Synthesis and Reactions of Antimalarial Bicyclic Peroxides

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Introduction.

A promising approach for treating malaria caused by parasites resistant to chloroquine and other quinine-related drugs is based on the development of antimalarial compounds containing an endoperoxide function in their molecular backbone [1-7]. Artemisinin (**1**), semisynthetic derivatives thereof, structurally related trioxanes of type **2**, as well as simpler trioxanes were found to exhibit potent antimalarial activity. Some of these compounds have been used as drugs in China, South East Asia, and Africa, for treatment of malaria caused by multi-drug resistant parasites. However, adverse pharmacological and clinical properties are motivating the search for other endoperoxides that may act as better drugs. A structurally simpler endoperoxide, yingzhaosu A (**3**), was isolated from an antimalarial traditional Chinese medicine and was subsequently obtained by total synthesis [8,9]. Apparently yingzhaosu A was obtained in minute amounts only, and no significant report on its antimalarial activity is available. However, the synthesis and anti-malarial screening of structurally related 7-oxo-2,3-dioxa-bicyclo[3.3.1]nonanes of type **4** was reported [10,11]. Although some compounds of type **4** exhibit potent anti-malarial activity, and clinical trials with arteflene (**4a**) are highly encouraging [12,13], their long and tedious synthesis does not seem suitable for large scale preparation.

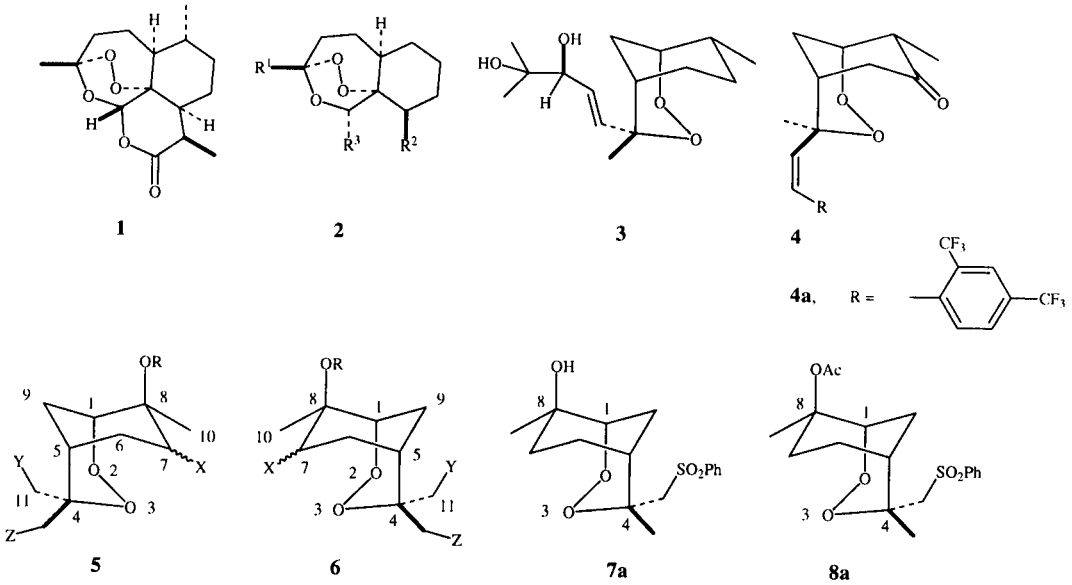
It is widely accepted that the parasiticidal activity of antimalarial peroxides like artemisinin and related compounds **1**, **2** (Scheme 1) is triggered by protein-free iron released by the parasite through digestion of hemoglobin. An initial Fenton-type reaction of iron(II) with the endoperoxide function, generating an oxygen-centered radical, is probably common to all peroxides. However, the nature of the reactive species which are directly responsible for killing the parasites may depend on the structure of the particular endoperoxidic compound [5,14-19]. For example, reactive species generated by iron-induced degradation of trioxanes **1**, **2** are bound to be different from those generated in the degradation of bicycloperoxides **3**, **4**. Studies on the iron(II) induced degradation of antimalarial endoperoxides having different structures, may contribute to the clarification of the still fragmentary picture of the mode of action of these compounds.

In the present paper we describe an efficient synthesis of antimalarial endoperoxide-sulfones of type **5** and **6** [20-22], a new synthesis of yingzhaosu A (**3**), and reactions of endoperoxides **7a** and **8a** with iron(II) salts.

Synthesis of Antimalarial Endoperoxide-Sulphones.

