Synthesis and Characterization of New Malolactonate Polymers and Copolymers for Biomedical Applications

Ranieri Bizzarri,[†] Federica Chiellini,[†] Roberto Solaro,[†] Emo Chiellini,*[,†] Sandrine Cammas-Marion,[‡] and Philippe Guerin[‡]

Department of Chemistry and Industrial Chemistry, University of Pisa, via Risorgimento 35, 56126 Pisa, Italy; and Laboratoire de Recherche sur les Polymeres, UMR C7581 CNRS, Université Paris Val de Marne, 2 à 4 rue Henry Dunant, 94320 Thiais, France

Received July 4, 2001; Revised Manuscript Received October 16, 2001

ABSTRACT: A new class of malolactonate polymers and copolymers were synthesized, starting from the corresponding lactones, and then characterized. Different lateral groups were selected for these polyesters to achieve a wide range of materials characteristics and possible biological recognition. The monomers were prepared according to two established procedures, which gave rather good overall yields. The polymers were obtained by the anionic ring-opening polymerization of the corresponding four-member ring monomers in the presence of a quaternary ammonium salt as the initiator. Final macromolecular and thermal characteristics were in agreement with the designed monomer structures. Molecular weights in the range 4−20 kDa were obtained, as a result of chain transfer reactions. The prepared polyesters displayed stability up to 200 °C, and, when tested in preliminary cell culture experiments, provided indications for future applications in the biomedical field.

Introduction

Bioerodible and biodegradable polymers are recognized as useful materials for many important biomedical applications. In the drug delivery field, for instance, they facilitate the excretion of the releasing device after overall drug depletion, thus also allowing for a predetermined release rate, which is frequently controlled by the polymer degradation pathway.[1] In tissue engineering, a quickly developing branch of biomedicine that attempts to solve the dramatic problem of tissue loss or organ failure,[2] degradable materials provide polymer scaffolds where the transplanted cells can remodel their intrinsic tissue superstructural organization and hence ultimately lead to the desirable 3D structure and physiological functionality of a regenerated organ.[3,4]

However, the use of biodegradable polymers requires careful investigation into their interaction and compatibility with the human organism, to avoid tissue damage and immunogenic phenomena due to both the whole polymeric matrix and its low molecular weight degradation products.[5] To date, natural or artificial polyesters constitute the most developed class of biomaterials because of their excellent mechanical properties and good biocompatibility.[6−9] Nevertheless, the strongly hydrophobic nature and lack of available reactive sites of most polyesters [poly(lactic acid), poly(glycolic acid), poly(lactic acid-*co*-glycolic acid), and poly(ϵ-caprolactone)] used for bioapplications require special synthetic methods to realize true biologically activated materials.[10,11]

Poly(malic acid) represents an interesting material for biomedical applications, since it is biocompatible[12] and degrades to nontoxic malic acid under physiological conditions.[13] The side-chain carboxylic groups can be functionalized to obtain a large set of polymers and copolymers with different hydrophobic/hydrophilic balances,[14,15] which proved useful for realizing biocompatible devices.[16−20] The stereogenic center in the poly(malolactonate) chains may be further exploited to tune the polymer characteristics and bioactivity. Convenient procedures for the preparation of both malolactone monomers and the corresponding polymers have been developed over the last 20 years starting from commercially available natural products.[21−23]

Following our continued interest in the production of bioerodible and biodegradable functional polymers for biomedical applications,[24−32] we synthesized and characterized a series of polyesters and copolyesters from new malolactonate monomers. Functionalization of the lateral chain of the malic residues was performed through esterification with readily available alcohols. Lateral groups were chosen either to make the material strongly hydrophobic, to target specific biological in vivo recognition of natural terpene structures, or to provide a reactive site for further functionalization. Indeed, our target was the realization of degradable polymers of high bioactivity which could be used as minor components of poly(2-hydroxyethyl methacrylate)-based semi-interpenetrating networks for tissue engineering applications. The biological responses of these new materials will be the subject of a forthcoming paper.[33]

Experimental Section

Materials. All chemicals were purchased from Aldrich Chemical Co. THF was dried by distillation over sodium. (*R*,*S*)-Benzyl malolactonate (**4i**) and malolactone (**5**) were prepared according to the original procedure developed by Guerin et al.[21,35]

Methods. TLC was performed on silica gel 60 F_{254} (Merck) with detection by UV light at 254 nm, and either iodine or hydroxamic acid staining. Flash chromatography: Merck Silica Gel 60 (230−400 mesh). Liquid chromatography: Merck Silica Gel 60 (70−230 mesh). FT-IR spectra were recorded on films or KBr pellets by a Perkin-Elmer 1600 spectrophotometer. ^{1}H/^{13}C NMR spectra were recorded by either a Varian Gemini

* Corresponding author. Telephone: international code + 050-918299. Fax: international code + 050-28438. E-mail: chlmeo@dcci.unipi.it.
[†] University of Pisa.
[‡] Université Paris Val de Marne.

10.1021/ma0111257 CCC: $22.00
Published on Web 01/18/2002

200 or a Bruker AF 300 spectrometer at room temperature on sample solution in perdeuterated solvents. Chemical shifts are referred to tetramethylsilane and expressed in ppm. Peak multiplicity was denoted by the following: s (singlet), bs (broad singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet). SEC analyses were carried out at 25 °C using a HPLC Perkin-Elmer 10 equipped with a Jasco RI detector and two PL mixed C5 columns connected in series, usingwith chloroform as the eluent at a flow rate of 1 mL/min. Monodispersed poly(styrene) samples were used as standards. Differential scanning calorimetry (DSC) analyses were carried out between −50 and +50 °C at 10 °C/min on 5−10 mg samples using a Mettler DSC-30 TA4000 system. Glass transition temperatures were measured from the inflection points in the thermograms relevant to the second heating cycles. Thermal gravimetric analyses (TGA) were recorded under dry nitrogen atmosphere in the 25−590 °C range at 10 °C/min by a Mettler TG 50 instrument; in every case, only the degradation onsets are reported.

2-Methyl-4-phenylmethyloxy-1-butene. Benzyl chloride (65.8 g, 520 mmol) was added dropwise to a mixture of 3-methyl-3-buten-1-ol (40 g, 464 mmol), NaOH 50% (200 g, 2500 mmol) and tetrabutylammonium bisulfate (8 g, 23 mmol), at 40 °C under vigorous stirring. After 4 h, the organic layer was separated and the acqueous phase was diluted to 700 mL with pure water and extracted with diethyl ether (3 × 200 mL). The organic phases were collected together, washed with brine (100 mL), and dried on Na_2SO_4 overnight. Solvent evaporation afforded a crude product, which was purified by distillation (bp 62−64 °C/0.2 mbar), to give pure 2-methyl-4-phenylmethyloxy-1-butene as a transparent oil (72.8 g, 90%). FT-IR (liquid film): 1650 ($\nu_{C=C}$) and 1104 (ν_{COC}) cm^{-1}. ^1H NMR ($CDCl_3$): 1.76 (*s*, 3H; C**H$_3$**), 2.32−2.39 (*t*, 2H; C**H$_2$**C═), 3.56−3.63 (*t*, 2H; CH_2CH_2**O**), 4.53 (*s*, 2H; C**H$_2$**Ph), 4.75 (m, 1H; ═C**H** cis), 4.79 (m, 1H; ═C**H** trans), and 7.32−7.36 ppm (m, 5H; Ph−**H**). ^{13}C NMR ($CDCl_3$): δ = 22.87 (**C**H_3), 38.05 (**C**H_2C═), 68.97 (CH_2**C**H_2O), 73.10 (**C**H_2−Ph), 111.66 (**C**H_2═), 127.71 (Ph: **C4**), 127.84 (Ph: **C2**, **C6**), 128.53 (Ph: **C3**, **C5**), 138.74 (Ph: **C1**), and 143.63 ppm (CH_3**C**═).

