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Five Roads That Converge at the Cyclic Peroxy-Criegee Intermediates: BF_3-Catalyzed Synthesis of β-Hydroperoxy-β-peroxylactones

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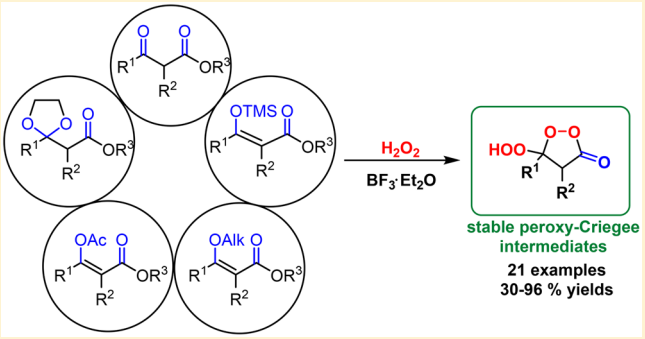
Supporting Information

ABSTRACT: We have discovered synthetic access to β-hydroperoxy-β-peroxylactones via BF_3-catalyzed cyclizations of a variety of acyclic precursors, β-ketoesters and their silyl enol ethers, alkyl enol ethers, enol acetates, and cyclic acetals, with H_2O_2. Strikingly, independent of the choice of starting material, these reactions converge at the same β-hydroperoxy-β-peroxylactone products, i.e., the peroxy analogues of the previously elusive cyclic Criegee intermediate of the Baeyer−Villiger reaction. Computed thermodynamic parameters for the formation of the β-hydroperoxy-β-peroxylactones from silyl enol ethers, enol acetates, and cyclic acetals confirm that the β-peroxylactones indeed correspond to a deep energy minimum that connects a variety of the interconverting oxygen-rich species at this combined potential energy surface. The target β-hydroperoxy-β-peroxylactones were synthesized from β-ketoesters, and their silyl enol ethers, alkyl enol ethers, enol acetates, and cyclic acetals were obtained in 30−96% yields. These reactions proceed under mild conditions and open synthetic access to a broad selection of β-hydroperoxy-β-peroxylactones that are formed selectively even in those cases when alternative oxidation pathways can be expected. These β-peroxylactones are stable and can be useful for further synthetic transformations.



INTRODUCTION

The recent surge of research in the chemistry of cyclic organic peroxides stems from the discovery of the potent antimalarial,[1−3] anthihelmintic,[4,5] cytotoxic,[6] fungicide,[7,8] and antiviral[9,10] activities. The key role of natural peroxide artemisinin and its derivatives in the treatment of malaria in the last decades was recognized with a Nobel Prize in Medicine in 2015.[11−13] In the search for synthetically available and affordable peroxides, it was shown that 5- and 6-membered cyclic peroxides display a broad spectrum of biological activity.[14−16] It is now apparent that cyclic organic peroxides, which used to be considered exotic and dangerous compounds of minor importance, can lead to breakthroughs in medicinal chemistry. Consequently, the development of selective synthetic approaches to these compounds became an important problem for modern organic chemistry.

Currently, the reaction of ketones or aldehydes with H_2O_2 and hydroperoxides serves as one of the main synthetic approaches to organic peroxides.[17−21] Although many publications describe reactions of hydrogen peroxide and monoketones,[22−27] the problem of peroxidation selectivity in the presence of several reactive centers has not found a general solution. For β-dicarbonyl compounds, this issue has been successfully addressed only in a small number of literature reports.[28−31] It was shown that β-diketones can be transformed into 1,2,4,5-tetraoxanes,[32,33] whereas δ-diketones can be converted into 1,2,4-trioxolanes (ozonides) (Scheme 1).[34,35] Peroxidation of malonic acids and their esters yields malonyl peroxides (Scheme 1).[36−39] In this context, peroxidation of β-ketoesters is potentially challenging because of the large difference in the reactivity of ketone and ester groups toward hydrogen peroxide. The only two previous reports described the formation of β-hydroperoxy-β-peroxylactones from the

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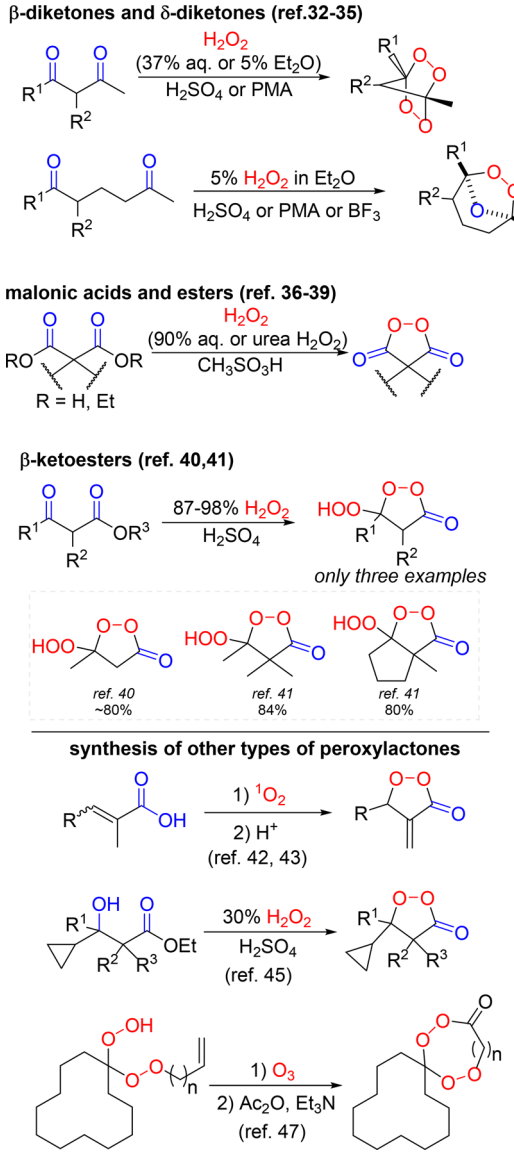
Scheme 1. Selection of Known Methods of Peroxidation of Dicarbonyl Compounds and Synthesis of Peroxylactones

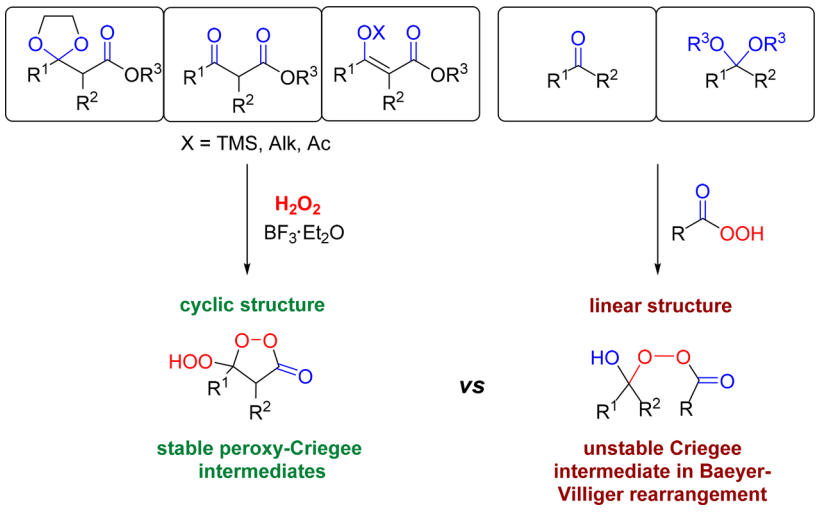


simplest β-ketoesters, the acetoacetic ester, and two α,α-disubstituted β-ketoesters[40,41] by using the explosive concentrated hydrogen peroxide (87−90%) (Scheme 1).

On the other hand, the related β-peroxylactones were obtained in several other ways (Scheme 1) that include photooxidation of α,β-unsaturated carboxylic acids with the subsequent acid-catalyzed cyclization,[42,43] photolysis of lactone with (diacetoxyiodo)benzene (DIB), and iodine under oxygen atmosphere[44] and treatment of β-hydroxy esters with H_2O_2 in the presence of H_2SO_4.[45] α-Keto-β-peroxylactone is considered to be an intermediate in oxidation of *p*-methoxyphenylpyruvic acid by oxygen.[46] Ozonolysis of (alkenyldioxy)-cyclododecyl hydroperoxides in CF_3CH_2OH with subsequent dehydration of the hydroperoxides[47] and reaction of epoxy ketones with H_2O_2[48,49] are other possible synthetic routes to peroxylactones. Although these approaches have synthetic value, they lack the simplicity and affordability associated with the use of dicarbonyl compounds and hydrogen peroxide as starting materials.

We have recently reported[50] that β-hydroxy-β-peroxylactones, the stable cyclic Criegee intermediates[51] constrained within a five-membered ring, can be prepared by mild reduction of respective hydroperoxyl peroxyesters (β-hydroperoxy-β-peroxylactones). This discovery is based on convenient and efficient BF_3-mediated synthesis of these bisperoxides from β-ketoesters and H_2O_2. In this work, we disclose a substantial study of the discovered reaction, investigate the scope of the new transformation, and complement it with expanded computational analysis that compares energy profiles for the alternative pathways. We also explore additional transformations of β-hydroperoxy-β-peroxylactones with the goal of evaluating the stability of bisperoxide moiety and measured oxidative properties of the new β-peroxylactones with cyclic voltammetry. An important fundamental finding of the study is that the target peroxides can be also obtained from silyl enol ethers, alkyl enol ethers, enol acetates, and cyclic acetals (Scheme 2). This finding substantially expands the choice of practical approaches to such cyclic peroxides. Remarkably, the β-hydroperoxy-β-peroxylactones are obtained from enol ethers and acetals despite the presence of possible oxidative transformations.[52−55]

Scheme 2. Stable and Unstable Peroxides from Di- and Monocarbonyl Compounds, Respectively



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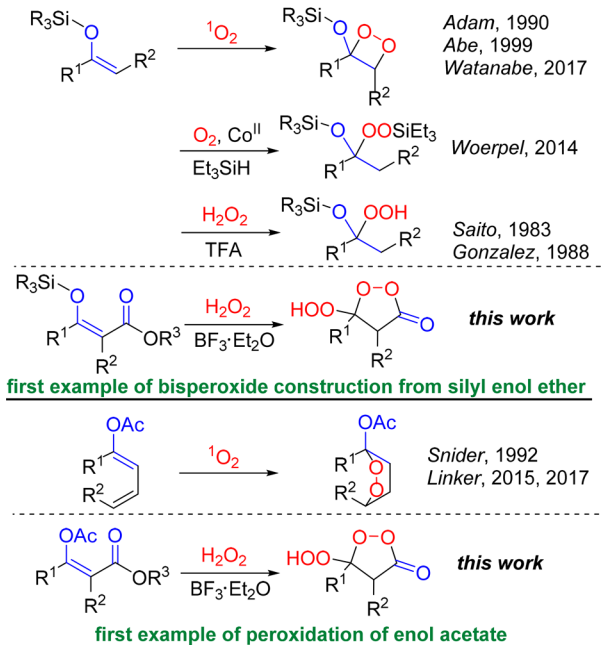
To the best of our knowledge, there are few reports describing peroxidation of silyl enol ethers, alkyl enol ethers,[56] enol acetates and acetals.[57−59] A literature search shows that only monoperoxy compounds were prepared from silyl enol ethers,[60−65] but bisperoxide synthesis was not described (Scheme 3). Peroxides from enol acetates were prepared

Scheme 3. Peroxidation of Silyl Enol Ethers and Enol Acetates



exclusively by photooxygenation of α-acetoxy diene compounds (Scheme 3).[66−68] In this paper, we disclose bisperoxidation of silyl enol ethers, alkyl enol ethers, enol acetates, and acetals with additional ester groups accompanied intermolecular cyclization between the hydroperoxyl fragment and ester group (Scheme 3).

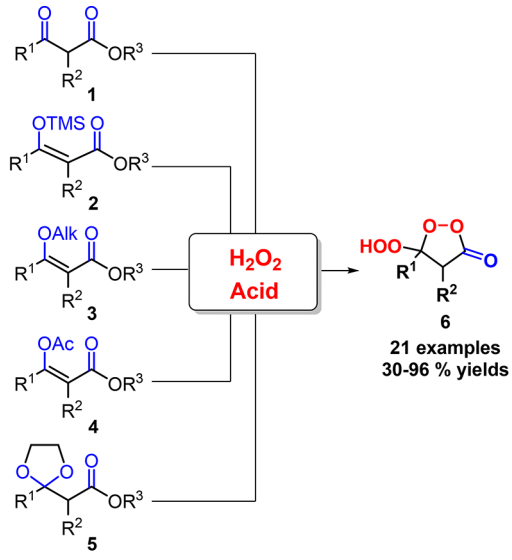
RESULTS AND DISCUSSION

Our goal was to develop a convenient and selective single-step access to β-hydroperoxy-β-peroxylactones **6** via BF_3-catalyzed cyclizations of a variety of acyclic precursors, β-ketoesters **1** and their silyl enol ethers **2**, alkyl enol ethers **3**, enol acetates **4**, cyclic acetals **5**, with H_2O_2 (Scheme 4). We have concentrated on the use of boron trifluoride as the peroxidation catalyst[69] because this catalyst was shown to work well in a previous synthesis of bishydroperoxides,[58] 1,1′-bishydroperoxydi(cycloalkyl) peroxides,[70] and 1,2,4-trioxanes[71,72] as well as various peroxides from acetals and enol ethers.[56]

The optimization of synthetic procedures for the preparation of β-hydroperoxy-β-peroxylactones **6** was carried out for 4-benzyl-5-hydroperoxy-5-methyl-1,2-dioxolan-3-one **6q**, obtained from ethyl 2-benzyl-3-oxobutanoate **1q** due to convenience of analysis of **6q**. In particular, we determined the effect of acid type and concentration, as well as the amount of hydrogen peroxide on the yield of β-peroxylactone **6q** (Table 1).

The reaction does not proceed in the presence of an equimolar amount of boron trifluoride, despite the large excess of hydrogen peroxide (Table 1, entry 1). This observation suggests that there are unproductive coordination complexes

Scheme 4. Synthesis of β-Hydroperoxy-β-peroxylactones 6a−u from β-Ketoesters 1a−u, Silyl Enol Ethers 2b,e,q, Alkyl Enol Ethers 3a,g,q, Enol Acetates 4g,n,q, Cyclic Acetals 5j,o,q, and Hydrogen Peroxide



1a, **3a**: $R^1 = CH_3$, $R^2 = H$, $R^3 = CH_2CH_3$, Alk = CH_2CH_3; **1b**, **2b**: $R^1 = CH_2CH_2CH_3$, $R^2 = H$, $R^3 = CH_2CH_3$; **1c**: $R^1 = CH(CH_3)_2$, $R^2 = H$, $R^3 = CH_2CH_3$; **1d**: $R^1 = CH_2CH(CH_3)_2$, $R^2 = H$, $R^3 = CH_2CH_3$; **1e**, **2e**: $R^1 = CH_2C(O)OCH_3$, $R^2 = H$, $R^3 = CH_3$; **1f**: $R^1 = CH_2C(O)OCH_2CH_3$, $R^2 = H$, $R^3 = CH_2CH_3$; **1g**, **3g**, **4g**: R^1 = Ph, $R^2 = H$, $R^3 = CH_2CH_3$, Alk = 1,4-dioxan-2-yl; **1h**: $R^1 = CH_2Ph$, $R^2 = H$, $R^3 = CH_2CH_3$; **1i**: R^1,R^2 = -$(CH_2)_3$-, $R^3 = CH_2CH_3$; **1j**, **5j**: R^1,R^2 = -$(CH_2)_4$-, $R^3 = CH_2CH_3$; **1k**: $R^1 = CH_3$, R^2 = Ad, $R^3 = CH_2CH_3$; **1l**: $R^1 = CH_3$, $R^2 = CH_2CCH$, $R^3 = CH_2CH_3$; **1m**: $R^1 = CH_3$, $R^2 = CH_2C(O)OCH_2CH_3$, $R^3 = CH_2CH_3$; **1n**, **4n**: $R^1 = CH_3$, $R^2 = CH_2CH_2C(O)OCH_2CH_3$, $R^3 = CH_2CH_3$; **1o**, **5o**: $R^1 = CH_3$, $R^2 = CH_2CH_2CN$, $R^3 = CH_2CH_3$; **1p**: $R^1 = CH_3$, $R^2 = CH_2CH_2C(O)CH_3$, $R^3 = CH_2CH_3$; **1q**, **2q**, **3q**, **4q**, **5q**: $R^1 = CH_3$, $R^2 = CH_2Ph$, $R^3 = CH_2CH_3$, Alk = 1,4-dioxan-2-yl; **1r**: $R^1 = CH_3$, $R^2 = CH_2(4\text{-}(CH_3)_3C\text{-}C_6H_4)$, $R^3 = CH_2CH_3$; **1s**: $R^1 = CH_3$, $R^2 = CH_2(4\text{-Cl-}C_6H_4)$, $R^3 = CH_2CH_3$; **1t**: $R^1 = CH_3$, $R^2 = CH_2(4\text{-Br-}C_6H_4)$, $R^3 = C(CH_3)_3$; **1u**: $R^1 = CH_2CH_2CH_3$, $R^2 = CH_2Ph$, $R^3 = CH_2CH_3$;

for BF_3 that effectively remove it from the reaction path when only 1 equiv of BF_3 is available. On the other hand, raising the excess of $BF_3{\cdot}Et_2O$ to 10 equiv leads to an increase of the target cyclic peroxide yield to 92% (entries 1−3). Entries 4−7 illustrate the key role of the excess of H_2O_2 on the product yield: the yield of 5-hydroperoxy-1,2-dioxolan-3-one **6q** decreases by 60% (entry 6) when 2 equiv of peroxide was used. When 1 equivt of H_2O_2 was used, only traces of desirable peroxide **6q** were observed (entry 7). Using less $BF_3{\cdot}Et_2O$ (entry 2) results in the formation of a mixture of the desired peroxide **6q** (37%) and the acyclic geminal bisperoxide (ethyl 2-benzyl-3,3-dihydroperoxybutanoate, 32%). Shorter reaction times (3 and 1 h) lowered the yield by 9% and 59%, respectively (entries 8 and 9).

An attempt to use urea/H_2O_2 complex instead of the ethereal solution of hydrogen peroxide showed that use of the latter is essential for reaching the high product yields (entries 5 and 10). Surprisingly, the application of the literature approach to β-hydroperoxy-β-peroxylactones, reported by Cubbon and Hewlett,[40] for synthesis of our target peroxide **6q** did not lead to the formation of β-peroxylactone with 0.24 equiv of H_2SO_4 (entry 11) or when an even larger amount of the acid was used.

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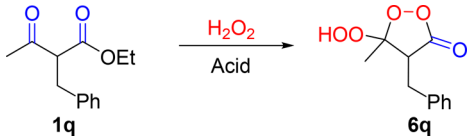
Table 1. Optimization of 4-Benzyl-5-hydroperoxy-5-methyl-1,2-dioxolan-3-one 6q Synthesis from Ethyl 2-Benzyl-3-oxobutanoate 1q and H_2O_2[a]



1q 6q

entry	H_2O_2 (type, equiv)[b]	acid (equiv)	time (h)	conv of **1q** (%)	yield of **6q** (%)
1	H_2O_2 (A, 10)	$BF_3{\cdot}Et_2O$ (1)	12	18	trace
2	H_2O_2 (A, 10)	$BF_3{\cdot}Et_2O$ (5)	12	86	37
3	**H_2O_2 (A, 10)**	**$BF_3{\cdot}Et_2O$ (10)**	**12**	**>95**	**92**
4	H_2O_2 (A, 5)	$BF_3{\cdot}Et_2O$ (10)	12	>95	81
5	H_2O_2 (A, 3)	$BF_3{\cdot}Et_2O$ (10)	12	>95	67
6	H_2O_2 (A, 2)	$BF_3{\cdot}Et_2O$ (10)	12	>95	32
7	H_2O_2 (A, 1)	$BF_3{\cdot}Et_2O$ (10)	12	37	trace
8	H_2O_2 (A, 10)	$BF_3{\cdot}Et_2O$ (10)	3	>95	83
9	H_2O_2 (A, 10)	$BF_3{\cdot}Et_2O$ (10)	1	91	33
10	H_2O_2 (B, 3)	$BF_3{\cdot}Et_2O$ (10)	24	91	43
11	H_2O_2 (C, 4)[c]	H_2SO_4 (0.24)	12	41	traces
12	H_2O_2 (C, 4)	H_2SO_4 (10)	12	54	traces
13	H_2O_2 (A, 10)	H_2SO_4 (10)	12	>95	77
14	H_2O_2 (A, 10)	$HClO_4$ (10)	12	92	78
15	H_2O_2 (A, 10)	HBF_4 (10)	12	87	67
16	H_2O_2 (A, 10)	$H_3PMo_{12}O_{40}{\cdot}xH_2O$ (1)	24	84	66
17	H_2O_2 (A, 10)	$P_2O_5{\cdot}24WO_3{\cdot}44H_2O$ (0.5)	24	90	57
18	H_2O_2 (A, 10)	$Na_2MoO_4{\cdot}2H_2O$ (2)	24	no rxn	
19	H_2O_2 (A, 10)	I_2 (5)	24	no rxn	
20	H_2O_2 (A, 10)	I_2 (0.1)	24	no rxn	
21	H_2O_2 (A, 10)	TBAI (2)	24	>95	7, 27[d]

[a]General procedure: An ethereal solution of H_2O_2 (2.048 M, 0.488−4.882 mL, 1.0−10.0 mmol, 1−10.0 equiv) was added with stirring to **1q** (220.3 mg, 1.00 mmol, 1.0 equiv). The mixture was cooled to 0 °C, and acid was added dropwise with stirring. The reaction mixture was then stirred at 20−25 °C for 1, 3, 12, or 24 h. [b]Type A: solution of H_2O_2 in Et_2O, molar concentration 2.048 M. T, type B: urea hydrogen peroxide. Ttype C: 90% H_2O_2. [c]Literature procedure.[40] [d]4-Phenylbutan-2-one (7)

Most likely, this result is associated with the instability of the keto group or benzyl moiety under these conditions[73] as well as the difficulties in applying heterogeneous reaction conditions of the Cubbon and Hewlett method to the small amounts of the substrate. Substitution of the dangerous concentrated H_2O_2 to an excess of ethereal H_2O_2 yields target peroxide **6q** in good yields (67−78%, entries 13−15) with use of a 10-fold excess of strong Bronsted acid (H_2SO_4, $HClO_4$, HBF_4). Good yields of peroxide **6q** can be also obtained under catalysis by heteropolyacids such as phosphomolybdic (entry 16) and phosphotungstic acids (entry 17), shown previously to be excellent peroxidation catalysts.[59,74−76] Use of other common peroxidation catalysts such as sodium molybdate[77] (entry 18) and iodine[78] (entries 19 and 20) did not promote the reaction. In the case of TBAI,[79] we observed oxidative fragmentation with the formation of 4-phenylbutan-2-one in 27% (entry 21).

