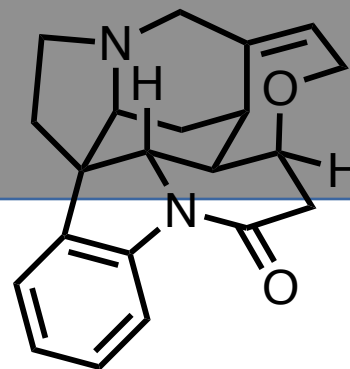


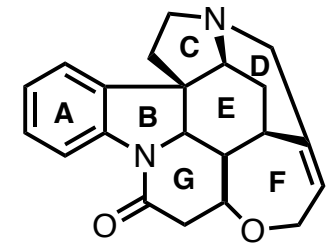
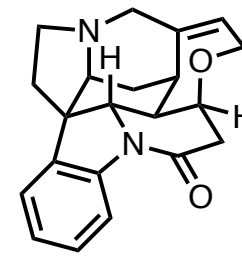
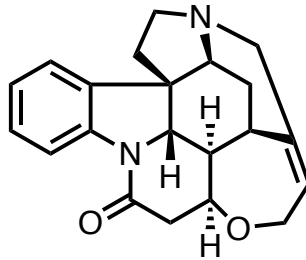
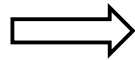
Strychnine: An Anthology



(-)-strychnine

Matt Nelli
27 February 2018
Synthesis Club

Strychnine: A Nasty Alkaloid



(-)-strychnine

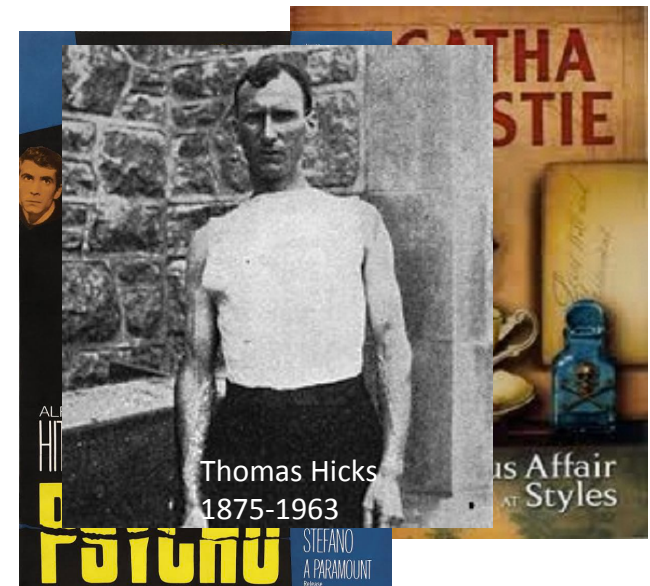
- *Strychnos nux-vomica*
- Also known as: poison nut tree
- Indigenous to India and southeast Asia



Sir Charles Bell, 1809

- Estimated LD_{50} = 15-30 mg/kg oral and 5-10 mg/kg intravenous
- Used as pest control in 16th and 17th Europe

- Onset of seizures after ~15 min, lasting 12-24 hours
- Death comes from cardiac arrest, asphyxiation, or multiple organ failure



The Most Complex Natural Product of It's Time



Pierre-Joseph Pelletier
1788-1842

- Isolated with Et₂O from Ignatius bean (closely related to the Strychnine tree) by Pelletier & Caventou
- Structure was not elucidated at the time

1818

"...for it's molecular size, it is the most complex substance known."

-Sir Robert Robinson, 1952.



Robert Burns Woodward
1917-1979

- First total synthesis completed by Robert Woodward

1954



Joseph Bienaimé Caventou
1795-1877



Sir Robert Robinson
1886-1975

1948

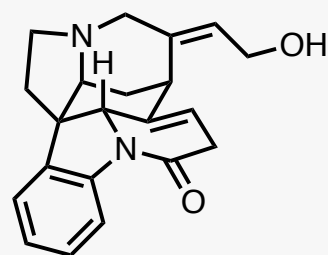
- Structure solved by Robert Woodward using degradative evidence and UV spectroscopy
- Sir Robert Robinson & Friedrich Leuchs led the extensive investigations into determining the structure throughout the early 1900s

- Between Robinson & Leuchs, >300 papers published examining the structure using degradative methods

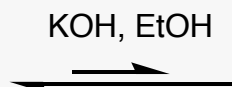
1992

- 40 years until the next synthesis

Woodward Synthesis: Retrosynthetic Analysis

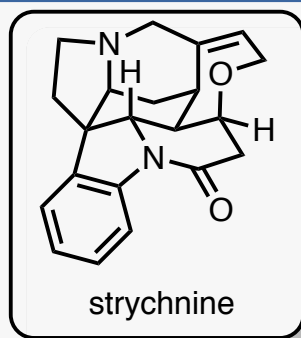


isostrychnine

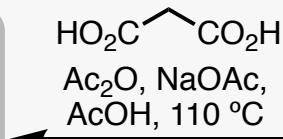


28% yield

Prelog, 1948

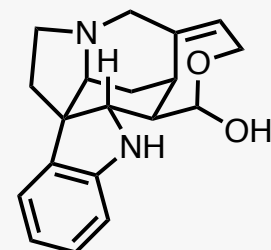


strychnine

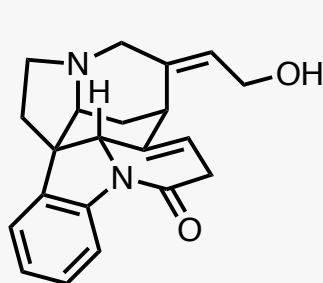


80% yield

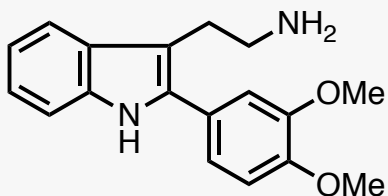
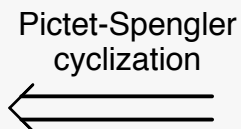
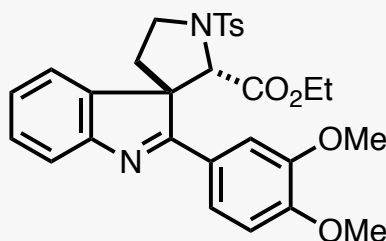
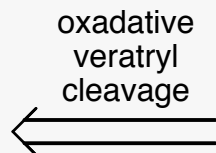
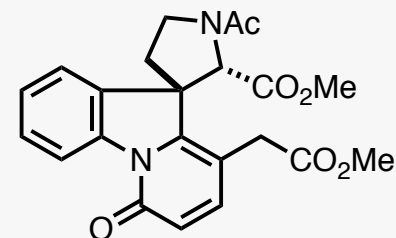
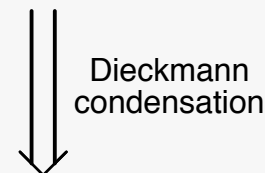
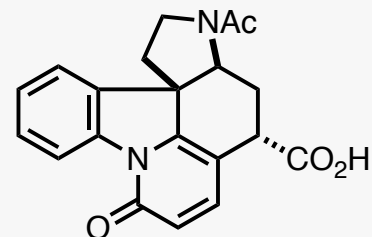
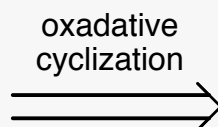
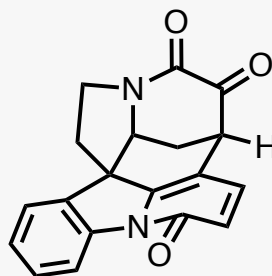
Robinson, 1953



