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First Asymmetric Total Syntheses of Fawcettimine-Type *Lycopodium* Alkaloids, Lycoposerramine-C and Phlegmariurine-A

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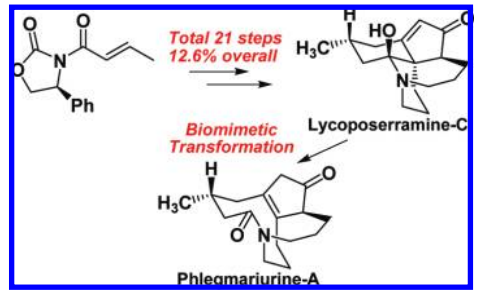
ABSTRACT



A successful asymmetric total synthesis of lycoposerramine-C involving such key steps as a cobalt-mediated Pauson−Khand reaction and vinyl Claisen rearrangement and its biomimetic transformation to phlegmariurine-A are described.

Lycopodium alkaloids have unique skeletal characteristics and a variety of biological activities, such as acetylcholine esterase (AChE) inhibition.[1] These have inspired many groups including ours[2] to develop the total syntheses of *Lycopodium* alkaloids.[3] Lycoposerramine-C (**1**)[4] isolated from *Lycopodium serratum* by us is a new fawcettimine-type *Lycopodium* alkaloid possessing a double bond at the C-6−C-7 positions of fawcettimine (**2**) (Figure 1). Although preliminary biological screening indicated that it possesses potent AChE inhibitory activity, further examination of the activity has been restricted by its limited availability in nature. To develop an efficient synthetic route to **1**, directly

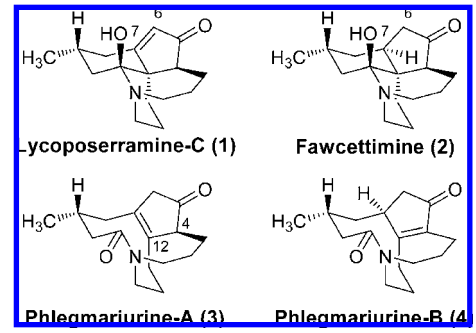


Figure 1. Structures of fawcettimine-type (**1**, **2**) and phlegmariurine-type alkaloids (**3**, **4**).

(1) For recent reviews, see: (a) Hirasawa, Y.; Kobayashi, J.; Morita, H. *Heterocycles* **2009**, *77*, 679. (b) Kobayashi, J.; Morita, H. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 2005; Vol. 61, p 1. (c) Ayer, W. A.; Trifonov, L. S. In *The Alkaloids*; Cordell, G. A., Brossi, A., Eds.; Academic Press: New York, 1994; Vol. 45, p 233. (d) Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752.

(2) (a) Nishikawa, Y.; Kitajima, M.; Kogure, N.; Takayama, H. *Tetrahedron* **2009**, *65*, 1608. (b) Nishikawa, Y.; Kitajima, M.; Takayama, H. *Org. Lett.* **2008**, *10*, 1987. (c) Shigeyama, T.; Katakawa, K.; Kogure, N.; Kitajima, M.; Takayama, H. *Org. Lett.* **2007**, *9*, 4069. (d) Katakawa, K.; Kitajima, M.; Aimi, N.; Seki, H.; Yamaguchi, K.; Furihata, K.; Harayama, T.; Takayama, H. *J. Org. Chem.* **2005**, *70*, 658.

