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The First Solid Enols of Anhydrides. Structure, Properties, and Enol/Anhydride Equilibria[1]

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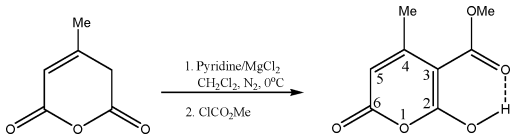
Received June 8, 2007



Reaction of β-methylglutaconic anhydride with NaOMe followed by reaction with methyl or phenyl chloroformate gave the corresponding *O*-methoxy (and *O*-phenoxy) carbonylation derivatives. Reaction of the anhydride with $MgCl_2$/pyridine, followed by methyl chloroformate gave C-methoxycarbonylation at C3 of the anhydride. The product (**4**) was previously suggested by calculation to be the enol of the anhydride **5** and this is confirmed by X-ray crystallography (bond lengths: C−OH, 1.297 Å; C1C2 1.388 Å; HO···O═C(OMe) distance 2.479 Å) making it the first solid enol of an anhydride. In $CDCl_3$, CD_3CN, or C_6D_6 solution it displays the OH as a broad signal at ca. 15 ppm, suggesting a hydrogen bond with the CO_2Me group. NICS calculations indicate that **4** is nonaromatic. With D_2O in $CDCl_3$ both the OH and the C5H protons exchange rapidly the H for D. An isomeric anhydride **5a** of **5** is formed in equilibrium with **4** in polar solvents. In solution, anhydride(s)/enol equilibria are rapidly established with K_{enol} of 6.40 (C_6D_6, 298 K), 0.52 (CD_3CN, 298 K), 9.8 ($CDCl_3$, 298 K), 22.8 ($CDCl_3$, 240 K), and decreasing K_{enol} in $CDCl_3$:CD_3CN mixtures with the increase in percent of CD_3CN. The percentage of the rearranged anhydride in $CDCl_3$:$(CD_3)_2CO$ increases with the increased percent of $(CD_3)_2CO$. In DMSO-d_6 and DMF-d_7 the observed species are mainly the conjugated base $\mathbf{4}^-$ and **5a**. Deuterium effects on the $\delta(^{13}C)$ values were determined. An analogous C2-OH enol of anhydride **15** substituted by 3-CO_2Me and 4-OCO_2Me groups was prepared. Its structure was confirmed by X-ray crystallography (CO bond length 1.298 Å, O···O distance 2.513 Å); δ(OH) = 12.04−13.22 ppm in $CDCl_3$, THF-d_8, and CD_3CN, and K_{enol} = ≥100, 7.7, and 3.4 respectively. In DMSO-d_6 enol **15** ionizes to its conjugate base. Substantial upfield shifts of the apparent δ("OH") proton on diluting the enol solutions are ascribed to the interaction of the H^+ formed with the traces of water in the solvent to give H_3O^+, which gives the alleged "OH proton" signal.

Introduction

In our previous work on enols of carboxylic acid derivatives Y′YC═C(OH)X we observed or isolated derivatives with different group X. An enol of carboxylic acid, X = OH, was observed by ^{1}H NMR as an intermediate that was converted in a few hours to the more stable acid.[2] Enols of esters, X = OR, were observed as short-lived intermediates in solution in systems Ar_2C═C(OH)OR having bulky aryl substituents,[3] and were isolated as stable solid species or observed in solution in $(MeO_2C)_n$-substituted cyclopentadienes, n = 3−5.[4] A large number of amides, X = NRR′, were either observed in solution or isolated as the solid species.[5] Cyanomonothiomalonamides

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10.1021/jo071206m CCC: $37.00
Published on Web 10/31/2007

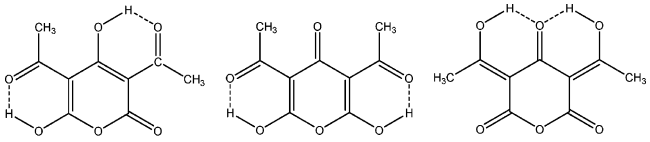
gave simultaneously the enols and thioenols of carboxylic and thiocarboxylic acids.[5h] However, although calculations of the relative pK_{enol} (=−log K_{enol}) value of eq 1

$$CH_3COX \overset{K_{enol}}{\rightleftharpoons} CH_2{=}C(OH)X \qquad (1)$$

for derivatives of carboxylic acids gave for the anhydride where X = OC(=O)H the lowest K_{enol} value among heteroatoms X[6] [B3LYP/6-31G** pK_{enol} values for X: OCHO, 17.6 < Br, 18.7 ≈ Cl, 18.6 < F, 19.8 < NMe_2, 21.2 ≈ NH_2, 21.3 < OH, 22.0 ≈ OMe, 22.3; for X = Cl, Br the pK_{enol} values are slightly lower than for X = OC(=O)H at MP2(full)/6-31G** and CCSD(T)/6-311**][6a] enols of anhydrides are rare species so far. The literature claim for formation of $H_2C{=}C(OH)OCOMe$ as an intermediate has little evidence.[7] It was also claimed that distillation of 2-phenylbutyric anhydride gave a mixture of the anhydride and a mono- and a dienol,[8] but we have shown experimentally that the product is not the enol but a mixture of ethyl phenyl ketene and α-phenylbutyric acid, and that the enol is computationally >13 kcal/mol less stable than the anhydride.[9] Enols of mixed acetic−sulfuric anhydride were also suggested,[10] but calculation suggested that the enol is highly unstable compared with the anhydride.[9]

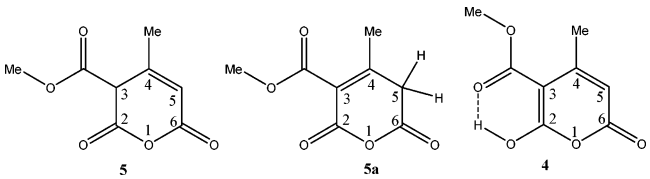
Enols were also claimed to exist in the 5-methyl-2*H*-pyran-2,6(3*H*)-dione (γ-methylglutaconic anhydride) system,[11] but calculations show that this is unlikely.[9] NMR data on the related 3-acetyl-2*H*-pyran-2,6(3*H*)-diones was interpreted in terms of mixtures of isomeric enols and anhydrides.[12]

The groups of Ang[13] and Hansen[14] have shown that 3,5-diacetyltetrahydropyran-2,4,6-trione appears in solution as a mixture of several tautomers and rotamers of hydrogen-bonded enols. They include singly and doubly hydrogen-bonded mono- and dienols on the 3,5-acetyl group(s) to the 4-carbonyl, but also species **1** and **2** which should be regarded as an enol and bis-enol of anhydride, hydrogen bonded to the CO of the acetyl group(s). This is noteworthy since the calculation indicates that enolization on a ketone-CO group is several orders of magnitude more favorable than that on an anhydride-CO.[6] An IR study suggests that **1** is the preferred species in the solid state. Structure **1** is supported by the ^{1}H NMR spectrum, which shows two different Me and two different OH groups. The broader δ(OH) at 16.05 is ascribed to the more acidic and more readily exchangeable C6-OH. The appearance of 15−20% of rotamer **2** is deduced from minor signals at δ 2.76 (Me) and 16.55 (OH).[13] However, two X-ray determinations had shown that in the solid state **3** is a bis-enol on the acetyl groups, hydrogen bonded to the 4-CO group.[15]



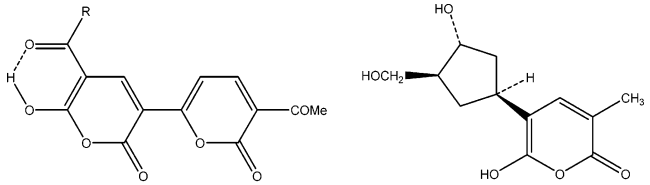
1 **2** **3**

Consequently, we conducted a computational search for possible candidates of enols of anhydrides which will be formed in preference over the anhydride, or of enols at other potential tautomeric sites.[9] The most likely candidate was the enol **4** of 3-(methoxycarbonyl)-2*H*-pyran-2,4(3*H*)-dione **5**, which according to B3LYP/6-31G** calculation is 7.7 kcal/mol more stable than **5** (pK_{enol} = −5.6), and which does not enolize at all on the ester carbonyl group.



5 **5a** **4**

The literature compounds **6a** and its analogue **6b** have the suggested skeleton,[16] and the authors indeed identify them as enols of anhydrides. In $CDCl_3$ the enolic hydrogen signal of **6a** in the ^{1}H NMR spectrum is at δ 8.28 ppm, a value at a much higher field than that of the enols of carboxylic acid amides and ester carrying two β-electron-withdrawing groups (EWGs).[4,5] In DMSO-d_6 where other NMR data are given, the δ(OH) is not reported and presumably the OH is not observed. No X-ray structure for the compound is available.



6a: R = OMe
6b: R = Me

7

In the Cambridge Structural Data Base only one structure may be regarded as a solid enol of an anhydride, i.e., compound **7** (nortetillapyrone) isolated from a marine sponge.[17] However, there are questions regarding this structure. The enolic hydrogen was not found, so that the compound is essentially ionic, and although the two ring C−CO bonds differ appreciably in length (1.38 and 1.45 Å), the two former anhydride carbonyl bond lengths are identical at 1.23 Å. No hydrogen bond is mentioned. We do not regard this structure as an unequivocal structure of a solid enol of an anhydride.

In the present paper we report studies on compounds **4**/**5** and related species, both in solution and in the solid state showing

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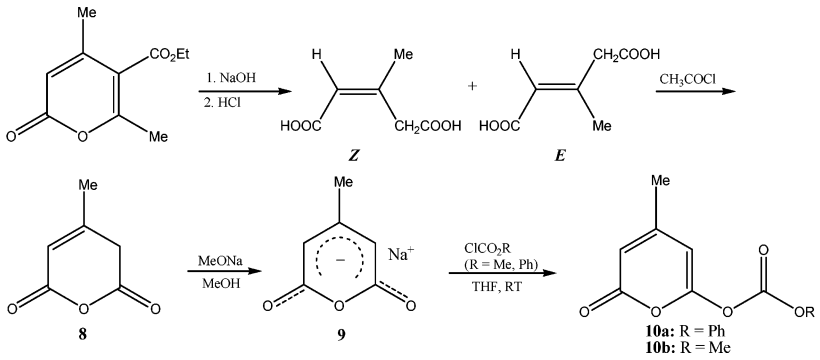
SCHEME 1



that our predictions based on the calculations are fulfilled. We describe for the first time the preparation of **4** and an analogue, their spectroscopic properties, and crystal structures, which are consistent with the suggested enol structure.

