Medium Effects on Formation of Cyclic Enolates from (2*E*,4*Z*)-3-Formyl-2,4-hexadienedioates, a Novel Ring-Chain Equilibrium: Importance of Hydrogen Bonding, Solvent Dipolarity/Polarizability, and Ion-Pairing Effects. Stereoisomerism of 3-Formyl-2,4-hexadienedioates

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Medium effects on the cyclization equilibrium of the anion of 1-monomethyl (2*E*,4*Z*)-3-formyl-2,4-hexadienedioate, involving an intramolecular conjugate nucleophilic addition of a carboxylate ion to an α,β-unsaturated aldehyde moiety, were studied by UV spectroscopy. The s-transoid conformer of the α,β-unsaturated aldehyde cyclizes faster than the s-cisoid conformer, but at equilibrium the product of the latter cyclization predominates. The cyclization, belonging to the geometrically favored 6-Endo-Trig category, involves transfer of the negative charge from the hard carboxylate ion to a soft conjugated enolate ion, in which two double bonds have been inserted between the oxygen atoms that share the charge. The cyclization equilibrium appears to be governed by selective stabilization of the carboxylate ion by hydrogen bonding and ion pairing, and selective solvation of the enolate ion by polarizable solvents. In a series of solvents comprising water and aliphatic alcohols, the observed change of equilibrium constants of the cyclization corresponds to a change of free energy difference ($\Delta\Delta G°$) on going from water to *tert*-butyl alcohol of 2.8 kcal/mol. Linear free energy relationships with various solvatochromic solvent polarity parameters were observed. The ion-pairing effects on the equilibrium in *tert*-butyl alcohol when potassium ion is replaced by its complex with 18-crown-6 and cryptand[2.2.2] amount to 1.5 and 1.8 kcal/mol, respectively. In organic solvents that cannot donate a hydrogen bond, the equilibrium constants of the cyclization are large. The cyclic enolate could be trapped by acylation, alkylation, or protonation. Some observations concerning substituent effects on the equilibrium have been recorded. Cyclic enolate formation was also observed with the anion of the 1,2-diester of (1*E*,3*Z*)-1,3-butadiene-1,2,4-tricarboxylic acid, where an α,β-unsaturated ester group is correspondingly converted to an enolate. In addition, a variety of isomeric 3-formyl-2,4-hexadienedioic acid derivatives were isolated and characterized; their interconversions show instructive neighboring-group effects.

Introduction

The 1-monomethyl ester of (2*E*,4*Z*)-3-formyl-2,4-hexadienedioic (β-formyl-*cis*,*cis*-muconic) acid (**1**) exists in the solid state and in solution as the cyclic hemiacetal **2** (Chart I), as shown by IR and ^{1}H NMR spectral data.[1,2] However, the anion formed from **2** upon addition of base is expected to exist in the open-chain form **3**, the latter being a weaker base than **4** by at least 7 orders of magnitude.[3] Thus, acidic aqueous solutions of **2** exhibit strong UV absorption at λ_{max} 265 nm, ϵ 19 000,[4] indicative of a planar 2,4-hexadienedioyl chromophore, whereas at pH >8 the absorption at λ_{max} 265 nm falls to ϵ 7500,[4] becoming akin to that of other 3-substituted and hence nonplanar (2*Z*,4*Z*)-2,4-hexadienedioates (Figure 1).[5] From the apparent spectrophotometric acidity constant of **2** of 5.6, the pH-independent equilibrium constants K_1 and K_2 (Chart I) could be roughly estimated as 10^2 and 10^{-6}, respectively.[2,3] We have now found that the carboxylate ion **3** exists in a mobile equilibrium with the cyclic enolate **5** (Chart II), responsible for the weak long-wavelength (λ_{max} 375 nm) absorption seen in aqueous solutions of **3** (Figure 1), and have investigated the considerable medium effects on the equilibrium. Hydrogen bonding, ion pairing, and solvent dipolarity/polarizability appear to be the major factors that determine the extent of cyclization of **3** to **5**. In addition, some observations concerning the stereochemistry of **2** and its analogues are reported.

Chart I

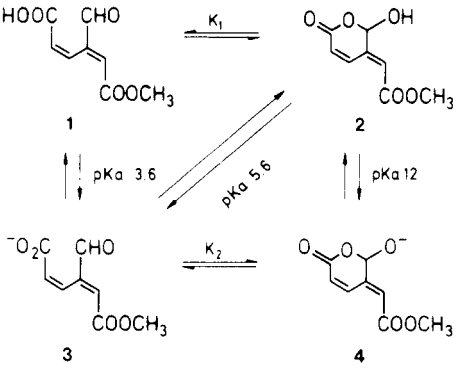
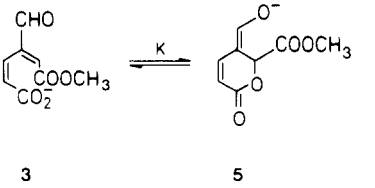


Chart II



Results

Trapping Experiments. The direct evidence that generation of **3** by deprotonation of **2** results in formation of **5** was provided by acylation and alkylation experiments.

(1) Ainsworth, A. T.; Kirby, G. W. *J. Chem. Soc. C* **1968**, 1483.
(2) Jaroszewski, J. W. *J. Org. Chem.* **1982**, *47*, 2013.
(3) The pK_a of **1** is hardly more than 3.6;[2] cf. pK_a of (*E*)-4-oxo-2-pentenoic acid of about 3.5: Hellström, N. *Nature* **1960**, *187*, 146. The pK_a of **2** can be assumed to be close to 12; cf. pK_a of glucose of 12.5: Beenackers, J. A. W. M.; Kuster, B. F. M.; van der Baan, H. S. *Carbohydr. Res.* **1985**, *140*, 169.
(4) Ettlinger, M. G.; Jaroszewski, J. W. *Tetrahedron Lett.* **1980**, *21*, 3503.
(5) Jaroszewski, J. W.; Ettlinger, M. G. *J. Org. Chem.* **1982**, *47*, 1212.

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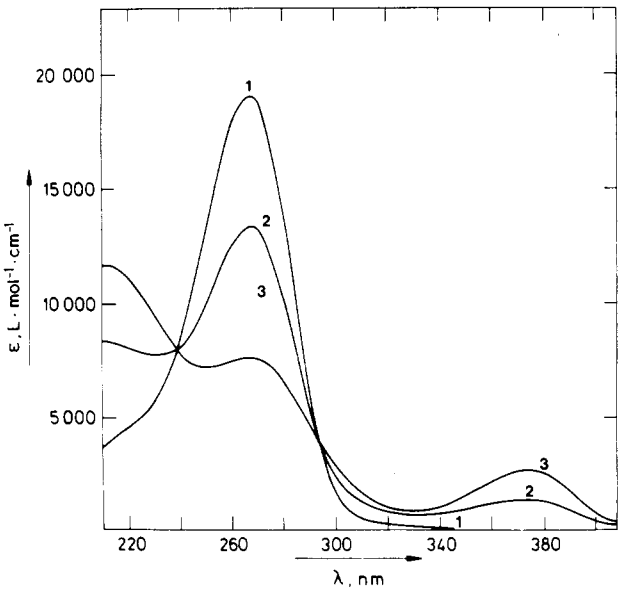
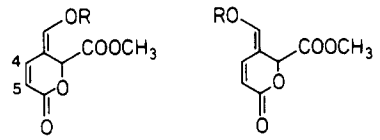


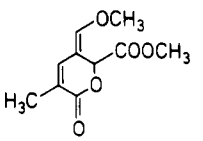
Figure 1. Electronic spectra of **2** at pH 3.0 (curve 1), pH 5.6 (curve 2), and pH 7.5 (curve 3) (0.05 M citrate–phosphate buffers).

Thus, dilute (0.01 M) solutions of **2** in acetonitrile were treated with equimolar amounts of 20% methanolic tetramethylammonium hydroxide, followed (after 20–30 min) by an excess of acetyl or 2,2-dimethylpropionyl chloride. The reaction must be carried out at relatively high dilution with respect to **2** in order to avoid extensive polymerization of the substrate. Evaporation of the solutions and crystallization of the residue afforded pure enol esters **6** and **7** in 80–85% yield. Use of methyl iodide as the trapping



6 R = $COCH_3$
7 R = $COC(CH_3)_3$
8 R = CH_3

9 R = $COCH_3$
10 R = $COC(CH_3)_3$
11 R = CH_3



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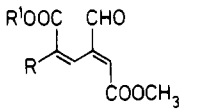
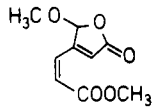
reagent yielded a far more complex reaction product, from which the enol ether **8** was isolated by chromatography in 33% yield along with byproducts **12** (3.5%), **13** (1%), **14** (2%), **16** (11%), **17** (6%), and **18** (6%). When the amount of methanolic base used in the reaction was doubled, the yield of **16** was increased to 35%.

Although the gross structures of **6–8** are immediately evident from routine spectroscopic data, a rigorous proof of the *Z* configuration of the exocyclic double bond required direct comparison with the corresponding *E* isomers **9–11**. These were obtained by heating **6**, **7**, or **8** in refluxing toluene containing catalytic amounts of iodine, to give equilibrium mixtures of the *Z* and *E* isomers in the ratio of 2:1 in each case. Photochemical, iodine-sensitized isomerization of **6–8** gave considerably less clean products. Chromatography of the equilibrium mixture of **8** and **11** afforded pure samples of both isomers, which exhibited distinctly different UV spectra, with λ_{max} 298 nm (ϵ 16 300) and λ_{max} 307 nm (ϵ 14 000) for the *Z* and the *E* isomer, respectively (in methanol). The isomers of the enol esters,



13 R = H R¹ = CH_3
14 R = R¹ = CH_3
15 R = H R¹ = $COCH_3$



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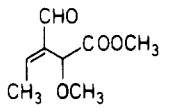

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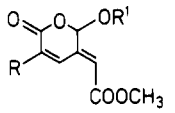


2 R = R¹ = H
18 R = CH_3 R¹ = H
19 R = H R¹ = $COCH_3$

which were highly unstable toward hydrolysis and decomposed upon attempted chromatography on silica gel, were separated only partially by fractional crystallization, and the *E* isomers were characterized by ^1H NMR spectra of the mixtures. The definitive clue to the configuration of the derivatives **6–11** was provided by the observation of large, five-bond couplings between Hα and H5 in **9–11** ($^5J_{\alpha,5}$ = 2 Hz along the zigzag path), whereas in **6–8** no coupling between Hα and H5 was observed.

When the addition of tetramethylammonium hydroxide and acetyl chloride to a solution of **2** in acetonitrile was carried out at −40 °C, the reaction yielded **15** instead of **6**. On standing, the oily anhydride **15** rearranged to **19**. Pure **19** was obtained by acetylation of **2** with acetic anhydride and pyridine or with acetyl chloride.

Configuration of the Enolate. Aged (5–10 min) solutions of **2** in acetonitrile, dimethyl sulfoxide, and similar solvents containing base exhibited intense, time-independent absorption at λ_{max} 377–381 nm (ϵ 27 000), causing a pale yellow coloration of the solution. Excess potassium acetate was typically used as base in these UV measurements, because hydroxides, unless added in strictly equimolar amounts, caused destruction of the chromophore. We observed that addition of **2** to saturated solutions of potassium acetate in dimethyl sulfoxide caused initially an *intense* yellow coloration of the solution (asymmetric, broad, growing absorption band at λ_{max} 387 nm with an inflection at about 405 nm). The intense color faded rapidly away to give a *pale* yellow solution (symmetrical, narrow, time-independent absorption band at λ_{max} 380, ϵ 27 000). The latter band had no significant intensity at 425 nm, whereas initially the absorption at 425 nm amounted to 10–15% of that at the maximum. The decrease of absorption at 425 or 415 nm followed a first-order rate law, with $k = 6 \times 10^{-2}$ s^{-1} at 25 °C; the rate of increase of the absorption at 380 nm was identical. The same time-dependent phenomena took place in other polar aprotic solvents.

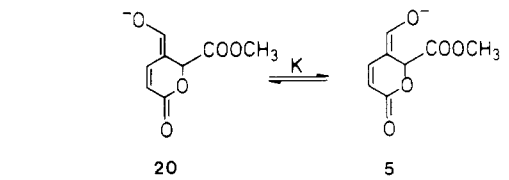
These results indicate that two enolates are initially present in the solution, but one of them, absorbing at longer wavelength, rapidly disappears as the reaction approaches equilibrium. Indeed, addition of base to a solution of **2** in acetonitrile, immediately followed by addition of acetyl chloride, gave a mixture consisting of **6** and **9** along with **15** (about 30% of each) and unreacted **2** (about 10%), as shown by ^1H NMR. The products **9** or **10** were not observed when the trapping reagent was added to an aged (about 15 min) solution of deprotonated **2**. Thus, the cyclization of **3** initially yields a considerable proportion of the *E* enolate **20**, but its concentration at equilibrium is negligible, the species responsible for the stationary absorption being mainly **5** (Chart III).

