be taken to account for the possibility that the specific properties of the solubilizing medium may alter the photochemical reaction.

The contribution of the reaction volume change to the total volume change can be significant. The failure to account for it may yield erroneous thermochemical data. For example, assuming $\Delta V'_{th} = \Delta V_{th} + \Delta V_{rx}$, where $\Delta V'_{th}$ is the uncorrected thermal volume change which includes both the reaction and thermal volume changes, then the uncorrected enthalpy change, $\Delta H'$, is given by

$$\Delta H' = E_{h\nu}[1 - (\alpha_{th} + \alpha'_{rx})]/\Phi_r \quad (16)$$

The uncorrected $\Delta H'$ values for the DBH, DPC, and TS photoreactions in acetonitrile are −20.7, −15.3, and +5.1 kcal/mol, whereas in water at 20 °C, the uncorrected ΔH values are −170.6, −194.9, and +8.5 kcal/mol, respectively.[32] The uncorrected values of DBH and DPC are *significantly* different than the corrected enthalpy values determined by PAC *with* the resolution of the thermal and reaction volume components. In contrast, the reaction volume change of TS in acetonitrile is negligible so the difference is small.

The difference between the corrected and uncorrected enthalpy values, $\Delta\Delta H$, is $\Delta V_{rx}C_p\rho/\beta$. The larger the photochemical reaction volume change or the smaller the $\beta/(C_p\rho)$ value of the solvent, the larger the difference. The micellar solutions have a very small $\beta/(C_p\rho)$ value, 0.2–0.3, so $\Delta\Delta$H is large. In contrast, the $\Delta\Delta H$ for the photoreactions in acetonitrile is significantly less than in water because its $\beta/(C_p\rho)$ value is quite large, 3.3. In general, $\Delta\Delta H$ for photoreactions will be smaller in organic solvents than in aqueous solutions because of the relative $\beta/(C_p\rho)$ values. Consequently, if either the solvent employed is water or ΔV_{rx} is large, the thermal and reaction volume changes can and should be experimentally resolved, preferably by the temperature-dependence method. Simply, if the photochemical reaction volume change is of interest, conduct the reaction in micellar solutions and resolve the change. To minimize its contribution to the total volume change, conduct the reaction in organic solvents with high $\beta/(C_p\rho)$ values. Clearly, we have chosen the photoreactions of DBH and DPC to dramatize the potential contribution of reaction volume changes to the total volume change. The magnitude of this contribution will obviously depend on the photoreaction and the solvent employed, but in general, the contribution will be considerably smaller than that observed for DBH and DPC.

Photoacoustic calorimetry has several advantages over conventional methods to measure photochemical reaction volume changes. These changes can be obtained either from partial molar volume data or by means of dilatometry only if the reactants and products are stable and isolable.[1] Such stability is not a requirement for PAC. Indeed, either the reactants or the products may be reactive intermediates and reaction volumes can be obtained. The interpretation of pressure-dependence measurements to obtain ΔV_{rx} are often complicated by assumptions.[1] No assumptions are necessary to determine the reaction volumes other than ΔV_{rx} is independent of either temperature or solvent composition. This seems justified given the linear plots and the small temperature range required for these experiments. Furthermore, these reaction volume changes can be time-resolved to provide information about the structural nature of reactive intermediates. For example, the rate and magnitude of the reaction volume change associated with excimer and exciplex formation can be determined.[33]

In conclusion, we have demonstrated the use of PAC to measure both thermal and reaction volume changes for photoinitiated reactions. The use of either the temperature-dependence or the binary-solvent method allows for the resolution of these two contributions to the total volume change. This technique has great potential in its applicability to a wide variety of chemical systems to provide thermodynamic, kinetic, and reaction volume information.

Acknowledgment. This work was supported by the National Science Foundation (CHE-871370), the Research Corp., and the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Registry No. DBH, 2721-32-6; DPC, 886-38-4; TS, 103-30-0.

(32) A previous photoacoustic experiment was done on DPC which did not account for the reaction volume change.[11] The observed uncorrected ΔH value for the photodissociation of DPC in benzene was −9.9 kcal/mol, in good agreement with our uncorrected value of −15.3 kcal/mol in acetonitrile.

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(35) This treatment classifies all nonthermal expansion contributions to the total acoustic wave as photochemical reaction volume changes. Consequently, the photochemical reaction volume changes will only be meaningful values if other nonthermal expansion contributions are small. Possible contributions, electrostriction, breakdown, or plasma formation, should be small for the systems examined.

Photooxygenation of Ascorbic Acid Derivatives and Model Compounds

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Abstract: Photooxygenation of ascorbic acid derivatives and model compounds produces hydroperoxy ketones as initial products. The reaction rate and initial product distribution depend on the acidity of the hydroxy group; the more acidic group reacts more readily. The C-2 carbonyl group of the 3-hydroperoxy ketones reacts readily with methyl alcohol to give a hydroperoxy hemiketal. Both the hydroperoxy ketones and their hemiketals decompose to oxalate esters upon warming to room temperature. The structure of oxalate **11a** was confirmed by X-ray crystal analysis. Hydroperoxy ketones **31** and **32** are in equilibrium at low temperature and give only one hemiketal (**34**) in CD_3OD. Analogous photooxygenation products and similar decomposition pathways occur with 2-hydroxytetronic acid derivatives. The presence of fluoride ion affects both the reaction of enediols with singlet oxygen and the decomposition of the unstable products.

L-Ascorbic acid (vitamin C) serves as a biological antioxidant. Previous study has centered on its importance as a reductant which can undergo reversible oxidation and reduction with the formation of free-radical intermediates.[1] Another role is as a redox buffer,

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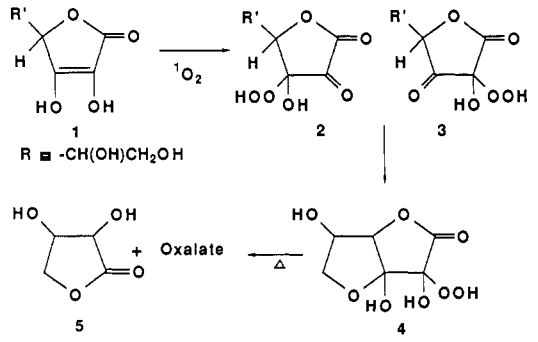
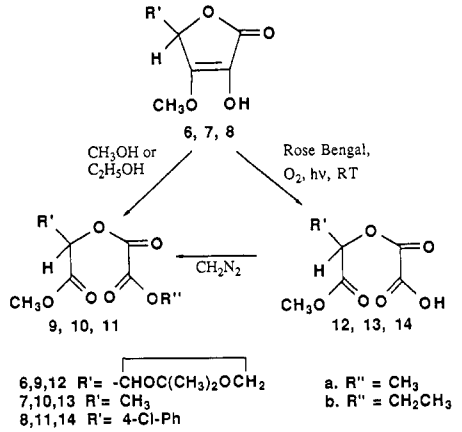
Scheme I



