Total Synthesis of Morphine



Krishna P Kaliappan

Professor of Chemistry, IIT Bombay

Opium and Morphine





Morphine, an alkaloid derived from the poppy, is one of the best known examples of a plant-derived medicine.

The word opium comes from ancient Greek meaning vegetable juice,

It is not known how early medicinal properties of poppy were discovered.

References to the use of the poppy are found in ancient Greek, Egyptian, Indian, Chinese, and in early Roman texts

Opium use became widespread in the Middle Ages through the Renaissance period for medicinal purposes as well as for pleasure, leading to addiction in many famous historical figures

In the mid-1800s, some English chemists stocked "opium soap, lead and opium pills, opiate lozenges, opiate plasters, opium enema, opium liniment, and other products such as vinegar of opium.

The potency of these materials that were sold to people could not be predicted or controlled until the active ingredient (which we now know is the alkaloid morphine) was identified and isolated in the opium resin.

History of Opium

Archeological evidence suggests that opium poppies were being grown as far back as during the Neolithic and Bronze ages, and likely to have been originated from north eastern part of Mediterranean in Asia

Opium was introduced to India, either by Alexander the Great in the fourth century, or by invading armies in the eighth century, although the fifteenth century marks the first recorded cultivation in India

Opium began to appear in China in the fourth century, reintroduced in Europe in the 1500s after Portuguese explorers 'discovered' its usage in China

Colonization and globalization provided Europeans with knowledge from countries that had continued to make scientific discoveries during the Dark Ages, but also led to exploitation, trade and diplomatic disagreements, and the systemic smuggling of opium

History of Morphine

The process to obtain opium from the poppy plant and then to extract the alkaloid morphine is a laborious problem

The Western establishment has long left this job to underpaid workers in Middle Eastern countries.

Until 1990s, Afghanistan was still the largest producer of opium.

The opium latex is present throughout the poppy plant but is concentrated in the developing fruit

The flowers of the poppy mature into capsules, which contain the latex.

Opium is only present in the wall of the maturing capsule for up to 10 days of its entire life cycle and will contain up to four times more morphine if the latex is collected in the early morning.

Since the process is extremely laborious, morphine is now increasingly obtained from 'poppy straw'; a by-product of poppy cultivation for use of the poppy seeds.

Isolation of Morphine

Daniel Ludwig (1625–1680), the court physician of the Duke of Saxe-Gotha who, after dissolving opium in an acid and then saturating it with an alkali, obtained a substance he called *Magisterium Opii*.

Robert Boyle (1627–1691) mixed opium in tartar (potassium carbonate) and alcohol in an attempt to isolate the active compound from opium, although he was unsuccessful.

Jean-François Derosne (1774–1855), a French apothecary, prepared opium salts which were likely a mixture of morphine and narcotine, and later in 1803 isolated narcotine.

It is believed that Armand Séquin (1767–1835) presented his experimental findings in isolating opium's active ingredient to the Institute of France in 1803–4, although his report to the Academy of Sciences was not published until 1814.

Despite all this, the credit for the isolation of morphine goes to the German apothecary Friedrich Wilhelm Adam Sertürner (1783–1841) who published his isolation of opium's active ingredient in 1805

Isolation of Morphine

Sertürner was born in 1783, and was working as a pharmacist's assistant when he reported the discovery of the chemical substance meconic (or poppy) acid in opium in 1805 and successfully isolated it at the age of only twenty-one

In the following year, he reported isolating the active narcotic substance in opium. He noted that this substance was soluble in acid water and was precipitated by ammonia, thereby giving it the characteristic of a weak base. He described it as a 'vegetable alkali'

He named the white crystalline powder 'morphium', after Morpheus, the Greek god of dreams.

He masked the bitter-tasting crystals with sugar syrup and trialed doses in rats, mice, cats and dogs.

Despite the fact that at least one of the dogs died during these trials, Sertürner used 100 mg of morphine in himself to relieve pain and tried it in three other young men as human experimental subjects.

Sertürner's work was originally largely ignored, and it took over a decade along with the help of French Chemist J.L. Gay-Lussac(1778–1850) before Sertürner's findings were published in 1817

Morphine's Medicinal Use

The commercial production of morphine began as early as in 1820s in Europe, and 1830s in the United States, but it was not listed in the London Pharmacopeia until 1836.

In the 1850s the work of Charles-Gabriel Pravaz (1791–1853) and Alexander Wood (1817– 1884) led to the creation of the hypodermic needle, and it was this advance that fueled morphine's meteoric rise in popularity

The combination of the increased potency of morphine over opium and the ability to inject the solution directly into the bloodstream provided swifter pain relief.

These properties propelled the use of morphine in treating soldiers during the Crimean War (1853–1856), the American Civil War (1861–1865), and the Franco-Prussian war (1870–1871).

In 1912 the United States and many other countries signed the International Opium Convention which controlled the import, manufacture and sale of morphine. Soon after, anti-narcotic laws began to appear in many countries.

Structural Elucidation

Morphine is the most commonly used opioid for moderate to severe pain in people with cancer in the UK and other European countries" and in the United States for non-malignant pain.

In the 1820s and 1830s, Justus von Liebig (1803–1873) and Henri Victor Regnault (1810–1878) determined the chemical formula for morphine to be $C_{34}H_{36}N_2O_6$ and $C_{34}H_{40}N_2O_6$, respectively but both were incorrect

In 1847, August Lauren (1809–1853), formed salts of morphine by excluding all humidity and by careful calculation was able to produce the correct chemical formula for morphine, $C_{34}H_{38}N_2O_6$

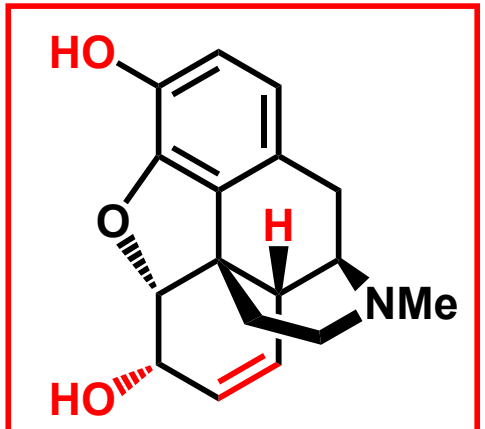
After achieving the chemical formula, the next step was to provide the correct structure for morphine

Robert Robinson, elucidated correct structures for morphine, codeine and thebaine

This knowledge helped Robinson and others to propose the correct structures for papaverine and narcotine

Isolation: 1. F. W. Sertürner, *Trommsdorf's Journal der Pharmazie*, **1805,** *13*, 1, 234 2. *Ann. chim. phys.*, **1817,** *5,* 21

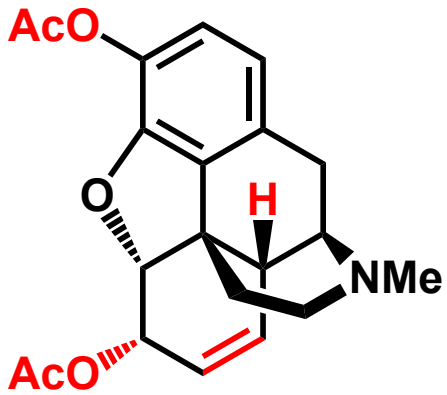
Total Synthesis of Morphine



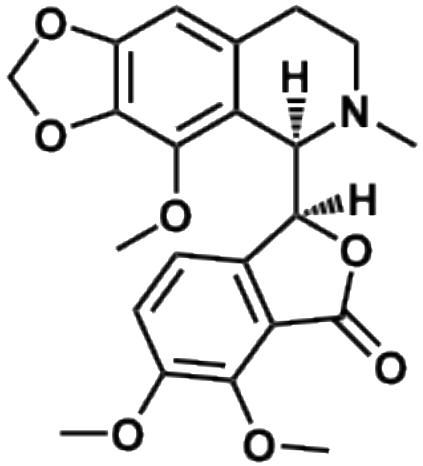
(-)-morphine

- Isolation of morphine is the beginning of an era where drugs from plants could be purified
- 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
- Sir Robert Robinson received his Noble Prize in 1947 for his pioneering work on investigation of plant products of biological importance, especially alkaloids



