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Bioinspired Total Synthesis of (±)-Yezo'otogirin C

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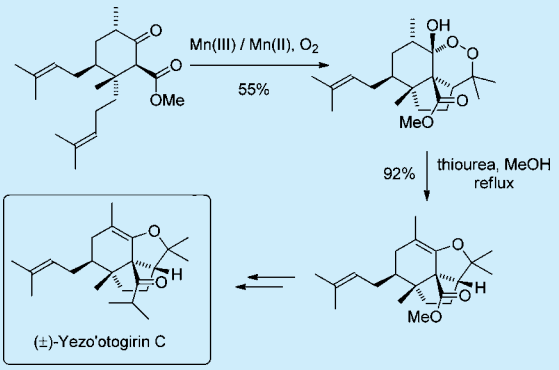
Supporting Information

ABSTRACT: The first and protective group-free total synthesis of (±)-yezo'otogirin C has been achieved from 3-methyl-4-prenylcyclohex-2-enone in eight steps with 23% overall yield. The tricyclic core of (±)-yezo'otogirin C was established via a bioinspired oxidative cascade cyclization strategy using Mn(II)/Mn(III) and O_2, followed by reduction of the peroxy-bridged intermediate using thiourea in refluxing methanol.



The genus *Hypericum* belongs to the botanical family of *Clusiaceae* Lindley and is divided into more than 50 sections including more than 400 species with a nearly worldwide distribution in temperate regions.[1] Plants of this genus have been used as traditional remedies for the treatment of burns, pain, swelling, inflammation, anxiety, and melancholia.[2] One of the well-known examples is *H. perforatum* L. (also known as St. John's wort),[3] which is a famous folk medicine for its wound-healing, anti-inflammatory, and antidepression uses.[4] Because of the high biological value of *H. perforatum* L., many related species in the *Hypericum* genus have been evaluated for antitumor, antibacterial, antifungal, antiviral, antioxidant, wound-healing, and anti-inflammatory activities.[5]

Yezo'otogirins A–C (**1**–**3**, Figure 1) are tricyclic terpenoids isolated from the aerial parts of *H. yezoense*.[6] These natural products contain a rare octahydroindeno[7,1-*bc*]furan tricyclic core structure with four to five stereogenic centers and are reported to be noncytotoxic against L1210 murine leukemia (in vitro). Since a known hyperforin analogue **4** (Figure 1) was also isolated from *Hypericum perforatum*,[7] hyperforin analogue **4** was hypothesized as the potential precursor for the biosynthesis of yezo'otogirin A (**1**).[6] Inspired by this plausible biogenetic proposal, we decided to develop a biomimetic synthesis of (±)-yezo'otogirin C (**3**) via an oxidative cascade cyclization approach.

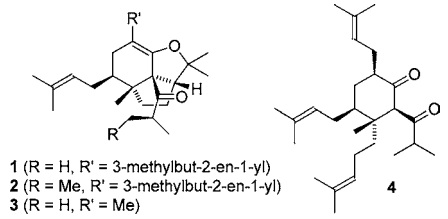
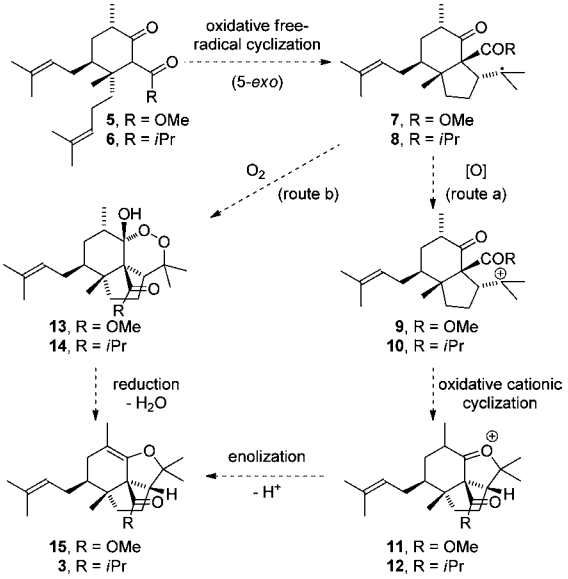


Figure 1. Structures of yezo'otogirins A–C (**1**–**3**) and a hyperforin analogue (**4**).

