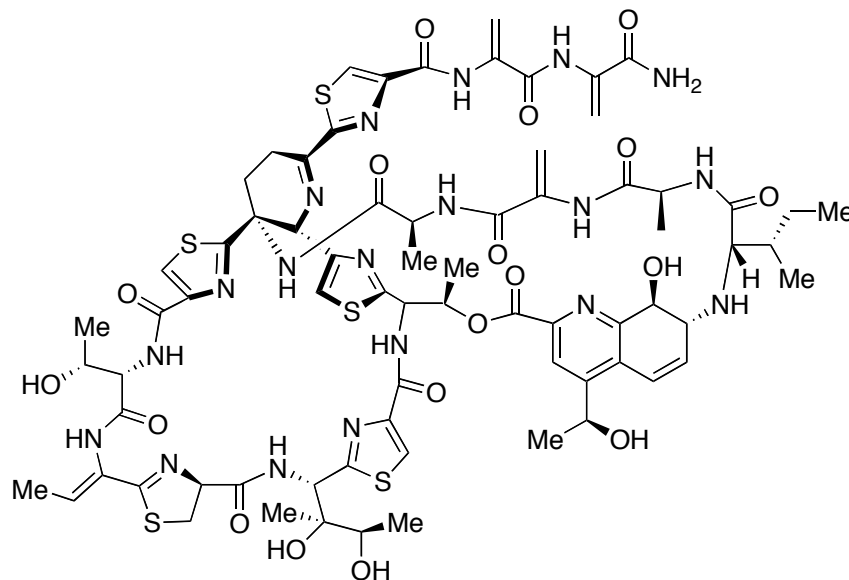


Total Synthesis of Thiostrepton



JACS, ASAP. K.C. Nicolaou, M. Zak, B. Safina, A. Estrada,
S.H. Lee, M. Nevalainen, M. Bella, C. Funke, F.J. Zecri, S. Bulat.

Isolation and Biological Activity

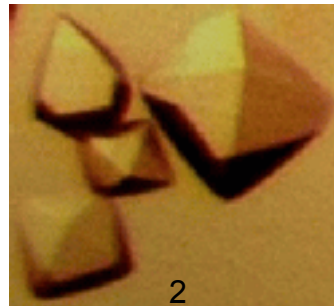
Thiostrepton, a thioazole-containing antibiotic first isolated from *Streptomyces azureus* in 1954, inhibits ribosome function, displaying activity against Gram- positive bacteria and *Plasmodium falciparum*, the causal agent of malaria.

It is commonly used to treat dog and cat skin irritation, especially irritation caused by a bacterial source.

Use in humans is limited by its low solubility in water and poor bioavailability.



While the structure was originally solved many years ago via degradative, spectroscopic, and X-ray techniques, it was not complete and coordinates were not placed in the public domain until 2001.



Thiostrepton crystals grown from chloroform.

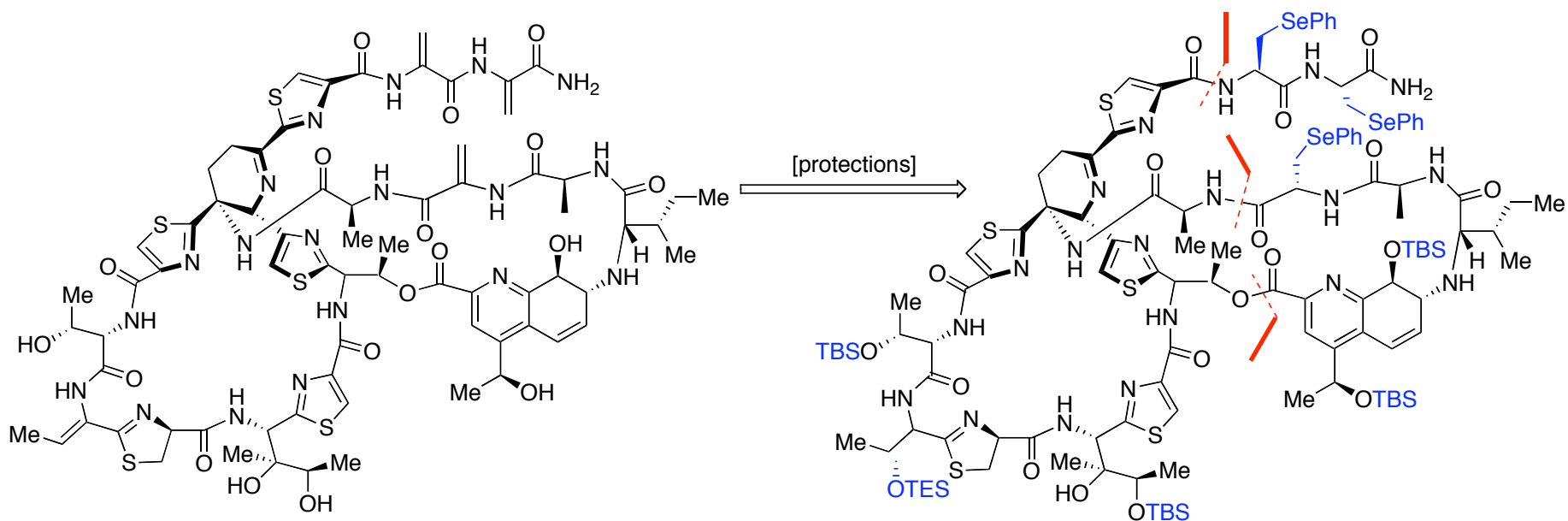
“Possessing a striking molecular architecture, thiostrepton was enticing to us not only because of its highly complex and sensitive functionality but also due to our desire to pay another visit to the land of heterocyclic chemistry. This allowed us to take on yet another arrogantly standing molecular devil, the likes of which had never been seen before.”

