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Two-step Synthesis of New γ-Lactones via Cyclization of 7-Chloro-2-(methoxycarbonyl)-4-6-dimethylocta-(2*E*,4*E*,6*E*)-trienoic acid

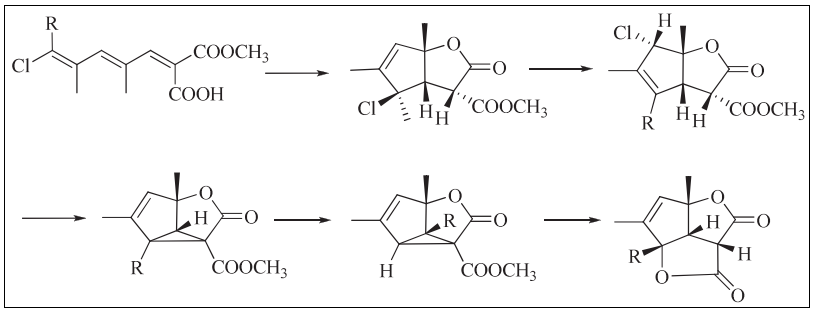
Jean-Marc Dillenschneider,[a] Laurent Dufossé,[b]* Mireille Fouillaud,[b] Nuthathai Sutthiwong,[b,c] Roger Labia,[a,d] and Alain Valla[a,d]*

[a]Laboratoire de Chimie des Substances Naturelles, URA 401 CNRS, MNHN, 63 rue Buffon, 75005, Paris, France [b]Laboratoire de Chimie des Substances Naturelles et des Sciences des Aliments, Université de La Réunion, ESIROI Département agroalimentaire, 2 rue Joseph Wetzell, F-97490 Sainte-Clotilde, La Réunion, France

[c]Thailand Institute of Scientific and Technological Research, Agricultural Technology Department, 35 Mu 3, Technopolis, Klong 5, Klong Luang, Pathum Thani 12120 Thailand

[d]Chimie et Biologie des Substances Naturelles FRE 2125 CNRS, MNHN, UBO, 6, rue de l'Université 29000 Quimper, France

*E-mail: laurent.dufosse@univ-reunion.fr; valla.alain@orange.fr



A new rapid synthesis of γ-lactones, cis fused with a cyclopentenic ring by thermal cyclization of 7-chloro-2-(methoxycarbonyl)-4-6-dimethylocta-7-phenyl (or methyl) (2*E*,4*E*,6*E*)-trienoic acids was reported. The key step implicates an intramolecular cyclization to a cyclopentenyl cation, according to an electrocyclic $\pi_{2s} + \pi_{2a}$ conrotatory process, published in a recent paper (from the corresponding diacids). We have investigated the thermal behavior of the corresponding half-esters since; if the cyclization obeys to the proposed mechanism, the diacids, half-esters must also cyclize in a similar manner. Saponification of these led to γ-dilactones via intermediary cyclopropanes. Mechanistic pathways were investigated.

INTRODUCTION

In a recent paper, published in this journal [1], we report that thermal cyclization of 2-((2*E*,4*E*)-5-chloro-2,4-dimethylhexa-2,4-dienylidene)malonic acids led to new γ-dilactones (Scheme 1).

The key step implicates an intramolecular cyclization of the diacid to a cyclopentenyl cation, according to an electrocyclic $\pi_{2s} + \pi_{2a}$ conrotatory process. The observed stereochemistry is that predicted by the Woodward–Hoffmann rules.

The scope of this new paper is to fix the limits of this reaction. So, in order to shed light on the suggested mechanistic pathways, we have investigated the thermal behavior of the corresponding half-esters. Since, if the cyclization obeys to the proposed mechanism in Scheme 2 [2], the diacids, half-esters must also cyclize in a similar manner. This new study permits us to isolate intermediates (unstable or stable), implied in the cyclization process.

Thus, thermal activation of **1a** and **1b** carried out in refluxing xylene (1 h, reflux) led to the previous γ-lactones-esters **2a** and **2b** (Scheme 2).