(*R*,*S*)-2-Methyl-4-(phenylmethyloxy)butan-1-ol (1a). A 1M solution of BH_3 in THF (33 mL, 33 mmol) was added dropwise (30 min) to 2-methyl-4-(phenylmethyloxy)-1-butene (12.2 g, 69.5 mmol) at 0−10 °C, and the solution was stirred at room temperature for 2 h. The excess hydride was decomposed by adding water (1 mL) at 0−10 °C. After hydrogen evolution, 3 M NaOH was added (11 mL, 33 mmol) followed by a dropwise (15 min) addition of 30% H_2O_2 (10.4 mL, 91 mmol), at a temperature below 10 °C. Stirring was maintained for further 1.5 h at room temperature. Then, 5% $NaHCO_3$ (100 mL) was added, the organic layer was separated, and the water phase was extracted with diethyl ether (3 × 100 mL). The organic phases were collected together, washed with brine (50 mL), and dried on Na_2SO_2 overnight. Solvent evaporation afforded a crude product which was purified by distillation (bp 95 °C/0.04 mbar), to give pure **1a** as a transparent oil (11.5 g, 84%). FT-IR (liquid film = 3406 (ν_{OH}): 1096 (ν_{COC}(ether)), and 1044 (ν_{CCO}(alcohol)) cm^{-1}. ^1H NMR ($CDCl_3$): 0.90−0.94 (s, 3H; C**H$_3$**), 1.47−1.89 (2m, 3H; CH_2C**H$_2$**C**H**), 2.75 (bs, 1H; O**H**), 3.37−3.65 (2 m, 4H; CH_2C**H$_2$**O + C**H$_2$**OH), 4.52 (s, 2H; C**H$_2$**-Ph), and 7.28−7.53 (m, 5H; Ph-**H**) ppm. ^{13}C NMR ($CDCl_3$): 17.27 (**C**H_3), 34.08 (**C**H), 34.14 (CH**C**H_2), 68.15 (CH_2**C**H_2O), 68.82 (**C**H_2OH), 77.26 (**C**H_2−Ph), 127.82 (Ph: **C4**), 127.87 (Ph: **C2**, **C6**), 128.57 (Ph: **C3**, **C5**), and 138.23 (Ph: **C1**) ppm.

α-Hydroxy−ω-methyloligo(lactic acid) (1e). Trimethylsilyl diazomethane (2.0 M in hexanes, 6 mL, 12 mmol) was added under vigorous stirring to a solution of oligo(lactic acid) [M_W = 470] (3.125 g, 6.65 mmol) in methanol (9.2 mL) and toluene (32.5 mL). The reaction mixture was stirred for 3h at room temperature. Solvent evaporation afforded a crude product that was purified by precipitation into cyclohexane, then dried under reduced pressure. Pure **1e** (2.1 g, 62%) was recovered as a pale yellow oil. ^1H NMR ($CDCl_3$): 1.3−1.6 (3H; C**H$_2$**CH), 3.7 (s, 3H; C**H$_3$**O), 4.2−4.4 (1H; C**H**OH), and 5.0−5.2 ppm (1H; C**H**OC═O).

(*R*,*S*)-4-((*R*,*S*)-2-Methyl-4-(phenylmethyl)oxybutyl)oxycarbonyl-2-oxetanone (4a). Trifluoroacetic anhydride (3.8 mL, 26 mmol) was added dropwise to a solution of 2-bromo-1,4-butanedioic acid (4 g, 20 mmol) in anhydrous THF (10 mL) at 0−5 °C, and the reaction mixture was stirred for 2 h at room temperature. Volatile compounds were removed under vacuum and the oily residue was stirred with **1a** for 14 h at 45 °C. The mixture was diluted in ether (60 mL), washed with water (20 mL) and brine (20 mL), and dried over Na_2SO_4 for 12 h. The residue was dissolved in ether (5 mL), water (25 mL) was added, and the pH was then adjusted to 7.2−7.3 with 2 N NaOH, while keeping the temperature below 30 °C. CH_2Cl_2 (60 mL) was added, and the heterogeneous mixture was stirred at 42 °C for 4 h. The organic phase was washed with water (100 mL) and brine (100 mL) and dried over Na_2SO_4 for 12 h. Solvent evaporation afforded an oily mixture, which was purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate 26/10), to give **4a** as a transparent oil (1.57 g, 28% on **1a**). FT-IR (liquid film): 1846 (ν(C═O lactone)) and 1746 (ν(C═O ester)) cm^{-1}. ^1H NMR ($CDCl_3$): 0.95−0.99 (m, 3H; C**H$_3$**), 1.41−1.60 (m, 1H; CHC**H$_2$**CH_2), 1.65−1.82 (m, 1H; CHC**H$_2$**CH_2), 1.99−2.16 (m, 1H; C**H**CH_3), 3.46−3.62 (dd + m, 3H; C**H$_2$**CHO + CH_2C**H$_2$**O), 3.70−3.82 (2 dd, 1H; C**H$_2$**CHO), 4.07−4.15 (m, 2H; C**H$_2$**OCO), 4.49 (s, 2H; OC**H$_2$**Ph), 4.80−4.86 (dd, 1H; C**H**O), and 7.25−7.35 ppm (m, 5 H; Ph−**H**). ^{13}C NMR ($CDCl_3$): 16.88 (**C**H_3), 30.10 (**C**HCH_3), 33.30 (CH**C**$H_2$$CH_2$), 43.60 (**C**$H_2$C═O), 65.47 (**C**HO), 67.95 (CH_2**C**H_2O), 71.08 (**C**H_2-OC═O), 73.19 (O**C**H_2Ph), 127.82 (Ph: **C2**, **C4**, **C6**), 128.58 (Ph: **C3**, **C5**), 138.52 (Ph: **C1**), 165.85 (CH_2**C**═), and 168.29 ppm (CH**C**═O).

(*R*,*S*)-4-(3-Methyl-2-buten-1-yl)oxycarbonyl-2-oxetanone (4b). The same procedure used for the **4a** synthesis was adopted for the preparation of **4b**. Reagents: 2-bromo-1,4-butanedioic acid (4 g, 20 mmol), **1b** (1.748 g, 20 mmol), and trifluoroacetic anhydride (3.8 mL, 26.4 mmol). Solvents: THF (10 mL) and CH_2Cl_2 (30 mL). Workup after lactonization: the organic phase was separated, washed with water (2 × 12 mL) and brine (2 × 12 mL), and dried over Na_2SO_4 for 12 h. Solvent evaporation afforded an oily mixture, which was purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate 35/10), to give **4b** as a transparent oil (1.05 g, 28% on **1b**). FT-IR (liquid film): 1846 (ν(C═O lactone)), 1744 (ν(C═O ester)), and 1676 (ν(C═C)) cm^{-1}. ^1H NMR ($CDCl_3$): 1.70−1.75 (2 s, 6 H; C**H$_3$**), 3.51−3.61 (dd, 1H; C**H$_2$**C═O), 3.71−3.82 (dd, 1H; C**H$_2$**C═O), 4.69−4.72 (*d*, 2H; C**H$_2$**O), 4.80−4.85 (dd, 1H; C**H**O), and 5.37−5.29 (m, 1H, C**H**═) ppm. ^{13}C NMR ($CDCl_3$): 18.19 (*cis*-**C**H_3), 25.87 (*trans*-**C**H_3), 43.56 (**C**H_2C═O), 63.22 (**C**H_2O), 65.47 (**C**HO), 117.45 (**C**H═), 141.07 (**C**═), 165.92 (CH_2**C**═O), and 168.22 (CH**C**═O) ppm.

(*R*,*S*)-4-(3-Methyl-3-buten-1-yl)oxycarbonyl-2-oxetanone (4c). The same procedure used for the **4a** synthesis was adopted for the preparation of **4c**. Reagents: 2-bromo-1,4-butanedioic acid (4 g, 20 mmol), **1c** (1.749 g, 20 mmol), and trifluoroacetic anhydride (3.8 mL, 26.4 mmol). Solvents: THF (10 mL) and CH_2Cl_2 (30 mL). Yield: 0.93 g (26%) of **4c** as transparent oil. FT-IR (liquid film): 1848 (ν(C═O lactone)), 1746 (ν(C═O ester)), and 1650 (ν(C═C)) cm^{-1}. ^1H NMR ($CDCl_3$): 1.75 (s, 3H; C**H$_3$**), 2.36−2.42 (*t*, 2H; C**H$_2$**C═), 3.51−3.62 (dd, 1H; C**H$_2$**C═O), 3.72−3.83 (dd, 1H; C**H$_2$**C═O), 4.32−4.39 (*t*, 2H; C**H$_2$**O), 4.73 (s, 1H; C**H**═), and 4.80−4.86 (2H; C**H**O + **C**H═) ppm. ^{13}C NMR ($CDCl_3$): 22.45 (**C**H_3), 36.72 (**C**$H_2$$CCH_3$), 43.74 (**C**$H_2$C═O), 64.35 (**C**$H_2$O), 65.44 (**C**HO), 113.08 (**C**H_2═), 141.10 (**C**CH_3), 165.85 (CH_2**C**═O), and 168.22 (CH**C**═O) ppm.

