Proposed Synthesis of Madurastatin D2

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CEM 852

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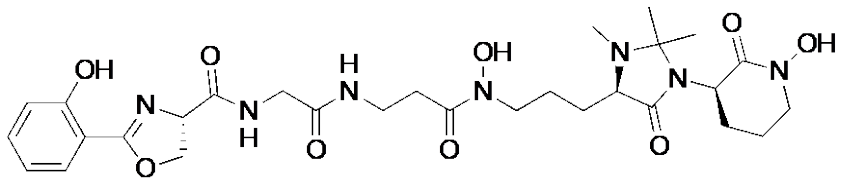
Biological Relevance of Madurastatin B2

- 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.*

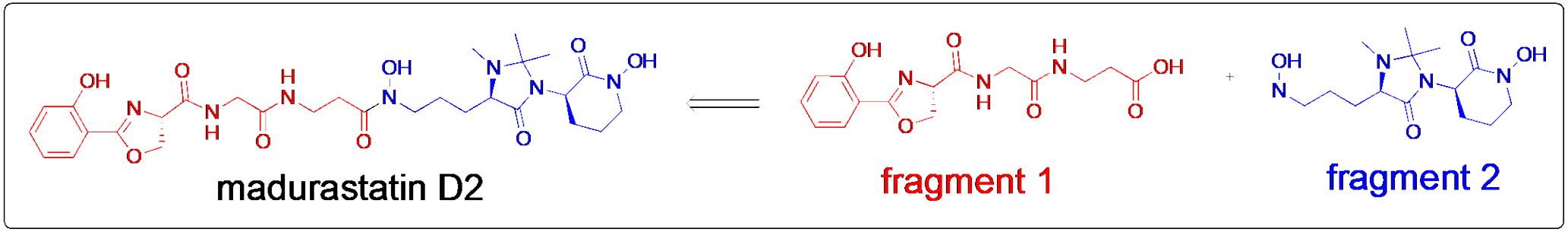


madurastatin D2

Yan, J.-X.; Chevrette, M. G.; Braun, D. R.; Harper, M. K.; Currie, C. R.; Bugni, T. S. Madurastatin D1 and D2, Oxazoline Containing Siderophores Isolated from an Actinomadura Sp. *Organic Letters* **2019**, *21* (16), 6275–6279.

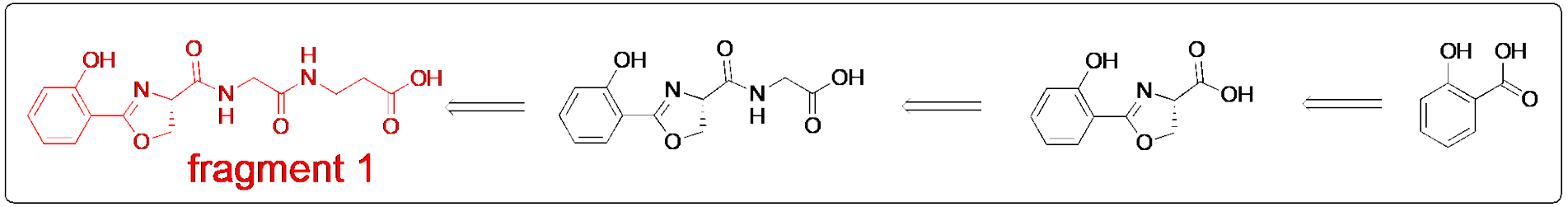
Convergent Synthesis to Madurastatin B2

Scheme 1. Proposed Convergent Synthesis of Madurastatin D2



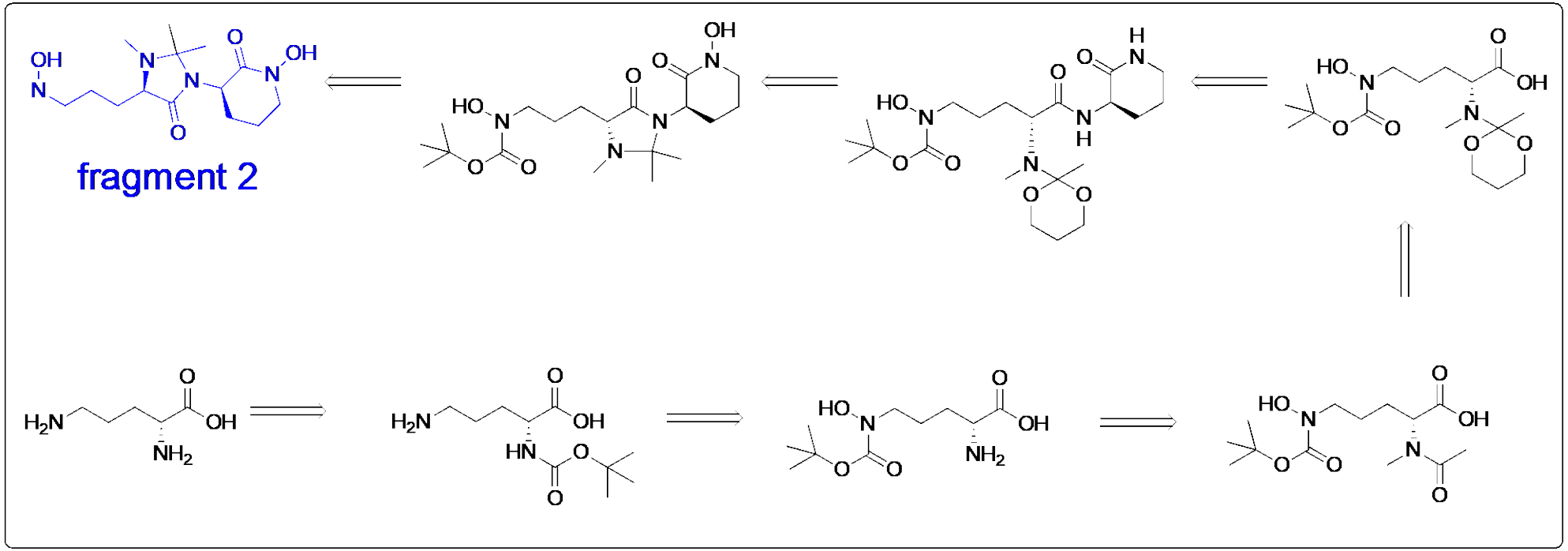
Proposed Retrosynthesis of Fragment 1

Scheme 2. Proposed Retrosynthesis of Fragment 1

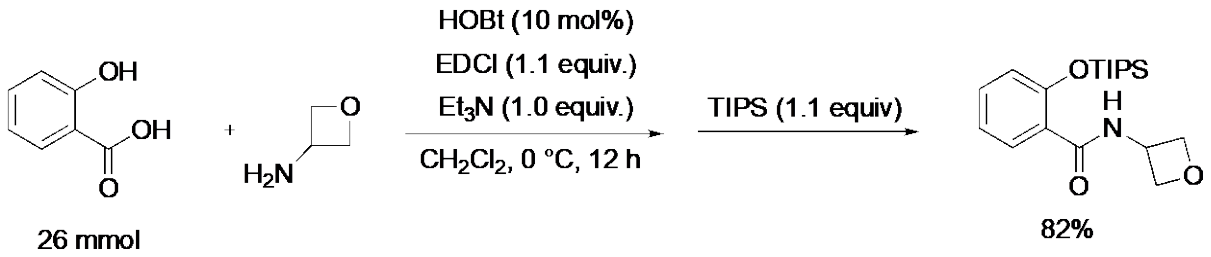


Proposed Retrosynthesis of Fragment 2

Scheme 3. Proposed Retrosynthesis of Fragment 2

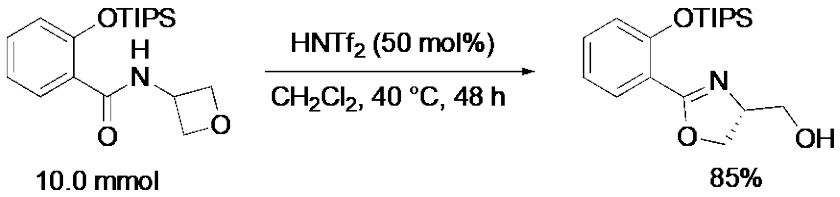


Starting Materials for Fragment 1



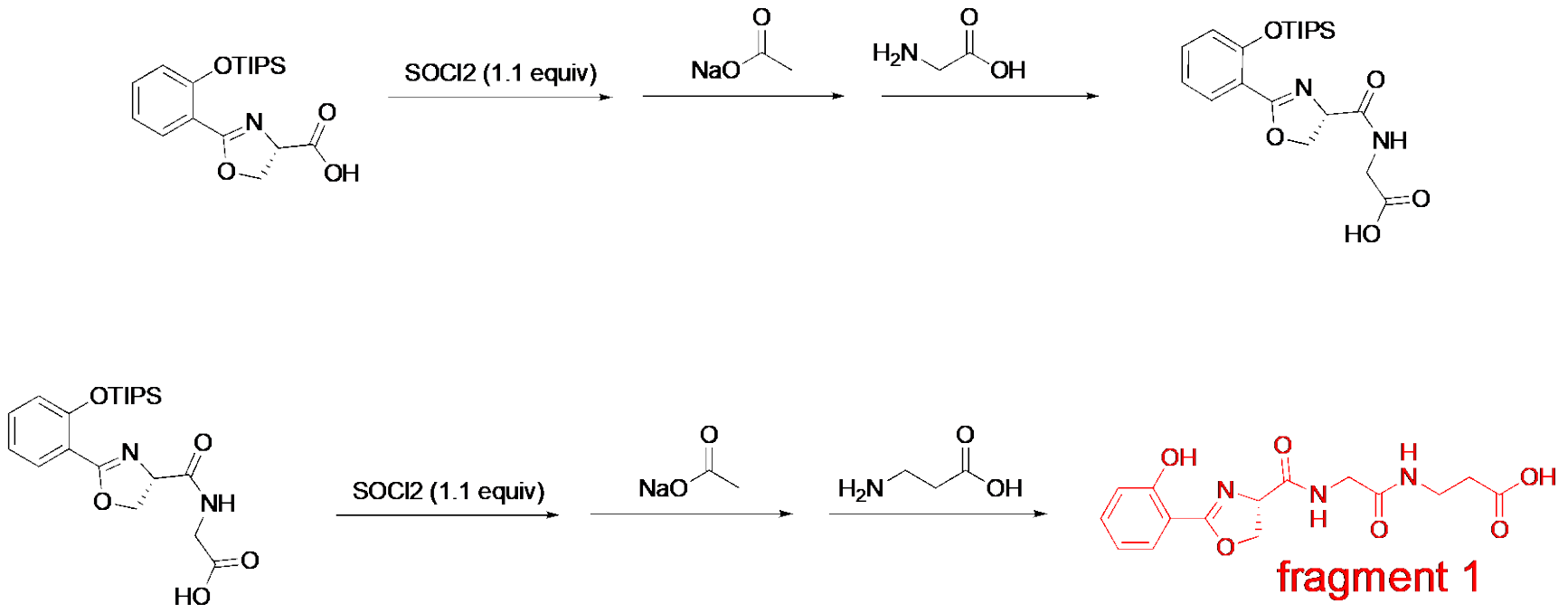
Huang, H.; Yang, W.; Chen, Z.; Lai, Z.; Sun, J. A Mild Catalytic Synthesis of 2-Oxazolines via Oxetane Ring-Opening: Rapid Access to a Diverse Family of Natural Products. *Chemical Science* **2019**, *10* (41), 9586–9590.

Cyclization to Oxazoline Moiety

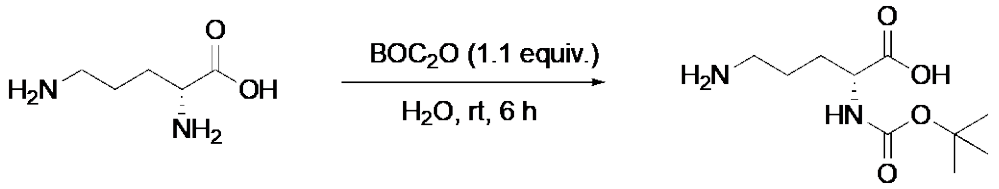


Huang, H.; Yang, W.; Chen, Z.; Lai, Z.; Sun, J. A Mild Catalytic Synthesis of 2-Oxazolines via Oxetane Ring-Opening: Rapid Access to a Diverse Family of Natural Products. *Chemical Science* **2019**, *10* (41), 9586–9590.

