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Biosynthesis of the C15-acetogenin laurepoxide may involve bromine-induced skeletal rearrangement of a Δ^4 -oxocene precursor

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Biosynthesis of the C15-acetogenin laurepoxide may involve bromine-induced skeletal rearrangement of a Δ^4 -oxocene precursor

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ABSTRACT

An electrophilic bromine catalyzed skeletal rearrangement of an Δ^4 -oxocene to an epoxy furan has been described. This skeletal rearrangement suggests a plausible mechanism for the biosynthesis of the C15-acetogenin laurepoxide.

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Introduction

Since the initial isolation of Laurencin in 1965, a wide variety of small and medium-ring ether, halogenated natural products have been isolated from *Laurencia* red algae.¹ The considerable structural diversity of these natural products has invited curiosity as to their biosynthetic origins, with representative members shown in Figure 1. In an elegant series of studies, Fukuzawa and Murai showed that haloether deacetyl laurencin, upon exposure to lactoperoxidase, halide and hydrogen peroxide, was transformed into a diverse array of other natural products including laureoxanyne, laurefucin, and notoryne (Scheme 1a).²⁻⁴ These findings are strongly suggestive of the existence of key transient bromonium species **1**, which can undergo an intramolecular bromoetherification and subsequent oxonium ylide-induced reactions to yield the observe products (Scheme 1a). Structural variants bromofucin⁵ and chlorofucin⁶ are also believed to be accessed via analogous bromonium intermediates. These biosynthetic proposals for electrophile-initiated transannulation have inspired the synthetic community. Kim exploited a selenoetherification approach in his syntheses of laurefucin⁷ and elatanyne,⁸ and a bromoetherification approach in his syntheses of *ent*-bromofucin,⁸ laureatin and iso-laureatin.⁹ Suzuki utilized an epoxidation followed by intramolecular ring opening sequence towards (*Z*)-laureatin.¹⁰

Figure 1. Representative C15-acetogenins

Less well understood is the biosynthesis of epoxy tetrahydrofuran natural products² such as laurepoxide¹¹ (Figure 1). Murai has shown that lactoperoxidase is capable of catalyzing the formation of 5-membered bromoethers from linear polyenes (Scheme 1b).³ Thus, it is plausible that epoxy tetrahydrofuran natural products arise from this type of reactivity, and the epoxide could be installed downstream via additional bromo-hydration reactions; but the latter has not been experimentally verified. Interestingly, Howell recently reported a skeletal rearrangement of an oxetane to yield an epoxy-furan structural motif similar to that found in the natural product laureoxolane (Scheme 1c).¹²

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Scheme 1. a) Fukuzawa and Murai's proposed biosynthesis of various bromoethers stemming from bromonium **1**. b) Proposed biosynthesis of brominated THF's from linear polyenes. c) Howell's skeletal rearrangement.

Intrigued by bromonium ion **1** and the potential chemistry of related ion **2** (Figure 2), we set out to study the chemistry of such intermediates in the context of biomimetic synthesis of halogenated *Laurencia* natural products. A possible fate of bromonium ion **2** would be bromoetherification to give the [5.2.1]-bicyclic core (**3**) found in bromofucin (Figure 2). An alternate fate of bromonium ion **2** would be intramolecular substitution by the oxocene to give oxocarbenium^{8, 10, 13} ion **4**. Here, we describe an electrophilic bromine promoted skeletal rearrangement of an 8-membered Δ^4 -oxocene via putative oxocarbenium ion **4**. The rearrangement suggests that it is possible that laurepoxide could arise from a bromonium ion similar to **2** via an intramolecular rearrangement process.

Figure 2. Oxocene-derived bromonium ions had been shown to rearrange to bromoether products as found in bromofucin. Here, we provide evidence for oxocarbenium ion intermediates that rearrange to give the laurepoxide framework via oxocarbenium ion **4**.

To obtain Δ^4 -oxocene **9**, the precursor to bromonium ion **2** we adapted Crimmins' synthesis of Δ^4 -oxocenes used in his synthesis of laurencin (Scheme 2).¹⁴ Crimmins' procedure utilizes an Evans' chiral auxiliary approach to achieve stereoselective allylation which sets the key positions at C7 and C12, and thus allowed us to easily select for the *S*-stereochemistry found at C7 in bromofucin. This nine-step procedure additionally has the benefit of scalability with Δ^4 -oxocene **5** accessible on a multigram scale. With **5** in hand, the next task was to install a homoallylic alcohol at C6 in a stereoselective fashion (Scheme 2). Compound **5** was hydrolyzed under mild conditions¹⁵ and the crude acid **6** was

