Lundurines A, B & C

Lundurines A, B and C - isolated from *Kopsia tenuis*, a plant native to north of Borneo

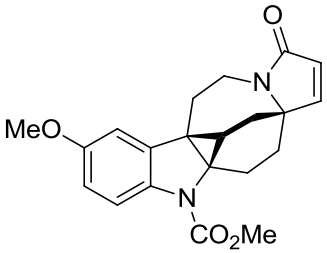
Show interesting cytotoxicity properties

These alkaloids feature a unique polyhydropyrroloazocine and cyclopropyl moiety fused to the indoline ring

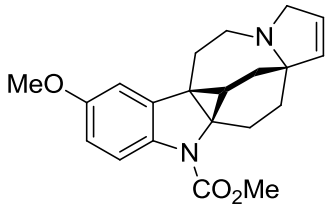
Reported total syntheses of Lundurine A and B were lengthy and involve over 20 linear synthetic steps

Thus difficult to synthesize useful quantities of final targets to study broad biological assays

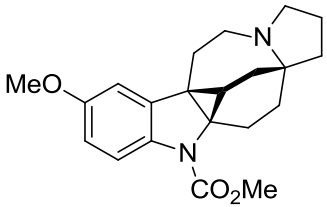
In this paper, a more efficient total synthesis (12-14 steps) of Lundurine A, B and the first total synthesis of Lundurine C (racemic and enantiopure) were reported



