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A Hydrogen Peroxide Based Access to Qinghaosu (Artemisinin)

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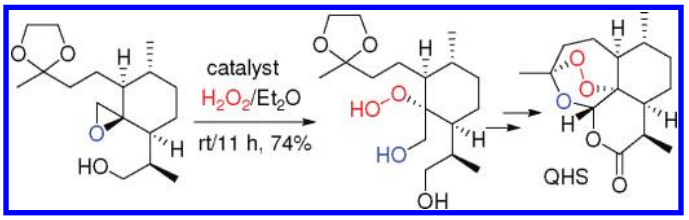
ABSTRACT



Attachment of H_2O_2 onto the highly hindered quaternary C-12a in an advanced qinghaosu (artemisinin) precursor has been achieved through a facile perhydrolysis of a spiro epoxy ring with the aid of a previously unknown molybdenum species without involving any special equipment or complicated operations. The resultant β-hydroxyhydroperoxide can be further elaborated into qinghaosu, illustrating an entry fundamentally different from the existing ones to this outstanding natural product of great importance in malaria chemotherapy.

Qinghaosu (QHS, artemisinin, **1**) is a sesquiterpene endoperoxide discovered by Chinese scientists in the early 1970s (Figure 1).[1] Its structure is completely different from that of traditional antimalarials and shows high potency in the treatment of even multidrug resistant cases. These unique features attracted enormous attention from scientific communities worldwide soon after the introduction to the Western countries by Klayman[1c] in 1985. Now, the ACTs (Artemisinin-based Combination Therapies) have been recommended by the World Health Organization (WHO) as first-line drugs to battle malaria.

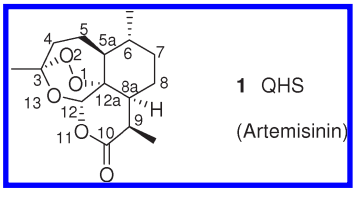


Figure 1. Strucure of qinghaosu (artemisinin).

To date, all the QHS used in the ACTs is extracted from a Chinese herb qinghao (wormwood plant, *Artemisia annua*) growing in Southern China and Vietnam; the same herb that grows in the northern areas does not produce QHS. And the content of QHS in the herb is rather low. Even with the high-yielding new *Artemesia* strains, one kilogram of dried qinghao leaves can produce, on average, only ~8 g of QHS.[2] The limited natural supply along with the academic interest stimulated by the unique structure of QHS has prompted many elegant studies[3−5] on its chemical synthesis.

Although the molecular architecture of QHS is not so pretentious among natural products that have already been synthesized, its synthesis does represent a lasting challenge over the years. This is because installation of the peroxy functionality requires stereoselective attachment of a peroxyl/hydroperoxyl group to the sterically highly congested C-12a position (QHS numbering). Despite the enormous efforts[3−5] by the investigators around

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(2) Van Noorden, R. *Nature* **2010**, *466*, 672–673.

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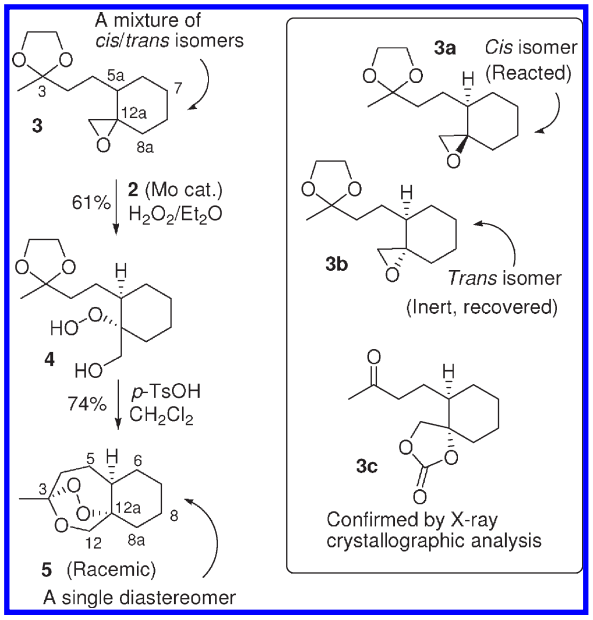
the world over the years, to date it remains impossible to realize this transformation without recourse to singlet oxygen, ozone (only one case), or $Et_3SiOOOH$[5c,6] (short-lived species generated *in situ* from Et_3SiH and ozone, for simplified QHS analogues so far). As all the reactions before and after this step only involve chemistries rather commonly employed in synthesis and potential alternatives often exist, it is no exaggeration that, in fact, the real challenge in the synthesis of QHS is the incorporation of a hydroperoxyl group onto the C-12a in a "fully" substituted precursor (i.e., making the O-1/C-12a σ bond).

