OL Organic Letters

pubs.acs.org/OrgLett Letter

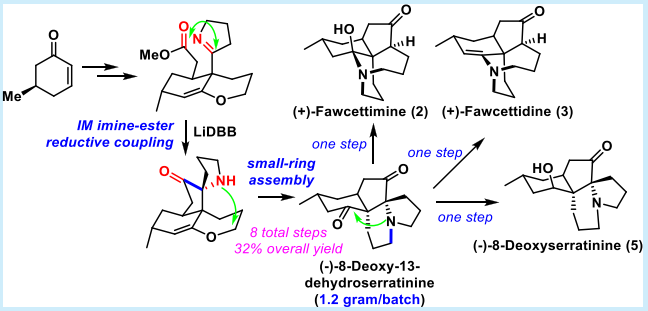
Concise Unified Access to (−)-8-Deoxy-13-dehydroserratinine, (+)-Fawcettimine, (+)-Fawcettidine, and (−)-8-Deoxyserratinine Using a Direct Intramolecular Reductive Coupling

Lin-Rui Zhong, Bing-Bing Huang, Xiao-Liang Yang, Shaozhong Wang, and Zhu-Jun Yao*

Cite This: *Org. Lett.* 2021, 23, 3578−3583 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A short, scalable, and collective total synthesis of four fawcettimine-type *Lycopodium* alkaloids in eight or nine steps is disclosed. A dense multi-small-ring *spiro*-α-aminocyclopentanone successfully served as the key intermediate, which was directly accessed by a LiDBB-mediated intramolecular reductive coupling of the aliphatic imine and an ester-carbonyl. Compared to those that employ classical Heathcock intermediate(s) containing a nine-membered ring, the new strategy shows the significant improvement of the synthetic step and redox economies as well as excellent stereochemical control.



Lycopodium alkaloids have been immensely appealing research topics since the isolation of lycopodine in 1881 due to their unique and diverse structures and attractive biological activities.[1] With over three hundred natural members, more than 90 *Lycopodium* alkaloids pertain to the subfamily of fawcettimine. Biosynthetically, the fawcettimine class is generated from lycopodine-type alkaloids via a C4−C13 to C4−C12 bond migration (Figure 1a).[2] The further division of fawcettimine-type alkaloids is based on the *N*-attachment; for example, the carbinolamine form commonly possesses a N−C_{13} connection, whereas the keto-amine form contains either a N−C_4 bond or a N−C_{17} bond. (Figure 1b).[2a,h]

The diverse and mutable structural features make the total synthesis of fawcettimine-type *Lycopodium* alkaloids challenging but intriguing work. Early in 1986, Heathcock and coworkers reported their pioneering synthesis of (±)-fawcettimine[3] in which the closure of the nine-membered ring, which led to the famous 6/5/9 tricyclic Heathcock intermediate[2] from a 6/5 bicyclic precursor, was designed as a key step. Further epimerization at the C_4 position afforded (±)-fawcettimine via spontaneous hemiaminal formation. Heathcock's protocol for accessing fawcettimine-type *Lycopodium* alkaloids via the 6/5/9 tricyclic intermediates is significant effective in obtaining both carbinolamine and keto-amine forms and has been widely adopted in the past several decades (Figure 1c).[4] However, a moderate or low efficiency often resulted when a medium-sized ring of Heathcock-type intermediates was formed due to unfavorable transannular interactions and entropic factors. Besides, the annulation of the medium-size rings needs to be carried out at a much lower concentration, which may further hinder the amplification and material

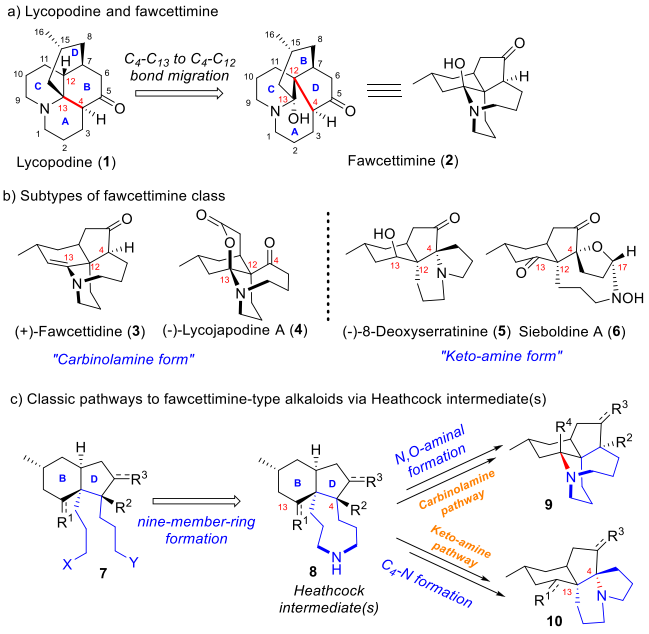


Figure 1. Protocols for the synthesis of fawcettimine-type *Lycopodium* alkaloids.

