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Annulative endoperoxidation of tetronates

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A novel, annulative endoperoxidation of tetronate derivatives bearing unsaturated side chains is presented. The reaction requires a simple setup and proceeds under mild conditions to generate tri-cyclic endoperoxides in modest diastereoselectivities and useful yields. A free-radical mechanism is proposed.

Endoperoxides are heterocyclic compounds containing an O–O bond in the ring. The antimalarial drug Artemisinin isolated from *Artemisia annua* is perhaps one of the more recognizable endoperoxide natural products,¹ inspiring the development of many semi-synthetic and synthetic analogs.^{2,3} The endoperoxide structural motif is also found in many other natural products with diverse biological activities including anticancer, antifungal, antiviral and anti-malarial.^{4–7} Among endoperoxides, 1,2-dioxolanes and 1,2 dioxanes are the most common. The synthesis of 1,2-dioxanes is typically carried out by radical reactions with triplet oxygen,^{8,9} or by means of metal-catalyzed radical ring expansion of cyclobutanols.^{8,10} 1,2-Dioxenes are available from reaction of singlet oxygen and dienes.^{11,12}

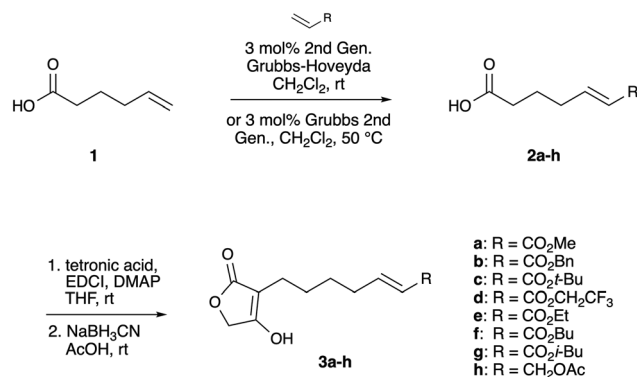
Tetronic acid (4-hydroxy-5[H]furan-2-one) derivatives are also prevalent in bioactive natural products.^{13–15} Some notable methods for the preparation of tetronic acids include intramolecular ketene trapping,¹⁶ olefination with cumulated ylides,¹⁷ Dieckmann cyclizations¹⁸ and ring expansions.^{14,19} The structure of tetronates contains latent electrophilic and nucleophilic sites, making them attractive synthetic intermediates. They have been used in metalations,¹⁴ Michael additions,²⁰ ring-contractions²¹ and metal-catalyzed transformations.^{21,22}

In connection with one of our projects aimed at exploring the utility of tetronates as polyfunctional substrates for synthesis, we prepared substrates **3a–h**, Scheme 1.

Commercially available 5-hexenoic acid **1** was subjected to cross metathesis^{23,24} with terminal alkene derivatives to give acid intermediates **2a–h**. Installment of a tetronic acid moiety

could be carried out using DCC, where the initial *O*-acyl intermediate is rearranged to the *C*-acylation product in the presence of DMAP.^{25–27} Using EDCI in place of DCC resulted in cleaner reactions, and the coupling reaction was carried out in tandem with a deoxygenation step using NaBH₃CN in acetic acid²⁶ to efficiently produce **3a–h**.

We planned to explore the reactivity of substrates **3a–h** towards intramolecular Michael additions. Serendipitously, we found that **3a** slowly underwent conversion in CDCl₃ solution at room temperature to give a ~3 : 1 mixture of products, from which the major isomer **4a** could be detected. Stirring **3a** in chloroform at room temperature for 6 days reproduced the formation of **4a** which could be isolated in 54% yield. Analysis of the NMR data for this compound revealed the presence of two methine units, which suggested the possibility of ring formation between the enolic form of the tetronate and the double bond of the unsaturated ester. Bach has reported that tetronates bearing olefinic side chains can undergo intramolecular [2 + 2] cycloadditions under photochemical conditions.^{28,29} In the case of **4a**, the possibility of a cyclobutane ring formation was discarded due to the chemical shift of one of the methine carbons at ~81 ppm which indicated that this position is oxygenated. An additional non-protonated



Scheme 1 Synthesis of substrates.

