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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 S⁵ 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 aminated 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

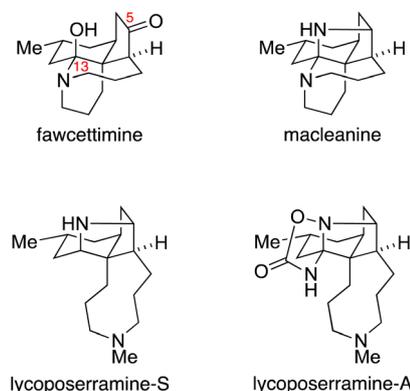


Fig. 1 Structures of selected fawcettimine-class *Lycopodium* alkaloids.

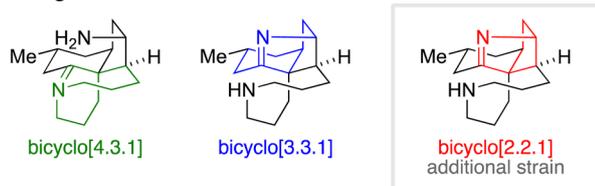
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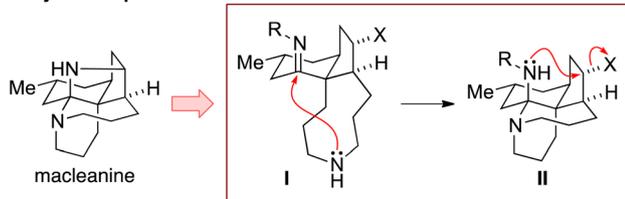
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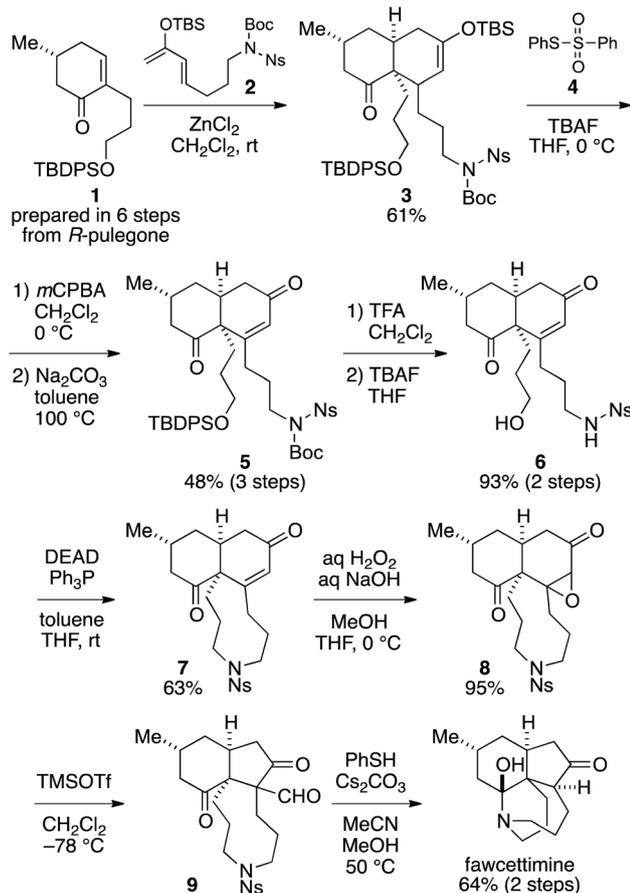
a. bridgehead imines



b. synthetic plan



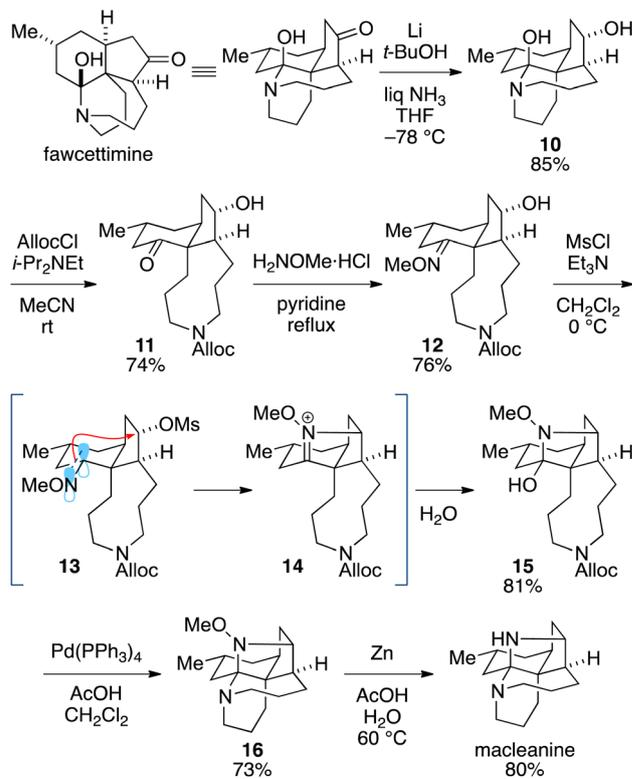
Scheme 1 Synthetic plan toward macleanine.



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



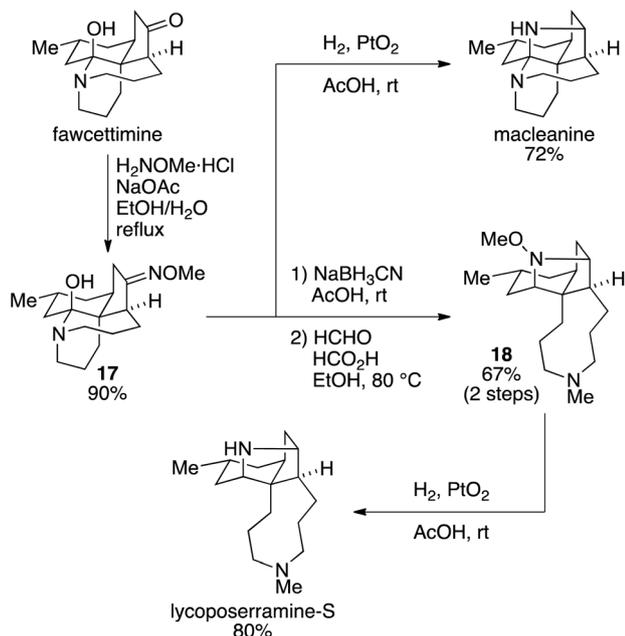
Scheme 3 Transformation of fawcettimine into macleanine.

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*

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

	bridgehead olefins			bridgehead imines	
	19a	19b	19c	20a	20c
OS ^b	15.2	12.5	NA ^d	—	—
ΔOS	0	2.7	NA ^d	—	—
ΔH _H ^c	-41.6	-38.6	-38.4	-30.7	-26.3
ΔΔH _H	0	3.0 ^e	3.2 ^e	0	4.4 ^f

^a All energies are in kcal mol⁻¹. ^b Ref. 18a. 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**.

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.

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References

- (a) S. P. Patil, *Future J. Pharm. Sci.*, 2020, **6**, 99; (b) P. Siengalewicz, J. Mulzer and U. Rinner, in *The Alkaloids: Chemistry and Biology*, ed. H.-J. Knölker, Academic Press, 2013, vol. 72, pp. 1–151; (c) J. i. Kobayashi and H. Morita, in *The Alkaloids: Chemistry and Biology*, ed. G. A. Cordell, Academic Press, 2005, vol. 61, pp. 1–57; (d) X. Ma and D. R. Gang, *Nat. Prod. Rep.*, 2004, **21**, 752; (e) W. A. Ayer and L. S. Trifonov, in *The Alkaloids*; ed. G. A. Cordell, Academic Press, 1994, vol. 45, pp. 233–266; (f) D. B. MacLean, in *The Alkaloids*; ed. A. Brossi, Academic Press, 1986, vol. 26, pp. 241–298; (g) D. B. MacLean, in *The Alkaloids*; ed. R. H. F. Manske, Academic Press, 1973, vol. 14, pp. 348–405; (h) D. B. MacLean, in *The Alkaloids*; ed. R. H. F. Manske, Academic Press, 1968, vol. 10, pp. 305–382.
- (a) H. Li and X. Lei, *Chem. Rec.*, 2018, **18**, 543; (b) R. A. Murphy and R. Sarpong, *Chem. – Eur. J.*, 2014, **20**, 42; (c) X. Wang, H. Li and X. Lei, *Synlett*, 2013, 1032; (d) A. Nakayama, M. Kitajima and H. Takayama, *Synlett*, 2012, 2014.
- (a) W. A. Ayer, Y.-T. Ma, J.-S. Liu, M.-F. Huang, L. W. Schultz and J. Clardy, *Can. J. Chem.*, 1994, **72**, 128; (b) H. Takayama, K. Katakawa, M. Kitajima, H. Seki, K. Yamaguchi and N. Aimi, *Org. Lett.*, 2001, **3**, 4165; (c) H. Takayama, K. Katakawa, M. Kitajima, K. Yamaguchi and N. Aimi, *Tetrahedron Lett.*, 2002, **43**, 8307.
- (a) T. Harayama, M. Takatani and Y. Inubushi, *Tetrahedron Lett.*, 1979, **20**, 4307; (b) T. Harayama, M. Takatani and Y. Inubushi, *Chem. Pharm. Bull.*, 1980, **28**, 2394; (c) X. Linghu, J. J. Kennedy-Smith and F. D. Toste, *Angew. Chem., Int. Ed.*, 2007, **46**, 7671; (d) K.-M. Liu, C.-M. Chau and C.-K. Sha, *Chem. Commun.*, 2008, 91; (e) J. A. Kozak and G. R. Dake, *Angew. Chem., Int. Ed.*, 2008, **47**, 4221; (f) Y. Otsuka, F. Inagaki and C. Mukai, *J. Org. Chem.*, 2010, **75**, 3420; (g) M. E. Jung and J. J. Chang, *Org. Lett.*, 2010, **12**,