directly carried onto Weinreb amide **7**.¹⁶ Treatment of **7** with allylmagnesium bromide yielded ketone **8** in 77% yield. L-Selectride has previously been shown to provide excellent Felkin-Ahn stereoselectivity on ketone reductions in previous C15-acetogenin syntheses,^{7, 17} and proved equally effective in our hands, yielding **9** in 66% yield as a single diastereomer. The reaction of **9** with NBS was explored next. We anticipated that treatment of **9** with NBS may result in bromonium ion formation followed by subsequent trapping with the pendant hydroxyl group to form **3**, which contains the [5.2.1]-oxabicyclic core of bromofucin. However, treatment of **9** with NBS in methylene chloride instead resulted in the isolation of tetrahydrofuran **10** as a single diastereomer in 45% yield.

Scheme 2. Synthesis of Δ^4 -oxocene and subsequent skeletal rearrangement.

The formation of **10** suggested that NBS combines with **9** to form a bromonium ion **2** which is not attacked by the hydroxyl group. Species **2** is instead trapped by transannular attack of the oxygen in the Δ^4 -oxocene to yield oxocarbenium ion **4**, which we subsequently undergoes intramolecular substitution by the hydroxyl group to yield the epoxy tetrahydrofuran **10** (Scheme 3a) as a single diastereomer. Compound **10** shares a skeletal framework with the natural product laureepoxide.¹¹

Compound **10** was isolated as a single diastereomer, with new stereocenters created at C7, C9 and C10. The relative stereochemistry at C10 was assigned by a NOESY experiment, which shows NOE between C12–C13, but not between C10–C12 nor C10–C13 (supporting information). A *cis*-conformation of the epoxide is suggested by the coupling constant (4.5 Hz), and the configuration C7 is further supported by the mechanism of epoxidation that involves inversion at C7 on intermediate **4**. The configuration at C9 could not be unambiguously assigned. A mechanism that involves concerted transannular opening of bromonium ion **2** to give oxocarbenium **4** would produce the *S*-configuration (as displayed in Scheme 3). However, we cannot rule out a mechanism involving a free carbocation, which could result in *R*-configuration at C9, providing relative stereochemistry that is consistent with the reported structure of

Scheme 3. a) Mechanistic rationale for the formation of **10**. b) Kim's synthesis of the core of *ent*-bromofucin. c) Suzuki and coworkers studied the reactivity of electrophilic bromine with **13**, a compound that is structurally and stereochemically similar to **9**. In the rearrangement to furan **2**, bromonium ion **14** and oxocarbenium ion **15** were proposed.

Scheme 4. Plausible biosynthesis of laureepoxide

laureepoxide.⁹

Recently, Kim reported the bromoetherification of **11** to yield the bicyclic core (**12**) of *ent*-bromofucin.⁸ Compound **11** is quite similar to **9** with the exception of the C12 bromine already being installed and on the opposite face of the benzyloxy group of **9**. This difference highlights the significant effect of backbone stereocenters in determining the fate of the bromonium ion, which in the case of **11** gives etherification in preference to oxocarbenium ion formation. (Scheme 3b).

The proposed facial selectivity for the formation of bromonium ion **2** and its rearrangement to oxocarbenium ion **4** is preceded by the work of Suzuki and co-workers¹⁰ (Scheme 3c) in their studies on the total synthesis of (+)-(*Z*)-laureatin. Δ^4 -oxocene **13**, which is structurally and stereochemically analogous to our compound **9**, was found to rearrange to keto-furan **16**. The authors proposed that bromonium ion formation occurs on the β -face of the alkene and proposed a conformational model (**14**) for the intermediate bromonium ion. Transannular attack was proposed to give oxocarbenium ion **15**—a structure consistent with the proposed intermediate **4**.

These results suggest that Δ^4 -oxocene **17** may serve as the biosynthetic precursor laureepoxide via intermediate bromonium ion **18** (Scheme 4). Opening of **18** to carbocation **19** would provide a pathway to the reported structure of laureepoxide via oxocarbenium **20**. By contrast, stereospecific opening of **18** would lead to the C-10 epimer of laureepoxide via intermediate oxocarbenium ion **21**. Additional study would be necessary to confirm the stereochemical assignments in the literature,⁹ but is very plausible that the open carbocation pathway involving **19** and **20** would be favored due to the severe steric compression in **21**.

In summary, we have discovered an electrophilic bromine promoted skeletal rearrangement of a Δ^4 -oxocene to yield the structural scaffold of C15-acetogenin laureepoxide. These observations highlight the need for additional study to further understand the biosynthesis of this natural product.

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