As shown in Scheme 1, upon treatment with an appropriate single-electron oxidant,[8] both substrates are expected to undergo a 5-*exo* radical cyclization to form the *cis*-hydrindans. Further oxidation of the resulting radical intermediate **7** and **8**

Scheme 1. Bioinspired Synthetic Strategies toward the Tricyclic Core of (±)-Yezo'otogirin C (3)



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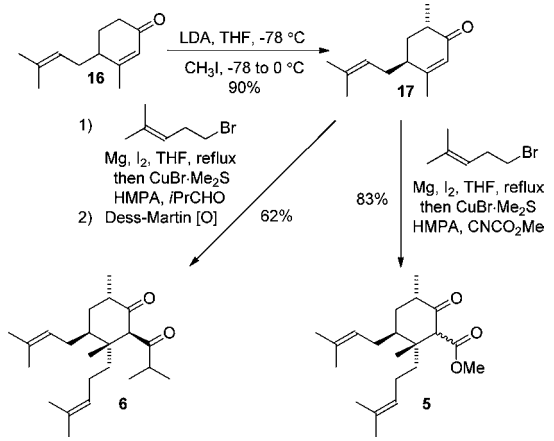
should afford cations **9** and **10**, which would undergo cationic cyclization to form the tricyclic intermediates **11** and **12** (route a). Final deprotonation and enolization should furnish the octahydroindeno[7,1-*bc*]furan tricyclic structure of yezo'otogirin C (**3**) and **15**, respectively. However, intermediates **11** and **12** would be unstable because of the high ring-strain of the tricyclic fused ring systems and would result in various elimination products via the dihydrofuran ring-opening.[8g] Based on this conformational analysis, formation of the oxa-5,5-bicyclic system that fused into a cyclohexane via the oxidative free-radical cascade cyclization would be challenging and is unprecedented to the best of our knowledge. To avoid the high ring strain of tricyclic intermediates **11** and **12**, an alternative biomimetic approach via trapping the radical intermediates **7** and **8** with an oxygen molecule (route b) would be employed.[8,9] The resulting peroxy-bridged compounds **13** and **14** would be readily converted to (±)-yezo'otogirin C (**3**) and **15**, respectively, under reductive conditions.[9a,10]

The cyclization precursors **5** and **6** were prepared from enone **16**, which can be readily prepared from 1,3-cyclohexanedione in three steps with 90% overall yield (up to 50 g scale) according to the literature procedures.[11] As shown in Scheme 2, α'-methylation of enone **16** with LDA and methyl

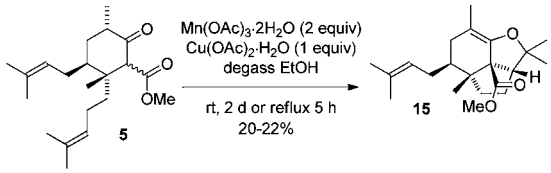
Scheme 2. Synthesis of Cyclization Precursors 5 and 6



iodide provided compound **17** as a single diastereomer in good yields. Conjugated addition of 4-methylpent-3-en-1-yl cuprate followed by quenching the enolate generated in situ with methyl cyanoformate afforded **5** as a mixture of highly enolizable β-keto esters in one pot.[12] Similarly, diketone **6** was obtained by the domino Michael/aldol reaction followed by oxidation of the resulting mixture of β-hydroxy ketone diastereomers.[13] The synthesis of **5** and **6** requires only two to three steps from a known compound **16** with 56−75% overall yield, respectively. The diastereoselectivity of both α'-methylation and conjugated addition reactions was presumably induced by the steric hindrance of the prenyl group of **16** and **17**.

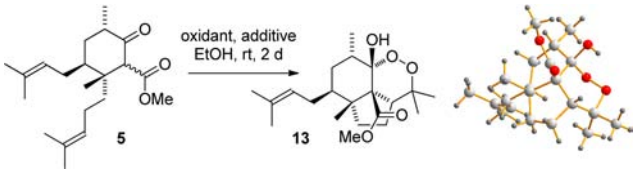
With the cyclization precursors in hand, oxidative free-radical cascade cyclization of β-keto ester **5** was studied since β-keto esters are known to be more active substrates.[14] In the absence of oxygen (route a in Scheme 1), oxidative cascade cyclization of **5** led to only a variety of elimination side products under a variety of oxidative conditions.[8] Finally, the expected cyclized product **15** was obtained in 20−22% yield using $Mn(OAc)_3\cdot 2H_2O$ and $Cu(OAc)_2\cdot H_2O$ in ethanol at room temperature for 2 days or under refluxing conditions for 5 h (Scheme 3). The low efficiency of this cyclization process is consistent with the rationale from the preliminary conformational analysis of cation intermediate **11**.