Results and Discussion

Synthesis. β-Methylglutaconic anhydride **8** was prepared according to the literature[18a−c] by cyclization of an *E*:*Z* mixture of β-methylglutaconic acids with acetyl chloride at rt. The acids were obtained as a 40:60 *Z*:*E* mixture by the hydrolysis of ethyl dehydracetate with NaOH.[18d,e] The sodium enolate **9** was obtained with methanolic NaOMe. Attempted acylation of C3 with phenyl or methyl chloroformates to obtain **4** directly, or **5** which may be further converted to **4**, or the phenyl ester analogue, led to *O*-acylation giving the carbonates **10a** and **10b** (Scheme 1). Three reagents in the presence of several bases were used to introduce the COOR group at C3 of **9**. With methyl chloroformate in the presence of NaH, *t*-BuOK, or LiH in THF at rt either the *O*-methoxycarbonylation product **10b** was formed or the anhydride **8** was recovered. With LiH in HMPA at −78 °C other products were obtained which, although not identified, had ^{1}H NMR spectra resembling those of *E* and *Z* β-methylglutaconic acid. With methyl cyanoformate, a reagent used for C-alkylation of an enolate ion,[19a] the anhydride was recovered when the base was LiH in THF, and products with spectra resembling the β-methylglutaconic acid were isolated with NaH or LDA. With methyl 1-imidazole carboxylate, another reagent for C-acylation,[19b] either a small amount of **10b** was obtained with NaH in THF or the imidazole ester was recovered with LiH in THF. More details are in Table S1 in the Supporting Information.

The structures of **10a** and **10b** were consistent with their NMR spectra, which display *two* vinylic hydrogens in the ^{1}H NMR spectra at δ of ca. 6.0 and 5.9 in $CDCl_3$ and with the MS fragmentation peaks of **10b**. Between 320 and 220 K the spectrum of **10a** in $CDCl_3$ changes very little, except for small temperature-dependent shifts.

An X-ray diffraction of **10a** confirmed unequivocally the suggested structure. The ORTEP drawing of **10a** is given in Figure 1 and selected bond lengths and angles are given in Table 1. The full crystallographic data are given in the Supporting Information.

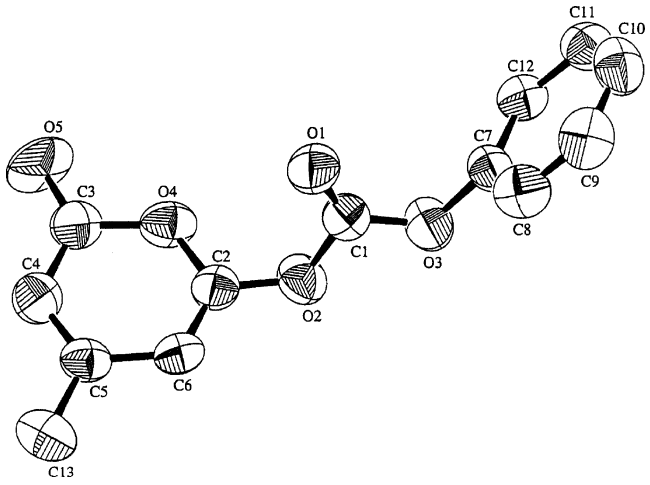


FIGURE 1. The ORTEP drawing of **10a**.

TABLE 1. Selected Bond Lengths and Angles of 10a

bond	length, Å	angle	deg
O1C1	1.172(7)	C1O2C2	116.7(5)
O2C1	1.362(7)	C1O3C7	117.7(5)
O2C2	1.341(7)	C2O4C3	121.0(5)
O3C1	1.303(7)	O1C1O2	124.9(6)
O3C7	1.388(7)	O1C1O3	129.6(7)
O4C2	1.337(7)	O2C1O3	105.5(6)
O4C3	1.385(7)	O2C2O4	112.2(6)
O5C3	1.195(7)	O2C2C6	124.6(6)
C2C6	1.319(8)	O4C2C6	123.1(6)
C3C4	1.419(9)	O4C3O5	116.5(6)
C4C5	1.340(8)	O4C3C4	115.7(6)
C5C6	1.406(8)	O5C3C4	127.8(7)
C5C13	1.479(9)	C3C4C5	122.3(6)
		C4C5C6	118.5(6)
		C4C5C13	123.3(7)
		C6C5C13	118.2(6)
		C2C6C5	119.3(6)

Synthesis and Structure of the Enol of Anhydride 4. A successful C-methoxycarbonylation of C3 was obtained by enolizing **8** with $MgCl_2$/pyridine in CH_2Cl_2.[20,21] The Mg presumably coordinates to the enol oxygen of **9**, and the coordinated species reacts with methyl chloroformate (Scheme 2). After purification, the ^{1}H NMR spectrum showed only traces

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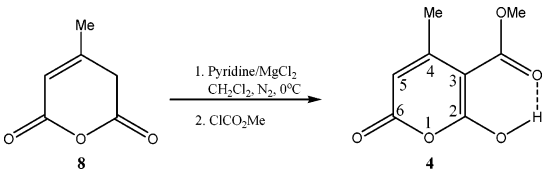
TABLE 2. The 5, 5a, and 4 Distribution and K_{Enol} Values in $CDCl_3$:CD_3CN Mixtures

$CDCl_3$:CD_3CN (v/v)	*T*, K	% **5**	% **5a**	% **4**	[**5a**]/[**5**]	K_{enol}[c]	δ(OH),[d] ppm
10:0[a]	298	1.9	7.4	90.7	3.9	9.8	15.29
10:1	298	2.8	11.2	86.0	4.0	6.1	15.22
10:2	298	2.9	14.6	82.5	5.0	4.7	15.06
10:4	298	3.9	20.6	75.5	5.3	3.1	14.88
10:6	298	4.5	25.7	69.8	5.7	2.3	
10:8	298	4.9	29.0	66.1	5.9	1.9	
10:10	298	5.0	33.0	62.0	6.6	1.6	14.85
10:12	298	5.8	35.3	58.9	6.1	1.4	
0:10[b]	298	7.3	58.1	34.6	7.9	0.52	15.49
10:0[a]	240	0.8	3.4	95.8	4.3	22.8	15.37
10:1	240	1.6	8.5	88.9	5.3	8.9	15.17
10:2	240	1.4	10.8	87.8	7.7	7.2	
10:4	240	1.7	14.1	84.2	8.3	5.3	
10:6	240	2.1	18.6	79.3	8.9	3.8	
10:8	240	1.8	17.8	80.4	9.9	4.1	
10:10	240	2.0	17.8	80.2	8.9	4.1	15.15
10:12	240	2.6	28.7	68.7	11.0	2.2	
10:14	240	2.9	31.1	66.0	10.7	1.9	
0:10[b]	240	1.2	39.5	59.3	32.9	1.46	

[a] Pure $CDCl_3$. [b] Pure CD_3CN. [c] K_{enol} = [**4**]/([**5**] + [**5a**]); based on integration of the MeO signals. [d] This signal is broad, except in pure $CDCl_3$ at 240 K. Its integration decreases with the increase of the percent of CD_3CN from 0.92 to 0.97 in pure $CDCl_3$ to 0.36 ± 0.1 in 10:4 (298 K) and 10:2 (240 K) $CDCl_3$:CD_3CN.

SCHEME 2

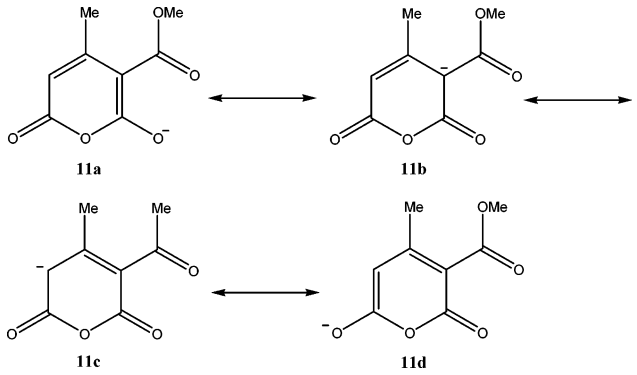


of another compound with a MeO signal, but it is unclear if this is the corresponding anhydride **5**. The NMR spectra are consistent with structure **4**. Most characteristic is a broad signal at ca. 15.5 ppm in $CDCl_3$, ascribed to the enolic OH that appears at a similar low field to those of enols of other carboxylic acid derivatives.[4,5] The δ(OH) in $CDCl_3$, CD_3CN, and $CDCl_3$:CD_3CN mixtures is given in Table 2 and it is at 15.26 ppm in C_6D_6 at 298 K. It is a broad signal at rt in all the solvents at 14.85−15.5 ppm, and due to this its integral is mostly <1 based on the vinylic proton of **4** as a reference. On cooling a $CDCl_3$ solution of **4** to 240 K the signal sharpens and its integral becomes close to unity. However, in 1:1 $CDCl_3$:CD_3CN at 240 K the signal remains broad. Also characteristic is the ^{13}C NMR signal at δ ca. 172.2 at 240 K ascribed to C_α of the enol. Low-field α-carbons were observed for other enols of carboxylic acid derivatives.

On attempts to obtain the enol analogue of **4** with a CO_2Ph rather than CO_2Me, by an identical reaction with $MgCl_2$/pyridine, the reaction product, which was not identified, was not the desired enol. Surprisingly the *O*-phenoxycarbonylation product **10a** is obtained by the reaction with $MgCl_2$/Et_3N.

