Organo-Catalyzed Ring Opening Polymerization of a 1,4-Dioxane-2,5-dione Deriving from Glutamic Acid

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The (3*S*)-[(benzyloxycarbonyl)ethyl]-1,4-dioxan-2,5-dione (BED) was prepared in four steps starting from glutamic acid and bromoacetyl bromide. According to X-ray diffraction analysis, the pendant functional group is located in equatorial position and points away from the six-membered ring. The organo-catalyzed ring-opening polymerization of BED was promoted with 4-dimethylaminopyridine (DMAP) and the combination of thiourea TU^{Cy} and (−)-sparteine. PolyBED samples of number-average molar mass M_n up to 36000 and narrow polydispersity ($M_w/M_n < 1.25$) were thereby prepared in a controlled manner under mild conditions (dichloromethane solution, 30 °C), as substantiated by size-exclusion chromatography, matrix-assisted laser desorption ionization time-of-flight−mass spectrometry (MALDI-TOF-MS) and nuclear magnetic resonance (NMR) spectroscopy. The pendant functional group does not interfere with the polymerization and BED was even found to be slightly more reactive than lactide. Despite the strongly dissymmetric substitution pattern of the 1,4-dioxan-2,5-dione core, the ensuing polyBED polymers present a random distribution of glycolic-[(benzyloxycarbonyl)ethyl]glycolic (gly glu) units, as supported by a $^1H-^{13}C$ HMBC 2D NMR experiment. The preparation of 1:1 adducts with *n*-pentanol confirmed that ring-opening of BED occurs almost indifferently on either of the endocyclic ester groups. Poly(α-hydroxyacids) featuring pendant carboxylic acids were finally obtained by acetylation of the terminal OH groups followed by hydrogenolysis.

Introduction

Polyhydroxyacids such as polylactic acid (PLA), polyglycolic acid (PGA), and their copolymers (PLGA) have attracted considerable interest in recent years as resorbable biomaterials as well as commodity thermoplastics derived from renewable resources.[1] A number of catalytic systems have been found to perform the ring-opening polymerization (ROP) of lactide under mild conditions and with high level of control in terms of molar mass, polydispersity, end-group fidelity as well as tacticity. In addition to well-defined, single-site metal complexes,[2a−e] which are the most widely used systems for the ROP of cyclic esters, several organo-catalysts have been shown recently to promote efficient ROP of lactide.[2d−h]

However, the lack of structural diversity of the polyesters derived from lactide and glycolide appears as an important limitation, and increasing efforts are currently devoted to the introduction of pendant groups along the polymer chain to modulate further the physicochemical properties of poly(α-hydroxyacids).[3−12] Accordingly, Baker et al. recently reported the ROP of several alkyl- and aryl-substituted 1,4-dioxan-2,5-diones, and the glass transition temperature for the ensuing polymers were found to vary in a broad range (from −40 °C to more than 100 °C, as to compared with ∼45 °C for PLA).[3a,4] The incorporation of pendant functional groups,[2e,f,3b] and especially proteinogenic side chains, is also of utmost interest to confer hydrophilicity, to increase degradation rate, and to graft biologically active compounds to the poly(α-hydroxyacids).[12] Although the preparation of such functionalized poly(α-hydroxyacids) is still in its infancy, significant progress has been achieved over the past few years, especially with monomers featuring pendant-protected hydroxyl groups. Vert et al. reported in the early 2000s the ROP of monomers **Ia**,**b** (Figure 1) deriving from gluconic acid with tin octanoate $SnOct_2$.[5,6] Around the same time, metal-catalyzed ROP of the serine-based 1,4-dioxan-2,5-diones **IIa**,**b** was investigated with success by Feng, Hennink, Collard, and Weck.[7] Comparatively, the preparation of poly(α-hydroxyacids) featuring pendant carboxyl groups has proved more challenging. Although Kimura demonstrated the feasibility of polymerizing monomer **IIIb** with $SnOct_2$ as early as in 1988,[8−10] only modest control and broad molar mass distributions (M_w/M_n from 1.4 to 3.5) were obtained. Recently, the metal-catalyzed ROP of functionalized 1,4-dioxan-2,5-diones has been extended to monomers **IVa,b** and **Va** derived from glutamic acid and lysine, respectively.[7d,10] But again rather drastic conditions were employed ($SnOct_2$, 140 °C in bulk), and the polymerization efficiency and control are not optimal (30−60% yield, $M_w/M_n \sim 1.4$).

The spectacular progress achieved over the past few years in metal-free ROP raises the question as to whether organocatalysts are applicable to the controlled preparation of functionalized poly(α-hydroxyacids). One common advantage imparted to organocatalysis is high functional group tolerance. Indeed, this has been exploited in the context of polymer synthesis to prepare well-defined complex architectures from polyfunctional initiators.[13] However, to the best of our knowl-

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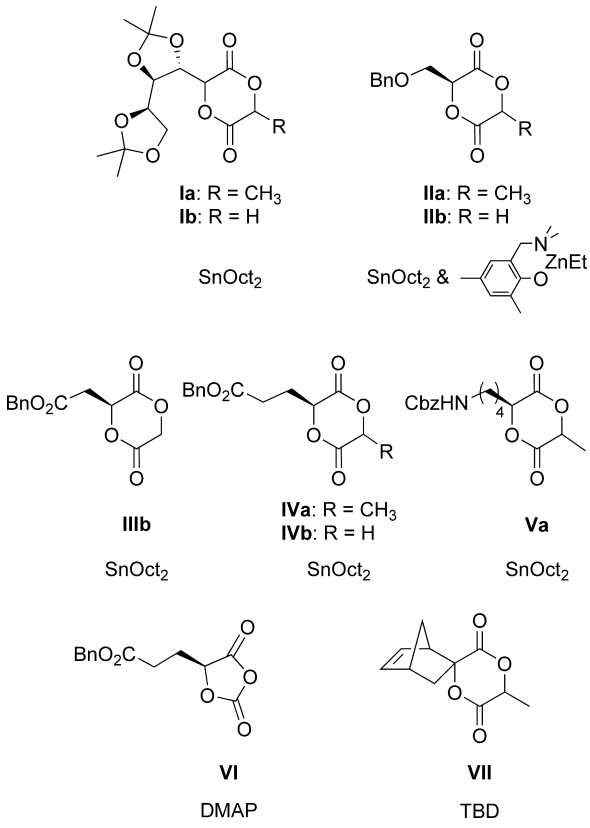


Figure 1. Main monomers investigated for the preparation of functionalized poly(α-hydroxyacids).

edge, the ability of organo-catalysts to promote the ROP of functionalized 1,4-dioxan-2,5-diones has not been substantiated thus far. Only the *O*-carboxyanhydride **VI**, an activated monomer derived from glutamic acid, has been polymerized under mild conditions using 4-dimethylaminopyridine (DMAP) as the catalyst.[14] As far as substituted 1,4-dioxan-2,5-diones are concerned, the only precedent of organo-catalyzed ROP is the recent work by Hillmyer and co-workers on monomer **VII**.[15] Taking advantage of the high activity of 1,5,7-triazabicyclododecene (TBD, a bicylic guanidine) as catalyst, the trisubstituted 1,4-dioxan-2,5-dione **VII** was readily polymerized under mild conditions and PLA composites with enhanced toughness were obtained by sequential ROP/ring-opening metathesis polymerization (ROMP). In order to evaluate if organo-catalyzed ROP is a viable route to functionalized poly(α-hydroxyacids) of controlled structure, we have investigated the metal-free polymerization of monomer **IVb** (referred to as BED), and report here the results of this study. Special attention has been devoted to the influence of the pendant functional group on the polymerizability of the 1,4-dioxan-2,5-dione moiety, as well as on the selectivity of ring-opening.

