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Total Syntheses of (+)-Alopecuridine, (+)-Sieboldine A, and (−)-Lycojapodine A

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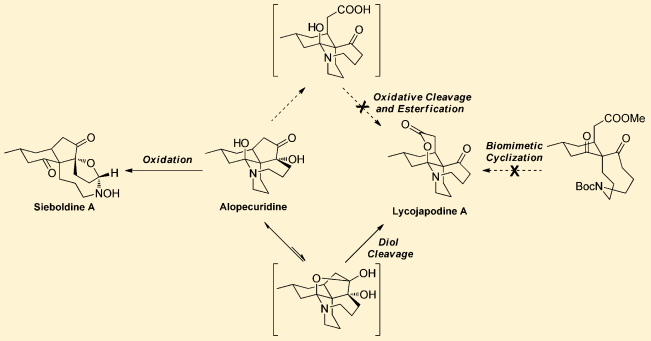
Supporting Information

ABSTRACT: (+)-Alopecuridine, (+)-sieboldine A, and (−)-lycojapodine A, three structurally unique and related lycopodium alkaloids, have been synthesized in enantiomeric forms through an efficient strategy. The main synthetic approach for (+)-alopecuridine features a semipinacol rearrangement of hydroxyl epoxide to construct the spiro 6,9-azacarbocycles with an all-carbon quaternary center and a late-stage SmI_2-mediated intramolecular coupling to form the 5-membered ring. Subsequently, the biomimetic synthesis of (+)-sieboldine A and (−)-lycojapodine A was accomplished successfully through two different bioinspired oxidations after a wide search for the oxidation methods. As a result, (+)-sieboldine A was derived from (+)-alopecuridine through an N-oxidation/nitrone formation process and (−)-lycojapodine A through an interesting cyclic hemiketal formation/oxidative diol cleavage pathway. These results confirmed the biogenetic relationship among the three alkaloids.



INTRODUCTION

The lycopodium alkaloids consist of over 200 structurally diverse natural products. These alkaloids have received considerable attention over the years, owing not only to their potential biological activities but also to their unique and intricate structures.[1] Among these compounds, (+)-alopecuridine (**1**), (+)-sieboldine A (**2**), and (−)-lycojapodine A (**3**) are three structurally related fawcettimine-type alkaloids (Figure 1)[2−4] that were isolated by Ayer et al. in 1974,[5] Kobayashi et al.

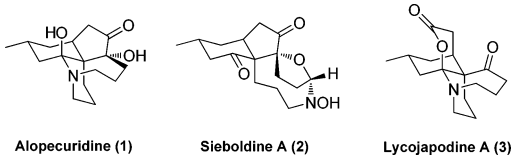


Figure 1. Alopecuridine (**1**), sieboldine A (**2**), and lycojapodine A (**3**).

in 2003,[6] and Zhao et al. in 2009,[7] respectively. In particular, both (+)-sieboldine A and (−)-lycojapodine A have important biological activities. (+)-Sieboldine A inhibits acetylcholinesterase (AChE) significantly (IC_{50} = 2.0 μM) and is cytotoxic against murine lymphoma L1210 cells (IC_{50} = 5.1 μg/mL),[6] while (−)-lycojapodine A has anti-HIV-1 activity (EC_{50} = 85 μg/mL) and exhibits acetylcholinesterase (AChE) inhibition (IC_{50} = 90.3 μM) as well.[7] From a structural point of view, all these compounds have a distinctive tetracyclic skeleton and sterically hindered two contiguous quaternary carbons, one of which is an all-carbon quaternary center. Additionally, sieboldine A and lycojapodine A even have an unprecedented *N*,*O*-acetal or *N*,*O*-ketal moiety, whose unstability makes them synthetically more challenging. Although the cyclic structure of sieboldine A or lycojapodine A is somewhat different from alopecuridine, they were supposed to have close biogenetic relationship with alopecuridine,[6,7] which made their biomimetic syntheses very attractive.

In 2010, Overman group disclosed an elegant asymmetric total synthesis of (+)-sieboldine A for the first time.[3] More recently, we have reported the total synthesis of (±)-alopecuridine, from which we also achieved the synthesis of (±)-sieboldine A via a biomimetic oxidation.[4] However, the total synthesis of lycojapodine A (**3**) has not been achieved to date probably because the unprecedented carbinolamine lactone motif is difficult to construct. Indeed, Yang and coworkers reported in 2010 that direct cyclization of the ester **4** would give an unnatural alkaloid **7**, which can be further oxidized to **8** instead of the desired **3** (Scheme 1).[8] Nearly at the same time, we also met failure in assembling this intriguing moiety either from compound **4** via a biomimetic cyclization or from **1** via an oxidative cleavage/esterfication process.[7] The undesired unnatural alkaloids **7** or **8** were always obtained in high yield through these approaches. The results indicated that the free amine of **4** or the intermediate **5**, generated by oxidative cleavage of **1**, tended to attack the ketone functionality inside of the 9-membered azacycle to form a

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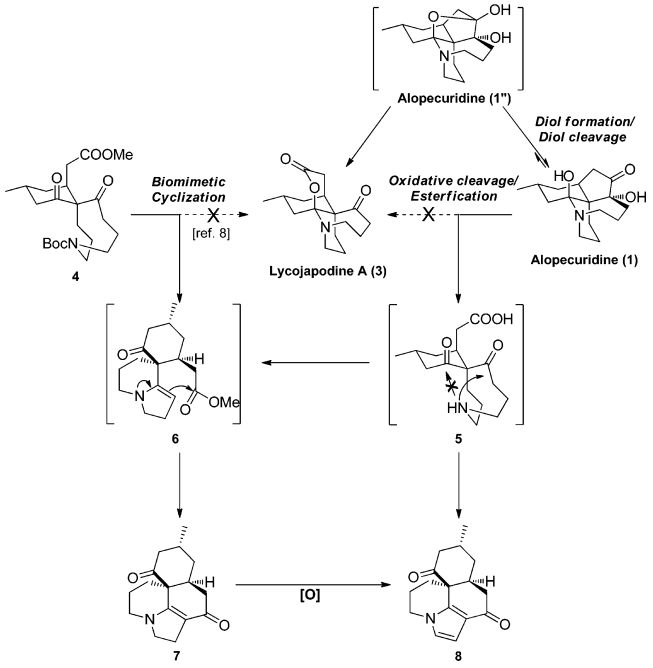
Scheme 1. Attempts To Synthesize Lycojapodine A (3)

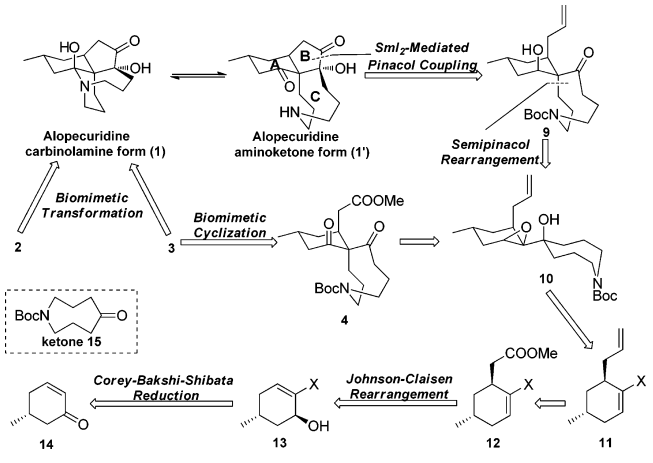


bicyclic [6,5] enamine **6** which could undergo subsequent intramolecular nucleophilic substitution/β-elimination reaction to give **7** or an in situ oxidized product **8**. Therefore, we reconsidered that the biogenetic pathway from alopecuridine to lycojapodine A would need the first formation of a required C–O bond between ketone carbonyl and hydroxyl at carbinolamine moiety (as shown in hemiketal **1″**, Scheme 1) and then cleavage of the resulting diol. Based on this analysis, we made an extensive screening of the oxidation conditions and finally realized the biomimetic transformation. Herein, we report our asymmetric total syntheses of (+)-alopecuridine (**1**) and (+)-sieboldine A (**2**) and the first biomimetic total synthesis of (−)-lycojapodine A (**3**) in detail.

