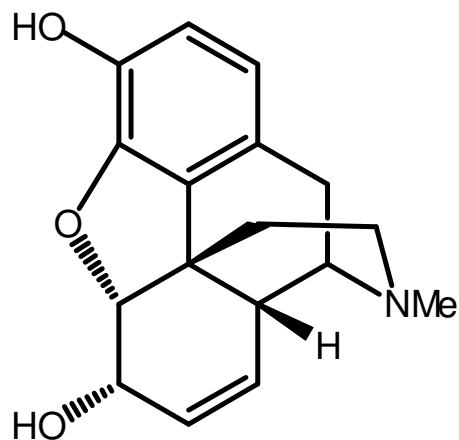


Morphine



Molecule in Review

Trevor Sherwood (Snyder Group)

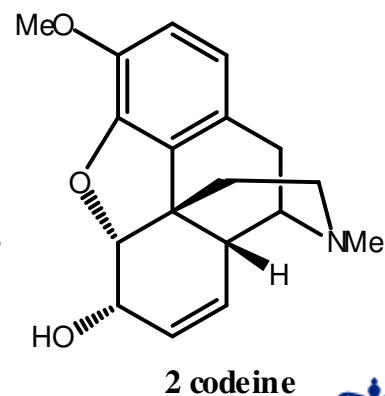
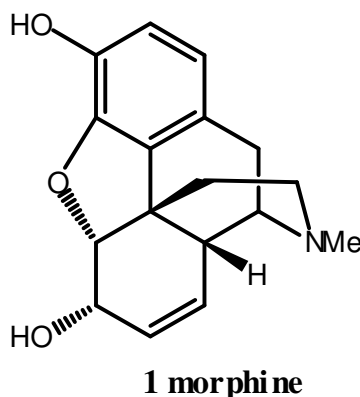
Synthesis Literacy Group

7/17/09

Columbia University Chemistry

Introduction

- The opium alkaloids are among the oldest known natural products, with recorded use by ancient Sumerians
- Isolation of morphine (Serturmer, 1805) predates Wohler's urea synthesis
- Morphine is exclusively isolated from the poppy plant for medicinal purposes
- Morphine and other members of the opioid class of alkaloids cause their effects via the opioid receptors
- Morphine and codeine differ only by a methyl group and are easily interconverted(1)