(–)-Lundurine A **1**

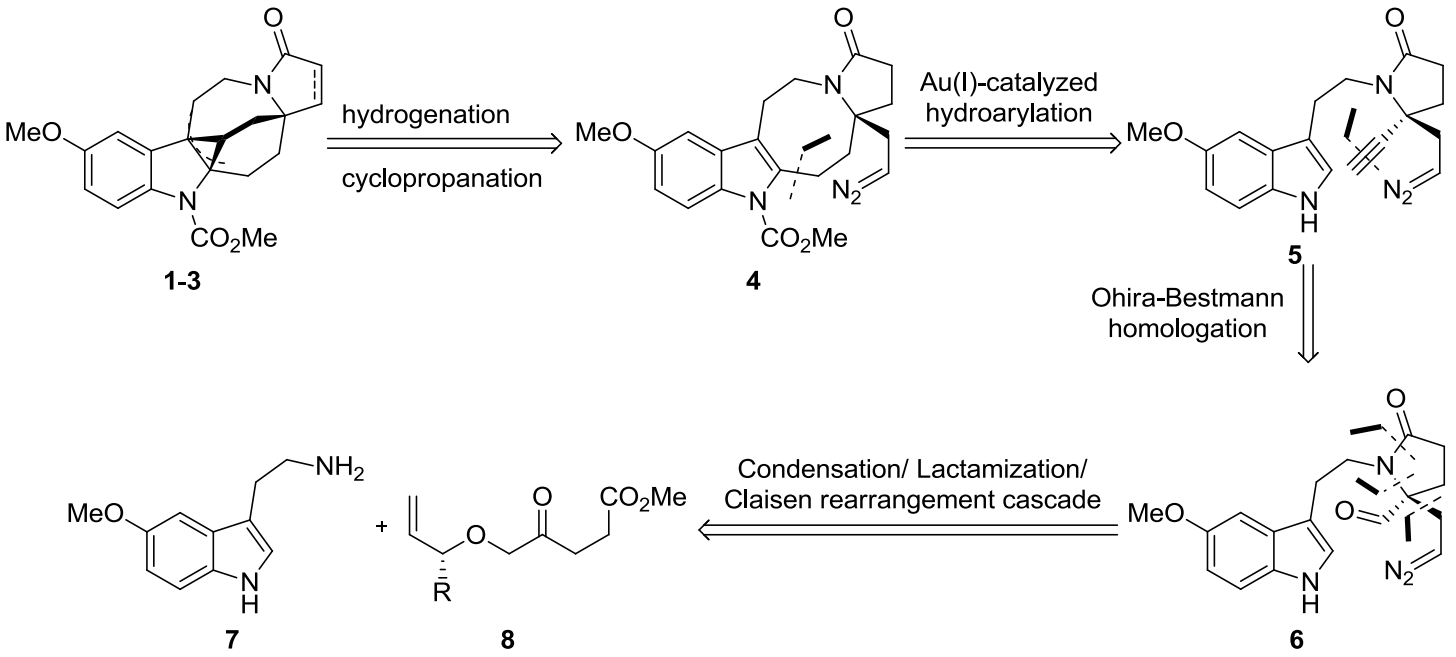


(–)-Lundurine B **2**

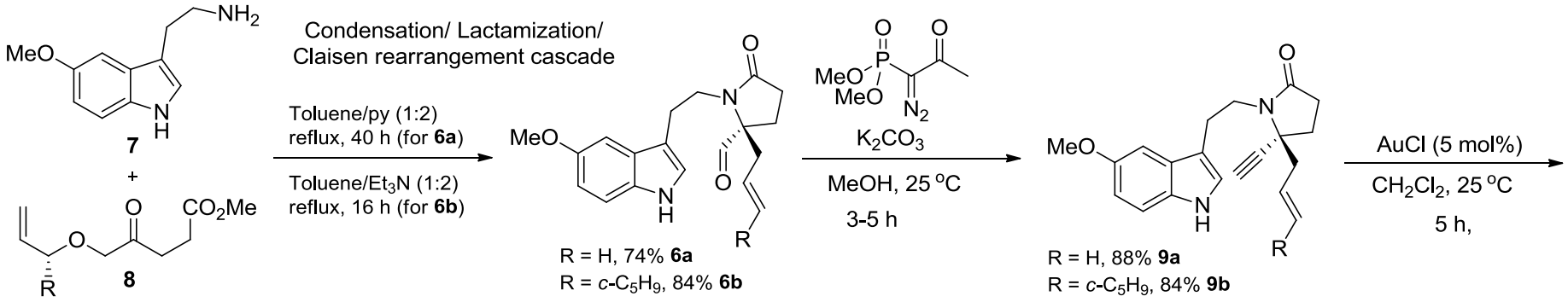


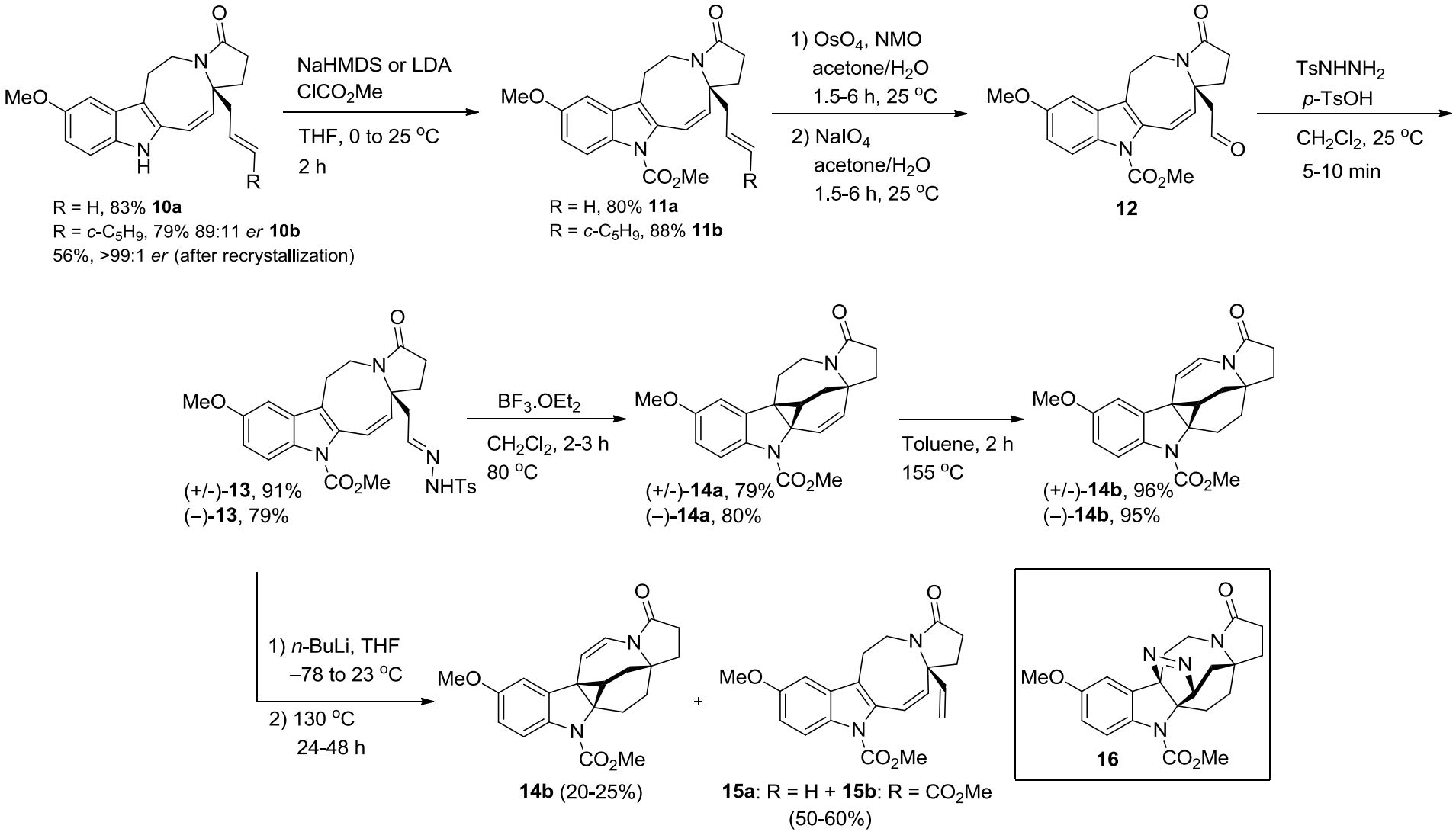
(–)-Lundurine C **3**

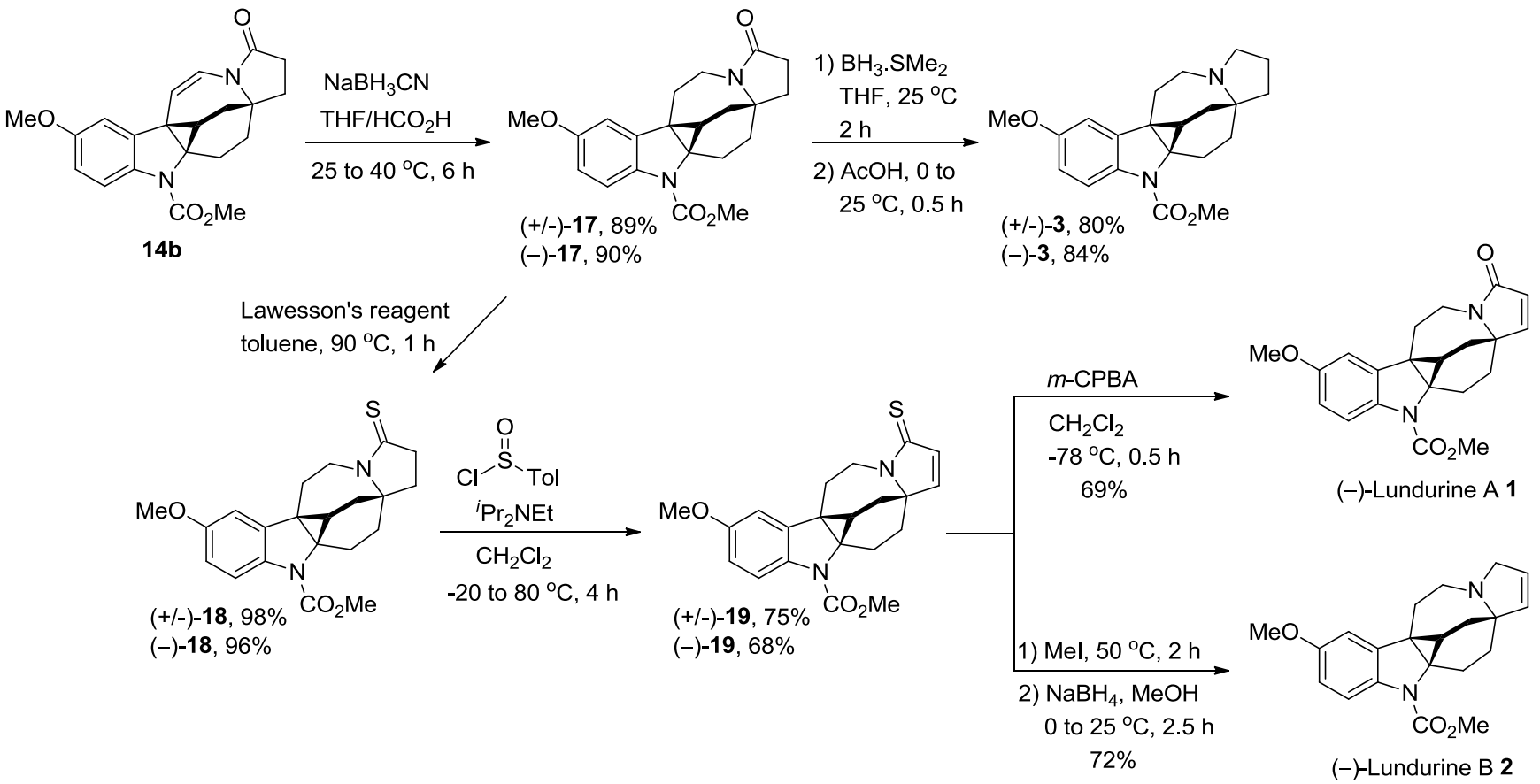
Retrosynthesis



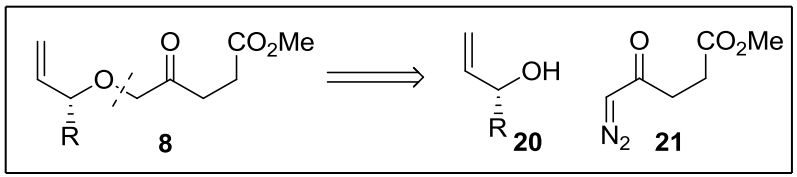
Synthetic approach



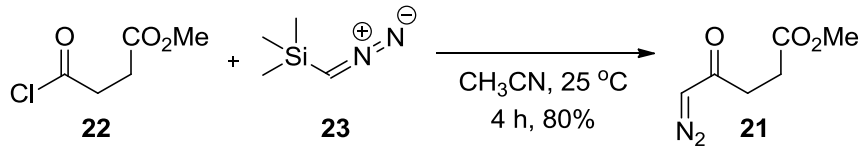

MeO
NaHMDS or LDA
ClCO2Me
THF, 0 to 25 °C
2 h
R = H, 83% 10a
R = c-C5H9, 79% 89:11 er 10b
56%, >99:1 er (after recrystallization)
1) OsO4, NMO
acetone/H2O
1.5-6 h, 25 °C
2) NaIO4
acetone/H2O
1.5-6 h, 25 °C
R = H, 80% 11a
R = c-C5H9, 88% 11b
12
TsNHNH2
p-TsOH
CH2Cl2, 25 °C
5-10 min
