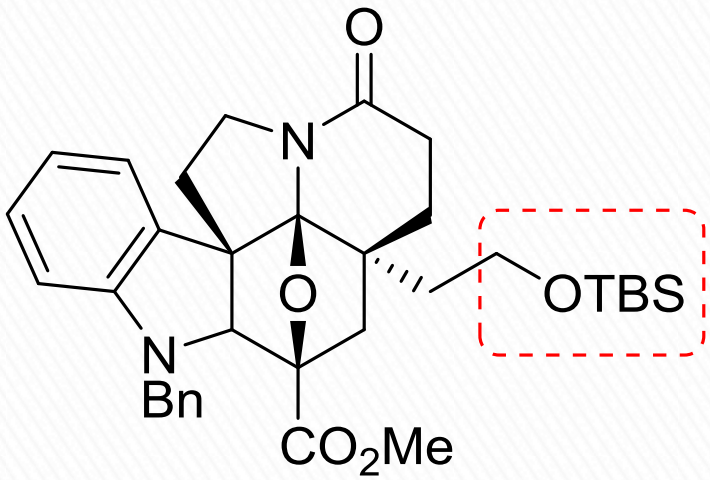
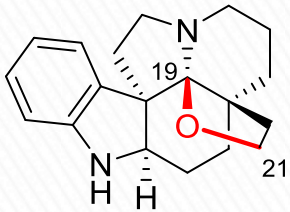
Divergent Total Synthesis of Alkaloids from the Pentacyclic *Aspidosperma* Skeleton



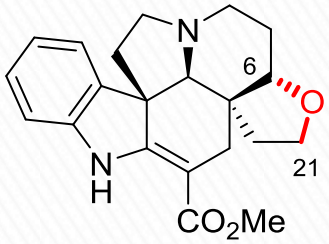
TJD group meeting
11/03/2014

Alice Gatland

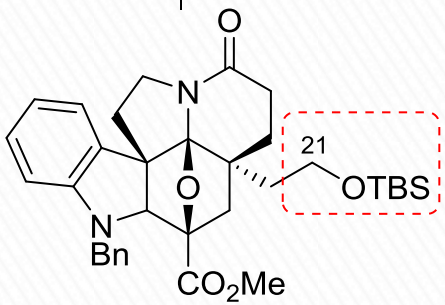


1) **(+)-fendleridine**

enantiomeric series

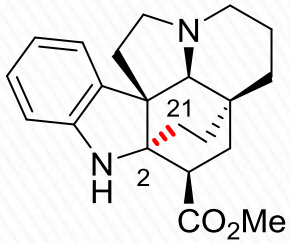


4) **(–)-deoxoapodine**

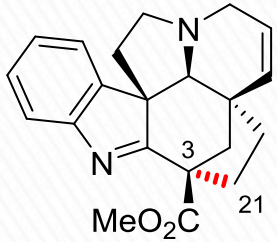


pentacyclic *Aspidosperma* alkaloid skeleton

1



2) **kopsinine**

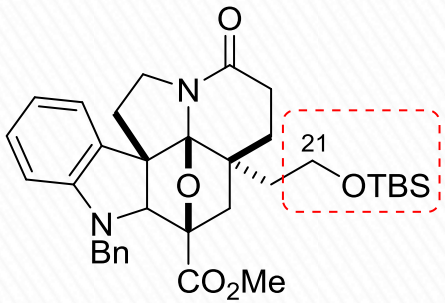


3) **(–)-kopsifoline D**

Dale Boger & co-workers
J. Am. Chem. Soc. **2014**, *136*, 3312-3317

Synthesis of Pentacyclic Skeleton (1)

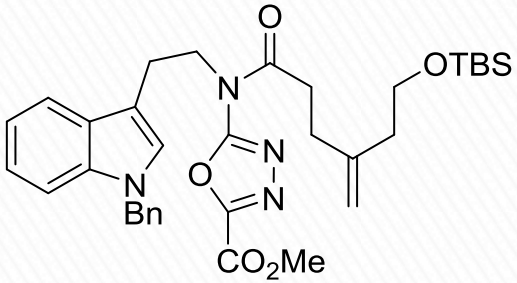
- Key step: [4+2]/[3+2] cycloaddition cascade to form pentacyclic system and set stereochemistry.



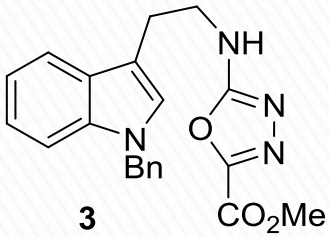
pentacyclic *Aspidosperma* alkaloid skeleton

1

[4+2], $-N_2$, [3+2]

