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Collective Synthesis of *Lycopodium* Alkaloids and Tautomer Locking Strategy for the Total Synthesis of (−)-Lycojapodine A

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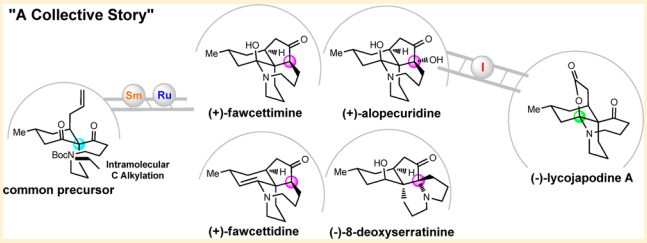
Supporting Information

ABSTRACT: The collective total synthesis of *Lycopodium* alkaloids (+)-fawcettimine (**1**), (+)-fawcettidine (**2**), (+)-alopecuridine (**4**), (−)-lycojapodine A (**6**), and (−)-8-deoxyserratinine (**7**) has been accomplished from a common precursor (**15**) based on a highly concise route inspired by the proposed biosynthesis of the fawcettimine- and serratinine-type alkaloids. An intramolecular *C*-alkylation enabled efficient installation of the challenging spiro quaternary carbon center and the aza-cyclononane ring. The preparation of the tricyclic skeleton as well as the establishment of the correct relative stereochemistry of the oxa-quaternary center were achieved by hydroxyl-directed SmI_2-mediated pinacol couplings. An unprecedented tandem transannular *N*-alkylation and removal of a Boc group was discovered to realize a biosynthesis-inspired process to furnish the desired tetracyclic skeleton. Of particular note is the unique and crucial tautomer locking strategy employed to complete the enantioselective total synthesis of (−)-lycojapodine A (**6**). The central step in this synthesis is the late-stage hypervalent iodine oxidant (IBX or Dess−Martin periodinane)/TFA-mediated tandem process, which constructed the previously unknown carbinolamine lactone motif and enabled a biomimetic transformation to generate (−)-lycojapodine A (**6**) in a single operation.



INTRODUCTION

The *Lycopodium* alkaloids[1] are a family of structurally diverse and complex natural products. To date, more than 250 *Lycopodium* alkaloids have been isolated and characterized. The combination of fascinating molecular architectures and significant biological activities of the *Lycopodium* alkaloids has provoked long-term interest in their total syntheses.[2] Among them, the fawcettimine-type alkaloids, including fawcettimine (**1**),[3] fawcettidine (**2**),[3,4] lycoflexine (**3**),[5] alopecuridine (**4**),[6] sieboldine A (**5**),[7] and lycojapodine A (**6**)[8] (Figure 1), have attracted broad attention worldwide in recent years and have been the subject of a number of remarkable total syntheses.[9] Of particular note is lycojapodine A (**6**), which was isolated by Zhao and co-workers in early 2009. While the relative structure of lycojapodine A (**6**) was secured by X-ray analysis, its absolute structure was still unknown. Compound **6** possesses a unique 6/6/6/7 tetracyclic skeleton with an unprecedented *carbinolamine lactone* motif, which renders it a striking synthetic target.[8] Indeed, the carbinolamine lactone motif also exists in aspidophytine,[10] haplophytine,[11] and zoanthamine alkaloids[12] and was proved to be a great synthetic challenge which stimulated significant efforts to advance methodologies for their total syntheses. Because of the challenging carbinolamine lactone motif, not surprisingly, the total synthesis of **6** still remains elusive.[13]

The serratinine-type *Lycopodium* alkaloids, such as 8-deoxyserratinine (**7**),[14] serratinine (**8**),[15] serratine (**9**),[16] and serratanidine (**10**),[14] represent another major class of

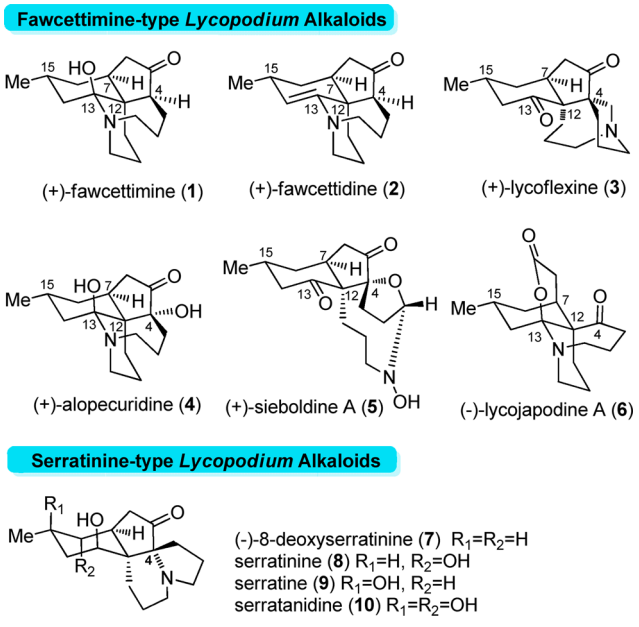


Figure 1. Representative *Lycopodium* alkaloids.

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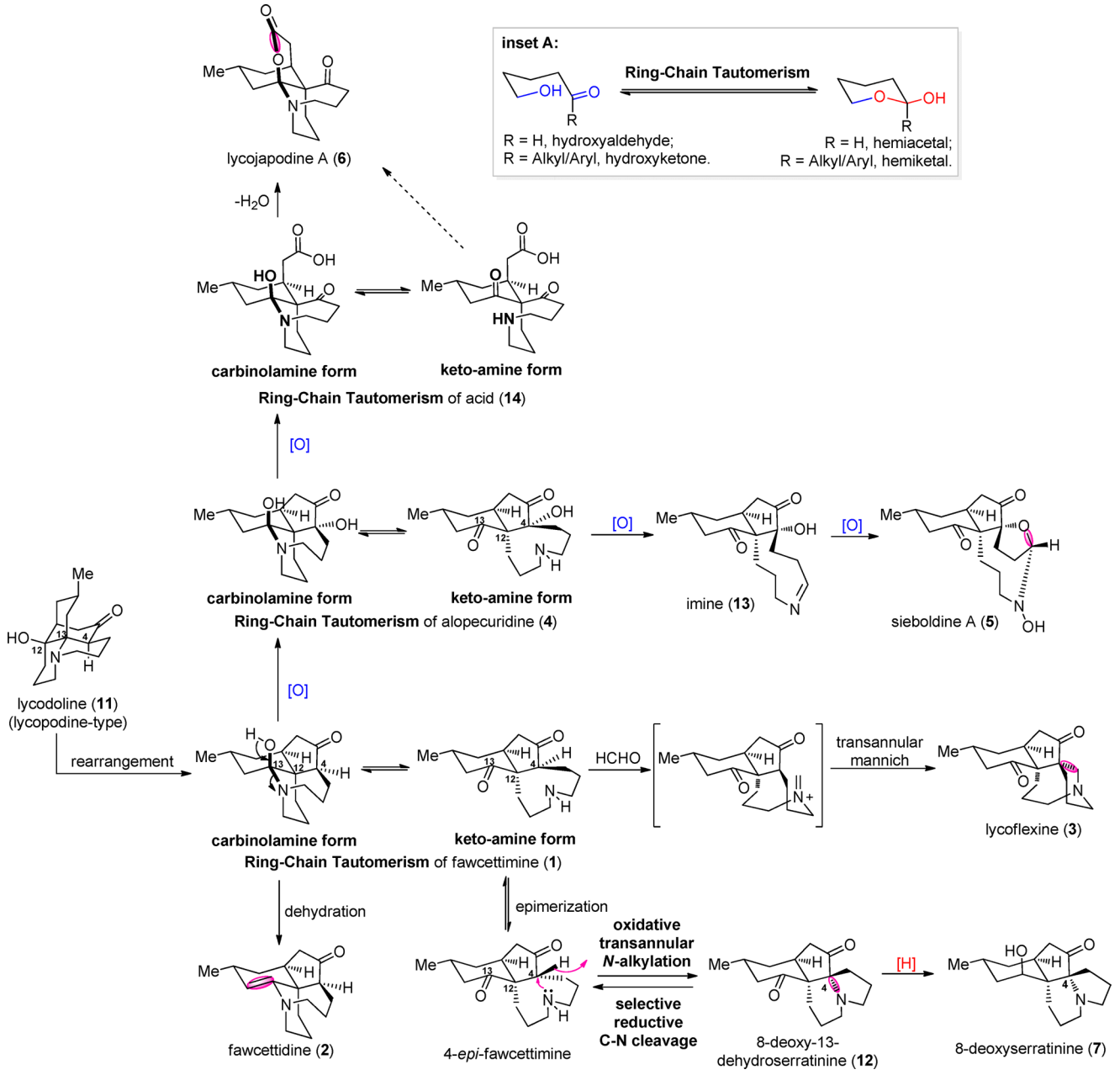
Scheme 1. Proposed Biogenetic Pathways for the Fawcettimine and Serratinine-Type *Lycopodium* Alkaloids



Lycopodium alkaloids, which are structurally relevant to the fawcettimine-type alkaloids. However, this family of natural products possess a more complex molecular architecture including a challenging 6/5/6/5 tetracyclic framework with two contiguous quaternary stereogenic centers. Not surprisingly, these intriguing molecular architectures served well to invite a number of synthetic studies.[17] However, relatively little progress and limited success for their total synthesis have been disclosed so far.

From a biosynthetic point of view, the fawcettimine-type alkaloids are unique in comparison with any other types of *Lycopodium* alkaloids because of the widespread ring−chain tautomerism (inset A, Scheme 1),[18] which is crucial to their biogenesis. Based on the biogenetic pathway proposed by Inubushi,[19] fawcettimine (**1**) could be derived from lycodoline (**11**) (lycopodine-type) through carbon-skeleton rearrangement (Scheme 1). Fawcettimine (**1**) exists as either the carbinolamine tautomer or the ketoamine tautomer.[9l,m,20] The carbinolamine form of **1** could undergo either dehydration to yield fawcettidine (**2**)[21] or further oxidation to produce alopecuridine (**4**). On the other hand, the ketoamine form of **1** could either react with formaldehyde to generate an iminium species, which subsequently undergoes a transannular Mannich reaction to furnish lycoflexine (**3**)[5,9d,i] or first epimerize to 4-epi-fawcettimine, which allows a transannular N alkylation (S_N2) to construct the C4−N bond and furnish 8-deoxy-13-dehydroserratinine (**12**), which has the tetracyclic skeleton of the serratinine-type alkaloids. Further selective reduction of **12** would afford 8-deoxyserratinine (**7**). Conceivably, we propose that the serratinine-type skeleton could also be transformed to the fawcettimine-type framework by selective C−N bond cleavage. Similar to fawcettimine (**1**), alopecuridine (**4**) is also present as carbinolamine form or keto-amine form. The keto-amine form of alopecuridine could generate the unstable imine

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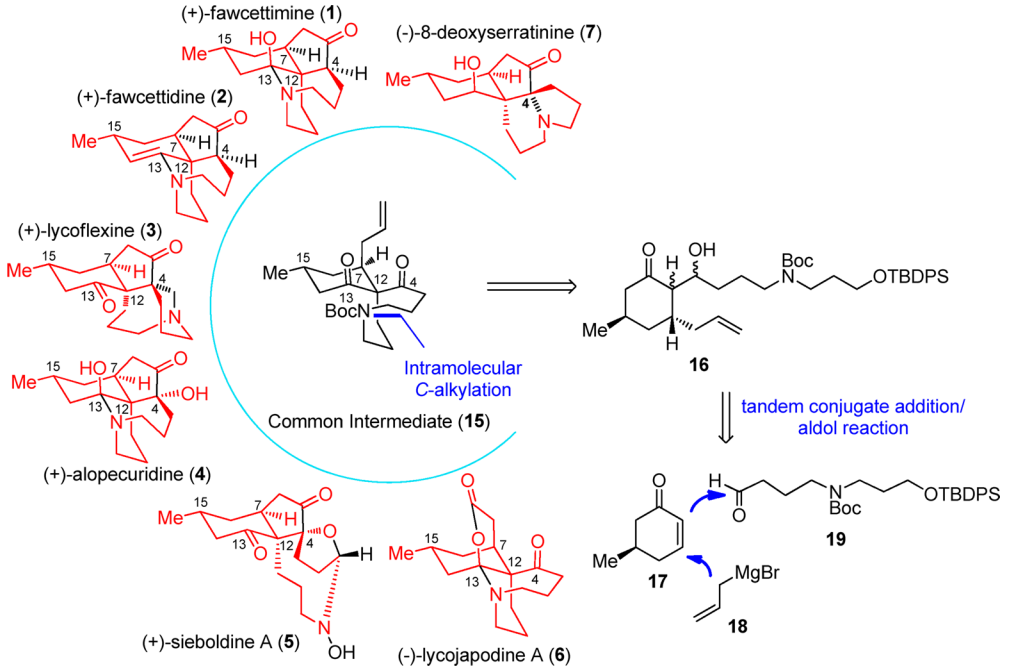
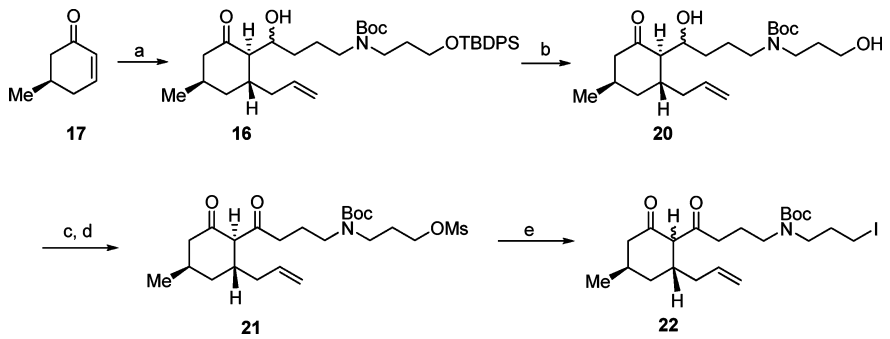
Scheme 2. Retrosynthetic Analysis for the Collective Synthesis of Fawcettimine and Serratinine-Type *Lycopodium* Alkaloids



Scheme 3. Efficient Syntheses of C-Alkylation Precursors 21 and 22[a]



[a]Reagents and conditions: (a) (i) **18**, CuBr, Me_2S, LiCl, THF, −78 °C; (ii) **19**, −78 °C, 75%; (b) $Et_3N{\cdot}HF$, 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%.

species (**13**) via tautomerization/oxidation sequence or vice versa. Further oxidation of imine **13** could afford sieboldine A (**5**).[22] Furthermore, according to the biogenetic pathway for lycojapodine A (**6**) proposed by Zhao et al.,[8] the carbinolamine form of **4** might undergo an oxidative cleavage to generate acid **14** (Scheme 1, carbinolamine form), which could furnish lycojapodine A (**6**) through further lactonization. However, acid **14** would also exist as either the carbinolamine form or ketoamine form due to the ring−chain tautomerism. Accordingly, the final lactonization was conceivably problematic because of the existence of the ketoamine tautomer of **14**.

Inspired by the intriguing biogenetic pathways for both fawcettimine- and serratinine-type alkaloids, we have been engaged in their total syntheses since 2009. In the previous communication, we reported the total syntheses of (+)-fawcettimine, (+)-fawcettidine, and (−)-8-deoxyserratinine through a highly concise route involving an intramolecular C alkylation to install the challenging spiro-configured quaternary carbon center and a hydroxyl-directed SmI_2-mediated pinacol coupling to construct the tricyclic skeleton and establish the correct stereochemistry.[23] The previous study also demonstrated the feasibility of biomimetic interconversions between the fawcettimine and serratinine-type alkaloids. However, the crucial "ring−chain tautomerism" issue involved in the biosynthesis had not been fully addressed. In addition, the scope of current strategy for the efficient synthesis of other *Lycopodium* alkaloids with distinct frameworks, especially (−)-lycojapodine A, remained to be further explored. Herein, we describe the full details of our investigation on the evolution of our synthetic strategy and the discovery of new methodologies that should have potential applications. Ultimately, our synthetic endeavors have led to the collective synthesis[24] of both fawcettimine- and serratinine-type alkaloids, including the enantioseletive total synthesis of (−)-lycojapodine A relying on a remarkable tautomer locking strategy.

RESULTS AND DISCUSSION

Synthesis Plan. The retrosynthetic analysis that guided our efforts to develop a unified route to achieve the collective total synthesis of both fawcettimine- and serratinine-type alkaloids is depicted in Scheme 2. We envisioned that **1**−**7** could be accessed from a common intermediate (**15**), which has

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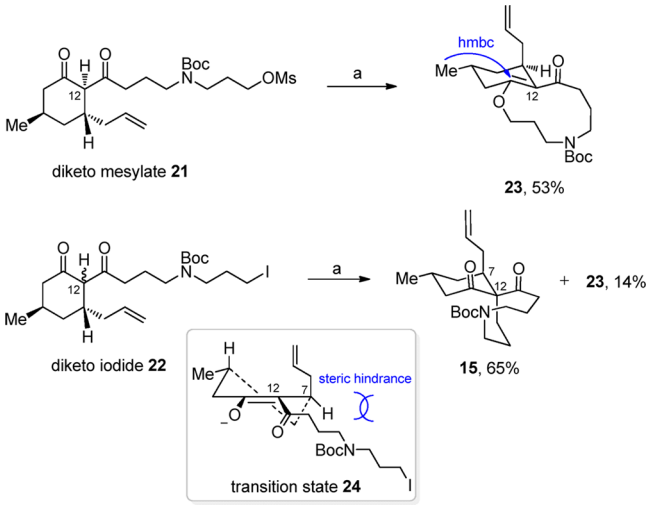
included the requisite functionality for expedient conversion to each of the target molecules. The key spiro-configured quaternary carbon center at C12 in diketone (**15**) could be installed through intramolecular C alkylation. We expected that intermediate (**16**) could be efficiently prepared via a tandem conjugate addition/aldol reaction from three readily available starting materials, including optically active enone (5*R*)-5-methylcyclohex-2-enone **17**,[25] allylmagnesium bromide **18**, and aldehyde **19**.

Efficient Synthesis of the Common Intermediate 15. As shown in Scheme 3, our synthesis commenced with a tandem conjugate addition/aldol reaction sequence.[26] This three component reaction was initiated by the treatment of enone **17** with freshly prepared allylcuprate at −78 °C followed by aldehyde **19**[27] to afford alcohol **16** as an inconsequential diastereomeric mixture. Desilylation of **16** under mild conditions smoothly generated keto diol **20**. Selective primary mesylation of **20** using Burke's protocol[28] followed by oxidation of the second alcohol with Dess−Martin periodinane (DMP) furnished diketo mesylate **21**. Iodination of **21** provided diketo iodide **22**.

