Natural Product Synthesis

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# Expedient Synthesis of (+)-Lycopalhine A

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*Dedicated to Prof. Dr. Johann Mulzer*

***Abstract:*** *Two amino acids play a key role in the first total synthesis of lycopalhine A.* L*-glutamic acid serves as a convenient chiral starting material for the 13-step synthesis, and* L*-proline promotes an unusual 5-endo-trig Mannich cyclization that generates the central pyrrolidine ring of the Lycopodium alkaloid. The bicyclo[3.3.0]octanol moiety of the molecule is formed through an intramolecular aldol addition that may occur spontaneously in nature.*

Lycopodium alkaloids continue to provide fascinating structures with which to probe the boundaries of synthetic chemistry.[1] The fawcettimine-type (**3**) alkaloids, in particular, have garnered significant attention due to their broad diversity and architectural complexity, and have inspired no small number of resourceful syntheses in the past decade.[2] In more recent years, the isolation of alkaloids with novel frameworks, such as lycopalhine A (**1**), palcernine A (**4**), palhinine A (**5**), and lycotetrastine A (**6**), has further broadened the synthetic appeal of this class of natural products (Figure 1).[3] Herein, we report our first studies into the

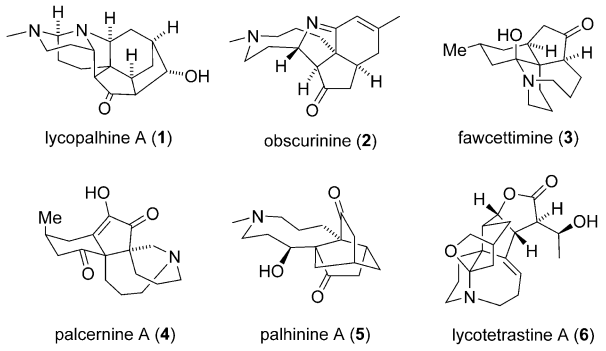
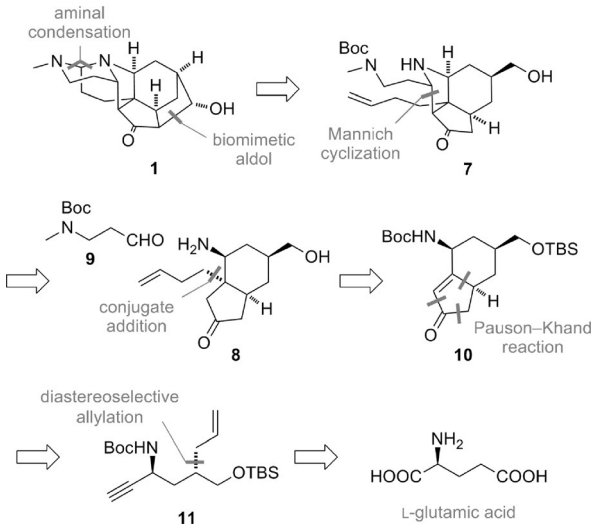



***Figure 1.*** Fawcettimine-type alkaloids as an inspiration for synthetic chemists.

synthesis of *Lycopodium* alkaloids, culminating in a concise total synthesis of lycopalhine A.

Lycopalhine A was recently isolated from *Palhinhaea cernua*, together with its presumed biosynthetic progenitor obscurinine (**2**).[4] The alkaloid features a complex hexacyclic ring system composed of one six-membered and two five-membered carbocycles, a piperidine and a hexahydropyrimidine heterocycle, and a densely substituted pyrrolidine core. The intricate skeleton contains nine stereogenic centers, eight of which are contiguous.

