Self-Sensitized Photooxygenation of 3,4-Dialkoxyfurans to Vitamin C or Its Derivatives

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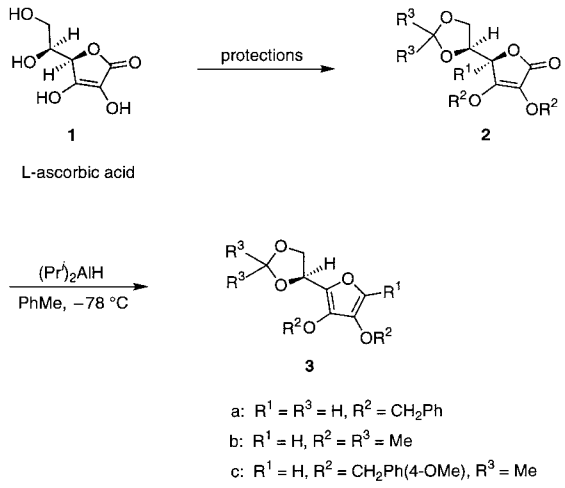
Self-sensitized photooxygenation of 3,4-dialkoxyfurans **3a**−**d** with molecular oxygen and UV- or sunlight at room temperature gave vitamin C derivatives **2a**−**d** in good to excellent yields. Furan **3c**, having photodegradable protecting groups, was also photooxygenated to give L-ascorbic acid (**1**) in a "one-pot" reaction. Furthermore, a novel photolytic transformation was developed for deuteration of furan **3b** at the C-2 position with D_2O to give furan **3d** in 95% yield. Toxicity of furans **3a**−**c** and butenolides **2a**−**c** against human embryonic cell, murine embryo fibroblasts, normal fibroblasts, HeLa, and Vero cell lines in the presence of oxygen and indirect solar light was found to be much less than those of the antipsoriasis drugs anthralin and 8-methoxypsoralen.

Introduction

3,4-Dialkoxyfurans are known to be much more reactive than furan itself.[1] Quantum mechanical calculations by PPP- and CNDO-methods showed that, in comparison to furan, 3,4-dialkoxyfurans possess enhanced partial negative charge at the C-2 and C-5 positions, higher acidity at the α-positions, a stronger and, at the same time, inverted dipole moment, and high reactivity even toward electrophiles.[1] As such, it occurred to us that 3,4-dialkoxyfurans may also readily react with oxygen to serve as efficient antioxidants. Thus, suitable analogues may be useful as therapeutic agents.

Psoriasis is a highly proliferative skin disease;[2a] its topical treatment often involves anthralin[2b] or psoralens[2c] (i.e., 8-methoxypsoralen, 8-MOP). Psoriatic cells have been shown to consume more molecular oxygen than normal epidermal cells,[3] and so drugs such as anthralin act as oxygen scavengers within the cell and thus lower the proliferative rate.[4] However, the generation of superoxide anion, a highly toxic species,[5] by anthralin inside the cell is a source of serious side effects.[6] On the other hand, 8-MOP, administered orally or topically, is activated by UV light which the patient is subjected to after administration. Photosensitization, and consequently antiproliferative effects, occur when psoralen reaches the skin, either by local absorption following topical application or through the circulation after ingestion and absorption through the gastrointestinal tract.[2c] However, mutagenic and photocarcinogenic properties related to these drugs are undesired side effects.[2c] The immune system, the Langerhans cells, and circulating T-lymphocytes may also be affected.[2d] Herein we report our findings that 3,4-dialkoxyfurans **3a**−**d** can function as efficient oxygen scavengers, yet do not produce superoxide. Newly synthesized furans **3a**−**c** and their photooxygenated products **2a**−**c** exhibited much less cellular toxicity than either anthralin or 8-MOP.

