/ Review

Total Syntheses of *Lycopodium* and Monoterpenoid Indole Alkaloids Based on Biosynthesis-Inspired Strategies

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Received October 4, 2019

The merits of biogenetic considerations in the chemical syntheses of natural products have been emphasized by describing the total syntheses of *Lycopodium* alkaloids; lycodine, flabellidine, lycopodine, and flabelliformine, as well as monoterpenoid indole alkaloids; C-mavacurine, kopsiyunnanine K, koumine, and 11-methoxy-19R-hydroxygelselegine.

Key words total synthesis; biogenetically inspired synthesis; biomimetic synthesis; alkaloid; *Lycopodium*; indole alkaloid

Introduction

Sir Robert Robinson's synthesis of tropinone (**1**) in 1917¹⁾ has infused synthetic chemists with a new concept, *i.e.*, biogenetically inspired synthesis of natural products. Although the synthesis does not exactly follow the biosynthesis of tropane alkaloids, it has realized a quite efficient synthesis of the core structure of the natural product by using the chemical equivalents of nature's building blocks, succinaldehyde (**2**), methylamine (**3**), and the calcium salt of acetonedicarboxylic acid (**4**) (Chart 1). By taking into consideration a biosynthetic pathway or a biogenetic hypothesis in the design of natural product synthesis, synthetic chemists would be able to conduct unique retrosynthetic analysis for the construction of complex natural products, to realize highly efficient synthetic steps and overall yield, or to evaluate the mechanistic validity of the proposed biogenetic process by chemical means. Therefore, synthetic chemists have looked to nature (biosynthesis) as a source of inspiration in tackling the highly challenging total syntheses of complex natural products. Based on this idea, a huge number of bioinspired (biomimetic) total syntheses of natural products have been developed in the past century.^{2–7)} In this review, some examples of biogenetically inspired syntheses

of *Lycopodium* alkaloids and monoterpenoid indole alkaloids conducted in our laboratory are introduced.

1. *Lycopodium* Alkaloids

Since the isolation of lycopodine (**5**) from *Lycopodium complanatum* (Lycopodiaceae) by Bödeker in 1881, chemical investigations of *Lycopodium* plants have been actively conducted by many researchers, and nearly 300 alkaloids with diverse structures have been found.^{8–11)} Among the *Lycopodium* alkaloids, huperzine A (**6**), which was isolated from *Lycopodium serratum* Thunb. in 1986, has been shown to exhibit potent acetylcholine esterase inhibitory activity and to improve memory disorders in Alzheimer's disease patients. Other useful biological activities of *Lycopodium* alkaloids have also been attracting researchers in natural product chemistry, synthetic chemistry, and medicinal chemistry. In particular, the highly diverse and unique skeletal characteristics of *Lycopodium* alkaloids have inspired many organic chemists to make attempts at the total syntheses of these alkaloids.^{12–15)}

1.1. Total Syntheses of Lycodine and Flabellidine Although the detailed biosynthetic route to *Lycopodium* alkaloids remains unknown, it was demonstrated by feeding experiments that the biosynthetic precursors of lycopodine (**5**) are pelletierine (**9**) and 4-(2-piperidyl)acetoacetate (**10**), both of which are derived from L-lysine (**8**)¹⁶⁾ (Chart 2). In this hypothetical route (Chart 2-A), we were interested in the tandem cyclization of dienamine **11A** into tetracyclic **12A**, which involves the formation of two bonds, *i.e.*, between C7–C12 and C4–C13, to construct lycodine skeleton **12A** from which lycopodine (**5**) and other representative *Lycopodium* alkaloids, lycodine (**7**) and huperzine A (**6**), would be biosynthesized. Taking the stereochemistry into account, the tandem cyclization of **11A** into **12A** would be refined to the elaborated mode as

Chart 1. Robinson's Tropinone Synthesis

This review of the author's work was written by the author upon receiving the 2018 Pharmaceutical Society of Japan Award.

