Biomimetic Synthesis of Hitorins A and B via an Intermolecular Alkoxy Radical-Olefin Coupling Cascade

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Supporting Information Placeholder

ABSTRACT: A biomimetic synthesis of hitorins A and B was achieved based on our modified biosynthetic proposal. In our synthesis, a radical cascade reaction between an alkoxy radical, generated from a hydroperoxide, and a monoterpene (+)-sabinene renders the tetrahydrofuran ring of hitorins A and B. In addition, experimental results supported that the oxidative cleavage of the tetrasubstituted olefin in a key intermediate is via a radical oxidation cascade followed by a Grob fragmentation.

Nature often uses cascade reactions, optimized over millions of years of evolution, as a strategy for assembly of complex chemical structures.[1] Uncovering these cascade reactions improves our understanding of both chemical reactivity and biosynthesis of natural products. Organic chemists are also inspired by these cascade reactions and are still learning to apply them in total synthesis in order to achieve synthetic efficiency.[2] In this work, we employed a radical cascade starting from a rare intermolecular alkoxy radical-olefin coupling reaction in our biomimetic synthesis.[3]

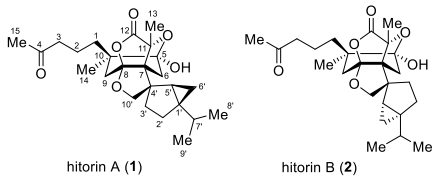
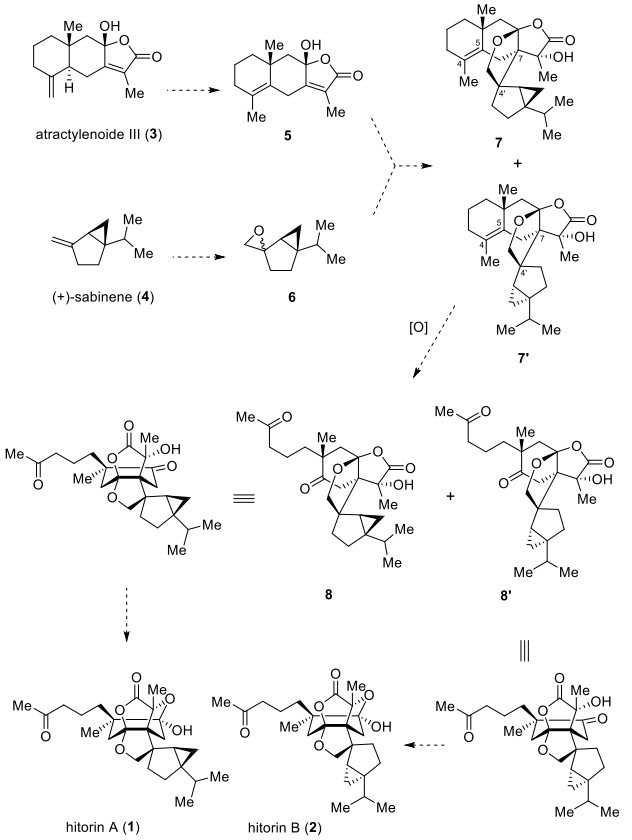


Figure 1. Hitorins A and B.

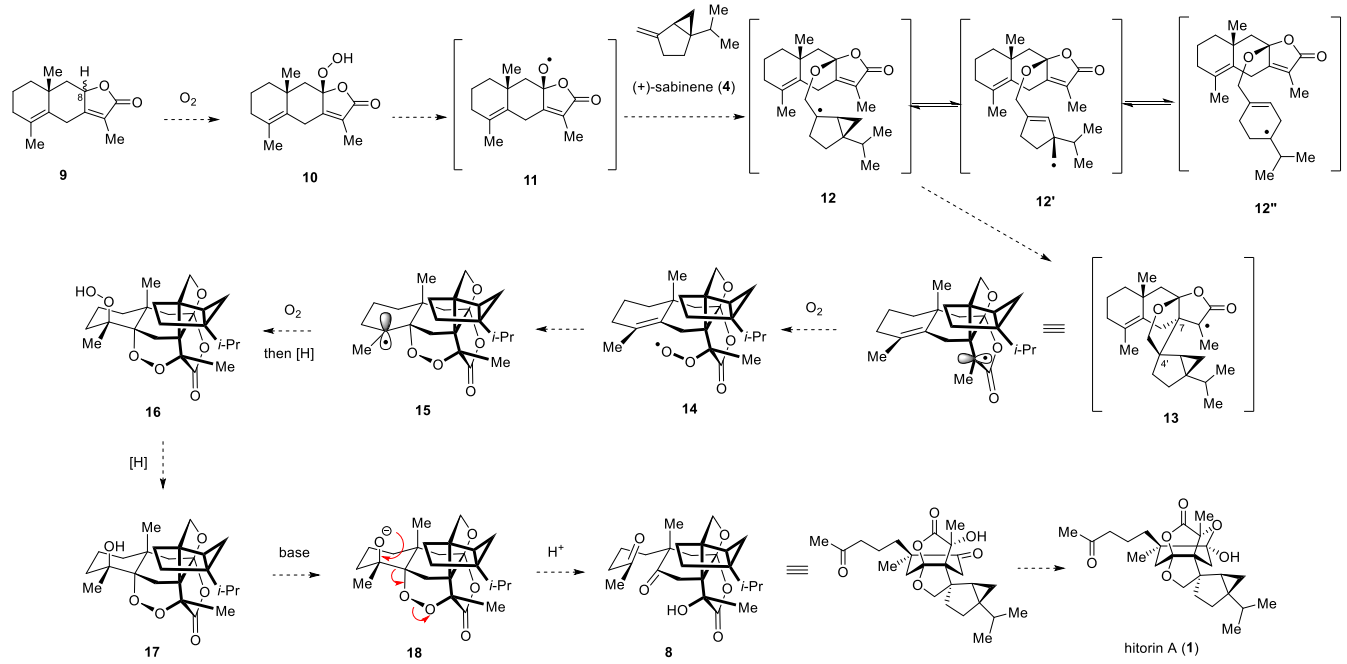
In October 2016, Kim et al. reported the isolation of two structurally unique C_{25} terpenoids, hitorins A (**1**) and B (**2**) from *Chloranthus japonicas* (Figure 1),[4] a plant used as a traditional medicine in Japan for the treatment of gastrointestinal disorders. Hitorins A and B contain an unprecedented 6/5/5/5/5/3 hexacyclic skeleton with two adjacent quaternary carbons. The isolation team proposed that, biogenetically, hitorins A (**1**) and B (**2**) were adducts of two other natural products, atractylenoide III (**3**) and (+)-sabinene (**4**). As shown in Scheme 1, olefin isomerization of atractylenoide III furnished compound **5**, and non-selective epoxidation of (+)-sabinene formed epoxide **6** as diastereomers. Then the two compounds **5** and **6** coupled to generate adducts **7** and **7**'. Nonetheless, the detailed mechanism of this key coupling step with the formation of a tetrahydrofuran ring was not specified. The isolation team believed that the C4'-C7 bond formation was not stereospecific, so both isomers **7** and **7**' were concurrently generated. Hitorins A (**1**) and B (**2**) are the hemiketals of compounds **8** and **8'**, respectively, which were proposed to be the respective oxidative cleavage products of compounds **7** and **7**'. Again, their proposal did not specify the detailed mechanism of this biological oxidative cleavage of the $\Delta^{4,5}$-tetrasubstituted alkene.

Scheme 1. Biosynthesis of hitorins A and B proposed by Kim et al.[4]



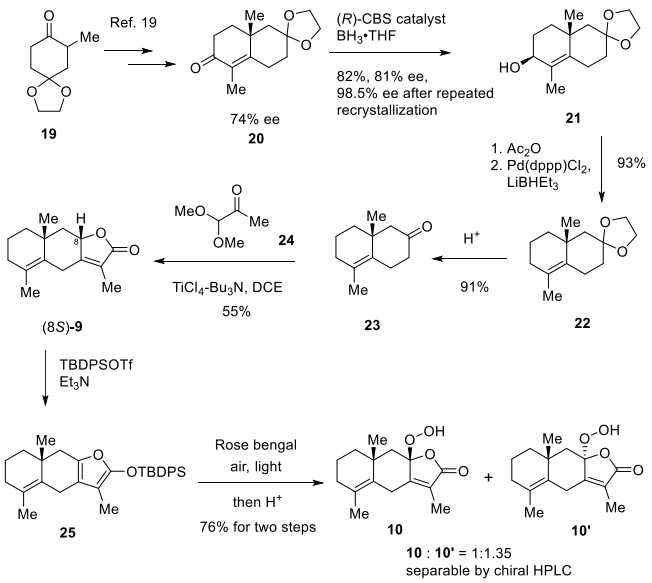
After carefully studying the potential mechanistic details of the formation of compound **7** from monomers **5** and **6**, we consider that a modification in the biosynthetic proposal of hitorins is necessary. Simple cationic or anionic mechanisms could not explain this coupling step in Kim's proposal because the regioselectivity and the reactivity of functional groups of **5** and **6** could not match. Pericyclic mechanisms could not explain the formation of compound **7** from monomers **5** and **6** either. As a reasonable alternative, we suggest a radical cascade process for the biosynthesis of **7**. In fact, our modified proposal using a radical cascade would not stop at compound **7** but continue to account for the oxidative cleavage of the $\Delta^{4,5}$-tetrasubstituted alkene, leading to direct precursors of hitorins.