Proton Exchange. When a solution of **4** in $CDCl_3$ was shaken with D_2O at 298 K and the ^1H NMR spectrum was immediately recorded, the signal at δ 15.48 disappeared immediately. The signal at δ 5.70 decreased in intensity and it disappeared faster at a higher concentration of D_2O. In the ^{13}C NMR spectrum the vinylic C5 doublet became a triplet and the intensity of the signal at δ 104.81 decreased significantly. The rapid exchange of the C5 proton seems unusual if the exchanging species is the enol **4** since enolization on the C6 carbonyl will form a

SCHEME 3



bis-enol with high ring strain. Moreover, the exchange requires the initial formation of the C5 carbanion, which will not be substantially stabilized by resonance, if at all, with the ring CO_2R. It is more likely that this exchange proceeds via a tautomer of **4**. The enolate ion of **4** is resonatively stabilized (cf. **11a**−**d**, Scheme 3) and proton or deuteron could return to the C2 and C6 oxygens (cf. **11a** and **11d**) and to C3 and to C5 (cf. **11b** and **11c**). Since **4** is more stable than its isomers, the anhydride **5**, and the rearranged anhydride **5a**, it is preferentially formed on H/D capture of **11a**. As described below, return to **5** and more to **5a** is also observed in more polar solvents which presumably promote ionization of **4** (Table 2).

A control experiment had shown that β-methylglutaconic anhydride **8** also exchanges its CH_2 and =CH protons in $CDCl_3$/D_2O, most likely via the enolate ion.

Anhydride/Enol Equilibrium in Solution. The solvent effect on the ^1H and ^{13}C NMR spectra indicates the presence of two or three isomeric species: the anhydride **5**, the tautomeric anhydride **5a**, and the enol **4**. From integration of the Me and MeO signals which usually do not overlap, the relative ratios of **5**, **5a**, and **4** given in Table 2 were determined.

In C_6D_6 at 298 K only two species are observed. The enol with singlets at δ 1.59, 3.06, 5.26, and a broad signal at 15.26 (Me, MeO, =CH, and OH, respectively) is the major species, being 86.5%, whereas the rearranged anhydride **5a** with δ 1.08 (Me), 1.88 (2H, CH_2), and 3.40 (MeO) consists of 13.5%. K_{enol} = [**4**]/[**5a**] = 6.40.[22] In CD_3CN at 298 K the three species are observed: **5** [δ 2.06 (Me), 3.78 (OMe), 4.49 (CH−CO_2), 6.18 (=CH)], **5a** [δ 2.04 (Me), 3.60 (CH_2), 3.84 (OMe], and **4** [δ 2.35 (Me), 3.93 (MeO), 5.67 (=CH), 15.7 (OH)]. The **5**:**5a**:**4** ratio is 7.3(±0.4):58.1(±0.1):34.6(±0.4), the errors quoted reflecting the difference in integration of the Me and MeO signals. K_{enol} = 0.52.[22]

From the coupled ^{13}C NMR spectra of this mixture the Me and MeO signals of **5**, **5a**, and **4** are at δ 20.0, 53.7; 19.5, 52.4; and 22.5, 53.1 ppm, respectively. The CH_2 of **5a** is at δ 36.9 and there are other signals of **4** at δ 87.5 and 104.

In 1:1 (v/v) $CDCl_3$:CD_3CN at 298 K the corresponding ^1H signals of **5**, **5a**, and **4** are at 1.85, 3.58, 4.21, 5.94; 1.85, 3.38, 3.63; and 2.14, 3.72, 5.43, 14.85 (br), respectively. The **5**:**5a**:**4** ratio is 5:33:62, K_{enol} = 1.60.[22] A few other small signals were observed but not identified. At 240 K the δ value is shifted to a lower field, the **5**:**5a**:**4** ratios are 2.0(±1.4):17.8(±1.0):80.2(±0.5), K_{enol} = 4.10 ± 0.07.[22]

The enol/anhydride ratio and the K_{enol} values were investigated in $CDCl_3$:CD_3CN ratios at 298 and 240 K and the data

(22) K_{enol} is defined in these cases as the ratio of [**4**] to the sum of the anhydrides [**5**] + [**5a**].

TABLE 3. The 5:5a:4 Distribution and K_{enol} Values in $CDCl_3$:CD_3COCD_3 Mixtures[a] at Room Temperature

$CDCl_3$:CD_3COCD_3 (v/v)	% **5**	% **5a**	% **4**	[**5a**]/[**5**]	K_{enol}[d]
10:0[b]	1.9	7.4	90.7	3.9	9.8
10:1	2.1	8.5	89.4	4.0	8.4
10:2	2.7	10.7	86.6	4.0	6.5
10:4	3.3	14.6	82.1	4.4	4.6
10:6	4.0	18.1	77.9	4.5	3.5
10:8	4.8	21.3	73.9	4.4	2.8
10:10	5.7	23.7	70.6	4.2	2.4
10:12	5.7	25.8	68.5	4.5	2.2
10:14	6.1	28.0	65.9	4.6	1.9
10:17	37.2[e,f]		62.8		1.7
10:20	40.0[e,f]		60.0		1.5
0:10[c]	55.8[e−g]		44.2		0.79

[a] The integral of the vinyl proton decreases on increasing the percent of CD_3COCD_3 and another broad signal is formed and shifts to high field at more CD_3COCD_3. [b] Pure $CDCl_3$, δ(OH) = 15.29. [c] Pure CD_3COCD_3. [d] K_{enol} = [**4**]/([**5**] + [**5a**]). Calculated from the integration of the MeO signal. [e] Sum of the percent ([**5**] + [**5a**]). [f] K_{enol} was calculated from the integration of the Me signal. [g] The MeO signals of **5** and **5a** overlap the CH_2 signal of **5a**.

are given in Table 2. The K_{enol} values decrease on increasing the CD_3CN content. The overall decrease of $K_{enol}(CDCl_3)/K_{enol}(CD_3CN)$ = 19 at 298 K and its extent becomes larger at 240 K. Simultaneously, the [**5a**]/[**5**] ratio increases with the increased percentage of CD_3CN from 3.9 in $CDCl_3$ to 7.9 in CD_3CN at 298 K and more so at 240 K.

The δ(OH) shifts to a higher field on increasing the percent of CD_3CN. Its integration significantly decreases, and this is ascribed to an exchange with the increasing percent of H_2O or D_2O in the CD_3CN.

The behavior in $CDCl_3$:CD_3COCD_3 mixtures (Table 3) resembles that in $CDCl_3$−CD_3CN. The percentage of **4** decreases ca. 2-fold from $CDCl_3$ to CD_3COCD_3, and **5** + **5a** become the major components in CD_3COCD_3 where K_{enol} decreases 14.5-fold. Except for a smaller [**5a**]/[**5**] ratio in $CDCl_3$ this ratio remains nearly constant at 4.3 ± 0.2 from 10:1 to 10:14 $CDCl_3$:CD_3COCD_3.

In DMSO-d_6 and DMF-d_7 the spectra differ from those in the solvents discussed above. A ca. 1 mol/L solution of **4** in DMSO-d_6 at rt displays four ^{1}H NMR singlets at 14.08 (1.1 H), 5.31 (1.0 H), 3.69 (5.2H), and 2.12 ppm (4.4H). When diluted 4-fold they appear at 10.80, 5.19, 3.66, and 2.12 ppm with integrals of 1.46H, 1.0H, 4.6H, and 3.8H, respectively. For compound **4** these will be ascribed to the OH, CH, MeO, and Me signals, respectively, except that a similar dilution effect in DMSO-d_6 on the "OH" signal of the enol of anhydride **15** is ascribed to its ionization to the enolate (see below).

Although **4** is less acidic than **15**, we ascribe the dilution effect to a similar (at least partial) ionization to the anion **11a**−**d** and a proton that is solvated by the traces of water in the solvent (see below). The spectra show signals ascribed to **11** and **5a** and the apparent higher than 3H integrals of the MeO and Me groups are due to their formation, coupled with the overlap of the CH_2 and OMe signals of **5a** with the MeO of **11** at 3.69−3.66 ppm and of the Me signals of **11** and **5a** at 2.12 ppm. An approximate calculation indicates that the **11**:**5a** ratios are 66:34 and 78:22 at high and low concentration, respectively, the latter value resembling that in DMF-d_7 at 240 K.

The ^{13}C NMR signals are broad, and assignment is not easy.

In DMF-d_7 the δ(^{1}H) signals are broad at rt, but sharpen at 240 K. δ(240K), **11**: 11.06 (br, 1.6H, "OH"), 5.35 (s, 1H, C5-H), 3.68 (s, 3.10H, OMe), 2.21 (s, 3.08H, Me). δ(240K), **5a**: 3.93 (s, 0.70H, CH_2), 3.84 (s, 1.14H, OMe), 2.08 (s, 1.06H, Me). On the basis of the MeO signal, the **11**:**5a** ratio is 73:27. The ^{13}C NMR data are given in the Experimental Section with a tentative assignment.

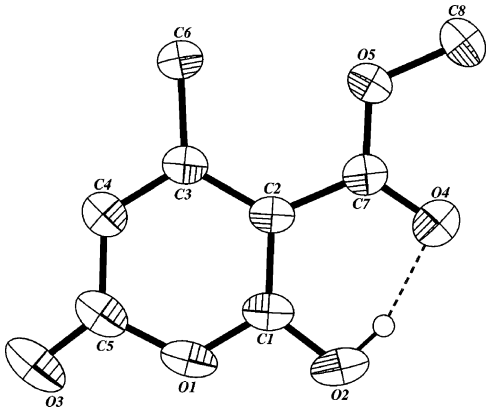


FIGURE 2. The ORTEP drawing of **4**.

TABLE 4. Selected Bond Lengths and Angles of 4

bond	length, Å	angle	deg
C1C2	1.388(3)	O1C1O2	111.6(2)
C1O2	1.297(3)	O1C1C2	123.0(2)
C1O1	1.325(3)	O2C1C2	125.3(2)
C2C3	1.435(3)	C1C2C3	117.5(2)
C4C5	1.422(3)	C1C2C7	115.4(2)
C2C7	1.457(3)	C3C2C7	127.19(19)
C5O1	1.414(3)	C4C3C2	118.93(19)
C3C4	1.354(3)	C4C3C6	118.7(2)
C5O3	1.199(3)	C2C3C6	122.36(19)
C7O4	1.236(3)	C3C4C5	123.2(2)
O2H	0.86(4)	C3C4H4	118.4
H···O4	1.65(4)	C5C4H4	118.4
O2···O4	2.479(3)	O2−H−O4	160(4)

Solid-State Structure of 4. Crystallization of compound **4** from CH_2Cl_2/C_6H_6 gave crystals suitable for X-ray diffraction, which was taken at 295 K. Selected bond lengths and angles are given in Table 4 and the ORTEP drawing is given in Figure 2.

