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Synthesis and Reactivity of 1,2-Dioxolanes from β,γ-Epoxy Ketones

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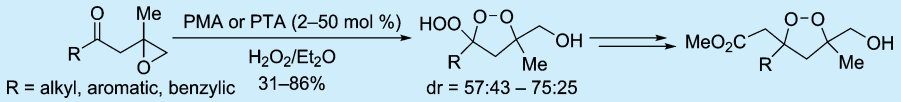
Supporting Information



ABSTRACT: Five-membered ring peroxides were prepared in one step in 31−86% yield from readily accessible β,γ-epoxy ketones and H_2O_2. The reaction proceeded via a tetrahydrofuran, which was converted to the thermodynamically favored 1,2-dioxolane. The product contains a leaving group, which can be displaced to synthesize analogues of the plakinic acid natural products.

Peroxide-containing natural products, including nardosinone,[1] the monoterpene isolated from *Adenosma caeruleum* (**1**),[2] epiplakinic acid C,[3] and epiplakinic acid E methyl ester[4] (Figure 1), represent a family of biologically active compounds

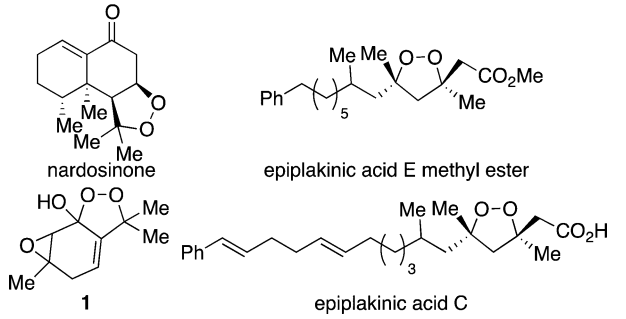
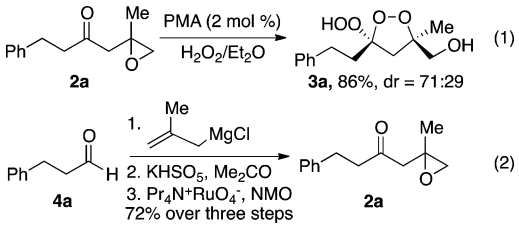


Figure 1. Peroxide-containing natural products.

that are difficult to isolate and synthesize.[5] Among methods used to prepare the 1,2-dioxolane core of these natural products, approaches using oxygen and ozone as the source of oxygen atoms have been effective.[6,7] In contrast, the use of H_2O_2 has been less successful. Acid- or base-mediated addition of H_2O_2 into diketones or α,β-unsaturated ketones gave dioxolanes in low yields,[8,9] with limited substrate scope,[10−16] or gave the 1,2-dioxolane as one component of a mixture.[17−19] In this Letter, we demonstrate that 1,2-dioxolanes can be prepared in one step using H_2O_2 and that the products can be functionalized to provide structural analogues of the plakinic acids.

Our synthesis of 1,2-dioxolanes involves connecting two electrophilic groups, an epoxide and a carbonyl group, with H_2O_2 to form the endoperoxide ring in one step.[20] For example, the addition of H_2O_2 to β,γ-epoxy ketone **2a** catalyzed by phosphomolybdic acid (PMA)[21,22] or phosphotungstic acid (PTA)[23] provided 1,2-dioxolane **3a** in 86% yield (eq 1, Scheme 1). This one-flask synthesis of dioxolanes avoided the handling of unstable hydroperoxyketal intermediates.[24] The synthesis of 1,2-dioxolanes is operationally simple because the starting materials,

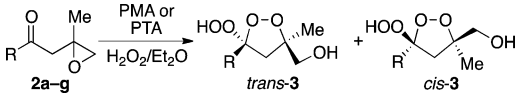
Scheme 1. Synthesis of a 1,2-Dioxolane



β,γ-epoxy ketones, can be synthesized in three steps from an aldehyde, requiring purification of only the final products (eq 2).

The synthesis of 1,2-dioxolanes was general for several epoxy ketones (Table 1). The reaction conditions were optimized for each epoxy ketone to form dioxolanes **3a−g** in the highest yield with the lowest catalyst loading. The reactions of alkyl and

Table 1. Synthesis of 1,2-Dioxolanes



R	time (h)	product	yield (%)	dr[a]
$(CH_2)_2Ph$	21	**3a**	86[c]	71:29
CH_2Ph	72	**3b**	54[d]	75:25
$(CH_2)_4CH_3$	8	**3c**	81[e]	71:29
$(CH_2)_2OX$[b]	25	**3d**	58[c]	67:33
Ph	2	**3e**	41[f]	57:43
4-CF_3-Ph	22	**3f**	33[c]	67:33
4-Me-Ph	4	**3g**	31[c]	75:25

[a]dr = *trans*-**3**/*cis*-**3**, as determined by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. [b]X = TBDPS. [c]Isolated yield using catalytic PMA (2 mol %). [d]Using catalytic PTA (50 mol %). [e]Using catalytic PTA (20 mol %). [f]Using catalytic PTA (10 mol %).

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benzylic ketones (**3a**–**d**) gave products in higher yield than reactions of aromatic ketones (**3e**–**g**). The reaction rate was slower when the carbonyl group was near an electron-withdrawing substituent (**3b**, **3d**, and **3f**), suggesting that a reactive intermediate developed a positive charge at the carbonyl carbon atom (vide infra). The dioxolanes could be formed using other catalysts such as Re_2O_7, $Mo(IV)O_2$, a complex of Na_2MoO_4 with glycine, and phosphoric acid,[20,25−27] but the reactions were slower.

Optimizing the 1,2-dioxolane synthesis required careful structural analysis because the dioxolane is the thermodynamic product, not the kinetic product. At short reaction times (1 h), a spectroscopically similar product, tetrahydrofuran **5**, was formed, but longer reaction times led to the formation of the desired dioxolane **3** (Figure 2). In the initial stages of optimization, it was

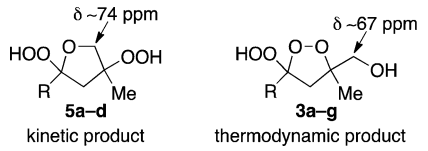
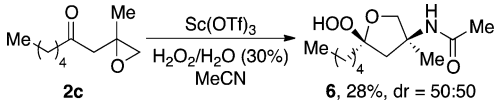


Figure 2. ^{13}C NMR chemical shifts of products.

difficult to assign these structures, but with several kinetic and thermodynamic products in hand, it became possible to assign their structures based on the slight differences in their ^1H and ^{13}C NMR spectra. In the tetrahydrofuran **5**, the methylene group bearing an oxygen atom exhibited chemical shifts that were downfield by about δ 7 ppm in the ^{13}C NMR spectra and δ 0.6–0.8 ppm in the ^1H NMR spectra compared to the corresponding dioxolane **3** (Figure 2).[28] Because these chemical shift differences alone are insufficient to assign structures unambiguously, we obtained X-ray crystal structures of several tetrahydrofurans (**5b** and **6**) and dioxolanes (**3a**,**b**,**e**–**g**) to confirm the structural assignments.

Further insight into the mechanism of 1,2-dioxolane formation emerged during optimization studies. When $Sc(OTf)_3$ was used as the catalyst with aqueous H_2O_2 and acetonitrile, acetamide **6** was formed (Scheme 2). This product resembles the

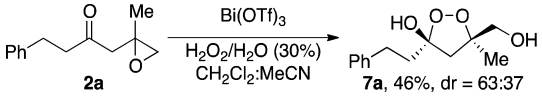
Scheme 2. Participating Solvent



tetrahydrofuran product **5** (Figure 2), except that a molecule of acetonitrile was incorporated instead of one of the equivalents of H_2O_2.[29] $Bi(OTf)_3$[30] also catalyzed the addition of aqueous H_2O_2 to epoxy ketone **2a**, but the product incorporated only 1 equiv of H_2O_2, forming hemiperketal **7a** (Scheme 3).

X-ray crystallographic data suggested a reason why the 1,2-dioxolane is thermodynamically favored. The kinetic and thermodynamic products exhibit general differences in C−O bond lengths, suggesting that hyperconjugation stabilizes the dioxolane more than the tetrahydrofuran.[31] In both types of five-

Scheme 3. Synthesis of a Hemiperketal



membered rings, the four relevant C−O bonds are generally shorter than typical C−O bond lengths (1.43 Å for ethers, 1.45 Å for peroxides).[32,33] For example, the short endocyclic C−O bond of tetrahydrofuran **6** (1.40 Å) and the short C−OO bonds of dioxolane **3f** (1.42 Å) suggest that donation of electrons from oxygen atoms into σ^*_{C-OO} bonds occurs (Figure 3). The σ^*_{C-OO}

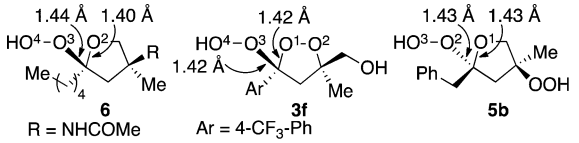
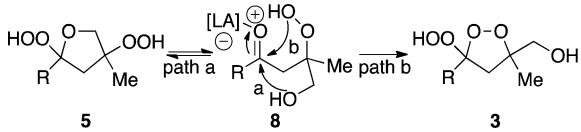


