

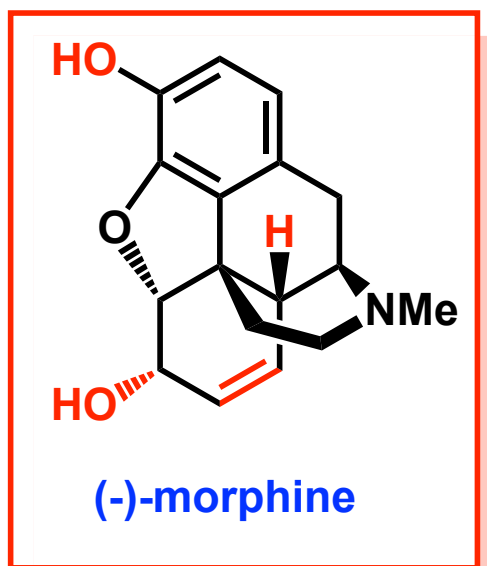


**Krishna P Kaliappan**  
*Professor of Chemistry, IIT Bombay*

**CH-588 Course on Organic Synthesis**

# Isolation of Morphine

- In 1806, a 21 year old pharmacist (Friedrich Serturner) isolated Morphine from opium produced by cut seed pods of the poppy *Papaver somniferum*

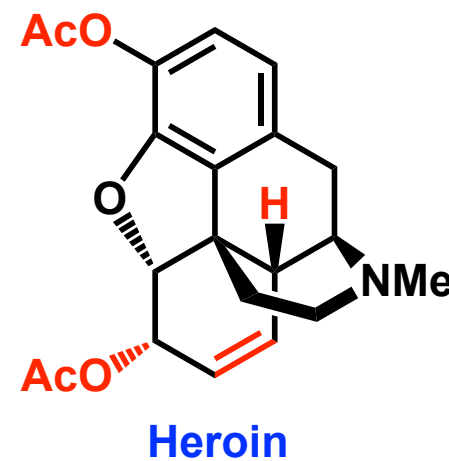


- This is actually the beginning of an era where drugs from plants could be purified

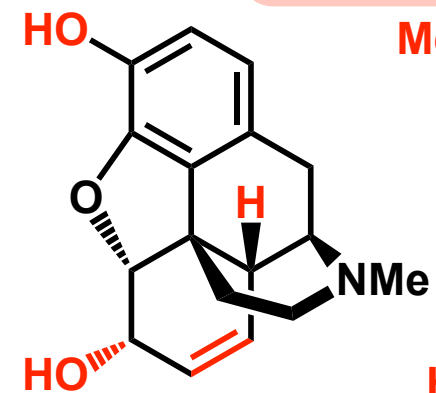
**Isolation:** 1. F. W. Sertürner, *Trommsdorf's Journal der Pharmazie*, 1805, 13, 1, 234

2. *Ann. chim. phys.*, 1817, 5, 21

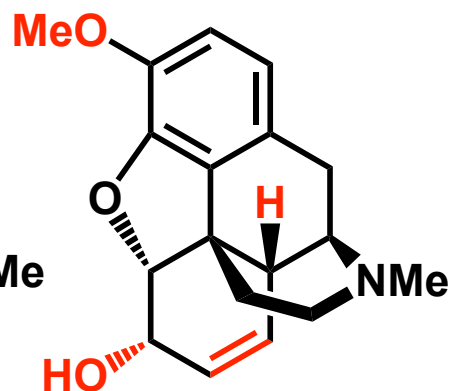
- Sir Robert Robinson proposed its correct structure in 1925
- The structure was confirmed by its first total synthesis by Gates in 1952 and by X-ray in 1955.
- More than 30 total and formal syntheses of morphine are reported
- However, only natural sources are the supplier for producing morphine and its analogues



