An Interdisciplinary Approach to the Synthesis and Biosynthesis of Biologically-active Polycyclic Natural Products

**Project 1:** loline alkaloids

\[
\text{Me} \quad \text{NH} \\
\text{H} \quad \text{N} \quad \text{O} \\
\text{N} \quad \text{O} \\
\text{N} \quad \text{H}
\]

\[
\text{NHMe} \\
\text{O} \\
\text{N} \\
\text{Me}
\]

\text{insecticidal insect anti-feedant}

\text*{lloline}

**Project 2:** diketopiperazines

\[
\text{HN} \quad \text{CO} \\
\text{HN} \\
\text{CO}
\]

\text*{diketopiperazine (DKP)}

\text{(+)-serantrypinone natural insecticide}

\text{[2.2.2]-diazabicyclic core}

\text*{malbrancheamide B calmodulin inhibitor}

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[2.2.2]-Diazabicyclic Diketopiperazine Natural Products

(-)-brebianamide A
antithelmintic

diketopiperazine
(cyclic dipeptide)

(+)-stephadacin A
anticancer

[2.2.2]-diazabicyclic core

(+)-malbrancheamide B
calmodulin inhibitor

Isolated from Malbranchea aurantiaca

Penicillium thmicola

(+)-serantripinone
natural insecticide
[2.2.2]-Diazabicyclic Diketopiperazine Natural Products

Proline-Tryptophan DKP

(-)-brevianamide A antihelmintic

[2.2.2]-diazabicyclic core

biogenic Diels-Alder cycloaddition

diketopiperazine azadiene

not synthetically feasible

endo selective (ca. 8:1)

not synthetically feasible

endo selective (ca. 8:1)
[2.2.2]-Diazabicyclic Diketopiperazine Natural Products

(-)-brevianamide A antithelminic

[2.2.2]-diazabicyclic core

biogenic Diels-Alder cycloaddition

diketopiperazine azadiene

Proline-Tryptophan DKP

\[
\text{[4+2]}
\]

toluene 110 °C

\[
\begin{align*}
\text{[endo transition state]} \\
\text{minimized: approach of dienophile anti to t-butyl aminal}
\end{align*}
\]

X-ray structure
[2.2.2]-Diazabicyclic Diketopiperazine Natural Products

(-)-brevianamide A
antihelmintic

[2.2.2]-diazabicyclic core

biogenic Diels-Alder cycloaddition

diketopiperazine azadiene

Proline-Tryptophan DKP

(–)-brevianamide A
antihelmintic

[2.2.2]-diazabicyclic core

biogenic Diels-Alder cycloaddition

diketopiperazine azadiene

Proline-Tryptophan DKP

Both electron deficient and
electron rich dieneophiles
Excellent facial selectivity
9 examples
up to 77% yield

Recently published with Katherine Nenninger and Erin Morris:
We recently completed a synthesis of the loline alkaloids:


R

<table>
<thead>
<tr>
<th>R¹</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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</thead>
<tbody>
<tr>
<td>Me</td>
<td>loline</td>
<td>norloline (temuline)</td>
<td>acetylnorloline</td>
<td>formylnorloline</td>
</tr>
<tr>
<td>H</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Ac</td>
<td>3</td>
<td>4</td>
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</tr>
<tr>
<td>CHO</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>
Synthesis and Biosynthesis of Loline Alkaloids

\[ \text{tethered amino-hydroxylation} \]

1) MsCl, pyr
2) CbzCl, NEt\(_3\)

MeOH, Cs\(_2\)CO\(_3\)

\( X\)-ray

loline skeleton established
Synthesis and Biosynthesis of Loline Alkaloids

This first-generation synthesis was recently published:
with M. Todd Hovey, Emily Eklund, Anshul Mainkar; Organic Letters, 2011, 13, 1246.
Biosynthesis of Lolines and Other Pyrrolizidine Alkaloids

Last Known Biosynthetic Intermediate

\[
\begin{align*}
&\text{Cultured Fungal Strain} \\
&\xrightarrow{\text{Isotopic Labels}} \\
&\text{Loline skeleton} \\
&\xrightarrow{>5\% \text{ isotope incorporation}} \\
&\text{pyrrolizidine skeleton}
\end{align*}
\]

Isotopic Labels

- C7 oxidation
- C2 oxidation

absouline

\[
\begin{align*}
\text{This has been made during the synthesis of acetylnorloline} \\
(\text{See: OL 2011})
\end{align*}
\]

Possible Biosynthetic Intermediate:
- C7 hydroxyaminopyrrolizidine

R = H, Ac