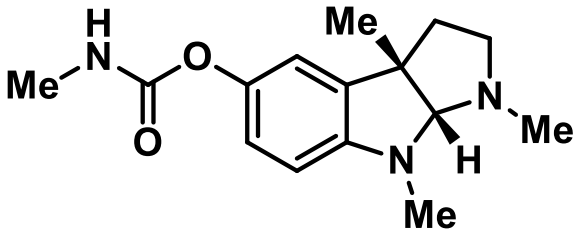
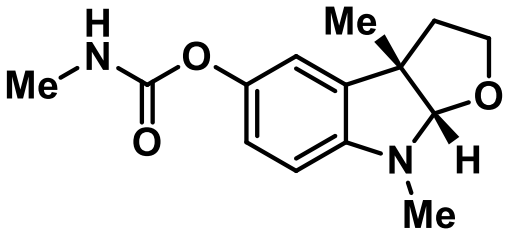
# Catalytic Asymmetric Synthesis of Either Enantiomer of the Calabar Alkaloids Physostigmine and Physovenine




(−)-physostigmine




(−)-physovenine

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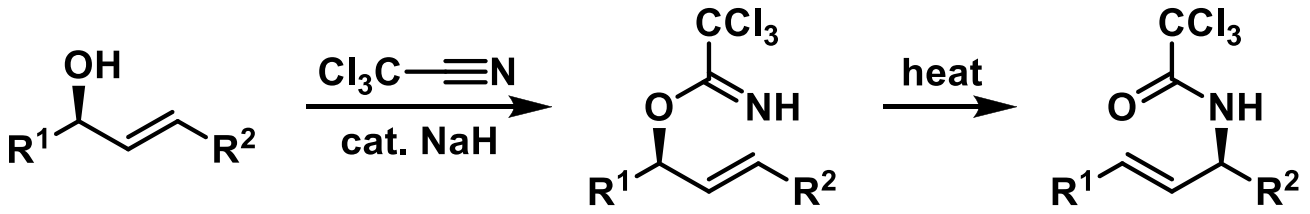
*J. Am. Chem. Soc.* **1998**, *120*, 6500-6503.

Presented by Derek Ahneman

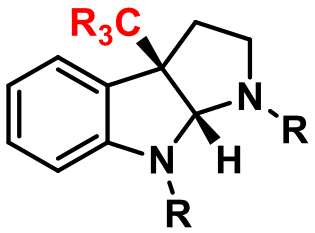
# Larry E. Overman, Ph.D.

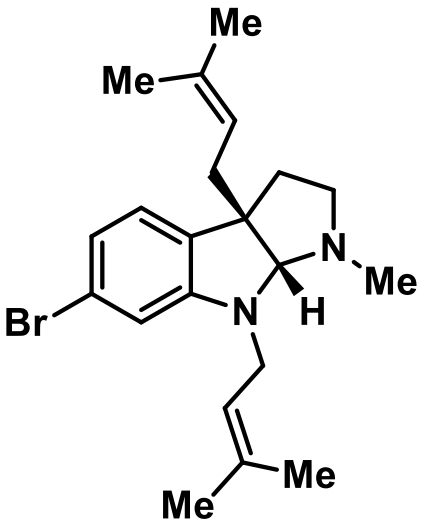
- Born in Chicago, 1943
- B.A., Earlham College, 1965
- Ph.D., University of Wisconsin, 1969
- NIH Postdoctoral Fellow, Columbia University, 1969-1971
- Joined University of California, Irvine faculty, 1971
- Distinguished Professor of Chemistry
- Member of the National Academy of Sciences
- Published over 350 scientific papers
- Research focuses on reaction development and the synthesis of pharmalogically active natural products
- Perhaps best known for developing the Overman Rearrangement (shown below)