Table I. Solvent Effect on Enolate Formation from 2 in Water and Alcohols

solvent	ϵ_{max},[d] L mol^{-1} cm^{-1}	K[e]	π^*[f]	α[f]	A[g]	B[g]
HOH[a]	2800	0.116	1.09	1.17	1.0	1.0
MeOH[a]	6800	0.337	0.60	0.93	0.75	0.50
EtOH[b]	13 500	1.00	0.54	0.83	0.66	0.45
n-PrOH[b]	16 200	1.50	0.52	0.78	0.63	0.44
i-PrOH[b]	20 500	3.15	0.48	0.76	0.59	0.44
n-BuOH[b]	17 000	1.70	0.47	0.79	0.61	0.43
s-BuOH[b]	20 200	2.97				
t-BuOH[c]	25 000	12.5	0.41	0.68	0.45	0.50

[a] Potassium acetate (10^{-2} M); no effect of complexation with 18-crown-6 or cryptand[2.2.2] was observed. [b] Potassium acetate/18-crown-6 complex (10^{-2} M); no effect of complexation with cryptand[2.2.2] was observed. [c] Potassium acetate/cryptand[2.2.2] (10^{-2} M). [d] λ_{max} 375 nm. [e] Equilibrium constant for cyclization calculated by assuming ϵ 27 000 for pure enolate. [f] Solvent dipolarity/polarizability and hydrogen bond donor acidity, from ref 27. [g] Anion- and cation-solvating tendency of the solvent, from ref 28.

Chart III



20 5

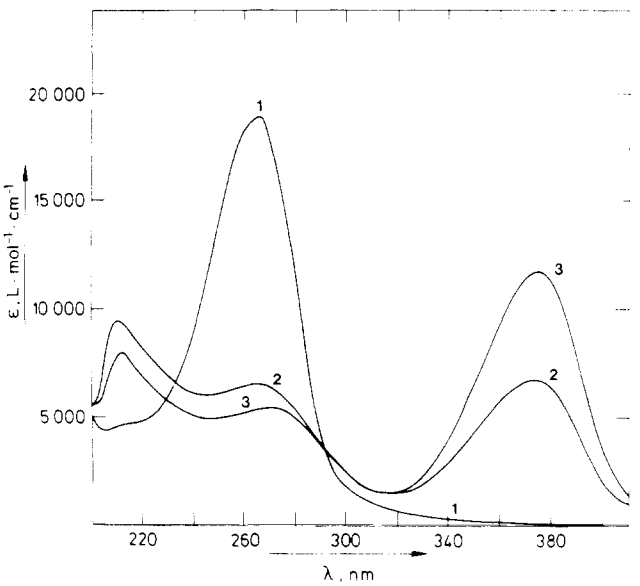


Figure 2. Electronic spectra of **2** in methanol containing traces of hydrochloric acid (curve 1) and in 10^{-2} M potassium acetate in methanol (curve 2) and ethanol (curve 3).

Solvent Effects on the Enolate Formation. A basic solution of **2** in water exhibited only weak absorption of **5** at 375 nm (Figure 1). However, when water was replaced by methanol or ethanol, the intensity of the long-wavelength band increased at the expense of the absorption around 265 nm (Figure 2), which is believed to reflect an increased equilibrium constant of cyclization (Chart II). A further increase in the intensity of the enolate band was observed in higher alcohols (Table I). In acetonitrile and a series of other aprotic solvents (benzene, 1,2-dimethoxyethane, 1,4-dioxane, tetrahydrofuran, dichloromethane, chloroform, acetone, dimethyl sulfoxide, dimethylformamide, dimethylacetamide, tetramethylurea, hexamethylphosphoric triamide, 1,2-propanediol carbonate, tetramethylene sulfone), the absorption of **3** around 265 nm disappeared completely, and the intensity of the long-wavelength band (λ_{max} 377–381 nm) increased to ϵ 26 000–27 000 (see Figure 3 as an example). In the least polar solvents, this intensity of the enolate band could only be attained by using the complex of potassium acetate and cryptand[2.2.2][6] as base (cf. the next section). In addition to the strong band at 377–381 nm, the enolate has a second, weak absorption band at λ_{max} 295–300 nm, ϵ 3400–3600 (Figure 3).

Variation of the intensity of the enolate band in a series of amides is shown in Table II. Figure 4 illustrates the influence of water on enolate formation in three organic solvents.

Table II. Solvent Effect on Enolate Formation from 2 in Amides

solvent[a]	ϵ_{max},[c] L mol^{-1} cm^{-1}	K[d]
N,*N*-dimethylamides[b]	27 000	
$CH_3NHCOOC_2H_5$	23 000	5.75
$CH_3CONHCH_3$	14 000	1.08
$HCONHCH_3$	11 000	0.69
$HCONH_2$	1500	0.06

[a] Potassium acetate/18-crown-6 (10^{-2} M). [b] Dimethylacetamide, dimethylformamide, tetramethylurea, hexamethylphosphoric triamide. [c] λ_{max} 375–380 nm. [d] Equilibrium constant calculated by assuming ϵ 27 000 for pure enolate.

Table III. Generation of Cyclic Enolate from 2 in *tert*-Butyl Alcohol by Using Various Counterions

base[a]	ϵ_{max}, L mol^{-1} cm^{-1}	K[b]	$\Delta G°$, kcal/mol
CH_3COOK	10 500	0.64	−0.3
CH_3COOK/18-crown-6	24 000	8.0	1.2
CH_3COOK/cryptand[2.2.2]	25 000	12.5	1.5
$CH_3COON(CH_3)_4$	25 000	12.5	1.5

[a] Solution (10^{-2} M) in *tert*-butyl alcohol, 5×10^{-5} M in **2**. [b] Equilibrium constant calculated by assuming ϵ 27 000 for pure enolate.

Table IV. Salt Effect on Generation of Cyclic Enolate from 2 in *tert*-Butyl Alcohol

concn[a]	ϵ_{max}, L mol^{-1} cm^{-1}	K[b]
1×10^{-2}	24 030	8.1
4×10^{-3}	24 200	8.6
2×10^{-3}	24 200	8.6
8×10^{-4}	24 500	9.8
4×10^{-4}	24 500	9.8
1×10^{-4}	23 800[c]	7.4

[a] Concentration of potassium acetate/18-crown-6 complex in *tert*-butyl alcohol, 6×10^{-5} M in **2**. [b] Equilibrium constant calculated by assuming ϵ 27 000 for pure enolate. [c] The decrease of intensity is presumably due to incomplete ionization of **2**.

Counterion Effects. In order for potassium acetate, the base used for deprotonation of **2**, to be solubilized in nonpolar solvents, complexation with 18-crown-6[6] was employed. The presence of 18-crown-6 had no effect on the intensity of the enolate band in water and methanol, but an increase of the intensity was observed in less polar

(6) 18-Crown-6: 1,4,7,10,13,16-hexaoxacyclooctadecane. Cryptand[2.2.2]: 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane. Cf.: Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017. Lehn, J. M. *Pure Appl. Chem.* **1977**, *49*, 857. Cram, D. J. *Angew. Chem.* **1986**, *98*, 1041.

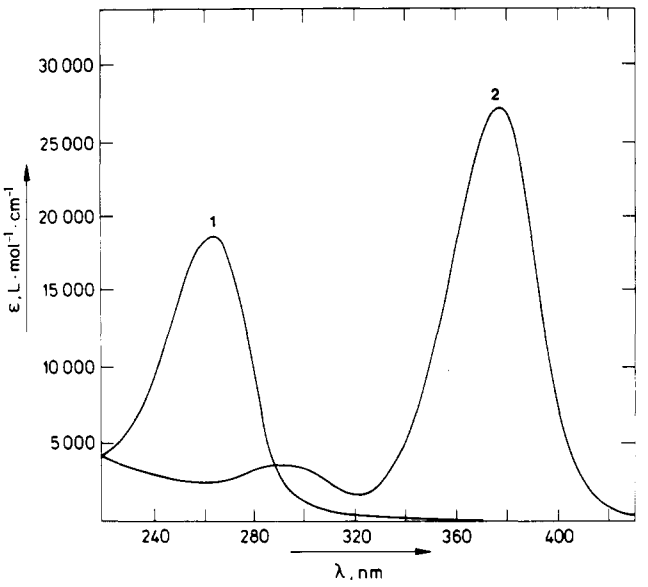


Figure 3. Electronic spectra of **2** in acetonitrile containing traces of hydrochloric acid (curve 1) and in 10^{-2} M potassium acetate/18-crown-6 complex in acetonitrile, at equilibrium (curve 2).

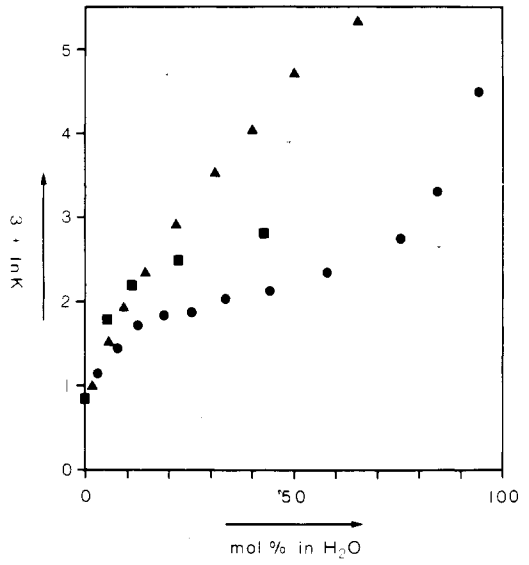


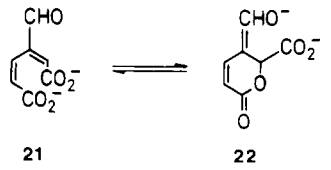
Figure 4. Variation of equilibrium constant for enolate formation (Chart II) in mixtures of water and organic solvents [●, acetonitrile; ▲, dimethyl sulfoxide; ■, *tert*-butyl alcohol (10^{-2} M potassium acetate as base)]. The equilibrium constants were calculated with the assumption of ε 27 000 for pure enolate.

alcohols. In *tert*-butyl alcohol, replacement of 18-crown-6 with cryptand[2.2.2] as the complexing agent caused a further increase of the intensity of the enolate band. These effects are illustrated in Table III. Also in nonpolar aprotic solvents the intensity of the enolate band was higher when potassium acetate was complexed with cryptand[2.2.2] rather than with 18-crown-6. The salt effect on the equilibrium appears small (Table IV).

Protonation of the Enolate. Acidification of freshly prepared aqueous solutions of **2** of pH 7–8, i.e., solutions containing the equilibrium mixture of **3** and **5** (Figure 1), led to UV absorption curves typical of **2**, demonstrating that little, if any, irreversible reaction took place under these conditions (except for the slow hydrolysis of **3** to **21**, which is not manifested as a change of the final spectra) (Chart IV).

Acidification of solutions containing the enolate **5** in solvents like dimethyl sulfoxide, dimethylacetamide, dimethylformamide (Figure 5), hexamethylphosphoric triamide, and tetramethylurea, using a large (10^2–10^3-fold) molar excess of concentrated hydrochloric acid, gave solutions with time-independent absorption at λ_{max} 306–309 nm (ε ca. 13 500), which we ascribe to the enol **23** (cf. λ_{max} 302 nm of **6** in dimethyl sulfoxide). A stable absorption band of the free enol could also be observed in alcohols (λ_{max} 305 nm, ε 13 500 in *tert*-butyl alcohol); in more polar alcohols, where the equilibrium concentration of **5** is low, the band of **23** appeared as a shoulder on the restored absorption band of **2** at 265 nm. In acetonitrile and tetramethylene sulfone, the initial enol band (λ_{max} 297 nm) rapidly decreased to about half of its original intensity, with formation of a new absorption band at 227 nm, presumably owing to ketonization. This reaction has not been investigated further. In nonpolar solvents, protonation of the enolate could not be observed because of salt precipitation upon acidification.

Chart IV



21 22

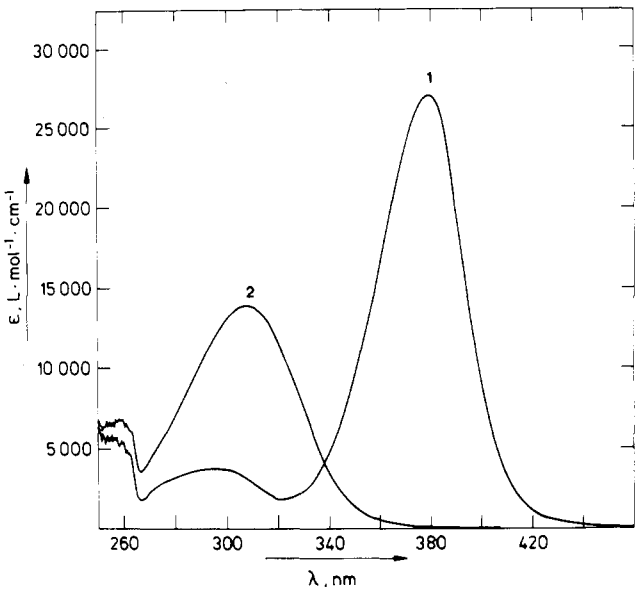
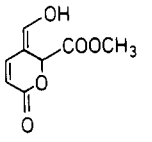


Figure 5. Electronic spectra of a solution of the enolate **5** in dimethylformamide containing 10^{-2} M potassium acetate/18-crown-6 complex (curve 1) and the latter solution after acidification with concentrated hydrochloric acid (curve 2).



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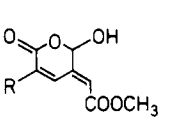
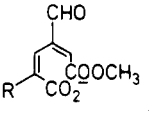
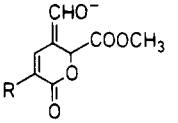
Substituent Effects on Formation of Cyclic Enolates. The derivatives **18** and **24**, prepared as described elsewhere,[2] exhibited in water at pH 8–9 absorption with λ_{max} 272 nm (ε 8000) and λ_{max} 276 nm (ε 7500), respectively, evidently owing to formation of **25** and **26**. No long-



18 R = CH_3
24 R = Cl



25 R = CH_3
26 R = Cl



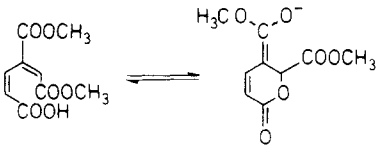
27 R = CH_3
28 R = Cl

Table V. Solvent Effect on Enolate Formation of 25 and 26

solvent[a]	ϵ_{max} with 25,[c] L mol^{-1} cm^{-1}	ϵ_{max} with 26,[d] L mol^{-1} cm^{-1}
1,4-dioxane	3500	3600
chloroform	7500	5500
tert-butyl alcohol	8300	9500
acetone	15 800	15 200
1,2-propanediol carbonate	15 800	13 000
acetonitrile	16 200	14 000
polar aprotic solvents[b]	19 000	18 200

[a] Potassium acetate/18-crown-6 complex (10^{-2} M). [b] Dimethylacetamide, dimethylformamide, dimethyl sulfoxide, tetramethylurea. [c] λ_{max} of the enolate 388–390 nm. [d] λ_{max} of the enolate 392–395 nm.

