Total Synthesis

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Scalable Enantioselective Total Synthesis of (−)-Goniomitine

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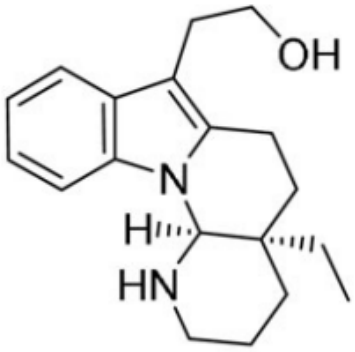
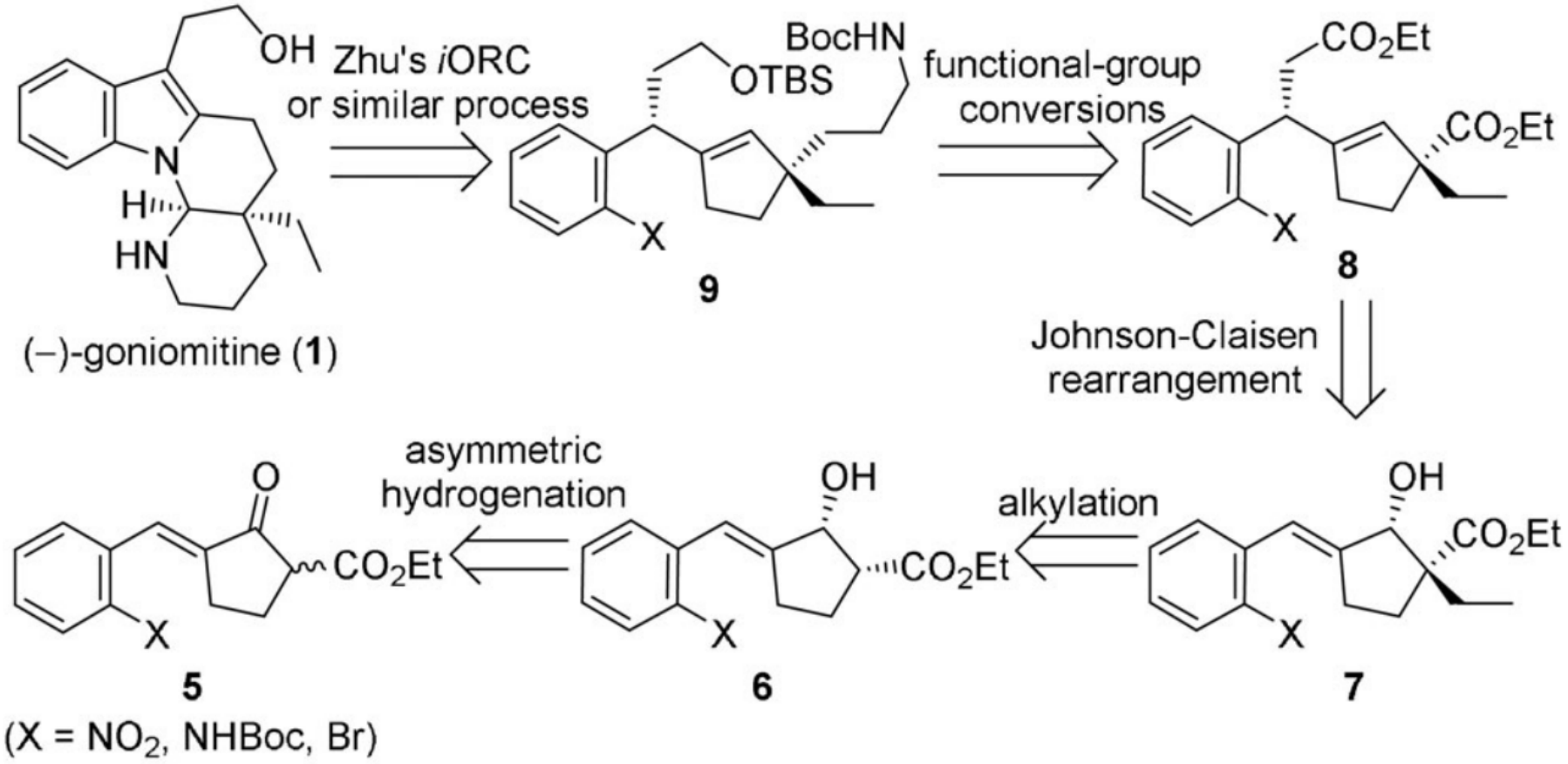
Dedicated to the 100th anniversary of Nankai University



(−)-goniomitine

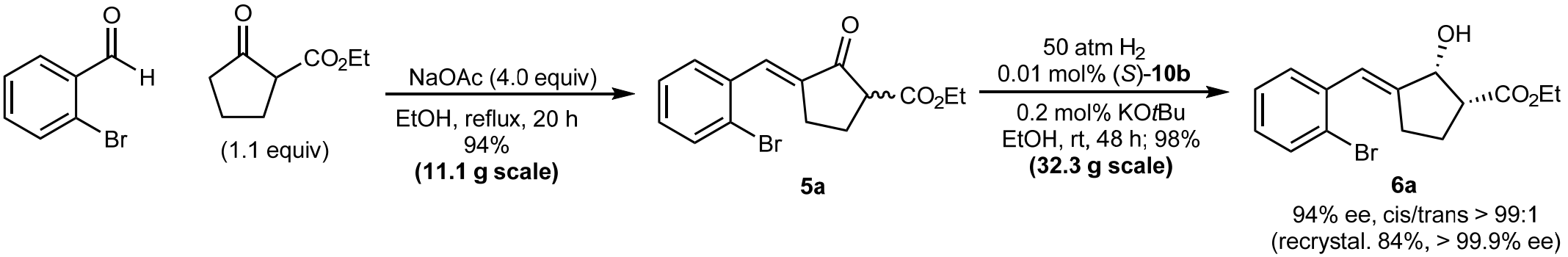
- an important member of the *Aspidosperma* family of indole alkaloids.
- isolated from the root bark of *Gonioma Malagasy* by Husson et al in 1987.
- a unique octahydroindolo[1,2-α][1,8]naphthyridine core together with a tryptophol moiety for antiproliferative activity.

