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Synthesis of novel α,α′,β-trisubstituted β-lactones

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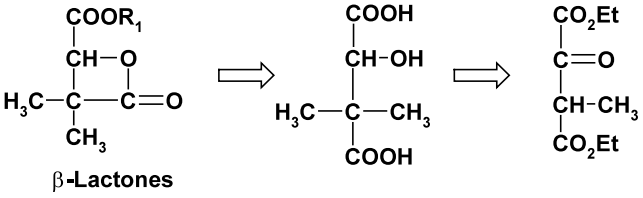
Abstract—A concise and efficient synthesis of α,α′,β-trisubstituted β-lactones is presented. These novel lactones are easily obtained in five steps and will be dedicated to anionic ring opening polymerization.

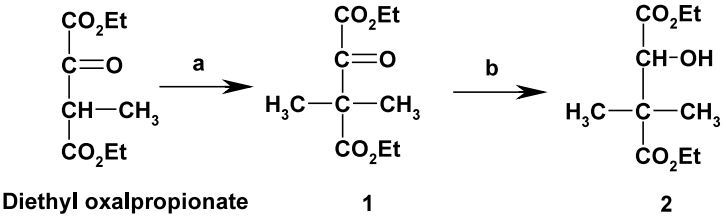
A large family of β-substituted β-lactones, prepared from racemic and optically active malic and alkylmalic acids as precursors, has been used in the synthesis of racemic and optically active polyesters.[1,2] These polymeric materials are degradable, bioassimilable and biocompatible.[3,4] They can be used in temporary therapeutic applications such as drug delivery systems. In this report, we are investigating the synthesis of more intricate β-lactones such as α,α′,β-trisubstituted β-lactones. These can be easily prepared in two steps from diacids, synthesized from commercial diethyl oxalpropionate in three stages (Scheme 1).

The R_1 group can be benzyl, butyl or allyl. The benzyl group is used for its protecting role. After catalytic hydrogenolysis either on the lactone or on the polyester, the carboxylic acid groups obtained will be reacted with bioactive or targeting molecules. The allyl group will be chemically modified after polymerization and turned to epoxides, diols or even carboxylic acid. The butyl group is used for its hydrophobic properties. The presence of two methyl groups on the lactone will increase the hydrophobicity of the polymer concerned.



Scheme 1. Retrosynthetic pathway.

The synthesis of these novel lactones is realized in five steps from precursor diethyl oxalpropionate. We have synthesized three different lactones. In the first step, racemic diethyl oxalpropionate is alkylated in basic conditions. To introduce the methyl substituent, we have employed potassium *t*-butoxide in anhydrous toluene in the presence of 18-crown-6 ether at room temperature (Scheme 2).[5] The alkylation is relatively fast because of the acidity of the proton flanked by ketone and ester groups. Diethyl 3,3-dimethyl-2-ketosuccinate **1** is obtained after purification by distillation under reduced pressure with 85% yield. The alkylation is followed by gas chromatography and the analysis of compound **1** by ^{1}H NMR has confirmed the presence of the two methyl groups by the single peak at 1.39 ppm integrating for six protons.



Scheme 2. *Reagents and conditions*: (a) *t*BuOK, crown ether, toluene, CH_3–I, 85%; (b) $NaBH_4$, EtOH, 70%.

Keywords: alkylation; dialkylmalic acids; lactonization; β-lactones.

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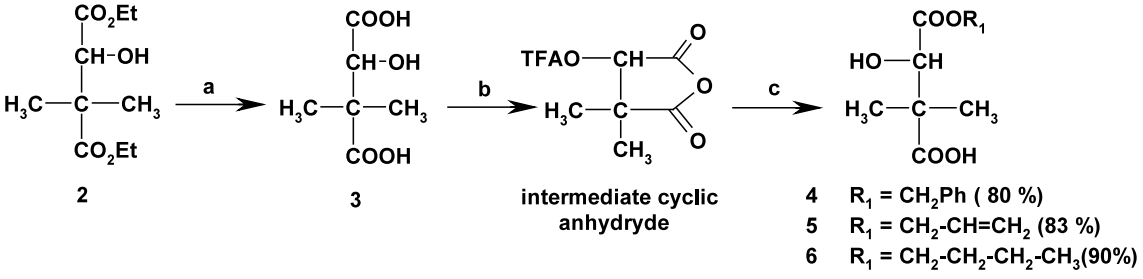
For the second step of our synthesis, the reduction of keto-diesters with $NaBH_4$ furnished racemic diethyl 3,3-dimethylmalate **2**.[6] This reaction is also followed by gas chromatography. The GC analysis displayed one peak corresponding to a racemic mixture of enantiomers **2**. The reduction of **1** resulted in the alcohol **2** with 70% yield.

The third step is concerned with the hydrolysis of ester groups. The corresponding 3,3-dimethylmalic acid **3** is obtained by basic treatment of diethyl 3,3-dimethylmalate **2** (Scheme 3).[7] The ^1H NMR spectra of diacid **3** confirmed the complete hydrolysis because of the disappearance of peaks corresponding to ethyl ester groups. The 3,3-dimethylmalic acid **3** is purified by recrystallization in $CHCl_3/CH_3CN$ with 60% yield.

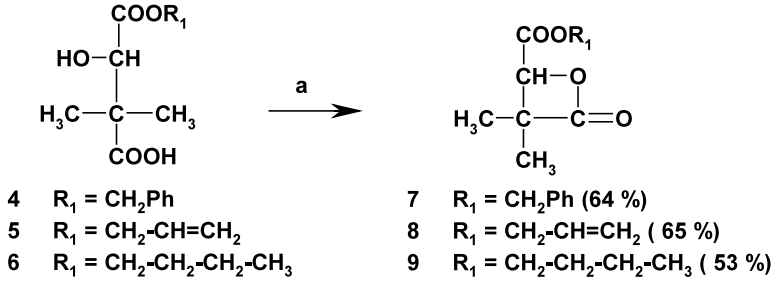
After the hydrolysis of ester groups, the diacid is treated by trifluoroacetic anhydride (TFAA) to provide the non-isolated intermediate cyclic anhydride.[8,9] The solvolysis of this intermediate with a variety of alcohols led to β-hydroxyacids having very good regioselectivity. In our case, we have chosen three different alcohols: benzyl, butyl and allyl alcohols. With the diacid **3**, we have successfully obtained the benzyl monoester **4** with 80% yield, the allyl monoester **5** with 83% yield and the butyl monoester **6** with 90% yield (Scheme 3). The ^1H NMR spectrum of **4** showed the presence of one singlet at 5.00 ppm and one multiplet at 7.20 ppm corresponding to CH_2 and aromatic protons of benzyl group respectively. For monoester **5**, we have observed the different protons of allyl group at 4.50 ppm (CH_2-O), 5.08 and 5.22 ppm ($\underline{CH_2}$=CH) and 5.82 ppm (CH_2=$\underline{CH}$). In the same way, we have observed the protons of butyl group at 0.86 ppm (CH_3), 1.32 ppm ($\underline{CH_2}$-CH_3), 1.57 ppm ($\underline{CH_2}$-CH_2-CH_3) and 4.13 ppm (OCH_2) for the monoester **6**.

The lactonization is the last step of our synthesis. Conceptually, β-lactones can be prepared by activation of either the carboxyl or hydroxyl groups of monoesters. Thus, α,α′,β-trisubstituted β-lactones were synthesized by reaction with diisopropylazodicarboxylate (DIAD) and triphenylphosphine (TPP) according to the Mitsunobu reaction (Scheme 4).[10,11] In this reaction, the lactones were obtained via hydroxyl group activation with inversion of configuration of asymmetric carbon atom according to the mechanism previously described on the optically active lactones.[1] Our three monoesters **4**, **5** and **6** were thus treated and the evolution of the reaction was controlled by thin layer chromatography. Each β-lactone was then purified by chromatography over silica gel with a mixture of ethyl acetate/cyclohexane and analyzed by IR and ^1H NMR. β-Lactones 4-benzyloxycarbonyl-3,3-dimethyl-2-oxetanone **7**, 4-allyloxycarbonyl-3,3-dimethyl-2-oxetanone **8** and 4-butyloxycarbonyl-3,3-dimethyl-2-oxetanone **9** are obtained with 64, 65 and 53% of yield respectively. The three structures are confirmed by IR; the presence of a band at 1850 cm^{-1} characterized the carbonyl function of the lactone. The ^1H NMR spectra displayed two singlets well separated corresponding to methyl groups at about 1.00 ppm. One methyl group of each lactone was downfield shifted by about 0.30 ppm due to the rigidity of the cycle.[12]

The synthesis of these α,α′,β-trisubstituted β-lactones will permit the study of anionic ring opening polymerization. With these three different β-lactones, it will be possible to have access to a large family of new homo-



Scheme 3. *Reagents and conditions*: (a) K_2CO_3, EtOH (reflux), 72 h, 60%; (b) TFAA; (c) $PhCH_2$-OH or CH_2=CH-CH_2-OH or CH_3-CH_2-CH_2-CH_2-OH.



Scheme 4. *Reagents*: (a) DIAD, TPP, THF.

polymers or/and copolymers aimed at biomedical studies.

