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Novel $\pi_{2s}+\pi_{2a}$ Electrocyclization of Triethylene-Malonic Acids: Exemplified for a One-Pot Synthesis of New $\gamma$-Dilactones cis-Fused with a Cyclopentene

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INTRODUCTION

$\gamma$-Lactones are key structural subunits of natural products [1] and valuable synthetic intermediates [2]. Compounds containing a $\gamma$-lactone moiety cis-fused with a cyclopentene are of considerable interest because of a wide range of biological activities and for their versatile chemistry. They are key intermediates in prostaglandin synthesis [3,4], components of essential oils and food [5–8], and reveal cytotoxic, antitumorous [9,10] and antifungal activities [11–13]. As a consequence of this importance, many syntheses of these compounds have been developed [14–24].

We report herein a suitable and quickly route to a series of dilactones 3 by thermal cyclization of 2-((2E,4E)-5-chloro-5-methyl (or 5-phenyl) 2,4-dimethylhexa-2,4-dienylidene)malonic acids 2 (official nomenclature: ACD/ChemSketch).

RESULTS AND DISCUSSION

The (2E,4E,6E)-7-chloro-2-(methoxycarbonyl)-4,6,7-trimethylocta (or 4,6-dimethyl, 7-phenyl)-2,4,6-trienoic acids 1 were prepared in good yield by a Stobbe-like condensation [25] of alkenals [26–30] and methyl propylidene malonate [31], using trimethylbenzyl ammonium hydroxide (Triton B) as a base (rt, 48 h.) [32,33]. The correspondent diacids 2 (2-((2E,4E)-5-chloro-2,4,5-trimethylhexa (or 2,4-dimethyl-5-phenyl)-2,4-diencylindene) malonic acid) were quantitatively obtained by smooth hydrolysis (NaOH 1 M, rt, 20 h.). Characteristics of these compounds are in accordance with those described in the literature for related products (ref. cited previously) [34,35].

Among these latter compounds, only the diacids 2 possessing the 4E,6E configuration led, by thermal activation (90°C, 1 h, 15 mm Hg), to the $\gamma$-dilactones 3: 4a,5,6a-trimethyl (or 4a-phenyl-5,6a-dimethyl)-2a,4a,6a,6b-tetraydro-2H,3H-1,4-dioxacycloptenta[c]pentalen-2,3-dione (Scheme 1). The $\delta$-lactones 4 obtained besides lactones 3 (in lowly yield): 6Z and 6E-(3-chlorobut-2-en-2-yl)-5-methyl-3,6-dihydro-2H-pyran-2-one were formed from prior isomerization (in our experimental conditions) of 4E,6E diacids to 4E,6Z diacids (see next paragraphs; $\delta$-lactones 4 as secondary products).

The formation of cyclopentenyl cations from pentadienyl cations were well documented [36–50].
Compound 3 involved the establishment of intermediaries γ-lactones 5 via a cyclopentenyl zwitterion, and one of these, 5c could be isolated (Scheme 2). It was generally admitted that the W form of the cation initially formed was more stable; however, equilibrium with the forms called U and sickle has been established, by rotation around C2–C3 and C5–C6 double bonds [51]. Relative ease of these transformations resulted in partial double bond character at central bond (weaker than at terminal bonds). The presence of a methyl group at C4 probably was in disfavour of the W form, thus, making easier the cyclization of the U form to a cyclopentenyl cation, according to an electrocyclic π2s + π2a conrotatory process, thermally allowed [52]. Kinetic measurements have shown that this cyclization was facilitated with the presence of methyl groups in position 3, and in positions 2 and 4 (which is our case) [38].

Subsequent quenching by the negative charge of the carboxylate anion gives the isolated lactones 3 (R = C6H5; R = CH3), or 4c (Z: C6 = C7; R = CH3 or C6H5 (see previous paragraphs); δ-lactones 4 as secondary products).

The observed stereochemistry in the bicyclic lactone 5c is that predicted by the Woodward–Hoffmann rules (Scheme 2).

The lactonization stage of diacid 2c, carried out in hexane at reflux, allowed to isolate quantitatively this γ-lactonic intermediate 5c (3S,3aS,4R,6aS)-4-chloro-4,5,6a-trimethyl-2-oxo-3,3a,4,6a-tetrahydro-2H-cyclopenta[b]furan-3-carboxylic acid) that cyclized quantitatively by heating at reflux in C6H6 to γ-dilactone 3c (Scheme 3).

The configuration of the bond C3α–C6α was set cis and this, at the bond C3–C3α, was deduced because of its coupling constants (J = 8 Hz), corresponding to a cis orientation [53,54]. C3α–C4 configuration has been established by 1D NOE, which shows strong correlation of H3a and 6a-CH3, and none between H3a and 4-CH3.

δ-Lactones 4 as Secondary Products. The configuration of the C6–C7 double bond of diacids 2 was identical to aldehydes used in these syntheses (β-chloro-α-methyl cinnamic (E major, 95%) and β-chloro-α-methyl-crotonic (E major, 60%)) [27–31].

Thermic activation of diacid 2c led to a mixture of lactones 3c and 4c (90/10). The dilactone 3c was the expected product because the C6–C7 double bond was E in diacid 2c. So, the dihydropyranone 4c could be considered as resulting from the cyclization of the diacid 2c′ (with the Z configuration at C6–C7), diacid forming by prior isomerization of diacid 2c. The formation of these two lactones can be summarized as follows (Scheme 4).