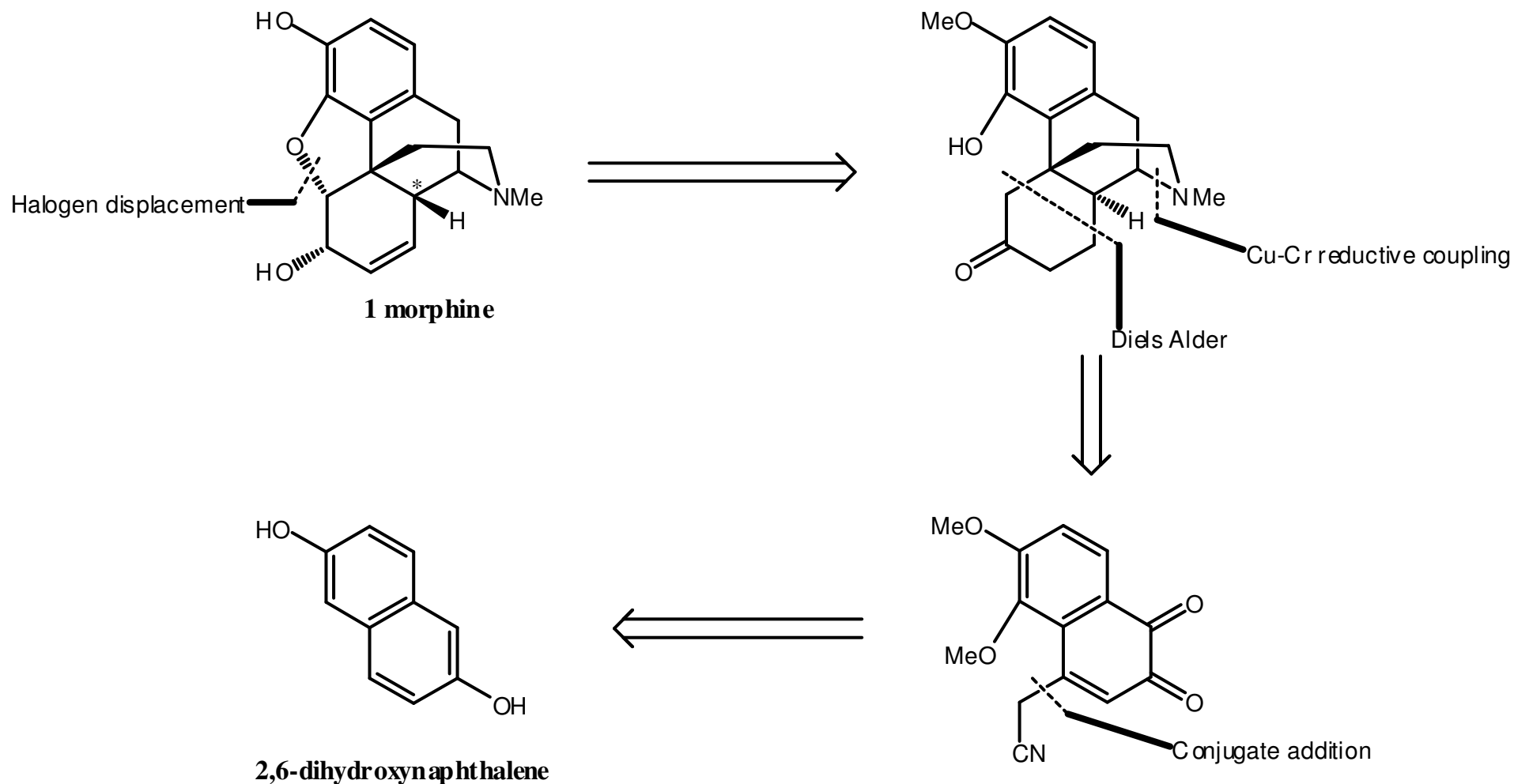
(1) J Med Chem, 1977, 20(1), 164

Sherwood 2 - CU Synthesis Lit Group - Morphine

Introduction

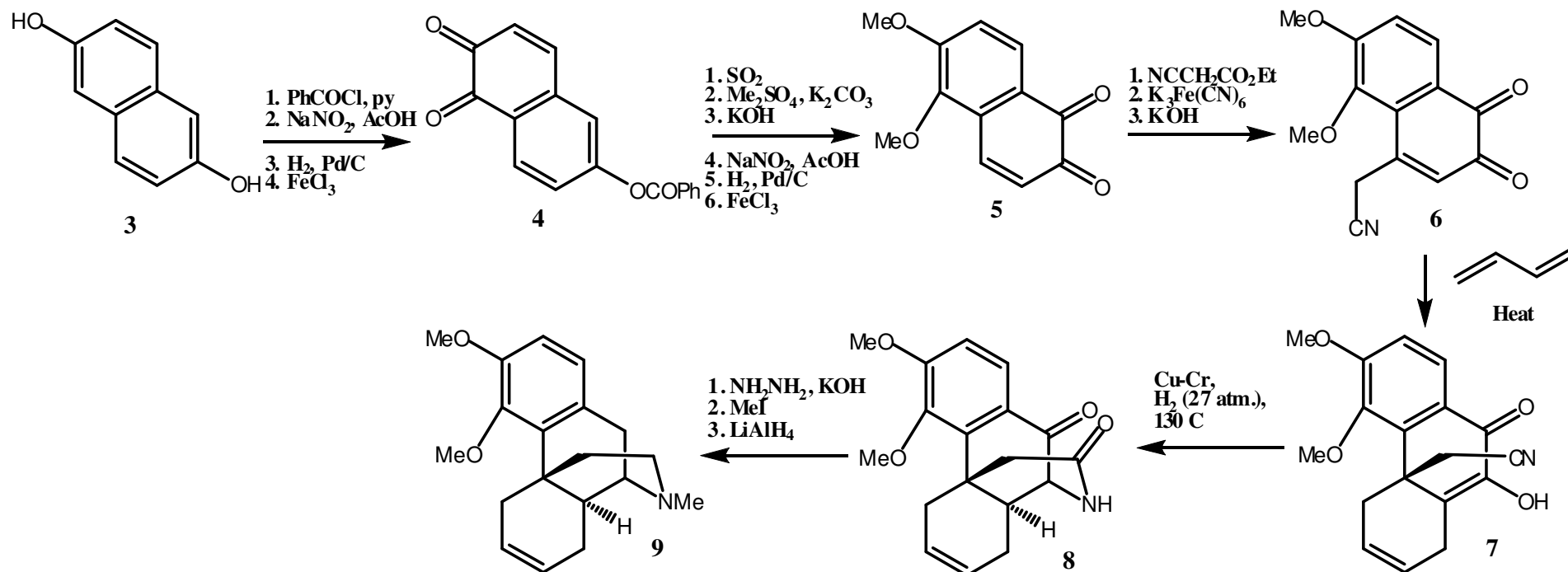
- Total Syntheses examined
 - Gates (1952) 1st total synthesis of morphine, includes resolution
 - M. Gates, G. Tschudi. *JACS*, **1956**, 78, 1380
 - Rice (1982) shortest formal synthesis when published
 - Rice, . *JOC*, **1980**, 45, 3135
 - Overman (1993) enantioselective
 - L. Overman, C. Hong, N. Kado. *JACS*, **1993**, 115, 11028
- Other Sources
 - Hudlicky, Tomas; Josephine Reed. *The Way of Synthesis*. WILEY-VCH: Weinheim, 2007.

