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Preparation of Antimalarial Endoperoxides by a Formal [2 + 2 + 2] Cycloaddition

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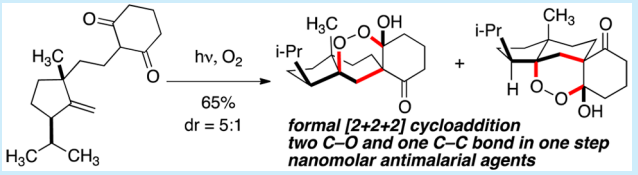
Supporting Information

ABSTRACT: A formal [2 + 2 + 2] cycloaddition reaction between a 1,3-dione, an olefin, and molecular oxygen mediated by light is reported, which delivers endoperoxides in good yield through the formation of two C−O and one C−C bond in one step. The resulting 1,2-dioxanes are stable compounds and can be further derivatized at the hemiacetal position via alkylation or acetylation. All compounds have been evaluated against *Plasmodium falciparum*, and the best compound displayed an IC_{50}-value of 180 nM. A potential mechanistic rationale for the formation of these compounds is presented.



Total synthesis remains a prime source for scientific discovery, not only for both novel reagents and transformations but also for interesting structures that can be obtained by branching off the main synthetic route. This process, sometimes referred to as diverted chemical synthesis or chemical editing,[1] has led to the development of novel drugs used in the clinic such as eribulin from halichondrin,[2] octreotide from somatostatin,[3] or useful tool compounds in biology.[4] In the context of our approach to the complex hexacyclic terpenoid striatin A (**1**),[5] we developed a route based on our successful preparation of cyrneine A.[6] As a required precursor to the establishment of the ABC ring system in **2**, we prepared the chiral intermediate **3** (Figure 1). Interestingly, we observed that this 1,3-dione displayed limited stability upon exposure to light and air and smoothly underwent a subsequent transformation to yield an endoperoxide **4** featuring a novel 1,2-dioxane scaffold.[7] Endoperoxides such as cardamom peroxide (**5**),[8] artemisinin (**6**),[9] or g-factors represented by **7**[10] have recently attracted much interest from a variety of disciplines, and a new generation of antimalarial agents has been developed based on this motif.[11] In view of this potential antimalarial application, and the interesting transformation involved in the formation of endoperoxides, we chose to investigate these unexpected series of reactions in detail. In this letter, we evaluate this unusual formal [2 + 2 + 2] reaction, prepare a series of endoperoxide hemiacetals, and identify nanomolar antimalarial agents based on this endoperoxide chemotype.

The synthetic approach started from commercially available (−)-limonene (**8**), which was transformed to the known intermediate **9** following the footsteps of Wender and co-workers (Scheme 1),[12] but by replacing an $OsO_4/NaIO_4$ mediated oxidative cleavage by an ozonolysis (see Supporting Information for details). The allylic alcohol **9** was subjected to a

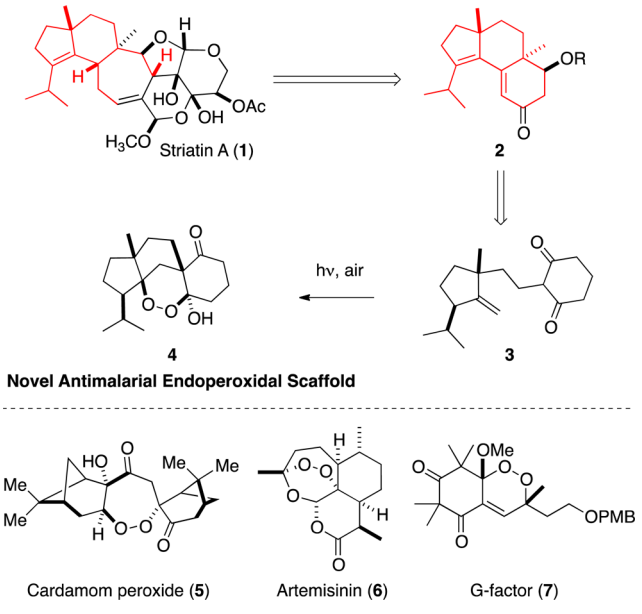


Figure 1. Discovery of a new antimalarial endoperoxide scaffold via diverted total synthesis.

subsequent Eschenmoser−Claisen rearrangement,[13] which established the quaternary stereogenic center and gave the amide **10** in excellent yield and selectivity (24:1). Several methods were evaluated to convert the amide **10** to the known aldehyde **11**,[12] and after tedious experimentation, the use of

