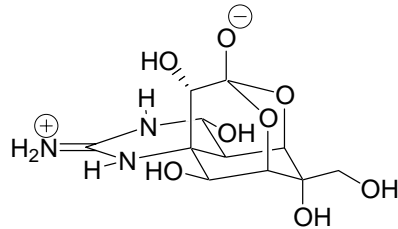


TETRODOTOXIN



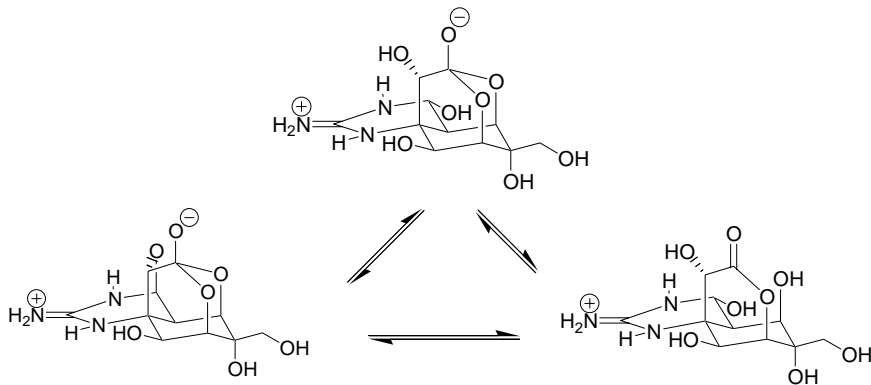
Presentation by Neil Vasan

**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

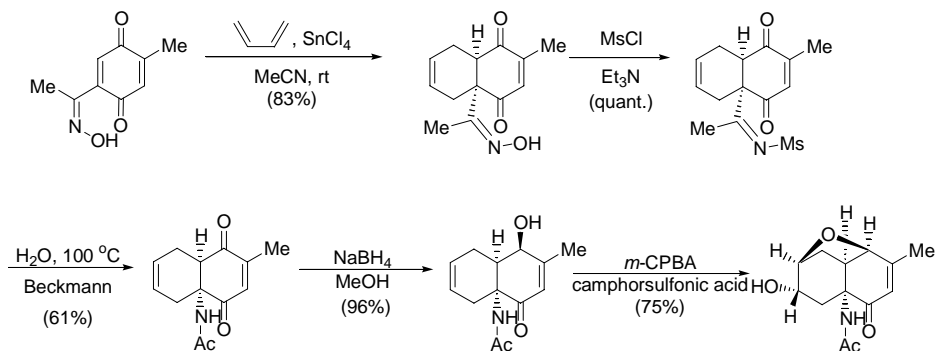
TTX: Structure



Equilibrium mixture among ortho ester, anhydride, and lactone forms

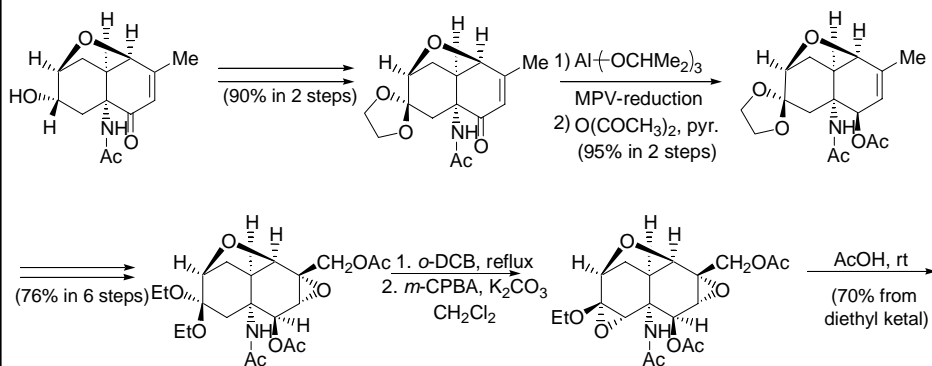
TTX: Kishi Synthesis

Synthesis of Cyclohexane chiral core



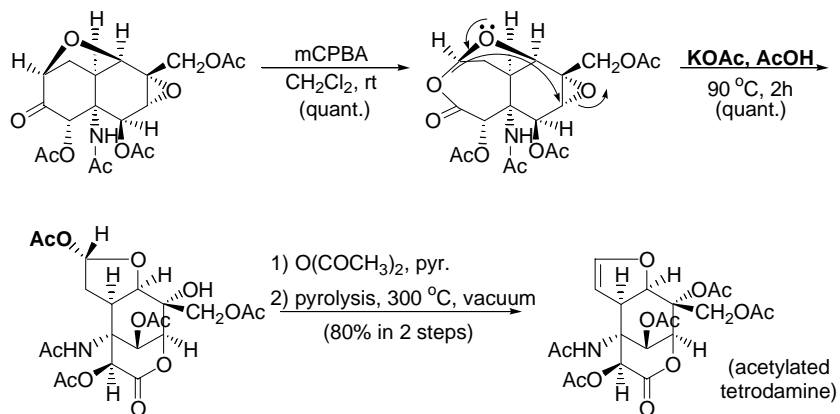
TTX: Kishi Synthesis

