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4-Alkyloxycarbonyl-2-oxetanones with two stereogenic centers as precursors of malic acid alkyl esters polystereoisomers.

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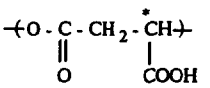
Abstract : Racemic and optically active 4-alkyloxycarbonyl-2-oxetanones containing two stereogenic centers have been prepared starting from racemic, (R) or (S) aspartic acid or malic acid as chiral synthons and by introducing an asymmetric alkyl ester group (2-methylbutyl) in the course of a β-substituted-β-lactone synthesis route. Different stereoisomers of the 4-[(2'-methyl)butyloxycarbonyl]-2-oxetanone have been prepared and characterized. It has been shown by using 400 MHz ^{1}H NMR and Eu(hfc)$_3$ as chiral shift reagent that enantiomeric or diastereomeric excess as high as 98 % could be retained during the synthesis route according to the specific experimental conditions. High molecular weight racemic and optically active poly(2-methylbutyl β-malate) have been prepared by anionic ring opening polymerization of the monomer feed. At last, it has been shown that racemic or optically active poly (2-methylbutyl β-malate-co-β-malic acid) can be obtained by copolymerization of 4-[(2'-methyl)butyloxycarbonyl]-2-oxetanone and 4-benzyloxycarbonyl-2-oxetanone and further catalytic hydrogenolysis of the benzyl protecting groups.

Introduction : In the field of therapeutic or environmental temporary applications, polymeric materials must be compatible with living species over their period of action, up to ultimate stage of the degradation. It is possible to take advantage of the biomass by using biopolymers or biomolecules for the preparation of biodegradable materials[1]. Moreover, the adjustment of the materials properties allows to the tailor-making of polymers with a biodegradable chiral backbone and pendant functional groups. Thus, suitable material properties, such as hydrophilic/hydrophobic balance, morphology, degradation rate, bioactive molecules attaching can be achieved by copolymerization and chemical modification. Poly (β-malic acid) (PMLA 100) is a very good candidate due to the presence of a carboxylic acid pendant group, besides the ester cleavable bond and the stereogenic center in the monomer unit[2].



PMLA 100

This polymer is now accessible from the biomass by three routes : both L-(S)-aspartic acid and L-(S)-malic acid yield poly (β-L-malic acid) and polymer degradation products L-malic acid by *"in vitro"* degradation[3-5]. Natural homochiral PMLA 100 can be obtained from the plasmodia extracts and from the culture medium of *Physarum polycephalum*[6]. PMLA 100 is the parent compound of a

