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Synthesis of Antimalarial 1,2,4-Trioxanes via Photooxygenation of a Chiral Allylic Alcohol

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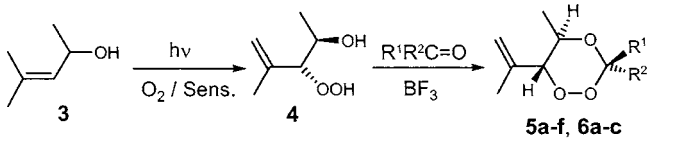
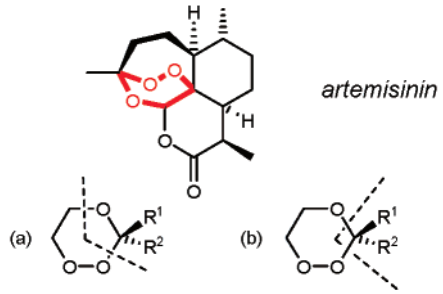
ABSTRACT



Photooxygenation of the chiral allylic alcohol 4-methyl-3-penten-2-ol (3) in nonpolar solvents and subsequent Lewis acid-catalyzed peroxyacetalization afforded a series of monocyclic and spirobicyclic 1,2,4-trioxanes (5, 6). Two products show significant anti-Malaria activity against *Plasmodium falciparum* when compared with chloroquine.

The search for efficient nontoxic drugs against several forms of Malaria is an important topic in medicinal chemistry, especially for those parasites that have developed multidrug resistance in recent times and are especially harmful such as *Plasmodium falciparum*.[1] A promising new lead structure is the 1,2,4-trioxane ring peroxide, which occurs in natural anti-Malaria active terpenoids such as artemisinin (or qinghaosu) and its analogues as well as the 1,2-dioxane structure found in yinghaosu A and C.[2] There has been intensive effort in the total synthesis,[3] in the synthesis of derivatives,[4] and in the elucidation of the peroxide-specific mode of action.[5] For the synthesis of the 1,2,4-trioxane skeleton, two major paths are applicable: (a) acid-catalyzed addition of cyclic peroxides (dioxetanes, endoperoxides) to carbonyl compounds[6] and (b) peroxyacetalization of β-hydroperoxyalcohols (Scheme 1).[7]

Scheme 1



The latter approach appears to be especially attractive since β-hydroperoxyalcohols are available by singlet oxygen

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(4) McCullough, K. J.; Nojima, M. *Curr. Org. Chem.* **2001**, *5*, 601−636.
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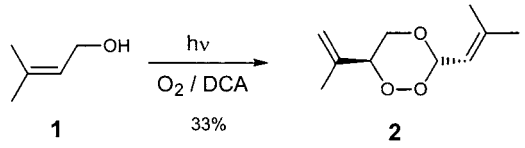
photooxygenation of allylic alcohols.[8] Furthermore, this way enables the introduction of a wide variety of functional groups at the level of the nonperoxidic starting materials.

In the course of our recent work on the photoinduced electron-transfer oxygenation of alkenes, we observed the formation of 1,2-dioxanes by trapping of arylated alkene radical cations with *triplet* oxygen.[9] Surprisingly, this reaction was also observed with prenol (2-methyl-2-buten-4-ol, **1**). When irradiated in acetonitrile in the presence of catalytic amounts of 9,10-dicyanoanthracene (DCA) and oxygen, the 1,2,4-trioxane **2** was formed in low yield (Scheme 2). A

