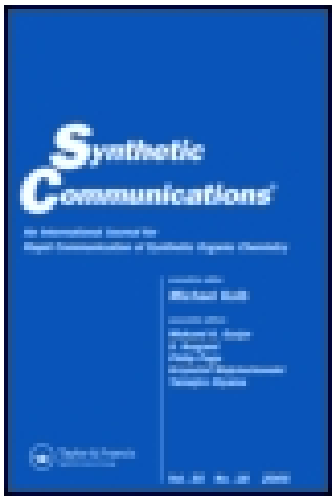

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SYNTHESIS OF NEW γ- AND δ-LACTONES BY ACID CYCLIZATION OF 2,4-DIETHYLENIC-DIACIDS

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SYNTHESIS OF NEW γ- AND δ-LACTONES BY ACID CYCLIZATION OF 2,4-DIETHYLENIC-DIACIDS

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ABSTRACT

We have developed an easy synthesis for new γ- and δ-lactones. Acid-catalyzed cyclization of 2,4-diethylenic-diacids yields new γ or δ-lactones, depending on the substitution pattern of the unsaturated side chain.

We recently reported the synthesis of a novel class of synthons, β-methylenealdehydes, and their use in the synthesis of 13 *Z* retinoic acids (1).

Because of the interplay between the stereochemistry of retinoids and their biological activity, any method of synthesizing these compounds requires a stereochemical control of the configurations of double bonds. We have studied the reactivity of the *E*, *E*-ethylenic linkage by reinvestigating the behavior of a dienic model in strong acid in order to extend the results previously reported (2,3).

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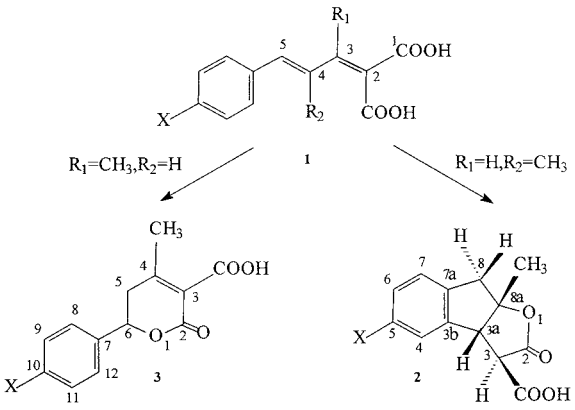
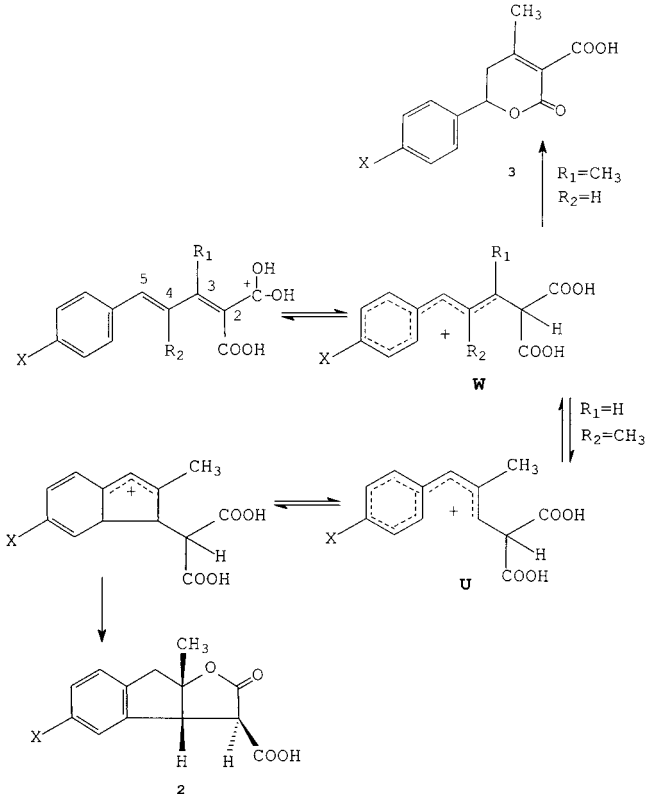


Scheme 1. a: X = H; b: X = CH_3O; c: X = Cl.



Scheme 2.

