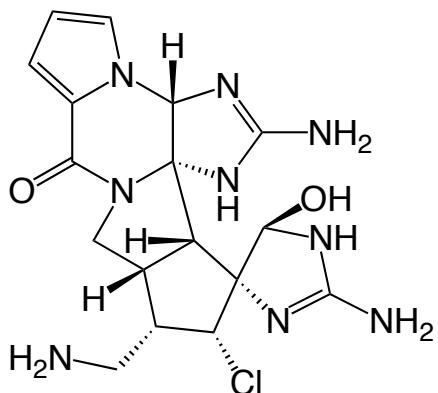


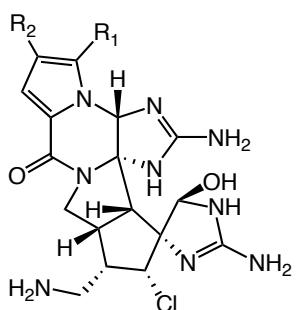
# Synthetic Efforts Toward Palau'amine

Doug Behenna, Ryan McFadden  
Eric Ashley, Jenn Stockdill  
Akihiko Iwashita

August 9, 2004



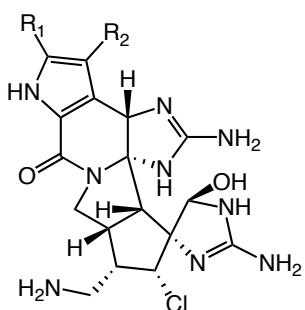
## Isolation of Palau'amine and Congeners



R<sub>1</sub> = R<sub>2</sub> = H Palau'amine  
R<sub>1</sub> = H, R<sub>2</sub> = Br 4-Bromo Palau'amine  
R<sub>1</sub> = R<sub>2</sub> = Br Dibromo Palau'amine

### Palau'amines

- Isolated from marine sponge *Styloctella aurantium*
- Structural determination by <sup>1</sup>H NMR
- Cytotoxic against P-388 (0.1 µg/mL), A549 (0.2 µg/mL), HT-29 (2µg/mL) and KB (10 µg/mL)
- Antibiotic against *Staphylococcus aureus* and *Bacillus subtilis*
- Antifungal against *Penicillium notatum*
- Kinnel, R. B. et. al. *J. Am. Chem. Soc.* **1993**, 115, 3376-3377 and *J. Org. Chem.* **1998**, 63, 3281-3886.

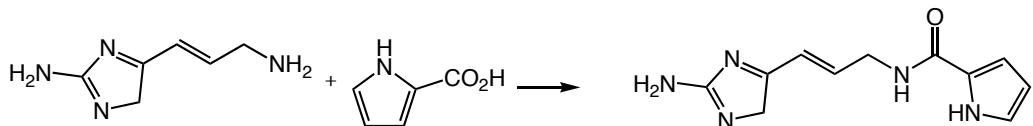
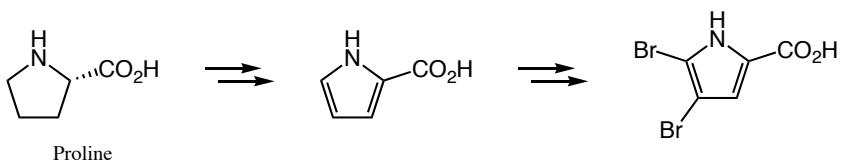
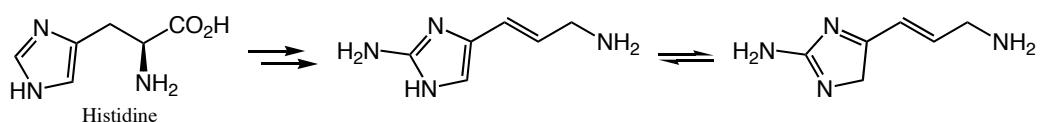


R<sub>1</sub> = R<sub>2</sub> = H Styloguanidine  
R<sub>1</sub> = H, R<sub>2</sub> = Br 3-Bromo Styloguanidine  
R<sub>1</sub> = R<sub>2</sub> = Br Dibromo Styloguanidine