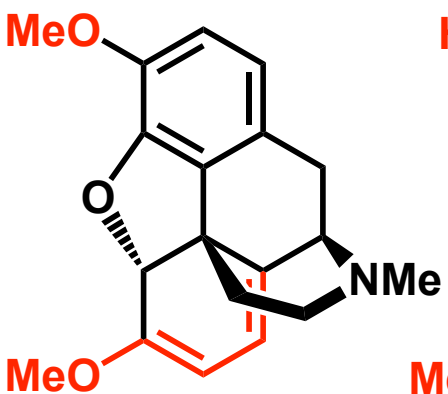
## Natural Opiates



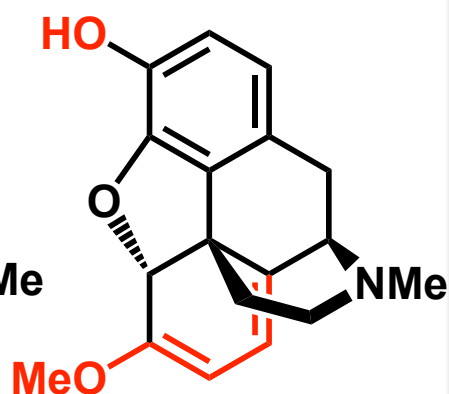
(-)-morphine



(-)-codeine

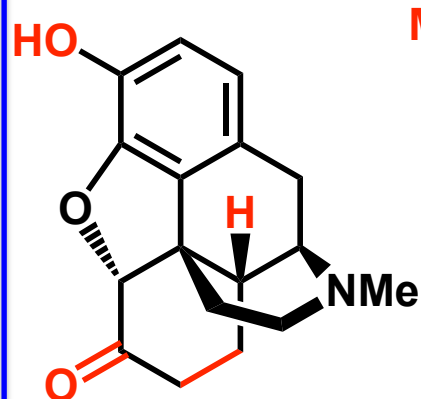


(-)-thebaine

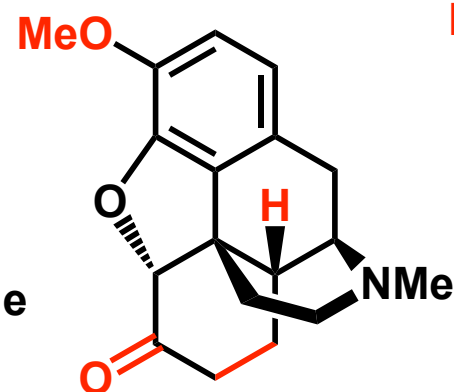


(-)-oripavine

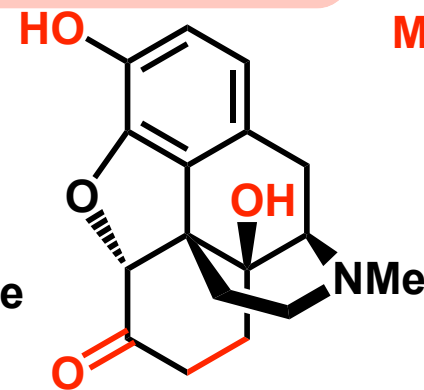
## Semisynthetic Opiates



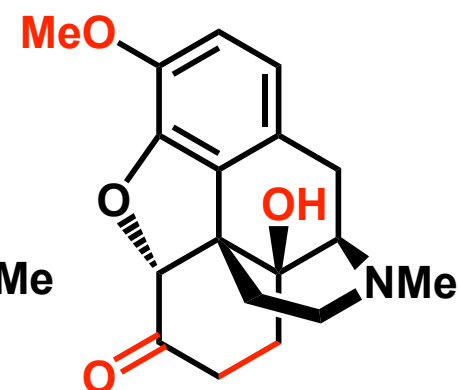
(-)-hydromorphone



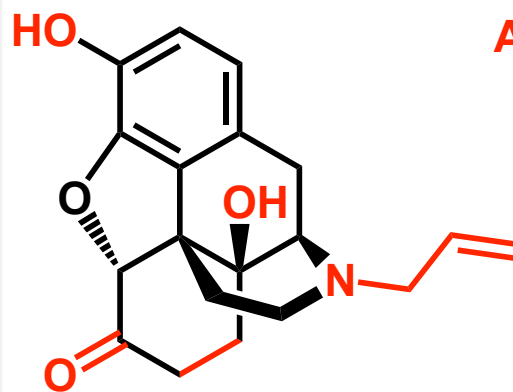
(-)-hydrocodone



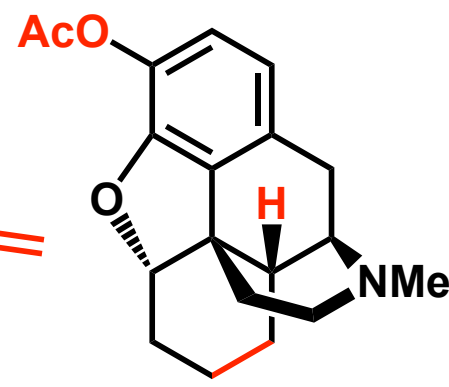
(-)-oxymorphone



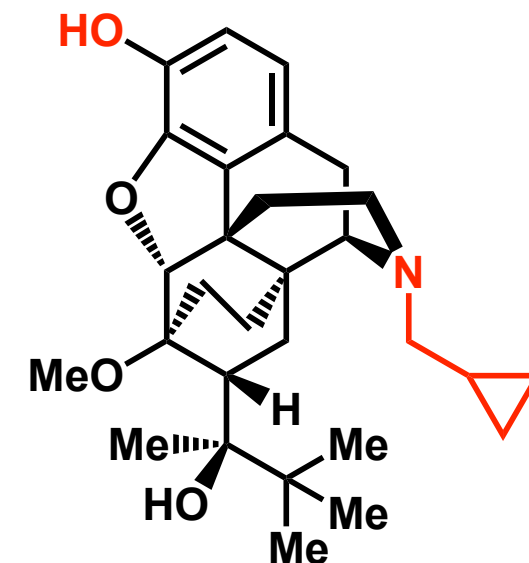
(-)-oxycodone



(-)-naloxone

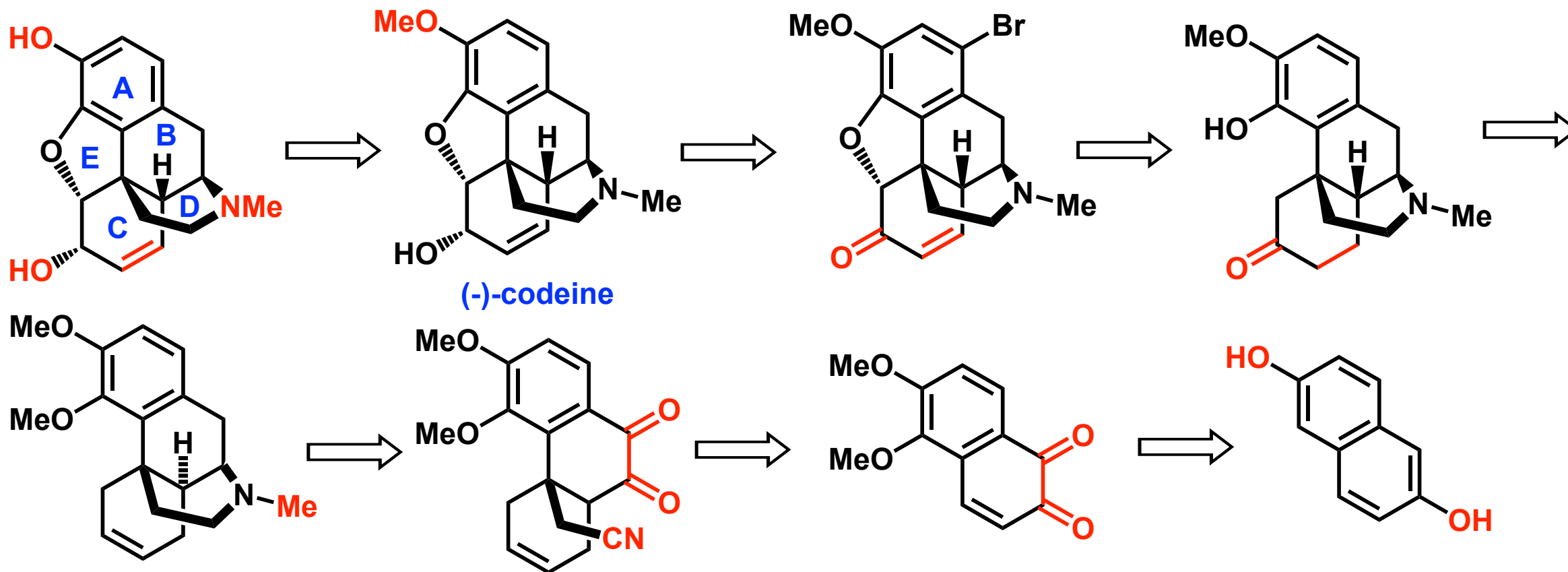


(-)-desomorphine

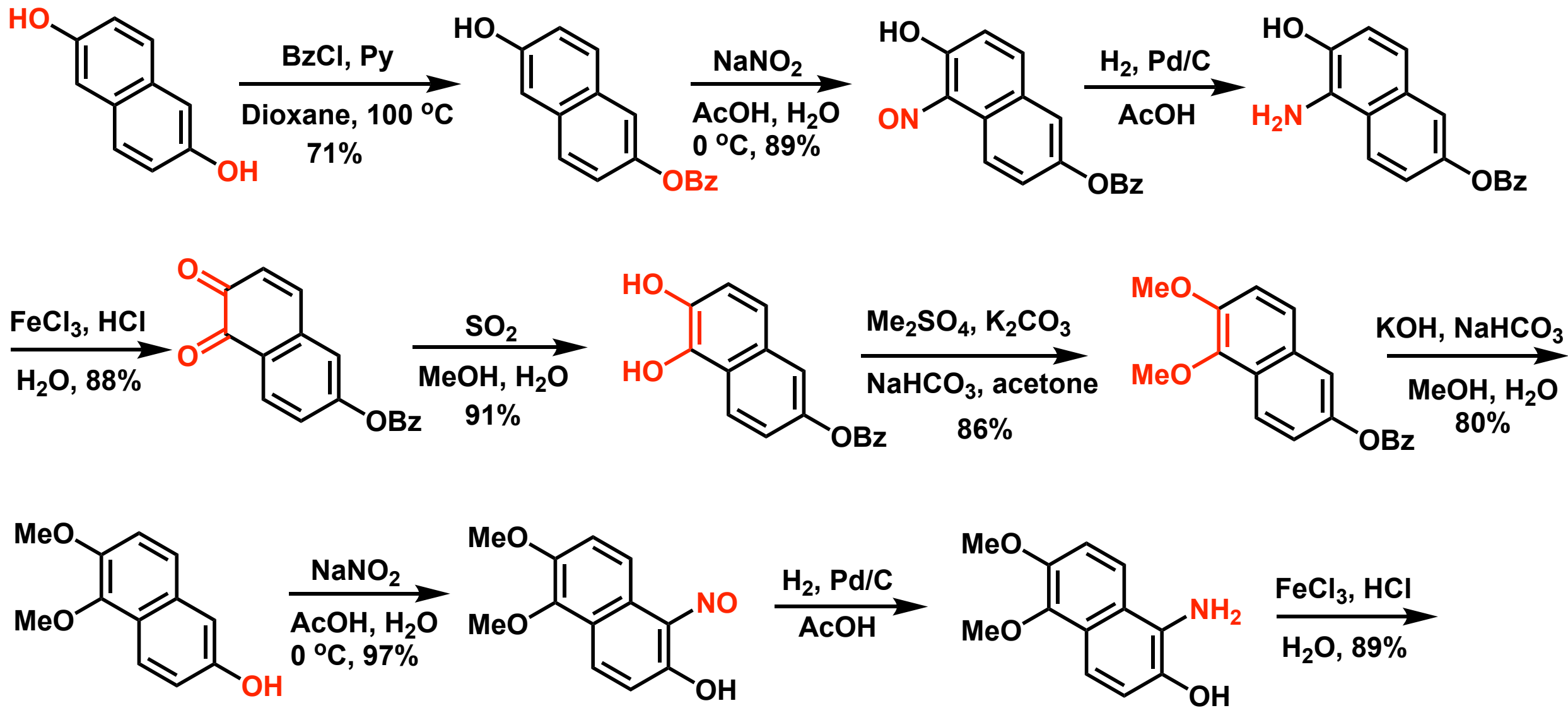


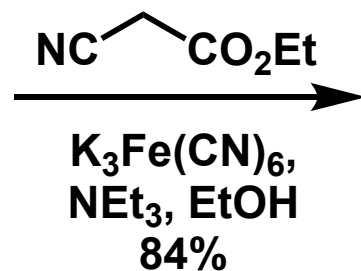
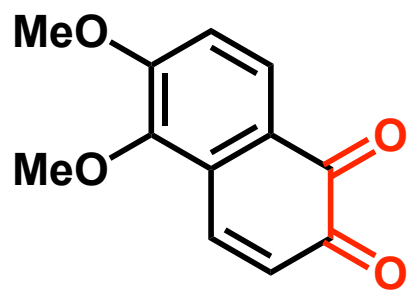
