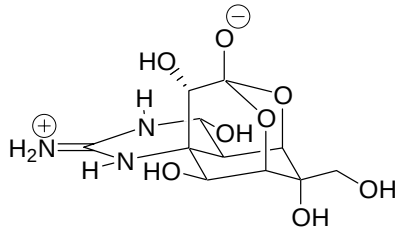
TETRODOTOXIN



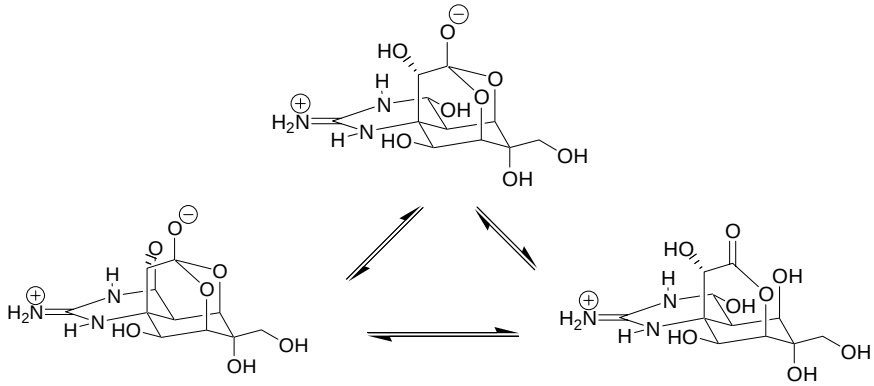
Presentation by Neil Vasan

Baran Lab Group Seminar
August 13, 2003

TTX: Background

- Toxic venom component of puffer fish or *fugu* (*Spheroides rubripes*), a Japanese delicacy (1 fish = ~$400)
- First isolated in 1909 and named after puffer fish order *Tetraodontidae*
- Structure first elucidated in 1964 by Woodward (confirmed by Kishi in 1965)
- First synthesis by Kishi, et. al. in 1972
- Toxicity attributed to selective blockage of Na^+ channels of skeletal muscles
- Lethal dose for adult human = .001 mg
- Upon ingestion, one feels tingling and lightheadedness but is lucid; paralysis and death ensue within 6-24 hours
- 70-100 deaths each year, mostly in rural Japan
- No known antidote exists

