MeOH). The major band was eluted and the material was rechromatographed using 9 $CHCl_3$:1 MeOH and again using ethyl acetate. The major band was eluted with MeOH and the solution was evaporated to a white glass that could not be induced to crystallize from EtOH: yield 255 mg (20%); uv (pH 1) 287 sh, 294 nm (14.0, 16.4); uv (pH 7 and 13) 287, 293 nm (18.0, 17.8); ^1H NMR (DMSO-d_6) δ 2.68 (s, SMe), 3.3 (s, OMe), 3.7 (m, 2 $H_{5'}$), 3.9 (m, $H_{4'}$), 4.5 (m, $H_{3'}$), 4.9 ($H_{2'}$), ca. 5 (broad, OH), 5.24 (d, $J_{1'2'}$ = 4 Hz, $H_{1'}$), 5.85 (broad, OH), 8.58 and 8.75 (2 s, purine H).

Anal. Calcd for $C_{12}H_{16}N_4O_4S \cdot 0.25C_2H_5OH$: C, 46.36; H, 5.45; N, 17.30. Found: C, 46.32; H, 5.31; N, 17.08.

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Registry No.—**1**, 50-66-8; **2**, 286-20-4; **3**, 55073-67-1; **4**, 55073-68-2; **6**, 55073-69-3; **7**, 55073-70-6; **8**, 4316-93-2; **9**, 52630-74-7; **10**, 52706-45-3; **11**, 55073-71-7; **12**, 4316-94-3; **13**, 55073-72-8; **14**, 55073-73-9; **15**, 5413-85-4; **16**, 55073-74-0; **17**, 55073-75-1; **18**, 55073-76-2; **19**, 55073-77-3; **20**, 55073-78-4; **21**, 55073-79-5; **22**, 55073-80-8; **23**, 55073-81-9; **24**, 55073-82-0; **25**, 52630-73-6; **26**, 55073-83-1; 5-deoxy-1,2-*O*-isopropylidene-3-*O*-tosyl-β-D-arabinofuranoside, 55073-84-2; 1,2-*O*-isopropylidene-3,5-*O*-ditosyl-β-D-arabinofuranoside, 55073-85-3.

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Naturally Occurring Lactones and Lactams. VIII.[1] Lactonization of Unsaturated β-Keto Esters. Total Synthesis of Carlic Acid, Carlosic Acid, and Viridicatic Acid

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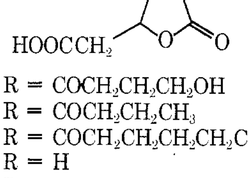
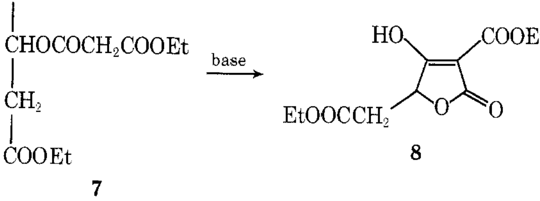
Treatment of diethyl *trans*-2-ethoxycarbonyl-3-oxo-4-hexenedioate (**11**) with concentrated sulfuric acid and subsequent hydrolysis gave the tetronic acid synthon **4**. In contrast diethyl cinnamoyl malonate (**19**) and diethyl crotonoyl malonate (**20**) were lactonized to δ-lactones. Extension of the synthetic principle to α-fumaroyl-β-keto esters provided a total synthesis of the naturally occurring tetronic acids carlosic acid (**2**) and viridicatic acid (**3**). Synthesis of carlic acid (**1**) along this route has been unsuccessful so far, whereas acylation of 5-methoxycarbonylmethyltetronic acid (**15**) with 4-chlorobutanoyl chloride and subsequent hydrolysis afforded the desired natural product.

As part of our attempts to develop general methods for the synthesis of the mold tetronic acids carlic acid (**1**, cf. **1a**), carlosic acid (**2**), and viridicatic acid (**3**), we have considered using the parent acid **4** as a synthon, since it has been demonstrated that Friedel–Crafts acylation of the tetronic acid nucleus may lead to natural products.[2-4]



1, R = $COCH_2CH_2CH_2OH$
2, R = $COCH_2CH_2CH_3$
3, R = $COCH_2CH_2CH_2CH_2CH_3$
4, R = H
5, R = $COCH_3$
6, R = Br

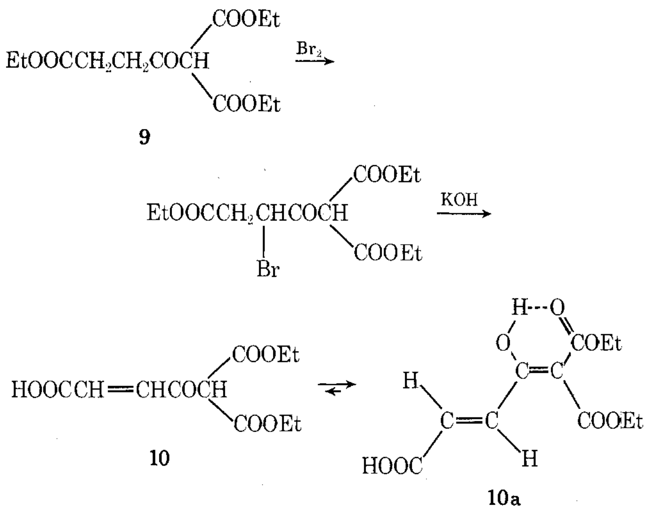
The synthon **4** has already been obtained in a minor quantity from a hydrogenation product of dimethyl ketipinate (dimethyl 3,4-dioxomuconate, **13**)[5] and from cyclization of the acetoacetyl derivative of dimethyl malate with potassium *tert*-butoxide in *tert*-butyl alcohol acting as condensing agent.[4] We therefore turned our interest to the ethoxycarbonylacetyl derivative of diethyl malate (**7**), since this compound on cyclization might give **8** from which the 3-ethoxycarbonyl group could easily be removed.



