AN ANTIMALARIALLY ACTIVE CYCLIC PEROXY KETAL[1]

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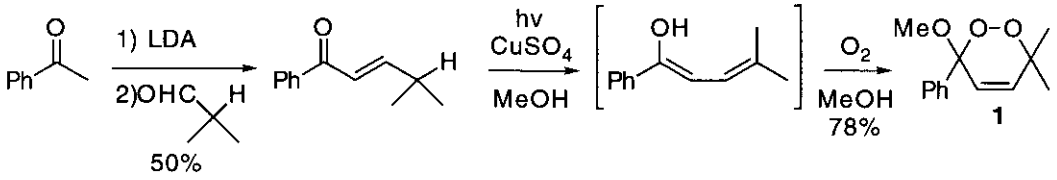
Abstract - Cyclic peroxy ketal (**1**), prepared using the Snider photoenolization-oxygenation procedure, has been found to have measurable antimalarial activity. Upon reaction with ferrous ions, peroxide (**1**) is converted mainly into hydroxylated epoxy ketone (**6**), and a mechanism involving several intermediates including a high-valent iron-oxo species is proposed to account for this chemical transformation.

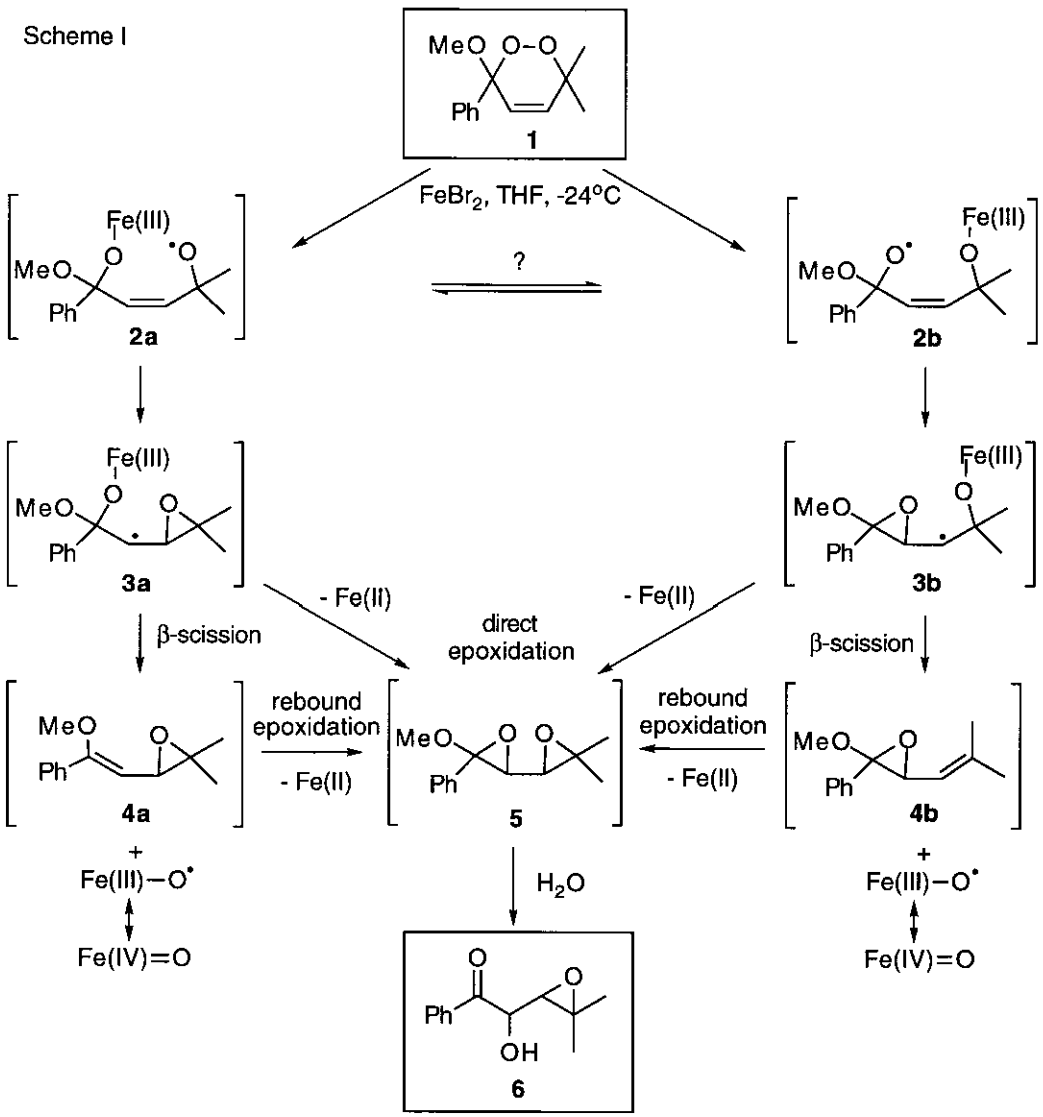
Approximately 300 million people worldwide currently suffer from malaria, and each year 1-2 million, mostly children, die from this infectious disease.[2,3] Although quinolines like quinine and chloroquine and mefloquine have been successful in curing individuals having malaria,[4,5] the culprit *Plasmodium falciparum* malaria parasites are now rapidly developing multidrug resistance to such drugs.[2] Ancient Chinese folk medicine has led organic chemists recently to isolate and to identify a non-alkaloidal, sesquiterpene, 1,2,4-trioxane lactone (artemisinin, qinghaosu) that itself, and especially as its lactol ether semi-synthetic derivatives (*e.g.* artemether, sodium artesunate), has rapidly cured over 1 million malaria patients.[6] The essential pharmacophore in these trioxanes is the endoperoxide functionality that is reduced by ferrous ions inside the malaria parasite to form several intermediates that may be cytotoxic: carbon-centered free radicals, potent alkylating epoxides, and reactive oxidizing species such as high-valent iron-oxo entities.[3] Using our current understanding of the chemical molecular mechanism by which these endo-peroxides are triggered by ferrous ions to kill the malaria parasites, we have designed some mechanism-based but structurally simplified endo-peroxides that have high *in vitro* antimalarial activities.[7] In continuation of this search for new antimalarial peroxides, we report here synthesis and ferrous ion reduction of new heterocyclic peroxy ketal (**1**).

