Functionalized Poly(α-hydroxy acid)s via Ring-Opening Polymerization: Toward Hydrophilic Polyesters with Pendant Hydroxyl Groups

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ABSTRACT: Two functionalized dilactones with protected hydroxyl groups, benzyloxymethyl methyl glycolide (**4a**) and benzyloxymethyl glycolide (**4b**), were synthesized and converted to the corresponding polyesters by ring-opening polymerization in the melt (at 110 °C using benzyl alcohol and $SnOct_2$ as initiator and catalyst, respectively, and at 130 °C using $SnOct_2$ as catalyst or in solution at 35 °C using ethylzinc phenolate and 2-propanol as catalyst and initiator, respectively). The obtained polymers were amorphous, with a glass transition temperature (T_g) between 15 and 45 °C. ^{13}C NMR analysis showed that poly(**4b**) was perfectly alternating, owing to a regioselective ring opening, whereas poly(**4a**) had a random distribution of methyl and benzyloxymethyl side groups. Both **4a** and **4b** could be copolymerized with L-lactide. Copolymers of L-lactide with **4b** showed crystallinity at 75% lactide content, whereas copolymers with **4a** were amorphous at the same lactide content. Monomer **4b** apparently reacts faster than lactide, resulting in composition drift and finally yielding a polymer rich in lactide and consequently in lactide blocks that are large enough to crystallize. Block copolymers were synthesized by sequential polymerization of L-lactide and **4a** using ethylzinc phenolate as catalyst. Deprotection of the benzyloxymethyl groups of poly(**4a**) and poly(**4b**) gave the corresponding hydroxylated polyesters, which were amorphous and semicrystalline, respectively, according to DSC analysis.

Introduction

Biodegradable polyesters are presently under investigation as matrices for controlled drug delivery and scaffolds for tissue engineering.[1−5] The introduction of functional groups is an important strategy to tailor and modulate properties of materials made of these polymers.[6−9]

Over the past few years several functionalized polyesters were described in the literature. These polyesters consist mainly of ε-caprolactone, lactide, or glycolide copolymerized with a more hydrophilic lactone, like malolactone, or protected sugars.[10−13] Ring-opening polymerization of functionalized dilactones was used to obtain the corresponding polyesters. These dilactones contain protected functionalities that, after polymerization and deprotection, yield polymers with hydrophilic pendant groups.[14−16] It is expected that the degradation time of these hydrophilic polymers is relatively short compared to e.g. poly(lactic-*co*-glycolic acid) (PL(G)A) (degradation time between 2 and 24 months) as a result of the enhanced hydration. Besides, the presence of pendant functional groups would allow further derivatization with, e.g., cytostatic agents, to yield biodegradable polymeric prodrugs,[17,18] or such polymers could be used as building blocks for the formation of supramolecular structures like polymeric micelles and hydrogels.[19−23]

In principle, two synthetic routes can be followed to synthesize functionalized polyesters. First, post-modification is possible, which, however, is sometimes associated with chain scission because of the strong alkaline reaction conditions that are used.[22−26] The second method to obtain functionalized polyesters is by ring-opening polymerization of functionalized monomers. This route has fewer drawbacks and is therefore preferred.[27] However, protection of the monomers' functional groups is necessary to prevent side reactions (e.g., hyper branching) during polymerization. The protecting groups must be inert to the polymerization conditions, but they should be removable under mild conditions after polymerization, leaving the polymeric backbone intact.

Poly(lactic acid) (PLA), an extensively studied poly(α-hydroxy acid), can be synthesized by a polycondensation reaction of lactic acid at high temperature. Molecular weight of the polycondensates is generally limited to about 3−4 kDa and higher molecular weight (30 kDa) can only be obtained with an appropriate catalyst.[28−31] High molecular weight polylactide (molecular weight above 100 kDa) can be routinely synthesized by ring-opening polymerization of the dilactone of lactic acid using one of the many catalyst/initiator systems that have been developed over the past years.[32−38] Advantages of this particular polymerization method include control over the chain length and low polydispersities.

With some catalysts the ring-opening polymerization can even be carried out in solution at room temperature.[36−38] An advantage of such mild conditions is that side reactions like

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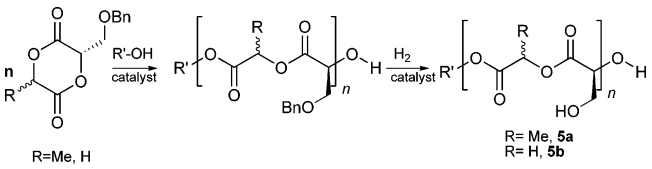
Scheme 1



transesterification, which parallel propagation, are minimized which contributes to low polydispersities of the obtained polymers. Moreover, the synthesis of block copolymers with well-defined structures is also possible using these initiators, in which case the process is referred to as living ring-opening polymerization.[27,39−41]

In the present study, we prepared poly(α-hydroxy acids) bearing hydroxyl groups along the main chain (Scheme 1), which are expected to be more hydrophilic than PL(G)A. For this purpose we synthesized two different monomers bearing a benzyl protected hydroxyl substituent (compounds **4a** and **4b**, Scheme 2).[42] To obtain the corresponding homopolymers and copolymers with lactide, a novel ethylzinc phenolate complex was used as catalyst which is able to polymerize dilactones, e.g., L-lactide in solution.[43] Zinc-containing catalysts are very effecttive in polymerizing lactide under mild conditions.[44] The same monomers as well as lactide were also polymerized at 110−130 °C in the melt using $SnOct_2$ as catalyst. Some of the resulting protected polymers were deprotected to obtain hydroxyl-functionalized polyesters. Finally, the hydrophilicity of the deprotected polymers has been evaluated.