Scheme 1. Preparation of 3,4-Dialkoxyfurans 3a−c from L-Ascorbic Acid (1)



Results and Discussion

3,4-Dialkoxyfurans **3a**−**c** were prepared from L-ascorbic acid (vitamin C, **1**) in three steps as shown in Scheme 1. After sequential protection of the hydroxy groups in

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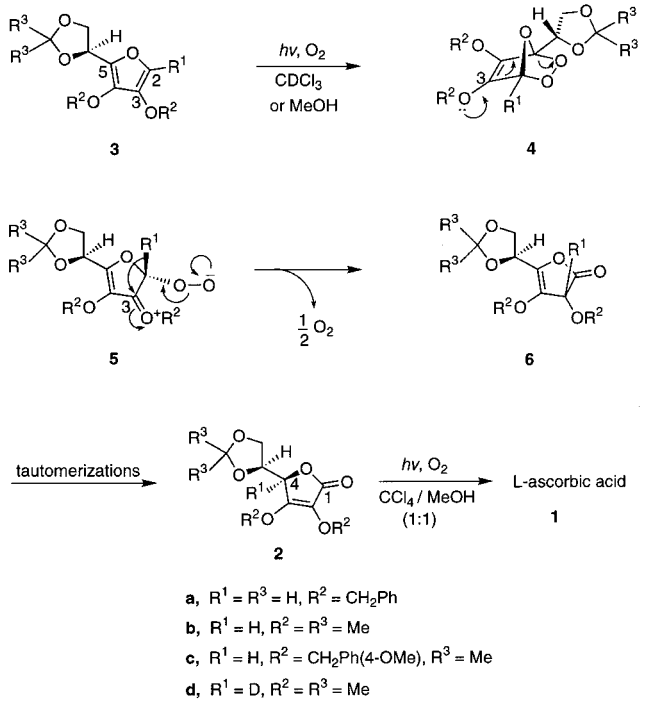
Scheme 2. Mechanism for the Conversion of Dialkoxyfurans 3 to Butenolides 2



1, the resultant butenolides[7] **2a**−**c** were treated with diisobutylaluminum hydride in toluene at −78 °C to give the desired furans **3a**−**c** (∼82% yield).

Upon irradiation with UV light (λ > 250 nm) under an oxygen atmosphere at room temperature, **3a** and **3b** in $CDCl_3$, MeOH, or 65:35 (mL/mL) MeOH/H_2O were respectively converted to butenolides **2a** and **2b** in 70−76% yields within 3 h (Scheme 2). The optical rotations of **2a** ($[\alpha]^{21}_D$ 39.869°, c = 1.17 g/100 mL, $CHCl_3$) and **2b** ($[\alpha]^{23}_D$ 9.758°, c = 1.00 g/100 mL, $CHCl_3$) obtained in this way were in good agreement with those synthesized directly from L-ascorbic acid (**1**) (Scheme 1). Photochemical conversion of triplet molecular oxygen ($^3O_2$) to singlet oxygen ($^1O_2$) often requires a sensitizer, such as rose bengal.[8] Although the conversion of **3a**,**b** to **2a**,**b** occurred in the presence of rose bengal, it was discovered that the photosensitizer was not necessary. This result is interesting since furans acting as sensitizers is not hitherto described. The ability of furans **3a** and **3b** to act as sensitizers may be due to the presence of electron-donating groups at C-3 and C-4 positions, which facilitate the intersystem crossing of an excited singlet to the triplet and therefore generation of $^1O_2$. To prove this, we irradiated, individually, **3a** and **3b** in the presence of oxygen and a singlet oxygen quencher such as 1,4-diazabicyclo[2.2.2]octane (DABCO). The reactions failed to produce the corresponding butenolides **2a** and **2b**, and only starting materials were recovered. Moreover, we found that the alkoxy groups in furans were essential for their conversions to butenolides, as evidenced in the unsuccessful photooxygenation of 2,5-dimethylfuran and dimethyl 3,4-furandicarboxylate, along with furfuryl alcohol and the corresponding *tert*-butyldimethylsilyl ether derivative under the same reaction conditions. Furthermore, the oxidation of furans **3a** and **3b** to the respective butenolides **2a** and **2b** did not take place in the dark even when the reaction temperature was raised to 77 °C.

The strong absorption of 3,4-dialkoxyfurans **3a** and **3b** in the 270−300 nm range suggested that the oxidation might be promoted by sunlight.[9a−c] This was ascertained by exposing an air-saturated solution of **3a** or **3b** in CCl_4 to sunlight for 8 h. In this way, butenolides **2a** or **2b** were isolated in 82−87% yield. Replacement of air with oxygen gas allowed for a more efficient reaction; quantitative yields were obtained after 6 h. The efficiency of the oxidation process was found to be solvent dependent. The half-life of **3a** was 3.5, 12.0, and ∼75 h for its oxidation to **2a** in CCl_4, $CDCl_3$, and MeOH, respectively, in which the corresponding lifetimes of $^1O_2$ are 700, 300, and 5.0 μs, respectively.[9d] Thus, we conclude that the rate of conversions of **3a** → **2a** and **3b** → **2b** depends on the lifetime of $^1O_2$ in reaction media.

