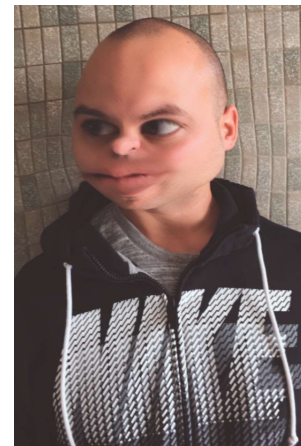
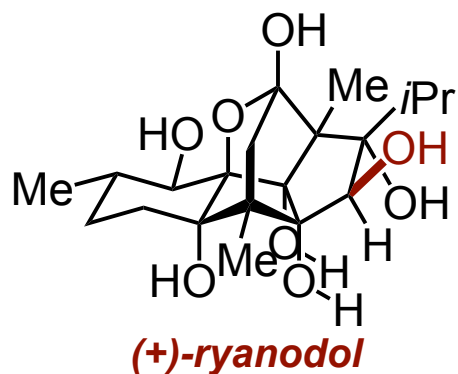
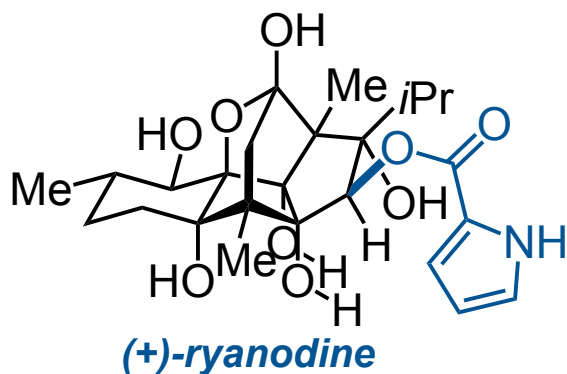




Ryan DeLuca

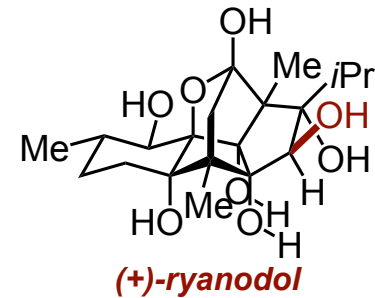
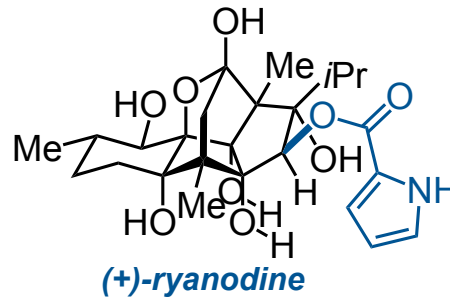
Total Syntheses of Ryanodol and Ryanodine

