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LETTER

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3-Alkoxy-1,2-Dioxolanes: Synthesis and Evaluation as Potential Antimalarial Agents

Charles E. Schiaffo,[†] Matthias Rottman,[‡,§] Sergio Wittlin,[‡,§] and Patrick H. Dussault*[,†]

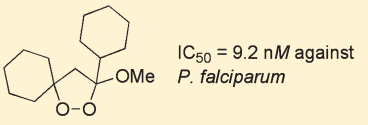
[†]Department of Chemistry, University of Nebraska—Lincoln, Lincoln, Nebraska 68588, United States

[‡]Swiss Tropical and Public Health Institute, Socinstrasse 57, CH-4002 Basel, Switzerland

[§]University of Basel, CH-4003 Basel, Switzerland

Supporting Information

ABSTRACT: A number of 3-alkoxy-1,2-dioxolanes exhibit promising levels of antimalarial activity against *Plasmodium falciparum*. A new route to the 1,2-dioxolane core is reported based on tandem peroxidation/cyclization of enones.



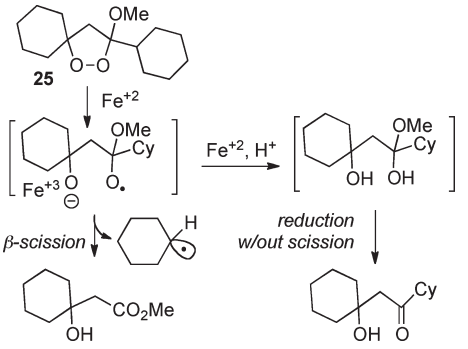
KEYWORDS: Malaria, peroxide, 3-alkoxy-1,2-dioxolane, dioxolane

Malaria is a global health epidemic affecting approximately 250 million people and causing over 800000 deaths annually.[1] The peroxide artemesinin, along with closely related artesunate and arteether, are a critical part of therapies against drug-resistant strains of *P. falciparum*, the most virulent form of the disease.[2] Strong antimalarial activity has also been observed with a number of artemisinin analogues.[3−7] However, reports of delayed parasite clearance in patients receiving artemisinin combination therapy (ACT) have led to renewed interest in structurally distinct classes of peroxides.[8] Promising levels of antimalarial activity have been observed from a number of relatively simple peroxide skeletons.[9,10−13] Struck by the high antimalarial activity of 1,2,4-trioxolanes (ozonides), one of which is currently in phase III trials,[13,14] we became interested in nearly isosteric 3-alkoxy-1,2-dioxolanes. We now report the synthesis of a number of alkoxydioxolanes along with in vitro antimalarial data.

The antimalarial activity of artemisinin is believed to derive from Fe(II)-mediated fragmentation of the peroxide to generate intermediate alkoxy radicals, which undergo rapid β-fragmentation or 1,5-hydrogen abstraction to generate reactive carbon radicals.[15,16] The ozonides discussed above have also been established to undergo Fe(II)-mediated cleavage to generate carbon radicals.[17] 1,2-Dioxolanes, which are nearly isosteric with ozonides, would appear to offer a promising platform for development of new peroxide antimalarials.[18] However, to date, few 1,2-dioxolanes have demonstrated significant antimalarial activity.[19] One reason may be the lack of an α-oxygen, resulting in a reduced propensity for β-scission in the derived alkoxy radicals.[20] We postulated that suitably substituted 3-alkoxy-1,2-dioxolanes might be excellent antimalarial candidates, providing a stable framework that would undergo activation by Fe(II) to furnish α-oxygenated alkoxy radicals predisposed toward β-scission (Scheme 1).

3-Alkoxy-1,2-dioxolanes are available from the corresponding 1,2-dioxolan-3-ols via acid- or base-promoted etherification.[21,22]

Scheme 1. Competing Modes of Alkoxydioxolane Activation



We initially pursued the 3,5,5-trimethyl-1,2-dioxolan-3-ol (**1**) and 5-butyl-3,5-dimethyl-1,2-alkoxydioxolan-3-ol (**3**) core structures (Scheme 2). A number of methods have been reported for the synthesis of 1,2-dioxolanols, including base-mediated addition of hydrogen peroxide to α,β-unsaturated ketones,[23,24] radical oxygenation of cyclopropanols,[25] thermolysis of azahydroperoxides,[26] or addition of singlet oxygen to methylallyl aldehydes.[27] However, none of these methods have been generally applied. Peroxide **1** was readily prepared through base-mediated addition of hydrogen peroxide to mesityl oxide.[24] However, as feared, application of similar conditions to the more hydrophobic 4-methyl-3-octen-2-one (**2**) mainly furnished the product of nucleophilic epoxidation.[21] Fortunately, cobalt-mediated oxygenation of **2**,[28] originally envisaged as a route to an intermediate 3-trialkylsilylperoxy alkanone, directly afforded the desired 1,2-dioxolan-3-ol **3**. Acid-catalyzed tranestherification to form the alkoxydioxolanes could be conducted on the 1,2-dioxolanol-3-ols (not shown)[21] but proceeded more cleanly on