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12. Selected spectroscopic data for compounds are as follows. Monoester **4**: ^{1}H NMR (CD_3COCD_3, 200 MHz) δ 1.06 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 4.30 (s, 1H, CH-OH), 5.00 (s, 2H, CH_2Ph), 7.20 (m, 5H, Ph). ^{13}C NMR (CD_3COCD_3, 50 MHz) δ 20, 21 (2×CH_3), 46 (C), 67 (CH_2), 76 (CH-OH), 129, 136 (Ph), 173, 176 (2×C=O). Mp 99°C. Anal. calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 61.91; H, 6.51%. Monoester **5**: ^{1}H NMR (CD_3COCD_3, 200 MHz) δ 1.06 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 4.30 (s, 1H, CH-OH), 4.50 (d, 2H, J=5.5 Hz, CH-CH_2-O), 5.08 (dd, 1H, J_{gem}=1.5 Hz, J_{cis}=10.5 Hz, CH_2=CH-), 5.22 (dd, 1H, J_{gem}=1.5 Hz, J_{trans}=17.5 Hz, CH_2=CH-), 5.82 (ddt, 1H, J_{cis}=10.5 Hz, J_{trans}=17.5 Hz, J=5.5 Hz, O-CH_2-CH=CH_2). ^{13}C NMR (D_2O, 50 MHz) δ 20, 22 (2×CH_3), 47 (C), 67 (CH_2O), 76 (CH), 120 (CH_2=CH), 132 (CH_2=CH), 174, 181 (2×C+O). Mp 67°C. Anal. calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.30; H, 7.25%. Monoester **6**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.86 (t, 3H, J=7 Hz, CH_3 butyl), 1.14 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.32 (qt, 2H, J=7 Hz, CH_2-CH_3), 1.57 (tt, 2H, J=7 Hz, CH_2-CH_2-CH_3), 4.13 (t, 2H, J=7 Hz, OCH_2), 4.37 (s, 1H, CH), 8.00 (m, 1H, COOH). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13 (CH_3 butyl), 19 (CH_2-CH_3), 20, 22 (2×CH_3), 30 (CH_2-CH_2-CH_3), 47 (C), 66 (OCH_2), 75 (CH), 174, 183 (2×C=O). Mp 47°C. Anal. calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 55.01; H, 8.47%. Lactone **7**: ^{1}H NMR (CD_3COCD_3, 200 MHz) δ 1.04 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 4.83 (s, 1H, CH lactone), 5.17 (s, 2H, CH_2Ph), 7.33 (m, 5H, Ph). ^{13}C NMR (CD_3COCD_3, 50 MHz) δ 17, 21 (2×CH_3), 58 (C lactone), 67 (CH_2), 77 (CH lactone), 128, 134 (Ph), 167, 172 (2×C=O). IR 1850 cm^{-1} (C=O lactone), 1750 cm^{-1} (C=O ester). MS (IE) m/z 234 (base peak), 178, 107, 91, 83, 72. Anal. calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.64; H, 6.12%. Lactone **8**: ^{1}H NMR (CD_3COCD_3, 200 MHz) δ 1.10 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 4.60 (d, 2H, J=6 Hz, CH-CH_2-O), 4.80 (s, 1H, CH lactone), 5.15 (dd, 1H, J_{gem}=1.5 Hz, J_{cis}=10.5 Hz, CH_2=CH-), 5.28 (dd, 1H, J_{gem}=1.5 Hz, J_{trans}=17 Hz, CH_2=CH-), 5.88 (ddt, 1H, J_{cis}=10.5 Hz, J_{trans}=17 Hz, J=6 Hz, O-CH_2-CH=CH_2). ^{13}C NMR (CD_3COCD_3, 50 MHz) δ 17, 21 (2×CH_3), 58 (C lactone), 66 (CH_2O), 77 (CH lactone), 119 (CH=CH_2), 132 (CH=CH_2), 168, 174 (2×C=O). MS (IE) m/z 184 (base peak), 157, 111, 95, 83, 55. Anal. calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.36; H, 6.73%. Lactone **9**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.00 (t, 3H, J=7 Hz, CH_3 butyl), 1.35 (s, 3H, CH_3), 1.46 (qt, 2H, J=7 Hz, CH_2-CH_3), 1.61 (s, 3H, CH_3), 1.74 (tt, 2H, J=7 Hz, CH_2-CH_2-CH_3), 4.32 (t, 2H, J=7 Hz, OCH_2), 4.71 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13 (CH_3 butyl), 17 (CH_3), 19 (CH_2-CH_3), 22 (CH_3), 30 (CH_2-CH_2-CH_3), 57 (C), 65 (OCH_2), 77 (CH), 167, 172 (2×C=O). MS (IE) m/z 200 (base peak), 100, 82, 55. Anal. calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.17; H, 8.16%.