Total Synthesis of All (-)-Agelastatin Alkaloids

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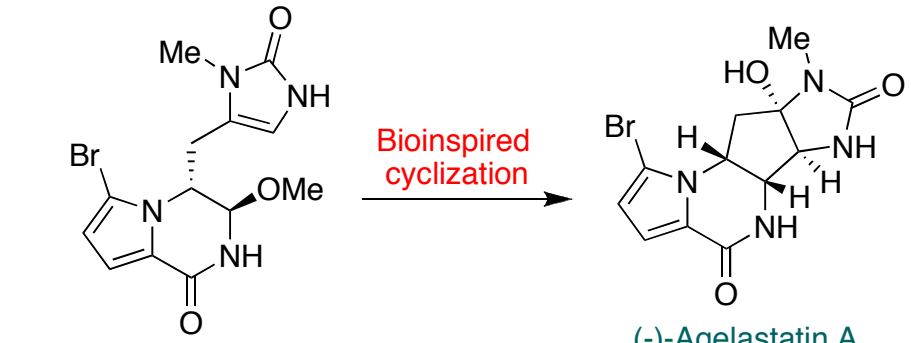
Chemical Science, Advance article



(+)-*O*-Me-pre-agelastatin A

(-)-Agelastatin A

1.4 g batch

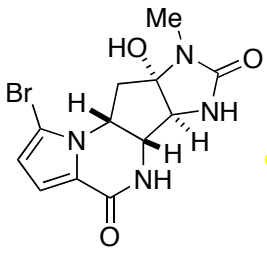
Marija Manojlović

Wipf group current literature meeting

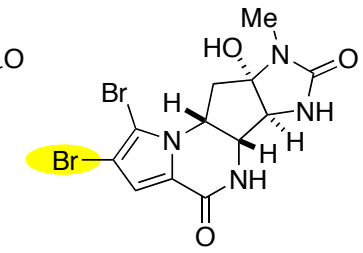
8-27-2010

Agelastatin alkaloids

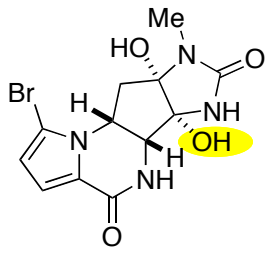
- 6 Agelastatins A-F isolated so far, differences in substitution pattern



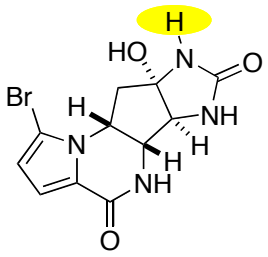
Agelastatin A



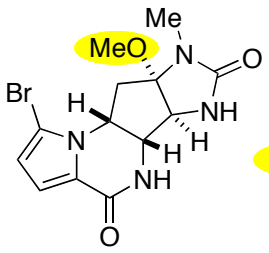
Agelastatin B



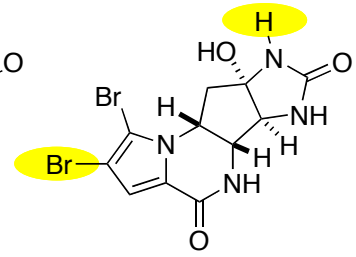
Agelastatin C



Agelastatin D



Agelastatin E



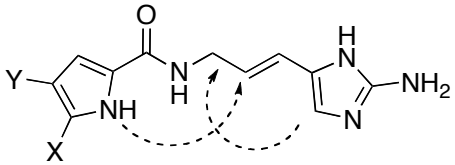
Agelastatin F

Pietra *et al. J. Chem. Soc., Chem. Commun.* **1993**, 1305.

Molinski *et al. J. Nat. Prod.* **1998**, *61*, 158.

Al-Mourabit *et al. J. Nat. Prod.* **2010**, *73*, 720.

- Agelastatin A biological activity:
  - Singnificant antitumor activity against wide range of tumor cells (in nM range)
  - Highly toxic towords anthropods (LC_{50}= 1.7 ppm in brine shrimp assay)
  - Insecticidal against beet army worm and corn root worm
  - Selectivly inhibits the glycogen synthase kinase-3b, a potential target for the treatment of Alzheimer's disease and bipolar disorder.
- Biosynthetically originate from simpler pyrrole-imidazole alkaloids



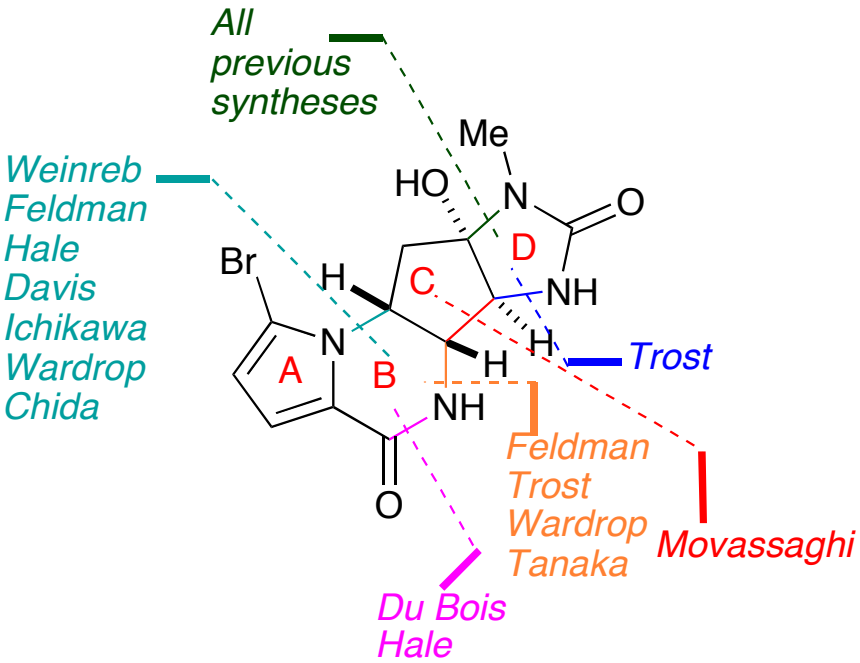
X = Y = H clathrodin
X = H, Y = Br hymenidin
X = Y = Br oroidin

Movasaghi, Siegel and Han, *Chem. Sci. Advance article.*

Trost and Dong, *CEJ* **2009**, *15*, 6910.

Previous synthetic work: Agelastatin A - benchmark for showcasing methodology

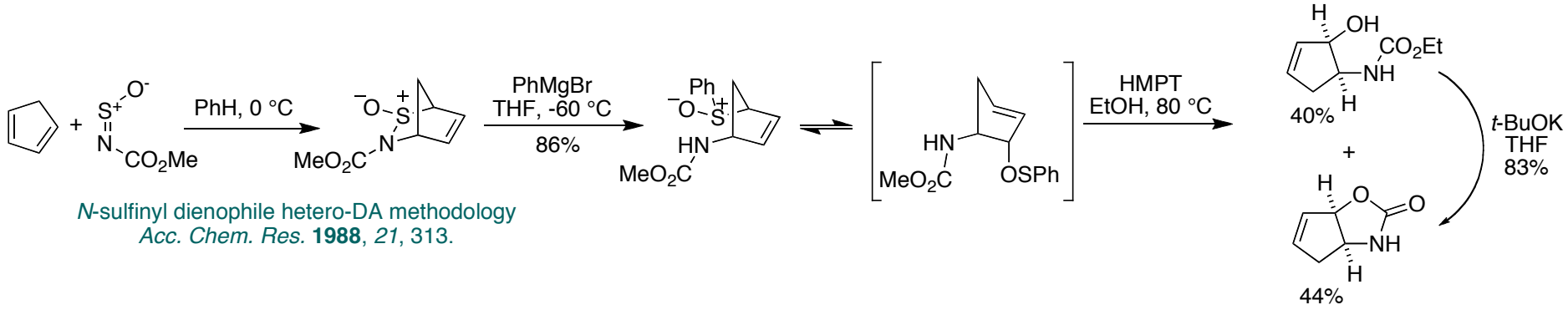
- 10 total syntheses published prior to the title paper
- First synthesis: Weinreb 1999, first asymmetric synthesis: Feldman 2002.



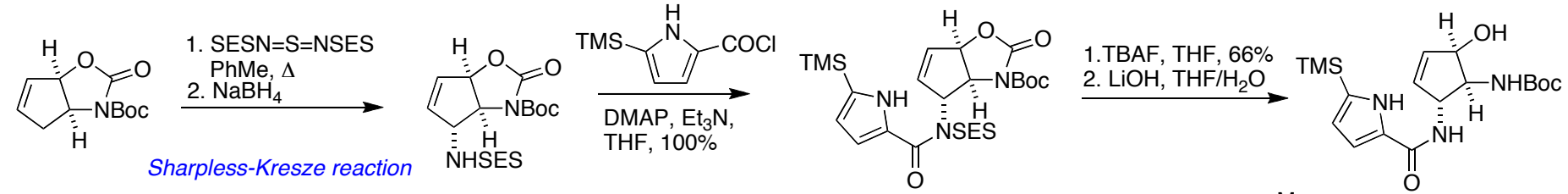
Weinreb: *JOC* **1998**, *63*, 7594 and *JACS* **1999**, *121*, 9574.
Feldman: *JACS* **2002**, *124*, 9060 and *JOC* **2002**, *67*, 7096.
Hale: *OL* **2003**, *5*, 2927 and *OL* **2004**, *6*, 2615.
Davis: *OL* **2005**, *7*, 621 and *SC* **2009**, *39*, 1914 (CL in Feb. 2005 by Mike Rishel).
Trost: *JACS* **2006**, *128*, 6054 and *CEJ* **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.
Du Bois: *ACIE* **2009**, *48*, 3802 (CL in May 2009 by Melissa).

- In all previous synthesis cyclopentane ring C is set early and the rest of molecule is elaborated around it
- Ring C contains 4 stereocenters and this highly substituted cyclopentane was target for showcasing various methodologies.

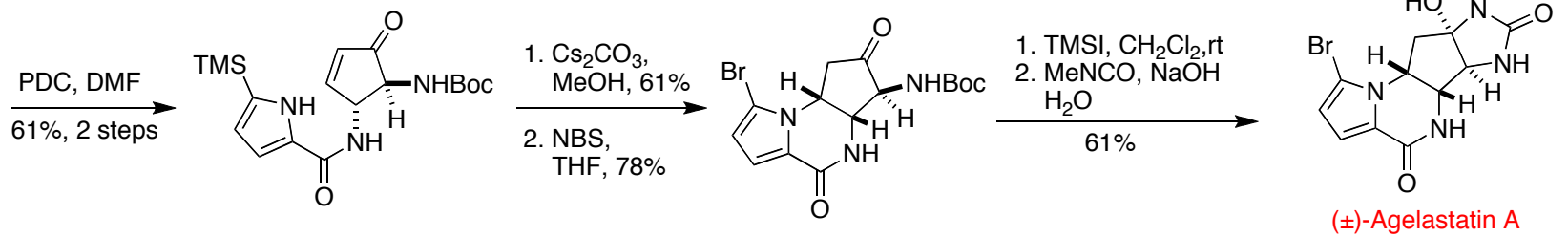
Weinreb's synthesis of (±)-Agelastatin A



N-sulfinyl dienophile hetero-DA methodology
Acc. Chem. Res. **1988**, *21*, 313.



Sharpless-Kresze reaction

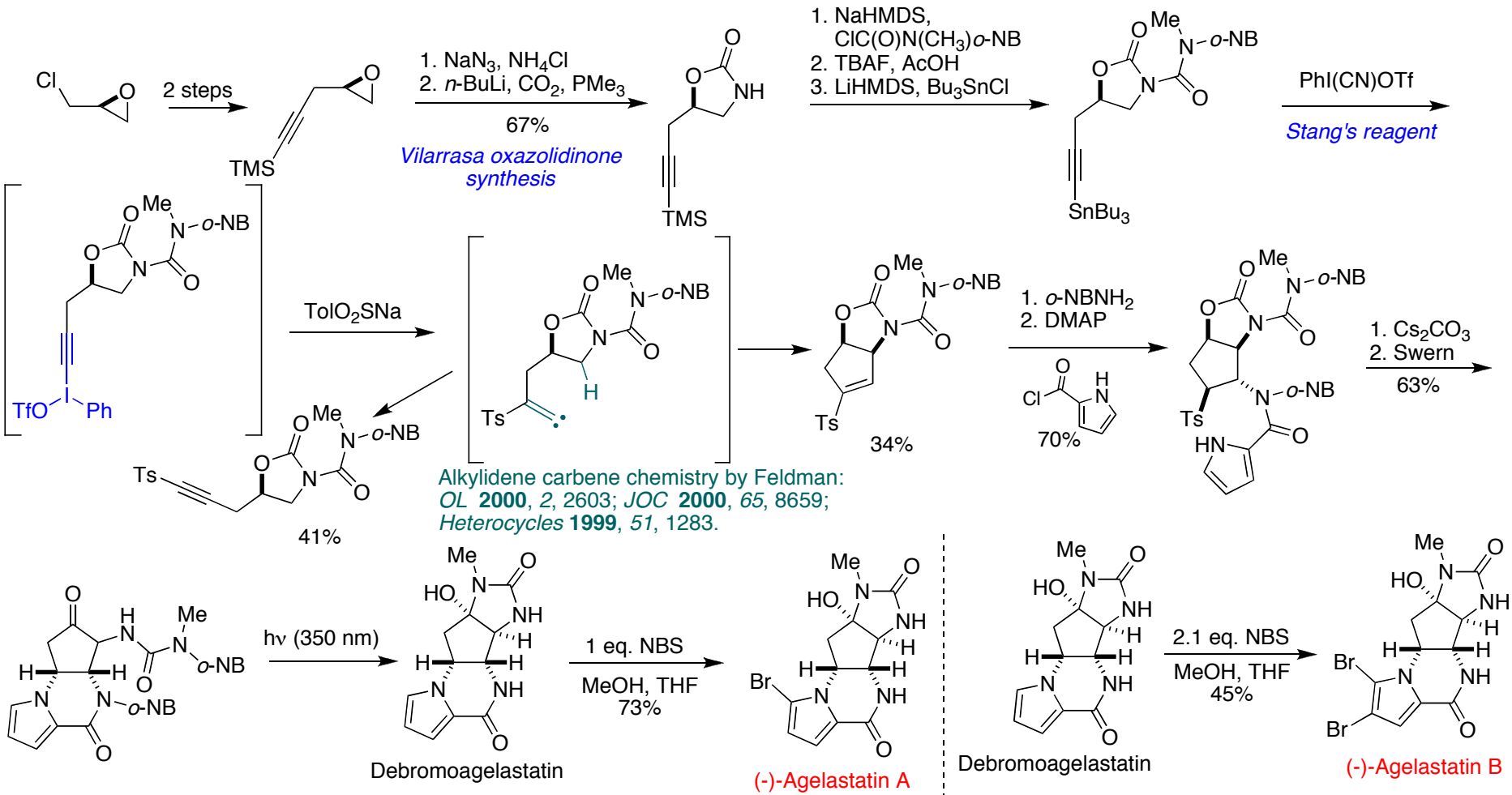


(±)-Agelastatin A
14 steps, 7% overall yield

- The first total synthesis of agelastatin A
- Key steps: hetero DA reaction, Sharpless-Kresze allylic amination (new SES reagent) and internal Michael addition of pyrrole nitrogen
- Why not brominate debromoagelastatin, previously made in Weinreb group?

JOC **1998**, *63*, 7594. *JACS* **1999**, *121*, 9574.

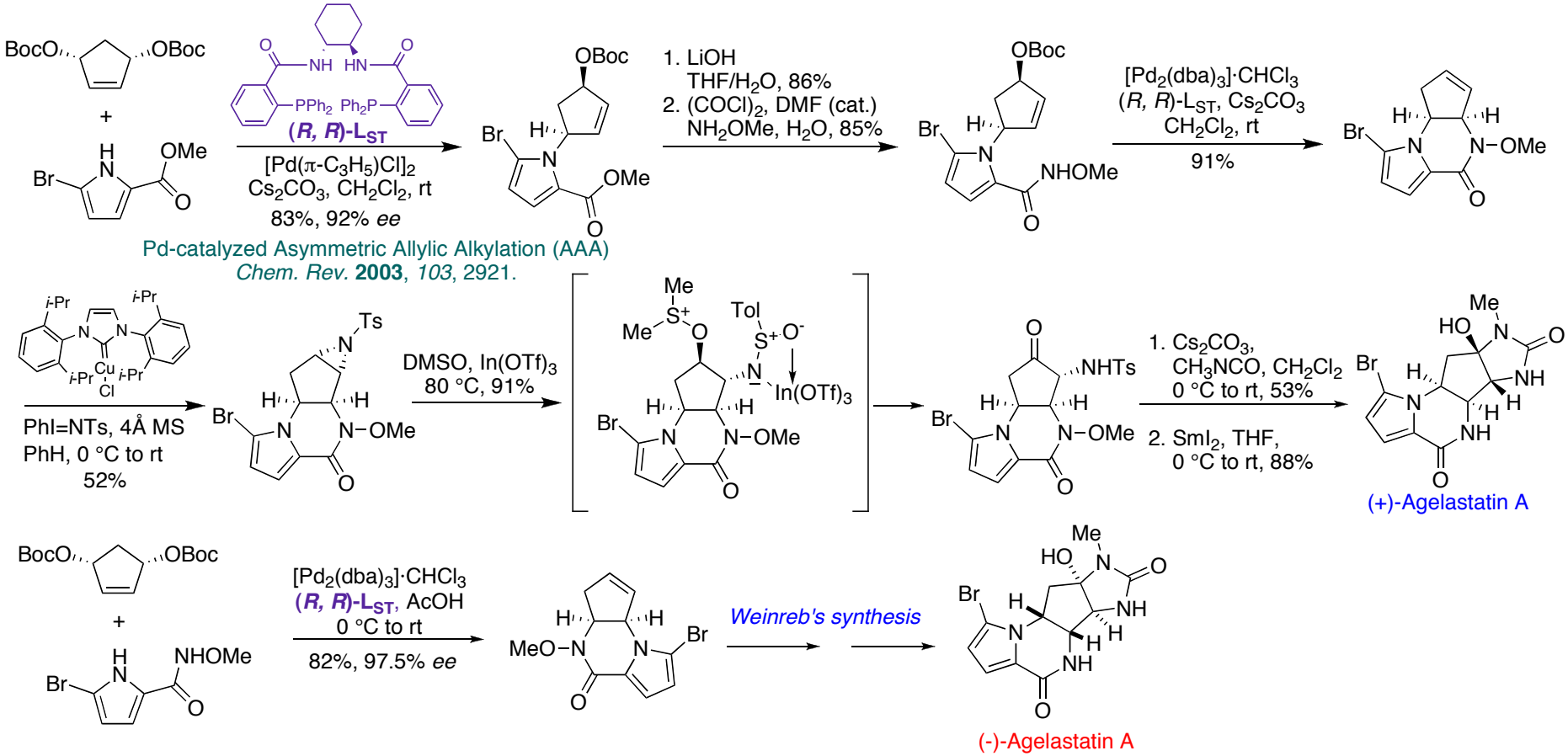
Feldman's Synthesis of (-)-Agelastatins A and B



- The first enantioselective total synthesis of (-)-agelastatin A
- Cyclopentane core was synthesized using alkylnyliodonium salt mediated cyclization

JOC **2002**, *67*, 7096. *JACS* **2002**, *124*, 9060.

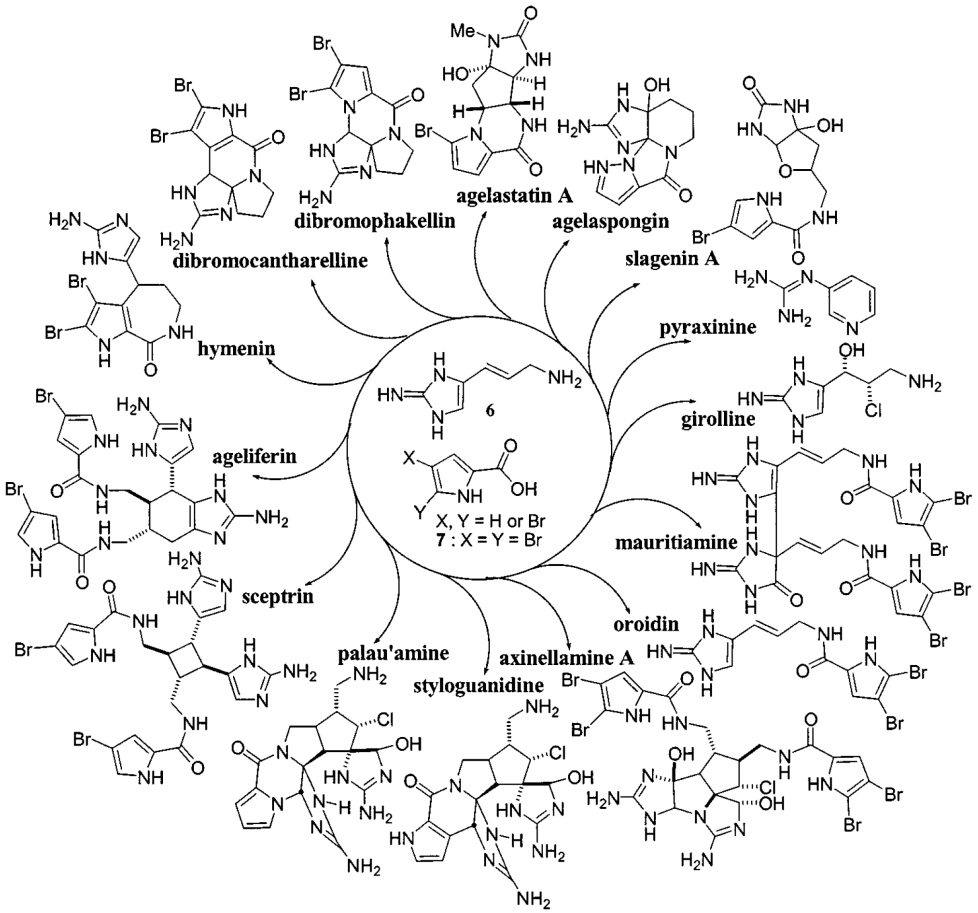
Trost's Synthesis of (+)- and (-)-Agelastatin A

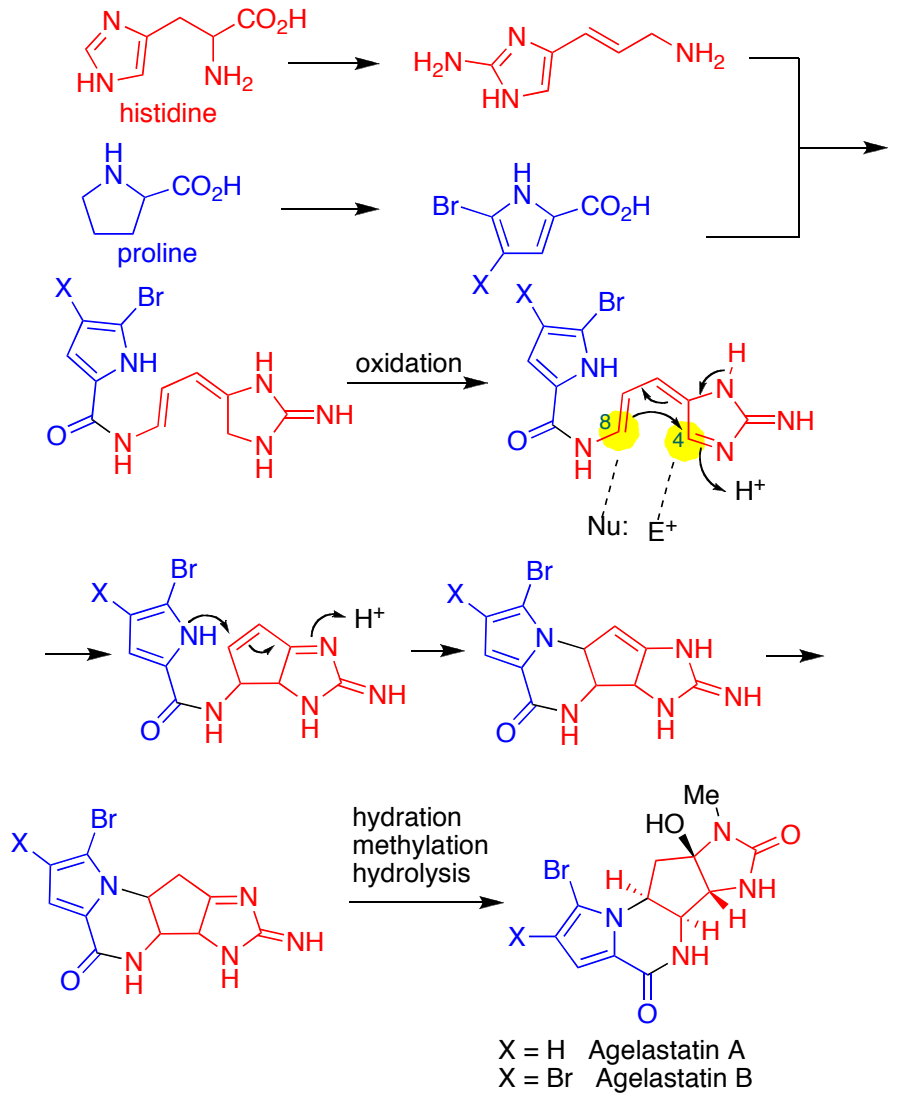


- New methodologies such as Pd-catalyzed asymetric allylic alkylation (AAA) using pyrrole as nucleophile and $In(OTf)_3$ catalyzed oxidative aziridine opening using DMSO were developed.
- Both enantiomers of Agelastatin A were synthesized from the same enantiomer of a stereoconducting catalyst.

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

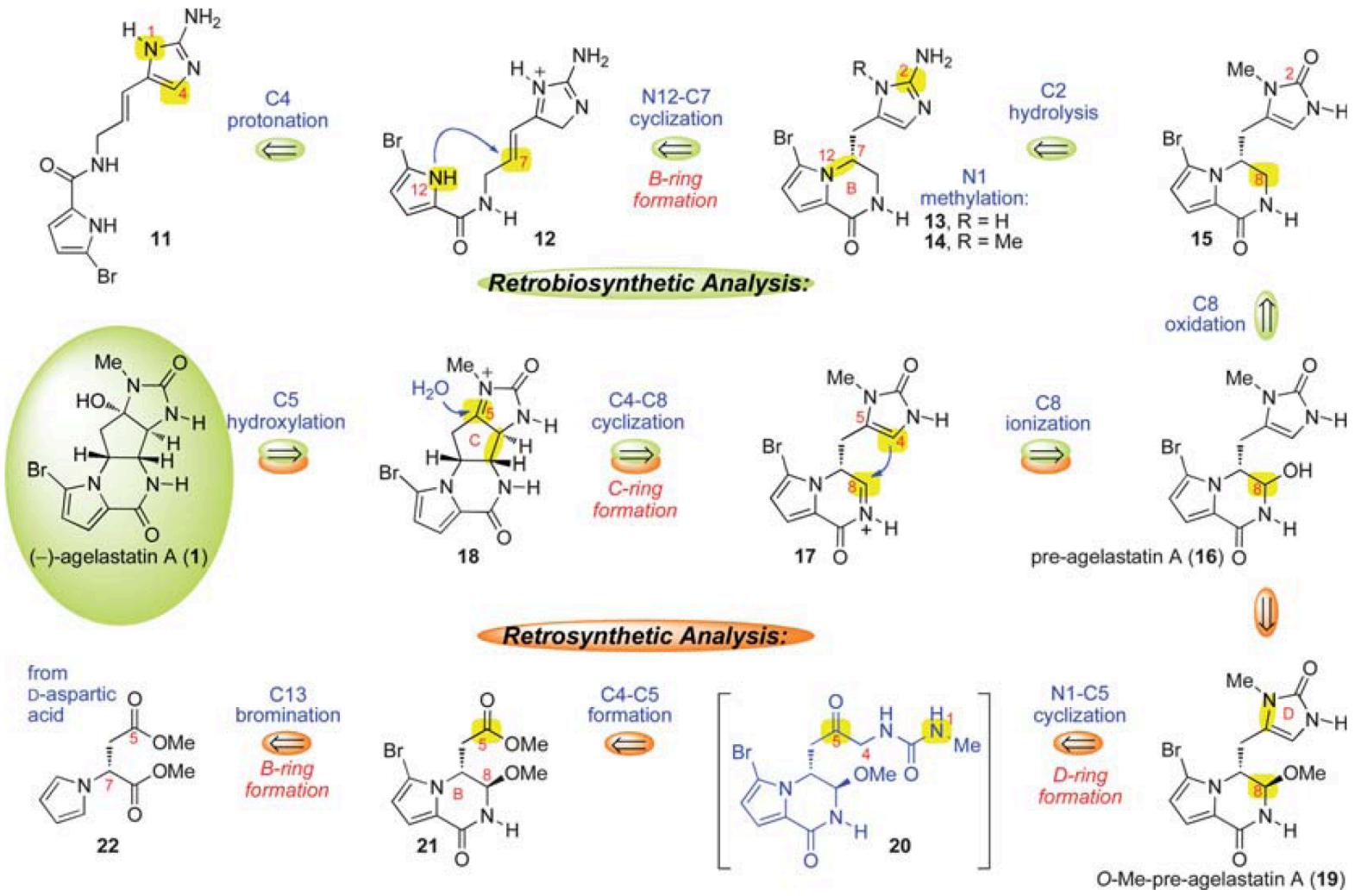
Biosynthesys of Oroidin-Based Pyrrole-Imidazole Alkaloids



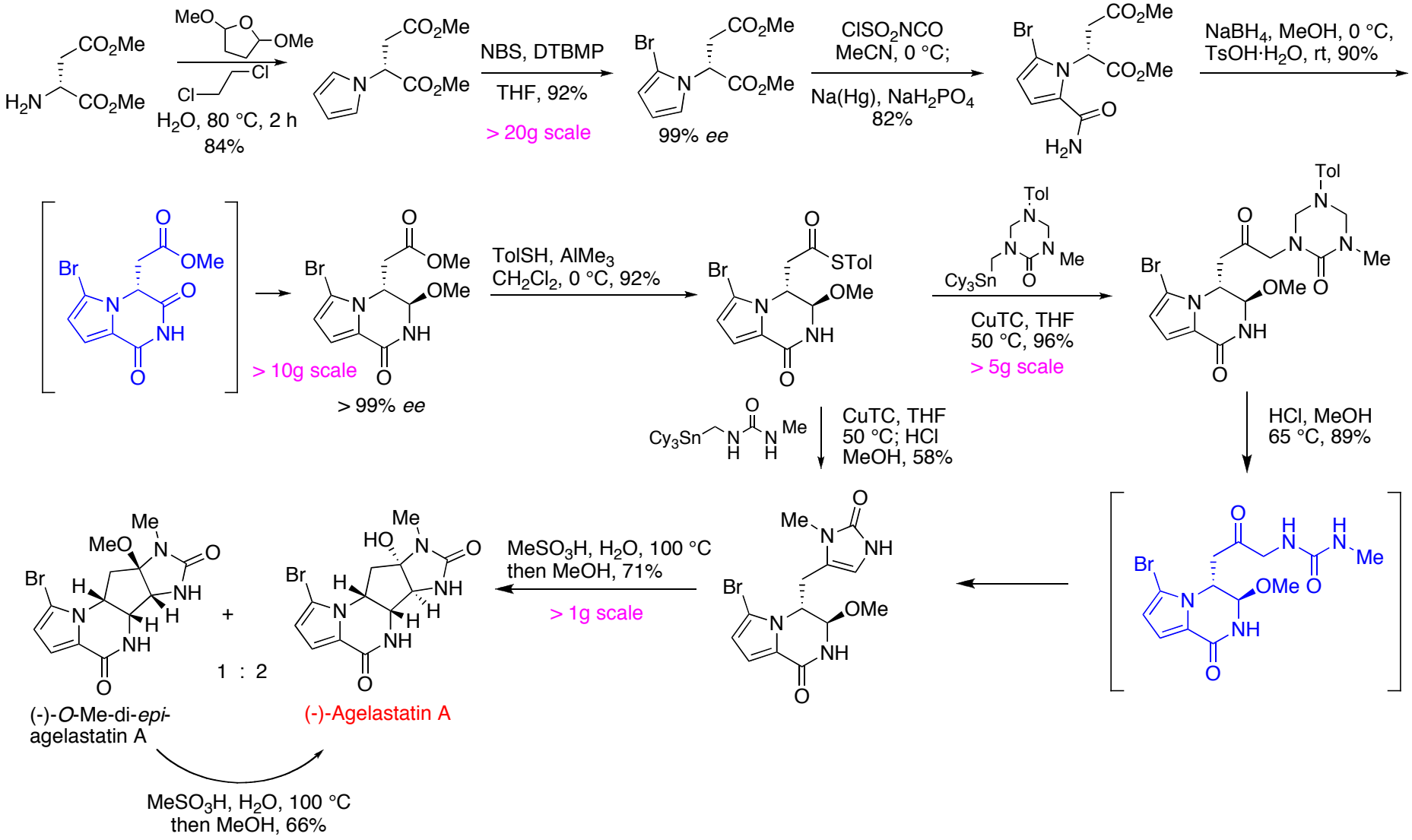


Ali Al Mourabit and Pierre Potier *Eur. J. Org. Chem.* **2001**, 237.

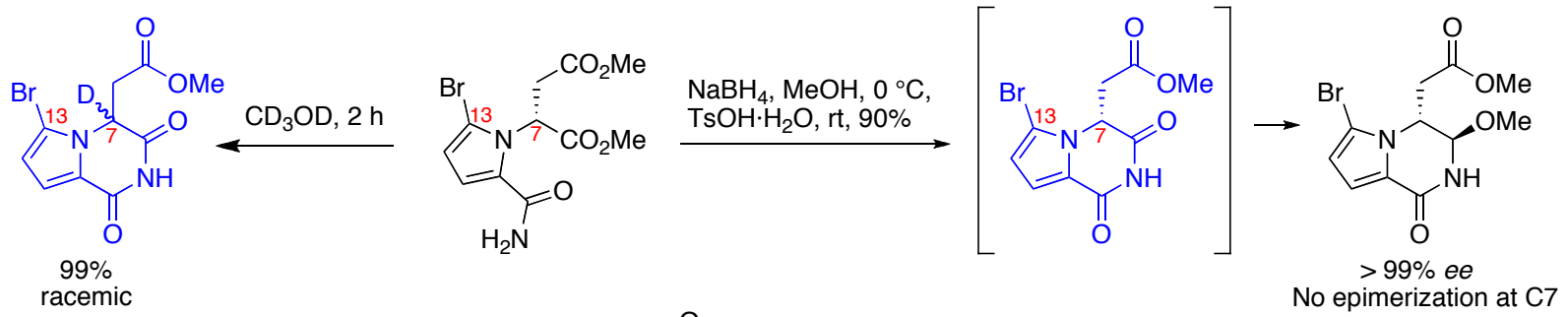
Title Paper: Biosynthetic Hypothesis and Design Plan for Total Synthesis of Agelastatins

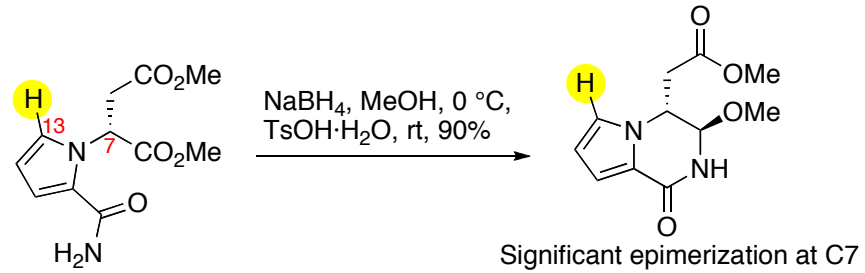


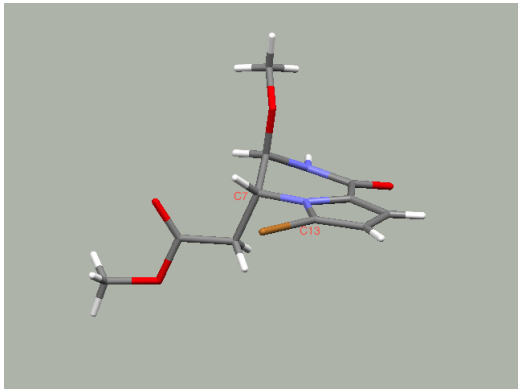
Title Paper: Synthesis of (-)-Agelastatin A

