Polymer Bulletin 36, 35–41 (1996)

Polymer Bulletin

4-Carboxy-2-oxetanone as a new chiral precursor in the preparation of functionalized racemic or optically active poly(malic acid) derivatives

Marie-Agnès Leboucher-Durand, Valérie Langlois, Philippe Guerin*

Laboratoire de Physico-Chimie des Biopolymères, UMR 27, Université Paris XII, CNRS, 2 à 8 rue Henri Dunant, F-94320 Thiais, France

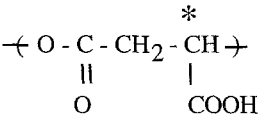
Received: 28 June 1995/Revised version: 20 July 1995/Accepted: 15 August 1995

Summary

Racemic and optically active 4-carboxy-2-oxetanones have been prepared, starting from racemic, (R)-4-benzyloxycarbonyl-2-oxetanone, by catalytic hydrogenolysis of the lateral benzyl protecting group. This new β-substituted-β-lactone (malolactonic acid), which was considered as totally unstable due to the presence of a carboxyl group, has been isolated, characterized and prepared in large quantities. The liberated carboxylic acid function can be used for coupling reactions with different types of molecules in the goal to tailor make functionalized multimeric macromolecules (reactive polymers, supported catalysts, liquid crystals polymers, macromolecular prodrugs). This possibility has been examplified by using 2, 4, 5-trichlorophenol as activating agent and chloramphenicol as bioactive molecule, which have been bound to malolactonic acid and then copolymerized by anionic ring opening polymerization in the presence of 4-benzyloxycarbonyl-2-oxetanone. It has been shown that this new route conducts to activated derivatives of poly (malic acid) and polymeric drug carriers patterns.

Introduction

The new concept of smart polymers, which consists in the tailor making of multimeric functionalized macromolecules for the strict adjustment of the material properties, conducts to the complexity of their structures and needs a diversification of the polymers. For example, in the field of synthetic biodegradable polymers, among devices for the controlled release of drugs, macromolecular prodrugs are investigated in response of conventional drug forms[1]. This design consists to couple drug molecules to a soluble biodegradable macromolecular carrier through cleavable covalent bonds ; targeting molecules can also be attached on the functional pendant group in the goal to increase the therapeutic efficiency[2]. Poly (β–malic acid) derivatives are very good candidates in the preparation of smart molecules for specific applications due to the presence of a carboxylic acid lateral group, besides the stereogenic center in the repeating unit and the ester cleavable bond[3].

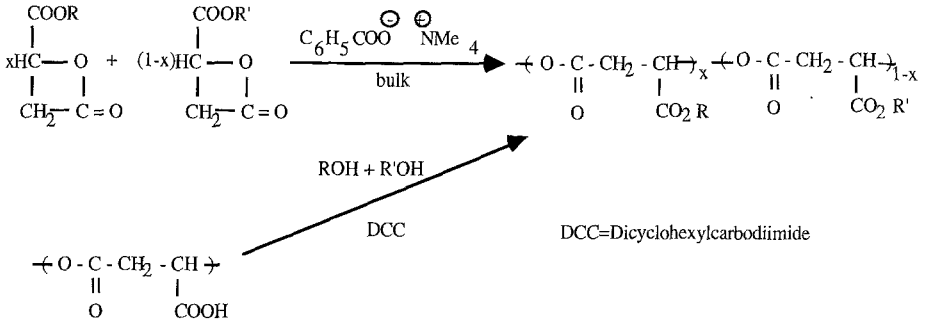


Poly(β–malic acid)-PMLA100

PMLA 100 is the parent compound of a large family of functional polymers, copolymers and stereocopolymers, which can be made by direct copolymerization and/or by chemical modification[4-6]. Two different routes were possible for the introduction of the different functional pendant ester groups (neutral for modulating solubility and rate degradation, bioactive, chiral or mesogenic) : by coupling the different corresponding

* Corresponding author

molecules on poly (β–malic acid) or by ring opening copolymerization of different β-substituted β–lactones bearing the selected pendant groups[7-8] . PMLA 100 is accessible by three routes : both D-(R)-, L-(S)- or racemic aspartic acid[9] and D-(R)-, L-(S)- or racemic malic acid[10] conduct to the polymer without inversion of configuration or racemization; moreover, monochiral L-(S)-PMLA 100 can be obtained from different microorganisms [11-13].



