CHEM 530
Literature Seminar in Organic Chemistry

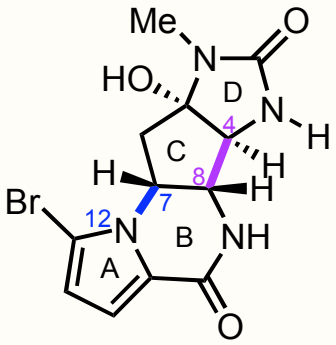
UIC

Total Synthesis of all (-)-Agelastatin Alkaloids

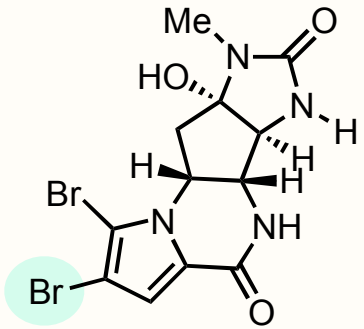
Movassaghi, M. *et al.* *Chemical Science*, **2010**, DOI: 10.1039/c0sc00351d

Stacy Snyder, Wardrop Group
September 29, 2010

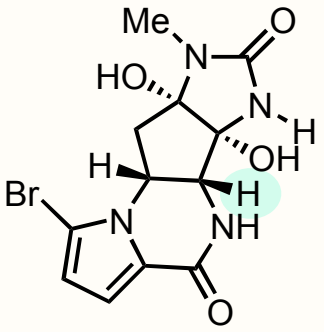
Agelastatin Alkaolids



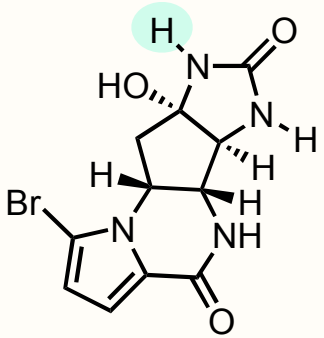
(-)-agelastatin A



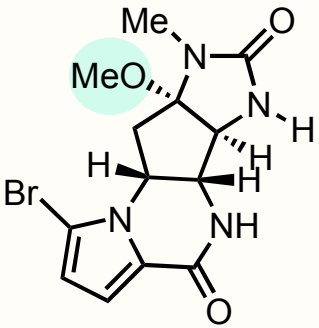
(-)-agelastatin B



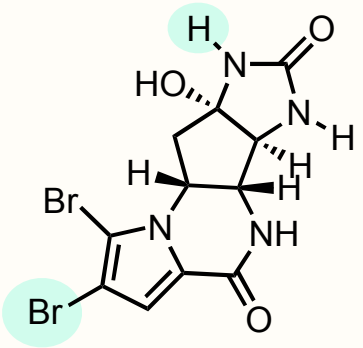
(-)-agelastatin C



(-)-agelastatin D



(-)-agelastatin E



(-)-agelastatin F

Biological Properties

Agelas dendromorpha
Coral Sea sponge

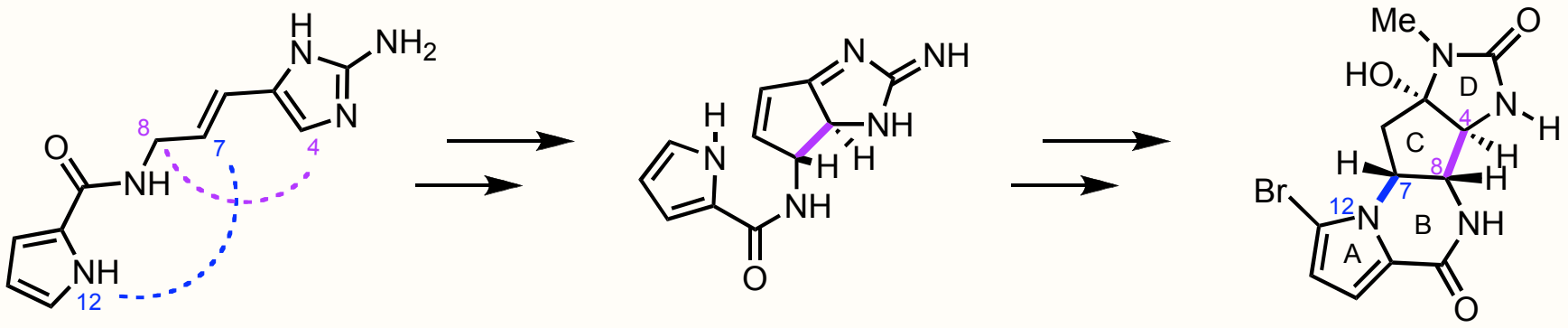
- Significant anti-tumor activity
- Slows metastasis and cancer cell proliferation
- Inhibits osteopontin (OPN) neoplastic transformation
- Selectively inhibits glycogen synthase kinase-3β, target for Alzheimer's disease and bipolar disorder

a. Mason, C. *et al., Mol. Cancer Ther.,* 2008, **7**, 548-558. b. Meijer, L. *et al., Chem. Biol.,* 2000, **7**, 51-63.