Experimental Section

Materials. All reactions were performed under inert atmosphere of argon, using standard Schlenk techniques. Solvents were dried and distilled prior to use: toluene (>99.9%), tetrahydrofurane (THF; >99.9%) and diethyl ether (>99.9%) over sodium, pentane (>99%) over calcium dihydride, and dichloromethane (CH_2Cl_2; >99.95%) over phosphorus pentoxide. Thiourea catalysts (TU^{Cy}, TU^{NMe_2}) were prepared according to literature procedures[16] and purified by three recrystallizations from chloroform. (−)-Sparteine (Aldrich, 99%) was distilled twice over calcium dihydride and stored under argon. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU; Aldrich, 98%) was distilled twice over calcium dihydride just prior to use. 4-Dimethylaminopyridine (DMAP; 99%, Aldrich) was purified by recrystallization from toluene and stored under argon. L-lactide (Purac) was purified by two recrystallizations from toluene and stored under argon at −20 °C. *n*-Pentanol (99+%) was dried over sodium and distilled before use. γ-Benzyl glutamic acid (Acros, 99%), sodium nitrite (Aldrich, 99,5%), dicyclohexylamine (Aldrich, 99%), bromoacetyl bromide (Acros, 98%), tetrabutylammonium iodide (Aldrich, 99%), triethylamine (Et_3N; Aldrich, 99.5%), and diisopropylethylamine (Aldrich, 99%) were used as received.

Characterizations. NMR Spectra were recorded in chloroform-*d* or acetone-d_6 on BRUKER Avance 300, 400, and 500 MHz spectrometers at room temperature. Chemical shifts are reported in ppm relative to Me_4Si as an external standard. ^1H NMR measurements were used to determine the monomer conversion and the chain end groups. The degree of polymerization DP was determined from the relative integration of the signals for the glycolate units and chain ends. HMBC spectra were recorded on BRUKER Avance 500 MHz spectrometer equipped with a cryo-probe TCI 5 mm indirect detection with $1/(2J_{XH}) = 50$ ms. The number-average and weight-average molar masses (M_n and M_w, respectively, in g/mol) and polydispersity indexes (M_w/M_n) of the polyester samples were determined by size exclusion chromatography (SEC) at 40 °C with a Waters 600 liquid chromatograph equipped with a Waters 2410 Refractive Index Detector. Tetrahydrofuran (THF) was used as the eluent and the flow rate was set up at 1.0 mL/min. A Waters pre-column and a Waters STYRAGEL column (HR 4E, 50−100000 g/mol) were used. Calibrations were performed using polystyrene standards (400−100000 g/mol).

The exact number-average molar masses were determined by size exclusion chromatography (SEC) at 40 °C with a Waters 510 liquid chromatograph equipped with a minDAWN Light Scattering Detector instrument (3 angles). Tetrahydrofuran was used as the eluent and the flow rate was set up at 1.0 mL/min. The refractive index increment ($dn/dc = 0.1137 \pm 0.00098$ mL/g) of dilute solutions of polymer was measured in THF at 30 °C with a differential refractometer (PSS-2010) working at 620 nm.

Matrix-assisted laser desorption ionization time-of-flight−mass spectrometry (MALDI-TOF-MS) analysis was performed on a Voyager System DE-STR from Applied Biosystems equipped with a 337 nm nitrogen laser. An accelerating voltage of 20 kV was applied. Mass spectra of 1000 shots were accumulated. The polymer sample was dissolved in dichloromethane at a concentration of 1 mg/mL. The cationization agent used was NaI dissolved in methanol at a concentration of 10 mg/mL. The matrix used was dithranol and was dissolved in dichloromethane at a concentration of 10 mg/mL. Solutions of matrix, salt, and polymer were mixed in a volume ratio of 3:1:1, respectively. The mixed solution was hand-spotted on a stainless steel MALDI target and left to dry. The spectrum was recorded in the reflectron mode. Baseline corrections and data analyses were performed using Data Explorer version 4.0 from Applied Biosystems.

The optical purity (>99.9%) of BED and compound **3** was checked by Chiral HPLC (Alliance system from Waters equipped with a photodiode array detector Waters 996). Separations were performed with Chiracel OD−H column using hexane +0.05% trifluoroacetic acid (80%) and isopropanol (20%) as eluents at the flow rate of 1 mL/min.

Melting points were measured with an Electrothermal digital melting point apparatus and are uncorrected.

Preparation of 2-Amino-pentanedioic Acid 5-Benzyl Ester (2). Methane sulfonic acid (0.82 mol, 53 mL) was added dropwise to a warmed (45 °C) suspension of benzyl alcohol (1.02 mol, 106 mL) and glutamic acid (**1**; 0.68 mol, 100 g) in toluene (100 mL). After 2 h at 45 °C, the homogeneous reaction mixture was stirred at 30 °C for additional 3 h. Water was added (200 mL) and the organic layer was eliminated. The aqueous layer was diluted with ethanol (100 mL). Compound **3** precipitated when pH was adjusted to 6 by the slow addition of ammoniac (20% aqueous solution, 110 mL). The white solid was washed twice with cold ethanol (150 mL), twice with water (150 mL), and dried under vacuum at 50 °C (105.2 g, 67%). Analytical data

are in agreement with reported literature data.[17] Mp: 175−177 °C (lit.: 172−180 °C). HPLC-MS: 100%, $[M + H]^+$: 238.18.

Preparation of 5-Benzyloxycarbonyl-2-hydroxy-pentanedioic Acid (3). A 2 mol/L aqueous solution of a $NaNO_2$ (210.0 mmol, 105 mL) was added dropwise in 30 min, at 30 °C, to a suspension of L-BnOGlu (**2**; 105.0 mmol, 25.0 g) in a mixture of H_2O and acetic acid (400 mL, ratio 8/2). The reaction mixture was then stirred at this temperature for 4 h, after which it became homogeneous. Water (200 mL) was then added and the title compound was extracted by ethyl acetate (3 × 150 mL). The organic layers were combined, washed with water and brine, and dried over sodium sulfate. The solvent was removed by evaporation to give 20.5 g of viscous oil (^{1}H and ^{13}C NMR data in agreement to literature data).[18]

Dicyclohexyamine (86.0 mmol, 17.3 mL) was added to a cold solution of the crude hydroxyacid in methyl-*t*-butylether (150 mL). The mixture was stirred for 30 min at this temperature. The salt was filtered, washed with cold methyl-*t*-butylether, and dried under vacuum to yield a white powder (24.85 g, 56% overall). ^{1}H NMR ($CDCl_3$, 300 MHz): δ_{ppm} 7.33 (m, 5H, Ph), 5.11 (s, 2H, C*H*$_2$Ph), 3.90 (dd, 1H, J = 7.6 and 3.9 Hz, C*H*OH), 2.96 (m, 2H, NC*H*(cyclohexyl)), 2.60 (m, 2H, $CH_2CH_2CO_2$), 2.18 (m, 1H, $CHHCH_2CO_2$), 2.00−1.10 (m, 22H, $CHHCH_2CO_2$, C*H*$_2$cyclohexyl, O*H*). Mp: 125−126 °C; optical purity > 99.9% (chiral HPLC).

Preparation of 5-Benzyloxycarbonyl-2-(2-bromo-acetyloxy)-pentandioic Acid (4). A solution of the dicyclohexylamine salt (**3**; 58.4 mmol, 24.5 g) in dichloromethane (100 mL) was mixed with Et_3N (58.4 mmol, 8.14 mL) and was added dropwise (30 min) to a chilled solution of bromoacetyl bromide (75.9 mmol, 6.60 mL) in dichloromethane (300 mL). The heterogeneous mixture was stirred for 4 h and was then diluted with dichloromethane (200 mL), washed twice with cold HCl (1 mol/L), twice with water and then brine. The organic layer was dried over sodium sulfate and the solvent was eliminated under reduced pressure to give a viscous oil (22.5 g). This oil was dissolved in dichloromethane (20 mL) and the solution was slowly poured over pentane (600 mL). The solvent was discarded and the residual oil was washed twice with pentane. The oil was dried under vacuum to yield light brown oil (19.65 g, 94%), and was engaged directly in the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_{ppm} 7.36 (m, 5H, Ph), 5.14 (s, 2H, C*H*$_2$Ph), 5.17 (dd, 1H, J = 7.6 and 3.9 Hz, C*H*OH), 3.86 (m, 2H, C*H*$_2$Br), 2.51 (m, 2H, $CH_2CH_2CO_2$), 2.18 (m, 1H, $CHHCH_2CO_2$), 2.28 (m, 1H, $CHHCH_2CO_2$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_{ppm} 173.4 (CH*C*OOH), 172.2 (*C*OOCH$_2$Ph), 166.6 (*C*OCH$_2$Br), 135.3 (*C*$_{ipso}$, Ph), 128.5−128.2 (*C*H, Ph), 72.0 (*C*HOCO), 66.6 (OCH$_2$Ph), 29.4 (*C*H$_2$CH$_2$CHO), 25.7 (CH$_2$*C*H$_2$CHO), 24.9 (*C*H$_2$Br). MS (DCI, NH_3) *m*/*z*: 376.3 ($M + NH_4^+$), 378.3 ($M + NH_4^+$), 298.4, 210.4, 165.3, 148.3.

