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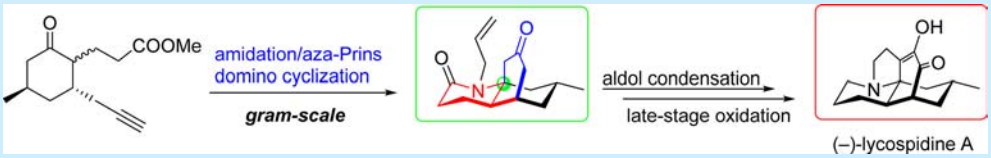
Asymmetric Total Synthesis of (−)-Lycospidine A

Shiyan Xu,[†] Jing Zhang,[†] Donghui Ma,[†] Dengyu Xu,[†] Xingang Xie,[†] and Xuegong She*[,†,‡]

[†]State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, People's Republic of China

[‡]Collaborative Innovation Center of Chemical Science and Engineering, Tianjin, 300071, People's Republic of China

Supporting Information

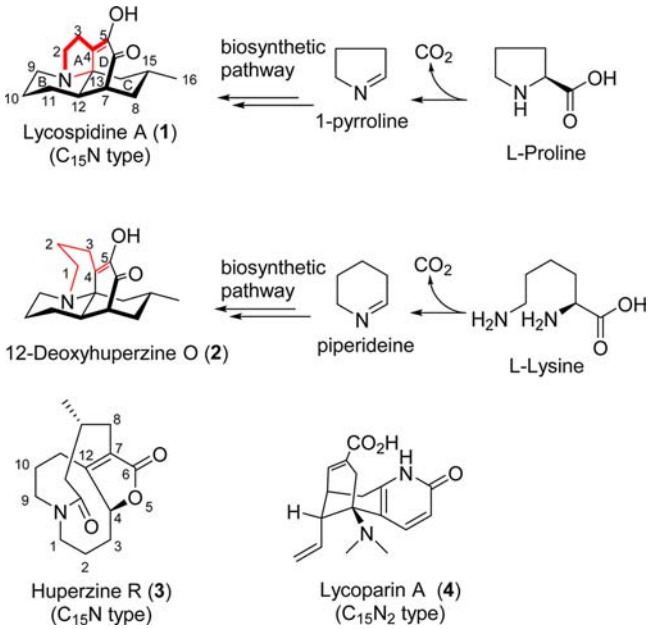


ABSTRACT: The first asymmetric total synthesis of the structurally unique *Lycopodium* alkaloid (−)-lycospidine A, containing an unprecedented five-membered ring, has been accomplished in only 10 steps with 21.6% overall yield from the known conveniently available sulfoxide. This protecting-group-free short synthesis relied on the use of a key amidation/aza-Prins domino cyclization reaction to rapidly construct the tricyclic skeleton and two continuous stereocenters (one of which is a bridged quaternary stereocenter). An intramolecular aldol condensation was successfully utilized to establish the unique five-membered ring, and a late-stage oxidation inspired by biosynthesis pathway was adopted to synthesize the diosphenol ring of (−)-lycospidine A.

Lycopodium complanatum (L.) Holub was used as a traditional Chinese herbal medicine for the treatment of arthritic pain, quadriplegia, and contusion.[1] Not surprisingly, a large number of *Lycopodium* alkaloids[2] with fascinating structures, such as lyconadin A,[3] complanadine A,[4] lycopladine A,[5] and lycopladine H,[6] were isolated and these intricate polycyclic molecular architectures were found to possess important biological properties, such as antipyretic and anticholinesterase activity.[7] Lycospidine A (Scheme 1, **1**), the first example of a $C_{15}N$ *Lycopodium* alkaloid containing an unprecedented five-membered A-ring, was isolated from *Lycopodium complanatum*, together with the known 12-deoxyhuperzine O (**2**), by Zhao and co-workers in 2013.[8] This novel $C_{15}N$ alkaloid exhibits an extraordinary [5,6,6,6] fused tetracyclic ring system with a unique aza five-membered A-ring and diosphenol D-ring, with four stereocenters (three of which are continuous stereocenters and C13 is a bridged quaternary stereocenter). To the best of our knowledge, only 14 natural C_{15} *Lycopodium* alkaloids have been reported so far, of which 13 belong to the $C_{15}N_2$-type. Huperzine R (**3**) was the only other *Lycopodium* alkaloid possessing a $C_{15}N$ skeleton due to the substitute of C with O in the 5-position.