Experimental Section

General Information. All reagents and solvents were used without purification, unless stated otherwise. *N*,*N*′-Dimethylformamide (DMF, Biosolve, Valkenswaard, The Netherlands) was dried and stored over 3 Å molecular sieves. Benzyl alcohol was obtained from Merck, Darmstadt, Germany. Peptide grade dichloromethane (DCM, Biosolve, Valkenswaard, The Netherlands) was used. Methyl-*tert*-butyl ether (MTBE, Biosolve, Valkenswaard, The Netherlands) and tetrahydrofuran (THF, Biosolve, Valkenswaard, The Netherlands) were distilled from sodium/benzophenone. Toluene (Acros, Geel, Belgium) was distilled from P_2O_5 and stored over 3 Å molecular sieves under argon. 2-Propanol (^{i}PrOH, Merck, Darmstadt, Germany) was distilled from CaH_2 and stored over 3 Å molecular sieves under argon. Ethylzinc phenolate complex was kindly provided by Prof. G. van Koten (Utrecht University, purity of 99+%). All reagents were purchased from Aldrich (Zwijndrecht, The Netherlands) unless stated otherwise. *O*-Benzyl-L-serine was purchased from Senn Chemicals (Dielsdorf, Switzerland). *N*,*N*′-Dimethylaminopyridine (DMAP) was purchased from Fluka (Zwijndrecht, The Netherlands). Reactions were monitored by thin-layer chromatography (TLC). R_f values were obtained using silica coated plastic sheets (Merck silica gel 60 F_{254}) with the indicated eluent. The compounds were visualized by UV light (254 nm) or by a 5% solution of ammonium molybdate in 2 M sulfuric acid followed by heating. Flash column chromatography was carried out using Acros silica gel (0.030−0.075 mm) and the indicated eluent. NMR measurements were performed at 298 K on a Varian Gemini-300 NMR machine, at 300 MHz (^{1}H) or 75 MHz (^{13}C). Chemical shifts (δ) are reported in ppm relative to tetramethylsilane (TMS) (^{1}H) or using the solvent peak as an internal reference (^{13}C). Mass spectra (electrospray) were recorded on a Micromass Quatro Ultima spectrometer. Thermographic analysis was done on a TA Instruments DSC Q1000 machine. Scans were taken from −50 to 190 °C at a heating rate of 10 °C/min. The results of the second run are reported. Inflection points of glass transition temperatures and endothermic maxima of melting points are reported. Gel permeation chromatography (GPC) was carried out on a Waters Aliance system, with a Waters 2695 separating module and a Waters 2414 Refractive Index detector. Two PL-gel 5 μm mixed-D columns fitted with a guard column (Polymer Labs, M_w range 0.2−400 kDa) were used in this setup. The columns were calibrated with polystyrene standards using HPLC grade chloroform (Biosolve, Valkenswaard, The Netherlands) as the mobile phase (1 mL/min). A 10 mM solution of LiCl in DMF was used in the same set up for the analysis of the deprotected polymers. The columns (thermostated at 40 °C) were calibrated with PEG standards and the flow rate was 0.7 mL/min.

Synthesis of (*S*)-3-(Benzyloxy)-2-hydroxypropanoic Acid (2). *O*-Benzyl-L-serine (Scheme 2, compound **1**, 30.0 g, 154 mmol) was dissolved in 400 mL of 1 M sulfuric acid and 400 mL of acetonitrile. $NaNO_2$ (21.7 g, 313 mmol) dissolved in 150 mL of water was added slowly. The reaction mixture was stirred under a nitrogen atmosphere for 16 h. A nitrogen gas evolution was observed. The aqueous layer was extracted with four 500 mL portions of dichloromethane. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo.

α-Hydroxy acid **2** (Scheme 2) was obtained as a yellow oil in 90% yield (27 g) and used without further purification.

^{1}H NMR ($CDCl_3$): δ = 3.74 (dd, 1 H, J = 4 Hz, J = 15 Hz, −CH−C*H*$_2$−O), 3.79 (dd, 1 H, J = 4 Hz, J = 15 Hz, −CH-C*H*$_2$−O), 4.36 (t, 1 H, J = 4 Hz, −C*H*-CH$_2$−O), 4.57 (s, 2 H, −O−C*H*$_2$−C_6H_5), 7.26−7.35 (m, 5 H, −C*H*$_{Ar}$). ^{13}C NMR ($CDCl_3$): δ = 70.3 (CH_2); 70.8 (CH_2); 73.5 (CH); 127.7 (CH_{Ar}); 127.9 (CH_{Ar}); 128.9 (CH_{Ar}); 137.1 (C_{Ar}); 176.2 (C=O). MS (ES): calculated [M + Na]$^+$, 219.1; measured [M + Na]$^+$, 219.0.

Synthesis of (*S*)-3-(Benzyloxy)-2-(2-bromopropanoyloxy)propanoic Acid (3a). α-Hydroxy acid **2** (25.4 g, 129 mmol) and triethylamine (17.9 mL, 129 mmol) were dissolved in 300 mL of DCM and added dropwise over 30 min to an ice-cooled solution of 2-bromopropionyl bromide (13.5 mL, 129 mmol) and DMAP (1.58 g, 12.9 mmol) in 150 mL of DCM. The mixture was stirred for 16 h at room temperature under a nitrogen atmosphere. The mixture was concentrated and salts were precipitated by addition of diethyl ether (ca. 500 mL). After filtration, the solvents were evaporated to yield compound **3a** as a mixture of diastereoisomers (Scheme 2). **3a** was obtained quantitatively as a light yellow oil and used in the next reaction without further purification.

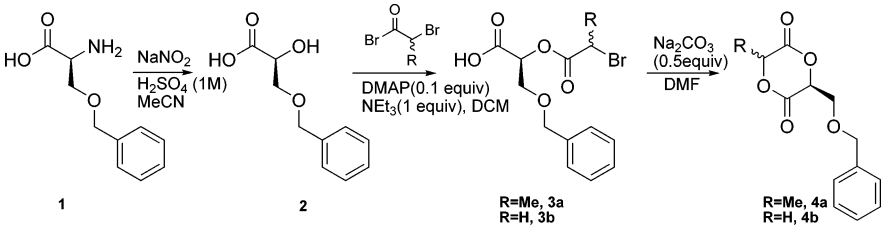
^{1}H NMR ($CDCl_3$): δ = 1.86 (dd, 3 H, J = 3 Hz, J = 4 Hz, −CH(Br)−C*H*$_3$), 3.85−3.93 (m, 2 H, −CH−C*H*$_2$−O), 4.49−4.62 (m, 3 H, −O−C*H*$_2$−C_6H_5+ −C*H*(Br)−CH_3), 5.31 (m, 1 H, −C*H*−CH_2−O), 7.24−7.33 (m, 5 H, −C*H*$_{Ar}$).^{13}C NMR ($CDCl_3$): δ = 39.0 (CH_3); 68.0 (CH); 72.6 (CH_2); 73.5 (CH); 127.7 (CH_{Ar}); 127.9 (CH_{Ar}); 128.4 (CH_{Ar}); 136.9 (C_{Ar}); 169.4 (C=O); 173.0 (C=O).

Synthesis of 3*S*-(Benzyloxymethyl)-6*S*-methyl-1,4-dioxane-2,5-dione (4a). Carboxylic acid **3a** (41.1 g, 124 mmol) was dissolved in 500 mL of DMF and added dropwise over 1 h to a solution of Na_2CO_3 (19.7 g, 186 mmol) in 3 L of DMF under rapid stirring. The reaction was left to stir for 16 h. The DMF was removed in vacuo. The residue was diluted with acetone (500 mL), and the resulting white precipitate was removed by filtration. Concentration in vacuo of the filtrate yielded a dark brown oil. This mixture of diastereoisomers was purified by flash column chromatography (MTBE:hexane = 1:1, R_f = 0.25) to yield diastereoisomer (S,S) of compound **4a** (42%, Scheme 2) as a white solid. This was crystallized from toluene and MTBE subsequently. $[\alpha]_d^{20} = -63°$ (c = 1, chloroform). Mp: 88 °C (lit.: 88 °C).[42]

^{1}H NMR ($CDCl_3$): δ = 1.56 (d, 3 H, J = 7 Hz, −CH−C*H*$_3$), 3.90 (d, 2 H, J = 3 Hz, −CH−C*H*$_2$−O), 4.59 (s, 2 H, −O−C*H*$_2$−C_6H_5), 5.11 (m, 2 H, −C*H*−CH$_2$−O + −C*H*−CH$_3$), 7.25−7.36 (m, 5H, −C*H*$_{Ar}$). ^{13}C NMR ($CDCl_3$): δ = 17.5 (CH_3); 68.5 (CH); 73.1 (CH_2); 73.9 (CH); 127.6 (CH_{Ar}); 127.9 (CH_{Ar}); 128.3 (CH_{Ar}). MS (ES): calculated [M + I]$^-$, 376.9886; measured [M + I]$^-$, 376.9904.

