Synthesis of Amphiphilic Poly((*R*,*S*)-β-malic acid)-*graft*-poly(ϵ-caprolactone): "Grafting From" and "Grafting Through" Approaches

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ABSTRACT: The synthesis of novel amphiphilic graft copolyesters based on hydrophobic poly(ϵ-caprolactone) (PCL) segments grafted all along a hydrophilic poly((*R*,*S*)-β-malic acid) (PMLA) backbone is proposed. These PMLA-*g*-PCL graft copolymers have been prepared in a controlled way using either the "grafting through" or the "grafting from" technique. Both approaches involve two different well-controlled ring-opening polymerization (ROP) mechanisms: anionic ROP of β-lactones, i.e., benzyl or allyl β-malolactonate (MLABz or MLAAllyl), and living ROP of ϵ-caprolactone (CL) through a so-called coordination−insertion mechanism. The grafting through approach relies upon the anionic copolymerization of MLABz and ω-malolactonate−PCL macromonomer as initiated by potassium carboxylic acid salt in the presence of 1 equiv of 18-crown-6 ether. The second route follows a four-step synthesis involving the anionic ROP of MLABz and MLAAllyl, the conversion of allylic groups into pendant hydroxyl functions owing to a free-radical reaction with thioethanol in the presence of 2,2′-azobis(2-methylpropionitrile), and then the CL polymerization as initiated from these pendant −OH groups after adequate activation into aluminum alkoxide active species. Whatever the synthetic approach, the final step consists of the deprotection of the MLABz repeating units along the backbone via a soft catalytic hydrogenation reaction. The amphiphilic character of the so-prepared graft copolyesters has been evidenced by some preliminary interfacial tension experiments using the pendant drop method.

Introduction

For about 40 years, living ionic polymerization has been the main technique for the synthesis of controlled macromolecular architectures with narrow molecular weight distribution. Nowadays, despite the continuing development of new strategies for the synthesis of well-defined (co)polymers, ionic polymerization remains the most reliable method for the synthesis of a wide variety of model (co)polymers.[1] For instance, most block copolymers with complex molecular architectures and tunable properties are selectively prepared by ionic polymerization.[2] Similarly, graft copolymers can be obtained by ionic copolymerization through various pathways referred to as the "grafting onto", "grafting from", and "macromonomer" technique (also called "grafting through"). The grafting onto method involves the reaction between nucleophilic end groups of living "side" chains and electrophilic sites along the main polymer chain or backbone.[3] In the grafting from approach, the backbone behaves as a polymeric multi-initiation site from which side chains are polymerized. Finally, the macromonomer approach brings in the polymerization of a regular monomer and a preformed side chain bearing a polymerizable end group.

In response to the demand for new biocompatible and biodegradable materials based on synthetic (co)polymers,[4] poly(β-malic acid) (PMLA) is an attractive water-soluble aliphatic polyester with carboxylic acid pendant groups that has proven to be biocompatible and degradable in vivo into malic acid, a nontoxic molecule.[5,6] Guérin et al. reported on the anionic polymerization of a large range of protected and/or functional malolactonates (including optically active derivatives) yielding a high molecular weight (co)poly(β-malic acid)-based structure.[7] More recently, some of us reported on the controlled synthesis of well-defined biodegradable and biocompatible amphiphilic poly((*R*,*S*)-hexyl β-malolactonate)-*graft*-poly((*R*,*S*)-β-malic acid) graft copolymers (PMLAHex-*g*-PMLA) according to a four-step strategy.[8] It involves first the anionic ring-opening copolymerization of (*R*,*S*)-benzyloxypropyl β-malolactonate and (*R*,*S*)-hexyl β-malolactonate initiated by tetraethylammonium benzoate, followed by the selective removal of the benzyloxy function, which generated a free pendant hydroxyl function suitable to initiate the ring-opening polymerization (ROP) of (*R*,*S*)-benzyl β-malolactonate (MLABz). The final step relied upon the selective removal of benzyloxy protective groups of MLABz repeating units of the grafts.

This paper focuses on the controlled synthesis of novel amphiphilic biodegradable and biocompatible poly((*R*,*S*)-β-malic acid)-*graft*-poly(ϵ-caprolactone) graft copolymers (PMLA-*g*-PCL) as obtained by either the macromonomer or the grafting from technique. The former method consists of the anionic ring-opening copolymerization of MLABz and ω-malolactonate−PCL macromonomer (MLA−PCL) initiated by potassium 11-hydroxydodecanoate added with 1 equiv of 18-crown-6 ether

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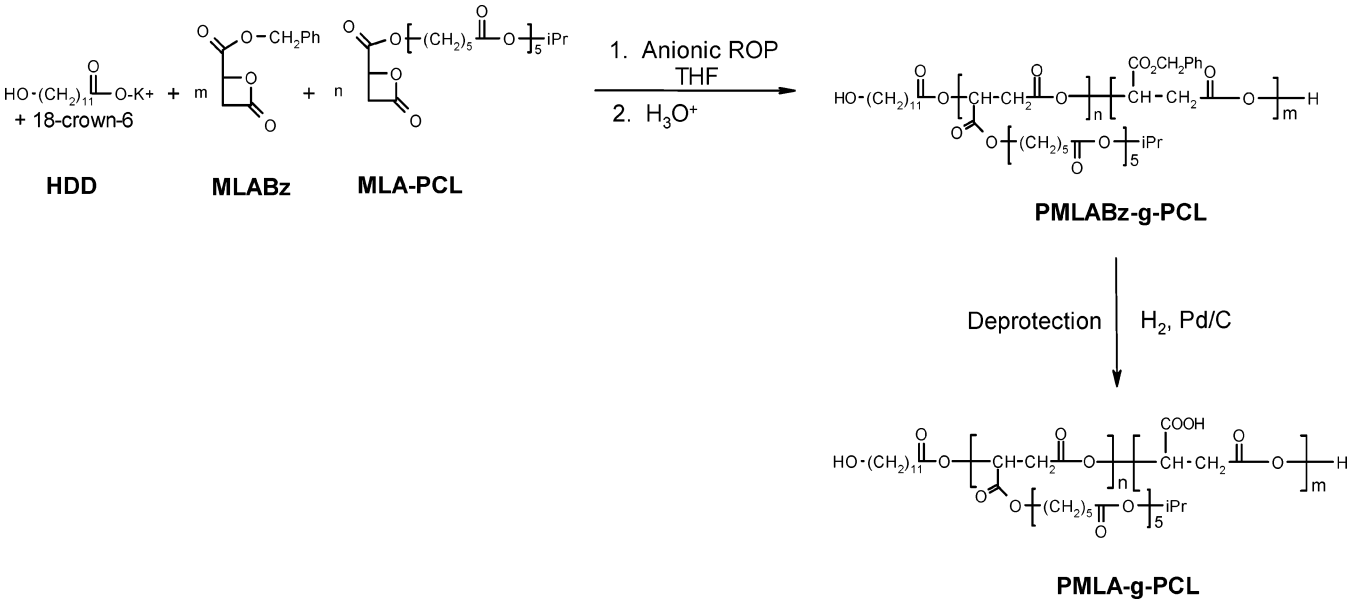
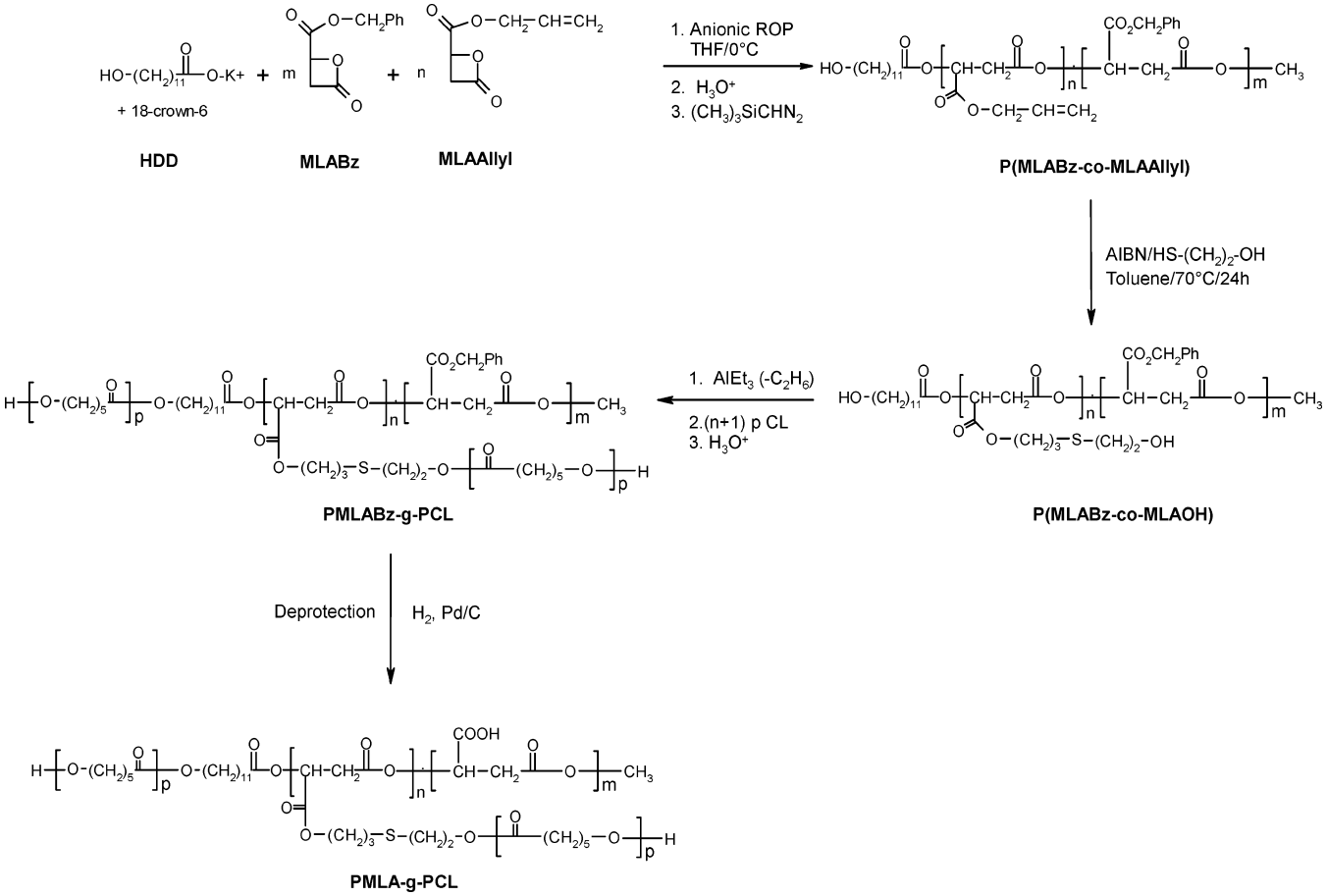
Scheme 1. Synthesis of PMLA-*g*-PCL Graft Copolymers through the Macromonomer Technique



