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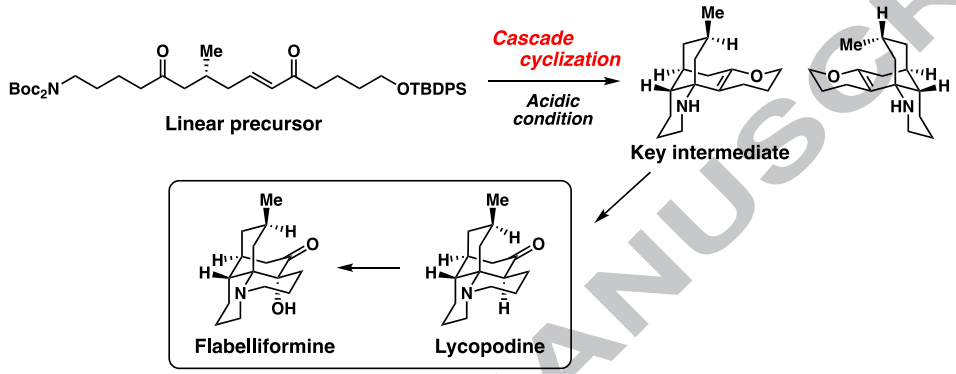

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Concise asymmetric total synthesis of lycopodine and flabelliformine via cascade cyclization reaction

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ABSTRACT

The shortest asymmetric total synthesis of lycopodine (**3**) and the first asymmetric total synthesis of flabelliformine (**4**) were accomplished by a strategy that features a cascade cyclization of linear substrate (**5**) to construct tetracyclic structure (**6**).

Introduction

The *Lycopodium* alkaloids are a family of structurally diverse and complex natural products. To date, more than 300 *Lycopodium* alkaloids have been isolated and characterized.[1] Among them, huperzine A (**1**), which belongs to lycodine (**2**) group (Fig. 1), showed potent activity in the reversible inhibition of acetylcholinesterase and increased learning and memory efficiency.[2] Lycopodine (**3**), another representative *Lycopodium* alkaloid, is a tetracyclic alkaloid in which all rings are six-membered, similar to lycodine (**2**). The characteristic chemical structure of **3**, which includes five asymmetric centers, has fascinated synthetic chemists for a long time. Since its isolation in 1881[3] and its structure elucidation in 1960,[4] a number of total and formal syntheses have been reported.[5] The asymmetric total syntheses by Carter in 2008[5n, 5o] and by She in 2016[5p] are notable. Carter reported the first enantioselective total synthesis via a diastereoselective intramolecular Michael addition and a successive Mannich cyclization. Later, She developed a protecting-group-free, 12-step route to furnish (–)-lycopodine (**3**) from commercially available (*R*)-(+)-pulegone. In the course of our chemical studies on *Lycopodium* alkaloids,[6] we have also initiated the total synthesis of this historically and chemically significant natural product. Herein, we describe the shortest total synthesis of (–)-lycopodine (**3**) and its conversion into flabelliformine (**4**). This synthesis features the cascade cyclization of linear substrate **5** to construct tetracyclic structure **6** that has the same stereochemistry at C7, 12, and 13 as natural lycopodine-type alkaloids.

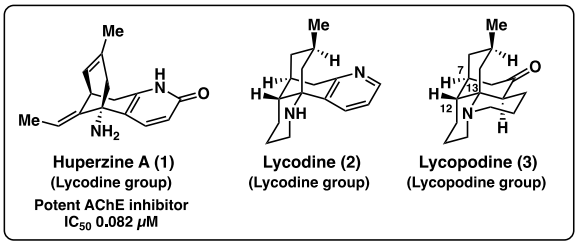
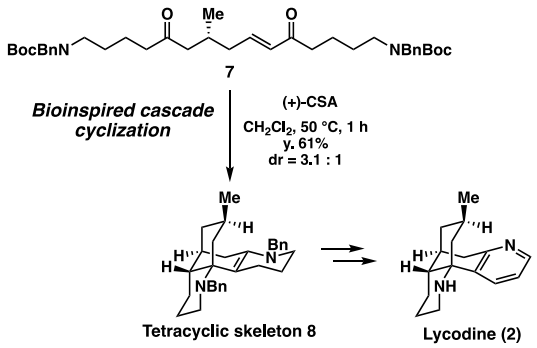


Fig. 1.

