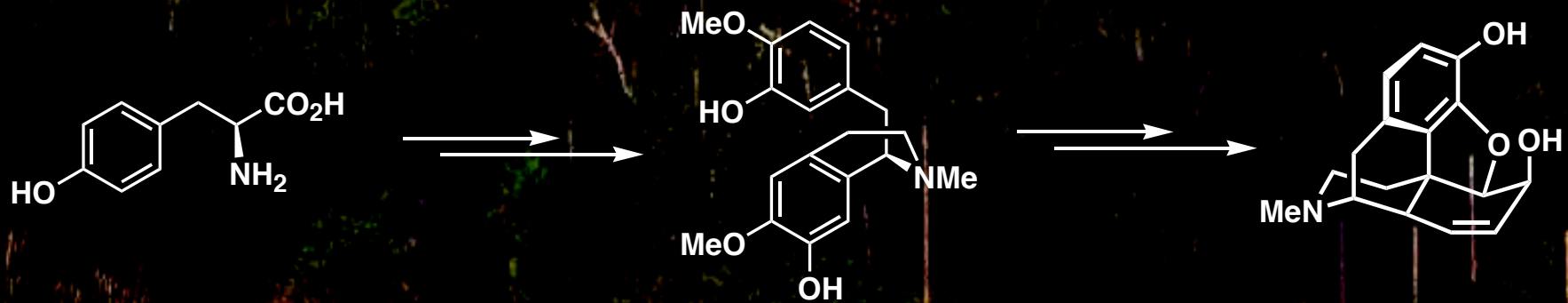


Synthesis of Morphine Alkaloids



Introduction

□ Cultivation:

- Opium is harvested from the immature poppy seed capsule

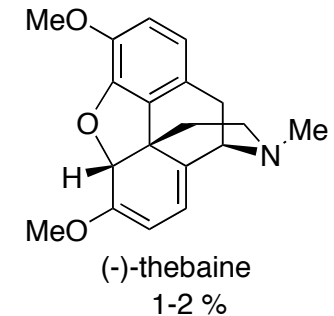
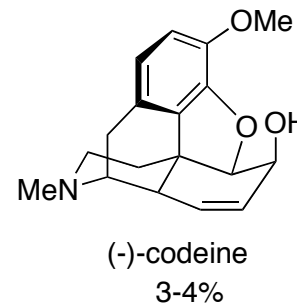
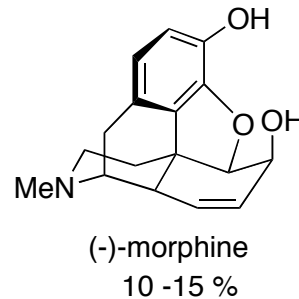


Fig 1: Lanced Poppy with raw opium exuding

- Primary areas of cultivation are south east and west asia and latin america
- An average Indian acreage of *P. somniferum* yields 25-30 kg of opium

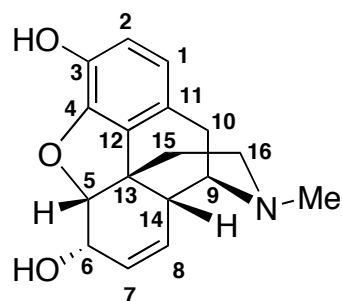
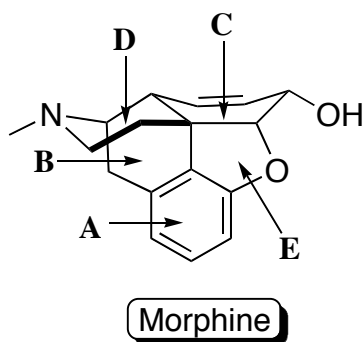
Introduction

□ History of Morphine as a Pharmaceutical

- Laudanum (16th Century):
 - Developed by Swiss alchemist Paracelus
 - alcoholic tincture of alcohol, opium, and other herbs
 - Eased suffering from the plague
- Heroin (1898):
 - Developed by Heinrich Dreser at Fredich Bayer and Company
 - Diacetyl derivative of morphine
 - Marketed to the German people as a cough remedy
- Morphine (Present day)
 - One of the most widely used drugs for treatment of severe pain

Introduction

□ Structure

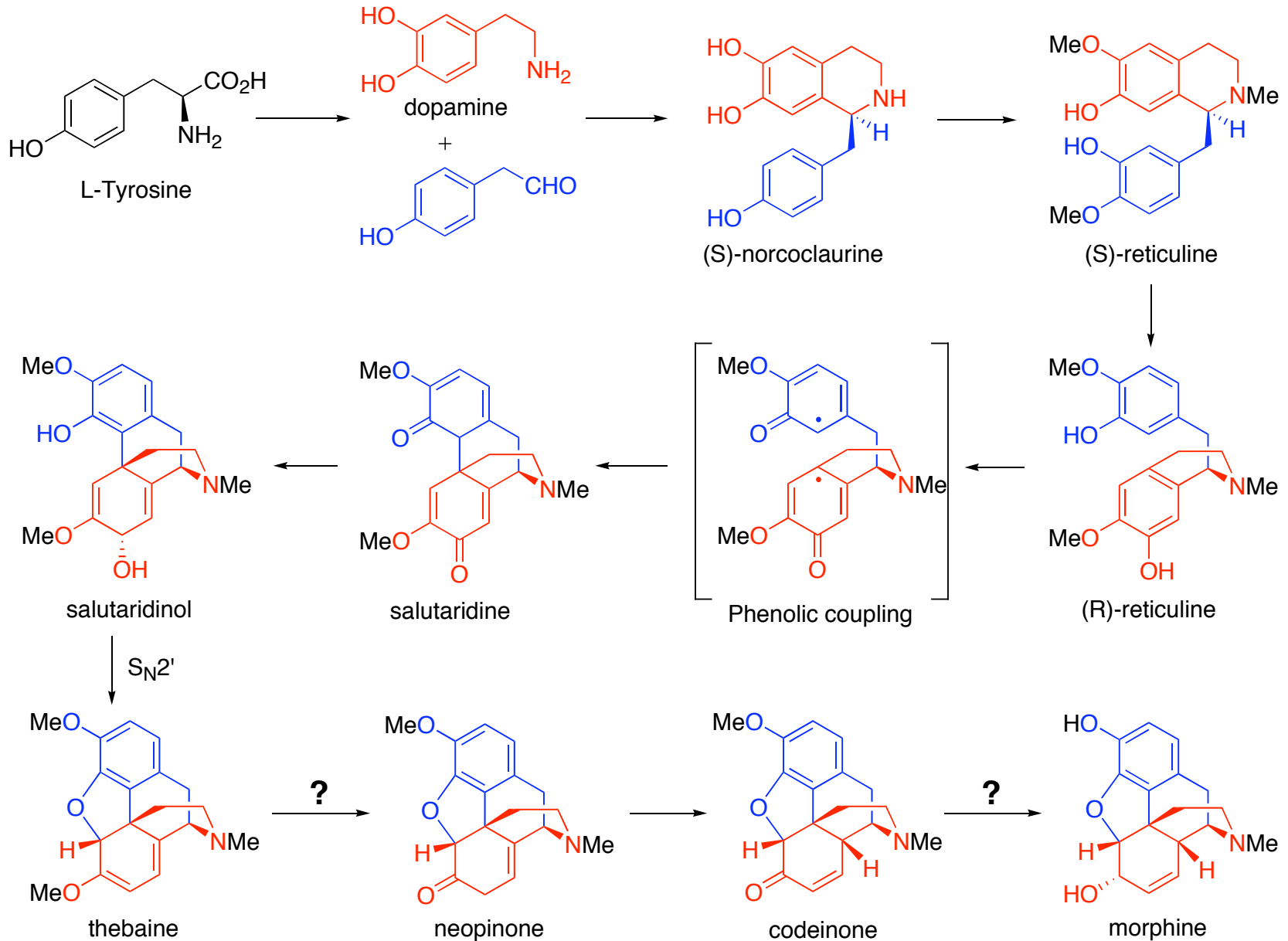


Key Features: 5 rings, 5 contiguous stereocenters, compact array of functionality

□ Synthesis

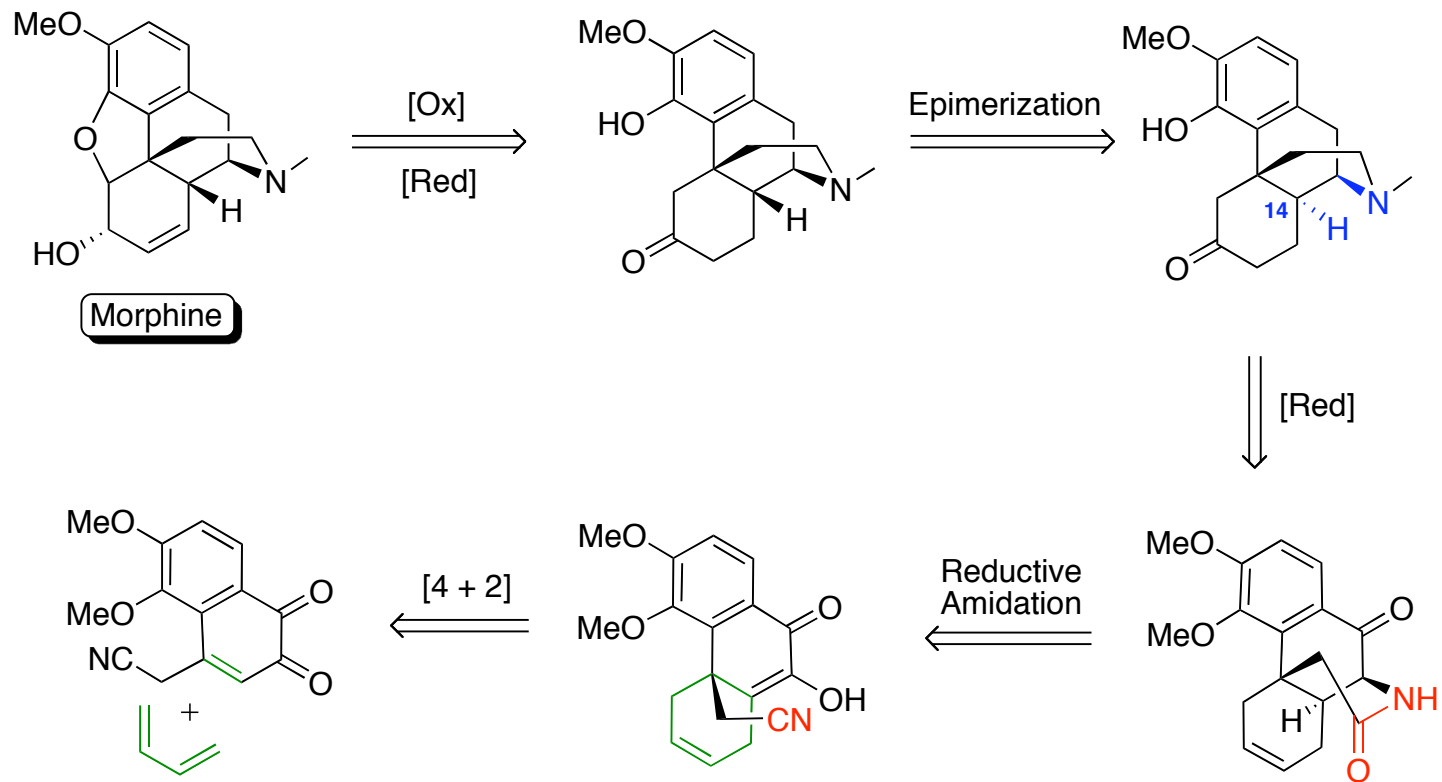
- Landmark synthesis was in 1952 by Gates
- Since then at least 18 more total and formal synthesis of Morphine have appeared
- This overview will encompass 6 unique routes