Gates Synthesis



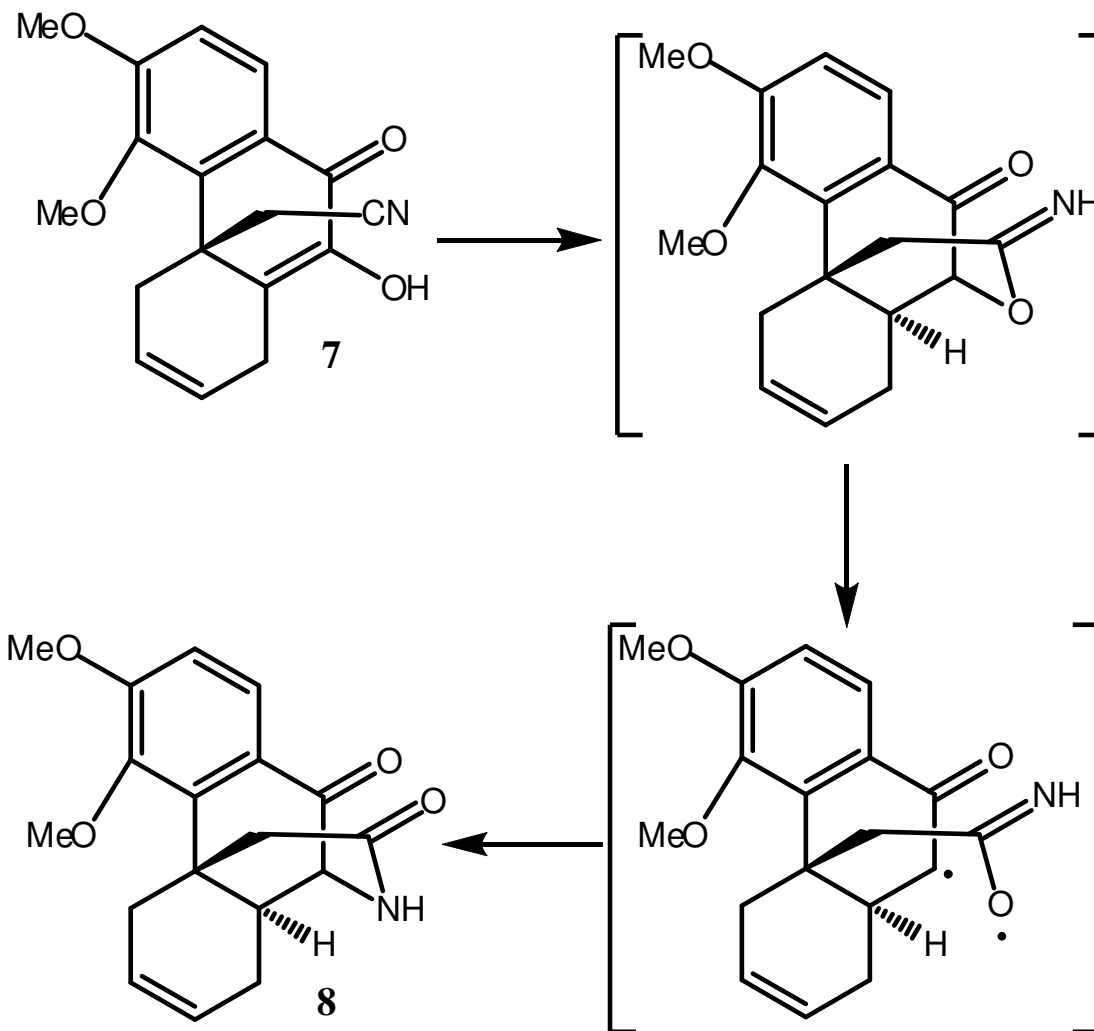
Sherwood 4 - CU Synthesis Lit Group - Morphine

