STRATEGIES IN SYNTHESIS 2

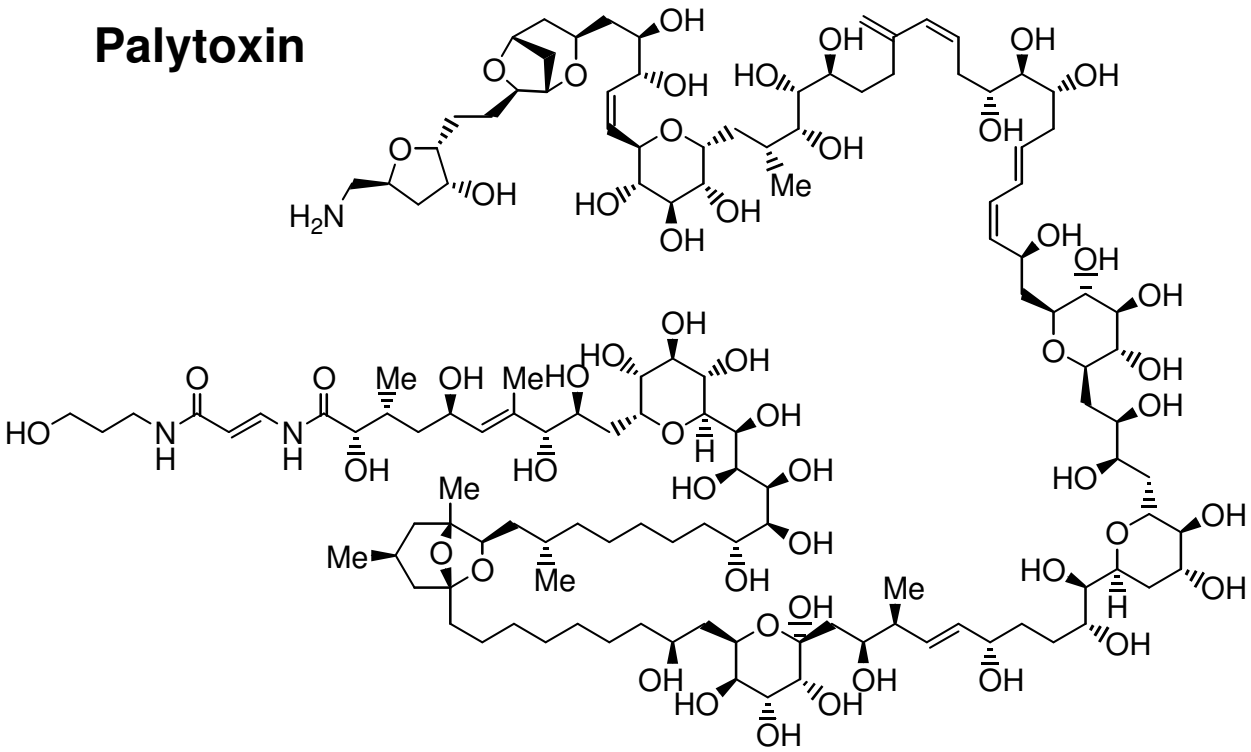
Professor T. J. Donohoe

MT 2007

6 Lectures: Tuesday at 10 am; Thursday at 9 am (weeks 6-8)

HANDOUT B

Palytoxin

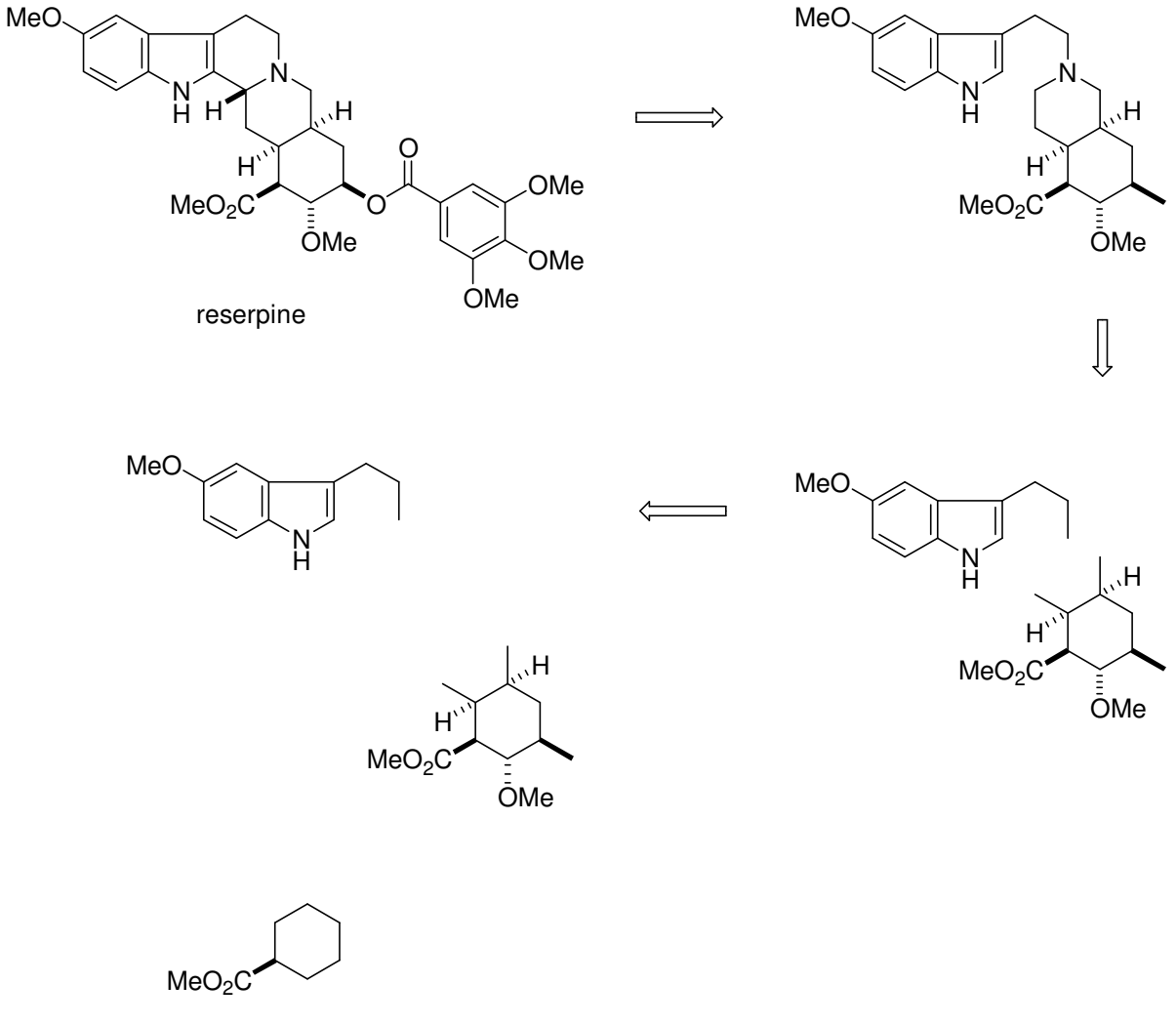


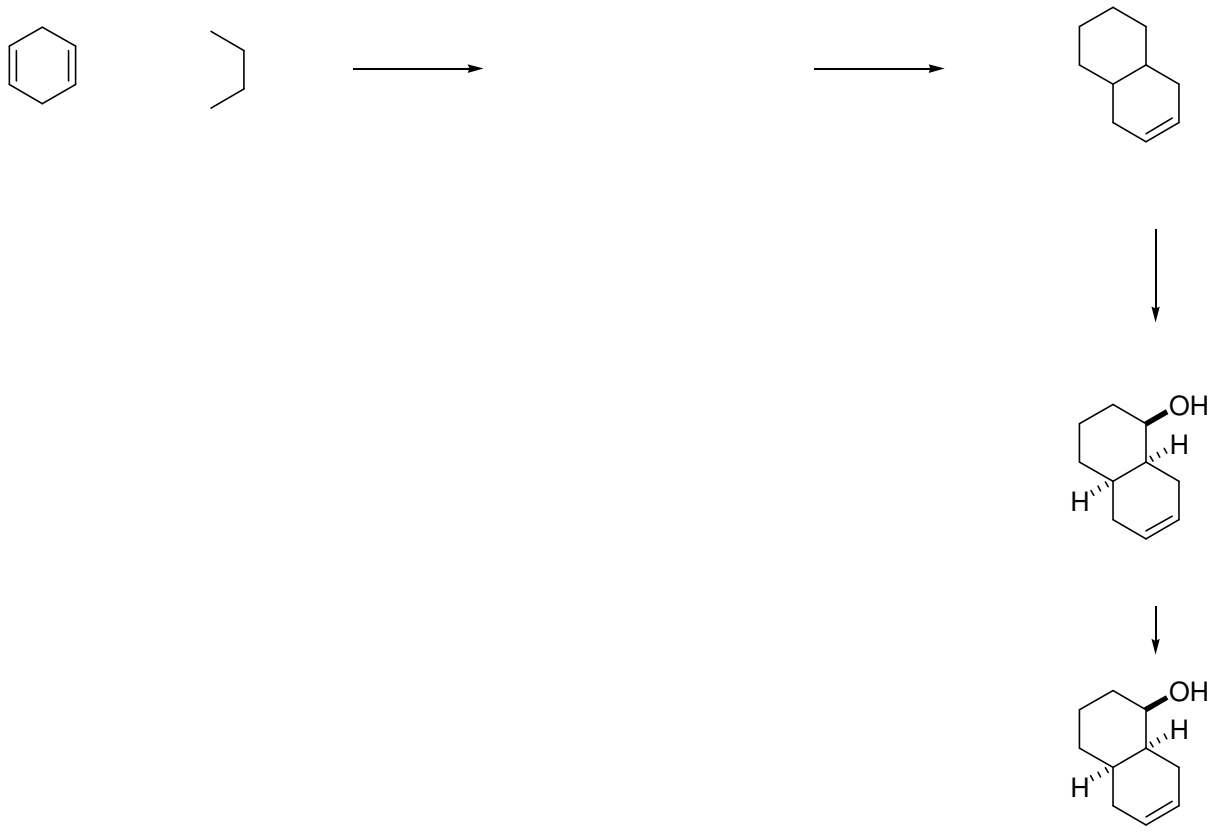