Synthesis of (*S*)-3-(Benzyloxy)-2-(2-bromoacetoxy)propanoic acid (3b). α-Hydroxy acid **2** (18.0 g, 91.8 mmol) and triethylamine (13 mL, 91.8 mmol) were dissolved in 250 mL of DCM and added dropwise over 30 min to an ice-cooled solution of bromoacetyl bromide (8.0 mL, 91.8 mmol) and DMAP (1.12 g, 9.2 mmol) in 125 mL of DCM. The mixture was stirred for 16 h at room

Scheme 2



temperature under a nitrogen atmosphere. The mixture was concentrated and salts were precipitated by addition of diethyl ether (ca. 500 mL). After filtration, the solvents were evaporated and compound **3b** (Scheme 2) was obtained quantitatively as a yellow oil and used in the next reaction without further purification.

^{1}H NMR ($CDCl_3$): δ = 3.8−4.0 (m, 4 H, −CH−CH_2−O + −CH_2Br), 4.6 (dd, 2 H, J = 5 Hz, J = 12 Hz, −O−CH_2−C_6H_5), 5.4 (dd, 1H, J = 2 Hz, J = 3 Hz, −CH-CH_2−O), 7.3 (m, 5H, −CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ = 25.1 (CH_2Br); 67.9 (CH_2); 72.9 (CH); 73.5 (CH_2); 127.6 (CH_{Ar}); 127.9 (CH_{Ar}); 128.4 (CH_{Ar}); 136.8 (C_{Ar}); 166.7 (C═O); 172.8 (C═O).

Synthesis of 3*S*-Benzyloxymethyl-1,4-dioxane-2,5-dione (4b). Carboxylic acid **3b** (32.3 g, 102 mmol) was dissolved in 500 mL of DMF and added dropwise over 1 h to a solution of Na_2CO_3 (16.2 g, 153 mmol) in 3 L of DMF under rapid stirring. The reaction mixture was stirred for 16 h. Next, the DMF was removed in vacuo. The residue was diluted with acetone (500 mL), and the resulting white precipitate was removed by filtration. Concentration of the filtrate yielded a dark brown oil. This was purified by flash column chromatography (ethyl acetate:hexane = 1:2, R_f = 0.25) to yield **4b** (40%) as a white solid. This was crystallized twice from toluene. $[\alpha]_d^{20}$ = +115° (c = 1, chloroform). Mp: 51 °C (lit.: 51 °C).[42]

^{1}H NMR ($CDCl_3$): δ = 3.9 (dd, 1 H, J = 2.5 Hz, J = 8 Hz, −CH−CHH−O), 4.1 (dd, 1 H, J = 2.5 Hz, J = 8 Hz, −CH−CHH−O), 4.5 (s, 2 H, −O−CH_2−C_6H_5), 4.8 (d, 1 H, J = 17 Hz, −O−CHH−C(O)O), 5.0 (d, 1 H, J = 17 Hz, −O−CHH-C(O)O), 5.1 (t, 1 H, J = 2.5 Hz, −CH−CH_2−O), 7.3 (m, 5 H, −CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ = 65.3 (CH_2); 70.6 (CH_2); 73.7 (CH_2); 76.3 (CH); 127.6 (CH_{Ar}); 128.2 (CH_{Ar}); 128.5 (CH_{Ar}); 136.2 (C_{Ar}); 163.6 (C═O); 164.5 (C═O). MS (ES): calculated $[M + I]^-$, 362.9730; measured $[M + I]^-$, 362.9723.

Melt Polymerizations. Melt polymerizations were done using $SnOct_2$ as catalyst with three different monomer/catalyst (M/C) molar ratios: 1000, 2000, and 5000. For a typical polymerization: Monomer (**4a**, 500 mg, 1.99 mmol) was loaded into a dry and silanized polymerization tube. Catalyst ($SnOct_2$) was added from a stock solution in pentane (for an M/C ratio of 1000: 8.5 μL from a 20 mg/mL stock). The tube was then placed under vacuum for 1 h, sealed under vacuum and immersed in an oil bath thermostated at 130 °C for 20 h. The resulting polymer was dissolved in chloroform and subsequently precipitated in cold methanol and dried in vacuo. Other M/C ratios were prepared accordingly.

Poly **4a:** ^{1}H NMR ($CDCl_3$): δ = 1.5−1.7 (m, 3H, −CH_3), 3.8−4.0 (m, 2H, −CH−CH_2−O), 4.4−4.7 (m, 2H, −O−CH_2−C_6H_5), 5.2−5.5 (m, 2H, −CH−CH_3 + −CH−CH_2−O), 7.2−7.4 (m, 5H, −CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ = 16.8 (CH_3); 68.4 (CH); 69.3 (CH_2); 72.5 (CH); 73.4 (CH_2); 127.7 (CH_{Ar}); 127.8 (CH_{Ar}); 128.4 (CH_{Ar}); 137.4 (C_{Ar}); 166.6−166.7 (C═O); 169.1−169.3 (C═O).

Poly **4b**: ^{1}H NMR ($CDCl_3$): δ = 3.8−4.0 (m, 2H, −CH−CH_2−O), 4.4−4.6 (m, 2H, −O−CH_2−C_6H_5), 4.6−4.9 (m, 2H, −O−CH_2−C(O)O), 5.3−5.5 (m, 1H, −CH−CH_2−O), 7.2−7.4 (m, 5H, −CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ = 60.8 (CH_2); 68.0 (CH_2); 72.5 (CH_2); 73.3 (CH); 127.6 (CH_{Ar}); 127.7 (CH_{Ar}); 128.3 (CH_{Ar}); 137.2 (C_{Ar}); 166.0 (C═O); 166.3 (C═O).

$SnOct_2$-catalyzed melt polymerizations of **4a** were also carried out using benzyl alcohol (BnOH) and $SnOct_2$ as initiator and catalyst, respectively. Three M/C/I ratios were used (40/1/1, 80/1/1, and 120/1/1). In a typical procedure for the 40/1/1 ratio: monomer (**4a**, 300 mg, 1.20 mmol) was loaded into a dried Schlenk tube under a dry nitrogen atmosphere. Initiator (BnOH, 3.20 mg; 30.8 μL from a 103 mg/mL toluene stock) and catalyst ($SnOct_2$, 12.2 mg; 116 μL from a 106 mg/mL toluene stock) were added, and the tube was placed under vacuum for 1 h. The tube was closed and immersed in an oil bath thermostated at 110 °C for 4 h. The resulting polymer was dissolved in chloroform and subsequently precipitated in cold methanol and dried in vacuo. The NMR spectra of this polymer was similar to those of the melt polymerization reported above. Other M/C/I ratios were prepared accordingly.

