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Preparation of Bicyclic 1,2,4-Trioxanes from γ,δ-Unsaturated Ketones

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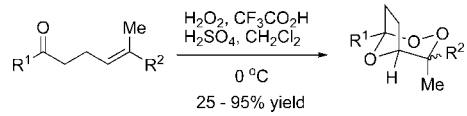
ABSTRACT



Treatment of γ,δ-unsaturated ketones with hydrogen peroxide and acid provides a rapid entry into the medicinally important 1,2,4-trioxane structure. Alkene substitution that stabilizes carbocationic intermediates proved to be important for the success of this transformation.

The 1,2,4-trioxane moiety of the sesquiterpene artemisinin (**1**, Figure 1) is considered to be an important component of the potent antimalarial activity of this natural product.[1] Artemisinin and its semisynthetic derivatives are some of the most successful drugs for the treatment of malaria.[2] Despite the effectiveness of artemisinin, malaria is still a worldwide epidemic responsible for millions of deaths annually, and strains of the *Plasmodium falciparum* parasite are growing increasingly resistant to older drug therapies.[3]

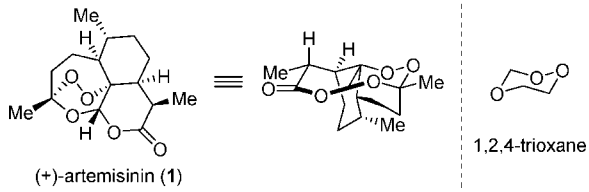


Figure 1. 1,2,4-Trioxanes.

Development of new syntheses of organic peroxides could address many challenges associated with malaria treatment, such as drug resistance and availability.[4] In addition to antimalarial properties, organic peroxides, such as artemisinin, have notable activity against tumor cells[5] and viruses like HIV[6] and hepatitus B.[7]

In this Letter, we describe the efficient synthesis of 1,2,4-trioxanes **3** from simple γ,δ-enones **2** in one synthetic operation, without the isolation of intermediates (Figure 2). This procedure complements the multistep methods reported by Wu[8] and Griesbeck[9] because it enables access to 1,2,4-trioxanes with different substitution patterns.

The synthesis of 1,2,4-trioxanes **3** was discovered when we attempted to form *geminal*-dihydroperoxides from unsaturated ketones **2** (Figure 2). Treatment of γ,δ-unsaturated

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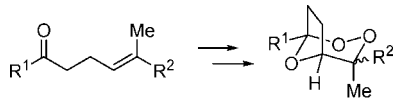
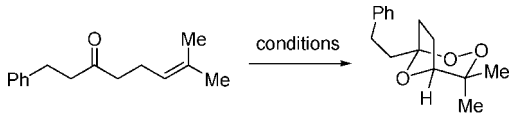


Figure 2. Synthesis of 1,2,4-trioxanes from γ,δ-unsaturated ketones.

ketones with acidic hydrogen peroxide solutions[10−13] gave trioxanes **3** and two identifiable decomposition products: peroxide oligomers[14] and Baeyer−Villiger oxidation products.[15,16] Oligomerization was decreased by slow addition of the γ,δ-unsaturated ketone **2** into the reaction mixture. Lowering the reaction temperature reduced the amount of Baeyer−Villiger oxidation observed for a number of substrates.[17] Finally, the addition of sulfuric acid made a marked improvement in the efficiency of the reaction. For example, the yield of 1,2,4-trioxane **5** from γ,δ-unsaturated ketone **4** could be improved from 8% to 53% by making slight adjustments to the reaction conditions (Table 1).

Table 1. Optimization of Rearrangement



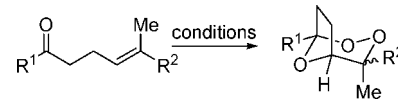
4 **5**

entry	conditions	Yield of **5**[a]
1	CF_3CO_2H (12 equiv), 50% H_2O_2 (8 equiv), CH_2Cl_2, 23 °C	8%
2	CF_3CO_2H (2 equiv), H_2SO_4 (2 equiv), 50% H_2O_2 (10 equiv), CH_2Cl_2, 0 °C	53%

[a] Yield based on purified reaction mixtures.

The formation of 1,2,4-trioxanes occurred most efficiently with acyclic aliphatic γ,δ-enones with trisubstituted alkenes. Ketoalkenes with short alkyl side-chains underwent the transformation most effectively, as shown by the formation of trioxanes **7**, **9**, and **11** (Table 2, entries 1−3). The synthesis

Table 2. Synthesis of 1,2,4-Trioxanes from γ,δ-Enones: Substrate Scope



entry	ketoalkene	product	yield[a]
1	**6**	**7**	95%[b]
2	**8**	**9**	67%
3	**10**	**11**	88%
4	**12**	**13**	25%
5	**14**	**15**	27%
6	**16**[c]	**17**	51%[d]

[a] Based on purified reaction mixtures. [b] As determined by ^{1}H NMR spectroscopic analysis of the product relative to CH_2Cl_2. [c] Mixture (90:10) of *E*/*Z* alkenes. [d] Mixture (3:1) of diastereomers.

of trioxanes **13** and **15** demonstrated that increasing the chain length and introduction of functional groups resulted in longer reaction times and decreased yields (Table 2, entries 4 and 5). If two different alkenes were present, only the more nucleophilic alkene[18] was oxidized (Table 2, entry 4). Functionalized alkenes were also tolerated (Table 2, entry 6).