Jen Crawford

18 December 2017

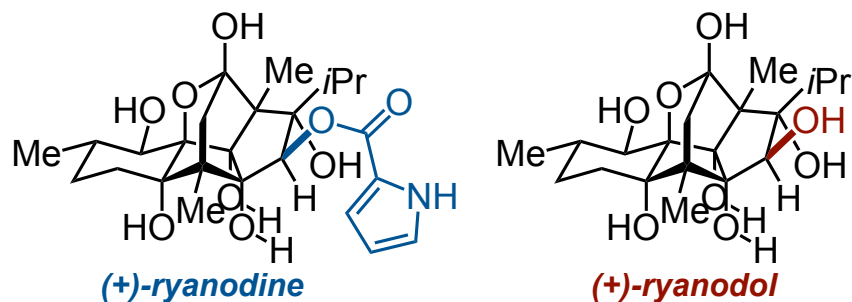
Synthesis Club

Ryanodine and Ryanodol



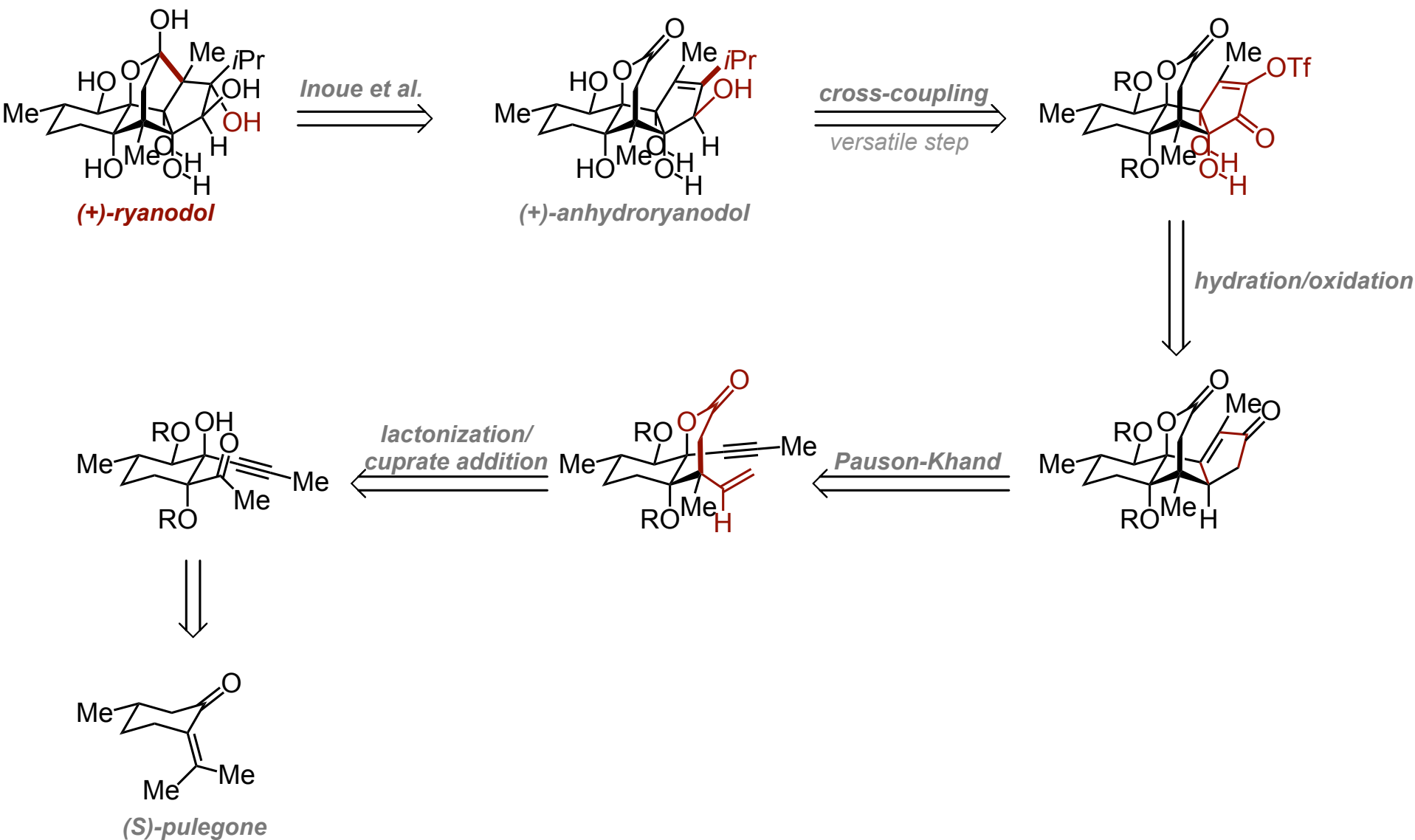
- Ryanodine = active insecticidal component in roots and stems of *Ryania speciosa*
- Binds to ryanodine receptors – controls Ca^{2+} uptake
 - Ca^{2+} important for movement and cognition in mammals
 - Implications for a variety of disease areas
- Structural History:
 - 1948: reported by Merck
 - 1967: Wiesner and co-workers elucidated the full structure of ryanodine
 - Correct structure identified through Inoue's total synthesis