Total synthesis see :- Y. Kishi et al. J. Am. Chem. Soc., 1989, **111**, 7525, 7530; ibid. 1994, **116**, 11205

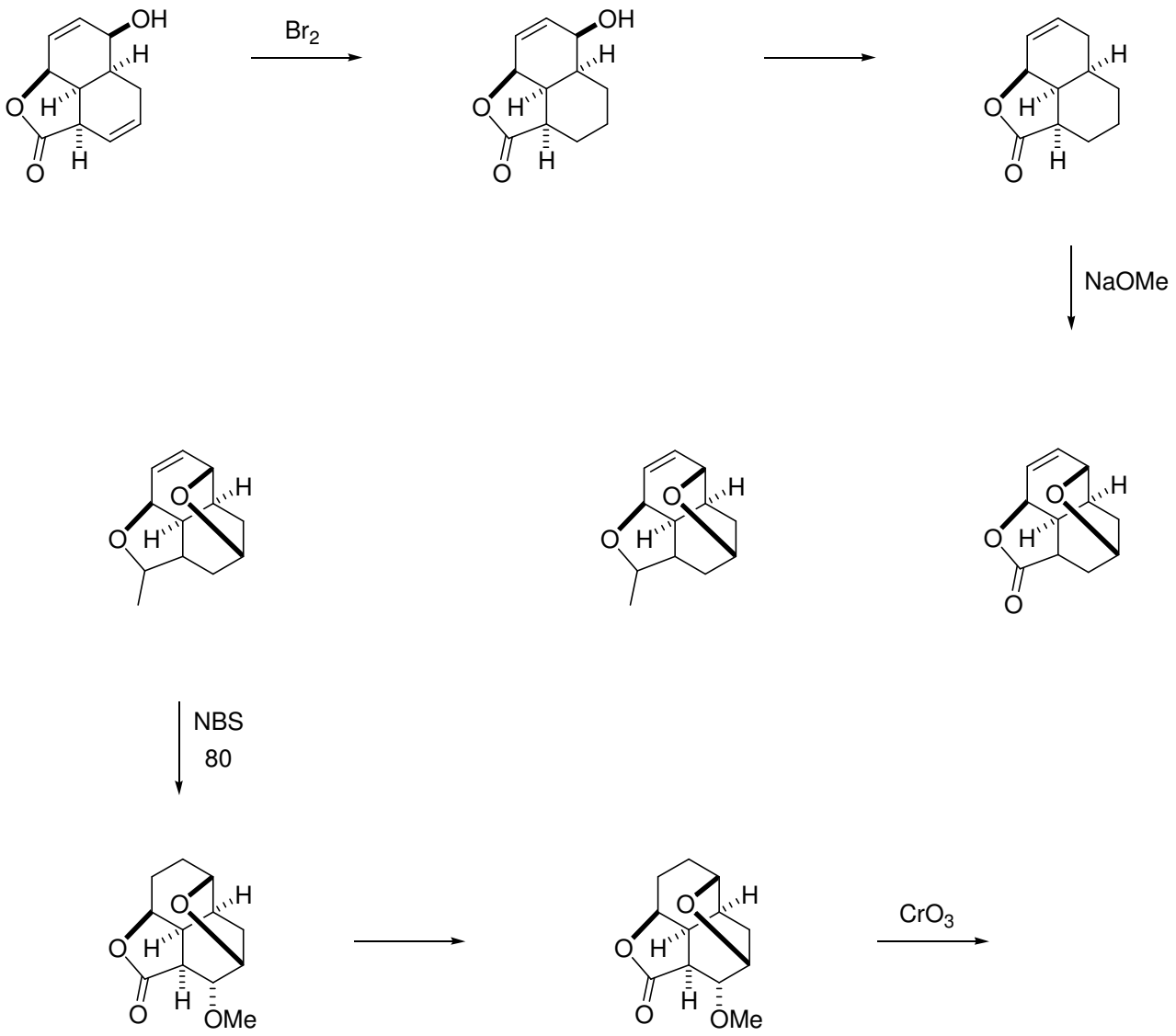
71 stereochemical elements (64 stereogenic centres, 7 geometrical)
Therefore there are 2^{71} possible stereoisomers ie:
2.3×10^{21} = 23000000000000000000 isomers !!!

