

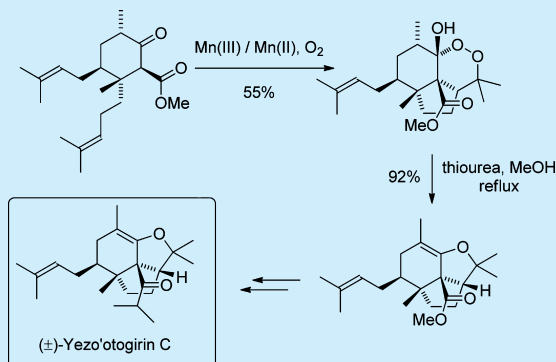
Bioinspired Total Synthesis of (±)-Yezo'otogirin C

Shuzhong He,^{†,‡} Wei Yang,[†] Lizhi Zhu, Guangyan Du, and Chi-Sing Lee*[‡]

Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Peking University Shenzhen Graduate School, Shenzhen University Town, Xili, Shenzhen 518055, China

S 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 O₂, 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 antidepressant 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

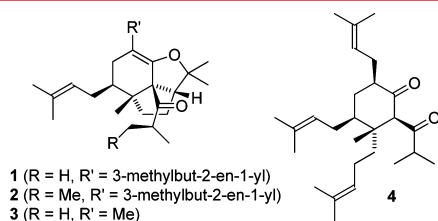


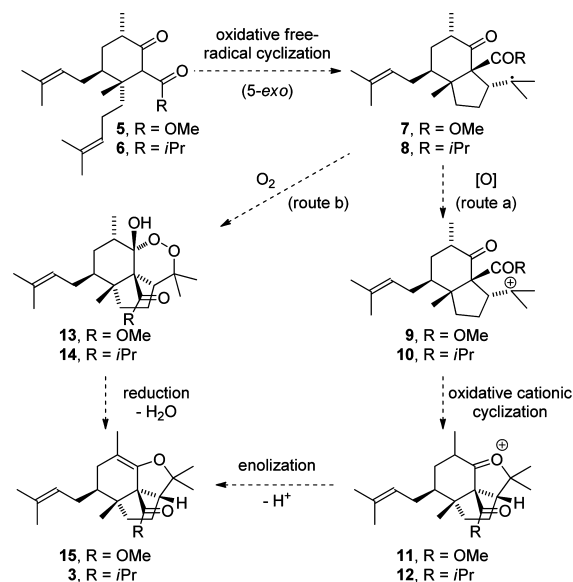
Figure 1. Structures of yezo'otogirins A–C (1–3) and a hyperforin analogue (4).

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.

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)



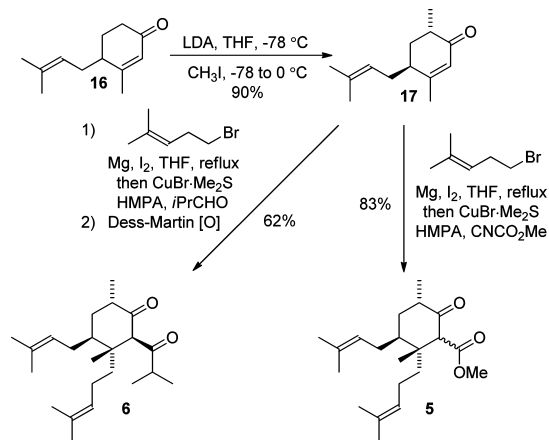
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should afford cations **9** and **10**, which would undergo cationic cyclization to form the tricyclic intermediates **11** and **12** (route a). Final deprotonation and enolization should furnish the octahydroinden[7,1-*bc*]furan tricyclic structure 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 (\pm)-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

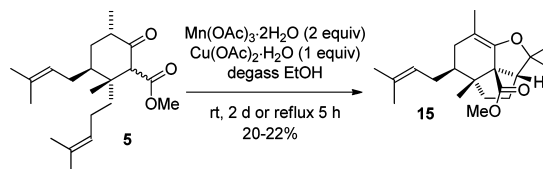


iodide provided compound **17** as a single diastereomer in good yields. Conjugated addition of 4-methylpent-3-en-1-yl cuprate followed by quenching the enolate generated in situ with methyl cyanoformate afforded **5** as a mixture of highly enolizable β -keto esters in one pot.¹² Similarly, diketone **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 $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$

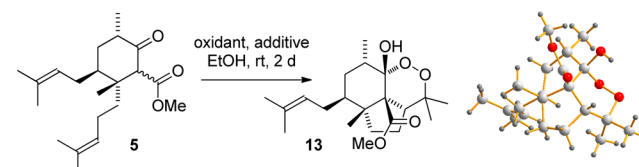
and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ in ethanol at room temperature for 2 days or under refluxing conditions for 5 h (Scheme 3). The low efficiency of this cyclization process is consistent with the rationale from the preliminary conformational analysis of cation intermediate **11**.