Scheme 1 : Synthesis of Poly(-β–malic acid esters) derivatives

The chemical route appears very versatile, as it opens the way to a large number of derivatives by changing the enantiomeric composition and the chiral centers distribution within the polymer chain, or by modifying the nature of the ester group. The strategy limitation for building such macromolecules lies in the possibility for synthesizing the corresponding monomers; especially in the formation of the pendant ester group by opening of a malic acid anhydride derivative during the multiple steps synthesis which depends on the reactivity of the used alcohol. In this paper, we wish to report the preparation of the racemic and optically active 4-carboxy-2-oxetanones which opens the route to a wide range of new β-substituted β-lactones conducting by ring opening polymerization and copolymerization to multimeric poly (β–malic acid) derivatives.

Experimental Part

All solvents were dried and purified by distillation. Anhydrous acetone was kept under reflux with $KMnO_4$ for 4 hours, dried under K_2CO_3 and distillated.

(R,S) and (R)-benzylmalolactonate, 1

This compound was prepared from racemic or L-(S)- aspartic acid as previously described (9). Enantiomeric excess of (R)-**1** ($[\alpha]_D^{20}$ = +8.0 [THF, c=2]) was ≥ 95 % as determined by ^1H NMR in the presence of Eu(hfc)3 (Sigma).

(R,S)-malolactonic acid, 2

1g ($4.85.10^{-3}$ mol) of 4-benzyloxy-2-oxetanone was dissolved in 10ml of anhydrous acetone in a round bottomed flask. 200mg of palladium (20% weight) were added and the round bottomed flask was placed in a hydrogenolysis system. The hydrogenolysis was conducted with hydrogen at room temperature during 8 hours. Malolactonic acid was obtained after filtration over Celite and evaporation of the solvent under reduced pressure.

yield=99% ; m_p=38°C ; ^1H NMR (90 MHz, acetone D6, δ ppm) : 3.84 - 4.13 (dq, 2H, CH_2 lactone) ; 4.97 -5.09 (2dd, 1H, CH lactone) ; 9.54 (s, 1H, CO_2H).

(R)-(+)-malolactonic acid, 2'

The same procedure was used by using R-(+)-benzylmalolactonate and liquid R-(+)-malolactonic acid was obtained. Yield=99% ; $[\alpha]_D^{20}$ =+9 (THF ; c=2).

2,4,5-trichlorophenylmalolactonate, 3

0.5g ($4.3.10^{-3}$mol) of 4-carboxy-2-oxetanone was placed in a round bottomed flask and kept under nitrogen atmosphere during one hour and then dissolved in 5 ml of anhydrous THF. 0.85 g ($4.31.10^{-3}$ mol) of 2,4,5-trichlorophenol was added dropwise, in 10 ml of anhydrous THF. The mixture was stirred magnetically and kept at 0°C. 0.89 g ($4.3.10^{-3}$ mol) of DCC in anhydrous THF (10 ml) was added dropwise and the mixture was stirred magnetically 2 hours at 0°C and then 40 hours at room temperature. After filtration over Celite, solvent was removed under reduced pressure to give crude 2,4,5-trichlorophenyl malolactonate, **3**. **3** was purified by crystallization in ethyl ether to obtain a white powder. Yield=63% ; m_p=126°C) ; ^1H NMR (90 MHz, $CDCl_3$, δppm) : 3.70 - 4.17 (dq, 2H, CH_2 lactone), 5.07 - 5.20 (2dd, 1H, CH lactone) ; 7.36 (s, 1H, Ha aromatic cycle) ; 7.59 (s, 1H, Hb aromatic cycle).

