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Tandem Oxidative Dearomatization/Intramolecular Diels–Alder Reaction for Construction of the Tricyclic Core of Palhinine A

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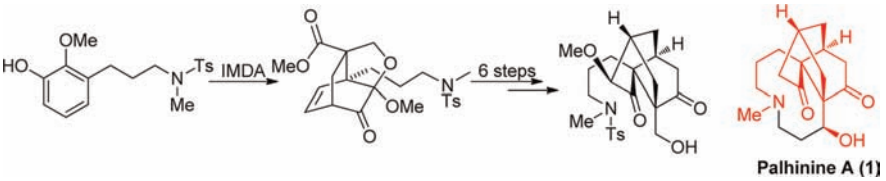
ABSTRACT



A concise construction of the 6/6/5 tricyclic core of *Lycopodium* alkaloid palhinine A (1) has been accomplished. The developed synthetic strategy featured a tandem oxidative dearomatization/intramolecular Diels–Alder reaction to construct C/D rings and an intramolecular 5-*exo-trig* radical cyclization to install the B ring of palhinine A (1). The developed approach paves the way for the total synthesis of palhinine A (1).

The *Lycopodium* alkaloids are a group of diverse and structurally related secondary metabolites. Most of them possess unique and fascinating skeletal characteristics and a variety of biological activities.[1−3] Palhinine A (**1**) (Figure 1), a novel $C_{16}N$-type *Lycopodium* alkaloid, was isolated from the whole plant of *Palhinhaea cernua* L. by Long et al. in 2010.[4] The structure of **1** was disclosed to contain a unique 5/6/6/9 tetracyclic ring system by comprehensive NMR spectroscopic analysis and a single-crystal X-ray study. Different from the fawcettimine-type *Lycopodium* alkaloid, palhinine A represents the first example of a *Lycopodium* alkaloid in which a new carbon–carbon bond formed between C-16 and C-4.[4] The highly compact arrangement of the fused polycyclic structure of palhinine A and two contiguous quaternary carbons (C-4 and C-12) served to be a great challenge to the science of chemical synthesis and attracted our research interest. Herein we report a concise approach for the construction of the tricyclic core of palhinine A (**1**) via a tandem oxidative dearomatization/intramolecular Diels–Alder(IMDA) reaction[5] and 5-*exo-trig* radical cyclization as key steps. The developed approach paves the way for the total synthesis of target **1**.

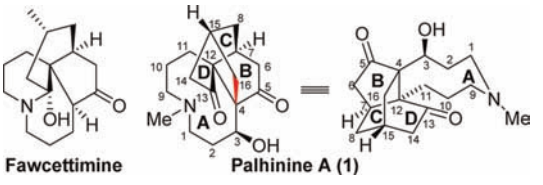


Figure 1. Structure of palhinine A (**1**).

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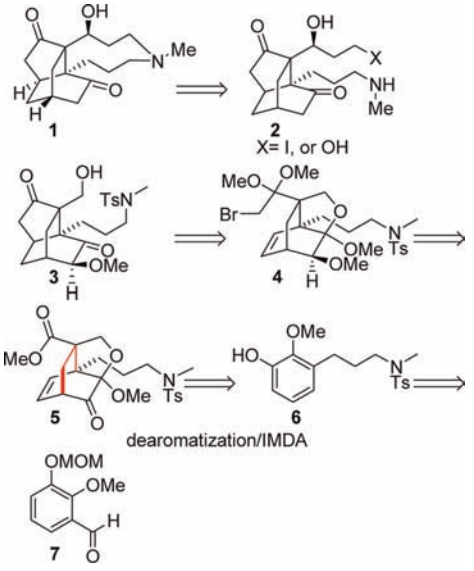
Retrosynthetically, **1** was envisioned to be obtained from **2** by an intramolecular Mitsunobu reaction or N-alkylation reaction, and ketone **2** could be established from the tricyclic core **3** through several chemical transformations. As for tricyclic core **3**, we expected that its five-membered B ring could be constructed via radical cyclization from bromo ketal **4**. Bicyclic bromo ketal **4** could be realized via functional group transformation of ester **5** which in turn could be derived from phenol **6** via a tandem oxidative dearomatization/IMDA reaction. Phenol **6** could easily be prepared from benzaldehyde **7** by a Wittig reaction and further transformations (Scheme 1).

