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Protecting-Group-Free Total Synthesis of (−)-Lycopodine via Phosphoric Acid Promoted Alkyne Aza-Prins Cyclization

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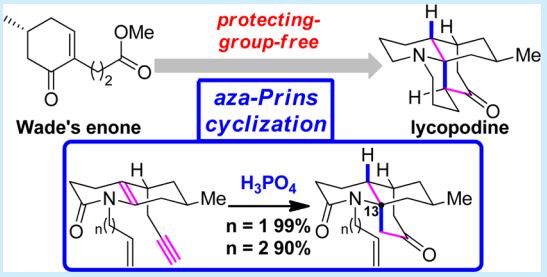
Supporting Information

ABSTRACT: A protecting-group-free route for the total synthesis of (−)-lycopodine was demonstrated in only 8 steps from Wade's fawcettimine enone (12 steps from commercial availiable (*R*)-(+)-pulegone). The key core of this alkaloid was constructed through a phosphoric acid promoted and highly stereocontrolled alkyne aza-Prins cyclization reaction, synchronously establishing the bridged B-ring and the C13 quaternary stereocenter. Importantly, the synthesis further features a new efficient approach for the preparation of other lycopodine-type alkaloids.



The *Lycopodium* alkaloids are a skeletally diverse and structurally complex family of natural products, comprising approximately 300 known compounds which are divided into four groups: lycopodine group, lycodine group, fawcettimine group, and phlegmarine group.[1] Several representatives of the lycopodine group are shown in Figure 1, such as lycopodine

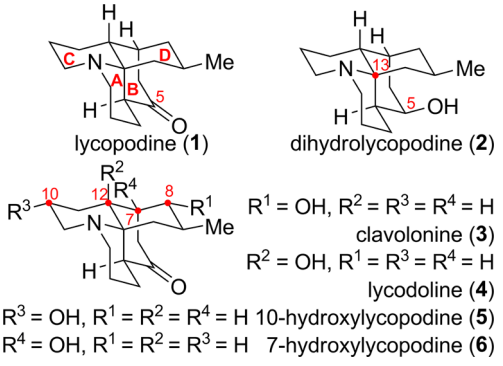


Figure 1. Lycopodine, dihydrolycopodine, and structurally related *Lycopodium* alkaloids.

(**1**),[2] dihydrolycopodine (**2**),[3] clavolonine (**3**),[4] lycodoline (**4**),[5] 10-hydroxylycopodine (**5**),[6] and 7-hydroxylycopodine (**6**).[7] Among them, lycopodine (**1**) is the archetypal member of this family which possesses the classic tetracyclic core skeleton. Lycopodine was originally isolated from *Lycopodium complanatum* L. by Bödeker in 1881,[2,8] and its natural congener dihydrolycopodine (**2**) was discovered in 1942 by Manske and Marion.[3,8a,b] These alkaloids have been widely used in traditional Chinese medicine and homeopathic therapies; for example, lycopodine (**1**) is a Chinese folk medicine for the treatment of skin disorders and analgesia. Later studies found that the intricate polycyclic scaffold in the lycopodium alkaloids possess various important biological properties, such as antipyretic and anticholinesterase activities.[1l,9]

Because of their fascinating polycyclic architectures and diverse biological activities, these alkaloids have attracted significant synthetic interest for several decades, and to date, 16 groups reported the syntheses on them.[10−13] For lycopodine synthesis, racemic lycopodine was first achieved by Stork[11a,b] and Ayer[11c] in 1968. Afterward, elegant total syntheses of this natural product were completed by Heathcock,[11d,e] Schumann,[11f] Wenkert,[11g] Kraus,[11h,i] Grieco,[11j] and Carter,[11k,l] respectively. In addition, several formal syntheses were also reported by Kim,[11m,n] Padwa,[11o] and Mori.[11p] Notably, the only asymmetric synthesis of lycopodine (**1**) was achieved by Carter[11k,l] in 2008. As for clavolonine, Wenkert[11g] reported its racemic synthesis in 1984, and recently Evans,[12a] Breit,[12b] and Fujikoka[12c] achieved its asymmetric synthesis. Because of their similar skeletal structure, the highly efficient synthesis of lycopodine would pave the way for the synthesis of other lycopodine-type alkaloids. Herein, we describe an enantioselective synthesis of **1** without any protecting-group manipulations. The key step is an aza-Prins cyclization of alkyne and enamide moiety, synchronously establishing the bridged B-ring and the C13 quaternary stereocenter.

We undertook a retrosynthetic analysis of (−)-lycopodine, as shown in Scheme 1. The target molecule **1** could be accessed from a tetracycle intermediate **7** via a final-stage functional group interconversion, in which (−)-dihydrolycopodine (**2**)

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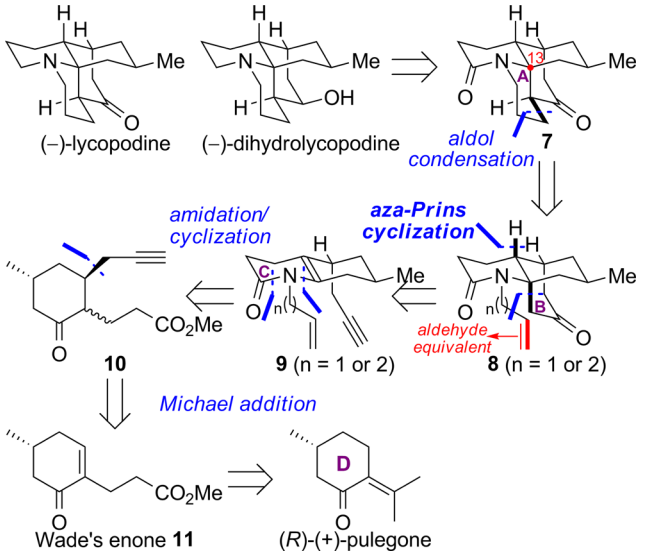
Scheme 1. Retrosynthetic Analysis of (−)-Lycopodine

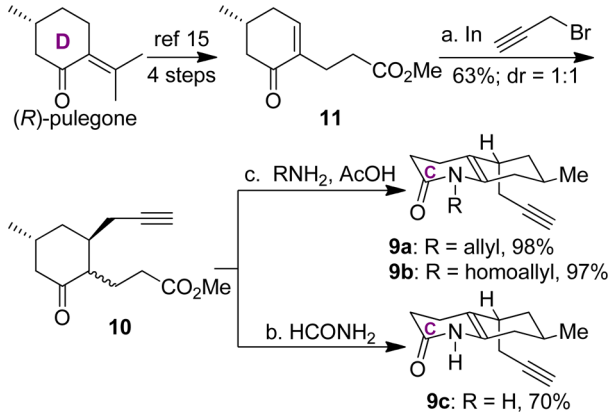


could be synthesized simultaneously. The A-ring of lycopodine lactam **7** would be constructed via an aldol/elimination/hydrogenation sequence from a pivotal tricyclic ketone **8**, in which a terminal olefin was accordingly devised as the equivalent of the aldehyde. For the formation of ketone **8**, a key aza-Prins cyclization was designed to construct the B-ring from alkyne-enamide **9**. However, to the best of our knowledge, the alkyne-enamide aza-Prins reaction is still undeveloped in establishing bridge-like rings.[14] Combined with the large steric hindrance of the C13-position and the presence of a terminal olefin which generally could involve a Prins reaction or rearrangement, this crucial cyclization would be the major challenge in our designed route. Subsequently, the C-ring of **9** could be constructed from alkyne-ketone **10** via a one-pot amidation and coinstantaneous cyclization. As for the preparation of **10**, it could be in turn obtained from Wade's fawcettimine enone **11** and propargyl bromide by a classical Michael addition. Wade's fawcettimine enone **11** is easily accessible from cheap (*R*)-(+)-pulegone through a four-step transformation based on the reference of Dake's fawcettimine synthesis.[15]

On the basis of the above analysis, we first investigated the synthesis of the basic building block **9** (Scheme 2). Readily available and optically pure ketone **11** was used as the starting material.[15] Michael addition of propargylindium reagent to Wade's fawcettimine enone **11** gave **10** as a 1:1 mixture of inseparable diastereomers in 63% yield.[16,17] Next, model substrate **9c** was chosen to test the key aza-Prins cyclization. After heating alkyne **10** in formamide at 170 °C for 3 h, alkyne-enamide **9c** was successfully obtained in 70% yield via a one-pot amidation and cyclization.[18] Gratifyingly, enamide **9a/b** were also smoothly generated under acetic acid at 130 °C with an excellent yield.[19] It is noteworthy that the B-ring of the natural product has been constructed efficiently and enamide **9a/9b** contain all the requisite skeletal atoms for lycopodine (**1**).

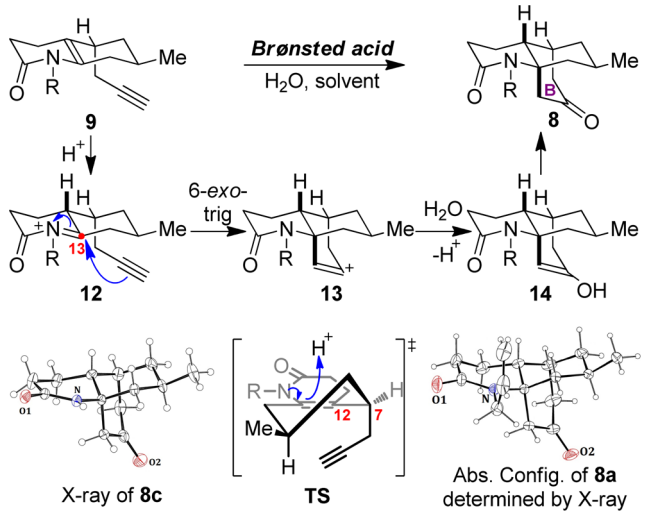
With alkyne-enamide **9** in hand, our next challenge was to construct B-ring of (−)-lycopodine with an alkyne aza-Prins reaction. As we envisioned in Table 1, enamide **9** was protonated to give *N*-acyliminium ion **12**, which was captured by intramolecular alkyne in a 6-*exo*-trig fashion to further

Scheme 2. Synthesis of the Alkyne-enamide 9[a]



[a]Reagents and conditions: (a) In (power), propargyl bromide, TMSCl, THF, dark, rt, 32 h; (b) $HCONH_2$, 170 °C, 3 h; (c) allylamine or homoallylamine, AcOH, toluene, 130 °C, 3 h.

Table 1. Alkyne Aza-Prins Cyclization of Alkyne-enamide 9



entry[a]	substrate	solvent (volume ratio)	*t*/h	product	yield/%[b]
1	**9c**	THF/6 M HCl (aq), 1:1	12	**8c**	23
2	**9c**	THF/6 M H_2SO_4 (aq), 1:1	12	**8c**	46
3[c]	**9c**	THF/HCO_2H/H_2O, 2:1:1	22	**8c**	/
4[c]	**9c**	THF/TFA/H_2O, 2:1:1	22	**8c**	/
5	**9c**	THF/85% H_3PO_4 (aq), 1:1	36	**8c**	84
6[c]	**9c**	HCO_2H/H_2O, 1:1	66	**8c**	/
7[d]	**9c**	**HCO_2H/85% H_3PO_4 (aq), 1:1**	**21**	**8c**	**96**
8[e]	**9a**	HCO_2H/85% H_3PO_4 (aq), 1:1	19	**8a**	99
9[f]	**9b**	HCO_2H/85% H_3PO_4 (aq), 1:1	18	**8b**	90

[a]Reaction conditions: alkyne-enamide **9c** (R = H, 12 mg, 0.0591 mmol) in solvent (1 mL), rt, air. [b]Isolated yields. [c]Most of starting material was recovered. [d]Alkyne-enamide **9c** (70 mg, 0.345 mmol) in solvent (4 mL). [e]Alkyne-enamide **9a** (R = allyl, 241 mg, 1.016 mmol) in solvent (3 mL). [f]Alkyne-enamide **9b** (R = homoallyl, 249 mg, 0.969 mmol) in solvent (3 mL).

provide alkene cation **13**, and then the unstable intermediate **13** quickly reacted with water to generate the enol **14**, which then further isomerized into the tricyclic product **8**. Based on the above analysis of reaction process, a Brønsted acid and an

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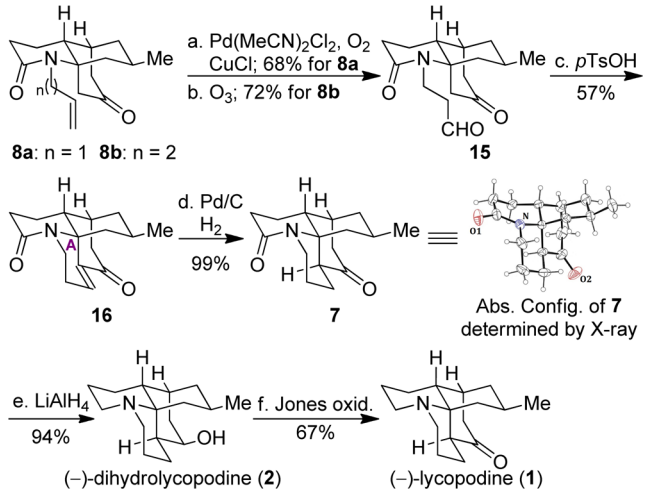
aqueous−organic solvent would be necessary in this cyclization. A series of Brønsted acids were tested for aza-Prins cyclization, and the results are summarized in Table 1. **8c** was afforded in low or moderate yield with hydrochloric acid or sulfuric acid with most of starting material decomposed (entries 1 and 2). Therefore, we turned our attention to some weaker acids, such as formic acid, trifluoroacetic acid, and phosphoric acid (entries 3−6). While formic acid and trifluoroacetic acid failed to promote this reaction, we were pleased to find that by using 85% H_3PO_4, **8c** was finally obtained in 84% yield with a little remaining starting material **9c**. We further noticed that, when **9c** was treated with 85% phosphoric acid in formic acid, tricyclic ketone **8c** was obtained as the sole product in almost quantitative yield (entry 7). The structure of **8c** was subsequently confirmed by X-ray crystallographic analysis.[20] This highly selective reaction may be attributed to a stereoselective enamine protonation, which was sterically guided by the axial propargylic group at C7 (see **TS** of Table 1).[21]

Encouraged by the positive result of the aza-Prins cyclization, we immediately applied the optimized reaction conditions to *N*-allyl **9a** and *N*-homoallyl **9b**. The substituted amide **9a**/**b** might accelerate the protonation of enamine and then enhance the alkyne aza-Prins reaction. As we predicated, the Prins reactions on **9a**/**b** are very clean under the previous conditions, giving the corresponding tricyclic ketone **8a** and **8b** in 99% and 90% yield, respectively (Table 1, entries 8 and 9). The absolute configuration of ketone **8a** was also unambiguously determined by single-crystal X-ray crystallography.[22] The terminal alkenyl group, which often could participate in a carbocation reaction, remained untouched under the aza-Prins conditions, probably because of a more favored geometry to attack the imine by the alkyne (6-*exo*-trig) rather than the alkene (n = 1,5-*endo*-trig, disfavored; n = 2, 6-*endo*-trig) group.

Having solved the key aza-Prins cyclization, we then turned to finish the total synthesis of (−)-lycopodine (**1**) and (−)-dihydrolycopodine (**2**). Palladium-catalyzed anti-Markovnikov oxidation[23] of lactam-ketone **8a** proceeded smoothly to provide a 68% yield of the required keto aldehyde **15** which can be also readily prepared by ozonolysis of the terminal alkene from **8b** in 72% yield (Scheme 3). Next, our attention was focused toward construction of the remaining piperidine ring via a tandem intramelocular aldol/elimination reaction. After screening various common acids and bases for this cyclization, we found 50% *p*-TsOH could realize the last cyclization and generate *α*,*β*-enone **16** in 57% yield. It should be noted that the yield and reaction rate of this step dropped significantly with a lesser amount of *p*-TsOH. A highly stereoselective hydrogenation of this enone led to lycopodine lactam **7** in a nearly quantitative yield, and its absolute configuration was also ascertained by X-ray crystallographic analysis.[22] Finally, reduction of lactam **7** under $LiAlH_4$ yielded (−)-dihydrolycopodine (**2**) in 94% yield, which matched nicely with the reported spectrum data.[24a−c] Then, (−)-dihydrolycopodine (**2**) was converted into (−)-lycopodine (**1**) using Jones' oxidizing reagent. The physical and spectral properties, including optical rotation of our synthetic **1**, were also in good agreement with the published data.[11i,k,24a,d]

In summary, we have completed the enantioselective total synthesis of (−)-lycopodine in 8 steps from Wade's fawcettimine enone (12 steps from commercially availiable (*R*)-(+)-pulegone). In addition, the bridged quaternary stereocenter at C13 was successfully constructed via the phosphoric acid promoted alkyne aza-Prins cyclization. Finally, the exclusion of the protecting group from the overall synthetic design will improve the synthesis efficiency. Further applications of this strategy described herein toward the synthesis of other lycopodine-type alkaloids are currently under investigation and will be reported in due course.

Scheme 3. Completion of the Synthesis of (−)-Lycopodine[a]



[a]Reagents and conditions: (a) $Pd(MeCN)_2Cl_2$ (10 mol %), CuCl (10 mol %), HMPA, O_2, $(CH_2Cl)_2$, rt, 43 h; (b) O_3, DCM, −78 °C, 15 min; then PPh_3, rt, 12 h; (c) *p*TsOH (50 mol %), benzene, reflux, 30 h; (d) 10% Pd/C, H_2, EtOAc, rt, 6 h; (e) $LiAlH_4$, THF/Et_2O (1:1), reflux, 6 h; (f) Jones reagent (2.7 M), acetone, 0 °C, 10 min.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02072.

X-ray crystallographic data for **8c** (CIF)
X-ray crystallographic data for **8a** (CIF)
X-ray crystallographic data for **7** (CIF)
Detailed experimental procedures and full spectroscopicdata for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(16) Alkyne-ketone **10** can also be synthesized from Wade's fawcettimine enone **11** via a three-step protocol involving Sakurai-type Michael addition, ozonolysis, and Ohira−Bestmann homologation. For the details, see the Supporting Information.

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(20) CCDC 1434870 (**8c**) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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