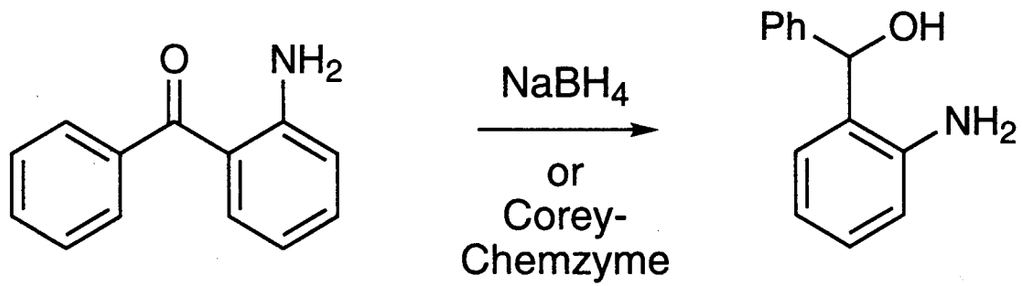
Rational Design of a Novel Amide Enolate Auxiliary

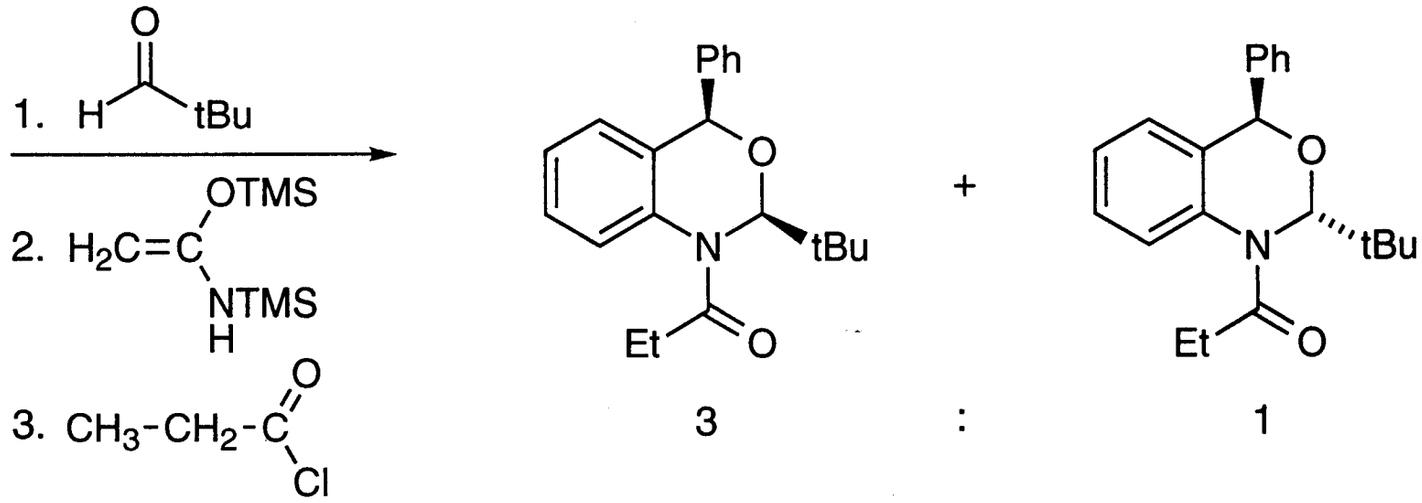
① Planarity of Nitrogen by Resonance Stabilization.

② Enhancement of Substituent Effect by Allyl-1,3-Strain.

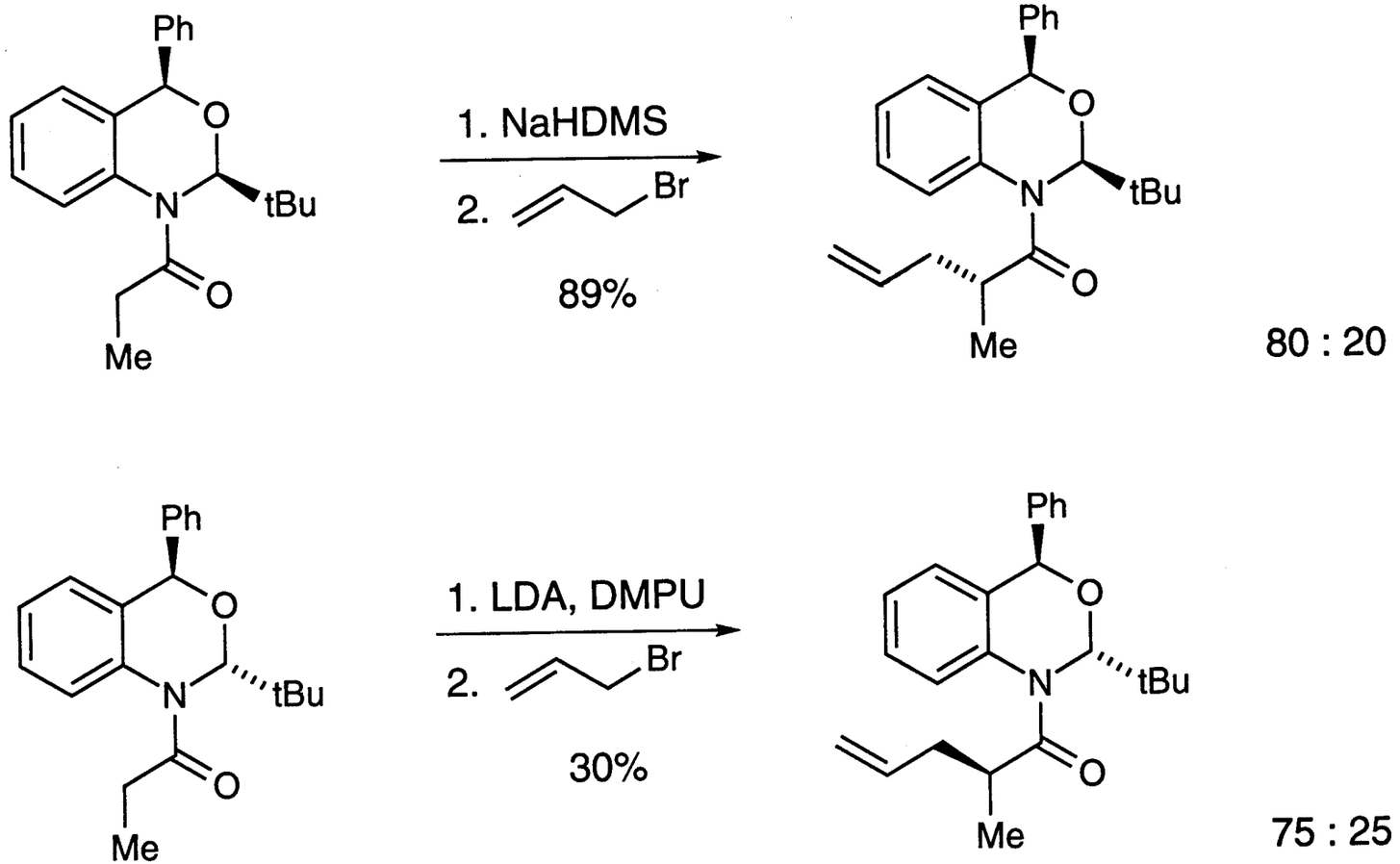
③ Easily Removable Auxiliary.

④ Easy Access.

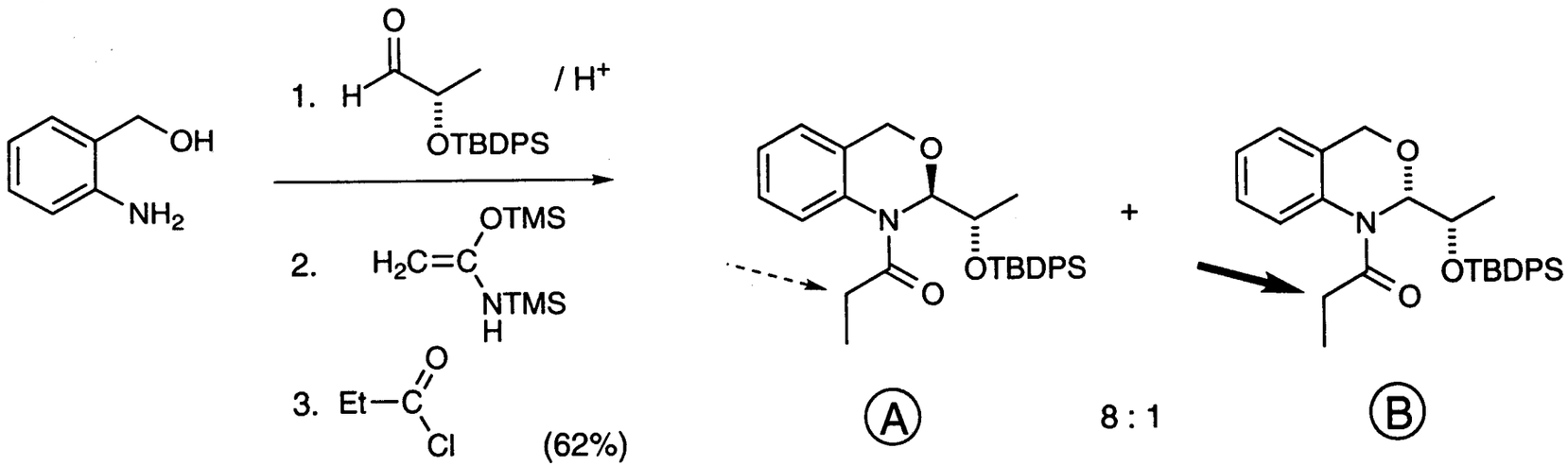

O
NH2
NaBH4
or
Corey-
Chemzyme
Ph
OH
NH2

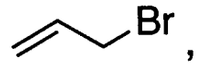
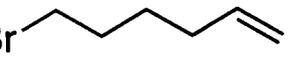