(+/-)-13, 91%
(–)-13, 79%
BF3.OEt2
CH2Cl2, 2-3 h
80 °C
(+/-)-14a, 79%
(–)-14a, 80%
Toluene, 2 h
155 °C
(+/-)-14b, 96%
(–)-14b, 95%
1) n-BuLi, THF
–78 to 23 °C
2) 130 °C
24-48 h
14b (20-25%)
15a: R = H + 15b: R = CO2Me
(50-60%)
16


MeO
O
N
CO2Me
14b
NaBH3CN
THF/HCO2H
25 to 40 °C, 6 h
(+/-)-17, 89%
(–)-17, 90%
1) BH3.SMe2
THF, 25 °C
2 h
2) AcOH, 0 to
25 °C, 0.5 h
(+/-)-3, 80%
(–)-3, 84%
Lawesson's reagent
toluene, 90 °C, 1 h
S
(+/-)-18, 98%
(–)-18, 96%
Cl
S
Tol
iPr2NEt
CH2Cl2
-20 to 80 °C, 4 h
(+/-)-19, 75%
(–)-19, 68%
m-CPBA
CH2Cl2
-78 °C, 0.5 h
69%
(–)-Lundurine A 1
1) MeI, 50 °C, 2 h
2) NaBH4, MeOH
0 to 25 °C, 2.5 h
72%
(–)-Lundurine B 2