Attempts to extend the scope of the rearrangement to form trioxabicyclo[3.3.1]nonane **19** failed, instead leading to dioxabicyclo[3.2.1]octane **20** (eq 1). Others have encountered difficulties in forming trioxabicyclo[3.3.1]nonanes.[8c]

Structural assignment of the products from these reactions required careful analysis (Scheme 1). Without authentic samples of structures **7** and **21**, both structures might be considered to be consistent with the ^{1}H NMR spectra. Two-dimensional NMR spectroscopy, however, could differentiate

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(14) Peroxide oligomers are potentially hazardous and explosive: Zabicky, J. *The Chemistry of Peroxides*; Rappoport, Z., Ed.; Wiley: Chichester, UK, 2006; Vol. 2, Chapter 7, pp 597−774. No difficulties were encountered in the handling or purification of these compounds on small scale. Details are provided in the Supporting Information.

(15) Treatment of carbonyl compounds with acidic hydrogen peroxide or its derivatives can yield peroxide oligomers and Baeyer−Villiger oxidation products: Renz, M.; Meunier, B. *Eur. J. Org. Chem.* **1999**, 737–750.

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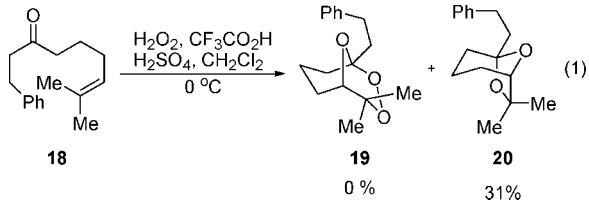
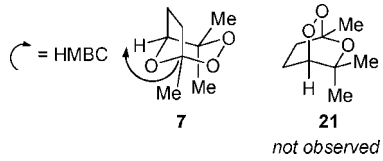


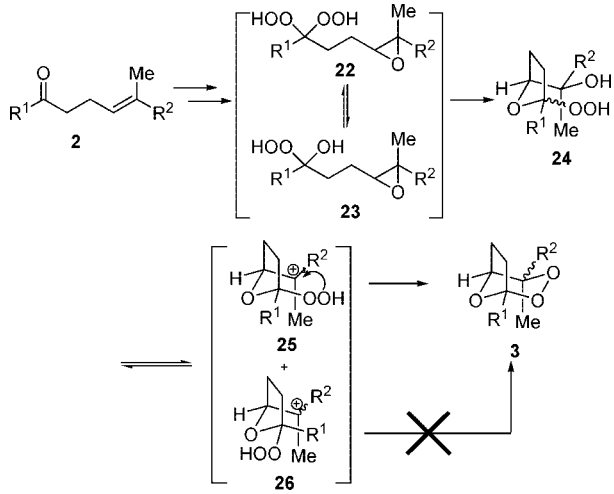
Scheme 1. Two Potential Products



between these structures. A cross-peak between the bridgehead proton and acetal carbon was observed when the HMBC experiment was optimized for $^{1}H-^{13}C$ coupling constants of 10 Hz. This result indicated that the structure of the rearrangement was the trioxabicyclo[3.2.1]octane **7**, and not trioxabicyclo[2.2.2]octane **21**. The proposed structure was later confirmed by X-ray crystallography.[19]

For the formation of 1,2,4-trioxane **3**, we propose the mechanism outlined in Scheme 2. Addition of hydrogen

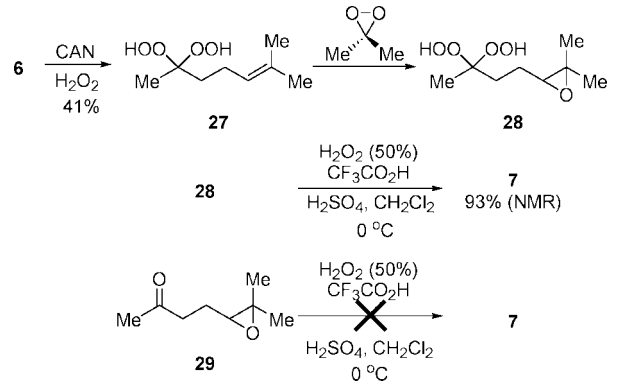
Scheme 2. Proposed Mechanism for 1,2,4-Trioxane Formation



peroxide to the carbonyl group,[13,20] followed by *in situ* epoxidation by trifluoroacetic peracid,[21] would afford a mixture of epoxides **22** and **23**. Cyclization of the hydroxyl group of hemiperoxyketal **23** would provide intermediate tetrahydrofuran **24**.[22] Cyclization to give tetrahydrofuran **24** could also occur by hydrolysis of epoxide **22** or **23** to form a diol (not shown) followed by hemiperoxyketalization.[23] The highly acidic conditions in the reaction mixture could promote the formation of cis and trans tertiary carbocations **25** and **26**. Ring closure to provide the 1,2,4-trioxane **3** occurs when the tertiary carbocation is generated and is in a cis relationship (intermediate **25**) with the anomeric hydroperoxide. Ring closure to afford the bicyclic 1,2,4-trioxane would not be expected to occur if the hydroperoxide and carbocation reside in a trans relationship, as seen in intermediate **26**.[8c]