The C1O2 bond length of 1.297 Å corroborates the anhydride structure. It resembles similar bond length in enols of other carboxylic acid derivatives.[4,5] It is closer to the single C1O1 bond length of 1.325(3) Å and to the C−O length of 1.333 Å in simple enols[23] than to the C═O double bond of 1.222(2) Å.[23] Indeed, the C5O3 bond length of the non-enolized anhydride carbonyl is 1.199 Å. Note that the C5O1 bond is longer (1.414(3) Å) and the difference between the two bond lengths (as well as the shorter C1O2 bond) can be ascribed to the partial positive charges on O1 and O2.

The C1C2 double bond of 1.388(3) Å is longer than the C3C4 double bond of 1.334(3) but shorter than the C4C5 single bond. Such elongation is typical for a push−pull alkene, due to the dipolar contributing structure O2O1C1$^+$−C2$^-$C7C3 to this bond. It is less elongated than similar bonds in enols "activated" at C_β by *two* EWGs with a C1C2 bond of 1.41 ± 0.01 Å.[4,5] The O2H bond of 0.86(4) Å is somewhat shorter than normal O−H bonds, but determination of hydrogens at rt by X-ray diffraction involves a considerable error. The O2···O4 nonbonding distance

(23) Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc., Perkin Trans 2*, **1987**, S1.

TABLE 5. ^{13}C NMR Signals (in ppm) of a Mixture Containing 4 and Deuteriated 4 in $CDCl_3$ at Room Temperature[a]

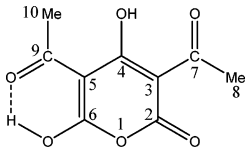
	A. 51% D[b]			B. 91% D[c]		
signal	4-H	4-D	δC(H) − δC(D)	4-H	4-D	δC(H) − δC(D)
Me	23.381	23.311	0.070	23.440	23.369	0.071
OMe	53.270			53.209		
enolic C3	87.261			87.328		
vinylic C5[d]	104.740 (s)	104.461 (t)	0.279	104.850 (s)	104.572 (t)	0.278
ring C6[e]	156.791			156.762		
vinylic C4	157.464	157.380	0.084	157.465	157.380	0.085
CO_2Me	172.052			171.887		
enolic *C*2	172.280			172.201		

[a] For experiment (c) at 240 K, the δ(**4-H**), δ(**4-D**), and δ(**4-H**) − δ(**4-D**) values were respectively: Me 23.893, 23.823, 0.070 ppm; C5 104.782(s), 104.490(t), 0.292 ppm; and C4 157.820, 157.725, 0.095 ppm. [b] 3 μL of D_2O was added to 55 mg of compound **4** in 0.5 mL of $CDCl_3$. [c] 100 μL of D_2O was added to 55 mg of compound **4** in 0.5 mL of $CDCl_3$. [d] The triplet signal of C5D partly overlaps the C5 signal of **4-H** at 104.752. C5 displayed a triplet after addition of 100 μL of D_2O and whose intensity decreased remarkably. Evidently, C5H exchanged with D_2O resulting in $^1J_{CD}$ = 26.5 Hz coupling. [e] C6 is converted from a doublet to a singlet due to the loss of CH coupling.

of 2.479(3) Å is in the range ascribed to strong hydrogen bonds.[24] The hydrogen bond angle of 160° shows that the bond is not far from linear.

We conclude that the solid-state structure of **4** clearly corroborates its enol of anhydride structure, and in view of the reservations concerning the structure of **7** this is the first unequivocal solid-state structure of such an enol.

Deuterium Isotope Effect on ^{13}C NMR Shifts. Hansen and co-workers[14] analyzed by deuterium isotope effects the ^{13}C NMR chemical shifts of the tautomeric dienol species of the formal 3,5-diacetyl tetrahydropyran-2,4,6-trione in $CDCl_3$.[25] The major species **1a** shows four large carbon isotope effects [Δ = δC(H) − δC(D)] of 0.55, 0.51, 0.56, and 0.65 for C4, C7, C6, and C9 at 300 K in $CDCl_3$ where C(H) and C(D) are the nonlabeled and the deuteriated forms. The tautomeric equilibria include **1a** and **3**, which is enolized on both COMe groups with hydrogen bonds to the 4-C═O, as well as other minor additional forms.[14] It is calculated that **3** is 3.3 kcal/mol more stable than **1**.



1a

We conducted four deuterium exchange experiments with compound **4** and recorded the corresponding changes in the ^{13}C NMR spectra at rt. (a) A sample of 55 mg of **4** in ca. 0.5 mL of $CDCl_3$ was shaken with 3 μL of D_2O. The immediately measured ^{1}H NMR spectrum at rt showed OH and CH integrals of 0.41 (vbr) and 0.49, respectively, and remains so after 24 h. Evidently, an equilibrium mixture in which the OH and 5-CH protons were partly exchanged by deuteron and both **4** (**4-H**) and its deuteriated derivative (**4-D**) coexisted was established. The ^{13}C NMR signals of **4-H** and **4-D** are given in Table 5A. (b) When 100 μL of D_2O was added to the same sample, 91% of CH and 5-CH were exchanged by the deuteron at rt. The corresponding signals are given in Table 5B. (c) When 0.5 or 1.5 μL of D_2O was added to 27 mg of **4** in 0.5 mL of $CDCl_3$ at 240 K, 33% and 57% of compound **4**, respectively, was deuteriated. Only the intensity of the Me, C4, and C5 of **4-H** signals decreased and the corresponding intensity of **4-D** increased on increasing the percent of D_2O. The signals of the ester CO and enolic C2 overlapped due to broadening at 240 K. (d) When 4 μL of D_2O was added to a saturated solution of **4** in 0.75 mL of C_6D_6, 59% of the OH and CH hydrogens were deuteriated. The isotope effect shifts observed were again on the Me, C5, and C4 at 22.410, 104.659, and 155.877 ppm, being respectively 0.070, 0.281, and 0.086 ppm upfield in **4-D**. The small differences in the δ(^{13}C) values in these experiments are partially due to the small effect of the different concentration of **4**, but the difference δC(H) − δC(D) is the same. The isotope effects are similar in experiments (a), (b), and (d), and the trend is the same in experiment (c).

The conclusion from Table 5 is that there is a small isotope effect of the deuterium on the ring C4 and Me, and a higher effect on C5. Since the experiment was repeated several times and a similar trend was observed for compound **15** (see below) we believe that the results are reliable. To our surprise we see no significant isotope effect in the ^{13}C shifts of the carbons around the hydrogen bond. Tentatively, this may reflect a weak hydrogen bond.

IR Spectra. The IR spectra of **4-H** and **4-D** were measured on the solid samples in KBr pellets. **4-H** displayed few C−H absorptions at 2963−3087 cm^{-1}, of which only that at 2963 cm^{-1} (ascribed to the CH_3) is shown by **4-D**, and at 1758 (C═O, vs) and 1629 (C═C, vs) cm^{-1}, which appear at 1756 (vs) and 1627 (vs) cm^{-1}, respectively, for **4-D**. Unidentified signals at 2360 and 2341 cm^{-1} appear for both **4-H** and **4-D**, and an absorption at 2300 cm^{-1} in **4-D** is ascribed to the isotopically shifted OH signal. A signal at 3483 cm^{-1} in **4-H** is assigned to a weak to moderately hydrogen-bonded OH. This signal should not be observed for the OD-containing **4-D** and the signal observed at 3479 cm^{-1} is assigned to residual **4-H** in **4-D**. A very weak signal at 2578 cm^{-1} for **4-H** (but not for **4-D**) could have been ascribed to a strong hydrogen-bonded enolic OH[5g,26] but it is too weak and is in contrast with the signal at 3483 cm^{-1} and the suggestion that the hydrogen bond in **4** is not strong.

Is 4 Aromatic? Since enol **4** has two double bonds and an oxygen lone pair in a pyran ring the question of its possible

(24) Perrin, C. L.; Nielson, J. B. *Annu. Rev. Phys. Chem.* **1997**, *48*, 511.

(25) Hansen had studied extensively the deuterium isotope effect on ^{13}C NMR chemical shifts. For another example see: Bolvig, S.; Duus, F.; Hansen, P. E. *Magn. Reson. Chem.* **1998**, *36*, 315.

(26) (a) Kopteva, T. S.; Shigorin, D. N. *Russ. J. Phys. Chem.* (*Engl. Transl.*) **1974**, *48*, 532. (b) Vener, M. V. In *Hydrogen-Transfer Reactions*; Hynes, J. T., Klinman, J. P., Limbach, H.-H., Schowen, R. L., Eds.; Wiley-VCH: Wenheim, Germany, 2007; Vol. 1, p 273. (c) Bertolasi, V.; Gilli, P.; Ferretti, V.; Gilli, G. *J. Am. Chem. Soc.* **1991**, *113*, 4917. (d) Tayyari, S. F.; Zeegers-Huyskens, Th.; Wood, J. L. *Spectrochim. Acta* **1979**, *35A*, 1265.