(-)-buprenorphine

- **Morphine**, the principal alkaloid of opium and the substance primarily responsible for its physiological effect, has attracted the attention of chemists for over **two hundred years**
- Morphine contains complex pentacyclic structure bearing **five contiguous stereocentres**
- Gates and Tschudi reported first total synthesis of morphine in **27 linear steps**

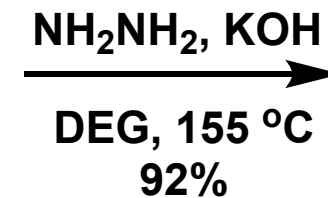
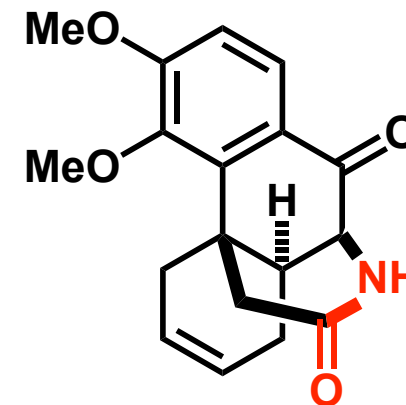
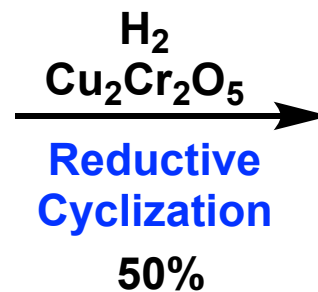
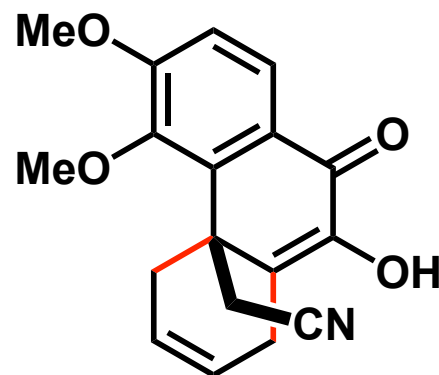
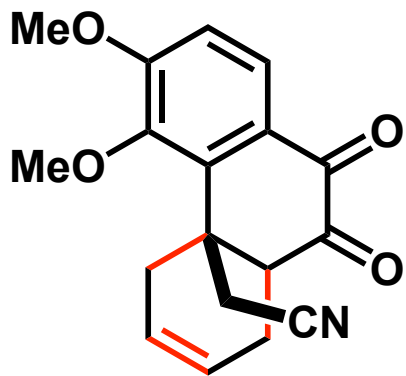
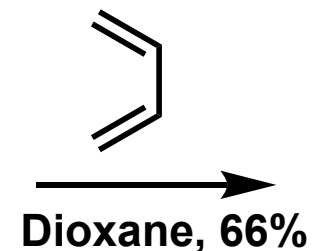
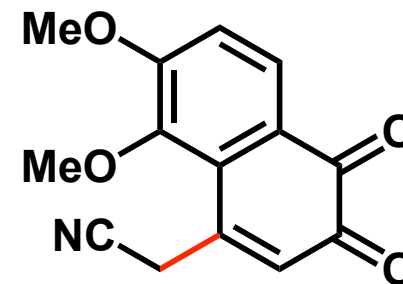
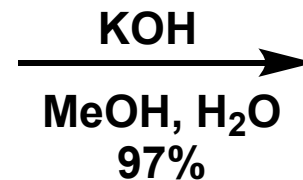
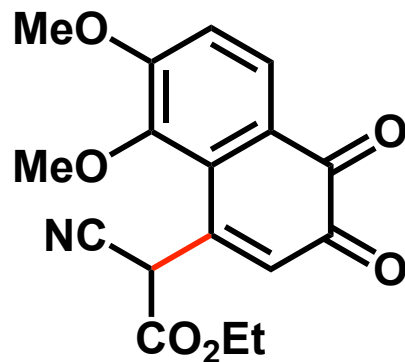


