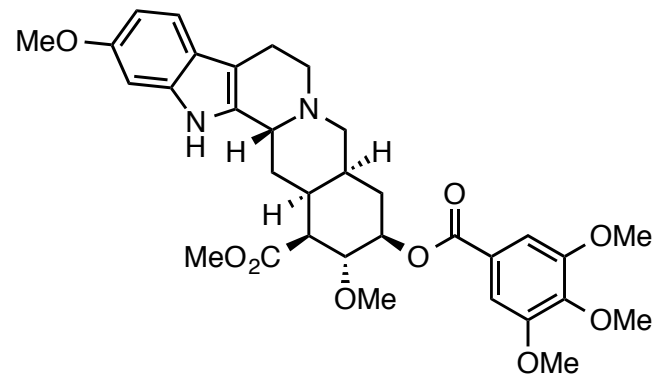


# Total Synthesis of the Reserpine

R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, R. W. Kierstead, *J. Am. Chem. Soc.* **1956**, *78*, 2023–2025.

R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, R. W. Kierstead, *Tetrahedron* **1958**, *2*, 1–57.



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Journal Club

Valentin Soulard - Group Renaud  
November, 19 2015

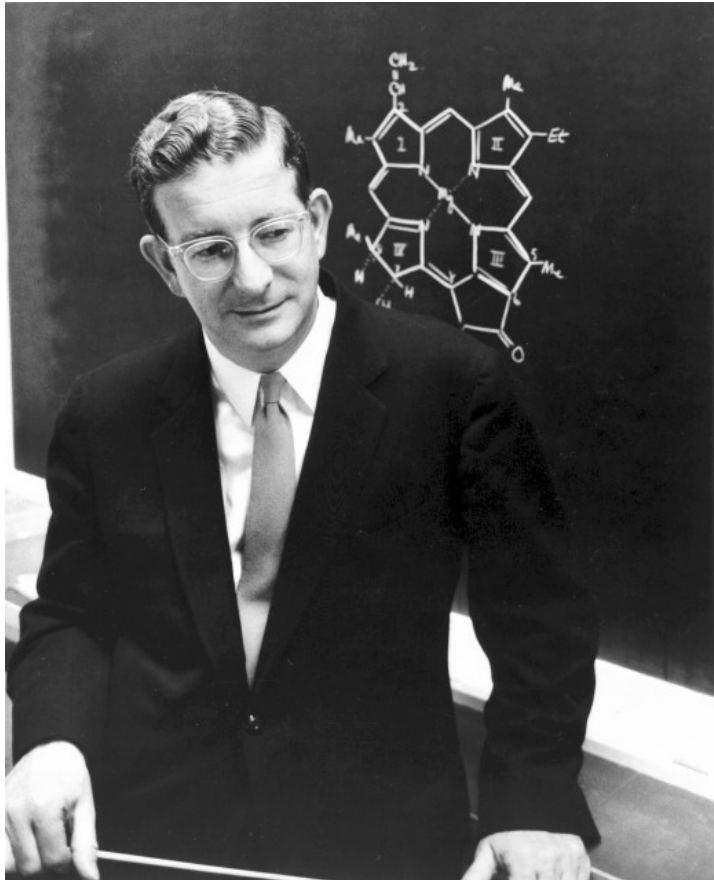
*u*<sup>b</sup>

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<sup>b</sup>  
UNIVERSITÄT  
BERN

# Robert Burns Woodward

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Born in 1917 - Boston, Massachusetts, USA

Attracted to chemistry at a very early age

1934 : Excluded from the MIT for negligence of his formal study

1936 : Bachelor degreee – MIT

1937 : PhD (James Flack Norris and Avery Adrian Morton) – MIT

1938 : Post-doctoral Fellow (Harvard) and then remained at Havard for the rest of his life

Died in 1979 (Heart Attack)

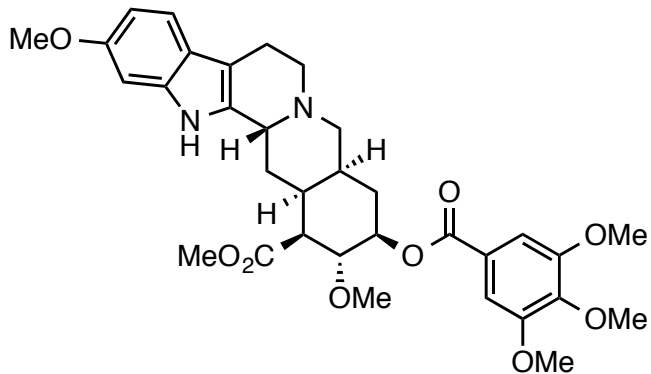
## Woodward's Era

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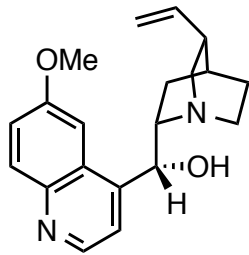
- > Work on the elucidation of the structure of natural products by UV spectroscopy
- > Main Area of research was the total synthesis of natural product.
- > Before his quinine synthesis, organic synthesis was still largely a matter of trial and error, and nobody thought that such complex structures could actually be constructed

# Woodward's Era

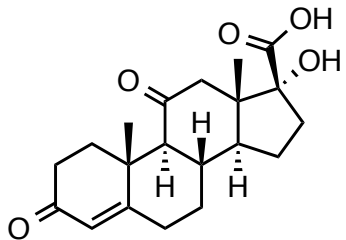
Nobel Prize in Chemistry in 1965  
Woodward-Hoffman rules