(*R*,*S*)-4-(3,7-Dimethyl-(*E*)-2,6-octadien-1-yl)oxycarbonyl-2-oxetanone (4d). The same procedure used for the **4a** synthesis was adopted for the preparation of **4d**. Reagents: 2-bromo-1,4-butanedioic acid (2 g, 10 mmol), **1d** (1.54 g, 10 mmol), and trifluoroacetic anhydride (1.9 mL, 13.2 mmol). Solvents: THF (5 mL) and CH_2Cl_2 (40 mL). Workup after lactonization: the organic phase was separated, ether (200 mL) was added, the solution was washed with brine (2 × 100 mL), and dried over Na_2SO_4 for 12 h. Solvent evaporation afforded an oily mixture, which was purified by flash chromatography

on silica gel (eluent: hexane/ethyl acetate 35/10), to give **4b** as a transparent oil (0.318 g, 12% on **1d**). FT-IR (liquid film): 1850 (ν(C=O lactone)), 1746 (ν(C=O ester)), and 1668 (ν(C=C)) cm^{-1}. ^1H NMR ($CDCl_3$): 1.52−1.72 (3 s, 9 H; C**H**$_3$), 2.06 (m, 4H; C**H**$_2$C=), 3.52−3.62 (dd, 1H; C**H**$_2$C=O), 3.72−3.83 (dd, 1H; C**H**$_2$C=O), 4.72−4.76 (*d*, 2H; C**H**$_2$O), 4.81−4.86 (dd, 1H; C**H**O), 5.01−5.06 (m, 1H; OCH_2CH=), and 5.30−5.37 (*t*, 1H; $(CH_2)_2CH$=) ppm. ^{13}C NMR ($CDCl_3$): 16.67 (**C**H_3CCH_2), 17.83 (*cis***C**H_3CCH_3), 25.80 (CH_2**C**H_2CH), 26.35 (*trans***C**H_3CCH_3), 39.63 (CH_2**C**H_2CH_3), 43.60 (**C**H_2C=O), 63.25 (**C**H_2O), 65.47 (**C**HO), 117.16 (OCH_2**C**H), 123.67 (CH_2CH_2**C**H), 132.12 (CH_3-**C**CH_3), 144.34 (CH_3**C**CH_2), 165.89 (CH_2**C**=O), and 168.22 (CH**C**=O) ppm.

(*R*,*S*)-4-α-(ω-Methyloxycarbonyloligo(lactyl))oxycarbonyl-2-oxetanone (4e). Dicyclohexylcarbodiimide (1.1 g, 5.46 mmol) was added to a solution of **1e** (2.1 g, 4.2 mmol) and **5** (0.48 g, 4.2 mmol) in THF (10 mL) at 0 °C, and the mixture was allowed to warm at room temperature and stirred for 2 days. The precipitated dicyclohexylurea was filtered off on Celite. Solvent evaporation afforded a crude mixture that was dissolved in a minimum of dichloromethane, cooled to 0 °C, and filtered again. Pure **4e** (1.6 g, 30%) was recovered as a clear oil after precipitation in cyclohexane. FT-IR (liquid film): 1850 (ν(C=O lactone)) and 1746 (ν(C=O ester)) cm^{-1}. ^1H NMR ($CDCl_3$): 1.3−1.6 (3H; C**H**$_3$CH), 3.7−3.8 (5H; C**H**$_3$O + C**H**$_2$C=O), 4.8 (1H; CH_2CHO), and 5.0−5.2 (1H; CH_3CHO) ppm.

(*R*,*S*)-4-Cholesteryloxycarbonyl-2-oxetanone (4f). The same procedure used for the **4e** synthesis was adopted for the preparation of **4f**. Reagents: dicyclohexylcarbodiimide (2.7 g, 13.1 mmol), **1f** (5 g, 12.9 mmol), and **5** (1.5 g, 12.9 mmol). Reaction time: 2 days. Workup: filtration on Celite afforded a crude mixture which was purified by liquidi chromatography (eluent: dichloromethane), to give **4f** as a white solid (2.8 g, 45. FT-IR (cast film): 1834 (ν(C=O lactone)) and 1736 (ν(C=O ester)) cm^{-1}. ^1H NMR ($CDCl_3$): 0.68 (s, 3H; Chol−C**H**$_3$-CCHCHCH_3), 0.85−2.04 (38 H; Chol−**H**), 2.33−2.39 (m, 2H; Chol−CHC**H**$_2$C=), 3.55−3.62 (dd, 1H; C**H**$_2$C=O), 3.74−3.82 (dd, 1H; C**H**$_2$C=O), 4.70−4.80 (m, 1H; Chol−C**H**O), 4.81−4.84 (dd, 1H; O=CCH_2C**H**O), and 5.39−5.41 (m, 1H; Chol−C**H**=) ppm. ^{13}C NMR ($CDCl_3$): 12.08, 18.93, 19.48, 21.25, 22.78, 23.03, 24.05, 24.50, 27.77, 28.24, 28.43, 32.04, 32.10, 36.00, 36.39, 36.76, 37.05, 38.02, 39.74, 39.91, 42.52, 43.65 (**C**H_2C=O), 50.20, 56.35, 56.88, 65.62 (**C**HC=O), 76.66 (**C**HO Chol), 118.82, 123.59, 139.12, 165.97 (CH_2**C**=O), and 167.73 (CH**C**=O) ppm.

(*R*,*S*)-4-(2-Methoxyethyl)oxycarbonyl-2-oxetanone (4g). The same procedure used for the **4e** synthesis was adopted for the preparation of **4g**. Reagents: dicyclohexylcarbodiimide (1.92 g, 9.3 mmol), **1g** (0.59 g, 7.76 mmol), and **5** (0.9 g, 7.76 mmol). Reaction time: 1 day. Workup: filtration on Celite afforded a crude mixture which was purified by two consecutive flash chromatography cycles (eluent 1, chloroform/acetone 12/1; eluent 2, acetone/hexane 12/10), to give **4g** as a white wax (0.609 g, 45%). FT-IR (liquid film): 1848 (ν(C=O lactone)), and 1750 (ν(C=O ester)) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.35 (s, 3H; C**H**$_3$), 3.53−3.63 (dd + m, 3H; C**H**$_2$C=O + CH_3OCH_2), 3.73−3.84 (dd, 1H; C**H**$_2$C=O), 4.33−4.38 (m, 2H; C**H**$_2$OC=O), and 4.85−4.90 (dd, 1H; **C**HO) ppm. ^{13}C NMR ($CDCl_3$): 43.69 (**C**H_2C=O), 59.07 (**C**H_3), 64.16 (**C**H_2OC=O), 65.27 (**C**HO), 70.00 (CH_3O**C**H_2), 165.87 (CH_2**C**=O), and 168.29 (CH**C**=O) ppm.

(*R*,*S*)-4-(2-Methylethenoyloxyethyl)oxycarbonyl-2-oxetanone (4h). The same procedure used for the **4a** synthesis was adopted for the preparation of **4h**. Reagents: dicyclohexylcarbodiimide (4 g, 19.4 mmol), **1h** (2.10 g, 16.2 mmol), and **5** (1.87 g, 16.2 mmol). Reaction time: 5 h. Workup: filtration on Celite afforded a crude mixture which was purified by chromatography (eluent: chloroform), followed by flash chromatography (eluent: acetone/hexane 10/4), to give **4g** as a pale yellow oil (0.328 g, 17%). FT-IR (liquid film): 1848 (ν(C=O lactone)), 1750 (ν(C=O ester)), 1720 (ν(C=O methacryl ester)), and 1638 (ν(C=C)) cm^{-1}. ^1H NMR ($CDCl_3$): 1.93 (s, 3H; C**H**$_3$), 3.60−3.67 (dd, 1H; C**H**$_2$C=O), 3.76−3.84 (dd, 1H; C**H**$_2$C=O), 4.39−4.42 (m, 2H; CHC=OOC**H**$_2$), 4.48−4.51 (m, 2H; CC=OOC**H**$_2$), 4.86−4.89 (dd, 1H; **C**HO), 5.60 (s, 1H; C**H**$_2$= trans), and 6.11 (s, 1H; C**H**$_2$= cis) ppm. ^{13}C NMR ($CDCl_3$): 18.40 (**C**H_3), 43.73 (**C**H_2C=O), 61.96 (**C**H_2OC=OCH), 64.10 (**C**H_2-OC=OC=), 65.26 (**C**HO), 126.59 (**C**H_2=), 135.88 (CH_3**C**=), 165.67 (CH_2**C**=O), 167.21 (=C**C**=O), and 168.12 (CH**C**=O) ppm.