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carbon at ~ 105 ppm in the ^{13}C NMR suggested the presence of a hemiketal group. The relative orientation of the two methine protons in **4a** was assigned as *cis*- by convincing nOe experiments, and the overall structure of **4a** established by X-ray crystallography, revealing the presence of an endoperoxide moiety, Fig. 1.

Substrates **3b–i** undergo endoperoxidation under the same conditions to give **4b–i**, Table 1.

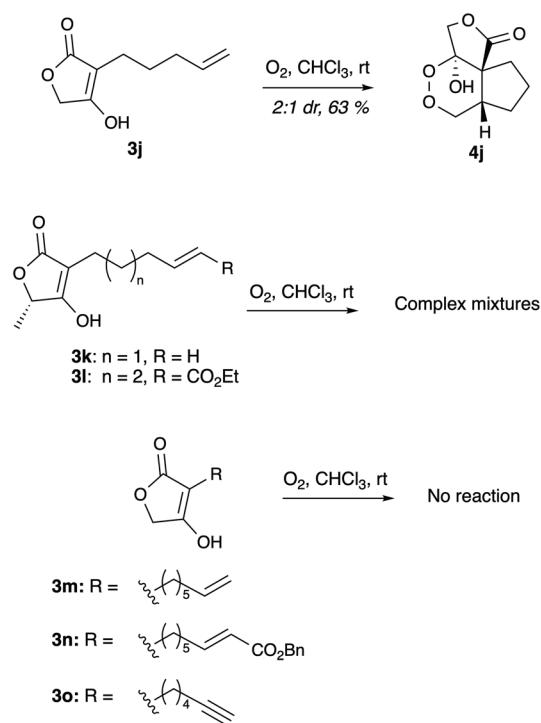
Although NMR analysis of the crude mixtures showed the presence of minor diastereomers, their isolation was hampered by several byproducts as complex mixtures accounting for the mass balance. LCMS analysis of the reaction crude from **3b** also confirmed the presence of a minor diastereomer. Gram-scale reaction of **3i** allowed the identification of a hydroperoxide byproduct after repeated chromatography (see below). The relative stereochemistry of the major isomers **4b–i** was assigned in analogy with that of **4a**. Formation of **4b** was also observed when the reaction was conducted in other solvents such as dichloromethane (26%), dichloroethane (26%), trifluorotoluene (36% at 60 °C), or acetonitrile (34%), but was completely suppressed in acetone, ethanol, diethyl ether or tetrahydrofuran. As observed for **3i**, the reaction is not limited to alkenes containing an ester group. X-ray crystallography confirmed that **4i** has the same relative stereochemistry as **4a**. Substrate **3j** produced **4j** in 63% as well. Compounds **3k** and **3l** bearing a stereocenter derived from ethyl lactate produced complex mixtures of what appeared as cyclized diastereomers and other inseparable byproducts. No reaction of **3m**, **3n** or **3o** was detected after 6 days, Scheme 2.

The precise mechanistic details for the formation of endoperoxides **4a–j** remain uncertain, however, the following control experiments can be informative. As expected, no cyclization or any other reaction was detected by ^1H -NMR after 6 days when a solution of **3b** was monitored in rigorously degassed CDCl_3 . The cyclization of **3b** was also completely suppressed in non-degassed CDCl_3 containing 0.5 M *trans*-piperylene.²⁹ Similarly, **3i** did not cyclize in the presence of one equivalent of the radical scavenger 2,6-di-*tert*-butylphenol. The reac-

Table 1 Endoperoxidation of **3a–i**

Substrate	dr ^a	Yield ^b	Product
3a	3 : 1	54%	4a : R = CO ₂ Me
3b	3 : 1	51%	4b : R = CO ₂ Bn
3c	3 : 1	47%	4c : R = CO ₂ <i>t</i> -Bu
3d	3 : 1	58%	4d : R = CO ₂ CH ₂ CF ₃
3e	3.5 : 1	44%	4e : R = CO ₂ Et
3f	4 : 1	36%	4f : R = CO ₂ Bu
3g	3 : 1	46%	4g : R = CO ₂ <i>i</i> -Bu
3h	1.4 : 1	49%	4h : R = CH ₂ OAc
3i	4 : 1	44%	4i : R = H
3i ^c	—	23%	4i : R = H

^a Diastereomeric ratio measured by ^1H or ^{13}C NMR³⁰ of the crude reaction mixture. ^b Refers to isolated yield of major isomer. ^c Refluxed in toluene.



