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Total Synthesis of Lycopalhine A

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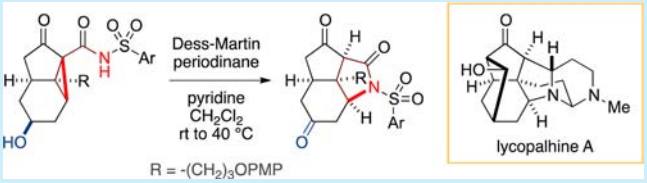
Supporting Information

ABSTRACT: The total synthesis of lycopalhine A has been accomplished. The synthesis features construction of the tricyclic system via cleavage of a cyclopropane ring and an ensuing intramolecular Michael addition, stereoselective introduction of a 2-aminoethyl moiety via a reaction of allyltrimethylsilane to a sulfonyliminium ion, and a stereoselective intramolecular aldol reaction.



Lycopalhine A (**1**, Figure 1) was isolated from *Palhinhaea cernua* by Zhao and co-workers.[1] On the basis of the core

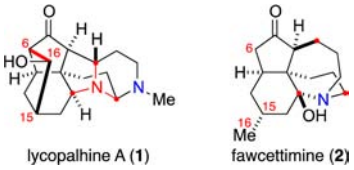
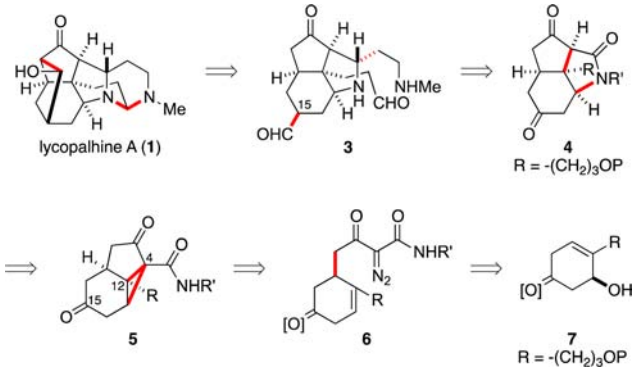


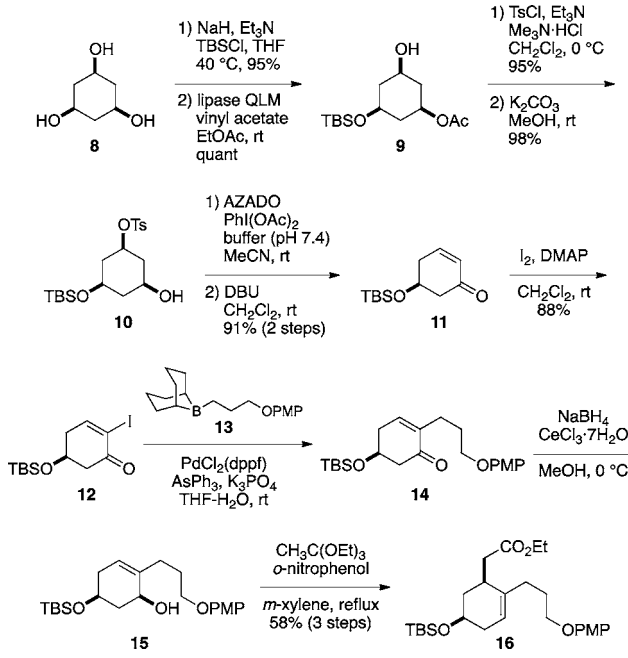
Figure 1. Structures of lycopalhine A and fawcettimine.

Scheme 1. Retrosynthesis



structure, lycopalhine A should be classified as a fawcettimine-type *Lycopodium* alkaloid,[2] although it possesses additional functional groups and ring systems. As compared with fawcettimine (**2**), the stereochemistry at C15 is inverted and C16 is connected to C6 to constitute a β-hydroxy ketone moiety and a cyclopentane ring. A pyrrolidine ring is formed with an additional nitrogen atom, which also forms an aminal moiety with the other nitrogen atom. The densely functionalized hexacyclic architecture of lycopalhine A renders it an attractive target for synthetic studies. Very recently, Trauner and Williams accomplished the first total synthesis of lycopalhine A with an elegant strategy.[3] We have been independently involved in synthetic studies toward lycopalhine A for the past two years. Herein, we disclose our total synthesis of lycopalhine A.