Gates Synthesis



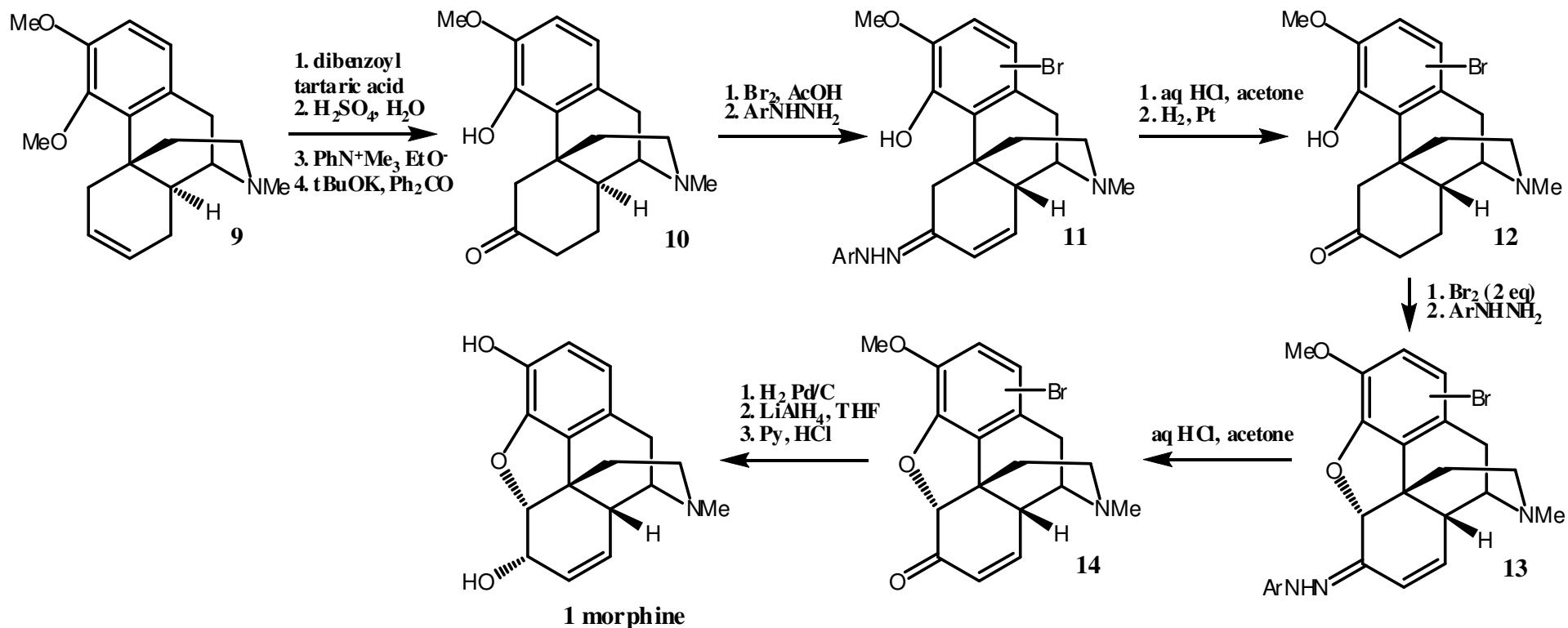
Sherwood 5 - CU Synthesis Lit Group - Morphine

Gates Synthesis



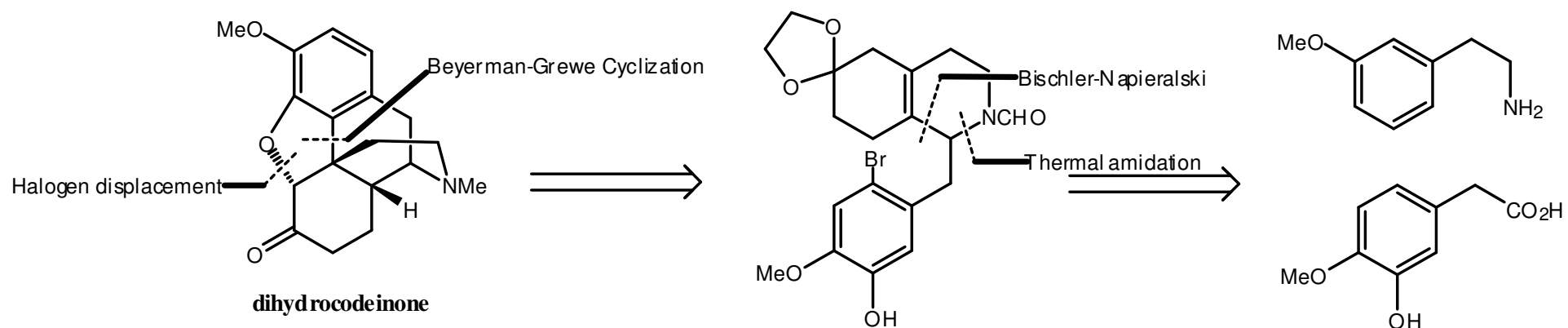
Sherwood 6 - CU Synthesis Lit Group - Morphine