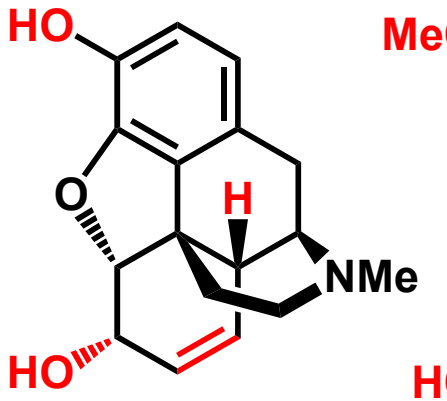
Heroin



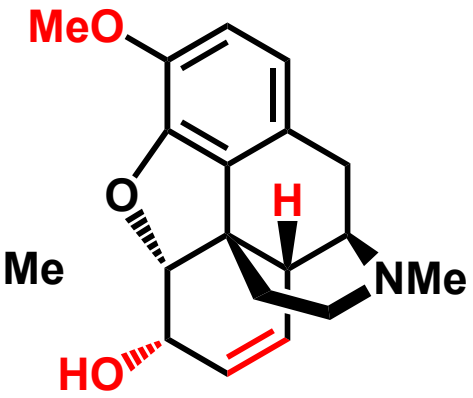
Narcotine

Natural and Synthetic Opiates

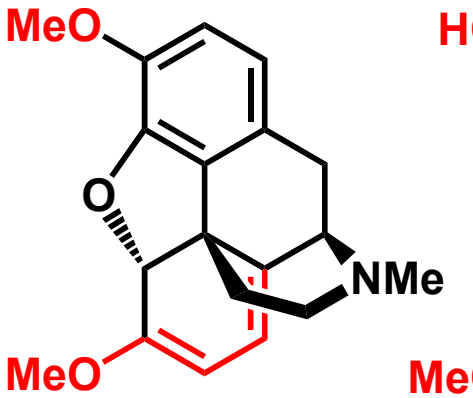
Natural Opiates



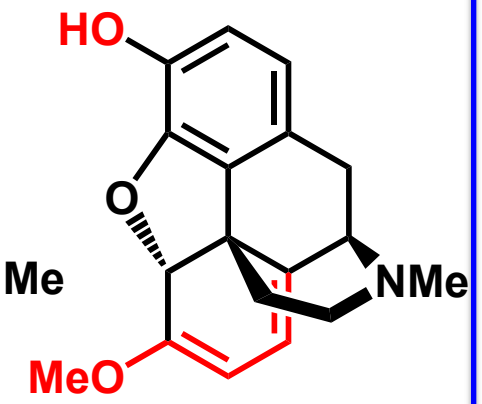
(-)-morphine



(-)-codeine

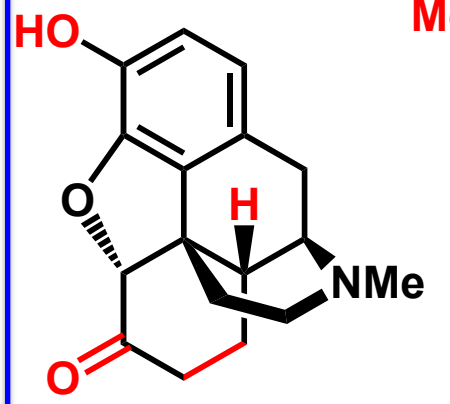


(-)-thebaine

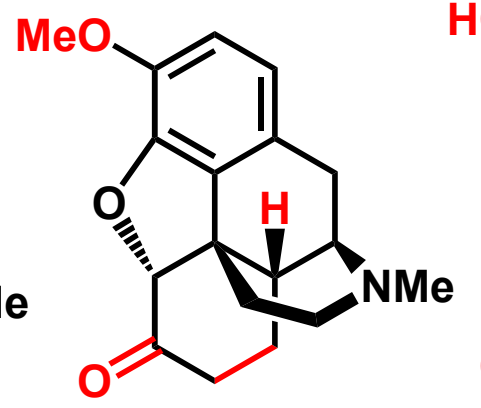


(-)-oripavine

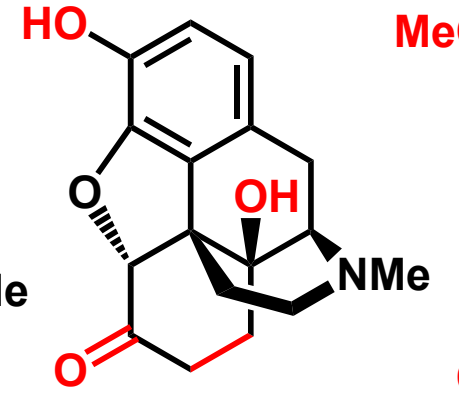
Semisynthetic Opiates



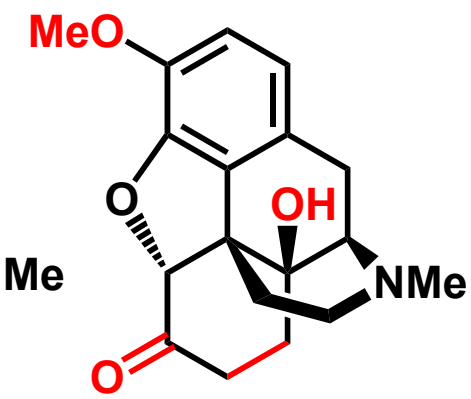
(-)-hydromorphone



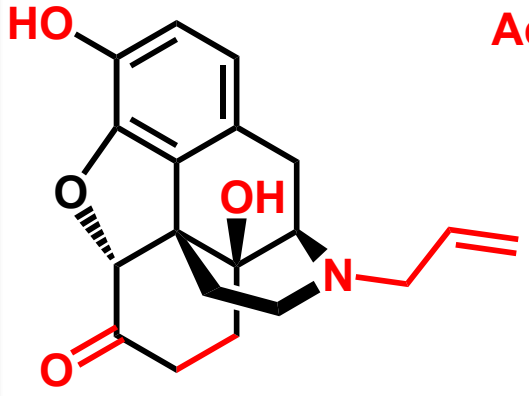
(-)-hydrocodone



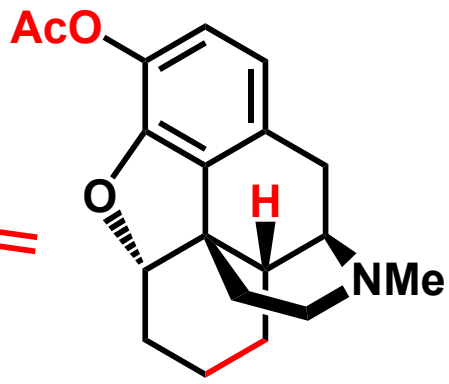
(-)-oxymorphone