Scheme 2. Biosynthesis of hitorins A and B proposed in this work (shown for the biosynthesis of hitorin A).



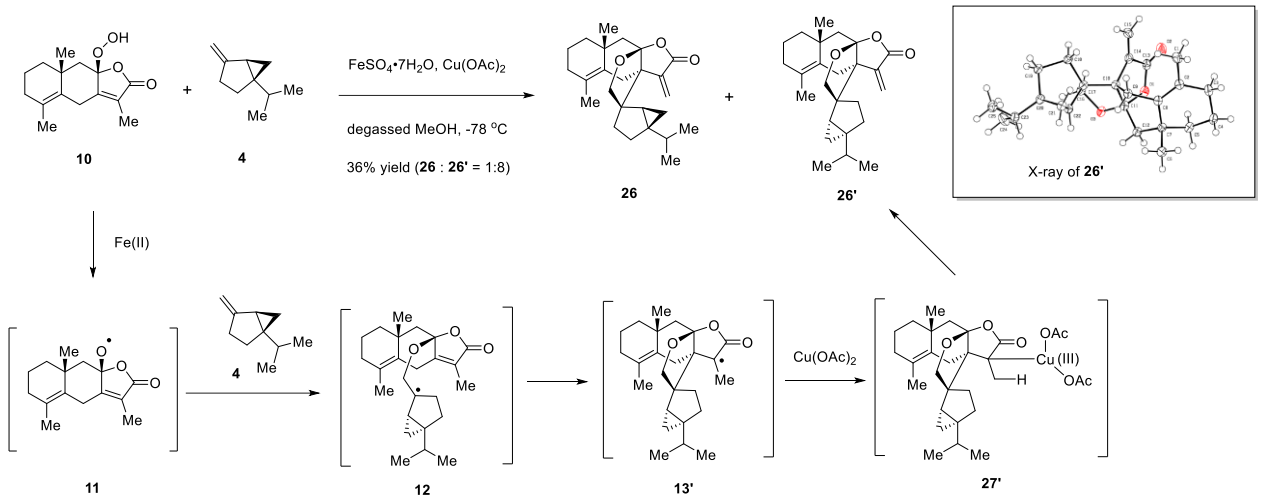
Our new proposal is outlined in Scheme 2, using the biosynthesis of hitorin A (**1**) as the example. Eudesmane derivative **9** would undergo peroxidation to generate hydroperoxide **10**. This peroxidation is a known process in nature, as exemplified by the isolation of some γ-hydroperoxybutenolide natural products.[5] Radical peroxidation of butenolide enolates has also been used in total synthesis.[6] The peroxidation of 2-hydroxyfuran or its anion probably occurs via a radical mechanism.[7] Then the weak O–O single bond of **10** would be cleaved to form an alkoxy radical **11**.[8] This highly electrophilic oxygen radical could react with (+)-sabinene **4** to form a stable tertiary carbon radical **12**.[9,10] The intramolecular version of alkoxy radical-olefin coupling has been proposed for prostacyclin biosynthesis with experimental support by Porter et al.[11] Radical **12** may be in equilibrium with less strained radicals **12**' and **12**".[12] Radical **12** would undergo intramolecular conjugate addition to the electron-deficient butenolide functionality to form the C4'-C7 bond of radical **13**, which sets the C4' configuration as *R*. This radical conjugate addition step is not stereospecific, and the C4'*S* diastereomer of **13** would eventually lead to the formation of hitorin B (**2**). We envision that radicals **12**' and **12**" would not undergo the radical conjugate addition like radical **12** because, if so, it would afford a strained *trans*-cyclooctene ring. In general, a cyclopropylmethyl radical opens fast (k: ~10^8 s^{-1}) to form a homoallyl radical, while the reverse reaction, if facilitated by the *gem*-dimethyl effect, is also fast (k: ~10^6 s^{-1}). The 5-*exo*-*trig* radical cyclization proceeds with a rate constant of 10^5~10^8 s^{-1}.[13] In the hitorin biosynthesis, the 5-*exo*-*trig* radical cyclization could be the productive pathway under the Curtin-Hammett principle,[14] leading to radical **13**. Radical **13** would then react with oxygen in the air to generate peroxy radicals **14** and 11-*epi*-**14** (the latter is not shown here),[15] and the new radical **14** would react with the electron-rich C=C bond to form a carbon radical **15**. Radical **15** would then react with a second molecule of oxygen to furnish compound **16** after quenching the peroxy radical intermediate with some reductant. Upon reduction of the hydroperoxide in **16**, intermediate **17** could undergo a Grob fragmentation,[16,17] furnishing compound **8**, and hitorin A (**1**) should form immediately after hemiketal formation. Hitorin B (**2**) would be produced similarly. Captivated by the intriguing chemistry embedded in the hitorin biosynthesis, we embarked on the biomimetic synthesis of hitorins A and B. Our successful synthesis of these two natural products, shown below, supported our modified proposal.

