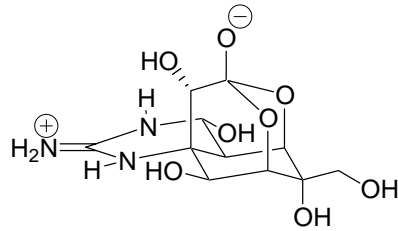


# TETRODOTOXIN



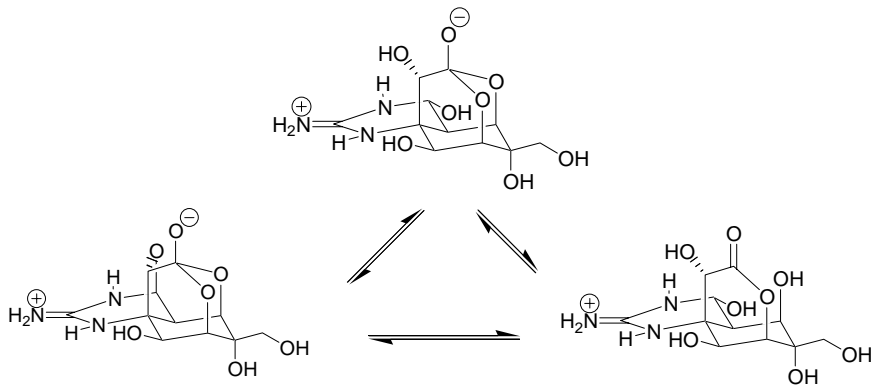
Presentation by Neil Vasan

**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<sup>+</sup> 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

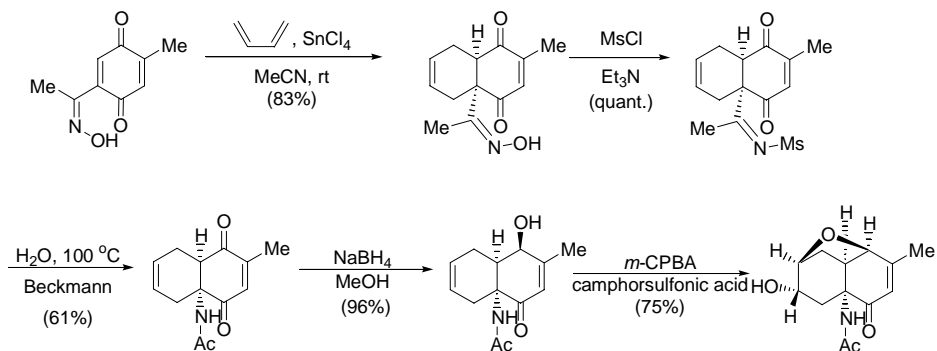
# TTX: Structure



Equilibrium mixture among ortho ester, anhydride, and lactone forms

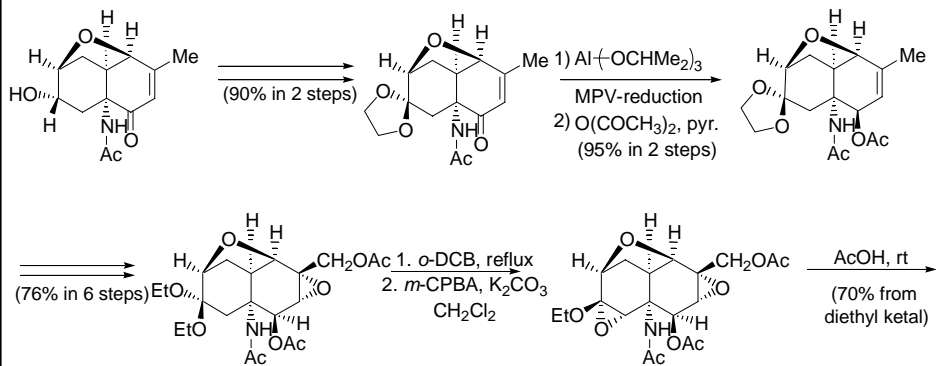
# TTX: Kishi Synthesis

Synthesis of Cyclohexane chiral core



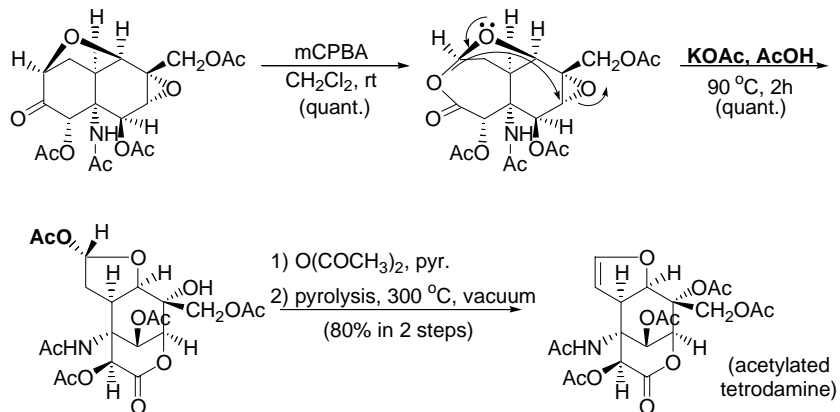
# TTX: Kishi Synthesis

Towards Tetrodamine



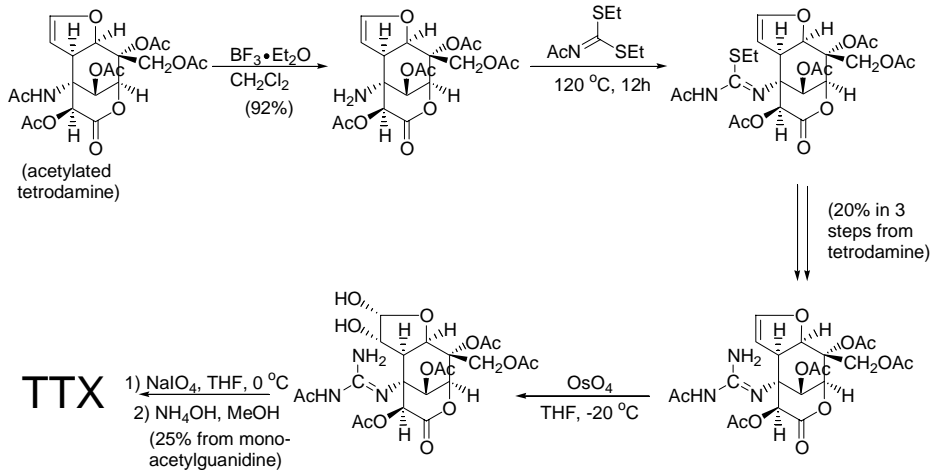
# TTX: Kishi Synthesis

Towards Tetrodamine



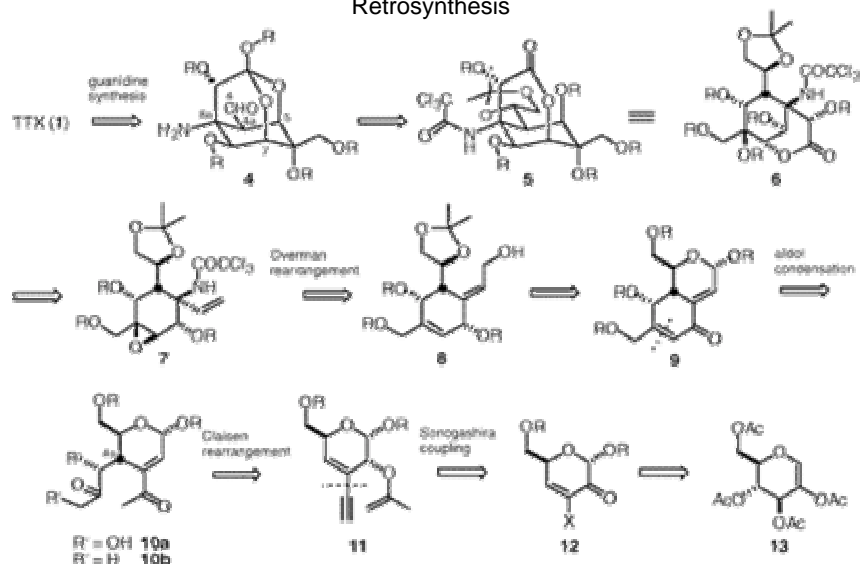
# TTX: Kishi Synthesis

Tetrodamine to Tetrodotoxin



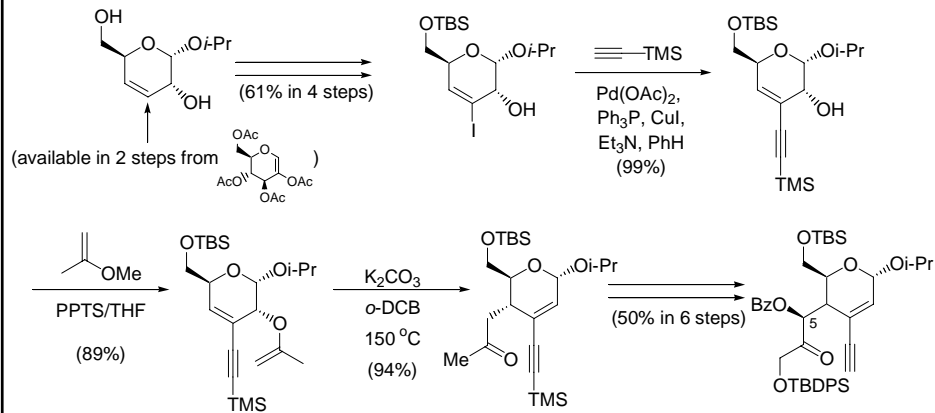
# TTX: Isobe Synthesis

Retrosynthesis



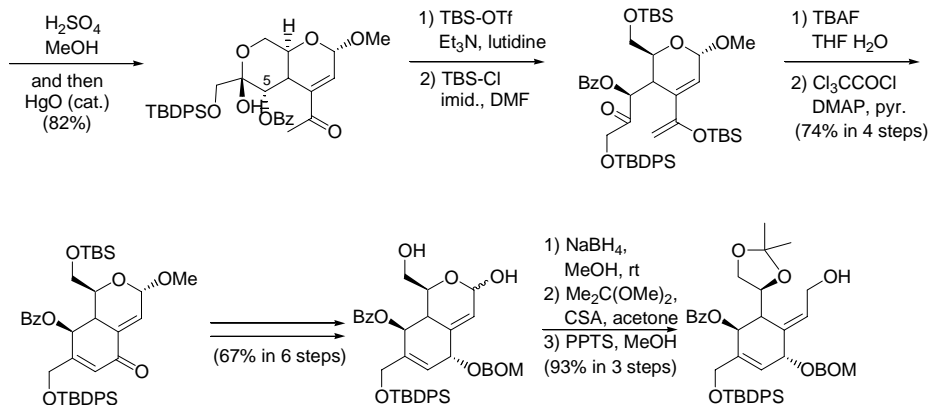
# TTX: Isobe Synthesis

Sonogashira Coupling and Claisen Rearrangement