Unfortunately, in our experimental conditions, it was not possible for us to isolate the diacid 2c′; so, we have operated under milder conditions for the thermal activation. Thus, the diacid 2c, heated in solution in non-polar solvents, (such as benzene at reflux), led to a mixture of lactones 3c, 4c and 5c (50/20/30). At lowest temperature, in hexane at reflux, lactone 5c was formed quantitatively and can be cyclized by heating (dry or in benzene) to the corresponding dilactone (Scheme 5).

So, the primary product of the cyclization of the diacid was lactone 5c, as showed the way in hexane. The isomerization of the diacid 2c to 2c′ was partially made in benzene and 2c′ that led to the dihydropyranone 4c.

The configuration of the C4–C5 double-bond of diacids 2 was E in all the compounds investigated. This fact was confirmed by a chemical pathway. We have previously
found that decarboxylation of diacids 2 in 2,6-dimethylpyridine led stereospecifically to Z,E monoacids 6 [55,56]. These monoacids resulted from stereospecific opening of the δ-lactone 4 initially formed, and the reaction mechanism was identical to this proposed by Corey for benzylidene-malonic compounds [57] (Scheme 6).

Furthermore, chemical shifts of the methyl groups in the positions 4 and 6 show that the configuration of a diacid 2 and a monoacid 6 is not altered (Table 1).

Thus, 2a has the configuration 4E,6E; 2b 4E,6Z; 2c 4E,6E and 2d 4E,6Z.

We had previously isolated a carboxylic α-ethylenic-δ-lactone of type 7 (R=C₆H₅, besides the corresponding δ-lactone 10), suggested as an intermediary in the decarboxylation of β-methyl ethylenic malonic acid [58]. According to Corey [57,59], this decarboxylation required a previous isomerization to the δ-ethylenic-δ-lactone (Scheme 7) [34]. In our experimental conditions, the β-ethylenic-δ-lactone (in brackets) has not been observed and was isomerized to the more stable lactone 10 (in this case). We had established that heating of compound 7 in benzene/Et₃N for 30 min led to a mixture of lactone 10 and acid 6) [58].

The malonic acids 2 (0.01 mole) were heated 1 h at 90 °C, under reduced pressure (15 mm Hg of pressure). The crude mixture was solubilized in ether, and the traces of monoacids 6 were extracted by a solution of saturated NaHCO₃. The γ-dilactones 3a slowly crystallized from the organic solution. The diacid 2a led to dilactone 3a and the diacid 2c furnish a mixture of lactones 3b and 5c, which were separated by column chromatography on silica gel (Merck 60 F 254 (CHCl₃/benzene: 30/70).

γ-Lactone 5c was produced by refluxing a solution of malonic acid 2c (0.01 mole) in hexane (50 mL) for 4 h. Distillation of the solvent under reduced pressure gave the crude lactone-acid 5, which was recrystallized from ether.

To optimize the yield of δ-lactones 4 and monoacids 6, a base-catalyzed decarboxylation was used [25]. Thus, a solution of malonic acid 2 (0.01 mole) in 2,6-dimethyl pyridine (20 mL) was refluxed for 1.5 h. After cooling to rt, the reaction was quenched by the addition of 20% HCl. The resulting mixture was extracted with ether. The crude δ-lactone was separated from the monoacid

Table 1

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Scheme 6. R=Me; C₆H₅.

Scheme 7. (R=C₆H₅).
by extraction of this later with a saturated solution of sodium hydrogen carbonate.

**EXPERIMENTAL**

Melting points were taken on a Leitz 350 heated stage microscope and are not corrected. UV spectra were realized in ethanol, and λ max are given in nm (ε). 1H NMR spectra (in CDCl₃) were recorded on a Bruker Avance DPX 400 and a WP80 DS instruments (Bruker, MA, USA) and were reported in ppm downfield from internal tetramethylsilane. Elemental analyses were indicated by elemental symbols. Dimethyl propylenemalonate and β-chloro α-ethylenaldehyde were synthesized according to well-known procedures (ref. cited previously). A volume of 150 mL of a methanolic triton B solution (40% in weight) were added to a mixture of aldehyde (0.1 mol) and dimethyl propylenemalonate (0.1 mol). The resulting solution was left at rt for 48 h. Dilution with 100 mL of water, extraction with ether of the by-products and addition of 20% HCl to the aqueous layer provided the crude half-ester that was extracted with ether. Sodium salts of 1a and 1c could be isolated through precipitation into a saturated solution of CO₂HNa, washed with ether and dried under reduced pressure. 1b and 1d were precipitated by acidification of the remaining soluble fraction, washed with water and dried over MgSO₄. The half-ester 1 (0.01 mol) was dissolved in 1 M aqueous NaOH. The resulting solution was left at room temperature overnight and acidified with 10% HCl. After ether extraction, followed by washing of the combined ether extracts with a saturated solution of NaHCO₃, the combined aqueous layers were acidified with a solution of 10% HCl and the resulting precipitator was collected and recrystallized. The data of these compounds are analogous to those described in previous papers [34].

**REFERENCES AND NOTES**
