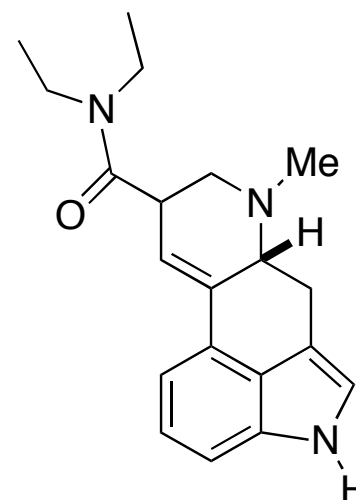
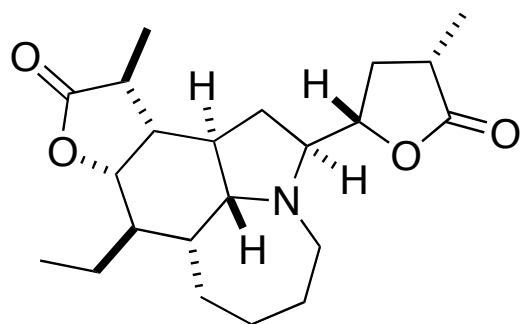


# Synthetic Studies Towards the Stemona and Ergot Alkaloids



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**University of Pittsburgh**  
**Wipf Research Group**  
**November 12, 2005**

# Presentation Outline

## **PART 1: Stemona Alkaloids**

- Stemona plants & historical uses
- Stemona alkaloids: isolation, classification, biological properties, etc
- Selected previous total syntheses and Wipf group work
- Current approaches

## **PART 2: Ergot Alkaloids**

- Ergot & history of ergotism
- Ergot alkaloids: isolation, classification, biological properties, etc
- Current approaches

# **PART 1: Stemona Alkaloids**

# Family: Stemonaceae

- A monocotyledon family made up of three genera:

1. *Stemona* - About 25 species, occurring from southern Asia and Malaysia to northern Australia

2. *Croomia* - Three species from Atlantic North America and Japan

3. *Stichoneuron* - Two species from eastern Asia

*Nat. Prod. Rep.* 2000, 17, 117

- *Stemona* plants occur as subshrubs or twining herbs, mostly with perennial tuberous roots



## Stemonaceae: Historical Uses

- Extracts from plants of the Stemonaceae family (*Stemona* and *Croomia* genera) have been used for centuries in Eastern folk medicines
- Example: Extracts from the tuberous roots of *Stemona Tuberosa*, *Stemona Japonica* and *Stemona Sessifolia* have been used by the Chinese and Japanese for:
  - Respiratory diseases such as tuberculosis and bronchitis
  - Antihelmintics in humans and cattle
  - Insecticides

*J. Agric. Food. Chem.* **2002**, *50*, 6383



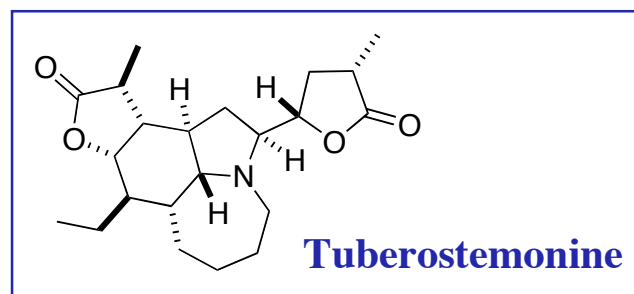
[www.clgc.rdi.ku.ac.th/research/stemona/stemona](http://www.clgc.rdi.ku.ac.th/research/stemona/stemona)



[www.bihrmann.com](http://www.bihrmann.com)

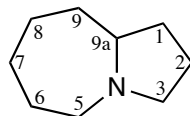
# Stemona Alkaloids: Isolation & Structural Elucidation

- Phytochemical studies have been limited to only eight species, mostly from *Stemona*
- Progress hampered by use of incorrectly identified plant material - caused by popular use of tuberous roots from different species sold on the market under the same names, eg. “Bai Bu” in China and “Bach Bo” in Vietnam
- Tuberostemonine was the first *Stemona* alkaloid to be isolated in 1934 by Suzuki
- Structure of tuberostemonine was determined by the combined efforts of a number of groups in the 1960’s using various methods: NMR, MS, X-ray and chemical analysis
- Since then more than 42 *Stemona* alkaloids have been isolated, mostly by Ren-sheng Xu and coworkers in the 80’s. The various structures were determined by X-ray analysis, spectroscopic methods and/or chemical studies

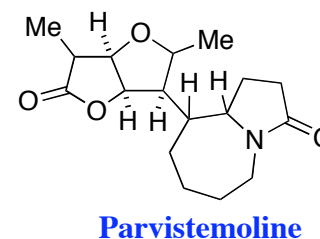
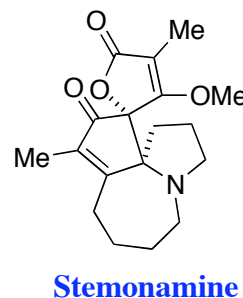
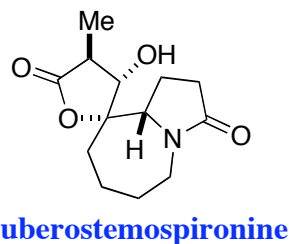
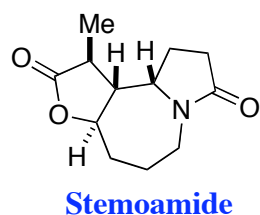
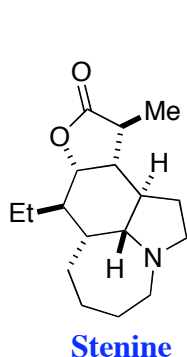


# Structural Classification of *Stemona* Alkaloids

- Large majority of the *Stemona* alkaloids are structurally characterized by the presence of a pyrrolo[1,2-*a*]azepine core