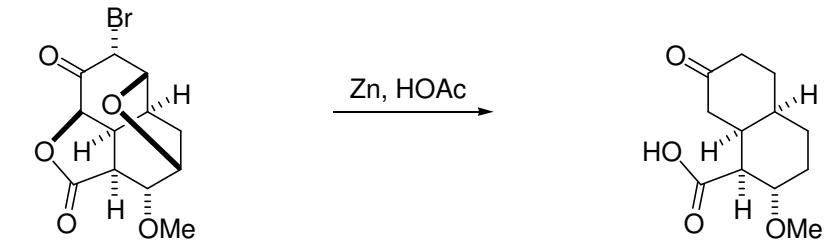
Reserpine

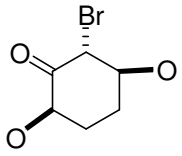
retrosynthesis

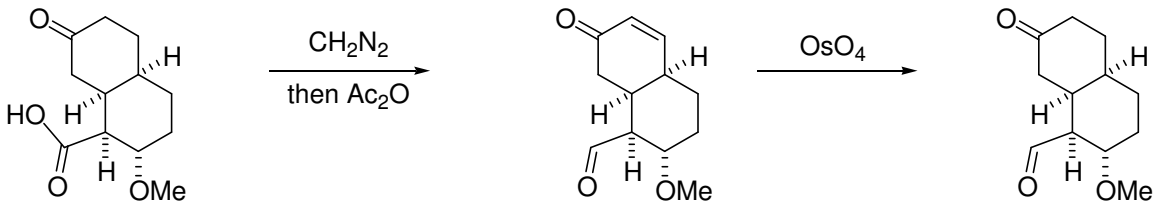


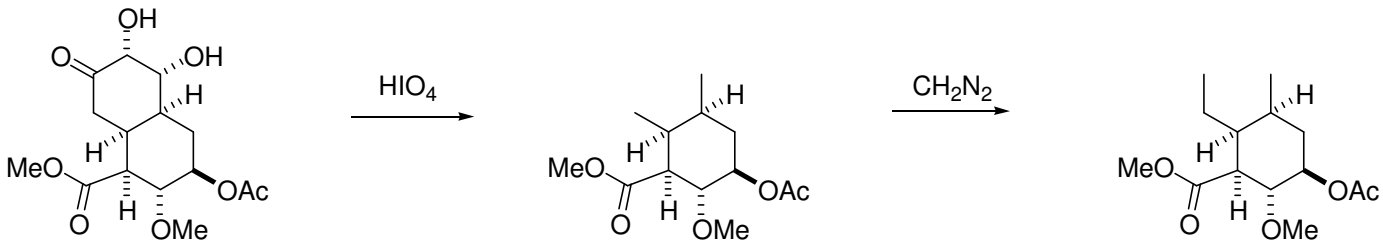

OH
H
H
OH
H
H

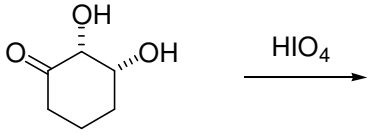

OH
H
O
H
O
H
Br_2
OH
H
O
H
O
H
H
O
H
O
H
NaOMe
H
O
O
H
H
O
H
O
H
O
H
NBS
80
H
O
O
H
H
O
OMe
H
O
O
H
H
O
OMe
CrO_3

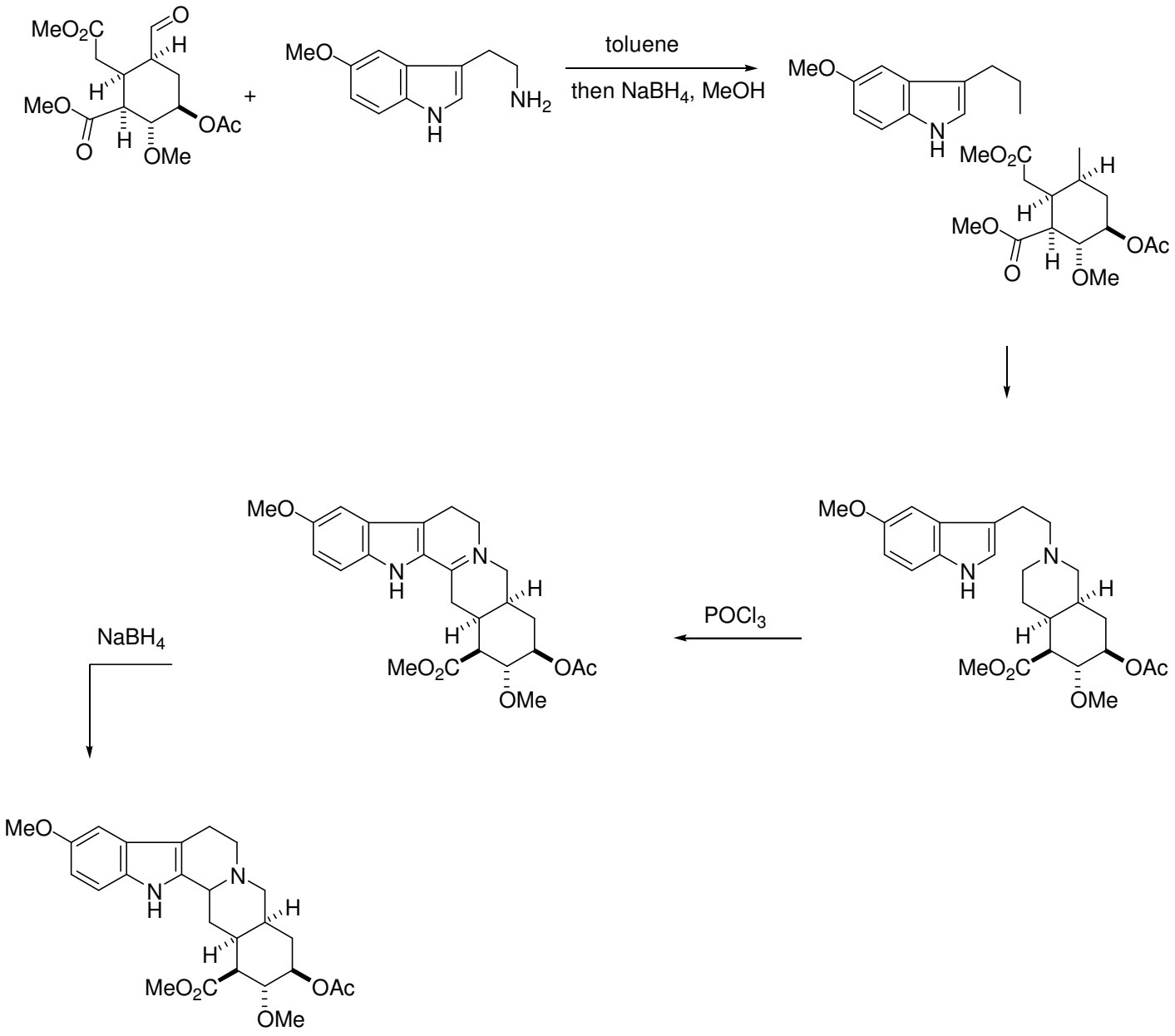

Br
O
O
H
O
H
O
H
OMe
Zn, HOAc
O
H
HO
H
O
H
OMe

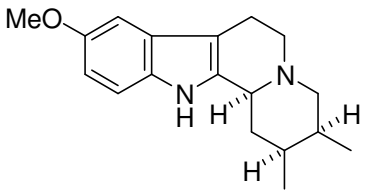

Br
O
O
O

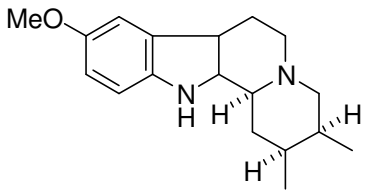

O
H
HO
H
O
H
OMe
CH2N2
then Ac2O
O
H
H
O
H
OMe
OsO4
O
H
H
O
H
OMe

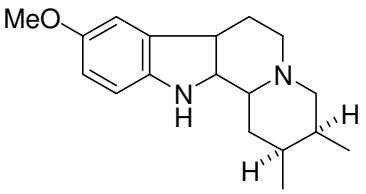

OH
O
OH
H
H
MeO
OAc
O
H
OMe
HIO4
H
H
MeO
OAc
O
H
OMe
CH2N2
H
H
MeO
OAc
O
H
OMe

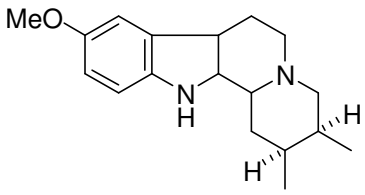

OH
O
OH
HIO4


toluene
then NaBH4, MeOH
POCl3
NaBH4

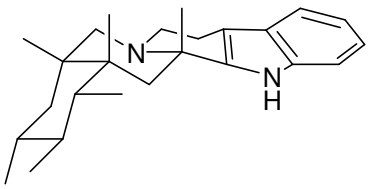


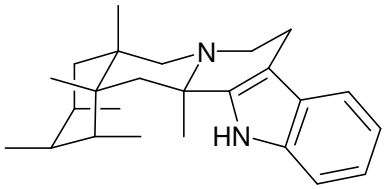


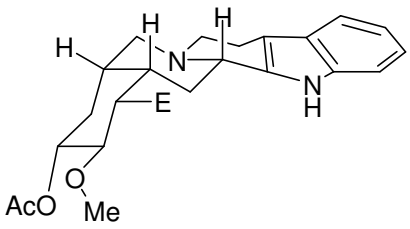




BUT



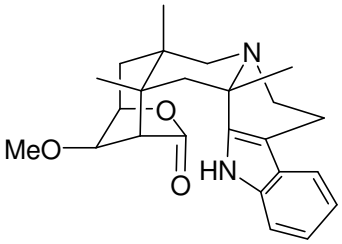




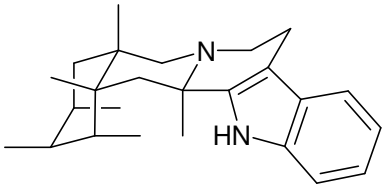
E- COOMe

1. KOH

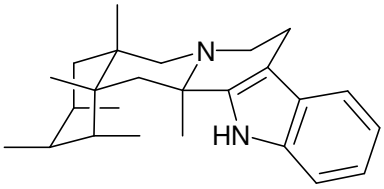
2. DCC



H^+



NaOMe



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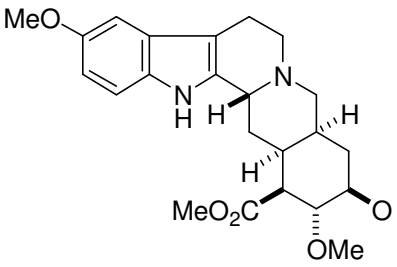
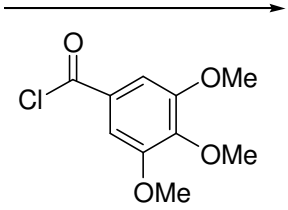
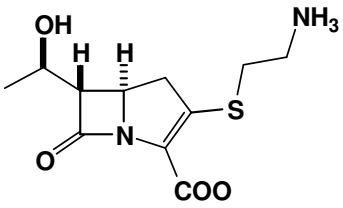
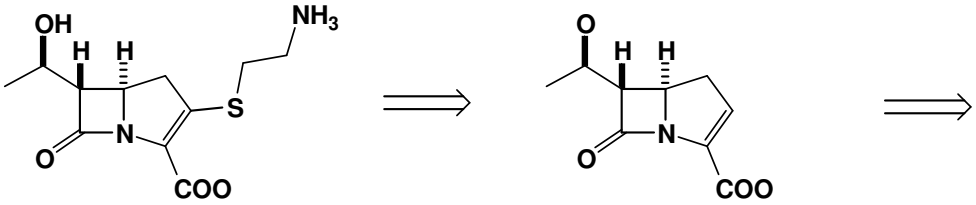


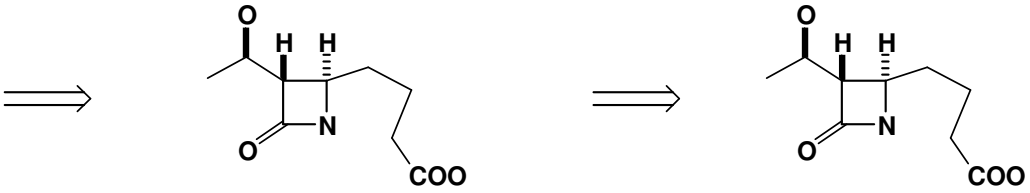


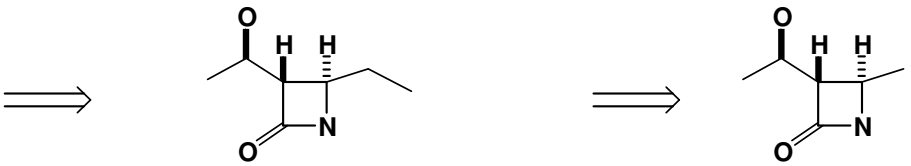
Thienamycin (Merck-1980)