Scheme 2. Preparation of 16



Our retrosynthesis is depicted in Scheme 1. Cleavage of the aldol and the aminal moieties would lead to dialdehyde **3** as a precursor. The formyl group at C15 could be introduced via an S_N2 reaction, and the 2-aminoethyl unit could be stereoselectively installed via a nucleophilic attack of a carbon nucleophile from the convex face of the tricyclic system, leading to **4**. Cleavage of the pyrrolidine ring in **4** would simplify the intermediate, and the formation of the pyrrolidine ring could be achieved via cyclopropane **5**. Thus, cyclopropanation of diazo compound **6** could form the C4−C12 bond. Subsequent cleavage of the cyclopropane ring at the β-position of the ketone functionality at C15 would generate an enone moiety, from

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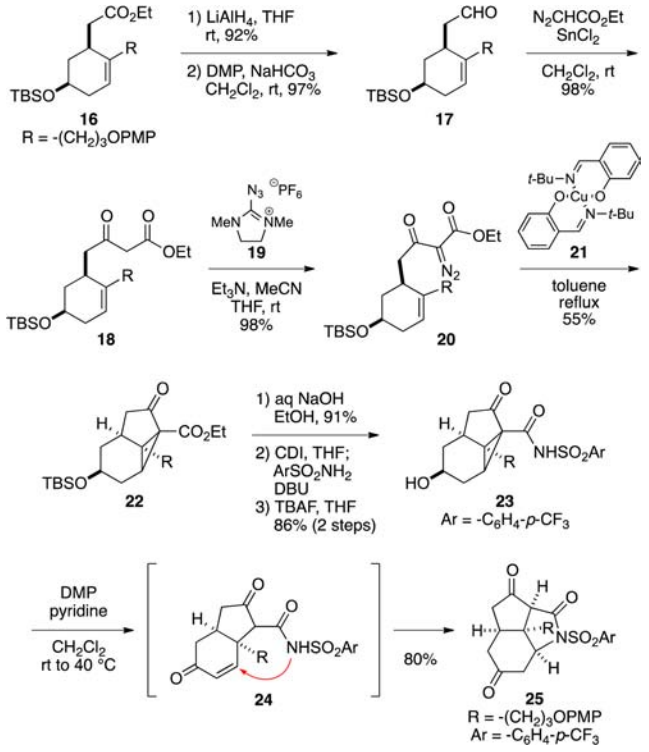
Scheme 3. Construction of the Tricyclic System



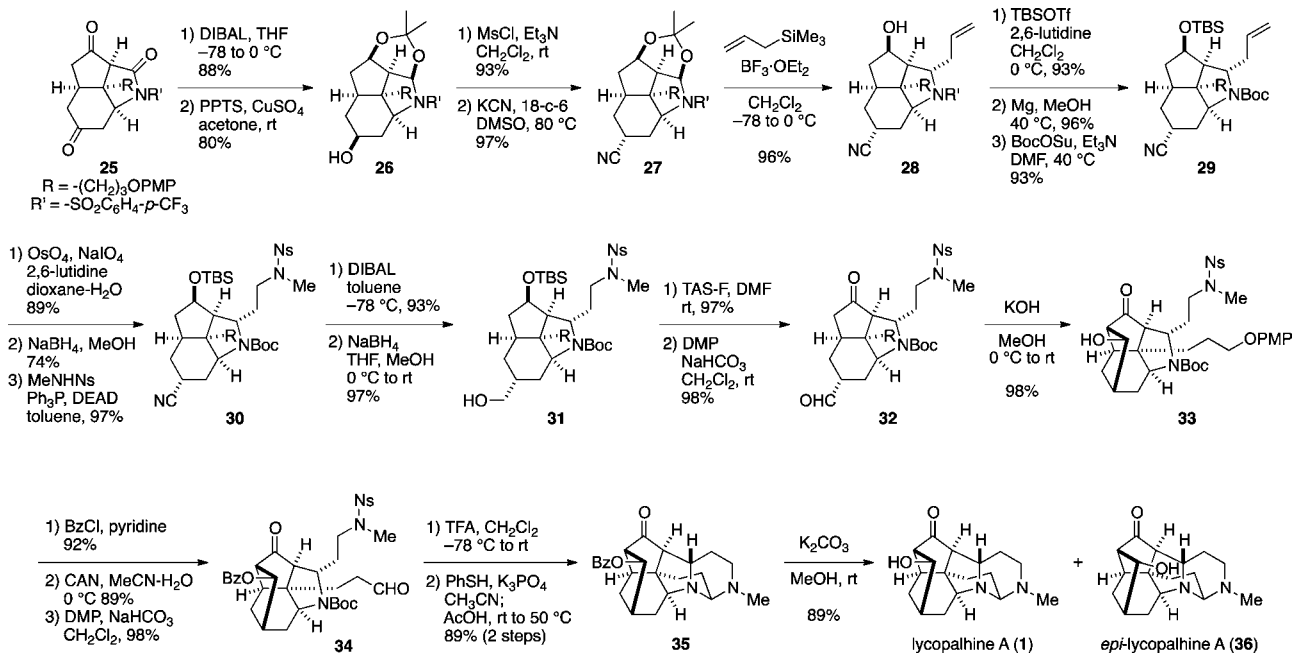
which a Michael addition would form the pyrrolidine ring.[4] The side chain on the cyclohexane ring in **6** could, in turn, be introduced by means of a Claisen–Johnson rearrangement, which required cyclohexenol **7** as a substrate.

