($-COOCH(CH_3)_2$), 60.8 ($-COOCH_2OH$), 21.8 ($-COOCH(CH_3)_2$). ESI-MS: obs, 119.09 *m*/*z*; calcd for $C_5H_{11}O_3$, 119.14 *m*/*z*. Anal. Calcd (Found): C 50.8 (50.85); H 8.5 (8.65).

Synthesis of Neopentyl 2-Hydroxyacetate (11).[50] A solution of glycolic acid (12.5 g, 164 mmol), 2,2-dimethyl-1-propanol (15.9 g, 180

mmol), and *p*-toluenesulfonic acid (0.125 g, 0.657 mmol) in THF (50 mL) was refluxed overnight in a Soxhlet extractor containing 4 Å molecular sieves. After cooling, the reaction was poured into 10% Na_2CO_3 and extracted into CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$. The solution was concentrated in vacuo to yield the desired product as a colorless oil, which was further purified by distillation (60 °C, 0.027 mmHg) (10.2 g, 69.8 mmol, 42%). ^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 4.18 (2H, s, $-COOCH_2OH$), 3.90 (2H, s, $-COOCH_2C(CH_3)_3$), 0.94 (9H, s, $-COOCH_2C(CH_3)_3$). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.0 MHz): δ = 173.6 ($-COOCH_2C(CH_3)_3$), 74.7 ($-COOCH_2OH$), 60.5 ($-COOCH_2C(CH_3)_3$), 31.4 ($-COOCH_2C(CH_3)_3$), 26.3 ($-COOCH_2C(CH_3)_3$). ESI-MS: obs, 147.01 *m/z* ([MH]$^+$); calcd for $C_7H_{15}O_3$, 147.10 *m/z*. Anal. Calcd (Found): C 57.5 (57.0); H 9.65 (9.8).

Synthesis of Isopropyl 2-acetoxyacetate (13).[51] A mixture of **9** (0.61 g, 5.16 mmol) and acetyl chloride (1.0 mL, 14.1 mmol) was stirred at room temperature for 2 h. The resulting solution was reduced under vacuum before the oily residue was extracted with CH_2Cl_2 (100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to yield **13** as a colorless oil (0.52 g, 3.25 mmol, 64%). ^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 5.08 (1H, sept, $^3J_{H-H}$ = 6.27 Hz, $-COOCH(CH_3)_2$), 4.55 (2H, s, $-COOCH_2OCOCH_3$), 2.15 (3H, s, $-COOCH_2OCOCH_3$), 1.26 (6H, d, $^3J_{H-H}$ = 6.27 Hz, $-COOCH(CH_3)_2$). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.0 MHz): δ = 170.4 ($-COOCH_2OCOCH_3$), 167.4 ($-COOCH_2OCOCH_3$), 69.3 ($-COOCH(CH_3)_2$), 61.0 ($-COOCH_2OCOCH_3$), 21.7 ($-COOCH(CH_3)_2$), 18.4 ($-COOCH_2OCOCH_3$). ESI-MS: obs, 161.21 *m/z* ([MH]$^+$); calcd for $C_7H_{13}O_4$, 161.08 *m/z*. Anal. Calcd (Found): C 52.5 (52.2); H 7.55 (7.5).

Synthesis of Neopentyl 2-acetoxyacetate (15).[51] This compound was synthesized using the same procedure as described for **13** using **11** (3.46 g, 23.7 mmol) and acetyl chloride (3.5 mL, 49.2 mmol) (1.87 g, 9.94 mmol, 41%). ^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 4.63 (2H, s, $-COOCH_2OCOCH_3$), 3.86 (2H, s, $-COOCH_2C(CH_3)_3$), 2.16 (3H, s, $-COOCH_2OCOCH_3$), 0.93 (9H, s, $-COOCH_2C(CH_3)_3$). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.0 MHz): δ = 170.4 ($-COOCH_2C(CH_3)_3$), 168.0 ($-COOCH_2OCOCH_3$), 74.5 ($-COOCH_2OCOCH_3$), 60.7 ($-COOCH_2C(CH_3)_3$), 31.4 ($-COOCH_2C(CH_3)_3$), 26.3 ($-COOCH_2C(CH_3)_3$), 20.5 ($-COOCH_2OCOCH_3$). ESI-MS: obs, 188.94 *m/z* ([MH]$^+$); calcd for $C_9H_{17}O_4$, 189.11 *m/z*. Anal. Calcd (Found): C 57.4 (57.3); H 8.6 (8.7).

Synthesis of 4-Benzyl 1-isopropyl 2-hydroxysuccinate (10).[50] This compound was synthesized using the same procedure as described for **9** from **4** (2.5 g, 11.2 mmol), *p*-toluenesulfonic acid (0.02 g, 0.105 mmol), and 2-propanol (50 mL) (1.51 g, 5.67 mmol, 51%). ^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 7.35 (5H, m, $-CH_{aromatic}$), 5.15 (2H, s, $-CH_2Ar$), 5.09 (1H, sept, $^3J_{H-H}$ = 6.27 Hz, $-COOCH(CH_3)_2$), 4.46 (1H, dd, $^3J_{H-H}$ = 6.03 Hz, $^3J_{H-H}$ = 4.51 Hz, $-CHCOO-$), 2.89 (1H, dd, $^2J_{H-H}$ = 16.57 Hz, $^3J_{H-H}$ = 4.51 Hz, $-CH_2COOCH_2Ar$), 2.82 (1H, dd, $^2J_{H-H}$ = 16.31 Hz, $^3J_{H-H}$ = 5.98 Hz, $-CH_2COOCH_2Ar$), 1.23 (6H, dd, $^2J_{H-H}$ = 18.41, Hz, $^3J_{H-H}$ = 6.27 Hz, $-COOCH(CH_3)_2$). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.0 MHz): δ = 172.9 ($-COOCH(CH_3)_2$), 170.3 ($-CH_2COOCH_2Ar$), 135.5 ($-C_{ipso-aromatic}$), 128.6 ($-CH_{meta-aromatic}$), 128.4 ($-CH_{para-aromatic}$), 128.3 ($-CH_{ortho-aromatic}$), 70.1 ($-COOCH(CH_3)_2$), 67.3 ($-CHCOO-$), 66.8 ($-CH_2Ar$), 38.8 ($-CH_2COOCH_2Ar$), 21.7 ($-COOCH(CH_3)_2$). ESI-MS: obs, 267.04 *m/z* ([MH]$^+$); calcd for $C_{14}H_{19}O_5$, 267.12 *m/z*. Anal. Calcd (Found): C 63.15 (62); H 6.8 (6.8).