A. Proposed Biosynthetic Pathway by the Spenser Group.

B. Elaborated Biosynthetic Hypothesis for Lycodine-type Alkaloids.

Chart 2. Hypothetical Biosynthetic Pathway for *Lycopodium* Alkaloids

Chart 3. Synthetic Plan Inspired by Hypothetical Biosynthesis

the cyclization of **11B** into **12B** described in Chart 2-B. Thus-formed tetracyclic intermediate **12B** would be metabolized into flabellidine (**13**) and lycodine (**7**) via removal of the two hydroxy groups at C7 and C15 followed by monoacetylation or aromatization at A-ring, respectively. Inspired by this plausible hypothesis, we conceived an alternative cascade cyclization participated by ene-iminium intermediate **15** (Chart 3), which could be regarded as the quasi-equivalent of dienamine **11B**.

As shown in Chart 3, we had expected that the stereochemistry at C15 would control the stereochemical course of the conjugate addition (from **15** to **16**) as well as the Mannich-like reaction (from **16** to **17**) to form a tetracyclic compound that has the same stereochemistry at C7, C12, and C13 as natural lycodine-type alkaloids. Furthermore, we anticipated that ene-

Biography

Born in 1954 in Matsumoto, Nagano Prefecture, Hiromitsu Takayama received his Bachelor's degree in Pharmaceutical Science from Chiba University in 1977 and his Ph.D. from the same university in 1982 under the supervision of Professor Shin-ichiro Sakai. After completing postdoctoral work (1982–1984) with Professor Ekkehard Winterfeldt (Institute of Organic Chemistry, Hannover University, Germany) courtesy of the financial support from the Alexander von Humboldt Foundation, he joined the research group of Professor Tohru Koizumi at the Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, as a research associate. He joined the Faculty of Pharmaceutical Sciences, Chiba University in 1986, 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 include the survey, total synthesis, and medicinal chemistry of biologically active natural products. He is a recipient of the Sato Memorial Award (2000), the Pharmaceutical Society of Japan Award for Divisional Scientific Promotions (2004), The Japanese Society of Pharmacognosy Award (2015), and The Pharmaceutical Society of Japan Award (2018). Currently, he is vice president of The Pharmaceutical Society of Japan.

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Chart 4. Synthesis of Linear Substrate for Cascade Cyclization

iminium intermediate **15** would be generated by the removal of the *tert*-butoxycarbonyl (Boc) group in linear diketone **14**. Using this strategy, we synthesized (–)-lycodine (**7**) and (+)-flabellidine (**13**), as follows.

Our synthesis commenced with the preparation of linear substrate **25** (Chart 4). The stereoselective construction of a methyl group at C15 was conducted by the diastereoselective Hosomi–Sakurai allylation of commercially available crotonamide **18** to give **19** in high yield and good diastereoselectivity. Upon ozonolysis of the terminal olefin in **19**, the resultant aldehyde in **20** was condensed with the enolate of ethyl acetate to give lactone **21**. Treatment of **21** with trimethylaluminum and *N,O*-dimethylhydroxylamine, followed by triethylsilyl (TES) protection, furnished *di*-Weinreb amide **22**. The coupling reaction of **22** with alkynyl anion prepared from **23** gave *di*-alkynylketone derivative **24**, which was subjected to hydrogenation, followed by dehydration to give linear enone **25**.

With linear enone **25** in hand, we examined the proposed bioinspired strategy for the construction of the tetracyclic lycopine skeleton (Chart 5). After numerous surveys of the reaction conditions, we found that exposure of **25** to an excess amount of (+)-10-camphorsulfonic acid (CSA) (20 equiv, CH₂Cl₂, 50°C, 1 h) yielded tetracyclic lycopine skeleton **27a** as the major product, probably *via* ene-iminium intermediate **26a**. In this reaction, diastereomeric **27b** was also produced

Chart 5. Bioinspired Cascade Cyclization and Structure Elucidation of the Products

Chart 6. Syntheses of (+)-Flabellidine and (–)-Lycodine

(total chemical yield 61%; **27a**:**27b** = 3.0:1). Reaction intermediate **26a**, which has a chair-like conformation with an equatorial methyl group at C15, would be more stable than alternative intermediate **26b**, which possesses an axial methyl group, resulting in the predominant formation of **27a**. The structures of **27a** and **27b** were elucidated by X-ray crystallo-

graphic analysis after conversion into *para*-bromobenzamide derivative **28** and benzamide derivative **29**, respectively.