Hydrogen peroxide (H_2O_2) is an apparently exploitable source for peroxy bonds, and it has been employed[7−10] in the synthesis of relatively simple/less hindered organic peroxides, with the initial bonding of H_2O_2 to a carbon framework most commonly via perketal[7] formation or alkylation by a carbocation generated *in situ* from hydrozines[8] or alkenes,[9] or a ring-opening reaction of epoxides[10] (oxiranes) or oxetanes.[11] However, because of the large structural difference between those peroxides derived from H_2O_2 and QHS, along with the apparent limitations of existing protocols, up to now synthesis of QHS using H_2O_2 has been a "mission impossible"; even the incorporation of H_2O_2 onto a cyclohexane-related substrate that is structurally complex enough to serve as an advanced precursor for QHS has never been achieved to date.

Scheme 1. Informative Model Reactions



During our study on synthesis of organic peroxides using H_2O_2 as the source of peroxy bonds, we observed that a molybdenum species (**2**[12]) prepared from Na_2MoO_4 and glycine could effectively catalyze the perhydrolysis of the epoxy ring in, for instance, compound **3** (a mixture of the *cis*/*trans* isomers) but did not affect the ketal functionality in the side chain to any significant extent (Scheme 1). And the resultant β-hydroxyhydroperoxide **4** could be readily converted to the corresponding trioxane **5**[13] by treatment with an acid. As never before had a trioxane so closely related to QHS been accessed so easily, this result naturally inspired us to envisage that the long-standing problem of attaching a hydroperoxyl group to the C-12a in the QHS framework might be solved just as well in a similar manner.

(3) Total synthesis of QHS: (a) Schimid, G.; Hofheinz, W. *J. Am. Chem. Soc.* **1983**, *105*, 624–625. (b) Xu, X. X.; Zhu, J.; Huang, D. Z.; Zhou, W. S. *Tetrahedron* **1986**, *42*, 819–828. (c) Avery, M. A.; Chong, W. K. M.; White, C. J. *J. Am. Chem. Soc.* **1992**, *114*, 974–979. (d) Avery, M. A.; White, C. J.; Chong, W. K. M. *Tetrahedron Lett.* **1987**, *28*, 4629–4632. (e) Liu, H. J.; Yeh, W. L.; Chew, S. Y. *Tetrahedron Lett.* **1993**, *34*, 4435–4438. (f) Constantino, M. G.; Beltrame, M., Jr.; da Silva, G. V. J. *Synth. Commun.* **1996**, *26*, 321–329. (g) Yadav, J. S.; Babu, R. S.; Sabitha, G. *Tetrahedron Lett.* **2003**, *44*, 387–389. (h) Yadav, J. S.; Thirupathaiah, B.; Srihari, P. *Tetrahedron* **2010**, *66*, 2005–2009. For a review, see: (i) Zhou, W.-S.; Xu, X.-X. *Acc. Chem. Res.* **1994**, *27*, 211–216.

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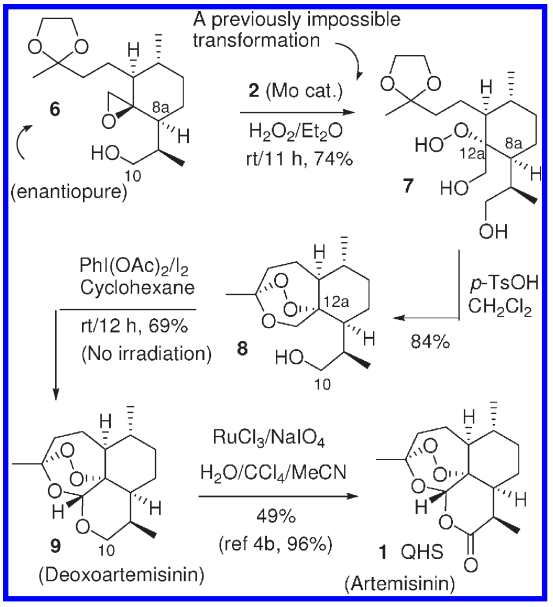
Before proceeding further with a more complicated substrate, we next looked into the model reaction further for stereochemical knowledge—should the relative configuration of the epoxy ring make no difference in the perhydrolysis, it might be possible to use a mixture of the C-12a epimers in the synthesis of QHS; the precursor could be much easier to prepare. Then, we noticed that the reaction with a mixture of **3a** and **3b** could never have gone to completion and the recovered **3** contained only one diastereomer as shown by ^{1}H NMR, which was later assigned as **3b** on the basis of its configurational relation to **3c**.[14]