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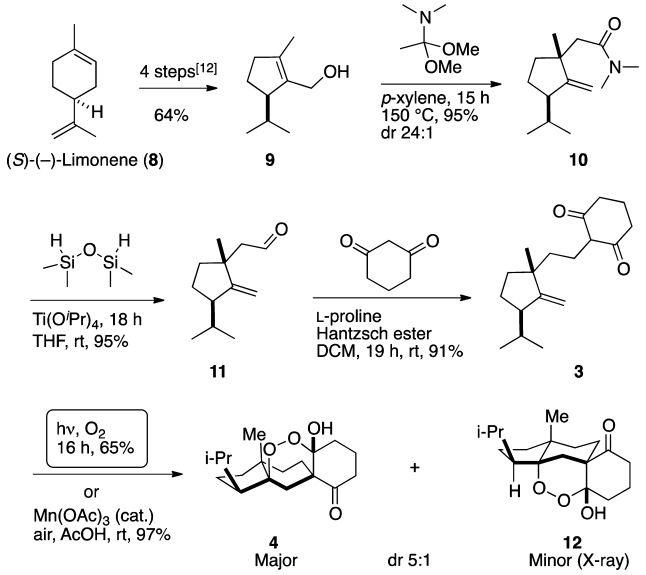
Scheme 1. Synthesis of the Endoperoxides 4 and 12 Starting from (*S*)-(−)-Limonene (8)

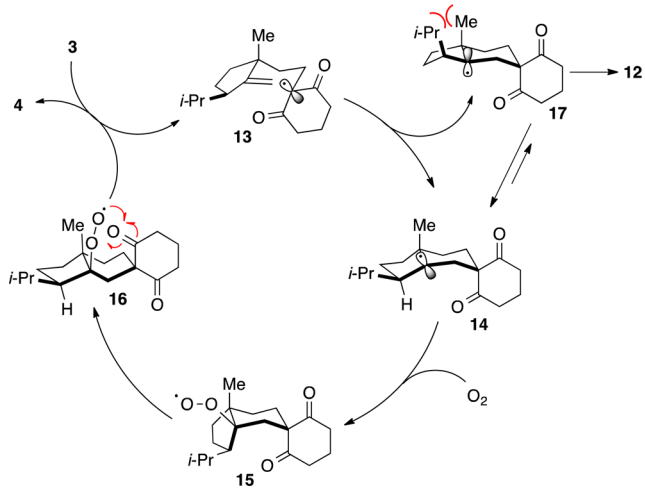


1,1,3,3-tetramethyldisiloxane in combination with $Ti(O^iPr)_4$ furnished the desired intermediate **11** in an excellent yield.[14]

We then subjected the aldehyde **11** to an L-proline catalyzed Knoevenagel condensation, and the double bond of the resulting enedione was chemoselectively reduced *in situ* using the Hantzsch ester to give the diketone **3** in very good yield (91%). Interestingly, upon storage when exposed to air and light in the laboratory, we observed decomposition by NMR and visual analysis. Further experiments by dissolving the diketone **3** in ethyl acetate exposed to air directly yielded the endoperoxides **4** and **12**, separable by flash chromatography, and which could be obtained in a 65% combined yield and a diastereomeric ratio of 5:1. The constitution and configuration of the endoperoxides **4** and **12** were secured by a combination of X-ray crystal structure analysis and NMR spectroscopy as well as derivative synthesis (*vide infra*). An excellent yield of 97% and the same diastereomeric ratio were obtained using a catalytic amount of $Mn(OAc)_3$ in acetic acid exposed to air at room temperature. These Mn-mediated conditions have been used for a variety of 1,3-diones by various groups,[15] and applications in the synthesis of complex molecules such as fusarisetin A have documented their utility.[15h]

The proposed mechanism (Scheme 2) and the stereochemical course of the reaction warrant a number of comments. As a first step, autoxidation[16] of the diketone **3** can be postulated, and the subsequently formed radical **13** attacks the proximal, exocyclic double bond. The tricyclic framework is forged via a 6-*endo*-*trig* cyclization and concomitant C−C bond formation, giving rise to the tertiary radical **14**. While the hybridization of the trivalent C atom remains unknown, the configuration determining step must involve subsequent radical addition to O_2 and peroxy radical **15** formation. The hydroperoxide can then form the hemiacetal **16** by attack to one of the C═O groups. It is likely that this radical will then carry the chain via H-abstraction of the diketone **3** precursor. The stereochemical course of the reaction remained puzzling at first, as the configuration obtained for the major isomer requires attack of O_2 via the sterically more encumbered face of **14**. However, we speculate that, in the course of the formation of the minor diastereoisomer **12**, the methyl and isopropyl