Target compounds of general structure **5** and **6** were designed. In these compounds either Y or Z represents an alkyl- or arylsulfonyl group, R represents a hydrogen atom, an alkyl, or acyl group, and X represents a hydro-

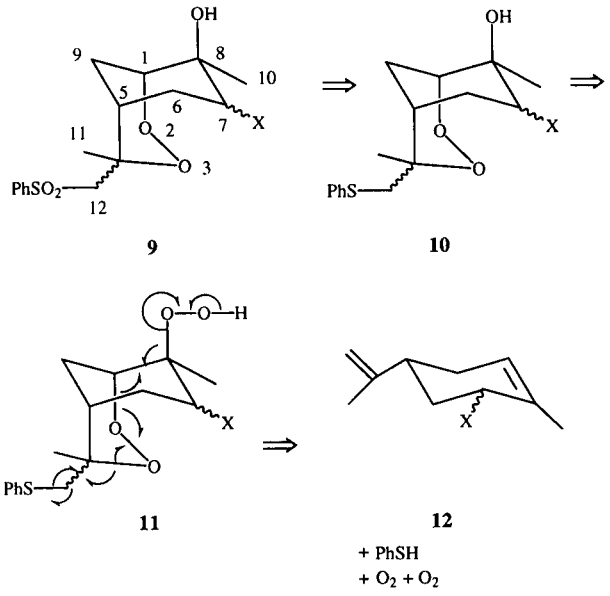
Scheme I



gen atom, an alkyl, or acyl group [20-22]. Such an array of substituents offers much flexibility in structural modification needed in structure activity studies.

A partial retrosynthetic analysis of compounds **9** leads to a monoterpene **12**, benzenethiol, and two equivalents of oxygen (Scheme 2). We found that these four components

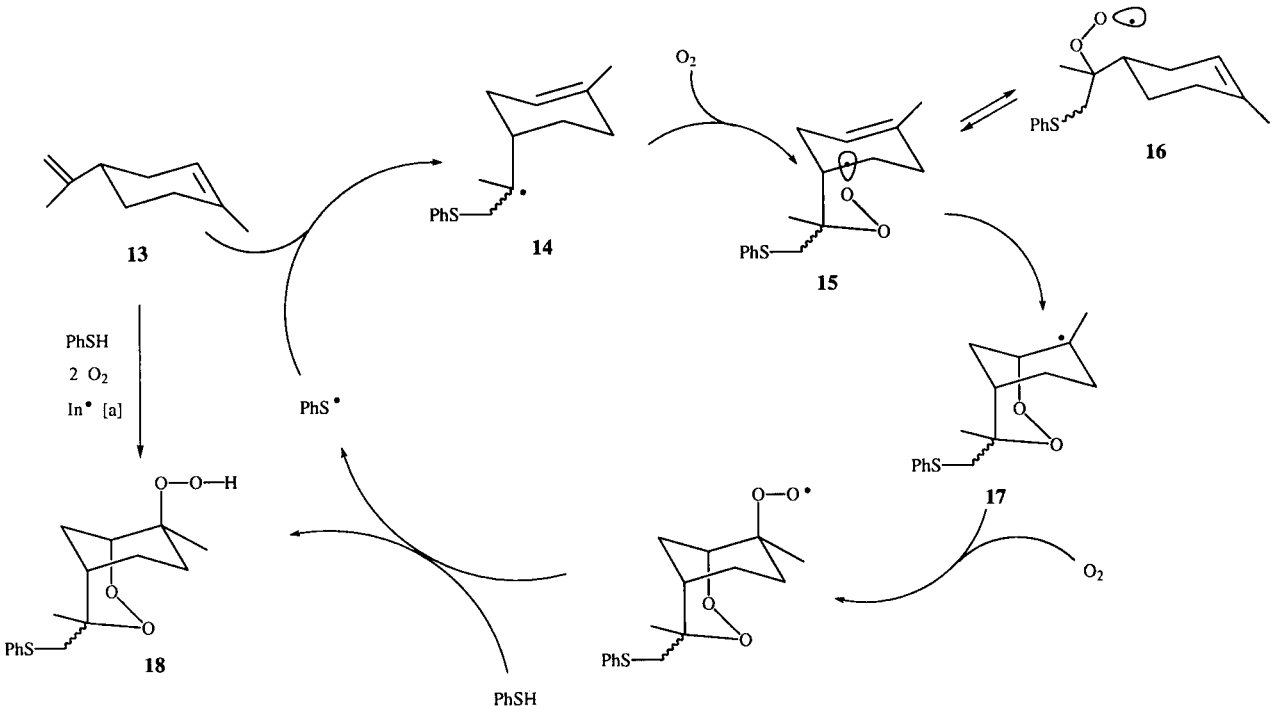
Scheme 2



can be induced to react through thiol-oxygen co-oxidation to give a hydroperoxide-endoperoxide **11**. This one operation process is based on a sequential free radical reaction whose mechanism is shown in Scheme 3 for the case of (*S*)-(−)-limonene (**13**). Despite potential pitfalls that may derive from competing reactions of intermediate radicals **14-17**, an efficient protocol for the synthesis of hydroperoxide-endoperoxide **18** was developed [20].