We also measured consumption of molecular oxygen by furan **3b** under sunlight. A slow and yet steady uptake of oxygen[10] by **3b** (0.886 g, 3.63 mmol) in CCl_4 (15 mL) proceeded in a catalytic hydrogenator under atmospheric pressure for 6 h. Results from ^{1}H NMR studies indicate paralleled rate of oxygen uptake and the conversion of **3b** → **2b**. The reaction was complete after a 99% mol equiv of **3b** uptake of oxygen gas (22.8 mL) was reached. The above photochemical transformation was then conducted in the presence of nitro blue tetrazolium[11] to check for the presence of superoxides. Gratifyingly, the UV absorption at 560 nm associated with nitro blue diformazan, the reaction product between nitro blue tetrazolium and superoxide, was not observed. As well, the conversion of furan **3b** to butenolide **2b** was also found to occur in the presence of superoxide dismutase in 80% yield. Given these two results, we are confident that the superoxide anion is not involved in these reactions. The conversion of **3** → **2** (85% yield) was also found to be achieved in the presence of a stoichiometric amount of a radical scavenger, 2,6-di-*tert*-butyl-4-methylphenol, which indicates that radical intermediates are not involved in the above conversions. In addition, the toxicity of furans **3a**−**c** and butenolides **2a**−**c** against various cell lines in the presence of sunlight and oxygen was found to be much less than anthralin and 8-MOP.

A proposed mechanism for the photooxidation of 3,4-dialkoxyfurans **3** to **2** is depicted in Scheme 2. Under photolytic conditions, furans **3** could convert $^3O_2$ to $^1O_2$, which would be consumed through [4 + 2] cycloaddition[12a] with furan to form endoperoxides **4**.[12b,13] Structural

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Table 1. Toxicity of Furans 3a−c, Butenolides 2a−c, Rose Bengal, Anthralin, and 8-Methoxypsoralen (8-MOP) in the Presence of Solar Light and Oxygen on the Growth of Cell Lines

	CC_{50}[a] (μM)				
compound	HEL	MEF	Hef522	HeLa	Vero
2a	>120	>120	>120	>120	>120
2b	>120	>120	>120	>120	>120
2c	>120	>120	>120	>120	>120
3a	83.25 ± 3.14	70.11 ± 2.61	90.05 ± 2.79	63.92 ± 1.35	78.51 ± 1.97
3b	93.04 ± 2.87	77.35 ± 3.04	95.76 ± 1.94	52.63 ± 0.86	84.12 ± 2.13
3c	87.69 ± 1.90	80.46 ± 2.51	98.14 ± 3.02	39.78 ± 1.15	95.69 ± 1.88
rose bengal	<0.05	<0.05	0.13 ± 0.04	<0.05	0.08 ± 0.01
anthralin	14.96 ± 0.45	9.67 ± 0.58	16.05 ± 1.32	6.99 ± 0.21	13.49 ± 0.76
8-MOP	4.25 ± 0.16	3.21 ± 0.07	7.08 ± 0.55	0.87 ± 0.06	5.28 ± 0.30

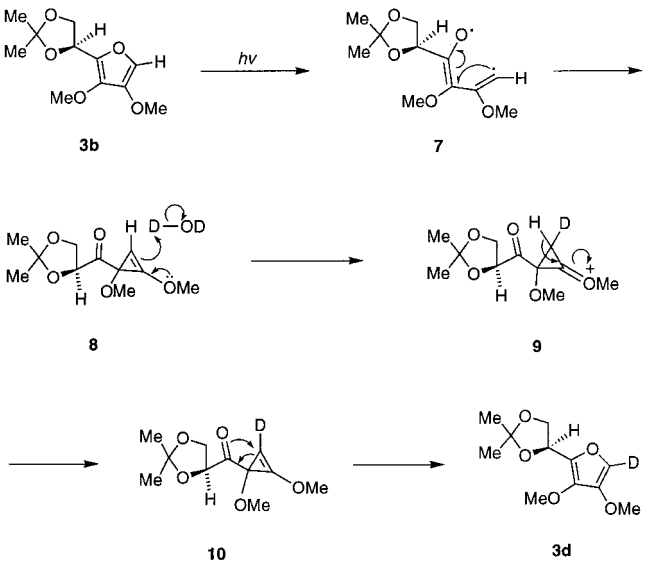
[a] Cytotoxic concentration required to reduce cell growth by 50%.