Table 1. Anionic Polymerization of β-Malolactonate Monomers

sample	feed **4i** (mol %)	time (days)	yield (%)	polymer **4i** (mol %)	M_w	M_w/M_n	T_g[a] (°C)
p(4b)	0	31[b]	37	0	11200	1.19	2.1
p(4c)	0	24[b]	28	0	9900	1.15	−13.6
p(4d)	0	16[b]	33	0	12800	1.23	−33.7
p(4e)	0	21[b]	31	0	6650	1.25	36.3
p(4f)	0	4[c]	91	0	24800	1.70	
p(4i)	0	8[b]	91	0	20900	1.23	33.7
c(4a)	55	24[b]	41	60	3100	1.15	1.2
c(4b)	39	24[b]	71	42	10600	1.43	13.6
c(4c)	49	24[b]	74	53	8800	1.47	8.8
c(4f)	79	4[c]	85	76	6500	1.73	42.2
c(4g)1	83	4[c]	62	85	12150	1.80[d]	28.3
c(4g)2	39	4[c]	68	43	16700	1.69[d]	14.1
c(4h)1	94	8[b]	71	96	5350	1.30	27.6
c(4h)2	91	8[b]	73	94	5500	1.26	28.0

[a] On second heating cycle. [b] In bulk. [c] In THF. [d] Bimodal distribution.

Table 2. Thermogravimetric Analysis of the Prepared Polyesters

sample	T_{d_1} (°C)[a]	Δw_1 (%)[b]	T_{d_2} (°C)[a]	Δw_2 (%)[b]
p(4d)	187	48 (53)	217	50
p(4e)	195	57	280	40
p(4f)	225	7.5	250	80
p(4i)	237	99		
c(4b)	194	18 (20)	238	81
c(4g)2	258	100		

[a] Degradation onset. [b] Weight loss.

Synthesis of Polyesters. The monomers or comonomer mixtures were placed in a Schlenk flask, the bottom of which was previously coated with tetraethylammonium benzoate by evaporation under vacuum from an ethanol solution (0.14−0.16 M) of the quaternary ammonium salt. The monomer/initiator ratio was set to 1000/1. The mixture was stirred under a nitrogen atmosphere for 4−31 days at 38−42 °C (see Table 2). The prepared polymers were purified by double precipitation in absolute ethanol from concentrated dichloromethane solutions (1/10 dichloromethane/ethanol volume ratio), and dried under high vacuum for 12 h prior characterization. FT-IR and ^1H NMR spectral data of the polymers are reported below.

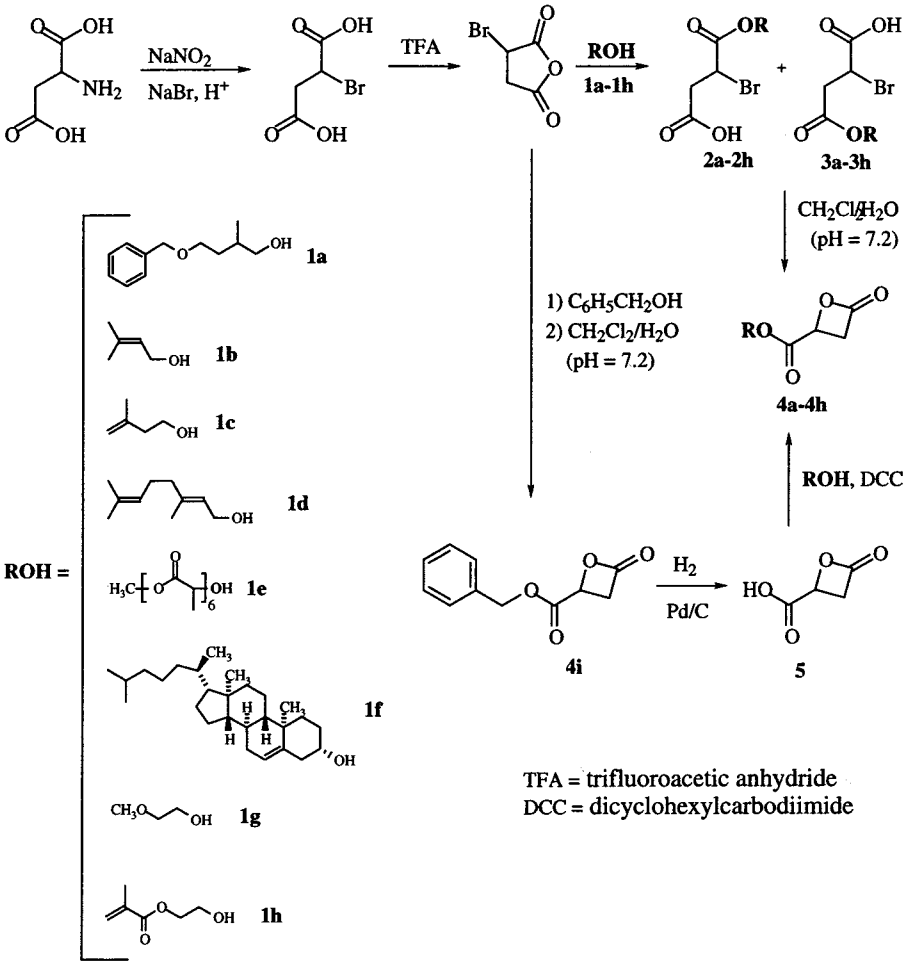
Poly((*R*,*S*)-3-methyl-2-buten-1-yl malolactonate) [p4b]. FT-IR (cast film): 1768, 1736, 1675, 1194, 1150, 1068, and 1045 cm^{-1}. ^1H NMR (CDCl): 1.67−1.73 (2 s, 6 H; C**H**$_3$), 2.84−3.06 (2H; C**H**$_2$C=O), 4.60−4.63 (*d*, 2H; C**H**$_2$O), 5.25−5.32 (*t*, 1H, C**H**=), and 5.47 (1H; C**H**O) ppm.

Poly((*R*,*S*)-3-methyl-3-buten-1-yl malolactonate) [p4c]. FT-IR (cast film): 1763, 1746, 1650, 1197, 1159, 1079, and 1054 cm^{-1}. ^1H NMR ($CDCl_3$): 1.72 (s, 3H; C**H**$_3$), 2.30−2.36 (*t*, 2H; C**H**$_2$C=), 2.97 (1H; C**H**$_2$C=O), 4.20−4.31 (2H; C**H**$_2$O), 4.71−4.79 (2 s, 2H; C**H**=), and 5.47 (1H; C**H**O) ppm.

Poly((*R*,*S*)-3,7-dimethyl-(*E*)-2,6-octadien-1-yl malolactonate) [p4d]. FT-IR (cast film): 1768, 1752, 1669, 1195, 1164, 1103, and 1054 cm^{-1}. ^1H NMR ($CDCl_3$): 1.59−1.67 (3 s, 9 H; C**H**$_3$), 2.04 (4H; C**H**$_2$C=), 2.98 (2H; C**H**$_2$C=O), 4.63−4.66 (*d*, 2H; C**H**$_2$O), 5.05 (1H; OCH_2CH=), 5.26−5.33 (*t*, 1H; $(CH_2)_2CH$=), and 5.46 (1H; C**H**O) ppm.

Poly((*R*,*S*)-α-(ω-methyloxycarbonyloligo(lactyl)) malolactonate) [p4e]. FT-IR (cast film): 1754, 1192, 1131, 1092, and 1054 cm^{-1}. ^1H NMR ($CDCl_3$): 1.47−1.56 (3H; C**H**$_3$CH), 3.03 (2H; C**H**$_2$C=O), 3.73 (s, 3H; C**H**$_3$O), 5.14 (1H; CH_3CHO), and 5.55 (1H; CH_2CHO) ppm.