As discussed previously, the effect of acid equivalents on the formation of β-peroxylactones was large, and the cyclization proceeded efficiently only in the presence of a large excess boron trifluoride (10 equiv). In the acidic media, peroxyesters are known to participate in the Baeyer−Villiger[80−82] and Criegee[83] reactions that involve the O−O bond scission. Under the present conditions, these reactions do not occur.

β-Hydroperoxy-β-peroxylactones can be obtained from enol ethers and acetals despite the presence of alternative oxidation pathways. Synthesis of β-hydroperoxy-β-peroxylactone **6q** was successfully carried out with silyl enol ether **2q**, alkyl enol ether **3q**, enol acetate **4q**, and cyclic acetal **5q** instead of β-ketoester **1q** as substrate (Table 2).

Surprisingly, only peroxide **6q** was formed in the reaction of enol ethers **2q−4q** and acetal **5q** with the H_2O_2/BF_3 system. We have not observed α-oxylated products despite the literature reports that this system acts as a peracid in oxidation reactions,[84,85] including the conversion of sulfides to sulfones[86] and aldehydes to carboxylic acids or esters.[87] Furthermore, it is known that reactions of silyl enol ethers from β-ketoesters with MCPBA,[88,89] *p*-nitrobenzenesulfonyl peroxide,[90] and DMDO[91] led to α-hydroxylated products. Enol acetates undergo anodic oxidation in the presence of acetic acid to form conjugated enones, α-acetoxy carbonyl compounds, *gem*-diacetoxy compounds, and triacetoxy compounds[92,93] and in the presence of the H_2O_2/NaOH system to form α-hydroxylated products.[94] In addition, α-acetoxy carbonyl compounds can be prepared from enol acetates in the presence of lead tetraacetate via rearrangement of epoxy acetate[95] or in the presence of peracids.[96]

Under the optimal conditions (Table 1, entry 3), the silyl enol ether **2q** and alkyl enol ether **3q** were transformed into peroxide **6q** in moderate yields of 51−73% (Table 2, entries 1 and 2). High yields (93% and 86%) of **6q** were achieved with use of $HClO_4$ instead of $BF_3{\cdot}Et_2O$ (Table 2, entries 1 and 2). Peroxidation of enol acetate **4q** (Table 2, entry 3) was achieved only in moderate yields (39−53%) of **6q** due to the low conversion of the starting material regardless to the order of addition of reagents and type of acid catalyst. With the use

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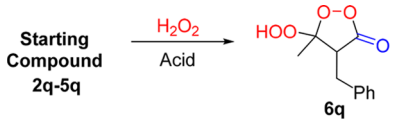
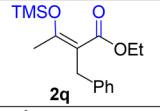
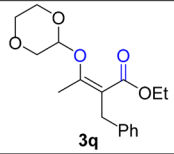
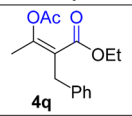
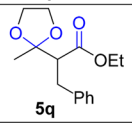
Table 2. Synthesis of 4-Benzyl-5-hydroperoxy-5-methyl-1,2-dioxolan-3-one (6q) from Silyl Enol Ether 2q, Alkyl Enol Ether 3q, Enol Acetate 4q, Cyclic Acetal 5q, and H_2O_2



№	Starting Compound	Yield of **6q**, %		
		Substrate/ H_2O_2 (10 equiv.) / $BF_3{\cdot}Et_2O$ (10 equiv.) [a]	**H_2O_2/ $BF_3{\cdot}Et_2O$/ Substrate** other order of addition [b]	**H_2O_2/$HClO_4$/ Substrate** other order of addition and $HClO_4$ instead of $BF_3{\cdot}Et_2O$ [c]
1	 **2q**	61	73	93
2	 **3q**	55	51	86
3	 **4q**	53	39	52
4	 **5q**	92	91	85

[a]Optimal reaction conditions for β-ketoesters: An ethereal solution of H_2O_2 (2.048 M, 4.882 mL, 10.00 mmol, 10.0 equiv) was added with stirring to starting compound **2q−5q** (1.0 mmol, 1.0 equiv). Later, $BF_3{\cdot}Et_2O$ (10.0 mmol, 10.0 equiv) was added dropwise with stirring to a solution at 0 °C. [b]Other order of addition of reagents: $BF_3{\cdot}Et_2O$ (10.0 mmol, 10.0 equiv) was added dropwise with stirring to ethereal solution of H_2O_2 (2.048 M, 4.882 mL, 10.00 mmol, 10.0 equiv) at 0 °C. Later, starting compound **2q−5q** (1.0 mmol, 1.0 equiv) was added dropwise with stirring to the mixture. [c]Other order of addition of reagents and with $HClO_4$ instead of $BF_3{\cdot}Et_2O$: $HClO_4$ (10.0 mmol) was added dropwise with stirring to ethereal solution of H_2O_2 (2.048 M, 4.882 mL, 10.00 mmol, 10.0 equiv) at 0 °C. Later, starting compound **2q−5q** (1.0 mmol) was added dropwise with stirring to the mixture. In footnotes *a*, *b*, *c* the reaction mixture was stirred at 20−25 °C for 12 h.

of acetal **5q**, high yields (85−92%) of **6q** were achieved both under the optimal conditions and with another order of reagent addition (Table 2, entry 4). Surprisingly, the easily oxidizable enol ethers **2q−4q** and acetal **5q** do not undergo observable destructive oxidation. Even in the presence of large excess of a strong oxidant and acid, enol ethers **2q−4q** and acetal **5q** are selectively converted to cyclic peroxide **6q**. It is possible that carbonyl coordination with the Lewis acid decreases donor ability of the double bond.

The conditions identified as optimal for synthesis of β-hydroperoxy-β-peroxylactone **6q** from the corresponding β-ketoester (Table 1, entry 3) were utilized for the synthesis of β-hydroperoxy-β-peroxylactones **6a−u** with varying degrees of substitution (Table 3).

The α-unsubstituted β-hydroperoxy-β-peroxylactones **6a−h** were obtained from β-ketoesters **1a−h** in good (61% for **6g**) to excellent yields (96% for **6b**). Fusion of the β-peroxylactone ring to a cycloalkane provided bicyclic peroxides **6i** and **6j** in 87% and 57%, respectively. The preparation of β-hydroperoxy-β-peroxylactones with bulky adamantyl (**6k**, 80%), propargyl (**6l**, 64%), ester (**6m**, 73%; **6n**, 66%), and nitrile (**6o**, 78%) functionalities as well as the tetraperoxide that combined a β-hydroperoxy-β-peroxylactone and a *gem*-dihydroxyperoxide moiety (**6p**, 56%) proceeded in good yields. The presence of a benzylic group increases the yields of β-hydroperoxy-β-peroxylactones; products **6q−u** were obtained in 76−93% yields. The flexibility of this approach in the selection of starting materials is illustrated by facile formation of β-hydroperoxy-β-peroxylactones from enols **2−4** and acetals **5** as well as the *t*-Bu esters of β-ketoesters (compound **6t**). β-Hydroperoxy-β-peroxylactones **6b** and **6e** were prepared from silyl enol ethers **2b** and **2e** (Table 3, notes c and d) in good (61% for **6e**) and high (88% for **6b**) yields. Use of the enol ethers **3a** and **3g** (Table 3, notes b and e) instead of β-ketoesters **1a** and **1g** increased the yields of **6a** (89%) and **6g** (73%). Synthesis of β-hydroperoxy-β-peroxylactone **6g** from enol acetate **4g** (Table 3, note f) led to the highest observed yield of **6g** (86%). However, synthesis of **6n** from enol acetate **4n** (Table 3, note h) was less efficient (30%) than from β-ketoester **1n** (66%). Peroxidation of acetals **5j** and **5o** (Table 3, notes g and i) provided good yields of the desirable β-hydroperoxy-β-peroxylactones **6j** (75%) and **6o** (74%).

The oxidative properties of the synthesized β-hydroperoxy-β-peroxylactones were investigated with cyclic voltammetry. It was shown that reduction potentials for the β-peroxylactones **6d** and **6q** (−1091 and −1026 mV, respectively) are lower than the potentials for bridged 1,2,4,5-tetraoxane (1,4-dimethyl-7-(1-*p*-tolylethyl)-2,3,5,6-tetraoxabicyclo[2.2.1]-heptane, −1319 mV) but greater than the potentials for cyclopropyl malonyl peroxide (−603 mV). These findings illustrate moderate oxidative properties of β-hydroperoxy-β-peroxylactones (Scheme S1, Supporting Information).

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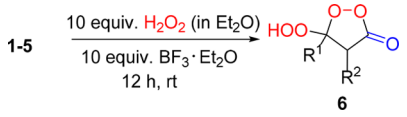
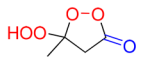
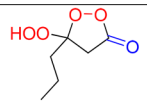
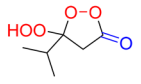
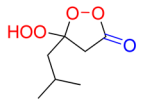
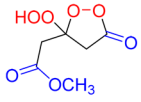
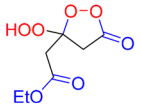
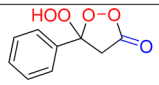
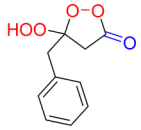
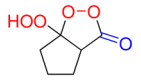
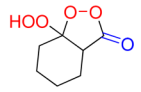
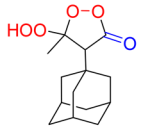
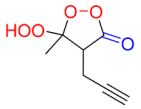
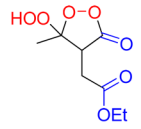
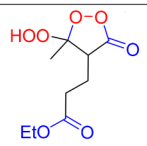
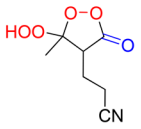
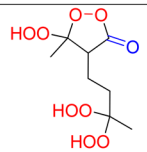
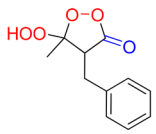
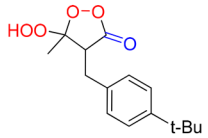
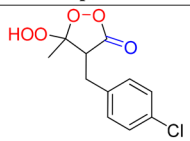
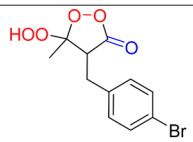
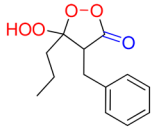
Table 3. Scope of β-Hydroperoxy-β-peroxylactones 6a−u[a] and Silyl Enol Ethers 2b,e,q, Alkyl Enol Ethers 3a,g,q, Enol Acetates 4g,n,q, and Cyclic Acetals 5j,o,q



 **6a**, 88 (from **3a**: 89)[b]	 **6b**, 96 (from **2b**: 88)[c]	 **6c**, 90
 **6d**, 64	 **6e**, 79 (from **2e**: 61)[d]	 **6f**, 78
 **6g**, 61 (from **3g**: 73)[e] (from **4g**: 86)[f]	 **6h**, 77	 **6i**, 87
 **6j**, 57 (from **5j**: 75)[g]	 **6k**, 80	 **6l**, 64
 **6m**, 73	 **6n**, 66 (from **4n**: 30)[h]	 **6o**, 78 (from **5o**: 74)[i]
 **6p**, 56	 **6q**, 92	 **6r**, 76
 **6s**, 93	 **6t**, 81	 **6u**, 90

[a]General procedure: An ethereal solution of H_2O_2 (2.048 M, 4.882 mL, 10.00 mmol, 10.0 equiv) was added with stirring to **1a−u** (1.00 mmol, 1.0 equiv). Later, $BF_3{\cdot}Et_2O$ (1.419 g, 10.00 mmol, 10 equiv) was added dropwise with stirring to the solution at 0 °C. The reaction mixture was stirred at 20−25 °C for 12 h. The values in parentheses indicate the yield of **6** starting from **2−5**. [b]Yield starting from ethyl 3-ethoxybut-2-enoate (**3a**). [c]Yield starting from ethyl 3-((trimethylsilyl)oxy)hex-2-enoate (**2b**). [d]Yield starting from dimethyl 3-((trimethylsilyl)oxy)pent-2-enedioate (**2e**). [e]Yield starting from ethyl 3-((1,4-dioxan-2-yl)oxy)-3-phenyl acrylate (**3g**). [f]Yield starting from ethyl 3-acetoxy-3-phenyl acrylate (**4g**). [g]Yield starting from ethyl 1,4-dioxaspiro[4.5]decane-6-carboxylate (**5j**). [h]Yield starting from diethyl 2-(1-acetoxyethylidene)pentanedioate (**4n**). [i]Yield starting from ethyl 4-cyano-2-(2-methyl-1,3-dioxolan-2-yl)butanoate (**5o**).

The nature of the second substrate at the α-position of β-ketoesters **8** greatly affects the peroxidation process. Thus, α,α-dimethyl β-ketoester **8a** formed the desired β-hydroperoxy-β-peroxylactone **9a** with excellent (86%) yield under optimized conditions (Table 1, entry 3), while α-methyl-α-benzyl β-ketoester **8b** was transformed into peroxide **9b** in a slightly lower yield (74%) and peroxidation of α,α-dibenzyl β-ketoester **8c** did not lead to formation of **9c** (Scheme 5).

The unambiguous NMR determination of the structure of organic peroxides can be challenging because of the possibility of condensation of several molecular units via the peroxide bridges and because of the possibility of acid-catalyzed skeletal rearrangements. To address this difficulty, we have performed

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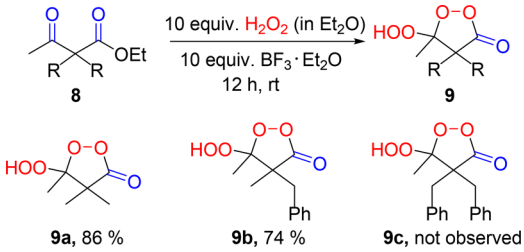
Scheme 5. Peroxidation of α,α-Disubstituted β-Ketoesters 8



X-ray crystallographic analysis of several representatives (**6q** and **6s**, Supporting Information) of this scarcely studied class of β-peroxylactones (Figure 1). In addition to confirming the

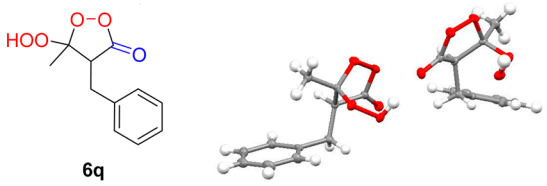
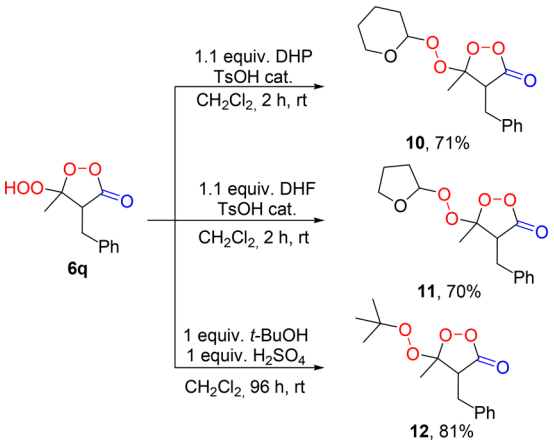


Figure 1. X-ray structure of β-hydroperoxy-β-peroxylactone **6q**.

presence of two peroxide units, the X-ray data unambiguously determined the nature of the diastereomeric product (formed as a single isomer according to ^{1}H and ^{13}C NMR spectra) for β-hydroperoxy-β-peroxylactones **6q** and **6s**.

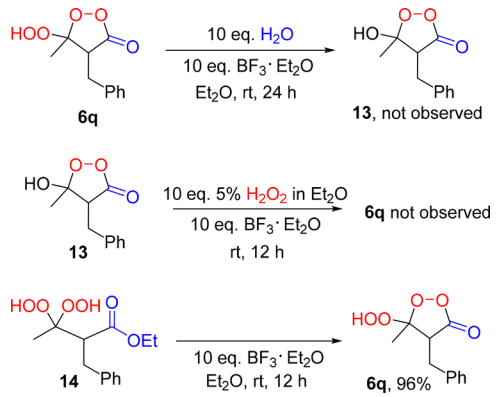
In order to gain first insights into the chemistry of this scarcely studied class of peroxides, we have investigated further synthetic transformations of β-hydroperoxy-β-peroxylactones. As expected from the synthetic conditions used for their preparation, the β-hydroperoxy-β-peroxylactone functionality is stable under the acidic conditions. We found that the hydroperoxide functionality in **6q** can be protected via installation of tetrahydropyranyl (THP), tetrahydrofuranyl (THF) and *t*-Bu groups (Scheme 6).

Scheme 6. Transformations of Hydroperoxy Group in β-Hydroperoxy-β-peroxylactone 6q



Mechanistic Studies. Control experiments designed to provide an insight in the mechanism of the product formation (Scheme 7), revealed that β-hydroperoxy-β-peroxylactone **6q** does not equilibrate with β-hydroxy-β-peroxylactone **13** under these conditions. On the other hand, acyclic bishydroperoxide **14** is converted into the β-hydroperoxy-β-peroxylactone **6q**

Scheme 7. Experimental Evaluation of the Stability of β-Peroxylactones



readily and in an almost quantitative yield. The low reactivity of these mono- and bisperoxides under the acidic conditions is likely to originate from the "inverse intramolecular α-effect" (the relatively inefficient stabilization of cationic center by an adjacent peroxide in comparison to ethers, further exacerbated here by the presence of a carbonyl substituent at the peroxide).[97,98]

Because of this effect, peroxides are more reluctant to be converted into cationic intermediates and may possess greater kinetic stability than the analogous ethers and alcohols that are readily transformed into oxacarbenium ions.

Computational Analysis of Reaction Pathways. To understand the relative stabilities of the possible intermediates involved in the formation of the new bisperoxides,[63,99] we decided to chart the energy landscape for the interaction of carbonyl compounds and H_2O_2 by using quantum-mechanical calculations.

As the first step, we have evaluated thermodynamics for the interaction of key hydroxyl containing functionalities with hydrogen peroxide. Interestingly, the transformation of carboxylic acids into peroxyacids in reaction with H_2O_2 is either weakly exergonic or thermoneutral. For the ketones, the situation is slightly different (Scheme 8). The addition of the first H_2O_2 molecule to acetone is slightly endergonic, and the resulting unstable mixed monoperoxide are unlikely to be persistent under the reaction conditions. On the other hand, the transformations of acetone and its hydrate into respective bishydroperoxy ketal are sufficiently exergonic to ensure the preferential formation of such bishydroperoxides at the equilibrium in the presence of sufficient amounts of hydrogen peroxide.