Former Synthetic Efforts

- 10 different synthesis
- 1999 - Weinrab, 1st total synthesis
- 2002 - Feldman, 1st enantioselective synthesis of (-)-A and (-)-B
- Wardrop - trichloroacetamide as protecting group, nucleophile, and urea
- Early C ring introduction, which correspond to biosynthetic hypothesis

Biosynthetic Hypotheses

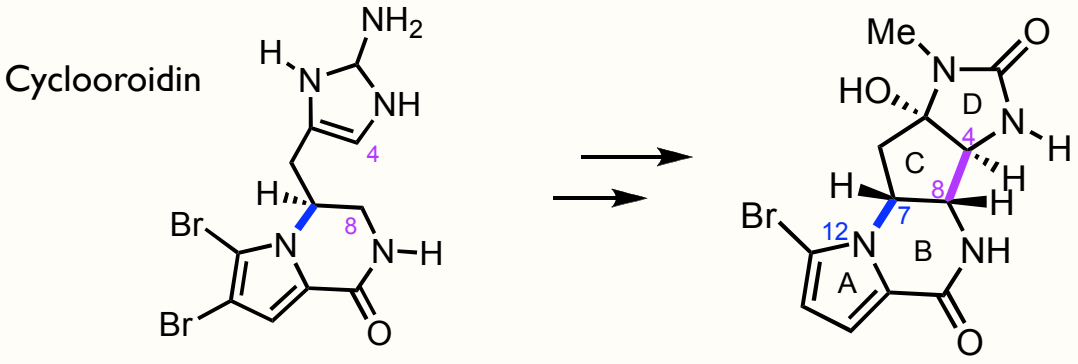


- Early biosynthesis of C ring followed by B ring
- C ring formed by C8-nucleophile trapping of C4-electrophile
- Stereochemistry attributed to enzyme control

a. Andrade, P. et al. *Tet. Lett.* **1999**, *40*, 4775. b. Mourabit, A. & Potier, P. E. *J. Org. Chem.*, **2001**, 237.

