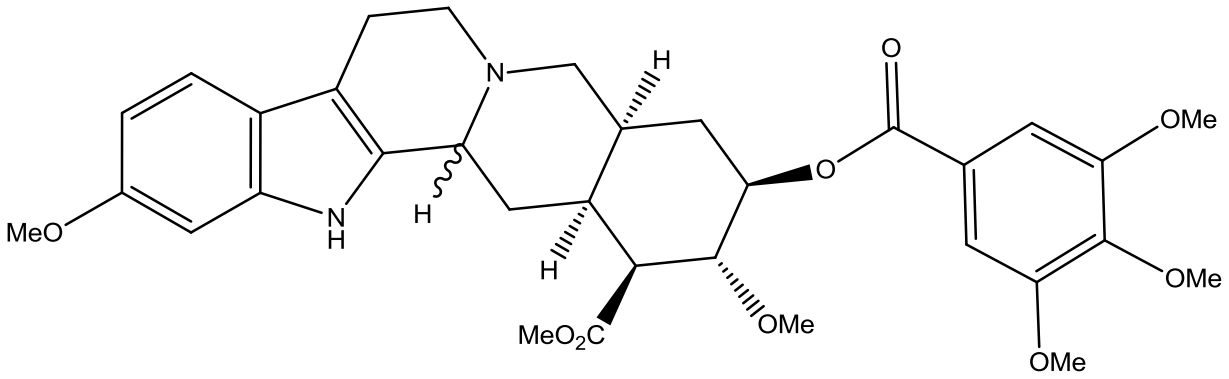
Total Synthesis of (±)-Reserpine



Stephen F. Martin, Slawomir Grzejszczak, Heinrich Rueger, and Sidney A. Williamson

