ELSEVIER

S0032-3861(96)00204-2

Polymer Vol. 37 No. 18, pp. 4215–4220, 1996

0032-3861/96/$15.00+0.00

Poly(β-malic acid): obtaining high molecular weights by improvement of the synthesis route

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(Received 29 January 1996)

Poly(β-malic acid), PMLA, was first synthesized with the aim of being used as a macromolecular prodrug. However, this biodegradable polymer is now the parent compound of a large family of functional polymers, copolymers and polystereoisomers. The requirement for high molecular weight polymers for a series of temporary therapeutic or specific applications needs to be conducted to examine the different steps of the synthesis route starting from either racemic or chiral aspartic acid. Drastic purifications of the intermediate products and of the β-substituted-β-lactone used as monomer has allowed the synthesis of polymers with high molecular weights, in a reproducible manner. In the case of racemic poly(β-malic acid benzyl ester), a precursor of PMLA, it is now possible to prepare polymers with a M_{SEC} superior to 150 000 (polystyrene standards). The specific catalytic hydrogenolysis of the lateral benzyl protecting groups can be carried out and leads to the corresponding PMLA with long molecular chains, which are necessary for certain applications *in vivo*. The results have been extended to different racemic and optically active derivatives of this poly(3-hydroxy acid) ester type. Consequently, reproducible characteristics of the corresponding polymeric materials can be obtained. Copyright © 1996 Elsevier Science Ltd.

(Keywords: poly(β-malic acid); poly(β-malic acid benzyl ester); high molecular weights)

Introduction

The use of a therapeutic molecule is limited by several drawbacks. The first and maybe the more important is the non-selectivity of the drug for diseased tissues or cells, resulting in high global toxicity. Most of the drugs are low molecular weight compounds and are consequently rapidly excreted from the body. Therefore, large and repeated doses must be administered in order to maintain a therapeutic action[1].

To increase the therapeutic index and to protect the normal tissues and cells against the toxic side-effects of the drugs, much effort has been focused on the design of drug-carrier conjugates. Moreover, the possibility of obtaining 'intelligent' carriers which are able to recognize their objective is of interest.

In 1975, Ringsdorf introduced the idea of tailor-made macromolecular prodrugs. The drug is attached via a spacer to a biostable or biodegradable polymer backbone; a solubilizer, a homing device and a device for controlling the physico-chemical properties are also bound to this pharmacologically active polymer[2,3]. In spite of its simplicity, the Ringsdorf model was the base for the development of macromolecular drug carriers[4,5].

Poly(β-malic acid), PMLA, has the structure of a macromolecular prodrug as defined by Ringsdorf. Indeed, this polymer has a lateral carboxylic acid function that can be modified in order to attach a drug and/or a homing device[6–8]. Moreover, the presence of the carboxylic acid function allows the solubility of the carrier in water[6–8]. Another important property of PMLA is its bioresorbability. The *in vitro* degradation of PMLA, which takes place by hydrolysis of the ester bonds of the main chain, produces malic acid which is a natural molecule[9–11]. Fournié *et al.*[12,13] have studied the *in vivo* behaviour of an end-chain[12] and repeat-unit[13] radiolabelled PMLA of 30 000 mol.wt. The results of these studies have shown that PMLA was massively and rapidly excreted by the kidney without complete degradation. This fast renal excretion is characteristic of small macromolecules[14]. In consequence, it is important to obtain high molecular weight PMLAs, in order to delay the renal excretion and to increase the blood half-life, leading to a higher accumulation of the prodrug in the organs.

In this paper, we report on improvements to the PMLA synthesis route, in order to obtain high molecular weight polymers. Purification of each precursor and of the monomer were studied and allowed really high molecular weight polymers to be obtained.

Experimental

All the solvents were dried and purified by distillation as previously described[15].

Gas chromatography was performed on a VARIAN 3300 Gas Chromatograph equipped with a SE 30 column (25 m × 0.25 mm i.d.). The temperature of the column was 120°C and was increased by 10°C min^{-1} to 160°C.

