Expedient Synthesis of (+)-Lycopaphine A

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Lycopodium alkaloids

- **complanadine A**: stimulates nerve growth factor (NGF) production in human glial cells
- **huperzine A**: reversible inhibitor of AChE
- **huperzine G**:
- **fastigiatine**: Lycopodine-type
- **lycopodine-type**: Lycopodium alkaloids
- **miscellaneous**: Fawcettimine-type
- **lycopalhine A**:
- **lyconadin A**: cytotoxic to murine lymphoma cells (IC₅₀ = 0.46 µg/mL) & human epidermoid carcinoma KB cells (IC₅₀ = 1.7 µg/mL)
  - * stimulates NGF production in human glial cells
- **nankakurine A**:
- **phlegmarine**:
Isolated in Guizhou Province, China from *Palhinhaea cernua* along with its proposed biosynthetic precursor obscurinine.

Structure & absolute configuration determined through spectroscopic/computational methods.

- Complex hexacyclic ring system containing:
  - 1x6 + 2x5 membered carbocycles, 1x piperidine ring & 1x hexahydropyrimidine ring on a highly substituted pyrrolidine core
  - Sensitive aminal functionality + strained aldol moiety
  - 9 stereogenic centres, 8 of which are contiguous

- Weak butyrylcholinesterase (BuChe) inhibitory activity:
  - (31.4% at 50 µM) compared to Tacrine (87.8% at 33 µM, + control)

*Chem. Commun.*, **2012**, 48, 9038
The biosynthesis of lycopodium alkaloids is not well established due to difficulty cultivating *lycopodium* species in the lab.

Current insight is largely based on feeding experiments with radiolabeled precursors.

- Lysine
- Cadaverine
- Lycopodine
- Lycopodane skeleton
- Lycophaline A
Proposed Biosynthesis

obscurinine → [O] → [H] → aldol condensation →

[O] → [H] → Polonovski-type reaction →

≡ cyclization → lycopalhine A
2 total syntheses of (+)-Lycopalhine to date:

- Trauner group – published 8\textsuperscript{th} January 2016
- Fukuyama group – 7\textsuperscript{th} March 2016
Fukuyama’s Retrosynthesis

Org. Lett., 2016, 18 (6), 1494–1496
Fukuyama’s Approach

E. J. Corey and Andrew G. Myers


mild diazo transfer for 1,3-dicarbonyls
water soluble guanidine byproduct

bis-(N-t-butylsalicylaldiminato)
copper (II) catalyst
- soluble catalyst \(\rightarrow\) higher yields
on scale compared to heterogenous Cu powder

Step McCabe @ Wipf Group

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Fukuyama’s Approach

DMP, pyridine, CH$_2$Cl$_2$, rt to 40 °C

KOH, MeOH, 0 °C to rt, 98%

synthesized on 490 mg scale
Retrosynthesis

Synthesis of Core Bicycle

\[
\text{LiHMDS, THF, -78 °C} \quad \text{DIBAL (5 equiv.)} \\
\text{THF, PhMe, -78 °C}
\]

\[
\text{90%} \quad \text{83%}
\]

**anti** diastereoselectivity

1. **K₂CO₃, MeOH**
2. TBSCI, imidazole
   \[\text{CH}_2\text{Cl}_2\]
   61% (2 steps)

\[
\text{dr } C(3) \ 10:1
\]

**Ohira-Bestmann reagent**

**Pauson-Khand reaction**

\[
\text{dr } C(3) \ 10:1
\]

gram quantities
(up to 1.3 grams 1 batch)

chlorosilane accelerated conjugate addition
5-endo-trig Mannich reaction

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{Et}_3\text{N}, \text{CH}_2\text{Cl}_2 \\
\text{H} & \quad \text{Boc} \\
\text{OH} & \quad \text{Boc} \\
\text{H} & \quad \text{OH} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

Entry\(^{[a]}\) Additives (equiv) Solvent \(T [^\circ\text{C}]\) Yield\(^{[b]}\) [%]
---
1 \(\text{Yb(OTf)}_3 (1.0)\) MeCN 0–RT –
2 \(\text{TiCl}_4 (2.0)/ \text{Et}_3\text{N} (4.0)\) \(\text{CH}_2\text{Cl}_2\) –30–RT –
3 \(\text{K}_2\text{CO}_3 (3.0)\) MeOH RT –
4\(^{[c]}\) \(\text{Et}_3\text{N} (3.0)\) PhMe RT–80 –
5 \(\text{pyrrolidine} (1.0)\) DMF RT 11
6 \(\text{pyrrolidine} (1.0)/\text{AcOH} (1.0)\) DMF RT 10
7 \(\text{d-proline} (1.0)\) DMF RT 20
8 \(\text{l-proline} (1.0)\) DMF RT 60
9\(^{[c]}\) \(\text{l-proline} (0.5)\) DMF RT 39
10 \(\text{l-phenylalanine} (1.0)\) 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 \(\text{Et}_3\text{N}\).
Completion of the Synthesis via a biomimetic aldol reaction

\[
\begin{align*}
\text{Boc}_2\text{O, CH}_2\text{Cl}_2, 72 \, \text{h}, 93\% \\
1. \ \text{IBX, EtOAc, } 80 \, ^\circ\text{C} \\
2. \ \text{K}_2\text{CO}_3, \text{MeOH} \\
&98\% (2 \text{ steps}) \\
\text{biomimetic aldol}
\end{align*}
\]

\[
\begin{align*}
\text{1. OsO}_4 (0.1 \text{ equiv.}) \ \text{NaIO}_4 (10 \text{ equiv.}) \\
2,6\text{-lutidine, dioxane/H}_2\text{O} \\
\text{Lemieux-Johnson oxidation} \\
2. \ \text{TFA, CH}_2\text{Cl}_2, 0 \, ^\circ\text{C} \text{ to rt} \\
&56\% (2 \text{ steps}) \\
\text{dr C(16) 5.5: 1}
\end{align*}
\]
Deuterium exchange between C6/C15 under basic conditions + the existence of both epimers in the experimental and isolated samples suggests equilibration with a thermodynamic preference for closed aldol product.

Steps McCabe @ Wipf Group
Conclusions

- First total synthesis of lycopalhine A
- First asymmetric synthesis utilizing a chiral pool approach

![Chemical structure](image)

- Key steps:
  - Biomimetic aldol
  - 5-endo-trig organocatalytic Mannich cyclization
  - Pauson-Khand reaction

<table>
<thead>
<tr>
<th>Synthesis</th>
<th>Steps</th>
<th>Overall Yield (mixture of C(16) epimers)</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fukuyama</td>
<td>41</td>
<td>~2%</td>
<td>13.0 mg</td>
</tr>
<tr>
<td>Trauner</td>
<td>13</td>
<td>~5.7%</td>
<td>4.0 mg</td>
</tr>
</tbody>
</table>

- Application of P-K/ organocatalytic Mannich approach to other lycopodium alkaloids