Synthesis of 4-Benzyl 1-isopropyl 2-acetoxysuccinate (14).[51] This compound was synthesized using the same procedure as described for **13** from **10** (0.60 g, 2.25 mmol) and acetyl chloride (1.0 mL, 14.1 mmol) (0.53 g, 1.72 mmol, 76%). ^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 7.35 (5H, m, $-CH_{aromatic}$), 5.43 (1H, t, $^3J_{H-H}$ = 6.27 Hz, $-CHCOO-$), 5.16 (2H, d, $^3J_{H-H}$ = 5.81 Hz, $-CH_2Ar$), 5.04 (1H, sept, $^3J_{H-H}$ = 6.27 Hz, $-COOCH(CH_3)_2$), 2.91 (2H, d, $^3J_{H-H}$ = 6.27 Hz, $-CH_2COOCH_2Ar$), 2.08 (3H, s, $-CHOCOCH_3$), 1.22 (6H, dd, $^2J_{H-H}$ = 15.54, Hz, $^3J_{H-H}$ = 6.27 Hz, $-COOCH(CH_3)_2$). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.0 MHz): δ = 170.0 ($-COOCH(CH_3)_2$), 169.0 ($-CH_2COOCH_2Ar$), 168.3 ($-CHOCOCH_3$), 135.4 ($-C_{ipso-aromatic}$), 128.6 ($-CH_{meta-aromatic}$), 128.5 ($-CH_{para-aromatic}$), 128.4 ($-CH_{ortho-aromatic}$), 69.8 ($-COOCH(CH_3)_2$), 68.5 ($-CHCOO-$), 66.9 ($-CH_2Ar$), 36.2 ($-CH_2COOCH_2Ar$), 21.6 ($-COOCH(CH_3)_2$), 20.2 ($-CHOCOCH_3$). ESI-MS: obs, 309.10 *m/z* ([MH]$^+$); calcd for $C_{16}H_{21}O_6$, 309.13 *m/z*. Anal. Calcd (Found): C 62.3 (62.0); H 6.5 (6.7).

Synthesis of 2-Acetoxy-4-(benzyloxy)-4-oxobutanoic Acid (12).[51] This compound was synthesized using the same procedure as described for **13** from **4** (0.61 g, 2.72 mmol) and acetyl chloride (3.0 mL, 42.2 mmol) (0.54 g, 2.03 mmol, 75%). ^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 7.36 (5H, m, $-CH_{aromatic}$), 5.53 (1H, t, $^3J_{H-H}$ = 6.01 Hz, $-CHCOO-$), 5.17 (2H, d, $^3J_{H-H}$ = 7.45 Hz, $-CH_2Ar$), 2.95 (2H, d, $^3J_{H-H}$ = 6.01 Hz, $-CH_2COOCH_2Ar$), 2.09 (3H, s, $-CHOCOCH_3$). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.0 MHz): δ = 175.7 ($-COOH$), 170.0 ($-CH_2COOCH_2Ar$), 169.0 ($-CHOCOCH_3$), 135.3 ($-C_{ipso-aromatic}$), 128.6 ($-CH_{meta-aromatic}$), 128.5 ($-CH_{para-aromatic}$), 128.4 ($-CH_{ortho-aromatic}$), 67.8 ($-CHCOO-$), 67.1 ($-CH_2Ar$), 36.0 ($-CH_2COOCH_2Ar$), 20.5 ($-CHOCOCH_3$). ESI-MS: obs, 289.1 *m/z* ([MNa]$^+$); calcd for $C_{13}H_{14}O_6Na$, 289.07 *m/z*. Anal. [M + 1/2H_2O] Calcd (Found): C 56.7 (56.4); H 5.5 (5.3).

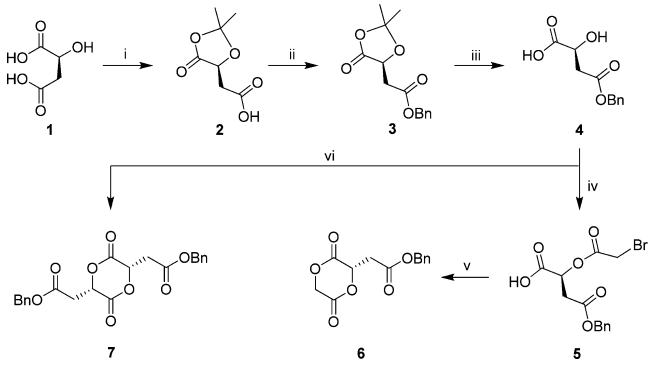
Synthesis of 4-Benzyl 1-neopentyl 2-acetoxysuccinate (16).[52] To a solution of **12** (0.57 g, 2.12 mmol), DMAP (0.026 g, 0.21 mmol), and 2,2-dimethyl-1-propanol (0.17 g, 1.88 mmol) in CH_2Cl_2 (25 mL) was added dropwise a solution of DCC (0.44 g, 2.12 mmol) in CH_2Cl_2 (25 mL). The resulting solution was stirred at room temperature overnight. DCU was removed by filtration, and the solution was concentrated in vacuo. The product was extracted into EtOAc (3 × 100 mL), filtered, and reduced under vacuum to yield the desired product as a brown oil (0.35 g, 1.04 mmol, 49%). ^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 7.33 (5H, m, $-CH_{aromatic}$), 5.53 (1H, t, $^3J_{H-H}$ = 6.05 Hz, $-CHCOO-$), 5.13 (2H, d, $^3J_{H-H}$ = 7.37 Hz, $-CH_2Ar$), 3.81 (2H, q, $^3J_{H-H}$ = 10.38 Hz, $-COOCH_2C(CH_3)_3$), 2.87 (2H, d, $^3J_{H-H}$ = 6.05 Hz, $-CH_2COOCH_2Ar$), 2.02 (3H, s, $-CHOCOCH_3$), 0.90 (9H, s, $-COOCH_2C(CH_3)_3$). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.0 MHz): δ = 171.4 ($-COOCH_2C(CH_3)_3$), 169.2 ($-CH_2COOCH_2Ar$), 168.9 ($-CHOCOCH_3$), 135.4 ($-C_{ipso-aromatic}$), 128.6 ($-CH_{meta-aromatic}$), 128.5 ($-CH_{para-aromatic}$), 128.4 ($-CH_{ortho-aromatic}$), 68.3 ($-CHCOO-$), 66.8 ($-CH_2Ar$), 60.4 ($-COOCH_2C(CH_3)_3$), 36.5 ($-CH_2COOCH_2Ar$), 31.9 ($-COOCH_2C(CH_3)_3$), 26.3 ($-COOCH_2C(CH_3)_3$), 20.6 ($-CHOCOCH_3$). ESI-MS: obs, 359.1 *m/z* ([MNa]$^+$); calcd for $C_{18}H_{24}O_6Na$, 359.15 *m/z*. Anal. Calcd (Found): C 64.3 (64.4); H 7.2 (7.3).