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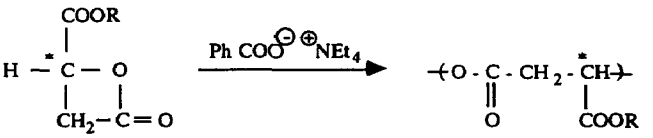
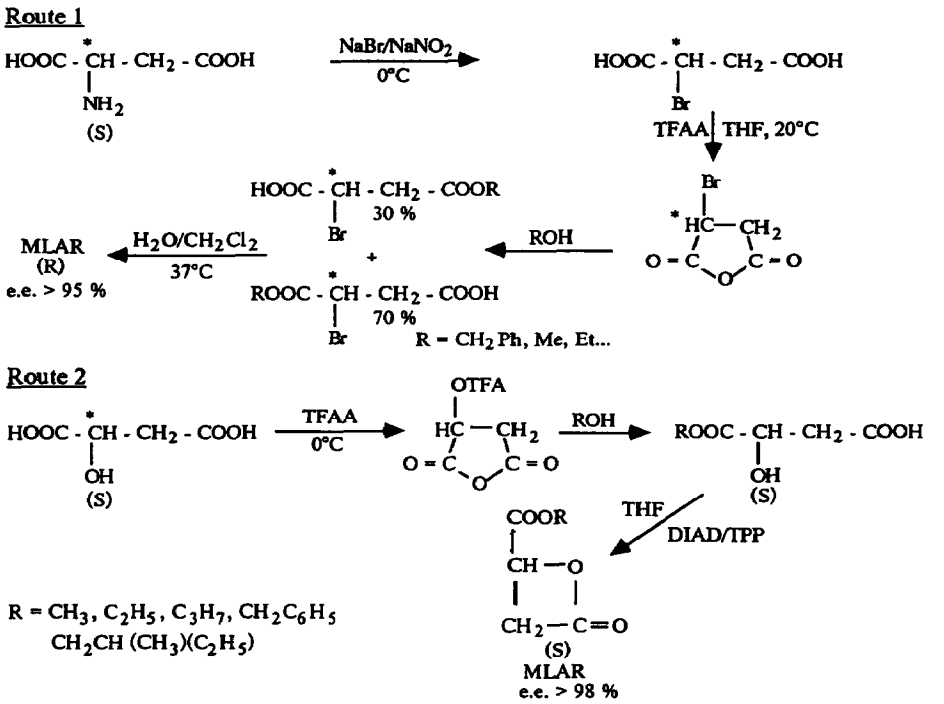
large family of functional polymers, copolymers and stereocopolymers which can be made by direct copolymerization and/or by chemical modification. The chemical route appears very versatile as it opens the way to a large number of derivatives by changing the enantiomeric composition and the stereogenic center distribution within the polymer chain or by modifying the nature of the ester pendant group[7]. Indeed, high molecular weight poly (β-malic acid) and its derivatives can be chemically synthesized in several steps and one step of which involve in the ring-opening polymerization of β-substituted-β-lactones.



Scheme 1 : Synthesis route to poly (β-malic acid esters)

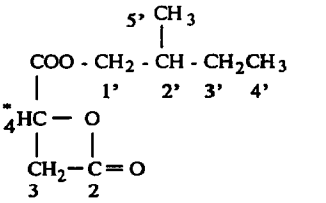
The limitation for building such macromolecules, with different types of ester groups, by direct copolymerization of different malolactonates with variable substituents in different proportions and distributions to fit the requirements for a specific application, is the synthesis of the corresponding monomers. Indeed, the chemistry of lactones is very complex and the chemical route corresponding to a specific compound has to be adapted. Moreover, the possibility of taking advantage of chirality for adjusting the properties of the resulting polymers, as in the case of polylactide [8], requires a strict control of the stereochemistry. In this paper, we wish to report preparation and characterization of different stereoisomers of an alkyl malolactonate with two stereogenic centers and the possibility of obtaining the corresponding high molecular weight racemic and optically active polymers and copolymers. If the presence of a stereogenic carbon in the polymer main chain is not frequent, the possibilities to introduce a second stereogenic center in the macromolecule are very exceptional. Moreover, optically active lactones are interesting, since, because of their reactivity due to the ring-strain, they can serve as optically active intermediates in several syntheses of bioactive molecules or as chiral compounds for enantiomer separation chromatography.

Results and discussion : Two chemical routes have been used in the preparation of racemic and optically active 4-benzyloxy-and 4-[(2'-methyl)butyloxycarbonyl]-2-oxetanones. The first method is now well established and starts from aspartic acid [2]. It is available for the first member of the malolactonic acid esters family, benzylmalolactonate (MLABe), and has been expanded to alkyl ester groups such as butyl or 2-methylbutyl. This synthesis has been improved by a detailed purification study and very high molecular weight have been obtained (M_{SEC} ≈ 150 000 in dioxane with polystyrene standards) with reproducible results[7]. The second method concerns the dehydration of malic acid monoesters using diisopropylazodicarboxylate and triphenylphosphine (Scheme 2). This new route is simple, reproducible and particularly interesting for obtaining monomers with high enantiomeric excesses ; it is carried out for monomers with benzyl or other alkyl ester groups (methyl, ethyl...)[4].