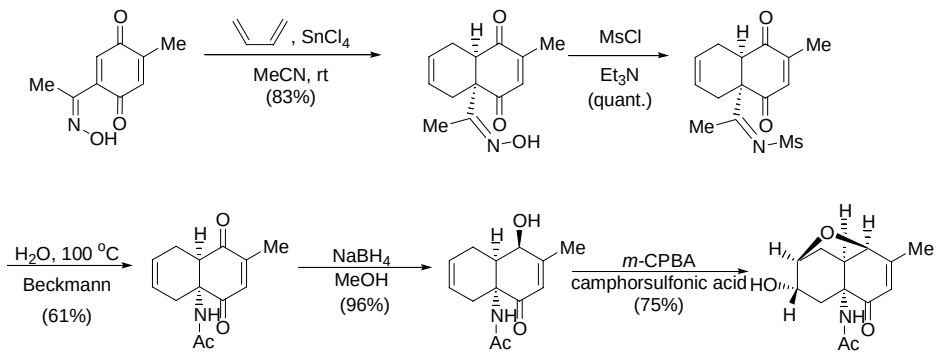
TTX: Structure



Equilibrium mixture among ortho ester, anhydride, and lactone forms

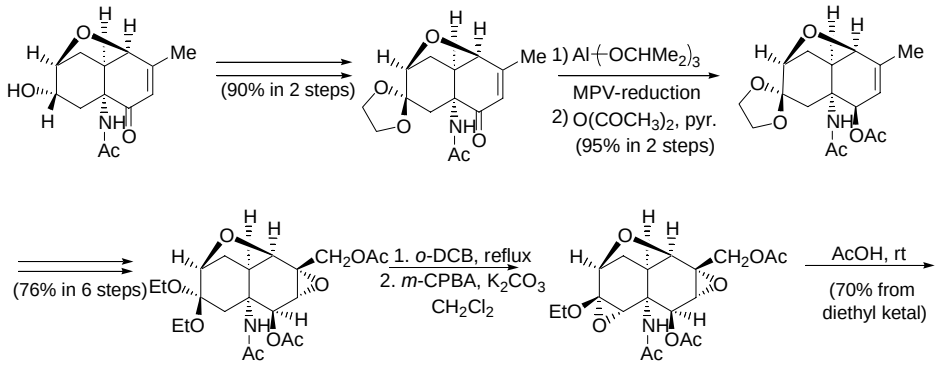
TTX: Kishi Synthesis

Synthesis of Cyclohexane chiral core



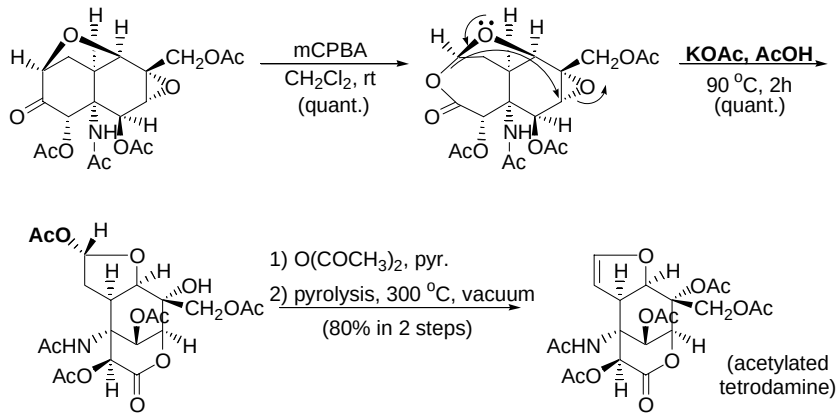
TTX: Kishi Synthesis

Towards Tetrodamine



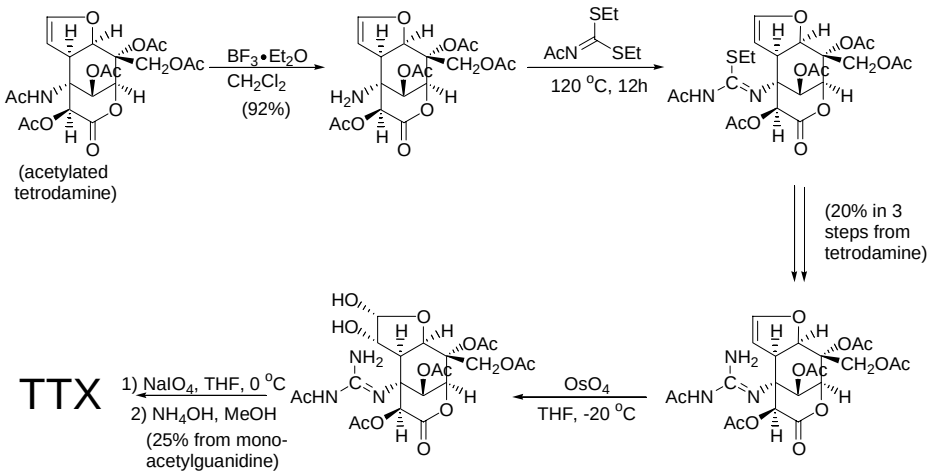
TTX: Kishi Synthesis

