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Application of the Helquist Annulation in *Lycopodium* Alkaloid Synthesis: Unified Total Syntheses of (−)-8-Deoxyserratinine, (+)-Fawcettimine, and (+)-Lycoflexine

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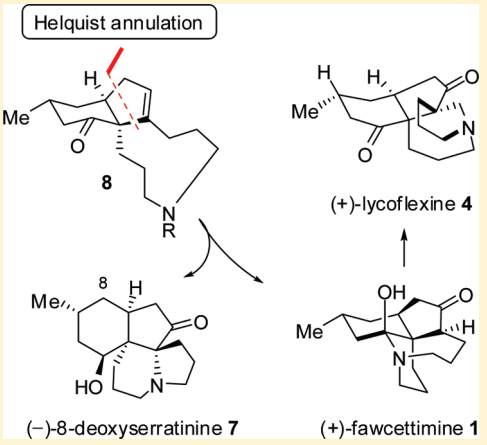
Supporting Information

ABSTRACT: A unified strategy for total synthesis of the *Lycopodium* alkaloids (−)-8-deoxyserratinine (**7**), (+)-fawcettimine (**1**), and (+)-lycoflexine (**4**) is detailed. The key features include a highly efficient Helquist annulation to assemble the cis-fused 6/5 bicycle, facile construction of the aza nine-membered ring system employing double N-alkylation strategy, providing access to the common tricyclic skeleton, asymmetric Shi epoxidation, delivering the desired β-epoxide stereospecifically to furnish (−)-8-deoxyserratinine (**7**), SmI_2 reduction of dihydroxylation derivative **35** to enable formation of (+)-fawcettimine (**1**), and a rapid biomimetic transformation of (+)-fawcettimine (**1**) into (+)-lycoflexine (**4**) via an intramolecular Mannich cyclization.



INTRODUCTION

The *Lycopodium* alkaloids are a diverse group of structurally complex natural products.[1] Owing both to their appealing, synthetically challenging polycyclic systems with a dense stereochemical array and wide-ranging biological activities, a wealth of total syntheses of *Lycopodium* alkaloids have been reported.[2] Among the known *Lycopodium* alkaloids, fawcettimine (**1**), alopecuridine (**2**), serratinine (**3**), and lycoflexine (**4**) are noteworthy due to their unique tetracyclic structures containing two contiguous quaternary stereocenters and the interesting biogenetic interconnections within this intriguing family. Fawcettimine (**1**) (Figure 1),[3] one of the parent members of *Lycopodium* alkaloids, was first isolated by Burnell in 1959. Since the first synthesis by Inubushi in 1979,[4] a number of other syntheses have been reported.[5] One of the seminal works in this regard came from the Heathcock group.[5a,b] They reported a protecting-group-free synthesis and investigated thoroughly the relationship of tautomeric ring−chain equilibria between keto carbinolamines and the corresponding diketo amines. In Toste's recent asymmetric synthesis of fawcettimine,[5c] a signature gold(I)-catalyzed cyclization to form the 6/5 bicycle was utilized successfully. Alopecuridine (**2**), the C-4 hydroxy derivative of fawcettimine (**1**), was isolated by Ayer in 1974.[6] However, alopecuridine is almost identical to fawcettimine but for a hydroxy group at C-4, which is known to be removed by reduction with calcium in ammonia; the total synthesis of alopecuridine has not been achieved to date.

Serratinine (**3**),[7] like fawcettimine, is another important *Lycopodium* alkaloid. The complicated stereochemistry within its unique skeleton renders it a synthetic challenge. The first total syntheses of serratinine (**3**) and 8-deoxyserratinine (**7**) were accomplished in racemic forms by the Inubushi group in 1974 and 1979, respectively.[8] Very recently, we have successfully achieved the first asymmetric total synthesis of (−)-8-deoxyserratinine (**7**) via a novel efficient route by which some of the critical issues such as synthetic efficiency and selectivity have been improved remarkably compared to its previous route.[9] Lycoflexine (**4**),[10] an unusual 17-carbon *Lycopodium* alkaloid possessing a carbon−nitrogen skeleton differing from those of other members of the fawcettimine class, was first isolated by the Ayer group in 1973. Lycoflexine (**4**) differs from fawcettimine (**1**) in that the nitrogen and C-4 are linked through a methylene bridge. Ayer proposed that a transannular Mannich cyclization of fawcettimine (**1**) could afford lycoflexine (**4**) along biogenetic lines. Of the aforementioned alkaloids,

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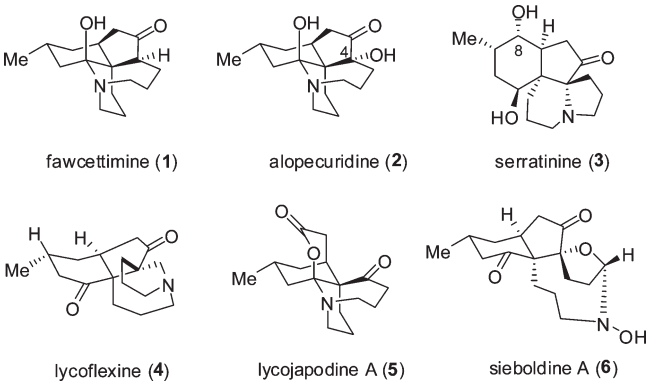
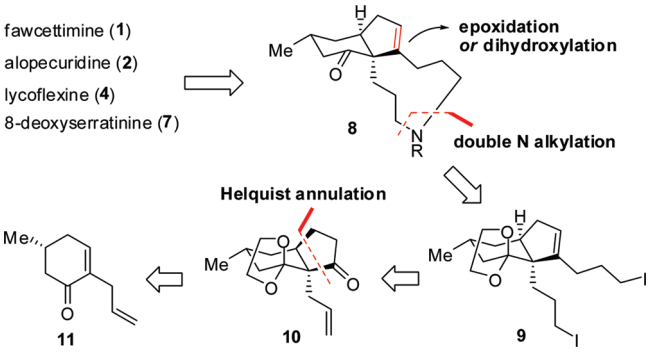


Figure 1. Structures of some *Lycopodium* alkaloids.

Scheme 1. Retrosynthetic Analysis of 8-Deoxyserratinine (7), Alopecuridine (2), Fawcettimine (1), and Lycoflexine (4)

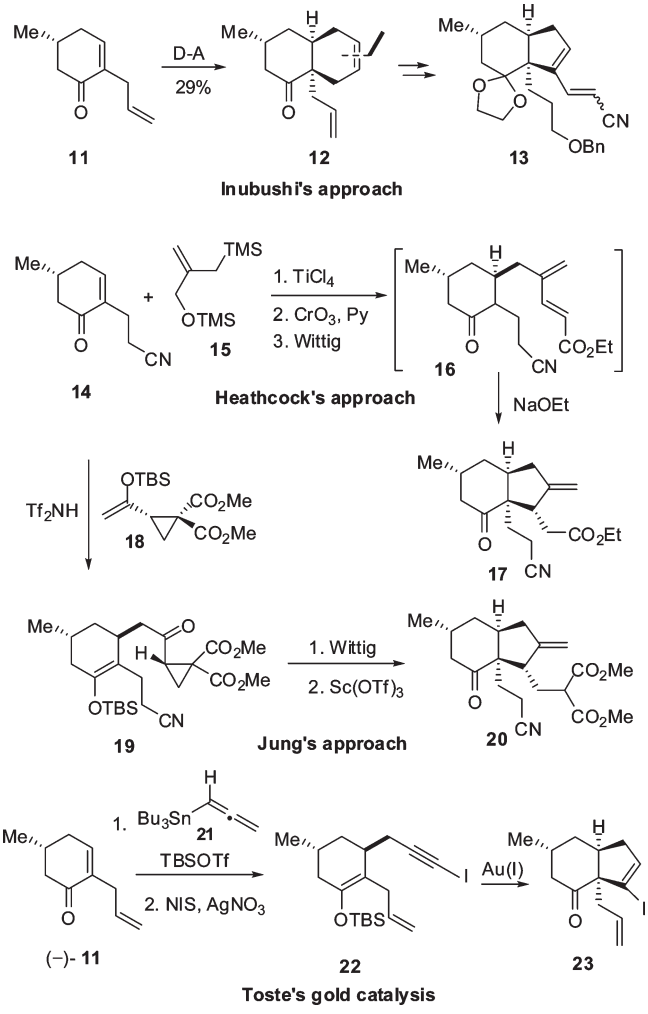


alopecuridine (**2**) was initially believed to be the cornerstone of our research program in terms of synthetic diversity. We confidently expected that both fawcettimine (**1**) and lycoflexine (**4**) could be achieved via facile deoxygenation at C-4 of alopecuridine (**2**). Moreover, we considered that if we accomplished the synthesis of alopecuridine (**2**), then the biomimetic syntheses of novel alkaloids sieboldine A (**6**)[11] and lycojapodine A (**5**)[12] would be possible because alopecuridine (**2**) is their logical biosynthetic precursor, thereby allowing accessibility to a maximal diversity of *Lycopodium* alkaloids. To this end, a flexible and general strategy is needed. Fortunately, we found that our developed strategy for (−)-8-deoxyserratinine (**7**) could well serve this purpose. In this full account, we describe our efforts in this regard, which culminated in the unified total syntheses of (−)-8-deoxyserratinine (**7**), (+)-fawcettimine (**1**), and (+)-lycoflexine (**4**).

RESULTS AND DISCUSSION

Retrosynthetic Analysis of 8-Deoxyserratinine (7), Alopecuridine (2), Fawcettimine (1), and Lycoflexine (4). Our synthetic design is outlined in Scheme 1. We proposed to acquire the four alkaloids from a common advanced intermediate **8**. The C−C double bond of tricycle **8** is the pivot of our unified strategy because it was envisioned either to be converted into an epoxide by which a cascade epoxide-opening reaction can take place to install the tetracyclic system of 8-deoxyserratinine (**7**), or to be dihydroxylated to yield alopecuridine (**2**). As we discussed above, alopecuridine (**2**) was an ideally versatile natural product en route to other members of this family from the standpoint of synthetic

Scheme 2. Representative Synthetic Strategies for Hydrindanone of *Lycopodium* Alkaloids



diversity. The key aza nine-membered ring of **8** was expected to be constructed by double N-alkylations of the bisiodide compound **9** with a nitrogen atom.[13] The iodo side chains of **9** were envisioned to arise from bisallyl substitutes. The hydrindanone core of **10** would be forged through the Helquist annulation[14] of known 2-allyl-5-methyl-cyclohex-2-en-1-one (**11**).