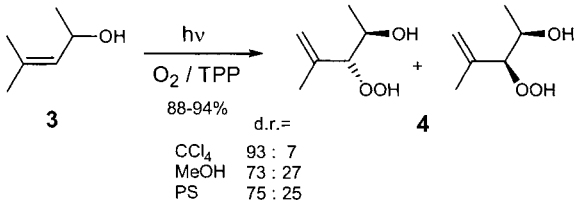
Scheme 2



plausible mechanism for this unusual transformation is the one-electron oxidation of **1** followed by deprotonation, oxygen trapping, and subsequent addition of neutral **1** to give the radical cation of **2**, which is eventually reduced. Albeit an interesting transformation, other allylic alcohols did not show this behavior and the activity against the *P. falciparum* parasite is marginal (Table 2). Thus, we proposed to develop a qualitative structure−activity relationship by variation of the trioxane structure **2**. From extensive model studies performed by Jefford et al.,[10] it became clear that homolytic cleavage of the acetal carbon−carbon bond, induced by single-electron reduction of the peroxy linkage, might be responsible for the biological activity of 1,2,4-trioxanes. Obviously, this path is not available for **2** because it would result in the formation of a vinylic radical. As an alternative to more promising compounds, the *singlet* oxygen photooxygenation of allylic alcohol **3** was investigated. The diastereoselectivity of this ene reaction is remarkably high in unpolar solvents and drops when protic solvents are used (Scheme 3).[11]

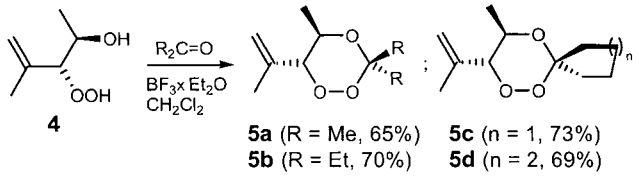
This *threo*-selectivity is rationalized in terms of the "hydroxy-directing effect" which is strongly influenced by competing hydrogen-bond acceptors.[12] To evaluate an en-

Scheme 3



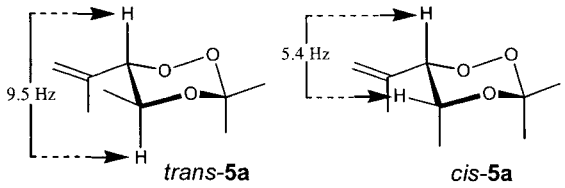
vironmentally more friendly approach, we have recently developed the polystyrene (PS) microcontainer photooxygenation[13] for the ene reaction of **3**. In this solvent-free approach, the diastereoselectivity drops remarkably in comparison to the reaction in CCl_4 due to the high (protic) substrate concentration. With this efficient source of β-hydroperoxyalcohol **4** in hand, we investigated the peroxyacetalization with a series of carbonyl components. Boron trifluoride etherate turned out to be the most efficient Lewis acid catalyst, and the *trans*-5,6-disubstituted trioxanes **5** were formed in good yields (Scheme 4). The corresponding

Scheme 4



products derived from the minor (*erythro*) diastereoisomeric hydroperoxyalcohol **4** could no longer be detected in the purified trioxanes from the hydroperoxide mixture obtained from photooxygenation in CCl_4. To unambiguously prove the relative configuration of these products, a 73:27 mixture of diastereoisomers **4** (from the photooxygenation in MeOH) was treated with acetone/BF_3 and a trans/cis mixture of **5a** isolated (Scheme 5). The $^3J_{HH}$ coupling constants clearly

Scheme 5



indicated that the major diastereoisomer ($^3J_{HH}$ = 9.5 Hz) has the trans configuration (from *threo*-**4**), and the minor

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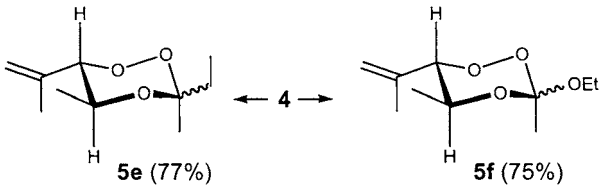
diastereoisomer ($^3J_{HH}$ = 5.4 Hz) has the cis configuration (from *erythro*-**4**). The peroxyacetalization with 2-butanone resulted in a 80:20 mixture of diastereoisomers **5e** (both 5,6-trans with $^3J_{HH}$ = 9.6 Hz) with the ethyl group in an equatorial position in the major component (cf. Scheme 6).