Preparation of L-3-(2-Benzyloxycarbonyl)ethyl-1,4-dioxane-2,5-dione (BED). Tetrabutylammonium iodide (0.26 mol, 92.0 g) was added to a solution of *i*Pr$_2$EtN (3.56 mol, 615 mL) in methyl*iso*butylketone (23.0 L), and the mixture was heated at 60 °C under inert atmosphere. A solution of the bromoacetyl compound (**4**; 1.78 mol, 639.0 g) in methyl*iso*butylketone (5.0 L) was added dropwise (over 6 h, pump). The reaction mixture was heated for 1 h and left overnight at room temperature under stirring. The reaction mixture was then washed with cold HCl (2 mol/L, 2 × 5.0 L) and water and dried over sodium sulfate. The solvent was eliminated under reduced pressure to give a light-yellow solid, which was triturated in a mixture of methyl*iso*butylketone and methyl*t*butylether (1/10, v/v) to yield an off-white powder (265.3 g, 54%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ_{ppm} 7.36 (m, 5H, Ph), 5.14 (s, 2H, C*H*$_2$Ph), 5.17 (dd, 1H, J = 9.3 and 5.3 Hz, C*H*OH), 4.90 (s, 2H, C*H*$_2$gly), 2.64 (t, 2H, J = 7.2 Hz, $CH_2CH_2CO_2$), 2.44 (m, 1H, $CHHCH_2CO_2$), 2.26 (m, 1H, $CHHCH_2CO_2$).^{13}C NMR ($CDCl_3$, 75 MHz): δ_{ppm} 171.9 (*C*OOCH$_2$Ph), 165.7 (CH*C*OOCH$_2$), 164.4 (*C*OCH$_2$OCO), 135.4 (*C*$_{ipso}$, Ph), 128.4−128.0 (*C*H, Ph), 73.8 (*C*HOCO), 66.4 (Ph*C*H$_2$O), 65.3 (CO*C*H$_2$OCO), 28.3 (*C*H$_2$CH$_2$CHO), 25.4 (CH$_2$*C*H$_2$CHO). Mp: 78−80 °C. HRMS (DCI CH_4) *m*/*z*: Calcd for $[C_{14}H_{15}O_6 + H]^+$, 279.0869; found, 279.0864. Anal. Calcd. for $C_{14}H_{15}O_6$: C, 60.43; H, 5.07. Found: C, 60.52; H, 4.93. Optical purity > 99.9% (chiral HPLC).

Crystal Structure Determination of BED. Data were collected at 173(2) K using an oil-coated shock-cooled crystal on a Bruker−AXS APEX II diffractometer with Mo Kα radiation (λ = 0.7103 Å; see Supporting Information). Semi-empirical absorption corrections were employed.[19] The structures were solved by direct methods (SHELXS-97)[20] and refined using the least-squares method on F^2.[21]

Typical Procedure for the Polymerization of BED Catalyzed by TU^{Cy}/(−)-Sparteine. Prior to polymerization, BED was passed on a short plug of silica (petroleum ether/ethyl acetate 70/30 v/v), recrystallized twice in toluene, and dried overnight under high vacuum.

In a dried Schlenk, a solution of *n*-pentanol in dichloromethane (40 μmol, 100 μL from stock solution, $[M]_0/[I]_0$ = 25) was added to a solution of monomer (1.0 mmol, 280 mg) in dichloromethane (700 μL). The reaction mixture was heated at 30 °C and catalysts (40 μmol TU^{Cy} + 40 μmol (−)-sparteine, 200 μL from a stock 0.2 mol/L dichloromethane solution) was added under argon. Aliquots of the reaction mixture were quenched with benzoic acid and the conversion was determined by ^{1}H NMR spectroscopy. At the end of the reaction, the reaction medium was diluted with 5 mL of dichloromethane, washed with cold HCl (2 mol/L), dried over sodium sulfate and concentrated. The polymer was precipitated by addition of the dichloromethane solution into cold methanol and dried under vacuum. The number-average molar mass was determined by SEC (M_n = 7890, M_w/M_n = 1.22) and the degree of polymerization was determined by ^{1}H NMR spectroscopy (DP = 28).

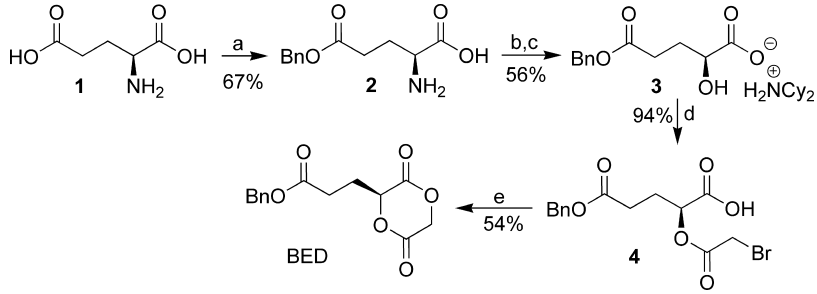
^{1}H NMR ($CDCl_3$, 300 MHz): δ_{ppm} 7.34 (m, ∼145H, Ph), 5.22 (m, ∼28H, C*H*O), 5.10 (s br, ∼55H, C*H*$_2$Ph), 4.86−4.52 (m, ∼56H, CH_2gly), 4.37 (m, C*H*OH), 4.19 (m, C*H*$_2$OH), 4.11 (m, 2H, $CH_2CH_2CH_2O$), 2.54−2.37 (m, ∼114H, $CH_2CH_2CO_2$Bn), 1.41 (m, 2H, $CH_3CH_2CH_2CH_2CH_2O$), 1.15 (m, 4H, $CH_3CH_2CH_2CH_2CH_2O$), 0.89 (t, 3H, J = 6.3 Hz, C*H*$_3$CH$_2$CH$_2$CH$_2$CH$_2$O). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 171.9 (*C*OBn), 168.2 (*C*Ogly), 166.3 (*C*Oglu), 135.8 (*C*$_{ipso}$, Ph), 128.6−128.3 (*C*H, Ph), 71.6 (*C*HOCO), 66.5 (Ph*C*H$_2$O), 60.8 (CO*C*H$_2$OCO), 29.2 (CH$_2$*C*H$_2$COOBn), 26.0 (*C*H$_2$CH$_2$COOBn).

Typical Procedure for the Polymerization of BED Catalyzed by DMAP. In a dried Schlenk, a solution of *n*-pentanol in dichloromethane (40 μmol, 100 μL from stock solution, $[M]_0/[I]_0$ = 25) was added to a solution of monomer (1.0 mmol, 280 mg) in dichloromethane (700 μL). The reaction mixture was heated at 30 °C and DMAP (100 μmol, 200 μL from a stock 0.5 mol/L dichloromethane solution) was added under argon. Aliquots of the reaction mixture were quenched with benzoic acid and the conversion was monitored by ^{1}H NMR spectroscopy. At the end of the reaction, the reaction medium was diluted with 5 mL of dichloromethane, washed with cold HCl (2 mol/L), dried over sodium sulfate, and concentrated. The polymer was precipitated by the addition of the dichloromethane solution into cold methanol and dried under vacuum. The number-average molar masses were determined by SEC and the degrees of polymerization were determined by ^{1}H NMR spectroscopy.