features of furan endoperoxides govern formation of different products.[12] We believe that the C-3 alkoxy group in **4** would induce a C−O bond cleavage to generate oxonium ion **5**,[14] which undergoes a 1,2-hydride shift[15] to afford β,γ-butenolides **6**. The oxygen atom that was lost during the conversion of **5** to **6** was transferred to a suitable acceptor such as dimethyl sulfide to produce dimethyl sulfoxide.[13,14,16] Finally, the C−C double bond in **6** shifts to the thermodynamically more stable α,β-position through tautomerizations to give vitamin C derivatives **2**, a class of nontoxic compounds (see Table 1).[17] To observe the endoperoxide intermediate, photooxygenation of **3b** at −75 °C in $CDCl_3/CFCl_3$ was carried out. After 4 h, the ^1H NMR spectrum, recorded at −70 °C, showed the presence of only the endoperoxide **4b**. When the solution was allowed to warm-up to room temperature, the spectrum of endoperoxide **4b** collapsed to that of butenolide **2b**. It should be noted that the reaction of dimethoxyfuran **3b** with other standard oxidants such as bromine or 3-chloroperbenzoic acid produced a mixture of unidentifiable compounds. As such, bimolecular oxygen transfer is a critical element of the mechanism.

Furan **3c**, possessing photodegradable groups,[18] was then synthesized as a precursor to vitamin C (**1**) in a "one-pot" reaction. Thus, irradiation of **3c** in a mixture of CCl_4 and MeOH (1:1) under an oxygen atmosphere produced ascorbic acid **(1)** in 74% yield after 7 h. Analysis of the above reaction after 2.0 h showed that butenolide **2c** is an intermediate for the formation of **1**, as expected. After 3.0 h, we isolated 2,3-bis(4-methoxybenzyl)-5,6-isopropylidene-L-ascorbic acid (**2c,** 40% yield) and 2,3-bis(4-methoxybenzyl)-L-ascorbic acid (30% yield). This indicates that photodegradation of isopropylidene group is faster than that of the 4-methoxybenzyl functionality. On the other hand, the same reaction under direct exposure to sunlight produced butenolide **2c** in 78% yield after 16 h. Indirect exposure of furans **3a−c** to sunlight in a mixture of DMSO-d_6 and D_2O (1:1) under oxygen atmosphere also generated butenolides **2a−c** in about 80% yield after 42 h.

According to the pathway shown in Scheme 2, the C-2 hydrogen in **3** is transferred to the C-4 position of **2**. To obtain evidence in support of this mechanism, we irradiated furan **3d** bearing a deuterium at the C-2 position in the presence of $^3O_2$ in $CDCl_3$ with UV light (λ > 250 nm). Butenolide **2d** bearing a deuterium at the C-4 position was obtained in 90% yield along with butenolide **2b** in 10% yield. In less anhydrous conditions, the yield of the deuterated butenolide **2d** decreased to 60%, whereas the yield of **2b** increased to 40%. These results lend support to the proposed mechanism involving a tautomerization of **6** to **2** (Scheme 2), rather than a photochemically allowed suprafacial 1,3-hydrogen shift.

Scheme 3. A plausible Mechanism for Photolytic Deuteration of 3,4-Dialkoxyfuran 3b



Furthermore, we developed an efficient and intriguing method for the preparation of deuterated furan **3d**. Irradiation of **3b** in a mixture of $CDCl_3$ and D_2O with UV light (λ > 250 nm) in the absence of oxygen gave **3d** in 95% yield. The proposed mechanism shown in Scheme 3 can account for the transformation. Cyclopropene intermediate **8**[19a,19b] is generated via diradical **7** by photolysis of **3b**. Deuterium exchange of **8** with D_2O to generate **10** via oxonium ion **9** could result from the electron-donating capability of the vinylic methoxy group. Finally, photoisomerization of **10** will give deuterated furan **3d**.