A separate run with pure **3b** also confirmed its practical inertness to the same perhydrolysis conditions. All of these observations taken together suggested that the perhydrolysis took place with a distinct facial preference and the attack of H_2O_2 occurred from the backside of the epoxy ring with an inversion of the configuration at the C-12a (QHS numbering). In light of these observations, compound **6** was selected for further studies.

Scheme 2. H_2O_2-Based Access to QHS



The results with epoxide **6** was rather pleasing. Despite the significantly increased steric crowding (compared with **3**) caused by the extra bulky substituent at the C-8a in epoxide **6**, the long-sought-after β-hydroxyhydroperoxide **7** still formed smoothly as anticipated (Scheme 2). And further exposure of **7** to *p*-TsOH in CH_2Cl_2 resulted in a facile intramolecular ketal exchange reaction, affording the trioxane **8**[15] in 84% yield. These two steps could be also completed in comparable overall yields without isolation/purification of the intermediate hydroperoxide **7** (like **4**, also not very stable).

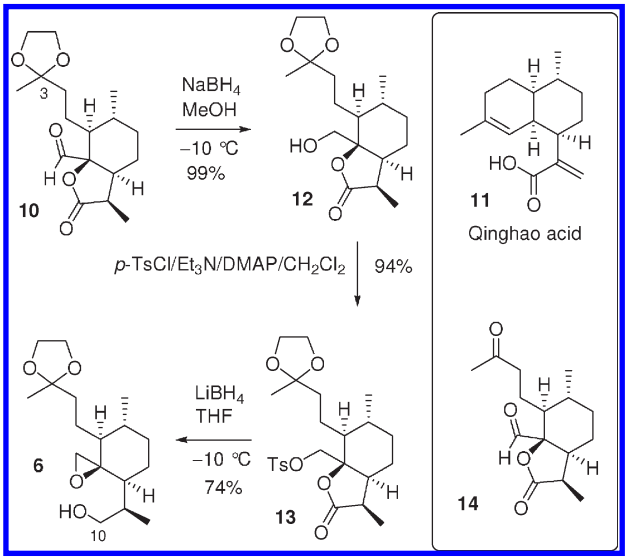
Up to this point, it has been experimentally proven that installation of a hydroperoxyl group onto the C-12a position in a fully equipped substrate, a tricky/critical step in the synthesis of QHS that previously could be completed only using singlet oxygen (or its like) with difficulty, indeed can be realized under the conditions readily attainable in any ordinary synthetic laboratories if a proper catalyst is employed, although the trioxane **8** is still one ring less compared with QHS.

Construction of the last ring was achieved under the $PhI(OAc)_2/I_2$[16a] conditions, which in the beginning was developed for oxidation of ethereal methine carbons in the synthesis of some steroidal spiroketals. Although no mechanistic information on this reaction is available in the literature, this cyclization appears to be mediated by radicals. Over the past 20 years, it has found applications in the synthesis of a range of different natural products[16b] (but not related to QHS).

It is interesting to note that, in the original procedure and most subsequent applications, use of a tungsten lamp was reported. However, in the present case lamp irradiation did not seem necessary. Under ordinary laboratory lighting conditions, the cyclization took place smoothly by stirring the mixture at ambient temperature, providing the desired product **9** (deoxoQHS, deoxoartemisinin, also a known[5d,f] potent antimalarial) in 69% yield.

It may be noteworthy here that such a strategy, i.e. using a substrate with a nonfunctionalized C-10 CH_2 to construct this final ring in the QHS framework, has never been explored before. Finally, **9** was smoothly converted to QHS **1** using the literature[4b] conditions ($RuCl_3/NaIO_4$).

