Natural Product Synthesis

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Total Syntheses of *Lycopodium* Alkaloids (+)-Fawcettimine, (+)-Fawcettidine, and (−)-8-Deoxyserratinine**

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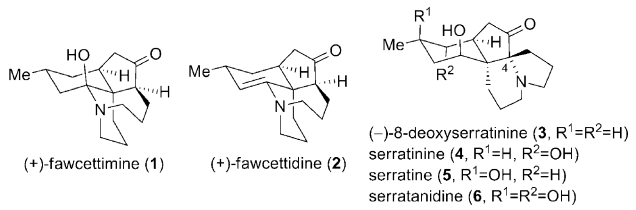
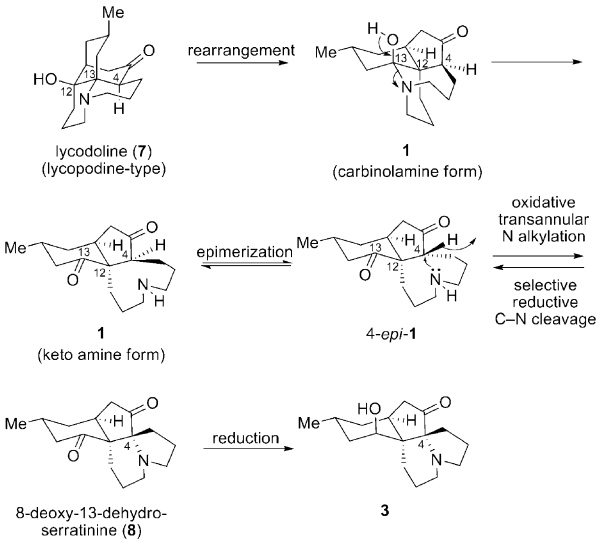
The *Lycopodium* alkaloids are a family of structurally complex natural products,[1] which have provoked long-term interests in their total syntheses because of their unique and fascinating architectures and potential biological activities.[2] In particular, fawcettimine-type *Lycopodium* alkaloids, such as fawcettimine (**1**)[3] and fawcettidine (**2**)[3,4] (Scheme 1), have attracted broad attention from the synthetic community in recent years, and a number of impressive total syntheses



Scheme 1. Structures of representative fawcettimine- and serratinine-type *Lycopodium* alkaloids.

have been accomplished.[5] Serratinine-type *Lycopodium* alkaloids, such as 8-deoxyserratinine (**3**),[6] serratinine (**4**), serratine (**5**), and serratanidine (**6**), are structurally related to the fawcettimine-type alkaloids, however, they possess a more complex molecular architecture with two vicinal quaternary stereogenic centers and a unique 6,5,6,5-tetracyclic framework. In contrast to fawcettimine-type alkaloids, relatively little progress and limited success have been made toward the total synthesis of serratinine-type alkaloids.[7] In 1979, Inubushi and co-workers reported the first total synthesis of (±)-8-deoxyserratinine (**3**) in 23 steps with 0.29% overall yield.[7a,b] Very recently, Yang and co-workers achieved the first asymmetric total synthesis of (−)-8-deoxyserratinine (**3**) in 15 steps.[5i,7c]

According to the biogenetic pathway proposed by Inubushi et al., both fawcettimine- and serratinine-type alkaloids could be derived from lycopodine-type alkaloids through rearrangement of the carbon-skeleton (Scheme 2).[8] The keto



Scheme 2. Proposed biogenetic pathway for fawcettimine- and serratinine-type *Lycopodium* alkaloids.

amine form of fawcettimine (**1**) can epimerize to 4-*epi*-fawcettimine, thus allowing a transannular N alkylation (S_N2) to construct the C4–N bond and furnish 8-deoxy-13-dehydroserratinine (**8**). Conceivably, the serratinine-type skeleton could also be transformed to the fawcettimine-type framework by selective C–N bond cleavage. The following selective reduction of **8** would afford 8-deoxyserratinine (**3**). Despite growing interest in the total synthesis of *Lycopodium* alkaloids, biomimetic interconversions between fawcettimine- and serratinine-type alkaloids have not been extensively explored. Herein, we report a biosynthesis-inspired strategy to accomplish the concise and collective total syntheses of (+)-fawcettimine (**1**), (+)-fawcettidine (**2**), and (−)-8-deoxyserratinine (**3**) from the common molecular scaffold 8-deoxy-13-dehydroserratinine (**8**).[9]

According to our retrosynthetic analysis (Scheme 3), key precursor **8** could be derived from compound **9** through a biomimetic transannular N alkylation. The challenging quaternary carbon center at C4 in **9** could be assembled by Matsuda's hydroxy-directed SmI_2-mediated pinacol coupling of aldehyde **10** to set up the correct relative stereochemis-

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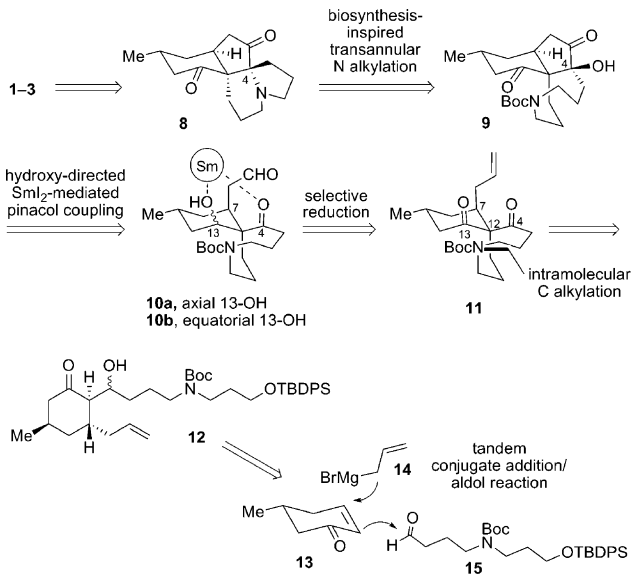
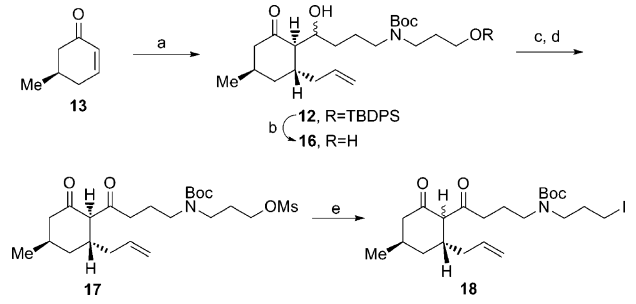


Scheme 3. Retrosynthetic analysis. Boc = *tert*-butoxycarbonyl, TBDPS = *tert*-butyldiphenylsilyl.

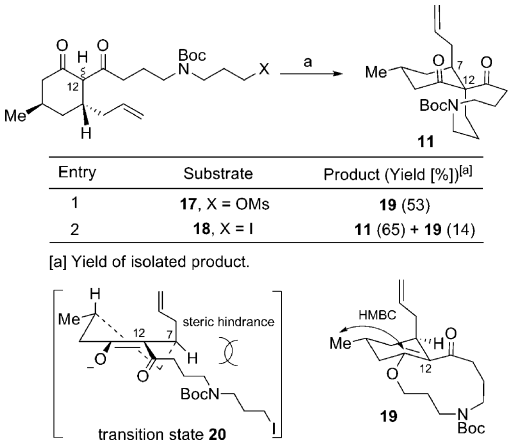
try.[10] The pinacol-coupling precursor **10** could be generated from diketone **11** through selective reduction. The key spiro-configured quaternary carbon center at C12 in diketone **11** could be installed by means of intramolecular C alkylation. We envisioned that intermediate **12** could be efficiently prepared through a tandem one-pot conjugate addition/aldol reaction protocol by using readily available starting materials, including optically active (*5R*)-5-methylcyclohex-2-enone **13**,[11] allylmagnesium bromide **14**, and aldehyde **15**.

Our synthesis started with the tandem conjugate addition/aldol reaction sequence (Scheme 4).[12] Enone **13** was treated with allylcuprate (freshly prepared from allylmagnesium bromide **14**) at −78 °C, and the resulting enolate was trapped with aldehyde **15**[13] to afford alcohol **12** as a mixture of diastereoisomers, which underwent desilylation to afford keto diol **16**. Selective mesylation of the primary alcohol following Burke's protocol[14] and subsequent oxidation of the secondary alcohol with Dess–Martin periodinane provided diketo mesylate **17**. Iodination of **17** gave another C-alkylation precursor, diketo iodide **18**.



Scheme 4. Reagents and conditions: a) 1) **14**, CuBr, Me_2S, LiCl, THF, −78 °C; 2) **15**, −78 °C, 73%; b) $Et_3N{\cdot}3HF$, MeCN, RT, 94%; c) collidine, MsCl, CH_2Cl_2, 4 °C; d) Dess–Martin periodinane, CH_2Cl_2, RT, 80% (two steps); e) NaI, acetone, RT, 84%. Ms = mesityl, THF = tetrahydrofuran.