O
1. H
tBu
OTMS
2. H2C=C
NTMS
H
3. CH3-CH2-C
O
Cl
(50%)
Ph
O
N
tBu
Et
O
3
+
Ph
O
N
tBu
Et
O
1
Chromatographic Separation

Selections


Ph
O
N
tBu
O
Me
1. NaHDMS
2.
Br
89%
Ph
O
N
tBu
O
Me
80 : 20
Ph
O
N
tBu
O
Me
1. LDA, DMPU
2.
Br
30%
Ph
O
N
tBu
O
Me
75 : 25

Even Better System



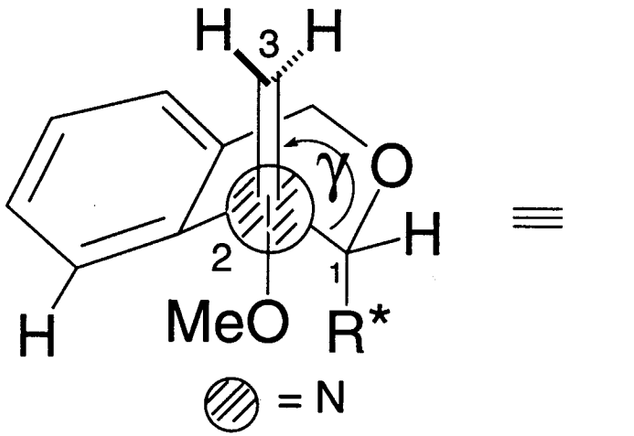
Deprotonation with KHMDS, alkylation with  , Et-Br, *n*-Pr-I,Br  .

Both (A) and (B) show selection ≥ 96 : 4 ! (B) slightly better.

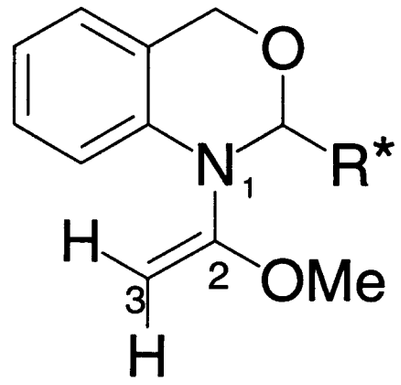
Removal with mild alkali (F^-).

M. Hiersemann, 1994

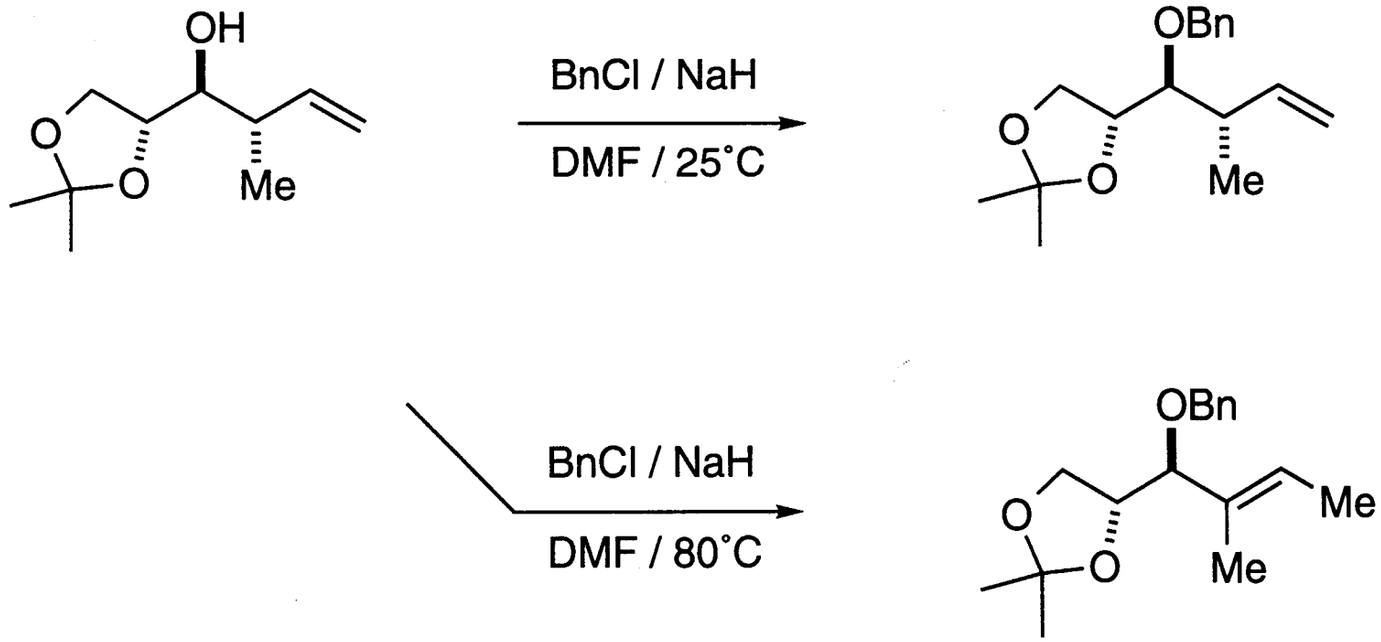
Calculated Rotational Barrier for



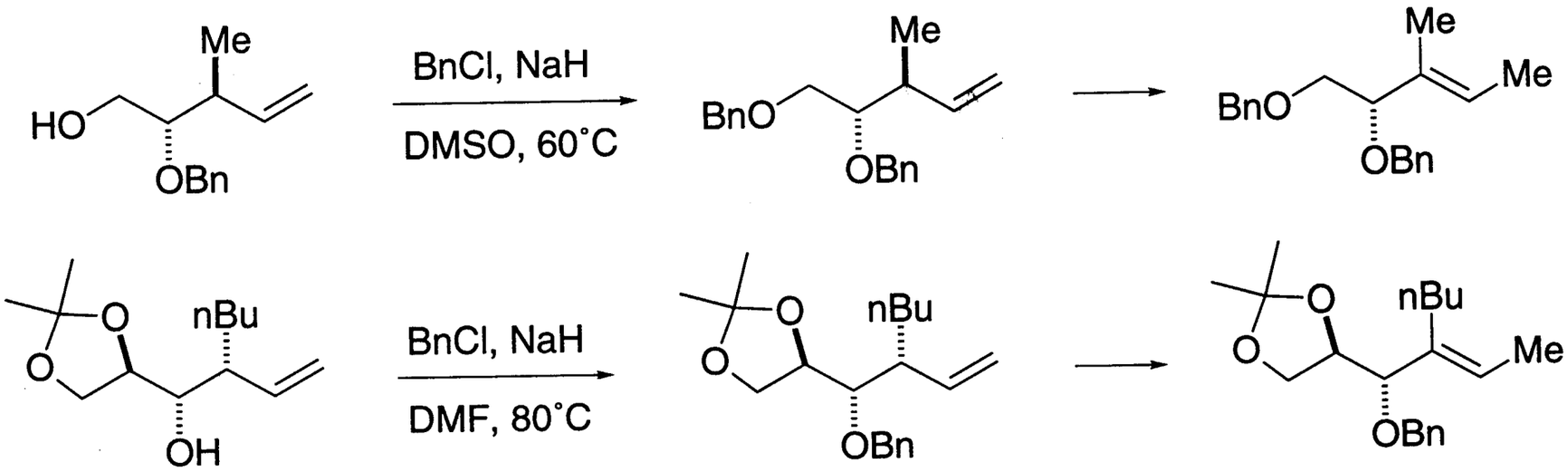
≡



Serendipity



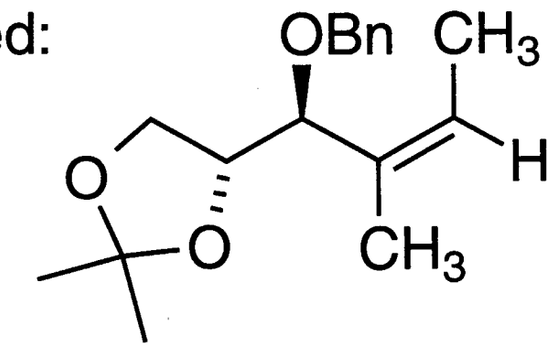
Further Examples



- not with LDA, KOH, KAPA, Di-Li-Ethylendiamine
- only in DMF (or DMSO)
- only O-benzyl ether rearranges not the free alcohol