Poly(benzyl malolactonate-co-trichlorophenyl malolactonate) (70/30), 4

The copolymer was synthesized by polymerizing 600 mg of 2,4,5-trichlorophenyl malolactonate and 813 mg of racemic benzylmalolactonate in the presence of benzoate of tetramethyl-ammonium (10^{-3} mol. per mol. of monomer) under nitrogen at 70°C during 9 days. Polymerization was controlled by I.R.. After cooling, crude resulting material was dissolved in acetone and precipitated with ethanol. Polymeric material **6** was separated and dried under vacuum (Yield=61% ; T_g≈22°C ; M_{sec}≈3 000, standard polystyrene, THF)

^1H NMR (90 MHz, $CDCl_3$, δ ppm) : 2.95 (s, 2H, CH_2 main chain) ; 5.12 (s, 1.6 H, $\underline{C}H_2$-C_6H_5) ; 5.51 (s, 1H, CH main chain) ; 7.04 (m, 0.2H, H aromatic) ; 7.28 (d, 4.1 H , C_6H_5) ; 7.44 (m, 0.2H, H aromatic).

(4 RS)-4-(chloramphenicol)oxycarbonyl-2-oxetanone, 5

The white powder lactone was synthesized using the same procedure as described for **3**, (Yield=98% ; m_p=120°C)

^1H NMR (90 MHz, CD_3COCD_3, δ ppm) : 3.74 - 3.43 (m, 3H,CH_2 lactone and $\underline{C}$H-NH) ; 4.38 (s, 2H, $\underline{C}H_2$-OCO) ; 4.90 (s, 1H, CH lactone) ; 5.16 (s, 1H, CH-OH) ; 6.15 (s, 1H, $CHCl_2$) ; 7.59 - 7.49 (d, 2H, H aromatic cycle) 8.06 - 7.96 (d, 2H, H aromatic cycle).

^{13}C NMR (22.5 MHz, CD_3COCD_3, δ ppm) : 43.52 (CH_2 lactone) ; 57.39 (CH-NH) ; 61.94 (COO-$\underline{C}H_2$) ; 65.67 (CH lactone) ; 66.73 (CH-OH) 70.71 ($CHCl_2$) ; 125.45 et 127.65 (C_6H_4) ; 164.76 (C=O amide) 167.03 (C=O lactone) ; 168.65 (C=O ester).

Poly(benzylmalolactonate-co-chloramphenicol malolactonate) (70/30), 6

The copolymer was synthesized using the same procedure as described above (Yield=80%, M_{sec}≈4 000, standard polystyrene, THF)

^1H NMR (90 MHz, CD_3OCD_3, δ ppm) : 3.03 (s, 2H, CH_2 main chain) ; 3.33 (s, 1H, $\underline{C}$HNH) ; 4.45 (s, 2H CH_2O) ; 5.17 (s, 3H, $\underline{C}H_2C_6H_5$ and $\underline{C}$HOH) ; 5.36 (s, 1H , $CHCl_2$) ; 5.58 (s, 1H, CH main chain) ; 7.34 (s, 5H, C_6H_5) ; 7.58 -8.20 (2d, 2H, aromatic)

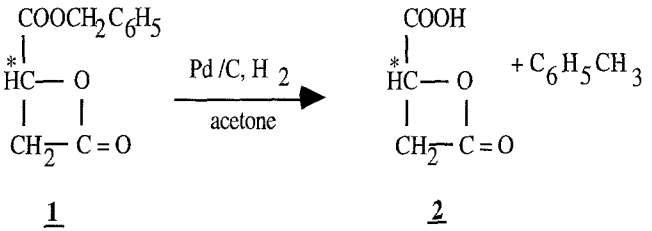
^{13}C NMR (22.5 MHz, CD_3COCD_3, δ ppm) : 36.47 (CH main chain) ; 55.03 (HNH) ; 67.73 (CHOH) ; 68.27 (CH_2 main chain) ; 69.79 ($CH_2C_6H_5$) ; 71.36 ($CHCl_2$) ; 124.21 and 129.19 ($C_6H_4NO_2$) ; 129.77 ($C_6H_5NO_2$) ; 165.30 and 169.09 (C=O)