With diketo mesylate **17** and diketo iodide **18** in hand, we began to investigate the challenging intramolecular C alkylation to install the spiro-configured quaternary carbon center at C12 (Scheme 5). Although the C alkylation of 1,3-dicarbonyl compounds with RX (R = alkyl; X = halide, tosylate,



Entry	Substrate	Product (Yield [%])[a]
1	**17**, X = OMs	**19** (53)
2	**18**, X = I	**11** (65) + **19** (14)

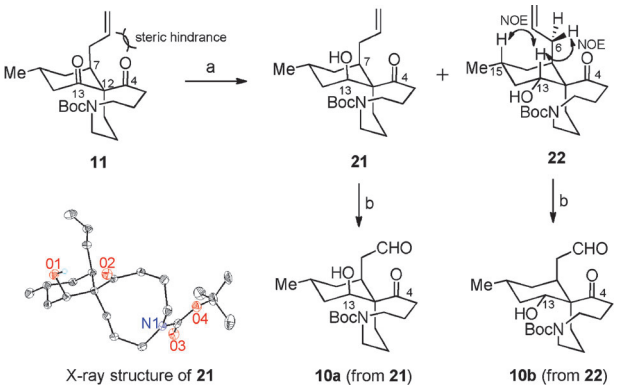
[a] Yield of isolated product.

Scheme 5. Intramolecular C-alkylation reaction to give spirodiketone **11**. Reagents and conditions: a) DBU, CH_3CN (0.014 M), RT. DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene.

mesylate, etc.) is a powerful method for the synthesis of α-substituted 1,3-dicarbonyl compounds, previous examples of intramolecular C alkylations of 1,3-dicarbonyl compounds with RX to install spiro-configured quaternary carbon centers for the synthesis of complex natural products are relatively rare.[15] Through an extensive screening of reaction conditions (base, solvent, temperature, and concentration), we found that diketo mesylate **17** gave only O-alkylation product **19** (Scheme 5, entry 1), while the desired C-alkylation product **11** was generated in good yield (65%) by the treatment of diketo iodide **18** with DBU under dilute conditions in CH_3CN (Scheme 5, entry 2). The quaternary carbon center at C12 was correctly installed by this remarkable transformation. The high stereoselectivity of **11** may be attributed to the steric effect caused by the axial allylic group at C7 (see transition state **20**).[16]

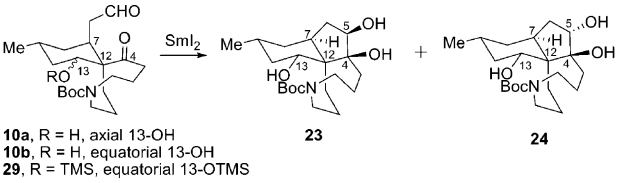
After we established the spiro-configured quaternary carbon center at C12 and the aza-cyclononane ring, we attempted to synthesize the pinacol-coupling precursor aldehyde **10** (Scheme 6). We anticipated that the carbonyl group at C4 in diketone **11** would be blocked because of the steric hindrance of the axial allylic group at C7, thus the carbonyl group at C13 could be selectively reduced to provide the 13-hydroxy ketone. Gratifyingly, selective reduction of diketone **11** was realized by using $NaBH_4$ in CH_2Cl_2/MeOH to afford **21** and **22** in 29% and 63% yield, respectively. The structure of **21** was confirmed by X-ray crystallographic analysis,[17] while the stereochemistry of **22** was determined by NOE analysis.[18] Lemieux–Johnson oxidation of **21** afforded **10a** in 86% yield. Compound **22** was also transformed into **10b** in quantitative yield.[19]

In order to set up the desired oxa-substituted quarternary carbon center at C4, we initiated studies on the



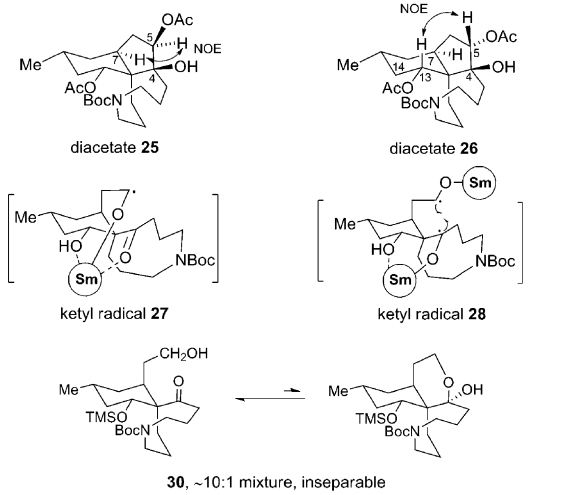
Scheme 6. Reagents and conditions: a) $NaBH_4$, CH_2Cl_2/MeOH (10/1), RT, **21**, 29%, **22**, 63%; b) OsO_4, $NaIO_4$, DABCO, dioxane/H_2O (2/1), RT, **10a** (86%), **10b** (quantitative). DABCO = 1,4-diazabicyclo[2.2.2]-octane.