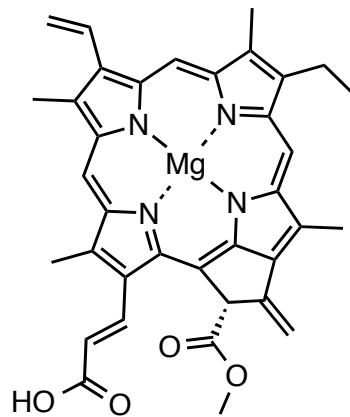
Reserpine



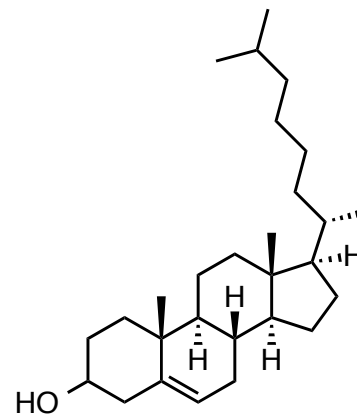
Quinine



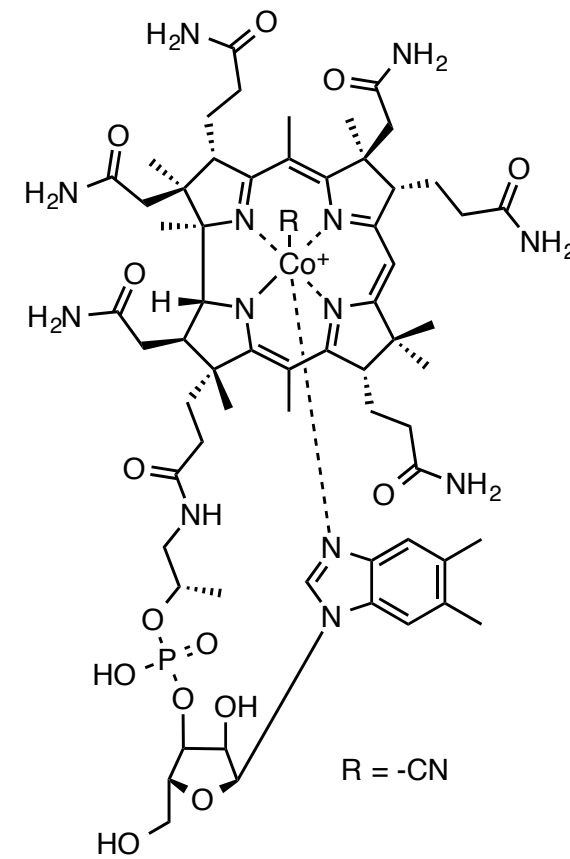
Cortisone



Chlorophyll



Cholesterol



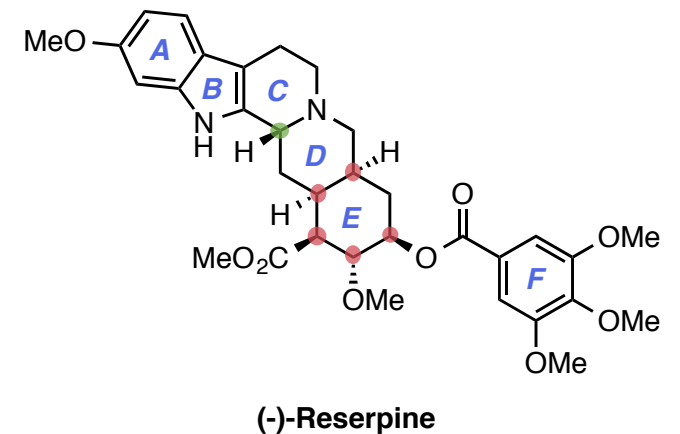
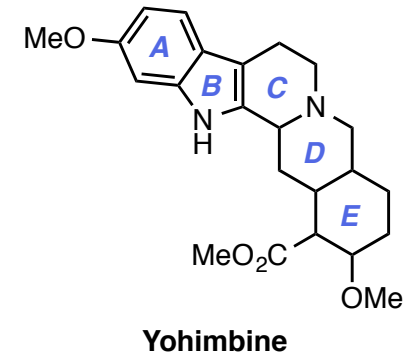
Vitamin B<sub>12</sub>

And the strychnine, lysergic acid, cephalosporin, colchicine ....