J. Am. Chem. Soc. **1985**, 107, 4072-4074

Presented by James Melnyk

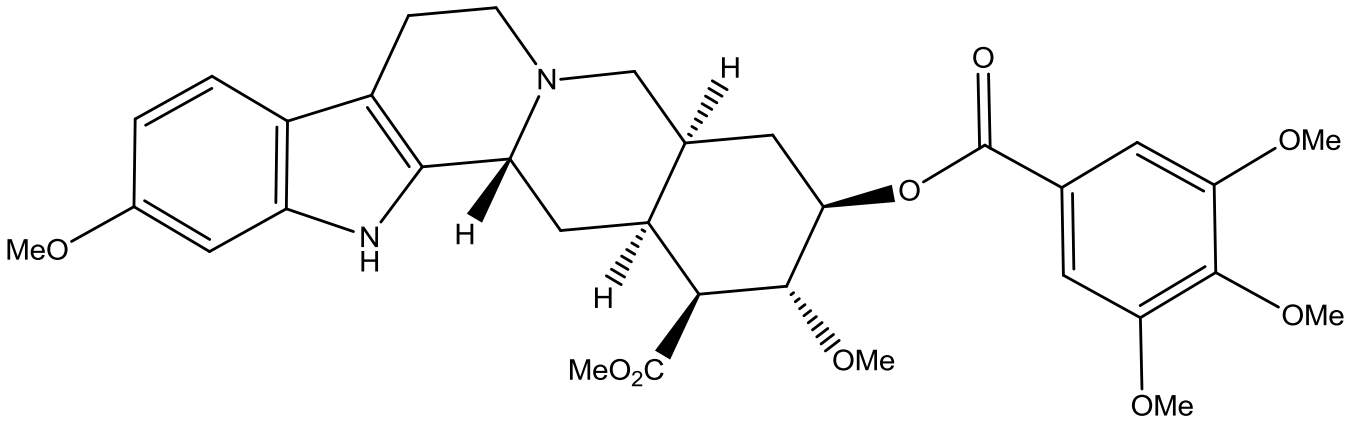
Stephen F. Martin

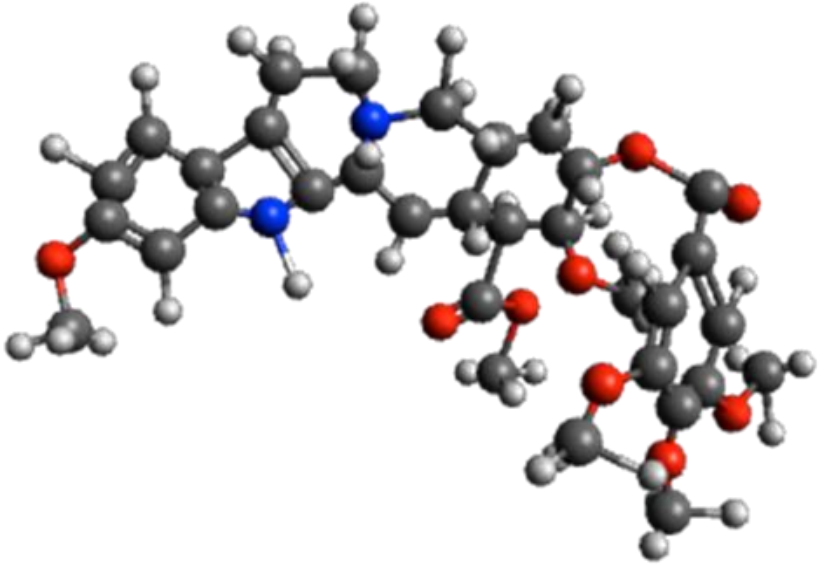
- A New Mexico native
- 1968: B.S. University of New Mexico
- 1972: Ph.D. Princeton University
  - Advisor: Edward C. Taylor
- 1972-73: Postdoctoral research – University of Munich
  - Advisor: Rudolf Gompper
- 1973-1974: Massachusetts Institute of Technology, NIH Postdoctoral Fellow
  - Advisor: George Buchi
- 1974: Joined the University of Texas Faculty
- M. June and J. Virgil Waggoner Regents Chair in Chemistry
- Research focuses on the development and application of new synthetic strategies to the syntheses of natural products

Reserpine

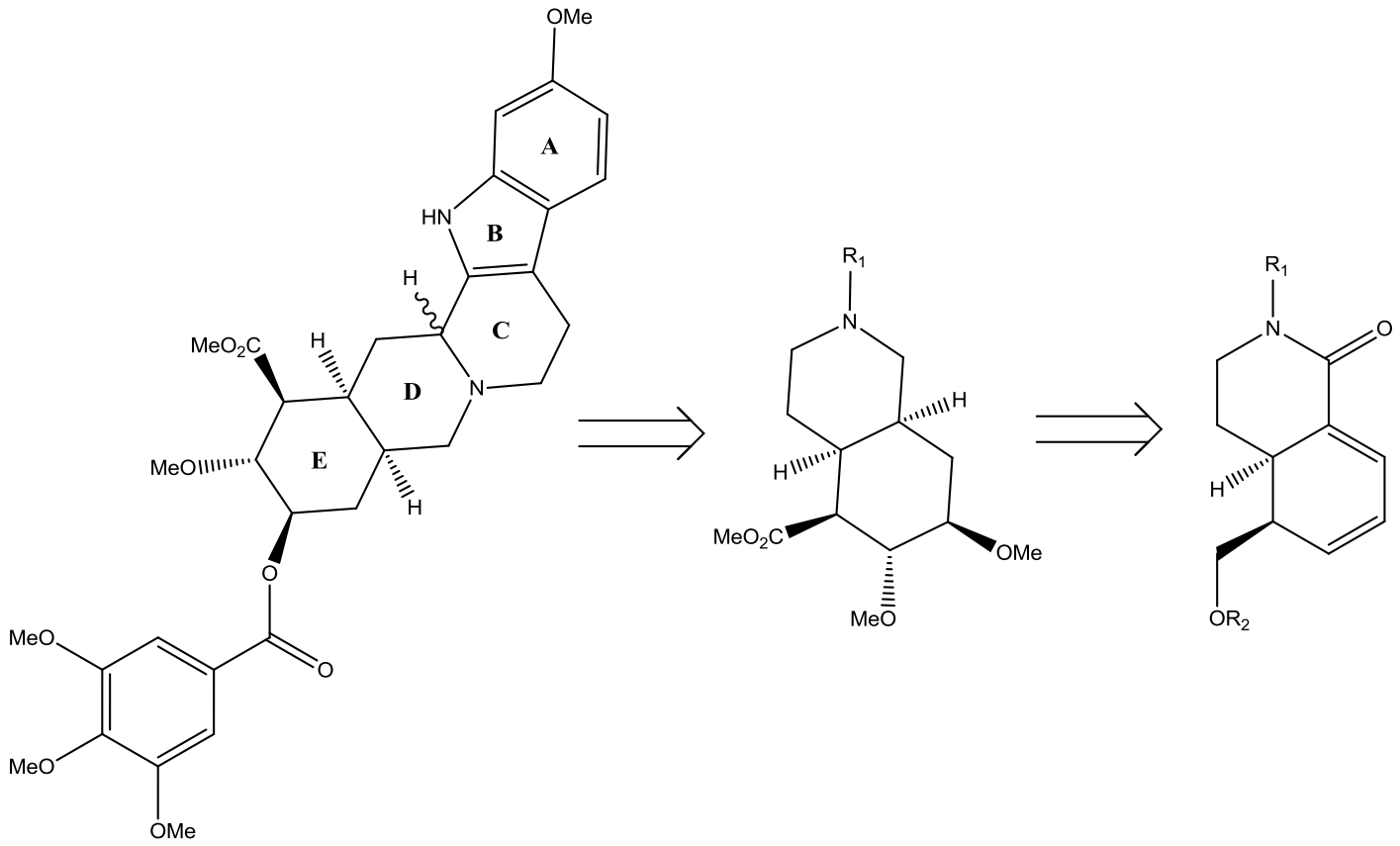
- Indole alkaloid first isolated from the Indian snake root, *Rauwolfia serpentina,* in 1952
- Molecular structure elucidated in 1953 and natural structure published in 1955
- Medicinal agent – antipsychotic and antihypertensive properties
- Irreversibly blocks the vesicular monoamine transport (VMAT) protein thus preventing movement of free serotonin, norepinephrine, and dopamine to the storage vesicles for release into the synaptic cleft
- Replenishing VMAT levels can take up to weeks thus causing Reserpine to have a long lasting effect
- Used sparingly today due to a number of undesirable side effects

