Versatile Construction of 6-Substituted *cis*-2,8-Dioaxabicyclo[3.3.0]octan-3-ones: Short Enantioselective Total Synthesis of Cheloviolenes A and B and Dendrillolide

Yuriy Slutskyy, Christopher R, Jamison, Peng Zhao, Juyeol Lee, Young Ho Rhee, and Larry Overman
University of California, Irvine and Pohang University of Science and Technology

Total Synthesis Presentation
Sophia Staerz
Background:

• Class of rearranged diterpenoids
  • Large group isolated in marine sponges
• Have a *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one ring system
• Structural subtypes differ in whether the hydrocarbon fragment resides on the concave or convex face
  • Cheloviolene A is on the convex face

![Cheloviolene A](image1.png)

![cis-3,8-dioxabicyclo[3.3.0]octan-3-one](image2.png)
Biological Activity

- Diterpenoids effect the structure of the Golgi apparatus
  - Most block protein transport from the Golgi apparatus to the plasma membrane
  - Norrisolide induces irreversible fragmentation and delocalization of Golgi membrane throughout the cytosol
  - Thought that diterpenoids react with primary amines, like in lysine side chains in a class of enzymes, to form pyrroles- which could account for the Golgi apparatus effects observed

![Norrisolide](image.jpg)
cheloviolene A

cheloviolene B
Retro-Synthesis
Synthesis of 3-chloro-5-alkoxybutenolide
Synthesis of 3-chloro-5-alkoxybutenolide

\[
\begin{align*}
&\text{Cl} = \text{OH} + \text{O} \\
&\text{HG-II} \quad \text{toluene, 60 °C} \\
&\text{92%} \\
&\text{CrO}_3, \text{ pyridine} \\
&\text{t-BuOOH, toluene, rt} \\
&\text{32%}
\end{align*}
\]
Starting Material Synthesis: Allene

\[ \text{OH} \xrightarrow{\text{propargyl bromide, THF, 70 °C}} \text{O} \xrightarrow{\text{KO\textsubscript{t}Bu, THF, 40 °C}} \]

67%
Synthesis of cis-perhydroazulene tertiary radical

(-)-fenchone

1. NH₂OH
2. H₂SO₄ (aq)

33%

Diisobutyl Aluminum Hydride

meta-Chloroperoxybenzoic Acid

KHMD, THF, 23 °C

87%

81%
Synthesis of cis-perhydroazulene tertiary radical

\[
\text{CN} \xrightarrow{\text{LiTMP, THF, 60 °C}} \text{CN} \xrightarrow{\text{Raney-Ni, H}_2 (50 \text{ atm})} \text{Me}_2\text{N} \xrightarrow{3:1 \text{MeOH}/\text{AcOH, 70 °C}} \text{OH}
\]

85%

\[
\text{OH} \xrightarrow{\text{m-CPBA, K}_2\text{CO}_3, \text{DMF, 120 °C}} \text{OH}
\]

Lithium tetramethylpiperidide
Radical Coupling

\[ \text{OH} \xrightarrow{\text{i. oxalyl chloride}} \text{THF, rt} \xrightarrow{\text{ii. H}_2\text{O, K}_2\text{HPO}_4} \]

(1 equiv)

Ir cat. (2 mol%)
60 °C, 34 W Blue LEDs; add \( n\text{-Bu}_3\text{N} \)
Single Electron transfer = SET
Final Steps to (+)-Cheloviolene A

[Chemical structural diagrams and reactions]

Lithium tetramethylpiperidide

Hexamethylphosphoramide

Pyridinium Chlorochromate
Synthesis of Cheloviolene B

\[ \text{OH} \xrightarrow{\text{i. oxalyl chloride, THF, rt}} \xrightarrow{\text{ii. } \text{H}_2\text{O, } \text{K}_2\text{HPO}_4} (1 \text{ equiv}) \xrightarrow{\text{Ir cat. (2 mol%)}} \text{60 °C, 34 W Blue LEDs; add } n\text{-Bu}_3\text{N} \]

Same Steps as Cheloviolene A

62%
Thank you!
Mechanism:

Palladium goes through a ligand exchange:
Mechanism: