

Cite this: *Org. Biomol. Chem.*, 2023, **21**, 6289Received 4th July 2023,  
Accepted 20th July 2023

DOI: 10.1039/d3ob01065a

rsc.li/obc

## Total syntheses of macleanine and lycoposerramine-S†

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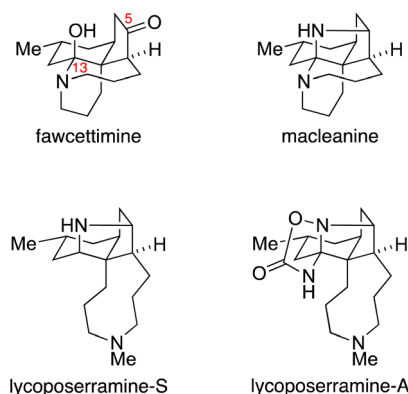
**Total syntheses of fawcettimine-class *Lycopodium* alkaloids having an imino bridge between C5 and C13 were accomplished. Fawcettimine was first prepared in 10 steps from a known compound, and the characteristic structures, including the imino bridge, were constructed via the formation of a bridgehead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

Hundreds of alkaloids have been isolated from *Lycopodium* species.<sup>1</sup> 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).<sup>2</sup> 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.<sup>3</sup> Although various total syntheses toward fawcettimine have been reported,<sup>4</sup> synthetic efforts toward these alkaloids with the imino bridge are limited. Only two synthetic studies toward lycoposerramines-A and S<sup>5</sup> and one total synthesis of lycoposerramine-S have been reported.<sup>6</sup> 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 amination 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).<sup>7</sup> Additional

strain caused by the bicyclo[2.2.1] system appeared to introduce difficulties.<sup>8</sup> 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<sub>N</sub>2 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,<sup>9</sup> starting from the known enone **1** (Scheme 2).<sup>4p</sup> 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.<sup>10</sup> 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,<sup>11</sup> 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.

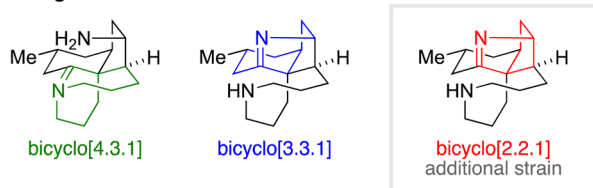
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† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d3ob01065a>

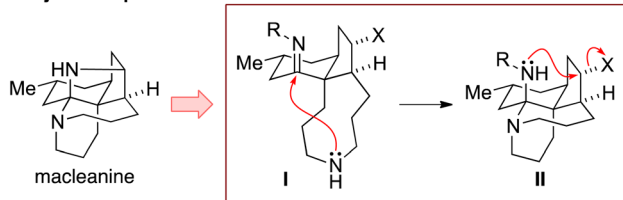
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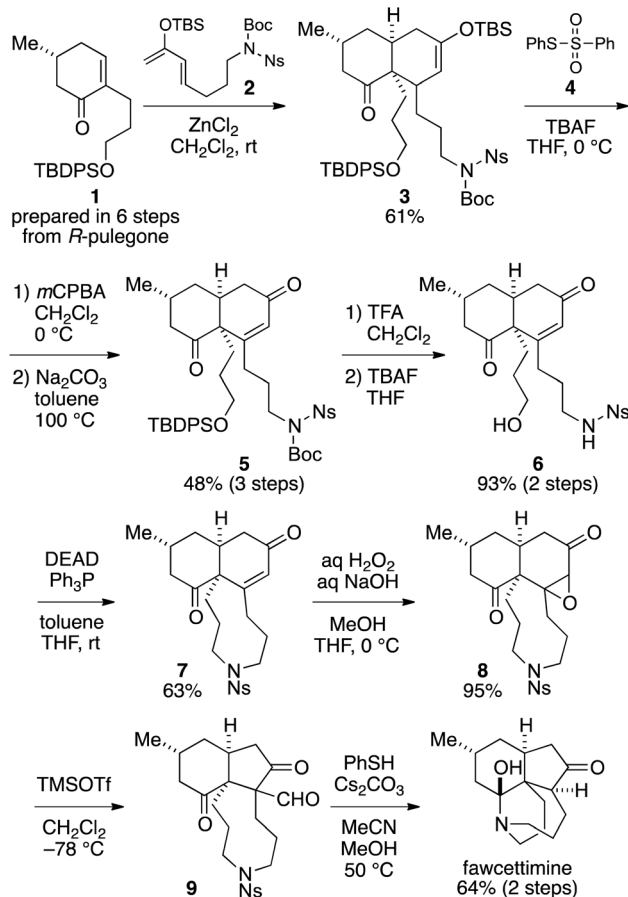
## a. bridgehead imines



