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Total syntheses of macleanine and lycoposerramine-S†

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Total syntheses of fawcettimine-class *Lycopodium* alkaloids having an imino bridge between C5 and C13 were accomplished. Fawcettimine was first prepared in 10 steps from a known compound, and the characteristic structures, including the imino bridge, were constructed *via* the formation of a bridgehead imine.

Hundreds of alkaloids have been isolated from *Lycopodium* species.[1] These alkaloids can be classified into several groups on the basis of their core structure. Among these groups, the fawcettimine-class is a major group of *Lycopodium* alkaloids (Fig. 1).[2] Fawcettimine has a *cis*-hydrindane core to which a nine-membered ring containing a nitrogen atom is fused. The nitrogen atom on the nine-membered ring forms a hemiaminal with a carbonyl function on the *cis*-hydrindane core, resulting in the formation of two heterocycles, a piperidine and an azepane. As minor constituents of the fawcettimine class, three alkaloids that have an imino bridge between C5 and C13 have been isolated.[3] Although various total syntheses toward fawcettimine have been reported,[4] synthetic efforts toward these alkaloids with the imino bridge are limited. Only two synthetic studies toward lycoposerramines-A and S [5] and one total synthesis of lycoposerramine-S have been reported.[6] However, no synthetic study on macleanine has thus far been reported. Herein we disclose our effort to synthesize fawcettimine-class alkaloids with an imino bridge between C5 and C13, resulting in the total syntheses of macleanine and lycoposerramine-S.

We first planned the synthesis of macleanine, which has an aminal moiety in the structure. Aminals can be prepared *via* dehydrative condensation of a ketone or an aldehyde with two amines. This process involves the formation of an imine as an intermediate. In the synthesis of macleanine, the imine must be formed at a bridgehead position (Scheme 1a).[7] Additional strain caused by the bicyclo[2.2.1] system appeared to introduce difficulties.[8] To avoid the formation of strained bridgehead imines, we planned the synthetic route as shown in Scheme 1b. Thus, the sequential formation of C–N bonds *via* an intramolecular addition of a secondary amine moiety to an imine (**I**), followed by an intramolecular S_N2 reaction (**II**), could construct the structure of macleanine without forming a bridgehead imine. The requisite substrate would be prepared from fawcettimine.

We synthesized fawcettimine on the basis of our synthesis of huperzine Q,[9] starting from the known enone **1** (Scheme 2).[4p] A Diels–Alder reaction of **1** with siloxydiene **2** produced the bicyclic compound **3**, which was converted into enone **5** *via* a three-step sequence involving the introduction of a phenylthio group, oxidation into a sulfoxide, and sulfoxide elimination under thermal conditions.[10] After the sequential cleavage of the *tert*-butyloxycarbonyl (Boc) and *tert*-butyldiphenylsilyl (TBDPS) groups, a Mitsunobu reaction of the resultant hydroxy nosylamide formed a nine-membered ring,[11] affording the tricyclic compound **7**. Nucleophilic epoxidation with hydrogen peroxide under basic conditions afforded epoxyketone **8**, which was subjected to ring contraction mediated by trimethylsilyl triflate (TMSOTf) as a Lewis acid to afford keto

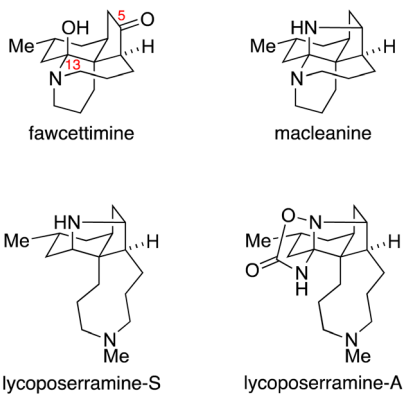

Fig. 1 Structures of selected fawcettimine-class *Lycopodium* alkaloids.