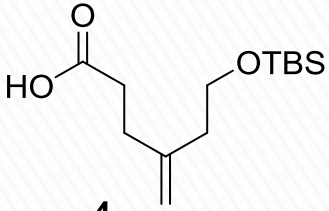


2



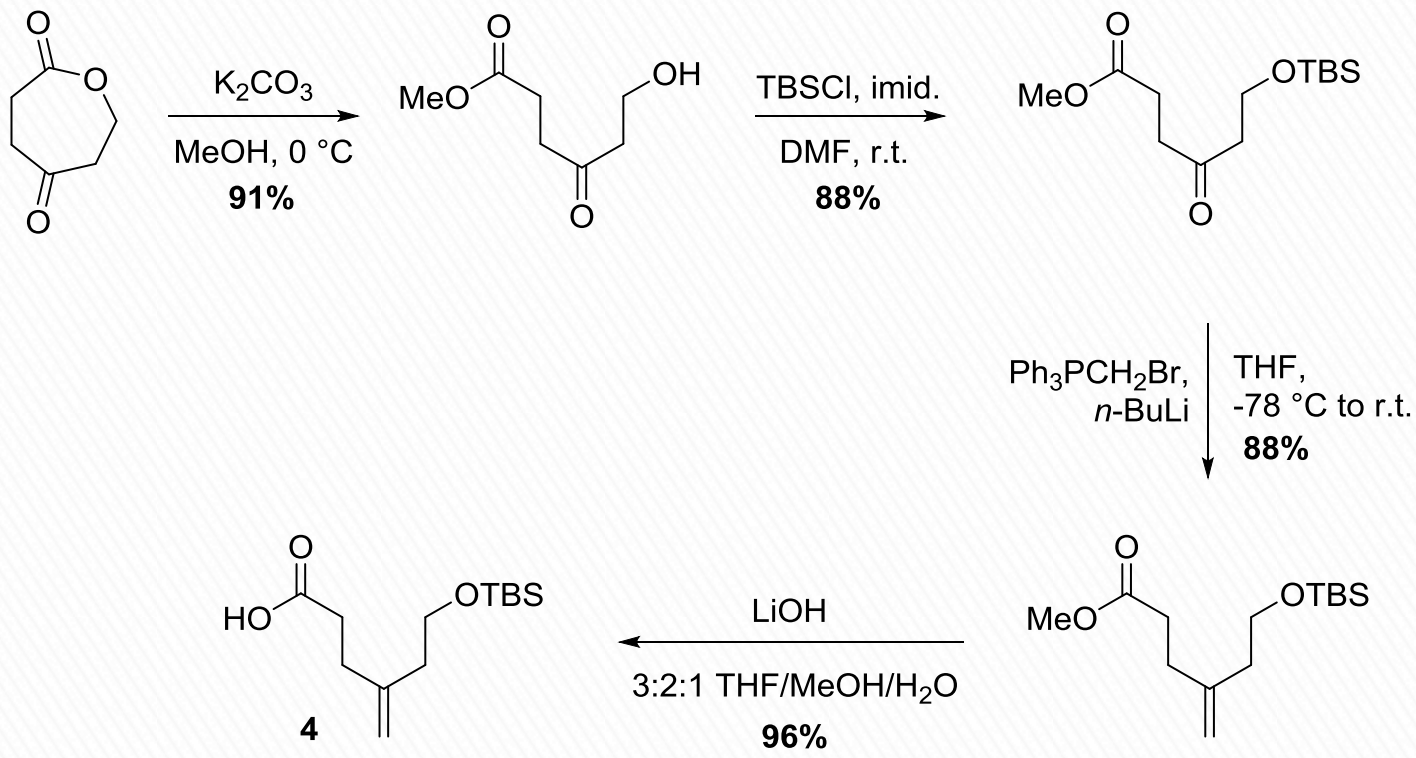
3

+



4

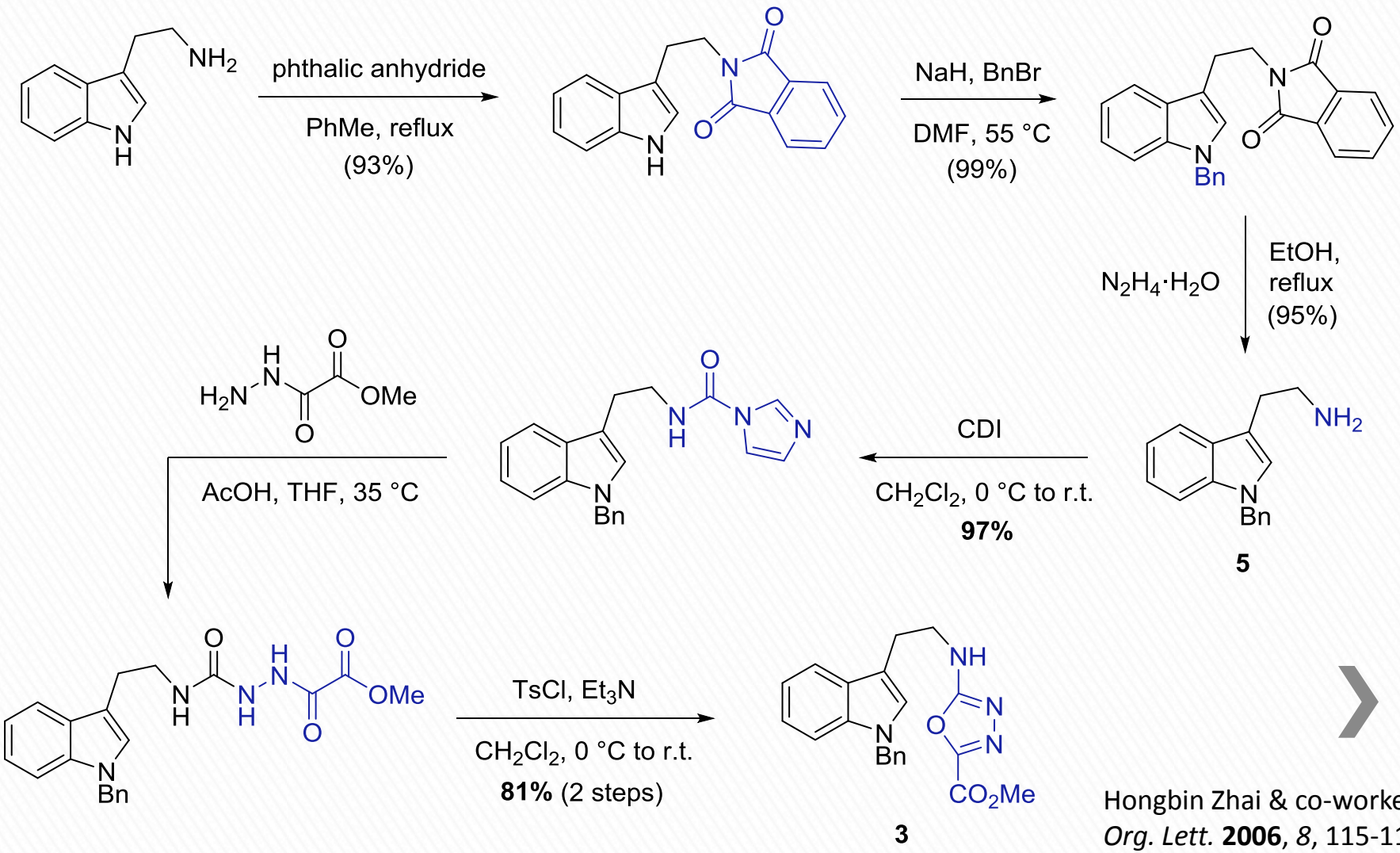
Synthesis of Acid Fragment (4)