Solution Polymerization. The polymerizations of **4a** and **4b** in solution were done using an ethylzinc phenolate (Figure 1) and 2-propanol as catalyst and initiator, respectively. The reactions were carried out under an inert nitrogen atmosphere in a glovebox. Three M/C/I ratios were prepared (40/1/1, 80/1/1 and 120/1/1). In a typical procedure for the 40/1/1 ratio: monomer (**4a**, 500 mg, 1.99 mmol) was loaded into a dry polymerization vessel and dissolved in dichloromethane (2 mL). The concentration of the monomer was kept at 1 mmol/mL in all cases. 2-Propanol was added from a 2% stock solution in dichloromethane (150 mg). Subsequently, the catalyst (13 mg) was added. The vessel was closed and stirred in an oil bath thermostated at 35 °C for 4 h. The reaction was stopped by addition of a small amount of acetic acid and purification was done by precipitation of the concentrated polymer solution in cold methanol. ^{1}H NMR data are the same as the above-reported data for $SnOct_2$ mediated polymers with the exception of the isopropyl doublet at 1.2 ppm which is not present in the $SnOct_2$ mediated polymers. Other ratios were prepared accordingly.

Random copolymers of **4a** and **4b** with 25%, 50% or 75% (mol/mol) L-lactide were prepared using the above standard procedure for the ethylzinc phenolate catalyzed polymerizations with M/C/I = 80/1/1: In a typical procedure for a 25% L-lactide content and 75% **4a**, L-lactide (144 mg, 1 mmol) and **4a** (750 mg, 3 mmol) were dissolved in dichloromethane and loaded into a dry reaction vessel under a dry inert atmosphere, 2-propanol was added from a 2% stock solution in dichloromethane (150 mg) and catalyst (13 mg) was added. The vessel was closed and placed in an oilbath thermostated at 35 °C. The mixture was left to react for 3 h at the same temperature, quenched with acetic acid and worked up according to the above-mentioned procedure. Other ratios were prepared accordingly.

Poly(LA-*ran*-**4a**): ^{1}H NMR ($CDCl_3$): δ = 1.4−1.7 (m, 9H, −CH_3 (LA and **4a**)), 3.8−4.0 (m, 2H, −CH−CH_2−O), 4.5−4.6 (m, 2H, −O−CH_2−C_6H_5), 5.1−5.4 (m, 4H, −CH (LA and **4a**)), 7.2−7.4 (m, 5H, −CH_{Ar}).

Poly(LA-*ran*-**4b**): ^{1}H NMR ($CDCl_3$): δ = 1.5−1.7 (m, 6H, −CH_3), 3.8−4.0 (m, 2H, −CH−CH_2−O), 4.5−4.6 (m, 2H, −O−CH_2−C_6H_5), 4.6−5.0 (m, 2H, −O−CH_2−C(O)O), 5.1−5.3 (m, 2H, −CH-CH_3), 5.4−5.5 (m, 1H, −CH-CH_2−O), 7.2−7.4 (m, 5H, −CH_{Ar}).

Block copolymers of **4a** with L-lactide were prepared using the above standard procedure for the ethylzinc phenolate catalyzed polymerizations. For the preparation of block copolymers of **4a** with L-lactide at an M/C/I = 80/1/1 and copolymer composition

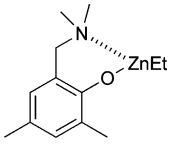


Figure 1. Structural formula of the ethylzinc phenolate catalyst.

of 75% L-lactide and 25% **4a**, the following procedure was applied: Lactide (563 mg, 3.90 mmol) and ^{i}PrOH (3.70 mg, 74 mg of a 5 wt % stock solution in dichloromethane) were dissolved in 2.5 mL of dichloromethane under N_2 atmosphere. After temperature equilibration in the oil bath (35 °C), catalyst (17 mg, directly weighed) dissolved in 0.5 mL of dichloromethane was added under vigorous stirring. After 2 h, virtually no monomer peaks were detected in the ^{1}H NMR spectrum, indicating complete conversion. After 1 h extra, a 0.7 mL sample (corresponding to ca. 100 mg of polymer or 0.69 mmol of lactide) was withdrawn from the reaction mixture for further analysis, and **4a** (250 mg, 1.05 mmol) in 0.80 mL of dichloromethane was added. The mixture was left to react for another 3 h at 35 °C, quenched with acetic acid, and worked up according to the above-mentioned procedure.

PLA-*b*-poly **4a**: ^{1}H NMR ($CDCl_3$): $\delta = 1.5-1.7$ (d, 9H, $J = 7$ Hz, $-CH_3$ (LA&**4a**)), 3.9−4.0 (m, 2H, $-CH-CH_2-O$), 4.5−4.6 (m, 2H, $-O-CH_2-C_6H_5$), 5.1−5.2 (q, 2H, $J = 1$ Hz, $-CH$-CH_3), 5.2−5.4 (m, 2H, $-CH$ (**4a**)), 7.2−7.4 (m, 5H, $-CH_{Ar}$).

Synthesis of Poly(lactic acid-*ran*-hydroxymethyl glycolic acid) (5a) and Poly(glycolic acid-*alt*-hydroxymethyl glycolic acid) (5b). In a typical procedure 100 mg of protected polymer **4a** was weighed into a reaction flask. The polymer was dissolved in distilled THF (25 mL) and 10% w/w (200 mg) of Pd/C (Palladium, 10 wt % (dry basis) on activated carbon, wet (50% water w/w), Degussa type E101 NE/W) (Aldrich, Zwijndrecht, The Netherlands) was added. The mixture was placed under a hydrogen atmosphere (balloon) by three consecutive steps of evacuation/refilling with H_2. The reaction took place for 16 h at room temperature. The catalyst was removed by filtration over a Hyflo filter. The filter was washed extensively with an additional 100 mL of distilled THF. Evaporation in vacuo gave the deprotected polymer in a quantitative yield (70 mg). NMR showed that no signals of the benzyl group were present.

5a: ^{1}H NMR ($CDCl_3$): $\delta = 1.4-1.6$ (m, 3H, $-CH_3$), 3.8−4.1 (m, 2H, $-CH_2-OH$), 5.0−5.3 (m, 2H, $-CH-CH_2-OH + -CH-CH_3$). GPC: M_n, 5600; M_w, 8200 Da.

5b: ^{1}H NMR ($CDCl_3$): $\delta = 3.6-3.8$ (m, 2H, $-O-CH_2-C(O)O$), 4.5−4.7 (m, 2H, $-CH_2-OH$), 4.9−5.1 (m, 1H, $-CH-CH_2-OH$). M_n, 1350; M_w, 1950 Da.

