

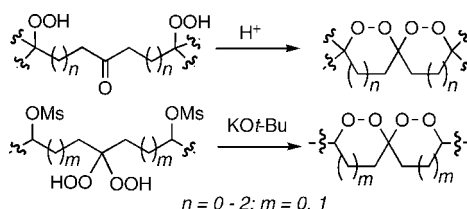
Synthesis of Spiro-bisperoxyketals

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ABSTRACT



Syntheses of spirocyclic bis-1,2-dioxolanes, bis-1,2-dioxanes, and bis-1,2-dioxepanes are achieved through intramolecular ketalizations of hydroperoxy ketones or intramolecular alkylations of *gem*-dihydroperoxides. The spiroperoxides have excellent thermal and chemical stability, and several display promising activity against *P. falciparum*.

The efficacy of artemisinin (**1**, Figure 1) against drug-resistant strains of *Plasmodium falciparum*, the most lethal form of malaria, has focused significant attention on the development of new classes of peroxide-based antimalarials.^{1,2} Although artemisinin and derivatives such as artemether (**2**) are used clinically, there is a need for new antimalarial agents that are accessible, stable, inexpensive, and able to achieve effective cures with limited dosing regimens.

Several synthetic 1,2,4,5-tetraoxanes, exemplified by **3** and **4** (Figure 1), have demonstrated promising levels of antimalarial activity.^{3–5} We became interested in the antimalarial potential of analogous tetraoxanes featuring a spiro relationship of the peroxide units. We now report the synthesis of a series of spiro-linked bisperoxyketals (Figure 2) as well as

preliminary data regarding their structure, reactivity, and antimalarial activity.

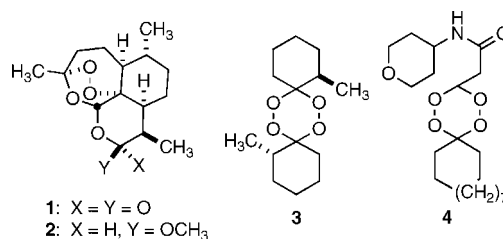


Figure 1. Existing peroxide-containing antimalarials.

We envisaged two complementary approaches to these targets (Figure 2). Spiroketals **5a–c**, which incorporate tertiary peroxides, would arise through intramolecular ketalization, an approach preceded by the facility of corresponding intermolecular reactions.^{6,7} Spiroketals **6a** and **6b** would arise through intramolecular alkylations of *gem*-dihydroperoxides.⁸ While the introduction of cyclic peroxides through intramolecular nucleophilic substitution has been

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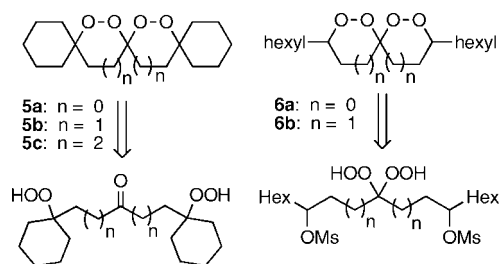


Figure 2. Retrosynthetic overview.

mainly explored for five-membered rings,⁹ sequential inter- and intramolecular alkylations of *gem*-dihydroperoxides by primary 1,*n*-diiodides has been applied to the synthesis of 1,2,4,5-tetraoxacycles.¹⁰ Moreover, we have applied intramolecular alkylations of hydroperoxyacetals to synthesis of monocyclic alkoxy-1,2-dioxanes.¹¹

The syntheses of tetracyclic spiroketals **5a–c**, illustrated in Scheme 1, were based upon intramolecular ketalization of a carbonyl group by tertiary hydroperoxides derived from regioselective Cobalt-mediated dioxygenations of trisubstituted alkenes.^{12,13}

The synthesis of the tetracyclic spiro-dioxolane (**5a**) began with oxidation of 2-cyclohexenylethanol, followed by a Prins reaction of the resulting aldehyde to generate alcohol **7**.¹⁴ Cobalt (II)-mediated dioxygenation using O'Neill's 2,2,6,6-tetramethylheptane-3,5-dione (THD) ligand proved unsuccessful either for the alcohol or the corresponding ketone¹³ but could be cleanly accomplished on the corresponding acetate to produce bis-silyl peroxide **9**. Treatment with *i*-Bu₂AlH achieved chemoselective cleavage of the ester to afford the secondary alcohol, which was oxidized to furnish ketone **10a**. Acid-promoted desilylation was accompanied by spontaneous cyclization to afford spiroketal **5a**.