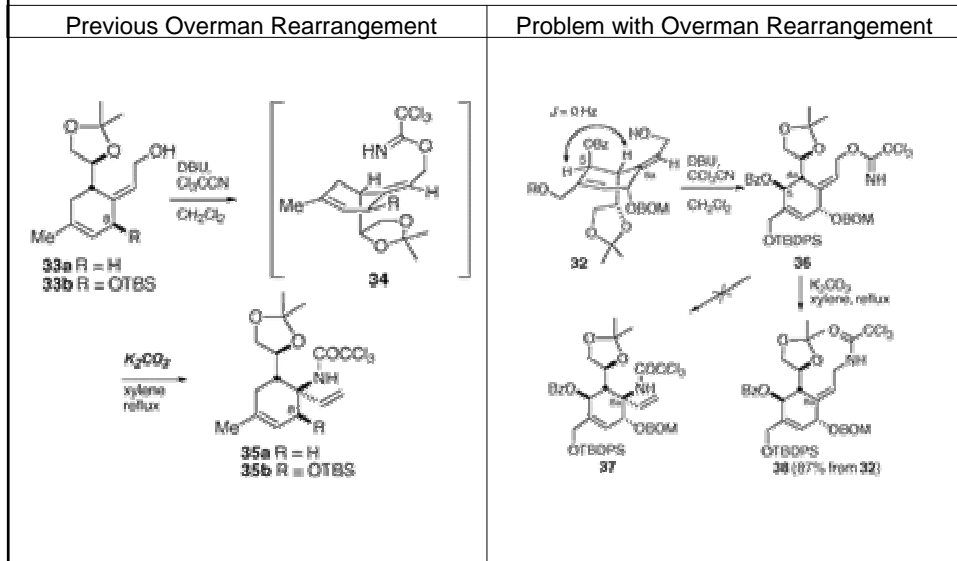


# TTX: Isobe Synthesis

Cyclohexenone and Exoolefin Synthesis

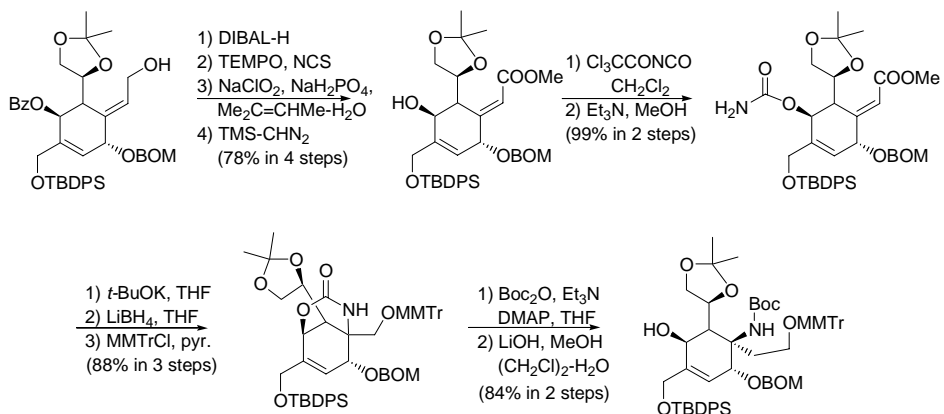


# TTX: Isobe Synthesis



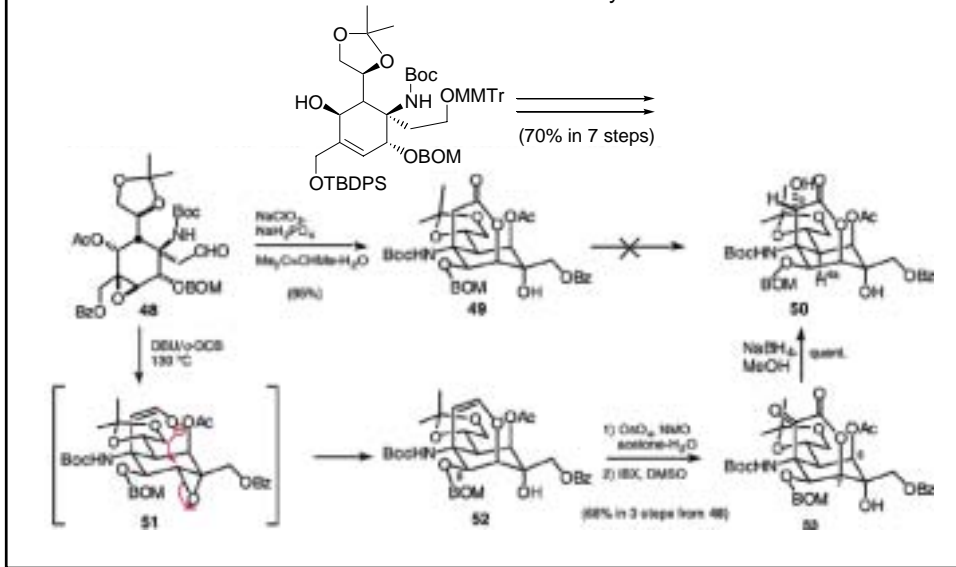
# TTX: Isobe Synthesis

Installation of Nitrogen Functionality: Conjugate Carbamate Addition



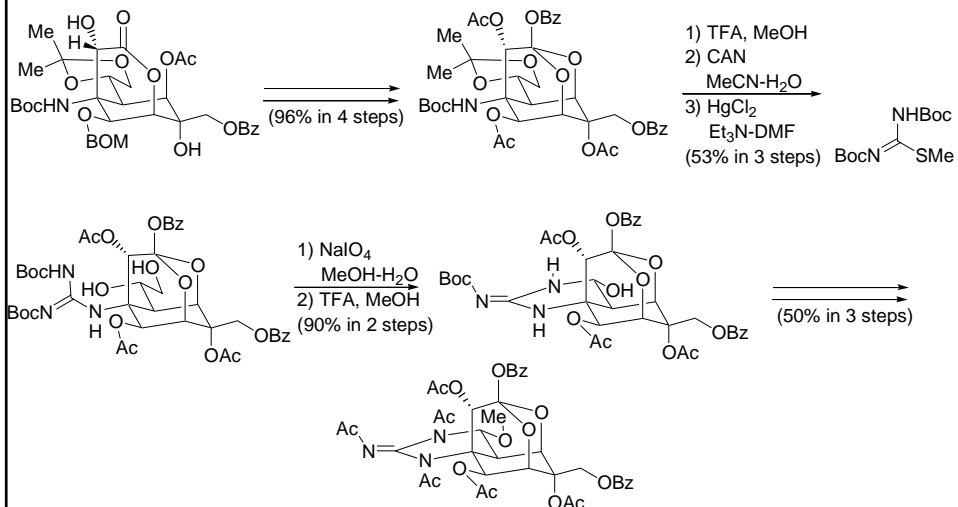