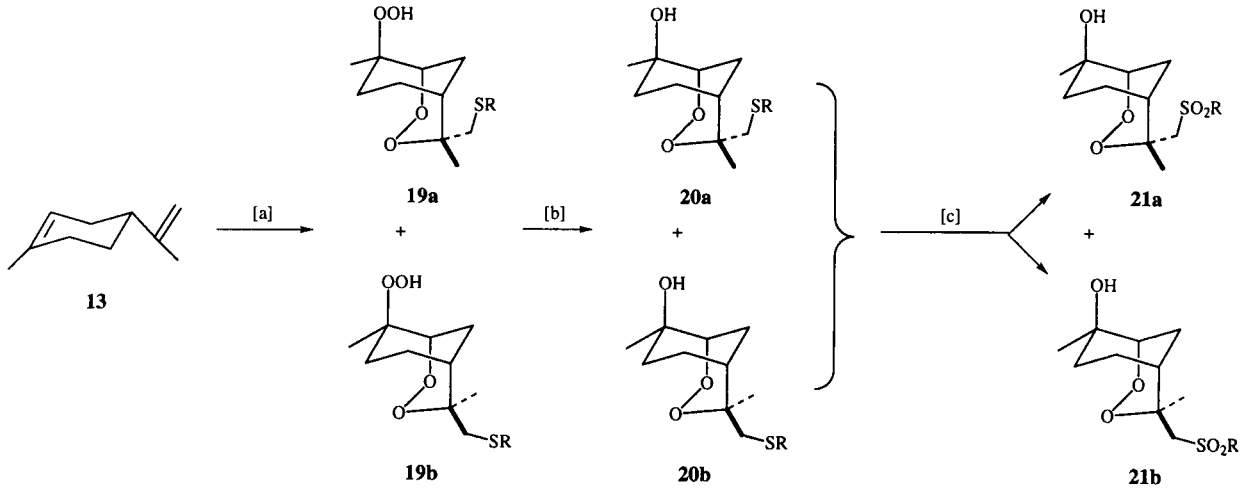
This method was applied using both aliphatic and aromatic thiols (Scheme 4). Two diastereomers of hydroperoxide-endoperoxides **19** were obtained. They were selectively reduced *in situ* to the corresponding hydroxy-peroxides **20**. Diastereomers were usually separated after oxidation to the corresponding hydroxy-endoperoxide-sulfones **21a** and **21b**. Hydroxy-endoperoxide-sulfones like **21a** and **21b** served as intermediates for the preparation of about 60 different endoperoxides of type **5** and **6** [20-22]. Some representative examples are shown on Scheme 5. 8-Hydroxy-4-sulfonylmethyl-2,3-dioxabicyclo-[3.3.1]nonanes **7** and **22-23** were obtained from (*R*)-(+)-limonene, (*S*)-(−)-limonene, and (*R*)-carveol. Acylation or alkylation of **7** and **22-23** led to derivatives, represented here by **8** and **24-26**. Some of these compounds, as for example **8a** and **26a** were found to exhibit antimalarial activity *in vitro* and *in vivo* of the same order of magnitude as artemisin [21,22].

Scheme 3



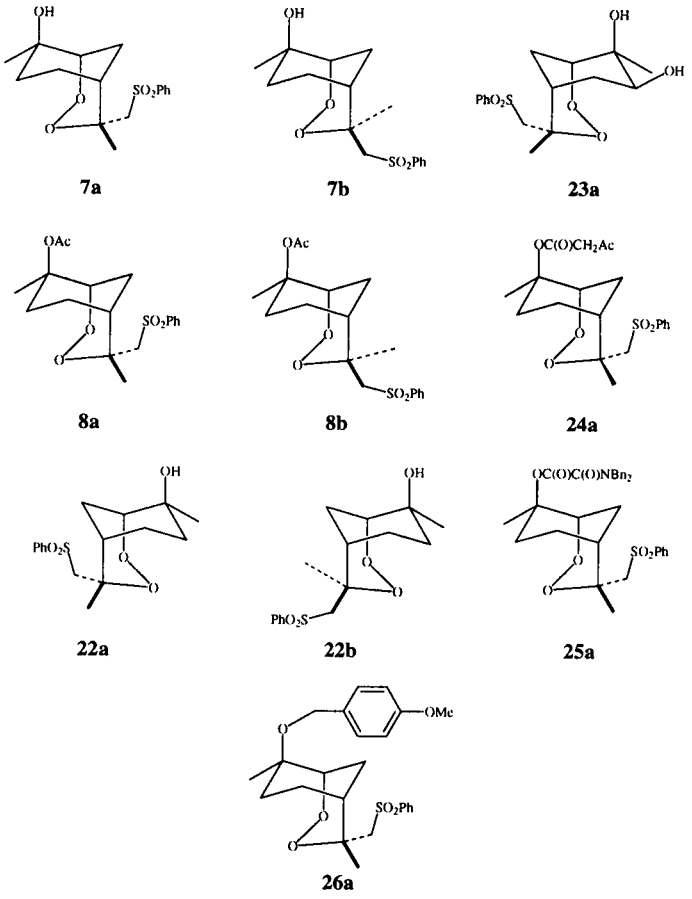
[a] In•: Radical initiator.