### Styloguanidines

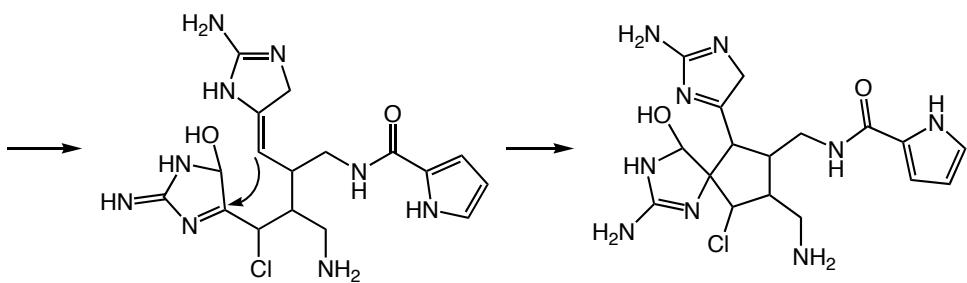
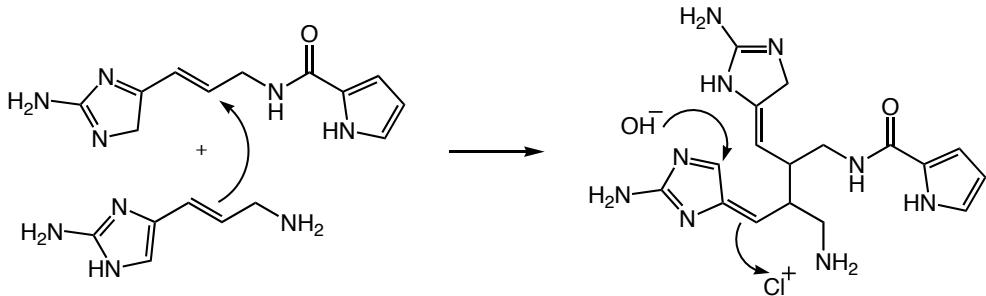
- Isolated from marine sponge *Styloctella aurantium*
- Structural determination by <sup>1</sup>H NMR
- All three compounds are potent chitinase inhibitors
- First reported by Kato, T. et. al. *Tetrahedron Lett.* **1995**, 36, 2133-2136.
- Also reported in Kinnel's second paper.

### Biosynthesis of Palau'amine

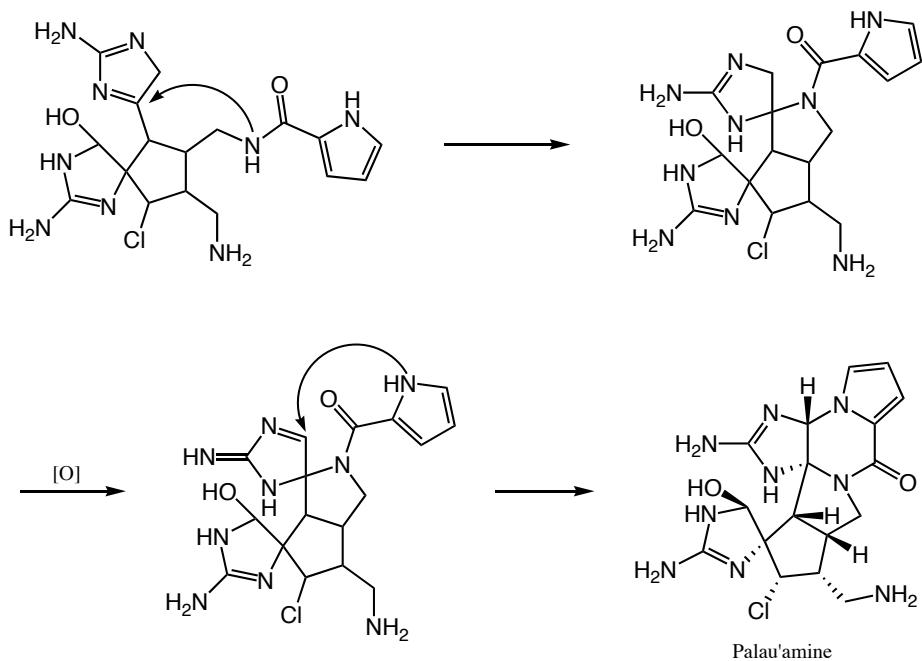


Mourabit, A. A.; Potier, P. *Eur. J. Org. Chem.*, **2001**, 237-243.

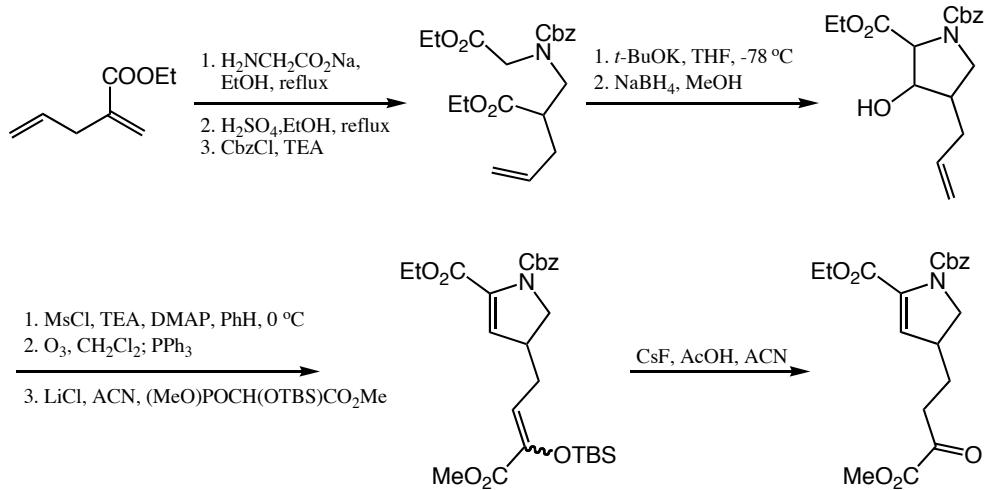
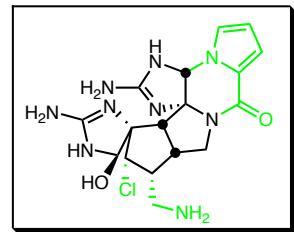
### Biosynthesis of Palau'amine



### Biosynthesis of Palau'amine

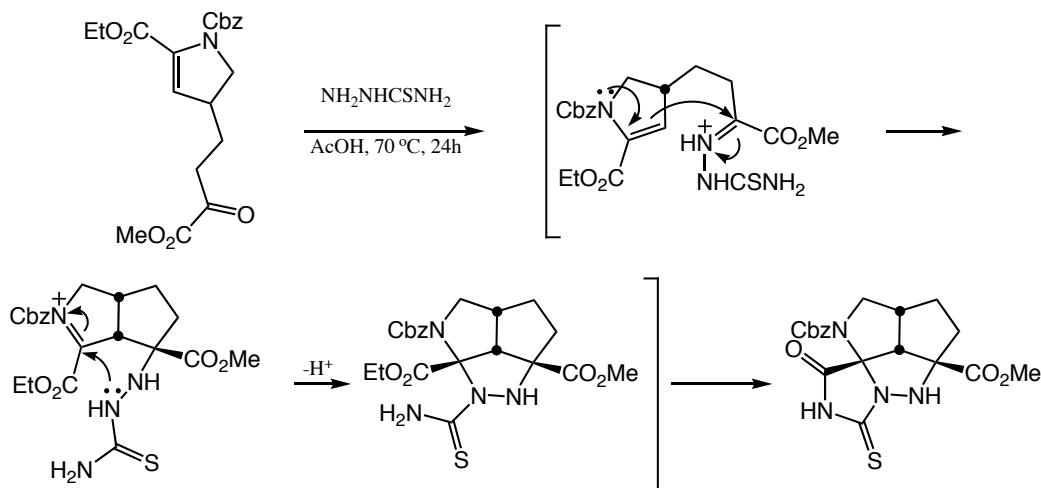
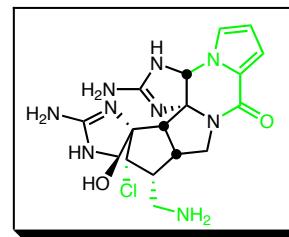


### Overman's Stereocontrolled Synthesis of the Tetracyclic Palau'amine Core



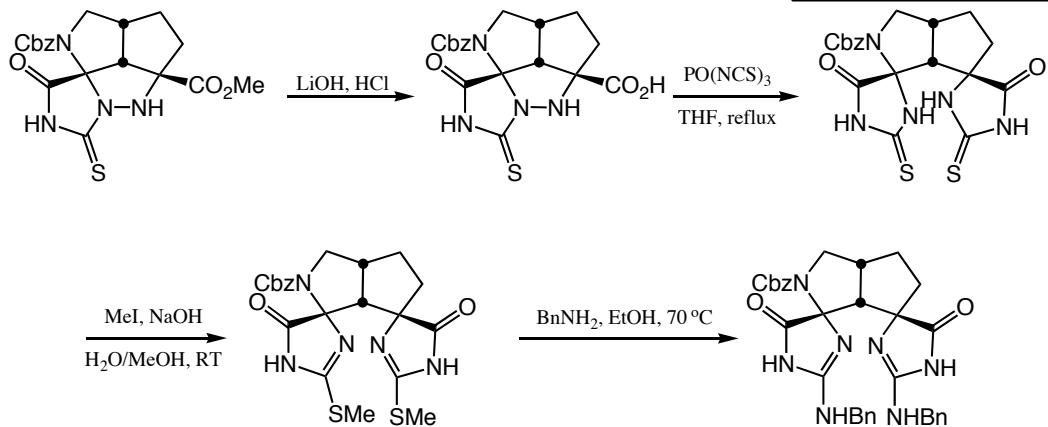
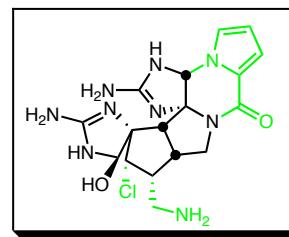
Overman, L.E. et al., *J. Am. Chem. Soc.* **1997**, *119*, 7159-7160.