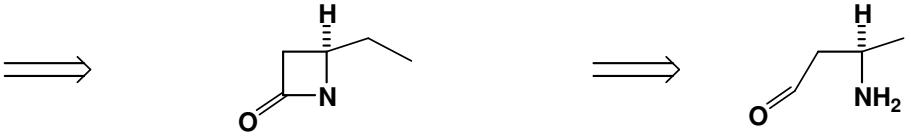


Retrosynthesis

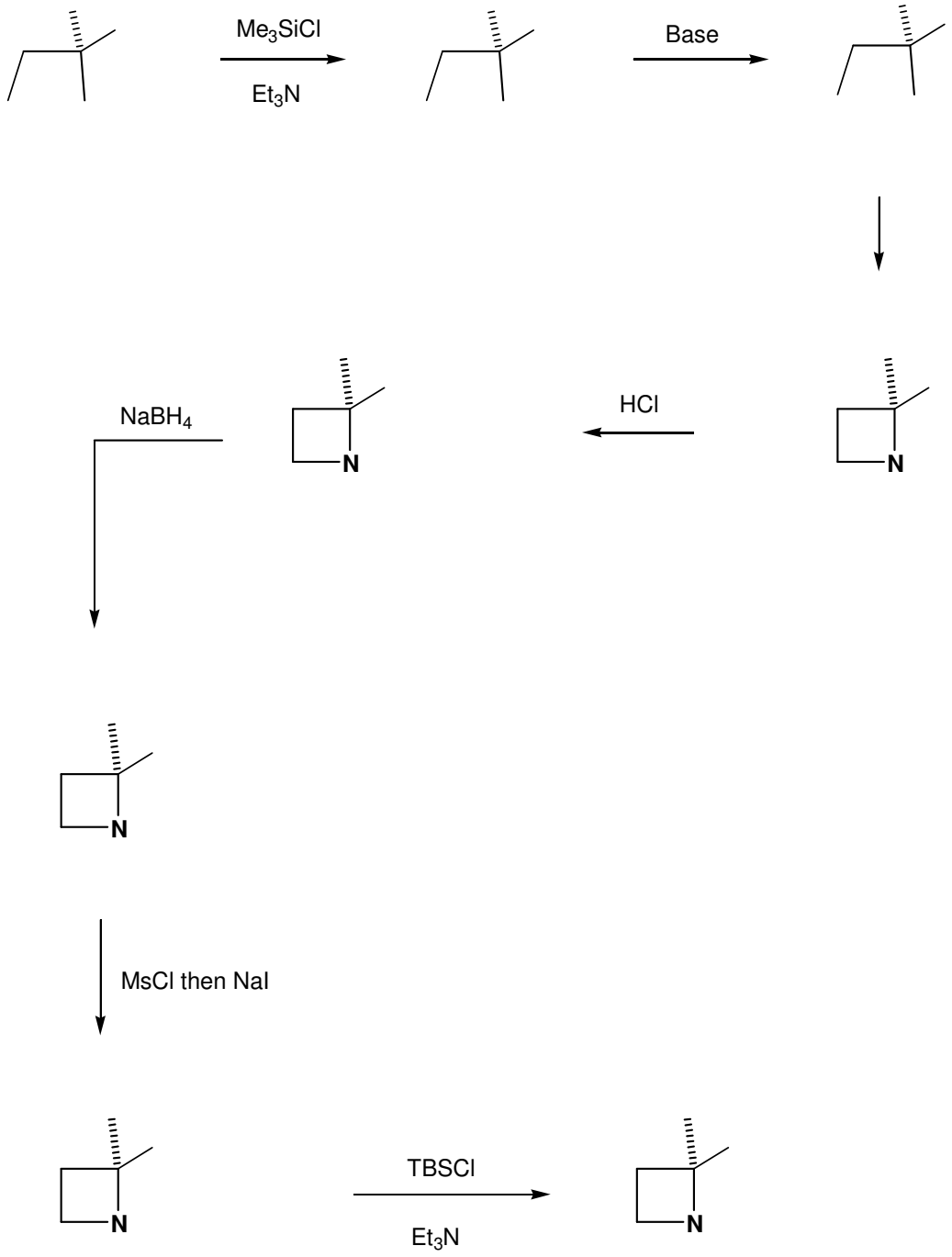