Scheme 2 : Synthetic route from optically active aspartic acid (route 1) and from malic acid (route 2)

In this case also, starting from the natural enantiomer, L-(S)-malic acid, the resulting malic acid ester polymer unit will have the same L-configuration as shown by degradation of the polymer conducting to L-malic acid (NMR and polarimetry determination)[10]. The ring closure occurs with inversion of configuration at the hydroxyl bearing carbon ; a second inversion of configuration takes place at the same carbon during the ring-opening polymerization. In the preparation of the malolactonates, racemic or L-(S)-malic acid, racemic or L-(S) and D-(R)-aspartic acid have been used. Racemic or (R) or (S)-2-methylbutanol have been added to trifluoroacetate of malic acid anhydride to prepare different stereoisomers of 3-[(2'-methyl)butyloxycarbonyl]-2-hydroxypropionate or to bromosuccinic acid anhydride for obtaining 3-[(2'-methyl)butyloxycarbonyl]-2-bromopropionate. The relationship between the configuration of the polymer and its thermal and physical properties requires the knowledge of enantiomeric and diastereomeric composition of the alkylmalolactonate precursors. Configurational analysis for each stereogenic center of the β-substituted-β-lactone stereoisomer has been carried out by high resolution ^1H NMR spectroscopy in presence of tris [3-heptafluoropropylhydroxymethylene)-d-camphorato] europium(III), $Eu(hfc)_3$.



1

a (4RS, 2'RS) c (4R, 2'RS)
b (4RS, 2'S) d (4R, 2'S)
e (4S, 2'S)

In the goal of assigning all peaks corresponding to(4RS, 2'RS) racemic lactone **1a**, expansions of ^1H NMR [1 +0.3 eq. $Eu(hfc)_3$] spectra corresponding to the stereosensitive proton regions of the different stereoisomers 1 have been compared.

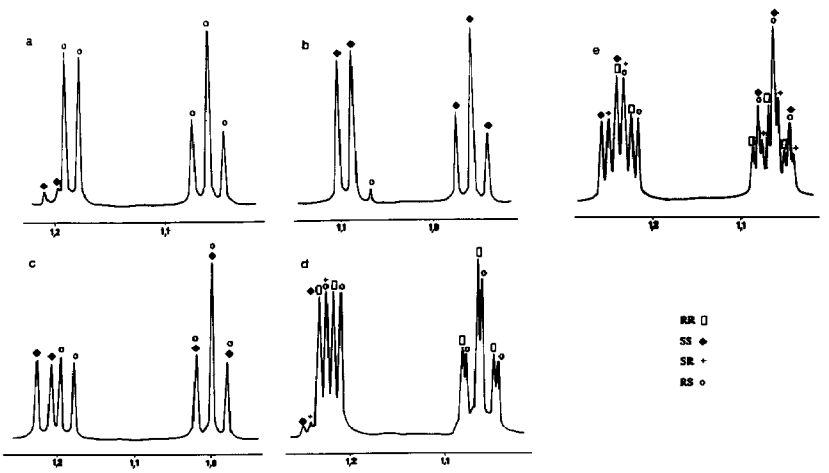


Figure I : ^1H NMR of the 4-[(2'-methyl)butyloxycarbonyl]-2-oxetanone in presence of Eu[hfc]$_3$ in $CDCl_3$.
Expansion of CH_3 regions : a) **1d** (4R,2'S), b) **1e** (4S,2'S), c) **1b** (4RS,2'S), d) **1c** (4R,2'RS), e) **1a** (4RS,2'RS).

Figure I displays expansions of CH_3 regions. When the lateral stereogenic center $C_{2'}$ was of (S) configuration, wathever the configuration (R) or (S) of the cyclic stereogenic center C_4, three peaks were observed for $_{4'}CH_3$ protons (regions 1.0-1.1 ppm) related to the different stereoisomers **1d** (4R,2'S) (figure Ia), **1e** (4S,2'S) (figure Ib) and **1b** a 1:1 mixture of (4R,2'S) and (4S,2'S) diastereoisomers (figure Ic). In the case of **1c**, a 1:1 mixture of (4R,2'R) and (4R,2'S) diastereoisomers, where the two configurations R and S are present in the stereogenic lateral center $C_{2'}$ (figure Id), $_{4'}CH_3$ protons displayed two triplets. These $_{4'}CH_3$ protons resonances expansions