Results and Discussion

Two chemical routes have been used in the preparation of racemic and optically active 4-benzyloxy- and 4-alkyloxycarbonyl-2-oxetanones. The first method is now well established and starts from aspartic acid[9] ; it is available for the first member of the malolactonic acid esters family, benzylmalolactonate (MLABe) and has been expanded to bulky alkyl groups such as butyl or 2-methylbutyl .

The second method[10] concerns the dehydration of malic acid monoesters using the MITSUNOBU's reaction (with diisopropylazodicarboxylate and triphenylphosphine as reagents). The new route is simple, reproducible and particularly interesting for obtaining monomers with very high enantiomeric excess (>98 %) ; it is carried out for monomers with benzyl or alkyl ester groups (methyl, ethyl, propyl...). In both synthesis routes, the opening of the malic acid anhydride derivative by an alcohol is the limiting step in the preparation of a wide spectrum of malolactonates. Many attempts to form a monoester with a bioactive or activating group by addition to trifluoroacetate of malic acid anhydride or to bromosuccinic acid anhydride have failed due to the unreactivity of the corresponding alcohol towards the cyclic intermediate. More than ten unusual and usual activating agents as imidazole, N-hydroxyimidazole, N-hydroxysuccinimide, 4-nitrophenol have been unsuccessfully experimented. For circumventing the difficulty, a new approach has been used. Racemic and optically active 4-benzyloxy-2-oxetanones, **1**, have been quantitatively hydrogenolysed in anhydrous acetone by using Pd/H_2 charcoal catalyst (scheme 2) at room temperature.

After filtration on celite, solvent and toluene evaporation, under vacuum, has conducted to malolactonic acid, **2**, (yield 99 %) as shown by ^1H NMR (signals at 5.09-4.96 - 3.95-3.72 ppm and one peak at 9.90 ppm corresponding to COOH) and IR (peaks at 1648 and 1848 cm^{-1}) spectroscopies.



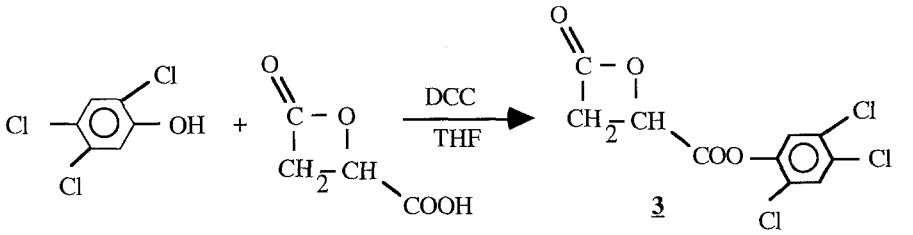
1 **2**

Scheme 2 : Synthesis of malolactonic acid

The racemic compound is a white solid which melts at 38° C and the (R)-optically active compound prepared from (R)-benzylmalolactonate (e.e ≥ 95 %) is a colorless liquid ($[\alpha]_D^{20} = +9.0$ [THF, c=2]). Malolactonic acid is stable without any particular precaution and can be stocked . This new β-substituted-β-lactone is soluble in usual organic solvents as tetrahydrofuran, dioxane, alcohols, ethyl acetate and diethylether.