7

8

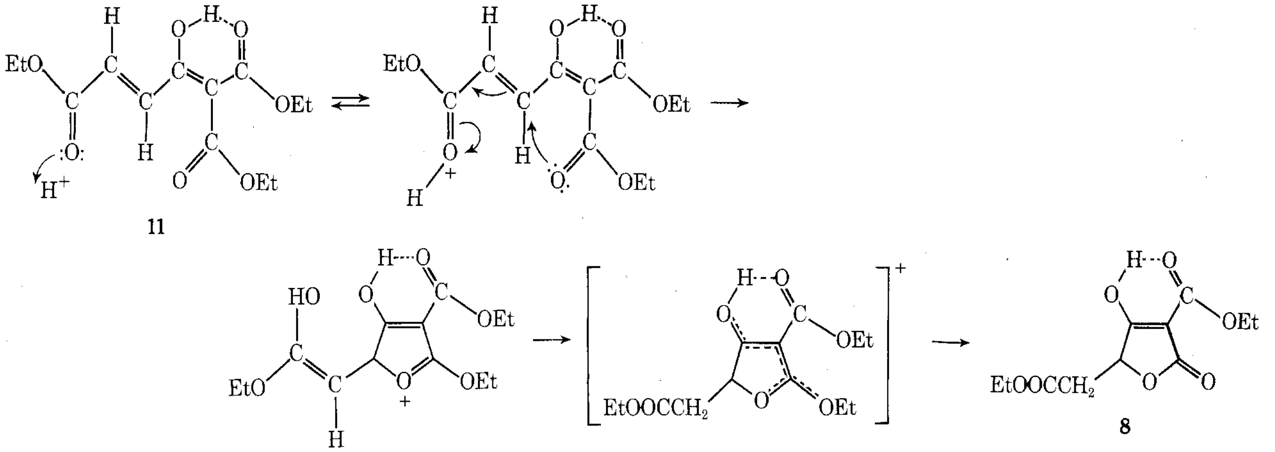
It proved, however, to be very difficult to find an appropriate reagent for the Dieckmann cyclization of **7**. Earlier reactions of this type have been carried out successfully with metallic sodium[6] and especially with diisopropylmagnesium bromide in ether[7] as bases. These reagents, as well as sodium hydride in various solvents, e.g., ether, benzene, toluene, or hexamethylphosphoric triamide, induced no cyclization.



In the light of the aforementioned cyclization of dimethyl acetoacetylmalate it was surprising to notice that even potassium *tert*-butoxide in *tert*-butyl alcohol did not give detectable amounts of **8**, the only isolable product being fumaric acid.

Considering our recent report on the synthesis of tetronic acids by cyclization of brominated β-keto esters an alternative route to **8** might be bromination of diethyl 2-ethoxycarbonyl-3-oxoadipate (**9**) and subsequent cyclization with 2.5 *N* potassium hydroxide. However, this procedure failed to give **8**, since elimination coincident with partial saponification was the predominant reaction, giving the unsaturated diester **10** as a crystalline solid in good yield. From the NMR data this compound exists predominantly in the enol form **10a**. This mode of reaction was not unexpected but equivalent to that of diethyl 3-oxoadipate.[8]

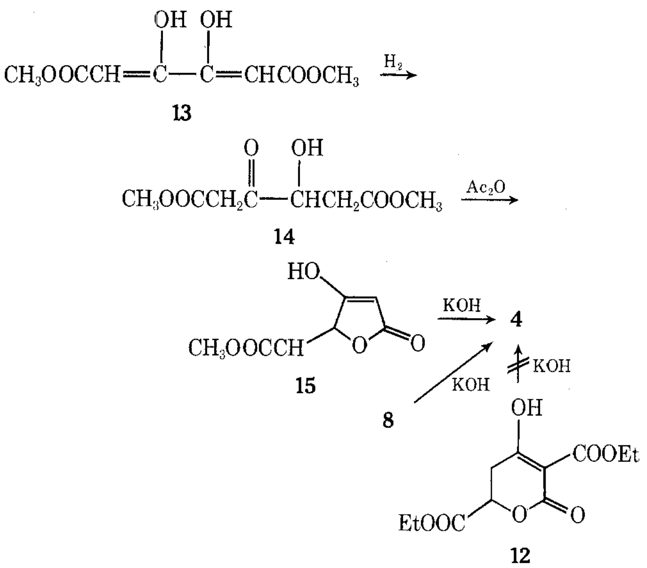
On searching through the existing literature on lactones we found that some unsaturated acids and esters have been lactonized under various conditions.[9–11] It was natural, therefore, to investigate the utility of **10** in this respect. Thus, when dissolved in concentrated sulfuric acid and left standing at 0° for 24 hr **10** after hydrolysis was transformed into a new solid product, the NMR spectrum of which revealed the absence of the characteristic ethylenic protons of the starting material. Furthermore, TLC and uv properties were in accordance with those of a tetronic acid or a similar system. On the basis of these findings and analytical data the structure **17** was assigned to this new compound. As a synthetic simplification the following investigations were carried out with the ethyl ester of **10**. This compound **11** was easily prepared by condensation of *trans*-β-ethoxycarbonylacrylyl chloride and diethyl malonate,[12] and on treatment with concentrated sulfuric acid behaved analogously. To gather information about the cource and time of reaction for the cyclization a number of NMR spectra were recorded directly on the reaction mixture, the very distinct signals of the ethylenic protons of **11** serving as an excellent means of inspecting the progress of the reaction. Immediately after dissolution these signals started fading away concomitant with the appearance of new signals at higher field. Furthermore, the originally equivalent ester methylene protons were divided into two groups of clearly different shift values. This was also the case—though to a minor extent—for the ester methyl groups. These observations lend support to the following ionic mechanism (mechanism I).[13]



(I)

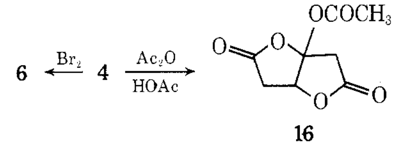
Acid-catalyzed Michael addition of one of the malonic ester groups of **11** to the ethylenic bond which has been made nucleophilic by the presence of the terminal ester group leads to the intermediate cyclic oxonium ion stabilized by extensive delocalization of the positive charge. The oxonium ethyl group is thereby rendered clearly different from the remaining two ester ethyl groups and should appear at a different shift value. In the hydrolysis step, expulsion of ethanol finally stabilizes the molecule. The time necessary for the complete disappearance of the ethylenic proton signals and thus for complete cyclization in a repeated number of runs amounted to 40 min, but already after 15 min only one-third of the original peak integration value was left. This indicates a half-life for the reaction in the range of 8–10 min.