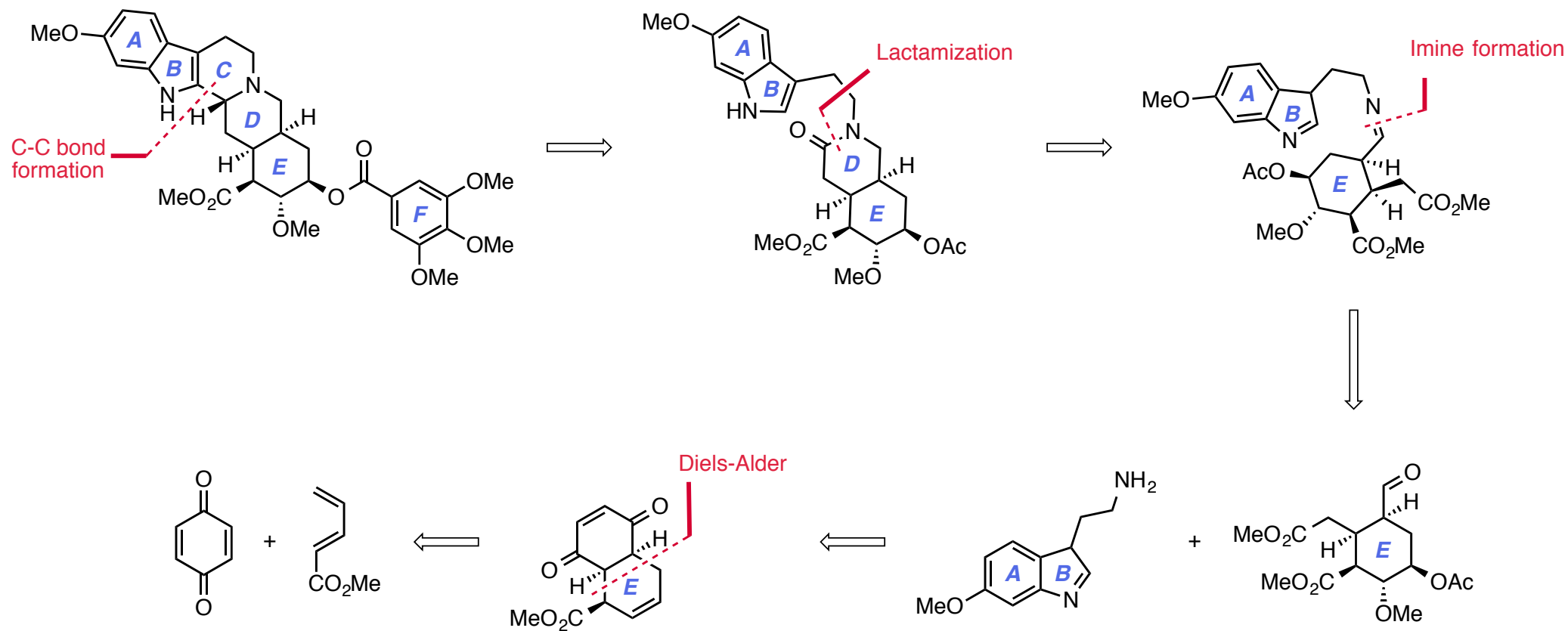
# (-)-Reserpine

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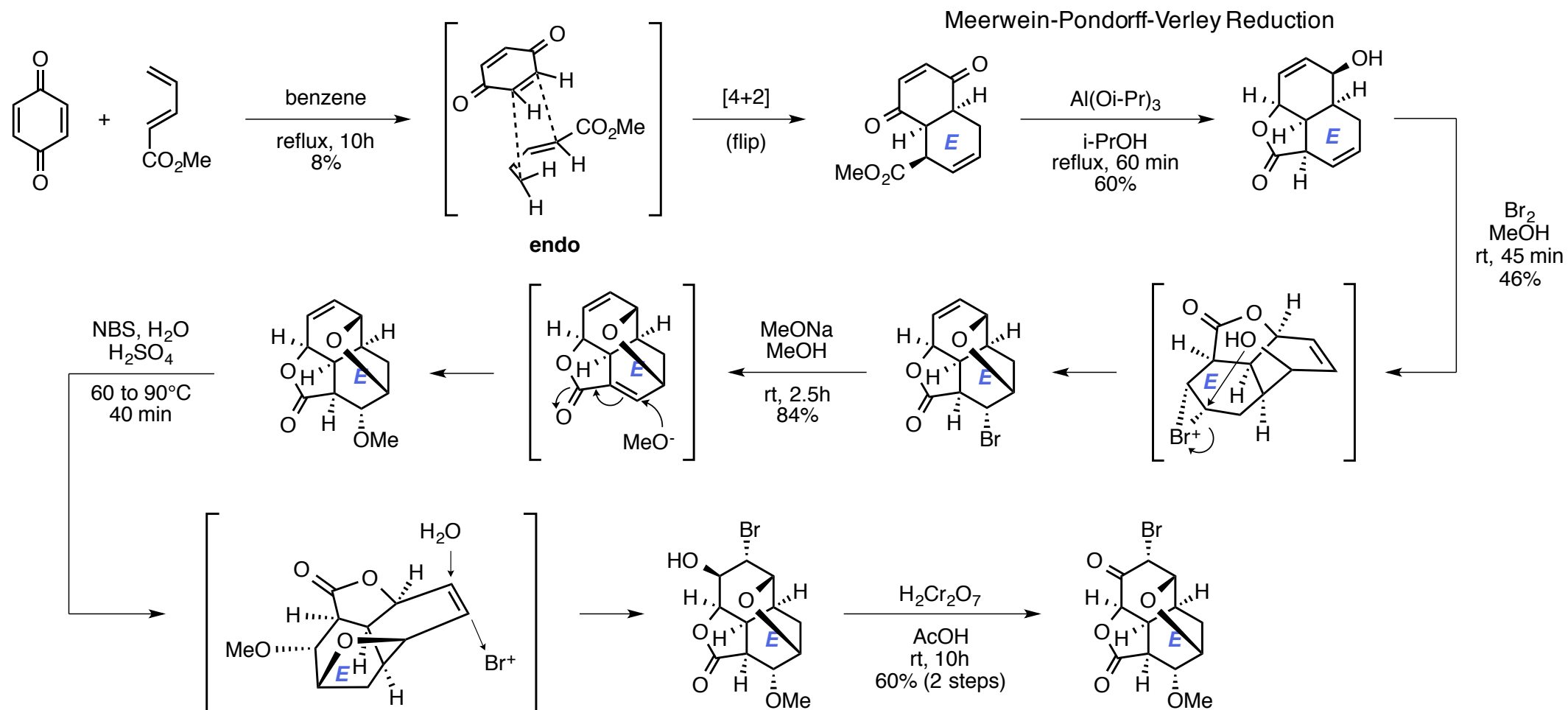
- > First isolated in 1952 by Schlittler et al. from *Rauwolfia serpentina*
- > The absolute configuration was found in 1955
- > In the class of yohimbine (alkaloid)
- > Use as a treatment of hypertensive nervous and mental disorder
- > 5 contiguous stereocenter in the E ring
- > Epimerization possible at C3