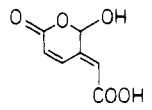
Chart V



30 31

wavelength absorption that could be ascribed to the enolates **27** and **28** could be observed in the aqueous solutions. However, strong enolate bands were observed in other solvents, with considerable solvent effects on the intensity of the bands (Table V). Acidification of the solutions containing the enolates in hydrogen bond accepting solvents (dimethylformamide, dimethylacetamide, tetramethylurea, dimethyl sulfoxide) produced stable enol bands around 302 nm for the methyl derivative (cf. λ_{max} 297 nm of **12** in acetonitrile) and 320 nm for the chloro derivative, with ϵ about 12 000 in each case.

Hydrolysis of **2** with base yielded **29**.[4] In alkaline aqueous media the acid gave an absorption band at λ_{max} 375 nm (ϵ 1300), evidently owing to formation of **22** (Chart IV). Formation of the enolate took place more slowly than



29

for **5**; in water at pH 10 and 29 °C, the first-order rate constant of formation of **22** was 2.39×10^{-2} s^{-1} (half-life 29 s). Measurement of the equilibrium intensity of the enolate band at various pH values gave an approximate pK_2 of 6.6 for **29**.

In slightly basic solutions of **2**, the intensity of the enolate band (**5**) gradually decreased from ϵ 2800 (Table I) to the final value of ϵ 1300 (first-order kinetics with a half-life of 5 min at pH 8 and room temperature), obviously because of the hydrolysis of **3** to **21**.

We also obtained preliminary results on cyclization of the anion derived from the acid **30**,[2] which contains a methyl ester group instead of the aldehyde group (Chart V). Although no long-wavelength absorption could be observed in alkaline aqueous solutions, and in *tert*-butyl alcohol the absorption was very weak, strong bands attributable to the enolate **31** were produced in other solvents (Figure 6, Table VI). Attempts to protonate **31** as described for **5**, **27**, and **28** were not successful, and neither were preliminary trapping experiments using methyl trifluoromethanesulfonate, the trimethyl ester corresponding to **30** being the only product isolated.

Reaction of 2 with Strong Base. As already mentioned, acidification of freshly prepared aqueous solutions containing **3** and **5** restored the absorption of **2** quantitatively. However, this applies only to neutral or slightly basic solutions, and in fact full reversibility could best be obtained with sodium or potassium acetate used for the deprotonation of **2**. Similarly, a series of absorption curves showing isosbestic points as in Figure 1 could only be obtained by using freshly prepared solutions in buffers, or aqueous acetates.

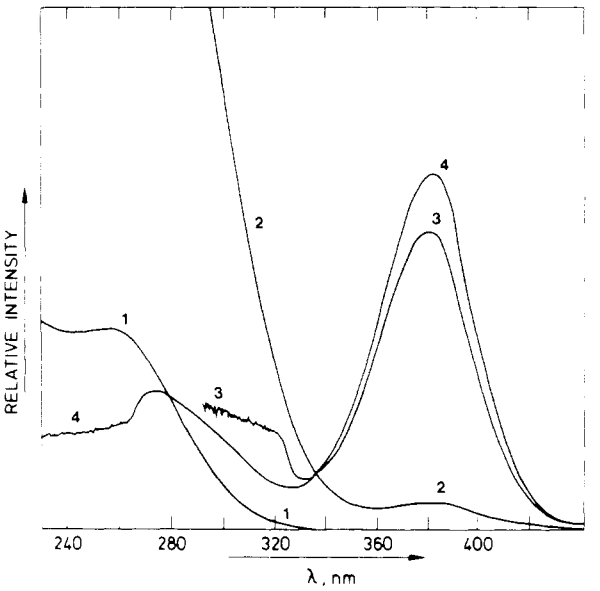


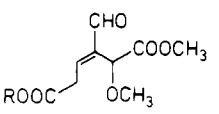
Figure 6. Electronic spectra of **30** in 0.01 M phosphate buffer of pH 7 (curve 1) and in various organic solvents containing 10^{-2} M potassium acetate/cryptand[2.2.2]. Curve 2: *tert*-butyl alcohol. Curve 3: acetone. Curve 4: dimethylacetamide (concentrations of **30** are not identical; for values of ϵ_{max} see Table VI). In acidic solutions, **30** absorbs at λ_{max} 244 nm (ϵ 9500).[2]

Table VI. Solvent Effect on Enolate Formation from 30

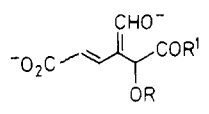
solvent[a]	ϵ_{max},[b] L mol^{-1} cm^{-1}
tert-butyl alcohol	≤400
1,4-dioxane	3300
acetonitrile	4000
dimethyl sulfoxide	7500
tetrahydrofuran	9000
dimethylformamide	10 000
acetone	11 000
dimethylacetamide	14 000
tetramethylurea	16 000
hexamethylphosphoric triamide	19 000

[a] Potassium acetate/18-crown-6 complex (10^{-2} M). [b] λ_{max} ca. 380 nm.

On the other hand, basification of solutions of **2** with 10^{-2}–10^{-3} M NaOH caused not only rapid hydrolysis of the ester group, giving **21**, but also an increase of absorption in the region between the bands of **21** and **22**. Acidification of such solutions yielded solutions with absorption at 265 nm (**29**), considerably lower than expected. The reaction was more rapid in more concentrated base; thus, in 0.1 M NaOH, a strong absorption maximum at 322 nm (ϵ 23 000) was formed within 2 h (Figure 7). Subsequent acidification to pH 1–2 gave a solution with no distinct maximum, demonstrating that a weakly absorbing product was formed. A similar reaction on a preparative scale using methanolic sodium methoxide, followed by neutralization, yielded **32**. The latter was methylated with diazomethane



32 R = H
33 R = CH_3



34 R = H R^1 = O^-
35 R = CH_3 R^1 = OCH_3

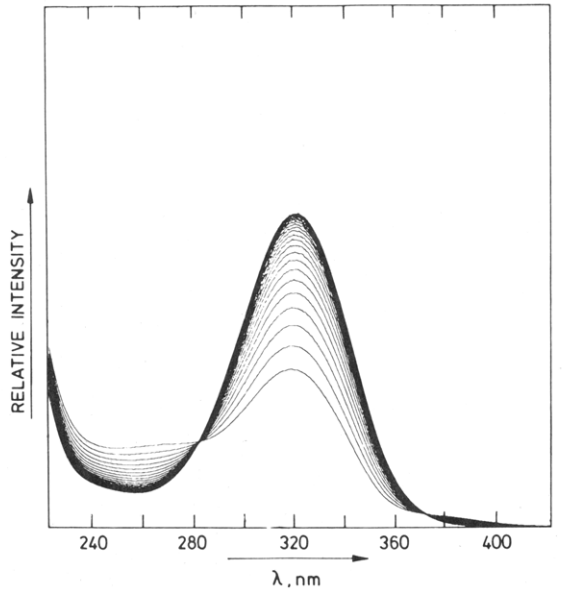
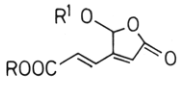


Figure 7. Electronic spectra of **2** in 0.1 M NaOH recorded with intervals of 5 min, showing the formation of **34**.

to give **33**, the stereochemistry of which was determined from the 24–25% NOEs observed between the olefinic and the aldehydic proton when either was irradiated. A similar result was obtained with **17**. Thus, the absorption at 322 nm (Figure 7) can be attributed to an enolate such as **34**, its analogue **35** being formed in methanol. The question of the configuration of **34** and **35** was not addressed.

Stereoisomeric 3-Formyl-2,4-hexadienedioic Derivatives. As reported previously,[1,2] the monoester **1** exists in solution predominantly as the hemiacetal **2**; in the present work we detected 1% of **1** in a dimethyl sulfoxide solution of **2** by ^{1}H NMR. Addition of **2** to an aqueous solution of bisulfite yielded the open-chain bisulfite adduct of **1** (^{1}H NMR).

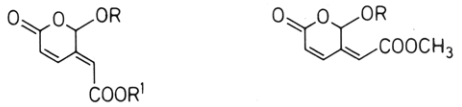
Heating of **2** in dilute hydrochloric acid caused hydrolysis of the ester group along with isomerization of both double bonds, yielding **36**; prolonged heating caused for-



36 R = R^1 = H
37 R = R^1 = CH_3
38 R = CH_3 R^1 = H
39 R = H R^1 = CH_3

mation of unidentified saturated products (no strong UV absorption, presence of multiplets around 3 ppm in the ^{1}H NMR spectrum), presumably formed by addition of water to the double bonds. Esterification of **36** with acidified methanol or with diazomethane yielded **37** or **38**, respectively. Oxidative methylation of **36** gave the trimethyl ester of (1*Z*,3*E*)-1,3-butadiene-1,2,4-tricarboxylic acid.[7]

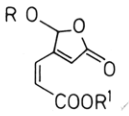
Mild treatment of **2** with methanol containing hydrogen chloride gave **40**[8] as the main product. Isomerization of **40** or **19** by heating in toluene containing iodine yielded equilibrium mixtures (ratios of 1:1) containing the latter and **42** or **43**, respectively, separated by chromatography.



2 R = H R^1 = CH_3
19 R = $COCH_3$ R^1 = CH_3
40 R = R^1 = CH_3
41 R = CH_3 R^1 = H

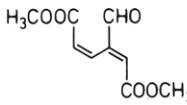
42 R = CH_3
43 R = $COCH_3$

Heating **2** in methanol containing hydrogen chloride yielded a mixture of **16** and **40** in a ratio of 5:2, together with a small amount of **13** and traces of several other unidentified products (^{1}H NMR). The same mixture was obtained by analogous treatment of **13** or **16**.

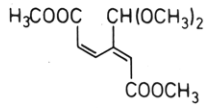


16 R = R^1 = CH_3
44 R = H R^1 = CH_3
45 R = CH_3 R^1 = H

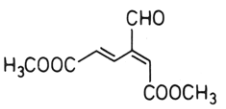
Prolonged heating of **2** in acidified methanol containing trimethyl orthoformate as a water scavenger yielded practically pure acetal **46**, easily hydrolyzable to **13**.[4] Isomerization of the latter by prolonged heating with iodine in toluene gave an equilibrium mixture of **47** and **50** (ratio of 3:1), separated by chromatography; a brief isomerization of **13** gave practically pure **47**.



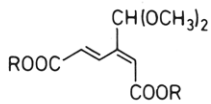
13



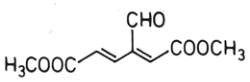
46



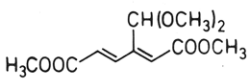
47



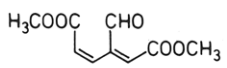
48 R = CH_3
49 R = H



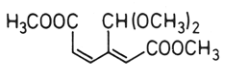
50



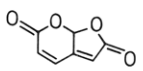
51



52



53



54

In contrast to the aldehyde **13**, the acetal **46** rapidly consumed iodine upon attempted equilibration, presumably because of reactivity of the allylic hydrogen, and thus isomeric acetals could not be obtained in this way. However, a partial, unsensitized photochemical isomerization of **46** gave a mixture of the latter and **48**. The mixture could be selectively hydrolyzed to a mixture of **13** and **48**, chromatography of which afforded pure **48**. Although the partial isomerization of **46** did not yield any appreciable amount of **51**, this isomer was formed upon acid-catalyzed methanolysis of **37** in the presence of trimethyl orthoformate and was separated from unchanged starting material by chromatography. Similar methanolysis of **16**

(7) The hitherto uncharacterized isomer of (1*E*,3*Z*)-1,3-butadiene-1,2,4-tricarboxylic acid, an important microbial metabolite. Cf.: Stanier, R. Y.; Ornston, L. N. *Adv. Microb. Physiol.* **1973**, *9*, 89.

(8) This material was previously obtained by ozonolysis of 2-methoxy-4-(dimethoxymethyl)phenol: Eriksson, T.; Gierer, J. *J. Wood Chem. Technol.* **1985**, *5*, 53.

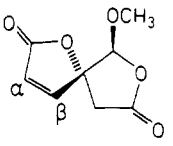
afforded **53**, along with unchanged **16** and small amounts of **37**.

Alkaline hydrolysis of **48**, followed by acidification, gave **49**, whereas similar treatment of **46** and **51** gave **41** and **39**, respectively. From **53**, an equimolar mixture of **41** and **45** was obtained. The reactions presumably involve saponification of the diesters and cyclization of the dicarboxylic acids upon acidification of the reaction mixture. Acid-catalyzed hydrolysis of **53** gave a complex product containing a significant proportion of **13**, and the reaction was not investigated any further; the isomer **52** has thus yet to be obtained.

As already described, alkaline hydrolysis of **2** yielded **29**. When **36** was treated similarly, only the starting material was recovered, and no isomeric products could be detected. However, in both cases, loss of material was observed, perhaps owing to formation of enolates such as **34**. Alkaline hydrolysis of **44**, obtained along with small amounts of **36** by mild acid treatment of **16** and isolated by chromatography, yielded **29**. The apparent spectrophotometric pK_a of **44** was 6.7.