TABLE 6. Selected Bond Lengths and Angles for 15[a]

bond	length (Å)	angle	deg
C1C2	1.378(3) [1.378(2)]	O1C1O2	111.55(18) [110.79(15)]
C1O2	1.298(3) [1.303(2)]	O1C1C2	123.10(19) [123.50(16)]
C1O1	1.329(2) 1.327(2)]	O2C1C2	125.34(19) [125.70(16)]
C2C3	1.431(3) [1.433(2)]	C1C2C3	115.40(17) [115.16(15)]
C2C8	1.452(3) [1.456(2)]	C1C2C8	116.52(18) [116.75(16)]
C3C4	1.341(3) [1.340(2)]	C3C2C8	128.07(17) [128.05(15)]
O2H	0.86(4) [0.88(3)]	C4C3C2	122.93(18) [122.89(15)]
H···O7	1.74(4) [1.71(3)]	C4C3O4	117.12(17) [116.97(15)]
O2−H···O7	2.513(2) [2.5217(19)]	C2C3O4	119.90(16) [119.95(14)]
C5O3	1.195(2) [1.195(2)]	C3C4C5	120.51(19) [120.55(16)]
C8O7	1.230(2) [1.223(2)]	C3C4H4	119.7 [119.7]
		C5C4H4	119.7 [119.7]
		O2−H···O7	147(4) [151(3)]

[a] The data are for two independent molecules in the unit cell.

aromaticity arises. NICS(0) and NICS(1) values[27] were calculated for the X-ray determined conformer **4** with a O−H···O═C−O hydrogen bond and for its 3.4 kcal/mol (ZPE-corrected energy, B3LYP/6-311G*) less stable isomer with a O−H···O−C═O hydrogen bond.[28a] The values for the more stable conformer were NICS(0) = −2.1 and NICS(1) = −3.1, and NICS(0) = −1.8 and NICS(1) = −2.9 for the less stable conformer. These values show a small diamagnetic ring current, smaller than in cyclopentadiene.[28b] Consequently, we regard **4** as a nonaromatic compound.

Methyl 2-Hydroxy-4-(methoxycarbonyloxy)-6-oxo-6*H*-pyran-3-carboxylate (15). In a search for additional examples of enols of anhydrides we first looked for 2,5-dimethoxycarbonylpyran-2,4,6-trione **12**, which contains twice the skeleton of **4**. Its 4-carbonyl can further activate the system for enol formation, and **12** can also give a symmetrical dienol. However, it may also enolize on the 4-carbonyl group.

Pyran-2,4,6-trione (**13**) is an enol in solution. Structures drawn for it in the literature, e.g., enol on C4═O[29a,b] or dienol at the 2,6-[29c,d] or 2,4-positions,[29e] were mostly with no supporting data. In $(CD_3)_2CO$ its NMR spectra is that of its enol on the 4-one group (**14**). Reaction with excess methyl chloroformate/pyridine did not give **12** by C-methoxycarbonylation but gave the carbonate **15**, presumably via methoxycarbonylation on the enolic OH group of **14**. Reaction with $MgCl_2$ as a catalyst gave **12**, and its various enolization reactions will be discussed elsewhere. Structure **15** is based on the ^{1}H NMR spectra and the X-ray diffraction. The ORTEP is given in Figure 3 and selected crystallographic data are given in Table 6. Full crystallographic data are given in the Supporting Information.

The C═C, C−OH, O−H, and C−OCO bond lengths of **15** differ by only 0−0.014 Å from those of **4**, and the discussion above applies here too, i.e., **15** is another example of a solid-state enol of anhydride. The differences are in the ca. 0.1 Å longer O···H distance, the slightly longer (2.513 Å) O···O distance, and the smaller bond angle of 147° for **15** than for **4**. These values suggest a slightly weaker hydrogen bond in **15** than in **4**.

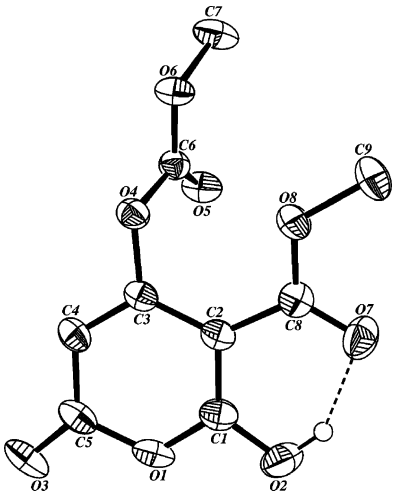


FIGURE 3. The ORTEP drawing of **15**.

Since **15** is the 4-OCO_2Me analogue of the 4-Me enol **4**, it can likewise ketonize in solution to the anhydride **16** and its isomeric rearranged anhydride **16a** (Scheme 4). The δ(OH) and K_{enol} values for **15**/**16a** in several solvents are given in Table 7. Small additional ^{13}C NMR signals to those of **16a** at δ 103.90 and 103.72 (^1J = 179.3, 179.4 Hz, ^3J = 3.3 and 3.6 Hz) and 56.41, 55.71 and 54.09, 53.20 in THF-d_8 and CD_3CN can be due to a small percentage of the anhydride **16**. They were not investigated further.

On shaking a solution of 50 mg of **15** in 0.5 mL of $CDCl_3$ with 2 μL of D_2O, the OH and CH signals decreased immediately to 0.56H and 0.55H and after 24 h to an equilibrium mixture with 0.63H and 0.46H. The C5 signal of the deuteriated **15-D** overlapped half of the C5 doublet of **15-H**. The ^{13}C shifts of **15-H** were at δ 53.707 (CO_2*Me*), 56.217 (OCO_2*Me*), 83.403 (C3), 96.887 (s, C5), 151.424 (O*C*O_2), 156.642 (C6), 162.289 (C4), 169.498 (C3-*C*O), 172.631 (C2). Only three signals were shifted in **15-D**: C3 by 0.014 ppm, C5 by 0.250 ppm, and C4 by 0.050 ppm. The C5 singlet of **15-H** becomes a triplet ($^1J_{CD}$ = 26.7 Hz) in **15-D**. After addition of 100 μL of D_2O to this sample the OH and CH intensities were only 7% and 5%, respectively. As with the enol **4**, the absence of significant shifts is surprising.

The IR spectrum in a KBr pellet of **15-H** (3441, 3100, 2969, 2360, 2341, 1774, 1647 cm^{-1}) resembles that of **15-D**, except for an intensity decrease of the 3100 cm^{-1} signal and a new isotope shift signal at 2311 cm^{-1}. No weak signals at the ca. 2600 cm^{-1} region were observed. The 3441 cm^{-1} band is

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(28) (a) Stanger, A. Unpublished results. (b) Stanger, A. *Chem. Eur. J.* **2006**, *12*, 2745.

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SCHEME 4

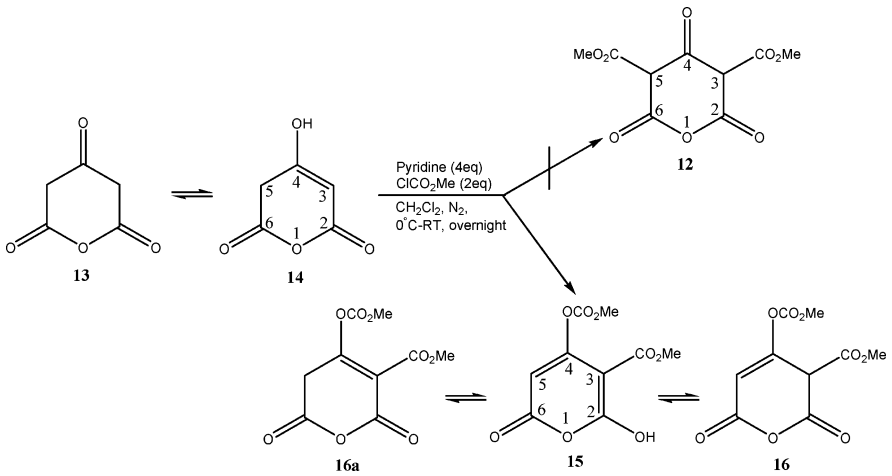


TABLE 7. δ(OH) and K_{enol} Values for the 15/16a System in Several Solvents at 298 K[a]

solvent	δ(OH), ppm	% enol **15**	% anhydride **16a**	K_{enol} = [**15**]/[**16a**]
$CDCl_3$	12.93	~100		≥100
THF-d_8[b]	12.14	88.5	11.5	7.7
CD_3CN[b]	12.04	77.1	22.9	3.4
DMSO-d_6	13.22	~100		(≥100)[c]

[a] Calculations of [**15**] and [**16a**] were based on the integration of the vinylic CH of **15** and the CH_2 of **16a**. [b] Compound **16** is probably present in small concentrations (see text). [c] If the signal is due to $\mathbf{15}^-$ (see text) the meaning of K_{enol} is unclear.

TABLE 8. ^{1}H NMR Data (ppm) for Different Concentrations of 15 in $CDCl_3$ and DMSO-d_6 at Room Temperature

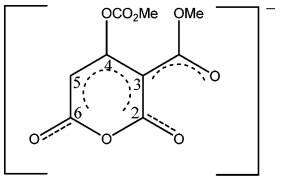
[**15**], mg/mL	δ(OH), ppm (integral[a])	δ(CH), ppm	δ(OMe), ppm
	in $CDCl_3$		
100	12.72 (1.31)	5.68	3.918, 3.909
50	11.72 br (1.03)	5.70	3.932, 3.925
25	10.42 vbr (0.29)	5.71	3.937, 3.931
12.5		5.71	3.940, 3.935
	in DMSO-d_6		
170[b]	14.02 (1.11)	4.80	3.72, 3.47
85[c]	11.87 (1.37)	4.77	3.73, 3.48
57[d]	11.00 (1.53)	4.77	3.74, 3.48
42.5[e]	9.65 (1.86)	4.76	3.74, 3.48
21.3[f]	5.89 (4.72)	4.74	3.74, 3.48
10.6[g]	4.71 (8.72)	4.73	3.74, 3.48

[a] Relative to an integral of 1.00 of the vinylic-CH. [b] 85 mg of **15** in 0.5 mL of DMSO-d_6. [c] 85 mg of **15** in 1.0 mL of DMSO-d_6. [d] 85 mg of **15** in 1.5 mL of DMSO-d_6. [e] 85 mg of **15** in 2.0 mL of DMSO-d_6. [f] 0.25 mL of sample in footnote *e* and 0.25 mL of DMSO-d_6 were mixed. [g] An additional 0.5 mL of DMSO-d_6 was added to the 2-fold concentrated sample.

ascribed to hydrogen-bonded OH. Hence, the hydrogen bond in **15** in solution is not very strong.

