A Synthesis of Alsmaphorazine B Demonstrates the Chemical Feasibility of a New Biogenetic Hypothesis

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1 and 2 isolated in 2010 by McRita and co-workers
1 inhibits in vivo nitric oxide production
2 does not show such behavior

The Biogenesis Hypothesis/Retrosynthetic Analysis
1,3 dipolar addition
to the α,β-unsaturated ketone

Is this proposed biosynthesis reasonable?
Need lots of akuammicine 5 for study!

Jacob Ishibashi | The Liu Research Group | Boston College | June 10, 2015
**Forward Synthesis**

Tryptamine

\[
\text{NaBH}_4, \text{MeOH} \quad \text{reduction} \quad \text{Reductive Amination Product}
\]

\[
\begin{align*}
\text{tryptamine} & \xrightarrow{\text{MeO, phenyl ketone}} \text{amine, imine formation} \\
& \xrightarrow{\text{NaBH}_4, \text{MeOH}} \text{reductive amination product}
\end{align*}
\]

**Preparation of compound 8: Zincke Reaction**

\[
\begin{align*}
\text{Nitroaromatic} & \xrightarrow{\text{HNMe}_2} \text{an aminal} \\
& \xrightarrow{\text{PT}} \text{Hydrolysis} \quad \text{84%}
\end{align*}
\]

\[
\begin{align*}
\text{Me}_2\text{N} & \xrightarrow{\text{PT}} \text{87%}
\end{align*}
\]
**Anionic Cyclizations: in the style of Markô (9 to 10)**

The reaction involves the following steps:
1. KOt-Bu, 80 °C
2. NaClO₂, NaH₂PO₄, t-BuOH, H₂O
3. Mel, DBU, MeCN

**Stereochemistry:**
syn-6/5 fusion is less strained than anti-6/5 fusion.

**Basic conditions:** Isomerize the olefin to conjugate with aldehyde, then aqueous workup provides 10.

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**Pinnick Oxidation (10 to 11)**

The reaction pathway involves:
1. Addition of H₂O₂ to the aldehyde
2. Formation of the cyclic peroxide
3. Ring opening with HOCl

In the present case, sodium phosphate monobasic acts both as a proton source to initiate the reaction and a proton sink for the acidic byproduct.
Oxidative Cleavage of PMB protecting group (11 to 12)

5, akuammicine 99%

All steps gram scale, 39% overall yield not counting synthesis of 8
Dihydroxylation Reaction (5 to 14)

Osmium is re-oxidized by N-methylmorpholine-N-oxide. Citric acid is a ligand for osmium, which accelerates the reaction.

Dess-Martin Oxidation (5 to 14)

Reduction with samarium diiodide (14 to 15/16)

Protonation and Tautomerization
Conditions tried from 20 to 2:
\( m\text{-CPBA, DMDO} \)

LiHMDS
\(-78\, ^\circ\text{C to RT} \)

\[ \text{15/16} \]

\[ \text{17/18} \text{ not isolated} \]

\[ \text{19} \]

\[ \text{20} \text{ 49\%, 3 steps} \text{ [X-ray Structure]} \]

\[ \text{21} \text{ 29\%, 3 steps} \]

\[ \text{2, alsamaphorazine B} \text{ 82\%} \text{ [X-ray Structure]} \]

"15 steps"
not counting synthesis of Zincke aldehyde
10.6\% overall yield
Heck Reaction (13 to 5)

Classic Heck Reaction

Base + HBr

R = Br

L_nPd^0

Oxidative Addition

L_nPd - Br

Base

L_nPd - Br

Hydride Elimination

R' - R

β-Migratory Insertion

bond rotation necessary to achieve syn-coplanar geometry for β-hydride elimination

In Hong and Vanderwal's example, the only syn-coplanar hydrogen is not on the carbon to which the coupling partner has bonded.