RESULTS AND DISCUSSION

Retrosynthetic Analysis. Our synthetic design is outlined in Scheme 2. As we previously reported, the *N*-hydroxy group

Scheme 2. Retrosynthetic Analysis[a]

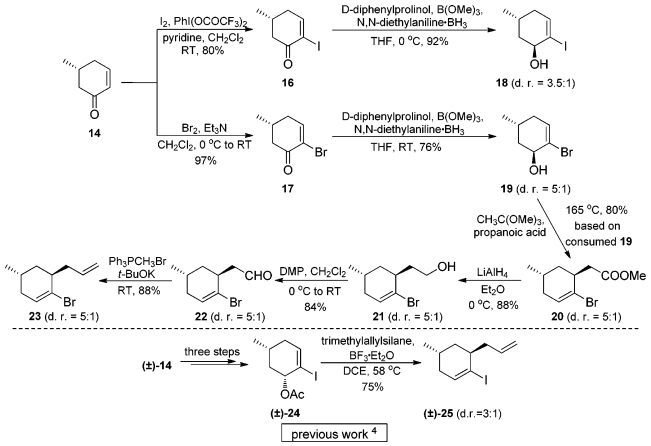


[a]Boc = *tert*-butoxycarbonyl, X = I or Br.

and the tetrahydrofuran ring in sieboldine A (**2**) could be introduced through a biomimetic oxidation from alopecuridine (**1**).[4] We considered that the key carbinolamine lactone moiety in lycojapodine A (**3**) could also be obtained from alopecuridine (**1**) through the biogenetic proposal of Zhao and co-workers[7] or be generated via a biomimetic cyclization of compound **4** under certain conditions.[8] Alopecuridine may exist in either a carbinolamine form **1** or an aminoketone form **1′**,[5] of which the five-membered ring B could be constructed though a late stage SmI_2-mediated pinacol coupling. As can be seen by the structure, the advanced intermediate **9** contains a sterically crowded α-quaternary-β-hydroxy carbonyl moiety and an aza-cyclononane ring, which could be efficiently constructed through a semipinacol rearrangement of epoxide **10**. If there is no racemization caused by Claisen rearrangement during the experiment, epoxide **10** could be assembled from chiral fragment **11** by coupling with ketone **15** and subsequent epoxidation. We further expected that the fragment **11** would be prepared from the well-known, optically active enone **14**[9] through Corey–Bakshi–Shibata (CBS) reduction,[10] Johnson–Claisen rearrangement,[11] and a series of functional group interconversions.

Improved Asymmetric Total Synthesis of Alopecuridine and Sieboldine A. In the beginning of our synthesis (Scheme 3), iodide **16** and bromide **17**, readily prepared from

Scheme 3. Synthesis of the Chiral Bromide 23



the known enone **14**,[12,13] were subjected to diastereoselective reduction with (*R*)-Corey–Bakshi–Shibata (CBS) reagent to afford the corresponding *trans*-allyl alcohols **18** and **19**, respectively.[14] After screening several solvents and temperatures, we found that the reaction of bromo enone **17** conducted in THF at room temperature could give the best *trans* selectivity (*trans*:*cis* = 5:1). Thus, the obtained inseparable diastereomers **19** was chosen for further transformations. Treatment of **19** with trimethyl orthoester at 165 °C in the presence of a small amount of propanoic acid generated bromo ester **20** in good yield (80% based on consumed **19**). Subsequent $LiAlH_4$ reduction of **20** followed by Dess–Martin oxidation[15] and Wittig methylenation produced fragment **23** with the same diastereoselectivity (dr = 5:1). Although the synthetic approach from **14** to bromoalkene **23** had two more steps than our previous reported racemic procedure for iodoalkene (±)-**25**, the diastereomer ratio of the final fragment was enhanced. In addition, the Lewis acid induced allylation,

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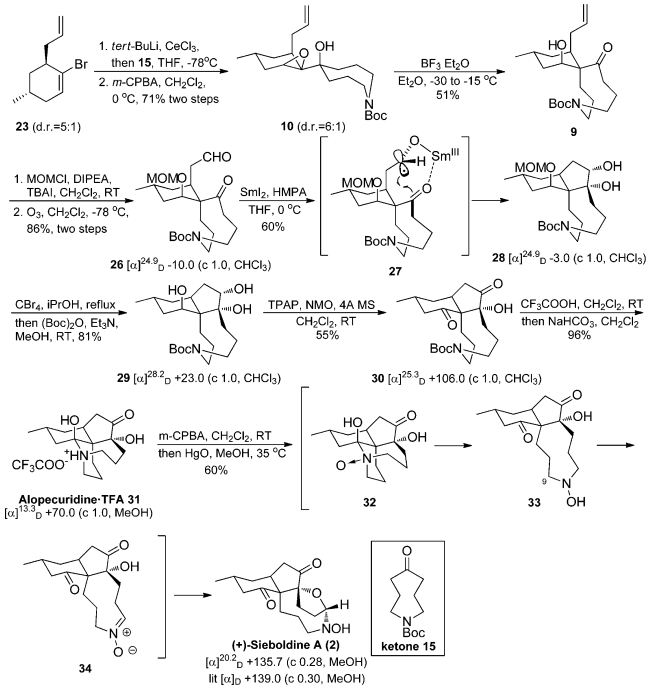
which may cause racemerization in asymmetric synthesis, was avoided in our present route.

We next coupled bromoalkene **23** and known ketone **15**[4] through the intermediacy of the vinylcerium species generated from the lithium salt of **23** (Scheme 4).[16] To avoid elimination,

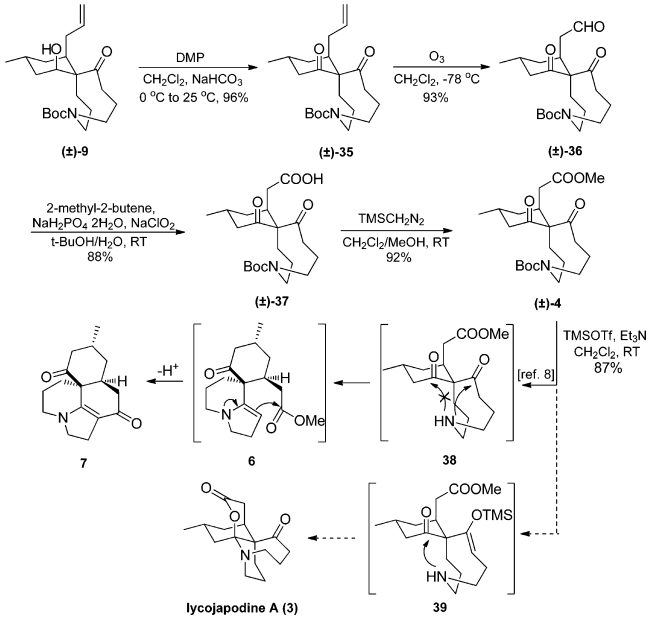
Scheme 4. Completion of Asymmetric Total Syntheses of (+)-Alopecuridine·TFA (31) and (+)-Sieboldine A (2)



the coupling product was directly epoxidized to give **10**, which are still inseparable diastereomers, in 71% yield over two steps (dr = 6:1).[17] Then, promoted by $BF_3{\cdot}Et_2O$, the semipinacol rearrangement of **10** took place to produce ketone **9** in 51% yield. The HPLC analysis showed that compound **9** was enantiomerically pure (>99% ee), which confirmed that there was no racemization during the coupling and epoxidation. Conversion of enantiopure ketone **9** to (+)-alopecuridine was accomplished in six synthesis steps similar to our racemic route. After a three-step sequence involving hydroxyl group protection, ozonolysis, and SmI_2 promoted intramolecular pinacol coupling,[18] the so obtained tricyclic compound **28** was further subjected to one-pot deprotection,[19] TPAP oxidation[20] and final N-Boc deprotection to deliver (+)-alopecuridine·TFA (**31**) ($[\alpha]^{13.3}_D$ = +70.0 (*c* 1.0, MeOH)).[21] The biomimetic oxidation from (+)-alopecuridine·TFA (**31**) to (+)-sieboldine A could then be achieved in a one-pot manner. It should be noted that the oxidation of *N*-hydroxide **33** with HgO[22] might form another N−C9 nitrone in addition to **34**, but we did not isolate any product corresponding to this regioisomer. Some unexpected side reactions might occur from this intermediate and cause the moderate yield of this oxidation. The synthetic (+)-sieboldine A exhibited a rotation of +135.7 (*c* = 0.28, MeOH), essentially identical to that of the natural product.[6]