Concentration Effect of 15 on the Chemical Shifts. **Enolate Formation in DMSO-d_6.** In $CDCl_3$, THF-d_8, and CD_3CN solution at 298 K, the enol **15** is the exclusive or the main component of the mixture. The previously observed trend of decreasing K_{enol} for enols of carboxamides[4,5] on increasing the polarity of these solvents was found here also. However, the *apparent* complete enolization in DMSO-d_6 is in strong contrast to the previous behavior, and requires a revised evaluation of the species formed in this solvent.

In a previous work it was suggested that amides activated by Y, Y′ = CN, CO_2R or a Meldrum's acid residue, which appear as the enols in $CDCl_3$ or CD_3CN solutions, are ionized in DMSO-d_6 or in DMF-d_7 to the enolate ions which are the observed species.[5d−f] We probed this question for **15** by determining three ^{13}C shift differences of **15**: between DMSO-d_6 and $CDCl_3$, DMSO-d_6 and THF-d_8, and DMSO-d_6 and CD_3CN. The values for C2, C5, the C3-*C*O_2Me, and the C3-CO_2*Me* were all negative (−3.24 to −4.15, −8.72 to −10.09, −3.54 to −4.53, and −1.99 to −3.16 ppm, respectively). The values for C3 (−0.21 to +0.26 ppm), C4 (1.12−1.83 ppm), and C6 (5.27−5.81 ppm) are positive. Ring positions C3 and C5 are expected to be shifted upfield in anion $\mathbf{15}^-$, with the smallest effect for C3, whose charge is delocalized effectively by resonance into the CO_2Me substituent (see analogues **11a**−**c** in Scheme 3), whereas C2 should be shifted upfield by induction of the extensive negative charge on the geminal oxygen. The assumption that we see in DMSO-d_6 the anion $\mathbf{15}^-$ and not **15**, and a solvent protonated species at δ 13.22, seems reasonable.



A study of the concentration effect of **15** on the δ values of the OH, CH, and OMe signals was undertaken. Table 8 shows how a gradual 8-fold and 16-fold decrease in [**15**] in $CDCl_3$ and in DMSO-d_6, respectively, decrease the δ values of these signals. In both solvents the changes in δ(CH) or in δ(MeO) were negligible and the effect on δ(OH) was upfield and large. In $CDCl_3$ a 4-fold dilution causes a significant 2.3 ppm shift and increased broadening, with a consequent **smaller** integral, and on an 8-fold dilution the signal disappeared. In DMSO-d_6 the effect is larger, by 9.3 ppm and an 8-fold **increase** in the integral for the full dilution.

The upfield shift of the "apparent OH proton" on dilution could be ascribed to intermolecular enol−enol association in the relatively concentrated solutions of **15** (0.05−0.41 M in $CDCl_3$ (Table 8)). This cannot be the explanation in DMSO-d_6 where the "OH" integral increases enormously on dilution, while other chemical shifts remain the same. However, ionization of the enolic OH in the polar solvent, which is corroborated by the NMR data, accounts for all changes (see below).

TABLE 9. ^{1}H NMR δ Values of a Constant Concentration of 15 in Different Ratios of $CDCl_3$:DMSO-d_6 at Room Tempearture[a]

$CDCl_3$:DMSO-d_6 (v/v)	δ(OH), ppm (integral[b])	δ(CH), ppm	δ(OMe), ppm
pure $CDCl_3$[c]	14.18 br (0.91)	5.71	3.95, 3.94
4:1 $CDCl_3$:DMSO-d_6	12.38 (1.42)	5.47	3.91, 3.82
3:2 $CDCl_3$:DMSO-d_6	11.21 (1.73)	5.13	3.85, 3.67
2:3 $CDCl_3$:DMSO-d_6	10.84 (1.72)	4.92	3.81, 3.60
1:4 $CDCl_3$:DMSO-d_6	9.84 (1.96)	4.83	3.78, 3.54
pure DMSO-d_6[d]	9.97 sh (1.82)	4.77	3.73, 3.48

[a] 0.1 mL of a 500 mg/mL solution of **15** in DMSO-d_6 was added to 0.4 mL of $CDCl_3$:DMSO-d_6 mixture, giving a final concentration of about 100 mg/mL (0.41 M). TMS was used as a standard. [b] Relative to the integral of 1.00 for the vinyl-CH. [c] 50 mg of the sample was dissolved in 0.5 mL of $CDCl_3$. [d] 0.1 mL of a 500 mg/mL solution of **15** in DMSO-d_6 was added to 0.4 mL of DMSO-d_6.

Reaction in $CDCl_3$:DMSO-d_6 Mixtures. To eliminate the concentration effect the δ values were determined at a constant concentration of 0.41 M of **15** while changing the $CDCl_3$:DMSO-d_6 ratio (Table 9). On mixing v/v of the two solvents the total volume change is negligible. Both the "OH" and the MeO signals shift significantly and slightly, respectively, to a higher field and the difference between the two δ(OMe) values increases on increasing the percent of DMSO-d_6. The change in δ("OH") is systematic, except on the change to a pure DMSO-d_6. In $CDCl_3$ the signal at 14.18 ppm is broad, but after addition of the first portion of DMSO-d_6, it becomes sharp and the relative intensity of the signals also increases. No other anhydride was observed. The δ(CH) decreases monotonously and significantly with the increase in the percent of DMSO-d_6. In THF-d_8 and CD_3CN, the anhydride **16a** was also observed. A similar trend, with nearly similar δ(CH) and δ(MeO) values, but with less extensive differences in the δ(OH), was observed for 0.28 M of **15**.

Similar trends were observed in $CDCl_3$:DMSO-d_6 mixtures formed by addition of increasing portions of one solvent to a constant volume of the other, i.e., when the concentration of **15** decreased. The δ(CH) and δ(MeO) values changed similarly to those in Table 9, and those of δ(OH) were changed more strongly.

These results indicate again that the species observed in DMSO-d_6 is not the enol, but its conjugate base, derived by ionization of the OH group. The "OH" signal is indeed an H_3O^+ signal, formed from the H^+ and the traces of H_2O in the DMSO-d_6. The ^{1}H and ^{13}C signals are those of the enolate ion. This suggestion is further corroborated by the following experiments.

(a) When a sample of 50 μL of CF_3CO_2H in 0.5 mL of DMSO-d_6 was diluted by DMSO-d_6 the "H^+" signal at 15.89 ppm shifts to 14.16, 13.29, 12.65, and 7.21 ppm on dilution by 2-, 3-, 4-, and 8-fold, respectively. Both the δ("H^+") and its shifts on dilution resemble the behavior of the "apparent OH" signal derived from compound **15** (Table 9).

(b) When 1, 3, 6, and 10 μL of H_2O were added to a solution of 62 mg of **15** in 0.5 mL of DMSO-d_6 (0.5 mL), the "apparent OH" signal shifts upfield and the integration increases from 13.91 (1.09H) to 9.30 (2.21H), to 7.83 (3.14H) and 6.16 (6.41H) ppm, respectively. On adding 35 mg of **15** to the most dilute solution, the signal shifts downfield to 6.96 (4.98H) ppm. No H_2O signal at 3.33 ppm[30] was observed and δ(CH) or δ(MeO) remained unchanged. These results suggest ionization to $\mathbf{15}^-$ and H^+, which forms H_3O^+ with the water present in or added to DMSO-d_6. The reversal of the upfield shift by increasing [**15**] at a constant volume is in line with the position of the signal being a weighted average of those of δ(H^+·DMSO) and δ(H_2O·DMSO)

(30) Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512.

TABLE 10. ^{1}H NMR of 15 in $CDCl_3$ and DMSO-d_6 before and after Addition of Et_3N at Room Temperature[a]

solvent	δ(OH), ppm (integral)	δ(CH), ppm	δ(OMe), ppm
$CDCl_3$	14.19 (br, 0.98H)	5.68	3.92, 3.91
$CDCl_3$ + 100 μL of Et_3N	9.07 (sh, 1.15H)	4.91	3.71, 3.50
DMSO-d_6	14.19 (sh, 1.04H)	4.80	3.72, 3.47
DMSO-d_6 + 100 μL of Et_3N	8.11 (sh, 1.20H)	4.76	3.75, 3.50
DMSO-d_6 +150 μL of Et_3N[b]	7.98 (sh, 1.23H)	4.76	3.75, 3.50

[a] 56 mg and 82 mg of **15** were dissolved in 0.6 mL of $CDCl_3$ and 0.5 mL of DMSO-d_6, respectively. [b] Part of the Et_3N does not mix with the solution and stay in the upper layer.

(c) (i) When 100 μL of Et_3N was added to 56 mg of **15** in 0.6 mL of $CDCl_3$, the rt ^{1}H NMR spectrum showed that the broad 0.98H OH signal at δ 14.19 became sharp and shifted to 9.07 with 1.15H integration. The CH signal shifted from δ 5.68 to 4.91, and the two MeO signals at δ 3.92 and 3.91 shifted to 3.71 and 3.50. Except for the δ(CH) value, the rt ^{1}H NMR spectrum resembles that of **15** in DMSO-d_6 (Table 10). (ii) To the solution of 82 mg of **15** in 0.5 mL of DMSO-d_6 was added 100 μL of Et_3N with shaking. The rt ^{1}H NMR spectrum showed that the sharp 1.04H signal at δ 14.19 shifted to 8.12 (1.20H), the CH signal at δ 4.80 shifted to 4.76, and the two MeO signals at δ 3.72 and 3.47 shifted to 3.75 and 3.50 (Table 10).

The ^{13}C NMR spectra are recorded in Table 11. Addition of Et_3N shifted upfield the MeO, C5, CO_2Me, and C2 signals which carry a negative charge on the anion (cf. Scheme 3). It did not affect C3, and caused a downfield shift of the OCO_2Me, C6, and C4 signals. These shifts were remarkably similar to those of **15** in DMSO-d_6, to which addition of Et_3N **did not** cause significant shifts. We conclude that whereas **15** is little or not at all ionized in the relatively low-polarity $CDCl_3$, but ionizes in the presence of the base, it is already completely ionized in the polar DMSO-d_6 even without an added base.

