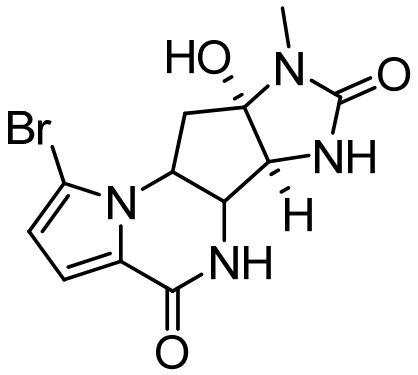
Bioinspired Total Synthesis of Agelastatin A

Jeremy Chris P. Reyes and Daniel Romo

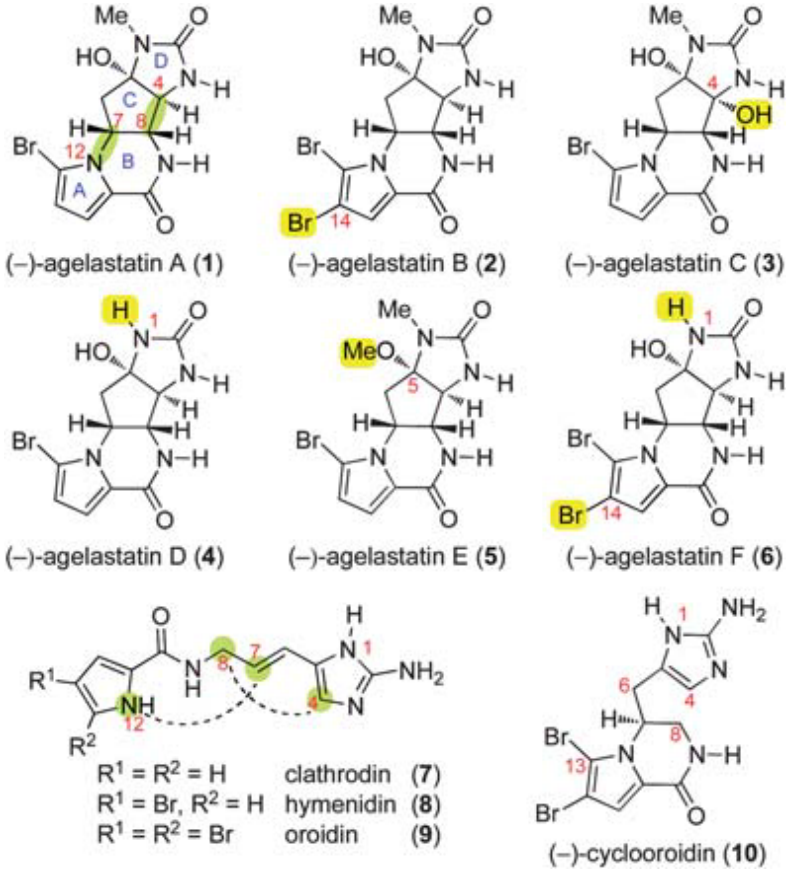


Agelastatin A

Benjamin R. Eyer
Wipf Group-Current Literature
August 25, 2012

Angewandte Chemie International Edition. **2012,** 51(28), 6870-6873
DOI: 10.1002/anie.201200959

Agelastatins: Isolation and Bioactivity



The molecular structures of all the agelastatin alkaloids and biogenetically related naturally occurring simpler pyrrole imidazole alkaloids

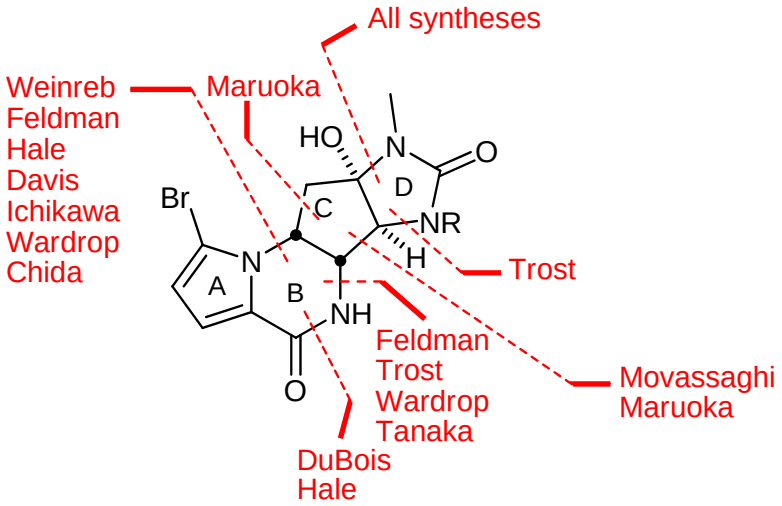
- Tetracyclic pyrrole-2-aminoimidazole alkaloids (PAIs) isolated from axinellid sponges
- 1993: Agelastatin A and B isolated from *Agelas dendromorpha*
- 1998: Agelastatin C and D isolated from *Cymbastela sp.*
- 2010: Agelastatin E and F isolated from *Agelas dendromorpha*

- Agelastatin A
  - Most bioactive of PAIs
  - Highly cytotoxic to human-cancer cell lines (IC_{50}'s 97-103 nm)
  - Potent inhibitor of osteopontin-mediated neoplastic transformation and metastasis
  - Potentially antiangiogenic, antidiabetic, and insecticidal

Nat. Prod. Rep. **2011**, 28, 1229–1260.
J. Chem. Soc. Chem. Commun. **1993**, *1305–1306.*
J. Nat. Prod. **2010**, 73, 720–723.
Oncol. Res. **2005**, 15, 11–20.
Mol. Cancer Ther. **2008**, 7, 548–558.
Chem. Biol. **2000**, 7, 51–63.