Gates Synthesis



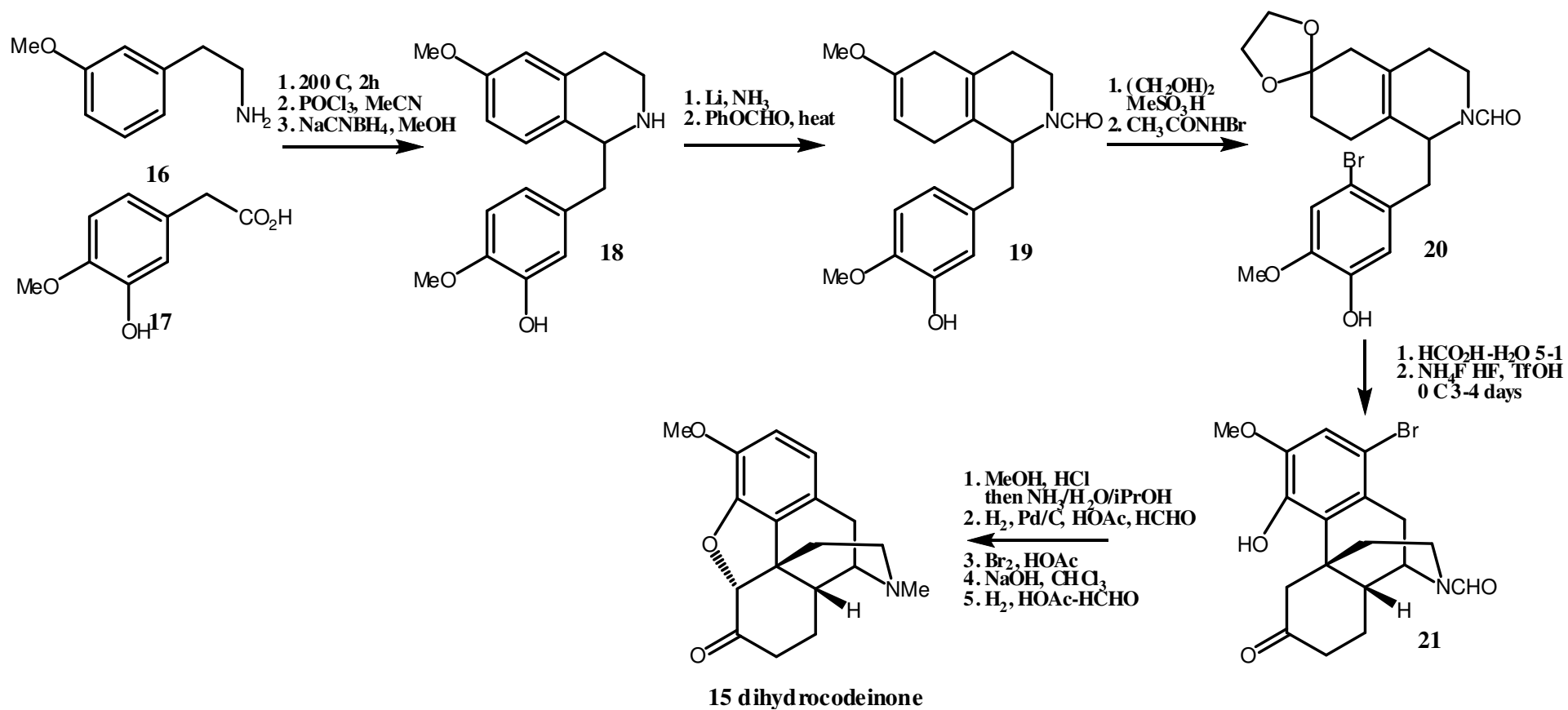
Sherwood 7 - CU Synthesis Lit Group - Morphine

Rice Synthesis



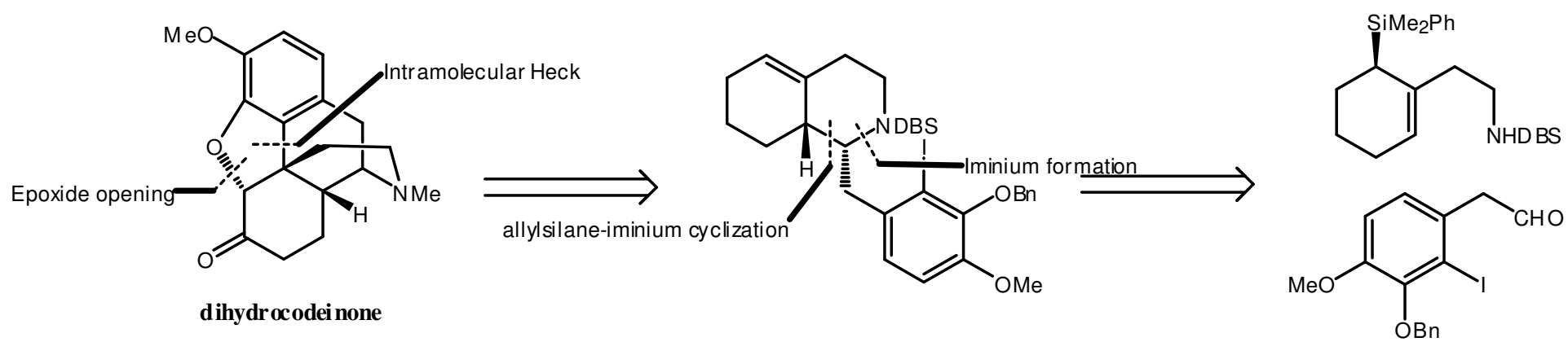
Sherwood 8 - CU Synthesis Lit Group – Morphine