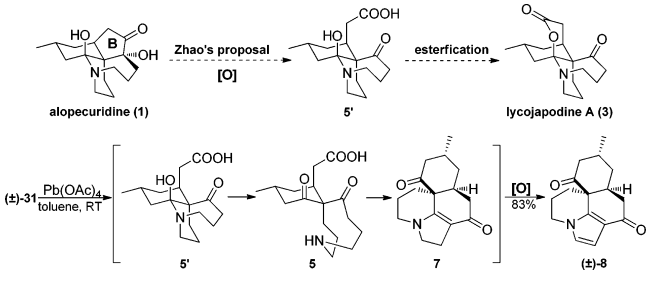
Biomimetic Synthesis of Lacojapodine A. Having achieved the asymmetric syntheses of **1** and **2**, we turned our attention to explore the biomimetic synthesis of lacojapodine A (**3**) with our abundant racemic material. In 2010, Yang and co-workers had reported that direct cyclization of diketone **38** would generate an unnatural alkaloid **7** in various conditions (Scheme 5).[8] It was obvious that the formation of the fused 6/5 ring was much more favorable than the formation of the

Scheme 5. Attempted Biomimetic Cyclization Approach to Lycojapodine A (3)



strained [4.3.1] bridge ring. However, we proposed that if we could in situ protect the carbonyl group of the aza-nine-membered ring as a silyl enol ether during *N*-Boc deprotection (see **39**), the free amine would probably attack the ketone in the six-membered ring to furnish the desired product. Therefore, we synthesized (±)-**4** from (±)-**9** in four straightforward steps including Dess−Martin oxidation,[15] ozonolysis, Pinnick oxidation,[23] and esterfication. However, when we added Et_3N and TMSOTf to the substrate (±)-**4**, it immediately converted to compound (±)-**7** in high yield. Further attempts by changing the solvent and temperature also gave the same result. At last, we were forced to give up this strategy and reconsider the proposed biomimetic path by Zhao and co-workers.[7] As they suggested, oxidative cleavage of ring B in alopecuridine (**1**) would lead to the formation of acid **5′**, which would then be transformed to lycojapodine A (**3**) under esterfication conditions (Scheme 6). Inspired by this proposal, we prepared some (±)-alopecuridine·TFA (**31**). Unfortunately, when (±)-**31** was subjected to oxidation under $Pb(OAc)_4$ in toluene, neither acid **5′** nor lacojapodine A (**3**) was observed. The only product was (±)-**8**, another unnatural alkaloid

Scheme 6. Attempted Oxidative Cleavage/Esterfication Approach to Lycojapodine A (3)



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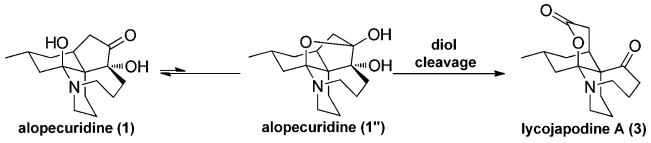
reported by Yang et al.[8] Although the outcome was disappointing, we realized that the existence of the five-membered B ring played an essential role in stabilizing the carbinolamine moiety. The cleavage of this ring would cause the conversion of acid **5′** from its carbinolamine form into its aminoketone form **5**. Then **5** would followed the same tandem process as **38** to give compound **7**, which was in situ oxidized to alkaloid **8** by $Pb(OAc)_4$.

On the basis of above results, we envisioned that the introduction of a C−O bond between ketone carbonyl and hydroxyl at carbinolamine moiety in the presence of ring B might avoid the unexpected tandem reaction since the cleavage of the ring B and the formation of related lactone ring could be carried out simultaneously. Accordingly, a new biogenetic pathway of lycojapodine A (**3**) was proposed. As shown in Scheme 7, alopecuridine (**1**) was probably in equilibrium with

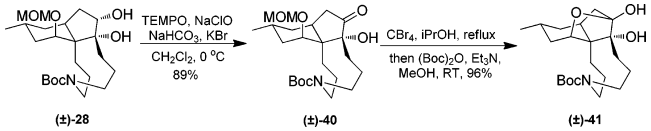
Scheme 7. Proposed Biomimetic Pathway of Lycojapodine A (3)



its hemiketal form **1″**, which actually contained the expected C−O bond. Subsequently, an oxidative cleavage of the so formed 1,2-diol moiety of **1″** would deliver lycojapodine A.

In order to validate this hypothesis, we first prepared a model substrate (±)-**41** from (±)-**28** through TEMPO oxidation[24] and deprotection (Scheme 8). To our delight, the NMR data

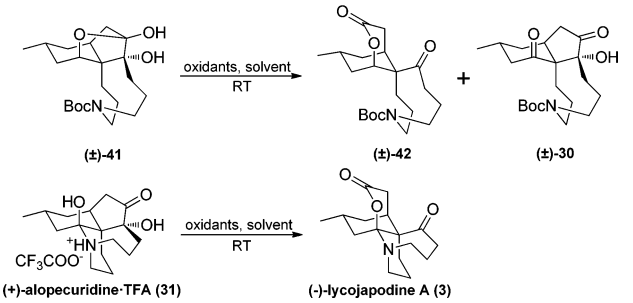
Scheme 8. Synthesis of Model Substrate



showed substrate (±)-**41** existed as a hemiketal. When (±)-**41** was subjected to the diol cleavage, we found that the commonly used $NaIO_4$ could not promote this reaction (Table 1, entry 1 from (±)-**41**), while some other oxidants, such as DMP, PCC, or TPAP (Table 1, entries 2−4), could oxidize the 1,2-diol group to give lactone (±)-**42** in moderate to good yield with diketone (±)-**30** as the byproduct. When we further changed the oxidant to MnO_2 (Table 1, entry 6), (±)-**42** could be obtained as the sole product in high yield.