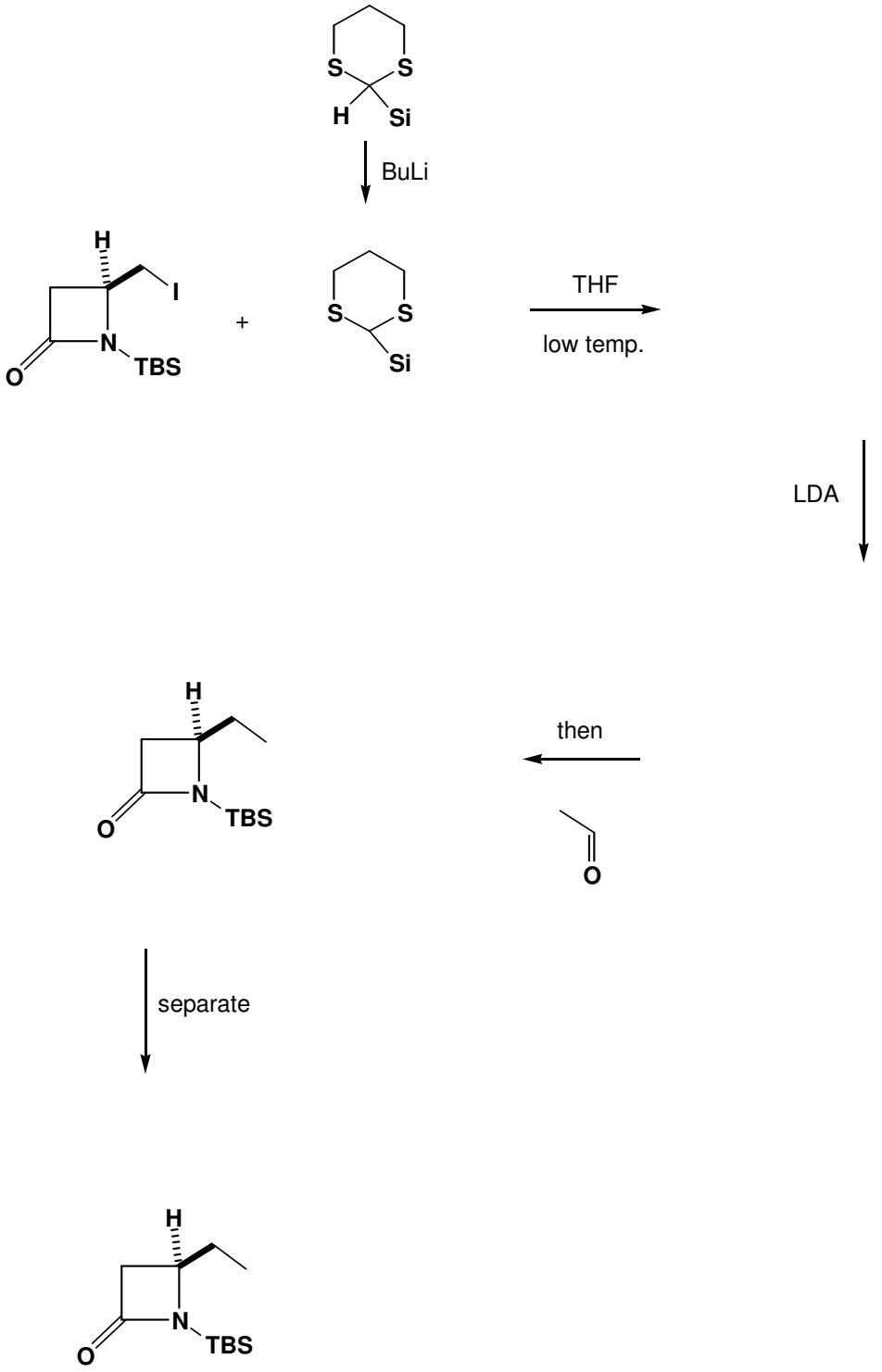


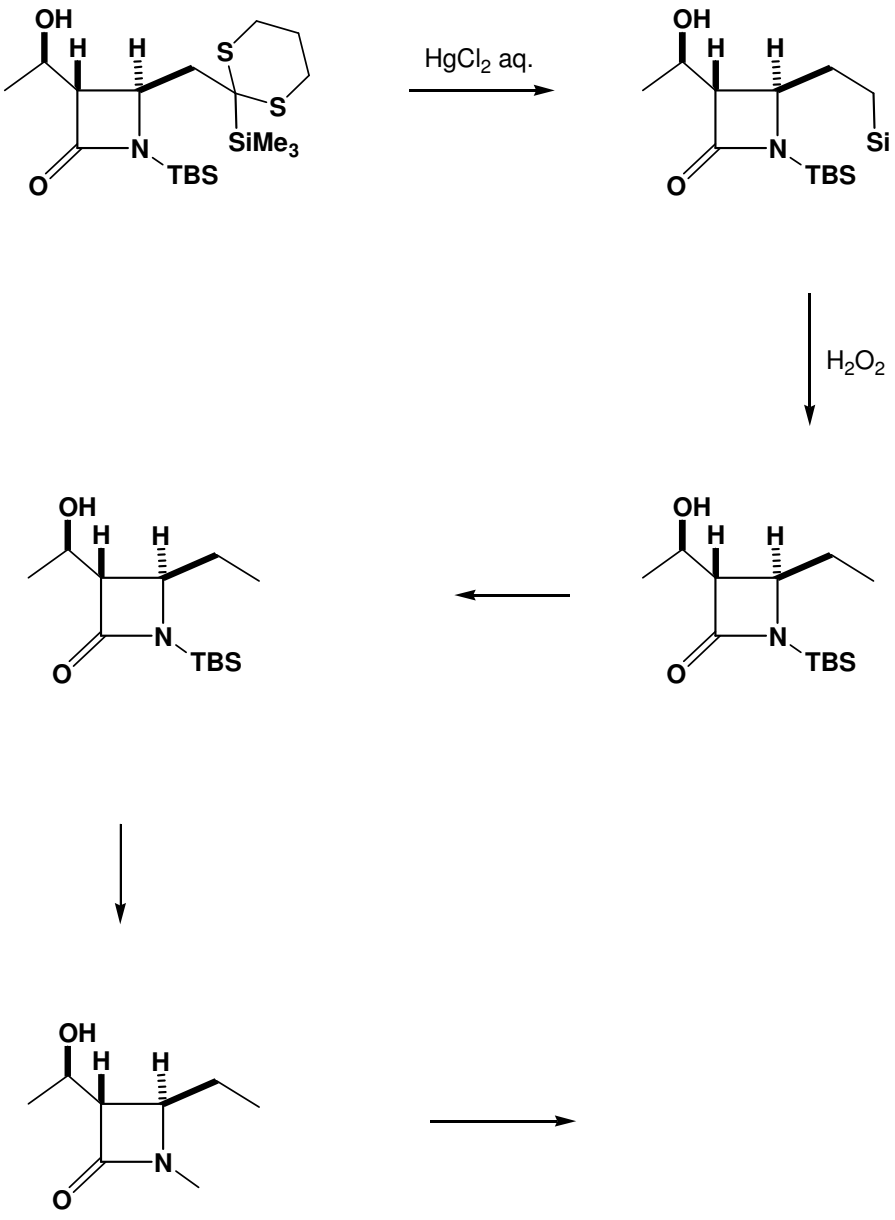