(figure Ia to Id) allowed us to determine the enantiomeric composition of the lateral chain stereogenic center $C_{2'}$ as well as the assignment of all the peaks of $_{2'}CH_3$ in the case of the racemic monomer **1a** containing a 1:1:1:1mixture of (4RS,2'RS) stereoisomers (figure Ie). In the case of $_{5'}CH_3$ protons resonance (1.2 ppm), observations were totally different. When the ring stereogenic center C_4 contained the two configurations (R) and (S), for monomer **1b** (4RS,2'S), we observed two doublets corresponding to the stereoisomers (4R,2'S) and (4S,2'S) (figure Ic). In the case of homochiral ring stereogenic center C_4, monomers **1d** (4R,2'S) and **1e** (4S, 2'S), $_{5'}CH_3$ protons resonances gave only two principal peaks in both cases, with small peaks corresponding to other stereoisomers: (4S,2'S) for **1d**, (4R,2'S) for **1e** (figure Ia and Ib). When the lateral chain stereogenic center $C_{2'}$ was R and S as in 1:1 diastereomers mixture (4R,2'S) and (4R,2'R) **1c**, we observed two doublets for $_{5'}CH3$ protons resonances (figure Id) as well as small peaks due to the presence of the (4R,2'S) and (4S,2'R) stereoisomers. $_{5'}CH_3$ allowed us to determine enantiomeric composition of cycle stereogenic center C_4. It was possible to calculate enantiomeric excess of this carbon using the relative intensity of peaks (Table 1).

Table 1 : Enantiomeric excess of ring stereogenic carbon C_4 calculated using the relative intensity of peaks in ^1H NMR.

Monomer	1d (4R, 2'S)		1b (4S, 2'S)	1c (4R, 2'RS)
e.e. (%)	84 [a]	98 [b]	76 [a]	86 [a]
Figure	1a	-	1b	1d

a Monomer prepared from aspartic acid (route 1); b Monomer prepared from malic acid (route 2)

Differences between enantiomeric excesses can be explained by specific experimental conditions. In the case of route 1 (L- or D-aspartic acid as precursors) enantiomeric excess can be adapted according to the temperature of the reactions ; when lactonization is carried out at 35°C and all other steps at room temperature, the enantiomeric excess is ≥ 95 %. Route 2 leads to very high enatiomeric excess (≈ 98 %) as previously demonstrated[2]. It is important to note that the $C_{2'}$ stereogenic center is not affected by the different reactions ; 2-methyl-1-butanol has been used with two different enantiomeric excesses (98 % and 80 %) and the same configuration compositions have been found in the monomers by ^1H NMR for C_4. Comparison between all the expansions of the $^5CH_3$ region allowed to assign all the peaks given by the protons of $_{5'}CH_3$ of (4RS, 2'RS) racemic monomer **1e** (4RS, 2'RS), (figure 1e).

The study on $_{1'}CH_2$ has shown that these lateral protons were only stereosensitive to the ring stereogenic center configuration. The situation for $_3CH_2$ protons in more complex due to the different behaviour for each proton of an ABX system (figure 2). H_A gave one splitted doublet with a fine structure if $C_{2'}$ has only one (S) configuration, but is not stereosensitive to the proximal stereogenic center ; H_B, on the contrary, is stereosensitive to C_3 configuration.