Rice Synthesis



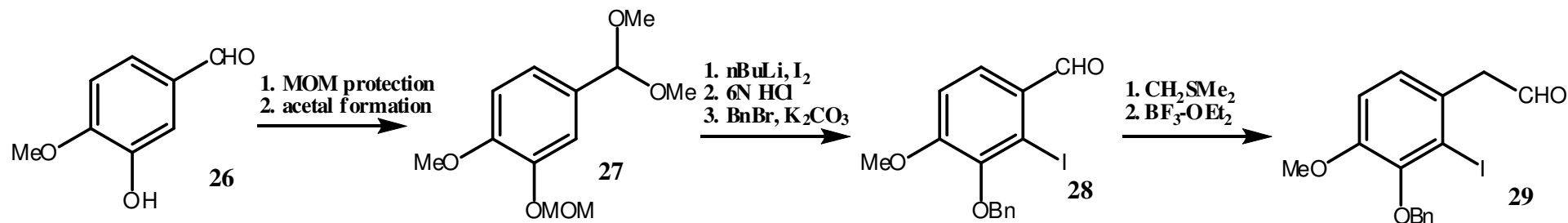
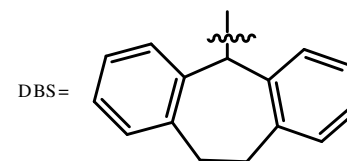
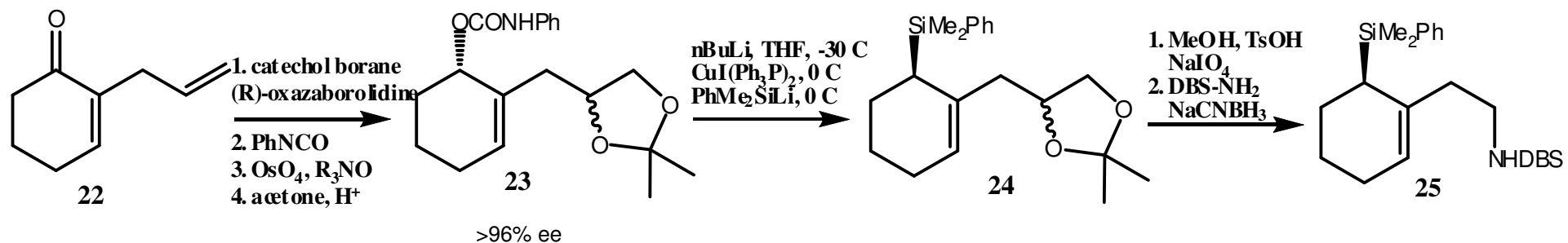
Sherwood 9 - CU Synthesis Lit Group – Morphine