Anticellular Activity. Inhibition of the proliferation of human embryonic cell (HEL), murine embryo fibroblasts (MEF), normal fibroblasts (Hef522), HeLa, and

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Vero cells by furans **3a**−**c**, butenolides **2a**−**c**, rose bengal, anthralin, and 8-MOP were carried out[20] in the presence of oxygen and solar light. The control cell lines received the same amount of oxygen. Toxicity of the tested compounds is expressed as the cytotoxic concentration required to reduce normal cell growth by 50% (CC_{50}). Results are summarized in Table 1.

Anthralin generates superoxide anion, a highly toxic species;[5,6] yet furans **3a**−**c** did not form superoxide in the photooxidation process. Thus, furans **3a**−**c** were found to be much less toxic than anthralin. As such, the second oxygen atom lost after ring opening of the endoperoxide (cf. step **5** → **6**) did not outweigh the benefit of not forming superoxide. On the other hand, oxygen-dependent photodegradation of 8-MOP will produce furocoumarin derivatives, which can react with membrane components, causing irreversible damage to the cell.[2c] As a result, 8-MOP exhibited higher toxicity than furans **3a**−**c**. Rose bengal as a sensitizer converted $^3O_2$ to $^1O_2$, which damaged the cells (Table 1). Under solar light, furans **3a**−**c** also converted $^3O_2$ to $^1O_2$; yet consumption of which by the furans produced nontoxic butenolides **2a**−**c**.

Conclusions

3,4-Dialkoxy-5-alkylfurans **3a**−**d** were developed as novel oxygen scavengers, yet they did not produce noxious superoxide. In the presence of UV- or sunlight and air, photooxygenation of **3a**−**d** proceeded through an unprecedented pathway at room temperature to give ascorbic acid **1** or its derivatives **2a**−**d** in good to excellent yields. Newly synthesized furans **3a**−**c** were found to be much less toxic than anthralin toward various cell lines. These properties may prove to be of great potential to the development of furans **3a**−**c** as antipsoriasis therapeutics.

Experimental Section

General. For anhydrous reactions, glassware was dried overnight in an oven at 120 °C and cooled in a desiccator over anhydrous $CaSO_4$ or silica gel. Reagents were purchased from Fluka Chemical Co. and used as is. Solvents, including dry ether and tetrahydrofuran (THF), were obtained by distillation from the sodium ketyl of benzophenone under nitrogen. Other solvents, including chloroform, dichloromethane, ethyl acetate, and hexanes were distilled over CaH_2 under nitrogen. Absolute methanol and ethanol were purchased from Merck and used as received.

Melting points were obtained with a Büchi 510 melting point apparatus. Infrared (IR) spectra were recorded on a Perkin-Elmer Paragon 1000 Fourier Transform spectrophotometer. Carbon-13 NMR and proton NMR spectra were obtained on a Varian XL-300 (300 MHz) spectrometer. Mass spectra were carried out on a VG 70−250 S mass spectrometer. Photolytic experiments were carried out by use of a 450-watt medium-pressure mercury Canrad-Hanovia lamp with a Pyrex filter. A sunlight lamp was obtained from Surprise. Com., Inc.

Purification on silica gel refers to gravity column chromatography on Merck Silica Gel 60 (particle size 230−400 mesh). Analytical TLC was performed on precoated plates purchased from Merck (Silica Gel 60 F_{254}). Compounds were visualized by use of UV light, I_2 vapor, or 2.5% phosphomolybdic acid in ethanol with heating.

