Photooxygenation

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Bicyclic Peroxides and Perorthoesters with 1,2,4-Trioxane Structures**

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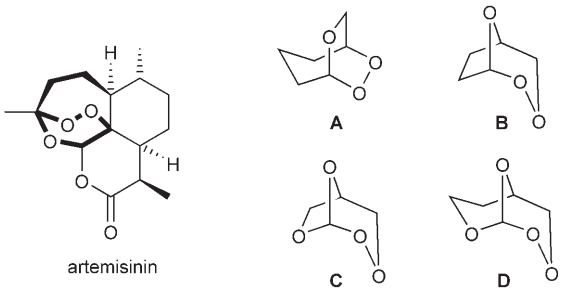
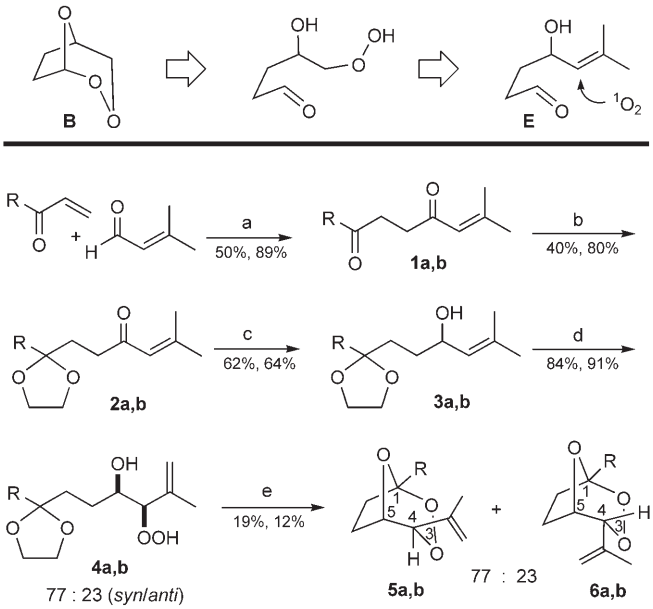
The search for new compounds active against malaria has led to an increasing demand for the synthesis of new cyclic organic peroxides.[1] The naturally occurring sesquiterpene lactone peroxide artemisinin (quinhaosu), which contains a 1,2,4-trioxane subunit, serves as the natural active principle and model compound.[2] However, the most aggressive parasite, *Plasmodium falciparum*, is showing first resistance effects to artemisinin and its semisynthetic derivatives (artemether, artesunate).[3] Consequently, there is an urgent need for new effective antimalarial agents, and three synthetic concepts for the development of novel peroxidic substances have evolved:[4] modification of natural artemisinin,[5] synthesis of novel cyclic peroxide structures,[6] and coupling of trioxanes to other potential pharmacologically active groups with the formation of "dual systems".[7] Many mono- and polycyclic peroxides prove to be active against malaria tropica. Activities similar to those of 1,2,4-trioxanes were found for 1,2-dioxanes, the core structure of the naturally occurring yinghaosu A and C.[8] Furthermore, Vennerstrom et al. reported on the synthesis of 1,2,4,5-tetroxanes[9] and 1,2,4-trioxolanes,[10] the latter showing the highest antimalarial activities currently known. Recently observed antitumor activities of artemisinin derivatives have called further attention to this class of compounds.[11]

In the context of our research on the photooxygenation of allylic alcohols,[12] we have explored a facile route for the synthesis of mono- and bicyclic 1,2,4-trioxanes: the Lewis acid catalyzed peroxyacetalization of unsaturated 1,2-hydroperoxy alcohols.[13] Several of these compounds show high in vitro activity against *P. falciparum*.[14] Similar structures with comparable high in vivo activities have also been described by Singh and co-workers.[15] We intended to expand this synthetic route for the preparation of more complex molecules, broadening the structural diversity of this route. We have now realized the synthesis of ring-contracted peroxides with a 1,2,4-trioxane substructure (type **B** in Scheme 1; **A** corresponds to the central trioxabicyclo[3.2.2]nonane of artemisinin).



Scheme 1. Artemisinin, core structure **A**, and targets **B**–**D**.

If one focuses on the ene reaction of singlet oxygen as the key step, the retrosynthesis of **B** leads to the allylic alcohol **E** (Scheme 2). A straightforward approach to the required substrate was a Stetter reaction between 3-methylcrotonaldehyde and alkylvinyl ketones.[16] Dicarbonyl compounds **1** were selectively protected and reduced to allylic alcohols **3**. Subsequent photooxygenation under solid-state conditions[17]



Scheme 2. Synthesis of 2,3,8-trioxabicyclo[3.2.1]octanes **5** and **6**; **a**: R = Me, **b**: R = Et. a) 3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride, CH_2Cl_2; b) ethylene glycol, TsOH; c) $LiAlH_4$, Et_2O; d) O_2, *hν*, PS-DVB-TSP polymer; e) $BF_3{\cdot}Et_2O$, CH_2Cl_2.