Towards Tetrodamine



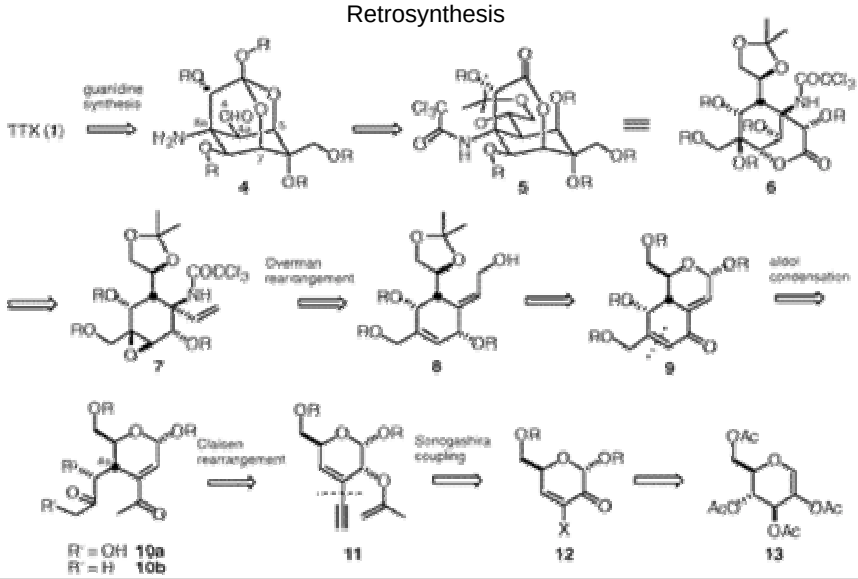
TTX: Kishi Synthesis

Tetrodamine to Tetrodotoxin



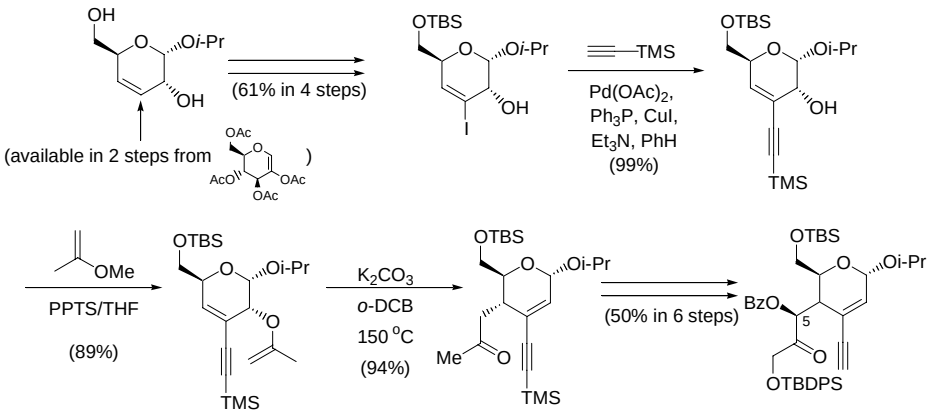
TTX: Isobe Synthesis

Retrosynthesis



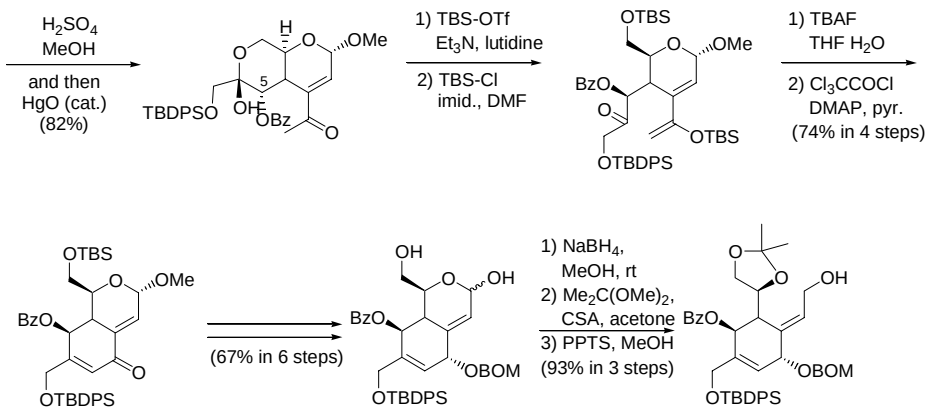
TTX: Isobe Synthesis

Sonogashira Coupling and Claisen Rearrangement

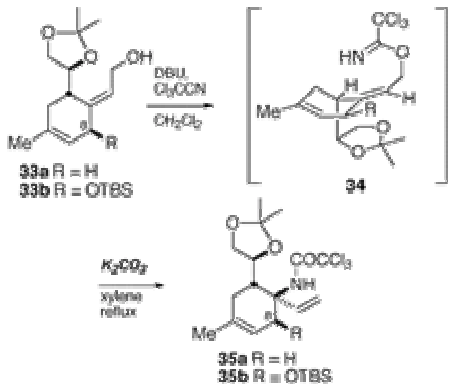
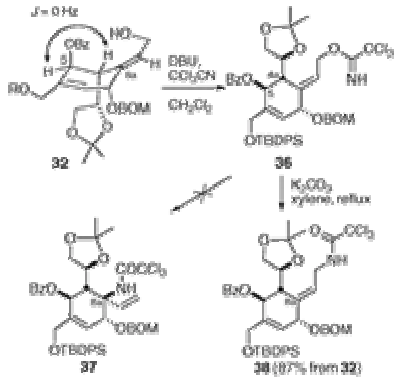