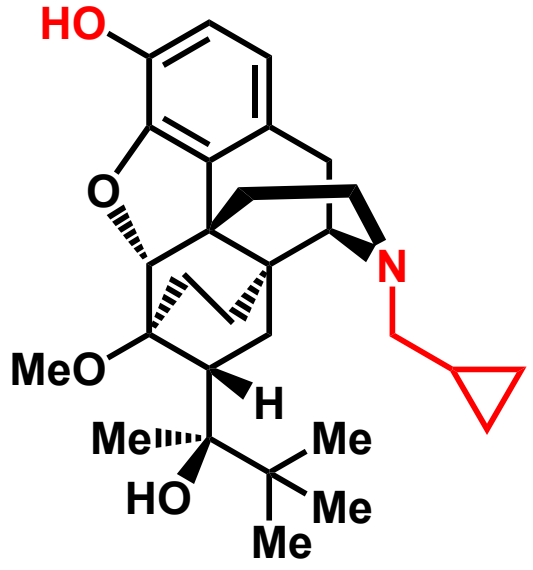
(-)-oxycodone



(-)-naloxone



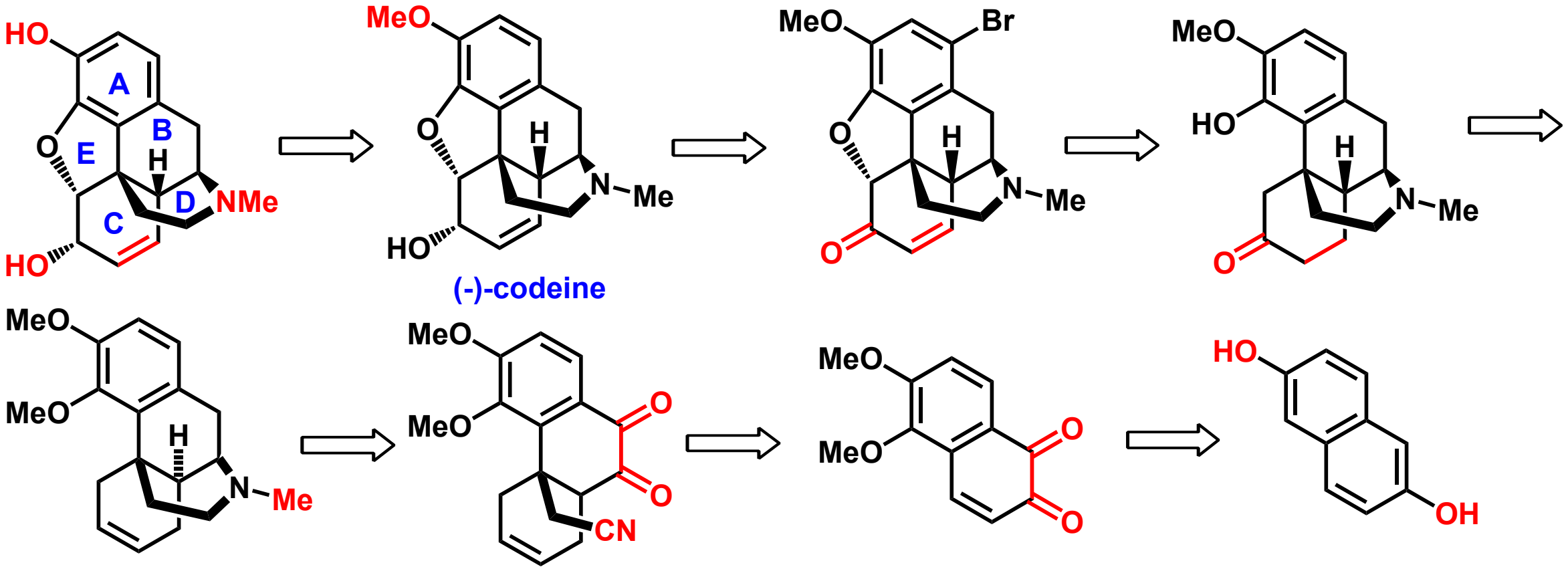
(-)-desomorphine



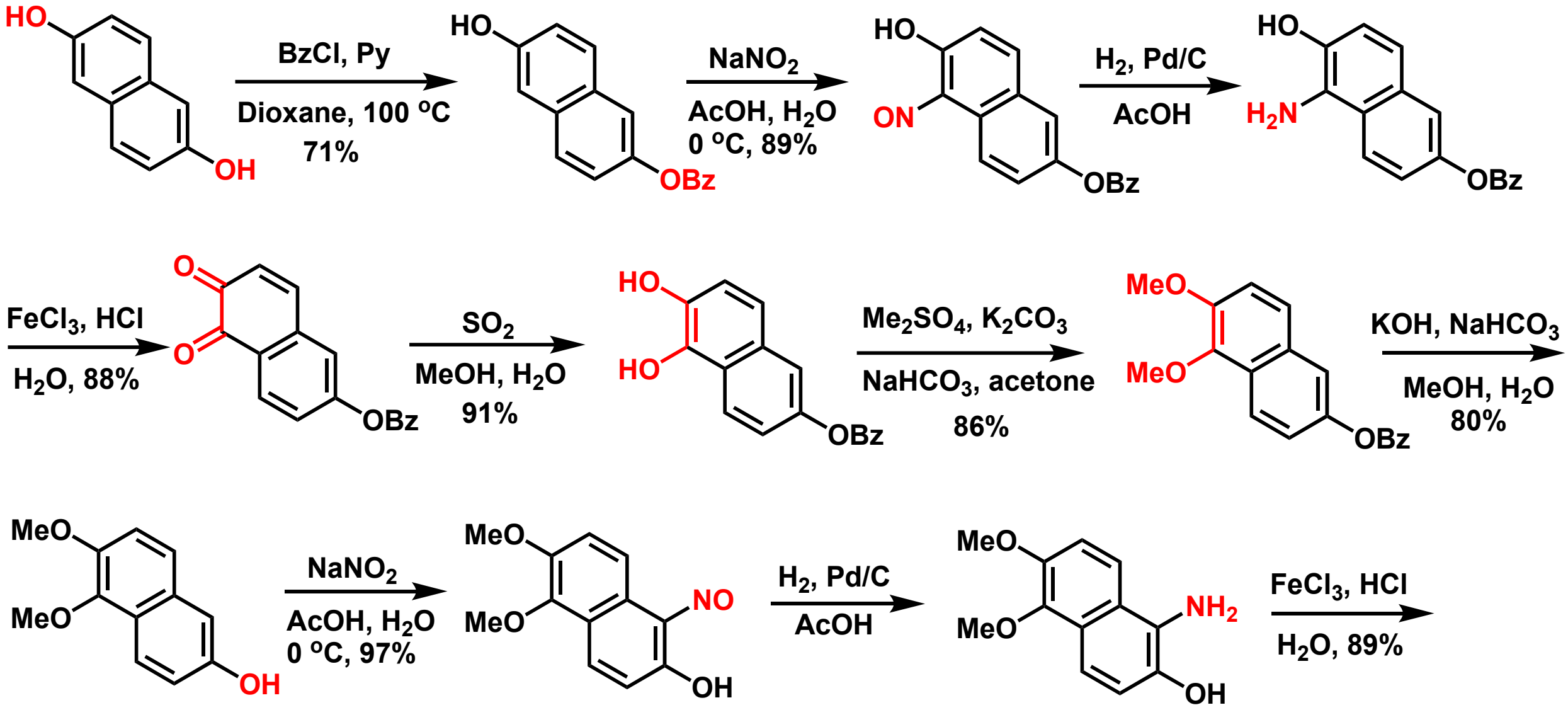
(-)-buprenorphine

Gates Total Synthesis of Morphine

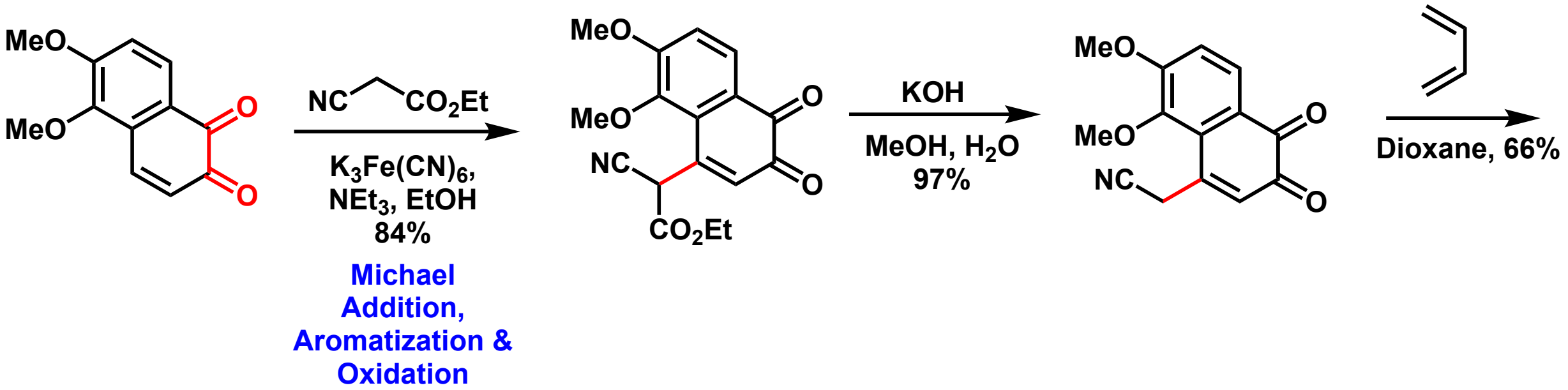
- **Morphine**, the principal alkaloid of opium and the substance primarily responsible for its physiological effect, has attracted the attention of chemists for over **two hundred years**
- Morphine contains complex pentacyclic structure bearing **five contiguous stereocentres**
- Gates and Tschudi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