Results and Discussion

Monomer Synthesis. Previously, we reported a versatile route to substituted heterodilactones including the synthesis of **4a** and **4b**.[42] Compound **4b** had already been described by a different, more difficult route.[16] The advantage of our route is that virtually any α-hydroxy acid can be used to obtain the desired dilactone. Moreover, the reaction conditions do not lead to racemization, which means that optically pure products were obtained. However, a drawback is that many reaction steps were involved, leading to low overall yields. Therefore, the dilactones used in the present study (compounds **4a** and **4b**) were synthesized according to the alternative route depicted in Scheme 2. It is a modification of a known procedure; acylation of an α-hydroxy acid followed by a ring closure.[45] Addition of a catalytic amount of DMAP to the acylation reaction resulted in a more efficient reaction than reported in terms of yield and reaction time. The intermediate products **3a** and **3b** were obtained in rather high purity after a simple extractive workup. The obtained dilactones were thoroughly purified by flash column chromatography, followed by two crystallization steps from dried toluene and dried MTBE. The overall yields of this reaction sequence were around 40% starting from 30 g of *O*-Bn-L-serine (**1**). The synthetic route presented in our previous paper yielded optically pure compounds from optically pure starting materials.[42] *O*-Bn-L-serine (**1**) maintains its chirality throughout the entire reaction sequence depicted in Scheme 2, and monomer **4b** was obtained as optically pure and crystalline material. However, with the addition of racemic 2-bromopropionyl bromide, a second stereo center is introduced which leads after the intramolecular ring closing reaction to the dilactones as a mixture of two diastereoisomers: the *S*,*S* and the *S*,*R* forms.[46,47] These diastereoisomers were separated by flash column chromatography and subsequent crystallization. In this study, only the (*S*,*S*) isomer was used for polymerization.

Table 1. Molecular Weights of Polymers of 4a and 4b (Scheme 2) and L-Lactide Synthesized Using $SnOct_2$ as Catalyst[a]

	M/C[b]	$M_n \times 10^3$ (g/mol)	M_w/M_n
poly **4a**	1000	5.8	2.1
	2000	4.5	1.7
	5000	5.0	1.9
poly **4b**	1000	6.8	1.3
	2000	4.0	2.2
	5000	10.5	2.1
polylactide	1000	10.0	2.1
	2000	70.5	2.3
	5000	209	2.3

[a] Weight-average molecular weight (M_w) and number-average molecular weight (M_n) were determined by GPC in chloroform using polystyrene as calibration standard. [b] Monomer/catalyst ratio (mol/mol).

Table 2. Molecular Weights and Glass Transition Temperature of Polymers of 4a (Scheme 2) Synthesized Using $SnOct_2$ as Catalyst and Benzyl Alcohol as Initiator

	M/C/I[a]	$M_{n,obj} \times 10^3$ (g/mol)	$M_n \times 10^3$ (g/mol)[b]	M_w/M_n	T_g (°C)
homopolymers	40/1/1	10	4.80	1.5	17
	80/1/1	20	8.60	1.4	18
	120/1/1	30	10.5	1.6	19

[a] Monomer/catalyst/initiator ratio. [b] Determined with GPC in chloroform using polystyrene as calibration standard.

Synthesis of Homopolymers of 4a and 4b. $SnOct_2$-catalyzed polymerizations of **4a** and **4b** were carried out in bulk at 130 °C under vacuum, conditions that are frequently used for L-lactide polymerizations.[48] Both dilactones were converted into the corresponding polymers at three different monomer-to-catalyst ratios in reasonable to good yields of 65−80%. However, Table 1 shows that the obtained molecular weights (with polydispersities around 2) were relatively low compared to control reactions with L-lactide, and that there is no clear relationship between molecular weights and monomer-to-catalyst ratios. Indeed, $SnOct_2$-mediated polymerizations are difficult to control without chain control agents like alcohols.[49] Monomer **4a** was therefore also polymerized in bulk with benzyl alcohol as initiator and $SnOct_2$ as catalyst at 110 °C under vacuum (results shown in Table 2). After 4 h, ^{1}H NMR analysis of the polymerization mixture indicated that the conversion was higher than 95% and the yields ranged from 80 to 90% after workup. The molecular weights of the polymers that were obtained in this way increased with decreasing initiator amounts and also smaller polydispersities were observed than for the polymers synthesized with only $SnOct_2$. However, the molecular weights remained smaller than objected which might be ascribed to the presence of traces of impurities in the monomer and/or $SnOct_2$.

To have better control over the molecular weight of the synthesized polymers, the monomers were polymerized in dry DCM solutions with a novel ethylzinc phenolate ((2-((dimethylamino) methyl)-4,6-dimethylphenoxy)(ethyl)zinc)) catalyst (shown in Figure 1) and 2-propanol as initiator. ^{1}H NMR analysis indicated by the disappearance of the monomer peaks that the reactions were complete in 3−4 h at 35 °C. Table 3 gives an overview of the characteristics of the polymers that were synthesized using varying amounts of equimolar ethyl zinc phenolate and initiator quantities. Table 3 shows that higher M_n values were obtained for the polymers that were synthesized

Table 3. Properties of Homopolymers of 4a and 4b (M) (Scheme 2) and Their (Block) Copolymers with Lactide (L) Synthesized Using the Ethylzinc Phenolate Catalyst and 2-Propanol as Initiator

	M	M/C/I[a]	feed ratio L/M	copolymer ratio (NMR)	$M_{n,obj} \times 10^3$ (g/mol)	$M_n \times 10^3$ (g/mol)[b]	M_w/M_n	T_g (°C)	T_m (°C)	ΔH_m (J/g)
homopolymers	**4a**	40/1/1			10	9.0	1.4	20		
		80/1/1			20	23	1.5	22		
		120/1/1			30	38	1.7	30		
	4b	40/1/1			9.5	5.5	1.9	15		
		80/1/1			19	10	1.4	20		
		120/1/1			28	11	1.2	25		
random copolymers	**4a**	80/1/1	25/75	19/81	18	11	1.9	31		
			75/25	73/27	14	13	1.7	45		
	4b		25/75	26/74	17	10	1.3	21		
			50/50	47/53	15	12	1.3	34		
			75/25	74/26	13	14	1.5	40	130	8.7
block copolymers	**4a**	80/1/1	50/50	43/56	16	15	1.2	30	134	3.2
						11[c]	1.2[c]	44[c]	143[c]	3.5[c]
			75/25	74/26	16	15	1.1	39	142	34
						12[c]	1.1[c]	43[c]	148[c]	55[c]

[a] Monomer/catalyst/initiator ratio. [b] Determined with GPC in chloroform using polystyrene as calibration standard. [c] Lactide block.

