

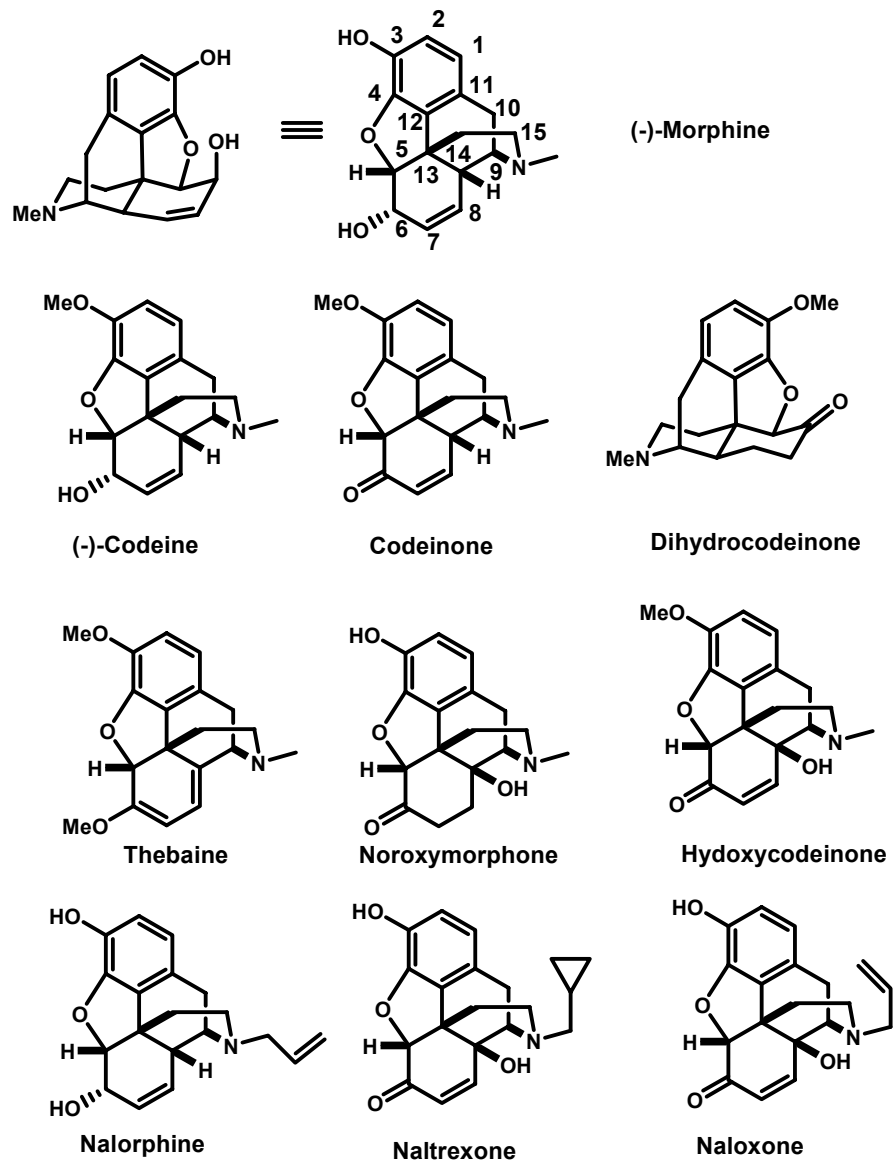
For excellent reviews on Morphine and Codeine, see

1. Hudlicky, T. *et al Studies in Natural Products Chemistry*, 1996, 18, 43
2. Taber, D.F. *et al Strategies and Tactics in Organic synthesis*, 2004, 5, 353
3. Maier, M. *Organic Synthesis Highlights II*, 1995, 357
4. Novak, B.H. *et al Curr. Org. Chem.* 2000, 4, 343
5. Blakemore, P.R. *et al, Chem. Comm.* 2002, 1159
6. Zezula, J. *et al, Synlett*, 2005, 388

The following work will be included in this talk due to the time limitation.