Scheme 2 Additional substrates.

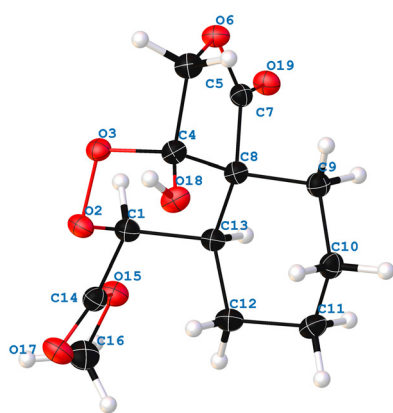


Fig. 1 Molecular structure of **4a** recorded at 100 K. Thermal ellipsoids plotted at the 50% probability level. C (black), H (white), and O (red).

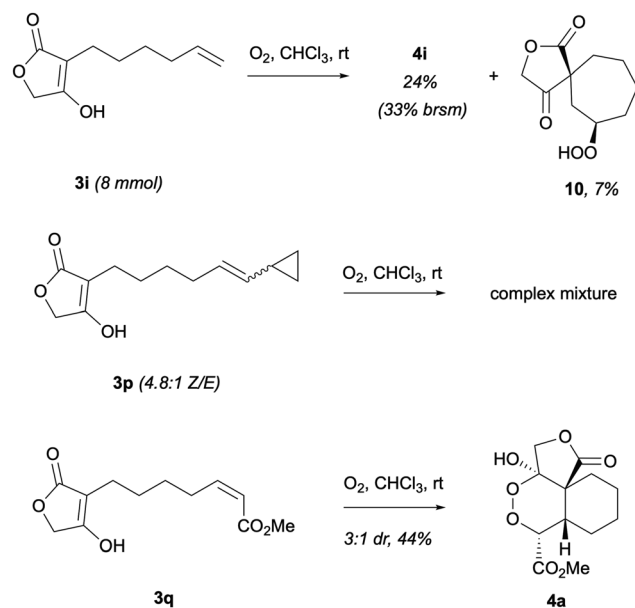
tion time for the formation of **4i** could be reduced to about 12 h by refluxing in toluene, but at the expense of chemical yield, presumably due to thermal decomposition. Conducting the reaction under an atmosphere of oxygen (balloon) or protecting the reaction vessel from ambient light did not appear to affect the rate of conversion. Overall, these experiments suggest a free radical mechanism initiated by molecular



oxygen addition or hydrogen atom abstraction. As proposed in Scheme 3A for **3a–h**, the reaction could start by oxygen addition into the double bond of the tetronic acid fragment, generating a peroxy radical and a tertiary carbon-centered radical **5**. 6-*exo-trig* radical cyclization is then followed by recombination of radicals in **6** to yield the endoperoxide products.³¹

The addition of molecular oxygen into alkenes commonly involves singlet oxygen,^{32,33} but the addition of triplet oxygen is also well-documented.^{34–39} The addition of triplet oxygen is generally a slow process, but can be assisted by either strain^{40,41} or the presence of electron-donating groups on the alkene.^{41,42} A second mechanism alternative is proposed in Scheme 3B, in which oxygen could abstract a hydrogen atom from **3** to form resonance-stabilized radical **7**. 6-*exo-trig* Ring-closure with the alkene moiety of the side chain would be followed by trapping of molecular oxygen, propagation and ketalization to form the endoperoxide products. Although hydrogen atom abstraction by triplet oxygen is generally considered kinetically disfavored, its involvement in the oxidation of stable enols has been proposed before.⁴³