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 atmosphere¹⁰ (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	$\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ (2)		20
2	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2)		trace
3	CAN (2)		trace
4	FeCl_3 (2)		
5	$\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (2)		44
6	$\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (2)	$\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ (0.2)	55
7	$\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (2)	KMnO_4 (0.2)	36
8	$\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (2)	$\text{Pb}(\text{OAc})_4$ (0.2)	31
9	$\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (2)	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.2)	35
10	$\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (2)	CrO_3 (0.2)	27
11	$\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (2)	CAN (0.2)	42
12	$\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (2)	FeCl_3 (0.2)	20
13	$\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (1)		38
14	$\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (0.5)		35
15	$\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (0.1)		35 (42)
16	$\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (0.1) ^c		35
17	$\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (0.1)	$\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ (0.1)	44 (51)
18	$\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (0.1)	KMnO_4 (0.1)	11 (24)
19	$\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (0.1)	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.1)	38 (52)
20	$\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (0.1)	CAN (0.1)	27 (31)

^aThe general procedures were followed. ^bIsolated yields (yields based on recovered starting materials). ^cThe reaction was carried at 50 °C.

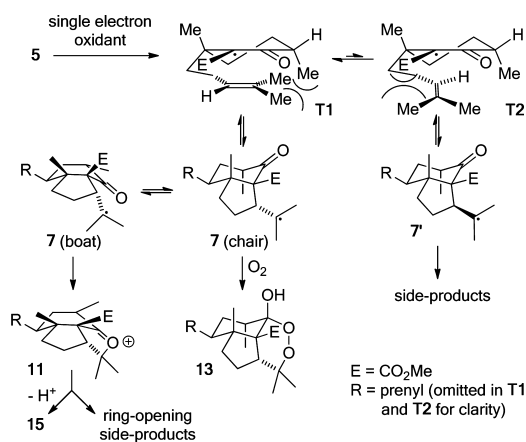
$\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ in ethanol at room temperature afforded 20% of the peroxy-bridged compound **13** as a single diastereomer (entry 1) along with some unidentified side products. The structures of **13** were characterized unambiguously by X-ray crystallography.¹⁵ Switching the oxidant to $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, CAN, or FeCl_3 gave unsatisfactory results (entry 2–4). Using $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ 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 $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$

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)₂·4H₂O with Mn(OAc)₃·2H₂O (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)₂·4H₂O (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)₂·4H₂O/Mn(OAc)₃·2H₂O or Mn(OAc)₂·4H₂O/Cu(OAc)₂·H₂O, 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

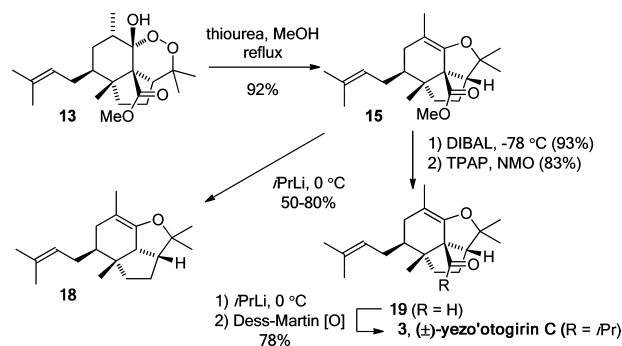
Scheme 4. Conformational Analysis of Reactive Intermediates



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 (\pm)-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 (\pm)-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 (\pm)-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 (\pm)-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 picrodendrin.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>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: lizc@pkusz.edu.cn.

Present Address

‡School of Pharmacy, University of Wisconsin at Madison, Madison, WI.

Author Contributions

†These authors contributed equally.

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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