Structure of Reserpine





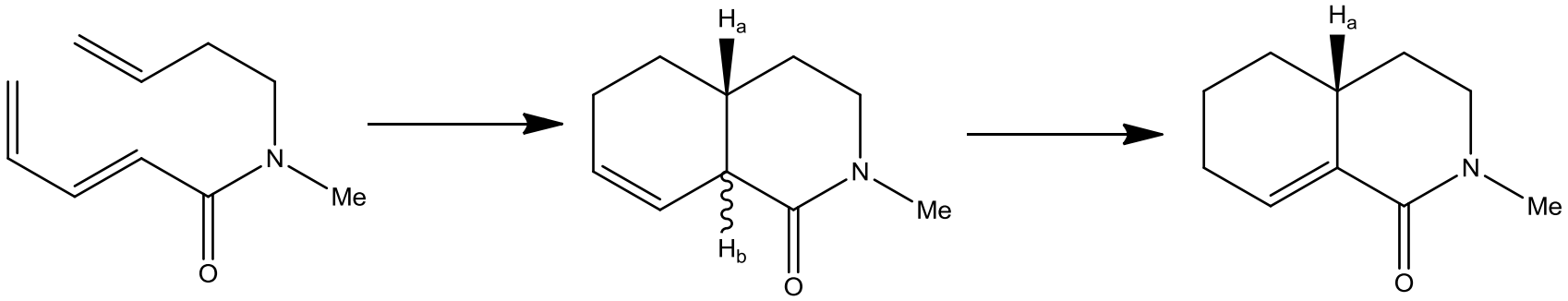
Retrosynthetic Analysis



- Synthetic challenge of reserpine is posed by the D/E ring system of the pentacylic nucleus
- Synthetic strategy necessitated the preparation of a functionalized hydroisoquinoline derivative that could then be modified to provide the D/E ring system

