ORGANIC LETTERS

2013
Vol. 15, No. 22
5846–5849

Divergent Total Syntheses of (−)-Lycopladine D, (+)-Fawcettidine, and (+)-Lycoposerramine Q

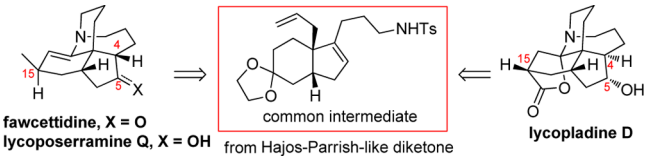
Chen Zeng, Changwu Zheng, Jingyun Zhao, and Gang Zhao*

Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

zhaog@mail.sioc.ac.cn

Received October 8, 2013

ABSTRACT



Enantioselective total syntheses of (+)-fawcettidine and (+)-lycoposerramine Q as well as the first total synthesis of (−)-lycopladine D from a common intermediate have been accomplished by a divergent path. The common intermediate was derived from a Hajos−Parrish-like diketone by a stereoselective Birch reduction and a Suzuki coupling. The synthesis of (−)-lycopladine D featured an allylic oxidation and a biomimetic aminoketalization while the route to (+)-fawcettidine and (+)-lycoposerramine Q highlighted an oxidative rearrangement.

Since the first *Lycopodium* alkaloid lycopodine was separated by Bödeker in 1881 from clubmoss *Lycopodium complanatum*,[1] over 200 lycopodium alkaloids have been isolated and classified into four major groups to date.[2] Members of this family are known to have cardiovascular and neuromuscular effects.[3] The unique polyfused/bridged system and impressive biological activities of these compounds have aroused great interest from synthetic chemists in recent decades.[4] One of the classes in the family named fawcettimine-type *Lycopodium* alkaloids (Figure 1), which usually feature a tetracyclic skeleton including a α-oriented methyl group at C-15 and account for nearly one-third of the members, has particularly attracted the attention of several groups in total synthesis. As the selected examples shown in Figure 1, recently, several impressive total syntheses toward fawcettidine (**1**),[5] lycojapodine A,[6] lycoflexine,[7] huperzine Q,[8] and lycoposerramine Q (**2**)[9] have been achieved.

Meanwhile, many new fawcettimine-type *Lycopodium* alkaloids with more diverse and novel architectures have

(1) Bödeker, K. *Justus Liebigs Ann. Chem.* **1881**, *208*, 363.

(2) For recent reviews on *Lycopodium* alkaloids, see: (a) Ma, X.; Gang, D.-R. *Nat. Prod. Rep.* **2004**, *21*, 752. (b) Hirasawa, Y.; Kobayashi, J.; Morita, H. *Heterocycles* **2009**, *77*, 679. (c) Siengalewicz, P.; Mulzer, J.; Rinner, U. In *The Alkaloids*; Knölker, H.-J., Ed.; Academic Press: New York, 2013; Vol. 72, pp 1−151.

(3) (a) Tang, X.-C.; Han, Y.-F.; Chen, X.-P.; Zhu, X.-D. *Acta Pharmacol. Sin.* **1986**, *7*, 507. (b) Hirasawa, Y.; Morita, H.; Kobayashi, J. *Org. Lett.* **2004**, *6*, 3389.