In contrast to the behavior of **2** in aqueous base, treatment of **2** with 1 equiv of methanolic base yielded **45** cleanly and rapidly. Increase of the amount of strong base resulted in the formation of **39**. As already described, formation of **32** occurs eventually after prolonged exposure to an excess of base.

In an attempt to obtain **54** from **45** by extrusion of methanol, the latter was heated briefly at 200 °C. The reaction resulted in a clean conversion of **45** into **55**, rather than in the formation of **54**. The relative configuration



55

of the spirolactone is suggested on the basis of NOE difference measurements. Thus irradiation of the high-field methylene resonance caused 16% enhancement of the resonance of the other methylene proton. Irradiation of the latter resonance caused 12% enhancement of Hβ; the low-field methylene proton is thus cis to the olefinic linkage. Irradiation of the methyl group caused enhancement of the acetal signal (5%) and of Hβ (2%). A 6% NOE was observed between the olefinic protons. On the other hand, no NOE was observed between Hβ and the acetal proton, expected if the relative stereochemistry was the alternative to that shown in **55**. Since the experiment has shown positively all NOEs expected for **55**, it is proposed that this structure correctly represents the product. This stereochemistry corresponds to the addition of the carboxy group to the double bond from the less hindered face, i.e., from the side of the ring opposite to the methoxy group.

Discussion

3-Substituted derivatives of 2,4-hexadienedioic (muconic) acid are important microbial metabolites arising by scission of aromatic precursors.[9] Less commonly by far, such products are encountered in flowering plants.[10] During the present work we have obtained representatives of all possible stereoisomeric types of 3-formyl-2,4-hexadienedioic acid derivatives: 2*E*,4*E* (**47**–**49**), 2*E*,4*Z* (**2**, **13**, **29**, **40**, **41**, **46**), 2*Z*,4*E* (**36**–**39**, **50**, **51**), and 2*Z*,4*Z* (**16**, **42**–**45**, **53**). The chemistry of 3-formyl-2,4-hexadienedioates is rich not only because of cis–trans isomerizations, often occurring under mild conditions as the result of anchimeric assistance,[1,5] but also because of hemiacetal and pseudoester[11] formation.

As expected, the sterically most stable 3-formyl-2,4-hexadienedioic derivatives are the extended 2*Z*,4*E* isomers **36**–**39**, formed from various 4*Z* derivatives in acid- or base-catalyzed isomerizations. The base-catalyzed reaction is presumably nucleophile-catalyzed;[12] the acid-catalyzed conversion of **2** to **36** may proceed via **29** and involve intramolecular nucleophilic catalysis.[5] The acid-catalyzed methanolysis of **2** and **16** and the hydrolysis of **16** and **53** demonstrate the stereochemical lability of the C-2–C-3 double bond; analogous isomerizations are known with 4-oxo-2-butenoic acids.[13] However, partial conversion of **16** and **37** to **53** and **51**, respectively, likewise allowing transient formation of carbocation intermediates, was possible without much isomerization of the 2*Z* bonds.

Noteworthy is the formation of **45** upon treatment of **2** with 1 equiv of base in methanol, being a case of acetal formation under alkaline conditions. The reaction presumably involves isomerization of the 2*E* double bond assisted[14] by the carboxylate ion (i.e., reversible addition to C-3, followed by rotation about the C-2–C-3 bond and ring opening; protonation of the cyclic intermediate on carbon gives **55**),[1,5,15] followed by ring closure via the hemiacetal anion. The isomerization of the 2*E* bond of **3** can also take place via **5**. An additional amount of strong base converts **45** to **39**. The isomerization of the C-2–C-3 double bond, involving assistance by the terminal carboxylate group, is expected to proceed readily only when the 1-carboxy group is esterified.[5] Accordingly, the alkaline hydrolysis of **2** yields **29** with retained 2*E* configuration, hydrolysis of the ester group being apparently faster than the stereomutation.

Steric effects on ester and acetal hydrolysis have been observed. Thus, whereas a brief reflux of **16** in aqueous acid gave a fair yield of the selectively hydrolyzed product **44**, identical treatment of **37** yielded solely **36**. Another example is provided by the acetal **46**, which was hydrolyzed to **13** under conditions where **48** was practically completely unreactive, presumably as the result of steric congestion in **46**, accelerating expulsion of methanol from the protonated intermediate.

(9) Dagley, S. *Adv. Microb. Physiol.* **1971**, *6*, 1. Clarke, P. H.; Ornston, L. N. In *Genetics and Biochemistry of* Pseudomonas; Clarke, P. H., Richmond, M. H., Eds.; Wiley-Interscience: London, 1975; p 191. Kieslich, K. *Microbial Transformations of Non-Steroid Cyclic Compounds*; Georg Thieme: Stuttgart, 1976; p 85. Barz, W.; Weltring, K.-M. In *Biosynthesis and Biodegradation of Wood Compounds*; Academic Press: Orlando, 1985; p 607.

(10) Jaroszewski, J. W.; Ettlinger, M. G. *Phytochemistry* **1981**, *20*, 819.

(11) Andreev, V. M.; Kugatova-Shemyakina, G. P.; Kazaryan, S. A. *Russ. Chem. Rev. (Engl. Transl.)* **1968**, *37*, 254.

(12) Cf.: Nozaki, K.; Ogg, R., Jr. *J. Am. Chem. Soc.* **1941**, *63*, 2583. Seltzer, S. *Enzymes* **1972**, *6*, 381. Feliu, A. L.; Smith, K. J.; Seltzer, S. *J. Am. Chem. Soc.* **1984**, *106*, 3046.

(13) Alder, K.; Farina, F. *An. Real. Soc. Espan. Fis. Quim.* **1958**, *54B*, 689. Farina, F.; Lora-Tamayo, M.; Martin, M. V. *Ibid.* **1964**, *60B*, 715. Conradie, W. J.; Garbers, C. F.; Steyn, P. S. *J. Chem. Soc.* **1964**, 594. Schroeter, S. H.; Appel, R.; Brammer, R.; Schenk, G. O. *Justus Liebigs Ann. Chem.* **1966**, *697*, 42. Seltzer, S.; Stevens, K. B. *J. Org. Chem.* **1968**, *33*, 2708. Pattenden, G.; Weedon, B. C. L. *J. Chem. Soc. C* **1968**, 1984. Farina, F.; Victory, P. *Tetrahedron Lett.* **1969**, 3219. Escobar, C.; Farina, F.; Sanudo, J. M. *An. Quim.* **1971**, *67*, 43. Meyers, A. I.; Nolen, R. L.; Collington, E. W.; Narwid, T. A.; Strickland, R. C. *J. Org. Chem.* **1973**, *38*, 1974. Landor, S. R.; Landor, P. D.; Kalli, M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2921.

(14) Isomerizations catalyzed by external nucleophiles are expected to be considerably slower; cf.: Garbers, C. F.; Schneider, D. F.; van der Merwe, J. P. *J. Chem. Soc. C* **1968**, 1982. Grove, M. D.; Weisleder, D. *J. Org. Chem.* **1973**, *38*, 815.

(15) A similar mechanism was recently postulated for stereomutation of (2*Z*,4*Z*)-6-oxo-2,4-heptadienoate: Feliu, A. L.; Seltzer, S. *J. Org. Chem.* **1985**, *50*, 447.

As shown by the acylation and alkylation experiments, generation of the anion **3** from **2** in acetonitrile caused practically complete conversion to the enolate **5**. The cyclization belongs to the 6-Endo-Trig category, which is favored according to the Baldwin rules.[16] There is strong evidence that **5** and its stereoisomer **20** are the thermodynamically and the kinetically favored product, respectively; the equilibrium constant between **20** and **5** (Chart III) is not known but appears to be large. The isomeric enolates correspond to the two conformations, s-cisoid and s-transoid,[17] of the aldehyde group in **3**; the s-transoid conformer appears hence to cyclize at a faster rate. Thus, the generation of **3** followed by an equilibration period before acylation afforded high yields of the enol esters **6** and **7**, whereas a considerable proportion of **9** and **10** was formed when the process was kinetically controlled with respect to the cyclization of **3**. Although the observed ratio of the enol esters may not represent exactly the ratio of **5** and **20** owing to possibly different acylation rates, the initial presence of **20** and its decay is clearly documented. At −40 °C, the cyclization of **3** is frozen.

Enolate trapping by methylation, being a slower process, gave 33% of the enol ether **8** along with C-methylation products **12**, **14**, and **18** and no appreciable amount of **11**. The relatively high proportion of **14** and **18** compared to **13** and **2** isolated from the reaction mixture is readily explicable in terms of the lower cyclization equilibrium constant of **25** than of **3** (see below). The two remaining compounds obtained in the reaction, i.e., **16** and **17**, are formed respectively by isomerization of **3** followed by methylation of the resulting **45** (cf. the above-described independent synthesis of **45** and the increase of the yield of **16** upon an increase of methoxide concentration in the reaction medium), and by decarboxylation of **32** formed via **35**.

Since the addition of equivalent amounts of base to more concentrated solutions of **2** caused polymerization of the substrate, the formation of the cyclic enolate **5** and accompanying reactions could not be studied directly by ^{1}H NMR spectroscopy using ordinary techniques. Consequently, no data about the extent of the possible isomerization of the 2*E* bond in **3**, either via **5** or via the intramolecular nucleophilic attack of the carboxylate ion at C-3, are available.[18] However, the equilibrium concentrations of the enolate **5** and how these were affected by the medium could be conveniently studied by UV spectroscopy. Since in all aprotic solvents investigated the intensity of the enolate band is constant (ϵ of 27 000 at 377–381 nm), the cyclization of **3** to **5** is essentially complete in these solvents. Assuming that the solvent effect on the absorptivity of **5** is small, approximate equilibrium constants for the formation of **5** can be calculated for solvents where the cyclization is not complete. The observed span of the equilibrium constants in alcohols (Table I) corresponds to a change of free-energy difference ($\Delta\Delta G°$) on going from water to *tert*-butyl alcohol of 2.8 kcal mol^{-1}. The values of ln *K* correlate with solvent polarity functions derived from the bulk dielectric constant (*D*) such as the Kirkwood function $(D-1)(2D+1)^{-1}$, or the related D^{-1} or $(D-1)(D+2)^{-1}$ functions, with correlation coefficients *r* of 0.98. Similar correlations are observed with the classical microscopic measures of solvent polarity such as the Kosower *Z* scale[19] and the Brownstein *S* scale,[20] the Dimroth E_T scale,[21] the Brooker χ scale,[22] or the Winstein *Y* scale.[23] The linear free energy relationship shown in eq 1,

$$\ln K = 11.9 + 7.2\pi^* - 18.8\alpha \quad (1)$$

with a correlation coefficient (*r*) of 0.977, a sum-of-squared-error of 0.63, and a mean deviation of 0.13, is obtained by using the Kamlet–Taft approach.[24] The variables π^* and α refer to the solvent dipolarity/polarizability index[25] and hydrogen-bond acidity index,[26] respectively.[27] The correlation with the Swain parameters[28,29] *A* and *B*, reflecting the anion- and cation-solvating tendency of the solvent, was better, with a correlation coefficient of 0.992, a sum-of-squared-error of 0.18, and a mean deviation of 0.08 (eq 2).

$$\ln K = 6.3 - 11.8A + 3.2B \quad (2)$$

The dependency values of the iteratively refined parameters were over 0.99 for the Kamlet–Taft equation (1) and 0.95–0.98 for the Swain equation (2), demonstrating a higher instability of the fit in the former case.[30]

The above correlations emphasize the importance of hydrogen bonding on the equilibrium between **3** and **5**. In **3**, the negative charge is concentrated in the carboxylate group; in **5**, the charge is delocalized over an approximately planar backbone of seven atoms. The cyclization thus involves the transfer of charge from the hard carboxylate ion to the soft enolate ion. The expected solvent effect on the cyclization equilibrium is therefore similar to that on the rate of decarboxylation of 3-benzisoxazolecarboxylate to 2-cyanophenolate.[31] The selective solvation of the open-chain carboxylate form by solvents that are good hydrogen-bond donors thus appears to be a principal factor governing the extent of cyclization of **3** to **5**. On the other hand, the soft enolate anion **5** is presumably stabilized by solvents of high polarizability. In this respect the transformation of **2** into **5** is reminiscent of the ionizations of 2,4,6-trinitrophenol and 2,4,6,2′,4′,6′-hexanitrodi-