Scheme 1. Synthesis of *β*-Malolactonate Monomers



Poly((*R*,*S*)-cholesteryl malolactonate) [p4f]. FT-IR (cast film): 1749, 1197, 1161, 1076, and 1055 cm^{-1}. ^1H NMR ($CDCl_3$): 0.67 (s, 3H; Chol−C**H**$_3$CCHCHCH$_3$), 0.84−2.03 (38 H; Chol−**H**), 2.31 (2H; Chol−CHC**H**$_2$C=), 3.00 (2H; C**H**$_2$C=O), 4.61 (1H; Chol−C**H**O), 5.35 (m, 1H; Chol−C**H**=), and 5.47 (1H; O=CCH$_2$C**H**O) ppm.

Poly((*R*,*S*)-phenylmethyl malolactonate) [p4i]. FT-IR (cast film): 1747, 1211, 1164, 1081, and 1054 cm^{-1}. ^1H NMR ($CDCl_3$): 2.91 (2H; C**H**$_2$C=O), 5.10 (s, 2H; OC**H**$_2$), 5.51−5.53 (1H; C**H**O), and 7.28 (5H; Ph−**H**) ppm. ^{13}C NMR ($CDCl_3$): 35.56 (**C**H$_2$C=O), 67.69 (**C**H$_2$O), 68.79 (**C**HO), 128.40 (Ph: **C2**, **C6**), 128.69 (Ph: **C3**, **C5**), 128.80 (Ph: **C4**), 135.21 (Ph: **C1**), 168.11 (CH$_2$**C**=O), and 168.29 (CH**C**=O) ppm.

Poly((*R*,*S*)-benzyl malolactonate-*co*-(*R*,*S*)-2-methyl-4-(phenylmethyl)oxybutyl malolactonate) 60:40 [c4a]. FT-IR (cast film): 1752, 1197, 1164, 1098, and 1054 cm^{-1}. ^1H NMR ($CDCl_3$): 0.91 (C**H**$_3$), 1.44 (CHC**H**$_2$CH$_2$), 1.65 (CHC**H**$_2$CH$_2$), 1.99 (C**H**CH$_3$), 2.95 (C**H**$_2$C=O), 3.47 (CH$_2$C**H**$_2$O), 4.00 (CHC**H**$_2$-O), 4.46 (CH$_2$OC**H**$_2$−Ph), 5.11 (Ph−C**H**$_2$OC=O), 5.52 (C**H**O), and 7.25−7.35 (Ph−**H**) ppm.

Poly((*R*,*S*)-(benzyl malolactonate-*co*-(*R*,*S*)-3-methyl-2-buten-1-yl malolactonate) 40:60 [c4b]. FT-IR (cast film): 1749, 1675, 1208, 1164, 1103, and 1054 cm^{-1}. **^1H NMR** ($CDCl_3$): 1.67−1.72 (2 *s*; C**H**$_3$), 2.95 (C**H**$_2$C=O), 4.60 (C**H**$_2$C=), 5.14 (C**H**$_2$−Ph), 5.27 (**CH**=), 5.47 (C**H**O), and 7.30 (Ph−**H**) ppm.

Poly((*R*,*S*)-(benzyl malolactonate-*co*-(*R*,*S*)-3-methyl-3-buten-1-yl malolactonate) 50:50 [c4c]. FT-IR (cast film): 1752, 1650, 1198, 1164, 1087, and 1056 cm^{-1}. ^1H NMR ($CDCl_3$): 1.7 (C**H**$_3$), 2.2−2.4 (C**H**$_2$C=), 2.8−3.1 (C**H**$_2$C=O), 4.1−4.3 (OC**H**$_2$CH$_2$), 4.6 (C**H**=), 4.8 (**CH**=), 5.0−5.2 (C**H**$_2$−Ph), 5.4−5.6 (C**H**O) and 7.2−7.3 (Ph−**H**) ppm.

Poly((*R*,*S*)-benzyl malolactonate-*co*-(*R*,*S*)-cholesteryl malolactonate) 80:20 [c4f]. FT-IR (cast film: 2950, 2867, 1748, 1163, and 1054 cm^{-1}. ^1H NMR ($CDCl_3$): (Chol−C**H**$_3$-CCHCHCH$_3$), 0.85−2.09 (Chol−**H**), 2.30 (Chol−CHC**H**$_2$C=), 2.92 (C**H**$_2$C=O), 4.63 (Chol−C**H**O), 5.14 (C**H**$_2$−Ph), 5.34 (Chol−C**H**=), 5.50 (O=CCH$_2$C**H**O), and 7.27 (Ph−**H**) ppm.

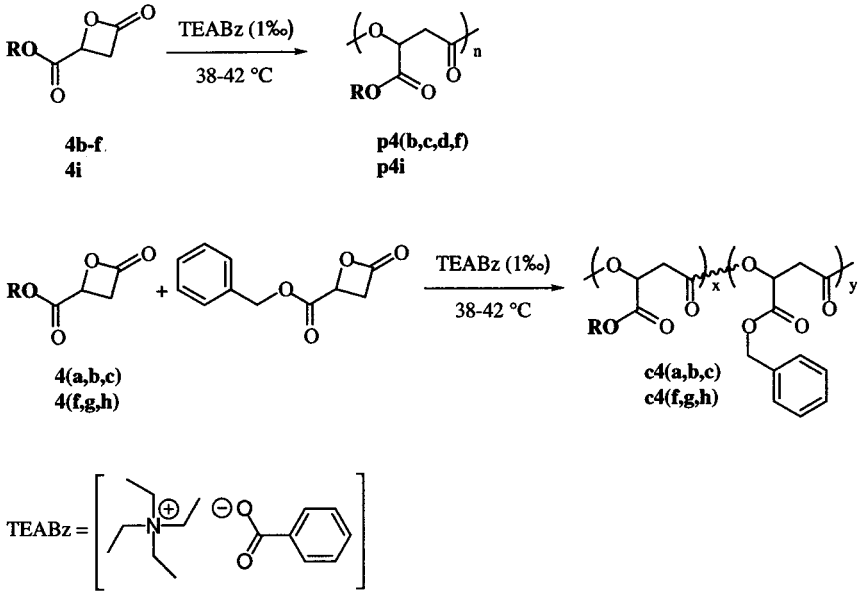
Poly((*R*,*S*)-(benzyl malolactonate-*co*-(*R*,*S*)-2-methoxyethyl malolactonate) 80:20 and 40:60 [c4g1, c4g2]. FT-IR (cast film): 1751, 1164, and 1054 cm^{-1}. ^1H NMR ($CDCl_3$): 3.00 (C**H**$_2$C=O), 3.31−3.35 (C**H**$_3$), 3.50−3.55 (CH$_3$OC**H**$_2$), 4.28 (C**H**$_2$-OC=O), 5.13 (C**H**$_2$−Ph), 5.51 (C**H**O), and 7.30 (Ph−**H**) ppm.

Poly((*R*,*S*)-benzyl malolactonate-*co*-(*R*,*S*)-2-methyletenoyloxyethyl malolactonate)) 5:95 and 10:90 [c4h1, c4h2]. FT-IR (cast film): 1750, 1640, 1162, and 1052 cm^{-1}. ^1H NMR ($CDCl_3$): 1.89 (C**H**$_3$), 2.91 (C**H**$_2$C=O), 4.28 (OC**H**$_2$C**H**$_2$), 5.09 (C**H**$_2$−Ph), 5.51 (C**H**O + C**H**= trans, 6.11 (C**H**= cis), and 7.27 (Ph−**H**) ppm.

Results and Discussions

Synthesis of Monomers. The preparation of the *β*-malolactonates was carried out using two different synthetic methodologies (Scheme 1). The first class of compounds, **4a**−**d**, and benzyl malolactonate were synthesized in three steps, according to a well-established procedure (aspartic acid route) beginning with racemic aspartic acid.[23,35] In the first step, the α-amino group of the amino acid was replaced with a bromine atom. The linear monoterpene side chains were introduced in the second step by reaction of the corresponding monoterpenols **1a**−**d** with activated bromosuccinic anhydride, which was previously formed through dehydration of bromosuccinic acid by trifluoroacetic anhydride. The preferential formation (71−74%) of lactonizable alkyl monoesters **2a**−**d** was confirmed by ^1H

Scheme 2. Synthesis of β-Malolactonate Polymers



NMR analysis of the product mixtures, in agreement with reported results.[35] Finally, intramolecular displacement reactions of the β-halocarboxylic acids led to the formation of lactones **4a**−**d**. Linear terpene alcohols **1b**−**d** were commercially available, whereas **1a** was synthesized from 3-methyl-3-buten-1-ol using a two-step procedure involving benzylation of the hydroxyl group followed by hydroboration/oxidation of the alkene linkage.

The second series of monomers **4e**−**h** was synthesized by direct esterification of malolactone, previously prepared by hydrogenolysis of benzyl malolactonate **4i**, obtained from aspartic acid. This procedure was preferred over the previous one since the bulkier or less hydrophobic alkyl groups introduced gave worse results in the esterification step and in the following workup. Indeed, this method has been successfully applied to a number of complex molecules.[18,37] It must be noted that **1e** was obtained from an oligo(lactic acid) chain by capping its carboxyl terminus with a methyl group to avoid competition with the malolactone **5** in the subsequent esterification. Spectroscopic characterization of the synthesized compounds was in agreement with the proposed structures of the lactone monomers. Overall yields (referred to the precursor alcohol) ranged from 12 to 45%. The yield was not significantly dependent on the nature of the side groups, except for **4c**, whose surfactant properties negatively influenced the reaction work up, and **4h**, which contains an acrylic group that is very reactive toward free-radical polymerization.

Synthesis of Polymers. The anionic ring-opening polymerization and copolymerization of the monomers (Scheme 2; Table 1) was carried out either in bulk or in anhydrous THF using tetraethylammonium benzoate (1‰ in mol) as the initiator. The polymerization temperature was kept in the 38−42 °C range. Lactones **4b**−**f** were homopolymerized, to obtain strongly hydrophobic materials. In the copolymerization of **4a**−**c** and **4f**−**h** with **4i**, the comonomer ratios were selected to produce materials with varying degrees of hydrophobicity or, as in the case of **4h**, to introduce functionalizable moieties in the poly(benzyl malolactonate). Monomer **4i** was also homopolymerizated as a reference. The polymerization kinetics were monitored by FT-IR analyses of the reaction mixtures, by recording the intensity of the lactone band at 1848 cm^{-1} at timed intervals. Upon complete disappearance of this band, the polymerization experiments were interrupted by the addition of a small amount of acid and the polymers were recovered by precipitation in alcoholic solvents. Reaction times ranged from 4 to 30 days (Table 1). Faster polymerization rates were recorded in THF rather than in the more viscous bulk phase, indicating a marked dependence of the reaction kinetics upon the molecular mobility of the growing polymeric chains. The higher isolation yields of **p4f** and **p4i** as compared with the other homopolymers (Table 1), were attributed to their more compact hydrophobic side groups, which favored polymer coagulation in protic nonsolvents such as ethanol. Indeed, the copolyesters of **4i** were obtained in almost constant yields, regardless of the comonomer structure.

The polymer samples, obtained as white amorphous materials, were soluble at room temperature in polar aprotic solvent such as DMSO, DMF, acetone, and chloroform. FT-IR analysis of the polymers showed the characteristic absorption bands of the two different ester groups in the 1750−1740, 1190−1160, and 1100−1050 cm^{-1} spectral regions. Peaks due to the presence of functional side chains were also observed (Figure 1).

NMR and SEC Characterizations. The NMR spectra of the polyesters were consistent with their expected structural features (Figure 2). Neither the rearrangment of the **p4b**−**d** vinyl bonds, nor thermal oligomerization of the **c4h1**−**c4h2** acrylic side chains were detected, thus indicating the stability of these groups under the polymerization conditions and during the workup procedures.

The presence of a small peak at 6.9 ppm was attributed to terminal fumaric vinyl protons formed by the main chain-transfer mechanism which affects the anionic ring opening polymerization of α-unsubstituted β-lactones.[38] Indeed, although the monomer/initiator ratio was set to obtain final molecular weights of about 10^5, SEC values were observed to be 1 order of magnitude lower (Table 1). It has been reported that high molecular weights for poly(benzyl malolactonate) can only be achieved only after three sequential vacuum distillations of the monomer.[35] Therefore, it seems very

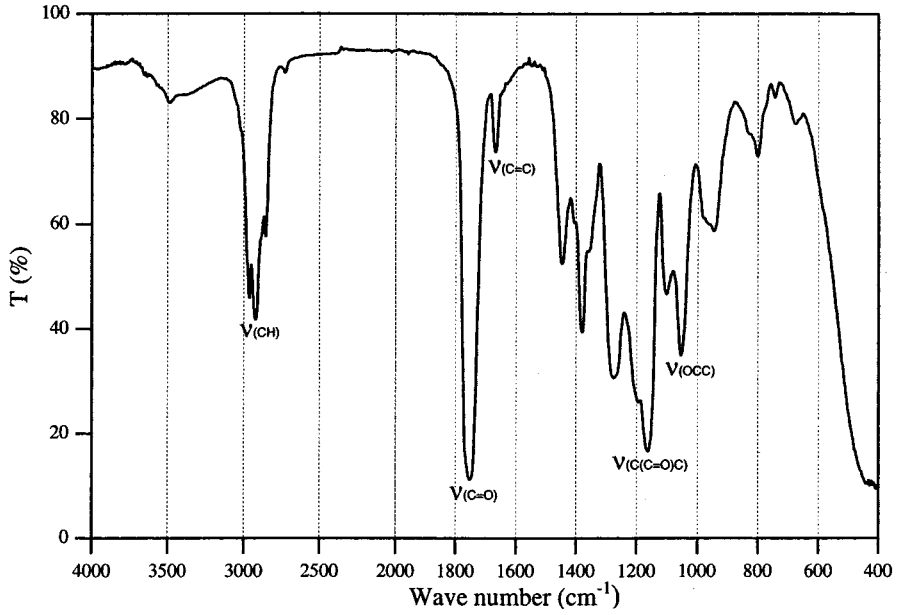


Figure 1. FT-IR spectra of **p4d**.

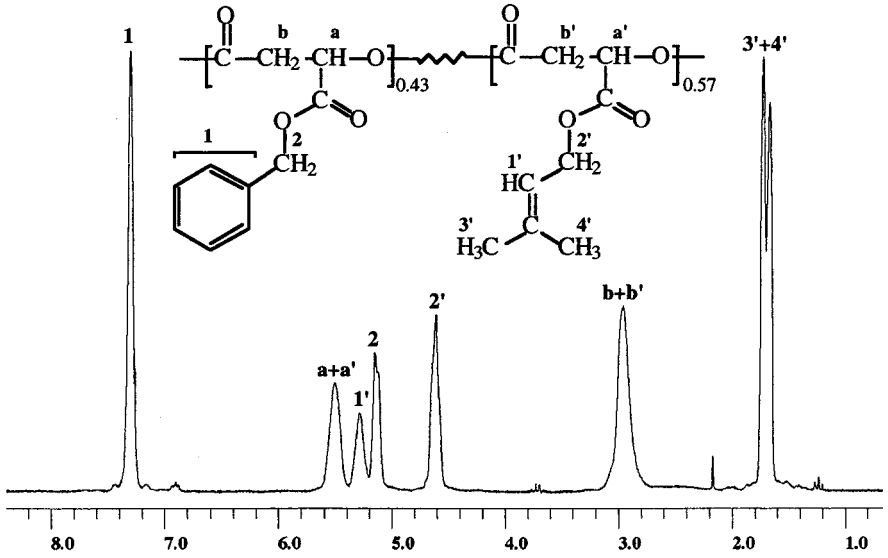


Figure 2. ^{1}H NMR spectra of **c4b**.

likely that the incidence of chain transfer reactions is connected with monomer impurities. Unfortunately, the limited thermal stability of the lactones investigated did not allow for purification by vacuum distillation. However, the obtained molecular weights appeared to be high enough for future medical applications, since the polymer bioactivity was shown to be only slightly influenced on the macromolecular length.[33] In addition, from a general viewpoint, lower molecular weights may allow for faster degradation rates, which for typical poly(alkyl malolactonate)s such as poly(benzyl malolactonate) are fairly slow.[34] In this regard, it is worth noting that selective deprotection of the benzyl side groups in the prepared copolymers should provide materials with higher hydrophilic characteristics and increased degradation rate under physiological conditions.[34]

The polymer molecular weights were not significantly dependent on the nature of side ester groups, as determined by SEC analysis (Table 1). Polydispersity indexes were between 1 and 2, in agreement with a poorly controlled living anionic polymerization. Higher polydispersity values were recorded for both homo and copolymers prepared in THF, where chain-transfer mechanisms are likely to be more active.

