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Opening of Substituted Oxetanes with H_2O_2 and Alkyl Hydroperoxides: Stereoselective Approach to 3-Peroxyalcohols and 1,2,4-Trioxepanes

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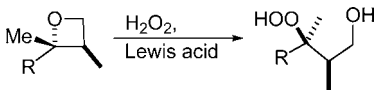
ABSTRACT



Lewis acid-catalyzed opening of oxetanes by hydrogen peroxide proceeds regioselectively and with good to moderate stereoselectivity to furnish enantiomerically enriched 3-hydroperoxyalkanols. The corresponding opening using alkyl hydroperoxides furnishes 3-peroxyalkanols. The hydroperoxyalkanols are easily converted into enantiomerically enriched 1,2,4-trioxepanes, building blocks for antimalarials.

In the course of synthetic approaches to 1,2-dioxolane-containing natural products,[1] we realized the need for an asymmetric synthesis of 1,3-hydroperoxyalkanols. Existing approaches to 1,3-peroxyalkanols, or for that matter, 1,2-dioxolanes, are largely racemic.[2−5] We now report an asymmetric synthesis of 1,3-hydroperoxyalcohols and 1,3-peroxyalcohols based upon the Lewis acid catalyzed perhydrolysis of substituted oxetanes (Figure 1). In addition, we

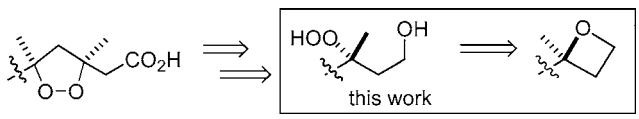


Figure 1. Perhydrolysis of oxetanes.

report the conversion of the hydroperoxide products into enantiomerically enriched 1,2,4-trioxepanes.

The acid-catalyzed opening of epoxides by hydrogen peroxide and alkyl hydroperoxides has been reported; however, there has been little systematic study of these reactions.[6] The alcoholysis of oxetanes has been previously applied to the synthesis of 3-alkoxyalkanols.[7] However, the only report describing the corresponding reaction of a hydroperoxide is an alumina-promoted opening of a racemic oxetane with *tert*-butyl hydroperoxide.[8] We therefore set out to investigate the corresponding reactions of enantiomerically enriched oxetanes. Oxetanes were prepared via cyclodehydration of enantiomerically enriched 1,3-diols. The diols were prepared via opening of 2,3-epoxyalcohols with Red-Al, $LiAlH_4$, or lithium dimethyl cuprate, as illustrated in Scheme 1.[9,10] Mosher ester analysis demonstrated that the epoxy alcohols and the derived diols were formed in ≥80% ee.[11]

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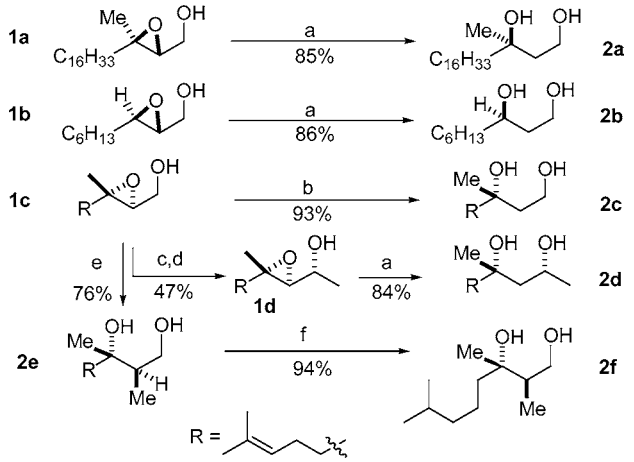
Scheme 1. Diol Synthesis[a]

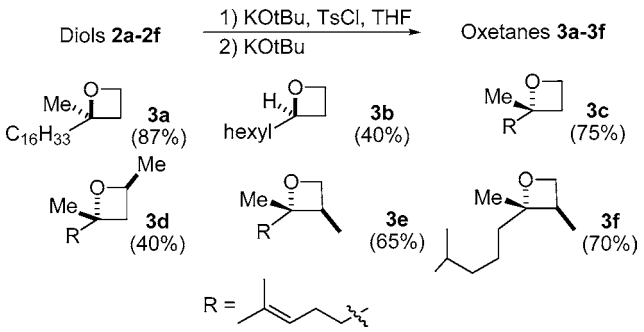


[a] Key: (a) Red-Al; (b) $LiAlH_4$; (c) Dess−Martin periodinane; (d) MeMgBr, separation; (e) Me_2CuLi; (f) Pd/C, H_2.