K.C. Nicolaou

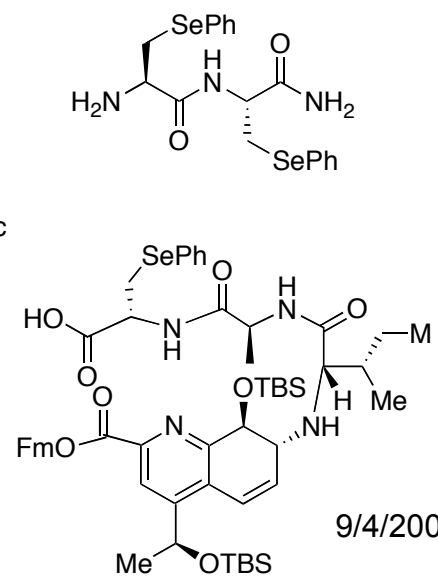
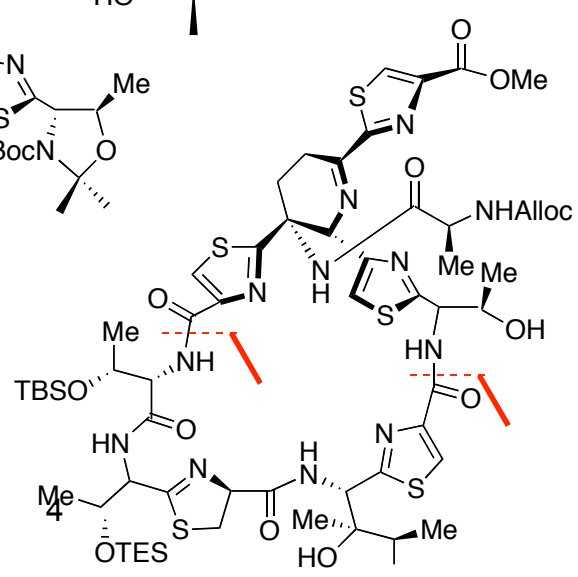
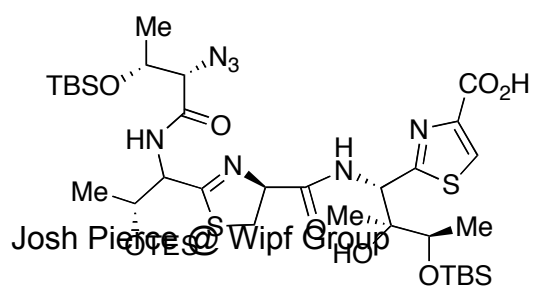
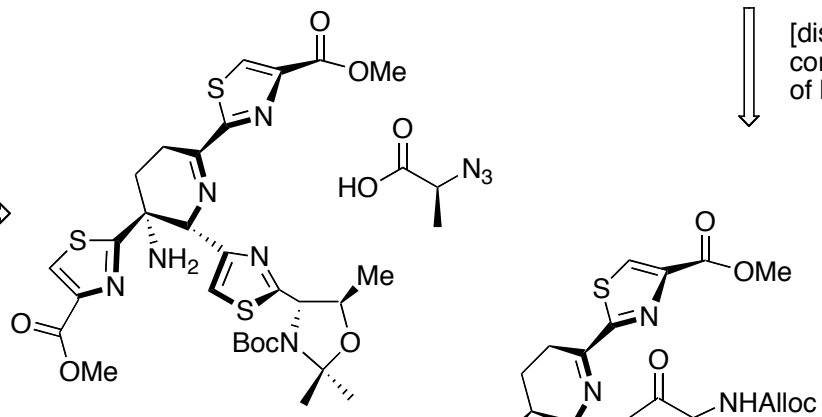
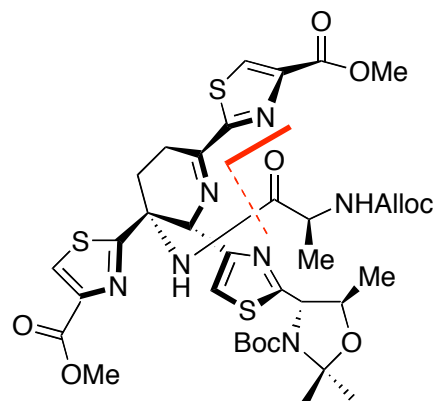
Joys of Molecules. I. Campaigns of Total Synthesis

JOC **2005**, 70, 7007.