In most cases, the polyesters had a monomodal molecular weight distribution which, in the case of the copolymers, suggested a statistical distribution of the two residues along the chain (Figure 3). This was also supported by the copolymer composition determined by ^{1}H NMR, which was very close to that of the feed mixtures (Table 1). Only **c4g1** and **c4g2** samples exhibited a bimodal distribution, more marked at the largest **4g** content, thus indicating the preferential tendency of this monomer to homopropagate (Figure 3). The presence of one sharp and one broad peak in the 3.28−3.36 ppm range of the copolyester ^{1}H NMR spectra was attributed to the side chain methyl group of monomeric units in sequence and flanked by **4i** units, respectively (Figure 4).

Thermal Characterization. DSC analysis of the investigated polymers did not show the presence of endothermal transitions, thus ruling out the presence of a crystalline phase. This result must be attributed to their atactic structures, due to the lack of stereoelec-

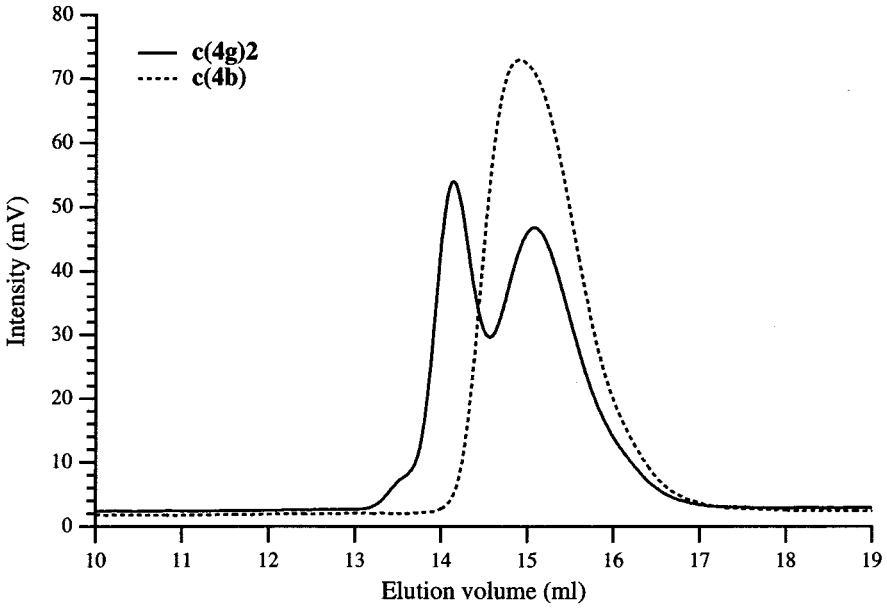


Figure 3. SEC analysis of **c4g2** and **c4b**.

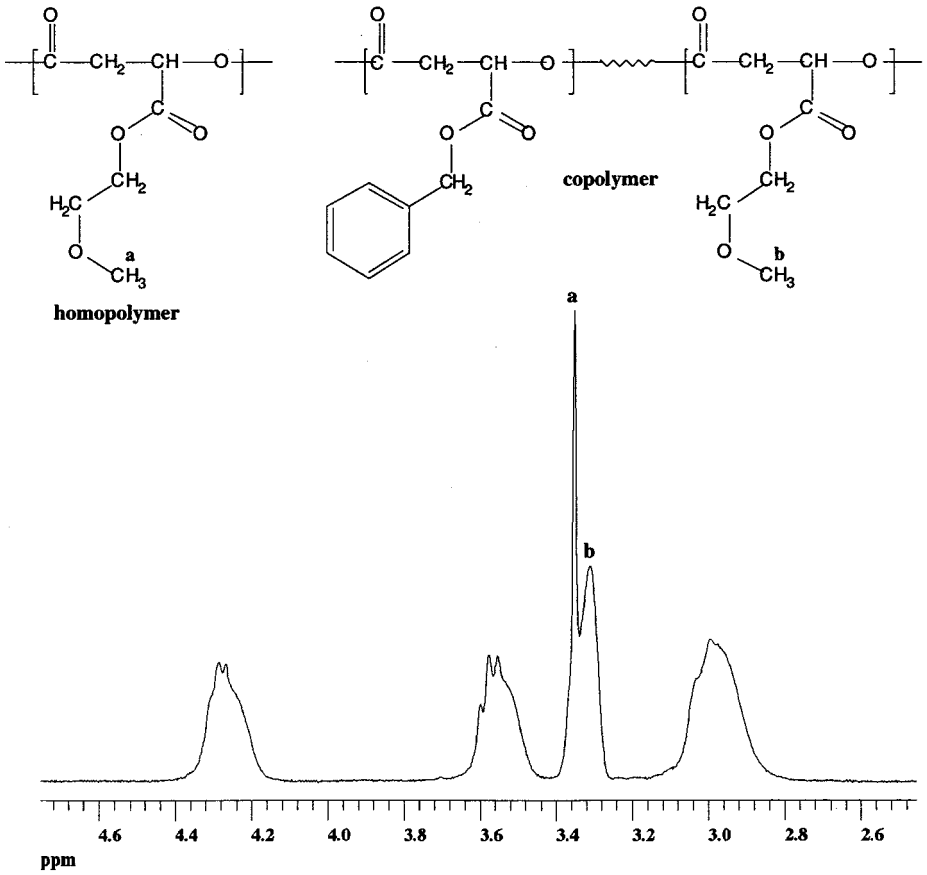


Figure 4. ^{1}H NMR of **c4g2**: enlargement of the 2.5−4.75 ppm region.

tivity in the polymerization process of the racemic monomers. Indeed, it has been reported that many isotactic poly(alkyl malolactonate)s obtained from enantiopure monomers are semicrystalline.[39−41] All polyesters except **p4f** showed well-defined glass transition temperatures (Table 1). The recorded T_g values spanned about 80 °C, depending upon the length as well as the nature of the side groups. For instance, significant differences were found between the T_g values of **p4d** (−34 °C) and **p4e** (36.3 °C), both polyesters containing long side chains but with different structures. T_g values computed for **c4b** (15.4 °C) and **c4c** (10.2 °C) by the Couchman−Fox equation[42] agreed well with experimental data, thus substantiating the random character of these copolymers. Only one T_g was detected for **c4g1**−**c4g2**, indicating that the two different components that constitute the copolyesters gave rise to a homogeneous phase in the solid state.

Thermogravimetric analyses of representative polyesters and copolyesters were carried out under a nitrogen atmosphere in order to verify if the side group structure affected the stability of the materials (Table

2). The homopolymers with linear lateral chains showed slightly lower onset degradation temperatures. Samples **p4d** and **p4e** showed two degradation steps of comparable size, whereas the bulky **p4f** degraded essentially only above 250 °C. Weight loss values suggested that the first and second degradation steps of **p4d** and **p4e** corresponded to the disruption of the lateral and backbone chain, respectively. On the other hand, the first degradative step of **p4f** may tentatively be attributed to the loss of two methane and one hydrogen molecules (weight loss $\approx$ 7.4%). In the last case, a stable conjugated structure would be generated in the cholesterol side group, thus providing the thermodynamic driving force for the reaction. Copolyesters **c4b** and **c4g1** displayed different thermal behaviors compared to that of their common parent homopolyester **p4i**. The introduction of a second lateral chain of hydrophobic nature (**c4b**) led to a decreased thermal stability of the final material (−30 °C at degradation onset), and a two-step degradation mechanism, with initial loss of the terpene group, was evidenced. On the contrary, complete disruption of more hydrophilic **c4g1** occurred in a single step and at a higher temperature. This suggests that the chain stability is related to the polarity of monomeric units and their ability to form effective inter and intrachain interactions.

Conclusions

Readily available alcohols were successfully employed to synthesize a set of alkyl malolactonate monomers displaying a wide range of physicochemical properties. The preparations were carried out according to two established synthetic strategies,[23,35] depending on the nature of the alkyl chain to be incorporated as the malolactonate lateral ester chain. The aspartic acid route proved effective when primary hydrophobic alcoholic derivatives were considered for the monomer synthesis, whereas more complicated or hydrophilic structures had to be linked directly to the side carboxyl group of β-malolactone. Final yields, ranging from 12 to 45% were related to the preparation method as well as to the nature of the monomer lateral chain.

