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A New Directing Mode for Singlet Oxygen Ene Reactions: The Vinylogous Gem Effect Enables a $^1O_2$ Domino Ene/[4 + 2] Process

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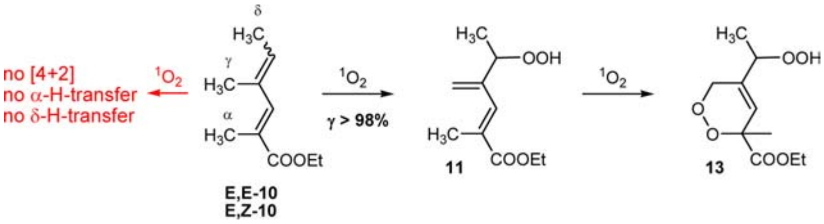
ABSTRACT



The singlet oxygen reactions of 4-methyl-2,4-hexadienoates E,E- and E,Z-4 proceed in a highly mode selective and regioselective domino process. The initial product is the allylic hydroperoxide 5 directed by a vinylogous gem effect. The subsequent $^1O_2$ [4 + 2] cycloaddition delivers a 3:2 diastereoisomeric mixture of 1,2-dioxanes 8 in a one-pot process. The identical protocol delivers from the more reactive α-methylated substrates E,E-10 and E,Z-10 with excellent primary regioselectivity the 1,2-dioxane 13.

From the perspective of atom economy, photochemical induced oxygenation is the ideal approach to hydroperoxides and endoperoxides as well as to the corresponding reduction products, allylic alcohols and 1,4-diols from alkenes and 1,3-dienes, respectively. Type II photooxygenation involves singlet oxygen ($^1O_2$) as the reactive species that is easily generated by energy transfer sensitization.[1] One of the most favorable singlet oxygen reactions is the Schenck ene reaction with monoalkenes that present allylic hydrogens.[2] Similar to other thermal ene reactions with electrophilic enophiles, this process prefers electron-rich alkenes: tetraalkylated alkenes are favored over trialkylated substrates by a factor of 10.[3] The different regioselectivity patterns, however, do not support a typical concerted process.[4] Beside the long-known "cis-effect",[5] the "gem effect" is most unusual because electron-poor substrates **A** (α,β-dialkylated acrylates and derivatives) add $^1O_2$ with high regioselectivity to give the allylic hydroperoxides **B** (Scheme 1).[6] Tiglic acid derivatives result in regioisomeric hydroperoxide ratios of 95:5 up to 98:2. This effect was also observed for α,β-unsaturated nitriles,[7] sulfoxides,[8] and sulfonates.[9] Also the corresponding dimethylstyrene showed gem-selectivity.[10] The hydroperoxides **B** can be reduced to the corresponding allylic alcohols that constitute typical Baylis–Hillmann–Morita products.[11] In the context of our research program on biological active water-soluble 1,2,4-trioxanes,[12] we investigated new routes to highly functionalized cyclic peroxides and envisaged a [4 + 2] singlet oxygen cycloaddition process from diene esters or acids, respectively. Thus, we initially studied whether the "gem-effect" is still operating, if the second "innocent" methyl group in tiglate derivatives **A** is exchanged by a vinyl group.

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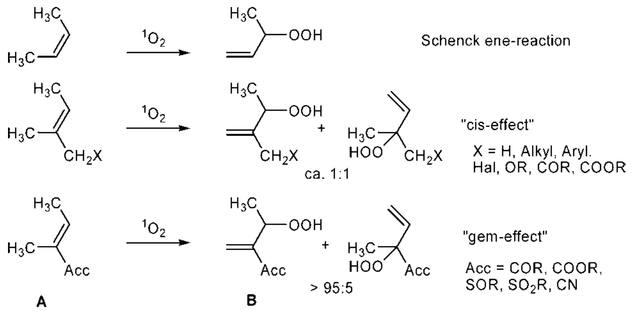
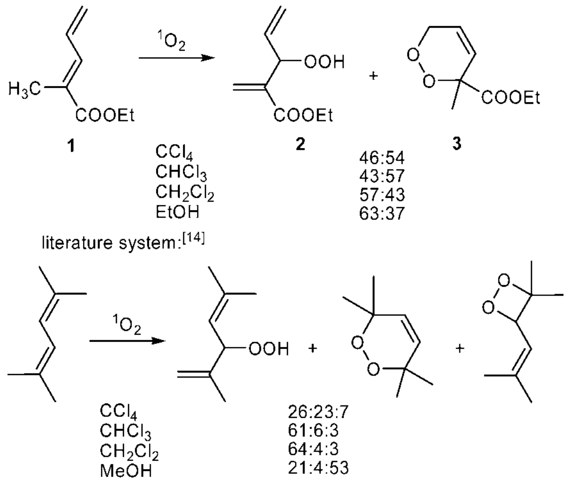
10.1021/ol4009602

Scheme 1. Regioselectivity Pattern in Ene Reactions with $^1O_2$



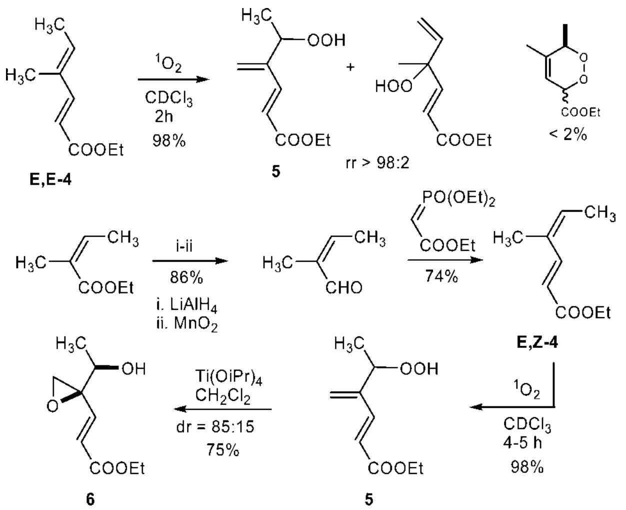
The photooxygenation of this substrate **1**[13] resulted in the allylic hydroperoxide **2**; however, also large amounts of the endoperoxide **3** were formed (Scheme 2). This competition shows a solvent dependence in agreement with nonfunctionalized 1,3-dienes, e.g. the well-studied 2,5-dimethyl-2,4-hexadiene.[14] Aprotic solvents favor the formation of the endoperoxide **3**, and protic solvents, the ene product **2**. In contrast to the purely methylated reference substrate, no dioxetanes were formed from the electronically deactivated substrate **1**.

Scheme 2. Photooxygenation of **1**



The overall reactivity of **1** is strongly reduced in comparison to the tiglate derivatives **A**; i.e., 5-fold longer irradiation times were necessary under identical conditions for **1** in comparison with methyl tiglate.[15] Further methylation compensated this effect, and to our surprise, many of these substrates did show an initial mode selective and regioselective ene reaction with singlet oxygen that was followed by a [4 + 2]-cycloaddition, i.e. a singlet oxygen ene/[4 + 2]-domino process.[16] As a typical example, the 1,3-diene ester E,E-**4**[17] was prepared and reacted with singlet oxygen in nonpolar deuterated solvents (taking advantage of the solvent deuterium isotope effect)[18] with *meso*-tetraphenylporphyrin (TPP) as a sensitizer. After a short reaction time, the allylic hydroperoxide **5** was observed as the sole product (Scheme 3). In the NMR spectrum of the crude reaction solution, only trace amounts of an endoperoxide were detected and no traces of the regioisomeric allylic hydroperoxide. Thus, the ene process dominates the singlet oxygen reactivity by far and the γ-hydrogen transfer is largely preferred. The influence of the cis-effect on the reactivity of E,E-**4** was investigated by comparison with the E,Z-**4** isomer that was available from methyl angelate by a three-step process. A slight reactivity decrease was detected for E,Z-**4** ($k_{E,E}/k_{E,Z}$ = 2.5, for *cis*/*trans*-2-butene k_c/k_t = 4−5)[19] due to the cis-effect, however, with no apparent change in regioselectivity. The allylic hydroperoxide **5** is highly sensitive and decomposes already during chromatographic purification. In order to establish the purity and structure, we treated **5** with substoichiometric amounts of titanium(IV) isopropoxylate[20] and isolated the epoxy alcohol **6** as a separable mixture of two diastereoisomers.

Scheme 3. Regioselective Ene Reaction of E,E-**4** and E,Z-**4** with $^1O_2$



Under the same photooxygenation reaction conditions, the initially formed product **5** did add another equivalent

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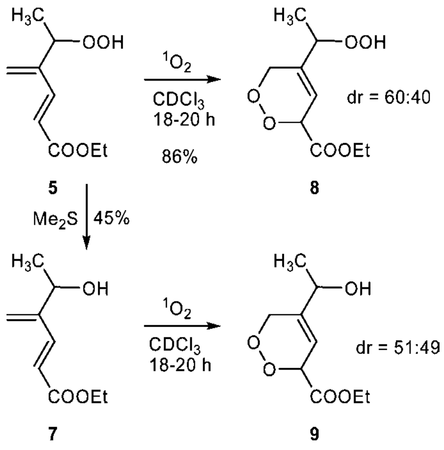
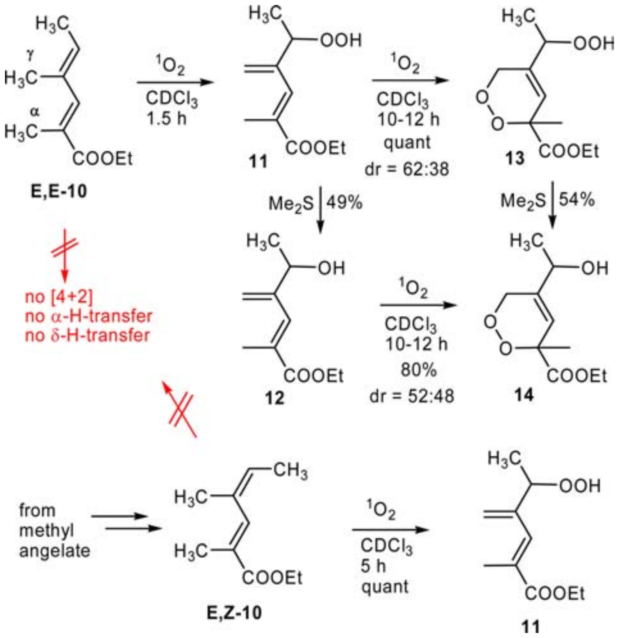
Scheme 4. Subsequent 4 + 2 Reaction of **5** and **7** with $^1O_2$

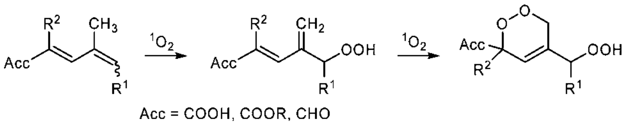


Scheme 5. Regioselective Photooxygenation of E,E-**10**, E,Z-**10**, and **12**



of $^1O_2$ after a prolonged reaction time and the hydroperoxyendoperoxide **8** (Supporting Information (SI)) was isolated in 86% yield as an unseparable mixture of diastereoisomers (Scheme 4). In order to improve the low diastereoselectivity of the second $^1O_2$ addition, we tried to apply the hydroxy-directing effect for 4 + 2-cycloadditions that was reported for chiral dienols as substrates.[21]

Scheme 6. General Domino Singlet Oxygenation of 1,3-Dienes Directed by the Vinylogous Gem Effect



Therefore, the hydroperoxide **5** was reduced to the allylic alcohol **7** with dimethylsulfide and converted into the endoperoxide **9** (SI). Surprisingly, a further decrease in diastereoselectivity was observed with a slight increase in ene reactivity.

Subsequently, the α-methylated 1,3-diene ester E,E-**10**[22] was investigated in order to evaluate the degree of vinylogous gem (γ-CH transfer) versus normal (α-CH transfer) gem-selectivity. Due to the additional methyl group in **10** (in comparison with **4**), the primary $^1O_2$ reaction is accelerated and the hydroperoxide **11** was observed as the sole product after 1.5 h (Scheme 5).

The subsequent [4 + 2]-cycloaddition with $^1O_2$ proceeded rapidly with the allylic hydroperoxide **11** as well as with the corresponding allylic alcohol **12**. These products were formed in identical mode and regioselectivity to form E,Z-**10**, available from methy tiglate.

The highly selective first step of the domino reaction with the di- and trimethylated substrates **4** and **10**, respectively, reveals a strong vinylogous gem-effect in singlet oxygen ene reactions. By this effect, the 1,3-diene structure is retained and subsequent Diels–Alder reactivity with $^1O_2$ is obtained. This type of a domino (or, more correctly, a diene-transmissive sequence, Scheme 6) photooxygenation process requires an acceptor group at the terminal carbon (Acc = COOR, COOH, CHO) and can be easily performed as a one-pot process.[15]

In summary, we have discovered a new directing effect in singlet oxygen ene reactions which also opens the avenue to domino processes for polyoxyfunctionalization in one-pot reactions.

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Supporting Information Available. Characterization of the substrates and the photooxygenation products by ^1H and ^{13}C NMR spectra in $CDCl_3$. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.