Total Synthesis of Resveratrol-Based Natural Products & Nucleophilic Carbene and HOAt Relay Catalysis in an Amide Bond Coupling

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Resveratrol

- A phytoalexin (antibiotics) produced naturally by several plants when under attack by bacteria or fungi.

- *In vivo* and *in vitro* activity against inflammation, heart disease, aging, and cancer.

- Found in the skin of red grapes and is a constituent of red wine (~ 100µM).

- Absent in white wine and grape juice.

- Popular notion: it is supporter of “French Paradox”.

  *(the observation that the French suffer relatively low incidence of coronary heart disease, despite having a diet relatively rich in saturated fats.)*
Resveratrol-Based Natural Products

1: resveratrol

2: ampelopsin D

3: pallidol

4: ampelopsin F

5: vaticanol C

6: hopeaphenol

7: paucifloral F

8: diptoindonesin A
Earlier Approaches

Niwa et al., Tetrahedron 2005, 61, 10285
Earlier Approaches

![Chemical Structures]

**Table 2.** Diversity of the products obtained by the treatment of resveratrol (1) with peroxidases

<table>
<thead>
<tr>
<th>Origins of peroxidases</th>
<th>Solvent</th>
<th>11 (%)</th>
<th>12 (%)</th>
<th>20 (%)</th>
<th>21 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Glycine max</em></td>
<td>aq Acetone</td>
<td>21.4</td>
<td>7.2</td>
<td>1.8</td>
<td>—</td>
</tr>
<tr>
<td><em>Arthromyces ramosus</em></td>
<td>aq Acetone</td>
<td>18.4</td>
<td>7.4</td>
<td>4.6</td>
<td>—</td>
</tr>
<tr>
<td>Horseradish</td>
<td>aq Acetone</td>
<td>12.6</td>
<td>10.2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><em>Glycine max</em></td>
<td>aq EtOH</td>
<td>12.1</td>
<td>9.5</td>
<td>5.2</td>
<td>8.6</td>
</tr>
<tr>
<td><em>Arthromyces ramosus</em></td>
<td>aq EtOH</td>
<td>13.1</td>
<td>5.0</td>
<td>4.6</td>
<td>8.2</td>
</tr>
</tbody>
</table>

The percentage in this table means the ‘degree of transformation (%DT)’. See Section 3.

**Low yields and Low selectivity**

*Niwa et al., Tetrahedron 2005, 61, 10285*
Earlier Approaches

Hou et al., ACIEE 2006, 45, 7609
Solution to Chemoselectivity Problem

1: resveratrol

Direct oligomerization

2: amapelopsin D

3: pallidol

Snyder et al. ACIEE 2007, 46, 8186
Solution to Chemoselectivity Problem

Hypothesis: Tri-aryl precursors can be lead to every family member (may be by altering the reagents and reaction conditions).

Snyder et al. ACIEE 2007, 46, 8186
Total Synthesis of Paucifloral F

9 \( \xrightarrow{\text{a) \( nBuLi \)}} \) 10 \( \xrightarrow{\text{MeO}} \) 11 \( \xrightarrow{\text{acid source, \(-78 \rightarrow -20^\circ \text{C}\)}} \) 12

7: Paucifloral F

c) [O] \( \xrightarrow{\text{overall yield}} \) 84%

d) \( \text{BBr}_3 \) 15 \( \xrightarrow{\text{quench with \( K_2\text{CO}_3, \text{MeOH} \)}} \) 14

acid = TFA
Total Synthesis of Ampelosin D & Isoampelophsin D

1. Reaction with nBuLi: 9 → 10
2. Reaction at -78 → -20 °C: 10 → 11 → 12
3. Base treatment: 12 → 13
4. Acid treatment: 13 → 16
5. HCl, MeOH, 80 °C: 16 → 2: ampelosin D

17: isoampelophsin D
Total Synthesis of quadrangularin A and Isopaucifloral F

Snyder et al. ACIEE 2007, 46, 8186
Total Synthesis of Pallidol

Permethylated Quadrangularin A

Why not H⁺ as the activating electrophile?
What is the role of Br ?