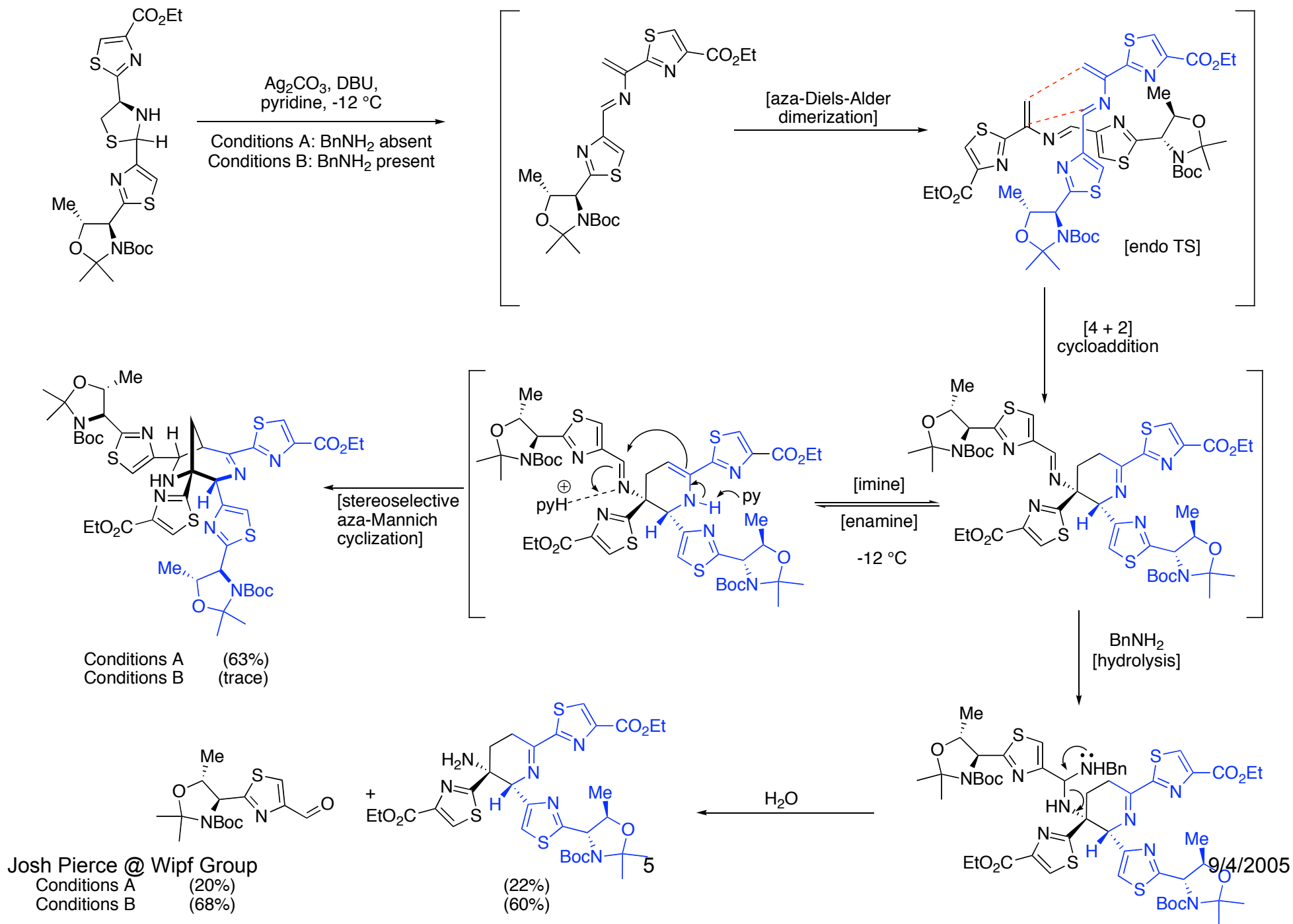
Retrosynthetic Analysis



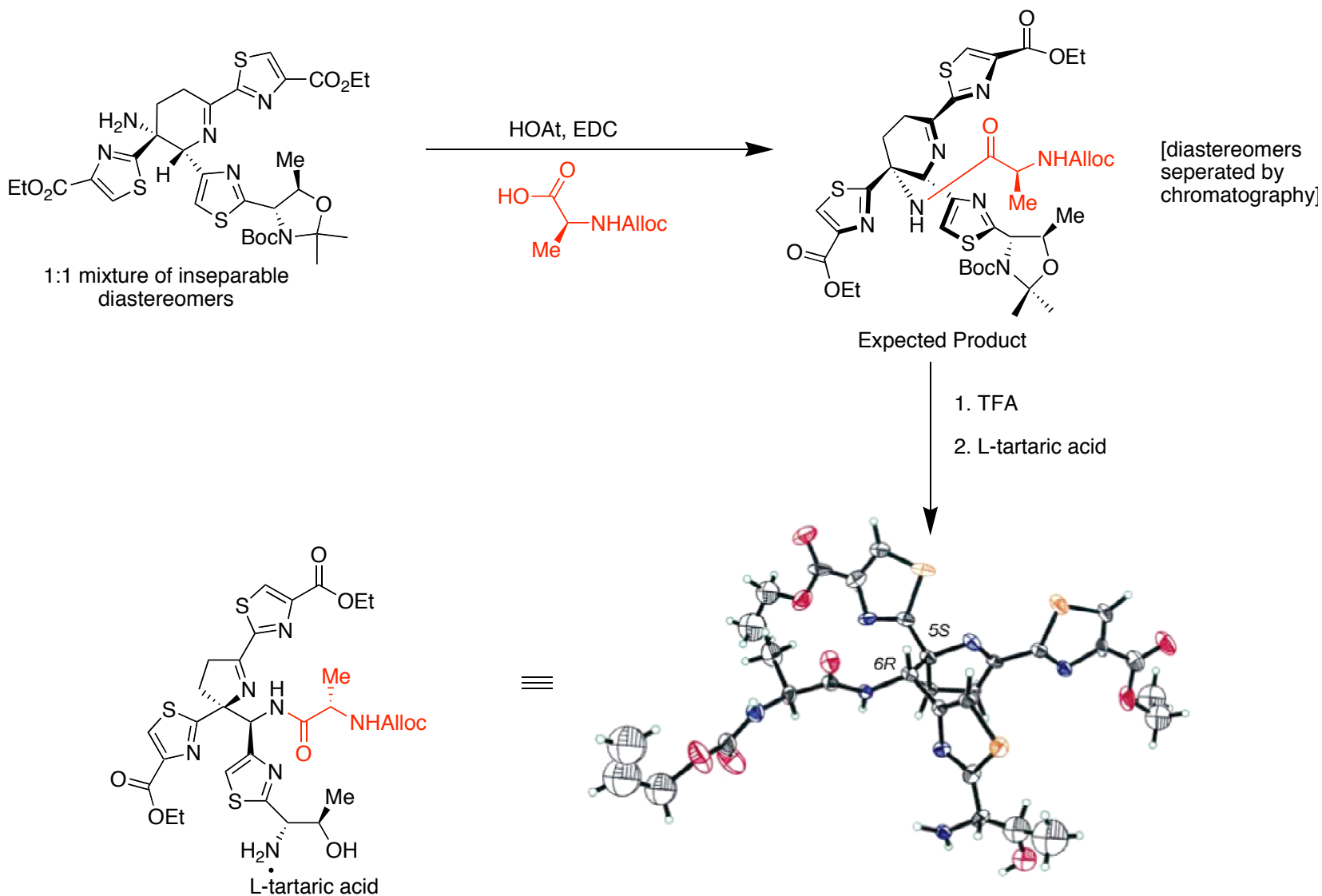
[disassembly of quinaldic acid-containing macrocycle and detachmer of bis-phenylselenium tail]



