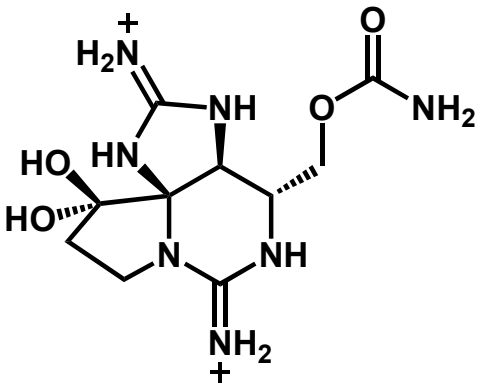
Total Synthesis of Saxitoxin



John Baird

April 11, 2006

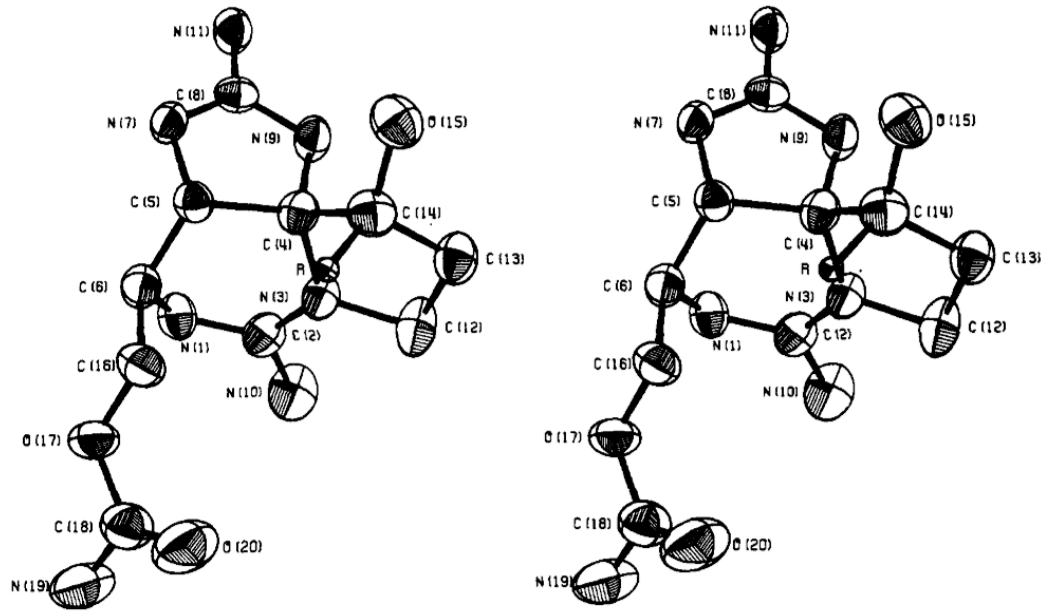
Isolation and Properties

First isolated in 1957 by Schantz et al

X-Ray Structure obtained in 1975

Freely soluble in water and methanol

Optical rotation +84.8^0



Stereo view of X-ray structure

Amorphous solid with formula $C_{10}H_{17}N_7O_4$

Reported to be one of the most toxic non-protein compounds known

mw 299.3 g/mol

Jacobi, P. A. et. al *Croat. Chem. Acta* **1986**, 267

Biological Properties of Saxitoxin

Potent neurotoxin isolated from toxic Alaska butter clams (*Saxidomus giganteus*) and soft shell clams (*Mytilus californias*)

Established in 1920's that shellfish became toxic during the time of "red tides" during which *Gonyaulax catenella* (algal species) blooms. Under optimal temperature and light conditions blooms of red algae proliferate to generate red tides

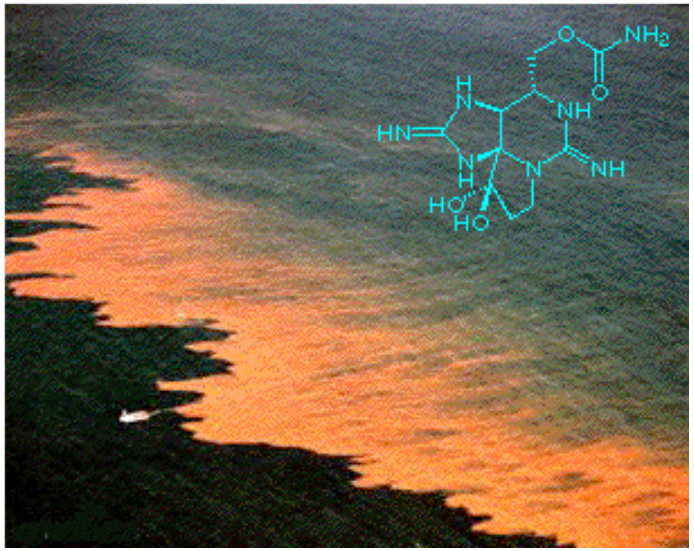
Responsible for paralytic shellfish poisoning.

No known cure, treatment available

Symptoms include tingling, numbness, weakness, and limp paralysis

Toxicity of 8μg/Kg in mice; 0.2-1.0 mg would prove fatal to humans;100x more poisonous than strychnine, 1000x (sarin gas), 2000x (NaCN)

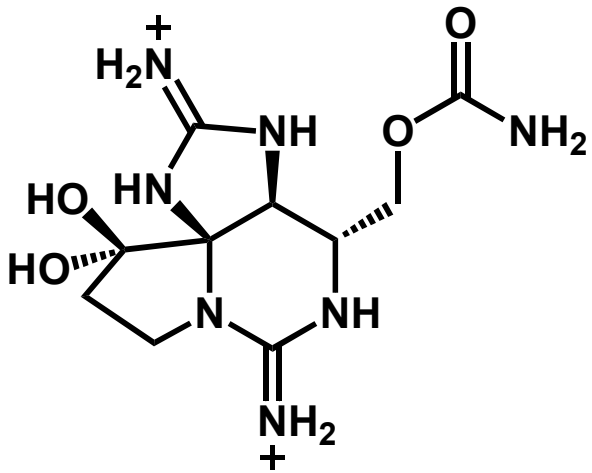
Biological action: blocks sodium ion channels in neuron membranes (medicinal interest)



http://www.chm.bris.ac.uk/motm/stx/saxi.htm

Jacobi, P. A. et. al *Croat. Chem. Acta* **1986**, 267

Key Synthetic Challenges



Molecule possesses:
All carbon atoms except one carry heteroatoms

3 contiguous stereogenic centers

Tricyclic skeleton posessing two guanidines

Polarity/solubility of the molecule makes manipulation/purification cumbersome

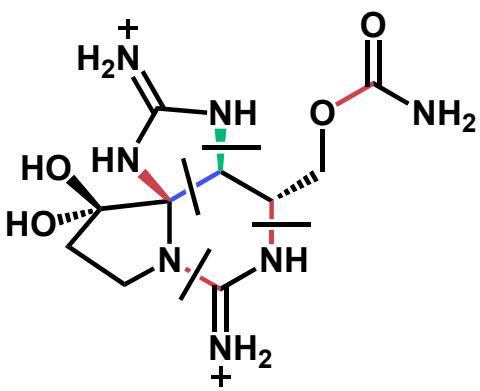
Total Syntheses

First by Kishi, made racemic saxitoxin in 1977, and later reported the synthesis of unnatural (-)-decarbamoylsaxitoxin in 1992.

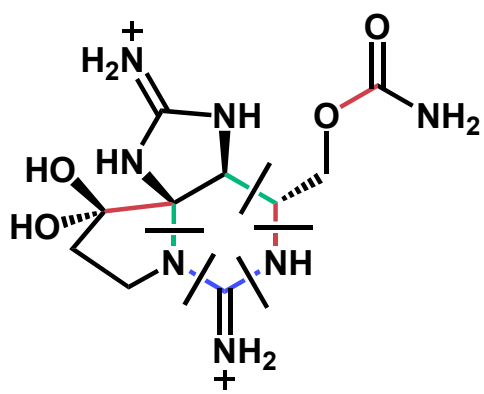
Second synthesis of racemic saxitoxin by Jacobi in 1984

Most recently, synthesis of natural (+)-Saxitoxin by Du Bois (2006)

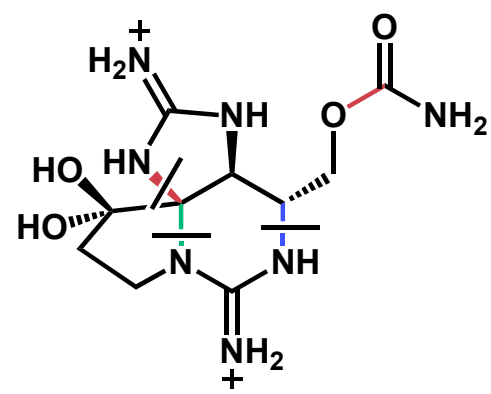
Kishi



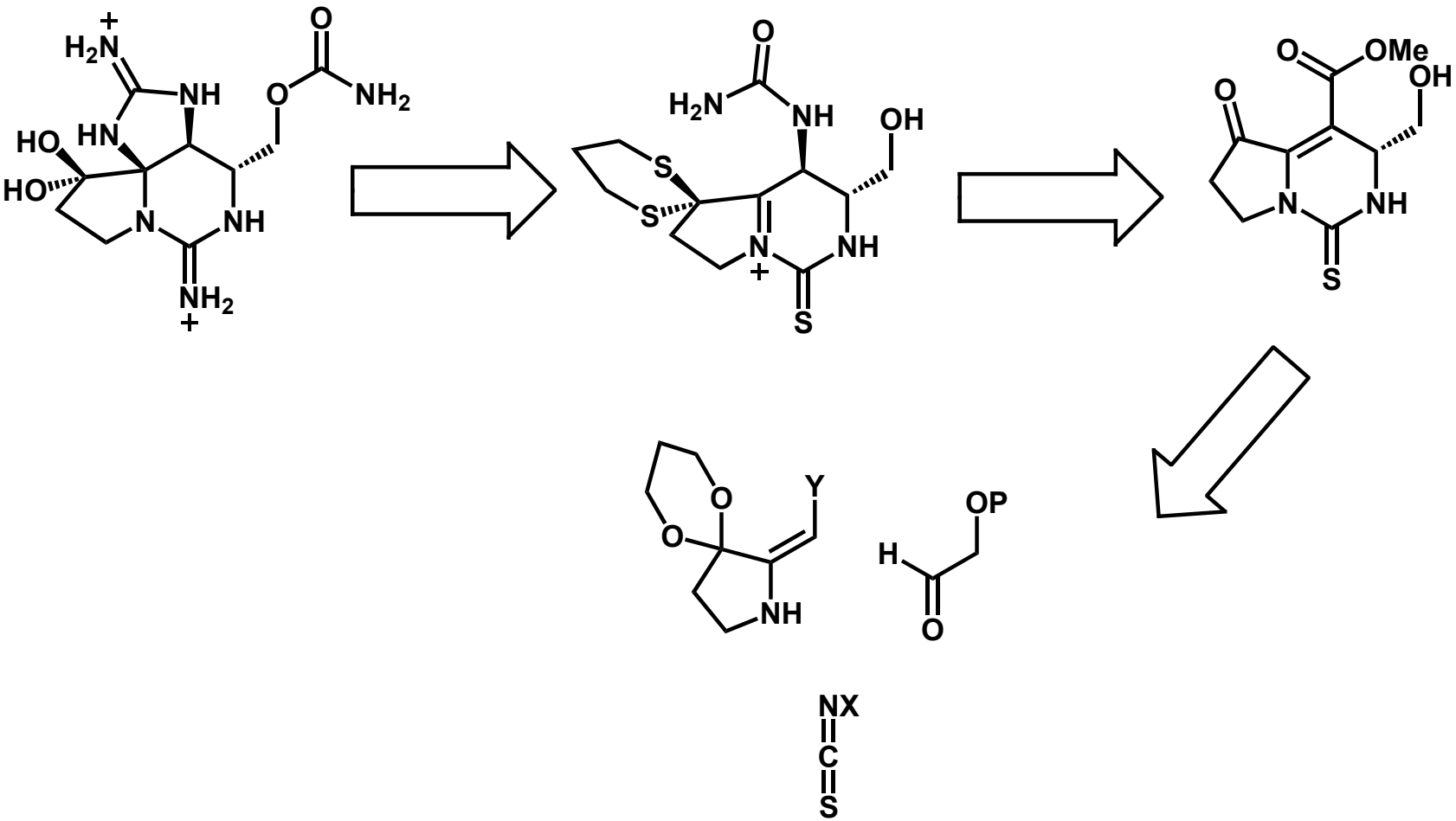
Jacobi



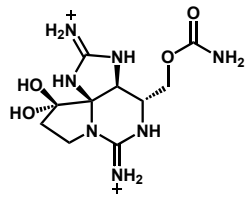
Du Bois

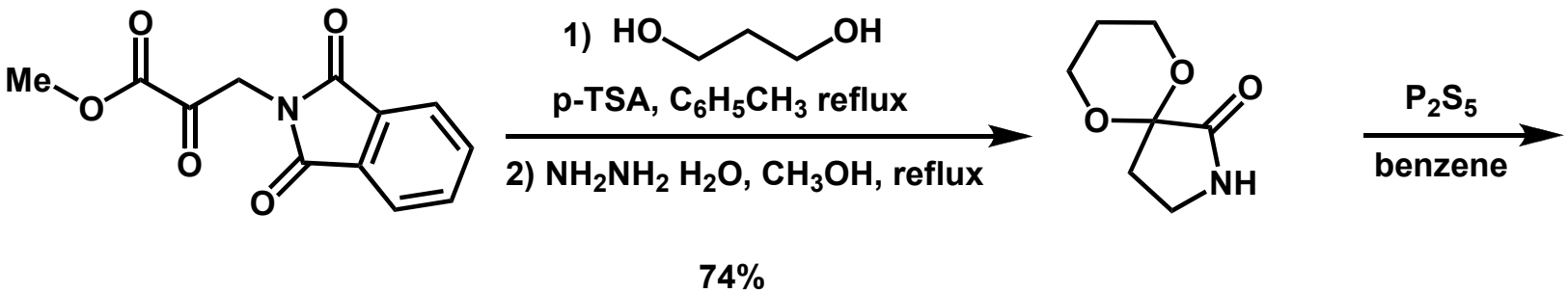


Kishi Retrosynthesis

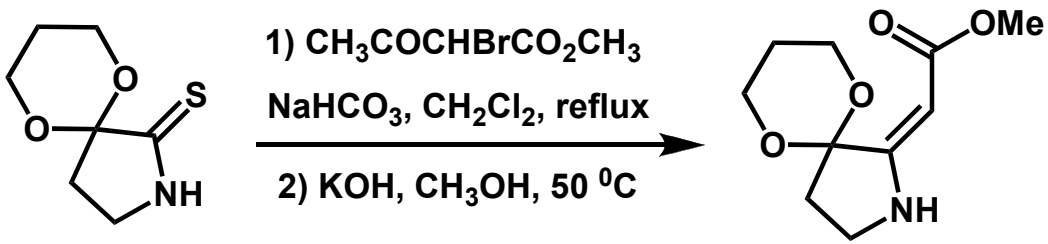


Preparation of Vinylogous Carbamate





74%



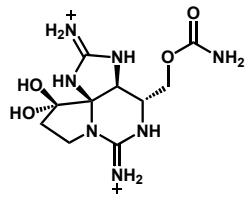
50% (from amide)

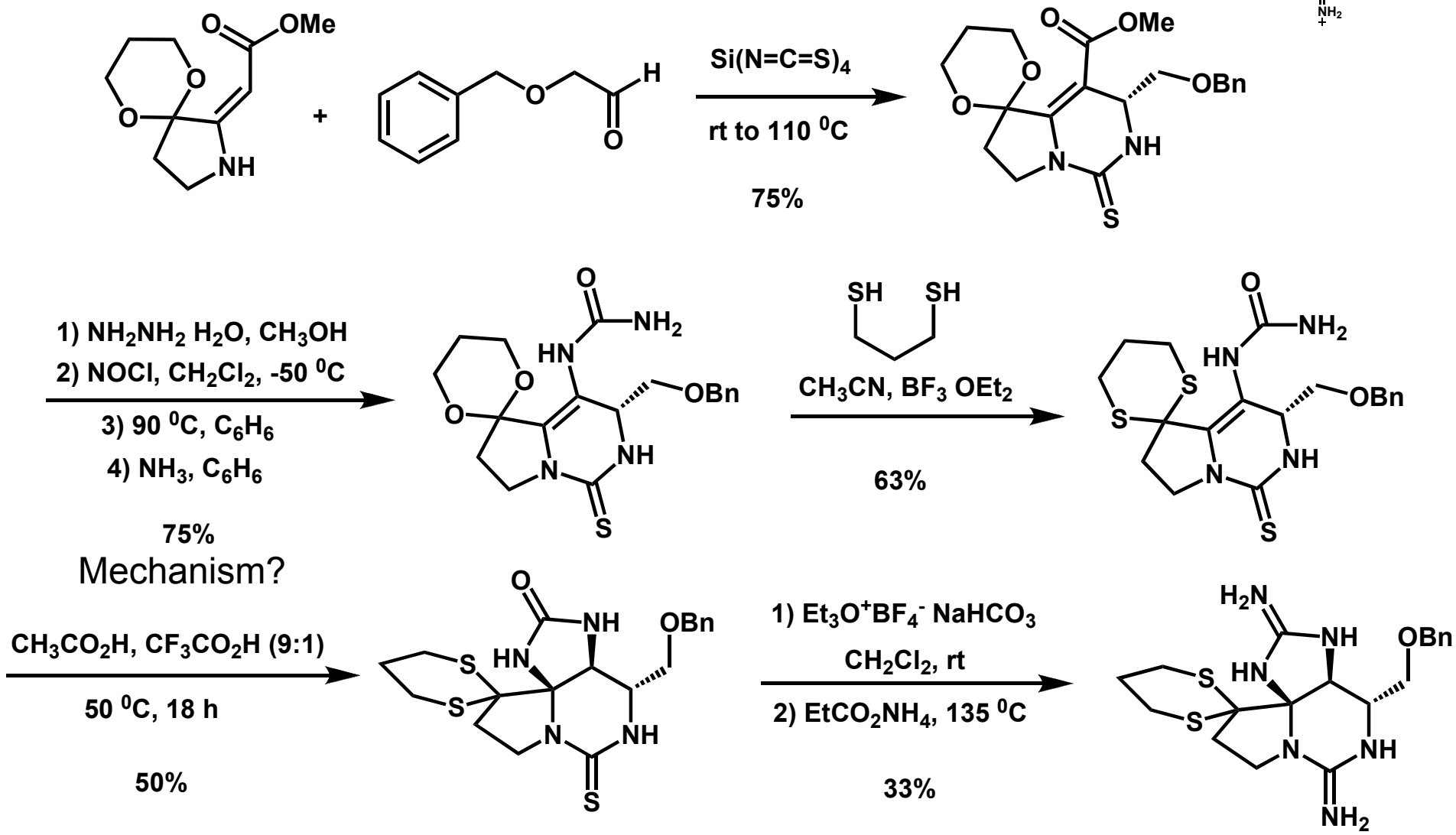
Please propose a mechanism for this reaction

Kishi, Y. et. al. *J. Am. Chem. Soc.* **1977**, *98*, 2818.

Kishi, Y. et. al. *Hetercycles.* **1980**,*14*, 1477.

Preparation of Diguanidine Core

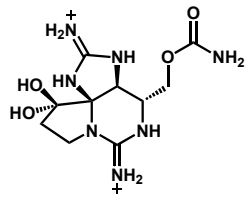


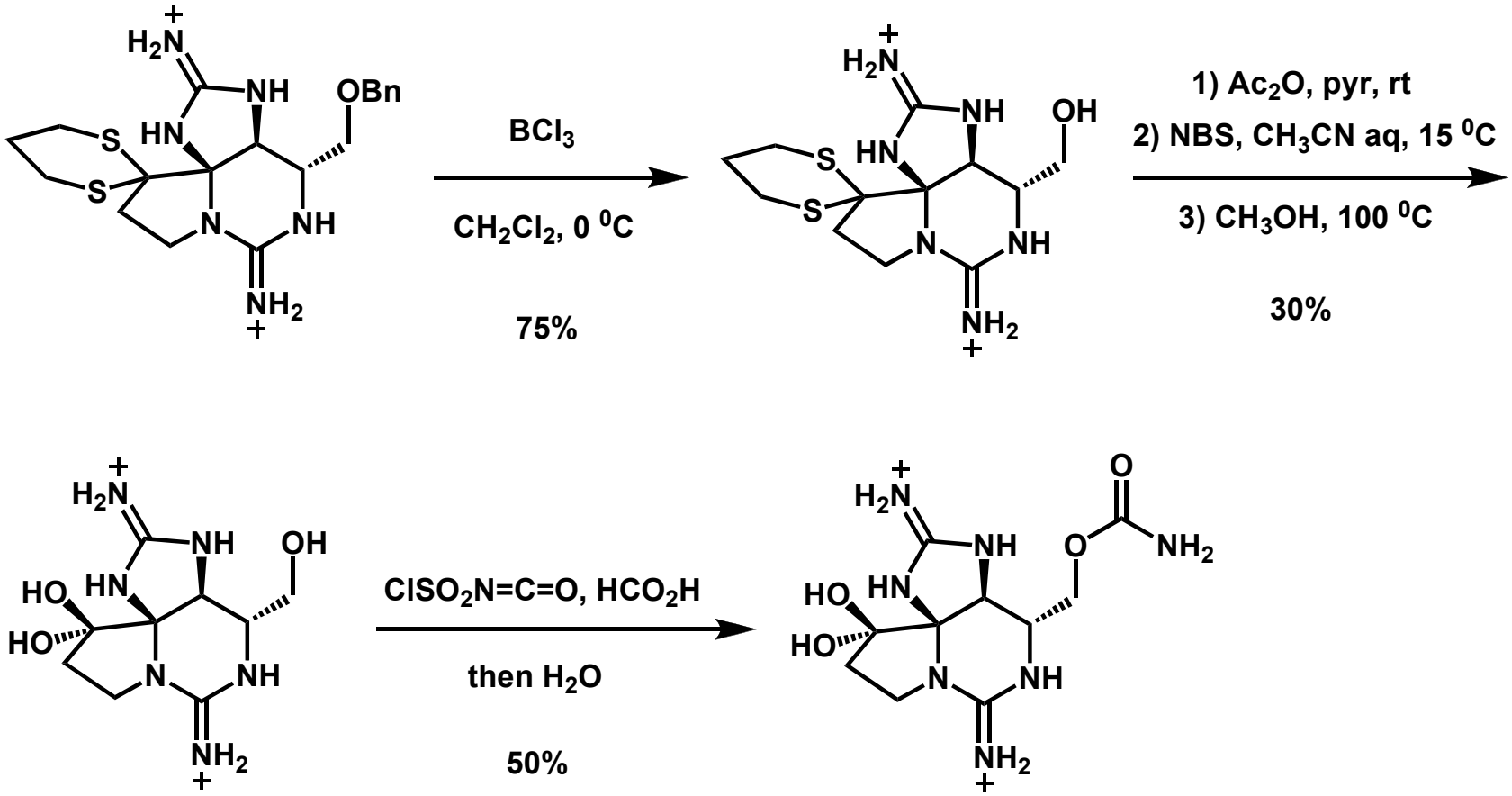


Kishi, Y. et. al. *J. Am. Chem. Soc.* **1977**, *98*, 2818.

Kishi, Y. et. al. *Hetercycles.* **1980**,*14*, 1477.

Completion of the Synthesis





Kishi, Y. et. al. *J. Am. Chem. Soc.* **1977**, *98*, 2818.

Kishi, Y. et. al. *Hetercycles.* **1980**,*14*, 1477.

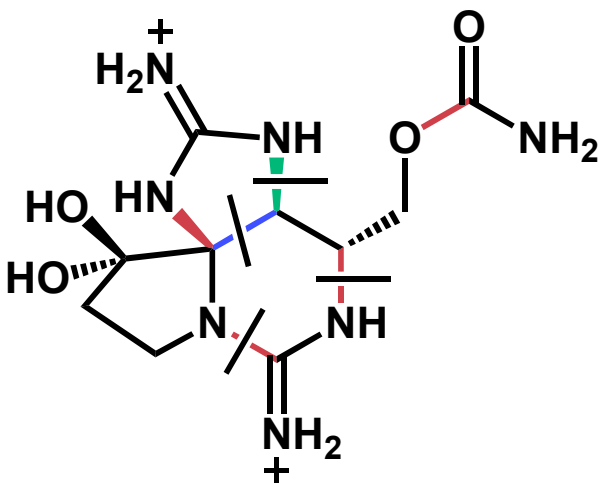
Kishi Synthesis- Summary

First total synthesis (racemic) 1977

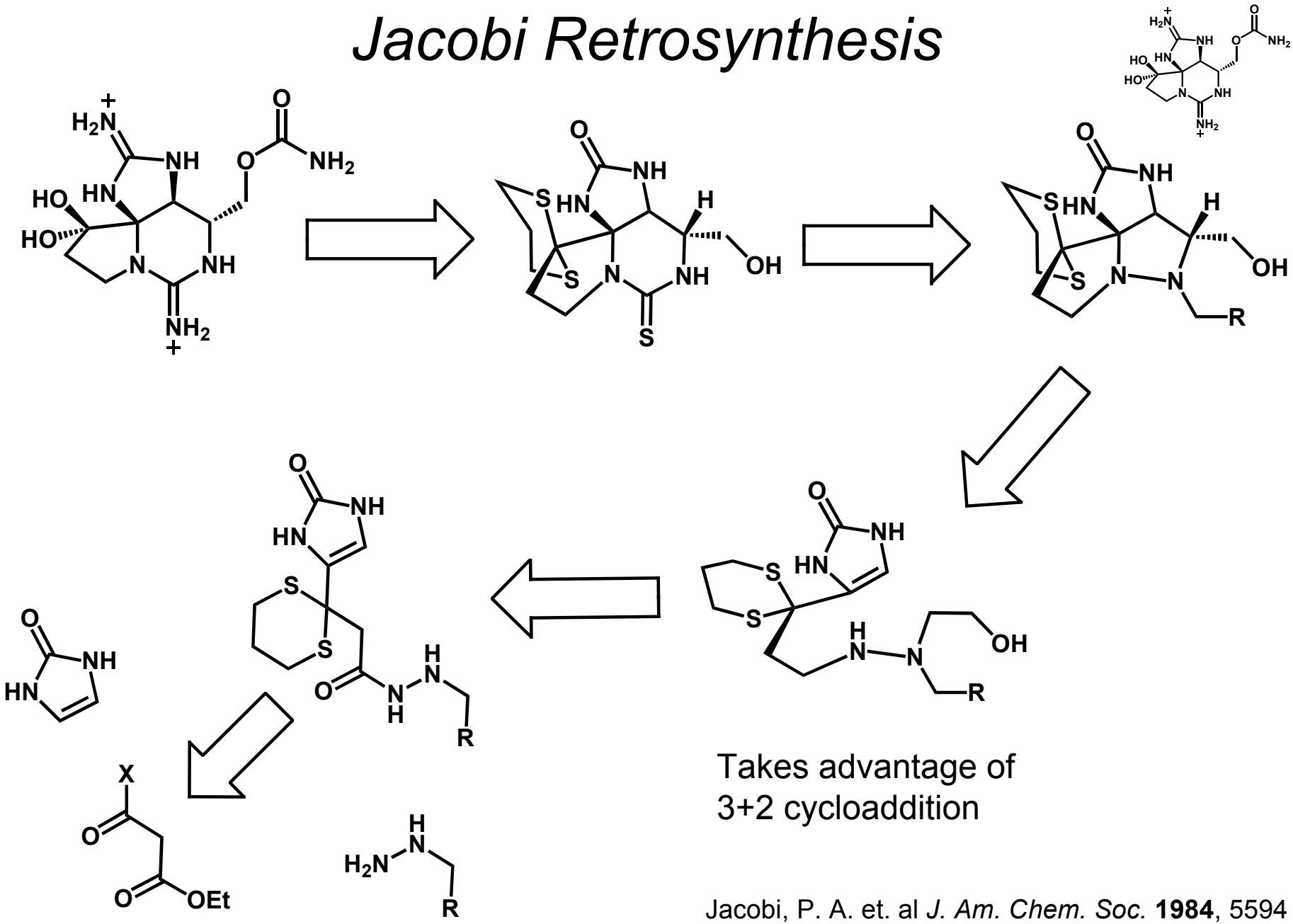
Key Steps:

Eschenmoser sulfide contraction
Curtius Rearrangement
Enamine condensation

17steps, 0.2% overall yield



Jacobi Retrosynthesis

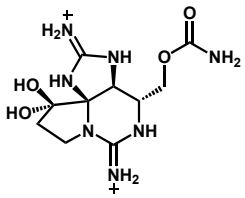


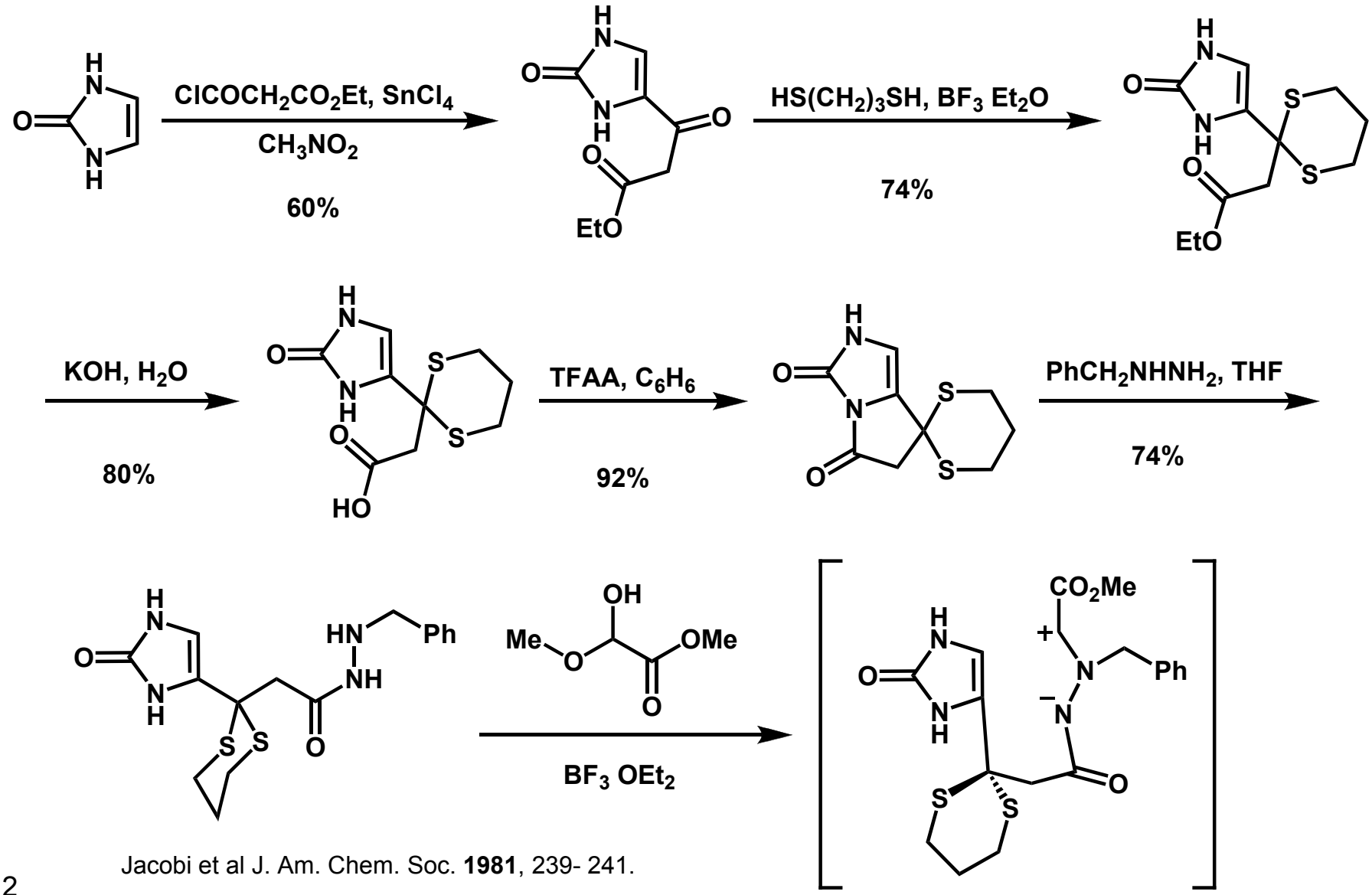
Takes advantage of
3+2 cycloaddition

Jacobi, P. A. et. al *J. Am. Chem. Soc.* **1984**, 5594

Jacobi, P. A. et. al *Croat. Chem. Acta.* **1986**, 2674

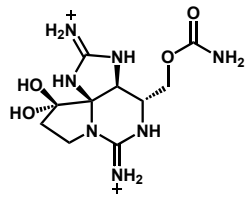
Preparation of Cycloaddition Precursor

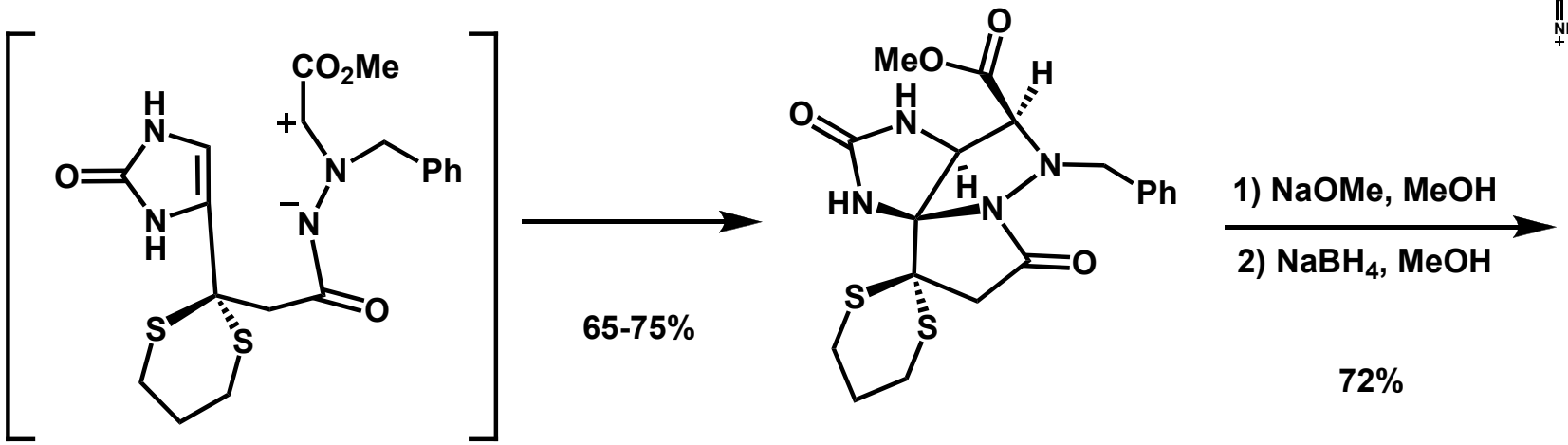


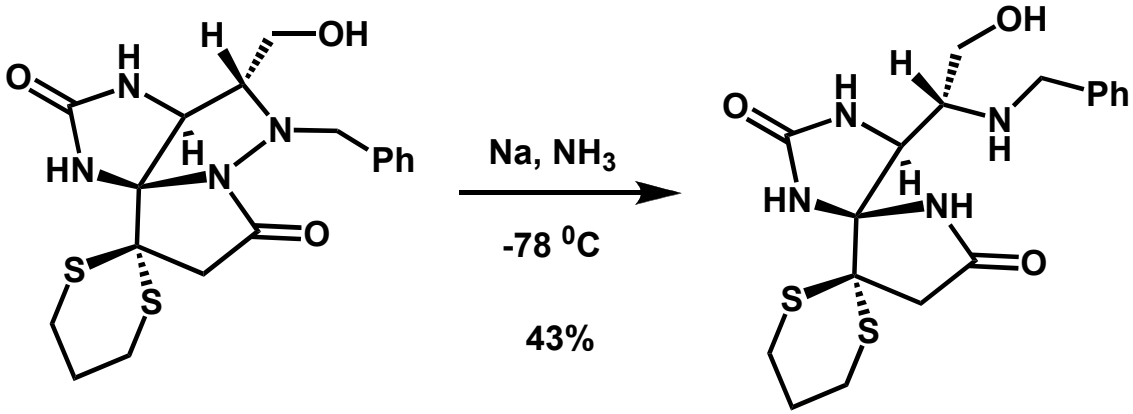


Jacobi et al J. Am. Chem. Soc. **1981**, 239- 241.

Preparation of Pyrazolidine





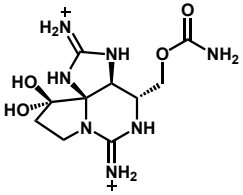


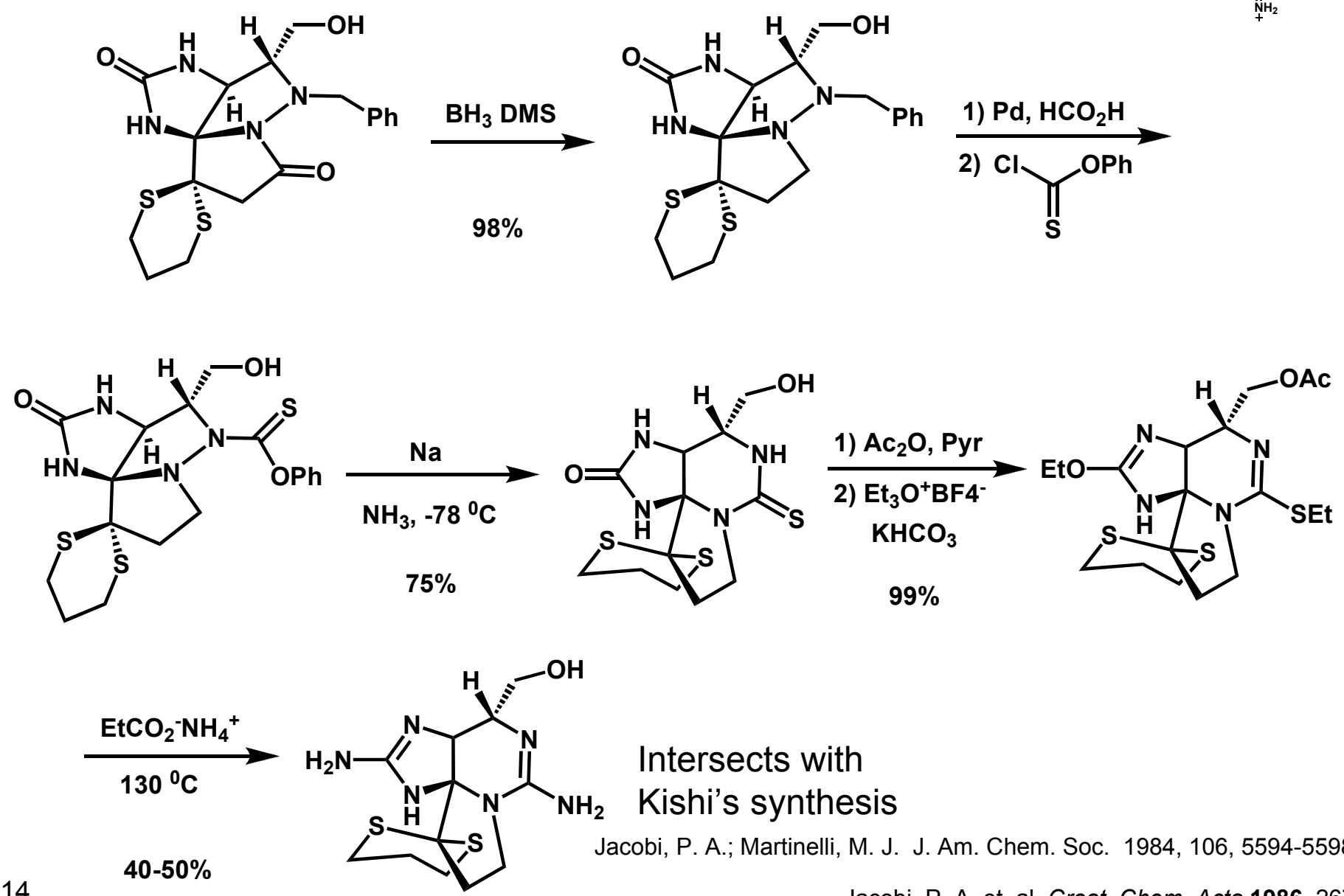
Further attempts at reduction gave decomposition

Jacobi, P. A.; Martinelli, M. J. J. Am. Chem. Soc. 1984, 106, 5594-5598

Jacobi, P. A. et. al *Croat. Chem. Acta* **1986**, 267

Completion of the Formal Synthesis



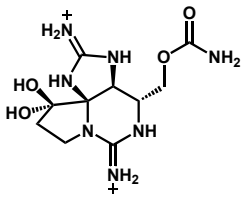


Intersects with
Kishi's synthesis

Jacobi, P. A.; Martinelli, M. J. J. Am. Chem. Soc. 1984, 106, 5594-5598

Jacobi, P. A. et. al *Croat. Chem. Acta* **1986**, 267

Jacobi Synthesis- Summary



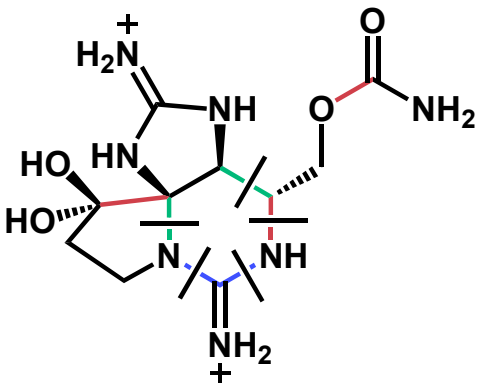
Intersected Kishi intermediate

Utilized [3+2] cycloaddition to access core

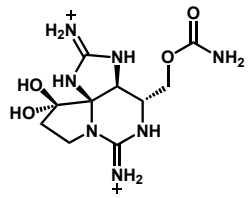
“Scalable and efficient” route has been used to prepare 1.0g of saxitoxin precursor

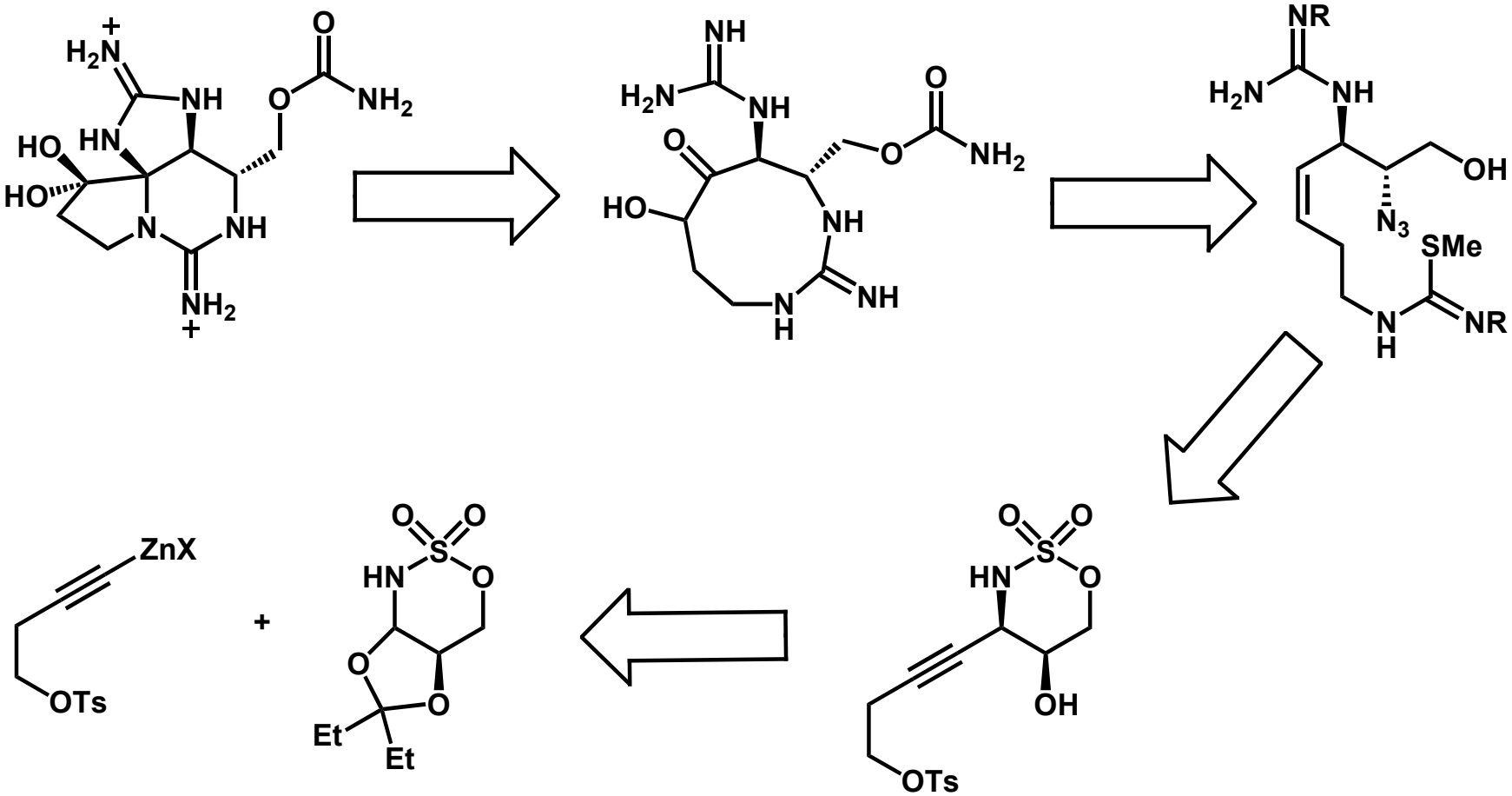
Second synthesis 1984 (racemic)

15 steps (3.3% yield)



Du Bois Retrosynthesis





Will take advantage of
C-H amination reaction

Fleming, J. J.; Du Bois, J. *J. Am. Chem. Soc.* **2006**, 3926

Novel Iminium Ion Equivalents

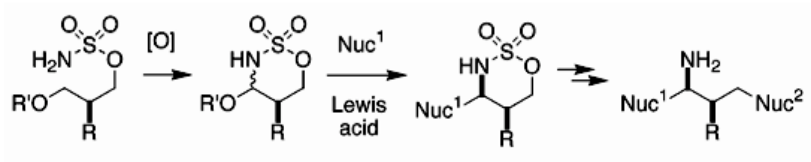
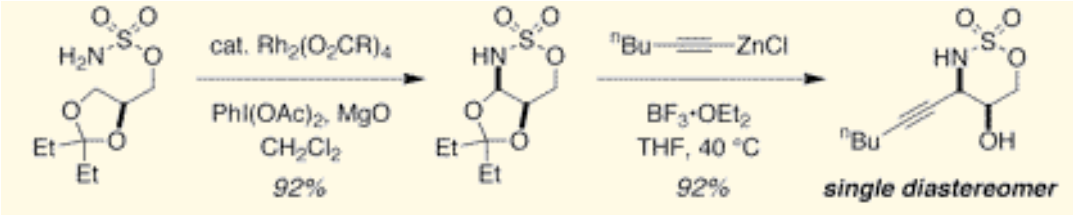
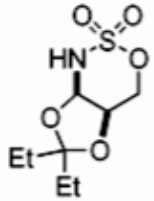
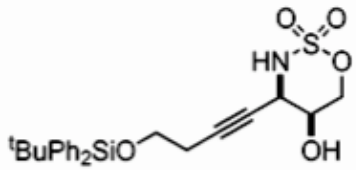
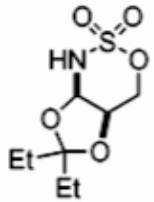
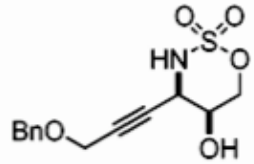
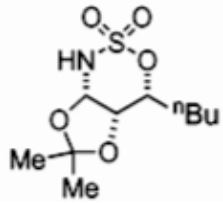
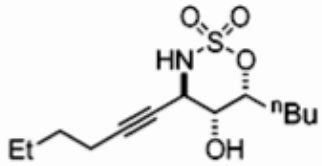


Figure 1. Novel *N*,*O*-acetal oxathiazinane heterocycles as reactive iminium ion equivalents.

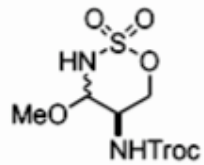
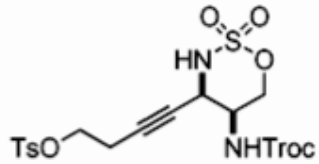
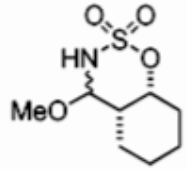
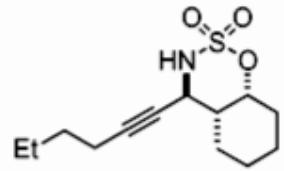
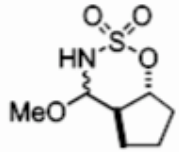
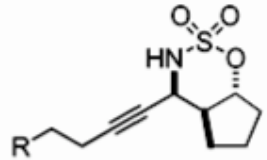


Entry	Substrate	Major isomer[a]	Selectivity[b]	Yield[c]
1			20:1	85
2			20:1	82
3			12:1	71

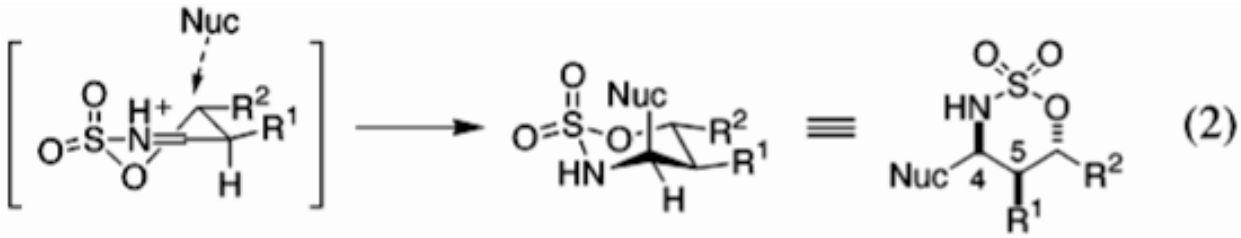
Du Bois, J. et. al, J. Am. Chem. Soc. 2003, 125, 2028

Novel Iminium Ion Equivalents Cont'd

Table 1. Alkynylzinc Addition Reactions with *N,O*-Acetals

Entry	Substrate	Major isomer[a]	Selectivity[b]	Yield[c]
4			8:1	70
5			20:1	76
6			R = Et 6:1 = OP 6:1	80 63[d]