# TTX: Isobe Synthesis

## Construction of Lactone Bicycle



# TTX: Isobe Synthesis

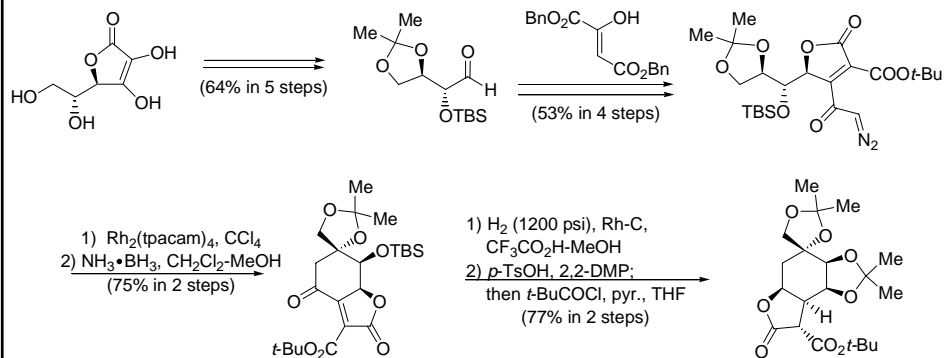
## Introduction of Guanidine





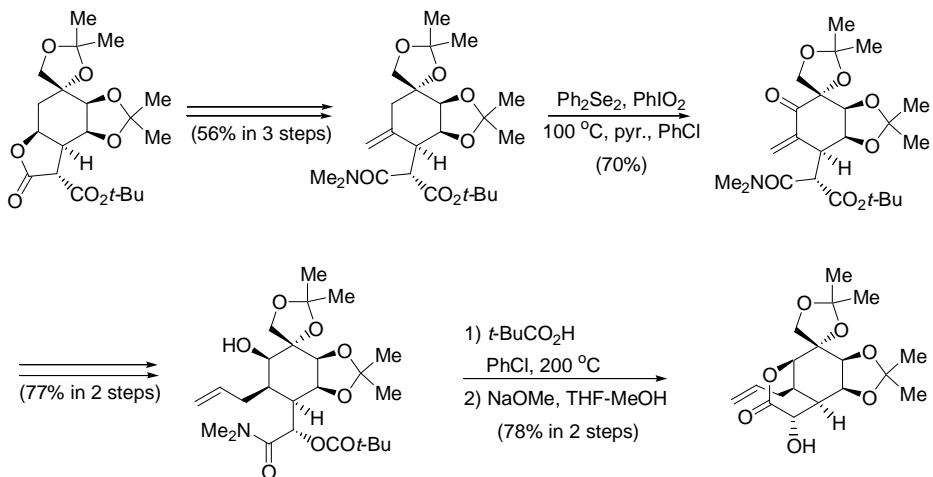
# TTX: Du Bois Synthesis

Rh-carbene C-H insertion



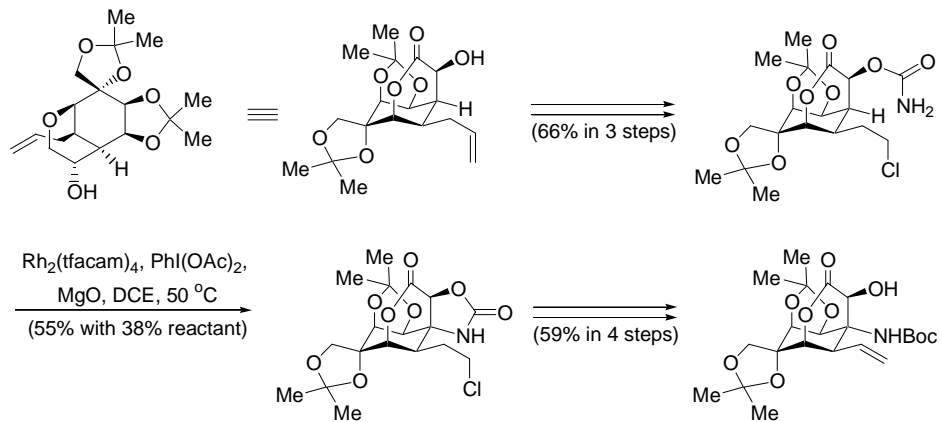
# TTX: Du Bois Synthesis

Construction of Lactone Bicycle



