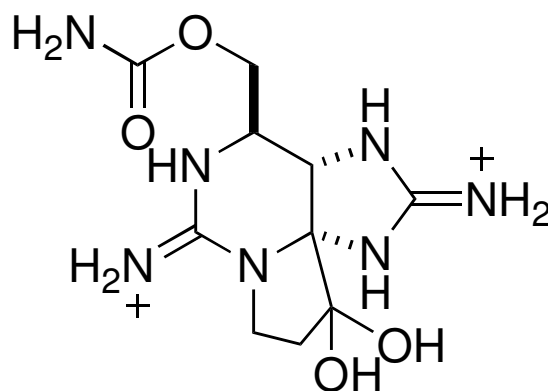


(+) - Saxitoxin



Molecule in Review

Rachel Tundel (Sames group)

Group

6/19/09

Chemistry

Synthesis Literacy

Columbia University

Outline

- Isolation and biological activity
- Major syntheses
 - Kishi (1977) – first racemic synthesis
 - Jacobi (1984) – racemic formal synthesis
 - Du Bois (2006) – first enantioselective total synthesis

Isolation and biological activity

- Isolated from butter clams (*Saxidomus giganteus*) in 1957 by Schantz.
- Crystal structure obtained in 1975 by two groups, independently
- Produced by butter clams and mussels that feed on dinoflagellate algae
- Algae are only toxic during certain seasons
- “Red tide” phenomenon observed when levels of toxic algae bloom high



Isolation: Schantz, E. J. et al. *J. Am. Chem. Soc.* **1957**, 79, 5235.
Crystal Structure: Schantz, E. J. et al. *J. Am. Chem. Soc.* **1975**, 98, 1238.
Review: Llewellyn, L. E. *Nat. Prod. Rep.* **2006**, 23, 200.

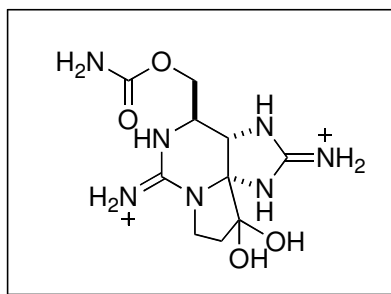
Isolation and biological activity

- One of the most toxic natural, non-protein molecules known; associated with paralytic shellfish poisoning (PSP) illnesses
- $LD_{50} = 5-10 \mu\text{g}/\text{kg}$ (mice)
- Potent, selective sodium channel blocker
- Symptoms of poisoning include dizziness, paralysis and respiratory failure
- No known antidote, just supportive treatment
- Analogues shown to have anesthetic properties—possible therapeutic agents?



Review: Llewellyn, L. E. *Nat. Prod. Rep.* **2006**, 23, 200.

Synthetic Challenges



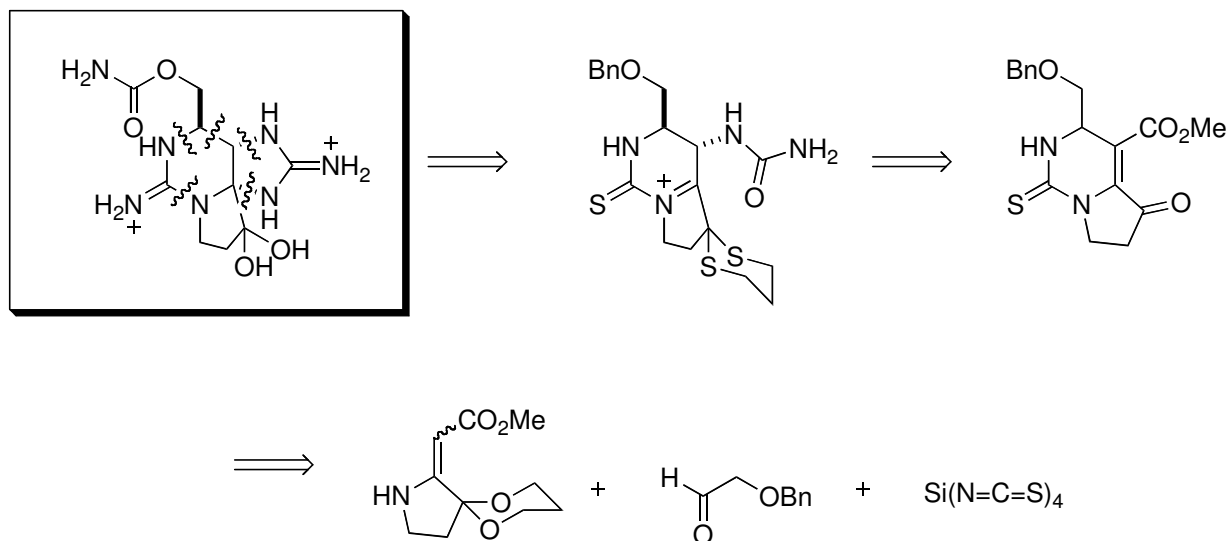
■ Key Synthetic Challenges:

- n 3 contiguous stereogenic centers
- n densely functionalized tetracyclic core
- n two polar guanidinium functionalities

Tundel 5 - CU Synthesis Lit Group - Saxitoxin

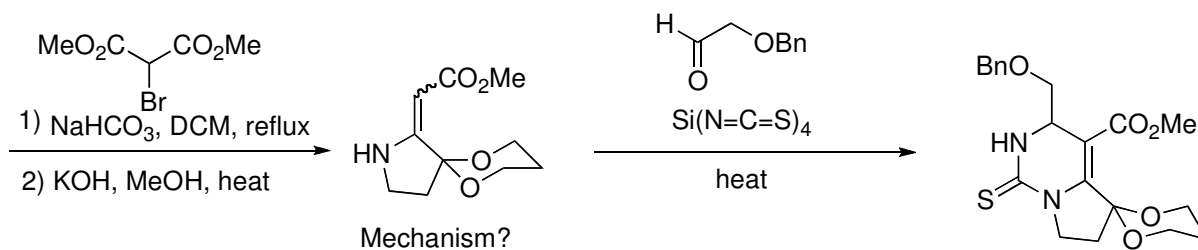
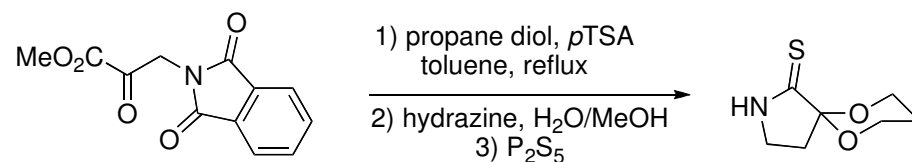
First synthesis – Kishi (1977)

- Retrosynthesis



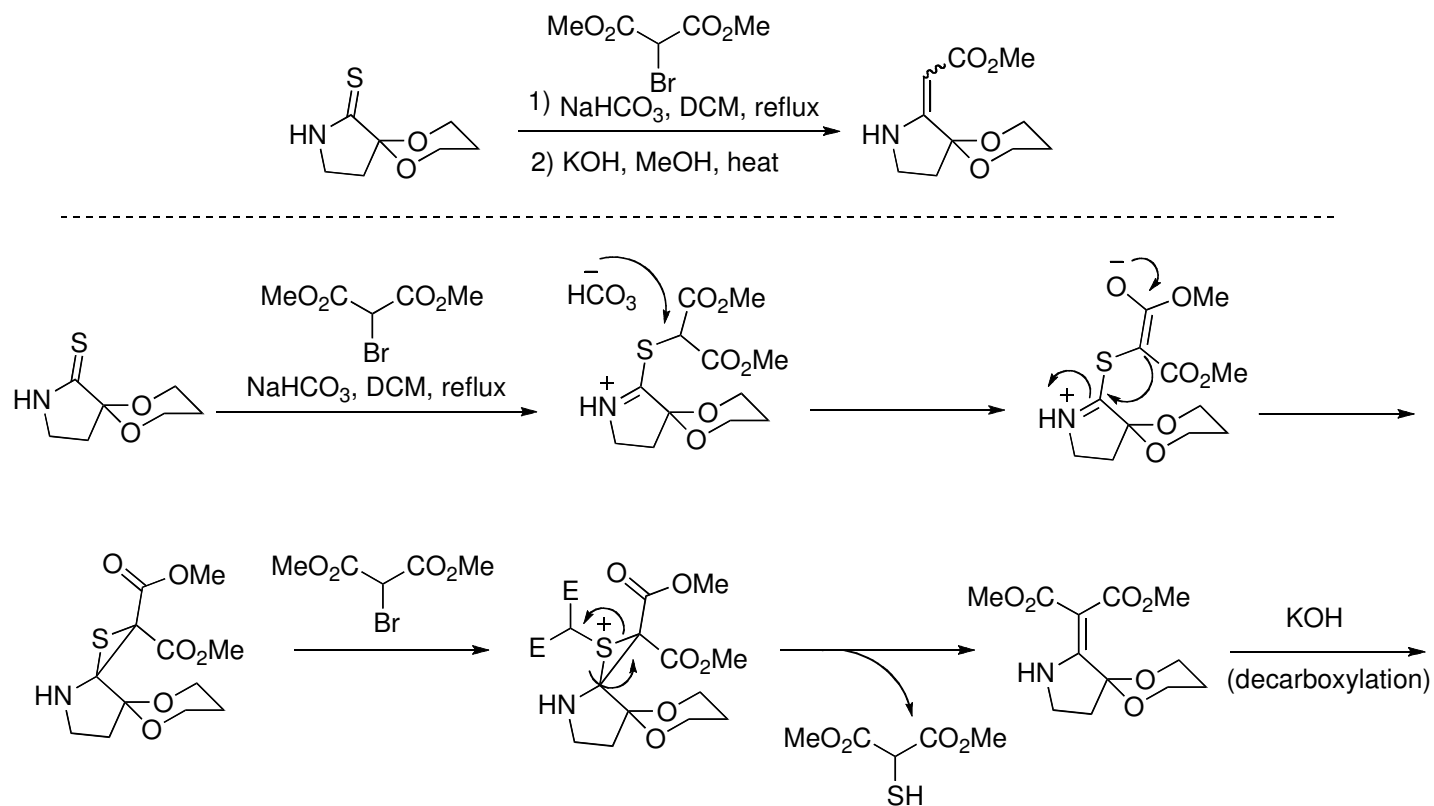
Tanino, H.; Nakata, T.; Kaneko, T.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 2818.
Kishi, Y. *Heterocycles*, **1980**, *14*, 1477.