Scheme 2. Synthesis of PMLA-*g*-PCL Graft Copolymers through the Grafting From Method



(HDD) in THF, followed by the selective removal of benzyloxy protective groups (Scheme 1). The second route follows a four-step strategy involving the anionic copolymerization of (*R*,*S*)-allyl β-malolactonate (MLAAllyl) and MLABz, followed by the conversion of allylic functions into pendant hydroxy groups able to initiate the ϵ-caprolactone (CL) ring-opening polymerization (ROP) after activation by $AlEt_3$, and finally the deprotection of the MLABz repeating units along the backbone (Scheme 2). To demonstrate the amphiphilic character of the resulting PMLA-*g*-PCL graft copolymers, preliminary interfacial tension measurements using the pendant drop method are also reported.

Experimental Section

Materials. MLABz and MLAAllyl were synthesized according to the aspartic route and purified as previously reported.[9] They were stored at −18 °C, then distilled under reduced pressure, and dried by three successive azeotropic distillations of toluene just before use. CL (Acros, 99%) was dried over

calcium hydride at room temperature for 48 h and then distilled under reduced pressure. Aluminum triisopropoxide ($Al(O^iPr)_3$; Aldrich, 98%) was purified by sublimation under reduced pressure and rapidly dissolved in dry toluene as previously described.[10] The accurate concentration of the initiator solution was determined by back complexiometric aqueous titration of Al^{3+} with standard solutions of Na_2EDTA and $ZnSO_4$ at pH 4.8.[10] 11-Hydroxydodecanoic acid (Aldrich, 97%) and 18-crown-6 (Acros, 99%) were dried by three successive azeotropic distillations of toluene. Potassium (Acros, 98%), naphthalene (Acros, 99%), trimethylsilyldiazomethane (2 N in hexane from Aldrich), methanol (Aldrich, 99.93%), 2-mercaptoethanol (Acros, 99%), 2,2′-azobis(2-methylpropionitrile) (Acros, 98%), *N*,*N*′-dicyclohexylcarbodiimide (Acros, 99%), 4-(dimethylamino)pyridine (Acros, 99%), triethylaluminum (1.8 M in toluene from Fluka), Pd/C (10 wt % from Aldrich), and hydrogen (Air Liquide, N50) were used without further purification. Toluene (Labscan, 99%) was dried by refluxing over CaH_2 and distilled under a nitrogen atmosphere. Tetrahydrofuran (Labscan, 99%) was first dried on 4 Å molecular sieves at room temperature for 72 h, then added to low molecular weight ω-lithium styrylpoly(styrene), and distilled under reduced pressure just before use.

Synthesis of MLA−PCL. The ROP of CL (1 g, 8.77×10^{-3} mol) was initiated by aluminum triisopropoxide in toluene solution (concentration 1 mol·L^{-1}, 1.75 mL) at 0 °C for an initial monomer concentration of 0.2 mol·L^{-1} (V_{tolu} = 42 mL) and an initial monomer-to-initiator molar ratio of 5. After 3 h, a few drops of HCl aqueous solution (0.1 mol·L^{-1}) was added, and the α-isopropoxy-ω-hydroxypoly(ϵ-caprolactone) (PCL-OH) was selectively recovered by precipitation in cold heptane (yield 97%). Aluminum residues were extracted as previously described (M_n = 630 g·mol^{-1}, M_w/M_n = 1.07 as determined by size exclusion chromatography using the Mark−Houwink parameters; see hereafter).[11] Malolactonic acid (MLA) was obtained by selective hydrogenation of MLABz in acetone at room temperature using 20 wt % Pd/C and hydrogen. After 7 h, the reaction medium was filtered on Celite, and MLA was recovered by flash distillation of the solvent (yield >99%). In a previously flame-dried and nitrogen-purged round-bottom flask, 177 mg (1.5×10^{-3} mol) of malolactonic acid and 155 mg (7.5×10^{-4} mol) of *N*,*N*′-dicyclohexylcarbodiimide were first dried under vacuum for 30 min, then solubilized in 8 mL of dry THF, and kept under a nitrogen atmosphere under vigorous stirring at room temperature for 6 h. The reaction medium rapidly turned white due to the formation of insoluble dicyclohexylurea. In a second previously flame-dried and nitrogen-purged round-bottom flask, 104 mg of PCL-OH (1.7×10^{-4} mol) and 38 mg of 4-(dimethylamino)pyridine (3.1×10^{-4} mol) were dried by three successive azeotropic distillations of toluene and dissolved in 8 mL of dry THF before being transferred into malolactonic anhydride suspension through a previously flamed and nitrogen-purged capillary. After a 48 h reaction time, the precipitated dicyclohexylurea was filtered off, and the macromonomer (MLA−PCL) was selectively recovered by precipitation into cold heptane (160 mL), filtered, and dried under reduced pressure at 40 °C until a constant weight was obtained (yield 62%, M_n = 730 g·mol^{-1}, M_w/M_n = 1.07). ^{1}H NMR ($CDCl_3$, δ (ppm); see Figure A in the Supporting Information for signal assignation): 0.8−0.9 (d, $6H_h$), 1.3−1.45 (m, $2H_c$), 1.45−1.9 (m, $4H_{b+d}$), 2.4 (t, $2H_e$), 3.55−3.9 (dd, $2H_{k+k'}$), 4−4.2 (t, $2H_f$), 4.25−4.4 (m, $3H_{g+a}$), 4.85 (t, $1H_j$).