Hetero-Diels-Alder Dimerization Reaction

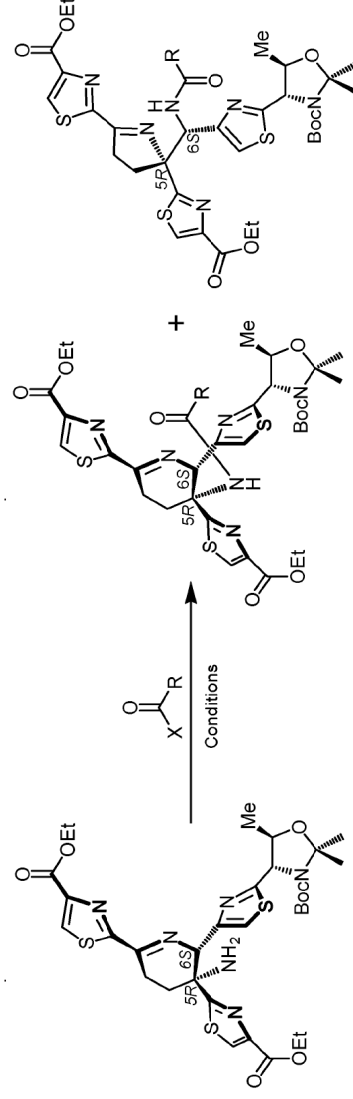


Unexpected Six- to Five-Membered Imine Ring Contraction during Attempted Coupling



Selective Capture of the Five- or Six-Membered Imine: Electrophile Effects

Josh Pierce @ Wipf Group

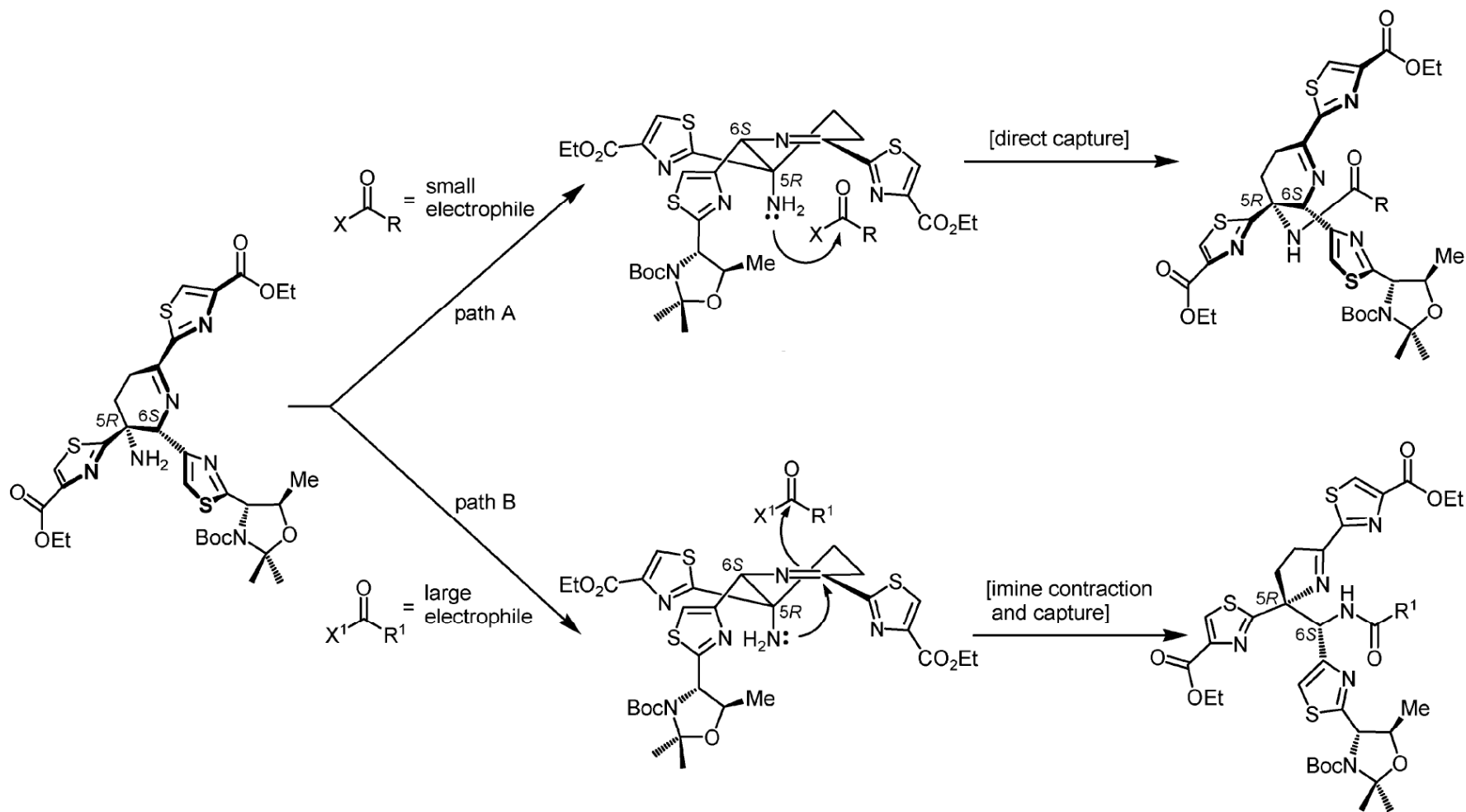


Entry	Electrophile Conditions	X	R	5-membered imine		Comments
				Product(s) [Ratio I (+ I') : II (+ II')]	Yield (%)	
1	 EDC (1.3 equiv), HOAT (1.2 equiv), DMF, 24 h, 25 °C			[0 : 100]	84	- large electrophile - exclusive 5-membered imine formation
2	 CH ₃ CN, 4 h, 25 °C			[0 : 100]	87	- large electrophile - exclusive 5-membered imine formation
3	 <i>i</i> -Pr ₂ NEt (10 equiv), 4-DMAP (0.2 equiv), CH ₂ Cl ₂ , 25 °C, 2 h			[75 : 25]	84	- medium-sized electrophile - mixture of 5- and 6-membered imines
4	 <i>i</i> -Pr ₂ NEt (3.0 equiv), THF, 0 °C, 2 h			[33 : 67]	76	- medium-sized electrophile - mixture of 5- and 6-membered imines
5	 <i>i</i> -Pr ₂ NEt (10 equiv), CH ₂ Cl ₂ , or THF, 25 °C, 2 h			[100 : 0]	83	- small electrophile - exclusive 6-membered imine formation
6	 Et ₃ N (8.0 equiv), THF, 0 °C, 1 h			[100 : 0]	70	- small electrophile - exclusive 6-membered imine formation