Standard Procedure for Preparation of 5-Substituted-3,4-dialkoxyfurans 3a−c. To a solution of butenolides **2a**−**c** (1.0 mmol) in toluene (17.0 mL) was added diisobutylaluminum hydride at −78 °C under argon. After stirring for 1.0 h at the same temperature, phosphate buffer (1.0 M, pH 7.2, 20 mL) solution was added. The organic layer was washed with water (20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by use of column chromatography (CH_2Cl_2 as eluant) to give the corresponding furans **3a**−**c** in about 82% yield. For **3a**: ^{1}H NMR ($CDCl_3$) δ 3.73 (dd, J = 8.00, 6.02 Hz, 1H, HC(7)), 3.84 (dd, J = 8.00, 6.02 Hz, 1H, HC(7)), 4.79 (dd, J = 6.02, 6.02 Hz, 1H, H-C(6)), 4.88 (s, 2H, OCH_2O), 4.95 (d, J = 15.60 Hz, 2H, $H_2COC(4)$), 5.04 (s, 2H, $H_2COC(3)$), 6.92 (s, 1H, H-C(2)), 7.30−7.37 (m, 10H, $2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 66.38, 68.33, 72.98, 75.09, 95.39, 124.10, 127.36, 128.15, 128.25, 128.34, 128.54, 136.30, 136.70, 137.80, 142.99; UV (EtOH): λ_{max} 269 (ϵ 19030), 275 (ϵ 18500), 298 (ϵ 17300); CIMS m/z: 353 ($M^+ + 1$), 352 (M^+). Anal. Calcd for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found: C, 71.55; H, 5.74. For **3b**: ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3H, CCH_3), 1.46 (s, 3H, CCH_3), 3.69 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.04 (dd, J = 7.00, 5.50 Hz, 1H, HC(7)), 4.11 (dd, J = 7.00, 5.50 Hz, 1H, HC(7)), 5.07 (dd, J = 5.50, 5.50 Hz, 1H, H-C(6)), 6.91 (s, 1H, H-C(2)); ^{13}C NMR ($CDCl_3$) δ 25.90, 26.13, 58.11, 61.21, 66.13, 68.94, 109.43, 122.74, 136.31, 138.24, 144.28; UV (EtOH): λ_{max} 267 (ϵ 18330), 274 (ϵ 17410), 296 (ϵ 18400); CIMS m/z: 229 ($M^+ + 1$), 228 (M^+). Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.89; H, 7.07. Found: C, 57.91; H, 7.12. For **3c**: ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 3H, CCH_3), 1.35 (s, 3H, CCH_3), 3.68 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.72 (dd, J = 7.00, 5.45 Hz, 1H, HC(7)), 3.83 (dd, J = 7.00, 5.45 Hz, 1H, HC(7)), 4.78 (dd, J = 5.45, 5.45 Hz, 1H, H-C(6)), 4.73 (s, 2H, OCH_2), 4.89 (s, 2H, OCH_2), 6.86 (s, 1H, H-C(2)), 6.96 (AB, 4H, C_6H_4), 7.02 (AB, 4H, C_6H_4); ^{13}C NMR ($CDCl_3$) δ 25.83, 26.10, 55.12, 66.08, 68.72, 72.70, 74.70, 109.23, 113.64, 113.85, 124.09, 128.47, 128.95, 129.96, 130.22, 136.59, 137.39, 142.96, 159.55; UV (EtOH): λ_{max} 270 (ϵ 21000), 278 (ϵ 19490), 297 (ϵ 18550); CIMS m/z: 441 ($M^+ + 1$), 440 (M^+). Anal. Calcd for $C_{25}H_{28}O_7$: C, 68.17; H, 6.41. Found: C, 68.20; H, 6.51.

2-Deuterio-3,4-dimethoxy-6,7-isopropyliden-5-ylfuran (3d). A solution of **3b** (114 mg, 0.491 mmol) in a mixture of $CDCl_3$ (1.6 mL) and D_2O (1.6 mL) was irradiated with UV light by use of a medium-pressure mercury lamp (450 W, λ > 250 nm) equipped with a Pyrex glass filter at room temperature under argon for 5 h. The solution contained >95% of **3d** as evidenced by NMR analyses. ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 3H, CCH_3), 1.49 (s, 3H, CCH_3), 3.72 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.10 (dd, J = 6.96, 6.57 Hz, 1H, HC(7)), 4.17 (dd, J = 6.96, 6.57 Hz, 1H, HC(7)), 5.14 (dd, J = 6.57, 6.57 Hz, 1H, H-C(6)); ^{13}C NMR ($CDCl_3$) δ 25.73, 25.92, 58.14, 61.22, 66.16, 68.99, 109.45, 122.54 (t, J = 125.00 Hz, D-C(2)), 136.29, 138.29, 144.19; UV (EtOH): λ_{max} 266 (ϵ 18,000), 275 (ϵ 16,500), 295 (ϵ 17,600); CIMS m/z: 230 ($M^+ + 1$), 229 (M^+).