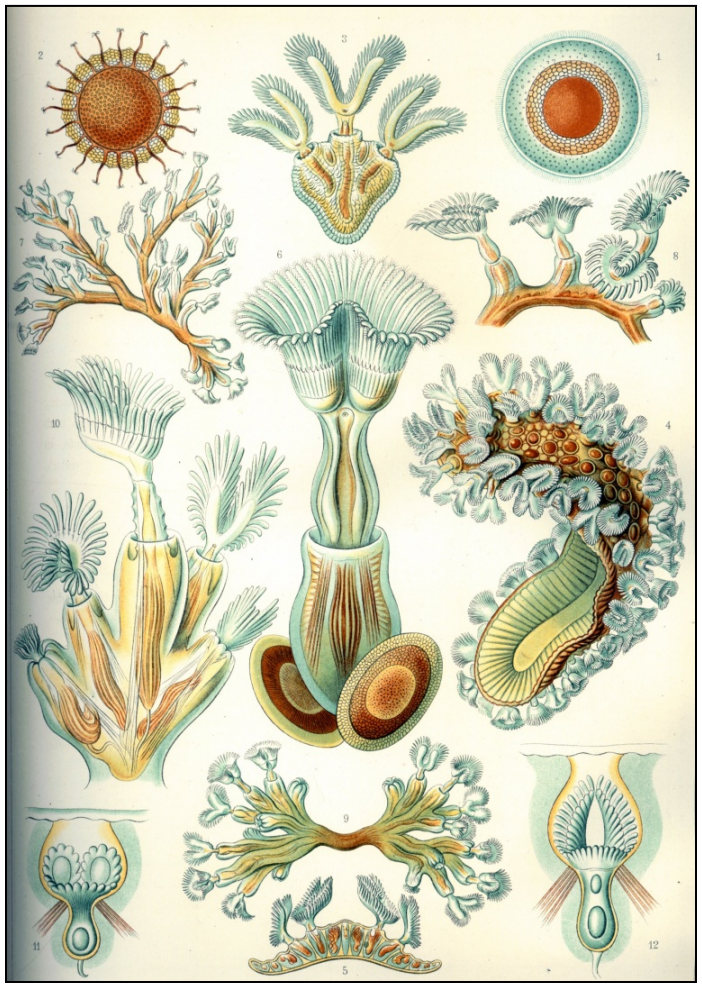
# Hexahydropyrroloindoles

• Diverse class of natural products that exists with a carbon substituent on the quaternary center (shown in red)
• Examples include the Calabar alkaloids Physostigmine and Physovenine, whose synthesis is reported
• Similar alkaloids include flustramine B, isolated from a marine bryozoan (on right)



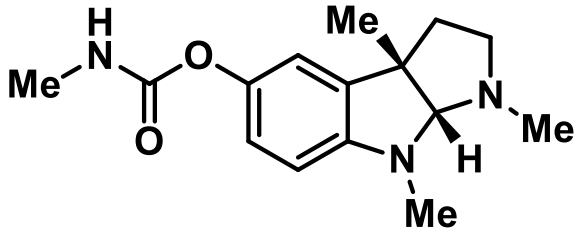




**flustramine B**



# History of Physostigmine

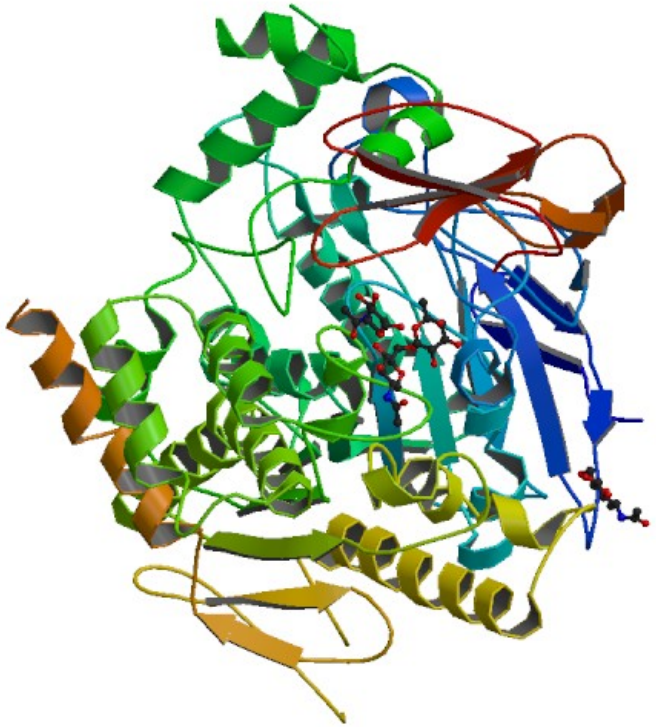
- Occurs naturally in the Calabar bean (on right)
- First isolated in pure form in 1864 by Jobst and Hesse
- First total synthesis completed in racemic form by Julian and Pikl in 1935
- Absolute configuration determined by Sir Robert Robinson 34 years after discovery
- Brossi, Greig, and co-workers have recently improved synthesis of physostigmine