The relative stereochemistry of diol **2d** was verified by ^{13}C NMR and NOE analysis of the derived 1,3-dioxane.[12]

Cyclization of the 1,3-diols to oxetanes is illustrated in Scheme 2. After initially employing a convenient literature

Scheme 2. Oxetane Synthesis



procedure based upon one-pot monotosylation/cyclization[13] of the dilithio dianion, we found that both the rate and yield of cyclization were improved by the addition of potassium *tert*-butoxide.[14] Eventually, we found that use of potassium *tert*-butoxide in tetrahydrofuran for both monotosylation and cyclization (either as a one-pot reaction or after a brief workup of the monotosylate) achieved a rapid and high-yielding closure (Scheme 2). The modified method was particularly efficient for synthesis of 2,2-disubstituted and 2,2,3-trisubstituted oxetanes and allowed synthesis of the 2,2,4-trisubstituted oxetane **3d**.

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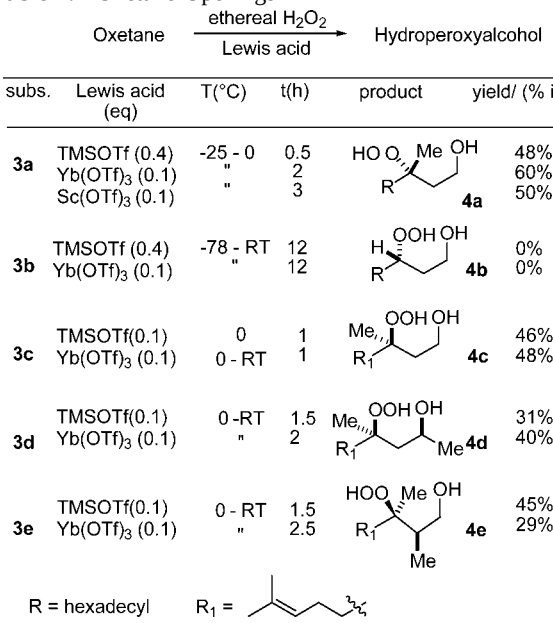
Table 1. Oxetane Openings



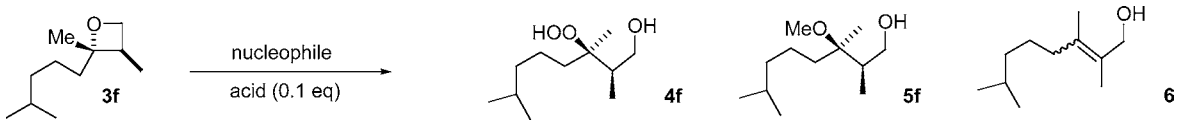
Ring opening was initially investigated with 2,2-disubstituted oxetane **3a** (Table 1) using "anhydrous" H_2O_2/ether.[15,16] No reaction was observed in the presence of $MgCl_2$, $ZnCl_2$, or BF_3OEt_2, while use of TFA, CSA, $BF_3{\cdot}OEt_2$, or H_2SO_4 produced low yields of hydroperoxyalcohol and significant amounts of 1,3-diol. However, perhydrolysis in the presence of catalytic amounts of TMSOTf, $Yb(OTf)_3$, or $Sc(OTf)_3$ provided good yields of 3-hydroperoxy-1-alkanol **4a**. The most successful conditions were next applied to oxetanes **3b**−**e**. Reactions of oxetanes **3c**−**e** occurred upon warming to near room temperature while the secondary oxetane **3b** failed to undergo the desired reaction even at room temperature. Stereochemical assignments and percent inversion are based upon reduction of the hydroperoxyalcohols to 1,3-diols and comparison against starting diols by optical rotation (**2a**,**c**) or ^1H NMR (**2d**,**e**); details are provided in the Supporting Information.

In the course of this work, we observed that that the unsaturated hydroperoxides derived from **3c**,**d** were prone to decomposition in the presence of excess Lewis acid. We therefore employed a saturated analogue (**3f**) to investigate the factors controlling reactivity and selectivity of $Yb(OTf)_3$-

(15) Ethereal hydrogen peroxide was prepared in small batches by extraction of 1−5 mL of 30% aqueous H_2O_2 with 10 mL of anhydrous ether; Nagata, R.; Saito, I. *Synlett* **1990**, 291−300. The organic layer was dried over $MgSO_4$ and used immediately. Excess ethereal H_2O_2 was never stored but rather quenched with aqueous sulfite or bisulfite at the end of each work period. Reaction workups employed an aqueous wash prior to any concentration.

(16) While we experienced no problems in the course of this work, organic solutions of anhydrous H_2O_2 and low molecular weight hydroperoxides should be treated as potential explosives, and experimenters should follow standard safety precautions, including minimization of scale and avoidance of redox-active metals or their salts: Medard, L. A. *Accidental Explosions: Types of Explosive Substances*; Ellis Horwood Limited: 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, pp 341−369.