Kishi synthesis

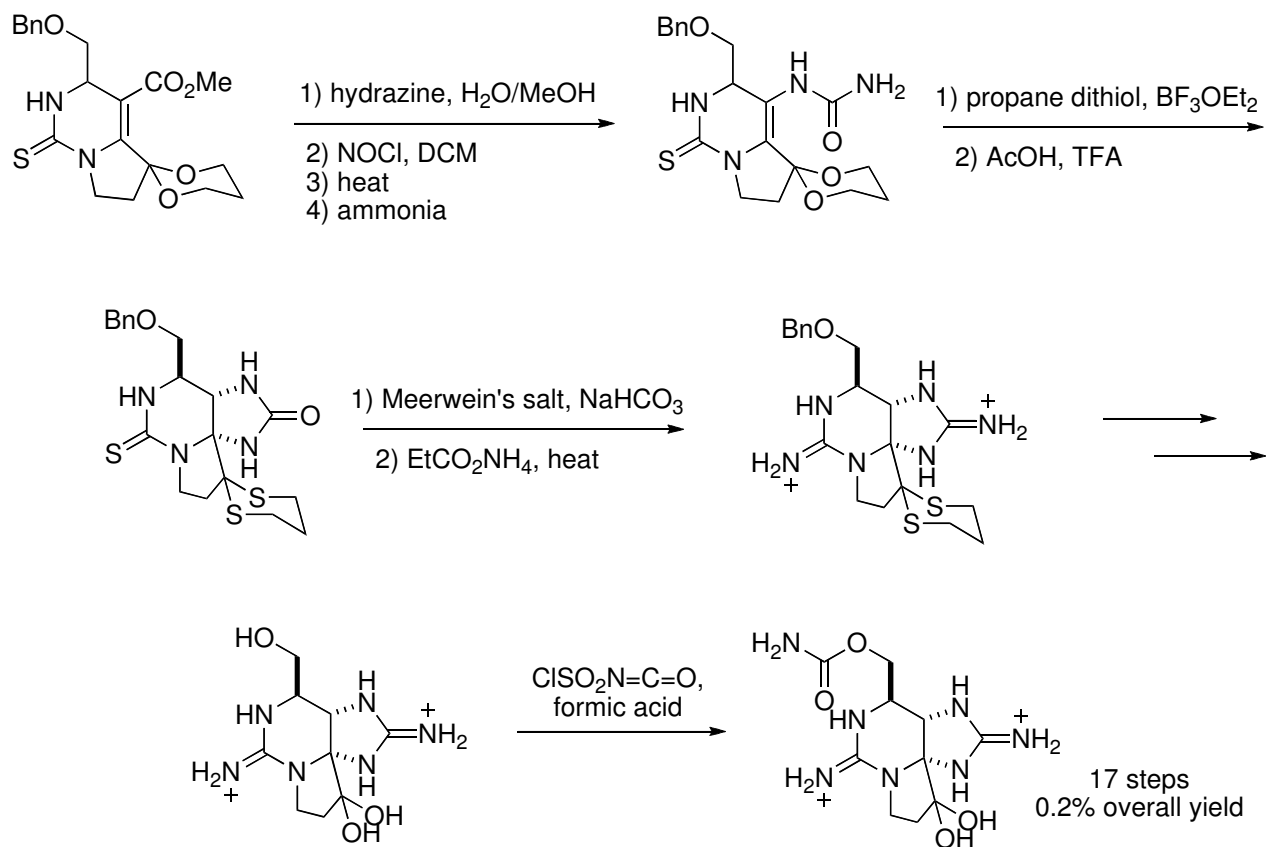


Kishi synthesis (cont.)

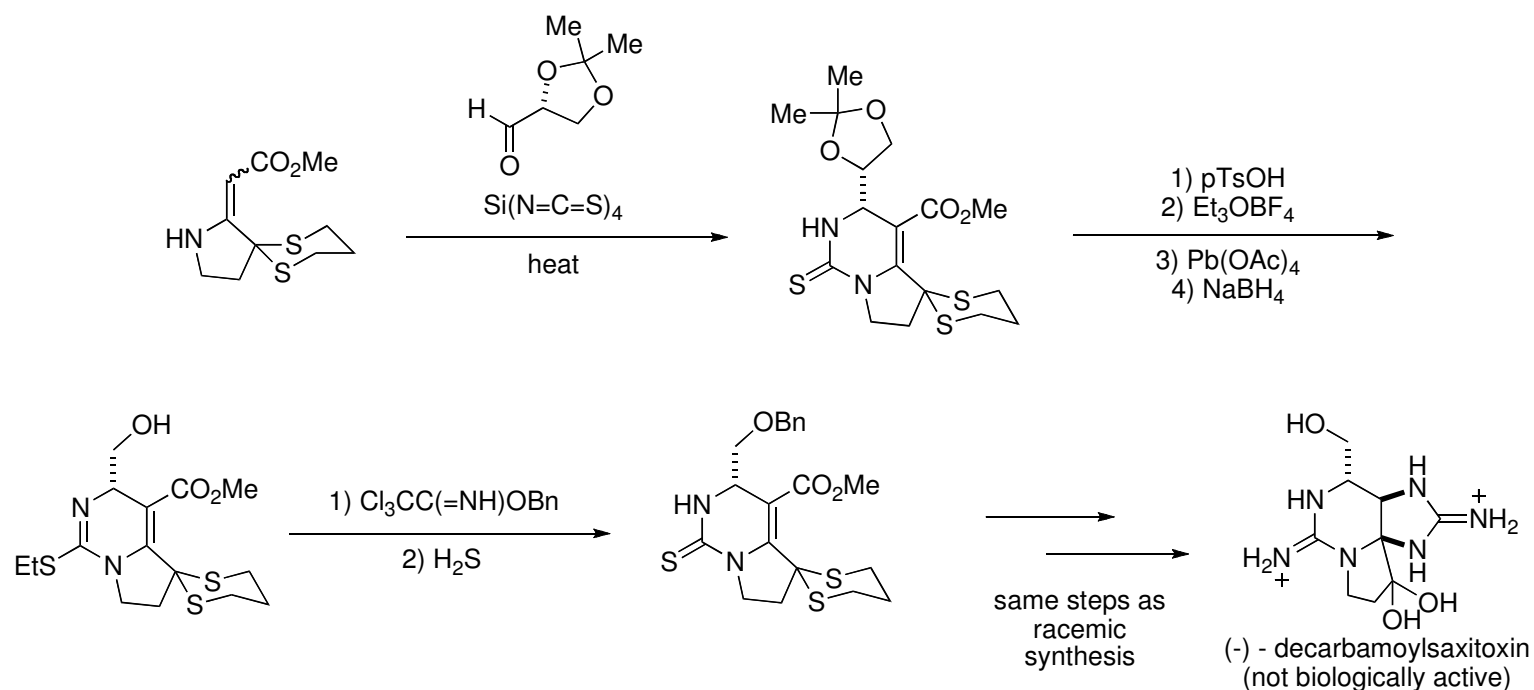
Eschenmoser coupling reaction



Kishi synthesis (cont.)

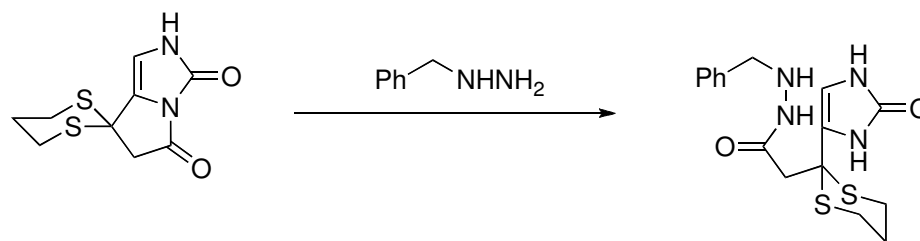
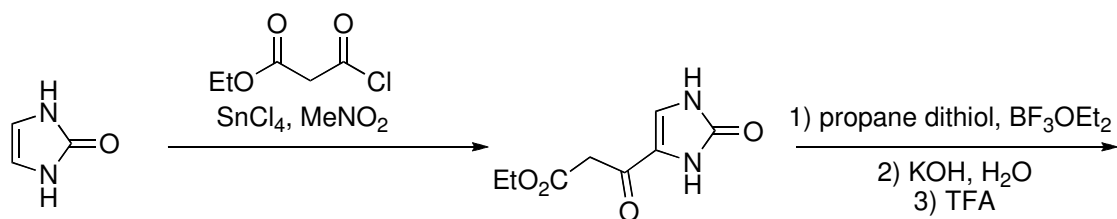