J. Am. Chem. Soc. **2010**, *132*, 3009-3012

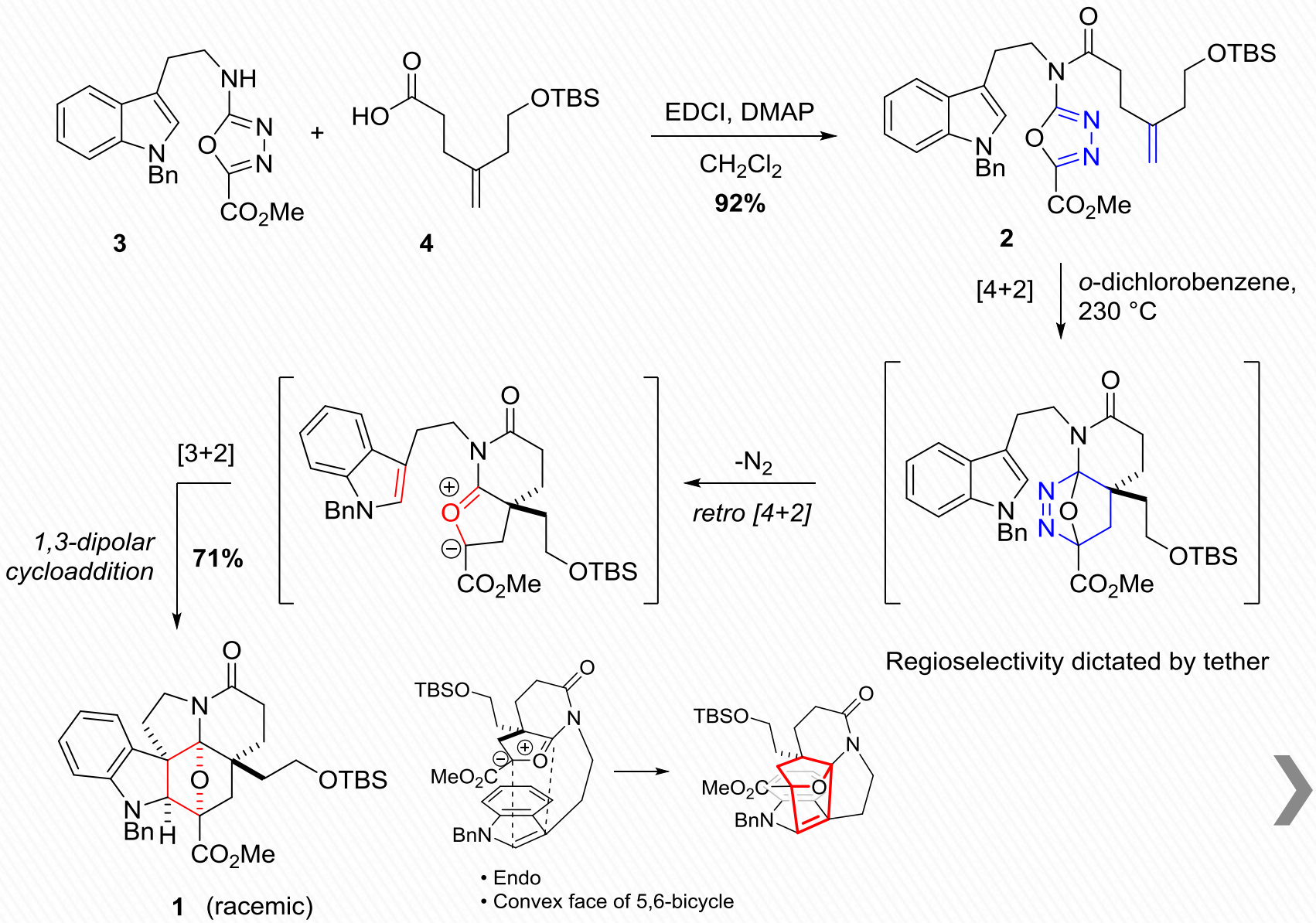
Synthesis of 1,3,4-oxadiazole 3

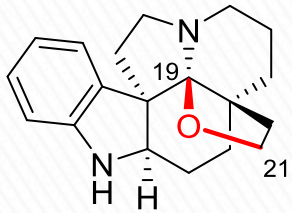
- 1-Benzyltryptamine (**5**) prepared according to literature procedure.