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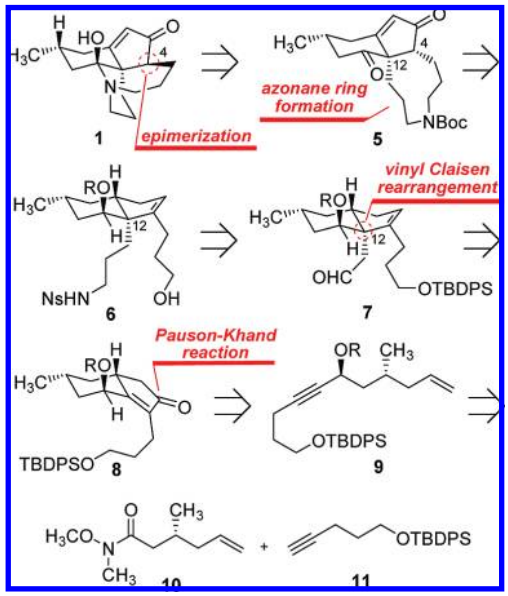
confirm its absolute configuration, and investigate its biomimetic chemical transformation into phlegmariurine-A (**3**), we planned the asymmetric total synthesis of **1**. Herein, we report the first asymmetric total synthesis of **1**, which involves the cobalt-mediated Pauson−Khand reaction and the vinyl Claisen rearrangement as key steps, as well as the efficient conversion of **1** into **3**.

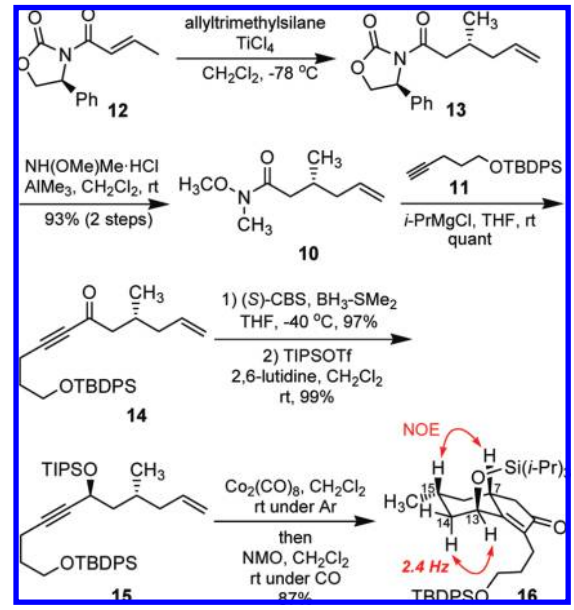
Our synthetic plan is shown in Scheme 1. Construction of the hemiaminal function in **1** was expected by removal of the *N*-Boc group and epimerization at C-4[5] in diketone derivative **5**. Tricyclic compound **5** could be obtained through azonane ring formation by applying the nosyl (Ns) strategy[6] to compound **6** and subsequent oxidative manipulation to prepare a cyclopentenone moiety. In the syntheses of fawcettimine-type alkaloids, the stereoselective construction of a bicyclic skeleton comprising an angular quaternary carbon center (C-12) is the most important requirement. We envisioned that this chiral center in aldehyde **7** would be stereoselectively obtained by vinyl Claisen rearrangement of the allyl alcohol derivative derived from **8**, which in turn could be constructed from 1,7-enyne compound **9** via the cobalt-mediated Pauson−Khand reaction. Substrate **9** for the Pauson−Khand reaction would be prepared by coupling optically active Weinreb amide **10** with alkyne **11**.

We initially prepared 1,7-enyne compound **15** for the Pauson−Khand reaction, which was synthesized from crotonamide **12** via a five-step operation (Scheme 2) that included the diastereoselective Hosomi−Sakurai allylation,[7] the direct conversion of oxazolidinone into Weinreb amide **10**,[8] coupling with alkynyl anion prepared from **11**, the asymmetric reduction of alkynyl ketone **14** with (*S*)-Corey−Bakshi−Shibata (CBS) reagent,[9] and TIPS protection of the resulting secondary hydroxyl group. Having succeeded in the synthesis of **15**, the stage was set for the intramolecular Pauson−Khand reaction[10] to construct a tetrahydroindenone core. After several attempts, we finally found that pretreatment of **15** with $Co_2(CO)_8$ in DCM at rt under Ar atmosphere, followed by manipulation of the resulting coordination product with 4-methylmorpholine *N*-oxide (NMO) in DCM at rt under CO atmosphere, produced the desired bicyclo compound **16** in 87% yield as the major product after