Synthesis of Hydrindanone 6/5 Bicyclic System. Given the importance of hydrindanone motif to the strategic planning, various methods for its synthesis have been devised. It is necessary to summarize them briefly prior to introduction of our work. As shown in Scheme 2, in Inubushi's pioneering synthesis,[4] they recognized the possibility to control the stereochemistry of the challenging quaternary stereocenter of **12** by using a Diels−Alder addition between butadiene and racemic 2-allyl-5-methyl-cyclohex-2-en-1-one (**11**) (29% yield). Scission of the double bond of the newly formed six-membered ring of **12** followed by reclosure of the five-membered ring via aldol and Wadsworth−Emmons reaction afforded substituted 6/5 bicycle **13**. In Heathcock's approach,[5a,b] Hosomi−Sakurai reaction of cyano enone **14** with bis-silane **15** provided an adduct intermediate (not shown) that underwent oxidation and Wittig condensation to produce dienoate **16**. Intermediate **16** was treated with ethanolic sodium ethoxide, leading to 6/5 bicyclic system **17** via an intramolecular

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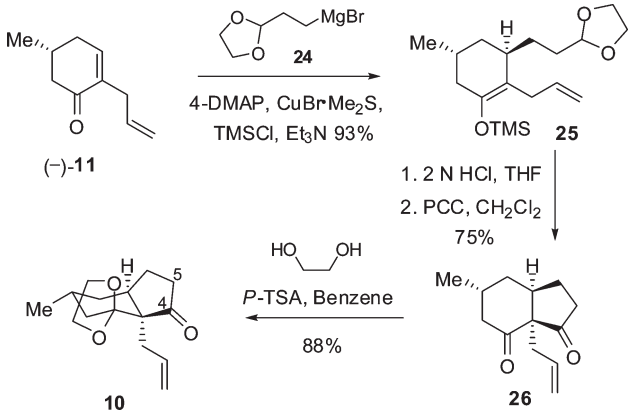
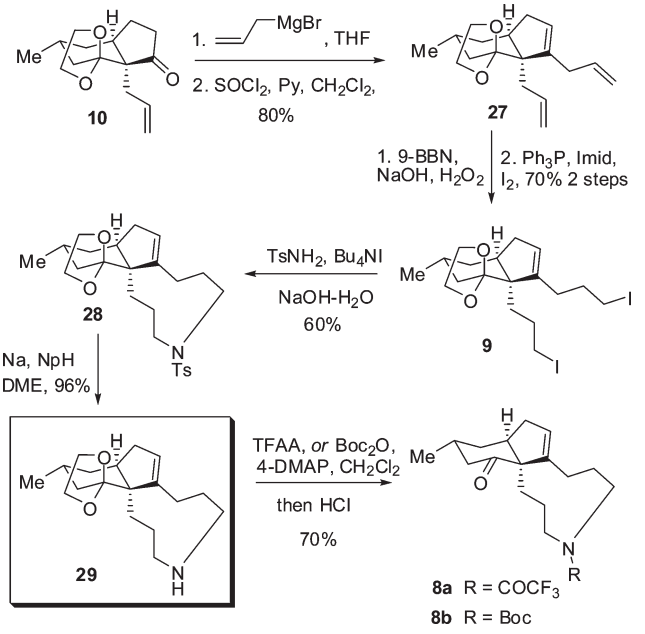
Scheme 3. Our Application of the Helquist Annulation in Cis 6/5 Bicycle Synthesis



Michael reaction. Very recently, Jung and co-workers reported a formal synthesis of fawcettimine based on Heathcock's results.[5e] In the Jung route, cyano enone **14** and silyl enol ether **18** were treated with triflimide to give ketone **19** stereospecifically. Wittig methenylation of **19** afforded the olefin (not shown), which was transformed into 6/5 bicyclic annulation product **20** through cyclopropane ring-opening under $Sc(OTf)_3$ conditions. Another synthetic approach toward hydrindanone has been reported by Toste et al. recently,[5c] who employed a sequence of conjugated propargylation, acetylene iodination, and gold(I)-catalyzed cyclization to construct hydrindanone derivative **23** in their elegant total synthesis of (+)-fawcettimine.

Our solution to this hydrindanone was originally inspired by Helquist's work, who developed a methodology for bicyclic annulation via copper-catalyzed conjugated addition of an acetal-containing Grignard reagent. To our knowledge, Helquist annulation was still an underutilized approach for the synthesis of polycyclic systems, and prior to us there had been no one who enlisted it to construct the framework of *Lycopodium* alkaloids. As outlined in Scheme 3, our synthesis began with (−)-2-allyl-5-methyl-cyclohex-2-en-1-one (**11**), which could be prepared in multigram quantities according to a known procedure.[15] With this enone in hand, we then tried the Helquist annulation and were gratified to find it was very successful. Conjugate addition of the acetal-containing Grignard reagent **24** derived from 2-(2- bromoethyl)-1,3-dioxolane to enone **11** performed well to provide trans silyl enol ether **25** diastereoselectively (93%). This enol ether, upon treatment with warm 2 N HCl, successfully underwent cascade desilylation, acetal hydrolysis, and intramolecular aldol cyclization to give a separable 2.5:1 mixture of cis-fused 6/5 alcohols (75%) having the correct configuration of the quaternary stereocenter. Oxidation of a mixture of the Helquist annulation products with PCC followed by brief treatment with ethylene glycol via azeotropic distillation afforded selectively protected cyclic acetal **10**, in which the carbonyl group within the cyclopentanone ring was untouched (88%). In contrast to prior precedents, our Helquist annulation strategy still has some merits: it is stereospecific, and the product diketone **26** contains all the desired stereochemistry. Further, the derivative **10** has a versatile cyclopentanone functionality, which can serve a dual purpose as an efficient cross-coupling part via enol triflation (equivalent to vinyl iodide **23**) or as a substrate for organometallic reagent 1,2-addition (i.e., allylmagnesium bromide) to elongate the side chain.