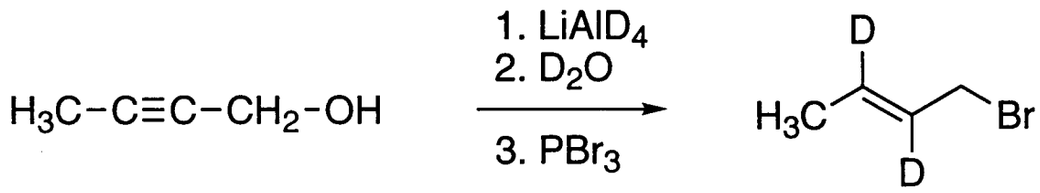
Mechanistic Investigations

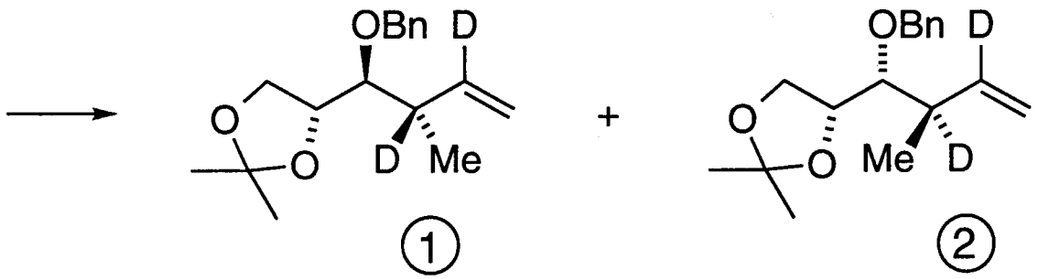
1) kinetically controlled:



(Z)-Isomer is stable, no E/Z-isomerization

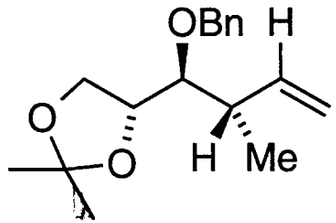
2) no H-D-exchange after quenching
with D_2O or in d_7-DMF or NaD





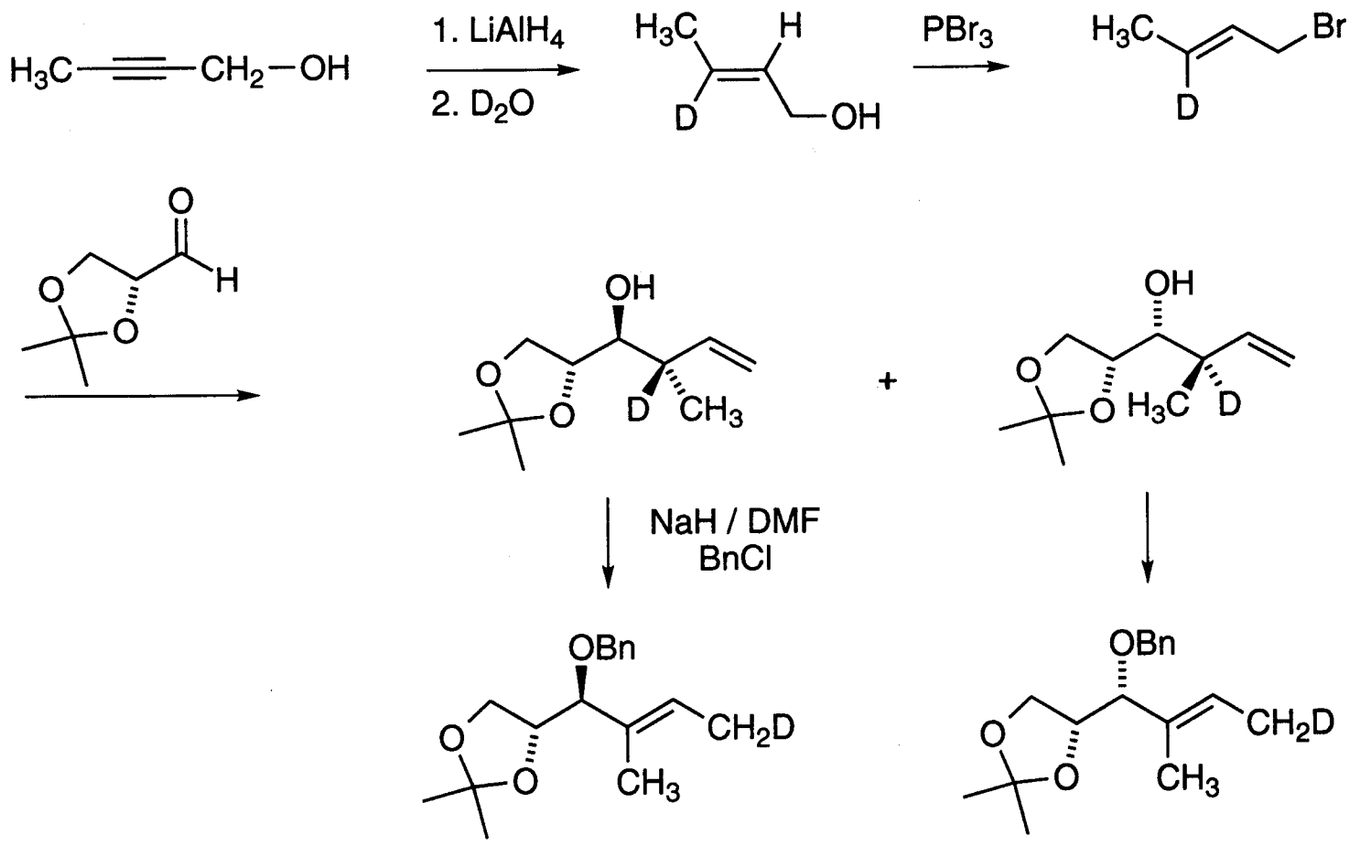
① ②

Rearrangement of ① or ② together with

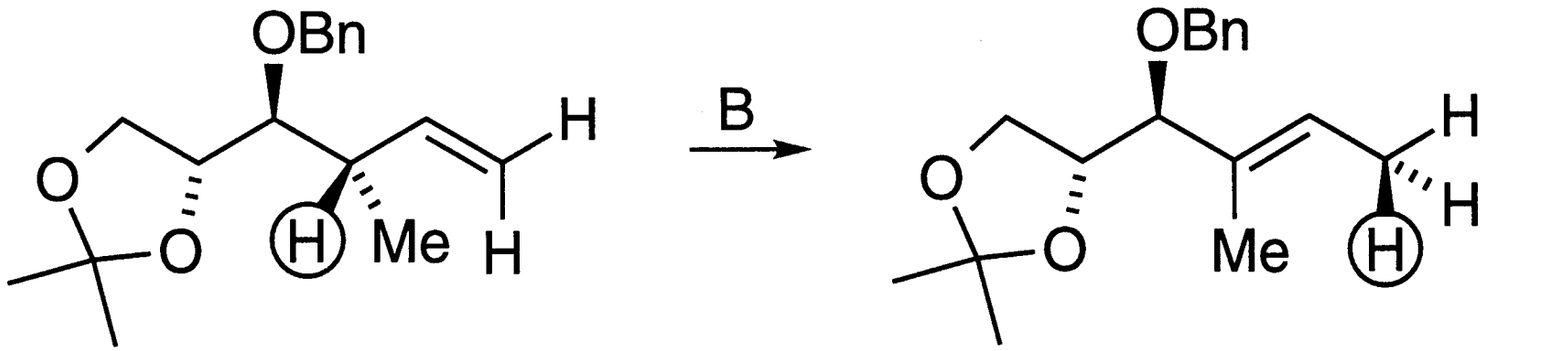


yields only d_0- or d_2-material, no d_1-material

3) strictly intramolecularly:

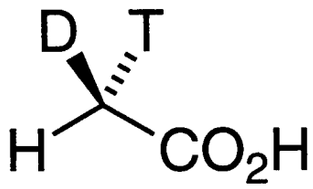


hence: strictly intramolecular 1,3-shift:

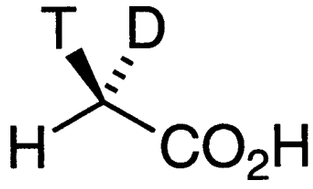


suprafacial or antarafacial?