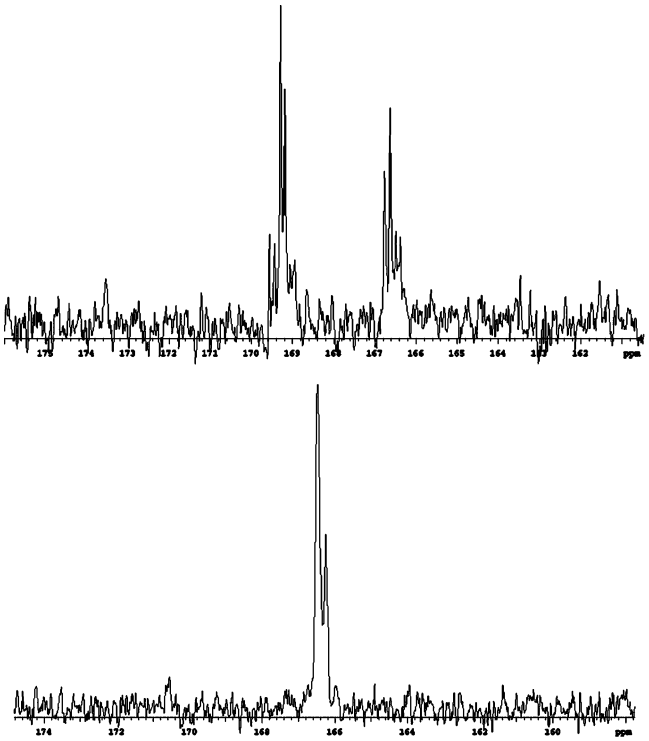


Figure 2. Carbonyl region of a ^{13}C NMR (75 MHz) spectrum of homopolymers of monomer **4a** (top) and **4b** (bottom). The same spectra were found for the polymers synthesized in the melt using $SnOct_2$ as catalyst (Table 1) and ethylzinc phenolate/2-propanol (Table 3).

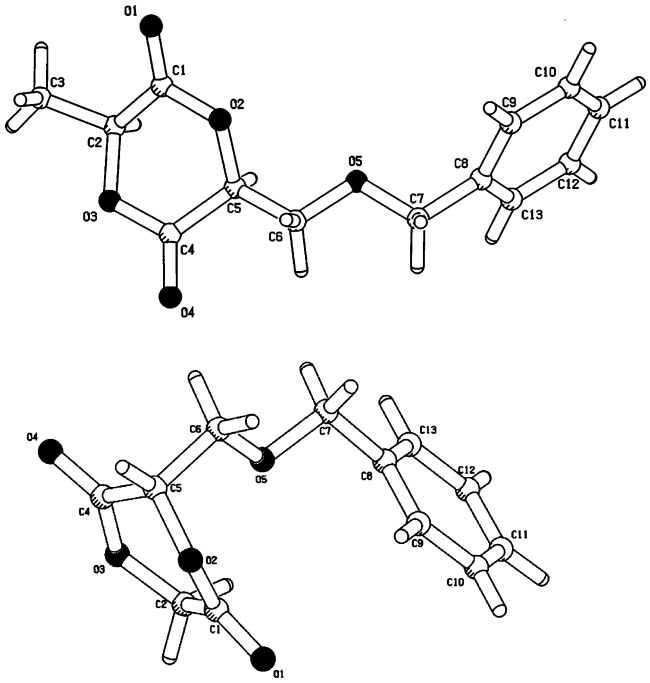


Figure 3. X-ray crystal structures of compound **4a** (top) and **4b** (bottom).[46−47]

with the ethylzinc phenolate catalyst as compared to the $SnOct_2$ polymers (results shown in Tables 1 and 2). Moreover, the number-average molecular weight (M_n) of the obtained polymers were close to the aimed values, indicating more controlled polymerizations using ethylzinc phenolate catalyst as compared to the $SnOct_2$ catalyst. The molecular weight distributions of the Zn-mediated polymers and the polymers yields (70−90%) are comparable to those of the BnOH initiated/$SnOct_2$ catalyzed polymers. Importantly, the protecting group remained stable during polymerization with both catalyst systems.

Interestingly, independent of the polymerization method, the ^{13}C NMR spectra of poly(**4a**) showed two multiplet signals in the carbonyl region, whereas poly(**4b**) showed only one doublet in this region (Figure 2). Obviously, the dilactone ring in compound **4b** is attacked by the growing chains in a regioselective way, most likely at the less hindered carbonyl site, giving a perfectly alternating polymer. Although $SnOct_2$ causes transesterification during polymerization of lactide,[50] either there is no transesterification during the polymerization of **4b** or it proceeds in a perfect fashion, again at the least hindered site. X-ray crystal structure analyses of monomers **4a** (*S*,*S* diastereoisomer) and **4b** revealed that both substituents on **4a** are at the equatorial position of the dilactone ring which has a twisted boat configuration (Figure 3, top).[46] The substituents are in such a position that there is hardly any difference in steric hindrance for attacking either of the carbonyl groups. Compound **4a** is therefore attacked in a random way yielding a random polymer. The crystal structure at the bottom of Figure 3 shows that compound **4b** clearly has two different steric bulks on each side of the dilactone ring.[47] A benzyloxymethyl substituent is on one side and two hydrogens are on the other. This steric difference results in a regioselective ring opening during polymerization.

We expected that poly(**4b**) is partially crystalline owing to its alternating character. However, DSC analysis did not show any crystallinity and only a T_g was detected for this polymer (Table 3). The benzyloxymethyl substituents have rotational

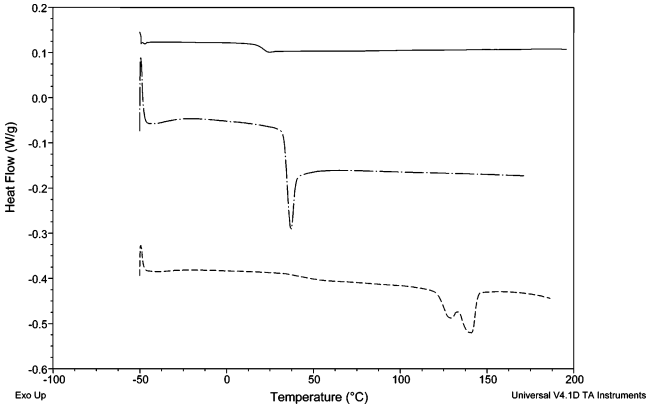


Figure 4. DSC thermograms of the random copolymers of **4b** with L-lactide synthesized with ethylzinc phenolate/2-propanol. 25% lactide (top), 50% lactide (middle) and 75% lactide (bottom).

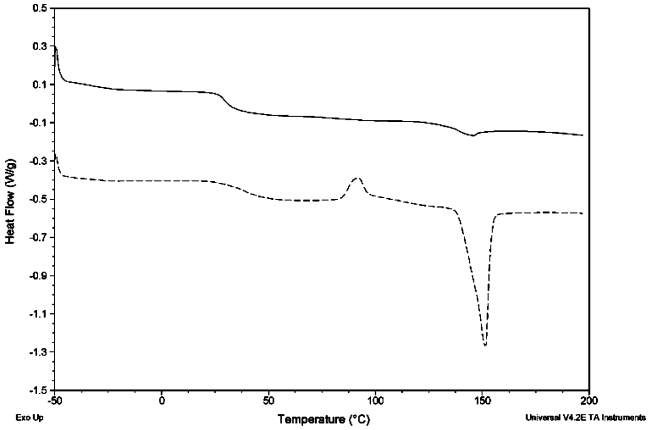


Figure 5. DSC thermograms of block copolymers of **4a** with L-lactide (top: 50 **4a**/50 PLA, bottom: 25 **4a**/75 PLA) synthesized with ethylzinc phenolate/2-propanol.