Our synthesis commenced with the preparation of the requisite cyclohexenol for the Claisen–Johnson rearrangement (Scheme 2). According to the reported procedure,[5] monoprotection of 1,3,5-cyclohexanetriol (**8**) with a TBS group and subsequent asymmetric acetylation using lipase QLM was carried out to afford **9** in excellent yield. Tosylation of the remaining hydroxy group,[6] followed by methanolysis of the acetate moiety, gave alcohol **10**, which was converted into enone **11** in a two-step sequence involving AZADO oxidation[7] and elimination of the tosylate. After iodination at the α-position of the enone, a Suzuki–Miyaura coupling[8] was conducted to furnish **14**. Luche reduction[9] of the enone moiety proceeded with complete stereoselectivity. The resulting cyclohexenol **15** was subjected to the Claisen–Johnson rearrangement to give ester **16**.

We next focused on the construction of the tricyclic system via cyclopropanation (Scheme 3). After a two-step conversion of ester **16** into aldehyde **17**, elongation of the side chain was conducted by means of a Roskamp reaction.[10] A diazo-transfer reaction to the resulting β-ketoester **18** with ADMP (**19**) afforded diazoester **20**,[11] which was heated in refluxing toluene in the presence of **21**,[12] giving **22** in 55% yield. Transformation of the ester moiety in **22** into a sulfonylimide, followed by cleavage of the TBS group with TBAF, furnished alcohol **23**. Upon oxidation of **23** with Dess–Martin periodinane (DMP),[13] the resulting ketone underwent a facile cleavage of the cyclopropane ring, and an ensuing intramolecular Michael addition of the imide moiety occurred spontaneously to give tricycle **25** in 80% yield.

With the requisite tricyclic system in hand, we next turned our attention to the introduction of a 2-aminoethyl moiety (Scheme 4). Reduction of **25** with DIBAL afforded a triol (a 3:1 diastereomeric mixture in regard to the hemiaminal moiety), two of which were tied up as an acetonide to afford **26**. A cyano group was then introduced via activation of the remaining hydroxy group as a mesylate and the subsequent S_N2 reaction with a cyanide ion provided nitrile **27** in 90% yield. Treatment of **27** with $BF_3{\cdot}OEt_2$ activated the hemiaminal moiety, generating a sulfonyliminium ion onto which allyltrimethylsilane attacked from the convex face to give **28** in 96% yield as a sole isomer. After protection of the liberated secondary alcohol with a TBS group, the sulfonyl group on the nitrogen atom was switched to a Boc group. After oxidative cleavage of the terminal olefin in **29** and reduction of the resulting aldehyde, a methylamine unit was

Scheme 4. Construction of the Core Structure and Completion of the Synthesis



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installed by means of a Mitsunobu reaction with *N*-methylnosylamide to afford **30**.[14,15]

Having succeeded in the stereoselective installation of the 2-aminoethyl moiety, we next constructed the hexacyclic system of lycopalhine A through an intramolecular aldol reaction and the formation of the aminal moiety. After a two-step reduction of the cyano group in **30** to afford alcohol **31**, the TBS ether was cleaved, and the resulting diol was oxidized with DMP to furnish ketoaldehyde **32**. The crucial intramolecular aldol reaction was effected by treatment with potassium hydroxide in methanol to provide hydroxy ketone **33** in 98% yield as the sole isomer.[16] After protection of the secondary alcohol as its benzoate, the PMP ether on the side chain was oxidatively cleaved, and the resulting alcohol was oxidized with DMP to give aldehyde **34**. Successive cleavage of the Boc and the Ns groups liberated the diamine moiety. Acidification with acetic acid promoted the formation of the aminal moiety, giving hexacyclic compound **35**. Finally, methanolysis of the benzoate moiety afforded lycopalhine A (**1**) with partial epimerization of the β-hydroxy ketone moiety.[3] The synthetic sample, which contained a small amount of its epimer (**36**), was identical to the natural product by comparison with the reported spectroscopic data (^{1}H and ^{13}C NMR, IR, MS).[1]

In conclusion, we have achieved a total synthesis of lycopalhine A (**1**). Our synthesis features the construction of the tricyclic system via cleavage of a cyclopropane ring and an ensuing intramolecular Michael addition, stereoselective introduction of a 2-aminoethyl moiety via a reaction of allyltrimethylsilane to a sulfonyliminium ion, and a stereoselective intramolecular aldol reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00338.

Experimental procedures, spectroscopic data, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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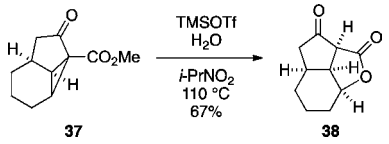

37 **38**

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(16) Treatment of ketoaldehyde **32** with DBU in THF afforded an epimeric aldol that could be converted into the desired hydroxy ketone **33** by treatment with KOH in methanol.

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