Scheme 4. Synthesis of Common Aza Tricyclic Intermediates 8



Synthesis of Common Aza Tricyclic Intermediates 8. As outlined in Scheme 4, allyl bromide Grignard reagent attacked the cyclopentanone **10**, providing the carbinol (not shown) in quantitative yield, which was subsequently exposed to thionyl chloride/pyridine and was dehydrated readily with complete regioselectivity, furnishing the endocyclic olefin **27** as the only product (80%). Prior to closure of the critical aza nine-membered ring, the key intermediate bisiodide **9** was prepared through iodination of the two corresponding terminal hydroxyl groups, which were obtained via selective hydroboration of the triene **27** with 9-BBN (70%, two steps) (Scheme 4). Through treatment of this bisiodide with $TsNH_2$ as the nucleophilic nitrogen source in the presence of Bu_4NI and NaOH in refluxing benzene, a smooth double N-alkylative ring closure was realized in a respectable 60% yield.[16]Removal of the tosyl group of **28** was effected by the use of sodium naphthalenide as reducing agent, providing amine **29** nearly quantitatively.[17] This amine is another key compound for our strategic flexibility. Trifluoroacetylation or Boc-protection of this amine and subsequent cleavage of the cyclic acetal could be carried out in one pot and afforded keto trifluoroacetyl amide **8a** and carbamate **8b**, respectively, in 70% yield.

Completion of Synthesis of (−)-8-Deoxyserratinine (7). With keto trifluoroacetyl amide **8a** in hand, the stage was now set for the challenging selective epoxidation. However, as demonstrated in Inubushi's synthesis, this manipulation posed a problem, as the standard *m*-CPBA procedure provided only minor amounts of β-epoxide **31** accompanied by its α-isomer as the predominant product.[18] This stereochemical outcome can be attributed to approach of the reagent from the convex face of the tricyclic system. After considerable efforts, it was found that this issue could be addressed satisfactorily through Shi asymmetric epoxidation with Shi D-fructose-derived catalyst **30**.[19] A complete stereoselective epoxidation took place to provide the desired β-epoxide **31** as the sole product in 60% yield along with the recovered starting material **8a** (96% yield, brsm). For completion of the 8-deoxyserratinine, the β-epoxide **31** was converted into

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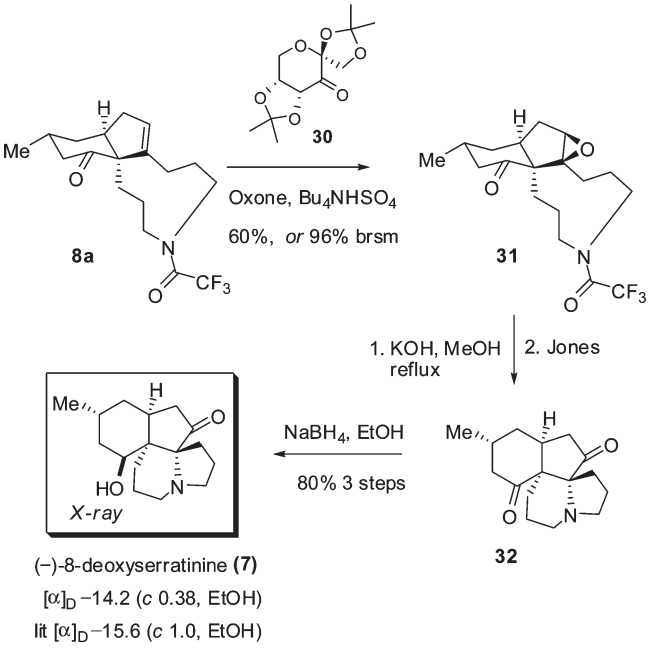
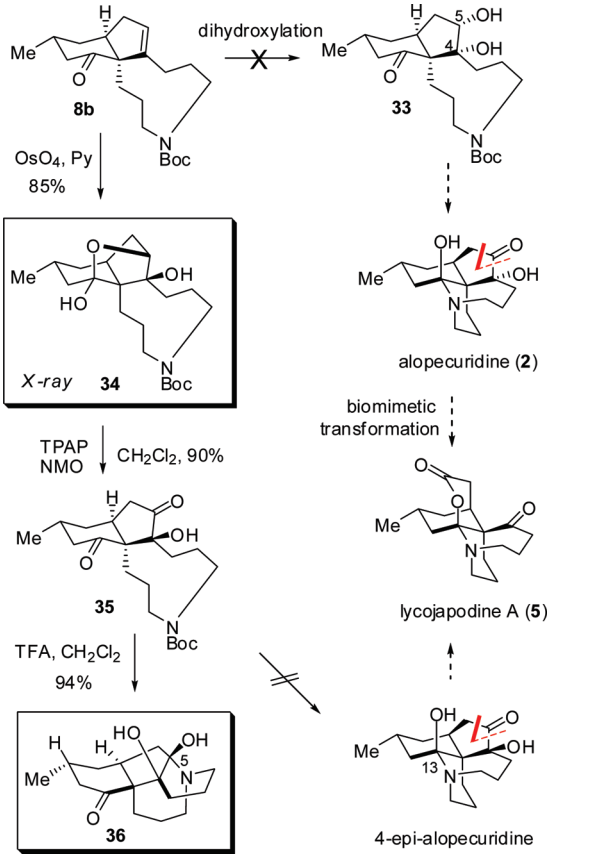
Scheme 5. Synthesis of (−)-8-Deoxyserratinine (7)



tetracyclic diketone **32** via Inubushi's protocol, that is, tandem cleavage of trifluoroacetamide and intramolecular epoxide ring-opening reaction to furnish tetracyclic amino alcohol (not shown) in a refluxing methanolic KOH solution and subsequent Jones oxidation of the amino alcohol intermediate. At this stage, we were pleased to find our diketone **32** was identical with the literature compound,[20] which was obtained from the degradation of natural (−)-serratinine (see Supporting Information). Selective reduction of the carbonyl functionality of the six-membered ring through careful addition of 2 equiv of $NaBH_4$ at 0 °C was realized, providing 8-deoxyserratinine (**7**). The synthetic 8-deoxyserratinine (**7**) exhibited a rotation of −14.2 (*c* 0.38, EtOH), essentially identical to that of the natural substance,[21] and its structure was again secured by single-crystal X-ray analysis (see Supporting Information). Therefore, the absolute configuration of 8-deoxy serratinine (**7**) has been established as shown in Scheme 5.