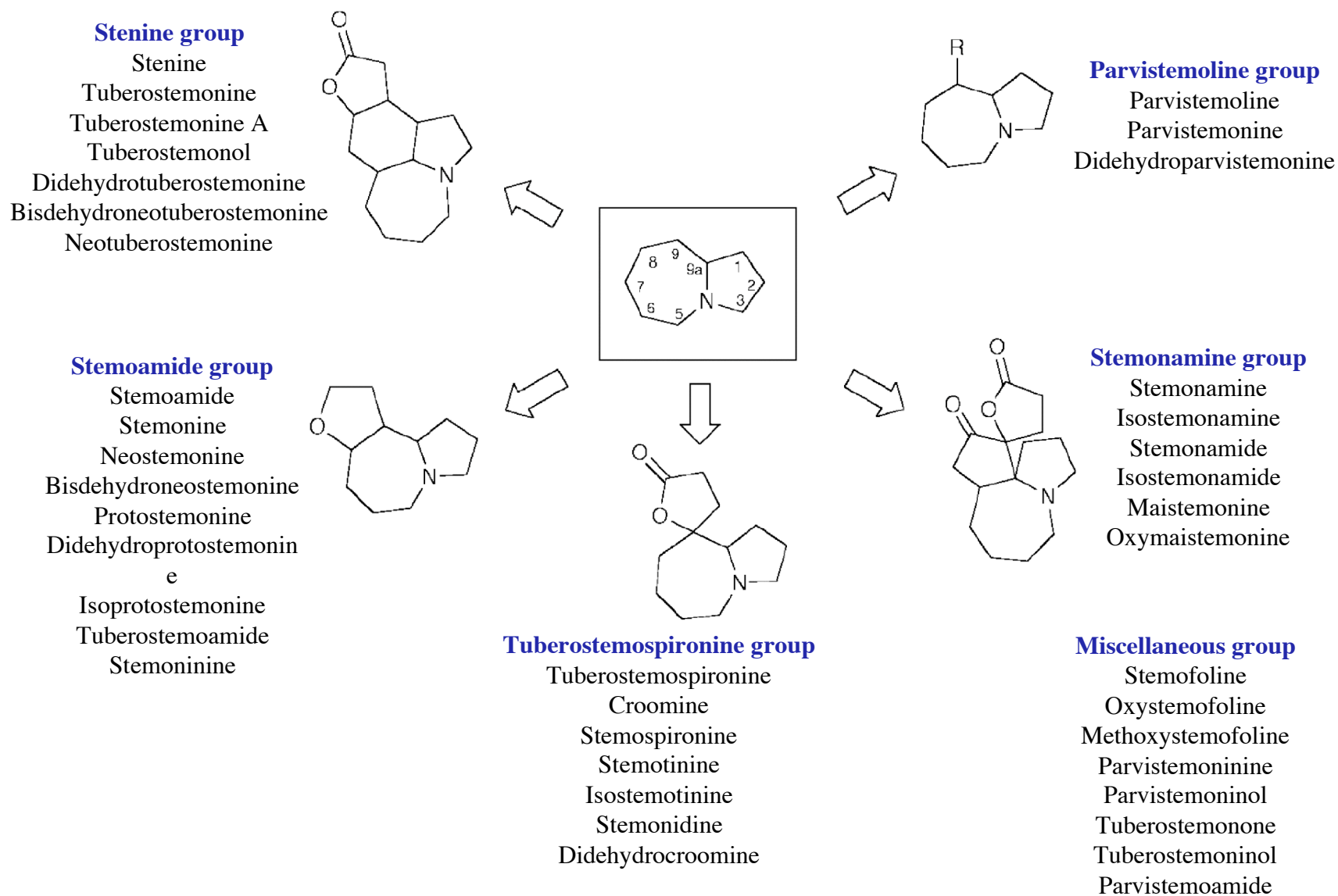
- Each member of the *Stemona* alkaloid family can be classified into five main groups according to their structural features - the name of each group being the name of the simplest member:



- A sixth miscellaneous group of compounds also exist where each member lacks the common azepine ring system