*Overman's Stereocontrolled Synthesis  
of the Tetracyclic Palau'amine Core*



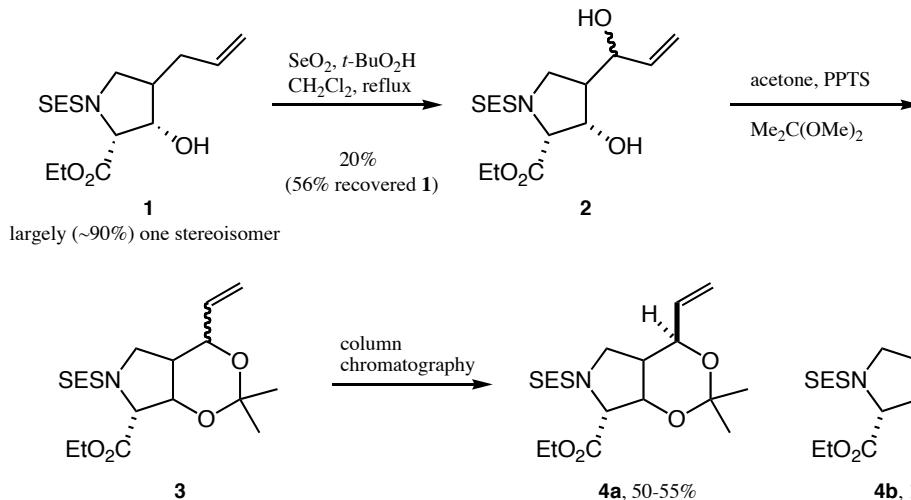
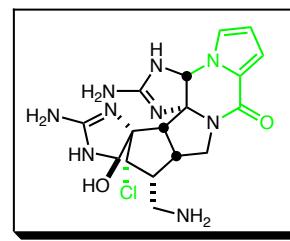
Overman, L.E. et. al., *J. Am. Chem. Soc.* **1997**, 119, 7159-7160.

*Overman's Stereocontrolled Synthesis  
of the Tetracyclic Palau'amine Core*

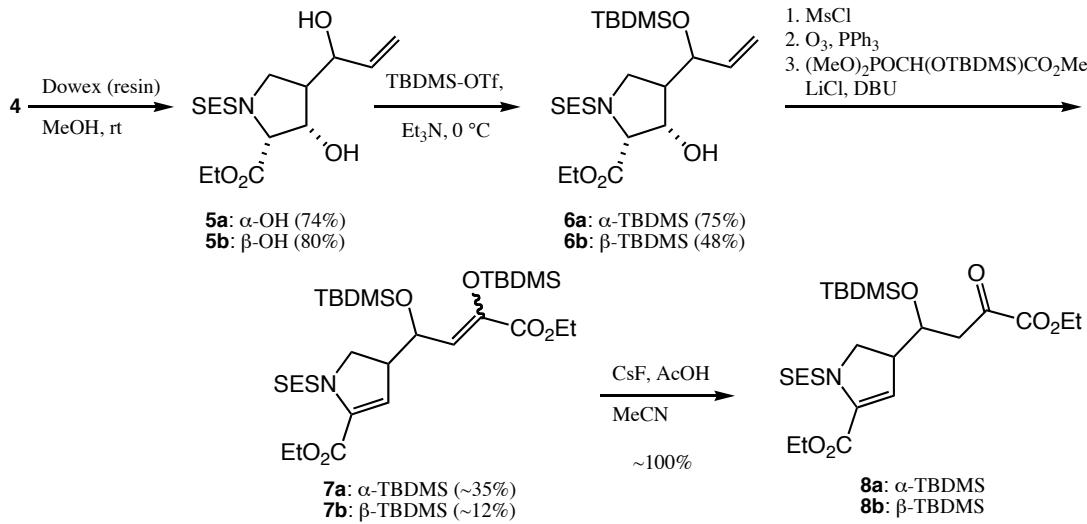
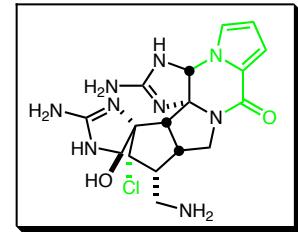


Overman, L.E. et. al., *J. Am. Chem. Soc.* **1997**, 119, 7159-7160.

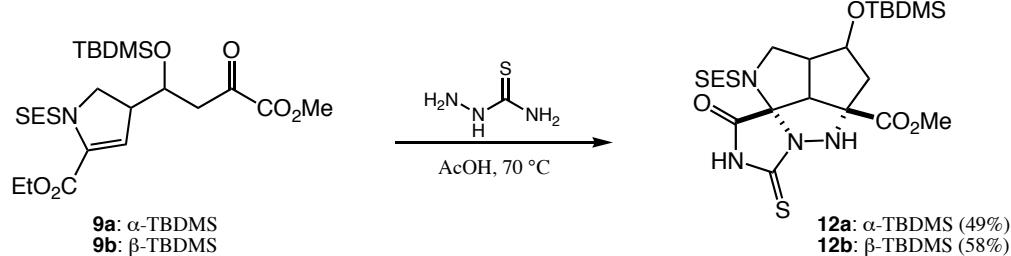
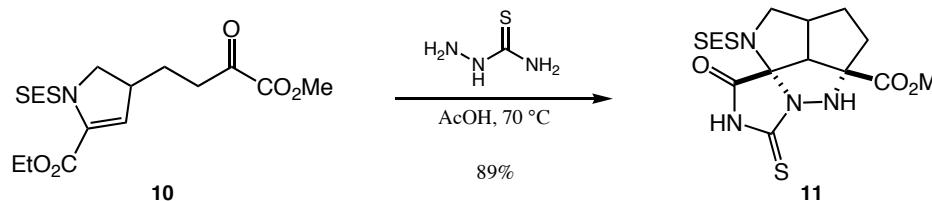
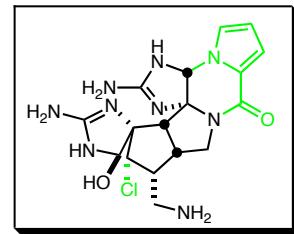
*Synthesis of Epimeric Cyclization Precursors*



*Synthesis of Epimeric Cyclization Precursors*

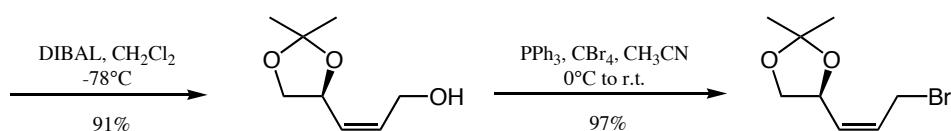
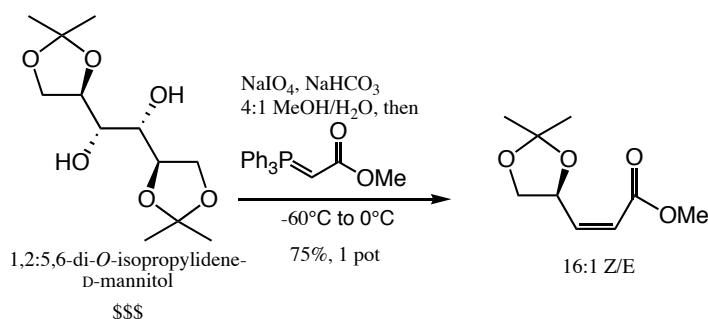
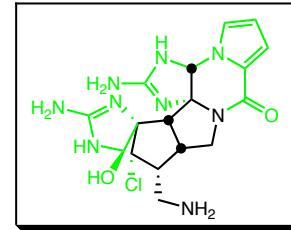