Synthetic Challenges and Previous Syntheses

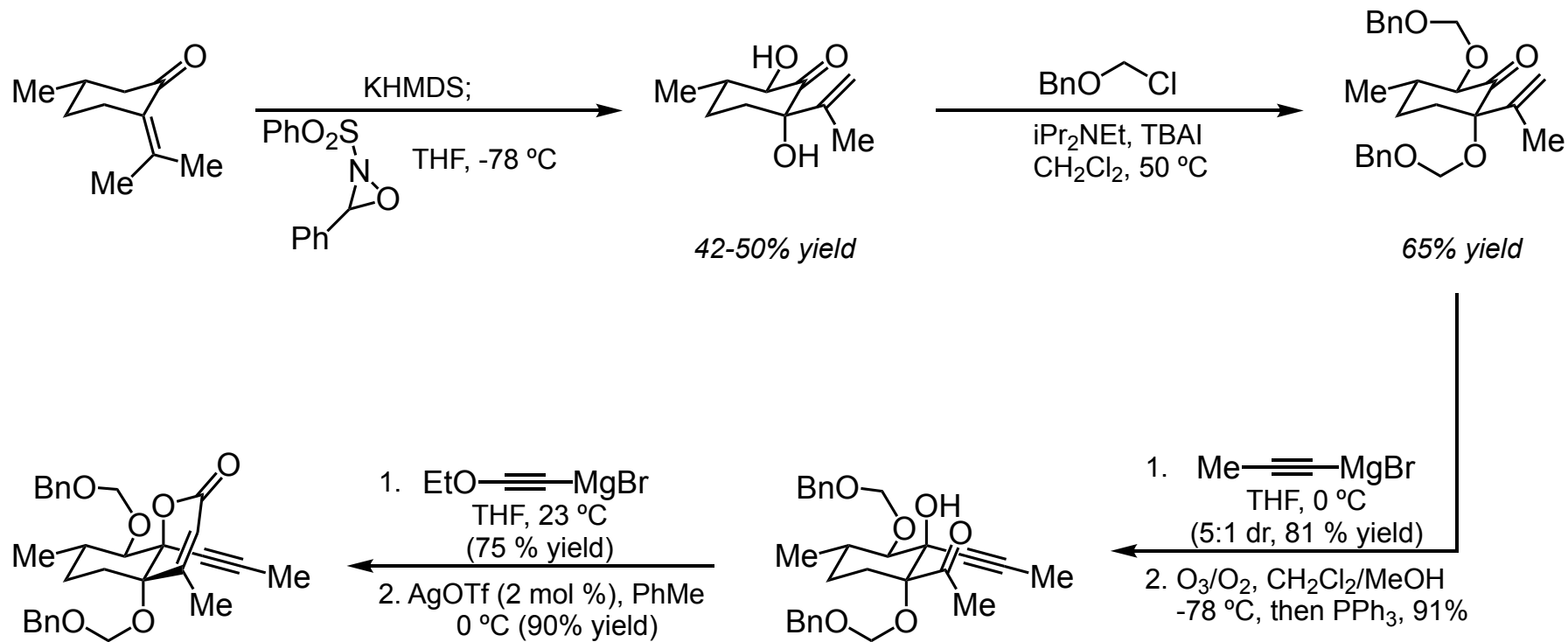


- 1979 – (+)-ryanodol, Deslongchamps, 37 steps
- 2014 – (+)-ryanodol, Inoue, 22 steps
- 2016 – (+)-ryanodol, Inoue, 37 steps
- 2016 – (+)-ryanodine, Inoue, 42 steps
- **2016 – (+)-ryanodol, Reisman, 2016, 15 steps**
- **2017 – (+)-ryanodine, Reisman, 2017, 18 steps**

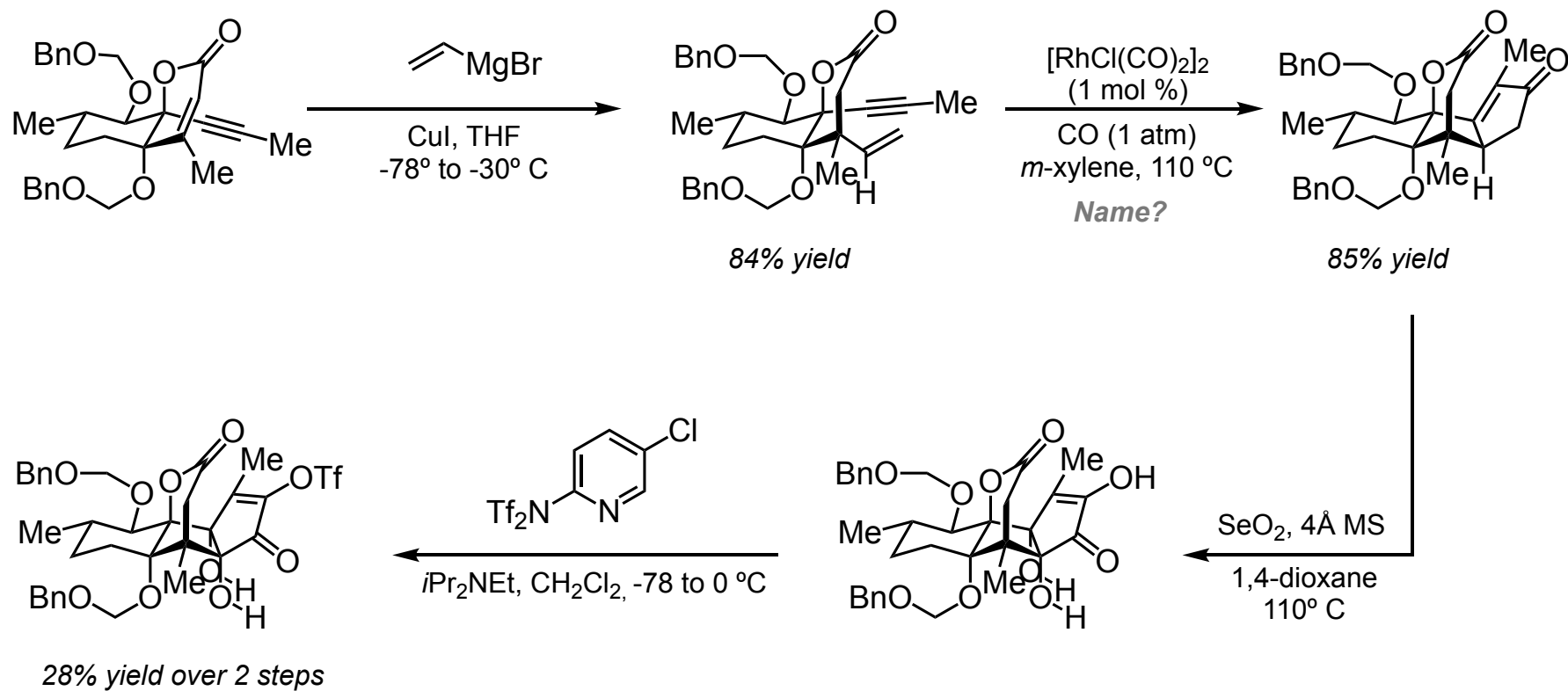
Reisman Synthesis of Ryanodol: Retrosynthetic Analysis