Chiral Methyl Groups

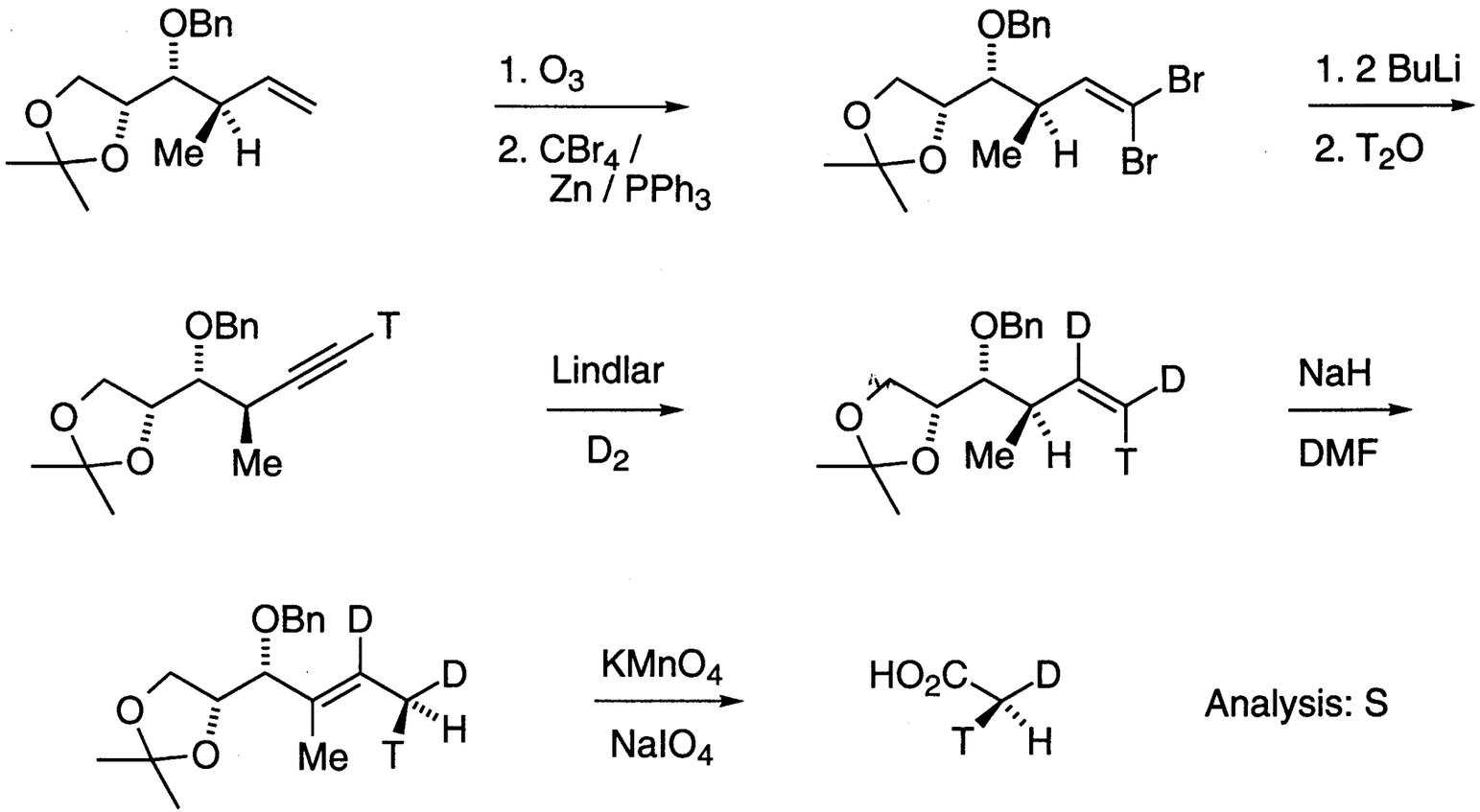


(S)

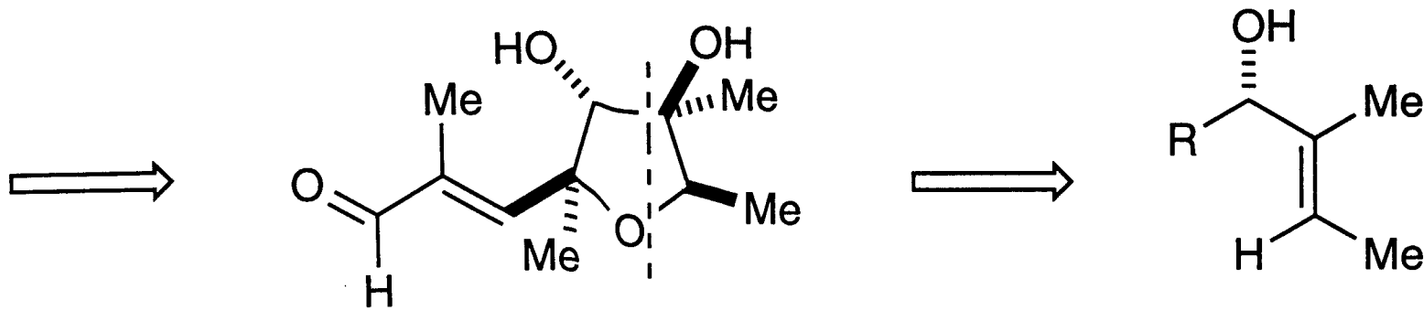


(R)

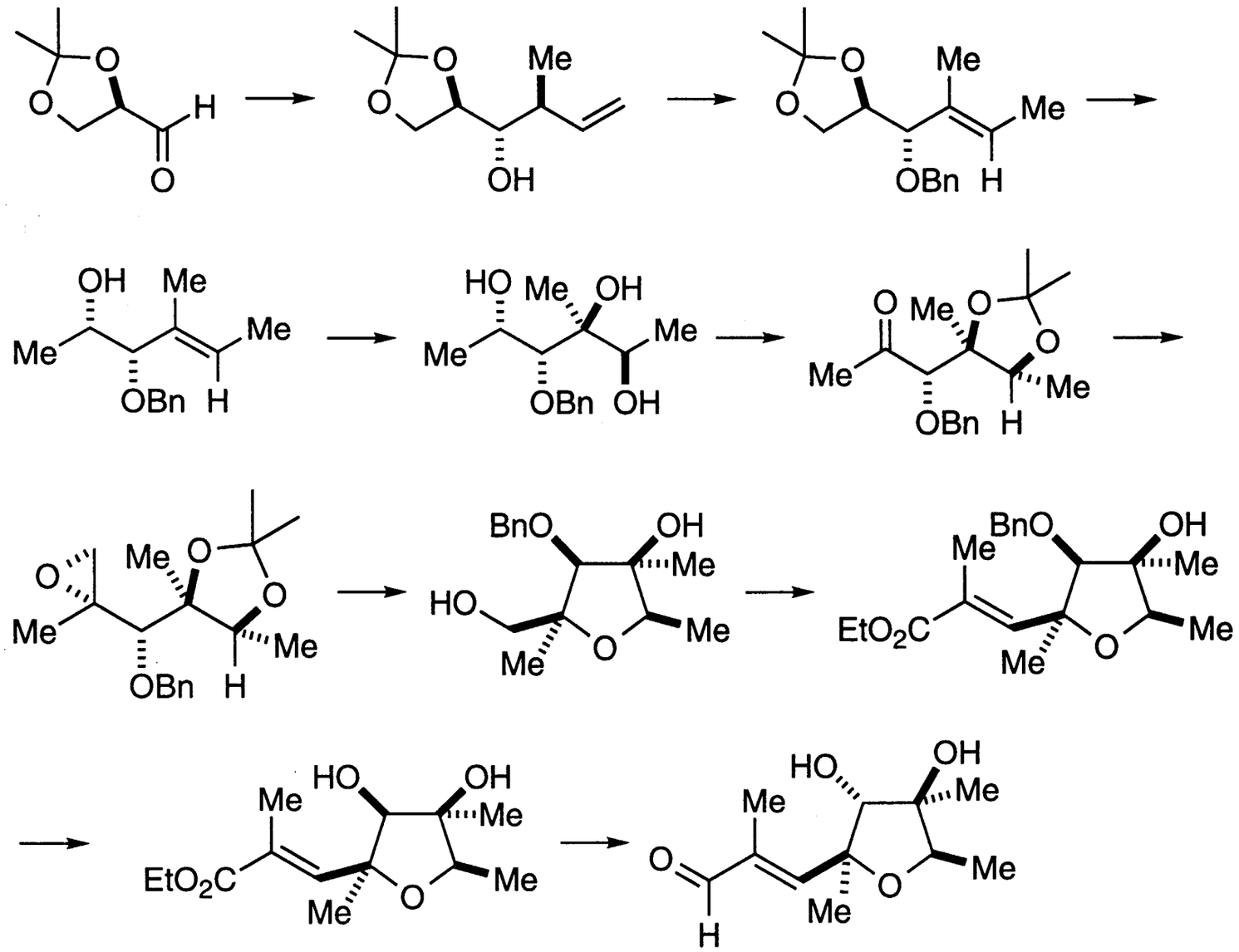
Our Synthesis



Citroviridine
Beri-Beri-Desease
ATP-ase-Inhibition

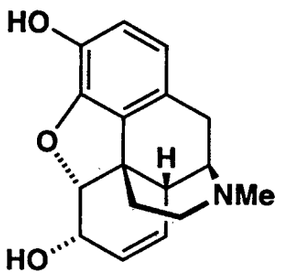


Citreoviral

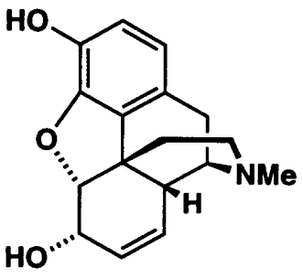


Citreoviral

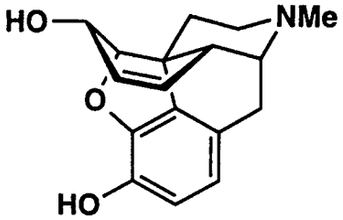
(-) - Morphine



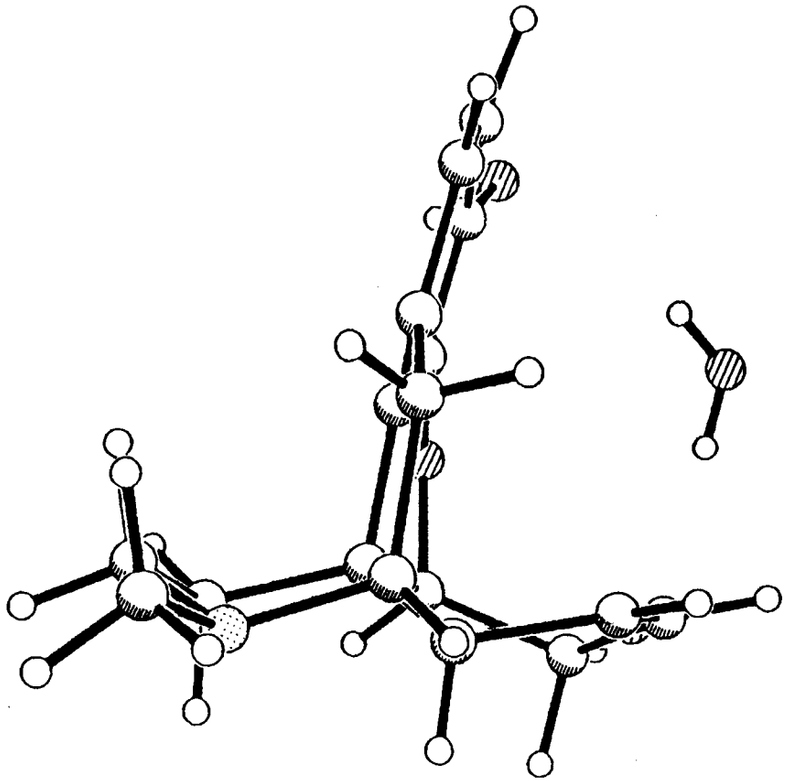
A

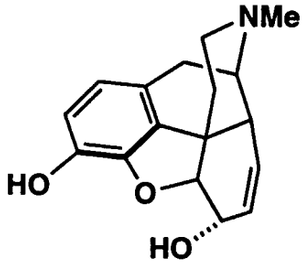


B

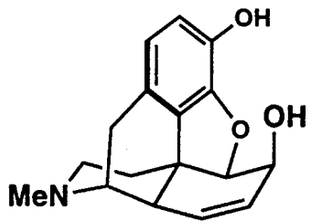


C

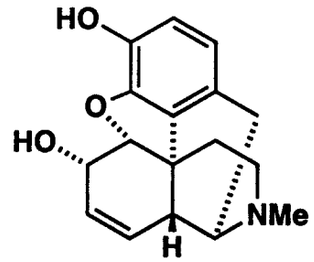




D

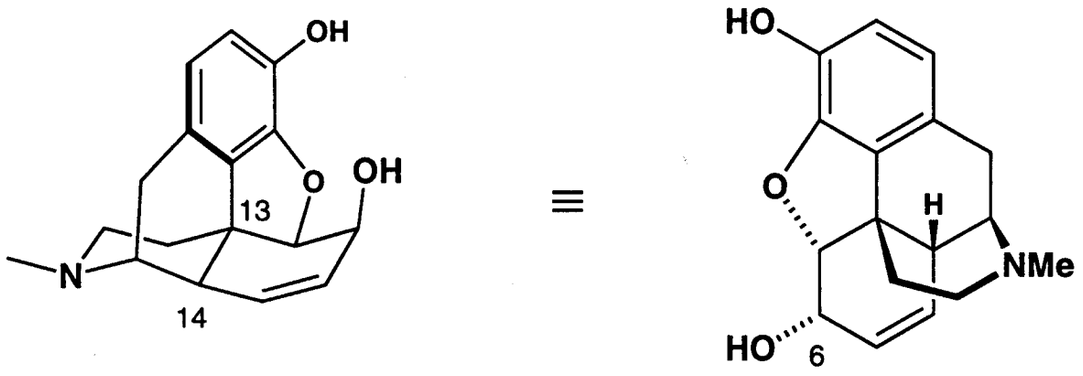


E



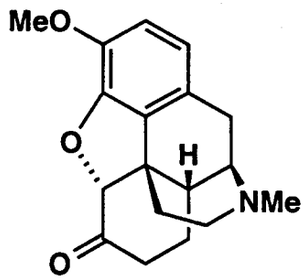
F

(-) - Morphine as a Synthetic Challenge

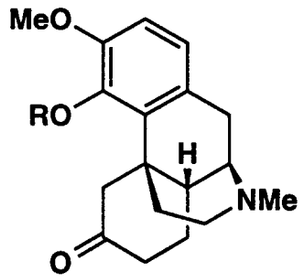


* Dense network of 3 carbocycles and 2 heterocycles.
* 5 vicinal stereogenic carbons.
* Benzylic quarternary stereocenter at C-13, a tertiary one at C-14.
* Substitution pattern of aromaric ring A.
* "Dissonant" functionality pattern.

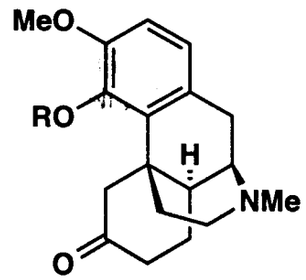
Known Synthetic Precursors



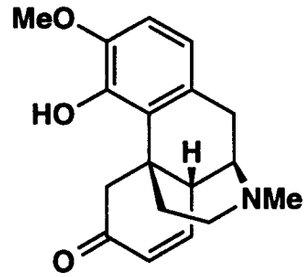
Dihydrocodeinone



Dihydrothebainone
and its O-methyl ether



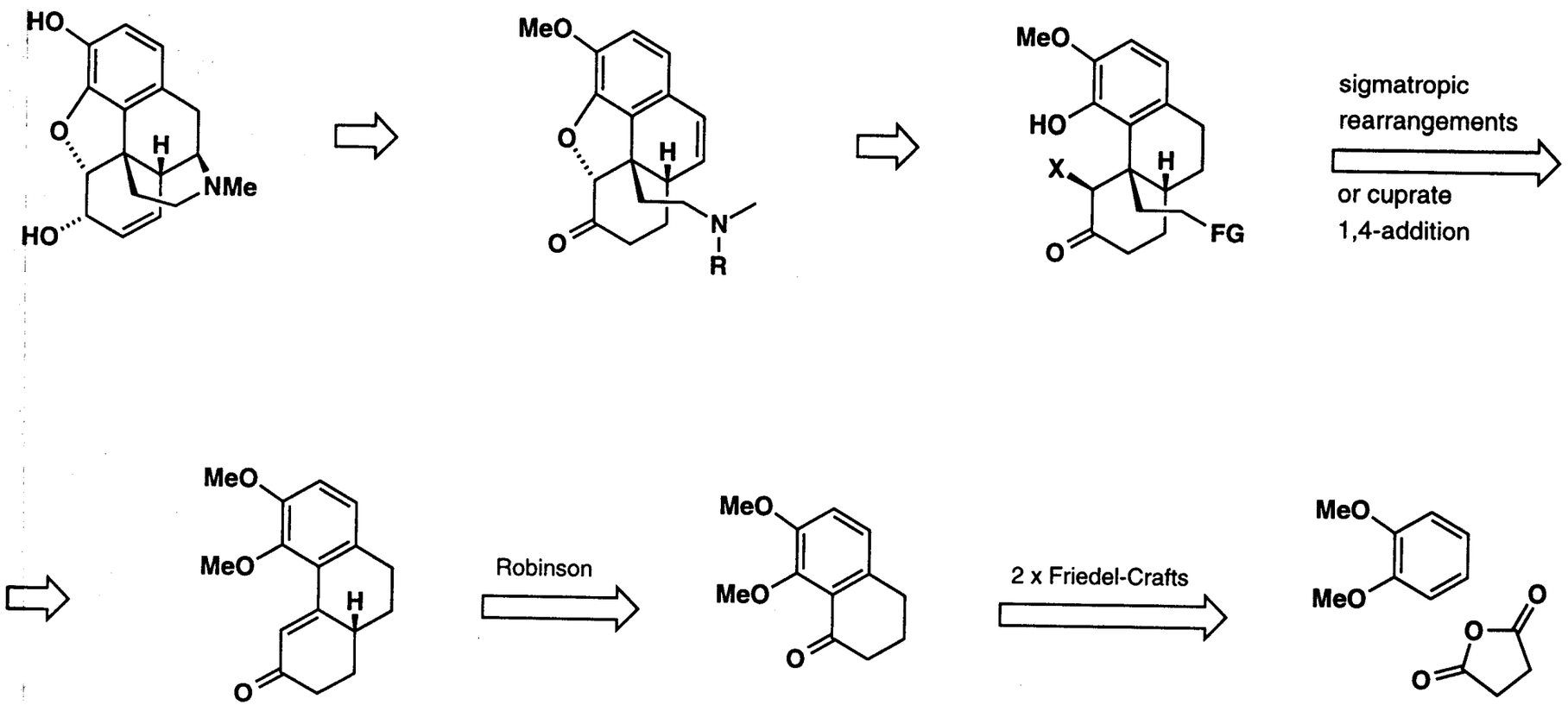
14-Epidihydrothebainone
and its O-methyl ether



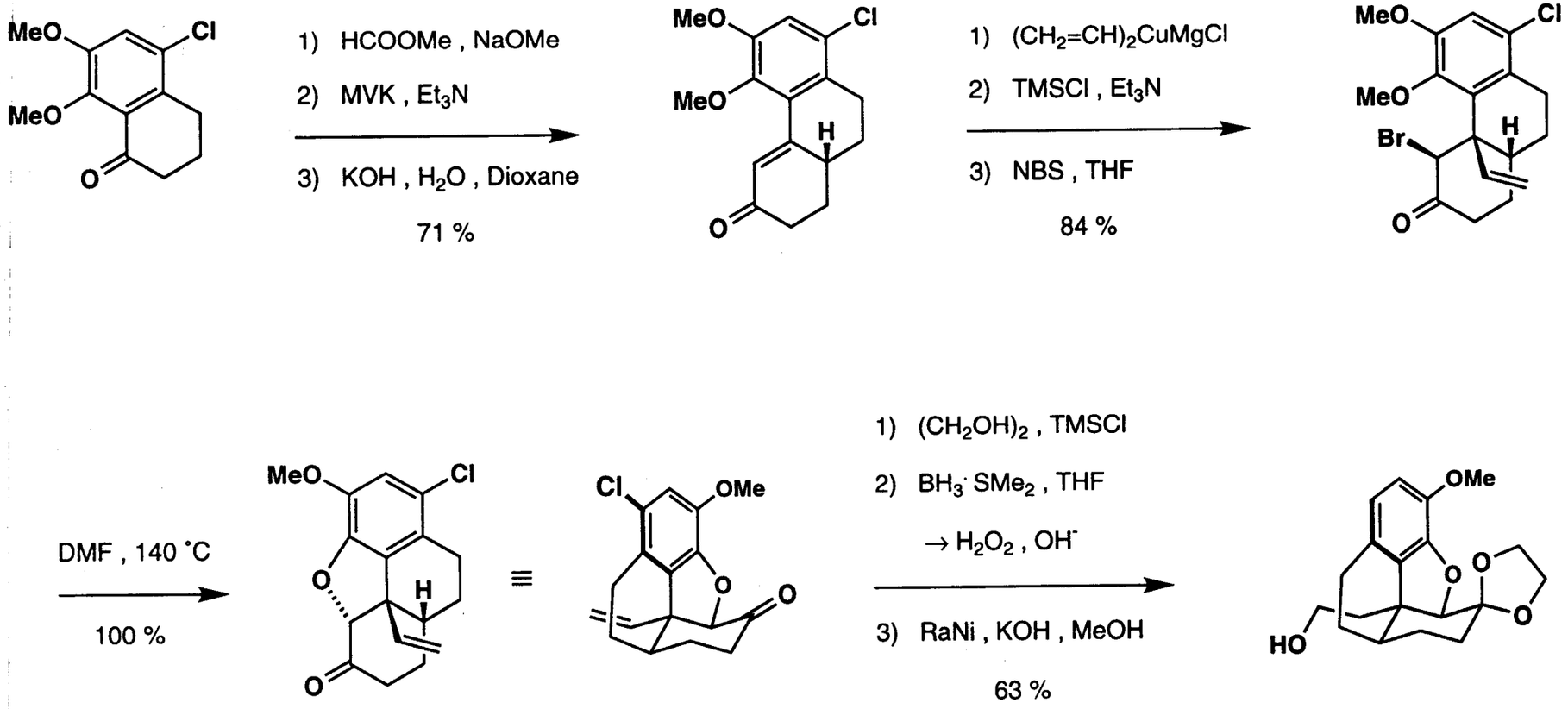
Thebainone A

All compounds can be converted to (-)-morphine in > 60 % yield.

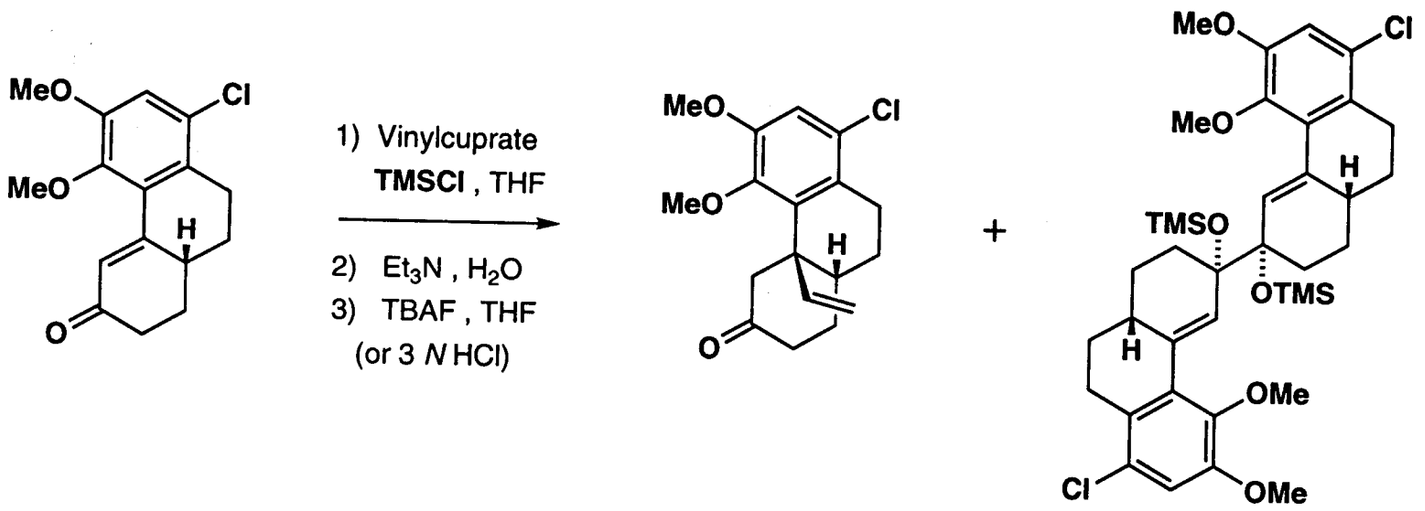
Retrosynthetic Analysis



A Formal Total Synthesis of (-)-Morphine



Chlorosilanes and Cuprates Revisited



Vinylcuprate :

