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

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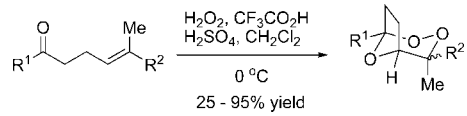
ABSTRACT



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]

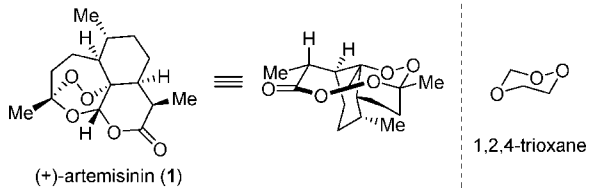


Figure 1. 1,2,4-Trioxanes.

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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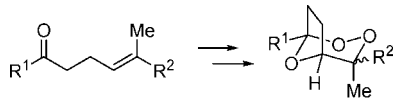
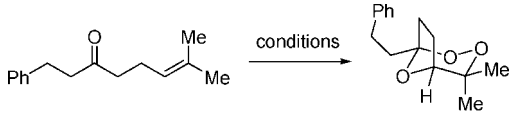


Figure 2. Synthesis of 1,2,4-trioxanes from γ,δ-unsaturated ketones.

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

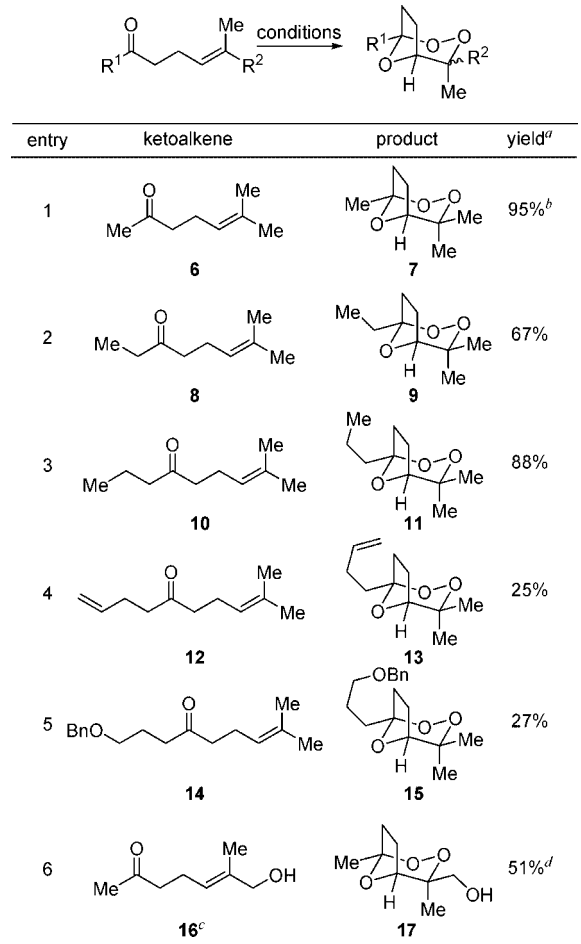


entry	conditions	Yield of **5**[a]
1	CF_3CO_2H (12 equiv), 50% H_2O_2 (8 equiv), CH_2Cl_2, 23 °C	8%
2	CF_3CO_2H (2 equiv), H_2SO_4 (2 equiv), 50% H_2O_2 (10 equiv), CH_2Cl_2, 0 °C	53%

[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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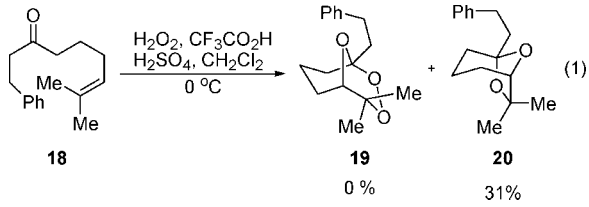
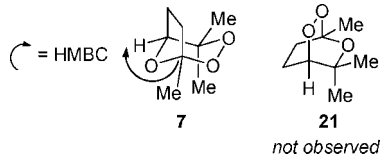


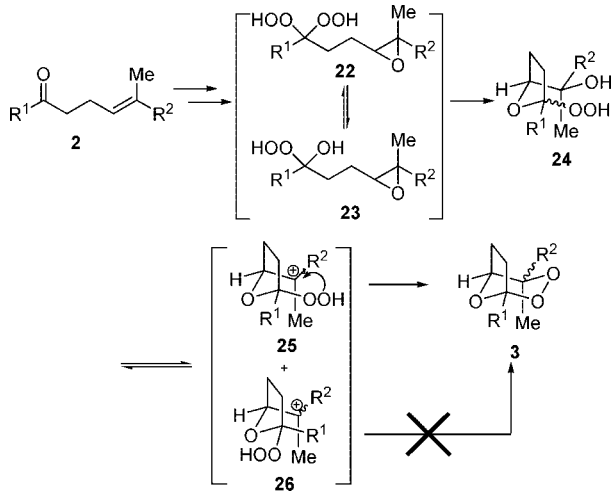
Scheme 1. Two Potential Products



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

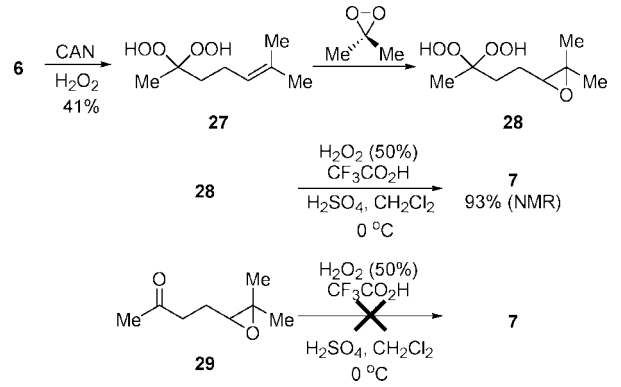
Scheme 2. Proposed Mechanism for 1,2,4-Trioxane Formation



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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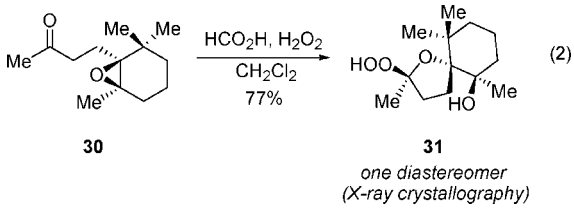
In addition to synthesizing hypothesized intermediates and transforming them to 1,2,4-trioxanes, some products have been isolated from reaction mixtures that are consistent with the proposed mechanism. Treatment of epoxide **30** to the reaction conditions provided primarily decomposition. Protonation 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)

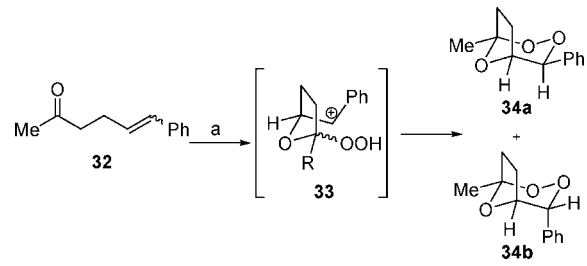
The presence of a carbocationic intermediate was probed with a substrate bearing a 1,2-disubstituted styryl group.[27] The product ratio of the resulting trioxanes **34a/b** was independent of the diastereomeric ratio of the starting alkene **32** (Table 3). The observation that the stereochemical integrity 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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