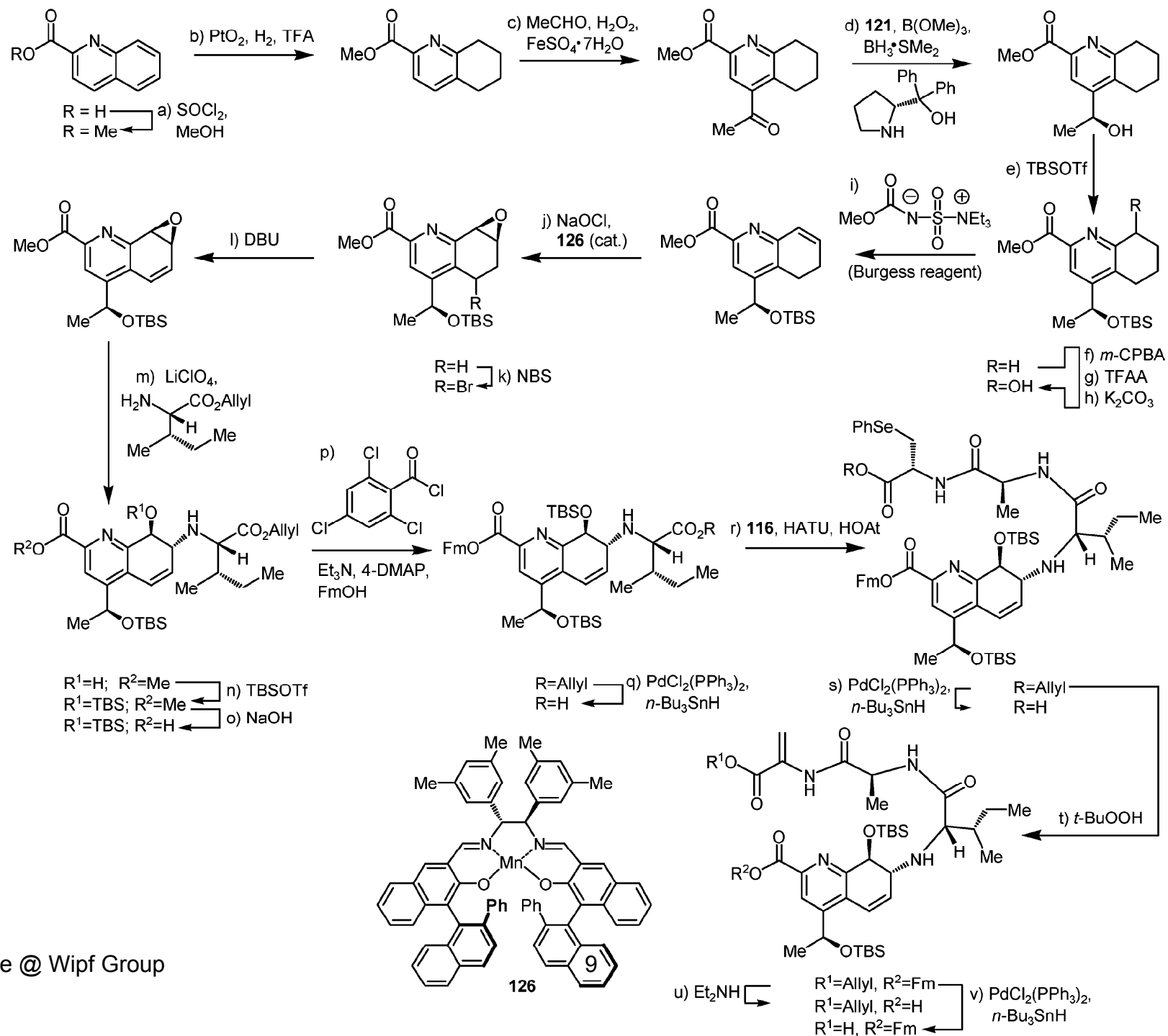
7

9/4/2005

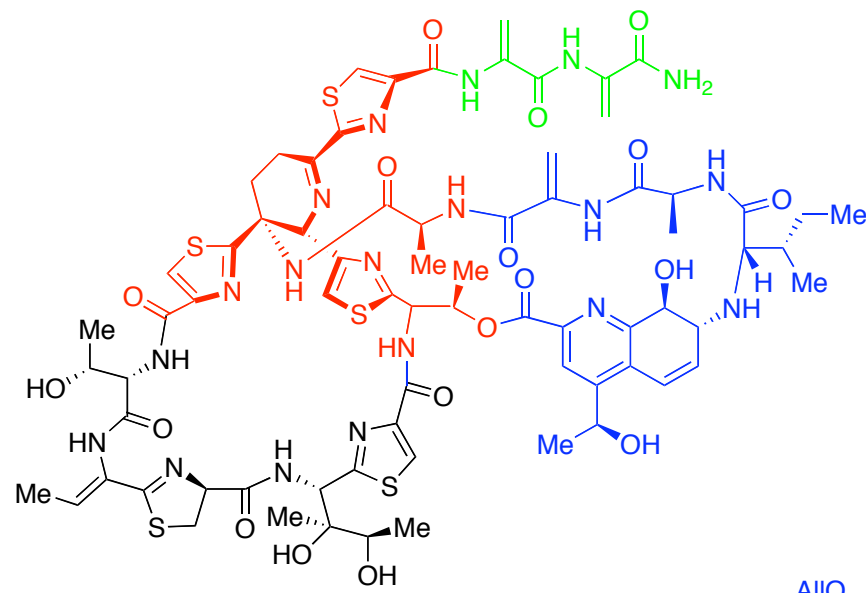
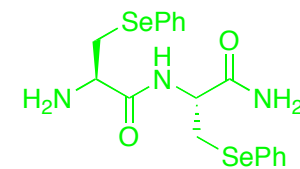
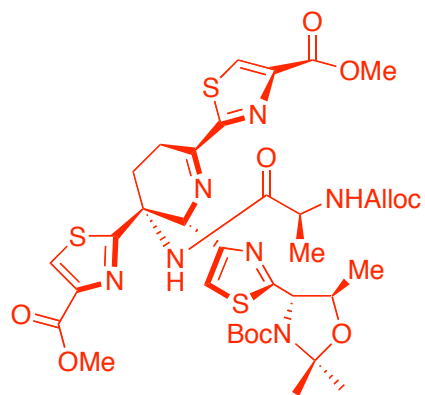
Proposed Mechanism for Imine Contraction



