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# D-Glucose-Derived 1,2,4-Trioxepanes: Synthesis, Conformational Study, and Antimalarial Activity

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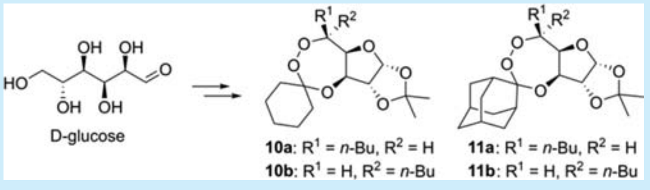
Supporting Information

**ABSTRACT:** New enantiomerically pure 1,2,4-trioxepanes **10a**,**b**/**11a**,**b** were synthesized from D-glucose. Their conformational behavior was studied by low-temperature NMR and substantiated by DFT calculations. On evaluation of in vitro antimalarial activity, the adamantyl derivative **11b** showed $IC_{50}$ values in the low micromolar range, particularly against the W2 chloroquine-resistant *Plasmodium falciparum* strain ($IC_{50}$ = 0.15 ± 0.12 $\mu$M).




In the past two decades, many efforts have been devoted to eradicate malaria, one of the most widespread and life-threatening parasitic diseases due to its increasing resistance to traditional antimalarial drugs.[1,2] In general, biologically active natural molecules inspire the evolution of the search for new lead compounds, as exemplified by artemisinin **1** (Figure 1).[3] In this direction, artemisinin combination therapies (ACTs), in which synthetic artemisinin derivatives[4] are combined with less potent but long lasting partner drugs, are the first line treatment for *Plasmodium falciparum* and *Plasmodium vivax* malaria. For example, Ranbaxy has commercialized the 1,2,4-trioxolane OZ277 (arterolane maleate, **2**) in combination with piperaquine phosphate for the treatment of malaria in India (Synriam).[5a,b] In addition, the 1,2,4-trioxolane OZ439 (artefenomel, **3**) is currently under clinical trials.[5c] It has been demonstrated that the endoperoxy bridge, an integral part of the 1,2,4-trioxane ring of artemisinin, is essential for the antimalarial activity.[6] In view of this finding, many new synthetic endoperoxides have been prepared and evaluated as antimalarial candidates,[7] including 1,2-dioxanes,[8] 1,2,4-trioxolanes,[9] 1,2,4-trioxanes,[10] and 1,2,4,5-tetraoxanes.[11] A very promising member of the last family, 1,2,4,5-tetraoxane RKA182 (**4**), is currently under preclinical trials.[11e] Among the endoperoxide families, the seven-membered 1,2,4-trioxepanes have received less attention,[12] and most of the existing approaches to 1,2,4-trioxepanes, via 1,3-hydroperoxy alcohol intermediates, are largely racemic. These methodologies involve (a) the cobalt-catalyzed oxygenation of cinnamyl alcohol,[13] (b) the thiol−olefin co-oxygenation of allylic alcohol,[14] (c) the acid-catalyzed reaction of tertiary alcohols with $H_2O_2$,[15] and (d) the singlet oxygen photo-oxygenation of homoallylic alcohols.[16]

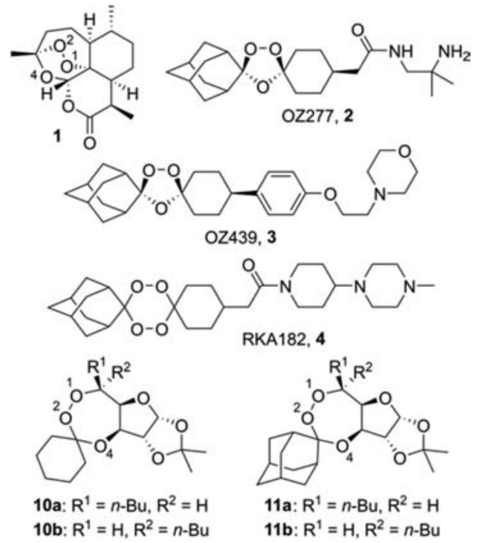



**Figure 1.** Structure of artemisinin (**1**), synthetic endoperoxide drug candidates **2**−**4**, and 1,2,4-trioxepanes **10a**,**b**/**11a**,**b**.

So far, only one asymmetric approach to 1,3-hydroperoxy alcohols and 1,2,4-trioxepanes is known on the basis of Lewis acid catalyzed perhydrolysis of substituted chiral oxetanes.[17] However, sugar-derived enantiomerically pure 1,2,4-trioxepanes, to the best of our knowledge, are unknown. In continuation of our interest in the synthesis of endoperoxides and in the study of their antimalarial activity,[8] we now report our preliminary results

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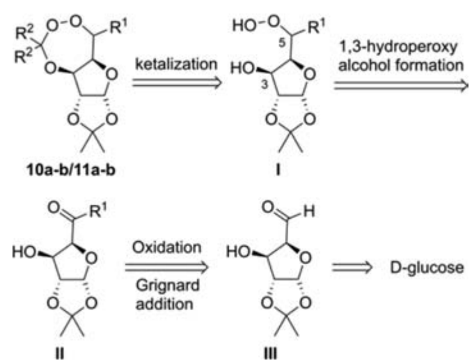
on the synthesis of D-glucose-derived 1,2,4-trioxepanes **10a,b**/**11a,b** (Figure 1) and their antimalarial activity.

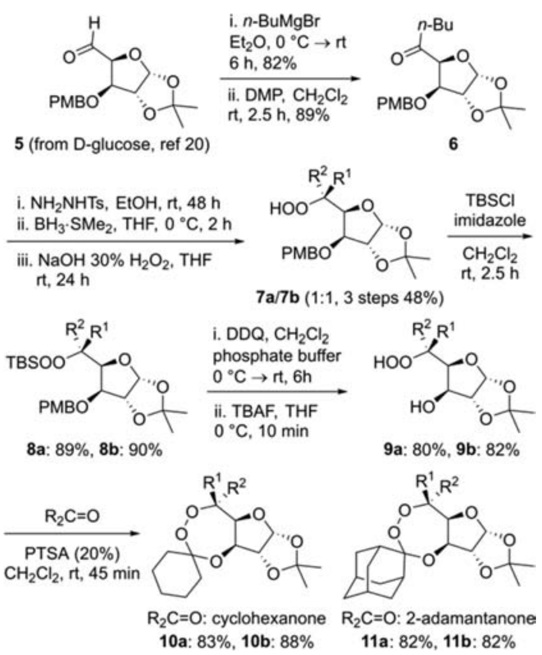
Although different synthetic methods for the preparation of 1,3-hydroperoxy alcohols are known, a methodology reported by Caglion and co-workers,[18,19] wherein ketone compounds are converted to the alkyl peroxides via *N*-tosylhydrazone derivatives followed by reduction to *N*-tosylhydrazine and substitution with $H_2O_2$ is almost unexplored. We thought of exploiting this approach with a D-glucose-derived C5 ketose **II** ($R^1$ = *n*-butyl) that would give access to the 5-hydroperoxy derivative **I**. The presence of a 1,3-hydroperoxy alcohol functionality in this D-glucose derivative will allow an easy access to 1,2,4-trioxepanes using a ketone like cyclohexanone or 2-adamantanone (Scheme 1).

**Scheme 1. Retrosynthetic Plan for the Synthesis of a D-Glucose-Derived 1,2,4-Trioxepanes**




Our synthetic plan started with the protected D-xylopentodialdose **5** (Scheme 2), easily prepared from D-glucose in four steps.[20] The aldehyde **5** was treated with *n*-butylmagnesium bromide to give a diastereomeric mixture (7:3) of two C5 epimers which was subjected to Dess–Martin periodinane (DMP) oxidation to get C5-ketone **6**. The *n*-butyl group at C5 of the *gluco*ketose was selected based on the proposal that the antimalarial activity of artemisinin and other cyclic peroxides is related to heme iron(II)-induced reductive cleavage of the peroxide bond, followed by radical rearrangement to generate reactive carbon-centered radicals.[21] Our recent findings[8a−c] with 1,2-endoperoxides demonstrated that the presence of an *n*-butyl group at the $\alpha$-position with respect to the peroxy bond makes possible a 1,5-*H*-transfer process to the initially formed oxy radical to generate reactive C-radical species that can alkylate heme or protein to kill the parasite. Thus, ketone **6** was converted to *N*-tosylhydrazone and then reduced with borane to give *N*-tosylhydrazine that was reacted with $H_2O_2$/NaOH to afford a C5 epimeric mixture of hydroperoxides. This mixture was separated by flash chromatography to obtain 1,3-hydroperoxy alcohols **7a** and **7b** as pure diastereoisomers in the 1:1 ratio.

**Scheme 2. Synthesis of Sugar-Derived 1,2,4-Trioxepanes 10a,b and 11a,b**[a]




[a]Key: **a**, $R^1$ = *n*-Bu, $R^2$ = H; **b**, $R^1$ = H, $R^2$ = *n*-Bu.

The relative stereochemistry at C5 in the epimeric pair **7a** and **7b** was assigned by comparative $^1$H NMR data of **7a** and **7b**. It is known that for a given C5-epimeric pair, derived from D-*gluco*furanose, the $J_{4,5}$ in the L-*ido* isomer is consistently larger than that of the corresponding D-*gluco* isomer.[22] The higher value of $J_{4,5}$ in the diastereomer **7a** (8.8 Hz) as compared to **7b** (7.6 Hz) indicated the L-*ido*-configuration for **7a** and D-*gluco*-configuration for **7b**. This assignment was further supported by a comparison of the chemical shifts of the H3 in both the isomers. The chemical shift of H3 is reported to be diagnostic such that in the L-*ido*-isomer it is significantly upfield as compared to that in the D-*gluco*.[22] In **7a**, the H3 appeared at $\delta$ 3.86 upfield as compared to **7b** at $\delta$ 4.05, further supporting the L-*ido*- and D-*gluco*-configuration at C5 to **7a** and **7b**, respectively. This fixed the configurations at C5 in **7a** and **7b** as 5*S* and 5*R*, respectively. Both isomers, with defined stereochemistry, were elaborated to target molecules in order to get the structure–activity relationship data. The subsequent steps were separately performed on pure isomers **7a** ($R^1$ = *n*-Bu, $R^2$ = H) and **7b** ($R^1$ = H, $R^2$ = *n*-Bu).

In order to obtain 1,3-hydroperoxy alcohol **9**, the deprotection of the C3-*O*-PMB group both in oxidative (DDQ) and mild acidic conditions (0.5 equiv of TfOH, 10% TFA, $CH_3SO_2H$, 0.1 equiv of $SnCl_4$, $Ph_3CBF_4$, 0.2 equiv of $SnCl_2$/TMSCl) failed in our hands, resulting in complex reaction mixtures. This may be attributed to the relative instability of the free hydroperoxy group toward the reaction conditions tested. Therefore, the hydroperoxy group in **7a** and **7b** was protected using *tert*-butyldimethylsilyl chloride (TBSCl) to get *O*-TBS-protected compounds **8a** and **8b**. In the next step, individual treatment of **8a** and **8b** with DDQ followed by treatment with TBAF in THF afforded the corresponding 1,3-hydroperoxy alcohols **9a** and **9b**. In the final step, the individual reaction of **9a** and **9b** with cyclohexanone in the presence of *p*-toluenesulfonic acid (PTSA) in $CH_2Cl_2$ afforded 1,2,4-trioxepanes **10a** and **10b**, respectively. Similarly, reaction of **9a** and **9b** with 2-adamantanone gave **11a** and **11b**, respectively, in good yields (Scheme 2). The $^1$H and $^{13}$C NMR data in $CDCl_3$ for compounds **10a** and **11a** showed sharp and well-defined NMR signals corresponding to a single stable low energy twisted chair (TC) conformation of the seven-membered 1,2,4-trioxepane ring, whereas compounds **10b** and **11b** showed broad signals suggesting more than one conformation of the seven-membered 1,2,4-trioxepane ring. The signal broadening was particularly noticeable for H3, H4, and H5 in the $^1$H NMR spectra as well as for C3, C4, C5, and C8 in the $^{13}$C NMR spectra.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In an attempt to overcome this problem, we recorded the $^1$H NMR spectrum of **10b** in $CDCl_3$ at higher and lower temperature. A significant change was noticed in the spectrum only at lower temperatures where at 0 °C coalescence signals started separating and at −20 °C well-defined peaks appeared suggesting the presence of two distinct conformers for **10b** (Figure 2). We reasoned that the broadening of signals in **10b** could be ascribed to the flipping of two different conformations of the seven-membered 1,2,4-trioxepane ring at room temperature.

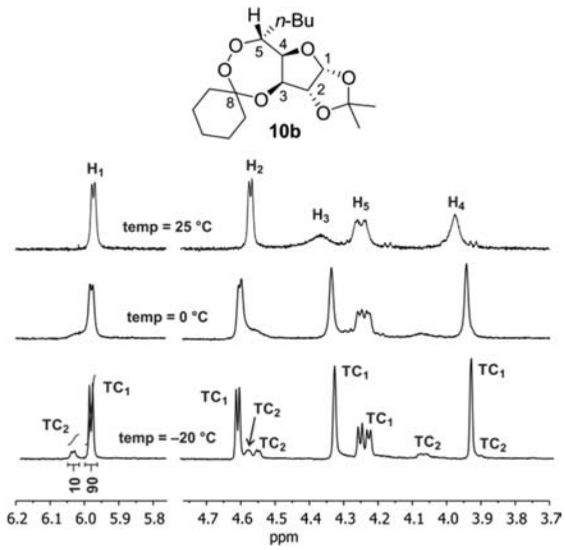


**Figure 2.** $^1$H NMR insets (400 MHz, $CDCl_3$) relative to the 1,2,4-trioxepane ring protons of **10b** at different temperatures.

To substantiate the above observations, we performed DFT calculations to obtain energy-minimized conformations of the 1,2,4-trioxepane ring in compounds **10a** and **10b**. A Monte Carlo conformational search using the MMFF94 molecular mechanics force field on **10a** and **10b** identified only two different accessible twisted-chair (TC) conformations of the seven-membered ring (**TC1** and **TC2**, Figure 3), while no energy accessible ring boat conformer was identified, probably due to the conformational restrictions imposed by the fixed tricyclic structure of **10**. The accessible TC conformers were then optimized in chloroform using DFT at the PCM/M06-2*X*/6-311G(d,p) level of theory and were confirmed to be true minima by inspection of the harmonic vibrational frequencies. Finally, two chair transition states (**TSa** and **TSb**, Figure 3) for the **TC1−TC2** pseudorotation were located for **10a** and **10b** at the same level of calculation. Analysis of the intrinsic reaction coordinate (IRC) confirmed that they correctly connect the calculated TC minima on the potential energy surfaces (PES).

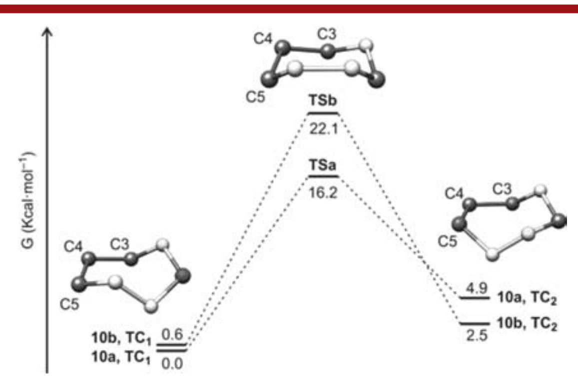


**Figure 3.** Energy profiles for the pseudorotation of TC conformers of **10a** and **10b**. Only the seven-membered ring atoms were depicted for the sake of clarity: carbon atoms, gray; oxygen atoms, white.

The energy barrier for the **TC1-TC2** interconversion of **10a** resulted 16.2 kcal·mol$^{-1}$, with a difference of 4.9 kcal·mol$^{-1}$ between the two conformers (**TC1:TC2** = 100:0 at 25 °C). On the other hand, **10b** has a much higher barrier value of 21.5 kcal·mol$^{-1}$ with a difference of only 1.9 kcal·mol$^{-1}$ between the conformers (**TC1:TC2** = 96:4 at 25 °C). Given these values, it is conceivable that for **10a** only the more stable conformer **TC1** is populated, resulting in well-defined and resolved spectra. On the other hand, for **10b**, a slow seven-membered ring conformational equilibrium exists between **TC1** and **TC2** on the NMR time scale, causing the broadening of the NMR signals of protons and carbons embedded in the ring. From the $^1$H NMR spectrum at −20 °C, the two distinct **10b** conformers **TC1** and **TC2** in 90:10 ratios are clearly distinguishable, in accordance with the stereochemical assignment and with the results of theoretical calculations (Figure 2).

Finally, the synthesized 1,2,4-trioxepanes were tested for in vitro antimalarial activity against both chloroquine-sensitive (D10) and chloroquine-resistant (W2) *Plasmodium falciparum* strains. The results obtained are reported in Table 1. The antimalarial activity is affected both by the C5 configuration and by the ketone-derived framework. The $IC_{50}$ values are less severely dependent on the C4−C5 relative stereochemistry in the case of adamantyl derivatives **11a** and **11b**, as compared to the cyclohexyl derivatives **10a** and **10b**. In any case, $IC_{50}$ in the low micromolar range were obtained for all compounds, except for **10a**. Compound **11b** was the most active of the series with $IC_{50}$ = 0.15 $\mu$M against W2 chloroquine-resistant *Plasmodium falciparum* strains.

**Table 1. Antimalarial Activity of 1,2,4-Trioxepanes 10 and 11 against Chloroquine-Sensitive (D10) and Chloroquine-Resistant (W2) *Plasmodium falciparum* Strains**

| entry | compd | D10 $IC_{50}$[a] ($\mu$M) | W2 $IC_{50}$[a] ($\mu$M) |
|---|---|---|---|
| 1 | **10a** | 1.9 ± 0.2 | 1.8 ± 0.7 |
| 2 | **10b** | 0.4 ± 0.3 | 0.3 ± 0.2 |
| 3 | **11a** | 0.5 ± 0.3 | 0.4 ± 0.2 |
| 4 | **11b** | 0.25 ± 0.11 | 0.15 ± 0.12 |
| 5 | **CQ** | 0.045 ± 0.02 | 0.6 ± 0.1 |

[a]Data are the mean ± SD of three different experiments in duplicate. Chloroquine (CQ) was used as assay control.

In summary, we have developed a novel synthetic procedure for the efficient preparation of D-glucose-derived tricyclic 1,2,4-trioxepanes **10a**,**b** and **11a**,**b** in good yields. Compounds **10a** and **11a** were found to be present in a single twist-chair low energy conformation, while **10b** and **11b** were present as two low energy TC conformations in equilibrium at room temperature on the NMR time scale. These results were substantiated by high-level DFT calculations.

For the first time, sugar-derived 1,2,4-trioxepanes have shown interesting and useful in vitro antimalarial activities in the low micromolar range, prompting us to further investigate analogous enantiopure seven-membered endoperoxides incorporated in sugar frameworks. The presence of three to six carbon frameworks in sugars with a well-defined configuration at each


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carbon atom and the synthetic flexibility of furanose/pyranose ring structures will give access to new libraries of endoperoxide derivatives for antimalarial activity testing.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01996.

Experimental, bioassays and computational details, and spectroscopic data (PDF)

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### Notes

The authors declare no competing financial interest.

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