Copper(II) Trifluoromethanesulfonate-Induced Cleavage Oxygenation of Allylic Hydroperoxides Derived from Qinghao Acid in the Synthesis of Qinghaosu Derivatives: Evidence for the Intermediacy of Enols

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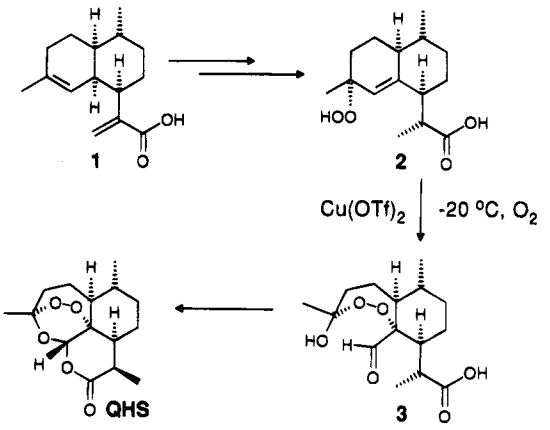
Abstract: The semisynthesis of qinghaosu (artemisinin) derivatives from qinghao (artemisinic) acid and related compounds is gaining increasing importance despite the fact that the key step in the transformation, the cleavage oxygenation of the intermediate allylic hydroperoxides to form peroxy hemiacetals, is not well understood. It has been found that the allylic hydroperoxide **10** derived from the methyl ester of qinghao acid under catalysis by trifluoromethanesulfonic acid (TfOH) in CH_2Cl_2 or copper(II) trifluoromethanesulfonate [$Cu(OTf)_2$] in MeCN forms a thermally labile intermediate. Chromatographic isolation of the intermediate at low temperature and analysis by low-temperature ^1H and ^{13}C NMR spectroscopies showed it to be the simple enol **16a**, a compound possessing unexpected stability. The enol **16a** undergoes autoxidation at room temperature or facile oxygenation at −20 °C in the presence of Cu(II) and oxygen to give the peroxy hemiacetal **12**. Thus, the catalyzed cleavage of cyclic allylic hydroperoxides proceeds via enol intermediates and it would seem that the propensity for subsequent oxygenation is related to the stability of the enol.

Introduction

Qinghaosu (QHS) and its derivatives are the most potent and rapid acting antimalarials currently in use. Multidrug resistance to chloroquine and mefloquine makes the malarial threat all the greater, and reliance on QHS drugs for effecting a cure, especially in Asia, is rapidly increasing.[1] This has thus placed great demand on access to QHS and its derivatives. A few years ago we discovered that QHS can be prepared efficiently from qinghao acid **1** via a novel cleavage oxygenation of allylic hydroperoxides catalyzed by copper(II) trifluoromethanesulfonate [$Cu(OTf)_2$] (Scheme 1).[2] A similar transformation was discovered at about the same time by Acton and Roth whereby the hydroperoxide **2** upon treatment with trifluoroacetic acid in hexane in air underwent a slow conversion to provide QHS.[3] Variations of the Acton−Roth method have been used extensively by others to prepare new QHS derivatives through modification of the structure of qinghao acid followed by submission of the modified acid to the oxygenation process.[4] We have used our own process to prepare QHS derivatives from structurally modified QHA precursors.[5] These semisyntheses represent the most effective means of obtaining QHS derivatives which themselves cannot be prepared from QHS.

Scheme 1



The manner in which the key transformation—the cleavage oxygenation of the hydroperoxide **2** to produce the peroxy hemiacetal **3** (Scheme 1)—proceeds is not properly understood.[6] As the cleavage of the hydroperoxide **2** is accompanied by incorporation of dioxygen, we initially proposed a free radical

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(1) A recent press release by the WHO (April 15, 1994) said that there are estimated to be 300−500 million clinical cases of malaria and 1.5−3.0 million deaths per year. A 2-year scientific study carried out in Thailand and Cambodia revealed that artemether, a derivative of qinghaosu, reduced the death rate by 3-fold in comparison to quinine in the treatment of multidrug-resistant malaria.

(2) Haynes, R. K.; Vonwiller, S. C. Provisional Patent no. P6989, September 1989. International Patent Application no. PCT/AU90/00456, September, 1990. WO 9308185, April 1993 (*Chem. Abstr.* **1993**, *119*, 181047q). Haynes, R. K.; Vonwiller, S. C. *J. Chem. Soc., Chem. Commun.* **1990**, 451.

(3) Roth, R. J.; Acton, N. *J. Nat. Prod.* **1989**, *52*, 1183. Roth, R. J.; Acton, N. *J. Chem. Educ.* **1991**, *68*, 612.

(4) Bustos, D. A.; Jung, M.; ElSohly, H. N.; McChesney, J. D. *Heterocycles* **1989**, *29*, 2773. Jung, M.; Li, X.; Bustos, D. A.; ElSohly, H. N.; McChesney, J. D. *Tetrahedron Lett.* **1989**, *30*, 5973. Jung, M.; Bustos, D. A.; ElSohly, H. N.; McChesney, J. D. *Synlett* **1990**, 743. Jung, M.; Yu, D.; Bustos, D. A.; ElSohly, H. N.; McChesney, J. D. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 741. Jung, M.; Bustos, D. A.; ElSohly, H. N.; McChesney, J. D. *Synlett* **1993**, 43. Liu, H.-J.; Yeh, W.-L.; Chew, S. Y. *Tetrahedron Lett.* **1993**, *34*, 4435.

(5) Haynes, R. K.; Vonwiller, S. C. *Synlett* **1992**, 481. Haynes, R. K.; Vonwiller, S. C. Int. Pat. Appl. PCT/AU92/00548, Oct 1992. Haynes, R. K.; King, G. R.; Vonwiller, S. C. *J. Org. Chem.* **1994**, *59*, 4743. Haynes, R. K.; Vonwiller, S. C.; Wang, H.-J. *Tetrahedron Lett.* **1995**, *36*, 4641. also: Jung, M.; Freitas, A. C. C.; McChesney, J. D.; ElSohly, H. N. *Heterocycles* **1994**, *39*, 23.

(6) For preliminary mechanistic studies, see: Acton, N.; Roth, R. J. *J. Org. Chem.* **1992**, *57*, 3610.

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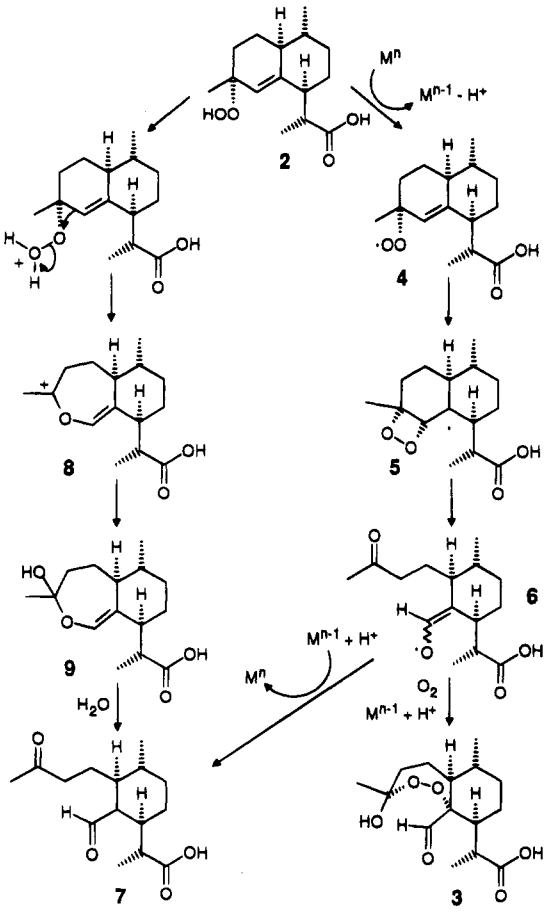
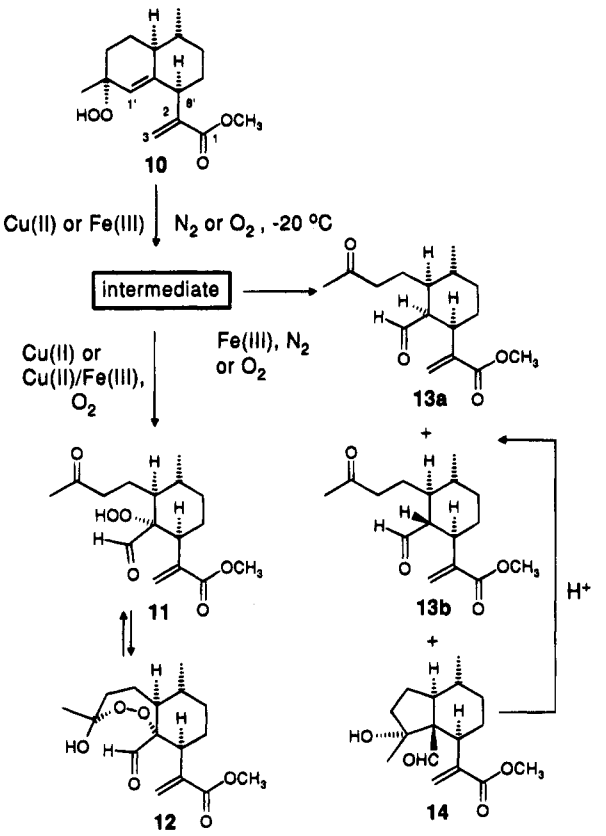
Scheme 2



Scheme 3



mechanism involving the generation of a peroxy radical **4** or its equivalent followed by insertion into the double bond to give a dioxetanyl alkyl radical intermediate **5**, which then undergoes opening to an enol radical **6** (Scheme 2).[2,7] Back electron transfer then leads to the ketoaldehyde **7**, or reaction with oxygen followed by back-electron transfer leads to the peroxy hemiacetal **3**. However, the obvious relationship between our transformation and that of Acton and Roth, in which there is no oxidizing agent capable of converting the hydroperoxide into a peroxy radical, is not easily reconciled with our original proposal. While the well-known acid-catalyzed Hock cleavage of allylic hydroperoxides may be used to account for the formation of the ketoaldehyde **7**, it is not clear how a radical intermediate capable of reacting with oxygen may be generated. Bond migration to electrophilic oxygen leads to the formation of a ring-expanded enol cation **8** or enol hemiacetal **9** which then undergoes hydrolysis to the final products[9] (Scheme 2).