Anionic Ring-Opening Polymerization of MLA−PCL. In a previously flame-dried and nitrogen-purged round-bottom flask, 1.0 g (7.8×10^{-3} mol) of naphthalene was mixed with 0.37 g (9.5×10^{-3} mol) of potassium and 39 mL of dry THF. After an overnight reaction, a deep green-colored solution of potassium naphthalene radical anion was obtained (concentration 0.2 mol·L^{-1}). In another previously flame-dried and nitrogen-purged round-bottom flask, 0.52 g (1.97×10^{-3} mol) of 18-crown-6 ether and 0.43 g (1.97×10^{-3} mol.) of 11-hydroxydodecanoic acid were dissolved in 10 mL of dry THF and then mixed with a stoichiometric amount of the potassium naphthalene radical anion in THF solution (10.0 mL, 1.97×10^{-3} mol, [HDD] = 0.1 mol·L^{-1}). The polymerization of MLA−PCL (4.7×10^{-2} g, 0.65×10^{-4} mol) was typically conducted in a previously flame-dried and nitrogen-purged round-bottom flask equipped with a three-way stopcock and a septum by initiation with the complex formed between potassium 11-hydroxydodecanoate and 18-crown-6 ether (0.1 mL, 1.0×10^{-5} mol) in THF (3 mL) at 0 °C. After 4 h, the polymerization was stopped by adding a few drops of aqueous HCl (0.1 mol·L^{-1}). After evaporation of the solvent, the product was dissolved in dichloromethane (20 mL) and extracted three times each with a saturated aqueous KCl solution (3 × 20 mL) and with deionized water (3 × 20 mL). Finally, the organic layer was poured into 8 volumes of cold heptane (160 mL). The polymer was recovered by filtration and dried under reduced pressure at 40 °C until a constant weight was obtained (yield 89%). Molecular parameters were determined by size exclusion chromatography (SEC) with reference to polystyrene standards (M_n(PS) = 8000 g·mol^{-1}, M_w/M_n = 1.4) by potentiometric titration of carboxylic acid end groups (M_n = 5400 g·mol^{-1}) and ^{1}H NMR ($CDCl_3$, δ (ppm); see Figure B in the Supporting Information for signal assignation): 1−1.2 (m, $18H_j$), 1.25 (m, $6H_h$), 1.6 (m, $4H_{b+d}$), 2.3 (t, $2H_e$), 3.5 (t, $2H_i$), 4.1 (t, $2H_f$).

Anionic Ring-Opening Copolymerization of MLABz and MLA−PCL. Copolymerization of MLABz (e.g., 0.33 g, 1.6 × 10^{-3} mol, 89 mol %) and MLA−PCL (e.g., 0.14 g, 1.9×10^{-4} mol, 11 mol %) was typically conducted in a previously flame-dried and nitrogen-purged round-bottom flask equipped with a three-way stopcock and a septum by initiation with the complex formed between potassium 11-hydroxydodecanoate and 18-crown-6 ether (0.5 mL, 5.0×10^{-5} mol) in THF (8 mL) at 0 °C for 3.5 h and then at room temperature for 20.5 h. After 24 h, the copolymerization was stopped by adding a few drops of aqueous HCl (0.1 mol·L^{-1}). After evaporation of the solvent, the product was dissolved in dichloromethane (20 mL) and extracted three times each with a saturated aqueous KCl solution (3 × 20 mL) and with deionized water (3 × 20 mL). Finally, the organic layer was poured into a large excess of cold heptane (160 mL). The copolymer was recovered by filtration and dried under reduced pressure at 40 °C until a constant weight was obtained (yield 99%). As determined by SEC with reference to polystyrene standards, M_n(PS) = 6300 g·mol^{-1} and M_w/M_n = 2.3. ^{1}H NMR ($CDCl_3$, δ (ppm); see Figure C in the Supporting Information for signal assignation): 1.0−1.2 (m, $6H_h$), 1.3−1.8 (m, $18H_j$+$6H_{b+c+d}$), 2.4 (t, $2H_e$), 2.7−3.1 (m, $2H_m$), 3.65 (t, $2H_i$), 4.1 (t, $2H_f$), 5.0−5.2 (m, $2H_n$), 5.5 (m, $1H_l$), 7.3 (s, $5H_o$).

Anionic Ring-Opening Copolymerization of MLABz and MLAAllyl. Copolymerization of MLABz (e.g., 0.86 g, 4.2 × 10^{-3} mol, 93 mol %) and MLAAllyl (e.g., 0.05 g, 3.2×10^{-4} mol, 7 mol %) was typically conducted in a previously flame-dried and nitrogen-purged round-bottom flask equipped with a three-way stopcock and a septum by initiation with the complex formed between potassium 11-hydroxydodecanoate and 18-crown-6 ether (0.9 mL, 9.0×10^{-5} mol) in THF (20 mL) at 0 °C. After 260 min, the copolymerization was stopped by adding a few drops of aqueous HCl (0.1 mol·L^{-1}). After evaporation of the solvent, the product was dissolved in dichloromethane (20 mL) and extracted three times each with a saturated aqueous KCl solution (3 × 20 mL) and with deionized water (3 × 20 mL). Finally, the organic layer was poured into 8 volumes of cold heptane (160 mL). The copolymer was selectively recovered by filtration and dried under reduced pressure at 40 °C until a constant weight was obtained (yield 92%). As determined by SEC with reference to polystyrene standards, M_n(PS) = 2900 g·mol^{-1} and M_w/M_n = 1.5. ^{1}H NMR ($CDCl_3$, δ (ppm)): 0.8−1.8 (m, $18H_b$), 2.3 (t, $2H_c$), 2.7−3.0 (m, $2H_e$), 3.6 (t, $2H_a$), 4.55 (m, $2H_h$), 5−5.2 (s, $2H_f$), 5.25 (s, $2H_j$), 5.55 (m, H_d), 5.8 (m, $1H_i$) and 7.3 (s, $5H_g$). M_n = 8100 g·mol^{-1} could be calculated from the ^{1}H NMR spectrum as discussed in the Results and Discussion.

Methylation of Poly(benzyl β-malolactonate-*co*-allyl β-malolactonate), α-Hydroxy, ω-Carboxylic Acid. In a previously flame-dried and nitrogen-purged round-bottom flask equipped with a three-way stopcock and a septum, 0.5 g of poly(benzyl β-malolactonate-*co*-allyl β-malolactonate), α-hydroxy, ω-carboxylic acid (6.3×10^{-5} mol, M_n(NMR) = 8100

g·mol^{-1}, $M_w/M_n = 1.5$) was dried by three successive azeotropic distillations of toluene (3 × 10 mL) and then dissolved in a mixture of 25 mL of toluene and 2.5 mL of anhydrous methanol. Trimethylsilyldiazomethane (5.7×10^{-4} mol, 0.3 mL, 9 equiv compared to the content of carboxylic acid end groups) was added while gas evolution was allowed through a connected oil valve. After 3 h, the reaction was stopped by the addition of a few drops of acetic acid in aqueous solution (0.1 mol·L^{-1}), and the volatiles were removed under reduced pressure. The copolymer was recovered by precipitation into 8 volumes of cold heptane (160 mL), filtered, and dried under reduced pressure at 40 °C until a constant weight was obtained (yield 86%). ^{1}H NMR ($CDCl_3$, δ (ppm); see Figure 4 for signal assignation): 0.8−1.8 (m, 18H$_b$), 2.3 (t, 2H$_c$), 2.7−3.0 (m, 2H$_e$), 3.5 (s, 3H$_k$), 3.6 (t, 2H$_a$), 4.55 (m, 2H$_h$), 5−5.2 (s, 2H$_f$), 5.25 (s, 2H$_j$), 5.5 (m, H$_d$), 5.8 (m, 1H$_i$) and 7.3 (s, 5H$_g$).

Conversion of Poly(benzyl *β*-malolactonate-*co*-allyl *β*-malolactonate) Allylic Functions to Hydroxyl Pendant Groups. In a previously flame-dried and nitrogen-purged round-bottom flask equipped with a three-way stopcock and a septum, 0.46 g of poly(benzyl *β*-malolactonate-*co*-allyl *β*-malolactonate), α-hydroxy, *ω*-methyloxycarbonyl (5.6×10^{-5} mol, M_n(NMR) = 8100 g·mol^{-1}, $M_w/M_n = 1.5$) was dried by three successive azeotropic distillations of toluene (3 × 10 mL) and mixed with 13 mg of 2,2′-azobis(2-methylpropionitrile) (AIBN) (7.8×10^{-5} mol). After 1 h under reduced pressure, the polymer/AIBN mixture was solubilized in 6 mL of dry toluene and mixed with 0.125 mL of mercaptoethanol (1.8×10^{-3} mol). The reaction was carried out at 70 °C for 24 h. Then the copolymer was recovered by precipitation into cold ethanol (60 mL) and dried under reduced pressure at 40 °C until a constant weight was obtained (yield 91%). As determined by SEC with reference to polystyrene standards, M_n(PS) = 2600 g·mol^{-1} and $M_w/M_n = 1.6$. ^{1}H NMR ($CDCl_3$, δ (ppm); see Figure 5 for signal assignation): 0.8−1.7 (m, 18H$_b$), 1.85 (m, 2H$_{i'}$), 2.45 (t, 2H$_c$), 2.5 (t, 2H$_{k'}$), 2.65 (t, 2H$_{j'}$), 2.8−3.1 (m, 2H$_e$), 3.4−3.9 (m, 2H$_a$+3H$_k$+2H$_{l'}$), 4.2 (m, 2H$_h$), 5.1−5.25 (s, 2H$_f$), 5.6 (m, H$_d$), and 7.3 (s, 5H$_g$).

