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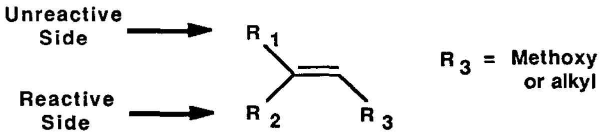
Regioselective Reaction of Singlet Oxygen with α,β–Unsaturated Esters

Michael Orfanopoulos[1] and Christopher S. Foote*
Department of Chemistry and Biochemistry
University of California, Los Angeles, California 90024

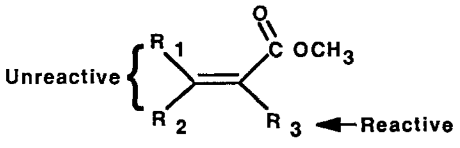
Abstract: The reaction of singlet oxygen with α,β-unsaturated esters shows a general preference for hydrogen abstraction on the alkyl group geminal to the ester.

The "ene" reaction of singlet oxygen with olefins has been studied extensively.[2] Many stereochemical aspects of this reaction are now well documented.[2c] Singlet oxygen reacts stereospecifically with olefins[3] and shows a high regioselectivity with enol ethers,[4] where oxygen adds on the same side as the alkoxy group. This unexpected regioselectivity has been shown to hold generally in simple trisubstituted olefins, where alkyl groups exert a strong directing effect toward attack on the most crowded side (*cis*-effect).[5]



Scheme I

The regioselectivity of singlet oxygen reactions with α,β-unsaturated cyclic ketones has also been reported; the carbonyl group was found to direct the entering oxygen so that it bonds to the carbon away from the carbonyl.[6] We now report that unsaturated esters also react with singlet oxygen regioselectively (Table I). As with ketones, this reaction shows *preferential abstraction of allylic hydrogens geminal to the ester* functionality. For example, **1a** gives 86% hydrogen abstraction from the R_3 methyl group and only 14% from the R_1 methyl group.

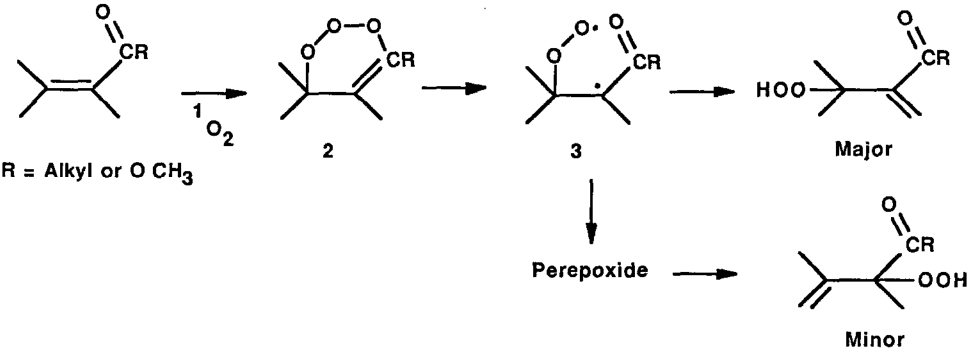


	R_1	R_2	R_3
1a	CH_3	H	CH_3
1b	CH_3	CH_3	H
1c	CH_3	CH_3	CH_3

Scheme II

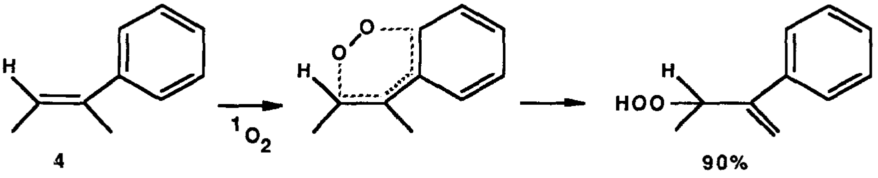
Unlike enol ethers or simple olefins, where the most crowded side of the olefin is the most reactive, the ester group activates the geminal hydrogens whether or not this group is on the crowded side of the double bond (compare entries 1 and 2 in Table I). Even cyclic systems obey this "geminal effect"; (for example, entry 6 (Table I) where the double bond is a part of the six membered ring). This behavior is in contrast to the usual behavior of cyclohexenes, which show a strong preference for attack at the methyl group to give product with an exocyclic methylene group.[2a] Only where R_3= ethyl (compound 5) is the preference smaller, probably due to rotation of the hydrogens out of the plane and consequent less favorable attack.[2a] These experiments demonstrate clearly that the photooxygenation of α,β-unsaturated esters follows a different mechanistic pathway from enol ethers or alkyl-substituted olefins.

The geminal effect might be attributed to formation of a trioxene intermediate, similar to that proposed by Ensley *et al.*[6] Formation of trioxene 2, followed by rupture of the weak O-O bond, might lead to intermediate 3, forcing geminal hydrogen abstraction (Scheme III). The minor product might result from rearrangement of 3 to a perepoxide, or in a competing normal ene reaction.