Scheme 1. Retrosynthetic Analysis



Scheme 2



(3) For recent reports on the total synthesis of Lycopodium alkaloids, see: (a) Chandra, A.; Pigza, J. A.; Han, J.; Mutnick, D.; Johnston, J. N. *J. Am. Chem. Soc.* **2009**, *131*, 3470. (b) Nilsson, B. L.; Overman, L. E.; Read de Alaniz, J.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 11297. (c) Yang, H.; Carter, R. G.; Zakharov, L. N. *J. Am. Chem. Soc.* **2008**, *130*, 9238. (d) Kozak, J. A.; Dake, G. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 4221. (e) Bisai, A.; West, S. P.; Sarpong, R. *J. Am. Chem. Soc.* **2008**, *130*, 7222. (f) Kozaka, T.; Miyakoshi, N.; Mukai, C. *J. Org. Chem.* **2007**, *72*, 10147. (g) Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 7671. (h) Beshore, D. C.; Smith, A. B., III. *J. Am. Chem. Soc.* **2007**, *129*, 4148. (i) Snider, B. B.; Grabowski, J. F. *J. Org. Chem.* **2007**, *72*, 1039.

(4) Takayama, H.; Katakawa, K.; Kitajima, M.; Yamaguchi, K.; Aimi, N. *Tetrahedron Lett.* **2002**, *43*, 8307.

(5) (a) Heathcock, C. H.; Smith, K. M.; Blumenkopf, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 5022. (b) Heathcock, C. H.; Blumenkopf, T. A.; Smith, K. M. *J. Org. Chem.* **1989**, *54*, 1548.

(6) (a) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373. (b) Kurosawa, W.; Kan, T.; Fukuyama, T. *Org. Synth.* **2002**, *79*, 186. (c) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353.

(7) Wu, M.; Yeh, J. *Tetrahedron* **1994**, *50*, 1073.

(8) The absolute configuration of the chiral center in Weinreb amide **10** ($[\alpha]^{22}_D$ −13.1 (*c* 0.23, $CHCl_3$)) was confirmed to be (*R*) by direct comparison with **10** ($[\alpha]^{22}_D$ −16.3 (*c* 0.08, $CHCl_3$)) prepared from (*R*)-(+)-citronellic acid in six steps.

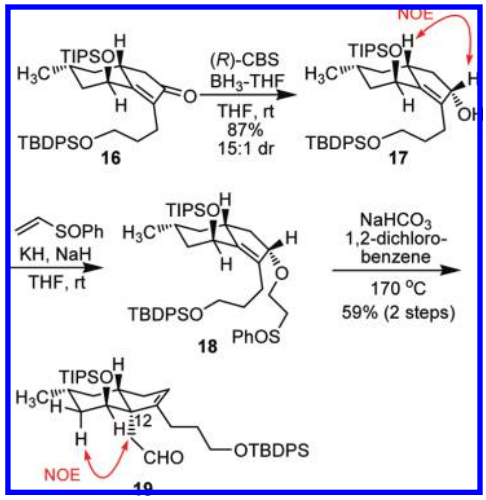
(9) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Parker, K. A.; Ledeboer, M. W. *J. Org. Chem.* **1996**, *61*, 3214.

(10) (a) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E. *J. Chem. Soc., Chem. Commun.* **1971**, *36*, 36. (b) Schore, N. E.; Croudace, M. C. *J. Org. Chem.* **1981**, *46*, 5436. (c) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289. (d) Jeong, N.; Chung, Y. K.; Lee, S. H.; Yoo, S.-E. *Synlett* **1991**, 204.

column chromatography. The diastereomer at C-13, which was generated by CBS reduction, could be easily separated by column chromatography, and the enantiomeric excess of **16** was determined to be 99% ee by chiral HPLC analysis.[11] The configuration at C-7 in **16** was determined by NOE experiment, as shown in Scheme 2. The configuration at C-13 was inferred from the coupling constants of the α and *β* protons on C-14 and that on C-13.