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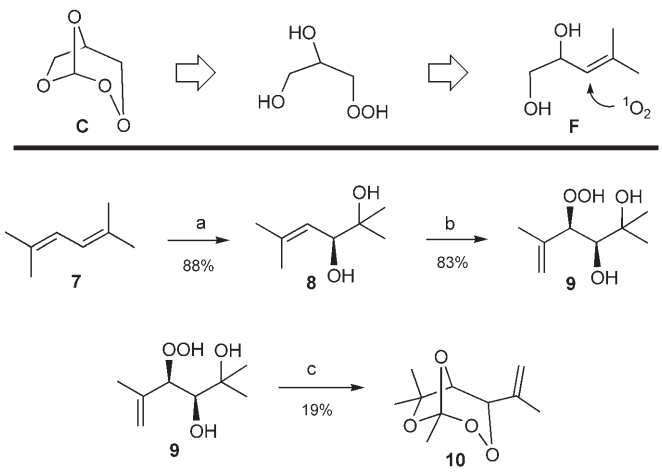
Supporting information for this article (general experimental data, syntheses, energetical and NMR properties, relaxed potential energy surfaces, and optimized structures) is available on the WWW under http://www.angewandte.org or from the author.

resulted in a *syn*/*anti* mixture of allylhydroperoxides **4**. An improvement of the low diastereoselecitvity to a ratio of 9:1 was achieved when the photooxygenation reaction was carried out in solution (CCl_4 or toluene). The intramolecular peroxyacetalization reaction was realized by treatment with boron trifluoride; separate acetal deprotection was not required. The moderate yields of this last step result from the dominating Lewis acid catalyzed C–C cleavage giving methacrolein and the corresponding aldehyde.[18]

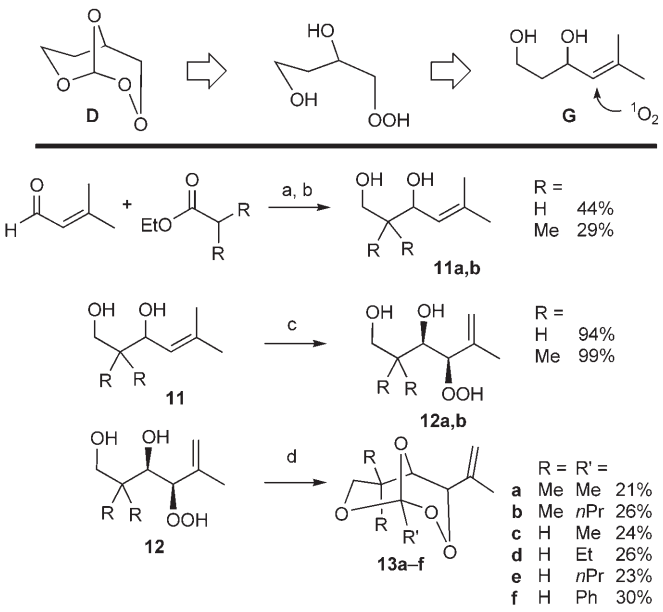
The target compounds **5** and **6** from both series were formed as mixtures of diastereoisomers with nearly identical d.r. values. Decisive for the assigment of the relative configuration was the 4-H ^{1}H NMR signal, since it shows a chemical shift difference of about $\delta = 0.8$ ppm for the *syn*/*anti* diastereosiomers (**5**: $\delta = 3.9$ ppm, **6**: $\delta = 4.7$ ppm). In all four cases the $^3J_{HH}$ coupling constants of about 1 Hz were not significant for the determination. The chemical shift and coupling assignments were supported by DFT and GIAO calculations (see below).

The synthesis of the analogous structure **C** with a perorthoester motif is depicted in Scheme 3. The unsaturated 1,2-diol **F**, which was obtained by enantioselective Sharpless bishydroxylation of the 1,3-diene **7** (93% *ee*), served as the



Scheme 3. Synthesis of 2,3,7,8-tetraoxabicyclo[3.2.1]octane **10**. a) AD-mix-α; b) O_2, *hν*, TPP, CCl_4, 10 °C; c) PPTS, $CH_3C(OMe)_3$, CH_2Cl_2. TPP = tetraphenylporphyrin, PPTS = pyridinium *para*-toluenesulfonate.

starting material for the $^1O_2$ ene reaction.[19] The photooxygenation of the allylic alcohol **8** in CCl_4 provided a mixture of *syn*/*anti* hydroperoxides **9** (only the major diastereoisomer is shown) in a ratio of 87:13 in 83% yield. The 2,3,7,8-tetraoxabicyclo[3.2.1]octane **10** was formed in 19% yield by intermolecular peroxyacetalization with trimethylorthoacetate in the presence of catalytic amounts of pyridinium *p*-toluene sulfonic acid. The yields for the last step could be improved in the case of the ring-expanded perorthoesters **13** by the route shown in Scheme 4. The key substrates **11** were obtained by aldol addition of 3-methylcrotonaldehyde and subsequent reduction. Photooxygenation in solution provided the hydroperoxides **12a**,**b** with diastereoselectivities of 83:17 and 94:6, respectively.