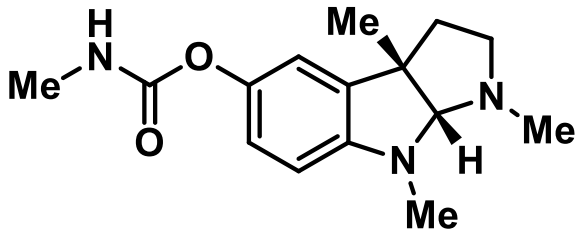

(±)-physostigmine

# Medicinal Applications of Physostigmine

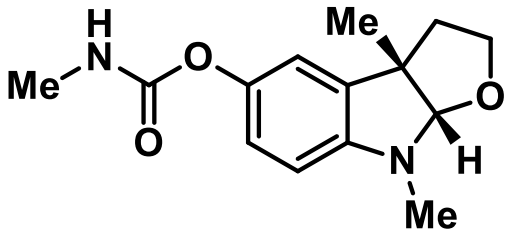
- Powerful inhibitor of acetyl cholinesterase (on right)
- Various clinical uses include:
    - To reduce intraocular pressure in glaucoma
    - To treat postoperative intestinal atony (loss of muscle strength) and myasthenia gravis (autoimmune neuromuscular disease)
    - To relieve symptoms of Alzheimer's disease
- Pharmaceutical limitations of physostigmine include:
    - Short duration of action
    - Narrow therapeutic window
    - Low selectivity between different cholinesterase enzymes



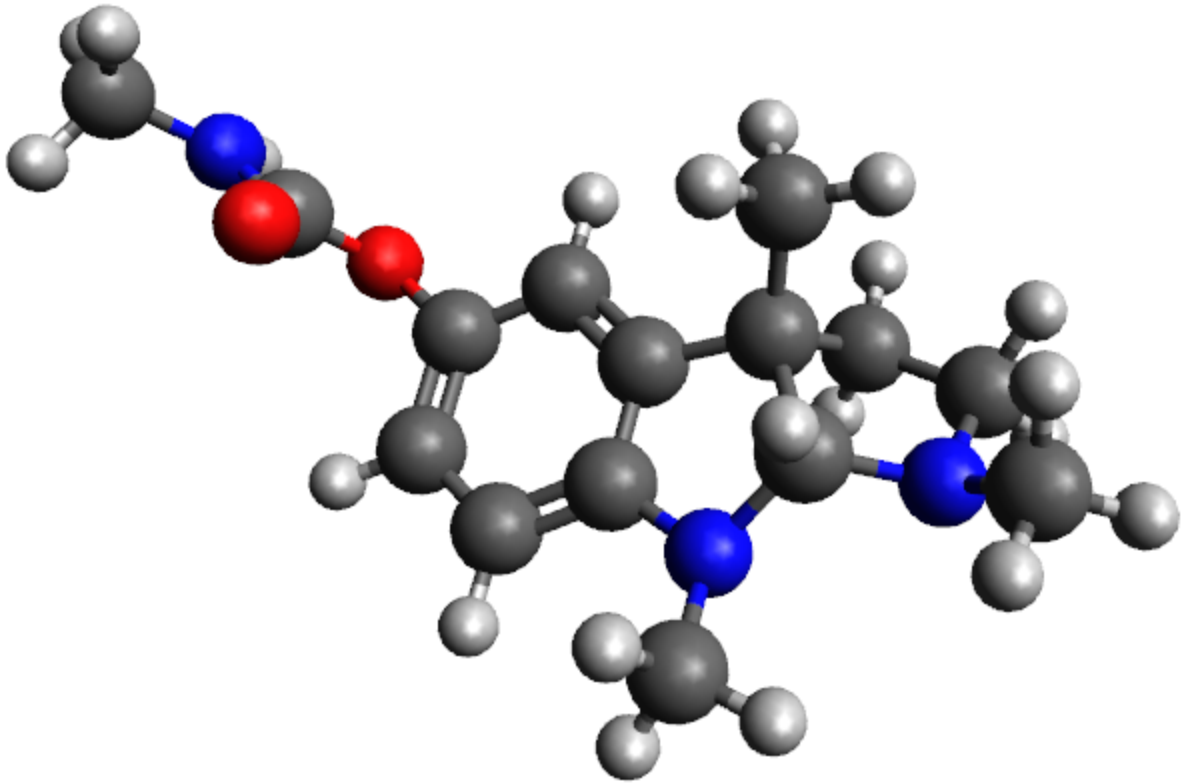
# Topology of Physostigmine and Physovenine



