Total Synthesis of Pseudolaric Acids A and B

Literature Group Meeting
Lizzie O’Bryan
March 4, 2009
Introduction

Biological Activity:
• Pseudolaric acids A-C were isolated in 1965 from the bark of *Pseudolarix kaempferi* Gordon

• Extract from root bark of *P. kaempferi* is used as a Chinese herbal medicine called *tujinpi* for the treatment of fungal infections

• Pseudolaric acid B is a potent antifungal, antifertility, and cytotoxic agent; has shown significant activity against multi-drug resistant cancer cell lines

Structural Features:
• Highly substituted tricyclic core containing 4 contiguous stereocenters

• Trans-substituted polyhydroazulene core

• Total syntheses:
  • Pseudolaric acid A: Chiu (2006),
  • Pseudolaric acid B: Trost (2008)

Psuedolaric acid A, $R = \text{Me}$
Psuedolaric acid B, $R = \text{CO}_2\text{Me}$
Chiu’s Retrosynthesis

pseudolaric acid A

Angew. Chem. Int. Ed. 2006, 45, 6197–6201
Synthesis of the CCCC Precursor

\[ \text{Chloroalkane} \xrightarrow{\text{4 steps}} \text{PMBO-alkene-ethylsulfide} \xrightarrow{\text{1. LDA, TESCl}} \text{PMBO-alkene-methylpyruvate} \]

\[ \text{76\%, 88\% ee} \]

\[ \text{PMBO-alkene} \xrightarrow{\text{1. TBSOTf, Et$_3$SiH, Pd/C}} \]

\[ \text{LiAlH}_4 \]

\[ \text{TBAF} \]

\[ \text{PMBO-alkene-ethylsulfide} \xrightarrow{\text{1. MeO, MeO}} \text{PMBO-alkene-ethylsulfide} \xrightarrow{\text{1. Swern, 2. Pinnick}} \text{PMBO-alkene-ethylsulfide} \]

\[ \text{52\% over 7 steps} \]

\[ \text{PMBO-alkene-ethylsulfide} \xrightarrow{\text{1. iBuOCOCI, Et$_3$N}} \text{PMBO-alkene-ethylsulfide} \xrightarrow{\text{1. CH$_2$N$_2$}} \]

\[ \text{61\% over 3 steps} \]

\[ \text{PMBO-alkene-ethylsulfide} \xrightarrow{\text{1. Swern, 2. Pinnick}} \text{PMBO-alkene-ethylsulfide} \]

\[ \text{52\% over 7 steps} \]
Cyclization Cycloaddition Cascade

Completion of Pseudolaric Acid A

In summary...

- Complete first total synthesis in 29 steps
- Key steps:
  - CCCC reaction
  - Cu catalyzed catalytic asymmetric aldol reaction
  - reductive elimination
- Low diastereoselectivity (1.6:1) of CCCC reaction leaves room for improvement
Trost’s Retrosynthesis

\[ \text{[5+2] cycloaddition} \]

\[ \text{epoxidation} \]

\[ \text{cyanide addition} \]

\[ \text{isomerization} \]

Synthesis of the [5+2] Cyclization Precursor

1. TBDPSCI
2. Et₂Zn, CH₂₂, cat*
3. Swern

84% over 3 steps

1. Ru*, H₂, MeOH, CH₂Cl₂
2. TBSCI

ee > 90%, dr > 20:1

62% over 5 steps

1. DIBAL
2. TMSCHN₂, LDA, then TMSCI
3. PPh₃I₂

[5+2] Cyclization and Isomerization

Cyclization with A: 48% yield
Cyclization with B: 88% yield

A, L = CH\textsubscript{3}CN

Cyclization yield:
48% with A
88% with B

Cyclization conditions:
- 20 mol% A in acetone
- 10 mol% B in DCE

Cyclization products:

- TBSO\textsubscript{Me}H\textsubscript{OTBDPS} (48% yield)
- TBSO\textsubscript{Me}H\textsubscript{OTBDPS} (15% yield)
- TBSO\textsubscript{Me}H\textsubscript{OTBDPS} (<5% yield)

Cyclization products:

- [\text{Ru}]^{+}\text{PF}_{6}^{-}
- [\text{Rh}]^{+}\text{SbF}_{6}^{-}

Cyclization with TBAF:
- 6 equiv TBAF
- 1.0 g 3A MS/mmol
- 90%, <1:20 C:D

Cyclization with TBAF yields:
- HO\textsubscript{Me}H\textsubscript{H}OH (90%, <1:20 C:D)
Attempts to Install the C-10 Stereocenter via Cyanide Addition

Revised Retrosynthesis...
Cyclization Attempts on the Tertiary Alkoxy carbonyl Selenide

i. TMS\text{ }\rightarrow_{\text{CeCl}_2}^{(7\text{ equiv})} \text{(7 equiv)}

ii. CDI (13 equiv)

$91\%$, $dr: 8:1-12:1$

1. DDQ, buffer
2. MnO$_2$, KCN
3. TBAF

$74\%$ over 3 steps

1. DMP
2. Ac$_2$O, pyr

$92\%$ over 2 steps

LDA (7 equiv)

$72\%$ over 2 steps
Synthesis and Cyclization of Secondary Alkoxy carbonyl Selenide

1. CDI (5 equiv)  
2. PhSeSePh, NaBH₄  
   92% over 2 steps

1. Bu₃SnH, AIBN  
   90%

1. DMP  
2. TMS = CeO₂  
   62% over 2 steps

1. 1M NaOH  
2. TMSCH₂N₂  
   78%

A:B:C = 1 : 0.2 : 2.4
Synthesis and Cyclization of Secondary Alkoxy-carbonyl Selenide...Take 2
Completion of the Synthesis

In summary...

- Complete first total synthesis of psuedolaric acid B in 28 steps, 1.4% overall yield

- Key steps:
  - Rh catalyzed [5 +2] cyclization
  - regioselective isomerization to 1,3-diene with TBAF
  - radical cyclization