Scheme 4. Synthesis of 2,3,8,9-tetraoxabicyclo[3.3.1]nonane **13**. a) LDA; b) $LiAlH_4$; c) O_2, *hν*, TPP, CCl_4, 10 °C; d) PPTS, $R'C(OMe)_3$ [$EtC(OEt)_3$ for **13d**], CH_2Cl_2. LDA = lithium diisopropylamide.

Finally, PPTS-catalyzed condensation of the allylic hydroperoxides **12** with several orthoesters provided the bicyclo-[3.3.1]nonanes **13**. The best yield was achieved in the synthesis of **13f** when trimethylorthobenzoate was used in a threefold excess.[20] The diastereoisomeric peroxides **13c** were separated by column chromatography and exhibited unambiguous NOE effects in ^{1}H NMR spectra which confirmed the assignment of the relative configurations. Preliminary in vitro tests against *P. falciparum* of representative examples of these new classes of peroxides revealed activities in the EC_{50} range of $1.9–2.0 \times 10^{-5}$ M for compounds **13**. The reference value of artemisinin is 10^{-8} M.[21]

The relative configurations of the 1,2,4-trioxepanes **10**[22] and 1,2,4-trioxocanes **13** was assigned based on NMR chemical shifts. In recently published works on bicyclic 1,2,4-trioxanes, simple H–H coupling patterns were used.[23] However, from our experience the relative configuration at the stereogenic center could not assigned solely on the basis of NMR coupling data since the dihedral angles determining the coupling constants are not significantly different. To overcome this problem, DFT calculations were performed in order to estimate the chemical shifts of 4-H, allowing eventually the assignment of the relative stereochemistry for each diastereoisomer. The Becke three-parameter hybrid functional[24] with the correlation functional of Lee, Yang, and Parr[25] (B3LYP) as it is implemented in the Gaussian 03[26] program was employed for all calculations. Relaxed potential energy scans of **5a** and **6a** at the B3LYP/6-31G level of theory resulted in the energetically favored conformations of the bicyclic structures and the isopropenyl group. The bicyclic ring structures of **5a** and **6a** are almost rigidly fixed owing to their bridged constitution, and thus they can only form two conformers, namely the trioxane-chair and trioxane-boat conformer. Owing to Boltzmann distribution, the latter does

not play a role at room temperature. For each of these ring conformers the local minima with respect to the relative orientation of the isopropenyl group were located and fully optimized at the B3LYP/6-311G(d) level of theory (Figure 1).

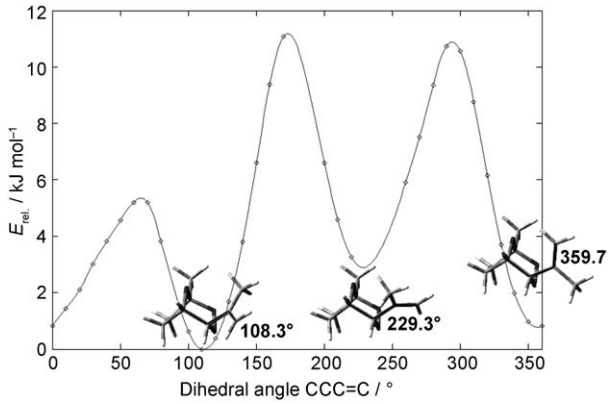


Figure 1. Relaxed potential energy surface of **5a** (B3LYP-6-31G).

The latter method and basis set combination has been chosen following Ref. [21], according to which it allows a sufficiently precise calculation of the chemical shifts. For each of these optimized structures the analytical Hessian was calculated (vibrational analysis) to ensure the absence of any negative eigenvalues. The absolute chemical shieldings (σ) were computed employing the GIAO approach and set into relation to the calculated absolute shifts of tetramethylsilane. The resulting relative shifts of 4-H (by consideration of the Boltzmann distribution of the rotamers) were $\delta = 3.7$ ppm (**5a**, exptl $\delta = 3.9$ ppm) and $\delta = 4.8$ ppm (**6a**, exptl $\delta = 4.7$ ppm), respectively, showing a significant difference of $\delta = 0.9$ ppm (exptl $\delta = 0.71$ ppm). Consequently, the assignment of the relative configurations of **5a** and **6a** in this publication is based on these calculations in combination with the respective experimental NMR data. The experimentally measured shifts of 4-H in **5a** and **6a** correspond very well to the calculated shifts and are therefore in their combination suitable for a reliable assignment of the relative stereochemistry. The calculations and simulations were also performed for the perorthoester **10**, confirming the fundamental conclusions concerning the chemical shifts and coupling constants (see the Supporting Information).

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