Previous synthetic work on Agelastatin A

- 12 total syntheses to date
- C-ring has all 4 stereogenic centers in Agelastatin A
  - Synthetic challenge
  - Previous syntheses focused on the cyclopentane then late stage B and D ring construction



Weinreb- *JOC* **1998**, 63,7594 and *JACS* **1999**, 121, 9574. (1st synthesis)

Feldman- *JACS* **2002**, 124, 9060 and *JOC* **2002**, 67, 7096. (1st asymmetric synthesis)

Hale- *OL* **2003**, 5, 2927 and *OL* **2004**, 6, 2615.

Davis- *OL* **2005**, 7, 621 and *Syn. Comm.* **2009**, 39, 1914.

(Wipf Group Current Lit. Feb. 2005)

Trost- *JACS* **2006**, 128, 6054 and *Chem. Eur. J.* **2009**, 15, 6910.

Ichikawa- *OL* **2007**, 9, 2989.

Wardrop- *OL* **2009**, 11, 1341.

Chida- *OL* **2009**, 11, 2687.

Tanaka- *OL* **2008**, 10, 5457 and *OL* **2009**, 11, 3402.

DuBois- *ACIE* **2009**, 48, 3802. (Wipf Group Current Lit. May 2009)

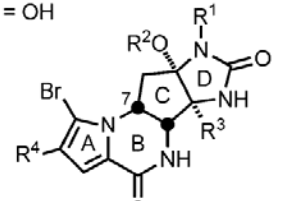
Movassaghi- *Chem. Sci.* **2010**, 1, 561. (Wipf Group Current Lit. Aug. 2010)

Maruoka- *JACS* **2012**, 134, 7516.

Proposed biogenetic synthesis of Oroidin-based pyrrole-imidazole alkaloids

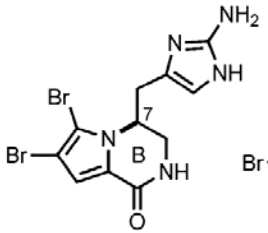
R^1 = Me; R^2, R^3, R^4 = H
(agelastatin A, **1**)
R^1 = Me; R^2, R^3 = H; R^4 = Br
(agelastatin B, **2**)
R^1 = Me; R^2, R^4 = H; R^3 = OH
(agelastatin C, **3**)

R^1, R^2, R^3, R^4 = H
(agelastatin D, **4**)
R^1, R^2 = Me; R^3, R^4 = H
(agelastatin E, **5**)
R^1, R^2, R^3 = H; R^4 = Br
(agelastatin F, **6**)

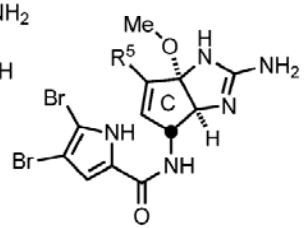


B then C

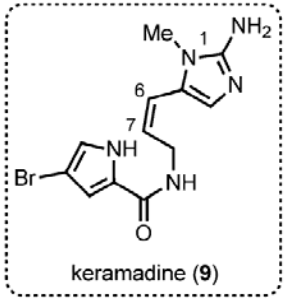
C then B



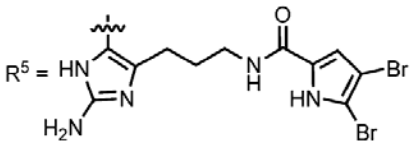
cyclooroidin (**7**)

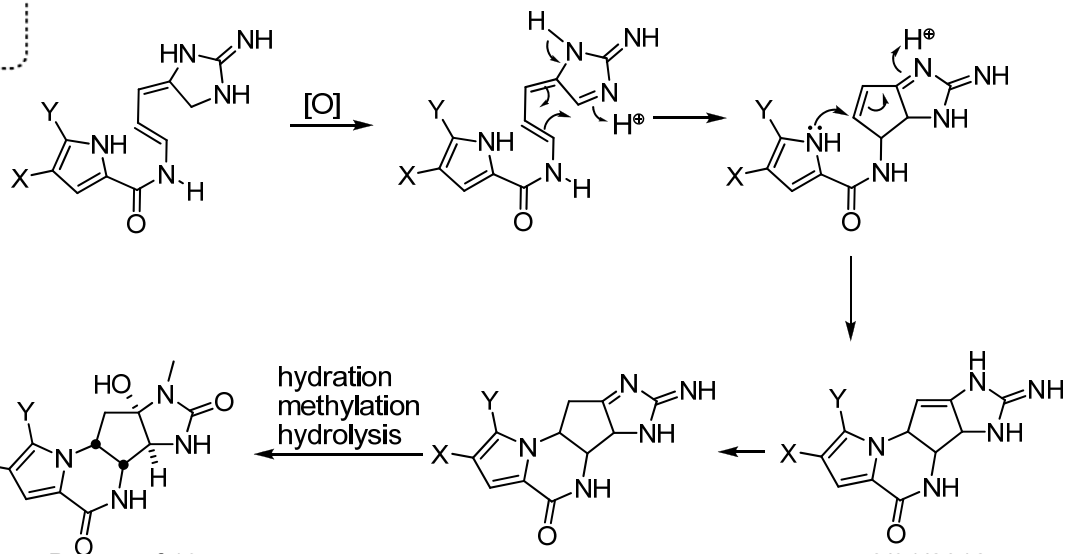


nagelamide J (**8**)



