Biomimetic Total Synthesis of (±)-Yezo'otogirin A

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Biomimetic Total Synthesis of (±)-Yezo'otogirin A†

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The total synthesis of yezo'otogirin A has been achieved via a biosynthetically-inspired strategy. Diastereoselective synthesis of pre-yezo'otogirin A, the proposed biosynthetic pre-cursor of yezo'otogirin A, was accomplished in eight steps from 3-ethoxy-2-cyclohexenone. A biomimetic oxidative radical cyclization was then used to construct the unique tricyclic ring system of yezo'otogirin A. The synthesis showcases the ability of biomimetic radical cyclizations to generate complex natural products from unprotected intermediates.

Flowering plants of the *Hypericum* genus have long been used in traditional medicine for the treatment of various conditions, including bacterial and viral infections. The biological activity of these plants is generally attributed to the presence of complex polycyclic polyprenylated acylphloroglucinol (PPAP) secondary metabolites, which have become popular synthetic targets in recent years.[1]

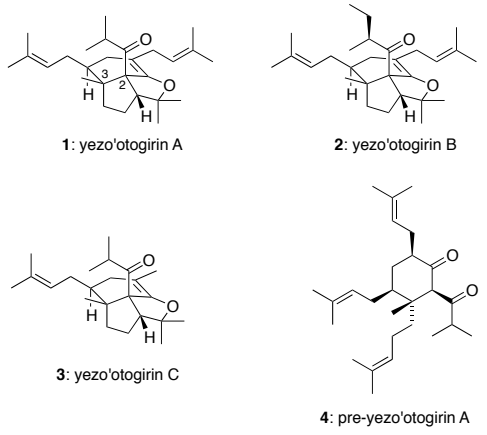
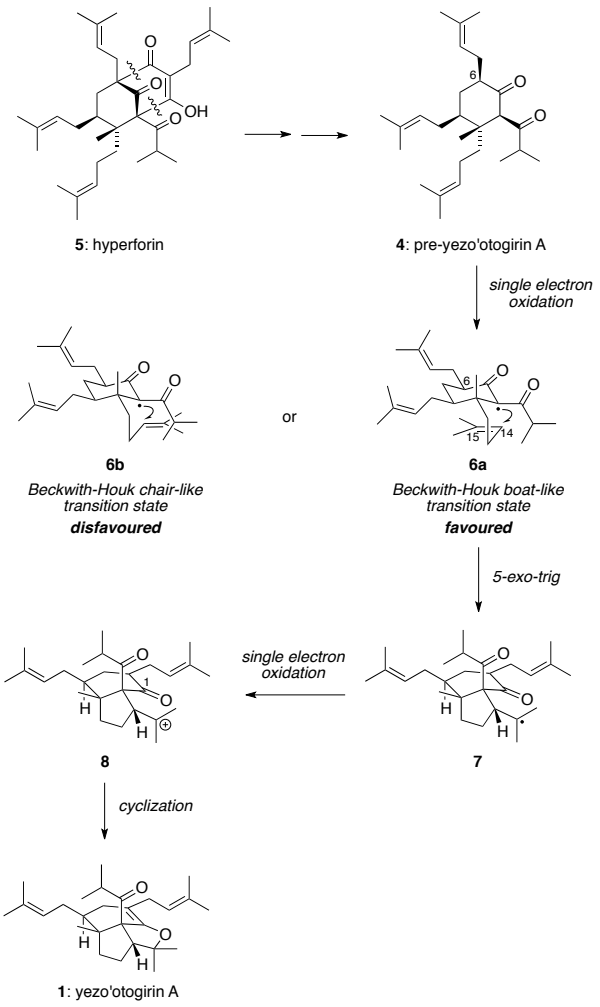


Figure 1. Yezo'otogirins A-C and pre-yezo'otogirin A.