## Intramolecular Cycloaddition Reactions



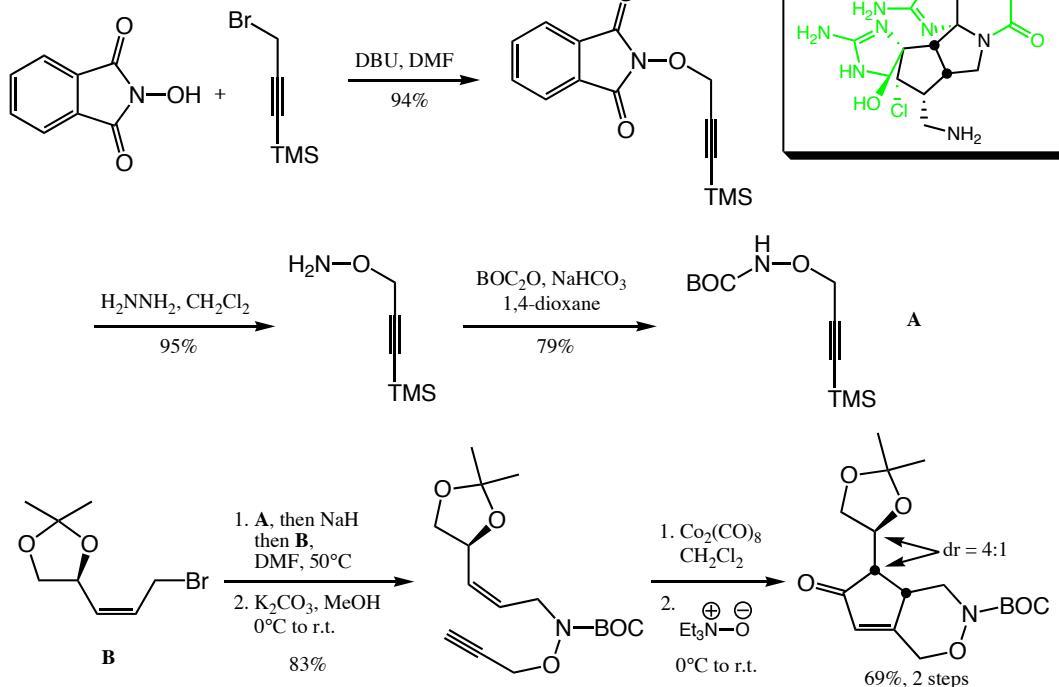
L. E. Overman *et al.* *J. Org. Chem.* **2002**, *67*, 7880-7883.

## The Pauson-Khand Approach



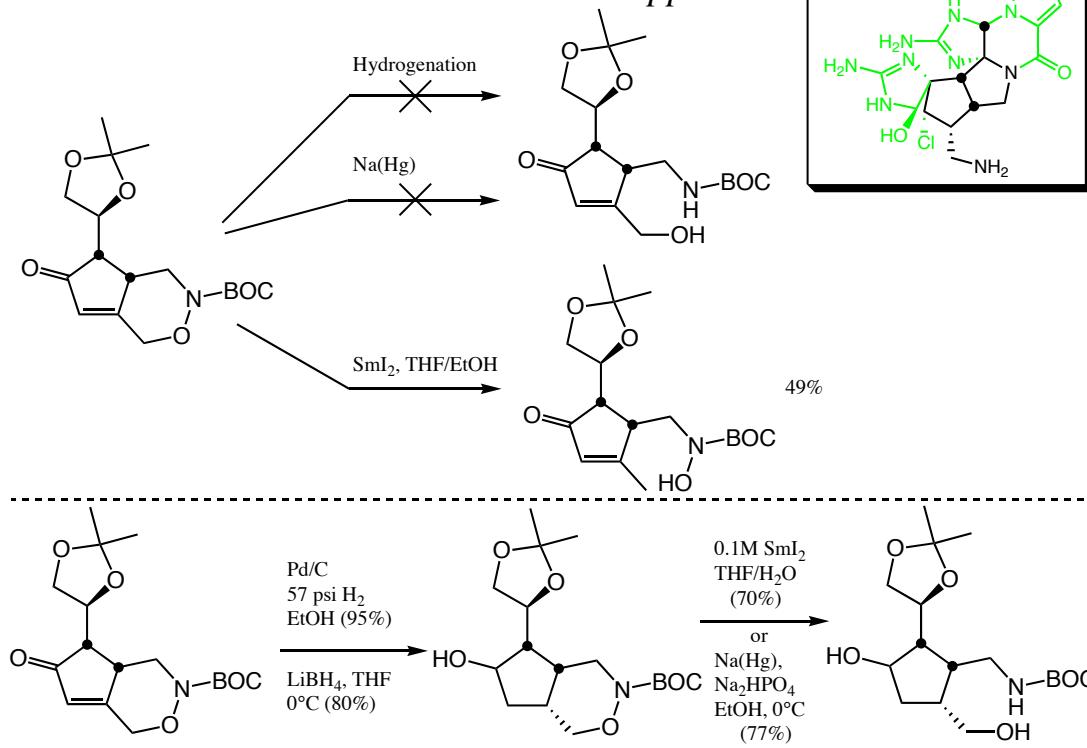
Austin, D. J., *et. al.*, *Org. Lett.* **2003**, *5*, 2203-2206.