Standard Procedure for Preparation of 2,3-Dialkoxy-5,6-alkylidene-L-ascorbic Acids 2a−d. A solution of **3a**−**d** (0.50 mmol) in $CDCl_3$ (2.70 mL) was irradiated by a 450-W medium-pressure Hanovia mercury lamp (λ > 250 nm) placed inside a water cooled (15−25 °C) Pyrex immersion well. Oxygen flow was maintained during photolysis, and the reaction temperature was kept near 20 °C by regulating the temperature of the water. After 3.0 h, the solvent was concentrated under reduced pressure, and the residue was purified by use of column chromatography (20% EtOAc in hexanes as eluant) to give the corresponding vitamin C derivatives **2a**−**d** in about 75% yield. For **2a**: mp 62−63 °C; IR (KBr) 1764 (C=O), 1681 (C=C) cm$^{-1;}$ H NMR ($CDCl_3$) δ 3.82 (dd, J = 8.60, 6.60 Hz, 1H, HC(6)), 3.91 (dd, J = 8.60, 6.60, 1H, HC(6)), 4.09−4.14 (ddd, J = 6.60, 6.60, 2.80 Hz, 1H, H-C(5)), 4.46 (d, J = 2.80 Hz, 1H, H-C(4)), 4.81 (s, 2H, OCH_2O), 5.02 (s, 2H, $H_2COC(2)$), 5.09 (d, J = 8.60 Hz, 2H, $H_2COC(3)$), 7.09−7.28 (m, 10H, $2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 65.56, 72.98, 73.45, 73.59, 74.64, 96.06, 121.04, 127.62, 128.45, 128.90, 135.13, 135.75, 156.39, 168.66; MS m/z: 368 (M^+); CIMS m/z: 369 ($M^+ + 1$), 368 (M^+). Anal. Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.58; H, 5.59. For **2b**: mp 91−92 °C; IR

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(KBr) 1760 (C=O), 1677 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (s, 3H, CCH_3), 1.36 (s, 3H, CCH_3), 3.82 (s, 3H, $H_3COC(2)$), 3.94 (dd, J = 8.40, 6.40 Hz, 1H, HC(6)), 4.02 ((dd, J = 8.40, 6.40 Hz, 1H, HC(6)), 4.12 (s, 3H, $H_3COC(3)$), 4.21−4.29 (ddd, J = 6.40, 6.40, 3.00 Hz, 1H, H-C(5)), 4.48 (d, J = 3.00 Hz, 1H, H-C(4)); ^{13}C NMR ($CDCl_3$) δ 25.52, 25.78, 59.43, 60.30, 65.20, 73.83, 74.43, 110.34, 123.20, 156.66, 168.88. MS m/z: 244 (M^+), 229 ($M^+ - CH_3$), 187 ($M^+ - CH_3 - C(CH_3)_2$); CIMS m/z: 245 ($M^+ + 1$), 244 (M^+), 229 ($M^+ - CH_3$), 187 ($M^+ - CH_3 - C(CH_3)_2$). Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.18; H, 6.71. For **2c**: Foam; IR ($CHCl_3$) 1763 (C=O), 1679 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (s, 3H, CCH_3), 1.37 (s, 3H, CCH_3), 3.77 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.94 (dd, J = 8.42, 6.41 Hz, 1H, HC(6)), 4.01 (dd, J = 8.42, 6.41 Hz, 1H, HC(6)), 4.14−4.20 (ddd, J = 6.41, 6.41, 2.90 Hz, 1H, H-C(5)), 4.46 (d, J = 2.90 Hz, 1H, H-C(4)), 4.98−5.10 (m, 4H, $2OCH_2$), 7.08 (AB, 4H, C_6H_4), 7.22 (AB, 4H, C_6H_4); ^{13}C NMR ($CDCl_3$) δ 25.51, 25.75, 54.92, 55.07, 65.09, 73.23, 73.84, 74.54, 109.98, 113.55, 113.78, 120.76, 127.35, 128.05, 129.64, 130.62, 130.74, 131.04, 156.72, 179.78, 169.08; CIMS m/z: 457 ($M^+ + 1$), 456 (M^+). Anal. Calcd for $C_{25}H_{28}O_8$: C, 65.78; H, 6.18. Found: C, 65.81; H, 6.22. For **2d**: mp 98−102 °C; IR (KBr) 1770 (C=O), 1675 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (s, 3H, CCH_3), 1.39 (s, 3H, CCH_3), 3.84 (s, 3H, $H_3COC(2)$), 4.03 (dd, J = 9.6, 6.40, 1H, HC(6)), 4.12 (dd, J = 9.6, 6.40, 1H, HC(6)), 4.09 (s, 3H, $H_3COC(3)$), 4.29 (dd, J = 6.40, 6.40 Hz, 1H, H-C(5)); CIMS m/z: 246 ($M^+ + 1$), 245 (M^+), 230 ($M^+ - CH_3$), 188 ($M^+ - CH_3 - C(CH_3)_2$).