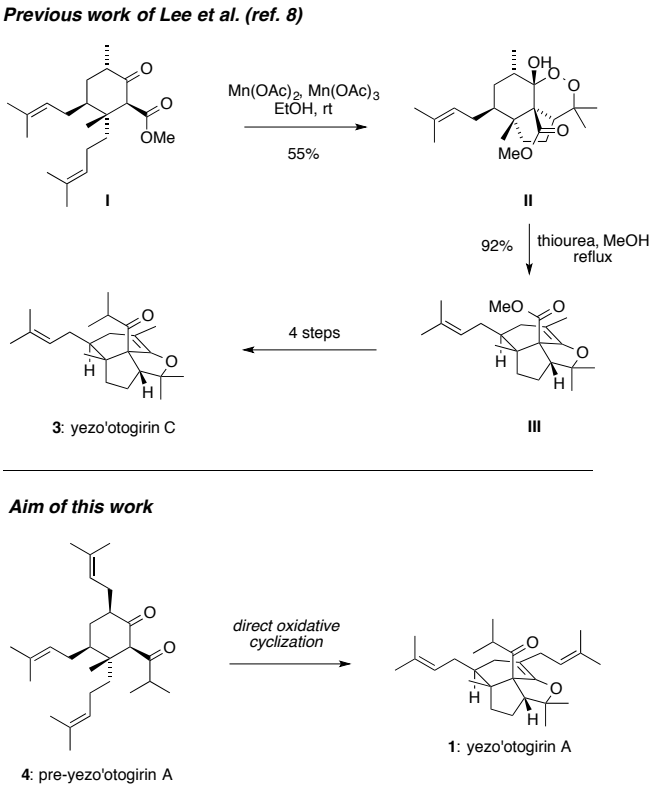
Yezo'otogirins A-C[2] (**1-3**, Figure 1) are an unusual family of rearranged PPAP natural products isolated from *Hypericum yezoense*. The yezo'otogirins each possess a compact, tricyclic ring system with an endocyclic enol ether. The three rings of the yezo'otogirins compose a shallow bowl shape, with an orthogonal ketone group attached to C-2 on the convex face of the bowl. The presence of four contiguous stereocentres, including two adjacent all-carbon quaternary stereocentres at C-2 and C-3, renders the yezo'otogirins challenging structures for total synthesis. However, co-isolation of the yezo'otogirins with the monocyclic natural product "pre-yezo'otogirin A" (**4**) suggests a possible biosynthesis via an oxidative radical cyclization mechanism. Thus, our objective in this research project was to synthesize **4** and then to develop a biomimetic radical cyclization to convert **4** into **1**.[3] We have previously used oxidative radical cyclizations in biomimetic total syntheses of the PPAPs ialibinones A and B,[4] and garcibracteatone.[5]

A detailed biosynthetic proposal for the origin of yezo'otogirin A is outlined in Scheme 1. Pre-yezo'otogirin A (**4**) is presumably formed in nature by degradation of hyperforin (**5**). Indeed, **4** has been previously co-isolated with **5** from *Hypericum perforatum* (St. John's wort).[6] Single electron oxidation of the β-dicarbonyl group of **4** could give stabilized radical **6**, which could then undergo a favourable *5-exo-trig* cyclisation onto the $\Delta^{14,15}$ double bond to give tertiary radical **7**. Molecular modelling studies indicate that **6** should preferentially cyclize via a Beckwith-Houk boat-like transition state[7] (**6a**), since the alternative chair-like transition state (**6b**) is disfavoured by a steric clash between the $\Delta^{14,15}$ alkene and the nearby isopropyl group. A further one-electron oxidation of radical **7** would generate tertiary carbocation **8**, which could be intercepted by intramolecular attack of the C-1 carbonyl oxygen to form the 6-5-5 ring system of **1**.



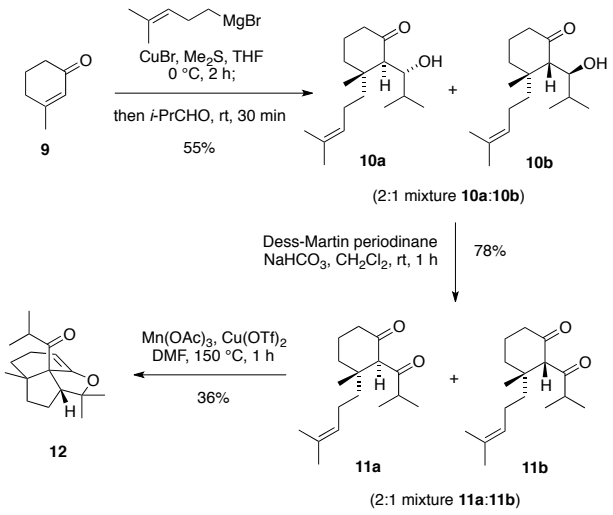
Scheme 1. Proposed biosynthesis of yezo'otogirin A.

While this manuscript was in preparation, a related biomimetic approach to yezo'otogirin C was reported by Lee et al.[8] However, their synthesis proceeded via the peroxy-bridged compound **II**, which was formed in 55% yield by oxidative radical cyclization of **I** using Mn(II) and Mn(III) under an oxygen atmosphere (Scheme 2). Reduction of **II** with thiourea then gave **III** in 92% yield, which contains the desired 6-5-5 yezo'otogirin ring system. Finally, **III** was converted into yezo'otogirin C in four simple steps. In contrast, the aim of our work was to achieve a direct oxidative cyclization of pre-yezo'otogirin A (**4**) into yezo'otogirin A (**1**) as this could lead to a more direct total synthesis, and also support our biosynthetic proposal.