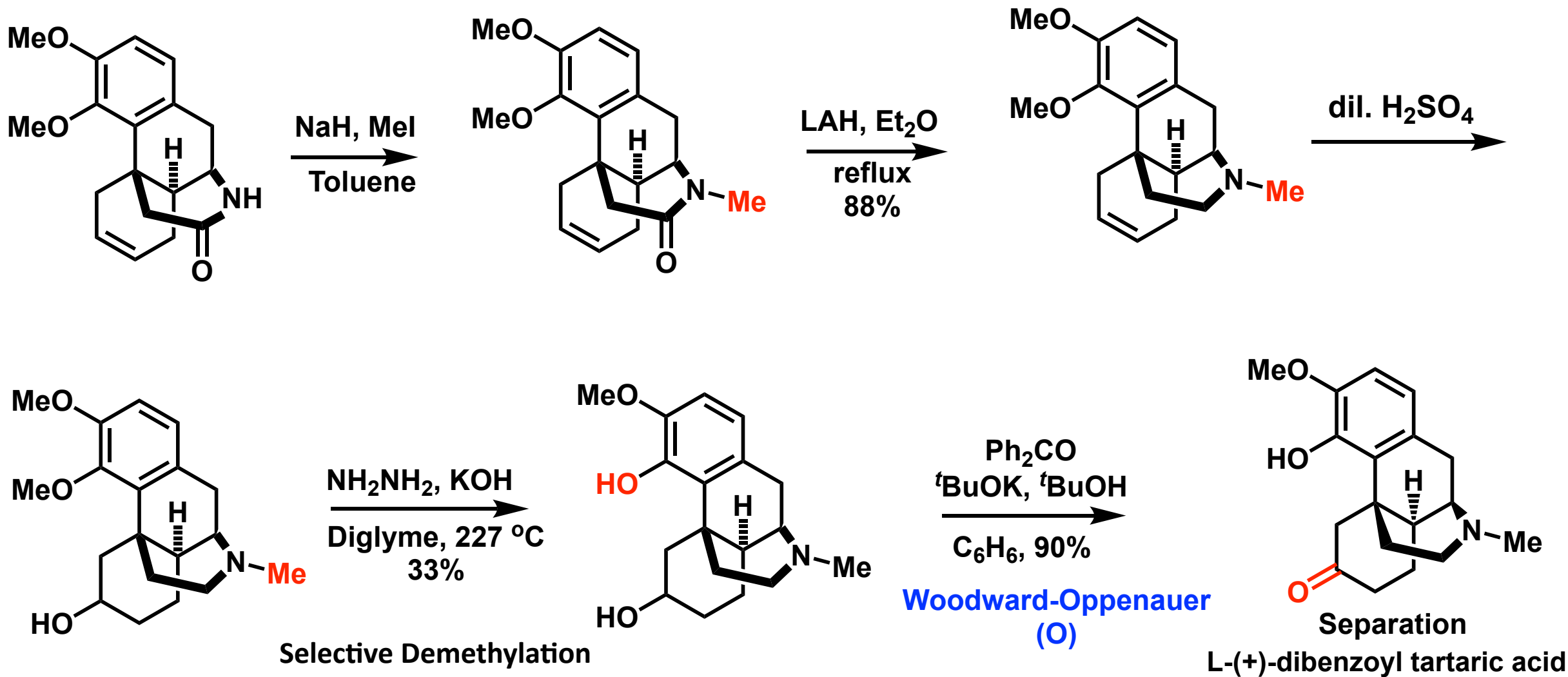
# Gates Total Synthesis of Morphine

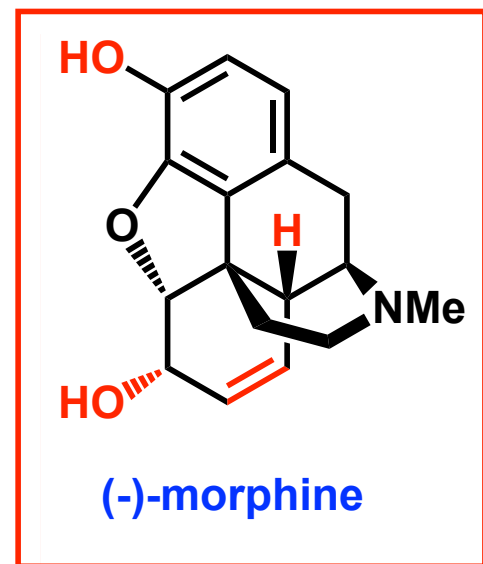
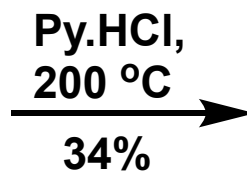
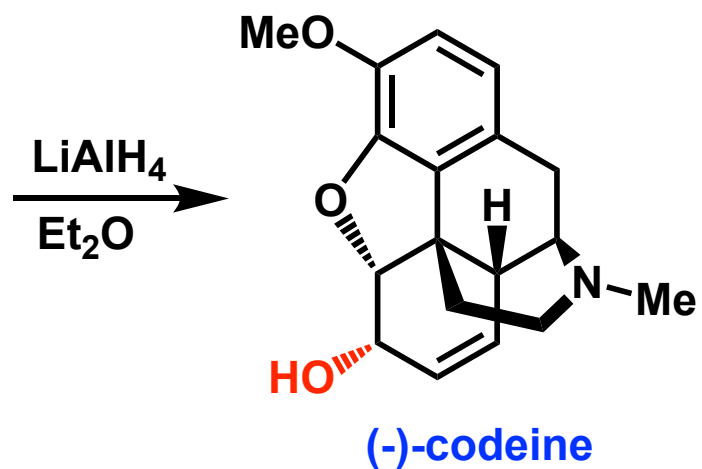
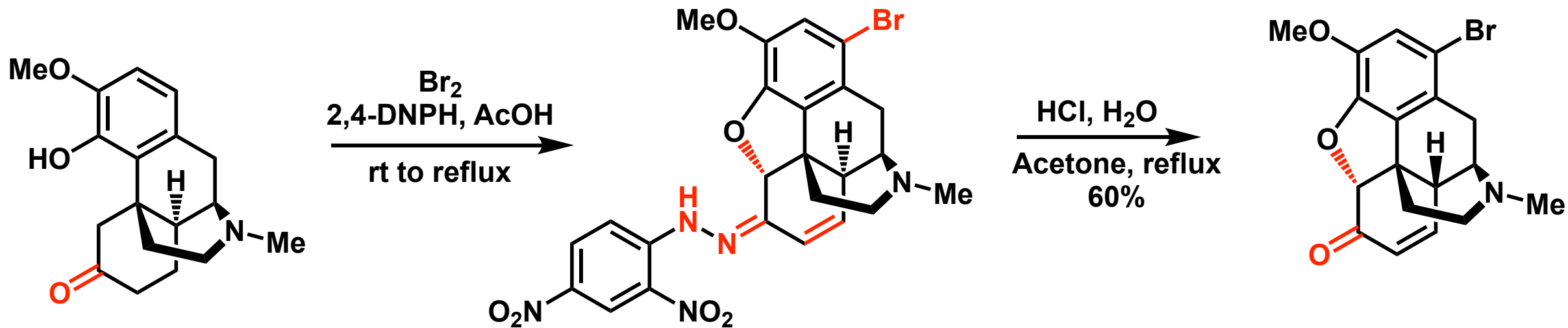