(4) For recent reports on the total syntheses of fawcettimine-class *Lycopodium* alkaloids, see: (a) Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 7671. (b) Kozak, J. A.; Dake, G. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 4221. (c) Otsuka, Y.; Inagaki, F.; Mukai, C. *J. Org. Chem.* **2010**, *75*, 3420. (d) Canham, S. M.; France, D. J.; Overman, L. E. *J. Am. Chem. Soc.* **2010**, *132*, 7876. (e) Ramharter, J.; Weinstabl, H.; Mulzer, J. *J. Am. Chem. Soc.* **2010**, *132*, 14338. (f) Yang, Y.-R.; Shen, L.; Huang, J.-Z.; Xu, T.; Wei, K. *J. Org. Chem.* **2011**, *76*, 3684. (g) Nakayama, A.; Kogure, N.; Kitajima, M.; Takayama, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 8025. (h) Zhang, X.-M.; Tu, Y.-Q.; Zhang, F.-M.; Shao, H.; Meng, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 3916. (i) Li, H.-H.; Wang, X.-M.; Lei, X.-G. *Angew. Chem., Int. Ed.* **2012**, *51*, 491. (j) Ge, H.-M.; Zhang, L.-D.; Tan, R.-X.; Yao, Z.-J. *J. Am. Chem. Soc.* **2012**, *134*, 12323. (k) Pan, G.-J.; Williams, R. M. *J. Org. Chem.* **2012**, *77*, 4801. (l) Shimada, N.; Abe, Y.; Yokoshima, S.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 11824. (m) Li, H.-H.; Wang, X.-M.; Hong, B.-K.; Lei, X.-G. *J. Org. Chem.* **2013**, *78*, 800. (n) Itoh, N.; Iwata, T.; Sugihara, H.; Inagaki, F.; Mukai, C. *Chem.—Eur. J.* **2013**, *19*, 8665. (o) Zaimoku, H.; Nishide, H.; Nishibata, A.; Goto, N.; Taniguchi, T.; Ishibashi, H. *Org. Lett.* **2013**, *15*, 2140.

(5) For isolation, see: Burnell, R. H. *J. Chem. Soc.* **1959**, 3091. For total syntheses, see refs 4b, 4i, 4k, and 4n.

(6) For isolation, see: He, J.; Chen, X.-Q.; Li, M.-M.; Zhao, Y.; Xu, G.; Cheng, X.; Peng, L.-Y.; Xie, M.-J.; Zheng, Y.-T.; Wang, Y.-P.; Zhao, Q.-S. *Org. Lett.* **2009**, *11*, 1397. For total synthesis, see ref 4m.

(7) For isolation, see: Ayer, W. A.; Fukazawa, Y.; Singer, P. P. *Tetrahedron Lett.* **1973**, *14*, 5045. For total syntheses, see refs 4e, 4f, 4k, and 4n.

(8) For isolation, see: Tan, C.-H.; Ma, X.-Q.; Chen, G.-F.; Zhu, D.-Y. *Helv. Chim. Acta* **2002**, *85*, 1058. For total synthesis, see ref 4g.

10.1021/ol402906y
Published on Web 11/04/2013

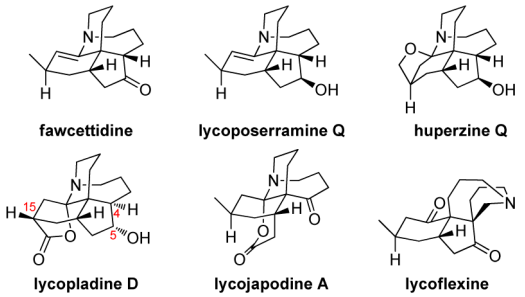


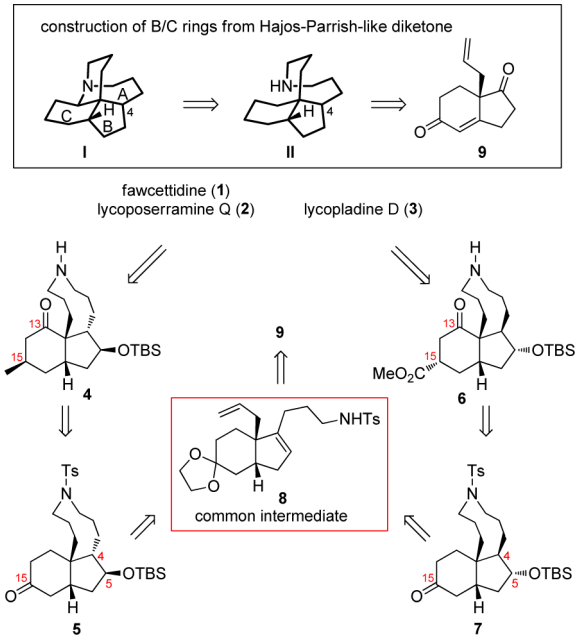
Figure 1. Selected fawcettimine-type *Lycopodium* alkaloids.