## b. synthetic plan



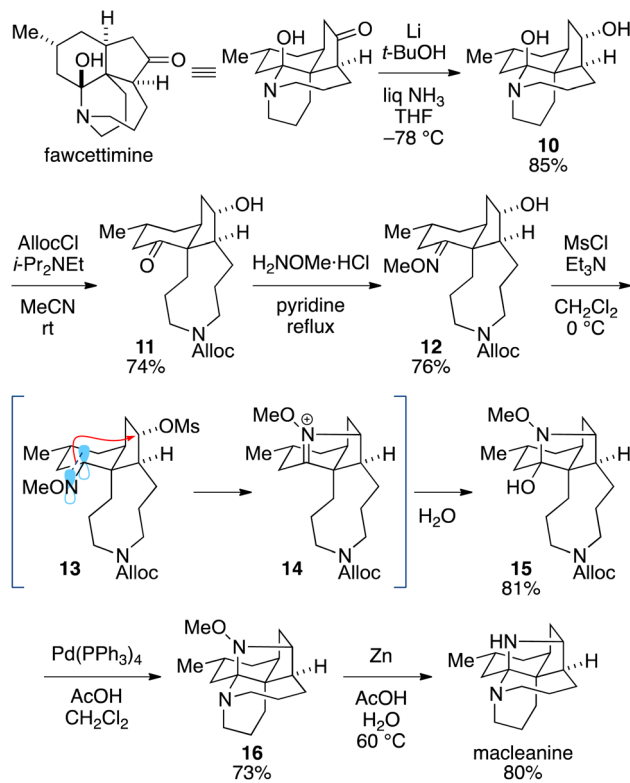
Scheme 1 Synthetic plan toward macleanine.



Scheme 2 Preparation of fawcettimine.

aldehyde **9**.<sup>12,13</sup> 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).<sup>14</sup> The Birch reduction of fawcettimine stereoselectively produced



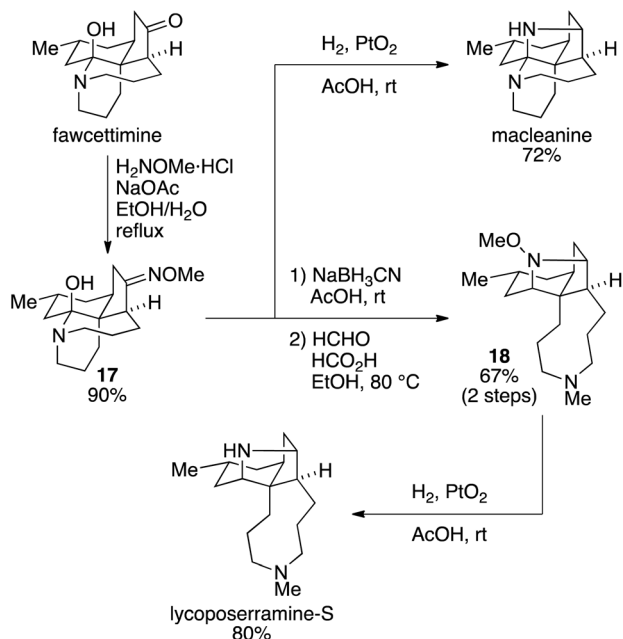
Scheme 3 Transformation of fawcettimine into macleanine.

alcohol **10**,<sup>9</sup> 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,<sup>15</sup> and led to more concise syntheses of the related alkaloids (Scheme 4). Thus, the conversion of fawcettimine into the corresponding oxime ether **17**,<sup>16</sup> followed by hydrogenation with platinum oxide (Adams catalyst) in acetic acid at room temperature, furnished macleanine in good yield.<sup>17</sup> 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),<sup>18</sup> 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  $15.2 \text{ kcal mol}^{-1}$ , whereas that of olefin **19b**, which has an additional ethylene bridge in the bicyclic system, is  $12.5 \text{ kcal mol}^{-1}$  (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:  $-38.6 \text{ kcal mol}^{-1}$  and  $-38.4 \text{ kcal mol}^{-1}$ , 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**.<sup>19</sup>

In conclusion, we achieved total syntheses of the fawcettimine-class alkaloids macleanine and lycoposerramine-S *via*

**Table 1** Olefinic strain energies (OS) of bridgehead olefins and imines<sup>a</sup>

	bridgehead olefins			bridgehead imines	
	<b>19a</b>	<b>19b</b>	<b>19c</b>	<b>20a</b>	<b>20c</b>
OS <sup>b</sup>	15.2	12.5	NA <sup>d</sup>	—	—
\Delta OS	0	2.7	NA <sup>d</sup>	—	—
\Delta H <sub>H</sub> <sup>c</sup>	-41.6	-38.6	-38.4	-30.7	-26.3
\Delta\Delta H <sub>H</sub>	0	3.0 <sup>e</sup>	3.2 <sup>e</sup>	0	4.4 <sup>f</sup>

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

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 the bridgehead imine.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

This work was financially supported by JSPS KAKENHI (Grant Number JP23H02602) and by the Research Support Project for Life Science and Drug Discovery [Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS)] from the Japan Agency for Medical Research and Development (AMED) under Grant Number JP23ama121044.

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