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A NOVEL SYNTHESIS OF OPTICALLY ACTIVE 4-BENZYLOXY- AND 4-ALKYLOXYCARBONYL-2-OXETANONES

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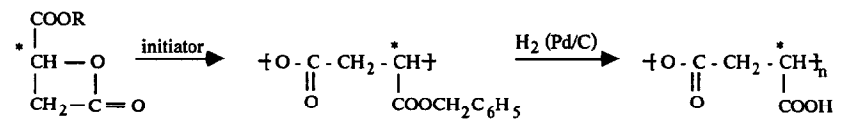
Abstract : optically active 4-benzyloxy- and 4-alkyloxycarbonyl-2-oxetanones **1** have been synthesized by intramolecular dehydration of optically active benzyl, methyl, methyl-2-butyl malates **6a,b,c**. The reaction has been performed using triphenylphosphine and diisopropylazodicarboxylate as reagents. Starting from L-(S)-malic acid as chiral synthon, (R)-β-substituted β-lactones **1** have been obtained with very high enantiomeric excesses (> 98 %) resulting in inversion at the hydroxyl bearing carbon, due to the hydroxyl group activation. Compounds **1** are used as monomers in the preparation of poly (β-malic acid) **3** derivatives.

Introduction

The possibility of taking advantage of chirality to modify and adjust properties of polymers and copolymers derived from poly (β-malic acid) **3** is essential with regard to use this biodegradable polyester for temporary therapeutic applications [1]. The enantiomeric composition and distribution of stereogenic centers in polymer chains affect properties of the resulting polymers such as the morphology or the rate of the degradation [2]. Ring opening polymerization or copolymerization of chiral β-substituted β-lactones leads to poly (β-malic acid) derivatives. For example, poly (β-malic acid), $PMLA^xH_{100}$ **3**, where x corresponds to the enantiomeric excess in the monomer feed, is prepared by catalyzed hydrogenolysis of the benzyl protective group present in poly (benzyl β-malate), $PMLA^xBe_{100}$ **2a**, a precursor obtained by ring opening polymerization of benzyl malolactone, MLA^xBe_{100} **1a**.



$PMLA^xBe_{100}$ **2a**

$PMLA^xH_{100}$ **3**

1

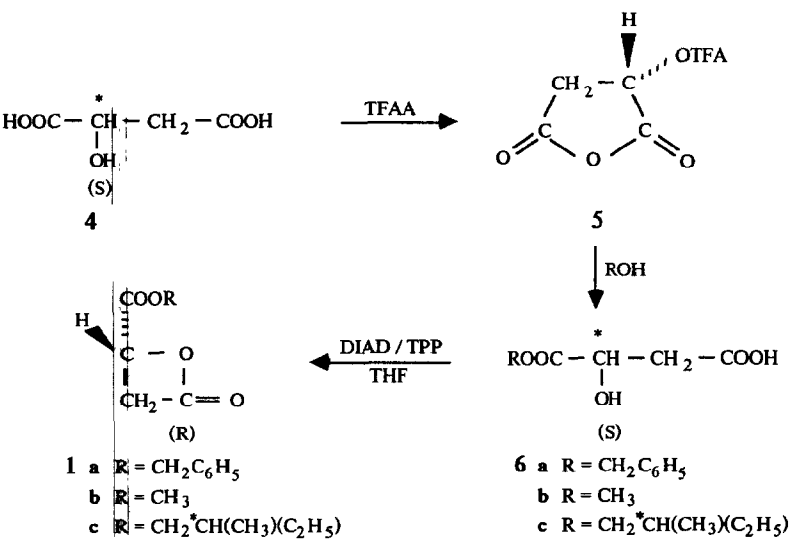
a R = $CH_2C_6H_5$
b R = CH_3
c R = $CH_2^*CH(CH_3)(C_2H_5)$

Benzyl malolactonate, the first member of the malolactonic acid esters family, can be synthesized starting from various compounds such as bromosuccinic acid [3], malic acid enantiomers [4] or aspartic acid enantiomers [5]. In the latter case, the amino acid was first transformed to bromosuccinic acid ; benzyl malolactonate was obtained by ring closure of the α-bromosuccinic acid monobenzylester. This method was applied to prepare alkyl malolactonates, but the yield depended very much on the alkyl group nature [6] (from 55 % when R = C_4H_9, to 22 % when R = CH_3). To overcome this problem, a different synthetic route was selected, namely the base catalyzed 2 + 2 cycloaddition between ketene and alkyl glyoxylates [6]. However the ketene route is limited to racemic alkyl malolactonates : using chiral amines (quinine and quinidine) as base catalysts, enantiomeric excesses of 36 % and 72 % respectively were obtained in the case of (R)- and (S)-methyl malolactonates enantiomers. It is worth to note that optically active MLABe was obtained with high enantiomeric excess (>95%) when prepared from (R)- or (S)- aspartic acid enantiomers [7].