In general, *Lycopodium* alkaloids were divided into four major classes (phlegmarine,[9] lycodine,[10] lycopodine,[11] and fawcettimine[12]).[13] Except for the four major classes, there were plenty of structurally diverse and complex *Lycopodium* alkaloids that have been isolated from the genus of *Lycopodium*,[14] which were thought to derive from the four major classes through carbon skeleton rearrangements, chemical bond cleavage, and further cyclization.[15] Biosyntheses of *Lycopodium* alkaloids, particularly the lycopodine-type alkaloids,[16] have been investigated in *L. tristachyum*, showing that *Lycopodium* alkaloids were derived from L-lysine. However, lycospidine A (**1**) is independent from all of the classes and subgroups biosynthetically. The unique five-membered ring in **1** indicates that carbons 2−5 in **1** are presumably derived from L-proline instead of the L-lysine

Scheme 1. Structures of Lycospidine A (1), 12-Deoxyhuperzine O (2), Other Two C_{15} *Lycopodium* Alkaloids and Biosynthetic Pathway of 1 and 2



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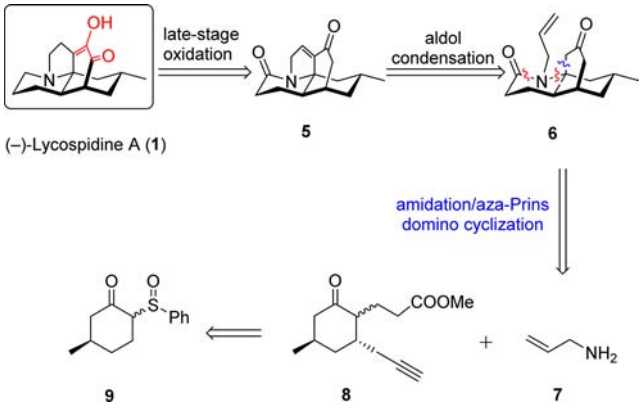
biosynthetically. Therefore, lycospidine A (**1**) represents a new class of *Lycopodium* alkaloid.[8] In addition, the unique structural feature and biosynthetic origin of **1** shed new insight into the structural diversity of *Lycopodium* alkaloid analogue libraries potentially accessible by engineered biosynthesis. Due to the unique structure, potential biological property, and significance in the biosynthesis of *Lycopodium* alkaloid, we developed an amidation/aza-Prins domino cyclization strategy to achieve the asymmetric total synthesis of (−)-lycospidine A (**1**).

Our retrosynthetic analysis of (−)-lycospidine A (**1**) was outlined in Scheme 2. The target molecule **1** could be obtained

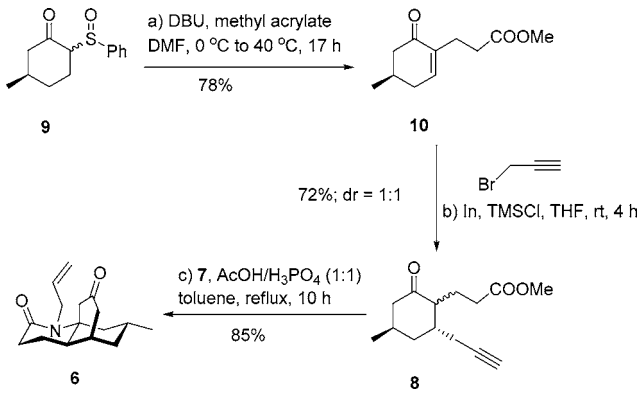
Scheme 2. Retrosynthetic Analysis of (−)-Lycospidine A (1)



from tetracyclic precursor **5** via late-stage oxidation inspired by biosynthesis pathway.[8] An intramolecular aldol condensation could be utilized to synthesize the unique five-membered ring. The tricyclic core skeleton **6** would be constructed from monocyclic precursor **8** by an amidation/aza-Prins domino cyclization[17] in one process. The known sulfoxide **9** could be converted to an α,β-unsaturated ketone via Michael addition and thermal elimination. Subsequently, a Michael-type addition was used to install a propargyl group to this α,β-unsaturated ketone, for the preparation of monocyclic precursor **8**.

