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SPECIAL FEATURE: BRIEF COMMUNICATION

A transannular approach toward lycopodine synthesis

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Abstract

A transannular reaction was proposed to access the *Lycopodium* alkaloid lycopodine. A key bicyclic precursor was synthesized via a ring-closing metathesis reaction. Initial evaluations of the transannular aza-Prins reaction to synthesize lycopodine were reported and discussed.

The *Lycopodium* genus is well known for producing alkaloids with novel structures (Fig. 1) [1–10]. Many of these natural products have important biological activities. For example, lycopodine (**1**), the first alkaloid isolated from the *Lycopodium* family [11], triggers apoptosis of cancer cells by modulating 5-lipoxygenase and serves as a potential candidate for anticancer drugs. Huperzine A (**2**) is an acetylcholinesterase inhibitor that can cross the blood–brain barrier; [12] thus, it is used to treat patients with neurodegenerative diseases. The alkaloid lycojapodine A (**6**) not only shows inhibitory activity against acetylcholinesterase but also demonstrates anti-HIV activity with EC_{50} (half-maximal effective concentration) value of 85 μg/mL [13]. Nevertheless, the biological activities of many other *Lycopodium* alkaloids are not known due to the scarcity or unavailability of the natural products for investigation, such as lycopladine H (**7**) [14]. The structural diversity of *Lycopodium* alkaloids led Ayer and Trifonov [4] to categorize these alkaloids into four classes: the lycodine class, the lycopodine class, the fawcettimine class, and the miscellaneous class. The novel structures of *Lycopodium* alkaloids make these natural products excellent candidates for total synthesis. Indeed, the *Lycopodium* alkaloids have attracted a number of chemists to explore different synthetic routes. Representative work include Ayer's [15] and Stork's [16] syntheses of lycopodine (both in 1968), Heathcock's (1986) [17] and Lei's (2012) [18] syntheses of fawcettimine, and Sarpong's [19] and Siegel's [20] syntheses of complanadine A (2010).

We envisioned a transannular strategy to access members from different *Lycopodium* categories. As shown in Scheme 1, lycopodine (**1**, from the lycopodine class), lycopladine H (**7**, from the miscellaneous class), and fawcettimine (**3**, from the fawcettimine class) could be derived from three bicyclic carbonyl compounds (**8**, **9**, and **11**, respectively) via transannular Mannich reactions [21]. Compounds **8**, **9**, and **11** are conceptually different oxidation products of the key intermediate **12**, and the olefin functionality in **12** would provide an excellent opportunity for ring-closing metathesis retrosynthetically. Compound **13** should be easily accessed from simple starting material **14** [22]. Therefore, different classes of *Lycopodium* alkaloids could potentially be synthesized by taking good advantage of the key intermediate **12**. Evans and Scheerer [23] reported the synthesis of clavolonine using a similar strategy. Inspired by this transannular Mannich approach, here

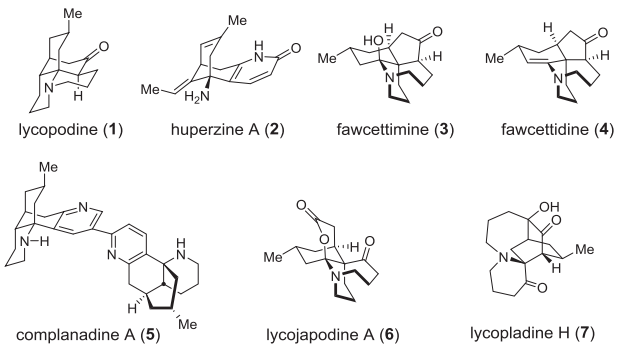

Fig. 1 Selected *Lycopodium* alkaloids

Supplementary information The online version of this article (https://doi.org/10.1038/s41429-019-0155-2) contains supplementary material, which is available to authorized users.