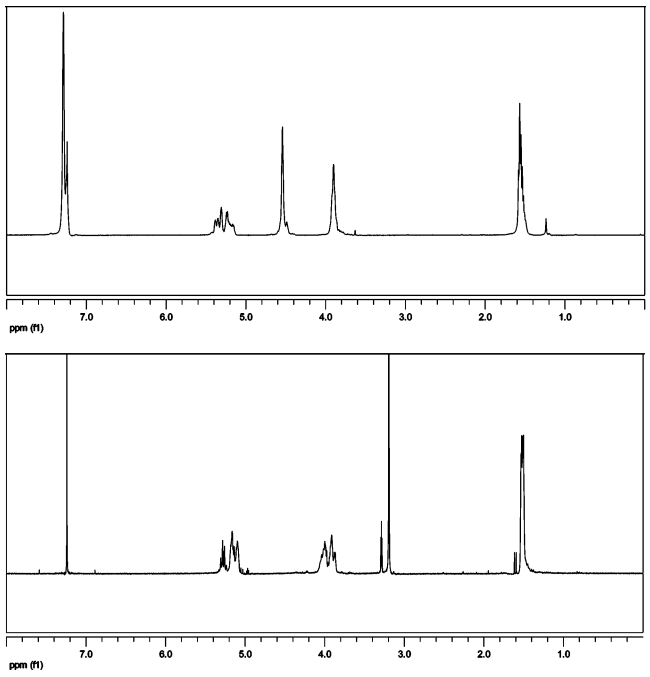


Figure 6. ^{1}H NMR spectra of deprotected poly **4a** (top: protected, bottom: deprotected). Chloroform and MeOH (both NMR solvents at 7.24 ppm and 3.39 and 3.2 ppm, respectively) are also visible in the spectrum of deprotected poly **4a**.

degrees of freedom, which are likely to prevent crystallization (vide infra). DSC analysis showed that, as expected, the random poly(**4a**) was fully amorphous with a T_g ranging from 20 to 30 °C, depending on the M_n (Tables 1 and 2).

Random and Block Copolymers of 4a and 4b with L-Lactide. Random copolymers of **4a** and **4b** with L-lactide were synthesized using the ethylzinc phenolate (Figure 1) as catalyst and 2-propanol as initiator. Also diblock copolymers of **4a** with L-lactide were synthesized. Table 3 summarizes the results. For the random copolymers the M_n and polydispersities were close to those of the homopolymers at the same catalyst and initiator amounts; i.e., M_n was between 10 and 15 kDa at M/C/I = 80/1/1. The yields were between 80 and 90%, and the copolymer composition, determined with ^{1}H NMR spectroscopy, equals the feed ratio, as can be expected from the high conversions. DSC analysis (Figure 4) shows that the random copolymers consisting of L-lactide and **4b** at low lactide levels (25 and 50%) were amorphous (T_g of 21 and 34 °C, see Table 3), whereas the copolymer with 75% L-lactide was partly crystalline (Figure 4, Table 3). However, copolymers of **4a** were fully amorphous even at high lactide contents (75%). DSC analysis showed a broad melting transition of the copolymer with 75% lactide and 25% **4b** between 110 and 145 °C with a ΔH_m of 8.7 J/g (Figure 4), which suggests a degree of crystallinity of 8.2% when compared to the enthalpy of fusion ΔH^0_m of perfect PLA crystals (106 J/g).[51] The observed melting transition temperature suggests that blocks with 15−25 lactic acid units are present in this copolymer.[52]

We previously demonstrated that lactic acid oligomers with a degree of polymerization (DP) >11 are able to crystallize.[50] Therefore, we calculated the probability of the formation of lactide blocks containing at least 12 lactic acid units as follows by applying simple random copolymerization statistics. Assuming equal reactivity of the two monomers L and M, the probability that a growing chain consisting of a single terminal lactide unit (M−L*) attaches to another L unit and thus continues to grow into a block of >1 units (M−L−L−X, in which X is (a sequence of) either L or M units) equals the monomer ratio of the feed (F_L). Likewise, the probability that a block of $>n$ lactide units is formed is shown in eq 1.

$$P_{\mathrm{DP}>n} = F_{\mathrm{L}}{}^{n} \tag{1}$$

If the reactivity of the two monomers is not equal, then the following equation can be derived

$$P_{\mathrm{DP}n} = \left(\frac{r \times f}{r \times f + 1}\right)^{n} \tag{2}$$

in which r represents the reactivity ratio between lactide and the comonomer ($r = k_L/k_M$) and f represents the ratio between the monomers present in the reaction mixture (for the instantaneously formed polymer: $f = F_L/F_M$). Equation 2 is a modification of the well-known copolymer sequence length distribution function and converts to eq 1 when $r = 1$.[53] Thus, assuming that no transesterification occurs, the probability of block lengths of at least 12 lactic acid units (thus more than 5 lactide units), which would be necessary for crystallinity to occur, can be calculated with either eq 1 or 2 for $n = 5$. Assuming that the reactivities of both monomers are equal (r

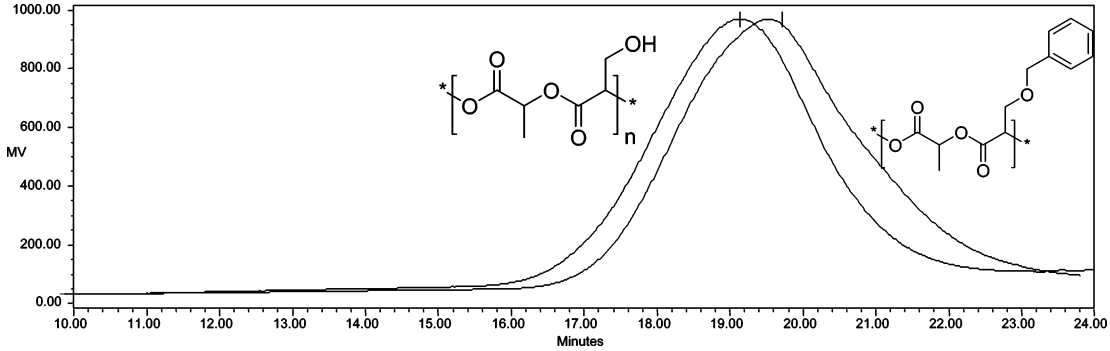


Figure 7. GPC overlay of protected (right) and deprotected (left) poly(**4a**).

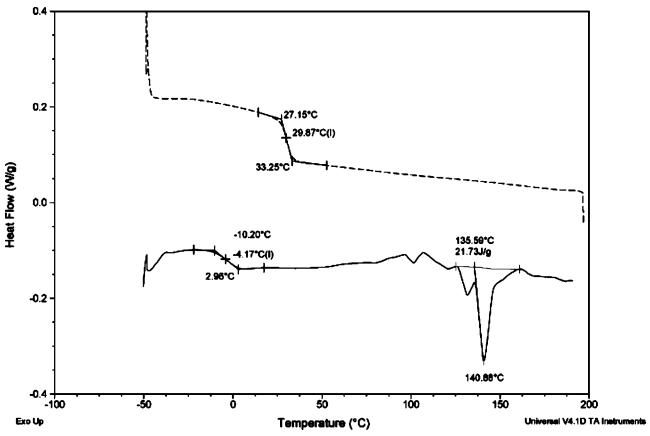


Figure 8. DSC thermograms of **5a** (top) and **5b** (bottom).

= 1) and, as a consequence, no composition drift occurs, the feed ratios $f = {}^1/_3$, 1, and 3 (25%, 50%, or 75% lactide) give a probability for the occurrence of crystallinity of 0.1%, 3%, or 24%, respectively. Transesterification would give lower degrees of crystallinity, whereas a difference in reactivity ($r \neq 1$) would give higher degrees of crystallinity. If one of the monomers is consumed more rapidly, it would give a copolymer that is enriched in longer lactide sequences either initially or by the end of the polymerization process. This is also reflected in a lower or higher $P_{DP>n}$ of the initially formed polymer when $r < 1$ or $r > 1$, respectively (eq 2).

Thus, assuming that the reactivities of both monomers are indeed more or less equal, a random copolymer should form in the copolymerization of lactide and **4a** or **4b** at a molar ratio of 75/25 with a 24% probability for the presence of lactic acid sequences longer than 10 units (5 lactide units). We did indeed observe crystallinity with **4b** but not with **4a**. This remarkable difference cannot be attributed to transesterification, since there is no reason to assume that transesterification would occur with the copolymerization of **4a** and not with **4b**. However, if much longer lactide sequences are required for crystallization, the degree of crystallinity will correspondingly decrease since $P_{DP>n}$ will decrease with increasing n. When the reactivity ratio $r = 1$, it may even decrease below detectable levels, but when $r \neq 1$ the degree of crystallinity should be higher as discussed above. We therefore conclude that $r \approx 1$ for **4a**, but $r < 1$ for the copolymerization of lactide with **4b** (the latter likely being the most reactive comonomer).[54−56] This difference in reactivity can be attributed to the difference in accessibility of the monomers' carbonyl groups as well as to an electronic effect. Because of the electron density donating character of alkyl substituents (methyl in the case of lactide and **4a**) the carbonyl carbon next to the alkyl-substituted (methyne) carbon will be less prone to nucleophilic attack (ring opening) than the carbonyl carbon next to the unsubstituted (methylene) carbon in **4b**. It is therefore most likely that the carbonyl of **4b** next to the methylene unit will be preferentially attacked by the initiator or growing species owing to the lower steric hindrance at that site as well as due to the higher sensitivity toward nucleophilic attack. This is consistent with the observed regioselectivity in the homopolymerization of **4b** (vide supra). Consequently, toward the end of the polymerization the feed becomes enriched in lactide, resulting in copolymers with long crystallizable lactic acid segments.

Block copolymers of **4a** with L-lactide were synthesized through initial polymerization of L-lactide (using the ethylzinc phenolate/2-propanol catalyst system) and subsequent addition of compound **4a**. Samples were taken for GPC analysis prior to the addition of **4a** to determine the lactide conversion. GPC showed an increase in M_n after the comonomer was added to the growing PLA block, indicating the living character of the polymerization reaction. The block copolymers were obtained in high yields (>90%). The copolymer compositions determined with ^{1}H NMR spectroscopy were consistent with the objected compositions (Table 3). DSC analysis of the block copolymers of **4a** and L-lactide showed that they were partly crystalline (Figure 5). The block copolymer containing 75% lactide showed 32% crystallinity of the PLA block, as can be concluded from the measured ΔH_m (37 J/g) compared to the ΔH_m of PLA (pure PLA crystals have a ΔH^0_m of 106 J/g).[51] The block copolymer containing 50% lactide showed a much lower crystalline fraction (3.5%). From this, we concluded that with increasing comonomer **4a** content the crystallinity of the PLA block was suppressed. Figure 5 also shows that both diblock copolymers have only one glass transition temperature which is indicative for miscibility of both blocks. The T_g of a fully mixed polymer blend is described by the Fox equation

$$F_{4a}\frac{1}{T_g\mathbf{4a}} + F_{pla}\frac{1}{T_g pla} = \frac{1}{T_g diblock} \qquad (3)$$

where F_{4a} and F_{pla} are the weight fractions of the polymer components. Using the measured T_g for the homopolymer of **4a** (295 K, Table 3, 80/1/1) and the measured T_g for the separate lactide blocks of the block copolymers (317 K, Table 3), the calculated T_g values for the diblock copolymers are 32 °C and 38 °C for the copolymers containing 50% and the 25% **4a**, respectively, which match the experimental data (30 and 39 °C, Table 3) very well.

Removal of the Protecting Group. The protecting groups of poly(**4a**) and poly(**4b**) were removed via a catalytic hydrogenation (second step in Scheme 1).[57] After several unsuccessful attempts (H_2 and Pd/C or Pd-Black with protic or aprotic conditions either with a balloon or with elevated hydrogen pressure) we successfully removed the benzyl ether groups by

hydrogenation using a balloon, THF as the solvent, and a Degussa-type Pd/C (10%) catalyst. Homopolymers of **4a** and **4b** were fully deprotected to give polymers **5a** and **5b** (Scheme 1) within 24 h under these conditions. The ^{1}H NMR analysis of polymer **5a** showed no detectable benzyl signals at 4.2 and 7.2 ppm (Figure 6). GPC analysis of the deprotected polymers shows that there was no chain scission under the reaction conditions of the deprotection step (Figure 7).

Deprotection of poly(**4b**) resulted in the formation of a semicrystalline polymer **5b** according to DSC (T_g = −4 °C, T_m = 135 °C and ΔH_m = 22 J/g, Figure 8), whereas the protected poly(**4b**) was fully amorphous (T_g = 17 °C). As shown above by ^{13}C NMR analysis (Figure 2), poly(**4b**) is a perfectly alternating polymer which, obviously, will still be the case for polymer **5b**. Apparently, alternating polymer **5b** is now able to crystallize, in contrast to poly(**4b**) where as suggested, the benzyl groups of the protected polymer interfered with crystallization. From DSC analysis it appeared that polymer **5a** is fully amorphous with a T_g of 30 °C (Figure 8). This is not surprising since ^{13}C NMR analysis showed that this polymer before deprotection has a random character, and thus also the deprotected polymer is expected to be amorphous.

The deprotected polymer **5a** did not dissolve in water, albeit that there was a clear swelling of the polymer observed in an aqueous environment due to water uptake in the polymeric matrix. Polymer **5b** did not swell under the same conditions, likely due to its semicrystalline nature. Detailed degradation studies of this polymer and related (co)polymers will be reported in a future paper. In conclusion, the hydroxylated polyesters as reported in this study can be regarded as promising materials for biomedical and pharmaceutical applications.

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