Total Synthesis of (±)-Alopecuridine and Its Biomimetic Transformation into (±)-Sieboldine A


Eric E. Buck
Current Literature
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Isolation and Background

- Alopecuridine was isolated from *L. alopecuroides* (foxtail club moss).
- There are 38 species in the genus *Lycopodiella*, which are found all over the world.
- *There is no known biological data associated with alopecuridine.*
Isolation and Background

- Sieboldine A was isolated from the club moss *L. sieboldii* collected in Kagoshima.

- Inhibits acetylcholinesterase (*IC*$_{50}$ = 2.0 μM) and is cytotoxic against murine lymphoma L1210 cells (*IC*$_{50}$ = 5.1 μg/mL. (Below: *Lycopodium Cernuum*)

Overman’s Synthesis of (+)-Sieboldine A

7 steps

1) Swern [O], 86%

2) \( N_2C(\text{COMe})P(\text{OMe})_2, K_2CO_3, \text{MeOH}, 90\% \)

(\( t\)-Bu\)_2P(\( o\)-biphenyl)AuCl, AgSbF\_6

1.1 equiv \( i\)-PrOH, CH\(_2\)Cl\(_2\) 78\%

Overman’s Synthesis of (+)-Sieboldine A

1) Ozonolysis; Me$_2$S; DBU 86%

2) 10 mol% Eu(fod)$_3$, ethyl vinyl ether, 86%

3) DIBAL-H

DMDO; BF$_3$•OEt$_2$, EtSH 53%

6 steps

sieboldine A

20 steps, 5.5 %

Kobayashi’s Proposed Biomimetic Pathway for Sieboldine A

Title Paper: Retrosynthesis

Title Paper: Synthesis of Intermediates

1) NaBH₄, CeCl₃•7 H₂O, MeOH
2) Ac₂O, Et₃N, DMAP, DCM,
97% over 2 steps

Me₃Si

BF₃•OEt₂, DCE, 58 °C
75%

N₂CHCOOEt, BF₃•OEt₂,
Et₂O, -30 °C, 55%
2) aq K₂CO₃, THF,
reflux, 75%

d.r. = 3:1

Title Paper: Addition and Epoxidation

\[
\text{Me}^-\text{d.r.} = 3:1
\]

\[
\begin{align*}
1) & \text{t-BuLi, CeCl}_3; \text{B, -78 °C} \\
2) & m-\text{CPBA, NaHCO}_3, \text{DCM, 0 °C}
\end{align*}
\]

3.5:1

66% over 2 steps

inseparable diastereoisomers

Title Paper: Semipinacol and Pinacol Rearrangement


![Chemical Reaction Diagram]

1) MOMCl
2) O₃; PPh₃
86% over 2 steps

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Title Paper: End Game Synthesis of Alopecuridine


1. \( 6 \text{ N HCl} \)
2. \( \text{Boc}_2\text{O} \) (80% over 2 steps)
3. \( \text{TPAP, NMO, 55\%} \)

alopecuridine•TFA
13 steps, 10.5\% yield

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Title Paper: Biomimetic Transformation of Alopecuridine


Summary

• Overman completed the first synthesis of (+)-sieboldine A in 20 steps (5.5% overall yield) with a key Au(I)-catalyzed cyclization and subsequent pinacol rearrangement.

• The Tu group finished the first synthesis of (+)-alopecuridine in 13 steps (10.5% overall yield) utilizing a key semipinacol rearrangement to install the 9-membered ring and a pinacol rearrangement to install the 5-membered ring.

• (+)-Sieboldine A was completed in 2 additional steps from (+)-alopecuridine via an oxidative rearrangement that also validated Kobayashi’s proposed biosynthesis.

• A natural sample of alopecuridine is no longer available and no known NMR spectroscopic data has been reported (crystal structure of acylated alopecuridine is reported). The author’s NMR data is similar to fawcettimine hydrobromide.