Figure 3. Differences in selected C−O bond lengths.

orbital should be a good electron acceptor: it is likely lower in energy than σ^*_{C-O} because the second oxygen atom would withdraw electron density[34,35] from the proximal oxygen atom. In contrast, the longer C−OO bond of tetrahydrofuran **6** (1.44 Å) compared to the shorter ones in the dioxolane **3f** (1.42 Å) indicates that the exocyclic oxygen atom of the peroxide group is likely donating little electron density into the endocyclic σ^*_{C-O} of tetrahydrofuran **6**.[36] This diminished donation from the peroxide oxygen atom is likely due to the large difference in energy between the nonbonding orbitals of the peroxide oxygen atom and σ^*_{C-O} of the tetrahydrofuran.[37,38] As a result, the tetrahydrofuran has one strong hyperconjugation interaction, whereas the 1,2-dioxolane has two such interactions and is thus more stabilized. These trends hold for other crystal structures in this series, and they mirror observations in the literature.[28,39,40] The tetrahydrofuran **5b** is an exception to this pattern of bond lengths, but it is also an exception in its reactivity: it is the slowest of the compounds to isomerize to the thermodynamic product (Table 1).

A mechanism that incorporates the above observations is outlined in Scheme 4. The addition of H_2O_2 to the more

Scheme 4. Mechanism of Peroxide Addition



substituted carbon atom of the protonated epoxide[22,41] would lead to ketone **8**, drawn complexed to a Lewis or Brønsted acid. In acetonitrile (Scheme 2), ring opening of the epoxide by solvent would be favored, leading to amide **6**.[29] The carbonyl carbon atom of ketone **8** could be attacked by either the hydroxyl group (path a) or the hydroperoxyl group (path b, Scheme 4). Because the hydroxyl group is a harder nucleophile,[42] it should add more rapidly to the activated carbonyl group. Upon longer exposure to the acidic conditions, the thermodynamically favored dioxolane **3** could form. In aqueous H_2O_2 (Scheme 3), the peroxyketal **3** could undergo hydrolysis, leading to peroxide **7a**.

In the course of manipulating the 1,2-dioxolane products, it was discovered that triethylamine reduced the peroxyketal to form hemiperketal **7a** and **7d** (Scheme 5).[43] This transformation led to products resembling the biologically active monoterpenoid peroxide **1** (Figure 1). Other amines, such as DBU, DABCO, *i*-Pr_2NEt, and pyridine, accomplished this reduction, but the reactions were slower. The reduction by triethylamine is a milder

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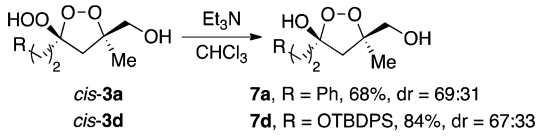
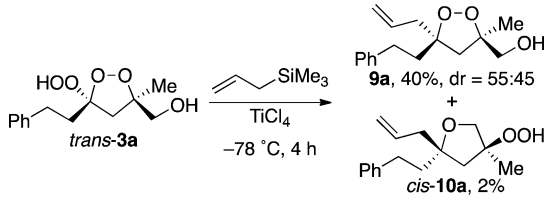
Scheme 5. Reduction of Dioxolanes to Hemiperketals



alternative to the use of more forcing conditions, such as Zn/HOAc or Mg/MeOH, which reduce both endo- and exocyclic peroxide bonds.[44] The reduction by triethylamine appears to be selective because hydroperoxides bearing electron-withdrawing groups are reduced more rapidly than alkyl hydroperoxides,[43,45] which are likely to be intermediates during the stereochemical isomerization at the acetal carbon atom (Scheme 5).

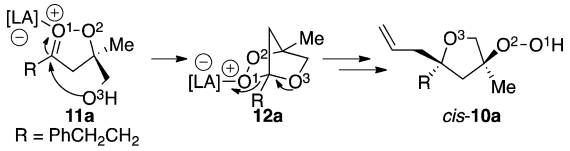
Transformations of the dioxolanes **3** demonstrate their utility for preparing analogues of the plakinic acids.[7] The exocyclic hydroperoxyl group of dioxolane **3a** can serve as a leaving group for nucleophilic substitution reactions (Scheme 6).[8,46] With the

Scheme 6. Allylation of Dioxolane 3a



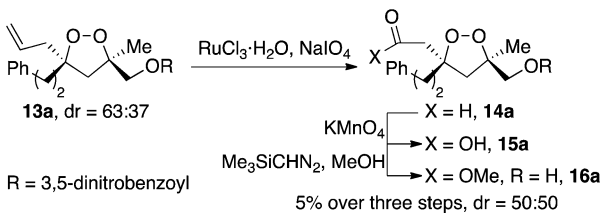
pendent nucleophilic oxygen atom (O3) unprotected, rearrangement to tetrahydrofuran *cis*-**10a** occurred, presumably through intramolecular attack onto the peroxycarbenium ion **11a** (Scheme 7). This hypothesis was confirmed by observing that

Scheme 7. Rearrangement to Tetrahydrofuran 10a



allylation of a protected version of dioxolane **3a** gave the protected allyl compound **13a** free of any rearrangement product (Scheme 8).