Received: March 22, 2021
Published: April 23, 2021

https://doi.org/10.1021/acs.orglett.1c00977
Org. Lett. 2021, 23, 3578−3583

accumulation. To avoid this negative influence on the synthesis of the nine-membered ring(s), Dake's team once elaborated the C and A rings of fawcettidine stepwise through a platinum(II)-catalyzed cyclization and Ramberg−Bäcklund reaction.[5] Meanwhile, Tu and co-workers also accomplished a 6/9 *spiro*-*β*-hydroxylated precursor with a semipinacol rearrangement instead of the corresponding Heathcock intermediate in their syntheses of (−)-lycojapodine A and two other alkaloids.[6] In addition, a 6/5/5 tricyclic intermediate was also employed in the syntheses of (+)-fawcettimine and three other alkaloids.[7] Herein, we wish to report a unified, step-saving, and scalable synthetic route to several representative fawcettimine-type *Lycopodium* alkaloids that employs a dense multi-small-ring compound as the key intermediate.

Our retrosynthetic analysis is outlined in Figure 2. (−)-8-Deoxy-13-dehydroserratinine (**11**), a keto-amine alkaloid, was

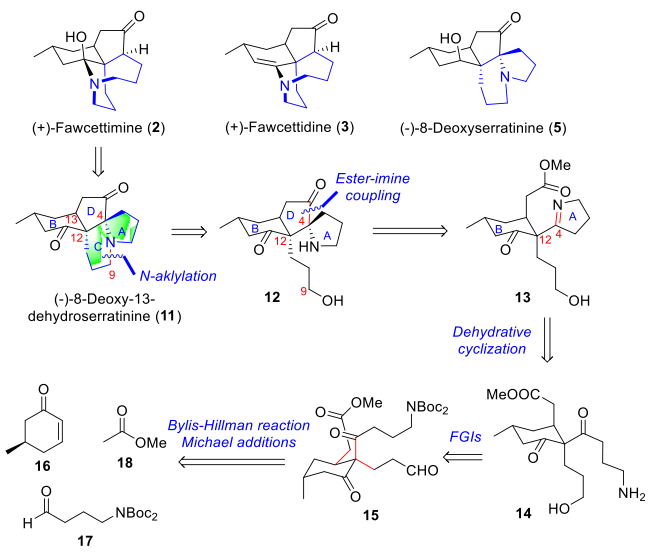
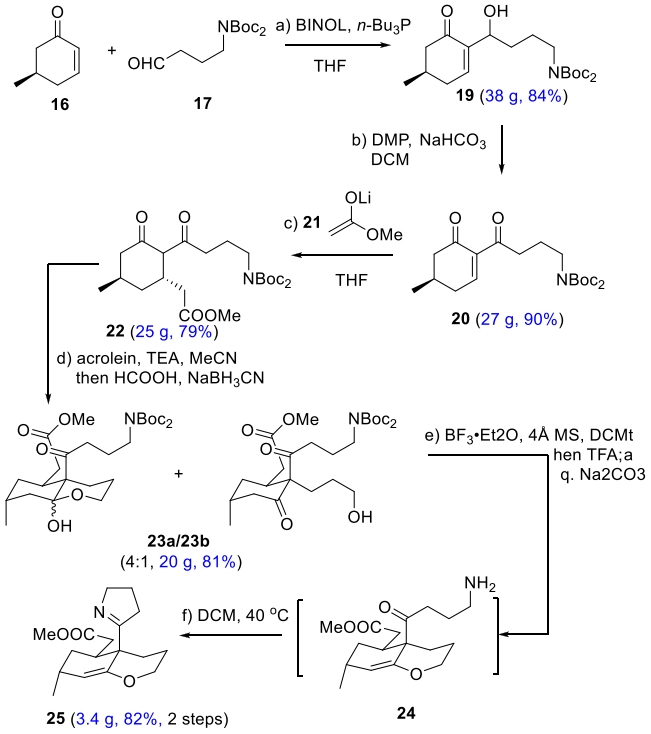


Figure 2. Retrosynthetic analysis of the *Lycopodium* alkaloids (−)-8-deoxy-13-dehydroserratinine (**11**), (+)-fawcettimine (**2**), (+)-fawcettidine (**3**), and (−)-8-deoxyserratinine (**4**).

designed as a natural late-stage intermediate common to the other three fawcettimine-type *Lycopodium* alkaloids.[4f,h,7−9] Contrary to the previous situations that use the Heathcock intermediates, the ring system combined with the A and C rings of **11** represent a perfect latent nine-membered ring, which can be immediately exposed through a potential C_4−N disconnection. Opening the piperidine ring (C ring) of **11** via a C_9−N disconnection gives a tricyclic *spiro*-*α*-cyclopentanone intermediate **12** with multiple small rings. However, the synthesis of such a fully functionalized spirocyclic pyrrolidine is thought to be challenging,[10] and multiple steps (including several redox steps) or peculiar precursors are usually needed to establish the requisite functionalities, multiple dense stereochemistries, and continuous quaternary carbons. If the direct formation of a C_4−C_5 bond (to form the D ring) could be achieved via the coupling of the imine and the ester carbonyl of **13**, it would be a shortcut to approach the above polycyclic intermediate and would thus greatly improve the step and redox economies of the synthesis. Following this crucial disconnection, the resulting cyclic imine **13** can be further prepared from the linear primary amine **14** via dehydrative cyclization. Further modification of the functional groups delivers a multisubstituted cyclohexanone intermediate **15** that contains a chiral all-carbon quaternary carbon, which could be concisely prepared by a four-step sequence[11] starting from the commercially and easily available materials (5*R*)-methylcyclohex-2-en-1-one (**16**),[12] *N*,*N*-di-Boc-4-aminobutanal (**17**),[13] and methyl acetate (**18**).

The synthesis commenced with a scalable preparation of the cyclohexanone **15**, which contains a chiral quaternary carbon.[8] The Morita−Baylis−Hillman condensation of the commercially available cyclohexenone **16** and aldehyde **17** afforded the *β*-hydroxyketone **19** (38 g per batch) in an 84% yield in the presence of *n*-Bu_3P and 1,1′-2-naphthol (Scheme 1). The

Scheme 1. Synthesis of the Cyclic Imine 25



treatment of **19** with Dess−Martin periodinane and sodium bicarbonate in dichloromethane afforded the 1,3-diketone **20** (90% yield). Further reaction with the *in situ*-generated enolate **21**, which was derived from methyl acetate and LiHMDS, provided **22** (79% yield) via a Michael addition from the opposite face of the chiral methyl group. The subsequent Michael addition of **22** to acrolein was carried out in MeCN with perfect stereochemical control by the steric hindrance of the ester. It is noteworthy here that use of acetonitrile as the solvent could further facilitate the selective reduction of the resulting aldehyde with sodium cyanoborohydride in the same flask after acidifying the first-stage reaction mixture with formic acid. This sequential Michael addition/$NaBH_3CN$ reduction treatment finally provided a mixture of hemiketal **23a** (major) and cyclohexanone **23b** (minor) in an 81% combined yield, wherein the requisite C_{12} quaternary carbon was correctly established.

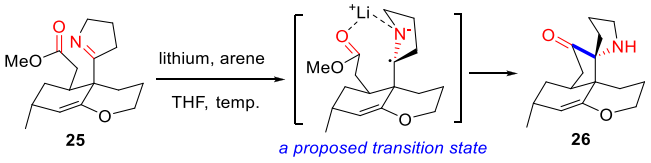
To prepare a substrate suitable for the designed reductive imine−ester coupling, the *N*-Boc groups of **23a** and **23b** were removed by a treatment with trifluoroacetic acid (Scheme 1). However, the reaction could not stop at the free-amine stage, and a substantial portion of the product underwent further hemiaminalization and dehydration to provide an enol-ether

https://doi.org/10.1021/acs.orglett.1c00977
Org. Lett. 2021, 23, 3578−3583

24. Fortunately, the enol-ether functionality of **24** also can be regarded as a special protecting form for both the ketone-carbonyl group (of the six-membered ring) and the hydroxyl group (of the linear chain); therefore, it was suitable for the next transformation. Based on our observation, a continuously sequential operation was finally optimized for the preparation of **24** and **25**. First, the mixture of **23a** and **23b** was treated with 0.3 equiv of boron trifluoride in DCM at 0 °C to rt. It was found that the enol-ether was formed completely while one of the two *N*-Boc groups of **23a** or **23b** was also removed. The removal of the remaining *N*-Boc group was carried out by a further treatment with trifluoroacetic acid. However, the purification of the free amine **24** via silica gel chromatography was found to be inefficient. To save the material, a solution of the unpurified amine **24** DCM was directly applied to the next step after neutralization and drying. The spontaneous formation of the cyclic imine in **25** took place slowly but efficiently when the above solution was heated at 40 °C. To avoid the side reactions brought by long-time heating, the reaction was interrupted after three days, and the expected imine **25** was separated. Usually, 56−66% of the amine **24** can be converted into the corresponding imine **25**, with a recovery yield of 87−97%. The recovered amine **24** was redissolved in DCM and heated for the second batch of the crop. After two additional recycles, the combined overall yield of imine **25** could be increased to 82% over two steps.[14]

With the cyclic imine **25** in hand, we started to explore the crucial intramolecular reductive imine−ester coupling (Table 1). Although several electrochemical approaches were reported

Table 1. Optimization of the Intramolecular Reductive Imine−Ester Coupling of 25[a]

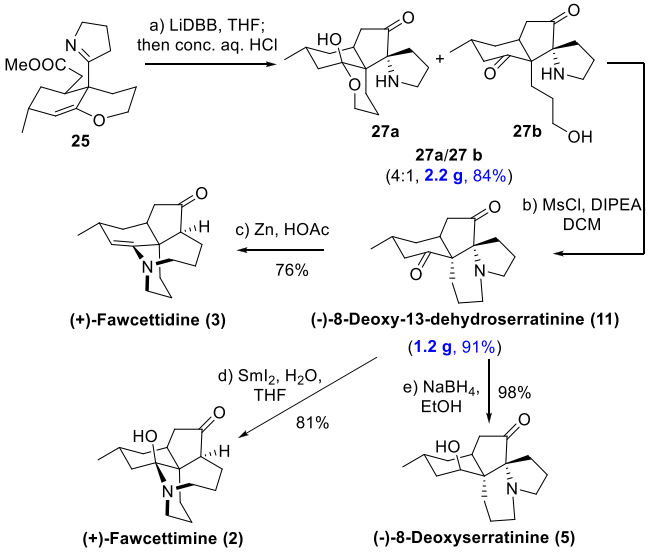


entry	arene	temperature (°C)	**26** (%)[b]
1[c]	naphthalene	−80	n.d.
2[d]	2,6-di-*tert*-butylnaphthalene	−80 to −40	7
3[d]	acenaphthene	−80 to −40	n.r.
4[c]	1,1′-binaphthyl	−80 to −60	n.d.
5[d]	diphenyl	−80 to −55	37
6[d]	4,4′-di-*tert*-butylbiphenyl	−60	56
7[d]	4,4′-di-*tert*-butylbiphenyl	−80	74
8[d]	4,4′-di-*tert*-butylbiphenyl	−98	84

[a]Reactions were performed at a set concentration of **25** (0.020 M), and lithium arenide (0.25 M) in THF was added. [b]Isolated yields. [c]Lithium arenide (0.3 equiv) was added. [d]Lithium arenide (3.0 equiv) was added; n.d. stands for not detected, and n.r. stands for no reaction.

for similar intramolecular couplings of aromatic imines and esters,[15] few have been explored on the corresponding aliphatic system, especially a complex aliphatic system that contains multiple continuous stereocenters. As a category of powerful reductants involving single-electron processes, lithium-arenides were employed in some challenging C−C bond formations.[11,16] Due to the uncertainty of the reductive C−C coupling between an aliphatic imine and an ester, metal−arene-based conditions were chosen by us as a feasible starting point for the examination. Lithium naphthalenide was first examined, but unfortunately the desired *spiro*-α-aminocyclopentanone **26** was not observed (Table 1, entry 1). To identify a matched combination, a variety of arenes were screened as parterns with lithium on this platform. To our delight, a small amount of the product **26** (7%) was detected when 2,6-di-*tert*-butylnaphthalene was applied (Table 1, entry 2). According to the general properties of lithium arenides, we suspected that a reductant milder than lithium naphthalenide might be preferred. The parallel tests of reductive couplings showed that lithium acenaphthalenide was too feeble to promote the reaction, and lithium 1,1′-binaphthylide seemed to be too powerful and resulted in messy reaction (Table 1, entries 3 and 4, respectively). Alternatively, the reaction with lithium diphenylide gave us a promising result and delivered an improved yield (37%) of the product **26** (Table 1, entry 5). A noticeable improvement was found in the reaction when using lithium 4,4′-di-*tert*-butylbiphenylide (LiDBB), affording a satisfying yield (74%) of the *spiro*-α-aminocyclopentaone **26** as a single diastereoisomer. It is worth noting here that the C_4 stereochemistry of **26** was indirectly determined by a comparison with the literature data of **11** in a late stage (Scheme 2). We speculate that the chelation of lithium ion

Scheme 2. Total Synthesis of the Fawcettimine Class



with the ester carbonyl and the steric effect of the α-amino radical finally led to the observed stereoselectivity. The detailed mechanism for the subsequent C−C bond formation, either by an anionic or free-radical process, remains to be explored. Further optimization showed that lower temperatures could further increase the yields (Table 1, entries 6−8), and the final reaction temperature was determined to be −98 °C.

To simplify the procedure for the scaled-up preparation, the purification of product **26** was waived after completing the reductive coupling of **25** under the optimized conditions. Instead, the resulting reaction mixture was treated with concentrated aqueous hydrochloric acid (Scheme 2). A mixture of **27a** and **27b** (4:1, 2.2 g) was afforded in an 84% yield. The subsequent reaction of **27a** and **27b** with methanesulfonyl chloride and *N*,*N*-diisopropylethylamine in DCM delivered the first natural fawcettimine-type alkaloid

https://doi.org/10.1021/acs.orglett.1c00977
Org. Lett. 2021, 23, 3578−3583

(−)-8-deoxy-13-dehydroserratinine (**11**, 1.2 g, 91% yield). Undoubtedly, the accomplished eight-step synthesis of (−)-8-deoxy-13-dehydroserratinine (**11**, 32% overall yield) shows excellent stereochemical control and much-improved step- and redox economies by using the developed direct intramolecular C−C bond formation between the imine and the ester. With an adequate quantity of the common intermediate **11** in hand, parallel one-step transformations of **11** were accomplished to three other fawcettimine-type alkaloids, (+)-fawcettimine (**2**), (+)-fawcettidine (**3**), and (−)-8-deoxyserratinine (**5**).[4f,h,7,9] The spectroscopic data of all four synthetic *Lycopodium* alkaloids are in good agreement with those reported previously (see the Supporting Information for the details).[7] To the best of our knowledge, the above achievement represents a new shortest benchmark for the enantiospecific total syntheses of fawcettimine-type *Lycopodium* alkaloids in the current literature.[3−7]