In the next stage, we explored energy profiles for the interaction of β-ketoacids and esters with hydrogen peroxide. From the two alternative pathways to the target cyclic structure, we favor the one that start from peroxidation of the carbonyl functions. Furthermore, based on the experimental observations reported in Scheme 7 and reiterated in Scheme 9 below, we suggest the ketoester is transformed into a bishydroperoxide first and that it is the latter species that undergoes the cyclization to form the β-peroxylactone. The cyclization of the mixed hydroxy/hydroperoxy ketal can be discarded based on the observation that β-hydroxy-β-peroxylactone is not transformed into β-hydroperoxy-β-peroxylactone under the reaction conditions. Apparently, the bisperoxide is formed and cyclized quickly to provide the cyclic

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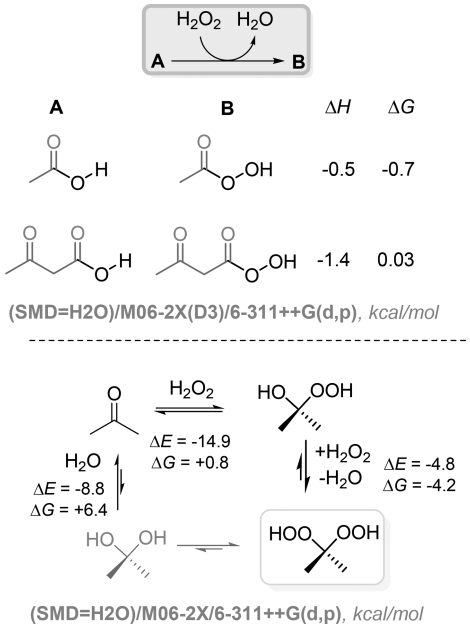
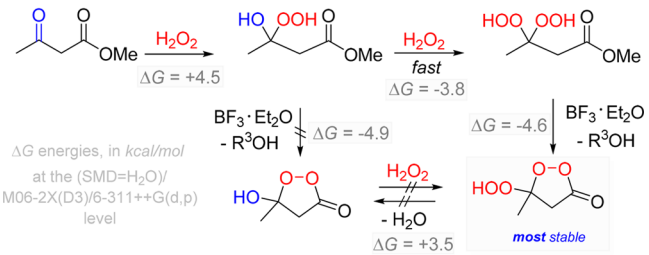
Scheme 8. Calculated Thermodynamic Parameters for the Interaction of H_2O_2 with Selected Carboxylic Acids and Acetone



Scheme 9. Suggested Mechanism for Synthesis of β-Hydroperoxy-β-peroxylactones with Calculated Free Energies for the Formation of the Intermediate Structures



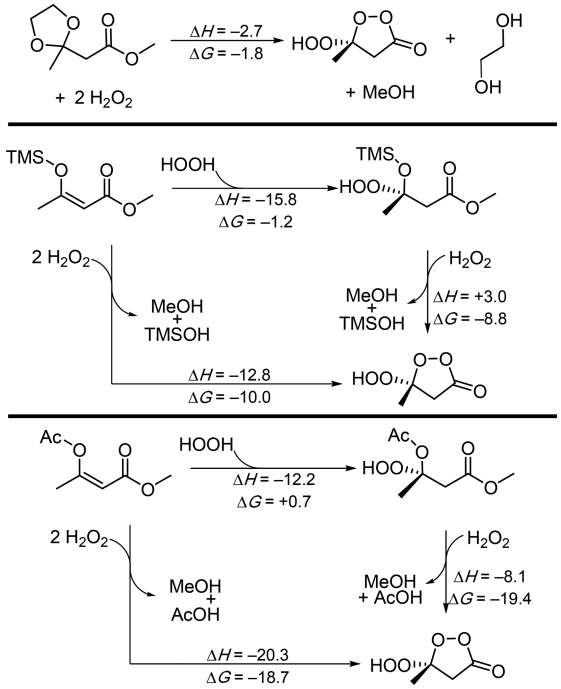
bisperoxide, the most stable species at this reaction hypersurface.

We have also evaluated thermodynamics for the formation of the cyclic β-hydroperoxy-β-peroxylactones from cyclic acetals, enol acetates, and silyl enol ethers. Gratifyingly, all of these transformations are exergonic, suggesting that the β-peroxylactones are indeed an energy minimum that connects a variety of the interconverting oxygen-rich species at this combined potential energy surface (Scheme 10). Especially noteworthy is the fact that β-peroxylactones can be formed exergonically from cyclic acetal, a functional group that is strongly stabilized by anomeric effects.[100] This observation provides another illustration of the increased thermodynamic stability of bisperoxides where the anomeric effects (generally dormant in monoperoxides) are reactivated.[34,35,97,101]

CONCLUSION

β-Hydroperoxy-β-peroxylactones can be prepared in moderate to excellent yields from five different types of substrates: β-ketoesters and their silyl enol ethers, alkyl enol ethers, enol acetates, and cyclic acetals. A broad scope of β-hydroperoxy-β-peroxylactones, both α-unsubstituted and α-mono- and α,α-disubstituted, was synthesized. A large excess of $BF_3{\cdot}Et_2O$ and

Scheme 10. Thermodynamic Landscape for Synthesis of β-Hydroperoxy-β-peroxylactones from Cyclic Acetals, Enol Acetates, and Silyl Enol Ethers Derived from β-Ketoesters



H_2O_2 is a key factor determining the selectivity and efficiency of formation of β-hydroperoxy-β-peroxylactones that allows to prepare the target cyclic peroxides in >90% yields.

The computationally evaluated thermodynamics for the formation of the β-hydroperoxy-β-peroxylactones from β-ketoesters, silyl enol ethers, enol acetates, and cyclic acetals confirm that the β-peroxylactone species correspond to an energy minimum that connects a variety of species at this combined potential energy surface. Furthermore, the β-hydroperoxy-β-peroxylactones are stable in acidic conditions and can be modified via hydroperoxyl group functionalization.

EXPERIMENTAL SECTION

Caution: Although we have encountered no difficulties in working with peroxides, precautions such as the performance of reactions within a fume hood and behind a safety shield should be taken. The use of redox-active transition-metal salts, heating, and vigorous shaking should be avoided!

NMR spectra were recorded on commercial instruments (300.13 MHz for ^1H, 75.48 MHz for ^{13}C) in $CDCl_3$. High-resolution mass spectra (HRMS) were measured using electrospray ionization (ESI-TOF).[102] The measurements were done in a positive-ion mode (interface capillary voltage −4500 V); mass range from m/z 50 to m/z 3000 Da; external/internal calibration was done with Electrospray Calibrant Solution. A syringe injection was used for solutions in MeCN (flow rate 3 μL/min). Nitrogen was applied as a dry gas; the interface temperature was set at 180 °C.

TLC analysis was carried out on standard silica gel chromatography plates. The melting points were determined on a Kofler hot-stage apparatus. Chromatography was performed on silica gel (40−60 μm).

Ethyl acetoacetate (**1a**), ethyl butyrylacetate (**1b**), dimethyl 1,3-acetonedicarboxylate (**1e**), ethyl benzoylacetate (**1g**, distilled before use under reduced pressure (15−20 mmHg)), ethyl 2-oxocyclopentanecarboxylate (**1i**), ethyl 2-oxocyclohexanecarboxylate (**1j**), diethyl acetylsuccinate (**1m**), H_2O_2 (37% solution in water), $BF_3{\cdot}Et_2O$, I_2, *p*-TsOH monohydrate, H_2SO_4, $HClO_4$ (70% solution in water), HBF_4 (48% solution in water), $NaHCO_3$, phosphomolybdic acid hydrate

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(formula weight: 1,825.25 g/mol), phosphotungstic acid hydrate (formula weight: 2880.05 g/mol), $Na_2MoO_4{\cdot}2H_2O$, tetrabutylammonium iodide, urea hydrogen peroxide, 3,4-dihydro-2*H*-pyran, 2,3-dihydrofuran, *t*-BuOH, Bu_4NClO_4, Et_3N, TMSCl, K_2CO_3, Na, NaH (60% in mineral oil), NaOH, TEBAC, triethyl orthoformate, $Cu(OAc)_2{\cdot}H_2O$, 1,4-dioxane, 5−6 M TBHP solution in decane, pyridine, acetyl chloride, $CuSO_4{\cdot}5H_2O$, ethylene glycol, and methyl iodide were purchased from commercial sources and were used as is. All solvents were distilled before use using standard procedures.

Distillation of the commercial ethyl benzoylacetate **1g** was performed under medium vacuum (10 mmHg). Fraction with bp = 129−134 °C was collected and used in peroxide synthesis.

A solution of H_2O_2 in Et_2O (2.048 mol/L, ∼9.8% weight) was prepared by the extraction with Et_2O (5 × 100 mL) from a 35% aqueous solution (100 mL) followed by drying over $MgSO_4$.[64,103] A solution of H_2O_2 in Et_2O (90% weight) was prepared by evaporation of a 9.8% solution of H_2O_2 in Et_2O.

Synthesis of Starting *β*-Ketoesters 1. *Procedure for the Synthesis of Ethyl 4-Methyl-3-oxopentanoate (**1c**).*[104] Isobutyric acid (2.91 g, 33.0 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (140 mL). Meldrum's acid (5.23 g, 36.3 mmol, 1.1 equiv) and 4-(dimethylamino)pyridine (6.11 g, 50.0 mmol, 1.5 equiv) were added, and the mixture was stirred at 20−25 °C for 15 min. After the mixture was cooled to 0 °C, a solution of dicyclohexylcarbodiimide (8.26 g, 40.0 mmol, 1.2 equiv) in dry CH_2Cl_2 (10 mL) was added and the reaction mixture stirred at 20−25 °C for 10 h. The precipitate containing dicyclohexylurea was filtered off, and the filtrate was washed with a 10% aqueous solution of citric acid (2 × 20 mL) and brine (20 mL) and dried over $MgSO_4$. The organic phase was concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 20−25 °C) and was applied to the next reaction step without purification. The crude 5-(1-hydroxy-2-methylpropylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione was refluxed in toluene (80 mL) with EtOH (20 mL) for 3 h. Then reaction mixture was concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 80−85 °C). The product **1c** was isolated by column chromatography on SiO_2 (PE/EtOAc = 10:1). Yield: 43% (2.24 g, 14.2 mmol). Yellow oil. R_f = 0.67 (PE/EtOAc = 20:1). Keto/enol ratio = 9/1. ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 12.12 (s, 0.1H), 4.96 (s, 0.1H), 4.17 (q, J = 7.1 Hz, 2H), 3.47 (s, 1.8H), 2.70 (sept, J = 6.9 Hz, 0.9H), 2.45−2.31 (m, 0.1H), 1.25 (t, J = 7.1 Hz, 3H), 1.11 (d, J = 6.9 Hz, 6H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 206.7, 167.5, 86.8, 61.4, 60.0, 47.2, 41.3, 19.8, 18.0, 14.2. The physical and spectral data were consistent with those previously reported.[104]

*Procedure for the Synthesis of Ethyl 5-Methyl-3-oxohexanoate (**1d**).*[105] NaH (60% in mineral oil, 1.20 g, 30.0 mmol, 1.5 equiv) was added to dry toluene (20 mL). The diethyl carbonate (3.54 g, 30.0 mmol, 1.5 equiv) was added to the stirred suspension. Then a solution of 4-methylpentanone-2 (2.00 g, 20.0 mmol, 1.0 equiv) in dry toluene (20 mL) was added dropwise. In the middle of the process of addition, one drop of absolute EtOH was added. The reaction mixture was refluxed with stirring for 3 h. After being cooled to 20−25 °C, the reaction mixture was acidified to pH ∼6 by careful addition of 5% aq HCl (50 mL). The organic layer was separated, and then aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure (15−20 mmHg) (bath temperature, ca. 40−45 °C). The product **1d** was isolated by column chromatography on SiO_2 (PE/EtOAc = 15:1). Yield: 47% (1.62 g, 9.4 mmol). Yellow oil. R_f = 0.21 (PE/EtOAc = 20:1). Keto/enol ratio = 9/1. ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 12.06 (s, 0.1H), 4.93 (s, 0.1H), 4.18 (q, J = 7.1 Hz, 2H), 3.39 (s, 1.8H), 2.40 (d, J = 6.9 Hz, 2H), 2.24−2.05 (m, 1H), 1.26 (t, J = 7.1 Hz, 3H), 0.92 (d, J = 6.6 Hz, 6H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 202.6, 167.3, 90.1, 61.4, 52.0, 49.8, 44.5, 24.4, 22.5, 22.5, 14.2. The physical and spectral data were consistent with those previously reported.[105]

*Procedure for the Synthesis of Diethyl 1,3-Acetonedicarboxylate (**1f**).*[106] Citric acid monohydrate (2.10 g, 10.0 mmol, 1.0 equiv) was added to chlorosulfonic acid (2.5 mL, 38 mmol, 3.8 equiv) in CH_2Cl_2 (3 mL) at 10 °C. After 5 h, the reaction mixture was cooled (0−5 °C), and EtOH (5 mL) was added carefully to ensure the temperature did not exceed 35 °C. After being stirred for 2 h at 35−40 °C, the reaction mixture was cooled, H_2O (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was washed with 5% solution of $NaHCO_3$ (10 mL) and H_2O (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure (15−20 mmHg) (bath temperature, ca. 30−35 °C). The product **1f** was isolated by column chromatography on SiO_2 (PE/EtOAc = from 20:1 to 2:1). Yield: 53% (1.07 g, 5.3 mmol). Yellow oil. R_f = 0.76 (PE/EtOAc = 20:1). Keto/enol ratio = 5/1. ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 12.08 (s, 0.17H), 5.11 (s, 0.17H), 4.18 (q, J = 7.1 Hz, 4H), 3.59 (s, 3.3H), 3.20 (s, 0.35H), 1.26 (t, J = 7.1 Hz, 6H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 195.5, 172.4, 170.0, 166.8, 92.1, 61.7, 61.5, 60.4, 49.1, 41.1, 14.3, 14.2, 14.1. The physical and spectral data were consistent with those previously reported.[106]

*Procedure for the Synthesis of Ethyl 3-Oxo-4-phenylbutanoate (**1h**).*[107] Substrate **1h** was synthesized according to the modified literature procedure.[4] To a suspension of phenylacetic acid (816.0 mg, 6.0 mmol, 1.0 equiv) in dry CH_2Cl_2 (10 mL) was added CDI (1.05 g, 6.5 mmol, 1.08 equiv). After the mixture was stirred for 0.5 h, Meldrum's acid (1.081 g, 7.5 mmol, 1.25 equiv) was added and the mixture stirred for an additional 12 h. Then the reaction mixture was poured into 5% HCl (30 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The extract was washed with 5% HCl (25 mL) and with H_2O (25 mL) and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 30−35 °C). To the residue was added EtOH (10 mL), and the resulting mixture was refluxed for 2 h. The obtained solution was concentrated, and 5% $NaHCO_3$ (30 mL) was added to the residue. The obtained mixture was extracted with ethyl acetate (3 × 10 mL). The extract was washed with H_2O (10 mL), filtered through thin layer of silica gel (2 cm), and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 30−35 °C). The product **1h** was isolated by column chromatography on SiO_2 (PE/EtOAc = from 20:1 to 2:1). Yield: 66% (817.0 mg, 4.0 mmol). Yellow oil. R_f = 0.67 (PE/EtOAc = 20:1). Keto form: ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 7.42−7.13 (m, 5H), 4.15 (q, J = 7.1 Hz, 2H), 3.81 (s, 2H), 3.43 (s, 2H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 200.5, 167.2, 133.3, 129.7, 128.9, 127.4, 61.5, 50.1, 48.4, 14.2. The physical and spectral data were consistent with those previously reported.[107]

*Procedure for the Synthesis of Ethyl 2-(Adamantan-1-yl)-3-oxobutanoate (**1k**).*[108] $Cu(OTf)_2$ (90.4 mg, 0.25 mmol, 0.05 equiv) was added to dry 1,2-dichloroethane (5 mL). Then a solution of 1-adamantanol (761.2 mg, 5.00 mmol, 1 equiv) and ethyl acetoacetate (650.7 mg, 5.00 mmol, 1 equiv) in dry 1,2-dichloroethane (10 mL) was added. The reaction mixture was refluxed with stirring for 2 h. After the mixture was cooled to 20−25 °C, 2 M HCl (10 mL) was added. The organic layer was separated, and the product was extracted from the aqueous phase with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 30−35 °C). The product **1k** was isolated by column chromatography on SiO_2 (PE/EtOAc = 20:1). Yield: 74% (978.2 mg, 3.7 mmol). Yellow oil. R_f = 0.57 (PE/EtOAc = 20:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 4.15 (q, J = 7.1 Hz, 2H), 3.17 (s, 1H), 2.21 (s, 3H), 2.00−1.94 (m, 3H), 1.80−1.62 (m, 13H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 203.3, 168.8, 70.1, 60.8, 40.2, 37.1, 36.8, 32.1, 28.8, 14.3. The physical and spectral data were consistent with those previously reported.[108]

*Ethyl 2-Acetylpent-4-ynoate (**1l**).* Product **1l** was synthesized according to the literature procedure.[109] Yield 67% (2.53 g, 15.0 mmol). Yellow oil. R_f = 0.63 (PE/EtOAc = 10:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 4.22 (q, J = 7.1 Hz, 2H), 3.68 (t, J = 7.0 Hz, 1H), 2.70 (d, J = 7.0 Hz, 2H), 2.29 (s, 3H), 1.98 (t, J = 2.6 Hz, 1H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 201.2, 168.2, 80.5, 70.4, 62.0, 58.4, 29.7, 17.5, 14.2. The physical and spectral data were consistent with those previously reported.[109]

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*Procedure for the Synthesis of Diethyl 2-Acetylpentanedioate (**1n**).* Na (0.69 g, 0.03 mol, 0.2 equiv) was added to dry EtOH (5 mL). The resulting solution of EtONa was cooled to room temperature and added to a mixture ethyl acetoacetate (29.25 g, 0.225 mol, 1.5 equiv) and ethyl acrylate (15.02 g, 0.15 mol, 1.0 equiv) with stirring. The reaction mixture was stirred overnight at 20−25 °C. Then CH_2Cl_2 (100 mL) was added, and the mixture was washed with a 5% solution of $NaHCO_3$ (2 × 50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 40−45 °C). Distillation of the remaining liquid under medium vacuum (8.00 mmHg) gave product **1n** as a third fraction (bp = 165−175 °C). Yield: 55% (19.10 g, 83.0 mmol). Colorless oil. R_f = 0.65 (PE/EtOAc = 20:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 4.18 (q, J = 7.2 Hz, 2H), 4.11 (q, J = 7.2 Hz, 2H), 3.53 (t, J = 7.2 Hz, 1H), 2.36−2.29 (m, 2H), 2.23 (s, 3H), 2.17−2.08 (m, 2H), 1.29−1.20 (m, 6H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 202.6, 172.7, 169.4, 61.6, 60.6, 58.5, 31.6, 29.2, 23.1, 14.3, 14.2. The physical and spectral data were consistent with those previously reported.[110]

*Procedure for the Synthesis of Ethyl 2-Acetyl-4-cyanobutanoate (**1o**).* Na (69.0 mg, 3.00 mmol, 2.0 equiv) was added to dry EtOH (1 mL). The resulting solution of EtONa was cooled to room temperature and added to a mixture ethyl acetoacetate (292.8 mg, 2.25 mmol, 1.5 equiv) and acrylonitrile (79.6 mg, 1.50 mmol, 1.0 equiv) with stirring. The reaction mixture was stirred overnight at 20−25 °C. Then CH_2Cl_2 (10 mL) was added, and the mixture was washed with 5% solution of $NaHCO_3$ (2 × 3 mL) and brine (3 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 40−45 °C). The product **1o** was isolated by column chromatography on SiO_2 (PE/EtOAc = 10:1). Yield: 80% (220.0 mg, 1.20 mmol). Yellow oil. R_f = 0.58 (PE/EtOAc = 10:1). Keto/enol ratio = 4/1. ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 12.87 (s, 0.2H), 4.22 (q, J = 7.1 Hz, 2H), 3.63 (t, J = 7.1 Hz, 0.8H), 2.43 (t, J = 7.1 Hz, 2H), 2.28 (s, 3H), 2.20−2.08 (m, 2H), 1.28 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 201.4, 168.4, 118.7, 62.1, 57.4, 29.6, 23.4, 15.2, 14.1. The physical and spectral data were consistent with those previously reported.[111]

*Procedure for the Synthesis of Ethyl 2-Acetyl-5-oxohexanoate (**1p**).* $CeCl_3{\cdot}7H_2O$ (111.8 mg, 0.30 mmol, 0.1 equiv) was heated at 150 °C for 2 h. After the solution was cooled to room temperature, cerium chloride was added with vigorous stirring to ethyl acetoacetate (390.0 mg, 3.00 mmol, 1.0 equiv). The mixture was stirred at room temperature for 5 min, and then methyl vinyl ketone (231.3 mg, 3.30 mmol, 1.1 equiv) and NaI (22.5 mg, 0.15 mmol, 0.05 equiv) were added. The reaction mixture was stirred at room temperature for 24 h and filtered. The precipitate was washed with a PE/EtOAc mixture (1:2, v/v). The solvent was evaporated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 20−25 °C). The product **1p** was isolated by column chromatography on SiO_2 (PE/EtOAc = 2:1). Yield: 73% (438.3 mg, 2.19 mmol). Colorless oil. R_f = 0.30 (PE/EtOAc = 2:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 4.17 (q, J = 7.2 Hz, 2H), 3.47 (t, J = 7.2 Hz, 1H), 2.48 (t, J = 7.1 Hz, 2H), 2.22 (s, 3H), 2.11 (s, 3H), 2.09−2.00 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 207.6, 202.9, 169.6, 61.6, 58.4, 40.6, 30.0, 29.1, 21.8, 14.2. The physical and spectral data were consistent with those previously reported.[34]

General Procedure for the Synthesis of β-Ketoesters 1q−s (GP1). Ethyl acetoacetate (19.5 g, 0.15 mol, 1.0 equiv) was added with vigorous stirring to the mixture of powdery NaOH (6.0 g, 0.15 mol, 1.0 equiv) and TEBAC (171.0 mg, 0.75 mmol, 0.005 equiv) in dry benzene (10 mL). After 15 min, the corresponding benzyl bromide (30.8−40.9 g, 0.18 mol, 1.2 equiv) was added with stirring dropwise at 50−60 °C. The reaction mixture was stirred at the same temperature for 3 h. Later, the residue was filtered and washed by Et_2O (3 × 20 mL). The combined organic fractions were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 40−45 °C). Distillation of the remaining liquid under medium vacuum (10 mmHg) gave products **1q−s**.

*Ethyl 2-Benzyl-3-oxobutanoate (**1q**).*[112] According to **GP1**, ethyl acetoacetate (19.5 g, 0.15 mol, 1.0 equiv) was treated with NaOH (6.0 g, 0.15 mol, 1.0 equiv) and benzyl bromide (30.8 g, 0.18 mol, 1.2 equiv) to afford ethyl 2-benzyl-3-oxobutanoate **1q** (25.7 g, 0.12 mol, 78%) as a colorless oil. Bp = 167−168 °C (10 mmHg). R_f = 0.76 (PE/EtOAc = 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 7.31−7.14 (m, 5H), 4.14 (q, J = 7.2 Hz, 2H), 3.77 (t, J = 7.6 Hz, 1H), 3.16 (d, J = 7.6 Hz, 2H), 2.18 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 202.6, 169.2, 138.3, 128.9, 128.7, 126.8, 61.6, 61.4, 34.1, 29.7, 14.1. The physical and spectral data were consistent with those previously reported.[50]

*Ethyl 2-(4-tert-Butylbenzyl)-3-oxobutanoate (**1r**).*[113] According to **GP1**, ethyl acetoacetate (19.5 g, 0.15 mol, 1.0 equiv) was treated with NaOH (6.0 g, 0.15 mol, 1.0 equiv) and 4-*tert*-butylbenzyl bromide (40.9 g, 0.18 mol, 1.2 equiv) to afford ethyl 2-(4-*tert*-butylbenzyl)-3-oxobutanoate (29.85 g, 0.11 mol, 72%) as a yellow oil. Bp = 183−185 °C (10 mmHg). R_f = 0.81 (PE/EtOAc = 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 7.29 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 8.1 Hz, 2H), 4.15 (q, J = 7.1 Hz, 2H), 3.77 (t, J = 7.6 Hz, 1H), 3.13 (d, J = 7.6 Hz, 2H), 2.19 (s, 3H), 1.29 (s, 9H), 1.20 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 202.7, 169.4, 149.6, 135.2, 128.6, 125.6, 61.6, 61.5, 34.5, 33.6, 31.5, 29.7, 14.1. The physical and spectral data were consistent with those previously reported.[50]

*Ethyl 2-(4-Chlorobenzyl)-3-oxobutanoate (**1s**).* According to **GP1**, ethyl acetoacetate (19.5 g, 0.15 mol, 1.0 equiv) was treated with NaOH (6.0 g, 0.15 mol, 1.0 equiv) and 4-chlorobenzyl bromide (37.0 g, 0.18 mol, 1.2 equiv) to afford ethyl 2-(4-chlorobenzyl)-3-oxobutanoate (22.5 g, 0.09 mol, 59%) as a yellow oil: bp = 108−110 °C (0.1 mmHg). R_f = 0.81 (PE/EtOAc = 5:1). Keto/enol ratio = 9/1. ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 12.94 (s, 0.1H), 7.23 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.72 (t, J = 7.6 Hz, 0.9H), 3.52 (s, 0.2H), 3.17−3.08 (m, 1.8H), 2.19 (s, 2.7H), 2.03 (s, 0.3H), 1.20 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 202.1, 169.0, 136.8, 132.6, 130.3, 128.8, 61.7, 61.3, 33.3, 29.7, 14.1. The physical and spectral data were consistent with those previously reported.[114]

*Procedure for the Synthesis of tert-Butyl 2-(4-Bromobenzyl)-3-oxobutanoate (**1t**).*[115] NaH (160.0 mg, 4.0 mmol, 1.0 equiv) as a 60% suspension in mineral oil was added with stirring to dry THF (5 mL) at 0 °C. Then *tert*-butyl acetoacetate (1.27 g, 8.0 mmol, 2.0 equiv) and 4-bromobenzyl bromide (1.0 g, 4.0 mmol, 1.0 equiv) were added with stirring at 0 °C. The reaction mixture was heated to 50 °C and stirred for 2 days. Then the mixture was concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 20−25 °C). H_2O (10 mL) was added, and the aqueous layer was washed CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with 5% solution of $NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 40−45 °C). The product **1t** was isolated by column chromatography on SiO_2 (PE/EtOAc = 10:1). Yield: 60% (772.2 mg, 2.4 mmol). Colorless oil. R_f = 0.46 (PE/EtOAc = 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 7.38 (d, J = 8.2 Hz, 2H), 7.05 (d, J = 8.2 Hz, 2H), 3.63 (t, J = 7.6 Hz, 1H), 3.11−3.01 (m, 2H), 2.19 (s, 3H), 1.39 (s, 9H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 202.4, 168.1, 137.6, 131.7, 130.8, 120.6, 82.5, 62.2, 33.3, 29.6, 28.0. The physical and spectral data were consistent with those previously reported.[115]

*Procedure for the Synthesis of Ethyl 2-Benzyl-3-oxohexanoate (**1u**).*[116] Ethyl 3-oxohexanoate (1.03 g, 6.50 mmol, 1.3 equiv) was added dropwise to a suspension of K_2CO_3 (5.52 g, 40.0 mmol, 8 equiv) in dry acetone (10 mL). Then benzyl bromide (857.0 mg, 5.0 mmol, 1 equiv), KI (41.5 mg, 0.25 mmol, 0.05 equiv), and dibenzo-18-crown-6 (90.0 mg, 0.25 mmol, 0.05 equiv) were added. The reaction mixture was refluxed for 10 h. Then an aqueous solution of 2 M HCl (25 mL) was added, and the product from the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temper-

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ature, ca. 40−45 °C). The β-ketoester **1u** was isolated by column chromatography on SiO_2 (PE/EtOAc = from 20:1 to 2:1). Yield: 71% (882.0 mg, 3.6 mmol). Colorless oil. R_f = 0.68 (PE/EtOAc = 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 7.31−7.11 (m, 5H), 4.13 (q, J = 7.1 Hz, 2H), 3.77 (t, J = 7.6 Hz, 1H), 3.15 (d, J = 7.6 Hz, 2H), 2.51 (dt, J = 17.3, 7.2 Hz, 1H), 2.31 (dt, J = 17.3, 7.2 Hz, 1H), 1.60−1.45 (m, 2H), 1.19 (t, J = 7.1 Hz, 3H), 0.83 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 204.8, 169.2, 138.4, 128.9, 128.6, 126.7, 61.5, 60.7, 44.8, 34.2, 16.9, 14.1, 13.6. The physical and spectral data were consistent with those previously reported.[117]

Synthesis of Enol Ethers 2−4 and Acetals 5. *General Procedure for the Synthesis of Silyl Enol Ethers* ***2****.*[118] Et_3N (1.53 g, 15.0 mmol, 1.5 equiv) was added to a solution of β-ketoester **1** (1.58−2.20 g, 10.0 mmol, 1.0 equiv) in dry benzene (20 mL) with stirring at 20 °C. Then trimethylchlorosilane (1.62 g, 15.0 mmol, 1.5 equiv) was added. The reaction mixture was stirred overnight at 20−25 °C. The precipitate was filtered, and the filtrate was concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 40−45 °C).

Ethyl 3-((Trimethylsilyl)oxy)hex-2-enoate, ***2b****.* Yield: 87% (2.00 g, 8.7 mmol). Colorless oil. ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 5.10 (s, 0.25H), 5.06 (s, 0.75H), 4.10 (q, J = 7.1 Hz, 2H), 2.71−2.63 (m, 1.5H), 2.10−2.02 (m, 0.5H), 1.54 (q, J = 7.5 Hz, 2H), 1.29−1.21 (m, 3H), 0.97−0.89 (m, 3H), 0.26 (s, 9H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 173.3, 168.3, 167.8, 165.9, 99.9, 99.2, 59.4, 59.2, 40.3, 35.2, 20.4, 20.0, 14.6, 14.5, 13.85, 13.69, 0.8, 0.3. The physical and spectral data were consistent with those previously reported.[119]

Dimethyl 3-((Trimethylsilyl)oxy)pent-2-enedioate, ***2e****.* Yield: 97% (2.39 g, 9.7 mmol). Slightly yellow oil. ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 5.22 (s, 1H), 3.81 (s, 2H), 3.69 (s, 3H), 3.65 (s, 3H), 0.27 (s, 9H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 169.8, 167.9, 164.7, 100.8, 52.1, 51.1, 39.8, 0.1. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $[C_{10}H_{18}SiNaO_5]^+$: 269.0816, found 269.0818.

Ethyl 2-Benzyl-3-((trimethylsilyl)oxy)but-2-enoate, ***2q****.* Yield: 92% (2.69 g, 9.2 mmol). Slightly yellow oil. ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 7.29−7.09 (m, 5H), 4.10 (q, J = 7.1 Hz, 2H), 3.66 (s, 2H), 2.36 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H), 0.22 (s, 9H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 169.4, 162.5, 142.1, 128.5, 128.1, 125.6, 113.0, 59.9, 32.5, 21.6, 14.4, 1.1. The physical and spectral data were consistent with those previously reported.[118]

Procedure for the Synthesis of Ethyl 3-Ethoxybut-2-enoate, ***3a****.* H_2SO_4 (100 μL) was added to the mixture of ethyl acetoacetate (6.5 g, 50.0 mmol, 1.0 equiv) and triethyl orthoformate (11.5 mL, 70.0 mmol, 1.4 equiv) with stirring at 0−10 °C. The reaction mixture was stirred overnight at 20−25 °C. Anhydrous K_2CO_3 (300.0 mg) was added, and the reaction mixture was filtered and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 40−45 °C). Distillation of the remaining liquid under medium vacuum (10 mmHg) gave product **3a**. Bp = 83−85 °C (10 mmHg). Yield: 77% (6.1 g, 38.6 mmol). Colorless oil. ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 4.95 (s, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.78 (q, J = 7.0 Hz, 2H), 2.25 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H). The physical and spectral data were consistent with those previously reported.[120]

General Procedure for the Synthesis of Enol Ethers ***3g*** *and* ***3q****.*[121] A solution of **1** (192.2−220.0 mg, 1.0 mmol, 1.0 equiv) and $Cu(OAc)_2{\cdot}H_2O$ (10.0 mg, 0.05 mmol, 0.05 equiv) in 1,4-dioxane (2 mL) was stirred at room temperature. To the reaction mixture was added dropwise a 5−6 M TBHP solution in decane (2.2 mmol, 2.2 equiv). The reaction mixture was refluxed for 3 h. After being cooled to room temperature, the reaction mixture was diluted EtOAc (50 mL) and filtered through SiO_2 layer (2−3 cm). The filtrate was concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 20−25 °C). The product **3** was isolated by column chromatography on SiO_2 (PE/EtOAc = from 15:1 to 1:1).

Ethyl 3-((1,4-Dioxan-2-yl)oxy)-3-phenyl Acrylate, ***3g****.* Yield: 49% (136.2 mg, 0.49 mmol). Yellow oil. R_f = 0.39 (PE/EtOAc = 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 7.61−7.57 (m, 2H), 7.43−7.34 (m, 3H), 5.68 (s, 1H), 5.26 (t, J = 2.1 Hz, 1H), 4.39−4.29 (m, 1H), 4.21 (q, J = 7.1 Hz, 2H), 4.02 (dd, J = 12.0, 2.1 Hz, 1H), 3.84−3.67 (m, 3H), 3.49 (dt, J = 11.6, 2.9 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 165.2, 165.0, 135.3, 130.4, 128.7, 127.7, 103.7, 96.1, 68.3, 66.1, 61.8, 60.0, 14.5. The physical and spectral data were consistent with those previously reported.[121]

Ethyl 3-((1,4-Dioxan-2-yl)oxy)-2-benzylbut-2-enoate, ***3q****.* Yield: 55% (168.5 mg, 0.55 mmol). Colorless oil. R_f = 0.33 (PE/EtOAc = 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 7.33−7.11 (m, 5H), 5.10 (t, J = 2.4 Hz, 1H), 4.18−4.08 (m, 2H), 3.82−3.52 (m, 8H), 2.07 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 167.9, 157.8, 139.8, 128.5, 128.2, 126.2, 114.6, 94.4, 68.4, 66.1, 61.7, 60.4, 34.7, 16.3, 14.3. The physical and spectral data were consistent with those previously reported.[121]

General Procedure for the Synthesis of Enol Acetates ***4g****,* ***4n****, and* ***4q****.* Acetyl chloride (535 μL, 588.8 mg, 7.5 mmol, 1.5 equiv) was added to a solution of **1** (0.96−1.15 g, 5.0 mmol, 1.0 equiv) in anhydrous pyridine (10 mL). The mixture was stirred at room temperature until the complete disappearance of **1**. The solution was then diluted with Et_2O (25 mL), washed with an aqueous saturated solution of $CuSO_4$ (2 × 25 mL) and H_2O (25 mL), dried over $MgSO_4$, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 20−25 °C). The product **4** was isolated by column chromatography on SiO_2 (PE/EtOAc = from 20:1 to 2:1).

Ethyl 3-Acetoxy-3-phenyl Acrylate, ***4g****.*[122] Yield: 38% (445.0 mg, 1.9 mmol). Colorless oil. R_f = 0.37 (PE/EtOAc = 2:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 7.62−7.54 (m, 2H), 7.47−7.36 (m, 3H), 6.27 (s, 1H), 4.20 (q, J = 7.1 Hz, 2H), 2.39 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 168.2, 164.3, 158.1, 133.5, 131.1, 128.9, 126.1, 106.3, 60.4, 21.1, 14.4. The physical and spectral data were consistent with those previously reported.[122]

Diethyl 2-(1-Acetoxyethylidene)pentanedioate, ***4n****.* Yield: 78% (1.06 g, 3.9 mmol). Colorless oil. R_f = 0.41 (PE/EtOAc = 2:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 4.20 (q, J = 7.1 Hz, 2H), 4.09 (q, J = 7.1 Hz, 2H), 2.58−2.49 (m, 2H), 2.41−2.32 (m, 2H), 2.25 (s, 3H), 2.18 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 173.0, 168.3, 167.1, 157.7, 120.9, 60.8, 60.5, 33.3, 23.0, 21.0, 19.6, 14.3. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $[C_{13}H_{21}O_6]^+$: 273.1333, found 273.1332.

Ethyl 3-Acetoxy-2-benzylbut-2-enoate, ***4q****.*[123] Yield: 50% (656.0 mg, 2.5 mmol). Colorless oil. R_f = 0.54 (PE/EtOAc = 2:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 7.32−7.11 (m, 5H), 4.13 (q, J = 7.1 Hz, 2H), 3.61 (s, 2H), 2.34 (s, 3H), 2.16 (s, 3H), 1.18 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 168.1, 167.3, 157.2, 139.4, 128.5, 128.4, 126.2, 121.6, 60.8, 33.2, 21.0, 19.5, 14.2. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $[C_{15}H_{19}O_4]^+$: 263.1278, found 263.1269. The physical and spectral data were consistent with those previously reported.[123]

General Procedure for the Synthesis of Acetals ***5j****,* ***5o****, and* ***5q****.* Toluene (20 mL) was added to **1** (0.85−1.10 g, 5.0 mmol, 1.0 equiv), and then ethylene glycol (620.7 mg, 10.0 mmol, 2.0 equiv) and *p*-toluenesulfonic acid monohydrate (190.2 mg, 1.0 mmol, 0.2 equiv) were added to the reaction mixture. The mixture was refluxed for 2 h with water removal by means of Dean−Stark apparatus. Then, the mixture was added to a separatory funnel, and washed with water (5 mL), 10% Na_2CO_3 (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 20−25 °C). The product **5** was isolated by column chromatography on SiO_2 (PE/EtOAc = from 20:1 to 2:1).

Ethyl 1,4-dioxaspiro[4.5]decane-6-carboxylate, ***5j****.*[124] Yield 80% (0.85 g, 4.0 mmol). Colorless oil. R_f = 0.61 (PE/EtOAc = 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 4.12 (q, J = 7.1 Hz, 2H), 3.99−3.82 (m, 4H), 2.64 (dd, J = 8.1, 5.5 Hz, 1H), 1.95−1.79 (m, 3H), 1.73−1.55 (m, 3H), 1.53−1.39 (m, 1H), 1.36−1.21 (m, 4H). ^{13}C{^{1}H}-NMR (75.48 MHz, $CDCl_3$, δ): 172.5, 108.8, 65.0, 64.6, 60.4, 50.1, 34.8, 27.4, 23.5, 23.1, 14.3. The physical and spectral data were consistent with those previously reported.[124]

Ethyl 4-cyano-2-(2-methyl-1,3-dioxolan-2-yl)butanoate, ***5o****.* Yield 67% (0.76 g, 3.3 mmol). Colorless oil. R_f = 0.69 (PE/EtOAc

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= 1:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 4.18 (q, J = 7.1 Hz, 2H), 4.03−3.90 (m, 4H), 2.76 (dd, J = 9.9, 4.8 Hz, 1H), 2.48−2.24 (m, 2H), 2.16−1.94 (m, 2H), 1.38 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 171.4, 119.0, 109.1, 64.99, 64.86, 61.1, 52.7, 24.0, 21.7, 15.8, 14.2.

Ethyl 2-(2-methyl-1,3-dioxolan-2-yl)-3-phenylpropanoate, ***5q***.[125] Yield 88% (1.16 g, 4.4 mmol). Colorless oil. R_f = 0.48 (PE/EtOAc = 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 7.31−7.12 (m, 5H), 4.11−3.98 (m, 6H), 3.09−2.93 (m, 3H), 1.49 (s, 3H), 1.08 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 172.1, 139.4, 128.9, 128.5, 126.4, 109.6, 65.1, 65.0, 60.5, 56.5, 34.4, 21.9, 14.2. The physical and spectral data were consistent with those previously reported.[126]

Synthesis of Disubstituted β-Ketoesters 8a−c. *Procedure for the Synthesis of Ethyl 2,2-Dimethyl-3-oxobutanoate,* ***8a***. Ethyl acetoacetate (1.30 g, 10.0 mmol, 1.0 equiv) was added to a suspension of K_2CO_3 (5.52 g, 40.0 mmol, 4.0 equiv) in anhydrous DMSO (8 mL). Later, methyl iodide (5.68 g, 40.0 mmol, 4.0 equiv) and dibenzo-18-crown-6 (100 mg) were added with stirring. The mixture was stirred at 20−25 °C overnight until the complete disappearance of ethyl acetoacetate. The reaction mixture was then diluted with H_2O (50 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (3 × 10 mL), dried over $MgSO_4$, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 40−45 °C). The product **8a** was isolated by column chromatography on SiO_2 (PE/EtOAc = from 20:1 to 5:1). Yield: 53% (838.0 mg, 5.3 mmol). Colorless oil. R_f = 0.69 (PE/EtOAc = 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 4.18 (q, J = 7.1 Hz, 2H), 2.14 (s, 3H), 1.35 (s, 6H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 206.0, 173.7, 61.4, 55.9, 25.8, 22.0, 14.1. The physical and spectral data were consistent with those previously reported.[127]

Procedure for the Synthesis of Ethyl 2-Benzyl-2-methyl-3-oxobutanoate, ***8b***. Ethyl 2-benzyl-3-oxobutanoate **1q** (1.10 g, 5.0 mmol, 1.0 equiv) was added to a suspension of K_2CO_3 (2.76 g, 20.0 mmol, 4.0 equiv) in anhydrous DMSO (5 mL). Later, methyl iodide (1.42 g, 10.0 mmol, 2.0 equiv) and dibenzo-18-crown-6 (50 mg) were added with stirring. The mixture was stirred at 20−25 °C overnight until the complete disappearance of ethyl 2-benzyl-3-oxobutanoate **1q**. The reaction mixture was then diluted with H_2O (20 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (3 × 5 mL), dried over $MgSO_4$, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 40−45 °C). The product **8b** was isolated by column chromatography on SiO_2 (PE/EtOAc = from 20:1 to 5:1). Yield: 84% (984.0 mg, 4.2 mmol). Colorless oil. R_f = 0.76 (PE/EtOAc = 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 7.30−7.17 (m, 3H), 7.09 (d, J = 7.6 Hz, 2H), 4.31−4.02 (m, 2H), 3.27 (d, J = 13.8 Hz, 1H), 3.05 (d, J = 13.8 Hz, 1H), 2.16 (s, 3H), 1.28 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 205.5, 172.6, 136.6, 130.3, 128.3, 127.0, 61.5, 61.0, 40.6, 26.6, 19.2, 14.1. The physical and spectral data were consistent with those previously reported.[128]

Procedure for the Synthesis of Ethyl 2,2-Dibenzyl-3-oxobutanoate, ***8c***. Ethyl acetoacetate (1.30 g, 10.0 mmol, 1.0 equiv) was added to a suspension of K_2CO_3 (5.52 g, 40.0 mmol, 4.0 equiv) in anhydrous DMSO (8 mL). Later, benzyl bromide (6.84 g, 40.0 mmol, 4.0 equiv), KI (50 mg), and dibenzo-18-crown-6 (100 mg) were added with stirring. The mixture was stirred at 20−25 °C overnight until the complete disappearance of ethyl acetoacetate. The reaction mixture was then diluted with H_2O (50 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (3 × 10 mL), dried over $MgSO_4$, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 40−45 °C). The product **8c** was isolated by column chromatography on SiO_2 (PE/EtOAc = from 20:1 to 5:1). Yield: 41% (1.28 g, 4.1 mmol). Colorless oil. R_f = 0.58 (PE/EtOAc = 10:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 7.30−7.19 (m, 6H), 7.17−7.07 (m, 4H), 4.11 (q, J = 7.1 Hz, 2H), 3.22 (s, 4H), 1.96 (s, 3H), 1.17 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 205.7, 171.9, 136.5, 130.2, 128.4, 127.0, 66.3, 61.4, 40.0, 29.2, 14.0. The physical and spectral data were consistent with those previously reported.[127]

Experimental Procedure for Table 1. *Experimental Procedure for Table 1, entries 1−9.* An ethereal solution of H_2O_2 (2.048 M, 0.488−4.882 mL, 1.00−10.00 mmol, 1−10 equiv) was added with stirring to **1q** (220.3 mg, 1.00 mmol, 1.0 equiv). Later, $BF_3{\cdot}Et_2O$ (141.9 mg -1.419 g, 1.00−10.00 mmol, 1−10 equiv) was added dropwise with stirring to the solution at 0 °C. The reaction mixture was stirred at 20−25 °C for 1, 3, or 12 h. After that time, CH_2Cl_2 (40 mL) and H_2O (0.5 mL) were added. Then $NaHCO_3$ was added with stirring until the pH reached 7.0. The precipitate was filtered off. The filtrate was dried over $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 20−25 °C). Product **6q** was isolated by chromatography on SiO_2 with elution using a PE/EtOAc mixture (5:1).

Experimental Procedure for Table 1, Entry 10. Urea hydrogen peroxide (940.0 mg, 10.00 mmol, 10.0 equiv) was added with stirring to a solution of **1q** (220.3 mg, 1.00 mmol, 1.0 equiv) in Et_2O (4.9 mL). Later, $BF_3{\cdot}Et_2O$ (1.419 g, 10.00 mmol, 10.0 equiv) was added dropwise with stirring to the solution at 0 °C. The reaction mixture was stirred at 20−25 °C for 24 h. After that time, CH_2Cl_2 (40 mL) and H_2O (0.5 mL) were added. Then $NaHCO_3$ was added with stirring until the pH reached 7.0. The precipitate was filtered off. The filtrate was dried over $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 20−25 °C). Product **6q** was isolated as described above. The yield of **6q** was 43% (96.4 mg, 0.43 mmol).

Experimental Procedure for Table 1, Entries 11 and 12. Ethyl 2-benzyl-3-oxobutanoate **1q** (220.3 mg, 1.00 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (0.6 mL), and one drop of 5% aq H_2SO_4 (0.3 μL) was added. H_2O_2 (90%, 150.0 mg, 4.00 mmol, 4.0 equiv) was added dropwise with stirring to the solution at 20 °C. The reaction mixture was then cooled to 0 °C, and 50% aq H_2SO_4 (34−719 μL, 0.24−10.00 mmol, 0.24−10.0 equiv) was added dropwise. The reaction mixture was stirred at 20−25 °C for 12 h. After that time, CH_2Cl_2 (50 mL) was added, and the organic layer was washed with brine (10 mL), a 5% aqueous $NaHCO_3$ solution (2 × 10 mL), and again with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 20−25 °C). Traces of target product **6q** were detected by ^{1}H NMR after the synthesis.

Experimental Procedure for Table 1, Entries 13−17. An ethereal solution of H_2O_2 (2.048 M, 4.882 mL, 10.00 mmol, 10 equiv) was added with stirring to **1q** (220.3 mg, 1.00 mmol, 1.0 equiv). Later, H_2SO_4 (980.0 mg, 10.00 mmol, 10 equiv), 70% aq $HClO_4$ (1.435 g, 10.00 mmol, 10 equiv), 48% aq HBF_4 (1.829 g, 10.00 mmol, 10 equiv), PMA (2340.0 mg, 1.00 mmol, 1.0 equiv), or PTA (3249.5 mg, 0.50 mmol, 0.5 equiv) was added with stirring to the solution at 0 °C. The reaction mixture was stirred at 20−25 °C for 12 or 24 h. After that time, CH_2Cl_2 (50 mL) was added, and the organic layer was washed with brine (10 mL), a 5% aqueous $NaHCO_3$ solution (2 × 10 mL), and again with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 20−25 °C). Product **6q** was isolated as described above.

Experimental Procedure for Table 1, Entries 18−20. An ethereal solution of H_2O_2 (2.048 M, 4.882 mL, 10.0 mmol, 10.0 equiv) was added with stirring to **1q** (220.3 mg, 1.00 mmol, 1.0 equiv). Later, $Na_2MoO_4{\cdot}2H_2O$ (483.8 mg, 2.00 mmol, 2.0 equiv) or I_2 (25.4−1270.0 mg, 0.10−5.00 mmol, 0.1−5.0 equiv) was added with stirring to the solution at 0 °C. The reaction mixture was stirred at 20−25 °C for 24 h. Target product **6q** was not detected by TLC during the reaction and after the synthesis.

Experimental Procedure for Table 1, Entry 21. An ethereal solution of H_2O_2 (2.048 M, 4.882 mL, 10.00 mmol, 10.0 equiv) was added with stirring to **1q** (220.3 mg, 1.00 mmol, 1.0 equiv). Later, TBAI (738.7 mg, 2.00 mmol, 2.0 equiv) was added with stirring to the solution at 0 °C. The reaction mixture was stirred at 20−25 °C for 24 h. Later, Et_2O (50 mL) was added. The reaction mixture was filtered

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off through SiO_2 (2−3 cm) and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 20−25 °C). Product **6q** was not detected. Byproduct 4-phenylbutan-2-one (**7**) was isolated by chromatography on SiO_2 with elution using a PE/EtOAc mixture (5:1). The yield of **7** was 27% (40.0 mg, 0.27 mmol).

*4-Phenylbutan-2-one, **7**.* Colorless oil. R_f = 0.68 (PE/EtOAc = 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 7.31−7.25 (m, 2H), 7.23−7.15 (m, 3H), 2.90 (t, J = 7.4 Hz, 2H), 2.76 (t, J = 7.4 Hz, 2H), 2.14 (s, 3H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 208.0, 141.1, 128.6, 128.4, 126.2, 45.3, 30.2, 29.9. The physical and spectral data were consistent with those previously reported.[129]

Experimental Procedure for Table 2. *Procedure for Experiments under Optimal Conditions for β-Ketoesters "Substrate/H_2O_2/BF_3·Et_2O" (First Column).* An ethereal solution of H_2O_2 (2.048 M, 4.882 mL, 10.00 mmol, 10.0 equiv) was added with stirring to enol ether **2q**−**4q** or acetal **5q** (262.3−306.4 mg, 1.00 mmol, 1.0 equiv). Later, BF_3·Et_2O (1.419 g, 10.00 mmol, 10.0 equiv) was added dropwise with stirring to the solution at 0 °C. The reaction mixture was stirred at 20−25 °C for 12 h. After that time, CH_2Cl_2 (40 mL) and H_2O (0.5 mL) were added. Then $NaHCO_3$ was added with stirring until the pH reached 7.0. The precipitate was filtered off. The filtrate was dried over $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 20−25 °C). Product **6q** was isolated as described above.

Procedure for Experiments with Other Order of Addition of Reagents "H_2O_2/BF_3·Et_2O/Substrate" (Second Column). BF_3·Et_2O (1.419 g, 10.00 mmol, 10.0 equiv) was added dropwise with stirring to an ethereal solution of H_2O_2 (2.048 M, 4.882 mL, 10.00 mmol, 10.0 equiv) at 0 °C. Later, enol ether **2q**−**4q** or acetal **5q** (262.3−306.4 mg, 1.00 mmol, 1.0 equiv) was added dropwise with stirring to the solution at 0 °C. The reaction mixture was stirred at 20−25 °C for 12 h. After that time, CH_2Cl_2 (40 mL) and H_2O (0.5 mL) were added. Then $NaHCO_3$ was added with stirring until the pH reached 7.0. The precipitate was filtered off. The filtrate was dried over $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 20−25 °C). Product **6q** was isolated as described above.

Procedure for Experiments with Other Order of Addition of Reagents and with $HClO_4$ instead of BF_3·Et_2O "H_2O_2/$HClO_4$/Substrate" (Third Column). $HClO_4$ 70% aq (1.435 g, 10.00 mmol, 10.0 equiv) was added dropwise with stirring to an ethereal solution of H_2O_2 (2.048 M, 4.882 mL, 10.00 mmol, 10.0 equiv) at 0 °C. Later, enol ether **2q**−**4q** or acetal **5q** (262.3−306.4 mg, 1.00 mmol, 1.0 equiv) was added dropwise with stirring to the solution at 0 °C. The reaction mixture was stirred at 20−25 °C for 12 h. After that time, CH_2Cl_2 (50 mL) was added, and the organic layer was washed with brine (10 mL), a 5% aqueous $NaHCO_3$ solution (2 × 10 mL), and again with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 20−25 °C). Product **6q** was isolated as described above.

General Experimental Procedure for Table 3. An ethereal solution of H_2O_2 (2.048 M, 4.882 mL, 10.00 mmol, 10.0 equiv) was added with stirring to **1a**−**u** (130.1−327.2 mg, 1.00 mmol, 1.0 equiv). Later, BF_3·Et_2O (1.419 g, 10.00 mmol, 10.0 equiv) was added dropwise with stirring to the solution at 0 °C. The reaction mixture was stirred at 20−25 °C for 12 h. After that time, CH_2Cl_2 (40 mL) and H_2O (0.5 mL) were added. Then $NaHCO_3$ was added with stirring until the pH reached 7.0. The precipitate was filtered off. The filtrate was dried over $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 20−25 °C). Product **6** was isolated by chromatography on SiO_2 (PE/EtOAc = from 5:1 to 2:1).

*5-Hydroperoxy-5-methyl-1,2-dioxolan-3-one, **6a**.* Yield was 88% (118.0 mg, 0.88 mmol) from ethyl acetoacetate (**1a**) and 89% (119.3 mg, 0.89 mmol) from ethyl 3-ethoxybut-2-enoate (**3a**). Colorless oil. R_f = 0.47 (PE/EtOAc = 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 9.17 (s, 1H), 3.22 (d, J = 17.8 Hz, 1H), 3.13 (d, J = 17.8 Hz, 1H), 1.67 (s, 3H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 173.7, 113.8, 39.6, 18.5. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $[C_4H_6NaO_5]^+$: 157.0107, found 157.0112. IR (thin layer): 3207, 2837, 1804, 1625, 1404, 1383, 1323, 1238, 1196, 1116, 1079, 837, 814 cm^{-1}. Anal. Calcd for $C_4H_6O_5$: C, 35.83; H, 4.51. Found: C, 35.77; H, 4.49.

*5-Hydroperoxy-5-propyl-1,2-dioxolan-3-one, **6b**.* Yield: 96% (155.6 mg, 0.96 mmol) from **1b** and 88% (142.6 mg, 0.88 mmol) from **2b**. Colorless oil. R_f = 0.46 (PE/EtOAc = 4:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 8.85 (s, 1H), 3.19 (d, J = 17.8 Hz, 1H), 3.05 (d, J = 17.8 Hz, 1H), 2.06−1.92 (m, 1H), 1.87−1.73 (m, 1H), 1.61−1.34 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 173.6, 115.9, 38.2, 33.9, 17.7, 14.0. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $[C_6H_{10}NaO_5]^+$: 185.0420, found 185.0423. IR (thin layer): 2970, 2940, 2879, 1804, 1467, 1404, 1329, 1203, 1121, 972, 833, 540 cm^{-1}. Anal. Calcd for $C_6H_{10}O_5$: C, 44.45; H, 6.22. Found: C, 44.35; H, 6.31.

*5-Hydroperoxy-5-isopropyl-1,2-dioxolan-3-one, **6c**.* Yield: 90% (145.9 mg, 0.90 mmol). White crystals. Mp = 45−46 °C. R_f = 0.39 (PE/EtOAc = 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 8.64 (s, 1H), 3.19 (d, J = 17.8 Hz, 1H), 3.02 (d, J = 17.8 Hz, 1H), 2.33 (sept, J = 7.0 Hz, 1H), 1.09 (d, J = 7.0 Hz, 3H), 1.04 (d, J = 7.0 Hz, 3H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 173.4, 118.3, 35.6, 31.6, 17.8, 17.3. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $[C_6H_{10}NaO_5]^+$: 185.0420, found 185.0417. IR (KBr): 3325, 3019, 2980, 1794, 1473, 1436, 1402, 1218, 1196, 1071, 990, 866, 593, 499 cm^{-1}. Anal. Calcd for $C_6H_{10}O_5$: C, 44.45; H, 6.22. Found: C, 44.32; H, 6.19.

*5-Hydroperoxy-5-isobutyl-1,2-dioxolan-3-one, **6d**.* Yield: 64% (112.7 mg, 0.64 mmol). White crystals. Mp = 46−47 °C. R_f = 0.31 (PE/EtOAc = 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 8.82 (s, 1H), 3.20 (d, J = 17.7 Hz, 1H), 3.09 (d, J = 17.7 Hz, 1H), 2.02−1.81 (m, 2H), 1.70 (dd, J = 14.0, 7.2 Hz, 1H), 1.02−0.94 (m, 6H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 173.5, 115.7, 40.6, 39.0, 24.6, 23.5, 23.2. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $[C_7H_{13}O_5]^+$: 177.0757, found 177.0754. IR (KBr): 3361, 2963, 2875, 2339, 1806, 1601, 1402, 1371, 1205, 1123, 977, 859, 593 cm^{-1}. Anal. Calcd for $C_7H_{12}O_5$: C, 47.73; H, 6.87. Found: C, 47.81; H, 6.83.

*Methyl 2-(3-Hydroperoxy-5-oxo-1,2-dioxolan-3-yl)acetate, **6e**.* Yield: 79% (151.8 mg, 0.79 mmol) from **1e** and 61% (117.1 mg, 0.61 mmol) from **2e**. Colorless oil. R_f = 0.43 (PE/EtOAc = 2:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 9.42 (s, 1H), 3.76 (s, 3H), 3.66 (d, J = 16.8 Hz, 1H), 3.19 (d, J = 16.8 Hz, 1H), 3.13 (d, J = 14.6 Hz, 1H), 2.97 (d, J = 14.6 Hz, 1H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 172.7, 167.8, 112.8, 52.9, 38.2, 36.2. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $[C_6H_8NaO_7]^+$: 215.0162, found 215.0165. IR (film): 3178, 2958, 2833, 2340, 1805, 1732, 1587, 1371, 1227, 1003, 837, 669 cm^{-1}. Anal. Calcd for $C_6H_8O_7$: C, 37.51; H, 4.20. Found: C, 37.18; H, 4.30.

*Ethyl 2-(3-Hydroperoxy-5-oxo-1,2-dioxolan-3-yl)acetate, **6f**.* Yield: 78% (160.8 mg, 0.78 mmol). Colorless oil. R_f = 0.43 (PE/EtOAc = 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 9.36 (s, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.67 (d, J = 18.2 Hz, 1H), 3.18 (d, J = 18.2 Hz, 1H), 3.12 (d, J = 16.1 Hz, 1H), 2.96 (d, J = 16.1 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 172.8, 167.3, 112.8, 62.1, 38.2, 36.4, 14.1. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $[C_7H_{10}NaO_7]^+$: 229.0319, found 229.0329. IR (thin layer): 2987, 2340, 1806, 1732, 1633, 1401, 1377, 1231, 1185, 1026, 837, 694 cm^{-1}. Anal. Calcd for $C_7H_{10}O_7$: C, 40.78; H, 4.89. Found: C, 40.82; H, 5.02.

*5-Hydroperoxy-5-phenyl-1,2-dioxolan-3-one, **6g**.* Yield: 61% (119.6 mg, 0.61 mmol) from **1g**, 73% (143.1 mg, 0.73 mmol) from **3g** and 86% (168.6 mg, 0.86 mmol) from **4g**. Colorless oil. R_f = 0.51 (PE/EtOAc = 7:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 9.01 (s, 1H), 7.57−7.43 (m, 5H), 3.41 (s, 2H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 172.8, 132.4, 130.6, 129.1, 126.2, 114.5, 41.3. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $[C_9H_9O_5]^+$: 197.0444, found 197.0446.

*5-Benzyl-5-hydroperoxy-1,2-dioxolan-3-one, **6h**.* Yield: 77% (161.0 mg, 0.77 mmol). White crystals, mp = 93−94 °C. R_f = 0.24 (PE/EtOAc = 2:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 8.75 (s, 1H), 7.49−7.18 (m, 5H), 3.27 (d, J = 14.7 Hz, 1H), 3.19 (d, J = 14.7 Hz, 1H), 3.11 (d, J = 17.8 Hz, 1H), 2.84 (d, J = 17.8 Hz, 1H).

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$^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$, δ): 172.8, 133.1, 130.3, 129.1, 128.1, 115.9, 37.7, 37.4. IR (KBr): 3335, 3021, 2947, 2338, 1795, 1731, 1498, 1442, 1401, 1183, 1087, 982, 859, 812, 703, 602, 489 cm^{-1}. Anal. Calcd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80, found C, 57.41; H, 4.75.

6a-Hydroperoxytetrahydrocyclopenta[c][1,2]dioxol-3(3aH)-one, ***6i***. Yield: 87% (139.3 mg, 0.87 mmol). Colorless oil. R_f = 0.40 (PE/EtOAc = 2:1). ^1H NMR (300.13 MHz, $CDCl_3$, δ): 9.17 (s, 1H), 3.56 (dd, J = 10.7, 4.4 Hz, 1H), 2.37−1.99 (m, 6H). $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$, δ): 177.0, 126.1, 49.3, 34.9, 29.0, 25.5. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $[C_6H_8NaO_5]^+$: 183.0264, found 183.0256. IR (thin layer): 3236, 2975, 1796, 1738, 1439, 1331, 1207, 1115, 944, 807, 661 cm^{-1}. Anal. Calcd for $C_6H_8O_5$: C, 45.01; H, 5.04. Found: C, 45.14; H, 5.37.

7a-Hydroperoxyhexahydro-3H-benzo[c][1,2]dioxol-3-one, ***6j***. Yield: 57% (100.0 mg, 0.57 mmol) from **1j** and 75% (130.6 mg, 0.75 mmol) from **5j**. Colorless oil. R_f = 0.25 (PE/EtOAc = 5:1). ^1H NMR (300.13 MHz, $CDCl_3$, δ): 8.74 (s, 1H), 2.86−2.75 (m, 1H), 2.35−2.22 (m, 2H), 1.89−1.24 (m, 6H). $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$, δ): 176.2, 113.7, 44.2, 27.1, 25.8, 22.5, 21.6. HRMS (APCI-TOF) m/z [M + H]$^+$ calcd for $[C_7H_{11}O_5]^+$: 175.0601, found 175.0609. IR (thin layer): 2960, 2874, 1707, 1453, 1418, 1286, 1231, 1197, 1174, 1095, 940, 656 cm^{-1}. Anal. Calcd for $C_7H_{10}O_5$: C, 48.28; H, 5.79. Found: C, 48.14; H, 5.47.

4-(Adamantan-1-yl)-5-hydroperoxy-5-methyl-1,2-dioxolan-3-one, ***6k***. Yield: 80% (214.6 mg, 0.80 mmol). Colorless oil. R_f = 0.54 (PE/EtOAc = 5:1). ^1H NMR (300.13 MHz, $CDCl_3$, δ): 8.55 (s, 1H), 2.76 (s, 1H), 2.08−1.97 (m, 6H), 1.80−1.68 (m, 12H). $^{13}C\{^1H\}$-NMR (75.48 MHz, $CDCl_3$, δ): 173.1, 116.1, 59.9, 39.8, 36.7, 34.5, 28.5, 19.7. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $[C_{14}H_{20}NaO_5]^+$: 291.1203, found 291.1204. IR (KBr): 3316, 2917, 2850, 1763, 1443, 1259, 1172, 1123, 867, 655, 579, 502 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.70; H, 7.58.

5-Hydroperoxy-5-methyl-4-(prop-2-yn-1-yl)-1,2-dioxolan-3-one, ***6l***. Yield: 64% (110.2 mg, 0.64 mmol). White crystals, mp = 60−61 °C. R_f = 0.37 (PE/EtOAc = 5:1). ^1H NMR (300.13 MHz, $CDCl_3$, δ): 8.61 (s, 1H), 3.30 (dd, J = 10.3, 4.7 Hz, 1H), 2.87−2.66 (m, 2H), 2.12 (t, J = 2.5 Hz, 1H), 1.78 (s, 3H). $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$, δ): 173.7, 114.1, 79.1, 71.2, 48.1, 18.8, 14.5. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $[C_7H_8NaO_5]^+$: 195.0264, found 195.0261. IR (KBr): 3296, 2340, 1794, 1608, 1426, 1382, 1354, 1275, 1249, 1192, 1123, 1094, 916, 839, 682, 665, 557 cm^{-1}. Anal. Calcd for $C_7H_8O_5$: C, 48.84; H, 4.68. Found: C, 48.93; H, 4.56.

Ethyl 2-(3-Hydroperoxy-3-methyl-5-oxo-1,2-dioxolan-4-yl)-acetate, ***6m***. Yield: 73% (160.7 mg, 0.73 mmol). Colorless oil. R_f = 0.32 (PE/EtOAc = 4:1). ^1H NMR (300.13 MHz, $CDCl_3$, δ): 9.39 (s, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.75 (dd, J = 7.8, 4.9 Hz, 1H), 3.01−2.76 (m, 2H), 1.63 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$, δ): 174.7, 171.0, 114.2, 61.9, 45.6, 29.7, 18.4, 14.2. HRMS (ESI-TOF) m/z [M + Na]$^+$. Calcd for $[C_8H_{12}NaO_7]^+$: 243.0475, found 243.0475. IR (thin layer): 3352, 2987, 2938, 2875, 2340, 1802, 1732, 1657, 1415, 1383, 1276, 1176, 1122, 1092, 1025, 866, 844, 578 cm^{-1}. Anal. Calcd for $C_8H_{12}O_7$: C, 43.64; H, 5.49. Found: C, 43.49; H, 5.80.

Ethyl 3-(3-Hydroperoxy-3-methyl-5-oxo-1,2-dioxolan-4-yl)-propanoate, ***6n***. Yield: 66% (154.0 mg, 0.66 mmol) from **1n** and 30% (70.3 mg, 0.30 mmol) from **4n**. Colorless oil. R_f = 0.57 (PE/EtOAc = 2:1). ^1H NMR (300.13 MHz, $CDCl_3$, δ): 9.09 (s, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.30 (dd, J = 8.4, 5.8 Hz, 1H), 2.75−2.59 (m, 2H), 2.22−2.02 (m, 2H), 1.67 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$, δ): 175.5, 173.1, 114.5, 61.1, 47.7, 30.2, 19.6, 18.2, 14.3. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $[C_9H_{14}NaO_7]^+$: 257.0632, found 257.0633. Anal. Calcd for $C_9H_{14}O_7$: C, 46.16; H, 6.03. Found: C, 46.11; H, 6.08. IR (thin layer): 3346, 2987, 1801, 1714, 1382, 1198, 1086, 1026, 858, 839, 582 cm^{-1}.

3-(3-Hydroperoxy-3-methyl-5-oxo-1,2-dioxolan-4-yl)-propanenitrile, ***6o***. Yield: 78% (146.0 mg, 0.78 mmol) from **1o** and 74% (138.5 mg, 0.74 mmol) from **5o**. White crystals, mp = 42−43 °C. R_f = 0.28 (PE/EtOAc = 5:1). ^1H NMR (300.13 MHz, $CDCl_3$, δ): 9.24 (s, 1H), 3.25 (dd, J = 8.7, 5.8 Hz, 1H), 2.88−2.65 (m, 2H), 2.35−2.23 (m, 1H), 2.14−2.00 (m, 1H), 1.67 (s, 3H). $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$, δ): 174.7, 118.6, 114.1, 47.3, 20.8, 18.2, 14.6. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $[C_7H_9NNaO_5]^+$: 210.0373, found 210.0378. IR (KBr): 3397, 2340, 2251, 1800, 1719, 1586, 1425, 1384, 1242, 1176, 1127, 1086, 862, 838, 658 cm^{-1}. Anal. Calcd for $C_7H_9NO_5$: C, 44.92; H, 4.85; N, 7.48. Found: C, 45.03; H, 5.02; N, 7.49.

4-(3,3-Dihydroperoxybutyl)-5-hydroperoxy-5-methyl-1,2-dioxolan-3-one, ***6p***. Yield: 56% (142.3 mg, 0.56 mmol). White crystals, mp = 101−102 °C. R_f = 0.32 (PE/EtOAc = 2:1). ^1H NMR (300.13 MHz, $CDCl_3$, δ): 8.94 (s, 1H), 8.27 (s, 2H), 3.24 (dd, J = 8.4, 1.9 Hz, 1H), 2.41−2.28 (m, 1H), 2.19−2.01 (m, 2H), 1.89−1.79 (m, 1H), 1.63 (s, 3H), 1.44 (s, 3H). $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$, δ): 175.1, 115.1, 112.6, 45.4, 28.5, 18.0, 17.9, 17.8. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $[C_8H_{14}NaO_9]^+$: 277.0530, found 277.0531. IR (KBr): 3392, 1794, 1785, 1459, 1382, 1320, 1235, 1194, 1103, 941, 863, 846, 830, 757, 570, 532 cm^{-1}. Anal. Calcd for $C_8H_{14}O_9$: C, 37.80; H, 5.55. Found: C, 37.51; H, 5.61.

4-Benzyl-5-hydroperoxy-5-methyl-1,2-dioxolan-3-one, ***6q***. Yield: 92% (206.3 mg, 0.92 mmol). White crystals, mp = 110−111 °C. R_f = 0.53 (PE/EtOAc = 2:1). ^1H NMR (300.13 MHz, $CDCl_3$, δ): 8.67 (s, 1H), 7.39−7.22 (m, 5H), 3.40−3.23 (m, 2H), 3.05 (dd, J = 13.8, 9.9 Hz, 1H), 1.20 (s, 3H). $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$, δ): 175.0, 136.9, 129.2, 128.9, 127.3, 114.3, 51.3, 30.7, 18.4. HRMS (ESI-TOF) m/z [M + Na]$^+$. Calcd for $[C_{11}H_{12}NaO_5]^+$: 247.0577, found 247.0581. IR (KBr): 3294, 2900, 1800, 1768, 1603, 1274, 1213, 1178, 1086, 844, 749, 698 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 59.03; H, 5.02.

4-(4-tert-Butylbenzyl)-5-hydroperoxy-5-methyl-1,2-dioxolan-3-one, ***6r***. Yield: 76% (213.0 mg, 0.76 mmol). White crystals, mp = 123−124 °C. R_f = 0.58 (PE/EtOAc = 2:1). ^1H NMR (300.13 MHz, $CDCl_3$, δ): 8.77 (s, 1H), 7.36 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 3.38−3.20 (m, 2H), 3.02 (dd, J = 14.4, 10.1 Hz, 1H), 1.32 (s, 9H), 1.23 (s, 3H). $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$, δ): 175.1, 150.3, 133.8, 128.9, 125.8, 114.4, 51.3, 34.6, 31.5, 30.1, 18.4. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $[C_{15}H_{20}NaO_5]^+$: 303.1203, found 303.1193. IR (KBr): 3379, 2971, 2953, 1780, 1414, 1267, 1221, 1103, 838, 566 cm^{-1}. Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.30; H, 7.03.

4-(4-Chlorobenzyl)-5-hydroperoxy-5-methyl-1,2-dioxolan-3-one, ***6s***. Yield: 93% (240.5 mg, 0.93 mmol). White crystals, mp = 108 °C. R_f = 0.29 (PE/EtOAc = 2:1). ^1H NMR (300.13 MHz, $CDCl_3$, δ): 8.79 (s, 1H), 7.32 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 3.35−3.18 (m, 2H), 3.03 (dd, J = 13.7, 9.5 Hz, 1H), 1.23 (s, 3H). $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$, δ): 174.7, 135.3, 133.2, 130.6, 129.1, 114.2, 51.1, 30.1, 18.5. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $[C_{11}H_{11}ClNaO_5]^+$: 281.0187, found 281.0177. IR (KBr): 3293, 2789, 2339, 1793, 1764, 1493, 1408, 1335, 1272, 1234, 1212, 1175, 1100, 1020, 925, 842, 825, 779, 626, 594, 552, 409 cm^{-1}. Anal. Calcd for $C_{11}H_{11}ClO_5$: C, 51.08; H, 4.29; Cl, 13.71. Found: C, 51.09; H, 4.22; Cl, 13.75.

4-(4-Bromobenzyl)-5-hydroperoxy-5-methyl-1,2-dioxolan-3-one, ***6t***. Yield: 81% (245.5 mg, 0.81 mmol) from *tert*-butyl 2-(4-bromobenzyl)-3-oxobutanoate (**1t**). White crystals, mp = 119 °C. R_f = 0.22 (PE/EtOAc = 5:1). ^1H NMR (300.13 MHz, $CDCl_3$, δ): 8.59 (s, 1H), 7.47 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.2 Hz, 2H), 3.33−3.17 (m, 2H), 3.01 (dd, J = 14.2, 10.0 Hz, 1H), 1.24 (s, 3H). $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$, δ): 174.6, 135.8, 132.1, 131.0, 121.3, 114.1, 51.0, 30.2, 18.6. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $[C_{11}H_{11}BrNaO_5]^+$: 324.9682, 326.9662, found 324.9675, 326.9659. IR (KBr): 3285, 2797, 1790, 1766, 1489, 1407, 1234, 1212, 1176, 1091, 1072, 1017, 926, 841, 822, 653, 552 cm^{-1}. Anal. Calcd for $C_{11}H_{11}BrO_5$: C, 43.59; H, 3.66; Br, 26.36. Found: C, 43.61; H, 3.64; Br, 26.17.

4-Benzyl-5-hydroperoxy-5-propyl-1,2-dioxolan-3-one, ***6u***. Yield: 90% (227.0 mg, 0.90 mmol). Colorless oil. R_f = 0.61 (PE/EtOAc = 5:1). ^1H NMR (300.13 MHz, $CDCl_3$, δ): 8.53 (s, 1H), 7.38−7.27 (m, 5H), 3.42−3.25 (m, 2H), 3.07 (dd, J = 14.2, 9.1 Hz, 1H), 1.64−1.53 (m, 1H), 1.34−1.05 (m, 3H), 0.72 (t, J = 7.0 Hz, 3H). $^{13}C\{^1H\}$NMR

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(75.48 MHz, $CDCl_3$, δ): 175.2, 137.2, 129.2, 128.9, 127.3, 116.4, 48.6, 33.7, 30.9, 17.0, 14.0. HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $[C_{13}H_{16}NaO_5]^+$: 275.0890, found 275.0894. IR (KBr): 3286, 3033, 2968, 2871, 1788, 1758, 1458, 1418, 1337, 1268, 1201, 1169, 1121, 1085, 1029, 941, 934, 840, 749, 696, 603 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 61.92; H, 6.28.

General Experimental Procedure for Scheme 4. An ethereal solution of H_2O_2 (2.048 M, 4.882 mL, 10.00 mmol, 10.0 equiv) was added with stirring to **8** (158.2−310.4 mg, 1.00 mmol, 1.0 equiv). Later, $BF_3{\cdot}Et_2O$ (1.419 g, 10.00 mmol, 10.0 equiv) was added dropwise with stirring to the solution at 0 °C. The reaction mixture was stirred at 20−25 °C for 12 h. After that time, CH_2Cl_2 (40 mL) and H_2O (0.5 mL) were added. Then $NaHCO_3$ was added with stirring until the pH reached 7.0. The precipitate was filtered off. The filtrate was dried over $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 20−25 °C). Product **9** was isolated by chromatography on SiO_2 (PE/EtOAc = 6:1).

*5-Hydroperoxy-4,4,5-trimethyl-1,2-dioxolan-3-one, **9a**.* Yield: 86% (140.0 mg, 0.86 mmol). White crystals, mp = 88−89 °C. R_f = 0.47 (PE/EtOAc = 5:1). ^1H NMR (300.13 MHz, $CDCl_3$, δ): 8.48 (s, 1H), 1.54 (s, 3H), 1.38 (s, 3H), 1.26 (s, 3H). $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$, δ): 178.9, 116.5, 47.9, 22.7, 16.6, 13.8. HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $[C_6H_{10}NaO_5]^+$: 185.0420, found 185.0412. IR (KBr): 3354, 1793, 1772, 1420, 1379, 1274, 1164, 1141, 1123, 1095, 880, 843, 577 cm^{-1}. Anal. Calcd for $C_6H_{10}O_5$: C, 44.45; H, 6.22. Found: C, 44.51; H, 6.18.

*4-Benzyl-5-hydroperoxy-4,5-dimethyl-1,2-dioxolan-3-one, **9b**.* Yield: 74% (176.1 mg, 0.74 mmol). White crystals, mp = 76−77 °C. R_f = 0.67 (PE/EtOAc = 5:1). **9b** was prepared as inseparable mixture of diastereomers, dr = 4/1. ^1H NMR (300.13 MHz, $CDCl_3$, δ): 8.56 (s, 0.8H), 8.45 (s, 0.2H), 7.42−7.24 (m, 4.6H), 7.18−7.08 (m, 0.4H), 3.28 (d, J = 14.1 Hz, 0.8H), 3.17 (d, J = 13.2 Hz, 0.2H), 2.91−2.74 (m, 1H), 1.68 (s, 0.6H), 1.35 (s, 2.4H), 1.19 (s, 3H). $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$, δ): 178.6, 134.1, 131.4, 130.7, 128.5, 128.4, 127.5, 116.4, 50.9, 36.2, 19.4, 14.5, 13.7. HRMS (ESI-TOF) m/z $[M+NH_4]^+$ calcd for $[C_{12}H_{18}NO_5]^+$: 256.1179, found 256.1186. IR (KBr): 3418, 1781, 1454, 1376, 1246, 1162, 1107, 1089, 868, 765, 705, 506 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.59; H, 5.89.

*4,4-Dibenzyl-5-hydroperoxy-5-methyl-1,2-dioxolan-3-one, **9c**.* Product **9c** was not detected after synthesis. Starting compound **8c** was isolated in 82% yield (253.0 mg, 0.82 mmol).

Experimental Procedures for Scheme 5. *Synthesis of Peroxide **10** by Reaction of 4-Benzyl-5-hydroperoxy-5-methyl-1,2-dioxolan-3-one (**6q**) with 3,4-Dihydro-2H-pyran (DHP).* *p*-TsOH·H_2O (19.0 mg, 0.10 mmol, 0.1 equiv) was added with stirring to a solution of 4-benzyl-5-hydroperoxy-5-methyl-1,2-dioxolan-3-one **6q** (224.21 mg, 1.00 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL). Later, DHP (92.5 mg, 1.10 mmol, 1.1 equiv) was added. The reaction mixture was stirred at 20−25 °C for 2 h. Later, CH_2Cl_2 (50 mL) was added, and the organic layer was washed with 5% aqueous $NaHCO_3$ solution (2 × 10 mL) and with brine (5 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 20−25 °C). Product **10** (inseparable mixture of diastereomers (1:1)) was isolated by chromatography on SiO_2 (PE/EtOAc = 5:1).

*4-Benzyl-5-methyl-5-((tetrahydro-2H-pyran-2-yl)peroxy)-1,2-dioxolan-3-one, **10**.* Yield: 71% (218.9 mg, 0.71 mmol). Colorless oil. R_f = 0.43 (PE/EtOAc = 5:1). ^1H NMR (300.13 MHz, $CDCl_3$, δ): 7.39−7.22 (m, 5H), 5.40−5.43 (m, 0.5H), 5.31−5.34 (m, 0.5H), 4.14−4.00 (m, 1H), 3.76−3.65 (m, 1H), 3.38−3.15 (m, 2.5H), 2.99 (dd, J = 14.1, 10.3 Hz, 0.5H), 1.82−1.56 (m, 6H), 1.26 (s, 1.5H), 1.16 (s, 1.5H). $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$, δ): 175.1, 174.9, 137.2, 137.0, 129.31, 129.30, 128.91, 128.87, 127.2, 114.6, 113.4, 102.7, 101.4, 62.7, 62.5, 52.2, 51.2, 30.9, 30.6, 27.7, 27.6, 25.1, 19.4, 19.3, 18.7. HRMS (ESI-TOF) m/z $[M + NH_4]^+$ calcd for $[C_{16}H_{24}NO_6]^+$: 326.1598, found 326.1596. IR (thin layer): 3031, 2947, 2873, 1802, 1604, 1497, 1456, 1443, 1380, 1262, 1174, 1109, 1084, 1040, 962, 896, 875, 816, 751, 701, 553 cm^{-1}. Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 62.38; H, 6.42.

*Synthesis of Peroxide **11** by Reaction of 4-Benzyl-5-hydroperoxy-5-methyl-1,2-dioxolan-3-one (**6q**) with 2,3-Dihydrofuran (DHF).* *p*-TsOH·H_2O (19.0 mg, 0.10 mmol, 0.1 equiv) was added with stirring to a solution of 4-benzyl-5-hydroperoxy-5-methyl-1,2-dioxolan-3-one **6q** (224.21 mg, 1.00 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL). Later, DHF (77.1 mg, 1.10 mmol, 1.1 equiv) was added. The reaction mixture was stirred at 20−25 °C for 2 h. Later, CH_2Cl_2 (50 mL) was added, and the organic layer was washed with 5% aqueous $NaHCO_3$ solution (2 × 10 mL) and with brine (5 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 20−25 °C). Product **11** (inseparable mixture of diastereomers (1:1)) was isolated by chromatography on SiO_2 (PE/EtOAc = 5:1).

*4-Benzyl-5-methyl-5-((tetrahydrofuran-2-yl)peroxy)-1,2-dioxolan-3-one, **11**.* Yield: 70% (206.0 mg, 0.70 mmol). Colorless oil. R_f = 0.49 (PE/EtOAc = 5:1). ^1H NMR (300.13 MHz, $CDCl_3$, δ): 7.39−7.21 (m, 5H), 5.88 (dd, J = 6.1, 1.8 Hz, 0.5H), 5.80−5.70 (m, 0.5H), 4.09−3.97 (m, 2H), 3.33−2.96 (m, 3H), 2.18−1.74 (m, 4H), 1.24 (s, 1.5H), 1.17 (s, 1.5H). $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$, δ): 175.1, 174.9, 137.3, 137.1, 129.3, 128.89, 128.86, 127.2, 114.4, 113.4, 108.6, 107.4, 68.2, 68.1, 52.2, 51.2, 30.6, 30.5, 29.8, 29.7, 23.8, 23.7, 19.2, 18.7. HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $[C_{15}H_{18}NaO_6]^+$: 317.0996, found 317.0998. IR (thin layer): 2986, 2895, 1801, 1497, 1456, 1380, 1234, 1175, 1079, 933, 845, 752, 701, 590 cm^{-1}. Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.22; H, 6.17. Found: C, 61.31; H, 6.23.

*Synthesis of Peroxide **12** by Reaction of 4-Benzyl-5-hydroperoxy-5-methyl-1,2-dioxolan-3-one (**6q**) with t-BuOH.* H_2SO_4 (98.0 mg, 1.00 mmol, 1.0 equiv) and *t*-BuOH (74.0 mg, 1.00 mmol, 1.0 equiv) were added with stirring to a solution of 4-benzyl-5-hydroperoxy-5-methyl-1,2-dioxolan-3-one **6q** (224.21 mg, 1.00 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at 20−25 °C for 4 days. Later, CH_2Cl_2 (50 mL) was added, and the organic layer was washed with H_2O (3 × 10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 20−25 °C). Product **12** was isolated by chromatography on SiO_2 (PE/EtOAc = 20:1).

*4-Benzyl-5-(tert-butylperoxy)-5-methyl-1,2-dioxolan-3-one, **12**.* Yield: 81% (227.1 mg, 0.81 mmol). Colorless oil. R_f = 0.27 (PE/EtOAc = 20:1). ^1H NMR (300.13 MHz, $CDCl_3$, δ): 7.38−7.24 (m, 5H), 3.30−3.20 (m, 2H), 3.08 (dd, J = 15.0, 11.1 Hz, 1H), 1.32 (s, 9H), 1.19 (s, 3H). $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$, δ): 175.5, 137.5, 129.2, 128.9, 127.1, 112.7, 82.2, 51.8, 30.9, 26.5, 18.9. HRMS (ESI-TOF) m/z $[M + Na]^+$. Calcd for $[C_{15}H_{20}NaO_5]^+$: 303.1203, found 303.1199. Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H: 7.19. Found: C, 64.26; H, 7.15. IR (thin layer): 3031, 2983, 2935, 1801, 1604, 1498, 1456, 1366, 1263, 1192, 1176, 1085, 921, 853, 748, 700, 589 cm^{-1}.

Experimental Procedures for Scheme 7. *Procedure for the Synthesis of 4-Benzyl-5-hydroxy-5-methyl-1,2-dioxolan-3-one, **13**.* Ph_3P (288.5 mg, 1.10 mmol, 1.1 equiv) in CH_2Cl_2 (2 mL) was added dropwise with stirring to a solution of **6q** (224.2 mg, 1.00 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) at 0−10 °C. The reaction mixture was stirred at 20−25 °C for 1 h and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 20−25 °C). Product **13** was isolated by chromatography on SiO_2 with elution using a PE/EtOAc mixture (5:1).

*4-Benzyl-5-hydroxy-5-methyl-1,2-dioxolan-3-one, **13**.* Yield: 62% (129.0 mg, 0.62 mmol). White crystals, mp = 95−96 °C. R_f = 0.49 (PE/EtOAc = 5:1). ^1H NMR (300.13 MHz, $CDCl_3$, δ): 7.37−7.22 (m, 5H), 3.28−3.17 (m, 3H), 3.00 (dd, J = 14.8, 11.6 Hz, 1H), 1.20 (s, 3H). $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$, δ): 175.9, 137.2, 129.2, 128.9, 127.2, 108.2, 53.1, 31.0, 23.0. HRMS (ESI-TOF) m/z $[M + Na]^+$. Calcd for $[C_{11}H_{12}NaO_4]^+$: 231.0628, found 231.0621. IR (KBr): 3651, 3425, 1764, 1458, 1399, 1268, 1228, 1194, 1075, 937, 757, 701, 608, 580 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.51; H, 5.68.

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*Procedure for the Synthesis of Bisperoxide, **14** (Procedure from Table 1, Entry 2).* An ethereal solution of H_2O_2 (2.048 M, 4.882 mL, 10.00 mmol, 10.0 equiv) was added with stirring to **1q** (220.3 mg, 1.00 mmol, 1.0 equiv). Later, $BF_3{\cdot}Et_2O$ (709.5 mg, 5.00 mmol, 5.0 equiv) was added dropwise with stirring to the solution at 0 °C. The reaction mixture was stirred at 20−25 °C for 12 h. After that time, CH_2Cl_2 (40 mL) and H_2O (0.5 mL) were added. Then $NaHCO_3$ was added with stirring until the pH reached 7.0. The precipitate was filtered off. The filtrate was dried over $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 20−25 °C). Products **6q** (37%) and **14** (32%) were isolated by chromatography on SiO_2 with elution using a PE/EtOAc mixture (5:1).

*Ethyl 2-benzyl-3,3-dihydroperoxybutanoate, **14**.* Yield 32% (86.5 mg, 0.32 mmol). Colorless oil. R_f = 0.22 (PE/EtOAc = 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, δ): 9.43 (s, 1H), 9.20 (s, 1H), 7.32−7.16 (m, 5H), 4.08 (q, J = 7.1 Hz, 2H), 3.51 (dd, J = 9.5, 5.6 Hz, 1H), 3.06−2.96 (m, 2H), 1.57 (s, 3H), 1.12 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$, δ): 172.1, 138.5, 129.0, 128.6, 126.8, 111.6, 61.7, 50.8, 33.8, 15.8, 14.0. HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $[C_{13}H_{18}NaO_6]^+$: 293.0996, found 293.0999. IR (film): 3320, 1800, 1715, 1455, 1377, 1219, 1084, 841, 750, 702 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.61; H, 6.52.

*Treatment of 4-Benzyl-5-hydroxy-5-methyl-1,2-dioxolan-3-one, **13**, with Hydrogen Peroxide.* An ethereal solution of H_2O_2 (2.048 M, 4.882 mL, 10.00 mmol, 10.0 equiv) was added with stirring to **13** (208.2 mg, 1.00 mmol, 1.0 equiv). Later, $BF_3{\cdot}Et_2O$ (1.419 g, 10.00 mmol, 10.0 equiv) was added dropwise with stirring to the solution at 0 °C. The reaction mixture was stirred at 20−25 °C for 12 h. After that time, CH_2Cl_2 (40 mL) and H_2O (0.5 mL) were added. Then $NaHCO_3$ was added with stirring until the pH reached 7.0. The precipitate was filtered off. The filtrate was dried over $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 20−25 °C). Compound **13** (197.8 mg, 0.95 mmol) was recovered (95%) by chromatography on SiO_2 with elution using a PE/EtOAc mixture (5:1).

*Treatment of 4-Benzyl-5-hydroperoxy-5-methyl-1,2-dioxolan-3-one, **6q**, with Water.* H_2O (180.0 mg, 10.00 mmol, 10.0 equiv) was added with stirring to **6q** (224.2 mg, 1.00 mmol, 1.0 equiv) in Et_2O (5 mL). Later, $BF_3{\cdot}Et_2O$ (1.419 g, 10.00 mmol, 10.0 equiv) was added dropwise with stirring to the solution at 0 °C. The reaction mixture was stirred at 20−25 °C for 12 h. After that time, CH_2Cl_2 (40 mL) and H_2O (0.5 mL) were added. Then $NaHCO_3$ was added with stirring until the pH reached 7.0. The precipitate was filtered off. The filtrate was dried over $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 20−25 °C). Compound **6q** (217.4 mg, 0.97 mmol) was recovered (97%) by chromatography on SiO_2 with elution using a PE/EtOAc mixture (5:1).

*Synthesis of **6q** by $BF_3{\cdot}Et_2O$-Catalyzed Cyclization of Ethyl 2-Benzyl-3,3-dihydroperoxybutanoate (**14**).* $BF_3{\cdot}Et_2O$ (1.419 g, 10.00 mmol, 10.0 equiv) was added dropwise with stirring to a solution **14** (270.3 mg, 1.00 mmol, 1.0 equiv) in Et_2O (5 mL) at 0 °C. The reaction mixture was stirred at 20−25 °C for 12 h. After that time, CH_2Cl_2 (40 mL) and H_2O (0.5 mL) were added. Then $NaHCO_3$ was added with stirring until the pH reached 7.0. The precipitate was filtered off. The filtrate was dried over $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg) (bath temperature, ca. 20−25 °C). Compound **6q** (215.2 mg, 0.96 mmol) was isolated by chromatography on SiO_2 with elution using a PE/EtOAc mixture (5:1).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b02218.

X-ray data for compound **6q** (CIF)

X-ray data for compound **6s** (CIF)

computational analysis, evaluation of oxidative properties of the β-hydroperoxy-β-peroxylactones with cyclic voltammetry, X-ray diffraction data, ^{1}H and ^{13}C NMR spectra, HRMS and IR spectra of all synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Borstnik, K.; Paik, I.-h.; Shapiro, T. A.; Posner, G. H. Antimalarial Chemotherapeutic Peroxides: Artemisinin, Yingzhaosu A and Related Compounds. *Int. J. Parasitol.* **2002**, *32*, 1661−1667.

(2) Slack, R. D.; Jacobine, A. M.; Posner, G. H. Antimalarial Peroxides: Advances in Drug Discovery and Design. *MedChemComm* **2012**, *3*, 281−297.

(3) Opsenica, D. M.; Šolaja, B. A. Antimalarial Peroxides. *J. Serb. Chem. Soc.* **2009**, *74*, 1155−1193.

(4) Muraleedharan, K. M.; Avery, M. A. Progress in the Development of Peroxide-Based Anti-Parasitic Agents. *Drug Discovery Today* **2009**, *14*, 793−803.

(5) Keiser, J.; Utzinger, J. Artemisinins and Synthetic Trioxolanes in the Treatment of Helminth Infections. *Curr. Opin. Infect. Dis.* **2007**, *20*, 605−612.

(6) Dembitsky, V. M.; Gloriozova, T. A.; Poroikov, V. V. Natural Peroxy Anticancer Agents. *Mini-Rev. Med. Chem.* **2007**, *7*, 571−589.

(7) Phillipson, D. W.; Rinehart, K. L. Antifungal Peroxide-Containing Acids from Two Caribbean Sponges. *J. Am. Chem. Soc.* **1983**, *105*, 7735−7736.

(8) Oh, D.-C.; Scott, J. J.; Currie, C. R.; Clardy, J. Mycangimycin, a Polyene Peroxide from a Mutualist *Streptomyces sp.* *Org. Lett.* **2009**, *11*, 633−636.

(9) Efferth, T.; Romero, M. R.; Wolf, D. G.; Stamminger, T.; Marin, J. J. G.; Marschall, M. The Antiviral Activities of Artemisinin and Artesunate. *Clin. Infect. Dis.* **2008**, *47*, 804−811.

(10) Jung, M.; Schinazi, R. F. Synthesis and *in vitro* Anti-Human Immunodeficiency Virus Activity of Artemisinin (Qinghaosu)-Related Trioxanes. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 931−934.

(11) Butler, A. R.; Wu, Y.-L. Artemisinin (Qinghaosu): a New Type of Antimalarial Drug. *Chem. Soc. Rev.* **1992**, *21*, 85−90.

(12) White, N. J. Qinghaosu (Artemisinin): The Price of Success. *Science* **2008**, *320*, 330−334.

(13) Lee, S. Artemisinin, Promising Lead Natural Product for Various Drug Developments. *Mini-Rev. Med. Chem.* **2007**, *7*, 411−422.

(14) Jefford, C. W. Synthetic Peroxides as Antimalarials. *Curr. Opin. Invest. Drugs (London, England: 2000)* **2004**, *5*, 866−872.

DOI: 10.1021/acs.joc.8b02218
J. Org. Chem. 2018, 83, 13427−13445

(15) Tang, Y.; Dong, Y.; Vennerstrom, J. L. Synthetic Peroxides as Antimalarials. *Med. Res. Rev.* **2004**, *24*, 425−448.
(16) Phyo, A. P.; Jittamala, P.; Nosten, F. H.; Pukrittayakamee, S.; Imwong, M.; White, N. J.; Duparc, S.; Macintyre, F.; Baker, M.; Möhrle, J. J. Antimalarial Activity of Artefenomel (OZ439), a Novel Synthetic Antimalarial Endoperoxide, in Patients with *Plasmodium Falciparum* and *Plasmodium Vivax* Malaria: an Open-Label Phase 2 Trial. *Lancet Infect. Dis.* **2016**, *16*, 61−69.
(17) McCullough, K.; Nojima, M. Recent Advances in the Chemistry of Cyclic Peroxides. *Curr. Org. Chem.* **2001**, *5*, 601−636.
(18) Terent'ev, A. O.; Borisov, D. A.; Vil', V. A.; Dembitsky, V. M. Synthesis of Five- and Six-Membered Cyclic Organic Peroxides: Key Transformations into Peroxide Ring-Retaining Products. *Beilstein J. Org. Chem.* **2014**, *10* (10), 34−114.
(19) Zmitek, K.; Zupan, M.; Iskra, J. α-Substituted Organic Peroxides: Synthetic Strategies for a Biologically Important Class of *gem*-Dihydroperoxide and Perketal Derivatives. *Org. Biomol. Chem.* **2007**, *5*, 3895−3908.
(20) Makhmudiyarova, N. N.; Khatmullina, G. M.; Rakhimov, R. S.; Meshcheryakova, E. S.; Ibragimov, A. G.; Dzhemilev, U. M. The First Example of Catalytic Synthesis of N-Aryl-Substituted Tetraoxazaspiroalkanes. *Tetrahedron* **2016**, *72*, 3277−3281.
(21) Tyumkina, T. V.; Makhmudiyarova, N. N.; Kiyamutdinova, G. M.; Meshcheryakova, E. S.; Bikmukhametov, K. S.; Abdullin, M. F.; Khalilov, L. M.; Ibragimov, A. G.; Dzhemilev, U. M. Synthesis, Molecular Structure, Conformation and Biological Activity of Ad-Substituted N-Aryl-Tetraoxaspiroalkanes. *Tetrahedron* **2018**, *74*, 1749−1758.
(22) Schwartz, C.; Dussault, P. H. In *Patai Chemistry of Functional Groups*; Rappoport, Z., Ed.; Wiley, 2009.
(23) van Tonder, J. H. *gem*-Bishydroperoxides. *Synlett* **2014**, *25*, 1629−1630.
(24) Gandhi, H.; O'Reilly, K.; Gupta, M. K.; Horgan, C.; O'Leary, E. M.; O'Sullivan, T. P. Advances in the Synthesis of Acyclic Peroxides. *RSC Adv.* **2017**, *7*, 19506−19556.
(25) Žmitek, K.; Zupan, M.; Stavber, S.; Iskra, J. The Effect of Iodine on the Peroxidation of Carbonyl Compounds. *J. Org. Chem.* **2007**, *72*, 6534−6540.
(26) Bunge, A.; Hamann, H.-J.; Liebscher, J. A Simple, Efficient and Versatile Synthesis of Primary *gem*-Dihydroperoxides from Aldehydes and Hydrogen Peroxide. *Tetrahedron Lett.* **2009**, *50*, 524−526.
(27) Ghorai, P.; Dussault, P. H.; Hu, C. Synthesis of Spirobisperoxyketals. *Org. Lett.* **2008**, *10*, 2401−2404.
(28) Milas, N. A.; Mageli, O. L.; Golubovic, A.; Arndt, R. W.; Ho, J. C. J. Studies in Organic Peroxides. XXIX. The Structure of Peroxides Derived from 2,4-Pentanedione and Hydrogen Peroxide. *J. Am. Chem. Soc.* **1963**, *85*, 222−226.
(29) Rieche, A.; Bischoff, C. Alkylperoxyde, XXX. Peroxyde Von Diketonen, I. Peroxyde des Acetylacetons. *Chem. Ber.* **1962**, *95*, 77−82.
(30) Rieche, A.; Seyfarth, H. E.; Brand, F. Isolierung von Dibenzyläther-Hydroperoxid Aus Den Peroxygenaten von Benzylalkohol und Dibenzyläther. *Justus Liebigs Ann. Chem.* **1969**, *725*, 93−98.
(31) Cocker, W.; Grayson, D. H. Reactions of Some Dicarbonyl Compounds. Part III. Oxidation of Some β-Diketones with Alkaline Hydrogen Peroxide. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1347−1352.
(32) Terent'ev, A. O.; Borisov, D. A.; Chernyshev, V. V.; Nikishin, G. I. Facile and Selective Procedure for the Synthesis of Bridged 1,2,4,5-Tetraoxanes; Strong Acids as Cosolvents and Catalysts for Addition of Hydrogen Peroxide to β-Diketones. *J. Org. Chem.* **2009**, *74*, 3335−3340.
(33) Terent'ev, A. O.; Yaremenko, I. A.; Vil', V. A.; Moiseev, I. K.; Kon'kov, S. A.; Dembitsky, V. M.; Levitsky, D. O.; Nikishin, G. I. Phosphomolybdic and Phosphotungstic Acids as Efficient Catalysts for the Synthesis of Bridged 1,2,4,5-Tetraoxanes from β-Diketones and Hydrogen Peroxide. *Org. Biomol. Chem.* **2013**, *11*, 2613−2623.
(34) Gomes, G. d. P.; Yaremenko, I. A.; Radulov, P. S.; Novikov, R. A.; Chernyshev, V. V.; Korlyukov, A. A.; Nikishin, G. I.; Alabugin, I. V.; Terent'ev, A. O. Stereoelectronic Control in the Ozone-Free Synthesis of Ozonides. *Angew. Chem., Int. Ed.* **2017**, *56*, 4955−4959.
(35) Yaremenko, I. A.; Gomes, G. d. P.; Radulov, P. S.; Belyakova, Y. Y.; Vilikotskiy, A. E.; Vil', V. A.; Korlyukov, A. A.; Nikishin, G. I.; Alabugin, I. V.; Terent'ev, A. O. Ozone-Free Synthesis of Ozonides: Assembling Bicyclic Structures from 1,5-Diketones and Hydrogen Peroxide. *J. Org. Chem.* **2018**, *83*, 4402−4426.
(36) Adam, W.; Cadiz, C.; Mazenod, F. Vacuum Flash Pyrolysis (VFP) of Malonyl Peroxides: Decarboxylation versus Decarbonylation of the Intermediary α-Lactones. *Tetrahedron Lett.* **1981**, *22*, 1203−1206.
(37) Adam, W.; Epe, B.; Schiffmann, D.; Vargas, F.; Wild, D. Reduktion von 1,2-Dioxetanen durch Thiole als mögliche Schutzreaktion gegen Photochemische Schädigung der DNA in der Zelle. *Angew. Chem.* **1988**, *100*, 443−445.
(38) Darmon, M. J.; Schuster, G. B. Thermal Chemistry of Cyclopropyl-Substituted Malonyl Peroxides. a New Chemiluminescent Reaction. *J. Org. Chem.* **1982**, *47*, 4658−4664.
(39) Terent'ev, A. O.; Vil', V. A.; Mulina, O. M.; Pivnitsky, K. K.; Nikishin, G. I. A Convenient Synthesis of Cyclopropane Malonyl Peroxide. *Mendeleev Commun.* **2014**, *24*, 345.
(40) Cubbon, R. C. P.; Hewlett, C. Organic Peroxides Containing Functional Groups. Part II. The Reaction of Hydrogen Peroxide with β- and γ-Oxo-Acids and Esters. *J. Chem. Soc. C* **1968**, *0*, 2983−2986.
(41) Gibson, D. H.; Wilson, H. L.; Joseph, J. T. β-Peroxy-β-propiolactols: Cyclic Analogs of the Baeyer-Villiger Intermediate. *Tetrahedron Lett.* **1973**, *14*, 1289−1292.
(42) Adam, W.; Griesbeck, A. Synthesis of the First α-Methylene-β-peroxylactone—Regiospecific Ene Reaction of $^1O_2$ with α,β-Unsaturated Carboxylic Acids. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1070−1071.
(43) Adam, W.; Hasemann, L.; Prechtl, F. α-Methylene-β-lactone, a Novel Heterocyclic Ring System via Deoxygenation of α-Methylene-β-peroxylactones with Triphenylphosphane. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1536−1537.
(44) Hernández, R.; Marrero, J. J.; Suárez, E.; Perales, A. Fragmentation of Alkoxy Radicals: Mechanistic Aspects of the Tandem β-Fragmentation-Intramolecular Functionalization Reaction. *Tetrahedron Lett.* **1988**, *29*, 5979−5981.
(45) Singh, C.; Srivastav, N. C.; Srivastava, N.; Puri, S. K. Synthesis of β-Peroxy-lactones using 30% H_2O_2. *Tetrahedron Lett.* **2005**, *46*, 2757−2759.
(46) Jefford, C. W.; Knöpfel, W.; Cadby, P. A. Oxygenation of Methyl p-Methoxyphenylpyruvate. α-Keto-β-Peroxylactone and Dioxetanol Intermediates. *Tetrahedron Lett.* **1978**, *19*, 3585−3588.
(47) McCullough, K. J.; Tokuhara, H.; Masuyama, A.; Nojima, M. New Approaches to the Synthesis of Spiro-Peroxylactones. *Org. Biomol. Chem.* **2003**, *1*, 1522−1527.
(48) Hamann, H.-J.; Bunge, A.; Liebscher, J. Reaction of Epoxyketones with Hydrogen Peroxide—Ethane-1,1-dihydroperoxide as a Surprisingly Stable Product. *Chem. - Eur. J.* **2008**, *14*, 6849−6851.
(49) Bunge, A.; Hamann, H.-J.; McCalmont, E.; Liebscher, J. Enantioselective Epoxidation of 2-Substituted 1,4-Naphthoquinones using *gem*-Dihydroperoxides. *Tetrahedron Lett.* **2009**, *50*, 4629−4632.
(50) Vil', V. A.; Gomes, G. d. P.; Bityukov, O. V.; Lyssenko, K. A.; Nikishin, G. I.; Alabugin, I. V.; Terent'ev, A. O. Interrupted Baeyer−Villiger Rearrangement: Building a Stereoelectronic Trap for the Criegee Intermediate. *Angew. Chem., Int. Ed.* **2018**, *57*, 3372−3376.
(51) This species is different from the Criegee intermediate involved in the rearrangement of primary ozonides.
(52) Bailey, W. F.; Shih, M. J. Oxidation of Ketals to Orthocarbonates: a Double Baeyer-Villiger Reaction. *J. Am. Chem. Soc.* **1982**, *104*, 1769−1771.
(53) Sugimura, T.; Fujiwara, Y.; Tai, A. Asymmetric Baeyer-Villiger Reaction: Diastereodifferentiating Peracid Oxidation of Chiral Acetal in the Presence of Lewis Acid. *Tetrahedron Lett.* **1997**, *38*, 6019−6022.
(54) Cong, R.; Zhang, Y.; Tian, W. A Concise Synthesis of the Steroidal Core of Clathsterol. *Tetrahedron Lett.* **2010**, *51*, 3890−3892.

DOI: 10.1021/acs.joc.8b02218
J. Org. Chem. 2018, 83, 13427−13445

(55) Krasutsky, P. A.; Kolomitsyn, I. V.; Krasutsky, S. G.; Kiprof, P. Double- and Triple-Consecutive O-Insertion into *tert*-Butyl and Triarylmethyl Structures. *Org. Lett.* **2004**, *6*, 2539−2542.
(56) Terent'ev, A. O.; Kutkin, A. V.; Platonov, M. M.; Vorontsov, I. I.; Antipin, M. Y.; Ogibin, Y. N.; Nikishin, G. I. Synthesis of Peroxide Compounds by the BF_3-Catalyzed Reaction of Acetals and Enol Ethers with H_2O_2. *Russ. Chem. Bull.* **2004**, *53*, 681−687.
(57) Jefford, C. W.; Li, Y.; Jaber, A.; Boukouvalas, J. A New Method for the Synthesis of *gem*-Dihydroperoxides. *Synth. Commun.* **1990**, *20*, 2589−2596.
(58) Terent'ev, A. O.; Kutkin, A. V.; Platonov, M. M.; Ogibin, Y. N.; Nikishin, G. I. A New Method for the Synthesis of Bishydroperoxides Based on a Reaction of Ketals with Hydrogen Peroxide Catalyzed by Boron Trifluoride Complexes. *Tetrahedron Lett.* **2003**, *44*, 7359−7363.
(59) Li, Y.; Hao, H.-D.; Zhang, Q.; Wu, Y. A Broadly Applicable Mild Method for the Synthesis of *gem*-Diperoxides from Corresponding Ketones or 1,3-Dioxolanes. *Org. Lett.* **2009**, *11*, 1615−1618.
(60) Adam, W.; Kades, E.; Wang, X. Photooxygenation of 3- and 2-Silyloxybenzofurans: Rearrangement of Dioxetanes *via* α-Silylperoxy Ketones to Ketoester Cleavage Products. *Tetrahedron Lett.* **1990**, *31*, 2259−2262.
(61) Einaga, H.; Nojima, M.; Abe, M. Photooxygenation ($^1O_2$) of Silyl Enol Ethers Derived from Indan-1-ones: Competitive Formation of Tricyclic 3-Siloxy-1,2-dioxetane and α-Silylperoxy Ketone. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2507−2512.
(62) Mori, N.; Sakoda, D.; Watanabe, H. Synthesis of (−)-Okundoperoxide and Determination of the Absolute Configuration of Natural (+)-Okundoperoxide. *Tetrahedron Lett.* **2017**, *58*, 3884−3886.
(63) Hurlocker, B.; Miner, M. R.; Woerpel, K. A. Synthesis of Silyl Monoperoxyketals by Regioselective Cobalt-Catalyzed Peroxidation of Silyl Enol Ethers: Application to the Synthesis of 1,2-Dioxolanes. *Org. Lett.* **2014**, *16*, 4280−4283.
(64) Saito, I.; Nagata, R.; Yuba, K.; Matsuura, T. Synthesis of α-Silyloxyhydroperoxides from the Reaction of Silyl Enol Ethers and Hydrogen Peroxide. *Tetrahedron Lett.* **1983**, *24*, 1737−1740.
(65) Gonzalez, A.; Galindo, A.; Mansilla, H.; Trigos, A. Biomimetic Synthesis of 1,10-sec-Eudesmanolides. *Tetrahedron* **1988**, *44*, 6745−6749.
(66) Snider, B. B.; Shi, Z. Total Synthesis of (±)-Chondrillin, (±)-Plakorin, and Related Peroxy Ketals. Development of a General Route to 3,6-Dihydro-1,2-dioxin-3-ols. *J. Am. Chem. Soc.* **1992**, *114*, 1790−1800.
(67) Klaper, M.; Linker, T. Intramolecular Transfer of Singlet Oxygen. *J. Am. Chem. Soc.* **2015**, *137*, 13744−13747.
(68) Bauch, M.; Klaper, M.; Linker, T. Intermediates in the Cleavage of Endoperoxides. *J. Phys. Org. Chem.* **2017**, *30*, e3607.
(69) Krow, G. R. In *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd.: 2001.
(70) Terent'ev, A. O.; Kutkin, A. V.; Platonov, M. M.; Starikova, Z. A.; Ogibin, Y. N.; Nikishina, G. I. Synthesis of 1,1′-Bishydroperoxydi(Cycloalkyl) Peroxides by Homocoupling of 11−15-Membered *gem*-Bis(Hydroperoxy)Cycloalkanes in the Presence of Boron Trifluoride. *Russ. Chem. Bull.* **2005**, *54*, 1214−1218.
(71) Griesbeck, A. G.; Hoinck, O.; Lex, J. Synthetic Approaches to Polar Antimalarial 1,2,4-Trioxanes from C5-Aldehyde and Ipsdienol. *Lett. Org. Chem.* **2006**, *3*, 247−249.
(72) Griesbeck, A. G.; Neudörfl, J.; Hörauf, A.; Specht, S.; Raabe, A. Antimalarial Peroxide Dyads from Natural Artemisinin and Hydroxyalkylated 1,2,4-Trioxanes. *J. Med. Chem.* **2009**, *52*, 3420−3423.
(73) Yaremenko, I. A.; Vil', V. A.; Demchuk, D. V.; Terent'ev, A. O. Rearrangements of Organic Peroxides and Related Processes. *Beilstein J. Org. Chem.* **2016**, *12*, 1647−1748.
(74) Li, Y.; Hao, H.-D.; Wu, Y. Facile Ring-Opening of Oxiranes by H_2O_2 Catalyzed by Phosphomolybdic Acid. *Org. Lett.* **2009**, *11*, 2691−2694.
(75) Yan, X.; Chen, J.; Zhu, Y.-T.; Qiao, C. Phosphomolybdic Acid Catalyzed Synthesis of 1,2,4,5-Tetraoxanes. *Synlett* **2011**, *2011*, 2827−2830.
(76) Kandur, W. V.; Richert, K. J.; Rieder, C. J.; Thomas, A. M.; Hu, C.; Ziller, J. W.; Woerpel, K. A. Synthesis and Reactivity of 1,2-Dioxolanes from β,γ-Epoxy Ketones. *Org. Lett.* **2014**, *16*, 2650−2653.
(77) Hao, H.-D.; Li, Y.; Han, W.-B.; Wu, Y. A Hydrogen Peroxide Based Access to Qinghaosu (Artemisinin). *Org. Lett.* **2011**, *13*, 4212−4215.
(78) Žmitek, K.; Zupan, M.; Stavber, S.; Iskra, J. Iodine as a Catalyst for Efficient Conversion of Ketones to gem-Dihydroperoxides by Aqueous Hydrogen Peroxide. *Org. Lett.* **2006**, *8*, 2491−2494.
(79) Wu, X.-F.; Gong, J.-L.; Qi, X. A Powerful Combination: Recent Achievements on Using TBAI and TBHP as Oxidation System. *Org. Biomol. Chem.* **2014**, *12*, 5807−5817.
(80) Krow, G. R. In *Organic Reactions*; John Wiley & Sons, Inc., 2004.
(81) Renz, M.; Meunier, B. 100 Years of Baeyer−Villiger Oxidations. *Eur. J. Org. Chem.* **1999**, *1999*, 737−750.
(82) ten Brink, G. J.; Arends, I. W. C. E.; Sheldon, R. A. The Baeyer−Villiger Reaction: New Developments toward Greener Procedures. *Chem. Rev.* **2004**, *104*, 4105−4124.
(83) Wang, Z. In *Comprehensive Organic Name Reactions and Reagents*; John Wiley & Sons, Inc.: 2010.
(84) McClure, J. D.; Williams, P. H. The Oxidation of Anisole and Diphenyl Ether with Trifluoroperoxyacetic Acid. *J. Org. Chem.* **1962**, *27*, 627−628.
(85) Terent'ev, A. O.; Boyarinova, K. A.; Nikishin, G. I. Oxidation of Alkenes with Hydrogen Peroxide, Catalyzed by Boron Trifluoride. Synthesis of Vicinal Methoxyalkanols. *Russ. J. Gen. Chem.* **2008**, *78*, 592−596.
(86) Mokhtary, M.; Lakouraj, M. M.; Niaki, M. R. Polyvinylpolypyrrolidone-Supported Boron Trifluoride (PVPP-BF_3): Highly Efficient Catalyst for Chemoselective Oxygenation of Sulfides to Sulfones by H_2O_2. *Phosphorus, Sulfur Silicon Relat. Elem.* **2012**, *187*, 321−326.
(87) Mokhtary, M.; Rastegar, N. M. PolyVinylPolyPyrrolidone-Supported Boron Trifluoride (PVPP-BF_3); Highly Efficient Catalyst for Oxidation of Aldehydes to Carboxylic Acids and Esters by H_2O_2. *Iran. J. Chem. Chem. Eng.* **2013**, *32*, 43−48.
(88) Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y. α-Hydroxylation of β-Dicarbonyl Compounds. *Tetrahedron Lett.* **1985**, *26*, 3563−3566.
(89) Lowinger, T. B.; Chu, J.; Spence, P. L. The Total Synthesis of (±)K252a. *Tetrahedron Lett.* **1995**, *36*, 8383−8386.
(90) Hoffman, R. V.; Johnson, M. C.; Okonya, J. F. Synthesis and Reactions of 3-(Nosyloxy)-2-keto Esters. *J. Org. Chem.* **1997**, *62*, 2458−2465.
(91) Yamamoto, K.; Hentemann, F. M.; Allen, J. G.; Danishefsky, S. J. On the Total Synthesis and Determination of the Absolute Configuration of Rishirilide B: Exploitation of Subtle Effects to Control the Sense of Cycloaddition of o−Quinodimethides. *Chem. - Eur. J.* **2003**, *9*, 3242−3252.
(92) Shono, T.; Matsumura, Y.; Nakagawa, Y. Electroorganic Chemistry. XII. Anodic Oxidation of Enol Esters. *J. Am. Chem. Soc.* **1974**, *96*, 3532−3536.
(93) Shono, T.; Okawa, M.; Nishiguchi, I. Electroorganic Chemistry. XXI. Selective Formation of α-Acetoxy Ketones and General Synthesis of 2,3-Disubstituted 2-Cyclopentenones through the Anodic Oxidation of Enol Acetates. *J. Am. Chem. Soc.* **1975**, *97*, 6144−6147.
(94) Zhu, J.; Klunder, A. J. H.; Zwanenburg, B. Total Synthesis of (−)-Kjellmanianone from Tricyclodecadienone. A Revision of its Absolute Configuration. *Tetrahedron* **1994**, *50*, 10597−10610.
(95) Johnson, W. S.; Gastambide, B.; Pappo, R. The Action of Lead Tetraacetate on an Enol Acetate. The Epimeric 16-Acetoxy Derivatives of Epiandrosterone Acetate, their Interconversion and Rearrangement. *J. Am. Chem. Soc.* **1957**, *79*, 1991−1994.
(96) Gardner, P. D. Organic Peracid Oxidation of Some Enol Esters Involving Rearrangement. *J. Am. Chem. Soc.* **1956**, *78*, 3421−3424.

DOI: 10.1021/acs.joc.8b02218
J. Org. Chem. 2018, 83, 13427−13445

(97) Juaristi, E.; Gomes, G. d. P.; Terent'ev, A. O.; Notario, R.; Alabugin, I. V. Stereoelectronic Interactions as a Probe for the Existence of the Intramolecular α-Effect. *J. Am. Chem. Soc.* **2017**, *139*, 10799−10813.
(98) Mayer, R. J.; Ofial, A. R. Nucleophilic Reactivities of Bleach Reagents. *Org. Lett.* **2018**, *20*, 2816−2820.
(99) Dussault, P. H.; Lee, I. Q.; Lee, H.-J.; Lee, R. J.; Niu, Q. J.; Schultz, J. A.; Zope, U. R. Peroxycarbenium-Mediated C−C Bond Formation: Applications to the Synthesis of Hydroperoxides and Peroxides. *J. Org. Chem.* **2000**, *65*, 8407−8414.
(100) Alabugin, I. V. *Stereoelectronic Effects: A Bridge Between Structure and Reactivity*; John Wiley & Sons, Ltd., 2016.
(101) Gomes, G. d. P.; Vil', V.; Terent'ev, A.; Alabugin, I. V. Stereoelectronic Source of the Anomalous Stability of bis-Peroxides. *Chem. Sci.* **2015**, *6*, 6783−6791.
(102) Tsedilin, A. M.; Fakhrutdinov, A. N.; Eremin, D. B.; Zalesskiy, S. S.; Chizhov, A. O.; Kolotyrkina, N. G.; Ananikov, V. P. How Sensitive and Accurate are Routine NMR and MS measurements? *Mendeleev Commun.* **2015**, *25*, 454−456.
(103) Dussault, P. H. In *Organic Peroxides. Safety Issues*; University of Nebraska−Lincoln: Lincoln, 2017.
(104) Erhardt, H.; Mohr, F.; Kirsch, S. F. Synthesis of the 1,3,4-Oxadiazole Core through Thermolysis of Geminal Diazides. *Eur. J. Org. Chem.* **2016**, *2016*, 5629−5632.
(105) Davis, J. M.; Truong, A.; Hamilton, A. D. Synthesis of a 2,3′;6′,3″-Terpyridine Scaffold as an α-Helix Mimetic. *Org. Lett.* **2005**, *7*, 5405−5408.
(106) Poldy, J.; Peakall, R.; Barrow, R. A. Identification of the First Alkenyl Chiloglottone Congener. *Eur. J. Org. Chem.* **2012**, *2012*, 5818−5827.
(107) Shimkin, A. A.; Shirinian, V. Z.; Mailian, A. K.; Lonshakov, D. V.; Gorokhov, V. V.; Krayushkin, M. M. Acylation of Meldrum's Acid With Arylacetic Acid Imidazolides as a Convenient Method for the Synthesis of 4-Aryl-3-oxobutanoates. *Russ. Chem. Bull.* **2011**, *60*, 139−142.
(108) Turmasova, A. A.; Spesivaya, E. S.; Konshina, D. N.; Konshin, V. V. Adamantylation of β-Dicarbonyl Compounds. *Russ. Chem. Bull.* **2012**, *61*, 1733−1735.
(109) Bräse, S.; Wertal, H.; Frank, D.; Vidović, D.; de Meijere, A. Intramolecular Heck Couplings and Cycloisomerizations of Bromodienes and Enynes with 1′,1′-Disubstituted Methylenecyclopropane Terminators: Efficient Syntheses of [3]Dendralenes. *Eur. J. Org. Chem.* **2005**, *2005*, 4167−4178.
(110) Kádas, I.; Morvai, V.; Árvai, G.; Tőke, L.; Szöllősy, Á.; Tóth, G.; Bihari, M. Syntheses of the Terpenoid Precursors Cyclopent-2-enone and Cyclohex-2-enone Diesters. *Monatsh. Chem.* **1995**, *126*, 107−117.
(111) Terent'ev, A. O.; Borisov, D. A.; Yaremenko, I. A.; Chernyshev, V. V.; Nikishin, G. I. Synthesis of Asymmetric Peroxides: Transition Metal (Cu, Fe, Mn, Co) Catalyzed Peroxidation of β-Dicarbonyl Compounds with *tert*-Butyl Hydroperoxide. *J. Org. Chem.* **2010**, *75*, 5065−5071.
(112) Beddow, J. E.; Davies, S. G.; Ling, K. B.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. Asymmetric Synthesis of β2-Amino Acids: 2-Substituted-3-Aminopropanoic Acids from N-Acryloyl SuperQuat Derivatives. *Org. Biomol. Chem.* **2007**, *5*, 2812−2825.
(113) Hu, M.; Ni, C.; Li, L.; Han, Y.; Hu, J. gem-Difluoroolefination of Diazo Compounds with $TMSCF_3$ or $TMSCF_2Br$: Transition-Metal-Free Cross-Coupling of Two Carbene Precursors. *J. Am. Chem. Soc.* **2015**, *137*, 14496−14501.
(114) Rafiee, E.; Khodayari, M.; Joshaghani, M. Direct Benzylation of 1,3-Dicarbonyl Compounds Catalyzed by $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ in Solvent-Free Conditions. *Can. J. Chem.* **2011**, *89*, 1533−1538.
(115) Lee, S. I.; Kim, K. E.; Hwang, G.-S.; Ryu, D. H. Highly Enantioselective Catalytic 1,3-Dipolar Cycloadditions of α-Alkyl Diazoacetates: Efficient Synthesis of Functionalized 2-Pyrazolines. *Org. Biomol. Chem.* **2015**, *13*, 2745−2749.
(116) Sheng, X.; Zhang, J.; Yang, H.; Jiang, G. Tunable Aerobic Oxidative Hydroxylation/Dehydrogenative Homocoupling of Pyrazol-5-ones under Transition-Metal-Free Conditions. *Org. Lett.* **2017**, *19*, 2618−2621.
(117) Wang, C.; Zhang, H.; Xu, F.; Niu, Y.; Wu, Y.; Wang, X.; Peng, Y.; Sun, J.; Liang, L.; Xu, P. Substituted 3-Benzylcoumarins as Allosteric MEK1 Inhibitors: Design, Synthesis and Biological Evaluation as Antiviral Agents. *Molecules* **2013**, *18*, 6057.
(118) Gillard, R. M.; Fernando, J. E. M.; Lupton, D. W. Enantioselective N-Heterocyclic Carbene Catalysis *via* the Dienyl Acyl Azolium. *Angew. Chem., Int. Ed.* **2018**, *57*, 4712−4716.
(119) Nguyen, V. T. H.; Bellur, E.; Appel, B.; Langer, P. Synthesis of 4-Alkyl- and 4-(ω-Chloroalkyl)-3-hydroxy-5-alkylidenebutenolides Based On Cyclizations of 4-Alkyl- and 4-(ω-Chloroalkyl)-1,3-bis(trimethylsilyloxy)buta-1,3-dienes with Oxalyl Chloride. *Synthesis* **2006**, *2006*, 2865−2872.
(120) Carbonnel, S.; Fayet, C.; Gelas, J. Introduction of a Carboxyl Group through an Acetal as a New Route to Carboxylic Acid Derivatives of Sugars. *Carbohydr. Res.* **1999**, *319*, 63−73.
(121) Kumar, G. S.; Pieber, B.; Reddy, K. R.; Kappe, C. O. Copper-Catalyzed Formation of C-O Bonds by Direct α-C-H Bond Activation of Ethers Using Stoichiometric Amounts of Peroxide in Batch and Continuous-Flow Formats. *Chem. - Eur. J.* **2012**, *18*, 6124−6128.
(122) Chary, B. C.; Kim, S. Gold(I)-Catalyzed Addition of Carboxylic Acids to Alkynes. *J. Org. Chem.* **2010**, *75*, 7928−7931.
(123) Sagot, E.; Pickering, D. S.; Pu, X.; Umberti, M.; Stensbøl, T. B.; Nielsen, B.; Chapelet, M.; Bolte, J.; Gefflaut, T.; Bunch, L. Chemo-Enzymatic Synthesis of a Series of 2,4-Syn-Functionalized (S)-Glutamate Analogues: New Insight into the Structure−Activity Relation of Ionotropic Glutamate Receptor Subtypes 5, 6, and 7. *J. Med. Chem.* **2008**, *51*, 4093−4103.
(124) Hitchcock, S. R.; Perron, F.; Martin, V. A.; Albizati, K. F. Efficient Synthesis of α-(Hydroxymethyl) Ketones Not Available Through Aldol-Type Processes. *Synthesis* **1990**, *1990*, 1059−1061.
(125) Paula, B. R. S.; Zampieri, D.; Rodrigues, J. A. R.; Moran, P. J. S. Bioreduction of α-Acetoxymethyl Enones: Proposal for an SN_2' Mechanism Catalyzed by Enereductase. *Adv. Synth. Catal.* **2016**, *358*, 3555−3571.
(126) Martin, V. A.; Murray, D. H.; Pratt, N. E.; Zhao, Y. B.; Albizati, K. F. Chemistry of Aldolate Dianions. Effects of β-heteroatom Substituents on Ketone Enolization. *J. Am. Chem. Soc.* **1990**, *112*, 6965−6978.
(127) Halder, J.; Das, D.; Nanda, S. Enantioselective Biocatalytic Reduction of 2,2-Disubstituted Ethylacetoacetates: an Indirect Desymmetrization Approach for the Synthesis of Enantiopure (S)-4-Hydroxy-3,3-Disubstituted Pentane-2-ones. *Tetrahedron: Asymmetry* **2015**, *26*, 1197−1208.
(128) Kurouchi, H.; Sugimoto, H.; Otani, Y.; Ohwada, T. Cyclization of Arylacetoacetates to Indene and Dihydronaphthalene Derivatives in Strong Acids. Evidence for Involvement of Further Protonation of O,O-Diprotonated β-Ketoester, Leading to Enhancement of Cyclization. *J. Am. Chem. Soc.* **2010**, *132*, 807−815.
(129) Van Arman, S. A.; Zimmet, A. J.; Murray, I. E. A Hantzsch Amido Dihydropyridine as a Transfer Hydrogenation Reagent for α,β-Unsaturated Ketones. *J. Org. Chem.* **2016**, *81*, 3528−3532.

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