been identified. Lycopladine D (**3**), which was isolated from *Lycopodium complanatum* by Kobayashi and co-workers in 2006, exhibits a unique carbinolamine lactone, a fused pentacyclic ring framework, and six stereogenic centers including an all-carbon quaternary center.[10] It is noteworthy that the stereochemistry at C-4, C-5, and C-15 differs from other fawcettimine class members, making it more interesting in total synthesis. Although lycopladine D (**3**) was isolated seven years ago, no total synthesis has been reported to date probably due to its unique structure from others. Interested by the fascinating structural diversities, here we have discovered a route to accomplish its total synthese as well as fawcettidine (**1**) and lycoposerramine Q (**2**) from a common intermediate. As shown in Scheme 1 (top), the core structure of fawcettimine-type *Lycopodium* alkaloids (**I**) could be obtained from the secondary amine (**II**), which was supposed to be the biomimetic pathway that has been employed in the analogous synthesis.[4] The intermediate **II**, as we designed, could be generated from the Hajos–Parrish-like diketone **9**, a very popular and easily accessible starting material in the synthetic chemistry. The other advantage of this method is that the stereochemistry at C-4 and C-5 could be modulated via the diastereoselective reduction and herein fawcettidine (**1**), lycoposerramine Q (**2**), and lycopladine D (**3**) can be synthesized via a divergent pathway.

Our retrosynthetic strategy is detailed in Scheme 1 (bottom). We envisioned that **1**–**2** or **3** could be respectively obtained from precursor **4** or **6** through a dehydration condensation or biomimetic aminoketalization transformation. The functional groups at C-15 and C-13 in **4** or **6** were expected to be constructed from carbonyl at C-15 in **5** or **7**. We imagined that both **5** and **7** could be assembled from a common intermediate **8**, which would be prepared from Hajos–Parrish-like diketone **9**.

As outlined in Scheme 2, our syntheses commenced with Hajos–Parrish-like diketone (*R*)-**9**, containing an

Scheme 1. Retrosynthetic Analysis



all-carbon quaternary center, which was easily prepared from 1,3-cyclopentadione by a three-step procedure.[11] The first challenge we faced was the selective 1,4-reduction of the enone in the presence of the terminal alkene and isolated carbonyl to construct the *cis*-fused 6,5-carbocyclic ring. Direct reduction from the diketone (*R*)-**9** proved to be problematic. The terminal alkene was also reduced by hydrogenation of **9** catalyzed by Pd/C. Reduction by *t*-BuCuH or $NiCl_2/NaBH_4$ gave a *trans*-fused bicycle ring as the major product. The diastereoselectivity was almost 1:1 when **9** was subjected to lithium in liquid ammonia. Herein the alternative hydroxyl-directed stereocontrolled Birch redution developed by Corey and co-workers was employed.[12] Selective reduction of the unconjugated carbonyl group in **9** with $NaBH_4$ at −78 °C afforded **10** with the desired selectivity,[13] which was then subjected to lithium in liquid ammonia to give **11** in 8:1 diastereoselectivity. The *cis*-fused isomer obtained as the major product was probably the result of intramolecular protonation of the radical anion by internal proton transfer from the secondary hydroxyl in the Birch reduction. With the *cis*-bicycle being established, Dess-Martin oxidation of the hydroxyl group followed by selective protection of the less sterically hindered carbonyl provided **12** in one pot.[14] Treatment of **12** with KHMDS followed by $PhNTf_2$ afforded the triflate, which coupled[15] with the boron species generated in situ from *N*-tosylallylamine and 9-BBN to furnish the common intermediate **8** in high yield.