Results and Discussion

Monomer Synthesis. The synthesis of 3-(*S*)-[(benzyloxycarbonyl)methyl]- and 3,6-(*S*)-[di(benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-diones (BMD, **6**, and malide, **7**, respectively) was achieved via an improved synthesis of β-benzyl malate from L-malic acid in three steps (Scheme 1). First, the reaction of L-malic acid, **1**, with 2,2-dimethoxypropane in the presence of catalytic *p*-toluenesulfonic acid (*p*TsOH) resulted in the selective acetonide protection of the α-hydroxy acid. Subsequent benzylation of the remaining β-carboxylic acid was achieved by reaction with benzyl bromide followed by deprotection of the acetonide group carried out at 40 °C in an AcOH/THF/H_2O (1:1:1) solvent mixture for 24 h to give a 48% yield over three steps. Coupling of the resultant α-hydroxy acid with bromoacetyl bromide and subsequent intramolecular cyclization in the presence of $NaHCO_3$ through slow addition into DMF resulted in the isolation of BMD, **6**, in a 55% yield (Scheme 1). A pseudo-high dilution cyclization technique was utilized to reduce the amount of byproduct formed such that significant predilution of **5** (0.14 M) in DMF before slow injection (0.707 mL h^{-1}) into a $NaHCO_3$/DMF suspension provided a substantial improvement in yield compared to previous syntheses of this monomer.[36]

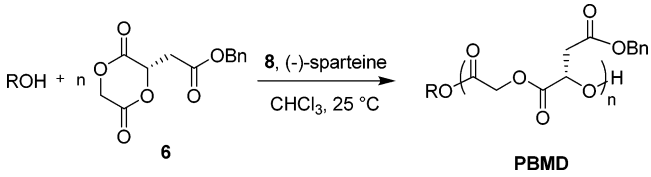
The α-hydroxy acid was additionally dimerized in refluxing toluene with catalytic *p*TsOH to yield malide, **7** (30%, Scheme

Scheme 1. Synthesis of 3-(*S*)-[(Benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione, **6**, and 3,6-(*S*)-[Di(benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione, **7**, from L-Malic Acid, **1**[a]



[a] Conditions: (i) $Me_2C(OMe)_2$, *p*TsOH; (ii) $PhCH_2Br$, NEt_3, acetone; (iii) AcOH, THF/H_2O; (iv) $BrC(O)CH_2Br$, NEt_3, DMAP, CH_2Cl_2; (v) $NaHCO_3$, DMF; (vi) Δ, *p*TsOH, toluene.

Scheme 2. Ring-Opening Polymerization of 3-(*S*)-[(Benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione, **6**, Using 1-(3,5-Bis(trifluoromethyl)phenyl)-3-cyclohexylthiourea, **8**, and (−)-Sparteine



1). Again, as with the synthesis of **6**, the yield of this final cyclization step was severely hindered by the formation of undesired oligomer byproducts and transesterification. Dilute conditions (0.05 M) were employed in an attempt to increase the yield; however, this provided no considerable improvement. Despite the poor yield of the final cyclization step, the overall synthesis of **7** provides an improvement on previously reported yields.[40]

Ring-Opening Polymerization Studies. Attempts to polymerize malide, **7**, with the thiourea **8**/(−)-sparteine system did not result in the isolation of any polymeric materials, most likely a consequence of the high steric hindrance and low ring strain of the monomer.[53,54] As such, our efforts were concentrated on the polymerization of BMD, **6**, as the less hindered glycolic acid unit was postulated to lead to a more facile polymerization. ROP of **6** catalyzed by **8** and (−)-sparteine using a range of initiators was initially investigated at 25 °C in $CHCl_3$ solution (Scheme 2). ^{1}H NMR spectroscopy provided a convenient method for monitoring the progress of the polymerization by observation of the reduction of the methylene resonance of the malate unit of the monomer at $\delta = 3.12$ ppm and the appearance of the corresponding broad multiplet at $\delta = 3.08-2.85$ ppm in PBMD. Upon completion of the allotted time, polymerizations were quenched by the removal of (−)-sparteine via a 1 M HCl wash with removal of **8** by its extraction into Et_2O. The polymers were precipitated into ice-cold petroleum ether (b.p. 40−60 °C).