HPLC equipment. (a) The normal phase HPLC was performed using a normal phase (150 mm × 4.6 mm i.d., Nucleosil, particle size 10 μm) column, HPLC grade solvents of methanol/hexane (2:1) and u.v. detection at 220 nm wavelength. (b) The reversed phase HPLC was realized using a Beckman 110B SDM pump equipped

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with a Spherisorb C6 column (150 mm × 4.6 mm). The eluent was a mixture of methanol/deionized water (3 : 1) with a flow rate of 1 ml min^{-1}. Ultraviolet detection was done at 220 nm wavelength.

(RS)-Bromosuccinic acid ***1***. 100 g (0.75 mol) of DL-aspartic acid and 426 g (5.5 eq., 4.13 mol) of NaBr were dissolved in 1600 ml of 2 N H_2SO_4. The solution was cooled in an ice bath. 62.1 g (1.2 eq., 0.9 mol) of $NaNO_2$ were smoothly added on the previous mixture kept in the ice bath; the addition took about 1.5 h. The mixture was stirred for 30 min at 0°C (ice bath). 8 g of urea were added and the mixture was stirred for 15 min at room temperature. The aqueous phase was extracted by 1000 ml of ethyl acetate and washed with 200 ml of ethyl acetate. Organic phases were gathered, washed with 20 ml of slightly acid water and dried over $MgSO_4$/decolorizing charcoal for 1 h. After filtration through celite, the solvent was evaporated to give a white powder.

Characteristics: m = 118 g; yield = 80%; m.p. = 168°C. ^{1}H n.m.r. (90 MHz, CD_3COCD_3): 2.86–3.43 (m, 2H); 4.56–4.73 (dd, 1H); 10.59 (s, 2H).

(RS)-Bromosuccinic acid ***2***. Experimental work-up was the same as described above starting with 100 g of DL-aspartic acid. Bromosuccinic acid **2** was recrystallized twice into acetonitrile.

Characteristics: m = 89 g; yield = 60%; m.p. = 175°C. ^{1}H n.m.r.: see **1**.

(RS)-Bromosuccinic acid ***3***. Experimental work-up was the same as described above starting with 200 g of DL-aspartic acid. Bromosuccinic acid **3** was recrystallized four times into acetonitrile.

Characteristics: m = 118.6 g; yield = 40%; m.p. = 175°C. ^{1}H n.m.r.: see **1**.

Mixture of RS-3-benzyloxycarbonyl-3-bromopropanoic acid ***4*** *and RS-2-bromo-3-benzyloxycarbonylpropanoic acid* ***5***. 100 g (0.51 mol) of diacid **1**, dried under vacuum at 45°C for 4 h, were kept under N_2 stream for 2 h. 190 ml of anhydrous THF were added under N_2 atmosphere. The mixture was cooled in an ice bath and 93 ml (1.3 eq., 0.66 mol) of trifluoroacetic acid anhydride (TFAA) were added. The mixture was stirred for 2 h at room temperature under N_2 atmosphere. THF, trifluoroacetic acid (TFA) formed and the TFAA excess were evaporated leading to a brown oil. This oil was immediately put under N_2 atmosphere and 53 ml (1 eq., 0.51 mol) of freshly distilled benzyl alcohol were added. The mixture was stirred under N_2 atmosphere at 45°C for 12 h to give 140 g of a monoester mixture as an orange oil.

Characteristics: m = 140 g (70% of lactonizable monoester **4**); yield = 96%. ^{1}H n.m.r. (90 MHz, CD_3COCD_3, δ ppm): 2.90–3.47 (m, 2H); 4.64–4.80 (dd, 1H); 5.16 (s, 2H, 30% of non-lactonizable monoester **5**); 5.23 (s, 2H, 70% of lactonizable monoester **4**); 7.36 (s, 5H).