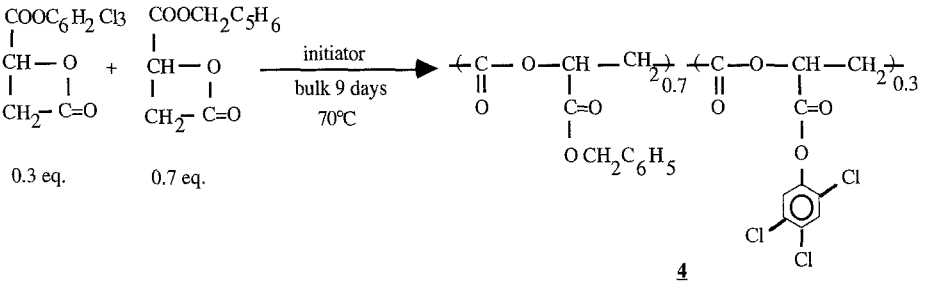
Two different molecules have been coupled to racemic malolactonic acid for exemplifying the preparation of complex malolactonates. At first 2,4,5-trichlorophenol has been reacted with racemic malolactonic acid in anhydrous tetrahydrofuran and in the

presence of dicyclohexylcarbodiimide (DCC) as coupling reagent at room temperature (scheme 3).



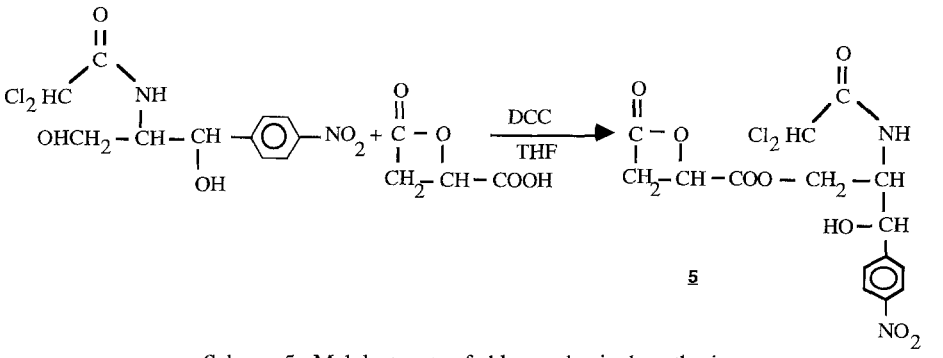
Scheme 3 : Preparation of malolactonate of 2, 4, 5-trichlorophenol

After purification, 4-[2,4,5-trichlorophenyloxycarbonyl]-2-oxetanone, **3**, is a white powder contrary to others racemic malolactonates (yield 63 %, mp 126 °C) which has been characterized by ^{1}H NMR and IR. A mixture of **3** (0.3 eq.) and racemic 4-benzyloxy-2-oxetanone (0.4 eq.) have been copolymerized in the usual conditions and has conducted to the corresponding random oligomers (Msec≈3 000),**4** (scheme 4), as determined by ^{1}H NMR. The interest of such polymeric material ,**4**,consists in the possibility to further substitution of the lateral activated ester groups by specific functionalized groups in a well-defined proportion, depending on the required properties of the polymer.



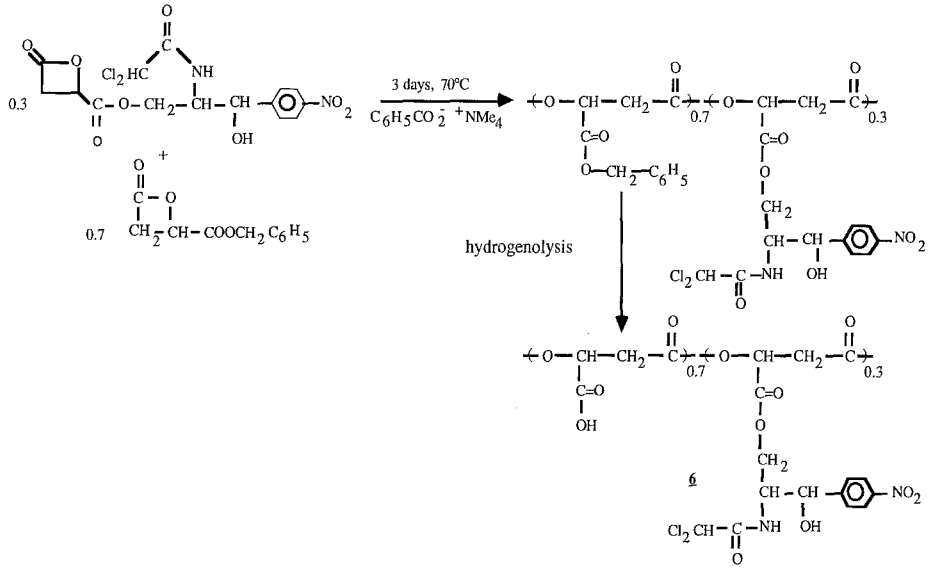
Scheme 4 : Preparation of a poly(β–malic acid) derivative containing 30 % of 2,4,5-trichlorophenol