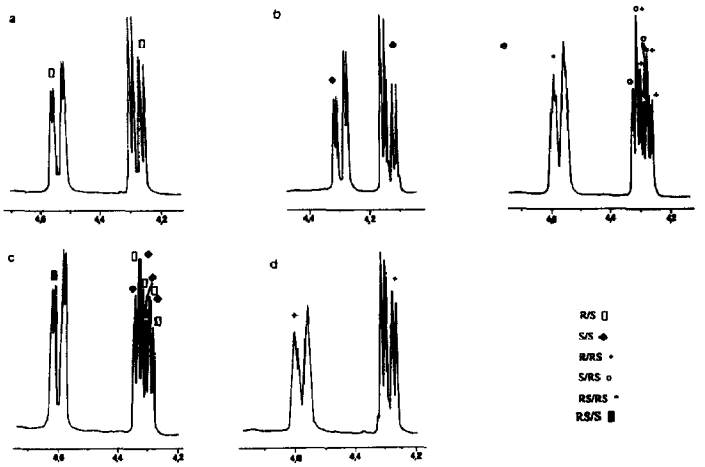


Figure II : ^{1}H NMR of the 4-[(2'-methyl)butyloxycarbonyl]-2-oxetanone in presence of Eu [hfc]$_3$ in $CDCl_3$ of $_3CH_2$ region : a) **1d** (4R,2'S), b) **1e** (4S,2'S), c) **1b** (4RS,2'S), d) **1c**(4R,2'RS), e) **1a** (4RS,2'RS).

Finally, figure III shows expansion of $_4$CH (cycle protons) regions. These protons were only sensitive to the configuration of this center. Indeed, $_4$CH protons gave only one broad peak whatever the configuration of lateral chain stereogenic center **1d**, **1e**, **1c** (figure IIIa,b,d); a small broad peak corresponds to the other enantiomer. Relative integration of these peaks allowed to determinate the enantiomeric composition of C_4 stereogenic center and results strictly agree with values calculated from $_5$CH$_3$ signals. Configurational structure of $C_{2'}$ influences only $_4$CH the signals resolution.

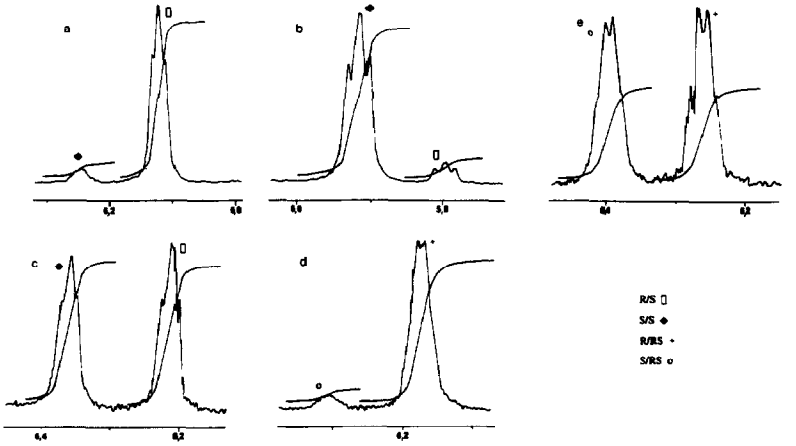
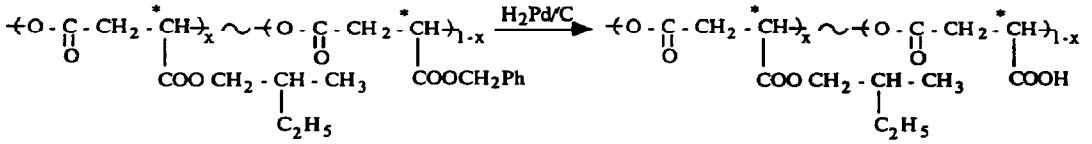


Figure III : ^{1}H NMR of the 4-[(2'-methyl)butyloxycarbonyl]-2-oxetanone in presence of Eu[hfc]$_3$ in $CDCl_3$ of $_4$CH region : a) **1d** (4R,2'S), b)**1e** (4S,2'S), c) **1b** (4RS,2'S), d) **1c** (4R,2'RS), e) **1a** (4RS,2'RS).

