PAPERS

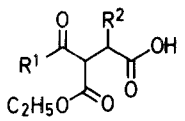
# Synthesis of 3-Ethoxycarbonyl-3-buten-4-olides and 3-Ethoxycarbonyl-4-butanolides

Françoise GAUDEMAR-BARDONE*, Margarita MLADENOVA**, René COUFFIGNAL

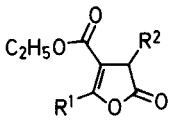
Université Pierre et Marie Curie, Laboratoire de Synthèse Organométallique, Bâtiment F, 4 Place Jussieu, F-75230 Paris Cedex 05, France

This paper describes a synthesis of 3-acyl-2-alkyl-3-ethoxycarbonylpropanoic acids from ethyl 2-oxoalkanoates and 2-bromoalkanoic acids. These acids are cyclised via intramolecular dehydration to give 2,4-dialkyl-3-ethoxycarbonyl-3-buten-4-olides or are condensed with allylzinc reagents to give the 4-alkenyl-2,4-dialkyl-3-ethoxycarbonyl-4-butanolides.

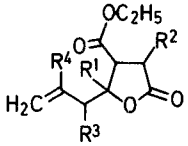
The γ-lactone structure is found in many natural products which demonstrate a biological activity and, from this point of view, the synthesis of such compounds is of considerable interest. Many methods for the synthesis of simple γ-lactones are known but they cannot be applied easily to the preparation of functional γ-lactones and specially to 3-ethoxycarbonyl-γ-lactones[1-7]. Thus, we report here the synthesis of two different series of 3-ethoxycarbonyl-γ-lactones, **2** and **3**, from 3-acyl-2-alkyl-3-ethoxycarbonylpropanoic acids **1**. As far as we know, compounds **1** and **3** have not previously been described.



**1**

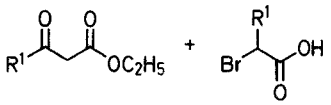


**2**



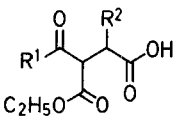
**3**

In connection with our own work, we first developed[8] a convenient access to the compounds **1**, from the corresponding β-ketoesters and α-bromoacids in the presence of sodium ethoxide (Scheme **A**, Table 1).



1. $C_2H_5ONa/C_2H_5OH/(C_2H_5)_3N/CuBr$ (cat.), reflux, 7h
2. $H_3O^{\oplus}$

70 - 86 %



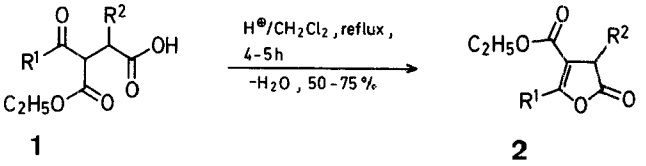
**1 a-k**

| 1 | $R^1$ | $R^2$ | 1 | $R^1$ | $R^2$ |
|---|---|---|---|---|---|
| a | $H_3C$ | H | g | $H_3C$ | $CH_3$ |
| b | $n$-$C_3H_7$ | H | h | $H_3C$ | $C_2H_5$ |
| c | $n$-$C_5H_{11}$ | H | i | $H_3C$ | $i$-$C_3H_7$ |
| d |  | H | j | $H_3C$ |  |
| e | $i$-$C_3H_7$ | H | k | $n$-$C_5H_{11}$ | $C_2H_5$ |
| f |  | H | | | |

Scheme **A**

When $R^2 \neq H$, the yields are obviously improved when catalysts such as copper(I) bromide and triethylamine are used. All the structures of these products have been confirmed by spectroscopic determinations. These ketoester acids **1** are slightly soluble in water and sometimes they decompose to a small extent during distillation. Thus, as the N.M.R. spectra of the crude products are correct, they were used as such for further reactions. The compounds **1g–k** are mixtures of diastereoisomers and it is difficult to assign the configuration of each isomer from the N.M.R. spectrum.

The compounds **2** (Table 2) are relatively little known[1,6,7]. They are prepared by intramolecular dehydration of acids **1** (Scheme **B**).

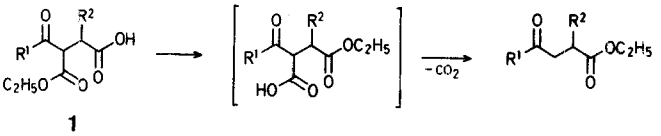


$H^{\oplus}/CH_2Cl_2$, reflux, 4-5h, $-H_2O$, 50-75 %

**1** **2**

Scheme **B**

The choice of reaction conditions (dehydrating catalyst, solvent, and temperature of the reaction) is very important here since the dehydration may be accompanied by a transesterification reaction followed by a decomposition of the intermediate product.



**1**

Thus, the phosphorus pentoxide/phosphoric acid mixture in dichloromethane solution proved to be the most effective and general reagent for cyclisation to give **2**. The use of sulphuric acid, *p*-toluenesulphonic acid, or acetic anhydride in benzene, cyclohexane, or toluene affords less satisfactory results. The structures of the compounds **2** are proved by I.R.[9,10] and N.M.R. spectrometry.

We have not been able to hydrolyse the ester function of **2** either in an acidic medium or in a basic medium. Under these conditions, the lactone ring is opened and the starting acid **1** is obtained. Thus, to avoid this ring-opening when the butenolides **2** are distilled, the pH of the medium must be nearly 7.

Our one-step synthesis of compounds **3** (Table 3) consists of the condensation of allylzinc reagents[11] with the propanoic acids **1** which react only at the carbonyl function, as shown in Scheme **C**.

**Table 1.** 3-Acyl-2-alkyl-3-ethoxycarbonylpropanoic Acids **1**

| Product | Yield [%] | m.p. [°C] or b.p. [°C]/torr | Molecular Formula[a] | I.R. (KBr) $\nu$ [cm$^{-1}$][b] | $^1$H-N.M.R. ($CCl_4$/TMS) $\delta$ [ppm][c] |
|---|---|---|---|---|---|
| **1a** | 80 | 126–128°/0.03 | $C_8H_{12}O_5$ (188.2) | 1735, 1720 | 1.29 (t, $CH_3$); 2.31 (s, $CH_3$); 2.85 (d, $CH_2$); 3.97 (t, CH, $J$ = 7.2 Hz); 4.25 (q, $CH_2$); 10.7 (s, OH) |
| **1b** | 75 | 130–132°/0.03 | $C_{10}H_{16}O_5$ (216.2) | 1740, 1725 | 0.90 (t, $CH_3$); 1.26 (t, $CH_3$); 1.4–2.0 (m, $CH_2$); 2.6 (t, $CH_2$); 2.87 (d, $CH_2$); 3.90 (t, CH, $J$ = 7.2 Hz); 4.19 (q, $CH_2$); 10.5 (s, OH) |
| **1c** | 76 | 134–135°/0.02 | $C_{12}H_{20}O_5$ (244.3) | 1745, 1730 | 0.90 (t, $CH_3$); 1.29 (t, $CH_3$); 1.0–2.0 (m, 3$CH_2$); 2.62 (t, $CH_2$); 2.87 (d, $CH_2$); 3.90 (t, CH, $J$ = 7.2 Hz); 4.21 (q, $CH_2$); 9.6 (s, OH) |
| **1d** | 82 | 138–139°/0.02 | $C_{13}H_{20}O_5$ (256.3) | 1745, 1730 | 1.27 (t, $CH_3$); 1.0–2.2 (m, 10H); 2.4–2.8 (m, $CH_2$); 2.86 (d, $CH_2$); 4.05 (t, CH, $J$ = 7.2 Hz); 4.20 (q, $CH_2$); 10.5 (s, OH) |
| **1e** | 70 | 126–127°/0.03 | $C_{10}H_{16}O_5$ (216.2) | 1745, 1730 | 1.02 (d, 2$CH_3$); 1.22 (t, $CH_3$); 2.5–3.5 (m, CH); 2.80 (d, $CH_2$); 4.10 (t, CH, $J$ = 7.2 Hz); 4.2 (q, $CH_2$); 10.9 (s, OH) |
| **1f** | 86 | 147–150°/0.02 | $C_{13}H_{14}O_5$ (250.2) | 1740, 1700 | 1.10 (t, $CH_3$); 2.50 (s, $CH_2$); 3.01 (d, $CH_2$); 4.10 (q, $CH_2$); 4.78 (t, CH, $J$ = 7.2 Hz); 7.3–8.3 (2m, 5$H_{arom}$); 10.2 (s, OH) |
| **1g**[d] | 70 | 133–135°/0.02 | $C_9H_{14}O_5$ (202.2) | – | – |
| **1h**[d] | 80 | 135–136°/0.02 | $C_{10}H_{16}O_5$ (216.2) | – | – |
| **1i**[d] | 70 | 138–140°/0.03 | $C_{11}H_{18}O_5$ (230.2) | – | – |
| **1j**[d] | 85 | 138° (petroleum ether) | $C_{14}H_{16}O_5$ (264.3) | – | – |
| **1k**[d] | 75 | 140–142°/0.02 | $C_{14}H_{24}O_5$ (272.3) | – | – |

[a] Satisfactory microanalyses obtained: C ±0.31, H ±0.28.
[b] Perkin-Elmer R 257 spectrophotometer.
[c] 60 MHz Perkin-Elmer R12 spectrometer.
[d] Mixture of isomers.

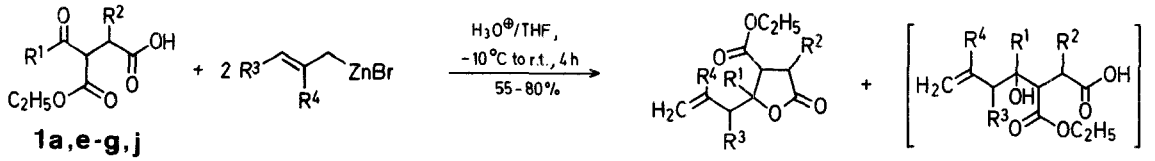
**Table 2.** 2,4-Dialkyl-3-ethoxycarbonyl-3-buten-4-olides **2**

| Product | Yield [%] | m.p. [°C] or b.p. [°C]/torr | Molecular Formula[a] | I.R. (KBr) $\nu$ [cm$^{-1}$][b] | $^1$H-N.M.R. ($CCl_4$/TMS)[c] $\delta$ [ppm] |
|---|---|---|---|---|---|
| **2a**[1] | 75 | 66–67°/0.05 | $C_8H_{10}O_4$ (170.2) | 1820, 1715, 1675 | 1.29 (t, $CH_3$); 2.34 (dd, $CH_3$, $J$ = 2.3 Hz); 3.35 (q, $CH_2$), 4.21 (q, $CH_2$) |
| **2b**[1] | 65 | 70–71°/0.05 | $C_9H_{12}O_4$ (184.2) | 1820, 1715, 1670 | 1.31 (t, $CH_3$); 1.46 (d, $CH_3$); 2.38 (d, $CH_3$, $J$ = 2.2 Hz); 3.2–3.7 (m, CH); 4.22 (q, $CH_2$) |
| **2c**[1] | 65 | 123–125°/20 | $C_{10}H_{14}O_4$ (198.2) | 1820, 1710, 1670 | 0.84 (t, $CH_3$); 1.29 (t, $CH_3$); 1.6–2.2 (m, $CH_2$); 2.38 (d, $CH_3$, $J$ = 2.2 Hz); 3.3–3.6 (m, CH); 4.22 (q, $CH_2$) |
| **2d** | 70 | 79–80°/0.1 | $C_{10}H_{14}O_4$ (198.2) | 1830, 1715, 1665 | 1.0 (t, $CH_3$); 1.29 (t, $CH_3$); 1.4–2.0 (m, $CH_2$); 2.5–3.0 (m, $CH_2$); 3.34 (t, $CH_2$, $J$ = 1.6 Hz); 4.21 (q, $CH_2$) |
| **2e** | 70 | 98–100°/0.1 | $C_{11}H_{16}O_4$ (212.2) | 1820, 1705, 1655 | 0.93 (t, $CH_3$); 1.29 (t, $CH_3$); 0.8–2.0 [m, $(CH_2)_2$]; 2.5–3.0 (m, $CH_2$); 3.36 (t, $CH_2$, $J$ = 1.5 Hz); 4.21 (q, $CH_2$) |
| **2f** | 60 | 104–105°/0.04 | $C_{13}H_{18}O_4$ (238.3) | 1830, 1715, 1660 | 1.5–2.2 (m, 10H); 1.29 (t, $CH_3$); 2.5–2.9 (m, CH); 3.33 (s, $CH_2$); 4.16 (q, $CH_2$) |
| **2g** | 50 | 60° (petroleum ether) | $C_{13}H_{12}O_4$ (232.2) | 1820, 1705, 1635 | 1.22 (t, $CH_3$); 3.55 (s, $CH_2$); 4.15 (q, $CH_2$); 7.5–8.0 (m, 5$H_{arom}$) |
| **2h** | 50 | 105–106°/0.1 | $C_{14}H_{22}O_4$ (254.3) | 1820, 1705, 1655 | 0.85 (t, $CH_3$); 0.91 (t, $CH_3$); 1.29 (t, $CH_3$); 0.8–2.4 [m, $(CH_2)_3$]; 2.6–3.0 (m, $CH_2$); 3.3–3.6 (m, CH); 4.26 (q, $CH_2$) |

[a] Satisfactory microanalyses obtained: C ±0.2, H ±0.2.
[b,c] As in Table 1.

It must be pointed out that allylmagnesium bromide, which in addition to being more difficult to prepare than allylzinc bromide, is not suitable for this reaction.

Under our experimental conditions the lactonisation takes place *in situ* since the N.M.R. spectrum of the crude products of each synthesis shows no trace of the corresponding acylic compound **4**. However, if the reaction is carried out only for short time (a few minutes), the N.M.R. spectrum of the crude mixture shows the presence of a small amount of the 3-ethoxycarbonyl-4-hydroxy acid **4**. This latter product is completly lactonised into **3** under distillation conditions. It is noteworthy that, within the limits of the precision of the N.M.R. spectrometry, crotylzinc bromide




| 3 | R¹ | R² | R³ | R⁴ | 3 | R¹ | R² | R³ | R⁴ |
|---|---|---|---|---|---|---|---|---|---|
| a | $H_3C$ | H | H | H | h | $i$-$C_3H_7$ | H | H | H |
| b | $H_3C$ | H | H | $CH_3$ | i | $i$-$C_3H_7$ | H | H | $CH_3$ |
| c | $H_3C$ | H | $H_3C$ | H | j | $H_3C$ | $CH_3$ | H | H |
| d | $H_3C$ | H |  | H | k | $H_3C$ | $CH_3$ | H | $CH_3$ |
| | | | | | l | $H_3C$ | $CH_3$ | $H_3C$ | H |
| e |  | H | H | H | m | $H_3C$ |  | H | H |
| f |  | H | H | $CH_3$ | n | $H_3C$ |  | H | $CH_3$ |
| g |  | H | $H_3C$ | H | o | $H_3C$ |  | $H_3C$ | H |

Scheme C

[$H_3C$—CH=CH—$CH_2ZnBr$] and the cinnamylzinc bromide [$C_6H_5$—CH=CH—$CH_2ZnBr$] react on the starting materials **1** with a complete allylic rearrangement.

When $R^2$ = H, geometric isomers *cis*-**3** and *trans*-**3** were separated by preparative H.P.L.C. (except for **3c** and **3g**) and the corresponding configurations assigned by N.M.R. spectrometry. For the compounds **3a–d**, the ethoxycarbonyl group exerts a shielding effect on the protons of the *cis*-methyl group linked to the cycle (*trans*-isomer)[3,4,12]. This assignment of the configuration was confirmed in the case of **3b** by Nuclear Overhauser Effect (N.O.E.) experiments (Bruker, 250 MHz). A similar procedure was applied for **3h**.

For **3e–g**, the *cis*-isomer is the one for which the ethoxycarbonyl and the phenyl groups are in a *cis*-position: in this

**Table 3.** 4-Alkenyl-2,4-dialkyl-3-ethoxycarbonyl-4-butanolides **3**

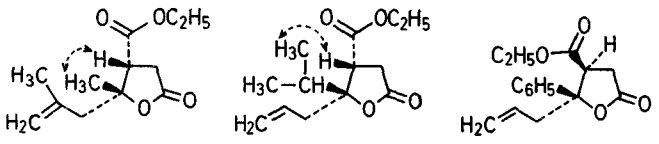
| Product | Yield [%] | *cis*/*trans* Ratio | m.p. [°C] or b.p. [°C]/torr | Molecular Formula[a] | Isomer | I.R. (KBr) $\nu$[cm$^{-1}$][b] | $^1$H-N.M.R. (solvent/TMS) $\delta$[ppm][c] |
|---|---|---|---|---|---|---|---|
| **3a**[d] | 80 | 30/70 | 91–92°/0.02 | $C_{11}H_{16}O_4$ (212.2) | *cis* | 3080, 1790, 1740, 1650 | ($CCl_4$): 1.31 (t, 3H, $J$ = 7.1 Hz, $CH_3$); 1.53 (s, 3H, $CH_3$); 2.1–3.5 (m, 5H, $2CH_2$ + CH); 4.22 (q, 2H, $J$ = 7.2 Hz, $CH_2$); 5.0–6.3 (m, 3H, $H_2C$=CH—) |
| | | | | | *trans* | 3080, 1785, 1740, 1650 | ($CCl_4$): 1.26 (s, 3H, $CH_3$); 1.31 (t, 3H, $J$ = 7.1 Hz, $CH_3$); 2.3–3.6 (m, 5H, $2CH_2$ + CH); 4.22 (q, 2H, $J$ = 7.1 Hz, $CH_2$); 4.8–6.3 (m, 3H, $H_2C$=CH—) |
| **3b**[d] | 75 | 40/60 | 95–97°/0.05 | $C_{12}H_{18}O_4$ (226.2) | *cis* | 3080, 1780, 1740, 1650 | ($CCl_4$): 1.31 (t, 3H, $J$ = 7.2 Hz, $CH_3$); 1.51 (s, 3H, $CH_3$); 1.80 (s, 3H, $CH_3$); 2.0–3.4 (m, 5H, $2CH_2$ + CH); 4.23 (q, 2H, $J$ = 7.1 Hz, $CH_2$); 4.6–5.1 (m, 2H, $H_2C$=) |
| | | | | | *trans* | 3080, 1785, 1740, 1645 | ($CCl_4$): 1.24 (s, 3H, $CH_3$); 1.31 (t, 3H, $J$ = 7.1 Hz, $CH_3$); 1.80 (s, 3H, $CH_3$); 2.2–3.6 (m, 5H, $2CH_2$ + CH); 4.23 (q, 2H, $J$ = 7.2 Hz, $CH_2$); 4.8–5.1 (m, 2H, $H_2C$=) |
| **3c** | 75 | 10/90 | 100–102°/0.07 | $C_{12}H_{18}O_4$ (226.2) | - | 3080, 1790, 1740, 1645 | ($CCl_4$): 1.14 (d, 3H, $J$ = 7 Hz, $CH_3$); 1.27 (s, 3H, *trans* $CH_3$); 1.30 (t, 3H, $J$ = 7.1 Hz, $CH_3$); 1.48 (s, 3H, *cis* $CH_3$); 2.2–3.7 (m, 4H, $CH_2$ + 2CH); 4.21 (q, 2H, $J$ = 7.1 Hz, $CH_2$); 5.0–6.2 (m, 3H, $H_2C$=CH—) |
| **3d**[d] | 60 | 20/80 | 140–142°/0.02 | $C_{17}H_{20}O_4$ (288.3) | *cis* | 3080, 1795, 1740, 1645 | ($CCl_4$): 1.33 (t, 3H, $J$ = 7.1 Hz, $CH_3$); 1.42 (s, 3H, $CH_3$); 2.5–4.0 (m, 4H, $CH_2$ + 2CH); 4.25 (q, 2H, $J$ = 7.2 Hz, $CH_2$); 4.9–5.9 (m, 2H, $H_2C$=); 5.9–6.8 (m, 1H, =CH); 7.4 (s, 5$H_{arom}$) |
| | | | | | *trans* | 3080, 1795, 1745, 1645 | ($CCl_4$): 1.05 (s, 3H, $CH_3$); 1.35 (t, 3H, $J$ = 7.2 Hz, $CH_3$); 2.1–3.9 (m, 4H, $CH_2$ + 2CH); 4.25 (q, 2H, $J$ = 7.1 Hz, $CH_2$); 5.1–5.6 (m, 2H, $H_2C$=); 6.1–6.7 (m, 1H, =CH); 7.35 (s, 5$H_{arom}$) |
| **3e**[d] | 65 | 50/50 | 155–156°/0.05; 90° (petroleum ether) | $C_{16}H_{18}O_4$ (274.3) | *cis* | 3060, 1785, 1735, 1640 | ($CCl_4$): 0.93 (t, 3H, $J$ = 7.2 Hz, $CH_3$); 2.6–3.0 (m, 5H, $2CH_2$ + CH); 3.73 (q, 2H, $J$ = 7.1 Hz, $CH_2$); 4.9–6.1 (m, 3H, $H_2C$=CH—); 7.30 (s, 5$H_{arom}$) |
| | | | | | *trans* | 3085, 1785, 1720, 1640 | ($CDCl_3$): 1.33 (t, 3H, $J$ = 7.1 Hz, $CH_3$); 2.0–3.7 (m, 5H, $2CH_2$ + CH); 4.27 (q, 2H, $J$ = 7.1 Hz, $CH_2$); 4.6–6.0 (m, 3H, $H_2C$=CH—); 7.40 (s, 5$H_{arom}$) |

**Table 3.** (Continued)

| Product | Yield [%] | *cis/trans* Ratio | m.p. [°C] or b.p. [°C]/torr | Molecular Formula[a] | Isomer | I.R. (KBr) $\nu$ [cm$^{-1}$][b] | $^1$H-N.M.R. (solvent/TMS) $\delta$ [ppm][c] |
|---|---|---|---|---|---|---|---|
| **3f** | 65 | 75/25 | 60°[e] petroleum ether) | $C_{17}H_{20}O_4$ (288.3) | *cis* | 3080, 1770, 1740, 1640 | ($CDCl_3$): 0.97 (t, 3H, $J$ = 7.1 Hz, $CH_3$); 1.68 (s, 3H, $CH_3$); 2.7–3.8 (m, 5H, $2CH_2$ + CH); 3.70 (q, 2H, $J$ = 7.2 Hz, $CH_2$); 4.75–5.05 (m, 2H, $H_2C$=); 7.40 (s, $5H_{arom}$) |
| | | | 66°[e] (petroleum ether) | | *trans* | 3080, 1790, 1715, 1645 | ($CDCl_3$): 1.37 (t, 3H, $J$ = 7.2 Hz, $CH_3$); 1.51 (s, 3H, $CH_3$); 2.2–3.7 (m, 5H, $2CH_2$ + CH); 4.33 (q, 2H, $J$ = 7.2 Hz, $CH_2$); 4.5–4.8 (m, 2H, $H_2C$=); 7.44 (s, $5H_{arom}$) |
| **3g** | 60 | 65/35° | 130–133°/0.02 | $C_{17}H_{20}O_4$ (288.3) | – | 3080, 1800, 1745, 1645 | ($CCl_4$): 0.87 (s, 3H, $CH_3$); 1.00 (t, 3H, *cis* $CH_3$); 1.39 (t, 3H, *trans* $CH_3$); 2.3–4.5 (m, 4H, $CH_2$ + 2CH); 3.77 (q, 2H, $J$ = 7.2 Hz, $CH_2$); 4.85–6.3 (m, 3H, $H_2C$=CH—); 7.4 (s, $5H_{arom}$) |
| **3h**[d] | 65 | 60/40 | 105–108°/0.05 | $C_{13}H_{20}O_4$ (240.3) | *cis* | 3080, 1790, 1740, 1648 | ($CDCl_3$): 0.97, 0.98 [2d, 3H each, $J$ = 6.8 Hz, $(CH_3)_2$]; 1.30 (t, 3H, $J$ = 7.1 Hz, $CH_3$); 2.13 (m, 1H, CH); 2.42 (dd, 1H, $J$ = 14.4 Hz, 9.2 Hz, HCH); 2.77 (dd, 1H, $J$ = 14.4 Hz, 5.3 Hz, HCH); 2.66, 3.02 (2dd, 1H each, $J$ = 18.2 Hz, 9.5 Hz, $CH_2$); 3.49 (t, 1H, $J$ = 9.5 Hz, CH); 4.22 (q, 2H, $J$ = 7.1 Hz, $CH_2$); 5.25–5.80 (m, 3H, $H_2C$=CH—)[f] |
| | | | | | *trans* | 3080, 1780, 1740, 1650 | ($CDCl_3$): 0.99, 1.01 [2d, 3H each, $J$ = 6.8 Hz, $(CH_3)_2$]; 1.30 (t, 3H, $J$ = 7.2 Hz, $CH_3$); 2.21 (m, 1H, CH); 2.70 (dd, 1H, $J$ = 18.3 Hz, 10.4 Hz, CH); 3.14 (dd, 1H, $J$ = 18.3 Hz, 8.7 Hz, CH); 3.35 (dd, 1H, $J$ = 10.4 Hz, 8.7 Hz, CH); 4.19 (q, 2H, $J$ = 7.2 Hz, $CH_2$); 5.13, 5.80 (2m, 3H, $H_2C$=CH—)[f] |
| **3i**[d] | 55 | 65/35 | 108–110°/0.05 | $C_{14}H_{22}O_4$ (254.3) | *cis* | 3080, 1790, 1740, 1650 | ($CDCl_3$): 0.96 [2d, 3H each, $J$ = 6.6 Hz, $(CH_3)_2$]; 1.30 (t, 3H, $J$ = 7.1 Hz, $CH_3$); 1.80 (s, 3H, $CH_3$); 2.0–3.5 (m, 5H, $2CH_2$ + CH); 4.25 (q, 2H, $J$ = 7.1 Hz, $CH_2$); 4.8–5.1 (m, 2H, $H_2C$=) |
| | | | | | *trans* | 3080, 1795, 1740, 1650 | ($CDCl_3$): 0.96 [2d, 3H each, $J$ = 6.6 Hz, $(CH_3)_2$]; 1.30 (t, 3H, $J$ = 7.1 Hz, $CH_3$); 1.80 (s, 3H, $CH_3$); 1.9–3.9 (m, 5H, $2CH_2$ + CH); 4.25 (q, 2H, $J$ = 7.1 Hz, $CH_2$); 4.8–5.2 (m, 2H, $H_2C$=) |
| **3j** | 65 | – | 100–102°/0.07 | $C_{12}H_{18}O_4$ (226.2) | – | – | – |
| **3k** | 70 | – | 105–107°/0.07 | $C_{13}H_{20}O_4$ (240.3) | – | – | – |
| **3l** | 50 | – | 100–102°/0.04 | $C_{13}H_{20}O_4$ (240.3) | – | – | – |
| **3m** | 65 | – | 139–140°/0.02 | $C_{17}H_{20}O_4$ (288.3) | – | – | – |
| **3n** | 65 | – | 141–142°/0.05 | $C_{18}H_{22}O_4$ (302.4) | – | – | – |
| **3o** | 65 | – | 146–147°/0.04 | $C_{18}H_{22}O_4$ (302.4) | – | – | – |