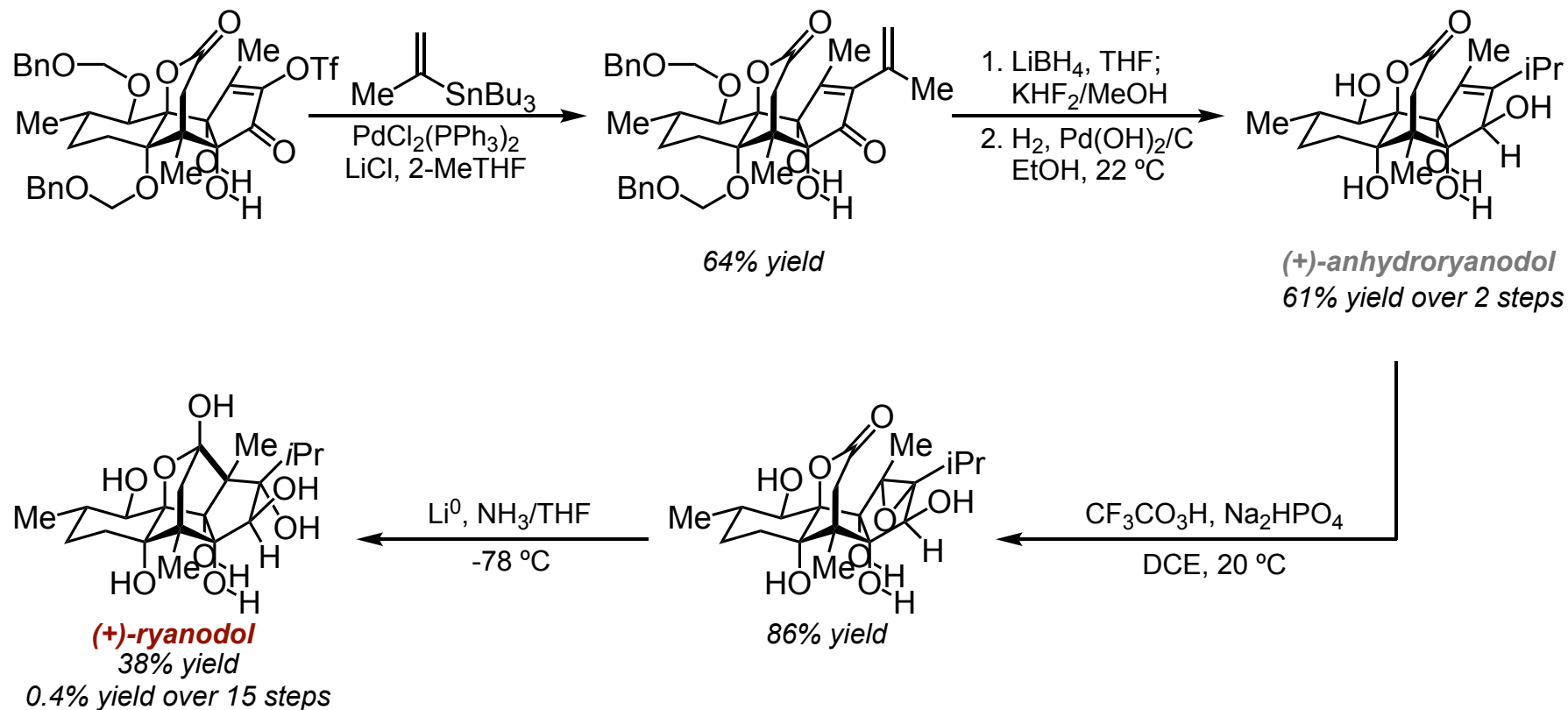
Total Synthesis of Ryanodol



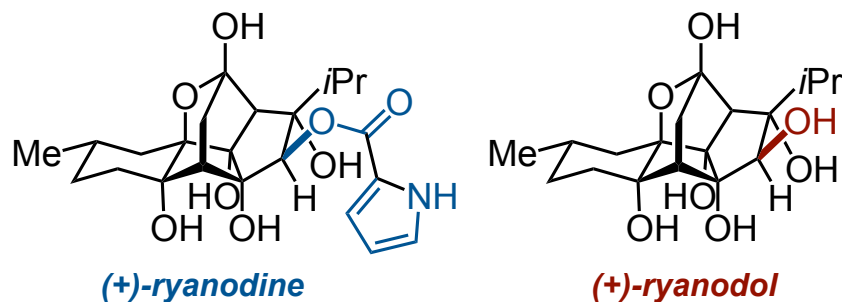
Total Synthesis of Ryanodol



Total Synthesis of Ryanodol

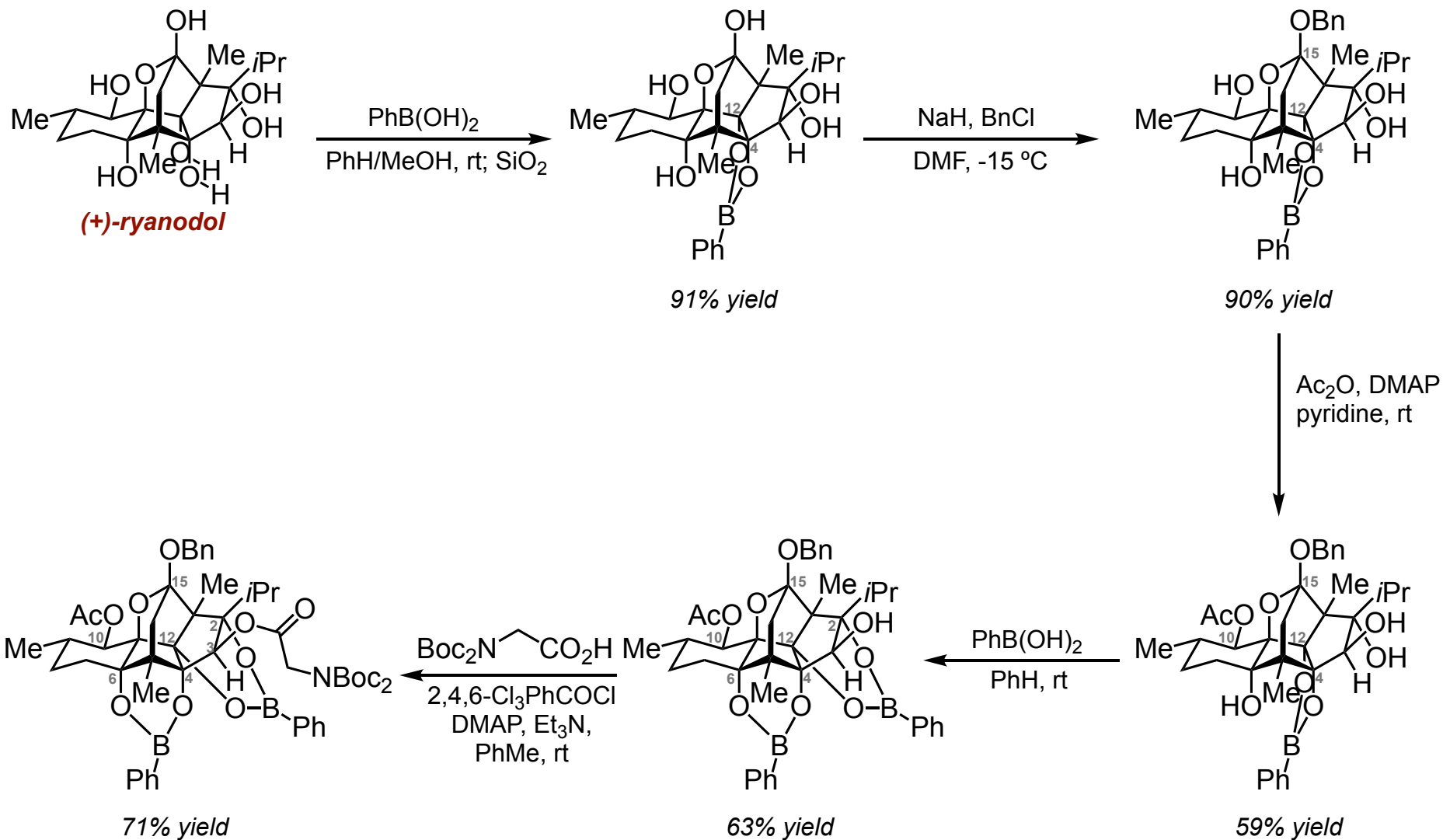


Challenges of Ryanodine