Scheme II



reducing oxidized tocopherol radicals in membranes[2] to maintain vitamin E level in tissues. These processes represent the known modes of antioxidant function. It has recently been demonstrated that L-ascorbic acid is also capable of highly efficient singlet-oxygen removal.[3] Bensasson et al. reported that the rate constant for singlet-oxygen quenching by ascorbic acid is 1.6×10^8 M^{-1} s^{-1}.[3a] The first report of dye-sensitized photooxidation of ascorbate was by Schenck and co-workers, who reported the formation of oxalic acid and threonolactone.[4] Other workers have since reported similar products.[5] However, these products are clearly secondary. We have previously reported that singlet oxygen reacts with L-ascorbic acid (**1**) at low temperature in an ene-type reaction[6] to give two unstable hydroperoxy ketones (**2** and **3**), which rearrange to hydroperoxydehydroascorbic acid (**4**) by intramolecular cyclization.[7] Upon warming and after hydrolysis, hydroperoxide **4** is converted to the previously observed products oxalic acid and L-threonolactone **5** (Scheme I).

In this paper, we report experiments that define the scope of the reactions of singlet oxygen with ascorbic acid derivatives, related enediols, and their derivatives. Studies of these structural models also provide further confirmation for the structures of compounds **2–4**.

Recently, Wasserman and Pickett reported that fluoride ion enhances the reaction rate of enols with singlet oxygen.[8] They suggested that this effect is caused by a strong hydrogen bond between the enol OH and the fluoride ion. This kind of fluoride ion effect was previously reported by Clark and Miller in the C-alkylation of β-carbonyl compounds and in the self-condensation of enols.[9] We report similar phenomena in the photooxygenation of ascorbic acid derivatives and model enolic compounds. Fluoride also catalyzes the decomposition of hydroperoxy ketones.

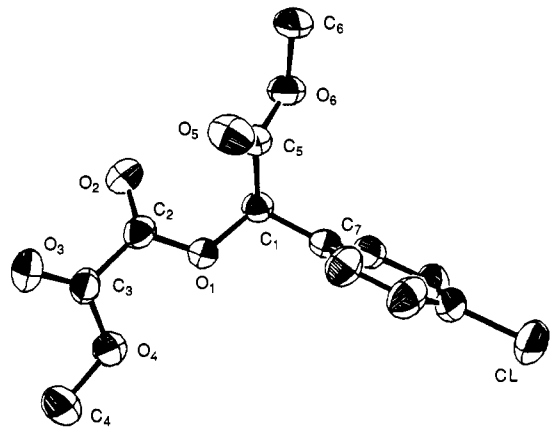


Figure 1. ORTEP view of the molecular structure of **11a**.

Table I. ^{13}C NMR Chemical Shifts of Photooxygenation Products of Ascorbic Acid Derivatives and Model Compounds[a]

compound	C-1	C-2	C-3	C-4	OMe
9a	157.15	156.65	166.66	74.32	53.83
					52.99
12	157.91	157.88	167.22	74.68	52.94
16	160.05	183.66	100.91	79.42	51.90
17	158.58	185.07	97.67	85.10	50.94
18	161.24	187.43	93.27	83.31	50.88
19	158.12	187.53	92.86	84.43	53.02
21a	170.45	94.29	105.02	81.97	51.83
					50.56
21b	170.45	94.29	105.08	81.98	51.78
22b	171.02	94.61	97.93	87.98	51.27
26	166.12	92.20	199.11	83.05	52.78
27	168.73	85.86	202.73	82.97	50.62
29	158.29	157.51	167.82	75.29	53.90
31	161.07	185.39	98.50	80.76	
32	169.75	90.84	202.56	83.57	
34	170.71	96.40	102.78	81.91	51.07
35	171.47	95.44	96.59	85.61	50.35
36	171.98	84.14	203.58	82.61	
37	162.48	161.64	169.47	74.74	

[a] All ^{13}C NMR spectra were obtained with a Bruker WP-200 or AM-360 spectrometer at −80 °C in CD_3OD or $(CD_3)_2CO$, except those of compounds **9a**, **12**, **29**, and **37**, which were obtained from Bruker AF-200, AM-360, and AM-500 instruments at room temperature in $CDCl_3$ or $(CD_3)_2CO$. Values are in δ (ppm). [b] C-1 and C-2 peaks of compound **9a**, **12**, and **38** were not separated.

Results

3-*O*-Methyl Ethers 6–8. In order to provide models for the photooxygenation of ascorbic acid, several compounds were synthesized. Acetonide methyl ester **6** was prepared by protecting the 5- and 6-hydroxy groups of L-ascorbic acid with acetone and reacting the more acidic 3-hydroxyl group with CH_2N_2.[10] Model

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Table II. ^{1}H NMR Chemical Shifts of Photooxygenated Products of Ascorbic Acid Derivatives and Model Compounds[a,b]

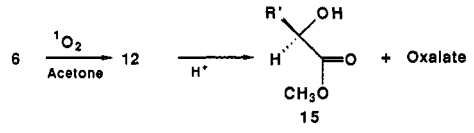
compound	H-4	H-5	H-6[c]		OCH_3
12	5.26 (d)	4.62 (q)	4.63 (m)	4.05 (m)	3.79 (s)
16	5.34 (d)	4.65 (q)	4.19 (m)	3.99 (m)	3.68 (s)
18	5.02 (d)	4.71 (q)	4.20 (m)	4.01 (m)	3.62 (s)
21b	4.62 (d)	4.45 (q)	4.06 (m)	3.77 (m)	3.43 (s)
26	5.41 (d)	4.78 (q)	4.21 (m)	4.02 (m)	3.68 (s)
29	5.25 (d)	4.67 (q)	4.11 (m)	4.04 (m)	3.93 (s)
31	4.84 (d)	4.45 (q)	4.18 (m)	3.98 (m)	
32	5.12 (d)	4.62 (q)	4.21 (m)	4.07 (m)	
34	5.03 (br)	4.72 (br, m)	4.05 (m)	3.89 (m)	3.18 (s)

[a] The spectra were obtained with Brucker WP-200 and AM-360 spectrometers in acetone-d_6. The following are the abbreviations used: d, doublet (J = 4.5–4.8 Hz; q, quartet (J = 5.0–5.2 Hz); s, singlet; m, multiplet. Values are δ (ppm) relative to internal TMS. All peaks at low temperatures in the ^{1}H NMR are broad. [b] At −70 or −50 °C and in CD_3OD or $(CD_3)_2CO$. [c] Chemically distinct hydrogens on CH_2.

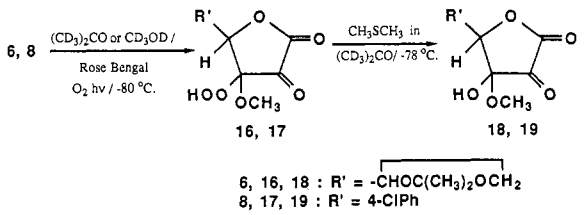
compounds **7**[11] and **8**[12] were also synthesized by methylation of 2-hydroxytetronic acids (3-hydroxyfuran-2,4(3*H*,5*H*)-diones).