Michael  
Addition,  
Aromatization &  
Oxidation





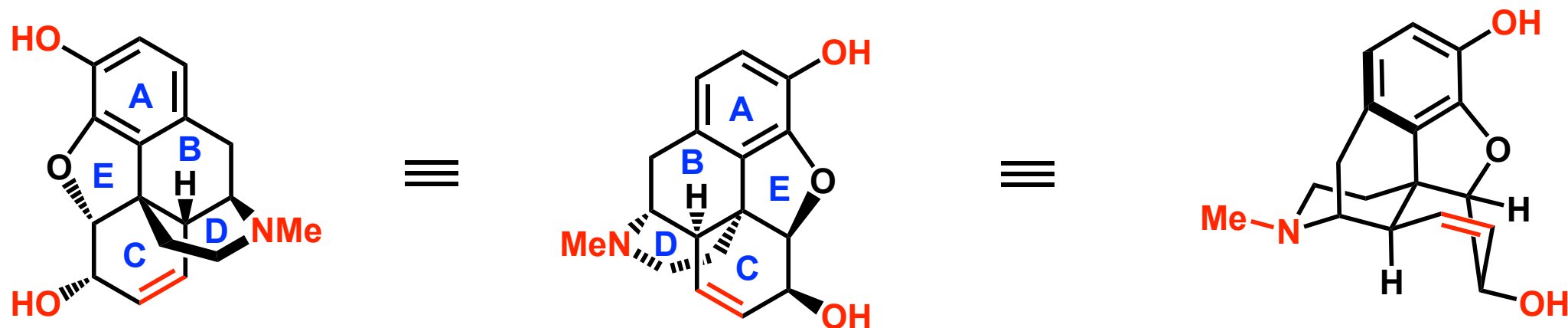


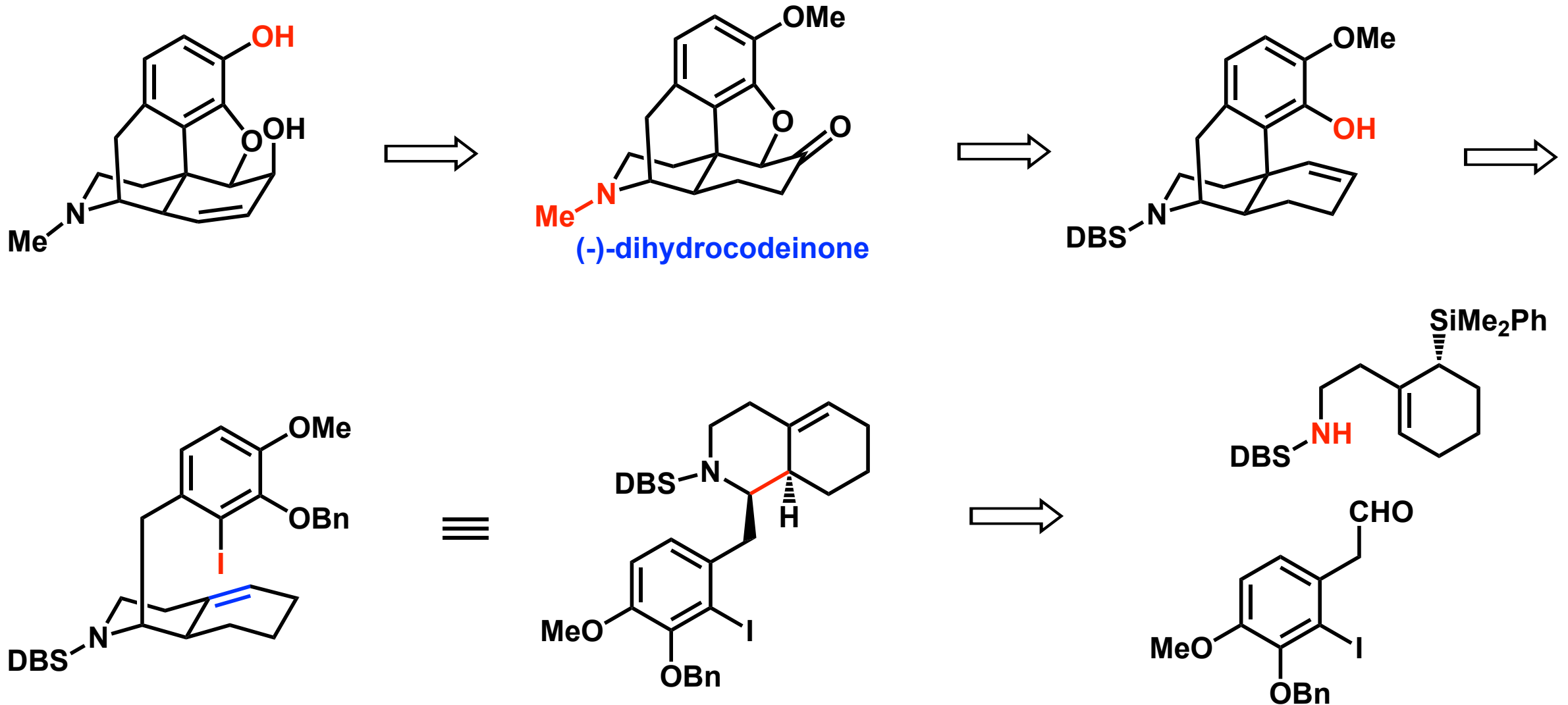
Total synthesis was completed in 27 linear steps with a 0.001 % overall yield

M. Gates, and coworker, *J. Am. Chem. Soc.*, 1956, 78, 1380

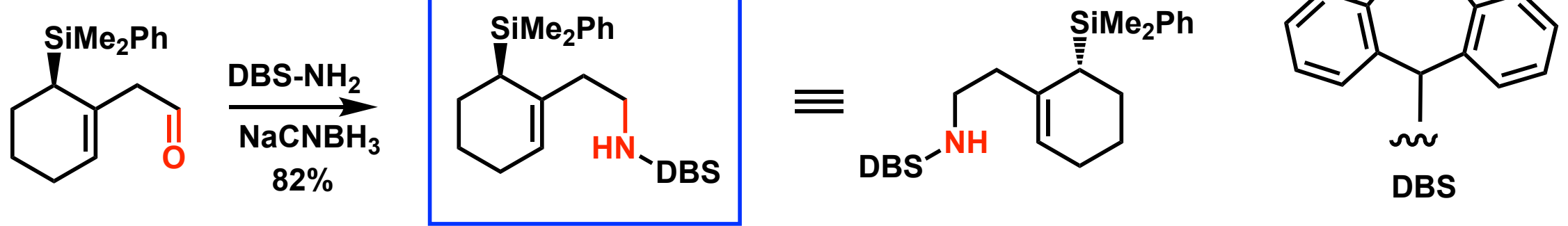
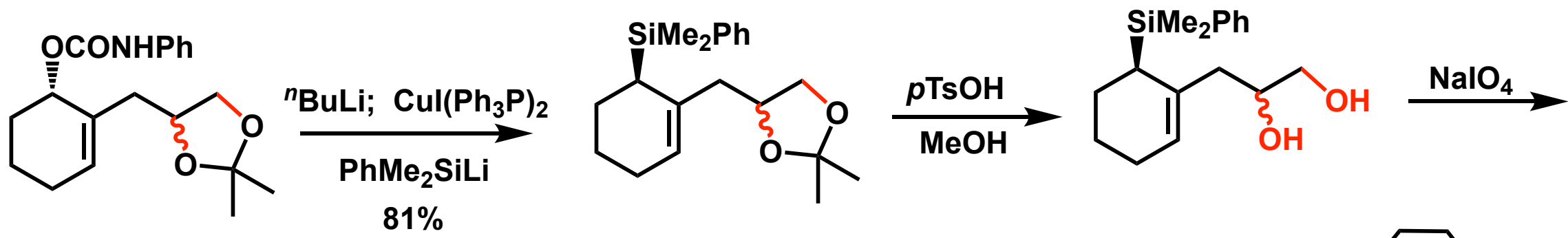
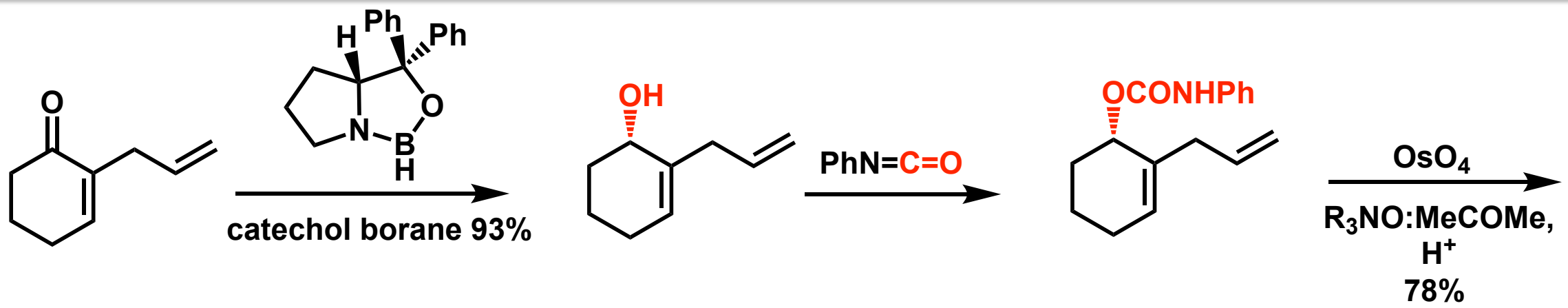


- Overman reported the total synthesis of morphine in 1993 starting from **isovanillin**
- Overman strategy was the first to form an enantioenriched **octahydroisoquinoline** and then employ an intramolecular **Heck reaction** to forge the critical quaternary center of the morphine skeleton

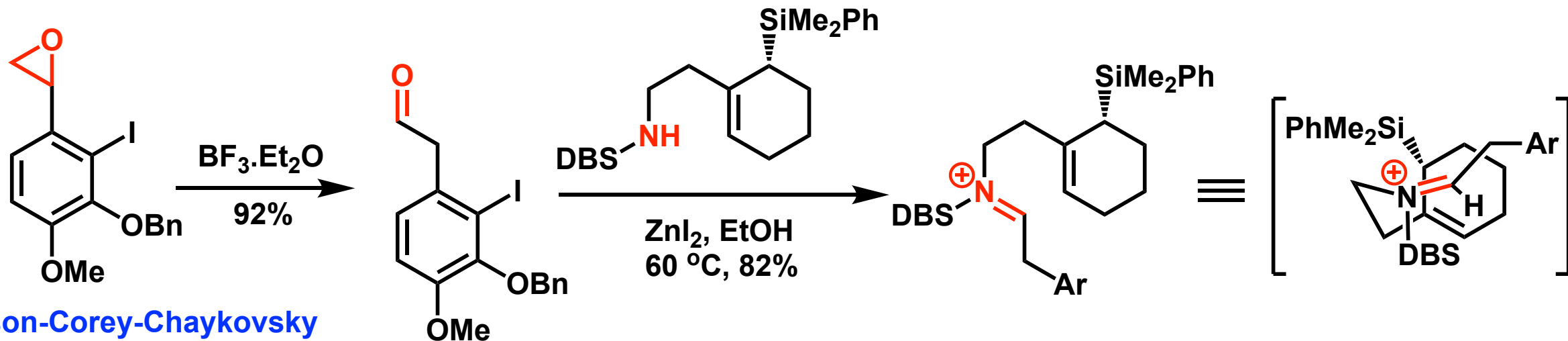
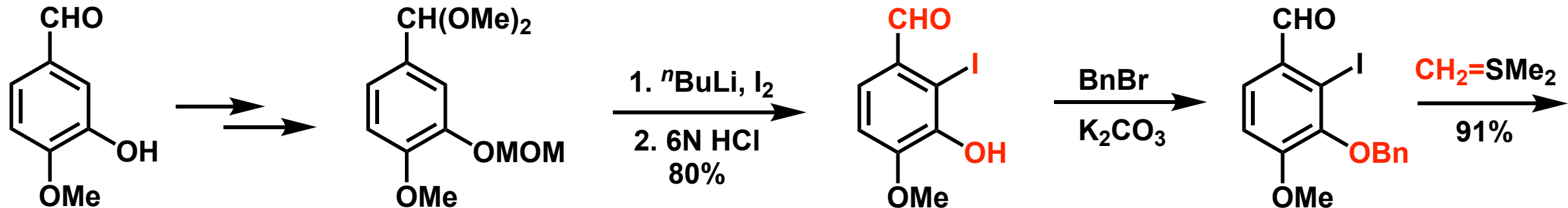




# Overman's Total Synthesis of Morphine

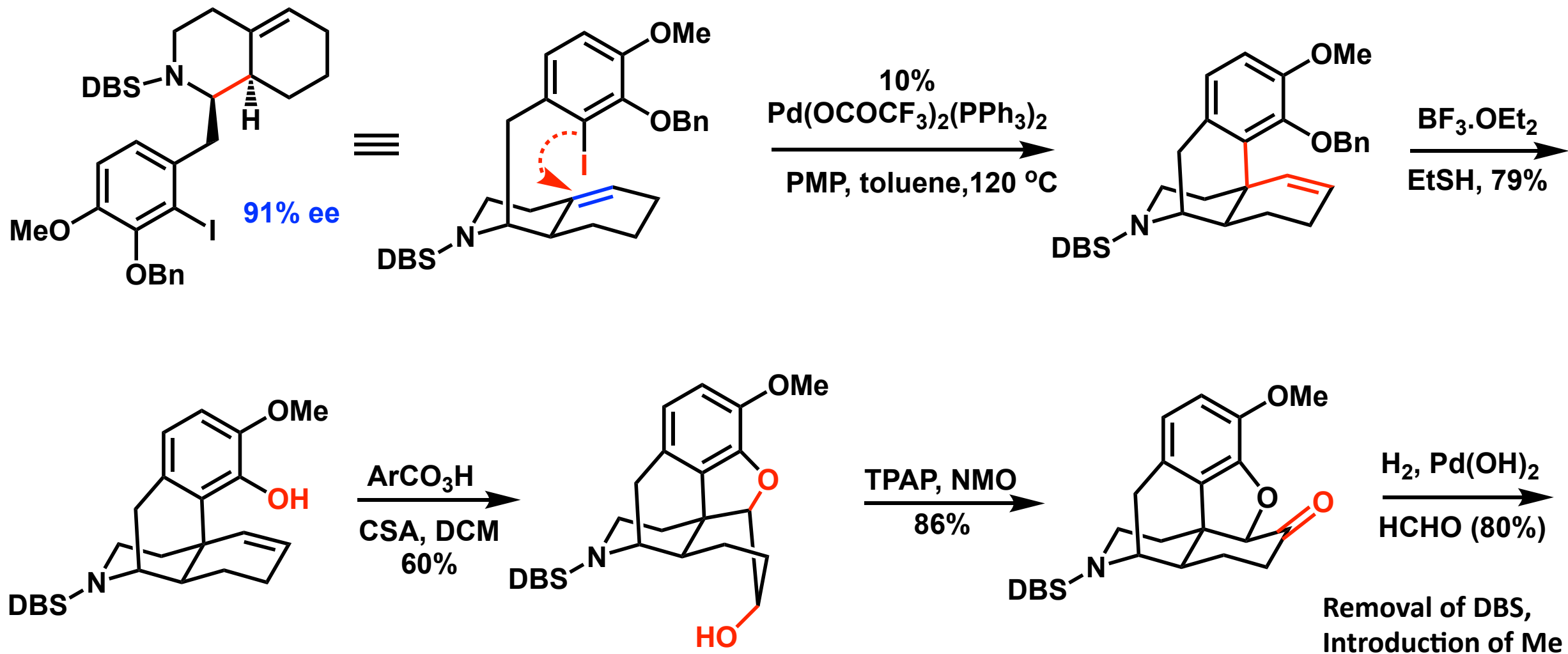


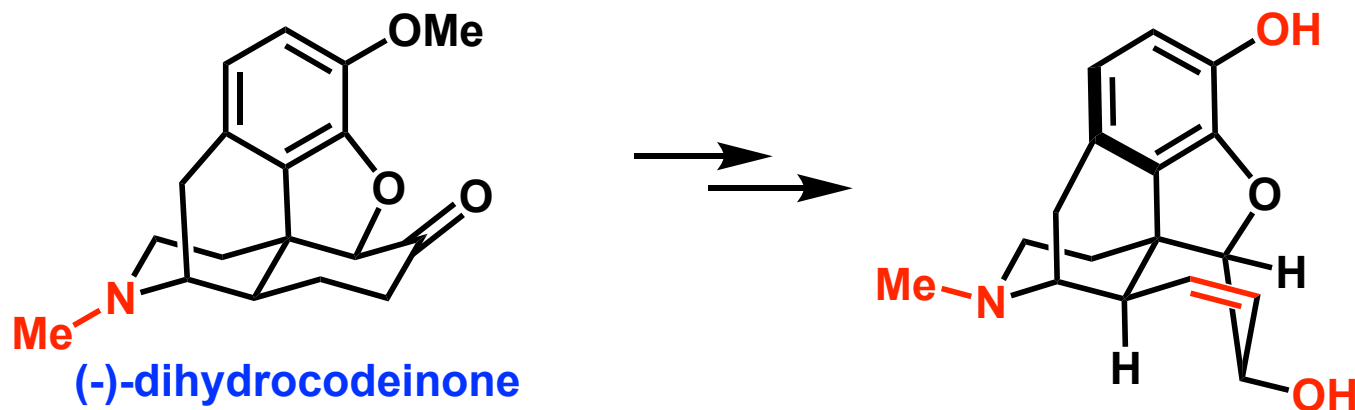
# Overman's Total Synthesis of Morphine



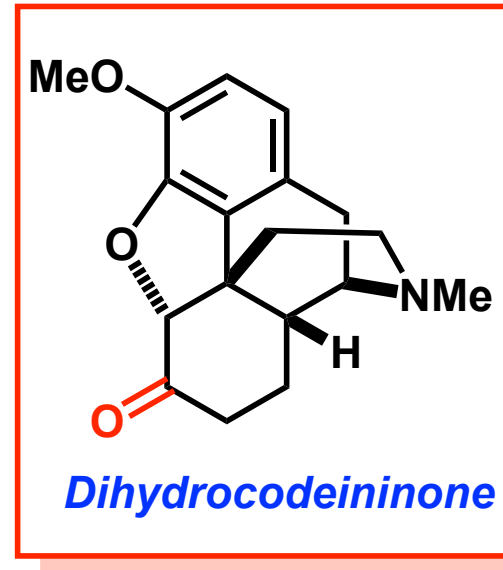
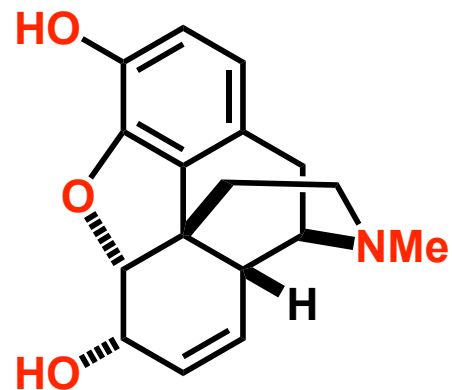
Johnson-Corey-Chaykovsky Reaction

