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Biogenetically Inspired Total Syntheses of *Lycopodium* Alkaloids, (+)-Flabellidine and (−)-Lycodine

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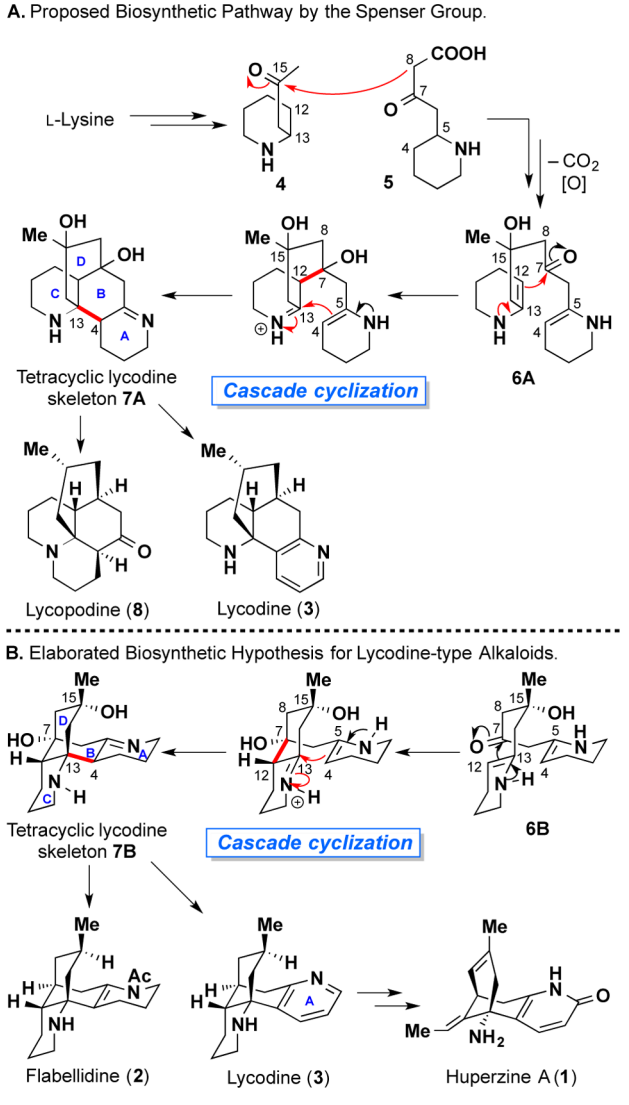
Supporting Information

ABSTRACT: The first asymmetric total synthesis of (+)-flabellidine (**2**) and the shortest total synthesis of (−)-lycodine (**3**) were accomplished by a strategy featuring the one-pot construction of a tetracyclic lycodine skeleton from a linear precursor, which was inspired by the biosynthetic consideration of *Lycopodium* alkaloids.

Lycopodium alkaloids are a topic of immense interest among synthetic chemists[1] because of their unique and fascinating structures, biogenesis, and wide-ranging biological activities.[2] Among the alkaloids in *Lycopodium* plants, huperzine A (**1**) (Scheme 1), a lycodine-type alkaloid, exhibits potent acetylcholine esterase (AChE) inhibitory activity (IC_{50}: 0.082 μmol)[3] and is anticipated to treat Alzheimer's disease and to improve geriatric memory loss. Structurally, lycodine-type alkaloids are characterized by a common bicyclo[3.3.1]nonane core flanked by two piperidine rings at various oxidation levels. Among them, flabellidine (**2**) was isolated from *L. complanatum* in 1942,[4a] and its structure was determined in 1964.[4b] Lycodine (**3**), one of the representative *Lycopodium* alkaloids, was isolated in 1958 and was assumed to be the biogenetic precursor of huperzine A (**1**).[5] To date, two racemic[6a−c] and three asymmetric[6d−f] total syntheses of lycodine (**3**) have been reported. On the other hand, the total synthesis of flabellidine (**2**) has not been achieved.

Based on feeding experiments, a plain biogenetic pathway of *Lycopodium* alkaloids was proposed by Spenser et al.[7] (Scheme 1A). Although information on the biosynthetic route of *Lycopodium* alkaloids is quite limited, it was demonstrated that pelletierine (**4**) and 4-(2-piperidyl)acetoacetate (**5**), both of which are derived from L-lysine, are the biosynthetic precursors of lycopodine (**8**). In this hypothetical route, we were interested in the cascade cyclization from dienamine **6A** to **7A**, which involves the formation of two bonds, the C7−C12 and C4−C13 bonds, to establish the tetracyclic lycodine skeleton. Taking the stereochemistry into account, the tandem reaction from **6A** to **7A** would be refined to the elaborated mode, such as the reaction from **6B** to **7B**, as shown in Scheme 1B. The thus-formed tetracyclic intermediate **7B** would be metabolized to flabellidine (**2**) and lycodine (**3**) via removal of the two hydroxyl groups at C7 and C15 followed by monoacetylation or aromatization at the A-ring, respectively. Inspired by this plausible hypothesis,[8] we envisioned an alternative cascade cyclization participated by ene-iminium intermediate **10**, which is conceived to be the quasi-equivalent of dienamine **6B** (Scheme 2).

Scheme 1. Hypothetical Biogenetic Pathway



As shown in Scheme 2, we expected that the stereochemistry at C15 would control the stereochemical course of the reaction intermediate of the conjugate addition reaction[7a] (from **10** to **11**) as well as the Mannich-like reaction[6a,b,9] (from **11** to **12**), to form tetracyclic structure **12** having the same stereo-

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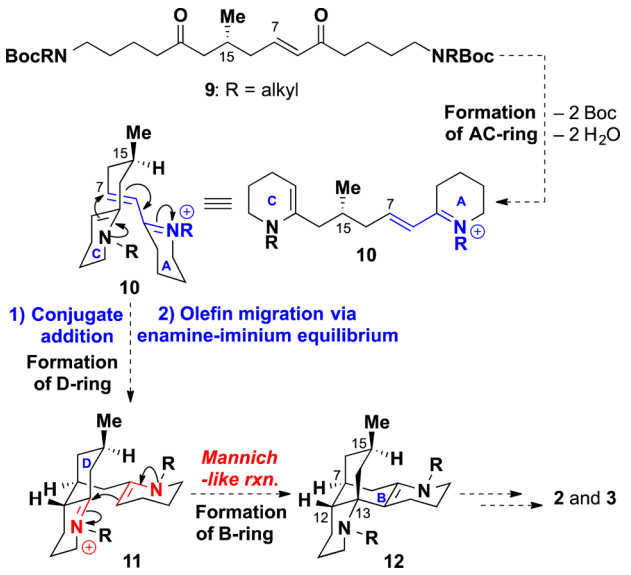
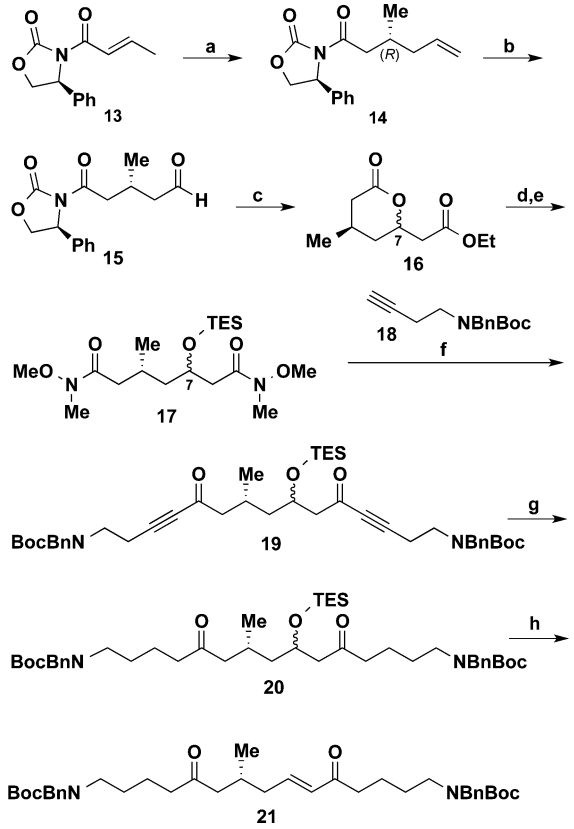
Scheme 2. Synthetic Plan Inspired by Hypothetical Biosynthesis



Scheme 3. Synthesis of Linear Substrate 21[α]



[α]Reagents and conditions: (a) $TiCl_4$, allyltrimethylsilane, CH_2Cl_2, −78 °C, 92% (dr = 13.4:1); (b) O_3, CH_2Cl_2, −78 °C, then PPh_3, rt, 90%; (c) LDA, AcOEt, THF, −78 °C 82% (dr = 1.2:1); (d) HCl·NH(OMe)Me, $AlMe_3$, CH_2Cl_2, −10 °C, 95%; (e) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 96%; (f) **18**, *i*-PrMgCl, THF, rt, 78%; (g) Pd/C, H_2 (1 atm), AcOEt, 0 °C, 99%; (h) HF·Py, CH_3CN, 0 °C, 71%.

chemistry at C7, 12, and 13 as those of natural lycodine-type alkaloids. Furthermore, we anticipated that ene-iminium intermediate **10** would be generated by the Boc deprotection of linear diketone **9**. Here, we describe a concise total synthesis of (+)-flabellidine (**2**) and (−)-lycodine (**3**), which is guided by our detailed biogenetic consideration of *Lycopodium* alkaloids, as mentioned above.

Our synthesis commenced with the preparation of linear precursor **21** (Scheme 3). The construction of a methyl group at C15, which is characteristic of *Lycopodium* alkaloids, was accomplished by the diastereoselective Hosomi−Sakurai allylation of commercially available crotonamide **13** to give **14** in high yield and good selectivity (92%, dr = 13.4:1).[10] Upon ozonolysis of the terminal olefin, **14** gave aldehyde **15**, which was condensed with the enolate of ethyl acetate to furnish lactone **16** in good yield. Next, treating **16** with trimethylaluminum and *N,O*-dimethylhydroxylamine, followed by TES protection, furnished di-Weinreb amide **17**. The coupling reaction of **17** with an alkynyl anion prepared from **18**[11] gave desired dialkynylketone **19**. After selective reduction of the alkyne group in **19** with Pd/C in AcOEt at 0 °C, the resulting linear compound **20** was converted into enone **21** through simultaneous desilylation and dehydration reactions.

With linear substrate **21** in hand, we examined the proposed bioinspired strategy to construct the tetracyclic lycodine skeleton (Scheme 4). After numerous surveys of the reaction conditions, we were pleased to find that exposure of **21** to an excess amount of (+)-CSA (20 equiv, CH_2Cl_2, 40 °C, 1.5 h) yielded tetracyclic lycodine skeleton **23a** as the major product, probably via ene-iminium intermediate **22a**. In this reaction, diastereomeric **23b** was also produced (total chemical yield 77%, **23a:23b** = 1.9:1).[12] The diastereomeric ratio of the two products could be improved to 3.0:1 by performing the reaction under the optimum conditions (20 equiv of (+)-CSA, CH_2Cl_2, 50 °C, 1 h). The structures of **23a** and **23b** were respectively elucidated by X-ray crystallographic analysis after conversion into *para*-bromobenzamide derivative **24** and benzamide derivative **25**.[13] Interestingly, treating **20** with an excess amount of (+)-CSA (20 equiv) in CH_2Cl_2 (50 °C, 1 h) resulted in the clean formation of **23a** and **23b** (total chemical yield 86%, **23a:23b** = 2.2:1).

For the completion of the total syntheses of **2** and **3**, the mixture of **23a** and **23b** was subjected to debenzylation and simultaneous Boc protection to give easily separable di-Boc compounds **26** and **27** (Scheme 5). The removal of Boc groups of the amines in **26** and the chemoselective acetylation exclusively gave (+)-flabellidine (**2**), which resulted in the first total synthesis of this alkaloid. Meanwhile, the selective oxidation of the A-ring with IBX[14] furnished (−)-lycodine (**3**).