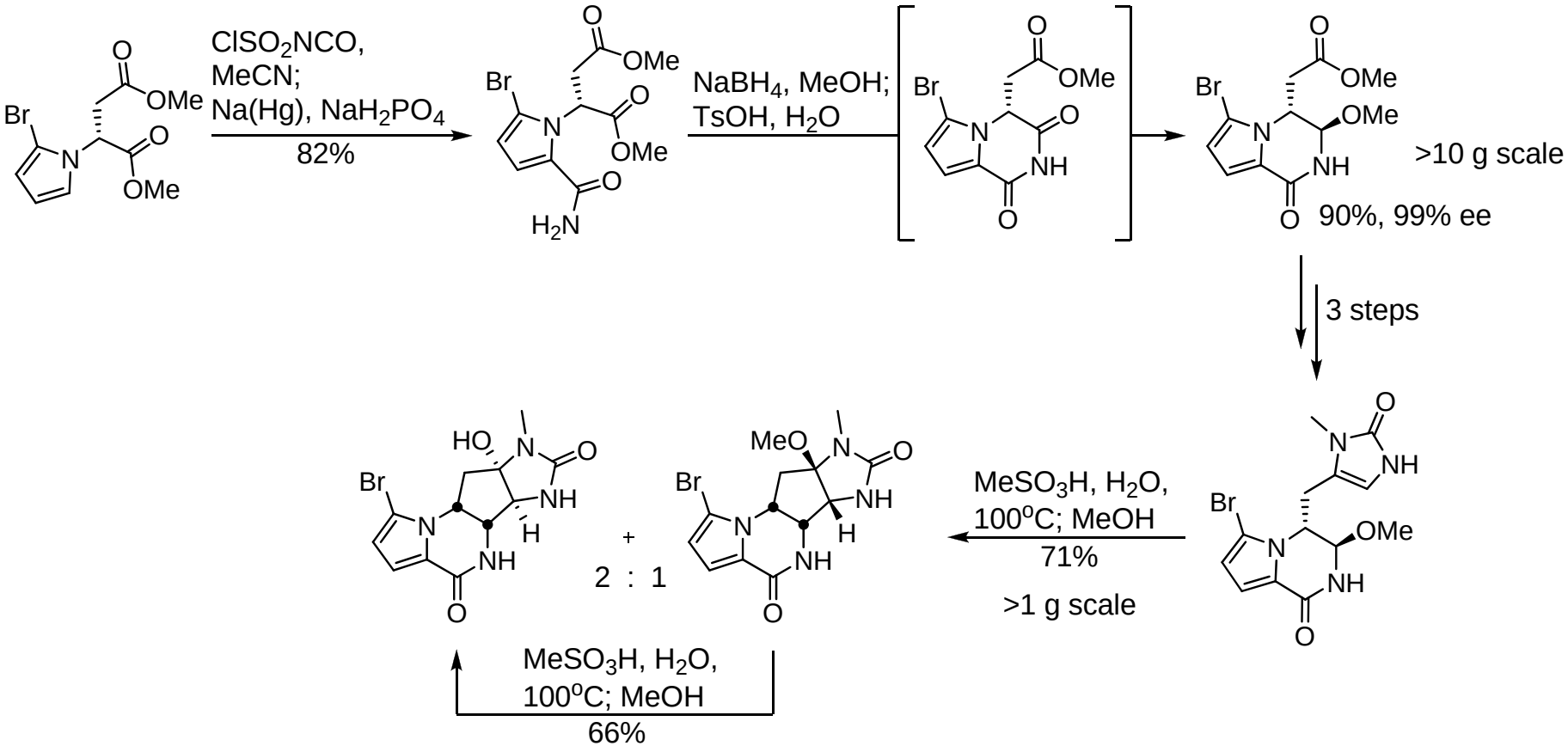
keramadine (**9**)





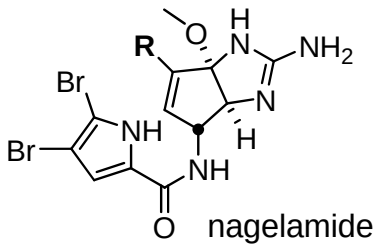
ACIE. **2012**, 51(28), 6870-6873.
Eur. J. Org. Chem. **2001**, 237–243.

Movassaghi's biosynthetic approach: B-ring then C-ring

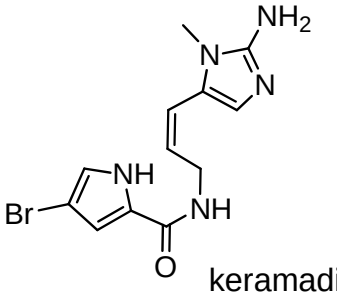


Chem. Sci. **2010**, 1, 561–566.

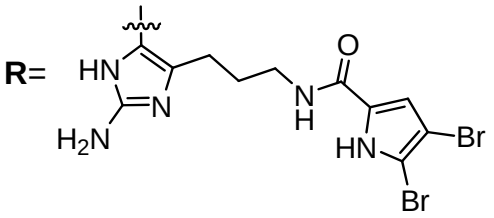
Title Paper's bioinspired approach: C-ring then B-ring