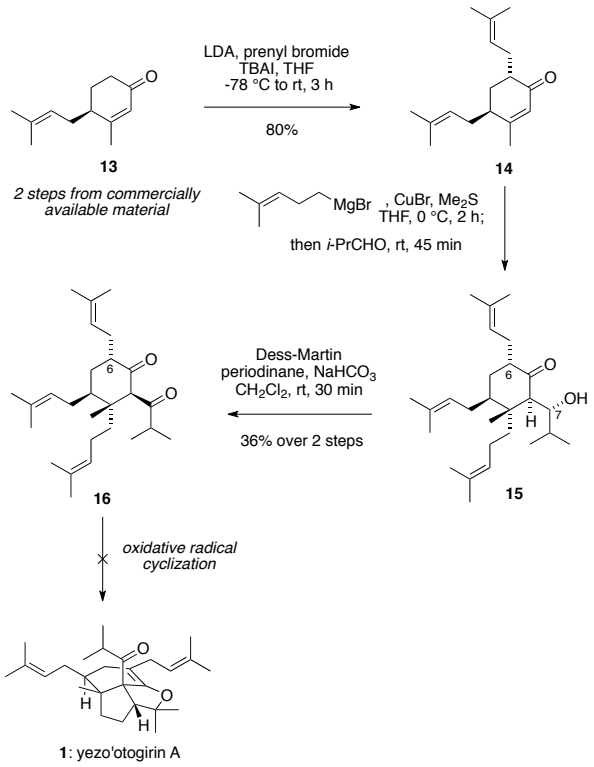
Scheme 2. Previous synthesis of yezo'otogirin C by Lee et al., and the aim of this work.

Before embarking on a total synthesis of yezo'otogirin A (**1**), we conducted a brief model study to test the validity of our oxidative radical cyclization approach (Scheme 3). Thus, 1,4-addition of an organocuprate species derived from (4-methylpent-3-enyl)magnesium bromide and CuBr to 3-methyl-2-cyclohexenone (**9**), followed by trapping of the resultant enolate with isobutyraldehyde, gave the anti-aldol products **10a** and **10b** as a 2:1 mixture in 55% overall yield.[9] Oxidation of **10a**/**10b** with Dess-Martin periodinane then gave the diastereomeric 1,3-diketones **11a** and **11b** in good yield. We then treated **11a**/**11b** with $Mn(OAc)_3$ and $Cu(OTf)_2$ in refluxing DMF to give **12**, which contains the complete tricyclic core of the yezo'otogirins, in 35% yield. Related oxidative radical cyclizations of β-dicarbonyl compounds mediated by $Mn(OAc)_3$ have been studied extensively,[10] with $Cu(OAc)_2$ commonly used as a co-oxidant. The general reaction pathway involves single electron oxidation of a β-dicarbonyl compound by $Mn(OAc)_3$, followed by addition of the resultant radical to an alkene.[11] This forms an alkyl radical, which is oxidized to a carbocation in the presence of $Cu(OAc)_2$. This carbocation can lose a proton to form an alkene, or be trapped by enols or alcohols to form cyclic ketones or ethers respectively. Recently, Burton et al. reported the use of $Cu(OTf)_2$ in place of $Cu(OAc)_2$ to facilitate trapping of the carbocation intermediates by esters, thus allowing the formation of highly functionalized bicyclic lactones.[12] However, the formation of polycyclic enols, such as **12**, with $Mn(OAc)_3$/$Cu(OTf)_2$ has not previously been reported.