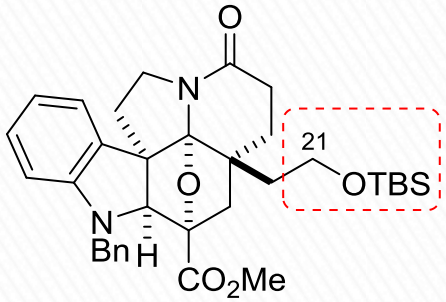
Hongbin Zhai & co-workers
Org. Lett. **2006**, *8*, 115-118

Pentacycle Synthesis

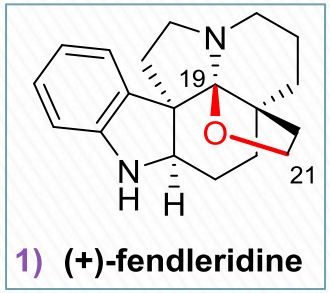


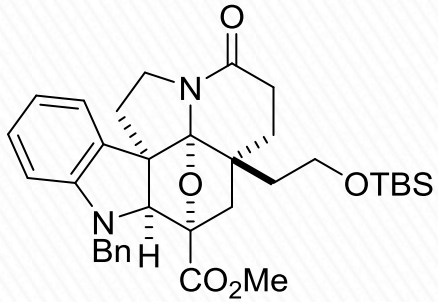


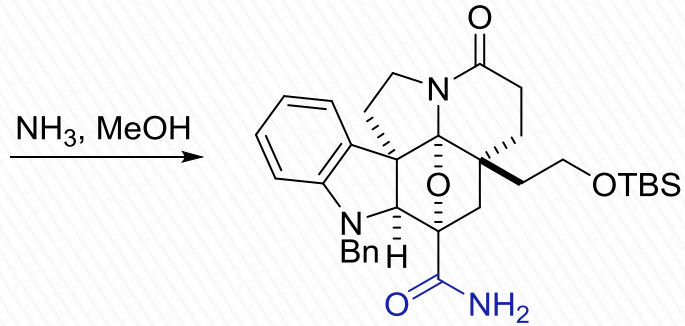
1) **(+)-fendleridine**

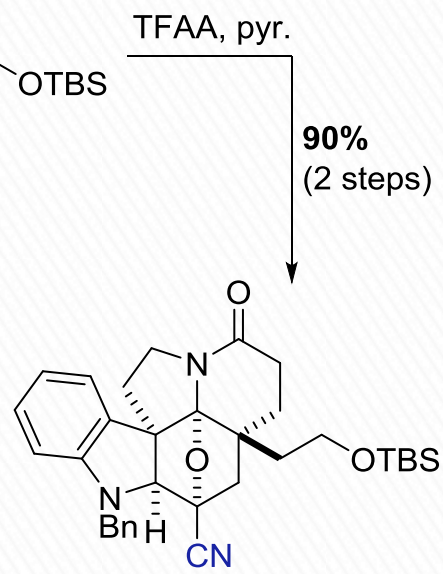


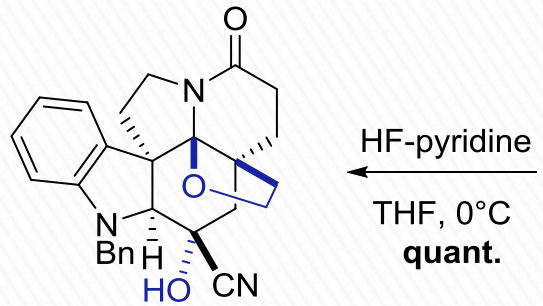
racemic
1

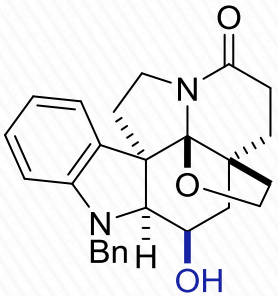




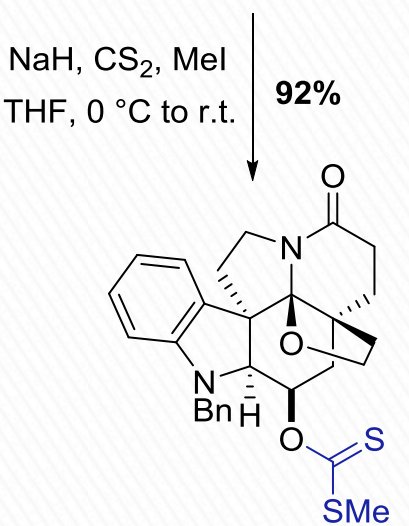




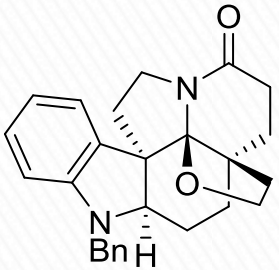


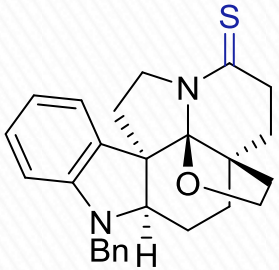