In conclusion, based on biosynthetic considerations, we have developed a new and concise synthetic route to lycodine-type alkaloids, which features the one-pot construction of a tetracyclic lycodine skeleton from a linear precursor. Using the product, we have achieved the first asymmetric total synthesis of (+)-flabellidine (**2**) (in 11 steps and 20.7% overall yield starting from commercially available **13**) and completed the shortest total synthesis of (−)-lycodine (**3**) (in 11 steps and 14.6% overall yield starting from **13**). The illustrated strategy can be used for the synthesis of several other kinds of lycodine-type alkaloids. Experiments are ongoing to examine the potential application of this strategy.

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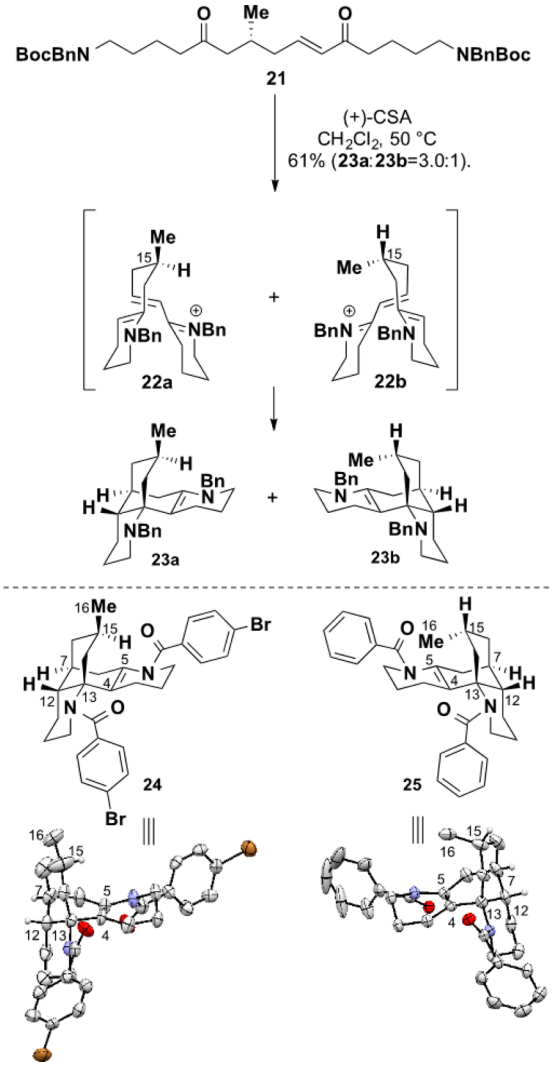
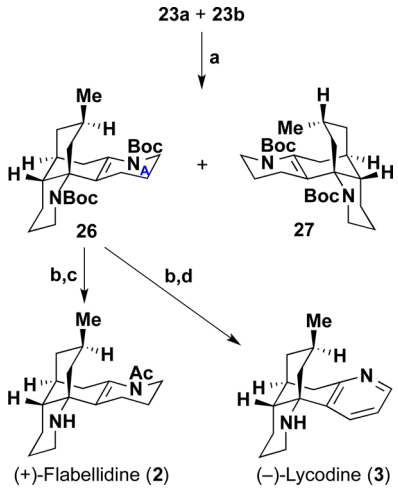
Scheme 4. Bioinspired Cascade Cyclization



Scheme 5. Syntheses of (+)-Flabellidine (2) and (−)-Lycodine (3)[α]



[α]Reagents and conditions: (a) $Pd(OH)_2/C$, H_2 (1 atm), Boc_2O, AcOEt/MeOH (2:1), rt, **26** (55%) and **27** (21%); (b) TFA, CH_2Cl_2, rt; (c) AcCl, Et_3N, THF, −78 °C, 88% (2 steps); (d) IBX, DMSO, 45 °C, 62% (2 steps).

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, copies of ^1H and ^{13}C NMR spectral data for synthetic (+)-flabellidine (**2**), (−)-lycodine (**3**), compounds **14**−**21**, **23a**−**26**, **S1**, **S2**, and **S5**, and CIF files for **24**, **25**, and **S5**. 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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(11) *N*-Boc-3-butyn-1-amine **18** was prepared in two steps from commercially available 3-butyn-1-ol. See Supporting Information.

(12) The reaction intermediate **22a** having a chairlike conformation with an equatorial methyl group at C15 would be more stable than the alternative intermediate **22b** with an axial methyl group, resulting in the predominant formation of **23a**.

(13) See Supporting Information.

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