# Overman's Total Synthesis of Morphine





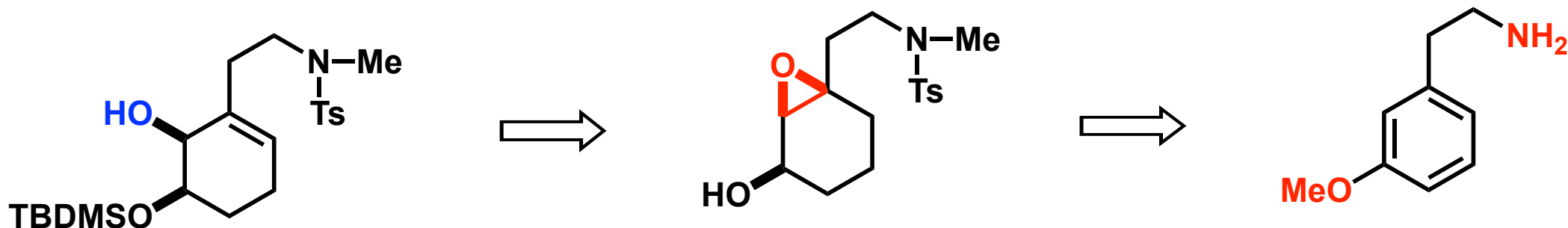
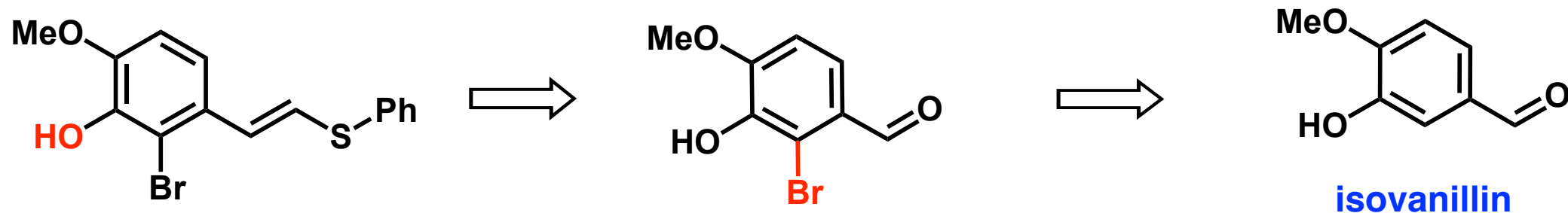
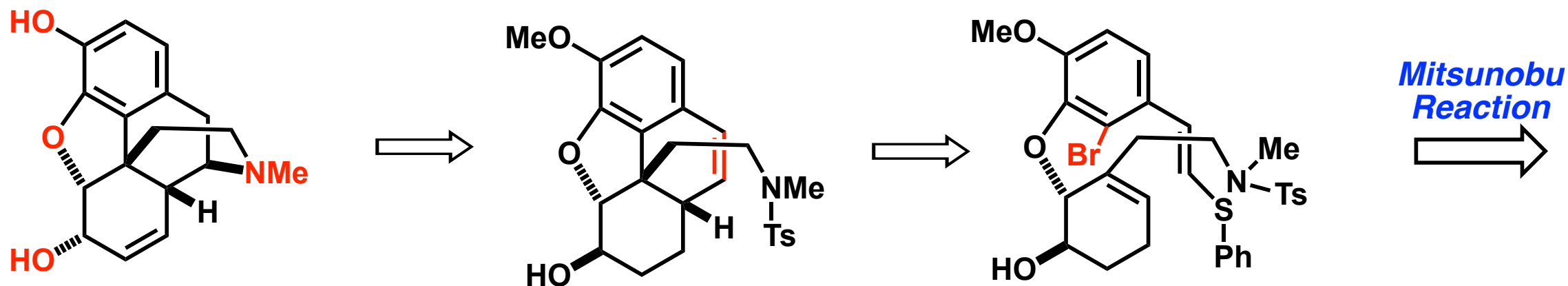
- The Formal total synthesis of **Morphine** reported by **L. E. Overman** and co-workers in **1993**
- The synthesis was started from **Isovanillin**
- The key chemical transformation in this synthesis involves, **Sequential iminium ion-allylsilane cyclization and intramolecular Heck insertion reaction**
- Their total synthesis was completed in **10 linear steps** with a **1.01% overall yield**



- Parker's approach towards the construction of the morphine ring system is based on a **tandem cyclization** of an ortho allyloxy aryl radical
- Parker report the short (**11 steps** from commercial materials), convergent, and stereospecific synthesis of ( $\pm$ )-**dihydroisocodeine**
- Oxidation to dihydrocodeinone completes the formal total synthesis of ( $\pm$ )-**morphine**