Overman Synthesis



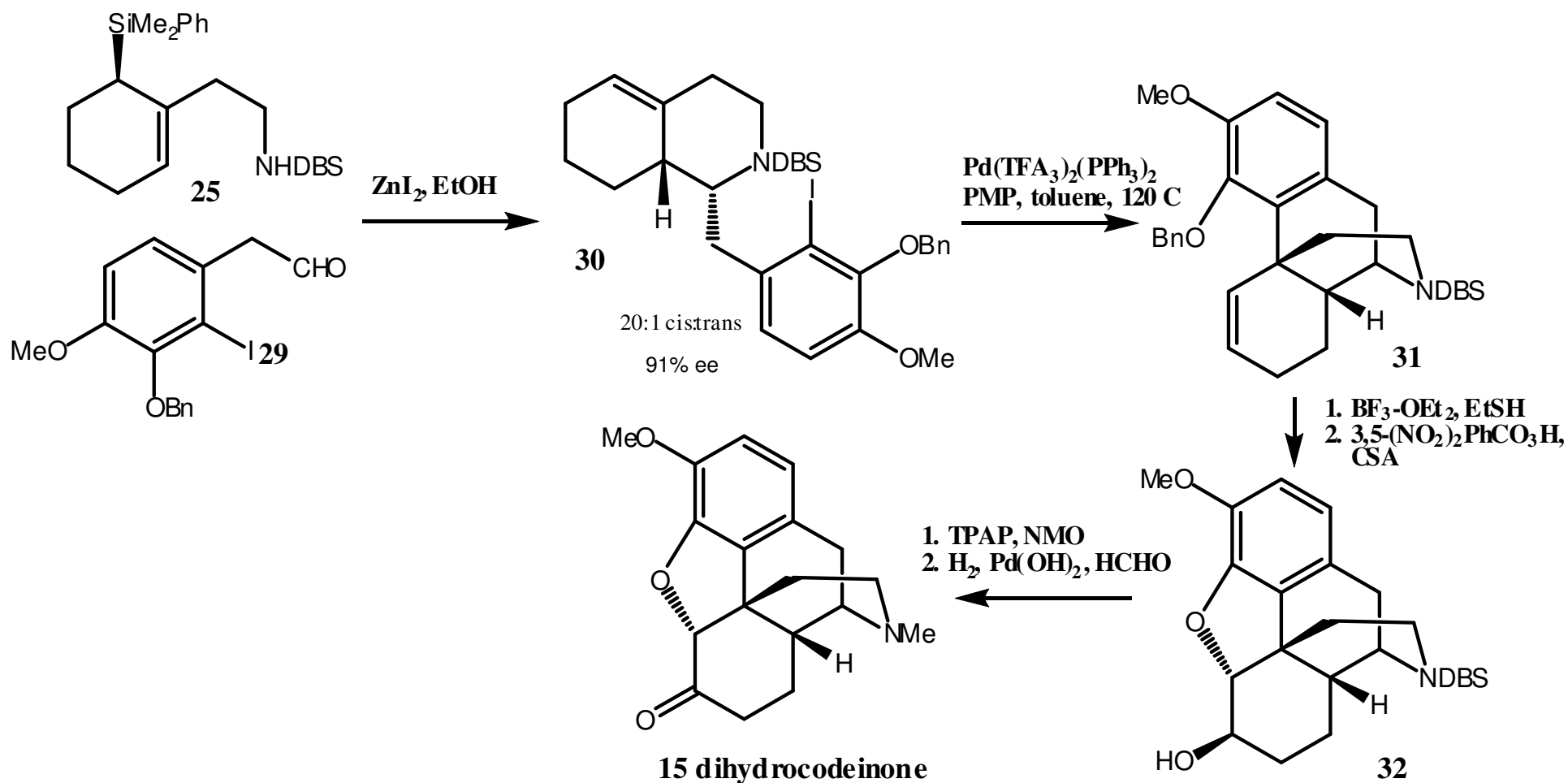
Sherwood 10 - CU Synthesis Lit Group – Morphine

Overman Synthesis



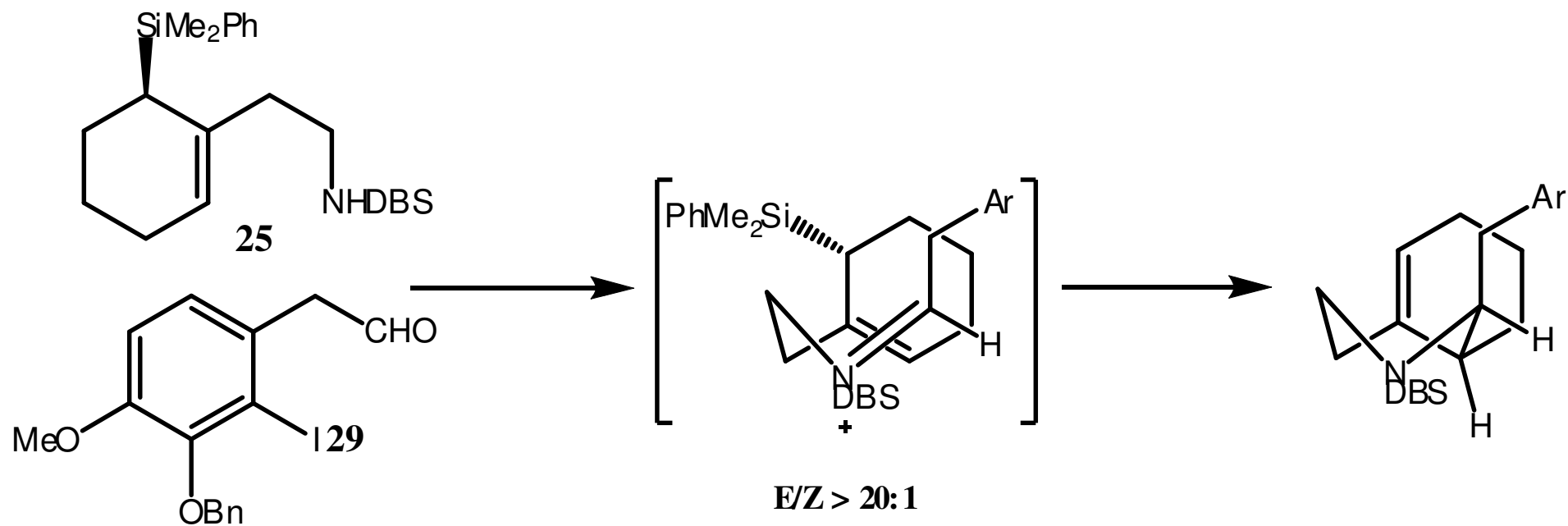
Sherwood 11 - CU Synthesis Lit Group – Morphine