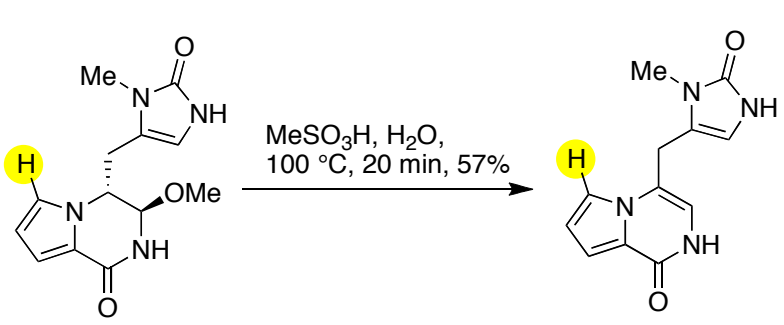


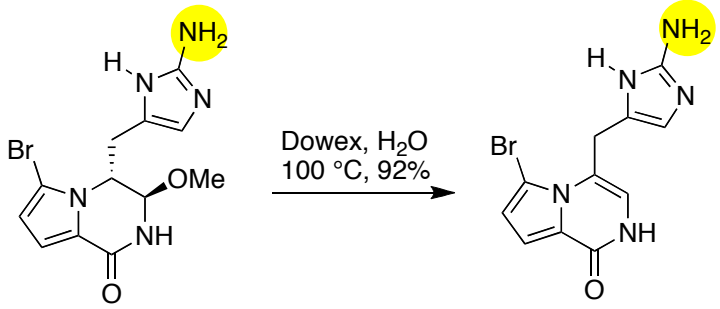
The Importance of C13 Bromine Substituent and Imidazolinone



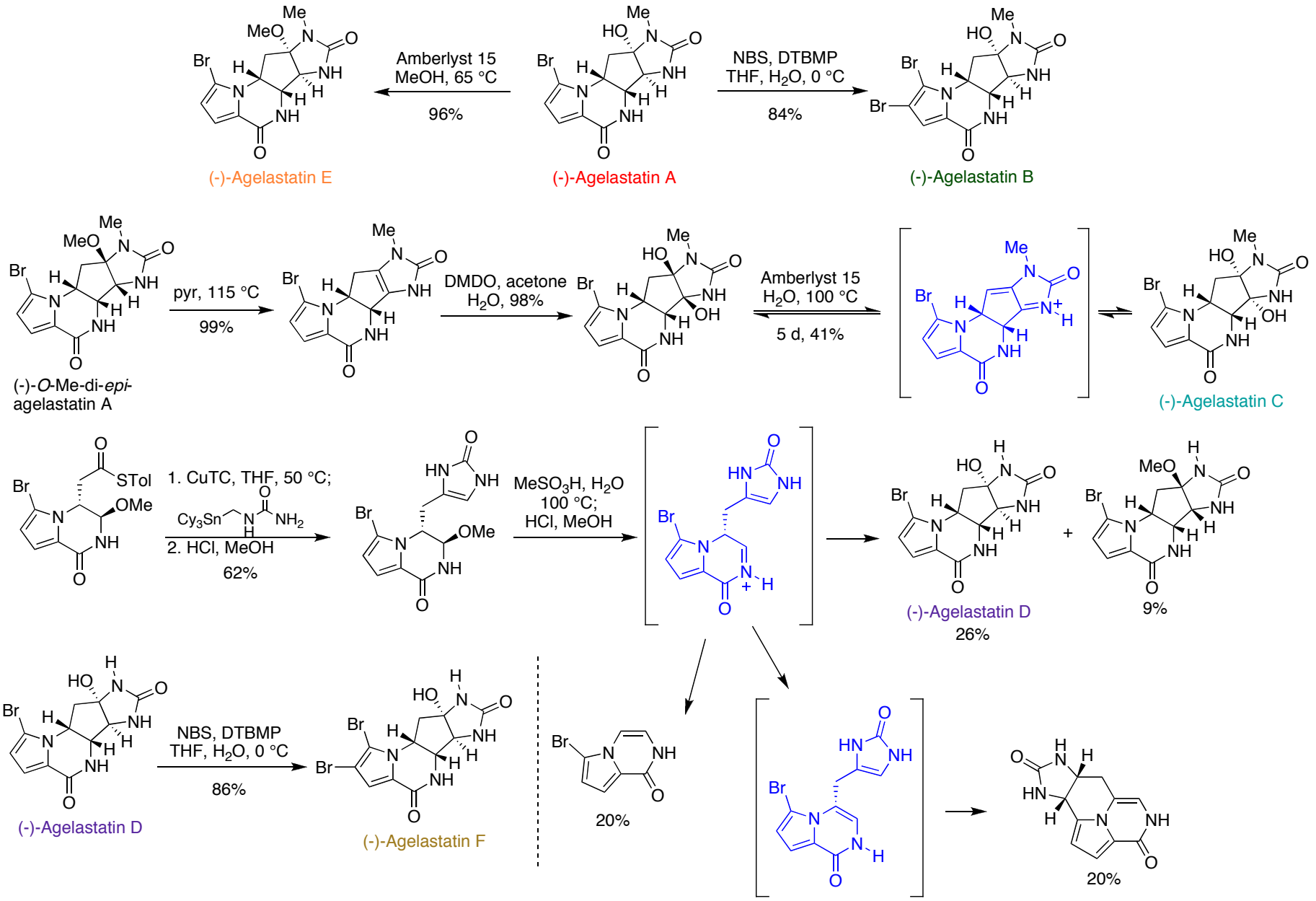








Title Paper: Synthesis of (-)-Agelastatins B-F



Conclusions

- All known agelastatin alkaloids were synthesized employing biosynthetically inspired strategy
- "Pre-agelastatin" derivatives were obtained in multi-gram quantities
- C13 bromine substitution was critical for the successful C-ring cyclization
- Agelastatin A was prepared in 1.4 g batch and bilogical and chemical studies of that compound are ongoing.
- Authors suggest higher probability for biosynthetic introduction of C13-bromopyrrole and imidazolone substructures prior to C-ring formation and this hypothesis is yet to be experimentally checked.