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Intramolecular Reactions of Hydroperoxides and Oxetanes: Stereoselective Synthesis of 1,2-Dioxolanes and 1,2-Dioxanes

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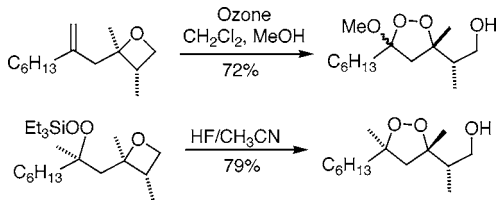
ABSTRACT



The 5-*exo* openings of oxetanes by hydroperoxides proceed rapidly and stereospecifically to furnish 1,2-dioxolanes. The corresponding 6-*exo* cyclizations are slower and proceed with moderate stereoselectivity. In the case of hydroperoxy acetals, 5-*exo* nucleophilic transfer of alkoxide competes effectively with 6-*exo* attack by the hydroperoxide.

1,2-Dioxolanes and 1,2-dioxanes are common substructures in peroxide natural products;[1] three examples are illustrated in Figure 1. Although numerous approaches have been

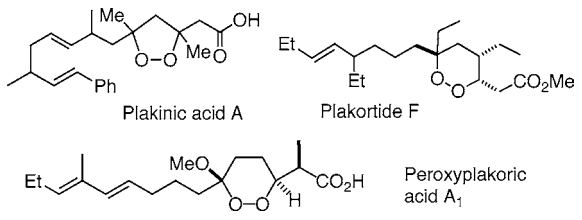
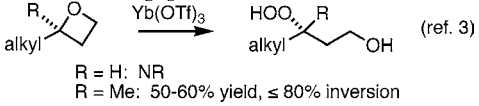


Figure 1. Examples of 1,2-dioxolane and 1,2-dioxane natural products

reported for the synthesis of five- and six-membered ring peroxides,[2] few are applicable to the stereoselective introduction of secondary or tertiary peroxide linkages. We now report the stereospecific 5-*exo* opening of oxetanes by hydroperoxides and hydroperoxy acetals to form 1,2-dioxolanes and 3-alkoxydioxolanes, as well as the slower but stereereoselective 6-*exo* cyclization of hydroperoxyoxetanes to form 1,2-dioxanes.

Our approach grew from investigations of intermolecular acid-catalyzed opening of oxetanes with hydrogen peroxide.[3] This methodology, while providing the first general approach to 3-hydroperoxyalkanols, is limited to tertiary oxetane centers, requires preparation of ethereal solutions of H_2O_2, and most seriously, proceeds with moderate and sometimes capricious stereoselection.[4]



We became curious as to whether these limitations could be avoided for the corresponding intramolecular reactions.

(1) Casteel, D. A. *Nat. Prod. Rep.* **1999**, *16*, 55.
(2) McCullough, K. J.; Nojima, M. *Curr. Org. Chem.* **2001**, *5*, 601.

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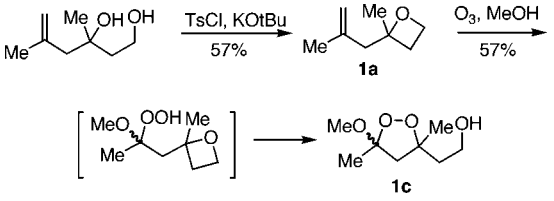
Encouraging precedent existed in reports of 5-*exo* and 6-*exo* cyclizations of hydroperoxides onto oxiranes.[5] As an initial test, we planned to investigate the acid-promoted 5-*exo* tet opening of an oxetane by a neighboring hydroperoxy ketal (Scheme 1). To our surprise, methanolic ozonolysis of