Anionic ring opening polymerization of the four-ring malolactonates by tetraethylammonium benzoate, either in bulk or in THF solution, led to polymers whose main features agreed with the designed monomer structures, as determined by FT-IR and ^{1}H NMR techniques.

Chain transfer reactions affected the living polymerization process, as the final molecular weight values were lower than the theoretical ones, and polydispersity indexes significantly higher than one. Actually, higher polydispersity indexes were obtained in polymerization reactions carried out in THF solution, thus indicating a dependence of chain transfer processes on the medium viscosity. Copolymerization provided a further method for the modification of the materials properties; statistical copolymers were always obtained, except when the strongest hydrophilic monomer was involved in the polymerization reaction.

The absence of stereoelectivity in the polymerization mechanism led to atactic macromolecular chains and the final polymeric materials were amorphous rather than semicrystalline, as determined from thermal analysis. However, all poly(alkyl malolactonate) showed well-shaped glass−rubber transitions, whose typical inflection point temperatures were dependent on the pendant chain structural characteristics. Thermogravimetric analysis indicated the materials were stable up to 180−200 °C; degradation pathways usually involved the preliminary loss of the pendant chain followed by the backbone disruption.

Our investigation focused essentially on the preparation of functional poly(alkyl malolactonate)s in an effective and reproducible way starting from very simple compounds. Some characteristics of the polymerization mechanism, such as the tendency of monomer **4g** to homopropagate or the statistical nature of the obtained polymers, do need further elucidation and experiments in this perspective are currently underway. It is also worth noting that the characteristics of the prepared polymers appear promising for future biomedical applications, as indicated by preliminary cell culture tests.[33]

Acknowledgment. The partial financial support by MURST through PRIN 2000 is gratefully acknowledged.Part of the work herewith reported has been developed within the framework of the E.C. funded project TATLYS G5RD-CT-2000-0294.

References and Notes

(1) Uhrich, K. E.; Cannizzaro, S. M.; Langer, R.; Shakesheff, K. M. *Chem. Rev.* **1999**, *99*, 3181.
(2) Langer, R.; Vacanti, J. P.; Vacanti, C. A.; Atala, A.; Freed, L. E.; Vunjak-Novakovic, G. *Tissue Eng.* **1995**, *1*, 151.
(3) Hubbell, J. A. *Curr. Opin. Biotech.* **1999**, *10*, 123.
(4) Langer, R. *J. Controlled Release.* **1999**, *62*, 7.
(5) Park, J. B.; Lakes, R. S. *Biomaterials: an Introduction*, 2nd ed; Plenum Press: New York and London, 1992; p 1.
(6) Chiellini, E.; Bizzarri, R.; Chiellini, F. *Biopolymers Book*; Wiley VCH: Weinheim, Germany, Vol. 4, Chapter 14, in press.
(7) Wong, W. H.; Mooney, D. J. In *Synthetic Biodegradable Polymer Scaffolds*; Atala, A., Mooney, D. J., Eds.; Birkhauser: Boston, MA, 1997.
(8) Lanza, R. P.; Langer, R.; Chick, W. L. *Principles of Tissues Engineering*; R G Landes Co. and Academic Press: Austin, TX, 1997.
(9) Vert, M. *Makromol. Chem., Macromol. Symp.* **1986**, *6*, 109.
(10) Barrera, D. A.; Zylstra, E.; Lansbury, P. T.; Langer, R. *J. Am. Chem. Soc.* **1993**, *115*, 11010.
(11) Barrera, D. A.; Zylstra, E.; Lansbury, P. T.; Langer, R. *Macromolecules* **1995**, *28*, 425.
(12) Fournié, P.; Domoraud, D.; Guerin, P.; Braud, C.; Vert, M.; Pontikis, R. *J. Bioact. Compat. Polym.* **1992**, *7*, 113.
(13) Braud, C.; Vert, M. *Polym. Bull.* **1992**, *29*, 177.
(14) Cammas-Marion, S.; Guerin, P. *Macromol. Symp.* **2000**, *153*, 167.
(15) Barbaud, C.; Cammas-Marion, S.; Guerin, P. *Polym. Bull.* **1999**, *43*, 297.
(16) Cammas-Marion, S.; Bear, M. M.; Harada, A.; Guerin, P.; Kataoka, K. *Macromol. Chem. Phys.* **2000**, *201*, 355.
(17) Cammas, S.; Bear, M. M.; Moine, L.; Escalup, R.; Ponchel, G.; Kataoka, K.; Guerin, P. *Int. J. Biol. Macromol.* **1999**, *25*, 273.
(18) Moine, L.; Cammas, S.; Amiel, C.; Renard, E.; Sebille, B.; Guerin, P. *Macromol. Symp.* **1998**, *130*, 45.
(19) Rossignol, H.; Boustta, M.; Vert, M. *Int. J. Biol. Macromol.* **1999**, *25*, 255.
(20) Stolnik, S.; Davies, M. C.; Illum, L.; Davis, S. S.; Boustta, M.; Vert, M. *J. Controlled Release.* **1994**, *30*, 57.
(21) Leboucher-Durand, M. A.; Langlois, V.; Guerin, P. *Polym. Bull.* **1996**, *35*, 36.
(22) Cammas, S.; Renard, I.; Boutault, K.; Guerin, P. *Tetrahedron Asymmetry* **1993**, *4*, 1925.
(23) Lenz, R. W.; Guerin, P. In *Polymers in Medicine*; Chiellini, E., Giusti, P., Eds.; Plenum Publishing Co.: New York, 1983; p 219.
(24) Chiellini, E.; S.Faggioni, Solaro, R. *J. Bioact. Compat. Polym.* **1990**, *5*, 16.
(25) Chiellini, E.; Solaro, R. *Makromol. Chem., Macromol. Symp.* **1992**, *54/55*, 483.
(26) Chiellini, E.; Solaro, R. *CHEMTECH* **1993**, *7*, 29.

(27) Chiellini, E.; Bemporad, L.; Solaro, R. *J. Bioact. Compat. Polym.* **1994**, *9*, 152.
(28) Chiellini, E.; Solaro, R.; Bemporad, L.; D'Antone, S.; Giannasi, D.; Leonardi, G. *J. Biomat. Sci., Polym. Ed.* **1995**, *7*, 307.
(29) Chiellini, E.; D′Antone, S.; Solaro, R. *Macromol. Symp.* **1997**, *123*, 25.
(30) Bizzarri, R.; Solaro, R.; Chiellini, E. *J. Bioact. Comput. Polym.* **1999**, *14*, 504.
(31) Chiellini, E.; Bizzarri, R.; Bonaguidi, P.; Talamelli, P.; Solaro, R. *J. Macromol. Sci.—Pure Appl. Chem.* **1999**, *A36*, 901.
(32) Bizzarri, R.; Talamelli, P.; Solaro, R.; Chiellini, E. *J. Bioact. Comput. Polym.* **2000**, *15*, 43.
(33) Bizzarri, R.; Chiellini, F.; Ober, C. K.; Saltzman, W. M.; Solaro, R. *Macromol. Chem. Phys.*, in press.
(34) Braud, C.; Bunel, C.; Vert, M. *Polym. Bull.* **1985**, *13*, 293.
(35) Guerin, P.; Vert, M.; Braud, C.; Lenz, R. W. *Polym. Bull.* **1985**, *14*, 187.
(36) Cammas, S.; Renard, I.; Langlois, V.; Guerin, P. *Polymer* **1996**, *37*, 4215.
(37) Leboucher-Durand, M. A.; Langlois, V.; Guerin, *Polym. Bull.* **1996**, *36*, 35.
(38) Mabille, C.; Masure, M.; Hemery, P.; Guerin, P. *Polym. Bull.* **1998**, *40*, 381.
(39) Arnold, S. C.; Lenz, R. W. *Macromol. Symp.* **1986**, *6*, 285.
(40) Guerin, P.; Vert, M. *Polym. Commun.* **1987**, *28*, 11.
(41) Bouteault, K.; Cammas, S.; Huet, F.; Guerin, P. *Macromolecules* **1995**, *28*, 3516.
(42) Couchman, P. R. *Macromolecules* **1978**, *11*, 1156.

MA0111257