Having realized our assumption on the model substrate, we focused on the real biomimetic transformation. We mainly screened the oxidants used in our model study to see whether they were also efficient in our real substrate. For comparison, the results are also summarized in Table 1. (+)-Alopecuridine·TFA (**31**) did not react with $NaIO_4$ (Table 1, entry 1 from (+)-**31**). However, unlike the model substrate, alopecuridine·TFA easily decomposed under the oxidation of DMP or TPAP (Table 1, entries 2 and 3). When PCC was used as the oxidant (Table 1, entry 4), we were pleased to observe a slow oxidation of the starting material to lycojapodine A, and a full conversion was achieved by using Collins' reagent, generating lycojapodine A (**3**) in 27−32% yield (Table 1, entry 5).[25] Eventually, we found that previously used MnO_2 could greatly

Table 1. Diol Cleavage of the Model Substrate (±)-41 and (+)-Alopecuridine·TFA (31)



entry	oxidant	solvent	from (±)-41 **42**[a] (%)	from (±)-41 **30**[a] (%)	from (+)-**31** **3**[a] (%)
1	$NaIO_4$ (4 equiv)	THF/H_2O = 5:1	*b*	*b*	*b*
2	DMP (4 equiv)	CH_2Cl_2	69	29	*c*
3	TPAP (0.25 equiv)/ NMO (3 equiv)	CH_2Cl_2	29	60	*c*
4	PCC (3 equiv)	CH_2Cl_2	46	23	trace[d]
5	$CrO_3{\cdot}2C_5H_5N$ (10 equiv)	CH_2Cl_2[e]	*f*	*f*	27−32
6	MnO_2	CH_2Cl_2	95	*g*	82

[a]Isolated yield. [b]No reaction at both room temperature and reflux. [c]A complex mixture was obtained. [d]Low conversion accompanied by decomposition. [e]The reaction temperature was 25 °C. [f]This condition was not tried on (±)-**41**. [g]Compound **30** was not detected.

improve the yield to 82% (Table 1, entry 6). Combined with our model study, the above results verified the existence of the isomerization from **1** to **1″**, whose diol group could also be efficiently cleavaged by MnO_2. The synthetic lycojapodine A was spectroscopically identical (^1H and ^{13}CNMR) to the reported values.[7] Its rotation ($[\alpha]^{16.5}_D$ = −144.1 (c 0.34, $CHCl_3$)) were identical to that of the natural product {$[\alpha]^{24.7}_D$ = −140.98 (c 0.2, $CHCl_3$)}, which also confirmed the absolute configuration of **3**.

CONCLUSION

In summary, we have described the asymmetric total syntheses of (+)-alopecuridine, (+)-sieboldine A, and (−)-lycojapodine A in 15, 16, and 16 steps from chiral enone **14**, featuring a semipinacol rearrangement and a SmI_2-promoted intramolecular pinacol coupling. In the course of our exploration on the biomimetic synthesis of (−)-lycojapodine A, three plausible ways were attempted, from which its biogenetic pathway from (+)-alopecuridine through our proposed diol formation/diol cleavage process was realized for the first time.

EXPERIMENTAL SECTION

General Experimental Details. Silica gel (200−300 mesh) and basic alumina (200−300 mesh), light petroleum ether (bp 60−90 °C), ethyl acetate, dichloromethane, and methanol were used for product purification by flash column chromatography. All solvents were purified and dried by standard techniques and distilled prior to use. All organic extracts were dried over Na_2SO_4 unless otherwise noted. IR spectra were recorded on a Fourier transform infrared spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution or in CD_3OD solution on 400 or 600 MHz instruments. The MS data were obtained with EI (70 eV) or ESI. High-resolution mass spectral analysis (HRMS) data were determined on a FT-ICR spectrometer. Enantioselectivities were determined by high-performance liquid

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chromatography (HPLC) analysis employing a Chiralpak IC column. Melting points were measured on a melting point apparatus and are uncorrected.

Bromo α,β-Unsaturated Ketone 17. To a stirred solution of α,β-unsaturated ketone **14** (1.522 g, 13.8 mmol) in CH_2Cl_2 (34 mL) under argon at 0 °C was added a solution of bromine (0.74 mL, 14.4 mmol, 1.05 equiv) in CH_2Cl_2 (34 mL) slowly (over 1 h). Then Et_3N (3.27 mL, 23.5 mmol, 1.7 equiv) was added, and the resulting mixture was allowed to warm at room temperature and stirred for 1.5 h before it was quenched with aqueous HCl (1 M). The layers were separated, and the organic layer was washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc/petroleum ether = 1:8) to give product **17** (2.537 g, 97% yield) as a colorless oil: $[\alpha]^{23.9}_D$ = −70.0 (*c* = 1.0, $CHCl_3$); IR (neat) 2959, 1691, 1603 cm^{-1}; ^1H NMR (400 MH_Z, $CDCl_3$) δ 7.38 (dd, *J* = 6.0, 2.8 Hz, 1H), 2.78−2.63 (m, 1H), 2.50 (ddd, *J* = 18.4, 6.4, 4.0 Hz, 1H), 2.39−2.24 (m, 2H), 2.15 (ddd, *J* = 18.4, 6.4, 2.8 Hz, 1H), 1.08 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MH_Z, $CDCl_3$) δ 191.4, 150.2, 123.7, 46.2, 36.3, 30.3, 20.7; ESI MS *m*/*z* = 189 and 191 $[M + H]^+$; HRMS ESI calcd for $C_7H_{13}BrNO$ $[M + NH_4]^+$ 206.0175 and 208.0160, found 206.0181 and 208.0159, error 2.9 and 0.5 ppm.

Bromoalkene 19. The flame-dried round-bottom flask (100 mL) under argon was charged with D-diphenylprolinol (204 mg, 0.81 mmol, 0.1 equiv), THF (13 mL), and $B(OMe)_3$ (0.09 mL, 0.81 mmol, 0.1 equiv). The mixture was stirred at room temperature for 0.5 h. Then borane−*N*,*N*-diethylaniline complex (1.44 mL, 8.1 mmol, 1 equiv) was added followed by addition of the solution of compound **17** (1.522 g, 8.1 mmol, 1 equiv) in THF (13 mL). The mixture was stirred for 1 h and then carefully quenched with MeOH at 0 °C. The solvent was removed with a rotary evaporator. The remaining oil was dissolved with Et_2O, washed with saturated Na_2CO_3 solution, 10% $NaHSO_4$, and brine, and dried over Na_2SO_4. The crude product was purified by column chromatography (EtOAc/petroleum ether = 1:16) to give product **19** as a colorless oil (1.246 g, 81% yield): $[\alpha]^{25.9}_D$ = −100.0 (*c* = 1.0, $CHCl_3$); IR (neat) 3369, 2953, 1643 cm^{-1}; ^1H NMR (400 MH_Z, $CDCl_3$) δ 6.18 (dd, *J* = 5.6, 2.4 Hz, 0.75H), 6.13 (d, *J* = 5.2 Hz, 0.15H), 4.33−4.16 (m, 1H), 2.41−2.23 (m, 1H), 2.23−2.12 (m, 1H), 2.12−1.86 (m, 2H), 1.80−1.64 (m, 1H), 1.55 (ddd, *J* = 13.2, 13.2, 4.4 Hz, 0.87H), 1.48−1.38 (ddd, *J* = 12.4, 12.4, 9.6 Hz, 0.17H), 1.07−0.92 (m, 3H); ^{13}C NMR (100 MH_Z, $CDCl_3$) δ 132.4, 131.4, 127.4, 124.7, 70.6, 70.2, 40.7, 39.9, 36.1, 36.0, 27.9, 22.6, 21.3, 20.9; ESI MS *m*/*z* = 191 and 193 $[M + H]^+$; HRMS ESI calcd for $C_7H_{11}BrNaO$ $[M + Na]^+$ 212.9891 and 214.9871, found 212.9884 and 214.9865, error 3.3 and 2.8 ppm.

Ester 20. To a solution of **19** (733 mg, 3.8 mmol) in trimethyl orthoacetate (40 mL) was added 20 drops of propanoic acid. The flask was equipped with a Dean−Stark apparatus and a condenser. The mixture was heated at 165 °C for 30 h, during which time the methanol produced and most of the excess trimethy1 orthoacetate were collected in the Dean−Stark apparatus. The residue was diluted with ether (60 mL) and the organic solution washed with 10% aqueous HC1, saturated $NaHCO_3$ solution, and brine. The organic phase was dried over Na_2SO_4 and concentrated to give the crude product. Flash chromatography on silica gel (EtOAc/petroleum ether = 1:100) afforded compound **20** as a colorless oil (645 mg, 68% yield, 80% yield based on consumed starting material): $[\alpha]^{26.4}_D$ = +53.0 (*c* = 1.0, $CHCl_3$); IR (neat) 2953, 1740, 1645 cm^{-1}; ^1H NMR (400 MH_Z, $CDCl_3$) δ 6.13−6.09 (m, 0.15H), 6.08−6.00 (m, 0.75H), 3.78−3.65 (m, 3H), 3.03−2.82 (m, 2H), 2.32 (dd, *J* = 16.4, 11.6 Hz, 0.85H), 2.20 (dd, *J* = 15.6, 10.0 Hz, 0.22H), 2.18−2.02 (m, 1H), 1.85−1.62 (m, 3H), 1.57 (ddd, *J* = 12.4, 12.4, 5.6 Hz, 0.90H), 1.15 (dd, *J* = 23.6, 12.0 Hz, 0.20H), 1.01−0.89 (m, 3H); ^{13}C NMR (100 MH_Z, $CDCl_3$) δ 172.7, 131.2, 130.4, 126.4, 125.4, 51.6, 51.6, 40.3, 40.0, 39.9, 39.4, 37.8, 36.4, 36.1, 36.0, 28.3, 22.9, 21.3, 21.1; ESI MS *m*/*z* = 247 and 249 $[M + H]^+$; HRMS ESI calcd for $C_{10}H_{15}BrNaO_2$ $[M + Na]^+$ 269.0153 and 271.0133, found 269.0153 and 271.0120, error 0.0 and 4.8 ppm.

Alcohol 21. The flame-dried round-bottom flask 50 mL under argon was charged with $LiAlH_4$ (110 mg, 2.86 mmol, 2 equiv) and Et_2O (7.2 mL). The mixture was stirred at 0 °C for 5 min. Then substrate **20** (353 mg, 1.43 mmol, 1 equiv) in Et_2O (7.2 mL) was added slowly. The mixture was stirred for 30 min at 0 °C and then carefully quenched with aqueous 10% NaOH. The resulting mixture was extracted with Et_2O, and the organic phase was washed with water and brine, dried with Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc/petroleum ether = 1:10) to give product **21** as a colorless oil (275 mg, 88% yield): $[\alpha]^{25.9}_D$ = −100.0 (*c* = 1.0, $CHCl_3$); $[\alpha]^{21.7}_D$ = +91.0 (*c* = 1.0, $CHCl_3$); IR (neat) 3331, 2921, 1644 cm^{-1}; ^1H NMR (400 MH_Z, $CDCl_3$) δ 6.09 (d, *J* = 6.4 Hz, 0.15H), 6.01 (dd, *J* = 2.4, 2.4 Hz, 0.74H), 3.86−3.64 (m, 2H), 2.64−2.46 (m, 1H), 2.27−2.00 (m, 2H), 1.98−1.90 (m, 0.20H), 1.85−1.43 (m, 5.76H), 1.15 (dd, *J* = 23.6, 12.0 Hz, 0.20H), 0.95 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MH_Z, $CDCl_3$) δ 130.5, 129.2, 128.6, 127.4, 61.0, 60.2, 39.9, 39.8, 39.3, 37.9, 36.2, 36.2, 36.1, 36.1, 28.5, 23.1, 21.5, 21.3; ESI MS *m*/*z* = 241 and 243 $[M + Na]^+$; HRMS ESI calcd for $C_9H_{15}BrNaO$ $[M + Na]^+$ 241.0204 and 243.0184, found 241.0198 and 243.0178, error 2.5 and 2.5 ppm.

Aldehyde 22. Substrate **21** (990 mg, 4.5 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (55 mL) under argon at room temperature. The solution was cooled to 0 °C. Then Dess−Martin oxidant (2.876 g, 6.8 mmol, 1.5 equiv) was added sequentially. The mixture was stirred at room temperature for 3 h. After the reaction was quenched with saturated $Na_2S_2O_3$, the resulting mixture was extracted with EtOAc. The organic phase was washed with saturated $Na_2S_2O_3$, saturated $NaHCO_3$, and brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was chromatographed (EtOAc/petroleum ether = 1:20) to give compound **22** (824 mg, 84% yield) as a colorless oil: $[\alpha]^{26.1}_D$ = +76.0 (*c* = 1.0, $CHCl_3$); IR (neat) 2920, 1724, 1645 cm^{-1}; ^1H NMR (400 MH_Z, $CDCl_3$) δ 9.79 (s, 1H), 6.16 (d, *J* = 6.4 Hz, 0.15H), 6.08 (dd, *J* = 2.4, 2.4 Hz, 0.74H), 3.09−2.99 (m, 1H), 2.92 (dd, *J* = 17.2, 3.2 Hz, 1H), 2.50 (ddd, *J* = 17.2, 10.0, 2.4 Hz, 1H), 2.21−2.06 (m, 1H), 2.03−1.95 (m, 0.20H), 1.85−1.54 (m, 3.68H), 1.14 (dd, *J* = 23.6, 12.0 Hz, 0.21H), 0.94 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MH_Z, $CDCl_3$) δ 201.3, 201.2, 131.6, 130.6, 126.0, 125.1, 49.2, 47.5, 39.9, 38.2, 37.7, 36.7, 36.0, 35.8, 28.3, 23.1, 21.3, 21.0; ESI MS *m*/*z* = 217 and 219 $[M + H]^+$; HRMS ESI calcd for $C_9H_{14}BrO$ $[M + H]^+$ 217.0228 and 219.0208, found 217.0223 and 219.0202, error 2.3 and 2.7 ppm.

Bromoalkene 23. A solution of potassium *tert*-butoxide (512 mg, 4.57 mmol, 2.5 equiv) in 5.5 mL of dry toluene was stirred under argon at room temperature as methyltriphenylphosphonium bromide (1.961 g, 5.49 mmol, 3.0 equiv) was added. The resulting bright yellow solution was stirred for 1 h and cooled to 0 °C before **22** (397 mg, 1.83 mmol, 1.0 equiv) was added in dry toluene (5.5 mL). The ice bath was removed, and the solution was stirred at room temperature for 1.5 h. After the reaction was quenched with saturated NH_4Cl, the resulting mixture was extracted with EtOAc. The organic phase was washed with water and brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was chromatographed (petroleum ether) to give compound **23** (346 mg, 88% yield) as a colorless oil: $[\alpha]^{28.8}_D$ = +94.0 (*c* = 1.0, $CHCl_3$); IR (neat) 2919, 1641, 1451 cm^{-1}; ^1H NMR (400 MH_Z, $CDCl_3$) δ 6.12 (d, *J* = 6.4 Hz, 0.15H), 6.02 (dd, *J* = 4.0, 2.8 Hz, 0.76H), 5.84−5.69 (m, 1H), 5.14−5.01 (m, 2H), 2.68−2.47 (m, 1H), 2.45−2.36 (m, 1H), 2.29−2.01 (m, 2H), 1.87−1.61 (m, 3H), 1.44 (ddd, *J* = 12.8, 12.8, 6.0 Hz, 0.84H), 1.17 (dd, *J* = 23.6, 12.0 Hz, 0.17H), 0.99−0.87 (m, 3H); ^{13}C NMR (100 MH_Z, $CDCl_3$) δ 136.7, 135.5, 130.9, 129.4, 128.3, 127.2, 117.0, 116.6, 42.7, 42.2, 39.2, 38.9, 37.4, 36.3, 36.1, 35.2, 28.4, 22.9, 21.5, 21.2; EI MS *m*/*z* = 214 (3) $[M]^+$, 216 (2) $[M]^+$, 173 (18), 175 (17), 135 (62), 93 (88); HRMS APCI Calcd for $C_{10}H_{16}Br$ $[M + H]^+$ 215.0435 and 217.0415, found 215.0434 and 217.0415, error 0.5 and 0.0 ppm.

Epoxide 10. Substrate **23** (303 mg, 1.41 mmol) was dissolved in THF (3 mL) under argon at room temperature. The solution was cooled to −78 °C. Then *t*-BuLi (1.6 M, 1.64 mL, 1.85 equiv) was added at the same temperature. After 5 min, anhydrous $CeCl_3$ (348 mg, 1.41 mmol, 1 equiv) in THF (6 mL) was added slowly to the reaction mixture at −78 °C. The mixture was stirred at −78 °C for another 20 min. Then substrate **15** (320 mg, 1.41 mmol, 1 equiv) in THF (1.5 mL) was added, and the reaction was quenched by saturated NH_4Cl 30 min later. The resulting mixture was extracted with Et_2O/EtOAc = 1:1 three times. The combined organic phases were washed

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with saturated NH_4Cl and brine, dried with Na_2SO_4, and concentrated in vacuo. The crude residue was directly subjected to the next reaction.

The crude residue was dissolved in CH_2Cl_2 (7 mL) under argon. The solution was cooled to 0 °C. Then $NaHCO_3$ (237 mg, 2.82 mmol, 2 equiv) and *m*-CPBA (243 mg, 95%, 1.41 mmol, 1 equiv) were added sequentially. The mixture was stirred at 0 °C for 45 min. After the reaction was quenched with water, the resulting mixture was extracted with Et_2O/EtOAc = 1:1. The organic phase was washed with saturated K_2CO_3 (three times), water, and brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was chromatographed (EtOAc/petroleum ether = 1:10) to give compound **10** (379 mg, 71% yield) as a colorless foam: $[\alpha]^{25.1}_D$ = +28.0 (*c* = 1.0, $CHCl_3$); IR (neat) 3469, 2926, 1689 cm^{-1}; ^1H NMR (400 MH_Z, $CDCl_3$) δ 5.87−5.68 (m, 1H), 5.07−4.94 (m, 2H), 3.72−3.37 (m, 2H), 3.35−3.29 (m, 1H), 3.24−3.07 (m, 2H), 2.83−2.74 (m, 0.13H), 2.37−2.29 (m, 0.78H), 2.19−2.06 (m, 2H), 2.04−1.89 (m, 2H), 1.85−1.75 (m, 2H), 1.73−1.54 (m, 6H), 1.51−1.41 (m, 2H), 1.44 (s, 9H), 1.26−1.16 (m, 1H), 0.94 (s, 1H), 0.85 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MH_Z, $CDCl_3$) δ 155.9, 155.6, 137.2, 116.3, 115.8, 79.2, 79.1, 75.3, 73.4, 67.7, 58.3, 56.9, 56.7, 47.0, 46.9, 46.7, 46.3, 39.2, 37.9, 35.4, 35.0, 34.2, 33.9, 33.7, 33.6, 33.1, 32.9, 32.6, 32.4, 31.9, 28.5, 28.5, 27.9, 25.8, 21.8, 21.5, 20.2; ESI MS *m*/*z* = 380 $[M + H]^+$; HRMS ESI calcd for $C_{22}H_{37}NO_4Na$ $[M + Na]^+$ 402.2615, found 402.2621, error 1.5 ppm.

β-Hydroxy Ketone 9. To a stirred solution of substrate **10** (93 mg, 0.25 mmol) in Et_2O (2.1 mL) under argon at −30 °C was added $BF_3{\cdot}Et_2O$ (0.06 mL). Then the mixture was stirred at −20 °C for 40 min and −15 °C for 40 min. After the reaction was quenched with water, the mixture was extracted with Et_2O/EtOAc = 1:1. The organic phase was washed with water and brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was chromatographed (EtOAc/petroleum ether = 1:8) to give **9** (47 mg, 51% yield) as a colorless foam and the other isomer (8 mg, 9% yield) as a white solid: $[\alpha]^{24.4}_D$ = +64.0 (*c* = 1.0, $CHCl_3$); IR (neat) 3545, 2971, 1693 cm^{-1}; ^1H NMR (400 MH_Z, $CDCl_3$) δ 5.68−5.56 (m, 1H), 4.99−4.89 (m, 2H), 4.14−4.04 (m, 1H), 3.68−3.33 (m, 2H), 3.27−3.14 (m, 1H), 3.07−2.91 (m, 1H), 2.90−2.58 (m, 3H), 2.23−1.79 (m, 6H), 1.76−1.65 (m, 2H), 1.65−1.39 (m, 3H), 1.46 (s, 9H), 1.35−1.22 (m, 2H), 1.21−1.10 (m, 1H), 0.86 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MH_Z, $CDCl_3$) δ 219.8, 157.0, 156.1, 138.2, 115.7, 79.7, 79.6, 68.7, 59.6, 59.2, 48.7, 47.6, 45.2, 43.8, 40.1, 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; ESI MS *m*/*z* = 397 $[M + NH_4]^+$; HRMS ESI calcd for $C_{22}H_{37}NO_4Na$ $[M + Na]^+$ 402.2615, found 402.2624, error 2.2 ppm. Enantiomeric excess is >99% determined by HPLC (Chiralpak IC, hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, 315 nm): major isomer, t_R = 11.68 min; minor isomer, t_R = 10.52 min.

Diketone (±)-35. Substrate (±)-**9** (90 mg, 0.24 mmol) was dissolved in CH_2Cl_2 (5 mL) under argon at room temperature. The solution was cooled to 0 °C. Then $NaHCO_3$ (70 mg, 0.83 mmol, 3.5 equiv) and Dess−Martin oxidants (151 mg, 0.36 mmol, 1.5 equiv) were added sequentially. The mixture was stirred at 25 °C for 4 h. After the reaction was quenched with saturated $Na_2S_2O_3$, the resulting mixture was extracted with EtOAc. The organic phase was washed with saturated $Na_2S_2O_3$, saturated $NaHCO_3$, and brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was chromatographed (EtOAc/petroleum ether = 1:8) to give compound (±)-**35** (86 mg, 96% yield) as a colorless foam: IR (neat) 2922, 1726, 1655 cm^{-1}; ^1H NMR (400 MH_Z, $CDCl_3$) δ 5.77−5.61 (m, 1H), 5.06−4.85 (m, 2H), 3.49−2.85 (m, 4H), 2.73−2.52 (m, 1H), 2.45−2.26 (m, 4H), 2.26−2.06 (m, 4H), 2.06−1.97 (m, 1H), 1.94−1.81 (m, 1H), 1.77−1.51 (m, 4H), 1.45 (s, 9H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.90−0.80 (m, 1H); ^{13}C NMR (100 MH_Z, $CDCl_3$) δ 211.2, 157.1, 155.7, 137.3, 116.0, 115.8, 79.7, 79.5, 70.4, 49.0, 47.6, 47.1, 47.0, 46.2, 44.9, 40.9, 39.9, 38.1, 37.7, 33.6, 33.1, 31.6, 31.2, 29.7, 28.9, 28.7, 28.4, 23.2, 22.6, 22.2, 21.9, 21.6, 21.1, 20.9; ESI MS *m*/*z* = 400 $[M + Na]^+$; HRMS ESI calcd for $C_{22}H_{36}NO_4$ $[M + H]^+$ 378.2639, found 378.2648, error 2.4 ppm.

Aldehyde (±)-36. Substrate (±)-**35** (80 mg, 0.21 mmol) was dissolved in CH_2Cl_2 (3 mL) at room temperature. The reaction mixture was cooled to −78 °C. After a brief oxygen purge (5 min), ozone was bubbled through the reaction mixture slowly until the reaction was completed by TLC. After PPh_3 (84 mg, 0.32 mmol, 1.5 equiv) addition, the reaction was stirred at room temperature for 4 h. Concentration of the reaction mixture gave a yellow oil, which was chromatographed (EtOAc/petroleum ether = 1:4) to give compound (±)-**36** (75 mg, 93% yield) as a colorless foam: IR (neat) 2925, 1725, 1693 cm^{-1}; ^1H NMR (400 MH_Z, $CDCl_3$) δ 9.72 (s, 1H), 3.53−3.20 (m, 1H), 3.14−2.83 (m, 3H), 2.83−2.55 (m, 3H), 2.48−2.38 (m, 1H), 2.38−2.16 (m, 5H), 2.14−2.00 (m, 2H), 1.94−1.57 (m, 4H), 1.47 (s, 9H), 1.42−1.32 (m, 1H), 1.03 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MH_Z, $CDCl_3$) δ 211.5, 210.8, 200.8, 157.1, 155.7, 79.9, 79.7, 70.0, 69.9, 49.0, 47.8, 46.9, 46.3, 45.1, 44.7, 37.8, 37.4, 34.6, 34.4, 34.3, 30.8, 30.6, 28.4, 23.4, 22.3, 21.6, 21.5, 21.2, 20.9; ESI MS *m*/*z* = 380 $[M + H]^+$, 402 $[M + Na]^+$; HRMS ESI calcd for $C_{21}H_{34}NO_5$ $[M + H]^+$ 380.2431, found 380.2429, error 0.5 ppm.

Acid (±)-37. To a stirred solution of aldehyde (±)-**36** (40 mg, 0.11 mmol) in *t*-BuOH/H_2O (4.2 mL/1.2 mL) at room temperature were added 2-methyl-2-butene (0.05 mL, 0.47 mmol, 4.5 equiv), $NaH_2PO_4{\cdot}2H_2O$ (18 mg, 0.12 mmol, 1.1 equiv), and $NaClO_2$ (34 mg, 0.38 mmol, 3.5 equiv). The resulting mixture was stirred for 30 min before it was quenched by saturated NH_4Cl. The resulting mixture was extracted with EtOAc, and the organic phase was washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was chromatographed (EtOAc/petroleum ether = 1:1) to provide (±)-**37** (37 mg, 88% yield) as a colorless foam: IR (neat) 3373, 2923, 1693 cm^{-1}; ^1H NMR (400 MH_Z, $CDCl_3$) δ 3.53−2.56 (m, 6H), 2.47−2.10 (m, 7H), 2.07−2.01 (m, 1H), 1.97−1.87 (m, 1H), 1.81−1.66 (m, 3H), 1.65−1.53 (m, 1H), 1.47 (s, 9H), 1.43−1.29 (m, 2H), 1.04 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MH_Z, $CDCl_3$) δ 211.3, 210.8, 177.8, 177.7, 157.2, 80.0, 79.8, 70.1, 60.4, 49.2, 47.7, 47.0, 46.9, 46.3, 45.0, 37.5, 37.3, 37.0, 34.9, 34.8, 33.8, 33.7, 30.5, 29.7, 28.4, 28.3, 23.3, 21.4, 21.0; ESI MS *m*/*z* = 396 $[M + H]^+$, 418 $[M + Na]^+$; HRMS ESI calcd for $C_{21}H_{34}NO_6$ $[M + H]^+$ 396.2381, found 396.2373, error 2.0 ppm.

Alkaloid (±)-7. Substrate (±)-**4** (24 mg, 0.06 mmol) was dissolved in CH_2Cl_2 (1.2 mL) under argon at room temperature. Then Et_3N (0.018 mL, 0.13 mmol, 2.2 equiv) and TMSOTf (0.012 mL, 0.07 mmol, 1.1 equiv) were added sequentially. The mixture was stirred at room temperature for 30 min. After the reaction with saturated $NaHCO_3$, the resulting mixture was extracted with $CHCl_3$ three times. The organic phase was combined and dried with Na_2SO_4 and concentrated in vacuo. The residue was chromatographed (MeOH/CH_2Cl_2 = 1:40) to give compound (±)-7 (13 mg, 87% yield) as a white solid: IR (neat) 3376, 2925, 1705, 1657, 1549 cm^{-1}; ^1H NMR (600 MH_Z, $CDCl_3$) δ 3.76 (ddd, *J* = 10.8, 10.8, 4.8 Hz, 1H), 3.34 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.31 (t, *J* = 10.8 Hz, 1H), 2.90−2.73 (m, 3H), 2.57−2.47 (m, 2H), 2.42−2.30 (m, 3H), 2.28−2.19 (m, 1H), 2.15 (dd, *J* = 16.8, 4.2 Hz, 1H), 1.94−1.83 (m, 2H), 1.68−1.50 (m, 3H), 1.07 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MH_Z, $CDCl_3$) δ 209.8, 188.1, 167.0, 109.3, 54.3, 52.8, 46.4, 45.0, 44.1, 39.8, 33.2, 29.9, 29.7, 23.6, 22.2, 19.2; EI MS *m*/*z* = 259 (19) $[M]^+$, 176 (48), 91 (16), 56 (35), 41 (100); HRMS ESI calcd for $C_{16}H_{22}NO_2$ $[M + H]^+$ 260.1645, found 260.1646, error 0.4 ppm.

Alkaloid (±)-8. To a stirred solution of alopecuridine·TFA (±)-**31** (6.6 mg, 0.017 mmol) in toluene (2 mL) under argon was added $Pb(OAc)_4$ (11 mg, 0.025 mmol, 1.5 equiv) at room temperature. The resulting solution was allowed to stir for 1 h and then quenched by water. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. Flash column chromatography (EtOAc/petroleum ether =1:1) afforded compound (±)-**8** (3.6 mg, 83%) as a white solid: IR (neat) 3364, 2922, 1702, 1644 cm^{-1}; ^1H NMR (600 MH_Z, $CDCl_3$) δ 6.63 (d, *J* = 3.0 Hz, 1H), 6.59 (d, *J* = 3.0 Hz, 1H), 4.10 (dd, *J* = 12.6, 6.6 Hz, 1H), 3.80 (ddd, *J* = 12.0, 12.0, 6.0 Hz, 1H), 2.73−2.66 (m, 1H), 2.63 (ddd, *J* = 13.2, 3.6, 3.6 Hz, 1H), 2.57 (dd, *J* = 16.8, 13.2 Hz, 1H), 2.44−2.37 (m, 2H), 2.31 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.33−2.25 (m, 1H), 2.08−2.01 (m, 1H), 1.97 (ddd, *J* = 14.4, 12.6, 4.2 Hz, 1H), 1.92−1.82 (m, 1H), 1.72−1.65 (m, 2H), 1.12 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MH_Z, $CDCl_3$) δ 211.5, 191.8, 142.4, 122.9, 118.8, 106.3, 51.9, 45.7, 45.5, 43.8, 42.1, 33.7, 29.8, 29.6, 22.3, 19.1; ESI MS *m*/*z* = 258 $[M + H]^+$; HRMS ESI Calcd for

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$C_{16}H_{20}NO_2$ $[M + H]^+$ 258.1489, found 258.1482, error 2.7 ppm; mp 246−247 °C.

α-Hydroxy Ketone (±)-40. To a stirred solution of (±)-**28** (47 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) at 0 °C were added saturated aqueous $NaHCO_3$ (0.22 mL), potassium bromide (2.6 mg, 0.02 mmol, 0.2 equiv), TEMPO (3.4 mg, 0.02 mmol, 0.2 equiv), and aqueous sodium hypochlorite (0.33 mL, 0.22 mmol, 2.0 equiv) sequentially. The reaction mixture was stirred at 0 °C for 6 h. After the reaction was quenched with saturated aqueous $KHSO_4$, the ice bath was removed and the reaction mixture allowed to warm to room temperature. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Flash column chromatography (EtOAc/petroleum ether = 1:2) afforded compound (±)-**40** (42 mg, 89%) as a colorless foam: IR (neat) 3382, 2926, 1739, 1689 cm^{-1}; ^1H NMR (600 MH_Z, $CDCl_3$) δ 4.46 (s, 2H), 3.88 (s, 1H), 3.66−3.49 (m, 2H), 3.28 (s, 3H), 3.00−2.90 (m, 1H), 2.90−2.78 (m, 1H), 2.43−2.27 (m, 4H), 2.18−2.08 (m, 1H), 1.94−1.79 (m, 4H), 1.77−1.65 (m, 3H), 1.65−1.59 (m, 1H), 1.58−1.51 (m, 1H), 1.51−1.40 (m, 1H), 1.46 (s, 9H), 1.37−1.30 (m, 1H), 1.17 (dd, J = 13.2, 13.2 Hz, 1H), 0.93 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MH_Z, $CDCl_3$) δ 212.8, 157.0, 97.0, 79.8, 79.5, 77.9, 56.4, 49.6, 49.5, 49.3, 37.8, 37.4, 34.7, 32.2, 28.5, 25.0, 24.3, 22.7, 22.0, 21.8, 20.4; ESI MS m/z = 426 $[M + H]^+$; HRMS ESI calcd for $C_{23}H_{40}NO_6$ $[M + H]^+$ 426.2850, found 426.2848, error 0.5 ppm.

Hemiketone (±)-41. To a stirred solution of substrate (±)-**40** (33 mg, 0.078 mmol) in iPrOH (3 mL) was added CBr_4 (103 mg, 0.31 mmol, 4 equiv) at room temperature. The mixture was refluxed for 3.5 h. Then the solvent was evaporated. The crude mixture was dissolved in MeOH (2.5 mL) under argon at room temperature. Then Et_3N (0.087 mL, 0.63 mmol, 8 equiv) and $(Boc)_2O$ (0.027 mL, 0.12 mmol, 1.5 equiv) were added sequentially to the reaction mixture. After 30 min, the solvent was evaporated, and the residue was diluted with water and extracted with EtOAc. The organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue obtained was purified by column chromatography (EtOAc/petroleum ether = 1:2) to afford (±)-**41** (29 mg, 96% yield) as a colorless foam: IR (neat) 3379, 2921, 1666 cm^{-1}; ^1H NMR (600 MH_Z, $CDCl_3$) δ 3.98 (s, 1H), 3.47−3.35 (m, 2H), 3.30−3.10 (m, 2H), 2.35−2.28 (m, 1H), 2.28−2.17 (m, 1H), 2.04−1.72 (m, 7H), 1.72−1.57 (m, 3H), 1.57−1.51 (m, 1H), 1.51−1.37 (m, 1H), 1.46 (s, 9H), 1.20−1.10 (m, 1H), 1.06−0.94 (m, 1H), 0.92 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MH_Z, $CDCl_3$) δ 156.8, 107.3, 82.0, 79.6, 78.0, 49.6, 48.4, 47.7, 36.2, 34.4, 32.2, 28.5, 24.7, 23.4, 23.2, 21.8, 21.2, 20.7; ESI MS m/z = 382 $[M + H]^+$; HRMS ESI calcd for $C_{21}H_{36}NO_5$ $[M + H]^+$ 382.2588, found 382.2593, error 1.3 ppm.

Lactone (±)-42. To a stirred solution of substrate (±)-**41** (10 mg, 0.026 mmol) in CH_2Cl_2 were added PCC (17 mg, 0.079 mmol, 3 equiv) and silica (17 mg) at room temperature. The mixture was stirred at room temperature for 3 h. Then the reaction mixture was filtered though a short basic Al_2O_3 column (EtOAc) and the filtrate was concentrated in vacuo. The resulting material was purified by column chromatography (EtOAc/petroleum ether = 1:4) to afford (±)-**42** (4.6 mg, 46% yield) as a colorless foam and (±)-**30** (2.3 mg, 23% yield) as a colorless foam: IR (neat) 2925, 1723, 1689 cm^{-1}; ^1H NMR (600 MH_Z, $CDCl_3$) δ 4.88 (s, 1H), 3.65−2.80 (m, 5H), 2.52−2.18 (m, 3H), 2.18−1.85 (m, 4H), 1.81−1.69 (m, 1H), 1.69−1.42 (m, 7H), 1.50 (s, 9H), 0.98 (d, J = 6.0 Hz, 3H); ^{13}C NMR (150 MH_Z, $CDCl_3$) δ 211.9, 171.4, 157.0, 155.9, 80.0, 79.7, 79.1, 54.1, 53.7, 49.3, 48.4, 47.0, 45.4, 35.6, 34.9, 32.2, 28.5, 26.9, 23.0, 22.1, 21.5, 21.3, 20.5, 19.9; ESI MS m/z = 380 $[M + H]^+$, 397 $[M + NH_4]^+$; HRMS ESI calcd for $C_{21}H_{37}N_2O_5$ $[M + NH_4]^+$ 397.2697, found 397.2691, error 1.5 ppm.

Lycojapodine 3. (a) Reaction using Collins' reagent: Alopecuridine·TFA **31** (2.7 mg for one pot, 6.87 μmol, 8.1 mg for three pots) was dissolved in CH_2Cl_2 (1 mL) under argon. The reaction mixture was cooled to 0 °C. Then freshly prepared Collins' reagent $CrO_3{\cdot}2C_5H_5N$ (0.18 mL, 0.38 M, 10 equiv) was added. The mixture was stirred at 25−30 °C for 1 or 2 h. Then the reaction mixture was filtered though a short basic Al_2O_3 column (EtOAc), and the filtrate was concentrated in vacuo. The resulting material was dissolved in $CHCl_3$, washed with saturated $NaHCO_3$, dried with Na_2SO_4, and concentrated in vacuo. The mixture obtained was purified by column chromatography with basic Al_2O_3 (EtOAc/petroleum ether = 0:1−1:4) to afford **lycojapodine A 3** (1.7 mg for three pots, 30% yield) as a white solid. (b) Reaction using MnO_2: To a stirred solution of alopecuridine·TFA **31** (1.6 mg for one pot, 4.07 μmol, 9.6 mg for six pots) in CH_2Cl_2 under argon was added MnO_2 (10.4 mg every time, 62.4 mg in total) every 6 h. The mixture was stirred at room temperature for 36 h. Then the reaction mixture was filtered though a short basic Al_2O_3 column (EtOAc) and the filtrate was concentrated in vacuo. The mixture obtained was purified by column chromatography with basic Al_2O_3 (EtOAc/petroleum ether = 0:1 to 1:4) to afford **lycojapodine A 3** (5.6 mg for six pots, 82% yield) as a white solid: $[\alpha]^{16.5}_D$ = −144.1 (c = 0.34, $CHCl_3$); IR (neat) 2926, 2868, 1737, 1685, 1181, 1128 cm^{-1}; ^1H NMR (600 MH_Z, $CDCl_3$) δ 3.89−3.80 (m, 1H), 3.44−3.35 (m, 1H), 3.06 (dd, J = 15.6, 5.4 Hz, 1H), 2.94 (d, J = 15.0 Hz, 1H), 2.78−2.70 (m, 1H), 2.70−2.63 (m, 1H), 2.52−2.40 (m, 2H), 2.33−2.27 (m, 1H), 2.21 (dd, J = 13.8, 12.0 Hz, 1H), 2.14−2.08 (m, 1H), 2.08−1.98 (m, 2H), 1.84−1.77 (m, 1H), 1.77−1.66 (m, 2H), 1.57−1.41 (m, 4H), 0.99 (d, J = 6.0 Hz, 3H); ^{13}CNMR (150 MH_Z, $CDCl_3$) δ 217.3, 170.6, 93.4, 54.9, 50.5, 49.2, 46.6, 41.4, 36.5, 36.0, 34.9, 31.5, 26.6, 24.4, 24.0, 21.2; ESI MS m/z = 278 $[M + H]^+$; HRMS ESI Calcd for $C_{16}H_{24}NO_3$ $[M + Na]^+$ 278.1756, found 278.1755, error 0.4 ppm; mp 176−177 °C.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectra of all new synthetic compounds including (+)-alopecuridine·TFA (**31**), (+)-sieboldine A (**2**), and (−)-lycojapodine A (**3**). 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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