It was not possible a priori to predict whether **11** would cyclize according to this mechanism or according to mechanism II proposed for compounds **19** and **20** below. If the course of mechanism II was taken, simple polarization considerations of the ethylenic bond would not allow for a reliable prediction of which of two possible carbonium ions would be the one most readily formed, since the difference in directing power of a keto group vs. an ester group is too small. This problem was even more pronounced because enolization of the keto group might totally change the picture. Further, the order of stability of the two oxonium ions, another fact which may influence the pathway, is difficult to anticipate. The only possible means of ruling out any inoperative mechanism was an analysis of the structure of the product. In this respect the NMR data are of little value since the possible products **8** and **12**, as the only crucial difference, would exhibit two similar ABX systems which could not be told apart directly, and uv spectral data of similar systems[14] are too few to make any clear distinction. Finally, an unambiguous structure assignment was made by chemical means. Following the reported procedure,[5] dimethyl ketipinate (**13**) was catalytically hydrogenated to yield after the absorption of 1 mol of hydrogen the



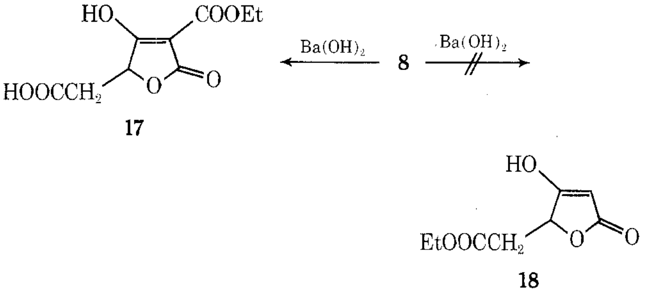
acyloin 14, which when refluxed in acetic anhydride afforded the methyl ester 15 of the synthon 4. Saponification of 15 by means of concentrated hydrochloric acid afforded 4. This compound was identical in all respects with the saponification product of 8.

In this way it was established that the cyclization product of 11 was the desired tetronic acid 8 and not the δ-lactone 12. As further pieces of evidence treatment of our hydrolysis product 4 with acetic acid–acetic anhydride afforded the dilactone 16 identical with that reported starting from dimethyl ketipinate,[5] and bromination of 4 gave 6, which is the common degradation product of the three naturally occurring tetronic acids 1, 2, and 3.

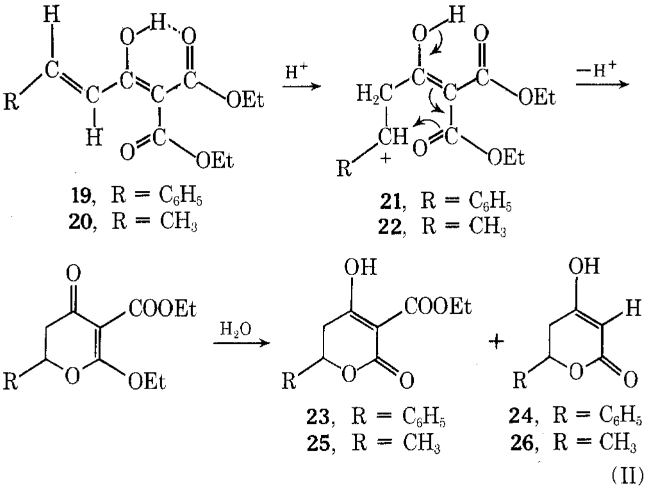


16

One procedure for the transformation of 3-ethoxycarbonyltetronic acids to 3-unsubstituted species is conversion to barium salt and subsequent acidification and decarboxylation.[15,16] Applying this method to 8 we obtained the saponification product 17 instead of the monoester 18. Treatment of 8 with 1 *N* potassium hydroxide or refluxing in water gave the free acid 4. Proper conditions for the selective decarboxylation to 18 were not found.



The generality of the lactonization procedure was studied with the cinnamoyl malonate 19 and the crotonoyl malonate 20 as substrates. For these compounds mechanism I depicted above for 11 obviously is invalid. Alternatively, the following reaction sequence consistent with the isolated products is suggested (mechanism II).

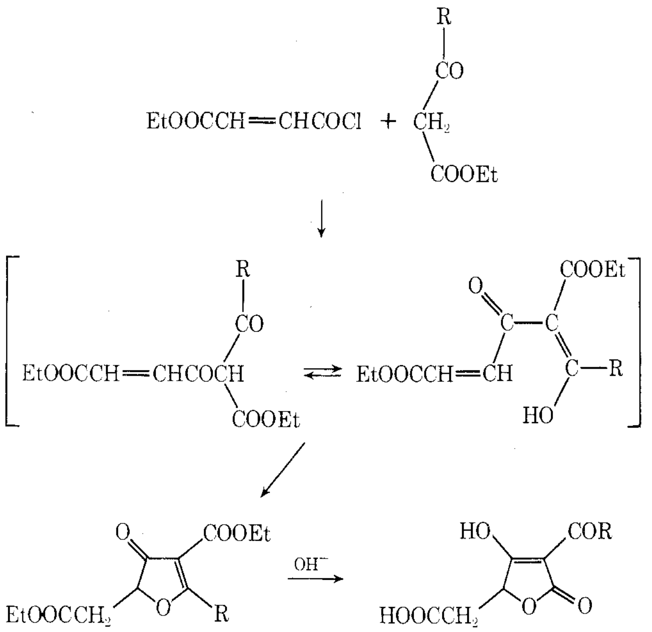


Maintaining the idea of a carbonium ion mechanism operating, this time with initial protonation of the ethylenic bond, it would be predicted for both that the lactones 23 and 25, respectively, were the most likely products. In the case of 19 the carbonium ion 21 should be greatly favored, since this is a benzylic cation to which resonance delocalization imparts a unique stability. The isolation of 23 in high yield confirmed this assumption. From NMR studies on the reaction mixture by inspection of the ethylenic proton signals a half-life of the reaction in the range of 20–25 min was roughly estimated. When dissolved in water and refluxed until the calculated amount of carbon dioxide had been evolved, 23 gave the lactone 24.[17] In the case of 20 the resonance effect of the carbonyl group is unidirectional, but the carbonium ion 22, being a normal secondary cation, has no special possibility of stabilization. This fact is reflected in the NMR investigations of the reaction from which the cyclization appeared to be more sluggish with a half-life of 80–90 min and from the low yield of product. In fact only the decarboxylated lactone 26 was isolated in a minor quantity.

The convenient lactonization of 11 led us to examine the possibility of a natural product total synthesis applying an extension of this principle. Thus for the synthesis of a 3-acylated tetronic acid diethyl malonate should be replaced by the appropriate β-keto ester and this condensed with *trans*-β-carbethoxyacrylyl chloride and cyclized with concentrated sulfuric acid.

Starting with ethyl acetoacetate as the simplest model substance condensation was attempted with sodium hydride in various solvents. The acetoacetate anion was created as a suspension in the solvent and a equivalent amount of acid chloride was added to the suspension. The strongly colored products had very complex NMR spectra which showed no ethylenic protons. This was believed, initially, to be due to a double attack to the acetoacetate anion on the acid chloride. After several experiments with various bases, ethylmagnesium bromide in methylene chloride was found to be the reagent of choice.[18] The bromomagnesioacetoacetate was readily soluble in methylene chloride and it was possible, therefore, to add this complex slowly to the acid chloride, thus preventing a double attack. Surprisingly, the clean reaction all the same gave a product without ethylenic protons. A closer examination revealed that the initially formed condensation product readily enolized via the acetoacetate keto group and the enol group added to the double bond forming the 3-oxo-4,5-dihydrofuran 27 (R = CH_3). A related reaction leading to 3-oxo-4,5-dihydrofurans has been encountered in the condensation of β-keto esters with α-halo acid chlorides.[19] Finally action of dilute sodium hydroxide rearranged 27 to the desired tetronic acid 5.

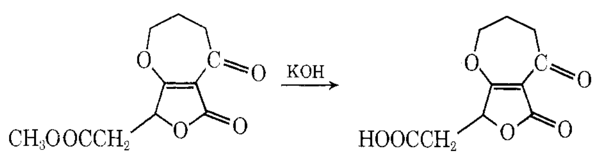
Substituting ethyl acetoacetate with ethyl 3-oxohexanoate and ethyl 3-oxodecanoate, the same sequence of reactions gave carlosic acid (2) and viridicatic acid (3), respec-



27

5, R = CH_3
2, R = $CH_2CH_2CH_3$
3, R = $CH_2CH_2CH_2CH_2CH_3$

tively.[1,20] Recently we have prepared ethyl 6-chloro-3-oxohexanoate, the requisite β-keto ester for the construction of the carlic acid side chain.[21] Condensation of this ester with *trans*-β-ethoxycarbonylacrylyl chloride and treatment of the condensation product with dilute base produced a compound $C_{10}H_{10}O_6$ of mp 187–190° [lit.[22] mp of (−)-carlic acid 176°]. Uv data were in accordance with those of 2 and 3 but NMR data disagreed with those expected for carlic acid. Finally, since the synthesis of carlic acid along this route seemed to have failed, the utility of the synthon 4 with respect to acylation was investigated. Recently the acylation of tetronic acids unsubstituted in the 3 position has been reported to proceed well in nitrobenzene with $TiCl_4$ as Friedel–Crafts catalyst.[4] As 4 contains two acidic groups capable of reacting with an acid chloride, 2 equiv of 4-chlorobutanoyl chloride was mixed with a solution of 4 in nitrobenzene. $TiCl_4$ catalyst was added and the reaction mixture was kept at 60° for 14 hr. On work-up no carlic acid was isolated. In contrast the methyl ester 15 was readily acylated when treated with an equivalent amount of 4-chlorobutanoyl chloride in nitrobenzene at 60° for 3 hr. Carlic acid methyl ester (28) was obtained in 68% yield. Hydrolysis to free carlic acid proceeded well with 3 *N* potassium hydroxide, yielding the desired natural product **1a.**



28 1a

Experimental Section

Microanalyses were performed at the Microanalytic Department of the University of Copenhagen. Melting points were determined on a Büchi apparatus. Nuclear magnetic resonance (NMR) spectra were recorded on a Jeol C-60 HL spectrometer with Me_4Si as internal standard. The chemical shifts are expressed in δ values (parts per million) downfield from Me_4Si. Coupling constants are expressed in hertz. Ultraviolet (uv) spectra were recorded on a Beckman Acta III spectrophotometer with absolute ethanol as solvent. The progression of the reactions was monitored conveniently by thin layer chromatography (TLC) with ether or a mixture of benzene–ethanol–acetic acid (9:2:1 v/v) as eluent.