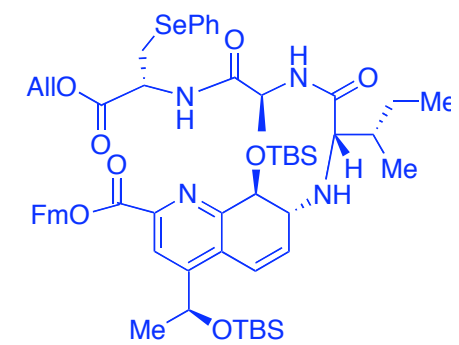
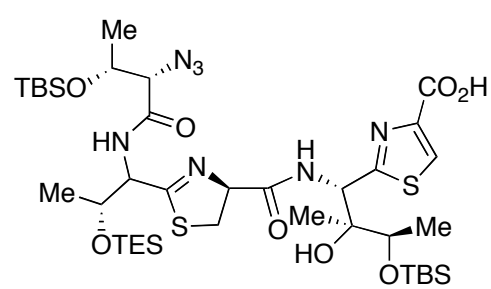
Synthesis of Quinaldic Acid Fragment



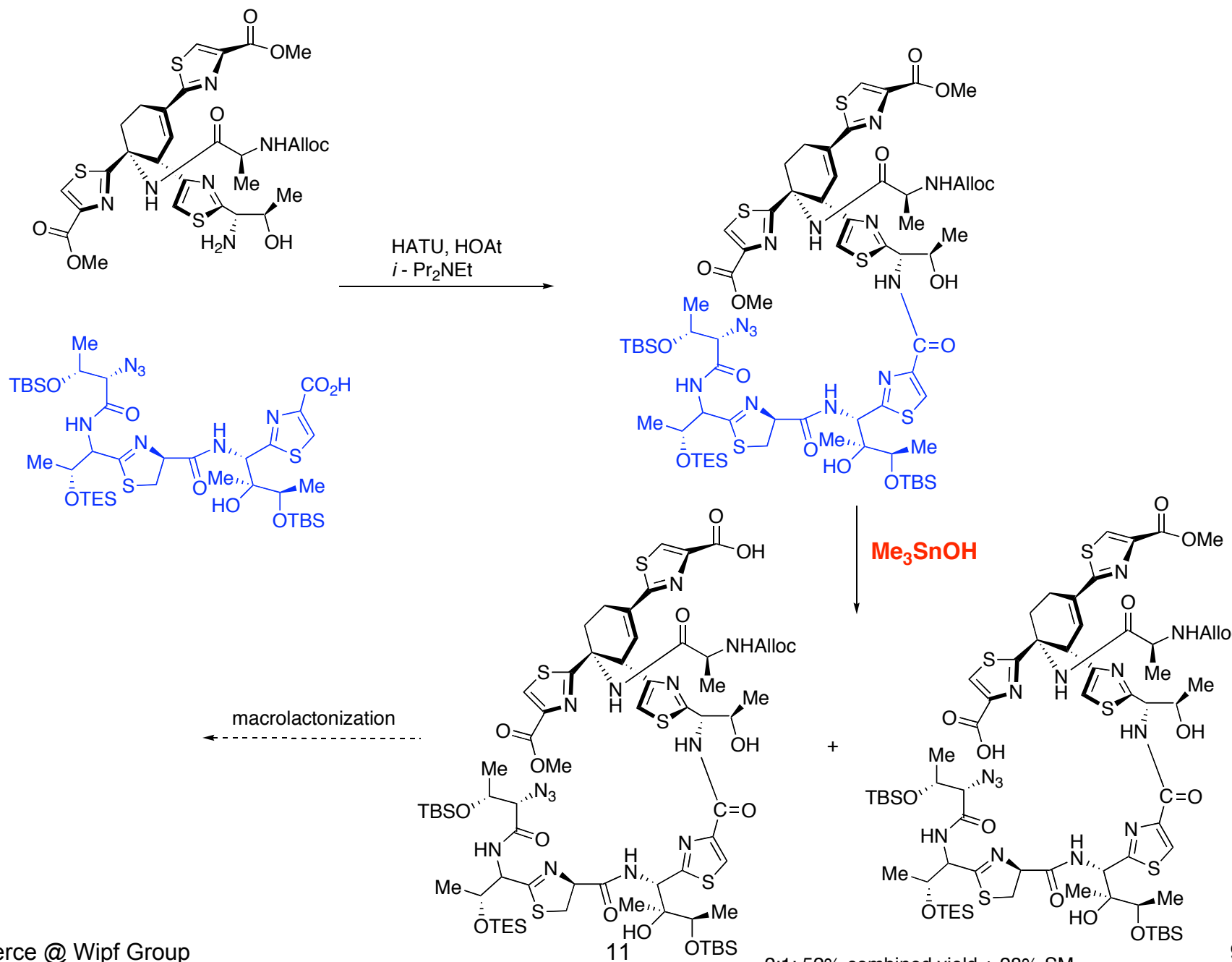