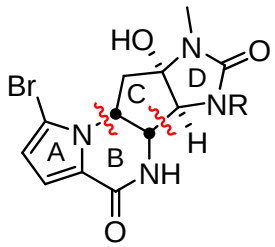


nagelamide J



keramadine

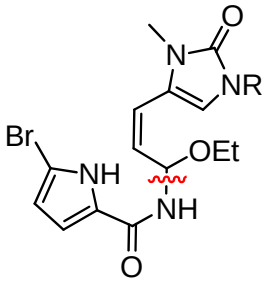


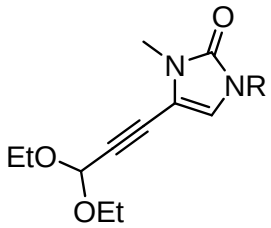


Agelastatin A

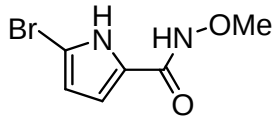
C-ring then B-ring formation

hydration

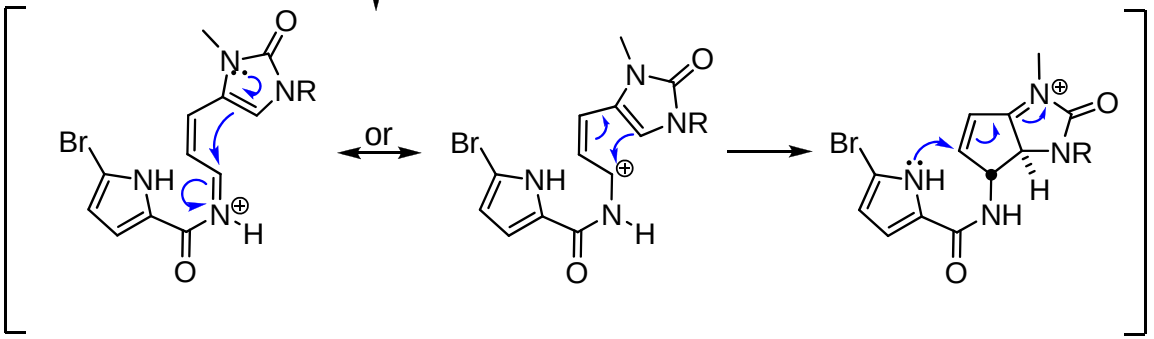




+

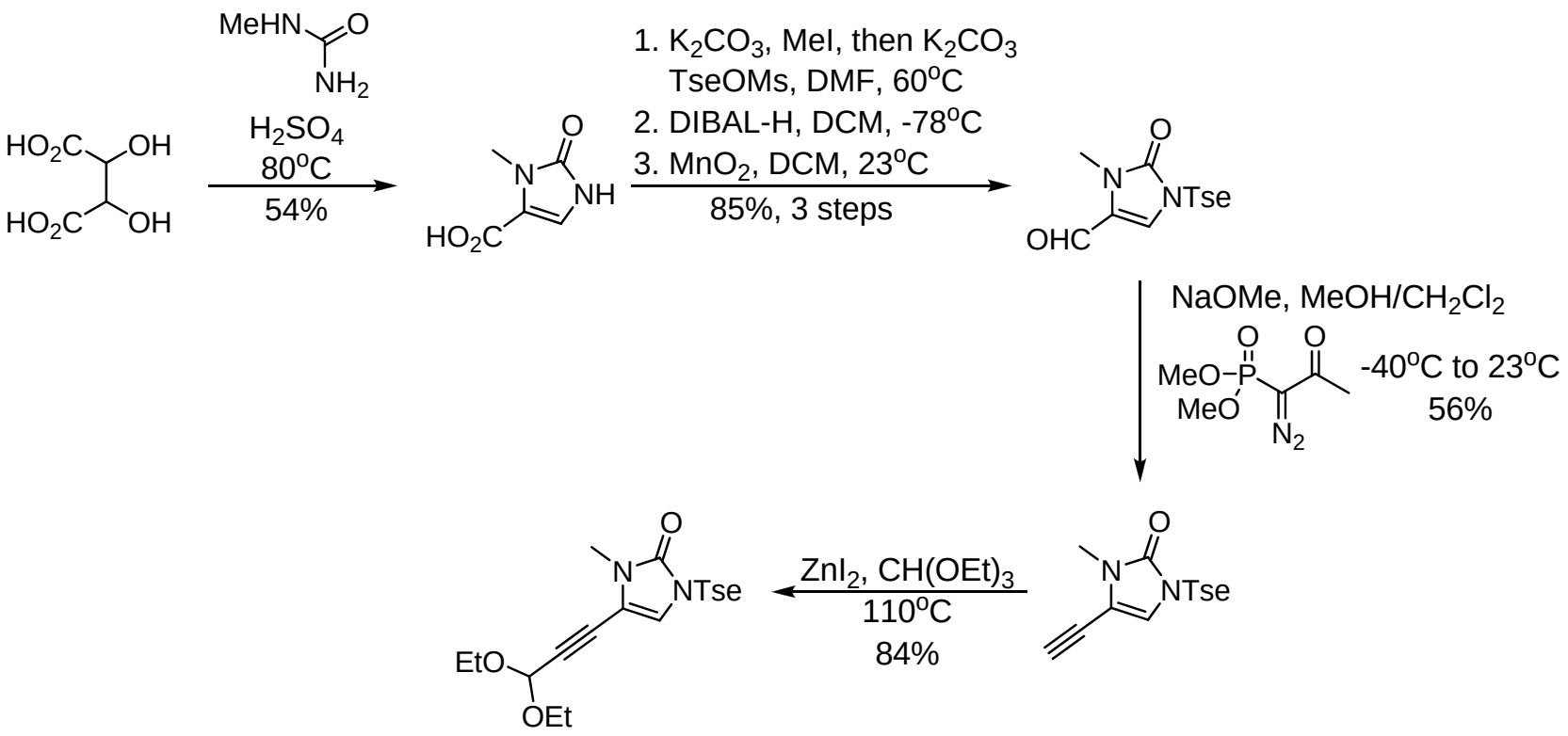


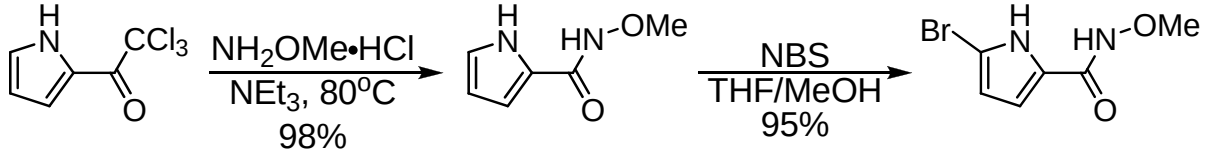
Proposed bioinspired cascade cyclizations



Tetrahedron Lett. **2000**, 41, 9917–9922.
Org. Lett. **2007**, 9, 2369–2371.
ACIE. **2012,** 51(28), 6870-6873

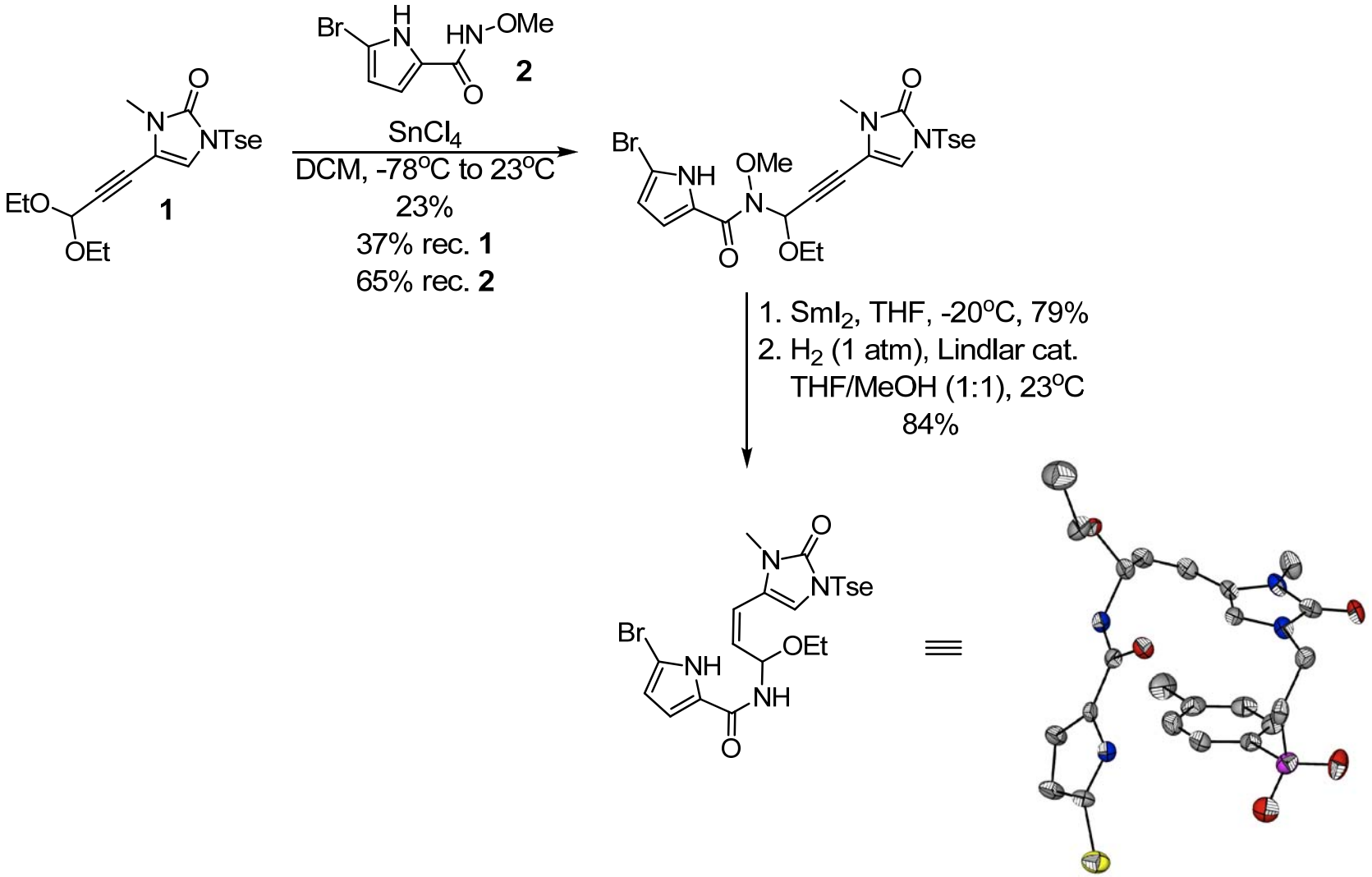
Synthesis of the Coupling Partners





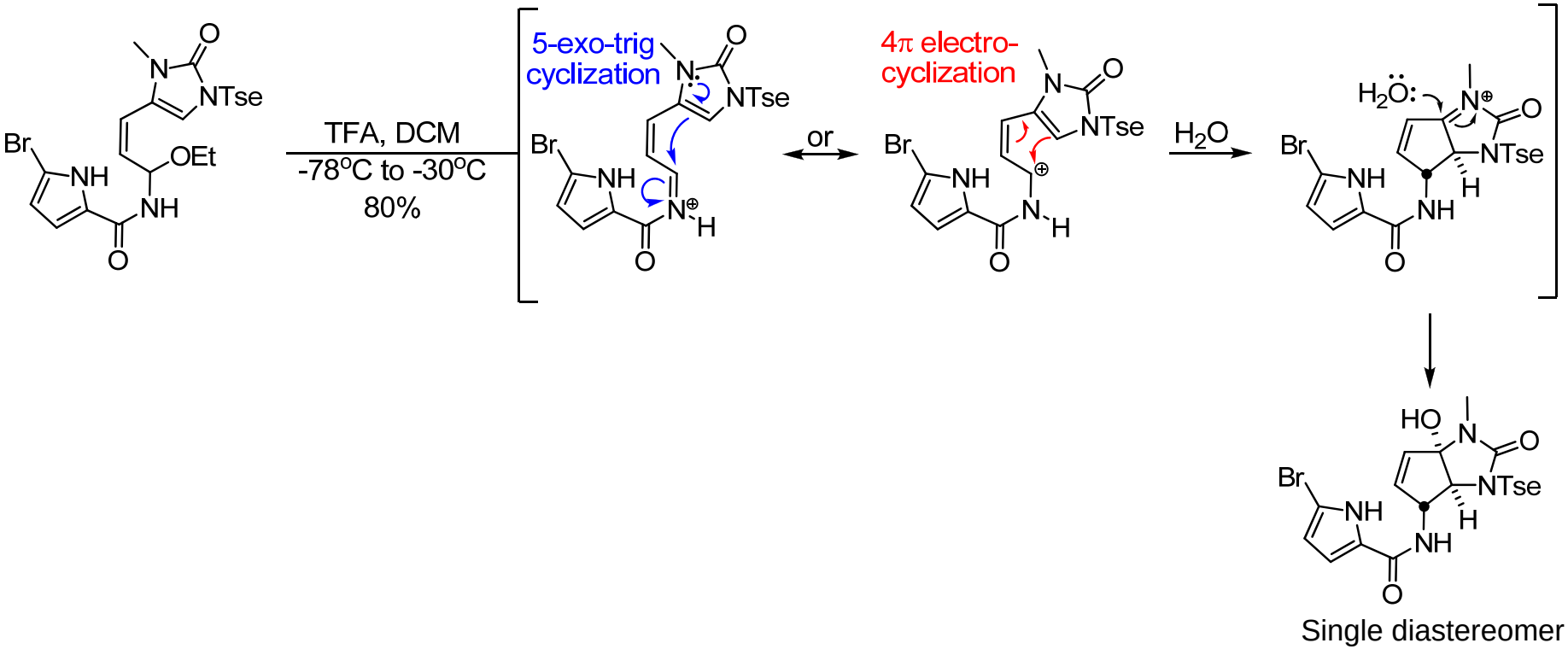
ACIE. **2012,** 51(28), 6870-6873

Coupling of imidazolone alkynyl acetal and pyrrole amide



ACIE. **2012,** 51(28), 6870-6873

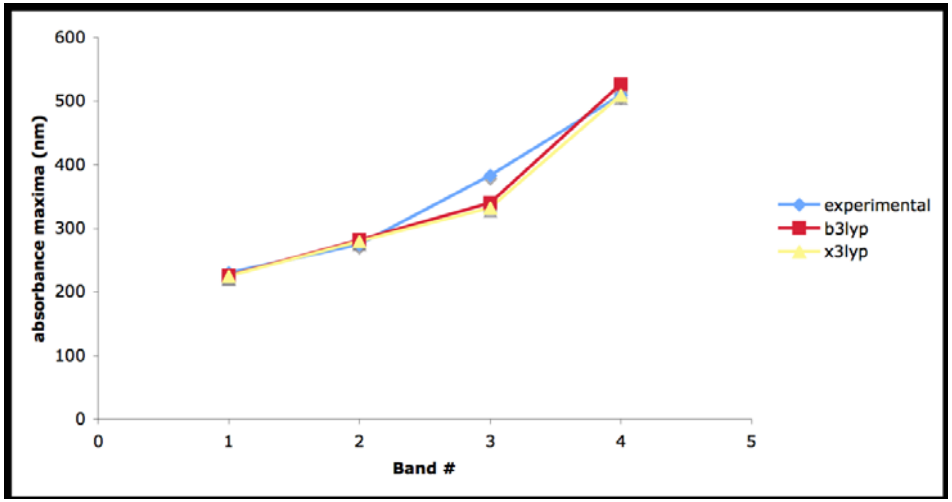
Biomimetic C-Ring Closure



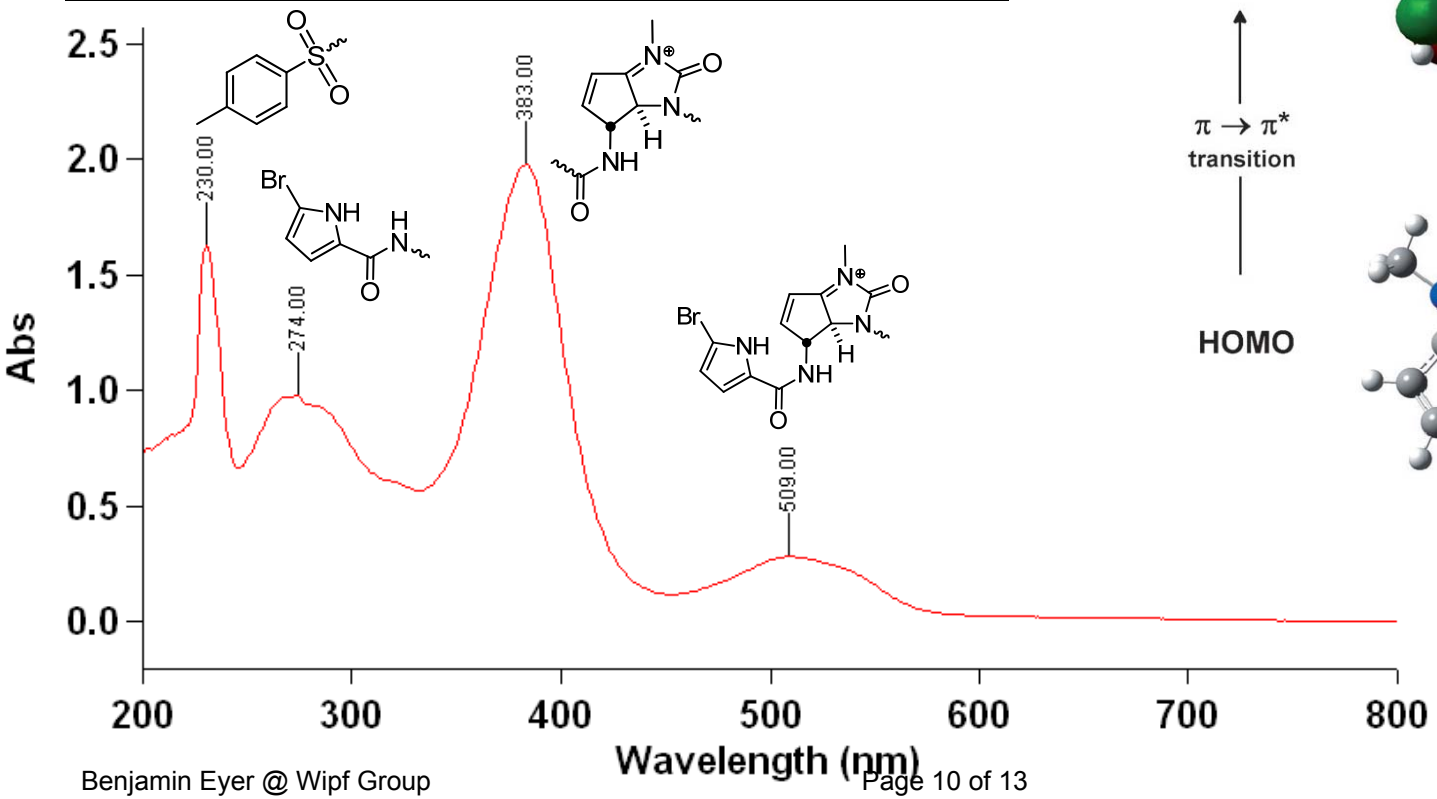
Addition of a variety of Lewis and Brønsted acids resulted in deer-red colored solution

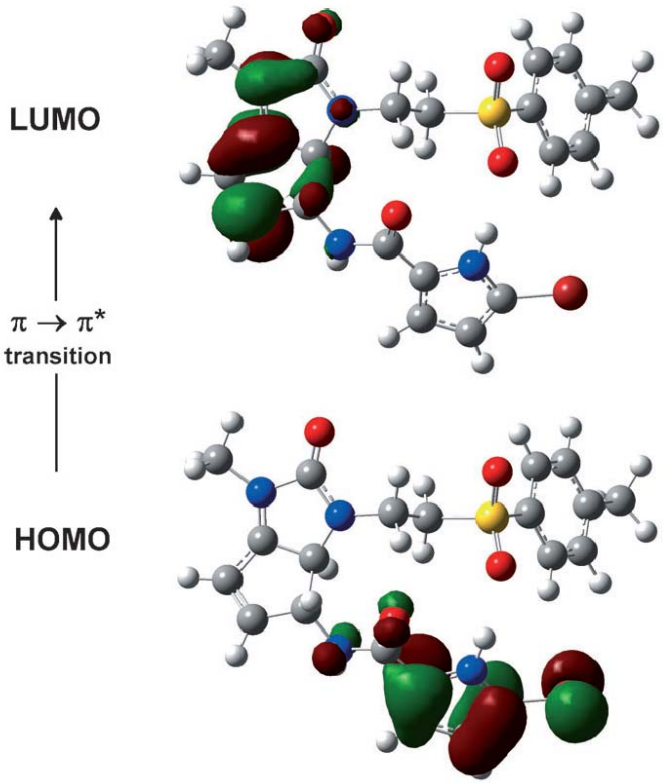
ACIE. **2012,** 51(28), 6870-6873

Probing the Reaction Mechanism



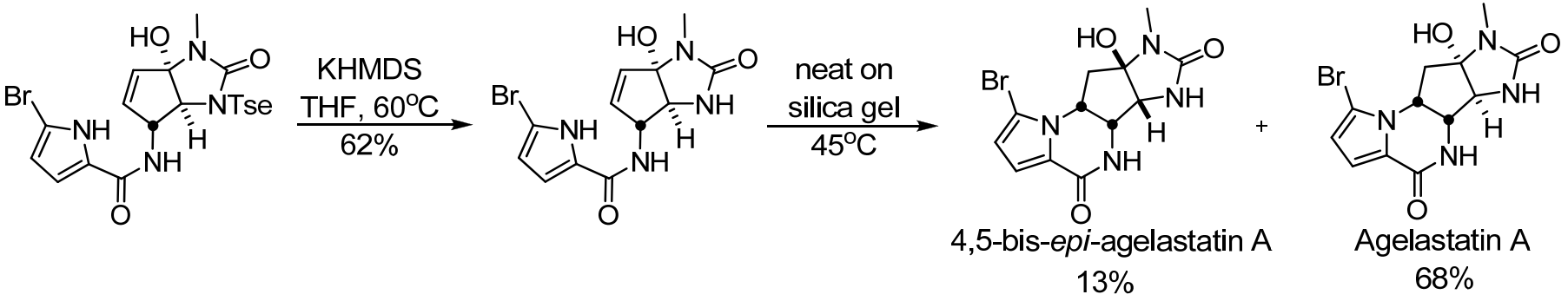
Experimental vs TD-DFT predicted absorption bands





ACIE. **2012,** 51(28), 6870-6873

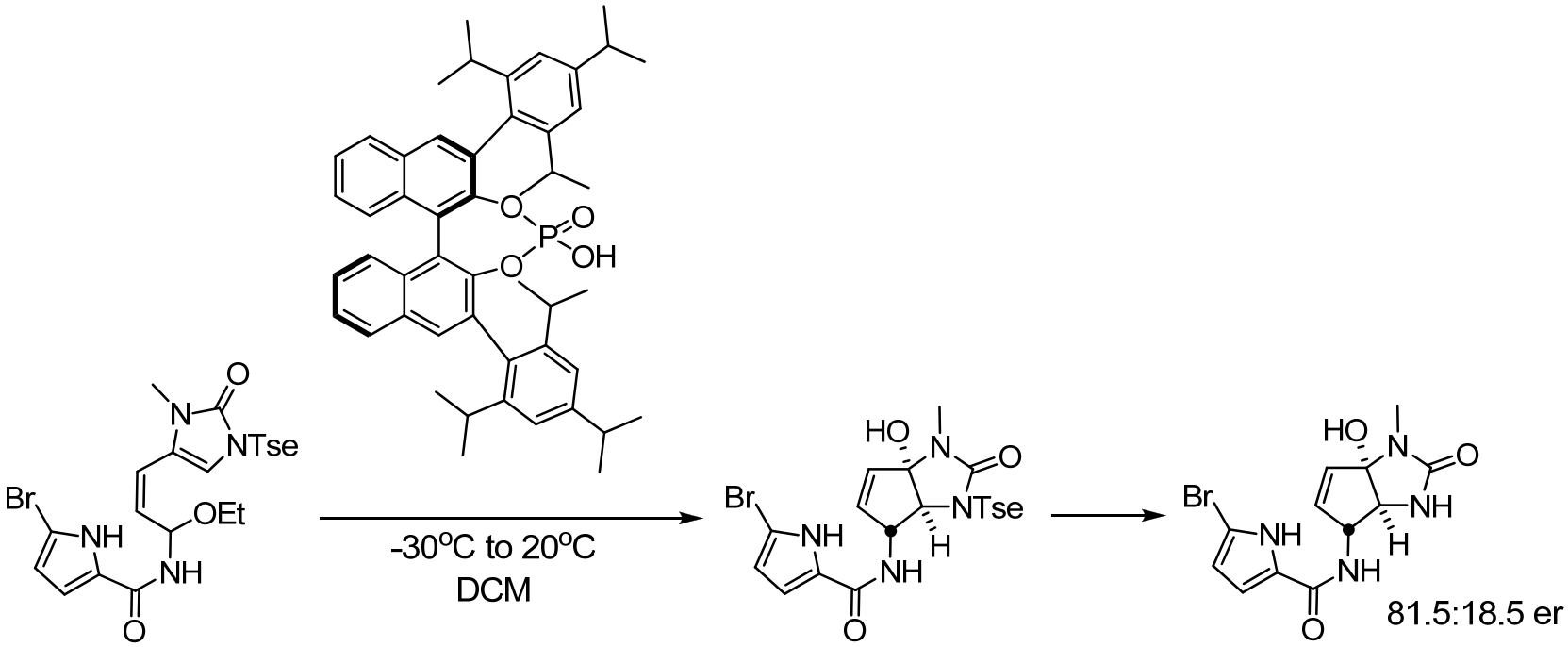
Completion of Synthesis: Closing the B-Ring



- Tse group removed to allow greater confirmational mobility
- 4,5-bis-*epi*-agelastatin formed by retro-Nazarov reaction (retro-5-*exo*-trig) then recyclization
- Absence of the Tse group, the C5 unprotected alcohol and the C13 bromine in the pyrrole ring essential to cyclization

ACIE. **2012,** 51(28), 6870-6873

Enantioselective Nazarov-type Cyclization



- Preliminary Studies with (R)-TRIP hydrogen phosphate show promise for an enantioselective route and further studies are currently underway

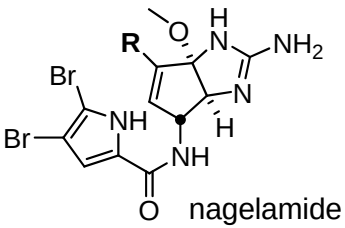
ACIE. **2012,** 51(28), 6870-6873

Summary

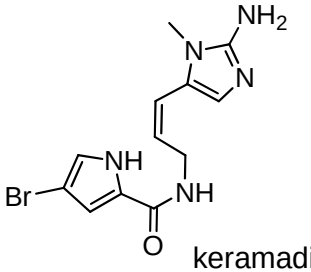
- Concise total synthesis of agelastatin A that complements Movassaghi's approach to the agelastatins (B-ring then C-ring)

- Completion of the total synthesis by two sequential, potentially biomimetic cyclizations (C-ring then B-ring)
  - C-ring: sets three contiguous centers diastereoselectively
  - B-ring: unique solvent-free conditions on silica gel with mild heating

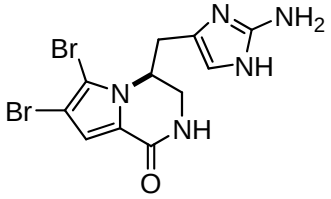
- Proposal for the biosynthesis of the agelastatins through a reaction sequence leading from an oxidized keramadine analogue via a nagelamide J like intermediate to agelastatin A
  - The assembly of C followed by B rings provides evidence for the proposed reactivity of a linear alkenyl imidazolone pyrrole



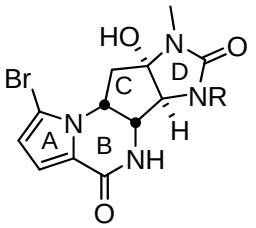
nagelamide J



keramadine



cyclooroidin



agelastatin A