Scheme 4



[a] RSH, $2O_2$, Di-*t*-butyl peroxalate (DBPO) (cat.), Heptane/Benzene, r.t.; 10 hours; or RSH, $2O_2$, 2,2'-Azobisisobutyronitrile (AIBN) *hv*, MeCN, 4°,10 hours; [b] Ph_3Pi; [c] 3-Chloroperoxybenzoic acid.

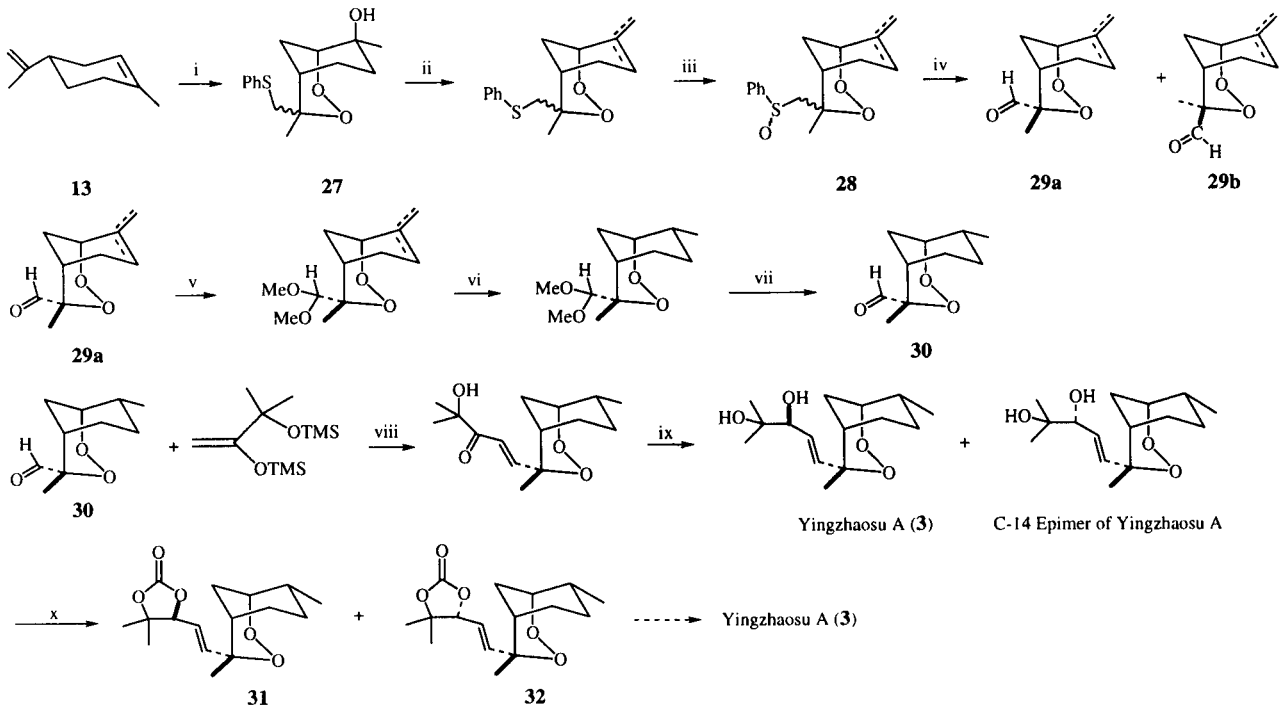
Scheme 5



Total Synthesis of Yingzhaosu A.