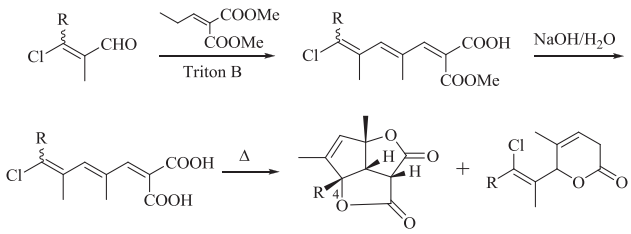
At lower temperature, in refluxing benzene, the less hindered compound **1b** (R=CH_3) led in a closely quantitative yield, the γ-lactone **3b**, which could be considered as the kinetic product in the cyclization stage (Scheme 2). Hence, this latter rearranged in refluxing xylene (1 h, reflux) to the γ-lactone **2b** (Scheme 3).

The chlorolactone **3b** possessed effectively the stereochemistry predicted by the selection rules. Relative configuration of the bond C_{3a}–C_{6a} was set cis (for steric concerns), and the one at the bond C_3–C_{3a} was deduced due to its coupling constants ($J = 8$ Hz), corresponding to a cis orientation [2,3]. C_{3a}–C_4 configuration has been established by 1D Nuclear Overhauser Effect (NOE), which shown strong correlation of H_{3a} and 6a-CH_3 and none between H_{3a} and 4-CH_3.

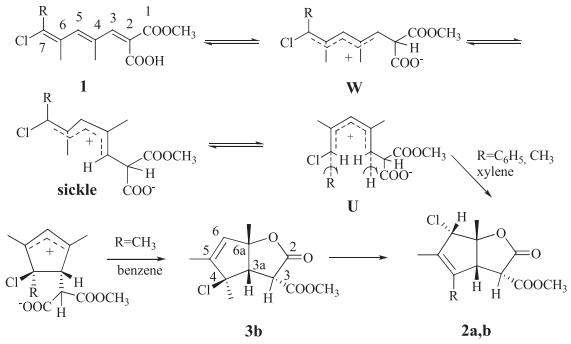
1,3 Transposition of the chlorine atom in lactone **3b** {**3b** ➔**2b**} was thermally authorized by a *supra-antara* concerted mechanism, but, because of steric hindrances, only a few examples are known [4–6].

Dehydrohalogenation of lactones **2a** by anhydrous diethylamine afforded cyclopropanes **4a** (diethylamine 2 eq, room temperature (r.t.), 15 min). Compound **4a**, extremely unstable, rearranged slowly to its isomer **5a** (MeOH, reflux,

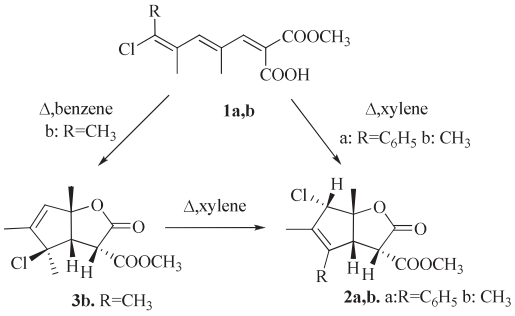
Scheme 1. **1** and **2**. a: R=C_6H_5 (6*E*); b: R=C_6H_5 (6*Z*); c: R=CH_3 (6*E*); d: R=CH_3 (6*Z*). **3**: R=C_6H_5; R=CH_3.



Scheme 2. **1a** (6*E*): R=C_6H_5; **1a** (6*Z*): R=C_6H_5; **1b** (6*E*): R=CH_3 **1b** (6*Z*): R=CH_3; **2a:** R=C_6H_5; b: R=CH_3; **3b**: R=CH_3. Numbering of carbons as used for the comparison of NMR spectra.



Scheme 3. (a) R=C_6H_5; (b) R=CH_3.