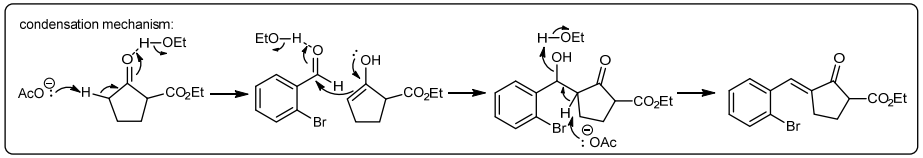
Liu Research Group
Total Synthesis Presentation
Ziyong Wang
1/16/2019

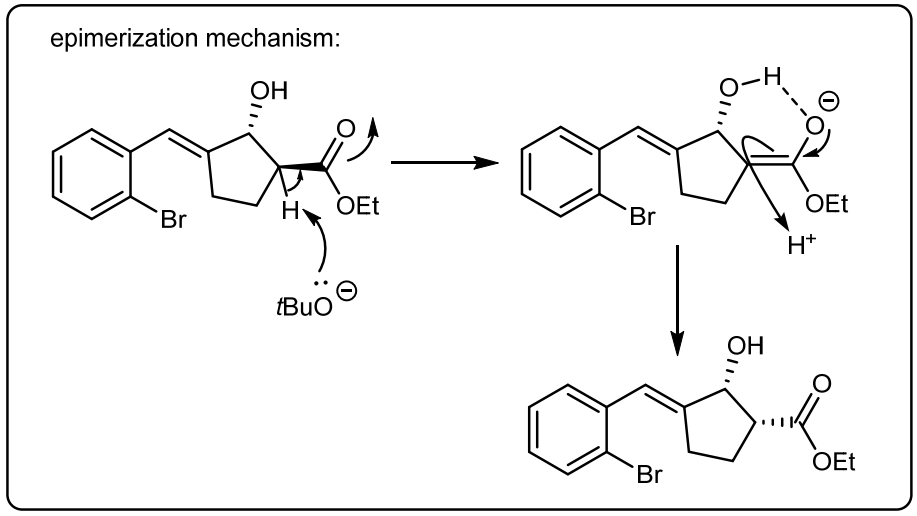


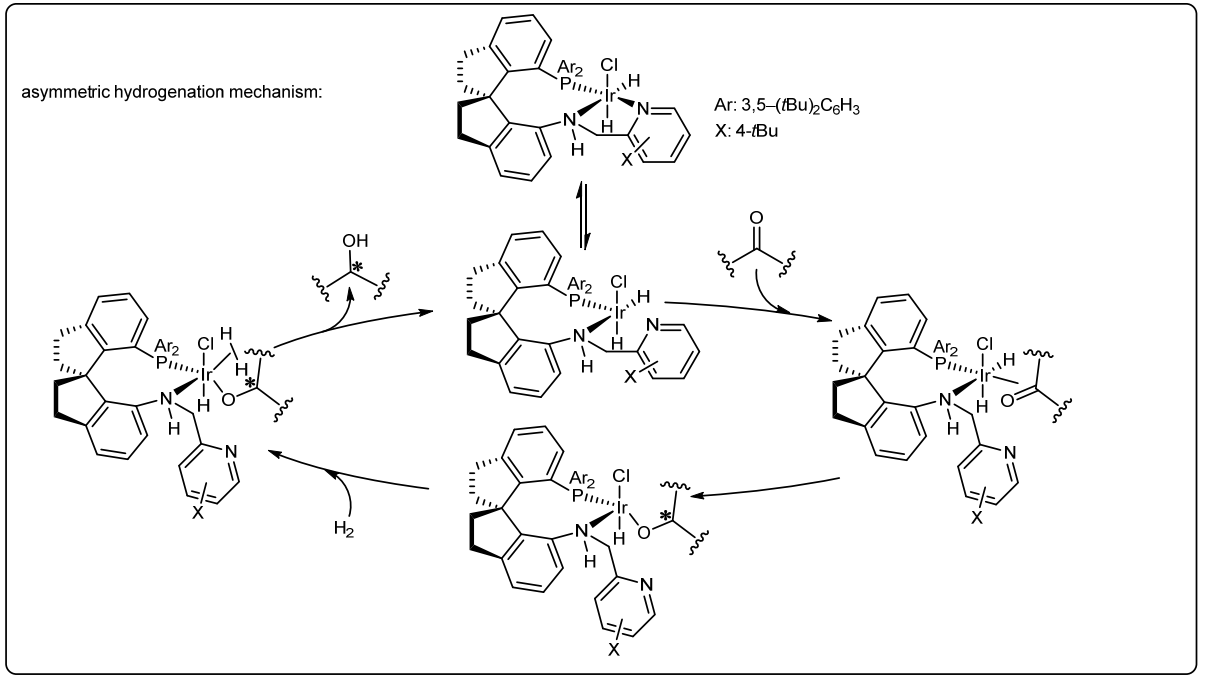
***i*ORC**: integrated oxidation/reduction/cyclization

