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Scope and Limitations of the Photooxidations of 2-(α-Hydroxyalkyl)furans: Synthesis of 2-Hydroxy-*exo*-brevicomin

Dimitris Noutsias, Antonia Kouridaki, and Georgios Vassilikogiannakis*

Department of Chemistry, University of Crete, Vasilika Vouton, 71003 Iraklion, Crete, Greece

**E-mail: vasil@chemistry.uoc.gr.*

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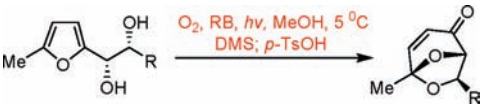
ABSTRACT



Photooxygenation of 2-(α-hydroxyalkyl)furans at 5 °C in MeOH followed by in situ reduction affords, in one synthetic operation, 6-hydroxy-3(2*H*)-pyranones and/or 5-hydroxy-2(5*H*)-furanones. The relative ratio of the final products is highly dependent on the substitution of the starting furan substrate. Photooxygenation of 2-(α,β-dihydroxyalkyl)furans followed by in situ reduction and ketalization with acid rapidly provides the 6,8-dioxabicyclo[3.2.1]oct-3-en-2-one framework. This new methodology was successfully applied to the synthesis of 2-hydroxy-*exo*-brevicomin.

It is well-known that with multifarious advantages and disadvantages to each discrete method, 2-(α-hydroxyalkyl)-furans can be oxidized to afford the corresponding 6-hydroxy-3(2*H*)-pyranones (**1** → **2**, Scheme 1) under a variety of conditions, including Br_2/MeOH,[1] peracids (e.g., *m*-CPBA,[2] magnesium monoperoxypthalate[3]), NBS,[4] dioxiranes (DMDO[5]), metal-based oxidations (PCC,[6] VO(acac)$_2$/*t*-BuOOH,[7] titanium(IV) silicalite 1/H_2O_2[8]), as well as with electrochemical oxidation.[9] The proliferation of methods available to undertake this transformation attests to the synthetic versatility of the 6-hydroxy-3(2*H*)-pyranone unit, and yet, major problems remain to anyone wishing to apply these protocols within a synthetic context mostly arising from the lack of selectivity and/or harshness associated with these existing oxidative methods.

With some tentative initial findings[10] in mind from early investigations in our field of interest, namely, the reactivity of furans with singlet oxygen,[11] we felt there might possibly exist a synthetically valuable and mild method using singlet oxygen as oxidant with which the 6-hydroxy-3(2*H*)-pyranone unit could be accessed that has not yet been properly investigated and deconvoluted.

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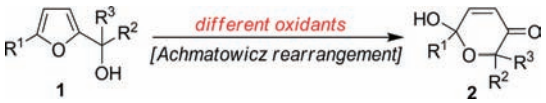
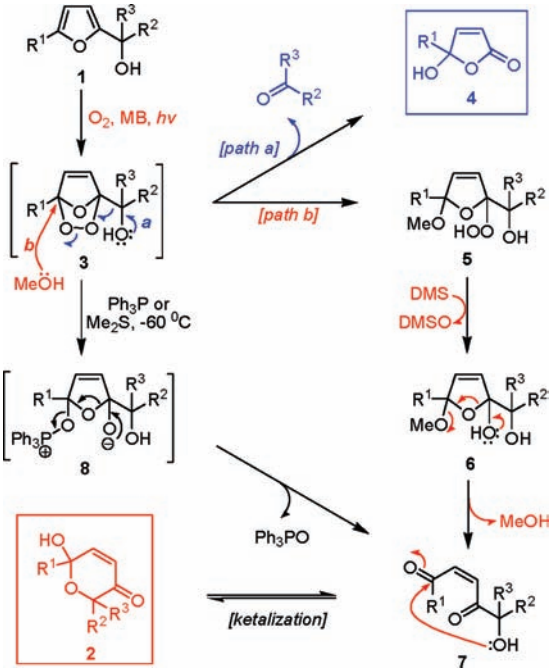
Scheme 1. Achmatowicz Rearrangement