Attempted Synthesis of Alopecuridine (2) and 4-*epi*-Alopecuridine. For installation of the two oxygen atoms at the C4−C5 bond of alopecuridine (**2**), cis-dihydroxylation of the double bond of C4−C5 was expected. As shown in Scheme 6, this routine transformation initially proved difficult in substrate **8b** and its analogues[22] because the double bond of C4−C5 was resistant to attack by oxidative reagents, presumably because of strong steric shielding exerted by the aza nine-membered ring. Eventually, use of pyridine as solvent with stoichimetric OsO_4 proved effective. To our surprise, the product was not the desired diol **33**. The configuration of the C-4 was incorrect compared to that of alopecuridine (**2**), and simultaneously the lactol was cyclized in the course of dihydroxylation. Single-crystal X-ray analysis (see the Supporting Information) confirmed our structural elucidation. To invert the selectivity of dihydroxylation and avoid the lactol formation, exposure of the corresponding cyclic acetal of **8b** to analogous conditions provided no observable product even at elevated temperature and prolonged reaction time. This rigid tetracyclic lactol framework of **34** was quite stable and inert to several oxidative reagents. Fortunately, Ley oxidation (TPAP, NMO) afforded tricyclic diketone **35** in 90% yield.[23]

Scheme 6. Attempted Synthesis of Alopecuridine (2) and 4-*epi*-Alopecuridine



The resulting diketone **35**, after removal of the Boc group with TFA, would be expected to give 4-*epi*-alopecuridine via carbinolamine formation at C-13 (Scheme 6). At the outset, we did not notice another possibility of carbinolamine formation at C-5 of cyclopentanone and then tried the oxidative cleavage for the synthesis of lycojapodine A but with no success. Later, with the aid of 2D NMR analysis, the correct structure of this cyclization was reassigned as keto carbinolamine **36**. Note that Heathcock's investigation[5b] into the chemoselectivty of carbinoamine formation at cyclopentanone being preferred over that at cyclohexanone for 4-*epi*-fawcettimine is applicable to our 4-*epi*-alopecuridine (see Figure 2).

Completion of the Synthesis of Fawcettimine (1) and Lycoflexine (4). Although the pursuit of alopecuridine (**2**) en route to lycojapodine A (**5**) stopped, as shown in Scheme 7, gratifyingly, SmI_2 reduction of the α-hydroxy ketone **35** gave tricyclic diketone **37** efficiently as we anticipated.[24] The resulting configuration of C-4 of **37** was inconsequential and remained unassigned according to Heathcock's conclusion that the unnatural 4*R* isomer, after removal of Boc group, could also be epimerized and spontaneously cyclized into fawcettimine. The spectral data and optical rotation for the synthetic fawcettimine (**1**) were consistent with those reported in the literature.[25]

With synthetic fawcettimine (**1**) in hand, and inspired by Ayer's hypothesis about the biogenetic pathway of lycoflexine (**4**), we naturally turned our attention to the biomimetic synthesis of lycoflexine (**4**) based on Ayer's proposal of Mannich cyclization.[26] Unlike Ayer's original procedure (acidic aqueous HCHO, 24 h, ca. 50%), we found a better choice for carrying out this reaction (Scheme 8).

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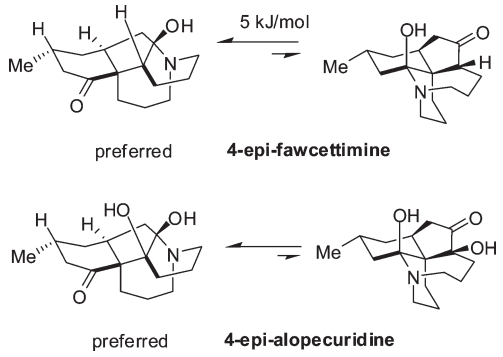
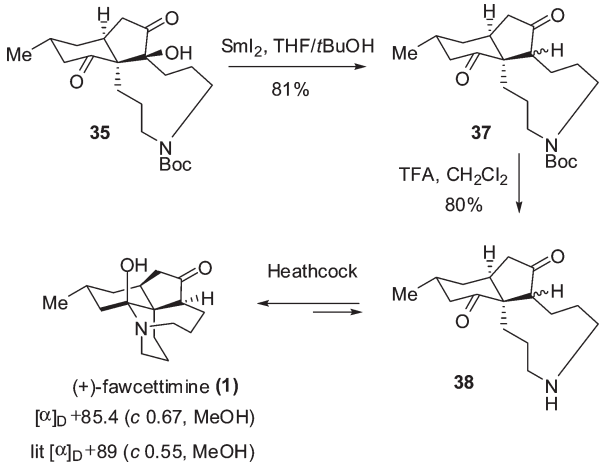
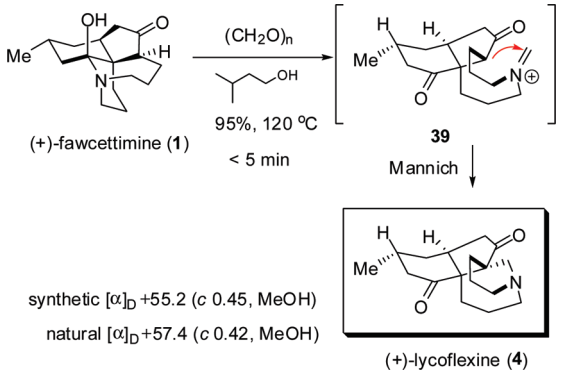


Figure 2. Selectivity of carbinoamine formation for 4-*epi*-fawcettimine and 4-epi-alopecuridine.