The possibility for obtaining high molecular weight polymers from monomers 1 has been shown by ring-opening homopolymerization of 1a (4RS, 2'RS) and 1e (4R,2'S) or by copolymerization in the presence of racemic and optically active MLABe, in bulk, using benzoate of tetraethylammonium as initiator. The two homopolymers presented Mp > 60 000 (SEC in THF, polystyrene standards; racemic poly [(2RS)-2-methylbutyl β-(RS)-malate)] was amorphous when poly [(2S)-2-methylbutyl β-(S)-malate)] presented a melting point at 120°C, indicating that the morphology is dependent on the configurational structure of the materials. Random racemic and optically active copolymers 2 containing 2-methylbutyl and benzyl ester groups have been prepared in variable proportions (85/15, 80/20, 60/40) starting from a mixture of the two corresponding racemic malolactonates or from (R)-benzylmalolactonate and 1e, leading to corresponding racemic or optically active poly (2-methylbutyl β-malate-co-β-malic acid) 3 after catalytic hydrogenolysis deprotection[10].



2 3

The interest of these copolymers is evident. The presence of carboxylic acid pendant groups can be used for modulating the degradation rate of temporary devices or for attaching compounds such as metalloporphyrins for catalytic enantioselective reactions or mesogenic groups for chiral liquid crystal polymers.

In conclusion, the mastery of the synthesis and the purification of an elarged spectrum of malolactonic acid esters with different but complementary chemical structures allows now the possibility to tailor make high molecular weight polyesters with reproducible characteristics and accurate properties. This polymer designed primarily for therapeutic temporary applications could be exploited in other fields of polymeric materials use.

Experimental part: DL-, D- and L- aspartic acids or DL-, L-malic acid used, were commercial products (Janssen). Racemic and (S)-2-methylbutanol (Janssen) have been used without further purification. Racemic and optically active benzyl and 2-methylbutyl malolactonates have been prepared according to previously reported synthesis routes (2-3). $Eu(hfc)_3$ (Janssen) was used for the preparation of a $CDCl_3$ stock solution (0.2 M). Suitable amounts of this preparation were mixed with the substrate solution (0.30 M) in NMR tubes. 400 MHz ^1H NMR spectra were recorded bu using a Bruker AC 400 apparatus at 22°C. The following spectral data have been found :

1a bp = 65°C under 2.10^{-2}mmHg.

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) : 0.81-0.90 (m, 6H) ; 1.10-1.20 (m, 1H) ; 1.30-1.45 (m, 1H) ; 1.69-1.77 (m, 1H) ; 3.50-3.60 (q, 1H) ; 3.70-3.78 (q, 1H) ; 3.95-4.02 (m, 1H) ; 4.05-4.10 (m, 1H) ; 4.80-4.85 (q, 1H).
^{1}H NMR (400 MHz, $CDCl_3$ + 0.3 eq. Eu[hfc]$_3$, δ ppm) : 1.04-1.09 (3t, 3H) ; 1.22-1.27 (3d,J 7,0Hz, 3H); 1.40-1.50 (m, 1H) ; 1.66-1.80 (m, 1H) ; 2.19-2.30 (m, 1H) ; 4.26-4.33 (2dd,J 6,1-5,6 Hz, 1H) ; 4.58-4.64 (2d,J 3,3Hz, 1H) ; 5.01-5.33 (3m,J 6,8-6,1 Hz, 2H) ; 6.25 (m, 1H) ; 50 % isomer (4R, 2'RS) ; 6.39 (m, 1H).

1b $[\alpha]_D^{25}$ = + 3.95, c = 2.0, dioxane
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) : see **1a**
^{1}H NMR (400 MHz, $CDCl_3$ + 0.3 eq. Eu[hfc]$_3$, δ ppm) : 0.9-1.02 (t,J 7,4 Hz, 3H) ; 1.16-1.20 (2d,J 6,8 Hz, 3H) ; 1.40-1.50 (m, 1H) ; 1.65-1.79 (m, 1H) ; 2.15-2.30 (m, 1H) ; 4.27-4.34 (2dd,J 6,5-6,3 Hz, 1H) ; 4.62-4.66 (2d,J 4,1 Hz, 1H) ; 5.12-5.37 (3m,J 6,7-6,0Hz, 2H) ; 6.21 (m, 1H) ; 6.37 [m, 1H, 50 % isomer (4S,2'S)] .