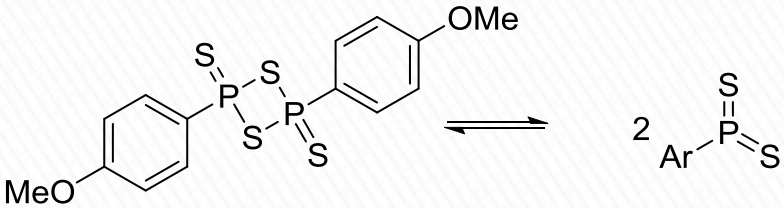
Na-selectride = NaBH(*s*-Bu)$_3$

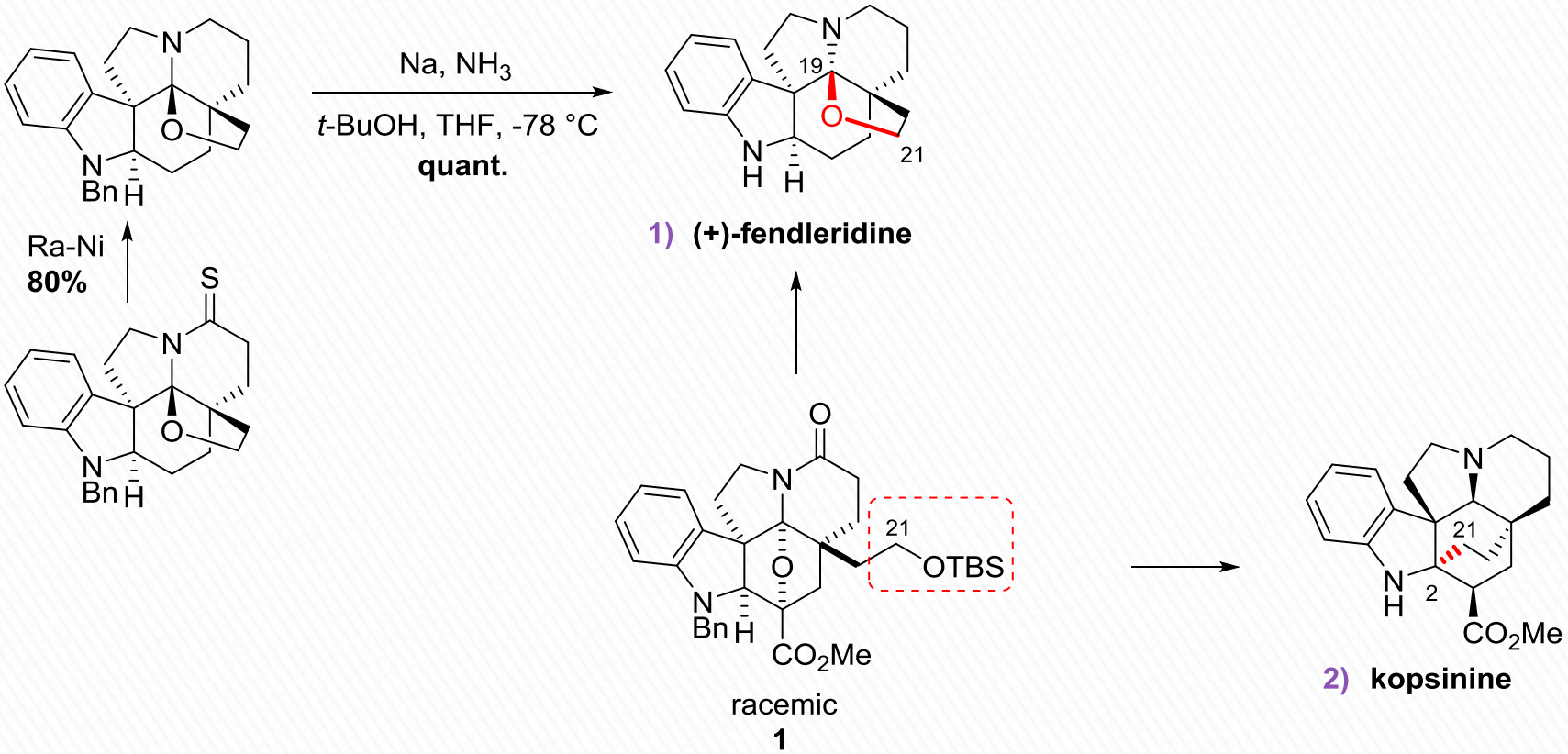


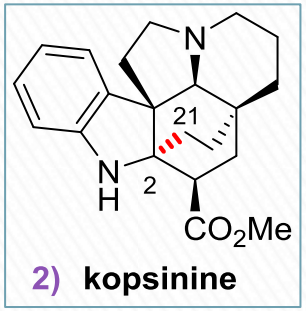
then chiral separation by chromatography

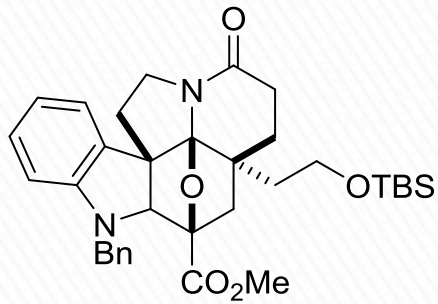







Na, NH3
t-BuOH, THF, -78 °C
quant.
Ra-Ni
80%
1) (+)-fendleridine
racemic
1
OTBS
CO2Me
2) kopsinine



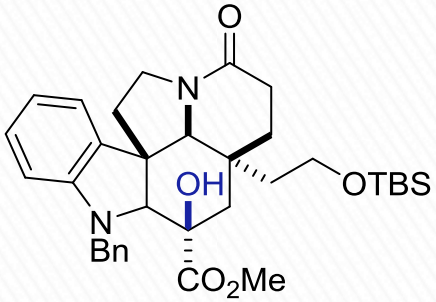


racemic
1

$NaCNBH_3$

AcOH, *i*-PrOH

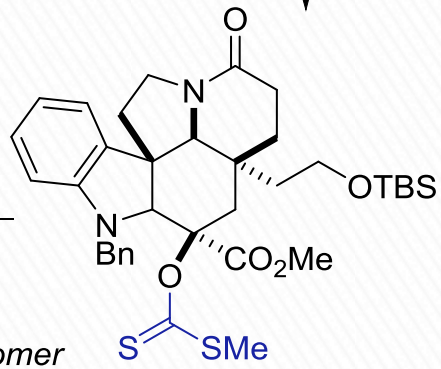
87%



NaH, CS_2, MeI

THF, 0 °C to r.t.

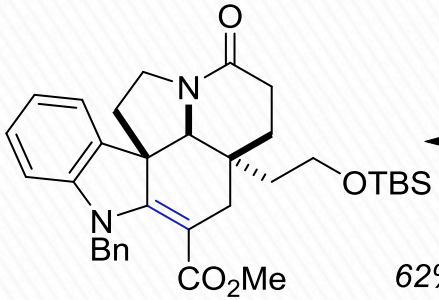
78%



C_6H_6, 130 °C

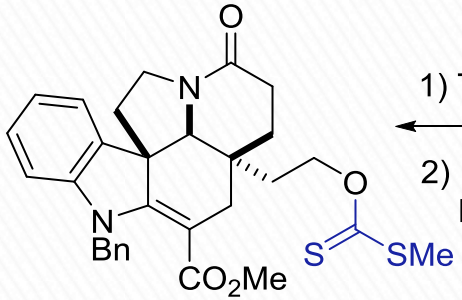
33%

62% other regioisomer



1) TBAF **98%**

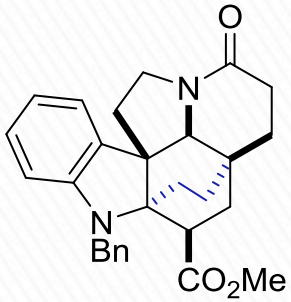
2) NaH, CS_2, MeI **86%**



SmI_2

THF/HMPA

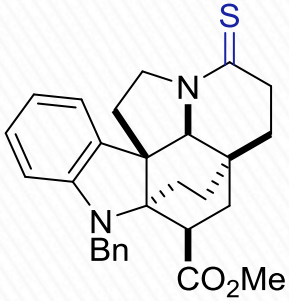
75%



Lawesson's reagent

PhMe, 90 °C

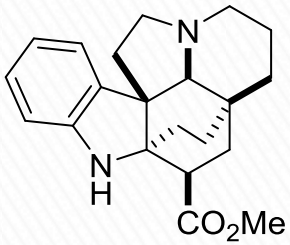
90%



Ra-Ni, H_2

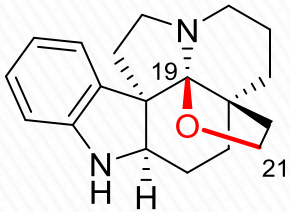
EtOH, 80 °C

95%



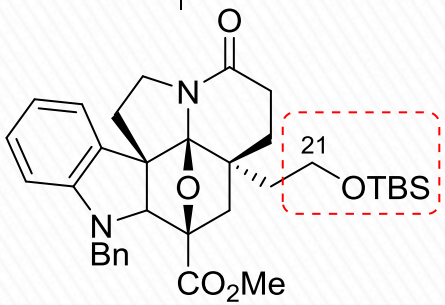
kopsinine

racemic



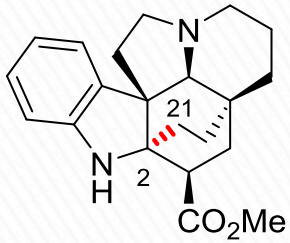
1) **(+)-fendleridine**

enantiomeric series

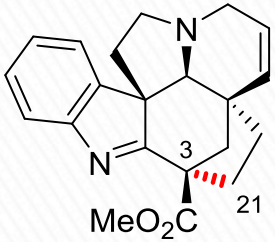


pentacyclic *Aspidosperma* alkaloid skeleton

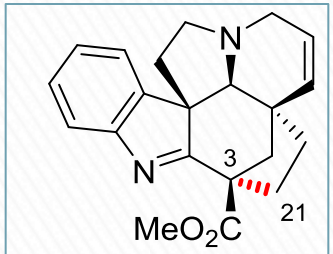
1



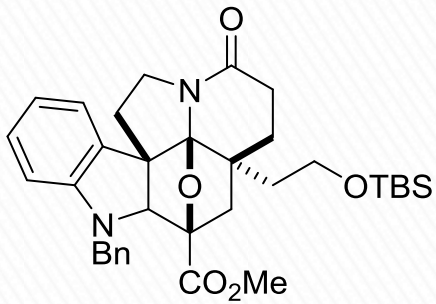