Hydroxy-endoperoxide-sulfide **27** (Scheme 6) was obtained by thiol-oxygen co-oxidation of (*S*)-(–)-limonene (**13**). Dehydration and oxidation to sulfoxide **28**, followed by a Pumerer rearrangement, afforded key aldehydes **29**. Aldehyde **29a** was chemoselectively reduced to aldehyde-iron(II) bromide. Scheme 8 shows a proposed mechanism. The β-cleavage of oxygen-centered radical **36** to ketosulfone **33** is in line with a mechanism proposed for iron(II)-induced degradation of arteflene **4a** [17,18]. By isolating two complementary fragments of **36**, *i.e.*, the unsaturated hydroxyaldehyde **34** and the ketosulfone **33**, we proved

Scheme 6



(i) (a) PhSH (Addition over ~ 12 hours), DBPO, O_2, Heptane-benzene, r.t., (b) Ph_3P, ~ 0°; (ii) $SOCl_2$, Pyridine, CH_2Cl_2, ~ 0°, then r.t.; (iii) MCPBA, EtOAc, –30°; (iv) (a) TFAA, 2,6-Lutidine, CH_2Cl_2, –30°, then 0°; (b) $NaHCO_3$, H_2O, ~ 0°, (c) Separation of isomers a and b; (v) $HC(OMe)_3$, Amberlyst 15; (vi) H_2/PtO_2, EtOAc, –10°; (vii) $HC(O)C(O)OH•H_2O$, $TsOH•H_2O$, CH_2Cl_2, r.t., then $NaHCO_3$ and $MgSO_4$; (viii) (a) $TiCl_4$, CH_2Cl_2, –78°, (b) Pyridine, –78° – 0°; (ix) $NaBH_4$, $EuCl_3•6\ H_2O$, MeOH, ~ 0°; (x) ImCOIm,THF, 2 hours, 55° then r.t. 12 hours.

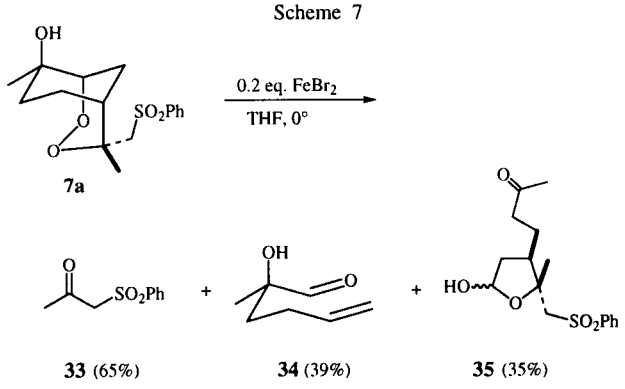
endoperoxide **30** and then through a Mukaiyama-type condensation to yingzhaosu A (**3**) and its C-14 epimer. The nmr data for compounds **30-32**, are identical with those reported in a previous synthesis [9]. Work on this synthesis is still in course.

Reactions of Endoperoxide-Sulphones with Iron(II) Salts.

The purpose of studying reactions of divalent iron salts with endoperoxide-sulfones **7a** and **8a** is to identify potentially cytotoxic transitory species and products that may account for the antimalarial activity of these, and possibly other of 2,3-dioxabicyclo[3.3.1]nonane derivatives.

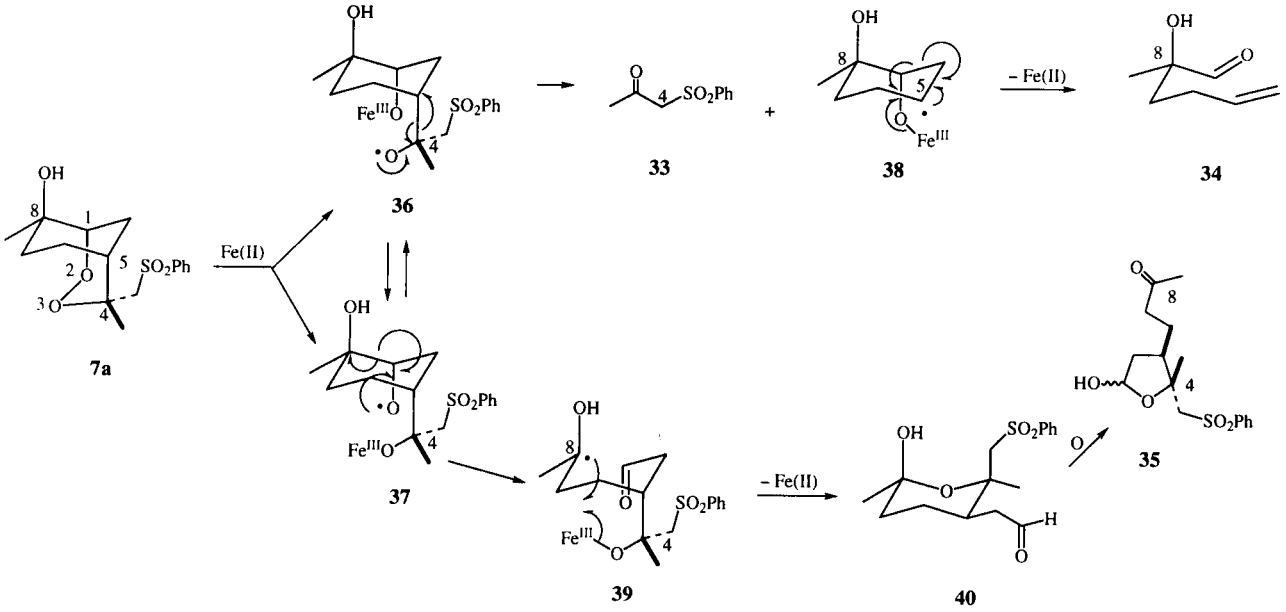
Scheme 7 describes the degradation of hydroxy-endoperoxide-sulfones **7a** induced by a catalytic amount of