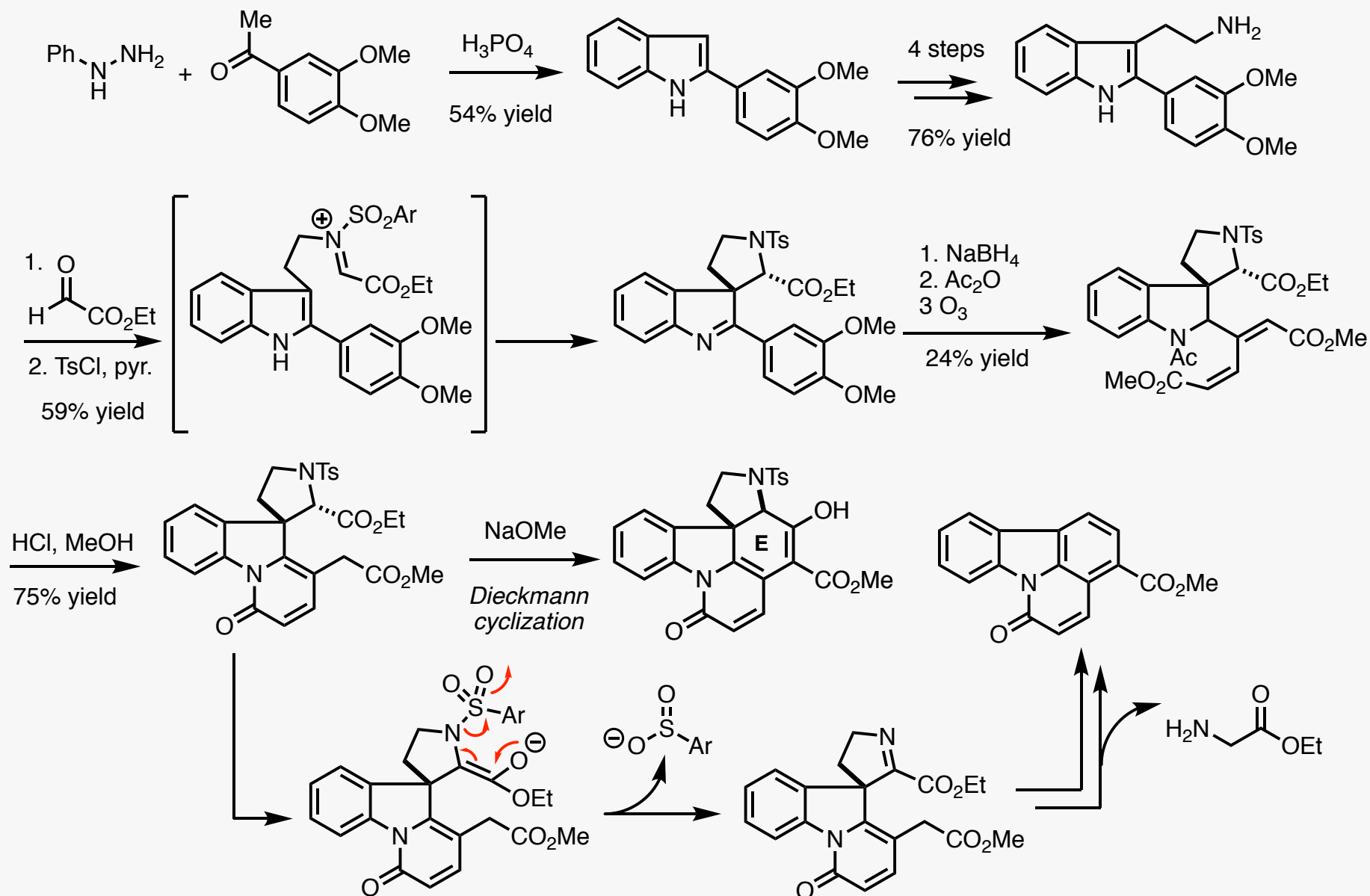
Wieland-Gumlich
aldehyde



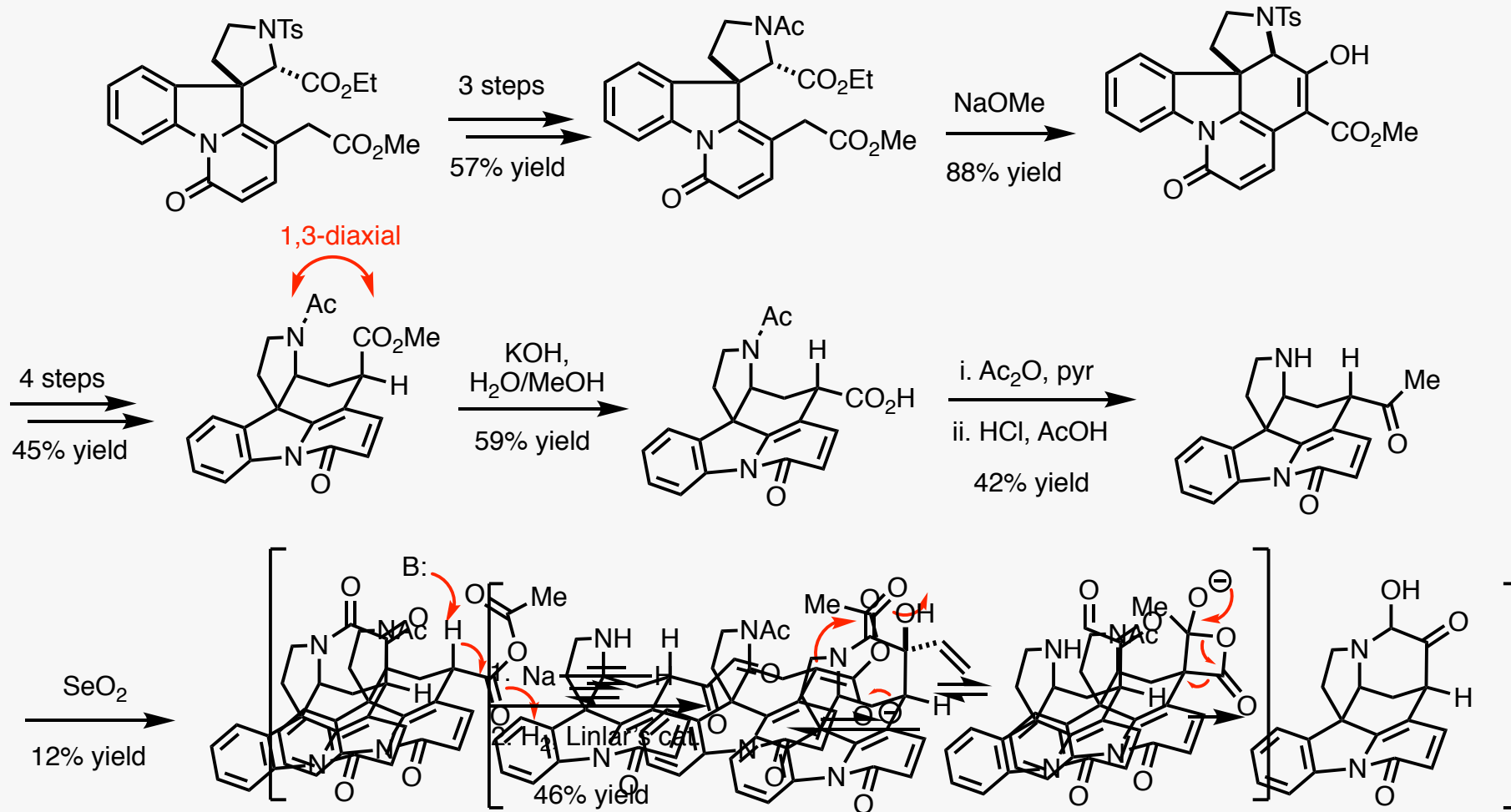
isostrychnine



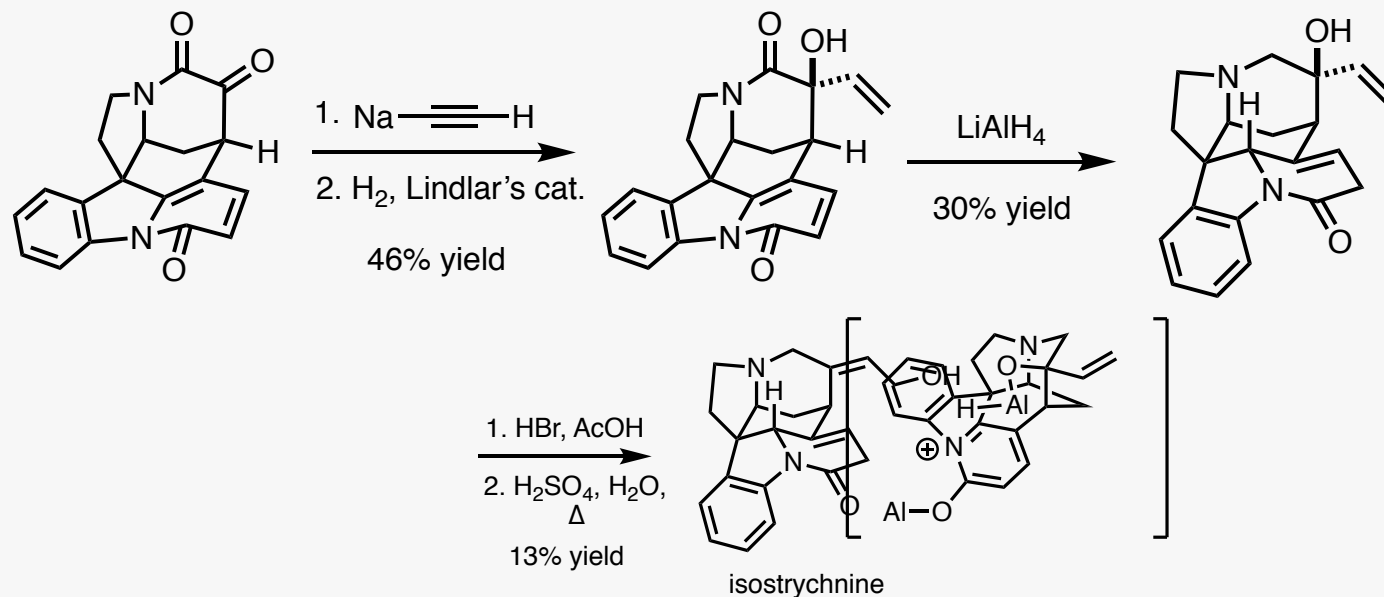
Woodward Synthesis: Rings A-C & G



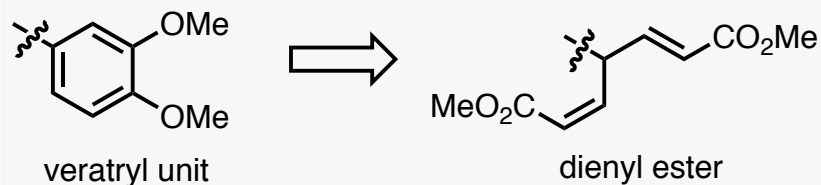
Woodward Synthesis: Rings E & D



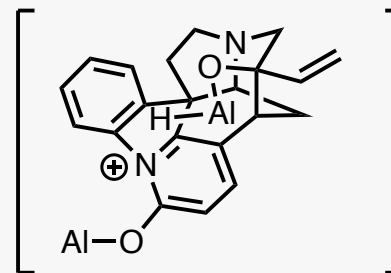
Woodward Synthesis: The End Game



Use of Masking Groups



Intramolecular Delivery of a Reagent



Highlighted Strychnine Syntheses



Larry E. Overman
1945-

**Rawal
1994**



Martin E. Kuehne
1931-2017

**Vanderwal
2011**



David MacMillan
1968-

**Overman
1993**



Viresh H. Rawal
1959-

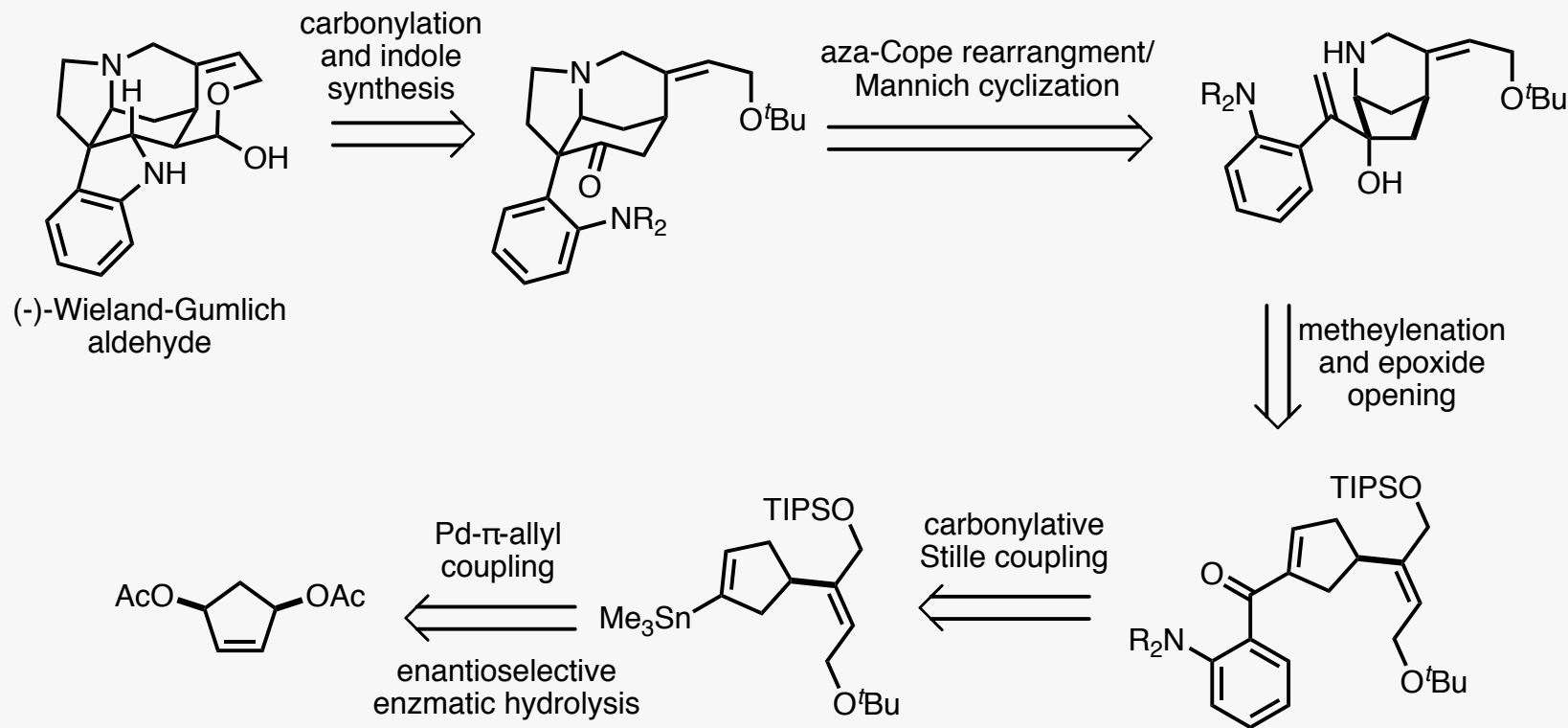
**Kuehne
1998**



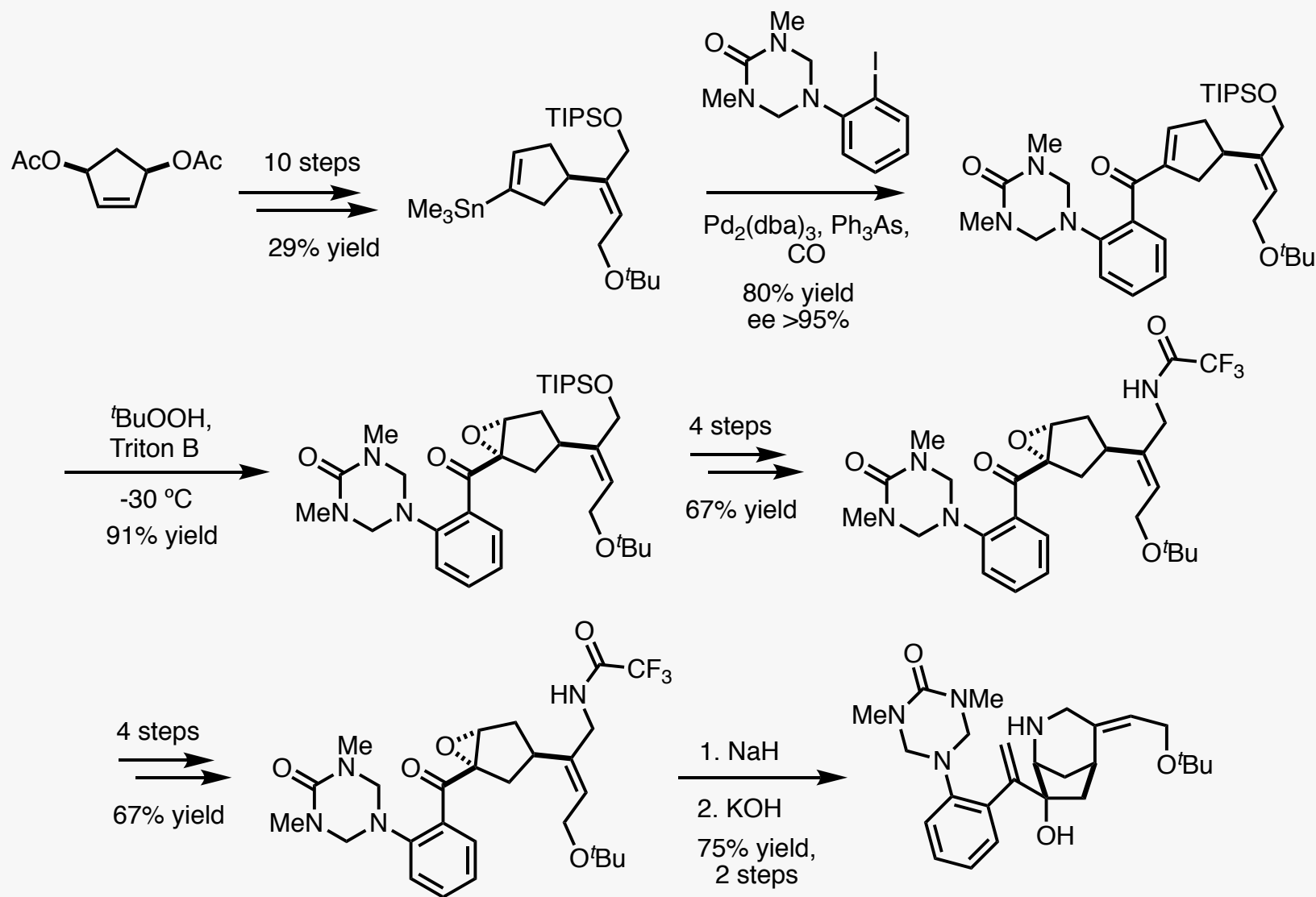
Chris D. Vanderwal
1974-

**MacMillan
2011**

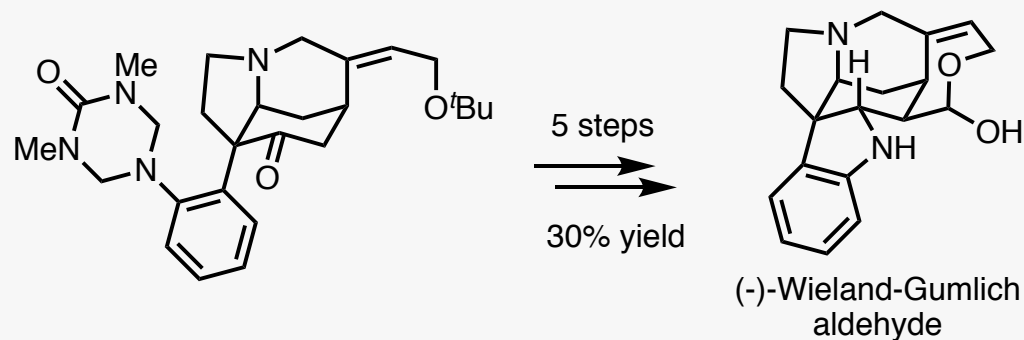
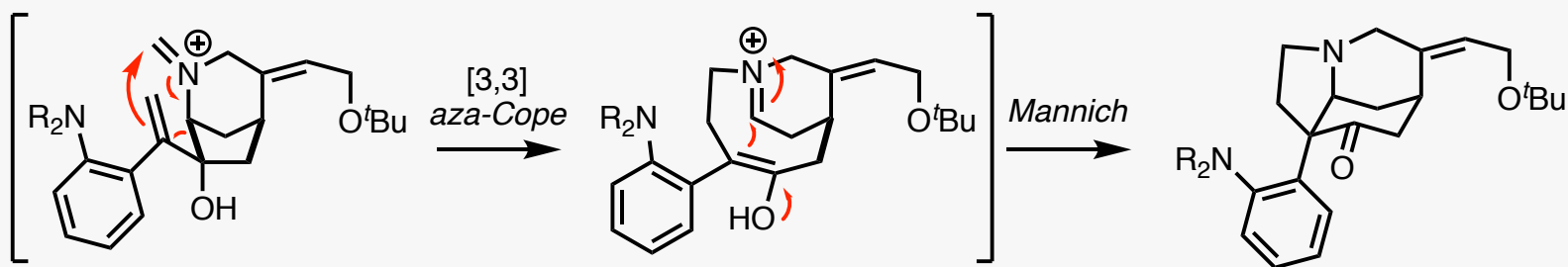
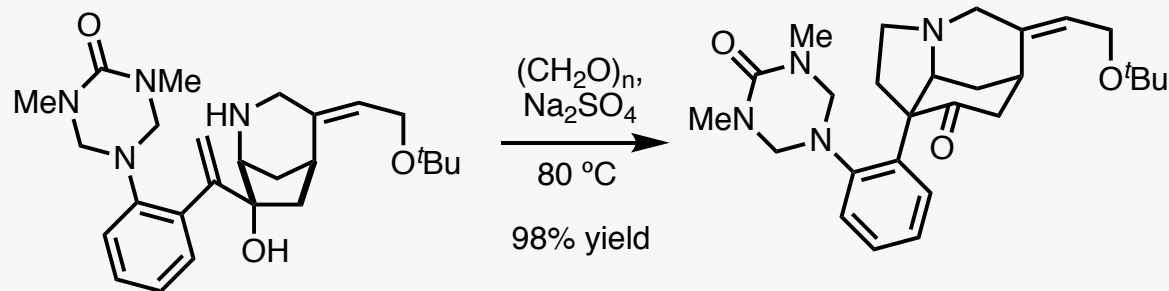
Overman Synthesis: Retrosynthetic Analysis