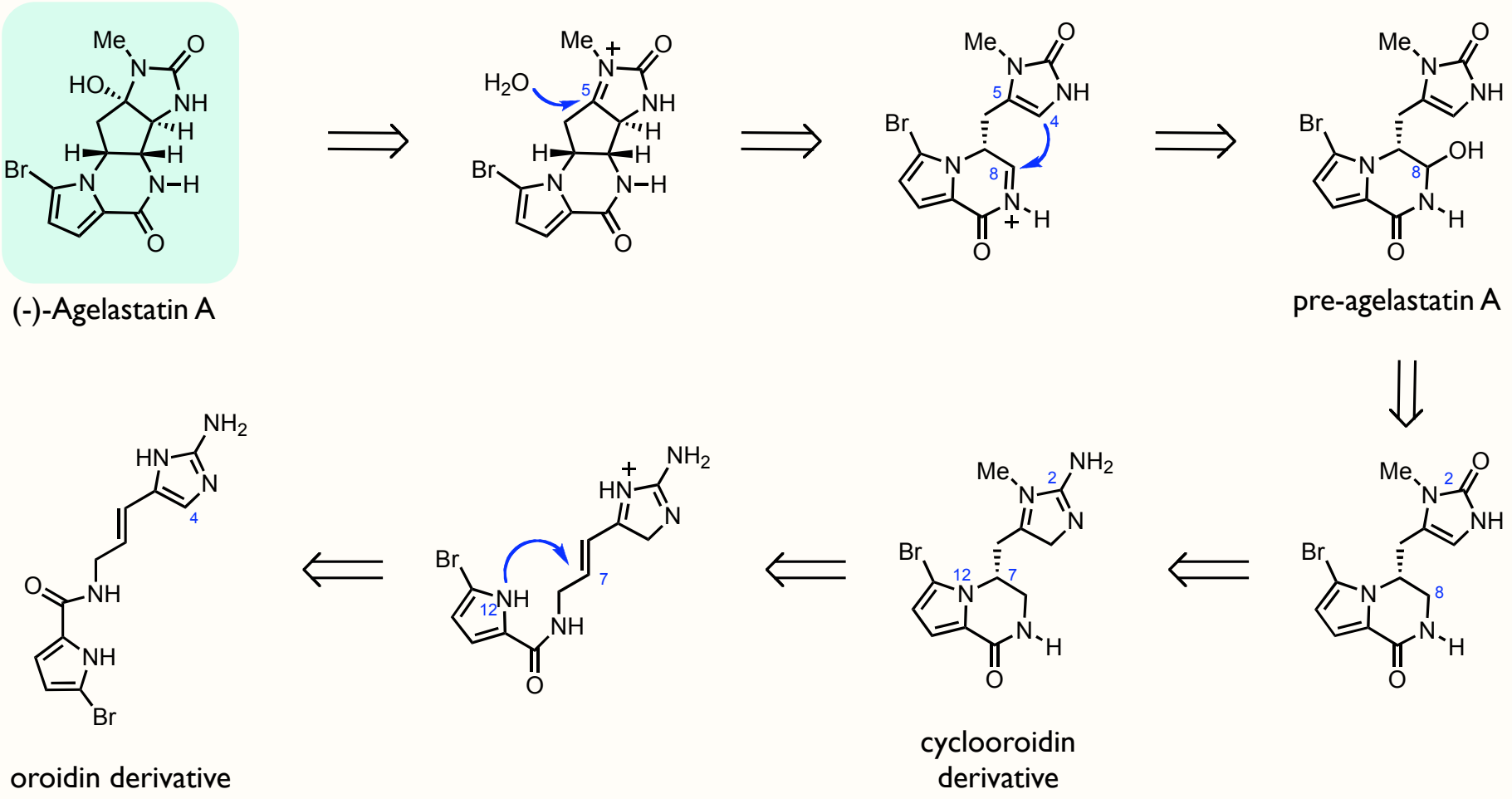
New Biosynthetic Hypothesis

- B ring formed before C ring
- Reverse polarity in C ring formation, C-4 nucleophilic attack on C-8 electrophile
- Substrate directed stereocontrol, enhanced by biosynthetic enzymes

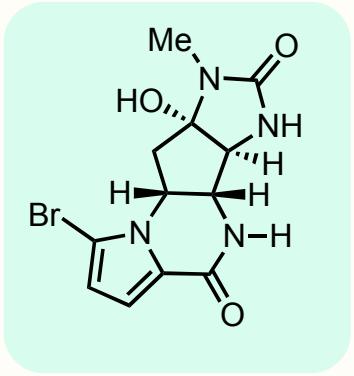


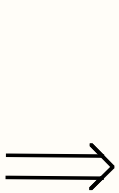
Poverlin, C. *et. al. Org. Let.*, **2006**, *8*, 819.

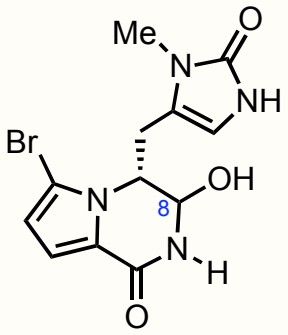
Retrobiosynthetic Analysis



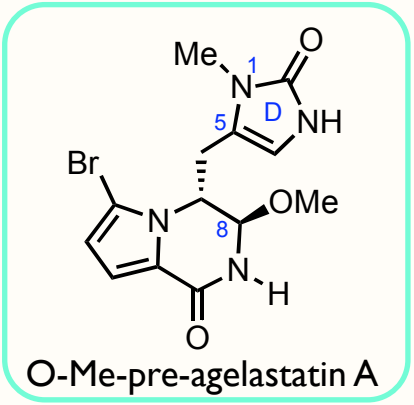
Retrosynthetic Analysis



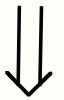




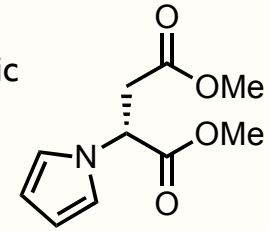
"pre-agelastatin intermediate"