[a] Satisfactory microanalyses obtained: C ±0.2, H ±0.1.
[b,c] As in Table 1.
[d] H.P.L.C. separations were performed on a column (240 × 40 mm I.D.) filled with silica gel H60 under a pressure of 12 bar, elution under a pressure of 6 bar, solvent: petroleum ether/ether: 60/40 for **3a**, **3d**, **3h**; 55/45 for **3b**; 50/50 for **3e**; and 65/35 for **3i**.
[e] Separated by crystallisation (petroleum ether) from the mixtures of the two isomers.
[f] Recorded at 250 MHz on a Bruker WM spectrometer.

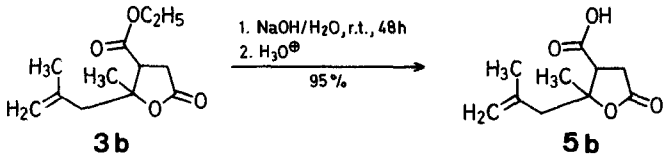
case, the alkoxy protons of the ethoxycarbonyl group resonate at higher field, while in the *trans*-isomer, the same protons resonate at lower field[3]. The *cis/trans*-ratio of isomers can be estimated by means of the integration curve referred to each signal mentioned above; the previous result was confirmed by H.P.L.C. separation of each isomer. Some tests were carried out with the purpose of changing the proportions of the isomers: variation of the reaction time, influence



**3b** (*cis*) N.O.E. = 11% **3h** (*trans*) N.O.E. = 17% **3e** (*cis*)

of the solvent (hexamethylphosphoric triamide, dimethoxyethane, dimethyl sulphoxide). Dimethyl sulphoxide is the only solvent which slightly changes (10% in favour of the *trans*-isomer) the stereochemistry of the reaction. When $R^2 \neq H$ all products are mixtures of isomers.

In contrast to the saponification of compounds **2**, the ester function of **3a** and **3b** can be hydrolysed in a basic medium with retention of the lactone cycle: 3-carboxy-4-butanolides **5** are prepared (Scheme **D**).




**3b** **5b**

Scheme **D**

For both *cis*-**3b** and *trans*-**3b**, the reaction takes place with a total retention of configuration and leads to the corresponding lactonic acid *cis*-**5b** or *trans*-**5b**.

**3-Acyl-2-alkyl-3-ethoxycarbonylpropanoic Acids 1; General Procedure:**

To a stirred solution of sodium ethoxide (prepared from 4.6 g of sodium, and 140 ml ethanol) are added the ethyl β-ketoester (100 mmol) in ethanol (70 ml) then the α-bromoacid (100 mmol) dissolved in ethanol (70 ml), triethylamine (3 ml), and copper(I) bromide (0.1 g). The mixture is heated to reflux for 7 h. Ethanol is removed under reduced pressure, the viscous residue is diluted with water (50 ml) and concentrated hydrochloric acid, extracted with ether (3 × 50 ml). The ether layer is washed with the minimum amount of water then dried with anhydrous magnesium sulphate. After evaporation, the residue is distilled under vacuum. Use of catalyst is not necessary for $R^2 = H$.

**2,4-Dialkyl-3-ethoxycarbonyl-3-buten-4-olides 2; General Procedure:**

A mixture of phosphorus pentoxide (6 g) and phosphoric acid (4 ml) is stirred and heated until entire dissolution. After cooling, acid **1** (25 mmol) dissolved in dichloromethane (20 ml) is introduced and the stirred mixture is heated for 4.5 h. The reaction is quenched by the addition of cold water (40 ml) and extracted with ether (50 ml). The ether layer is washed with saturated sodium hydrogen carbonate solution until pH = ~ 7, dried with anhydrous magnesium sulphate, and concentrated. The residue is distilled in vacuo.

**4-Alkenyl-2,4-dialkyl-3-ethoxycarbonyl-4-butanolides 3; General Procedure:**

All reactions are performed under a nitrogen atmosphere in a 250 ml flask equipped with a thermometer, a mechanical stirrer and a pressure equalising addition funnel. All allylzinc reagents are prepared according to Ref.[11]. To the solution of allylzinc reagent (50 mmol) in tetrahydrofuran (25 ml) is added at −10°C acid **1** (22.5 mmol) in tetrahydrofuran (5 ml). The reaction is exothermic. The cooling bath is removed and the stirred solution is maintained at room temperature for 4 h, then hydrolysed with water (30 ml) and hydrochloric acid (5 ml). The organic layer is washed with water (10 ml), dried with anhydrous magnesium sulphate, then concentrated. The residue is distilled under reduced pressure.

**4-Alkenyl-3-carboxy-4-methyl-4-butenolides 5:**

A mixture of lactone **3a** or **3b** (2.5 mmol) and sodium hydroxyde (0.2 g) dissolved in water (5 ml) is stirred until homogeneity then kept 48 h at room temperature. After acidification (pH = ~ 1), the water is removed under vacuum, the residue is dissolved in ether, and then filtered. Evaporation gives a crystalline product.

*cis*-**5b**; yield: 90%; m.p. 130–131°C ($CCl_4$).

$C_{10}H_{14}O_4$ (198.2) calc. C 60.59 H 7.12 found 60.35 7.29

$^1$H-N.M.R. ($CDCl_3$): δ = 1.60 (s, $CH_3$); 1.82 (s, $CH_3$); 2.0–3.7 (m, $2CH_2$, CH); 4.7–5.2 (m, $=CH_2$); 13.3 ppm (s, OH).

*trans*-**5b**; yield: 95%; m.p. 122–123°C ($CCl_4$).

$C_{10}H_{14}O_4$ (198.2) calc. C 60.59 H 7.12 found 60.81 7.05

$^1$H-N.M.R. ($CDCl_3$): δ = 1.40 (s, $CH_3$); 1.84 (s, $CH_3$); 2.5–3.8 (m, $2CH_2$, CH); 4.8–5.2 (m, $=CH_2$); 13.5 ppm (s, OH).

*We thank Dr. Nicole Goasdoue for recording the N.M.R. spectra at 250 MHz and for their interpretation.*

Received: February 21, 1985

* Address for correspondence

** Permanent adress: Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria.

[1] Sprankling, C.H.G. *J. Chem. Soc.* **1897**, *71* 1159.

[2] Itoh, M., Taguchi, T., Chung, V.V., Tokuda, M., Suzuki, A. *J. Org. Chem.* **1972**, *37*, 2357.

[3] Fukunishi, K., Inoue, Y., Kishimoto, Y., Mashio, F. *J. Org. Chem.* **1975**, *40*, 628.

[4] Reutrakul, V., Kusamran, K., Wattanasin, S. *Heterocycles* **1977**, *6*, 715.
Reutrakul, V., Pohmakotr, M. *J. Sci. Soc. Thailand* **1975**; *1*, 130; *C.A.* **1977**, *86*, 89486.

[5] Pohmakotr, M., Reutrakul, V., Phongpradit, T., Chansri, A. *Chem. Lett.* **1982**, 687.

[6] Takeda, A., Tsuboi, S., Sakai, T. *J. Org. Chem.* **1974**, *39*, 2601.

[7] Braude, E.A., Timmons, C.J. *J. Chem. Soc.* **1953**, 3313.

[8] Preliminary report: Gaudemar-Bardone, F., Mladenova, M., Couffignal, R. *Tetrahedron Lett.* **1984**, *25*, 1047.

[9] Gelin, R., Chignac, M. *Bull. Soc. Chim. Fr.* **1965**, 144.

[10] Freeman, J.P., Kassner, J.A., Grabiak, R.C. *J. Org. Chem.* **1975**, *40*, 3402.

[11] Gaudemar, M. *Bull. Soc. Chim. Fr.* **1958**, 1475; **1962**, 974.

[12] Savostianoff, D., Pfau, M. *Bull. Soc. Chim. Fr.* **1967**, 4162.