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Mixed peroxides from the chloroperoxidase-catalyzed oxidation of conjugated dienoic esters with a trisubstituted terminal double bond†

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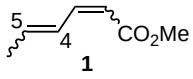
Abstract—The chloroperoxidase (CPO)-catalyzed oxidations of conjugated dienoic esters with a trisubstituted terminal double bond were studied by using *tert*-butyl hydroperoxide as the terminal oxidant. Most of the substrates gave disubstituted mixed peroxides as the major products.

Chloroperoxidase (CPO) from *Caldariomyces fumago*[1,2] has been used extensively over the last few years as a catalyst in the halide-independent oxidation of alkenes.[3–18] Recently,[19] we showed that in the case of dienes conjugated to an ester group, **1**, the ratio of epoxidation to allylic oxidation depends on the stereochemistry of the C4–C5 double bond. Our continuing interest in the substrate structural features that control this ratio, led us to study the oxidation of conjugated dienoic esters with a trisubstituted terminal double bond. As far as we know, CPO does not catalyze the reaction of trisubstituted alkenes,[16] the only reported[12] exception being substrate **2**, that leads to the exclusive formation of the epoxide **3** (Scheme 1).



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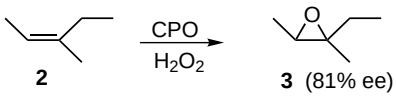
In this communication, we report the CPO-catalyzed oxidation of dienes, which are conjugated to an ester group, with a trisubstituted terminal double bond, to give disubstituted mixed peroxides. We also discuss a possible mechanism for these interesting transformations.



2 **3** (81% ee)

Scheme 1.

All reactions were carried out in the absence of light, in a phosphate buffer (100 mM, pH 6), by using 0.2 mmol of substrate, 2000 units of commercially available CPO and 2 equiv. of 70% *tert*-butyl hydroperoxide (*t*BHP),[20,21] which was added in two aliquots to give a total volume of 5 ml. All the reactions were done under anaerobic conditions (under a nitrogen flow), except for the reaction of substrate **12**. They were monitored by gas chromatography and the products were separated by flash column chromatography (SiO_2, 10–30% Et_2O in pentane) and identified with 500 MHz ^1H and ^{13}C NMR and GC–MS. All product yields reported were calculated after completion of the reactions (2–3 hours). Substrates **4**, **8**, **10** and **12** were prepared according to known methods by using the Brittelli reaction[22] as a key step for their synthesis.† The dienone **17** was commercially available. All the substrates were stable under the reaction conditions without enzyme.

The CPO-catalyzed oxidation of methyl (2*E*)-5-methyl-2,4-hexadienoate **4** gave the epoxide **5** as the major product (48%) with low enantioselectivity (5% ee), accompanied by the *E*,*E*-aldehydic ester **6** (28%) derived from the allylic hydroxylation of the *exo* methyl

Keywords: chloroperoxidase; oxidation; dienoic esters; mixed peroxides; epoxidation.

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† Dedicated to Professor G. J. Karabatsos on the occasion of his 70th birthday.

† In each case, the appropriate starting aldehyde was reacted with bromoacetic acid to produce a carboxylic acid, which was then esterified and the resulting ester was purified by flash column chromatography.

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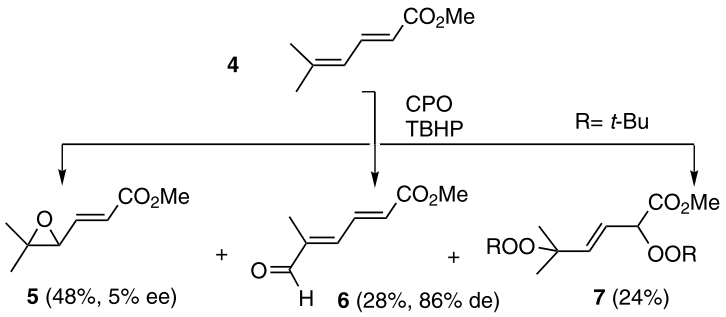
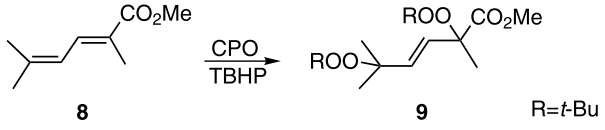


Scheme 2. CPO-catalyzed oxidation of **4**.

group (86% de), and the disubstituted mixed peroxide **7** (24%) (Scheme 2).

When the C2 hydrogen in diene **4** was replaced by a methyl group, producing methyl (2*E*)-2,5-dimethyl-2,4-hexadienoate **8**, the only isolated product (50% yield) was compound **9**, accompanied by a small amount of allylic hydroxylation products (under 2%). No epoxide was observed in this case (Scheme 3).

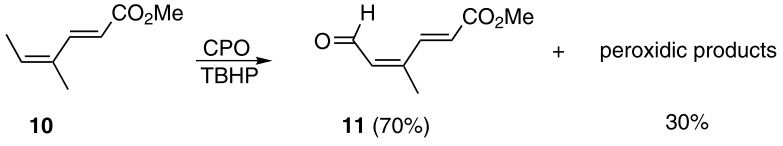


Scheme 3. CPO-catalyzed oxidation of **8**.

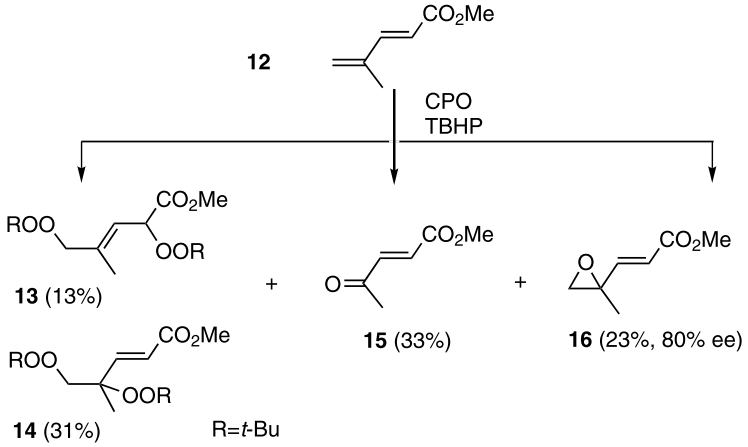
The CPO-catalyzed oxidation of methyl (2*E*,4*Z*)-4-methyl-2,4-hexadienoate **10** gave the aldehydic ester **11** as the major product (70%), and a mixture of peroxidic compounds (30%) which could not be isolated (Scheme 4). Surprisingly, no epoxide was formed, which is the usual product of the reaction of a *Z* double bond with CPO.

The methyl (2*E*)-4-methyl-2,4-pentadienoate **12** was also oxidized under aerobic conditions. In addition to the mixed peroxides **13** and **14** (13% and 31% relative yields, respectively) and the epoxide **16** (23%, 80% ee), the carbon–carbon cleavage product, ketone **15**, was also formed in 33% yield (Scheme 5). Its formation was not surprising according to our previous related work on CPO-catalyzed oxidations of conjugated dienoic esters.[19]

The above results show that CPO is an efficient catalyst for the oxidation of conjugated dienoic esters with a trisubstituted terminal double bond. In all cases, reactions of **4**, **8**, **10** and **12** with CPO led to the formation of mixed peroxides in considerable amounts.[‡] Interestingly, no mixed peroxides were obtained in the reaction of **17**, where the diene is conjugated to a ketone instead of an ester group (Scheme 6). Epoxide **18** was the major product (83%)

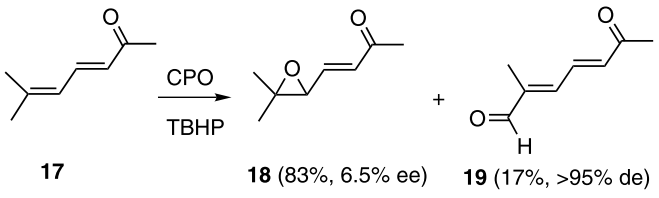


Scheme 4. CPO-catalyzed oxidation of **10**.



Scheme 5. CPO-catalyzed oxidation of **12**.

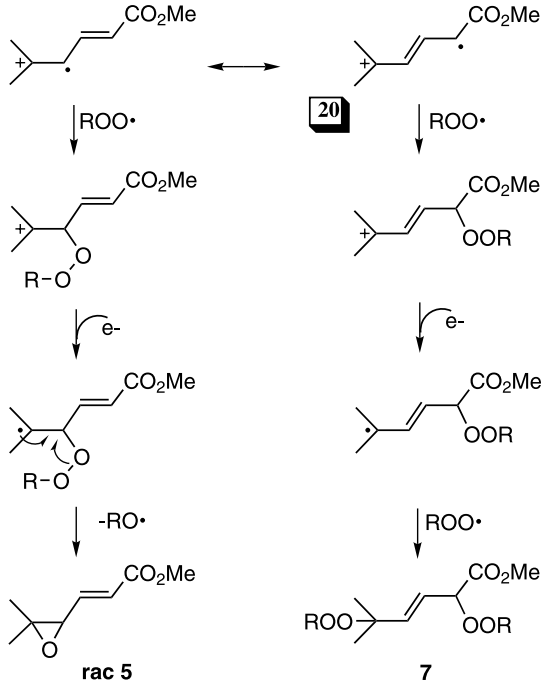
[‡] It is interesting to note here that synthesis of analogous mixed peroxides through radical intermediates has appeared recently in the literature.[24,25]



Scheme 6. CPO-catalyzed oxidation of ketone **17**.

with very low enantioselectivity (6.5% ee), the minor product being the aldehydic ester **19** (17%) derived from allylic hydroxylation of the *exo* methyl group (diastereoselectivity over 95%).

A possible explanation for the formation of all of these products, including the mixed peroxides **7**, **9**, **13** and **14**, under anaerobic conditions, is via the intermediacy of the radical cation **20** (Scheme 7). An analogous intermediate was proposed in order to explain the formation of products from the four isomers of methyl (2,4)-hexadienoate in our previous studies,[19] as well as the cyclodimerization product of methyl (2*E*)-2,4-pentadienoate.[23] The radical cation **20** may be formed either through direct electron transfer from the substrate to an oxoiron(IV) π-radical cation, or through electron transfer from an enzymatically derived *tert*-BuOO radical, which is an established intermediate during CPO-catalyzed reactions.[26,27] In an effort to clarify whether the oxoiron(IV) π-radical cation is responsible for the formation of intermediate **20**, further studies on the mechanism of these biotransformations are currently under investigation in our group.



Scheme 7.

Acknowledgements

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