Ethyl Chlorocarbonylacetate. Ethyl hydrogen malonate (180 g, 1.36 mol) was cooled at 0° and thionyl chloride (50 ml) was added dropwise in 30 min. The mixture was allowed to warm at room temperature and left at this temperature for 24 hr. Distillation gave a forerun of excess thionyl chloride and then pure title compound was collected, bp 74° (11 mm), yield 167 g (81%).[23]

Diethyl Ethoxycarbonylacetylmalate (7). Diethyl malate (95 g, 0.5 mol) was dissolved in dry ether (200 ml) at 0°. Ethyl chlorocarbonylacetate (75 g, 0.5 mol) was added rapidly without any noticeable reaction. To this mixture pyridine (45 g, slight excess) was added dropwise with precipitation of the hydrochloride. After complete addition and stirring for a further 2 hr 4 *N* hydrochloric acid (200 ml) was added to remove excess pyridine and the organic phase was separated and dried (Na_2SO_4). The ether was distilled off in vacuo, leaving 150 g of slightly colored oil. Two distillations gave 89 g (59%) of colorless product: bp 138–140° (0.05 mm); $n^{25}D$ 1.4374; NMR ($CDCl_3$) δ 1.29 (6 H, t, J = 7 Hz), 2.92 (2 H, d, J = 6 Hz, $COCH_2CH$), 3.43 (2 H, s, $COCH_2CO$), 4.21 (2 H, q, J = 7 Hz), 4.24 (2 H, q, J = 7 Hz), 4.27 (2 H, q, J = 7 Hz), 5.55 (1 H, t, J = 6 Hz, CH_2CHO). Anal. Calcd for $C_{13}H_{20}O_8$: C, 51.30; H, 6.76. Found: C, 51.31; H, 6.63.

Attempted Cyclization of Diethyl Ethoxycarbonylacetylmalate (7). Potassium *tert*-butoxide (12.0 g, 0.11 mol) was suspended under nitrogen in *tert*-butyl alcohol (45 ml) distilled from calcium hydride. The triester 7 (30.4 g, 0.1 mol) was added dropwise with evolution of heat. When the addition was complete the mixture was refluxed for 40 min and left overnight at ambient temperature. After chilling at 0° 4 *N* hydrochloric acid (30 ml) and water (200 ml) were added. The aqueous solution was extracted with ether (2 × 100 ml) and the combined ether extracts were dried (Na_2SO_4). The ether was removed in vacuo and further volatile material distilled off at 110° (15 mm). From the remaining oil (27.5 g) a solid separated. Redissolution of the oil in ether (100 ml) and filtration gave 2.7 g of white solid material of mp 220° identified as fumaric acid.

***trans*-1-Ethyl Hydrogen 2-Ethoxycarbonyl-3-oxo-4-hexenedioate (10a).** The triester 9 (144 g, 0.5 mol) was dissolved in chloroform (400 ml) and chilled at 0°. A solution of bromine (80 g, 0.5 mol) in chloroform (400 ml) was added dropwise over a period of 3 hr. After standing at ambient temperature for 12 hr the solvent was removed in vacuo, leaving 188 g of yellow oil, $n^{24}D$ 1.4750. With vigorous stirring 18.8 g of this oil was added dropwise to 3 *N* potassium hydroxide (100 ml) at 0°. After 4 hr the reaction mixture was acidified with 4 *N* hydrochloric acid (60 ml) and extracted with ether (3 × 50 ml). The ether layer was separated, dried (Na_2SO_4), and evaporated in vacuo to give 12.3 g of solid product. Recrystallization from chloroform–light petroleum (boiling range 50–70°) afforded 8.9 g (69%) of **10:** mp 102–104° (lit.[12] mp 107°); NMR ($CDCl_3$) δ 1.34 (6 H, t, J = 7 Hz), 4.31 (4 H, q, J = 7 Hz), 6.76 (1 H, d, J = 15.5 Hz), 7.56 (1 H, d, J = 15.5 Hz), 11.53 (2 H, br, s).

3-Ethoxycarbonyl-5-carboxymethyltetronic Acid (17). Solid 10 (5.2 g, 0.02 mol) was added in portions to magnetically stirred concentrated sulfuric acid (20 ml) at 0°. When all solid material had been completely dissolved the reaction mixture was left at 0° for 26 hr, after which time it was poured onto ice (60 g). The aqueous phase was exhaustively extracted with ether and the ether and some water from the extraction process were removed in vacuo to leave 4.5 g of slightly colored solid of mp 130–134°. A sample for analysis recrystallized from benzene–ethyl acetate had mp 137–139° when heated quickly. When heated slowly the compound started melting at 137° but the liquefaction was not complete until at 180°. This may be due to transesterification: NMR (DMSO-d_6) δ 1.27 (3 H, t, J = 7.5 Hz), 2.21–3.15 (2 H, m, eight lines), 4.19 (2 H, q, J = 7.5 Hz), 4.91–5.16 (1 H, m, four lines), 12.08 (2 H, s); uv λ_{max} 223 nm (log ϵ 4.04) and 246 (4.12).

Anal. Calcd for $C_9H_{10}O_7$: C, 46.96; H, 4.38. Found: C, 46.75; H, 4.46.

3-Ethoxycarbonyl-5-ethoxycarbonylmethyltetronic Acid (8). *trans*-Diethyl 2-ethoxycarbonyl-3-oxo-4-hexenedioate (11, 28.6 g, 0.1 mol) was added dropwise with stirring to concentrated sulfuric acid (100 ml) at 0°. After standing at this temperature for 24 hr the mixture was poured on ice (600 g) and exhaustively extracted with ether. Drying (Na_2SO_4) and evaporation of the solvent gave 25.4 g of a viscous yellow oil. The oil was redissolved in ether (25 ml) and chilled at −15°. Filtration of the precipitated crystals produced 13.2 g of snow-white material. Repeating this procedure a total of 17.4 g (67%) was obtained: mp 77–79°; uv λ_{max} 220 nm (log ϵ 4.09) and 244 (4.18); NMR ($CDCl_3$) δ 1.25 (3 H, t, J = 7 Hz), 1.37 (3 H, t, J = 7 Hz), 2.45–3.19 (2 H, m), 4.15 (2 H, q, J = 7 Hz), 4.36 (2 H, q, J = 7 Hz), 5.20 (1 H, dd, J = 4.5 and 7.0 Hz).

Anal. Calcd for $C_{11}H_{14}O_7$: C, 51.16; H, 5.47. Found: C, 51.35; H, 5.51.