Proposed TS model

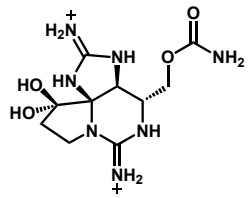


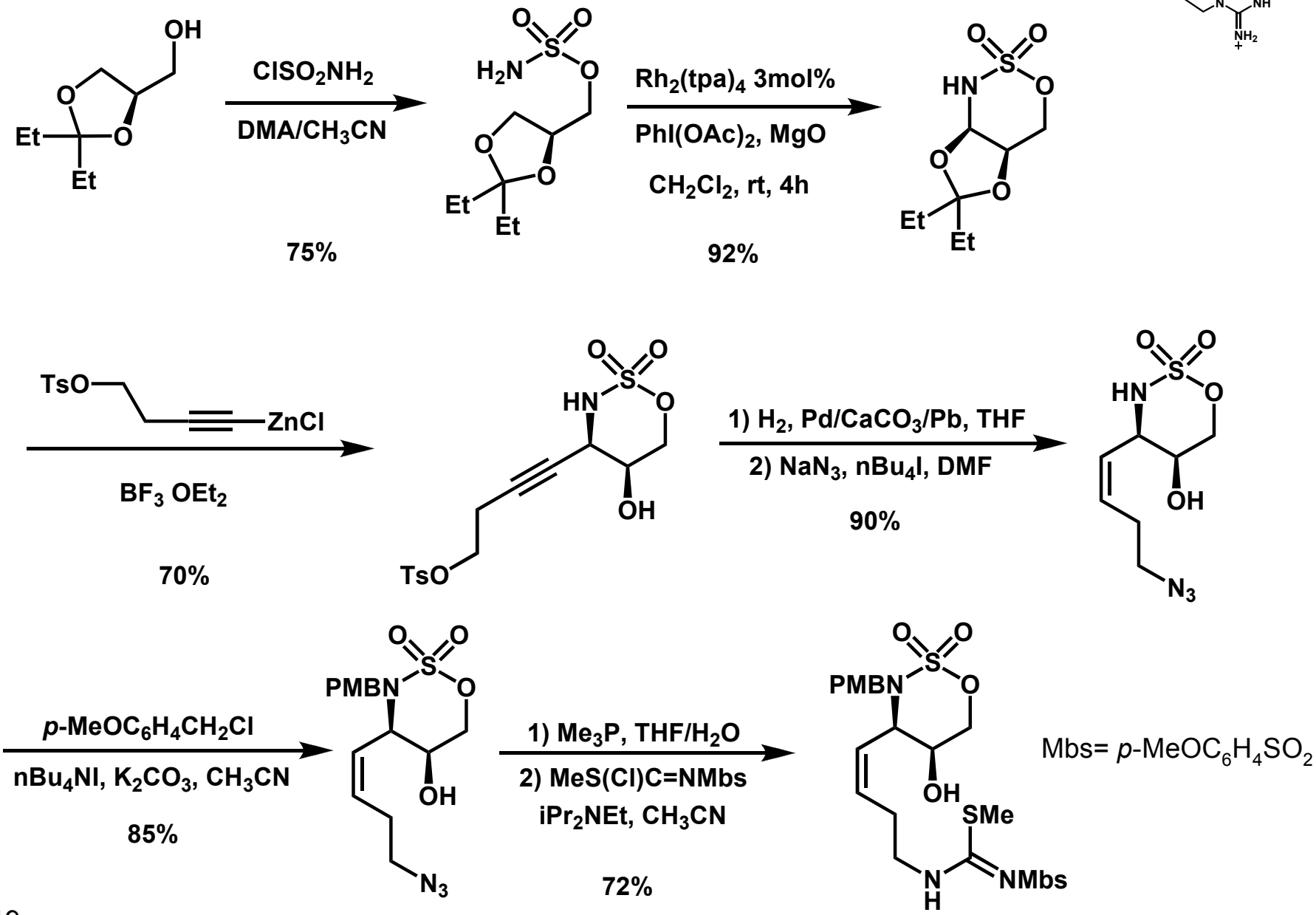
(2)