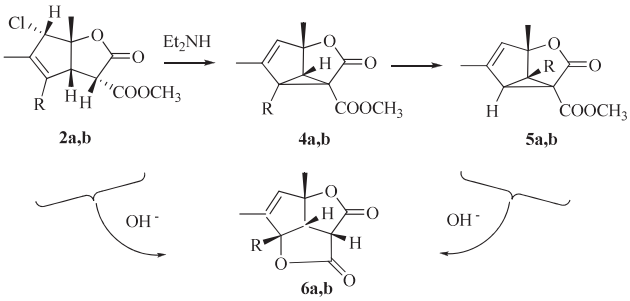


15 min). In the same conditions, **2b** gave a complex mixture, which slowly evolved to the dilactone **6b** (Scheme 4).

The 1,3-transposition of **4** ➔ **5** seems to be particular to this series and represents, to our knowledge, the first example in the literature. Noteworthy, migration of a radical has been observed in cationic species [7,8]. Saponification (NaOH, CH_3OH/H_2O: 75/25, reflux 30 min) of lactones **2–5** afforded the dilactone **6** (Scheme 4).

Taking into account the results of the above figure, we may propose that formation of dilactones **6** in the saponification reaction could be processed via an intermediary cyclopropanic acid (not isolated) which rearrange spontaneously to the

Scheme 4



corresponding γ-lactone. These types of rearrangements have been reported (Scheme 5) [9,10].

In the same experimental conditions (and with various catalysis: paratoluenesulfonic acid or p-toluenesulfonic acid (PTSA), molecular sieves, bentonite, $TiCL_4$ etc.), the corresponding diester **7** (obtained by treating the sodium salts of diacids, half-esters by methyl iodide in HMPT) did not cyclize, implying, apart stereochemical implications, that at least one free carboxylic function was necessary (Scheme 6).

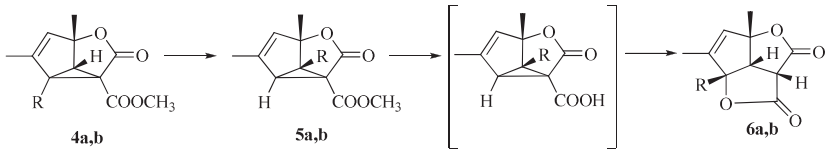
EXPERIMENTAL

Melting points were taken on a Leitz 350 heated stage microscope (Ernst Leitz GMBH, Germany) and are not corrected. UV spectra were realized in ethanol, and λ max is given in nanometers (ε). NMR spectra (in $CDCl_3$) were recorded on a Bruker Avance DPX 400 (Bruker Biospin S.A.S., France) and a WP80 DS instrument and were reported in parts per million (ppm) downfield from internal tetramethylsilane. Elemental analyses were indicated by elemental symbols. Dimethyl propylidenemalonate and β-chloro α-ethylenic aldehydes were synthesized to well-known procedures [11–17].

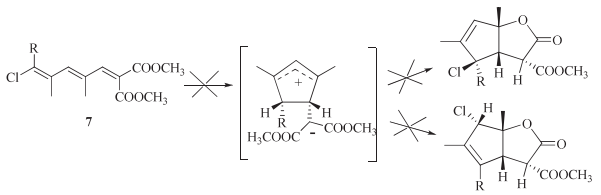
Characteristics of compounds **1** and **7** are in accordance with those described in the literature for related products [1]. Dimethyl propylidenemalonate and β-chloro α-ethylenic aldehydes were synthesized according to well-known procedures [1]. Malonic acid, half-esters **1**. About 150 mL of a methanolic triton B solution (40% by weight) was added to a mixture of aldehyde (0.1 mole) and dimethyl propylidenemalonate (0.1 mole). The resulting solution was left at r.t. 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, which was extracted with ether. Sodium salts of **1a** and **1c** could be isolated by precipitation into a saturated solution of $NaHCO_3$, 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 $MgSO_4$.

1a (*E* C6-C7): yield 90%; yellow crystals; mp 80°C (AcOEt/petroleum ether; b: benzene); $_{CO}$ 1730, 1710; λ

Scheme 5



Scheme 6



max 250, 320 (unstable at rt). *Anal.* calcd. for $C_{17}H_{17}ClO_4$: C, 63.64; H, 5.35; Cl, 11.05. Found: C, 63.47; H, 5.47; Cl, 11.03. ^{1}H NMR: R s: 7.30; 6-CH_3 s: 2.15; 4-CH_3: d 6.41 (1.75); H_5 m: 6.41; H_3 d: 7.20 (1); OCH_3 s: 3.75. **1b** (*Z* C6-C7): yield 40%; yellow crystals; mp 150°C (AcOEt/petroleum ether; b: benzene); ν_{CO} 1740, 1695; λ max 295 (ε: 15,600). *Anal.* calcd. for $C_{17}H_{17}ClO_4$: C, 63.64; H, 5.35; Cl, 11.05. Found: C, 63.51; H, 5.48; Cl, 11.00. ^{1}H NMR: R s: 7.40; 6-CH_3 s: 1.86; 4-CH_3: d 1.91 (1); H_5 m: 6.73; H_3 d: 7.53 (1); OCH_3 s: 3.86. **1c** (*E* C6-C7): white crystals; mp 92°C (cyclohexane); ν_{CO} 1740, 1695; λ max 292 (ε: 17,000). *Anal.* calcd. for $C_{12}H_{15}ClO_4$: C, 55.70; H, 5.85; Cl, 13.70. Found: C, 55.54; H, 5.96; Cl, 13.68. ^{1}H NMR: R q: 1.90 (1.5); 6-CH_3 q: 2.03 (1.5); 4-CH_3: d 1.83 (0.8); H_5 m: 6.40; H_3 d: 7.38 (0.8); OCH_3 s: 3.84.**1d** (*Z* C6-C7): yield 10%; White crystals; mp 114°C (cyclohexane); ν_{CO} 1720, 1695; λ max 287 (ε: 14,000). *Anal.* calcd. for $C_{12}H_{17}ClO_4$: C, 55.70; H, 5.85; Cl, 13.70. Found: C, 55.59; H, 5.98; Cl, 13.58. ^{1}H NMR: R q: 1.91 (1.5); 6-CH_3 q: 2.05 (1.5); 4-CH_3: d 1.76 (0.8); H_5 m: 6.44; H_3 d: 7.43 (0.8); OCH_3 s: 3.86.

γ-Lactones 2a and **2b**. A solution of malonic acid, half-ester **1a** and **1b** (0.01 mole) in benzene (50 mL) was refluxed for 1 h. Distillation of the solvent under reduced pressure gave quantitatively the crude lactones-esters **2a** and **2b**.

γ-Lactone 3b. A solution of malonic acid, half-ester **1c** (0.01 mole) in hexane (50 mL) was refluxed for 1 h. Distillation of the solvent under reduced pressure gave quantitatively the crude lactone-ester **3b**. **3b**: yield 100%; white crystals; mp 86°C (petroleum ether); ν_{CO} 1770, 1740; λ max 205 (ε: 3500). *Anal.* calcd. for $C_{12}H_{15}ClO_4$: C, 55.70; H, 5.85; Cl, 13.70. Found: C, 55.59; H, 5.96; Cl, 13.57. ^{1}H NMR: R s: 1.30; 5-CH_3 d: 1.38 (1.5); 6-CH_3 s: 1.47; H_3: d 3.25 (8.5); H_{3a} d: 3.66 (8.5); H_6 q: 5.13 (1.5); OCH_3 s: 3.38. ^{13}C NMR 4-CH_3: 25.4; 5-CH_3: 11.6; 6a-CH_3: 24.2; C_3: 61.4; C_{3a}: 53.4; C_4: 77.8; C_5: 146.4; C_6: 131.4; C_{6a}: 93.5; CO: 167.5; C_3-$\underline{CO}OCH_3$: 168.6; CH_3O: 51.4.

