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Synthesis of Spiro-bisperoxyketals

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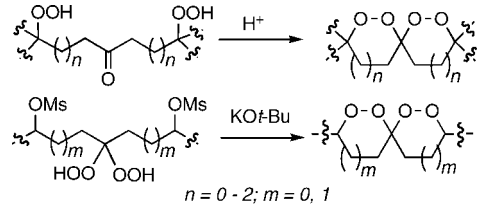
ABSTRACT



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.

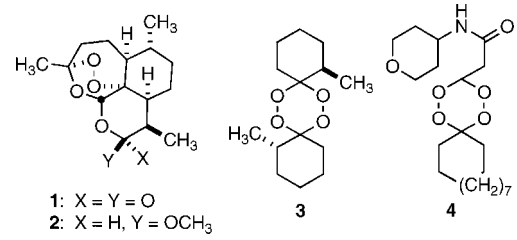


Figure 1. Existing peroxide-containing antimalarials.

We envisaged two complementary approaches to these targets (Figure 2). Spiroketals **5a**−**c**, which incorporate tertiary peroxides, would arise through intramolecular ketalization, an approach precedented 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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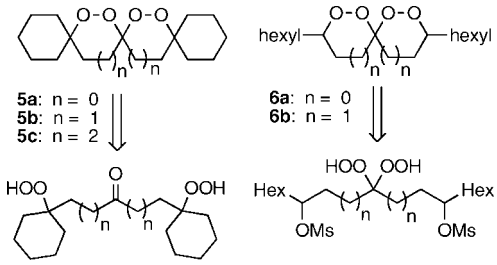


Figure 2. Retrosynthetic overview.

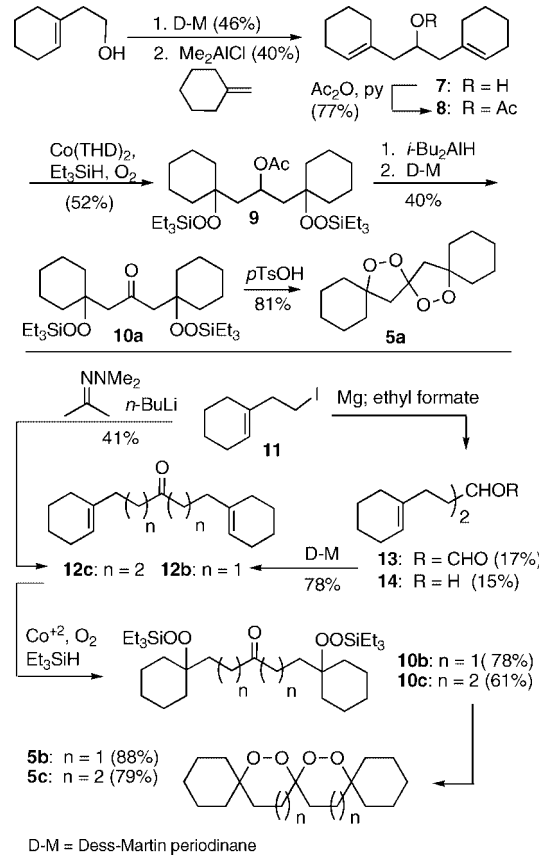
mainly explored for five-membered rings,[9] sequential inter- and intramolecular alkylations of *gem*-dihydroperoxides by primary 1,*n*-diiodides has been applied to the synthesis of 1,2,4,5-tetraoxacycles.[10] Moreover, we have applied intramolecular alkylations of hydroperoxyacetals to synthesis of 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 ketone[13] but could be cleanly accomplished on the corresponding acetate to produce bis-silyl peroxide **9**. Treatment with *i*-Bu_2AlH 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**.

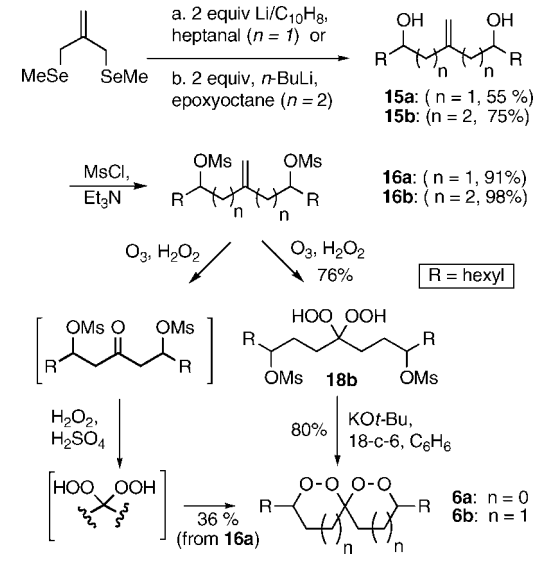
For the syntheses of the six- and seven-membered tetracyclic spirocycles, the Co-mediated bisdioxygenation could be directly executed on trisubstituted dienones **12b** and **12c** (Scheme 1). The resulting tertiary bisperoxy ketones **10b** and **10c** underwent tandem desilylation and ketalization,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