For the completion of the total syntheses of **7** and **13**, a mixture of **27a** and **27b** was subjected to debenzoylation and simultaneous Boc protection to give easily separable *di*-Boc compounds **30** and **31** (Chart 6). The removal of Boc groups of the amines in **30** and the chemoselective acetylation exclusively gave (+)-flabellidine (**13**), which resulted in the first total synthesis of this alkaloid. Meanwhile, selective oxidation

of *A*-ring with 2-iodoxybenzoic acid (IBX) furnished (–)-lycodine (**7**).

As described above, based on the strategy inspired by biosynthesis, we have accomplished the first asymmetric total synthesis of (+)-flabellidine (**13**) (in 11 steps and 20.7% overall yield starting from commercially available **18**), and completed the shortest total synthesis of (–)-lycodine (**7**) (in 11 steps and 14.6% overall yield starting from **18**).¹⁷⁾

1.2. Total Syntheses of Lycodine and Flabelliformine

We next planned the total synthesis of Lycodine-type alkaloids by expanding the bioinspired strategy developed above. We had expected a similar cascade reaction starting from linear substrate **32**, in which the nitrogen atom on the right end of compound **25** is replaced with an oxygen atom, to produce tetracyclic compound **34** (Chart 7). The dihydropyran ring in **34** would be incorporated by the conjugate addition of oxonium intermediate **33**. Thus-obtained tetracyclic compound **34** would be directly converted into lycodine (**5**).

Our synthesis began with the preparation of linear substrate **32** (Chart 8) for realizing the cascade cyclization reaction. Removal of Evans's oxazolidinone moiety in **19** with lithium thiolate gave thioester **35** in 88% yield. Coupling of **35** with iodide **36** in the presence of Zn and 5 mol% PdCl₂(PPh₃)₂ gave ketone **37** in good yield. On the other hand, enone **40**

Chart 7. Synthetic Plan for Lycodine

Chart 8. Synthesis of Linear Substrate **32**

Chart 9. Cascade Cyclization of **32** and Structure Elucidation of the Products

Chart 10. Syntheses of Lycopodine and Flabelliformine

was also prepared by coupling with thioester **38** and iodide **39**. Thus-obtained ketone **37** and enone **40** were subjected to olefin cross metathesis reaction using a second-generation Hoveyda–Grubbs catalyst to give desired linear substrate **32** in good yield.

With linear substrate **32** in hand, we examined the reaction conditions for the key cascade cyclization step (Chart 9). Although the chemical yield needed improvement, we were able to obtain desired compound **34a** in 11% yield together with diastereomeric isomer **34b** in 28% yield, when **32** was treated with methanesulfonic acid in methanol at 40°C. The structures of **34a** and **34b** were elucidated by X-ray crystallographic analysis after conversion into 3,5-dinitrobenzamide derivatives **41a** and **41b**, respectively.

Starting from tetracyclic intermediate **34a**, we completed the total syntheses of lycopodine (**5**) and flabelliformine (**42**), as follows (Chart 10). Referring to Heathcock's work,¹⁸⁾ treatment of **34a** with HBr in AcOH at room temperature (r.t.) gave the ammonium bromide salt, which was then basified with NaOH to give lycopodine (**5**) in 80% yield by pyrrolidine ring formation. Further, α -hydroxylation of the ketone in **5** gave flabelliformine (**42**) in 46% yield, thereby realizing the first