Key Building Blocks



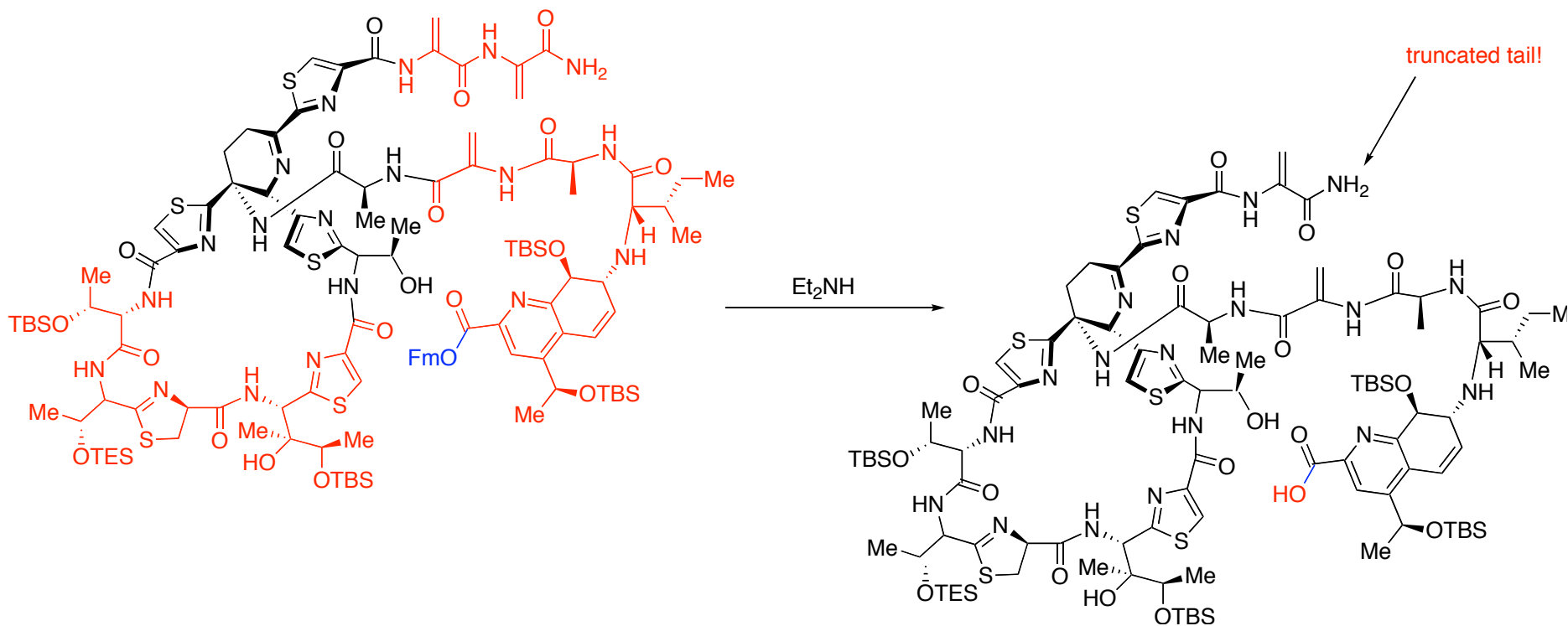
thioestrepton



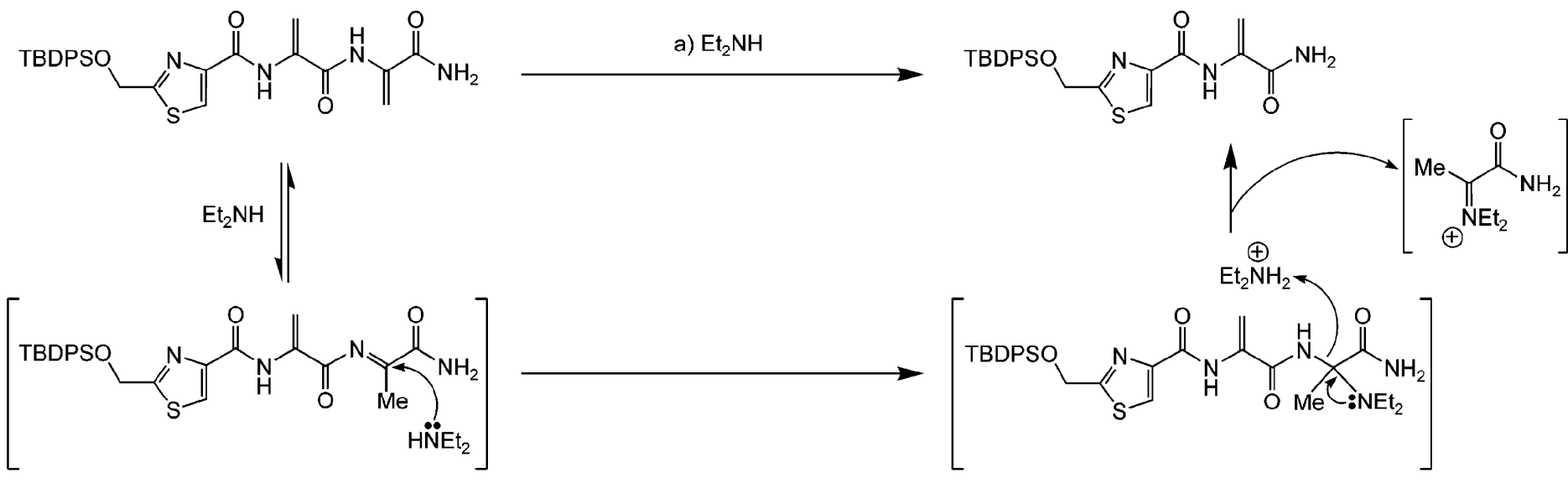
Me₃SnOH as a Mild Method for Methyl Ester Hydrolysis