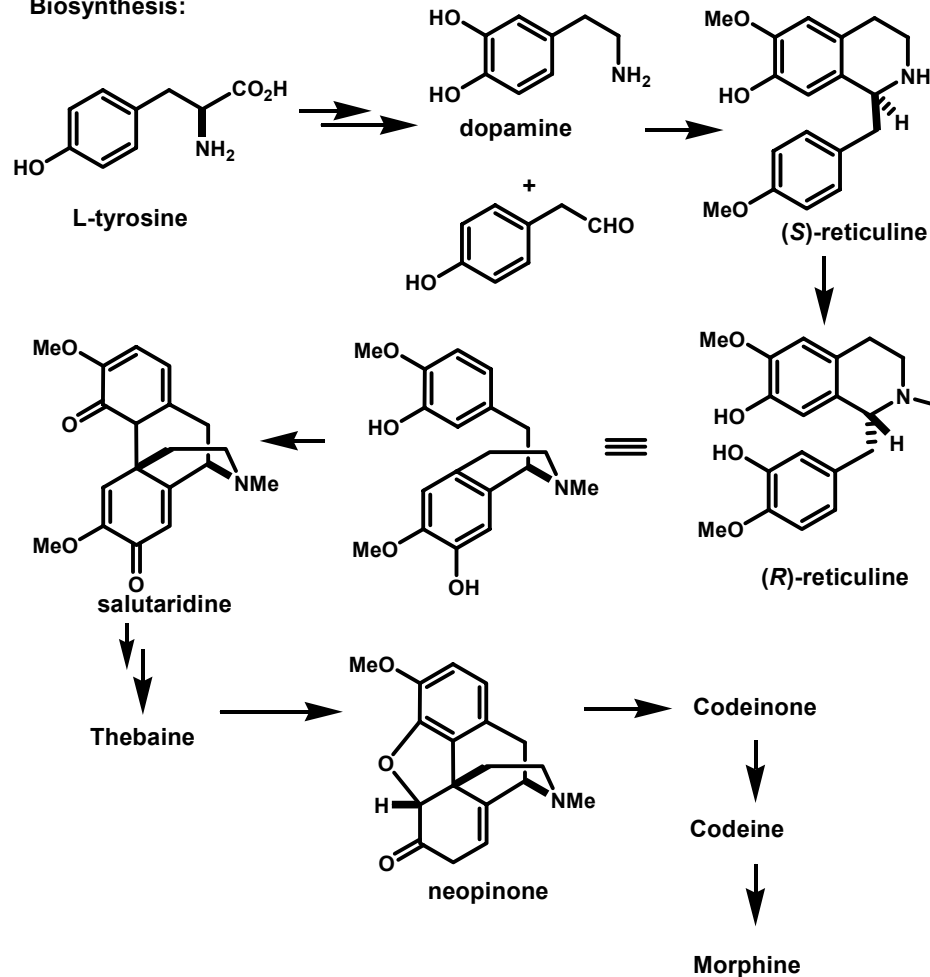
Gates	1952	(-)-Morphine
Rice	1980	(-)-Dihydrocodeinone
Evans	1982	O-Me-thebainone-A
Fuchs	1988	Codeine
Tius	1992	Thebainone-A
Parker	1992	Dihydrocodeinone
<b>Overman</b>	<b>1993</b>	<b>(-)-Dihydrocodeinone</b>
Mulzer	1996	(-)-Dihydrocodeinone
Parsons	1996	Morphine
White	1997	(+)-Morphine
Hudlicky	1998	10-hydroxy- <i>ent</i> -epi-dihydrocodeinone
Cheng	2000	Desoxycodine-D
Ogasawara	2001	(-)-Dihydrocodeinone ethylene ketal
Taber	2002	(-)-Morphine
Trost	2002	(-)-Codeine
Michels	2005	14-Hydroxycodine

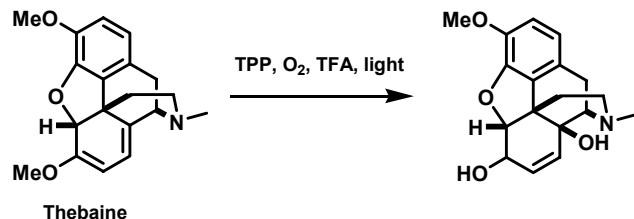
Raw opium contains approximately 25 different alkaloids by weight, depending on the variety. The chief alkaloids are Morphine (4-21%), Codeine (0.8-2.5%), Thebaine (0.5-2%), Papaverine (0.5-2.5%), Noscapine (4-8%), Meconic Acid (3-5%).



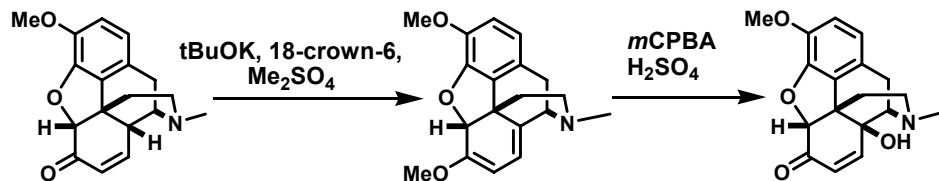
Morphine and codeine are the principal ingredients from opium poppy latex extract. The legal medicinal use of morphine in the US is more than 80 tons/year and the world wide illicit market for narcotics is probably more than \$760 billion.

## Biosynthesis:



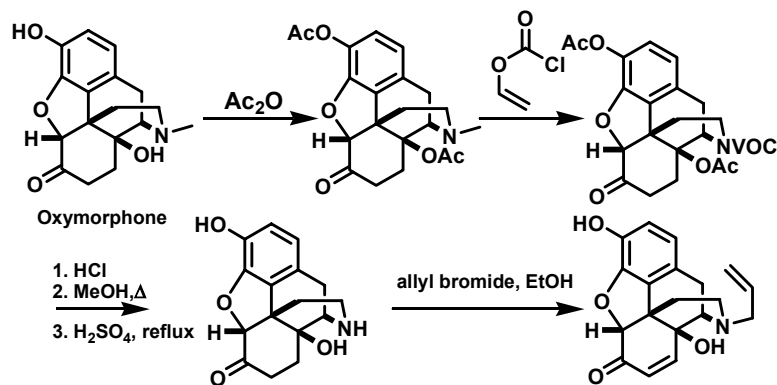


*Tetrahedron Lett.* 1994, 31, 5727



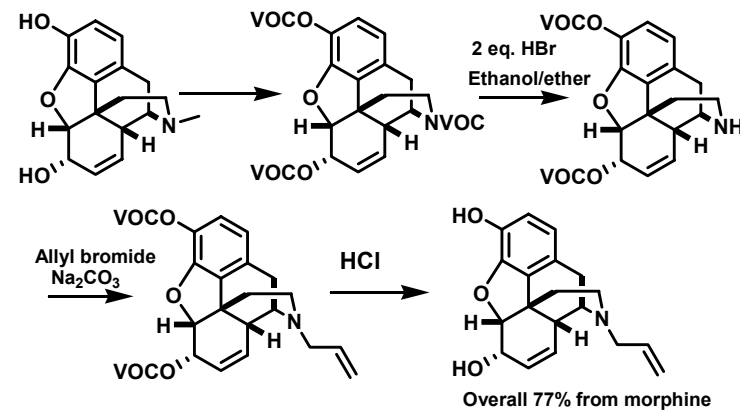
*Heterocycles*, 1998, 49, 43

*J. Org. Chem.*, 1996, 61, 6774



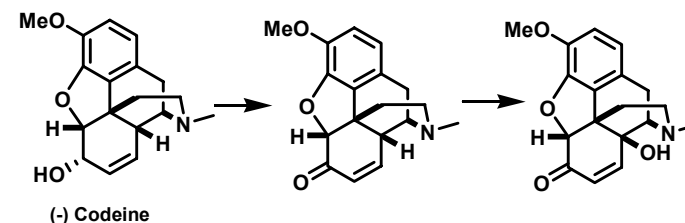
*Tetrahedron Lett.*, 1977, 1567

Naloxone



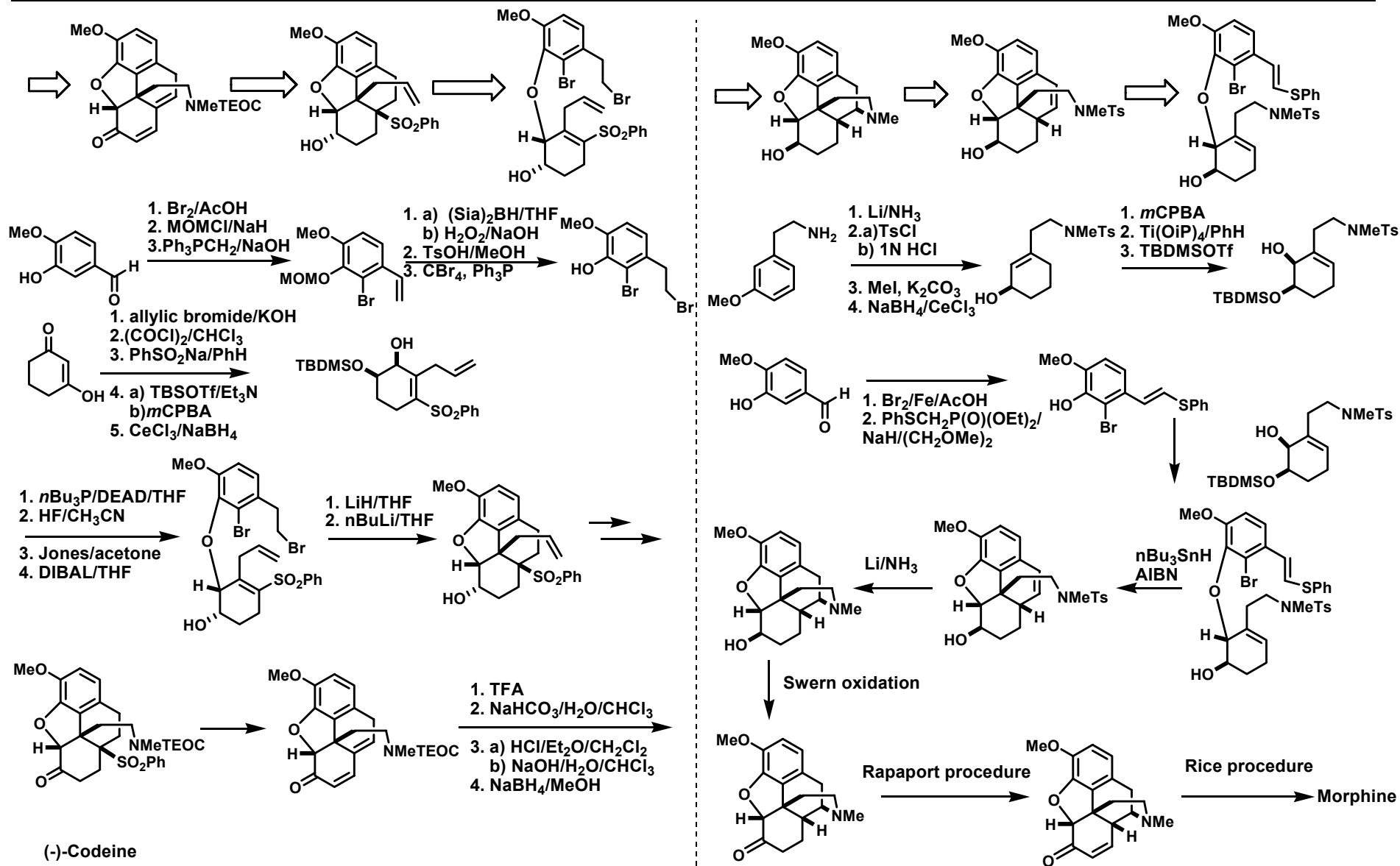
*Tetrahedron Lett.*, 1977, 1571

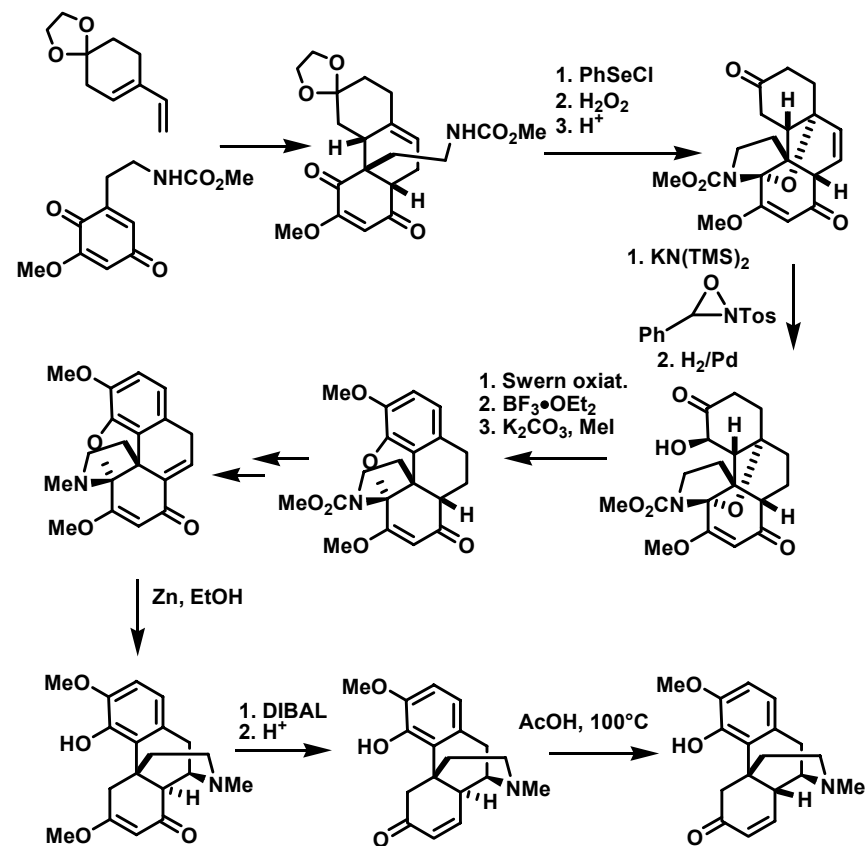
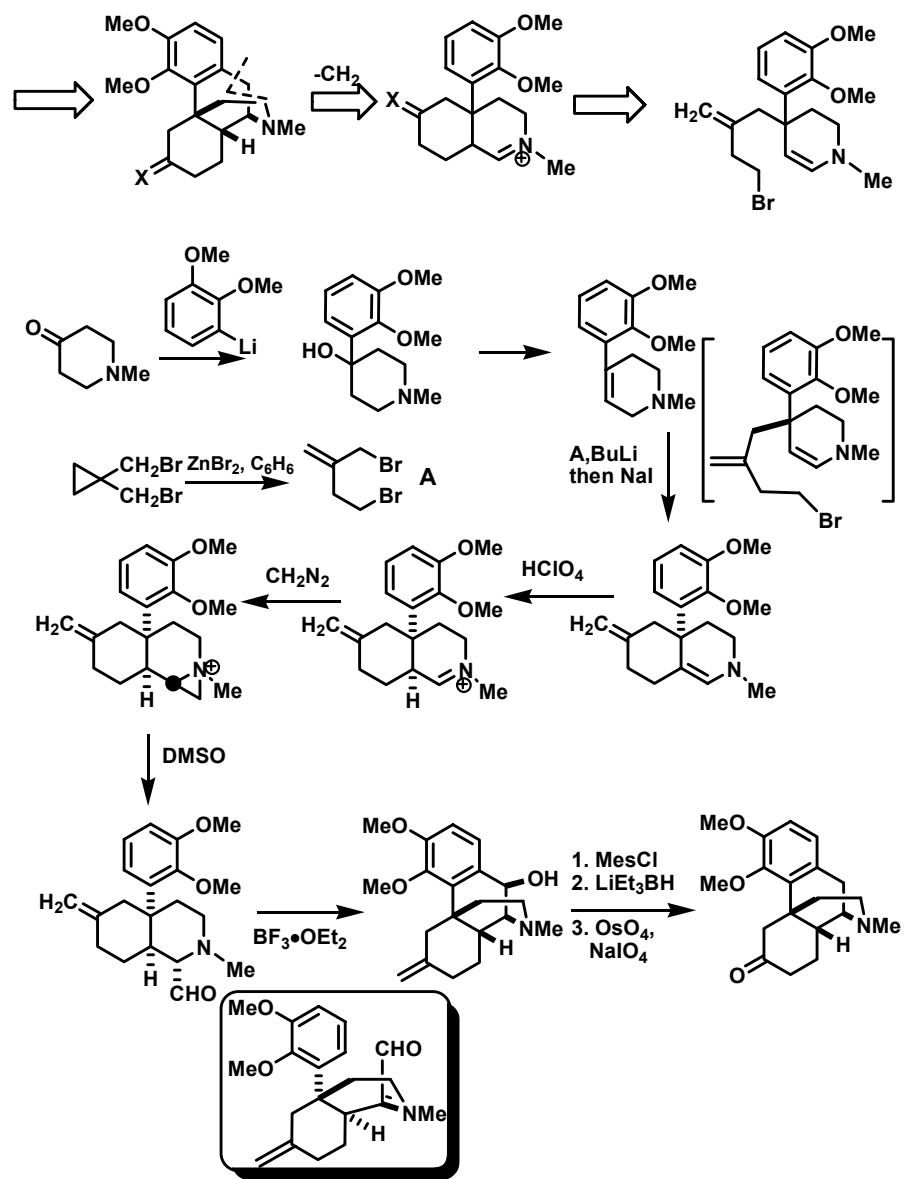
Overall 77% from morphine