Chart 11. Other *Lycopodium* Alkaloids Synthesized in Our Laboratory

asymmetric total synthesis of this alkaloid.¹⁹⁾

1.3. Asymmetric Total Syntheses of Other *Lycopodium* Alkaloids The *Lycopodium* alkaloids synthesized in our laboratory, other than those mentioned above, are illustrated in Chart 11. They are classified according to hypothetical biogenesis into the Fawcettimine-type (fawcettimine,²⁰⁾ fawcettidine,²⁰⁾ lycoposerramine-B,²¹⁾ lycoposerramine-C,²²⁾ phlegmariurine-A,²²⁾ huperzine-Q,²³⁾ and lycopoclavamine-A²⁴⁾, the Phlegmarine-type (lycoposerramine-V,²⁵⁾ lycoposerramine-W,²⁵⁾ lycoposerramine-X,²⁶⁾ and lycoposerramine-Z²⁶⁾, the Lycodine-type (lycoposerramine-R^{27,28)}, and the Quinolizidine-type (cermizine D,²⁹⁾ ceruine,²⁹⁾ cermizine,³⁰⁾ and senepodine G³⁰⁾). In those syntheses, consideration of the biogenetic relationships for each alkaloid type was quite instructive because the absolute configurations could be predicted when planning the asymmetric total syntheses of those alkaloids.

2. Monoterpenoid Indole Alkaloids

Strictosidine (45), which is biosynthesized by the condensation of tryptamine (43) and secologanin (44), is the key intermediate for the *in vivo* elaboration of numerous groups of monoterpenoid indole alkaloids having rich structural di-

Chart 12. Biosynthetic Relationships and Skeletons of Four Main Types of Monoterpenoid Indole Alkaloids

versity.³¹⁾ According to their structural characteristics, monoterpenoid indole alkaloids are classified into four major types (with many subdivisions), *i.e.*, *Corynanthe*, *Strychnos*, *Aspidosperma*, and *Iboga*. (Chart 12) Biogenetically, the *Corynanthe* skeleton represented by geissoschizine (46) is the first compound to be formed from strictosidine (45). The skeletal changes in the monoterpene part of *Strychnos* alkaloids have resulted in many alkaloids classified into *Aspidosperma* and *Iboga* types. In this section, our biomimetic total syntheses of

Chart 13. Hypothetical Biosynthetic Pathway of *C-Mavacurine*- and *Akuammiline*-Type Alkaloids

Chart 14. Initial Synthetic Plan for *C-Mavacurine*-Type Alkaloids

Chart 15. Synthesis of Cyclization Precursor Diazo Compound **52** Chart 17. Conformations of Geissoschizine and **60**

Chart 16. A Plausible Mechanism of the Unexpected Ring Expansion

some monoterpene indole alkaloids related to *Corynanthe* and *Aspidosperma* types will be described.

2.1. Total Synthesis of *C-Mavacurine*-Type Alkaloids
C-Mavacurine-type alkaloids, such as pleiocarpamine (**47**), normavacurine (**48**), and *C-mavacurine* (**49**), are considered

to be biogenetically derived from geissoschizine (**46**) by the ring closure between C16 and N₁.^{32,33} Geissoschizine (**46**) is also supposed to be a common biogenetic intermediate to provide *Akuammiline*-type alkaloids represented by rhazamal (**50**) (Chart 13). There are no reports of the total syntheses of *C-Mavacurine*-type natural products by the direct coupling of C16 and N₁ in the *Corynanthe* skeleton, probably because its highly strained property owing to its pentacyclic framework has made synthesis difficult.

Our initial synthetic plan is shown in Chart 14. We considered that the ring closure between C16 and C7 and/or C16 and N₁ would occur if an electrophilic carbon species is generated

at C16 in a *Corynanthe*-type substrate. For this purpose, we designed diazo compound **52**, which was prepared from geissoschizine (**46**) through the Regitz diazo transfer reaction.

Our synthesis commenced with the preparation of diazo compound **52** via ($\pm$)-**46**, as shown in Chart 15. According to Vincent's report,³⁴ α,β -unsaturated ester **55** was prepared

Chart 18. Synthesis of Pleiocarpamine, Normavacurine, and C-Mavacurine

from tryptamine (**43**). The $\text{Ni}(\text{cod})_2$ -mediated reductive cyclization of **55** afforded *trans*-**56** as the major product in 55% yield together with desired *cis*-**56** in 31% yield. Then, we examined the conversion of *trans*-**56** into *cis*-**56**. After several attempts, we found that treatment of iminium **57** with Noyori catalyst and formic acid/ Et_3N in *N,N*-dimethylformamide (DMF) in the presence of titanium tetraisopropoxide at 30°C gave *cis*-**56** predominantly (*cis:trans* = 5.3:1). Thus obtained *cis*-**56** was treated with excess lithium diisopropylamide (LDA) and then with methyl formate to provide ($\pm$)-geissoschizine (**46**) in 80% yield. Next, ($\pm$)-**46** was converted into diazo compound **52** in 60% yield by employing tosyl azide in the presence of Et_3N .