Scheme 7. Synthesis of (+)-Fawcettimine (1)



Scheme 8. Biomimetic Synthesis of (+)-Lycoflexine (4)



Upon treatment with paraformaldehyde in heated 3-methylbutan-1-ol (120 °C oil bath),[27] synthetic fawcettimine (**1**) was completely transformed into lycoflexine (**4**) instantly (less than 5 min by TLC monitoring) and cleanly, in 95% isolated yield. The remarkable ease of the transannular Mannich cyclization supports Ayer's working hypothesis of a biomimetic process (Scheme 8). The synthetic lycoflexine (**4**) showed NMR spectra identical to those of authetic sample, generously provided by Prof. Zhao of KIB, which was reisolated in the course of discovery of lycojapodine A (**5**). Our synthetic lycoflexine (**4**) exhibited a rotation of +55.2 (*c* 0.45, MeOH) and was consistent with that of Zhao's sample ([α]$_D$ +57.4, *c* 0.42, MeOH); therefore, the absolute configuration of lycoflexine (**4**) was established.[28]

In summary, we have developed an efficient and general strategy to *Lycopodium* alkaloid synthesis, furnishing (−)-8-deoxyserratinine (**7**), (+)-fawcettimine (**1**), and (+)-lycoflexine (**4**), in which Helquist annulation and double N-alkylations play the key roles in construction of the common framework. Stereospecific Shi epoxidation for 8-deoxyserratinine (**7**) and unexpected dihydroxylation, Ley oxidation, and SmI_2 reduction for fawcettimine (**1**) were utilized. Biomimetic synthesis of (+)-lycoflexine (**4**) is also presented based on a rapid intramolecular Mannich cyclization.

EXPERIMENTAL SECTION

General Methods. All reactions were performed under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled over sodium−potassium alloy. Dichloromethane, toluene, dimethylformamide (DMF), acetonitrile, and benzene were distilled over calcium hydride. Yields refer to chromatographically and spectroscopically homogeneous materials, unless otherwised noted. Reagents were used as received without further purification, unless otherwise stated. Silica gel (200−300 mesh) was used for flash column chromatography. NMR spectra were recorded on 400 or 500 MHz spectrometers and calibrated using undeuterated solvent as an internal reference. IR spectra were recorded with KBr pellets. Optical rotations were determined on a polarimeter. HRMS data were recorded via positive ion electrospray or electron impact mass spectrometry using a time-of-flight analyzer.

Silyl Enol Ether 25. To a stirred mixture containing 1.02 g (42.5 mmol) of fresh magnesium turnings in 16.5 mL of THF were added a small crystal of iodine and then a solution of 2-(2-bromoethyl)-1,3-dioxolane (8.06 g, 44.5 mmol) in 45 mL of THF over 25 min; a water cooling bath was used to maintain the reaction temperature below 25 °C. The resulting Grignard reagent mixture continued to stir for 1 h at rt before being transferred into a stirred precooled mixture of 4-DMAP (5.54 g, 45.4 mmol) and CuBr·Me_2S (0.856 g, 4.1 mmol) in 30 mL of THF at −78 °C via a cannula. Next, the resulting reaction mixture was stirred at −78 °C for 1 h, and then TMSCl (5.6 mL) and a solution of enone **11** (3.07 g, 20.5 mmol) in 30 mL of THF were added dropwise, respectively, at the same temperature. The reaction was allowed to warm slowly to −10 °C over 6 h and finally quenched by addition of 16.8 mL of triethylamine and diluted with 100 mL of petroleum ether and 50 mL of water. The resulting slurry was filtered through Celite, which was washed with petroleum ether and Et_2O (1:1 mixture). The phases were separated, and the aqueous layer was extracted with ether. The combined organic layers were dried with Na_2SO_4 and concentrated. The crude product was purified with flash column chromatography (petroleum ether/ether 100:1, 1% triethylamine) to provide 6.20 g (93%) of **25** as a clear oil: [α]$_D$ = +97.4 (*c* = 0.31, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}) 2953, 2910, 2878, 1675, 1456, 1410, 1251, 1201, 1142, 1037, 842; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.71 (1H, dt, *J* = 17.1, 7.9 Hz), 4.94 (2H, m), 4.81 (1H, t, *J* = 4.6 Hz), 3.96 (2H, t, *J* = 6.5 Hz), 3.83 (2H, t, *J* = 6.5 Hz), 3.09 (1H, dd, *J* = 14.7, 5.4 Hz), 2.50 (1H, dd, *J* = 14.6, 7.7 Hz), 2.06−2.01 (2H, m), 1.87 (1H, m), 1.74−1.52 (5H, m), 1.27 (1H, m), 1.17 (1H, dt, *J* = 12.5, 5.5 Hz), 0.93 (3H, d, *J* = 6.5 Hz), 0.15 (9H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.2, 137.2, 116.8, 114.5, 104.8, 64.8, 64.7, 38.6, 35.6, 34.5, 32.6, 32.3, 26.9, 24.8, 21.8, 0.7; HR ESI *m*/*z* calcd for $C_{18}H_{33}O_3Si$ [M + H]$^+$ 325.2198, found 325.2196.