We next investigated the challenging intramolecular C alkylation to install the C12 spiro-configured quaternary carbon center (Scheme 4). Although the C alkylation of 1,3-dicarbonyl

Scheme 4. Intramolecular C-Alkylation To Yield Spiro-diketone 15[a]

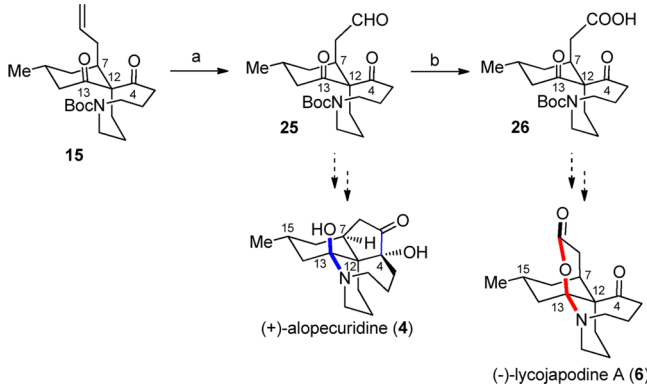


[a]Reagents and conditions: (a) DBU, MeCN (0.014 M), rt.

compounds represents a powerful means for the synthesis of α-substituted 1,3-dicarbonyl substrates, previous examples of its intramolecular form to install a spiro-configured quaternary carbon center are relatively rare.[29] In our case, after extensive reaction condition screening (base, solvent, temperature, and concentration), we found that, while diketo mesylate **21** only yielded O-alkylation product **23**, the desired C-alkylation product **15** was smoothly generated in good yield (65%) by the treatment of diketo iodide **22** with DBU in acetonitrile.[30] The spiro quaternary carbon center at C12 was created efficiently in this remarkable transformation. The rationale for the high stereoselectivity of **15** observed in this reaction could be attributed to the steric effect caused by the axial allylic group at C7 (see transition state **24**).[31]

Initial Attempts with Diketo Aldehyde 25 and Diketo Acid 26. Having established the spiro-configured quaternary carbon center and the aza-cyclononane ring, we initially attempted to access fawcettimine-type alkaloids from the common intermediate **15** in a straightforward fashion. Specifically, Lemieux−Johnson oxidation of diketone **15** afforded aldehyde **25**,[32] which was subjected to Pinnick oxidation conditions to give acid **26** in quantitative yield (Scheme 5). Since **25** and **26** shared the same oxidation state

Scheme 5. Syntheses of Diketo Aldehyde 25 and Diketo Acid 26[a]



[a]Reagents and conditions: (a) OsO_4, $NaIO_4$, DABCO, dioxane−H_2O (2/1), rt, 15 h, 92%; (b) $NaClO_2$, NaH_2PO_4, *t*-BuOH−H_2O−2-methyl-2-butene, rt, 5 h, quant.

with (+)-alopecuridine (**4**) and (−)-lycojapodine A (**6**), respectively, further efforts were made to synthesize either **4** from aldehyde **25** or **6** from acid **26**.

We first examined the feasibility of constructing the 5-membered ring and the oxa-quaternary carbon center at C4 with diketo aldehyde **25**. Upon treatment of **25** with SmI_2, intramolecular pinacol coupling occurred to yield keto diol **27** exclusively in excellent yield (81%), and none of the other isomer (the desired C4−C5 coupled product) was detected during the reaction. The stereochemistry of **27** was confirmed by 2D NMR analysis.[33] Although the rationale for the regioselectivity observed herein was still unclear, the high stereoselectivity of **27** observed during the coupling reaction could be attributed to the chelate effect of the C4 carbonyl upon the formation of ketyl radical **28**. Further oxidation of vicinal diol **27** proved to be challenging, and several oxidation conditions were screened (Scheme 6, entries 1−3). When Dess−Martin periodinane (DMP) that has been known to be capable of oxidatively cleaving vicinal diols[34] was used, the oxidatively cleaved product **25** was obtained as the major product in 48% yield (Scheme 6, entry 1). On the other hand, α-ketol **29** was obtained as the major product in good yield (53%) along with a small amount (17%) of diketo aldehyde **25** when using 2-iodoxybenzoic acid (IBX) as an oxidant (Scheme 6, entry 2), which presumably was due to hindrance of vicinal diol **27**.[35] Finally, the Ley oxidation condition[36] was examined and proven to be the optimum condition. As a result, α-ketol **29** was generated as a single product in 63% yield (Scheme 6, entry 3). Aside from SmI_2-mediated pinacol coupling, we also studied intramolecular crossed benzoin reaction[37] with **25** catalyzed by Rovis's NHC (N-heterocyclic carbene) catalyst **30**,[38] with the hope of switching the regioselectivity. Although diketo aldehyde **25** underwent intramolecular crossed benzoin

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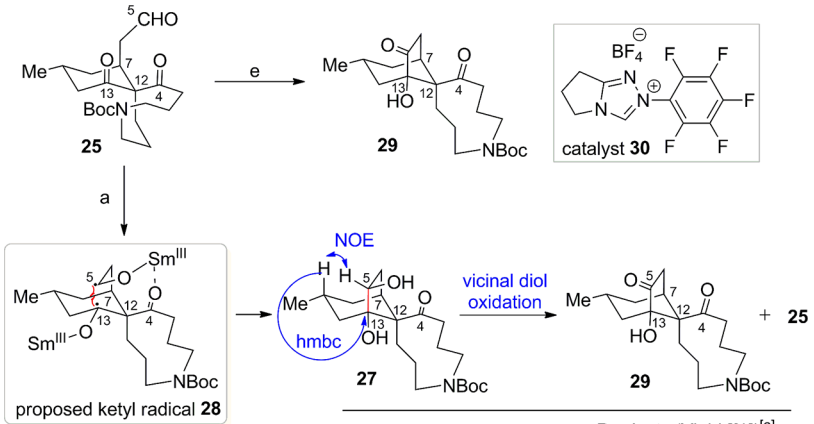
Scheme 6[a]

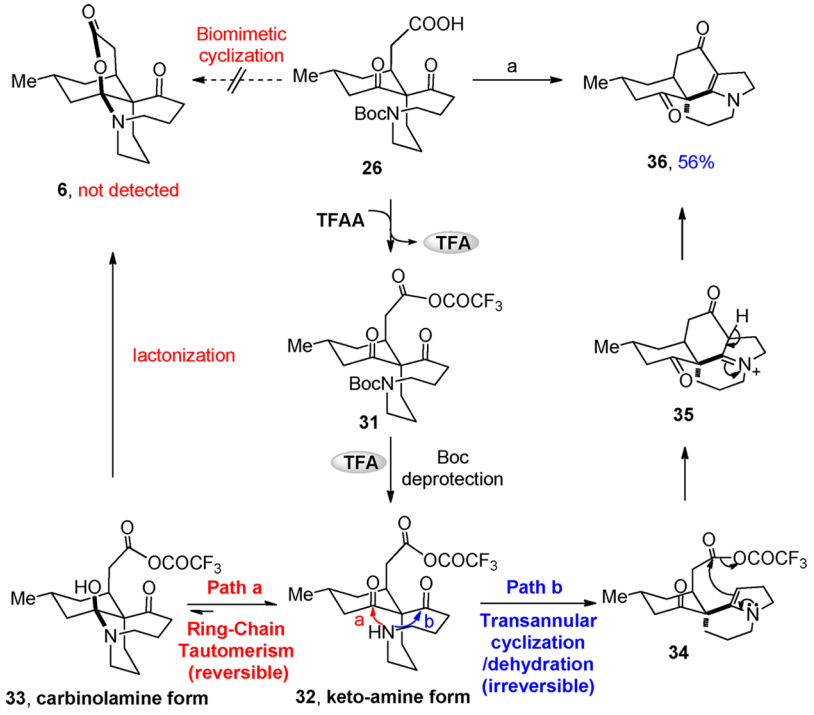


Entry	Conditions	Products (Yield [%])[a]
1	b	**29** (28) + **25** (48)
2	c	**29** (53) + **25** (17)
3	d	**29** (63)

[a] Yield of isolated product.

[a]Reagents and conditions: (a) SmI_2, HMPA, −78 °C to rt, THF, 81%; (b) Dess−Martin periodinane, CH_2Cl_2, rt; (c) IBX, DMSO, rt; (d) TPAP, NMO·H_2O, 4 Å MS, CH_2Cl_2, rt; (e) catalyst **30** (20 mol %), Et_3N, $CHCl_3$, rt, 12 h, 66%.

Scheme 7. Approaches toward the Synthesis of (−)-Lycojapodine A (6) via Biomimetic Cyclization[a]



[a]Reagents and conditions: (a) TFAA, $CHCl_3$, 50 °C, 12 h.

reaction smoothly with catalyst **30**, the undesired isomer **29** was obtained in 66% yield as the sole product.

When our synthetic endeavors toward (+)-alopecuridine (**4**) using diketo aldehyde **25** failed, we then turned our attention to diketo acid **26**. Inspired by the proposed biogentic pathway for (−)-lycojapodine A (**6**), **26** could potentially be the proper substrate for a biomimetic cyclization that ultimately led to **6**. Unfortunately, after extensive screening of reaction conditions, we only obtained the unnatural alkaloid **36** rather than the desired (−)-lycojapodine A (**6**), which was also observed by Yang and co-workers.[13a] Compound **36** was generated in good yield (56%) exclusively upon the treatment of **26** with TFAA (trifluoroacetic anhydride) in chloroform (Scheme 7). Mechanistically, mixed anhydride **31** was initially formed upon the treatment of **26** with TFAA; thus, 1 equiv of TFA was released, which triggered the deprotection of the Boc group at 50 °C and gave intermediate **32**. Conceivably, two different reaction pathways could be expected at this stage: (1) keto amine **32** could attack the carbonyl at C13 and tautomerize to the carbinolamine tautomer **33**, which would undergo further

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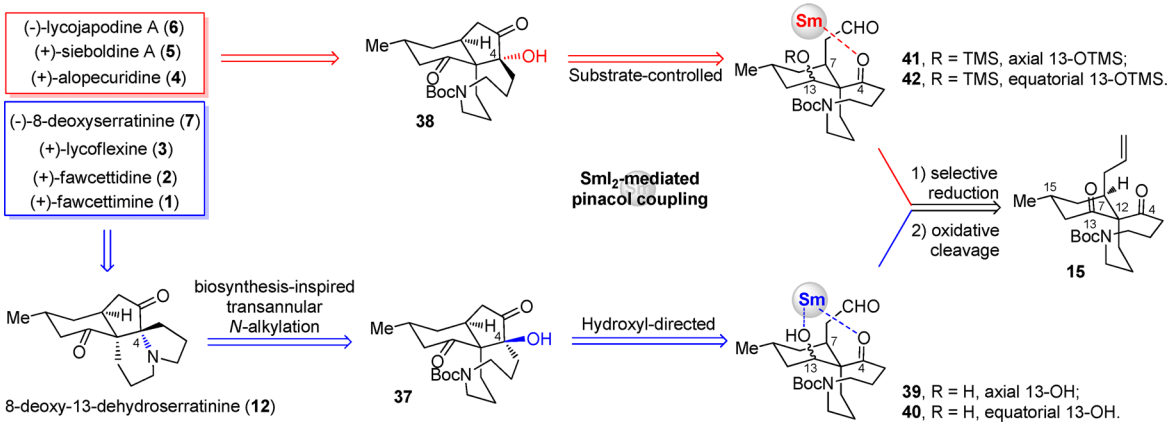
Scheme 8. Evolved Synthetic Strategy

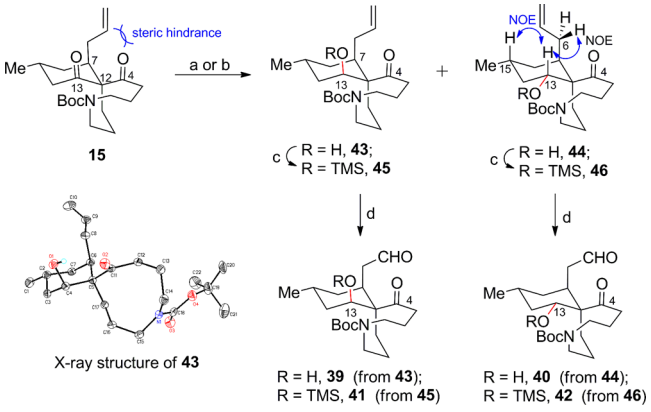


lactonization to furnish the desired (−)-lycojapodine A (**6**) (Scheme 7, path a). Tautomerization between keto amine **32** and carbinoamine **33** would be a reversible equilibrium. (2) Alternatively, keto amine **32** could easily undergo transannular cyclization due to the ring strain of 9-membered aza-cyclononane ring, followed by dehydration to yield enamine **34**. Further intramolecular nucleophilic substitution could be expected to yield tetracyclic iminium salt **35**, which would eventually transform to the thermodynamically stable enamine **36** (Scheme 7, path b). Due to the irreversible transannular cyclization/dehydration in path b, compound **36** was obtained as the sole product during this reaction. Based on this result, we concluded that we might not be able to access (−)-lycojapodine A (**6**) unless we could find solutions to suppress the competitive transannular cyclization and drive the keto amine−carbinolamine equilibrium to favor the formation of carbinolamine form.

Evolved Synthetic Strategy. While direct transformations of neither diketo aldehyde **25** nor diketo acid **26** proved to be successful, we evolved a new synthetic strategy for the syntheses of **1**-**7** from the common intermediate **15** (Scheme 8). With the aim of exploring the potential biomimetic interconversions between fawcettimine and serratinine-type alkaloids, we envisioned that target alkaloids **1**−**3** and **7** would be derived from a common scaffold 8-deoxy-13-serratinine **12**, and the key aza-quaternary carbon center at C4 in **12** could be installed through a biomimetic transanular N alkylation from **37**. As mentioned previously, **4** served as the biogenetic precursor for both **5** and **6**; thus, **4**−**6** could be derived from the common intermediate **38**. The challenging oxa-quaternary carbon centers at C4 in both α-ketols **37** and **38** could be assembled by SmI_2-mediated pinacol coupling of different aldehyde precursors,[39] while the C4 carbon center in α-ketol **37** was expected to be installed by Matsuda's hydroxyl-directed SmI_2-mediated pinacol coupling of 13-hydroxy aldehydes **39** or **40**.[40] We envisioned that without the chelate effect of free hydroxyl group at C13, the relative stereochemistry at C4 in α-ketol **38** could also be fixed correctly during SmI_2-mediated pinacol coupling of 13-OTMS aldehydes **41** or **42**. Finally, all four aldehydes **39**-**42** would be smoothly generated from the common intermediate **15** through selective reduction and oxidative alkene cleavage.

Selective Reduction and Syntheses of Four Pinacol Coupling Precursors 39−42. Because of the steric hindrance of the axial allylic group at C7 and the torsional strain of the aza-cyclononane ring, we anticipated that the carbonyl group at C4 in **15** would be blocked, thus the carbonyl group at C13 could be selectively reduced to provide 13-hydroxy ketone (Scheme 9). Gratifyingly, upon treatment of diketone **15** with

Scheme 9. Selective Reduction[a]



[a]Reagents and conditions: (a) $NaBH_4$, MeOH, rt, **43**, 87%; (b) $NaBH_4$, CH_2Cl_2/MeOH (10/1), rt, **43**, 29%, **44**, 63%; (c) TMSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (d) OsO_4, $NaIO_4$, DABCO, dioxane/H_2O (2/1), rt, for **39**, 86% from **43**; for **40**, quant from **44**; for **41**, 96% for two steps from **43**; for **42**, 46% for two steps from **44**.

$NaBH_4$ in methanol, **43** was generated exclusively in 87% yield. Interestingly, a solvent effect was observed for this reduction reaction,[41] and the other stereoisomer **44** could also be isolated as the major product in 63% yield along with 29% of **43**, when a mixture of CH_2Cl_2/MeOH (10/1) was used. The structures of **43** and **44** were unambiguously confirmed by X-ray diffraction analysis[42] and NOE analysis,[33] respectively. Further Lemieux−Johnson oxidation of **43** afforded **39** in 86% yield. Substrate **44** was also transformed into **40** in quantitative yield. Moreover, a two-step procedure was developed for the syntheses of another two TMS (trimethylsilyl)-protected aldehydes **41** and **42**. Specifically, trimethylsilylation of the secondary alcohol at C13 and subsequent Lemieux−Johnson oxidation provided **41** and **42** in 96% and 46% yield from **43** and **44**, respectively.

SmI_2-Mediated Intramolecular Pinacol Coupling. We next initiated studies on SmI_2-mediated pinacol coupling of all four aldehyde precursors **39**−**42** with the hope of setting up the correct stereochemistry of oxa-quaternary carbon centers at C4 for both α-ketols **37** and **38**. In the early 1990s, Matsuda and co-workers observed that the configuration of the hydroxyl

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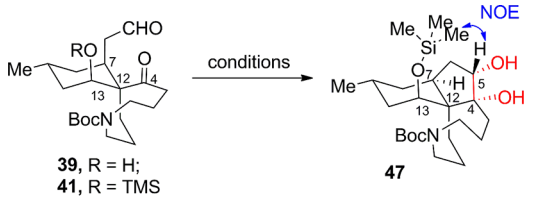
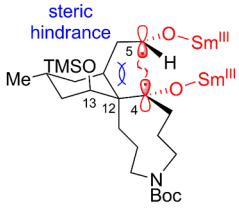
Scheme 10. SmI_2-Mediated Intramolecular Pinacol Coupling with Aldehydes 39 and 41[a]



Entry	Substrates	Conditions	Products (yield [%][a])
1	**39**	a or b	complex mixture
2	**41**	a	**47** (86)
3	**41**	b	**47** (80)

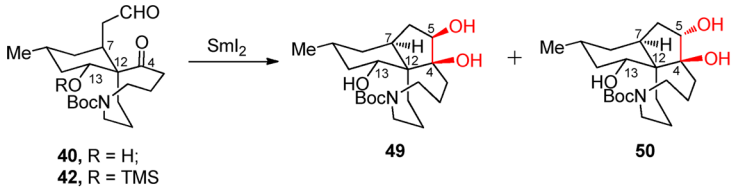
[a] Yield of isolated product.



ketyl radical **48**
(formed in entry 3)

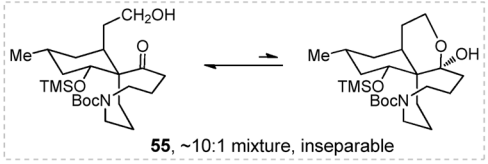
[a]Reagents and conditions: (a) SmI_2 (5 equiv), THF, rt; (b) SmI_2 (5 equiv), HMPA (20 equiv), THF, −78 °C to rt.

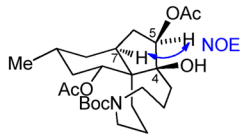
Scheme 11. Hydroxyl-Directed SmI_2-Mediated Intramolecular Pinacol Coupling with Aldehydes 40 and 42[a]

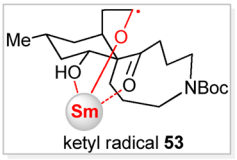


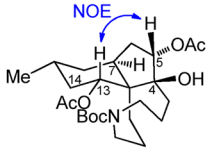
Entry	Substrates	Conditions	Products (yield [%][a])
1	**40**	a	**49** (72) + **50** (18)
2	**40**	b	**50** (67)
3	**42**	a or b	**55** (34)

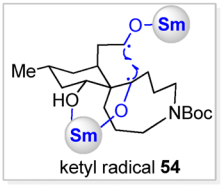
[a] Yield of isolated product.