Scheme 3. One of the Possible Routes to Epoxide **6**



The epoxide **6** can be accessed from, among other possible alternatives, the known[4e] aldehyde **10** (Scheme 3, with

(11) Dussault, P. H.; Trullinger, T. K.; Noor-e-Ain, F. *Org. Lett.* **2002**, *4*, 4591–4593.

(12) A white powder (mp >200 °C) insoluble in water and many common organic solvents (such as acetone, $CHCl_3$, CH_3CN, THF, Et_2O, DMSO, DMF), with the elemental analysis data (C, H, N, Mo) fit to the formula of $HO_2CCH_2NH_2 \cdot HOMo(O_2)OMo(O_3) \cdot 2H_2O$. Cf. also the Supporting Information.

(13) For an optically active C-6 Me analogue (prepared using ozone to introduce the peroxy band), see ref 5g.

the relative configuration secured by X-ray crystallographic analysis of the corresponding ketone **14**), which in turn is readily attainable[4e] from qinghao acid (artemisinic/arteanuic acid, **11**, which was also the common starting material for all those singlet oxygen based semisyntheses[4]), a natural product present[17] in the herb qinghao in significantly higher contents than QHS and now also accessible[18] by fermentation.[19]

In summary, with the aid of a novel yet readily prepared molybdenum species, perhydrolysis of a highly hindered epoxide specially designed for the synthesis of QHS has been realized in a stereoselective manner with remarkable ease. Such a facile installation of a hydroperoxyl functionality onto the C-12a position of the precursor makes it possible for the first time to construct QHS without recourse to singlet oxygen (or the like) and thus introduces a brand-new approach to the synthesis of this important natural antimalarial agent. Although the present route by no means is perfect already, the simplicity (i.e., no needs for special equipments and/or facilities and complicated operations), facileness, and reproducibility associated with the key perhydrolysis should provide a useful complement to the existing methodologies for introducing the peroxy functionality in QHS and hopefully may facilitate the eventual appearance of a large-scale practical synthesis of QHS. Finally, the knowledge gained from this work may help to develop a range of trioxanes simpler than but still closely related to QHS as potential antimalarials.

Acknowledgment. This work was supported by the National Basic Research Program of China (the 973 Program, 2010CB833200), the National Natural Science Foundation of China (21032002, 20921091, 20672129, 20621062, 20772143), and the Chinese Academy of Sciences (KJCX2. YW.H08).

Supporting Information Available. Experimental procedures and spectral data, ^{1}H and ^{13}C NMR spectra for **6**, **7**, **8**, **9**, **10**, **12**, **13**, and **1**, cif files for **3c** and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) The crystallographic data have been deposited to the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, U. K.; e-mail: deposit@ccdc.cam.ac.uk, with the identifying number for ketone **3c** and **14** (the ketone related to ketal **10**) being CCDC 823527 and CCDC 823526, respectively. The ORTEP plots are given in the Supporting Information.

(15) This compound has been obtained previously by sequential treatment with BF_3-Et_2O/MeOH/PhH/reflux/6 h (methanolysis), $LiAlH_4$/ Et_2O/0 °C/1 h (reduction of aldehyde and ester groups) and BF_3-Et_2O/CH_2Cl_2/0 °C/24 h (ketalization). See: Singh, C.; Chaudhary, S.; Kanchan, R.; Puri, S. K. *Org. Lett.* **2007**, *9*, 4327–4329.

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(17) The herb qinghao that grows in the northern areas also contains **11**.

(18) (a) Martin, V. J. J.; Pitera, D. J.; Withers, S. T.; Newman, J. D.; Keasling, J. D. *Nat. Biotechnol.* **2003**, *21*, 796–802. (b) Ro, D.-K.; Paradise, E. M.; Ouellet, M.; Fisher, K. J.; Newman, K. L.; Ndungu, J. M.; Ho, K. A.; Eachus1, R. A.; Ham, T. S.; Kirby, J.; Chang, M. C. Y.; Withers, S. T.; Shiba, Y.; Sarpong, R.; Keasling, J. D. *Nature* **2006**, *440*, 940–943.

(19) It should be mentioned that the route in Scheme 3 is only meant to show a possible access to this perhydrolysis substrate.