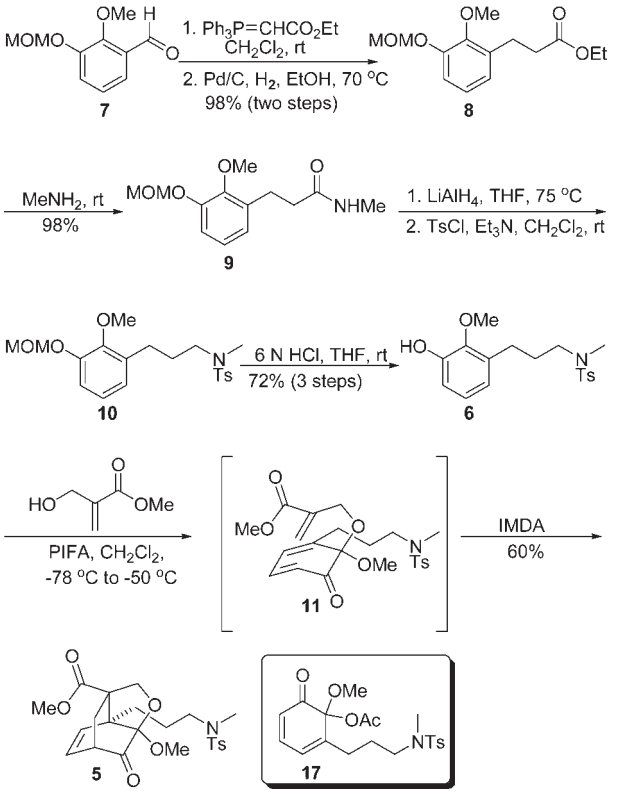
Scheme 1. Retrosynthetic Analysis



Our synthesis started from the known benzaldehyde **7**.[6] Sequential transformations including the Wittig reaction with carboethoxytriphenylphosphorane, hydrogenation, and condensation with methylamine successfully provided amide **9** in good yield (Scheme 2). Reduction of **9** with lithium aluminum hydride, then protection of the resulting amine, and subsequent removal of the MOM group with 6 N HCl afforded phenol **6** in 72% overall yield in three steps.

With compound **6** in hand, we then explored the key tandem oxidative dearomatization/IMDA reaction for construction of the bridged C/D rings. When phenol **6** and hydroxymethylacrylate were treated with $PhI(OAc)_2$ in CH_2Cl_2, only the oxidative dearomatization product acetate ketal **17** was obtained. We then changed the oxidant to $PhI(OCOCF_3)_2$ and performed the reaction at 0 °C. To our delight, the tandem oxidative dearomatization/IMDA reaction occurred smoothly to give the desired bicyclic intermediate **5** in 46% yield. The yield could be increased to 60% when this reaction was performed at −78 °C and slowly warmed to −50 °C for 2 h. Using this approach the bicyclic core and two contiguous quaternary carbon atoms have been established in a single step (Scheme 2).

Scheme 2. Synthesis of **5**



Having succeeded in the preparation of the bridged ring intermediate **5**, we then turned our attention to construction of the B ring of palhinine A (Scheme 3). Initially, the