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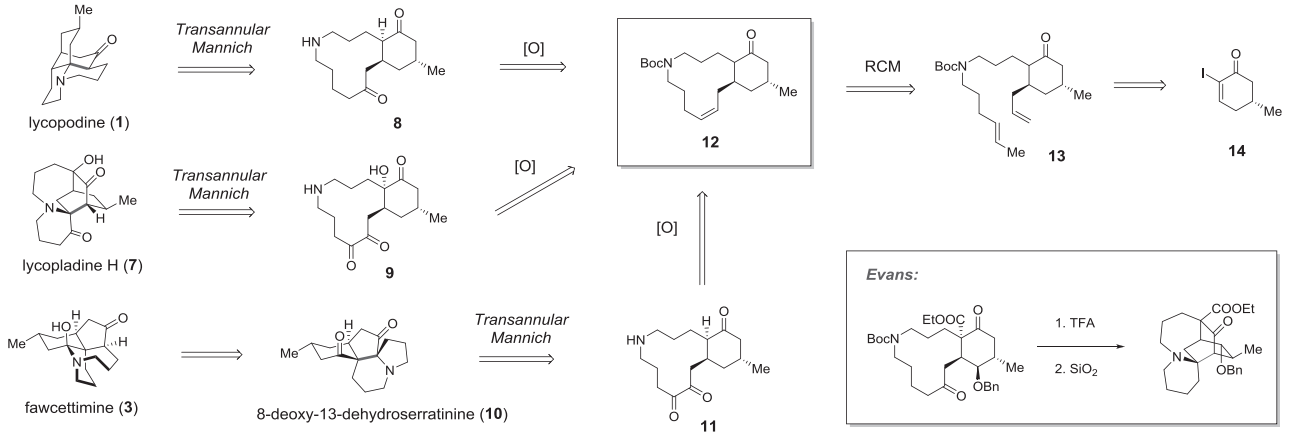
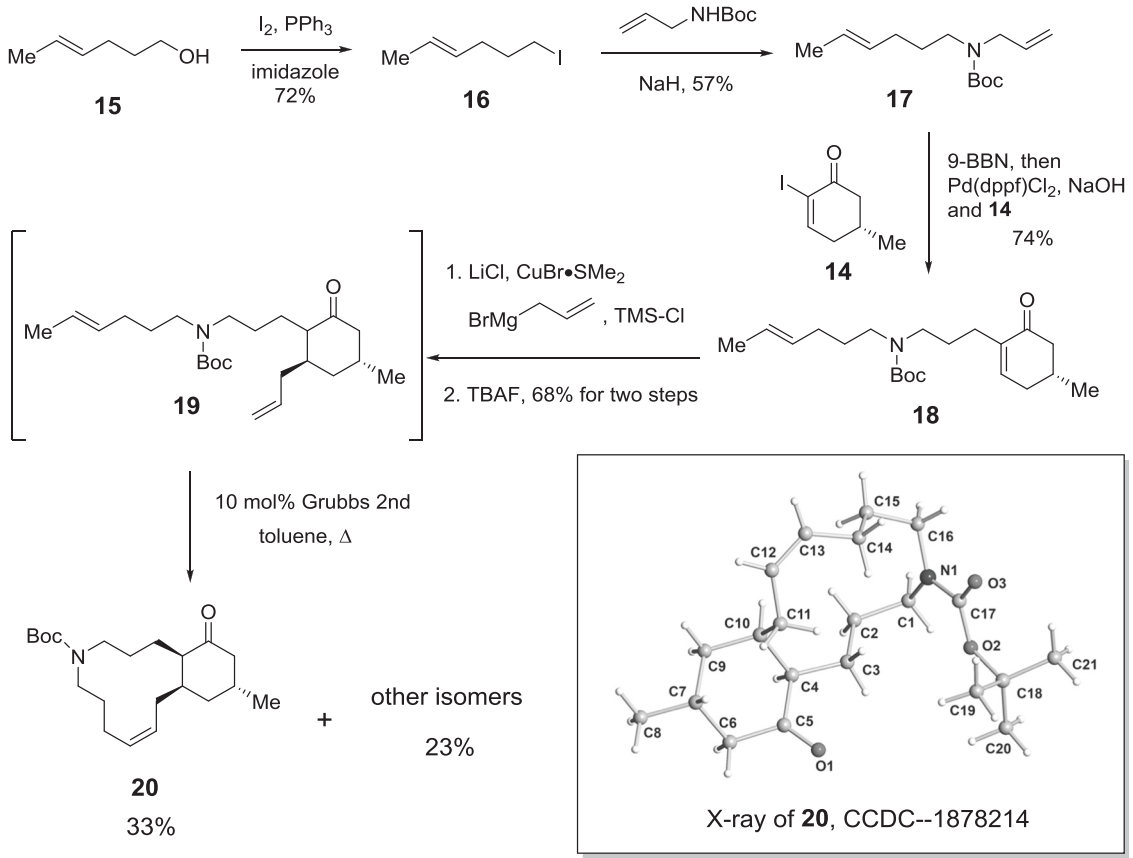


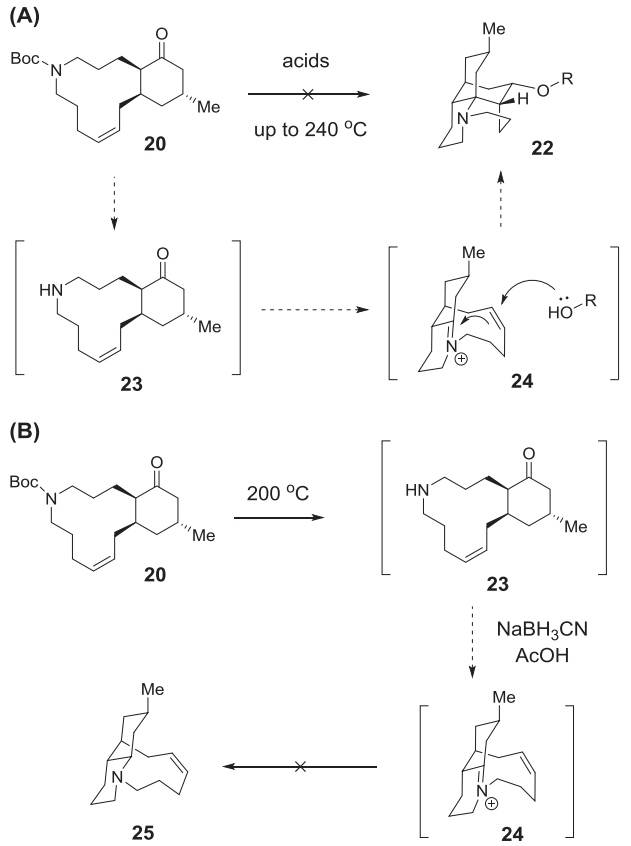
Scheme 1 The initial strategy design using transannular Mannich reactions from a common intermediate and the key step in Evans' synthesis of clavolonine



Scheme 2 Synthesis of metathesis product **20**

we report our progress toward lycopodine synthesis using a similar transannular strategy.

As shown in Scheme 2, we started our preparation of compound **12** by iodination of commercially available alcohol **15**, leading to iodide **16** in 72% yield [24]. *N*-alkylation of Boc-protected allylamine with **16** gave carbamate **17** in 57% yield. Hydroboration of carbamate **17** on the less hindered alkene was followed by *B*-alkyl Suzuki coupling with compound **14** to afford enone **18** in 74% yield [25]. Conjugate addition was conducted with the aid



Scheme 3 Attempts for lycopodine synthesis

of LiCl, forming a silyl enol ether [26]. The crude silyl enol ether was directly deprotected with tetrabutylammonium fluoride, and ketone **19** was formed in 68% yield over two steps. Next, a ring closing metathesis (RCM) reaction was explored to connect the two carbon chains of compound **19**. Although the desired product could be obtained using Grubbs' second-generation catalyst in refluxing dichloromethane as the solvent, this RCM reaction gave a better result when toluene, a solvent with a higher boiling point, was used with only 10 mol% Grubbs' second-generation catalyst [27]. Thus, bicyclic ketones **20** was formed in 33% yield, together with other isomers in 23% yield. X-ray crystallography confirmed the structure of **20**.

Given the fact that the olefin in the macrocycle of **20** is electronically unbiased, we decided to employ the conformational bias of **20** to differentiate the two olefinic carbons. Specifically, we explored the possibility of synthesizing the lycopodine framework using compound **20** through a transannular aza-Prins cyclization via intermediates **23** and **24** (Scheme 3). Therefore, compound **20** was subjected to acidic conditions with elevated temperatures for the transannular cyclization. Nonetheless, none of the conditions we tried led to the formation with a structure like **22** in a detectable amount. These results could result either from unsuccessful formation of iminium **24** or from unsuccessful C–C bond formation in the aza-Prins step. In order to probe the formation of iminium **24**, we removed the Boc group of compound **20** under thermal conditions, and the putative compound **23** was subjected to reductive amination conditions. However, we could not detect the formation of compound **25**, which indicated that the iminium formation step needed further investigations.

In conclusion, an advanced intermediate **20** was synthesized in a straightforward way. This intermediate could potentially be useful in the synthesis of lycopodine via transannular cyclization strategies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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