With diazo compound **52** in hand, we next investigated the cyclization under carbene-generating conditions. Among the binuclear rhodium complex catalysts used, a separable product was obtained in 54% yield only when $\text{Rh}_2(\text{OAc})_4$ was employed as the catalyst. However, the product was unexpected structure **58** generated by *D*-ring expansion. The use of mononuclear rhodium complex $(\text{PPh}_3)_3\text{RhCl}$ or copper catalyst $\text{Cu}(\text{MeCN})\cdot\text{BF}_4$ did not promote the reaction at room temperature. When $\text{JohnPhosAu}(\text{MeCN})\text{SbF}_6$ was used as the catalyst, ring-expanded product **58** was again obtained in 36% yield together with β -hydride elimination product **59** (36% yield). The ring expansion giving **58** would proceed by the 1,2-alkyl migration of the C20 ethylidene side chain onto the metal carbenoid at C16, as illustrated in Chart 16.

Given the above results, we reformulated our synthetic plan by taking the molecular conformation of *Corynanthe*-type alkaloids into consideration. Normal-type *Corynanthe* alkaloids, such as geissoschizine (**46**), are known to take the *trans*-quinolizidine form (**46a**),³⁵ but can likewise adopt the *cis*-quinolizidine conformer (**46b**) through the inversion of the lone electron pair of nitrogen atom (N_4) (Chart 17). We anticipated that when compound **52** took the *cis*-quinolizidine

Chart 19. Representative New Alkaloids Found in *Kopsia arborea*

Chart 20. CD Spectra of Kopsiyunnanine K and 64

Chart 21. Possible Biogenetic Route to Kopsiyunnanine K

form, the distance of the reaction sites (between C16 and C7 and/or C16 and N_1) was reduced, effecting the desired cyclization. Then, we attempted to modify the lone electron pair of N_4 in compound **52** so that **52** would take the *cis*-quinolizidine form. We chose N_4 -borane complex (**60**) and prepared it by treatment of **52** with the BH_3 -tetrahydrofuran (THF) complex (Chart 18). Nuclear Overhauser effect (NOE) experiments of compound **60** (observation of signal between H-6 β and H-21 β) revealed that the complex had the *cis*-quinolizidine form, as expected (Chart 17).

Chart 22. Synthesis of Kopsiyunnanine K

With cyclization precursor **60** in hand, we examined again various metal catalysts for the cyclization. The $Rh_2(\text{cap})_4$ catalyst gave cyclized product **61** in 55% yield as an inseparable mixture of diastereomers at C16 (approx. 7:1) through a carbene N–H insertion reaction. The amine–borane bond in product **61** was easily cleaved by heating **61** in the presence of trimethylamine oxide to give ($\pm$)-pleiocarpamine (**47**) and compound **62** (16-*epi*-pleiocarpamine) in 12% and 84% yields, respectively. All spectroscopic data of synthetic **47** were completely identical with reported data. Reduction of methyl ester **62** with $LiAlH_4$ afforded ($\pm$)-normavacurine (**48**) in 84% yield, and **48** was further converted into ($\pm$)-*C*-mavacurine (**49**) in 75% yield by treatment with excess methyl iodide. The spectral and physical properties of synthetic **48** and **49** were in good agreement with the reported data of the natural products.

Chart 23. Hypothetical Biogenetic Route to Koumine

As described, we have achieved the biomimetic total syntheses of ($\pm$)-pleiocarpamine (47), ($\pm$)-normavacurine (48), and ($\pm$)-C-mavacurine (49) via a direct cyclization by a carbene N-H insertion reaction between C16 and N_1 in *Corrynanthe* compound 60. For this key cyclization, the N_4 modification of the substrate using an amine-borane complex was indispensable to fix the molecular conformation to a robust *cis*-quinolizidine structure.³⁶⁾

2.2. Total Synthesis and Structure Elucidation of Kopsiunnanine K The genus *Kopsia*, which belongs to Family Apocynaceae, is a rich source of monoterpene indole alkaloids possessing structural diversity as well as a wide range of biological activities.³⁷⁾ As a result of our continuing chemical studies on novel bioactive alkaloids, we were able to accomplish the structure elucidation of several unique monoterpene indole alkaloids from *Kopsia arborea* native to Yunnan Province in China^{38–46)} (Chart 19).

Further investigations have led to the isolation of an intriguing new alkaloid named kopsiunnanine K (63). From spectroscopic analyses, kopsiunnanine K was proposed to be a monoterpene indole alkaloid bearing an azepine-fused tetrahydro- β -carboline ring system, which has never been discovered in monoterpene indole alkaloids. The absolute

Chart 24. Biomimetic Total Synthesis of Koumine -1-

configurations at C16 and C20 were deduced as follows. The circular dichroism (CD) spectrum of 63 showed the opposite Cotton effect to that of decarbomethoxydihydrogambirtannine (64), a *Yohimbane*-type alkaloid possessing 3*S* configuration, which led us to propose that the configuration at C16 in 63 is *R* (Chart 20).

The configuration at C20 was deduced from a biogenetic point of view (Chart 21). Biogenetically, 63 would be generated from an *Aspidosperma*-type alkaloid, vincadifformine (see also Chart 12), via (–)-eburnamine (65) that co-exists in *K. arborea*. Cleavage of the bond between C2 and C21 in 65 would occur by an initial protonation at C2 of the indole moiety to give C/E-ring opening intermediate A. Next, hydrolysis of the iminium function in A would give aldehyde B. By oxidation and esterification of the aldehyde function in B followed by the formation of an aldehyde group at C16 from the hemiaminal function in B, possible biogenetic precursor C of kopsiunnanine K (63) would be generated. Then, 63 would be formed by the Pictet-Spengler reaction of C. This hypoth-

esis allowed us to suggest that **63** has a rearranged skeleton with C20R configuration.

To clarify the structure as well as the absolute configuration at C16 and C20 of **63**, an asymmetric total synthesis was performed (Chart 22). We initially prepared ester derivative **69** from δ -valerolactone (**66**) via a five-step operation: alkylation of **66** with EtI, methanolysis, methoxymethyl (MEM) protection of primary alcohol, alkaline hydrolysis of **67**, and condensation of the resultant carboxylic acid with chiral alcohol **68**. The asymmetric Ireland–Claisen rearrangement of MEM-protected allyl alcohol⁴⁷⁾ derivative **69** was performed under the optimum conditions using potassium hexamethyldisilazide (KHMDs) and trimethylsilylchloride (TMSCl) in toluene. Methylation of resultant carboxylic acid **70** gave ester **71** in 90% yield with 92% enantiomeric excess (*ee*) in 2 steps. The efficient chirality transfer process of the Ireland–Claisen rearrangement would be explained by using the transition state depicted in Chart 22. In the chair-like transition state, the phenyl group would take the pseudo-equatorial position. Furthermore, in the ketene acetal moiety, the side chain with the MEM group would favor the equatorial position with the aid of the chelate effect. Next, an amine function was introduced to **71** by deprotection of the MEM group followed by the Mitsunobu reaction with nosyl (Ns) amine to afford amide **72**. After ozonolysis of **72**, alkylation of the resultant amide with indole unit **73** was executed to give aldehyde **74**. Deprotection of the Ns group in **74** followed by the intramolecular diastereoselective Pictet–Spengler reaction of the resultant amine in the presence of trifluoroacetic acid gave kopsiunnanine K (**63**) as a single diastereomer in a quantitative yield. Recrystallization of the product afforded optically pure **63**. The structure and the 16*R*, 20*R* configuration of synthetic **63** were confirmed by X-ray crystallographic analysis. Synthetic **63** was identical in all respects with the natural compound, including the optical property. Therefore, the structure and the absolute configuration of kopsiunnanine K were established, as shown in formula **63**.⁴⁸⁾

2.3. Total Syntheses of Gelsemium Alkaloids There are three plant species in the genus *Gelsemium*. Among them, *Gelsemium elegans* Benth. (Gelsemiaceae) native to Southeast Asia and southern China is a toxic plant. Nevertheless, it has been used in traditional Chinese medicine for the treatment of skin ulcers and dermatitis and as a remedy for cancer-related pain.⁴⁹⁾ In our previous study, we were able to prove that the plant of origin of ‘Yakatsu,’ an ancient medicine stored in The Shosoin Repository in Japan for over 1250 years, was *G. elegans*.⁵⁰⁾ Phytochemical studies of this plant by us^{51–54)} and other groups have led to the isolation and structure elucidation of more than one hundred monoterpenoid indole alkaloids with diverse chemical structures.⁵¹⁾ Among the six classes of *Gelsemium* alkaloids,⁵¹⁾ the so-called *Gelsedine*-type alkaloids were found to exhibit potent cytotoxic activity against A431 epidermoid carcinoma cells.⁵⁵⁾ Further, koumine (**78**), one of the major constituents of this plant, was found to exhibit toxicity toward cancer cells,⁵⁶⁾ neuroprotective effects,⁵⁷⁾ and anti-inflammatory effects.⁵⁸⁾ However, due to the small quantities of the natural products, a comprehensive biological evaluation of these alkaloids could not be accomplished. Therefore, to accelerate further investigation of pharmacological activities, we embarked on the total synthesis of these classes of alkaloids. In this section, the biomimetic total syntheses

of koumine (**78**) and 11-methoxy-19*R*-hydroxygelselegine (**90**) will be described.

A hypothetical biogenetic route to koumine (**78**) is shown in Chart 23. Like other monoterpenoid indole alkaloids, strictosidine (**45**) is considered to be the primal biogenetic precursor of this alkaloid. By the intramolecular carbon–carbon bond formation between C16 and C5 in *Corynanthe*-type alkaloid geissoschizine (**46**), *E*-koumidine (**75**) belonging to the *Sarpagine*-type would be formed. Then, an oxidation at the allylic position of **75** and a subsequent *C/D* ring cleavage would give hypothetical biogenetic precursor **77**, and an intramolecular S_N2' reaction in **77**^{59,60)} would result in the coupling between C7 and C20, producing koumine (**78**). For the synthesis of this cage structure alkaloid, we planned to mimic this hypothetical biogenetic key reaction at the final stage of the total synthesis, and started chemical synthesis using known chiral diol derivative (**79**) as the starting material.

Starting from known chiral diol **79**,⁶¹⁾ keto-amine **80** was prepared in four steps (Chart 24). Then, **80** was alkylated with alkyne derivative **81** to afford alkyne-ketone **82**. Silyl ether **83** was prepared and subsequent gold(I)-catalyzed cyclization gave 6-*exo-dig-mode* cyclized product **84** having *E*-olefin in 85% yield.⁶²⁾ Thus-obtained cyclized product was converted into ketone **85** by introducing the C1 unit to C17 in compound **84**. By Fischer indole synthesis using ketone **85** with a phenylhydrazine derivative, indole compound **86** was obtained. The chemo- and diastereoselective introduction of a hydroxy group at C17 was achieved by hydroboration using 9-borabicyclo[3.3.1]nonane (9-BBN) to give **87**, which was subjected to the Birch reduction at -78°C to afford *Sarpagine*-type *unnatural* indole alkaloid **76**, which corresponds to one of the possible biogenetic intermediates of koumine (**78**).

Next, according to the biogenetic speculation mentioned above, the *C/D* ring opening in **76** was carried out with methyl chloroformate to give compound **88** (Chart 25). The carbamate was reduced to an *N*-methyl group and the allylic alcohol was

Chart 25. Biomimetic Total Synthesis of Koumine -2-

acetylated. Finally, the intramolecular coupling reaction between C7 and C20 in **89** was achieved by palladium catalysis in the presence of sodium hydride (NaH) to furnish koumine (**78**) in good yield. Thus, we have achieved the total synthesis of (–)-koumine in 18 steps in a biomimetic manner.⁶³⁾

The proposed biosynthesis of 11-methoxy-19*R*-hydroxygelselegine (**90**), which has a pentacyclic oxindole structure with

Chart 26. Hypothetical Biogenetic Route to 11-Methoxy-19*R*-hydroxygelselegine

seven chiral centers, is shown in Chart 26. *Humantenine*-type oxindole alkaloid **91** would also be derived from *Sarpagine*-type alkaloid **75** by oxidation of the indole nucleus. Then, the C19–C20 double bond in *Humantenine*-type alkaloid **91** would be oxidized to form epoxy derivative **92**. By a subsequent attack of the nitrogen on the epoxy carbon, aziridinium intermediate **93** would be generated. Then, the ring opening between C21 and *N*₄ by the attack of water would give rise to alkaloid **90**.⁶⁴⁾ In order to realize this biogenetic hypothesis in a chemical flask, we designed a synthesis of this alkaloid starting from compound **85**, which is a synthetic intermediate of koumine (**78**).

A synthetic intermediate of koumine was utilized as follows (Chart 27). A Fischer indole synthesis using ketone **85** and 2-methoxy-phenylhydrazine derivative in the presence of pyridine·HCl gave desired 11-methoxyindole derivative **94**. The introduction of a hydroxy group at C17 was again achieved by hydroboration using 9-BBN to give **95**. A Birch reduction at –30°C gave sarpagine-type natural product gardnerine (**96**) by the removal of benzyl and allylic hydroxy groups in **95**. Next, according to biogenetic considerations, C/D ring cleavage of **96** was carried out using trichloroethyl chloroformate to afford **97**. Then, treatment of **97** with two equivalents of osmium tetroxide afforded oxindole-diol **98** as the sole product *via* a stereoselective pinacol-type rearrangement and a simultaneous stereoselective dihydroxylation of the double bond. After installation of a methoxy group on *N*₁ of oxindole, the diol in **99** was converted into epoxy derivative **100** by a conventional procedure. Removal of the protecting group on *N*₄ in **100** gave secondary amine **92**, which was then heated in dioxane to afford desired aziridine derivative **93**. Finally, aziridine derivative **93** was treated with CF₃CO₂H in THF to generate natural product **90** by a ring opening

Chart 27. Biomimetic Synthesis of 11-Methoxy-19*R*-hydroxygelselegine

between C21 and N_4 . Thus, we have achieved the biomimetic synthesis of structurally unique alkaloid, 11-methoxy-19R-hydroxygelselegine (**90**), in a highly stereoselective manner.

Further, the divergent transformation of 14-hydroxygelseginine into biogenetically related *Gelsemium* alkaloids, i.e., (–)-gelsefuranidine,⁵³⁾ (–)-gelselegandine B,⁶⁵⁾ (–)-gelselegandine C,⁶⁵⁾ and (–)-gelsemolenine A,⁶⁶⁾ was accomplished recently.⁶⁷⁾

Conclusion

In this review, we have introduced some examples of biogenetically inspired syntheses of *Lycopodium* alkaloids and monoterpenoid indole alkaloids conducted in our laboratory, and emphasized the merits of biogenetic considerations in the chemical syntheses of natural products. We have many opportunities to learn from nature the elegance and efficiency of the assembly of complex natural molecules in living things. Such lessons would be beneficial for the design of unique synthetic approaches as well as the development of new synthetic methodologies by synthetic organic chemists. Further, in combination with recent developments in omics studies of the biosynthesis of natural products, the strategies of bioinspired synthesis will certainly contribute to the further advancement of the total syntheses of more complex natural products.

Acknowledgments These studies were carried out at the Graduate School of Pharmaceutical Sciences, Chiba University. I would like to thank the staff and students of this laboratory, particularly Drs. Mariko Kitajima and Noriyuki Kogure, as well as many other students whose names do not appear in this review. I would also like to express my sincere appreciation to Professors Emeritus S. Sakai and N. Aimi of Chiba University for their encouragement in this research field. These studies were financially supported by the Japan Society for the Promotion of Science (JSPS) and by several other foundations.

Conflict of Interest The author declares no conflict of interest.

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