*Nat. Prod. Rep.* **2000**, 17, 117

# Structural Classification of *Stemona* Alkaloids

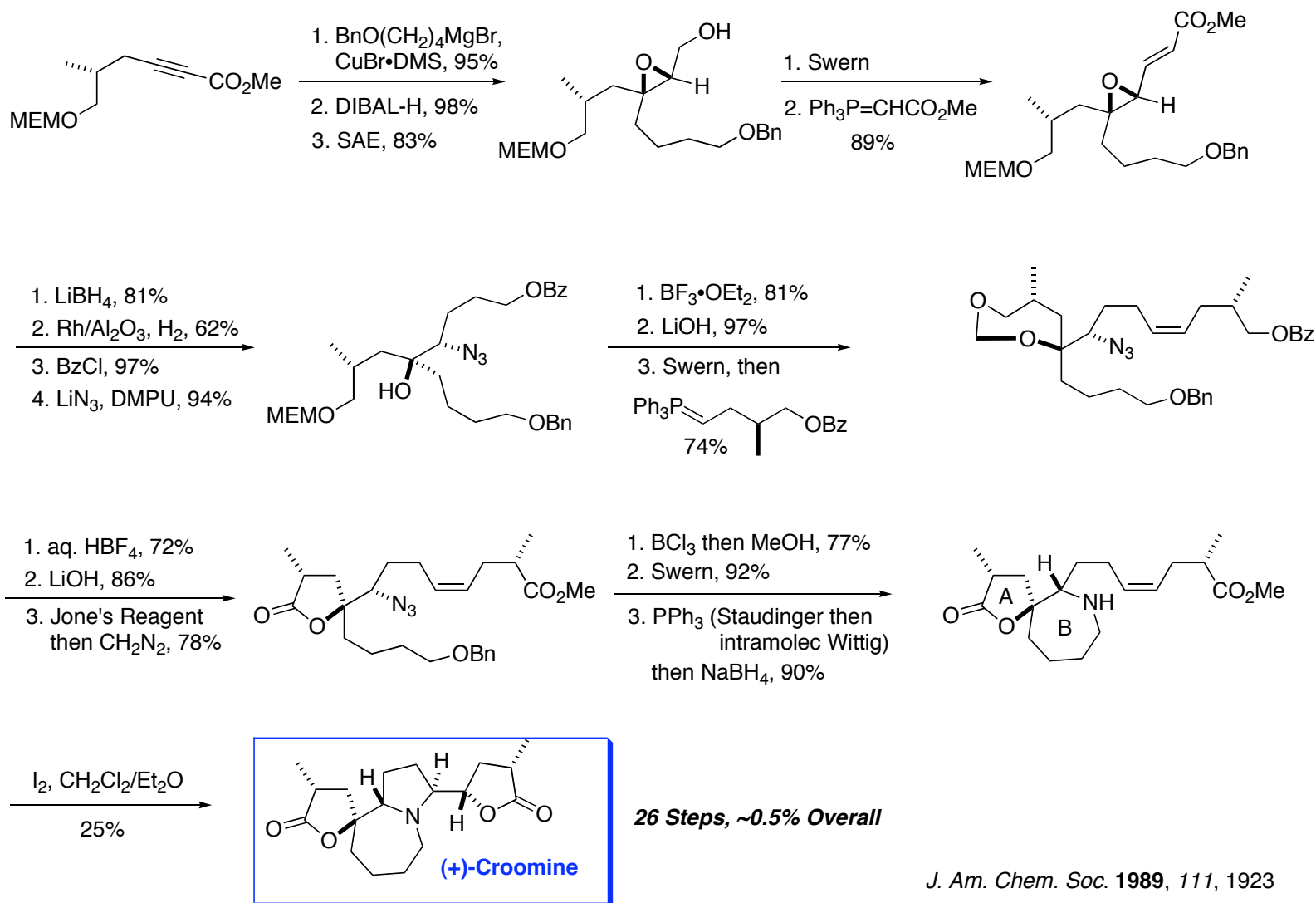




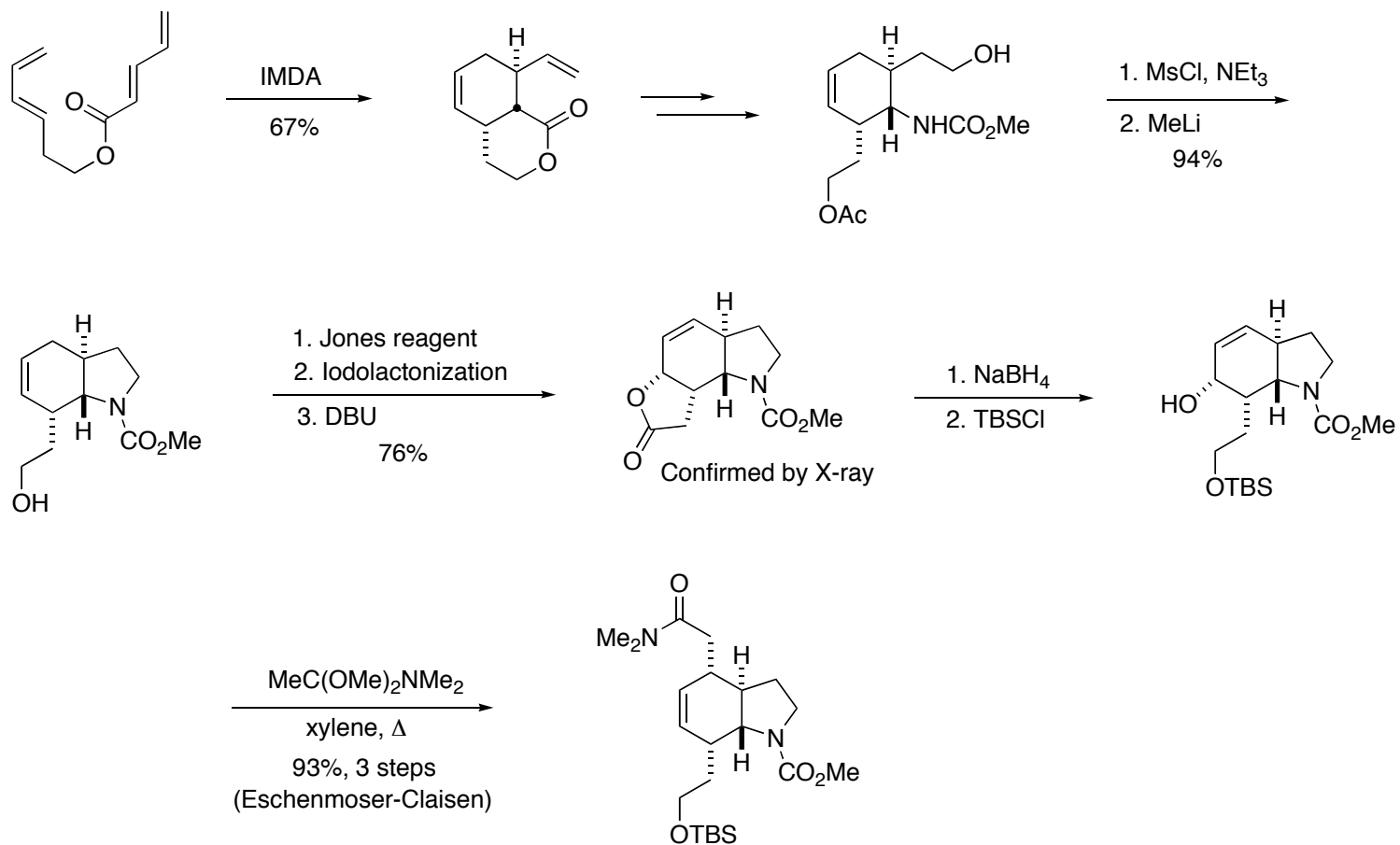
# Biological Studies on *Stemona* Alkaloids

- Limited evidence that any pure *Stemona* alkaloid has therapeutic potential in humans
- Tuberostemonine has antihelmintic activity
- Tuberostemonine found to be a glutamate inhibitor (blocks neuromuscular transmission) in crayfish *Brain Res.* **1985**, 334, 33
- Tuberostemonine has potent antifeeding activity *J. Agric. Food. Chem.* **2002**, 50, 6383
- Stemonine, stemospiroline and stemofoline have some insecticidal activity, eg. active against *Bombyx mori* (silkworm larvae) *Agric. Biol. Chem.* **1978**, 42, 457

# (+)-Croomine (Williams)



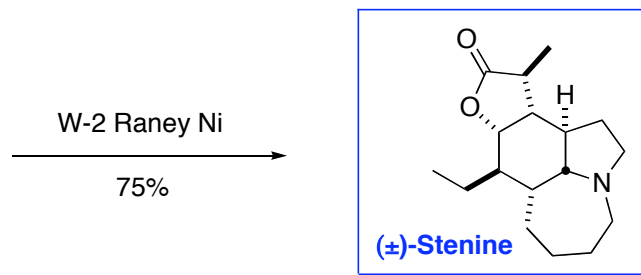
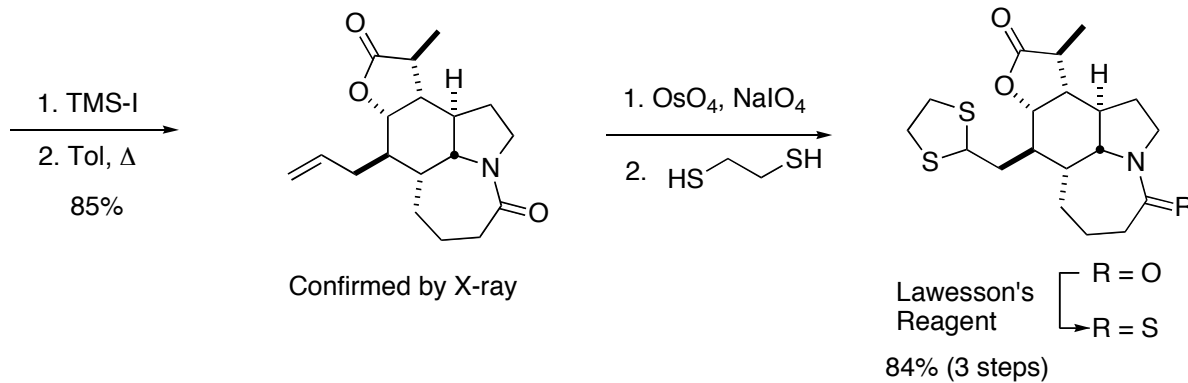
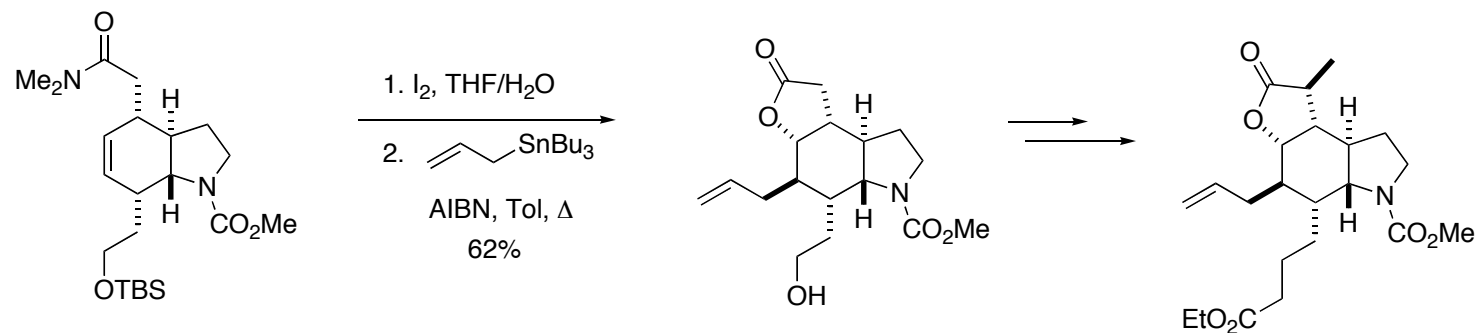
# (±)-Stenine (Hart & Chen)