We now wish to report a new simple and reproducible synthesis of optically active benzyl and alkyl malolactonates with excellent enantiomeric excesses by intramolecular dehydration of malic acid monoesters, using diisopropylazodicarboxylate and triphenylphosphine as reagents, according to a procedure established by Miller in the case of isopropyl 2-hydroxy-3-methyl succinate ring closure.[10,11]

Results and Discussion

Starting from malic acid 4 only three steps are necessary to prepare β-substituted β-lactones 1 :



Treatment of optically active L-(S)-malic acid 4 with 2 equivalents of trifluoroacetic anhydride (TFAA) at room temperature, followed by evaporation of TFAA excess and trifluoroacetic acid formed, provided the corresponding trifluoroacetate of malic acid anhydride 5 quantitatively. Treatment of the solid residue with one equivalent of anhydrous benzyl alcohol at room temperature, overnight, provided an oil which was treated by

dissolution, washing and again extraction to give crude benzyl-2-hydroxy-3-succinate. After chromatography, pure racemic or optically active monoester **6a** (yield 76 %) was obtained. In the preparation of optically active methyl-2-hydroxy-3-succinate **6b**, 3 equivalents of anhydrous methyl alcohol were added to **5** ; in opposition to **6a**, optically active **6b** was solid (mp = 79°C, yield 90 %).

Optically active (S)-2-methyl-1-butyl-(S)-2-hydroxy-3-succinate **6c** has been prepared from L-malic acid and (S)-2-methyl-1-butanol according the same procedure as **6a** (oil, yield 85 % after chromatography).

The third step is concerned with the use of the diisopropylazodicarboxylate/triphenylphosphine (DIAD/TPP) for an intramolecular dehydration of **6a**. To a solution of optically active (S)-**6a** and TPP (1 eq.) in anhydrous tetrahydrofuran (THF) at 0°C was added a solution of diisopropylazodicarboxylate (1 eq.) in anhydrous THF under N_2. After the mixture was stirred at 0°C, the reaction was continuated at room temperature. After solvent removal and treatment of the resulting oil with cooled diethyl ether, most of H_2DIAD and triphenylphosphine oxide Ph_3PO crystallized out and were removed by filtration. Further purification was made by chromatography to give (R)-benzyl malolactonate (yield 59 %). The optically active β-lactone **1a** was then distilled under vacuum to give pure (R)-benzyl malolactonate. The low yield (about 11 %) is due to thermal polymerization during distillation. Enantiomeric excess of (R)-**1a** has been determined by using 400 MHz ^{1}H NMR and Eu [hfc]$_3$ chiral shift reagent as previously described [7] : enantiomeric excesses as high as 98 % can be retained during the three steps synthetic route. This result has been confirmed on the resulting polymer ; poly (β-(S)-benzyl malate) ^{13}C NMR spectrum displayed only four peaks corresponding to a very highly isotactic optically active polymer.[8,9]

It is important to note that the dehydration reaction occured with inversion of configuration at the hydroxyl bearing carbon ; this result can be explained by an exclusively hydroxyl group activation versus a carboxy group activation. Due to this activation mode, starting from natural L-(S)-malic acid, poly ((S)-malic acid) **3** will be obtained by ring opening polymerization of **1a** and hydrogenolysis of the benzyl protecting group ; the ultimate biodegradation product of this polymer will be, again, the L-natural enantiomer of malic acid. (R)-methyl malolactonate **1b** has been prepared according to the same Mitsunobu procedure (yield 46 %, e.e.>98%). At last the preparation of optically active (S)-2-methyl-1-butyl-(R)-malolactonate **1c** (yield 62 %, e.e. > 98 %) has shown, this synthetic route could be extended to a large number of malic acid monoesters. **1c** is particularly interesting, due to the presence of a second stereogenic center in the lactone, which will allow the possibility of preparing stereocopolymers with two asymmetric carbons atoms in the monomer unit.

