

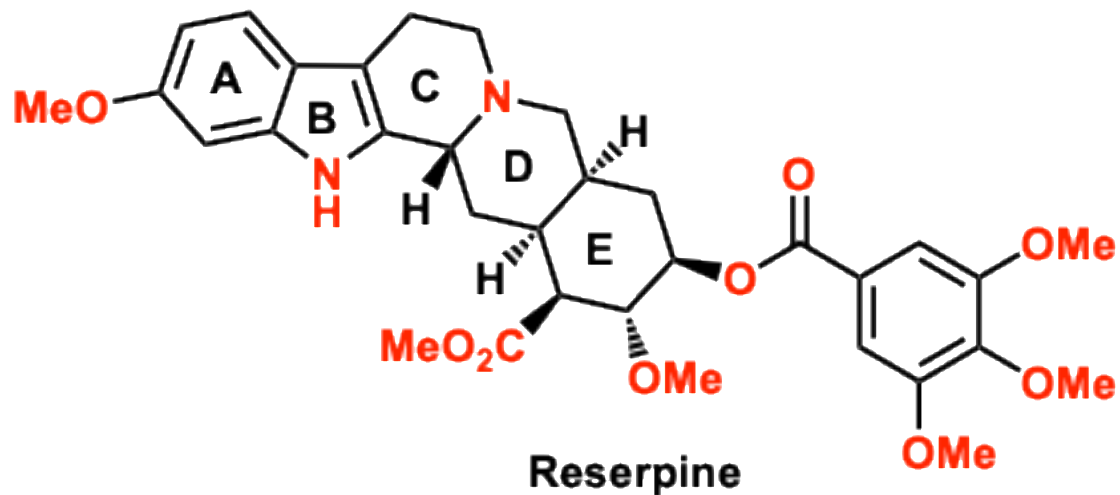
Total Synthesis of Reserpine & Yohimbine



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Professor of Chemistry, IIT Bombay

CH-845 Course on Organic Synthesis

Reserpine & Yohimbine

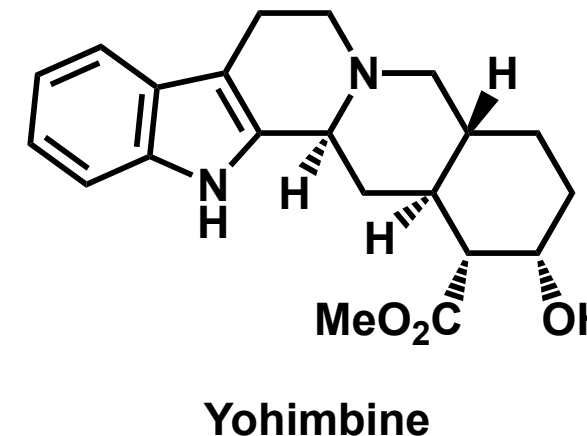


Reserpine was isolated from the dried root of the Indian 'Snake root'

Reserpine had been used for the treatment of snake bites, insanity etc

Its structure was elucidated in 1953 and the absolute configuration was established in 1955

The first total synthesis of this indole-based alkaloid was reported by R. B. Woodward in 1956 and since then there are several syntheses



In 1880, Hesse first isolated yohimbine from *Aspidosperma quebracho-blanco*, Schlecht., and it was later found to be the major alkaloid of *Corynanthe yohimbe*, Schum., by Spiegel in 1896

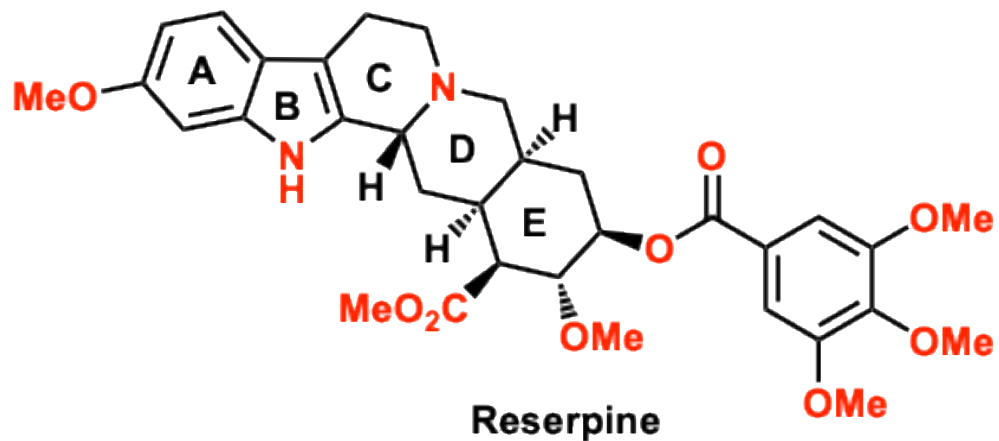
The correct constitution was suggested by Witkop in 1943

Isolation: Hesse, O. Ber. Dtsch. Chem. Ges. **1880**, 13, 2308

Spiegel, L. Chem. Ztg. **1896**, 20, 970

Witkop, B. Justus Liebigs Ann. Chem. **1943**, 554, 83

Structural Challenges & Synthetic Strategies for Reserpine



One of the most complex natural products of its size

There are 5 contiguous chiral centers

21 atoms arranged in 5 rings

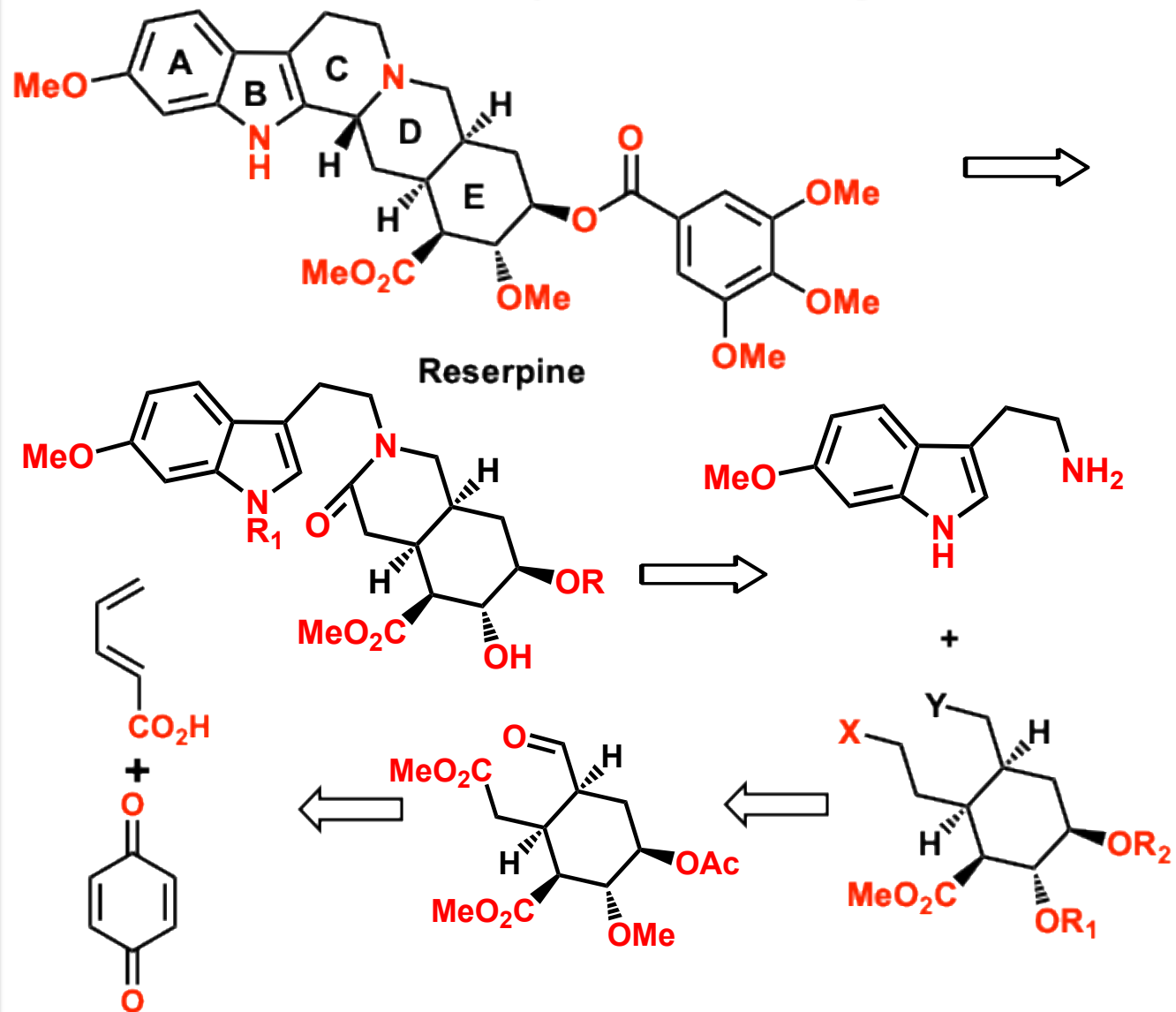
Most of the Synthesis focused on ‘**Synthesis of E-ring**’ first

Construction of **E ring** followed by D, AB and C

Diels-Alder reaction also has been utilized to get the **cis** ring junction of DE ring

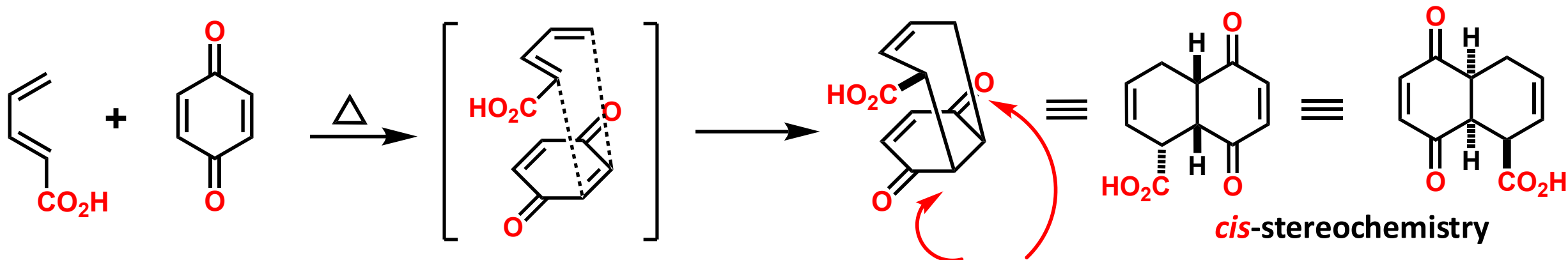
CD ring junction is epimerizable under acidic conditions

Woodward's Retrosynthesis for Reserpine



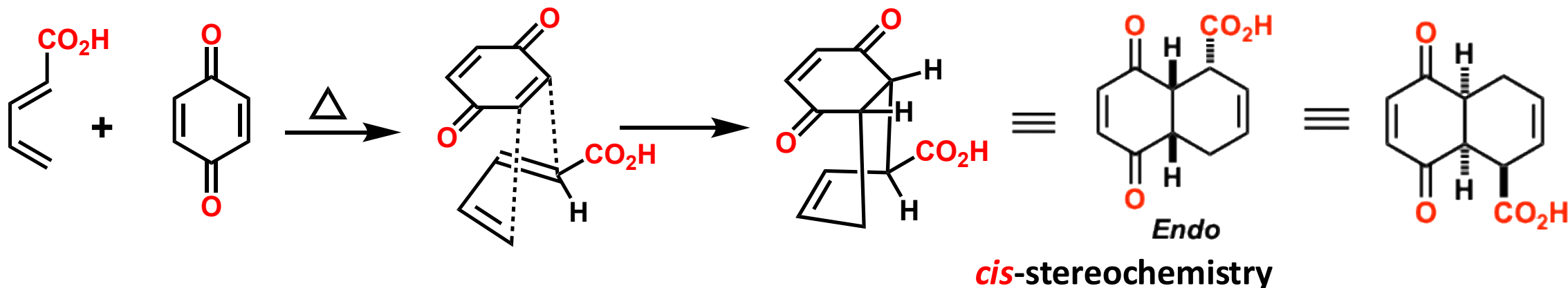
Diels-Alder Reaction Strategy to DE Ring of Reserpine

Bottom Face Approach of the Dienophile

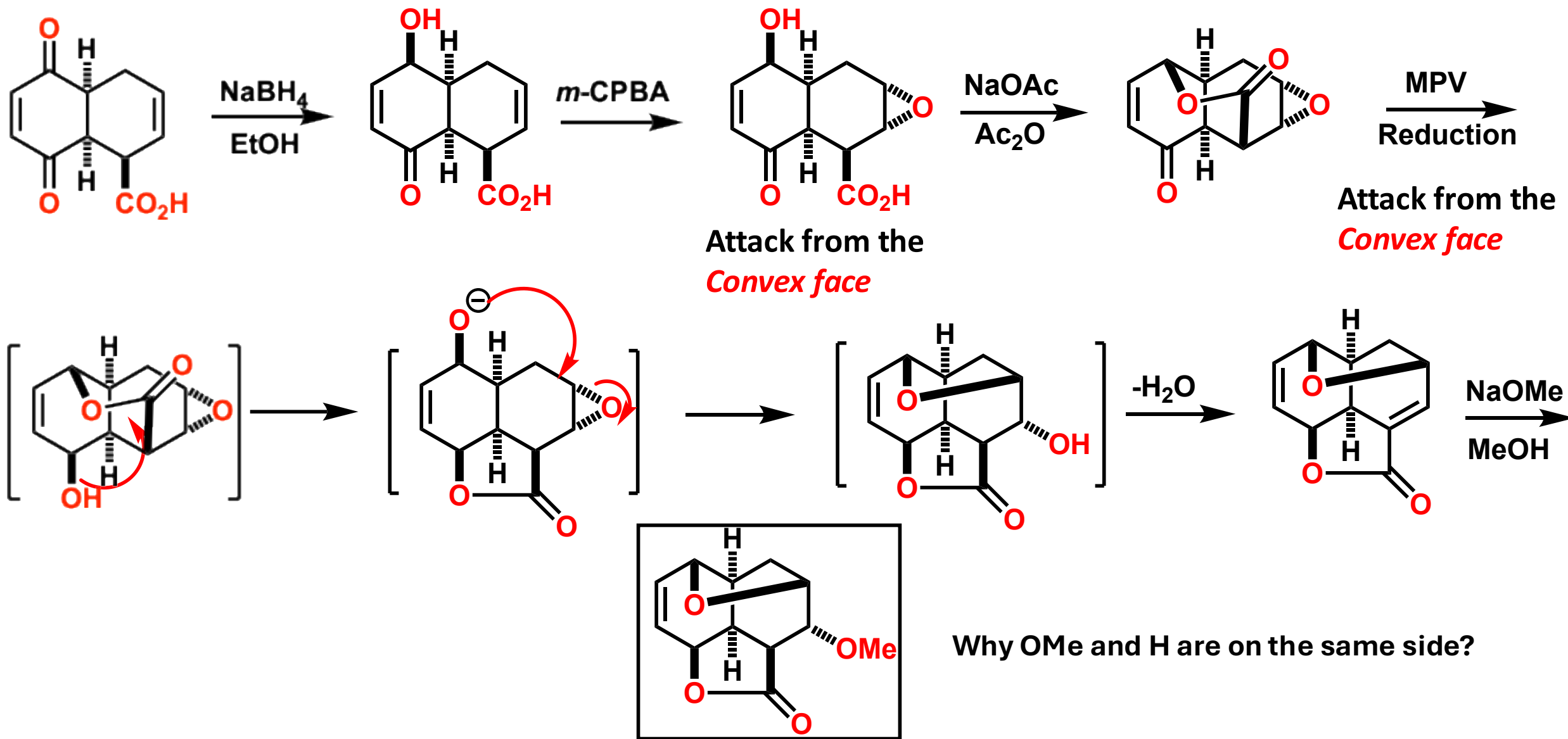


Attack from the *Convex face*

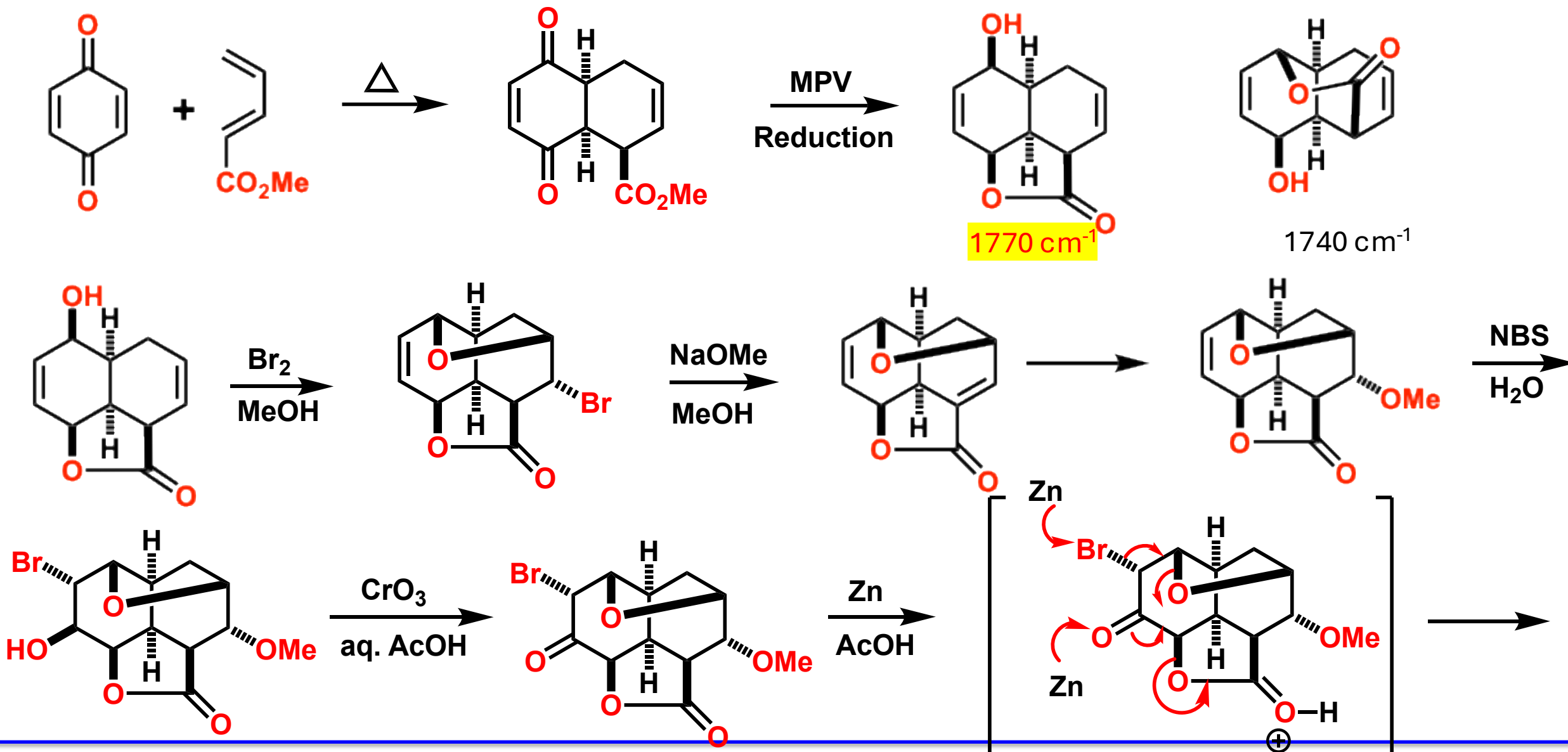
Top Face Approach of the Dienophile



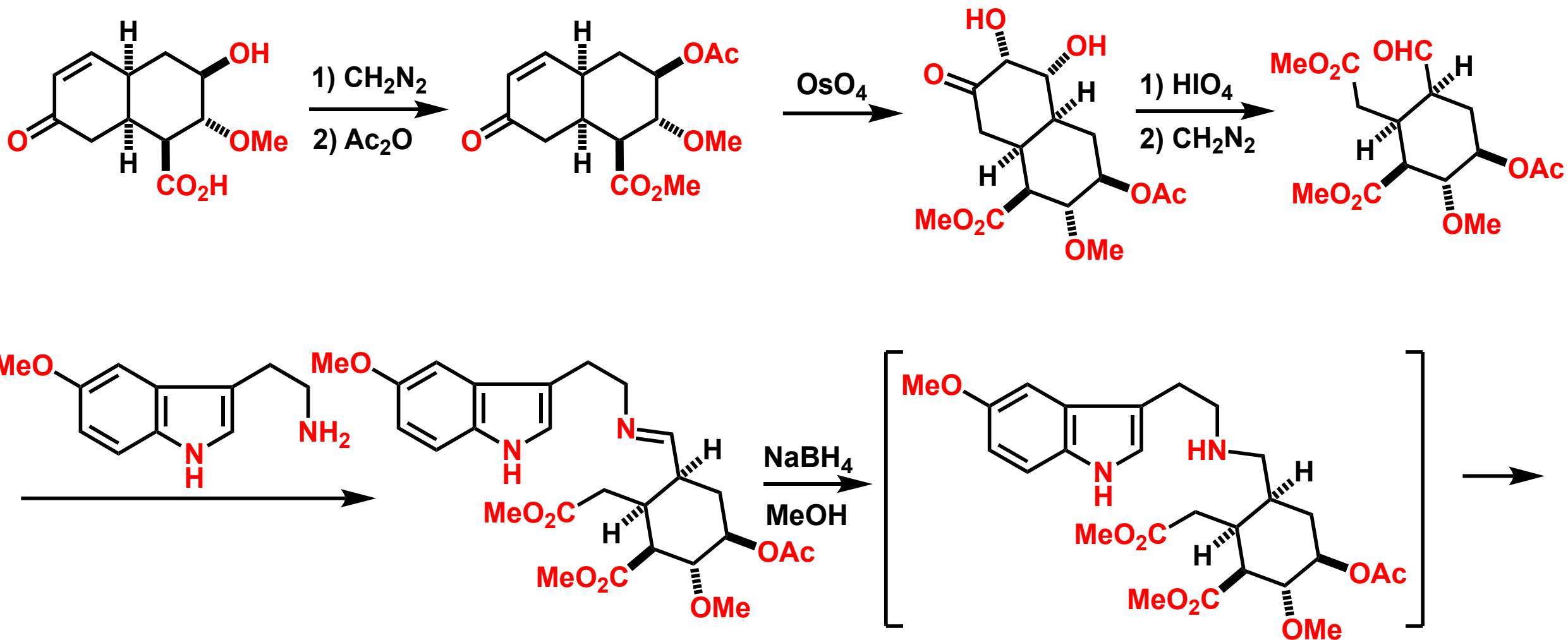
Diels-Alder Reaction Strategy to DE Ring of Reserpine



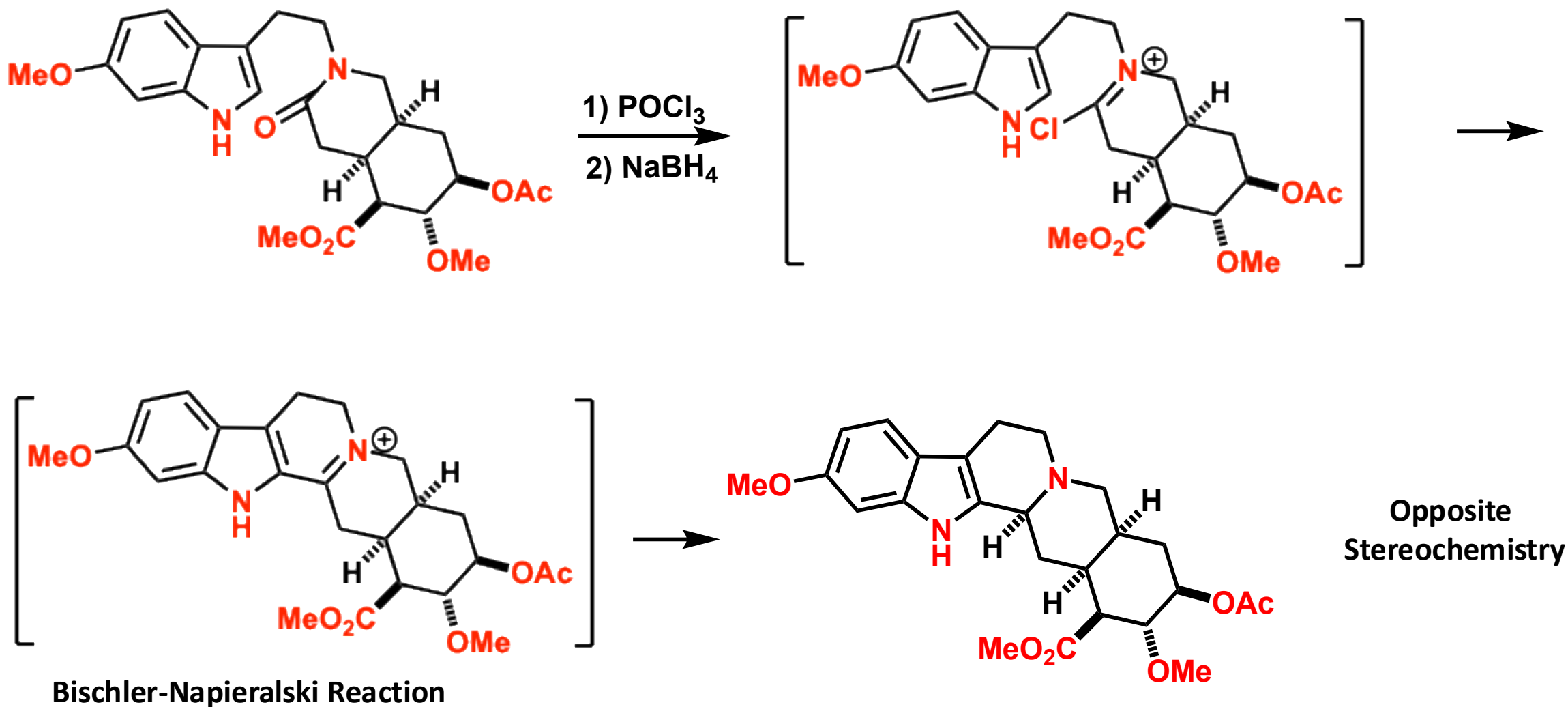
Improved Method for the Synthesis of DE Ring of Reserpine



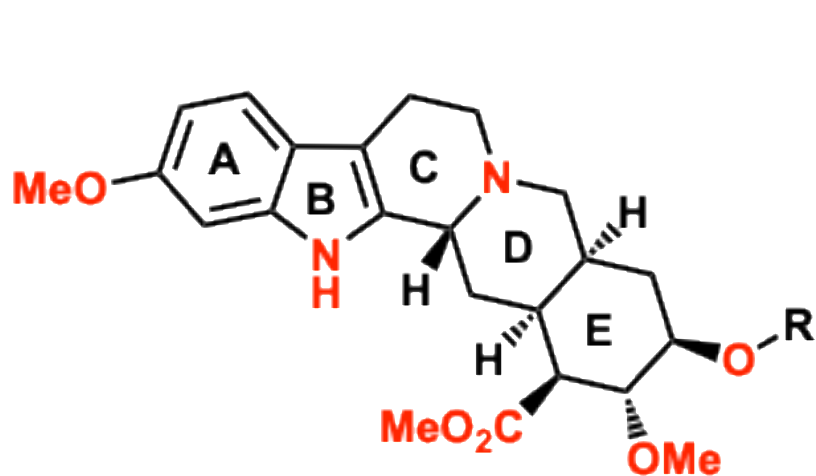
Total Synthesis of Reserpine



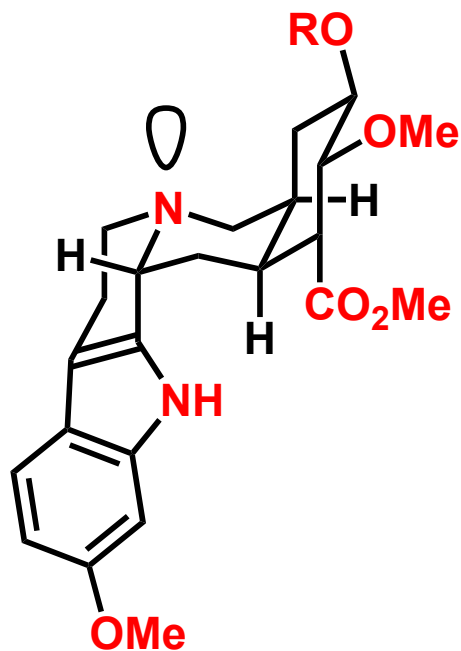
Total Synthesis of Reserpine



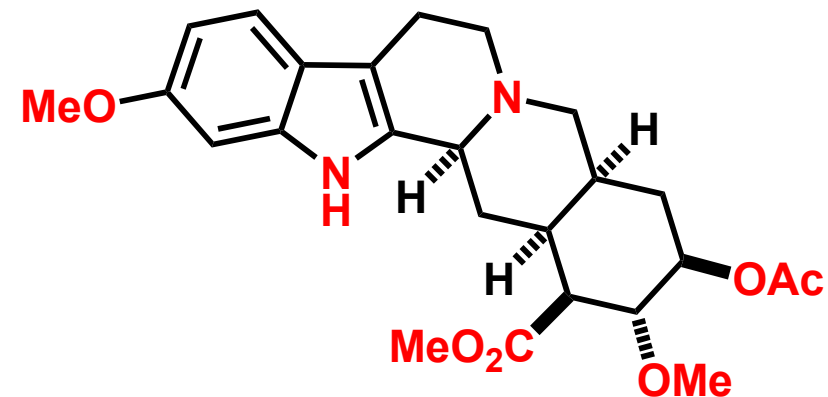
Total Synthesis of Reserpine



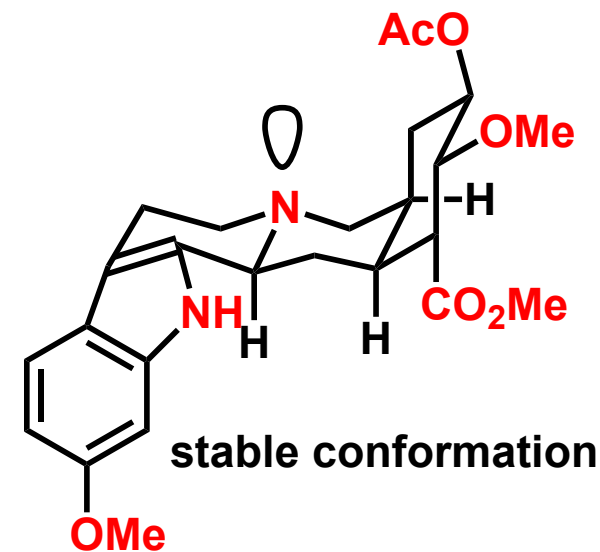
Reserpine



Stable Conformation of Reserpine

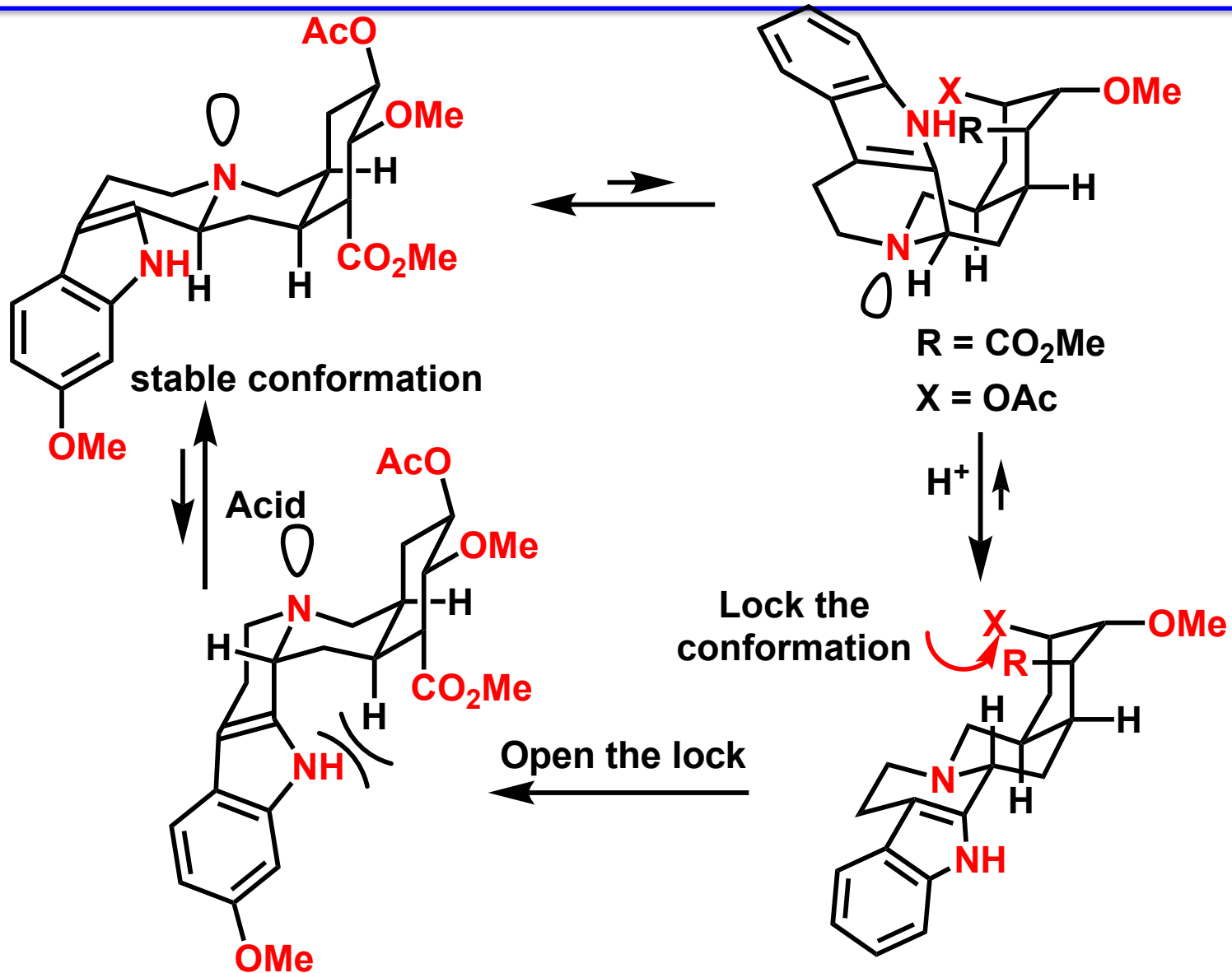


Opposite Stereochemistry

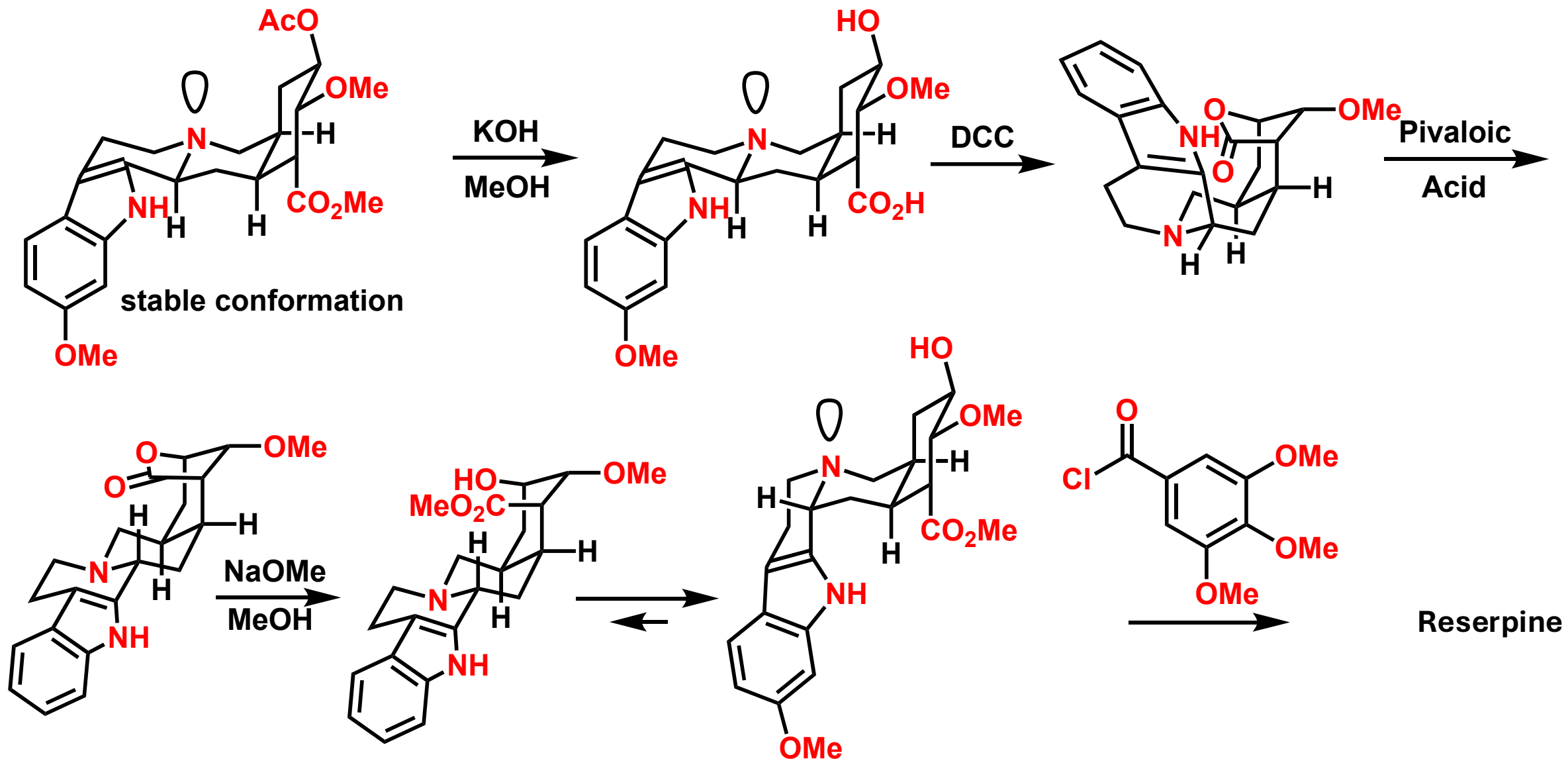


stable conformation

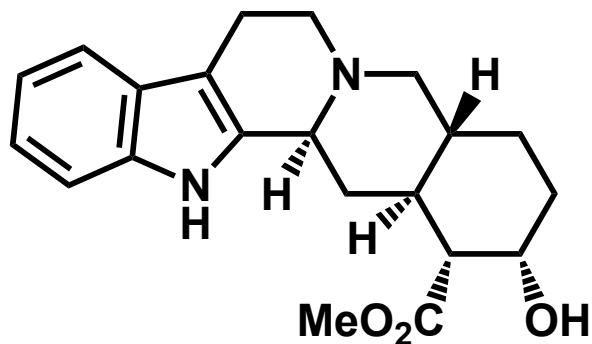
Conformational Equilibrium



Total Synthesis of Reserpine



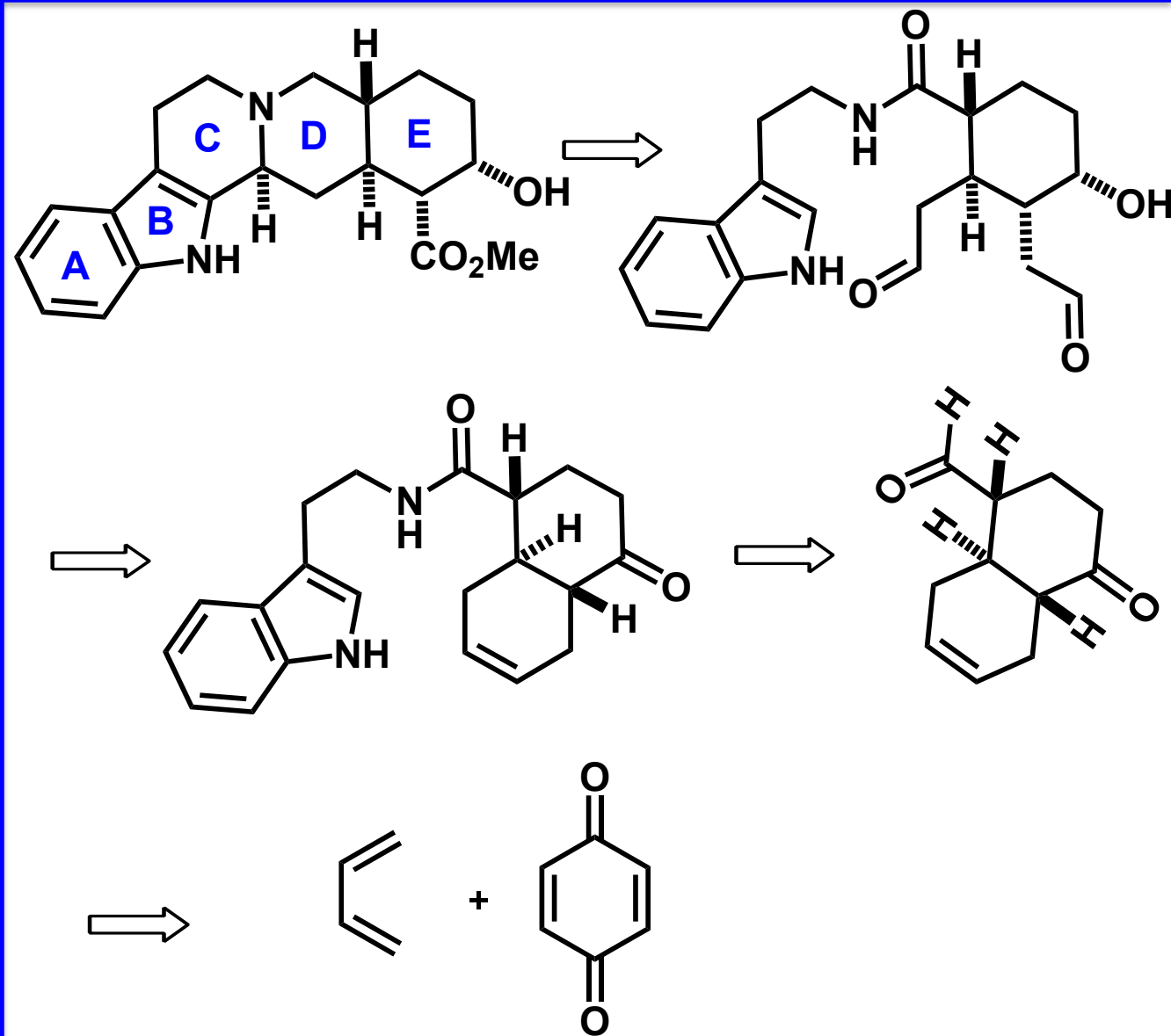
Van Tamelen's Total Synthesis of Yohimbine



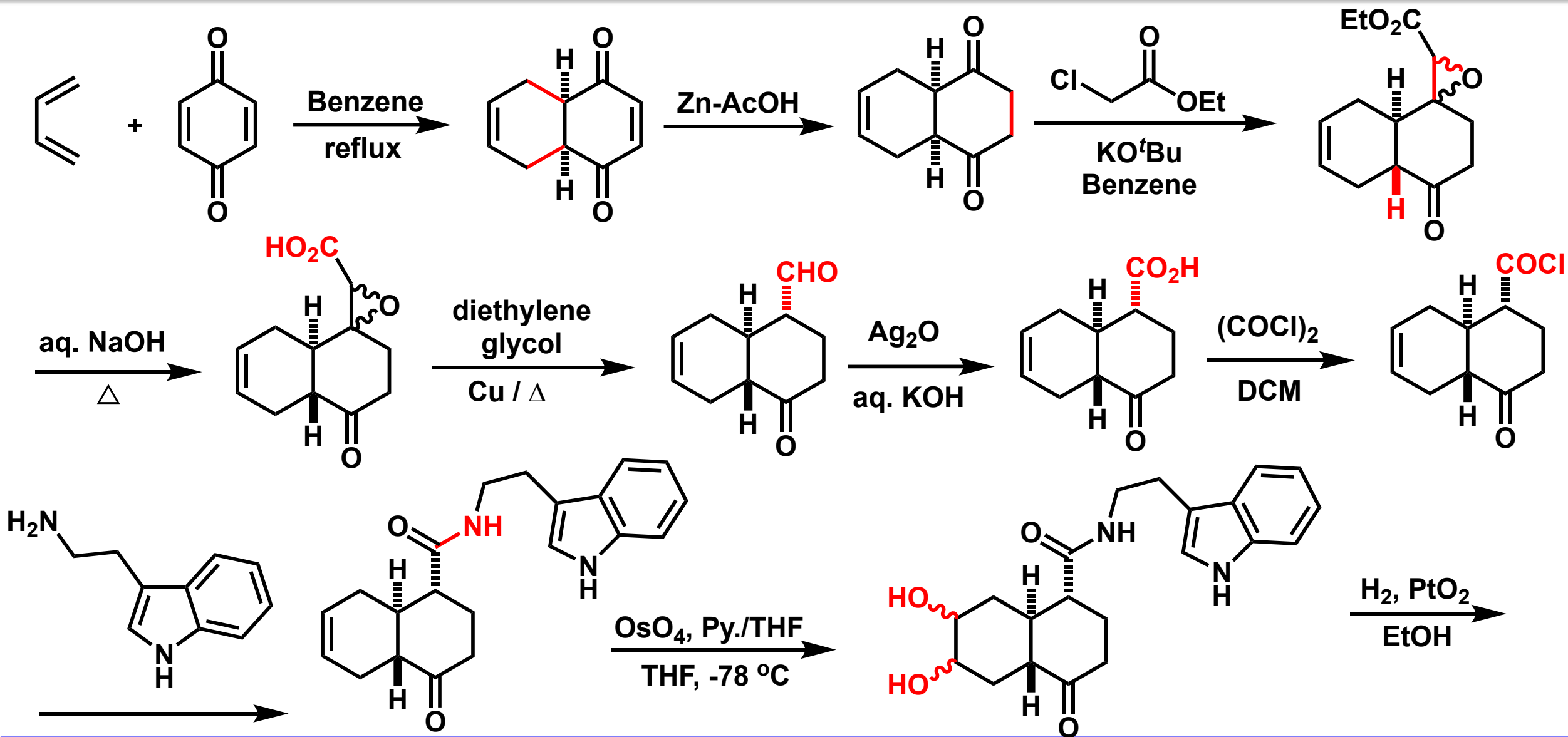
Yohimbine

- The first total synthesis of yohimbine was communicated by Van Tamelen *et al* in 1958
- The first step and the key step in the synthesis is the stereoselective construction of the functionally rich E ring by a Diels-Alder reaction, which closely followed the first step in Woodward's classic reserpine synthesis
- Of the total of five stereocenters, two of the contiguous stereocenters were formed by this crucial reaction

Tamelen, E. V., et al. *J. Am. Chem. Soc.* **1958**, 80, 5006–5007



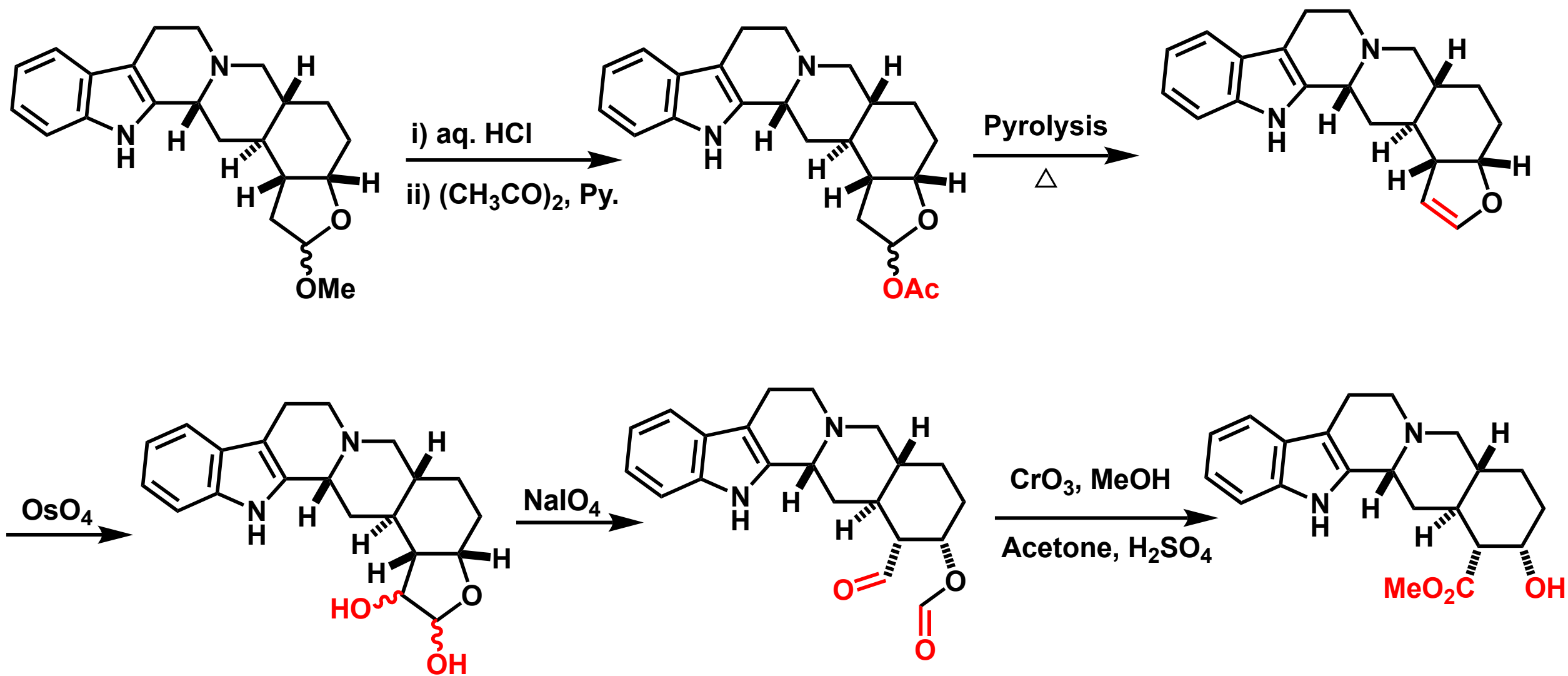
Total Synthesis of Yohimbine



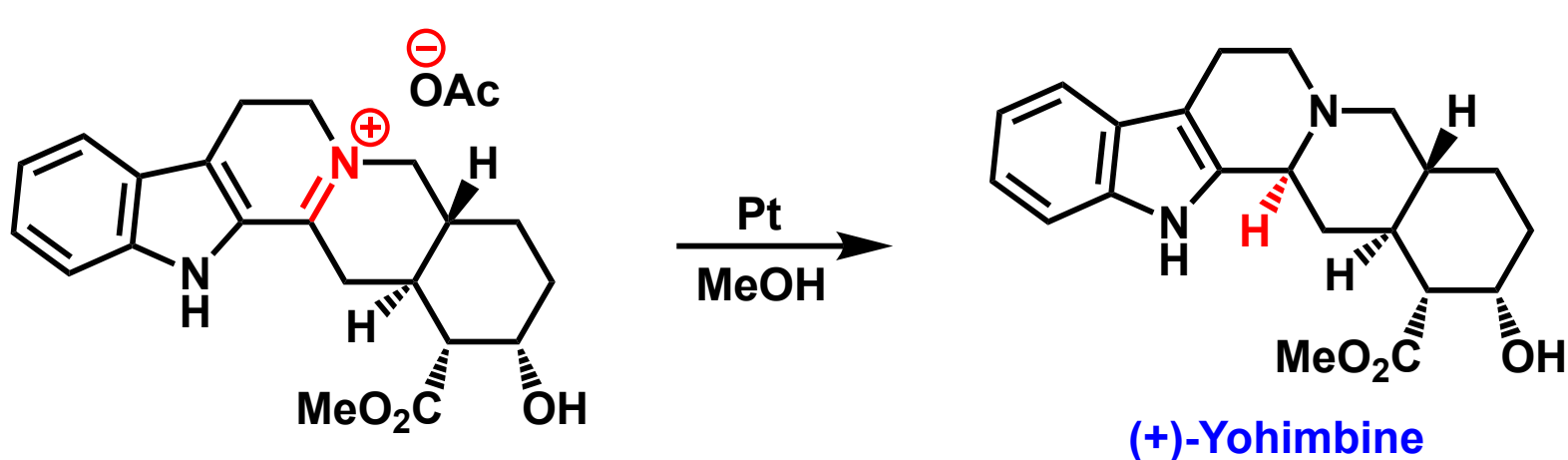
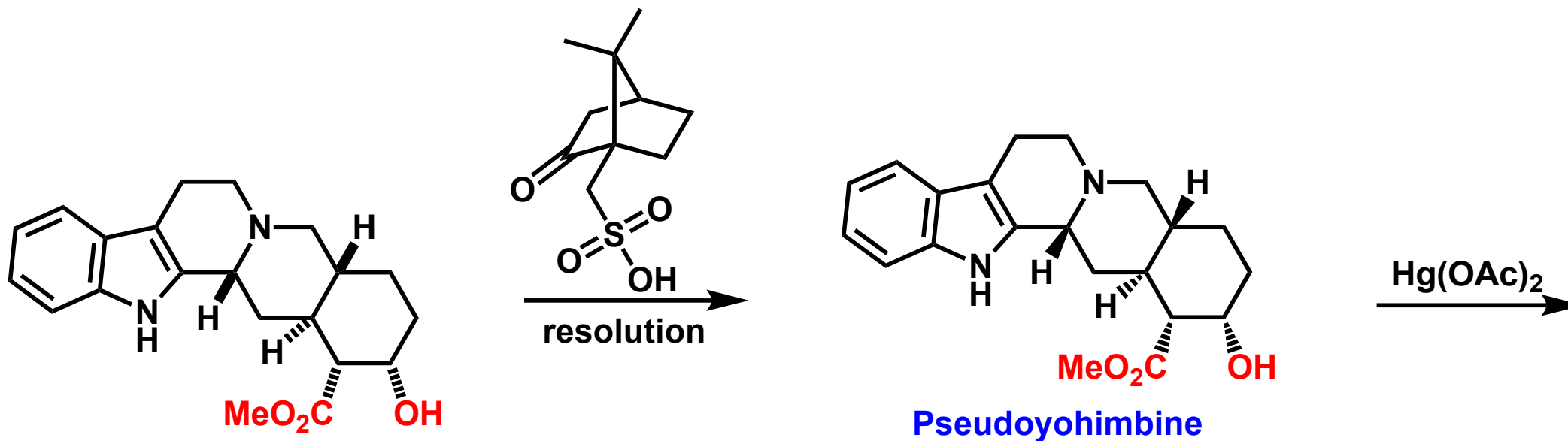
CH-845 Course on Organic Synthesis; Course Instructor: Krishna P. Kaliappan



Total Synthesis of Yohimbine



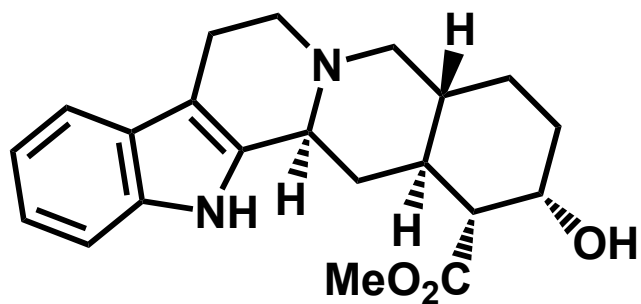
Total Synthesis of Yohimbine



For Epimerization: W. O. Godtfredsen and S. Vandegál, *Acta Chim. Scand.*, **1956**, 10, 1414

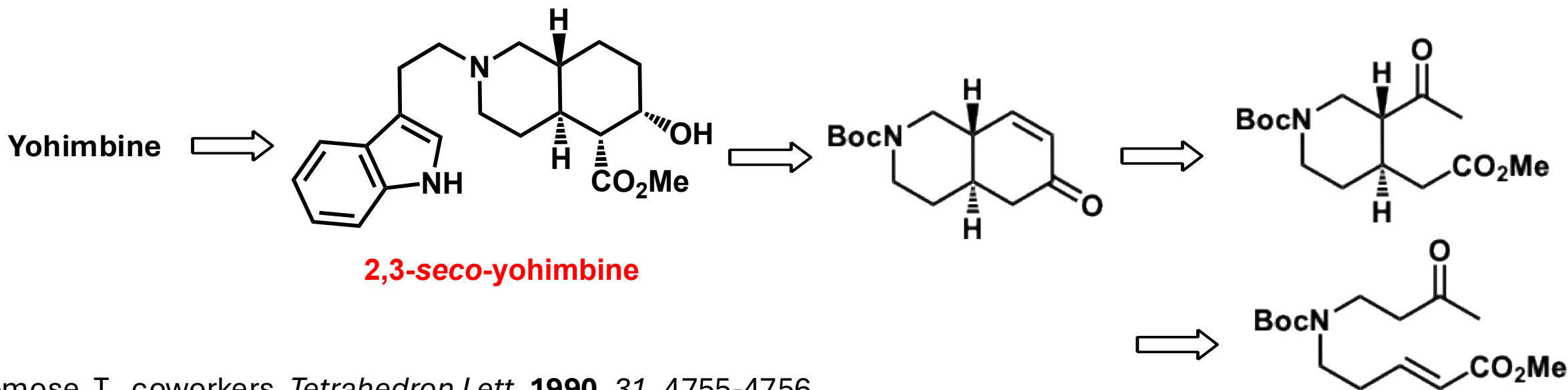
Tamelen, E. V., et al. *J. Am. Chem. Soc.* **1958**, 80, 5006–5007

Momose's Total Synthesis of Yohimbine



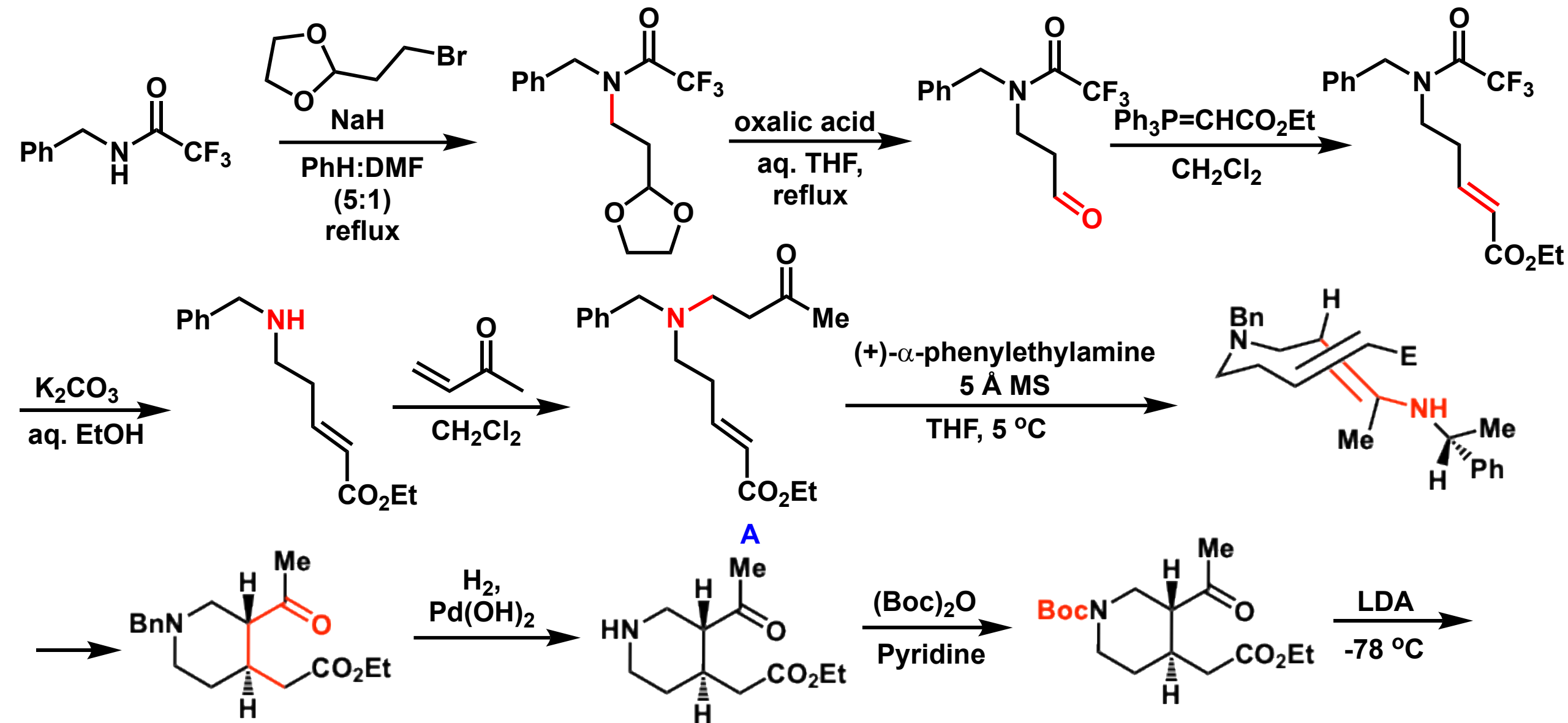
(+)-Yohimbine

- In 1990, Momose and coworkers reported the first formal asymmetric synthesis of yohimbine
- The key step in Momose's strategy featured an asymmetric intramolecular Michael reaction to prepare the D ring of yohimbine alkaloids
- The conversion of 2,3-seco-yohimbine to yohimbine was already known

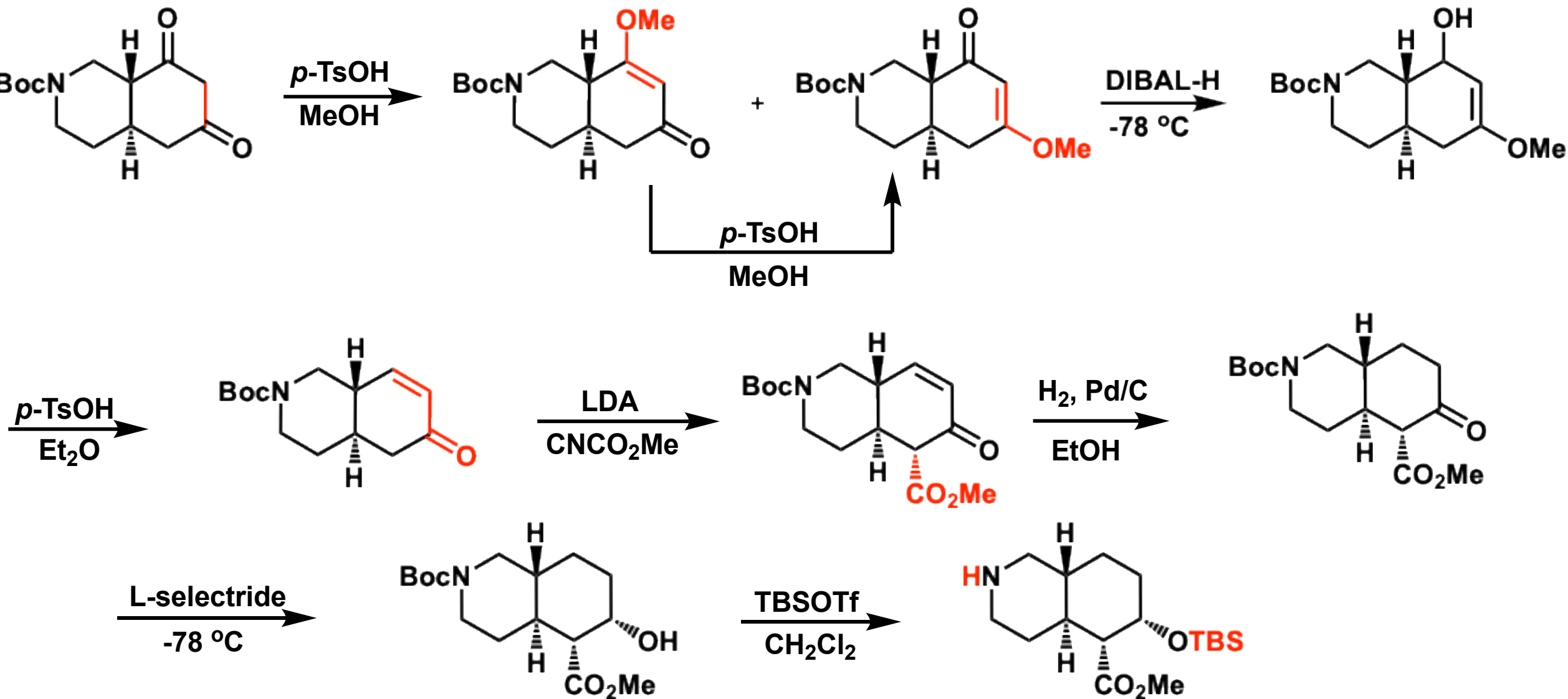


Momose, T., coworkers, *Tetrahedron Lett.* **1990**, 31, 4755-4756

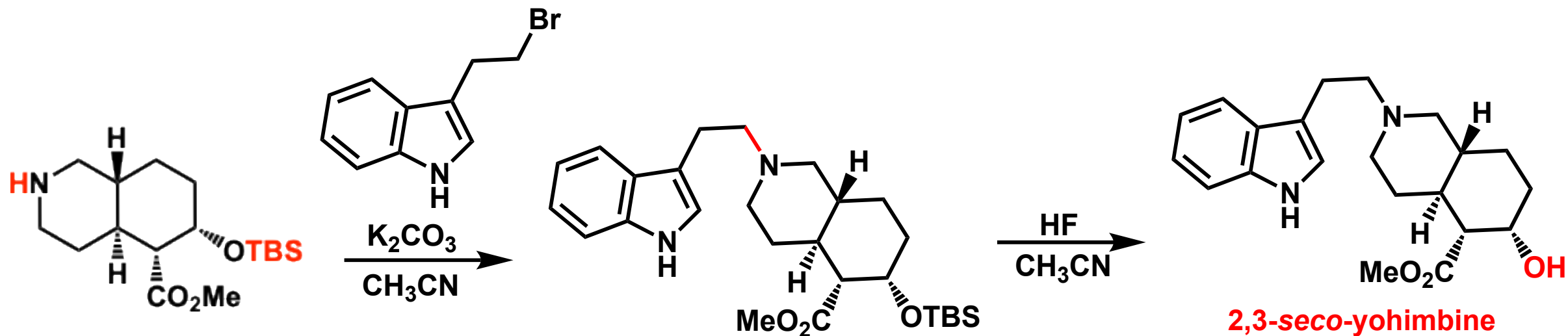
Momose's Total Synthesis of Yohimbine



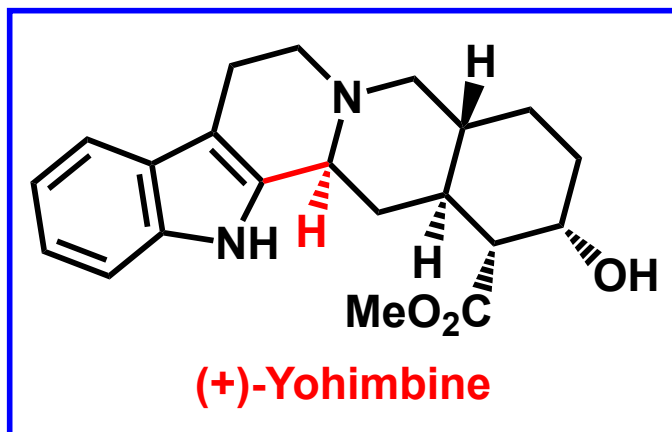
Momose's Total Synthesis of Yohimbine



Total Synthesis of Yohimbine



i) $\text{Hg}(\text{OAc})_2$,
5% aq. AcOH ,
 H_2S
ii) NaBH_4



Sakai, S.; co-workers, *Tetrahedron* **1973**, 29, 2015

Summary

- The first total synthesis of yohimbine was communicated by Van Tamelen *et al* in 1958
- The first step and the key step in the synthesis is the stereoselective construction of the functionally rich E ring by a Diels-Alder reaction, which closely followed the first step in Woodward's classic reserpine synthesis
- The Diels-Alder reaction was commenced from *p*-benzoquinone and 1,3-butadiene
- The completion of the total synthesis was accomplished in 20 linear steps with an overall yield of 0.024% from Diels Alder adduct

Tamelen, E. V., *et al.* *J. Am. Chem. Soc.* **1958**, 80, 5006–5007

- In 1990, Momose and coworkers reported the first formal asymmetric synthesis of yohimbine
- The key step in Momose's strategy featured an asymmetric intramolecular Michael reaction to prepare the D ring of yohimbine alkaloids
- They commenced from the known ketone A and accomplished the synthesis of 2,3-*seco*-yohimbine in 13 linear steps with an overall yield of 25.6%

Momose, T., coworkers, *Tetrahedron Lett.* **1990**, 31, 4755-4756