Biosynthesis of Morphine



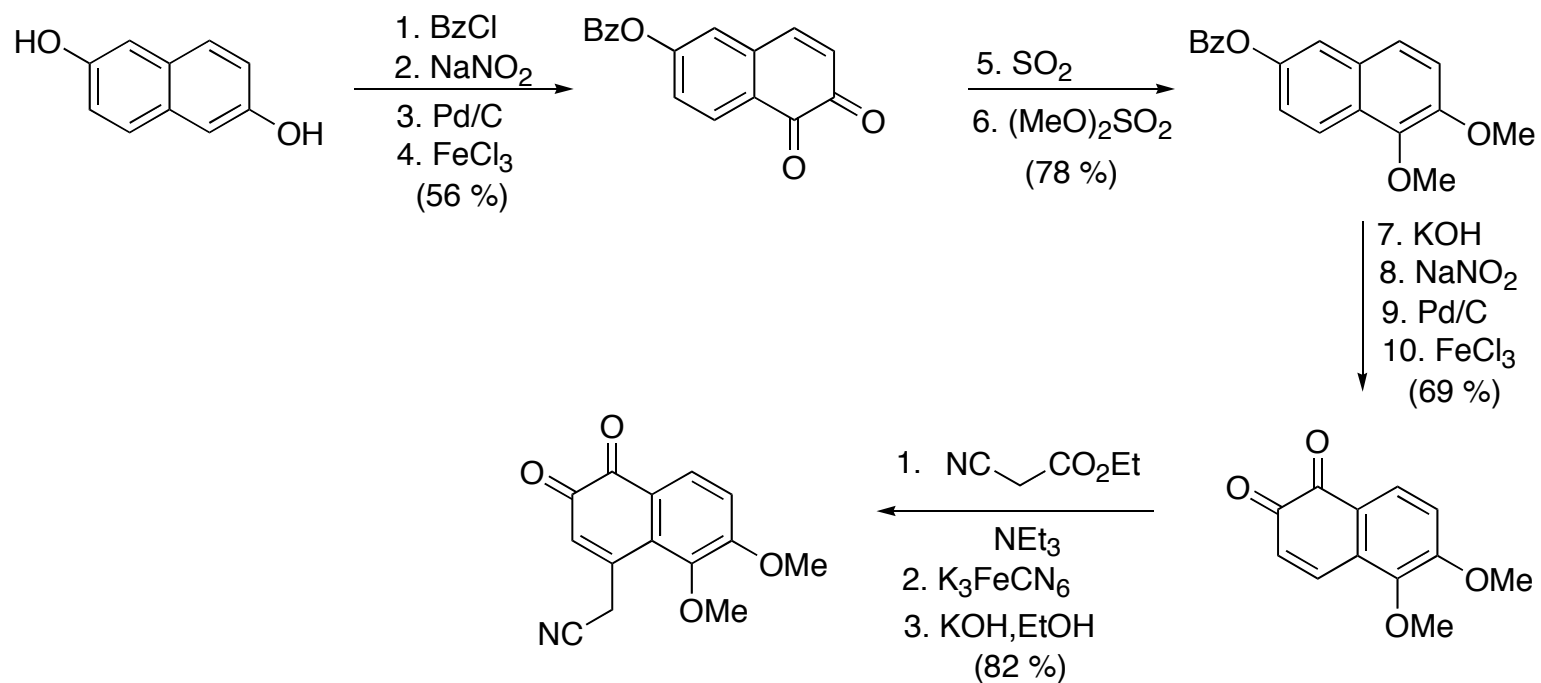
Gates Synthesis

□ Retrosynthesis



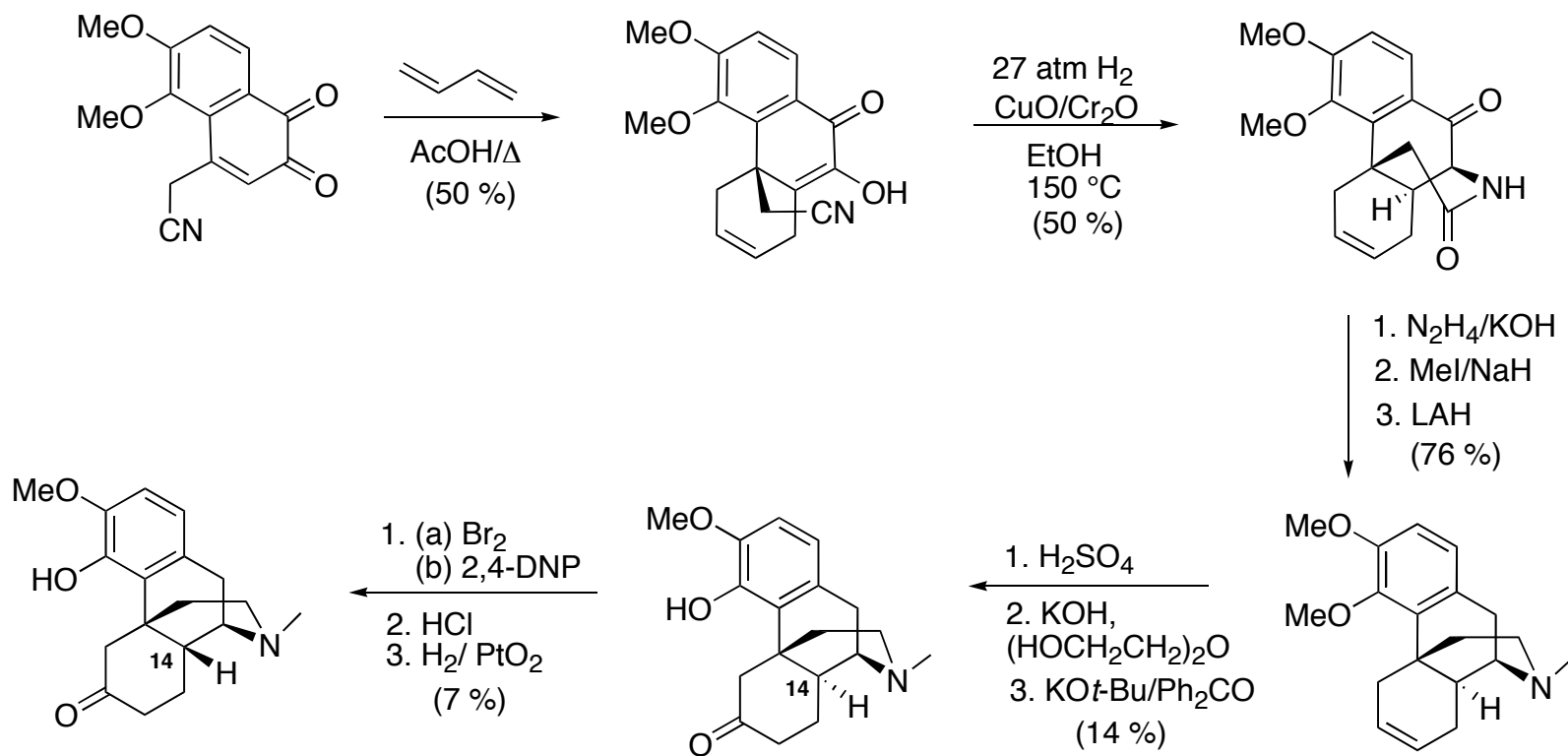
Gates Synthesis

□ Forward Synthesis: Diene



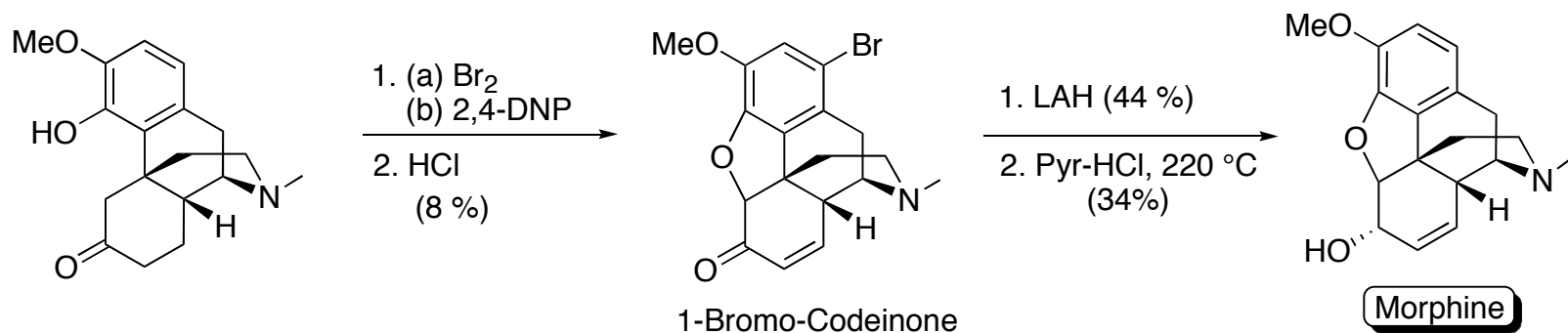
Gates Synthesis

□ Forward Synthesis: Morphine



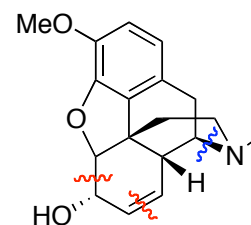
Gates Synthesis

□ Forward Synthesis: Morphine



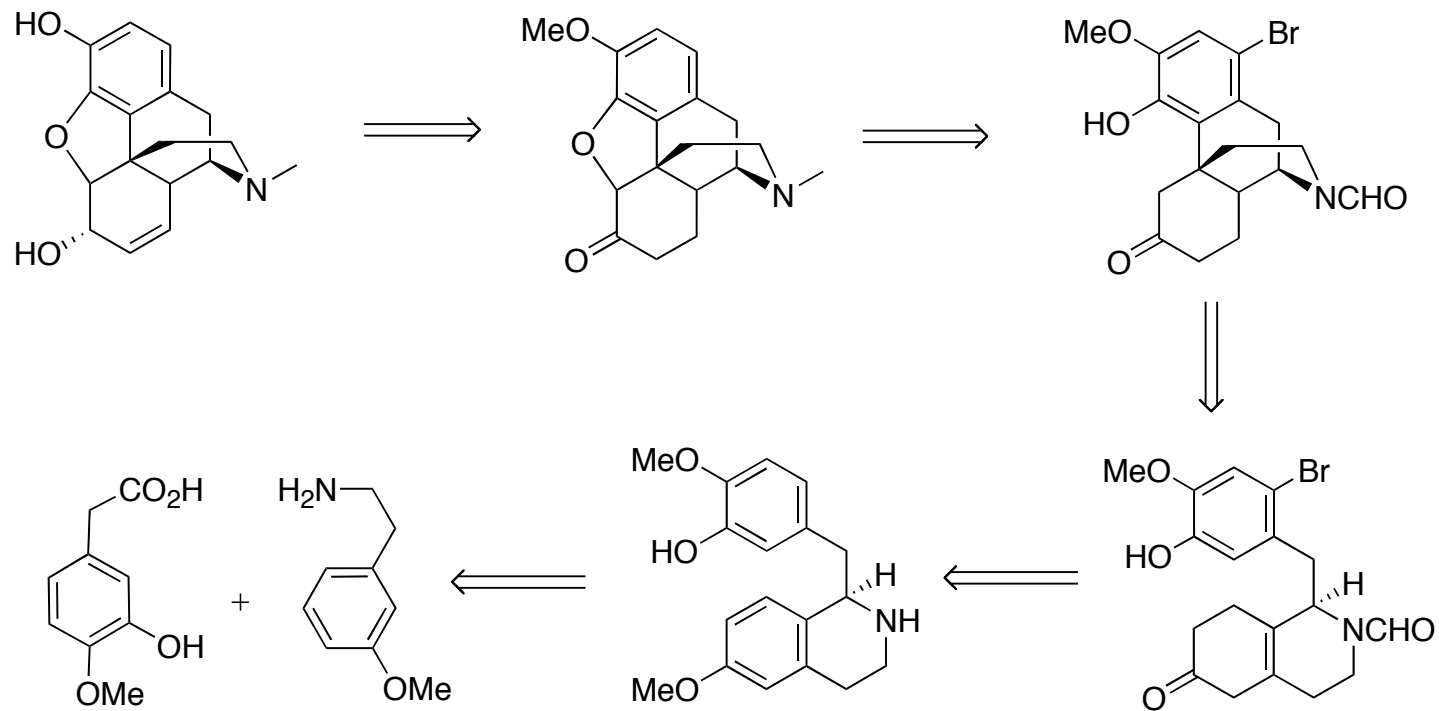
□ Analysis: Gates Method

- 29 Steps
- Overall Yield: 0.0014%
- Key Disconnections: Diels-Alder & Reductive Amidation