Preparation of Adducts 5 and 6. In a round-bottom flask, catalyst (0.1 mmol) was added to a solution of BED (1.0 mmol, 280 mg) in dichloromethane (10.0 mL) and *n*-pentanol (10.0 mmol, 1.0 mL). The reaction mixture was stirred at room temperature for 1 h and completion was controlled by ^{1}H NMR spectroscopy. The two compounds were separated by flash chromatography (CH_2Cl_2/MeOH, 99/1).

Compound **5.** ^{1}H NMR ($CDCl_3$, 300 MHz): δ_{ppm} 7.34 (m, 5H, Ph), 5.11 (s, 2H, C*H*$_2$Bn), 4.74 and 4.62 (AB system, 2H, J = 15.9 Hz, CH_2), 4.37 (m, 1H, C*H*OH), 4.11 (t, 2H, J = 6.9 Hz, OC*H*$_2$CH$_2$CH$_2$), 3.21 (d, 1H, J = 5.7 Hz, O*H*), 2.59 (m, 2H, CH$_2$C*H*$_2$), 2.28 (m, 1H, C*H*HCH$_2$), 2.06 (m, 1H, CH*H*CH$_2$), 1.63 (m, 2H, C*H*$_2$), 1.32 (m, 4H, C*H*$_2$C*H*$_2$), 0.89 (t, 3H, J = 6.4 Hz,C*H*$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_{ppm} 173.8 (*C*OOCH$_2$Ph), 173.0 (CH*C*OOCH$_2$), 167.2 (*C*OCH$_2$OCO), 135.8 (*C*$_{ipso}$, Ph), 128.1−128.5 (*C*H, Ph), 69.4 (CH$_2$*C*HOHCO), 66.3 (Ph*C*H$_2$O), 65.7 (CO*C*H$_2$OCO), 61.2 ($CH_3CH_2CH_2CH_2C$*H*$_2$O), 29.4 (CO*C*H$_2$CH$_2$CHOH), 29.1 (COCH$_2$*C*H$_2$CHOH), 28.0

Scheme 1. Improved Procedure for the Preparation of BED[a]



[a] Reagents and conditions: (a) BnOH, $MeSO_3H$; (b) $NaNO_2$, $AcOH/H_2O$; (c) Cy_2NH, *t*-$BuOCH_3$; (d) $BrCH_2COBr$, Et_3N, 0 °C, CH_2Cl_2; (e) *n*-Bu_4NI, *i*-Pr_2NEt, *i*-$BuCOCH_3$.

($CH_3CH_2CH_2\underline{C}H_2CH_2O$), 27.8 ($CH_3CH_2\underline{C}H_2CH_2CH_2O$), 22.1 ($CH_3\underline{C}H_2CH_2CH_2CH_2O$), 13.8 ($\underline{C}H_3CH_2CH_2CH_2CH_2O$). MS (EI): 91, 108, 189, 259, 349, 367 ($M + H^+$).

Compound **6.** ^1H NMR ($CDCl_3$, 300 MHz): δ_{ppm} 7.35 (m, 5H, Ph), 5.17 (dd, 1H, $J = 8.1$, 4.8 Hz, C*H*), 5.12 (s, 2H, CH_2Bn), 4.22 (d, 2H, $J = 5.4$ Hz, CH_2OH), 4.11 (t, 2H, $J = 6.6$ Hz, CH_2O), 2.57 (m, 2H, CH_2CH$_2$), 2.24 (m, 2H, C*HH*CH$_2$), 1.63 (m, 2H, CH_2), 1.31 (m, 4H, CH_2CH_2), 0.90 (t, 3H, $J = 6.9$ Hz, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_{ppm} 172.5 (*C*(O)OCH$_2$Ph), 171.9 (CH*C*(O)OCH$_2$), 169.1 (*C*(O)CH$_2$OC(O)), 135.6 (C_{ipso}, Ph), 128.1−128.5 (*C*H, Ph), 71.8 (*C*HOC(O)), 66.5 (C(O)*C*H$_2$OH), 65.9 (Ph*C*H$_2$O), 60.3 ($CH_3CH_2CH_2CH_2\underline{C}H_2O$), 29.6 (C(O)$\underline{C}H_2CH_2CHOC(O)$), 28.0 (C(O)CH$_2$*C*H$_2$CHOC(O)), 27.8 ($CH_3CH_2CH_2\underline{C}H_2CH_2O$), 26.1 ($CH_3CH_2\underline{C}H_2CH_2CH_2O$), 22.1 ($CH_3\underline{C}H_2CH_2CH_2CH_2O$), 13.8 ($\underline{C}H_3CH_2CH_2CH_2CH_2O$). MS (EI): 91, 131, 189, 146, 201, 290, 338, 367 ($M + H^+$).

Typical Procedure for Kinetic Studies (DP100). In a dried Schlenk, a solution of *n*-pentanol in dichloromethane (50 μmol, 500 μL from stock solution) was added to a solution of BED (5.0 mmol, 1.40 g) in dichloromethane (3.5 mL). The reaction mixture was heated at 30 °C and catalyst (0.1 mmol TU^{Cy} + 0.1 mmol (−)-sparteine, 500 μL from a stock 0.2 mol/L dichloromethane solution) was added under argon. At determinate times, aliquots of the reaction mixture were quenched with benzoic acid and the conversion was monitored by ^1H NMR spectroscopy and average molar masses determined by SEC chromatography. After complete conversion, the polymer was precipitated by addition of the dichloromethane solution into cold methanol and dried under vacuum. The number-average molar masses were determined by SEC and the degrees of polymerization were determined by ^1H NMR spectroscopy.

Preparation of a Poly(α-hydroxyacid) Featuring Pendant Carboxyl Groups. *(1) Polymerization.* In a dried Schlenk, a solution of *n*-pentanol in dichloromethane (20 μmol, 100 μL from a stock 0.2 mol·L^{-1} solution, $[M]_0/[I]_0 = 50$) was added to a solution of BED (1.0 mmol, 280 mg) in dichloromethane (700 μL). The reaction mixture was heated at 30 °C, TU^{NMe_2} catalyst and (−)-sparteine in dichloromethane (40 μmol of each one, 200 μL from stock solution) was added under argon. After 3 h, the reaction completion was confirmed by ^1H NMR spectroscopy and number-average molar masses were determined by SEC ($M_n = 11370$, $M_w/M_n = 1.16$). ^1H and ^{13}C NMR spectra are in agreement with those reported for the polymer prepared with TU^{Cy} as catalyst.

(2) Purification. The reaction mixture was diluted with 2 mL of dichloromethane and the catalytic system trapped overnight with Amberlyst15 (150 mg). The complete removal of both TU^{NMe_2} and (−)-sparteine was checked by ^1H and ^{19}F NMR spectroscopy. SEC chromatography confirmed the absence of side reactions ($M_n = 11250$, $M_w/M_n = 1.14$). ^1H NMR ($CDCl_3$, 300 MHz): δ_{ppm} 7.34 (m, ∼260H, Ph), 5.22 (m, ∼50H, C*H*O), 5.10 (s br, ∼100H, CH_2Ph), 4.86−4.52 (m, ∼102H, CH$_2$ Gly), 4.37 (m, C*H*OH), 4.19 (m, CH_2OH), 4.11 (m, 2H, CH$_2$CH$_2$CH_2O), 2.54−2.37 (m, ∼209H, CH_2CH_2CO$_2$Bn), 1.41 (m, 2H, CH$_3$CH$_2$CH$_2$CH_2CH$_2$O), 1.15 (m, 4H, CH$_3$CH_2CH_2CH$_2$CH$_2$O), 0.89 (t, 3H, $J = 6.3$ Hz, CH_3CH$_2$CH$_2$CH$_2$CH$_2$O).