Photooxygenation of **6–8** at room temperature in CH_3OH using rose bengal as the sensitizer gave about 80% of the oxalate methyl esters **9a**, **10a**, and **11a** and 20% of the corresponding acids **12–14** (Scheme II). The esters were purified by silica gel column chromatography. The oxalic acid monoesters were easily converted to methyl esters **9a**, **10a**, and **11a** by reaction with CH_2N_2 in methyl alcohol. Ethyl ester **9b**, purified by silica gel column chromatography, was produced by photooxygenation of **6** in ethyl alcohol. We confirmed the structure of **11a** by X-ray crystallography as methyl 2-(4-chlorophenyl)-2-[(methoxalyl)oxy]acetate (Figure 1).[13] Structures **9a**, **9b**, and **10a** were confirmed by comparison of their spectral data with those of **11a**. The structure of **9a** was further confirmed by comparison with reported spectral values[14] and by NMR (COSY, DEPT, and ^{1}H–^{13}C heterocorrelation 2-D NMR).[15] ^{13}C and ^{1}H spectra of these and other compounds are shown in Tables I and II, respectively.

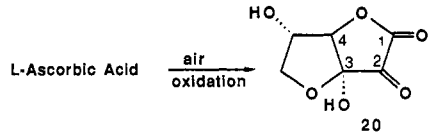
On photooxygenation of **6** in acetone at room temperature, oxalate **12** was the only product observed spectroscopically. Many attempts were made to isolate **12** with low-temperature silica gel and alumina column chromatography, but a small amount of threonate **15**[16] was the only product that could be separated. It is likely that oxalate **12** rapidly hydrolyzes to **15** under mildly acidic conditions.



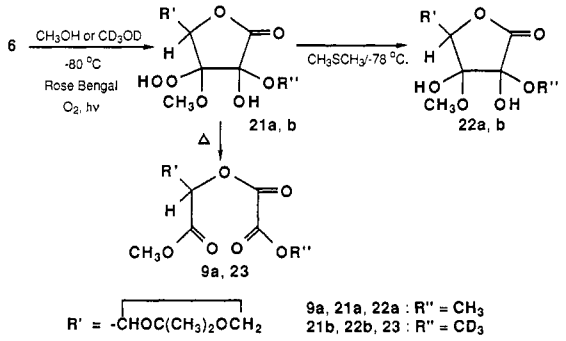
Detection of Unstable Compounds. An unstable mixture of hydroperoxy ketones is the initial product of the photooxygenation of L-ascorbic acid at low temperature.[7] This kind of hydroperoxy ketone was recently proposed by Hamilton as an intermediate in the oxygenation of L-ascorbic acid in biological systems.[17] Very similar hydroperoxy ketones are formed on photooxygenation of related enol ethers at low temperature. Photooxygenation of **6** and **8** in CD_3OD or acetone-d_6 at −80 °C using rose bengal as the sensitizer (λ >460 nm) gave only one product, identified by low-temperature ^{13}C NMR as ene product **16** and **17**, respectively. Usually, only 50–60% reaction occurred, because the rose bengal was bleached. In acetone-d_6, hydroperoxy ketones **16** and **17** are slowly reduced by dimethyl sulfide to give hydroxy ketones **18** and **19** along with dimethyl sulfoxide.[18] An upfield shift of 5–7 ppm for C-3 in the ^{13}C NMR spectrum (in acetone-d_6 at −78 °C; see Table I) occurs as the hydroperoxides are reduced to the alcohols. Upon warming the reaction mixture from **6** to room temperature, hydroperoxy ketone **16** gave oxalates **12** in acetone, **9a**[13] in methyl alcohol, and **9b** in ethyl alcohol, respectively.



Hemiketal **18** was identified by comparison of its spectra with those of similar compounds.[19] L-Ascorbic acid has several oxidized forms in aqueous solution, depending on pH. In particular, **18** closely resembles dehydroascorbic acid **20**, studied by Matusch in aqueous solution using NMR.[19e] The ^{13}C NMR chemical shift of C-2 (186.5 ppm) and C-3 (98.3 ppm) of **20** are very useful in establishing the structure of **18** (C-2 = 187.43 ppm and C-3 = 93.27 ppm).



We looked for detectable intermediates in the decomposition of **16** and **17** to **9a** and **11a**, respectively, in methyl alcohol. A solution of hydroperoxy ketone **16** in CD_3OD or acetone-d_6 containing CD_3OD was followed using low-temperature ^{13}C NMR (Table I). The C-2 (at 183.66 ppm) and C-3 (at 100.91 ppm) carbonyl peaks disappeared as new peaks at 94.29 and 105.02 ppm grew in. These peaks are characteristic of hemiketals. The new compound is assigned as hydroperoxy hemiketal **21b**. The rate of its formation depends on the concentration of methyl alcohol. In pure CD_3OD, hydroperoxy ketone **16** was converted to **21b** within 24 h at −78 °C.



Hydroperoxy hemiketal **21b** (R'' = CD_3) was slowly reduced by dimethyl sulfide to **22b** (6 days at −78 °C) and dimethyl sulfoxide. All attempts to isolate **22b** were unsuccessful, but the similarity of the ^{13}C NMR chemical shifts (C-2 = 94.61 ppm and C-3 = 97.93 ppm) of **22b** with those of hydrated dehydroascorbic acid monomer **24** (C-2 = 95.1 ppm and C-3 = 97.1 ppm in water)[19e] is consistent with the bishemiketal structure shown for **22b** and further confirms the structure of **21b** (C-2 = 94.29 ppm

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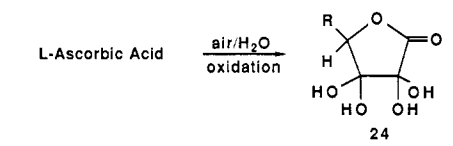


24

and C-3 = 105.02 ppm). Similar results were obtained with **21a** (R″ = CH_3), but the presence of methyl alcohol made the spectrum more complicated.

To obtain further evidence for the conversion of hydroperoxy ketone **16** to **21a** in methyl alcohol, a catalytic amount of methyl alcohol was added to the reaction mixture from the photooxygenation of **6** in acetone-d_6 at −78 °C. Two new methoxy peaks were observed in the low temperature ^{13}C NMR spectrum at 51.83 and 50.56 ppm. These methoxy peaks were not completely resolved in the ^1H NMR because of overlap with methyl alcohol. However, the C-3 methoxy peak of **16** shifted from δ 3.68 (**16**) to δ 3.43 (**21b**) in CD_3OD, showing that the C-2 carbonyl in **16** was converted to hemiketal **21b**. On warming the reaction mixture to room temperature, the formation of **9a** (from **21a** in CH_3OH) and **23** (from **21b** in CD_3OD) was observed by gas chromatography, ^1H NMR, and mass spectrometry.