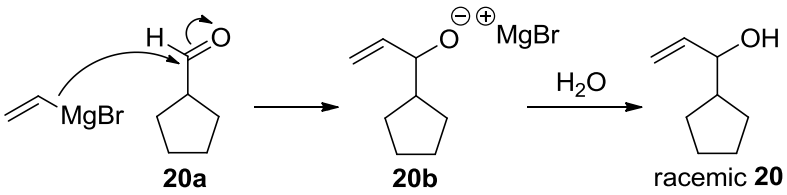
Mechanistic explanation



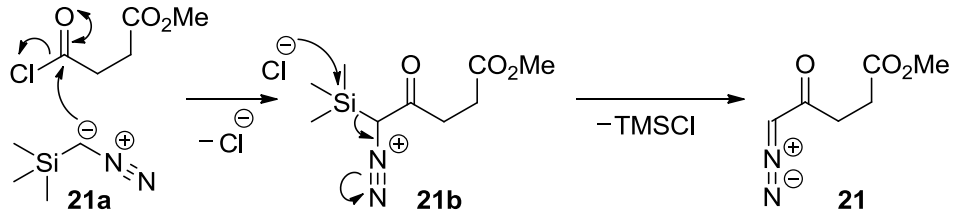
Synthesis of azo compound 21



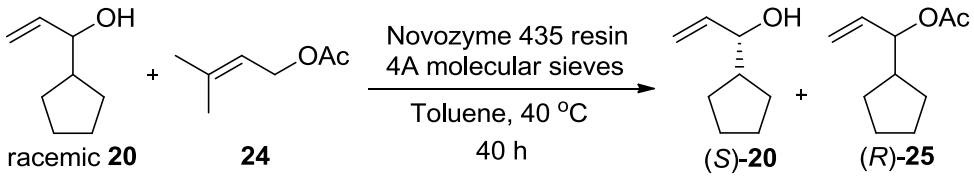
Synthesis of alcohol 20

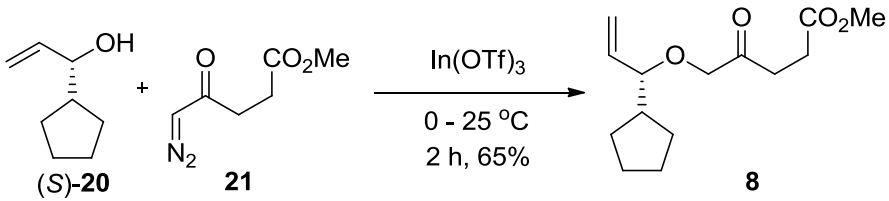


Mechanism

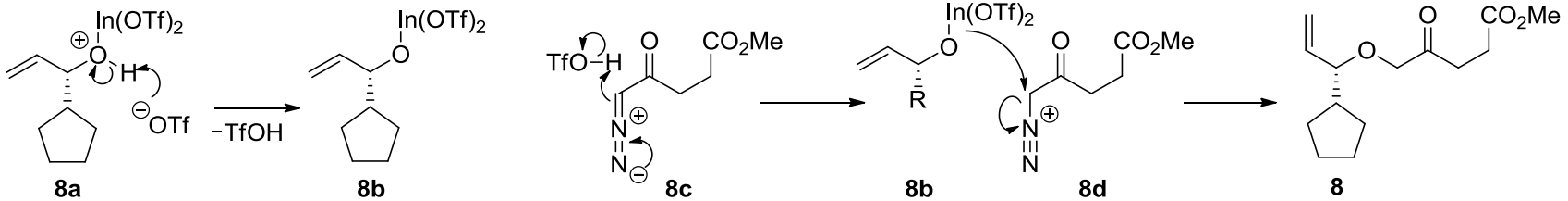


Enzymatic Kinetic Resolution: To obtain the (*S*)-20

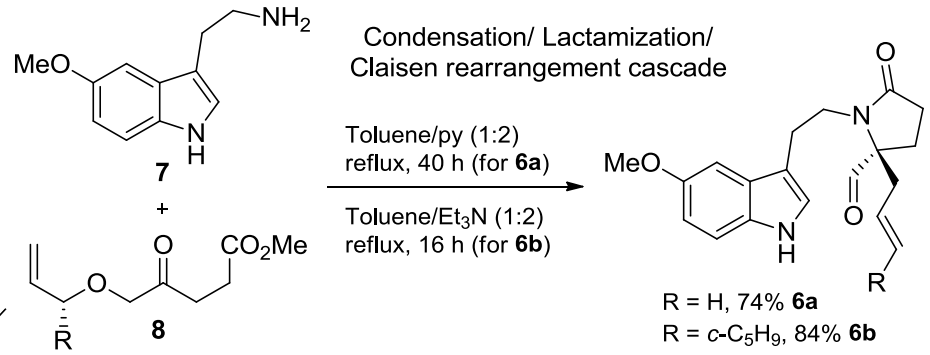




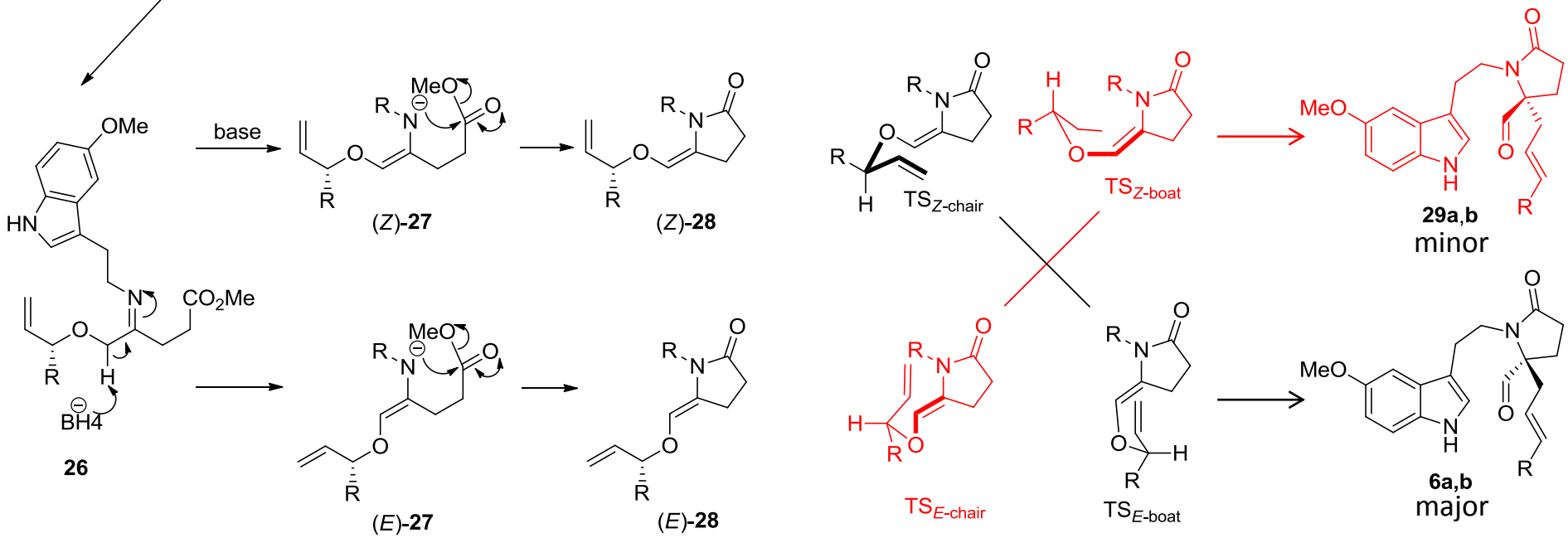
Mechanism



Enantioselective Claisen Rearrangement



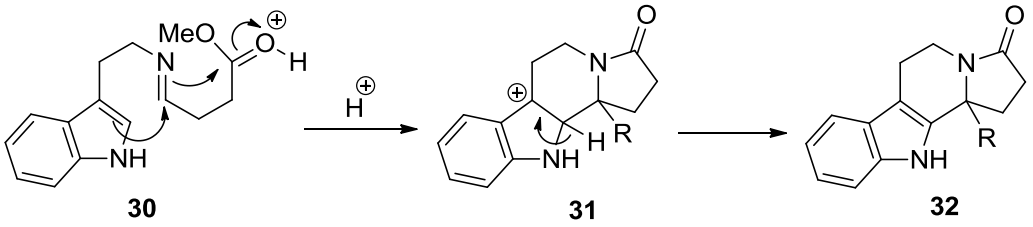
Basic conditions are necessary to avoid Picket-Spengler type reaction

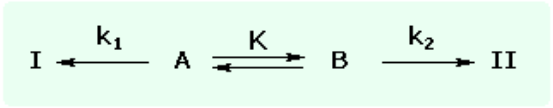


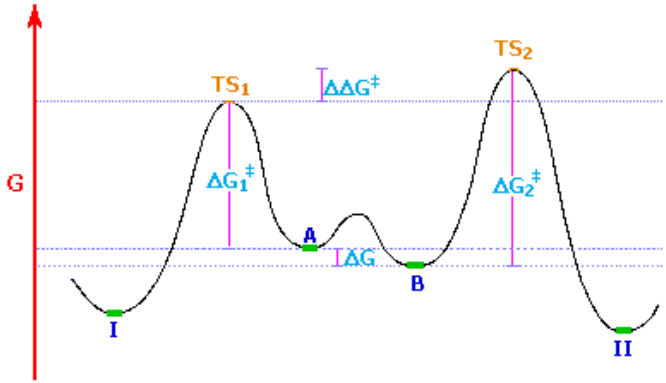
Both *Z*- and *E*- isomers are stable even at 100 °C for several hours

Curtin-Hammett principle is not applicable

Picket-Spengler type reaction: under acidic conditions

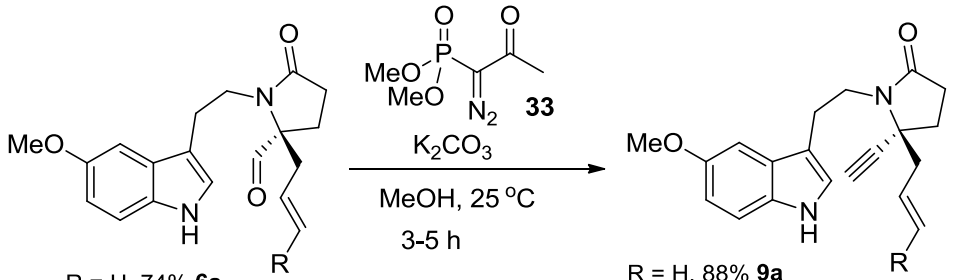






Curtin-Hammett principle

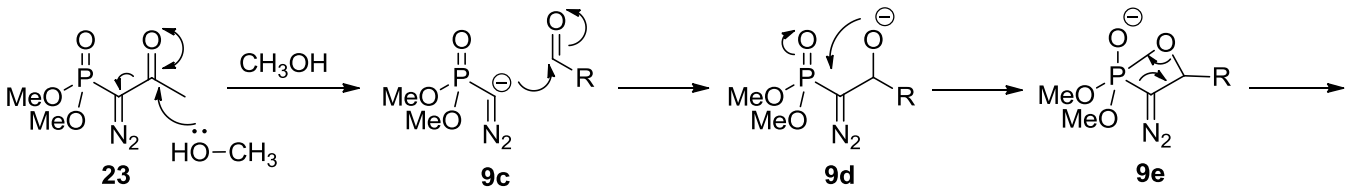
Ohira-Bestmann reagent

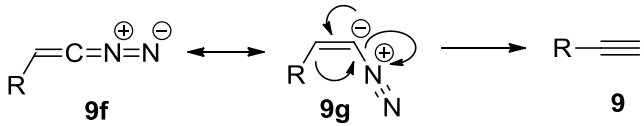


R = H, 74% **6a**
R = *c*-C_5H_9, 84% **6b**

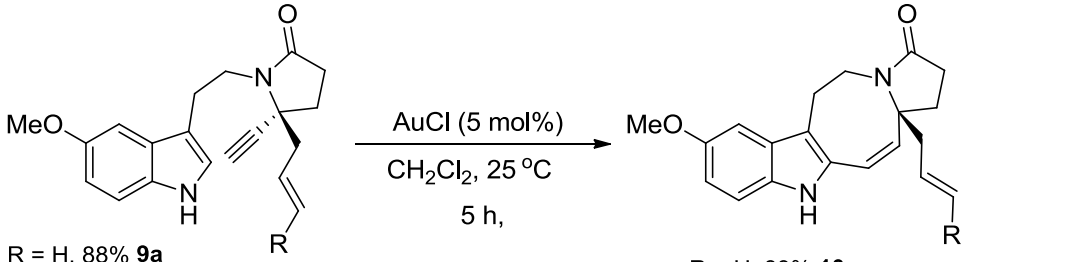
R = H, 88% **9a**
R = *c*-C_5H_9, 84% **9b**