Snyder et al. *ACIEE* 2007, 46, 8186
Total Synthesis of Ampelopsin F

Permethylated Ampelopsin D

[Br2 →]

[Friedel–Crafts alkylation, 53%]

4: ampelopsin F

Snyder et al. ACIEE 2007, 46, 8186
Total Synthesis of analogue of Hemsleyananol E

Snyder et.al. ACIEE 2007, 46, 8186
Total Synthesis of analogue of Hemsleyanol E

Snyder et al. *ACIEE* 2007, 46, 8186
Nucleophilic Carbene and HOAt Relay Catalysis in an Amide Bond Coupling

- Conventional amide bond formation utilizes acids and amines as coupling partners and relies on stoichiometric activating agents for the acid functionality.
- Only two amines are reported so far for catalytic amidation using NHCs as catalyst.

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>4-aminobenzene</td>
<td>24</td>
<td><img src="image" alt="Product" /></td>
<td>91</td>
</tr>
</tbody>
</table>

Reaction and its Proposed Catalytic Cycle

\[ \text{1-hydroxy-7-azabenzotriazole} \]

Carbene Mechanism

**Amine and α-haloaldehyde Substrate Scope**

![Chemical Structures](image)

*Figure 1.* α-Haloaldehyde substrate scope.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Yield (%)</th>
<th>Entry</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>89</td>
<td>6</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>85</td>
<td>7</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>73</td>
<td>8</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>89</td>
<td>9</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>72</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Atom-Economical Amidation

Table 2. Atom-Economical Amidation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(+)-6a</td>
<td>7a Me</td>
<td>86&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&gt;19:1</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>7b Me</td>
<td>75&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15:1</td>
</tr>
<tr>
<td>3</td>
<td>(+/-)-6b</td>
<td>7c Me</td>
<td>72&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&gt;19:1</td>
</tr>
<tr>
<td>4</td>
<td>EtO&lt;sub&gt;2&lt;/sub&gt;C</td>
<td>7d</td>
<td>80&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>7e</td>
<td>82&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
</tr>
</tbody>
</table>

Base is used in catalytic Amount

Proof of Mechanism: Use of Chiral Carbenes

\[
\begin{align*}
\text{PhCH}_{2}\text{Cl} + \text{HOAt (20 mol%), DABCO (1.1 eq)} & \rightarrow \text{PhCH}_{2}\text{NHCl} \\
\text{PhMe (0.05 M), PhCH}_{2}\text{NH}_{2} & \text{23 °C, 24 h} \\
\text{62% yield} & \text{80% ee}
\end{align*}
\]

\[
\begin{align*}
\text{C}_{6}\text{H}_{5}\text{BrCHO} + \text{HOAt (20 mol%), DABCO (1.4 eq)} & \rightarrow \text{C}_{6}\text{H}_{5}\text{NHMeCH}_{2}\text{Me} \\
\text{CH}_{2}\text{Cl}_{2} (0.03 \text{M), 23 °C} & \text{40 % yield} \text{<2% ee}
\end{align*}
\]

Earlier Approaches

a) CH$_3$OH, H$_2$SO$_4$, reflux; b) PhCH$_2$Br, K$_2$CO$_3$, DMF, RT; c) LiAlH$_4$, Et$_2$O, RT; d) SOCl$_2$, Et$_3$N, benzene, 0°C→RT; e) PPh$_3$, xylene, reflux; f) Br$_2$, tert-butanol, RT; g) nBuLi, toluene, RT→reflux; h) AlCl$_3$, PhNMe$_2$, CH$_2$Cl$_2$, 0°C
Synthesis of resveratrol

1) cat. Pd(dba)$_2$, KF, $n$-Bu$_4$NCl
toluene, room temperature

2) removal of CH$_2$=CHSiMe$_3$ excess

3) K$_2$CO$_3$, DMF, 70 °C

Synthesis of resveratrol

Synthesis of resveratrol