Prior Work – Diels-Alder Reaction

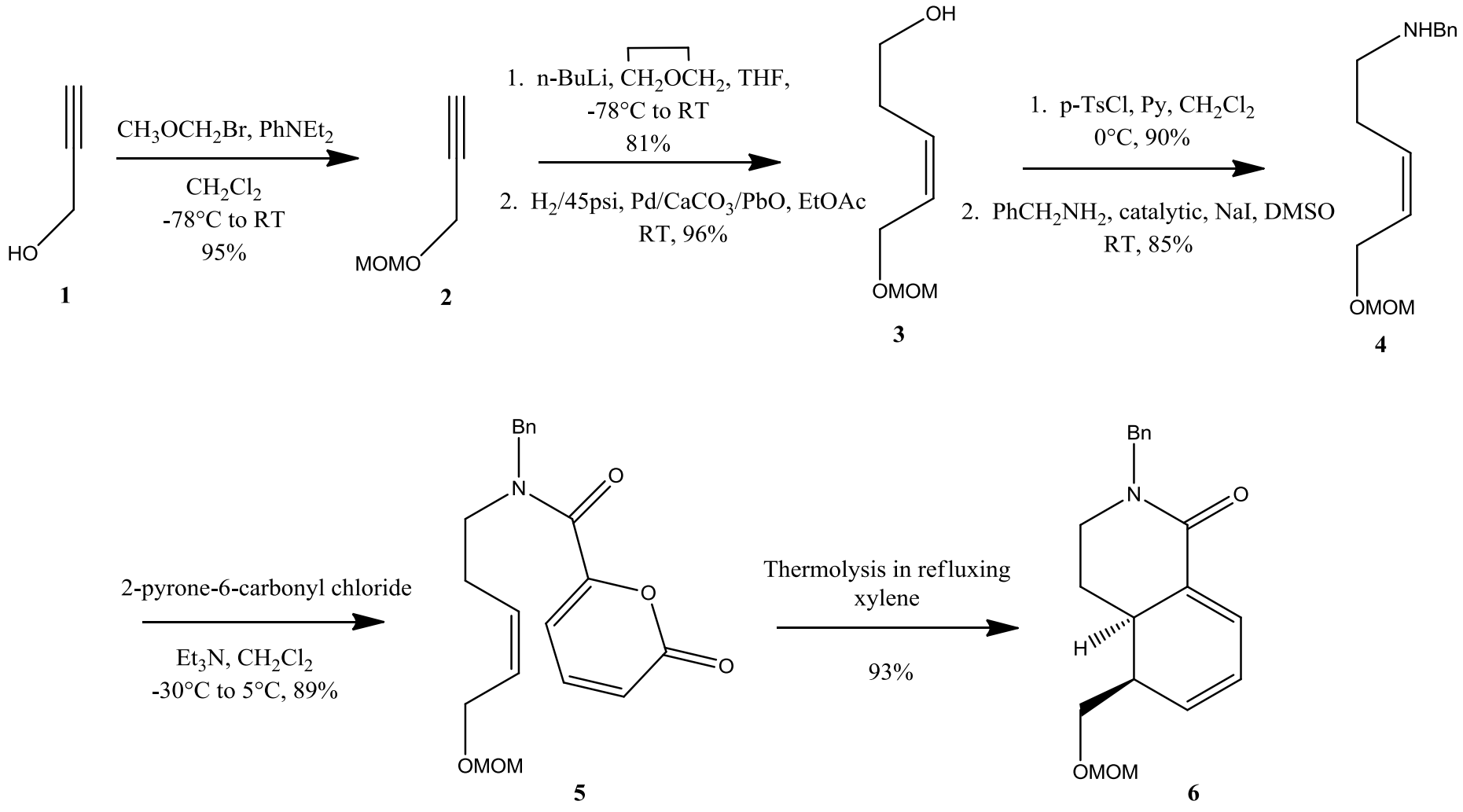
- Preparation of a substituted hydroisoquinoline system was made possible due to previously developed methodology featuring an intramolecular Diels-Alder Reaction using aza-trienes



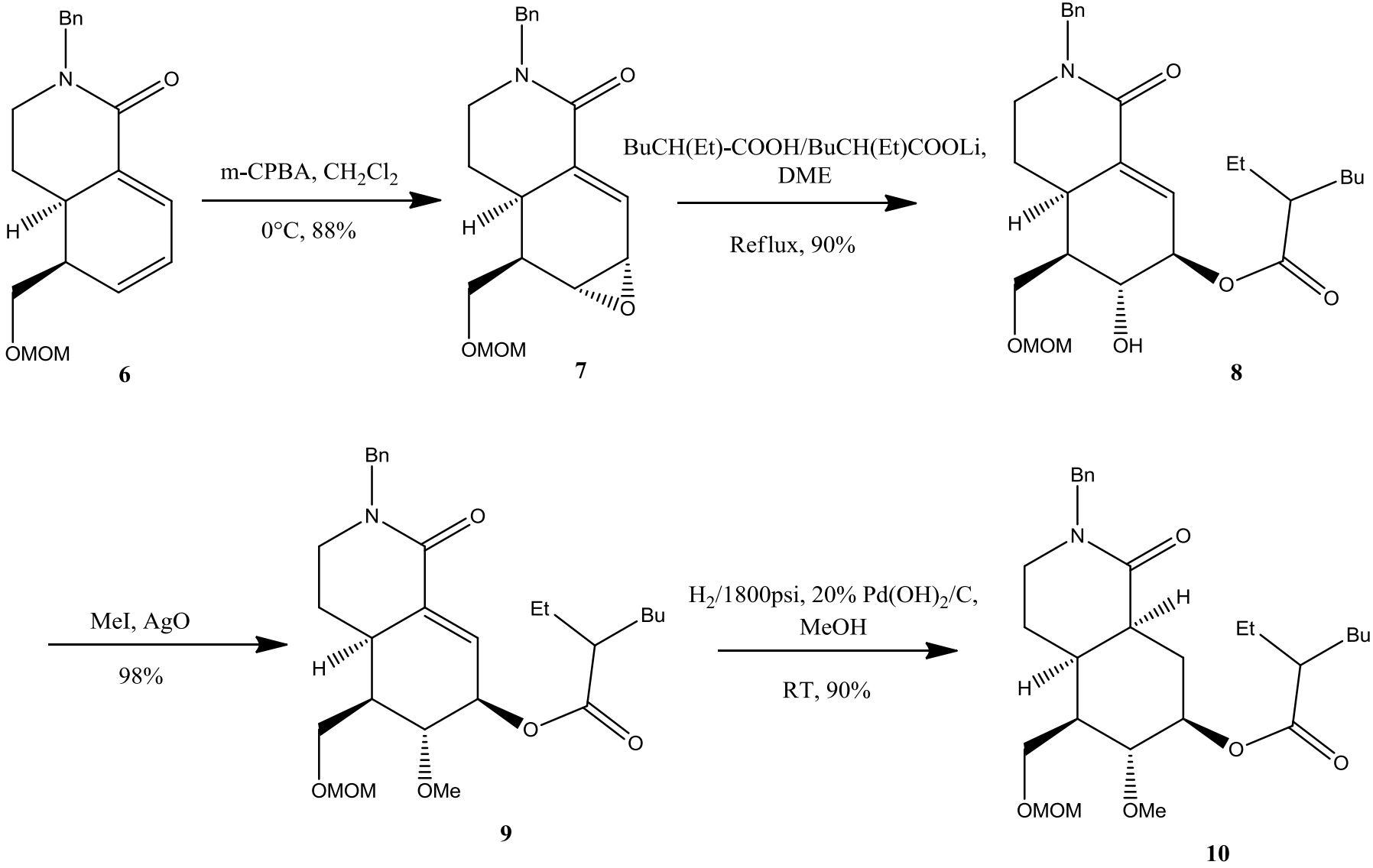
- Transformation occurs by thermolysis at 300 °C in a sealed container

Stephen F. Martin, Sidney A. Williamson, R. P. Gist, and Karl M. Smith, *J. Org. Chem.,* **1983**, 48, 5170-5180

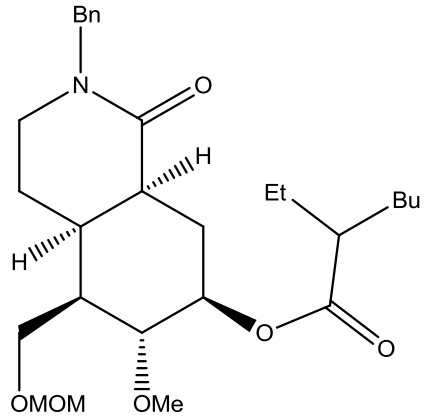
(±)-Reserpine Total Synthesis – Part 1



(±)-Reserpine Total Synthesis – Part 2



(±)-Reserpine Total Synthesis – Part 3



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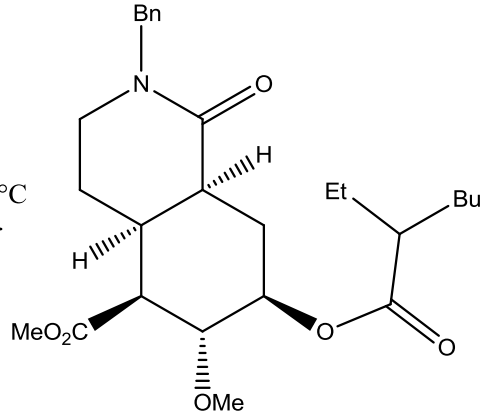
1. p-TsOH, MeOH, 45°C
2. PDC, DMF, RT
3. CH_2N_2, MeOH/Et_2O, 0°C

75%



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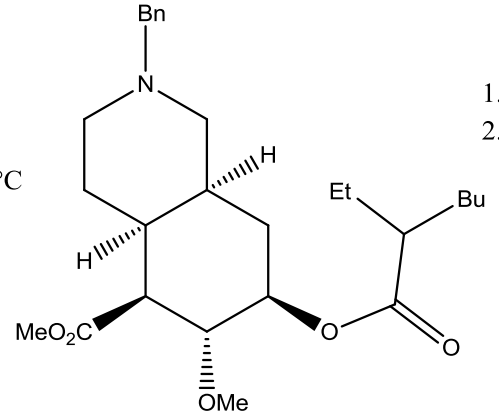
AlH_3, THF, -70°C to -20°C

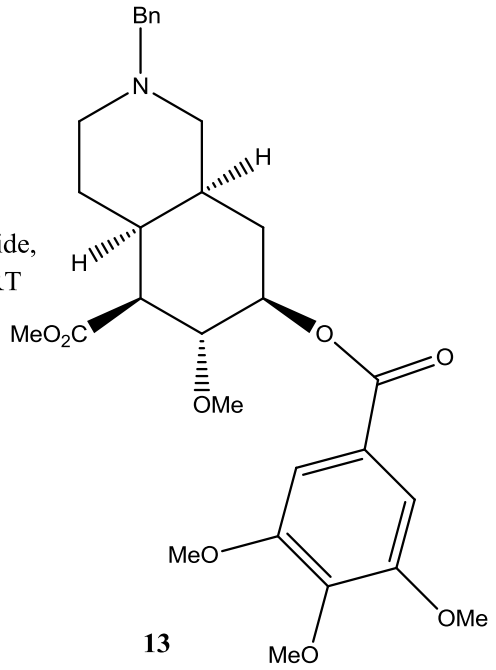
79%



12

1. p-TsOH, MeOH, 85°C
2. 3,4,5-tri-methoxybenzoyl chloride, Py, catalytic DMAP, CH_2Cl_2, RT

74%



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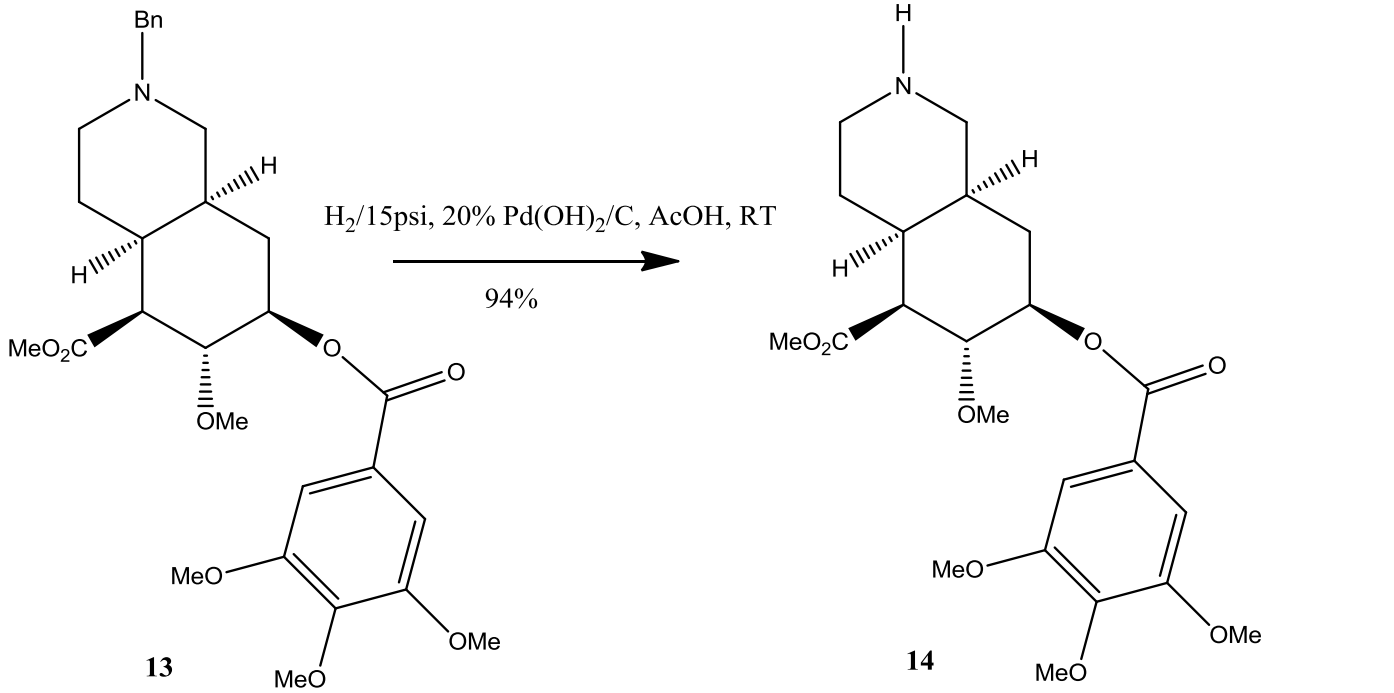
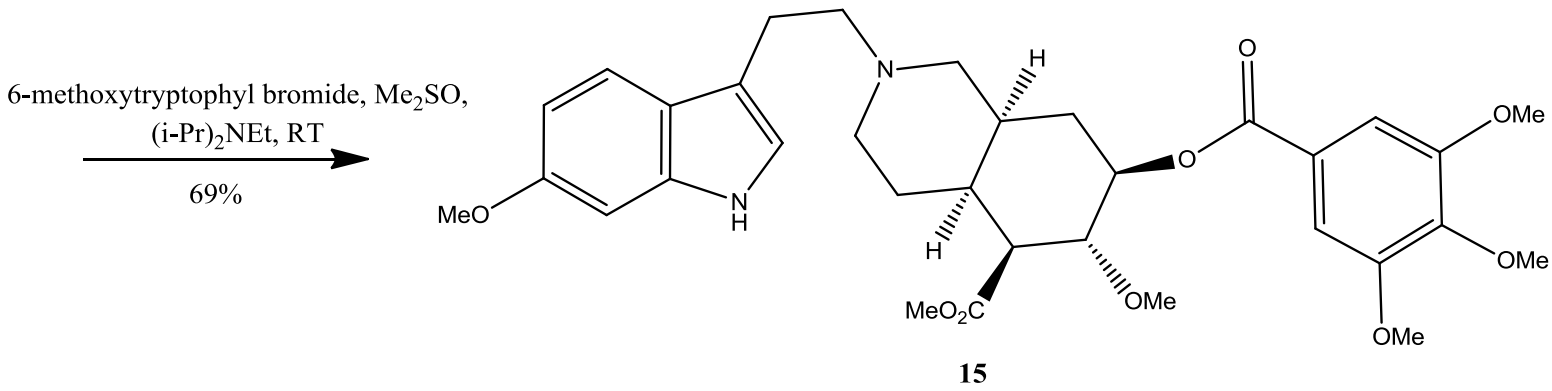
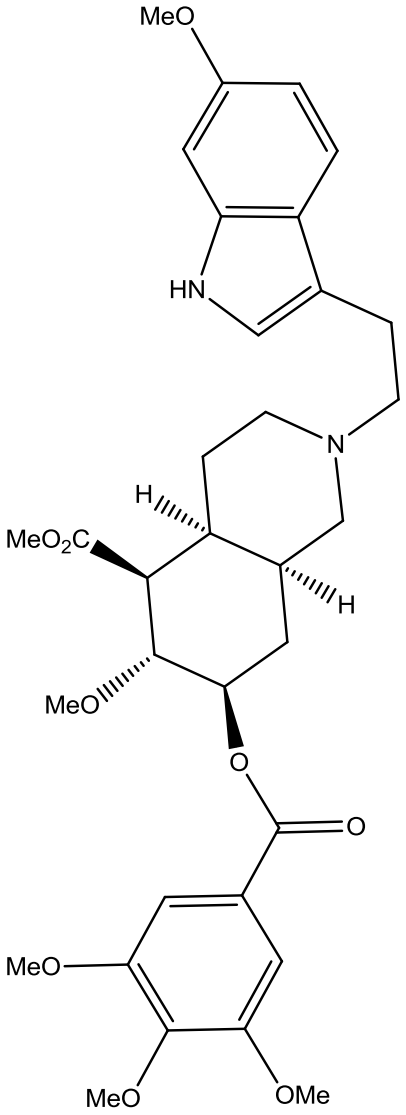
(±)-Reserpine Total Synthesis – Part 4





(±)-Reserpine Total Synthesis – Part 5



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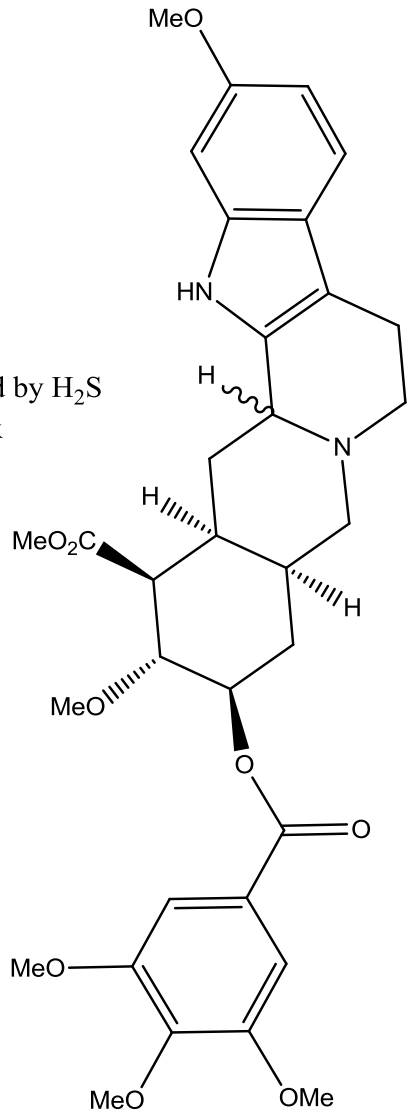
1. $Hg(OAc)_2$, 5% Aq. AcOH, 85°C followed by H_2S
2. Zn in 7% Aq. $HClO_4$/acetone/THF, reflux

Reserpine: 35%
Isoreserpine: 8%



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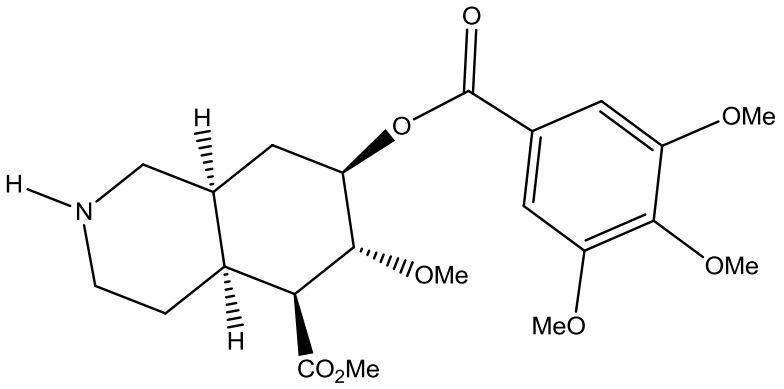
Conclusion

- Novel synthesis of (±)-Reserpine completed in 15 steps featuring use of an intramolecular Diels-Alder cycloaddition for the construction of the functionalized hydroisoquinoline



- Individual steps were generally moderate to high yielding
- General synthetic strategy has potential for the synthesis of other alkaloid natural products