Synthesis of (-) - decarbamoylsaxitoxin (1992)



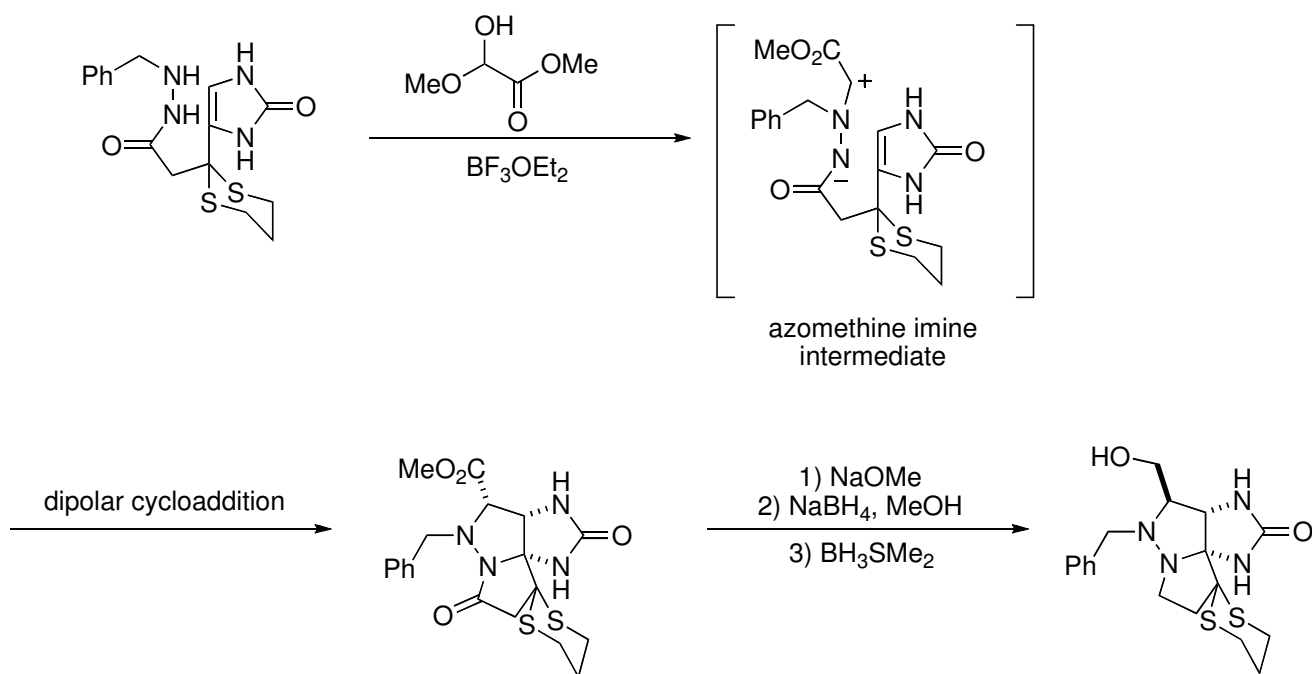
Hong, C. Y.; Kishi, Y. *J. Am. Chem. Soc.* **1992**, *114*, 7001.