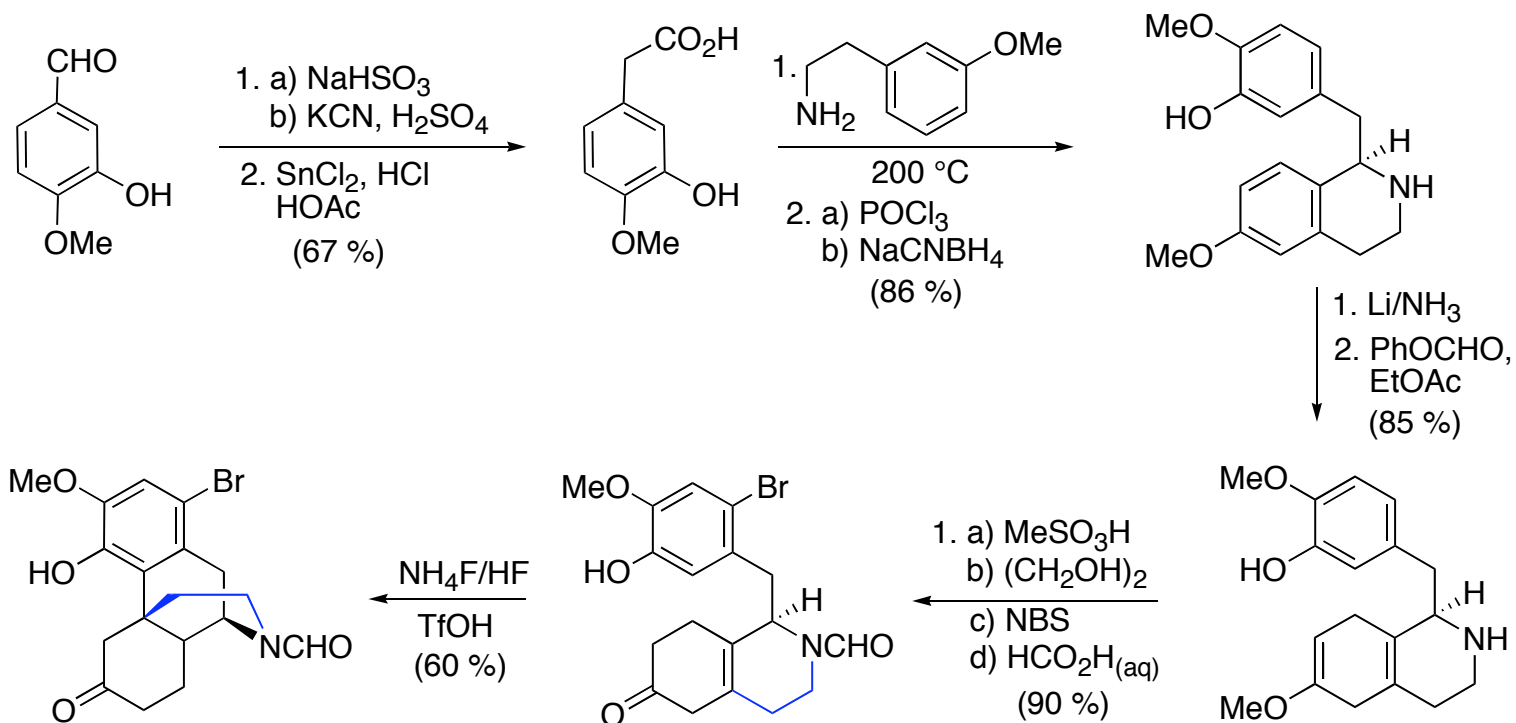
Rice Synthesis

□ Retrosynthesis



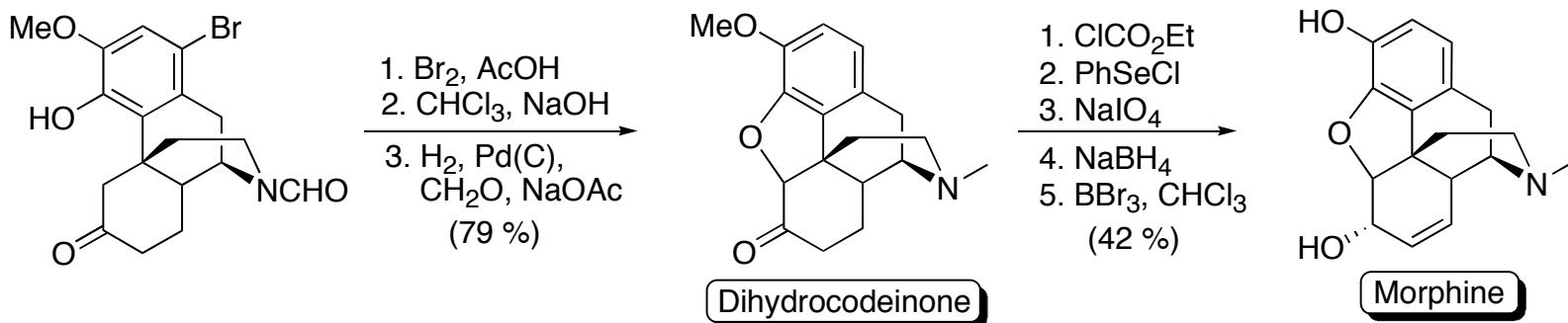
Rice Synthesis

□ Forward Synthesis: Grewe cyclization



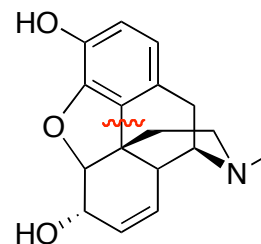
Rice Synthesis

□ Forward Synthesis: End Game



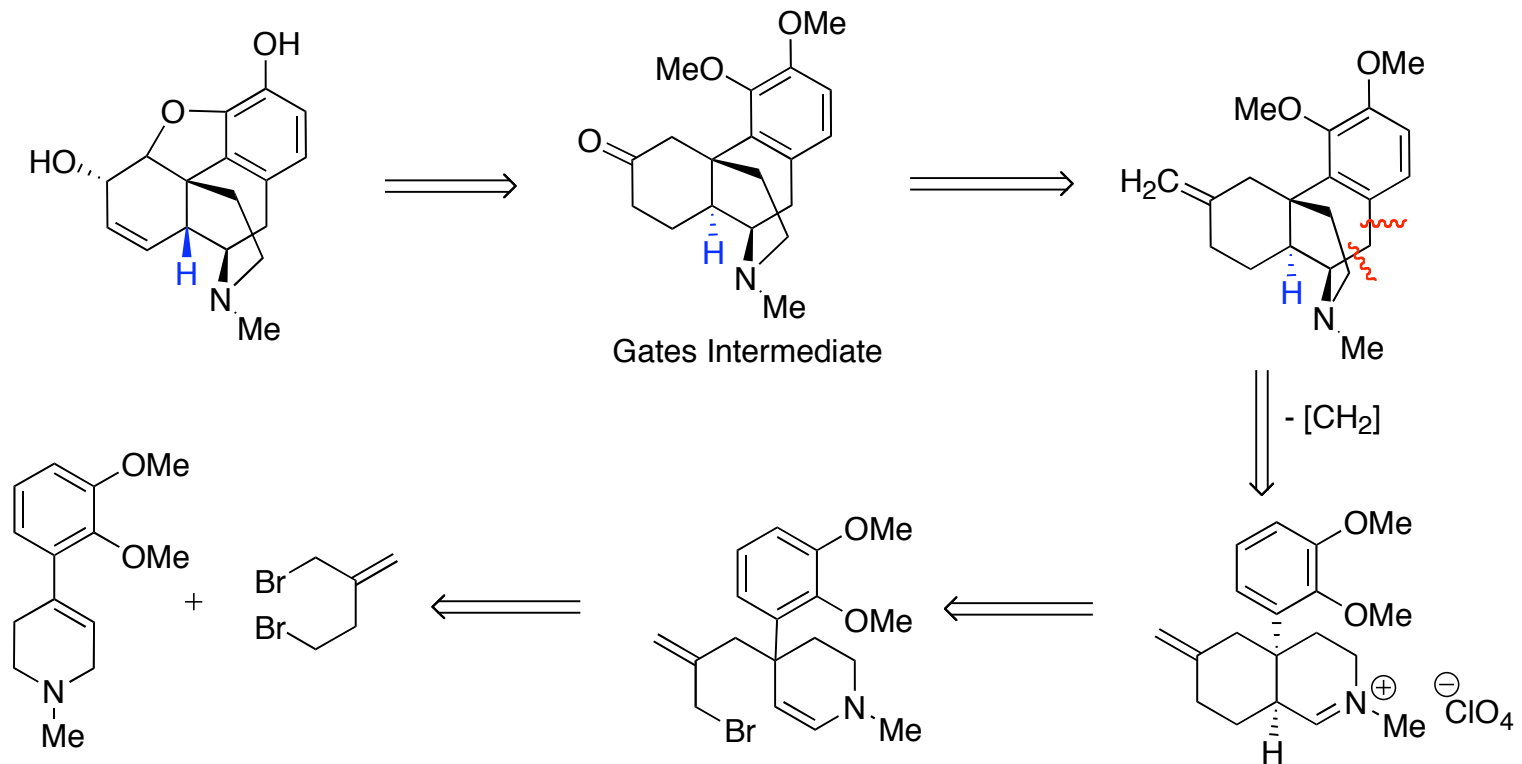
□ Analysis: Rice Method

- 16 steps
- Overall yield 12 %
- Grewe cyclization was key disconnection
- Practical method for conversion of dihydrocodeinone to morphine