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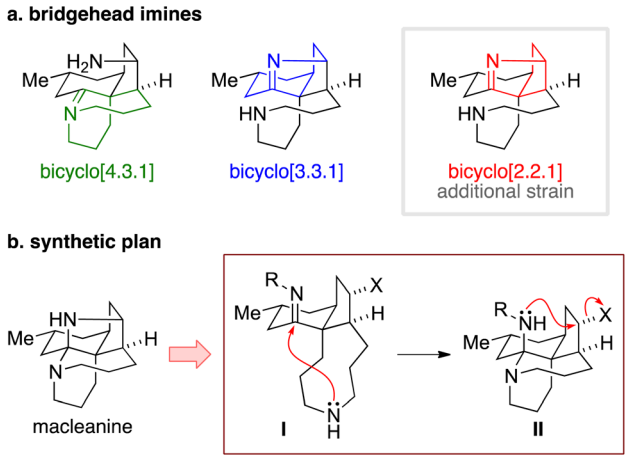
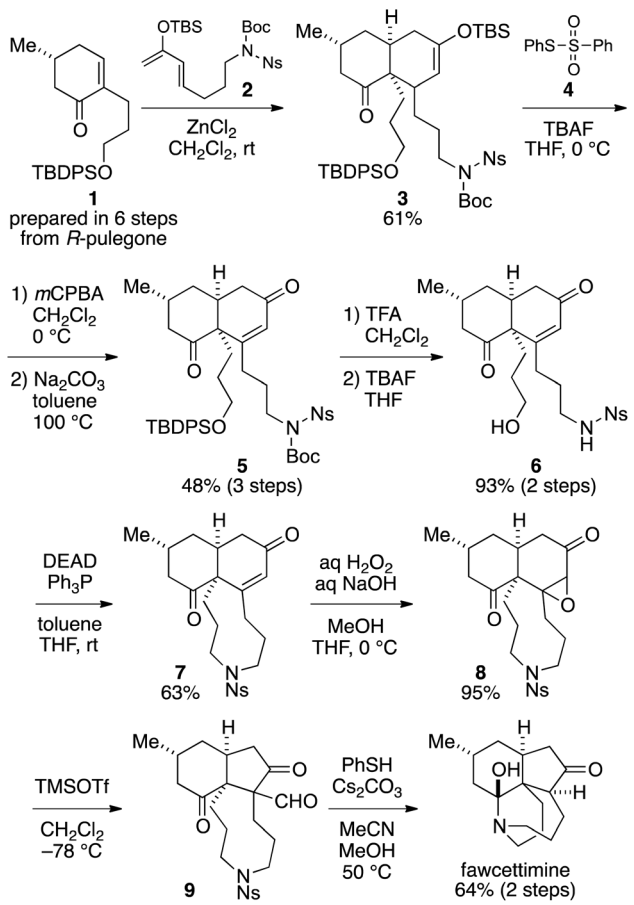


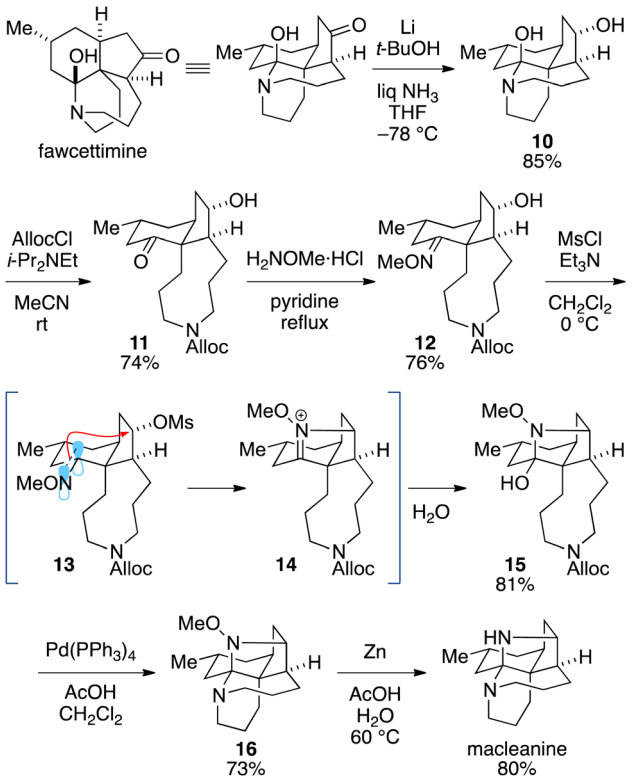
Scheme 1 Synthetic plan toward macleanine.



Scheme 2 Preparation of fawcettimine.

aldehyde **9**.[12,13] The nosyl and formyl groups were cleaved simultaneously by treatment with benzenethiol under basic conditions to yield fawcettimine.