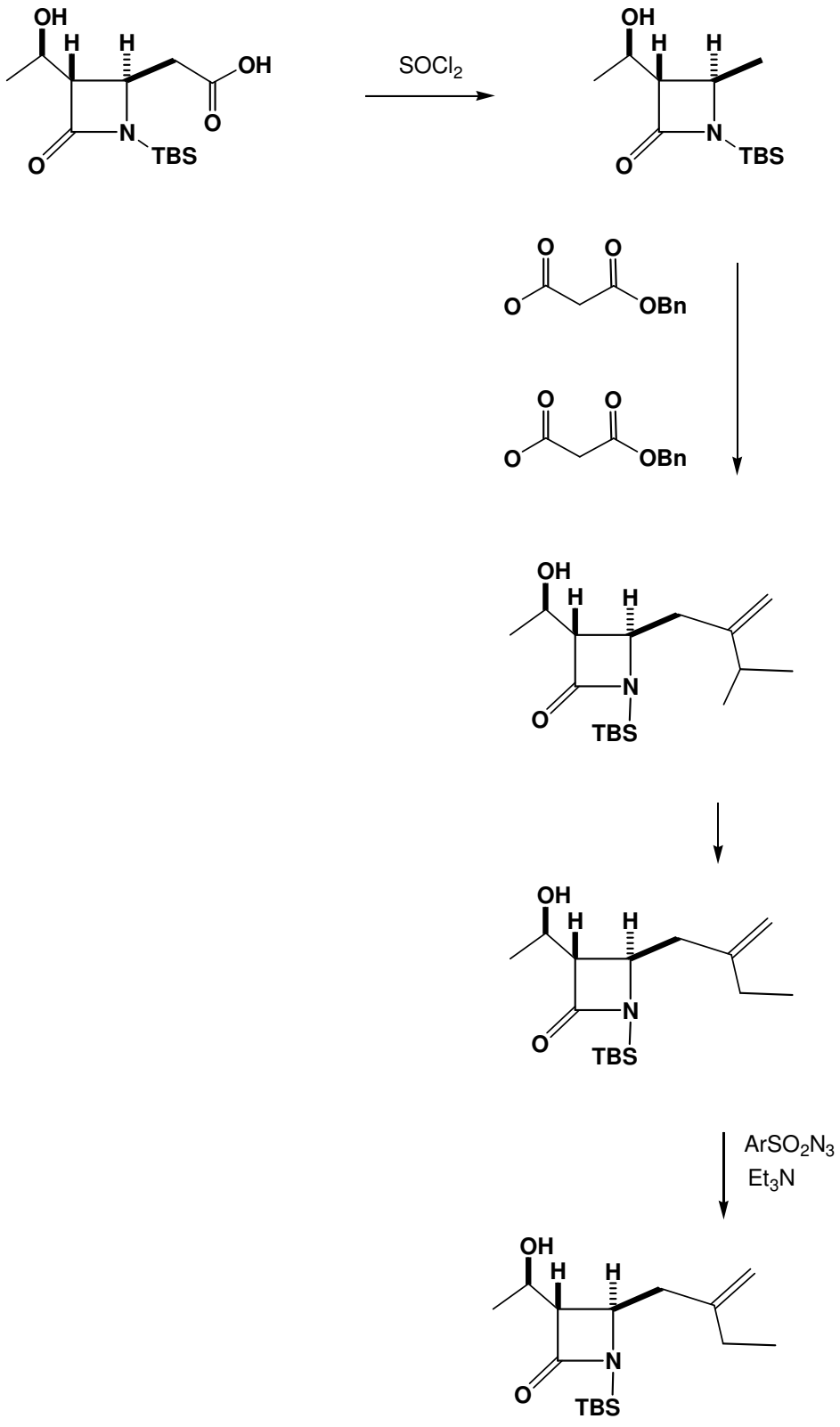
Now the synthesis is detail.