Scheme 2. Proposed Mechanistic Cycle for Endoperoxide Formation via Autooxidation

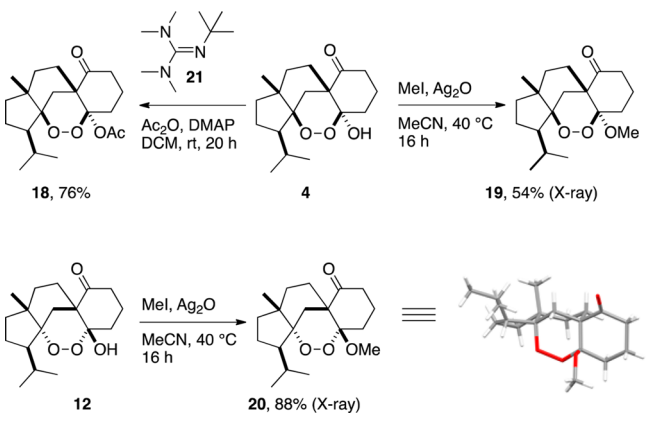


groups of **17** are forced in close proximity, which would render this pathway higher in energy. In addition, formation of the *cis*-bicyclo[4.3.0]nonane framework could be preferred over the corresponding *trans* isomer for structural reasons, or a beneficial electronic influence of a carbonyl group on the SOMO in **14** could be postulated.

We then tested both endoperoxides **4** and **12** against the malaria parasite *Plasmodium falciparum*. Interestingly, the minor compound **12** displayed an IC_{50} value of 0.18 μM, whereas the major compound **4** was 40 times less active (7.1 μM). Both compounds showed very little toxicity against rat myoblasts, and a high selectivity index of around 1000 for compound **12** can be considered remarkable and suggests potential as a lead structure.

Based on this encouraging result, a number of derivatives were subsequently synthesized with the goal of improving the antiplasmodial activity. In order to obtain the acetoxy derivative **18**, standard acetylation conditions such as Ac_2O/DMAP in pyridine or triethylamine only resulted in low conversion or even decomposition at higher temperatures.[10c,15e,17] The use of a stronger base such as the Barton base **21** finally addressed these issues, and the acetylated product **18** was obtained in 76% yield (Scheme 3). Earlier studies on different endoperoxides demonstrated that acetal formation could lead to improved values.[10b,18] Acetalization of the OH group of both

Scheme 3. Derivative Synthesis



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diasteroisomers **4** and **12** under standard conditions (*p*-TsOH (cat.) in MeOH) led to very slow formation of the methylated species **19** and **20**. An improved method consisted of alkylation with CH_3I and Ag_2O, which provided the methylated products **19** and **20** in good yields.[19] The configuration and constitution of both compounds were secured by X-ray crystal structure analysis.

Unfortunately, all derivatives displayed lower antiplasmodial activity when compared to the hemiacetal isomer **12**, while the cytotoxicity values remained in the same range (Table 1).

Table 1. Antiplasmodial and Cytotoxic Evaluation of the Endoperoxides

compound	IC_{50} [a,c]	LD_{50} [a,d]	SI[e]
4	7.1	165	23
12	0.18	169	939
18	32.2	168	5
19	24.3	59	2
20	3.0	175	58
artemisinin[b]	0.0035	349	98 500
chloroquine[b]	0.0063	107	17 145

[a]All results are reported as IC_{50} values in μM. [b]Artemisinin and chloroquine were additionally tested for confirmation reasons. [c]*Plasmodium falciparum* NF54 strain. [d]Rat myoblast L6 cells. [e]The selectivity index (SI) is defined by LD_{50}/IC_{50}.

Overall, it appears that the hemiacetal function is crucial for antiplasmodial activity. This is in contrast to other SAR-studies, whereas a 10× increase in activity could be observed.[10b,18,19]

In conclusion, an operationally simple, formal [2 + 2 + 2] reaction involving oxygen was utilized for the preparation of novel endoperoxide antimalarial scaffolds. The mechanism of this reaction was postulated to involve autoxidation of the 1,3-dione, subsequent radical ring closure followed by trapping with O_2, and hemiacetal formation. A series of derivatives were prepared, and antiplasmodial activity with IC_{50} values in the nano- and micromolar range were observed, with little cytotoxicity. This approach therefore allows for straightforward access to antimalarial agents from simple and cheap building blocks.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02773.

Detailed experimental procedures, full characterization, and copies of all spectra. (PDF)

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Notes

The authors declare no competing financial interest.

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