Scheme 3. Synthesis of hydroperoxide 10.



Although structure **9** with an 8*R* configuration is a known compound, the synthetic route from artemisin is costly.[18] New chemistry allowed us to prepare hydroperoxide **10** by a different route. As shown in Scheme 3, enone **20** (74% ee) was prepared from **19** according to literature.[19] CBS reduction of enone **20** provided allylic alcohol **21** with amplified optical purity (81% ee).[20] Repeated recrystallization of alcohol **21** from hexanes furnished samples with 98.5% ee, which were used in subsequent investigations. Alcohol **21** was acetylated, followed by reduction via palladium chemistry to afford compound **22**.[21] After ketal deprotection, a one-pot procedure directly provided the unstable butenolide (8*S*)-**9** (50% yield

Scheme 4. The key alkoxy radical-olefin coupling cascade and a preliminary mechanistic model.



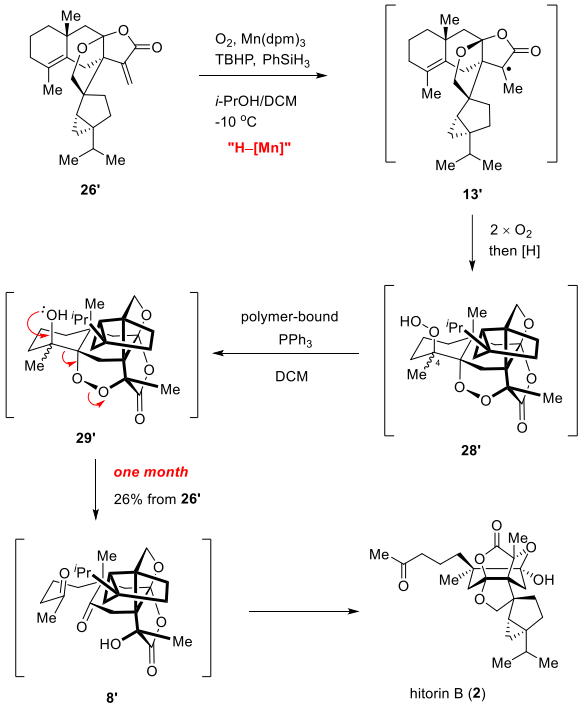
from **22**) via titanium-enolate chemistry.[22] Butenolide (8*S*)-**9** is prone to produce undesired hydroperoxides in the air (not shown). But happily, a two-step procedure afforded the desired hydroperoxide **10** as a 1:1.35 diastereomeric mixture via singlet oxygen Diels-Alder reaction with siloxyfuran **25**.[23] The minor component in the hydroperoxide mixture is the desired stereoisomer **10**. Pure hydroperoxide **10** was obtained via HPLC separation using chiral columns.

We then evaluated different conditions to couple (+)-sabinene **4** with hydroperoxide **10** as proposed in Scheme 2. We initially screened Fe(II), Cu(I) and Cu(II) salts, as well as UV light on mixtures of hydroperoxides **10** and **10'** with different olefins. We later found that pure hydroperoxide **10** reacted with (+)-sabinene **4**, mediated by $FeSO_4 \cdot 7H_2O$ and $Cu(OAc)_2$ in degassed methanol,[24] to generate lactones **26** and **26'** in a 1:8 ratio in a combined yield of 36% (Scheme 4).[25] A preliminary mechanistic model of generating **26'** is proposed and shown here: Fe(II) reduces hydroperoxide **10** to generate alkoxy radical **11**, alkoxy radical **11** would then react with (+)-sabinene (**4**) in a manner similar to that in Scheme 2 to form radical **13'**. Formation of compound **26'** presumably involves radical oxidation by Cu(II)[26] or a Heck-type reaction involving a formal β-H elimination of intermediate **27'**.[27] The crystal structure of compound **26'** was obtained (CCDC-1870111), confirming the proposed stereochemistry. Compound **26** should be formed with a similar mechanism. The two compounds **26** and **26'** were separated via HPLC using chiral columns.