# Retrosynthetic Analysis

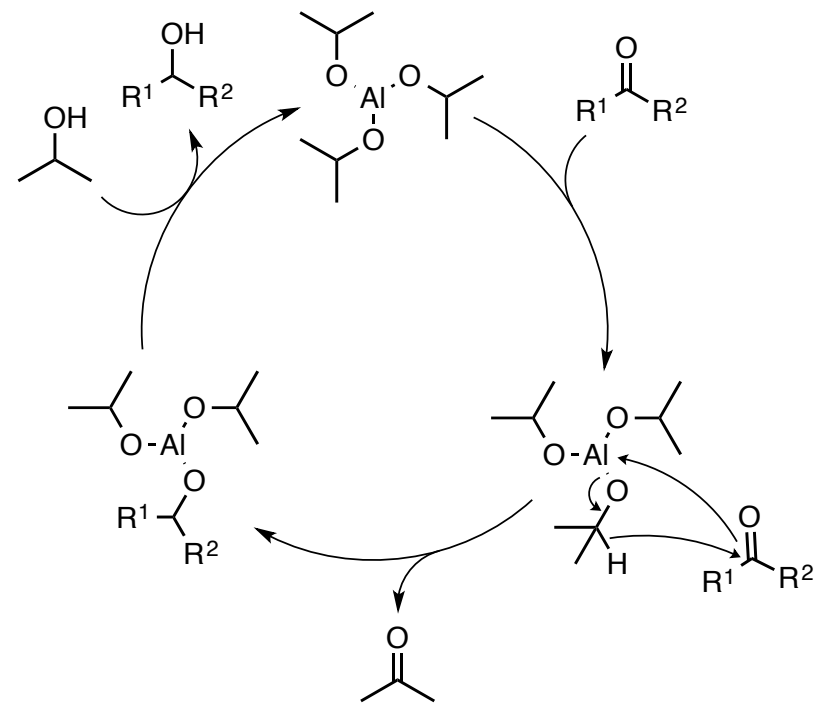
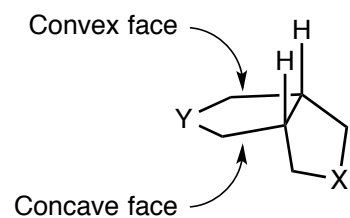
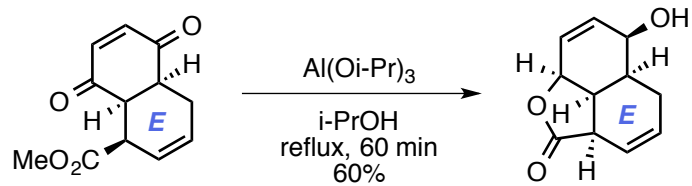


# Ring E synthesis



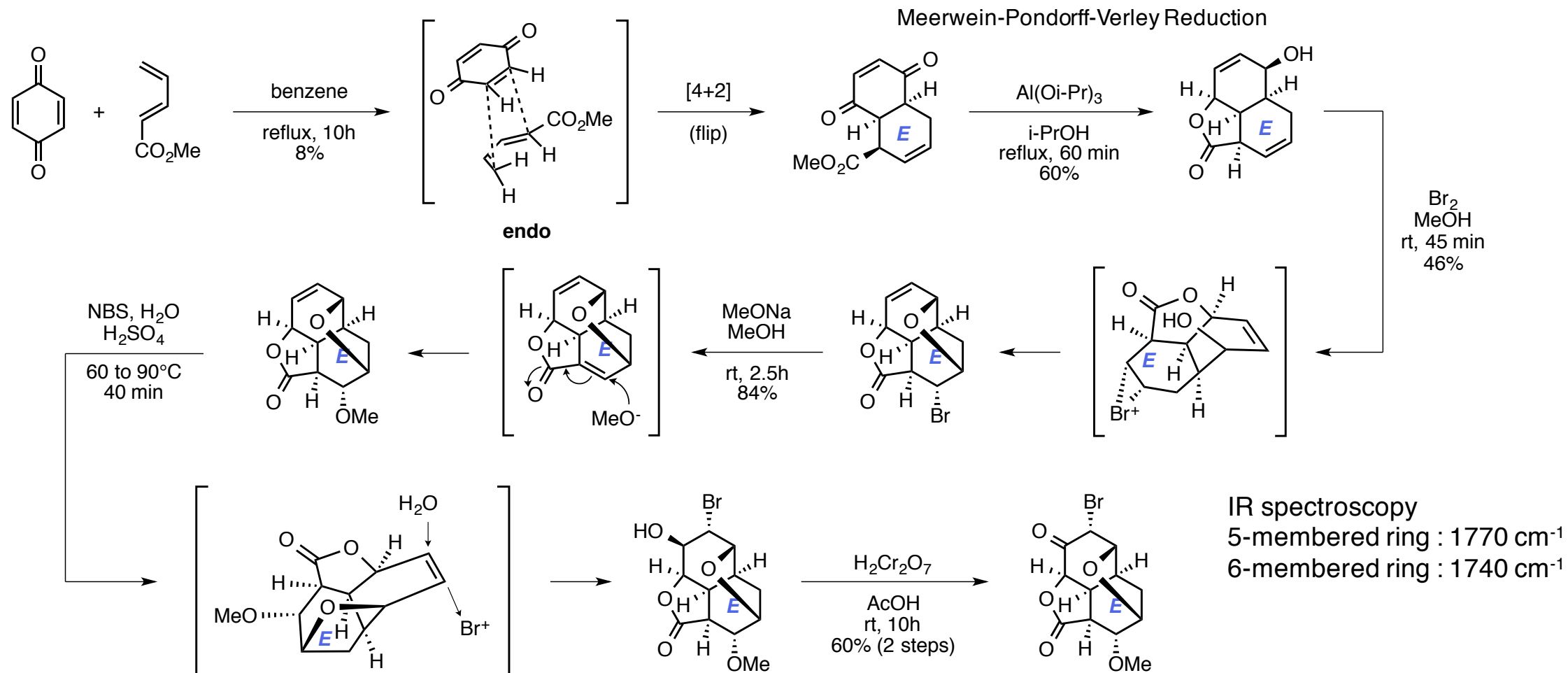
R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, R. W. Kierstead, *J. Am. Chem. Soc.* **1956**, *78*, 2657–2657.