(3) Acetylation. Anhydride acetic (1.0 mL) and DMAP (30 mg) were added to the precedent solution and the reaction mixture was stirred for 2 h at room temperature. The complete protection of the terminal alcohols was confirmed by ^1H NMR spectroscopy and the number-average molar mass was checked by SEC ($M_n = 12240$, $M_w/M_n = 1.12$). DMAP and excess of anhydride acetic were removed by acidic aqueous work-up (2 mL of cold 2 mol/L HCl). The solvent was removed under reduced pressure to yield the acetylated polymer as a white sticky material. ^1H NMR ($CDCl_3$, 300 MHz): δ_{ppm} 7.33 (m, ∼260H, Ph), 5.22 (m, ∼50H, C*H*O), 5.10 (s br, ∼100H, CH_2Ph), 4.86−4.52 (m, ∼102H, CH$_2$gly), 4.11 (m, 2H, CH$_2$CH$_2$CH_2O), 2.54−2.37 (m, ∼209H, CH_2CH_2CO$_2$Bn), 2.06 (s, 3H, CHOCOCH_3, CH$_2$OCOCH_3), 1.60 (m, 2H, CH$_3$CH$_2$CH$_2$CH_2CH$_2$O), 1.31 (m, 4H, CH$_3$CH_2CH_2CH$_2$CH$_2$O), 0.89 (t, 3H, $J = 6.3$ Hz, CH_3CH$_2$CH$_2$CH$_2$CH$_2$O).

(4) Deprotection. Palladium on charcoal (10%, 100 mg) was added to the acetylated polymer dissolved in propanone (5 mL). The mixture was stirred under a hydrogen atmosphere (1 atm) for 2 h at room temperature. The catalyst was removed by filtration over Celite and the solvent was eliminated under reduced pressure to yield a white solid. The polymer was washed three times with chloroform (1.0 mL) and dried under vacuum to yield white foam. The complete deprotection was confirmed by ^1H NMR spectroscopy. The number-average molar mass of the fully deprotected polymer was determined by SEC ($M_n =$ 10 250, $M_w/M_n = 1.13$). ^1H NMR (acetone-d_6, 300 MHz): δ_{ppm} 5.44 (m, ∼50H, C*H*O), 5.05−4.85 (m, ∼100H, CH_2gly), 4.25 (m, CH$_2$CH$_2$CH_2O), 2.66−2.19 (m, ∼200H, CH_2CH_2CO$_2$H), 1.75 (m, 2H, CH$_3$CH$_2$CH$_2$CH_2CH$_2$O), 1.44 (m, 4H, CH$_3$CH_2CH_2CH$_2$CH$_2$O), 0.99 (t, 3H, $J = 6.3$ Hz, CH_3CH$_2$CH$_2$CH$_2$CH$_2$O). ^{13}C NMR (acetone-d_6, 75 MHz): δ ppm 175.2 (*C*OOH), 170.3 (*C*Ogly), 168.6 (*C*Oglu), 73.4 (*C*HOCO), 62.6 (CO*C*H$_2$OCO), 30.3 (CH$_2$*C*H$_2$COOH), 28.0 (*C*H$_2$CH$_2$COOH).

Results and Discussion

Monomer Preparation. The functionalized 1,4-dioxan-2,5-dione BED had been previously prepared in four steps (∼10% overall yield) starting from glutamic acid and bromoacetyl bromide.[10] The initial procedure was slightly modified (Scheme 1), which increased the overall yield (19% on >250 g scale) and avoided chromatographic purification. γ-Benzylation followed by diazotation of glutamic acid led to the corresponding α-hydroxyacid, whose dicyclohexylammonium salt **3** was readily isolated by crystallization. Subsequent reaction with bromoacetyl bromide in the presence of triethylamine afforded compound **4**. The key cyclization step was then performed under conditions inspired from those reported by Collard and Weck for the synthesis of **IIa**, **IVa**, and **Va** (bromine to iodine exchange prior to cyclization).[7d] Compound **4** was slowly added (∼5 mmol/min) at 60 °C to a solution of diisopropylethylamine (1 equiv) containing a catalytic amount of tetrabutylammonium iodide (15 mol %). Methyl*iso*butylketone was preferred as solvent over the commonly used dimethylformamide and

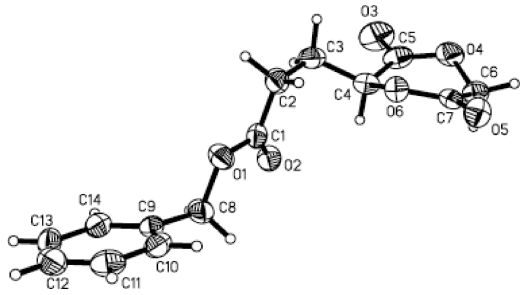


Figure 2. Molecular view of BED in the solid state (thermal ellipsoids at 50% probability).

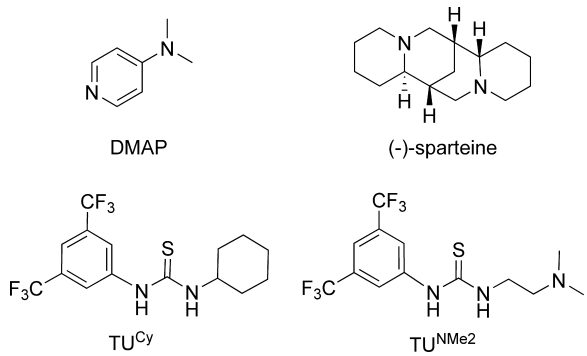


Figure 3. Structure of the organo-catalysts used for the ROP of BED.

acetone. The structure of BED was unambiguously established by ^{1}H and ^{13}C NMR spectroscopy, and its optical purity (>99.9%) was assessed by chiral HPLC performed on two samples deriving from L- and *rac*-glutamic acids (see Supporting Information).

Crystals of BED suitable for X-ray diffraction analysis were obtained upon cooling a hot methyl*t*-butylketone solution to room temperature (Figure 2). As typically observed for 1,4-dioxane-2,5-diones,[7c,d,22] BED adopts a twisted boat conformation in the solid state. The pendant (benzyloxycarbonyl-)ethyl group is located in equatorial position and points away from the six-membered ring. This arrangement contrasts with that observed by Hennink et al. for (3*S*)-3-(benzyloxymethyl)-1,4-dioxane-2,5-dione (**IIa**), the lateral group being located here in axial position, folded toward the six-membered ring.[7c]

Polymerization of BED. The organo-catalyzed ring-opening polymerization of BED was investigated with 4-dimethylaminopyridine (DMAP) and the combination of thiourea TU^{Cy} and (−)-sparteine, that both proved active toward lactide under mild conditions (Figure 3).[16,23,24] Reactions were carried out at 30 °C in dichloromethane solution ([BED]$_0$ = 1 mol/L) with *n*-pentanol as initiator, monomer to initiator ratios from 10 to 200, and 1 to 5 mol % catalyst (Table 1). Both catalytic systems were found to efficiently promote the ROP of BED, complete monomer conversions being achieved in a few minutes to a few hours. According to SEC analyses, polymers with number-average molar mass M_n increasing from ∼3000 (for M_0/I_0 = 10) to ∼36000 (for M_0/I_0 = 200) and narrow distributions (M_w/M_n < 1.27) were obtained. The TU^{Cy}/(−)-sparteine system is significantly more active than DMAP (see for example entries 2 vs 5), comparable to that observed with lactide.[16,23] In addition, the functionalized monomer BED was found to be slightly more reactive than lactide under similar conditions: the TU^{Cy}/(−)-sparteine system required only 15 min to achieve complete conversion of 100 equivalents of BED vs 90 min for lactide (entries 9 and 10). This behavior contrasts with the deactivation usually induced by the introduction of pendant functional groups to the 1,4-dioxane-2,5-dione core. The unique reactivity of BED most likely results from the less sterically demanding glycolic unit and a slight inductive activation of the 1,4-dioxane-2,5-dione by the pendant (benzyloxycarbonyl)ethyl group.