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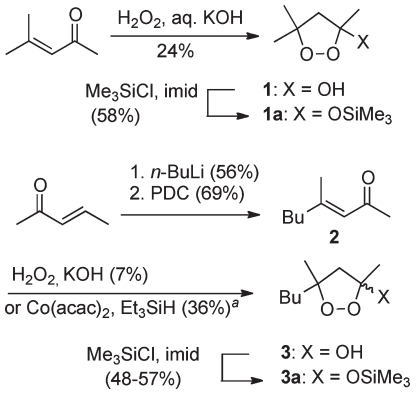
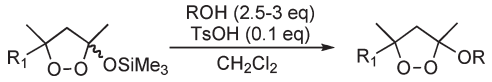
Scheme 2. Synthesis of Dioxolanol Core Structures



[a] On the basis recovered starting material.

Table 1. Initial Alkoxydioxolane Synthesis and Bioassay



subs	R_1	R	dioxolane (yield)	IC_{50} NF54 (nM)[a]
1a	Me	Bu	**4** (51%)	>10000
1a	Me	1-AdCH_2	**5** (65%)	290
3a	Bu	Propyl	**6** (64%)	>4000
3a	Bu	AdCH_2[b]	**7** (62%)	140
3a	Bu	Ph$(CH_2)_2$	**8** (80%)	76
		artesunate		2.5
		chloroquine		11

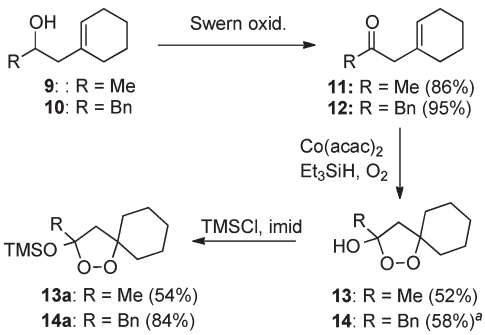
[a] See refs 29 and 30. [b] Ad = 1-adamantyl.

the corresponding trimethylsilyl ethers (**1a** and **3a**; Table 1). Three of the alkoxydioxolanes (**5**, **7**, and **8**) demonstrated significant in vitro activity against *P. falciparum* with dioxolane **8** displaying an IC_{50} less than 100 nM.[29,30] On the basis of these results, we became interested in surveying influences of the following structural elements: a spirocyclic constraint at C_5/C_5, the size of the C_3 alkoxide, and the nature of the putative radical leaving group at C_3.

The synthesis of 1,2-dioxolanes incorporating a spirocyclic constraint is illustrated in Scheme 3. Prins reaction of methylenecyclohexane with acetaldehyde or phenylacetaldehyde furnished homoallyl alcohols **9** and **10**,[31] which underwent Swern oxidation to furnish β,γ-unsaturated ketones **11** and **12**. Co-mediated dioxygenation (O_2, Et_3SiH) by a modification of Isayama's protocol directly furnished 1,2-dioxolan-3-ols **13** and **14**.[32,33] Although the dioxolanols could be carried on directly, purification was more easily conducted on the derived trimethylsilyl ethers, **13a** and **14a**. Dioxolanol **17**, which incorporates a better radical leaving group (benzyl) at C_3, was prepared via a benzyl/methallyl ketone, as illustrated in Scheme 4.

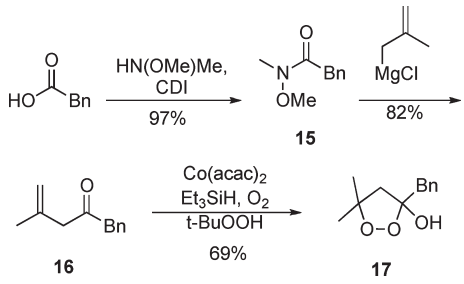
We were unsuccessful in applying a similar approach to a more hindered 1,2-dioxolan-3-ol (**20**) incorporating both a $C_5/C_{5'}$ spirocycle and a branched side chain at C_3 (not shown). However, this target could be prepared via dioxygenation of a cyclopropanol.[25] As illustrated in Scheme 5, conversion of dicyclohexylketone to the corresponding trimethylsilyl enol ether, followed by Simmons−Smith cyclopropanation, furnished

Scheme 3. Synthesis of 5,5′-*spiro*-1,2-Dioxolan-3-ols

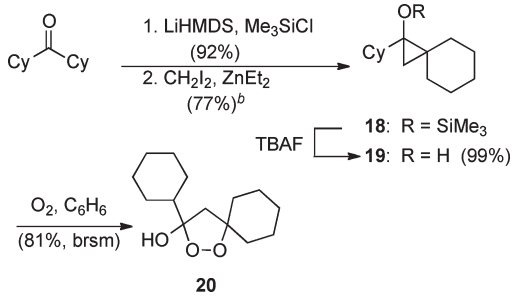


[a] Added *t*-BuOOH (stoichometric).