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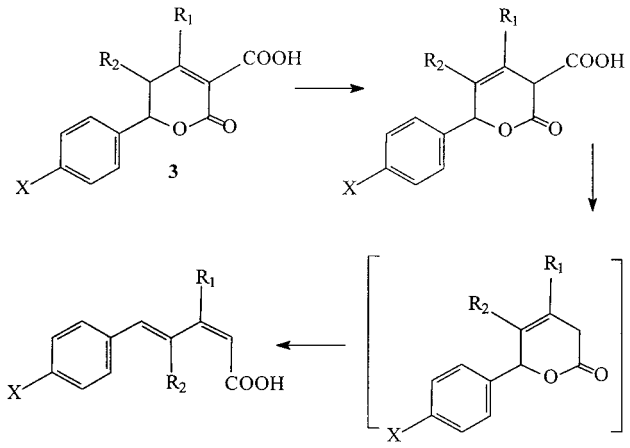

Scheme 3.

The acid-catalyzed cyclization of 2-carboxy-5-aryl-2,4-pentadienoic acids **1** leads to the formation of γ-lactones **2** or δ-lactones **3** (4) (Scheme 1), depending on the substitution pattern of the diethylenic side chain.

These reactions involve the initial formation of a pentadienyl cation. The most stable form of this cation is probably the 'W' or 'all-trans' form, leading to the δ-lactones **3** ($R_1 = CH_3$, $R_2 = H$). There is a conformational change to a 'U' form when $R_1 = H$ and $R_2 = CH_3$. Cyclization of the latter to a cyclopentenyl cation by electrocyclic reaction followed by internal lactonization gave the bicyclic γ-lactones **2** (5–7) (Scheme 2).

The derivative **3** was shown unambiguously to have a δ-lactone structure rather than a γ-lactone by base catalyzed decarboxylation to give the $2Z4E$ monoacids **4** according to the following mechanism (8) (Scheme 3).

ACKNOWLEDGMENTS

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5. A typical procedure for cyclization step is: 1 g of **1** was added to 20 cm^3 concentrated sulphuric acid ($R_1 = H$, $R_2 = CH_3$: 0°C, 10 min.; $R_1 = CH_3$, $R_2 = H$: 0°C, 4 h). The reaction mixture was poured over 100 g of ice and extracted with diethyl ether. The organic layer was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by recrystallization from ether ($R_1 = H$, $R_2 = CH_3$) or by flash chromatography eluting with 80/20 CH_2Cl_2/CH_3OH and recrystallization from ether ($R_1 = CH_3$, $R_2 = H$). **2a**. White crystals (75%) F: 152°C. Anal. calc. For $C_{13}H_{12}O_4$: C, 67.23; H, 5.21; O, 27,56. Found: C, 67.08; H, 5.38; O, 27.66. IR (KBr) ν_{CO} 1765, 1720 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 7.28 (m, 4H, $H_{4,5,6,7}$); 4.13 (d, 1H, $J = 3.3$, H_3); 3.78 (d, 1H, $J = 3.3$, H_{3a}); 3.49 (d, 1H, $J = 17.6$, H_8); 3.25 (d, 1H, $J = 17.6$, $H_{8'}$); 1.77 (s, 3H, CH_3). ^{13}C NMR: 170.8 (COOH); 168.8 (C═O); 142.4, 140.5, ($C_{3b,7a}$); 128.6, 128.0, 125.3, 125.2 ($C_{4,5,6,7}$); 93.6 (C_{8a}); 54.9, 54.7 ($C_{3,3a}$); 45.2 (C_8); 24.8 (CH_3). **3a.** White crystals (65%) F: 104°C. Anal. calc, For $C_{13}H_{12}O_4$: C, 67.23; H, 5.21; O, 27,56. Found: C, 67.16; H, 5.25; O, 27.61. IR (KBr) ν_{CO} 1746, 1715 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 7.46–7.40 (m, 5H, $H_{8,9,10,11}$); 5.49 (dd, 1H, $J = 12.4$, $J' = 3.6$, H_5); 3.08 (dd, 1H, 1H $J = 19.0$, $J' = 12.4$, H_6); 2.85 (dd, 1H, $J = 19.1$, $J' = 3.6$, $H_{6'}$); 2.61 (s, 3H, CH_3). ^{13}C NMR: 172.8 (COOH); 167.6 (CO); 162.9 (C_3); 136.2 (C_4); 130.0 (C_{10}); 129.3, 129.0 ($C_{8,12}$ and $C_{9,11}$); 77.8 (C_5); 40.6 (C_6); 23.8 (CH_3).
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