It is worth noting that only cyclisation has taken place in the diisopropylazodicarboxylate/triphenylphosphine reaction ; no formation of olefins has been observed due to elimination during intramolecular dehydration.[12,13] In conclusion, this new route presents several interests. It opens the way to the preparation of optically active malolactonates with excellent enantiomeric excesses. Secondly, it allows the synthesis of alkyl malolactonates with acceptable yields and consequently it provides also possibilities to tailor make by copolymerisation derivatives of bioresorbable poly (β-malic acid) for temporary therapeutic applications.

Experimental

Materials

Chemicals were purchased from Janssen Chemical. L-malic acid was dried under vacuum at 40°C for 4 h.

Preparation of 5

L-malic acid (10 g, 7.5 10^{-2} mol.) was placed in a 100 mL round-bottomed flask and cooled in an ice bath. Trifluoroacetic anhydride (2 eq. 0.15 mol.) was added and the suspension was stirred magnetically at 0°C for 1h. (within 15 min., the solution became homogeneous) and 2h. at room temperature. The trifluoro acetic acid formed and TFAA excess were removed by vacuum distillation at room temperature to give the trifluoroacetate of malic acid anhydride 5 as a white solid with a quantitative yield. 5 was immediatly kept under nitrogen atmosphere.

Preparation of 6a

5 was dissolved in 8.2 mL of anhydrous benzyl alcohol (1 eq.). The mixture was stirred overnight at room temperature. The oil was dissolved in ethyl acetate (200 mL) and extracted with three portions of aqueous 1M $NaHCO_3$. The combined aqueous solutions were washed with ethyl acetate and then acidified to pH = 2 with 1.2 N HCl. The aqueous layer was extracted with several portions of ethyl acetate. These latter organic extracts were combined, washed with brine, dried over $MgSO_4$, filtered and evaporated to give crude **6a** as an oil. Chromatography on silica gel with 80 % ethyl acetate in petroleum ether gave 12.8 g (76 % yield) of this monoester as an oil. $[\alpha]_D^{25}$ = -16.0 (c = 1, THF). ^1H NMR (90 MHz, CD_3COCD_3, δ ppm) : 2.93 (m, 2H) ; 4.01-4.09 (d, 1H) ; 4.65 (m, 1H) ; 5.18 (s, 2H) ; 7.37 (s, 5H). ^{13}C NMR (CD_3COCD_3, δ ppm) : 48.93 ($\underline{C}H_2$); 76.85 ($\underline{C}H_2$) ; 78.09 ($\underline{C}H$) ; 138.45-146.57 ($\underline{C}_6H_5$) ; 181.82 ($\underline{C}$=O) ; 183.25 ($\underline{C}$=O).

Preparation of 6b

The experimental set-up and work-up were the same as described above. 5 was treated with anhydrous methanol (3 eq.) at room temperature for 4 h. to give a white solid (mp = 71°C) with quantitative yield. The crude monoester **6b** was recristallized in hexane/ethylacetate (50/50) to give pure monoester **6b** as a white solid (mp = 75°C) with 87 % yield. $[\alpha]_D^{25}$ = -5.0 (c = 2, dioxane). ^1H NMR (90 MHz, CD_3COCD_3, δ ppm) : 2.68-2.79 (dd, 2H) ; 3.71 (s, 3H) ; 4.53 (t, 1H).

Preparation of 6c

The experimental set-up and work-up were the same as described for **6a**. 5 was treated with anhydrous (S)-2-methyl-1-butanol (1 eq.) at room temperature overnight. The crude monoester **6a** was purified by chromatography over silica gel with 80 % ether in petroleum ether to give pure monoester **6a** (80 % yield). $[\alpha]_D^{25}$ = -9.0° (c = 2, THF). ^1H NMR (90 MHz, CD_3COCD_3, δ ppm) : 0.90-0.96 (m, 6H) ; 0.96-1.40 (m, 2H) ; 1.40-1.70 (m, 1H) ; 2.70-2.80 (dd, 2H) ; 3.95-4.02 (m, 2H) ; 4.53 (t, 1H).

Preparation of 1a

To a solution of monoester **6a** (12 g, 5.3 10^{-2} mol.) and PPh_3 (1 eq.) in 168 mL of dry THF at 0°C was added a solution of diisopropylazodicarboxylate (DIAD, 1 eq.) in 32.6 mL of dry THF with a double-tripped needle

under N_2. After the mixture was stirred at 0°C for 30 min., the ice bath was removed, and the reaction mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure, and the resulting yellow oil was triturated with cold diethyl ether. Most of H_2 DIAD and Ph_3PO crystallized out and were removed by filtration. The filtrate was concentrated and purified by chromatography on silica gel with CH_2Cl_2/petroleum ether (3/2) to give 6.4 g the β-lactone as an oil (59 % yield). This β-lactone **1a** was then distilled under vacuum in a short pass-still column to give pure monomer **1a** as an clear oil (11 % yield). $[\alpha]_D^{25}$= +5.50 (c = 2.0, dioxane). ^1H NMR (400 MHz, $CDCl_3$, δ ppm) : 3.55-3.80 (dd, 2H) ; 4.85-4.90 (q, 1H) ; 5.28 (s, 2H) ; 7.47 (s, 5H). IR (γ, cm^{-1}) : γ_{CO} = 1844, 1744. e.e. > 98 % (determined by ^1H NMR with chemical shift reagent). ^1H NMR (400 MHz, $CDCl_3$ + 0.3 eq. Eu[hfc]$_3$, δ ppm) : 4.03-4.18 (dd, 2H) ; 4.45-5.01 (t, 1H, enantiomer R) ; 5.70-5.80 (s, 2H) ; 7.39-7.58 (m, 5H).

Preparation of 1b

The experimental set-up and work-up were the same as described above. **6b** was treated with TPP (1 eq.) in dry THF and with DIAD (1 eq.) in dry THF. The crude monomer **1b** was purified by chromatography over silica gel with CH_2Cl_2/petroleum ether (60/40) as eluant to give **1b** with 56 % yield. **1b** was then distilled under vacuum in a short pass-still column to give pure β-lactone **1b** as a clear oil (24 % yield). $[\alpha]_D^{25}$ = +1.50 (c = 2.0, dioxane). ^1H NMR (400 MHz, $CDCl_3$, δ ppm) : 3.60-3.84 (m, 2H) ; 3.87 (s, 3H) ; 4.87-4.90 (dd, 1H). IR (γ, cm^{-1}) : γ_{CO} : 1850, 1750. e.e. > 98 % (determined by ^1H NMR with chemical shift reagent) ^1H NMR (400 MHz, $CDCl_3$ + 0.3 eq. Eu[hfc]$_3$, δ (ppm) : 4.35-4.67 (m, 2H) ; 4.10 (s, 3H, enantiomer R) ; 6.10-6.13 (dd, 1H, enantiomer R).

Preparation of 1c

The experimental set-up and work-up were the same as described above. **6c** was treated with TPP (1 eq.) in dry THF and with DIAD (1 eq.) in dry THF. The crude monomer **1c** was purified by chromatography over silica gel with ether/petroleum ether (60/40) as eluant to give **1c** with 62 % yield. **1c** was then distilled under vacuum in a short pass-still column to give pure β-lactone **1c** as a clear oil (20 % yield). $[\alpha]_D^{25}$ = +2.50 (c = 2, THF). e.e. > 98 % (determined by ^1H NMR with a chemical shift reagent). ^1H NMR (400 MHz, $CDCl_3$, δ ppm) : 0.80-1.00 (m, 6H) ; 1.10-1.50 (m, 2H) ; 1.70-1.90 (m, 1H) ; 3.60-3.90 (qd, 2H) ; 4.00-4.20 (m, 2H) ; 4.85 (t, 1H). ^1H NMR (400 MHz, $CDCl_3$, + 0.3 eq. Eu[hfC]$_3$, δ ppm) : 0.95-1.05 (t, 3H) ; 1.10-1.20 (d, 3H) ; 1.30-1.80 (m, 2H) ; 2.00-2.20 (m, 1H) ; 4.20-4.50 (qd, 2H) ; 4.80-5.00 (m, 2H) ; 5.90 (t, 1H, enantiomer R).

Method for ^1H NMR spectra with chemical shift reagent.

Tris [3-heptafluoropropylhydroxymethylene)-d-camphorato] Europium (III) (Eu[hfc]$_3$) (Janssen Chimica) was used for the preparation of a $CDCl_3$ stock solution (0.42 M). Suitable amounts of this Eu[hfc]$_3$ stock solution were mixed with the substrate solution (0.32 M) in NMR tubes. 400 MHz ^1H NMR spectra were recorded. The enantiomeric composition was determined from the areas of shifted NMR resonance peaks using a computer and by comparison between the racemic and optically active compounds spectra in the presence of Eu [hfc]$_3$. For **1a**, **1b** and **1c** no peak corresponding to the enantiomer (S) was detectable from the different enantiotopic protons.

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