(16) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
(17) Cf. the rotational isomerism of acrolein: De Maré, G. R. *Can. J. Chem.* **1985**, *63*, 1672.
(18) If the equilibrium between **3** and **5** also contains a significant proportion of the 2*Z* isomer of **3**, acidification of such solutions should lead to an UV absorption stronger than the original absorption of **2**, because of the formation of **42** (R = H). In fact, for freshly prepared aqueous solutions, no appreciable increase of the absorption was observed, whereas for aged solutions, the absorption after acidification was actually lower. This is believed to be due to the formation of species like **34**, but may also be related to the presence of **44** (R = R^1 = H), formed by isomerization of **3** and hydrolysis of the ester group. In nonaqueous solvents, investigation of the reversibility of formation of **5** by acidification was not possible due to formation of **23**, as described in the text.
(19) Kosower, E. M. *J. Am. Chem. Soc.* **1958**, *80*, 3258. Kosower, E. M. *An Introduction to Physical Organic Chemistry*; Wiley: New York, 1968.
(20) Brownstein, S. *Can. J. Chem.* **1960**, *38*, 1590.
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(22) Brooker, L. G. S.; Craig, A. C.; Haseltine, D. W.; Jenkins, P. W.; Lincoln, L. L. *J. Am. Chem. Soc.* **1965**, *87*, 2443.
(23) Fainberg, A. H.; Winstein, S. *J. Am. Chem. Soc.* **1956**, *78*, 2770. Fainberg, A. H.; Winstein, S. *Ibid.* **1957**, *79*, 5937.
(24) Taft, R. W.; Abboud, J.-L. M.; Kamlet, M. J.; Abraham, M. H. *J. Solution Chem.* **1985**, *14*, 153. Kamlet, M. J.; Taft, R. W. *Acta Chem. Scand., Ser. B* **1985**, *39*, 611.
(25) Kamlet, M. J.; Abboud, J. L.; Taft, R. W. *J. Am. Chem. Soc.* **1977**, *99*, 6027.
(26) Taft, R. W.; Kamlet, M. J. *J. Am. Chem. Soc.* **1976**, *98*, 2886.
(27) Kamlet, M. J.; Abboud, J.-L. M.; Abraham, M. H.; Taft, R. W. *J. Org. Chem.* **1983**, *48*, 2877.
(28) Swain, C. G.; Swain, M. S.; Powell, A. L.; Alunni, S. *J. Am. Chem. Soc.* **1983**, *105*, 502.
(29) For a recent, general review of solvent parameters, see: Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; VCH: Weinheim, 1988.
(30) The data analysis was performed by using the MLAB computer program, Division of Computer Research and Technology, National Institutes of Health, Bethesda, Maryland, U.S.A.
(31) Kemp, D. S.; Paul, K. G. *J. Am. Chem. Soc.* **1975**, *97*, 7305. Kemp, D. S.; Cox, D. D.; Paul, K. G. *Ibid.* **1975**, *97*, 7312.

phenylamine, which, unlike ionization of carboxylic acids to the hard carboxylate ions, are favored by dilution of aqueous solutions with less polar but more polarizable organic solvents.[32]

For the amides shown in Table II, there is no solvent-property data to assess the mechanism of the solvent effect, although hydrogen bonding is presumably important in this series, too. Data for mixtures of the organic solvents and water (Figure 4) show that even small amounts of the solvents increase the enolate concentration appreciably, presumably owing to specific interactions of the solvent molecules with **5**. For water–acetonitrile mixtures, ln K is approximately linear with mole fraction of acetonitrile until about 15 mol %, corresponding to the concentration region where acetonitrile saturates the water network without disturbing it.[33]

The described charge properties of **3** and **5** render the former more apt than the latter to form ion pairs with small cations. Ion pairing is thus expected to influence the cyclization equilibrium constants. This is supported by the data in Table III: increase of the effective size of the counterion results in a higher concentration of **5**. The effect is not due to low activity of the acetate ion and incomplete deprotonation of **2** in the absence of the complexing agents, as shown by Table IV. Thus the equilibrium enolate concentration is not sensitive to changes in base concentration, and a considerably lower acetate ion concentration than usually used (10^{-2} M) is sufficient to fully deprotonate **2**. In polar solvents such as acetonitrile and dimethyl sulfoxide, the complexation of potassium had no effect on the intensity of the enolate band, and the cyclization equilibrium constants in these and similar solvents are probably very large.

Hydrolysis of the ester group in **3** to give **21** decreases the rate as well as the equilibrium constant of cyclization, since the average distance between the negative charges is decreased on going from **21** to **22** (it is assumed that the absorptivity of **22** is not very different from that of **5**). Introduction of a methyl group or chlorine atom into **3** likewise decreases the cyclization equilibrium constant (Table V), presumably because of enolate destabilization by electron donation.[34] Although the absorptivities of enolates **27** and **28** are not known and the cyclization equilibria cannot be estimated, the data (Table V) show considerable solvent effects in aprotic solvents as well. Since 18-crown-6 was used as a complexing agent rather than cryptand[2.2.2], ion pairing presumably affects the equilibria, especially in the solvents of low polarity. The configuration of the enolates **22**, **27**, and **28** is probably Z, as judged from the similarity of their UV spectra with that of **5**.

It is remarkable that even the ester **30** produces strong UV absorption in aprotic solvents (Figure 6), presumably owing to formation of **31**. Although the maximal intensities of the enolate band (Table VI) must correspond to a high degree of cyclization, no exact data on the equilibrium constants are available. The configuration of the enolate **31** has yet to be determined.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded at 60 MHz with Varian A60, T60A or EM360L spectrometers; NOE measurements were carried out with a Bruker AM250 spectrometer. IR spectra were recorded on Perkin-Elmer Model 457 or 781 spectrophotometers. UV spectra were obtained with a Unicam SP1800 or a Shimadzu UV 265 instrument. Mass spectra (70 eV) were measured with an AEI MS902 instrument or a Finnigan 1015 S/L quadrupole spectrometer. Elemental analyses were performed by P. Hansen, Chemical Laboratory II, University of Copenhagen. Melting points were determined in capillaries and are corrected. Merck silica gel 60 (0.063–0.2 mm) was used for column chromatography.

Alcohols of the highest available purity were distilled before use; *tert*-butyl alcohol was purified by partial freezing. 1,4-Dioxane, chloroform, dichloromethane, 1,2-dimethoxyethane, and tetrahydrofuran were passed through activated alumina. Benzene was dried with sodium and distilled. Spectroscopic grade acetone and acetonitrile were used without purification. Dimethyl sulfoxide was dried with calcium hydride and vacuum distilled. Formamide and 1,2-propanediol carbonate were fractionated under reduced pressure. Other amides were dried with barium oxide and vacuum distilled. Tetramethylene sulfone was treated with potassium permanganate and sodium pyrosulfate, dried with phosphorus pentoxide, and vacuum distilled. Potassium acetate was dried at 110 °C. Complexes with 18-crown-6 and cryptand[2.2.2] were prepared by dissolving equimolar amounts of the reagents in methanol and evaporation.[35]

Methyl (*E*)-(2-Hydroxy-6-oxo-3,6-dihydro-2*H*-pyran-3-ylidene)acetate (2). The synthetic procedure and the physical and spectroscopic properties of the material were as described before.[2] The ^{1}H NMR spectrum (250 MHz) of a solution of **2** in $(CD_3)_2SO$, in addition to the signals of **2** [δ 3.73 ($COOCH_3$), 4.32 (OH), 6.12 (H2), 6.30 (Hα and H5), 8.04 (H4) [$^3J_{4,5}$ = 10 Hz]], exhibited a weak signal at δ 9.54 (intensity about 1% of that of H4), presumably due to the aldehyde group of the open-chain form **1** in equilibrium with **2**. In D_2O saturated with $NaDSO_3$, a bisulfite adduct to the open-chain form **1** could be observed by ^{1}H NMR (60 MHz) during several minutes before it decomposed to many unidentified products: δ 4.86 ($COOCH_3$), 5.39 [CH(O-D)SO_3^-], 6.18 (H5), 6.41 (H2), 7.17 (H4) [$^3J_{4,5}$ = 12.5 Hz, $^4J_{2,4}$ = 2 Hz].

Methyl (*Z*)- and (*E*)-3-[(Acetyloxy)methylene]-6-oxo-3,6-dihydro-2*H*-pyran-2-carboxylate (6 and 9). A solution of **2** (484 mg, 2.6 mmol) in acetonitrile (400 mL) was treated with 2.6 mmol of methanolic tetramethylammonium hydroxide (ca. 1 mL of a 20% solution). After ca. 0.5 h, the resulting yellow solution of the enolate **5** was treated dropwise with freshly distilled acetyl chloride until the yellow color disappeared. The solution was evaporated, the residue taken up in ethyl acetate and filtered, and the filtrate evaporated. Examination of the solid residue by ^{1}H NMR revealed the presence of essentially pure **6**, recrystallized from acetone–hexane: yield 500 mg (84%); mp 116–118 °C; IR (KBr) 1775 (s), 1750 (s), 1720 (s), 1650 (m) cm^{-1}; UV (CH_3CN) λ_{max} 275 nm (ϵ 17 800); ^{1}H NMR ($CDCl_3$) δ 2.28 ($OCOCH_3$), 3.78 ($COOCH_3$), 5.97 (sharp d, H5), 5.98 (br s, H2), 6.96 (br d, H4), 7.67 (br s, Hα) [$^3J_{4,5}$ = 10 Hz, $^5J_{\alpha,5} \approx 0$ Hz]; mass spectrum, m/e (relative intensity, fragment) 226 (10, M), 184 (48, M – CH_2CO, m* for 226 → 184 observed), 125 (100, 184 – $COOCH_3$, m* for 184 → 125 observed). The enol acetate was highly unstable in hydroxylic solvents, which quickly developed UV absorption typical of **5**.

Anal. Calcd for $C_{10}H_{10}O_6$: C, 53.10; H, 4.46. Found: C, 53.35; H, 4.65.

When the above procedure was repeated with addition of acetyl chloride immediately after addition of the base, the crude reaction product contained **6** (30%), **9** (30%), **15** (30%), and unreacted **2** (10%) (^{1}H NMR).

Heating of **6** (300 mg) in toluene (200 mL) with iodine (10 mg) during 3 h under reflux gave cleanly a 2:1 mixture of **6** and **9**, the ratio being unchanged on prolonged reaction (^{1}H NMR). Irradiation (Pyrex-filtered radiation from a medium-pressure mercury arc) of **6** during 2.5 h in acetonitrile containing iodine gave a photostationary equilibrium containing ca. 40% of **9**. Rapid chromatography of the mixtures of **6** and **9** on silica gel resulted

(32) Grunwald, E.; Price, E. *J. Am. Chem. Soc.* **1964**, *86*, 4517. Fong, D.-W.; Grunwald, E. *J. Phys. Chem.* **1969**, *73*, 3903. Cf.: Iwachido, T.; Oosawa, S.; Tôei, K. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2415.

(33) Balakrishnan, S.; Easteal, A. J. *Aust. J. Chem.* **1981**, *34*, 943.

(34) Halogens exhibit opposing inductive and resonance effects, and the latter effect apparently predominates here. Cf. the effect of the alkyl groups and halogens on enolization of β-diketones: Burdett, J. L.; Rogers, M. T. *J. Am. Chem. Soc.* **1964**, *86*, 2105.

(35) Pedersen, C. J. *J. Am. Chem. Soc.* **1970**, *92*, 386.

in loss of all material, but the mixtures were enriched in **9** to some 80% by repeated fractional crystallization: ^{1}H NMR ($CDCl_3$) δ 2.28 ($OCOCH_3$), 3.78 ($COOCH_3$), 5.47 (br s, H2), 5.98 (dd, H5), 7.35 (br d, H4), 7.62 (m, Hα) [$^3J_{4,5}$ = 10 Hz, $^5J_{\alpha,5}$ = 2 Hz].

Methyl (*Z*)- and (*E*)-3-[[(2,2-Dimethylpropionyl)oxy]-methylene]-6-oxo-3,6-dihydro-2*H*-pyran-2-carboxylate (7 and 10). The enol ester **7** was obtained as described above for **6**, replacing acetyl chloride with pivaloyl chloride: yield 550 mg (78%) from 484 mg of **2**; mp 123–124 °C (recrystallized from ether); IR (KBr) 1755 (s), 1725 (s), 1650 (s) cm^{-1}; UV (CH_3CN) λ_{max} 275 nm (ϵ 17 200); ^{1}H NMR ($CDCl_3$) δ 1.33 [$OCOC(CH_3)_3$], 3.78 ($COOCH_3$), 5.98 (sharp d, H5), 5.99 (br s, H2), 7.00 (br d, H4), 7.70 (br s, Hα) [$^3J_{4,5}$ = 10 Hz, $^5J_{\alpha,5} \approx 0$ Hz]; mass spectrum, *m/e* (relative intensity, fragment) 268 (4, M), 184 [37, M – $COC(CH_3)_3$], 125 (100, 184 – $COOCH_3$).

Anal. Calcd for $C_{13}H_{16}O_6$: C, 58.18; H, 6.01. Found: C, 58.05; H, 6.22.

Addition of pivaloyl chloride immediately after addition of base to acetonitrile solutions of **2** resulted in formation of **10** along with **7** (ratio of 1:1), as already described for **6** and **9**.

Isomerization of **7** as described for **6** gave a mixture of **7** and **10** in a ratio of 2:1, unaltered by continuation of the reaction for an additional 2 h (^{1}H NMR). A sample of **10** contaminated with ca. 20% of **7** was obtained from the equilibrium mixture by repeated fractional crystallization: ^{1}H NMR ($CDCl_3$) δ 1.33 [$OCOC(CH_3)_3$], 3.78 ($COOCH_3$), 5.49 (br s, H2), 5.99 (dd, H5), 7.37 (br d, H4), 7.66 (br s, Hα) [$^3J_{4,5}$ = 10 Hz, $^5J_{\alpha,5}$ = 2 Hz].

Methyl (*Z*)-3-(Methoxymethylene)-6-oxo-3,6-dihydro-2*H*-pyran-2-carboxylate (8). To a solution of **2** (920 mg, 5 mmol) in acetonitrile (450 mL) was added 5 mmol of methanolic tetramethylammonium hydroxide (ca. 2 mL of a 20% solution), followed after 15 min by 20 mL of methyl iodide (freshly passed through an alumina column). The solution was stirred overnight in the dark at room temperature. The precipitate of tetramethylammonium iodide was removed by filtration, the solution evaporated, and the dark, oily residue (ca. 1 g) fractionated on a 50 × 2 cm silica gel column, eluted with benzene–ethyl acetate (4:1). The following fractions (monitored by TLC and ^{1}H NMR) were obtained (in the order of elution): 33 mg of a 1:3 mixture of **13** and **14** (1% and 2% yields, respectively), 114 mg of **16** (11%), 55 mg of **17** (6%), 60 mg of **18** (6%; the crude material obtained here gave a ^{1}H NMR spectrum identical with that of an authentic[2] sample and was not purified further), 40 mg of **12** (3.5%), and 330 mg of **8** (33%); further descriptions of **12–14**, **16**, and **17** are given below under appropriate headings.

The major reaction product (**8**) was recrystallized from ether–petroleum ether: mp 108–109 °C; IR (KBr) 1750 (s), 1720 (s), 1650 (s) cm^{-1}; UV (CH_3OH) λ_{max} 298 nm (ϵ 16 300), λ_{max} 302 nm in dimethyl sulfoxide, 306 nm in water; ^{1}H NMR ($CDCl_3$) δ 3.77 and 3.90 (OCH_3 and $COOCH_3$), 5.68 (sharp d, H5), 5.85 (br s, H2), 6.63 (br s, Hα), 6.85 (br d, H4) [$^3J_{4,5}$ = 10 Hz, $^5J_{\alpha,5} \approx 0$ Hz]; mass spectrum, *m/e* (relative intensity, fragment) 198 (5, M), 139 (100, M – $COOCH_3$).

Anal. Calcd for $C_9H_{10}O_5$: C, 54.55; H, 5.09. Found: C, 54.35; H, 5.11.

When the above procedure was repeated with 10 mmol of tetramethylammonium hydroxide (4 mL of the methanolic solution), the workup yielded 325 mg (33%) of **16**, most conveniently isolated from the reaction mixture by short-path distillation (120 °C, 0.1 mmHg).

Methyl (*E*)-3-(Methoxymethylene)-6-oxo-3,6-dihydro-2*H*-pyran-2-carboxylate (11). The *Z* isomer **8** (370 mg) was refluxed for 1 h in 300 mL of toluene containing 10 mg of iodine. Evaporation of the solvent yielded a 2:1 mixture of **8** and **11**; prolonged reaction did not lead to a change in the ratio (^{1}H NMR) (no isomerization was observed in the absence of iodine). Chromatography of the equilibrium mixture on silica gel (45 × 2.5 cm column) with benzene–ethyl acetate (2:1) afforded pure **11** (eluted before **8**), recrystallized from ether–petroleum ether: yield 100 mg (27%); mp 106–107 °C (depressed by an admixture of **8**); IR (KBr) 1760 (s), 1725 (s), 1655 (s) cm^{-1}; UV (CH_3OH) λ_{max} 307 nm (ϵ 14 000), λ_{max} 308 nm in dimethyl sulfoxide; ^{1}H NMR ($CDCl_3$) δ 3.75 and 3.84 (OCH_3 and $COOCH_3$), 5.28 (br s, H2), 5.75 (dd, H5), 6.48 (br s, Hα), 7.28 (br d, H4) [$^3J_{4,5}$ = 10 Hz, $^5J_{\alpha,5}$ = 2 Hz]; mass spectrum, *m/e* (relative intensity, fragment) 198 (6, M), 139 (100, M – $COOCH_3$).

Anal. Calcd for $C_9H_{10}O_5$: C, 54.55; H, 5.09. Found: C, 54.50; H, 5.15.

Heating of **11** in toluene in the presence of iodine yielded the same equilibrium mixture as obtained from **8**. Irradiation (Pyrex-filtered radiation from a medium-pressure mercury arc) of **8** in acetonitrile in the presence of iodine likewise caused equilibration, although the reaction was less clean.

Methyl (*Z*)-3-(Methoxymethylene)-5-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-carboxylate (12). The enol ether was obtained as a byproduct of methylation of the enolate **5** with methyl iodide (see synthesis of **8**). Recrystallization of the appropriate chromatographic fraction (40 mg) from ether–petroleum ether gave 30 mg of pure **12** (2.8% from **2**): mp 127–128 °C; IR (KBr) 1750 (s), 1715 (s), 1645 (s) cm^{-1}; UV (CH_3CN) λ_{max} 297 nm; ^{1}H NMR ($CDCl_3$) δ 1.94 (br s, CH_3), 3.76 and 3.85 (OCH_3 and $COOCH_3$), 5.82 (br s, H2), 6.46 (br s, Hα), 6.60 (br s, sharpened on irradiation at δ 1.94; H4); mass spectrum, *m/e* (relative intensity, fragment) 212 (4, M), 153 (100, M – $COOCH_3$).

Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.50; H, 5.70. Found: C, 56.50; H, 5.69.

Dimethyl (2*E*,4*Z*)-3-Formyl-2,4-hexadienedioate (13).[4] The diester was obtained as a 1:3 mixture with **14**, as a byproduct of methylation of the enolate **5** with methyl iodide (see synthesis of **8**), characterized by ^{1}H NMR only. A pure sample of **13** was obtained by hydrolysis of **46**. Thus, the acetal (3 g) was stirred with 200 mL of 0.01 M HCl during 6 h at room temperature, the solution was extracted with four 150-mL portions of ether, the extracts were dried ($MgSO_4$) and evaporated, and the residue was recrystallized from ether–petroleum ether: yield 2.1 g (86%) of **13**; mp 64–65 °C; IR (KBr) 1720 (s), 1660 (m), 1605 (m) cm^{-1}; UV (CH_3OH) λ_{infl} 250 nm (ϵ 8000); ^{1}H NMR ($CDCl_3$) δ 3.70 and 3.82 ($COOCH_3$), 6.18 (dd, H5), 6.57 (q, H2), 7.08 (dd, H4), 9.52 (s, CHO) [$^3J_{4,5}$ = 12 Hz, $^4J_{2,4}$ = 2 Hz, $^5J_{2,5}$ = 1 Hz]; mass spectrum, *m/e* (relative intensity, fragment) 197 (3, M – 1), 180 (18, M – H_2O), 169 (20, M – CHO), 167 (21, M – OCH_3), 166 (35, M – CH_3OH), 139 (100, M – $COOCH_3$).

Anal. Calcd for $C_9H_{10}O_5$: C, 54.55; H, 5.09. Found: C, 54.55; H, 5.05.

Dimethyl (2*Z*,4*E*)-2-Methyl-4-formyl-2,4-hexadienedioate (14). The diester was obtained, as a 3:1 mixture with **13**, as a byproduct of methylation of the enolate **5** with methyl iodide (see synthesis of **8**): ^{1}H NMR ($CDCl_3$) δ 2.13 (CH_3), 3.68 and 3.81 ($COOCH_3$), 6.48 (H5), 6.87 (H3), 9.48 (CHO) [$^4J_{3,Me} \approx {}^4J_{3,5} \approx 2$ Hz]; cf. ^{1}H NMR spectrum of **13** and the shielding effect of the methyl group on olefinic protons. An analytically pure sample of this material was not obtained.

Acetic (2*Z*,4*E*)-4-Formyl-5-(methoxycarbonyl)-2,4-pentadienoic Anhydride (15). The reaction between **2** and acetyl chloride was carried out as described for the synthesis of **6**, except that the solution of **2** was chilled to −40 °C prior to the addition of base; no yellow coloration of the solution indicative of the formation of **5** was seen. The usual workup afforded **15** as a colorless oil, characterized solely by ^{1}H NMR ($CDCl_3$): δ 2.25 (CH_3CO), 3.78 ($COOCH_3$), 6.17 (d, H2), 6.63 (br s, H5), 7.15 (dd, H3), 9.58 (s, CHO) [$^3J_{2,3}$ = 12 Hz, $^4J_{3,5}$ = 2 Hz]. The material quickly decomposed on standing, giving **19** as the main product (^{1}H NMR).

Methyl (*Z*)-2-Methoxy-5-oxo-2,5-dihydro-3-furanpropenoate (16). The ester was obtained as a byproduct of methylation of the enolate **5** with methyl iodide (see synthesis of **8**). Rechromatography of appropriate fractions in the same system yielded pure, oily **16**: yield 105 mg (10.5% from **2**); IR (film) 1800 (m), 1770 (s), 1730 (s), 1645 (w), 1630 (w), 1590 (w) cm^{-1}; UV (CH_3OH) λ_{max} 257 nm (ϵ 12 000); ^{1}H NMR ($CDCl_3$) δ 3.55 (OCH_3), 3.80 ($COOCH_3$), 6.13 (br s, H2), 6.22 and 6.56 (each d, respectively Hα and Hβ of the propenoate moiety), 6.53 (br s, H4 of the dihydrofuran moiety) [$^3J_{\alpha,\beta}$ = 13 Hz]; mass spectrum, *m/e* (relative intensity, fragment) 198 (0.5, M), 167 (14, M – OCH_3), 166 (15, M – CH_3OH), 154 (18, M – CO_2), 139 (100, M – $COOCH_3$).

Anal. Calcd for $C_9H_{10}O_5$: C, 54.55; H, 5.09. Found: C, 54.45; H, 5.34.

The ester was also formed as a 5:2 mixture with **40** upon heating of **2** in methanol containing 3% of HCl during 2 h (^{1}H NMR); the mixture could be separated by chromatography on silica gel with ether–petroleum ether (1:3).

Methyl (*E*)-2-Methoxy-3-formyl-3-pentenoate (17). The oily aldehyde was obtained as a byproduct of methylation of the enolate **5** with methyl iodide (see synthesis of **8**) and purified by rechromatography in the same system: UV (C_2H_5OH) λ_{max} 222 nm; ^1H NMR ($CDCl_3$) δ 2.14 (CH_3), 3.42 (OCH_3), 3.74 ($COOCH_3$), 4.93 (H2), 6.87 (H4), 9.40 (CHO) [$^3J_{4,Me}$ = 7 Hz]; mass spectrum, *m/e* (relative intensity, fragment) 172 (1, M), 157 (2, M - CH_3), 140 (10, M - CH_3OH), 113 (100, M - $COOCH_3$); an analytically pure sample of this material was not obtained. The configuration of the double bond was established from a NOE difference spectrum (see text).

Methyl (*E*)-[2-(Acetyloxy)-6-oxo-3,6-dihydro-2*H*-pyran-3-ylidene]acetate (19). The hemiacetal **2** (300 mg) was dissolved in a mixture of acetic anhydride and pyridine (2 mL of each) and left for 3 h at room temperature. Evaporation of the dark product and rapid chromatography [2 × 20 cm silica gel column, ether–petroleum ether (1:2)] yielded 320 mg (86%) of **19** as a colorless thick oil. The material could also be obtained by prolonged heating of **2** with an excess of neat acetyl chloride: IR (film) 1740 (s), 1720 (s), 1640 (w), 1585 (w) cm^{-1}; UV (CH_3OH) λ_{max} 264 nm; ^1H NMR ($CDCl_3$) δ 2.12 (CH_3CO), 3.79 ($COOCH_3$), 6.21 (br s, Hα), 6.31 (dd, H5), 6.95 (br s, H2), 8.33 (br d, H4) [$^3J_{4,5}$ = 10 Hz, $^5J_{\alpha,5}$ = 2 Hz].

Anal. Calcd for $C_{10}H_{10}O_6$: C, 53.10; H, 4.46. Found: C, 53.25; H, 4.30.

(*E*)-(2-Hydroxy-6-oxo-3,6-dihydro-2*H*-pyran-3-ylidene)-acetic Acid (29).[4] The hemiacetal **2** (1 g) was hydrolyzed in 0.1 M NaOH (250 mL) during 5 min at 0 °C. The solution was acidified (2 M HCl), saturated with NaCl, and extracted with five 100-mL portions of ether, the extract dried ($MgSO_4$) and evaporated, and the residue recrystallized from ether–acetone: yield 500 mg (54%); mp 150–153 °C dec; IR (KBr) 3400–2500 (m), 3300 (s), 1720–1700 (s), 1640 (m), 1580 (m) cm^{-1}; UV λ_{max} 265 nm (ϵ 19 000) in 0.01 M HCl, λ_{max} 265 nm (ϵ 8000) in 0.1 M phosphate buffer (the latter solution also exhibits absorption of **22** at λ_{max} 375 nm, ϵ 1300, see text); ^1H NMR [$(CD_3)_2CO$] δ 4.7–5.1 (br, OH and COOH), 6.19 (br d, H5), 6.28 (br s, H2 and Hα), 8.16 (br d, H4) [$^3J_{4,5}$ = 10 Hz].

Anal. Calcd for $C_7H_6O_5$: C, 49.42; H, 3.55. Found: C, 49.55; H, 3.79.

Treatment of **44** (270 mg) with 0.1 M NaOH as described above also yielded **29** (170 mg or 68%), as identified by ^1H NMR.

1-Monomethyl and Dimethyl Esters of (*E*)-2-Methoxy-3-formyl-3-hexenedioic Acid (32 and 33). The hemiacetal **22** (100 mg) in 5 mL of methanol was treated with a 3-fold molar excess of sodium methoxide in methanol. After 2 h at room temperature, the solution was neutralized with a cation exchanger (Dowex 50W, H^+ form) and evaporated and the residue chromatographed on a 1 × 30 cm silica gel column using ether–petroleum ether (2:1) containing 1% of acetic acid, to give 70 mg (60%) of **32** as a colorless gum: ^1H NMR ($CDCl_3$) δ 3.40 (OCH_3), 3.73 ($COOCH_3$), 3.73 (d, CH_2), 5.02 (s, CH), 6.93 (t, olefinic, ^3J = 7 Hz), 9.1 (br, COOH), 9.52 (CHO). Methylation with ethereal diazomethane yielded **33**: ^1H NMR ($CDCl_3$) δ 3.37 (OCH_3), 3.67 and 3.72 (2 $COOCH_3$), ca. 3.70 (CH_2, overlapped by the ester signals), 4.97 (s, CH), 7.00 (t, olefinic, ^3J = 7 Hz), 9.50 (CHO). The configuration of the double bond was established from a NOE difference spectrum. An analytically pure sample was not obtained.

(*E*)-2-Hydroxy-5-oxo-2,5-dihydro-3-furanpropenoic Acid (36). The hemiacetal **2** (2.5 g) was refluxed in 200 mL of 0.5 M HCl during 1 h. The solution was treated with charcoal, saturated with NaCl, and extracted with six 100-mL portions of ether. The extract was dried ($MgSO_4$) and evaporated and the residue washed with ether to give 1.1 g (48%) of fine, white crystals of **36**, recrystallized from ether–acetone: mp ca. 220 °C dec (dependent on rate of heating); IR (KBr) 3500–2500 (m), 1740 (s), 1700 (s), 1650 (m), 1595 (m) cm^{-1}; UV (0.01 M HCl) λ_{max} 261 nm (ϵ 25 000), λ_{max} 259 nm in methanol; ^1H NMR [$(CD_3)_2CO$] δ 3.80 (br, OH and COOH), 6.45 (br s, H2 and H4), 6.58 and 7.49 (each d, respectively Hα and Hβ of the propenoic acid moiety) [$^3J_{\alpha,\beta}$ = 16 Hz].

Anal. Calcd for $C_7H_6O_5$: C, 49.42; H, 3.55. Found: C, 49.38; H, 3.78.

The acid **36** (100 mg) was dissolved in 30 mL of 0.1 M NaOH at 0 °C. After 5 min, the solution was acidified and the product isolated as described above and examined by ^1H NMR; only unchanged starting material was observed (recovery 73 mg or 73%).

Hydrolysis of **37** (100 mg) as described for **16** (see the synthesis of **44**) yielded 60 mg (70%) of **36**.

Methyl (*E*)-2-Methoxy-5-oxo-2,5-dihydro-3-furanpropenoate (37). The acid **36** (100 mg) was refluxed in 50 mL of 3% methanolic HCl during 30 min, the solution evaporated, and the residue chromatographed on a 30 × 1.5 cm silica gel column with benzene–ethyl acetate (3:1) to give 90 mg (84%) of **37**, recrystallized from ether–petroleum ether: mp 79–80 °C; IR (KBr) 1810 (s), 1780 (s), 1720 (s), 1645 (m), 1605 (s) cm^{-1}; UV (CH_3OH) λ_{max} 259 nm (ϵ 26 000); ^1H NMR ($CDCl_3$) δ 3.57 (OCH_3), 3.82 ($COOCH_3$), 6.00 (br s, H2), 6.32 (br s, H4), 6.45 and 7.47 (each d, respectively Hα and Hβ of the propenoate moiety) [$^3J_{\alpha,\beta}$ = 16 Hz]; mass spectrum, *m/e* (relative intensity, fragment) 198 (1, M), 167 (4, M - OCH_3), 166 (2, M - CH_3OH), 139 (11, M - $COOCH_3$), 123 (50, M - OCH_3 - CO_2), 79 (100), 51 (92).

Anal. Calcd for $C_9H_{10}O_5$: C, 54.55; H, 5.09. Found: C, 54.25; H, 4.93.

Methyl (*E*)-2-Hydroxy-5-oxo-2,5-dihydro-3-furanpropenoate (38). The acid **36** (500 mg) dissolved in methanol was treated with a slight excess of ethereal diazomethane, the excess diazomethane destroyed with acetic acid, the solution evaporated, and the residue recrystallized thrice from ether–acetone: yield 350 mg (65%). The ester could also be obtained from **37** (200 mg) by stirring with 50 mL of 1 M HCl during 2 h at room temperature: yield 150 mg (81%); mp 134–135 °C; IR (KBr) 3280 (s), 1780 (s), 1760 (s), 1705 (s), 1645 (m), 1590 (s) cm^{-1}; UV (CH_3OH) λ_{max} 259 nm; ^1H NMR [$(CD_3)_2CO$] δ 3.78 ($COOCH_3$), 6.52 (br s, H2 and H4), 6.63 and 7.53 (each d, respectively Hα and Hβ of the propenoate moiety), 7.20 (OH) [$^3J_{\alpha,\beta}$ = 16.5 Hz].

Anal. Calcd for $C_8H_8O_5$: C, 52.18; H, 4.38. Found: C, 52.10; H, 4.43.

(*E*)-2-Methoxy-5-oxo-2,5-dihydro-3-furanpropenoic Acid (39). The hemiacetal **2** (200 mg) was treated with tetramethylammonium hydroxide in methanol as described for the synthesis of **45**, but using twice as much of the base; a similar workup afforded 85 mg (42%) of **39**, recrystallized from tetrahydrofuran–hexane: mp 148–150 °C; IR (KBr) 3500–2500 (m), 1800 (m), 1760 (s), 1680 (s), 1635 (m), 1605 (m) cm^{-1}; UV (CH_3OH containing a trace of HCl) λ_{max} 259 nm (ϵ 26 000); ^1H NMR [$(CD_3)_2CO$] δ 3.28 (br, COOH), 3.58 (OCH_3), 6.26 (br s, H2), 6.57 (br s, H4), 6.51 and 7.51 (each d, respectively Hα and Hβ of the propenoic acid moiety) [$^3J_{\alpha,\beta}$ = 16 Hz].

Anal. Calcd for $C_8H_8O_5$: C, 52.18; H, 4.38. Found: C, 52.30; H, 4.18.

The acid was also formed upon alkaline hydrolysis of **51** (50 mg) carried out as described for **48** (see synthesis of **49**) (^1H NMR).

Methyl (*E*)-(2-Methoxy-6-oxo-3,6-dihydro-2*H*-pyran-3-ylidene)acetate (40). The hemiacetal **2** (300 mg) was dissolved in 30 mL of 3% methanolic HCl at 0 °C and the solution evaporated as quickly as possible (ca. 15 min). The residue was chromatographed on a 30 × 1.5 cm silica gel column with benzene–ethyl acetate (4:1) to give 200 mg of **40** (62%) as a colorless oil: IR ($CHCl_3$) 1730 (s), 1640 (w), 1580 (w) cm^{-1}; UV (H_2O) λ_{max} 265 nm (ϵ 19 000); ^1H NMR ($CDCl_3$) δ 3.62 (OCH_3), 3.80 ($COOCH_3$), 5.60 (br s, H2), 6.14 (br s, Hα), 6.18 (dd, H5), 8.21 (br d, H4) [$^3J_{4,5}$ = 10 Hz, $^5J_{\alpha,5}$ = 2 Hz]; mass spectrum, *m/e* (relative intensity, fragment) 198 (2, M), 167 (16, M - OCH_3), 166 (10, M - CH_3OH), 139 (63, M - $COOCH_3$), 79 (90), 51 (100).

Anal. Calcd for $C_9H_{10}O_5$: C, 54.55; H, 5.09. Found: C, 54.25; H, 5.33.

The ester was also formed as a 2:5 mixture with **16** upon heating of **2** in methanol containing 3% of HCl for 2 h (^1H NMR).

(*E*)-(2-Methoxy-6-oxo-3,6-dihydro-2*H*-pyran-3-ylidene)-acetic Acid (41). The acetal **46** (1 g) was stirred with 100 mL of 2 M NaOH during 6 h at room temperature. The solution was saturated with NaCl, acidified with 1 M HCl, and extracted with five 100-mL portions of ether. The dried ($MgSO_4$) extract was treated with charcoal and evaporated and the residue recrystallized from ether–petroleum ether to give 500 mg (67%) of **41**: mp 118–120 °C dec (gas evolution); IR (KBr) 3300–2800 (s), 1720 (s), 1700 (s) cm^{-1}; UV (0.01 M HCl) λ_{max} 265 nm; ^1H NMR [$(CD_3)_2CO$] δ 3.59 (OCH_3), 5.83 (br s, H2), 6.20 (dd, H5), 6.30 (br s, Hα), 8.21 (br d, H4), 10.70 (COOH) [$^3J_{4,5}$ = 10 Hz, $^3J_{\alpha,5}$ = 2 Hz].

Anal. Calcd for $C_8H_8O_5$: C, 52.18; H, 4.38. Found: C, 52.05; H, 4.52.

Methyl (*Z*)-(2-Methoxy-6-oxo-3,6-dihydro-2*H*-pyran-3-ylidene)acetate (42). The *E* isomer **40** (100 mg) was heated under reflux for 4 h in 100 mL of toluene with 15 mg of iodine, the solution was evaporated, and the 1:1 mixture of **40** and **42** obtained (^{1}H NMR) was resolved on a 2 × 25 cm silica gel column using ether–petroleum ether (1:3). The yield was 41 mg of **40** (eluted first, 41% recovery) and 32 mg of **42** (32%), recrystallized from ether–petroleum ether: mp 71–73 °C; IR (KBr) 1720 (s), 1710 (s), 1630 (m), 1595 (w) cm^{-1}; UV (CH_3OH) λ_{max} 266 nm (ϵ 23 000); ^{1}H NMR ($CDCl_3$) δ 3.68 (OCH_3), 3.81 ($COOCH_3$), 6.11 (br s, Hα), 6.20 (d, H5), 6.66 (br s, H2), 6.95 (d, H4) [$^3J_{4,5}$ = 10 Hz].

Anal. Calcd for $C_9H_{10}O_5$: C, 54.55; H, 5.09. Found: C, 54.35; H, 5.21.

Methyl (*Z*)-[2-(Acetyloxy)-6-oxo-3,6-dihydro-2*H*-pyran-3-ylidene]acetate (43). The *E* isomer **19** (200 mg) was heated under reflux for 3 h in 100 mL of toluene containing 15 mg of iodine. Evaporation of a sample of the solution showed the presence of **19** and **43** in a ratio of 1:1 (^{1}H NMR); additional equilibration (1 h) did not change the ratio. The solution was evaporated and the residue resolved on a 2 × 25 cm silica gel column using ether–petroleum ether (1:1), to give (in order of evolution) 80 mg of **19** (40% recovery) and 90 mg of **43** (45%), recrystallized from tetrahydrofuran–hexane: mp 95–96 °C; IR (KBr) 1755 (s), 1740 (s), 1705 (s), 1635 (m), 1600 (m) cm^{-1}; UV (CH_3OH) λ_{max} 265 nm (ϵ 24 000); ^{1}H NMR ($CDCl_3$) δ 2.08 (CH_3CO), 3.78 ($COOCH_3$), 6.15 (br s, Hα), 6.22 (sharp d, H5), 7.03 (br d, H4), 7.83 (br s, H2) [$^3J_{4,5}$ = 10 Hz].

Anal. Calcd for $C_{10}H_{10}O_6$: C, 53.10; H, 4.46. Found: C, 53.11; H, 4.47.

Methyl (*Z*)-2-Hydroxy-5-oxo-2,5-dihydro-3-furanpropenoate (44). The acetal **16** (340 mg) was hydrolyzed during 15 min in 50 mL of refluxing 0.1 M HCl. The solution was rapidly chilled and extracted with three 50-mL portions of ether, the dried ($MgSO_4$) extract evaporated, and the residue taken up in methylene chloride. The insoluble part (50 mg or 17%) was identified as **36** (^{1}H NMR). The soluble part was rapidly chromatographed on a 20 × 2 cm silica gel column with benzene–ethyl acetate (2:1). About 70 mg (20% recovery) of **16** was eluted before 120 mg (38%) of **44**: mp 72–72.5 °C (from ether–petroleum ether); IR (KBr) 3260 (br, s), 1760 (s), 1740 (s), 1720 (s), 1630 (w), 1610 (w) cm^{-1}; UV (CH_3OH) λ_{max} 256 nm (ϵ 13 500), λ_{max} 259 nm (ϵ 13 400) at pH 2, 260 nm (ϵ 7500) at pH 9; ^{1}H NMR ($CDCl_3$) δ 3.82 ($COOCH_3$), 5.00 (br, OH), 6.27 and 6.68 (each d, respectively Hα and Hβ of the propenoate moiety), 6.40 and 6.47 (both br s, protons of the dihydrofuran moiety) [$^3J_{\alpha,\beta}$ = 13 Hz]; mass spectrum, *m/e* (relative intensity, fragment) 184 (0.3, M), 167 (1, M – OH), 166 (2, M – H_2O), 153 (6, M – OCH_3), 152 (7, M – CH_3OH), 140 (45, M – CO_2), 125 (25, M – $COOCH_3$), 123 (41, M – OH – CO_2), 79 (68), 51 (100).

Anal. Calcd for $C_8H_8O_5$: C, 52.18; H, 4.38. Found: C, 51.90; H, 4.60.

(*Z*)-2-Methoxy-5-oxo-2,5-dihydro-3-furanpropenoic Acid (45). The hemiacetal **2** (500 mg) in 200 mL of methanol was treated with 1 mmol of methanolic tetramethylammonium hydroxide (ca. 1 mL of a 20% solution). After 20 min at room temperature, the solution was neutralized with an excess of a cation exchanger (Dowex 50 W, H^+ form) and evaporated and the residue rapidly chromatographed on a 2 × 30 cm silica gel column using ether–petroleum ether (3:1) containing 2% of acetic acid, to give 435 mg (87%) of pure **45**, recrystallized from ether–petroleum ether: mp 97–100 °C; IR (KBr) 3500–2500 (m), 1820 (m), 1760 (s), 1695 (s), 1640 (m), 1590 (m) cm^{-1}; UV (CH_3OH) λ_{max} 260 nm; ^{1}H NMR ($CDCl_3$) δ 3.56 (OCH_3), 6.08 (br s, H2), 6.59 (br s, H4), 6.25 and 6.65 (each d, respectively Hα and Hβ of the propenoic acid moiety), 6.6 (br, COOH) [$^3J_{\alpha,\beta}$ = 12.5 Hz].