Comparison of K_{enol} and δ Values for 4 and 15. Enols **4** and **15** differ by the 4-substituent, which is a Me in **4** and the more electron-withdrawing OCO_2Me in **15**. As expected, the electron-withdrawal increases K_{enol} and at 298 K K_{enol}(**15**)/K_{enol}(**4**) = 6.5 in CD_3CN. K_{enol} is also higher in $CDCl_3$, but an accurate ratio is unavailable since K_{enol}(**15**) $\geq$ 100, whereas the K_{enol}(**4**) in $CDCl_3$ is 9.8. That in DMSO-d_6 **15** is completely ionized, and **4** is at least partially ionized, indicates a severe limitation to enol formation by using powerful β-EWGs. It should be kept in mind that in highly polar solvents the observed species may be the enolate ion rather than the enol.

The δ(OH) values in solution are at 2.3 ($CDCl_3$) and 3.4 ppm (CD_3CN) upfield for **4** than for **15**. This is in contrast with the enols of amides where the enol with the higher K_{enol} has a lower value of δ(OH).[4,5] This may reflect a weaker intramolecular hydrogen bonding in solution, observed also in solid **15** compared with solid **4** where the O···O nonbonding distances are 2.513 and 2.479 Å, respectively.

Experimental Section

β-Methylglutaconic Anhydride (8). (a) Reaction of ethyl isodehydroacetate with NaOH gave a 4:6 *E*:*Z* mixture of β-methylglutaconic acids.[18d,e] ^{1}H NMR (DMSO-d_6, 298 K), *E*-isomer: δ

TABLE 11. ^{13}C NMR of 15 in $CDCl_3$ and DMSO-d_6 before and after Addition of Et_3N at Room Temperature

solvent	OMe	C3	C5	OCO_2Me	C6	C4	CO_2Me	C2
$CDCl_3$[a]	53.75, 56.20	83.32	96.75	151.41	156.74	162.30	169.69	172.69
$CDCl_3 + Et_3N$ (100 μL)[b]	50.35, 55.05	83.36	88.30	152.03	163.30	164.76	165.43	167.48
DMSO-d_6[a]	50.59, 55.80	83.58	86.66	152.33	162.36	164.13	165.24	168.54
DMSO-$d_6 + Et_3N$ (150 μL) [b,c]	50.39, 55.61	83.22	86.61	152.30	162.48	163.97	165.25	168.39

[a] Identical samples to the corresponding ones in Table 10. [b] 56 mg and 82 mg of **15** were dissolved in 0.6 mL of $CDCl_3$ and 0.5 mL of DMSO-d_6, respectively. [c] Part of the Et_3N does not mix with the solution and stay in the upper layer.

2.09 (s, 1H), 3.12 (s, 0.7H), 6.84 (s, 0.3H), 12.24 (s, 1H); *Z*-isomer: δ 1.89 (s, 0.6H), 3.63 (s, 0.4H), 6.93 (s, 0.2H), 12.24 (s, 1H).

(b) Anhydride **8** was prepared by cyclization of the *E*:*Z* mixture of β-methylglutaconic acids with acetyl chloride.[18a−c] Anal. Calcd for $C_6H_6O_3$: C, 57.14; H, 4.76. Found: C, 56.98; H, 4.90. ^1H NMR ($CDCl_3$, 298 K) δ 2.08 (q, $J = 1.1$ Hz), 3.44 (q, $J = 0.6$ Hz), 6.08 (q, $J = 1.5$ Hz); ^{13}C NMR ($CDCl_3$, 298 K) δ 22.12, 36.26, 114.64, 155.52, 159.77, 164.76.

Reaction of β-Methylglutaconic Anhydride with Methyl Chloroformate. (a) Sodium (0.12 g, 5 mmol) was added to methanol (20 mL) with stirring until complete dissolution. β-Methylglutaconic anhydride (0.63 g, 5 mmol) in methanol (10 mL) was then added dropwise and the mixture was stirred at rt for 24 h. Evaporation of the solvent gave the sodium salt **9** as a yellow solid. ^1H NMR (DMSO-d_6, 298 K) δ 1.78 (s, 3H, Me), 4.43 (s, 2H, 2CH). ^{13}C NMR (DMSO-d_6, 298 K) δ 21.22 (qt, $J_q = 126$ Hz, Me), 86.14 (d of quintets, $J_d = 163$ Hz, $J_{quintet} = 5.0$ Hz, CH), 159.19 (C−Me), 165.98 (CO).

A suspension of the sodium salt in THF (40 mL) was stirred for 24 h, after which methyl chloroformate (0.94 g, 10 mmol) in THF (10 mL) was added dropwise and stirring continued for an additional 24 h. The NaCl (ca. 0.25 g) formed was filtered, the solvent was evaporated, and purification of the residue by TLC (2:3 EtOAc/petroleum ether) gave **10b** as a yellow liquid. ^1H NMR ($CDCl_3$, 298 K) δ 2.21 (t, $J = 1.0$ Hz, 3H, Me), 3.94 (s, 3H, MeO), 5.86 (d, $J = 1.1$ Hz, 1H, =CHCOO), 6.01 (t, $J = 1.7$ Hz, 1H, CH=C(O)O−COMe); ^1H NMR (CCl_4, 298 K) δ 1.41 (t, $J = 1.0$ Hz, 3H, Me), 3.14 (s, 3H, MeO), 5.01 (q, $J = 1.1$ Hz, 1H, CH-ring), 5.10 (q, $J = 1.1$ Hz, 1H, CH=). ^{13}C NMR ($CDCl_3$, 298 K) δ 21.65 (qdd, $J_q = 128$ Hz, $J_{d1} = 5.2$ Hz, $J_{d2} = 3.6$ Hz, Me), 55.13 (q, $J = 149$ Hz, MeO), 94.41 (dm, $J_d = 176$ Hz, ring-CH=), 109.87 (d of quintets, $J_d = 170$ Hz, $J_{quintet} = 5.3$ Hz, =CH), 150.74 (=CMe), 155.08 (COOMe), 157.21 (COO), 158.48 (COO). MS (70 eV) 184 (20%, M), 140 (7%, M − CO_2), 112 (93%, M − CO_2 − CO), 97 (100%, M − Me − CO − CO_2), 53 (93%).

(b) To a solution of β-methylglutaconic anhydride (1 g, 7.7 mmol) in a 15% KOH solution (3 mL) was added dropwise a 30% KOH solution (10 mL). The precipitated potassium salt was filtered, washed with a small quantity of ethanol, and dried in vaccuo to give 1.2 g of the K salt of **9**. ^1H NMR (DMSO-d_6, 298 K) δ 1.77 (s, 3H), 4.41 (s, 2H). ^{13}C NMR (DMSO-d_6, 298 K) δ 21.25 (qt, $J_q = 126$ Hz, $J_t = 5.0$ Hz, Me), 86.11 (d of quintets, $J_d = 163$ Hz, $J_{quintet} = 4.7$ Hz, CH), 159.17 (CMe), 166.03 (COO).

The reaction of the potassium salt with methyl chloroformate followed the same procedure as for the sodium salt and gave the same result.

Reaction of the Sodium Salt of β-Methylglutaconic Anhydride with Phenyl Chloroformate. Dry THF (40 mL) was added to a solution of a freshly prepared sodium salt from Na (0.23 g) and β-methylglutaconic anhydride (1.26 g) (**9**·Na^+). Phenyl chloroformate (3 mL) was added and the mixture was stirred for 24 h. The formed NaCl was filtered, the solvent was evaporated, and the residue was dissolved in dry ether to which petroleum ether was added. The red solution was kept for 16 h at −16 °C and the precipitate formed was filtered to afford 2-phenoxycarbonyl-3-methylglutaconic anhydride **10a**, mp 96−8 °C. Anal. Calcd for $C_{13}H_{10}O_5$: C, 63.42; H, 4.09. Found: C, 63.27; H, 4.28. The X-ray data are in Figure 1, Table 2, and the Supporting Information.

^1H NMR ($CDCl_3$, 298 K) δ 2.21 (d, $J = 1.1$ Hz, 3H, Me), 5.96 (d, $J = 1.1$ Hz, 1H, ring-CH=), 6.02 (t, $J = 1.1$ Hz, 1H, =CH), 7.24 (m, 2H, Ph−H), 7.31 (m, 1H, Ph−H), 7.43 (m, 2H, Ph−H). ^{13}C NMR ($CDCl_3$, 298 K) δ 21.76 (qdd, $J_q = 129$ Hz, $J_{d1} = 4.7$ Hz, $J_{d2} = 3.9$ Hz, Me), 95.31 (dm, $J_d = 174$ Hz, ring-CH=), 110.18 (d of quintets, $J_d = 171$ Hz, $J_{quintet} = 5.6$ Hz, =CH), 120.47 (ddd, $J_1 = 165$ Hz, $J_2 = 8.1$ Hz, $J_3 = 4.0$ Hz, Ph−C), 126. 91 (dt, $J_d = 163$ Hz, $J_t = 7.6$ Hz, Ph−C), 129.73 (dd, $J_1 = 164$ Hz, $J_2 = 9.0$ Hz, Ph−C), 148.87 (br, Ph−C_{ipso}−O), 150.42 (q, $J = 6.1$ Hz, =CMe), 154.44 (COO), 158.10 (m, COOPh), 159.74 (d, $J = 5.6$ Hz, COOCH=). The ^1H and ^{13}C NMR spectra in CCl_4 resemble those in $CDCl_3$, except that a few signals appear at a higher field than in $CDCl_3$.