Scheme 6



Instead of ketones, acetals or ortho esters can also be used for the peroxyacetalization. For synthesis of the spirobicyclic product **5c**, the alternative transacetalization using an excess of cyclopentanone diethyl acetal could be applied with 71% yield. More interestingly, the combination of **4** and triethylorthoacetate in the presence of BF_3 led to the formation of the cyclic perortho ester **5f** in good yields (75%%) and low diastereoselectivity (approximately 54:46, both 5,6-trans diastereoisomers). To the best of our knowledge, compound **5f** is the first perortho ester with a 1,2,4-trioxane substructure described in the literature. The structures of all new mono- and spirobicyclic 1,2,4-trioxanes were unambiguously proven by NMR and MS analyses.[14] Especially informative were the ^{13}C NMR shifts of the peroxyacetal carbons C(3) (102−103 ppm) for the 3,3'-bisalkylated compounds **5a**,**b**,**d**, which were strongly low-field shifted for not only the perortho ester **5f** but, surprisingly, also for the cyclopentano-spiroannulated trioxane **5c** (Table 1; data for **5e** is for the major diastereoisomer).

Table 1. ^{13}C NMR Shifts of the 1,2,4-Trioxanes **5a**−**f**

	C(3)	C(5)	C(6)
5a	102.3	66.2	88.4
5b	106.0	65.8	88.4
5c	114.7	68.4	88.6
5d	102.8	65.6	88.8
5e	104.1	66.3	88.8
5f	113.8	66.1	87.8

An analogous approach has been developed by Singh et al. using the photooxygenation of the terpene alcohol geraniol.[15] They report relatively high activities against *P. falciparum*, with one compound exceeding the chloroquine value.

(14) Representative experimental procedure for **5e**. To a solution of 1.0 g of **4** (7.6 mmol) in 20 mL of diethyl ether were added at room temperature an excess of 2-butanone (5 g, 70 mmol) and a catalytic amount of BF_3-XEt_2O (0.2 mL). After stirring for 12 h at rt, the solution was diluted with 25 mL of ether, washed with brine and water, and dried over $MgSO_4$. Solvent evaporation and column chromatography yielded 1.1 g (77%) of **5e**.

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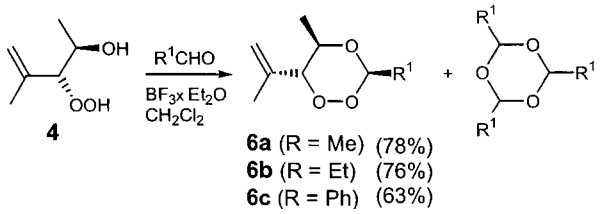
As an extension of our work, we also investigated the Lewis-acid-catalyzed peracetalization of **4** with aldehydes (Scheme 7). In these cases, however, inseparable mixtures

Scheme 7



of 1,2,4-trioxanes **6** and aldehyde trimers were obtained in good yields (ca. 40−50% trimer content; total yields are given in Scheme 7). Only one diastereoisomer was detected for all three 1,2,4-trioxanes **6a**−**c** with cis configurations of the substituents at C(3) and C(5).

The anti-Malaria activities were tested against the K1 strain of *P. falciparum* and revealed that, in comparison with the standard drug chloroquine, appreciable effects could be detected with the simple acyclic 1,2,4-trioxane **5b**; even better results were obtained with the spirobicyclic compound **5c** (Table 2), whereas the 3-vinyl derivative **2** was nearly inactive.

Table 2. Activities of Synthetic 1,2,4-Trioxanes against the K1 Strain of *Plasmodium falciparum*[a]

compound	activity
rac-**2**	1762
rac-**5b**	276
rac-**5c**	178
chloroquine	65
artemisinine	1.2

[a] All values are the mean of two independent assays and given in ng/mL.

These activities are still 2 orders of magnitude weaker than the potent artemisinin derivatives.[5,16] The synthetic approach is remarkably simple and uses easily available starting materials. Furthermore, the structural flexibility is high, and currently a series of other allylic alcohols and carbonyl compounds are being applied.

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