Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue

Check for updates

Cite this: *Org. Biomol. Chem.*, 2023, **21**, 6289

Received 4th July 2023,
Accepted 20th July 2023

DOI: 10.1039/d3ob01065a

rsc.li/obc

Total syntheses of macleanine and lycoposerramine-S†

Masahiro Okuyama,‡ Nariyoshi Umekubo,‡ Kenta Akimoto, Takahisa Shimizu, Kazuhiro Kubokoya, Nagayasu Nakajima, Yoshitake Nishiyama and Satoshi Yokoshima *

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

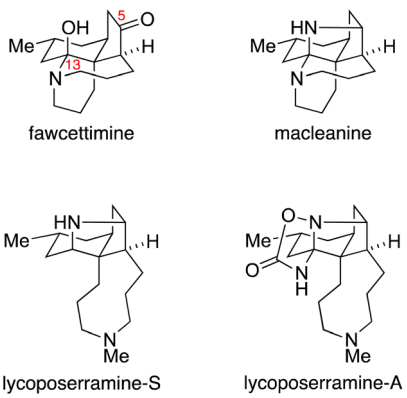
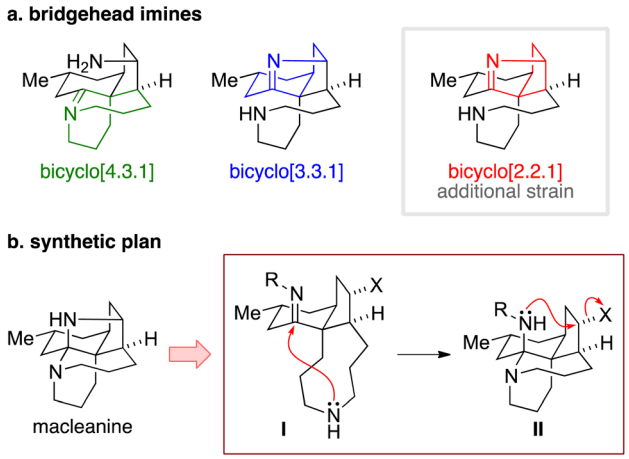


Fig. 1 Structures of selected fawcettimine-class *Lycopodium* alkaloids.

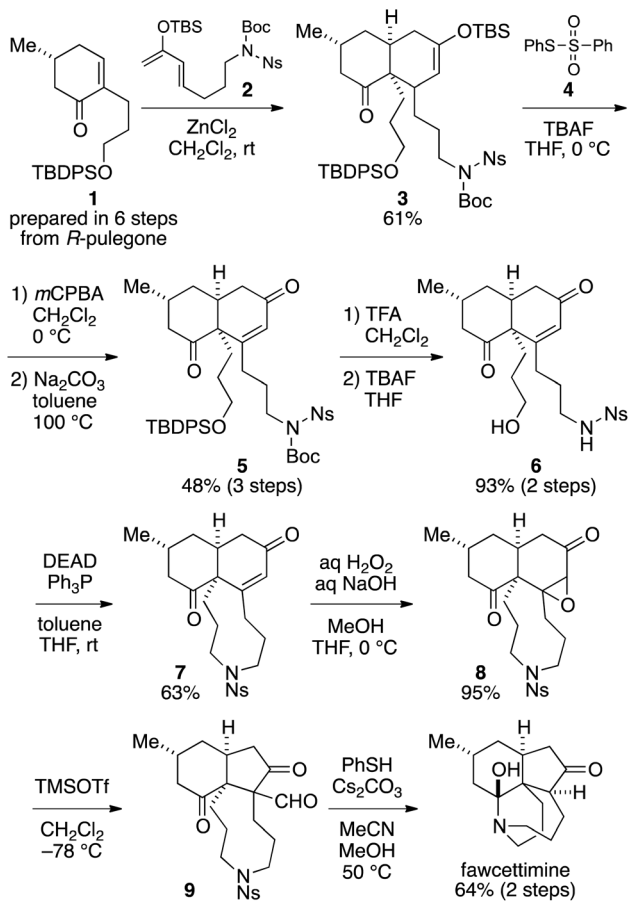
Graduate School of Pharmaceutical Sciences, Nagoya University, Nagoya 464-8601, Japan. E-mail: yokosima@ps.nagoya-u.ac.jp

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

‡These authors contributed equally.