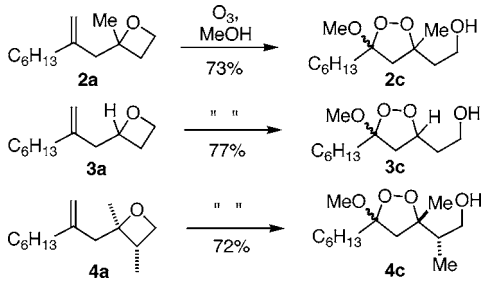
Scheme 1. Spontaneous 5-*Exo* Cyclization



oxetane **1a** did not furnish the anticipated hydroperoxy ketal, but instead afforded alkoxydioxane **1c** as a 1:1 mixture of *cis* and *trans* isomers. Analysis of the crude reaction mixture (TLC, NMR) verified that the cyclic products were formed in the reaction flask, and not upon workup or purification. The facility of the cyclization is surprising, as similar closures onto epoxides typically require the presence of acid catalysts.[5]

Ozonolysis of unsaturated oxetanes **2a** and **3a** resulted in the direct formation of 1,2-dioxolanes **2c** and **3c** as 1:1 mixtures of *cis* and *trans* diastereomers (Scheme 2).[6] The

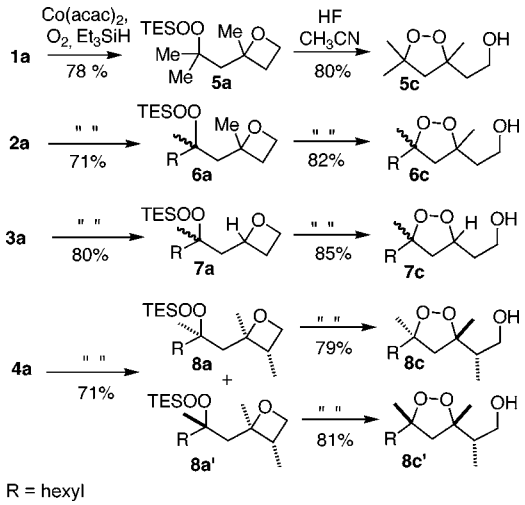
Scheme 2. 5-*Exo* Cyclization of Hydroperoxyacetals



successful cyclization onto a secondary oxetane is noteworthy given the failure of the corresponding intermolecular reaction.[3] The stereospecificity of cyclization was investigated with oxetane **4a**, a substrate incorporating an additional methyl group as a stereochemical marker. Ozonolysis of the 1,1-disubstituted alkene in **4a** would be expected to generate a mixture of epimeric hydroperoxy acetals; a nonstereospecific cyclization could form up to four diastereomeric products. Instead, ozonolysis of **4a** furnished a 1:1 mixture of two diasteromers epimeric at the C_5 peroxy acetal.

The unsaturated oxetanes also provided an opportunity to investigate 5-*exo* cyclizations of alkyl hydroperoxides (Scheme 3). Cobalt-mediated reductive dioxygenation[7] of **1a** furnished

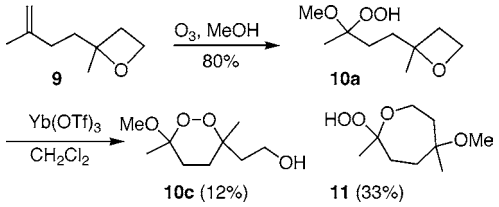
Scheme 3. Cyclization of Oxetane Hydroperoxides



triethylsilyl peroxide **5a**, which underwent deprotection with aqueous HF to directly produce 1,2-dioxolane **5c**. Triethylsilyl peroxides **6a** and **7a**, prepared as inseparable 1:1 mixtures of isomers upon oxygenation of **2a** and **3a**, underwent deprotection to furnish **6c** and **7c** as 1:1 mixtures of diastereomers. Peroxides **8a** and **8a′**, isolated as individual diastereomers upon oxygenation of **4a**, underwent deprotection/cyclization to furnish diastereomerically pure dioxolanes **8c** and **8c′**, respectively.[8]

Moving to the 6-*exo* series revealed a tremendous difference in reactivity (Scheme 4). Ozonolysis of homoallyl

Scheme 4. Competing 6-*Exo* Cyclization and 5-*Exo* Alkoxide Transfer from a Hydroperoxyacetal



oxetane **9** furnished a 1:1 mixture of diasteromeric hydroperoxy ketals **10a** which could be isolated and purified by silica chromatography. Treatment with protic or Lewis acid resulted in the slow formation of alkoxy-1,2-dioxane (**10c**, mixture of diastereomers) accompanied by a hydroperoxyoxepane (**11**). The structure of the latter was confirmed by

(3) Dussault, P. H.; Trullinger, T. K.; Noor-e-Ain, F. *Org. Lett.* **2002**, *4*, 4591.

(4) Dai, P. Ph.D. Thesis, University of Nebraska—Lincoln, 2004.

(5) Porter, N. A.; Funk, M. O.; Gilmore, D.; Isaac, R.; Nixon, J. *J. Am. Chem. Soc.* **1976**, *98*, 6000. Bascetta, E.; Gunstone, F. D.; Scrimgeour, C. M. *Chem. Phys. Lipids* **1984**, *35*, 349. Bloodworth, A. J.; Spencer, M. D.; *Tetrahedron Lett.* **1990**, *31*, 5513. Xu, X.-X.; Dong, H.-Q. *Tetrahedron Lett.* **1994**, *35*, 9429.

(6) Experimental procedures, including syntheses of the unsaturated oxetanes, are described in the Supporting Information.

(7) Tokuyasu, T.; Kunikawa, S.; Masuyama, A.; Nojima, M. *Org. Lett.* **2002**, *4*, 3595.

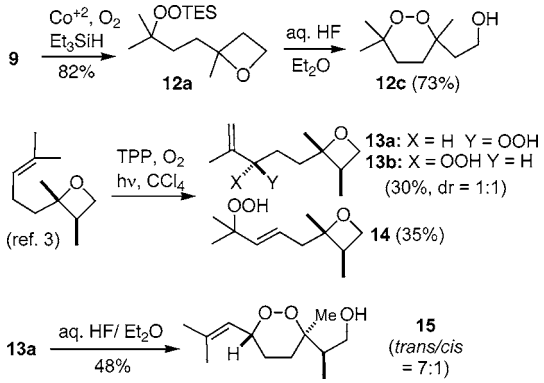
(8) The stereochemical assignments for **8a** and **8a′** assume inversion of configuration during opening of the oxetane to form the 1,2-dioxolane.

reduction to a hydroxyketone. These results are reminiscent of halocyclizations of unsaturated peroxy acetals,[9] in which 5-*exo* attack by alkoxide competes with the desired 6-*exo* attack by hydroperoxide. In our case, attack by alkoxide results in formation of a hydroperoxycarbenium ion which is trapped by the liberated primary alcohol to introduce the oxepane ring system.

We next investigated the corresponding 6-*exo* cyclizations of alkyl hydroperoxides (Scheme 5). Treatment of silylated tertiary peroxide **12a** with aqueous HF/ether resulted in rapid deprotection to a free hydroperoxide (1−2 h, TLC)[10] followed by a slower cyclization (1−2 days) to the 1,2-dioxane **12c**.[11] Application of the same conditions to a stereoisomerically pure hydroperoxide (**13a**) derived from photooxygenation of an unsaturated oxetane[4] furnished 1,2-dioxane **15** as a 7:1 mixture of *trans* and *cis* diastereomers.

In conclusion, cyclization of hydroperoxides and hydroperoxy acetals onto oxetanes provides a stereoselective method for formation of 1,2-dioxolanes and 1,2-dioxanes.

Scheme 5. 6-*Exo* Cyclizations of Alkyl Hydroperoxides



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Supporting Information Available: Substrate synthesis, experimental procedures, and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051407H

(9) Tokuyasu, T.; Masuyama, A.; Nojima, M.; McCullough, K. J. *J. Org. Chem.* **2000**, *65*, 1069. Dussault, P. H.; Davies, D. R. *Tetrahedron Lett.* **1996**, *37*, 463.

(10) Smith, L. L.; Hill, F. L. *J. Chromatogr.* **1972**, *66*, 101. Alkyl hydroperoxides stain red-pink upon exposure to a TLC dip derived from *N,N′*-dimethyl-*p*-phenylenediamine, whereas dialkyl peroxides change color only upon standing or warming.

(11) Deprotection in aq HF/CH_3CN resulted in the formation of a 1,2,4-azatrioxacane byproduct.