(9) For isolation, see: Takayama, H.; Katakawa, K.; Kitajima, M.; Yamaguchi, K.; Aimi, N. *Tetrahedron Lett.* **2002**, *43*, 8307. For racemic total synthesis, see ref 4n.

(10) Ishiuchi, K.; Kubota, T.; Hoshino, T.; Obara, Y.; Nakahata, N.; Kobayashi, J. *Bioorg. Med. Chem.* **2006**, *14*, 5995.

(11) (a) Ruprah, P. K.; Cros, J.-P.; Pease, J. E.; Whittingham, W. G.; Williams, J. M. J. *Eur. J. Org. Chem.* **2002**, 3145. (b) Lacoste, E.; Vaique, E.; Berlande, M.; Pianet, I.; Vincent, J.-M.; Landais, Y. *Eur. J. Org. Chem.* **2007**, 167. (c) Zhang, X.-M.; Wang, M.; Tu, Y.-Q.; Fan, C.-A.; Jiang, Y.-J.; Zhang, S.-Y.; Zhang, F.-M. *Synlett* **2008**, 2831.

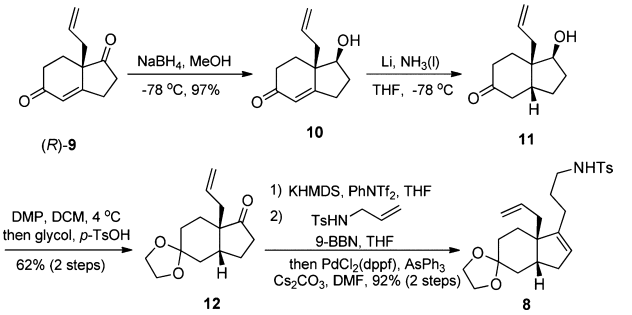
(12) Corey, E. J.; Lee, J. *J. Am. Chem. Soc.* **1993**, *115*, 8873.

(13) Isaacs, R. C.; DiGrandi, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 3938.

(14) Ciceri, P.; Joachim Demnitz, F. W. *Tetrahedron Lett.* **1997**, *38*, 389.

(15) Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **1998**, *120*, 6818.

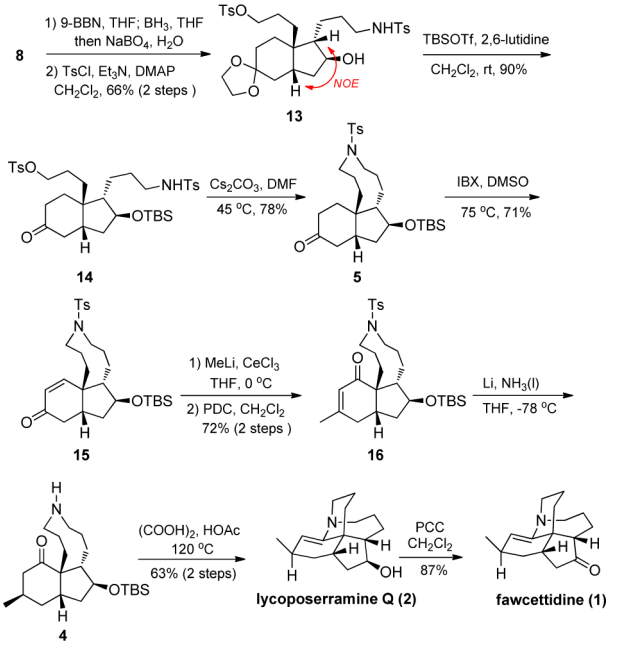
Scheme 2. Synthesis of Common Intermediate **8**



With the common intermediate **8** in hand, the synthetic routes toward fawcettidine (**1**) and lycoposerramine Q (**2**) from **8** are illustrated in Scheme 3. Successive hydroboration of **8** was achieved with 9-BBN and a borane−THF complex and subsequent oxidation by $NaBO_4$ afforded a diol,[16] which was selectively transformed into *O*-tosyl derivative **13** with *p*-toluenesulfonyl chloride at −10 °C. The stereochemistry of **13** was determined by a NOESY experiment. Simultaneous silylation of hydroxyl with TBSOTf and deprotection of the ketal with 0.8 M HCl in **13** afforded **14** in 90% yield. Treatment of compound **14** with Cs_2CO_3 provided **5** with an azonane ring by an intramolecular S_N2 reaction. **5** was then dehydrogenated to **15** by IBX oxidation developed by Nicolaou and coworkers.[17] After nucleophilic addition of **15** with a methylcerium reagent,[18] the resulting tertiary allylic alcohol was elaborated to **16** by a PDC-mediated oxidative rearrangement.[19] Reductive cleavage of the *N*-tosyl amide in **16** accompanied by 1,4-reduction of the conjugated double bond with lithium in liquid ammonia provided the amino ketone **4**. Finally, treating **4** with oxalic acid in AcOH[4k] at 120 °C furnished lycoposerramine Q (**2**). Oxiation of **2** with PCC afforded fawcettidine (**1**).[20]

Encouraged by the successful syntheses of **1** and **2**, we next explored the synthesis of lycopladine D from the common intermediate **8** (Scheme 4). Selective hydroboration of **8** was achieved with 9-BBN and following oxidation by $NaBO_4$ afforded primary alcohol **17**, which was transformed into azonane ring **18** by a modified intramolecular Mitsunobu reaction.[21] The latter compound was elaborated to **7** in a one-pot operation involving hydroboration/oxidation with $BH_3 \cdot THF/NaBO_4$ and successive deprotection of the ketal by 4 M HCl followed by silylation with TBSCl. The stereochemistry of **7** at C-4, C-5 was opposite to that of **13** as a result of the steric hindrance of the

Scheme 3. Route to Fawcettidine (**1**) and Lycoposerramine Q (**2**)

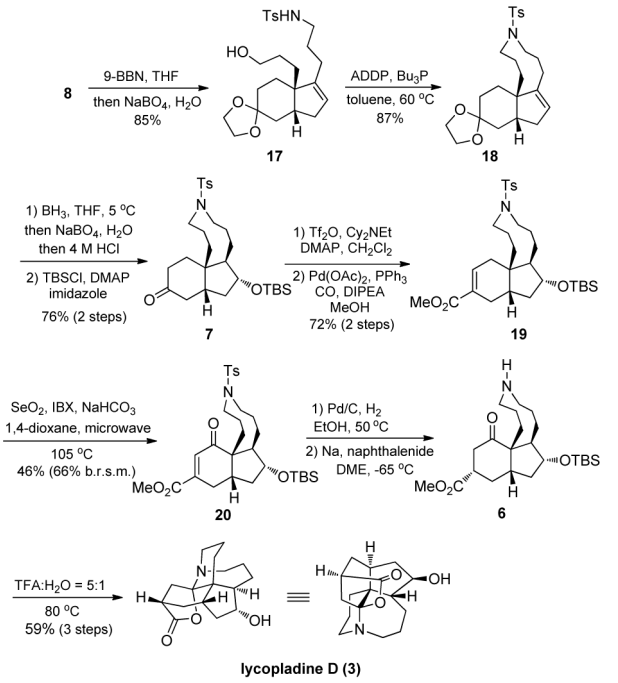


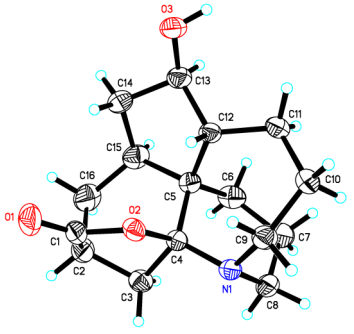
azonane ring of **18**. **7** was then subjected to Tf_2O using Cy_2NEt as a hindered base, and the resulting enol triflate was further converted into the methyl ester compound **19** by a palladium catalyzed[22] carbonylation reaction in methanol.