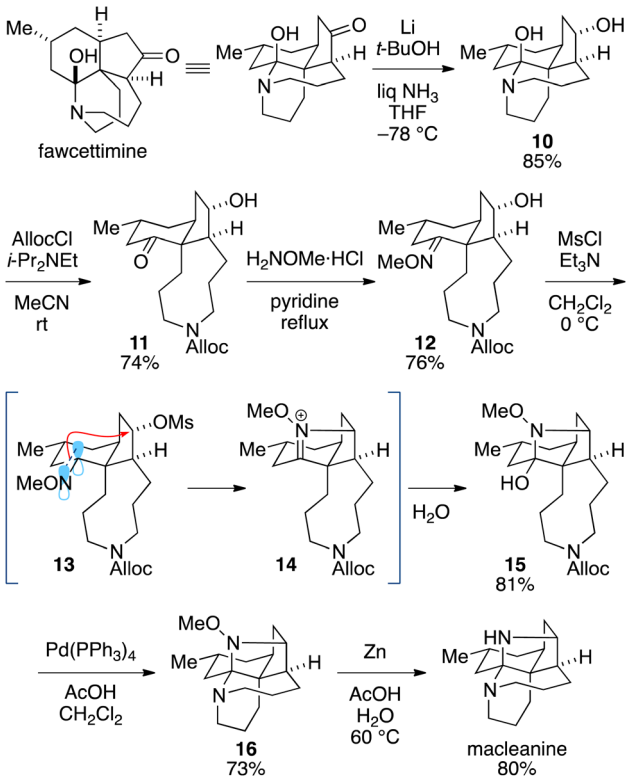
Scheme 1 Synthetic plan toward macleanine.



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

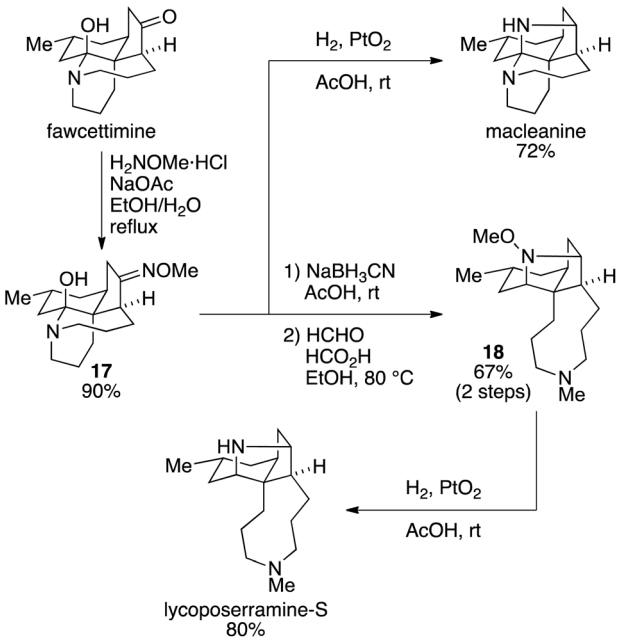


Scheme 3 Transformation of fawcettimine into macleanine.

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

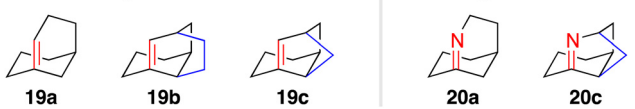


Scheme 4 Synthesis of fawcettimine-class alkaloids with an imino bridge.

[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

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.

References

1 (*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.

2 (*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.

3 (*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.

4 (*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. Girellini, 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 kcal mol^{-1}. This means that it is more strained than imine **20a**.