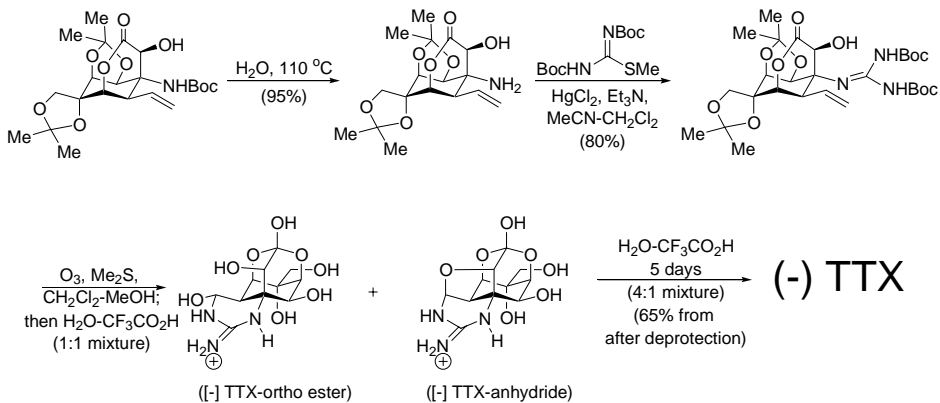
# TTX: Du Bois Synthesis

## 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 <sub>2</sub> Se <sub>2</sub> -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

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## TTX: Acknowledgements

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