Expedient Enantioselective Synthesis of Cermizine D

About Lycopodium alkaloids

• Cernuine was isolated by Marion and Manske in 1948, consisting of a fused tetracyclic ring system containing an aminal moiety;
• Cermizine D, Cermizine C, Senepodine G were isolated in 2004 by Kobayashi and co-workers from the club moss *Lycopodium cernuum*.
• Cermizine D - exhibited cytotoxicity against murin lymphoma L1210 cells (7.5 µg/mL).

Plausible biogenesis

pelletierine $\rightarrow$ HOOC$\rightarrow$A

A $\rightarrow$ Senepodine G

Senepodine G $\rightarrow$ Cermizine C

Cermizine C $\rightarrow$ $\triangle^1$-piperideine

Cermizine C $\rightarrow$ Cernuine

Cernuine $\rightarrow$ Cermizine D

First total synthesis of *Lycopodium alkaloids* by Takayama – Retrosynthesis

Total synthesis of cernuane-type and quinolizidine-type Lycopodium alkaloids by Takayama

Synthesis of key intermediate 5

Synthesis of cermizine C (3) and senepodine G (4) from intermediate 5

Stereoselective synthesis of homoallylamine 6

Completion of the total syntheses of (-)-cernuine (1) and (+)-cermizine D (2)

Retrosynthetic Analysis of cermizine D by Carter

Synthesis of Common Intermediate 4

[Chemical reaction diagram with intermediates and reagents]
The conversion of the common intermediate 4 into sulfone 3
Improved Routes to Sulfone Fragment

\[ \text{Improved Routes to Sulfone Fragment} \]

\[ \text{NaHMDS} \]
\[ \text{PhSCH}_2\text{I, THF} \]
\[ -78 \degree \text{C, 1 h} \]
\[ 70\%, 10:1 \text{ dr} \]

\[ \text{LiBH}_4 \]
\[ \text{MeOH, THF} \]
\[ 97\% \]

1) \((\text{NH}_4)_6\text{Mo}_7\text{O}_{24} \cdot 4\text{H}_2\text{O}\)
\[ \text{H}_2\text{O}_2, \text{EtOH}, 94\% \]
2) \(\text{Ph}_3\text{P}, \text{I}_2, \text{Imid.} \]
\[ 84\% \]
3) \(\text{Pd/C, H}_2 \]
\[ \text{EtOH, 99}\% \]

\[ \text{EtO} \]
\[ \text{O} \]
\[ \text{SO}_2\text{Ph} \]
\[ \text{Li} \]
\[ \text{THF, -78 \degree C} \]
\[ 83\% \]
\[ 4:1 \text{ E/Z} \]

\[ \text{Me}_2\text{CuLi} \]
\[ \text{THF, Li} \]
\[ -78 \degree \text{C to -20 \degree C} \]
\[ 55\% (1:1.2 \text{ dr}) \]
Completion of the synthesis of cermizine D

\[
\text{LDA, THF -78 °C, 1 min; 4, 15 min}
\]

\[
\text{93% yield 1.5:1 dr (22:2)}
\]

\[
\text{DMP, CH}_2\text{Cl}_2; \text{NaBH}_4, \text{MeOH 93% yield (2 steps), 1.5:1 dr}
\]

\[
\text{Raney Ni, EtOH reflux; TMSCl, MeOH}
\]

\[
\text{Ph}_3\text{P,CBr}_4
\]

\[
\text{Et}_3\text{N, CH}_2\text{Cl}_2 \quad \text{60% (3 steps)}
\]

\[
\text{2 HCl}
\]
Summary

• A short, practical synthesis of cermizine D has been developed. ([9 steps with cuprate addition strategy (via 21) or 16 steps using the PhSCH₂I alkylation approach (via 18)] compares favorably to Takayama’s 18-step approach.)

• Key steps in this synthesis include an organocatalyzed, heteroatom Michael addition to construct the common intermediate 4 and a sulfonealdehyde coupling/desulfurization sequence to join the two subunits.

• The common intermediate strategy provides access to over 85% of the carbon skeleton (14 of 16 carbon atoms) and both nitrogen atoms of cermizine D.