*J. Org. Chem.* **1990**, *55*, 6236

*J. Org. Chem.* **1993**, *58*, 3840

# (±)-Stenine (Hart & Chen)

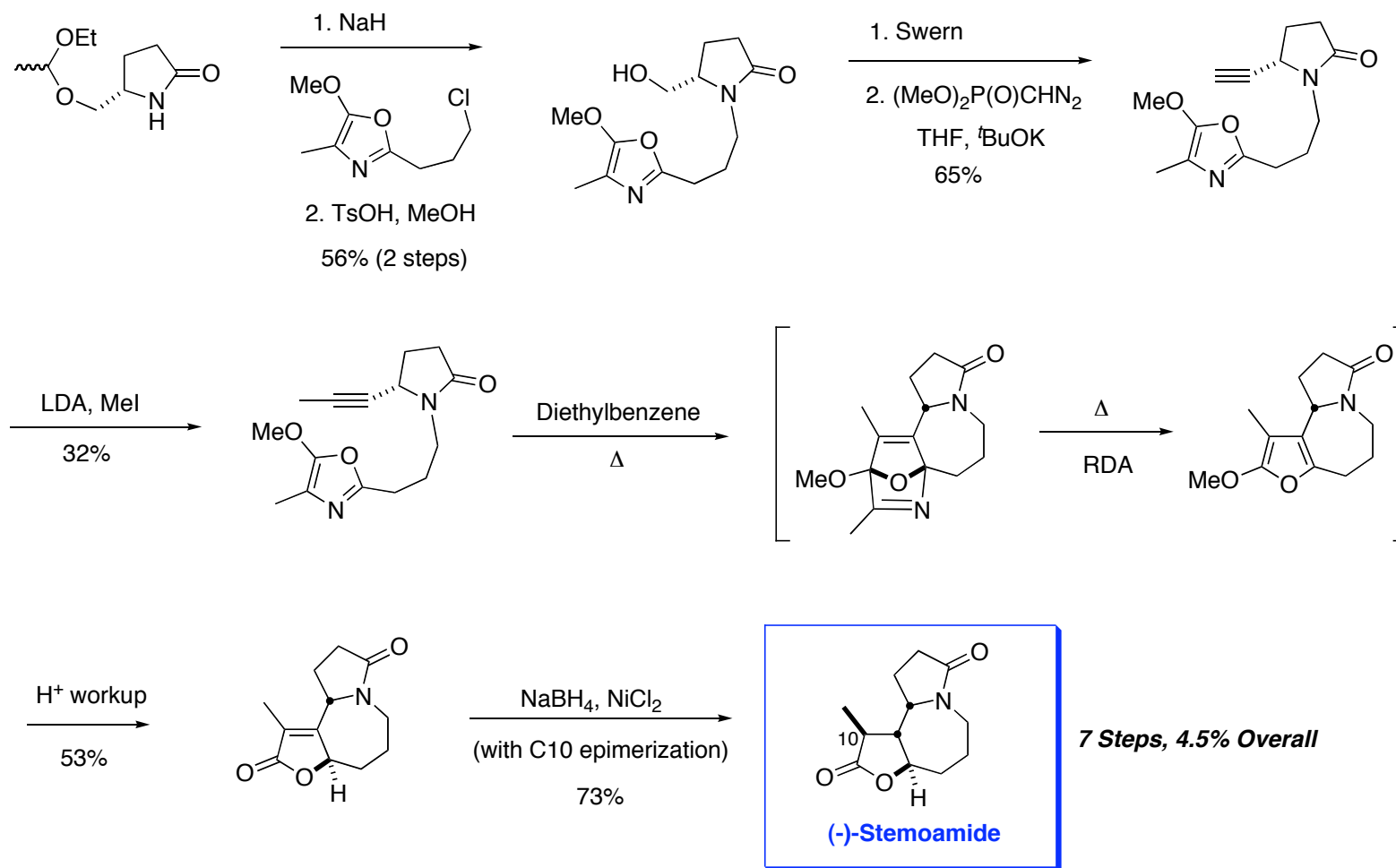


**25 Steps, 5% Overall**

*J. Org. Chem.* **1990**, *55*, 6236

*J. Org. Chem.* **1993**, *58*, 3840

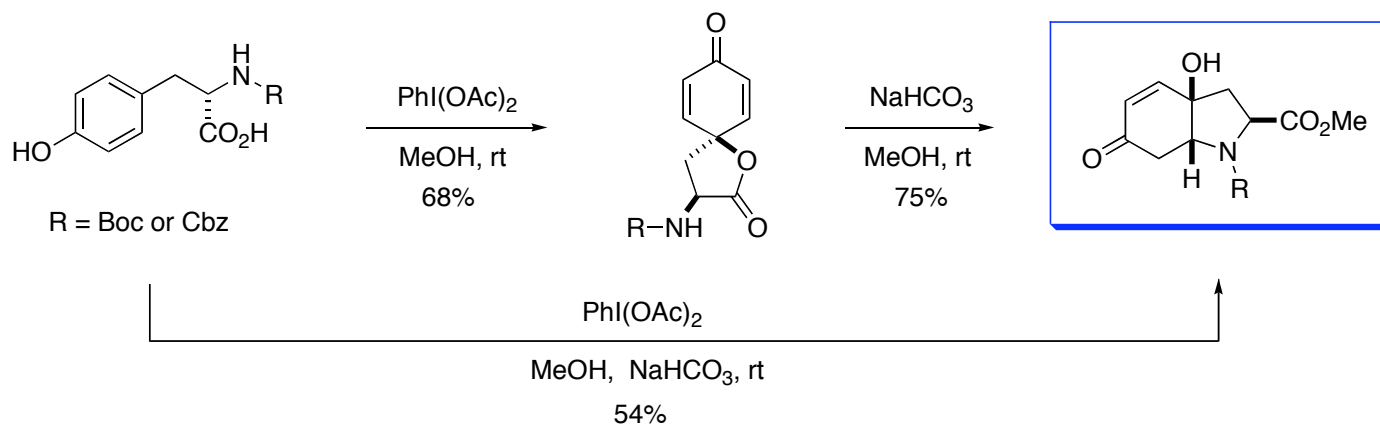
# (-)-Stemoamide (Jacobi)



*J. Am. Chem. Soc.* **2000**, *122*, 4295

# Wipf Group Research

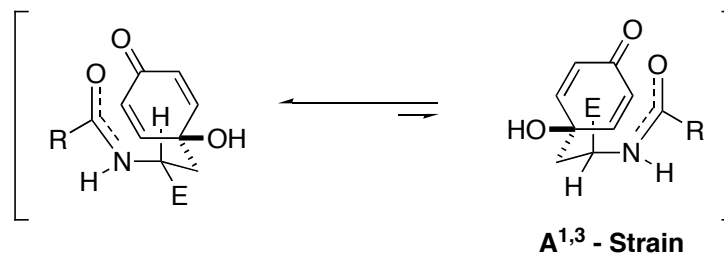
- Efficient stereoselective preparation of the hydroindole ring system of the *Stemona* alkaloids by oxidative cyclization of tyrosine:



\*\* Reaction has been scaled to > 100 g

*Tetrahedron Lett.* **1992**, *33*, 5477

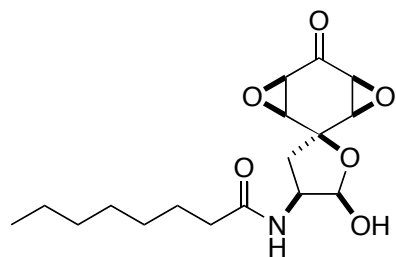