Additional experiments also supported a radical pathway. The reaction of **3i** on a gram scale produced **4i** in modest yield, but allowed the identification of hydroperoxide **10** as a minor component after repeated chromatographic purifications, Scheme 4. The formation of **10** is consistent with



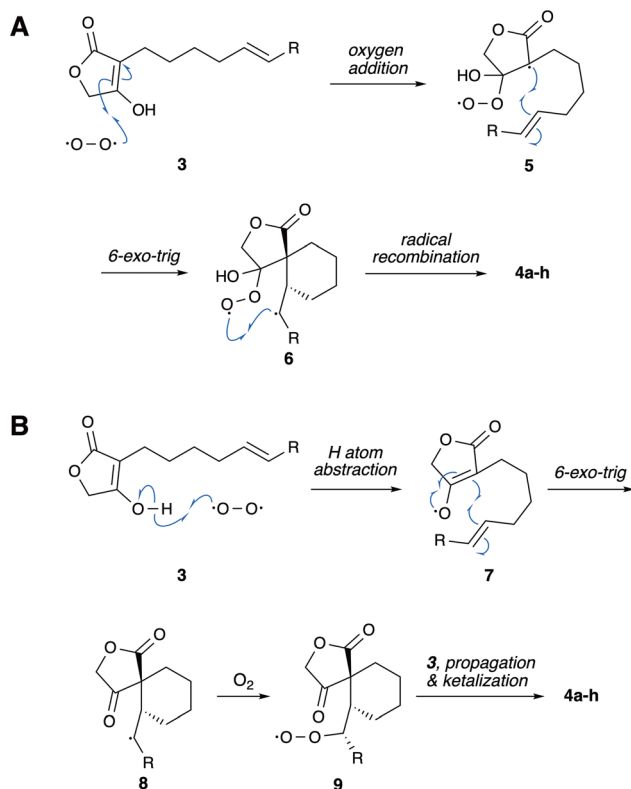
Scheme 4 Additional experiments.

mechanism B where 7-*endo-trig* cyclization of **7** is followed by oxygen trapping and propagation. The relative stereochemistry of **10** is proposed as shown in Scheme 4 based on the observation that the ketone and hydroperoxide groups in this compound do not form a hemiketal ring, which suggest that these groups are oriented on opposite faces of the seven-member ring. Compound **3p** containing a radical clock was also prepared. Although no reaction was observed in degassed CDCl_3 , reaction of **3p** in CHCl_3 produced a complex mixture from which $^1\text{H-NMR}$ analysis of the crude mixture showed disappearance of the cyclopropyl methylene resonances, suggesting that this moiety was involved in the transformation, and in agreement with a free radical mechanism.

Substrate **3q** bearing a *Z*-alkene produced endoperoxide **4a**, identical to the product obtained from **3a**, which supports the formation of discrete radical intermediates, rather than a concerted process (Scheme 4).

In order to gain additional insight into the mechanistic alternatives proposed in Scheme 3, we conducted computational studies at the M06-2X/def2-SVP level on a simplified tetronic acid bearing a methyl group as the side chain. Comparison of the energy barriers for oxygen addition (mechanism A) and hydrogen atom abstraction (mechanism B) slightly favor the latter, however, the small energy difference (1.4 and 3.5 kcal mol^{-1} for ΔE and ΔH , respectively) between these alternatives indicates that neither mechanism could be decisively discarded (see SI for details).