The synthesis of (−)-lycospidine A (**1**) commenced from the known sulfoxide **9**, which was prepared from commercially available (*R*)-(+)-pulegone as reported in refs 18 and 19 (Scheme 3). Using DBU, sulfoxide **9** was converted to α,β-unsaturated ketone **10** in 78% yield via Michael addition and thermal elimination.[19] Through Michael-type addition with a propargylindium reagent, α,β-unsaturated ketone **10** was transformed to

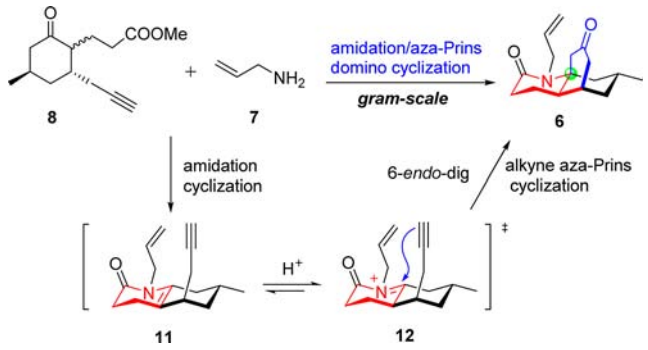
Scheme 3. Preparation of Key Tricyclic Ketone 6



monocyclic precursor **8** as a 1:1 mixture of inseparable diastereomers in 72% yield.[20]

With precursor **8** in hand, we subsequently investigated the feasibility of the key amidation/aza-Prins domino cyclization reaction. A series of Brönsted acids were tested for the key amidation/aza-Prins domino cyclization, and the results are summarized in Table 1. Under the conditions of hydrochloric acid

Table 1. Reaction Condition Survey for Key Amidation/aza-Prins Domino Cyclization Reaction[a]



entry	acids (mole ratio)	time (h)	*t* (°C)	prod	yield[b] (%)
1	HCl	10	reflux	n.d.	
2	H_2SO_4	10	reflux	n.d.	
3	AcOH	3	reflux	**11**	97
4	HCOOH	3	reflux	**11**	35
5	85% H_3PO_4	10	reflux	n.d.	
6	HCOOH/85% H_3PO_4 (1:1)	10	rt	n.d.	
7	HCOOH/85% H_3PO_4 (1:1)	10	reflux	**6**	25
8	AcOH/85% H_3PO_4 (1:1)	10	rt	n.d.	
9	AcOH/85% H_3PO_4 (1:1)	10	100	**6**	15
10	AcOH/85% H_3PO_4 (1:1)	5	reflux	**6**	64
11	AcOH/85% H_3PO_4 (1:1)	10	reflux	**6**	90
12	AcOH/85% H_3PO_4 (1:1)	15	reflux	**6**	86
13	AcOH/85% H_3PO_4 (1:1)	10	reflux	**6**,	85[c]

[a]Unless otherwise specified, the reaction was carried out with **8** (1.0 mmol), and **7** (1.5 mmol) in the presence of acids (5.0 mmol) and toluene (10.0 mL). [b]Isolated yields. [c]Run on gram scale.

or sulfuric acid, starting material was decomposed (entries 1 and 2). Therefore, we turned our attention to using some mild acids such as HCOOH and AcOH, which just afforded dicyclic enamide **11** (entries 3 and 4). And when 85% H_3PO_4 was used, starting material was decomposed (entry 5). To our delight, desired tricyclic ketone **6** could be obtained in 25% yield when HCOOH/85% H_3PO_4 (1:1) was used (entry 7). After the reaction parameters (acids, reaction time and temperature) were altered, tricyclic ketone **6** could be obtained with the best yield (90%) in the presence of AcOH/85% H_3PO_4 (1:1) in toluene under reflux for 10 h (entry 11). It is worth mentioning that this procedure could be carried out on a large scale (up to 2 g of **6** prepared per batch) with a slightly reduced yield (entry 13).This amidation/aza-Prins domino cyclization formed three chemical bonds, 6/6 dicycles, and two continuous stereocenters (one of which is a bridged quaternary stereocenter) in one process consisting of four steps. A possible reaction mechanism is depicted in Table 1. Using a Brönsted acid, monocyclic precursor **8** reacted with allylamine **7**, cyclizing to give dicyclic enamide **11**,[21] which would be subsequentally protonated to give N-acyliminium ion **12**, followed by capture by an intramolecular alkyne in a 6-*endo*-dig