- Selectivity attributed to  $A^{1,3}$  - strain:



*J. Am. Chem. Soc.* **1995**, *117*, 11106

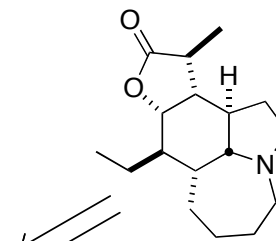
# Wipf Group Research

- Oxidation of tyrosine - used for the synthesis of a variety of targets:



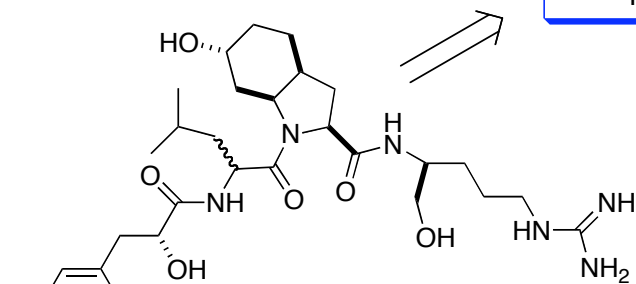
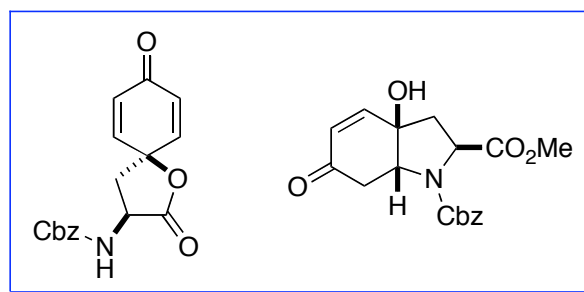
**Functionalized aranosin core**

*J. Org. Chem.* **1993**, *58*, 1649



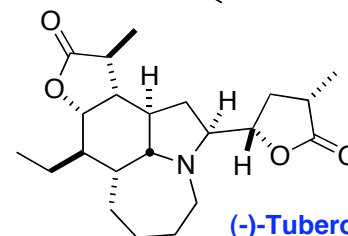
**(-)-Stenine**

*J. Am. Chem. Soc.* **1995**, *117*, 11106



**Aeruginosin 298-A**

*Org. Lett.* **2000**, *2*, 4213

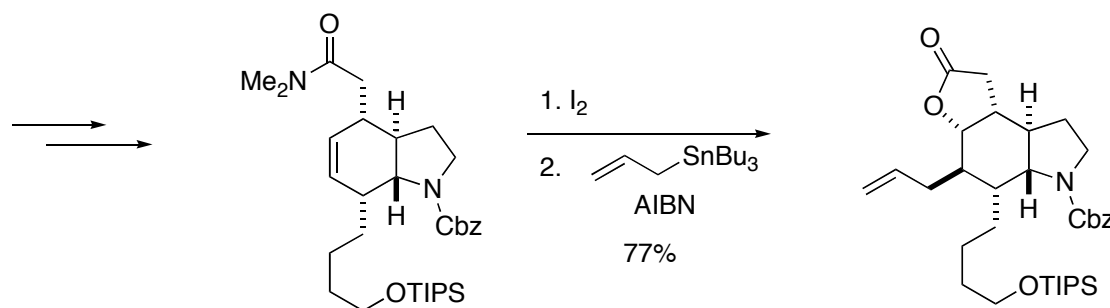
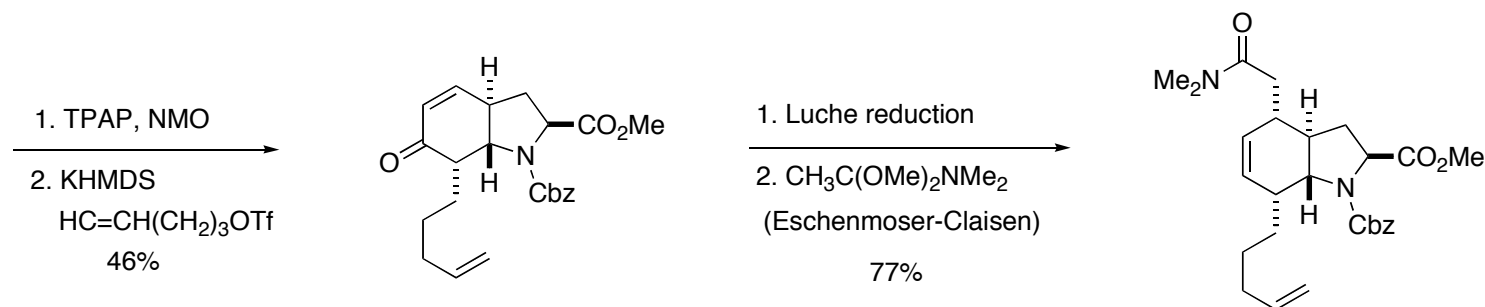
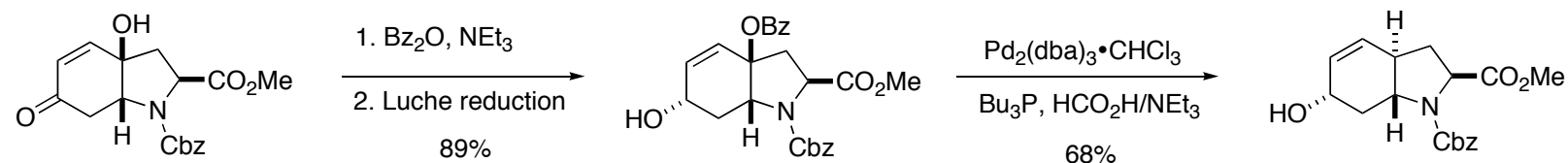


