Total Synthesis of (+)-Scholarisine A


Current literature
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About (+)-Scholarisine A

- Monoterpenoid indole alkaloid;
- Isolated from the leaves of *Alstonia scholaris* in 2008, a plant used in traditional Chinese medicine to treat various respiratory diseases;
- A dense, polycyclic compound:
  - an indolenine fused to a strained carbocyclic cage;
  - several tertiary and quaternary stereocenters;
  - potentially labile imine and bridging lactone functional groups.

Proposed biosynthesis of Scholarisine A

- Derived from picrine.
- The oxygen bridge between C-2 and C-5 and the C5-N4 bond could be cleaved and formed an aldehyde carbon at C-5.
- An enamine among N-4, C-21, and 20 might be formed by double bond migration from C-19/20 to C-20/21 of the intermediate.
- Nucleophilic addition to form a new C-C bond between C20/5 and an imine at N4/C21.
- Formation of a lactone bridge ring through an intramolecular condensation reaction.
First total synthesis of (+)-Scholarisine A by Smith

(+)-scholarisine A (1)

\[ \text{cyclization and oxidation} \]

\[ \text{homologation and reduction} \]

3

4

5

6

(-)-7

Total synthesis of (+)-Scholarisine A by Snyder

(+)-scholarisine A (1)

- FGI
- C-H arylation
- Epimerization
- Lactamization
- Tandem radical cyclization/Keck allylation

Summary

- 14 steps from known enone 19 (**15 steps** from commercial materials).
- Key discoveries:
  - an efficient and diastereoselective pyrone **Diels–Alder reaction** to rapidly form the appropriately functionalized [2.2.2]-bicycle;
  - a **radical cyclization/Keck allylation** to concurrently forge the [3.3.1]-bicycle and C-20 quaternary center;
  - an indolenine annulation at a nonenolizable tertiary center via a novel late-stage radical **C–H arylation**;
  - the use of a pendant hydroxyl group to facilitate the chemoselective reduction of an extremely unreactive lactam.
Thank you!