Ring-Opening Polymerization of ϵ-Caprolactone Using Poly(benzyl *β*-malolactonate-*co*-propyl-3-thioethan-2-ol *β*-malolactonate) Macroinitiator. In a previously flame-dried and nitrogen-purged round-bottom flask equipped with a three-way stopcock and a septum, 0.425 g of poly(benzyl *β*-malolactonate-*co*-propyl-3-thioethan-2-ol *β*-malolactonate) (6.3×10^{-5} mol, $M_n = 6700$ g·mol^{-1}, $M_w/M_n = 1.6$) was dried by three successive azeotropic distillations of toluene (3 × 10 mL). Then the dried polymer was reacted with 1.2 equiv of triethylaluminum relative to the hydroxy content (2.3×10^{-4} mol, 11 mL) in toluene at 50 °C for 2 h while ethane evolved through a connected oil valve. After the mixture was cooled to room temperature, 2 mL of ϵ-caprolactone (1.8×10^{-2} mol) was added and polymerized for 72 h. The polymerization was stopped by adding a few drops of a HCl aqueous solution (0.1 mol·L^{-1}). Aluminum residues were removed by washing the organic phase three times with an aqueous solution of ethylenediaminetetraacetic acid (EDTA) buffered at pH 4.8 (0.1 mol·L^{-1}) (3 × 20 mL) and with deionized water (3 × 20 mL). The organic layer was finally poured into a large excess of cold heptane (160 mL). The copolymer was recovered by filtration and dried under reduced pressure at 40 °C until a constant weight was obtained (yield 94%). As determined by SEC with reference to polystyrene standards, M_n(PS) = 14000 g·mol^{-1} and $M_w/M_n = 1.8$. ^{1}H NMR ($CDCl_3$, δ (ppm)): 1.4 (m, 18H$_b$ + 2H$_{i'}$), 1.65−1.8 (t, 4H$_{PCL}$), 2.4 (t, 2H$_{PCL}$), 2.9 (m, 2H$_e$), 3.65 (t, 2H$_{a+k}$), 4.1 (t, 2H$_{PCL}$), 5.1 (s, 2H$_f$), 5.5 (m, H$_d$), 7.25 (s, 5H$_g$). $M_n = 6400$ g·mol^{-1} for the PCL blocks was calculated from the ^{1}H NMR spectrum as discussed in the Results and Discussion.

Removal of Benzyl Ester Protective Groups. In a round-bottom flask, 0.18 g of the graft copolymer above was dissolved in 250 mL of acetone at room temperature, and the resulting solution then mixed with 0.04 g of Pd/C (10 wt %). A continuous flow of hydrogen was bubbled into the solution for 10 h. After filtration through Celite, a clear copolymer solution was obtained. The solvent was evaporated under reduced pressure (10 mmHg) before recovery of the polymer by extensive drying at 40 °C under reduced pressure (yield 92%). ^{1}H NMR (CD_3COCD_3, δ (ppm)): 1.2−1.4 (m, 18H$_b$ + 2H$_{i'}$ + 6H), 1.55 (m, 4H$_{PCL}$), 2.3 (t, 2H$_{PCL}$), 2.9−3.1 (m, 2H$_e$), 3.55 (t, 2H$_a$), 4.1 (t, 2H$_{PCL}$), 5.5 (s, H$_d$).

Characterization. ^{1}H NMR (300 MHz) spectra were recorded using a Bruker AMX-300 apparatus at room temperature in $CDCl_3$ except as otherwise mentioned (30 mg/0.6 mL). SEC was performed in THF at 35 °C using a Polymer Laboratories liquid chromatograph equipped with a PL-DG802 degasser, an isocratic HPLC pump, LC 1120 (flow rate 1 mL/min), a Rheodin manual injection (loop volume 200 μL, solution concentration 2 mg/mL), a PL-DRI refractive index detector, and four columns: a PL gel 10 μm guard column and three PL gel mixed-B 10 μm columns (linear columns for separation of MW_{PS} ranging from 500 to 10^6). Molar masses and their distribution were calculated with reference to polystyrene standards. The surface tensions were determined using a drop shape analysis system, DSA 10 Mk2, equipped with a thermostated chamber and a circulator, Thermo Haake DC 10. Mass spectrometry measurements were performed on a Waters QToF2 apparatus equipped with an orthogonal electrospray ionization (ESI) source (Z-spray) operated in positive ion mode. *ω*-Hydroxy-PCL and MLA−PCL macromonomer were dissolved in acetonitrile to approximately achieve 10^{-4} mol·L^{-1} concentration, as estimated from the molar mass determined by ^{1}H NMR spectroscopy. The solutions were infused into the ESI source at a rate of 5 μL·min^{-1} with a Harvard syringe pump. Typical ESI conditions were capillary voltage 3.1 kV, cone voltage 80 V, source temperature 80°C, and desolvation temperature 120 °C. Dry nitrogen was used as the ESI gas. The quadrupole was set to pass ions from 100 to 3000 Th, and all ions were transmitted into the pusher region of the time-of-flight analyzer where they were mass-analyzed with a 1 s integration time. Data were acquired in continuum mode until acceptable averaged data were obtained.

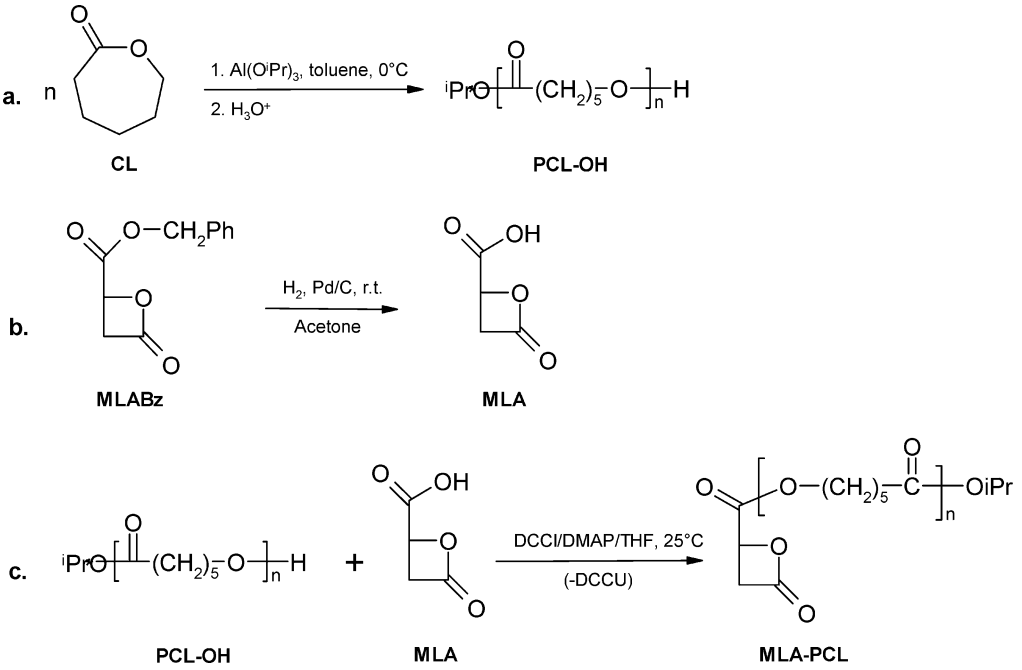
Results and Discussion

(Macro)monomer Preparation. MLABz and MLAAllyl have been synthesized through a well-established three-step procedure starting from racemic aspartic acid.[9] Global yields depend on the *β*-substituted *β*-malolactone reaching 30% and 60% for MLABz and MLAAllyl, respectively.