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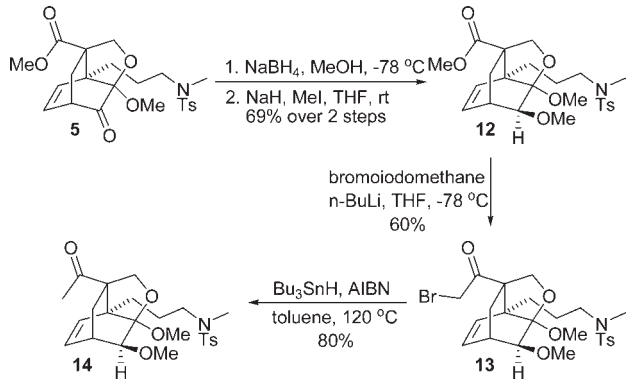
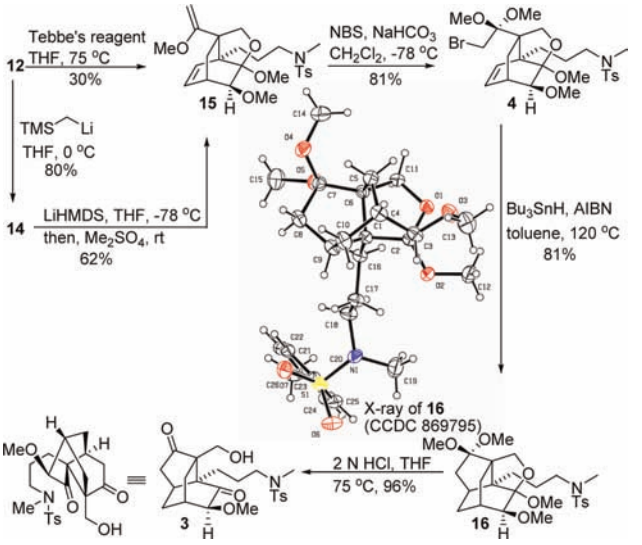
five-membered ring was proposed to be installed via an α-carbonyl radical cyclization[7] with the double bond. Reduction of ketone **5** with $NaBH_4$ followed by protection of alcohol gave exclusively *β*-OMe ester **12**. Subsquent treatment of ester **12** with bromoiodomethane and *n*-BuLi afforded bromo ketone **13**. However, when ketone **13** was treated with tributyltin hydride and AIBN in toluene at 120 °C for 3 h, the radical cyclization reaction did not occur but debromination product **14** was obtained in high yield. Maybe this was due to the carbonyl-substituted radicals being more stable than their alkyl-substituted counterparts.[8]

Scheme 3. Radical Cyclization Reaction



With this idea in mind, it was desirable to synthesize bromo ketal **4**. Treatment of ester **12** with Tebbe's reagents[9] afforded the methyl enol ether **15**. However this transformation did not occur at 0 °C or room temperature; when it was heated to reflux, the reaction mixture became complex and only 30% of product **15** was isolated. Thus, a two-step sequence was applied to prepare **15**. Treatment of **12** with $TMSCH_2Li$ and quenching with MeOH gave methyl ketone **14**[10] which was converted to methyl enol ether **15** by treatment with LDA/Me_2SO_4.[11] In this manner the overall yield increased to 49% from ester **12**. Methoxy bromination of **15** with NBS/MeOH[12] gave bromo ketal **4** which smoothly underwent an intramolecular 5-*exo*-*trig* radical cyclization to afford tetracyclic ketal **16** in 72% overall yield in two steps. This strategy for the construction of the B ring using a radical cyclization reaction may provide a new access to establish other fawcettimine-type *Lycopodium* alkaloids. Finally, removal of the ketal protecting group gave tricyclic core **3** in 96% yield. The structural validity of the tetracyclic product **16** was confirmed by X-ray single crystallographic analysis as shown in Scheme 4.

Scheme 4. Synthesis of Tricyclic Core **3**



In conclusion, a concise approach for construction of the tricyclic core of palhinine A (**1**) has been demonstrated. The developed synthetic sequence features a tandem oxidative dearomatization/IMDA reaction to stereoselectively construct the bridged ring and two contiguous all-carbon quarternary centers followed by a radical cyclization reaction to form the B ring. Application of this strategy to the synthesis of palhinine A is ongoing in our laboratory.

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

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The authors declare no competing financial interest.