Effect of Fluoride Ion. Photooxygenation of **6–8** at room temperature in nonpolar solvents ($CHCl_3$, CH_2Cl_2, CCl_4, etc.) using tetraphenylporphine (TPP) as sensitizer does not give detectable products, because the sensitizer is rapidly bleached. However, in the presence of tetrabutylammonium fluoride or 18-crown-6/KF, enol ethers **6–8** completely disappeared within 2 h to give oxalates **12–14**, respectively. However, hydroperoxy ketones, the initial products of photooxygenation of these enol ethers, were not detected even at −80 °C. This observation suggests that fluoride ion also acts to increase the rate of decomposition of unstable compounds. In a later section, further observations on the role of fluoride ion in these reactions are reported.

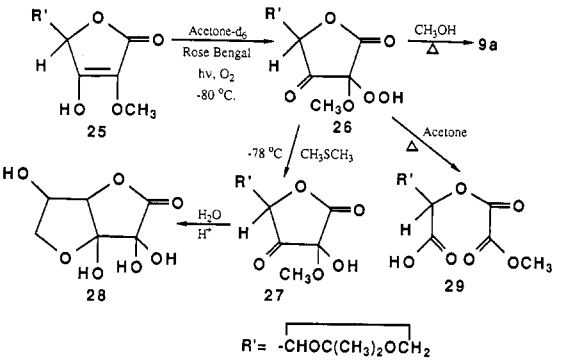
5,6-Isopropylidene-2-*O*-methyl-L-ascorbic Acid (25).[10] Photooxygenation of 2-*O*-methyl derivative **25** is fast and gives a single ene product, **26**, in acetone-d_6 or CD_3OD at low temperaure (100% reaction within 4 h) (Scheme III). Hydroperoxy ketone **26** is reduced by dimethyl sulfide to give **27** in CD_3OD and acetone-d_6. The reaction was monitored by low temperature ^{13}C NMR (see Table I). On warming to room temperature in methyl alcohol, **26** was converted to oxalates **29** (38%) and **9a** (62%), a ratio of acid to ester similar to that from **16**, which gives ester **9a** (over 80%) and acid **12** (20%). Hydroxy ketone **27** was converted at room temperature by hydrolysis under mildly acidic conditions to dehydroascorbic acid monomer **28**, identified by comparison of its ^1H and ^{13}C NMR values with reported values.[18] To confirm the structure of **28**, we prepared authentic samples by a literature route[18] and by reducing the corresponding hydroperoxide **4** from ascorbic acid with dimethyl sulfide at low temperature; the ^{13}C NMR of these samples were identical with that of **28**. The ^{13}C NMR chemical shifts of **28** were completely assigned by DEPT ^{13}C NMR (see Figure 2) and ^1H–^{13}C heterocorrelation 2-D NMR.[14] These results show that the initial product of photooxygenation of **25** has structure **26**.

Although 3-hydroperoxy ketone **16** reacts readily with methyl alcohol at −78 °C to give a hemiketal, 2-hydroperoxy ketone **26** does not react under these conditions, even if fluoride is added to the reaction mixture[9], in agreement with expectation that the C-2 carbonyl is more reactive than the C-3 carbonyl. Hydroperoxy ketone **26** also gave methyl ester **9a** in methyl alcohol and compound **29** in acetone on warming the reaction mixture to room temperature. No hemiketal intermediate in this reaction was detected.

5,6-Isopropylidene-L-ascorbic Acid (30).[20] As with ascorbic acid, rose bengal sensitized oxygenation of **30** in CD_3OD at −80 °C leads to rapid formation of unstable ene products, 3-hydroperoxy ketone **31** and 2-hydroperoxy ketone **32**, in 34% and 66% yield, respectively. These approximate yields were determined

(20) Jackson, K. G. A.; Jones, J. K. N. *Can. J. Chem.* **1969**, *47*, 2498.

Scheme III



Scheme IV

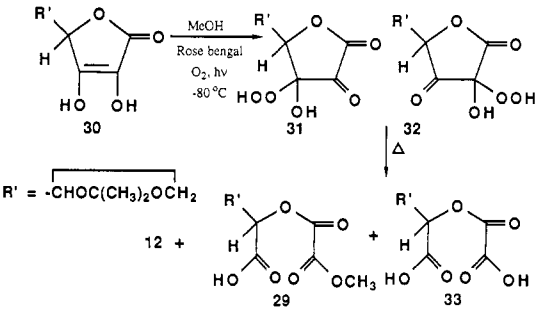


Table III. Products of Photooxygenation of **30** in CH_3OH (%)[a]

condn	12	29	33
25 °C	16.8	46.3	36.9
−10 °C[b]	17.5	59.8	22.7
−70 °C[b]	15.6	56.8	27.6
20 h[c]	15.3	66.7	18.0
80 h[c]	19.0	72.2	8.8

[a] 0.02 M in CH_3OH, yields were determined by integration of C-4 H and methoxy peaks using a Bruker AM-360. [b] After reaction, immediately heated to room temperature. [c] After photooxygenation at −80 °C, in dry ice/acetone bath.

by comparing integrations of C-4 H peaks in the ^1H NMR and peak intensities of carbonyl groups in the ^{13}C NMR of **31** and **32**. The structures of hydroperoxy ketones **31** and **32** were assigned by comparison of their spectral data with those of **16**, **17**, and **26**. Upon warming of the reaction mixture to room temperature in CH_3OH, the characteristic hydroperoxy ketone peaks disappeared and new ester carbonyl peaks appeared in the ^{13}C NMR spectrum. The 500-MHz ^1H NMR spectrum shows that three different oxalates, monoacid **12**, **29**, and diacid **33**, are formed from photooxygenation of **30** in methyl alcohol at room temperature. These compounds were identified by comparison of the ^1H NMR and ^{13}C NMR spectra with those previously observed for **12** and **29** and integration of methoxy and C-4 H peaks.

The product distribution varied depending on the reaction conditions. Oxalate **29**, which probably originates from 3-hydroperoxide **31**, was always produced in larger amounts than **12**, which presumably came from 2-hydroperoxide **32**, even though less **31** (34%) was initially formed than **32** (66%) in the photooxygenation of **30** in CH_3OH. For example, photooxygenation of **30** in methyl alcohol at −70 °C gives **12** (16%), **29** (57%), and **33** (27%) (Scheme IV).[21] The product ratio was determined by integration of the methoxy and C-4 H peaks of the oxalates in the ^1H NMR spectrum. However, after storage for 2 days at −78 °C followed by warming to room temperature, the ^1H NMR spectrum showed that **29** was produced in over 70% yield (see Table III).

(21) To confirm the monoesters **12** and **29** are produced only from hydroperoxy ketones, the diacid **33** was treated with methyl alcohol; no evidence for formation of monoesters from **33** was observed.