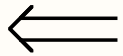


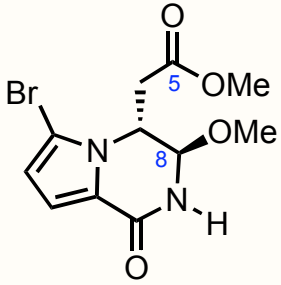
O-Me-pre-agelastatin A

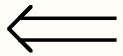


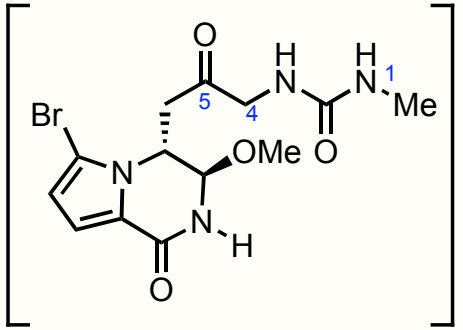
from D-aspartic acid



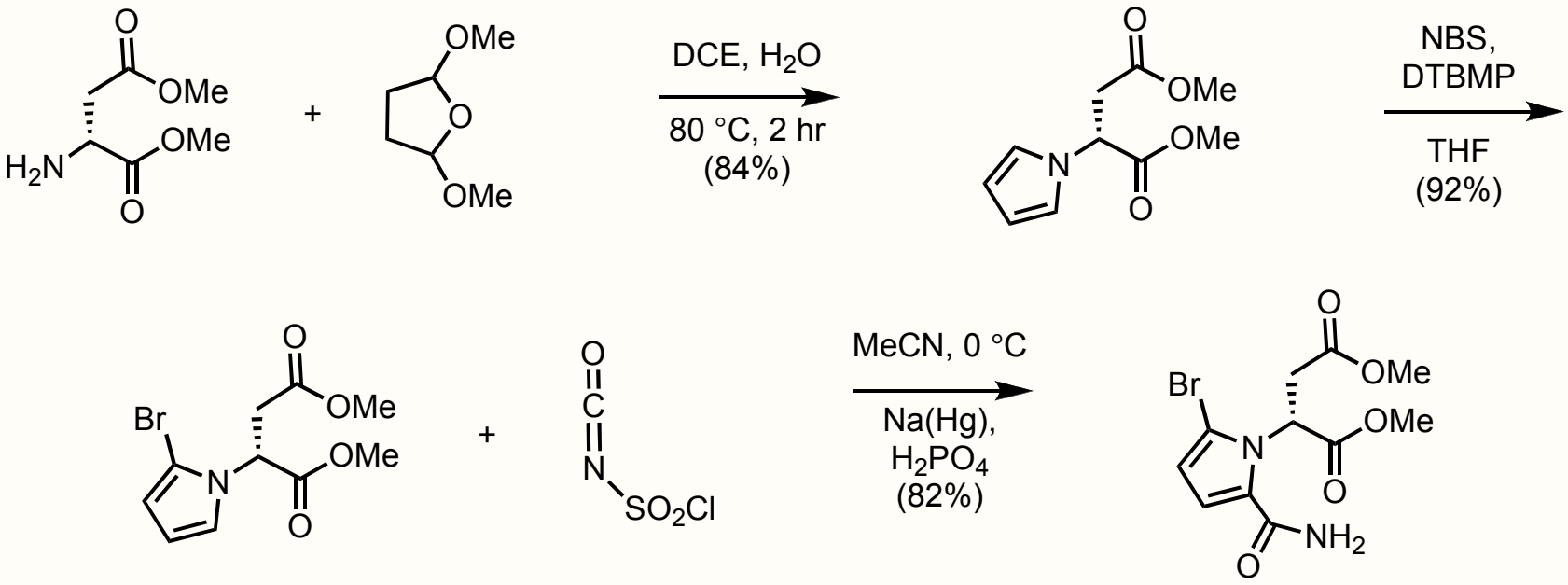




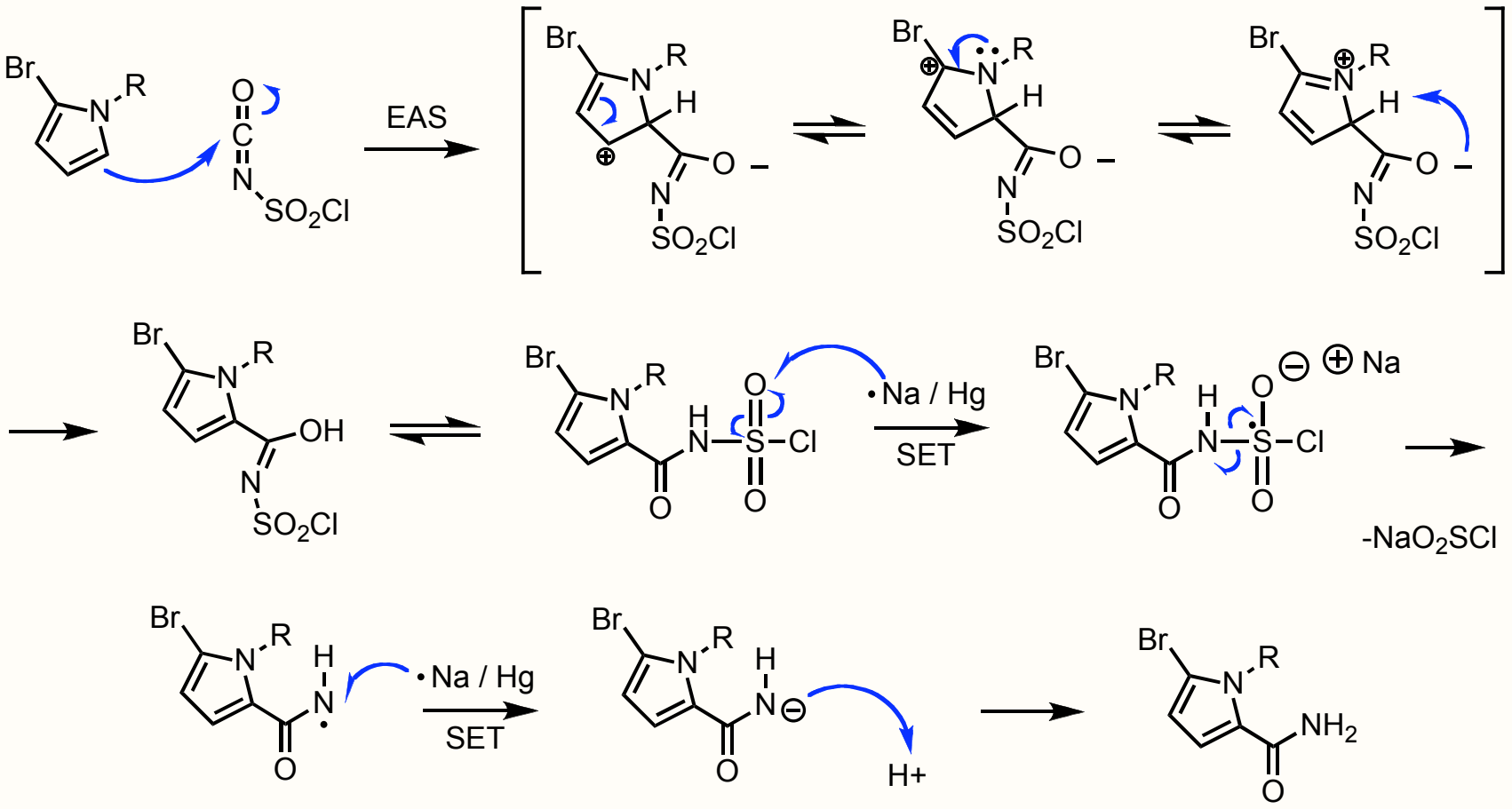




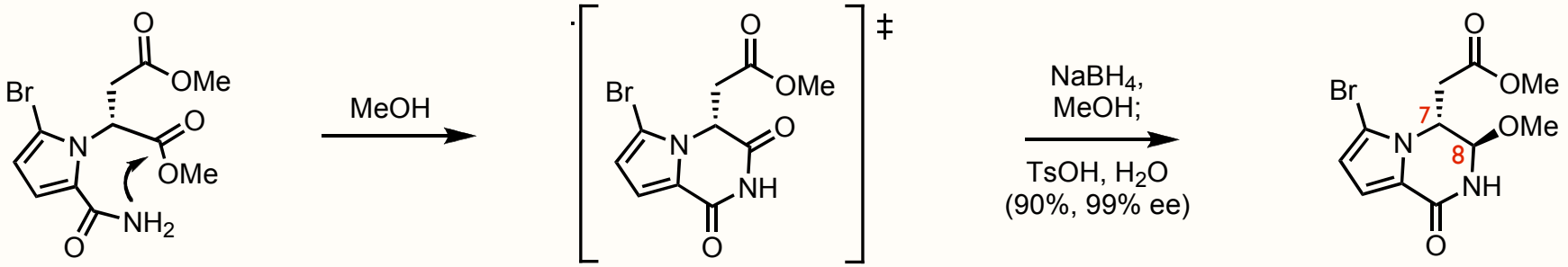
Formation of "A" Ring

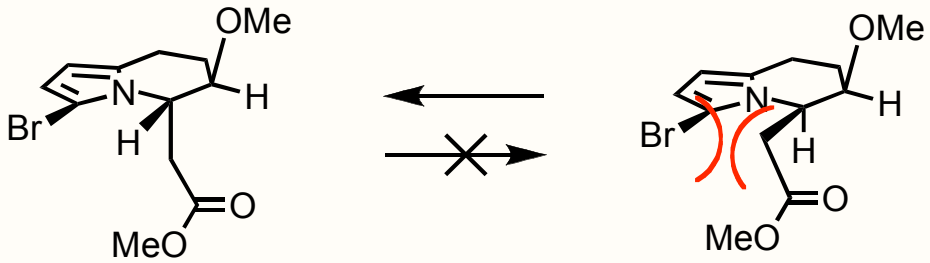


Mechanism

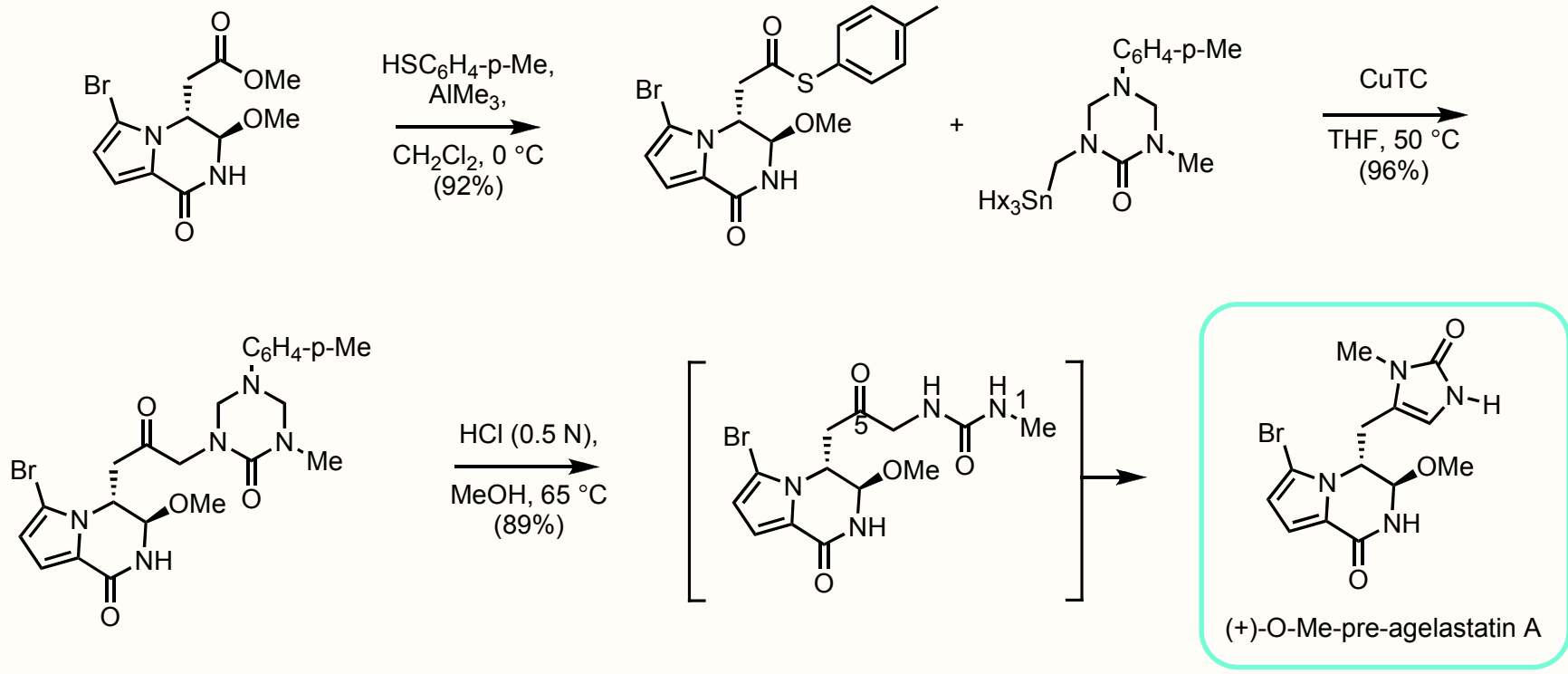


Formation of B Ring