Next, we turned our attention to the construction of a quaternary center at C-12 in the fawcettimine skeleton. For this purpose, we employed the vinyl Claisen rearrangement by which a useful aldehyde functionality to extend the side chain would be gained (Scheme 3). Reduction of enone **16**

Scheme 3



with (*R*)-CBS reagent gave allyl alcohol **17** in good yield with excellent selectivity (α-H:*β*-H = 1:15), the stereochemistry of which was demonstrated by NOE experiments, as shown in Scheme 3. By applying Mandai's conditions,[12] we prepared sulfoxide **18**, which was then heated at 170 °C in 1,2-dichlorobenzene with excess $NaHCO_3$ to produce **19** in 59% yield. NOE experiment indicated that C-12 had the expected (*S*) configuration.

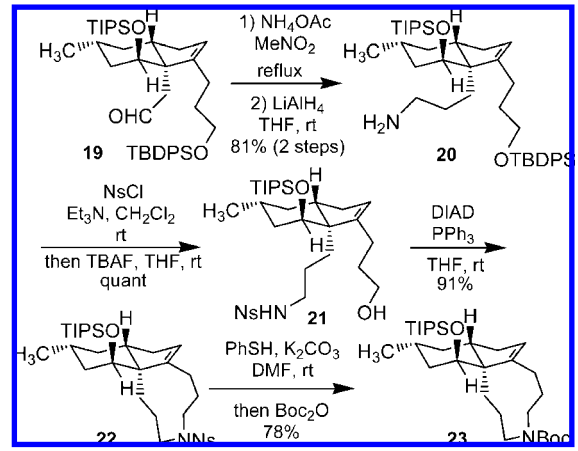
Having succeeded in the synthesis of aldehyde **19**, we proceeded to perform the transformation into **1** (Scheme 4). Conversion of **19** into α,*β*-unsaturated nitro compound by the nitro-aldol reaction, followed by reduction with $LiAlH_4$ gave primary amine **20** in 81% yield (2 steps). Substrate **21** for the intramolecular Mitsunobu reaction[13] was obtained by a one-pot operation from **20**, i.e., installation of the Ns group to the primary amine in DCM, dilution of the reaction mixture with THF, and subsequent treatment with TBAF at rt. Under a highly diluted condition, azonane ring compound **22** was obtained in excellent yield by treating **21** with

(11) The enantiomeric excess was determined by HPLC analysis on a CHIRAL PACK IB column (*n*-hexane; flow 0.35 mL/min).

(12) (a) Mandai, T.; Ueda, M.; Hasegawa, S.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.* **1990**, *31*, 4041. (b) Kaliappan, K. P.; Ravikumar, V. *Org. Lett.* **2007**, *9*, 2417.

(13) Mitsunobu, O. *Synthesis* **1981**, 1.

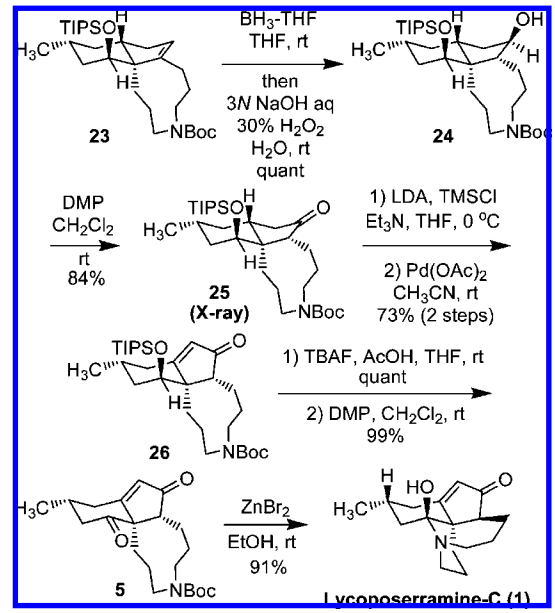
Scheme 4



diisopropyl azodicarboxylate (DIAD) at 0 °C. The protecting group on the secondary amine was switched to the Boc group to afford the desired tricyclic compound **23**.