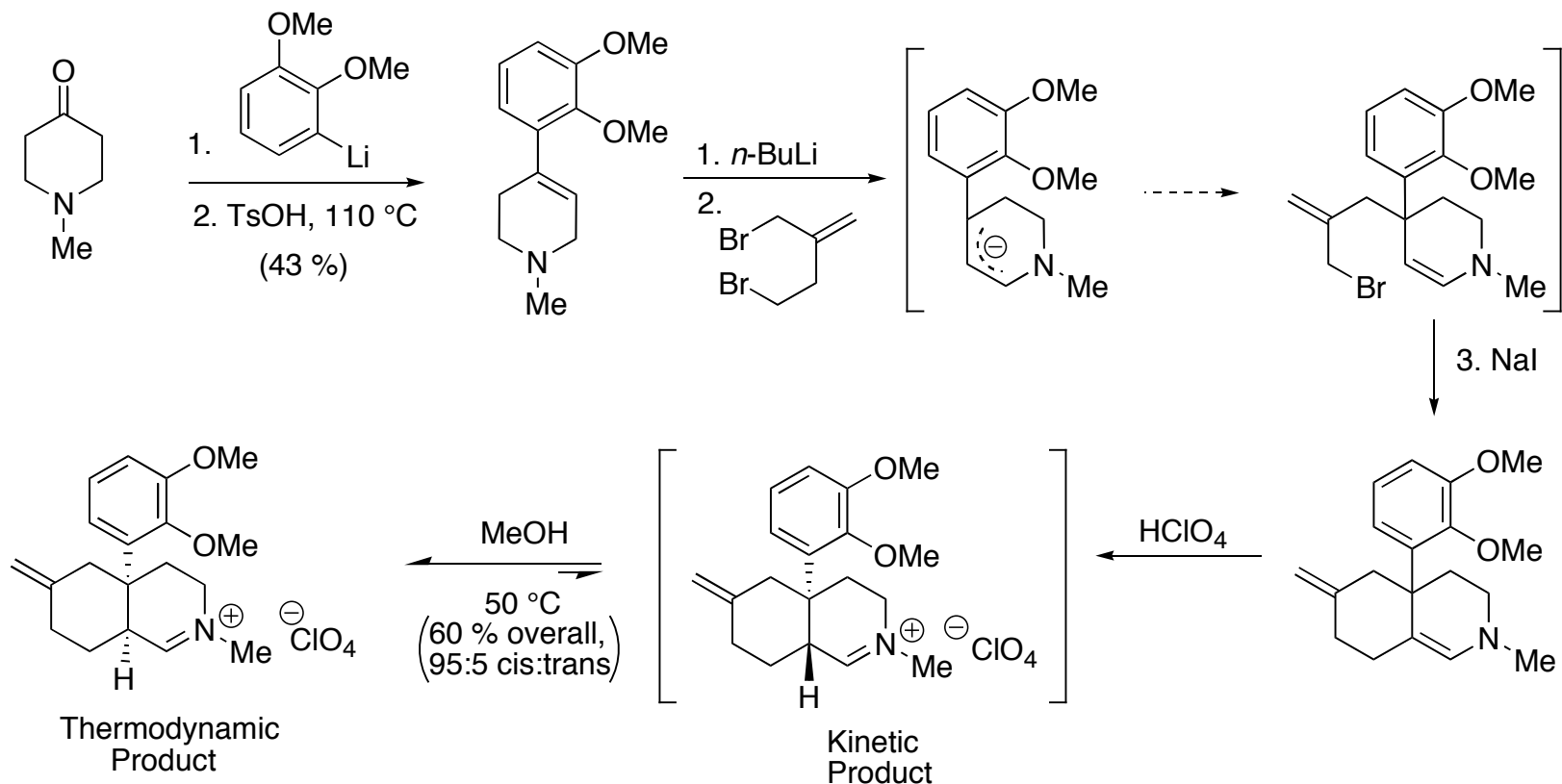
Evans Synthesis

□ Retrosynthesis



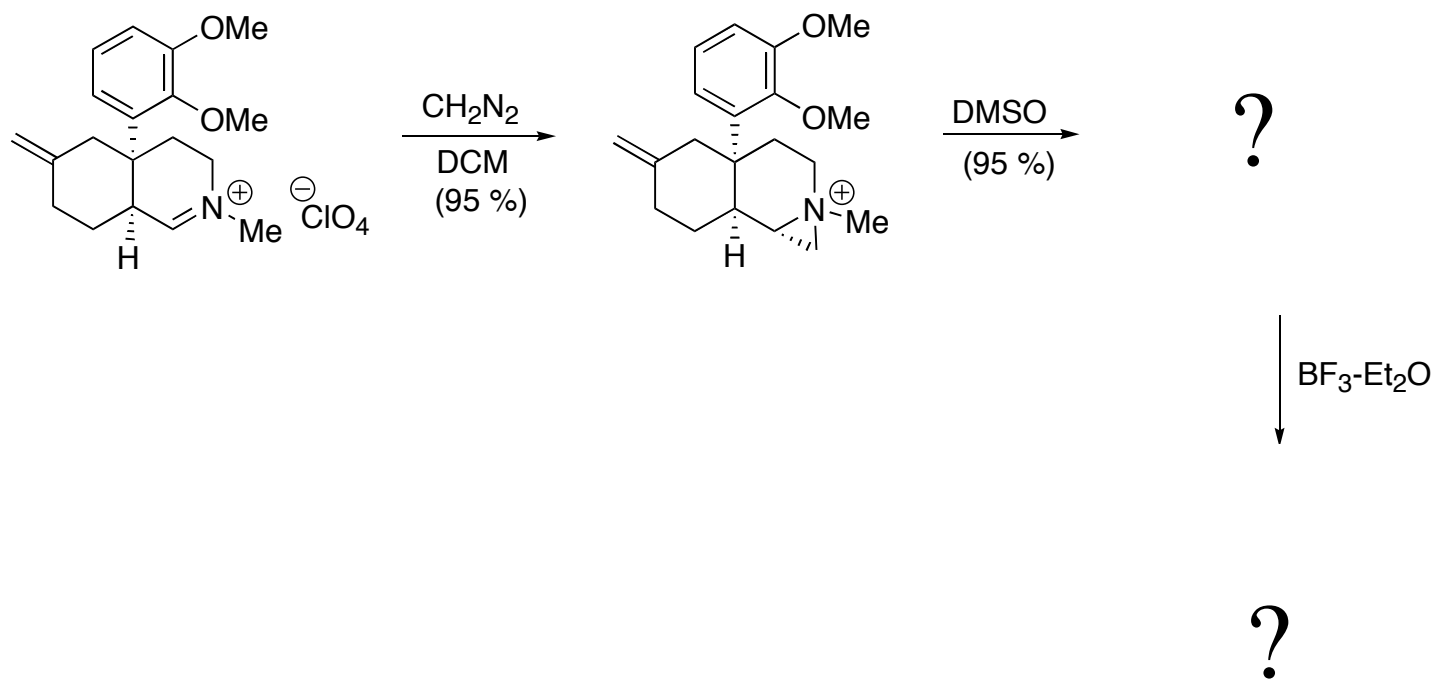
Evans Synthesis

□ Forward Synthesis: Immonium Perchlorate



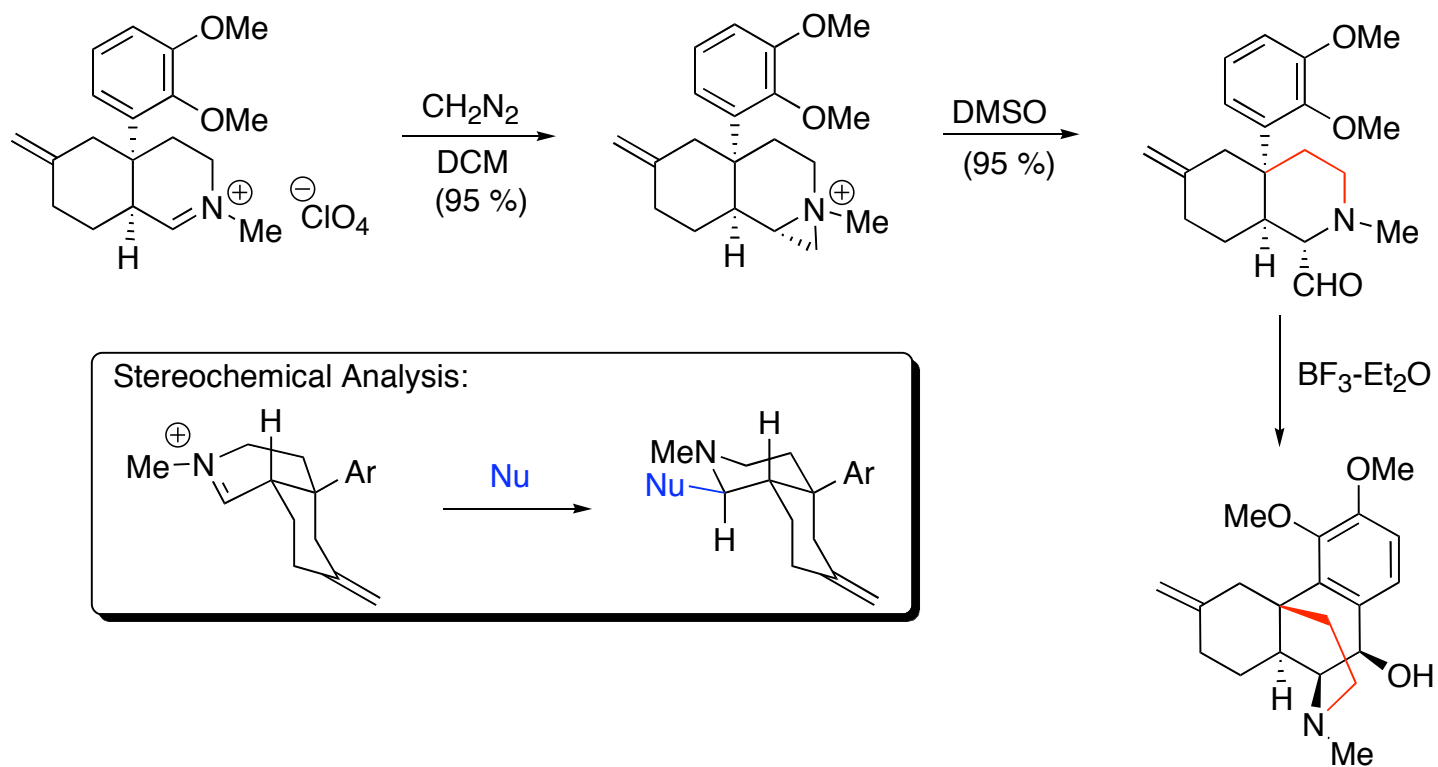
Evans Synthesis

□ Forward Synthesis:



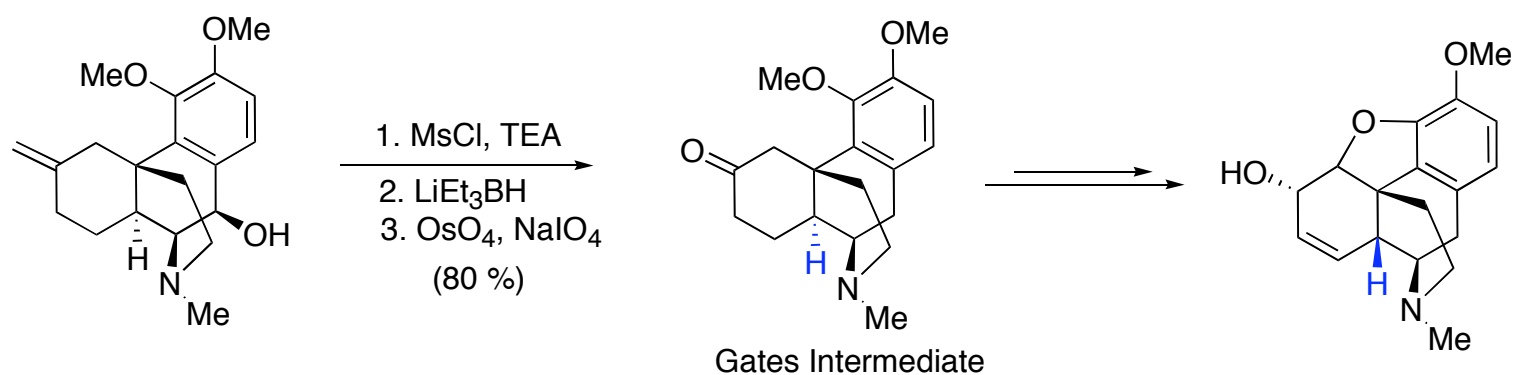
Evans Synthesis

□ Forward Synthesis:



Evans Synthesis

□ Forward Synthesis: End Game

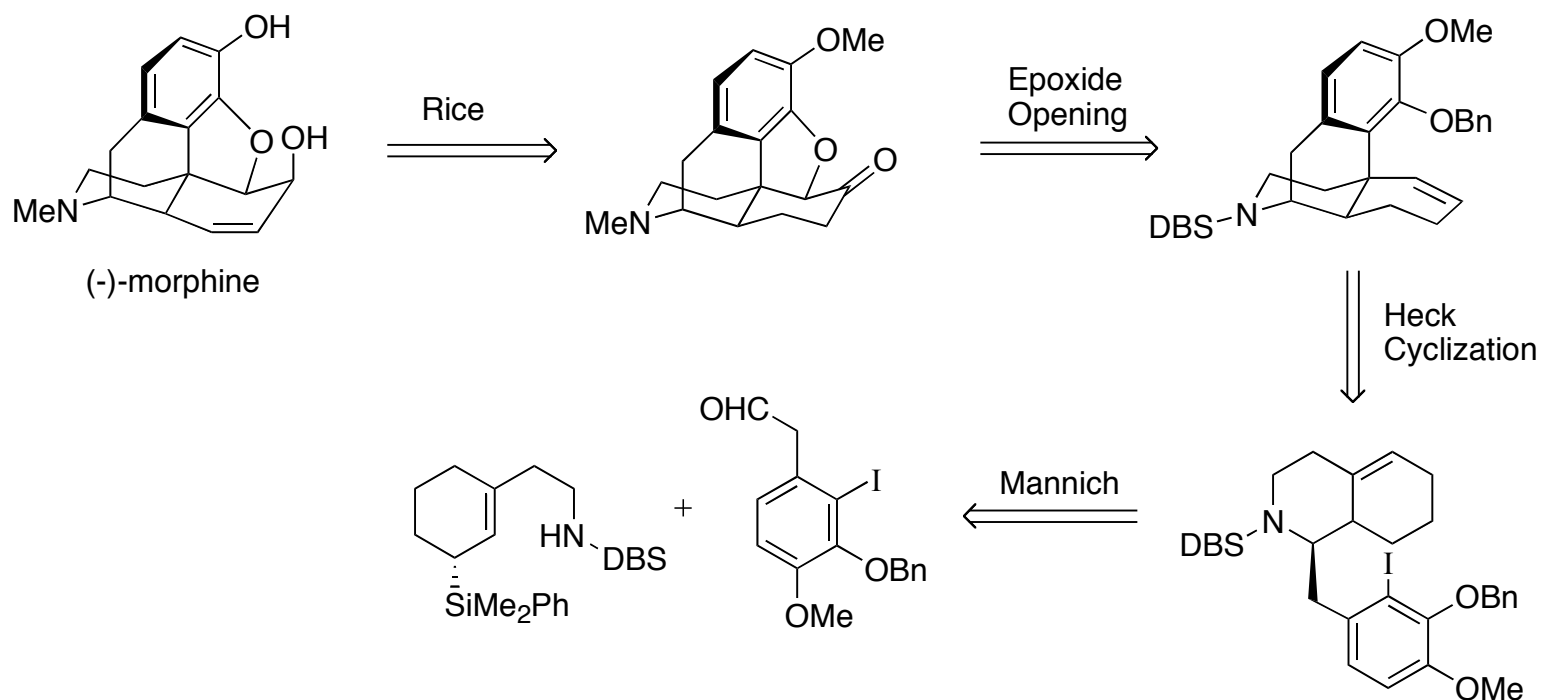


□ Analysis: Evans Synthesis

- Short sequence to achieve the gates intermediate (10 steps)
- Cleaver and original disconnect
- Major limitation is having to go through gates intermediate

