Proposed Synthesis of Madurastatin D2

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Biological Relevance of Madurastatin B2

- Madurastatin B2 is a phenolate-hydroxamate siderophore isolated from *Actinomadura sp*.
  - Siderophores are metabolites used by bacteria and plants to sequester iron.
  - Iron is abundant but mostly insoluble and inaccessible to life.
  - Siderophores overcome this challenge and increase fitness.
- Madurastatin B2 has demonstrated biological activity against MRSA and *B. subtilis*.

Convergent Synthesis to Madurastatin B2

Scheme 1. Proposed Convergent Synthesis of Madurastatin D2

madurastatin D2 = fragment 1 + fragment 2
Proposed Retrosynthesis of Fragment 1

Scheme 2. Proposed Retrosynthesis of Fragment 1
Proposed Retrosynthesis of Fragment 2

Scheme 3. Proposed Retrosynthesis of Fragment 2

fragment 2
Starting Materials for Fragment 1

Cyclization to Oxazoline Moiety

Condensation Reactions to Fragment 1
Starting Reagents for Fragment 2

\[
\text{H}_2\text{N}\quad\text{O} \quad \xrightarrow{\text{BOC}_2\text{O} (1\text{ equiv})} \quad \text{H}_2\text{O}, \text{rt}, 6\text{ h}
\]

\[
\text{H}_2\text{N}\quad\text{NH}_2
\]

\[
\text{H}_2\text{N}\quad\text{HN} \quad \text{O} \quad \text{O}
\]
Hydroxamine Formation

$N$-Acylation and Methylation via Ru Catalyst

Protection of Carbonyl
Synthesis of Lactam
Synthesis of Fragment 2

\[
\begin{align*}
\text{substrate} & \xrightarrow{\text{choline peroxydisulfate (1.1 equiv.)}} \text{neat, rt, 1 h} & \xrightarrow{\text{HCl}} & \text{fragment 2}
\end{align*}
\]
Synthesis of Madurastatin D2

[Chemical reaction diagram]