Mixture of RS-3-benzyloxycarbonyl-3-bromopropanoic acid ***6*** *and RS-2-bromo-3-benzyloxycarbonylpropanoic acid* ***7***. Experimental work-up was the same as described above with 50 g of diacid **2**. The mixture of monoesters was dissolved into 150 ml of ether, washed with 3 × 100 ml of water and dried over $MgSO_4$/decolorizing charcoal for 2 h. After filtration through celite, the solvent was evaporated to lead to a bright yellow oil.

Characteristics: m = 71.6 g (70% of lactonizable monoester **6**); yield = quantitative. ^{1}H n.m.r.: see **4**, **5**.

Mixture of RS-3-benzyloxycarbonyl-3-bromopropanoic acid ***8*** *and RS-2-bromo-3-benzyloxycarbonylpropanoic acid* ***9***. Experimental work-up was the same as described above with 100 g of diacid **3** (same experimental work-up as the one used for the mixture of monoesters **6**, **7**, same purification).

Characteristics: m = 138.9 g (70% of lactonizable monoester **8**); yield = 95%. ^{1}H n.m.r.: see **4**, **5**.

RS-4-benzyloxycarbonyl-2-oxetanone ***L1***. 50 g (70% of lactonizable monoester **4**, 0.122 mol) of the monoesters mixture **4**, **5** were put in a beaker. 250 ml of water was added and a solution of 2 N NaOH was added until the pH reached 7.2. The aqueous phase was added over 250 ml of benzene at 45°C. The mixture was vigorously stirred at 45°C for 3 h. After decantation, the organic phase was washed with 2 × 250 ml of 5% $NaHCO_3$ aqueous solution, 2 × 250 ml of slightly acid water and water until neutrality, and then dried over $MgSO_4$. After filtration, the benzene was eliminated to lead to 14.2 g of crude lactone **L1**. This lactone **L1** was then purified by three distillations under vacuum.

Characteristics: m = 2 g; yield = 9% with respect to lactonizable monoester **4**. b.p. = 114–116°C under 2 × 10^{-2} mmHg. Elementary analysis: found: C = 64.19%, H = 4.87%, O = 30.9%; calculated: C = 64.08%; H = 4.85%, O = 31.07%. I.r. (ν, cm^{-1}): 1825 and 1740 (C–O). ^{1}H n.m.r. (90 MHz, CD_3COCD_3, δ ppm): 3.57–4.14 (m, 2H); 5.04–5.16 (dd, 1H); 5.27 (s, 2H); 7.40 (s, 5H).

RS-4-benzyloxycarbonyl-2-oxetanone ***L2***. Experimental work-up was the same as described above with 50 g of the monoesters mixture **4**, **5**. The lactone **L2** was purified by chromatography on silica gel (eluent: dichloromethane/petroleum ether, 9/1) before the distillations.

Characteristics: m = 3.7 g; yield = 15% with respect to lactonizable monoester **4**. b.p. = 118°C under 2 × 10^{-2} mmHg. I.r. and ^{1}H n.m.r.: see **L1**.

RS-4-benzyloxycarbonyl-2-oxetanone ***L3***. Experimental work-up was the same as described above (lactone **L2**) with 50 g of the monoesters mixture **6**, **7**.

Characteristics: m = 2.3 g; yield = 9% with respect to lactonizable monoester **6**. b.p. = 116–118°C under 2 × 10^{-2} mmHg. I.r. and ^{1}H n.m.r.: see **L1**.

RS-4-benzyloxycarbonyl-2-oxetanone ***L4***. Experimental work-up was the same as described above (lactone **L2**) with 40 g of the mixture of monoesters **8**, **9**.

Characteristics: m = 4 g; yield = 20% with respect to lactonizable monoester **8**. b.p. – 116–118°C under 2 × 10^{-2} mmHg. I.r. and ^{1}H n.m.r.: see **L1**.

RS-4-benzyloxycarbonyl-2-oxetanone ***L5***. Experimental work-up was the same as described above (lactone **L4**) with 40 g of the mixture of monoesters **8**, **9**. Organic phase containing the lactone **L5** was washed with 2 × 150 ml of acid water (pH = 1), water until neutrality and dried over $MgSO_4$. After filtration, the solvent was

eliminated to lead to 15 g of crude lactone **L5**. This monomer was then purified by chromatography on silica gel and by distillation under vacuum.

Characteristics: $m = 1.9$ g; yield = 9% with respect to lactonizable monoester **8**. b.p. = 116–118°C under 2×10^{-2} mmHg. I.r. and ^{1}H n.m.r.: see **L1**.

*RS-4-benzyloxycarbonyl-2-oxetanone **L6**.* Experimental work-up was the same as described above (lactone **L4**) with 40 g of the mixture of monoesters **8**, **9**. Organic phase containing the lactone **L6** was washed with water and dried over $MgSO_4$. After filtration, the solvent was eliminated to lead to 15 g of crude lactone **L6**. This monomer was then purified by chromatography on silica gel and by distillation under vacuum.

Characteristics: $m = 2.3$ g; yield = 12% with respect to lactonizable monoester **8**. b.p. = 116–118°C under 2×10^{-2} mmHg. I.r. and ^{1}H n.m.r.: see **L1**.

*Poly(β-benzyl malate) **P1**.* Preparation of the initiator: the tetraethylammonium benzoate was recrystallized in a mixture of DMF/THF and dried under vacuum (10^{-2} mmHg) for 24 h at room temperature. 0.1 g (3.98×10^{-4} mol) of the initiator were put into 10 ml of absolute ethanol freshly distilled.

Polymerization: 122 μl of the initiator solution (10^{-3} eq.) were placed in the polymerization flask; the alcohol was eliminated under vacuum (10^{-2} mmHg) at room temperature. The tetraethylammonium benzoate was dried under vacuum (10^{-2} mmHg) at room temperature for 2 h. The vacuum was broken under inert atmosphere and the initiator was kept under N_2 atmosphere. 1 g of the lactone **L1** was kept under N_2 stream for 2 h and then transferred under N_2 in the polymerization flask containing the initiator. The polymerization was conducted at 37°C for 3 days (disappearance of the lactone peak at 1825 cm^{-1}). The polymer was dissolved in acetone, one drop of concentrated HCl was added and the polymer was precipitated into ethanol. The $PMLA^{50}BE_{100}$ **P1** was dried under vacuum at 40°C for 48 h.

Characteristics: $m = 0.786$ g; $T_g = 37$°C. S.e.c. (dioxane, polystyrene standards): $\bar{M}_n = 9\,000$; $\bar{M}_w = 17\,000$; $I_p = 1.8$; $M_{s.e.c.} = 26\,000$. I.r. (ν, cm^{-1}): 1740 (C–O). ^{1}H n.m.r. (90 MHz, CD_3COCD_3, δ ppm): 3.01 (m, 2H); 5.14 (s, 1H); 5.23 (m, 1H); 7.32 (s, 5H).

*Poly(β-benzyl malate) **P2**.* Experimental work-up was the same as described above with 1 g of the lactone **L2**.

Characteristics: $m = 0.800$ g; $T_g = 37$°C. S.e.c. (dioxane, polystyrene standards): $\bar{M}_n = 25\,000$; $\bar{M}_w = 42\,000$; $I_p = 1.8$; $M_{s.e.c.} = 41\,000$. I.r. and ^{1}H n.m.r.: see **P1**.

*Poly(β-benzyl malate) **P3**.* Experimental work-up was the same as described above with 1 g of the lactone **L3**.

Characteristics: $m = 0.810$ g; $T_g = 37$°C. S.e.c. (dioxane, polystyrene standards): $\bar{M}_n = 24\,000$; $\bar{M}_w = 79\,000$; $I_p = 3.3$; $M_{s.e.c.} = 70\,000$. I.r. and ^{1}H n.m.r.: see **P1**.