In this paper we now present an analysis of both processes and the identification of intermediates which provide the key for an understanding of these important oxygenation reactions.

Results

During both the $Cu(OTf)_2$- and the $Fe(phen)_3(PF_6)_3$-catalyzed cleavage reactions of the hydroperoxide **10** of qinghao acid methyl ester in MeCN, formation of a common unstable intermediate which has two fates is observable by TLC (Scheme 3). In the presence of Cu(II) or Cu(II)/Fe(III) and O_2, cleavage, and oxygenation take place to give the hydroperoxy ketoaldehyde **11** and peroxy hemiacetal **12**. In the presence of Fe(III) alone with O_2, cleavage takes place without oxygenation to give the ketoaldehydes **13a,b** and aldol **14**. Trifluoromethanesulfonic acid (TfOH) in CH_2Cl_2 cleanly effects the cleavage reaction to provide, under N_2, the same ketoaldehydes **13a,b**.

With the Acton–Roth results in mind, the TfOH-catalyzed reaction was examined by low-temperature ^1H NMR spectroscopy in order to detect intermediates that may be possible precursors to radicals. Monitoring the hydroperoxide **10** in the presence of TfOH in CD_2Cl_2 from 180 K showed a clear progression from a discrete intermediate at 230 K to a second major intermediate at 250 K to the ketoaldehydes **13a,b** upon warming to room temperature (Figure 1). The second intermediate was identified as the aldol **14** (Scheme 3). The only other species present at 250 K are incipient amounts of the two ketoaldehydes. Confirmation was made through comparison of spectra with those of authentic samples of the aldol and ketoaldehydes at 250 K and the ketoaldehydes at 300 K.[10] The first intermediate was not the enol hemiacetal **15**, as might be expected from a Hock-type cleavage;[9] the methyl singlet at 2.12 ppm could not be accommodated by such a structure.

The possibility that this first-formed intermediate in the acid-catalyzed reaction was the same as the intermediate observed by TLC in the Cu(II)- and Fe(III)-catalyzed reactions was next investigated.[11] The hydroperoxide **10** was treated with $Fe(phen)_3(PF_6)_3$ at −20 °C in MeCN under N_2 and quenched immediately upon color change of the reaction mixture from blue to red (*ca.*

(7) Treatment of allylic fatty acid hydroperoxides with $Cu(OTf)_2$ under O_2 gives dioxolanyl hydroperoxides, an observation which provides strong support for the generation of peroxy radicals with this catalyst (see ref 8). Nevertheless, the mechanism of the transformation has been the subject of controversy: Courtneidge, J. L. *J. Chem. Soc., Chem. Commun.* **1992**, 381.

(8) Haynes, R. K.; Vonwiller, S. C. *J. Chem. Soc., Chem. Commun.* **1990**, 1102.

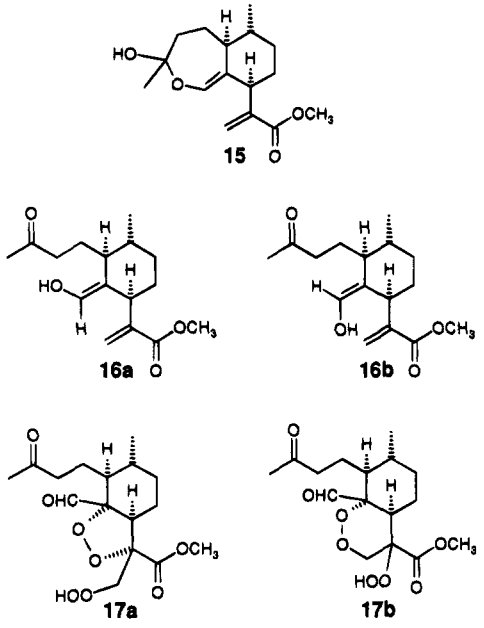
(9) For reviews, see: Frimer, A. A. *Chem. Rev.* **1979**, *79*, 363–365. In particular, see: H. Kropf, *Method der Organischen Chemie (Houben-Weyl)*; Band E13; *Organische Peroxo-Verbindungen, Teilband II*; Georg Thieme Verlag: Stuttgart, Germany, 1988; Chapter B, pp 1084–1095 and references therein.

(10) The formation of aldols as primary products of the cleavage of allylic hydroperoxides has been observed with a number of other examples: Haynes, R. K.; Vonwiller, S. C.; Warner, J. A. Unpublished work.

(11) At that stage it was uncertain whether the TLC species was in fact the intermediate or a secondary product of quenching on silica.

2−5 min), a point at which the intermediate was seen by TLC to be the predominant species.[12] Although unstable at room temperature, the intermediate was sufficiently stable below −20 °C to enable isolation. By careful low-temperature workup and low-temperature chromatography ($T < -20$ °C), the intermediate was successfully isolated free of the ketoaldehyde.

Remarkably, NMR spectroscopy revealed that this product was the enol **16a** and that this corresponded to the first-formed



intermediate in the TfOH-catalyzed reaction. The enol has the same chemical shifts as the intermediate from the acid-catalyzed reaction except that the signal at 6.3 ppm is present as a doublet and an additional doublet with similar splitting appears at 6.8 ppm (Figure 2).[13] D_2O exchange caused the latter signal (observed at 5.8 in $CDCl_3$) to disappear and the doublet at 6.3 ppm to collapse to a singlet (Figure 3). The large vicinal coupling of 10.3 Hz in the OH signal in the ^1H NMR spectrum suggests slow exchange either due to hydrogen bonding or to steric encumbrance by the flanking groups. Furthermore, we discovered that the enol transformed readily into a new enol (**16b**) with similar characteristics (Figure 2). This species also displays an OH signal with a large vicinal coupling as indicated by the D_2O exchange experiment (Figure 3).

Other NMR data are unequivocally supportive of the enol structures. H1′ in hydroperoxide **10** appears at δ 4.98 ppm, whereas in enol **16a**, the corresponding proton appears significantly further downfield, at 6.33 ppm (Table 1).[14] This deshielding is apparent in other aldehyde enols.[15] Furthermore, a ketonic methyl signal at 2.12 ppm supports the monocyclic structure and rules out enol hemiacetal formation as already mentioned. In the aldol **14**, the corresponding methyl signal

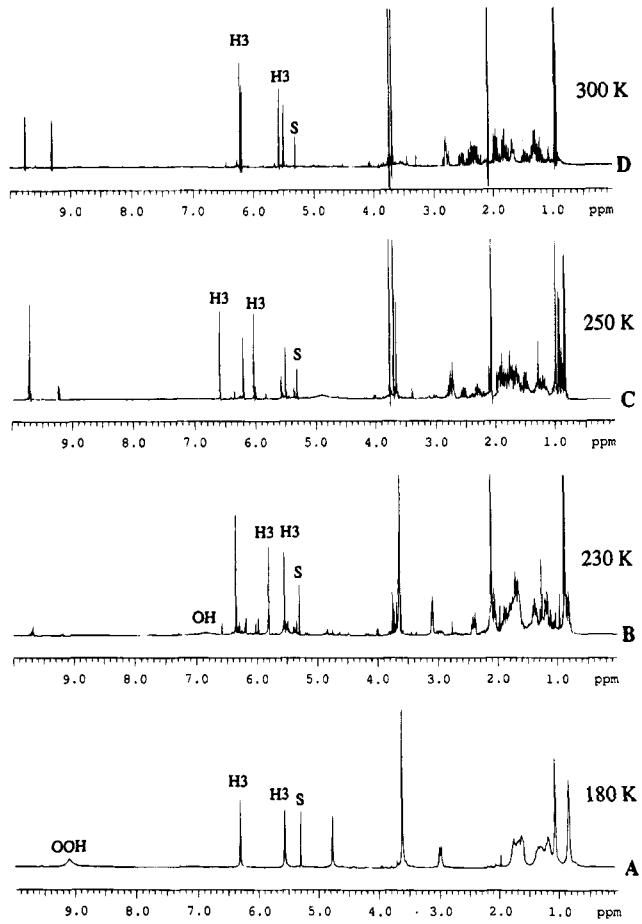


Figure 1. ^1H NMR spectra (400 MHz, CD_2Cl_2) run at variable temperature (180−300 K) showing progress of the reaction of the allylic hydroperoxide **10** with trifluoromethanesulfonic acid (TfOH) (S = residual protonated solvent): (A) 180 K, hydroperoxide **10**; (B) 230 K, enol **16a**; (C) 250 K, predominantly aldol **14**; (D) 300 K, ketoaldehyde **13a,b**.