Scheme 3. Oxidative Free-Radical Cascade Cyclization of β-Keto Ester 5 under Oxygen-Free Conditions



The oxidative cascade cyclization reactions of **5** were then carried out with a variety of oxidants under an oxygen atmosphere[10] (route b in Scheme 1). As shown in Table 1,

Table 1. Oxidative Free-Radical Cascade Cyclization of β-Keto Ester 5 in the Presence of Oxygen



entry	oxidant (equiv)	additive (equiv)	yield (%)
1	$Mn(OAc)_3\cdot 2H_2O$ (2)		20
2	$Cu(OAc)_2\cdot H_2O$ (2)		trace
3	CAN (2)		trace
4	$FeCl_3$ (2)		
5	$Mn(OAc)_2\cdot 4H_2O$ (2)		44
6	$Mn(OAc)_2\cdot 4H_2O$ (2)	$Mn(OAc)_3\cdot 2H_2O$ (0.2)	55
7	$Mn(OAc)_2\cdot 4H_2O$ (2)	$KMnO_4$ (0.2)	36
8	$Mn(OAc)_2\cdot 4H_2O$ (2)	$Pb(OAc)_4$ (0.2)	31
9	$Mn(OAc)_2\cdot 4H_2O$ (2)	$Cu(OAc)_2\cdot H_2O$ (0.2)	35
10	$Mn(OAc)_2\cdot 4H_2O$ (2)	CrO_3 (0.2)	27
11	$Mn(OAc)_2\cdot 4H_2O$ (2)	CAN (0.2)	42
12	$Mn(OAc)_2\cdot 4H_2O$ (2)	$FeCl_3$ (0.2)	20
13	$Mn(OAc)_2\cdot 4H_2O$ (1)		38
14	$Mn(OAc)_2\cdot 4H_2O$ (0.5)		35
15	$Mn(OAc)_2\cdot 4H_2O$ (0.1)		35 (42)
16	$Mn(OAc)_2\cdot 4H_2O$ (0.1)[c]		35
17	$Mn(OAc)_2\cdot 4H_2O$ (0.1)	$Mn(OAc)_3\cdot 2H_2O$ (0.1)	44 (51)
18	$Mn(OAc)_2\cdot 4H_2O$ (0.1)	$KMnO_4$ (0.1)	11 (24)
19	$Mn(OAc)_2\cdot 4H_2O$ (0.1)	$Cu(OAc)_2\cdot H_2O$ (0.1)	38 (52)
20	$Mn(OAc)_2\cdot 4H_2O$ (0.1)	CAN (0.1)	27 (31)

[a]The general procedures were followed. [b]Isolated yields (yields base on recovered starting materials). [c]The reaction was carried at 50 °C.

$Mn(OAc)_3\cdot 2H_2O$ in ethanol at room temperature afforded 20% of the peroxy-bridged compound **13** as a single diastereomer (entry 1) along with some unidentified side products. The structures of **13** were characterized unambiguously by X-ray crystallography.[15] Switching the oxidant to $Cu(OAc)_2\cdot H_2O$, CAN, or $FeCl_3$ gave unsatisfactory results (entry 2−4). Using $Mn(OAc)_2\cdot 4H_2O$ as the precursor of Mn(III) provided the peroxy-bridged compound **13** in 44% yield (entry 5). Encouraged by these results, the reaction conditions were further optimized by using a combination of $Mn(OAc)_2\cdot 4H_2O$

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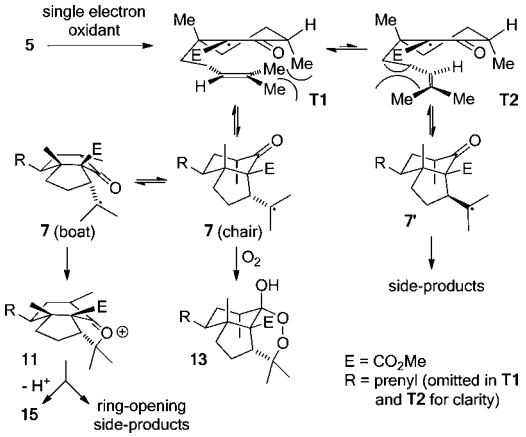
with a catalytic amount of various oxidants.[9b,c] After a survey of different oxidant combinations (entry 6−12), the optimal conditions were found to use $Mn(OAc)_2·4H_2O$ with $Mn(OAc)_3·2H_2O$ (Kurosawa and Nishino's conditions),[9b] which afforded 55% of peroxy-bridged compound **13** (entry 6).

The effects of the oxidant loading were also investigated. Surprisingly, decreasing the oxidant loading from 2 to 0.1 equiv led to only a slight decrease in the yields of **13** (35−38%, entry 13−15). The reaction rates are generally slower, and an incomplete reaction resulted with 0.1 equiv of $Mn(OAc)_2·4H_2O$ (entry 15). A complete reaction could be achieved at 50 °C in 2 days but gave the same isolated yield (entry 16) due to the decomposition of **13** under the reaction conditions. With 0.1 equiv of $Mn(OAc)_2·4H_2O/Mn(OAc)_3·2H_2O$ or $Mn(OAc)_2·4H_2O/Cu(OAc)_2·H_2O$, the oxidative cascade cyclization reactions gave 44 and 38% (51 and 52% based on recovered starting materials) of **13** (entry 17 and 19). Encouraged by these results, cyclization of diketone **6** was investigated on the basis of the optimal conditions for **5**. However, diketone **6** was found to be much less active than β-keto ester **5**. Only a trace amount of **14** was observed (LC−MS analysis) at room temperature, and decomposition of diketone **6** and **14** was observed under the high reaction temperature conditions.

The results of the oxidative cascade cyclization of **5** were rationalized by the conformational analysis of the reactive intermediates. As shown in Scheme 4, the radical intermediate

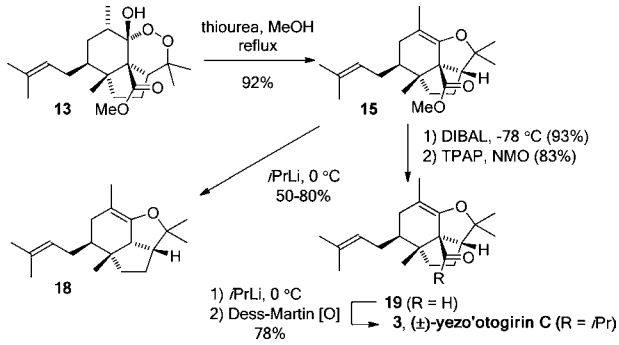
Scheme 4. Conformational Analysis of Reactive Intermediates



generated from β-keto ester **5** could undergo 5-*exo* cyclization through transition states **T1** and **T2** leading to 7 (chair) and 7′, respectively. The *endo* transition state **T1** is considered to be more favorable according to Beckwith's transition-state model,[16] which is consistent with our experimental results. Radical 7′ bearing a β-*i*-Pr could not undergo further cyclization but led to various side products. Radical 7 (chair) has the right geometry for reaction with an oxygen to form peroxy-bridged compound **13**. However, 7 (chair) required a ring flip to form 7 (boat) for further cyclization with the ketone to form the highly strained tricyclic cation **11**, which could lead to **15** or a variety of side products via ring-opening. This conformational analysis provided a reasonable rationale for the formation of **13** under the oxygen atmosphere being more favorable than the formation of **15** under the oxygen-free environment.

To complete the total synthesis of (±)-yezo'otogirin C (**3**), peroxy-bridged compound **13** was converted into **15** with thiourea in refluxing methanol[9a,10] (Scheme 5). However,

Scheme 5. Total Synthesis of (±)-Yezo'otogirin C



compound **15** was found to be stable upon treatment with a large excess of *i*-PrMgBr under high-temperature conditions. Treatment of a stoichiometric amount of *i*-PrLi at −78 °C to room temperature also resulted in no reaction. Surprisingly, when an excess of *i*-PrLi was used at 0 °C or room temperature, the decarboxylation product (**18**) was isolated in good yields (50−80%). This side product would result from double addition of *i*-PrLi followed by a retro-aldol reaction or Krapcho-type decarboxylation. The methyl ester of **15** was then reduced with DIBAL, and the resultant alcohol was oxidized to the corresponding aldehyde **19**. Addition of *i*-PrLi to the latter followed by Dess−Martin oxidation completed the synthesis of (±)-yezo'otogirin C (**3**). The NMR spectral data are identical to those in the literature.

In summary, we have achieved the first total synthesis of (±)-yezo'otogirin C (**3**) via a bioinspired oxidative cascade cyclization strategy under an oxygen atmosphere. The synthesis required only eight steps from a known enone **16** with 23% overall yield without using any protecting groups. Since all of the stereogenic centers of the natural product were established stereoselectively by the solo stereogenic center of **16** via substrate control, this synthesis would be readily extended to an asymmetric version by employing the enantiomerically enriched form of **16** as the starting material, which can be prepared according to the literature procedures.[17] We are currently exploring the utilities of this oxidative cascade cyclization strategy in the synthesis of picrodendrins.[18]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) CCDC-924074 (**13**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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