In summary, we have accomplished in this communication a short, scalable, and collective synthesis of four typical fawcettimine-type *Lycopodium* alkaloids, namely, (−)-8-deoxy-13-dehydroserratinine, (+)-fawcettimine, (+)-fawcettidine, and (−)-8-deoxyserratinine, with much-improved step- and redox economies. The newly developed and successful LiDBB-mediated intramolecular reductive coupling of the alphalic imine and the ester-carbonyl served as a shortcut to the crucial fully functionalized and complex *spiro*-α-aminocyclopentanone intermediate. The concise formation and application of the dense small-ring intermediate also significantly improved the whole synthesis efficiency compared to those of traditional syntheses via Heathcock intermediates. Finally, a gram-scale synthesis of the natural alkaloid **11** was demonstrated within eight steps and a 32% overall yield. Further parallel transformations of **11** to three other natural *Lycopodium* alkaloids are also achieved within one step. We believe that the novel intermediates, key methodology, and overall strategy developed in this work will facilitate the synthesis of other *Lycopodium* alkaloids as well as the related pharmaceuticals.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00977.

Experimental procedures and NMR spectra for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Zhu-Jun Yao − *State Key Laboratory of Coordination Chemistry and Jiangsu Key Laboratory of Advanced Organic Materials, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing, Jiangsu 210023, China;* orcid.org/0000-0002-6716-4232; Email: yaoz@nju.edu.cn

Authors

Lin-Rui Zhong − *State Key Laboratory of Coordination Chemistry and Jiangsu Key Laboratory of Advanced Organic Materials, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing, Jiangsu 210023, China*

Bing-Bing Huang − *State Key Laboratory of Coordination Chemistry and Jiangsu Key Laboratory of Advanced Organic Materials, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing, Jiangsu 210023, China*

Xiao-Liang Yang − *State Key Laboratory of Coordination Chemistry and Jiangsu Key Laboratory of Advanced Organic Materials, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing, Jiangsu 210023, China*

Shaozhong Wang − *State Key Laboratory of Coordination Chemistry and Jiangsu Key Laboratory of Advanced Organic Materials, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing, Jiangsu 210023, China;* orcid.org/0000-0002-7766-4433

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00977

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financially support from the National Key Research and Development Program (2018YFC0310900), the National Natural Science Foundation of China (21532002, 21761142001, and 21778031), and the Shenzhen Science and Technology Program (KQTD20190929174023858) are greatly appreciated.

■ REFERENCES

(1) Bödeker, K. Lycopodin, das erste Alkaloid der Gefässkryptogamen. *Justus Liebigs Ann. Chem.* **1881**, *208*, 363−367.

(2) For recent reviews of *Lycopodium* alkaloids, see: (a) Ma, X.-Q.; Gang, D.-R. The *Lycopodium* alkaloids. *Nat. Prod. Rep.* **2004**, *21*, 752−772. (b) Kobayashi, J.; Morita, H. The *Lycopodium* Alkaloids. In *The Alkaloids: Chemistry and Biology*, Vol. *61*; Cordell, G. A., Ed.; Academic Press: NY, New York, 2005; pp 1−57;. (c) Morita, H.; Hirasawa, Y.; Kobayashi, J. The *Lycopodium* Alkaloids. *Heterocycles* **2009**, *77*, 679−729. (d) Siengalewicz, P.; Mulzer, J.; Rinner, U. *Lycopodium* Alkaloids − Synthetic Highlights and Recent Developments. In *The Alkaloids: Chemistry and Biology*, Vol. *72*; Knölker, H.-J., Ed.; Academic Press: NY, New York, 2013, 1−151. (e) Wang, X.-M.; Li, H.-H.; Lei, X.-G. Challenges and Strategies to the Total Syntheses of Fawcettimine-Type and Serratinine-Type *Lycopodium* Alkaloids. *Synlett* **2013**, *24*, 1032−1043. (f) Murphy, R. A.; Sarpong, R. Heathcock-Inspired Strategies for the Synthesis of Fawcettimine-Type *Lycopodium* Alkaloids. *Chem. - Eur. J.* **2014**, *20*, 42−56. (g) Zhong, L.-R.; Yao, Z.-J. Michael addition-based cyclization strategy in the total synthesis of *Lycopodium* alkaloids. *Sci. China: Chem.* **2016**, *59*, 1079−1087. (h) Xiao, C.-X.; Cao, L.; Wang, J.; Miao, Y. L.; Fan, C.-A. Advances in the Collective Synthesis of *Lycopodium* Alkaloids. *Youji Huaxue* **2017**, *37*, 810−823. (i) Li, H.-H.; Lei, X.-G. Fawcettimine-Type *Lycopodium* Alkaloids as a Driving Force for Discoveries in Organic Synthesis. *Chem. Rec.* **2018**, *18*, 543−554.

(3) (a) Heathcock, C. H.; Smith, K. M.; Blumenkopf, T. A. Total synthesis of (±)-fawcettimine (Burnell's base A). *J. Am. Chem. Soc.* **1986**, *108*, 5022−5024. (b) Heathcock, C. H.; Blumenkopf, T. A.; Smith, K. M. Total synthesis of (±)-fawcettimine. *J. Org. Chem.* **1989**, *54*, 1548−1562.

(4) For selected total syntheses of fawcettimine-type *Lycopodium* alkaloids via Heathcock intermediates, see: (a) Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. Total synthesis of (±)-Fawcettimine. *Angew. Chem., Int. Ed.* **2007**, *46*, 7671−7673. (b) Liu, K.-M.; Chau, C.-M.; Sha, C.-K. Intermolecular radical addition reactions of α-iodo cycloalkenones and a synthetic study of the formal synthesis of enantiopure fawcettimine. *Chem. Commun.* **2008**, 91−93. (c) Otsuka, Y.; Inagaki, F.; Mukai, C. Total Syntheses of (+)-Fawcettimine and (+)-Lycoposerramine-B. *J. Org. Chem.* **2010**, *75*, 3420−3426. (d) Jung, M. E.; Chang, J. J. Enantiospecific Formal Total Synthesis of (+)-Fawcettimine. *Org. Lett.* **2010**, *12*, 2962−2965. (e) Nakayama,

A.; Kogure, N.; Kitajima, M.; Takayama, H. Asymmetric Total Synthesis of a Pentacyclic *Lycopodium* Alkaloid: Huperzine-Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 8025−8028. (f) Yang, Y.-R.; Shen, L.; Huang, J.-Z.; Xu, T.; Wei, K. Application of the Helquist Annulation in *Lycopodium* Alkaloid Synthesis: Unified Total Syntheses of (−)-8-Deoxyserratinine, (+)-Fawcettimine, and (+)-Lycoflexine. *J. Org. Chem.* **2011**, *76*, 3684−3690. (g) Pan, G. J.; Williams, R. M. Unified Total Syntheses of Fawcettimine Class Alkaloids: Fawcettimine, Fawcettidine, Lycoflexine, and Lycoposerramine B. *J. Org. Chem.* **2012**, *77*, 4801−4811. (h) Li, H.-H.; Wang, X.-M.; Lei, X.-G. Total Syntheses of *Lycopodium* Alkaloids (+)-Fawcettimine, (+)-Fawcettidine, and (−)-8-Deoxyserratinine. *Angew. Chem., Int. Ed.* **2012**, *51*, 491−495. (i) Itoh, N.; Iwata, T.; Sugihara, H.; Inagaki, F.; Mukai, C. Total Syntheses of (±)-Fawcettimine, (±)-Fawcettidine, (±)-Lycoflexine, and (±)-Lycoposerramine-Q. *Chem. - Eur. J.* **2013**, *19*, 8665−8672. (j) Zaimoku, H.; Taniguchi, T. Redox Divergent Synthesis of Fawcettimine-Type *Lycopodium* Alkaloids. *Chem. - Eur. J.* **2014**, *20*, 9613−9619. (k) Xu, K.; Cheng, B.; Li, Y.; Xu, T. T.; Yu, C. M.; Zhang, J.; Ma, Z. Q.; Zhai, H. B. Stereocontrolled Total Syntheses of (±)-Fawcettimine, (±)-Lycoflexine, and (±)-Lycoflexine N-Oxide. *Org. Lett.* **2014**, *16*, 196−199. (l) Leger, P. R.; Murphy, R. A.; Pushkarskaya, E.; Sarpong, R. Synthetic Efforts toward the *Lycopodium* Alkaloids Inspires a Hydrogen Iodide Mediated Method for the Hydroamination and Hydroetherification of Olefins. *Chem. - Eur. J.* **2015**, *21*, 4377−4383. (m) Hong, B.-K.; Li, H.; Wu, J.-B.; Zhang, J.; Lei, X.-G. Total Syntheses of (−)-Huperzine Q and (+)-Lycopladines B and C. *Angew. Chem., Int. Ed.* **2015**, *54*, 1011−1015. (n) Tanimura, S.; Yokoshima, S.; Fukuyama, T. Total Synthesis of Huperzine Q. *Org. Lett.* **2017**, *19*, 3684−3686.

(5) Kozak, G. J. A.; Dake, R. Total Synthesis of (+)-Fawcettidine. *Angew. Chem., Int. Ed.* **2008**, *47*, 4221−4223.

(6) (a) Zhang, X.-M.; Tu, Y.-Q.; Zhang, F.-M.; Shao, H.; Meng, X. Total Synthesis of (±)-Alopecuridine and Its Biomimetic Transformation into (±)-Sieboldine A. *Angew. Chem., Int. Ed.* **2011**, *50*, 3916−3919. (b) Zhang, X. M.; Shao, H.; Tu, Y. Q.; Zhang, F. M.; Wang, S. H. Total Syntheses of (+)-Alopecuridine, (+)-Sieboldine A, and (−)-Lycojapodine A. *J. Org. Chem.* **2012**, *77*, 8174−8181.

(7) Hou, S.-H.; Tu, Y.-Q.; Liu, L.; Zhang, F.-M.; Wang, S.-H.; Zhang, X.-M. Divergent and Efficient Syntheses of the Lycopodium Alkaloids (−)-Lycojaponicumin C, (−)-8-Deoxyserratinine, (+)-Fawcettimine, and (+)-Fawcettidine. *Angew. Chem., Int. Ed.* **2013**, *52*, 11373−11376.

(8) Zhong, L.-R.; Yang, Y.-J.; Huang, B.-B.; Yao, Z.-J. An Eight-Step Total Synthesis of Pyrroloquinolone-Type *Lycopodium* Alkaloid via a Tandem Annulation Approach. *Chin. J. Chem.* **2020**, *38*, 1560−1564.