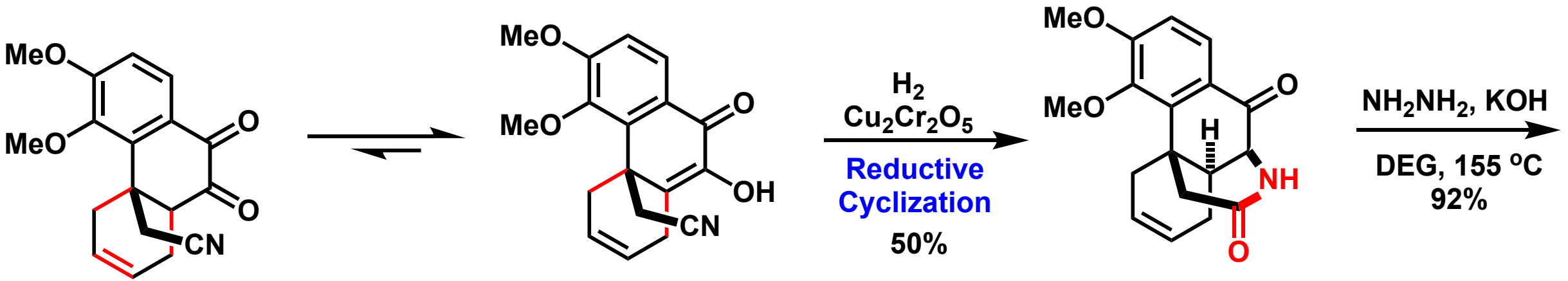


Gates Total Synthesis of Morphine

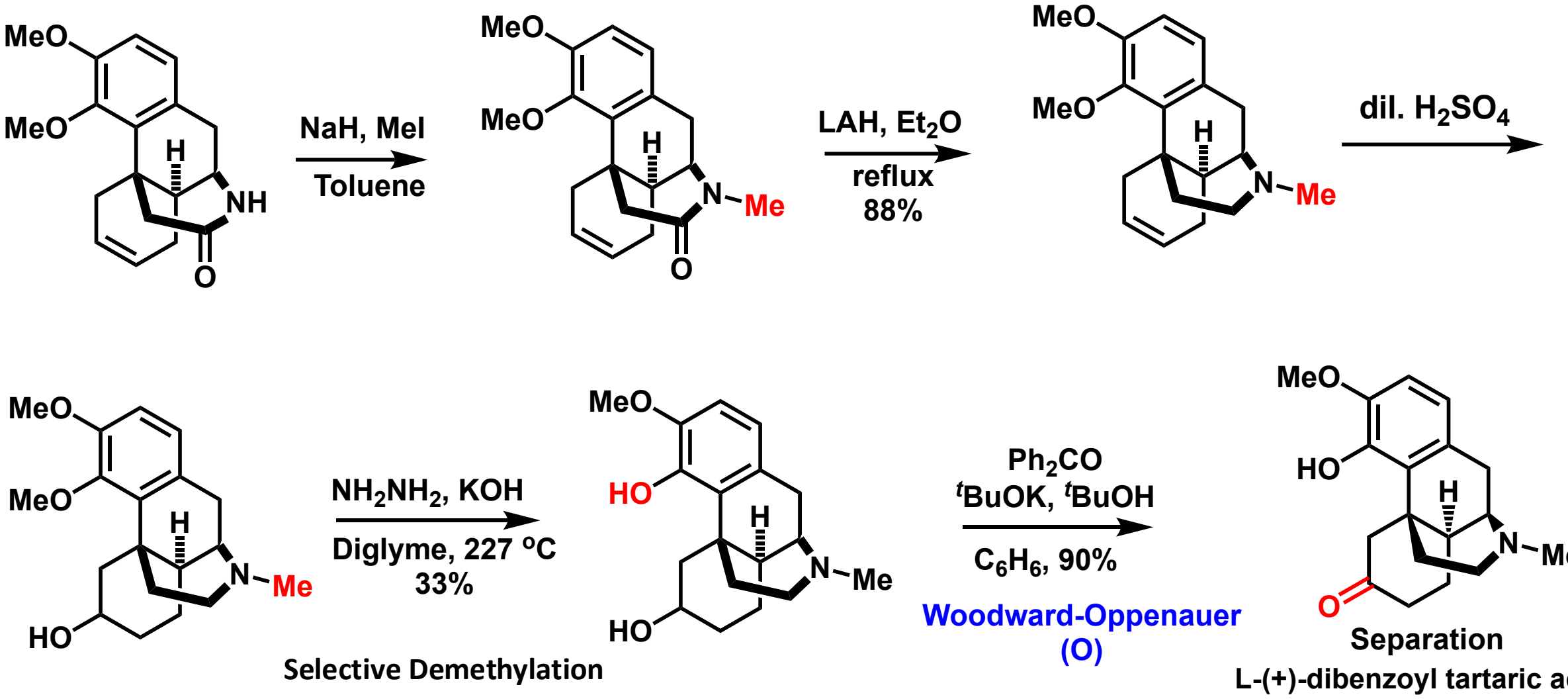


Gates Total Synthesis of Morphine

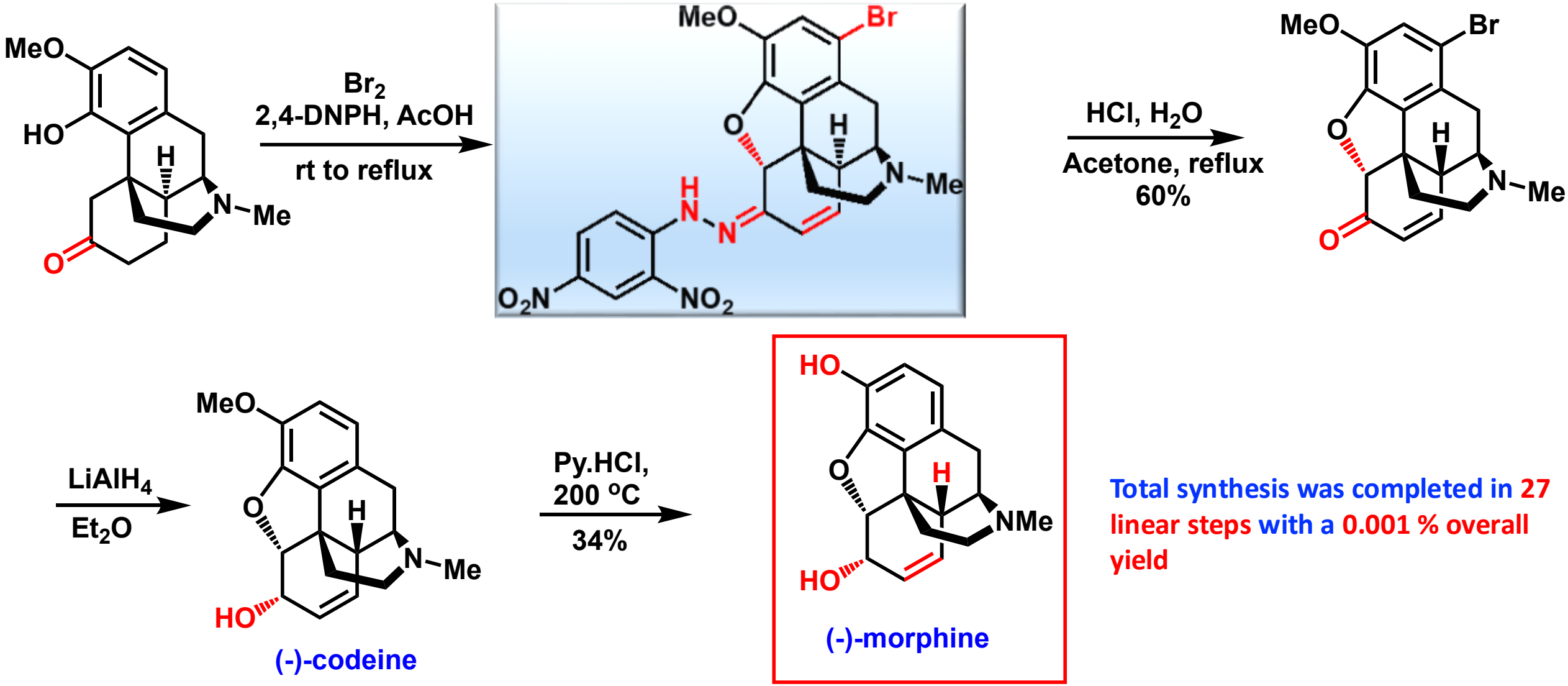




Gates Total Synthesis of Morphine



Gates Total Synthesis of Morphine



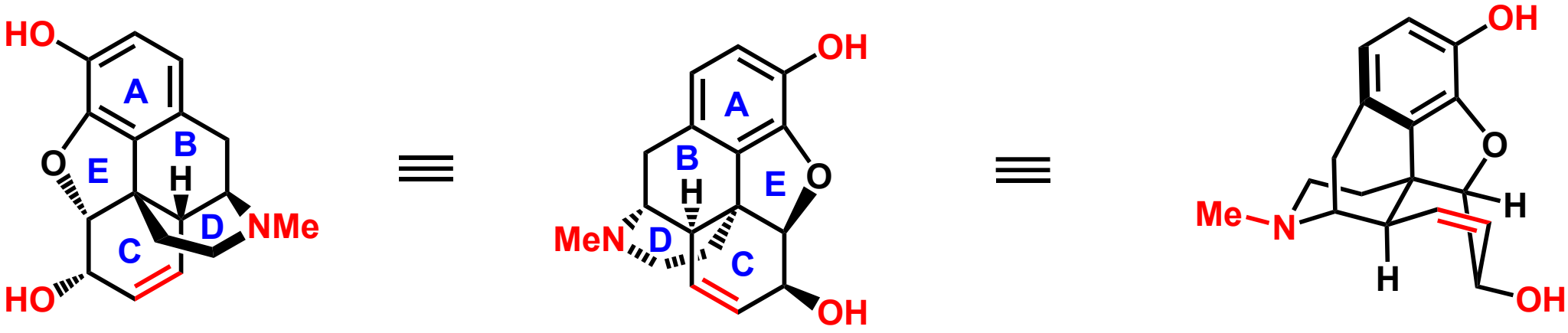
Total synthesis was completed in 27 linear steps with a 0.001 % overall yield

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

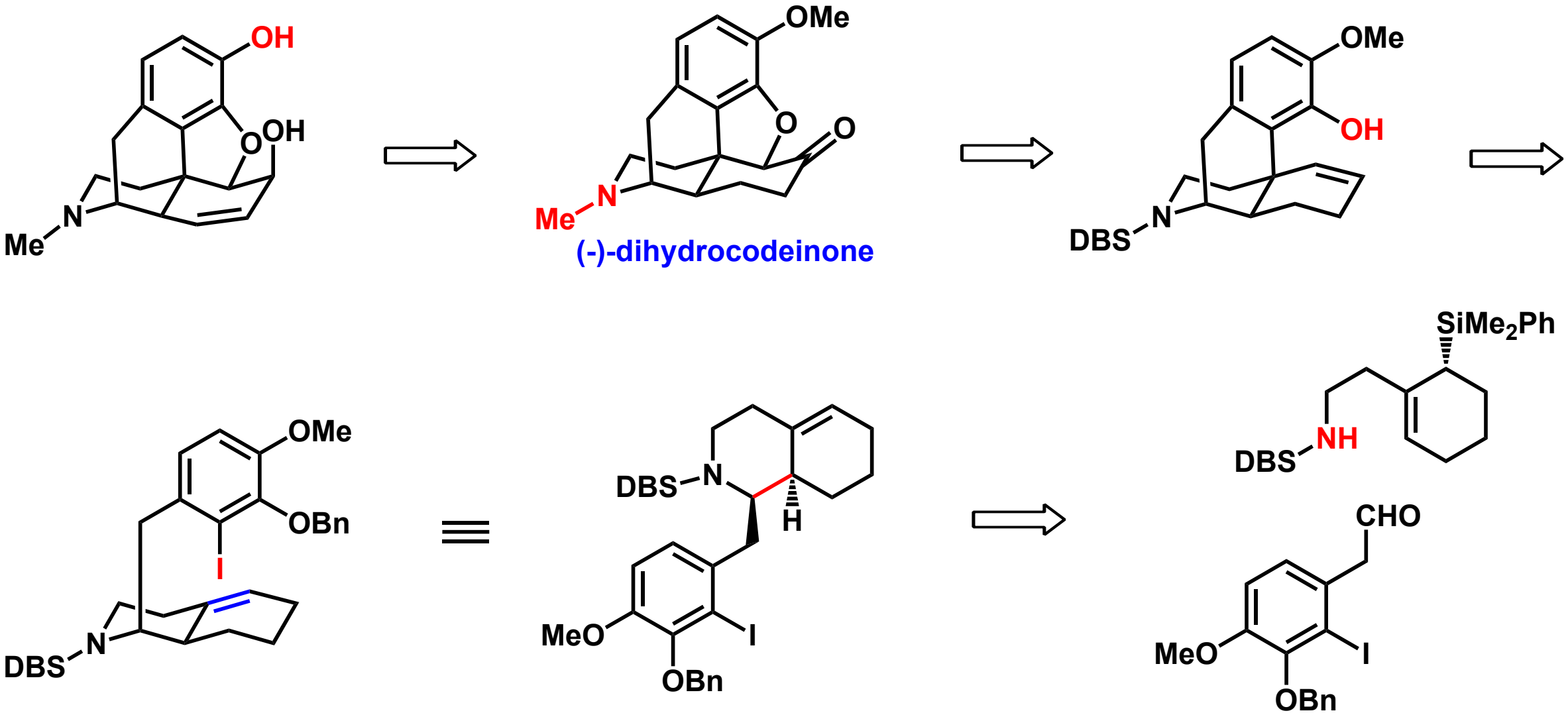
Overman's Total Synthesis of Morphine

- Overman reported the total synthesis of morphine in 1993 starting from isovanillin