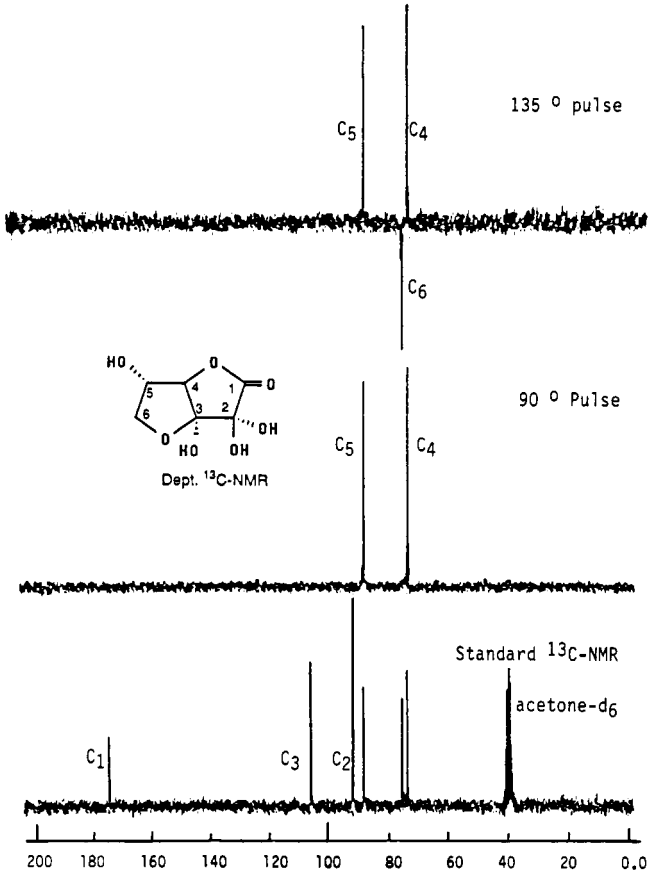


Figure 2. DEPT ^{13}C NMR of **28**.

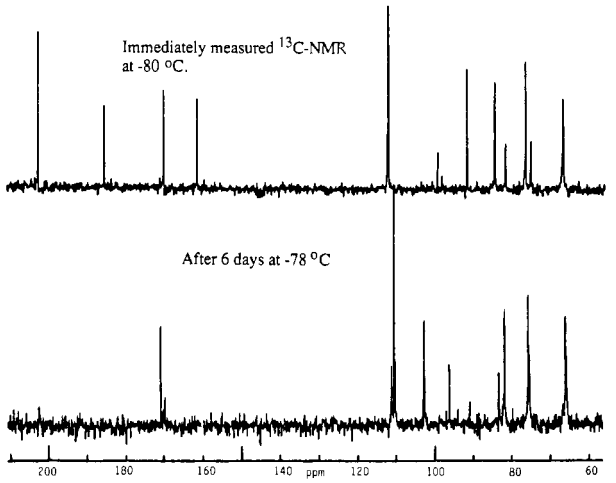
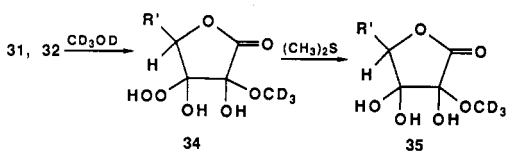


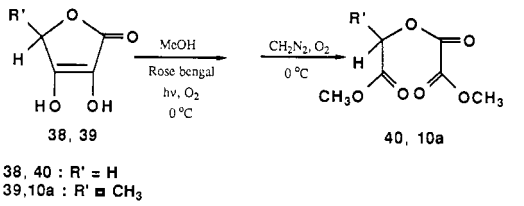
Figure 3. ^{13}C NMR of photooxygenation products of **30** in CD_3OD at −80 °C.

When the mixture from photooxygenation of **30** in CD_3OD stood at −78 °C for 24 h, the intensity of the C-2 and C-3 peaks of **31** and **32** (especially **31**) decreased and new two peaks at 102.78 and 96.40 ppm, corresponding to hemiketal **34**, appeared (see Figure 3). After 6 days at −78 °C, the yield of **34** from **31** and **32** was 100% and over 80%, respectively. Compound **34** was



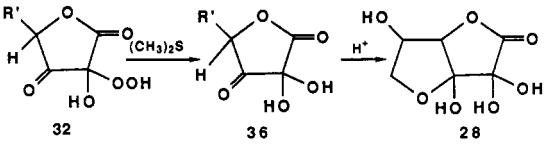
reduced at low temperature to **35** by dimethyl sulfide. The reaction rate is also increased by addition of 18-crown-6/KF, because fluoride ion acts as a basic catalyst.[9] This observation is in accord with results with ascorbic acid, where hydroperoxy ketones **2** and

Scheme V

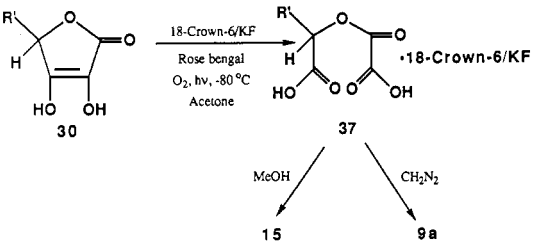


3 rearrange and cyclize to hydroperoxide **4**.[7]

To confirm the formation of **34**, photooxygenation of **30** was carried out in acetone-d_6 with a small amount of methanol and a catalytic amount of 18-crown-6/KF at −80 °C. A new methoxy peak at δ 3.18 in the ^1H NMR (see Table II) and 51.07 ppm in the ^{13}C NMR appeared. This peak corresponds to the C-2 methoxy of hemiketal **34**. As with compound **16**, addition of CH_3OH to the C-2 carbonyl of **31** is much faster than reduction of the hydroperoxy group by dimethyl sulfide. Therefore, we could not detect the reduction product from **31**. However, hydroperoxide **32** was slowly reduced by dimethyl sulfide to give **36**, which gives dehydroascorbic acid **28** under acidic conditions, suggesting that 2-hydroxyperoxide **32** has a longer lifetime than 3-hydroperoxide **31** in methyl alcohol.



Photooxygenation of **30** also showed a strong fluoride ion effect.[8,9] Enediol **30** is very slightly soluble in acetone at room temperature. However, with 18-crown-6/KF, we could prepare a 0.1 M solution in acetone at −78 °C. Photooxygenation of **30** in acetone or acetonitrile is sluggish, and only bleaching of the sensitizer occurs at all temperatures. However, if 18-crown-6/KF or tetrabutylammonium fluoride is added, **30** is completely converted to oxalate complex **37** at −78 °C within 3 h. Compound **37** was isolated and its structure confirmed by ^1H and ^{13}C NMR spectra, FAB mass spectrometry, and elemental analysis. Complex **37** reacts with diazomethane to produce oxalate **9a** and gives threonate **15** on stirring in methyl alcohol for 2 h. All attempts to determine the X-ray crystal structure of **37** were unsuccessful.