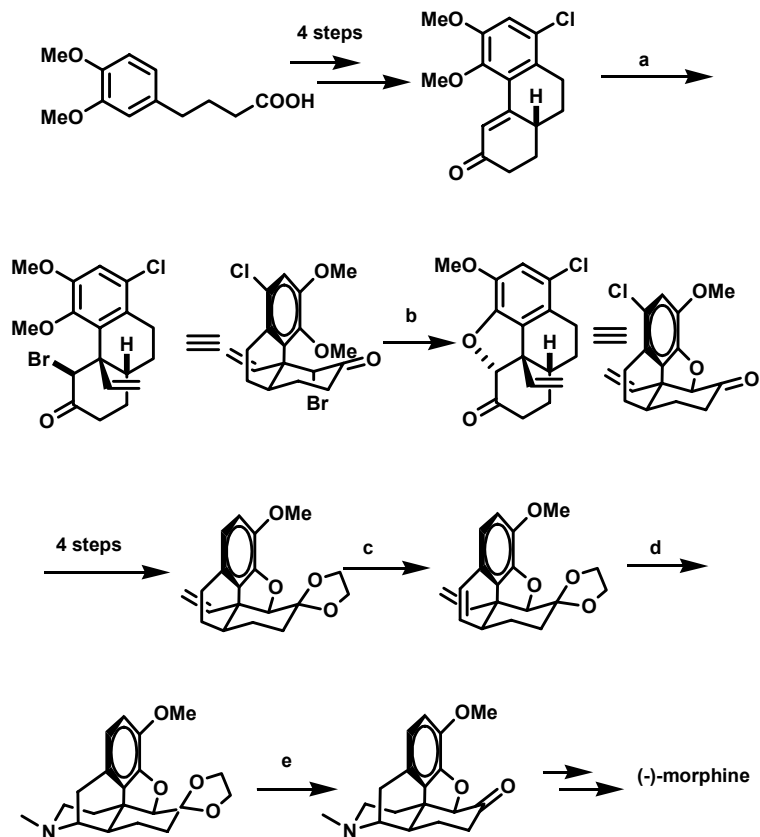


*J. Am. Chem. Soc.* 2005, ASAP









a)  $(\text{H}_2\text{C}=\text{CH})_2\text{CuMgCl}$ , THF,  $-78\text{ }^\circ\text{C}$  to  $0\text{ }^\circ\text{C}$ ; ii) TMSCl,  $\text{Et}_3\text{N}$ ,  $0\text{ }^\circ\text{C}$  to  $25\text{ }^\circ\text{C}$ ; iii) NBS, THF (63-80%). b) DMF,  $140\text{ }^\circ\text{C}$  (99%). c) NBS,  $(\text{PhCOO})_2$ ,  $\text{CCl}_4$ , reflux (68 - 81%). d) Li,  $\text{NH}_3$ , THF, *t*-BuOH (79 %). e) 3 N HCl,  $90\text{ }^\circ\text{C}$  (95 %).