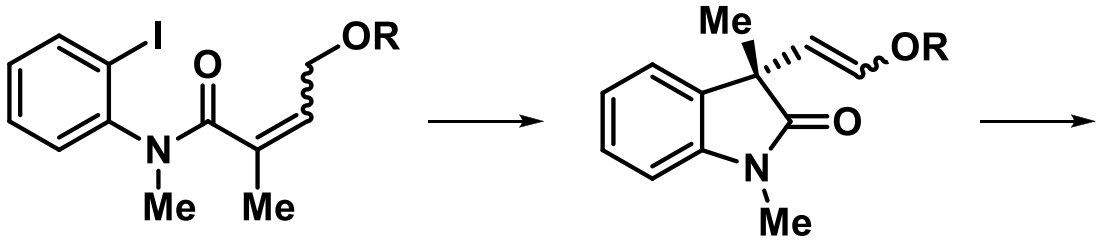

(?)-physostigmine

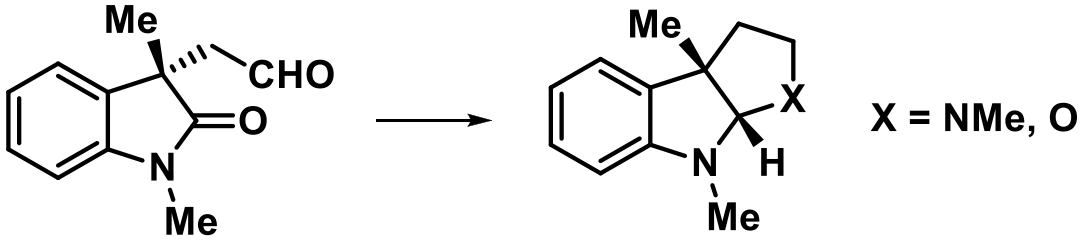


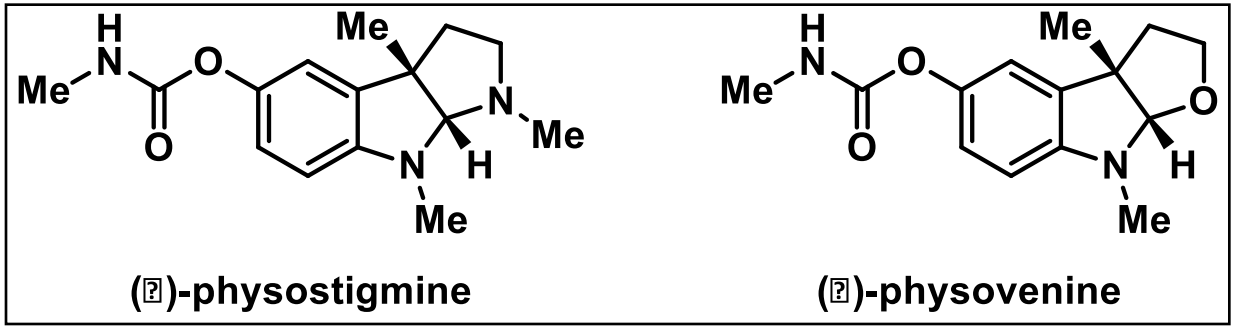

(?)-physovenine



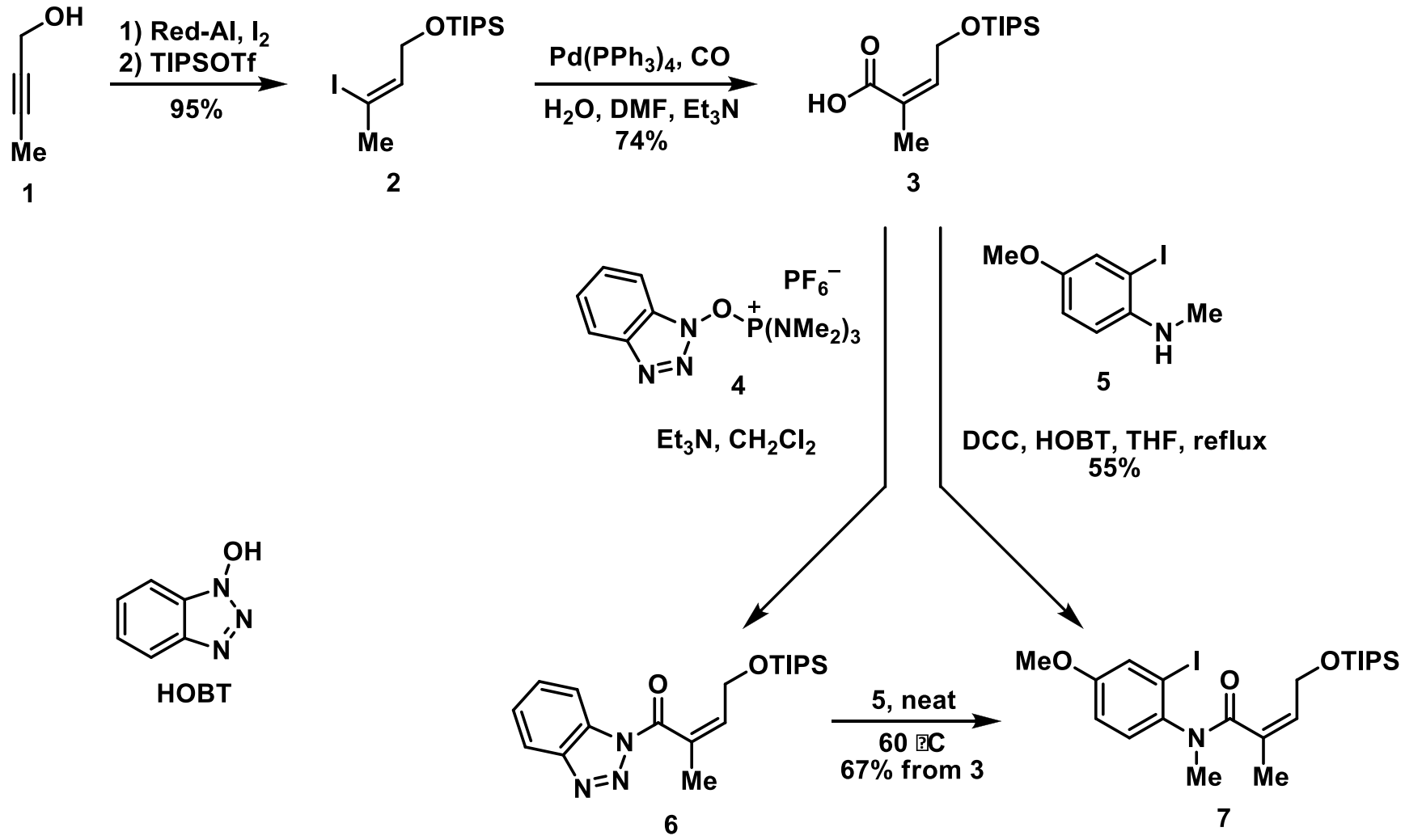
# General Synthetic Strategy



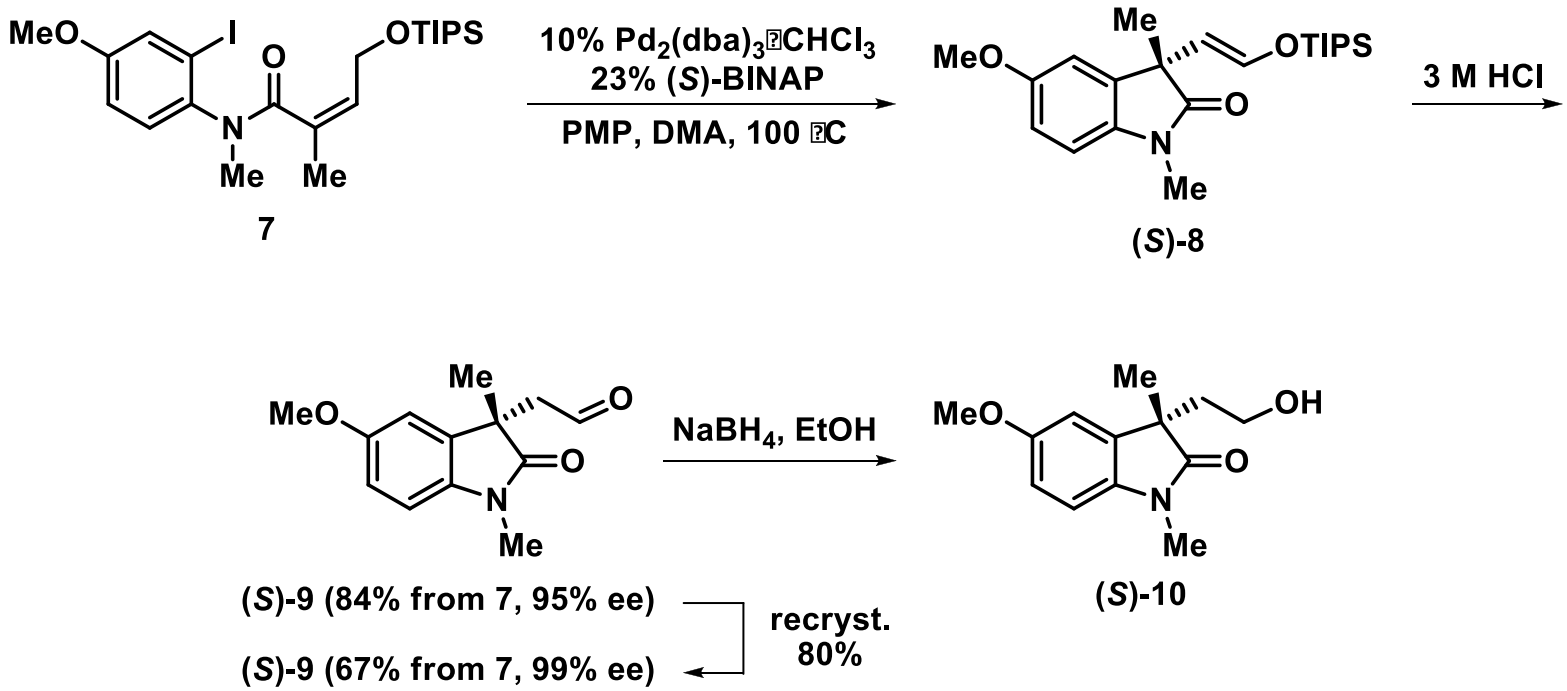