Mechanism





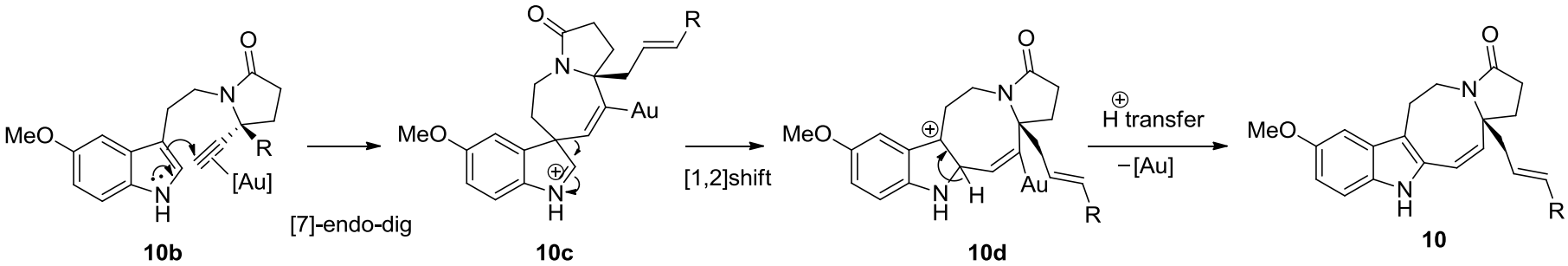
Rare 8-endo-dig gold(I) catalyzed hydroarylation



R = H, 88% **9a**
R = *c*-C_5H_9, 84% **9b**

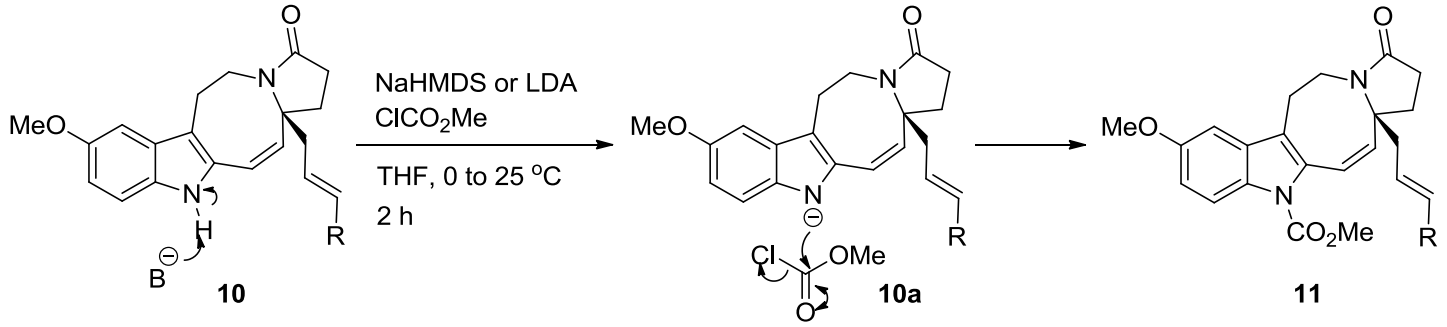
R = H, 83% **10a**
R = *c*-C_5H_9, 79% 89:11 *er* **10b**
56%, >99:1 *er* (after recrystallization)

Mechanism

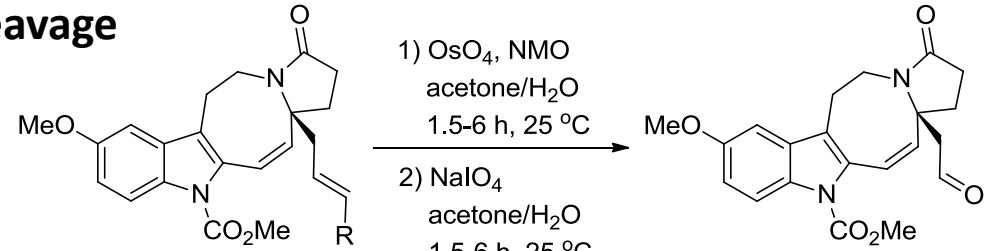


10b **10c** **10d** **10**

Overall, an 8-endo-dig reaction?
Known to be catalysed by Au(III)catalysts in the presence of Ag salts
No explanation has been provided why Au(I) catalyzes the reaction