2) **kopsinine**



3) **(–)-kopsifoline D**

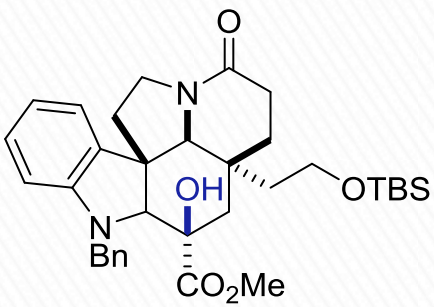


3) (–)-kopsifoline D

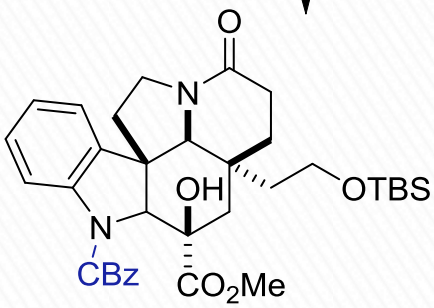


racemic
1

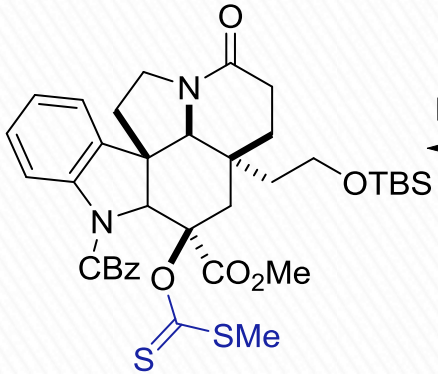
$NaCNBH_3$
AcOH, *i*-PrOH
88%



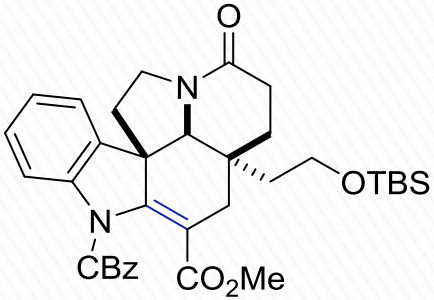
1) Ra-Ni, H_2 **92%**
2) $ClCO_2Bn$ **97%**



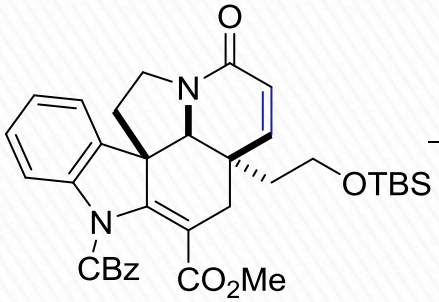
NaH, CS_2, MeI
THF
93%



PhMe, 150 °C
60%

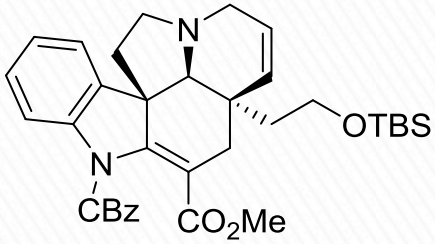


1) LDA, PhSeCl **81%**
2) *m*-CPBA **90%**

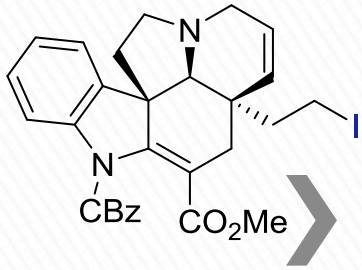


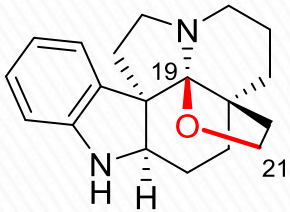
then chiral separation

Me_3OBF_4,
2,6-*t*-Bu_2Py
then $NaBH_4$,
MeOH
52%



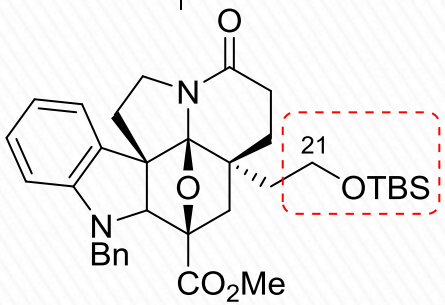
1) TBAF **98%**
2) Et_3N, MsCl
then NaI **68%**





