Total Syntheses of (+)-Lyconadin A and (-)-Lyconadin B

Lizzie O’Bryan
June 20, 2007
Literature Group Meeting
Background

- (+)-Lyconadin A and (-)-lyconadin B were isolated by Kobayashi and coworkers in 2001 and 2006 respectively.
- Isolated from club moss *Lycopodium complanatum*.
- Lyconadin A possesses modest anticancer activity.
- Smith’s is the first reported total synthesis of these alkaloids.

Smith’s Retrosynthesis

(+)-lyconadin A, 1

(-)-lyconadin B, 2

\[
\begin{align*}
\text{Me} & \quad \text{O} \\
\text{CbzN} & \quad \text{Me} \\
\text{OTBS} & \quad \text{NNMe}_2 \\
\text{Me} & \quad \text{Me} \\
\text{OTBS} &
\end{align*}
\]
Synthesis of the Hydrazone

1. $\text{HN(Me)OMe, AlMe}_3, \text{CH}_2\text{Cl}_2, 0^\circ\text{C}$
2. $\text{TBSCI, DMAP, Et}_3\text{N, CH}_2\text{Cl}_2$

$\text{Me,CO}_2\text{H}$

$\text{Me,CO}_2\text{Me}$

$\text{Me,CO}_2\text{Me}$

$\text{Me,CO}_2\text{Me}$

Synthesis, 1973, 487
JOC, 1996, 61, 6994.
Synthesis of the Iodide
Coupling of the Hydrazone and Iodide

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\begin{align*}
\text{Me,} & \quad \text{OTBS} \\
\text{N} & \quad \text{Cbz} \\
\text{OTBS} & \quad \text{I} \\
\end{align*}
\]

\[
\begin{align*}
n\text{BuLi, HMPA} & \quad \text{THF} \\
PCC & \\
\text{HCl, DMSO} & \\
\end{align*}
\]
Synthesis of the Tetracyclic Core

1. NaBH$_4$, MeOH

2. CbzCl, EtOAc/NaHCO$_3$, CH$_2$Cl$_2$

H$_2$, Pd($\text{OH}_2$)/C, MeOH/EtOAc

HCl, MeOH/H$_2$O reflux

JACS, 1972, 94, 5003.
Synthesis of the Tetracyclic Core (cont)

1. NIS, CH₂Cl₂
2. HCl, MeOH/H₂O

1. Dess-Martin
2. Mander's reagent, LDA, HMPA, THF

1. PdCl₂, Et₃SiH, 2,6-lutidine
2. Cs₂CO₃, DMSO, rt

Mander's reagent:

JOC, 1998, 63, 5050.
JACS, 1980, 102, 4743.
End Game

Completion of (+)-Lyconadin A involved a one-pot decarboxylation, mediated by Me₄NOAc, olefin isomerization, and condensation to arrive at the natural product.

(-)-Lyconadin B was accessed in a similar fashion following hydrogenation, with LiCl used to mediate the decarboxylation.
Summary of Smith’s Synthesis

• Completed first total synthesis of (+)-Lyconadin A and (-)-Lyconadin B from a common advanced intermediate

• Key step was in the formation of the tricyclic ring system via an intramolecular aldol/conjugate addition addition cascade
Castle’s Partial Synthesis

- Envisioned forming 6 and 7 membered rings of Lyconadin A via a tandem radical cyclization.
- Explore feasibility of this approach for Lyconadin A with model system.

Model system for 7-exo-6-exo acyl radical cyclization:
Synthesis of the Model System

1. NaOH
2. NaH, PMB-Cl
   TBAI, THF

1. LiAlH₄
2. TBS-Cl, imid
3. DDQ

1. MsCl, LiBr, Et₃N
2a. NaH, DEADC, THF
   b. NaI, CH₃CN

1. NaBH₄, MeOH
2. TBS-OTf, 2,6-lutidine
   CH₂Cl₂

R = CO₂Et
R = CON(OMe)Me

R = CON(OMe)Me

MeNH(OMe)⁺HCl
⁻PrMgCl

R = CO₂Et
R = CON(OMe)Me
Synthesis of the Model System (cont)

1. CSA, 0°C
2. Swern

1. NaClO₂, NaH₂PO₄
2-methyl-2-butene

Et₃B, air, (TMS)₃SiH
PhH, rt, 93%

Proposed Pathway for Tandem Cyclization

$R_1 = \text{OTBS}, R_2 = \text{H}$
$R_1 = \text{OH}, R_2 = \text{H}$
$R_1 = \text{H}, R_2 = \text{TBS}$
Summary of Castle’s Efforts Towards Lyconadin A

- 7-exo-6-exo acyl radical cyclization provides correct stereochemistry for Lyconadin A at the methyl position, but not at the carbonyl ring junction $\alpha$ to the carbonyl.

- Tandem cyclizations with and without TBS gave a single diastereomer.