Towards Tetrodamine



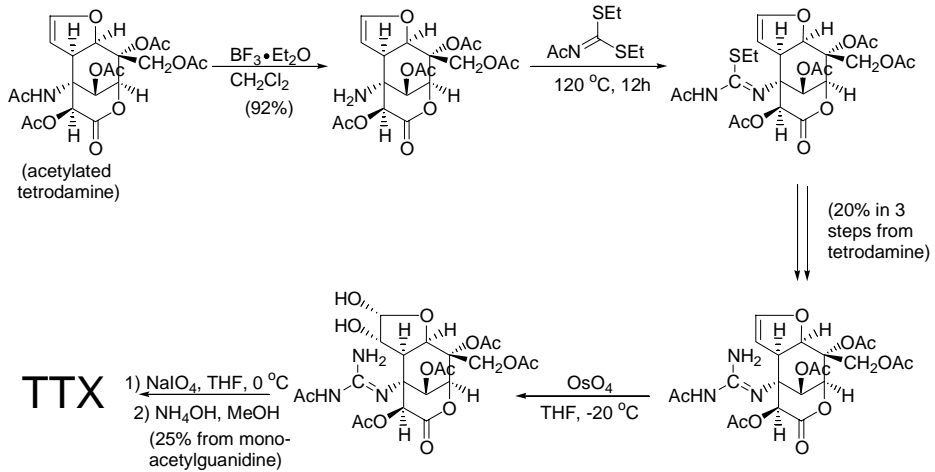
TTX: Kishi Synthesis

Towards Tetrodamine



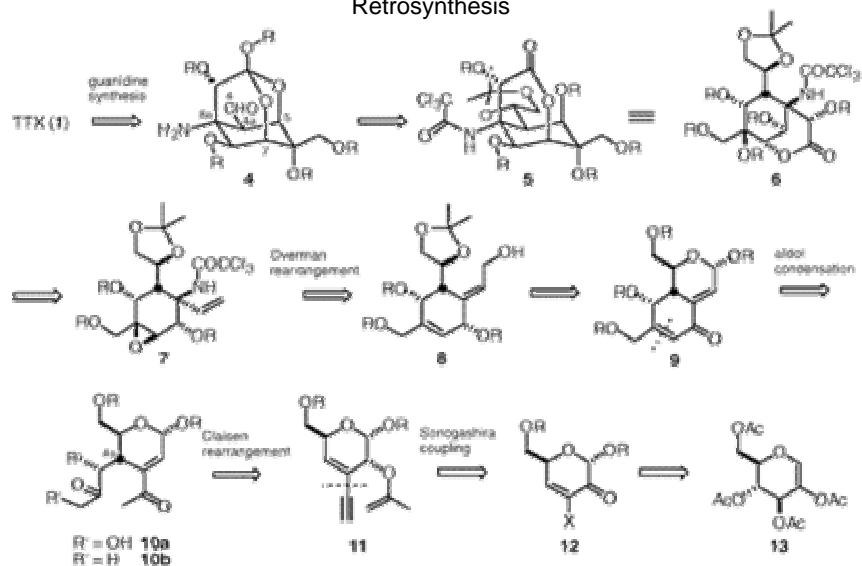
TTX: Kishi Synthesis

Tetrodamine to Tetrodotoxin



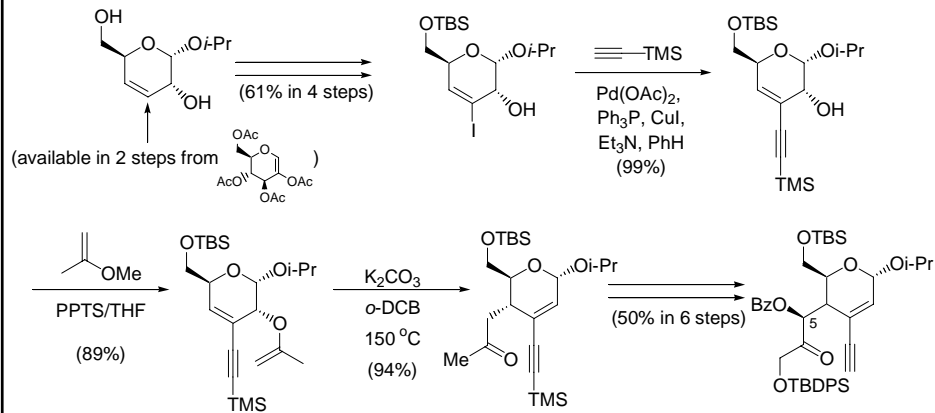
TTX: Isobe Synthesis

Retrosynthesis



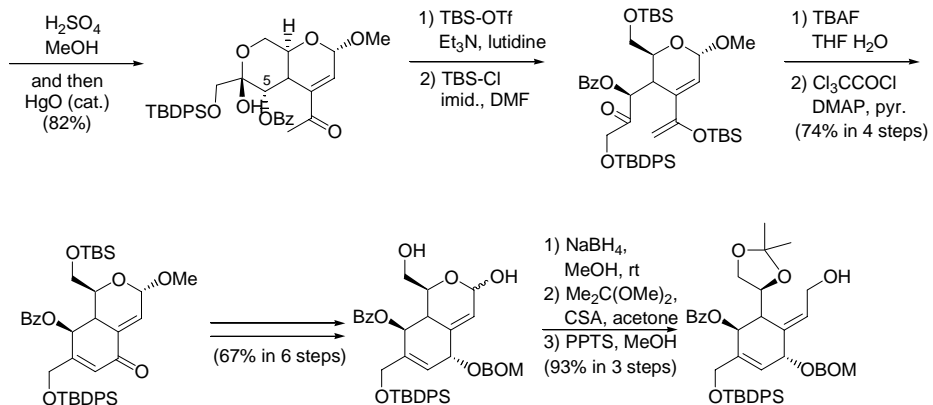
TTX: Isobe Synthesis

Sonogashira Coupling and Claisen Rearrangement

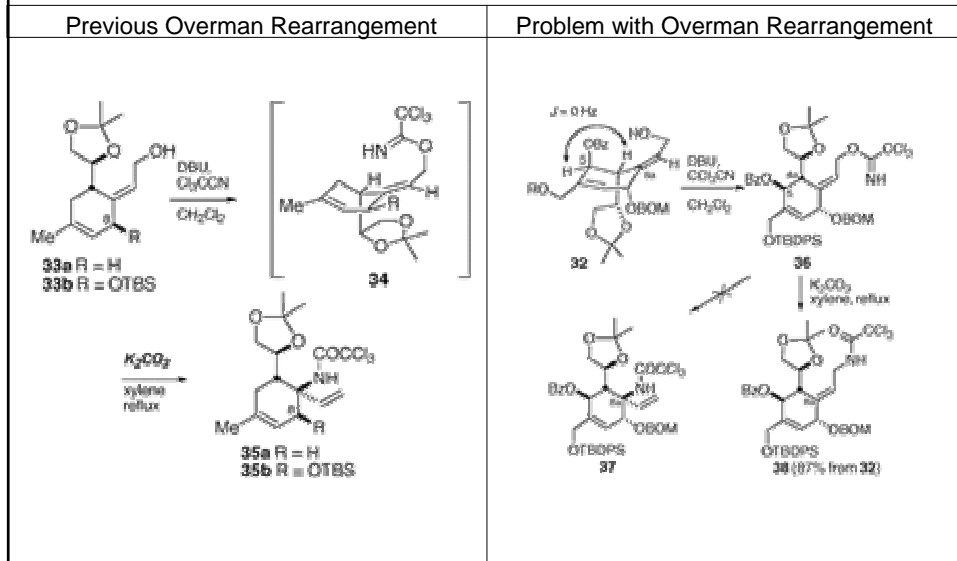


TTX: Isobe Synthesis

Cyclohexenone and Exoolefin Synthesis