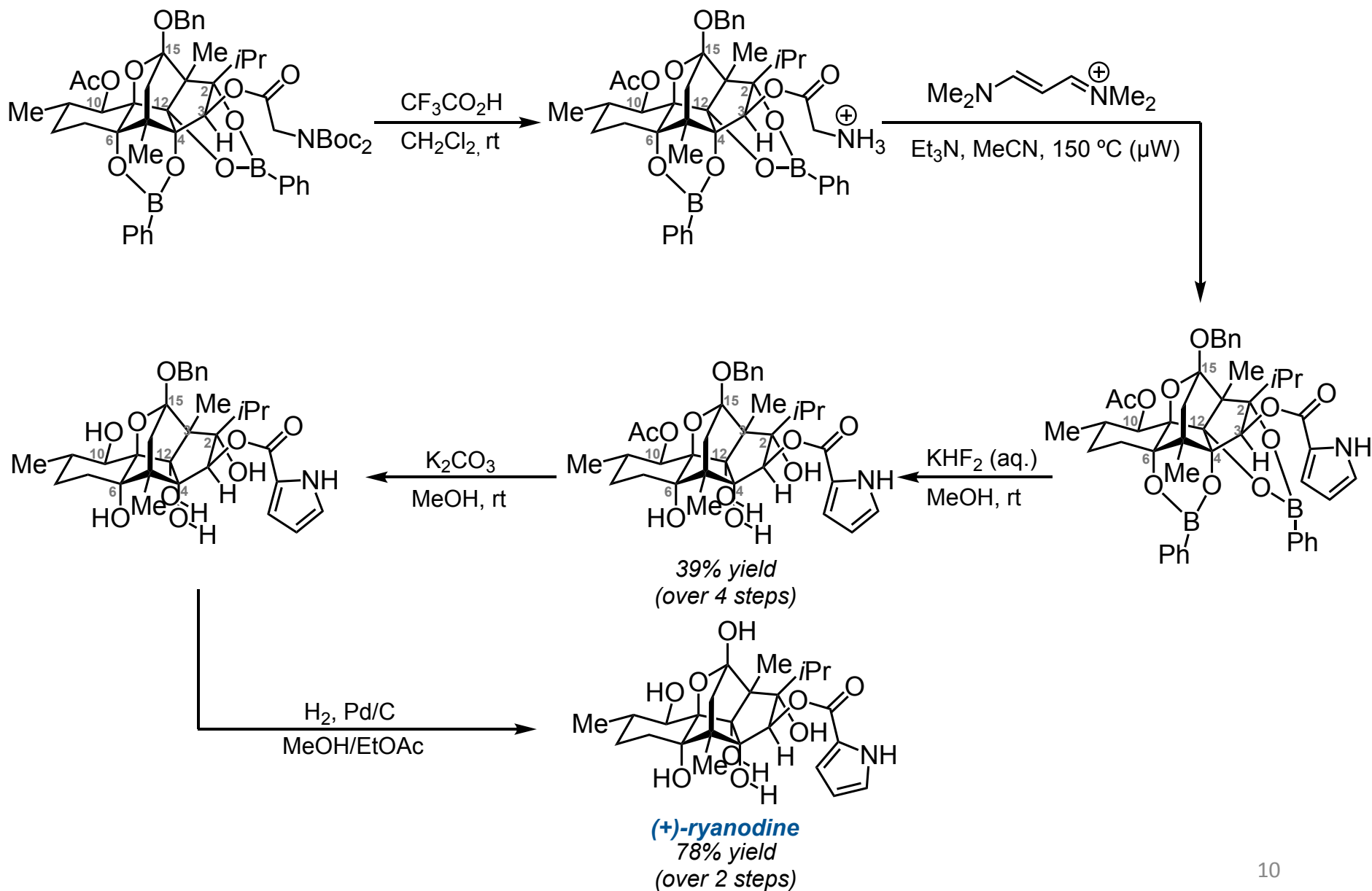


- Pyrrole-2-carboxylate ester at C3 critical for binding
 - Also least reactive alcohol in ryanodol
- Difficult to convert ryanodol to ryanodine