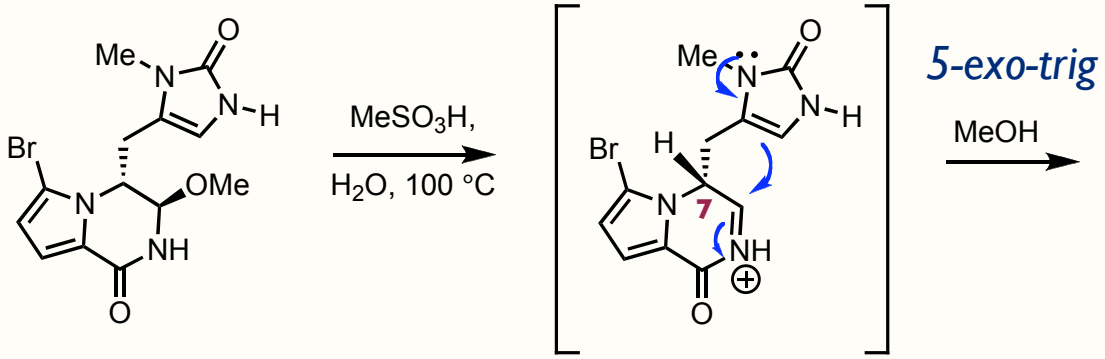


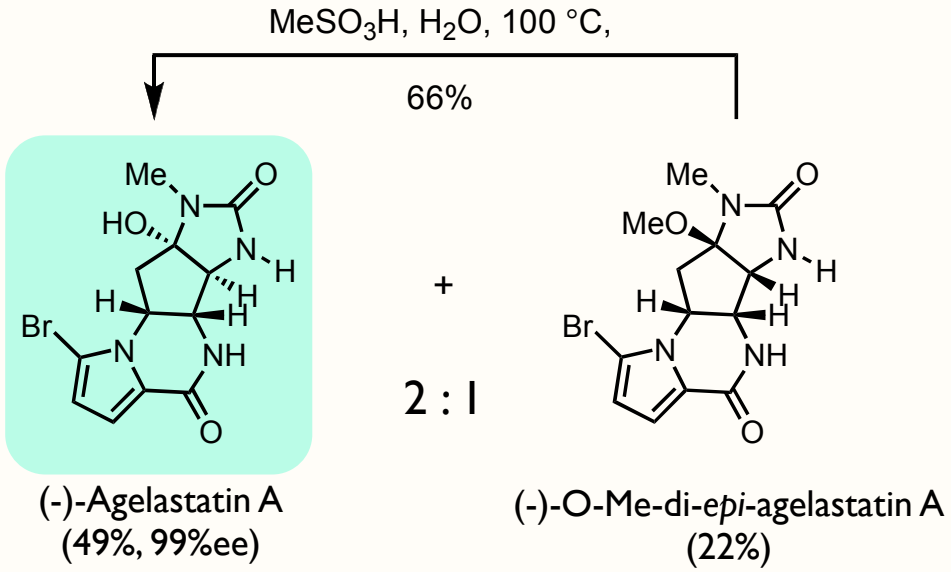


O-Me-Pre-Agelastatin A



Completion of (-)-Agelastatin A





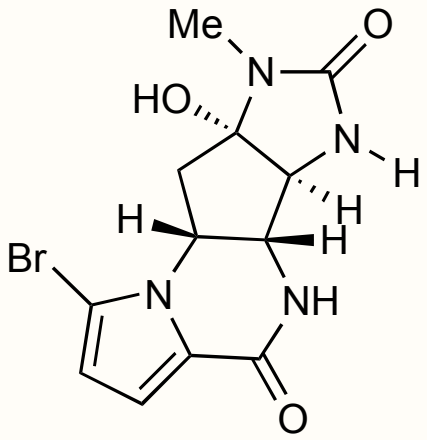
(-)-Agelastatin A
(49%, 99%ee)

(-)-O-Me-di-*epi*-agelastatin A
(22%)