[a]Reagents and conditions: (a) SmI_2 (5 equiv), THF, rt; (b) SmI_2 (5 equiv), HMPA (20 equiv), THF, −78 °C to rt.

group in the starting material had some influence in controlling the stereochemical outcome of the SmI_2-mediated coupling reactions.[40,43] Later they developed various types of hydroxyl-directed SmI_2-mediated transformations and also demonstrated its applicability to complex natural product synthesis.[43c]

Inspired by Matsuda's studies, we envisioned the free hydroxyl group at C13 in starting materials **39** or **40** could completely control the formation of the desired quaternary stereocenter at C4 with the required stereochemistry for α-ketol **37**. In contrast, without the stereoinduction of hydroxyl group at C13 in the substrates **41** or **42**, the oxa-quaternary carbon center at C4 in α-ketol **38** would also be set up correctly during SmI_2-mediated pinacol coupling reactions due to the steric effect. Initially, **39** and **41** were used as coupling substrates in our investigation. While **39** failed to afford any coupled products under various conditions (Scheme 10, entry 1), we were pleased to find that pinacol coupling of **41** occurred smoothly with SmI_2 either in the presence (Scheme 10, entry 2) or absence of HMPA (Scheme 10, entry 3) and furnished **47** as the sole product in excellent yields. Tu and co-workers had adopted a similar intramolecular pinacol coupling strategy to furnish the first total synthesis of (±)-alopecuridine.[9j] While the configuration at C5 in **47** was confirmed by NOE analysis,[33] the stereochemistry at C4 was later confirmed by subsequent converting diol **47** to the known α-ketol **38** (see Scheme 12).[9j] The high stereoselectivity of **47** observed during pinacol couplings may be attributed to the steric effect caused by the axial trimethylsilyl ether group at C13 in the formation of ketyl radical **48**.

Aldehydes **40** and **42** were also subjected to the pinacol coupling reaction mediated by SmI_2 (Scheme 11). We observed that pinacol coupling of **40** occurred smoothly and provided interesting stereochemical outcomes under different conditions. Specifically, treatment of **40** with SmI_2 gave two coupling products 4,5-*cis* diol **49** in 72% isolated yield and 4,5-*trans* diol **50** in 18% isolated yield (Scheme 11, entry 1). However, when the pinacol coupling was carried out in the presence of HMPA, **50** was isolated as the sole product in 67% yield (Scheme 11, entry 2). Subsequent oxidation of **49** and **50** afforded the known α-ketol **37**,[9i] which confirmed the oxa-quaternary stereocenters at C4 in **49** and **50** (see Scheme 14). Acetylation of **49** and **50** generated two diacetate derivatives **51** and **52**,

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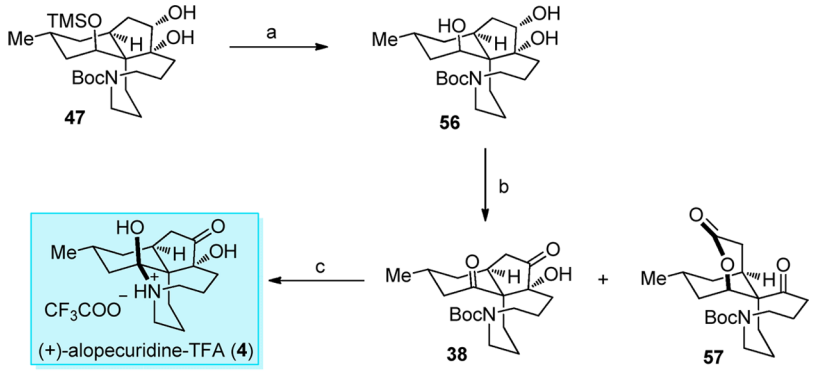
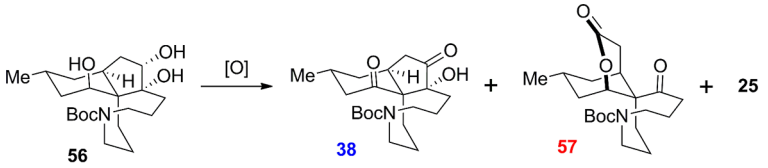
Scheme 12. Total Synthesis of (+)-Alopecuridine (4)[a]



[a]Reagents and conditions: (a) TBAF, THF, rt, 92%; (b) TPAP, NMO·H_2O, 4 Å MS, CH_2Cl_2, rt, 4 h, 50% for **38**, 28% for **57**; (c) TFA, $CHCl_3$, rt, then $NaHCO_3$, 94%.

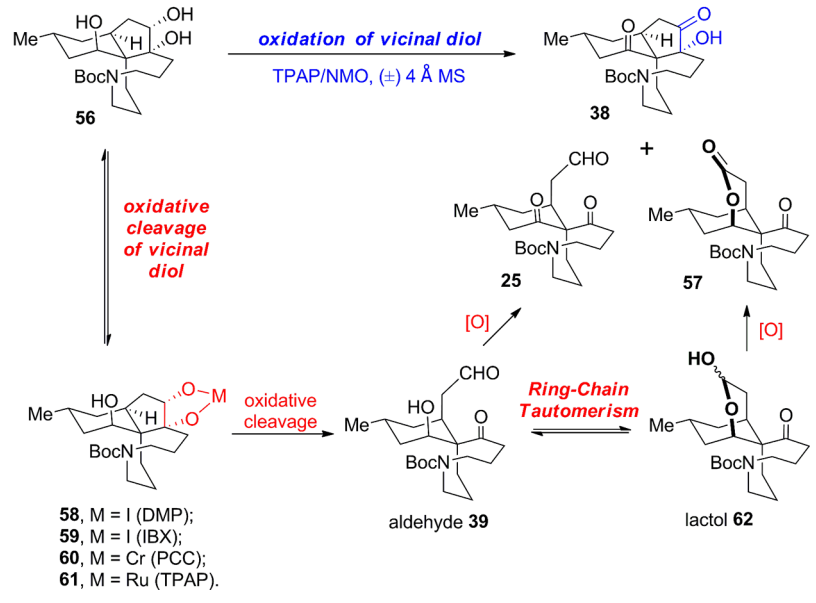
Scheme 13. Oxidation of Triol 56



Entry	Conditions	Products (yield [%][a])
1	TPAP, NMO·H_2O, 4 Å MS, CH_2Cl_2, rt	**38** (50) + **57** (28)
2	PCC, CH_2Cl_2, rt	**25** (36) + **57** (33)
3	Dess-Martin periodinane, CH_2Cl_2, rt	**25** (90)
4	IBX, DMSO, rt	**25** (61) + **57** (18)
5	Dess-Martin periodinane, 4 Å MS, CH_2Cl_2, rt	**25** (57) + **57** (23)
6	IBX, 4 Å MS, DMSO, rt	**25** (30) + **57** (53)
7	**TPAP, NMO·H_2O, CH_2Cl_2, rt**	**38 (89)**
8	Dess-Martin periodinane, H_2O, CH_2Cl_2, rt	**39** (78)

[a] Yield of isolated product.

Proposed Mechanism:



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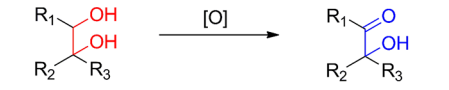
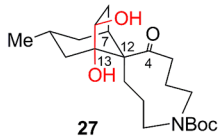
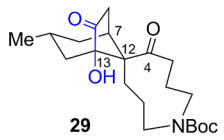
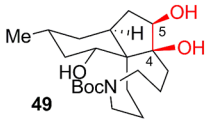
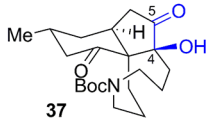
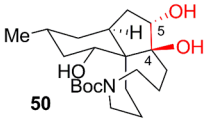
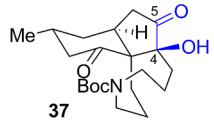
Scheme 14. Oxidation of Vicinal Diols to the Corresponding α-Ketols



Entry	Substrates	Conditions	Desired Products	Products (yield [%][a])
1	 **27**	A	 **29**	**29** (63)
2		B		**29** (78)
3	 **49**	A	 **37**	**37** (74)
4		B		**37** (78)
5	 **50**	A	 **37**	**37** (56)
6		B		**37** (96)

Condition A: TPAP, NMO·H_2O, 4 Å MS, CH_2Cl_2, rt;
Condition B: TPAP, NMO·H_2O, CH_2Cl_2, rt
[a] Yield of isolated product.

respectively. The stereochemistry at C5 in **51** and **52** was determined by NOE analysis,[33] and thus, the relative configurations of **49** and **50** were established as 4,5-*cis* and 4,5-*trans*, respectively. Finally, the reaction of **42** with SmI_2 either in the absence or presence of HMPA resulted in the reduction of aldehyde to afford alcohol **55** instead of producing any desired products (Scheme 11, entry 3).

The observed stereochemical outcome was consistent with Matsuda's finding,[40,43] and could be rationalized by two proposed chelation models, in which the pinacol couplings in the absence or presence of HMPA are likely to generate different cyclic ketyl radicals and produce distinct products. In the absence of HMPA, the single ketyl radical was generated through reduction of the aldehyde moiety, followed by chelation of the Sm^{III} cation with the δ hydroxyl group to form the 8-membered ketyl **53**, which ultimately produced 4,5-*cis* diol **49** as the major product. In the presence of HMPA,[44] a ketyl radical pair was produced, which likely further formed a 6-membered ketyl radical transition state **54** by chelation of the Sm^{III} cation with the β hydroxyl group. Presumably due to the strong dipole−dipole repulsion between the two cationic Sm^{III} complexes, the pinacol coupling proceeded through the diketyl coupling pathway to afford the 4,5-*trans* diol **50** as the sole product.

Total Synthesis of (+)-Alopecuridine (4). With diol **47** in hand, we were able to access alopecurdine (**4**) within several steps (Scheme 12). Removal of the trimethylsilyl group with TBAF afforded triol **56** in 92% yield. On the basis of our pervious results (see Scheme 6), Ley oxidation proved to be suitable for the substrates containing a vicinal diol moiety. Herein, the desired α-ketol **38** was generated in moderate yield (50%) upon Ley oxidation, with 28% byproduct **57**. Finally, (+)-alopecuridine·TFA (**4**) was obtained after removal of the Boc group from **38** with TFA followed by neutralization with $NaHCO_3$. Synthetic alopecuridine·TFA (**4**), $[\alpha]_D$ +69.8 (*c* 0.50, MeOH), exhibited ^1H and ^{13}C NMR spectra indistinguishable from those reported for the natural product.[45] Thus, the asymmetric total synthesis of (+)-alopecuridine (**4**) was accomplished in 13 steps, and the absolute configuration of **4** was also established by total synthesis.

Oxidation of Vicinal Diols. During Ley oxidation of triol **56**, an undesired lactone **57** was also isolated as the minor product in 28% yield (Scheme 13, entry 1), which provoked our interest to further investigate this oxidation reaction. The results are summarized in Scheme 13. Interestingly, oxidation of **56** with PCC and hypervalent iodine oxidants (DMP, IBX, etc) only gave oxidative cleavage products **25** and lactone **57** without any desired α-ketol **38** (Scheme 13, entries 2−4). A plausible mechanism was proposed in order to rationalize the formation of three products: Based on the previous studies by Frigerio and Santagostino, DMP would easily react with vicinal diol to form a 5-membered cyclic diolate irreversibly (**58**, Scheme 13).[34f] Therefore, intermediate **58** could undergo oxidative cleavage smoothly to afford aldehyde **39**, which would either be further oxidized to generate diketo aldehyde **25** or tautomerize to give lactol **62**, which was further oxidized to furnish lactone **57**. More recently, Moorthy and co-workers[35] demonstrated that IBX exhibited similar reactivity as DMP with strained and sterically hindered vicinal diols due to the formation of a similar 5-membered cyclic diolate (**59**, Scheme 13). In the PCC case, we supposed similar 5-membered cyclic diolate (**60**, Scheme 13) could exist and lead to the final oxidized products **25** and **57**. Finally, when **56** was treated with Ley conditions, aside from the formation of desired α-ketol **38**, a reversible formation of 5-membered cyclic diolate **61** could also occur, further oxidative cleavage of **61** would afford aldehyde **39**, at which point, both **25** and **57** could be generated theoretically. However, only **57** was obtained after the reaction, presumably due to the presence of 4 Å MS (molecular sieves). This postulation was further supported by the following control experiments (Scheme 14, entries 5 and 6), where the isolated yields of lactone **57** were significantly improved in the presence

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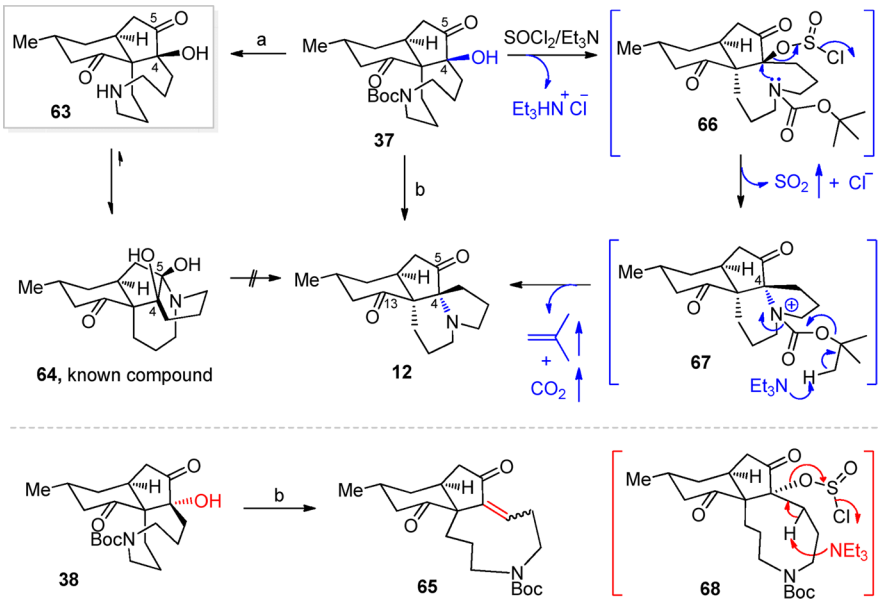
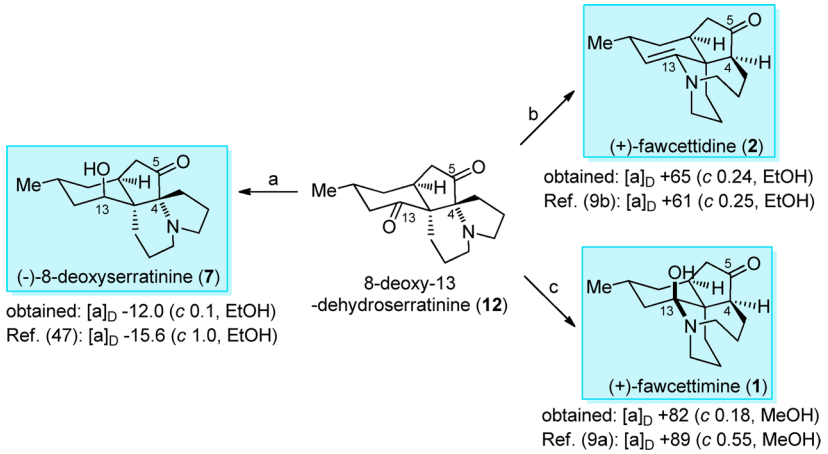
Scheme 15. Synthesis of 8-Deoxy-13-dehydroserratinine (12)[a]



[a]Reagents and conditions: (a) TFA, $CHCl_3$, rt, 92%; (b) $SOCl_2/Et_3N$, THF, −78 to 0 °C, for **12**, 98%; for **65**, 53%.

Scheme 16. Total Syntheses of (+)-Fawcettimine (1), (+)-Fawcettidine (2), and (−)-8-Deoxyserratinine (7)[a]



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

of 4 Å MS. In order to better understand the role of 4 Å MS during this process, we repeated the Ley oxidation of triol **56** in the absence of 4 Å MS (Scheme 14, entry 7). To our surprise, α-ketol **38** was obtained exclusively in excellent yield (89%). Thus, 4 Å MS was proved to be crucial in the formation of lactone **57**, which might play dual roles: (1) favor the formation of cyclic diolates **58**−**61** and consequently prompt the oxidative cleavage of the vicinal diol and (2) drive the aldehyde−lactol tautomerism to favor the formation of lactol tautomer **62**. Finally, during the oxidation of **56** with DMP in the presence of H_2O (5 equiv), aldehyde **39** was generated as the sole product (Scheme 14, entry 8), which provided direct evidence to support our proposed mechanism.

Since the TPAP/NMO·H_2O conditions represented the optimal oxidation conditions for triol **56**, we applied this improved protocol to the oxidations of other vicinal diols, and the results are summarized in Scheme 14. Each substrate was oxidized by TPAP both in the presence (Scheme 14, conditions A) and absence of 4 Å MS (Scheme 14, conditions B) for comparison. We first revisited the oxidation of diol **27**. In comparison to 63% yield under normal Ley conditions (Scheme 14, entry 1), the desired α-ketol **29** was obtained in 78% yield using the improved protocol (Scheme 14, entry 2). We later tried to convert triols **49** and **50** to the known α-ketol **37**,[9i] and in both cases, oxidation reactions using the improved protocol furnished the desired α-ketol **37** in greater yield than those in the presence of 4 Å MS (Scheme 14, entries 3−6). We expect this protocol could serve as a general and efficient method for oxidizing vicinal diols to the corresponding α-ketols.

Synthesis of 8-Deoxy-13-dehydroserratinine (12). With α-ketol **37** in hand, we then focused on the construction of the C4−N bond by using transannular N alkylation (Scheme 15). In initial attempts, we conducted a two-step protocol: removal of the Boc group to furnish compound **63** followed by transannular N alkylation.[46] However, due to the intramolecular carbinoamine formation of **64**, further attempts to use the free amine for the transannular N alkylation failed.[9i]

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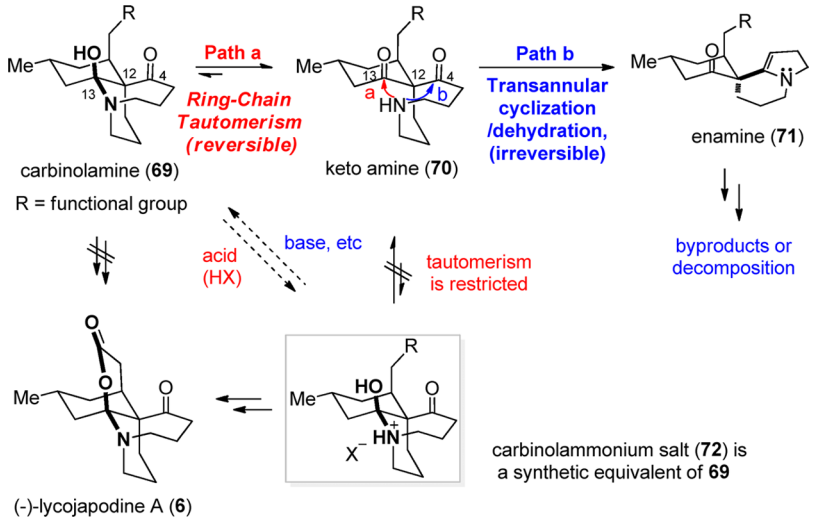
Scheme 17. Tautomer Locking Strategy in the Total Synthesis of (−)-Lycojapodine A (6)



Surprisingly, upon treatment of α-ketol **37** with $SOCl_2$ and Et_3N in THF, the desired 8-deoxy-13-dehydroserratinine (**12**) was obtained in nearly quantitatively yield (98%). In order to elucidate the mechanism of this remarkable process, we conducted several control experiments: (1) upon treatment of **37** with either $SOCl_2$ or Et_3N alone in THF, no reaction occurred and **37** was recovered; (2) Boc-protected piperidine was also subjected to the same reaction conditions; as a result, no reaction was observed; (3) the reaction of **38** with $SOCl_2$/Et_3N in THF resulted in the dehydration of hydroxyl group at C4 to form enone **65** (*Z*/*E* mixture) in 53% yield without any transannular N alkylation products. Based on these results, we speculated that the cascade might be involved with (1) $SOCl_2$ reacting with the C4 hydroxyl group of **37** in the presence of Et_3N to form intermediate **66** as a good leaving group at C4; (2) transannular nucleophilic attack of the lone pair on the nitrogen atom from the back face to afford the ionic acyl ammonium intermediate **67**; and (3) base-triggered removal of the Boc group in **67** furnishing the desired N alkylation product **12**. On the contrary, when **38** was reacted with $SOCl_2$/Et_3N in THF, the similar intermediate **68** was also formed. However, the nitrogen lone-pair electrons in **68** were oriented in the *syn* position to the leaving group at C4, in which case only dehydration occurred to yield enone **65**.