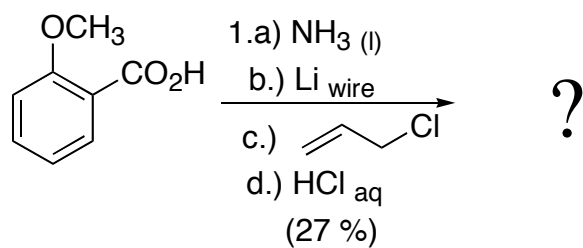
Overman Synthesis

□ Retrosynthesis



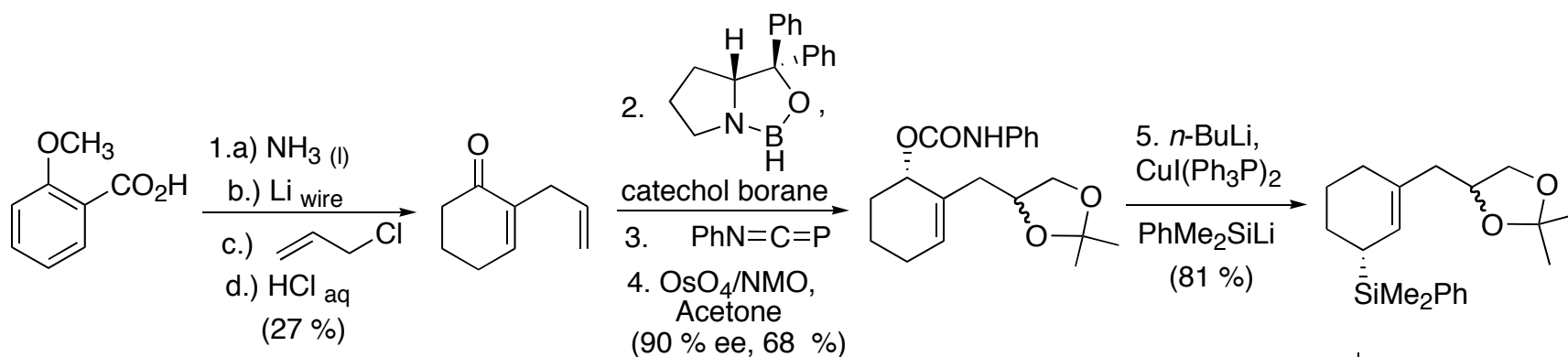
Overman Synthesis

□ Forward Synthesis: amine component

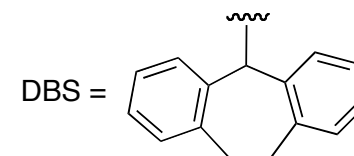
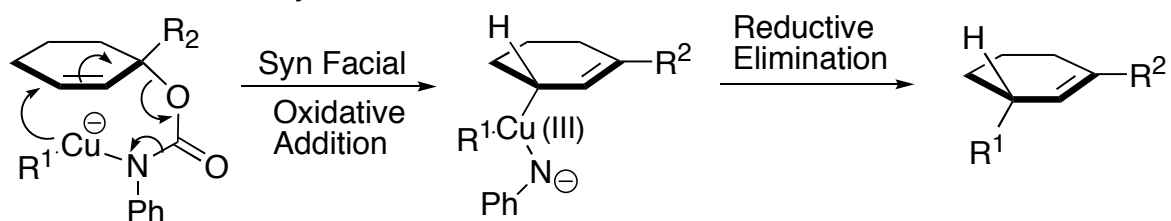


Overman Synthesis

□ Forward Synthesis: amine component

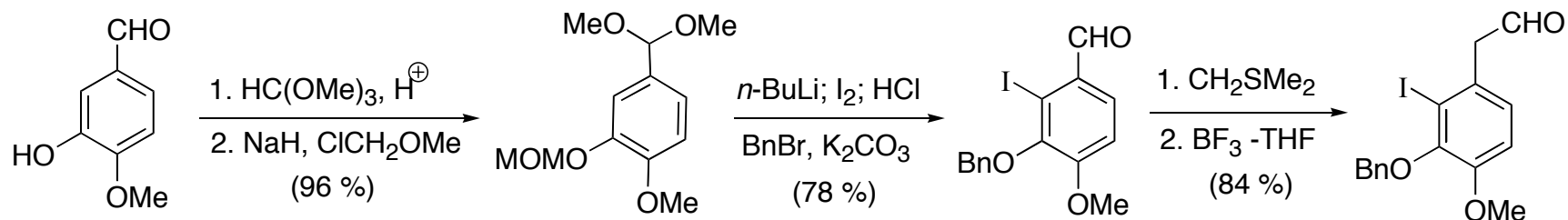


Stereochemical Analysis:

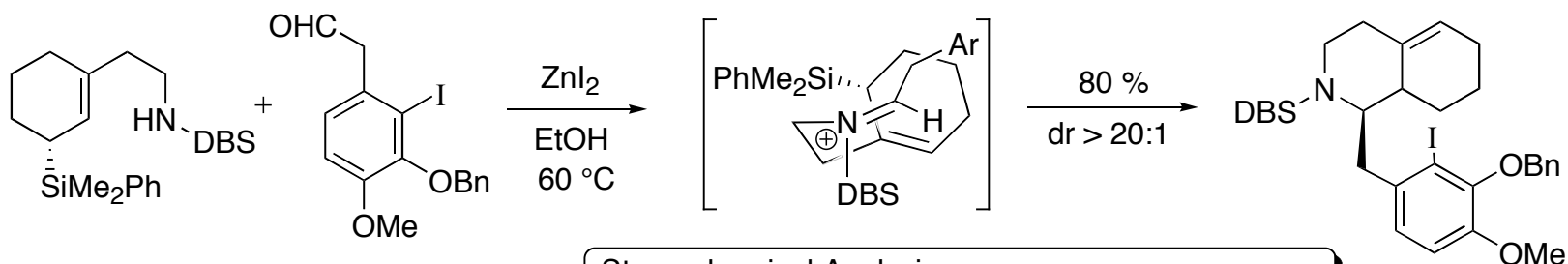


Overman Synthesis

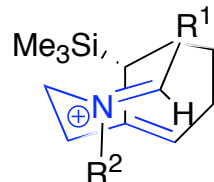
□ Forward Synthesis: aldehyde component



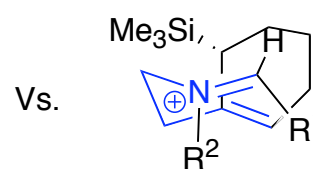
□ Forward Synthesis: mannich reaction



Stereochemical Analysis:



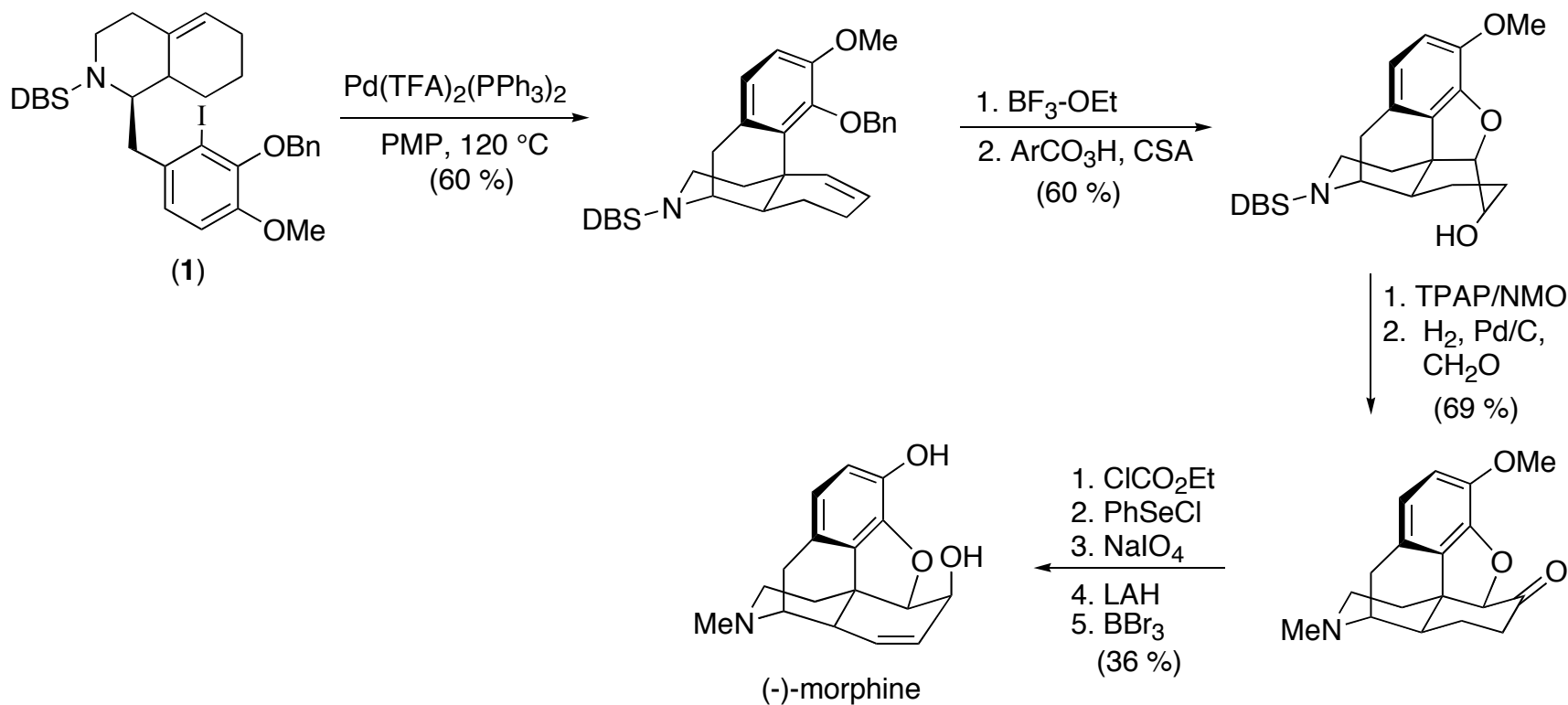
Favored for large R^1



Favored for small R^1

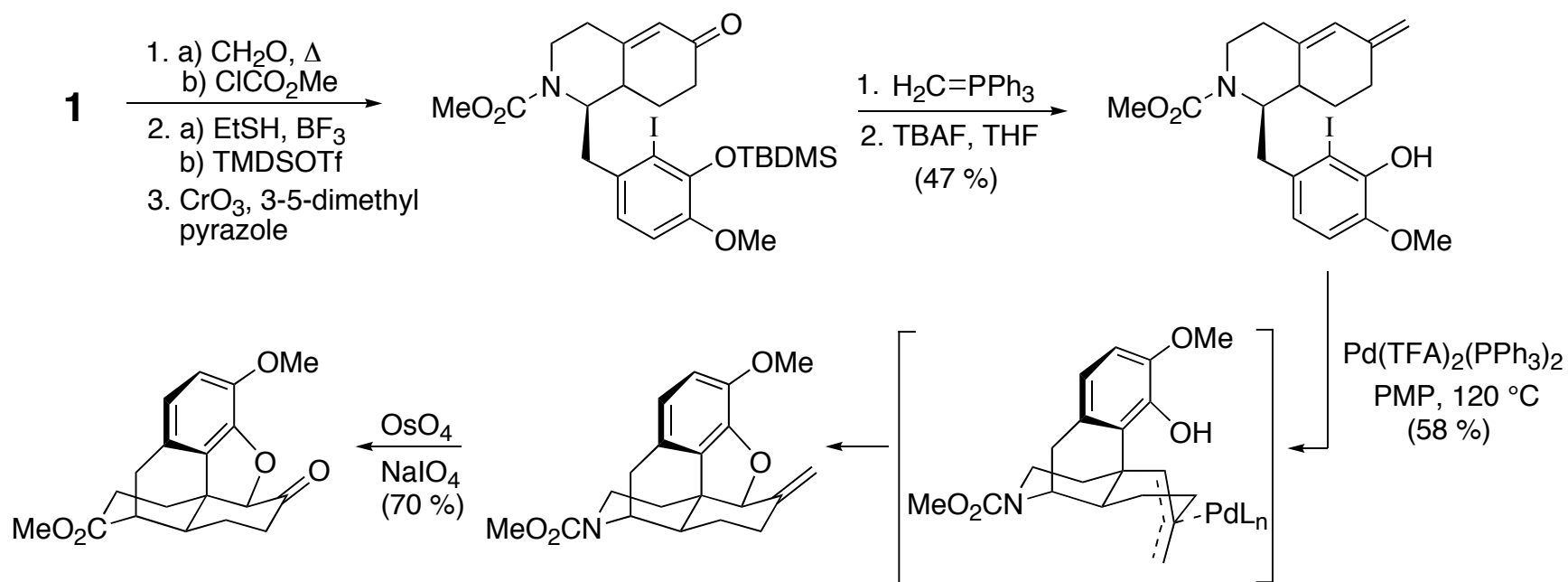
Overman Synthesis

□ Forward Synthesis: Heck Cyclization and End Game



Overman Synthesis

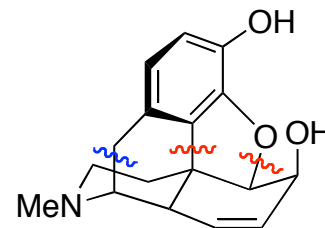
□ Forward Synthesis: Bis-Heck Cyclizations



Overman Synthesis

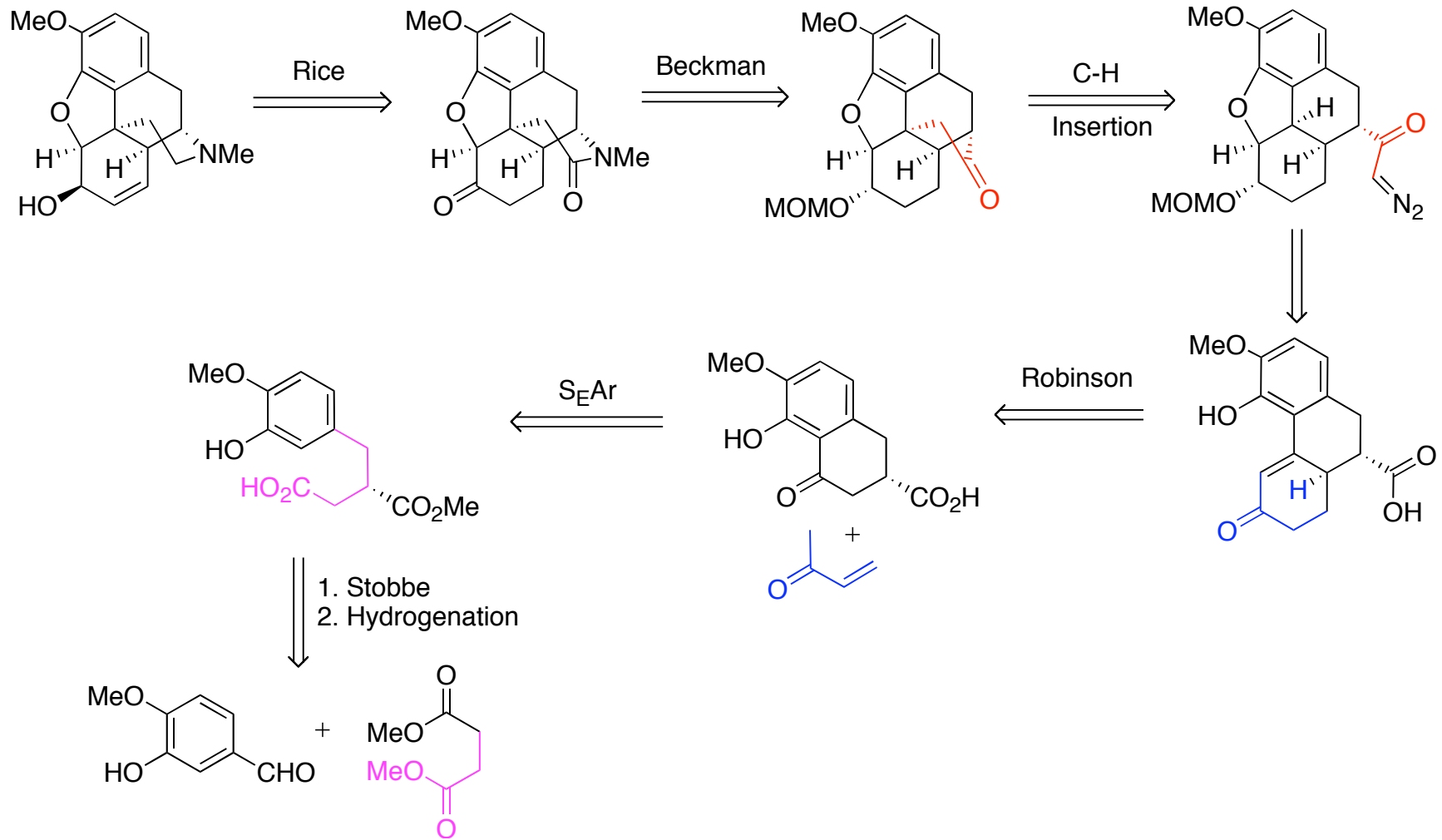
□ Analysis: Overman Approach

- 1st enantioselective synthesis that did not contain a resolution
- Natural and unnatural morphine available
- 23 steps with an overall yield of 0.56 % (single heck)
- 26 steps with an overall yield of 0.184 % (bis-cyclization)
- Key disconnections were the Heck and Mannich



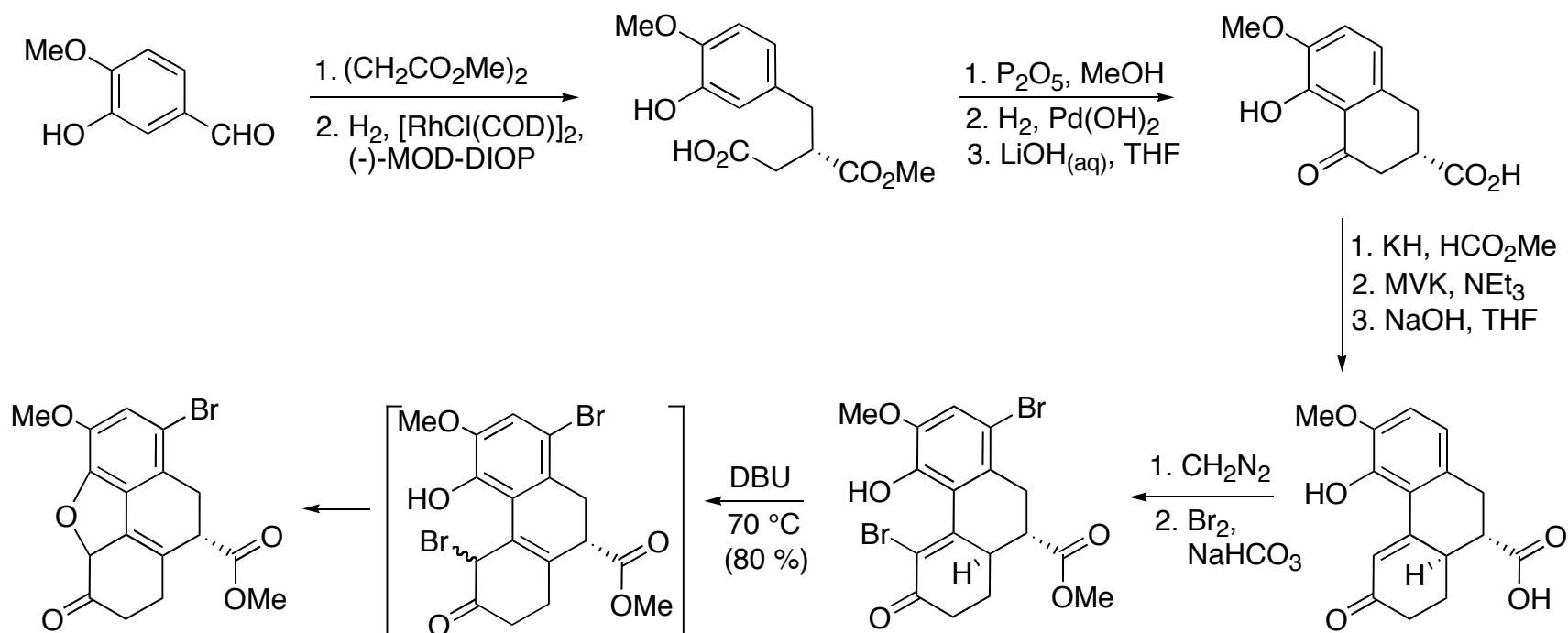
White Synthesis

□ Retrosynthesis



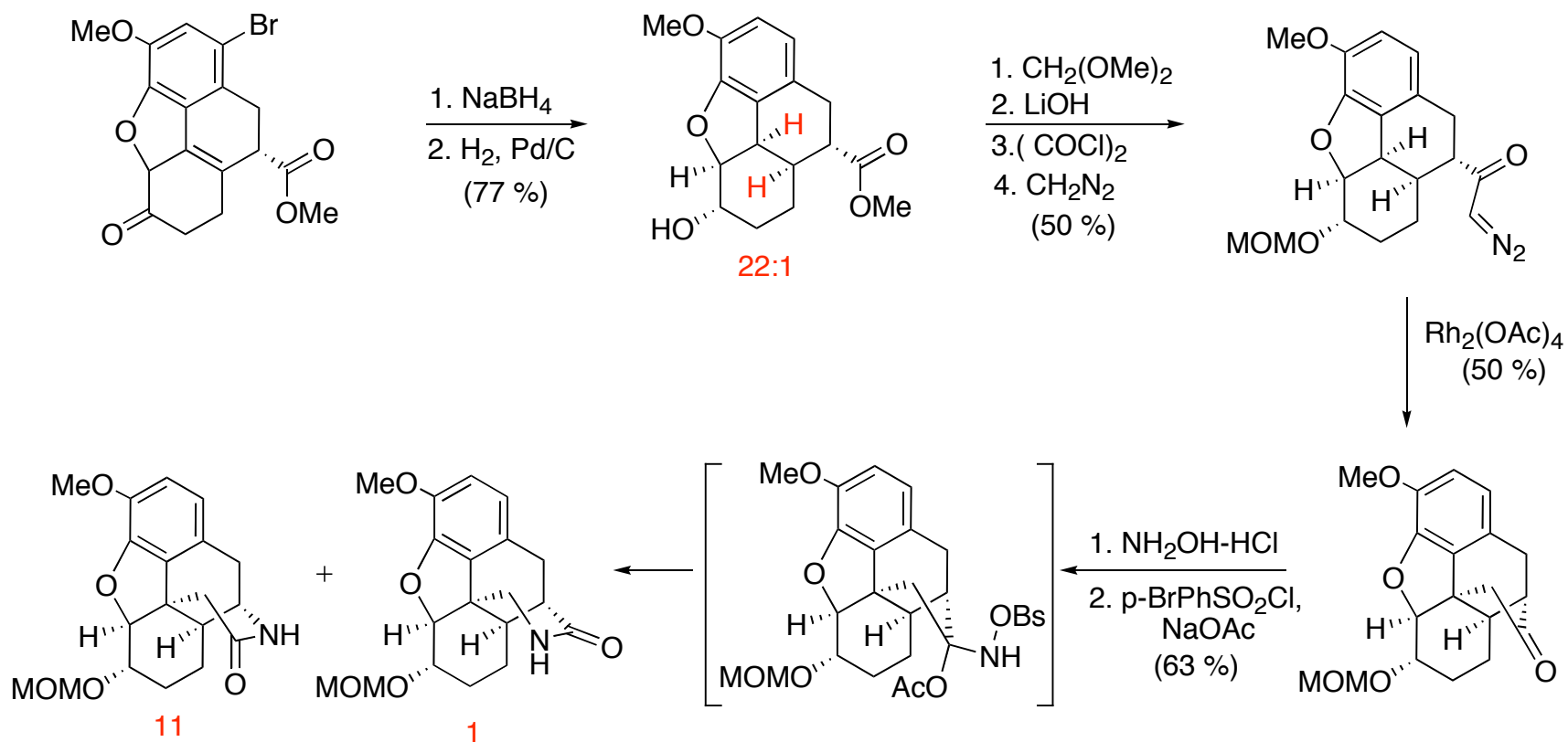
White Synthesis

□ Forward Synthesis:



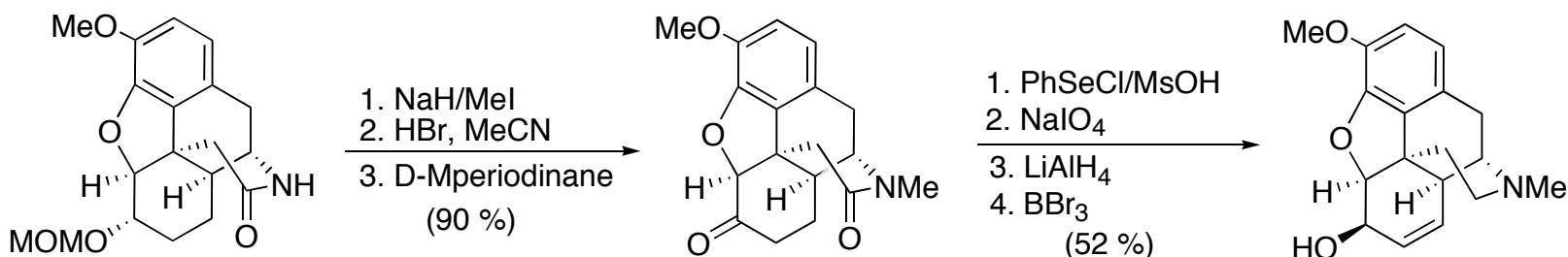
White Synthesis

□ Forward Synthesis:



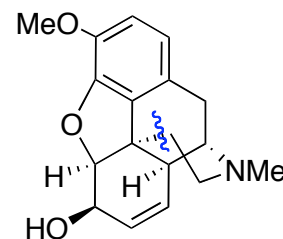
White Synthesis

□ End Game:



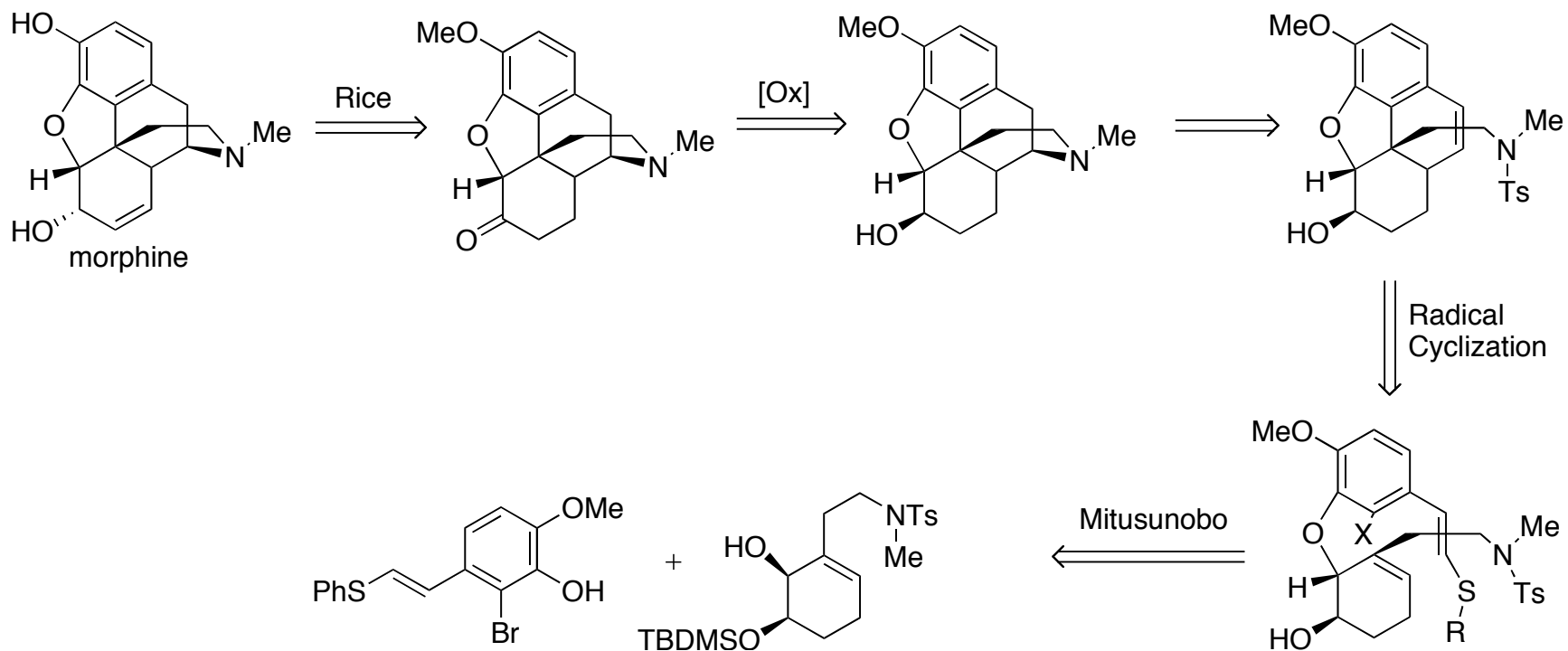
□ Analysis: White Approach

- 29 steps
- Overall yield of 1.73 %
- Asymmetry was introduced early via enantioselective hydrogenation
- Key disconnect was the Rhodium (II) catalyzed C-H insertion



Parker Synthesis

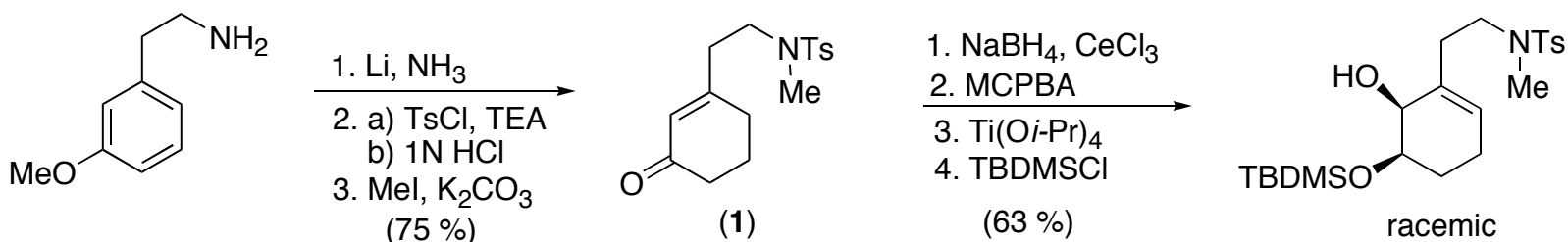
□ Retrosynthesis:



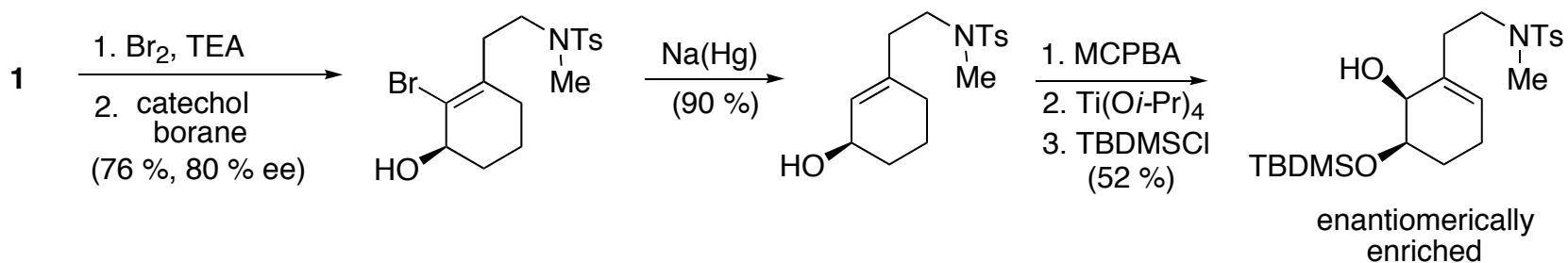
Parker Synthesis

□ Forward Synthesis:

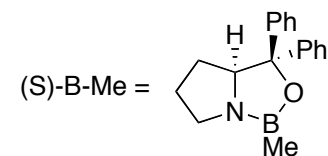
• Racemic Route:



• Asymmetric Route:

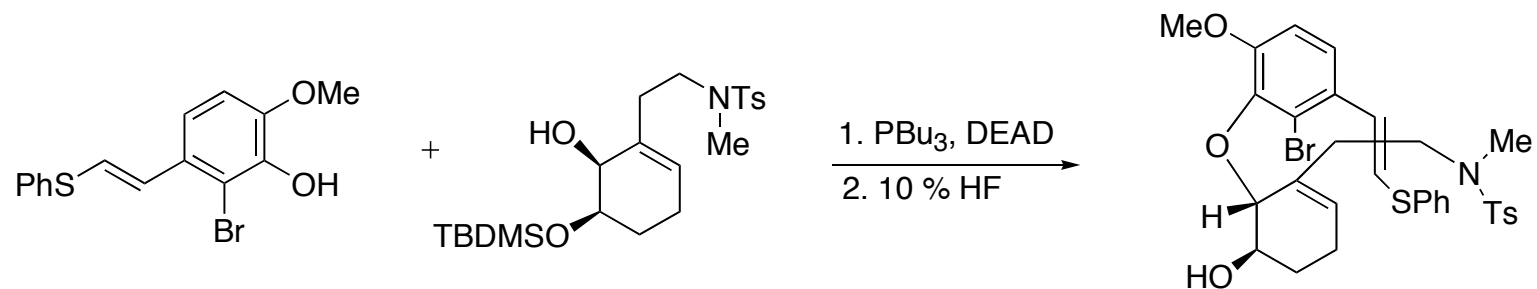
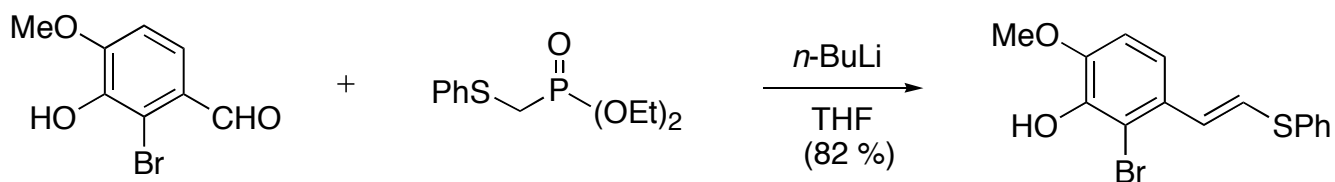


Failed routes included direct CBS reduction of **1** (35 % ee) and Sharpless kinetic resolution of the allylic alcohol (44 % ee)



