

AN ANTIMALARIALY ACTIVE CYCLIC PEROXY KETAL¹

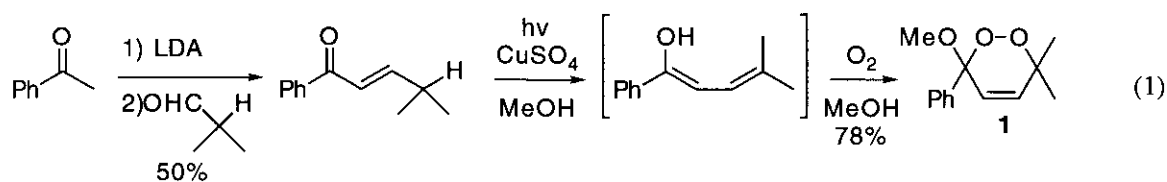
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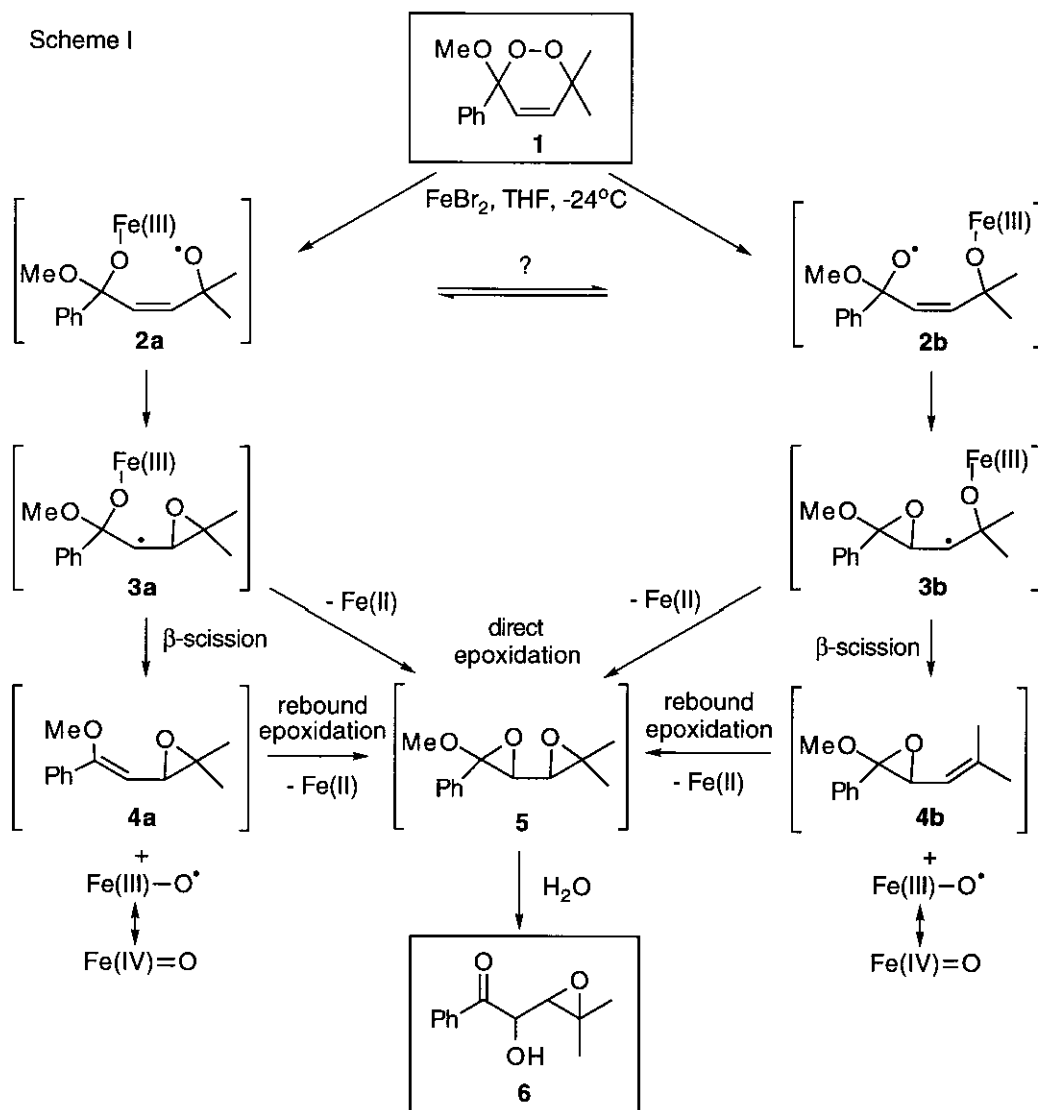
Abstract - Cyclic peroxy ketal (1), prepared using the Snider photoenolization-oxygenation procedure, has been found to have measurable antimalarial activity. Upon reaction with ferrous ions, peroxide (1) is converted mainly into hydroxylated epoxy ketone (6), and a mechanism involving several intermediates 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 protocol⁸⁻¹⁰ 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).



Scheme I

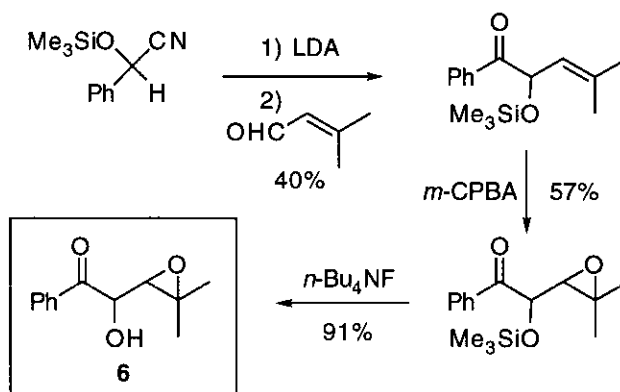


In Scheme I, ferrous ion reduction can proceed with iron associated with either of the cyclic peroxide oxygen atoms, leading to either or both oxygen-centered radicals (**2a**) and/or (**2b**). These oxy-radicals then can cyclize to form the corresponding epoxy carbon-centered radicals (**3a**) and (**3b**).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

ACKNOWLEDGMENT

We thank the NIH (AI 34885) for financial support and Professor Terry Shapiro, Dr. Donna Klinedinst, and Mr. Jared Cumming for preliminary *in vitro* antimalarial testing of peroxide (**1**) at Hopkins.

REFERENCES AND NOTES

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Received, 6th May, 1997