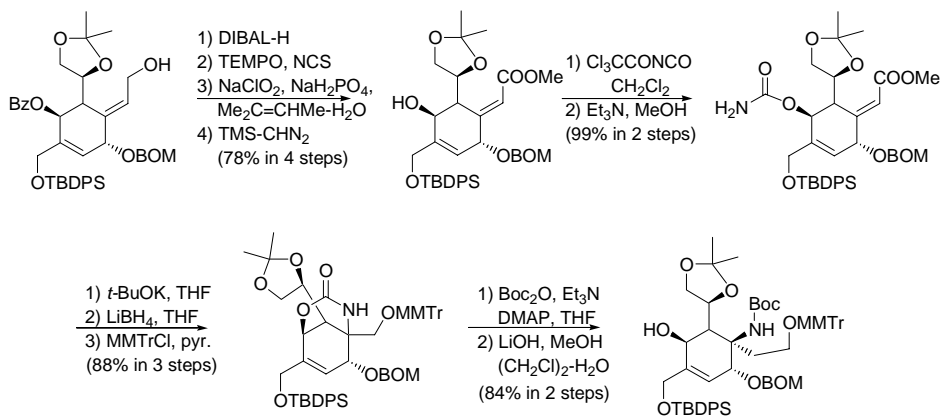


TTX: Isobe Synthesis



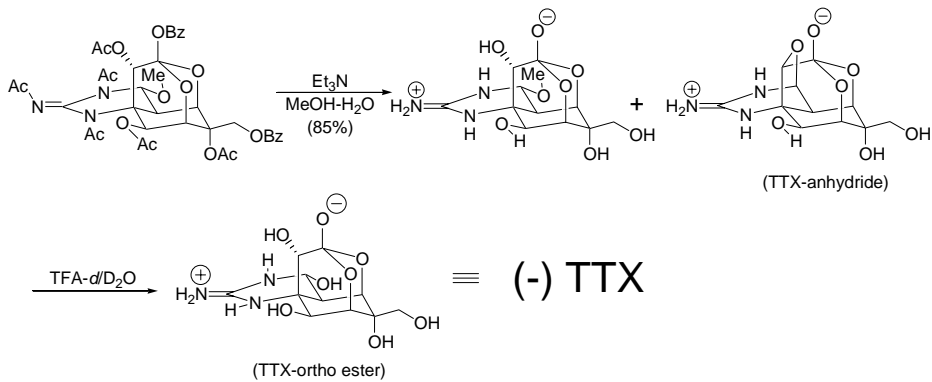
TTX: Isobe Synthesis

Installation of Nitrogen Functionality: Conjugate Carbamate Addition

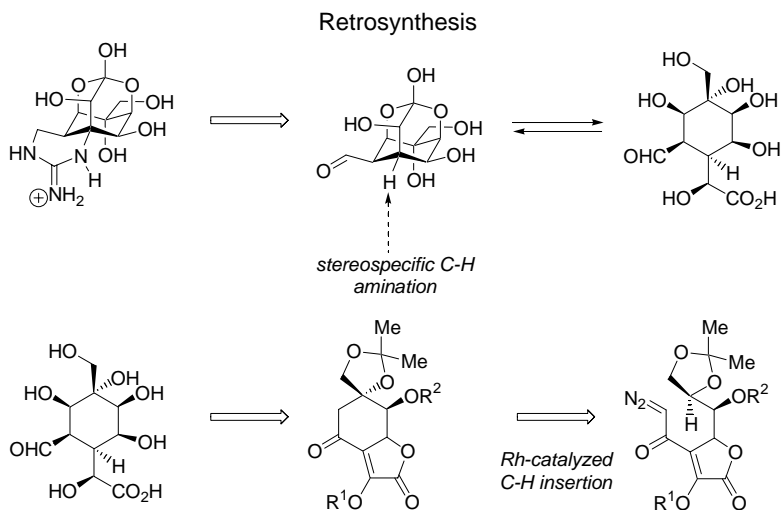


TTX: Isobe Synthesis

Deprotection and Final Conversion

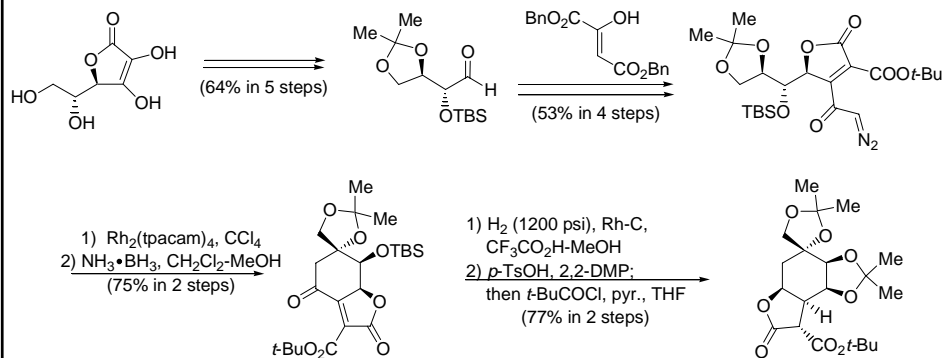


TTX: Du Bois Synthesis



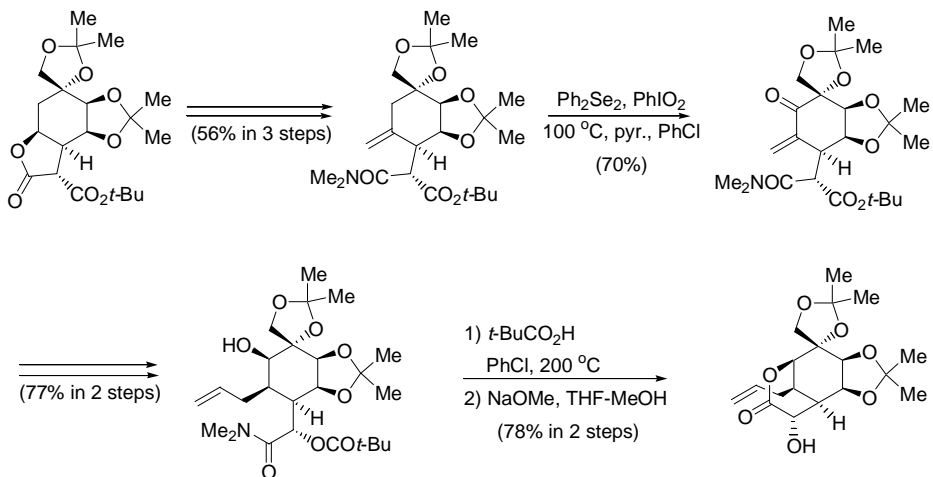
TTX: Du Bois Synthesis

Rh-carbene C-H insertion



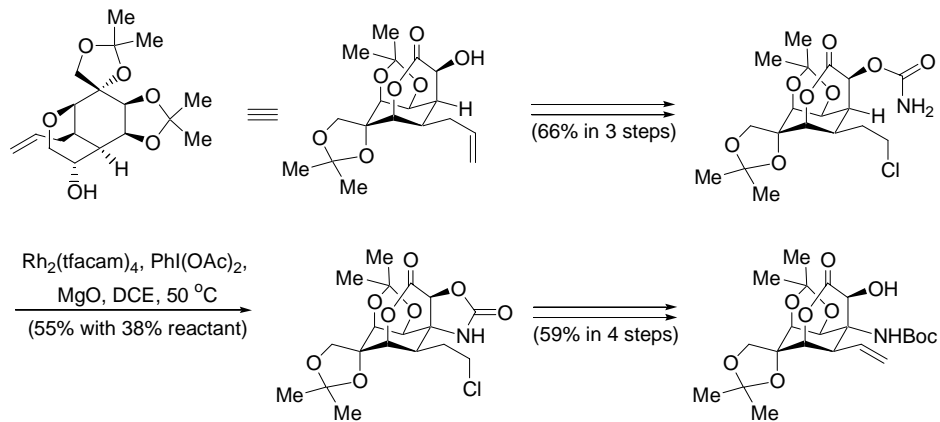