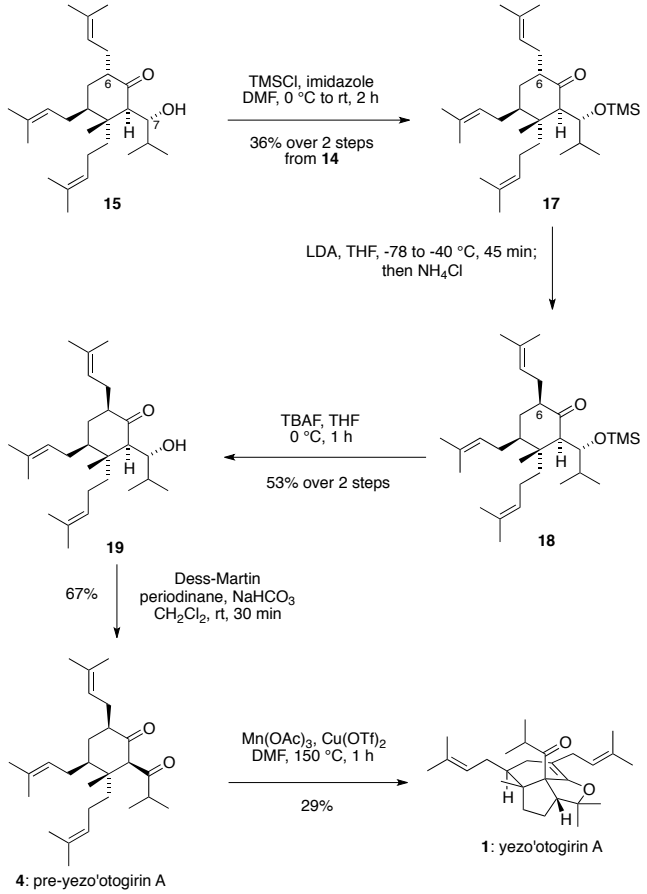
Scheme 3. Model oxidative radical cyclization for the synthesis of the yezo'otogirin 6-5-5 ring system.

As outlined in Scheme 4, our first attempt at the total synthesis of yezo'otogirin A began with the known enone **13** (formed in two high-yielding steps from 3-ethoxy-2-cyclohexenone according to Shibasaki et al.[13]). Alkylation of **13** with LDA and prenyl bromide gave **14** in 80% yield, as the major component of a 10:1 mixture of diastereomers.[14] The use of catalytic TBAI was found to improve the yield of this alkylation reaction significantly. Conjugate addition of the organocuprate derived from (4-methylpent-3-enyl)magnesium bromide and CuBr to enone **14** generated an enolate that was treated *in situ* with isobutyraldehyde to give the *anti*-aldol adduct **15**. Dess-Martin oxidation of **15** then gave 6-*epi*-pre-yezo'otogirin A (**16**) in 36% yield over two steps. However, exposure of **16** to a variety oxidizing systems (such as $PhI(OAc)_2$, $PhI(O_2CCF_3)_2$, CAN, $Mn(OAc)_3/Cu(OAc)_2$ and $Mn(OAc)_3/Cu(OTf)_2$) failed to generate any yezo'otogirin A. We believe that the configuration of the C-6 prenyl group is the reason for the lack of success of this reaction. The axial C-6 prenyl group of **16** would sterically hinder the desired cyclization, or even participate in an undesired *5-exo-trig* cyclization itself.



Scheme 4. Initial synthetic approach to yezo'otogirin A.

Thus, in order to synthesize yezo'otogirin A (**1**) via our proposed biomimetic oxidative cyclization, we believed it was necessary to obtain pre-yezo'otogirin (**4**) as a single diastereomer, with complete control of the C-6 stereocentre. This was achieved in a few extra steps according to Scheme 5. Protection of the C-7 hydroxyl group of **15** with TMSCl gave TMS-ether **17** in 36% over two steps. Epimerization of **17** at C-6 using LDA followed by protic work-up then furnished **18**, which was deprotected with TBAF to give **19** in 53% yield over two steps. Oxidation of **19** with Dess-Martin periodinane gave pre-yezo-otogirin A (**4**) in 67% yield. We were then pleased to observe oxidative cyclization of **4** using $Mn(OAc)_3$ and $Cu(OTf)_2$ in DMF at 150 °C to give yezo'otogirin A (**1**) in 29% yield, presumably via the mechanism outlined in Scheme 1. Screening of a variety of alternative oxidants (as mentioned previously) and different solvents failed to generate **1**. Indeed, the use of $Cu(OTf)_2$ in conjunction with $Mn(OAc)_3$ was found to be essential for the reaction to proceed. ^1H and ^{13}C data for **1** and **4** were identical to the previously reported data of Kobayashi et al.[2]



Scheme 5. Total synthesis of yezo'otogirin A.

Conclusions

We have achieved a concise, diastereoselective synthesis of the rearranged PPAP natural product, yezo'otogirin A (**1**), in nine steps (3% overall yield) from commercially available material. An oxidative radical cyclization of the probable biosynthetic pre-cursor, pre-yezo'otogirin A (**4**), was used to construct the unusual 6-5-5 ring system of **1**. The success of the oxidative radical cyclization indicates that a similar reaction mechanism could be involved in the biosynthesis of the yezo'otogirins. However, the notably higher yield reported by Lee et al. for their oxidative cyclization of **I** to **III** via cyclic peroxide **II** (Scheme 2) suggests that this is perhaps the more likely biosynthetic pathway. Future work will focus on the enantioselective synthesis of yezo'otogirins A-C, and the evaluation of their biological activity.

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Notes and references

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c000000x/

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