CH_2=CHMgCl , 5-10 % CuBr · SMe_2

$(CH_2=CH)_2CuMgCl$

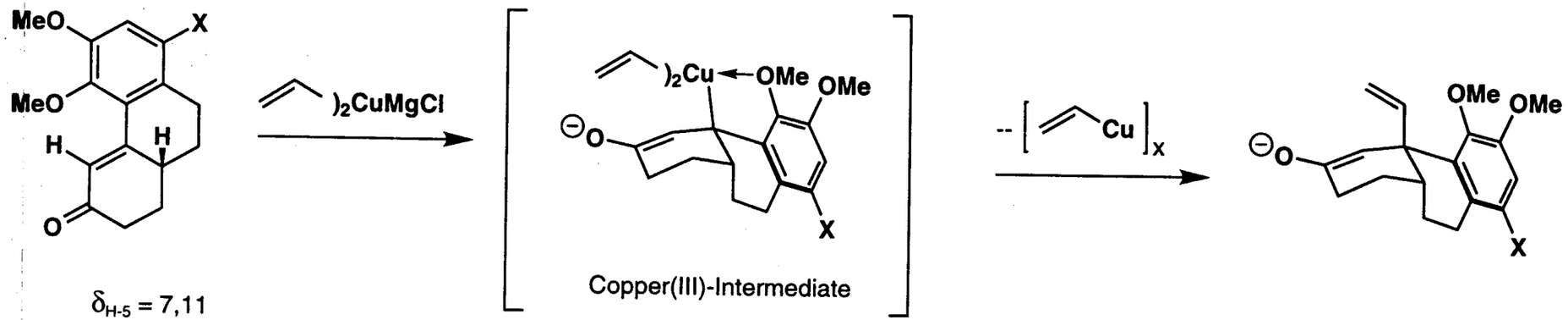
$(CH_2=CH)_2CuLi$

$(CH_2=CH)_2Cu(CN)Li_2$

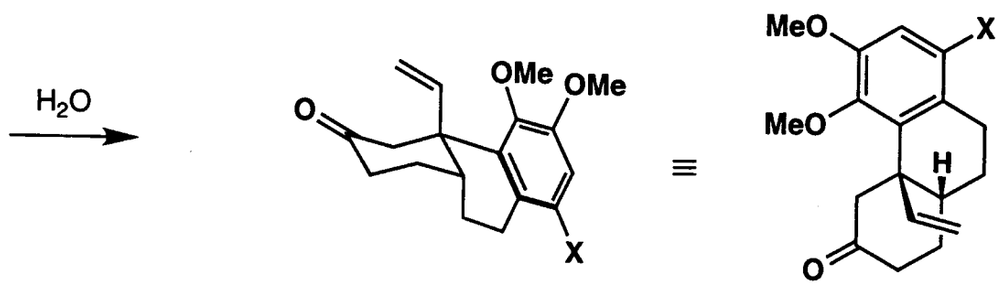
$(CH_2=CH)MeCu(CN)Li_2$

Complex mixtures , low yields of 1,4-adduct
Difficult to reproduce and scale up
Tedius preparation of cuprates and workup
Low atom economy

The *Ortho* -Methoxy Group is Crucial for 1,4-Addition

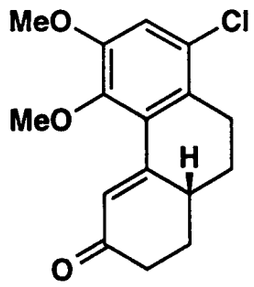


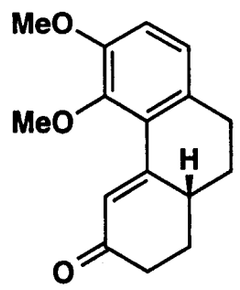
$\delta_{H\text{-}5}$ = 7,11

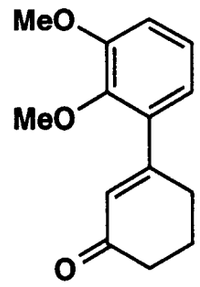


1,4 - *Versus* 1,2-Addition

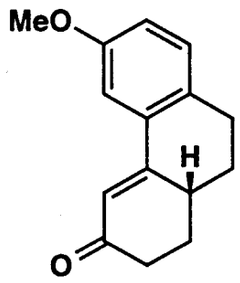
1,4-Addition :

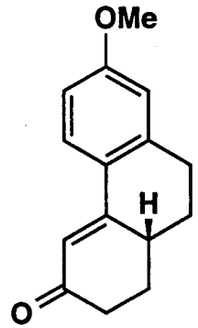


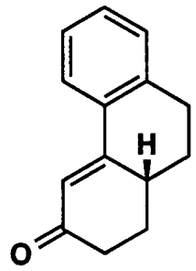


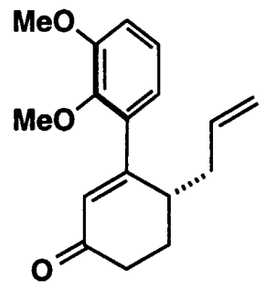


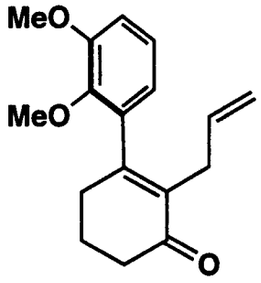
1,2-Addition :



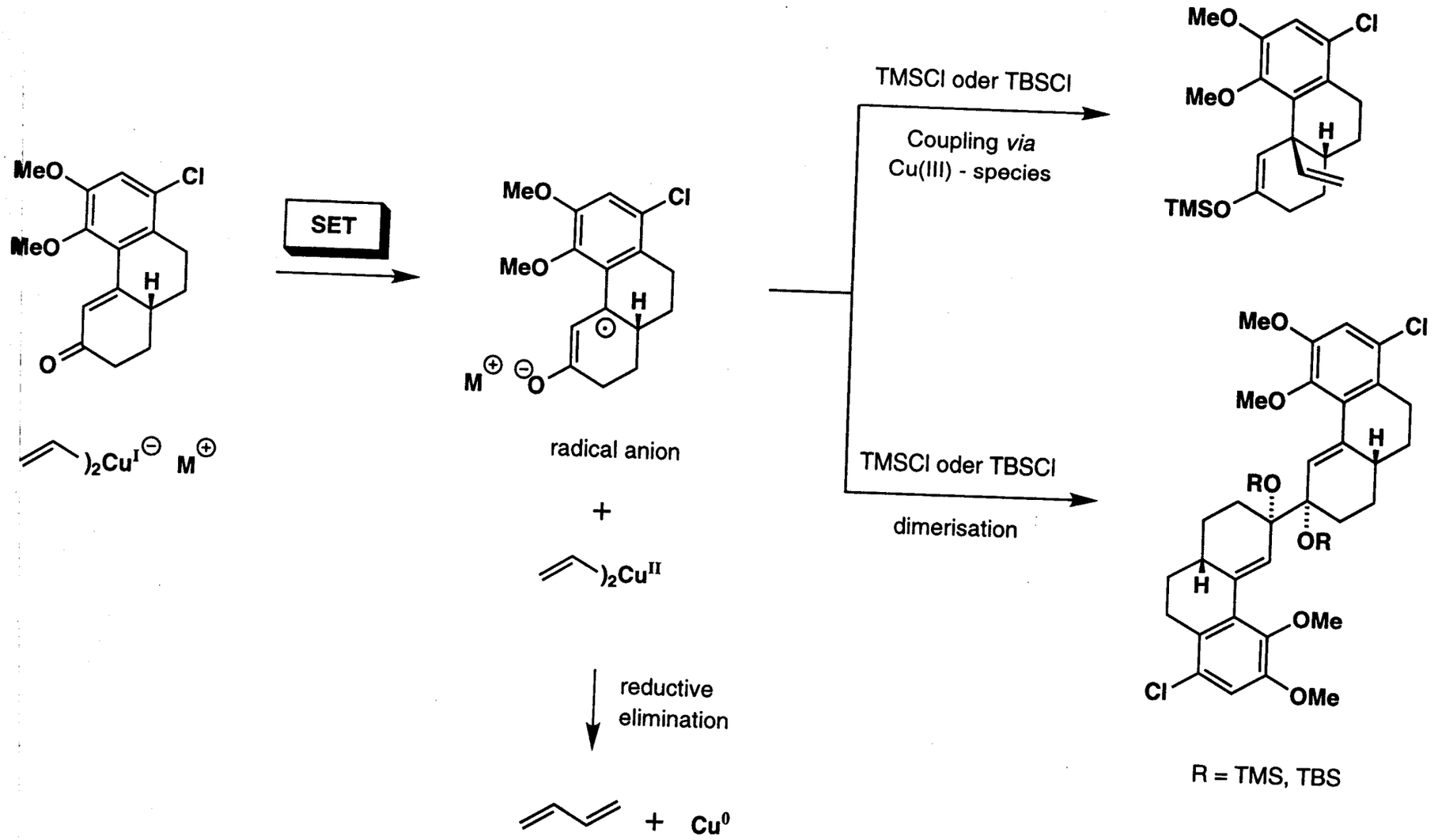




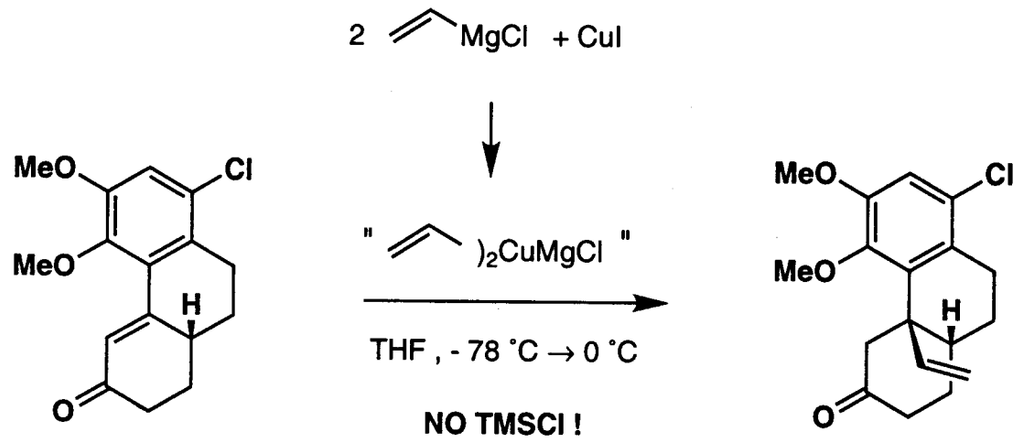




Evidence for an SET - Mechanism



Less Is More !