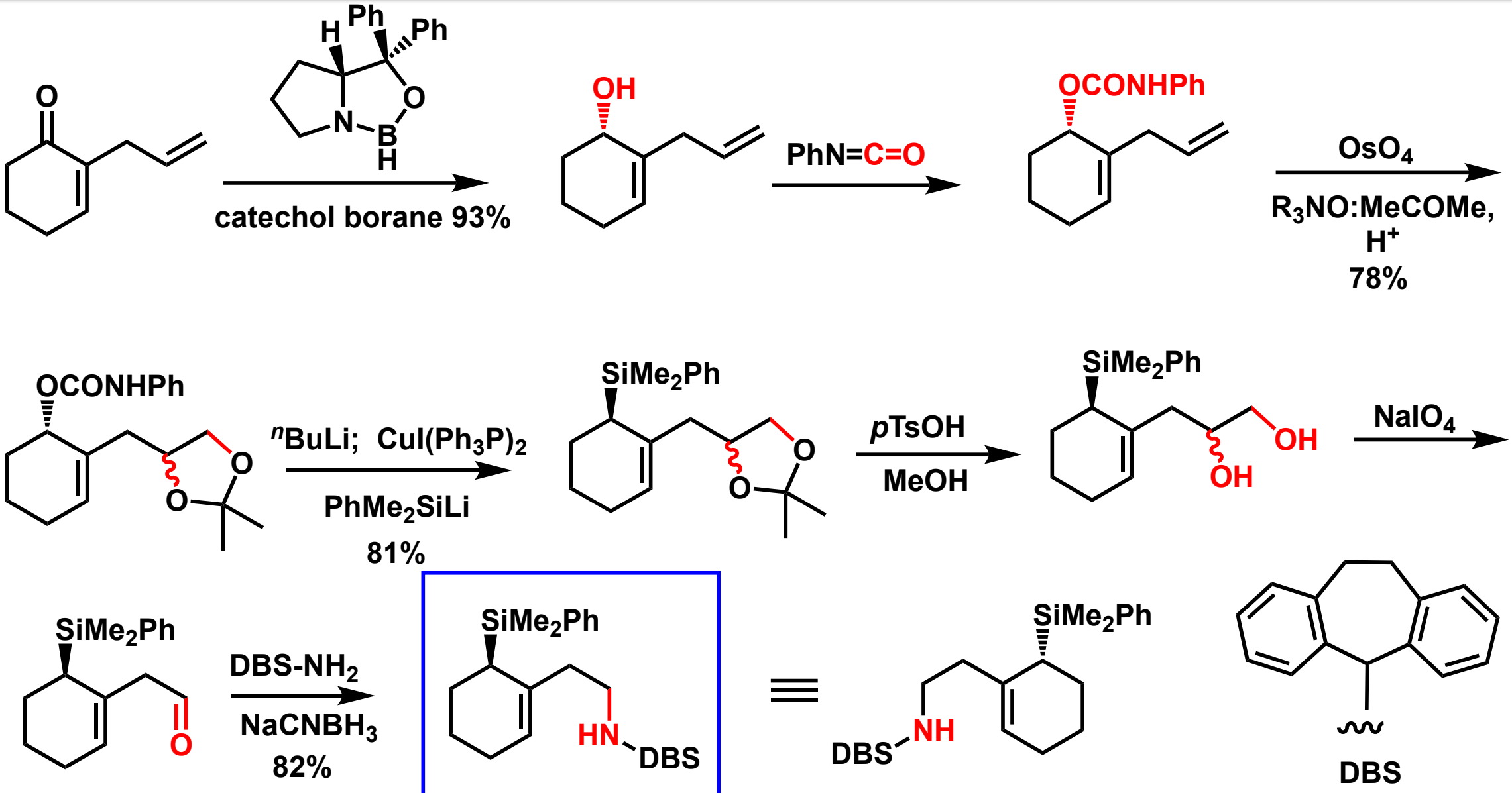
- Overman strategy was the first to form an enantioenriched octahydroisoquinoline and then employ an intramolecular Heck reaction to forge the critical quaternary center of the morphine skeleton



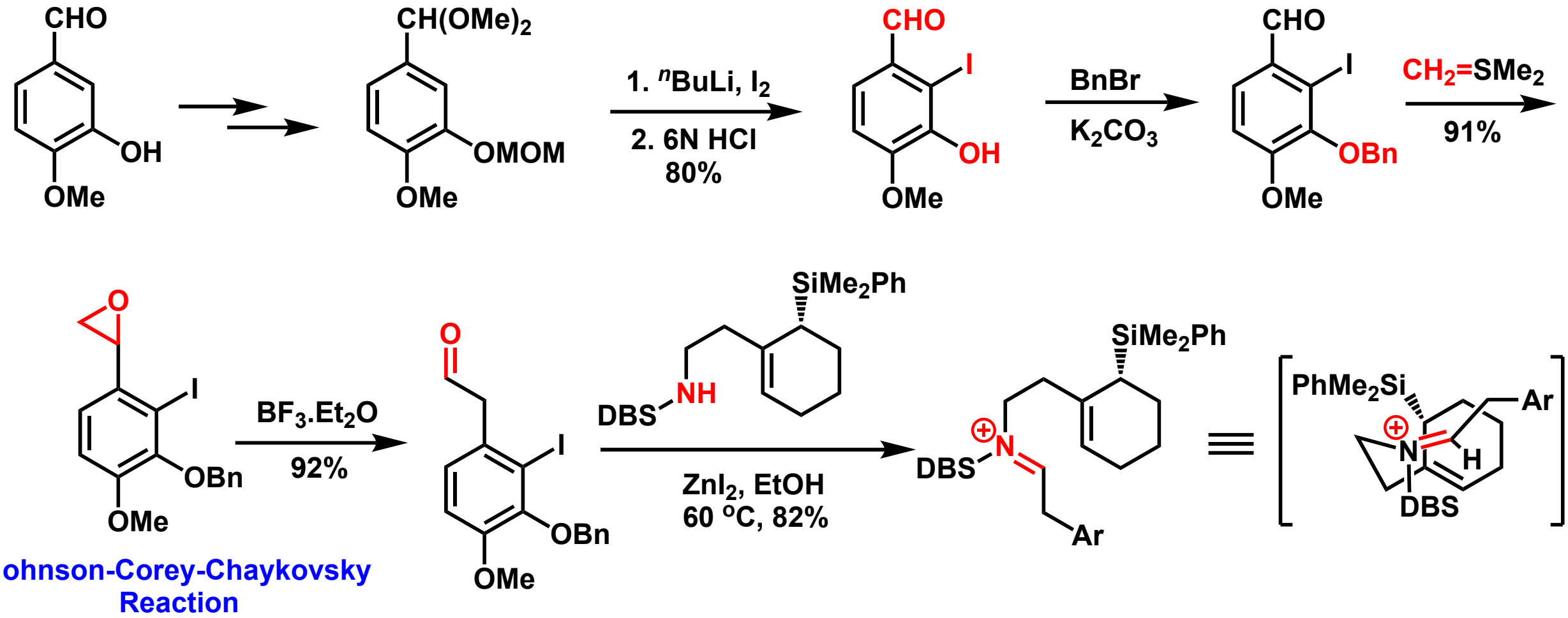
Overman's Retrosynthesis



Overman's Total Synthesis of Morphine

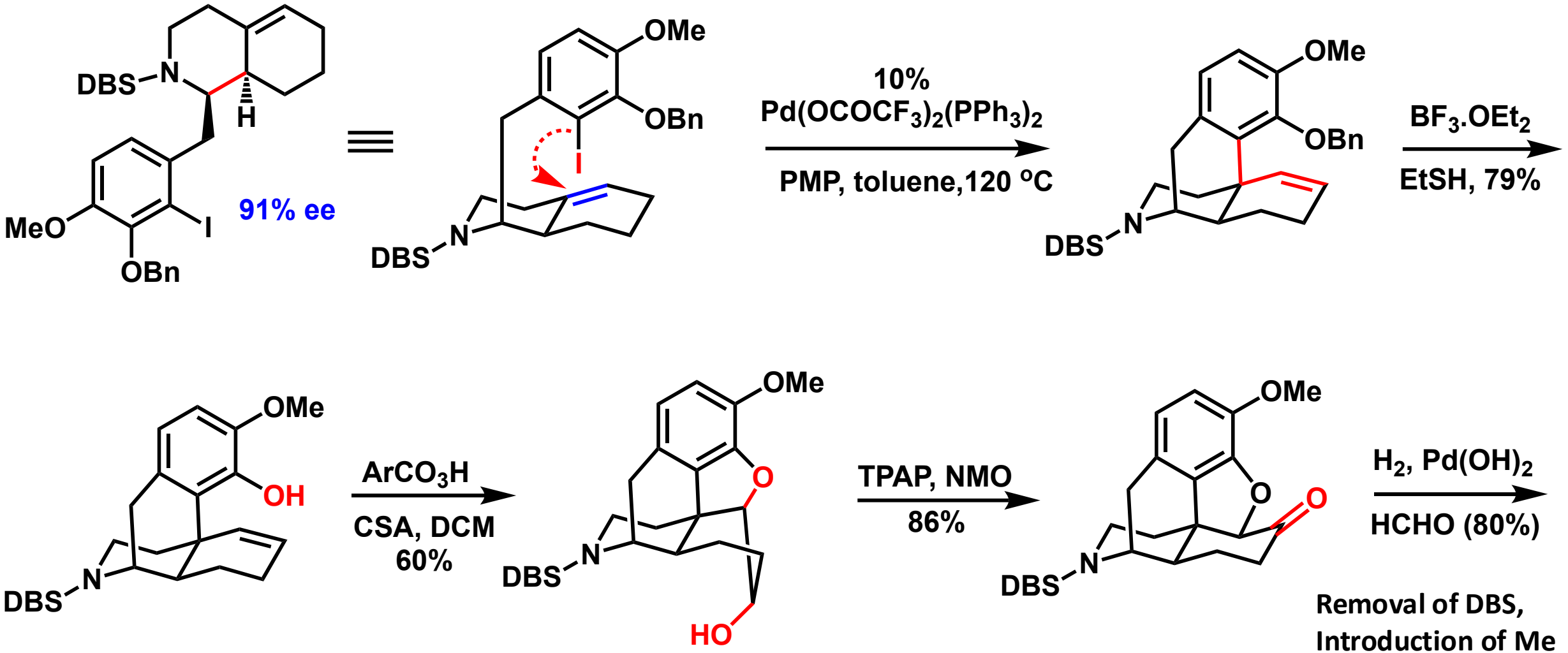


Overman's Total Synthesis of Morphine

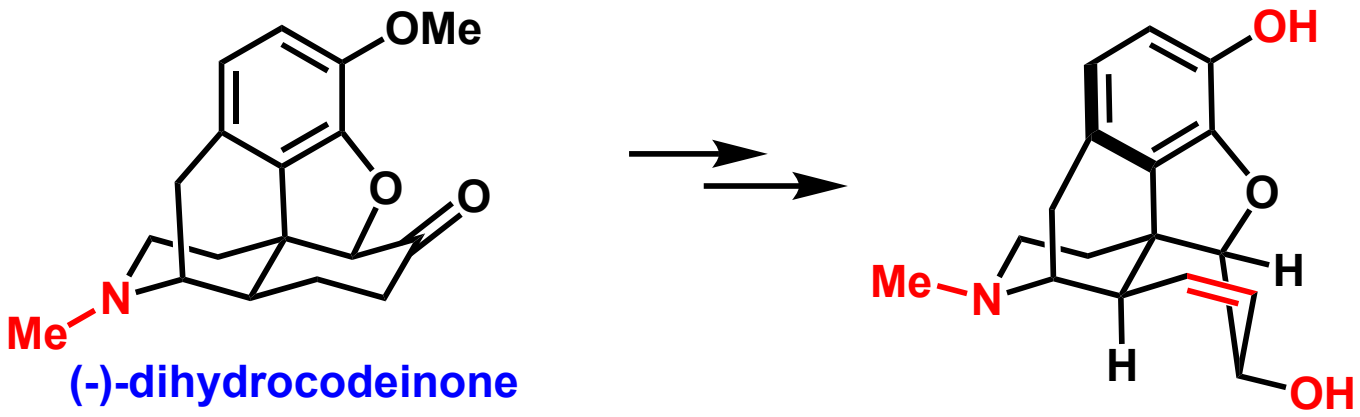


Johnson-Corey-Chaykovsky Reaction

Overman's Total Synthesis of Morphine

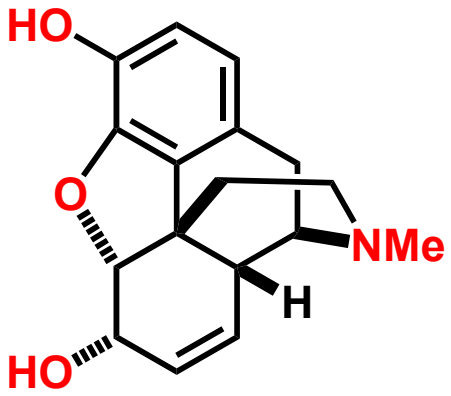


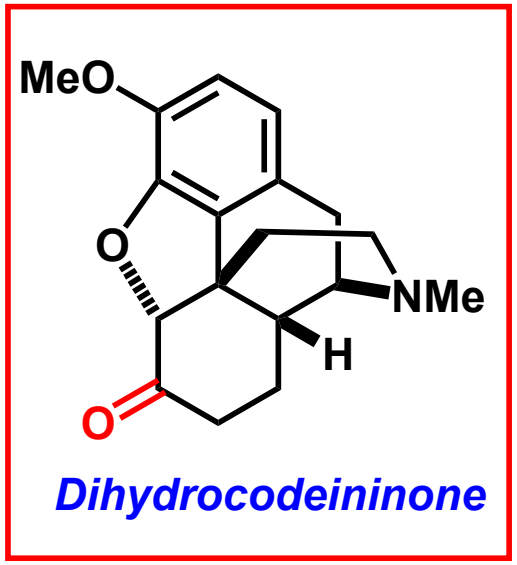
Overman's Total Synthesis of Morphine



- 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 Total Synthesis of Morphine