# Meerwein-Ponndorff-Verley Reduction



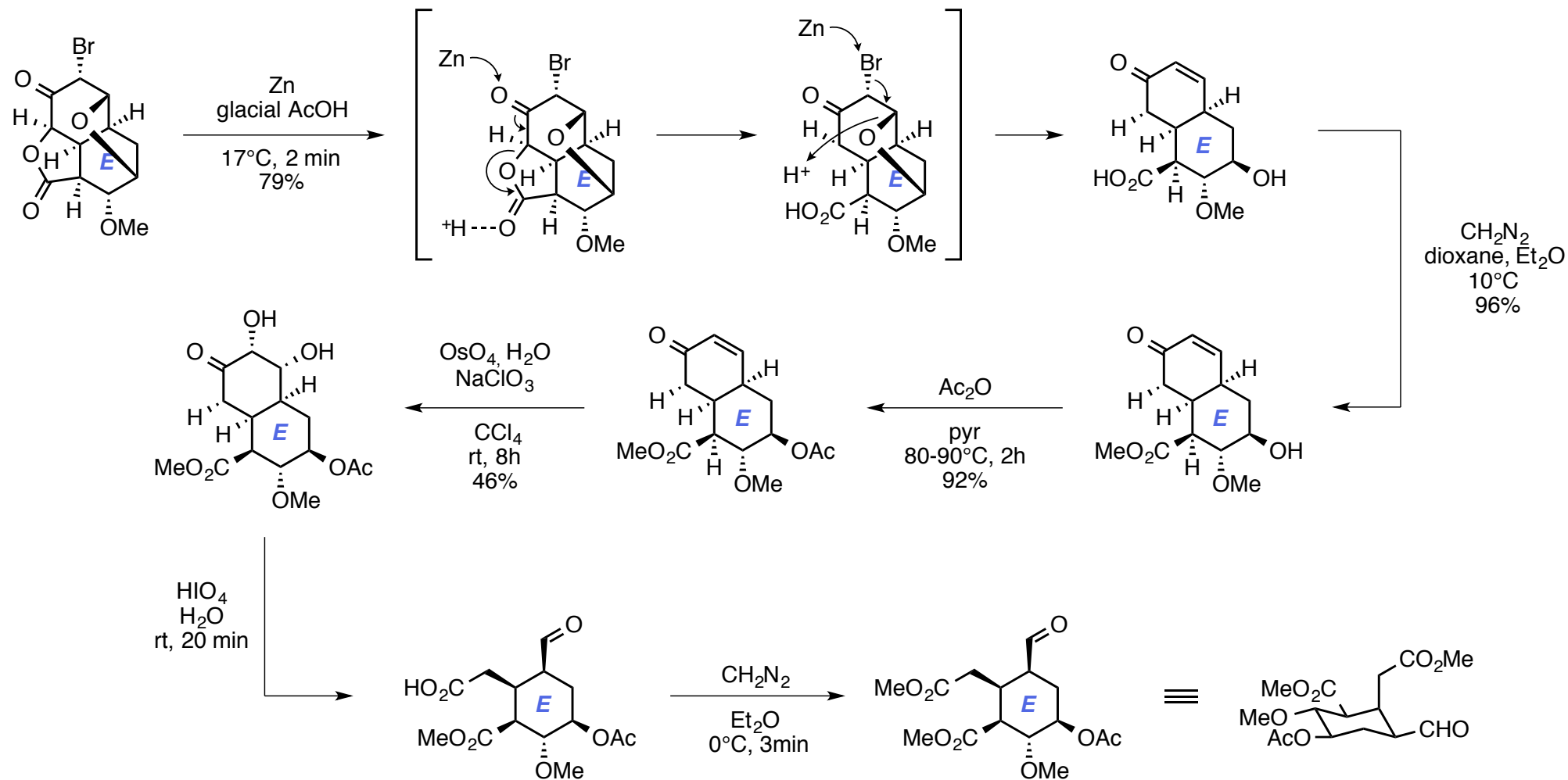


# Ring E synthesis

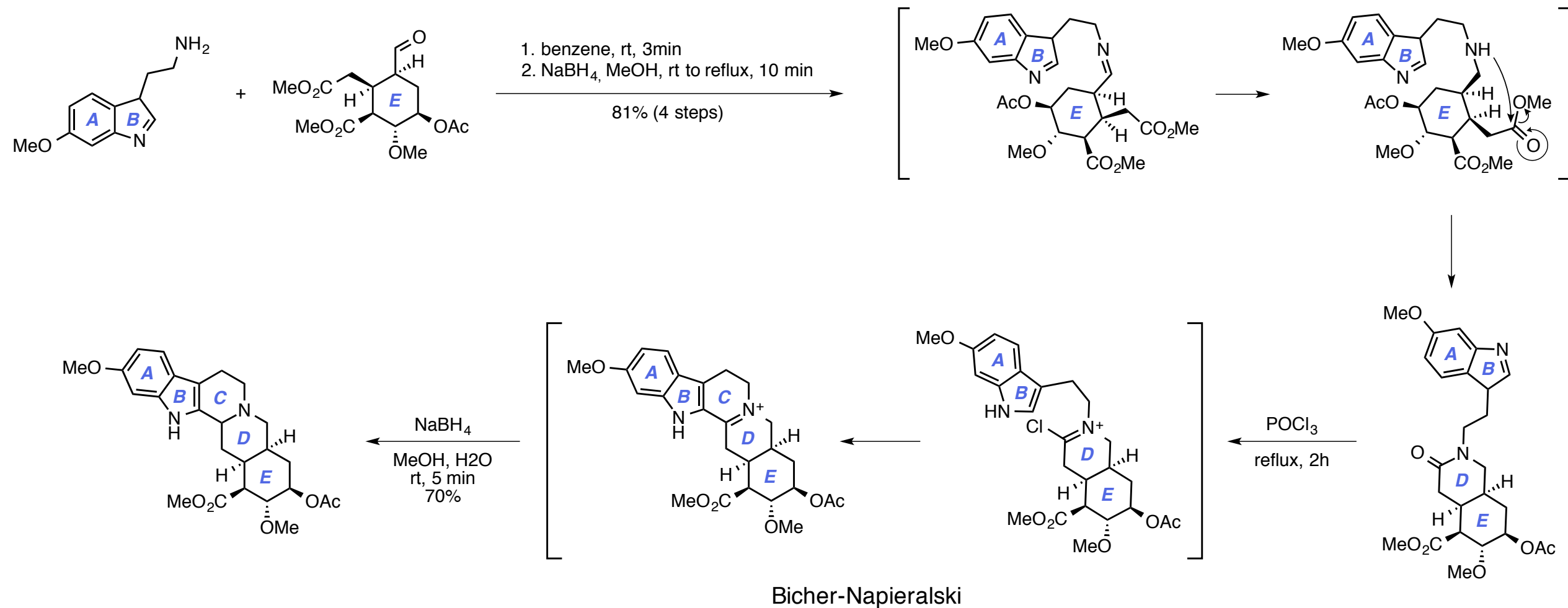


R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, R. W. Kierstead, *J. Am. Chem. Soc.* **1956**, *78*, 2657–2657.

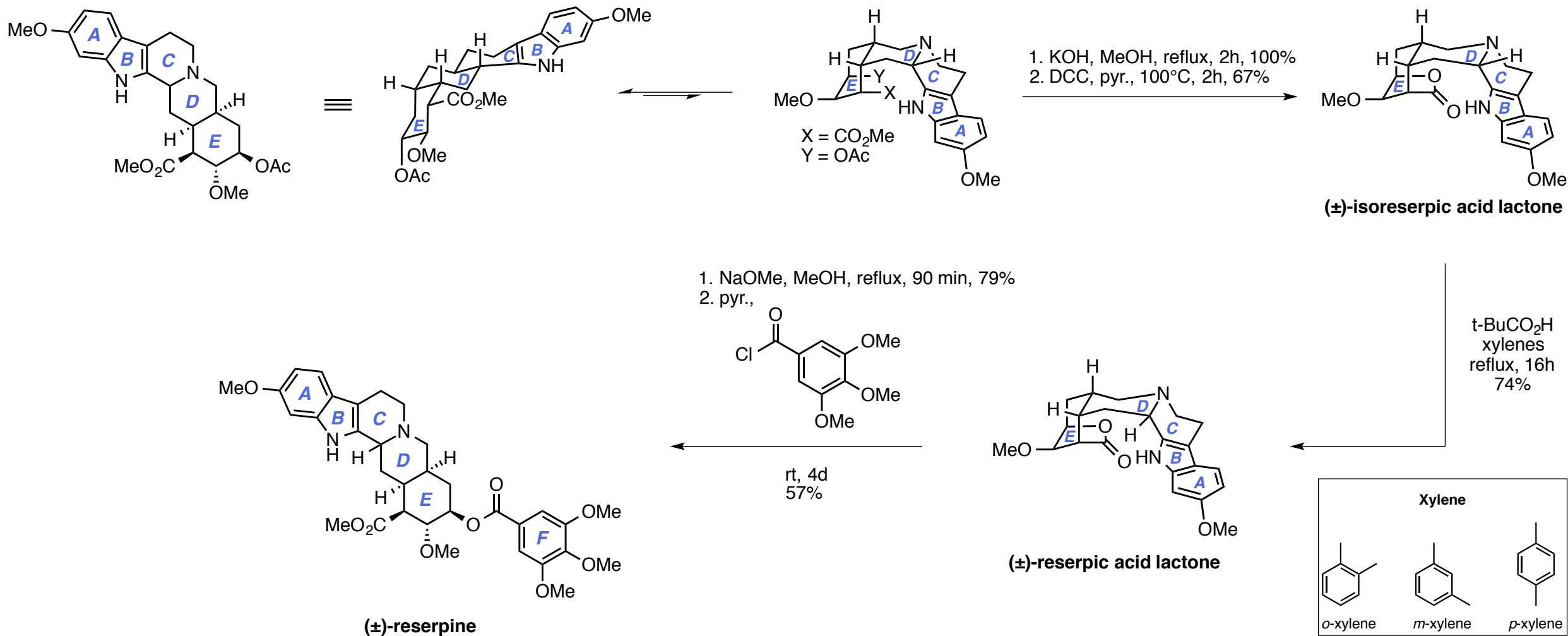
# Ring E synthesis



# Ring C and D synthesis

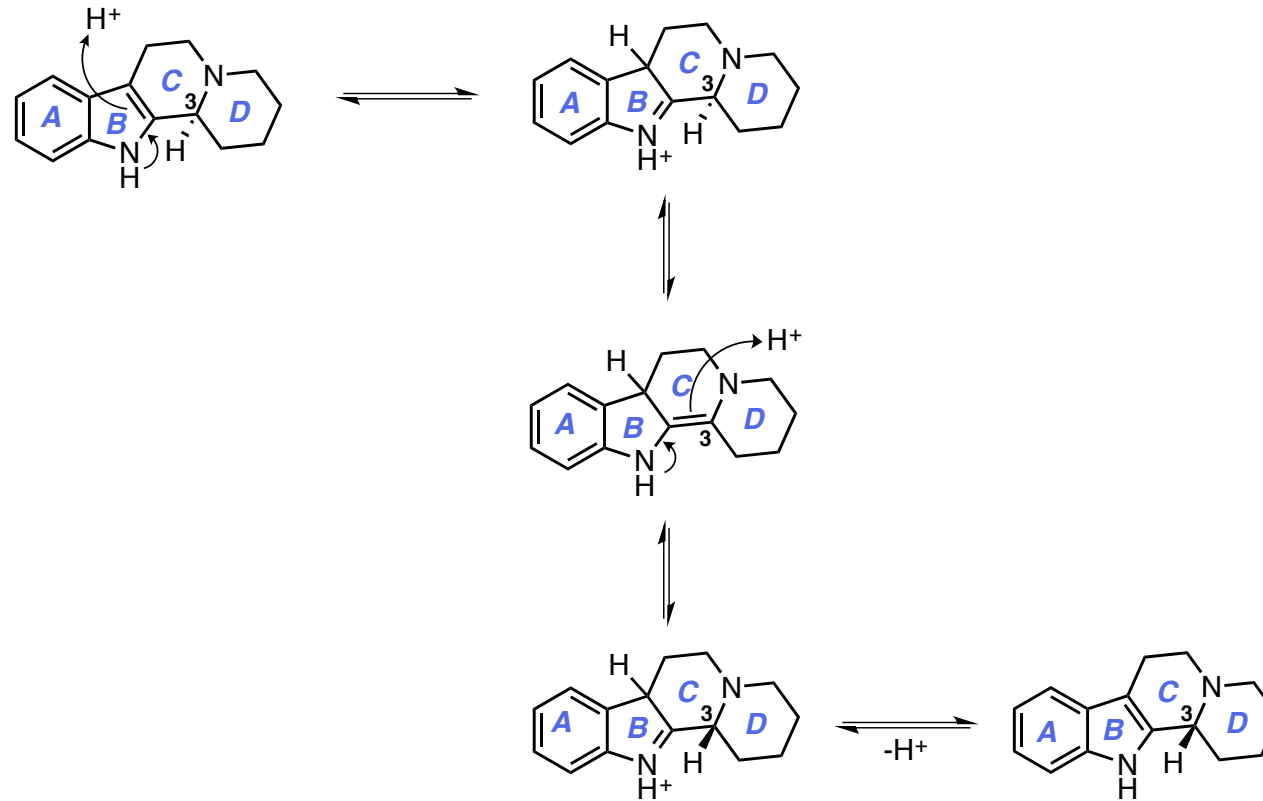


# Total Synthesis of (±)-Reserpine

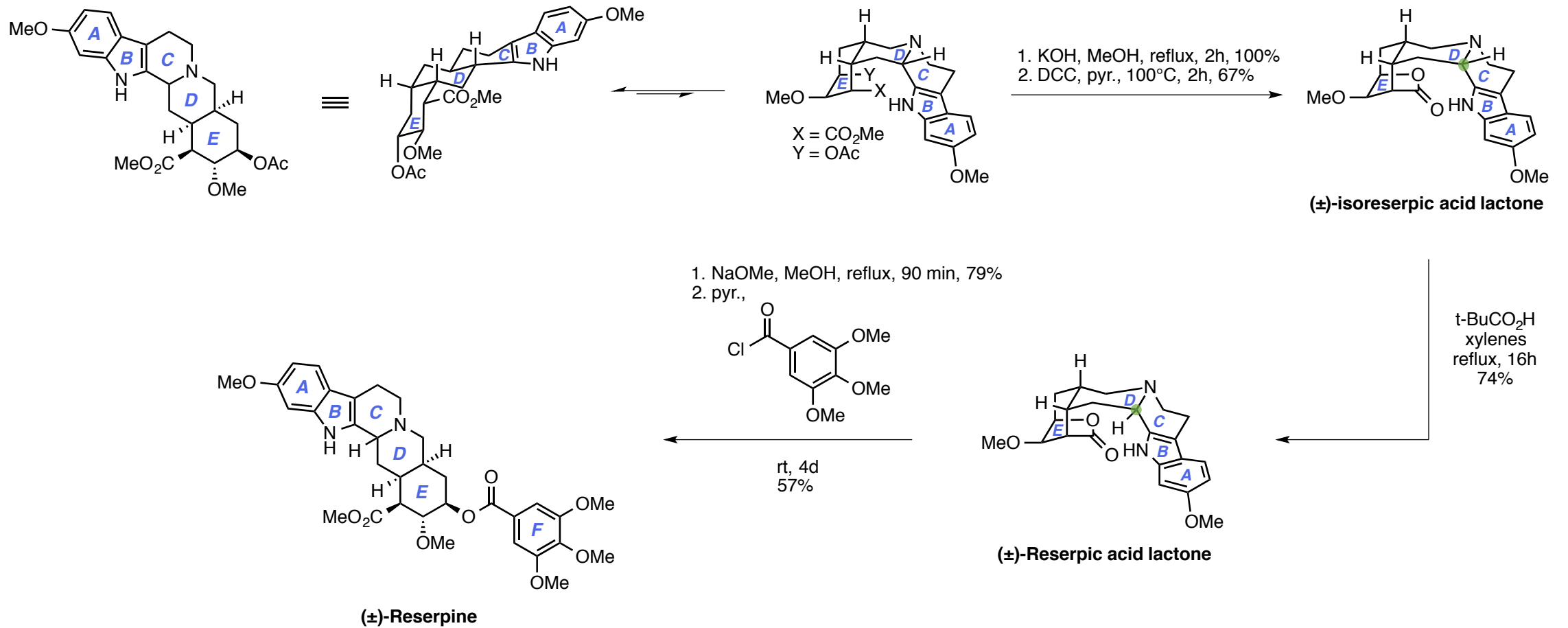


# Epimerization at C3

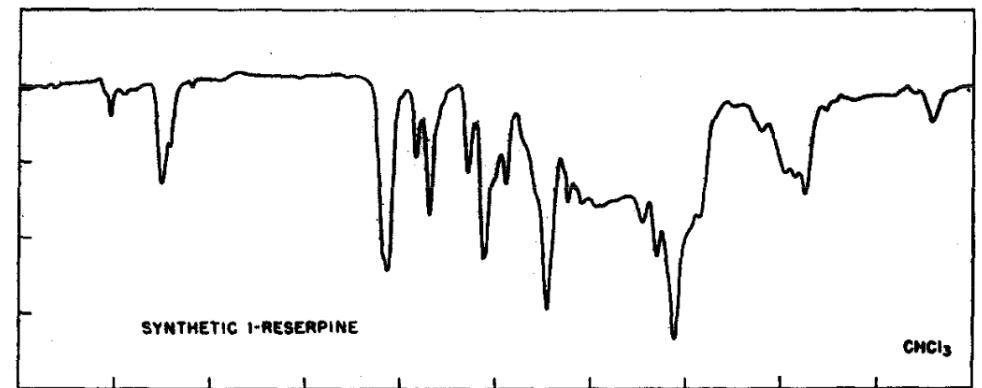
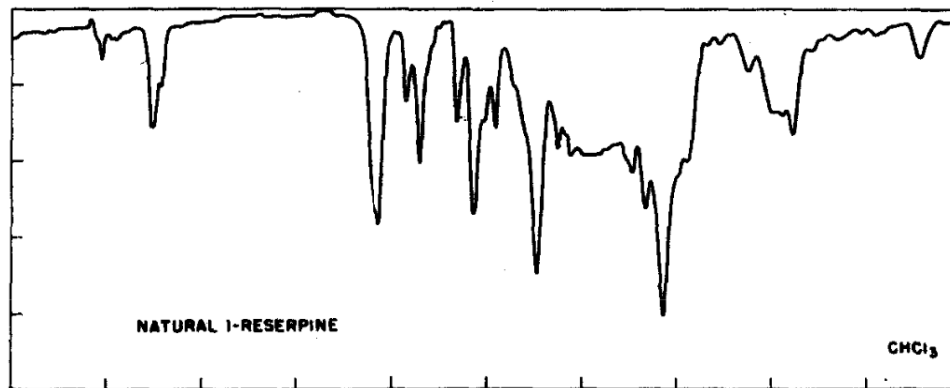
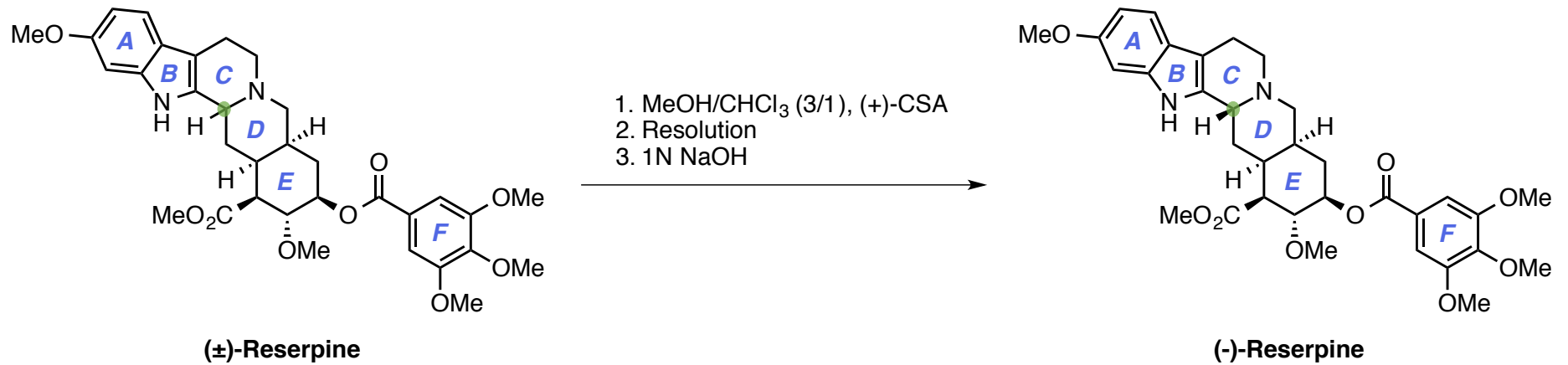
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# Total Synthesis of (±)-Reserpine



# Chiral Resolution of ( $\pm$ )-Reserpine to (-)-Reserpine



# Conclusion

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- > Highly functionalized 6 members ring performed by a Diels-Alder reaction
- > Epimerization under acidic condition to generate the good enantiomer
- > Performed only with IR and elemental analysis were used as guides.
- > Described as one of Woodward's greatest contribution to organic synthesis.

“It is sometimes said that you have demonstrated that nothing is impossible in organic synthesis. This is perhaps a slight exaggeration. You have, however, in a spectacular way expanded and enlarged the domain of the possible.” –A. Fredga: Woodward's Nobel presentation speech (1965).

# Thank you for your attention