*Poly(β-benzyl malate) **P4**.* Experimental work-up was the same as described above with 1 g of the lactone **L4**.

Characteristics: $m = 0.820$ g; $T_g = 37$°C. S.e.c. (dioxane, polystyrene standards): $\bar{M}_n = 61\,000$; $\bar{M}_w = 110\,000$; $I_p = 1.8$; $M_{s.e.c.} = 174\,000$. I.r. and ^{1}H n.m.r.: see **P1**.

*Poly(β-benzyl malate) **P5**.* Experimental work-up was the same as described above with 1 g of the lactone **L5**.

Characteristics: $m = 0.820$ g; $T_g = 37$°C. S.e.c. (dioxane, polystyrene standards): $\bar{M}_n = 54\,000$; $\bar{M}_w = 120\,000$; $I_p = 2.2$; $M_{s.e.c.} = 174\,000$. I.r. and ^{1}H n.m.r.: see **P1**.

*Poly(β-benzyl malate) **P6**.* Experimental work-up was the same as described above with 1 g of the lactone **L6**.

Characteristics: $m = 0.880$ g; $T_g = 37$°C. S.e.c. (dioxane, polystyrene standards): $\bar{M}_n = 73\,000$; $\bar{M}_w = 121\,000$; $I_p = 1.7$; $M_{s.e.c.} = 174\,000$. I.r. and ^{1}H n.m.r.: see **P1**.