K. Parker *et al.*, *J. Am. Chem. Soc.*, **1992**, *114*, 9688

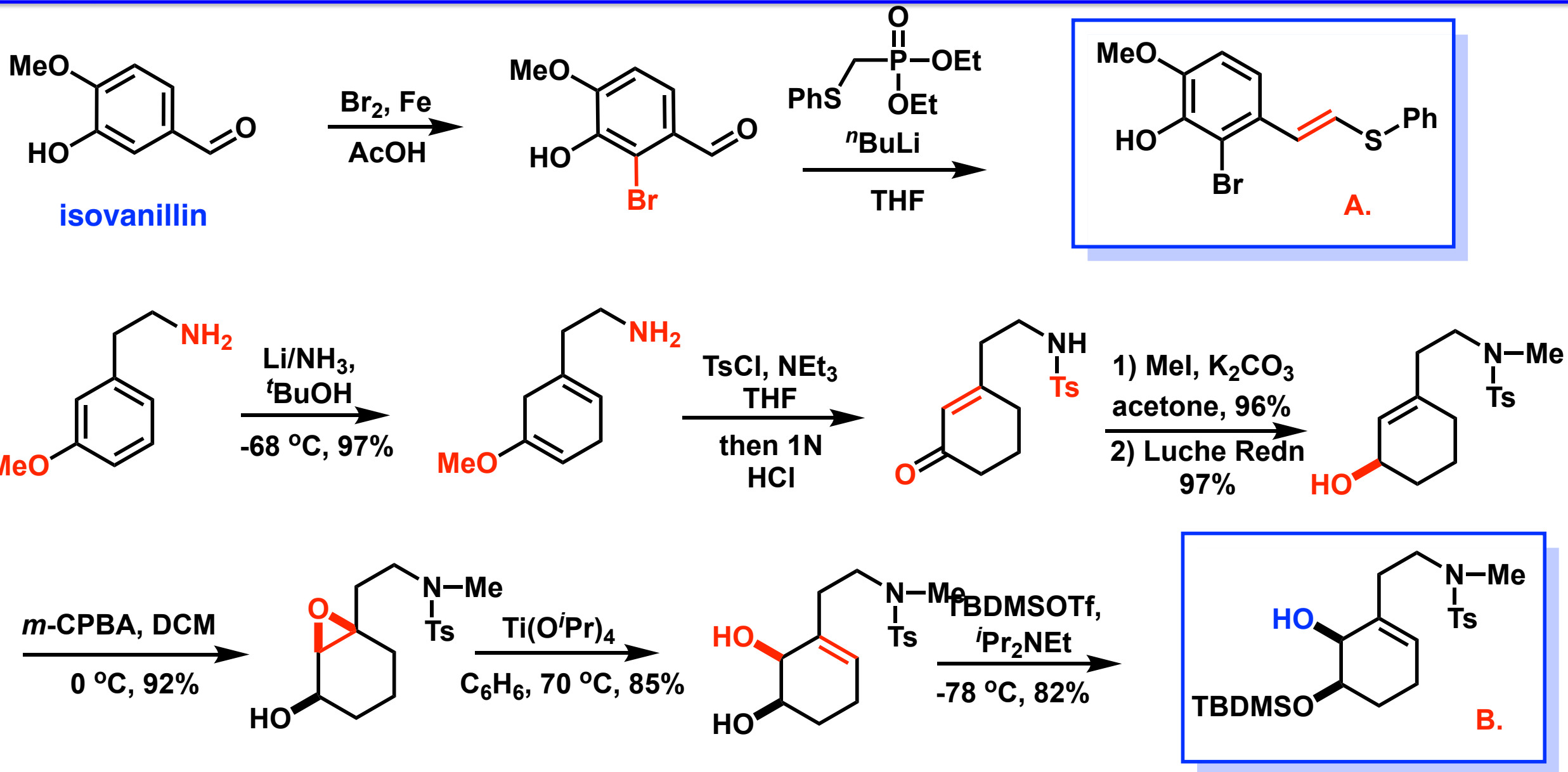
# Parker's Retrosynthesis



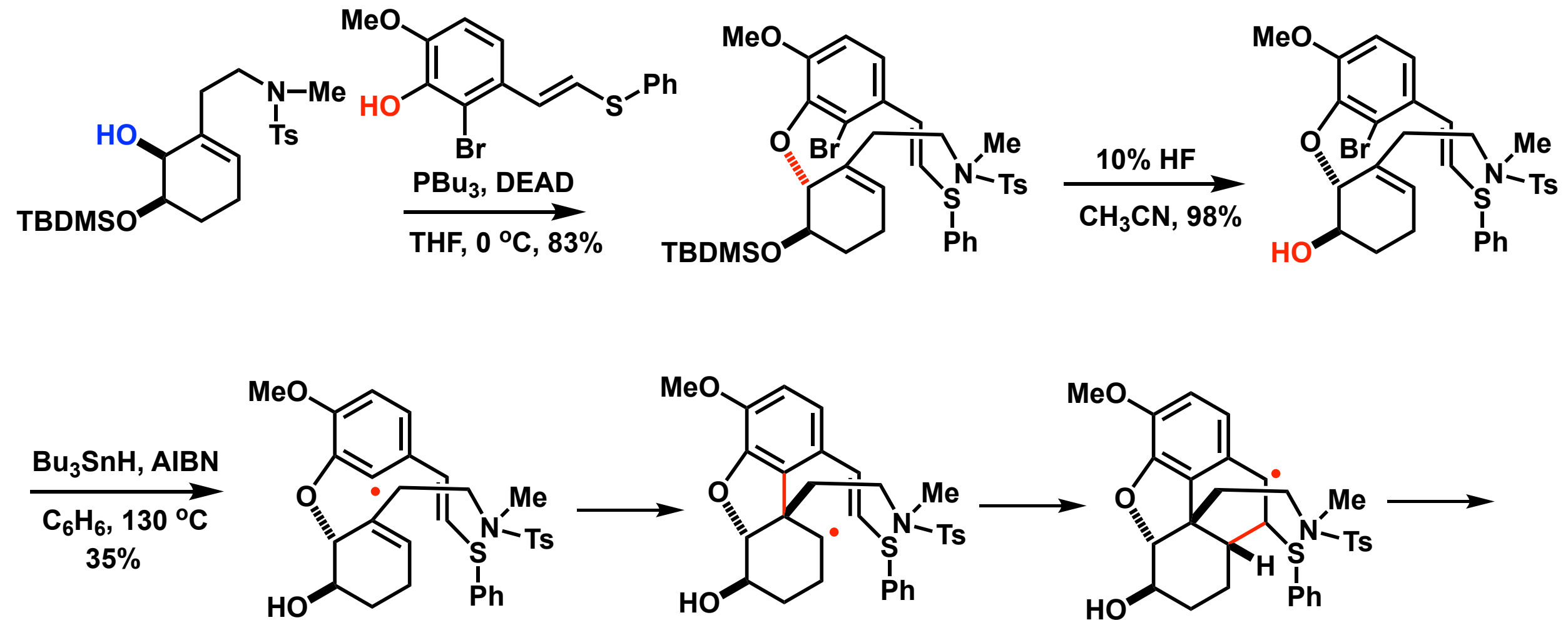
K. Parker *et.al.*, *J. Am. Chem. Soc.*, 1992, 114, 9688



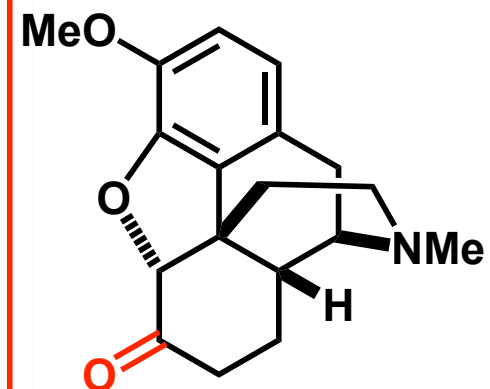
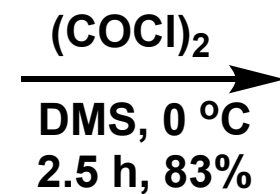
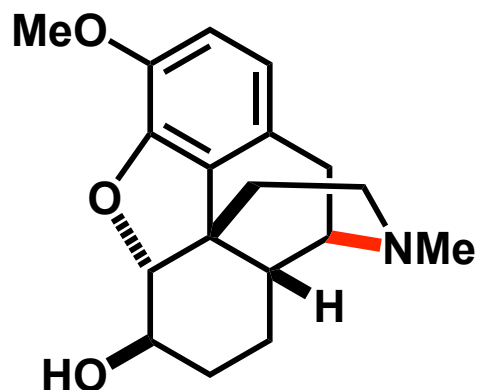
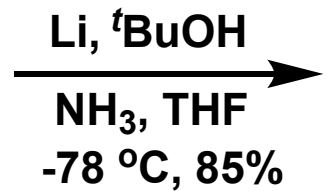
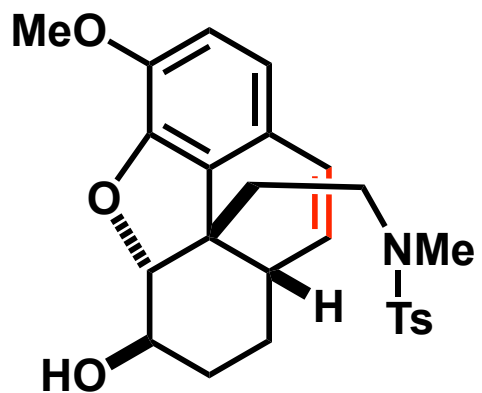
# Synthesis of A & B Fragments of Morphine



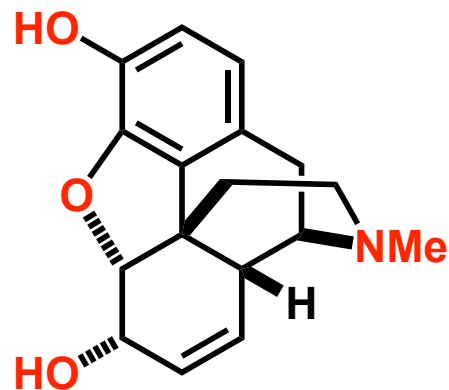
# Coupling of A & B Fragments of Morphine



# Parker's Total Synthesis of Morphine



*Dihydrocodeininone*



*(+)-morphine*