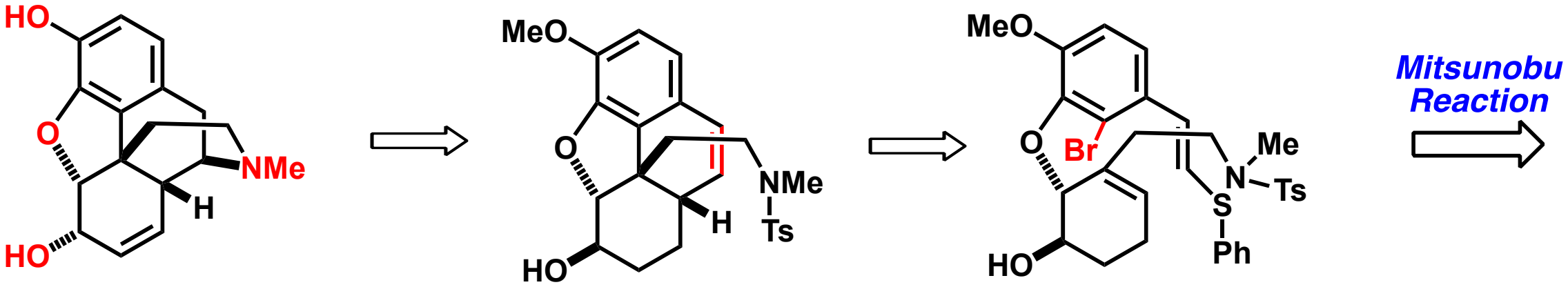


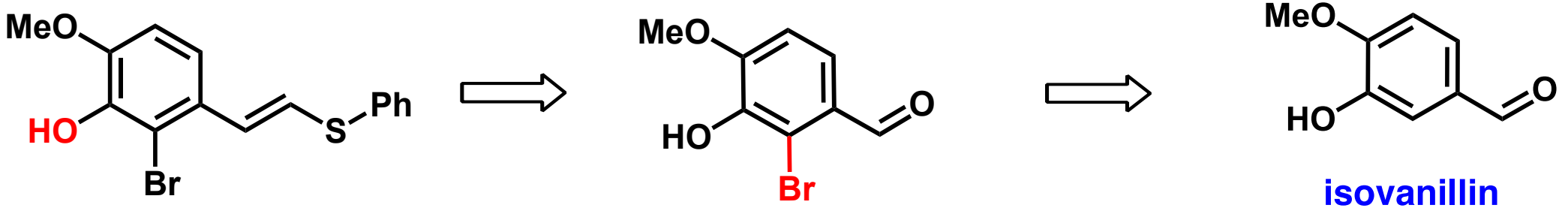
Dihydrocodeininone

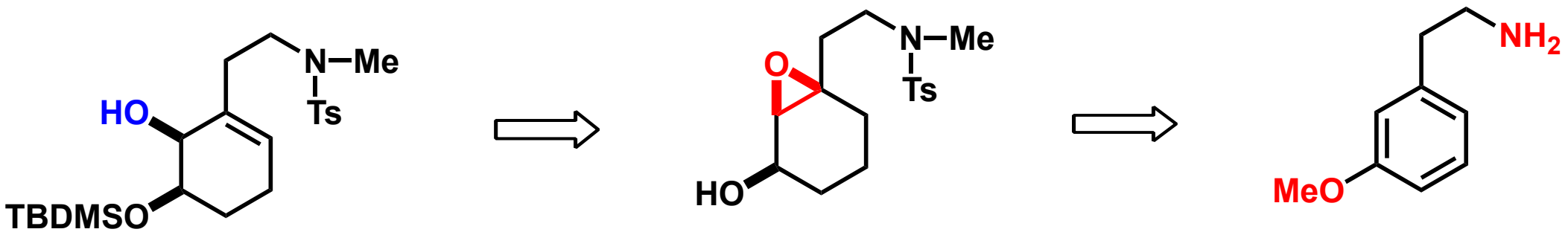
- Parker's approach towards the construction of the morphine ring system is based on a tandem cyclization of an ortho allyloxy aryl radical
- Parker report the short (11 steps from commercia materials), convergent, and stereospecific synthesis of (±)-dihydroisocodeine
- Oxidation to dihydrocodeinone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