Rearrangement of lactone-ester 3b into lactone-ester 2b. A solution of lactone-ester **3b** (0.01 mole) in xylene (50 mL) was refluxed for 1 h. Distillation of the solvent under reduced pressure gave practically quantitatively the crude lactone-ester **2b**, which recrystallized from petroleum ether. **2b**: yield 100%; white crystals; mp 118°C (petroleum ether); ν_{CO} 1770, 1740; λ max 205 (ε: 3500). *Anal.* calcd. for $C_{12}H_{15}ClO_4$: C, 55.70; H, 5.85; Cl, 13.70. Found: C, 55.57; H, 5.97; Cl, 13.55 . ^{1}H NMR: R and 5-CH_3 m: 10.05 and 1.38; 6-CH_3 s: 1.65; H_3: d 3.25 (2.3); H_{3a} m: 3.13; H_6 m: 4.57 (1.5); OCH_3 s: 3.27. ^{13}C NMR 4-CH_3 and 5-CH_3: 12.0 and 12.3; 6a-CH_3: 23.0; C_3: 57.9; C_{3a}: 50.7; C_4: 133.4; C_5: 134.8; C_6: 73.8.4; C_{6a}: 92.9; CO: 167.9; C_3-$\underline{CO}OCH_3$: 169.9; CH_3O: 53.3.

γ-Lactone 2a. Lactone **3a** (0.05 mole) in ether was treated by 2 eq of anhydrous diethylamine for 15 min at rt. The solution was then cooled, and the unstable lactone **4a** slowly crystallizes. **4a**: yield 80%; m.p.: 114°C; ν_{CO} 1770, 1720; ^{1}H NMR: 4-CH_3 m: 7.33; 5-CH_3: d: 1.63 (2); H_6 m: 5.63; 6a-CH_3 s: 1.75; H_{3a} d: 3.74 (0.8); OCH_3 s: 3.44. ^{13}C NMR: R (4-C_6H_5) 128.4, 129.0; 5-CH_3: 15.2; 6a-CH_3 19.9; C_4: 55.7; C_6: 132.6; C_3-$\underline{CO}OCH_3$: 169.5; OCH_3: 52.7; CO: 167.2, 163.5.

γ-Lactone 5a. The obtained lactone **4a** was heated in refluxing benzene for 30 min (or in MeOH, 60°C, 10 min). The benzene was distilled under reduce pressure, and the crude product was extracted with ether. After cooling, as mentioned earlier, lactone **5a** slowly crystallizes. **5a**: yield 80%; m.p.: 117°C; ν_{CO} 1770, 1730; *Anal.* calcd. for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67; O, 22.51. Found: C, 71.64; H, 5.84; O, 22.70; ^{1}H NMR R (C_6H_5) m: 7.33; 5-CH_3 m: 2.01; 6a-CH_3 s: 1.30; H_4 m: 5.55; H_6 m: 3.55; OCH_3 s: 3.58. ^{13}C NMR R (C_6H_5) 128.6, 128.8, 129.27, 141.6; 5-CH_3: 15.9; 6a-CH_3 95.2; C_4: 55.0; C_6: 95.2; C_3-$\underline{CO}OCH_3$: 167.3; OCH_3 52.6; CO: 163.6.

γ-Dilactones 6a and **6b**. γ-Lactones **3a, 3b** and **5a, 5b** (0.01 mole) were refluxed for 2 h in a solution of 2 M solution of sodium hydroxide (3 eq) in methanol/water (50/50). After acidification by a cold solution of 1-M HCl, lactones **6a** and **6b** were extracted with ether (3 × 50 mL). The solution was washed with water and dried over $MgSO_4$. After filtration of the $MgSO_4$ and distillation of an half of ether, the γ-dilactones slowly crystallized from ether. **3a**: yield 90%; mp: 161°C (ether); ν_{CO} 1795, 1755; λ max 212 (ε: 10.150). *Anal.* calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22; O, 23.68.

