Recent Progress in Total Synthesis of *Lycopodium* Alkaloids

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Abstract: Our recent efforts on the asymmetric total synthesis of three types of *Lycopodium* alkaloids, i.e., lycodine–type (lycodine and flabellidine), fawcettimine–type (huperzine Q, fawcettimine, and fawcettidine), and miscellaneous–type (lycoposerramine–R) alkaloids, are described, and the merits of biogenetic consideration in the chemical synthesis of natural products are emphasized.

1. Introduction

Plants belonging to the genus *Lycopodium*, Family Lycopodiaceae, are widely distributed all over the world. Since the isolation of lycopodine (1) from *Lycopodium complanatum* by Bödeker in 1881,\(^1\) chemical investigations of the constituents of *Lycopodium* plants have been actively undertaken by many groups, and nearly 300 alkaloids with various skeletons have been found.\(^2\) Among the *Lycopodium* alkaloids, huperzine A (2), isolated from *Lycopodium serratum* Thunb. in 1986, has been shown to have acetylcholine esterase (AChE) inhibitory activity (IC\(_{50}\): 0.082 μM) and to improve memory disorders in Alzheimer’s disease patients.\(^3\) In addition to these unique activities, it was recently reported that some *Lycopodium* alkaloids possessing skeletons different from that of huperzine A (2) were able to enhance nerve growth factor (NFG) mRNA expression and production in human glial cells,\(^4\) had anti-HIV-1 activity,\(^5\) or inhibited lipopolysaccharide (LPS)–induced pro-inflammatory factors in BV2 microglia and macrophages.\(^6\) Because of their useful biological activities, *Lycopodium* alkaloids are an attractive research target in the fields of natural product chemistry, synthetic chemistry, and medicinal chemistry. The number of hits provided by SciFinder when the terms "Lycopodium" and "synthesis" were searched has been increasing yearly, as shown in Figure 1. In particular, the highly diverse and unique skeletal characteristics of *Lycopodium* alkaloids have inspired many groups to take on the challenging task of the total syntheses of these alkaloids.\(^7\)

In 2010, the author published the results of chemical studies of *Lycopodium* alkaloids in this journal,\(^8\) in which the total syntheses of several alkaloids with various skeletons (Figure 2) have been reported. In this review, recent progress in the total synthesis of *Lycopodium* alkaloids in our laboratory is described.

2. Asymmetric Total Synthesis of Lycodine and Flabellidine

Although information on the biosynthetic route of *Lycopodium* alkaloids is quite limited, it was demonstrated by feeding experiments that pelletierine (5) and 4-(2-piperidyl) acetate (6), both of which are derived from L-lysine (4), were the biosynthetic precursors of lycopodine (1) (Scheme 1).\(^7\) In this hypothetical route proposed by Spenser (Scheme 1; A), we were interested in the tandem cyclization from dienamine 7A to tetracyclic 8A, which involves the formation of two bonds, the C7–C12 and C4–C13 bonds, to establish the lycodine skeleton (8A), from which lycopodine (1) and a representative *Lycopodium* alkaloid, lycodine (3), would be biosynthesized. Taking the stereochemistry into account, the tandem cyclization from 7A to 8A would be refined to the elaborated mode, such as the cyclization from 7B to 8B, as shown in Scheme 1; B. Thus–formed tetracyclic intermediate 8B would be metabolized to flabellidine (9) and lycodine (3) via removal of the two
hydroxyl groups at C7 and C15 followed by monoacetylation or aromatization at A\(^\text{II}\) ring, respectively. Inspired by this plausible hypothesis, we envisaged an alternative cascade cyclization participated by ene\(^\text{II}\)iminium intermediate 11 (Scheme 2), which is conceived to be the quasi\(^\text{II}\) equivalent of dienamine 7B.

As shown in Scheme 2, we expected that the stereochemistry at C15 would control the stereochemical course of the conjugate addition reaction (from 11 to 12) as well as the Mannich-like reaction to form tetracyclic structure 13 having the same stereochemistry at C7, C12, and C13 as those of natural lycodine\(^\text{II}\) type alkaloids. Furthermore, we anticipated that ene-iminium intermediate 11 would be generated by the Boc deprotection of linear diketone 10. According to this idea, we embarked on the total synthesis of \((-\text{)}\)lactone 17. Next, treatment of 17 with trimethylaluminum and N,O\(^\text{II}\)dimethylhydroxylamine, followed by TES protection, furnished di\(^\text{II}\)Weinreb amide 18. The coupling reaction of 18 with alkynyl anion prepared from 19 gave desired di\(^\text{II}\)alkynyl-ketone 20. After selective reduction of the alkyn group in 20 with Pd/C in AcOEt, resulting linear compound 21 was converted into enone 22 through the simultaneous desilylation and dehydration reactions.