Scheme 1. Syntheses of Spiro-bisperoxyketal **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**



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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

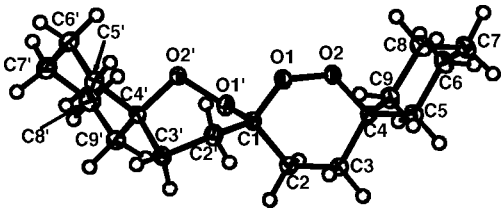

Figure 3. ORTEP plot of **5b** at 50% probability; primed atoms are generated by the symmetry operation $-x+3/2$, $-y+1$, z.

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 H_2O_2/I_2 or H_2O_2/H_2SO_4 to generate a mixture of three diastereomeric spiro-bicyclic peroxyketals **6a** (see Figure 4).[6] The result

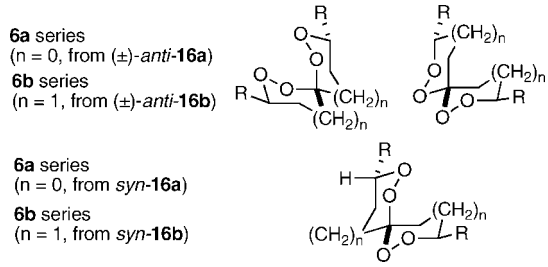

Figure 4. Configurational possibilities for **6a** and **6b**.

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-bisperoxyketals **5a**−**c** were stable to room temperature storage. The tetracyclic spirocycle **5b** melts

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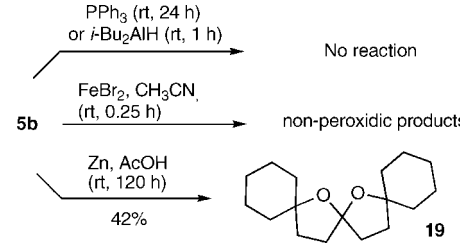
without decomposition near 132 °C and displayed evidence of self-accelerating decomposition only upon heating to nearly 240 °C (DSC); similar behavior was observed for **5c**. Furthermore, **5b** was unreactive toward *i*-Bu_2AlH or PPh_3 (Scheme 3). Treatment with ferrous bromide resulted in

Scheme 3. Reactivity of Tetracycle **5b**



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-bisperoxyketals must await a more detailed study, we conducted some preliminary experiments on **5b** and **6b**. Nonperoxidic 6,6-spiroketals exhibit a preference for isomers which minimize steric interactions while maximizing the number of axial anomeric C−O linkages.[17] Evidence of both *exo*- and *endo*-anomeric interactions have been observed in simple six-membered ring peroxides,[18] which typically favor chairlike conformations.[19–21] However, the crystal structure of **5b** found one of the two 1,2-dioxanes in a twist-chair conformation (Figure 3).

In the case of the bicyclic spiroketals **6a** and **6b**, the cyclization of a mixture of *syn*- and *anti*-precursors was anticipated to generate three configurational isomers (Figure 4).[17,22] The major diasteromer of **6b**, which could be isolated in pure form, displayed only 10 ^{13}C signals and was unchanged upon exposure to strongly acidic conditions ($TsOH{\cdot}H_2O$, CH_2Cl_2). The remaining two diasteromers were incompletely resolved even by HPLC, but appeared to undergo equilibration upon prolonged storage or upon treatment with acid.

Several of the bisperoxyketals were tested against a chloroquine-resistant strain (NF54) of *P. falciparum* in

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cultures of human red blood cells; the IC_{50} of artemisinin is presented for comparison (Table 1). The tetracyclic spiro-

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 bicylic 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 faciliate stereodefined 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, reactivity, and antimalarial activity of this class of compounds is in progress.[23]

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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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(23) While we experienced no hazards in the course of this work, any preparative work with peroxides should be conducted with an awareness of the potential for spontaneous and exothermic decomposition reactions: Medard, L. A. *Accidental Explosions: Types of Explosive Substances*; Ellis Horwood Ltd.: Chichester, 1989; Vol. 2. Patnaik, P. A. *Comprehensive Guide to the Hazardous Properties of Chemical Substances*; Van Nostrand Reinhold: New York, 1992. Shanley, E. S. In *Organic Peroxides*; Swern, D., Ed.; Wiley-Interscience: New York, 1970; Vol. 3, p 341. *Safety And Handling Of Organic Peroxides (AS-109)*; The Society of the Plastics Industry, Inc.: Washinton, DC, Aug 1999. http://www.Plasticsindustry.Org/About/Organicperoxide.html.