Scheme 2. Competing Pathways



To outline the idea and place it in context with what is known already, the mechanisms invoked for such singlet oxygen oxidations must first be examined. It is very reasonable to assume that 6-hydroxy-3(2*H*)-pyranone **2** might be the final product of the $^1O_2$-oxidation of 2-(α-hydroxyalkyl)furans of type **1** via intermediate formation of enedione **7** (Scheme 2). There is, however, a competing fragmentation pathway which frequently leads to the formation of the 5-hydroxy-2(5*H*)-furanone nucleus **4** (via path **a**, Scheme 2).[12] It has been observed that when the photooxidations were performed at low temperature, and the intermediate ozonides **3** were also reduced at low temperature by dimethyl sulfide (DMS) or PPh_3, the formation of 6-hydroxy-3(2*H*)-pyranone **2** was seen to dominate (**3** → **8** → **7** → **2**, Scheme 2).[12,13] This adapted $^1O_2$ technology was successfully applied as one of the key steps in the total synthesis of cryptofauronol,[13a] as well as in the synthesis of secodolastanes,[13b] cyathin,[13c] and taxane[13d] diterpene skeletons. In the first case, the problem of concurrent oxidation of the disubstituted double bond when either Br_2/MeOH[1] or *m*-CPBA[2] were used as oxidant was eliminated.[13a] Similarly, the highly chemoselective singlet oxygen oxidation of a furan nucleus to yield the corresponding intermediate 1,4-enedione, in the presence of two trisubstituted double bonds on the 2-alkyl side chain, was achieved in the total synthesis of litseaverticillols.[14] Application of the literature protocols for the direct oxidation of furans to 1,4-enediones, involving treatment with either Br_2/MeOH,[1] *m*-CPBA,[2] or magnesium monoperoxypthalate (MMPP),[3] had led to rapid bromination or epoxidation of the side chain double bonds.

These prior investigations, however, leave an important question unanswered: Which one of the two possible paths (fragmentation **a** or intermolecular nucleophilic opening **b**, Scheme 2) would prevail if the reaction was run in a nucleophilic solvent such as MeOH at temperatures much closer to the ambient ideal? In other words, can the oxidation mechanism be manipulated and diverted, by the introduction of a nucleophilic solvent (MeOH), in order to promote the desired reaction pathway. To this end, there was a need to explore the photooxygenation of 2-(α-hydroxyalkyl)-furans in MeOH at more user-friendly temperatures (e.g., 5 °C), in order to understand how this adjustment would affect the final product distribution, (5-hydroxy-2(5*H*)-furanone of type **4** vs 6-hydroxy-3(2*H*)-pyranones of type **2**). The 6-hydroxy-3(2*H*)-pyranone unit is a highly prized synthetic intermediate by virtue of the fact that it contains at least three reactive sites for further synthetic elaboration, so development of a mild and selective methodology for its synthesis would be of great value. Finally, it is important to note that from a practical standpoint, as already intimated, low-temperature photooxidations are not easy reactions to perform, and developing a method that operates much closer to room temperature is therefore highly desirable.

An investigation aimed at clarifying all these issues started with the simplest possible substrate, namely, the completely unsubstituted 2-(α-hydroxymethyl)furan (**1a**, Scheme 3). When furan **1a** was subjected to a standard set of singlet oxygen ($^1O_2$) photooxygenation conditions (catalytic quantities of rose bengal as photosensitizer, oxygen bubbling through the reaction mixture with irradiation from a visible spectrum light) for 4 min, the formation of an equimolar mixture of hydroperoxides

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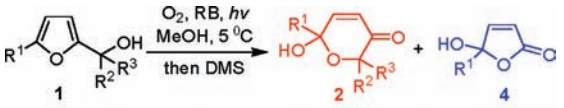
Scheme 3. Photooxidation of 2-(α-Hydroxyalkyl)furans



furan	R^1	R^2	R^3	2 (%)[a]	4 (%)[a]
1a	H	H	H	50	50
1b	H	H	*n*-Bu	2	98
1c	H	H		-	100
1d	H	Me	Me	-	100
1e	Me	H	H	97	3
1f	Me	H	*n*-Bu	85	15
1g	Me	Me	Me	80	20
1h	Me	H		-	100
1i	Me	H	Ph	-	100
1j	Ph	H	H	75	25
1k	Ph	H	*n*-Bu	2	98
1l	Me	H		92	8
1m	Me	H		91	9
1n	H	H		2	98

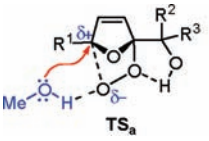
[a] Relative ratios were determined by ^{1}H NMR of the crude photooxidation mixture.