Results and discussion

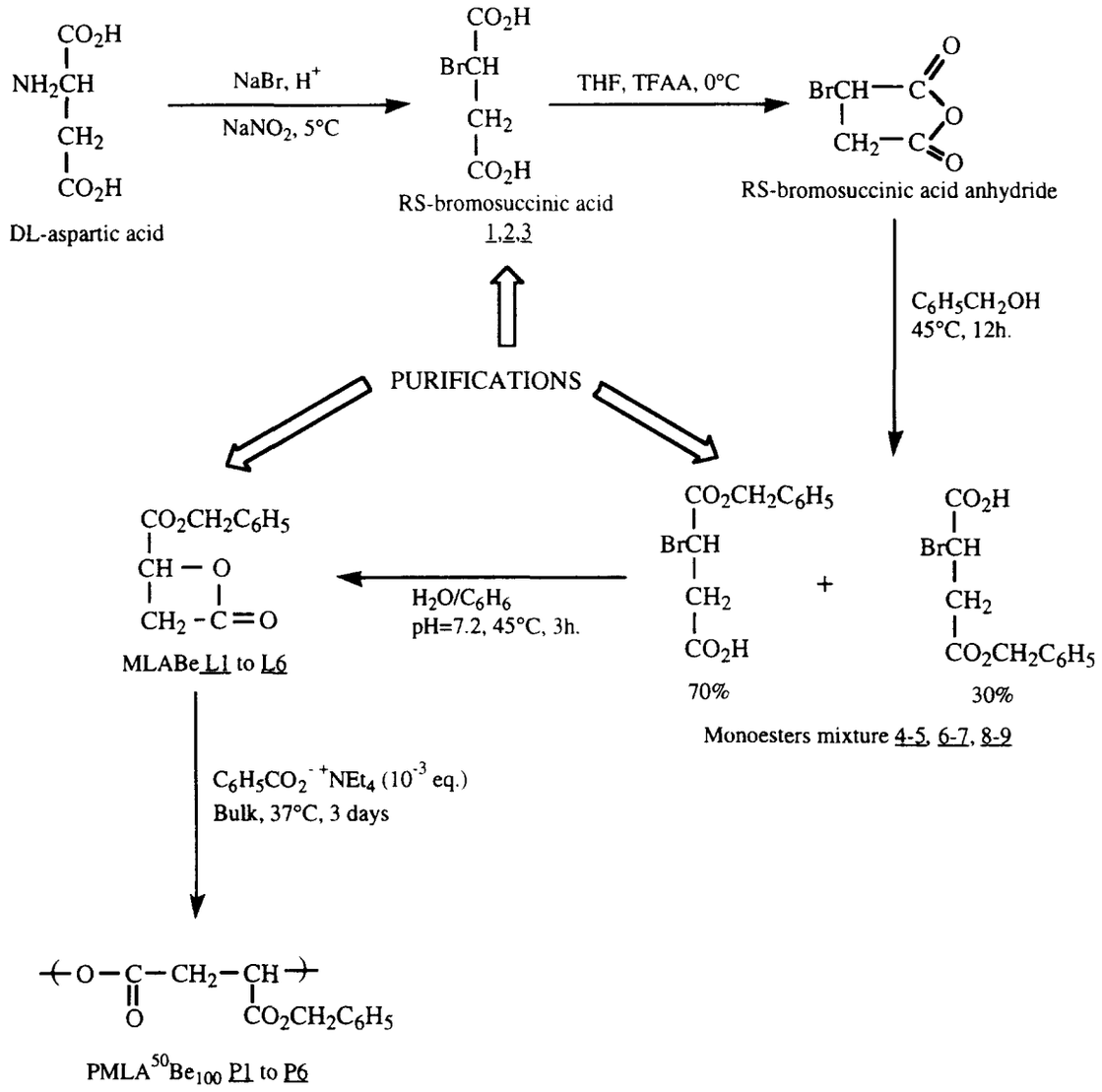
The synthesis of high molecular weight poly(β-malic acids) required the preparation of a β-substituted β-lactone, the 4-benzyloxycarbonyl-2-oxetanone or benzyl malolactonate (MLABe). Indeed, direct polycondensation of malic acid or its derivatives led anyway to oligomers. MLABe can be prepared according to several synthesis routes starting from either aspartic acid[15–17] or malic acid[18]. Whatever the method used, the purification procedures have to take into account the fragility of the β-substituted β-lactone as well as its high boiling point (120°C under 10^{-2} mmHg). Consequently, molecular weights of the polymers described were quite low and no reproducible results were obtained. For example, the first polymer prepared starting from RS-bromosuccinic acid had a molecular weight of 5000 (s.e.c. in dioxane, polystyrene standards)[19]. On the other hand, Lenz *et al.* have described the synthesis of a racemic $PMLA^{50}Be_{100}$ starting from DL-malic acid and having a molecular weight of 60 000 (s.e.c. in dioxane, polystyrene standards)[18]. Finally, Guérin *et al.* have obtained, from L-aspartic acid, an optically active $PMLA^{90}Be_{100}$ with a molecular weight of 40 000 (s.e.c. in dioxane, polystyrene standards)[16].

For this study, we have chosen the synthesis route starting from DL-aspartic acid. Indeed, this method presents the advantage of being simple and relatively short. *Scheme 1* describes this synthesis procedure and shows the compounds we have purified.

First, we have prepared the benzyl malolactonate, MLABe **L1**, without any purification of the intermediate compounds. Elementary analysis of the crude lactone showed the presence of 4% of bromide. MLABe **L1** was purified by washing followed by distillation under vacuum. The elementary analysis of the purified lactone has shown the disappearance of the bromide. MLABe **L1** gave access to a poly(β-benzyl malate), $PMLA^{50}Be_{100}$ **P1**, having a molecular weight of 26 000 (*Table 1*).

Because this molecular weight was very low in comparison to the calculated one (200 000; calculated from the ratio monomer/initiator) and to the one given in the literature (40 000; Guérin *et al.*)[16], we have studied the influence of purification of the monomer and of the intermediate compounds on the values of molecular weights (*Scheme 1*).

