

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/lcyc20>

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

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Published online: 16 Aug 2006.

To cite this article: Alain Valla, Zo Andriamialisoa, Frédéric Zentz, Virginie Prat, Alain Laurent & Michel Giraud (2001) SYNTHESIS OF NEW γ - AND δ -LACTONES BY ACID CYCLIZATION OF 2,4-DIETHYLENIC-DIACIDS, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:2, 279-282, DOI: [10.1081/SCC-100000210](https://doi.org/10.1081/SCC-100000210)

To link to this article: <http://dx.doi.org/10.1081/SCC-100000210>

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SYNTHETIC COMMUNICATIONS, 31(2), 279–282 (2001)

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

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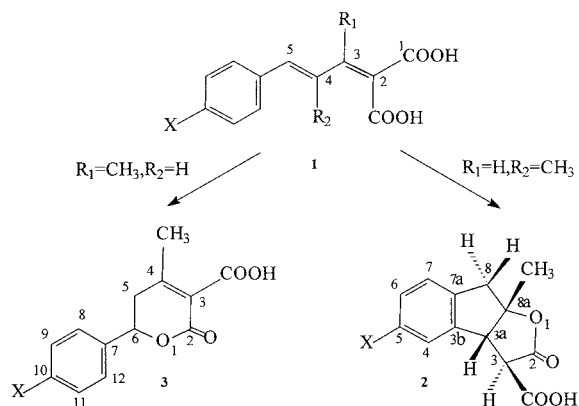
ABSTRACT

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.

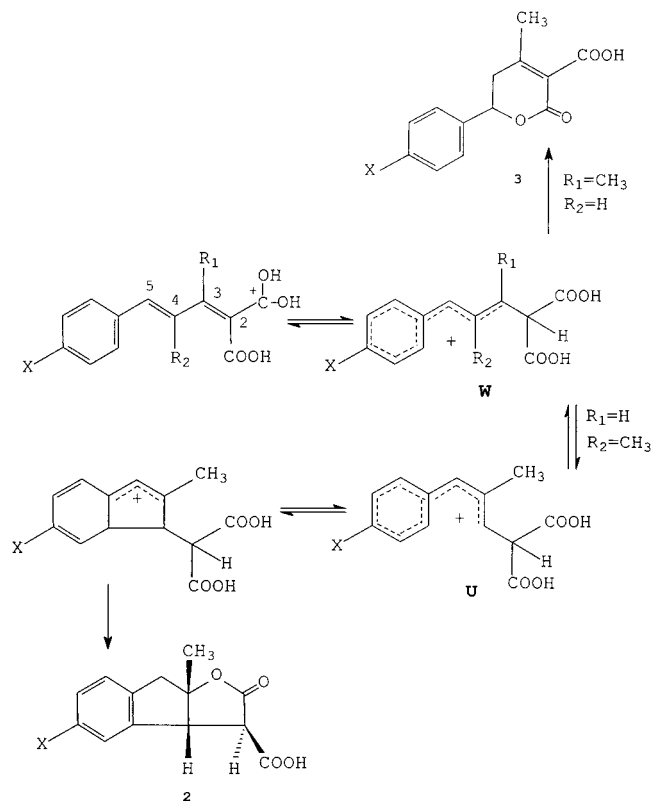
We recently reported the synthesis of a novel class of synthons, β -methylene-aldehydes, and their use in the synthesis of 13 *Z* retinoic acids (1).

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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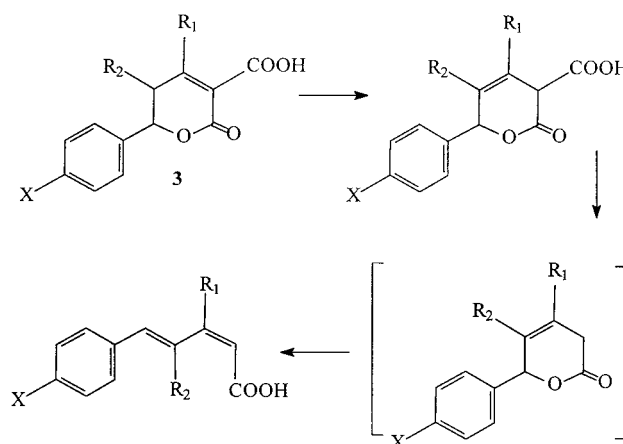


Scheme 1. a: $X = H$; b: $X = CH_3O$; c: $X = Cl$.



Scheme 2.





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** ($R_1 = \text{CH}_3$, $R_2 = \text{H}$). There is a conformational change to a 'U' form when $R_1 = \text{H}$ and $R_2 = \text{CH}_3$. 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

We are indebted to Dr. Owen Parkes for improvement of our English.

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5. A typical procedure for cyclization step is: 1 g of **1** was added to 20 cm³ concentrated sulphuric acid (R₁ = H, R₂ = CH₃: 0°C, 10 min.; R₁ = CH₃, R₂ = 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 (Na₂SO₄), and evaporated under reduced pressure. The residue was purified by recrystallization from ether (R₁ = H, R₂ = CH₃) or by flash chromatography eluting with 80/20 CH₂Cl₂/CH₃OH and recrystallization from ether (R₁ = CH₃, R₂ = H). **2a**. White crystals (75%) F: 152°C. Anal. calc. For C₁₃H₁₂O₄: 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, CDCl₃): 7.28 (m, 4H, H_{4,5,6,7}); 4.13 (d, 1H, *J* = 3.3, H₃); 3.78 (d, 1H, *J* = 3.3, H_{3a}); 3.49 (d, 1H, *J* = 17.6, H₈); 3.25 (d, 1H, *J* = 17.6, H_{8'}); 1.77 (s, 3H, CH₃). ¹³C 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 (C₈); 24.8 (CH₃). **3a**. White crystals (65%) F: 104°C. Anal. calc. For C₁₃H₁₂O₄: 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, CDCl₃): 7.46–7.40 (m, 5H, H_{8,9,10,11}); 5.49 (dd, 1H, *J* = 12.4, *J'* = 3.6, H₅); 3.08 (dd, 1H, 1H *J* = 19.0, *J'* = 12.4, H₆); 2.85 (dd, 1H, *J* = 19.1, *J'* = 3.6, H_{6'}); 2.61 (s, 3H, CH₃). ¹³C NMR: 172.8 (COOH); 167.6 (CO); 162.9 (C₃); 136.2 (C₄); 130.0 (C₁₀); 129.3, 129.0 (C_{8,12} and C_{9,11}); 77.8 (C₅); 40.6 (C₆); 23.8 (CH₃).
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Received in the UK October 21, 1999



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