 - Regioselectivity problems – four tertiary, two secondary, and one acetalic alcohol
 - Pyrrole difficult to introduce – direct acylation unsuccessful
 - 10 steps (lots of PGs)

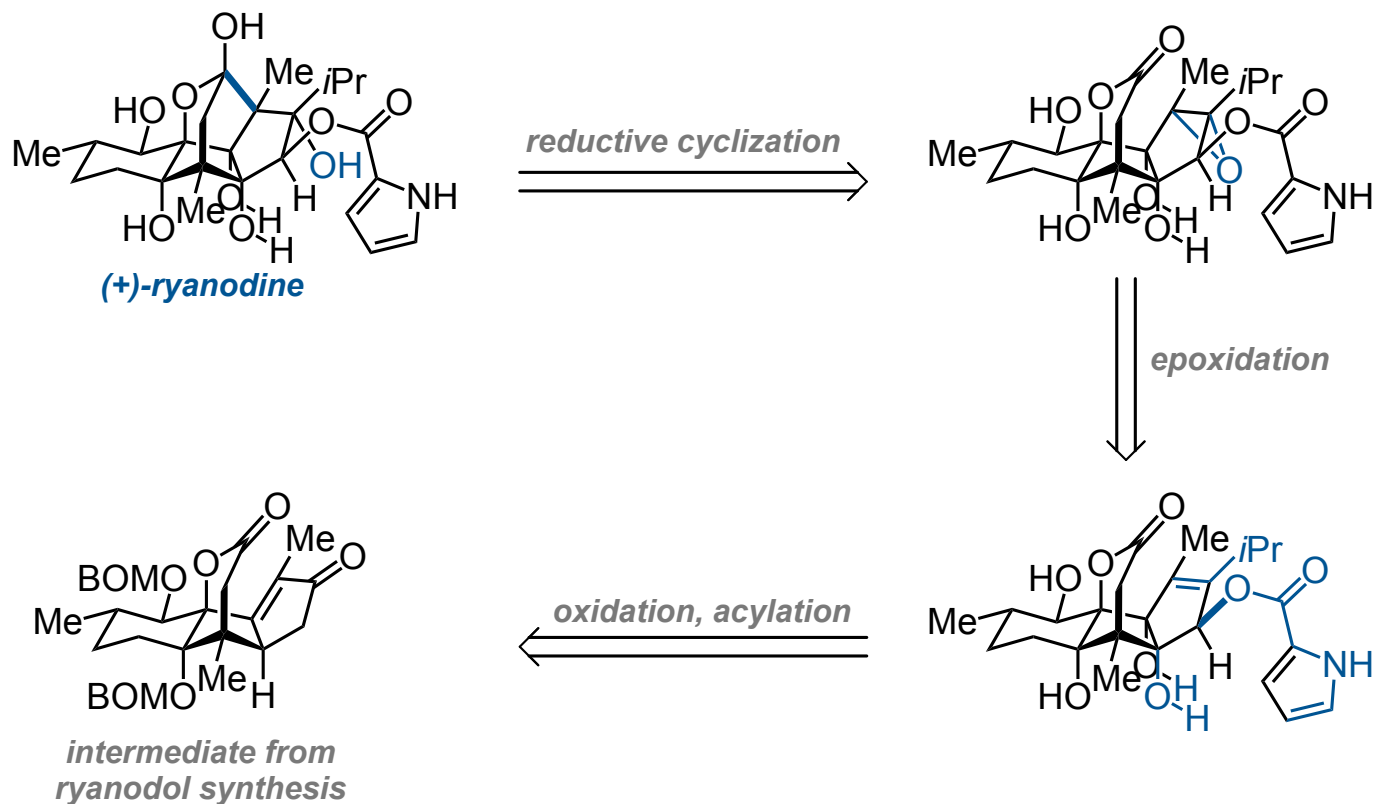
Converting Ryanodol to Ryanodine (Inoue)