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

Parker's Retrosynthesis

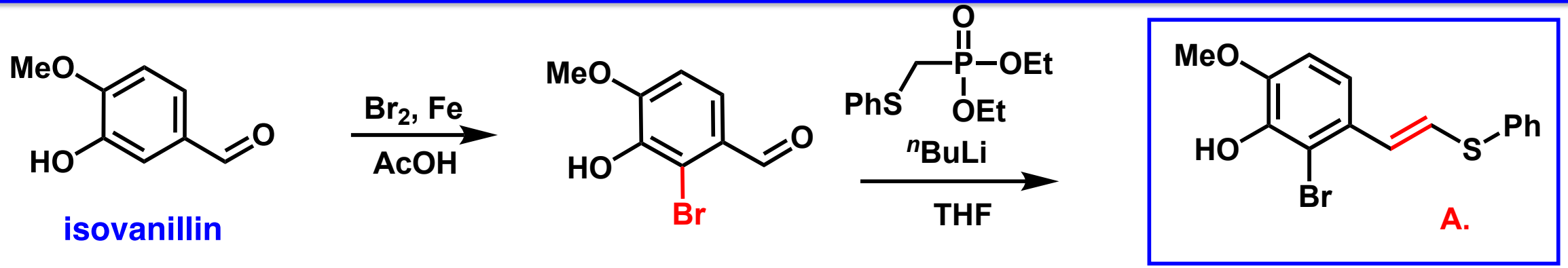


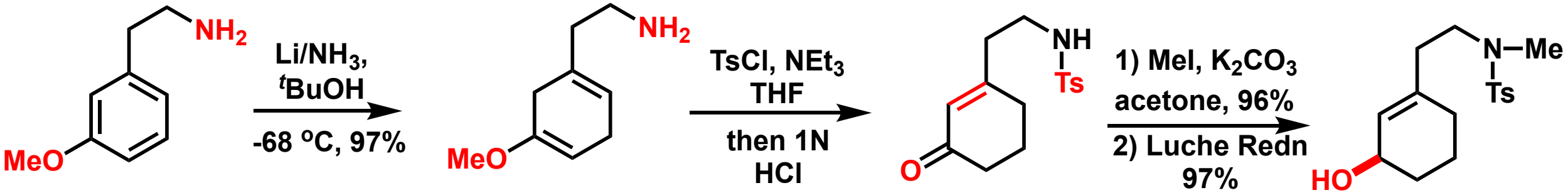


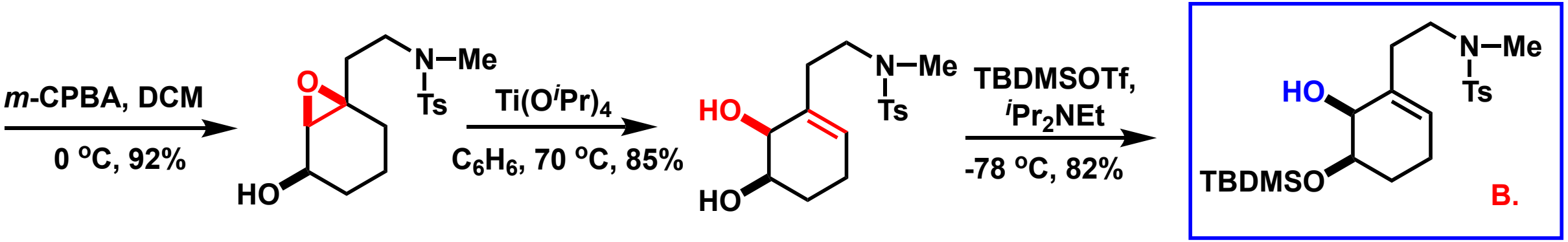


K. Parker *et.al., J. Am. Chem. Soc.*, **1992,** *114,* 9688

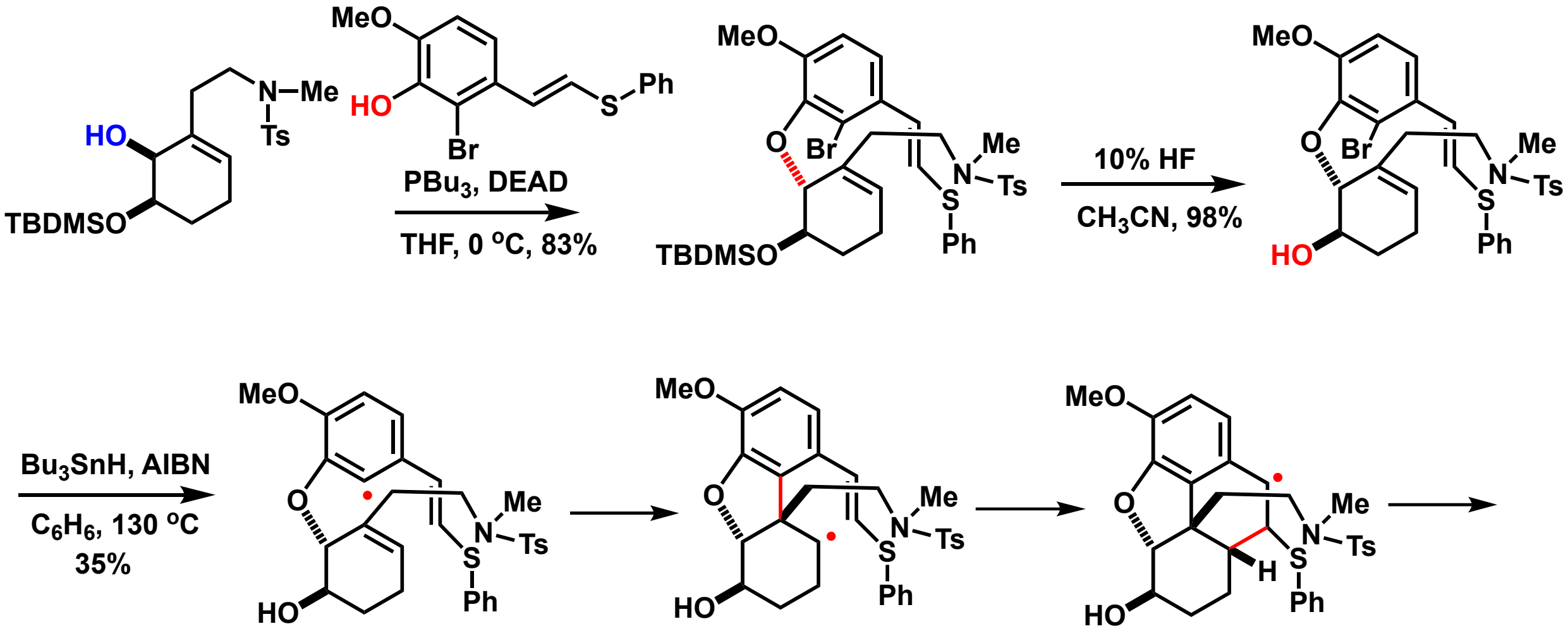
Synthesis of A & B Fragments of Morphine







Coupling of A & B Fragments of Morphine



Parker's Total Synthesis of Morphine