*The Pauson-Khand Approach*



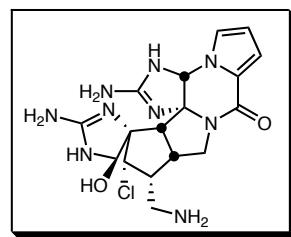
Austin, D. J., et. al., *Org. Lett.* **2003**, 5, 2203-2206.

*The Pauson-Khand Approach*

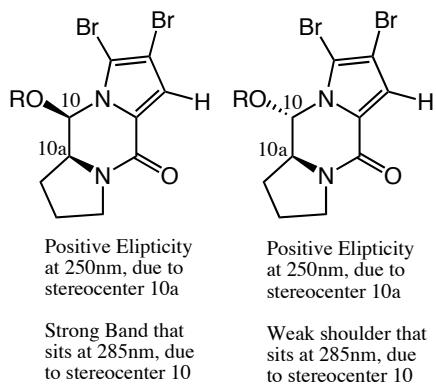


Austin, D. J., et. al., *Org. Lett.* **2003**, 5, 2203-2206.

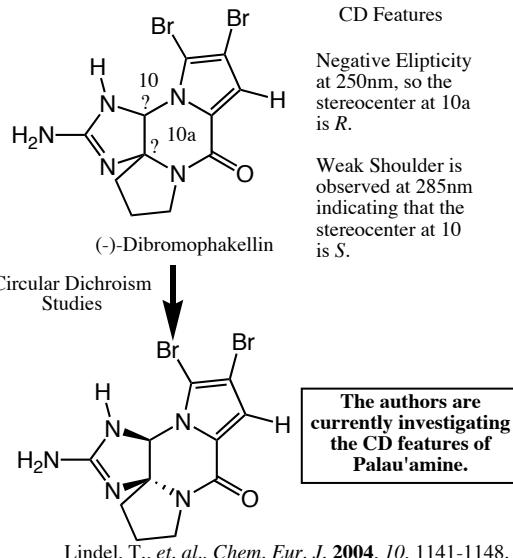
*Studies on Absolute Configuration  
of a Pyrrolopyrazinone related to  
Palau'amine*



CD Spectral Features of two synthetic models:

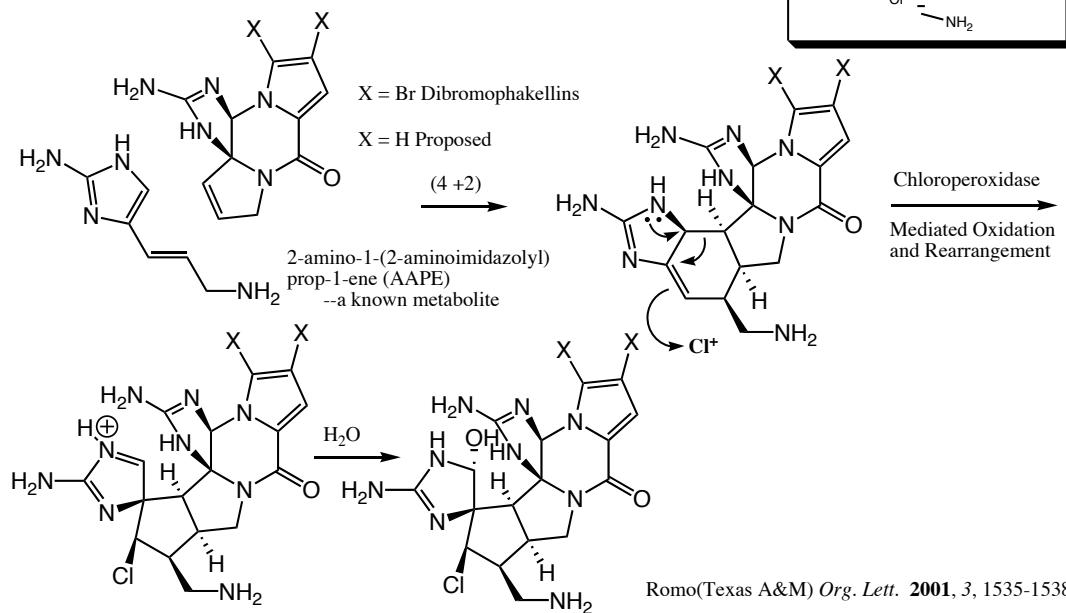


Whether R is Ac, R-MTPA, S-MTPA or just H, the CD spectrum is virtually unchanged!