The benzylmalolactonate MLABe **L2**, obtained as the MLABe **L1**, was purified by chromatography on silica gel before the distillations. The molecular weight of the corresponding polymer, $PMLA^{50}Be_{100}$ **P2**, was determined to be 42 000 (*Table 1*). This molecular weight, corresponding to the one given by Guérin *et al.*[16], was



Scheme 1 Synthesis route to the PMLABe

Table 1 Characteristics of the different $PMLA^{50}Be_{100}$

Polymers	Yield[a] (%)	$\bar{M}_n$[b]	$\bar{M}_p$[b]	I_p[b]	$M_{s.e.c.}$[b]
P1	9	9000	17000	1.8	26000
P2	15	25000	42000	1.8	41000
P3	9	24000	79000	3.3	70000
P4	20	61000	110000	1.8	174000
P5	9	54000	120000	2.2	174000
P6	12	73000	121000	1.7	174000

[a] The yield in purified lactone is given with respect to the lactonizable monoester (**4**, **6** or **8**)
[b] Molecular weights were determined by s.e.c. in dioxane, polystyrene standards. Mosmo was measured by osmometry in toluene

still lower than the expected one (200000; calculated from the ratio monomer/initiator). Therefore, purification procedures of the following intermediate compounds were studied: bromosuccinic acid and the monoester mixture. The monoester mixture was washed with water before being used for the lactonization reaction. The crude bromosuccinic acid was purified by several recrystallizations, two or four, in acetonitrile. The melting point of this compound increased from 168°C for the crude acid **1** to 175°C for the recrystallized ones, **2** and **3**.

The molecular weights of the corresponding $PMLA^{50}Be_{100}$ were increased from 41000 to 70000 (with bromosuccinic acid recrystallized twice, $PMLA^{50}Be_{100}$ **P3**) and to 174000 (with bromosuccinic acid recrystallized four times, $PMLA^{50}Be_{100}$ **P4** to **P6**).

As shown in *Table 1*, the different techniques used to wash the crude lactone did not influence the molecular weights of the corresponding polymers (**P4** to **P6**). However, washing with pure water will be preferred because some acid impurities can remain in the two other cases leading to a possible degradation of the monomer and/or to some transfer reactions or termination during the polymerization step.

Throughout this study, we have demonstrated that purifications of all the intermediate compounds as well as of the monomer are essential in order to obtain high molecular weights of poly(β-benzyl malate).

In order to confirm the high degree of purity of our lactones, we have analysed them by normal phase high performance liquid chromatography (h.p.l.c.) (*Figure 1*). This chromatogram showed the presence of a very small

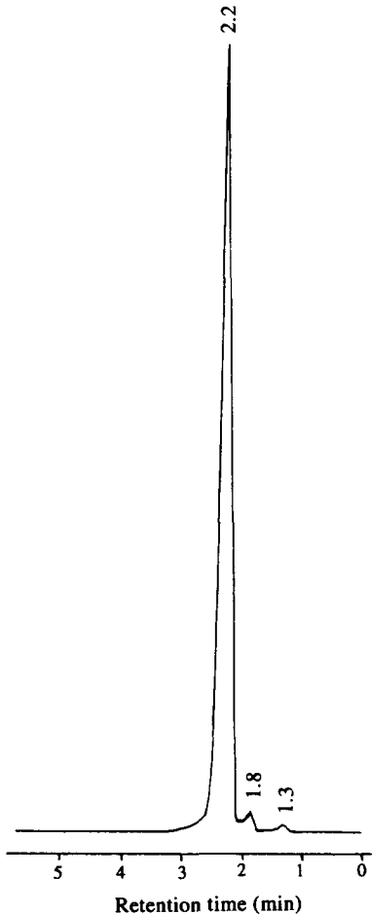


Figure 1 Normal phase h.p.l.c. chromatogram of the MLABe obtained from aspartic acid

amount of impurities (peaks at 1.3 min and at 1.8 min) while the lactone gave an important peak at 2.2 min.