With linear substrate 22 in hand, we examined the proposed bioinspired strategy to construct the tetracyclic lycodine skeleton (Scheme 4). After numerous surveys of the reaction conditions, we found that exposure of 22 to an excess amount of \((+\text{-})\)-CSA (20 equiv, CH\(_2\)Cl\(_2\), 50 ℃, 1 h) yielded tetracyclic lycodine skeleton 24\(_a\) as the major product, probably via ene-iminium intermediate 23\(_a\). In this reaction, diastereomeric 24\(_b\) was also produced (total chemical yield 61%, 24\(_a\):24\(_b\) 3.0:1). Reaction intermediate 23\(_a\), which has a chairlike conformation with an equatorial methyl group at C15, would be more stable than alternative intermediate 23\(_b\), which has an axial methyl group, resulting in the predominant formation of 24\(_a\). The structures of 24\(_a\) and 24\(_b\) were respectively elucidated by X-ray crystallographic analysis after conversion into para-bromobenzamide derivative 25 and benzamide derivative 26. Interestingly, treating 21 with an excess amount of \((+\text{-})\)-CSA (20 equiv) in CH\(_2\)Cl\(_2\) (50 ℃, 1 h) resulted in the clean formation of 24\(_a\) and 24\(_b\) (total chemical yield 86%, 24\(_a\):24\(_b\)=2.2:1).

For the completion of the total syntheses of 3 and 9, the mixture of 24\(_a\) and 24\(_b\) was subjected to debenzylation and simultaneous Boc protection to give easily separable di-Boc
compounds 27 and 28 (Scheme 5). The removal of Boc groups of the amines in 27 and the chemoselective acetylation exclusively gave \((\star)_{f}^{N}\) labellidine (9), which resulted in the first total synthesis of this alkaloid. Meanwhile, the selective oxidation of \(A\)-ring with IBX furnished \((\star)_{r}^{N}\) lycodine (3).

As described above, based on biosynthetic considerations, we have achieved the first asymmetric total synthesis of \((\star)_{f}^{N}\) labellidine (9) (in 11 steps and 20.7% overall yield starting from commercially available 14), and completed the shortest total synthesis of \((\star)_{r}^{N}\) lycodine (3) (in 11 steps and 14.6% overall yield starting from 14).  

3. Asymmetric Total Synthesis of Lycoposerramine–R

Lycoposerramine–R (29), isolated from *Lycopodium serratum* by our group in 2009, possesses a unique tetracyclic ring system consisting of a pyridone ring, a 5/6 cis fused ring, and four asymmetric centers. Biogenetically, 29 would be produced from lycodine (3) by bond migration in precursor 30 to form a novel tetracyclic skeleton with a cyclopentene ring system. However, the absolute configuration of the natural product as well as its biological activities has not been clarified thus far. Thus, to determine the absolute configuration and to develop an efficient synthetic route for 29, we embarked on the asymmetric total synthesis of 29.

![Scheme 3. Synthesis of linear substrate for cascade cyclization.](image)

![Scheme 4. Bioinspired cascade cyclization and structure elucidation of the products.](image)

![Scheme 5. Syntheses of \((\star)_{f}\)-flabellidine (9) and \((\star)_{r}\)-lycodine (3).](image)

![Figure 3. Hypothetical biogenetic pathway of lycoposerramine–R.](image)
metric total synthesis of lycoposerramine–R.

Our initial synthetic plan for lycoposerramine–R (29) is shown in Scheme 6. The pyridone ring in 29 could be constructed at the last stage by transformation of tricyclic key intermediate 31, which could be derived from diketone 32 by regioselective reductive amination. Diketone 32 could be obtained from enone 33 via the Wharton rearrangement and the stereoselective addition of a methyl group. Enone 33 could be synthesized via the Diels–Alder reaction of dienophile 34 with diene 35.

We started with the synthesis of key intermediate 31 (Scheme 7). The Diels–Alder reaction of dienophile 34 with aminosiloxydiene 35 in the presence of dibutylhydroxytoluene (BHT) followed by acid hydrolysis afforded enone 36 in a quantitative yield. Next, enone 36 was treated with hydrogen peroxide to give an epoxide, which was then subjected to Wharton rearrangement conditions. IBX oxidation of the resultant allylic alcohol produced enone 37. The stereoselective introduction of a methyl group at C15 was achieved by treating enone 37 with organocuprate to afford separable diketone 32 and its 15-epimer in 89% total yield with dr=7:1. Reductive amination of diketone 32 followed by Cbz protection afforded tricyclic key intermediate 31 in a regio- and stereoselective manner.5

Having succeeded in the development of an efficient synthetic route to obtain tricyclic key intermediate 31 in the racemic form, we next attempted the synthesis of optically active enone 36 utilizing the asymmetric Diels–Alder reaction. For this purpose, we prepared various dienophiles (38a–d) having an oxazolidinone–type chiral auxiliary group, and attempted to perform the diastereoselective Diels–Alder reaction under various conditions with an eye to producing optically active enone 36 (Scheme 8). However, we obtained unsatisfactory results in terms of both chemical yield and enantiomeric excess. Thus, we revised our strategy for the preparation of optically active 31 and adopted the chiral pool synthesis.

We speculated that tricyclic key intermediate 31 could be derived from diketone 39 by regio– and stereoselective reductive amination (Scheme 9), as was demonstrated by the conversion of 32 into 31. Diketone 39 could be obtained from enone 40 via stereoselective copper–mediated conjugate addition and stereoselective intramolecular aldol cyclization. Enone 40 could be derived from known phenylsulfonyl 41 via the introduction of a C3 unit.

We chose (R)–pulegone (42) as the starting material, whose absolute configuration at the chiral center was assumed to be identical with that of C15 in 29, based on biogenetic consider-
Stereoselective installation of a C3 unit at the β position of the α,β-unsaturated carbonyl group in 40 was achieved by the copper-mediated conjugate addition of acetal–containing Grignard reagent 44 to yield a mixture of adducts, which were then treated with aqueous hydrogen chloride at 50°C to give cis–fused 5/6 bicyclic compound 45 in 81% yield (two steps) and having the correct configuration of the quaternary stereocenter at C12 via intramolecular aldol cyclization. Oxidation of 45 with Dess–Martin reagent afforded diketone 39 in 91% yield. Reductive amination of diketone 39 followed by Cbz protection afforded desired key intermediate 31, which was cyclized between the C13 carbonyl group and nitrogen, and its regioisomer 46, which was cyclized between the C4 carbonyl group and nitrogen, in the ratio of 3.6:1. The structures including the stereochemistry of the aminomethine nitrogen, and its regioisomer 46, were respectively elucidated by X-ray crystallographic analysis after conversion into para-bromobenzamide derivatives. In the case of the racemic synthesis of 31 described above, the conversion of compound 32 into tricyclic compound 31 was completely regioselective. However, in the case of compound 39, the regioselectivity of the conversion decreased (31:46 = 3:6:1), probably due to the difference in reactivity between 32 and 39 towards the hydrogenative debenzylation. Actually, the debenzylation of 32 was completed in less than one hour, whereas that of 39 required four hours. Therefore, we assume that the nucelophilicity (or reactivity) towards the two carbonyl groups of the primary amine intermediate generated by the rapid removal of the Cbz group in 32 and that of the secondary amino group derived from 39 are slightly different, resulting in the difference in regioselectivity between compounds 32 and 39.

With optically active key intermediate 31 in hand, we next pursued the development of a new and efficient method for the construction of the pyridone ring (Scheme 11). Treatment of 31 with allylmagnesium bromide in THF gave carbamate 47, which was then treated with KOH in EtOH and subsequently subjected to Cbz re-protection of the secondary amine to afford allyl compound 48. Compound 48 was converted into diene 49 via regioselective dehydration with SOCl₂ in the presence of pyridine. The hydroboration reactions of the terminal (C1–C2) and endo (C4–C5) olefins in 49 were respectively achieved by treating 49 with 9-BBN and then with BH₃/THF in THF. Subsequent oxidation afforded diol 50 as a single diastereomer. At the final stage, the construction of the pyridone ring was accomplished by the aza-Wittig reaction. Thus, Jones oxidation of diol 50 followed by the in situ formation of acyl azide 51, treatment of 51 with triphenylphosphine and refluxing in toluene to form 52, and auto-oxidation of resultant dihydropropyridine 52 produced pyridone 53 in 53% yield. Finally, deprotection of the Cbz group in 53 gave (−)-lycoposerramine–R (29). Synthetic 29 was identical in all respects with the natural product, including the optical property. Therefore, the absolute configuration of lycoposerramine–R was established.¹¹

4. Asymmetric Total Synthesis of Huperzine Q and Fawcettimines

Among the Lycopodium alkaloids, fawcettimine (54)–type alkaloids in particular are highly structurally diverse compounds (Figure 4), and this structural diversity has continued to inspire many groups to design strategies for the total syntheses of these alkaloids.²² Huperzine Q (55) isolated from H.
serrata by Zhu\textsuperscript{12} is a novel fawcettimine–type alkaloid that consists of a unique pentacyclic skeleton possessing a spirohe-miaminal moiety and six asymmetric centers, including a quaternary carbon center. Although its structure and relative stereochemistry were determined by X-ray crystallographic analysis, its absolute configuration and biological activities have not been fully investigated so far. In order to develop an efficient synthetic route to 55 and to confirm its absolute configuration, we planned the asymmetric total synthesis of 55.

Our synthetic plan is shown in Scheme 12. Biogenetically, huperzine Q (55) would be derived from fawcettimine derivative 56 by intramolecular spiroaminal formation with a primary alcohol at C16 and a secondary amine. Then, we aimed at the efficient synthesis of 56, which could be obtained through azonane ring formation utilizing the intramolecular Mitsunobu reaction and subsequent functional group transformations of 57. We envisioned that the successive chiral centers (C5, C4, and C12) in 57 could be constructed from bicyclic cyclopentenone 58 by vinyl Claisen rearrangement and the subsequent hydroboration–oxidation process. We expected that bicyclic compound 58 could be elaborated from chiral diol 59 via the novel stereoselective Pauson–Khand reaction (PKR).

We commenced with the coupling reaction of methyl 4-chloro-4-oxobutyrate (60) and known alkyne 61 to afford ynone compound 62 in 91\% yield (Scheme 13).

\begin{equation}
62 \rightarrow \text{optically active lactone} \quad 63 \quad \text{(one pot)}
\end{equation}

\begin{align*}
63 & \rightarrow \text{allyl unit} \quad 64_a, 64_s \quad \text{quant.}
\end{align*}

\begin{equation}
53 \rightarrow (-)-\text{Lycoposerramine-R (29)}
\end{equation}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Representative fawcettimine–type alkaloids}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme12.png}
\caption{Retrosynthesis of huperzine Q.}
\end{figure}

We commenced with the coupling reaction of methyl 4-chloro-4-oxobutyrate (60) and known alkyne 61 to afford ynone compound 62 in 91\% yield (Scheme 13). 62 was transformed into optically active lactone 63 in a one–pot operation involving the Noyori reduction and successive cyclization in the acidic condition. Then, an allyl unit was introduced to the \(\alpha\) position of the carbonyl group in 63 to furnish 64\(\_a\) and 64\(\_s\) in quantitative yields in the ratio of 2.3:1. These epimers were easily separated by column chromatography, and the conversion of 64\(\_a\) into 64\(\_s\) was achieved by treatment with LHMDS and the subsequent addition of a hindered acid (BHT: butylated hydroxytoluene) at low temperature to afford kinetically controlled product 64\(\_s\) in good yield and excellent selectivity (64\(\_a\):64\(\_s\) = 1:16.5). The subsequent reduction of lactone 64\(\_s\) afforded diol 65 for use in PKR.

Initially, we attempted to perform PKR with diol 65 and obtained 67, the undesired C7 epimer, as the major product (67:68 = ca. 15:1) (Scheme 14). Mechanistic consideration indicated that reaction intermediate 66 would have a chairlike conformation in which the side chain at C–15 occupied the equatorial position, thereby controlling the stereochemistry at
On the basis of this consideration, we devised silyl-tethered compound 69 with the expectation that it would alter the conformation of the reaction intermediate to afford a bicyclic product having the desired C7 stereochemistry. After several attempts to optimize the reaction conditions, we finally found a one-pot operation that would efficiently transform 65 into 68 in 92% yield.

Next, we turned our attention to the construction of a quaternary carbon center at C12 (Scheme 15). MOM groups were introduced to the two hydroxyl groups in 68 and the resulting protected enone was stereoselectively reduced with (R)-CBS reagent to furnish allylic alcohol 71 having the desired stereochemistry at C5. Sulfoxide 72 prepared by treatment of 71 with vinyl sulfoxide was heated at 170 °C in 1,2-dichlorobenzene with excess NaHCO3 to afford desired aldehyde 73 in excellent yield. Treatment of aldehyde 73 with the Wittig reagent gave diene compound 74 in 95% yield. Next, we prepared substrate 76 for the Mitsunobu reaction from diene 74 via a sequential reaction that involved the simultaneous hydroboration-oxidation at two positions (C4-C5 and C9-C10) to give diol 75, the introduction of a nitrogen function to a primary hydroxyl group at C9, and the subsequent removal of a TBDPS group. With Ns-hydroxyl derivative 76 in hand, we tried to construct an azonane ring and found that the treatment of 76 with diethyl azodicarboxylate (DEAD) in the presence of PPh3 in toluene at 70 °C afforded 77 in excellent yield. At this stage, the X-ray crystallographic analysis of 77 was performed, which enabled us to confirm the absolute configuration of all the chiral centers.

For the completion of the total synthesis of 55, we converted 77 into fawcettimine derivative 80 as follows.
Removal of the two MOM groups with trimethylsilyl bromide gave corresponding diol 78 in a quantitative yield. Then, the selective acylation of the primary alcohol at C16 and the subsequent Dess–Martin oxidation of the secondary alcohol at C13 were carried out in a one-pot operation to afford 79. Subsequent removal of the Ns group and the acetyl groups was also achieved in a one-pot operation to furnish fawcettimine derivative 80 efficiently. Then, we attempted to convert 80 into spiroaminal form 55 based on a biogenetic hypothesis. After considerable effort, we found that this spirohemiannular formation occurred by treating 80 with (+)-camphorsulfonic acid in refluxing toluene to furnish (−)-huperzine Q (55) in 86% yield. Direct comparison with natural huperzine Q isolated from L. serratum revealed that synthetic 55 was identical in all respects with the natural product, including the optical rotation, thereby establishing its structure including its absolute configuration. 

Scheme 16. Completion of total synthesis of huperzine Q.

By selective removal of the hydroxyl group at C16 in compound 68, which is a synthetic intermediate of 55, we were also able to accomplish the total synthesis of fawcettimine (54) and fawcettidine (81) (Scheme 17). 

Scheme 17. Total synthesis of fawcettimine and fawcettidine.

5. Conclusion

Lycopodium alkaloids have consistently captured the attention of many natural product chemists and synthetic organic chemists due to their important biological activities and unique skeletal characteristics. In the last 10 years, more than 80 papers on the total syntheses of Lycopodium alkaloids have appeared. In many cases, new synthetic methodologies have been developed for the completion of the total synthesis of structurally complex alkaloids. In this review, our recent efforts on the asymmetric total synthesis of three different types of alkaloids, i.e., lycodine-type, fawcettimine-type, and miscellar-type (lycoposerramine–R) alkaloids, have been introduced, and the merits of biogenetic consideration in the chemical synthesis of natural products have been demonstrated. We believe that tackling the formidable challenges presented by the total synthesis of these alkaloids will certainly contribute to the further advancement of synthetic organic chemistry.

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References

PROFILE

Hiromitsu Takayama received his Bachelor of Science degree in Pharmaceutical Science (1977) and his PhD (1982) from Chiba University. After completing postdoctoral work (1982–1984) under Professor Ekkehard Winterfeldt (Institute of Organic Chemistry, Hannover University, Germany) courtesy of the financial support from the Alexander von Humboldt Foundation, he joined a research group at the Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, as a research associate. In 1986, he moved to the Faculty of Pharmaceutical Sciences, Chiba University, and was promoted to associate professor in 1994 and to full professor at Chiba University Graduate School of Pharmaceutical Sciences in 2004. His research interests span the survey, total synthesis, and medicinal chemistry of biologically active natural products.