The second type of attachment was related to the coupling of chloramphenicol , an antibiotic agent, for approaching the concept of macromolecular prodrug. This compound has been bound to racemic malolactonic acid by using DCC as coupling reagent in tetrahydrofuran (scheme 5). Malolactonate of chloramphenicol, **5** , after purification (yield 90%), is also a white powder (mp 120°C). Characterization of **5** has shown that the attachment of chloramphenicol takes place through the primary alcohol function.



Scheme 5 : Malolactonate of chloramphenicol synthesis

5 has been copolymerized with racemic benzylmalolactonate as in the precedent experiment. Futhermore, benzyl protecting groups of this polymeric material (M_{sec}=4 000) had been removed by an H_2/Pd charcoal catalysed hydrogenolysis to the usual conditions conducting to a degradable temporary therapeutic device pattern, **6** (scheme 6).



Scheme 6 : Preparation of poly(β-malic acid-co-β-malate of chloramphenicol) (70/30)

In conclusion, the access to racemic and optically active malolactonic acid opens the route to the preparation of a wide spectrum of new specific β-substituted-β-lactones and therefore to the development of new polymeric devices. The attachment of antitumor agents, porphyrins, biocides, metallo-complexes and mesogenic groups are under study. Moreover, this method of coupling is extending to alkylmalolactonates which constitute also an enlarged reserve of monomers with two chiral centers in the lactone ring for the preparation of new degradable and diastereomeric polymeric materials.

References

1 VERT M.; *Makromol. Chem.*,Macroml. Symp., **1986**, *6*, 109
2 VERT M.; *Critical Reviews in Therapeutic Drug Carrier Systems*, CRC Press, **1986**, *2*, 291
3 VERT M., LENZ R. W. ; *Polym. Prepr.*, **1979**, *20*, 608
4 CAMMAS S. ; LEBOUCHER M.A. ; RENARD I. ; BOUTAULT K. ; GUERIN PH., Biodegradable Plastics and Polymers (Doi Y. and Flukuda K. editors), Elsevier, **1994**, *534*
5 ARNOLD S.C. ; LENZ R.W., *Makromol. Chem.*, Macromol. Symp., **1986**, *6*, 285
6 GUERIN Ph. ; FRANCILLETTE J. ; BRAUD C. ; VERT M., *Makromol. Chem.*,Macromol. Symp. **1986**, *6*, 305
7 BRAUD C. ; BUNEL C. ; VERT M., *Polym. Bull.*, **1985**, *13*, 293
8 CARON A. ; BRAUD C. ; BUNEL C. ; VERT M., *Polym. Bull.*, **1985**, *14*, 187
9 GUERIN Ph. ; BRAUD C. ; VERT M. ; LENZ R. W., *Polym. Bull.*, **1985**, *14*, 187
10 CAMMAS S. ; RENARD I. ; BOUTAULT K. ; GUERIN Ph., *Tetrahedron Asymmetry*, **1994**, *5*, 1589
11 SHIMADA K. ; MATSUSHIMA K., Agric.*Biol. Chem.*, **1969**, *33*, 544
12 FISCHER H. ; ERDMANN S. ; HOLLER E., *Biochemistry*, **1989**, *28*, 5219
13 NAGATA N. ; NAKAHARA T. ; TABUCHI T., *Bio. Sci. Biotech. Biochem.*, **1993**, *4*, 638