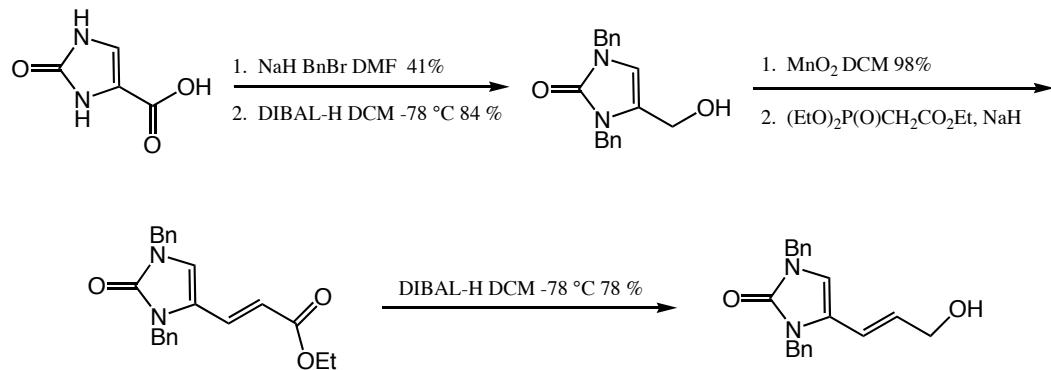
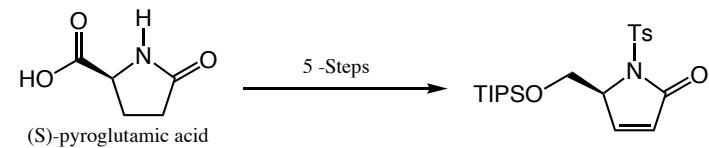
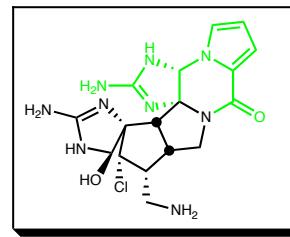


*Another Biosynthetic Hypothesis Driven Synthetic Effort*

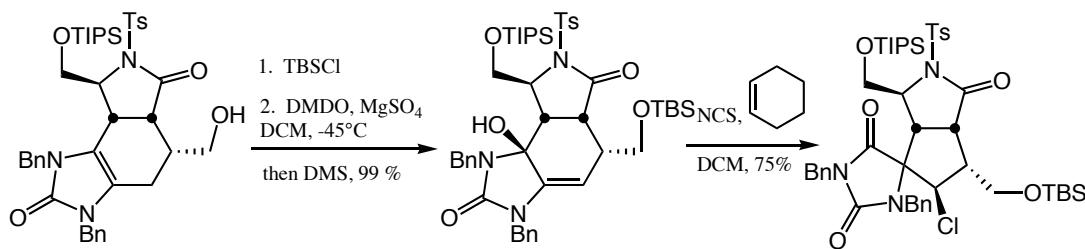
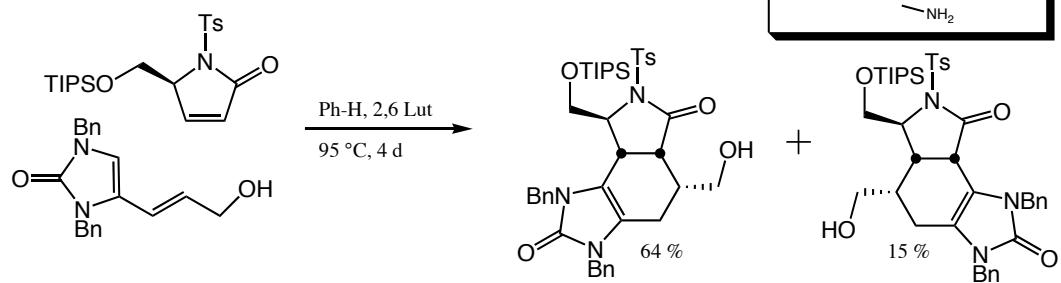
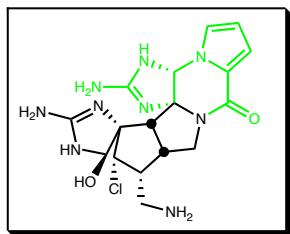
The Hypothesis:



## Building the Diels-Alder Fragments



## Key Diels-Alder / Ring Contraction Sequence



## Palau'amine Retrosynthetic Summary