MLA−PCL was obtained by esterification of MLA with PCL-OH. Well-defined low molecular weight PCL-OH chains were synthesized by initiating the ROP of CL by Al(O^{i}Pr)$_3$ in toluene at 0 °C for an initial $[CL]_0/[Al(O^iPr)_3]_0$ molar ratio of 5 (eq a, Scheme 3). Under such prevailing conditions, the polymerization of CL was demonstrated to be perfectly living and characterized by an average number of active sites per aluminum atom close to 1.[12] After complete monomer conversion and hydrolysis of the aluminum alkoxide active sites, PCL-OH with a narrow polydispersity index was isolated. As determined by SEC by reference to a polystyrene standard calibration, using the Mark−Houwink relationship $[\eta] = KM^a$ for PS and PCL ($K_{PS} = 1.25 \times 10^{-4}$ dL g^{-1}, $a_{PS} = 0.707$, $K_{PCL} = 1.09 \times 10^{-3}$ dL g^{-1}, $a_{PCL} = 0.600$), a molecular weight of 630 and a polydispersity index of 1.07 were calculated. MLA was prepared by selective catalytic hydrogenation of MLABz under mild experimental conditions (see eq b, Scheme 3). Then esterification between PCL-OH and MLA was carried out using *N*,*N*′-dicyclohexylcarbodiimide (DCCI) and 4-(dimethylamino)pyridine (DMAP) as water scavenger and catalyst, respectively (eq c, Scheme 3).

As evidenced by ^{1}H NMR spectroscopy, PCL chains are quantitatively end-capped with a malolactonate moiety. Indeed, the signal corresponding to the α-

Scheme 3. Synthesis of MLA−PCL



hydroxymethylene-PCL end group (−CH_2OH) at 3.6 ppm completely disappeared (see Figure A given in the Supporting Information). A further confirmation for the quantitative esterification of the polyester hydroxyl end groups comes from spectrometry measurements. Figure 1 shows the ESI mass spectra of both PCL-OH (Figure 1A) and MLA−PCL (Figure 1B).

One of the main features of the ESI mass spectrum of PCL-OH is that the mass difference between two consecutive peaks is ca. 114.07, i.e., the molecular weight of the CL repeating unit, −C(O)$(CH_2)_5$O− (exact mass 114.0681). The most intense signal, detected at *m/z* 653.38, corresponds to ^{i}PrO[C(O)$(CH_2)_5$O]$_5$H·Na^+ cation, which possesses five CL repeating units together with isopropoxy and hydroxy end groups. This agrees with the expected macromolecular structure and the SEC data (M_n = 630 g·mol^{-1}, M_w/M_n = 1.07). In-depth analysis of the mass spectrum reveals the presence of additional mass distributions that could be identified as ^{i}PrO[C(O)$(CH_2)_5$O]$_5$H·K^+ (noted "a" in Figure 1A) and ^{i}PrO[C(O)$(CH_2)_5$O]$_5$H·H^+ (noted "b" in Figure 1A).

In the case of MLA−PCL macromonomer, doubly charged species are clearly detected since the mass difference between two consecutive signals reaches ca. 57.04 (114.0681/2 = 57.034). The maximum in the ESI mass spectrum appears at *m/z* 729.42, but it could not be unambiguously attributed as the molecular ion distribution of doubly charged species is strongly dependent on the oligomer molar mass. In other words, oligomers of lower molar mass can carry fewer charges than those of higher molar mass.[13] Such a behavior upon ESI ionization probably arises from the covalent binding of the malolactonate moiety at the PCL chain extremity. Regardless of the assignment of specific signals, the most important feature is that no residual PCL-OH could be detected in the ESI mass spectrum (neither singly or doubly charged species), thus confirming the completion of the esterification reaction as attested by the following polymerization experiments.

Synthesis of PMLA-*g*-PCL through the Macromonomer Technique. Before study of the graft copolymer synthesis, the efficiency of MLA−PCL macromonomer to homopolymerize and thus the reactivity of the terminal malolactonate moiety toward anionic ROP have been investigated. The anionic polymerization of MLA−PCL was carried out according to previously established experimental conditions that strongly limit the occurrence of undesirable transfer and termination reactions by proton abstraction.[14] By reducing both the polymerization temperature to 0 °C and the initial concentration in monomer to 0.2 mol·L^{-1}, the polymerization of MLABz as initiated in THF by potassium 11-hydroxydodecanoate in the presence of HDD is "living" and proceeds selectively through the *O*-alkyl cleavage of the endocyclic ester bond of malolactonate monomer. Accordingly, the anionic homopolymerization of MLA−PCL macromonomer (0.2 mol·L^{-1}) was initiated by HDD in THF at 0 °C for an initial monomer-to-initiator molar ratio of 7 (DP_{theor} = 7). After 4 h of reaction time, the ^{1}H NMR spectrum of the polymerization product is characterized by the disappearance of cyclic malolactonate methine protons at 4.9 ppm (see Figure B in the Supporting Information). Complete consumption of the macromonomer was further confirmed by SEC. Indeed the molecular weight distribution of the polymerization product is monomodal and shifted to lower retention volume compared to that of MLA−PCL macromonomer (Figure 2). Assuming the selective formation of poly(MLA−PCL) α-hydroxydodecanoate, ω-carboxylic acid, nonaqueous potentiometric titration of carboxylic acid functions has been carried out to determine the average molar mass. P(MLA−PCL) was solubilized in a toluene/methanol (8/2) solution at room temperature and titrated by tetramethylammonium hydroxide solution. The resulting average molar mass (M_n) of 5400 g·mol^{-1} agrees very well with the theoretical M_n of 5300 g·mol^{-1} ($M_{n,theor}$ = ((DP_{theor})($M_{n,MLA-PCL}$) + MW_{HDA}, where $M_{n,MLA-PCL}$ and MW_{HDA} are the molar masses of MLA−PCL (M_n = 730 g·mol^{-1}, as determined by ESI mass spectrometry (ESI-MS) analysis) and 11-hydroxydodecanoic acid, respectively). Therefore, the cyclic malolactonate moiety is selectively and quantitatively fixed at the PCL chain end group and, more importantly, is active in anionic ring-opening polymerization.

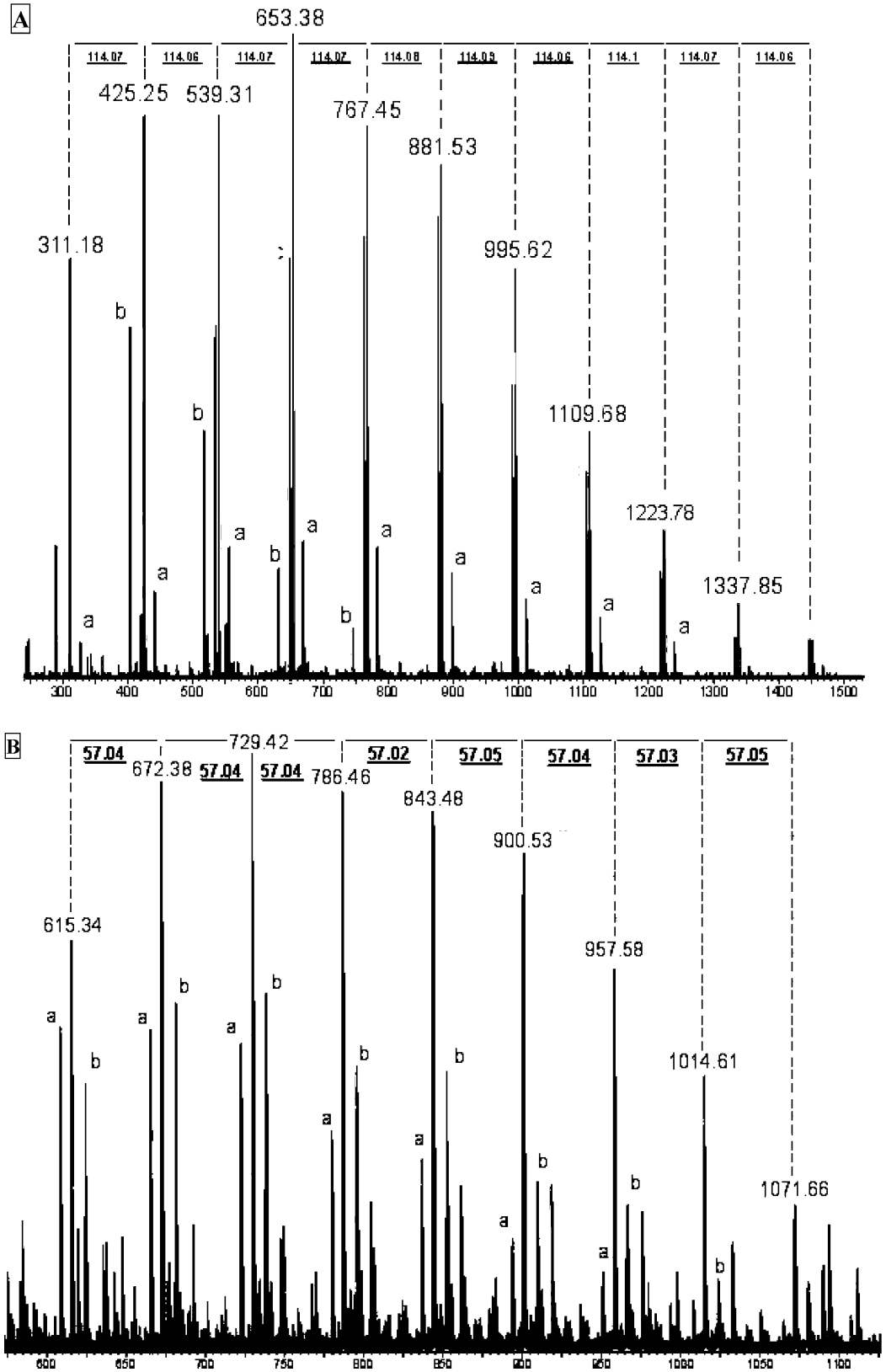


Figure 1. ESI mass spectra (Waters QToF2) of PCL-OH (A) and MLA−PCL (B) used as intermediates in the synthesis of poly((*R*,*S*)-β-malic acid)-*graft*-poly(ϵ-caprolactone) graft copolymers through the macromonomer technique (1 mg/1 mL in acetonitrile).

Accordingly, the next step can rely upon the investigation of the graft copolyester synthesis.

According to the two-step strategy depicted in Scheme 1, poly((*R*,*S*)-benzyl β-malolactonate)-*graft*-poly(ϵ-caprolactone) graft copolymers (PMLABz-*g*-PCL) of various compositions were synthesized by initiating the anionic ring-opeining copolymerization of a mixture of MLABz and MLA−PCL by HDD in THF for an initial comonomer-to-initiator ratio of 40 and an initial total comonomer concentration ($[MLABz + MLA-PCL]_0$) of 0.2 mol·L^{-1} (Table 1). As already mentioned, to drastically reduce the occurrence of undesirable transfer and termination reactions, copolymerizations were initiated at 0 °C. Due to the quite long reaction time required

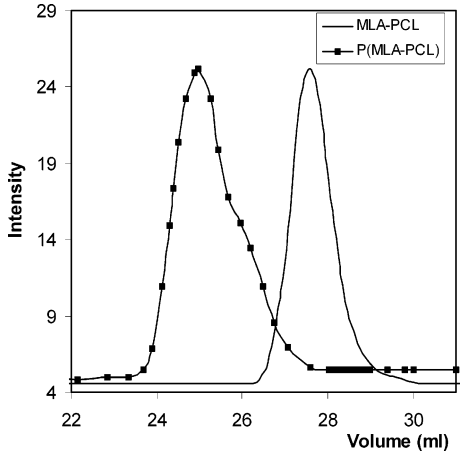


Figure 2. SEC traces of MLA−PCL (full line) ($M_{n,PS}$ = 850, M_w/M_n = 1.07) and its homopolymer P(MLA−PCL) as obtained by anionic polymerization (square full line) ($M_{n,PS}$ = 8000, M_w/M_n = 1.4).

Table 1. Molecular Characteristics of PMLABz-*g*-PCL As Obtained by Ring-Opening Copolymerization of MLABz and MLA−PCL Initiated by Potassium 11-Hydroxydodecanoate Mixed with HDD in THF for [MLABz + MLA−PCL]$_0$ = 0.2 mol·L^{-1}and [MLABz + MLA−PCL]$_0$/[HDD] = 40

	[MLABz]/[MLA−PCL]					
entry	at the start[a]	copolymer[b]	reaction time (h)	yield (%)	$M_{n,exp}$[c] (g·mol^{-1})	M_w/M_n[c]
1	66/1	21/1	3.5	72	2000	1.3
2	49/1	19/1	3.5	72	2000	1.4
3	8/1	9/1	25	99	6300	2.3

[a] Initial MLABz/MLA−PCL macromonomer molar ratio. [b] MLABz/MLA−PCL macromonomer molar ratio as determined by ^{1}H NMR from the relative intensity of the methylene oxycarbonyl protons of MLABz and the methylene protons of PCL. [c] As determined by SEC with reference to polystyrene standards.

for higher MLA−PCL molar fraction in the feed (entry 3 in Table 1), the temperature was allowed to increase to room temperature after ca. 3.5 h at 0 °C. These operating conditions directly affect the molecular weight distribution of the copolymer, which broadens. The copolymer composition was determined by ^{1}H NMR spectroscopy from the relative intensity of CL repeating methylene unit protons at 4.1 ppm (−$CO_2CH_2(CH_2)_4$−) and the methylene protons of the MLABz repeating units at 5.1 ppm (−$CO_2CH_2C_6H_5$). It comes out that the resulting graft copolymers are characterized by a higher MLA−PCL macromonomer content compared to that of the feed, indicating that MLA−PCL reacts faster than MLABz in such experimental conditions.

The second step in the synthesis of the amphiphilic PMLA-*g*-PCL graft copolymers consists of the catalytic hydrogenation of benzyl ester functions anchored all along the poly(malolactonate) backbone (see Table 2).[14,15] ^{1}H NMR spectra of the as-obtained copolymers recorded in $(CD_3)_2CO$ show the complete disappearance of benzylic protons, i.e., no signal from 6 to 9 ppm, attesting for the quantitative deprotection reactions (see Figure 3). As previously reported,[14] the generated carboxylic acid functions form strong hydrogen bonding with the ester carbonyl functions, at least in a solvent such as acetone-d_6 ($(CD_3)_2CO$), so that no resonance signal typical of carboxylic acid protons around 10 ppm could be detected at low field.

Table 2. Molecular Characteristics of Amphiphilic PMLA-*g*-PCL Obtained by the Macromonomer Technique

entry	sample	f_{PCL}(NMR)[a] (%)	F_{PCL}(NMR)[b] (%)
1	PMLA-*g*-PCL**1**	4.5	15.5
2	PMLA-*g*-PCL**2**	5.0	16.0
3	PMLA-*g*-PCL**3**	10.0	28.7

[a] f_{PCL}(NMR) = experimental PCL molar fraction in PMLA-*g*-PCL graft copolymers = $100[I_{4.1}/(I_{4.1} + 2I_{5.5})]$ (see Figure 3). [b] F_{PCL}(NMR) = experimental PCL weight fraction in PMLA-*g*-PCL grafts copolymers = $[M_{n,MLA-PCL}(f_{PCL}(2I_{4.2})/100I_{3.6})]/[(M_{n,MLA-PCL}-(f_{PCL}(2I_{4.2})/100I_{3.6})) + (206(1 - f_{PCL})(2I_{4.2})/100I_{3.6})]$.

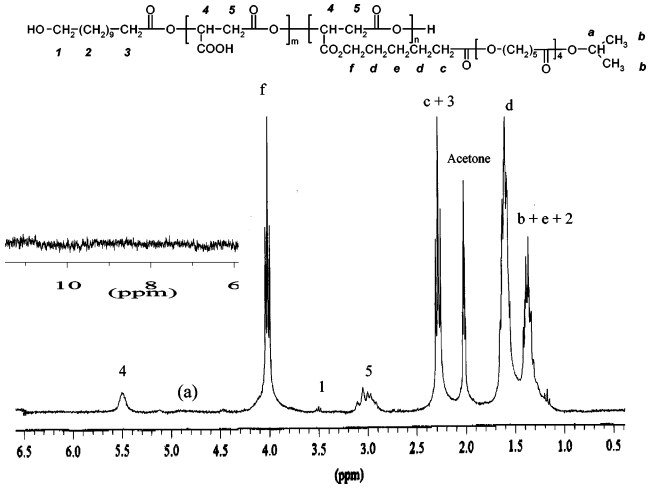


Figure 3. ^{1}H NMR spectrum in $(CD_3)_2CO$ of PMLA-*g*-PCL obtained by catalytic hydrogenation of PMLABz-*g*-PCL (entry 3, Table 2).

Synthesis of PMLA-*g*-PCL through the Grafting From Technique. As shown in Scheme 2, the first step in the synthesis of PMLA-*g*-PCL graft copolymers through the grafting from technique involves the anionic ring-opening copolymerization of MLAAllyl and MLABz using HDD as initiator in THF at 0 °C for a comonomer concentration of 0.2 mol·L^{-1}. After selective derivatization of the carboxylic acid end groups in methyl ester,[14] the second step consists of the conversion of pendant allylic functions into hydroxy groups by reaction with mercaptoethanol in the presence of AIBN in toluene at 70 °C. The third step implies the controlled ROP of CL initiated by the as-formed pendant hydroxyl functions, previously activated by $AlEt_3$. The fourth and last step corresponds to the selective deprotection of the benzyl ester groups by catalytic hydrogenation.