The structure of the obtained polyBED was assessed by mass spectrometry and NMR spectroscopy. Figure 4 depicts the matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrum of a polymer sample prepared from 25 equiv of BED with TU^{Cy}/(−)-sparteine as catalyst (entry 5; see Supporting Information for a MALDI-TOF mass spectrum associated to a polymer prepared with DMAP as catalyst). A single population is observed with mass increment of 278.3 g/mol (that is the molar mass of BED), and *m*/*z* values corresponding to polymers of formula *n*-PentO(BED)$_n$H·Na$^+$. This indicates the exclusive initiation with *n*-pentanol, the integrity of the pendant functional groups and the absence of transesterification reactions. ^{1}H NMR spectroscopy (Figure 5) corroborated the incorporation of the initiator as an ester chain end, the characteristic CH_2 ester signal (e) appearing at 4.10 ppm. The spectrum also showed signals corresponding to the glycolic (k) and (benzyloxycarbonyl)ethylglycolic (f,g,h) units. The degree of polymerization, as estimated from the relative integrations (g,h/e) and (k/e) (DP$_{NMR}$ = 28), is close to the initial monomer to initiator ratio ([BED]$_0$/[*n*-pentOH]$_0$ = 25). Signals (i) and (j) associated with the aromatic and benzylic protons, respectively, are found at the expected chemical shifts (7.34 and 5.10 ppm) and their integrations relative to (e) are also consistent with a degree of polymerization of about 28. According to these mass and NMR data, the polymerization of BED proceeds selectively by ring-opening of the 1,4-dioxane-2,5-dione core, without affecting the pendant ester groups. Such functional group tolerance had been previously observed during the DMAP-catalyzed ROP of the *O*-carboxyanhydride derived from glutamic acid.[14c] The fact that undesirable transesterification reactions with the pendant groups are also absent with a less reactive monomer, such as BED, and a more active catalyst, such as the TU^{Cy}/(−)-sparteine system, opens new opportunities for the preparation of functionalized polymers.

Interestingly, the ^{1}H NMR spectrum of the polyBED sample also showed two small multiplet signals at 4.37 and 4.19 ppm (f′ and k′) associated with two types of hydroxyl chain ends, namely a (benzyloxycarbonyl)ethylglycolic COCH(CH_2CH_2-CO_2Bn)OH moiety and a glycolic $COCH_2OH$ unit. This indicates that ring-opening of BED had occurred on either of the ester groups of the 1,4-dioxane-2,5-dione core with low differentiation, despite their dissymmetric substitution pattern. Accordingly, the organo-catalyzed ROP of BED leads to polymers presenting a random rather than alternated distribution of glycolic (gly) and [(benzyloxycarbonyl)ethyl]glycolic (glu) units. The random character of the polyBED was further corroborated by a ^{1}H−^{13}C HMBC 2D NMR experiment (Figure 6). In addition to the CH_2gly−COglu and CHglu−COgly correlation marks expected for an alternated distribution, CH_2gly−COgly and CHglu−COglu correlations marks were observed. Thus, the polymers derived from ROP of BED consist in the random enchainment of (gly glu) units, and the absence of transesterification reactions, as apparent from mass spectrometry, implies that no more than two consecutive units are of the same nature, so that the pendant functional groups are regularly distributed all along the polymer backbone.

To get more insight into the selectivity of the ring-opening, BED was reacted with an excess of *n*-pentanol in the presence of the organo-catalyst. With both DMAP and TU^{Cy}/(−)-

Table 1. Polymerization of BED Initiated by *n*-Pentanol and Catalyzed with 4-Dimethylaminopyridine (DMAP) or Thiourea TU^{Cy}/(−)-Sparteine[a]

entry	catalyst	M_0/I_0	cat/I_0	time (min)	DP_{NMR}[b]	M_n (g/mol)[c]	M_w/M_n[c]
1	DMAP	10	1	420	10	2870	1.27
2	DMAP	25	2.5	1080	26	8950	1.16
3	DMAP	50	5	1080	58	14200	1.19
4	DMAP	100	5	1440	80[d]	18690	1.23
5	TU^{Cy}/(−)−sparteine	25	1/1	20	28	7890	1.22
6	TU^{Cy}/(−)-sparteine	50	2/2	30	48	13840	1.13
7	TU^{Cy}/(−)-sparteine	100	2/2	60	92	20660	1.16
8	TU^{Cy}/(−)-sparteine	200	4/4	60	nd	36200	1.12
9	TU^{Cy}/(−)-sparteine	100	5/2.5	15	110	24640	1.17
10[e]	TU^{Cy}/(−)-sparteine	100	5/2.5	90	104	21150	1.06

[a] Polymerizations of BED in CH_2Cl_2 solution (initial concentration = 1 mol/L) at 30 °C, monomer conversion >98% according to ^{1}H NMR spectroscopy. [b] Obtained from ^{1}H NMR spectroscopy. [c] Number-average molar mass (M_n) and polydispersity index (M_w/M_n) obtained from size exclusion chromatography (in tetrahydrofuran, THF) using polystyrene standards. [d] Monomer conversion = 80%. [e] Polymerization of L-lactide.

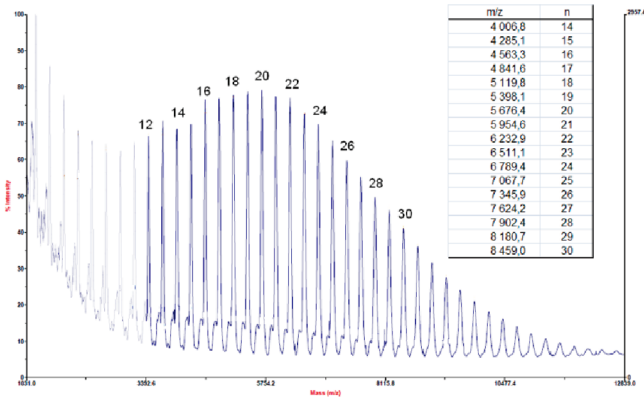


Figure 4. MALDI-TOF MS (region m/z 1000−12800) of a polyBED prepared by polymerization of BED with *n*-pentanol (CH_2Cl_2, 25 °C, $[BED]_0/[n\text{-pentOH}]_0/[TU^{Cy}]/[(-)\text{-sparteine}]$ 25/1/1/1, $[BED]_0$ = 1 mol/L); $m/z = 88.1\ (M_{n\text{-pentOH}}) + n \times 278.3\ (M_{BED}) + 23.0\ (Na^+)$.

sparteine, ring-opening took place rapidly and irreversibly to give a 1/0.75 mixture of adducts **5** and **6** (Figure 7). Both compounds were fully characterized after separation by column chromatography. The ^{1}H NMR spectrum of the major derivative **5** displays an AB system at 4.74 and 4.62 ppm for the diastereotopic hydrogens of the CH_2 glycolic unit, and a doublet of doublets at 4.37 ppm (J = 4.2 and 7.5 Hz) for the terminal C*H*OH group. For the minor compound **6**, the terminal methylene group CH_2OH appears at 4.22 ppm (d, J = 5.1 Hz), while the methine moiety of the glu unit resonates as a doublet of doublets at 5.17 ppm (J = 4.8 and 7.8 Hz). This result confirms that the ring-opening of BED occurs almost indifferently at the two ester groups of the 1,4-dioxane-2,5-dione core, in agreement with the random character of the polyBED. The conformation of the monomer as observed in the solid-state might explain why the pendant functional group does not significantly influence the regioselectivity of the ring-opening in this case, as the steric hindrance is possibly compensated by some inductive effects.