Results and discussion

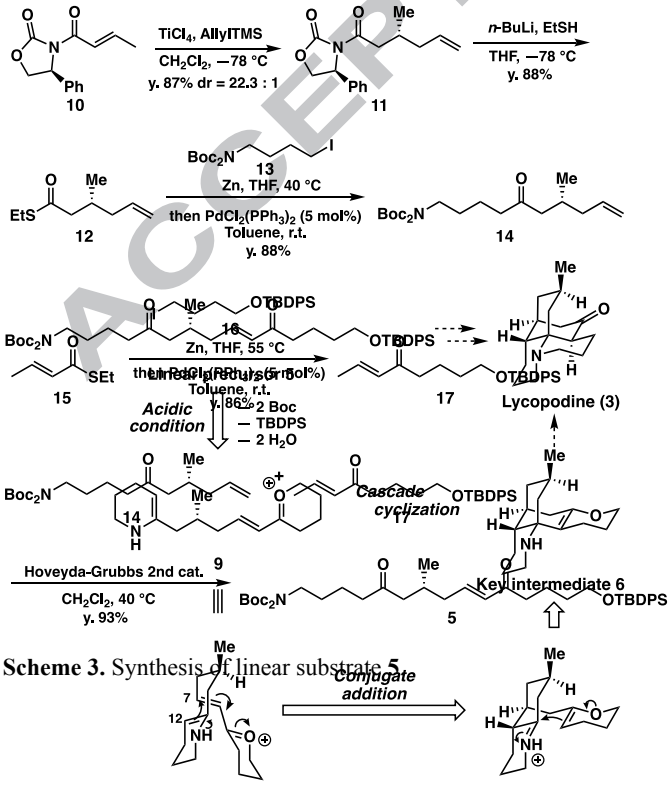
In 2014, we developed a strategy for the concise asymmetric total synthesis of lycodine (**2**)[6e] by capitalizing on a hint gained



Scheme 1. Previous work by our group.

from the biosynthetic pathway of *Lycopodium* alkaloids (Scheme 1).[7] Treatment of linear substrate **7** under the acidic condition gave tetracyclic lycodine skeleton (**8**) via cascade conjugate addition reactions that mimics the proposed biosynthesis of lycodine (**2**). By further developing this strategy, we expected that a similar cascade reaction starting from linear substrate **5** would occur to produce tetracyclic compound **6** (Scheme 2). The dihydropyran ring in **6** would be incorporated by the conjugate addition of oxonium intermediate **9**, and **9** would be generated when we substitute an oxygen atom for the nitrogen atom on the right end of compound **7**. Thus-obtained tetracyclic compound **6** would be directly converted into lycopodine (**3**) by referring to Heathcock's approach.[5f]

Our synthesis began with the preparation of linear substrate **5** for the cascade cyclization reaction (Scheme 3). The Hosomi-Sakurai allylation of commercially available crotonamide (**10**) furnished **11** in high yield and excellent diastereoselectivity, and **11** had the same stereochemistry at C15 as (–)-lycopodine (**3**). Removal of Evans's oxazolidinone moiety in **11** with lithium

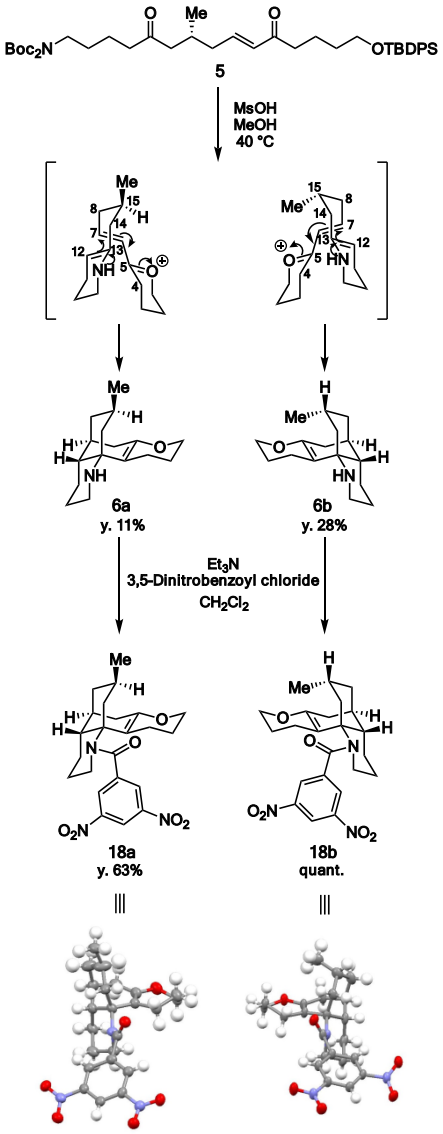


Scheme 2. Synthetic plan in this work.

