I. Introduction

- Lycopodium alkaloids: antipyretic and anticholinesterase activity.
- Lycospidine A: isolated from *Lycopodium complanatum* by Zhao and co-workers in 2013\(^1\).
- 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.

![Diagram of Lycospidine A]

- Biosynthetically derived from L-proline.
- The first asymmetric total synthesis in 10 steps with 21.6% overall yield.

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II. Retrosynthesis

- Key step: amidation/aza-Prins domino cyclization.
- Late-stage oxidation inspired by biosynthesis pathway.
- Intramolecular aldol condensation to synthesize the unique five-membered ring.
III. Forward synthesis

Michael addition/ thermal elimination

Michael-type addition with propargylium reagent

Amidation/ aza-Prins domino cyclization

1. Reaction of compound 8 with propargylamine in the presence of acetic acid and phosphoric acid (1:1) in toluene under reflux for 10 hours yields compound 6 in 85% yield.

2. The amidation reaction proceeds through the formation of a Michael adduct followed by a Prins cyclization to form the macrocyclic product.

3. The Prins cyclization involves the migration of a hydroxyl group and the formation of a new carbon-carbon bond.

4. The resulting product undergoes further transformations, including dehydration and protonation, to yield the final product 6.
Ozonolysis

Aldol condensation
Late-stage oxidation

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\begin{align*}
15 & \xrightarrow{\text{NaH, TMSCl; } m\text{-CPBA, THF, RT, } 3 \text{ h}} 84\%  \\
5 & \xrightarrow{\text{NaH, TMSCl; } m\text{-CPBA, THF, } 0 \degree C, 8 \text{ h}} 82\%  \\
14 &
\end{align*}
\]