Two poly(benzyl β-malolactonate-*co*-allyl malolactonate) (P(MLABz-*co*-MLAAllyl)) graft copolymers were synthesized from different initial comonomer molar fractions, while the targeted copolymer molar mass was kept constant ($M_{n,theor}$ = 10000 g·mol^{-1}) (Table 3). Assuming that each chain of P(MLABz-*co*-MLAAllyl) is end-capped by a hydroxyl group at one end and a carboxylic acid function at the other chain end, the experimental molar mass can be calculated by ^{1}H NMR spectroscopy ($M_{n,exp}$) from the relative intensity of the methine protons within the main polyester chain at 5.5 ppm (−*CH*(COOR)CH_2COO−) and the terminal methylene protons at 0.8−1.7 ppm ($HOCH_2$*(CH_2)$_9$*CH_2-COO−). The molar composition of each copolymer was determined from the relative intensity of α-vinylic methylene protons at 4.6 ppm (−CO_2CH_2CH═CH_2) and the methylene protons of the poly(malolactonate) repeating units at 2.9 ppm (−CH(CO_2R)CH_2CO_2−). The

Table 3. Molecular Characteristics of P(MLABz-*co*-MLAAllyl) Synthesized by Ring-Opening Copolymerization of MLABz and MLAAllyl by Potassium 11-Hydroxydodecanoate Mixed with 18-Crown-6 Ether in THF at 0 °C for [MLABz + MLAAllyl]$_0$ = 0.2 mol·L^{-1}

entry	polym time (min)	convn[a] (%)	$M_{n,theor}$[b] (g·mol^{-1})	[MLABz]/[MLAAllyl] at the start[c]	[MLABz]/[MLAAllyl] co-polymer[d]	$M_{n,exp}$[e] (g·mol^{-1})	M_w/M_n[f]
1	260	92	9200	14/1	13/1	8100	1.5
2	340	100	10000	8/1	8/1	8400	1.2

[a] Global comonomer conversion as determined by gravimetry. [b] $M_{n,theor}$ = [MLABz + MLAAllyl]$_0$/[HDD]$_0$(convn)(MW$_{MLABz}$$f_{MLABz}$ + MW$_{MLAAllyl}$$f_{MLAAllyl}$) + MW$_{HDD}$, where f_{MLABz} and $f_{MLAAllyl}$ are the molar fractions of MLABz and MLAAllyl in the copolymer, respectively, and MW$_{MLABz}$ and MW$_{MLAAllyl}$ are the molar masses of MLABz and MLAAllyl, respectively. [c] Initial MLABz/MLAAllyl molar ratio. [d] MLABz/MLAAllyl molar ratio as determined by ^{1}H NMR from the relative intensity of the methylene oxycarbonyl protons of MLABz and the α-vinylic methylene protons of MLAAllyl. [e] As determined by ^{1}H NMR spectroscopy: $M_{n,exp}$ = [9I_3/$I_{0.8-1.7}$][($I_{4.6}$/I_3)MW$_{MLAAllyl}$ + (1 − $I_{4.6}$/I_3)MW$_{MLABz}$]. [f] As determined by SEC using PS standards.

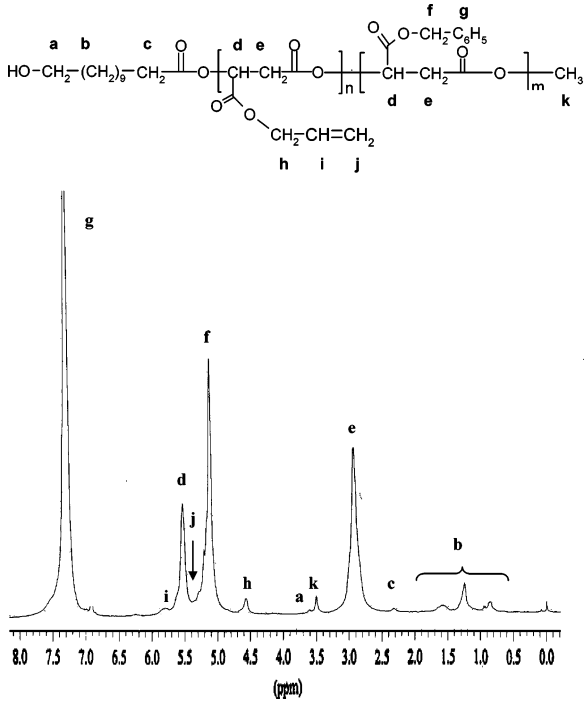


Figure 4. ^{1}H NMR spectrum in $CDCl_3$ of P(MLABz-*co*-MLAAllyl) as obtained by anionic ring-opening copolymerization of (*R*,*S*)-benzyl β-malolactonate and (*R*,*S*)-allyl β-malolactonate, followed by methylation of carboxylic end groups (entry 1, Table 4)

comonomer compositions at the start and in the copolymers are very close to each other, while the experimental molar masses of the copolymers are only slightly lower than predicted values. This can be explained by the inherent experimental error of ^{1}H NMR spectroscopy. The monomodal molecular weight distributions are quite narrow according to SEC.

To avoid undesirable side reaction with triethylaluminum that will be used for activating the CL ROP in a next step, the carboxylic acid end groups of P(MLABz-*co*-MLAAllyl) chains were reacted first with an excess of trimethylsilyldiazomethane for 1 h at room temperature in toluene/methanol (9/1).[14] Figure 4 shows the ^{1}H NMR spectrum of the resulting α-hydroxy, ω-methyl ester P(MLABz-*co*-MLAAllyl) (entry 1 in Table 4) displaying a typical signal at 3.5 ppm characteristic of the ω-methyl ester end groups (H_k).

Table 4. Molecular Characteristics of P(MLABz-*co*-MLAO-H) Copolymers As Obtained by Reaction of P(MLABz-*co*-MLAAllyl) with Mercaptoethanol Using AIBN in Toluene at 70°C for 24 h[a]

entry	sample	$M_{n,exp}$[b] (g·mol^{-1})	$f_{MLAAllyl}$[b] (%)	f_{MLAOH}[b] (%)	M_w/M_n[c]
1	P(MLABz-*co*-MLAAllyl) **1**	8100	7.6		1.5
2	P(MLABz-*co*-MLAOH) **1**	7000		5.1	1.6
3	P(MLABz-*co*-MLAAllyl) **2**	8400	13		1.2
4	P(MLABz-*co*-MLAOH) **2**	9200		13	1.3

[a] Entries 1 and 3 refer to entries 1 and 2, respectively, in Table 3, i.e., to the copolymers before methylation). [b] As determined by ^{1}H NMR spectroscopy: M_n(P(MLABz-*co*-MLAAllyl)) = (9I_e/I_b)[(I_h/I_e)MW$_{MLAAllyl}$ + (1 − I_h/I_e)MW$_{MLABz}$]; M_n(P(MLABz-*co*-MLAOH)) = (2I_d/I_c)[(I_i/2I_d)MW$_{MLAOH}$ + (1 − I_i/2I_d)MW$_{MLABz}$]; $f_{MLAAllyl}$ = 100I_h/I_e and f_{MLAOH} = 100I_i/2I_d. [c] As determined by SEC using PS standards.

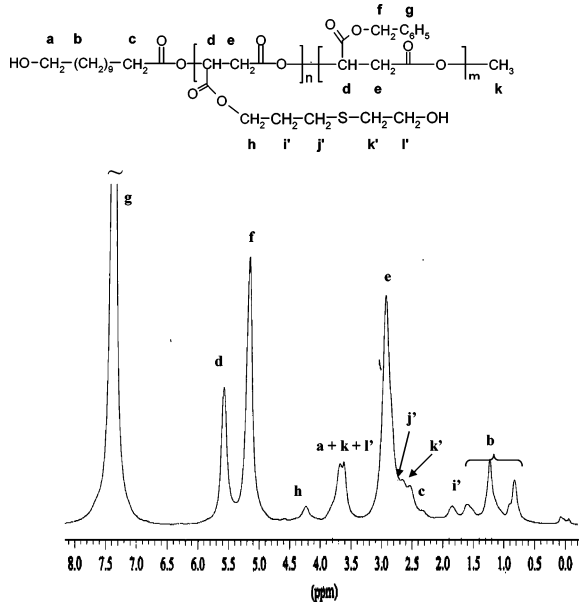


Figure 5. ^{1}H NMR spectrum in $CDCl_3$ of P(MLABz-*co*-MLA-OH) (entry 4 in Table 4).