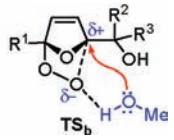
(see **5**, Scheme 2) and fragmentation product **4a** was observed by ^{1}H NMR spectra of the crude reaction mixture. Overnight treatment of this reaction mixture with dimethyl sulfide afforded an equimolar mixture of 6-hydroxy-3(2*H*)-pyranone **2a** and 5-hydroxy-2(5*H*)-furanone **4a**. Any additional substitution at the furylic position (see furans **1b**−**d**, Scheme 3) resulted in almost exclusive formation of the undesired fragmentation product **4a**.

The next modification to the photooxidation substrate to be investigated was substitution at the 5-position of the furan, initially focusing on replacing the hydrogen with a methyl group (**1e**−**g**, Scheme 3). This minor change altered completely the outcome of the reaction, favoring the formation of 6-hydroxy-3(2*H*)-pyranones **2e**, **2f**, and **2g**. Curiously, however, this methyl-substitution, when combined with the presence of a prenyl or a phenyl group at the furylic position (**1h** and **1i**, Scheme 3), afforded almost exclusively 4-hydroxybutenolides **4** via the once again dominant fragmantation pathway.

When the methyl group at the 5-position of the furan was replaced with a phenyl (**1j**, Scheme 3), formation of pyranone **2j** ($R^2 = R^3 = H$) predominated. Pyranone **2j** was isolated as an equillibrium mixture with the open 1,4-enedione of type **7**. In contrast, almost completely dominant was fragmentation when furanol **1k** (R^2 = H, R^3 = *n*-Bu) was subjected to photooxidation.

These results show clearly that the substitution pattern at position-5 (R^1) of the starting 2-(α-hydroxyalkyl) furan **1** is absolutely crucial in determining the course of the reaction. Thus, when R^1 = H, almost exclusive formation of the fragmentation product 4-hydroxybutenolide **4** was observed; while, when R^1 = methyl or phenyl formation of 6-hydroxy-3(2*H*)-pyranone **2** dominated. These results are consistent with the R^1-substituent stabilizing a developing positive charge during the nucleophilic attack of MeOH onto the intermediate ozonide ($\mathbf{TS_a}$). It is also reasonable to propose that the extra intramolecular hydrogen bond possible only in the case of $\mathbf{TS_a}$ makes it a more stable when compared to its regioisomer, $\mathbf{TS_b}$.





The upshot of the stabilizing effect of the alkyl substituent at position 5 is that nucleophilic opening (path **b**, Scheme 2) is kinetically favored when compared to the alternative fragmentation pathway (path **a**). A similar mechanistic explanation had been invoked previously, to explain the regioselective attack of MeOH, EtOH, and *i*-PrOH onto the more sterically hindered 2-position of a 2-alkylfuran endoperoxide.[15] To a lesser extent, the substitution of the furylic position (R^2 and R^3) also plays a role in determining the product distribution. Higher order substitution at the furylic position leads to an increase of the fragmentation pathway (e.g., **1a** vs **1b** vs **1d**, **1e** vs **1f** vs **1g**, and **1j** vs **1k**). It is also obvious that when R^3 = prenyl or phenyl (substrates **1c**, **1h**, and **1i**) exclusive formation of the fragmentation products was observed. These latter results may be rationalized by a faster elimination of a very stable conjugated aldehyde, or benzaldehyde, compared to the alternative attack of methanol. In agreement with our previous observations,[14] the prenyl side chain of substrates **1c** and **1h** did not undergo a singlet oxygen ene reaction under the reaction conditions.

Another important finding is the predominant formation of the desired 6-hydroxy-3(2*H*)-pyranone **2l** and **2m** when the R^3 substituent contains a carbonyl at the *β*-position. Once again, and in agreement with the previous results, when R^1 becames hydrogen (substrate **1n**, Scheme 3) almost exclusive formation of the fragmentation product was observed.

With all these results in mind, exploration of the photooxygenation of 2-(α,*β*-dihydroxyalkyl)furans seemed appropriate for the following two reasons. First, it was necessary to investigate the infuence that the extra hydroxyl at the *β*-position of the alkyl side-chain has on the product distribution (**12** vs fragmentation product **4e**, Scheme 4). Second, it was anticipated that a useful and efficient *one-pot* synthesis of 6,8-dioxabicyclo[3.2.1]oct-3-en-2-ones (**13**, Scheme 4) could be developed.