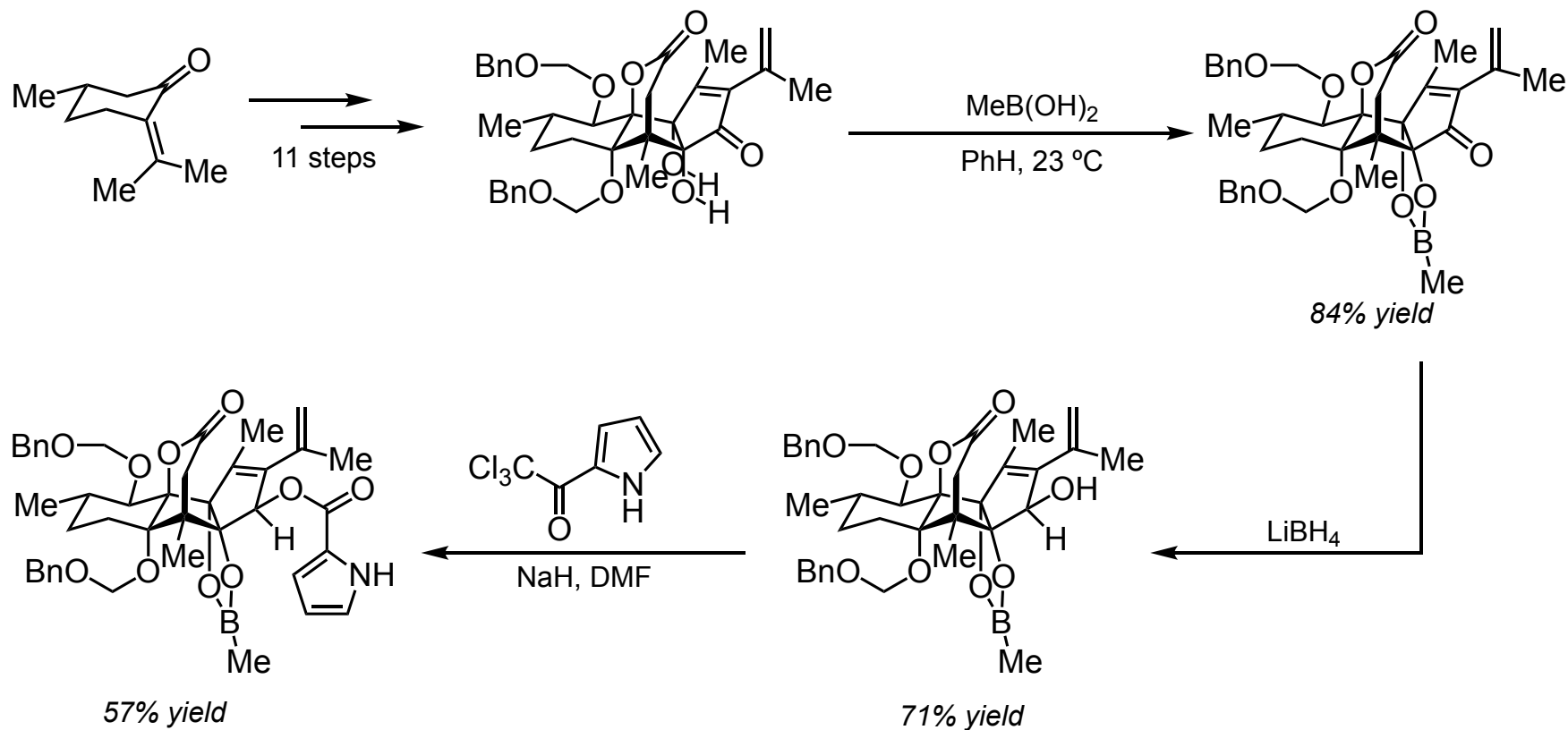
Converting Ryanodol to Ryanodine (Inoue)