Aerobic endoperoxidation of 1,3-dicarbonyl compounds such as Meldrum acid derivatives⁴⁴ tetramic acids⁴⁵ or tetronates⁴⁶ has been reported in the literature, but only in the presence of a metal catalyst. Indeed, treatment of **3i** with manganese triacetate in acetic acid⁴⁶ in the presence of air produced endoperoxide **4i** in 31% unoptimized yield. **3i** also



Scheme 3 Proposed mechanisms. (A) Oxygen addition. (B) Hydrogen atom abstraction.



reacted with manganese triacetate in acetic acid in the absence of oxygen to give a diastereomeric mixture of spirocyclic products in 9% unoptimized yield, in which cyclization of **7** was followed by hydrogen abstraction instead of oxygen trapping (see SI). This observed reactivity is consistent with the ability of tetronates **3a–l** to participate in radical reactions. We are aware of only one report describing metal-free aerobic endoperoxidation of a related alkylidenetetronic acid, where radical autooxidation of a tertiary allylic position followed by six-member endoperoxide ring formation was proposed.^{47,48}

Elaboration of the products can give access to other interesting compounds, Scheme 5. For example, hydrogenolysis of endoperoxide **4a** efficiently delivered hemiketal **11**. X-ray analysis of **11** showed the relative stereochemistry from **4a** was preserved. Reduction of **4b** bearing a benzyl ester can be carried out with activated zinc in acetic acid⁴⁹ instead. Attempted reduction of hemiketal **11** or **12** by treatment with triethylsilane and a Lewis acid⁴⁴ was unsuccessful, presumably due to structural restrictions imposed by the tricyclic system, preventing oxonium ion formation. **4i** can also be reduced with zinc in acetic acid to produce hemiketal **13**. Spirocyclic compounds are frequently found in natural products^{50,51} and are of medicinal interest,^{52,53} therefore, hemiketal **13** was heated with TBSCl to deliver spirocyclic tetronate **14** in 24% unoptimized yield (Scheme 5).

In summary, we present herein an annulative endoperoxidation of tetronates containing unsaturated side chains. The reaction requires only a simple setup and proceeds under mild conditions, without the need of metal catalyst or specialized equipment to produce tetronate-derived tricyclic endoperoxides containing up to four contiguous stereocenters. Modest diastereoselectivities and useful yields are observed in most cases. The ease of formation of endoperoxides **4a–j** war-rants

further study of this interesting annulative reaction, as well as biological evaluation of the products and derivatives.

Author contributions

RT-A conceived and oversaw the project. NR, SS, SKA and RT-A conducted experiments. CJW and BGB acquired crystallographic data and solved X-ray structures, MRT conducted computational studies. RT-A wrote the manuscript. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data underlying this study are available in the published article and its SI: experimental procedures, X-ray data for **4a**, **4i** and **11**, characterization data and copies of ¹H, ¹³C and ¹⁹F NMR spectra for all new compounds. See DOI: <https://doi.org/10.1039/d5ob00663e>.

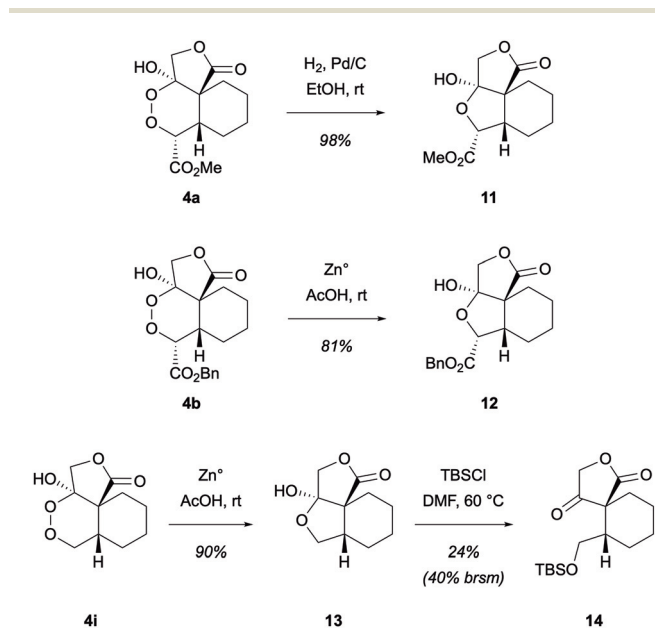
CCDC 2405026, 2476611 and 2405027 contains the supplementary crystallographic data for this paper.^{54a–c}

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Scheme 5 Elaboration of products.



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