For the syntheses of the six- and seven-membered tetracyclic spirocycles, the Co-mediated bisdioxygenation could be directly executed on trisubstituted dienones **12b** and **12c** (Scheme 1). The resulting tertiary bisperoxy ketones **10b** and **10c** underwent tandem desilylation and ketalization, as before, to directly form the tetracyclic spiroketals **5b** and **5c**.

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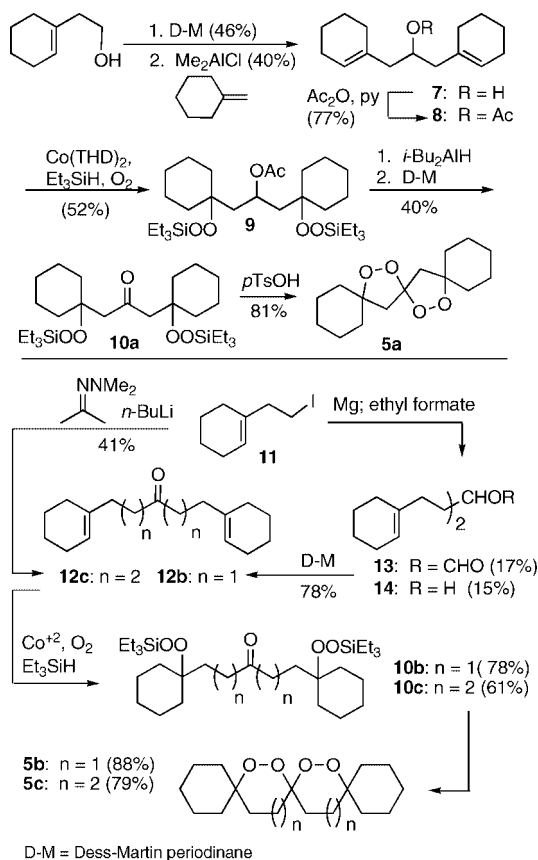
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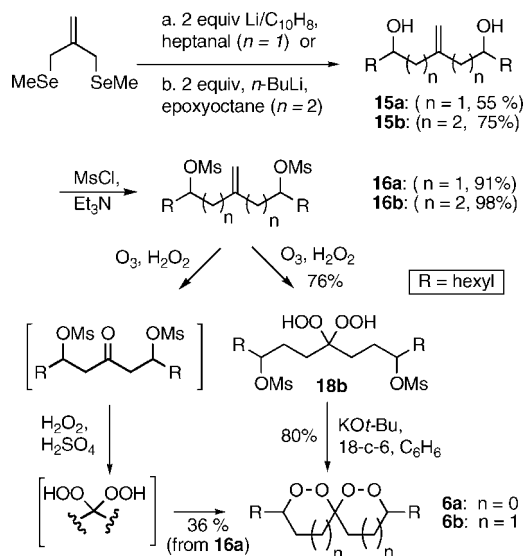
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Scheme 1. Syntheses of Spiro-bisepoxyketal **5a–c**



For syntheses of the bicyclic peroxyketals **6a** and **6b** (Scheme 2), intramolecular perketalization would be disadvantaged by the lack of a method for regioselective introduction of the precursor secondary hydroperoxides. Our ap-

Scheme 2. Syntheses of Spiro-**6a** and -**6b**



proach therefore focused on 2-fold intramolecular alkylation of 1,1- bishydroperoxides. The synthesis of the spiro-dioxolane **6a** began with 2-fold reaction of heptanal with dilithiated isobutylene to form diol **15a** as an inseparable mixture of *syn*- and *anti*-diastereomers. Ozonolysis of the

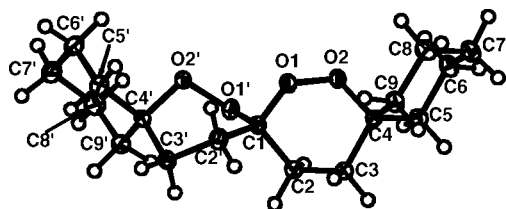


Figure 3. ORTEP plot of **5b** at 50% probability; primed atoms are generated by the symmetry operation $-x+3/2, -y+1, z$.

bismethanesulfonate (**16a**) in the presence of excess H_2O_2 did not furnish the desired *gem*-1,1-dihydroperoxide but instead the corresponding ketone, reflecting the influence of the allylic sulfonates on the regioselectivity of carbonyl oxide formation.¹⁵ The 3,3-bismesyloxy ketone was unstable toward β -elimination and was directly reacted with $\text{H}_2\text{O}_2/\text{I}_2$ or $\text{H}_2\text{O}_2/\text{H}_2\text{SO}_4$ to generate a mixture of three diastereomeric spiro-bicyclic peroxyketals **6a** (see Figure 4).⁶ The result

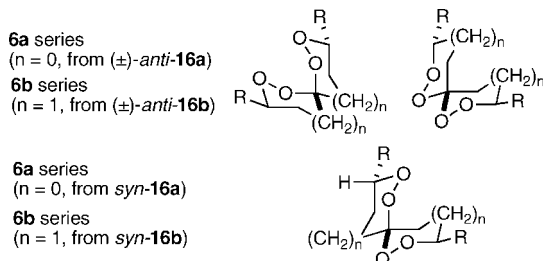


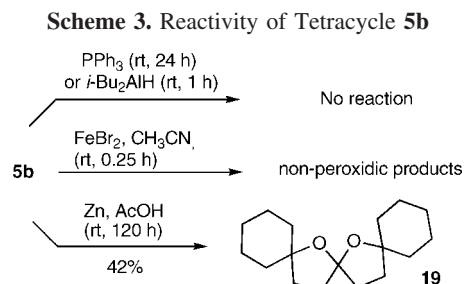
Figure 4. Configurational possibilities for **6a** and **6b**.

presumably reflects formation and spontaneous cyclization of the intermediate *gem*-dihydroperoxide.

For the synthesis of the spiro-bis-1,2-dioxane **6b**, the cyclization precursor **18b** was prepared through ozonolysis of bismesyloxyalkene **16b** in the presence of excess H_2O_2 (Scheme 2).⁶ Reaction of *gem*-dihydroperoxide **18b** with KO-*t*-Bu in the presence of 18-crown-6 resulted in the rapid formation of spiro bis-1,2-dioxane **6b** as a mixture of three diastereomers (see Figure 4). The major diastereomer, which could be purified by flash chromatography, was a low-melting solid which slowly yellowed upon storage at room temperature. The other two diastereomers were incompletely separated even by HPLC.

The tetracyclic spiro-bis(1,2-dioxane) **5a–c** were stable to room temperature storage. The tetracyclic spirocycle **5b** melts

without decomposition near 132 °C and displayed evidence of self-accelerating decomposition only upon heating to nearly 240 °C (DSC); similar behavior was observed for **5c**. Furthermore, **5b** was unreactive toward *i*-Bu₂AlH or PPh₃ (Scheme 3). Treatment with ferrous bromide resulted in



relatively rapid cleavage to nonperoxidic products. Reduction by Zn/HOAc occurred over a period of days to furnish a new, nonperoxidic spiroketal (**19**). The strongly acidic conditions of spiroketal formation (Scheme 1) suggests the spiroketals are also resistant to Hoch/Criegee-type skeletal rearrangements.¹⁶

Although a full analysis of the conformation of the spiro-bis(1,2-dioxane) **6a** and **6b**, the cyclization precursor **18b** was prepared through ozonolysis of bismesyloxyalkene **16b** in the presence of excess H_2O_2 (Scheme 2).⁶ Reaction of *gem*-dihydroperoxide **18b** with KO-*t*-Bu in the presence of 18-crown-6 resulted in the rapid formation of spiro bis-1,2-dioxane **6b** as a mixture of three diastereomers (see Figure 4). The major diastereomer, which could be purified by flash chromatography, was a low-melting solid which slowly yellowed upon storage at room temperature. The other two diastereomers were incompletely separated even by HPLC.

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cultures of human red blood cells; the IC₅₀ of artemisinin is presented for comparison (Table 1). The tetracyclic spiro-

reactivity, and antimalarial activity of this class of compounds is in progress.²³

Table 1. Activity against the NF54 Strain of *P. falciparum*^a

spiroketal	IC ₅₀ , ng/mL (trials)
5a	70 (3)
5b	1508 (4)
5c	>5000 (2)
6a	2483 (4)
6b	126 (4)
1	2.1 (4)

^a Details in the Supporting Information.

bis-1,2-dioxepane (**5c**) and spiro-bis-1,2-dioxane (**5b**) demonstrated little or no activity. However, the tetracyclic spiro-bis-1,2-dioxolane (**5a**) and the bicyclic spiro-bis-1,2-dioxane (**6b**) displayed relatively strong antimalarial activity, a significant outcome given the minimal level of skeletal functionalization.

In conclusion, we have demonstrated new approaches to spirobisperoxyketals. The successful construction of spiro-1,2-dioxolane and -1,2-dioxane skeletons through intramolecular nucleophilic displacements should facilitate stereo-defined synthesis and study of individual spiroketal stereoisomers. The ease of the intramolecular peroxyketalizations suggests potential extensions to other spirocyclic systems, including perorthoester analogs. Further studies into the synthesis,

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Supporting Information Available: Details regarding preparation, characterization, and antimalarial testing of new compounds, as well as DSC and crystallographic data for **5b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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