**(-)-Tuberostemonine**

*J. Am. Chem. Soc.* **2002**, *124*, 14848

*J. Am. Chem. Soc.* **2005**, *127*, 225

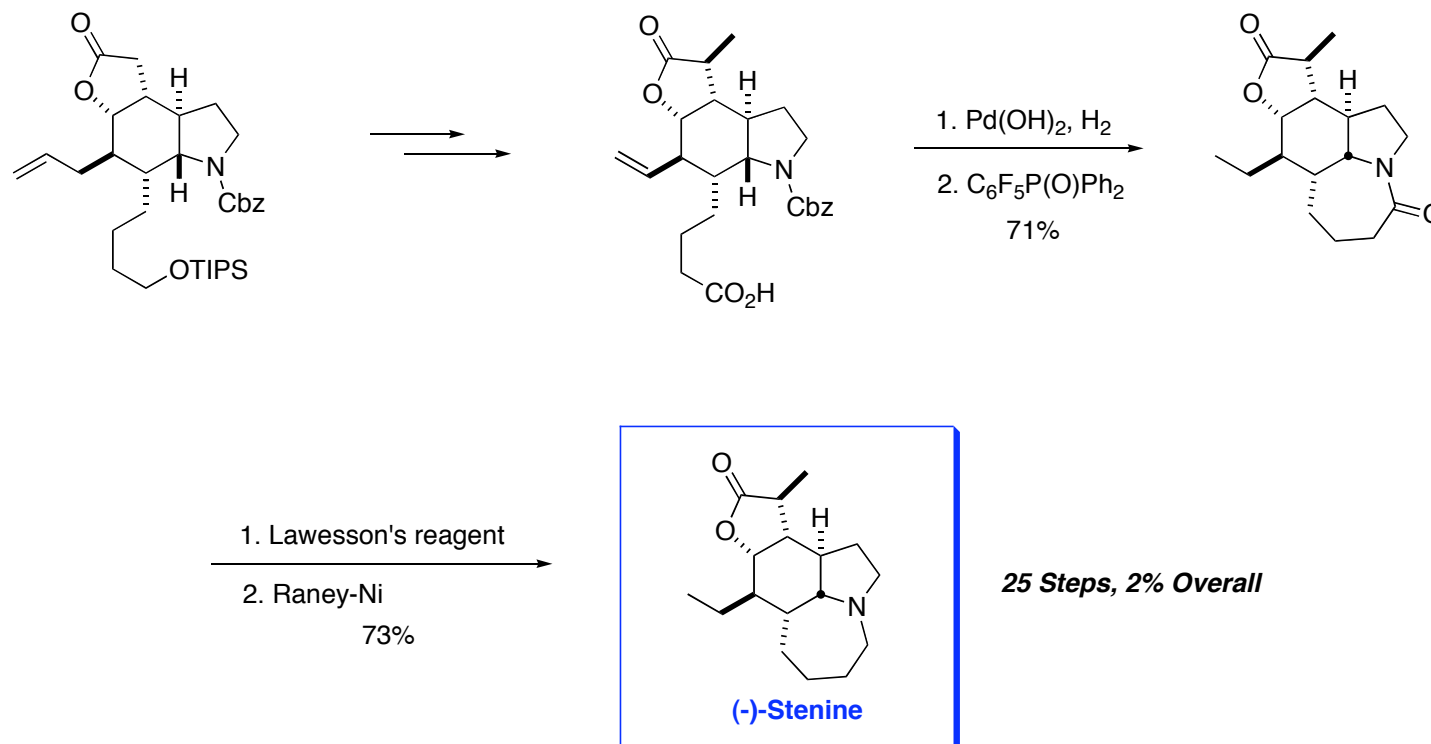
# Total Synthesis of (-)-Stenine (Wipf)