The Snider photoenolization and oxygenation protocol[8-10] allowed easy preparation of cyclic peroxide (**1**) as shown in eq. 1.[11] Preliminary *in vitro* testing showed this structurally simple cyclic peroxide (**1**) to have measurable antimalarial activity against *Plasmodium falciparum* parasites. In order to understand the chemical mechanism by which **1** might kill malaria parasites, it was subjected to ferrous ion reduction,[2,3] leading mainly to unstable hydroxylated epoxy ketone (**6**) that was isolated in 50% yield; Scheme I is proposed to account in a reasonable fashion for formation of this epoxy ketone (**6**).



(1)

Scheme I

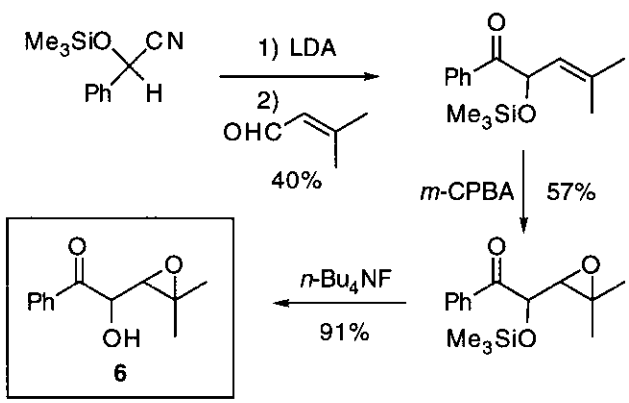


In Scheme I, ferrous ion reduction can proceed with iron associated with either of the cyclic peroxide oxygen atoms, leading to either or both oxygen-centered radicals (**2a**) and/or (**2b**). These oxy-radicals then can cyclize to form the corresponding epoxy carbon-centered radicals (**3a**) and (**3b**). β-Scission of a

high-valent iron-oxo species, forming olefins (**4a**) and/or (**4b**), and then intermolecular rebound epoxidation could produce diepoxide (**5**); also diepoxide (**5**) might be formed *via* direct intramolecular epoxidation from epoxy radicals (**3**). Quenching the reaction mixture with water would then rapidly hydrolyze methoxy epoxide (**5**) into the observed major product hydroxy ketone (**6**), isolated as only one stereoisomer.