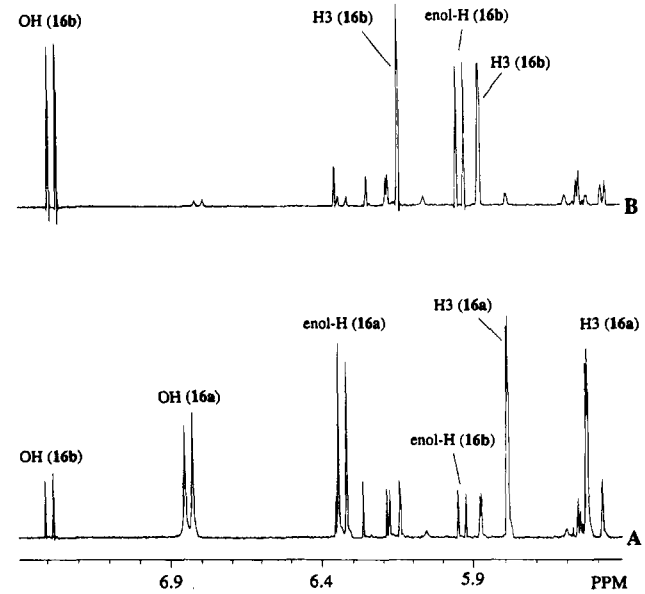


Figure 2. Downfield region of ^1H NMR spectrum (400 MHz, CD_2Cl_2, 230 K) of the isolated enol: (A) *ca.* 1 h after chromatographic isolation showing predominance of enol **16a**; (B) *ca.* 20 h after isolation showing almost complete isomerization to enol **16b**.

appears upfield at 1.09 ppm consistent with the replacement of the adjacent carbonyl group with a carbinol group. The ^{13}C NMR data are also consistent. C1′ in hydroperoxide **10** appears at 121.9 ppm, whereas in enol **16a**, the corresponding signal is

(12) It is uncertain whether the color change is due to ligand exchange involving Fe(III) and the product or to extraneous reduction of Fe(III) to Fe(II). The conversion of **10** to **13** is due solely to Fe(III); treatment of **10** with the Fe(II) catalyst, $Fe(phen)_3(PF_6)_2$, gave after 24 h at room temperature only a *trace* of the allylic alcohol resulting from reduction of the hydroperoxide.

(13) Presumably, proton exchange in the TfOH case prevents these couplings from being observed and is responsible for the broad signal centered at δ 6.84.

(14) For ease of discussion, numbering of protons and carbons in compounds **11**, **12**, **13a,b**, **14**, and **16a,b** corresponds to that of the starting hydroperoxide **10**. In the Experimental Section, assignments are numbered according to the systematic names of each compound.

(15) For example, in 2-methylprop-1-en-1-ol, C*H*OH appears at 6.12 ppm (ref 23b), in 1-(hydroxymethylene)cyclohexane, C*H*OH appears at 6.18 ppm (ref 23c), and a fused 1-hydroxymethylene-2,2,6,6-tetraalkylcyclohexane has C*H*OH at 6.26 ppm [ref 24c (supporting information)].

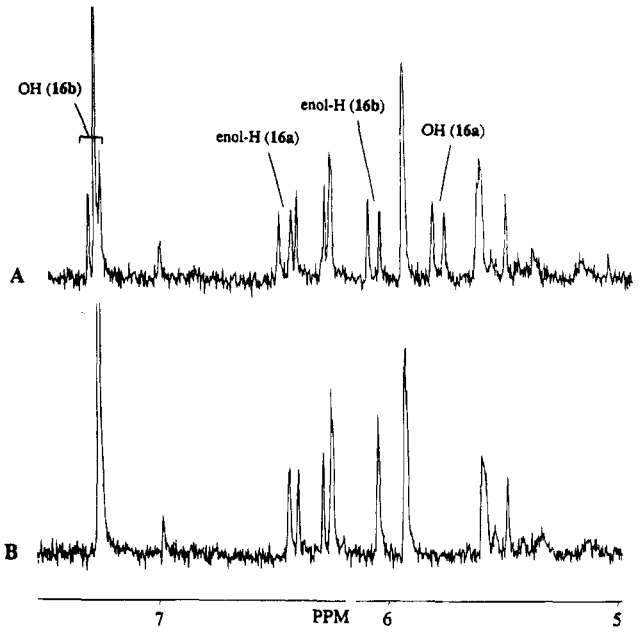


Figure 3. Downfield region of ^1H NMR spectrum (200 MHz, $CDCl_3$, 293 K) of a sample containing a 1:1 mixture of enols **16a,b**: (A) basic spectrum; (B) after D_2O exchange.

downfield at 146.3 ppm. C8a′, on the other hand, undergoes a significant upfield shift from 147.9 ppm in **10** to 110.2 ppm in **16a**. Similar trends have been reported for related enols[16] and enol ethers.[17] The ^{13}C NMR spectra also clearly distinguish **11**, **12**, and **14**. In the aldol **14** the quaternary signals due to C2′ and C8a′ appear at 80.8 and 66.0 ppm, respectively. However, upon attachment of a peroxy substituent to C8a′, the signals shift downfield such that C8a′ appears at 92.3 ppm in **11** and 92.3 ppm in **12**. Compound **11** is clearly an "open" hydroperoxide as indicated by a ketonic methyl resonance at 2.14 ppm in the ^1H NMR spectrum and a ketone carbonyl at 209.1 ppm in the ^{13}C NMR spectrum. That **12** is a peroxy hemiacetal is indicated by resonances at 105.9 ppm for C2′ and 1.22 ppm for 2′-CH_3, consistent with replacement of the adjacent carbonyl oxygen with two oxygen-bearing substituents.

An intriguing feature is the appearance of the enol isomers. The spectrum of compound **16b** is very similar to that of **16a** (Table 1). H1′ in **16b** appears at 5.94 ppm. In the ^{13}C NMR spectrum, C1′ is at 143.2 ppm and C8a′ is at 112.2 ppm, again diagnostic of the enol functional group. The nature of the isomerism was addressed by considering the signal due to H8′ as an indicator of conformational changes of the ring and double-bond geometry as determined by nuclear Overhauser effect measurements.[18] The results were surprising. The signal due to doubly-allylic H8′ in the starting hydroperoxide **10** appears at 3.14 ppm as a broad doublet with a vicinal coupling to H7′β of 12.6 Hz, indicative of a trans-diaxial relationship. Thus, the acrylate ester side chain in **10** is equatorial. In the enol **16a**, H8′ appears at 3.10 ppm, indicating that it is still adjacent to two double bonds. However, with a vicinal coupling of 4.0 Hz, this is now clearly equatorial. Thus, the acrylate ester side chain is forced into an axial position, possibly as a result of $A^{1,3}$ strain due to interaction with the enol functionality.[19] H8′ in the spectrum of the second enol isomer **16b** appears at 3.54 ppm as a broad doublet of 5.6 Hz, also suggesting that the acrylate ester side chain adopts an axial disposition. Thus, $A^{1,3}$ strain overrides the effect of 1,3-diaxial interactions and this is further favored by the lower steric requirements of the sp^2 centers of the acrylate side chain. Significantly, in going from the enol **16** to the aldol **14**, H8′ regains an axial disposition as suggested by its appearance at 2.86 ppm as a doublet of doublets with a trans-diaxial coupling of 13.3 Hz to H7′β and an axial-equatorial coupling of 3.4 Hz to H7′α. Oxygenation to give hydroperoxide **11** and peroxy hemiacetal **12** or protonation to give ketoaldehydes **13a,b** also results in an axial H8′ as indicated by trans-diaxial couplings to H7′β ranging from 9.6 to 13.3 Hz.

NOE experiments conducted at 230 K on the first-formed enol **16a** indicate (*E*)-geometry; preirradiation at 3.1 ppm (H8′) led to enhancement at 6.4 ppm (H1′, enolic-H) (10%) while preirradiation at 6.8 ppm (OH) led to enhancement at 2.2 ppm (unassigned) (23%). The second enol is (*Z*) as in **16b**; preirradiation at 7.3 ppm (OH) led to enhancement at 3.5 ppm (H8′) (15.7%) while preirradiation at 5.9 ppm (H1′, enolic-H) led to enhancement at 1.5 ppm (unassigned) (8.8%). The manner in which the (*E*)−(*Z*) isomerization takes place is not easily rationalized and is unlikely to proceed via the aldehyde.[20]

The enol **16a** was isolated at low temperature and treated with $Cu(OTf)_2$ under O_2 at −20 °C in MeCN. Within 40 min the enol was converted into the hydroperoxy ketoaldehyde **11** and the peroxy hemiacetal **12**. In the absence of the catalyst, negligible oxygenation took place.

The hydroperoxide **10** was treated under varying conditions with O_2 in order to delineate the role of the copper(II) and acid catalysts (Table 2). With TfOH (0.1 equiv) at −25 °C in CH_2Cl_2 (entry 1), rapid conversion into the ketoaldehyde **13** and aldol **14** took place. Upon warming to room temperature the aldol disappeared. The product mixture then consisted of the keto-aldehydes **13a,b** and a small amount of peroxy hemiacetal **12**. However, with 0.01 equiv of TfOH in CH_2Cl_2, at −25 °C (entry 2), the enol was formed very cleanly and rapidly and only traces of the ketoaldehyde were detected by TLC. Remarkably, the enol was stable during prolonged stirring at −25 °C and only when the solution was warmed to room temperature did it decompose to give ketoaldehydes **13a,b**, aldol **14**, hydroperoxide **11**, peroxy hemiacetal **12**, and another compound that has tentatively been assigned as either the 3-(hydroperoxymethyl)-

(16) For example, 2-methylprop-1-en-1-ol has Cα at 136.2 ppm and Cβ at 105.9 ppm (ref 23a) and the fused 1-(hydroxymethylene)-2,2,6,6-tetraalkylcyclohexane reported by Nicolaou has signals at 139.9 and 120.0 ppm although assignments have not been made [ref 24c (supporting information)].

(17) Barillier, D.; Strobel, M. P.; Morin, L.; Paquer, D. *Tetrahedron* **1983**, *39*, 767.