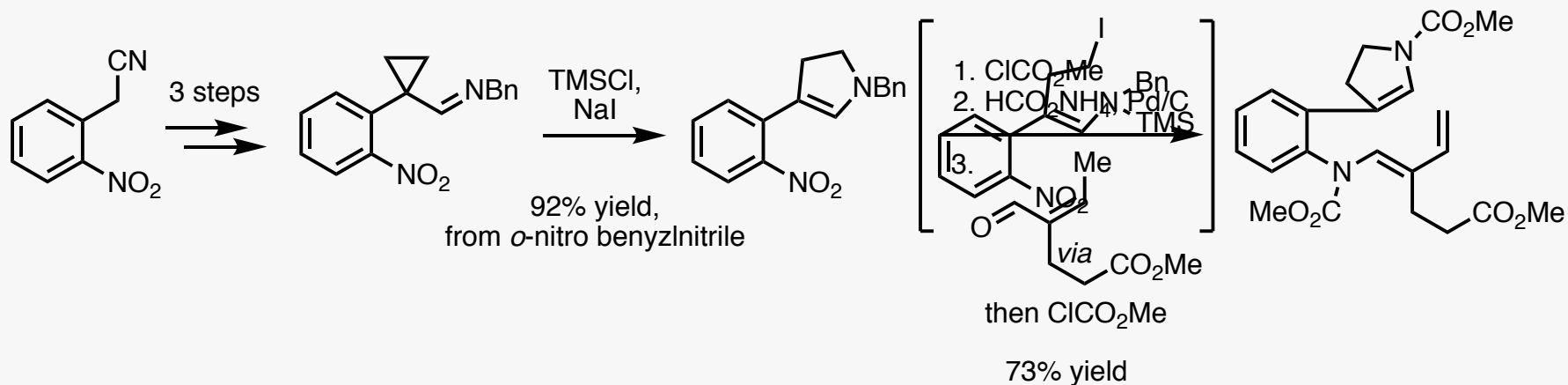
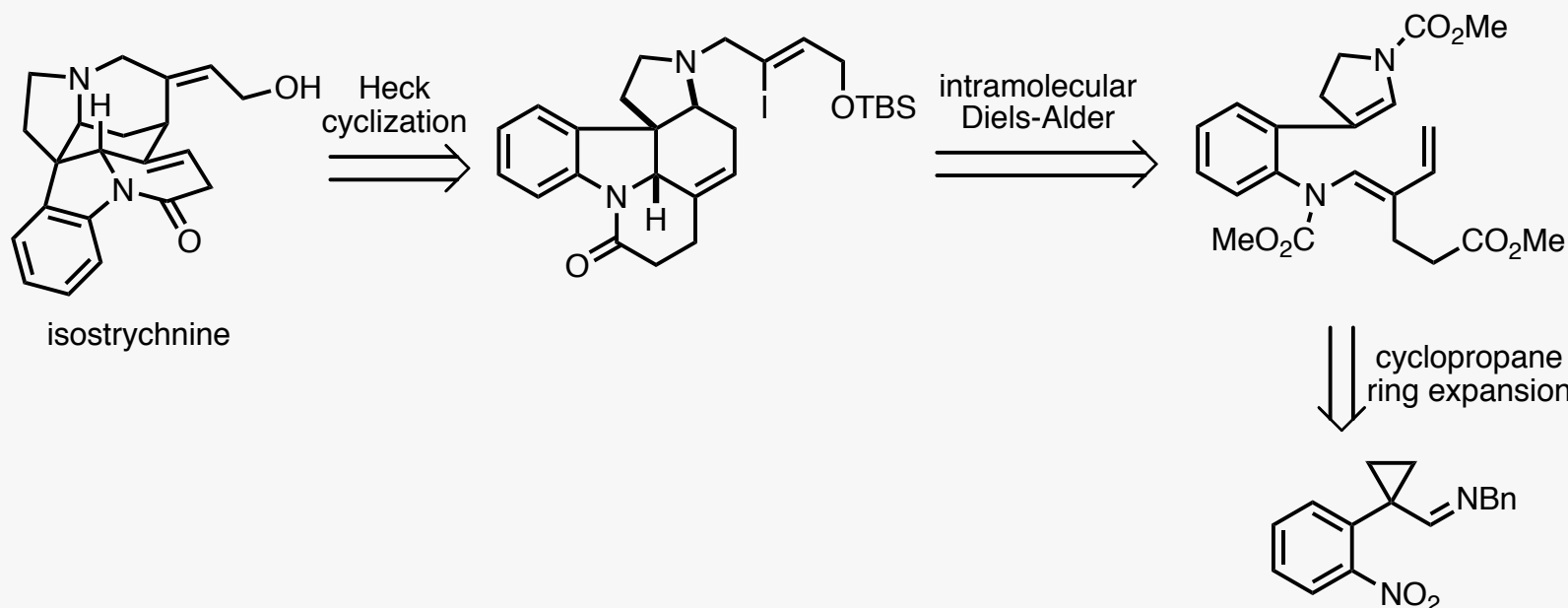
Overman Synthesis: aza-Cope Precursor



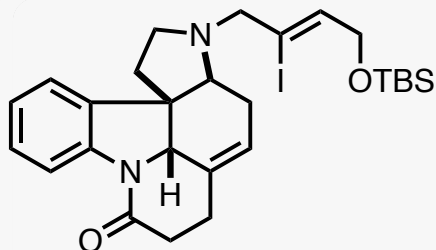
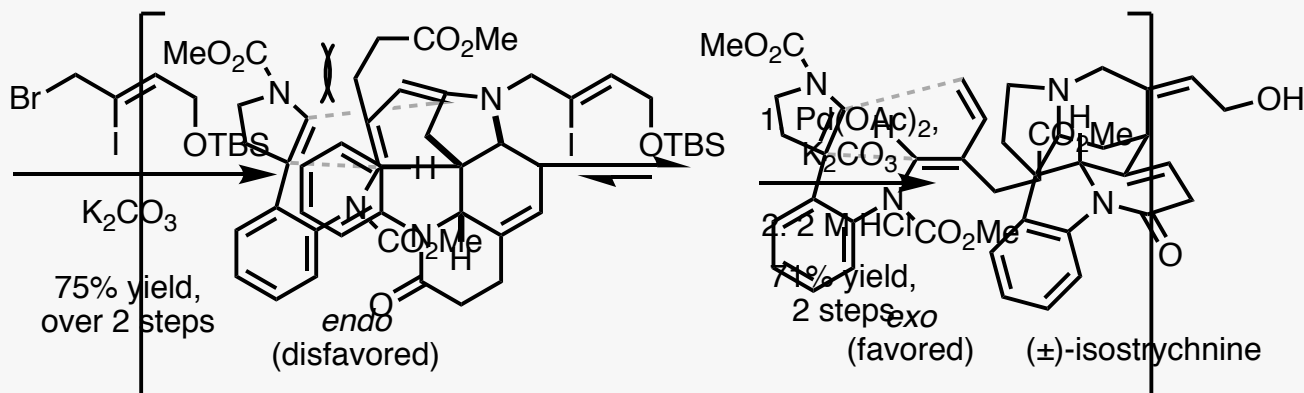
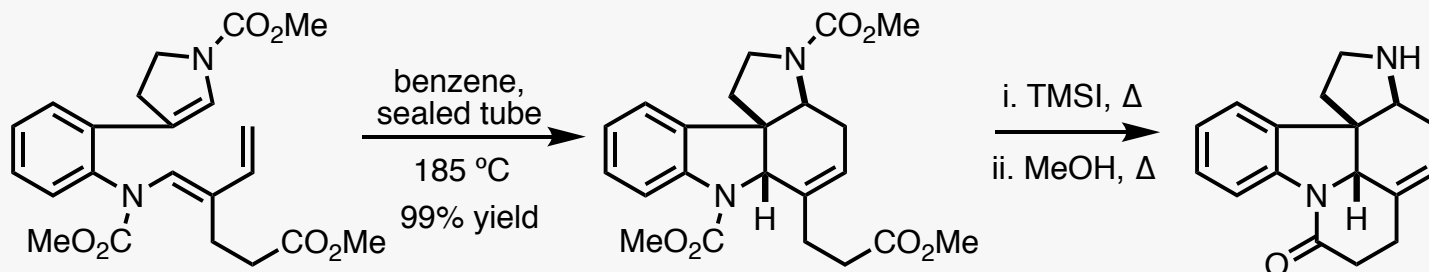
Overman Synthesis: aza-Cope-Mannich Sequence