To confirm the structure of hydroxylated epoxy ketone (**6**), it was prepared independently as shown in Scheme II. Although its precursor silyl ether is stable,[11] the epoxy ketone (**6**) decomposed on standing at room temperature. Although Scheme II allows generation of two stereoisomers of epoxy ketone (**6**), only one of these diastereomers corresponds to epoxy ketone (**6**) formed in Scheme I by ferrous ion reduction of cyclic peroxide (**1**).

Scheme II



To test for the intermediacy of a high-valent iron-oxo species, generated as shown in Scheme I, ferrous bromide reduction of cyclic peroxide (**1**) was performed in THF at 0 °C in the presence of hexamethyl Dewar benzene (HMDB); about 25% rearrangement of HMDB into hexamethylbenzene occurred.[12] A control reaction under the same reaction conditions but using the trioxane artemisinin in place of cyclic peroxide (**1**) produced hexamethylbenzene in 45-50% yields, and a separate control reaction showed that ferrous bromide itself does not cause rearrangement of HMDB. Thus, it seems likely that at least some of diepoxide (**5**) in Scheme I is formed *via* a rebound epoxidation and that a high-valent reactive iron-oxo species may be involved in the mechanism by which peroxide (**1**) kills malaria parasites.[3,12]

Various structural analogs of cyclic peroxide (**1**) are now being prepared to study the relationship between their chemical structure and antimalarial activity; results of this SAR study as well as complete antimalarial testing results will be reported in a full paper in due course.

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REFERENCES AND NOTES

1. This publication is dedicated to Professor Koji Nakanishi with admiration and respect on the occasion of his 75th birthday.
2. S.R. Meshnick, T.E. Taylor, and S. Kamchonwongpaisan, *Microbiol. Rev.*, **1996**, *60*, 301.
3. J.N. Cumming, P. Ploypradith, and G.H. Posner, *Adv. Pharmacol.*, **1997**, *37*, 253.
4. T.R. Sweeney, *Med. Res. Rev.*, **1981**, *1*, 281.
5 R.S. Goldsmith in *Basic and Clinical Pharmacology*, 5th ed. B.G. Katzung, Ed., Appleton and Lange, Norwalk, CT, 1992, p. 735.
6. W.-S. Zhou and X.X. Xu, *Acc. Chem. Res.*, **1994**, *27*, 211.
7. G.H. Posner, D. Wang, L. Gonzalez, X. Tao, J.N. Cumming, D. Klinedinst, and T.A. Shapiro, *Tetrahedron Lett.*, **1996**, *37*, 7225.
8. B.B. Snider and Z. Shi, *J. Am. Chem. Soc.*, **1992**, *114*, 1790. See also B.B. Snider, Z. Shi, S.V. O'Neill, K.K. Kreuter, and T. Arakaki, *J. Org. Chem.*, **1994**, *59*, 1726.
9. For synthesis of cyclic peroxy hemiketals see: a) C.-Y. Qian, T. Yamada, H. Nishino, and K. Kurosawa, *Bull. Chem. Soc. Japan*, **1992**, *65*, 1371; b) C.-Y. Qian, H. Nishino, K. Kurosawa, and J.D. Korp, *J. Org. Chem.*, **1993**, *58*, 4448; c) P.H. Dussault and K.R. Woller, *J. Am. Chem. Soc.*, **1997**, *119*, 3824.
10. For a naturally occurring cyclic peroxy hemiketal, see W.-Y. Tsui and G.D. Brown, *Tetrahedron*, **1996**, *52*, 9735.
11. Characterization of new compounds was achieved spectroscopically and by high resolution mass spectroscopy.
12. G.H. Posner, J.N. Cumming, P. Ploypradith, and C.H. Oh, *J. Am. Chem. Soc.*, **1995**, *117*, 5885.

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