TTX: Isobe Synthesis

Cyclohexenone and Exoolefin Synthesis

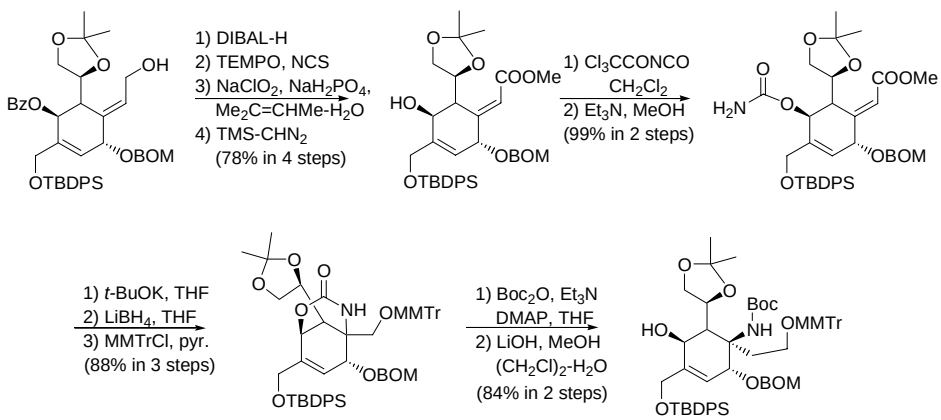


TTX: Isobe Synthesis

Previous Overman Rearrangement	Problem with Overman Rearrangement
	

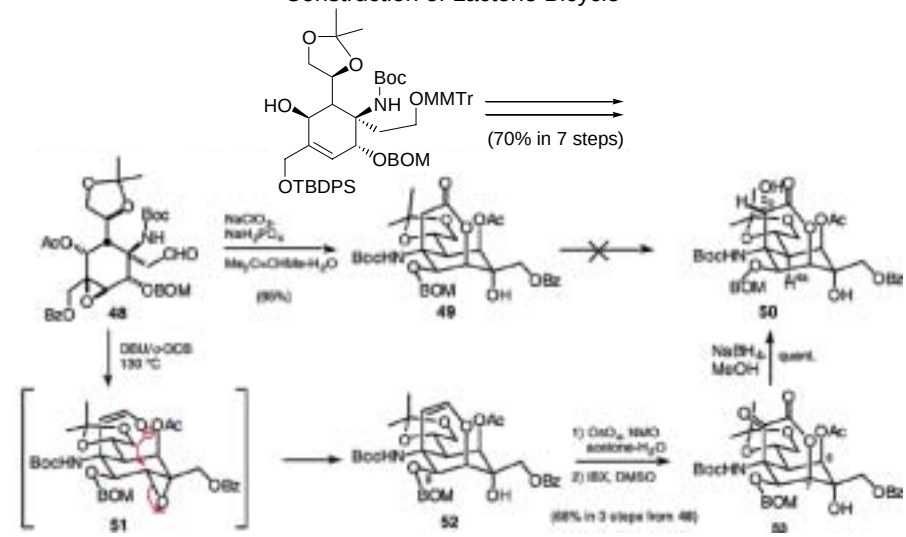
TTX: Isobe Synthesis

Installation of Nitrogen Functionality: Conjugate Carbamate Addition



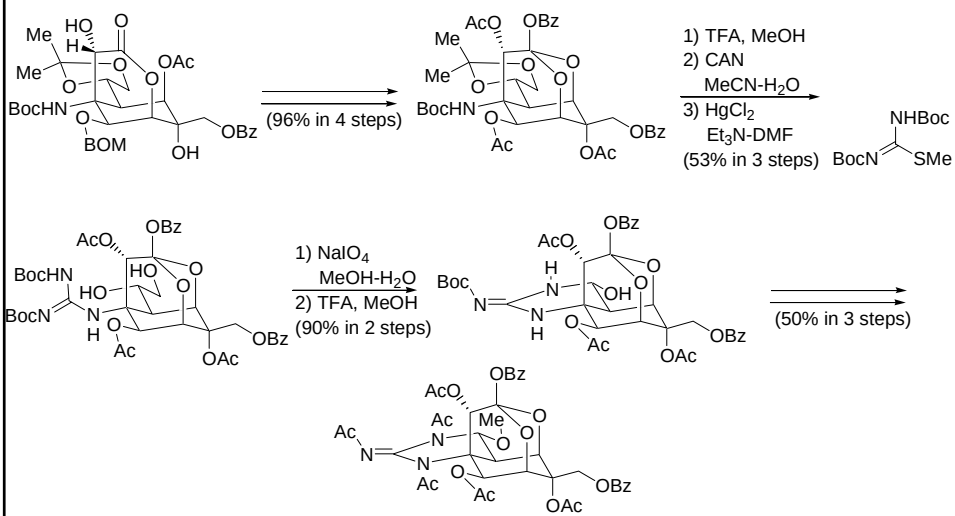
TTX: Isobe Synthesis

Construction of Lactone Bicycle



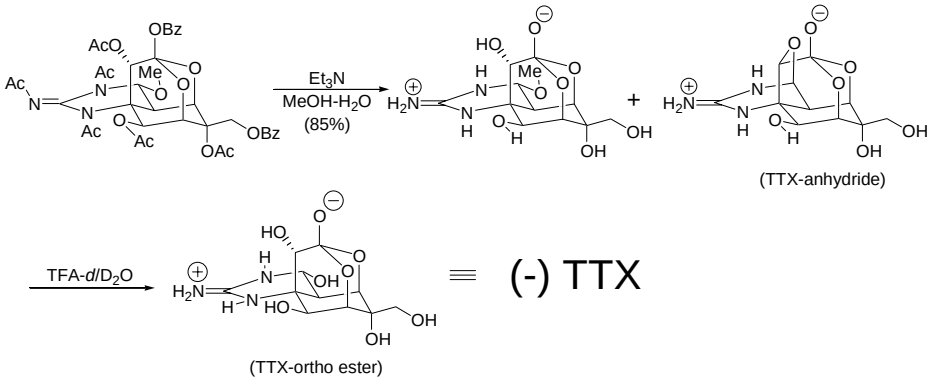
TTX: Isobe Synthesis

Introduction of Guanidine



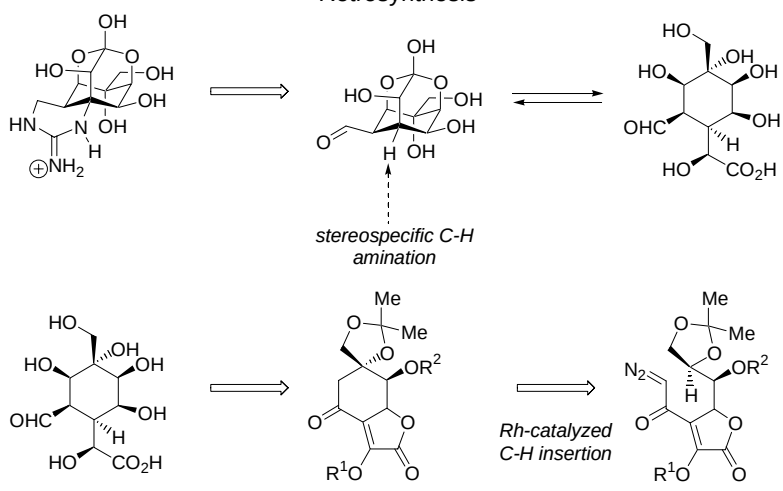
TTX: Isobe Synthesis

Deprotection and Final Conversion



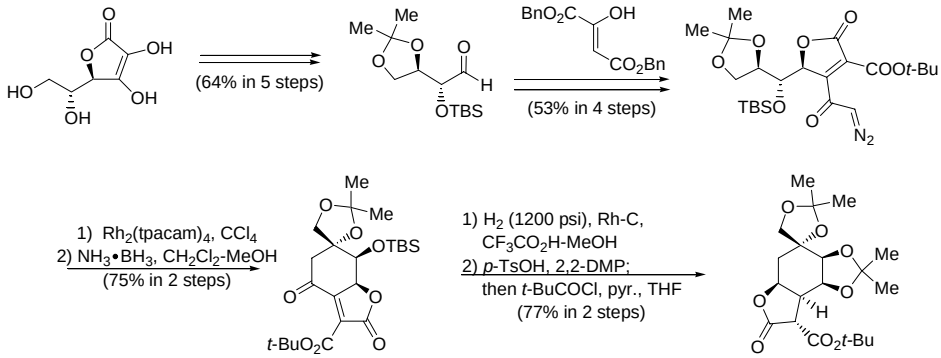
TTX: Du Bois Synthesis

Retrosynthesis