Scheme 4. Synthesis of a 3-Benzyl-1,2-dioxolan-3-ol



Scheme 5. Dioxolanol via Oxidative Ring Expansion[a]



[a] Cy = cyclohexyl. [b] Includes ~10% of **19**.

trimethylsilyloxycyclopropane **18**, accompanied by varying amounts of **19**, presumably reflecting during work up. Desilylation with TBAF furnished a tetrasubstituted cyclopropanol (**19**), which could be converted to **20** by stirring in benzene under an atmosphere of oxygen.

Acid-catalyzed S_N1 transetherification of the dioxolanols or their trimethylsilyl ethers with primary alcohols furnished 3-alkoxydioxolanes **21**−**25** (Table 2). The alkoxydioxolanes proved to possess remarkable chemical stability, failing to react with either PPh_3 (≥24 h, room temperature) or *i*-Bu_2AlH (≥4 h, room temperature).

The results of in vitro testing for compounds **21**−**25** (Table 2), when taken together with the results described in Table 1, suggest clear trends in terms of antimalarial structure−activity relationships. Activity is enhanced by a spirocyclohexyl constraint at $C_5/C_{5'}$ and by the presence of steric bulk at C_3. Dioxolanes **21** and **25**, which combine a spirocyclohexyl unit

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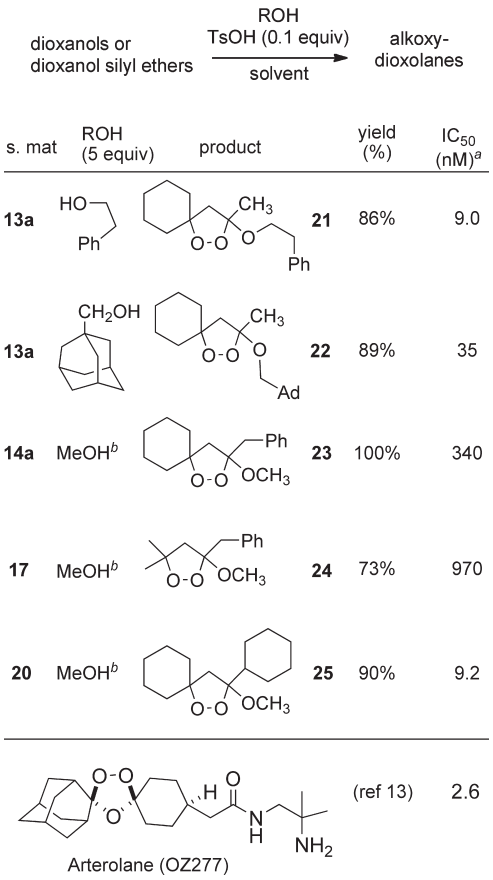
Table 2. Additional Alkoxydioxolanes



[a] NF54 strain of *P. falciparum* (refs 29 and 30). [b] Solvent.

with either a bulky C_3 alkyl substituent or a large C_3 alkoxide displayed IC_{50} values below 10 nM.

Finally, we were interested in investigating the Fe(II) reactivity of the alkoxydioxolanes, and, in particular, the extent of cleavage of the derived alkoxy radicals (see Scheme 1). Alkoxydioxolane **25**, one of our most active of our initial leads, underwent reaction with $FeBr_2$ to furnish the corresponding 3-hydroxyester in 80% yield (reaction illustrated in Scheme 1), supporting the postulated formation and fragmentation of an alkoxy-substituted alkoxy radical.[15,16] Similar results have been reported for a monocyclic alkoxydioxolane.[23]

In conclusion, we have developed new and expanded routes to 1,2-dioxolan-3-ols and 3-alkoxy-1,2-dioxolanes. The latter are demonstrated to provide a highly promising platform for development of a new family of antimalarial peroxides.

■ ASSOCIATED CONTENT

Supporting Information. Complete experimental procedures and characterization data; ^1H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: 402-472-6951. E-mail: pdussault1@unl.edu.

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