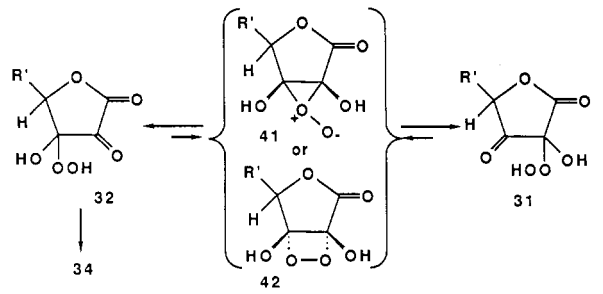


2-Hydroxytetronic Acid Derivatives.[11] Two 2-hydroxytetronic acid derivatives (**38** and **39**) were prepared and photooxygenated under the same conditions as the ascorbic acid derivatives. After the rose bengal sensitized photooxygenation of **38** and **39** in the presence of a filter solution (cutoff below 460 nm) in methyl alcohol at 0 °C, the reaction mixtures containing mono- and diacid were treated with diazomethane to give dimethyl esters (Scheme V). Dimethyl esters **40** and **10a** were purified by silica gel column chromatography and the structures were confirmed by comparison of the spectral data with those of **11a**. These results agree well with those for photooxygenation of ascorbic acid derivative **30** and further confirm the proposed mechanistic schemes.

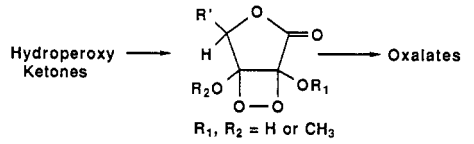
Discussion

We showed previously that the initial product of photooxygenation of L-ascorbic acid is a mixture of hydroperoxy ketones **2** and **3**. The present results support our earlier conclusions and permit a more detailed description of the reaction schemes leading to the observed products. The decomposition of hydroperoxy

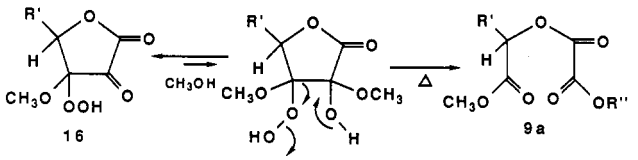
Scheme VI



ketones at room temperature to oxalates could be explained by a dioxetane pathway similar to that proposed for analogous α-keto cyclic enol ethers.[22] Hamilton,[23] however, has pointed out that highly strained dioxetanes are not necessarily intermediates in the decomposition of the hydroperoxy ketones to corresponding carbonyl compounds.



Both 3-hydroperoxy ketone **16** and 2-hydroperoxy ketone **26** gave the same oxalate dimethyl ester **9a** in CH_3OH on warming to room temperature. This suggests that **9a** can be obtained not only via a metastable hydroperoxy hemiketal but also by other pathways, since **16** reacts readily with CH_3OH at low temperture to give hydroperoxy hemiketal **21a**, but no hydroperoxy hemiketal is detected from **26**. This could be explained if methyl alcohol



attack directly on the C-3 carbonyl of **26** gives the hemiketal only in small amount at equilibrium and it rapidly cleaves to give dimethyl ester **9a** on warming the reaction mixture to room temperature. This mechanism is analogous to one suggested by Hamilton for the enzymatic cleavage of ascorbate.[17]

The product distribution from the photooxygenation of **30** is very dependent on reaction conditions. In acetone with fluoride ion, for example, only oxalate complex **37** was detected. In methyl alcohol, the product distribution depends on temperature (see Table III). As mentioned in an earlier section, oxalate **29** is always the major product from the photooxygenation of **30** in methyl alcohol, despite formation of two hydroperoxy ketones **31** and **32**. When the initial mixture was kept in a dry ice acetone bath, the relative abundance of **29** increased with time. The product distribution suggests that an equilibrium between **31** and **32** occurs at low temperature, as with the products from ascorbic acid. Additional evidence for the equilibrium is that only hydroperoxy hemiketal **34** was detected in the ^{13}C NMR at −70 °C from **31** and **32** in CD_3OD. Scheme VI is proposed as a reasonable working model for the formation of **34** from **31** and **32**. Initially, nucleophilic attack by the hydroperoxy group of **32** on the reactive C-3 carbonyl produces perepoxide **41** or dioxetane **42** as an intermediate. The intermediate rearranges to **31**, which is easily converted to the more stable **34** in methyl alcohol, as the α-keto ester is an extremely reactive group, which provides the driving force for the rearrangement from **32** to **31**. No evidence for formation of intermediates **41** and **42** was found, even at −80 °C. As shown in Table III, formation of oxalate monoester **12** from **32** does not depend much on reaction conditions, but formation of monoester **29** and diacid **33** are sensitive to temperature.

It was observed previously that the hydroperoxy ketones from photooxygenation of ascorbic acid (**1**) rearranged to hydroperoxy hemiketal **4** by intramolecular cyclization.[7] In this case, the C-6 OH adds to the relatively unreactive C-3 carbonyl, because intramolecular cyclization is more favorable than intermolecular reaction.

The reaction rate of singlet oxygen with enol ethers **6** and **25** seems to correlate with the acidity of the hydroxy group. The 2-methoxy derivative **25**, with a C-3 OH (pK_a = 3.2),[24] reacts with singlet oxygen about 5 times faster than **6**, with a C-2 OH (pK_a = 7.9).[24] The photooxygenation of diol **30** (pK_1 = 4.2, pK_2 = 11.8) gives 2-hydroperoxide **32** as the major product, from attack at the more acidic C-3 OH.[24] The ratio of **32**/**31** is about 2.

Conclusion

Reaction of singlet oxygen with enediols and enol ethers possessing abstractable acidic hydrogens gives hydroperoxy ketones of the "ene" type. The enediol functionality gives two kinds of hydroperoxy ketones which are in equilibrium, presumably through a dihydroxy dioxetane or perepoxide. Upon warming to room temperature, the hydroperoxy ketones cleave to oxalates. The initial product distribution depends on the acidity of hydroxy groups, with the more acidic hydroxy group being more easily converted to hydroperoxy ketone.

Experimental Section

Enol esters **6** and **25** were prepared by methylation with diazomethane and dimethyl sulfate, respectively, from 5,6-isopropylidene-L-ascorbic acid,[10] and **30** was also prepared by literature methods.[19] 2-Hydroxytetronic acid derivatives **7**, **8**,[12] **39**, and **40** were prepared by known methods.[11]

Rose bengal and tetraphenylporphine were obtained from Aldrich. THF was distilled from sodium under a N_2 atmosphere, with benzophenone as indicator. All other commercially available reagents were used without further purification.

