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Divergent Total Synthesis of the *Lycopodium* Alkaloids Huperzine A, Huperzine B, and Huperzine U

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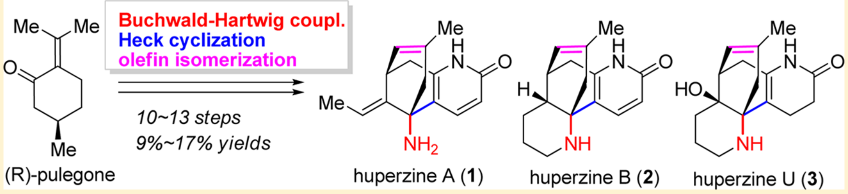
S *Supporting Information*



ABSTRACT: Huperzine A, huperzine B, and huperzine U are congeners isolated from the Chinese herb *Huperzia serrata* (=*Lycopodium serratum*) in minuscule amounts. The most efficient total synthesis of huperzine A, the first asymmetric total syntheses of huperzine B, and the first total synthesis of huperzine U have been achieved efficiently in overall yields of 17%, 10%, and 9%, respectively, each spanning 10−13 steps from (*R*)-pulegone. The featured steps include palladium-catalyzed Buchwald−Hartwig coupling and Heck cyclization reactions and an Ir-catalyzed olefin isomerization reaction. This work has established the absolute configurations of huperzine B and huperzine U and revealed that natural huperzine A, huperzine B, and huperzine U possess the same set of absolute stereochemistries, thus providing support for the potential role of huperzine B and huperzine U in the biosynthesis of huperzine A.

■ INTRODUCTION

The *Lycopodium* alkaloids are a family of architecturally diverse natural products with various biological activities that have attracted broad attention from both the chemical and medicinal communities.[1] Notably, huperzine A (**1**), the most significant *Lycopodium* alkaloid, has aroused tremendous interest because of its nootropic effects.[2] Huperzine A (**1**),[3] huperzine B (**2**),[3] and huperzine U (**3**)[4] are congeners isolated from the Chinese herb *Huperzia serrata* (=*Lycopodium serratum*) in minuscule amounts (200, 100, and 0.38 ppm for **1**, **2**, and **3**, respectively, from the dry plant). Huperzine A is the most potent natural product possessing acetylcholinesterase (AChE) inhibition activity. It is clinically used as a symptomatic treatment of early to moderate Alzheimer's disease (AD) with comparable efficacy to tacrine, galantamine, and donepezil.[1a] In comparison to huperzine A, huperzine B (**2**) displays weaker AChE inhibition activity but a higher therapeutic index.[5] The bis(huperzine B) derivative FS0311 (**4**) exhibits similar AChE inhibition potency as donepezil but higher potency than huperzine A. Meanwhile, this derivative antagonizes cognitive deficits induced by scopolamine or transient brain ischemia.[6] The biological activities of huperzine U (**3**), however, have not been reported, possibly as a result of the scarceness of this natural product.

Structurally, huperzine A (**1**), huperzine B (**2**), and huperzine U (**3**) belong to the lycodine subgroup, which features a bicyclo[3.3.1]nonane core flanked by two piperidine rings at various oxidation levels (Figure 1). For huperzine A, only one piperidine ring exists, with the missing one hypothetically being cleaved by late-stage enzymatic oxidations.[1a] Huperzine U (**3**) contains a rare dihydropyridone motif and a tertiary hydroxyl substituent at C12.

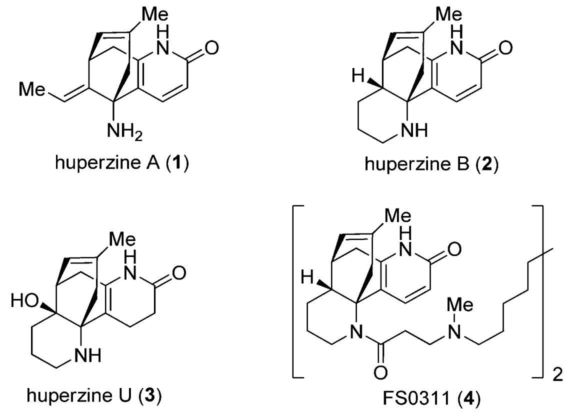


Figure 1. Structures of huperzine A (**1**), huperzine B (**2**), and huperzine U (**3**) from *Huperzia serrata* (=*Lycopodium serratum*) and FS0311.

Biosynthetic studies of *Lycopodium* alkaloids have been limited to the feeding experiments conducted by Hemscheidt and Spenser, which established pelletierine metabolized from lysine as the basic building block of all *Lycopodium* alkaloids (Scheme 1).[7] Notably, phlegmarine was previously proposed to

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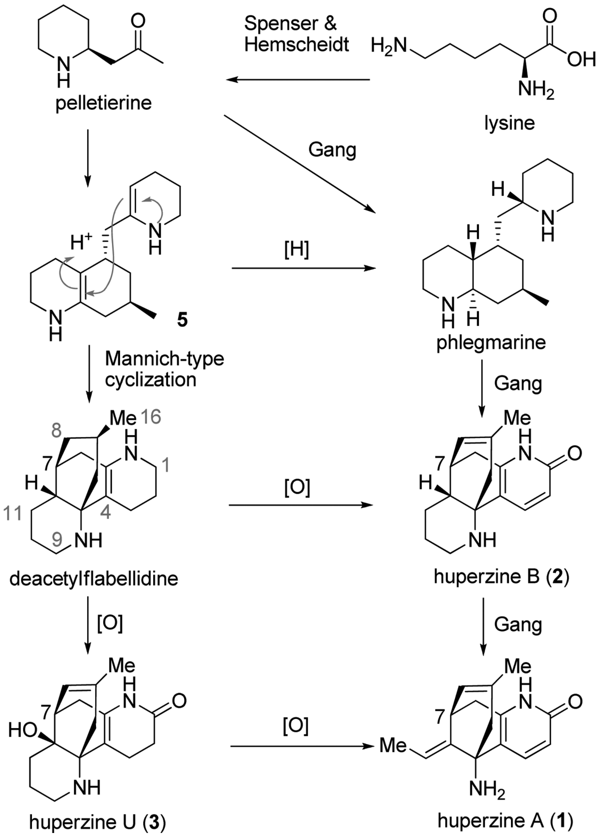
Scheme 1. Proposed Biosynthesis of 1, 2, and 3



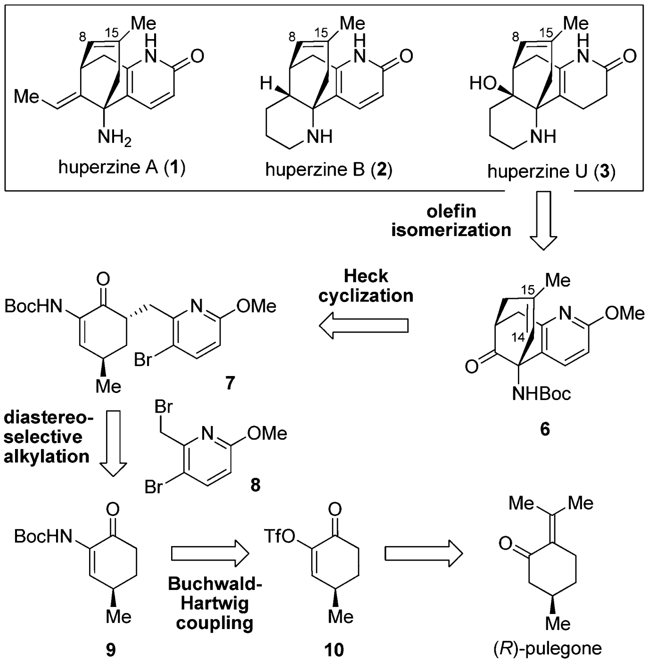
be the second general intermediate to *Lycopodium* alkaloids.[1a] Nevertheless, compound **5** could in principle be the general intermediate to all *Lycopodium* alkaloids, including phlegmarine, considering that **5** is more properly functionalized (Scheme 1). Accordingly, deacetylflabellidine,[8] a known alkaloid that might stem from **5** via a Mannich-type cyclization, could reasonably be proposed as the common biosynthetic precursor to **1**, **2**, and **3** (Scheme 1). Importantly, the proposed biosynthetic pathways structurally correlate these molecules and intrinsically entail the stereochemical coherence among them (specifically, the absolute stereochemistry at C7), but this has yet to be verified. Considering the impact this issue may have on the biogenesis of these significant natural products, a conclusive vindication would be of paramount importance. Actually, to date the absolute configuration has been established only for huperzine A (**1**). Particularly noteworthy is that huperzine U (**3**) was originally considered to be a racemic compound because of its reported zero optical rotation.[4] Although huperzine A has been the topic of numerous synthetic papers,[9] to date only two racemic total syntheses of huperzine B (**2**) have been accomplished,[10] and no total synthesis of huperzine U (**3**) has been reported.

Previously we communicated the most efficient total synthesis of (−)-huperzine A (**1**) to date.[9s] In this paper, we present a full account of the divergent total synthesis of huperzine A (**1**), huperzine B (**2**), and huperzine U (**3**) and the absolute configuration assignments of the latter two natural products with biosynthetic implications.

■ RESULTS AND DISCUSSION

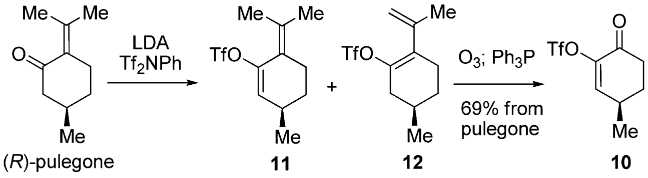
Retrosynthetic Analysis. The retrosynthetic analysis is illustrated in Scheme 2. We envisioned that both the exocyclic olefinic bond in **1** and the piperidine ring in **2** and **3** could be traced back to an α-amino ketone function, and all of the $\Delta^{15(8)}$ double bonds in **1**−**3** could stem from olefin isomerization of a $\Delta^{14(15)}$ double bond, thus reducing targets **1**−**3** to a common precursor **6**. The subsequent bond disconnection would allow **6** to be produced from **7** via an intramolecular Heck reaction, which entails a *trans* relative stereochemistry in **7**. This defined stereochemistry could be created via diastereoselective alkylation of the key intermediate **9** with bromide **8**. An unprecedented Buchwald−Hartwig coupling reaction of the simple α-trifloxy enone **10** with Boc-NH$_2$ would generate **9**. The chiral compound **10** was envisaged to stem from (*R*)-pulegone in a chiral-pool synthetic strategy.

Scheme 2. Retrosynthetic Analysis for 1, 2, and 3



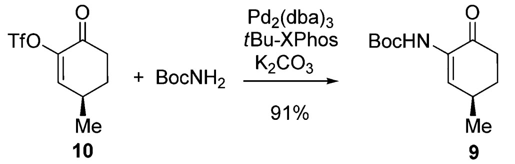
Synthesis of 9. The synthetic journey commenced with the elaboration of (*R*)-pulegone into **10** (Scheme 3). (*R*)-Pulegone (100% ee) was triflated with LDA/PhNTf$_2$ to give a mixture of **11** and **12** in a ratio of 6/1, as determined by ^{1}H NMR spectroscopy. Subsequent exposure to ozonolysis generated **10** in 69% yield over the two steps.

Scheme 3. Synthesis of 10



We next focused on the synthesis of **9**, which entails a Buchwald−Hartwig coupling reaction.[11] With Pd$_2$(dba)$_3$ as the catalyst and *t*-Bu-XPhos as the ligand, the conditions were briefly examined (Table 1). The optimal conditions involved potassium carbonate as the base and toluene as the solvent, which delivered **9** in 91% yield with complete conservation of the optical purity (100% ee). With cesium carbonate as the base, **9** was obtained with slightly diminished yield (83%) and optical purity (96% ee). The ligand *t*Bu-XPhos could be mostly

Table 1. Buchwald−Hartwig Coupling Reaction of 10 with Boc-NH_2

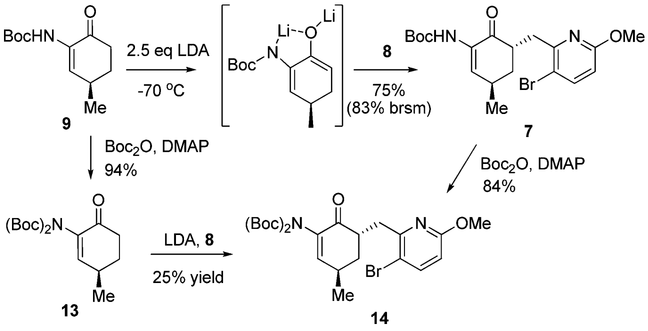


entry	base	solvent	yield (%)	ee (%)
1	K_2CO_3	*t*-BuOH	43	–
2	K_2CO_3	toluene	91	100
3	Cs_2CO_3	toluene	83	96

recovered (ca. 90%) and reused. Noticeably, prior to our investigations, the Buchwald−Hartwig coupling reaction of simple *α*-trifloxy enones, which provides facile access to *α*-amino enones, has never been reported.

Synthesis of 7. The alkylation reaction between **9** and bromide **8** was investigated next (Scheme 4). This is a dianion-powered alkylation reaction since it was found to be necessary to use 2−3 equiv of base (vs **9**) to achieve a good yield of the alkylation product. Thus, the *α*-alkylation of **9** with **8** was realized with 2.5 equiv of LDA at −70 °C, furnishing **7** in 75% yield (83% brsm) with 96% ee and >20/1 dr. In contrast, the reaction of **13** with **8** generated **14** in only 25% yield.

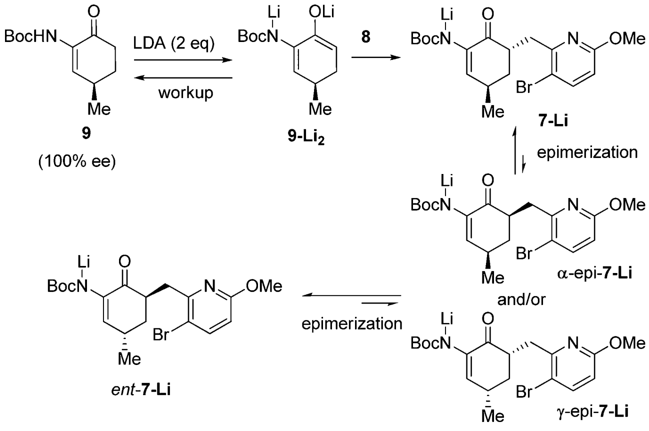
Scheme 4. Alkylation of 9 and 13



Maintaining the reaction mixture at a low temperature was critical to achieve a high enantiomeric excess of the product. When the alkylation reaction was conducted with 2.2 equiv of LDA at −25 °C, the product was obtained in 83% yield with 75% ee and 10/1 dr. The rationale for the racemization at elevated temperature is depicted in Scheme 5. Racemization of **9** under the reaction conditions was not deemed possible since recovered **9** completely retained its optical purity (100% ee). This enabled us to conclude that the racemization occurred on the alkylation product **7-Li**, stemming from alkylation of **9-Li_2** by **8**. The monolithiated species **7-Li** might transform into *ent*-**7-Li** through stepwise epimerizations via *α-epi*-**7-Li** and/or *γ-epi*-**7-Li**.

Synthesis of 6. The Heck cyclization has gained widespread acceptance in natural product synthesis,[12] including Mann's formal racemic synthesis of **1**.[9n] Nevertheless, it has rarely been applied to enamine-type substrates.[13] Actually, none of the attempted substrates **7**, **14**, **15a**, **15b**, and **16a−e** (Figure 2) succeeded in producing a Heck cyclization product. Interestingly, **14** underwent an unprecedented intramolecular *γ*-arylation to give **17** in good yield (Scheme 6).[14] The structure of **17** was confirmed by X-ray crystallographic analysis.[35]

Scheme 5. Rationale for the Racemization in the Alkylation Reaction



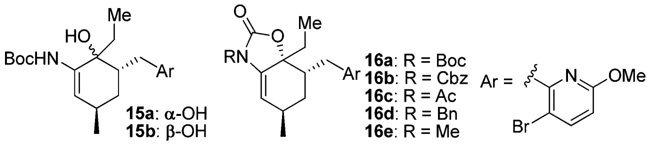
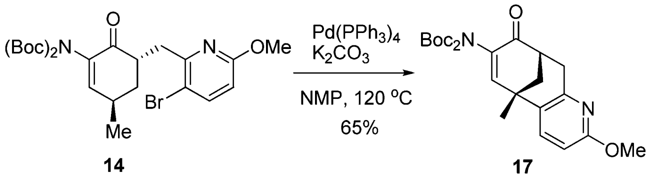


Figure 2. Structures of **15a**, **15b**, and **16a−e**.

Scheme 6. Pd-Catalyzed Intramolecular *γ*-Arylation of 14



Ketone **7** was reduced to a 1/1 mixture of **18a** and **18b** in quantitative yield. Both **18a** and **18b** could successfully undergo the intramolecular Heck reaction to furnish **19a** and **19b** in yields of ca. 40%. The structure of **19a** was established through X-ray crystallographic analysis.[35] Both **19a** and **19b** were found to undergo Ley−Griffith oxidation to afford **6** in nearly quantitative yield (Scheme 7).[35] The three-step sequence was further optimized with the mixture being directly used (Table 2). Under the optimal conditions (entry 8), ketone **6** could be isolated in 63% yield with 96% ee over three steps from **7**. This procedure allowed the multigram-scale synthesis of **6** in a consistent yield.

Scheme 7. Synthesis of 6 via Heck Cyclization

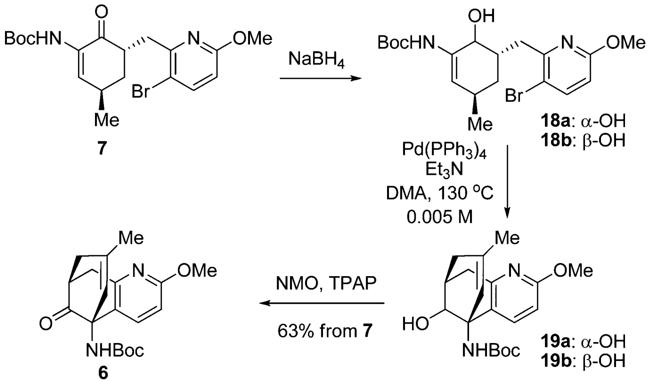


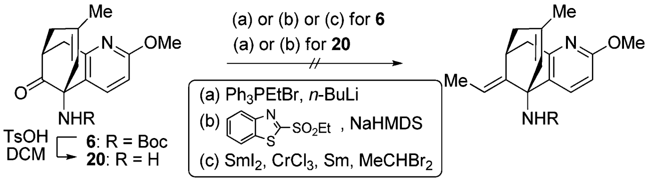
Table 2. Optimization of the Heck Cyclization in the Three-Step Sequence

entry	base	solvent	conc. (mol/L)	yield (%)[a]
1	Et_3N	DMA	0.03	40
2	K_2CO_3	DMA	0.03	<5
3	Ag_3PO_4	DMA	0.03	<5
4	DIPEA	DMA	0.03	23
5	Et_3N	DMF	0.03	25
6	Et_3N	toluene	0.03	<5
7	Et_3N	DMA	0.01	53
8	Et_3N	DMA	0.005	63

[a] Yields of **6** over the three steps from **7**.

Attempted Installation of the Exocyclic Double Bond on 6. Ketone **6** with a proper level of functionalization could serve as a perfect synthetic precursor for various lycodine-type alkaloids. For the synthesis of huperzine A, we needed to install an exocyclic double bond onto **6**. Despite appearing deceptively simple, the construction of the exocyclic double bond was actually quite challenging. Attempted Wittig reaction, Julia olefination, and Takai−Utimoto olefination[15] were unsuccessful. Treatment of **6** with TsOH gave **20**, which was unstable, probably because of its propensity to undergo dimerization and/or oligomerization. Olefination of **20** was also unsuccessful (Scheme 8).

Scheme 8. Attempted Olefinations of 6 and 20



Total Synthesis of Huperzine A. An addition−elimination-based protocol was then developed to meet the challenge (Scheme 9). Thus, the addition reaction between **6** and ethylmagnesium bromide was investigated (Table 3). Under the optimized conditions (entry 4), **21a**/**21b** in a ratio of 7/1 were isolated in an overall yield of 74% along with a 20% yield of **19**, which could be completely recycled by the Ley−Griffith oxidation. The structure of **21a** was confirmed by X-ray crystallographic analysis.[35] When **6** was first converted to **20** and the latter was treated with EtMgBr, **22a** and **22b** could be isolated in yields of 55% and 31%, respectively. Although the detailed mechanism could be elusive, the *N*-Boc group did play a role in determining the facial selectivity of the Grignard addition reaction.

Scheme 9. Grignard Addition Reaction of 6

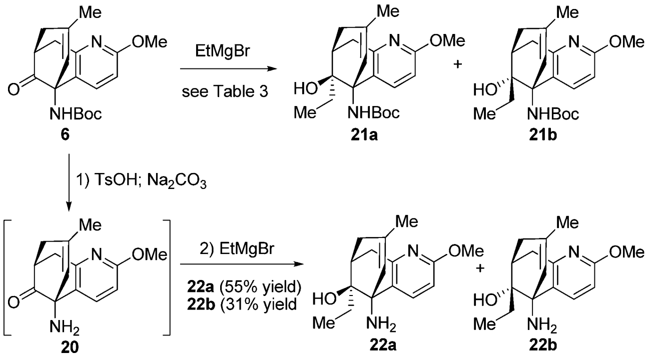


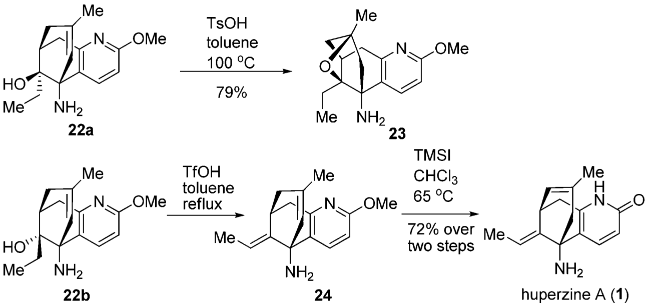
Table 3. Optimization of the Grignard Addition Reaction of 6

entry	method[a]	*T* (°C)	result
1	A	−65	**6** (80%), **21** (17%)
2	A[b]	−65	**6** (>95%)
3	B	−65	**6** (55%), **21** (37%)
4	B	−25	**21** (74%), **19** (20%)
5	B	0	**21** (45%), **19** (38%)

[a] Method A: EtMgBr added to **6**. Method B: **6** added to EtMgBr. [b] A Lewis acid ($CeCl_3$, $BF_3 \cdot Et_2O$, $MgCl_2$, or LiCl) was used.

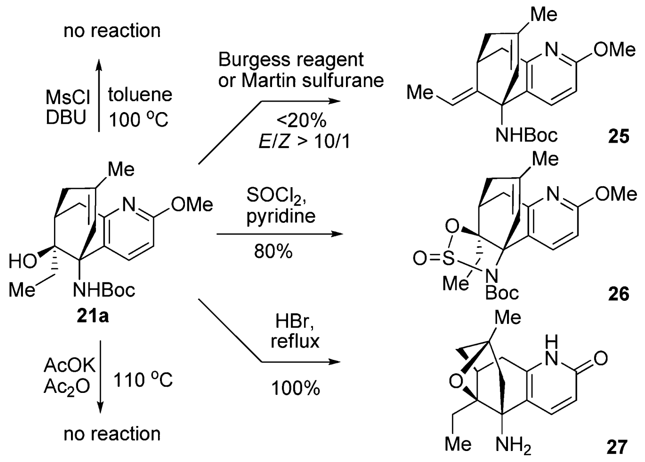
With the addition products in hand, we sought to realize the dehydration reaction. Interestingly, when **22a** was treated with TfOH in toluene, a cagelike pentacyclic ether **23** was isolated in 79% yield (Scheme 10). In contrast, under the same conditions, **22b** successfully underwent a dehydration reaction to give **24**, which after demethylation with TMSI and concomitant olefin isomerization delivered huperzine A (**1**) in 72% yield over two steps. This synthesis of huperzine A was plagued by the low yield of **22b** in the Grignard addition reaction.

Scheme 10. Total Synthesis of Huperzine A from 22b



Dehydration of **21a** was next investigated (Scheme 11). Exposure of **21a** to Burgess reagent or Martin sulfurane generated olefin **25** in low yield. Treatment of **21a** with $SOCl_2$ in the presence of pyridine furnished **26** in 80% yield, which failed to produce **25** under various conditions. When **21a** was

Scheme 11. Attempted Dehydration of 21a



exposed to concentrated HBr in refluxing toluene, pentacycle **27** was isolated.

Eventually it was discovered that $SOCl_2$ in toluene in the absence of pyridine could effect a slow dehydration of **21a**/**21b** to form **25** as a sole isomer along with a trace amount of **24** (Scheme 12); a minor amount of Wagner−Meerwein rearrangement product **28** was also isolated. In toluene, the (**25** + **24**)/**28** ratio was 2.6/1, while in DMF or DMA, **28** could be isolated as the major product along with **29**, which exhibited high propensity toward hydrolysis to give **28** (Table 4). The structure of **28** was originally assigned as **28-A** on the basis of MS and 2D-NMR techniques,[9s] but **28-B** could not be excluded, and the real structure of **28** needs further investigation (Scheme 13). Olefin isomerization of **25** with HBr and concomitant demethylation delivered huperzine A (**1**) in 57% yield over two steps. This synthesis of huperzine A covers 10 steps from (*R*)-pulegone with 17% overall yield.

Scheme 12. Total Synthesis of Huperzine A from 21

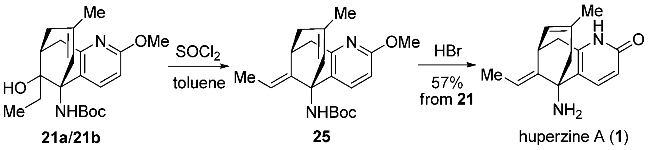
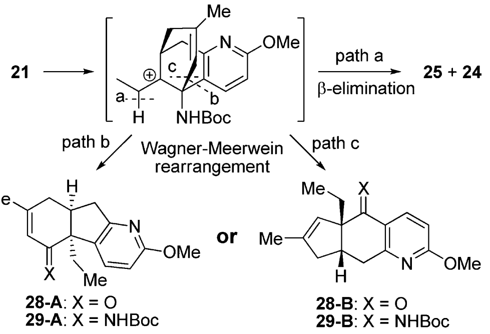


Table 4. Dehydration and Wagner−Meerwein Rearrangement of 21

entry	solvent	temp	result[a]
1	toluene	RT	**25**/**24** (59%), **28** (23%)
2	DMF	RT	**25** (37%), **28**/**29** (50%)
3	DMA	RT	**25** (43%), **28**/**29** (48%)
4	DMA	60 °C	**25** (32%), **28**/**29** (55%)

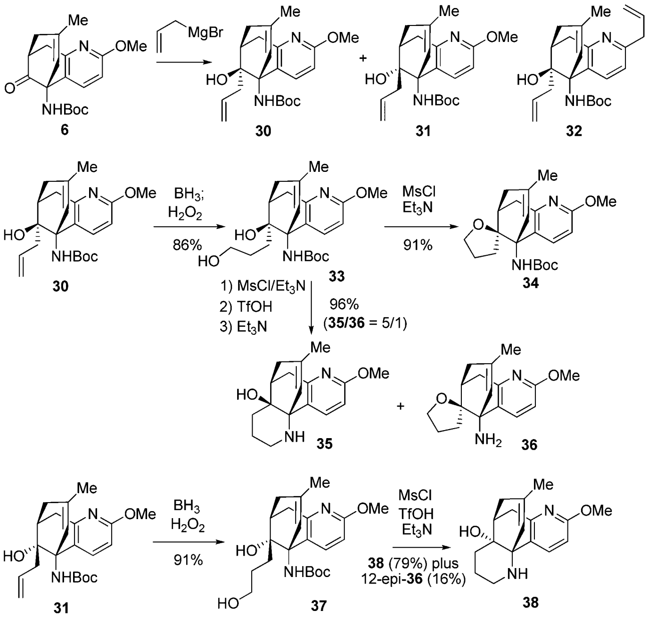
[a]Yields determined by ^1H NMR analysis.

Scheme 13. Dehydration of 21 Leading to 25/24 (Path a) and Two Possible Structures of 28 (28-A and 28-B) Derived via Wagner−Meerwein Rearrangement of 21 (Paths b and c)



Construction of the Lycodine Framework. For the synthesis of huperzine B and huperzine U, **6** needs first to have the piperidine ring installed. The allylation of **6** performed at −78 °C with allylmagnesium chloride proceeded smoothly to deliver the addition products **30** and **31** (which were separable by regular chromatography) in a nearly quantitative combined yield with a diastereoselectivity of 1.6/1 (Scheme 14). The decreased diastereoselectivity (1.6/1 at −78 °C) compared with that for ethylation of **6** (dr 7/1 at −25 °C; Table 3, entry 4), could be attributed to the enhanced reactivity of the allyl Grignard reagent. The major diastereomer **30** along with its stereochemistry was established through X-ray crystallographic analysis.[35] Maintaining the reaction mixture at low temperature was necessary. When the reaction was conducted at −25 °C, the formation of a significant amount of **32** was observed.

Scheme 14. Synthesis of 35 and 38

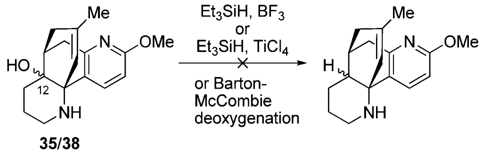


The hydroboration/oxidation of **30** proceeded uneventfully at 0 °C to produce **33** in good yield (86%). With **33** in hand, the focus shifted to the construction of the piperidine ring (Scheme 14). When **33** was exposed to MsCl in the presence of Et_3N, the *O*-alkylation product **34** was formed predominantly (91% yield) without detection of any *N*-alkylation product. This result could be explained by the steric preference for the C12-OH group as well as the weak nucleophilicity of the carbamate nitrogen atom. In line with this rationale, after the conversion of **33** to its mesylate derivative, the reaction mixture was immediately treated with TsOH. Once the deprotection of the carbamate was completed, Et_3N was added, since prolonged exposure to acidic conditions would trigger the cycloetherification of the C12-OH group (vide infra). This procedure provided **35** and **36** in a ratio of 1/1.4. Further, employment of TfOH as the amine liberating agent enhanced the selectivity to 5/1, affording **35** in a satisfactory yield of 80%. Delightfully, by means of the identical sequence, **31** could be converted to **38** via the intermediacy of **37** in a similarly good yield.

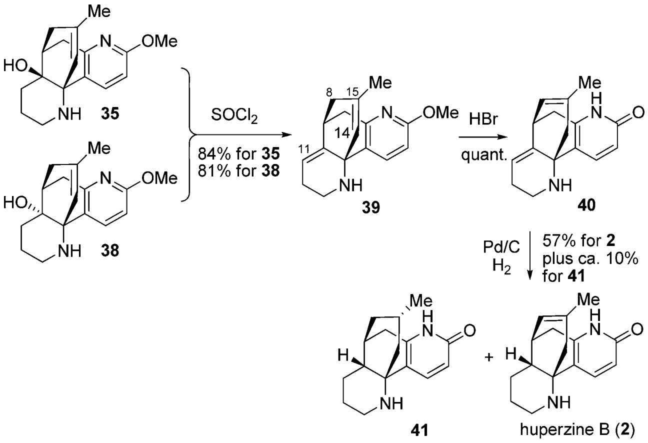
Total Synthesis of Huperzine B. Deoxygenative reduction of **35** and **38** was investigated in an attempt to set up the C12 stereocenter directly. Unfortunately, neither could give the desired product under various tested conditions. Exposure of **35**/**38** to Et_3SiH in the presence of BF_3 or $TiCl_4$ gave either no reaction or (for **35**) cyclization product (vide infra). The Barton−McCombie deoxygenation protocol ($NaH/CS_2/MeI$, then Bu_3SnH/AIBN) was also attempted but proved to be unsuccessful (Scheme 15).[16]

A three-step sequence was then developed to complete the total synthesis of huperzine B (**2**) (Scheme 16). The dehydration reaction performed separately on **35** and **38** with $SOCl_2$ furnished **39** in similarly good yields (84% from **35**, 81%

Scheme 15. Attempted Direct Deoxygenative Reduction of 35/38



Scheme 16. Total Synthesis of Huperzine B (2)



from 38). Compound **39** was further subjected to olefin migration by HBr with concomitant demethylation, affording **40** in quantitative yield. Subsequent catalytic hydrogenation with Pd/C proceeded in a regio- and stereoselective manner to selectively saturate the $\Delta^{11(12)}$ olefin, furnishing **2** in 57% yield along with a minor amount of **41**. Intriguingly, it was found to be critical to have the $\Delta^{15(8)}$ double bond in position before the hydrogenation since the reaction performed on **39** was found to be non-regioselective. The ^{1}H and ^{13}C NMR spectroscopic data of synthetic **2** matched those reported for huperzine B. Comparison of the specific optical rotation data {$[\alpha]^{25}_{D}$ −46.6 (*c* 0.16, MeOH); lit.[3] $[\alpha]^{26}_{D}$ −54.2 (*c* 0.20, MeOH)} enabled us to establish the absolute configuration of natural huperzine B as identical to that of synthetic **2**. Consequently, natural huperzine B and huperzine A possess the same set of absolute stereochemistries.

Total Synthesis of Huperzine U. Olefin isomerization ($\Delta^{14(15)} \rightarrow \Delta^{15(8)}$) is the critical step in our planned total synthesis of huperzine U. There is a strong propensity for this isomerization reaction to take place, as evidenced by the conversion of **24**/**25** to **1** (Schemes 10 and Scheme 12) and the conversion of **39** to **40** (Scheme 16), suggesting a thermodynamic driving force. In all of these cases, the $\Delta^{11(12)}$ olefinic bond appeared to be compatible with the C15 carbocation intermediate formed under acidic conditions. In the presence of the C12-OH group, however, the carbocation-based processes were not regarded as viable methods since the OH group could readily capture the carbocation intermediate. This was evidenced by the quantitative conversion of **21a** to **27** under acidic conditions (Scheme 11). As expected, treatment of **35** with TfOH (1.0 equiv) afforded **42** along with the recovered starting material (Scheme 17). No olefin isomerization product was observed.

Scheme 17. Attempted Olefin Isomerization of 35 Leading to 42

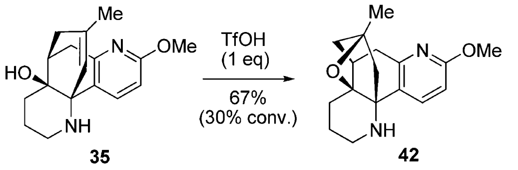
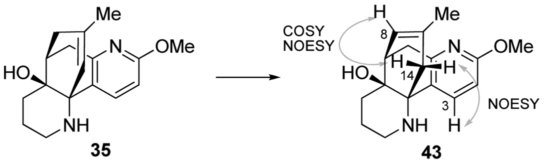


Table 5. Ir-Catalyzed Olefin Isomerization of 35



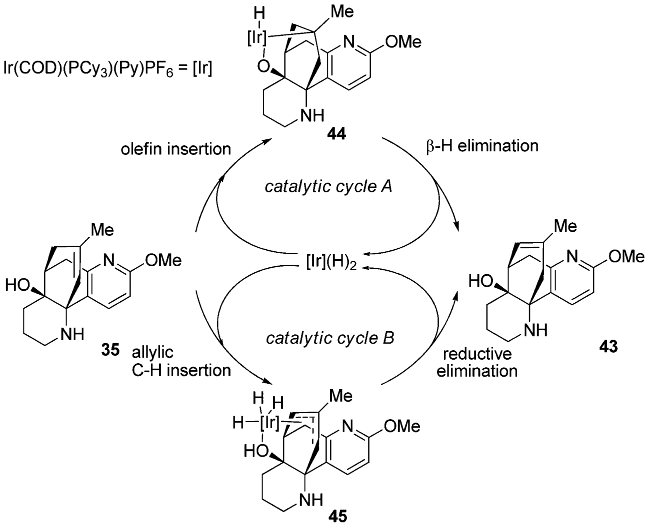
entry	pressure of H_2	result
1	0	no reaction
2	80 atm	no reaction
3	1 atm	98% yield

To address this challenge, we resorted to transition-metal-catalyzed olefin isomerization.[17−23] Crabtree's catalyst, [Ir(COD)(PCy$_3$)(Py)]PF$_6$ (denoted as [Ir]) was recruited for the investigation. Upon exposure of **35** to the catalyst in CH$_2$Cl$_2$ under inert (nitrogen) or high-pressure hydrogen (80 atm) atmosphere, no reaction was observed (Table 5, entries 1 and 2). Interestingly, when **35** was placed in a hydrogen atmosphere at normal pressure in the presence of the catalyst, the reaction proceeded slowly to provide **43** in a nearly quantitative yield (entry 3). The structure of **43** was confirmed by 2D NMR analysis. To the best of our knowledge, this represents the first example where a trisubstituted olefin was isomerized by a transition-metal catalyst. In addition, it demonstrates the strategic application of olefin isomerization in natural product synthesis with a readily available catalyst. By contrast, previous examples of olefin isomerization in total synthesis have generally been limited to allyl ethers in protecting group manipulations.[24]

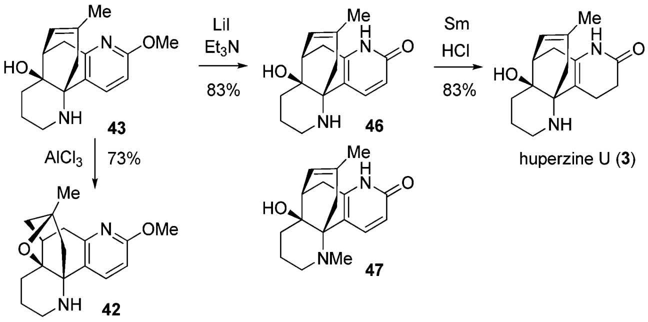
In view of the fact that no reaction occurred in the absence of either the catalyst or hydrogen, the complex [Ir](H)$_2$ formed should be the operative catalyst.[25] This was validated by the observed success of olefin isomerization catalyzed by preformed [Ir](H)$_2$ under an argon atmosphere. On the basis of this evidence, two mechanistic scenarios were proposed (Scheme 18). In the hydride addition mechanism (catalytic cycle A), [Ir](H)$_2$ would undergo addition of Ir−H across the olefin double bond of **35** to give **44**, which would advance to **43** via *β*-H elimination.[18,20] In the *π*-allyl mechanism (catalytic cycle B), **35** would combine with [Ir](H)$_2$ via allylic C−H insertion to form an Ir(V) species, η^3-allyl complex **45**, which would decompose to **43** through reductive elimination.[22b] In view of the presence of Ir−H bonds in the catalyst, the first scenario was the preferred one.[17] The exact reason that no isomerization occurred under a high-pressure hydrogen atmosphere could be elusive. Presumably, H$_2$ saturated the metal center by forming a tetrahydride Ir(V) complex[26] and impeded further coordination with the substrate, thus precluding the desired reaction.

The total synthesis of huperzine U was then accomplished from **43** (Scheme 19). Demethylation of the methoxypyridine ring was explored. Treatment of **43** with NaSEt in DMF gave no reaction at lower temperatures (80−110 °C) and decomposed products at a higher temperature (120 °C).[27] The use of BBr$_3$[28] or BCl$_3$[29] in CH$_2$Cl$_2$ at room or refluxing

Scheme 18. Proposed Mechanisms for the Ir-Catalyzed Olefin Isomerization of 35



Scheme 19. Total Synthesis of Huperzine U (3)



temperature proved abortive. When **43** was subjected to $AlCl_3$ in DCE at RT, **42** was isolated as the major product.[30] Employment of the original Harrison's conditions was unsuccessful.[31] Nevertheless, by modifying Harrison's conditions we were able to obtain the demethylation product. Thus, exposure of **43** to LiI in refluxing toluene resulted in a mixture of **46** and **47** with a ratio of ca. 2/1. Compound **47** was derived from **46** via *N*-methylation by the byproduct MeI. The use of Et_3N as a scavenger of MeI successfully enhanced the ratio. When 20 equiv of Et_3N was added, the reaction offered **46** and **47** in a ratio of 36/1 as determined by ^1H NMR analysis of the crude mixture, and the desired product **46** was isolated in 83% yield. Finally, semihydrogenation of the pyridone ring was accomplished by employing Kamochi's procedure, furnishing huperzine U (**3**) in 83% yield.[32] Other conditions such as H_2/Pd[33] or Mg/MeOH[34] were futile.

The ^1H and ^{13}C NMR spectroscopic data for synthetic **3** matched those reported for huperzine U. The value of the specific optical rotation of synthetic **3**, albeit small {$[\alpha]_D$ +8.6 (*c* 0.85, MeOH)}, was not equal to zero as originally reported. Fortunately, comparison of the CD data {synthetic **3** (*c* 2.0 × 10^{-4} mol/L, CH_3OH): $[\theta]_{245}$ +1.1 × 10^4, $[\theta]_{319}$ −1.4 × 10^2; natural huperzine U (*c* 1.8 × 10^{-3} mol/L, CH_3OH): $[\theta]_{240}$ +1.7 × 10^4, $[\theta]_{313}$ −6.4 × 10^2}[4] enabled us to establish the absolute stereochemistry of huperzine U as identical to that of synthetic **3**. Consequently, natural huperzine U and huperzine A possess the same set of absolute stereochemistries. Meanwhile, it points to the possibility that the originally reported optical rotation of huperzine U may have been mistaken.

■ CONCLUSION

In summary, by employing a unified synthetic strategy, the most efficient total synthesis of huperzine A (**1**) to date, the first asymmetric total synthesis of huperzine B (**2**), and the first total synthesis of huperzine U (**3**) were collectively accomplished in overall yields of 17%, 10%, and 9%, respectively, each spanning 10−13 steps from (*R*)-pulegone. The synthetic routes feature (1) the first example of a Buchwald−Hartwig coupling reaction with a simple *α*-trifloxy enone substrate, (2) a rare example of Heck cyclization of an enamine-type substrate, and (3) the first example of Ir-catalyzed isomerization of a trisubstituted olefin. This work has for the first time established the absolute configurations of huperzine B and huperzine U and revealed that natural huperzine A, huperzine B, and huperzine U possess the same set of absolute stereochemistries. This provides support for the proposed biosynthetic pathways depicted in Scheme 1. The concise and efficient nature of the synthetic routes renders them highly valuable for supplying sufficient amount of these sparse natural products for biological and medicinal purposes.

■ EXPERIMENTAL SECTION

General Methods. All nonaqueous reactions were run under a positive pressure of nitrogen. Anhydrous solvents were obtained using standard drying techniques. Commercial-grade reagents were used without further purification unless stated otherwise. Flash chromatography was performed on 300−400 mesh silica gel with the indicated solvent systems. ^1H NMR spectra were recorded on a 400 MHz spectrometer using TMS (0.00 ppm) or residual chloroform (7.26 ppm) as an internal standard. Chemical shifts (*δ*) are reported in parts per million downfield from TMS. Data are reported as chemical shift (s = singlet, br = broad, d = doublet, t = triplet, q = quartet, hept = heptet, m = multiplet; *J* = coupling constant in Hz, integration.). ^{13}C NMR spectra were recorded on a 100 MHz spectrometer using proton decoupling, unless otherwise noted. Chemical shifts are reported in parts per million downfield from TMS. The central resonance of $CDCl_3$ (77.00 ppm) was used as the internal standard. $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. HRMS was performed using either an FTMS-ESI or FTMS-MALDI spectrometer.

***tert*-Butyl ((5*S*,9*S*,11*S*)-11-Allyl-11-hydroxy-2-methoxy-7-methyl-5,8,9,10-tetrahydro-5,9-methanocycloocta[*b*]pyridin-5-yl)carbamate (30) and *tert*-Butyl ((5*S*,9*S*,11*R*)-11-Allyl-11-hydroxy-2-methoxy-7-methyl-5,8,9,10-tetrahydro-5,9-methanocycloocta[*b*]pyridin-5-yl)carbamate (31).** To a solution of ketone **6** (689 mg, 2.0 mmol) in THF (10 mL) was added a solution of allylmagnesium chloride (3.0 mL, 2.0 M in THF) slowly at −78 °C. After the mixture was stirred at that temperature for 3 h, the reaction was quenched with saturated aqueous NH_4Cl (10 mL). (If the reaction was conducted at −25 °C, the byproduct **32** could be obtained as a dense colorless liquid.) The resulting mixture was then allowed to warm to room temperature, extracted with CH_2Cl_2 (20 mL × 3), dried over Na_2SO_4, concentrated, and purified by chromatography (hexane/EtOAc = 30/1) to give **30** (467 mg, 60%) and **31** (298 mg, 38%) as dense colorless liquids. Data for **30**: mp 185−187 °C; $[\alpha]_D^{27}$ +12.5 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.52 (d, *J* = 8.6 Hz, 1H), 6.52 (d, *J* = 8.6 Hz, 1H), 6.20−6.08 (m, 1H), 5.45 (s, 1H), 5.12 (d, *J* = 10.0 Hz, 1H), 5.04 (d, *J* = 17.0 Hz, 1H), 4.97 (br s, 1H), 4.48 (br s, 1H), 3.89 (s, 3H), 3.17 (dd, J_1 = 19.4 Hz, J_2 = 7.2 Hz, H-6), 2.72 (d, *J* = 19.4 Hz, H-6), 2.72 (dd, J_1 = 18.3 Hz, J_2 = ca. 5 Hz, H-8), 2.51−2.42 (m, 2H), 2.10 (dd, J_1 = 14.0 Hz, J_2 = 8.5 Hz, 1H), 1.82 (d, *J* = 18.3 Hz, H-8), 1.63 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 162.1, 157.0, 154.0, 134.9, 134.0, 133.7, 130.1, 127.4, 117.3, 107.7, 80.7, 76.1, 61.8, 53.4, 39.3, 39.1, 37.2, 35.2, 28.4, 22.8; IR (thin film): 3264, 2976, 2935, 2906, 1678, 1598, 1533, 1475, 1424, 1365, 1310, 1289, 1254, 1170, 1091, 1041, 918, 822, 673, 631, 573 cm^{-1}; LRMS (ESI): 387 (M + H)$^+$; HRMS (MALDI-ESI): calcd for $C_{22}H_{31}N_2O_4$ (M + H)$^+$: 387.2278, found: 387.2289. Data for **31**: mp 173−175 °C; $[\alpha]_D^{27}$ +47.6 (*c* = 1.47, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, *J* = 8.5 Hz, 1H), 6.52 (d, *J* = 8.5 Hz, 1H), 6.24−6.12 (m, 1H), 5.76 (br, 1H), 5.15 (d, *J* = 8.0 Hz, 1H), 5.12 (d, *J* = 16.1 Hz, 1H), 4.99 (s, 1H), 4.90−5.00 (br s, 1H), 3.87 (s, 3H), 3.52 (dd, J_1 = 18.6 Hz, J_2 = 8.1 Hz, H-6), 2.55−2.45 (m, 3H), 2.40−2.31 (m, 2H), 1.94 (d, *J* = 18.5 Hz, H-8), 1.59 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.8, 157.0, 156.6, 135.3, 134.6, 133.7, 128.5, 127.6, 117.2, 106.7, 81.2, 74.9, 63.2, 53.4, 40.1, 38.7, 37.7, 34.7, 28.3, 22.5; IR (thin film): 3327, 2977, 2914, 1686, 1593, 1522, 1474, 1426, 1368, 1307, 1285, 1255, 1166, 1078, 1038, 983, 915, 823, 738, 618 cm^{-1}; LRMS (ESI): 387 (M + H)$^+$; HRMS (MALDI-ESI): calcd for $C_{22}H_{31}N_2O_4$ (M + H)$^+$: 387.2278, found: 387.2272. Data for **32**: $[\alpha]_D^{25}$ +48.2 (*c* = 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.20−6.08 (m, 1H), 6.10−5.98 (m, 1H), 5.40 (s, 1H), 5.21−4.95 (m, 5H), 4.42 (br s, 1H), 3.53 (d, *J* = 7.0 Hz, 2H), 3.27 (dd, J_1 = 19.2 Hz, J_2 = 7.5 Hz, H-8), 2.84 (d, *J* = 19.2 Hz, H-8), 2.74 (dd, J_1 = 18.4 Hz, J_2 = 6.2 Hz, H-6), 2.52 (t, *J* = 7.0 Hz, 1H), 2.46 (dd, J_1 = 14.1 Hz, J_2 = 5.7 Hz, 1H), 2.07 (dd, J_1 = 14.1 Hz, J_2 = 8.6 Hz, 1H), 1.84 (d, *J* = 18.4 Hz, H-6), 1.63 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 157.0, 155.9, 135.7, 134.9, 134.6, 134.2, 131.5, 127.1, 120.0, 117.5, 116.9, 80.7, 75.9, 62.1, 42.4, 39.4, 39.2, 37.1, 35.2, 28.4, 22.8; IR (thin film): 3285, 2981, 2922, 1678, 1527, 1457, 1368, 1289, 1252, 1166, 1062, 988, 912, 831, 646 cm^{-1}; LRMS (ESI): 397 (M + H)$^+$; HRMS (MALDI-ESI): calcd for $C_{24}H_{33}N_2O_3$ (M + H)$^+$: 397.2486, found: 397.2483.

***tert*-Butyl ((5*S*,9*S*,11*S*)-11-Hydroxy-11-(3-hydroxypropyl)-2-methoxy-7-methyl-5,8,9,10-tetrahydro-5,9-methanocycloocta-[*b*]pyridin-5-yl)carbamate (33).** To a solution of **30** (638 mg, 1.65 mmol) in THF (16 mL) was added borane tetrahydrofuran complex solution (3.30 mL, 1.0 M in THF) at 0 °C. After consumption of the starting material, 1 N NaOH (8 mL) and H_2O_2 (5 mL, 30%) was added to the reaction mixture. After the mixture was stirred at room temperature for 3 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (2 mL), and the resulting mixture was extracted with CH_2Cl_2 (20 mL × 3), dried over Na_2SO_4, concentrated, and purified by chromatography (hexane/EtOAc = 3/1) to give **33** (574 mg, 86%) as a white solid: mp 174−176 °C; $[\alpha]_D^{23}$ −16.3 (*c* = 1.27, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.5 Hz, 1H), 6.51 (d, *J* = 8.5 Hz, 1H), 5.46 (s, 1H), 5.07 (s, 1H), 4.99 (br, 1H), 3.87 (s, 3H), 3.74−3.58 (m, 2H), 3.12 (dd, J_1 = 19.0 Hz, J_2 = 7.0 Hz, 1H), 3.18−3.06 (br, 1H), 2.76 (d, *J* = 19.0 Hz, 1H), 2.74 (dd, J_1 = 18.1 Hz, J_2 = 7.0 Hz, 1H), 2.65 (t, *J* = 7.0 Hz, 1H), 1.85 (d, *J* = 18.1 Hz, 1H), 1.91−1.80 (m, 1H), 1.75−1.66 (m, 2H), 1.63 (s, 3H), 1.60−1.54 (m, 1H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0, 157.2, 153.6, 134.0, 133.9, 130.2, 127.4, 107.9, 80.9, 76.0, 63.4, 62.1, 53.4, 39.5, 37.1, 34.2, 31.2, 28.4, 26.7, 22.7; IR (thin film): 3527, 4277, 2951, 2922, 1665, 1597, 1534, 1474, 1422, 1298, 1255, 1165, 1086, 1035, 993, 920, 838, 696, 680, 617 cm^{-1}; LRMS (ESI): 405 (M + H)$^+$; HRMS (MALDI-ESI): calcd for $C_{22}H_{33}N_2O_5$ (M + H)$^+$: 405.2384, found: 405.2392.

***tert*-Butyl ((2′*S*,5*S*,9*S*)-2-Methoxy-7-methyl-4′,5,5′,8,9,10-hexahydro-3′*H*-spiro[5,9-methanocycloocta[*b*]pyridine-11,2′-furan]-5-yl)carbamate (34).** To a solution of **33** (30 mg, 0.074 mmol) in DCM (1.5 mL) were added triethylamine (31 μL, 0.22 mmol) and methanesulfonyl chloride (8.6 μL, 0.11 mmol) at room temperature, and the mixture was stirred for 48 h. Then the reaction was quenched with H_2O (1 mL), and the mixture was extracted with CH_2Cl_2 three times. The combined organic layers were dried over anhydrous Na_2SO_4 before the solvent was removed under reduced pressure. The residue was purified via flash chromatography on silica gel (hexane/EtOAc = 20/1) to give **34** (26 mg, 91%) as a colorless oil: $[\alpha]_D^{27}$ +76.2 (*c* = 0.665, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.5 Hz, 1H), 6.49 (d, *J* = 8.5 Hz, 1H), 5.68 (br s, 1H), 4.96 (br s, 1H), 4.09−4.01 (m, 1H), 3.95−3.88 (m, 1H), 3.86 (s, 3H), 3.28 (dd, J_1 = 19.1 Hz, J_2 = 8.3 Hz, H-6), 2.77 (d, *J* = 19.1 Hz, H-6), 2.68 (dd, J_1 = 17.4 Hz, J_2 = 4.6 Hz, 1H), 2.42−2.36 (m, 1H), 2.19−2.09 (m, 1H), 2.00−1.85 (m, 2H), 1.82 (d, *J* = 17.7 Hz, 1H), 1.68−1.59 (m, 1H), 1.64 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.9, 155.4, 153.4, 136.2, 132.8, 130.0, 127.3, 106.8, 86.1, 79.3, 68.6, 60.4, 53.3, 39.8, 37.3, 36.2, 31.8, 28.4, 26.0, 23.0; IR (thin film): 3393, 2974, 2910, 1725, 1594, 1475, 1424, 1366, 1309, 1251, 1163, 1073, 1038, 1005, 977, 935, 911, 878, 819, 776, 737, 703, 616 cm^{-1}; LRMS (ESI): 387 (M + H)$^+$; HRMS (ESI): calcd for $C_{22}H_{31}N_2O_4$ (M + H)$^+$: 387.2278, found: 387.2282.

(4a*S*,5*S*,10b*S*)-8-Methoxy-12-methyl-2,3,4,4a,5,6-hexahydro-1*H*-10b,5-prop[1]eno-1,7-phenanthrolin-4a-ol (35) and (2′*S*,5*S*,9*S*)-2-Methoxy-7-methyl-4′,5,5′,8,9,10-hexahydro-3′*H*-spiro[5,9-methanocycloocta[*b*]pyridine-11,2′-furan]-5-amine (36). To a solution of **33** (574 mg, 1.42 mmol) in DCM (14 mL) were added triethylamine (0.59 mL, 4.26 mmol) and methanesulfonyl chloride (0.165 mL, 2.13 mmol) at room temperature. After consumption of the starting material, trifluoromethanesulfonic acid (0.38 mL, 4.26 mmol) was added to the reaction mixture. After the mixture was stirred at room temperature for 30 min, triethylamine (1.18 mL, 8.52 mmol) was added. After 3 h of further reaction, 1 N NaOH (10 mL) was added, and the resulting solution was vigorously stirred overnight, extracted with CH_2Cl_2 (20 mL × 3), dried over Na_2SO_4, concentrated, and purified by chromatography (EtOAc) to give **35** (325 mg, 80%) and **36** (64 mg, 16%) as dense colorless liquids. Data for **35**: $[\alpha]_D^{25}$ +56.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.5 Hz, 1H), 6.55 (d, *J* = 8.5 Hz, 1H), 5.11 (s, 1H), 3.88 (s, 3H), 3.20 (dd, J_1 = 18.8 Hz, J_2 = 7.0 Hz, H-6), 2.83 (dd, J_1 = 13.2 Hz, J_2 = 4.8 Hz, 1H), 2.79 (d, *J* = 18.8 Hz, H-6), 2.67 (dd, J_1 = 18.8 Hz, J_2 = 7.0 Hz, H-8), 2.57 (td, J_1 = 13.1 Hz, J_2 = 3.3 Hz, 1H), 2.74−2.42 (br, 2H), 2.34 (t, *J* = 7.1 Hz, 1H), 2.08−1.96 (m, 1H), 1.92 (d, *J* = 18.8 Hz, H-8), 1.73 (td, J_1 = 13.1 Hz, J_2 = 4.5 Hz, 1H), 1.67−1.61 (m, 1H), 1.60 (s, 3H), 1.39−1.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.8, 153.4, 135.8, 135.2, 129.4, 129.3, 107.9, 69.1, 59.0, 53.3, 40.6, 40.1, 37.7, 37.5, 29.4, 22.6, 22.0; IR (thin film): 3146, 2957, 2933, 1595, 1576, 1475, 1449, 1314, 1254, 1176, 1103, 1027, 959, 884, 870, 834, 792, 641, 622, 559 cm^{-1}; LRMS (ESI): 287 (M + H)$^+$; HRMS (ESI): calcd for $C_{17}H_{23}N_2O_2$ (M + H)$^+$: 287.1754, found: 287.1758. Data for **36**: $[\alpha]_D^{26}$ +88.3 (*c* = 0.435, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.5 Hz, 1H), 6.51 (d, *J* = 8.5 Hz, 1H), 5.57 (s, 1H), 4.24−4.15 (m, 1H), 3.96−3.87 (m, 1H), 3.86 (s, 3H), 3.31 (dd, J_1 = 19.3 Hz, J_2 = 8.6 Hz, H-6), 2.81 (d, *J* = 19.3 Hz, H-6), 2.68 (dd, J_1 = 18.1 Hz, J_2 = 5.4 Hz, H-8), 2.55−2.47 (m, 1H), 2.12−1.93 (m, 3H), 1.88 (d, *J* = 18.1 Hz, H-8), 1.79−1.69 (m, 1H) 1.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4, 154.0, 135.4, 134.7, 128.3, 126.5, 107.5, 84.2, 69.7, 59.8, 53.4, 39.5, 37.5, 35.2, 31.0, 26.1, 22.8; IR (thin film): 2918, 1675, 1595, 1500, 1475, 1424, 1378, 1309, 1260, 1190, 1068, 1033, 895, 823, 736, 702, 651, 614, 524 cm^{-1}; LRMS (ESI): 309 (M + Na)$^+$; HRMS (ESI): calcd for $C_{17}H_{22}N_2NaO_2$ (M + Na)$^+$: 309.1574, found: 309.1576.

***tert*-Butyl ((5*S*,9*S*,11*R*)-11-Hydroxy-11-(3-hydroxypropyl)-2-methoxy-7-methyl-5,8,9,10-tetrahydro-5,9-methanocycloocta-[*b*]pyridin-5-yl)carbamate (37).** To a solution of **31** (120 mg, 0.31 mmol) in THF (3 mL) was added borane tetrahydrofuran complex solution (0.62 mL, 1.0 M in THF) at 0 °C. After consumption of the starting material, 1 N NaOH (2 mL) and H_2O_2 (1 mL, 30%) were added to the reaction mixture. After the mixture was stirred at room temperature for 3 h, saturated aqueous $Na_2S_2O_3$ (2 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (10 mL × 3), dried over Na_2SO_4, concentrated, and purified by chromatography (hexane/EtOAc = 3/1) to give **37** (115 mg, 92%) as a white solid: mp 177−179 °C; $[\alpha]_D^{27}$ 79.2 (*c* = 1.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.6 Hz, 1H), 6.47 (d, *J* = 8.6 Hz, 1H), 6.16 (br, 1H), 5.02 (s, 1H), 4.95 (br, 1H), 3.87 (s, 3H), 3.72 (m, 1H), 3.65 (m, 1H), 3.52 (dd, J_1 = 18.8 Hz, J_2 = 8.3 Hz, H-6), 3.46 (br, 1H), 2.70 (t, 1H), 2.52 (d, *J* = 18.8 Hz, H-6), 2.32 (dd, J_1 = 18.6 Hz, J_2 = 4.0 Hz, H-8), 1.99 (d, *J* = 18.6 Hz, H-8), 2.07 (d, *J* = 17.8 Hz, 1H), 1.94−1.87 (m, 2H), 1.76−1.63 (m, 2H), 1.58 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.9, 157.2, 156.5, 134.2, 133.6, 128.6, 127.4, 106.7, 81.4, 74.7, 63.8, 63.6, 53.4, 38.5, 38.0, 33.8, 32.7, 28.3, 27.3, 22.4; IR (thin film): 3328, 3051, 2931, 1686, 1593, 1525, 1474, 1426, 1368, 1342, 1062, 1039, 982, 887, 737, 703, 619 cm^{-1}; LRMS (ESI): 405 (M + H)$^+$; HRMS (ESI): calcd for $C_{22}H_{33}N_2O_5$ (M + H)$^+$: 405.2384, found: 405.2393.

(4a*R*,5*S*,10b*S*)-8-Methoxy-12-methyl-2,3,4,4a,5,6-hexahydro-1*H*-10b,5-prop[1]eno-1,7-phenanthrolin-4a-ol (38) and (2′*R*,5*S*,9*S*)-2-Methoxy-7-methyl-4′,5,5′,8,9,10-hexahydro-3′*H*-spiro[5,9-methanocycloocta[*b*]pyridine-11,2′-furan]-5-amine (12-*epi*-36). To a solution of **37** (161 mg, 0.40 mmol) in DCM (4 mL) were added triethylamine (0.16 mL, 1.20 mmol) and methanesulfonyl chloride (46.2 μL, 0.60 mmol) at room temperature. After consumption of the starting material, trifluoromethanesulfonic acid (0.11 mL, 0.60 mmol) was added. The mixture was stirred at room temperature for 30 min, and triethylamine (0.32 mL, 2.40 mmol) was added. After 3 h of further reaction, the resulting solution was vigorously stirred with 1 N NaOH (3 mL) overnight, extracted with CH_2Cl_2 (10 mL × 3), dried over Na_2SO_4, concentrated, and purified by chromatography (hexane/EtOAc = 2/1) to give **38** (90 mg, 79%) as a white dense liquid and 12-*epi*-**36** (18 mg, 16%) as a colorless oil. Data for **38**: $[\alpha]_D^{26}$ 104.8 (c = 2.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 8.5 Hz, 1H), 6.50 (d, J = 8.5 Hz, 1H), 5.32 (s, 1H), 3.89 (s, 3H), 3.42 (dd, J_1 = 18.8 Hz, J_2 = 7.8 Hz, H-6), 3.01 (ddd, J_1 = 13.3 Hz, J_2 = 2.3 Hz, J_3 = 2.0 Hz, 1H), 2.87 (td, J_1 = 13.3 Hz, J_2 = 3.0 Hz, 1H), 2.67 (d, J = 18.8 Hz, H-6), 2.50 (dd, J_1 = 18.6 Hz, J_2 = 6.0 Hz, H-8), 2.31 (t, J = 7.3 Hz, 1H), 2.09 (d, J = 18.6 Hz, H-8), 2.02 (dd, J_1 = 13.6 Hz, J_2 = 4.8 Hz, 1H), 1.84 (qt, J_1 = 13.3 Hz, J_2 = 4.2 Hz, 1H), 1.61 (s, 3H), 1.60 (m, 1H), 1.50 (br d, J = 13.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.8, 154.4, 134.5, 134.3, 130.2, 129.4, 107.3, 69.4, 59.4, 53.3, 41.4, 39.9, 38.5, 37.8, 30.5, 22.5, 21.2; IR (thin film): 3301, 2914, 1594, 1474, 1426, 1338, 1306, 1267, 1248, 1174, 1107, 1036, 898, 824, 737, 704 cm^{-1}; LRMS (ESI): 287 (M + H)$^+$; HRMS (ESI): calcd for $C_{17}H_{23}N_2O_2$ (M + H)$^+$: 287.1754, found: 287.1765. Data for 12-*epi*-**36**: $[\alpha]_D^{26}$ 53.2 (c = 0.82, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, J = 8.5 Hz, 1H), 6.49 (d, J = 8.5 Hz, 1H), 5.26 (s, 1H), 3.93 (m, 1H), 3.86 (s, 3H), 3.83 (m, 1H), 3.39 (dd, J_1 = 18.3 Hz, J_2 = 7.8 Hz, H-6), 2.64 (d, J = 18.3 Hz, H-6), 2.55–2.46 (m, 1H), 2.48 (d, J = 6.1 Hz, 1H), 2.16–2.10 (m, 1H), 2.09 (d, J = 17.4 Hz, 1H), 2.03–1.91 (m, 2H), 1.83–1.76 (m, 1H), 1.54 (s, 3H), 1.51 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6, 154.1, 135.9, 133.6, 132.9, 132.0, 107.1, 87.0, 68.2, 56.6, 53.3, 39.8, 39.0, 36.0, 31.1, 27.0, 22.4; IR (thin film): 3385, 3315, 2926, 1727, 1593, 1471, 1438, 1424, 1343, 1306, 1248, 1188, 1068, 1036, 921, 826, 735 cm^{-1}; LRMS (ESI): 287 (M + H)$^+$; HRMS (ESI): calcd for $C_{17}H_{23}N_2O_2$ (M + H)$^+$: 287.1754, found: 287.1763.

(5*S*,10b*R*)-8-Methoxy-12-methyl-2,3,5,6-tetrahydro-1*H*-10b,5-prop[1]eno-1,7-phenanthroline (39). To a solution of **35** (30 mg, 104 μmol) in *N*,*N*-dimethylacetamide (1 mL) was added $SOCl_2$ (30 μL, 0.42 mmol) at room temperature. The mixture was stirred at this temperature for 9 h and then poured into a saturated aqueous solution of Na_2CO_3 and extracted with CH_2Cl_2 three times. The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified via flash chromatography on silica gel (hexane/EtOAc = 3/1) to give **39** (24 mg, 84%) as a colorless oil: $[\alpha]_D^{27}$ 148.5 (c = 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.2 Hz, 1H), 6.50 (d, J = 8.2 Hz, 1H), 5.59 (dd, J_1 = 4.8 Hz, J_2 = 2.0 Hz, 1H), 5.28 (s, 1H), 3.86 (s, 3H), 3.28 (dd, J_1 = 18.6 Hz, J_2 = 8.3 Hz, H-6), 2.95 (m, 2H), 2.79 (d, J = 18.6 Hz, H-6), 2.65 (ddd, J_1 = 13.6 Hz, J_2 = 10.0 Hz, J_3 = 4.2 Hz, 1H), 2.50 (dd, J_1 = 17.8 Hz, J_2 = 6.3 Hz, H-8), 2.11 (m, 1H), 2.07 (d, J = 17.8 Hz, H-8), 1.88 (m, 1H), 1.59 (s, 3H), 1.50 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0, 155.6, 140.8, 133.8, 133.4, 133.0, 131.0, 115.4, 107.2, 54.3, 53.3, 42.7, 42.2, 39.3, 36.2, 26.2, 22.8; IR (thin film): 2908, 2829, 1590, 1578, 1471, 1422, 1325, 1308, 1269, 1189, 1114, 1073, 944, 828, 665 cm^{-1}; LRMS (ESI): 269 (M + H)$^+$; HRMS (ESI): calcd for $C_{17}H_{21}N_2O$ (M + H)$^+$: 269.1648, found: 269.1646.

(5*R*,10b*R*)-12-Methyl-2,3,5,6-tetrahydro-1*H*-5,10b-prop[1]eno-1,7-phenanthrolin-8(7*H*)-one (40). Alkene **39** (24 mg, 88 μmol) was dissolved in 1.0 M aqueous HBr (2 mL), and the solution was refluxed for 10 h and then cooled to room temperature. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with dichloromethane three times. After drying over anhydrous Na_2SO_4, the solution was concentrated under reduced pressure, and the residue was purified by flash chromatography (DCM/MeOH = 10/1) to afford **40** (22 mg, 100%) as a white solid: mp 230–232 °C; $[\alpha]_D^{28}$ −73.0 (c = 1.34, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.26 (br, 1H), 7.76 (d, J = 9.2 Hz, 1H), 6.44 (d, J = 9.2 Hz, 1H), 5.66 (t, J = 3.8 Hz, 1H), 5.41 (d, J = 3.7 Hz, 1H), 3.07 (t, J = 3.7 Hz, 1H), 2.96 (m, 2H), 2.85 (m, 1H), 2.74 (d, J = 16.8 Hz, 1H), 2.51 (d, J = 16.8 Hz, 1H), 2.03 (br s, 2H), 2.01 (d, J = 16.8 Hz, 1H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 143.2, 139.5, 139.1, 133.8, 124.6, 122.2, 117.5, 116.5, 53.0, 46.7, 39.4, 39.2, 36.7, 26.3, 22.7; IR (thin film): 3278, 2962, 1873, 1656, 1613, 1553, 1462, 1377, 1303, 1263, 1165, 1120, 1095, 1009, 807, 738, 703, 659 cm^{-1}; LRMS (ESI): 255 (M + H)$^+$; HRMS (ESI): calcd for $C_{16}H_{19}N_2O$ (M + H)$^+$: 255.1492, found: 255.1494.

(4a*R*,5*R*,10b*R*)-12-Methyl-2,3,4,4a,5,6-hexahydro-1*H*-5,10b-prop[1]eno-1,7-phenanthrolin-8(7*H*)-one (Huperzine B, 2) and (4a*R*,5*S*,10b*R*,12*S*)-12-Methyl-2,3,4,4a,5,6-hexahydro-1*H*-5,10b-propano-1,7-phenanthrolin-8(7*H*)-one (41). To a solution of **40** (5.6 mg, 22 μmol) in EtOH (1 mL) was added Pd/C (10%) catalyst (2.3 mg, 22 μmol). Then the mixture was allowed to stir at room temperature under balloon pressure of H_2 for 12 h. The insoluble solid was filtered, and the solvent was removed under reduced pressure. The residue was purified via flash chromatography on silica gel (DCM/MeOH = 10/1) to give huperzine B (**2**) (3.2 mg, 57%) as a white solid, along with minor amount of **41** (ca. 0.6 mg, 10%). Data for **2**: mp 268–270 °C; $[\alpha]_D^{25}$ −46.6 (c = 0.16, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.71 (br, 1H), 7.71 (d, J = 9.3 Hz, 1H), 6.46 (d, J = 9.3 Hz, 1H), 5.47 (d, J = 4.7 Hz, 1H), 2.86 (dd, J_1 = 17.8 Hz, J_2 = 5.3 Hz, 1H), 2.74 (d, J = 13.3 Hz, 1H), 2.42 (d, J = 18.3 Hz, 1H), 2.37 (m, 1H), 2.30 (dd, J_1 = 13.3 Hz, J_2 = 1.5 Hz, 1H), 2.06 (d, J = 17.9 Hz, 1H), 1.87 (d, J = 17.1 Hz, 1H), 1.69 (m, 1H), 1.54 (s, 3H), 1.66–1.50 (m, 2H), 1.47 (m, 1H), 1.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 143.1, 140.5, 132.3, 126.0, 118.0, 118.0, 53.2, 47.8, 41.6, 40.4, 34.4, 29.5, 27.9, 25.2, 22.9; IR (thin film): 3296, 2925, 2854, 1655, 1614, 1553, 1456, 1406, 1376, 1310, 1123, 1097, 836, 736, 652 cm^{-1}; LRMS (ESI): 257 (M + H)$^+$; HRMS (ESI): calcd for $C_{16}H_{21}N_2O$ (M + H)$^+$: 257.1648, found: 257.1653. Data for **41**: mp 252–254 °C; $[\alpha]_D^{25}$ −88.6 (c = 0.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 9.6 Hz, 1H), 6.48 (d, J = 9.6 Hz, 1H), 2.98 (dd, J_1 = 18.6 Hz, J_2 = 6.5 Hz, 1H), 2.74 (br d, J = 13.3 Hz, 1H), 2.48 (d, J = 18.6 Hz, 1H), 2.38 (t, J = 12.3 Hz, 1H), 2.11–1.99 (m, 3H), 1.67–1.41 (m, 8H), 1.32–1.28 (m, 1H), 0.61 (d, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 144.0, 140.5, 119.2, 117.8, 52.9, 46.9, 43.6, 41.1, 38.7, 32.5, 30.4, 27.9, 26.0, 25.6, 22.6; IR (thin film): 3302, 2922, 2851, 1660, 1621, 1552, 1464, 1325, 1261, 1135, 1097, 967, 866 cm^{-1}; LRMS (ESI): 259 (M + H)$^+$; HRMS (ESI): calcd for $C_{16}H_{23}N_2O$ (M + H)$^+$: 259.1805, found: 259.1810.

(4a*S*,6*R*,7a*R*,12b*S*)-10-Methoxy-6-methyl-1,2,3,4,6,7,7a,8-octahydro-6,12b-methanofuro[2,3-*e*][1,7]phenanthroline (42). To a solution of alkene **35** (10 mg, 0.035 mmol) in CH_2Cl_2 (0.5 mL) was added trifluoromethanesulfonic acid (3.1 μL, 0.035 mmol). The mixture was allowed to stir at room temperature for 20 h and then poured into a saturated aqueous solution of Na_2CO_3 and extracted with CH_2Cl_2 three times. The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified via flash chromatography on silica gel (EtOAc) to give ether **42** (2.0 mg, 20%) as a colorless solid along with recovered starting material **35** (7.0 mg, 70%): mp 153–154 °C; $[\alpha]_D^{24}$ −36.8 (c = 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 8.6 Hz, 1H), 6.60 (d, J = 8.6 Hz, 1H), 3.90 (s, 3H), 3.07–2.92 (m, 2H), 2.81–2.72 (m, 1H), 2.35–2.25 (m, 1H), 2.18–2.08 (m, 1H), 2.03 (td, J_1 = 12.0 Hz, J_2 = 3.2 Hz, 1H), 2.02–1.93 (m, 1H), 1.75–1.57 (m, 4H), 1.52–1.43 (m, 2H), 1.43 (s, 3H), 1.33 (dd, J_1 = 12.0 Hz, J_2 = 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.6, 150.8, 137.6, 128.3, 108.7, 81.3, 80.5, 62.4, 59.2, 53.2, 44.3, 41.7, 41.6, 33.5, 26.4, 24.1, 21.1; IR (thin film): 2928, 2862, 1598, 1576, 1473, 1421, 1342, 1316, 1135, 1116, 1033, 1002, 876, 828, 739, 637 cm^{-1}; LRMS (ESI): 287 (M + H)$^+$; HRMS (ESI): calcd for $C_{17}H_{23}N_2O_2$ (M + H)$^+$: 287.1754, found: 287.1751.

(4a*S*,5*R*,10b*S*)-8-Methoxy-12-methyl-2,3,4,4a,5,6-hexahydro-1*H*-5,10b-prop[1]eno-1,7-phenanthrolin-4a-ol (43). To a solution of alkene **35** (260 mg, 0.91 mmol) in CH_2Cl_2 (5 mL) was added Crabtree's catalyst (36 mg, 0.045 mmol). Then the mixture was allowed to stir at room temperature under balloon pressure of H_2 for 5 days. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography on silica gel (EtOAc/MeOH = 5/2) to give alkene **43** (255 mg, 98%) as a colorless oil: $[\alpha]_D^{26}$ +40.0 (c = 0.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 8.6 Hz, 1H), 6.62 (d, J = 8.6 Hz, 1H), 5.41 (d, J = 5.0 Hz, 1H), 3.90 (s, 3H), 3.10 (dd, J_1 = 18.0 Hz, J_2 = 5.7 Hz, 1H), 2.82−2.72 (m, 2H), 2.46 (t, J = 5.4 Hz, 1H), 2.36 (td, J_1 = 13.1 Hz, J_2 = 2.9 Hz, 1H), 2.33 (br s, 2H), 2.26 (d, J = 17.8 Hz, 1H), 1.91 (qt, J_1 = 12.9 Hz, J_2 = 4.5 Hz, 1H), 1.79 (d, J = 17.3 Hz, 1H), 1.68 (td, J_1 = 13.1 Hz, J_2 = 4.3 Hz, 1H), 1.64−1.57 (m, 1H), 1.55 (s, 3H), 1.42−1.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.6, 152.7, 137.1, 132.6, 128.7, 123.5, 108.8, 68.0, 57.6, 53.3, 44.8, 41.7, 40.9, 37.1, 29.7, 22.9, 22.8; IR (thin film): 3396, 2927, 2849, 1599, 1571, 1482, 1428, 1325, 1266, 1099, 1029, 823, 760, 625, 558 cm^{-1}; LRMS (ESI): 287 $(M + H)^+$; HRMS (ESI): calcd for $C_{17}H_{23}N_2O_2$ $(M + H)^+$: 287.1754, found: 287.1758.

(4a*S*,5*R*,10b*S*)-4a-Hydroxy-12-methyl-2,3,4,4a,5,6-hexahydro-1*H*-5,10b-prop[1]eno-1,7-phenanthrolin-8(7*H*)-one (46). An oven-dried sealed tube under an atmosphere of Ar was charged with alkene **43** (108 mg, 0.378 mmol), LiI (355 mg, 1.89 mmol), TEA (1.04 mL, 7.55 mmol), and toluene (4 mL). The mixture was allowed to stir at 140 °C for 7 h. Then the solvent was removed under reduced pressure, and the residue was dissolved in MeOH. The insoluble solid was filtered, and the MeOH was removed under reduced pressure. The residue was purified via flash chromatography on silica gel (EtOAc/MeOH = 5/1) to give pyridone **46** (85 mg, 83%) as a colorless oil. (If the starting material reacted with LiI without TEA, the byproduct **47** could be formed.) Data for **46**: $[\alpha]_D^{24}$ −14.8 (c = 1.25, MeOH); ^1H NMR (400 MHz, CD_3OD): δ 7.79 (d, J = 9.5 Hz, 1H), 6.41 (d, J = 9.5 Hz, 1H), 5.35 (d, J = 5.1 Hz, 1H), 2.91 (dd, J_1 = 17.9 Hz, J_2 = 5.5 Hz, 1H), 2.73 (dt, J_1 = 13.5 Hz, J_2 = 2.1 Hz, 1H), 2.48 (d, J = 17.7 Hz, 1H), 2.38−2.23 (m, 3H), 1.94 (qt, J_1 = 13.1 Hz, J_2 = 4.3 Hz, 1H), 1.69 (d, J = 16.6 Hz, 1H), 1.66 (dd, J_1 = 13.3 Hz, J_2 = 4.3 Hz, 1H), 1.56 (s, 3H), 1.52 (d, J = 13.6 Hz, 1H), 1.42−1.34 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 165.5, 143.9, 141.9 133.6, 132.9, 121.1 118.2, 68.3, 57.7, 44.2, 42.1, 41.7, 33.2, 31.0, 23.3, 22.7; IR (thin film): 3277, 2923, 2852, 1656, 1611, 1553, 1456, 1377, 1261, 1188, 1091, 1014, 801, 736, 626 cm^{-1}; LRMS (ESI): 273 $(M + H)^+$; HRMS (ESI): calcd for $C_{16}H_{21}N_2O_2$ $(M + H)^+$: 273.1598, found: 273.1604. Data for **47**: $[\alpha]_D^{25}$ −10.5 (c = 0.25, $CHCl_3$); ^1H NMR (400 MHz, CD_3OD): δ 7.67 (d, J = 9.5 Hz, 1H), 6.42 (d, J = 9.5 Hz, 1H), 5.35 (d, J = 5.0 Hz, 1H), 2.97 (dd, J_1 = 17.9 Hz, J_2 = 5.5 Hz, 1H), 2.91 (br s, 1H), 2.84 (s, 3H), 2.63−2.52 (m, 4H), 2.38 (t, J = 5.3 Hz, 1H), 2.05−1.90 (m, 1H), 1.91 (d, J = 16.7 Hz, 1H), 1.71−1.59 (m, 1H), 1.61 (s, 3H), 1.51 (d, J = 13.1 Hz, 1H), 1.37−1.29 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 165.0, 142.7, 141.0, 132.0, 122.5, 121.3, 117.3, 68.8, 60.2, 49.5, 41.0, 39.6, 39.5, 32.7, 30.6, 23.1, 20.3; IR (thin film): 3374, 2961, 2923, 2851, 1656, 1611, 1552, 1459, 1376, 1261, 1097, 1023, 864, 800, 735, 703, 617 cm^{-1}; LRMS (ESI): 287 $(M + H)^+$; HRMS (ESI): calcd for $C_{17}H_{23}N_2O_2$ $(M + H)^+$: 287.1754, found: 287.1761.

(4a*S*,5*R*,10b*S*)-4a-Hydroxy-12-methyl-2,3,4,4a,5,6,9,10-octahydro-1*H*-5,10b-prop[1]eno-1,7-phenanthrolin-8(7*H*)-one (Huperzine U, 3). To a solution of pyridone **46** (24 mg, 0.088 mmol) in 20% HCl (2 mL) at 0 °C was added Sm powder (132 mg, 0.88 mmol), and the solution was stirred at room temperature for 10 min. Then aqueous NaOH solution was added until the pH reached 14. Water was removed under reduced pressure, and the residue was dissolved in MeOH. The insoluble solid was filtered, and the MeOH was removed under reduced pressure. The residue was purified via flash chromatography on silica gel (EtOAc/MeOH = 5/1) to give **3** (20 mg, 83%) as a white solid: mp 264−266 °C; $[\alpha]_D^{26}$ +8.6 (c = 0.85, MeOH); CD (c = 2.0 × 10^{-4} mol/L, MeOH): $[\theta]_{245}$ +1.1 × 10^4, $[\theta]_{319}$ −1.4 × 10^2; ^1H NMR (400 MHz, CD_3OD): δ 5.38 (br d, J = 5.3 Hz, 1H), 3.09 (dt, J_1 = 12.9 Hz, J_2 = 1.9 Hz, 1H), 2.81 (td, J_1 = 12.9 Hz, J_2 = 3.0 Hz, 1H), 2.58−2.46 (m, 2H), 2.45−2.26 (m, 5H), 2.16 (dd, J_1 = 13.4 Hz, J_2 = 4.1 Hz, 1H), 2.02 (d, J = 16.7 Hz, 1H), 1.99 (dd, J_1 = 13.1 Hz, J_2 = 4.4 Hz, 1H), 1.96−1.93 (m, 1H), 1.70 (br, 1H), 1.69 (s, 3H), 1.56 (br d, J = 13.3 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 173.0, 134.7, 132.2, 123.8, 107.8, 68.2, 63.6, 42.3, 41.7, 38.2, 33.0, 31.0, 30.0, 22.7, 20.2, 20.0; IR (thin film): 3225, 2924, 2852, 1691, 1663, 1559, 1436, 1384, 1330, 1304, 1266, 1209, 1112, 1040, 1008, 816, 732, 697 cm^{-1}; LRMS (ESI): 275 $(M + H)^+$; HRMS (ESI): calcd for $C_{16}H_{23}N_2O_2$ $(M + H)^+$: 275.1754, found: 275.1756.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H and ^{13}C NMR spectra of related compounds, X-ray structure for **30**, and CD spectrum for huperzine U (**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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