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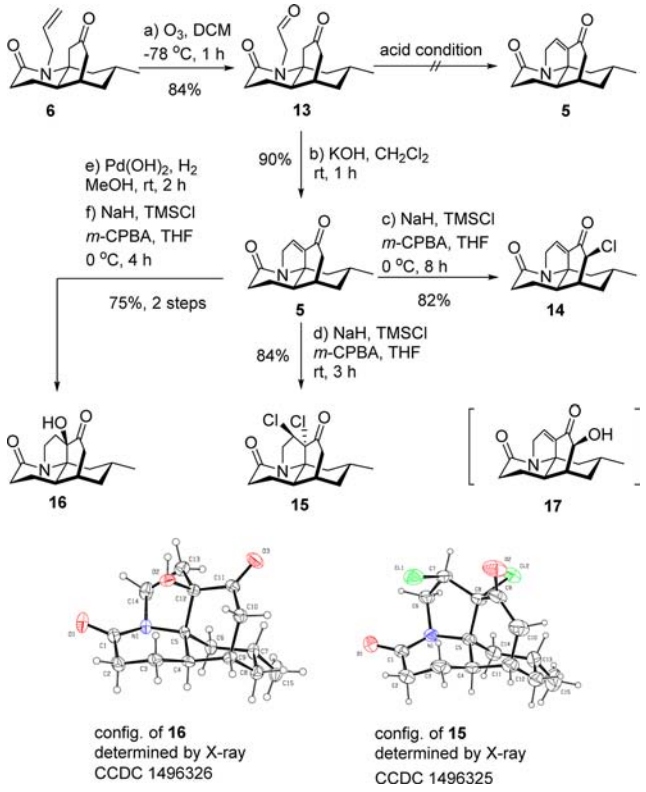
fashion (alkyne aza-Prins cyclization[22]) to further provide tricyclic ketone product **6**. The high stereoselectivity of this cyclization may be attributed to the stereoselective enamine protonation, which was sterically guided by the axial propargylic group.

After establishing the tricyclic skeleton of (−)-lycospidine A (**1**), the next challenge was to construct the unique five-membered ring (Scheme 4). Ozonolysis cleavage of the terminal alkene of **6**

Scheme 4. Synthesis of the Core Tetracyclic Framework

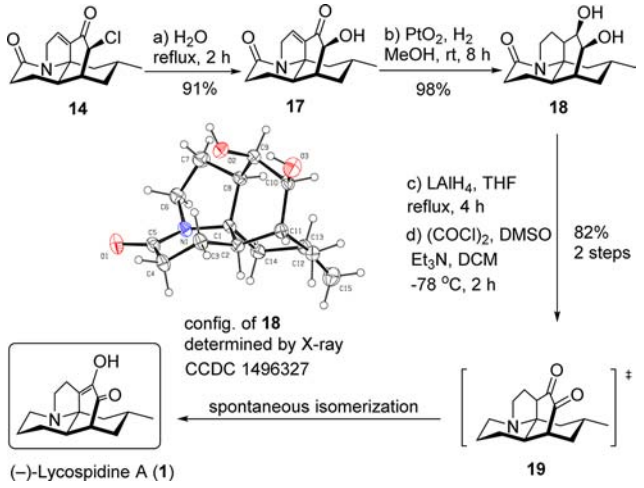


afforded aldehyde **13** in 84% yield. Initial attempts of utilizing aldol condensation to construct this five-membered ring in the presence of acids (such as *p*-TsOH, HCl, H_2SO_4, $BF_3{\cdot}Et_2O$, $TiCl_4$) were proved to be unsuccessful, and just the decomposition of substrate was found. However, when this reaction system proceeded under the conditions of KOH in EtOH at rt, only a trace of tetracyclic α,β-unsaturated ketone **5** was detected, along with the aldehyde **13** being consumed completely. This result implied that this aldol condensation could proceed to form product **5**, which subsequently would be hydrolyzed and decomposed in EtOH (protic solvent). It was presumed that the exchange of protic to aprotic solvent would impede the decomposition of the amide. With this ideal, this reaction was attempted again after changing the solvent to CH_2Cl_2 (aprotic solvent). Fortunately, the reaction was effected to afford tetracyclic product **5** in 90% yield.

Having efficiently constructed the tetracyclic framework **5**, late-stage oxidation was required to complete the synthesis of (−)-lycospidine A (**1**) (Scheme 4). Under common oxidation conditions, ketone **5** could not be directly oxidized to afford α-hydroxyl ketone **17**. When NaH was chosen as the base, the reaction proceeded at 0 °C, and α-chloroketone **14** was obtained in 82% yield. Interestingly, when this reaction proceeded at rt, just dichloroketone **15** resulted in 84% yield. However, after the α,β-unsaturated double bond in ketone **5** was reduced with H_2, α-hydroxyl ketone **16** (OH in the α-position jointed with the 5-membered ring) was obtained under the same conditions. The structures and relative configurations of dichloroketone **15** and α-hydroxyl ketone **16** were unambiguously determined by single-crystal X-ray diffraction analysis.[23]

Although α-hydroxyl ketone **17** could not be achieved directly from tetracyclic ketone **5**, α-chloroketone **14** could be obtained smoothly in satisfactory yield. Therefore, we attempted to obtain α-hydroxyl ketone **17** from α-chloroketone **14** via a detoured approach (Scheme 5). After different conditions were screened, α-

Scheme 5. Complete the Synthesis of (−)-Lycospidine A (1)



chloroketone **14** could be converted to α-hydroxyl ketone **17** via hydrolysis of α-chloroketone under reflux in H_2O with 91% yield.[24] Then reduction of α-hydroxyl ketone **17** with H_2 afforded vicinal diol **18** as a single diastereoisomer in nearly quantitative yield; the structure and relative configuration of **18** were also confirmed by X-ray crystallographic analysis.[23] Finally, reduction of amide to the corresponding amine and a Swern oxidation[25] of vicinal diol to vicinal diketone occurred, which spontaneously isomerized to form the stable diosphenol ring of (−)-lycospidine A (**1**). The first asymmetric total synthesis of (−)-lycospidine A (**1**) was accomplished by a protecting-group-free strategy. The spectroscopic data (^1H NMR, ^{13}C NMR and HRMS) of the synthetic product are in agreement with those reported for the natural product. The sign of rotation for our synthetic **1** ($\alpha_D^{24.6}$ = −9.0° (*c* 0.3, MeOH)) was consistent with that reported for natural lycospidine A ($\alpha_D^{24.5}$ = −8.8° (*c* 0.3, MeOH)).

In summary, the first asymmetric total synthesis of the *Lycopodium* alkaloid (−)-lycospidine A (**1**) has been accomplished in only 10 steps with 21.6% overall yield from the known sulfoxide via a protecting-group-free strategy. The tricyclic ketone with two continuous stereocenters (one of which is bridged quaternary stereocenter) was constructed from the monocyclic precursor through an amidation/aza-Prins domino cyclization. An intramolecular aldol condensation was employed to establish the unique five-membered ring, and a detoured approach was utilized to introduce α-hydroxy via a α-chloroketone. Finally, a Swern oxidation was adopted to synthesize the diosphenol ring of (−)-lycospidine A (**1**). Additional efforts to apply this strategy to the synthesis of 12-deoxyhuperzine O (**2**) along with other related natural products are being conducted in our laboratory and will be reported in due course.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02322.

Detailed experimental procedures and full spectroscopic data for all new compounds (PDF)
X-ray crystallographic data for **15** (CIF)
X-ray crystallographic data for **16** (CIF)
X-ray crystallographic data for **18** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: shexg@lzu.edu.cn.

Notes

The authors declare no competing financial interest.

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(23) CCDC 1496325 (**15**), CCDC 1496326 (**16**), and CCDC 1496327 (**18**) contain the supplementary crystallographic data for this paper. These 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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