6/5 Bicyclic Diketone 26. To a solution of silyl enol ether **25** (6.20 g, 19.14 mmol) in 130 mL of THF was added 32 mL of 2 N aqueous HCl at rt. The reaction mixture was allowed to stir at rt for 1 h and then was placed in a 50 °C oil bath and stirred for 1.5 h. After being cooled to rt, the reaction mixture was extracted with ether. The combined

extracts were washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated, and the crude product was purified with flash column chromatography (petroleum ether/ethyl acetate 20:1 → 5:1) to provide a 2.97 g (75%) mixture of alcohol isomers. To a solution of mixture of alcohol isomers (2.97 g, 14.3 mmol) in DCM (120 mL) were added Celite (5.0 g) and PCC (5.22 g, 24.3 mmol). The reaction mixture was stirred for 4 h at rt and then was filtered through a short pad of Celite. The collected filtrate was further purified with flash column chromatography (petroleum ether/ethyl acetate 50:1) to provide **26** (2.89 g, 98%) as a colorless oil: $[\alpha]_D = +101.7$ ($c = 0.5$, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}) 3078, 2970, 2916, 1749, 1730, 1291, 1231, 1121, 1103, 920; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.67 (1H, m), 5.09 (2H, m), 2.58 (1H, m), 2.49 (2H, d, $J = 7.5$ Hz), 2.39 (1H, m), 2.30−2.20 (2H, m), 2.14 (2H, m), 1.96 (1H, m), 1.74 (3H, m), 1.03 (3H, d, $J = 6.5$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 214.2, 208.0, 132.8, 118.9, 66.8, 47.0, 41.1, 35.9, 32.9, 30.0, 24.0, 21.5; HR EI m/z calcd for $C_{13}H_{18}O_2$ $[M]^+$ 206.1307, found 206.1323.

Double N-Alkylative Ring Closure Product 28. A 100 mL three-necked flask was equipped with a reflux condenser and two 25 mL dropping funnels. The flask was charged with benzene (30.0 mL), NaOH (1.18 g, 29.5 mmol), Bu_4NI (73 mg, 0.20 mmol), and H_2O (2.8 mL). The mixture was refluxed at 100 °C, and then a solution of bisiodide **9** (75.0 mg, 0.14 mmol) in benzene (7.0 mL) and a solution of $TsNH_2$ (41.0 mg, 0.24 mmol) in benzene (7.0 mL) were added dropwise through two dropping funnels over 30 min, respectively. The reaction mixture was refluxed for 2 h, cooled to rt, poured into H_2O (10.0 mL), extracted with ether (20 mL × 3), washed with brine (10 mL × 2), dried with Na_2SO_4, concentrated in vacuo, and flash chromatographed (petroleum ether/ethyl acetate 20:1) to provide **28** (38 mg, 60%) as a colorless oil: $[\alpha]_D = +67.4$ ($c = 0.7$, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}) 3432, 3027, 2948, 2919, 1599, 1456, 1339, 965, 937, 814, 714, 548; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.68 (2H, d, $J = 8.4$ Hz), 7.29 (2H, d, $J = 8.0$ Hz), 5.66 (1H, m), 3.85 (4H, m), 3.45 (1H, m), 2.96 (1H, m), 2.76−2.68 (1H, m), 2.60−2.53 (1H, m), 2.41 (3H, m), 2.23−1.13 (16H, m), 0.89−0.85 (3H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.6, 142.9, 134.7, 129.4, 129.0, 127.6, 113.0, 64.6, 63.0, 58.0, 50.1, 43.8, 41.1, 38.9, 36.7, 33.7, 29.5, 25.0, 23.7, 22.6, 22.3, 22.2, 21.5; HR EI m/z calcd for $C_{25}H_{35}NO_4S$ $[M]^+$ 445.2287, found 445.2297.

Tetracyclic Hemiacetal 34. To a solution of **8b** (18.3 mg, 0.0527 mmol) in pyridine was added OsO_4 (4% in water, 0.402 mL, 0.0632 mmol) at rt. The resulting mixture was stirred for 4 h at rt and then quenched by saturated $Na_2S_2O_3$ solution. The mixture was stirred at 45 °C for 4 h, extracted with ether (10.0 mL × 3), washed with brine (1.0 mL × 2), dried over Na_2SO_4, and concentrated. The crude product was purified with flash column chromatography (petroleum ether/ethyl acetate 10:1) to provide **34** (17.1 mg, 85%) as a colorless crystal: mp 156−157 °C; $[\alpha]_D = +18.8$ ($c = 0.53$, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}) 3285, 2966, 2931, 1688, 1470, 1413, 1172, 1151, 1121, 967, 779, 758; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.34 (1H, s, br), 4.28 (1H, s, br), 3.73 (1H, s), 3.48−3.32 (2H, m), 3.03 (1H, d, $J = 14.0$ Hz), 2.94 (1H, t, $J = 12.5$ Hz), 2.24−2.00 (2H, m), 1.91−1.52 (9H, m), 1.43 (9H, s), 1.40−0.92 (5H, m), 0.86 (3H, d, $J = 6.5$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.6, 107.7, 85.5, 84.1, 79.5, 50.5, 49.6, 48.4, 39.4, 33.2, 33.1, 31.1, 28.7, 28.5, 28.3, 26.4, 23.4, 21.3; HR EI m/z calcd for $C_{21}H_{35}NO_5$ $[M]^+$ 381.2515, found 381.2517.