(9) Li, H.-H.; Wang, X.-M.; Hong, B.-K.; Lei, X.-G. Collective Synthesis of *Lycopodium* Alkaloids and Tautomer Locking Strategy for the Total Synthesis of (−)-Lycojapodine A. *J. Org. Chem.* **2013**, *78*, 800−821.

(10) For selected methodologies for spirocyclic pyrrolidines, see: (a) Zhuo, C.-X.; Cheng, Q.; Liu, W.-B.; Zhao, Q.; You, S.-L. Enantioselective Synthesis of Pyrrole-Based Spiro- and Polycyclic Derivatives by Iridium-Catalyzed Asymmetric Allylic Dearomatization and Controllable Migration Reactions. *Angew. Chem., Int. Ed.* **2015**, *54*, 8475−8479. (b) Clarke, A. K.; James, M. J.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. Silica-Supported Silver Nitrate as a Highly Active Dearomatizing Spirocyclization Catalyst: Synergistic Alkyne Activation by Silver Nanoparticles and Silica. *Angew. Chem., Int. Ed.* **2016**, *55*, 13798−13802. (c) Saruengkhanphasit, R.; Collier, D.; Coldham, I. Synthesis of Spirocyclic Amines by Using Dipolar Cycloadditions of Nitrones. *J. Org. Chem.* **2017**, *82*, 6489−6496. (d) Wang, Y. Y.; Bode, J. W. Olefin Amine (OLA) Reagents for the Synthesis of Bridged Bicyclic and Spirocyclic Saturated N-Heterocycles by Catalytic Hydrogen Atom Transfer (HAT) Reactions. *J. Am. Chem. Soc.* **2019**, *141*, 9739−9745. (e) Lepovitz, L. T.; Martin, S. F. Diversity-Oriented Synthesis of Bioactive Azaspirocycles. *Tetrahedron* **2019**, *75*, 130637. (f) Lee, S.; Lei, H.; Rovis, T. A Rh(III)-Catalyzed Formal [4 + 1] Approach to Pyrrolidines from Unactivated Terminal Alkenes and Nitrene Sources. *J. Am. Chem. Soc.* **2019**, *141*, 12536−12540. (g) Flodén, N. J.; Trowbridge, A.; Willcox, D.; Walton, S. M.; Kim, Y.; Gaunt, M. J. Streamlined Synthesis of C(sp^3)-Rich *N*-Heterospirocycles Enabled by Visible-Light-Mediated Photocatalysis. *J. Am. Chem. Soc.* **2019**, *141*, 8426−8430. (h) Sveiczer, A.; North, A. J. P.; Mateu, N.; Kidd, S. L.; Sore, H. F.; Spring, D. R. Spirocycles as Rigidified sp^3-Rich Scaffolds for a Fragment Collection. *Org. Lett.* **2019**, *21*, 4600−4604. (i) Espinosa, M.; Noda, H.; Shibasaki, M. Synthesis of Unprotected Spirocyclic β-Prolines and β-Homoprolines by Rh-Catalyzed C−H Insertion. *Org. Lett.* **2019**, *21*, 9296−9299. (j) Lin, S.; Chen, Y.; Li, F.; Shi, C.; Shi, L. Visible-light-driven spirocyclization of epoxides via dual titanocene and photoredox catalysis. *Chem. Sci.* **2020**, *11*, 839−844. (k) Uyanik, M.; Sahara, N.; Katade, O.; Ishihara, K. Chemoselective Oxidative Spiroetherification and Spiroamination of Arenols Using I^+/Oxone Catalysis. *Org. Lett.* **2020**, *22*, 560−564. (l) Wang, Y. H.; Tian, J.-S.; Tan, P.-W.; Cao, Q.; Zhang, X.-X.; Cao, Z.-Y.; Zhou, F.; Wang, X.; Zhou, J. Regiodivergent Intramolecular Nucleophilic Addition of Ketimines for the Diverse Synthesis of Azacycles. *Angew. Chem., Int. Ed.* **2020**, *59*, 1634−1643. (m) Shennan, B. A.; Smith, P. W.; Ogura, Y.; Dixon, D. J. A modular and divergent approach to spirocyclic pyrrolidines. *Chem. Sci.* **2020**, *11*, 10354−10360.

(11) Ge, H.-M.; Zhang, L.-D.; Tan, R.-X.; Yao, Z.-J. Protecting Group-Free Total Synthesis of (−)-Lannotinidine B. *J. Am. Chem. Soc.* **2012**, *134*, 12323−12325.

(12) (*R*)-5-Methylcyclohex-2-enone (**16**) is commercially available or can be prepared according to the following: Fleming, I.; Maiti, P.; Ramarao, C. Stereocontrol of 1,5-related stereocentres using an intermediate silyl group—the diastereoselectivity of nucleophilic attack on a double bond adjacent to a stereogenic centre carrying a silyl group. *Org. Biomol. Chem.* **2003**, *1*, 3989−4004.