Controlled Character of the Polymerization. As mentioned before, increasing the monomer to initiator ratio (from 10 to 200) led to polyBED of increasing molar mass (M_n from 3000 to 36000, see Table 1). With both catalytic systems, the number-average molar mass (M_n) of the polyBED samples increases linearly with the monomer to initiator ratio (Figure 8a) and monomer conversion (Figure 8b), and the polydispersity index M_w/M_n remains fairly low (1.16−1.27 for DMAP and 1.12−1.22 for TU^{Cy}) up to high monomer conversions (see Supporting

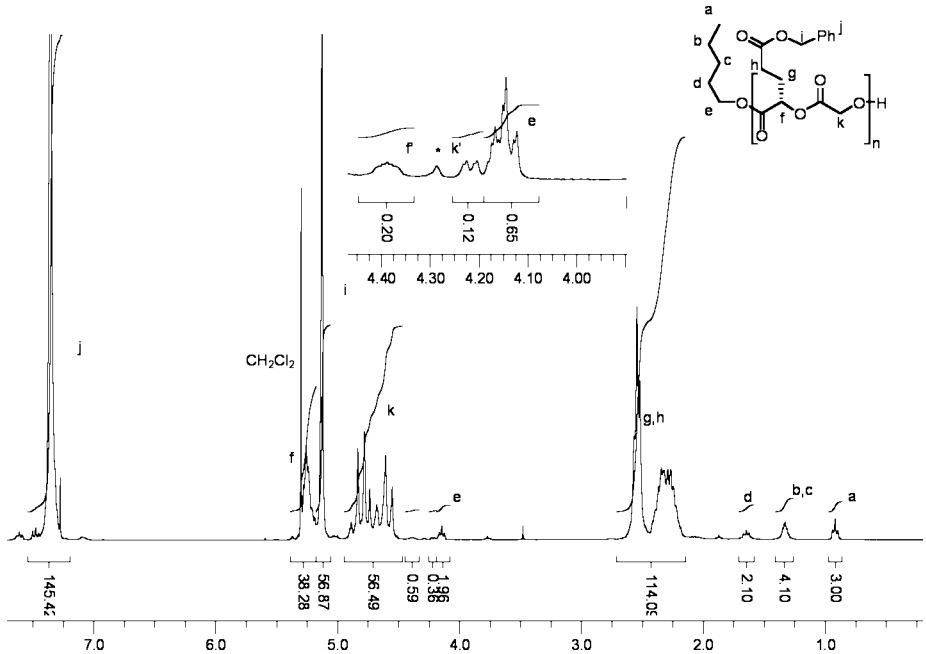


Figure 5. ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of a polyBED sample obtained by polymerization of BED with *n*-pentanol as initiator (CH_2Cl_2, 30 °C, $[BED]_0/[n\text{-pentOH}]_0/[TU^{Cy}]/[(-)\text{-sparteine}]$ 25/1/1/1, $[BED]_0$ = 1 M). *Residual TU^{Cy}.

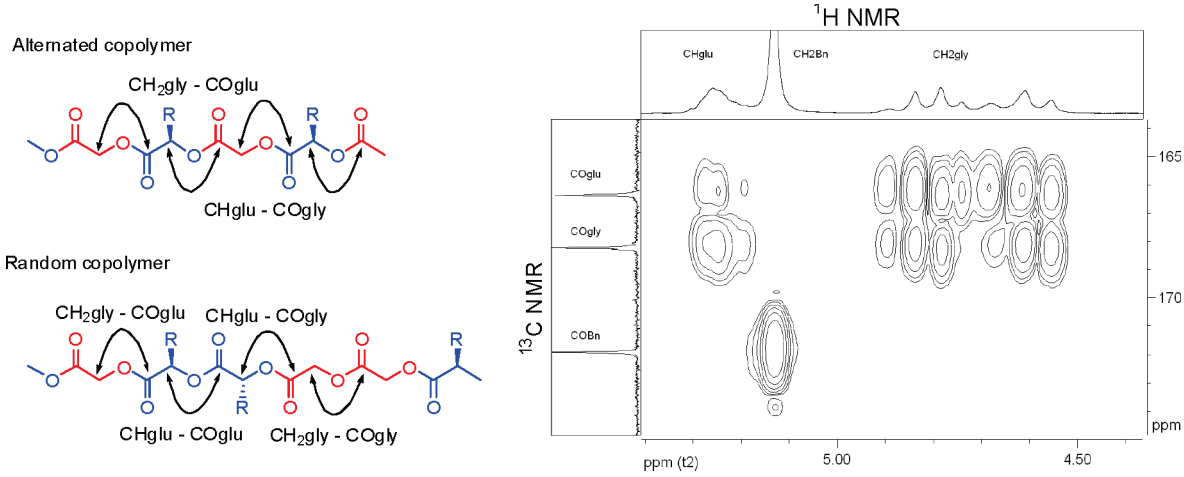


Figure 6. CH−CH_2/CO region of $^1H-^{13}C$ HMBC NMR spectrum of a polyBED sample obtained by polymerization of BED with *n*-pentanol as initiator (CH_2Cl_2, 30 °C, $[BED]_0/[n\text{-pentOH}]_0/[TU^{Cy}]/[(-)\text{-sparteine}]$ 100/1/2/2, $[BED]_0$ = 1 M).

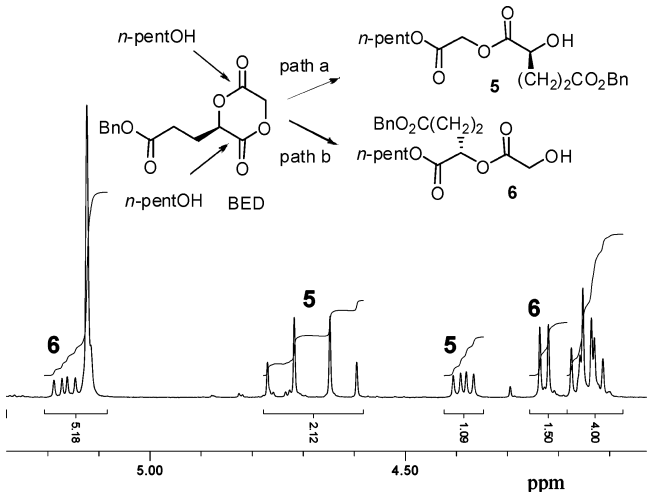


Figure 7. Ring-opening of BED with an excess of *n*-pentanol and TU^{Cy}/(−)-sparteine as catalyst ($[BED]_0/[n\text{-pentOH}]_0/[TU^{Cy}]/[(-)\text{-sparteine}]$ 1/10/1/1): ^1H NMR spectrum of the crude reaction mixture (4.0−5.5 ppm region).

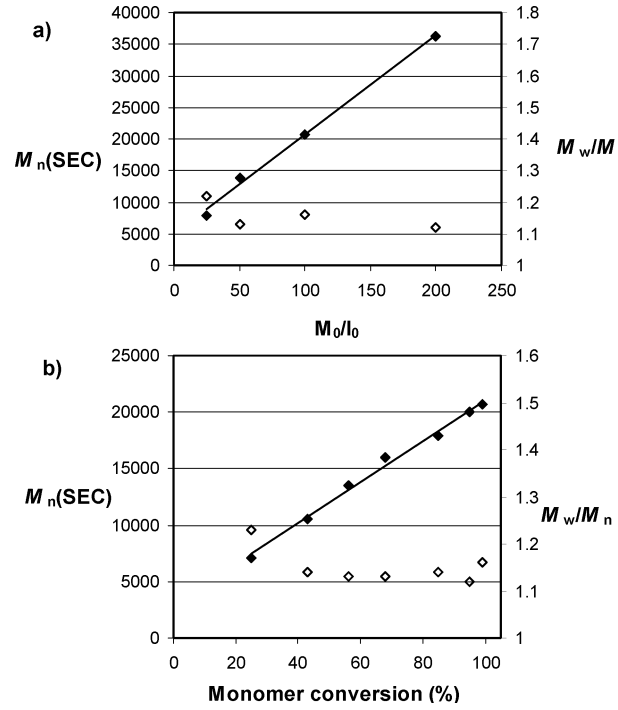


Figure 8. (a) Plot of number-average molar mass M_n (◆) and polydispersity index M_w/M_n (◇; estimated by size exclusion chromatography SEC) vs monomer to initiator ratio (CH_2Cl_2, 30 °C, $[n\text{-pentOH}]_0/[TU^{Cy}]/[(-)\text{-sparteine}]$ = 1/1/1 to 1/4/4, $[BED]_0$ = 1 mol/L). (b) Plot of M_n (◆) and M_w/M_n (◇; estimated by SEC) vs monomer conversion (estimated by ^1H NMR spectroscopy) (CH_2Cl_2, 30 °C, $[BED]_0/[n\text{-pentOH}]_0/[TU^{Cy}]/[(-)\text{-sparteine}]$ = 100/1/2/2, $[BED]_0$ = 1 mol/L).