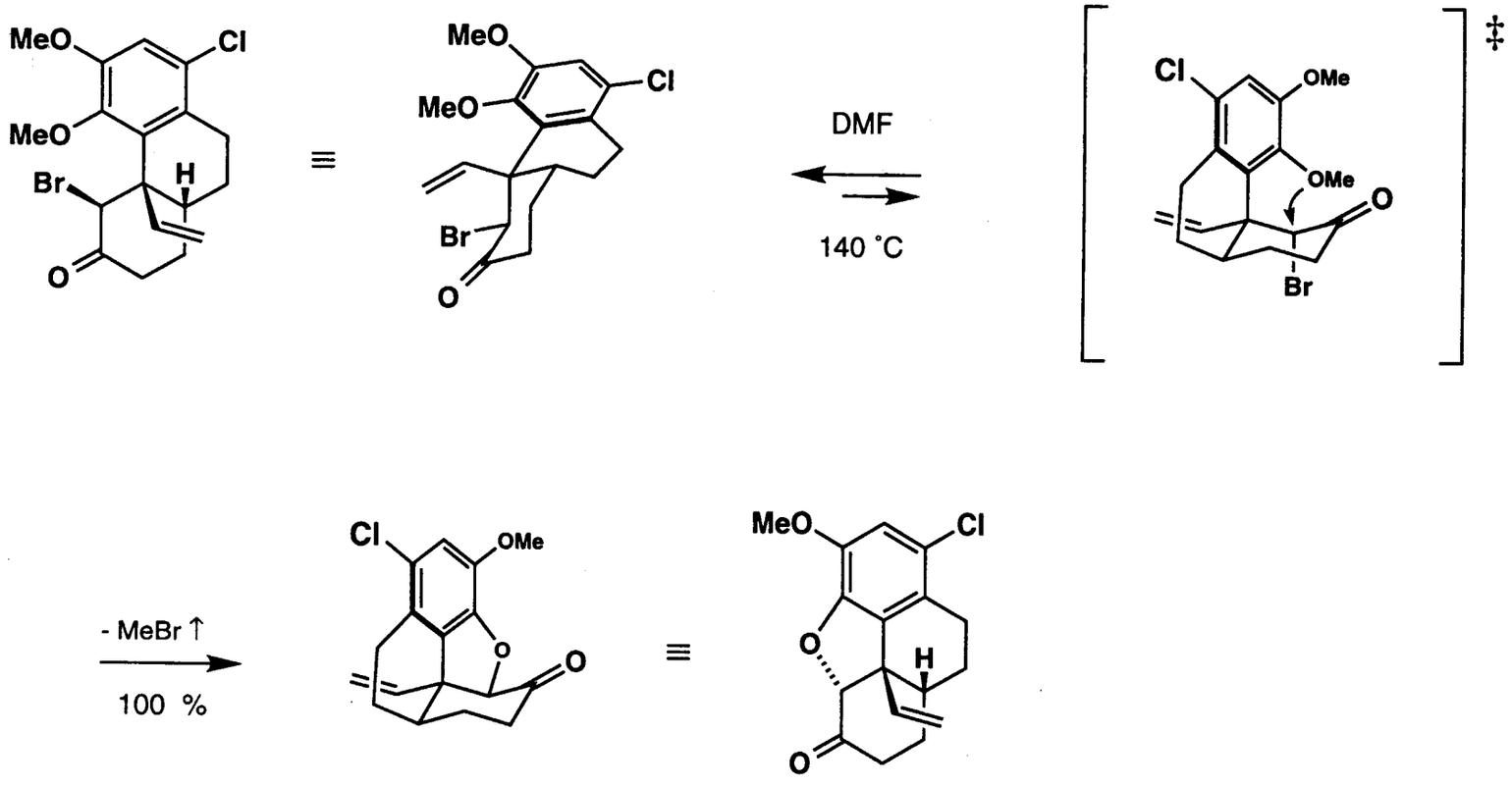


Excellent Yields (80-90 %)

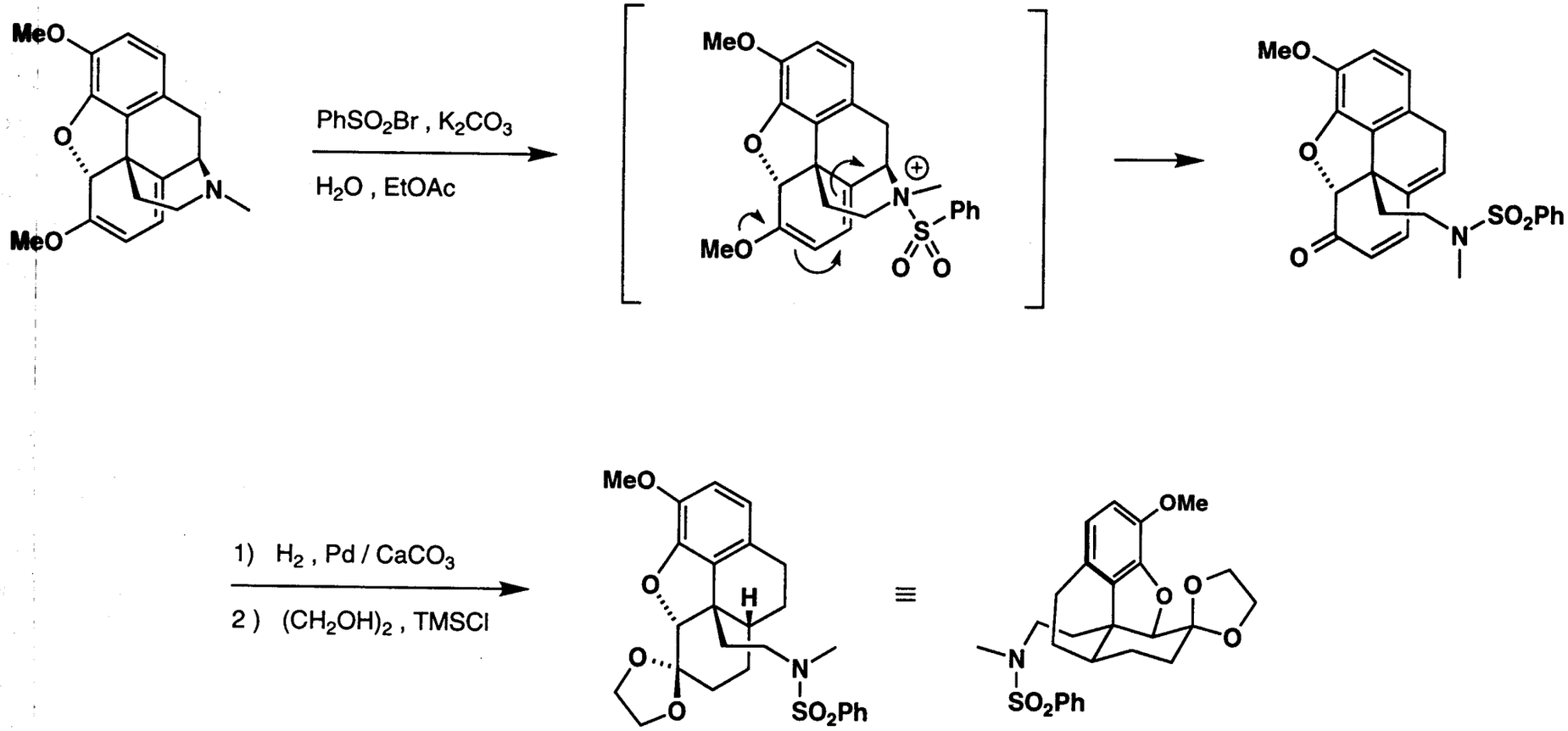
Cuprate cheap and easy to handle

No epimer or 1,2-adducts

A Close Look at E-Ring Closure



A Relay Substance is Easily Accessible from (-)-Thebaine



A Formal Total Synthesis of (-)-Morphine (contin'd)