Initial studies investigated the ROP of **6** under conditions previously reported for lactide ROP, initiating from neopentanol in the presence of 10 mol % of **8** and 5 mol % of (−)-sparteine as cocatalysts. At a monomer-to-initiator ratio of 50 ([M]/[I] = 50), the ROP of **6** achieved 79% monomer conversion after 180 min. While analysis of the resultant polymer indicated that the polymerization was well controlled (M_n = 7420 g mol^{-1}; PDI = 1.17), prolonged reaction times did not lead to increased levels of monomer conversion. Indeed exposure to increased

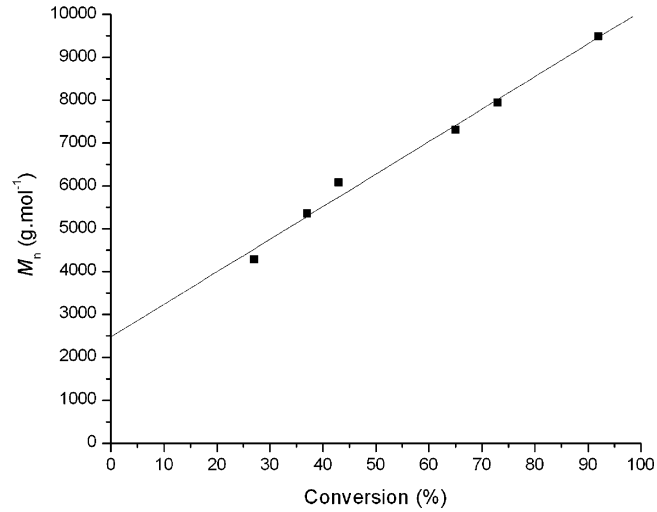


Figure 2. Plot of M_n versus monomer conversion (measured by ^{1}H NMR spectroscopy) for the ROP of **6** ([M]/[I] = 50, $[\mathbf{6}]_0$ = 0.32 M) using 25 mol % of **8** and 5 mol % of (−)-sparteine as cocatalysts and neopentanol as initiator.

reaction times led to a decrease in molecular weight and a broadening of the PDI consistent with the occurrence of transesterification side reactions. In an attempt to achieve higher conversions, we first investigated the effect of polymerization temperature. Raising the temperature to 60 °C resulted in retardation of the polymerization with only 15% monomer conversion being observed after 180 min. This observation is consistent with decreased ring strain of the monomer, resulting from the increased bulk of the ring substituents, limiting the exothermicity of the ring-opening process thus leading to ring opening being preferred at lower temperatures.[53,54] Maintaining the polymerization temperature at 25 °C, we decided to increase the loading of **8** in an attempt to increase the selectivity for ROP over transesterification. To this end, employing a 15 mol % loading of **8** resulted in increased monomer conversions such that, for a [M]/[I] = 50, 96% monomer conversion was observed after 120 min. Furthermore, high levels of control over the polymerization resulted in a polymer exhibiting M_n = 9900 g mol^{-1} and PDI = 1.16. A further increase in loading of **8** to 25 mol % resulted in a further decrease in the time required for high monomer conversions to be achieved such that after only 30 min PBMD with M_n = 9500 g mol^{-1} and PDI = 1.15 was obtained. Higher loadings of **8** (35+ mol %) increased the rate of polymerization further but resulted in a small loss of control with a broadening of PDI attributed to transesterification. Interestingly, the ROP of **6** is complete approximately 4 times faster (t = 30 min, monomer conversion = 92%) than the ROP of lactide (t = 120 min) under identical conditions, possibly a consequence of the reduced steric demands of the glycolic acid unit.

Investigation of the polymerization control resulted in the observation of a linear correlation between M_n and monomer conversion (Figure 2) and between M_n and initial monomer-to-initiator ratio (Figure 3). However, notably both charts do not display a zero intercept, which indicates that the rate of propagation is greater than the rate of initiation. The isolation of oligomers in attempted single turnover experiments, even in the presence of a large excess of initiator, further confirms this hypothesis. Nonetheless, following standard workup, analysis of a low DP PBMD ([M]/[I] = 20) with M_n = 6750 g mol^{-1} and PDI = 1.17 by ^{1}H NMR spectroscopy confirmed a DP = 24 polymer based on the integration of the *tert*-butyl neopentanyl

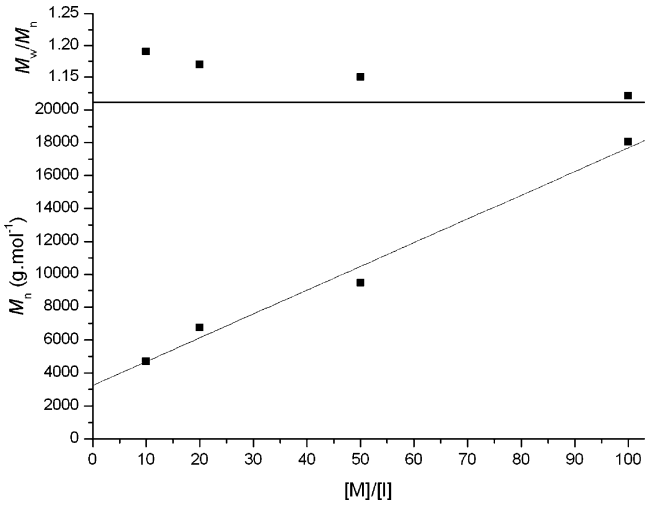


Figure 3. Plot of [M]/[I] versus M_n and PDI for ROP of **6** ($[\mathbf{6}]_0$ =0.32 M) using 25 mol % of **8** and 5 mol % of (−)-sparteine as cocatalysts and neopentanol as initiator.

resonances against those of the main-chain methine protons. Interestingly, the α-chain end was assigned to two distinctive singlets at $\delta = 0.92$ and 0.89 ppm (Figure 4), arising from the nonselective ring opening of the asymmetric **6** by neopentanol during the initiation step, clearly demonstrating a notable electronic difference between the two resultant chain ends. Further analysis of the polymer by MALDI-TOF MS revealed a single distribution centered around $m/z = 5394.0$, which corresponds to a sodium-charged DP20 polymer chain with a neopentanol end group; a regular spacing equal to the molecular weight of the repeat unit of **6** ($m/z = 264$) demonstrates the lack of significant transesterification of the polymer chains (Figure 5).

In an attempt to characterize the two different α-chain groups and thus enable estimation of the preference for ring opening at either ester, model compounds **15** and **16** were synthesized via condensation reaction of glycolic acid or β-benzyl malate, **4**, with neopentanol and subsequent acetylation of the remaining alcohol group by treatment with acetyl chloride (Scheme 3). Examination of the ^{1}H NMR spectra of **15** and **16** reveal singlet resonances at $\delta = 0.93$ and 0.90 ppm, respectively, providing a good correlation to those observed on the polymer chain ends (Figure 6). Integration of the polymer chain end resonances from three polymer samples reveals approximately a 2:1 ratio (glycolate/malate opening), which corresponds to a 67 ± 1% selectivity toward ring opening at the least hindered glycolate ester of the ring.

Initiator Versatility. In order to further study the initiator efficiency, ROP of **6** was initiated from a more sterically hindered secondary alcohol, specifically 2-propanol. A range of PBMD with varying [M]/[I] were prepared in a comparable manner to that previously described, and again, correlation of the [M]/[I] and monomer conversion with M_n resulted in a linear relationship with a nonzero intercept. Analysis of the polymers using ^{1}H NMR spectroscopy and MALDI-TOF MS analysis

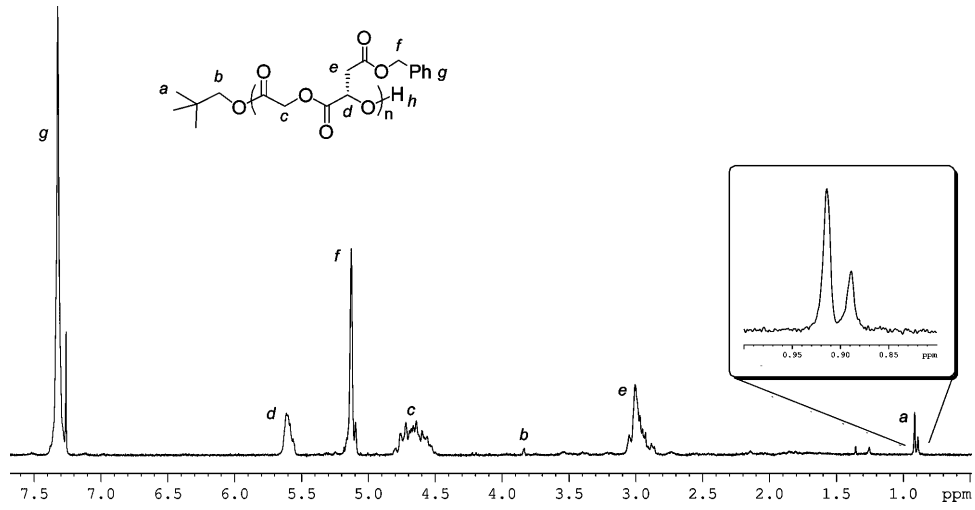
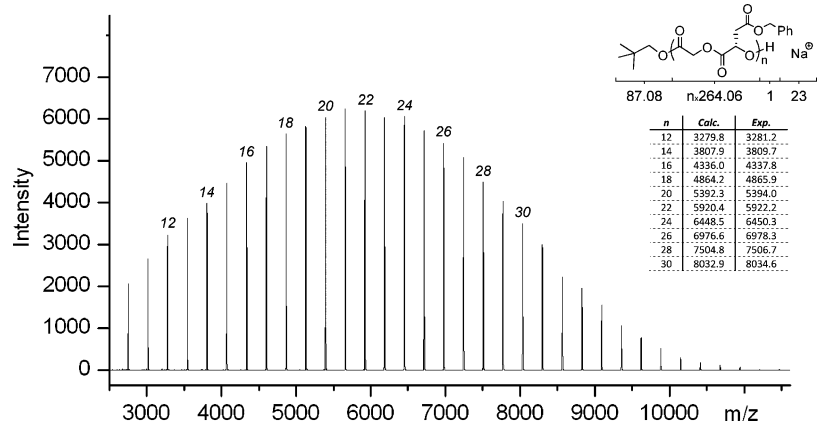


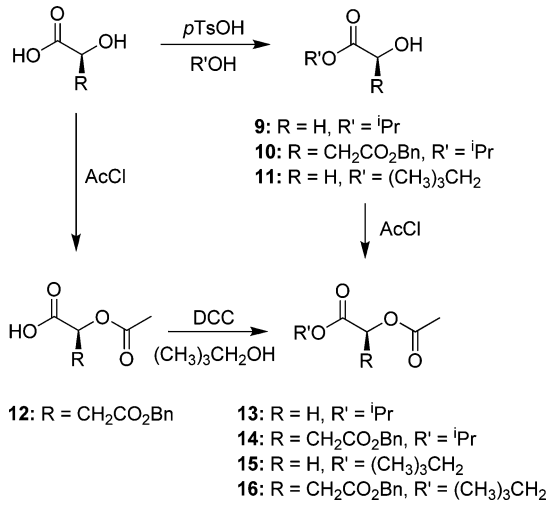
Figure 4. ^{1}H NMR spectrum of PBMD ([M]/[I] = 20) initiated from neopentanol (400 MHz; $CDCl_3$).



n	Calc.	Exp.
12	3279.8	3281.2
14	3807.9	3809.7
16	4336.0	4337.8
18	4864.2	4865.9
20	5392.3	5394.0
22	5920.4	5922.2
24	6448.5	6450.3
26	6976.6	6978.3
28	7504.8	7506.7
30	8032.9	8034.6

Figure 5. MALDI-TOF MS analysis of a PBMD ([M]/[I] = 20) initiated from neopentanol.

Scheme 3. Synthesis of Glycolate and β-Benzylmalate End Group Models



confirmed end group fidelity of a PBMD ([M]/[I] = 20) with M_n = 11 020 g mol^{-1} and PDI = 1.12, with the major peak at 5366.0 *m/z* again corresponding to a sodium-charged DP20 polymer chain with an isopropyl α-chain end. Interestingly, despite DP (measured by ^{1}H NMR) again roughly correlating to the [M]/[I] ratio, the M_n of each polymer, as determined by GPC analysis, was higher than that obtained when ROP was initiated from neopentanol (Table 1). We tentatively postulate that this discrepancy arises as a consequence of the formation of low molecular weight impurities, such as cyclic oligomers occurring within the initiation period, consuming initiating alcohol but producing low molecular weight species that are indistinguishable from the polymer by NMR spectroscopy, thus distorting the measurement of DP with respect to GPC analysis of the polymers.

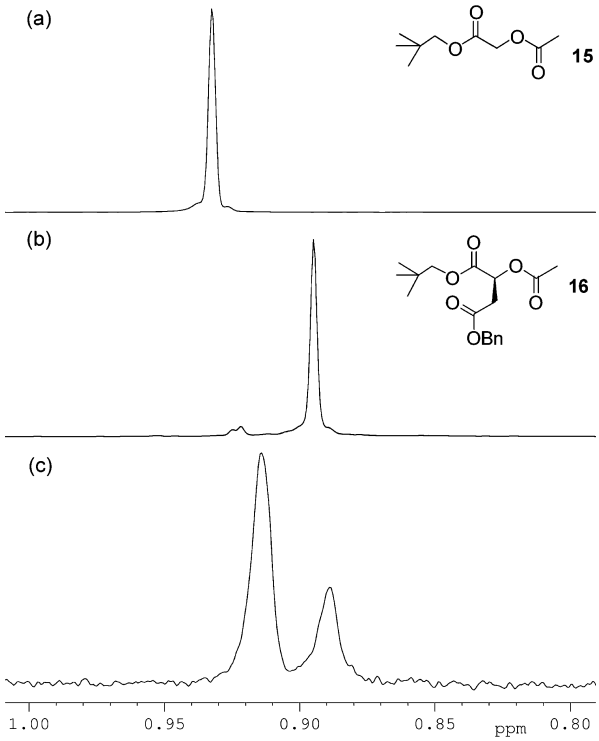


Figure 6. Expansion of δ = 0.80 to 1.00 ppm region of ^{1}H NMR spectra (400 MHz; $CDCl_3$) showing the neopentyl methyl resonances of (a) **15**, (b) **16**, and (c) PBMD prepared by the ring-opening polymerization of **6** initiated from neopentanol using **8**/(−)-sparteine.

Close analysis of the ^{1}H NMR spectrum of the polymer again revealed two α-chain end methyl resonances (from the isopropyl group), a doublet at δ = 1.24 ppm, and an overlapping doublet of doublets centered at δ = 1.21 ppm. Comparison to model compounds suggested that, as expected, the doublet at δ = 1.24 ppm results from initial ring opening of a glycolate ester of **6**, whereas the overlapping doublet of doublets arises from ring opening of the monomer to generate a malate ester with an adjacent chiral center leading to the inequivalence of the methyl resonances. Integration of these resonances suggests that initiation from 2-propanol also results in approximately a 69 ± 1% selectivity toward ring opening at the less hindered carbonyl of the monomer. While indeed this suggests that the initiator efficiency relates to the molecular weight of the resultant polymer, the unchanged distribution of glycolate ester to malate ester end groups indicates that steric effects may not be the primary factor determining initiator efficiency. To this end, we broadened our investigations with respect to initiating alcohol.

Initiation of the ROP of **6** changing only the alcoholic initiator (Table 2) resulted in a significant spread of polymer molecular weights. Initiation from benzyl alcohol, ethanol, 1-phenylethanol, and 2-butanol ([M]/[I] = 20) resulted in PBMD with molecular weights of 5920, 8800, 6600, and 13 300 g mol^{-1}, respectively, and narrow PDIs (Table 2). End group fidelity and DP of the polymers were confirmed by both MALDI-TOF MS and ^{1}H NMR spectroscopy. Again, we note that DP (measured by ^{1}H NMR) remains largely invariant, whereas M_n (measured by GPC) changes dramatically with different initiators. Notably, however, these results show that steric hindrance is not the major contributing factor to correlation of polymer molecular weight to that predicted from the monomer-to-initiator ratio. Comparison of a PBMD initiated from 1-phenylethanol to those initiated from ethanol and 2-propanol reveals that, despite being the most sterically hindered, initiation from 1-phenylethanol results in the polymer with the lowest molecular weight (M_n = 6600 g mol^{-1}), presumably a consequence of more efficient initiation resulting from the electron-deficient nature of the initiator.

Further attempts to optimize the initiator efficiency of the polymerization focused on the synthesis and application of initiators that were good models for the putative propagating species. To this end, isopropyl-2-hydroxyacetate, **9**, and 4-benzyl-1-isopropyl 2-hydroxysuccinate, **10**, were applied to initiate ROP. Analysis of the resultant polymers by GPC revealed the lowest molecular weights, correlating most closely to the DP measured by ^{1}H NMR end group analysis, while maintaining low polydispersities throughout the polymerization. Poor initiation commonly also leads to a broadening of the PDI of the resultant polymers arising from the rapid propagation of initiated chains with new chains being initiated. To further investigate the observed effects, a competition experiment between neopentanol and 2-propanol initiators was performed. ROP of **6** using a 1:1 molar ratio of alcohols and a target overall [M]/[alcohol] = 10 ([M]/[I] = 20 with respect to each initiating alcohol) resulted in a polymer with a monomodal distribution with M_n = 6780 g mol^{-1} and PDI = 1.18 by GPC analysis, comparable to polymers obtained by initiation from neopentanol with a [M]/[I] = 20. Analysis of the polymer by ^{1}H NMR spectroscopy revealed both neopentanol and 2-propanol end groups in a 2:1 ratio. These data suggest that the increased initiator efficiency of neopentanol compared to 2-propanol results in the majority of the initial ring opening of **6** to occur through neopentanol; however, the increased rate of initiation

Table 1. Effect of [M]/[I] for Neopentanol versus 2-Propanol Initiation of the Ring-Opening Polymerization of **6**[a]

initiating alcohol	[M]/[I]	time (min)	monomer conversion (%)	DP[b]	M_n (NMR)[b] (g mol^{-1})	M_n (GPC)[c] (g mol^{-1})	PDI[c]
neopentanol	10	5[d]	98	13	3520	4700	1.19
neopentanol	20	10[d]	98	24	6430	6750	1.17
neopentanol	50	20[d]	92	43	11440	9490	1.15
neopentanol	100	40[d]	96			18070	1.12
2-propanol	10	6[e]	98	12	3230	9530	1.17
2-propanol	20	12[e]	97	24	6400	11020	1.12
2-propanol	50	25[e]	99	41	10880	18200	1.14
2-propanol	100	50[e]	97			26050	1.11

[a] $[\mathbf{6}]_0 = 0.32$ M; 5 mol % of (−)-sparteine; $CHCl_3$. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by GPC analysis. [d] With 25 mol % of **8**. [e] With 35 mol % of **8**.

Table 2. Effect of Alcohol Initiator in the Ring-Opening Polymerization of **6**[a]

initiating Alcohol	[M]/[I]	time (min)	DP[b]	M_n [c] (g mol^{-1})	PDI[c]
9	20	6[d]	18	4700	1.14
10	20	6[e]	19	5650	1.12
benzyl alcohol	20	8[d]		5920	1.17
1-phenylethanol	20	8[e]	16	6600	1.17
neopentanol	20	10[d]	24	6750	1.17
ethanol	20	12[d]	23	8800	1.12
2-propanol	20	12[e]	24	11020	1.12
2-butanol	20	20[e]	28	13300	1.10
benzyl amine	20	8[d]		7390	1.19
1,3-propanediol	20	8[d]	20[f]	11380	1.14

[a] $[\mathbf{6}]_0 = 0.32$ M; 5 mol % of (−)-sparteine; $CHCl_3$. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by GPC analysis. [d] With 25 mol % of **8**. [e] With 35 mol % of **8**. [f] DP per alcohol.

of neopentanol with respect to 2-propanol and relative propagation rates of the more activated growing polymer chains result in very few new polymer chains being initiated after the primary initiation event, despite the presence of excess 2-propanol.

Further initiator versatility was investigated to prepare a telechelic PBMD ([M]/[I] = 40) ([M]/[I] = 20 per alcohol group) by initiation from 1,3-propanediol with the polymerization achieving 99% monomer conversion within 8 min and the resultant polymer displaying $M_n = 11\,380$ g mol^{-1} and PDI = 1.14 as determined by GPC analysis. The initiator tolerance was also tested using benzyl amine. PBMD ([M]/[I] = 20) was successfully prepared showing no significant difference in rate or control compared to alcohols reaching 99% monomer conversion in 8 min with $M_n = 7390$ g mol^{-1} and PDI = 1.19.

Block Copolymers. Further extension of this methodology was investigated to enable the synthesis of block copolymers. Primarily, the synthesis of amphiphilic poly(ethylene oxide)-*b*-PBMD block copolymers by initiation from commercially available PEO_{2K} and PEO_{5K} ($M_n \sim 2000$ and 5000 g mol^{-1}, respectively) macroinitiators was investigated. ROP of **6** (target [M]/[I] = 20) with PEO_{2K}-monomethylether ($M_n = 3400$ g mol^{-1}, PDI = 1.05) as the initiator resulted in >99% monomer conversion after 30 min. GPC analysis of the copolymer confirmed PBMD chain growth (PEO_{2K}-*b*-$PBMD_{20}$; $M_n = 9260$ g mol^{-1}, PDI = 1.13). Successful block copolymer preparation was also achieved with initiation from PEO_{5K} ($M_n = 8200$ g mol^{-1}, PDI = 1.04), realizing the desired block copolymer PEO_{5K}-*b*-$PBMD_{20}$ ($M_n = 12\,340$ g mol^{-1}, PDI = 1.15).

Block copolymers were also demonstrated to be accessible with poly(L-lactide), PLLA, prepared from poly(L-lactide) as a macroinitiator for the polymerization of **6** ([M]/[I] = 20). PLLAs ([M]/[I] = 20 and 50) were synthesized by ROP of L-lactide using identical conditions as described above with 35 mol % of **8** and 5 mol % of (−)-sparteine, initiated from neopentanol. Complete monomer conversion for [M]/[I] = 20 and 50 was

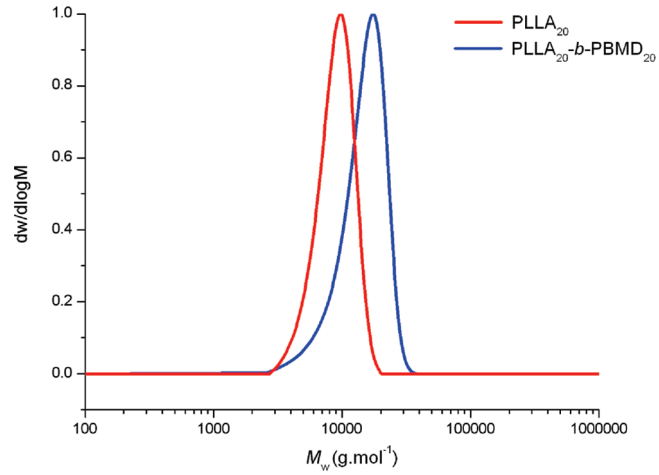
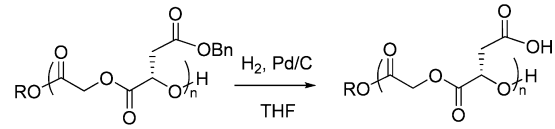


Figure 7. GPC traces of $PLLA_{20}$−OH ($M_n = 8360$ g mol^{-1}, PDI = 1.11) and $PLLA_{20}$-*b*-$PBMD_{20}$ ($M_n = 19\,080$ g mol^{-1}, PDI = 1.18) prepared by ring-opening polymerization of **6** from a PLLA macroinitiator.

Scheme 4. Deprotection of Poly(3-(*S*)-[(benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione), PBMD, Using Hydrogenolysis



PBMD **PGMA**

achieved after 30 and 75 min, respectively. Chain growth of **6** ([M]/[I] = 20) from $PLLA_{20}$−OH was confirmed by ^{1}H NMR spectroscopy, showing the presence of both the lactide methyl and malate resonances at $\delta = 1.58$ and 3.08−2.85 ppm, respectively. Additionally, GPC analysis revealed an increase in molecular weight from 8360 g mol^{-1} ($PLLA_{20}$−OH) to 19 080 g mol^{-1} ($PLLA_{20}$-*b*-$PBMD_{20}$), with a narrow PDI being maintained (Figure 7). Chain growth from $PLLA_{50}$−OH ($M_n = 14\,020$ g mol^{-1}, PDI = 1.09) was also achieved, resulting in the successful synthesis of $PLLA_{50}$-*b*-$PBMD_{20}$ ($M_n = 24\,160$ g mol^{-1}, PDI = 1.07).

Deprotection of PBMD. Deprotection of the pendant carboxylic acid groups of PBMD (DP20; $M_n = 5950$ g mol^{-1}; PDI = 1.16) was accomplished by hydrogenolysis using H_2 over Pd/C and resulted in hydrophilic poly(glycolic-*co*-malic acid)s (PGMA) (Scheme 4). Clean and complete removal of the benzyl protecting groups was deduced from the disappearance of all the aromatic and benzylic signals from both the ^{1}H (Figure 8) and ^{13}C NMR spectra. Further confirmation was obtained from the change in solubility of the resulting polymer from the PBMD (soluble in $CHCl_3$, insoluble in MeOH) to the PGMA (soluble in MeOH, insoluble in $CHCl_3$). This process did not result in degradation of the poly(ester) backbone, as shown by the lack

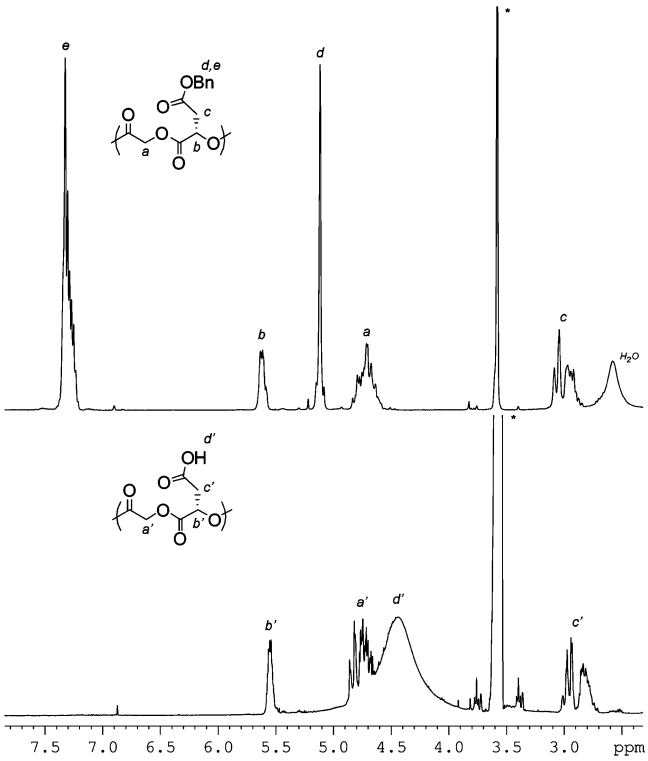


Figure 8. ^{1}H NMR spectra of (i) $PBMD_{20}$ and (ii) $PGMA_{20}$ (THF-d_8, 400 MHz; ∗ indicates residual solvent signal).

of resonances associated with changes to the electronic environment of the methine protons associated with a neighboring hydroxy proton in the ^{1}H NMR spectrum that would be apparent upon cleavage of the backbone. Furthermore, analysis of the polymer by aqueous GPC showed a single narrow distribution with a $M_n = 2410$ g mol^{-1} and PDI = 1.12 (compared to PEG standards). We postulate that the hydrophobic nature of the poly(ester) backbone results in tightly coiled polymers thus leading to low molecular weight values by aqueous GPC analysis.

Degradation of PGMA. Degradations were performed in H_2O on PGMA ([M]/[I] = 20) at a concentration of 0.55 mmol L^{-1}. The degradations were monitored via acid−base titration using a 0.50 mmol L^{-1} aqueous NaOH solution with four drops of a phenolphthalein in methanol solution as the pH indicator. Phenolphthalein produces a strong pink color when the pH of the solution reaches 8.2, thus providing a simple method with which to determine the extent of the degradation. Degradation was complete after 6 days, determined when 3 equiv of the NaOH solution was required to neutralize the reaction. Aqueous GPC analysis provided a simple method to monitor the molecular weight loss during the degradation. The M_n gradually decreased over time along with a broadening of the PDI that plateaued after 6 days, in agreement with the titration experiment. Examination of ^{1}H NMR spectra during the degradation in D_2O demonstrates a gradual reduction of resonances attributed to PGMA at δ = 5.93−5.85 and 3.32−3.22 ppm with a corresponding increase of new resonances at δ = 4.54−4.48 and 3.19−3.01 ppm resulting from the degradation products. Mass spectrometry of the degradation solution after 6 days confirmed the presence of a range of degradation products including malic acid ($[M + Na]^+ = 157.01$), glycolic acid dimer ($[M + Na]^+ = 157.01$), malic/glycolic acid dimer ($[M + Na]^+ = 215.02$), and malic acid dimer ($[M + Na]^+ = 273.02$).

Conclusions

In conclusion, we have successfully demonstrated an improved synthesis of both BMD, **6**, and malide, **7**, monomers from L-malic acid. Homopolymerization of **6** using the organocatalytic **8**/(−)-sparteine system enabled the synthesis of functional poly(ester)s with pendant benzyl protected carboxylic acid groups to high monomer conversions in the absence of transesterification side reactions. The choice of initiator was demonstrated to be important, such that initiating species that more closely resembled the propagating species led to lower molecular weight polymers. Nonetheless, the versatility of the polymerization system was shown with successful initiation from a range of alcohols and amines including the use of PEO and PLLA as macroinitiators in the preparation of block copolymers. Removal of the benzyl protecting groups was successful without any polymer backbone scission to yield hydrophilic poly(ester)s, and studies of the resultant PGMAs in H_2O showed that degradation occurred within 6 days as determined by titration, aqueous GPC analysis, ^{1}H NMR, and mass spectrometry. The derivation of this versatile functional poly(ester) from a biorenewable resource thus provides a potential route to a range of functional poly(ester)s via this platform.

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Supporting Information Available. Additional charts and MALDI-TOF/NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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