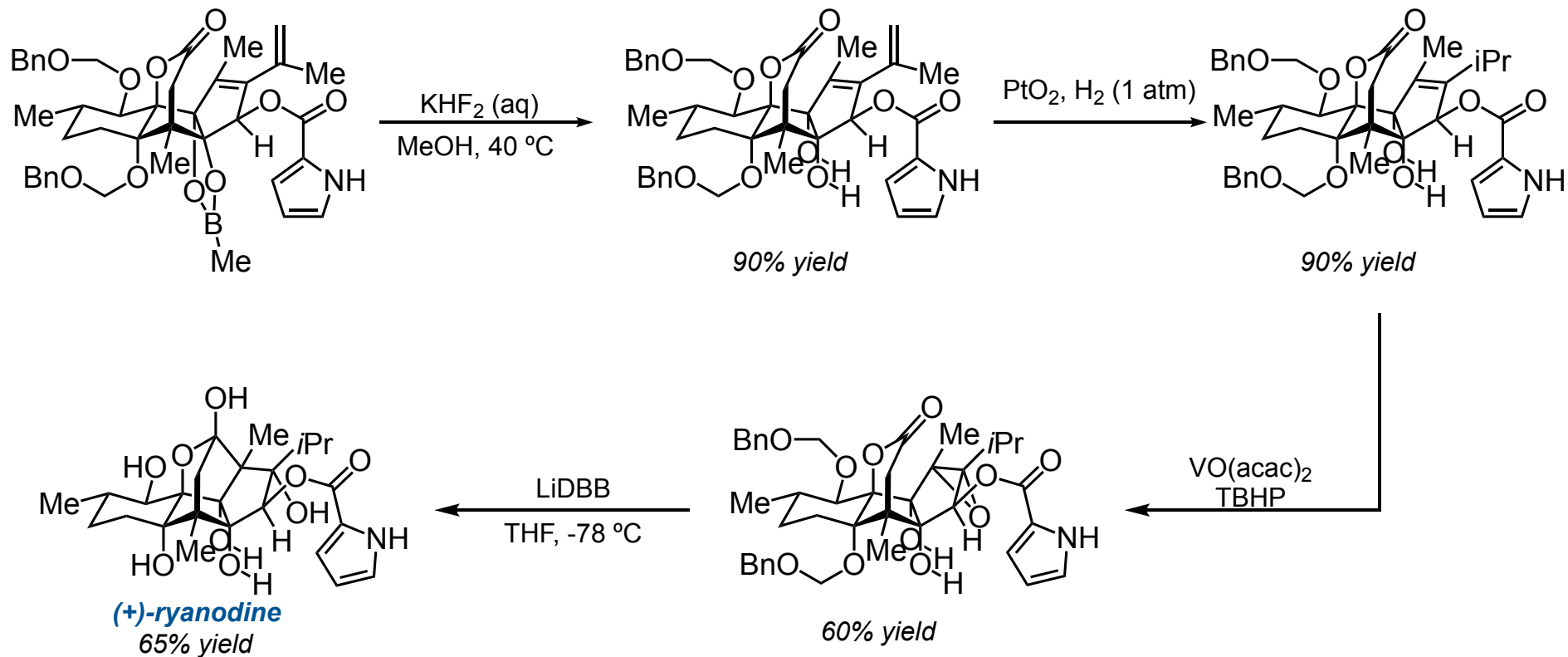
Reisman Synthesis of Ryanodine: Retrosynthetic Analysis



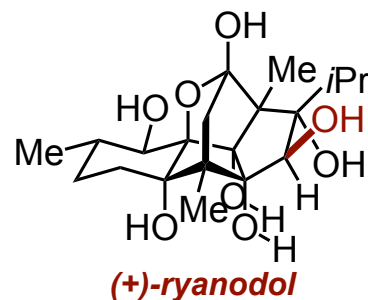
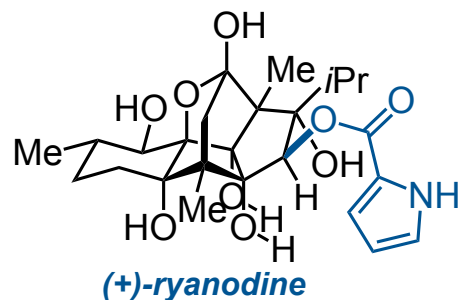
Total Synthesis of Ryanodine



Total Synthesis of Ryanodine



Conclusions



- Ryanodine-like molecules are important inhibitors of Ca^{2+} channels
 - Eleven contiguous stereocenters, eight oxygenated carbons, five fused rings
- C3 ester very important for binding to ryanodine receptors
- Reisman syntheses
 - Streamline oxygen incorporation
 - Earlier ester incorporation