thiolate gave thioester **12** in 88% yield. Next, coupling of **12** with iodide **13**[8] in the presence of Zn and 5 mol% $PdCl_2(PPh_3)_2$[9] gave ketone **14** in good yield. On the other hand, enone **17** was also prepared by the Fukuyama coupling[9] using thioester **15** prepared from crotonic acid[10] and iodide **16**.[11] Thus-obtained ketone **14** and enone **17** were subjected to olefin cross metathesis reaction using a second-generation Hoveyda-Grubbs catalyst to give desired linear substrate **5**.

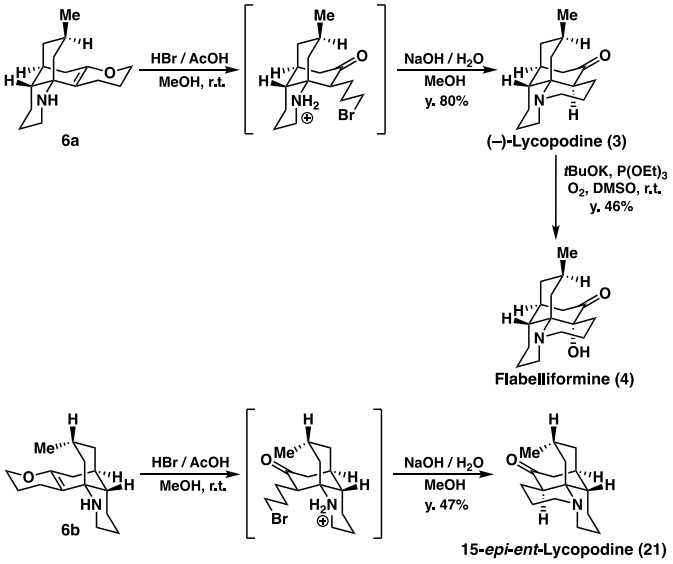
With linear substrate **5** in hand, we thoroughly examined the reaction conditions for the key cascade cyclization step. Although the chemical yield needed improvement, we were able to obtain desired compound **6a** in 11% yield together with diastereomeric isomer **6b** in 28% yield, when **5** was treated with methanesulfonic acid in methanol at 40 °C. The structures of **6a** and **6b** were elucidated by X-ray crystallographic analysis after conversion into 3,5-dinitrobenzamide derivatives **18a** (CCDC 1878845) and **18b** (CCDC 1878846), respectively.

Starting from tetracyclic intermediate **6a**, we completed the total synthesis of lycopodine (**3**) and flabelliformine (**4**) as follows. Referring to Heathcock's work,[5f] treatment of **6a** with HBr in AcOH at r.t. gave the ammonium bromide salt, which was then basified with NaOH to give lycopodine (**3**) in 80% yield by pyrrolidine ring formation. **6b** was also converted into **21**, which corresponds to 15-*epi*-*ent*-lycopodine, by the same procedure used for the conversion of **6a** into lycopodine (**3**). Further, α-hydroxylation[12] of the ketone in **3** gave flabelliformine (**4**)[13] in 46% yield, thereby realizing the first asymmetric total synthesis of this alkaloid. The synthetic **3** and **4** were respectively identical



Scheme 4. Cascade cyclization.

in all respects with the natural products, which were isolated from *Lycopodium clavatum* in our laboratory.



Scheme 5. Synthesis of lycopodine (**3**) and flabelliformine (**4**).

Acknowledgments

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In conclusion, we have completed the shortest asymmetric total synthesis of lycopodine (**3**) (in 7 steps from commercially available **10**) and the first asymmetric total synthesis of flabelliformine (**4**), via a novel cascade cyclization reaction as the key step. Further studies are underway in our laboratory to optimize the reaction conditions of the key cyclization step and to examine the application of this strategy to the synthesis of other lycopodine-type alkaloids.

Highlights

The shortest-step asymmetric total synthesis of lycopodine was accomplished.
The first asymmetric synthesis of flabelliformine was achieved.
The strategy includes a novel cascade cyclization to construct tetracyclic structure.