Found: C, 70.89; H, 5.41; O, 23.78. ^{1}H NMR R m: 7.40; 5-CH_3 d: 1.63 (1.3); 6a-CH_3 s: 1.77; H_{2a} d: 4.05 (11.5); H_{3a} q: 5.93 (1.3); H_3 d: 3.50 (11.5). ^{13}C NMR **3a** R: 124.2; 128.5; 129.0; 146.7. 5-CH_3: 12.2. 6a-CH_3 24.8. 3-CH: 57.7. 4-C: 94.1; 3a-CH: 49.9. 6-CH: 133.3. 5-C-CH_3: 138.3. 6a-CH_3: 24.8. 4-C: 94.1. 6a-C: 94.3. CO: 167.9, 168.1. **3b**: yield 90%; mp: 123°C (pentane); ν_{CO} 1785, 1755; λ max 212 (ε: 2.600). *Anal.* calcd. for C_{11} $H_{12}O_4$: C, 63.45; H, 5.81; O, 30.74. Found: C, 63.29; H, 5.99; O, 30.08. ^{1}H NMR R s: 1.60; 5-CH_3 d: 1.81 (1.3); 6a-CH_3 s: 1.60; H_{2a} d: 4.08 (11.5); H_{3a} q: 5.66 (1.3); H_3 d: 3.28 (11.5). **3b** R: 23.1. 5-CH_3: 11.7. 6a-CH_3 25.0. .4-C: 93.5; 3-CH: 55.4. 3a-CH: 50.6. 6-CH: 132.2. 5-C-H_3: 146.7. 6a-CH_3: 24.8. 4-C: 93.5. 6a-C: 94.1; CO: 168.1, 168.3.

Diester 7. About 0.01 mole of the malonic acid, half-ester **1** (sodium salt) was dissolved into 10 mL of hexamethylphosphoric triamide (HMPT). Then 0.01 mole of ICH_3 was added, and the solution was left at rt overnight. After acidification (HCl 20%), the crude mixture was extracted with ether, and the traces of malonic acid, half-ester were removed by a saturated solution of HCO_3Na. The neutral fraction of diesters was purified by column chromatography (SiO2 Merck 60 F 254—ethyl acetate/cyclohexane—30:70). **7a** (*E*) yield: 100% (oil); ν_{CO} 1730, 1710; λ max 324 (ε: 14,000), 254 (12,550). *Anal.* calcd. for C_{18} $H_{19}ClO_4$: C, 64.56; H, 5.73; Cl, 10.58. Found: C, 64.34; H, 5.91; Cl, 10.58. ^{1}H NMR R s: 7.28; 4-CH_3 s: 2.01 (1.3); 6a-CH_3 d: 1.61 (1.5); H_5 m: 6.36; H_3 d: 7.01 (1.5); OH_3 2 s: ep 3.71. **7a (*Z*)** yield: 100% (oil); ν_{CO} 1720, 1605; λ max 290 (ε: 13,300), 262 (11,300). *Anal.* calcd. for C_{18} $H_{19}ClO_4$: C, 64.56; H, 5.73; Cl, 10.58. Found: C, 64.36; H, 5.88; Cl, 10.41. ^{1}H NMR R s: 7.28; 4-CH_3 s: 1.86; 6a-CH_3 d: 1.91 (1.5); H_5 m: 6.66; H_3 d: 7.38 (1.5); OH_3 2 s: 3.11, 3.86. **7b (*E*)** yield: 100% (oil); ν_{CO} 1720, 1610; λ max 290 (ε: 15,700), 262 (11,300). *Anal.* calcd. for C_{13} $H_{17}ClO_4$: C, 57.24; H, 6.29; Cl, 12.99. Found: C, 57.11; H, 6.43; Cl, 12.91. ^{1}H NMR R q: 1.92 (1.5); 4-CH_3 q: 2.03 (1.5); 6a-CH_3 d: 1.75 (1.5); H_5 m: 6.41; H_3 d: 7.34 (1.5); OCH_3 2 s: 3.91, 3.86.

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