With a sufficient amount of fawcettimine in hand, we next attempted our planned synthesis of macleanine (Scheme 3).[14] The Birch reduction of fawcettimine stereoselectively produced

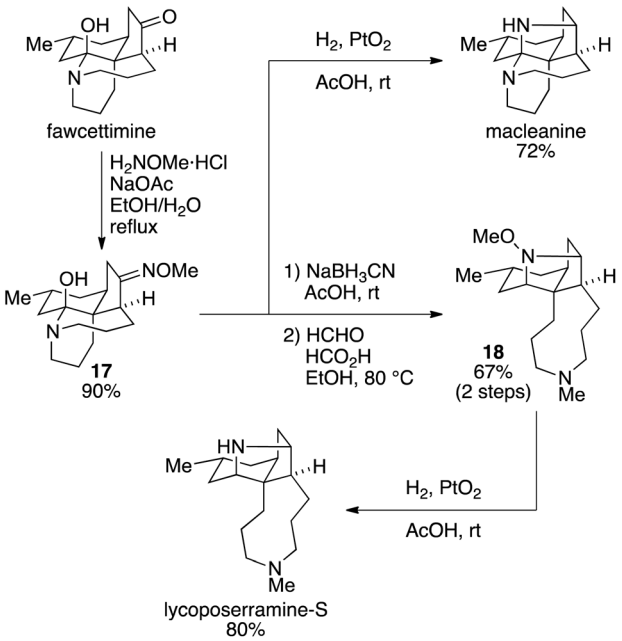


Scheme 3 Transformation of fawcettimine into macleanine.

alcohol **10**,[9] and then the hemiaminal moiety was cleaved by a reaction with allyl chloroformate (AllocCl). The resultant ketone **11** was transformed into its oxime ether. Attempted mesylation of the secondary alcohol moiety in **12**, to our surprise, produced methoxylamine **15**. In this transformation, the mesylate formed *in situ* might be attacked by the oxime ether moiety to form the *N*-methoxyiminium ion **14**, which was then trapped by water. Removal of the Alloc group with a palladium catalyst in dichloromethane and acetic acid afforded the pentacyclic aminal **16**. Reductive cleavage of the N–O bond with zinc in aqueous acetic acid produced macleanine.

These results show that the aminal formation *via* an iminium ion proceeded more smoothly than expected,[15] and led to more concise syntheses of the related alkaloids (Scheme 4). Thus, the conversion of fawcettimine into the corresponding oxime ether **17**,[16] followed by hydrogenation with platinum oxide (Adams catalyst) in acetic acid at room temperature, furnished macleanine in good yield.[17] In addition, the reduction of oxime ether **17** with sodium cyanoborohydride in acetic acid, followed by reductive methylation, afforded tetracyclic amine **18**, which could be converted into lycoposerramine-S *via* cleavage of the N–O bond.

In our synthesis, the additional bridge in the 2-azabicyclo [3.3.1] system might facilitate the formation of a bridgehead imine. Maier and Schleyer evaluated the stability of bridgehead double bonds using the olefinic strain energy (OS),[18] which is related to the heat of hydrogenation of the olefins by a constant difference. According to their report, the OS of bicyclo



Scheme 4 Synthesis of fawcettimine-class alkaloids with an imino bridge.

[3.3.1]non-1-ene (**19a**) is 15.2 kcal mol^{-1}, whereas that of olefin **19b**, which has an additional ethylene bridge in the bicyclic system, is 12.5 kcal mol^{-1} (Table 1). These results indicate that the additional bridge lowers the strain. Unfortunately, the OS of olefin **19c** has not been reported. However, density functional theory (DFT) calculations have shown that olefins **19b** and **19c** have approximately the same heats of hydrogenation: −38.6 kcal mol^{-1} and −38.4 kcal mol^{-1}, respectively; thus, olefin **19c** is also less strained than bicyclo[3.3.1]non-1-ene (**19a**). The heats of hydrogenation of the imines were also calculated, and comparing them revealed the same tendency; an additional bridge lowered the heat of hydrogenation, indicating that imine **20c** is less strained than imine **20a**.[19]

In conclusion, we achieved total syntheses of the fawcettimine-class alkaloids macleanine and lycoposerramine-S *via* the formation of a bridgehead imine. We also showed that an additional bridge in the 2-azabicyclo[3.3.1] system could facilitate the formation of a bridgehead imine.

Table 1 Olefinic strain energies (OS) of bridgehead olefins and imines[a]

	19a	19b	19c	20a	20c
OS[b]	15.2	12.5	NA[d]	—	—
$\lvert\Delta OS\rvert$	0	2.7	NA[d]	—	—
ΔH°_H[c]	−41.6	−38.6	−38.4	−30.7	−26.3
$\Delta\Delta H^\circ_H$	0	3.0[e]	3.2[e]	0	4.4[f]

[a] All energies are in kcal mol^{-1}. [b] Ref. 18*a*. The energies are calculated using Allinger's MM1 force field program. [c] B3PW91/6-311+G(d,p). [d] Not available. [e] Energy relative to the calculated heat of hydrogenation of olefin **19a**. [f] Energy relative to the calculated heat of hydrogenation of imine **20a**.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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