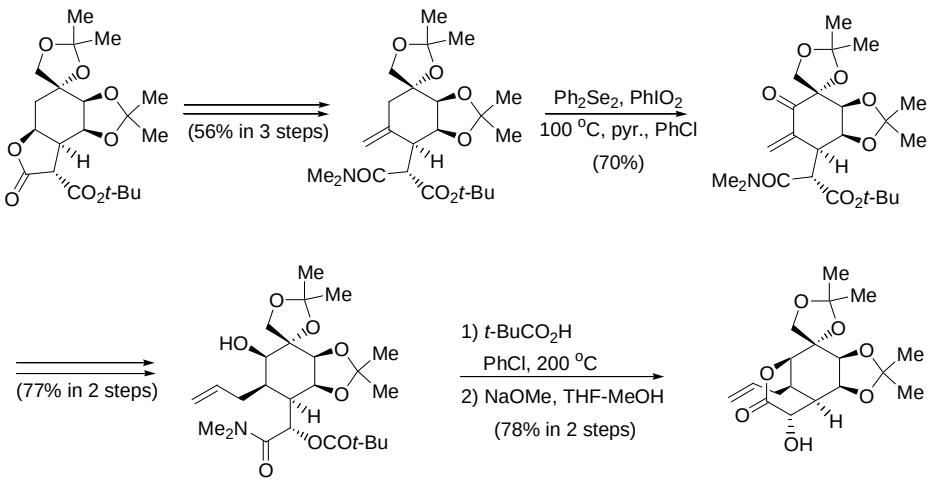
TTX: Du Bois Synthesis

Rh-carbene C-H insertion



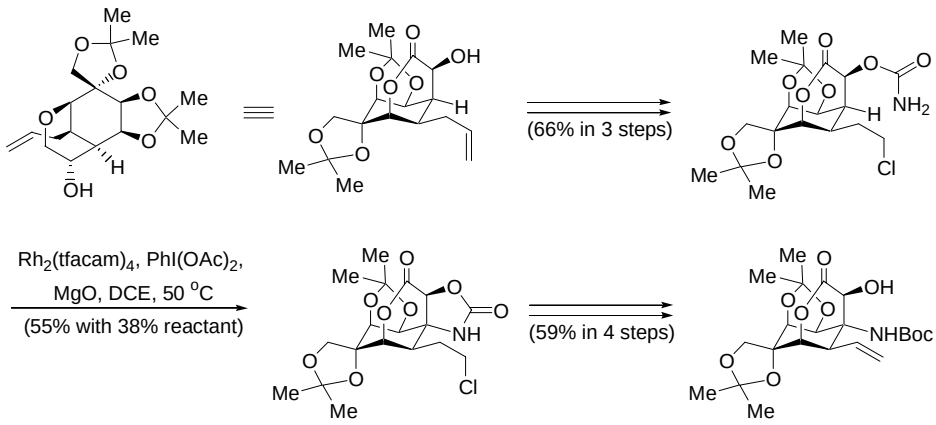
TTX: Du Bois Synthesis

Construction of Lactone Bicycle



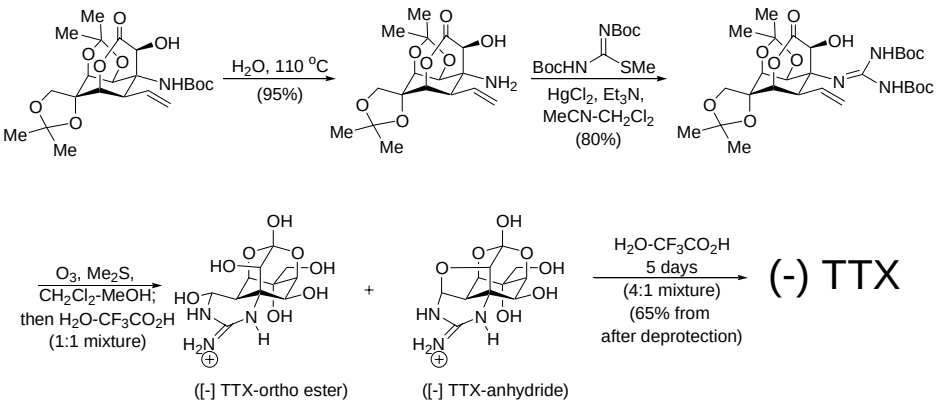
TTX: Du Bois Synthesis

Rh-nitrene C-H insertion



TTX: Du Bois Synthesis

Guanidine Insertion and Final Steps



Comparisons and Contrasts

Chemist	KISHI	ISOBE	DU BOIS
Date	Sept. 1972	Jan. 2003	June 2003
Type	Racemic	Asymmetric	Asymmetric
Highlights	Diels-Alder synthesis of skeleton; 6 chiral centers established on cyclohexane core ring; Only ketal and acetyl protecting groups; Common reagents employed to carry out elegant chemistry	Claisen rearrangement; Sonogashira coupling; Intramolecular carbamate-ester