SmI_2-mediated pinacol coupling of **10** (Scheme 7).[20] Based on Matsuda's studies of hydroxy-directed SmI_2-mediated transformations,[10] we envisioned that formation of the desired quaternary stereocenter at C4 with well-defined stereochemistry could be completely controlled by the hydroxy group at C13 in starting material **10**. Both **10a** and **10b** were used as coupling substrates in our investigation. While **10a** failed to afford any coupling products under various conditions (Scheme 7, entry 1), we were pleased to find that pinacol coupling of **10b** occurred smoothly and provided interesting stereochemical outcome under different conditions. Specifically, treatment of **10b** with SmI_2 in THF at RT afforded two coupling products, 4,5-*cis* diol **23** and 4,5-*trans* diol **24** in 72% and 18% yield of isolated product, respectively (Scheme 7, entry 2). However, **24** was isolated as the sole product in 67% yield when the pinacol coupling was carried out in the presence of HMPA (Scheme 7, entry 3). The oxa-substituted quaternary stereocenters at C4 in **23** and **24** were confirmed by their subsequent oxidation to known compound **9**[5b] (see Scheme 8). Furthermore, acetylation of **23** and **24** afforded the two diacetate derivatives **25** and **26**,

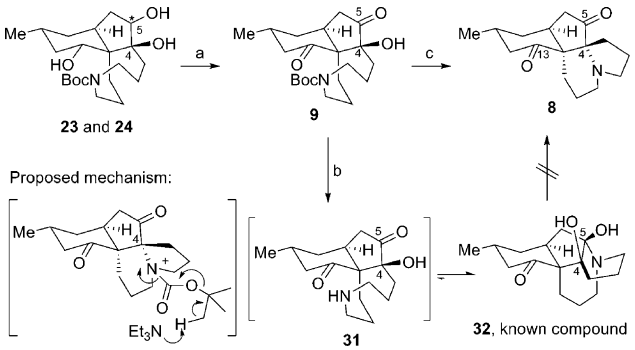


Entry	Substrate	Conditions	Product (Yield [%])[a]
1	**10a**	A or B	complex mixture
2	**10b**	A	**23** (72) + **24** (18)
3	**10b**	B	**24** (67)
4	**29**	A or B	**30** (34)

Conditions A: SmI_2 (5 equiv), THF, RT;
Conditions B: SmI_2 (5 equiv), HMPA (20 equiv), THF, −78 °C to RT
[a] Yield of isolated product.



Scheme 7. Hydroxy-directed SmI_2-mediated intramolecular pinacol coupling. Ac = acetyl, HMPA = hexamethylphosphoramide, TMS = trimethylsilyl.



Scheme 8. Reagents and conditions: a) TPAP, NMO·H_2O, 4 Å MS, RT, for **23**, 74%; for **24**, 56%; b) TFA, $CHCl_3$, RT, 92%; c) $SOCl_2$/Et_3N, THF, −78 °C to 0 °C, 98%. NMO·H_2O = *N*-methylmorpholine-*N*-oxide monohydrate, M.S. = molecular sieves, TFA = trifluoroacetic acid, TPAP = tetrapropylammonium perruthenate.

respectively. The stereochemistry at C5 in **25** and **26** were determined by NOE experiments, which confirmed the relative configurations of **23** and **24** as 4,5-*cis* and 4,5-*trans*, respectively.[18] Substrate **29** (trimethylsilyl ether of **10b**) was synthesized for control experiments, and subjected to the same coupling conditions.[18] The reaction of **29** with SmI_2 both in the absence and presence of HMPA resulted in the reduction of the aldehyde to form alcohol **30** instead of the desired coupling products (Scheme 7, entry 4).[21]

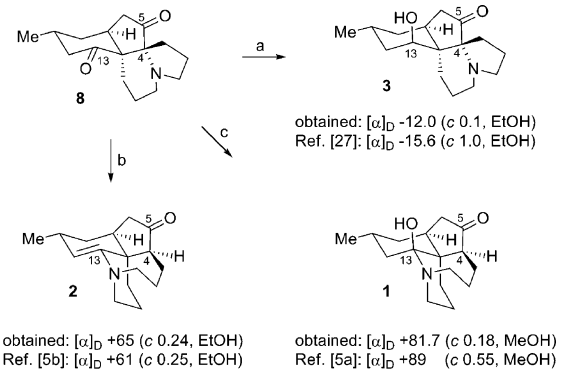
Our results were consistent with previous reports by Matsuda.[10] The observed stereochemical outcome could be explained by two proposed chelation models, in which the pinacol couplings are likely to proceed via different cyclic ketyl radicals, depending on the absence or presence of HMPA. In the absence of HMPA, only the aldehyde moiety of **10b** was reduced to the ketyl radical upon initial reduction by SmI_2. Chelation of the Sm^{III} cation with the δ hydroxy group formed eight-membered ketyl radical **27**, which afforded 4,5-*cis* diol **23** as the major product. In the presence of HMPA, a ketyl radical pair was generated through single-electron transfer from SmI_2, because HMPA could increase the reducing ability of SmI_2 by coordination to SmI_2.[22] The

six-membered ketyl radical **28** was formed by chelation of the Sm^{III} cation with the β hydroxy group. The pinacol coupling occurred through the diketyl coupling pathway, in which the 4,5-*trans* diol **24** was generated as a single product, presumably because of the strong dipole–dipole repulsion between the two cationic Sm^{III} complexes.

After we installed the desired oxa-substituted quaternary carbon center at C4, we examined the construction of the C4–N bond by using transannular N alkylation (Scheme 8). Oxidation of triols **23** and **24** by Ley oxidation smoothly furnished compound **9**.[23] In initial attempts, we used a two-step protocol: removal of the Boc group to give compound **31**, followed by transannular N alkylation.[24] However, further efforts to use the free amine for the transannular N alkylation failed, presumably because of intramolecular carbinolamine formation.[5i]

The desired 8-deoxy-13-dehydroserratinine (**8**) was obtained in nearly quantitative yield (98%) by the treatment of compound **9** with $SOCl_2$ and Et_3N in THF. The remarkable efficiency of this transformation suggests a mechanism involving the transannular nucleophilic attack of the nitrogen to afford the ionic acyl ammonium intermediate followed by the base-triggered removal of the Boc group (Scheme 8).[25] The key tetracyclic intermediate **8**, which is obtained by this biosynthesis-inspired N-alkylation protocol, was identical to the previously reported 8-deoxy-13-dehydroserratinine.[5i,7c,26]

With key precursor **8** in hand, we were able to access both fawcettimine- and serratinine-type *Lycopodium* alkaloids in a collective manner (Scheme 9). Selective reduction of the carbonyl group at C13 with $NaBH_4$ at 0°C provided (−)-8-deoxyserratinine (**3**) in 98% yield. Furthermore, reductive



Scheme 9. Reagents and conditions: a) $NaBH_4$, EtOH (dry), 0°C, 98%; b) Zn, HOAc, 140°C, 95%; c) SmI_2, H_2O, THF, 0°C, 51%.

cleavage of the C4–N bond of **8** occurred under harsh reducing conditions (Zn/HOAc, 140°C, 8 h), the subsequent dehydration formed the enamine moiety and furnished (+)-fawcettidine (**2**) in excellent yield (95%).[27] Finally, we attempted to selectively cleave the C4–N bond with SmI_2 following Honda's protocol to give fawcettimine (**1**).[28] The late-stage reductive carbon–nitrogen bond cleavage proved to be challenging because the two carbonyl groups at C5 and C13 were likely to be reduced as well under these conditions. After careful optimization of the reaction conditions, we were pleased to find that by the treatment of substrate **8** with SmI_2 in THF at 0°C, with 2.5 equivalents of water as a proton source, we could obtain (+)-fawcettimine (**1**) in 51% yield. The spectroscopic data of the synthetically obtained compounds fully matched the data reported previously.[18]

In conclusion, we have demonstrated the feasibility of collective total syntheses of both fawcettimine- and serratinine-type *Lycopodium* alkaloids (+)-fawcettimine, (+)-fawcettidine, and (−)-8-deoxyserratinine from a common precursor based on a highly concise route (all syntheses were accomplished in 12 steps). Our synthesis features: 1) an intramolecular C alkylation to install the challenging spiro-configured quaternary carbon center and the aza-cyclononane ring; 2) a hydroxy-directed SmI_2-mediated pinacol coupling to establish the correct relative stereochemistry of the oxa-substituted quaternary center; 3) most notably, the unprecedented tandem transannular N alkylation and removal of the Boc group to realize a biosynthesis-inspired process to afford the desired tetracyclic skeleton. Total syntheses of other related members of fawcettimine- and serratinine-type *Lycopodium* alkaloids by using the strategies highlighted herein are currently underway and will be reported in due course.

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