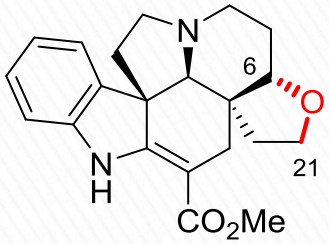
1) **(+)-fendleridine**

enantiomeric series

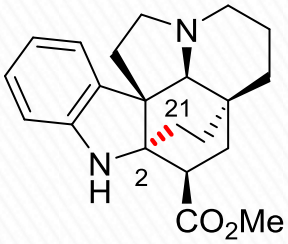


pentacyclic *Aspidosperma* alkaloid skeleton

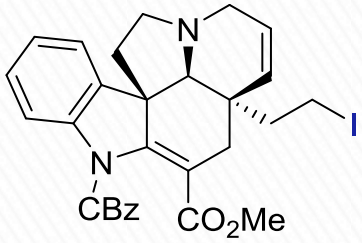
1



4) **(–)-deoxoapodine**



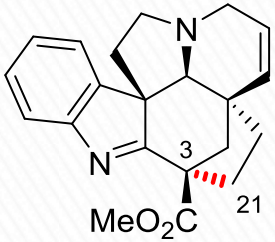
2) **kopsinine**



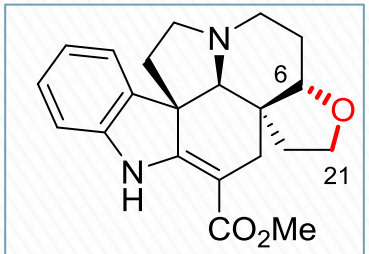
$BF_3 \cdot OEt_2$, Me_2S

then Et_3N

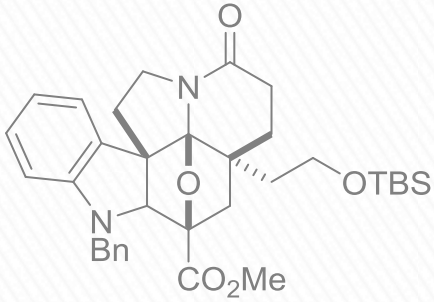
79%



3) **(–)-kopsifoline D**



4) **(–)-deoxoapodine**

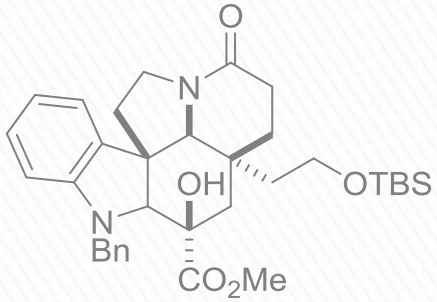


racemic
1

$NaCNBH_3$

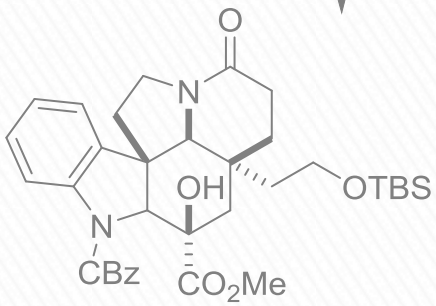
AcOH, *i*-PrOH

88%



1) Ra-Ni, H_2 **92%**

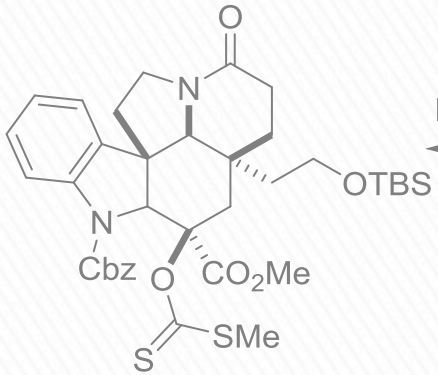
2) $ClCO_2Bn$ **97%**



NaH, CS_2, MeI

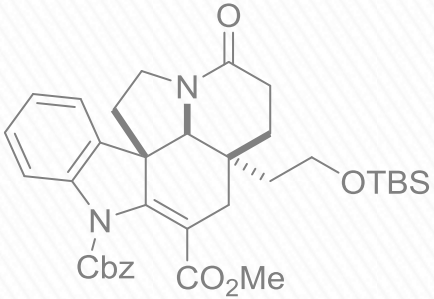
THF

93%



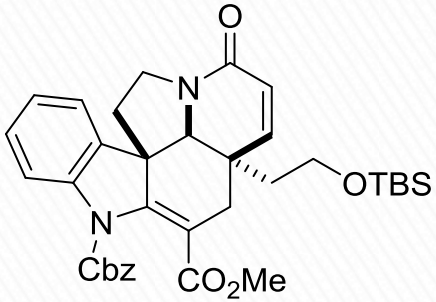
PhMe, 150 °C

60%



1) LDA, PhSeCl **81%**

2) *m*-CPBA **90%**

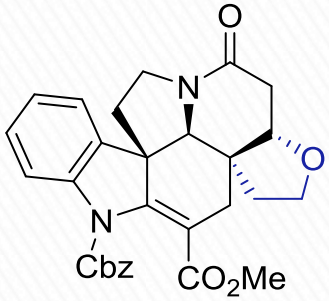


then chiral separation

TBAF

THF, -5 °C

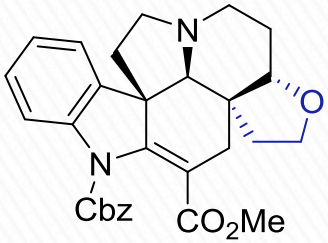
70%

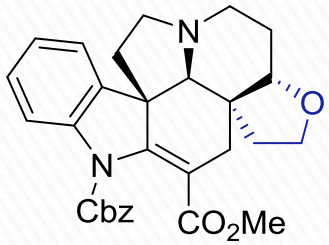


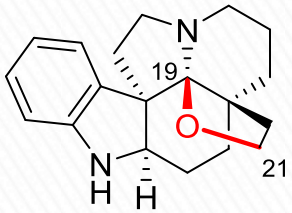
$BH_3 \cdot THF$

THF, 0 °C

70%



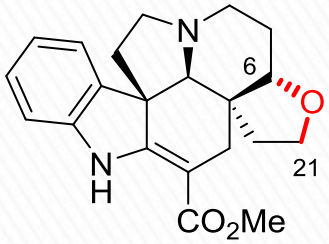




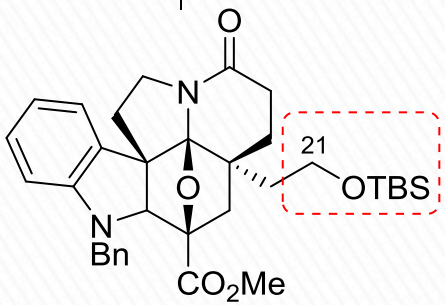
1) **(+)-fendleridine**

$BF_3 \cdot OEt_2$, Me_2S | CH_2Cl_2 **82%**

enantiomeric series

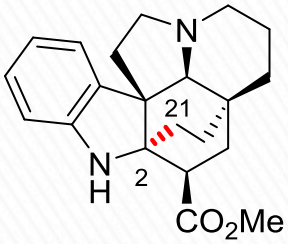


4) **(–)-deoxoapodine**

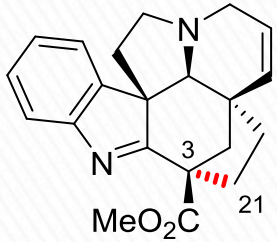


pentacyclic *Aspidosperma* alkaloid skeleton

1



2) **kopsinine**



3) **(–)-kopsifoline D**