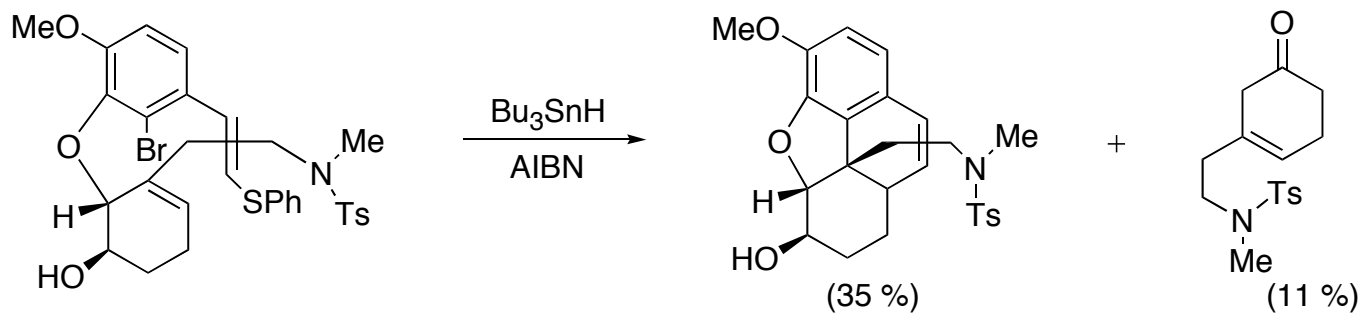
Parker Synthesis

□ Forward Synthesis: Mitsunobu Coupling



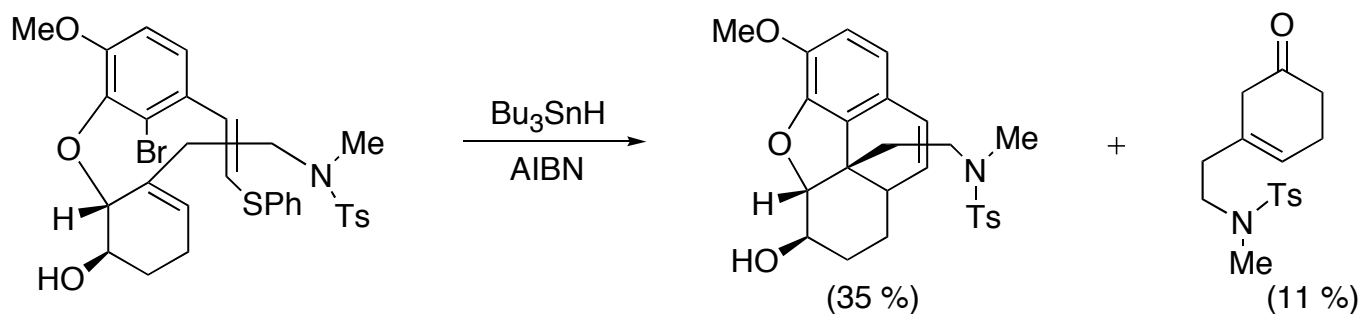
Parker Synthesis

□ Forward Synthesis: Radical Cyclization



Parker Synthesis

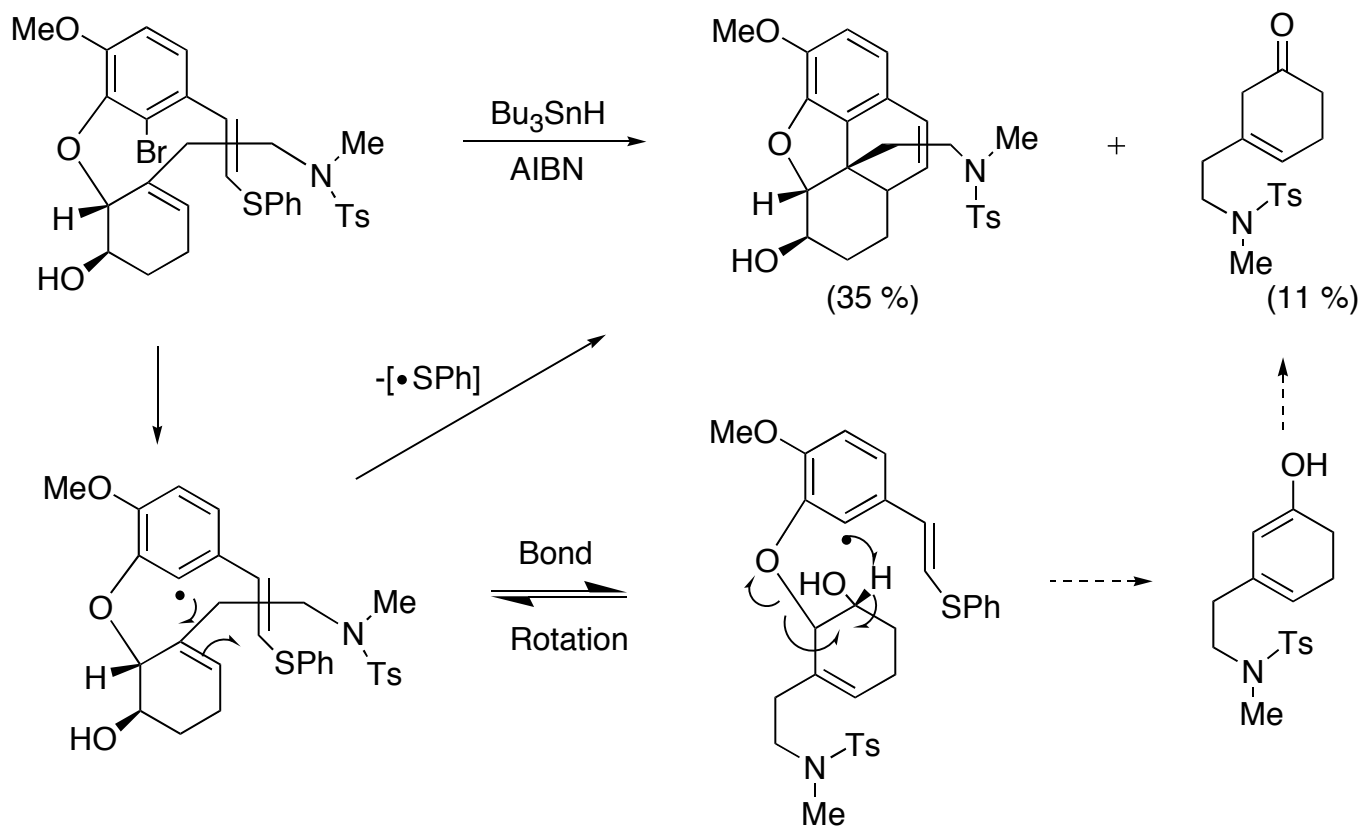
□ Forward Synthesis: Radical Cyclization



Draw a mechanism that accounts for formation of the side product

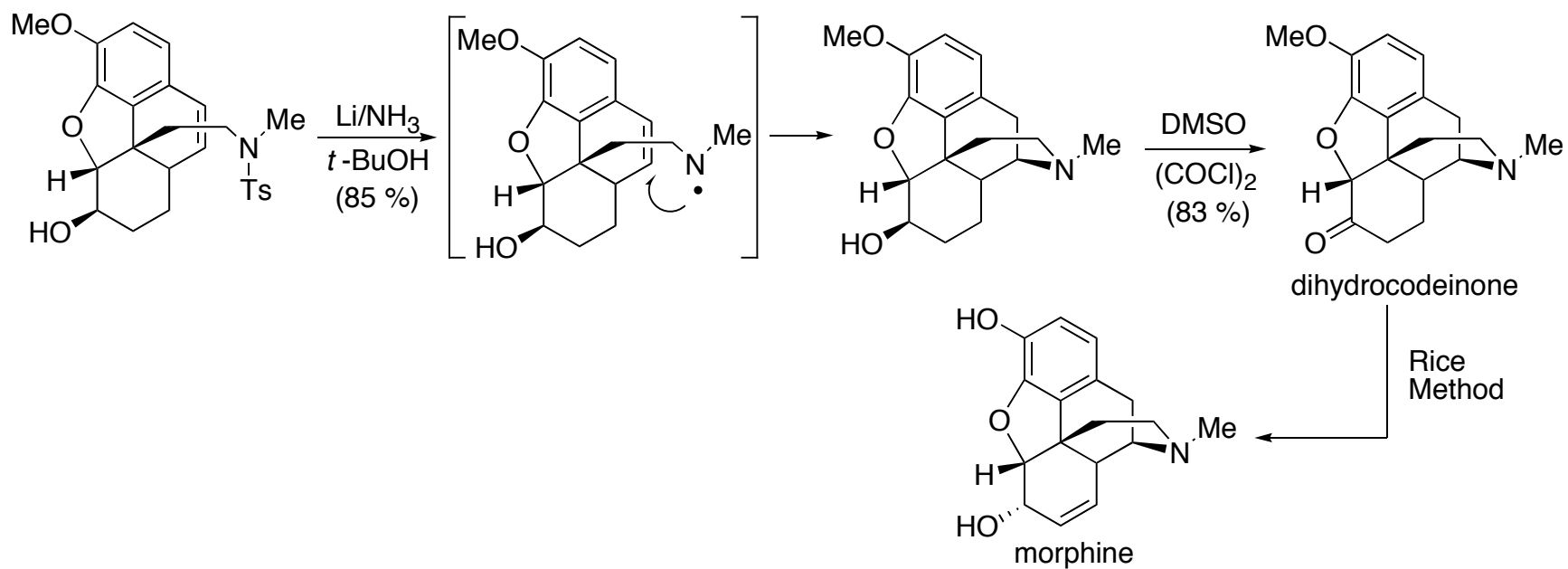
Parker Synthesis

□ Forward Synthesis: Radical Cyclization



Parker Synthesis

□ End Game

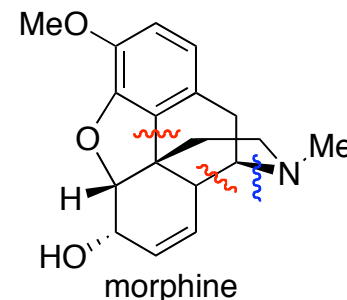


Parker Synthesis

□ Analysis: Parker Method

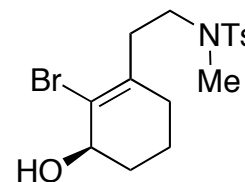
(+/-) Morphine:

- 22 steps
- Overall yield of 2.07 %
- Radical cyclization was the key disconnect
- First published in August, 1992



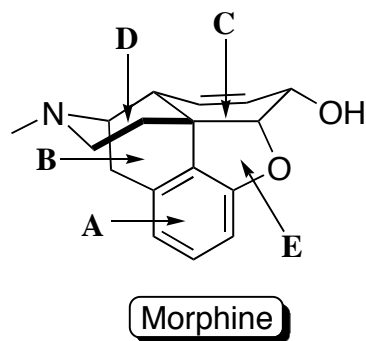
(-) Morphine:

- 24 steps
- Overall yield of 1.7 %
- CBS reduction of α -bromo enone was key step
- Published in January, 2006



Conclusions

- Disconnection approaches have evolved with the methods of synthetic chemistry



Gates (1952): Diels-Alder	}	Racemic
Rice (1980): Grewe Cyclization		
Evans (1982): Iminium Salts		
Overman (1993): Heck chemistry	}	Asymmetric
White (1997): C-H insertion		
Parker (2006): Radical Cyclization		

- Morphine approaches will continue to grow
(Only Rice has come close to synthetically viable route)
- Continued need for developing morphine derivatives which can attenuate addictive properties

References

Review:

Taber, D.F. *The Enantioselective Synthesis of Morphine: Strategies and Tactics in Organic Synthesis* **2004**, 5, 353

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Rice, C.; Brossi, A. *J. Org. Chem.* **1980**, 45, 592

Evans, D.A.; Mitch, C.H. *Tetrahedron Lett.* **1982**, 23, 285

Overman, L.E. *Pure and Appl. Chem.* **1994**, 66, 1423

White, J.D. *J. Org. Chem.* **1999**, 64, 7871

Parker, K.A. *J. Org. Chem.* **2006**, 71, 449