*J. Am. Chem. Soc.* **1995**, *117*, 11106

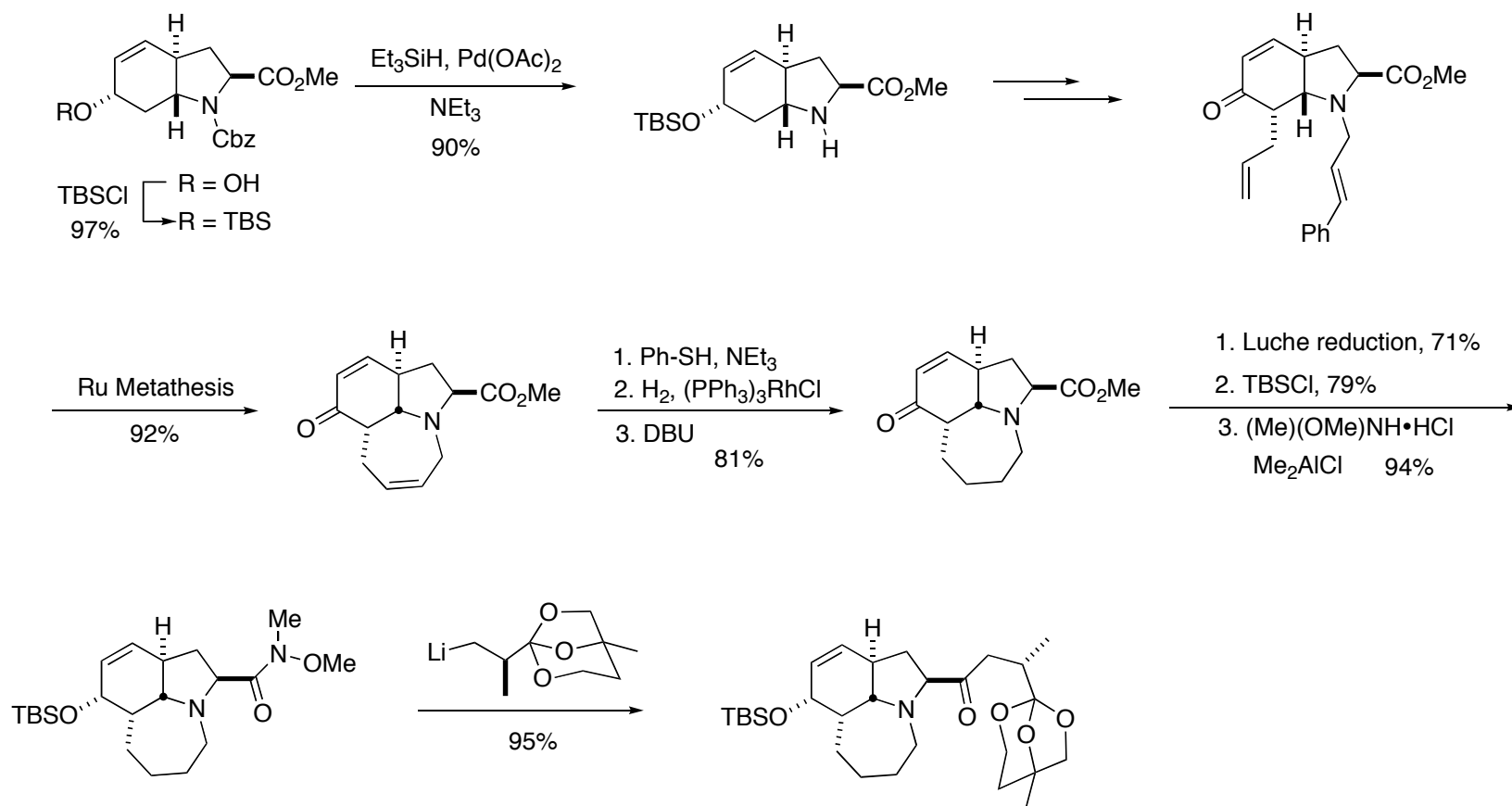


# Total Synthesis of (-)-Stenine (Wipf)



*J. Am. Chem. Soc.* **1995**, *117*, 11106

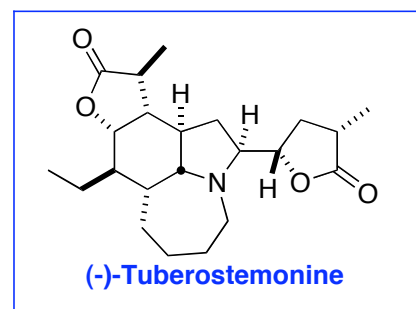
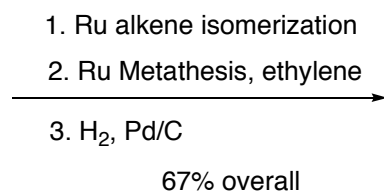
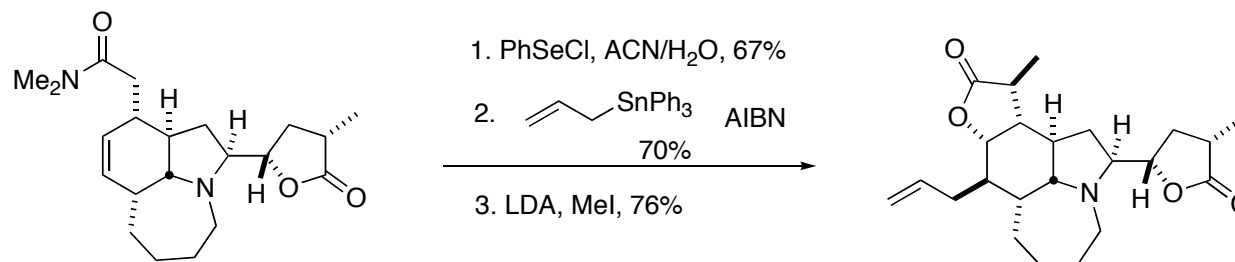
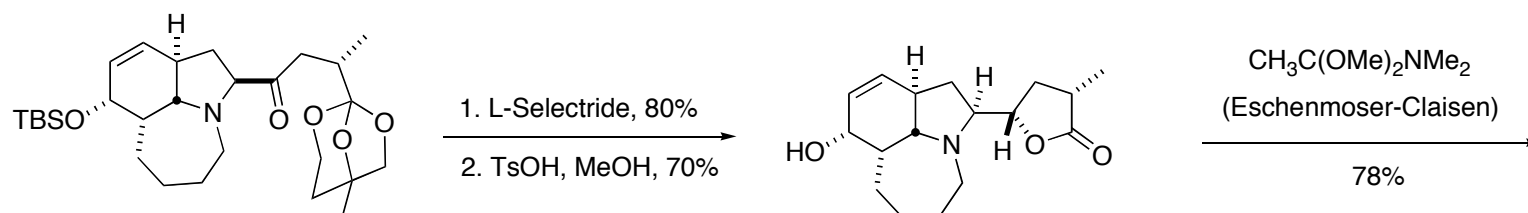
# Total Synthesis of (-)-Tuberostemonine (Wipf)



*J. Am. Chem. Soc.* **2002**, *124*, 14848

*J. Am. Chem. Soc.* **2005**, *127*, 225

# Total Synthesis of (-)-Tuberostemonine (Wipf)



**24 Steps, 1.4% Overall**

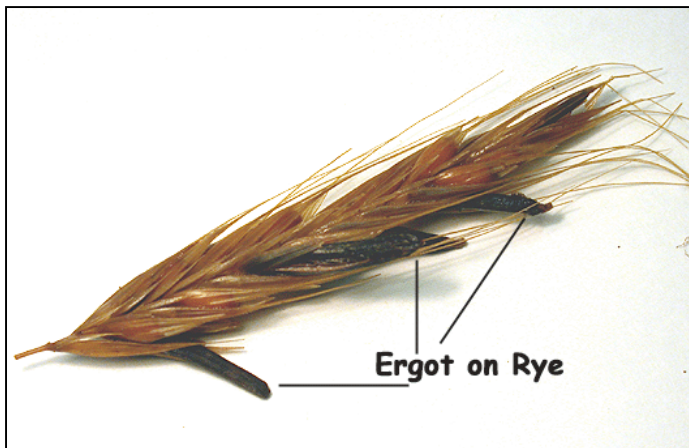
*J. Am. Chem. Soc.* **2002**, *124*, 14848