Total Synthesis of (-)-Agelastatin A

- 8 steps
- 22% overall yield
- 20g scale
- Obtain 1.4g batch of (-)-Agelastatin A

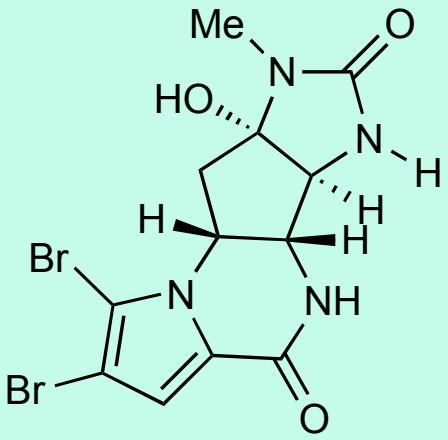
(-)-Agelastatin B



(-)-agelestatin A

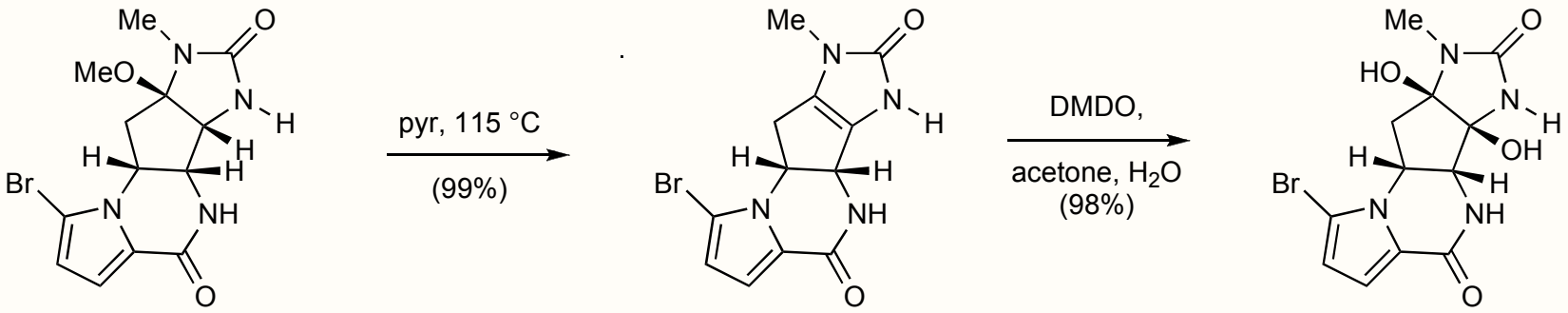
NBS,
DTBMP

THF : H_2O, 0° C
(84%)

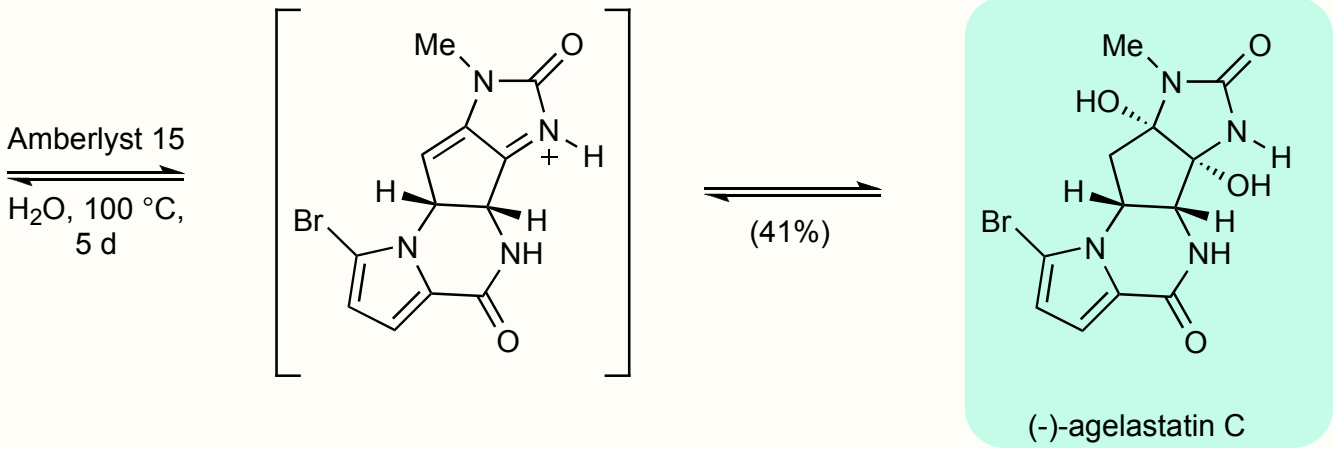


(-)-agelestatin B

(-)-Agelastatin C

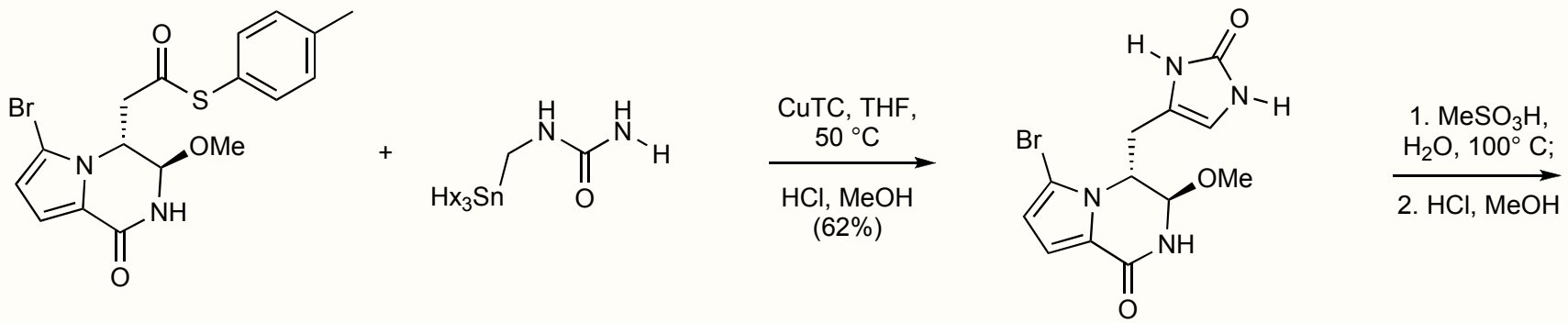


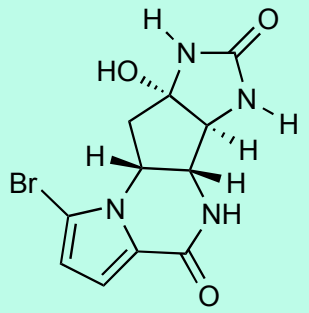
(-)-O-Me-di-*epi*-agelastatin A



(-)-agelastatin C

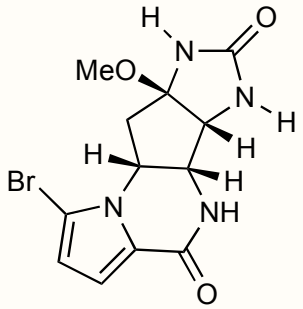
(-)-Agelastatin D





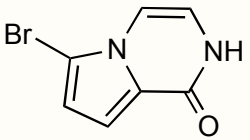
(-)-agelastatin D
26%

+



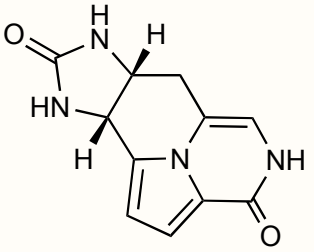
9%

+



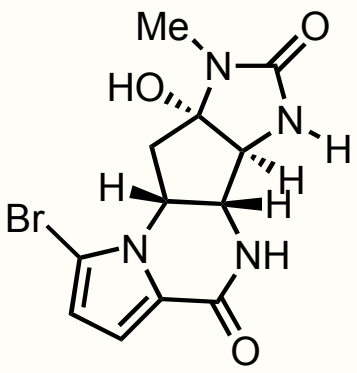
20%

+



20%

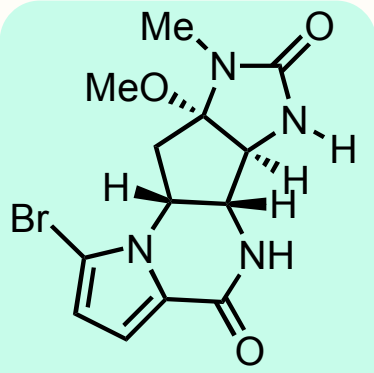
(-)-Agelastatin E & F



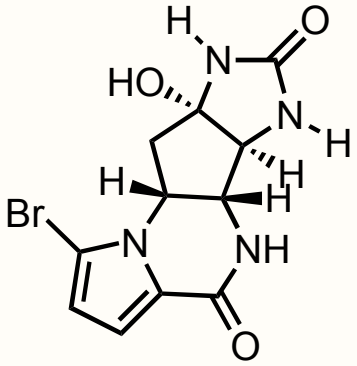
(-)-agelastatin A

Amberlyst 15

MeOH, 65 °C
2 h
(96%)



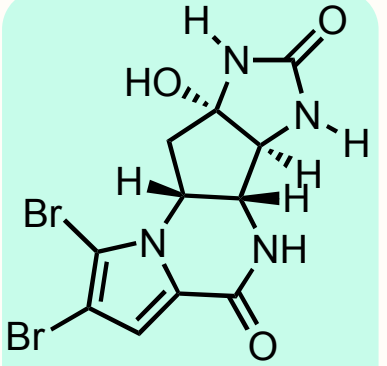
(-)-agelastatin E



(-)-agelastatin D

NBS, DTBMP

THF, H_2O, 0 °C
(86%)



(-)-agelastatin F

Conclusion

- Total synthesis of (-)-agelastatins A - F based on new biosynthetic hypothesis
- First total synthesis of (-)-C, D, E, and F
- Shortest synthesis of (-)- A to date
- Developed a new imidazolone annulation strategy
- Results support the late stage 5-*exo*-trig C-ring formation

Thank you for
your attention!