Table 2. Opening of Saturated Oxetane



nucleophile	solvent	catalyst	T (°C)	t (h)	**4** (%)	**5** (%)	% inversion	**6** (%)
H_2O_2 (from ether)	Et_2O	$Yb(OTf)_3$	rt	4	37		88	
	CH_2Cl_2	$Yb(OTf)_3$	−78	0.5	46		84	
H_2O_2 (from CH_2Cl_2)	CH_2Cl_2	$Yb(OTf)_3$	−78	0.08	0			40
	CH_2Cl_2/ Et_2O	$Yb(OTf)_3$	rt	4	24			
MeOH	MeOH	H_2SO_4	rt	0.5		56	92	
	MeOH	$Yb(OTf)_3$	rt	2		47	92	

promoted perhydrolysis (Table 2). Reaction of **3f** with ethereal H_2O_2 proceeded at room temperature to furnish **4f** with a higher degree of inversion than had been observed for **3e**, the unsaturated analogue. The perhydrolysis proved to be strongly dependent upon solvation. Use of H_2O_2/CH_2Cl_2, obtained from the ethereal solution via iterative addition and evaporation, resulted in rapid formation of **4f** even at −78 °C. However, the use of ether-free H_2O_2 (prepared via direct extraction of 30% H_2O_2 into CH_2Cl_2) resulted only in elimination to the homoallyl alcohol. Dilution of the ether-free hydroperoxide solution with an equal volume of ether restored the original reactivity. Interestingly, opening of the oxetanes with methanol, either in the presence of catalytic Yb^{3+} or stoichometric H_2SO_4, proceeded with a higher degree of inversion than perhydrolysis, an outcome that may result from the much higher concentration of nucleophile.

As shown in Scheme 3, the reaction conditions could be extended to the reaction of tertiary oxetanes with alkyl hydroperoxides to produce 3-peroxyalkanols. Mosher ester analysis of peroxide **8**, along with comparison of the Mosher esters of the derived diol with those derived from **2c**, indicated ring opening proceeded with ∼90% inversion (see Supporting Information for details). Attempted opening of the sterically encumbered 2,2,3-trisubstituted oxetane **3f** with cumyl hydroperoxide resulted only in elimination to the alkenol **6**.

Ketalization of the 1,3-hydroperoxyalkanols was investigated as a route to enantiomerically enriched 1,2,4-trioxepanes (Table 3), important subunits in both synthetic and natural antimalarials.[2,17,18] Reaction of 1,3-hydroperoxyalcohols **4a** or **4c** with 2-methoxypropene in the presence of acid produced trioxepanes **10a** and **10c** in moderate yields.

Scheme 3. Opening with Alkyl Hydroperoxides

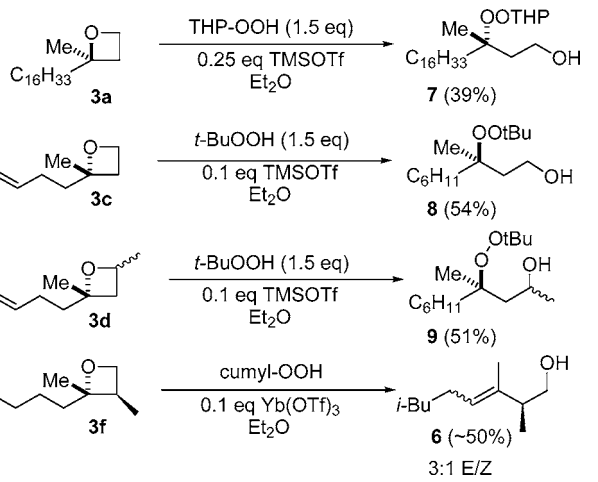
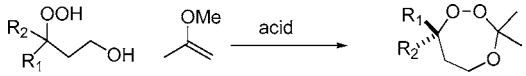


Table 3. Application to 1,2,4-Trioxepanes



subs	acid	T (°C)	time (h)	yield (%)	trioxepane	R_1	R_2
4a	PPTS (0.2 equiv)	rt	0.5	39	**10a**	Me	$C_{16}H_{33}$
4c	CSA (trace)	0 to rt	4	50	**10c**	C_6H_{11}	Me

In summary, the ring opening of enantiomerically enriched oxetanes with hydrogen peroxide or alkyl hydroperoxide provides the first general method for the asymmetric synthesis of 3-hydroperoxyalkanols, 3-peroxyalkanols, and 1,2,4-trioxepanes. Application of this methodology toward the total synthesis of 1,2-dioxolane-containing natural products will be reported in due course.

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Supporting Information Available: Experimental procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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