1c $[\alpha]_D^{25}$ = -0.75, c = 2.0, dioxane
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) : see **1a**
^{1}H NMR (400 MHz, $CDCl_3$ + 0.3 eq. Eu[hfc]$_3$, δ ppm) : 1.04-1.08 (2t,J 7,4 Hz, 3H) ; 1.22-1.25 [dd,J 6,8 Hz, 92 % isomer (4R,2'RS)] ; 1.26-1.27 [dd, 8 % (4S,2'RS)] ; 1.39-1.50 (m, 1H) ; 1.65-1.78 (m, 1H) ; 2.15-2.35 (m, 1H) ; 4.27-4.31 [dd,J 6,5 Hz, 93 % isomer (4R,2'RS)] ; 6.32 [m, 7 % isomer (4S,2'RS)].

1d $[\alpha]_D^{25}$ = + 3.5, c = 2.0, dioxane
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) : see **1b**
^{1}H NMR (400 MHz, $CDCl_3$ + 0.3 eq. Eu[hfc]$_3$, δ ppm) : 1.04-1.07 (t,J 7,4 Hz, 3H) ; 1.21-1.23 (d,J 6,8 Hz, 92 % isomer (4R,2'S)] ; 1.24-1.25 [d, 8 % isomer (4S,2'S)] ; 1.35-1.47 (m, 1H) ; 1.62-1.75 (m, 1H) ; 2.10-2.20 (m, 1H) ; 4.23-4.29 (dd,J 6,5 Hz, 1H) ; 4.54-4.59 (dd,J 4,1 Hz, 1H) ; 5.05-5.17 (2m,J 6,7-6,0 Hz, 2H) ; 6.19 [m, 93 % isomer (4R, 2'S)] ; 6.34 [m, 7 % isomer (4S,2'S)].

1e $[\alpha]_D^{25}$ = + 4.25, c = 2.0, dioxane
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) : see **1a**
^{1}H NMR (400 MHz, $CDCl_3$ + 0.3 eq. Eu[hfc]$_3$, δ ppm) : 0.94-0.97 (t,J 7,4 Hz, 3H) ; 1.08-1.09 (d, 3H, 9 % isomer (4R,2'S)] ; 1.09-1.12 (d,J 6,7 Hz, 3H, 91 % isomer (4S,2'S)] ; 1.30-1.43 (m, 1H) ; 1.56-1.70 (m, 1H) ; 2.05-2.16 (m, 1H) ; 4.12-4.18 (dd,J 6,5 Hz, 1H) ; 4.31-4.36 (2d,J 4,4 Hz, 1H) ; 4.85-4.98 (2m,J 6,7-6,0 Hz, 2H) ; 5.80 [m, 1H, 12 % isomer (4R,2'S)] ; 5.90 [1H, 88 % isomer (4S,2'S)].

2 ^{1}H NMR (400 MHz, CD_3COCD_3, δ ppm) : 0.90-0.95 (m, 6H) ; 1.17-1.53 (md, 2H) ; 1.73-1.77 (m, 1H) ; 2.95-3.13 (m, 2H) ; 3.95-4.09 (d, 2H) ; 5.53-5.60 (dd, 1H).

^{13}C NMR (75.47 MHz, CD_3COCD_3, δ ppm) : 11.56 ($\underline{C}H_3$) ; 16.67 ($\underline{C}H_3$) ; 26.58 ($\underline{C}H_2$) ; 34.93 ($\underline{C}H_2$) ; 36.22 ($\underline{C}H$) ; 67.93 ($\underline{C}H_2$) ; 69.49 ($\underline{C}H$) ; 168.89 ($\underline{C}$=O) ; 169.08 ($\underline{C}$=O).

Polymerizations have been carried out, in bulk, with $C_6H_5COO^-$ $^+NEt_4$ as initiator at 37°C (3 days). Polymers were dissolved in acetone and precipitated with ethanol. After separation polymers were dried under vacuum. Molecular weights of the different samples were evaluated by SEC, using a Waters apparatus equipped with a styrogel columns. Hydrogenolysis of benzyl protecting groups in copolymers has been made according the usual procedure in dioxane in the presence of 20 % Pd charcoal catalyst [11].

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