Strategies in the Construction of Class III Galbulimima Alkaloids

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Chem 535
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Isolation of Galbulimima Alkaloids

• Discovered in the bark of Galbulimima belgraveana in 1948 by Webb
• In 1965, 28 congeners were isolated (22 structures determined) by Binns
• Mander group has determined 5 structures and isolated 2 more alkaloids

Three Classes of Galbulimima Alkaloids

Class I

Class II

Class III

<table>
<thead>
<tr>
<th>Alkaloid</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
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<tr>
<td>himandrine</td>
<td>OBz</td>
<td>OMe</td>
<td>H</td>
<td>OH</td>
</tr>
<tr>
<td>himbosine</td>
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<td>OCOPh</td>
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G.B. 13

G.B. 16

Himbacine

Himgravine

G.B. 13

Himgaline
Himbacine

- Most well studied (6 syntheses)
- Chackalamannil in 1996 provided efficient route to racemic himbacine (12 steps, 9.7% overall yield)
- Discovered ent-himbacine was potent protease activated receptor 1 (PAR-1) antagonist
- Structure activity relationship (SAR) studies led to discovery of SCH 530348 (now known as Vorapaxar), currently in Phase III clinical trials for acute coronary syndrome

Himbacine in Alzheimer’s Disease

• Himbacine and its derivatives are looked at as treatment for Alzheimer's Disease
• Alzheimer’s is often associated with loss of cholinergic function
• Potent antagonist of muscarinic M₂ subtype receptor

Three Classes of Galbulimima Alkaloids

Early Syntheses of G.B. 13:

- **Mander (2003)**
  a. 30 steps
  b. 0.2% overall yield

- **Chacklamannil (2006)**
  a. 31 steps
  b. 0.5% overall yield

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Syntheses of Class III G.B. Alkaloids

Movassaghi (2006)

Evans (2007)

Ma (2010)

Sarpong (2009)

Himaline
Construction of the Aldehyde

Construction of the Aldehyde

Synthesis of G.B. 13

Synthesis of G.B. 13

1. $\text{Et}_3\text{N} \cdot \text{(HF)}_3$ in THF, 19 steps, 1.7% overall yield

2. $\text{ClCO}_2\text{Bn}$, Na$_2$CO$_3$, H$_2$O, CH$_2$Cl$_2$, 65%, 19 steps, 1.7% overall yield

3. IBX, TsOH·H$_2$O, DMSO, benzene, 65°C, 80%

4. TMSI, CH$_2$Cl$_2$, 0°C, 89%

CDE Ring Moiety

Class I

Himbacine

Class II

Alkaloid | R¹ | R² | R³ | R⁴
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Class III

G.B. 13

Himgaline

G.B. 16
Formal [3+3] Cycloaddition

Evans’ Synthesis of G.B. 13 and Himgaline

Movassaghi (2006)

Ma (2010)

Sarpong (2009)

Evans (2007)
Construction of Decalin Ring

Construction of Decalin Ring

Synthesis of ent-G.B. 13

Synthesis of ent-G.B. 13

Synthesis of ent-G.B. 13

Synthesis of *ent*-G.B. 13

Synthesis of ent-Himgaline

- Previously observed 16-oxohimgaline in acidic workup of G.B. 13
- Proposed biosynthesis of himgaline is a conjugate addition of the amine followed by reduction of the ketone
- Evans used acetic acid to push the equilibrium to 16-oxohimgaline and borohydride reduction

Sarpong’s Synthesis of G.B. 13

Movassaghi (2006)

Ma (2010)

Sarpong (2009)

Evans (2007)

Himgaline
Installation of the Pyridine Surrogate

Rhodium-Catalyzed Hydroarylation

Synthesis of G.B. 13 via Late Stage Pyridine Reduction

Ma’s Synthesis of G.B. 13 and G.B. 16

Movassaghi (2006)

Ma (2010)

Evans (2007)

Sarpong (2009)

Himgaline
AB Ring Building Block

DE Ring Building Block

Late-Stage Intermediate

1) LDA, TMSCl, THF, -78°C
2) TiCl₄, CH₂Cl₂, -78°C, 88%

1) IBX, DMSO, 70°C
2) DBU, CH₂Cl₂, 84% (two steps)

Pd/C, H₂, iPrOH, 97%

DMP, NaHCO₃
CH₂Cl₂, 99%
Synthesis of G.B. 13

Synthesis of G.B. 13

19 steps
6.1% overall yield
Synthesis of G.B. 16

Synthesis of G.B. 16

19 steps
5.5% overall yield

Construction of the AB Rings
Construction of the C Ring

Movassaghi

Evans

Sarpong

Ma
Construction of the DE Rings

Movassaghi

Evans

Sarpong

Ma

Chemical structures and reactions are shown for each author's approach to constructing the DE rings.
## Summary

<table>
<thead>
<tr>
<th>Key Features</th>
<th>Movassaghi</th>
<th>Evans</th>
<th>Sarpong</th>
<th>Ma</th>
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<tr>
<td>Steps</td>
<td>19</td>
<td>31</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>Overall Yield</td>
<td>1.7%</td>
<td>1.0%</td>
<td>1.2%</td>
<td>6.1%</td>
</tr>
<tr>
<td><strong>Key Features</strong></td>
<td><strong>“Transient-δ-imino ketone” strategy led to the development of the formal [3+3] cycloaddition</strong></td>
<td><strong>Chiral auxiliary to form AB rings via enantioselective Diels-Alder</strong></td>
<td><strong>Unprecedented rhodium catalyzed hydroarylation of a ketone</strong></td>
<td><strong>Convergent synthesis with the flexibility of two equally complex building blocks</strong></td>
</tr>
<tr>
<td></td>
<td>• Determined the absolute stereochemistry of G.B. 13</td>
<td>• Describes the synthesis of himgaline from G.B. 13</td>
<td>• Pyridine ring used as mask for piperidine ring</td>
<td>• Enables access to two additional G.B. alkaloids: G.B. 16 and Himandrine</td>
</tr>
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Future Directions

- Biological studies of G.B. 13, G.B. 16, and himgaline
- Derivatization of these natural products
- SAR studies to find new drug candidates

![GB13 structure](image-url)
Acknowledgements

Professor Burke
Burke Group
Professor Hergenrother
Chem 535 Class

...and everyone here
Roskamp Reaction
Flash Vacuum Pyrolysis

- Syringe
- 24/40 rubber septum
- Heating tape
- Quartz tube
- Dewar
- Ball and socket joints
- To vacuum
- 600 °C
Allylic Transposition
Chiral Imine Michael Addition
Mukaiyama Michael Addition

1) LDA, TMSCl, THF, -78°C
2) TiCl₄, CH₂Cl₂, -78°C, 88%