Rawal Synthesis: Retrosynthetic Analysis



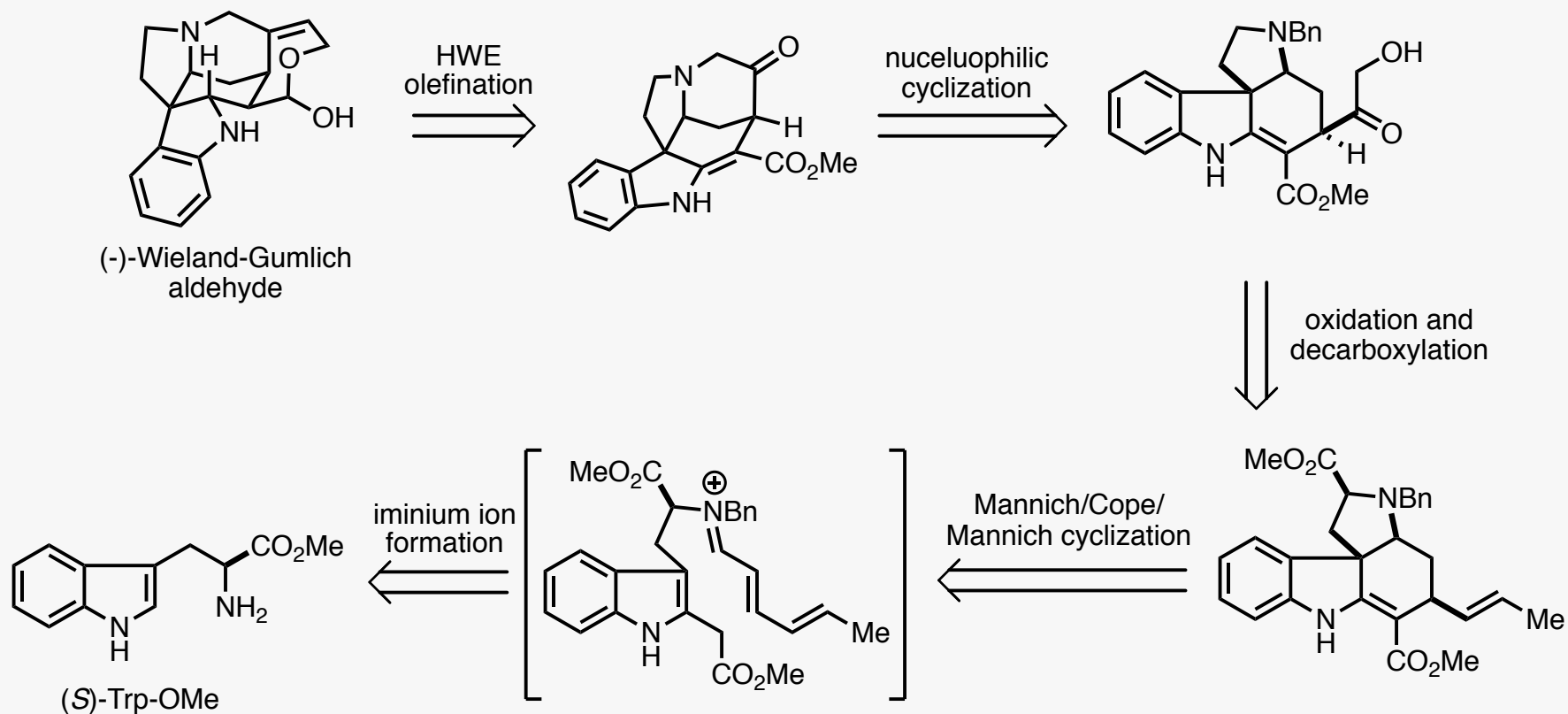
Rawal Synthesis: Diels-Alder & Heck Cyclization