Photooxygenations were performed with either a Varian-Eimac 300-W Xenon lamp or a 650-W Sylvania tungsten–halogen lamp (DWY). The output of the lamp was filtered with a 0.1 M K_2CrO_4 solution (in NH_4OH/NH_4Cl at pH 10) to remove light below 460 nm.[25] The photolysis was carried out in Pyrex tubes inside a temperature-controlled cell described previously.[26] Oxygen was passed through a drying tube containing anhydrous $CaCl_2$ and molecular sieves and bubbled through the solution being photooxygenated via a Teflon tube.

Analytical gas chromatography was done using a Hewlett-Packard Model 5800 equipped with a 25-m 50% phenyl/50% methyl silicone capillary coluymn and a FID detector. IR was done on a Perkin-Elmer Model 137 instrument; mass spectra were done on an AEI MS-902 instrument or an AEI MS-9 for FAB mass spectrometry. Low-temperature ^1H and ^{13}C NMR data were obtained on a Bruker WP-200 operating at 200 MHz for ^1H NMR and 50 MHz for ^{13}C NMR. Chemical shift values are reported in δ (ppm) relative to internal TMS standard. 2-D NMR (COSY), DEPT (for ^{13}C NMR), and ^1H–^{13}C heterocorrelation 2-D spectra were obtained with Bruker AF-200 or Bruker AM-500 instruments.[16]

Photooxygenation of 6. Enol ether **6** (0.23 g, 1.0 mmol) was combined with 20 mL of a 6 × 10^{-4} M solution of rose bengal in acetone, methyl alcohol, or ethyl alcohol and photooxygenated for 3 or 4 h at −70 °C with the 650-W DWY lamp. The resulting mixture was concentrated under vacuum to yield crude products as a yellowish oil. When acetone was used as solvent, threonate **15** was separated by silica gel column chromatography with acetonitrile/CH_2Cl_2 as eluent, yield 5% as an oil. Methyl 3,4-*o*-isopropylidene-L-threonate, **15**: ^1H NMR ($CDCl_3$): δ 1.37 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 2.93 (br, 1 H, OH), 3.78 (s, 3 H, CH_3O), 3.95–4.16 (m, 3 H, CH_2O and >CHO), 4.4 (dt, J = 1.7, 3 Hz, 1 H, >CHOH). ^{13}C NMR ($CDCl_3$): 172.71 (s), 110.01 (s), 76.12 (d),

(22) (a) Utaka, M.; Nakatani, M.; Taketa, A. *J. Org. Chem.* **1986**, *51*, 1140. (b) Utaka, M.; Nakatani, M.; Taketa, A. *Tetrahedron Lett.* **1983**, *24*, 803.

(23) (a) Hamilton, G. A. In *Molecular Mechanism of Oxygen Activation*; Hayaishi, O., Ed.; Academic Press: New York, 1974; p 405–451. (b) Fraser, M. S.; Hamilton, G. A. *J. Am. Chem. Soc.* **1982**, *104*, 4203.

(24) The pK_a values are for the parent compounds, 2-*O*-methyl- and 3-*O*-methyl-L-ascorbic acid, and L-ascorbic acid itself. Probably, the pK_a of these compounds are very similar. See ref 10.

(25) *Synthetic Organic Photochemistry*; Horspool, W. M., Ed.; Plenum Press: New York, 1984; p 493.

(26) Ogilby, P. R.; Foote, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 3424.

70.08 (d), 65.48 (t), 53.03 (q), 25.98 (q), 25.17 (q) ppm. IR (film): 3510, 1755, 1080 cm^{-1}. Mass spectrum: *m/e* 244 (M^+).

Methyl 3,4-*o*-isopropylidene-2-*o*-(methoxalyl)-L-threonate, **9a**: When methanol was used as solvent, oily product **9a** was separated by silica gel column chromatography (ethyl acetate/hexane), in 60% yield. ^1H NMR ($CDCl_3$): δ 5.23 (d, J = 4.5 Hz, 1 H, >CHO), 4.61 (q, J = 5.1 Hz, 1 H, >CHO), 4.21–4.01 (m, 2 H, CH_2O), 3.93 (s, 3 H, CH_3O), 3.81 (s, 3 H, CH_3O), 1.43 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): see Table I. IR (film): 2960, 1770, 1750, 1440, 1370, 1200, 1010 cm^{-1}. Mass spectrum: *m/e* 276 (M^+).

Photooxygenation of **6** in ethanol produced **9b** as an oil, isolated by SiO_2 chromatography with ethyl acetate/hexane, yield 50%. Methyl 3,4-*o*-isopropylidene-2-*o*-(ethoxalyl)-L-threonate, **9b**: ^1H NMR ($CDCl_3$): δ 5.21 (d, J = 4.8 Hz, 1 H, CHO), 4.63 (q, J = 5.9 Hz, 1 H, CHO), 4.39 (q, J = 6.9 Hz, 2 H, OCH_2), 4.21–4.01 (m, 2 H, CH_2O), 3.81 (s, 3 H, OCH_3), 1.47 (s, 3 H, CH_3), 1.39 (t, J = 7 Hz, CH_3), 1.37 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): 166.71, 156.95, 156.72, 74.16, 74.05, 65.68, 63.53, 52.97, 25.96, 25.33, 13.89. IR (film): 1770, 1760 cm^{-1}. Mass spectrum: *m/e* 290 (M^+). Anal. Calcd for $C_{12}H_{18}O_8$: C, 49.65; H, 6.25. Found: C, 49.52, H, 6.31.

Methyl 3,4-*o*-isopropylidene-2-*o*-(methoxaloyl-d_3)-L-threonate, **23**, was separated from photooxygenation of **6** in CD_3OD as an oil by SiO_2 column chromatography. ^1H NMR ($CDCl_3$): δ 1.37 (s, 3 H), 1.47 (s, 3 H), 3.81 (s, 3 H), 3.89–4.17 (m, 2 H), 4.58 (q, 1 H, J = 5.1 Hz), 5.23 (d, 1 H, J = 5.1 Hz). Mass spectrum: *m/e* 293 ($M^+ + NH_4$), by chemical ionization using NH_3 as ion source.

Low-Temperature Photooxygenation of 6. Enol ether **6** (0.23 g) was dissolved in 5 mL of CD_3OD or acetone-d_6, and 2 or 3 mg of rose bengal was added to the solution. Photooxygenation was carried out in a 10-mm NMR tube at −80 °C for 4 h with a K_2CrO_4 filter solution. The resulting solution was allowed to stand in a liquid nitrogen bath and the ^{13}C NMR immediately measured at −80 °C. When CD_3OD was used as solvent, only hydroperoxy ketone **16** was detected. After standing at −78 °C overnight, hydroperoxy ketone **16** was completely converted to hemiketal **21**. Excess dimethyl sulfide was added to the solution, and the resulting mixture was kept at −78 °C for 1 week. **21** was completely reduced to hemiketal **22**. In acetone-d_6, only 60% of enol ether **6** was converted to **16**, because rose bengal was bleached, in contrast to the case in CD_3OD. Hydroperoxy ketone **16** in acetone-d_6 was reduced to **18** by dimethyl sulfide.