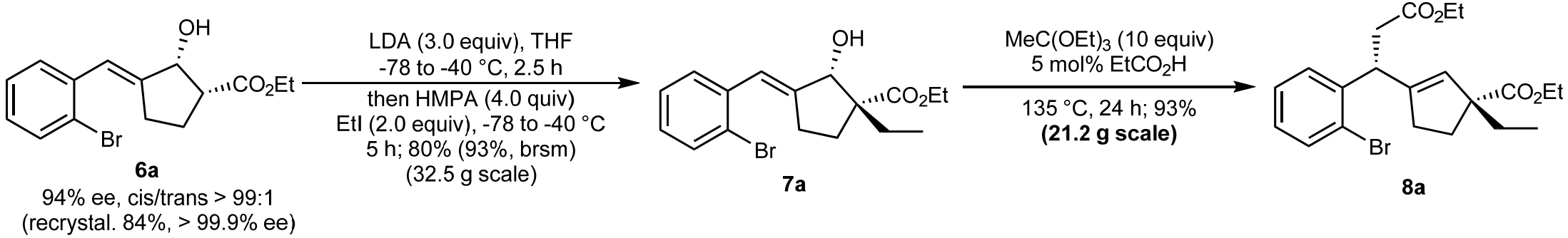
Scheme 1. Retrosynthesis of (–)-goniomitine (**1**)

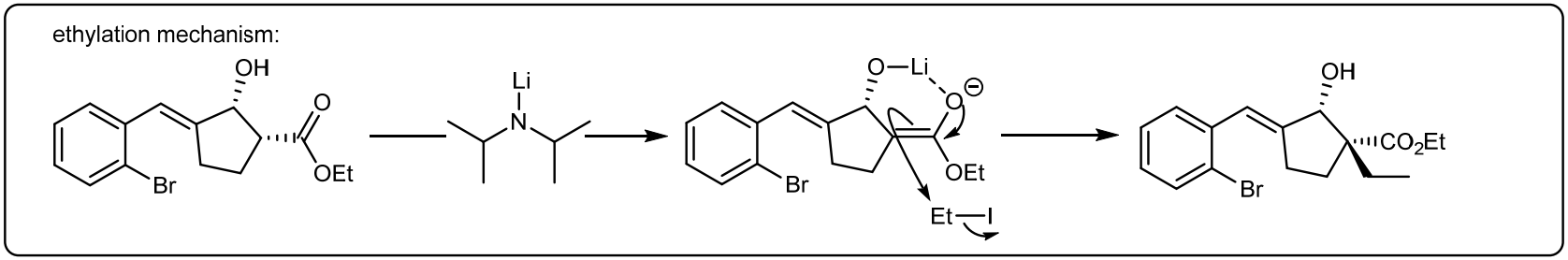

(1.1 equiv)
NaOAc (4.0 equiv)
EtOH, reflux, 20 h
94%
(11.1 g scale)
5a
50 atm H2
0.01 mol% (S)-10b
0.2 mol% KOtBu
EtOH, rt, 48 h; 98%
(32.3 g scale)
6a
94% ee, cis/trans > 99:1
(recrystal. 84%, > 99.9% ee)

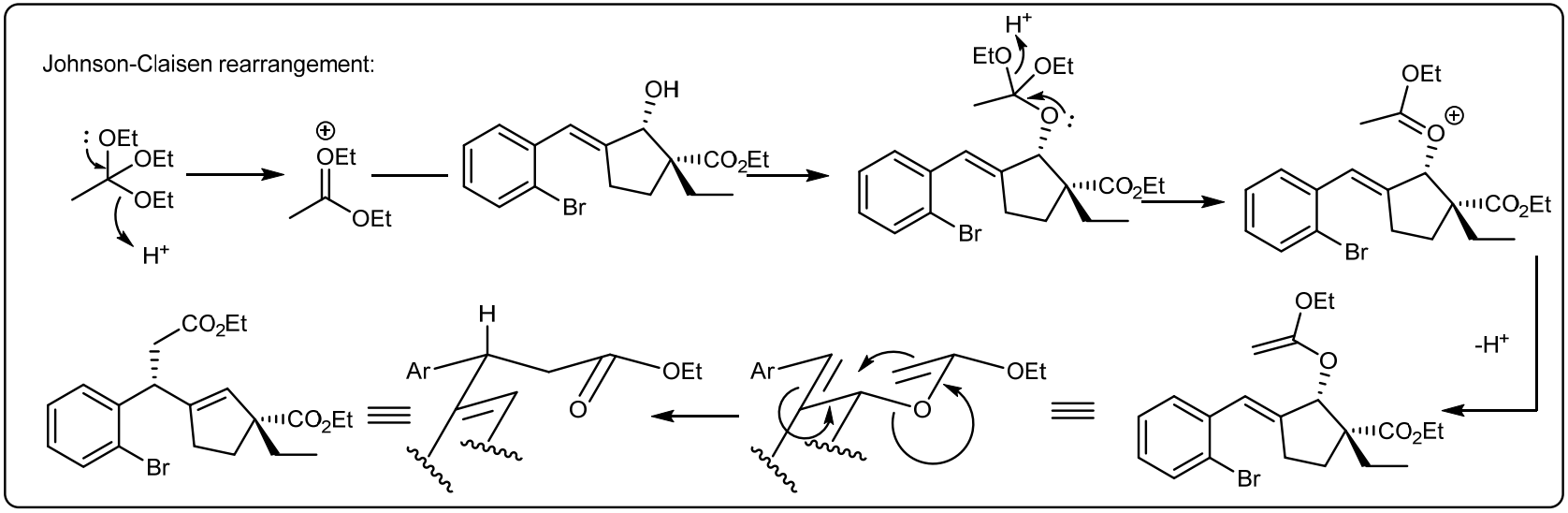

condensation mechanism:

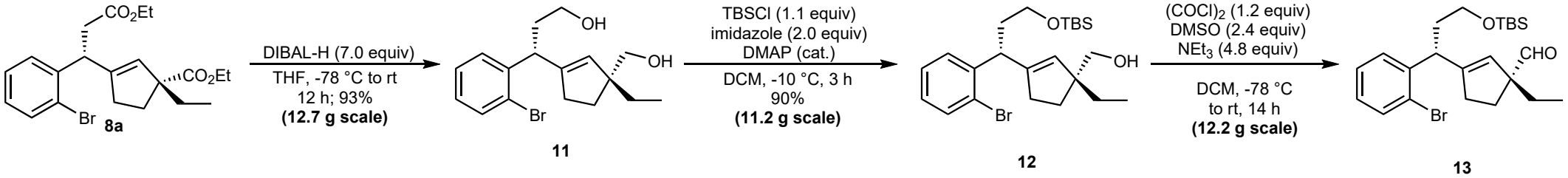

epimerization mechanism:
tBuO

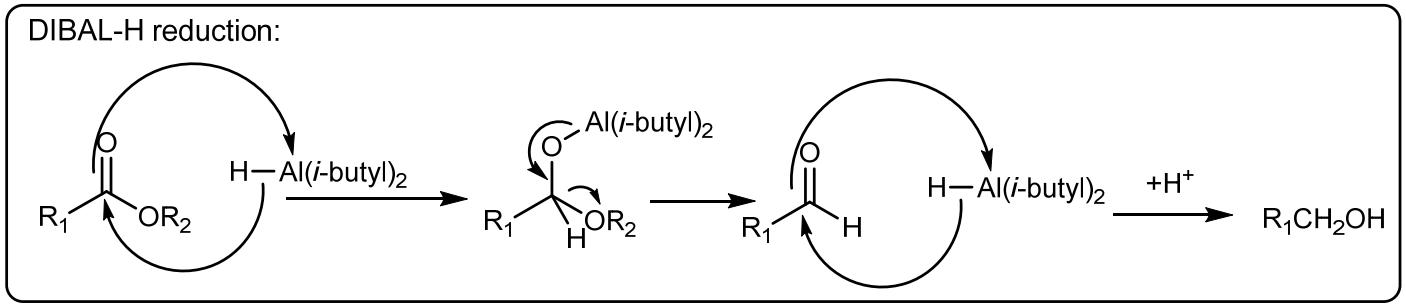

asymmetric hydrogenation mechanism:
Ar: 3,5–(tBu)2C6H3
X: 4-tBu
H2

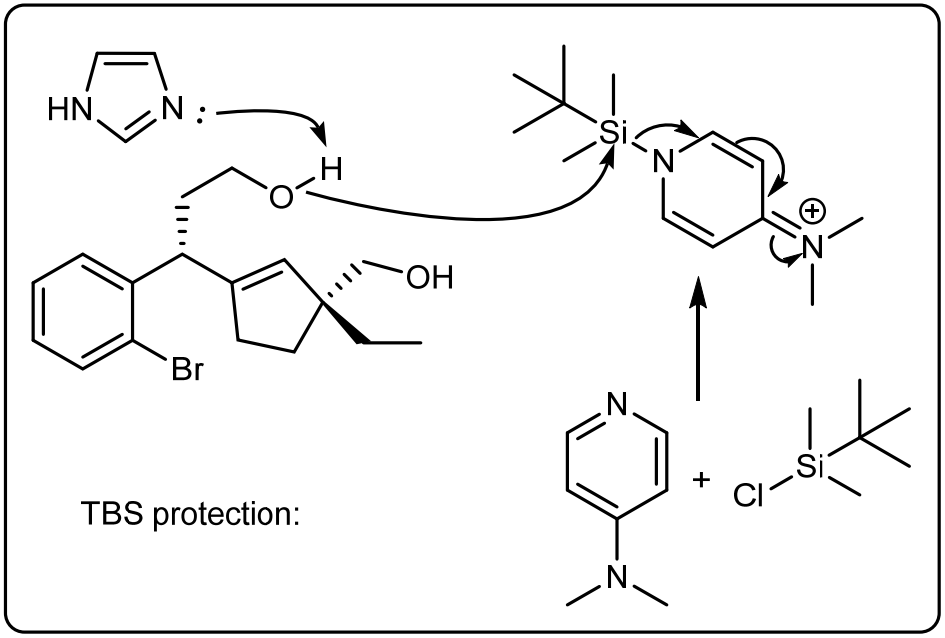

OH
CO2Et
Br
6a
94% ee, cis/trans > 99:1
(recrystal. 84%, > 99.9% ee)
LDA (3.0 equiv), THF
-78 to -40 °C, 2.5 h
then HMPA (4.0 quiv)
EtI (2.0 equiv), -78 to -40 °C
5 h; 80% (93%, brsm)
(32.5 g scale)
7a
MeC(OEt)3 (10 equiv)
5 mol% EtCO2H
135 °C, 24 h; 93%
(21.2 g scale)
8a