- 2962; (h) J. Ramharter, H. Weinstabl and J. Mulzer, *J. Am. Chem. Soc.*, 2010, **132**, 14338; (i) Y.-R. Yang, L. Shen, J.-Z. Huang, T. Xu and K. Wei, *J. Org. Chem.*, 2011, **76**, 3684; (j) H. Li, X. Wang and X. Lei, *Angew. Chem., Int. Ed.*, 2012, **51**, 491; (k) G. Pan and R. M. Williams, *J. Org. Chem.*, 2012, **77**, 4801; (l) N. Itoh, T. Iwata, H. Sugihara, F. Inagaki and C. Mukai, *Chem. – Eur. J.*, 2013, **19**, 8665; (m) S.-H. Hou, Y.-Q. Tu, L. Liu, F.-M. Zhang, S.-H. Wang and X.-M. Zhang, *Angew. Chem., Int. Ed.*, 2013, **52**, 11373; (n) K. Xu, B. Cheng, Y. Li, T. Xu, C. Yu, J. Zhang, Z. Ma and H. Zhai, *Org. Lett.*, 2014, **16**, 196; (o) C. Zeng, J. Zhao and G. Zhao, *Tetrahedron*, 2015, **71**, 64; (p) X. Zeng, Z. Jia and F. G. Qiu, *Tetrahedron Lett.*, 2020, **61**, 152329.
- 5 (a) M. C. Elliott, N. N. E. El Sayed and J. S. Paine, *Org. Biomol. Chem.*, 2008, **6**, 2611; (b) M. C. Elliott and J. S. Paine, *Org. Biomol. Chem.*, 2009, **7**, 3455.
- 6 N. Shimada, Y. Abe, S. Yokoshima and T. Fukuyama, *Angew. Chem., Int. Ed.*, 2012, **51**, 11824.
- 7 (a) P. M. Warner, *Chem. Rev.*, 1989, **89**, 1067; (b) J. Y. W. Mak, R. H. Pouwer and C. M. Williams, *Angew. Chem., Int. Ed.*, 2014, **53**, 13664; (c) J. Liu, X. Liu, J. Wu and C.-C. Li, *Chem*, 2020, **6**, 579.
- 8 D. W. Rogers, L. S. Choi, R. S. Giirellini, T. J. Holmes and N. L. Allinger, *J. Phys. Chem.*, 1980, **84**, 1810.
- 9 S. Tanimura, S. Yokoshima and T. Fukuyama, *Org. Lett.*, 2017, **19**, 3684.
- 10 In the synthesis of huperzine Q, the corresponding transformation occurred through the oxidation of a silyl enolate with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ).
- 11 (a) T. Fukuyama, C.-K. Jow and M. Cheung, *Tetrahedron Lett.*, 1995, **36**, 6373; (b) T. Kan, H. Kobayashi and T. Fukuyama, *Synlett*, 2002, 0697; (c) T. Kan and T. Fukuyama, *Chem. Commun.*, 2004, 353.
- 12 Compounds **8** and **9** were obtained as single diastereomers.
- 13 H. O. House and R. L. Wasson, *J. Am. Chem. Soc.*, 1957, **79**, 1488.
- 14 Results provided in Scheme 3 were investigated using racemic fawcettimine.
- 15 (a) E. C. Taylor, J. E. Dowling and B. Bhatia, *J. Org. Chem.*, 1999, **64**, 441; (b) N. Yamazaki, T. Kusanagi and C. Kibayashi, *Tetrahedron Lett.*, 2004, **45**, 6509; (c) Y. Yoshimura, J. Inoue, N. Yamazaki, S. Aoyagi and C. Kibayashi, *Tetrahedron Lett.*, 2006, **47**, 3489; (d) M. Amat, M. Pérez, A. T. Minaglia and J. Bosch, *J. Org. Chem.*, 2008, **73**, 6920; (e) Y. Li, C. Feng, H. Shi and X. Xu, *Org. Lett.*, 2016, **18**, 324; (f) X. Xie, B. Wei, G. Li and L. Zu, *Org. Lett.*, 2017, **19**, 5430.
- 16 K. Katakawa, M. Kitajima, N. Aimi, H. Seki, K. Yamaguchi, K. Furihata, T. Harayama and H. Takayama, *J. Org. Chem.*, 2005, **70**, 658.
- 17 The NMR data of TFA or HCl salt of synthetic macleanine matched the reported data.
- 18 (a) W. F. Maier and P. V. R. Schleyer, *J. Am. Chem. Soc.*, 1981, **103**, 1891; (b) M. Szostak and J. Aubé, *Chem. Rev.*, 2013, **113**, 5701.
- 19 The heat of hydrogenation of 1-azabicyclo[4.3.1]dec-10-ene (Scheme 1) was calculated as $-37.1 \text{ kcal mol}^{-1}$. This means that it is more strained than imine **20a**.