TTX: Du Bois Synthesis

Construction of Lactone Bicycle



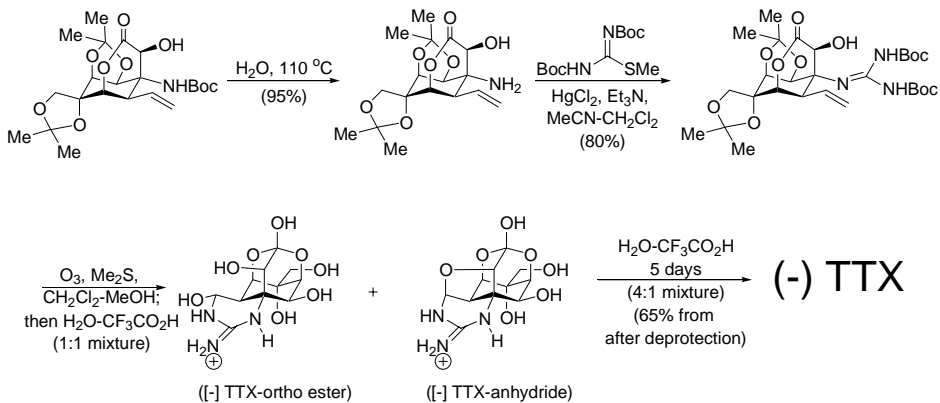
TTX: Du Bois Synthesis

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 ₂ Se 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:** Woodward, R. B. *Pure. Appl. Chem.* **1964**, 9, 49-74.
 Tsuda, K., et. al. *Chem. Pharm. Bull.* **1964**, 12, 1357-1374.
 Goto, T.; Kishi, Y.; Takahashi, S.; Hirata, Y. *Tetrahedron* **1965**, 21, 2059-2088.
- Absolute stereochemistry:** Furusaki, A., et. al. *Bull. Chem. Soc. Jpn.* **1970**, 43, 3332-3341.
- Bioorganic studies:** Narahashi, T.; Moore, J. W.; Scott, W. R. *J. Gen. Physiol.* **1964**, 47, 965-974.
 Hucho, F. *Angew. Chem, Int. Ed. Engl.* **1995**, 34, 39-50.
 Numa, S.; Noda, M. *Ann. N.Y. Acad. Sci.* **1986**, 479, 338-355.
- Other analog syntheses:** Nishikawa, T., et. al. *Angew. Chem., Int. Ed.* **1999**, 38, 3081-3084.
 Asai, M., et. al. *Tetrahedron* **2001**, 57, 4543-4558.
 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.
- Isobe synthesis:** Isobe, M., et. al. *J. Am. Chem. Soc.* **2003**, *125*, 8798-8805.
- Overman Rearrangement:** Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218-224.
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.
- Du Bois Synthesis:** Hinman, A.; Du Bois, J., personal communication. (to be published in JACS)
- 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.
Ph₂Se₂ 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