Recently, we have established a new synthesis route starting from DL-, L- or D-malic acid[20]. After purification of the intermediate compounds and of the monomer, the racemic lactone obtained has been analysed by reverse phase h.p.l.c. and gas chromatography (g.c.). As shown by the reversed phase h.p.l.c. chromatogram, only a very small amount of impurities remained in this lactone (*Figure 2*).

Moreover, this chromatogram is very similar to the one corresponding to the lactone prepared from DL-aspartic acid: an important peak at 4.2 min corresponding to the lactone and three small peaks (3.1 min, 1.7 min and 1.3 min) corresponding to impurities.

The degree of purity of the monomer obtained from DL-malic acid was determined by g.c. to be about 97%. We assumed that the degree of purity of the lactone obtained from DL-aspartic acid was the same as the one calculated for the lactone prepared from DL-malic acid, *ca.* 97%. The molecular weight of the PMLABe obtained from the MLABe prepared from DL-malic acid has been determined to be 115 000 (dioxane, polystyrene standards)[21].

In conclusion, we have demonstrated that the purification procedures we established have allowed the preparation of high molecular weight polymers. In addition, these molecular weights were very close to the theoretical molecular weight expected for a living anionic

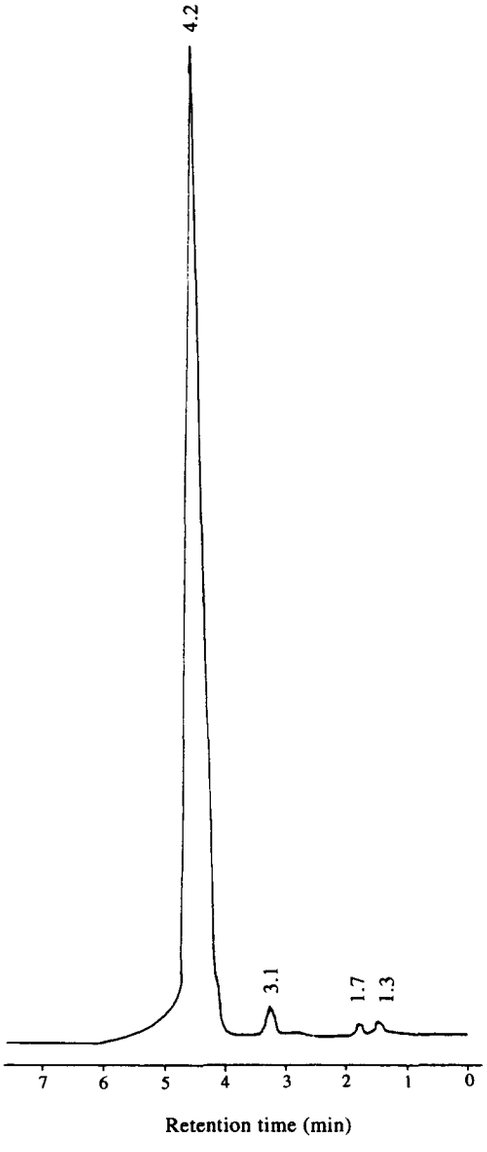


Figure 2 Reversed phase h.p.l.c. chromatogram of the MLABe obtained from malic acid

polymerization (calculated from the ratio monomer/initiator).

Moreover, it has been shown that no main chain degradation occurred during the specific catalytic hydrogenolysis[10]. Consequently, molecular weights of PMLAs obtained by hydrogenolysis of PMLA^{50}Be$_{100}$ **P4** to **P6** should be higher than the threshold of renal excretion (about 50 000). Therefore, synthesis of such high molecular weight PMLAs can allow the study of *in vivo* behaviour of PMLA using radiolabelled polymers as described by Fournié *et al.*[12,13].

At last, the purification procedures we established can be extended to other types of monomer bearing different alkyl or alkenyl groups and allow also the synthesis of high molecular weight racemic or optically active PMLA derivatives with various groups as pendant groups or directly introduced in the main chain[22–24].

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