Synthesis of the Stenine Ring System from Pyrrole

Bates, R. W.; Sridhar, S.
The Stemonaceae family is still the only source of the *Stemona* alkaloids

The *Stemona* alkaloids are:

• structurally characterized by the presence of the pyrrolo[1,2-a]azepine core and pyrido[1,2-a]azepine core

• currently comprises 139 alkaloids

The *Stemona* alkaloids can be organized into eight groups:

• stenine (I),
• stemoamide (II),
• tuberostemospironine (III),
• stemonamine (IV),
• parvistemoline (V),
• stemofoline (VI) (all of which contain the pyrrolo[1,2-a]azepine core)

• stemocurtisine (VII) displaying the pyrido[1,2-a]azepine nucleus,
• miscellaneous group


(±)-Stenine

EtAlCl₃, CHCl₃, 85 °C

intramolecular Diels-Alder reaction

1. Mesytilene, Δ
2. MeOH

Curtius rearrangement

ring D: Claisen–Eschenmoser rearrangement and iodolactonization
ring B: intramolecular lactam formation
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ring B: intramolecular lactam formation

(-)-Stenine

1. MCPBA, hexane, DCM, -15 °C-rt
2. $\text{H}_2\text{IO}_6$, THF, H$_2$O, rt
$I_2$, NaHCO$_3$, rt

ring B: intramolecular nitrogen alkylation
Frankowski, K. J.; Golden, J. E.; Zeng, Y.; Lei, Y.; Aube, J. *J. Am. Chem. Soc.* **2008**, *130*, 6018

(-)-Stenine

![Chemical Reaction Diagram](https://example.com/chemical_diagram.png)

Tandem Diels-Alder/Schmidt reaction

ring D: iodolactonization

(±)-Neostenine

ring C / D:

ring A / B:
intramolecular [4+2] cycloaddition rearrangement cascade reaction
The *Stemona* alkaloids are attractive synthetic targets due to the diversity of structures found in this family of alkaloids.

Recently, it has been reported that neostenine, a stereoisomer of stenine, has antitussive activity comparable to that of codeine.

Using pyrroles in natural product synthesis is challenging:
• highly electron-rich nature of the pyrrole ring promote certain productive reactions, but it can also cause some problems.

Additional synthetic strategies has been used to construct the pyrrole moiety in pyrrole-containing natural products.
McMillan’s catalyst
THF, -20 °C

NaBH₄, EtOH, rt
75%, 95% ee (two steps)
i) 1) (CF₃CO)₂O, Et₂O, rt, 83%; 2) ICl, DCM, rt, 88%
ii) 1) PVP, MeOH, rt, quant.; 2) TBSCl, imidazole, DCM, rt, quant.

i) 1) CCl₃COCl, Et₂O, rt, 95%; 2) ICl, DCM, rt, 90%
ii) 1) NaOMe, MeOH, rt, 90%; 2) TBSCI, imidazole, DCM, rt, 80%
CBr₄, PPh₃, CaCO₃: 60%
CBr₄, PPh₃, Et₃N: no reaction

Ambrelyst-15, MeOH, 14h, rt: 0%
PPTS, MeOH, 10h, rt: 0%
TBAF, THF, 14h, rt: 48% corresponding fluoride

no diastereoselectivity using zinc (Zn)
slight improvement with stannous chloride (SnCl₂)
Possible Mechanism of Ruthenium-Catalyzed Cyclocarbonylation

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**Cyclocarbonylation of Allenol - Ru$_3$(CO)$_{12}$, CO**

<table>
<thead>
<tr>
<th>reagent and solvent</th>
<th>catalyst loading / mol%</th>
<th>yield of butenolid (%)</th>
<th>yield of enone (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>dioxane, Et$_3$N (6 eq)</td>
<td>4</td>
<td>40</td>
<td>30$^a$</td>
</tr>
<tr>
<td>Et$_3$N (neat)</td>
<td>4</td>
<td>20</td>
<td>40$^b$</td>
</tr>
<tr>
<td>2,4,6-collidine (neat)</td>
<td>4</td>
<td>50</td>
<td>5$^c$</td>
</tr>
<tr>
<td>dioxane, collidine (6 eq)</td>
<td>4</td>
<td>68</td>
<td>14$^c$</td>
</tr>
</tbody>
</table>

$^a$ A ca. 2:1 mixture of E/Z isomers. $^b$ A ca. 10:1 mixture. $^c$ One isomer.
CONCLUSION

Additional contribution to the synthesis of the stemona alkaloids using an new synthetic approach

The high electron density of the pyrrole ring can complicate some reactions but can be controlled by using the trifluoroacetyl group, that can easily and rapidly be removed.