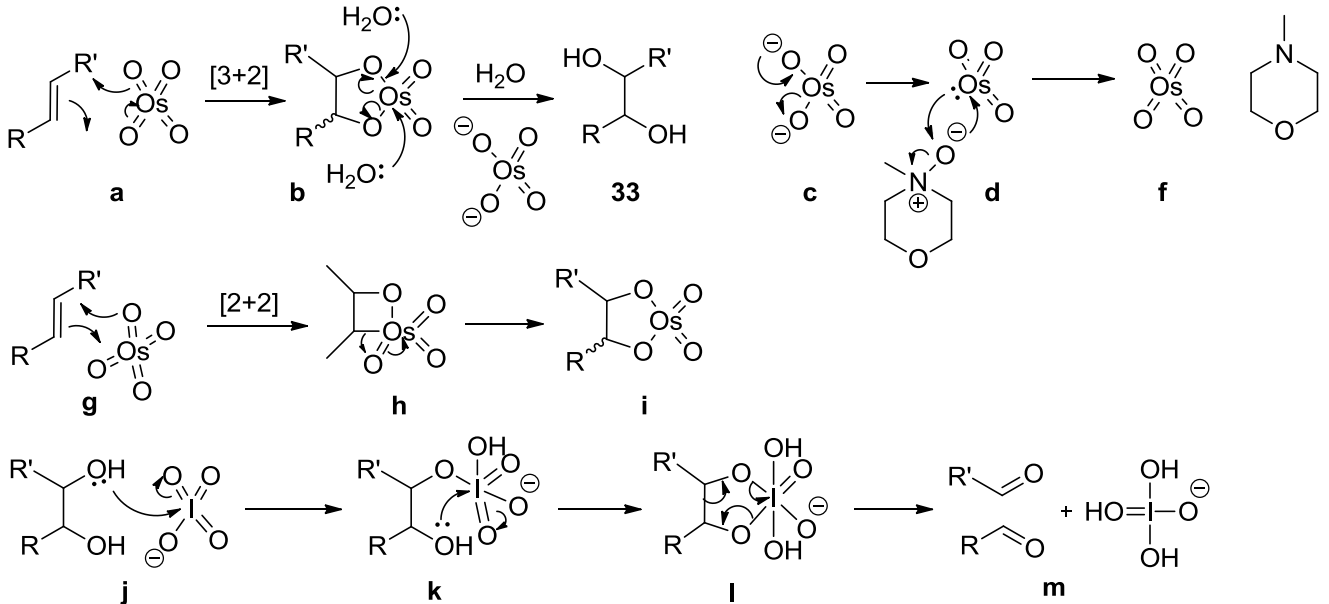


Johnson-Lemiex cleavage

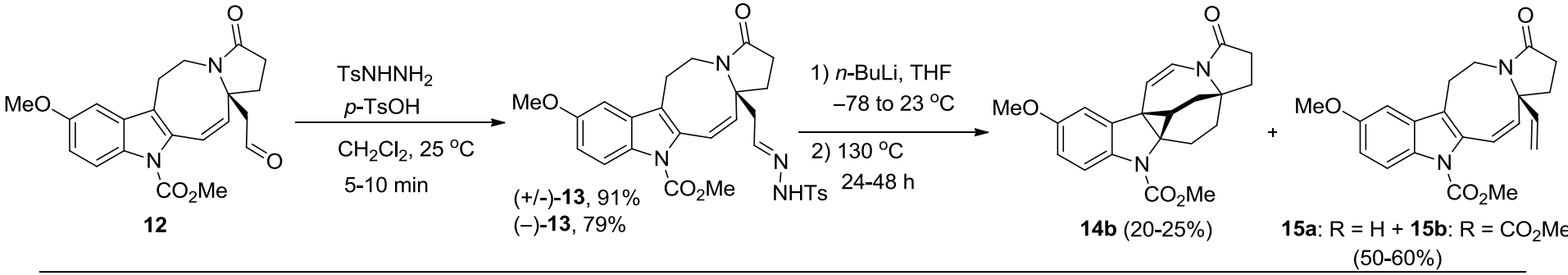


R = H, 80% **11a**
R = *c*-C_5H_9, 88% **11b**

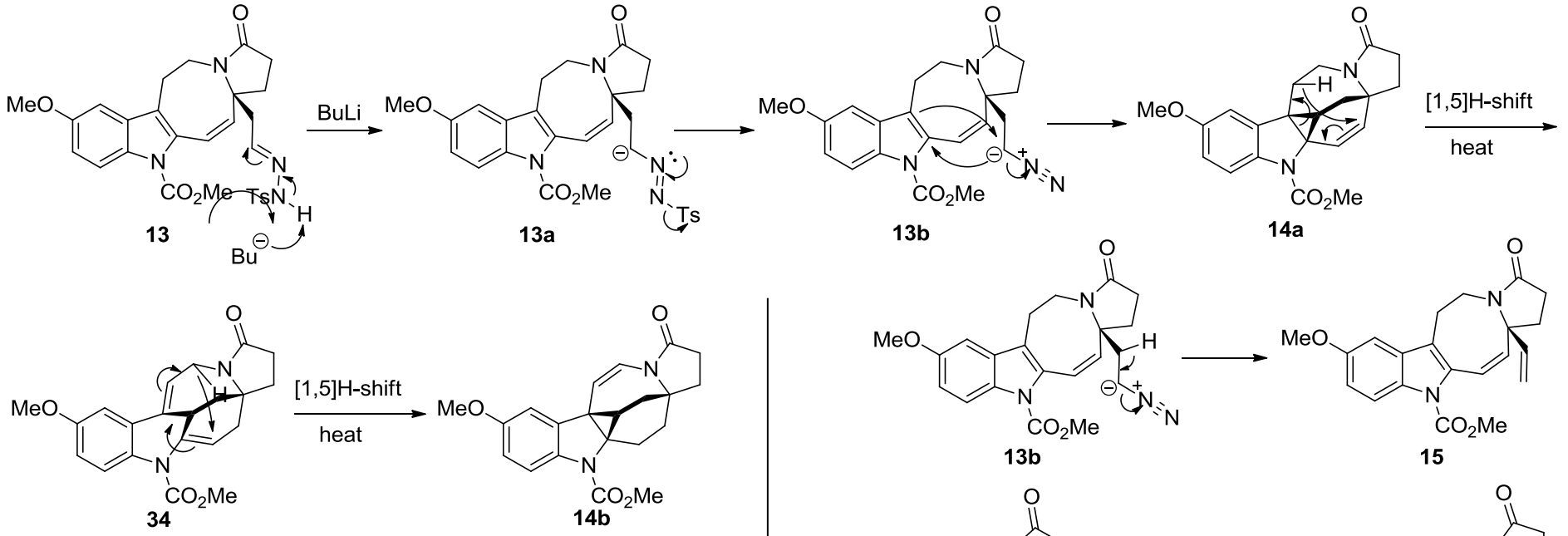
Mechanism



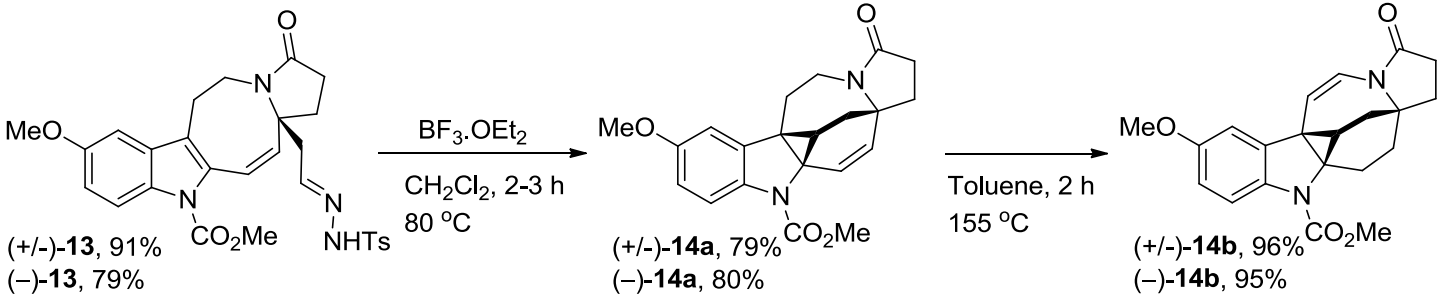
Homodienyl Retro-Ene / Ene rearrangement

