

Synthesis of the Lycopodium Alkaloid (+)-Lycoflexine

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Abstract: The first total synthesis of (+)-lycoflexine (**1**), a constituent of *Lycopodium clavatum* var. *inflexum*, has been accomplished in eight steps with 13% overall yield. Our synthesis covers four one-pot reactions, including a tandem Sakurai/aldol sequence, a novel hydroboration/oxidation procedure, a deprotection/transannular Mannich reaction, and as a highlight, a tandem catalysis cascade combining an enynene ring-closing metathesis and a selective hydrogenation.

Lycopodium alkaloids¹ are a huge family of diverse but structurally related compounds (see Figure 1 for some examples) with impressive and challenging structures and interesting biological activities, such as acetylcholinesterase inhibition [e.g., huperzine A (**2**),² lycojapodine A (**3**),³ or sieboldine A⁴].

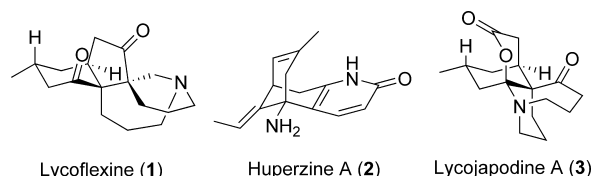
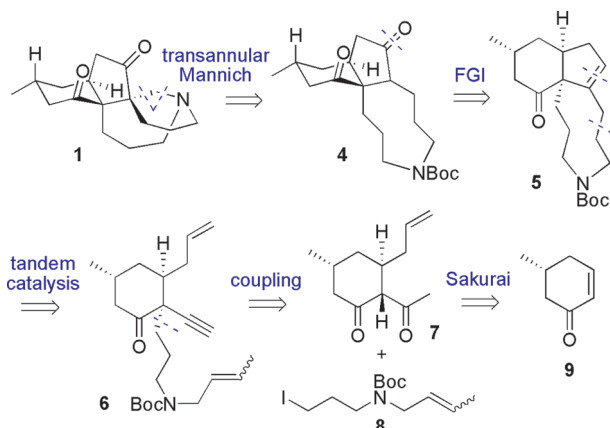


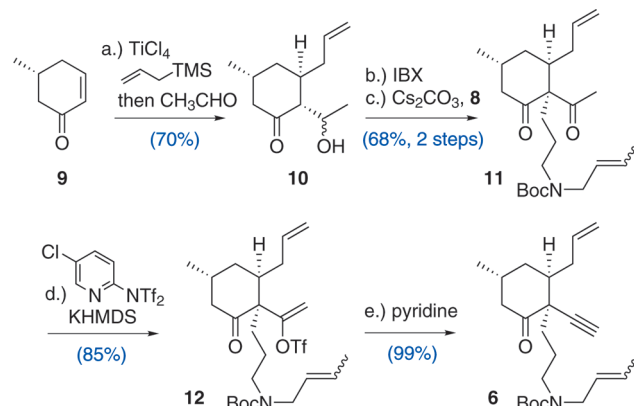
Figure 1. Selected *Lycopodium* alkaloids.

Lycoflexine (**1**) (also known as lycobergine) belongs to the class of fawcettimine-related alkaloids and was isolated by Ayer *et al.*⁵ in the early 1970s by extraction of *Lycopodium clavatum* var. *inflexum* collected in the Eastern Transvaal (Republic of South Africa). Its structure consists of an exceptional tetracyclic carbon–nitrogen skeleton including a spiro-annulated six-membered ring and four stereogenic centers, of which two are adjacent quaternary carbons. Despite the interesting, complex molecular architecture of lycoflexine, no total synthesis has been reported to date.

Scheme 1. Retrosynthetic Analysis



Our retrosynthetic analysis of lycoflexine (**1**) is outlined in Scheme 1. The final step of our synthesis refers to the biosynthetic proposal of Ayer *et al.*⁵ As a suitable substrate for such a conversion, we identified the tricyclic diketo compound **4**, which can be generated from substrate **5**.⁶ The latter compound can be accessed via an enynene ring-closing metathesis (RCM) reaction of precursor **6**, which is easily obtained from diketone **7** derived from the well-known optically active enone **9**.⁷

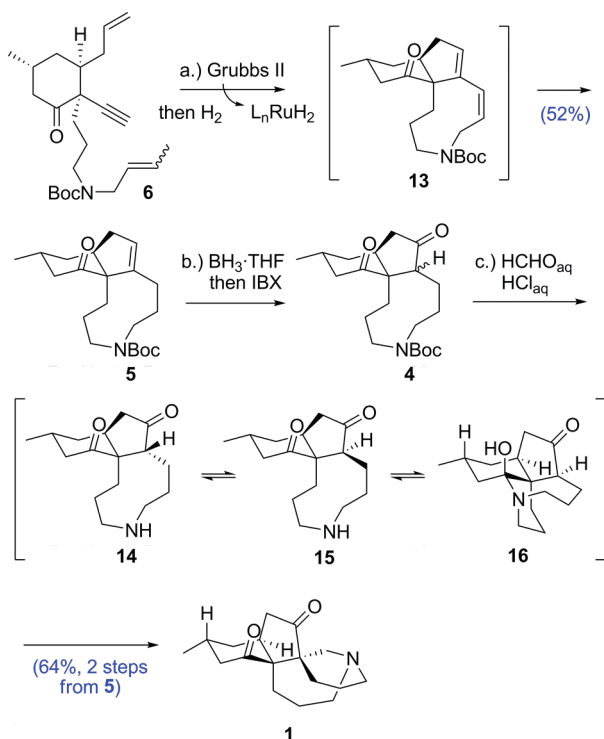
Scheme 2. Synthesis of Precursor **6**^a

^a Conditions: (a) (i) TiCl_4 , allyltrimethylsilane, DCM, -78°C ; (ii) acetaldehyde, 70%. (b) IBX, EtOAc, reflux. (c) Cs_2CO_3 , **8**, DMF, -15°C , 68% (two steps). (d) Comins' reagent, KHMDS, THF, -78°C , 85%. (e) Pyridine, 60°C , 99%.

As is depicted in Scheme 2, the synthesis of key intermediate **6** started with a tandem Sakurai/aldol sequence that converted enone **9** into alcohol **10** as an inconsequential diastereomeric mixture.⁸ After mild oxidation with IBX,⁹ the resulting diketo compound **7** was alkylated with iodocarbamate **8**¹⁰ to provide compound **11** with satisfying yield. After some optimization, triflation of the less-hindered carbonyl moiety was achieved with Comins' reagent.¹¹ Treatment of the resulting vinyl triflate **12** with pyridine at elevated temperature finally yielded dienyne **6**.¹²

In our first attempts, the envisaged enynene RCM was carried out under standard conditions with Grubbs' second-generation catalyst.¹³ Although the formation of the desired tricyclic diene **13** was observed, the yield was only slightly higher than 30%. As no other byproducts could be isolated, we rationalized that the diene is probably of moderate stability and prone to decomposition. On the basis of Grubbs' findings that metathesis catalysts can be converted into active hydrogenation catalysts by treatment with dihydrogen,^{14,15} we decided instead to attempt a tandem catalysis sequence and selectively hydrogenate the less-substituted double bond in situ. Gratifyingly, the desired tricyclic carbamate **5** was formed in 52% yield from **6** (Scheme 3).

To complete our synthesis, only two steps were missing. Direct oxidation of organoboranes to the corresponding ketones is known,

Scheme 3. Final Steps toward Lycoflexine (**1**)^a

^a Conditions: (a) (i) Grubbs' second-generation (20 mol %), 1,2-dichloroethane, reflux; (ii) H_2 , 10 atm, 70 °C, 52%. (b) (i) $BH_3 \cdot THF$, THF, 50 °C; (ii) IBX, EtOAc, reflux. (c) $HCHO(aq)$, 0.5 M HCl, EtOH, reflux, 64% (two steps).

though mostly based on rather aggressive and toxic chromium reagents.¹⁶ We thus developed a novel protocol that allowed us to oxidize the organoborane in situ with IBX to obtain an inconsequential diastereomeric mixture of diketo compounds **4**. It is noteworthy that both diastereomers also can be used to synthesize fawcettimine (**16**), another prominent member of the *Lycopodium* alkaloid family.¹⁷ Our total synthesis of lycoflexine was concluded by a final tandem reaction. The *N*-Boc protecting group was removed using dilute aqueous HCl, and by analogy to the biomimetic conversion of fawcettimine to lycoflexine, excess formaldehyde was used to generate an iminium species, which smoothly underwent a transannular Mannich reaction to furnish (+)-lycoflexine (**1**).^{18,19}

The identity of our compound with authentic lycoflexine was established by comparison with the spectroscopic data (1H and ^{13}C NMR as well as CD) kindly provided by Professor Takayama, who had reisolated and characterized the compound.²⁰ In this way, the absolute configuration of **1** also was confirmed by total synthesis.

In conclusion, we have achieved the first total synthesis of (+)-lycoflexine. The extensive use of tandem and one-pot reactions (Sakurai/aldol, enynene RCM/hydrogenation tandem catalysis,

hydroboration/oxidation, *N*-Boc deprotection/transannular Mannich cyclization) makes the sequence remarkably concise and efficient (eight steps from **9** with an overall yield of 13%). It is flexible and therefore should be suitable for the synthesis of several other *Lycopodium* alkaloids as well.

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Supporting Information Available: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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