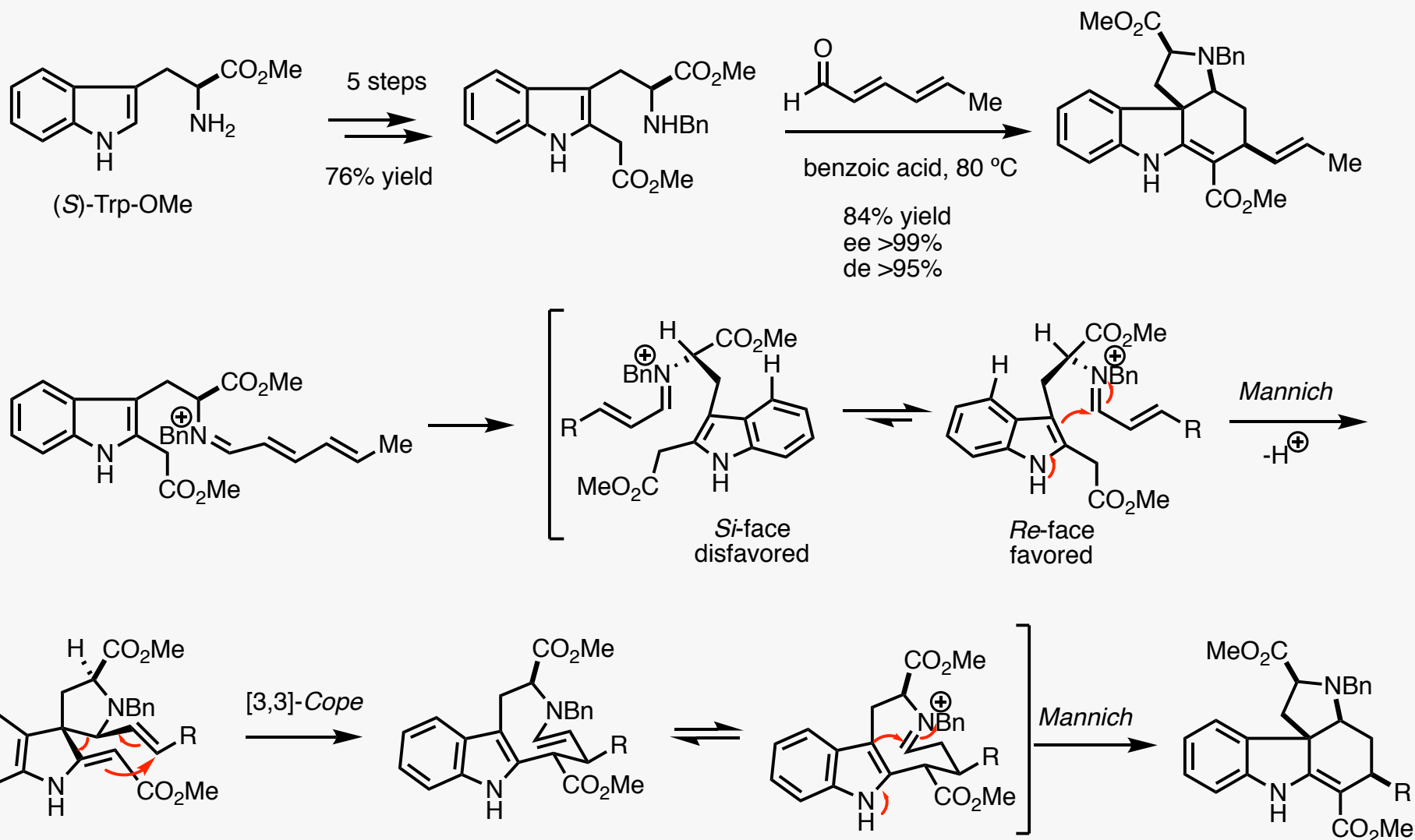
Rawal's Intermediate

Intermediate for several formal strychnine syntheses

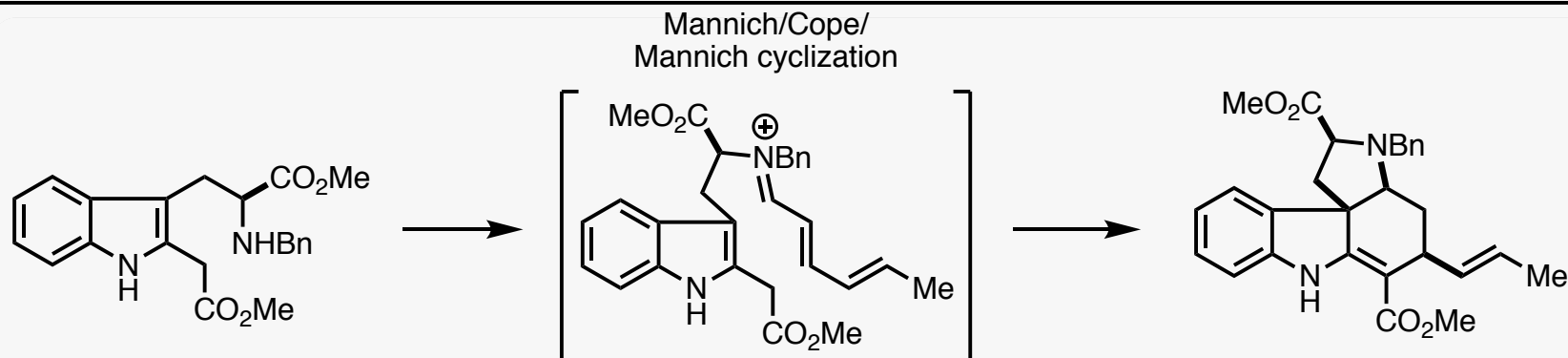
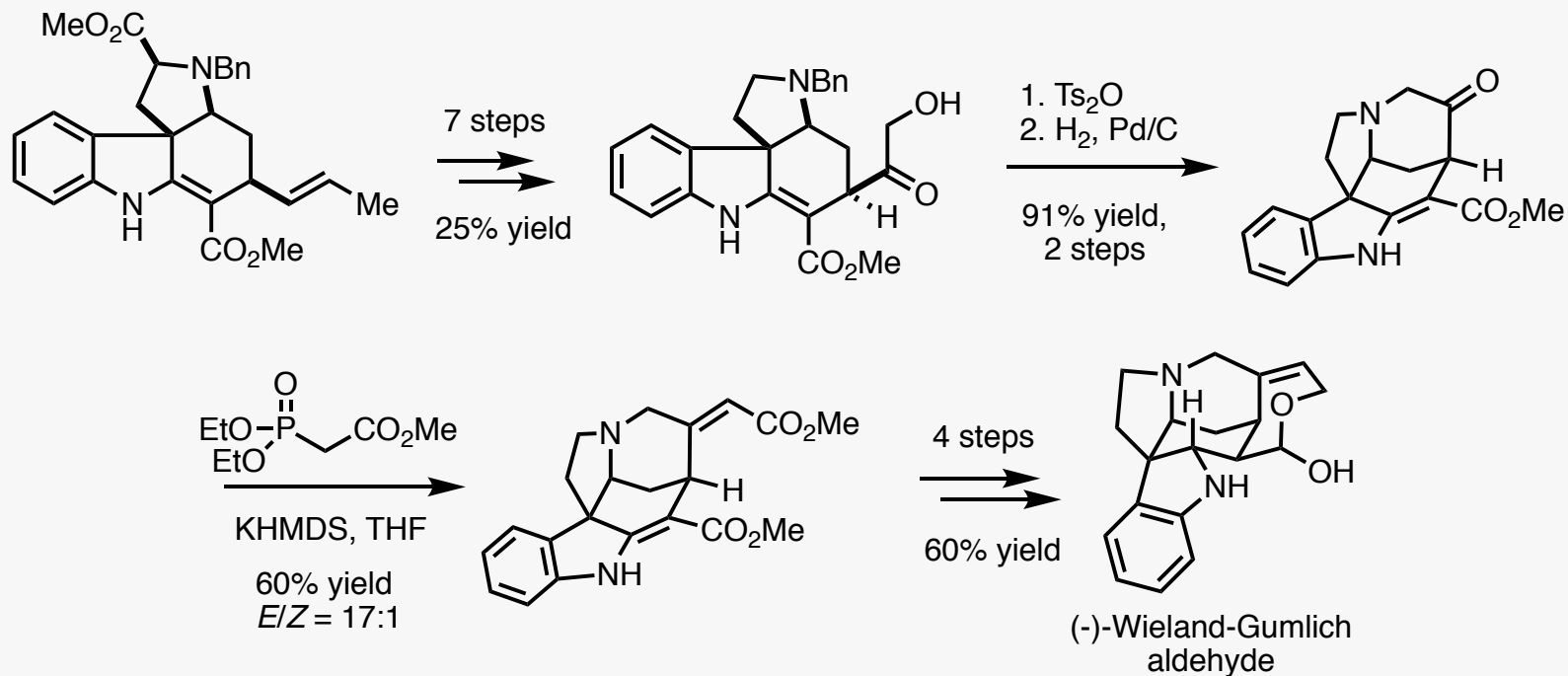
Kuehne Synthesis: Retrosynthetic Analysis



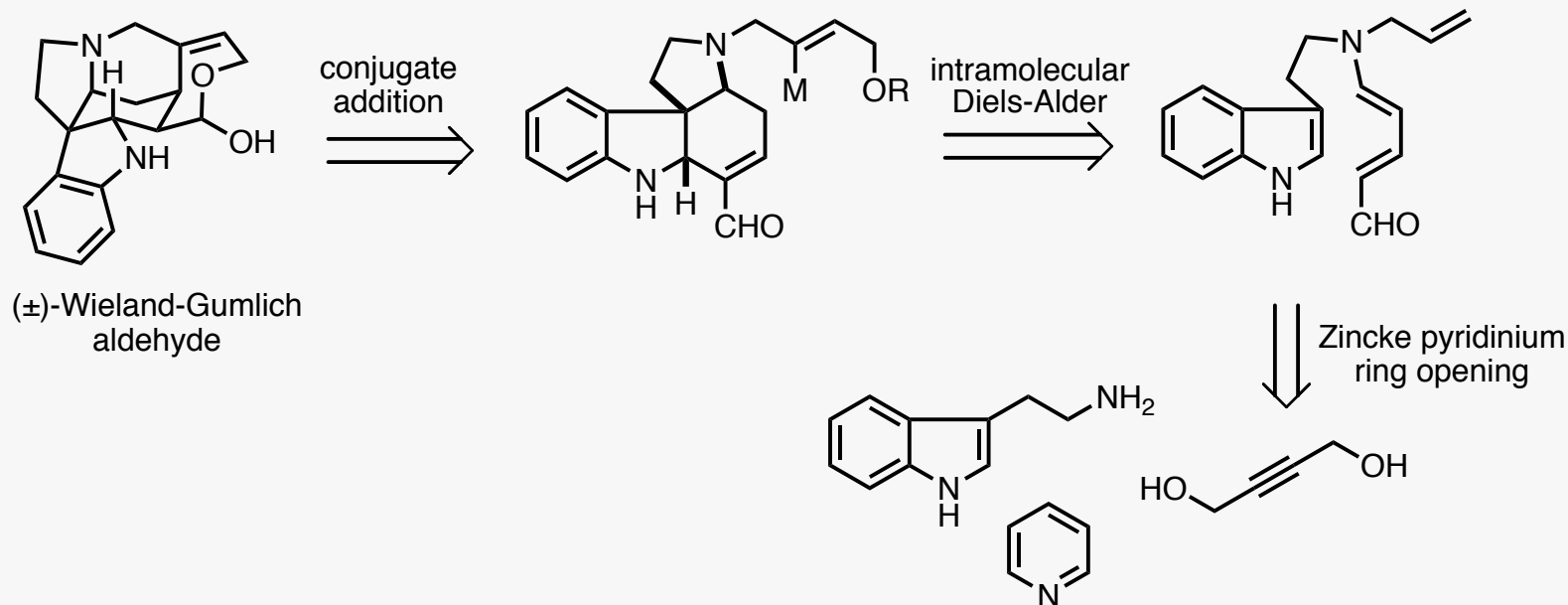
Kuehne Synthesis: Mannich/Cope/Mannich Sequence



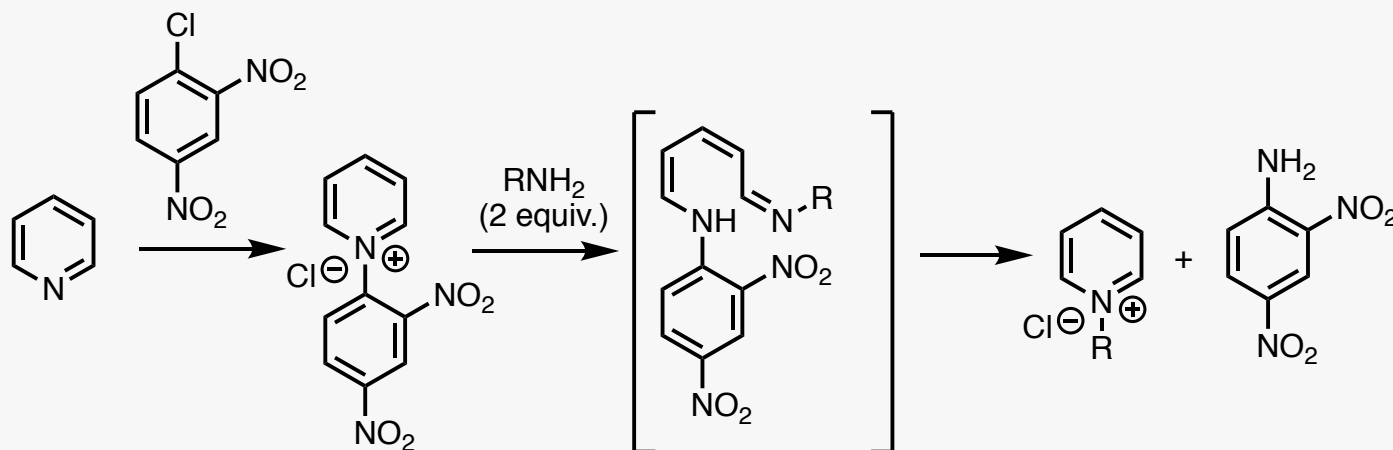
Kuehne Synthesis: End Game



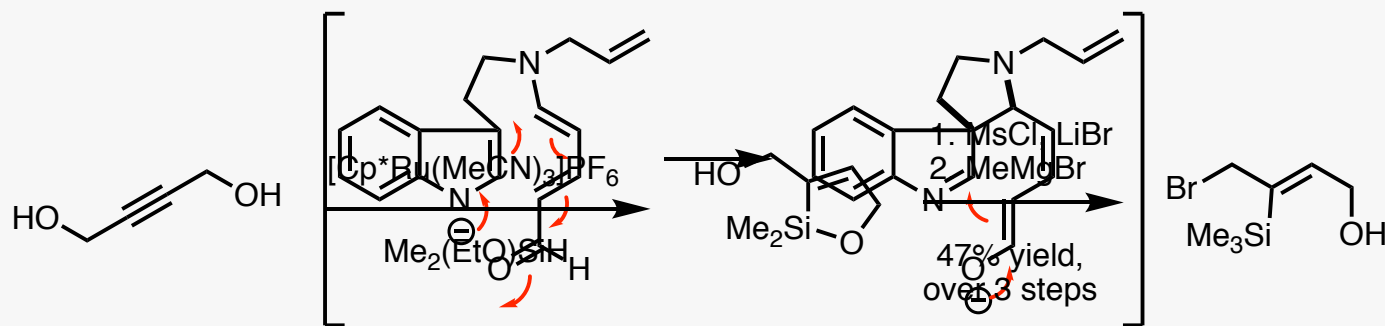
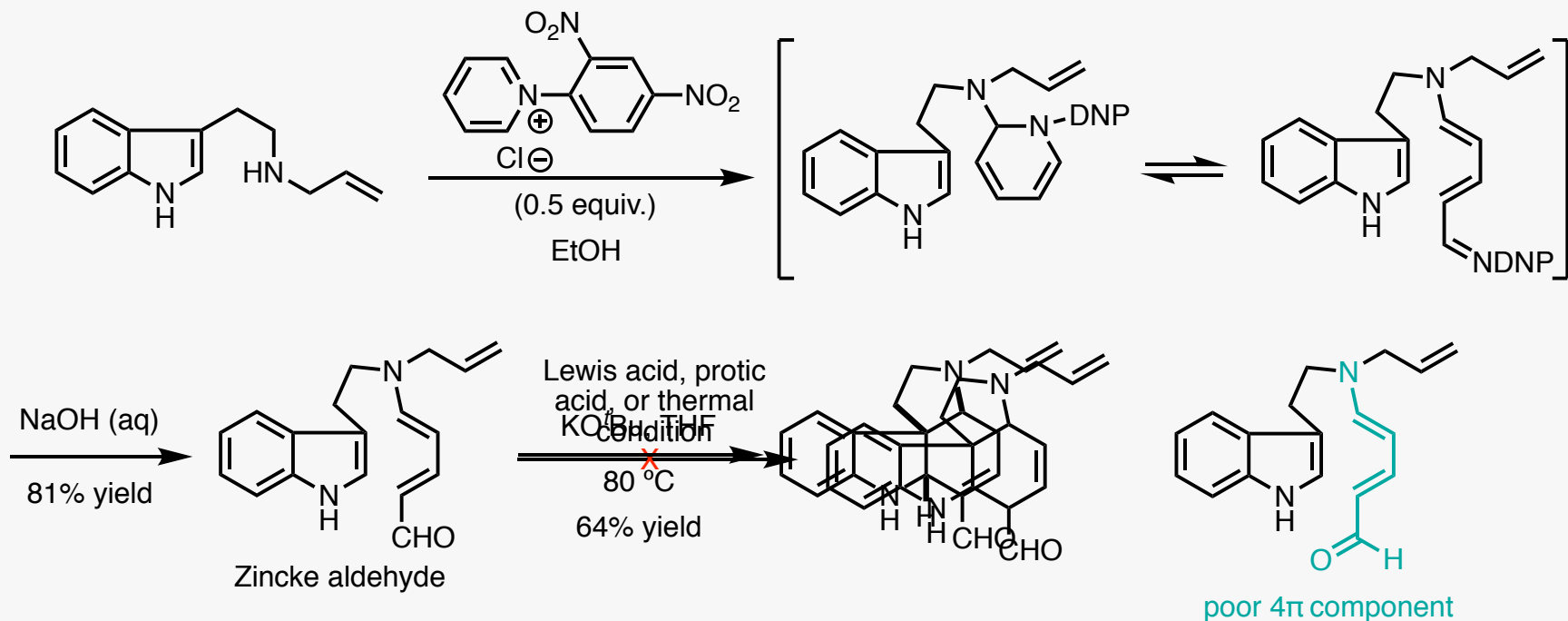
Vanderwal Synthesis: Retrosynthetic Analysis



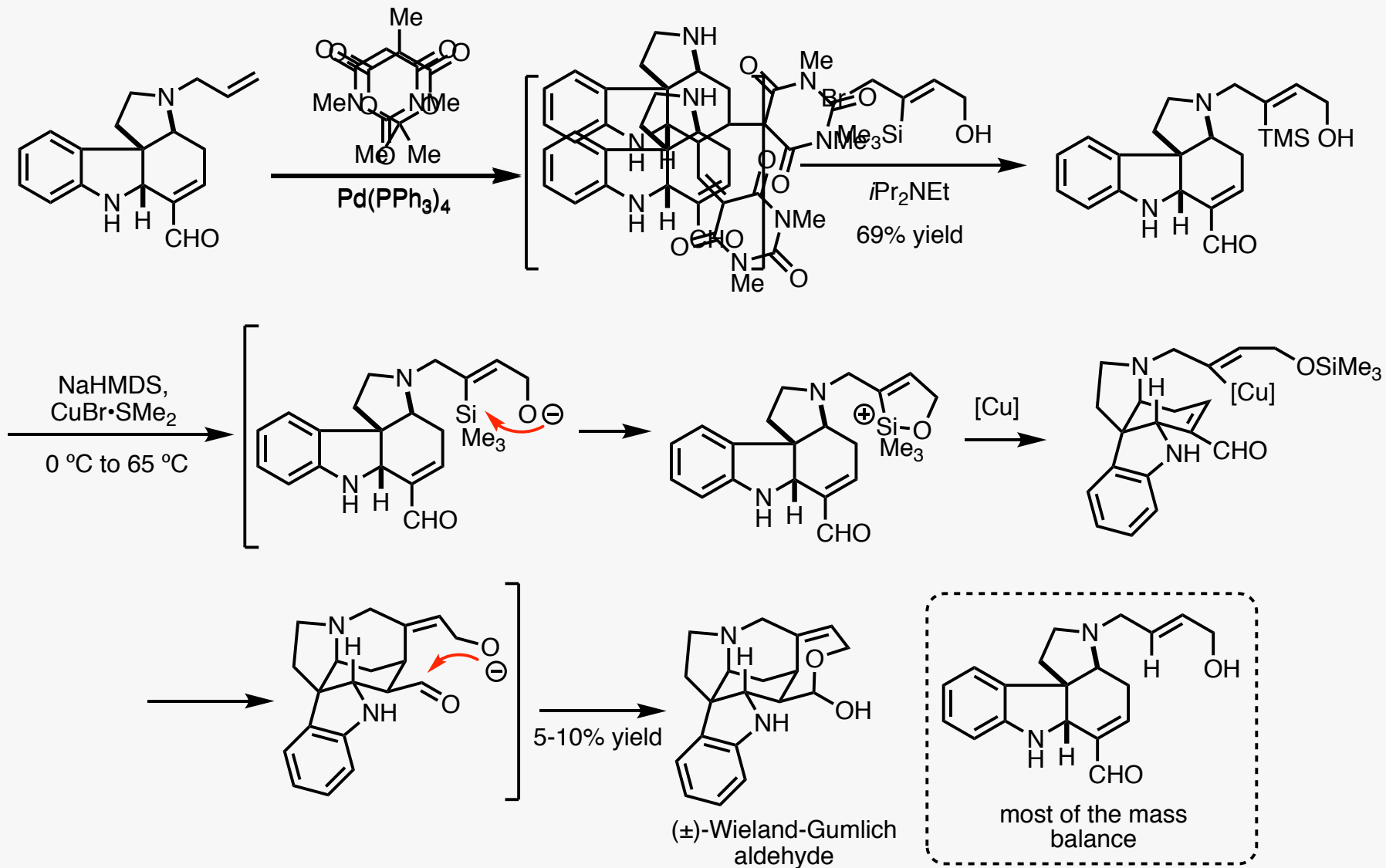
Zincke Reaction



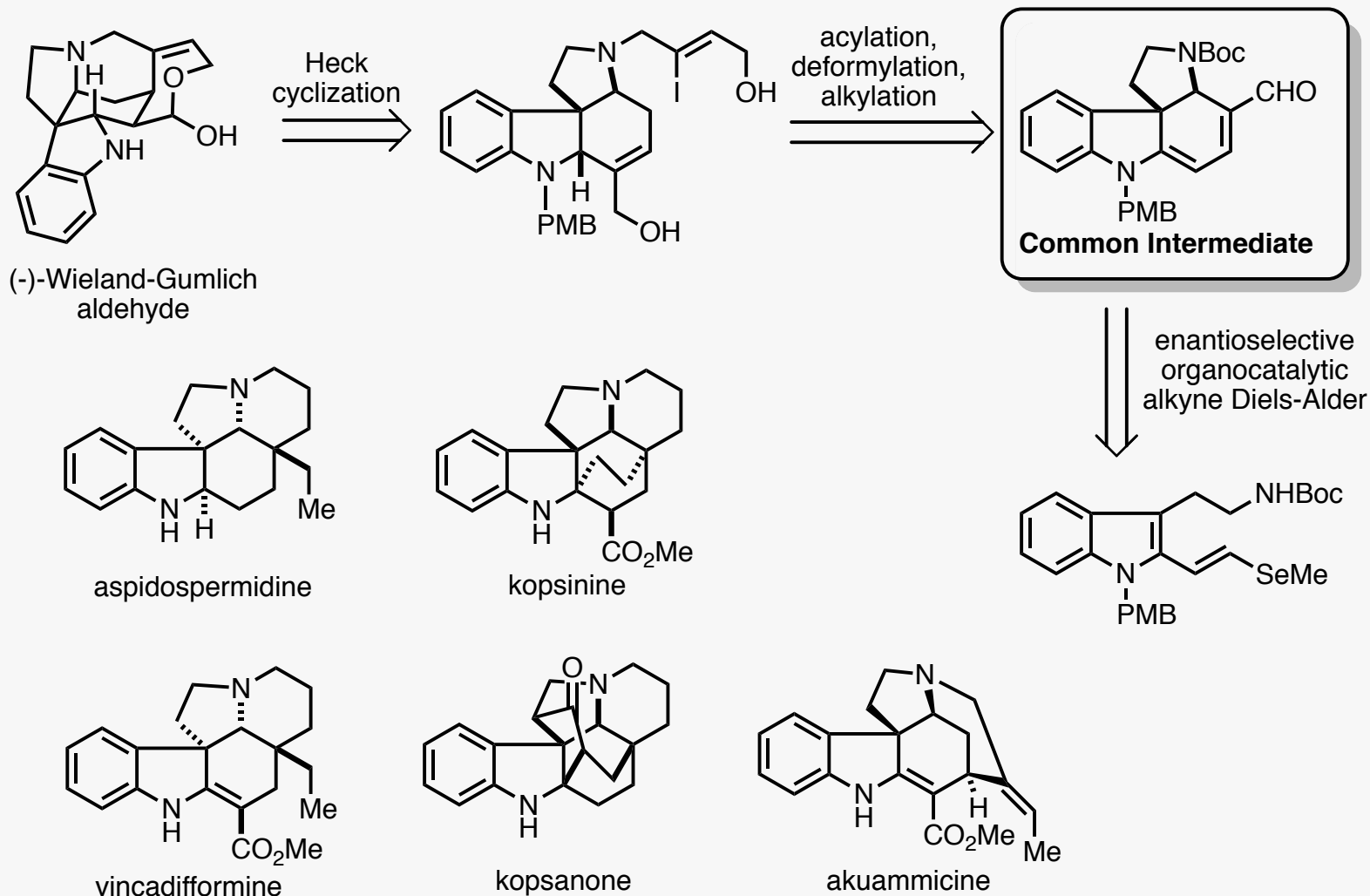
Vanderwal Synthesis: Zincke Aldehyde Formation



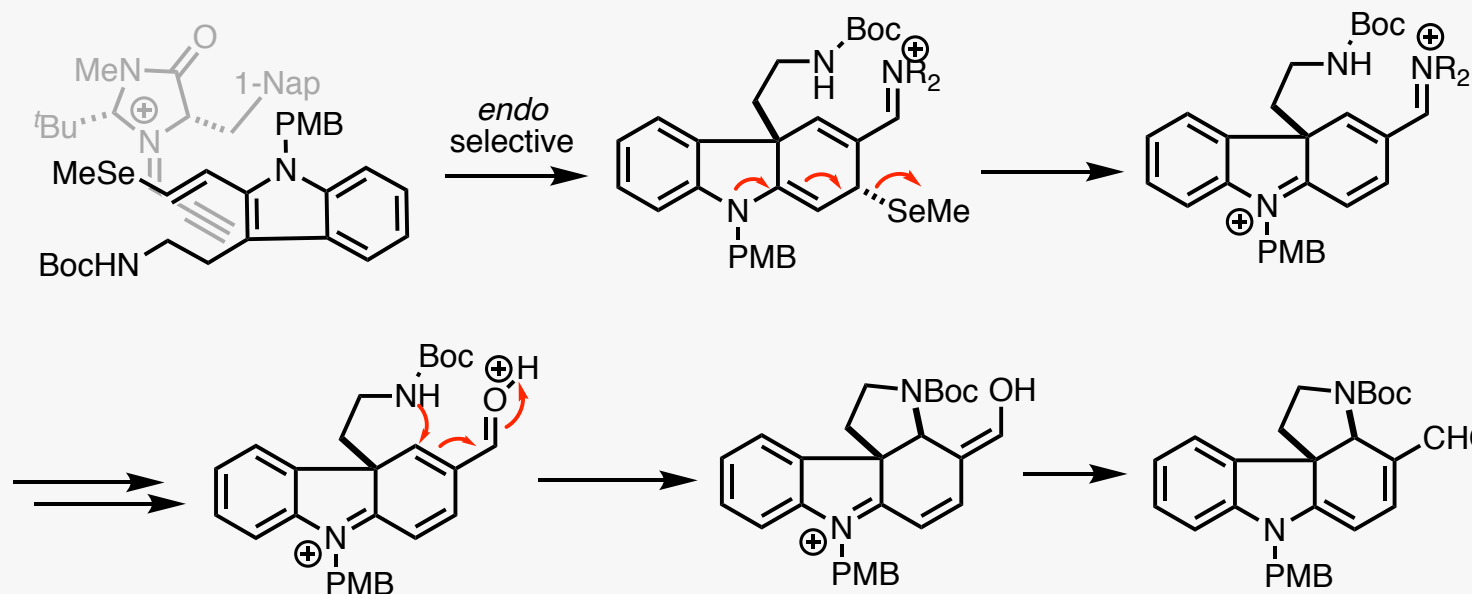
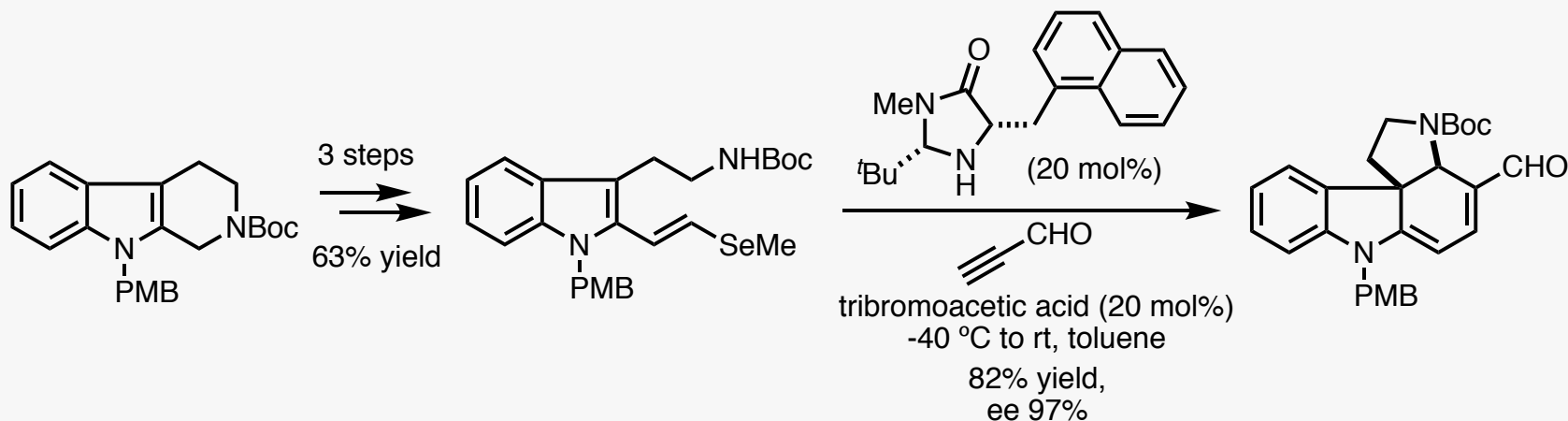
Vanderwal Synthesis: Brook Rearrangement/Conjugate Addition



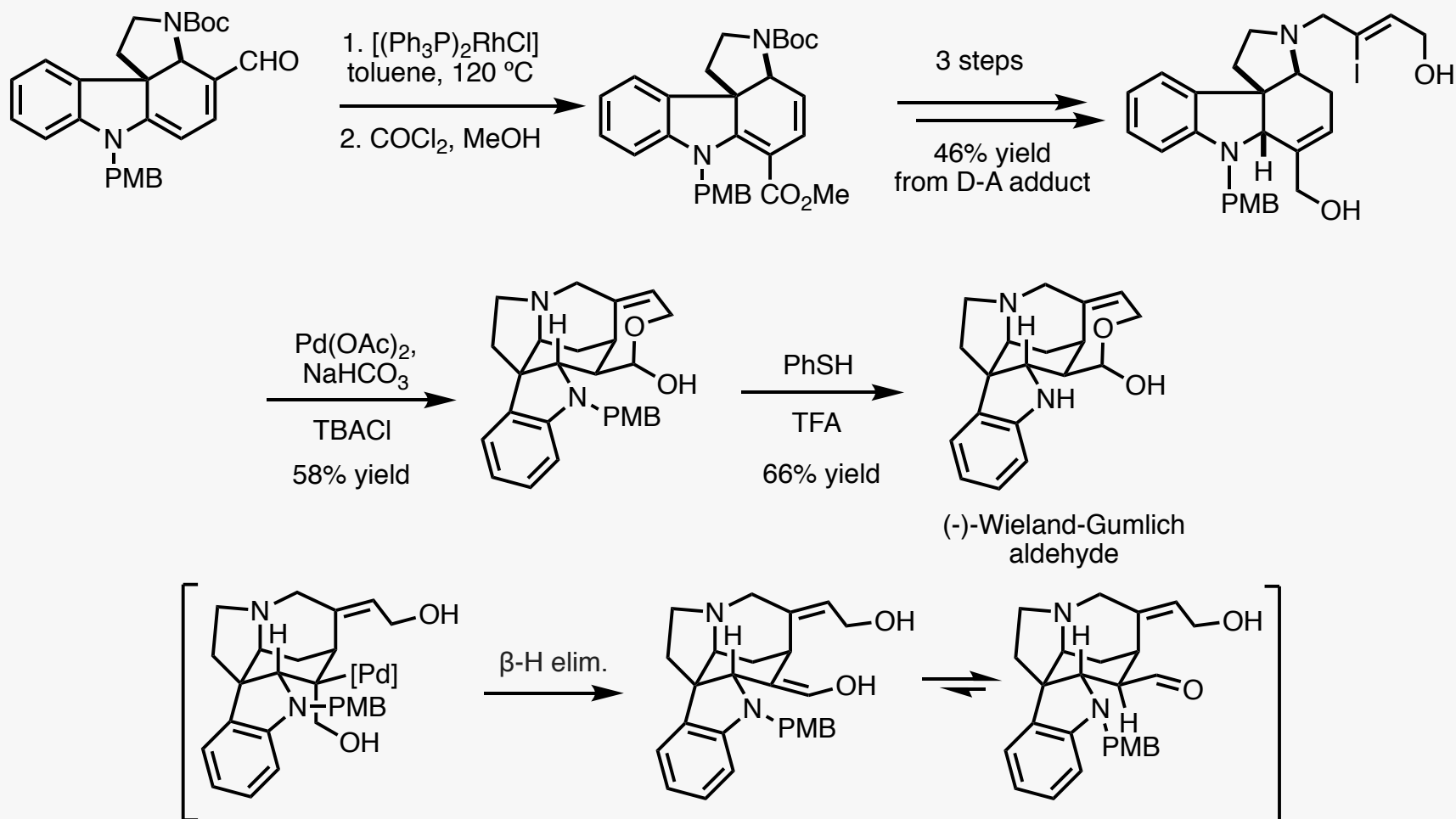
MacMillan Synthesis: Retrosynthetic Analysis



MacMillan Synthesis: Stereoselective Diels-Alder



MacMillan Synthesis: Heck Cyclization



Conclusion