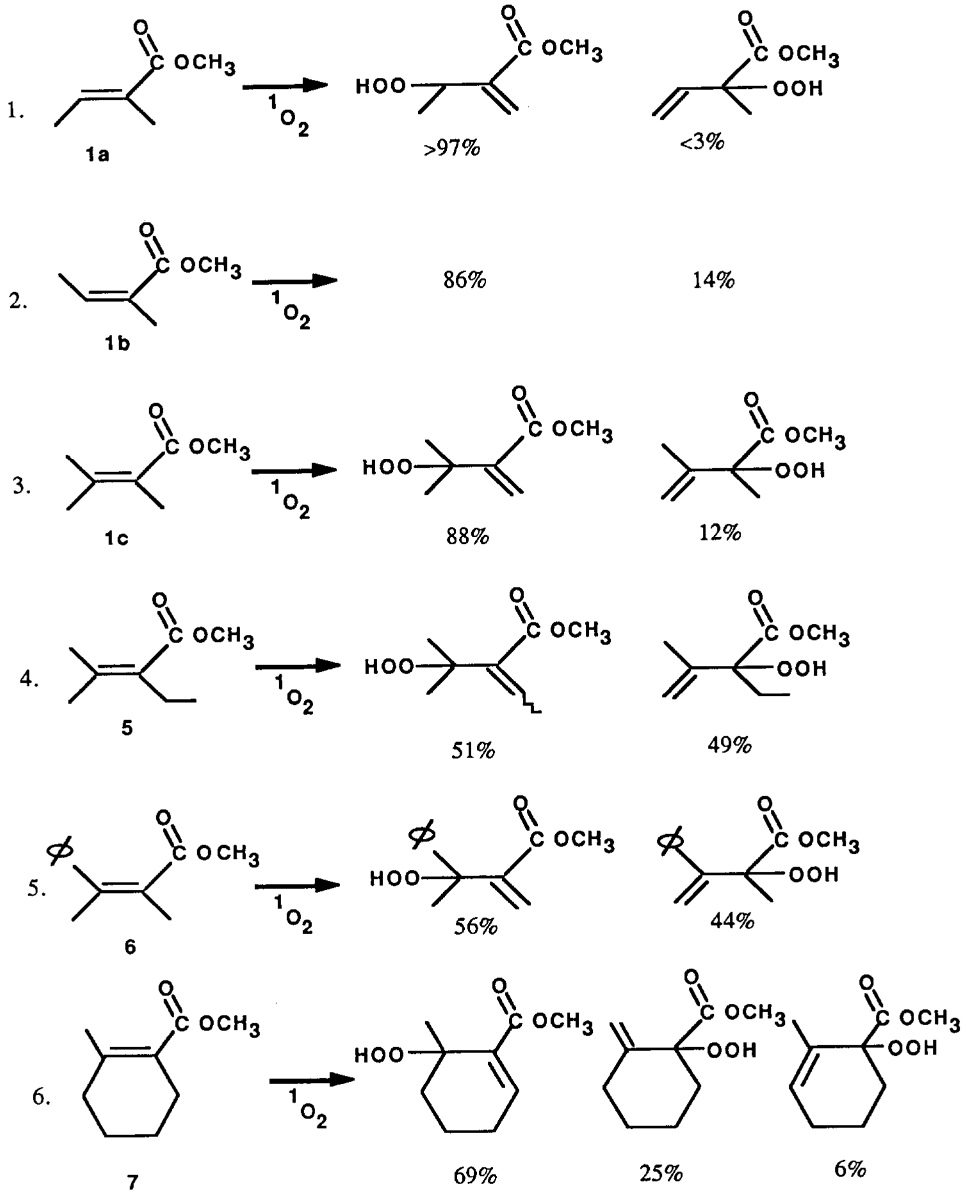
Scheme III

Photooxygenation of E-2-phenyl-2-butene 4 also shifts the double bond 90% toward the methyl group geminal to the phenyl ring.[2c] The unsaturation in the phenyl group may act in the same way as the carbonyl group to force geminal addition, although an exciplex is more likely in this case than a covalent intermediate. Stilbenes which have no methyl groups on the carbon geminal to the phenyl undergo Diels-Alder addition to the phenyl group.[4b] When an ester group is substituted for the olefinic hydrogen in 4 to give starting material 6 (entry 5, Table I), competition for the geminal positions between the ester and the phenyl leads to nearly equal attack at the two methyl groups. These explanations are speculative; it is hoped to provide firmer evidence for the mechanism.[8]



Scheme IV

Table I. Regioselectivity of Reaction of Singlet Oxygen with α,β-Unsaturated Esters



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7. Structures and purities were determined by IR and NMR (by comparison with known spectra where possible). G. C. confirmed isomeric purities. α,β-Unsaturated esters were prepared as follows. Reformatsky coupling of methyl-2-bromopropionate with acetaldehyde gave methyl-(3-hydroxy-2-methyl)-1-butanoate. Treatment of the mesylate with NaOH in methanol gave an isomeric mixture of α,β-unsaturated esters; preparative gas chromatography gave **1a** and **1b** in isomerically pure form. Esters **1c**, **5**, and **6** were synthesized from methyl-2-bromo-propionate or methyl-2-bromobutyrate with the corresponding ketone, followed by dehydration and preparative G.C. isomeric purification. Olefin **7** was prepared by Diels-Alder reaction of butadiene and methyl-2-butynoate followed by catalytic hydrogenation (10% Pd/C in benzene) and G.C. purification. Photooxidations were carried out at -15°C in acetone (entries 1, 2, 3) and Freon-11 (entries 4, 5, 6) with mesoporphyrin IX dimethylester (10^{-4} M) as sensitizer. Yields were nearly quantitative (G. C., internal standard). Analyses were carried out by NMR ; in some cases, the measurements were checked by gas chromatography on a capillary column.

8. Dedicated to Harry H. Wasserman on the occasion of his 65th birthday. Supported by NSF Grant No. CHE 83-11804

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