Jacobi synthesis

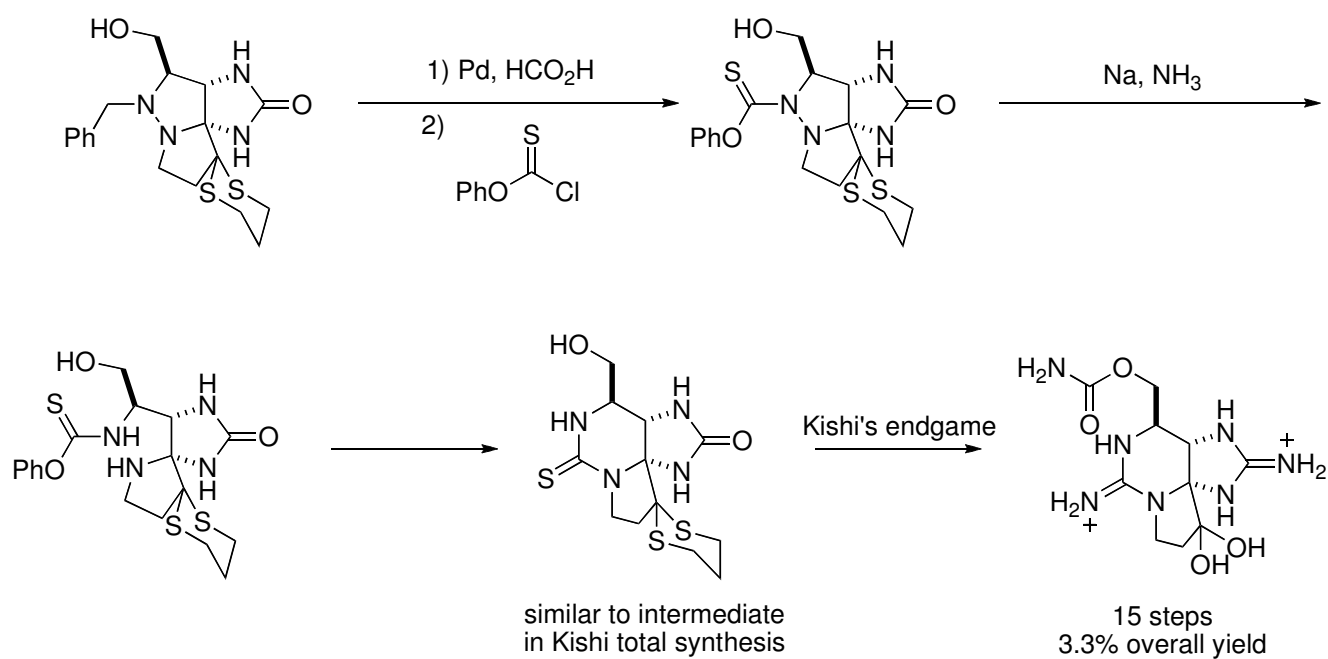


Tundel 12 - CU Synthesis Lit Group - Saxitoxin

Jacobi synthesis (cont.)

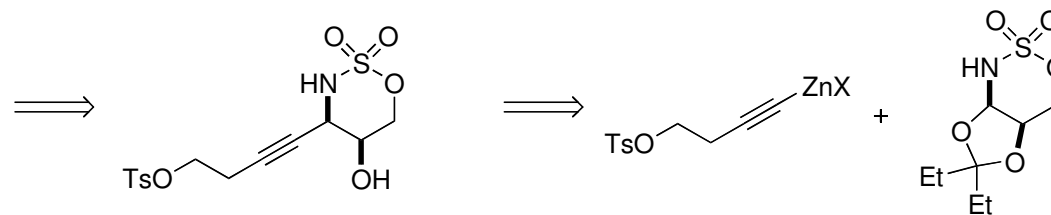
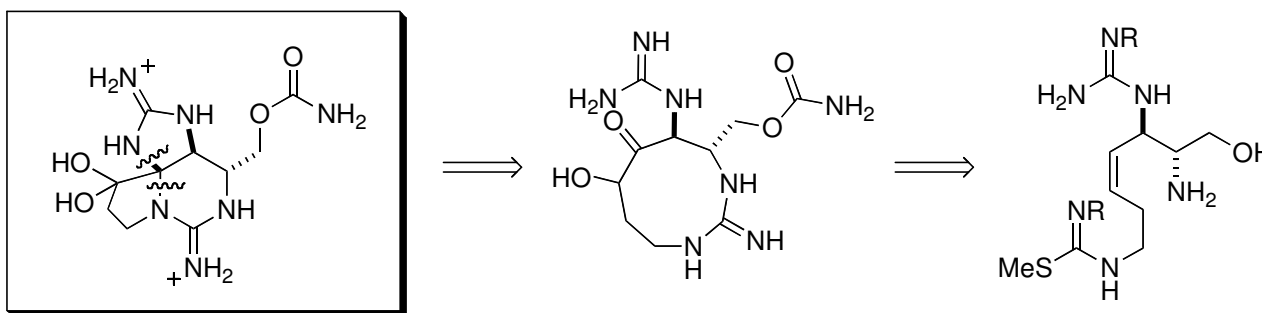


Jacobi synthesis (cont.)



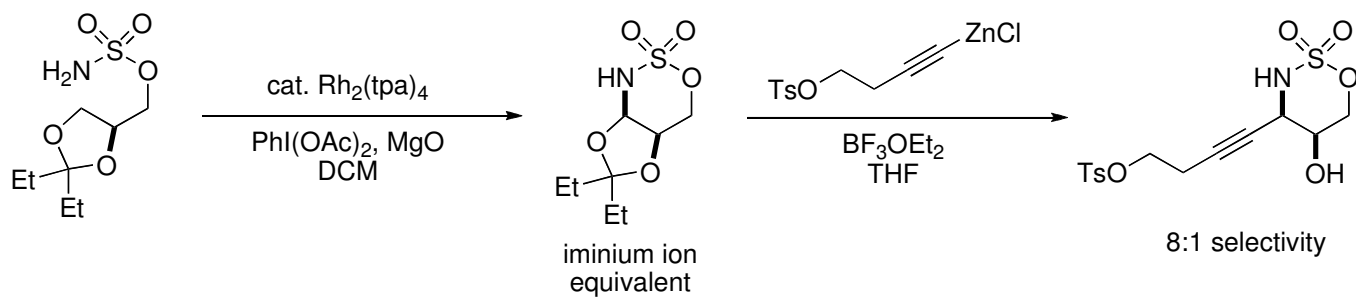
Du Bois synthesis (2006)