Scheme 7

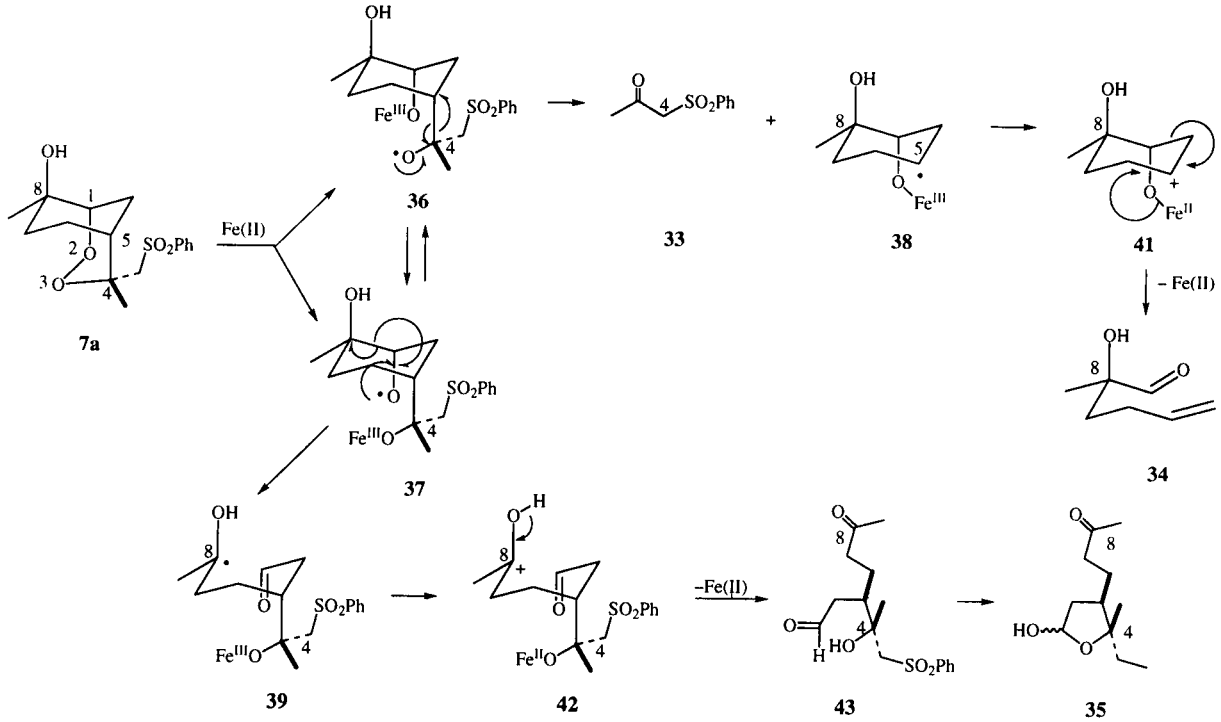


that carbon-centered radical **38** is indeed an intermediate species. However it occurred to us that hydroxyaldehyde **34** may be generated either through a direct homolytic cleavage as shown in Scheme 8, or through an heterolytic cleavage of an intermediate carbenium ion **41**. Carbenium ion **41** can be generated through the oxidation of radical **38** by iron(III) as shown in Scheme 9 [23]. The formation of hemiacetal **35** can be rationalized by a mechanism involving the oxidation of carbon-centered radical **39** to carbenium ion **42**, that through a proton shift, gives the hydroxy-ketoaldehyde **43** which spontaneously ring-close to the cyclic hemiacetal **35**. The possible involvement of cyclohexyl carbenium ions is further supported by comparison of the products obtained in the reaction hydroxy-