Anal. Calcd for $C_8H_8O_5$: C, 52.18; H, 4.38. Found: C, 52.45; H, 4.22.

Dimethyl (2*E*,4*Z*)-3-(Dimethoxymethyl)-2,4-hexadienedioate (46).[4] The hemiacetal **2** (5 g) was refluxed during 6 h in a 4:1 mixture of 3% methanolic HCl and trimethyl orthoformate and the solution evaporated to give a quantitative yield of practically pure, oily acetal **46**. An analytical sample was obtained by column chromatography on neutral alumina (Brockmann III) with benzene–ethyl acetate (3:1) as solvent: IR (film) 1725 (s), 1670 (w), 1620 (w) cm^{-1}; UV (CH_3OH) λ_{infl} 245 nm (ϵ 5700); ^{1}H NMR ($CDCl_3$) δ 3.37 (OCH_3), 3.71 (2 $COOCH_3$), 5.15 (br s, CH), 5.99 (sharp d, H5), 6.22 (br s, H2), 6.96 (br d, H4) [$^3J_{4,5}$ = 12 Hz]; mass spectrum, *m/e* (relative intensity, fragment) 213 (3, M – OCH_3), 185 (9, M – $COOCH_3$), 75 [100, $CH(OCH_3)_2$].

Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.20; H, 6.43.

Dimethyl (2*E*,4*E*)-3-Formyl-2,4-hexadienedioate (47). The 2*E*,4*Z* isomer **13** (200 mg) was refluxed for 2 h in 50 mL of toluene with 5 mg of iodine. The solution was evaporated and the residue recrystallized from petroleum ether to give 110 mg (55%) of **47**: mp 57–58 °C; IR (KBr) 1725 (s), 1705 (s), 1640 (m) cm^{-1}; UV (CH_3OH) λ_{max} 262 nm (ϵ 18 500); ^{1}H NMR ($CDCl_3$) δ 3.82 and 3.88 ($COOCH_3$), 6.60 (br s, H2), 7.00 (sharp d, H5), 8.11 (dq, H4), 9.72 (d, CHO) [$^3J_{4,5}$ = 16.5 Hz, $^4J_{2,4}$ = 1 Hz, $^4J_{4,CHO}$ = 2 Hz].

Anal. Calcd for $C_9H_{10}O_5$: C, 54.55; H, 5.09. Found: C, 54.50; H, 5.14.

Dimethyl (2*E*,4*E*)-3-(Dimethoxymethyl)-2,4-hexadienedioate (48). The 2*E*,4*Z* isomer **46** (400 mg) was irradiated in acetonitrile (200 mL, Pyrex flask) during 6 h by using a medium-pressure mercury arc. The solution was evaporated and the product (**46** and **48** in a ratio of 1:1, by ^{1}H NMR) hydrolyzed for 4 h in 0.01 M HCl, as described for the synthesis of **13**. The product was chromatographed on a 2 × 20 cm alumina column (Brockmann III) with toluene–ethyl acetate (4:1), to give 150 mg (38%) of oily **48**: IR (film) 1730 (s), 1622 (s), 1605 (s) cm^{-1}; UV (CH_3OH) λ_{max} 262 nm (ϵ 20 000); ^{1}H NMR ($CDCl_3$) δ 3.32 (OCH_3), 3.79 (2 $COOCH_3$), 5.08 (br s, CH), 6.37 (br s, H2), 6.47 (sharp d, H5), 8.40 (br d, H4) [$^3J_{4,5}$ = 16.5 Hz]; mass spectrum, *m/e* (relative intensity, fragment) 244 (0.01, M), 213 (3, M – OCH_3), 185 (5, M – $COOCH_3$), 75 [100, $CH(OCH_3)_2$].

Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.25; H, 6.41.

(2*E*,4*E*)-3-(Dimethoxymethyl)-2,4-hexadienedioic Acid (49). The dimethyl ester **48** (280 mg) was stirred with 50 mL of 2 M NaOH during 6 h at room temperature. The solution was saturated with NaCl, acidified with 1 M HCl, and extracted with six 50-mL portions of ether. The dried ($MgSO_4$) extract was evaporated and the residue recrystallized from ether–petroleum ether to give 106 mg (40%) of **49**: mp 138–142 °C dec (gas evolution); IR (KBr) 3300–2500 (s), 1700 (s), 1650 (s), 1615 (m) cm^{-1}; ^{1}H NMR [$(CD_3)_2CO$] δ 3.35 (OCH_3), 5.20 (br s, CH), 6.38 (br s, H2), 6.48 (br d, H5), 8.42 (br s, H4), 10.15 (br, COOH) [$^3J_{4,5}$ = 16.5 Hz].

Anal. Calcd for $C_9H_{12}O_6$: C, 50.01; H, 5.60. Found: C, 50.25; H, 5.64.

Dimethyl (2*Z*,4*E*)-3-Formyl-2,4-hexadienedioate (50). The 2*E*,4*Z* isomer **13** (200 mg) was equilibrated for 7 h as described for the preparation of **47**. The product (**47** and **50** in a ratio of 3:1, by ^{1}H NMR) was rapidly chromatographed on a 2 × 30 cm silica gel column eluted with ether–petroleum ether (1:4) to give 25 mg (12.5%) of yellowish **50** (eluted first), recrystallized from pentane: mp 48–50 °C; IR (KBr) 1720 (s), 1700 (s), 1625 (w), 1595 (m) cm^{-1}; UV (CH_3OH) λ_{max} 261 nm; ^{1}H NMR ($CDCl_3$) δ 3.78 and 3.83 ($COOCH_3$), 6.57 (sharp d, H5), 6.67 (br s, H2), 7.30 (br d, H4), 10.59 (d, CHO) [$^3J_{4,5}$ = 16 Hz, $^4J_{2,CHO}$ = 2 Hz].

Anal. Calcd for $C_9H_{10}O_5$: C, 54.55; H, 5.09. Found: C, 54.72; H, 4.95.

The aldehyde was considerably less stable than **13** and **47**, quickly turning to a yellow polymeric mass at room temperature.

Dimethyl (2*Z*,4*E*)-3-(Dimethoxymethyl)-2,4-hexadienedioate (51). The ester **37** (600 mg) was refluxed in 100 mL of methanol–trimethyl orthoformate (4:1) containing 3% of hydrogen chloride for 2 h. The mixture was evaporated and the residue chromatographed on a 4 × 35 cm silica gel column eluted with ether–petroleum ether (1:1) to give 280 mg (38%) of **51** (eluted before unchanged **37**), recrystallized from ether–petroleum ether: mp 55.5–56.5 °C; IR (KBr) 1710 (s), 1635 (m), 1615 (s) cm^{-1}; UV (CH_3CN) λ_{max} 261 nm (ϵ 20 000); ^{1}H NMR ($CDCl_3$) δ 3.44 (OCH_3), 3.77 (2 $COOCH_3$), 6.05 (sharp s, CH), 6.18 (br s, H2), 6.61 (sharp d, H5), 7.23 (br d, H4) [$^3J_{4,5}$ = 16.0 Hz]; mass spectrum, *m/e* (relative intensity, fragment) 213 (8, M – OCH_3), 185 (15, M – $COOCH_3$), 75 [100, $CH(OCH_3)_2$].

Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.12; H, 6.59.

Dimethyl (2Z,4Z)-3-(Dimethoxymethyl)-2,4-hexadienedioate (53). The ester **16** (300 mg) was partially converted to **53** and the product purified as described for the conversion of **37** into **51** to give, in the order of elution from the column, 100 mg (27%) of oily **53**, 40 mg of a mixture of **37** and **46**, and 150 mg of **16** (50% recovery). **53**: IR (film) 1720 (s), 1640 (m) cm^{-1}; UV (CH_3OH) λ_{max} 248 nm (ϵ 7900); ^1H NMR ($CDCl_3$) δ 3.46 (OCH_3), 3.72 and 3.75 ($COOCH_3$), 5.98 (s, CH), 5.99 (sharp d, H5), 6.26 (br s, H2), 6.73 (br d, H4) [$^3J_{4,5}$ = 12.5 Hz]; mass spectrum, *m/e* (relative intensity, fragment) 213 (4, M - OCH_3), 185 (20, M - $COOCH_3$), 75 [100, $CH(OCH_3)_2$].

Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.29; H, 6.71.

Alkaline hydrolysis of **53** (50 mg) carried out as described for **48** (see synthesis of **49**) gave a mixture of **41** and **45** in a ratio of 1:1 (^1H NMR). Acid-catalyzed hydrolysis of **53** (100 mg) carried out as described for **46** (see synthesis of **13**) gave a complex mixture containing **13** as a main product (^1H NMR), not further investigated.

(5R*,6S*)-2,8-Dioxo-6-methoxy-1,7-dioxaspiro[4.4]nonane (55). A flask containing **45** (50 mg) was immersed for 2 min in an oil bath heated to 200 °C, to give practically pure **55** as a thick oil: IR (film) 1800-1760 (s), 1600 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.65 and 3.09 (each d, CH_2, $^2J_{AB}$ = 17.5 Hz), 3.54 (OCH_3), 5.24 (CH), 6.27 and 7.49 (each d, respectively H3 and H4, $^3J_{3,4}$ = 6 Hz); mass spectrum, *m/e* (relative intensity, fragment) 184 (0.2, M), 153 (14, M - OCH_3), 124 (100, M - OCH_3 - HCO).

Anal. Calcd for $C_8H_8O_5$: C, 52.18; H, 4.38. Found: C, 52.47; H, 4.11.

Trimethyl (1Z,3E)-1,3-Butadiene-1,2,4-tricarboxylate (56). A mixture of 250 mg of **36**, 3 g of silver oxide, and 4 mL of methyl iodide in 25 mL of acetone was shaken overnight, filtered, and evaporated and the residue chromatographed on a 2 × 28 cm silica gel column, using benzene-ethyl acetate (4:1). Evaporation of appropriate fractions afforded 60 mg (18%) of the triester, eluted before 60 mg of **37**; the product was recrystallized from ether-petroleum ether: mp 51-52 °C; IR (KBr) 1755 (s), 1720 (s), 1630 (m), 1615 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.78 (2 $COOCH_3$), 3.91 ($COOCH_3$), 6.14 (d, H4), 6.17 (s, H1), 7.26 (d, H3) [$^3J_{3,4}$ = 16 Hz].

Anal. Calcd for $C_{10}H_{12}O_6$: C, 52.63; H, 5.30. Found: C, 52.80; H, 5.14.

Registry No. **1**, 119183-12-9; **2**, 81158-22-7; **3**, 119183-13-0; **5**, 119183-14-1; **6**, 119183-15-2; **7**, 119183-16-3; **8**, 119183-17-4; **9**, 119183-18-5; **10**, 119183-19-6; **11**, 119183-20-9; **12**, 119183-21-0; **13**, 119183-22-1; **14**, 119207-75-9; **15**, 119183-23-2; **16**, 119183-24-3; **17**, 119207-76-0; **18**, 81158-24-9; **19**, 119183-25-4; **23**, 119183-26-5; **24**, 81158-25-0; **25**, 119183-27-6; **26**, 119183-28-7; **29**, 119183-29-8; **30**, 81158-30-7; **31**, 119183-30-1; **32**, 119183-31-2; **33**, 119183-32-3; **36**, 119183-33-4; **37**, 119183-34-5; **38**, 119183-35-6; **39**, 119183-36-7; **40**, 119183-37-8; **41**, 119183-38-9; **42**, 119183-39-0; **43**, 119183-40-3; **44**, 119183-41-4; **45**, 119183-42-5; **46**, 119183-43-6; **47**, 119183-44-7; **48**, 119183-45-8; **49**, 119183-46-9; **50**, 119183-47-0; **51**, 119183-48-1; **53**, 119183-49-2; **55**, 119183-50-5; **56**, 119183-51-6.

Catalytic Synthesis of Vinyl Carbamates from Carbon Dioxide and Alkynes with Ruthenium Complexes

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Terminal alkynes react with carbon dioxide and secondary amines in the presence of ruthenium complexes to afford vinyl carbamates in one step. The reaction has been performed with phenylacetylene, hexyne, and acetylene and with dialkylamines, morpholine, piperidine, and pyrrolidine. Mononuclear ruthenium complexes such as $RuCl_2(PR_3)$(arene) and $RuCl_2$(norbornadiene)$(pyridine)_2$ for monosubstituted alkynes in the range 100-125 °C and [$RuCl_2$(norbornadiene)]$_n$ or even $RuCl_3 \cdot 3H_2O$ in the case of acetylene at 90 °C appear to be the best catalyst precursors. The addition of the carbamate takes place essentially at the terminal carbon of the alkyne and ruthenium-vinylidenes are suggested as catalytic active species to account for the observed regioselectivity.

Vinyl carbamates, or enol carbamates, have been shown to be useful intermediates for the access to agricultural chemicals, pharmaceutical product intermediates, or precursors of transparent polymers.[1] General methods leading to alkyl carbamates involving isocyanates or chloroformates, or using catalytic carbonylation processes of amines[2] or nitroarenes[3] in the presence of alcohols, are not suitable for the direct access to enol carbamates. These unsaturated carbamates have been previously prepared either by dehydrohalogenation of α-halogeno-[4] or β-halogenoalkyl carbamates[5] or by addition of amines to the vinyl chloroformates[6,7] resulting from dehydrohalogenation[8] or from enolmercury(II) derivatives.[6] The in situ generation of alkylidenecarbenes in the presence of isocyanates has also led to N-monosubstituted vinyl carbamates.[9] Each of these multistep syntheses of enol carbamates uses phosgene at one stage.

We have been looking for processes allowing the replacement of phosgene by carbon dioxide which, in con-

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