Tricyclic α-Hydroxyketone 35. To a stirred solution of **34** (31.0 mg, 0.081 mmol) in DCM were added tetrapropylammonium perruthenate (15.0 mg, 0.041 mmol) and *N*-methylmorpholine *N*-oxide (0.051 mL, 4.8 N, 0.243 mmol). The resulting solution was stirred at rt for 10 min, quenched with addition of saturated $NaHSO_3$, extracted with ether (10.0 mL × 3), washed with brine (1.0 mL × 2), dried over Na_2SO_4, and concentrated. The crude product was purified with flash column chromatography (petroleum ether/ethyl acetate 20:1) to provide **35** (27.6 mg, 90%) as a clear oil: $[\alpha]_D = +137.0$ ($c = 0.45$, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}) 3461, 2965, 2927, 2873, 1756, 1688, 1486, 1412, 1366, 1170, 1134; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.25 (1H, s), 3.85−2.82 (4H, m), 2.55−1.64 (15H, m), 1.46 (9H, s), 1.37−1.31(1H, m), 1.06 (3H, d, $J = 6.5$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 220.4, 216.6, 157.4, 83.2, 79.3, 59.3, 46.9, 46.3, 44.6, 39.6, 35.0, 31.3, 28.5, 26.3, 24.5, 23.2, 21.9, 18.9; HR EI m/z calcd for $C_{21}H_{33}NO_5$ $[M]^+$ 379.2359, found 379.2352.

Tricyclic Diketone 37. To a stirred solution of **35** (10.0 mg, 0.026 mmol) in THF/*t*-BuOH (4:1) was added samarium diiodide (0.1 M in THF, 0.87 mL, 0.087 mmol). The resulting solution was stirred at rt for 10 min, opened to air, quenched with addition of saturated $NaHCO_3$, extracted with ether (10.0 mL × 3), washed with brine (1.0 mL × 2), dried over Na_2SO_4, and concentrated. The crude product was purified with flash column chromatography (petroleum ether/ethyl acetate 10:1) to provide **37** (7.8 mg, 81%) as a white solid: IR (KBr) ν_{max} (cm^{-1}) 3440, 2957, 2927, 1744, 1692, 1480, 1414, 1366, 1167, 1128, 772; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.77−3.50 (2H, m), 2.94−2.74 (2H, m), 2.44−1.59 (17H, m), 1.41 (9H, s), 1.05 (3H, dd, $J = 6.4$, 4.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 215.2, 214.7, 156.8, 79.7, 60.37, 59.9, 50.1, 49.4, 47.3, 46.9, 46.6, 44.7, 44.5, 42.5, 42.2, 38.9, 38.3, 31.6, 30.9, 30.1, 28.5, 28.4, 25.5, 23.4, 22.3, 22.1, 22.0, 21.6, 21.0.

Fawcettimine (1). To a solution of **37** (4.5 mg, 0.0123 mmol) in CH_2Cl_2 (1.0 mL) was added trifluoroacetic acid (0.050 mL) at 0 °C. The resulting solution was stirred at rt for 3 h, quenched with addition of saturated $NaHCO_3$, and extracted with chloroform (10.0 mL × 3), and the combined organic phases were washed with saturated $NaHCO_3$ (2.0 mL × 2) and brine (2.0 mL × 2), dried over Na_2SO_4, and concentrated. The crude product was purified with flash column (chloroform/methanol 15:1) to provide fawcettimine (2.6 mg, 80%) as a yellowish foam: $[\alpha]_D = +85.4$ ($c = 0.67$, MeOH); IR (KBr) ν_{max} (cm^{-1}) 3425, 2953, 2923, 2867, 2689, 2620, 1734, 1460; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.95 (1H, s, br), 3.80−2.80 (4H, m), 2.61 (1H, dd, $J = 17.5$, 14.0 Hz), 2.32−1.83 (10H, m), 1.74−1.38 (6H, m), 0.98 (3H, d, $J = 6.5$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 218.1, 77.2, 59.5, 54.1, 50.2, 47.8, 43.1, 41.7, 41.4, 34.4, 31.5, 27.3, 26.1, 23.6, 21.5, 20.6.

Lycoflexine (4). To a solution of synthetic fawcettimine (**1**) (11.0 mg, 0.041 mmol) in isoamyl alcohol (1 mL) was added paraformaldehyde (11.0 mg, 0.366 mmol). The mixture was placed in a 120 °C oil bath, stirred for 5 min, cooled to rt, filtered, and concentrated. The crude product was purified with flash column chromatography (chloroform/methanol 50:1) to provide lycoflexine (11.0 mg, 95%) as a yellow solid: $[\alpha]_D = +55.2$ ($c = 0.45$, MeOH); IR (KBr) ν_{max} (cm^{-1}) 3431, 2925, 2868, 1727, 1697, 1631, 1459; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.22−3.11 (2H, m), 3.02−2.94 (1H, m), 2.90−2.77 (2H, m), 2.70−2.60 (2H, m), 2.39−2.07 (8H, m), 1.99−1.71 (5H, m), 1.63−1.53 (1H, m), 1.40−1.32 (1H, m), 1.03 (3H, d, $J = 6.5$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 217.9, 213.7, 60.5, 58.2, 56.6, 53.3, 53.2, 46.7, 40.3, 39.9, 36.0, 31.2, 29.0, 28.0, 25.7, 22.3, 19.2; HR ESI m/z calcd for $C_{17}H_{26}NO_2$ $[M + H]^+$ 276.1963, found 276.1961.

■ ASSOCIATED CONTENT

Supporting Information. NMR spectra and CIF files for synthetic 8-deoxyserratinine (**7**) and compound **34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) During the early stage of preparation of this manuscript, one elegant synthesis of lycoflexine has been published by Mulzer et al.: Ramharter, J.; Weinstabl, H.; Mulzer, J. *J. Am. Chem. Soc.* **2010**, *132*, 14338–14339. Mulzer used similar conditions as Ayer did, namely, acidic aqueous HCHO in extended reaction time (48 h) employed to accomplish this important biomimetic transformation. The first asymmetric total synthesis of lycoflexine including the assignment of the absolute configuration was reported by the Mulzer group.

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References 13 and 26 were corrected in the version that reposted April 19, 2011.