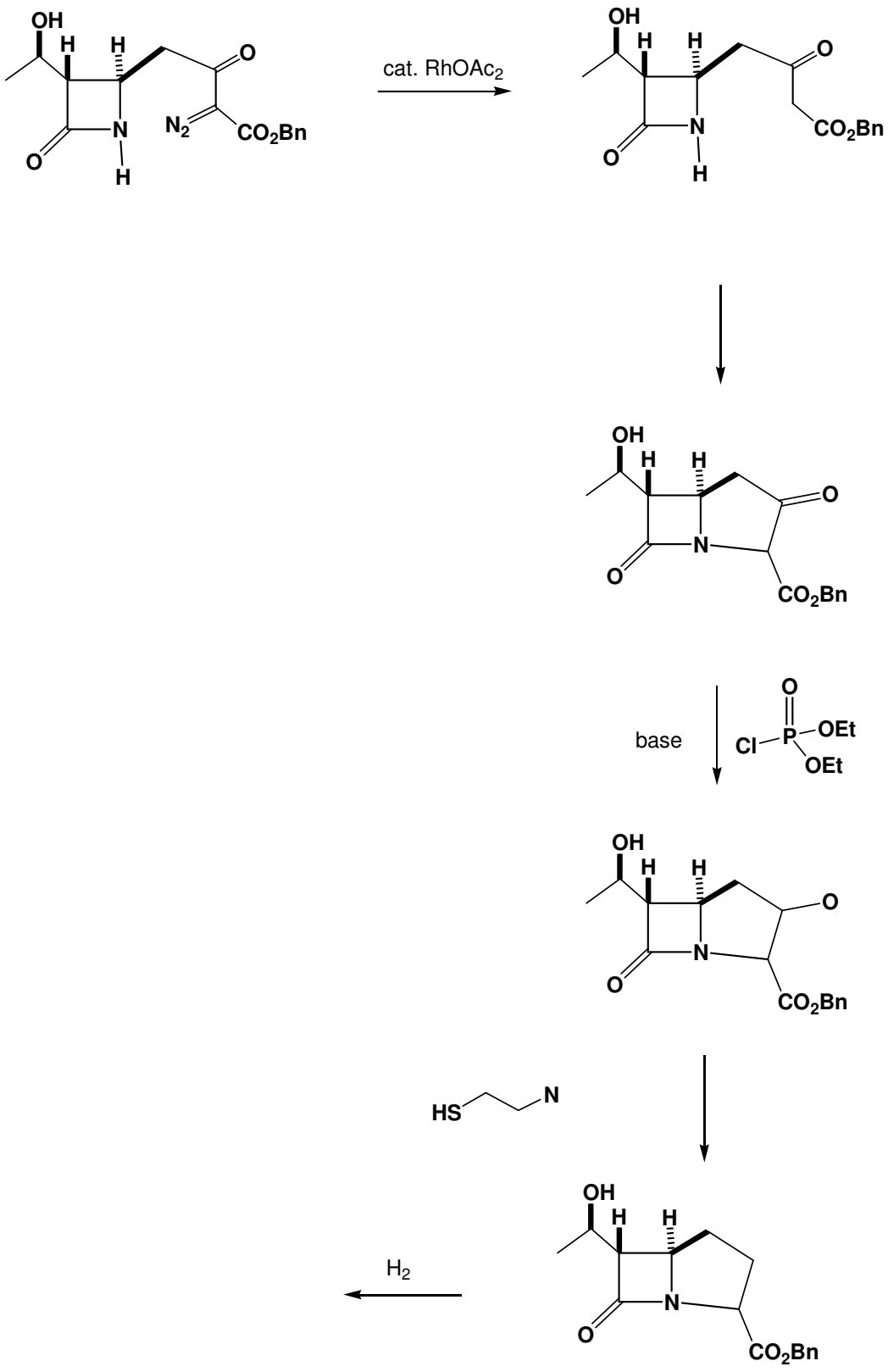


The CO_2R synthon uses UMPOLUNG methodology




OH
H
H
S
S
SiMe3
N
TBS
O
HgCl2 aq.
Si
H2O2


OH
H
H
OH
O
N
TBS
O
SOCl2
OH
H
H
N
TBS
O
O
O
OBn
O
O
O
OBn
OH
H
H
N
TBS
O
OH
H
H
N
TBS
O
ArSO2N3
Et3N
OH
H
H
N
TBS
O

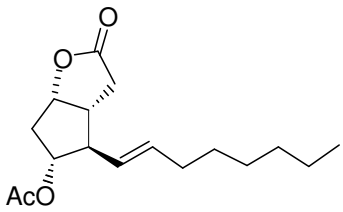

OH
H
H
O
N2
CO2Bn
O
N
H
cat. RhOAc2
OH
H
H
O
CO2Bn
O
N
H
OH
H
H
O
O
N
CO2Bn
base
O
Cl
P
OEt
OEt
OH
H
H
O
O
N
CO2Bn
HS
N
OH
H
H
H2
O
N
CO2Bn

Some handy hints for retrosynthesis

1) Make the synthesis

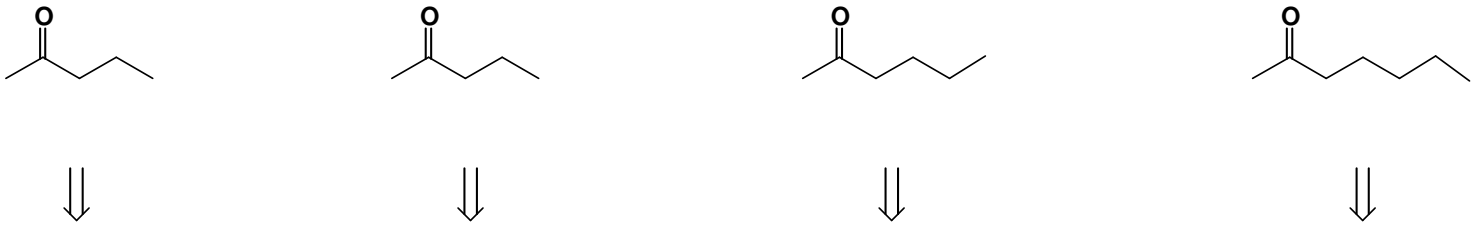
Use convergent rather than

2) Use only disconnections corresponding to

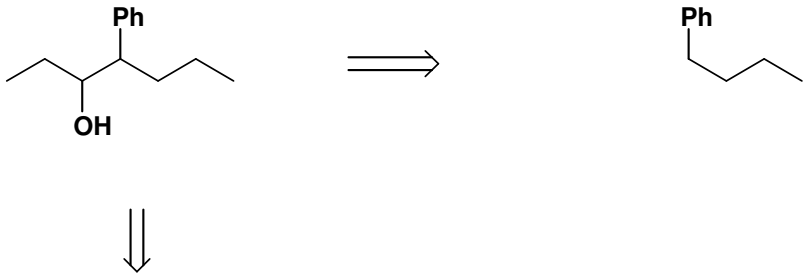


3) Disconnect C-X bonds wherever possible (this includes RCO

4) Disconnect C-C bonds by using nearby functional groups or by



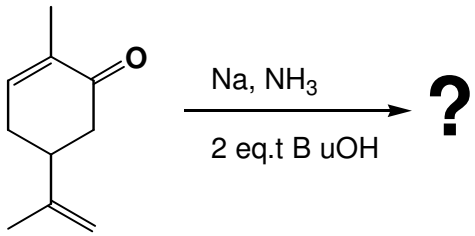
Also, it makes more sense to disconnect in the middle



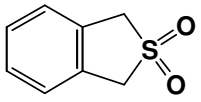
5) Disconnect back to readily recognisable

ANSWERS TO PROBLEMS

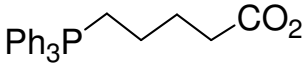
Q. What would happen if we added >2 eq. of tBuOH?



Synthesis?



How do you make the ylid?



Some problems to think about:

Disconnect the following and then devise forward syntheses: