Total Synthesis of Phalarine

Li, C.; Chan, C.; Heimann, A.C.; Danishefsky, S.J.


*Presented by Brad Hutnick*
*April 2, 2007*
Overview

• Background
• Proposed Synthesis
• Rearrangement
• Actual Synthesis
• Summary
Phalarine
Blue Canary Grass

\textit{Phalaris coerulescens}

Found naturally in Mediterranean Europe

Short-lived perennial that can grow up to 150cm (6ft)

Circumstantial evidence that it causes acute toxicity, probably through heart failure, in horses

\textit{Information from the Department of Primary Industries, Victoria, Australia}
Biosynthetic Proposal

\[ \text{N-methyl-\(\beta\)-carboline} \]

\[ \text{Gramine Derivative} \]
Biomimetic Synthesis

Biomimetic Synthesis Summary

• The normal reactivity of the carboline needed to be overcome in order to achieve the right regioisomeric product.

• Under the reaction conditions, the “natural bias” could not be overcome.

• Even if nature uses this route, it appears to not be viable for this synthesis, and was abandoned.
New Synthetic Approach

• Ring-expansion of an azaspiroindolenine
Rearrangement Mechanism

Steps:
1. Initial structure
2. Protonation
3. Ring expansion
4. Rearrangement

Leads to a racemic product

Should be stereospecific
Rearrangement Mechanism

>95% ee
Racemic
Total Synthesis

1. TFA, CH₂Cl₂, 0°C, 98%
2. CSA, PhMe, 130°C, 72%

Zn dust, AcOH 88%

A
Fischer Indole Synthesis

A \xrightarrow{\text{NaNO}_2, \text{aq. HCl, } -5 \degree C} [\text{Japp-Klingemann}] \xrightarrow{\text{aq. KOH, EtOH, } -5 \degree C, 81\%} B

B \xrightarrow{\text{TsOH, PhMe, } 80 \degree C} <5\%
Gassman Indole Synthesis

1. MeSCH₂CO₂Et, SO₂Cl₂, CH₂Cl₂, -78 °C
2. A, proton sponge, CH₂Cl₂, -78 °C
3. Et₃N, CH₂Cl₂, -78 °C to RT
Completion of Synthesis

1. BH₃ · THF, 0 °C
2. Raney-Ni, EtOH, 90%

Phalarine
Summary

• Racemic phalarine was synthesized in 10 steps.
• The key step was the rearrangement of the azaspiroindolenine to the phalarine precursor.
• Additional work is needed to make the rearrangement and synthesis enantioselective.