Our retrosynthetic analysis (Scheme 1) began with the disconnection of the most labile bonds, that is, the linchpin




***Scheme 1.*** Retrosynthetic analysis of lycopalhine A. Boc = *tert*-butyloxycarbonyl, TBS = *tert*-butyldimethylsilyl.

aminal, which could foreseeably arise through a late-stage condensation of two secondary amines and an aldehyde. We also assumed that the aldol moiety of the alkaloid, despite the strained nature of the bicyclo[3.3.0]octanol subsystem, could be generated with relative ease near the end of the synthesis by mimicking its potential biosynthetic formation. These considerations yielded pyrrolidine **7** as a logical precursor, wherein the requisite carbonyl groups are masked as a terminal alkene and a primary alcohol. We rationalized that the highly substituted pyrrolidine ring would best be attained through an intramolecular Mannich cyclization of aminoketone **8** with aldehyde **9**. We were well aware that this transformation, in practice, would represent an audacious key step. Baldwin-disfavored[5] 5-*endo*-trig Mannich reactions occur in aza-Cope/Mannich cyclization cascades but are rarely triggered by condensation of an aminoketone with an enolizable aldehyde.[6] Amine **8** could be conferred by conjugate addition to cyclopentenone **10**, formed in turn through a diastereoselective Pauson–Khand reaction from

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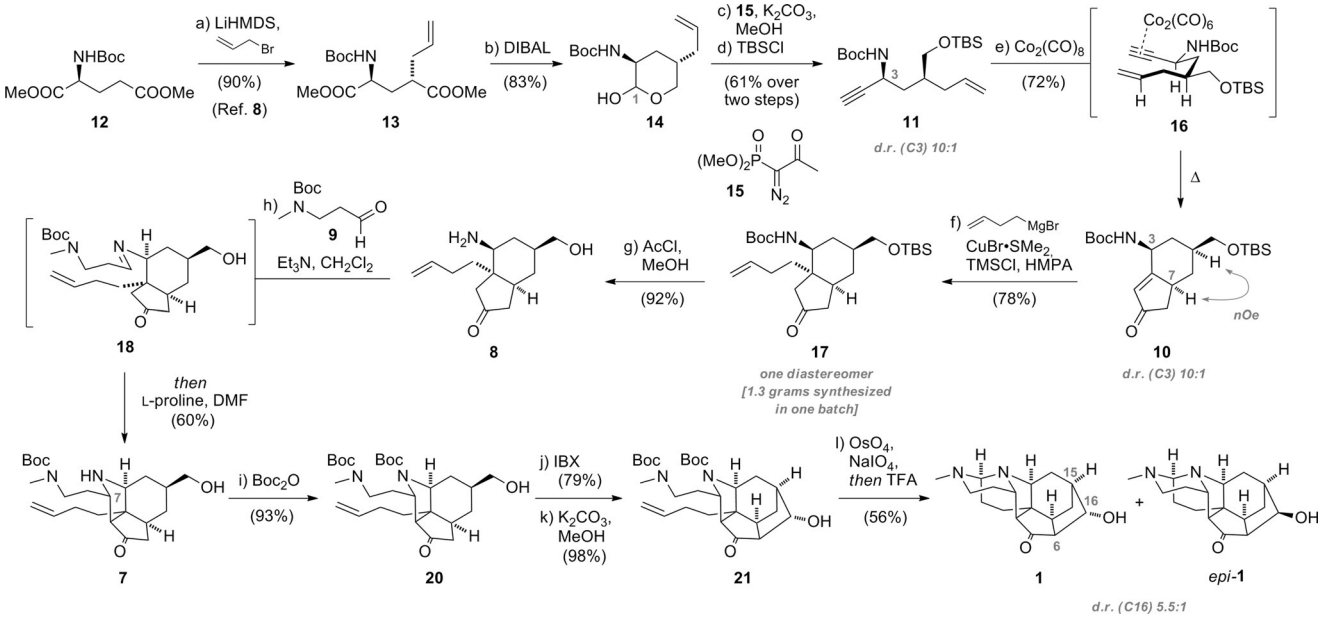