Total Syntheses of (+)-Fawcettimine (1), (+)-Fawcettidine (2), and (−)-8-Deoxyserratinine (7). Having established the key aza-quaternary carbon center at C4 in **12**, we were able to access both fawcettimine- and serratinine-type *Lycopodium* alkaloids from the common intermediate **12** (Scheme 16). Selective reduction of the carbonyl group at C13 with $NaBH_4$ at 0 °C smoothly afforded (−)-8-deoxyserratinine (**7**) in 98% yield. Furthermore, under harsh reducing conditions (Zn/HOAc, 140 °C, 8 h), reductive cleavage of the C4−N bond of **12** followed by dehydration to form the enamine moiety occurred and furnished (+)-fawcettidine (**2**) in excellent yield (95%).[47] Finally, we attempted to selectively cleave the C4−N bond under mild conditions to furnish fawcettimine (**1**).[48] Since the two carbonyl groups at C5 and C13 were also likely to be reduced as well under reductive conditions, the late-stage reductive carbon−nitrogen bond cleavage proved to be challenging. Delightfully, by treatment of substrate **12** with SmI_2 in THF and 2.5 equiv of water as a proton source at 0 °C, (+)-fawcettimine (**1**) could be obtained in moderate yield (51%). With (+)-fawcettimine (**1**) in hand, (+)-lycoflexine (**3**) could be easily obtained in a single operation based on previous studies reported by both the Mulzer group[9d] and the Yang group.[9i] The spectroscopic data of these synthetic samples **1**, **2**, and **7** fully matched with those previously reported.[33]

Tautomer Locking Strategy in the Total Synthesis of (−)-Lycojapodine A (6). With the proposed biogenetic precursor (+)-alopecurdine (**4**) in hand, we finally turned our attention to (−)-lycojapodine A (**6**), the remaining member that has not been synthesized so far. As mentioned previously (see Scheme 7), we realized that it would be extremely crucial to develop an effective tautomer locking strategy to favor the formation of the carbinolamine tautomer and sequester the competitive irreversible transannular cyclization/dehydration for the endgame steps (Scheme 17). According to the proposed biogenetic pathway for (−)-lycojapodine A (**6**) as well as our unsuccessful biomimetic cyclization attempts using diketo acid **26**, carbinolamine **69** would be essentially considered as the key intermediate to access **6** (see Scheme 1, carbinolamine form of acid **14**, and Scheme 7, carbinolamine mixed anhydride **33**). However, because of the reversible tautomerism, carbinolamine **69** could also isomerize to keto amine **70**, which would subsequently undergo irreversible transannular cyclization/dehydration to afford enamine **71**. In the previous synthetic studies we observed that upon treatment of carbinolamine **69** with acid (i.e., TFA) carbinolammonium salt **72** was generated.[49] It seemed likely that this would offer us a solution to lock the carbinolamine tautomer. Thus, the desired reaction pathway for intermediate **72** could occur to furnish (−)-lycojapodine A (**6**). Therefore, we envisioned that both basic conditions and basic workup should be avoided to prevent neutralizing carbinolammonium salt **72** and subsequently releasing the carbinolamine tautomer **69** during the transformations to generate **6**.

Biomimetic Studies Based on the Modified Biogenetic Pathway. Based on the tautomer locking strategy, we further proposed a modified biogenetic pathway for (−)-lycojapodine A (**6**) (Scheme 18) where we expected the alopecuridinium acid derivative, i.e. carbinolammonium trifluoroacetate form of **4**, would be the proper biogenetic precursor compared to the

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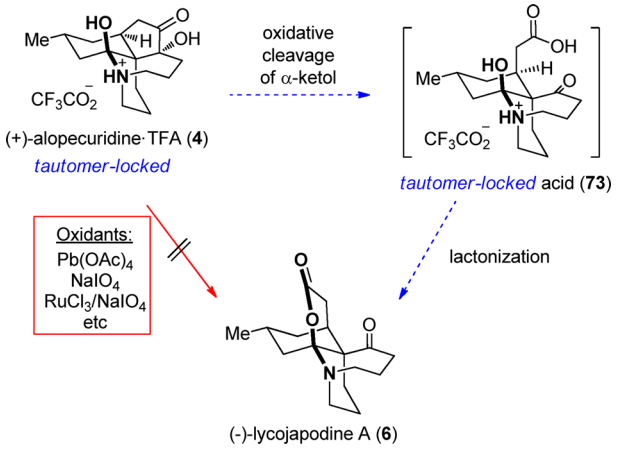
Scheme 18. Biomimetic Studies Based on the Modified Biogenetic Pathway

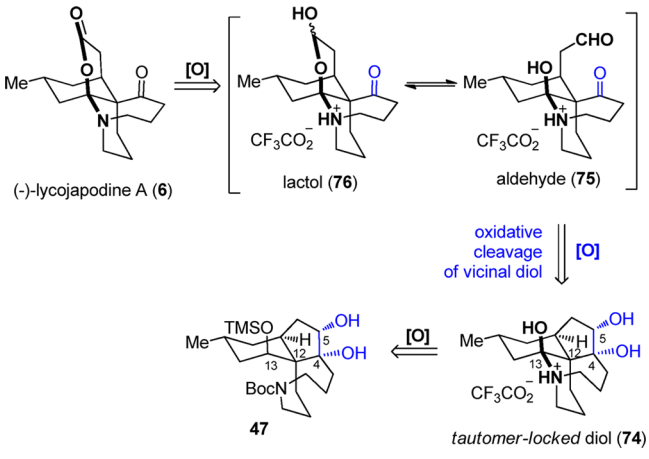


carbinolamine form of **4**. Next we attempted to examine our biogenesis hypothesis with synthetic (+)-alopecuridine·TFA (**4**) (carbinolammonium trifluoroacetate form, secured by ^{1}H and ^{13}C NMR spectra[33]). Although **4** was subjected to various reaction conditions which were known to be effective for oxidative cleavage of the α-hydroxy ketone moiety ($Pb(OAc)_4$,[50] $NaIO_4$,[51] $RuCl_3/NaIO_4$,[52] etc), unfortunately, no desired product **6** was observed, nor could we recover starting material **4**, which was presumably due to the facile decomposition of **4** under these conditions.

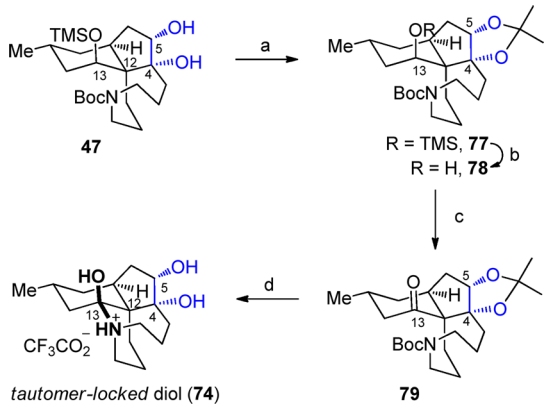
Total Synthesis of (−)-Lycojapodine A (6). Since initial biomimetic transformation of (+)-alopecuridine·TFA (**4**) had failed, at this point, inspired by the formation of lactone **57** during the oxidation reaction of triol **56** (see Scheme 13), we envisioned that the carbinolamine lactone motif of **6** could also be assembled via a similar tandem oxidative cleavage/lactol formation/oxidation process with proper oxidants. Thus, the revised endgame strategy to access (−)-lycojapodine A (**6**) was proposed in Scheme 19. Compound **6** could be derived from diol **74** via a tandem reaction with the intermediates aldehyde **75** and lactol **76**, while the locked tautomer **74** would be efficiently generated from the diol **47** within several operations.

As depicted in Scheme 20, protection of the 4,5-*cis* diol moiety of diol **47** afforded 1,2-acetonide **77** in quantitative

Scheme 19. Revised Synthetic Plan Based on Tautomer Locking Strategy



Scheme 20. Rapid Synthesis of Tautomer-Locked Diol 74[a]



[a]Reagents and conditions: (a) 2,2-dimethoxypropane, *p*-TSA, acetone, quant; (b) TBAF, THF, rt, 99%; (c) TPAP, NMO·H_2O, 4 Å MS, CH_2Cl_2, rt, 95%; (d) concd HCl, MeOH, reflux then TFA, quant.

yield. Removal of the trimethylsilyl group with TBAF and subsequent oxidation of the secondary alcohol using Ley oxidation provided ketone **79**. At this point, the only step remaining to give diol **74** was to remove both 1,2-acetonide and Boc protecting groups. Initial attempts using TFA resulted in selective removal of the Boc group with the acetonide functionality remaining intact. Finally, diol **74** was obtained quantitatively by the treatment of substrate **79** with concentrated HCl in methanol under reflux overnight, and the deprotected product was further dissolved in TFA to afford the tautomer-locked diol **74** (carbinolammonium trifluoroacetate form, confirmed by ^{1}H and ^{13}C NMR spectra[33]).

With diol **74** in hand, the late-stage tandem oxidation process was investigated (Scheme 21). Since this unprecedented tandem process was supposed to be triggered by oxidative cleavage of the 4,5-*cis* diol moiety, diol **74** was treated with various oxidants ($Pb(OAc)_4$, $NaIO_4$, TPAP/NMO, DMP/CH_2Cl_2, IBX/DMSO, etc.). However, the desired product **6** was not detected using these oxidants either in the presence or absence of 4 Å MS, and in most cases starting material **74** was decomposed (Scheme 21, entries 1−4). Finally, we were able to isolate (−)-lycojapodine A (**6**) for the first time in 9% yield applying Moorthy's conditions (Scheme 21, entry 5).[35] The solvent TFA presumably stabilized the carbinolammonium trifluoroacetates **74**−**76** by preventing the release of the corresponding carbinolamine tautomers. Furthermore, when 4 Å MS was added to the reaction (Scheme 21, entry 6), **6** was isolated in moderated yield (38%). Eventually, prolonging the reaction time with elevated reaction temperature could also increase the isolated yield to 54% (Scheme 21, entry 7), which represented the best result for this reaction by far. However, when IBX was replaced by DMP, no reaction occurred and the starting material **74** was recovered (Scheme 21, entry 8).

Biomimetic Transformation of (+)-Alopecuridine (4) into (−)-Lycojapodine A (6). After establishing a feasible route to access (−)-lycojapodine A (**6**) via our tandem oxidation endgame strategy, with an aim to prove the biogenesis hypothesis for (−)-lycojapodine A (**6**), we revisited our modified biogenetic pathway using (+)-alopecuridine·TFA (**4**) (Scheme 22). Gratifyingly, upon the treatment of **4** with IBX and 4 Å MS in TFA (Scheme 22, entry 1), (−)-lycojapodine A (**6**) was isolated in 51% yield. Moreover, when IBX was replaced by Dess-Martin periodinane (Scheme

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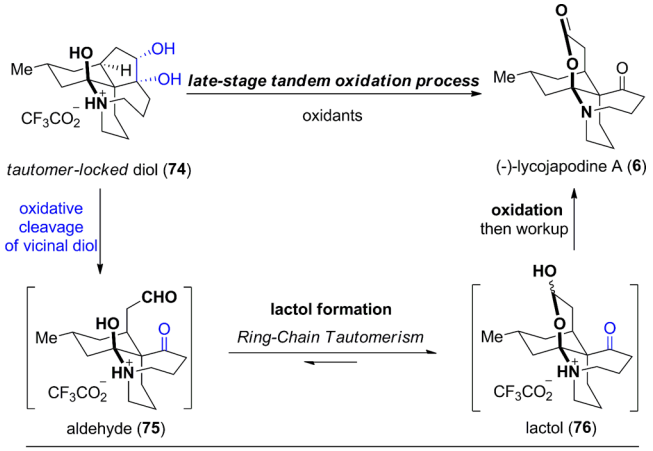
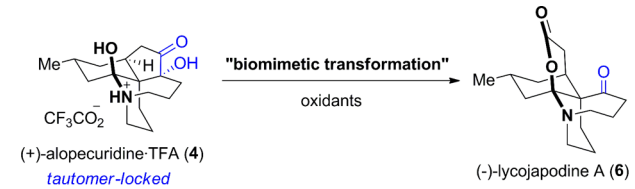
Scheme 21. Late-Stage Tandem Oxidation Process To Access (−)-Lycojapodine A (6)



Entry	Conditions	Product (yield [%][a])
1	$Pb(OAc)_4$, $NaIO_4$, Jones, etc	SM decomposed[b]
2	TPAP, NMO·H_2O, (±) 4 Å MS, CH_2Cl_2, rt;	SM decomposed[b]
3	DMP, (±) 4 Å MS, CH_2Cl_2, rt	SM decomposed[b]
4	IBX/DMSO, (±) 4 Å MS, rt	SM decomposed[b]
5	IBX/TFA, rt, 10 h	**6** (9)
6	IBX/TFA, 4 Å MS, 30 °C, 22 h	**6** (38)
7	**IBX/TFA, 4 Å MS, 30 °C, 1 d, then 40 °C, 1 d**	**6 (54)**
8	Dess-Martin periodinane/TFA, 4 Å MS, 30 °C, 18 h	no reaction

[a] Yield of isolated product. [b] SM = Starting Material

Scheme 22. Biomimetic Transformation of (+)-Alopecuridine (4) into (−)-Lycojapodine A (6)



Entry	Conditions	Product (yield [%][a])
1	**IBX/TFA, 4 Å MS,30 °C, 16 h**	**6 (51)**
2	**Dess-Martin periodinane/TFA, 4 Å MS,30 °C, 4 h**	**6 (86)**
3	IBX/DMSO, rt	SM decomposed[b]
4	Dess-Martin periodinane/CH_2Cl_2, rt	SM decomposed[b]

[a] Yield of isolated product. [b] SM = Starting Material

22, entry 2), the biomimetic transformation of (+)-alopecuridine·TFA (**4**) occurred smoothly and furnished **6** in excellent yield (86%). To the best of our knowledge, these results represent the first example of oxidative cleavage of an α-ketol into a keto acid using hypervalent iodine oxidants.[53] On the other hand, when (+)-alopecuridine·TFA (**4**) was subjected to either IBX/DMSO (Scheme 22, entry 3) or DMP/CH_2Cl_2 (Scheme 22, entry 4), in both cases starting material **4** was decomposed without producing any desired product. These control experiments exhibited the crucial roles of TFA and 4 Å MS for this biomimetic process.

Finally, after careful examination, removal of the Boc group from α-ketol **38** to afford (+)-alopecurdine·TFA (**4**) and its subsequent biomimetic transformation into (−)-lycojapodine A (**6**) were successfully merged into a single and more efficient operation (Scheme 23). Specifically, α-ketol **38** was first dissolved in TFA at rt, while Boc was removed in less than 2 h, and the keto ammonium trifluoroacetate form of alopecuridine (**4**) was formed. At this stage, the attempt to add DMP and 4 Å MS into the reaction only resulted in the recovery of alopecuridine (**4**) without obtaining any desired (−)-lycojapodine A (**6**). In order to completely lock the carbinolamine tautomer, the keto ammonium trifluoroacetate form of alopecuridine (**4**) was allowed to stay in TFA for additional 16 h at rt. Subsequently, DMP and 4 Å MS were added into the solution, and the reaction was quenched after an additional 4 h to furnish (−)-lycojapodine A (**6**) in excellent yield (83%). Synthetic lycojapodine A (**6**), $[\alpha]_D$ −137 (*c* 0.20, $CHCl_3$), exhibited ^1H and ^{13}C NMR spectra indistinguishable from those reported for the natural isolate.[33] Thus, the total synthesis of (−)-lycojapodine A (**6**) was accomplished either in 15 steps through late-stage tandem oxidation process or 13 steps through one-pot biomimetic transformation, and the absolute configuration of **6** was also established.

CONCLUSION

Collective total syntheses of both fawcettimine- and serratinine-type *Lycopodium* alkaloids (+)-fawcettimine (**1**), (+)-fawcettidine (**2**), (+)-alopecuridine (**4**), (−)-lycojapodine A (**6**), and (−)-8-deoxyserratinine (**7**) were accomplished from a common precursor on the basis of a highly concise route (all were accomplished in either 12 or 13 steps).

A number of synthetic steps in the syntheses are noteworthy: (a) the intramolecular *C*-alkylation was applied to install the challenging spiro quaternary carbon center and the aza-cyclononane ring; (b) the hydroxyl-directed SmI_2-mediated pinacol coupling was used to establish the correct relative stereochemistry of the oxa-quaternary center; (c) the unprecedented tandem transannular *N*-alkylation and removal of Boc group realized a biosynthesis-inspired process to afford the desired tetracyclic skeleton; (d) the unprecedented, late-stage IBX/TFA-mediated tandem oxidation process through a novel tautomer locking strategy was used to afford (−)-lycojapodine A (**6**) efficiently; (e) a biomimetic transformation into (−)-lycojapodine A (**6**) from (+)-alopecurdine (**4**) was also achieved based on a modified biogenetic pathway for (−)-lycojapodine A.

Moreover, the combination of a tautomer locking protocol and a remarkable late-stage IBX/TFA-mediated tandem oxidation process for the effective construction of the challenging carbinolamine lactone motif, our improved Ley oxidation protocol for oxidation of vicinal diols, as well as the use of hypervalent iodine oxidants like IBX or DMP for oxidative cleavage of α-ketol into keto acid may find further synthetic applications.

EXPERIMENTAL SECTION

General Experimental Methods. ^1H NMR and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer at ambient temperature with $CDCl_3$ as the solvent unless otherwise stated. Chemical shifts are reported in parts per million relative to chloroform (^1H, δ 7.26 ppm; ^{13}C, δ 77.00 ppm). Data for ^1H NMR are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constants. Infrared spectra were recorded on a Fourier transform infrared spectrophotometer. High-resolution mass spectra were

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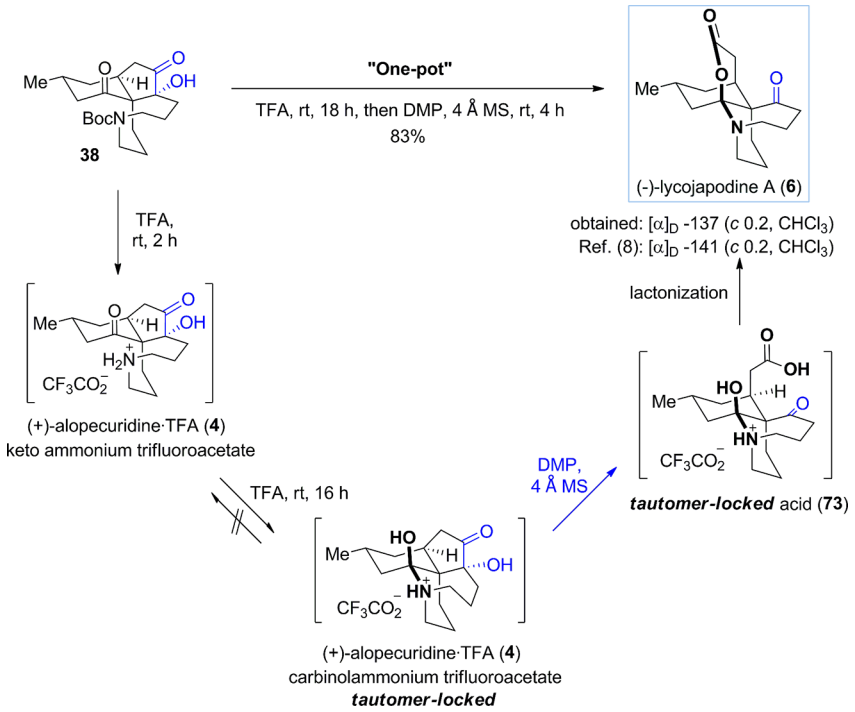
Scheme 23. One-Pot Operation to (−)-Lycojapodine A (6)



obtained on a FT-ICR spectrometer. Optical rotations were recorded on a digital polarimeter at 589 nm and are recorded as $[\alpha]^{21}_{D}$ (concentration in grams/100 mL solvent). Analytical thin-layer chromatography was performed using 0.25 mm silica gel 60-F plates. Flash chromatography was performed using 200−400 mesh silica gel. Yields refer to chromatographically and spectroscopically pure materials, unless otherwise stated. Methylene chloride, toluene, and 1,2-dichloroethane were distilled from calcium hydride; tetrahydrofuran were distilled from sodium/benzophenone ketyl prior to use. All reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted.

Aldehyde 19. To a stirred solution of TBDPS-protected 3-hydroxypropanal (13.2 g, 42.3 mmol)[54] in chloroform (180 mL) was added 4-amino-1-butanol (3.90 mL, 42.3 mmol) dropwise. The mixture was stirred at rt for 2 h under argon, and then sodium borohydride (8.25 g, 211 mmol) was added in one portion, followed with anhydrous methanol (18 mL), and the reaction mixture was stirred at rt for an additional 40 h. The reaction was quenched with water and extracted with EtOAc, and the combined extracts were washed with saturated $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give the crude product (16.3 g), which was redissolved in chloroform (165 mL). Di-*tert*-butyl dicarbonate (9.33 g, 42.3 mmol) was added to the solution, and the reaction mixture was stirred overnight at rt and then concentrated in vacuo to afford a crude oil residue, which was purified by flash silica gel chromatography (PE/EtOAc = 4/1) to afford primary alcohol **80** (16.5 g, 80%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.70−7.67 (m, 4H), 7.42−7.36 (m, 6H), 3.70−3.69 (m, 2H), 3.64 (t, J = 6.1 Hz, 2H), 3.30−3.23 (m, 4H), 1.79 (s, 2H), 1.61−1.53 (m, 4H), 1.42 (s, 9H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 135.3, 133.5, 129.5, 127.5, 79.1, 62.0, 61.5, 46.7, 44.2, 31.6, 29.5, 28.4, 28.3, 28.2, 26.7, 24.4, 19.0, 19.0; IR (neat) ν_{max} 3415, 2928, 2857, 1691, 1670 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{28}H_{44}NO_4Si$ 486.3034, found 486.3043. The primary alcohol **80** (14.5 g, 30 mmol) was dissolved in 250 mL anhydrous CH_2Cl_2, pyridium chlorochromate (9.65 g, 45 mmol) and silica gel (9.65 g) were added sequentially, and the reaction mixture was stirred at rt for 4 h. The reaction was concentrated in vacuo and purified by silica gel column chromatography (PE/EtOAc = 7/1 to 4/1) to afford aldehyde **19** (13.2 g, 92%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.66−7.64 (m, 4H), 7.43−7.36 (m, 6H), 3.67 (t, J = 6.1 Hz, 2H), 3.27 (s, 2H), 3.21 (s, 2H), 2.42 (t, J = 7.1 Hz, 2H), 1.84−1.79 (m, 2H), 1.76 (m, 2H), 1.41 (s, 9H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 155.4, 135.3, 133.4, 129.4, 127.5, 79.1, 61.4, 46.1, 44.2, 40.9, 31.5, 30.9, 28.2, 26.6, 20.6, 19.0; IR (neat) ν_{max} 2931, 2858, 1692, 1558, 1541 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{28}H_{42}NO_4Si$ 484.2878, found 484.2876.

Compound 16. Lithium chloride (2.20 g, 55 mmol) was first heated at 110 °C under high vacuum in a 500 mL flask for 2−3 h, copper bromide (7.34 g, 51.0 mmol), anhydrous THF (230 mL), and methyl sulfide (4.53 mL, 61 mmol) were added sequentially, and the mixture was stirred for 30 min until the formation of a yellow solution. Then the reaction mixture was cooled to −78 °C, and allylMgBr **18** (1 M in Et_2O, freshly prepared, 44 mL, 44 mmol) was added dropwise. The solution was stirred for 1 h, (5*R*)-5-methylcyclohex-2-enone **17** (4.79 mL, 41 mmol) was added, and the mixture was stirred for an additional 1 h at −78 °C before a solution of aldehyde **19** (9.0 g, 18.6 mmol) in anhydrous THF (20 mL) was added. The final mixture was stirred at −78 °C for an additional 3 h before being quenched by addition of satd aq NH_4Cl at −78 °C and then warmed to rt. The aqueous layer was extracted with CH_2Cl_2, the combined organic extracts were dried over Na_2SO_4, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography on silica gel (PE/EtOAc = 5/1) to afford two diastereomeric mixtures **16** (8.96 g, 73%) as a slightly yellow oil. Data for two isomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.61 (m, 4H), 7.43−7.36 (m, 6H), 5.74−5.66 (m, 1H), 5.05−5.01 (m, 2H), 3.86 (s, 1H), 3.67 (t, J = 5.9 Hz, 2H), 3.27−3.15 (m, 4H), 2.40 (s, 1H), 2.16 (s, 6H), 1.76 (s, 3H), 1.64−1.59 (m, 4H), 1.52 (s, 2H), 1.41 (s, 9H), 1.05 (s, 9H), 0.98 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.3, 155.9, 135.5, 133.7, 129.6, 127.6, 117.2, 79.3, 70.9, 61.6, 60.0, 48.7, 46.5, 44.2, 37.9, 37.0, 34.8, 32.8, 31.7, 29.7, 28.4, 28.4, 26.8, 24.7, 21.2, 19.2; IR (neat) ν_{max} 3420, 2928, 2858, 1694, 1473 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{38}H_{58}NO_5Si$ 636.4079, found 636.4079.

Keto Diol 20. The substrate **16** (8.90 g, 14 mmol) was dissolved in 100 mL of anhydrous CH_3CN, and $Et_3N{\cdot}3HF$ (11.76 mL, 70 mmol) was added at rt. After being stirred for 70 h at rt, the reaction mixture was concentrated in vacuo and purified on silica gel (PE/EtOAc = 1/1 to 1/2) to provide keto diol **20** (5.24 g, 94%) as a slightly yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74−5.64 (m, 1H), 5.05−5.00 (m,

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2H), 3.78 (s, 2H), 3.53 (s, 2H), 3.34 (s, 2H), 3.14 (s, 2H), 2.50−2.39 (m, 2H), 2.15 (m, 7H), 1.64 (m, 5H), 1.51−1.49 (s, 2H), 1.44 (s, 9H), 0.96 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.5, 157.0, 135.4, 117.4, 80.0, 70.6, 59.5, 58.3, 48.6, 47.0, 42.6, 37.9, 36.9, 35.0, 33.5, 30.6, 29.7, 29.6, 29.5, 28.4, 25.1, 20.8; IR (neat) ν_{max} 3421, 2924, 1691, 1665, 1479 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{22}H_{40}NO_5$ 398.2901, found 398.2899.

Diketo Mesylate 21. To a solution of keto diol **20** (4.69 g, 11.7 mmol) in CH_2Cl_2 (230 mL) was added collidine (4.70 mL, 35.2 mmol) at rt. The solution was cooled to 0 °C, and methanosulfonyl chloride (1.0 mL, 12.9 mmol) was added dropwise. After being stirred at 4−7 °C for 24 h, the reaction mixture was quenched with water and extracted with CH_2Cl_2, the combined organic extracts were washed with 0.5% HCl (aq) and dried over Na_2SO_4, and the filtrate was concentrated in vacuo to provide a crude residue, which was used directly in the next step. The crude compound was redissolved in CH_2Cl_2 (200 mL), and the solution was cooled to 0 °C. Dess−Martin periodinane (7.46 g, 17.6 mmol) was added, and the reaction mixture was warmed to room temperature and stirred at rt for 3 h. Then satd aq $NaHCO_3$ and satd aq $Na_2S_2O_3$ were added to the mixture at 0 °C, and the solution was stirred for additional 1 h. The aqueous phase was separated and extracted with CH_2Cl_2, the combined organic extracts were dried over Na_2SO_4, and the filtrate was concentrated in vacuo and purified on silica gel (PE/EtOAc = 2/1) to provide diketo mesylate **21** (4.43 g, 80%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (m, 1H), 5.03−4.97 (m, 2H), 4.21 (t, J = 6.1 Hz, 2H), 3.29−3.21 (m, 4H), 2.99 (s, 3H), 2.58−2.38 (m, 4H), 2.15−1.76 (m, 9H), 1.41 (s, 9H), 1.22−1.14 (m, 2H), 0.95 (d, J = 5.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.3, 200.0, 183.0, 155.4, 136.6, 135.2, 117.6, 116.4, 111.0, 79.8, 67.5, 48.5, 46.8, 44.8, 43.5, 40.1, 40.0, 39.4, 38.3, 37.3, 35.7, 34.6, 33.9, 33.0, 28.9, 28.8, 28.3, 22.5, 22.1, 21.9, 20.7; IR (neat) ν_{max} 2927, 1691, 1639, 1602, 1456, 1414 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{23}H_{40}NO_7S$ 474.2520, found 474.2519; $[\alpha]^{21}_D$ +115.0 (c 2.0, $CHCl_3$).

Diketo Iodide 22. The diketo mesylate **21** (4.19 g, 8.85 mmol) was dissolved in anhydrous acetone (170 mL), and sodium iodide (13.4 g, 88.5 mmol) was added in one portion at rt. After being stirred for 19 h at rt, the reaction mixture was concentrated in vacuo and purified on silica gel (PE/EtOAc = 4/1) to afford two inseparable diastereomers (3.77 g, 84%) as a yellow oil. Data for two isomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81−5.63 (m, 1H), 5.06−4.98 (m, 2H), 3.31−3.11 (m, 7H), 2.62−2.37 (m, 4H), 2.16−1.65 (m, 9H), 1.44−1.43 (m, 9H), 1.27−1.15 (m, 1H), 0.97 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.2, 155.5, 136.6, 135.3, 117.6, 116.5, 111.0, 79.7, 67.6, 48.6, 47.6, 40.1, 40.0, 39.5, 38.3, 35.8, 34.6, 34.0, 33.0, 32.4, 29.0, 28.4, 22.5, 22.0, 20.8; IR (neat) ν_{max} 2955, 2926, 1694, 1591 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{22}H_{37}INO_4$ 506.1762, found 506.1772; $[\alpha]^{21}_D$ +133.0 (c 1.0, $CHCl_3$).

***C*-Alkylation Product 15.** To a solution of diketo iodide **22** (2.15 g, 4.25 mmol) in anhydrous MeCN[30] (300 mL, concentration: 0.014 M) was added DBU (2.59 mL, 17 mmol) at rt, and the reaction was stirred for 40 h until the reaction was complete. The reaction mixture was concentrated in vacuo and purified on silica gel (PE/EtOAc = 10/1 to 4/1) to afford *O*-alkylation byproduct **23** (225 mg, 14%) and *C*-alkylation product **15** (1.04 g, 65%) both as white powder. For *C*-alkylation Product **15**: mp 79.5−82.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76−5.65 (m, 1H), 4.98−4.94 (m, 2H), 3.38 (s, 1H), 3.14−2.96 (m, 4H), 2.72−2.55 (m, 1H), 2.42−1.91 (m, 10H), 1.78−1.55 (m, 4H), 1.47 (s, 9H), 0.99 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3, 157.1, 137.3, 115.9, 79.8, 70.4, 47.6, 47.0, 40.0, 37.7, 33.2, 31.2, 29.8, 28.5, 23.3, 21.7, 21.0; IR (neat) ν_{max} 2928, 1684, 1480 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calculated for $C_{22}H_{35}NO_4Na$ 400.2458, found 400.2459; $[\alpha]^{21}_D$ −11.8 (c 1.0, $CHCl_3$). For *O*-alkylation product **23**, the structure was determined by 2D-NMR analysis; see the Supporting Information for details: mp 126.5−129.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (m, 1H), 4.87 (d, J = 13.2 Hz, 2H), 4.04−3.93 (m, 2H), 3.35−3.22 (m, 4H), 2.83 (s, 1H), 2.66−2.62 (m, 1H), 2.55−2.42 (m, 2H), 2.13−2.06 (m, 3H), 1.87−1.61 (m, 6H), 1.37 (s, 9H), 0.93 (d, J = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 201.6, 164.0, 163.3, 156.3, 156.0, 138.0, 119.8, 118.9, 115.2, 79.3, 67.6, 66.9, 48.8, 48.1, 47.0, 42.1, 38.8, 34.4, 33.1, 32.6, 29.6, 28.5, 28.3, 25.9, 25.3, 23.8, 21.8; IR (neat) ν_{max} 2923, 2869, 1691, 1635, 1600, 1459 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{22}H_{35}NO_4Na$ 400.2458, found 400.2456; $[\alpha]^{21}_D$ +57.4 (c 1.0, $CHCl_3$).

Aldehyde 25. To a solution of **15** (45 mg, 0.119 mmol) in dioxane/water (v/v = 2/1, totally 9 mL) were added DABCO (69.0 mg, 0.597 mmol), $NaIO_4$ (258 mg, 1.19 mmol), and OsO_4 (1.2 mL, 0.0119 mmol, 2.5 wt % solution in *tert*-butyl alcohol) sequentially, and the reaction was stirred at rt and monitored by TLC. After the reaction was complete, EtOAc and satd aq $Na_2S_2O_3$ were added, the aqueous phase was separated and extracted with EtOAc, the combined organic extracts were dried over Na_2SO_4, and the filtrate was concentrated in vacuo and purified on silica gel (PE/EtOAc = 4/1) to afford aldehyde **25** (38.0 mg, 81%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 3.45−3.28 (m, 1H), 3.10−2.85 (m, 3H), 2.83−2.54 (m, 3H), 2.51−2.17 (m, 6H), 2.16−1.82 (m, 4H), 1.80−1.59 (m, 3H), 1.48 (s, 9H), 1.04 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.5, 210.8, 200.9, 157.1, 79.9, 70.1, 47.8, 46.9, 44.7, 37.5, 34.4, 34.4, 30.8, 29.7, 28.4, 23.4, 21.5, 21.0; IR (neat) ν_{max} 2928, 1721, 1691, 1480, 1410, 1229, 1166 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{21}H_{34}NO_5$: 380.2432, found 380.2436; $[\alpha]^{21}_D$ +11.3 (c 1.0, $CHCl_3$).

Diketo Acid 26. To a stirred solution of aldehyde **25** (13 mg, 0.034 mmol) and 2-methyl-2-butene (40 μL) in *t*-butyl alcohol/water (v/v = 3/1, totally 2.0 mL), was added a solution of $NaClO_2$ (12 mg, 0.103 mmol) and NaH_2PO_4 (12.5 mg, 0.103 mmol) in 0.5 mL of water dropwise at 0 °C, and the resulting solution was stirred at 0 °C for 0.5 h, warmed to rt, and stirred for additional 5 h. The reaction was quenched by addition of satd aq NH_4Cl at 0 °C, warmed to rt, and extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, and the filtrate was concentrated in vacuo to afford diketo acid **26** (14 mg, quant) as a colorless solid:[13] mp 62.5−63.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.46 (s, 1H), 3.24 (s, 1H), 3.01 (s, 2H), 2.89 (s, 1H), 2.67 (m, 3H), 2.46−2.36 (m, 2H), 2.35−2.09 (m, 6H), 2.03 (d, J = 14.7 Hz, 1H), 1.91 (s, 1H), 1.73 (d, J = 5.1 Hz, 3H), 1.49 (d, J = 19.5 Hz, 9H), 1.03 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6, 210.7, 176.7, 157.1, 80.0, 76.7, 70.1, 47.7, 46.9, 37.1, 34.8, 33.7, 30.5, 29.7, 28.5, 23.4, 21.4, 21.0; IR (neat) ν_{max} 2928, 1695, 1482, 1414, 1366, 1166 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{21}H_{33}NNaO_6$ 418.2200, found 418.2209; $[\alpha]^{22}_D$ −30.0 (c 0.1, $CHCl_3$).

Diol 27. To a solution of aldehyde **25** (40 mg, 0.105 mmol) and HMPA (370 μL, 2.11 mmol) in THF (degassed, 10 mL) at −78 °C was added SmI_2 (0.1 M in THF, freshly prepared, 5.3 mL, 0.527 mmol). The resulting mixture was stirred at −78 °C for 1 h, warmed slowly to rt, and stirred at this temperature for additional 12 h. The reaction mixture was quenched with satd aq Rochelle's salt at 0 °C and diluted with EtOAc. The aqueous layer was separated and extracted with EtOAc. The organic extracts were combined and dried over Na_2SO_4, and the filtrate was concentrated in vacuo and purified by silica gel column chromatography (PE/EtOAc = 4/1) to afford **27** (32 mg, 81%) as a white solid. The relative stereochemistry of **27** was determined by 2D-NMR analysis; see the Supporting Information for details: mp 173.5−174.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (d, J = 5.4 Hz, 1H), 3.32 (d, J = 10.5 Hz, 1H), 3.23−2.98 (m, 2H), 3.01 (s, 1H), 2.82 (s, 1H), 2.52 (s, 1H), 2.37 (s, 2H), 2.26−2.10 (m, 2H), 2.01−1.73 (m, 5H), 1.73−1.53 (m, 4H), 1.51−1.33 (m, 12H), 0.94 (d, J = 5.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 155.8, 81.0, 79.6, 75.4, 41.3, 41.2, 36.5, 35.9, 34.1, 29.7, 28.5, 24.8, 23.3, 22.6, 22.4, 21.4; IR (neat) ν_{max} 3420, 2927, 2868, 1681, 1412, 1365, 1168, 1088 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{21}H_{36}NO_5$ 382.2588, found 382.2586; $[\alpha]^{22}_D$ +2.40 (c 0.5, $CHCl_3$).

Ketol 29 from Keto Diol 27. To a stirred solution of keto diol **27** (25 mg, 0.066 mmol) in anhydrous CH_2Cl_2 (3.5 mL) at rt were added 4-methylmorpholine *N*-oxide monohydrate (27 mg, 0.20 mmol), 4 Å MS (54 mg), and TPAP (1.2 mg, 0.033 mmol) sequentially. The resulting mixture was stirred at rt for 3 h. After the reaction was complete, the reaction mixture was directly purified by silica gel chromatography (PE/EtOAc = 2/1) to afford ketol **29** (15 mg, 63%) as a light yellow solid: mp 65.3−67 °C; ^{1}H NMR (400 MHz, $CDCl_3$)

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δ 4.00−3.47 (m, 1H), 3.25−2.78 (m, 4H), 2.51 (s, 1H), 2.32 (s, 2H), 2.23−2.11 (m, 1H), 2.05 (dt, J = 8.3, 6.9 Hz, 4H), 1.86 (m, 2H), 1.84−1.54 (m, 7H), 1.47 (s, 9H), 0.97 (d, J = 5.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.0, 216.6, 156.8, 82.3, 79.8, 63.3, 49.3, 45.5, 39.3, 39.1, 34.1, 33.7, 33.1, 32.9, 29.7, 28.5, 24.8, 24.0, 23.7, 23.0, 22.2, 21.5, 21.4; IR (neat) ν_{max} 3515, 2928, 2870, 1754, 1686, 1413, 1367, 1165 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{21}H_{34}NO_5$ 380.2431, found 380.2421; $[\alpha]^{22}_D$ +15.0 (c 0.02, $CHCl_3$).

Ketol 29 from Diketo Aldehyde 25. To a solution of diketo aldehyde **25** (28.4 mg, 0.0748 mmol) and triethylamine (10.2 μL, 0.0748 mmol) in $CHCl_3$ (4 mL) was added NHC catalyst **30** (5.4 mg, 0.015 mmol) at rt. The resulting mixture was stirred at rt for 12 h. The mixture was concentrated in vacuo and purified by silica gel column chromatography (toluene/acetonitrile = 9/1) to afford compound **29** (18.6 mg, 66%) as a light yellow solid.

Compound 36. To a solution of compound **26** (4.2 mg, 0.011 mmol) in $CHCl_3$ (1 mL), was added trifluoroacetic anhydride (20 μL, 0.143 mmol) dropwise at 0 °C. The resulting mixture was stirred at 50 °C for 12 h. The reaction mixture was concentrated in vacuo and dissolved in CH_2Cl_2 (5 mL). To this solution was added solid sodium bicarbonate (50 mg, 0.6 mmol). The resulting mixture was stirred at rt for 1 h. After filtration and concentration in vacuo, compound **36** (1.6 mg, 56%) was gained as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (td, J = 10.6, 5.5 Hz, 1H), 3.42−3.20 (m, 2H), 2.91−2.70 (m, 3H), 2.53 (dd, J = 18.9, 15.8 Hz, 2H), 2.42 (dd, J = 12.4, 7.9 Hz, 2H), 2.37−2.31 (m, 1H), 2.25−2.15 (m, 1H), 1.9−1.82 (m, 2H), 1.70−1.57 (m, 2H), 1.53 (dd, J = 13.5, 2.5 Hz, 1H), 1.45−1.39 (m, 3H), 1.08 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.0, 188.8, 166.4, 109.5, 54.2, 52.8, 46.6, 45.0, 44.3, 40.1, 33.3, 30.0, 29.9, 23.8, 22.3, 19.3; IR (neat) ν_{max} 3395, 2917, 2866, 1705, 1605, 1561, 1520, 1455, 1266, 1187 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{16}H_{22}NO_2$ 260.1645, found 260.1643; $[\alpha]^{21}_D$ −87.0 (c 0.1, $CHCl_3$).

Procedures for the Syntheses of Hydroxyl Ketones 43 and 44. *Method A: $NaBH_4$/MeOH.* To a solution of the *C*-alkylation product **15** (380 mg, 1.01 mmol) in 15 mL of anhydrous MeOH, was added sodium borohydride (77.7 mg, 2.01 mmol) at rt. The reaction mixture was stirred at rt for 3.5 h. The reaction mixture was concentrated in vacuo, diluted with CH_2Cl_2 and quenched by satd aq $NaHCO_3$. The aqueous phase was separated and extracted with CH_2Cl_2, and the combined organic extracts were dried over Na_2SO_4, and the filtrate was concentrated in vacuo and purified on silica gel (PE/EtOAc = 10/1 to 1/1) to afford hydroxy ketone **43** (333 mg, 87%) as a colorless solid.[9j]

Method B: $NaBH_4$/MeOH/CH_2Cl_2. The *C*-alkylation product **15** (396 mg, 1.05 mmol) was dissolved in 80 mL of anhydrous CH_2Cl_2, sodium borohydride (81.0 mg, 2.10 mmol), and anhydrous methanol (8 mL) were added sequentially. The reaction mixture was stirred at rt for 5 h before quenched by satd aq $NaHCO_3$. The aqueous phase was separated and extracted with CH_2Cl_2, and the combined organic extracts were dried over Na_2SO_4, and the filtrate was concentrated in vacuo and purified on silica gel (PE/EtOAc = 10/1 to 1/1) to afford hydroxyl ketone **43** (114 mg, 29%) as a colorless solid and hydroxy ketone **44** (250 mg, 63%) as a colorless oil. For hydroxyl ketone **43**, its structure was determined by X-ray diffraction analysis; see the Supporting Information for details: mp 122.3−123.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70−5.59 (m, 1H), 4.98−4.94 (m, 2H), 4.10 (s, 1H), 3.64−3.60 (m, 2H), 3.44−3.38 (m, 1H), 3.25−3.20 (m, 1H), 3.06−2.64 (m, 4H), 2.18−1.86 (m, 6H), 1.74−1.60 (m, 5H), 1.49 (s, 9H), 1.33−1.25 (m, 3H), 0.89 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.0, 157.1, 138.2, 115.8, 79.8, 68.7, 59.6, 48.7, 47.5, 45.2, 43.7, 39.9, 36.4, 36.4, 32.1, 31.5, 31.3, 29.5, 28.5, 23.0, 22.1, 21.8, 21.1, 20.2; IR (neat) ν_{max} 3547, 2925, 1688, 1638, 1481, 1456 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{22}H_{37}NO_4Na$ 402.2615, found 402.2613; $[\alpha]^{21}_D$ +71.2 (c 1.0, $CHCl_3$). For hydroxyl ketone **44**, the relative stereochemistry was determined by 2D-NMR analysis; see the Supporting Information for details: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68−5.58 (m, 1H), 5.00−4.94 (m, 2H), 4.22 (dd, J = 12.0, 3.6 Hz, 1H), 3.62 (t, J = 13.0 Hz, 1H), 3.42−3.15 (m, 2H), 3.07−2.76 (m, 3H), 2.41 (dd, J = 18.1, 7.7 Hz, 1H), 2.20−2.03 (m, 3H), 1.96−1.90 (m, 2H), 1.81−1.62 (m, 5H), 1.52−1.45 (m, 10H), 1.29−1.16 (m, 2H), 0.92 (d, J = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.1, 220.0, 157.1, 136.7, 116.3, 116.2, 79.6, 69.4, 69.3, 60.0, 59.6, 49.5, 48.3, 45.2, 43.6, 41.4, 37.3, 34.3, 32.6, 31.7, 30.6, 29.7, 28.5, 27.3, 25.3, 23.8, 23.3, 23.2, 22.4, 22.1; IR (neat) ν_{max} 3560, 2926, 1684, 1480 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{22}H_{37}NO_4Na$ 402.2615, found 402.2614; $[\alpha]^{21}_D$ −14.2 (c 1.0, $CHCl_3$).

Aldehyde 39. To a solution of **43** (30.2 mg, 0.08 mmol) in dioxane/water (v/v = 2/1, totally 9 mL) were added DABCO (46.0 mg, 0.40 mmol), $NaIO_4$ (171.9 mg, 0.80 mmol), and OsO_4 (100.8 μL, 0.008 mmol, 2.5 wt % solution in *tert*-butyl alcohol) sequentially, and the reaction was stirred at rt and monitored by TLC. After the reaction was complete, ethyl acetate and satd aq $Na_2S_2O_3$ were added, the aqueous phase was separated and extracted with EtOAc, the combined organic extracts were dried over Na_2SO_4, and the filtrate was concentrated in vacuo and purified on silica gel (PE/EtOAc = 3/2) to afford aldehyde **39** (26.0 mg, 86%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 4.27−4.09 (m, 1H), 3.49 (s, 1H), 3.30−2.90 (m, 5H), 2.62 (s, 1H), 2.34−1.69 (m, 8H), 1.63−1.47 (m, 11H), 1.33−1.22 (m, 3H), 0.95−0.87 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5, 157.0, 79.9, 68.7, 58.9, 58.4, 49.2, 47.9, 47.1, 44.2, 36.2, 33.3, 32.4, 31.8, 31.5, 29.6, 29.1, 28.5, 26.7, 23.5, 23.1, 22.2, 21.8, 21.0, 20.3, 14.1; IR (neat) ν_{max} 3441, 2925, 1692, 1481, 1456 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{21}H_{35}NO_5Na$ 404.2407, found 404.2410; $[\alpha]^{21}_D$ +34.4 (c 1.0, $CHCl_3$).

Aldehyde 40. To a solution of **44** (140 mg, 0.368 mmol) in dioxane/water (v/v = 2/1, totally 18 mL) were added DABCO (211 mg, 1.84 mmol), $NaIO_4$ (795.8 mg, 3.68 mmol), and OsO_4 (467 μL, 0.0368 mmol, 2.5 wt % solution in *tert*-butyl alcohol) sequentially. The reaction was stirred at rt and monitored by TLC. After the reaction was complete, ethyl acetate and satd aq $Na_2S_2O_3$ were added. The aqueous phase was separated and extracted with EtOAc, the combined organic extracts were dried over Na_2SO_4, and the filtrate was concentrated in vacuo and purified by silica gel column chromatography (PE/EtOAc = 1/1) to afford aldehyde **40** (140.5 mg, quant) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1H), 4.10−4.07 (m, 1H), 3.54 (t, J = 12.1 Hz, 1H), 3.36−3.27 (m, 1H), 3.14 (m, 2H), 3.03−2.96 (m, 2H), 2.85−2.81 (m, 1H), 2.69−2.60 (m, 2H), 2.38 (dd, J = 17.8, 7.4 Hz, 1H), 2.18−2.15 (m, 1H), 2.00−1.93 (m, 2H), 1.79−1.62 (m, 4H), 1.53−1.38 (m, 10H), 1.31−1.17 (m, 3H), 0.92 (d, J = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.4, 199.9, 157.0, 79.7, 69.7, 69.5, 59.4, 58.9, 49.8, 48.5, 45.9, 44.7, 44.0, 37.0, 34.1, 33.8, 33.1, 32.6, 32.2, 28.4, 26.9, 25.6, 23.6, 23.2, 23.2, 22.5, 21.8; IR (neat) ν_{max} 3544, 2927, 2868, 1723, 1684, 1558, 1481, 1412 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{21}H_{35}NO_5Na$ 404.2407, found 404.2410; $[\alpha]^{21}_D$ −7.7 (c 1.0, $CHCl_3$).

Aldehyde 41. Compound **43** (309.7 mg, 0.816 mmol) was dissolved in 40 mL of anhydrous CH_2Cl_2, the resulting solution was cooled to −78 °C, then 2,6-lutidine (387 μL, 3.264 mmol) was added dropwise, followed by TMSOTf (297 μL, 1.632 mmol). After being stirred at −78 °C for 3 h, the reaction was quenched by addition of satd aq $NaHCO_3$ at −78 °C and then warmed to rt. The aqueous layer was extracted with CH_2Cl_2, the combined organic extracts were dried over Na_2SO_4, and the filtrate was concentrated in vacuo to give a crude oil, which was used directly in the next step. The crude compound (0.816 mmol) was redissolved in dioxane/water (v/v = 2/1, totally 60 mL), and then DABCO (467 mg, 4.08 mmol), $NaIO_4$ (1.763 g, 8.16 mmol), and OsO_4 (4.14 mL, 0.0816 mmol, 2.5 wt % solution in *tert*-butyl alcohol) were added sequentially. The reaction mixture was stirred at rt and monitored by TLC. After the reaction was complete, ethyl acetate and satd aq $Na_2S_2O_3$ were added. The aqueous phase was separated and extracted with EtOAc, the combined organic extracts were dried over Na_2SO_4, and the filtrate was concentrated in vacuo and purified by silica gel column chromatography (PE/EtOAc = 4/1) to afford aldehyde **41** (354.6 mg, 96% for two steps) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 4.31 (s, br, 1H), 3.63 (m, 1H), 3.32 (m, 1H), 3.15 (m, 1H), 3.04 (d, J = 17.7 Hz, 1H), 2.91 (d, J = 12.7 Hz, 1H), 2.75 (s, 1H), 2.56−2.31 (m, 2H), 2.15 (s, 1H), 2.10−1.73 (m, 4H), 1.73−1.58 (m, 3H), 1.49 (s, 9H), 1.42−1.23 (m, 4H), 0.86 (d, J = 6.4 Hz, 3H), 0.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.7, 204.2, 157.2, 79.6, 74.0, 67.0, 59.4, 46.2, 37.4, 35.3, 28.8, 28.4,

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22.7, 21.8, 20.9, 20.6, 20.2; IR (neat) ν_{max} 2951, 2914, 1720, 1692, 1410, 1365 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{24}H_{43}NO_5SiNa$ 476.2802, found 476.2807; $[\alpha]^{21}_D$ +11.2 (*c* 1.0, $CHCl_3$).

Aldehyde ***42***. Compound **44** (39.9 mg, 0.105 mmol) was dissolved in 10 mL of anhydrous CH_2Cl_2, the resulting solution was cooled to −78 °C, then 2,6-lutidine (49 μL, 0.420 mmol) was added dropwise, followed by TMSOTf (38.4 μL, 0.210 mmol). After being stirred at −78 °C for 3 h, the reaction was quenched by addition of satd aq $NaHCO_3$ at −78 °C and then warmed to rt. The aqueous layer was extracted with CH_2Cl_2, the combined organic extracts were dried over Na_2SO_4, and the filtrate was concentrated in vacuo to give a crude oil, which was used directly in the next step. The crude compound (30 mg, 0.07 mmol) was redissolved in dioxane/water (v/v = 2/1, totally 9 mL), and then DABCO (40 mg, 0.35 mmol), $NaIO_4$ (151 mg, 0.70 mmol), and OsO_4 (88.7 μL, 0.007 mmol, 2.5 wt % solution in *tert*-butyl alcohol) were added sequentially. The reaction mixture was stirred at rt and monitored by TLC. After the reaction was complete, ethyl acetate and satd aq $Na_2S_2O_3$ were added. The aqueous phase was separated and extracted with EtOAc, the combined organic extracts were dried over Na_2SO_4, and the filtrate was concentrated in vacuo and purified by silica gel column chromatography (PE/EtOAc = 4/1) to afford aldehyde **42** (21.9 mg, 46% for two steps) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1H), 4.08 (dd, *J* = 10.6, 4.2 Hz, 1H), 3.53−3.15 (m, 2H), 2.90−2.87 (m, 1H), 2.75−2.72 (m, 2H), 2.54−2.39 (m, 2H), 2.29−2.03 (m, 5H), 1.70−1.58 (m, 4H), 1.47 (s, 9H), 1.35−1.22 (m, 4H), 0.90 (d, *J* = 5.9 Hz, 3H), 0.11−0.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.9, 201.0, 157.1, 79.5, 70.6, 69.1, 59.7, 48.8, 47.9, 44.8, 44.3, 43.2, 40.1, 33.8, 33.2, 32.3, 28.5, 26.4, 25.6, 23.8, 23.2, 22.3, 21.9, 14.1, 0.7, 0.6; IR (neat) ν_{max} 2953, 2927, 1724, 1692, 1482, 1454, 1411 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{24}H_{43}NO_5SiNa$ 476.2803, found 476.2810; $[\alpha]^{21}_D$ +7.0 (*c* 0.1, $CHCl_3$).

SmI_2-Mediated Intramolecular Pinacol Coupling Protocol for Diol 47. *Method A.* To a solution of aldehyde **41** (262 mg, 0.58 mmol) in anhydrous THF (degassed, 35 mL) at −78 °C was added SmI_2 (0.1 M in THF, freshly prepared, 29.0 mL, 2.90 mmol).[55] The resulting mixture was quickly warmed to rt and stirred for an additional 3 h. The reaction mixture was quenched with satd aq Rochelle's salt at 0 °C and diluted with EtOAc. The aqueous phase was separated and extracted with EtOAc, the combined organic extracts were dried over Na_2SO_4, and the filtrate was concentrated in vacuo and purified by silica gel column chromatography (PE/EtOAc = 5/1) to afford diol **47** (227 mg, 86%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 4.18 (s, 1H), 4.12 (s, 1H), 3.57 (m, 2H), 3.10−2.94 (m, 2H), 2.83 (dd, *J* = 17.1, 6.7 Hz, 1H), 2.74 (s, 1H), 2.05 (m, 8H), 1.82−1.61 (m, 5H), 1.51 (s, 9H), 1.30−1.16 (m, 2H), 1.16−1.04 (m, 1H), 0.85 (d, *J* = 6.3 Hz, 3H), 0.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 82.8, 81.7, 79.8, 69.9, 52.8, 50.8, 49.9, 41.2, 38.4, 37.8, 33.0, 31.0, 28.6, 28.4, 24.0, 22.0, 19.5, 0.5; IR (neat) ν_{max} 3413, 2948, 2923, 2359, 2340, 1677, 1482 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{24}H_{46}NO_5Si$ 456.3140, found 456.3145; $[\alpha]^{21}_D$ +11.0 (*c* 0.5, $CHCl_3$).

Method B. To a solution of aldehyde **41** (160 mg, 0.352 mmol) and HMPA (618 μL, 3.52 mmol) in THF (degassed, 20 mL) at −78 °C was added SmI_2 (0.1 M in THF, freshly prepared, 17.6 mL, 1.76 mmol). The resulting mixture was stirred at −78 °C, slowly warmed to rt, and stirred for 3 h at rt. The reaction mixture was quenched with satd aq Rochelle's salt and diluted with EtOAc. The aqueous layer was separated and extracted with EtOAc, the combined organic extracts were dried over Na_2SO_4, and the filtrate was concentrated in vacuo and purified by silica gel column chromatography (PE/EtOAc = 5/1) to afford **47** (128 mg, 80%) as a colorless oil. The relative stereochemistry of **47** was determined by 2D-NMR analysis; see the Supporting Information for details.

Hydroxyl-Directed SmI_2-Mediated Intramolecular Pinacol Protocol from 40. *Method A.* To a solution of aldehyde **40** (106 mg, 0.288 mmol) in anhydrous THF (degassed, 10 mL) at −78 °C was added SmI_2 (0.1 M in THF, freshly prepared, 14.4 mL, 1.44 mmol). The resulting mixture was quickly warmed to room temperature and stirred for an additional 5 h. The reaction mixture was quenched with satd aq Rochelle's salt and diluted with EtOAc. The aqueous phase was separated and extracted with EtOAc, the combined organic extracts were dried over Na_2SO_4, and the filtrate was concentrated in vacuo and purified by silica gel column chromatography (PE/EtOAc = 2/1 to 1/1) to afford triol **49** (79.0 mg, 72%) as a slightly yellow oil and triol **50** (19.0 mg, 18%) as a slightly yellow powder.

Method B. To a solution of aldehyde **40** (17.0 mg, 0.044 mmol) and HMPA (156.6 μL, 0.891 mmol) in anhydrous THF (degassed, 4.0 mL) at −78 °C was added SmI_2 (0.1 M in THF, freshly prepared, 2.23 mL, 0.223 mmol). The resulting mixture was stirred for 1 h at −78 °C, and then warmed to rt and stirred for additional 1 h. The reaction mixture was quenched with satd aq Rochelle's salt and diluted with EtOAc. The aqueous phase was separated and extracted with EtOAc, the combined organic extracts were dried over Na_2SO_4, and the filtrate was concentrated in vacuo and purified by silica gel column chromatography (PE/EtOAc = 2/1) to afford triol **50** (11.4 mg, 67%) as a slightly yellow powder. For triol **49**: ^1H NMR (400 MHz, $CDCl_3$) δ 4.52 (t, *J* = 8.0 Hz, 1H), 4.16 (d, *J* = 10.1 Hz, 1H), 3.95 (s, 1H), 3.67−3.20 (m, 5H), 2.88−2.67 (m, 3H), 2.22−2.04 (m, 5H), 1.81 (s, br, 3H), 1.64 (d, *J* = 10.4 Hz, 4H), 1.46−1.31 (m, 10H), 1.03−1.01 (m, 1H), 0.92 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 87.0, 79.8, 79.5, 73.7, 50.8, 47.6, 44.7, 39.7, 38.3, 33.6, 32.3, 31.9, 29.7, 29.3, 28.6, 26.4, 24.6, 23.1, 22.7, 21.9, 20.5, 14.11; IR (neat) ν_{max} 3375, 2924, 1666, 1480, 1454, 1414 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{21}H_{37}NO_5Na$ 406.2564, found 406.2562; $[\alpha]^{21}_D$ +5.0 (*c* 1.0, $CHCl_3$). For triol **50**: mp 76.0 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 4.90 (s, 1H), 4.42−4.27 (m, 2H), 3.58−3.10 (m, 6H), 2.75 (s, 1H), 1.97−1.78 (m, 7H), 1.65−1.58 (m, 4H), 1.45 (s, 9H), 1.29−1.18 (m, 2H), 1.08−1.01 (m, 1H), 0.91 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 83.8, 80.0, 79.6, 79.3, 71.8, 71.3, 68.0, 51.1, 50.6, 47.5, 46.6, 46.1, 38.9, 38.5, 38.2, 34.9, 32.2, 29.7, 28.5, 25.8, 23.3, 22.8, 22.2, 22.0, 21.6, 14.1; IR (neat) ν_{max} 3351, 2920, 1661, 1478, 1454, 1417 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{21}H_{37}NO_5Na$ 406.2564, found 406.2563; $[\alpha]^{21}_D$ −6.8 (*c* 1.0, $CHCl_3$).

Diacetate ***51***. The triol **49** (17.2 mg, 0.045 mmol) was dissolved in 0.7 mL of anhydrous pyridine, then DMAP (2.7 mg, 0.023 mmol) and Ac_2O (21.0 μL, 0.225 mmol) were added sequentially. The reaction mixture was stirred at rt and monitored by TLC. After the reaction was complete, the reaction mixture was concentrated in vacuo and purified by silica gel column chromatography (PE/EtOAc = 4/1) to afford diacetate **51** (17.5 mg, 83%) as a colorless oil. The relative stereochemistry of **51** was determined by 2D-NMR analysis; see the Supporting Information for details: ^1H NMR (400 MHz, $CDCl_3$) δ 5.30 (dd, *J* = 11.7, 4.5 Hz, 1H), 5.23−5.19 (m, 1H), 4.02−3.97 (m, 1H), 3.78 (t, *J* = 12.3 Hz, 1H), 3.72 (t, *J* = 12.8 Hz, 1H), 3.67−3.44 (m, 1H), 3.28 (dd, *J* = 13.9, 6.2 Hz, 1H), 3.10−3.03 (m, 1H), 2.82−2.73 (m, 1H), 2.50 (s, 1H), 2.19−2.15 (m, 1H), 2.09−2.07 (m, 3H), 1.98 (s, 5H), 1.80−1.73 (m, 2H), 1.67−1.55 (m, 4H), 1.47 (s, 9H), 1.33−1.25 (m, 3H), 1.07 (dd, *J* = 17.7, 8.6 Hz, 1H), 0.90 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 170.7, 157.5, 85.2, 85.0, 79.0, 72.8, 51.0, 50.8, 48.3, 47.7, 44.5, 43.9, 41.5, 41.4, 37.2, 32.7, 32.5, 29.6, 28.6, 26.2, 26.0, 25.7, 23.1, 22.0, 21.7, 21.6, 21.4, 21.1, 21.0, 20.9; IR (neat) ν_{max} 3446, 2926, 1732, 1692, 1558, 1540, 1487 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{25}H_{41}NO_7Na$ 490.2775, found 490.2784; $[\alpha]^{21}_D$ −72.5 (*c* 0.4, $CHCl_3$).

Diacetate ***52***. The triol **50** (9.6 mg, 0.025 mmol) was dissolved in 1.0 mL of anhydrous pyridine, and then DMAP (1.5 mg, 0.013 mmol) and Ac_2O (12.0 μL, 0.125 mmol) were added sequentially. The reaction mixture was stirred at rt and monitored by TLC. After the reaction was complete, the reaction mixture was concentrated in vacuo and purified on silica gel (PE/EtOAc = 2/1) to afford diacetate **52** (9.8 mg, 84%) as a colorless oil. The relative stereochemistry of **52** was determined by 2D-NMR analysis; see the Supporting Information for details: ^1H NMR (400 MHz, $CDCl_3$) δ 5.67 (dd, *J* = 11.7, 4.7 Hz, 1H), 4.70 (dt, *J* = 10.6, 5.3 Hz, 1H), 3.74−3.45 (m, 2H), 3.31−3.25 (m, 1H), 3.15−3.08 (m, 1H), 2.94−2.87 (m, 1H), 2.79−2.66 (m, 1H), 2.30−2.29 (m, 1H), 2.22−1.76 (m, 11H), 1.62−1.51 (m, 4H), 1.46 (s, 9H), 1.40−1.25 (m, 4H), 1.15−1.07 (m, 1H), 0.91 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 171.1, 157.2, 83.7, 82.2, 82.1, 79.1, 73.0, 72.9, 50.1, 50.0, 47.7, 47.2, 45.0, 44.4, 41.3, 37.5, 32.3, 32.2, 32.0, 31.6, 31.0, 30.4, 28.6, 25.6, 25.5, 25.1, 22.6, 22.4, 21.8, 21.6,

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21.4, 21.2, 14.1; IR (neat) ν_{max} 3502, 2921, 1717, 1686, 1486, 1455, 1412 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{25}H_{41}NO_7Na$ 490.2775, found 490.2782; $[\alpha]^{21}_D$ +8.5 (*c* 0.4, $CHCl_3$).

Compound ***55***. To a solution of aldehyde **42** (21.9 mg, 0.048 mmol) and HMPA (84.8 μL, 0.480 mmol) in THF (degassed, 5.0 mL) at −78 °C was added SmI_2 (0.1 M in THF, freshly prepared, 2.4 mL, 0.24 mmol). The resulting mixture was stirred for 1 h before being warmed to rt and stirred for additional 2 h. The reaction mixture was quenched with satd aq Rochelle's salt and diluted with EtOAc. The aqueous layer was separated and extracted with EtOAc, the combined organic extracts were dried over Na_2SO_4, and the filtrate was concentrated in vacuo and purified by silica gel column chromatography (PE/EtOAc = 6/1) to afford **55** as inseparable mixtures of primary alcohol and hemiketal (ratio = 10/1, total 7.4 mg, 34%) as a slightly yellow oil. Data for inseparable mixtures: ^1H NMR (400 MHz, $CDCl_3$) δ 4.18 (dd, *J* = 11.4, 4.0 Hz, 2H), 3.64−3.22 (m, 4H), 2.84−2.59 (m, 3H), 2.33−2.19 (m, 1H), 2.08−1.96 (m, 5H), 1.67−1.37 (m, 14H), 1.27−1.21 (m, 3H), 0.90 (d, *J* = 6.1 Hz, 3H), 0.11−0.06 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.0, 157.2, 98.4, 79.4, 69.6, 68.8, 61.2, 60.4, 49.7, 48.8, 48.0, 44.3, 43.0, 40.6, 37.3, 32.2, 31.2, 28.6, 28.6, 27.1, 25.4, 23.1, 22.1, 1.0, 0.6; IR (neat) ν_{max} 3462, 2951, 2918, 2868, 2850, 1697, 1482, 1456, 1415 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{24}H_{46}NO_5Si$ 456.3140, found 456.3142; $[\alpha]^{21}_D$ +2.5 (*c* 0.32, MeOH).

Triol ***56***. To a solution of diol **47** (57 mg, 0.125 mmol) in anhydrous THF (6 mL), was added TBAF (0.626 mL, 0.626 mmoL) dropwise at 0 °C. The resulting mixture was stirred at rt for 45 h. The reaction mixture was concentrated in vacuo and purified directly by silica gel column chromatography (PE/EtOAc = 10/1) to afford triol **56** (44 mg, 92%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 4.32−4.30 (m, 1H), 4.15 (s, 1H), 3.41 (t, *J* = 13.7 Hz, 2H), 3.17−2.94 (m, 3H), 2.65 (s, 1H), 2.19 (m, 3H), 2.15−1.74 (m, 5H), 1.65 (m, 3H), 1.59−1.39 (m, 10H), 1.39−1.22 (m, 3H), 1.22−1.04 (m, 2H), 0.88 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 82.0, 81.9, 79.9, 68.5, 51.5, 50.0, 49.5, 41.0, 39.6, 37.2, 32.9, 30.5, 28.6, 28.5, 25.6, 23.3, 22.2, 19.4; IR (neat) ν_{max} 3450, 2925, 1668, 1414, 1264 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{21}H_{38}NO_5$ 384.2744, found 384.2749; $[\alpha]^{21}_D$ +17.6 (*c* 0.5, $CHCl_3$).

Normal Ley Oxidation for the Synthesis of Ketol ***38***. To a stirred solution of triol **56** (32 mg, 0.083 mmol) in anhydrous CH_2Cl_2 (3.5 mL) at rt were added 4-methylmorpholine *N*-oxide monohydrate (29 mg, 0.21 mmol), 4 Å MS (58 mg) and TPAP (1.4 mg, 0.0042 mmol) sequentially. The resulting mixture was stirred at rt for 5 h. After the reaction was complete, the reaction mixture was directly purified by silica gel chromatography (PE/EtOAc = 2/1) to afford ketol **38** (15.7 mg, 50%) as a colorless oil[7] and lactone **57** (8.8 mg, 28%) as a white solid. Data for ketol **38**: ^1H NMR (400 MHz, $CDCl_3$) δ 3.74 (dd, *J* = 13.6, 3.5 Hz, 1H), 3.70−3.60 (m, 1H), 2.90−2.79 (m, 2H), 2.71−2.61 (m, 1H), 2.59−2.47 (m, 1H), 2.47−2.41 (m, 1H), 2.41−2.37 (m, 1H), 2.37−2.29 (m, 1H), 2.15 (m, 1H), 2.12−1.96 (m, 4H), 1.93−1.86 (m, 1H), 1.86−1.73 (m, 3H), 1.73−1.62 (m, 2H), 1.45 (s, 9H), 1.33−1.40 (m, 1H), 1.07 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.3, 211.4, 156.7, 79.7, 78.7, 64.9, 49.8, 48.5, 47.9, 41.5, 36.0, 33.6, 31.2, 28.5, 26.3, 23.9, 23.2, 22.8, 22.3; IR (neat) ν_{max} 3392, 2925, 2870 1747, 1690, 1478, 1414 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{21}H_{33}NO_5Na$:402.2251, found 402.2256; $[\alpha]^{21}_D$ +88.0 (*c* 0.1, $CHCl_3$). The relative stereochemistry of **57** was determined by 2D-NMR analysis; see the Supporting Information for details. Data for lactone **57**: mp 193.1−195 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 4.86 (dd, *J* = 5.7, 2.5 Hz, 1H), 3.31 (s, 1H), 3.07 (dd, *J* = 12.5, 6.9 Hz, 5H), 2.45 (dd, *J* = 7.0, 3.2 Hz, 1H), 2.39 (s, 1H), 2.34 (s, 1H), 2.22 (d, *J* = 23.6 Hz, 2H), 2.16−2.13 (m, 1H), 2.11−1.99 (m, 2H), 1.96−1.86 (m, 1H), 1.76 (m, 2H), 1.60−1.54 (m, 2H), 1.52 (d, *J* = 2.0 Hz, 1H), 1.49 (s, 9H), 0.99 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9, 171.4, 156.9, 155.8, 79.9, 79.7, 79.1, 54.0, 53.6, 49.3, 48.3, 45.4, 35.5, 34.8, 32.1, 28.4, 26.9, 22.9, 22.0, 21.5, 21.2, 20.5, 19.8; IR (neat) ν_{max} 2919, 1731, 1691, 1410, 1365, 1169, 1109 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{21}H_{34}NO_5$ 380.2432, found 380.2436; $[M + Na]^+$ calcd for $C_{21}H_{33}NNaO_5$ 402.2251, found 402.2249; $[\alpha]^{26}_D$ +21.6 (*c* 0.5, CH_2Cl_2).

Improved Ley Oxidation for the Synthesis of Ketol ***38***. To a stirred solution of triol **56** (32 mg, 0.083 mmol) in anhydrous CH_2Cl_2 (3.5 mL) at rt were added 4-methylmorpholine *N*-oxide monohydrate (29 mg, 0.21 mmol) and TPAP (1.4 mg, 0.0042 mmol) sequentially. The resulting mixture was stirred at rt for 3 h. After the reaction was complete, the reaction mixture was directly purified by silica gel chromatography (PE/EtOAc = 2/1) to afford ketol **38** (27.9 mg, 89%) as a colorless oil.

*(+)-Alopecuridine (****4****)*. To a solution of ketol **38** (12.8 mg, 0.034 mmol) in anhydrous chloroform (3 mL) was added trifluoroacetic acid (300 μL) dropwise at 0 °C. The resulting mixture was stirred at rt for 0.5 h. The reaction mixture was concentrated in vacuo and dissolved in CH_2Cl_2 (5 mL).To this mixture was added $NaHCO_3$ solid (240 mg). The resulting mixture was stirred at rt for 2 h and filtered. The filtrate was concentrated in vacuo to afford (+)-alopecuridine (**4**) (12.3 mg, 94%) as a pale white solid. Spectroscopic data are in accordance with literature reported values: mp 78.6−80 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 11.47 (s, 1H), 8.55 (s, 1H), 3.90−3.78 (m, 1H), 3.53 (td, *J* = 14.3, 4.2 Hz, 1H), 3.21 (dd, *J* = 13.7, 5.1 Hz, 1H), 3.02−2.93 (m, 1H), 2.87 (dd, *J* = 16.6, 13.4 Hz, 1H), 2.64−2.52 (m, 1H), 2.38−2.08 (m, 9H), 2.07−1.95 (m, 1H), 1.94−1.76 (m, 3H), 1.76−1.64 (m, 1H), 1.43 (ddd, *J* = 18.5, 10.9, 5.7 Hz, 1H), 0.98 (d, *J* = 8.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.7, 95.0, 80.4, 76.7, 53.9, 50.0, 49.8, 41.3, 40.6, 40.5, 36.1, 31.9, 31.3, 29.7, 29.6, 29.4, 25.0, 23.8, 22.7, 21.9, 21.5, 19.3; ^1H NMR (400 MHz, CD_3OD) δ 3.75−3.54 (m, 3H), 3.23−3.13 (m, 1H), 2.39 (m, 3H), 2.37−1.87 (m, 9H), 1.75 (ddt, *J* = 16.1, 12.5, 7.2 Hz, 3H), 1.54−1.42 (m, 1H), 1.02 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 216.0, 95.5, 89.2, 81.2, 56.2, 55.7, 54.1, 52.6, 52.0, 51.8, 50.3, 46.9, 41.8, 41.6, 40.2, 35.5, 32.8, 32.0, 26.5, 25.3, 24.9, 23.7, 23.0, 22.1, 21.6, 20.8, 19.4; IR (neat) ν_{max} 2924, 1741, 1660, 1459, 1260, 1197 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{16}H_{26}NO_3$ 280.1907, found 280.1911; $[\alpha]^{25}_D$ +69.8 (*c* 0.5, MeOH).

Normal Ley Oxidation for the Synthesis of Ketol ***37***. To a stirred solution of triol **49** (38.0 mg, 0.0991 mmol) in anhydrous CH_2Cl_2 (5 mL) at rt were added 4-methylmorpholine *N*-oxide monohydrate (68.3 mg, 0.495 mmol), 4 Å MS (136.6 mg), and TPAP (7.2 mg, 0.020 mmol) sequentially. The resulting mixture was stirred at rt for 4−5 h. After the reaction was complete, the reaction mixture was directly purified on silica gel (PE/EtOAc = 2/1) to afford ketol **37** (28.0 mg, 74%) as a slightly yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 5.26−5.20 (m, −OH, 1H), 3.82 (dt, *J* = 13.4, 4.4 Hz, 1H), 3.60−3.50 (m, 1H), 3.39−3.35 (m, 1H), 3.24−3.16 (m, 1H), 2.88−2.84 (m, 1H), 2.55−2.33 (m, 4H), 2.20 (d, *J* = 12.7 Hz, 1H), 2.08−1.88 (m, 5H), 1.84−1.67 (m, 4H), 1.47 (s, 9H), 1.37−1.31 (m, 1H), 1.08 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.6, 216.8, 157.5, 83.2, 79.5, 59.3, 47.0, 46.4, 44.7, 39.6, 35.0, 31.4, 31.3, 29.7, 28.6, 26.4, 24.5, 23.3, 22.0, 18.9; IR (neat) ν_{max} 3467, 2924, 1753, 1684, 1558, 1540, 1486, 1456, 1410 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{21}H_{33}NO_5Na$ 402.2251, found 402.2254; $[\alpha]^{21}_D$ +103.0 (*c* 1.0, $CHCl_3$).

Improved Ley Oxidation for the Synthesis of Ketol ***37***. To a stirred solution of triol **49** (28.0 mg, 0.073 mmol) in anhydrous CH_2Cl_2 (4 mL) at rt were added 4-methylmorpholine *N*-oxide monohydrate (50.5 mg, 0.365 mmol), 4 Å MS (101 mg), and TPAP (3.0 mg, 0.0073 mmol) sequentially. The resulting mixture was stirred at rt for 3 h. After the reaction was complete, the reaction mixture was directly purified on silica gel (PE/EtOAc = 2/1) to afford ketol **37** (21.0 mg, 76%) as a slightly yellow oil.

*8-Deoxy-13-dehydroserratinine (****12****)*. To a stirred solution of ketol **37** (21.6 mg, 0.057 mmol) and Et_3N (119.1 μL, 0.854 mmol) in anhydrous THF (4.0 mL) at −78 °C was added $SOCl_2$ (62.2 μL, 0.854 mmol) dropwise. The reaction mixture was stirred for 1 h at −78 °C, warmed to 0 °C, and stirred for additional 1.5 h. After the reaction was complete (monitored by TLC), the reaction mixture was quenched with satd aq $NaHCO_3$ and diluted with CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2, the combined organic extracts were dried over Na_2SO_4, and the filtrate was concentrated in vacuo and purified by silica gel column chromatography (CH_2Cl_2/MeOH = 10/1) to afford 8-deoxy-13-dehydroserratinine (**12**) (14.6 mg, 98%) as a colorless oil:[17c] ^1H NMR (400 MHz, $CDCl_3$) δ 3.36−

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3.32 (m, 1H), 2.84 (m, 1H), 2.71−2.60 (m, 2H), 2.52 (dd, J = 19.4, 9.0 Hz, 1H), 2.44−2.32 (m, 2H), 2.20 (dd, J = 12.7, 4.2 Hz, 1H), 2.14−2.05 (m, 2H), 2.02−1.88 (m, 4H), 1.78−1.70 (m, 4H), 1.61−1.53 (m, 2H), 1.05 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.4, 213.0, 76.1, 57.7, 51.4, 49.1, 47.0, 37.6, 37.2, 32.0, 30.8, 25.0, 24.7, 22.0, 21.4, 20.7; IR (neat) ν_{max} 2918, 2849, 1739, 1698, 1455, 1410 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{16}H_{24}NO_2$ 262.1802, found 262.1796; $[\alpha]^{21}_D$ −2.0 (c 0.2, $CHCl_3$).

Enone ***65***. To a stirred solution of **38** (8.2 mg, 0.022 mmol) and Et_3N (45 μL, 0.324 mmol) in anhydrous THF (3.0 mL) at −78 °C was added $SOCl_2$ (24 μL, 0.324 mmol) dropwise. The reaction mixture was stirred for 1 h at −78 °C, warmed to 0 °C, and stirred for an additional 1.5 h at 0 °C. After the reaction was complete (monitored by TLC), the reaction mixture was quenched with satd aq $NaHCO_3$ and diluted with CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2, the combined organic extracts were dried over Na_2SO_4, and the filtrate was concentrated in vacuo, and purified by silica gel column chromatography (CH_2Cl_2/MeOH = 10/1) to afford enone **65** (4.2 mg, 53%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (ddd, J = 15.3, 12.0, 7.0 Hz, 1H), 3.96−3.52 (m, 1H), 3.46−3.20 (m, 2H), 3.08 (ddd, J = 53.4, 17.8, 8.5 Hz, 2H), 2.78−2.61 (m, 2H), 2.48 (m, 1H), 2.42−2.20 (m, 3H), 2.06 (m, 5H), 1.79 (dd, J = 9.4, 4.0 Hz, 2H), 1.42 (d, J = 2.5 Hz, 9H), 1.06 (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.4, 202.8, 155.1, 141.4, 140.3, 138.9, 79.8, 79.6, 60.6, 59.8, 48.1, 47.0, 46.7, 46.6, 45.4, 44.5, 41.1, 41.0, 38.6, 38.3, 31.3, 31.2, 30.0, 29.9, 29.4, 28.7, 28.6, 28.5, 28.4, 23.0, 22.3, 22.2; IR (neat) ν_{max} 2956, 2916, 2848, 1698, 1646, 1472, 1458 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{21}H_{31}NO_4Na$ 384.2145, found 384.2147; $[\alpha]^{22}_D$ +50 (c 0.1, $CHCl_3$).

(−)-8-Deoxyserratinine ***(7)***. To a solution of 8-deoxy-13-dehydroserratinine (**12**) (4.4 mg, 0.0168 mmol) in anhydrous ethanol (2.0 mL) was added sodium borohydride (1.3 mg, 0.0337 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 30 min, and then 0.2 mL of acetone was added to quench the reaction. The reaction mixture was concentrated in vacuo and purified by silica gel column chromatography (CH_2Cl_2/MeOH = 20/1) to afford (−)-8-deoxyserratinine (**7**) (4.3 mg, 98%) as a white solid. Spectroscopic data are in accordance with literature reported values:[17c] mp 226.5−228.2 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 3.51 (s, 1H), 2.95 (dd, J = 21.2, 9.1 Hz, 1H), 2.85 (m, 1H), 2.71−2.62 (m, 2H), 2.48 (dd, J = 18.7, 11.1 Hz, 1H), 2.37−2.28 (m, 2H), 2.17−2.11 (m, 1H), 2.04−1.97 (m, 2H), 1.92−1.78 (m, 4H), 1.62−1.55 (m, 3H), 1.49−1.47 (m, 1H), 1.42−1.29 (m, 3H), 1.15−1.08 (m, 1H), 0.91 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 218.0, 78.8, 74.5, 53.4, 51.2, 49.6, 49.4, 49.2, 49.0, 48.8, 48.6, 48.4, 45.9, 39.9, 39.0, 34.1, 33.0, 25.8, 22.8, 22.5, 21.8, 21.5, 21.0; IR (neat) ν_{max} 2949, 2919, 2849, 1735, 1458 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{16}H_{26}NO_2$ 264.1958, found 264.1955; $[\alpha]^{21}_D$ −12.0 (c 0.1, EtOH).

(+)-Fawcettidine ***(2)***. To a solution of 8-deoxy-13-dehydroserratinine (**12**) (5.4 mg, 0.0207 mmol) in anhydrous AcOH (4.0 mL) was added active zinc powder (400 mg). The resulting mixture was heated to 140 °C and stirred for 8 h at the same temperature. After cooling, the excess Zn powder was removed by filtration and washed several times with methanol. The filtrate was concentrated in vacuo, diluted with water, and extracted with EtOAc, the combined organic extracts were washed with satd aq $NaHCO_3$, dried over Na_2SO_4, and the filtrate was concentrated in vacuo to afford (+)-fawcettidine (**2**) (4.8 mg, 95%) as a colorless oil. Spectroscopic data are in accordance with literature reported values:[9b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (d, J = 5.2 Hz, 1H), 3.14−3.10 (m, 1H), 3.07−2.97 (m, 2H), 2.73 (ddd, J = 16.6, 7.5, 1.4 Hz, 1H), 2.33−2.23 (m, 2H), 2.19−2.04 (m, 2H), 1.99−1.82 (m, 4H), 1.79−1.55 (m, 5H), 1.39−1.32 (m, 2H), 1.05 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.9, 145.7, 127.3, 60.3, 56.2, 51.9, 46.1, 44.1, 39.0, 37.2, 34.1, 31.2, 29.1, 27.7, 23.7, 20.8; IR (neat) ν_{max} 2922, 2850, 1737, 1662, 1455 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{16}H_{24}NO$ 246.1852, found 246.1850; $[\alpha]^{24.5}_D$ +65 (c 0.24, EtOH).

(+)-Fawcettimine ***(1)***. To a solution of 8-deoxy-13-dehydroserratinine (**12**) (3.1 mg, 0.0119 mmol) and water (0.534 μL, 0.0296 mmol) in THF (degassed, 1.5 mL) at 0 °C was added SmI_2 (0.1 M in THF, freshly prepared, 590 μL, 0.0593 mmol). The resulting mixture was stirred for 40 min at 0 °C, quenched with satd aq Rochelle's salt, and diluted with CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2, the combined organic extracts were dried over Na_2SO_4, and the filtrate was concentrated in vacuo and purified by silica gel column chromatography (CH_2Cl_2/MeOH = 1/1) to afford (+)-fawcettimine (**1**) (1.6 mg, 51%) as a colorless oil. Spectroscopic data are in accordance with literature reported values:[9f] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.50−3.43 (m, 1H), 3.26 (dt, J = 14.1, 3.9 Hz, 1H), 2.91 (dd, J = 14.8, 5.4 Hz, 1H), 2.77−2.71 (m, 1H), 2.62 (dd, J = 17.7, 13.8 Hz, 1H), 2.29−2.08 (m, 8H), 1.98−1.83 (m, 5H), 1.63 (d, J = 14.4 Hz, 1H), 1.50−1.47 (m, 2H), 1.43−1.35 (m, 1H), 0.95 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.1, 105.0, 60.1, 53.5, 50.0, 48.2, 44.2, 43.2, 41.9, 35.7, 31.9, 28.5, 28.1, 23.7, 22.3, 21.8; IR (neat) ν_{max} 2917, 2849, 1730 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{16}H_{26}NO_2$ 264.1958, found 264.1956; $[\alpha]^{25}_D$ +81.7 (c 0.18, MeOH).

Ketal ***77***. To a solution of diol **47** (83.2 mg, 0.183 mmol) and p-TsOH (3.17 mg, 0.018 mmol, 0.1 equiv) in dried acetone (15 mL) was added 2,2-dimethoxypropane (0.937 mL) at 0 °C. The resulting mixture was stirred at rt for 3.5 h. The reaction was quenched with Et_3N, concentrated in vacuo and purified on silica gel (PE/EtOAc = 10/1) to afford the ketal **77** (91 mg, quant.) as a white solid: mp 110.8−111.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (d, J = 8.0 Hz, 1H), 4.07 (s, 1H), 3.67−3.39 (m, 3H), 2.96 (d, J = 20.9 Hz, 1H), 2.89 (dd, J = 14.1, 9.6 Hz, 2H), 2.15 (dd, J = 14.0, 7.4 Hz, 3H), 1.98−1.73 (m, 6H), 1.61−1.50 (m, 5H), 1.48 (s, 9H), 1.40 (s, 3H), 1.38 (s, 3H), 0.86 (d, J = 6.5 Hz, 3H), 0.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 157.0, 108.1, 94.5, 89.8, 78.9, 70.4, 50.7, 48.7, 47.8, 47.6, 42.7, 37.6, 36.5, 32.4, 29.4, 28.9, 28.70, 28.4, 28.4, 24.4, 22.0, 21.4, 19.5, 0.7; IR (neat) ν_{max} 2928, 1697 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{27}H_{50}NO_5Si$ 496.3452, found 496.3451; $[\alpha]^{21}_D$ +7.8 (c 1.0, $CHCl_3$).

Alcohol ***78***. To a solution of ketal 77 (70 mg, 0.141 mmol) in anhydrous THF (5 mL) was added TBAF (0.71 mL, 0.71 mmoL) dropwise at 0 °C. The resulting mixture was stirred at rt for 45 h. The reaction mixture was concentrated in vacuo and purified directly by silica gel column chromatography (PE/EtOAc = 10/1) to afford alcohol **78** (58 mg, 99%) as a white solid: mp 104−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (d, J = 7.9 Hz, 1H), 3.87 (m, 2H), 3.81 (m, 1H), 3.76−3.66 (m, 1H), 3.63 (d, J = 13.3 Hz, 1H), 3.50 (d, J = 13.8 Hz, 1H), 2.84−2.61 (m, 2H), 2.15 (m, 2H), 2.13−1.93 (m, 5H), 1.84 (m, 3H), 1.52(m, 2H), 1.47 (s, 9H), 1.37 (s, 6H), 1.24 (m, 1H), 0.87 (d, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1, 108.1, 94.6, 89.0, 79.3, 68.2, 60.3, 49.5, 47.9, 47.7, 42.7, 39.2, 36.0, 32.4, 31.5, 29.5, 29.1, 28.5, 28.4, 28.0, 24.5, 23.3, 22.6, 22.2, 21.7, 21.1, 19.2, 14.2, 14.1; IR (neat) ν_{max} 3468, 2923, 2968, 2866, 1671 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{24}H_{42}NO_5$ 424.3057, found 424.3049; $[\alpha]^{21}_D$+6.5 (c 1.0, $CHCl_3$).

Ketone ***79***. To a stirred solution of alcohol **78** (32.2 mg, 0.76 mmol) in anhydrous CH_2Cl_2 (5 mL) at rt were added 4-methylmorpholine N-oxide monohydrate (31.4 mg, 0.228 mmol), 4 Å MS (62.8 mg), and TPAP (1.3 mg, 0.0038 mmol) sequentially. The resulting mixture was stirred at rt for 7 h. After the reaction was complete, the reaction mixture was directly purified by silica gel column chromatography (PE/EtOAc = 2/1) to afford ketone **79** (30.5 mg, 95.3%) as a white solid: mp 71.4−73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 (t, J = 9.0 Hz, 1H), 3.41−3.29 (m, 2H), 3.08−2.97 (m, 2H), 2.97−2.85 (m, 1H), 2.73−2.62 (m, 1H), 2.53 (dd, J = 15.9, 8.2 Hz, 1H), 2.34−2.16 (m, 3H), 2.16−1.99 (m, 5H), 1.91 (dt, J = 15.6, 5.1 Hz, 1H), 1.79−1.65 (m, 1H), 1.54 (dt, J = 14.0, 5.5 Hz, 2H), 1.45 (s, 9H), 1.41 (s, 3H), 1.33 (d, J = 4.9 Hz, 3H), 0.98 (d, J = 5.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.3, 214.8, 156.5, 155.9, 109.9, 109.7, 93.0, 92.8, 87.0, 86.9, 79.0, 78.9, 65.0, 64.8, 49.3, 48.1, 48.1, 47.5, 47.3, 47.0, 47.0, 34.3, 34.2, 32.9, 32.7, 31.8, 31.7, 31.0, 30.8, 29.5, 29.4, 28.5, 28.2, 25.3, 25.1, 24.8, 24.5, 23.5, 22.6, 22.4, 22.3; IR (neat) ν_{max} 2926, 2869, 1688, 1455, 1410, 1364, 1233, 1200, 1159, 1055, 918, 731 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{24}H_{39}NO_5$: 422.2901, found 422.2899; $[\alpha]^{21}_D$ +27.1(c 10.0, $CHCl_3$).

Diol ***74***. To a solution of ketone **79** (18.5 mg, 0.049 mmol) in MeOH (2.5 mL) at rt, was added concd HCl (250 μL). The reaction mixture was stirred at reflux for 12 h. The reaction mixture was

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concentrated in vacuo to remove the solvent, diluted with EtOAc, and washed with satd aq $NaHCO_3$ solution, and the aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layers were dried over Na_2SO_4, and the filtrate was concentrated in vacuo to afford the crude product. The crude product was dissolved in 2 mL of anhydrous TFA, and the resulting mixture was stirred at rt for 2 h. The reaction mixture was concentrated in vacuo to afford diol **74** (17.4 mg, quant) as a colorless solid: mp 74−76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1H), 7.74 (s, 1H), 4.33 (d, J = 3.3 Hz, 1H), 3.92−3.77 (m, 2H), 3.48 (d, J = 14.7 Hz, 2H), 3.33 (d, J = 9.0 Hz, 1H), 3.04 (d, J = 14.2 Hz, 1H), 2.80 (t, J = 13.8 Hz, 1H), 2.40−2.26 (m, 3H), 2.10 (d, J = 18.1 Hz, 4H), 1.97 (d, J = 12.4 Hz, 1H), 1.77 (t, J = 12.2 Hz, 2H), 1.67 (d, J = 10.6 Hz, 2H), 1.63−1.53 (m, 1H), 0.97 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.3, 95.7, 94.5, 88.0, 53.1, 52.2, 50.5, 45.7, 41.7, 38.8, 35.2, 32.0, 29.7, 27.9, 27.0, 26.4, 25.0, 22.6, 21.5, 20.0; IR (neat) ν_{max} 2918, 1780, 1654, 1247, 1152 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{16}H_{28}NO_3$ 282.2063, found 282.2062; $[\alpha]^{21}_D$ +4.3 (c 10.0, $CHCl_3$).

Procedures for the Synthesis of Lycojapodine A. *Method A.* To a solution of diol **74** (6.8 mg, 0.017 mmol) in anhydrous trifluoroacetic acid (1 mL) were added IBX (57 mg, 0.204 mmol) and 4 Å MS (14 mg) at rt. The resulting mixture was stirred at 30 °C for 1 d and 40 °C for 1 d. The reaction mixture was concentrated in vacuo and dissolved in EtOAc (5 mL). To this solution was added satd aq $NaHCO_3$. The aqueous layer was extracted with EtOAc (5 mL × 3). The combined organic layers were dried over Na_2SO_4, and the filtrate was concentrated in vacuo and purified by silica gel column chromatography (CH_2Cl_2/MeOH = 100/1 to 60/1) to afford lycojapodine A (**6**) (2.6 mg, 54%) as a white solid. Spectroscopic data are in accordance with literature reported values: mp 164−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (t, J = 14.1 Hz, 1H), 3.40 (m, 1H), 3.07 (dd, J = 15.4, 4.4 Hz, 1H), 2.94 (d, J = 14.4 Hz, 1H), 2.73 (m, 1H), 2.68 (m, 1H), 2.48 (m, 1H), 2.45 (m, 1H), 2.31 (m, 1H), 2.22 (m, 1H), 2.10 (m, 1H), 2.04 (m, 1H), 2.02 (m, 1H), 1.81 (m, 1H), 1.73 (m, 1H), 1.69 (m, 1H), 1.54 (m, 1H), 1.50 (m, 1H), 1.48 (m, 1H), 1.44 (m, 1H), 0.99 (d, J = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.4, 170.7, 93.4, 55.0, 50.5, 49.2, 46.7, 41.4, 36.5, 36.0, 35.0, 31.5, 26.7, 24.4, 24.0, 21.2; IR (neat) ν_{max} 2926, 2869, 1737, 1685, 1180, 1129 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{16}H_{24}NO_3$ 278.1750, found 278.1752; $[\alpha]^{25}_D$ −137.0 (c 0.2, $CHCl_3$).

Method B for (−)-Lycojapodine A. To a solution of (+)-alopecuridine (**4**) (4.5 mg, 0.0114 mmol) in anhydrous trifluoroacetic acid (1 mL) were added IBX (38 mg, 0.137 mmol) and 4 Å MS (9 mg) at rt. The resulting mixture was stirred at 30 °C for 28 h. The reaction mixture was concentrated in vacuo and dissolved in EtOAc (5 mL). To this solution was added satd aq $NaHCO_3$. The aqueous layer was extracted with EtOAc (5 mL × 3). The combined organic layers were dried over Na_2SO_4, and the filtrate was concentrated in vacuo and purified by silica gel column chromatography (CH_2Cl_2/MeOH = 100/1 to 60/1) to afford (−)-lycojapodine A (**6**) (1.6 mg, 51%) as a white solid.

Method C for (−)-Lycojapodine A. To a solution of (+)-alopecuridine (**4**) (4.0 mg, 0.011 mmol) in anhydrous trifluoroacetic acid (1 mL) were added Dess−Martin periodinane (26 mg, 0.060 mmol) and 4 Å MS (15 mg) at rt. The resulting mixture was stirred at rt for 4 h. The reaction mixture was concentrated in vacuo, dissolved in EtOAc (5 mL), and quenched with satd aq $NaHCO_3$ at rt. The aqueous layer was extracted with EtOAc (5 mL × 3). The combined organic layers were dried over Na_2SO_4, and the filtrate was concentrated in vacuo and purified by silica gel column chromatography (CH_2Cl_2/MeOH = 100/1 to 60/1) to afford (−)-lycojapodine A (**6**) (2.6 mg, 86%) as a white solid.

Method D ("One-Pot") for (−)-Lycojapodine A. A solution of ketol **38** (3.4 mg, 0.009 mmol) in anhydrous trifluoroacetic acid (1 mL) was stirred at rt for 18 h. To the above mixture were added Dess−Martin periodinane (23 mg, 0.054 mmol) and 4 Å MS (7 mg) sequentially at rt. The resulting mixture was stirred at rt for 4 h, concentrated in vacuo, diluted with EtOAc (5 mL), and quenched with satd aq $NaHCO_3$. The aqueous layer was extracted with EtOAc (5 mL × 3). The combined organic layers were dried over Na_2SO_4, and the filtrate was concentrated in vacuo and purified by silica gel column chromatography (CH_2Cl_2/MeOH = 100/1 to 60/1) to afford (−)-lycojapodine A (**6**) (2.1 mg, 83%) as a white solid.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra of all new compounds reported and X-ray data of compound **43**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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