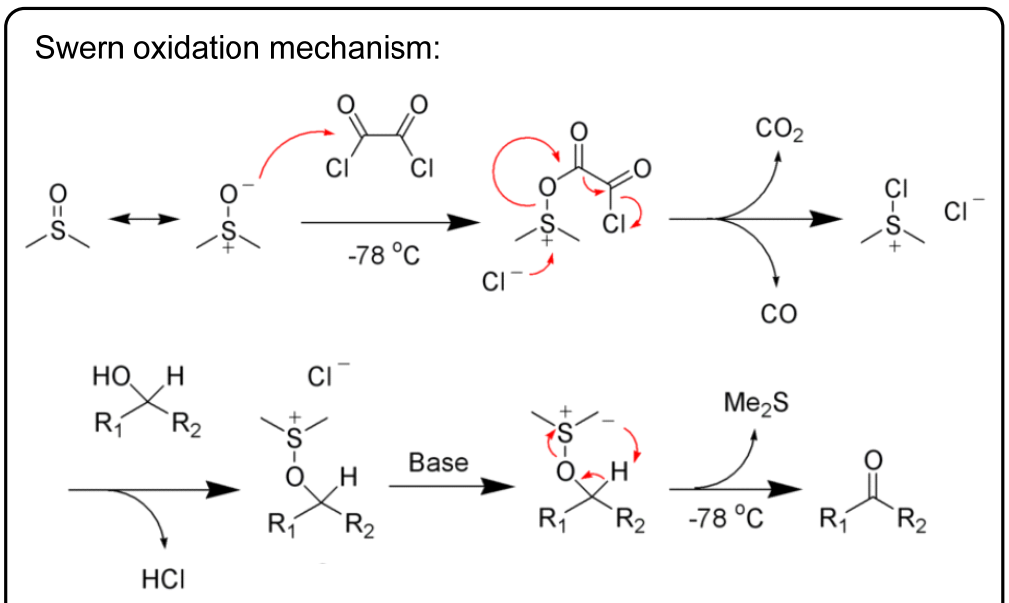

ethylation mechanism:
OH
O
OEt
Br
Li
N
O—Li
Et—I

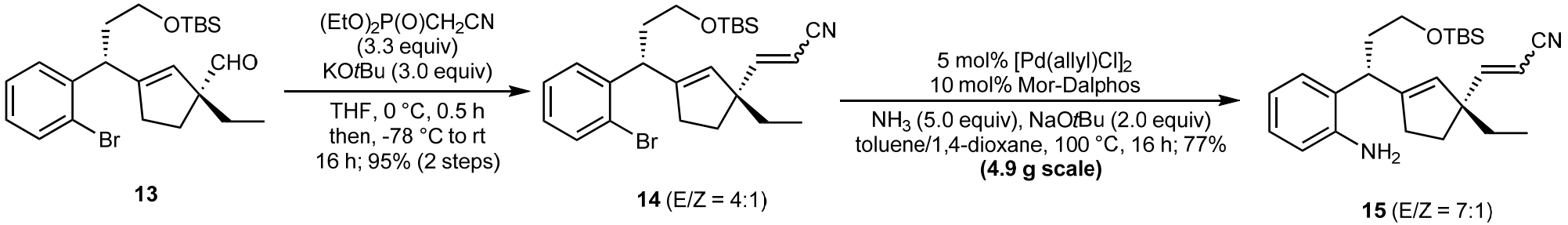

Johnson-Claisen rearrangement:
OEt
H+
EtO
CO2Et
Br
Ar
H
O
-H+


8a
DIBAL-H (7.0 equiv)
THF, -78 °C to rt
12 h; 93%
(12.7 g scale)
11
TBSCl (1.1 equiv)
imidazole (2.0 equiv)
DMAP (cat.)
DCM, -10 °C, 3 h
90%
(11.2 g scale)
12
(COCl)2 (1.2 equiv)
DMSO (2.4 equiv)
NEt3 (4.8 equiv)
DCM, -78 °C
to rt, 14 h
(12.2 g scale)
13


DIBAL-H reduction:
H—Al(i-butyl)2
Al(i-butyl)2
+H+
R1CH2OH


TBS protection:


Swern oxidation mechanism:
-78 °C
CO2
CO
Base
HCl
Me2S
-78 °C

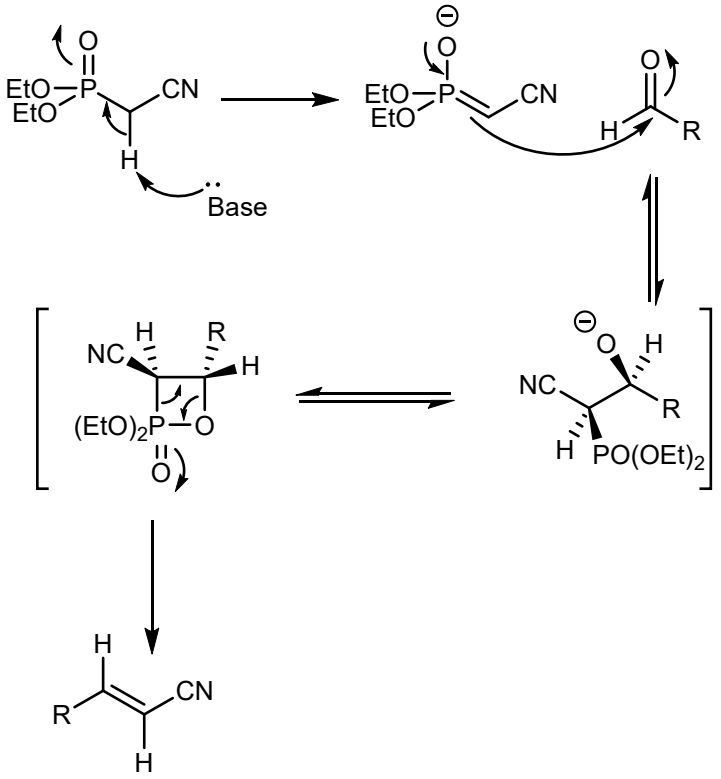


13

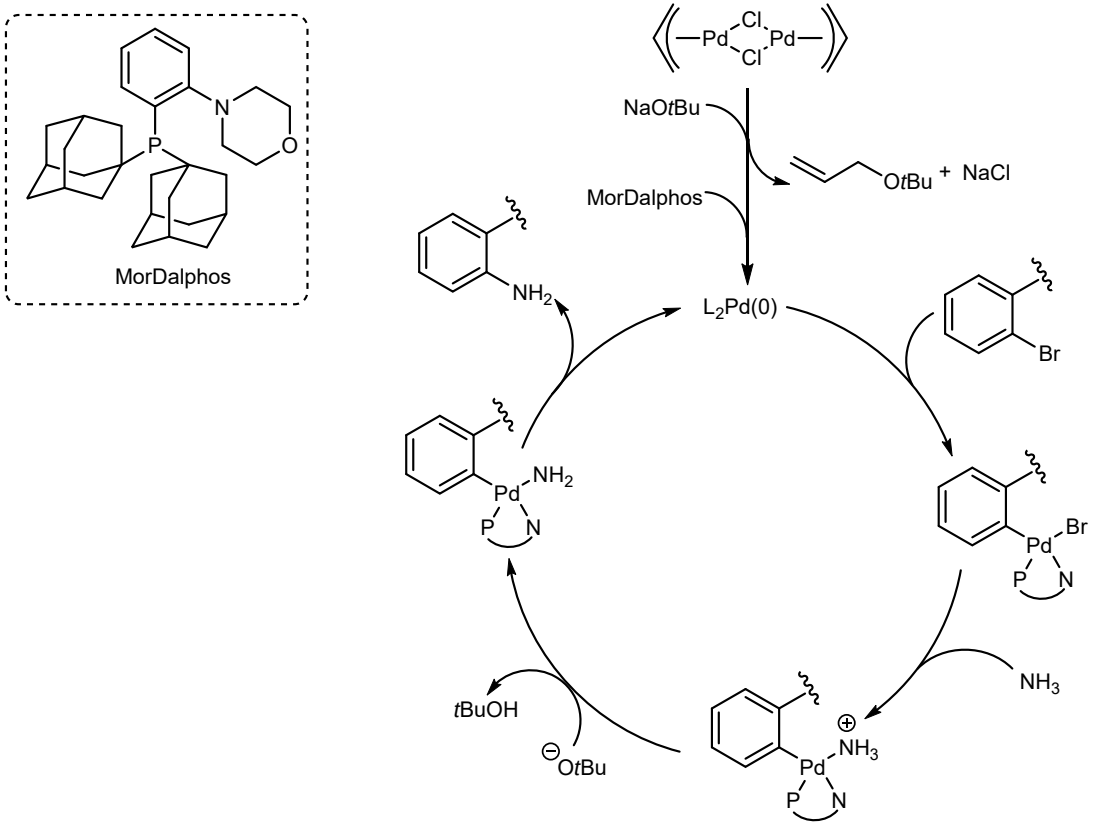
14 (E/Z = 4:1)

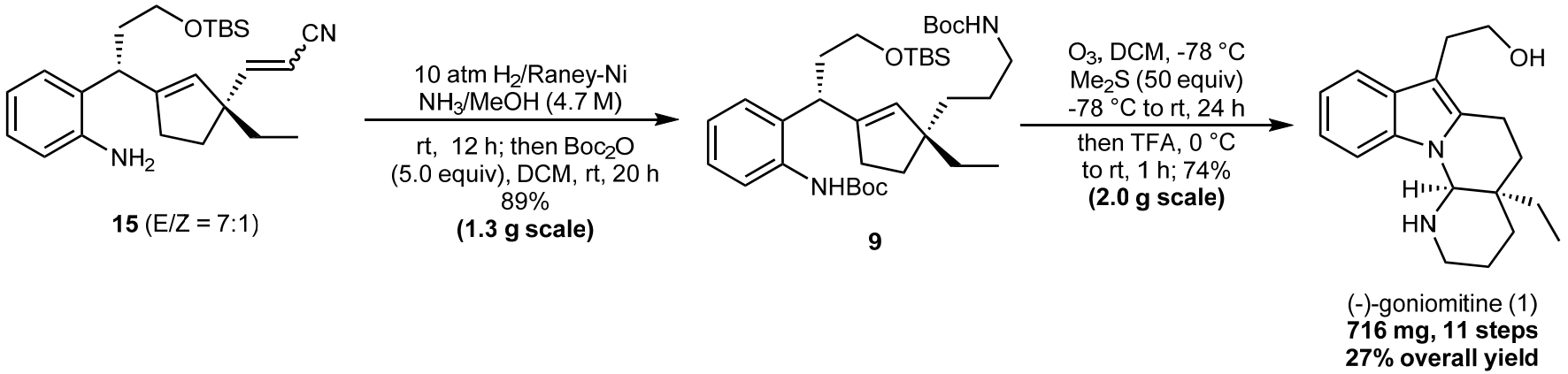
15 (E/Z = 7:1)