(13) Iradier, F.; Arrayas, R. G.; Carretero, J. C. Synthesis of Medium-Sized Cyclic Amines by Selective Ring Cleavage of Sulfonylated Bicyclic Amines. *Org. Lett.* **2001**, *3*, 2957−2960.

(14) We tested a considerable number of influence factors on this dehydration reaction, but few worked. We suspect that the steric hindrance of substrate **24** might be unfavorable for imine formation, while the resulting imine **25** shows a higher reactivity under some tested conditions, such as the imine- or enamine-driven intramolecular nucleophilic attack to the ester under most base, acid, Lewis acid, heating, or microwave irradiation conditions.

(15) (a) Shono, T.; Kise, N.; Kunimi, N.; Nomura, R. Electroreductive Coupling of Aromatic Imines and Electrophiles in the Presence of Chlorotrimethylsilane. *Chem. Lett.* **1991**, *20*, 2191−219. (b) Kise, N.; Ohya, K.; Arimoto, K.; Yamashita, Y.; Hirano, Y.; Ono, T.; Ueda, N. Electroreductive Intramolecular Coupling of Aromatic β- and γ-Imino Esters: A New Synthetic Method for N-Alkoxycarbonyl-2-aryl-3-ones and *cis*-2-Aryl-3-ols of Pyrrolidines and Piperidines. *J. Org. Chem.* **2004**, *69*, 7710−7719. (c) Kise, N.; Morimoto, S. Electroreductive acylation of aromatic imines with acylimidazoles. *Tetrahedron* **2008**, *64*, 1765−1771. (d) Takenaga, Y.; Umesaki, Y.; Sakurai, T.; Kise, N. Electroreductive five- and six-membered cyclization of aromatic β- and γ-imino esters derived from (*S*)-aspartic acid and (*S*)-glutamic acid. *Tetrahedron* **2012**, *68*, 2579−2589. (e) Shimizu, M.; Takao, Y.; Katsurayama, H.; Mizota, I. Synthesis of Indolin-3-ones and Tetrahydro-4-quinolones from α-Imino Esters. *Asian J. Org. Chem.* **2013**, *2*, 130−134. (f) Shimizu, M.; Katsurayama, H.; Mizota, I.; Zhu, Y. A Facile Synthesis of 2-Methyl-3-oxoindoline-2-carboxylates Utilizing Aza-Brook Rearrangement as a Crucial Step. *J. Heterocycl. Chem.* **2019**, *56*, 2479−2486.

(16) Selected reviews and applications of lithium arenides, see: (a) Yus, M.; Martinez, P.; Guijarro, A. Direct Transformation of Allylic and Benzylic Thiols, Thioethers, and Disulfides into Organolithium Compounds. *Synth. Commun.* **2003**, *33*, 2365−2376. (b) Yus, M.; Moreno, B.; Foubelo, F. Reductive ring opening of oxygen-containing benzo-fused heterocycles by an arene-catalysed lithiation. *Synthesis* **2004**, *7*, 1115−1118. (c) Yang, A.; Butela, H.; Deng, K.; Doubleday, M. D.; Cohen, T. Organolithiums by reductive lithiation: the catalytic aromatic method versus the use of preformed aromatic radical-anions. Naphthalene can behave as a catalyst or an inhibitor.

https://doi.org/10.1021/acs.orglett.1c00977
Org. Lett. 2021, 23, 3578−3583

Tetrahedron **2006**, *62*, 6526−6535. (d) Rees, N. V.; Baron, R.; Kershaw, N. M.; Donohoe, T. J.; Compton, R. G. Alkali Metal Reductions of Organic Molecules: Why Mediated Electron Transfer from Lithium Is Faster than Direct Reduction. *J. Am. Chem. Soc.* **2008**, *130*, 12256−12257. (e) Nador, F.; Moglie, Y.; Ciolino, A.; Pierini, A.; Dorn, V.; Yus, M.; Alonso, F.; Radivoy, G. Direct reductive amination of aldehydes using lithium-arene(cat.) as reducing system. A simple one-pot procedure for the synthesis of secondary amines. *Tetrahedron Lett.* **2012**, *53*, 3156−3160. (f) Xuan, M. Y.; Paterson, I.; Dalby, S. M. Total Synthesis of Alotaketal A. *Org. Lett.* **2012**, *14*, 5492−5495. (g) Hill, R. R.; Rychnovsky, S. D. Generation, Stability, and Utility of Lithium 4,4'-Di-*tert*-butylbiphenylide (LiDBB). *J. Org. Chem.* **2016**, *81*, 10707−10714. (h) Kock, M.; Jones, P. G.; Lindel, T. Total Synthesis and Absolute Configuration of Raputindole A. *Org. Lett.* **2017**, *19*, 6296−6299. (i) Han, A.; Tao, Y. J.; Reisman, S. A 16-step synthesis of the isoryanodane diterpene (+)-perseanol. *Nature* **2019**, *573*, 563−567. (j) Xu, C.; Han, A.; Virgil, S. C.; Reisman, S. E. Chemical Synthesis of (+)-Ryanodine and (+)-20-Deoxyspiganthine. *ACS Cent. Sci.* **2017**, *3*, 278−282.

https://doi.org/10.1021/acs.orglett.1c00977
Org. Lett. 2021, 23, 3578−3583