The synthesis of compound **26** and **26'** set the stage to test our proposed biosynthetic steps following the generation of radical **13** (see Scheme 2). As shown in Scheme 5, under hydroperoxidation conditions,[28,28e] radical **13'** was formed from pure **26'** via hydrogen atom transfer.[29] Radical **13'** then underwent our proposed radical cascade reaction involving O_2, rendering a putative hydroperoxide mixture **28'** as epimers at C4, together with other unknown compounds. After selective reduction of the hydroperoxide of compound **28'** to alcohol by polymer-bound PPh_3 (finished in about one hour as shown in mass spectrometry),[28e,30] continued stirring of the reaction mixture for a month led to the completion of the Grob fragmentation of the putative peroxide **29'**,[16,17] leading to hitorin B (**2**) in 26% yield from compound **26'**.[31] The ^{1}H-NMR spectrum of hitorin B (**2**) matched the reported data, while we found its ^{13}C-NMR spectrum was concentration-dependent,[32,33] and the spectrum of a concentrated synthetic sample matched the reported data. Hitorin A (**1**) was also prepared in a similar fashion in 18% yield from pure compound **26**.

In summary, a radical cascade reaction starting from an alkoxy radical-olefin coupling was proposed for the biosynthesis of hitorins A and B. Our modified proposal led to the first biomimetic synthesis of these two natural products. Our synthesis would disclose nature's expertise to synthesize secondary metabolites using alkoxy radicals. Detailed mechanistic studies and biological evaluations of some advanced intermediates are underway.

Scheme 5. Synthesis of hitorin B.



ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterizations of new compounds.

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Notes

The authors declare no competing financial interests.

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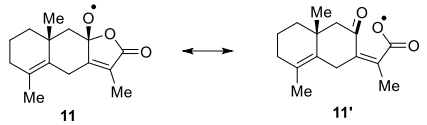
(10) The resonance structure **11'** may explain its stability, leading to selective intermolecular addition to olefins rather than intramolecular pathways of 1,5-H abstraction or β-fragmentation. The conformation of **11** may also play a role in its reaction pattern and the probability of 1,5-H abstraction could be reduced.



11 **11'**

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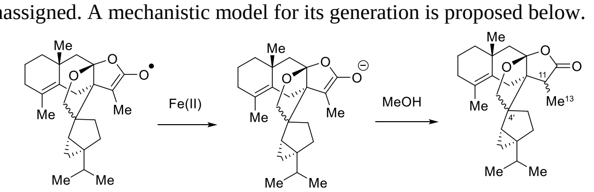
(25) A by-product, 11,13-dihydro-**26**, was also isolated in about 28% yield, probably as a mixture of stereoisomers. We were unable to isolate the major component in pure form so the stereochemistry of C4' and C11 is unassigned. A mechanistic model for its generation is proposed below.



13'' 11,13-dihydro-**26**

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(31) A by-product, 11-*epi*-**7'**, was also isolated from this reaction mixture in 14% yield. At least two TLC spots were able to fragment to form hitorin B. The smaller spot fragmented very quickly, usually within hours, but the larger spot, which was a mixture with other compounds, took one month to secure complete fragmentation. So here structures **28'** and **29'** are proposed to be epimers at C4.

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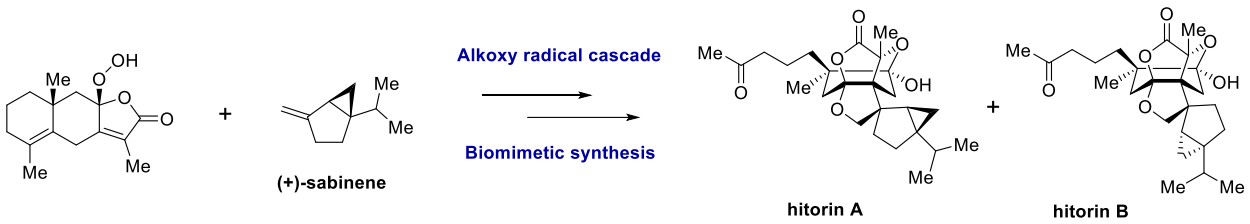
(33) All the ^{13}C NMR spectra of hitorin B (**2**) and both the ^{1}H and ^{13}C NMR spectra of hitorin A (**1**) were recorded using a coaxial insert with the sample solution inside and an outer tube containing only $CDCl_3$ (to assist locking). All other NMR spectra were recorded using regular 5-mm NMR tubes.

TOC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