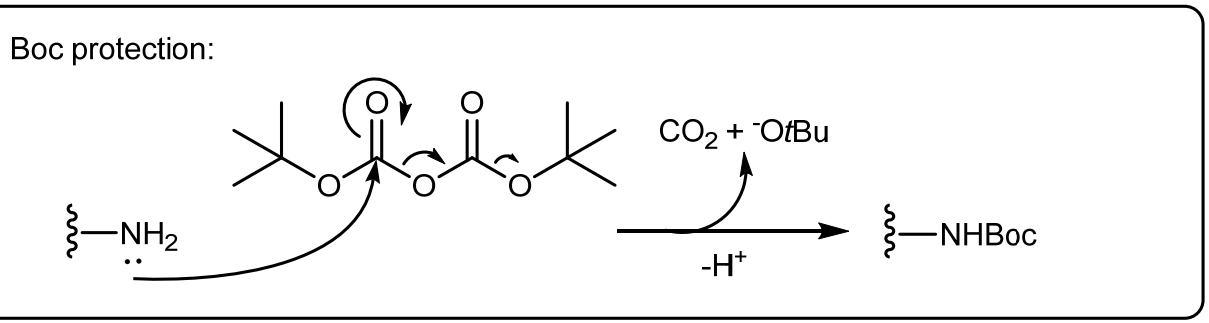
Horner-Wadsworth-Emmons Olefination

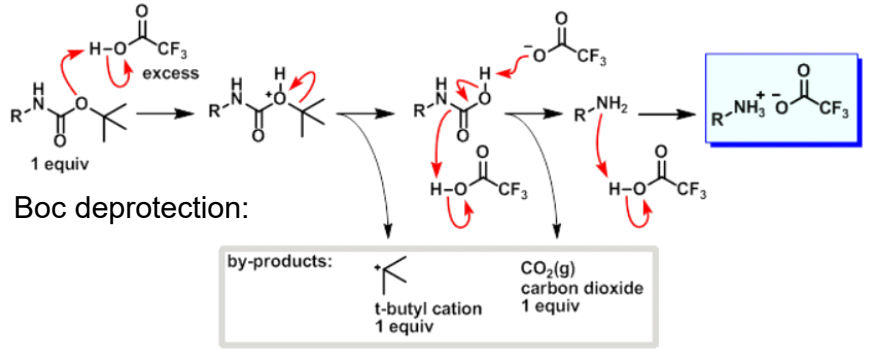


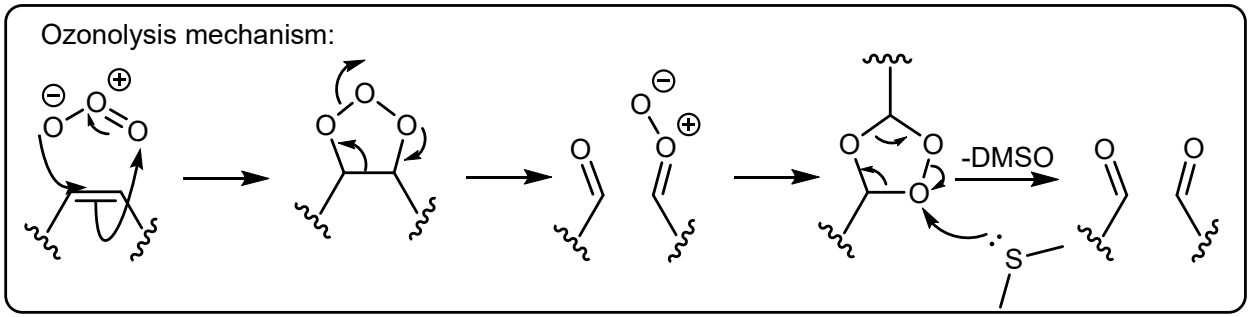
Pd-MorDalphos catalyzed amination mechanism:

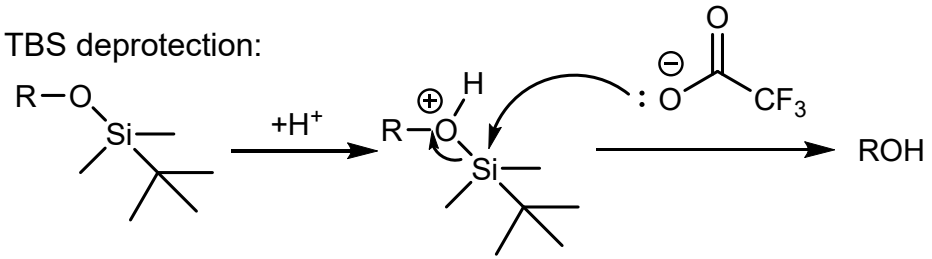


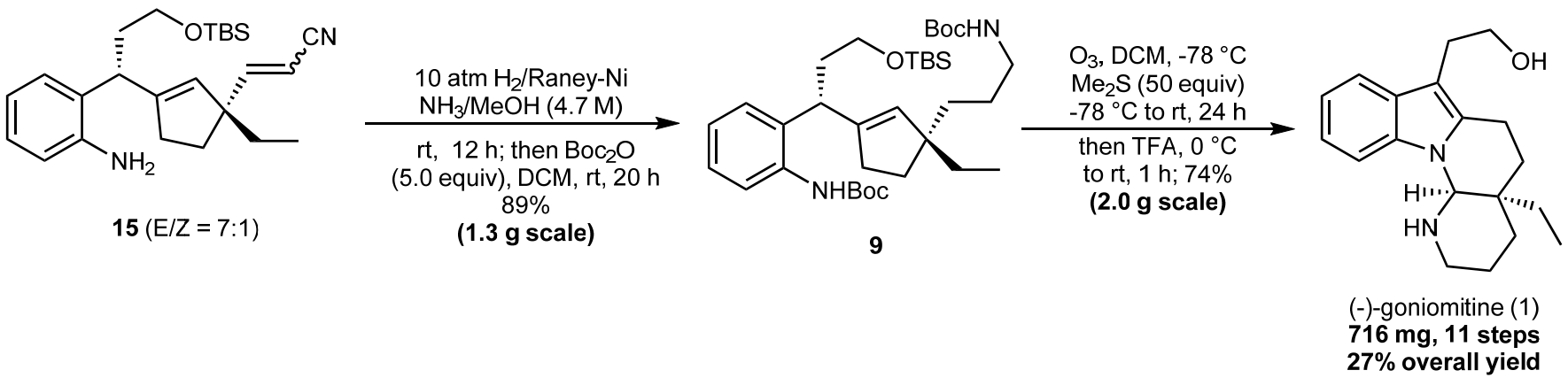

OTBS
CN
NH2
15 (E/Z = 7:1)
10 atm H2/Raney-Ni
NH3/MeOH (4.7 M)
rt, 12 h; then Boc2O
(5.0 equiv), DCM, rt, 20 h
89%
(1.3 g scale)
BocHN
OTBS
NHBoc
9
O3, DCM, -78 °C
Me2S (50 equiv)
-78 °C to rt, 24 h
then TFA, 0 °C
to rt, 1 h; 74%
(2.0 g scale)
OH
N
H
HN
(-)-goniomitine (1)
716 mg, 11 steps
27% overall yield


Boc protection:
NH2
CO2 + -OtBu
-H+
NHBoc


excess
1 equiv
Boc deprotection:
by-products:
t-butyl cation
1 equiv
CO2(g)
carbon dioxide
1 equiv


Ozonolysis mechanism:
-DMSO
S


TBS deprotection:
+H+
ROH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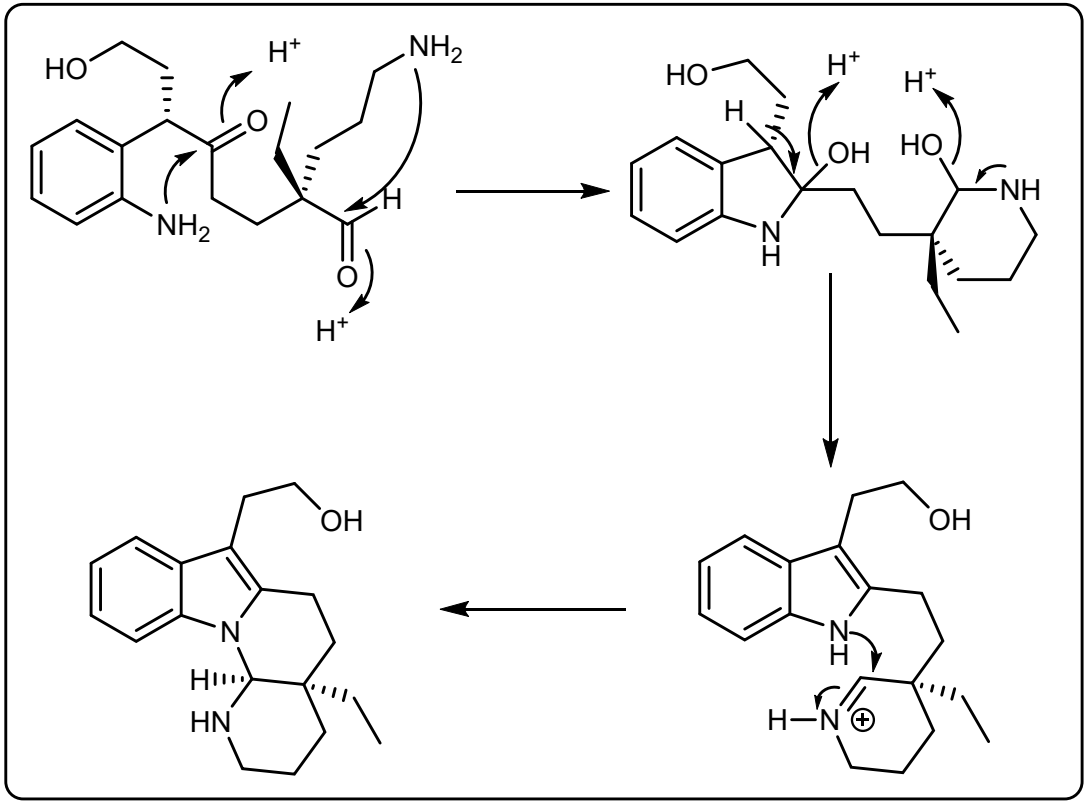
HO
H+
NH2
O
NH2
H
O
H+
HO
H+
H
OH
H+
HO
NH
N
H
OH
N
H
H—N
OH
N
H
HN