*J. Am. Chem. Soc.* **2005**, *127*, 225

# **PART 2: Ergot Alkaloids**

## Ergot: *Claviceps purpurea*

- Ergot: Originates from an old French word “argot”, meaning “spur”
- Ergot is a fungal disease of rye and other cereal crops - invades grain and replaces them with hard fungal bodies called sclerotia (resting body of a fungus)
- Ergot fungal growth is suited to cool, damp climates - common in Europe, especially France and Germany



[www.botany.hawaii.edu](http://www.botany.hawaii.edu)

# Ergotism/History

- Ergotism is a disease which occurred frequently in the Middle Ages - caused by the ingestion of food made with grains infected with ergot, eg. bread
- Two types of ergotism:
  1. “Gangrenous” form: Intense burning pain in limbs and gangrene due to vasoconstrictive properties of ergot. In severe cases, limbs would become black and dry (mummify)

**NOTE:** Ergotism was also known as “Holy fire” or “St. Anthony’s fire”



[abdellab.sunderland.ac.uk](http://abdellab.sunderland.ac.uk)



[grandfinale.at.infoseek.co.jp](http://grandfinale.at.infoseek.co.jp)

## Ergotism/History

2. “Convulsive” form: Sufferers could become delirious, lethargic, manic and have hallucinations with double vision due to neurotoxic properties of ergot. In extreme cases, epileptic-type seizures leading to death
- Ergotism and witchcraft? Salem witchcraft trials of 1692 in North America may have been due to ergotism



[www.uh.edu/engines/epi1037.htm](http://www.uh.edu/engines/epi1037.htm)

- The last reported European outbreak of ergotism occurred in 1951 in a French village - caused more than 200 cases and 4 deaths

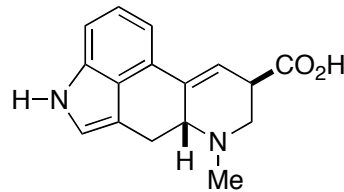
*Modern drug discovery*, 1999, 2, 20-21, 23-24, 28, 31

# Ergot Alkaloids

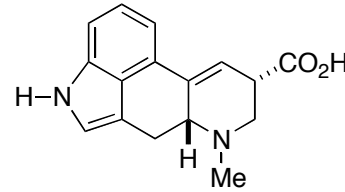
- The first ergot alkaloid to be isolated from sclerotia of the ergot fungus was ergotamine in 1918 by Stoll

Stoll, A.: Swiss patent 79879 (1918); German patent 357272 (1922)

- The natural ergot alkaloids (>40) contain either lysergic acid (pharmacologically active, name ends with -ine) or isolysergic acid (pharmacologically inactive, name ends with -inine) as the parent structure



Lysergic acid



Isolysergic acid

*Chem. Rev.* **1950**, 47, 197

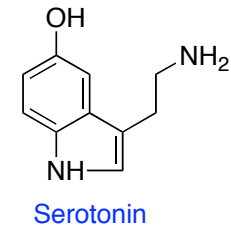
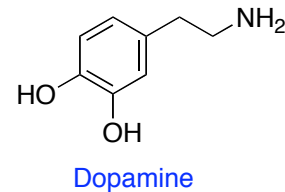
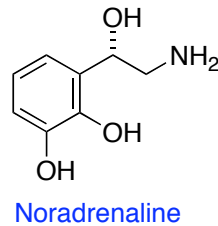
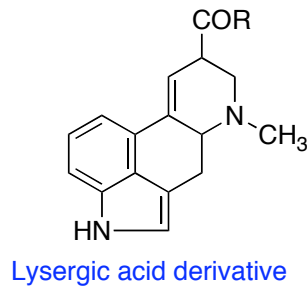
- The ergot alkaloids are classified into three main groups:
  1. Clavine type - Simplest members considered as precursors to the other groups of ergot alkaloids in the biogenetic pathway
  2. Water-soluble lysergic acid type: Are often amide derivatives of lysergic and isolysergic acids
  3. Water-insoluble lysergic acid type: Are mainly peptide derivatives of lysergic and isolysergic acids

*The Lancet Neurology*, **2003**, 2, 429



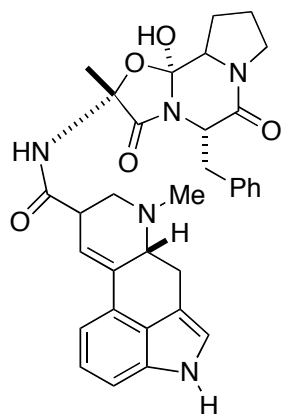
# Biological activity

- The ergot alkaloids possess a wide spectrum of biological activity - act on the CNS
- Derivatives of lysergic acid have affinities for the receptors of the neurotransmitters noradrenaline, dopamine and serotonin - possibly due to structural analogy between the ergoline ring system and these neurotransmitters
- They may act as agonists, antagonists or play a dual role as partial-agonist and antagonist



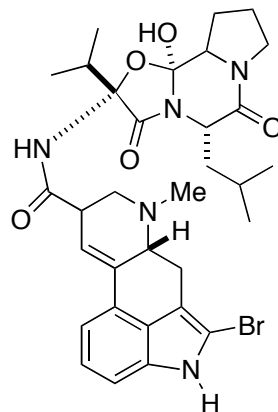
*Appl. Microbiol. Biotechnol.* **2001**, 57, 593

# Ergot alkaloids - examples and uses



**Ergotamine**

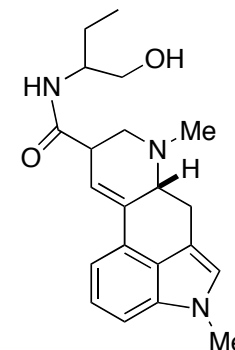
Migraine relief



**2-Bromo- $\alpha$ -ergokryptine**

Semisynthetic

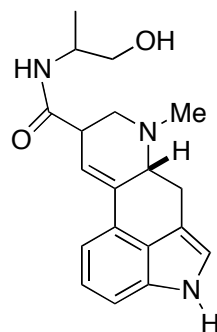
- anti-Parkinson's
- reduce lactation in women



**Methysergide**

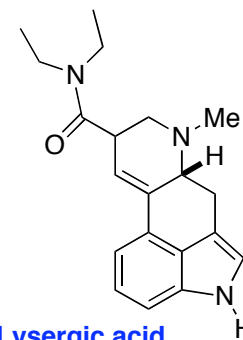
Semisynthetic

- Migraine relief



**Ergonovine**

- Induces labour (oxytocic)
- Decrease excessive uterine bleeding post-childbirth



**Lysergic acid diethylamide (LSD)**

Synthetic derivative of lysergic acid

- Powerful hallucinogen

# Acknowledgements

**Prof. Peter Wipf**

**Dr. David Mareska**

**Dr. Steven Geib (X - Ray)**

**Wipf Group Members (past & present)**