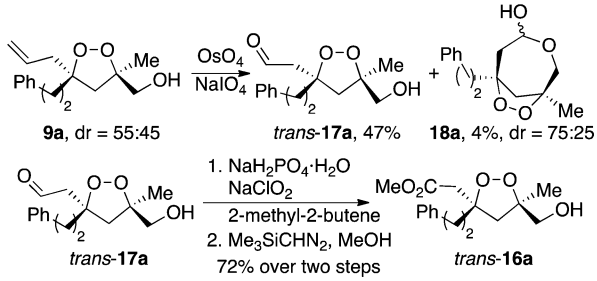
Scheme 8. Functionalization of Protected Dioxolane 13a



Oxidation of the allyl group of protected 1,2-dioxolanes allowed for the synthesis of analogues of the plakinic acids (Scheme 8), but this sequence proceeded with low yields. Dioxolane **13a**, which was obtained by acylating dioxolane **9a**, was oxidized to aldehyde **14a**, which was unstable to chromatography. This reaction afforded recovered allylated dioxolane **13a** as the major product (**13a**:**14a** = 67:33). Attempts to increase the conversion of the oxidation led to decomposition, however. Oxidation of the unpurified aldehyde **14a** to the corresponding carboxylic acid **15a** also resulted in a product that was unstable to purification. The acid, however, could be converted to ester **16a**, which was stable to chromatography.

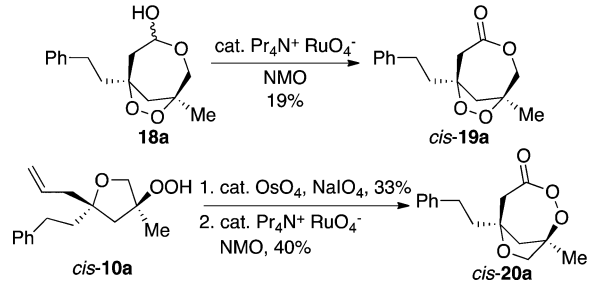
Manipulations of the unprotected allylated dioxolane **9a** were more successful. Oxidation of the major stereoisomer of alkene **9a** gave aldehyde *trans*-**17a**, and the minor stereoisomer formed the lactol **18a**, which could be removed by chromatography (Scheme 9). The aldehyde *trans*-**17a** was converted in 72% yield to ester *trans*-**16a** (Scheme 9), whose structure resembles that of the plakinic acids (Figure 1).

Scheme 9. Functionalization of Unprotected Dioxolane 9a



Another difficult structural assignment emerged upon exploring these oxidations. The lactol **18a** obtained from the minor stereoisomer of dioxolane **9a** was oxidized to form lactone *cis*-**19a** (Scheme 10). Similarly, oxidation of tetrahydrofuran *cis*-

Scheme 10. Oxidation to Lactones



10a, the minor product formed upon allylation of *trans*-**3a** (Scheme 6), led to peroxylactone *cis*-**20a** (Scheme 10). Lactone *cis*-**19a** and peroxylactone *cis*-**20a** shared similar carbonyl stretching frequencies (1736 and 1740 cm^{-1}, respectively) and ^{13}C NMR chemical shifts for the carbonyl carbon atom (δ 171.9 and 170.1 ppm, respectively).[47] Differences in two-dimensional NMR spectra (particularly HMBC and COSY) assisted in assigning the structures.[28] Eventually, X-ray crystallography confirmed the structure of lactone *cis*-**19a**, which permitted the structural assignment of the peroxylactone *cis*-**20a**.

In conclusion, we have demonstrated a new method to form 1,2-dioxolanes in a single step using acid-catalyzed addition of H_2O_2 to β,γ-epoxy ketones. The resulting dioxolanes possess functional groups that enable elaboration, leading to the synthesis of plakinic acid analogues.[15] Because the enantioselective epoxidation of homoallylic alcohols can be used to prepare enantiopure β,γ-epoxy ketones,[48] this method should lead to the synthesis of homochiral 1,2-dioxolanes.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization, stereochemical proofs, X-ray crystallographic data (CIF), and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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