- Retrosynthesis

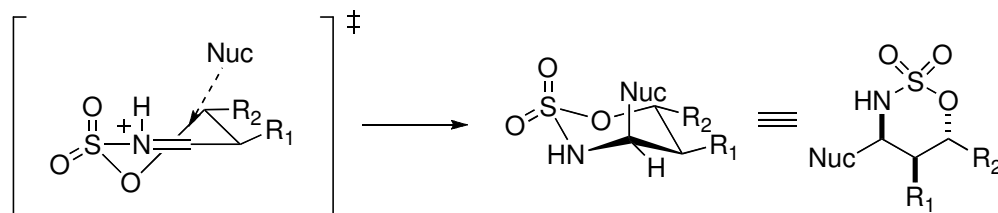


Fleming, J. J.; Du Bois, J. J. *Am. Chem. Soc.* **2006**, *128*, 3926.
Fleming, J. J.; McReynolds, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 9964.

Du Bois Synthesis

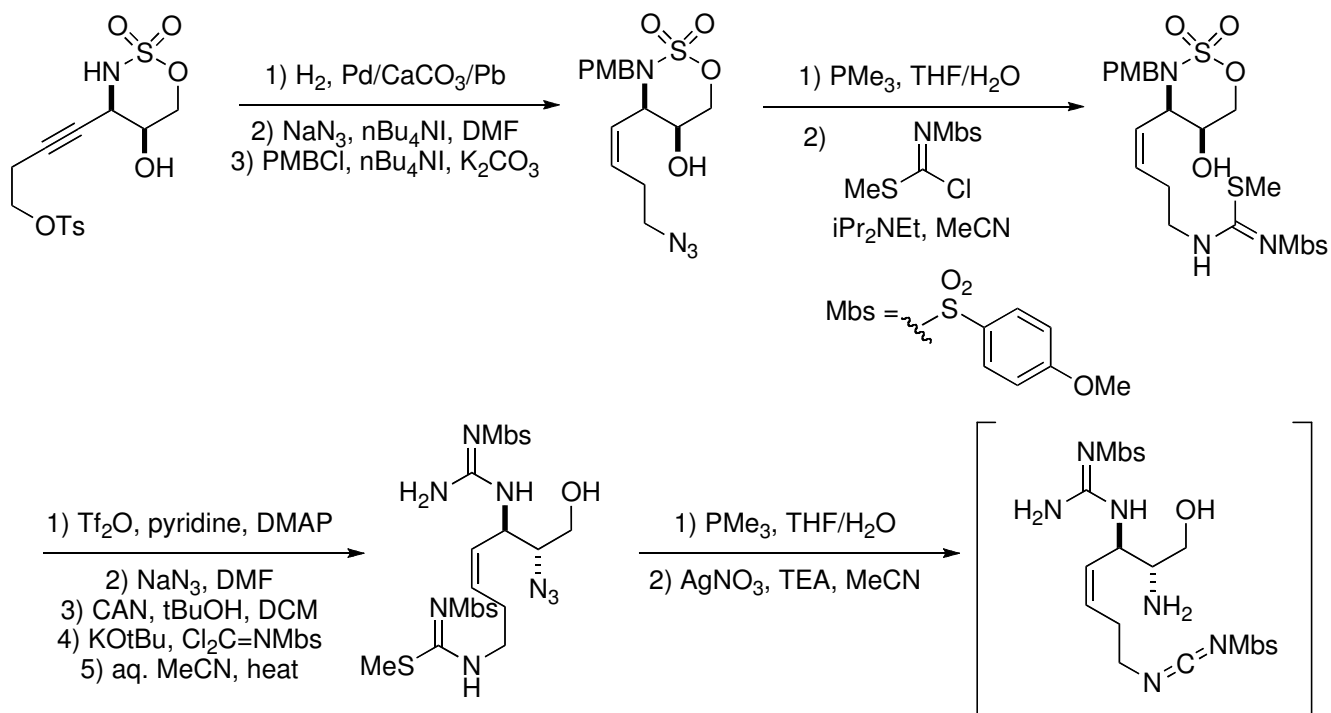


Proposed TS model:

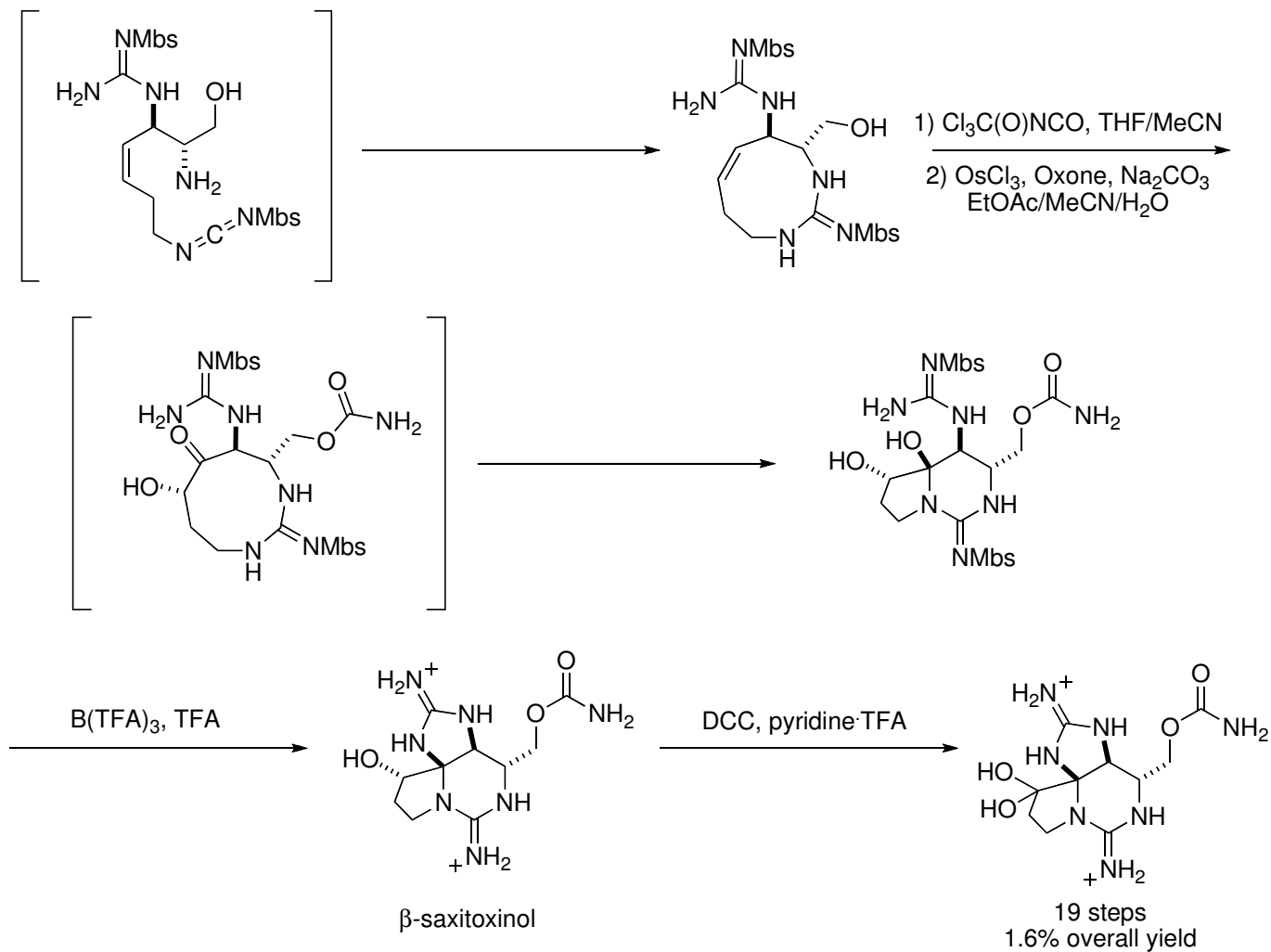


Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 2028.

Du Bois Synthesis



Du Bois Synthesis



Tundel 18 - CU Synthesis Lit Group - Saxitoxin

Summary

- Kishi (1977 & 1992)
 - First racemic total synthesis
 - Use of chiral aldehyde makes synthesis enantioselective for unnatural (-) - decarbamoylsaxitoxin
- Jacobi (1984)
 - [3+2] cycloaddition to construct core
- Du Bois (2006)
 - C-H amination and diastereoselective addition to iminium ion equivalent involved in stereochemistry-setting steps
 - Tricyclic core formed via condensation of 9-membered ring intermediate

Key References

- Isolation/Biology:
 - Llewellyn, L. E. *Nat. Prod. Rep.* **2006**, *23*, 200.
- Kishi (1977 & 1992)
 - Tanino, H.; Nakata, T.; Kaneko, T.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *98*, 2818.
 - Kishi, Y. *Heterocycles*, **1980**, *14*, 1477.
 - Hong, C. Y.; Kishi, Y. *J. Am. Chem. Soc.* **1992**, *114*, 7001.
- Jacobi (1984)
 - Jacobi, P. A.; Martinelli, M. J.; Polanc, S. *J. Am. Chem. Soc.* **1984**, *106*, 5594.
- Du Bois (2006)
 - Fleming, J. J.; Du Bois, J. *J. Am. Chem. Soc.* **2006**, *128*, 3926.
 - Fleming, J. J.; McReynolds, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 9964.