3-Methoxycarbonyl-4-methylglutaconic Anhydride (4). To a heterogeneous suspension of dry $MgCl_2$ (190 mg, 2 mmol) in dry CH_2Cl_2 (5 mL) was added β-methylglutaconic anhydride (252 mg, 2 mmol) under nitrogen. The mixture was cooled to 0 °C and pyridine (316 mg, 4 mmol) was added. After stirring for 15 min, methyl chloroformate (198 mg, 2 mmol) was added and stirring was continued for 2 h at 0 °C, and overnight at rt. After cooling to 0 °C, 2 N HCl (20 mL) was added. The solution was extracted with $CHCl_3$ (3 × 20 mL), the combined organic extracts were dried ($MgSO_4$), the solvent was evaporated, and the residue was washed with ether, giving 80 mg (22%) of a gray powder of **4**, mp 124−6 °C. Anal. Calcd for $C_8H_8O_5$: C, 52.17; H, 4.35. Found: C, 52.31; H, 4.44. ^1H NMR ($CDCl_3$, 240 K) δ 2.37 (s, 3H, Me), 3.97 (s, 3H, MeO), 5.69 (s, 1H, =CH), 15.49 (br, 1H, OH); ^{13}C NMR ($CDCl_3$, H-coupled, 240 K) δ 23.85 (qd, $J_q = 130$ Hz, $J_d = 5.9$ Hz, Me), 53.72 (q, $J_{CH} = 149$ Hz, OMe), 87.32 (m, C3), 104.81 (dq, $J_d = 172.5$ Hz, $J_q = 5.8$ Hz, =C5), 157.24 (d, $J_{CH} = 5.9$ Hz, C6), 157.69 (q, $J_{CH} = 6.1$ Hz, *C*4), 172.22 (s, C2), 172.27 (q or m, CO_2Me). ^{13}C NMR (DMF-d_7, 240 K) δ (**4**$^-$): 21.98 (qd, J_q =128.8 Hz, $J_d = 5.4$ Hz, Me), 50.92 (q, $J_q = 146.5$ Hz, OMe), 92.74 (m, C3), 95.23 (dm, $J_d = 168.0$ Hz, C5), 167.53 (d or q, $J = 4.2$ Hz, C3-*C*O ?); δ (**5a**): 19.55 (q, $J_q = 128.9$ Hz, Me), 36.99 (tq, $J_t = 132.6$ Hz, $J_q = 3.7$ Hz, CH_2), 52.46 (q, $J_q = 148.1$ Hz, OMe), 120.07 (m, C3). Other signals at 164.91, 164.56, 163.99, 159.14, and 158.98 are not easy to assign.

Many attempts to crystallize **4** from CH_2Cl_2, EtOAc + petroleum ether (40−60 °C), benzene, THF, and THF + benzene had failed. Finally, the compound was dissolved in a vial in CH_2Cl_2, and benzene was added just until a precipitate started to form. The vial was capped with a lid having a small opening. The CH_2Cl_2 was evaporated slowly and after a few days appropriate crystals for X-ray diffraction were formed. The X-ray data are in Figure 2, Table 5, and the Supporting Information.

Pyran-2,4,6-trione (13). 13 was prepared from acetone dicarboxylic acid and acetic anhydride according to Meltzer et al.[31] The NMR showed it to be the enol **14**. Anal. Calcd for $C_5H_4O_4$: C, 46.89; H, 3.15. Found: C, 46.71; H, 3.22. ^1H NMR ($(CD_3)_2CO$, 298 K) δ 3.68 (s, 2H, CH_2), 5.33 (s, 1H, =CH), 11.0 (s, 1H, OH). ^{13}C NMR ($(CD_3)_2CO$, 298 K) δ 33.88 (td, $J_t = 133.1$ Hz, C5), 89.63 (dt, $J_d = 169.3$ Hz, $J_t = 3.0$ Hz, C3), 161.68 (d, $J = 3.1$ Hz, C2), 164.54 (t, $J = 7.3$ Hz, C6), 170.57 (td, $J_t = 8.1$ Hz, $J_d = 2.9$ Hz, C4). In DMSO-d_6 at 298 K δ(OH) = 12.38 (s, 1H).

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Methyl 2-Hydroxy-4-(methoxycarbonyloxy)-6-oxo-6*H*-pyran-3-carboxylate (15). To a suspension of **13** (1.28 g, 10 mmol) in CH_2Cl_2 (35 mL) was added pyridine (3.20 g, 40 mmol) and methyl chloroformate (2.2 g, 23 mmol). The mixture was stirred overnight at rt. The solvent was evaporated, the residue was washed with ether and then suspended in $CHCl_3$ (60 mL), and 32% HCl solution (40 mL) and ice (60 g) were added. The $CHCl_3$ layer was separated and the aqueous phase was extracted with $CHCl_3$ (2 × 60 mL). The combined organic phase was dried ($MgSO_4$), the solvent was evaporated, and the residue was washed with ether, giving a yellow powder (0.87 g, 36%), mp 109−110 °C. Light yellow crystals suitable for X-ray diffraction were obtained from CH_2Cl_2.

Anal. Calcd for $C_9H_8O_8$: C, 44.27; H, 3.30. Found: C, 44.61; H, 3.30. ^{1}H NMR ($CDCl_3$, 298 K) δ 3.90 (s, 3H, Me), 3.91 (s, 3H, Me), 5.67 (s, 1H, =C*H*), 12.93 (1H, br s, OH). ^{13}C NMR ($CDCl_3$, 298 K) δ 53.75 (q, J = 149.3 Hz, CO_2*Me*), 56.20 (q, J = 149 Hz, OCO_2*Me*), 83.32 (d, J_d = 5.3 Hz, C3), 96.75 (d, J_d = 176.3 Hz, C5), 151.41 (q, J = 4.1 Hz, O*C*O_2Me), 156.74 (d, J = 3.2 Hz, C6), 162.30 (d, J = 5.0 Hz, C4), 169.69 (q, J = 3.6 Hz, *C*O_2Me), 172.69 (s, C2).[1] H NMR (CD_3CN, 298 K) δ (**15**): 3.89 (s, 3H, Me), 3.91 (s, 3H, Me), 5.73 (s, 1H, CH), 12.04 (br s, 1H, OH); δ (**16a**): 3.82 (s, CO_2Me), 3.98 (s, 2H, CH_2), the OCO_2Me signal overlaps that of **15**; ^{13}C NMR (^{1}H-coupled, CD_3CN, 298 K) δ (**15**): 53.72 (q,^1J = 149.7 Hz, O*Me*), 56.16 (q, ^1J = 149.3 Hz, O*Me*), 83.79 (d, ^3J = 5.1 Hz, C3), 96.45 (d, ^1J = 176.4 Hz, C5), 151.41 (q, ^3J = 4.0 Hz, O***C***O_2Me), 157.09 (d, ^2J = 3.2 Hz, C6), 162.87 (d, ^2J = 5.0 Hz, C4), 169.77 (q, ^3J = 3.7 Hz, ***C***O_2Me), 172.62 (s, C2); δ (**16a**): 34.37 (t, ^1J = 136.2 Hz, C5), 52.76 (q,^1J = 148.7 Hz, CO_2*Me*), 56.66 (q, ^1J = 149.8 Hz, OCO_2*Me*), 112.15 (t, C3), 149.89 (q, ^3J = 4.0 Hz, O***C***O_2Me), 157.85 (s, C2), 160.92 (d or q, ***C***O_2Me), 161.52 (t, ^2J = 7.9 Hz, C4), 162.16 (t, ^2J = 9.4 Hz, C6). δ (**16**, tentative): 54.69 (small, Me), 56.09 (small, Me), 103.90 (small, dd, ^1J = 179.4 Hz, ^3J = 3.3 Hz, C5). ^{1}H NMR (THF-d_8, 298 K) δ (**15**): 3.873 + 3.866 (2s, 6H, 2Me), 5.68 (s, 1H, CH), 12.14 (s, 1H, OH); δ (**16a**): 3.78 (s, CO_2Me), 4.01 (s, 2H, CH_2), the OCO_2Me signal probably overlaps that of **15**.

^{13}C NMR (^{1}H-coupled, THF-d_8, 298 K) δ (**15**): 52.58 (q,^1J = 149.0 Hz, CO_2*Me*), 55.33 (q, ^1J = 148.8 Hz, OCO_2*Me*), 83.82 (br, C3), 95.38 (d, ^1J = 175.8 Hz, C5), 151.35 (q, ^3J = 4.0 Hz, O*C*O_2-Me), 156.55 (s, ^2J = 3.2 Hz, C6), 163.01 (s, C4), 168.78 (s, *C*O_2-Me), 171.78 (s, C2); δ (**16a**): 33.83 (t, ^1J = 135.8 Hz, C5), 51.93 (q, ^1J = 148.1 Hz, CO_2*Me*), 55.83 (q, ^1J = 149.4 Hz, OCO_2*Me*), 112.23 (t, C3), 150.07 (q, O*C*O_2Me), 157.27 (s, C2), 160.72 (q, *C*O_2Me), 161.01 (t, C4), 161.52 (t, ^2J = 9.3 Hz, C6); δ (**16**, tentative): 53.20 (small, Me), 55.71 (small, Me), 103.72 (dd, ^1J = 179.3 Hz, ^3J = 3.6 Hz, C5).

^{1}H NMR (DMSO-d_6, 298 K) δ (**15**): 3.48 (s, 3H, CO_2Me), 3.74 (s, 3H, OCO_2Me), 4.76 (s, 1H, CH), 13.22 (s, 1H, "OH"). ^{13}C NMR (^{1}H-coupled, DMSO-d_6, 298 K) δ (**15**): 50.59 (q, ^1J = 145.7 Hz, CO_2*Me*), 55.80 (q, ^1J = 148.3 Hz, OCO_2*Me*), 83.58 (s, C3), 86.66 (d, ^1J = 171.0 Hz, C5), 152.33 (q, ^3J = 4.1 Hz, O*C*O_2Me), 162.36 (s, C6), 164.13 (s, C4), 165.24 (q, ^3J = 3.8 Hz, *C*O_2Me), 168.54 (s, C2).

Acknowledgment. We are grateful to Dr. Shmuel Cohen for the X-ray diffraction determinations, to Professor Amnon Stanger for the NICS calculations, and to Prof. Silvio Biali for discussions. We thank the Israel Science Foundation for support.

Supporting Information Available: Full crystallographic data of **4**, **10a**, and **15** (CIF files), Table S1 giving the products isolated from attempted C-alkylation of **9** in the presence of various bases, NICS data, IR spectra, and spectra of deuterium isotope effect on δ(^{13}C NMR) of **4-H**/**4-D** and **15-H**/**15-D**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO071206M