Oxathiazinane heterocycles are easily prepared chiral building blocks

Du Bois, J. et. al, J. Am. Chem. Soc. 2003, 125, 2028

Preparation of Oxathiazinane



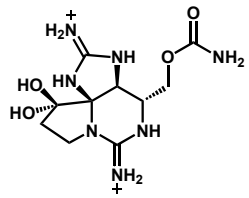


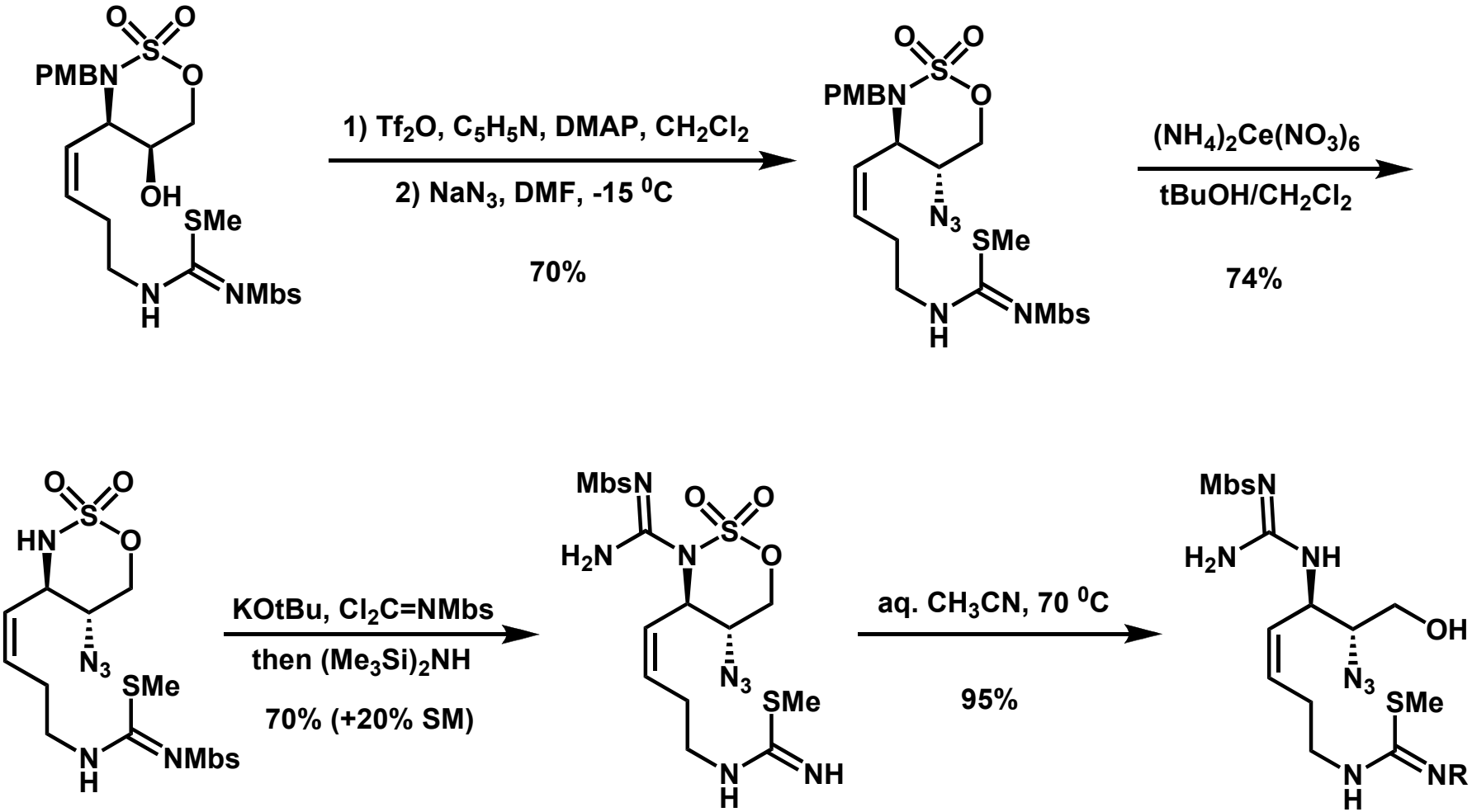
Mbs= p-$MeOC_6H_4SO_2$

Du Bois, J. et. al, J. Am. Chem. Soc. 2003, 125, 2028

Fleming, J. J.; Du Bois, J. *J. Am. Chem. Soc.* **2006**, 3926

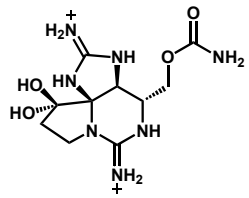
Preparation of Elaborated Azide

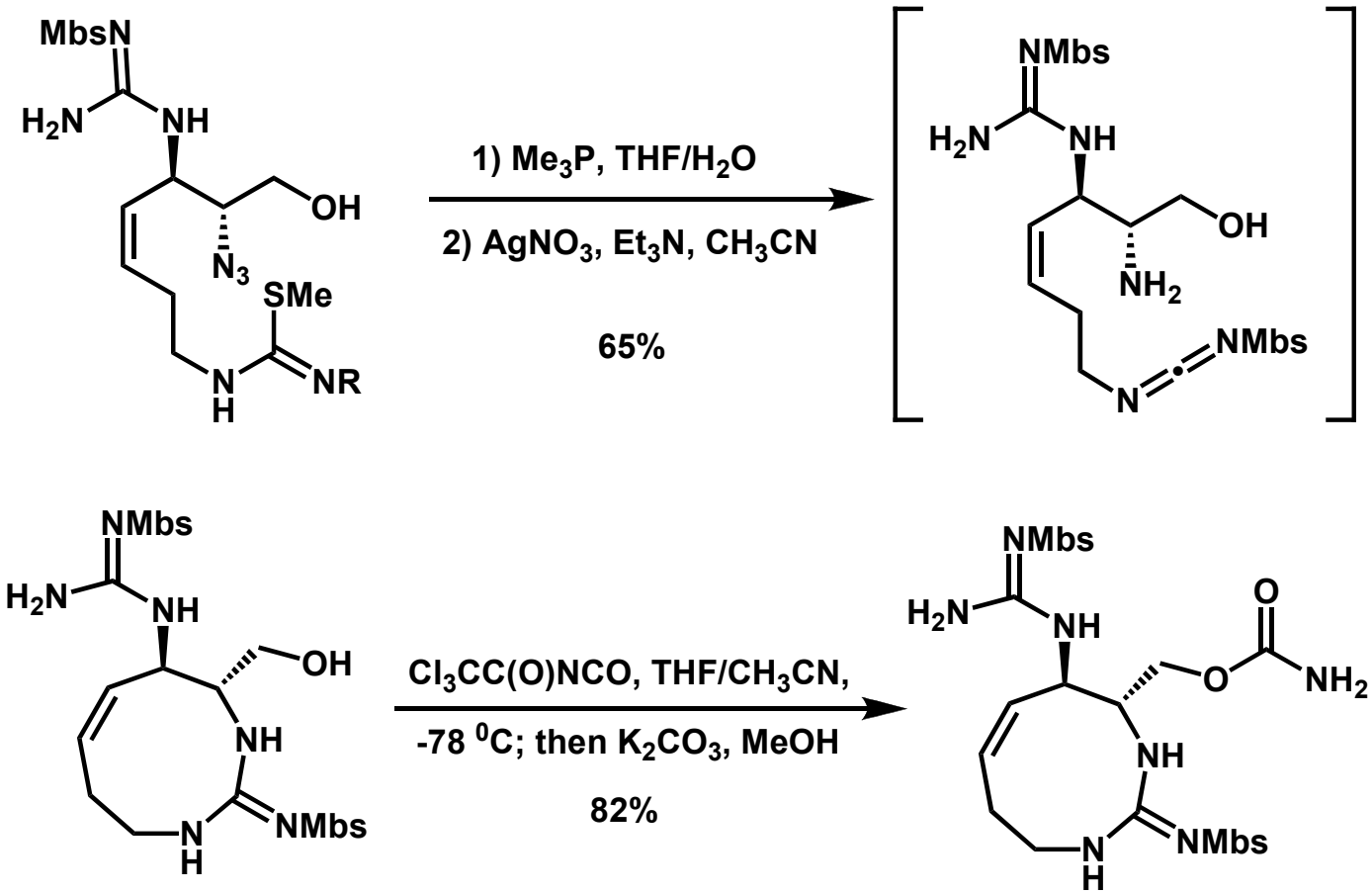




Fleming, J. J.; Du Bois, J. *J. Am. Chem. Soc.* **2006**, 3926

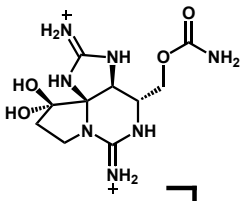
Preparation of 9-membered Ring

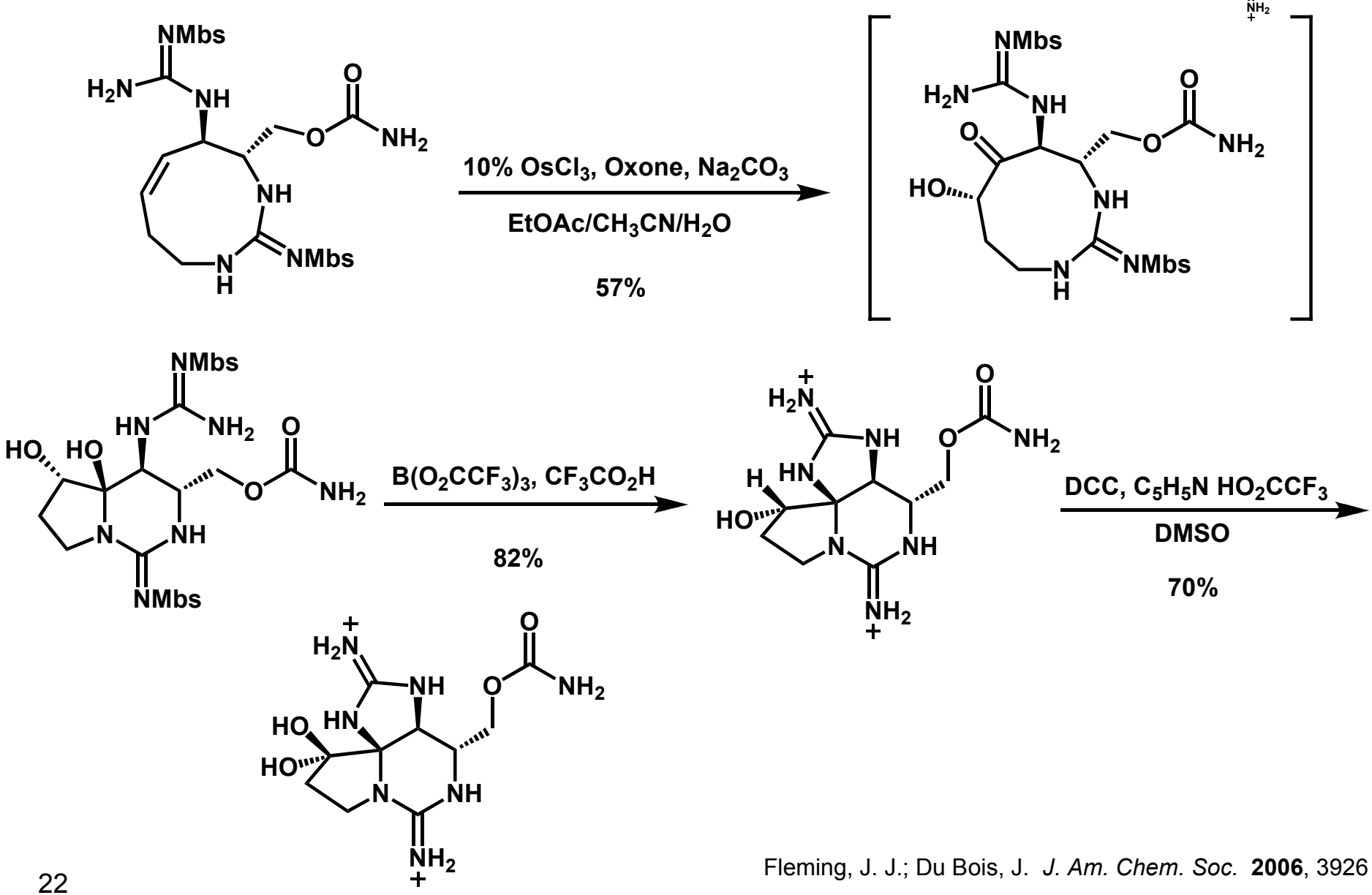




Fleming, J. J.; Du Bois, J. *J. Am. Chem. Soc.* **2006**, 3926

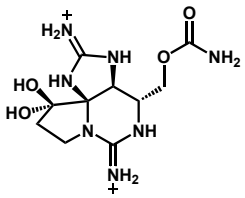
Completion of the Synthesis





Fleming, J. J.; Du Bois, J. *J. Am. Chem. Soc.* **2006**, 3926

Du Bois Synthesis- Summary



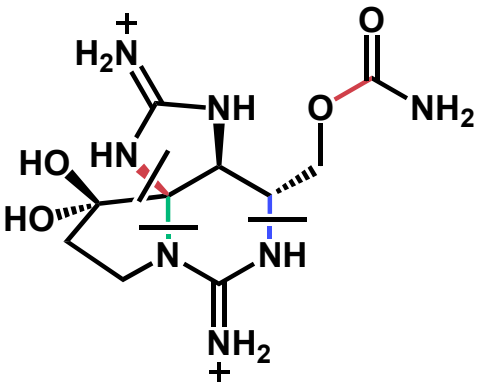
First total synthesis of (+) saxitoxin

Utilized C-H amination and oxathiazinane iminium ion equivalent developed within the Du Bois labs

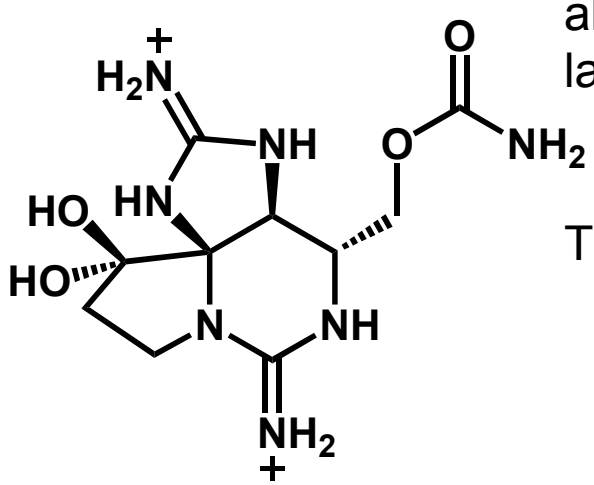
Key strategies relied upon stereocontrolled formation of the 9-membered ring and condensation to prepare the bicyclic guanidine core

19 steps from commercially available (R) glycerol acetamide

1.6% overall yield



Conclusion



Three syntheses within the past 29 years; although first non-racemic synthesis published last month.

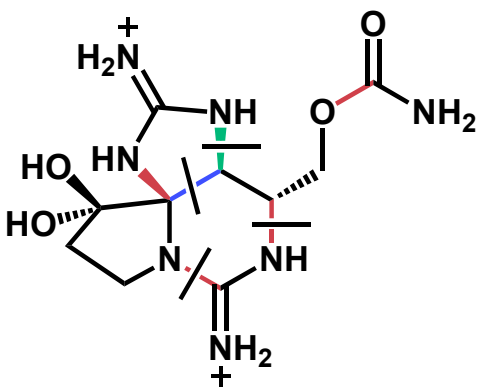
Three very different approaches to the core:

Kishi- build each cyclic guanidine upon pyrrolidine

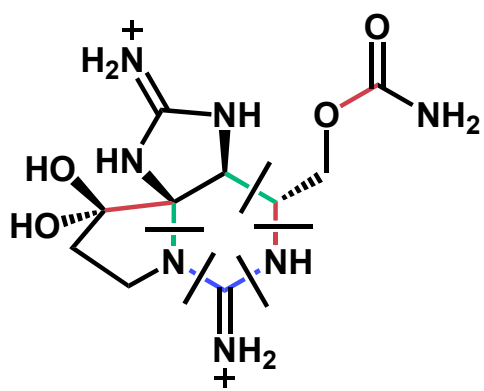
Jacobi- [3+2] cycloaddition

Du Bois- condensation of 9-membered ring

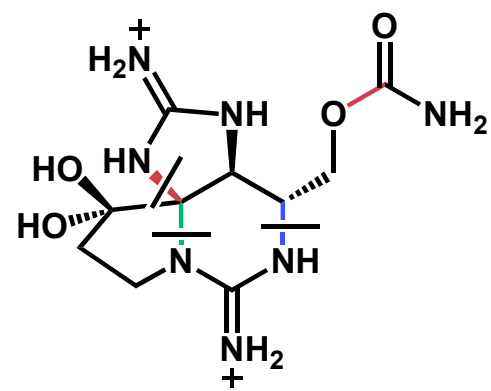
Kishi



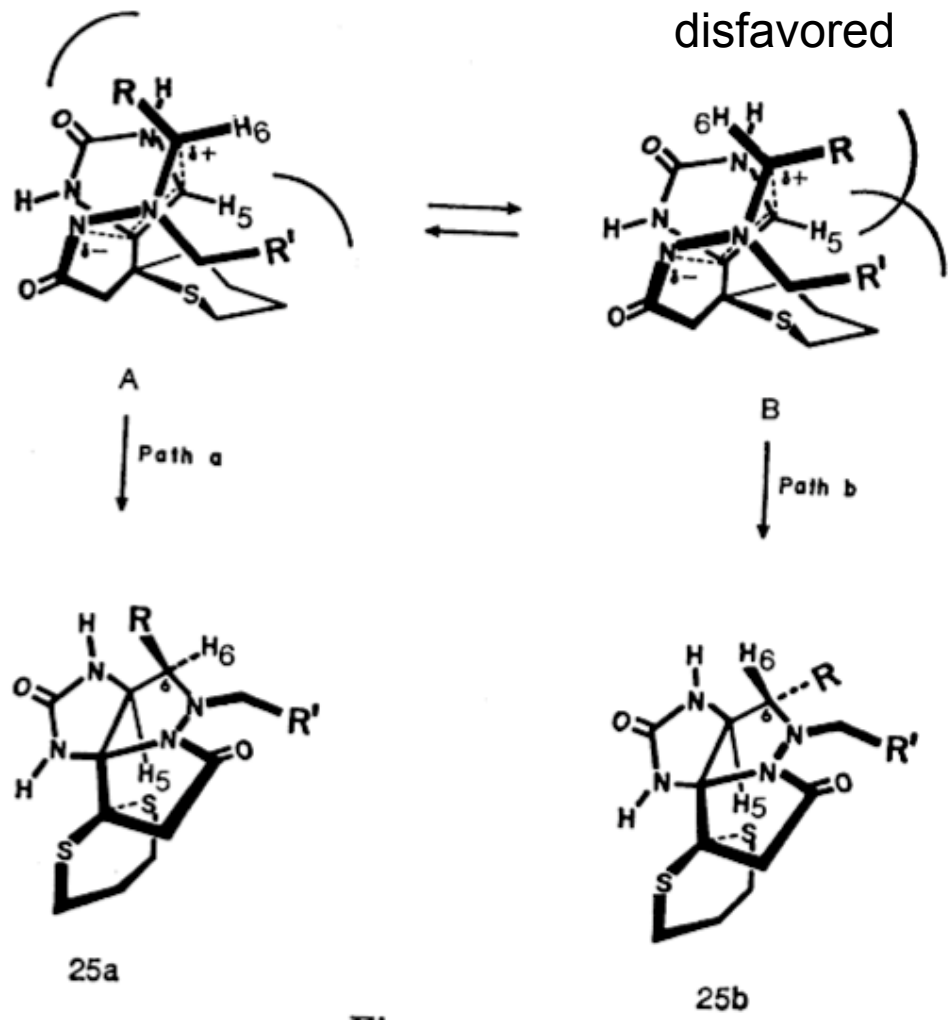
Jacobi



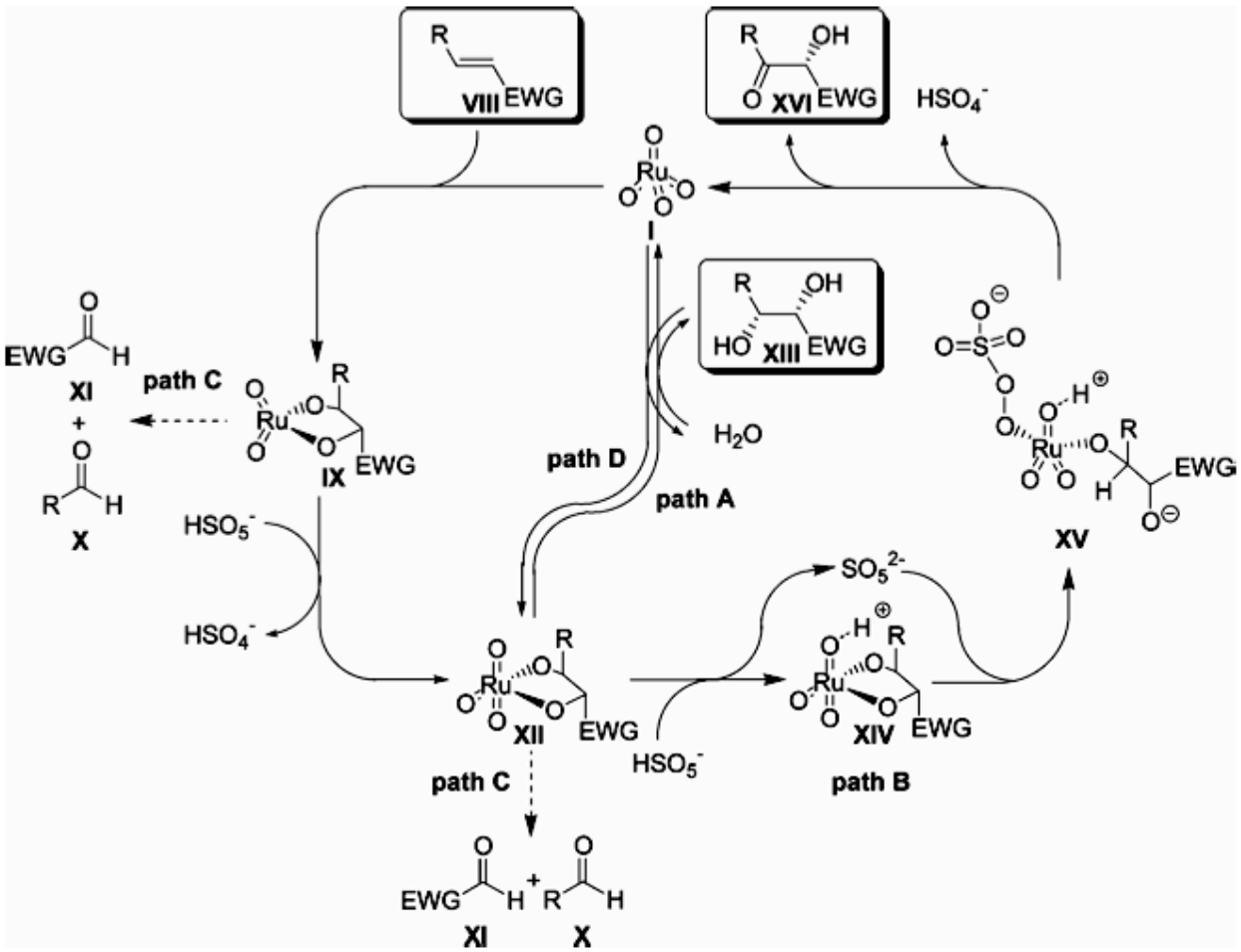
Du Bois



3+2 cycloaddition selectivity



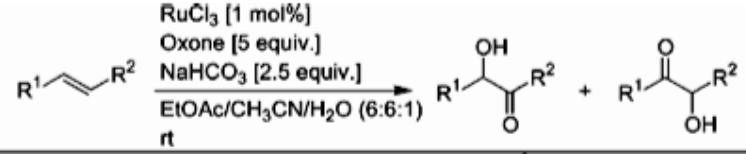
Keto hydroxylation Reaction

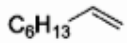
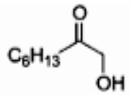
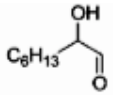
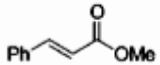
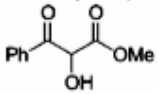
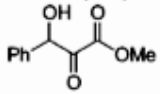
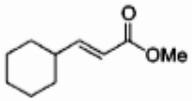
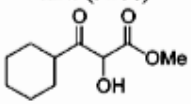
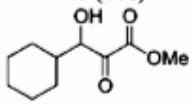
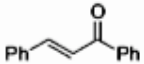
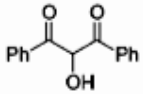
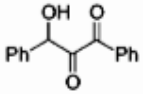
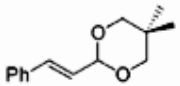
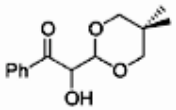
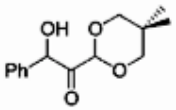
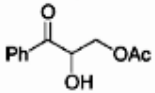
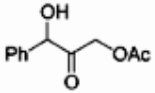


Plietker, JOC, 2004, 8287

Keto hydroxylation cont'd

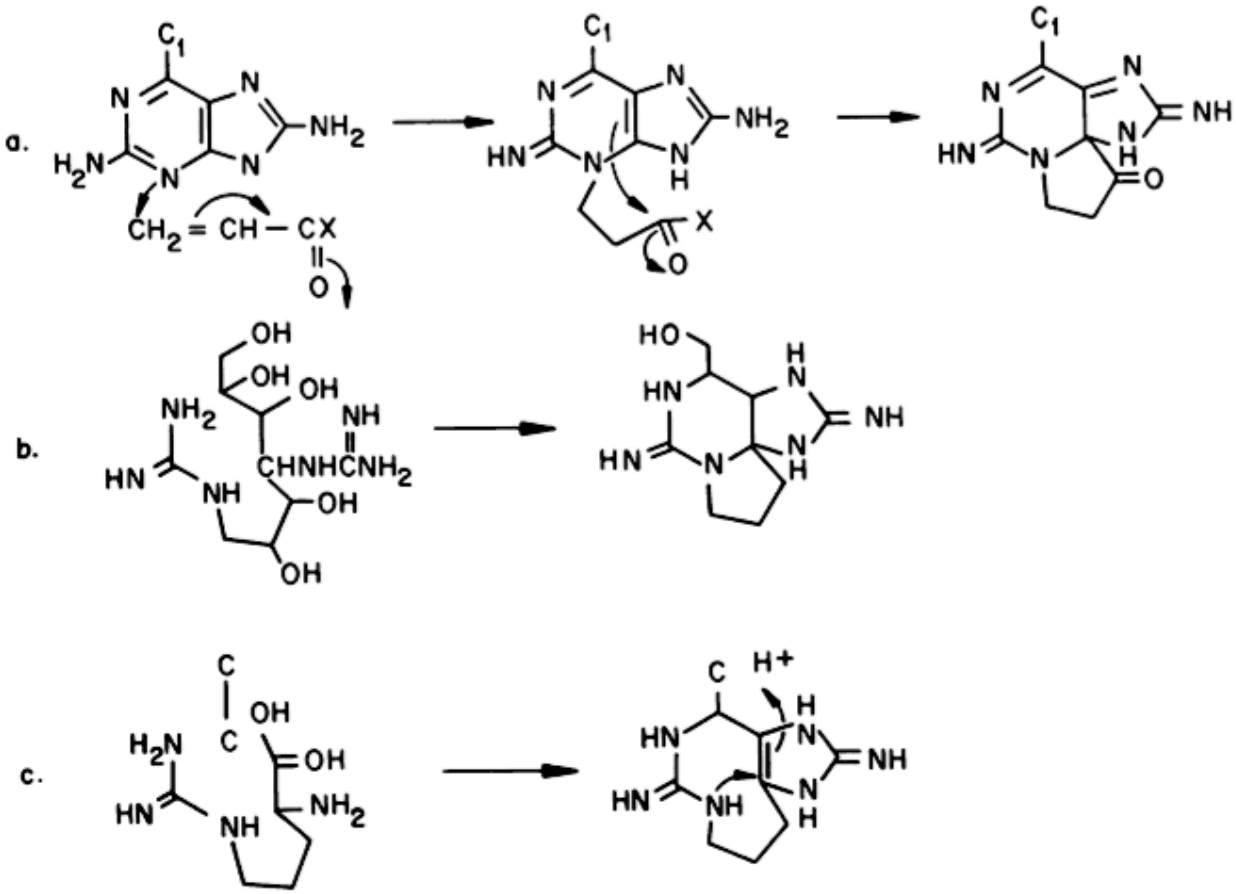
TABLE 7. Ketohydroylation of Olefins: Functional Group Tolerance



entry[a]	alkene	acyloin[b]		yield[%][c]
4	 **9**	 **10a** (96%)	 **10b** (4%)	64
5	 **11**	 **12a** (92%)	 **12b** (8%)	76
6	 **13**	 **14a** (96%)	 **14b** (4%)	82
7	 **15**	 **16a** (97%)	 **16b** (3%)	54
8	 **17**	 **18a** (94%)	 **18b** (6%)	64
9	**19**	 **20a** (87%)	 **20b** (13%)	68

Proposed Biosynthesis

Scheme 1



Biosynthesis

Scheme 4