The ensuing allylic oxidation of **19** proved to be difficult, presumably due to the steric hindrance of the vicinal quaternary carbon. After numerous conditions were evaluated, we observed that treatment of **19** with SeO_2 followed by oxidation with DMP produced **20** in 15% yield.[23] The low yield resulted from the elimination of the hydroxyl of the corresponding allyl alcohol intermediate and decomposition of the TBS protecting group. To avoid the side reactions, we hypothesized that the allyl alcohol intermediate could be oxidized in situ by an appropriate oxidant. After carefully screening, we found that in situ oxidation using IBX with $NaHCO_3$ as a buffer significantly improved the yield to 35%.[24] Finally, this yield could be improved to 46% (66% b.r.s.m.) at 105 °C in 1 h in a microwave reactor.[25] Hydrogenation of **20** under 30 atm of hydrogen followed by removal of the *p*-toluenesulfonyl group from nitrogen led to **6**. The final critical biomimetic aminoketalization was achieved

(16) Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930.
(17) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245.
(18) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.
(19) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 683.
(20) Spectral data of the synthetic fawcettidine and lycoposerramine-Q were consistent with the reported data; see: refs 4b, 4n.
(21) Tsunoda, T.; Yamamiya, Y.; Ito, S. *Tetrahedron Lett.* **1993**, *34*, 1639.
(22) Snider, B. B.; Vo, N. H.; Neil, S. V.; Foxman, B. M. *J. Am. Chem. Soc.* **1996**, *118*, 7644.
(23) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 7154.
(24) Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312.
(25) For a review of microwave-assisted organic synthesis, see: Caddick, S.; Fitzmaurice, R. *Tetrahedron* **2009**, *65*, 3325.
(26) Miyashita, M.; Sasaki, M.; Hattori, I.; Sakai, M.; Tanino, K. *Science* **2004**, *305*, 495.
(27) CCDC 936082 (**3**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 4. Approach to Lycopladine D (**3**)





X-ray crystal structure of lycopladine D

by treatment of **6** with aqueous TFA at 80 °C to produce lycopladine D.[26]

The synthetic compound was identical with the natural material, including ^{1}H NMR, ^{13}C NMR data, and mass spectra. X-ray crystallographic analysis of single crystal of **3** unambiguously confirmed the structure.[27] The consistency of the optical rotation of the product also determined the absolute configuration of the naturally occurring **3**.

In summary, we have achieved the syntheses of (+)-fawcettidine and (+)-lycoposerramine Q, as well as the first total synthesis of (−)-lycopladine D in 15, 14, and 15 steps from known compound **9** by a divergent path.[28] The syntheses highlight the following: (1) a stereoselective Birch reduction by way of intramolecular protonation and a Suzuki coupling with in situ generated boron species to afford the *cis*-fused intermediate **8**; (2) **1**−**2** and **3** could be respectively obtained from diastereoisomers **5** and **7**, both of which were produced from the common intermediate **8** by changing the sequence of cyclization and hydroboration oxidation of the double bond at C-4, C-5; (3) an allylic oxidation with large steric hindrance and a biomimetic aminoketalization. Due to the great efficiency of this synthetic strategy, endeavors in achieving the total syntheses of other fawcettimine-type alkaloids are being pursued in our laboratory, and the results will be reported in due course.

Acknowledgment. This work was financially supported by the NSFC (20172064, 203900502, and 21032006), the 973 program (2010CB833204), and the Excellent Young Scholars Foundation of National Natural Science Foundation of China (No. 20525208).

Supporting Information Available. Experimental procedures, characterization data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

(28) For selected recent work on the divergent syntheses of natural products, see: (a) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183. (b) Bian, M.; Wang, Z.; Xiong, X.; Sun, Y.; Matera, C.; Nicolaou, K. C.; Li, A. *J. Am. Chem. Soc.* **2012**, *134*, 8078.

The authors declare no competing financial interest.