To test the viability of the suggested mechanism, intermediates were synthesized independently and subjected to the reaction conditions. Epoxy ketal **28** was obtained by treatment of ketoalkene **6** with aqueous hydrogen peroxide and cerium ammonium nitrate (CAN)[24] followed by epoxidation with dimethyldioxirane (Scheme 3).[25] Exposure of

Scheme 3. Synthesis of Proposed Intermediates



epoxy ketal **28** to acid with or without hydrogen peroxide produced trioxane **7**.[19] These results show that *geminal*-dihydroperoxides like **22** (Scheme 2) are competent intermediates in the formation of trioxanes **3**.

The hydroperoxy ketal portion of the intermediates was necessary for the synthesis of 1,2,4-trioxanes. When the epoxide **29**[26] was subjected to the reaction conditions, none of the desired trioxane **7** was observed (Scheme 3). This result indicates that formation of the peroxy ketal or hemiketal (e.g., **22** or **23**, Scheme 2) before epoxidation is necessary for production of 1,2,4-trioxanes **3**.

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(25) Reaction conditions have not been optimized.

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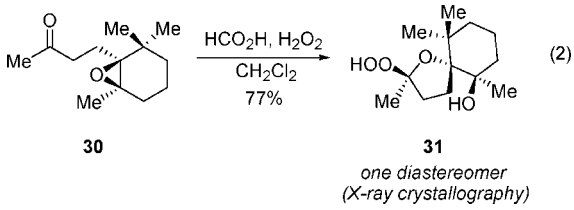
In addition to synthesizing hypothesized intermediates and transforming them to 1,2,4-trioxanes, some products have been isolated from reaction mixtures that are consistent with the proposed mechanism. Treatment of epoxide **30** to the reaction conditions provided primarily decomposition. Protonation with a weaker Brønsted acid yielded the diastereomerically pure tetrahydrofuran **31** (eq 2), a product that is structurally related to intermediate **24** (Scheme 2).[19] The isolation of the tetrahydrofuran **31** with an anomeric hydroperoxide suggests the formation of the tetrahydrofuran ring occurs prior to carbocation formation. The weaker acid is not likely to generate a tertiary carbocation (e.g., **25** or **26**, Scheme 2), so the reaction stops at the tetrahydrofuran stage.



30 **31**

one diastereomer
(X-ray crystallography)

(2)

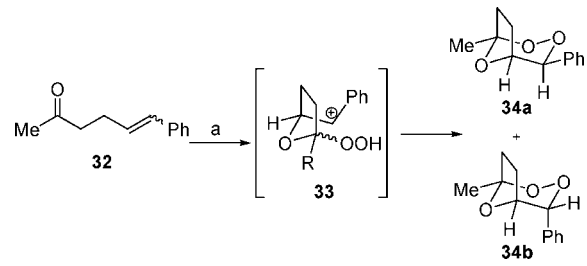
The presence of a carbocationic intermediate was probed with a substrate bearing a 1,2-disubstituted styryl group.[27] The product ratio of the resulting trioxanes **34a/b** was independent of the diastereomeric ratio of the starting alkene **32** (Table 3). The observation that the stereochemical integrity of the alkene was not maintained in the product is consistent with carbocationic intermediates.[28]

In conclusion, the reaction of trisubstituted γ,δ-unsaturated ketones with acidic hydrogen peroxide solutions afforded 1,2,4-trioxanes efficiently. This reaction is believed to occur by hemiperoxyketalization, epoxidation, and ring closure onto a carbocationic intermediate. The stabilization of this carbocation (**25**, Scheme 2) is a critical feature for the success of this transformation.

(27) In other experiments, 1,2-disubstituted alkenes without the phenyl group did not form the desired 1,2,4-trioxanes. It appears that the additional stability of the proposed carbocationic intermediate **33** (Table 3) conferred by the phenyl substituent allowed the product to form from a disubstituted alkene.

(28) Loss of stereochemistry was also observed in trisubstituted alkene substrates (Table 2, entry 6).

Table 3. Synthesis of 1,2,4-Trioxanes **34a/b** from a 1,2-Disubstituted Alkene[a]



entry	substrate	E/Z ratio	overall yield of **34**	ratio **34a/34b**
1	**32**	64:36	21%	86:14[b]
2	**32**	98:2	46%	90:10[c]

[a] Reagents and conditions: (a) H_2O_2 (50%), CF_3CO_2H, H_2SO_4, 0 °C, 24 h. [b] As determined by ^1H NMR spectroscopic analysis of the unpurified reaction mixture. [c] Ratio as determined by isolated yield.

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

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