Scheme 8

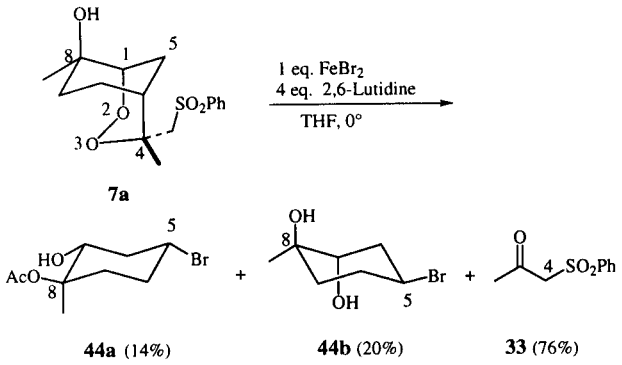


Scheme 9

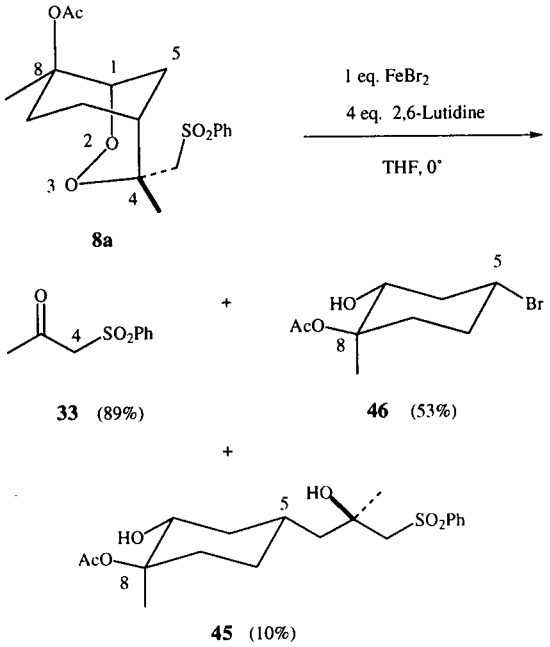


endoperoxide-sulfones **7a** with one equivalent of iron(II) bromide (Scheme 10) with those obtained in the analogous reaction of acetoxyendoperoxide-sulfones **8a** (Scheme 11). While hydroxy-endoperoxide-sulfones **7a** afforded a mixture of epimeric cyclohexyl bromides **44a** and **44b**, acetoxy-endoperoxide-sulfones **8a** afforded a single cyclohexyl bromide **46**. It is suggested (Scheme 12) that cyclohexyl radical **48**, obtained through β-scission of oxygen-centered radical **47**, is oxidized to carbenium ion **49**, which is stabilized by the acetoxy group as in **50**. Nucleophilic substitution by bromide ion would then occur *trans* to the acetoxy group leading stereoselectively to cyclohexyl bromide **46**. In the absence of the shielding effect of the acetoxy group, as in the positively charged intermediate **50**, two epimeric bromides **44a** and **44b** are obtained. An additional indication of the involvement of carbenium ions is provided by product analysis of the reaction of acetoxy-endoperoxide-sulfones **8a** with 1 equivalent of iron(II) acetate and 5 equivalents of tetra-*n*-butylammonium acetate in *N*-methyl-2-pyrrolidinone (Scheme 13).

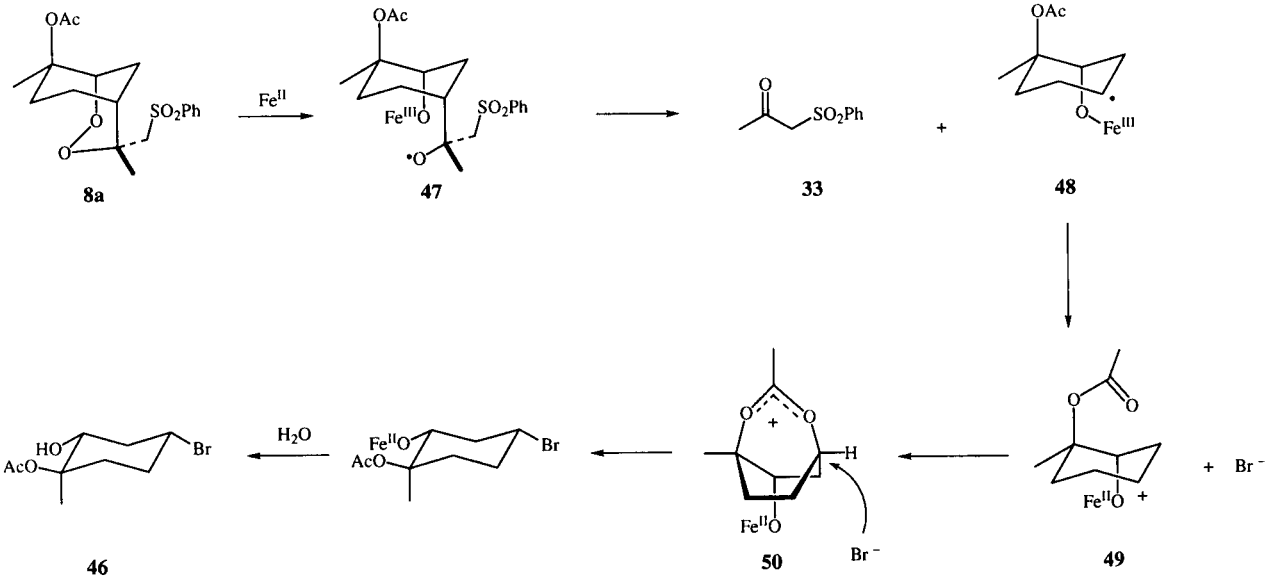
Scheme 10



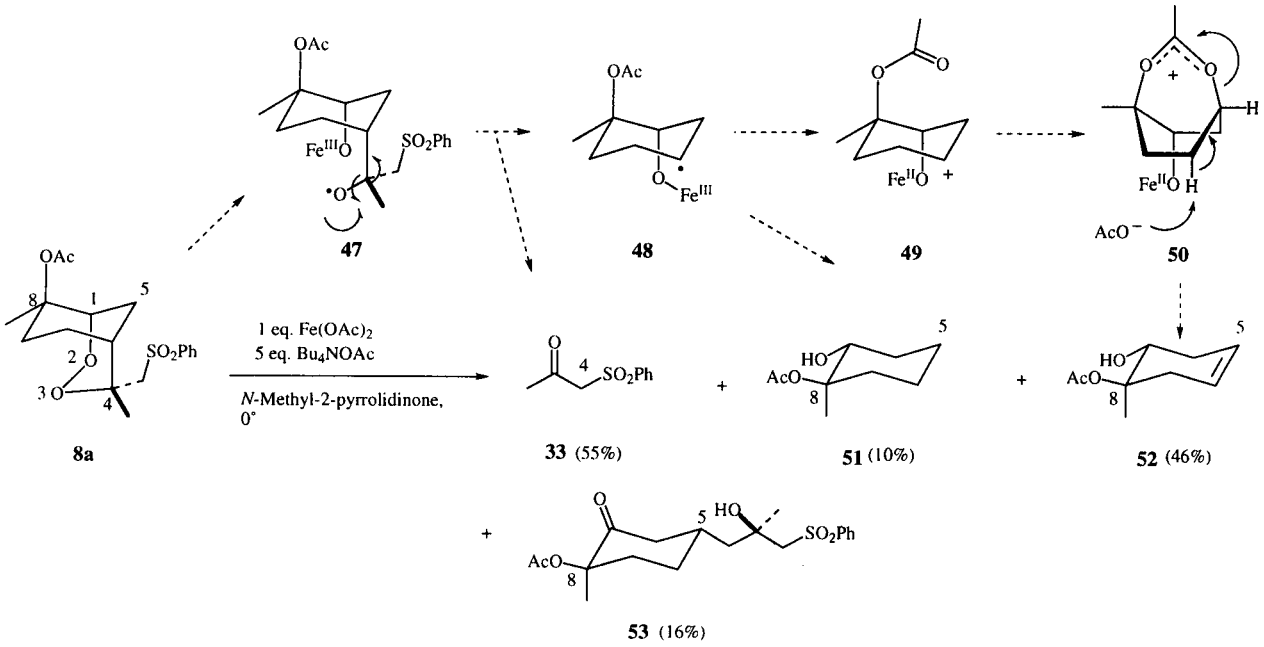
Scheme 11



Scheme 12



Scheme 13



Cyclohexane **51** is obtained by direct hydrogen atom transfer to radical **48**, hydroxyketone **53**, can be obtained by the Kornblum [24] reaction of endoperoxide **8a** with tetra-*n*-butylammonium acetate, or through radical degradation triggered by abstraction of the hydrogen atom positioned on C-1. However, the formation of cyclohexene **52** in high yield can only be rationalized through β-elimination of the less hindered axial proton in carbenium ion **50**. Such an elimination is accelerated by the basic acetoxy anion in the polar *N*-methyl-2-pyrrolidinone.

Conclusions.

Highly potent antimalarial endoperoxide-sulfones **5** and **6** were obtained through an efficient synthetic method involving, in its key step, the thiol-oxygen co-oxidation of simple monoterpenes. This method has also been utilized in a new synthesis of the natural product yingzhaousu A. Iron(II)-induced degradation of two of the new antimalarial endoperoxide-sulfones was studied. This study revealed that in the sequential process, which follows a Fenton-type lysis of the peroxide function, carbon-centered radicals and carbenium ions are generated, and electrophilic products like ketosulfones and aldehydes are formed. Such species may react with vital intraparasitic biomolecules. It is therefore conceivable that one, or more, of these transitory species, or reaction products, may account for the antimalarial activity of endoperoxide-sulfones of type **5** and **6**.

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