3-Ethoxycarbonyl-5-carboxymethyltetronic Acid (17). The parent diethyl ester 8 (2.60 g, 0.01 mol) was dissolved in a solution of barium hydroxide (3.5 g) in water (100 ml) and left at room temperature for 18 hr. The white precipitate was filtered, dissolved in 4 *N* hydrochloric acid (30 ml), and heated briefly at 70°. After chilling at 0° the aqueous solution was extracted with ethyl acetate (3 × 15 ml). The pooled organic extracts were dried (Na_2SO_4) and evaporated in vacuo to leave a solid mass. The mass was broken up, washed with ether, and filtered to give 0.74 g of white solid, mp 130°. Recrystallization from ethyl acetate raised the melting point to 137–139° when heated quickly. Further data were identical with those given above.

5-Carboxymethyltetronic Acid (4). A solution of the diester 8 (13.0 g, 0.05 mol) in a mixture of water (250 ml) and potassium hydroxide (16.3 g of 86% pellets) was left at room temperature for 5 days, after which time 4 *N* hydrochloric acid was added to pH <1. The aqueous solution was exhaustively extracted with ether and the ether was stripped off, leaving 5.0 g of white solid, mp 185°. One recrystallization from ethyl acetate raised the melting point to 187–191° (lit.[5] mp 187–191°). In an alternative procedure, which is more rapid but gives lower yield, 8 (7.8 g, 0.03 mol) was dissolved in water (60 ml) and heated to boiling. A vigorous evolution of gas started and within 30 min the theoretical amount of carbon dioxide (720 ml) had been collected. Exhaustive ether extraction and evaporation of the ether in vacuo gave a crude product which was recrystallized from benzene–acetic acid, yield 1.35 g (28%) of white material: mp 187–191°; NMR (DMSO-d_6) δ 2.17–3.11 (2 H, m), 4.96 (1 H, s) 4.95–5.21 (1 H, m), 10.30 (2 H, s); uv λ_{max} 222 nm (log ϵ 4.06).

3-Bromo-5-carboxymethyltetronic Acid (6). The parent acid 4 (1.3 g, 8.2 mol) was suspended in acetic acid (20 ml) and heated at 35–40°. A solution of bromine (0.8 g) in acetic acid (5 ml) was added dropwise, producing a clear solution which was stirred for a further 2 hr. The solvent was distilled off in vacuo, leaving a slightly colored solid, mp 172–175° dec. Recrystallization from acetic acid raised the melting point to 195–197° (lit.[24] mp 198–199°), NMR (DMSO-d_6) δ 2.25–3.15 (2 H, m), 5.05–5.28 (1 H, m, four lines).

2,5-Dioxo-7-acetoxyfuro[3,2-*b*]furan (16). A solution of 5-carboxymethyltetronic acid (4, 950 mg) in a mixture of acetic acid (9 ml) and acetic anhydride (1.5 ml) was refluxed for 30 min. The solvent was distilled off at 50° (11 mm) and the residue was dissolved in ethyl acetate (50 ml) and extracted with saturated aqueous sodium hydrogen carbonate, then water. Drying (Na_2SO_4) of the organic phase and evaporation of the solvent in vacuo left an oil (500 mg) which rapidly crystallized. The solid material was filtered and recrystallized from toluene: mp 108–109° (lit.[5] mp 109.5–111°); NMR ($CDCl_3$) δ 2.55–3.60 (4 H, m), 2.13 (3 H, s), 5.09–5.25 (1 H, m, four lines). This was in accordance with previous data.[5]

3-Ethoxycarbonyl-6-phenyltetrahydropyran-2,4-dione (23). Diethyl cinnamoylmalonate (14.5 g, 0.05 mol) was dissolved in concentrated sulfuric acid (50 ml) and left at 0° for 24 hr. Work-up performed as for 8 gave an oil (13.1 g) which rapidly solidified. Washing with cold ether, filtration, and recrystallization from ethyl acetate afforded 10.1 g (77%) of the title compound: mp 97–99°; NMR ($CDCl_3$) δ 1.39 (3 H, t, J = 7.5 Hz), 2.60–3.33 (2 H, m), 4.38 (2 H, q, J = 7.5 Hz), 5.20–5.50 (1 H, m, four lines), 7.31 (5 H, s), 11.31 (1 H, s); uv λ_{max} 251 nm (log ϵ 4.06).

Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.11; H, 5.38. Found: C, 64.30; H, 5.49.

6-Phenyltetrahydropyran-2,4-dione (24). **23** (1.3 g, 0.005 mol) was dissolved in water (30 ml) and refluxed until the gas evolution ceased (30 min). Upon cooling the precipitated solid was filtered and recrystallized from benzene to yield 450 mg of the title compound: mp 126–130° (lit.[17] mp 120–127°); NMR (DMSO-d_6) 2.25–3.15 (2 H, m), 5.05 (1 H, s), 5.25–5.55 (1 H, m, four lines), 7.35 (5 H, s), 11.40 (1 H, s); uv λ_{max} 242 nm (log ϵ 4.01).

6-Methyltetrahydropyran-2,4-dione (26). Diethyl crotonoylmalonate (11.9 g, 0.05 mol) was dissolved in concentrated sulfuric acid and left for 72 hr at 0°. Work-up as above gave 8.1 g of yellow oil. The oil was dissolved in light petroleum (boiling range 50–70°) and placed at 0° for 6 days. The precipitated crystals were filtered and washed with cold ether to give 1.1 g of product. Recrystallization from benzene–ethyl acetate gave analytically pure **26**: mp 121–122°; NMR (DMSO-d_6) δ 1.29 (3 H, d, J = 6 Hz), 2.35 (2 H, d, J = 8 Hz), 4.09–4.68 (1 H, m), 4.91 (1 H, s), 11.21 (1 H, s, br); uv λ_{max} 239 nm (log ϵ 4.07).