Photooxygenation of 6 with Fluoride Ion. A KF complex of 18-crown-6 ether was prepared by stirring anhydrous potassium fluoride (0.12 mol) with a solution of the 18-crown-6 ether (0.1 mol) in 60 mL of methanol under N_2 overnight.[27] The white, solid complex was dried under vacuum.[25] Enol ether **6** (460 mg, 2 mmol) and 500 mg (1.5 mmol) of the complex were combined with 10 mL of 2×10^{-4} M TPP in $CHCl_3$ and photooxygenated for 2 h at 0 °C with the 650-W DWY lamp. The resulting mixture was concentrated under vacuum to yield a brownish, oily residue. The ^1H NMR spectrum showed signals for oxalate **8** and crown ether. ^1H NMR ($CDCl_3$): δ 7.8 (br, OH), 5.29 (d, J = 4.3 Hz, >CHO, 1 H), 4.68 (m, >CHO, 1 H), 4.02–4.21 (m, CH_2O_2H), 3.79 (s, OCH_3), 1.41 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3), 3.68 (s, 24 H, crown ether).

Photooxygenation of 25. Enol ether **25** (0.23 g, 1 mmol) was photooxygenated in 5 mL of acetone-d_6 at −80 °C with rose bengal. The enol ether disappeared within 2 h and initially gave hydroperoxy ketone **26**, which was converted to **27** and **29** by reduction with dimethyl sulfide for 5 days at −78 °C and warming to room temperature, respectively. To the solution of **26**, a catalytic amount of 18-crown-6/KF complex and 5 drops of methanol were added, and the ^{13}C NMR spectrum was monitored for 3 days; no change was found. Upon warming to room temperature, the reaction mixture gave dimethylated **9a** (68%) and monomethylated **29** (32%). The ratio was determined by integration of methoxy peaks in the ^1H NMR spectrum of the product mixture.

Photooxidation of 30 with 18-Crown-6/KF Complex. Ascorbic acid derivative **30** (0.21 g, 1 mmol) and 0.36 g (1.1 mmol) of 18-crown-6/KF complex were combined with 10 mL of acetone saturated with rose bengal and photooxygenated at −70 °C for 3 h. During this time, crude **37** precipitated as a white solid. The resulting mixture was filtered rapidly, and the collected solid was washed with two portions of cold acetone to yield 0.28 g of **37** as a light reddish solid containing some rose bengal. Pure **37** was obtained by recrystallization from acetonitrile and ethyl ether; mp 127–129 °C (dec.). IR (KBr): 1710 cm^{-1} (C=O). ^1H NMR (CD_3CN): δ 7.6 (br, 2 OH), 5.15 (d, J = 5.5 Hz, 1 H), 4.54 (q, J = 5.5 Hz, 1 H), 3.96–4.49 (m, 2 H), 3.62 (s, 24 H), 1.42, 1.34 (s, 2 CH_3). Anal. Calcd for $C_{21}H_{36}O_{14}KF$: C, 44.2; H, 6.34; K, 6.85; F, 3.33. Found: C, 44.06; H, 6.34; K, 6.85; F, 3.33.

Photooxygenation of 7, 8, 38, and 39. The 2-hydroxytetronic acid derivatives were photooxygenated under the same conditions as **5**.

Methyl 2-[(methoxalyl)oxy]acetate (**40**) was obtained as an oil by treatment with CH_2N_2 of the photooxygenated products of 2-hydroxytetronic acid **38** in methyl alcohol, yield 70%. ^1H NMR ($CDCl_3$): 4.81 (s, 2 H), 3.93 (s, 3 H), 3.79 (s, 3 H). ^{13}C NMR ($CDCl_3$): 166.61 (s), 157.28 (s), 156.73 (s), 62.18 (t), 53.85 (q), 52.64 (q) ppm. IR (film): 2980, 1780, 1775, 1440, 1210, 1170, 910 cm^{-1}. Anal. Calcd for $C_6H_8O_6$: C, 40.92; H, 4.58. Found: C, 40.91; H, 4.54. Mass spectrum: *m/e* 176 (M^+).

Methyl 2-methyl-2-[(methoxalyl)oxy]-L-acetate (**10a**) was isolated as an oil from the photooxygenation mixture of **7** in methyl alcohol by SiO_2 chromatography, yield 54%. ^1H NMR ($CDCl_3$): 5.24 (q, 1 H, J = 7.1 Hz), 3.93 (s, 3 H), 3.77 (s, 3 H), 1.62 (d, 3 H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 169.49 (s), 156.94 (s), 156.86 (s), 70.68 (d), 53.50 (q), 52.49 (q), 16.77 (q) ppm. IR (film): 1785, 1770 cm^{-1} (C=O). Anal. Calcd for $C_7H_{10}O_6$: C, 44.21; H, 5.26. Found: C, 44.18; H, 5.13. Mass spectrum: *m/e* 190 (M^+).

Methyl 2-(4-chlorophenyl)-2-[(methoxalyl)oxy]acetate (**11a**) was purified by SiO_2 chromatography as an oil, which crystallized on chilling. Recrystallization from acetone/hexane gave colorless crystals, yield 38%; mp 105.3 °C. Mass spectrum: *m/e* 286 (M^+). IR (KBr): 2980, 1764, 1755, 1738, 1495, 1437, 1325, 1215, 1175, 1166, 1098, 1030, 785 cm^{-1}. ^1H NMR ($CDCl_3$): 7.42 (aromatic, 4 H), 6.02 (s, 1 H), 3.93 (s, 3 H), 3.76 (s, 3 H). ^{13}C NMR ($CDCl_3$): 167.52, 157.20, 156.55, 135.90, 130.98, 129.25, 129.11, 75.44, 53.83, 53.13 ppm. Anal. Calcd for $C_{12}H_{11}O_6Cl$: C, 50.28; H, 3.86; Cl, 12.37. Found: C, 50.33; H, 4.01; Cl, 12.37.

X-ray Crystallographic Determination of 11a. Colorless crystals of **11a** were grown by vapor diffusion of pentane into a $CHCl_3$ solution. A rectangular parallelopiped single crystal was mounted in a glass capillary. Diffraction data were collected at room temperature on a Picker diffractometer equipped with a graphite monochromator. Unit-cell parameters were determined by a least-squares refinement of 34 reflections $20° < 2\theta < 10°$). The intensities were corrected for Lorentz and polarization effects but not for absorption. All non-hydrogen atoms were located with the direct methods program MULTAN.[28] The hydrogen positions were calculated and not refined. More detailed information of refinement and parameters are given in the supplementary material.

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Supplementary Material Available: Summary of detailed crystal data, a listing of anisotropic and positional and equivalent isotropic temperature factors, and tables of bond lengths and angles derived from crystallographic analysis of **11a** (7 pages). Ordering information is given on any current masthead page.

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