Observation of Endoperoxide 4b through Photooxygenation of Furan 3b at Low Temperature. A solution of **3b** (0.20 mmol) in $CDCl_3/CFCl_3$ (1.2 mL, 3:1) was irradiated with a 450-W medium-pressure Hanovia mercury lamp (λ > 250 nm). During the irradiation, oxygen was bubbled through the solution which was kept at −75 °C. After 4.0 h the reaction was complete, and the ^1H NMR spectrum recorded at −70 °C showed only the endoperoxide **4b**. ^1H NMR ($CDCl_3/CFCl_3$, −70 °C) δ 1.50 (br s, 6H, 2 CCH_3), 3.59 (br s, 6H, 2 OCH_3), 4.21 (dd, J = 9.51, 6.70 Hz, 1H, HC(7)), 4.35 (dd, J = 9.51, 6.70 Hz, 1H, HC(7)), 5.26 (dd, J = 6.70, 6.70 Hz, 1H, H-C(6)), 6.24 (s, 1H, H-C(2)). At −27 °C, the ^1H NMR spectrum showed the presence of both endoperoxide intermediate **4b** and butenolide **2b** (~1:2). At ambient temperature, product **2b** was present exclusively.

Conversions of Furans 3a−c to Respective Butenolides 2a−c in the Presence of Sunlight. To a solution of **3a**, **3b**, or **3c** (0.10 mmol) in CCl_4 containing CH_3SCH_3 (0.065 mmol) was bubbled air for 1.0 min. The ^1H NMR spectrum at 25 °C was taken immediately; then the solution was exposed to sunlight. After 8 h, the spectrum of **3a−c** changed to that of **2a−c**, respectively, and CH_3SCH_3 was converted to $CH_3S(O)CH_3$. In the large scale reactions (2.0 mmol of **3a−c**), **2a** (82% yield), **2b** (87% yield), and **2c** (85% yield) were isolated.

Photolysis of Furan 3c to Ascorbic Acid (1). A solution of **3c** (440 mg, 0.998 mmol) in a mixture of CCl_4 (4.0 mL) and MeOH (4.0 mL) was irradiated with UV light by use of a medium-pressure mercury lamp (450 W, λ > 250 nm) equipped with a Pyrex glass filter at room temperature under oxygen for 7 h. Then, the solution was concentrated, and diethyl ether was added to afford a solid. Filtration and crystallization of the solid with EtOH gave ascorbic acid (**1**) in 74% yield. It was identical with an authentic sample. Filtrate was evaporated, and the resultant 4-methoxybenzaldehyde was also characterized.

Toxicity Test Procedure in Vitro. Human embryonic cell (HEL), murine embryo fibroblasts (MEF), normal fibroblasts (Hef522), HeLa, and Vero cell lines were cultured in DMEM supplemented with 10% FBS, 2.0 mM glutamine, 100 U/mL penicillin, and 100 μg/mL streptomycin in a humidified atmosphere with 5% CO_2 and 20% O_2 at 37 °C. After 24 h, furans **3a−c**, butenolides **2a−c**, rose bengal, anthralin, and 8-MOP, at various concentrations, were added, and the cultures were exposed indirectly to solar light during the day and to the sunlight lamp at night. The cell numbers of the control cultures as well as those cultures supplemented with the test compounds were determined after 12, 24, 48, 72, and 96 h of growth. The CC_{50} values were estimated from dose−response curves compiled from two independent experiments and represent cytotoxic concentration (μM) required to reduce normal cell growth by 50% after 96 h incubation (Table 1).

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