2-Methyl-3-ethoxycarbonyl-4-oxo-5-ethoxycarbonylmethyl-4,5-dihydrofuran (27, R = CH_3). To ethyl acetoacetate (26.0 g, 0.2 mol) in methylene chloride (100 ml) was added ethylmagnesium bromide in the same solvent at 0° until the evolution of ethane ceased. The clear solution was transferred to a dropping funnel and added dropwise to a solution of *trans*-3-ethoxycarbonylacrylyl chloride (32.5 g, 0.2 mol) in methylene chloride (50 ml) at 0°. After complete addition and standing at ambient temperature for 12 hr the reaction mixture was poured into ice-cold 2 *N* hydrochloric acid (300 ml) and shaken thoroughly. The organic layer was separated, washed with brine (200 ml), and dried ($NaSO_4$). Evaporation of the solvent in vacuo left 51.5 g of oily product. The oil (3 × 2.0 g) was chromatographed on three silica gel plates with ether as eluent. The bands with R_f 0.63 on reextraction with ether gave 2.90 g of slightly colored **27**: NMR (CCl_4) δ 1.25 (3 H, t, J = 7 Hz), 1.31 (3 H, t, J = 7 Hz), 2.28–3.13 (2 H, m), 2.55 (3 H, s), 4.11 (2 H, q, J = 7 Hz), 4.18 (2 H, q, J = 7 Hz), 4.59–4.86 (1 H, m, four lines).

3-Acetyl-5-carboxymethyltetronic Acid (5). Crude **27** (25.0 g) was dissolved in tetrahydrofuran (50 ml) and 2.5 *N* potassium hydroxide (100 ml) was added at 0°. The mixture was stirred at ambient temperature for 12 hr and then extracted with ether (3 × 50 ml). The aqueous phase was acidified with 4 *N* hydrochloric acid to pH <1 and exhaustively extracted with ether to give 21.5 g of an oil which partly solidified. Filtration and washing with ether afforded 13.7 g of **5**, mp 160–165°. Recrystallization from acetic acid yielded 11.3 g of analytically pure product: mp 178–180° (lit.[20] mp 176–177°); NMR (DMSO-d_6) δ 2.30–3.10 (2 H, m), 2.44 (3 H, s), 4.72–4.91 (1 H, m, four lines), 10.14 (2 H, s, br); uv λ_{max} 228 nm (log ϵ 3.78) and 267 (4.09).

(±)-Carlosic Acid (2). Ethyl 3-oxohexanoate (7.9 g, 0.05 mol) in methylene chloride (50 ml) was condensed with *trans*-3-ethoxycarbonylacrylyl chloride (8.2 g, 0.05 mol) in methylene chloride (50 ml) exactly as described above for ethyl acetoacetate to give 13.2 g of crude oil: NMR (CCl_4) δ 1.03 (3 H, t, br), 1.14 (3 H, t, J = 7 Hz), 1.32 (3 H, t, J = 7 Hz), 1.40–1.95 (2 H, m), 2.27–3.18 (4 H, m), 4.11 (2 H, q, J = 7 Hz), 4.19 (2 H, q, J = 7 Hz), 4.60–4.85 (1 H, m, four lines). The oil (2.8 g) was dissolved in tetrahydrofuran (10 ml) and a mixture of water (50 ml) and sodium hydroxide (2 g) was added. After stirring for 12 hr work-up as above afforded 2.2 g of a brown solid. Recrystallization from ethyl acetate gave 1.8 g of analytically pure title compound: mp 160–163° [lit.[22] mp of (−) form 181°]; NMR [$CDCl_3$–DMSO-d_6 (4:1)] 0.98 (3 H, t, br), 1.36–2.01 (2 H, m), 2.43–3.16 (4 H, m), 4.80–5.03 (1 H, m, four lines), 10.68 (2 H, s); uv λ_{max} 228 nm (log ϵ 3.87) and 268 (4.11).[26]

Anal. Calcd for $C_{10}H_{12}O_6$: C, 52.63; H, 5.30. Found: C, 52.55; H, 5.51.

(±)-Viridicatic Acid (3). Ethyl 3-oxodecanoate (9.3 g, 0.05 mol) and *trans*-3-ethoxycarbonylacrylyl chloride (8.2 g, 0.1 mol) condensed as above gave 15.0 g of crude oil. The oil (3.0 g) was treated as described for **2** with a mixture of water (50 ml) and sodium hydroxide (2.0 g) to yield 800 mg of product. Recrystallization twice from ethyl acetate gave 500 mg of pure **3**: mp 158–160° [lit.[25] mp of (−) form 174.5°]; NMR (DMSO-d_6) δ 0.88 (3 H, deformed t), 1.08–1.95 (6 H, m), 2.50–3.10 (4 H, m), 4.80–5.03 (1 H, m, four lines), 11.15 (2 H, s); uv λ_{max} 232 nm (log ϵ 3.92) and 267 (4.13).[26]

Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.24; H, 6.29. Found: C, 56.10; H, 6.20.

Attempted Synthesis of (±)-Carlic Acid (1a). Ethyl 6-chloro-3-oxohexanoate (9.63 g, 0.05 mol) and *trans*-3-ethoxycarbonylacrylyl chloride (8.2 g, 0.05 mol) condensed as above gave 16.1 g of crude oil. Further treated as above, this oil (3.6 g) gave a solid (850 mg) which upon recrystallization from ethyl acetate had mp 187–190° [lit.[22] mp of (−)-carlic acid 176°]; NMR [$CDCl_3$–DMSO-d_6 (4:1)] 1.12–1.50 (4 H, m), 2.43–3.14 (3 H, m), 4.82–5.09 (1 H, m, four lines), 11.89 (2 H, s, br) (this is not in accordance with the expected spectrum); uv λ_{max} 228 nm (log ϵ 3.74) and 275 (4.12).

Anal. Calcd for $C_{10}H_{10}O_6$: C, 53.10; H, 4.46. Found: C, 52.90; H, 4.36.