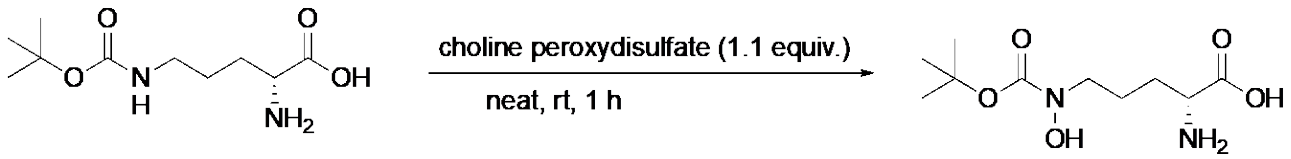
Condensation Reactions to Fragment 1



Starting Reagents for Fragment 2

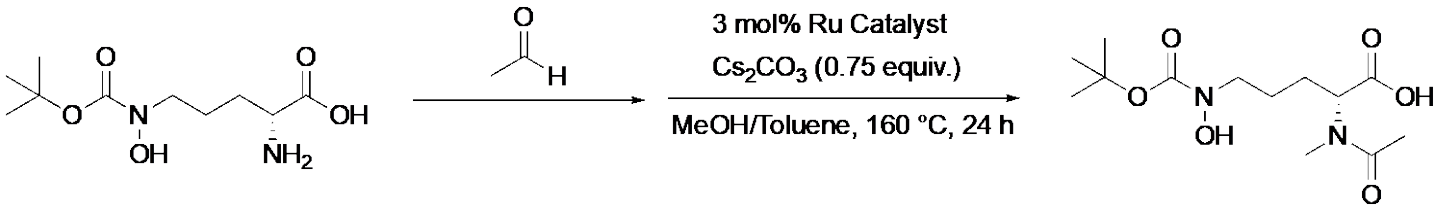


Hydroxamine Formation



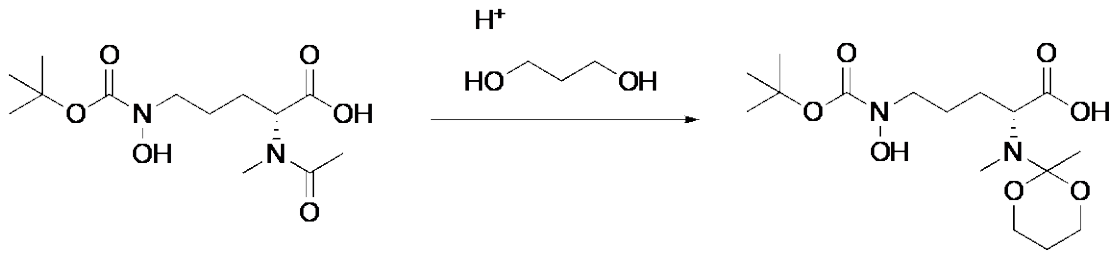
A. Banan, H. Valizadeh, A. Heydari, A. Moghimi, *Synlett*, **2017**, *28*, 2315-2319.

N-Acylation and Methylation via Ru Catalyst

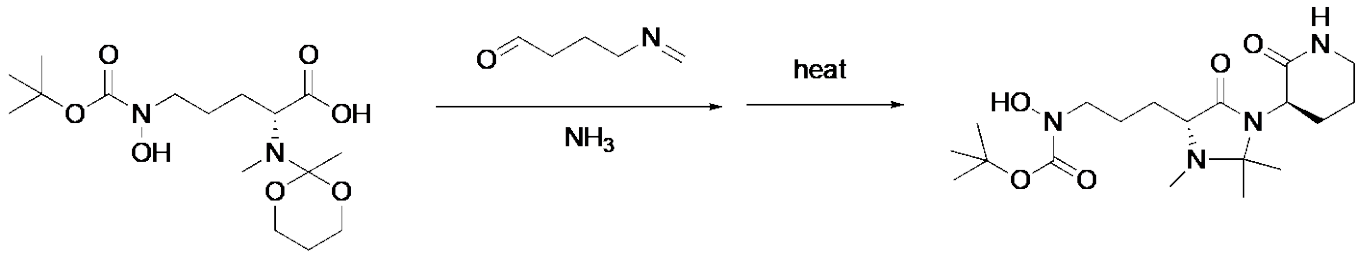


B. Paul, D. Panja, S. Kundu, *Org. Lett.*, **2019**, *21*, 5843-5847.

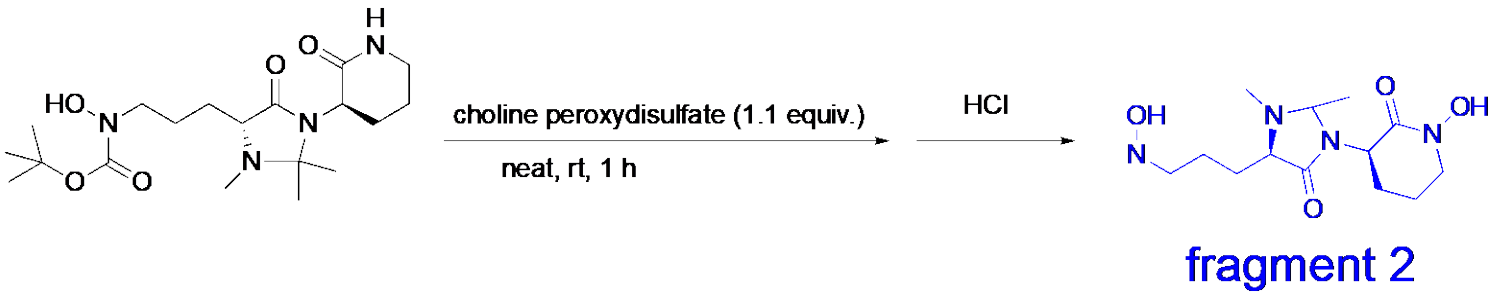
Protection of Carbonyl



Synthesis of Lactam



Synthesis of Fragment 2



Synthesis of Madurastatin D2