Information for related plots associated with DMAP-catalyzed ROP of BED). These observations indicate that transesterification reactions do not occur to a significant extent, in agreement with that observed by MALDI-TOF mass spectrometry. The absence of undesirable side-reactions was further supported by first-order kinetic rate of polymerization, as deduced from ^1H NMR monitoring of monomer consumption (see Supporting Information). To estimate the exact molar mass of polyBED, two samples (prepared with monomer to initiator ratios of 25 and 100) were analyzed with a SEC apparatus equipped with a three-angle light scattering detector (using dn/dc = 0.1137 mL/g, as determined at 620 nm). In line with that expected from the presence of pendant lateral groups, the hydrodynamic volumes of polyBED are significantly higher than those of polylactide and, in fact, the RI response of polyBED only slightly deviates from that of the polystyrene standards in the range M_n 8000−30000 (correction factor = 0.95 for polyBED vs 0.58 for polylactide[25]).

In addition, the living character of the ROP of BED was supported by a second feed experiment (Figure 9). A polyBED with M_n = 7530 and M_w/M_n = 1.21 was first prepared by ROP of 25 equiv. of BED initiated with *n*-pentanol in the presence of 1 equiv of TU^{Cy}/(−)-sparteine. Polymerization was then restarted by addition of 25 equiv of monomer to yield a polyBED of about twice the number-average molar mass (M_n = 13130) and still low polydispersity index (M_w/M_n = 1.17).

Purification and Deprotection of PolyBED. DMAP and (−)-sparteine are easily removed from polyBED by acidic treatment, but trace amount of TU^{Cy} remained even after several precipitations in methanol. To facilitate the removal of the thiourea compound, TU^{NMe_2} tagged with a tertiary amine group[14b] was used as the catalyst. TU^{NMe_2} requires the presence of (−)-sparteine to promote efficiently the ROP of BED and notwithstanding, shows slightly lower activity than TU^{Cy}.

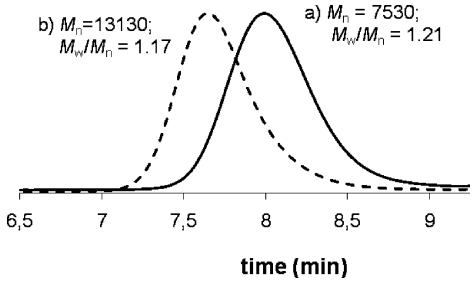


Figure 9. SEC traces of (a) polyBED DP_{th} = 25 (full line) and (b) polyBED DP_{th} = 50 (dashed line).

Table 2. Polymerization of BED Initiated by *n*-Pentanol and Catalyzed with TU^{NMe_2}/(−)-Sparteine[a]

	M_n (g/mol)[b]	M_w/M_n[b]
polymerization	11370	1.16
purification	11250	1.14
acetylation	12240	1.12
hydrogenolysis	10250	1.13

[a] Polymerizations of BED in CH_2Cl_2 solution at 30 °C with [BED]/[*n*-pentOH]$_0$ = 50, [*n*-pentOH]$_0$/[TU^{NMe_2}]/[(−)-sparteine] = 1/2/2, [BED]$_0$ = 1 mol/L). According to ^{1}H NMR spectroscopy, monomer conversion >98% after 180 min and DP = 48. [b] Number-average molar mass (M_n) and polydispersity index (M_w/M_n) obtained from size exclusion chromatography (in tetrahydrofuran, THF) using polystyrene standards.

Accordingly, a polymer sample of DP ∼50 was prepared in 180 min (Table 2). The two catalyst components TU^{NMe_2} and (−)-sparteine were completely removed from the polymer sample by acidic treatment with Amberlyst 15, as apparent from the ^{19}F and ^{1}H NMR spectra. Deprotection of the pendant functional groups was then achieved following the same protocol used for the polymer derived from gluOCA.[14c] The terminal hydroxyl groups were first acetylated with acetic anhydride to prevent competitive reactions (especially lactonization). The pendant carboxyl groups were then deprotected by hydrogenolysis using Pd/C as catalyst. The complete removal of the benzyl protecting groups was deduced from the disappearance of all of the aromatic signals from the ^{1}H NMR spectrum (Figure 10). In addition, SEC analyses showed that none of these three steps (purification by acidic treatment, acetylation, and hydrogenolysis) affected the polymer backbone both M_n and M_w/M_n remaining fairly constant.

Conclusion

The organo-catalysts DMAP or TU^{Cy}/(−)-sparteine combination were found to promote the efficient ring-opening polymerization of a functionalized 1,4-dioxan-2,5-dione, namely, (3*S*)-[(benzyloxycarbonyl)ethyl]-1,4-dioxan-2,5-dione BED. The polymerization takes place under mild conditions with a high level of control. The pendant functional group does not interfere with the polymerization and BED was even found to be slightly more reactive than lactide. Despite the strongly dissymmetric substitution pattern of the 1,4-dioxan-2,5-dione core, the ring-opening of BED occurs almost indifferently on either of the endocyclic ester groups so that the ensuing polyBED polymers present a random distribution of glycolic-[(benzyloxycarbonyl)ethyl]glycolic (gly-glu) units. The absence of undesirable transesterification reactions insures that the functional groups are distributed over the polymer backbone. After acetylation of the terminal OH groups and deprotection by hydrogenolysis, well-controlled poly(α-hydroxyacids) featuring pendant carboxylic acid groups are obtained.

The organo-catalyzed ROP of functionalized 1,4-dioxan-2,5-diones, thus, appear as an attractive route to poly(α-hydroxyacids) with pendant functional groups.[26] According to preliminary investigations, this approach is not limited to the two organo-catalytic systems reported here, and can be extrapolated to more active catalysts. The bicyclic guanidine DBU (1,8-diazabicyclo[5.4.0]-undec-7-ene)[27] was indeed found to polymerize 100 equivalents of BED within only 10 min at room temperature (with a catalyst loading of 0.2 mol % with respect to the alcohol initiator), leading to a polyBED of controlled molar mass (M_n = 22810 g/mol) and narrow distribution (M_w/M_n = 1.13).

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Supporting Information Available. (1) Chiral HPLC chromatograms of (*rac*-**3**) and (**3**), (*rac*-BED) and (BED); (2) Crystallographic data for BED; (3) MALDI-TOFF MS of a polyBED prepared by DMAP-catalyzed ROP of BED; (4) Plot of the number-average molar mass and molecular distribution versus monomer to initiator ratio and plot of the degree of polymerization versus monomer conversion for DMAP-catalyzed ROP of BED; (5) Semilogarithmic plot of BED conversion versus time; (6) ^{1}H NMR spectra for polyBED deprotection sequence; and (7) crystallographic information file for BED (CIF; CCDC 773604). This material is available free of charge via the Internet at http://pubs.acs.org.

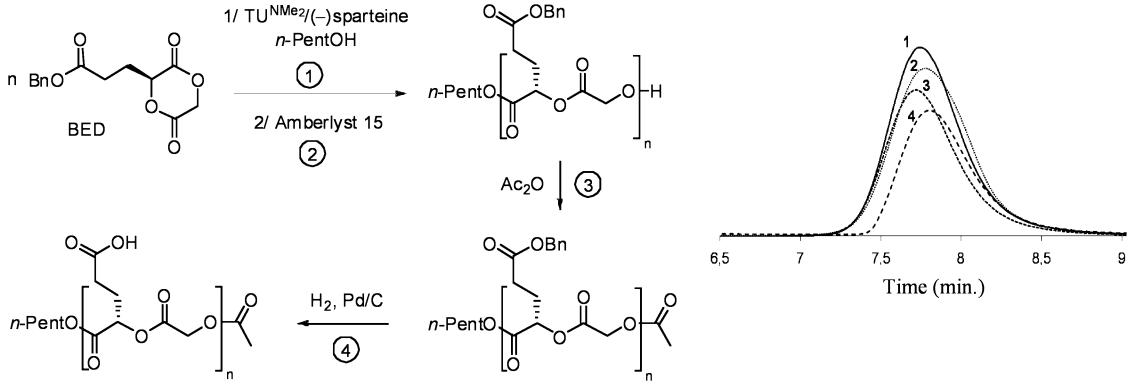

Figure 10. Reaction sequence for polyBED purification and deprotection; related SEC traces.

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