To this end, 2-(α,*β*-dihydroxyalkyl)furans **11a**−**c** were easily prepared using Wittig reactions between different phosphonium ylides and 5-methyl furaldehyde **9**, followed

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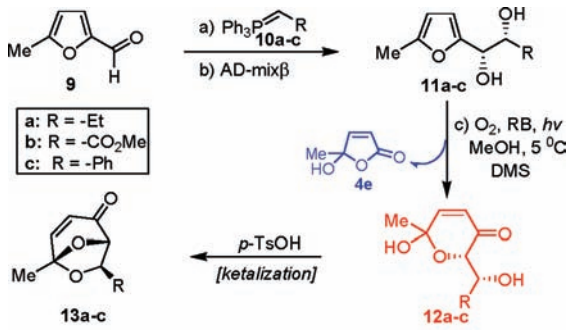
Scheme 4. Photooxidation of 2-(α,β-Dihydroxyalkyl)furans: One-Pot Synthesis of 6,8-Dioxabicyclo[3.2.1]oct-3-en-2-ones



furan-diol	R	12 (%)[a]	4e (%)[a]	13 (%)[b]
11a	Et	64	36	53
11b	CO_2Me	89	11	75
11c	Ph	71	29	60

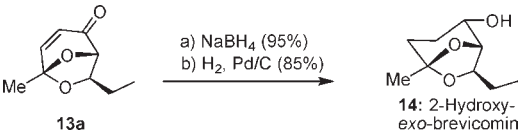
[a] Relative ratios were determined by ^1H NMR of the crude photooxidation mixture. [b] Isolated yield.

by Sharpless asymmetric dihydroxylation (SAD)[16] of the resulting olefins. Wittig coupling of the phosphonium ylide **10b** gave almost exclusively the *trans*-olefin and, as expected, the following SAD reaction afforded the *threo*-1,2-diol **11b**. Wittig coupling of the phosphonium ylides **10a** and **10c** resulted into the formation of *cis*/*trans* mixtures of geometrical isomers (1.3:1 in case of **10a**, and 1.5:1 in case of **10c**). SAD reactions of these two mixtures of geometrical isomers resulted in the unexpected predominat formation of the *threo*-1,2-diols **11a** and **11c**. Similar results have been recently reported[17] and were attributed to a *cis*−*trans* isomerization, occurring during the reaction itself, combined with the known faster dihydroxylation of a *trans* double bond when compared with its *cis* isomer.

Furandiols **11a**−**c** were subjected to the previously described $^1O_2$ photooxidation and reduction conditions. In situ treatment with catalytic amount of *p*-TsOH afforded the desired 6,8-dioxabicyclo[3.2.1]oct-3-en-2-ones **13a**−**c** in good overall isolated yield (Scheme 4). Several different classes of natural products including the pteriatoxins and pinnatoxins[18] and the didemniserinolipids[19] contain such a motif.

The product distribution for the substrates **11a** and **11c** is similar to substrate **1f**, while furandiol **11b** behaves similarly to furanol **1m**. In other words, the extra hydroxyl at the β-position of the side chain does not have significant effect on the distribution of the final products.

Scheme 5. Synthesis of 2-Hydroxy-*exo*-brevicomin



The synthetic potential of this new methodology was demonstrated by a rapid and enantioselective synthesis of 2-hydroxy-*exo*-brevicomin[20] (**14**, Scheme 5). With compound **13a** already in hand, the synthesis of the natural product was completed by diasterospecific reduction using $NaBH_4$, followed by double bond hydrogenation. The spectroscopic data of synthetic hydroxy-*exo*-brevicomin were in full agreement with those of the natural product.[20d,h,i]

The procedures developed herein, in which oxygen from the air is excited to transiently generate singlet oxygen in situ, are green, clean, and highly atom economic.[21] Many standard laboratory oxidants used to attain similar results, employ toxic heavy metals, or are reagents that require their own laborious synthesis. In contrast, when using singlet oxygen there is no waste either in terms of its generation, or in its application (wherein both oxygen atoms are transferred and incorporated into the oxidation substrate).

For all these reasons, using singlet oxygen to access the sought after 6-hydroxy-3(2*H*)-pyranone unit from 2-(α-hydroxyalkyl)furans is particularly attractive from a synthetic standpoint. The original concept has also been neatly extended to show how readily and effectively a 2-(α,β-dihydroxyalkyl)furan can yield the 6,8-dioxabicyclo[3.2.1]oct-3-en-2-one framework from a *one-pot* singlet oxygen initiated reaction sequence.

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Supporting Information Available. Experimental procedures, full spectroscopic data, and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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