(±)-Carlic Acid Methyl Ester (28). 5-Methoxycarbonylmethyltetronic acid (**15**, 0.86 g, 5 mmol) was dissolved in nitrobenzene (25 ml) and 4-chlorobutanoyl chloride (0.73 g, 5 mmol) was added. To this mixture titanium tetrachloride (1.5 ml) was cautiously added with vigorous stirring to produce, finally, a clear solution. The reaction mixture was immersed in an oil bath at 60° for 3 hr and then left at ambient temperature for 50 hr. The reaction mixture was poured all at once into a mixture of concentrated hydrochloric acid (50 ml) and crushed ice (100 g) and extracted with chloroform (3 × 30 ml) and ether (30 ml). The combined organic extracts in turn were extracted with saturated aqueous sodium hydrogen carbonate (2 × 50 ml) and the aqueous phase was separated and extracted with ether (30 ml) to remove traces of nitrobenzene. The sodium hydrogen carbonate extract was acidified to pH <1 by dropwise addition of concentrated hydrochloric acid and reextracted with chloroform (4 × 15 ml). The pooled chloroform extracts were dried (Na_2SO_4) and the solvent was removed in vacuo to leave 1.20 g of viscous brown oil, which after standing for 2 days at 5° crystallized. Attempted recrystallization from benzene at this stage failed and the crude product was chromatographed on a 1-in. column packed with 60 g of silica gel with chloroform–acetic acid (19:1) as eluent. This procedure afforded a product which when recrystallized from benzene gave 0.7 g (68%) of pure **28:** mp 119–121°; NMR ($CDCl_3$) δ 2.00–2.59 (2 H, m, five lines), 2.63–3.26 (2 H, m), 3.45 (2 H, t, J = 8 Hz), 3.70 (3 H, s), 4.82 (2 H, t, J = 7 Hz), 4.70–4.96 (1 H, m); uv λ_{max} 221 nm (log ϵ 3.65) and 274 (4.25).

Anal. Calcd for $C_{11}H_{12}O_6$: C, 55.00; H, 5.04. Found: C, 54.95; H, 5.13.

(±)-Carlic Acid (1a). Carlic acid methyl ester (0.70 g) was dissolved in 3 *N* potassium hydroxide (10 ml) and left at room temperature for 72 hr. The solution was acidified with concentrated hydrochloric acid to pH <1 and evaporated to dryness in vacuo. The remaining solid mass was extracted with boiling chloroform (8 × 10 ml) and the chloroform was removed, leaving 0.54 g of crystalline material, mp 176–180°. One recrystallization from ethyl acetate–ethanol gave 0.50 g (76%) of pure carlic acid: mp 177–180° [lit.[22] mp of (−)-carlic acid 176°]; NMR (DMSO-d_6) δ 1.90–2.48 (2 H, m, five lines), 2.50–3.15 (2 H, m), 3.36 (2 H, t, J = 8 Hz), 4.70 (2 H, t, J = 7.5 Hz), 4.55–5.00 (1 H, m); uv λ_{max} 226 nm (log ϵ 3.73) and 273 (4.23).[26]

Anal. Calcd for $C_{10}H_{10}O_6$: C, 53.10; H, 4.46. Found: C, 52.90; H, 4.57.

Registry No.—**1**, 55088-89-6; **1a**, 55088-90-9; **2**, 54423-52-8; **3**, 54397-56-7; **4**, 54397-59-0; **5**, 55088-91-0; **6**, 55088-92-1; **7**, 55088-93-2; **8**, 54397-58-9; **9**, 40421-01-0; **10**, 55088-94-3; **10a**, 55088-95-4; **11**, 55088-96-5; **15**, 54423-53-9; **16**, 55088-97-6; **17**, 54397-60-3; **19**, 55088-98-7; **20**, 55088-99-8; **23**, 55089-00-4; **24**, 41479-98-5; **26**, 33177-29-6; **27** (R = CH_3), 53252-38-3; **28**, 54397-61-4; ethyl chlorocarbonylacetate, 36239-09-5; ethyl hydrogen malonate, 1071-46-1; thionyl chloride, 7719-09-7; diethyl malate, 7554-12-3; fumaric acid, 110-17-8; bromine, 7726-95-6; ethyl acetoacetate, 141-97-9; *trans*-3-ethoxycarbonylacrylyl chloride, 26367-48-6; ethyl 3-oxohexanoate, 3249-68-1; 3-oxodecanoate, 13195-66-9; ethyl 6-chloro-3-oxohexanoate, 54362-87-7.

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Synthetic Study of (±)-Canadensolide and Related Dilactones. Double Lactonization of Unsaturated Dicarboxylic Acids via Acyl Hypoiodite Intermediates

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Stereospecific oxidation of **12a** and **12b**, followed by methylenation, yielded **1b** and **1a**, respectively. The latter product was identified as (±)-canadensolide and has resulted in a revision of the stereochemistry previously proposed for this natural dilactone. Furthermore, a new stereospecific double lactonization reaction of olefinic dicarboxylic acids has been found. Besides a demonstration with some model compounds, it has been used to lactonize **54** and **57** giving **1b** and **1a**, respectively.

Canadensolide (**1a**) is a mold metabolite produced by *Penicillium canadense* and has an antigerminative activity against fungi, e.g., *Botrytis alii.* It was isolated from the culture filtrate, along with other closely related compounds, and their structures were assigned by McCorkindale et al.[1] A structural feature of canadensolide is its di-γ-lactone system, and the analogous di-γ-lactone structure has been found in other acetogenins, dihydrocanadensolide[1] (**2**), avenaciolide[2] (**3a**), 4-isoavenaciolide[3] (**3b**), and ethisolide[3] (**3c**), and in the sesquiterpenoids picrotoxinine[4] (**4a**) and picrotine[4] (**4b**).

We were interested in the synthesis of canadensolide and related di-γ-lactone systems.[5] Our synthetic design envisaged a double lactonization of unsaturated tricarboxylic acids, such as **5** or **6**, which would lead to the dilactonic carboxylic acid (**7**). The extra carboxyl group in **7** might then be utilized for the introduction of an exocyclic methylene group.