conjugate addition; All OH groups differently protected for future analog synthesis	Rhodium-catalyzed carbene and nitrene C-H insertions; Ph_2Se_2-promoted allylic oxidation; Shows power of organometallic chemistry in total synthesis
# of Steps	29	67	32
Yield	0.66%	1.22%	0.49%

TTX: References

Structure:
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Nishikawa, T., et. al. *J. Am. Chem. Soc.* **2002**, *124*, 7847-7852.

TTX: References

Kishi synthesis:	Kishi, Y., et. al. *Tetrahedron Lett.* **1970**, *59*, 5127-5128. Kishi, Y., et. al. *Tetrahedron Lett.* **1970**, *59*, 5129-5132. Kishi, Y., et. al. *J. Am. Chem. Soc.* **1972**, *94*, 9217-9219. Kishi, Y., et. al. *J. Am. Chem. Soc.* **1972**, *94*, 9219-9221.
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Sonogashira Coupling:	Sonogashira, K., et. al. *Tetrahedron Lett*. **1975**, *16*, 4467-4470.
α-hydroxyl Lactone:	Corey, E. J.; Ghosh, A. K. *Tetrahedron Lett.* **1988**, *26*, 3205-3206.
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Rh-carbene C-H insertion:	Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Rd. Engl.* **2001,** *40*, 598-600.
Rh-nitrene C-H insertion:	Guthikonda, K.; Du Bois, J., *J. Am. Chem. Soc.* **2002**, *124*, 13672-13673.
Ph_2Se_2 allylic oxidation:	Barton, D. H. R.; Crich, D. *Tetrahedron* **1985**, *41*, 4359-4364.

TTX: Acknowledgements

- Prof. Justin Du Bois, Stanford University
- The Baran Laboratory, TSRI