# Physostigmine/Physovenine Synthesis: Part 1/3

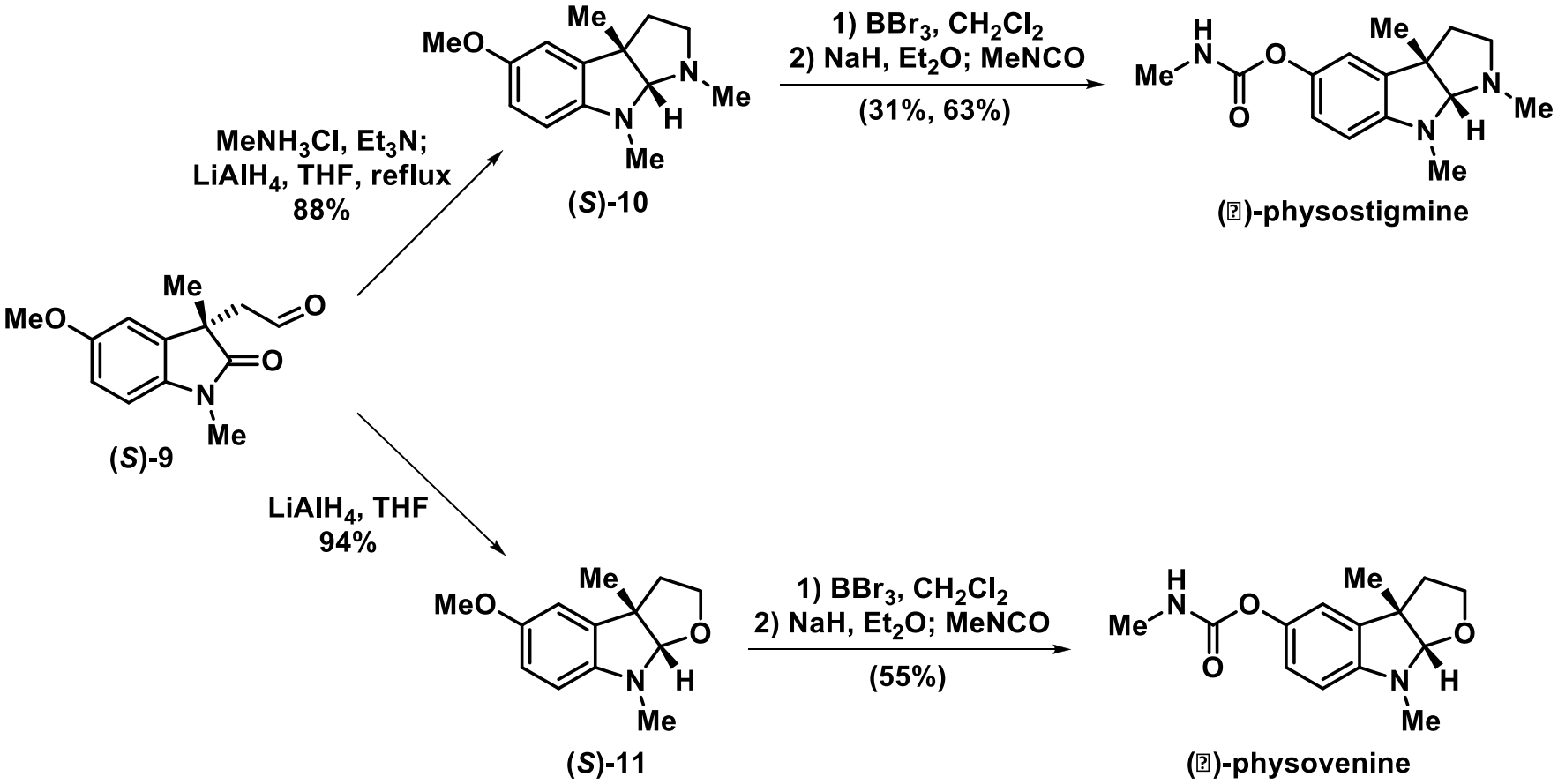


# Physostigmine/Physovenine Synthesis: Part 2/3



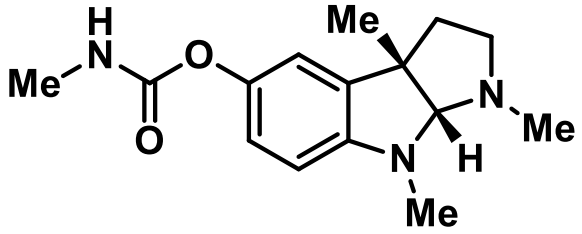

- Reduction of (*S*)-**9** to (*S*)-**10** was performed to determine the enantiopurity by chiral HPLC
- (*S*)-**9** was carried forward in >99% ee

# Physostigmine/Physovenine Synthesis: Part 3/3

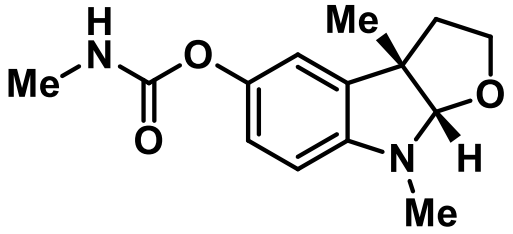


# Conclusion

• Physostigmine was synthesized in 5.4% yield over 9 steps (15-20% on larger scale)
• Physovenine was synthesized in 16.3% yield over 9 steps
• Developed a versatile route to hexahydropyrroloindoles
• Either enantiomer of the natural products can be prepared
• Asymmetric intramolecular Heck strategy useful due to the ability to append various groups to the quaternary carbon




(□)-physostigmine




(□)-physovenine