(18) Attempts to derivatize the isolated enol by treatment with dimethyl sulfate/K_2CO_3 or diazomethane were unsuccessful: the enol remained unreactive at −20 °C, and while enol ether formation was observed at room temperature with the former reagent, this did not compete well with the formation of the ketoaldehyde **13** and other side products.

(19) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons, Inc.: New York, 1994; pp 737−740.

(20) A reviewer has suggested reversible addition of water to the enol to give the hydrate. As this is only observed with the isolated enol, this would have to be catalyzed by the very low concentrations of HCl in the CD_2Cl_2. It should be noted that the rate of isomerization varied from sample to sample and this may support the likelihood that traces of water are responsible. However, one might expect the hydrate to be more stable than the enol by virtue of the removal of $A^{1,3}$ strain. Alternatively, the isomerization may go via the cation radical of the enol or formyl radical which may form as a result of traces of hydroperoxide **11** and oxygen in the sample. The (*Z*)-enol has not been observed in the TfOH-catalyzed reaction, presumably because subsequent aldolization competes with isomerization.

(21) A more complete characterization of this compound is required before a definite assignment of structure can be made. However, if either of the proposed structures are correct, then they arise presumably as a result of competing intramolecular 5-exo-trig or 6-endo-trig cyclization of the peroxy radical from **11** onto the double bond of the unsaturated ester group followed by trapping with oxygen. While differentiation of both structures by NMR is difficult, it has been found that peroxy radical cyclizations onto simple alkyl substituted double bonds tend to go almost exclusively via the 5-exo-trig mode (see: Porter, N. A.; Funk, M. O.; Gilmore, D.; Isaac, Nixon, J. *J. Am. Chem. Soc.* **1976**, *98*, 6000).

(22) Hart, H. *Chem. Rev.* **1979**, *79*, 515. Pratt, D. V.; Hopkins, P. B. *J. Am. Chem. Soc.* **1987**, *109*, 5553.

Table 1. Summary of Key ^1H and ^{13}C NMR Signals for Compounds **10**–**12**, **13a,b**, **14**, and **16a,b**

	chemical shift (ppm) at 400 MHz							
assignment	**10**[a]	**11**[a]	**12**[a]	**13a**[a]	**13b**[a]	**14**[a]	**16a**[b]	**16b**[b]
H1′	4.98	9.34	9.62	9.34	9.70	9.78	6.33	5.94
2′-CH_3	1.21	2.14	1.22	2.13	2.14	1.09	2.12	1.98
H8′	3.14 (br d, J = 12.6 Hz)	3.20 (dd, J = 13.3, 3.5 Hz)	2.98 (dd, J = 9.6, 7.1 Hz)	2.85 (ddd, J = 11.7, 11.7, 3.5 Hz)	2.80 (br ddd, J = 12.7, 4.4 Hz)	2.86 (dd, J = 13.3, 3.4 Hz)	3.10 (br d, J = 4 Hz)	3.54 (br d, J = 5.6 Hz)
H8a′				2.32 (ddd, J = 11.1, 11.1, 5.4 Hz)	2.86 (dddd, J = 4, 4, 4, 1.3 Hz)			
C1	168.2	170.4	166.2	167.1	167.1	170.7	169.0	171.1
C1′	121.9	203.1	201.4	205.0	206.1	206.6	146.3	143.2
C2	142.1	139.6	139.7	142.8	141.8	141.4	142.6	140.1
C2′	81.4	209.1	105.9	209.2	208.6	80.8	214.4	210.0
C3	125.4	129.0	125.0	127.0	125.0	130.3	120.8	124.6
C8a′	147.9	92.3	92.3	unassigned	unassigned	66.0	110.2	112.2

[a] In $CDCl_3$ at 300 K. [b] In CD_2Cl_2 at 230 K.

Table 2. Products (% Yield) from Reactions of the Hydroperoxide of Qinghao Acid Methyl Ester[a]

entry	catalyst (eq), solvent	**11**	**12**	**13a**	**13b**	**14**	**17**
1	TfOH (0.1), CH_2Cl_2[b]	0	6	27	33	0	0
2	TfOH (0.01), CH_2Cl_2[b]	4.5	16	18	37	8	9
3	TfOH (0.04), CH_3CN[c]	0	0	62	20	14	0
4	TfOH (0.01), hexane[d]	8.7	13.6	3.0	3.5	1.5	8.7
5	$Cu(OTf)_2$ (0.1), CH_3CN[e]	34	21.9	0	0	0	3.6
6	$Cu(OTf)_2$ (0.1), CH_3CN[f]	52.8	17	0	0	2.1	9.3
7	Cu(II) (0.1)/Fe(III) (0.02), CH_3CN[g]	35	23.4	0	0	0	4.5
8	$Cu(OTf)_2$ (0.6), CH_3CN[h]	9.7	22	5.8	4.9	11.7	9.7
9	Fe(III) (0.1), CH_3CN[i]	0	0	40	27	29	0

[a] Reactions were carried out under an oxygen atmosphere. Yields were determined by integration of diagnostic resonances in the ^1H NMR spectrum (see the Experimental Section) against 1,3,5-trinitrobenzene as an internal standard. [b] At −25 °C for 1.5 h, followed by slow warming to 20 °C over 1 h, then at 20 °C for 13 h. [c] Catalyst added in 0.01 equiv increments over 1 h at −25 °C, then at −25 °C for 1 h, then as for *b*. [d] At −20 °C for 10 min followed by warming to 20 °C and stirring for 14 h. [e] At −20 °C for 7 h. [f] At −5 °C for 1.75 h. [g] With $Fe(phen)_3(PF_6)_3$ followed by $Cu(OTf)_2$ at −25 °C for 4.8 h. [h] $Cu(OTf)_2$ added in 0.1 equiv lots at 30 min intervals at −20 °C, followed by warming to 20 °C over 2 h. [i] At −25 °C for 5 h.

1,2-dioxolane **17a** or the 4-hydroperoxy-1,2-dioxane **17b**.[21] Amounts are given in the table. In MeCN at −25 °C (entry 3) conversion of the hydroperoxide required 0.04 equiv of TfOH to effect complete reaction to give the enol and small amounts of the ketoaldehyde and aldol. Warming to room temperature gave the ketoaldehydes and aldol as the sole products. No oxygenation took place under these conditions; hydroperoxide **11**, peroxy hemiacetal **12**, and peroxide **17** were not detected. In contrast, the replacement of TfOH with $Cu(OTf)_2$ in MeCN (entries 5–8) had a dramatic effect. With 0.1 equiv in MeCN over 7 h at −20 °C, the oxygenation products **11** and **12** were formed in combined yields of over 50%, with none of the ketoaldehyde or aldol and minimal peroxide (**17**) being formed (entry 5). Use of a larger quantity of $Cu(OTf)_2$ (0.6 equiv) did result in formation of ketoaldehyde and aldol, together with the peroxide **17** (entry 8). TfOH (0.01 equiv) in hexane (entry 4) induced slow conversion to the enol at room temperature and thence formation of the oxygenation products **11**, **12**, and **17**, in addition to the ketoaldehyde and aldol. The use of $Fe(phen)_3(PF_6)_3$ as a catalyst in MeCN (entry 9) had the same effect as TfOH in that ketoaldehyde and aldol formation occurred at the expense of oxygenation. A combination of the iron and copper catalysts enabled the oxygenation to proceed at a slightly faster rate although the final result in terms of products formed was the same (entry 7).

Discussion

It is clear now that enol formation plays an important role in the oxygenation process under both acid and copper(II) catalysis.

The kinetic stability of a number of simple enols has been well documented,[22,23] but there are few examples in which aldehyde enols have been characterized by NMR spectroscopy.[23,24] We are aware of only one other case describing actual isolation of a simple enol by chromatography.[24,25]

The congruence between our process and that of Acton and Roth is now manifest. The autoxidation of simple enols has been known for some time.[26] Presumably, under the Acton–Roth conditions, the hydroperoxide is exposed to a low concentration of acid due to the biphasic nature of trifluoroacetic acid in hexane, enabling the cleavage reaction to take place to give the enol.[27] This is reflected in the result obtained with TfOH in hexane (Table 2, entry 4) in which the enol is clearly observed to form, even at room temperature. At the elevated temperature the enol undergoes autoxidation at a rate that is competitive with protonation. On the other hand, treatment of the allylic hydroperoxide with TfOH in CH_2Cl_2 or MeCN under O_2 at −25 °C gave enol or ketoaldehyde only, and even at elevated temperatures, autoxidation to the peroxy hemiacetal and hydroperoxide was inefficient. Under our conditions, autoxidation can only be catalyzed by the Cu(II) species and proceeds relatively quickly at lower temperatures. $Cu(OTf)_2$ alone in CH_3CN effected cleavage oxygenation at −5 °C over 2 h, while the use of TfOH in hexane at room temperature led to slow enol formation followed by oxygenation over several

(23) (a) Capon, B.; Rycroft, D. S.; Watson, T. W.; Zucco, C. *J. Am. Chem. Soc.* **1981**, *103*, 1761. (b) Chin, C. S.; Lee, S. Y.; Park, J.; Kim, S. *J. Am. Chem. Soc.* **1988**, *110*, 8244. (c) Bergens, S. H.; Bosnich, B. *J. Am. Chem. Soc.* **1991**, *113*, 958.

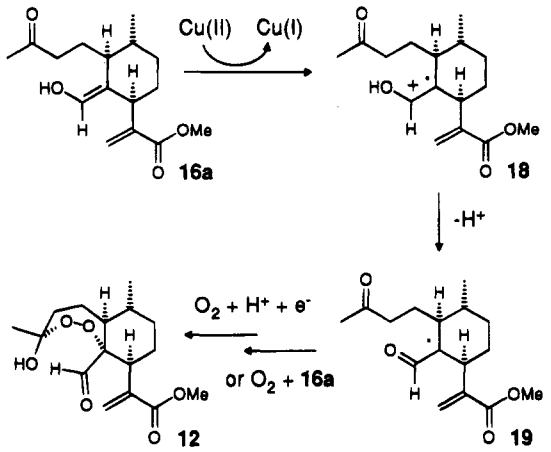
(24) A sterically hindered fused 1-(hydroxymethylene)-2,2,6,6-tetraalkylcyclohexane has been noted as a minor product in the synthesis of taxol precursors: (a) Kende, A. S.; Johnson, S.; Sanfilippo, P.; Hodges, J. C.; Jungheim, L. N. *J. Am. Chem. Soc.* **1986**, *108*, 3513. (b) Nicolaou, K. C.; Claiborne, C. F.; Nantermet, P. G.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1994**, *116*, 1591. (c) Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634 and supporting information.

(25) The isolation of enol **16** is highly sensitive to the condition of the silica gel; the use of silica that had been dried and degassed under high vacuum at room temperature caused the enol to quantitatively isomerize to the ketoaldehyde **13**.

(26) Kohler, E. P.; Tishler, M. *J. Am. Chem. Soc.* **1932**, *54*, 1594. Kohler, E. P.; Tishler, M.; Potter, H. *J. Am. Chem. Soc.* **1935**, *57*, 2517. Attenburrow, J.; Connett, J. E.; Graham, W.; Oughton, J. F.; Ritchie, A. C.; Wilkinson, P. A. *J. Chem. Soc.* **1961**, 4547. Enslin, P. R. *Tetrahedron* **1971**, *27*, 1909. Zimmerman, H. E.; Linder, L. W. *J. Org. Chem.* **1985**, *50*, 1637.

(27) Jung and others (see ref 4) employ a variation in which Dowex resin is used as the heterogeneous acid catalyst.

Scheme 4



hours. However, at lower temperatures (−25 °C), $Cu(OTf)_2$ slowly (6−7 h) converted the allylic hydroperoxide into the enol and thence the oxygenation products. Under low acid (both protic and Lewis) concentrations, isomerization to the keto-aldehyde is less significant. Formation of the ketoaldehyde and aldol in the presence of higher concentrations of $Cu(OTf)_2$ indicates that either the Lewis acidity of, or traces of protic acid in, the $Cu(OTf)_2$ overwhelms redox properties of the catalyst in inducing tautomerization or aldolization of the enol.

The autoxidation is likely to proceed via electron transfer from the enol **16a** (or **16b**) to the Cu(II)[28] to provide a *cation radical* **18** and Cu(I), followed by proton loss to generate the formyl (or enol) radical **19** (Scheme 4).[29] Addition of oxygen to form the peroxy radical is followed by back electron transfer from Cu(I) and protonation or, in a chain process, by hydrogen transfer to the peroxy radical from the starting enol.[30] In the absence of a metal catalyst the radical chain process appears to be best sustained in a nonpolar solvent such as hexane.

Finally, we note that enol ethers structurally related to **16** have been used for the preparation of qinghaosu derivatives.[31] However, the transformations of the enol ethers are mechanistically distinct from the present case; these involve the generation of 1,2-dioxetanes by the use of singlet oxygen and acid-catalyzed rearrangement.[32]

Conclusion

The present work indicates that the catalyzed cleavage of cyclic allylic hydroperoxides proceeds via enol intermediates.[33] While the autoxidation of enols is well-known, the presence of an oxidizing catalyst enables a more efficient oxygenation to occur. The current work, in contributing to an understanding of how the cleavage oxygenation of Scheme 1 takes place, provides a gateway to rational synthetic design of new trioxane systems.

Experimental Section

General Methods and Materials. Melting points were recorded on a Reichert melting point stage and are uncorrected. ^1H NMR spectra were recorded on Bruker AC-200F (200 MHz) and AMX-400 (400 MHz) spectrometers, with samples dissolved in $CDCl_3$, or CD_2Cl_2 for low-temperature work. Samples run in $CDCl_3$ were referenced to tetramethylsilane while those in CD_2Cl_2 were referenced to residual protonated solvent. ^{13}C NMR spectra were recorded on the above instruments at 50 and 100 MHz, respectively. IR spectra were recorded on a Perkin Elmer 1600 Series Fourier transform spectrometer or a Digilab FTS 20/80 Fourier transform spectrometer as indicated. Mass spectrometry was carried out on an AEI MS9 spectrometer connected to a Kratos DC 90 data handling system for high-resolution spectra. Chromatographic separations were carried out by flash chromatography with Merck silica gel 60 (230−400 mesh, ASTM), which was used without prior treatment. Analytical TLC was carried out with Merck precoated aluminum TLC plates coated with silica gel 60 F 254 (0.2 mm). HPLC was carried out on a Waters 6000A system equipped with a refractive index detector and UV detector under conditions as described in the Experimental Section.

MeCN was dried over P_4O_{10}, fractionally distilled under nitrogen, and stored over 4 Å molecular sieves under nitrogen. CH_2Cl_2 was dried over P_4O_{10} and freshly distilled under nitrogen prior to use. Diethyl ether was fractionally distilled from 18 M H_2SO_4. Copper(II) trifluoromethanesulfonate [$Cu(OTf)_2$] (Aldrich, dried under high vacuum at 100 °C (0.01 mmHg) for 3 h) and tris(phenanthroline)iron(III) tris(hexafluorophosphate) [$Fe(phen)_3(PF_6)_3$] (prepared according to the method of Kochi,[34] dried under high vacuum at 50 °C (0.1 mm) for 3 h) were dissolved individually in MeCN immediately prior to use. Trifluoromethanesulfonic acid (TfOH) (Aldrich) was dissolved in anhydrous CH_2Cl_2 (0.11 M) under nitrogen immediately prior to use. Qinghao acid was extracted[35] from *Artemisia annua* grown in Tasmania.

Methylation of Qinghao Acid. A mixture of qinghao acid (523 mg, 2.23 mmol), methyl *p*-toluenesulfonate (504 mg, 2.71 mmol, 1.2 equiv), and K_2CO_3 (341 mg, 2.47 mmol, 1.1 equiv) in acetone (20 mL) was heated under reflux for 1 h. Water (80 mL) was added, and the methyl ester was extracted into ether (3 × 40 mL). The combined organic extracts were washed with ammonia solution (25%, 40 mL) and brine (2 × 50 mL) and dried (Na_2SO_4). The solvent was removed and the crude product purified by flash chromatography (ether/light

(28) For related enol ether oxidations, see: Snider, B. B.; Kwon, T. *J. Org. Chem.* **1990**, *55*, 4786. Rathore, R.; Kochi, J. K. *Tetrahedron Lett.* **1994**, *35*, 8577. The copper catalyzed α-oxygenation of carbonyl compounds in the presence of amine bases has been studied in detail and presumably proceeds via the copper(II) enolate, see: Volger, H. C.; Brackman, W.; Lemmers, J. W. F. M. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 1203. Brackman, W.; Gaasbeek, C. J.; Smith, P. J. *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 437. Van Rheenen, V. *Tetrahedron Lett.* **1969**, 985. Sayre, L. M.; Jin, S.-J. *J. Org. Chem.* **1984**, *49*, 3498. Jin, S.-J.; Arora, P. K.; Sayre, L. M. *J. Org. Chem.* **1990**, *55*, 3011.

(29) In principle, the Fe(III) catalyst in MeCN should be capable of oxidizing the enol as it has a similar reduction potential (see ref 34) to copper(II) in MeCN (see: Nelson, I. V.; Carson, R. C.; Iwamoto, R. T. *J. Inorg. Nucl. Chem.* **1961**, *22*, 279) in excess of $E° = 1.1$ V vs SCE. However, both here and in previous work,[8] we find that it is ineffective and suggest that possible competing back electron transfer to give the enolate *prior* to reaction of the enol radical with oxygen may be occurring.

(30) The question that still needs to be answered is how the hydroperoxide **10** is converted into the enol. The enol acetal **15**, a logical first intermediate of the Hock cleavage may collapse directly to the enol **16a**. However, we have never been able to detect this species by ^1H NMR spectroscopy. Alternatively, the dioxetanyl radical intermediate as initially proposed by us may provide the enol radical directly, and this in turn can be reduced to give the enol. Of significance is that the hydroperoxide **10** has been observed to undergo autoxidation in the absence of solvent upon storage at −20 °C to give the oxygenation products **11** and **12** directly. This we attributed to traces of peroxidic contaminants present in the ether solvent used to transfer **10** which may act as radical initiators. For autoxidations of cyclic alkenes induced by *tert*-butyl hydroperoxide and an initiator, see: Courtneidge, J. L.; Bush, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1531. Courtneidge, J. L.; Bush, M.; Loh, L.-S. *Ibid.* **1992**, 1539. The use of sulfuric acid distilled ether precluded this "decomposition".

(31) Schmid, G.; Hofheinz, W. *J. Am. Chem. Soc.* **1983**, *105*, 624. Xu, X.-X.; Zhu, J.; Huang, D.-Z.; Zhou, W.-S. *Tetrahedron* **1986**, *42*, 819. Ye, B.; Wu, Y.-L. *J. Chem. Soc., Chem. Commun.* **1990**, 726. Posner, G. H.; Oh, C. O.; Milhous, W. K. *Tetrahedron Lett.* **1991**, *32*, 4235. Lansbury, P. T.; Nowak, D. M. *Tetrahedron Lett.* **1992**, *33*, 1029. Avery, M. A.; Chong, W. K. M.; Jennings-White, C. *J. Am. Chem. Soc.* **1992**, *114*, 974. Posner, G. H.; Oh, C. O. *J. Am. Chem. Soc.* **1992**, *114*, 8328. Rong, Y.-J.; Wu, Y.-L. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2147. Rong, Y.-J.; Wu, Y.-L. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2149. Posner, G. H.; Oh, C. O.; Wang, D.; Gerena, L.; Milhous, W. K.; Meshnick, S. R.; Asawamahasadka, W. *J. Med. Chem.* **1994**, *37*, 1256.

(32) Asveld, E. W. S.; Kellog, R. M. *J. Am. Chem. Soc.* **1980**, *102*, 3644. Jefford, C. W.; Favarger, S.; Ferro, S.; Chambaz, D.; Bringhen, A.; Bernardinelli, G.; Boukouvalas, J. *J. Am. Chem. Soc.* **1983**, *105*, 624.

(33) We have found that not all cyclic allylic hydroperoxides undergo concomitant oxygenation. It would seem that the propensity for oxygenation is related to the stability of the enol. Rapid aldolization or prototropic rearrangement to the carbonyl compound supervenes in these cases: Haynes, R. K.; Vonwiller, S. C. *J. Chem. Soc., Chem. Commun.* **1990**, 449.

(34) Wong, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 5593. Schlesener, C. J.; Amatore, C.; Kochi, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 3567.

(35) Vonwiller, S. C.; Haynes, R. K.; King, G.; Wang, H.-J. *Planta Med.* **1993**, *59*, 562.

petroleum, 10:90) to yield qinghao acid methyl ester (522 mg, 94%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (3H, d, $J = 6$ Hz), 0.9−1.5 (6H, m), 1.59 (3H, s), 1.6−2.0 (4H, m), 2.4−2.6 (1H, m), 2.6−2.8 (1H, m), 3.74 (3H, s), 4.96 (1H, br s), 5.43 (1H, br s), 6.37 (1H, br s).

Photooxygenation of Qinghao Acid Methyl Ester. The methyl ester of qinghao acid (252 mg, 1.01 mmol) was dissolved in MeCN (20 mL) and irradiated (tungsten filament, 500 W) in the presence of Rose Bengal sensitizer, under a slow stream of oxygen, for 6 h at −30 °C. The solvent was removed by evaporation, and the residue was submitted to flash chromatography (ether/light petroleum, 30:70) to give the (tertiary) hydroperoxide, methyl [2′*R*,4a′*S*,5′*R*,8′*R*]-2-(2′,5′-dimethyl-2′-hydroperoxy-2′,3′,4′,4a′,5′,6′,7′,8′-octahydronaphthalen-8′-yl)propenoate (**10**), as a colorless viscous oil (234 mg, 82%) which crystallized during storage at −20 °C. IR ($CHCl_3$): 3536 m (OH), 3416 br s (OH), 1713 s (C=O, ester), 1440 m, 1277 s, 1154 s cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (3H, d, $J_{Me,5'} = 6.4$ Hz, 5′-CH_3), 1.18−1.27 (1H, m, H5′), 1.21 (3H, s, 2′-CH_3), 1.27−1.38 (2H, m), 1.51 (1H, dddd, $J_{gem} = 12.5$, $J_{7'\beta,8'} = 12.5$, $J_{7'\beta,6'\beta} = 3.5$ Hz, H7′β), 1.53 (1H, dddd, $J = 13.0$, $J = 7.3$, $J = 3.0$, $J = 0.8$ Hz), 1.72−1.79 (1H, m), 1.80 (1H, dddd, $J_{gem} = 12.3$, $J_{7'\alpha,8'} = 3.5$, $J_{7'\alpha,6'\alpha} = 3.5$, $J_{7'\alpha,6'\beta} = 3.5$ Hz, H7′α), 1.83 (1H, dddd, $J = 12.6$, $J = 3.3$, $J = 3.3$ Hz), 1.97 (1H, ddd, $J = 13.1$, $J = 10.8$, $J = 3.5$ Hz), 2.05 (1H, dddd, $J = 13.1$, $J = 7.5$, $J = 5.8$ Hz), 3.14 (1H, br d, $J_{8',7'\beta} = 12.6$ Hz, H8′), 3.74 (3H, s, OCH_3), 4.98 (1H, ddd, $J_{1',8'} = 1.6$, $J = 1.6$, $J = 0.8$ Hz, H1′), 5.58 (1H, dd, $J_{gem} = 1.1$, $J_{3,8'} = 1.1$ Hz, H3), 6.36 (1H, d, $J_{gem} = 1.1$ Hz, H3), 7.58 (1H, br s, $W_{h/2} = 2.0$ Hz, OOH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.9, 24.0, 24.2, 28.5, 31.7, 35.1, 39.3, 44.4, 45.0, 52.1 (CO_2CH_3), 81.4 (C2′), 121.9 (C1′), 125.4 (CH_2=C), 142.1 (CH_2=*C*), 147.9 (C8a′), 168.2 (CO_2CH_3). MS (negative CI in MeOH): *m/z* 280 (M, 25%), 263 (55), 247 (100), 231 (80). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.78; H, 8.85.

Cleavage Oxygenation To Give the Dicarbonyl Hydroperoxide 11 and Peroxy Hemiacetal 12. The tertiary hydroperoxide (106.3 mg, 0.38 mmol) in MeCN (5 mL) was treated with $Fe(phen)_3(PF_6)_3$ (0.6 mL, 0.02 M in MeCN, 0.03 equiv) and then with $Cu(OTf)_2$ (0.5 mL, 0.1 M in MeCN, 0.1 equiv) at 0 °C under an oxygen atmosphere. The reaction mixture was stirred for 30 min, with slow warming to room temperature, and then poured onto a mixture of ether and water. The aqueous phase was extracted with ether, and the combined extracts were washed with water until colorless and then with brine. The organic phase was dried ($MgSO_4$), and the solvent was removed under reduced pressure to leave a viscous oil, analysis of which by ^{1}H NMR spectroscopy indicated that it consisted predominantly of the oxygenation products **11** and **12**. These were isolated by flash chromatography (ether/light petroleum, 60:40) as an unstable viscous oil (62.5 mg, 53%). Prolonged exposure of the mixture of oxygenation products to silica gel resulted in decomposition to a more polar material. The oxygenation products were an equilibrium mixture of the free dicarbonyl hydroperoxide, methyl [1′*R*,2′*S*,5′*R*,6′*S*]-2-[1′-formyl-1′-hydroperoxy-5′-methyl-6′-(3″-oxobutyl)cyclohex-2′-yl]propenoate (**11**), and the peroxy hemiacetal, methyl [5a′*S*,6′*R*,9′*S*]-2-(3′*H*-3′,6′-dimethyl-9a′-formyl-3′-hydroxyperhydro-1′,2′-benzodioxepin-9′-yl)propenoate (**12**). IR ($CHCl_3$): 3580−3450 (br s), 1732 (s, C=O), 1714 (vs, C=O), 1167 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) (as ascertained from the mixture) for **11**: δ 0.99 (3H, d, $J_{Me,5'} = 6.4$ Hz, 5′-CH_3), 0.96−1.20 (2H, m), 1.26−1.39 (3H, m), 1.56−2.24 (4H, m), 2.14 (3H, s, H4″), 2.59 (1H, ddd, $J_{gem} = 17.6$, $J_{2'',1''} = 9.3$, $J_{2'',1''} = 6.1$ Hz, H2″), 2.71 (1H, ddd, $J_{gem} = 17.6$, $J_{2'',1''} = 9.3$, $J_{2'',1''} = 6.1$ Hz, H2″), 3.20 (1H, dd, $J_{2',3'\beta} = 13.3$, $J_{2',3'\alpha} = 3.5$ Hz, H2′), 3.84 (3H, s, OCH_3), 5.60 (1H, s, H3), 6.38 (1H, s, H3), 9.34 (1H, dd, $J = 1.5$, $J = 1.5$ Hz, CHO), 10.40 (1H, s, OOH). ^{1}H NMR for **12**: δ 0.93 (3H, d, $J_{Me,6'} = 6.4$ Hz, 6′-CH_3), 0.96−1.20 (2H, m), 1.22 (3H, s, 3′-CH_3), 1.26−1.39 (3H, m), 1.56−2.24 (4H, m), 2.32−2.45 (1H, m, H6′), 2.98 (1H, dd, $J_{9',8'\beta} = 9.6$, $J_{9',8'\alpha} = 7.1$ Hz, H9′), 3.80 (3H, s, OCH_3), 5.47 (1H, s, H3), 6.26 (1H, s, H3), 9.62 (1H, d, $J_{CHO,5a'} = 2.5$ Hz, CHO). Preirradiation at δ 9.6 (CHO, **12**) resulted in enhancements at δ 5.47 (H3, **12**) of 1% and at δ 3.80 (OCH_3) of 1%. ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1, 20.4, 20.6, 22.1, 22.5, 23.5, 27.0, 27.3, 27.8, 29.6, 29.9, 32.1, 33.8, 34.7, 35.1, 40.7, 41.7, 43.4, 43.9, 46.4, 52.3 (OCH_3, **12**), 52.9 (OCH_3, **11**), 58.6, 92.3 (C1′, **11**), 92.3 (C9a′, **12**), 105.9 (C3′, **12**), 125.0 (C3, **12**), 129.0 (C3, **11**), 139.6 (C2, **11**), 139.7 (C2, **12**), 166.2 (C1, **12**), 170.4 (C1, **11**), 201.4 (CHO, **12**), 203.1 (CHO, **11**), 209.1 (C3″, **11**). MS (EI): *m/z* 280 (M − O_2, 1%), 262 (5), 177 (33), 43 (100). MS (positive CI, CH_4): *m/z* 341 (M + C_2H_5, 7%), 295 [(M − O) + 1, 26], 249 (100).

Cleavage of the Hydroperoxide of Qinghao Acid Methyl Ester with $Fe(phen)_3(PF_6)_3$ under Nitrogen. (a) Preparation of the Ketoaldehydes 13 and the Aldol 14. A solution of the hydroperoxide **10** (3.12 mg, 0.111 mmol) in MeCN (3 mL) under nitrogen was cooled to −10 °C, and then $Fe(phen)_3(PF_6)_3$ (0.56 mL, 0.02 M in MeCN, 0.1 equiv) was added. After a delay of a few seconds, the solution rapidly changed from blue to red and TLC analysis indicated complete conversion to the enol **16**, the ketoaldehyde **13**, and the aldol **14**. After 30 min the mixture gradually converged to the ketoaldehyde **13** and the aldol **14**. A solution of $NaHCO_3$ (10%, 5 mL) was added, and the resulting mixture was extracted with ether. The combined extracts were washed with brine and dried (Na_2SO_4), and the solvent was removed by evaporation. The residue was fractionated by flash chromatography (ether/petroleum ether, 40:60) to give, first, in order of elution, the aldol, methyl [1′*R*,3a′*S*,4′*R*,7′*S*,7a′*S*]-2-(1′*H*-1′,4′-dimethyl-7a′-formyl-1′-hydroxyperhydroinden-7′-yl)propenoate (**14**), as a white solid (2.1 mg, 7%), mp 71−74 °C, of limited stability. IR (KBr): 3472, 3442 (m, OH), 2951 (s), 2871 (m), 2851 (m), 2765 (w), 1707 (s, C=O), 1698 (vs, C=O), 1618 (m), 1441 (m), 1378 (m), 1284 (s), 1266 (m), 1199 (m), 1157 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.89 (3H, d, $J_{Me,4'} = 6.5$ Hz, 4′-CH_3), 1.05 (1H, dddd, $J = 13.2$, $J = 13.2$, $J = 11.4$, $J = 4.4$ Hz), 1.09 (3H, s, 1′-CH_3), 1.5−1.7 (3H, m), 1.77 (1H, dddd, $J = 14.0$, $J = 11.7$, $J = 3.8$, $J = 2.6$ Hz, H2′β), 1.8−2.1 (6H, m), 2.86 (1H, dd, $J_{7',6'\beta} = 13.3$, $J_{7',6'\alpha} = 3.4$ Hz, H7′), 4.51 (1H, d, $J_{OH,2'\beta} = 2.5$ Hz, OH), 6.05 (1H, s, H3), 6.61 (1H, s, H3), 9.78 (1H, dd, $J = 1.2$, $J = 0.8$ Hz, CHO). Preirradiation at δ 1.09 (1′-CH_3) led to enhancements at δ 1.8 (H2′β) of 3.5%, δ 2.86 (H7′) of 0.8%, and δ 9.78 (CHO) of 1.7%. Preirradiation at δ 2.86 (H7′) led to enhancements at δ 1.7 (unassigned) of 7.6%, δ 2.1 (unassigned) of 8.4%, and δ 4.5 (OH) of 3.5%. Preirradiation at δ 4.5 (OH) led to an enhancement at δ 2.85 (H7′) of 9.8%. ^{13}C NMR: δ 20.2 (CH_3), 24.6 (CH_2), 24.6 (CH or CH_3), 30.8 (CH_2), 32.5 (CH or CH_3), 35.9 (CH_2), 38.2 (CH_2), 39.5 (CH or CH_3), 52.8 (OCH_3), 53.7 (CH), 66.0 (C7a′), 80.8 (C1′), 130.3 (C=CH_2), 141.4 (*C*=CH_2), 170.7 [*C*(O)OCH_3], 206.6 (CHO). MS (EI) *m/z*: 280 (M, <1%), 262 (11), 204 (39), 190 (64), 177 (83), 131 (83), 43 (100). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.32; H, 8.37. Next, was eluted the ketoaldehyde as a colorless viscous oil (15.6 mg, 50%) and as an equimolar mixture of diastereomers, methyl [1′*R*,2′*R*,3′*S*,4′*R*]-2-[2′-formyl-4′-methyl-3′-(3″-oxobutyl)cyclohex-1′-yl]propenoate (**13a**) and methyl [1′*R*,2′*S*,3′*S*,4′*R*]-2-[2′-formyl-4′-methyl-3′-(3″-oxobutyl)cyclohex-1′-yl]propenoate (**13b**). These were partially separated by HPLC (ethyl acetate/petroleum ether, 22:78, Whatman Partisil 10 M20, **13a**: R_T 48 min, **13b**: R_T 52 min). IR ($CHCl_3$) for **13a**: 2931 (s), 2816 (w), 2718 (w), 1719 (vs, C=O, ketone, ester, aldehyde), 1627 (m), 1450 (s), 1282 (s), 1156 (s) cm^{-1}. IR ($CHCl_3$) for **13b**: 2931 (s), 2731 (w), 1719 (vs sh, C=O), 1710 (vs, C=O, ketone, ester, aldehyde), 1627 (m), 1440 (s), 1267 (s), 1165 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$) for **13a**: δ 0.96 (3H, d, $J_{Me,4'} = 6.3$ Hz, 4′-CH_3), 1.16−1.56 (5H, m), 1.76−1.92 (3H, m), 2.13 (3H, s, H4″), 2.32 (1H, ddd, $J = 11.4$, $J = 11.4$, $J = 4.8$ Hz), 2.32 (1H, ddd, $J_{2',1'} = 11.1$, $J_{2',3'} = 11.1$, $J_{2',CHO} = 5.4$ Hz, H2′), 2.47 (1H, ddd, $J = 16.8$, $J = 11.7$, $J = 5.1$ Hz), 2.85 (1H, ddd, $J_{1',2'} = 11.7$, $J_{1',6'\beta} = 11.7$, $J_{1',6'\alpha} = 3.5$ Hz, H1′), 3.74 (3H, s, OCH_3), 5.60 (1H, s, H3), 6.25 (1H, s, H3), 9.34 (1H, d, $J_{CHO,2'} = 5.6$ Hz, CHO). ^{1}H NMR ($CDCl_3$) for **13b**: δ 0.99 (3H, d, $J_{Me,4'} = 6.5$ Hz, 4′-CH_3), 1.2−1.4 (3H, m), 1.6−1.9 (3H, m), 1.975 (1H, dddd, $J = 13.2$, $J = 3.2$, $J = 3.2$, $J = 3.2$ Hz), 2.04 (1H, ddd, $J = 10.0$, $J = 10.0$, $J = 5.8$ Hz), 2.14 (3H, s, H4″), 2.3−2.4 (1H, m), 2.60 (1H, ddd, $J = 17$, $J = 10$, $J = 5$ Hz), 2.80 (1H, br ddd, $J_{1',6'\beta} = 12.7$, $J_{1',2'} = 4$, $J_{1',6'\alpha} = 4$ Hz, H1′), 2.86 (1H, dddd, $J = 4$, $J = 4$, $J = 4$, $J = 1.3$ Hz, H2′), 3.78 (3H, s, OCH_3), 5.54 (1H, dd, $J = 1.4$, $J = 0.6$ Hz, H3), 6.28 (1H, dd, $J = 0.6$, $J = 0.6$ Hz, H3), 9.79 (1H, d, $J_{CHO,2'} = 4.3$ Hz, CHO). ^{13}C NMR for **13a**: δ 20.5 (CH_3), 24.2 (CH_2), 30.8 (CH or CH_3), 32.8 (CH_2), 34.1 (CH), 35.8 (CH_2), 38.8 (CH_2), 40.8 (CH), 42.4 (CH), 52.9 (OCH_3), 58.6 (CH), 127.0 (C=CH_2), 142.8 (*C*=CH_2), 167.1 [*C*(O)OCH_3], 205.0 (CHO), 209.2 (C=O, ketone). ^{13}C NMR for **13b**: δ 20.5 (CH_3), 24.4 (CH_2), 26.4 (CH_2), 30.0 (CH or CH_3), 33.3 (CH), 35.7 (CH_2), 41.0 (CH_2), 41.1 (CH), 46.0 (CH), 51.0 (CH), 52.0 (OCH_3), 125.0 (C=CH_2), 141.8 (*C*=CH_2), 167.1 [*C*(O)-OCH_3], 206.1 (CHO), 208.6 (C=O, ketone). MS (mixture) (EI): *m/z*

280 (M, 0.5%), 279 (1), 262 (57), 149 (20), 93 (27), 43 (100). HRMS (mixture): *m/z* calcd for $C_{16}H_{24}O_4$ M^+ 280.1674, found M^+ 280.1676.

The aldol was obtained in higher yields by the use of the following method. The hydroperoxide (30.1 mg, 0.107 mmol) in CH_2Cl_2 (5 mL) was treated with a solution of TfOH (95 μL, 0.11 M in CH_2Cl_2, 0.1 equiv) at −25 °C for 5 min under nitrogen. The reaction was quenched with $NaHCO_3$ solution, and the resulting mixture was extracted into ether as described above. Flash chromatography (ether/petroleum ether, 25:75) afforded the aldol as a colorless solid (5 mg, 17%).

(b) Isolation of the Enol: Typical Procedure. The hydroperoxide **10** (69.7 mg, 0.25 mmol) was dissolved in MeCN (5 mL) and treated with a solution of $Fe(phen)_3(PF_6)_3$ (1.5 mL, 0.017 M in MeCN, 0.025 mmol) at −25 °C (bath) under a slow stream of nitrogen. After a 4 min delay the purple solution rapidly became red, at which point the reaction mixture was poured onto an ice-cold mixture of ether (30 mL) and saturated $NaHCO_3$ solution (20 mL). The mixture was shaken quickly, and the ether layer was separated and poured into a flask immersed in a cold bath (−25 °C). From this point onward the ether layer was kept at below −25 °C during all operations. The aqueous layer was extracted with more ice-cold ether (2 × 10 mL), and the combined ether extracts were washed once with cold water, cooled to −25 °C under nitrogen, and transferred via syringe and septum into a flask under nitrogen leaving residual aqueous solution behind as a frozen mass. The ether solution was dried (Na_2SO_4) and transferred one more time to another dry flask equipped with a magnetic stirrer bar and stirrer, and connected to a vacuum manifold, and cooled to between −40 and −30 °C. The solvent was removed under high vacuum (0.01 mmHg) and condensed consecutively into two parallel traps cooled with liquid nitrogen. This generally took 40−50 min. The residue was dissolved in cold ether/pentane (50:50, 3 mL) and applied via syringe to a jacketed column (flash silica, 16 × 1.8 cm i.d.) precooled with ethanol (held at −40 °C and circulated by means of a peristaltic pump to maintain an effluent temperature of *ca.* −20 °C) and maintained under a flow of nitrogen. Fractions were eluted with ether/pentane (50:50) and collected in stoppered test tubes which were stored in a cold bath at −40 °C. The relevant fractions were combined in a flask under argon, and the solvent was removed under vacuum as above. The residue, under argon, was dissolved in CD_2Cl_2 and transferred to an NMR tube via syringe and septum. A spectrum was run at 230 K immediately.

The first-formed enol, methyl [2′*S*,5′*R*,6′*S*]-(*E*)-[1′-(hydroxymethylenyl)-5′-methyl-6′-(3″-oxobutyl)cyclohex-2′-yl]propenoate (**16a**), provided the following data. ^{1}H NMR (400 MHz, CD_2Cl_2, 230 K): δ 0.86 (3H, d, J = 7.0 Hz, 5′-CH_3), 2.12 (3H, s, H4″), 2.43 (1H, ddd, J = 15.3, J = 7.3, J = 4.4 Hz), 3.10 (1H, br d, J = 4 Hz, $W_{h/2}$ = 10.4 Hz, H2′), 3.62 (3H, s, OCH_3), 5.54 (1H, J = 2 Hz, H3), 5.79 (1H, d, J = 1.7 Hz, H3), 6.33 (1H, d, J = 10.3 Hz, enol-H), 6.84 (1H, d, J = 10.3 Hz, OH). Preirradiation at 3.1 ppm (H2′) led to enhancement at 6.3 ppm (enol-H, 10%). Preirradiation at 6.8 ppm (OH) led to enhancement at 2.2 ppm (unassigned, 23%). ^{13}C NMR (CD_2Cl_2, 230 K): δ 19.7, 22.3, 23.7, 28.6, 30.1, 30.7, 32.7, 37.3, 40.5, 52.1 (OCH_3), 110.2 (β-enolic), 120.8 (C=CH_2), 142.6 (*C*=CH_2), 146.3 (α-enolic), 169.0 [*C*(O)OCH_3], 214.4 (*C*=O, ketone).

The more stable enol, methyl [2′*S*,5′*R*,6′*S*]-(*Z*)-[1′-(hydroxymethylene)-5′-methyl-6′-(3″-oxobutyl)cyclohex-2′-yl]propenoate (**16b**), predominated after several hours. ^{1}H NMR (400 MHz, CD_2Cl_2, 230 K): δ 0.88 (3H, d, J = 7.2 Hz, 5′-CH_3), 1.98 (3H, s, H4″), 3.54 (1H, br d, J = 5.6 Hz, $W_{h/2}$ = 10.3 Hz, H2′), 3.72 (3H, s, OCH_3), 5.87 (1H, d, J = 2 Hz, H3), 5.94 (1H, d, J = 10.2 Hz, enol-H), 6.15 (1H, d, J = 1.5 Hz, H3), 7.28 (1H, d, J = 10.2 Hz, OH). Preirradiation at 7.3 ppm led to enhancement at 3.5 ppm (H2′, 15.7%). Preirradiation at 5.9 (enol-H) led to enhancement at 1.5 ppm (unassigned, 8.8%). ^{13}C NMR (CD_2Cl_2, 230 K): δ 19.1, 21.8, 23.6, 27.7, 30.2, 32.0, 33.7, 42.3, 45.4, 53.2 (OCH_3), 112.2 (β-enolic), 124.6 (C=CH_2), 140.1 (*C*=CH_2), 143.2 (α-enolic), 171.1 [*C*(O)OCH_3], 210.0 (*C*=O, ketone).

Reaction of the Enol with $Cu(OTf)_2$ in the Presence of O_2. The enol was prepared from the hydroperoxide **10** (38.2 mg, 0.136 mmol) as above and dissolved in MeCN (6 mL) at −35 °C under nitrogen. The solution was maintained under these conditions for 2 h, and when no decomposition was observed, it was divided into two. The two solutions were held at −20 °C, and then O_2 was introduced as a slow stream for 2 min before treating one solution with $Cu(OTf)_2$ (0.16 mL, 6.8 μmol, 0.1 M in MeCN). After 40 min, complete conversion to the oxygenation products was detected by TLC, while in the uncatalyzed reaction, no oxygenation took place with only the enol and some ketoaldehyde being detected. The $Cu(OTf)_2$ reaction was quenched by pouring onto saturated $NaHCO_3$ solution and extracting with ether. The combined extracts were washed with brine and dried (Na_2SO_4), and the solvent was removed by evaporation. ^{1}H NMR spectroscopic analysis of the crude product mixture showed the presence of hydroperoxide **11**, peroxy hemiacetal **12**, and the peroxide **17** as the major products in a ratio of 7:70:23.

Isolation of Byproduct 17. The byproduct from the cleavage oxygenation of the hydroperoxide **10** was isolated by flash chromatography (ethyl acetate/light petroleum, 35:65) and had the following characteristics. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.91 (3H, d, J = 6.4 Hz), 0.95−1.94 (9H, m), 2.14 (3H, s), 2.40−2.70 (2H, m), 3.74 (3H, s, OCH_3), 4.35 (1H, d, J = 13.0 Hz), 4.77 (1H, d, J = 13.0 Hz), 8.65 (1H, br s, $W_{h/2}$ = 4 Hz, OOH), 9.92 (1H, s, CHO). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.1, 20.4, 21.3, 33.0, 34.6, 43.5, 48.5, 50.6, 52.3, 81.3, 88.7, 204.3 (CHO), 208.0 (C=O, ketone). Quaternary signals due to the ester carbonyl and an additional OO−*C*−C=O did not appear due to insufficient sample.

Low-Temperature NMR Experiment: Reaction of the Hydroperoxide 10 with TfOH. A basic ^{1}H NMR spectrum of the hydroperoxide **10** (30.1 mg, 0.108 mmol) in CD_2Cl_2 (0.6 mL) was acquired at 180 K under a nitrogen atmosphere. TfOH [0.1 mL from a solution obtained from TfOH (0.1 mL) in CD_2Cl_2 (0.3 mL), *ca.* 2.6 equiv] was added into the NMR tube at 180 K. The tube was shaken quickly and a ^{1}H NMR spectrum obtained. Additional spectra were obtained as the temperature of the probe was increased by 5−10 K increments to 300 K. The results are shown in Figure 1. The same result was also achieved when 0.01 equiv of triflic acid was used to catalyze the reaction.

Catalyzed Reactions of the Hydroperoxide 10 in the Presence of O_2: General Procedure. A solution of the hydroperoxide **10** (0.1−0.2 mmol, *ca.* 0.02 M in MeCN or CH_2Cl_2) was cooled to the designated temperature (see Table 2) under a slow stream of O_2 and treated with a solution of the catalyst. The reactions were monitored by TLC (ether/light petroleum, 50:50). After stirring under the designated conditions with regard to temperature and time, the reaction mixture was poured into saturated $NaHCO_3$ solution and extracted with ether. The combined extracts were washed with brine and dried (Na_2SO_4), and the solvent was removed by evaporation. To the residue was then added trinitrobenzene (0.2−0.8 mmol), and the whole was redissolved in ether. The solution was evaporated in a pear-shaped flask, and then the residue was quantitatively dissolved in $CDCl_3$ (0.5 mL) and analyzed by ^{1}H NMR spectroscopy (200 MHz). The following diagnostic peaks were integrated against the peak for 1,3,5-trinitrobenzene at δ 9.4 (3H): hydroperoxide **11** (δ 10.39, OOH); peroxy hemiacetal **12** (δ 9.60, d, CHO); ketoaldehyde **13b** (δ 9.78, d, CHO; 6.27, s, H3); ketoaldehyde **13a** (δ 9.33, d, CHO; 6.24, s, H3); aldol **14** (δ 9.77, s, CHO; 6.05, s, H3); peroxide **17** (δ 9.91, br s, CHO).

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Supporting Information Available: Full-width ^{1}H NMR spectra (400 MHz) of ketoaldehydes **13a,b** in CD_2Cl_2 at 250 and 300 K, aldol **14** in CD_2Cl_2 at 250 K, enol **16a** derived from TfOH in CD_2Cl_2 at 230 K with isolated enol **16a** in CD_2Cl_2 at 230 K, enols **16a,b** *ca.* 1 h after isolation in CD_2Cl_2 at 230 K, enol **16b** *ca.* 20 h after isolation in CD_2Cl_2 at 230 K, hydroperoxide **11** and peroxy hemiacetal **12** in $CDCl_3$, and the product mixture resulting from treatment of isolated enol **16** with $Cu(OTf)_2$ and O_2 at −20 °C (200 MHz) (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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