For the total synthesis of **1**, compound **23** was converted into diketone **5** as follows (Scheme 5). By the conventional

Scheme 5



hydroboration−oxidation procedure[14] and subsequent Dess−Martin oxidation, **23** was transformed into ketone **25** in good yield as colorless crystals. At this stage, X-ray crystallographic analysis of **25**[15] enabled us to determine the configuration of the chiral center at C-4 as (*S*). By applying the Ito−Saegusa oxidation,[16] **25** was regioselectively converted into α,*β*-unsatur-

(14) Brown, H. C.; Liotta, R.; Brener, L. *J. Am. Chem. Soc.* **1977**, *99*, 3427.

(15) See the Supporting Information.

(16) Itoh, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

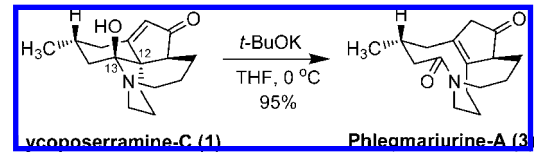
ated ketone **26**. Removal of the TIPS group in **26** with TBAF in AcOH and successive Dess−Martin oxidation of the resulting alcohol gave the desired diketone **5**.

As the final stage, we attempted removal of the Boc group and simultaneous isomerization at C-4 to form the hemiaminal function. This resulted in the total synthesis of **1**. As the conventional procedure with TFA[3g] to remove the *N*-Boc group gave only a complex mixture, we examined the reagents and conditions. When 5 equiv of $ZnBr_2$ was used, a trace amount of **1** was obtained together with the deprotected compound. The optimum conditions were the employment of 20 equiv of $ZnBr_2$ in EtOH at rt to furnish **1** in 91% yield. Synthetic **1** was identical in all respects with the natural product, including the optical property: synthetic, $[\alpha]^{24}_D$ +70.4 (*c* 0.19, $CHCl_3$); natural, $[\alpha]^{24}_D$ +64.6 (*c* 0.21, $CHCl_3$).

Next, we investigated the chemical transformation of **1** into **3**, which would be biogenetically generated by a C-12−C-13 bond scission in **1**. According to this idea, we treated **1** with NaOMe in MeOH at rt and obtained a mixture of **3** and **4**.[4] In the present study, we found that **3** was formed selectively in excellent yield by treating **1** with *t*-BuOK in THF (Scheme 6).

In conclusion, we have achieved the first asymmetric total synthesis of lycoposerramine-C (**1**) (21 steps, 12.6% overall yield), starting from crotonamide **12**. The highlights of this synthesis are the following: (1) the stereoselective construction of a 6−5 bicyclic α,β-unsaturated ketone by the cobalt-mediated Pauson−Khand reaction; (2) the stereoselective reduction of enone with CBS reagent and the subsequent vinyl Claisen rearrangement to construct an angular quaternary carbon center; (3) the construction of an azonane ring with the Ns strategy; and (4) the formation of the 1-azabicyclo[4.3.1]decane ring system by deprotection of the nitrogen group accompanying C4 isomerization. In addition, we have succeeded in the efficient biomimetic transformation of lycoposerramine-C (**1**) into phlegmariurine-A (**3**). The synthesis of other fawcettimine-type alkaloids is underway.

Scheme 6



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Supporting Information Available: Experimental procedures, copies of ^1H and ^{13}C NMR spectral data for **5** and **10**−**26**, synthetic lycoposerramine-C (**1**) and phlegmariurine-A (**3**), and a CIF file for ketone **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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