The second step involves the conversion of allylic functions into hydroxyl ones by reaction with mercaptoethanol, leading to poly(benzyl β-malolactonate-*co*-propyl-3-thioethan-2-ol β-malolactonate) random copolymers (P(MLABz-*co*-MLA-OH)) (entries 2 and 4 in Table 4). This reaction was carried out in toluene at 70 °C for 24 h using AIBN as radical promoter.[16,17] ^{1}H NMR spectroscopy attests for the completion of the homolytic reaction by the disappearance of allylic protons at 5.8 and 5.35 ppm (H_i and H_j in Figure 4) to the benefit of α-hydroxyl methylene ($H_{l'}$ in Figure 5) and α-thioether methylene ($H_{k'}$ in Figure 5) protons from the short lateral chains at 3.6 and 2.6 ppm, respectively, and by the shift of methylene α-allylic protons (H_h) from 4.55 down to 4.3 ppm. Taking into account the inherent experimental error of ^{1}H NMR spectroscopy, the conversion of allylic functions into hydroxy groups does not detrimentally affect the molecular parameters (M_n and M_w/M_n) of the so-obtained copolymers (Table 4).

In the next step, the polymerization of CL was initiated by the hydroxy functions attached all along the poly(malonate) backbone after adequate activation by adding a slight excess of triethylaluminum ([AlEt$_3$]$_0$/

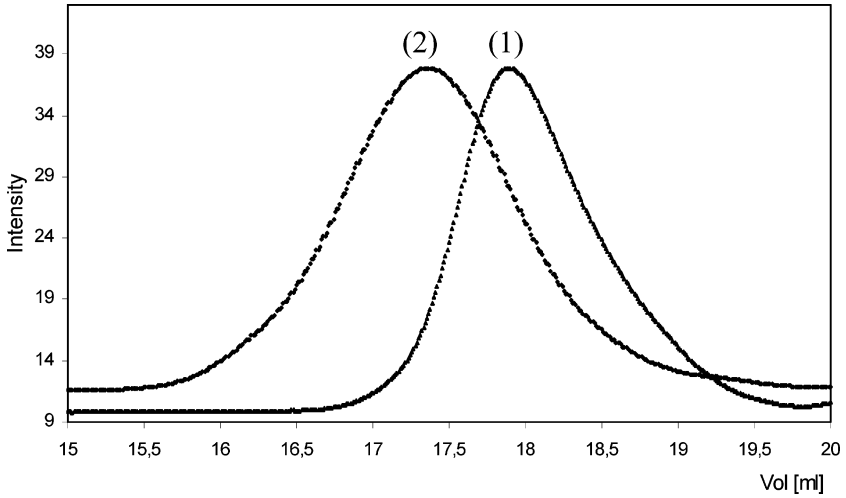


Figure 6. SEC traces of P(MLABz-*co*-MLAOH) **2** (1) (entry 4 in Table 4) and polymalolactonate-*graft*-poly(ϵ-caprolactone) graft copolymer as obtained by the grafting from technique, PMLABz-*g*-PCL **2** (2) (entry 2 in Table 5).

Table 5. Molecular Characteristics of PMLABz-*g*-PCL Synthesized by Ring-Opening Polymerization of CL from P(MLABz-*co*-MLAOH)[a]

entry	sample	macroinitiator backbone	$[CL]_0/[OH]_0$	$f_{PCL,theor}$[b] (%)	$f_{PCL,exp}$[c] (%)	$M_{n,PCL,exp}$[c] (g·mol^{-1})	$M_{n,copo}$[d] (g·mol^{-1})	M_w/M_n[d]
1	PMLABz-*g*-PCL **1**	P(MLABz-*co*-MLAOH) **1**	142	89.7	93.7	6400	14000	1.8
2	PMLABz-*g*-PCL **2**	P(MLABz-*co*-MLAOH) **2**	34	66.0	86.4	2200	3700	1.6

[a] Entries 1 and 2 refer to entries 2 and 4 in Table 4. [b] Theoretical molar fraction of PCL. [c] The experimental PCL molar fraction ($f_{PCL,exp}$) and molar mass ($M_{n,PCL,exp}$) have been determined from ^{1}H NMR spectra: $f_{PCL,exp} = 100[I_{4.1}/(I_{4.1} + I_{5.1})]$ and $M_{n,PCL,exp} = 114.14(I_{4.1}/I_{3.6})$. [d] As determined by SEC using PS standards.

$[OH]_0 = 1.2$). The lactone ROP has been carried out in toluene at room temperature for an initial CL concentration of 1 mol·L^{-1} and for $[CL]_0/[OH]_0$ initial molar ratios of 142 and 34 starting from P(MLABz-*co*-MLAOH) copolymers **1** and **2**, respectively. After a 72 h reaction time, a few drops of a HCl aqueous solution (0.1 mol·L^{-1}) was added, and PMLABz-*g*-PCL graft copolymers were recovered by precipitation from a large excess of heptane. The grafting of the PCL segments onto the P(MLABz-*co*-MLAOH) copolymers was attested by SEC, which, for instance, shows the shift of the trace of the PMLABz-*g*-PCL **2** graft copolymer to lower elution volume compared to that of P(MLABz-*co*-MLAOH) **2** copolyester (Figure 6). Again ^{1}H NMR spectra allowed determination of the copolymer composition and PCL graft molar masses (Table 5).

The last step in the synthesis of amphiphilic PMLA-*g*-PCL graft copolymers relies upon the selective catalytic hydrogenation of benzyl ester functions. As evidenced by ^{1}H NMR spectroscopy from the relative intensity of benzyloxycarbonyl protons at 7.3 ppm and the methine repetitive protons at 5.55 ppm, only 40% of the protective groups could be removed, even under intensive hydrogenation for 20 h. Compared to the data related to the graft copolymers obtained by the macromonomer technique, such a behavior typically observed for PMLABz-*g*-PCL graft copolymer characterized by a much higher grafting density can only be explained by some screening effect of PCL grafts toward the heterogeneous catalytic hydrogenation, limiting therefore the access to the benzylic moieties along the main backbone.

Preliminary Interfacial Tension Measurements. The amphiphilic character of these new biocompatible PMLA-*g*-PCL graft copolymers is evidenced by interfacial tension measurements. Purposely and as a representative example, a 2 g·L^{-1} solution of PMLA-*g*-PCL **3** (entry 3 in Table 2) in chloroform was dipped into Millipore Milli-RO water. Figure 7 shows the time evolution of the chloroform/water interfacial tension (IFT) induced by the investigated graft copolymer. At 25 °C, the IFT values drop from 29 to 4 mN/m, demonstrating the tensioactive properties of this new type of amphiphilic graft copolymers.

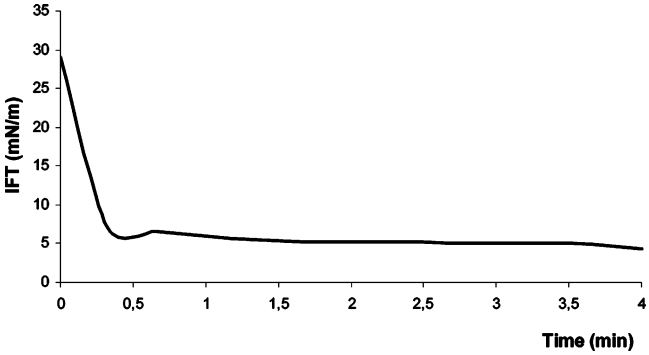


Figure 7. Time dependence of the IFT of a 2 g·L^{-1} PMLA-*g*-PCL **3** chloroform solution in water at 25 °C (entry 3 in Table 2).

In conclusion, we have reported two new synthetic approaches for grafting hydrophobic poly(ϵ-caprolactone) chains onto a highly hydrophilic poly((*R*,*S*)-β-malic acid) backbone. Both the grafting from and grafting through (i.e., macromonomer) techniques were successful and allowed for controlling the graft copolyester composition and molecular weight. As expected, these graft copolyesters display amphiphilic properties as attested by preliminary interfacial tension measurements. The tensioactive behavior of these new graft copolymers and their ability to form micelles in aqueous media are under current investigation and will be the subject of a forthcoming paper.

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Supporting Information Available: ^{1}H NMR spectra of MLA−PCL, poly(MLA−PCL), and PMLABz-*g*-PCL (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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