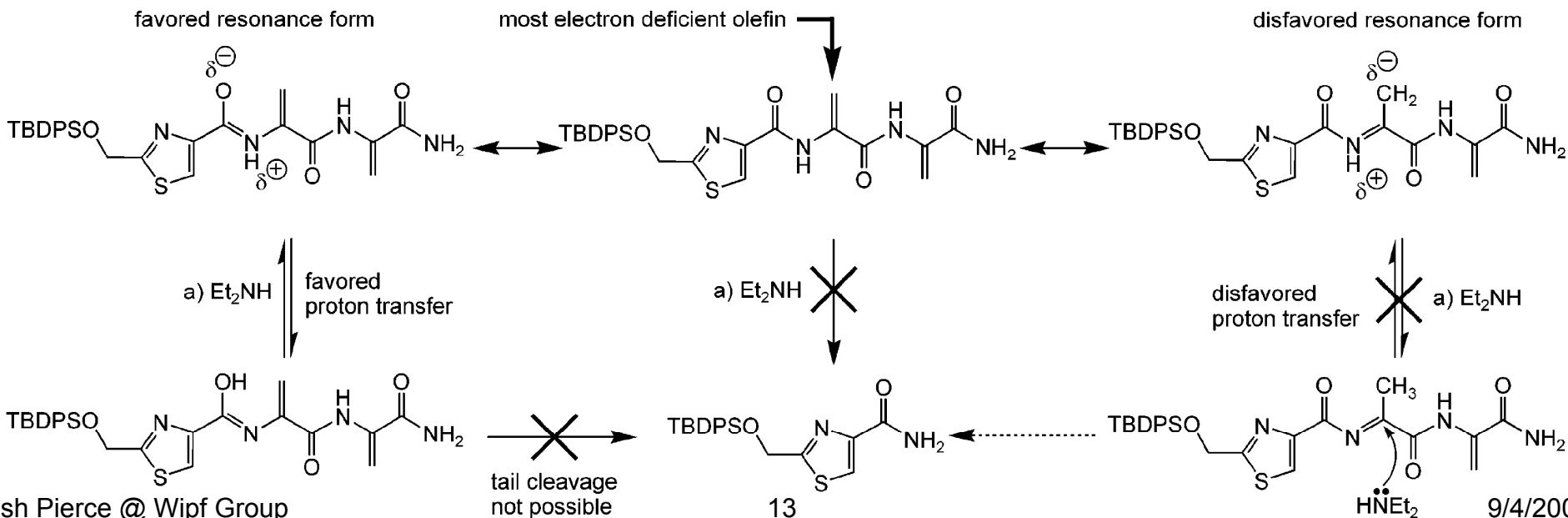
Unexpected Bis-dehydroalanine Tail Cleavage



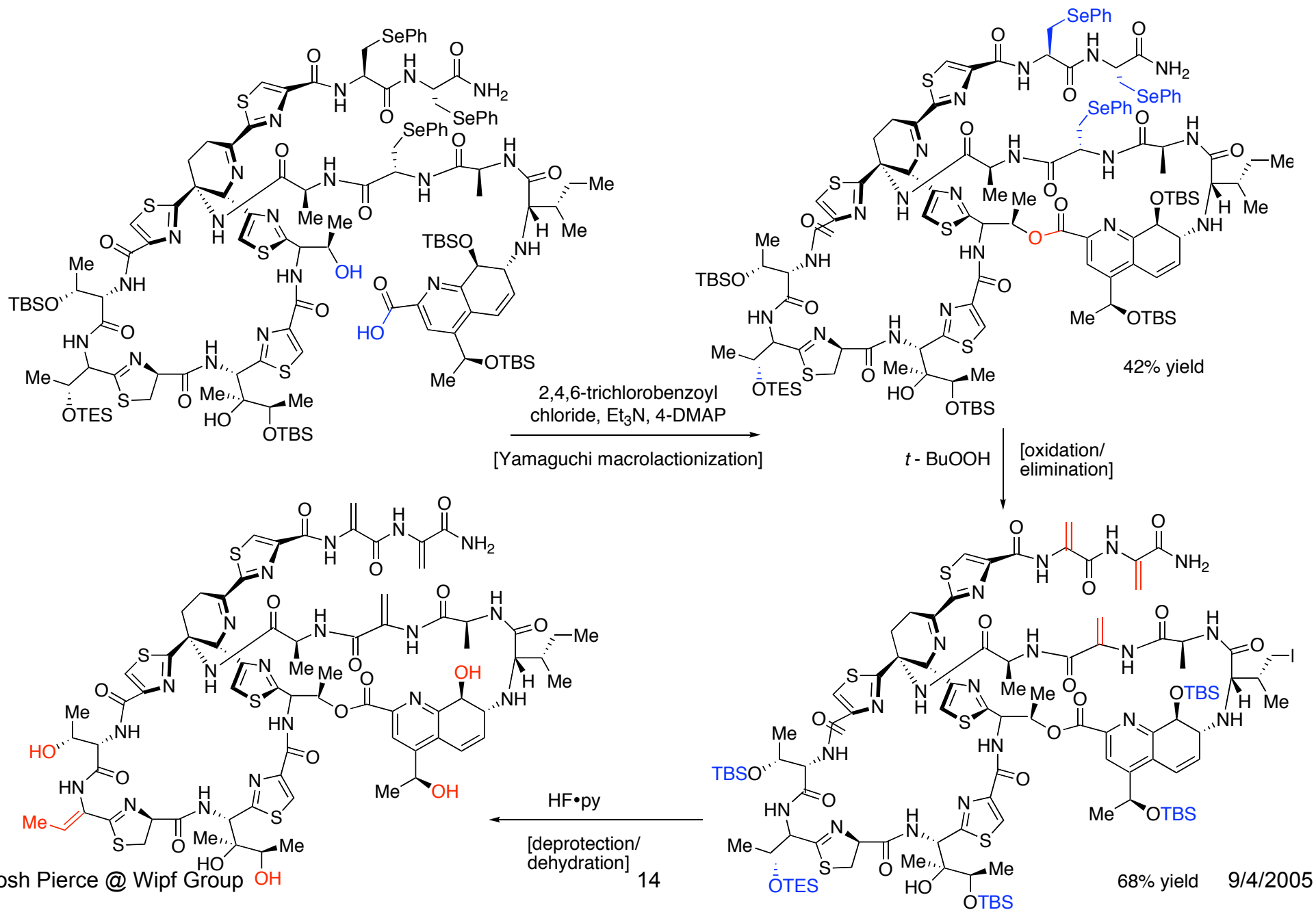
Mechanistic Rationale for the Exclusive Formation of Singly Truncated Product



B



Completion of the Synthesis



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- (b) Nicolaou, K. C.; Safina, B. S.; Zak, M.; Estrada, A. A.; Lee, S. H. *Angew. Chem., Int. Ed.* **2004**, 43, 5087-5092.
- (c) Nicolaou, K. C.; Nevalainen, M.; Zak, M.; Bulat, S.; Bella, M.; Safina, B. S. *Angew. Chem., Int. Ed.* **2003**, 42, 3418-3424.
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- (e) Nicolaou, K. C.; Safina, B. S.; Funke, C.; Zak, M.; Zecri, F. J. *Angew. Chem., Int. Ed.* **2002**, 41, 1937-1940.