Overman Synthesis



Sherwood 12 - CU Synthesis Lit Group – Morphine

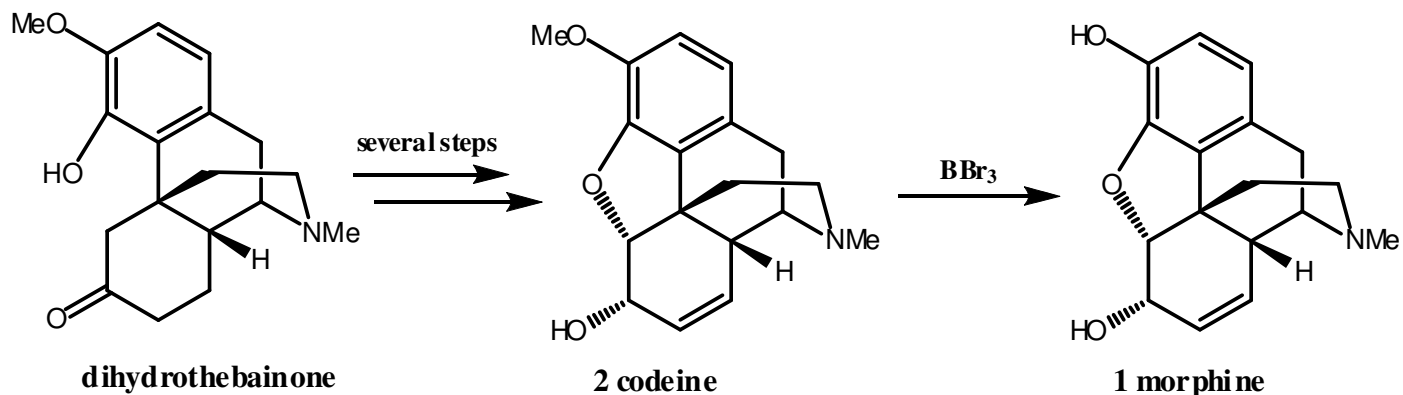
Overman Synthesis



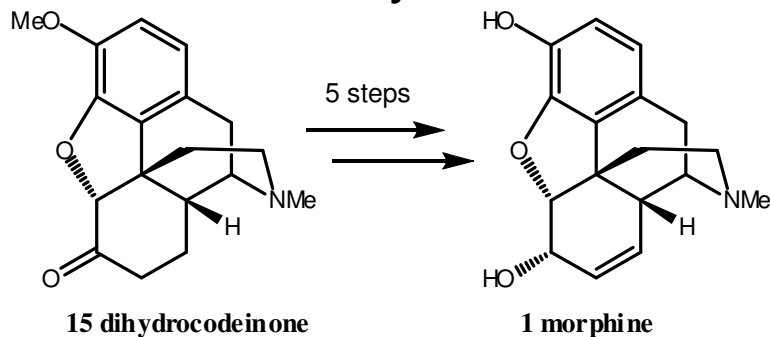
Sherwood 13 - CU Synthesis Lit Group – Morphine

Formal syntheses of morphine

- Rice formal synthesis extension(1,2)



- Overman formal synthesis extension(3)



(1) *J Med Chem*, **1977**, 20(1), 164

(2) *J Med Chem*, **1976**, 19(10), 1171

(3) *Proc Jpn Acad*, **1960**, 36, 145

Sherwood 14 - CU Synthesis Lit Group – Morphine

Final Comments

- Gates synthesis
 - First reported
 - Cu-Cr method creatively forges bridged heterocycle
 - 31 steps
 - Requires resolution to obtain enantiopure material
- Rice Synthesis
 - Beyerman-Grewe cyclization to form last ring
 - 14 steps to dihydrocodeinone
 - Requires resolution at end to obtain enantiopure material
- Overman Synthesis
 - Allylsilane-Iminium cyclization and Heck reaction to close core
 - 14 steps to dihydrocodeinone following longest linear sequence
 - No resolution necessary to achieve enantiopure material