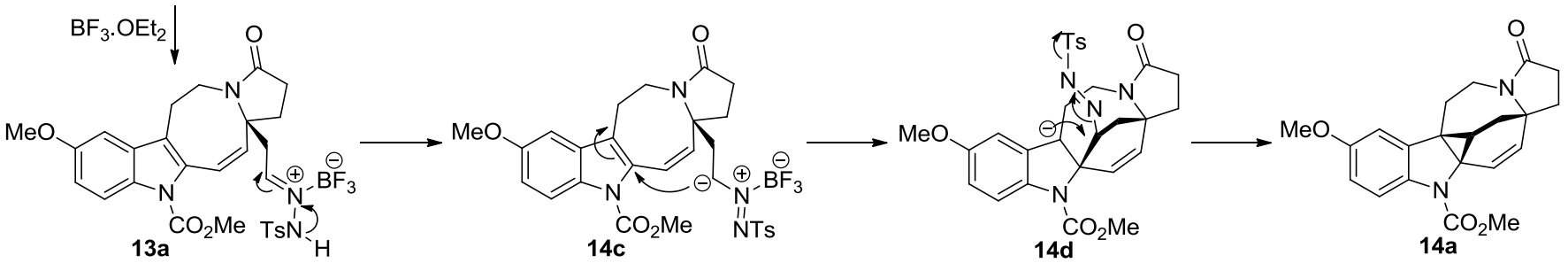


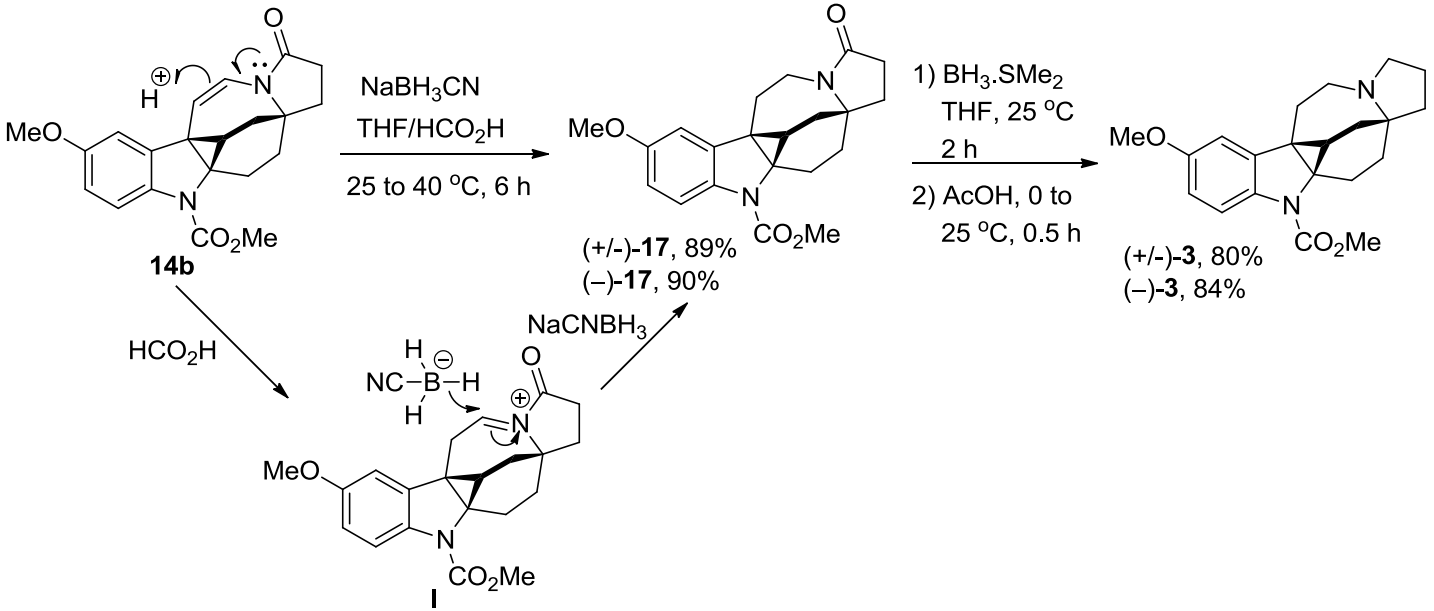
Mechanism

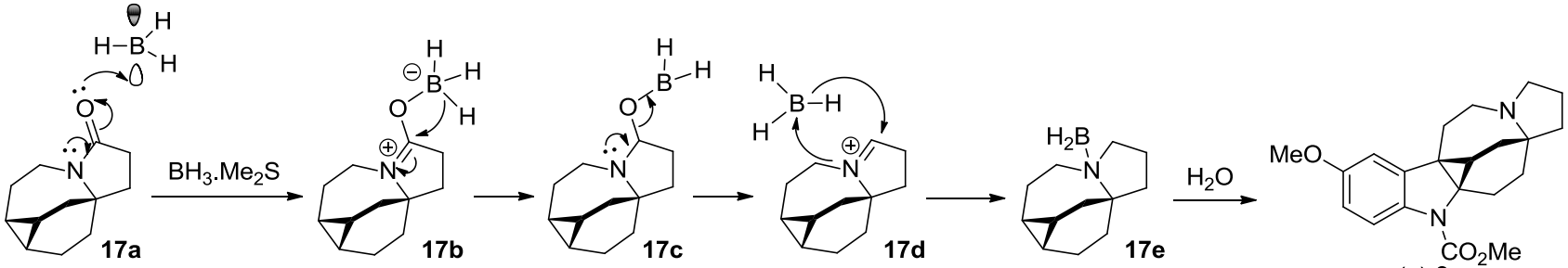


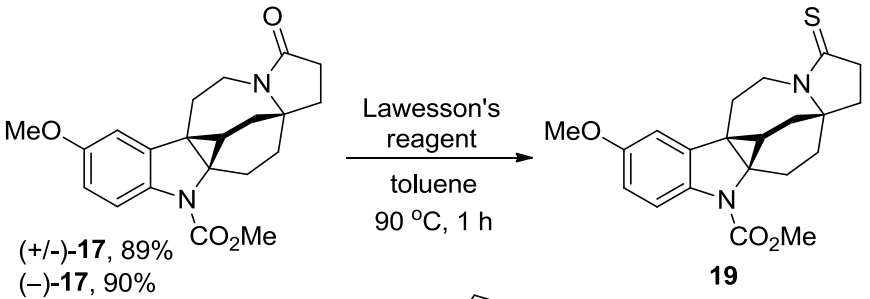
14a to **14b** *via* Homodienyl Retro-Ene / Ene rearrangement

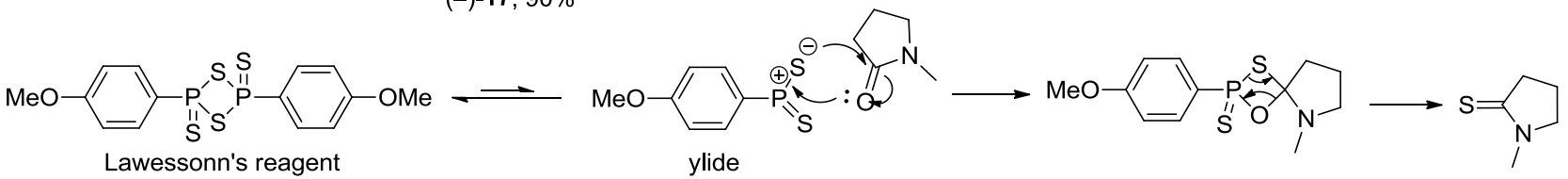

MeO
N
O
CO2Me
N
NHTs
BF3.OEt2
CH2Cl2, 2-3 h
80 °C
(+/-)-13, 91%
(–)-13, 79%
(+/-)-14a, 79%
(–)-14a, 80%
Toluene, 2 h
155 °C
(+/-)-14b, 96%
(–)-14b, 95%

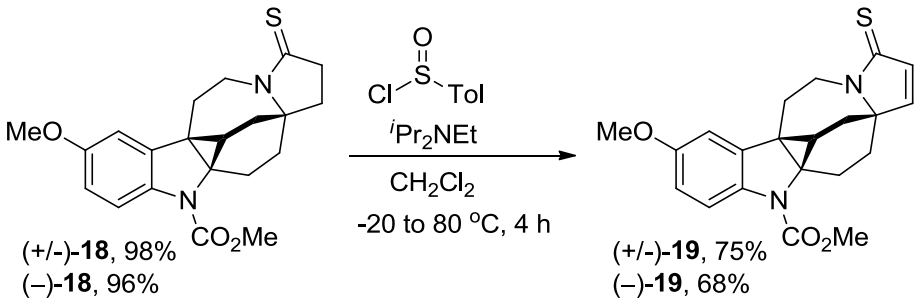

BF3.OEt2
MeO
N
O
CO2Me
TsN
H
BF3
13a
14c
NTs
Ts
14d
14a

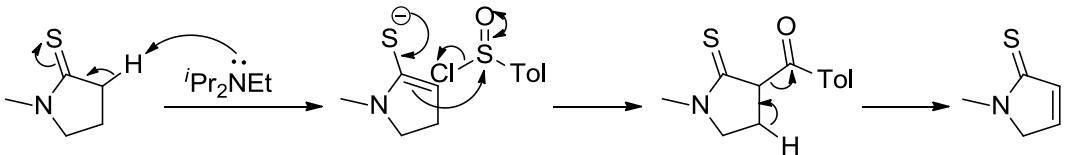

MeO
N
O
CO2Me
14b
NaBH3CN
THF/HCO2H
25 to 40 °C, 6 h
(+/-)-17, 89%
(–)-17, 90%
1) BH3.SMe2
THF, 25 °C
2 h
2) AcOH, 0 to
25 °C, 0.5 h
(+/-)-3, 80%
(–)-3, 84%
HCO2H
NaCNBH3
NC–B–H
H
I

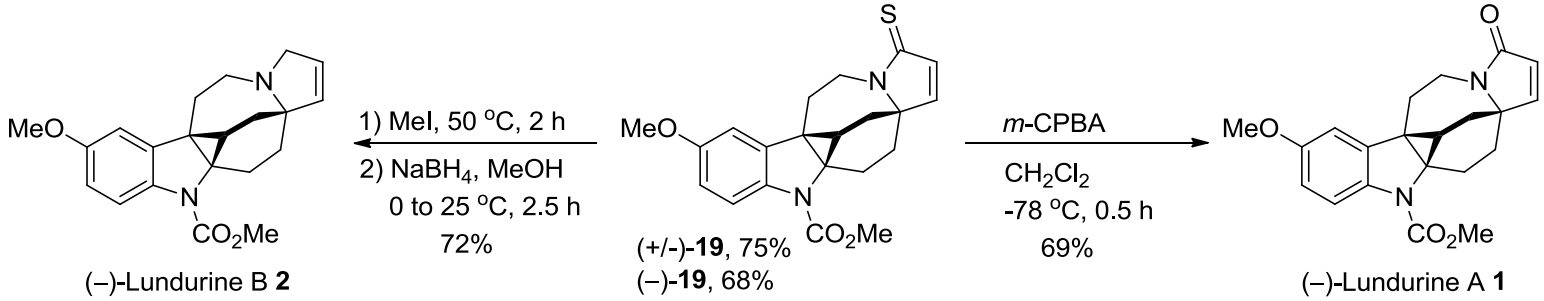

BH3.Me2S
17a
17b
17c
17d
17e
H2O
MeO
N
CO2Me
(–)-3

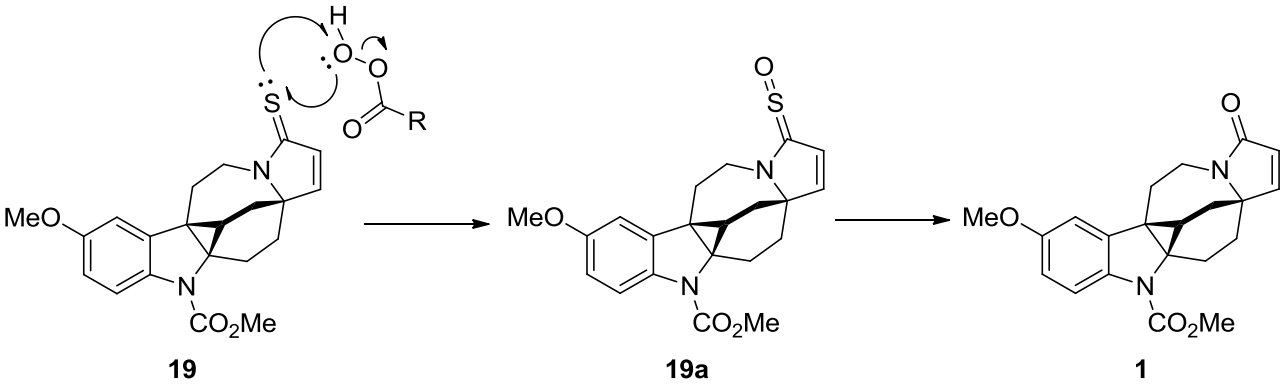

MeO
N
CO2Me
(+/-)-17, 89%
(–)-17, 90%
Lawesson's reagent
toluene
90 °C, 1 h
19

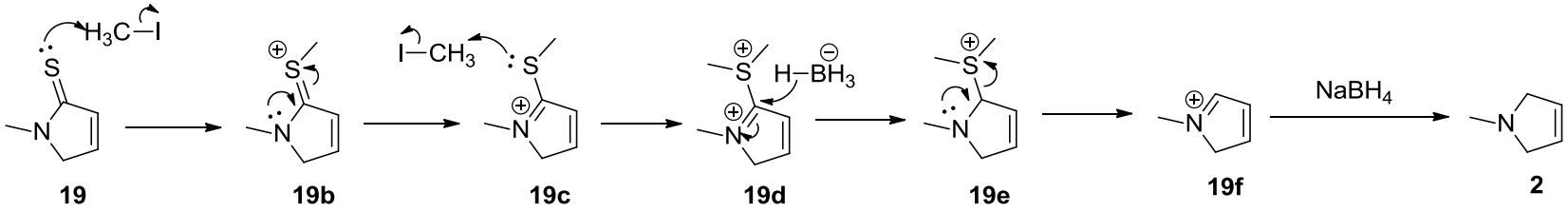

MeO
OMe
Lawessonn's reagent
ylide


MeO
N
CO2Me
(+/-)-18, 98%
(–)-18, 96%
Cl
Tol
iPr2NEt
CH2Cl2
-20 to 80 °C, 4 h
(+/-)-19, 75%
(–)-19, 68%


iPr2NEt
Cl
Tol
H


MeO
N
CO2Me
(–)-Lundurine B 2
1) MeI, 50 °C, 2 h
2) NaBH4, MeOH
0 to 25 °C, 2.5 h
72%
S
(+/-)-19, 75%
(–)-19, 68%
m-CPBA
CH2Cl2
-78 °C, 0.5 h
69%
O
(–)-Lundurine A 1


H
O
S
R
MeO
N
CO2Me
19
19a
1


H3C–I
I–CH3
H–BH3
NaBH4
19
19b
19c
19d
19e
19f
2