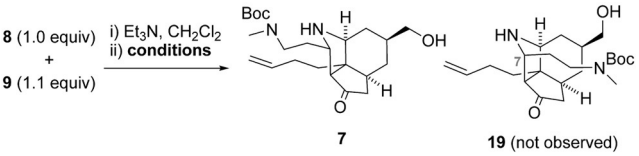

***Scheme 2.*** Total synthesis of lycopalhine A. a) LiHMDS, THF, −78 °C, then allyl bromide; b) DIBAL (5.0 equiv), THF/PhMe, −78 °C; c) dimethyl (1-diazo-2-oxopropyl)phosphonate **15**, $K_2CO_3$, MeOH, 0 °C→RT; d) TBSCl, imidazole, $CH_2Cl_2$, 0 °C→RT; e) $Co_2(CO)_8$, PhMe, 70 °C; f) 3-butenylmagnesium bromide (4.5 equiv), CuBr·$SMe_2$ (20 mol %), TMSCl, HMPA, THF, −78 °C→−30 °C, then AcOH, RT; g) AcCl (10 equiv), MeOH, 45 °C; h) **9** (1.1 equiv), $Et_3N$, $CH_2Cl_2$, then L-proline, DMF, RT; i) $Boc_2O$, $CH_2Cl_2$, RT, 72 h; j) IBX, EtOAc, 80 °C; k) $K_2CO_3$, MeOH, RT, l) $OsO_4$, $NaIO_4$, 2,6-lutidine, dioxane/$H_2O$ (3:1 v/v), RT, then TFA, $CH_2Cl_2$, 0 °C→RT. Boc = *tert*-butyloxycarbonyl, DIBAL = diisobutylaluminum hydride, DMF = dimethylformamide, HMPA = hexamethylphosphoramide, IBX = 2-iodoxybenzoic acid, LiHMDS = lithium bis(trimethylsilyl)amide, TBS = *tert*-butyldimethylsilyl, TFA = trifluoroacetic acid, THF = tetrahydrofuran, TMS = trimethylsilyl.

propargylic carbamate **11**. This intermediate would ultimately be derived from L-glutamic acid.

Our actual synthesis of lycopalhine A, guided by these considerations, is presented in Scheme 2. To begin, dimethyl ester **12**, prepared from L-glutamic acid on a decagram scale in a one-pot procedure (see the Supporting Information),[7] was allylated with high *anti* diastereoselectivity in a procedure described by Hanessian and co-workers.[8] Chemoselective reduction of **13** by controlled addition of diisobutylaluminum hydride (DIBAL) afforded lactol **14** as a 1:1 mixture of diastereomers (C1). Alkynylation of **14** was complicated by the epimerization of the neighboring amine stereocenter under the basic conditions required to open the six-membered lactol. Optimized conditions using Ohira–Bestmann reagent **15**[9] and silyl protection of the resulting alcohol afforded alkyne **11** and its C3 epimer as an inseparable 10:1 mixture.[10] The ensuing Pauson–Khand reaction proceeded under thermal conditions and afforded enone **10** with the desired C7 stereoselectivity, confirmed by nuclear Overhauser effect (NOE) analysis, as a 10:1 mixture with the cyclized C3 epimer. The diastereoselectivity of related intramolecular Pauson–Khand reactions in the context of *Lycopodium* alkaloid synthesis has previously been explored by the groups of Zard,[11] Takayama,[2d] and Mukai.[2i] The authors propose that chair-like conformations of intermediate **16** translate to the desired configuration of the bicyclo-[4.3.0]nonenone.[12] TMSCl-promoted conjugate addition of butenylmagnesium bromide to the enone[13] and cleavage of the resulting silyl enol ether with acetic acid afforded **17**, featuring the sole quaternary stereocenter of the molecule, as a single diastereomer upon purification. The first six steps of the synthesis were easily scalable and provided gram quantities of advanced intermediate **17**. Global deprotection with acetyl chloride in methanol then produced free aminoketone **8**.

The intramolecular 5-*endo*-trig Mannich cyclization proved to be a challenging transformation. Acidic conditions resulted mainly in self-condensation of the aldehyde. However, mixing amine **8** and aldehyde **9** with triethylamine followed by concentration under reduced pressure granted

***Table 1:*** Conditions for the intramolecular Mannich cyclization.




| Entry[a] | Additives (equiv) | Solvent | *T* [°C] | Yield[b] [%] |
|---|---|---|---|---|
| 1 | $Yb(OTf)_3$ (1.0) | MeCN | 0–RT | – |
| 2 | $TiCl_4$ (2.0)/ $Et_3N$ (4.0) | $CH_2Cl_2$ | −30–RT | – |
| 3 | $K_2CO_3$ (3.0) | MeOH | RT | – |
| 4[c] | $Et_3N$ (3.0) | PhMe | RT–80 | – |
| 5 | pyrrolidine (1.0) | DMF | RT | 11 |
| 6 | pyrrolidine (1.0)/ AcOH (1.0) | DMF | RT | 10 |
| 7 | D-proline (1.0) | DMF | RT | 20 |
| **8** | **L-proline (1.0)** | **DMF** | **RT** | **60** |
| 9[c] | L-proline (0.5) | DMF | RT | 39 |
| 10 | L-phenylalanine (1.0) | MeCN | RT | 30 |

[a] Reactions conducted under nitrogen atmosphere for 18–24 h. [b] Yield of isolated product. [c] Reaction performed without preformation of imine by treatment with $Et_3N$.

the unstable crude imine **18**. Redissolving the imine in dimethylformamide (DMF) and exposure to pyrrolidine afforded **7** with the desired *S*-configured C7 stereochemistry in low yields, but with no trace of the undesired *R*-configured diastereomer **19** or 6-*endo*-trig regioisomers (Table 1, entry 5). A substantial increase in reaction yield was observed when using L-proline as the additive (entry 8). Although the reaction proceeded without preformation of the imine and with substoichiometric quantities of the amino acid (entry 9), lower yields led us to use a full equivalent of the additive. The reaction also proceeded in the presence of both D-proline (entry 7) and L-phenylalanine (entry 10), albeit in reduced yields. The tendency of primary and secondary, but not tertiary, amines to promote the reaction suggests a mechanism involving matched enamine catalysis rather than simple deprotonation of the ketone.

To complete the synthesis of lycopalhine A, the newly formed pyrrolidine was protected by using di-*tert*-butyl dicarbonate to yield dicarbamate **20** before oxidizing the remaining primary alcohol with 2-iodoxybenzoic acid (IBX). The potentially biomimetic intramolecular aldol reaction to form **21** occurred quickly and in excellent yield when using potassium carbonate in methanol.[14] The diastereoselectivity of the reaction likely reflects a thermodynamic preference of **21** for a β-hydroxyl group positioned on the concave face of the molecule, away from the congested inner ring system. A Lemieux–Johnson oxidative cleavage of the olefin followed by dual deprotection and acid-catalyzed aminal formation afforded **1**.

The spectroscopic data and optical properties of our synthetic sample were identical in all respects to those reported for the natural product.[3a] Indeed, an inseparable side product (*epi*-**1**) purified together with lycopalhine A directly matched an uncharacterized impurity in the spectra of Zhao's isolated sample. Two-dimensional NMR spectroscopy of the mixture[15] identified the minor product as the C16 epimer of lycopalhine A, which likely exists in equilibrium with the major isomer through a retro-aldol/aldol-type mechanism. Deuterium exchange of the protons at C6 and C15 under basic conditions,[16] as well as the presence of epimers in both the isolated and synthetic samples, suggests that lycopalhine A exists as a thermodynamic mixture favoring the closed aldol product and lends further credibility to a spontaneous cyclization in its biosynthesis.

In summary, we have developed an expedient synthesis of the complex *Lycopodium* alkaloid lycopalhine A that relies on two readily available amino acids for its completion. L-glutamic acid provides an inexpensive chiral entry point that, to the best of our knowledge, has not been used previously in the synthesis of fawcettimine-type alkaloids. L-proline promotes a 5-*endo*-trig intramolecular Mannich cyclization with an α-unsubstituted aldehyde under mild conditions. We anticipate that this organocatalytic approach and the scalable intermediates encountered in the course of this endeavor will prove valuable for future studies of complex *Lycopodium* alkaloids.

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**Keywords:** aldol reaction · amino acids · *Lycopodium* alkaloids · Mannich reaction · total synthesis

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[16] At the recommendation of a reviewer, deuterium exchange studies were performed with $K_2CO_3$ and MeOD at ambient temperature. Exchange of protons at C6 and C15 after 2 hours was consistent with retro-aldol ring opening, epimerization of the aldehyde, and tautomerization of the enol, followed by ring closure. See the Supporting Information for details.

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