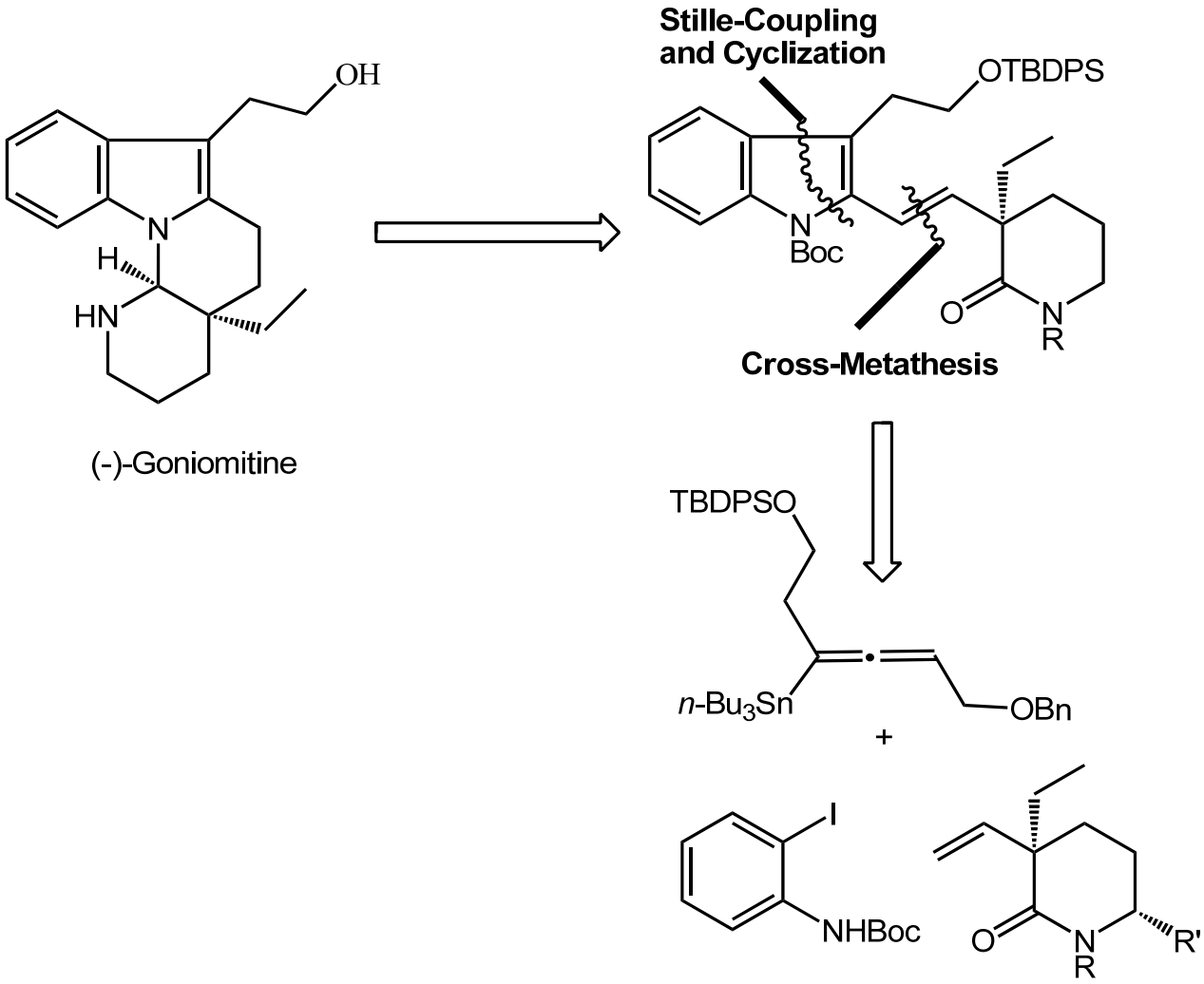
Literature Report

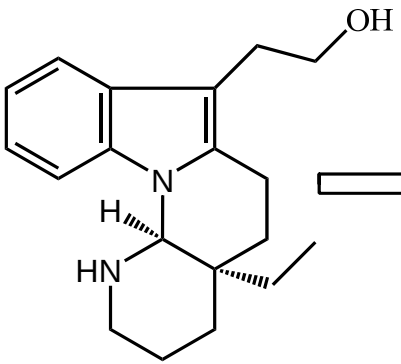
Mu-Wang Chen Checker: Zhi-Shi Ye

Total Synthesis of (-)- and (+)- Goniomitine

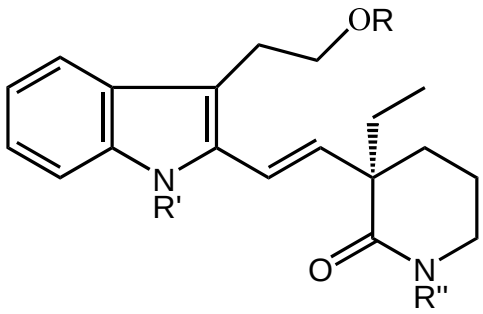
Mukai, C. ***** *et al*
Org. *Lett*. **2011**, *13*, 1796-1799


OH
N
H
HN
(-)-Goniomitine
Stille-Coupling
and Cyclization
OTBDPS
N
Boc
O
N
R
Cross-Metathesis
TBDPSO
n-Bu3Sn
OBn
+
I
NHBoc
O
N
R
R'

Retrosynthesis of (-)-Goninomitine



(-)-Goniomitine (**1**)



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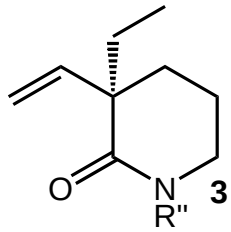

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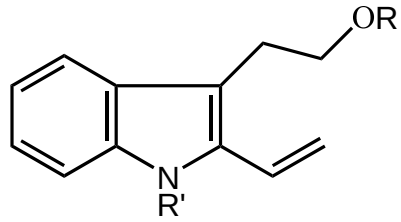
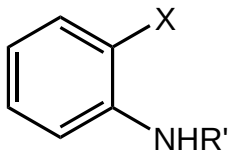
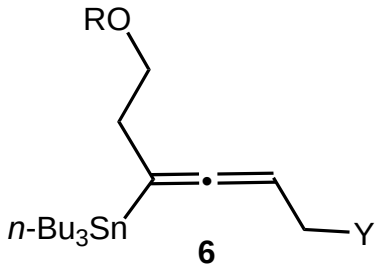


4



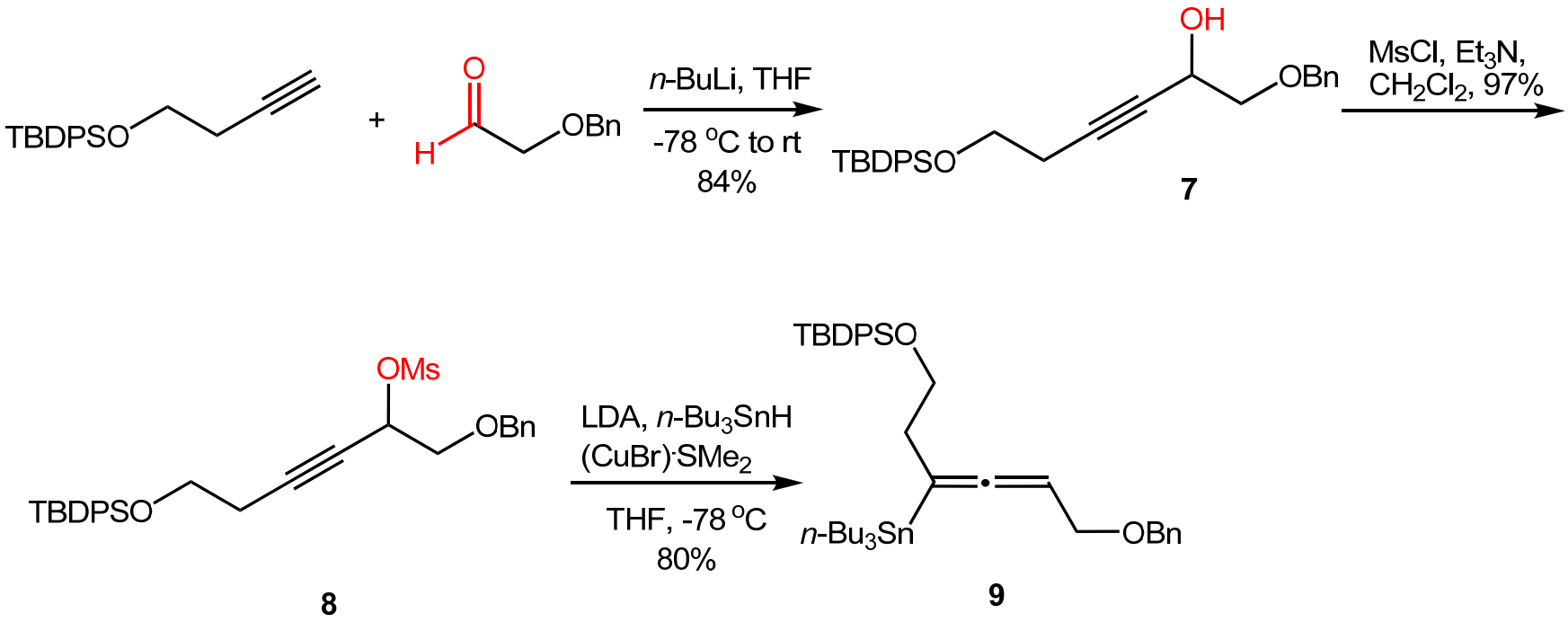
5

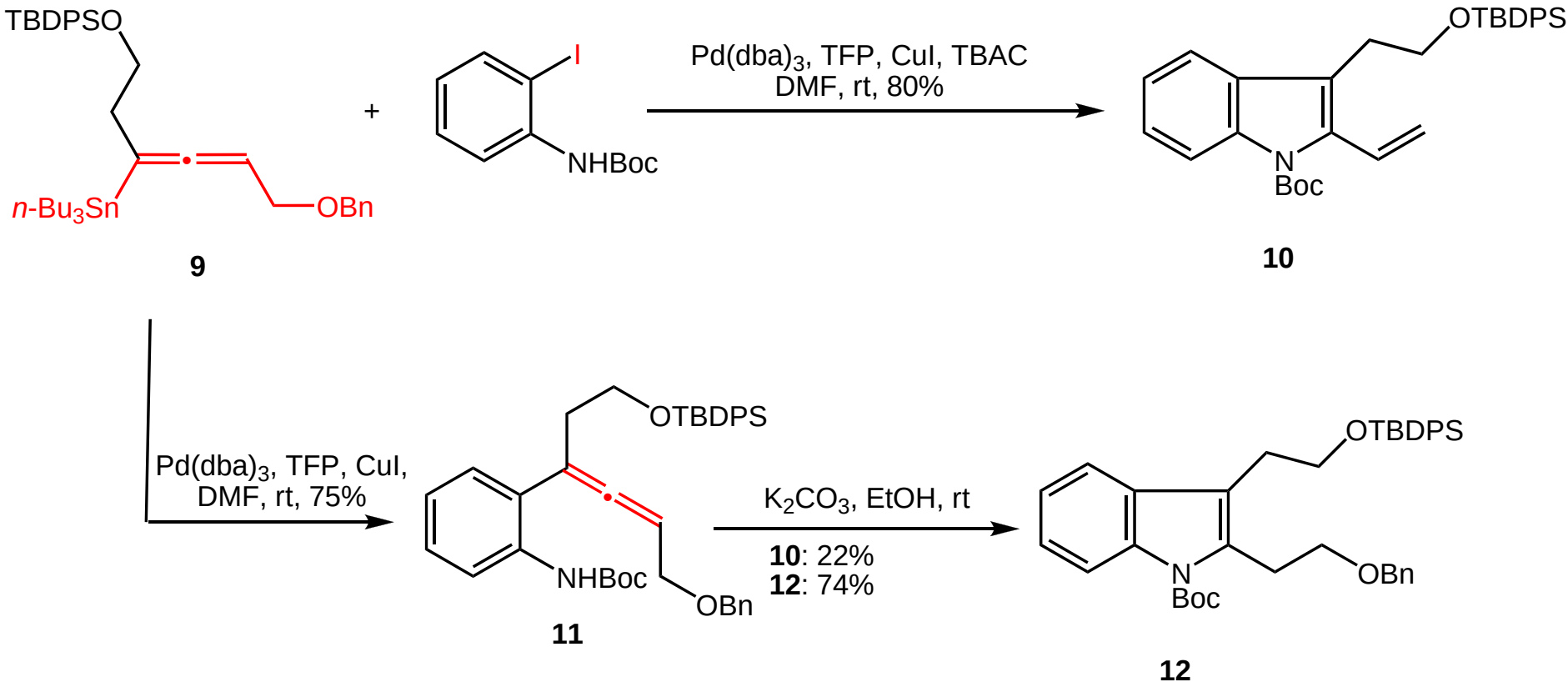
+



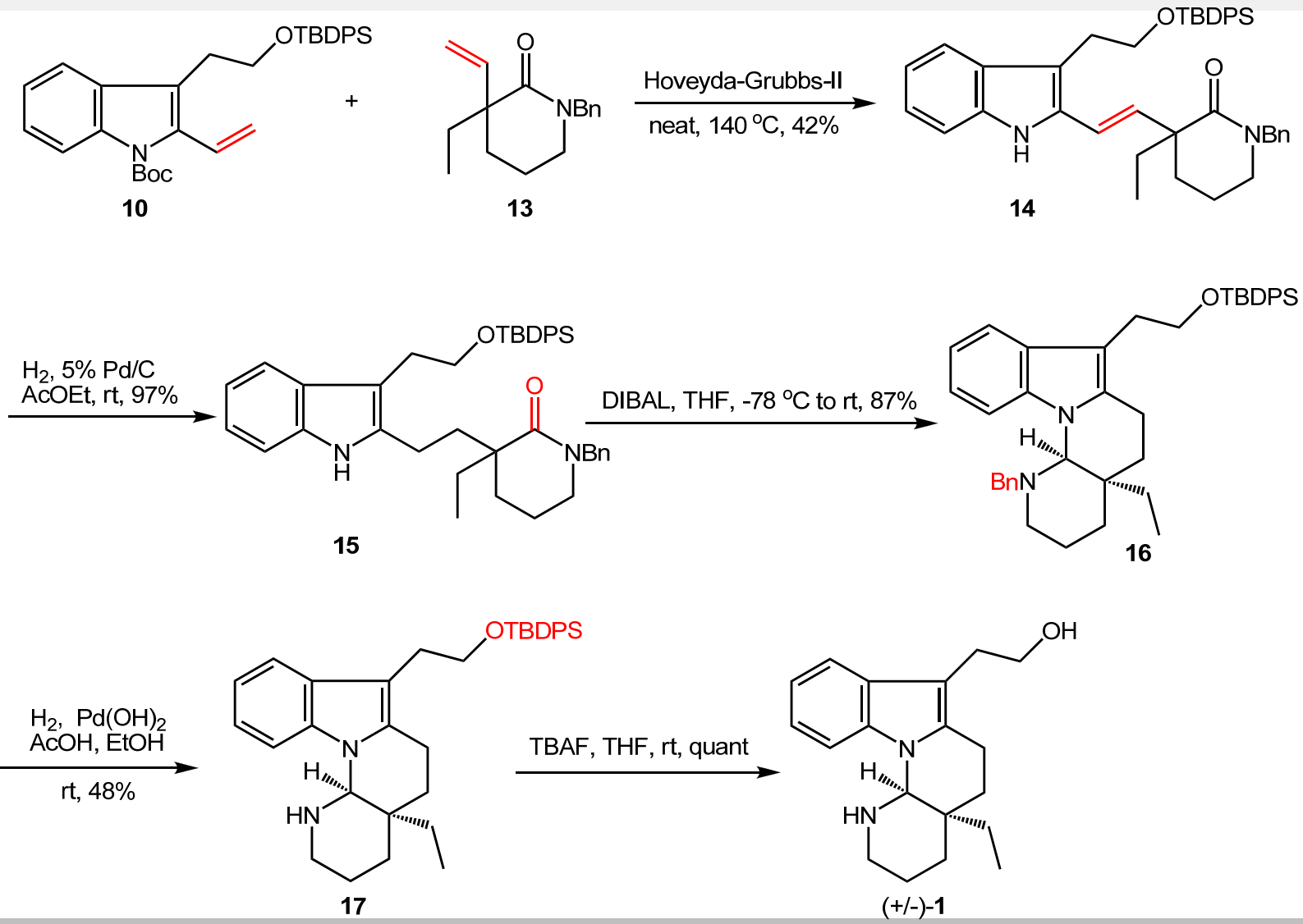
6

Synthesis of 2-Vinylindole Derivative **10**

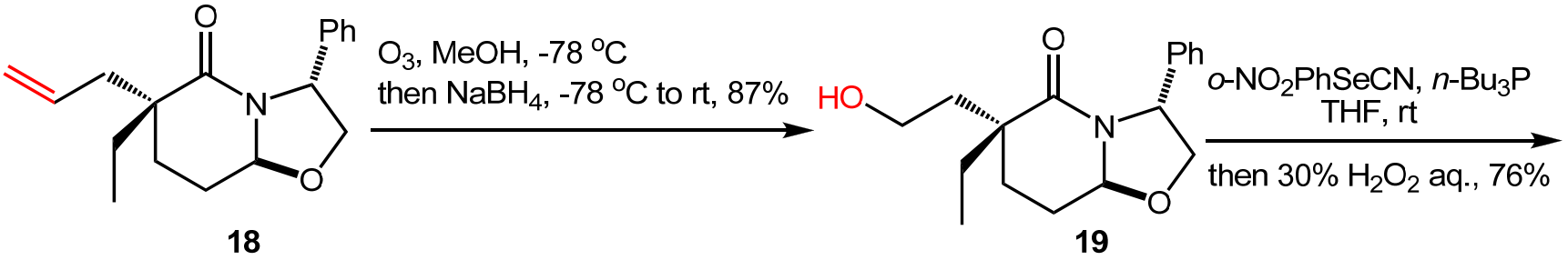


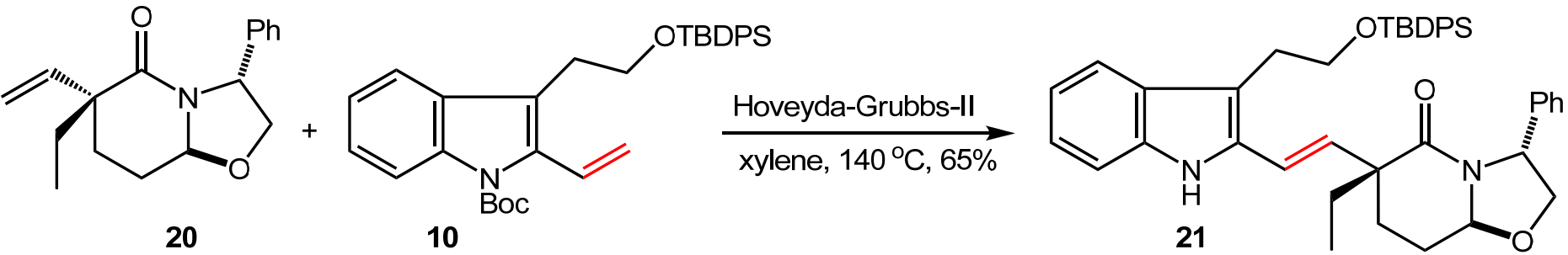

TBDPSO
n-Bu3Sn
OBn
9
+
I
NHBoc
Pd(dba)3, TFP, CuI, TBAC
DMF, rt, 80%
OTBDPS
N
Boc
10
Pd(dba)3, TFP, CuI,
DMF, rt, 75%
OTBDPS
NHBoc
OBn
11
K2CO3, EtOH, rt
10: 22%
12: 74%
OTBDPS
N
Boc
OBn
12

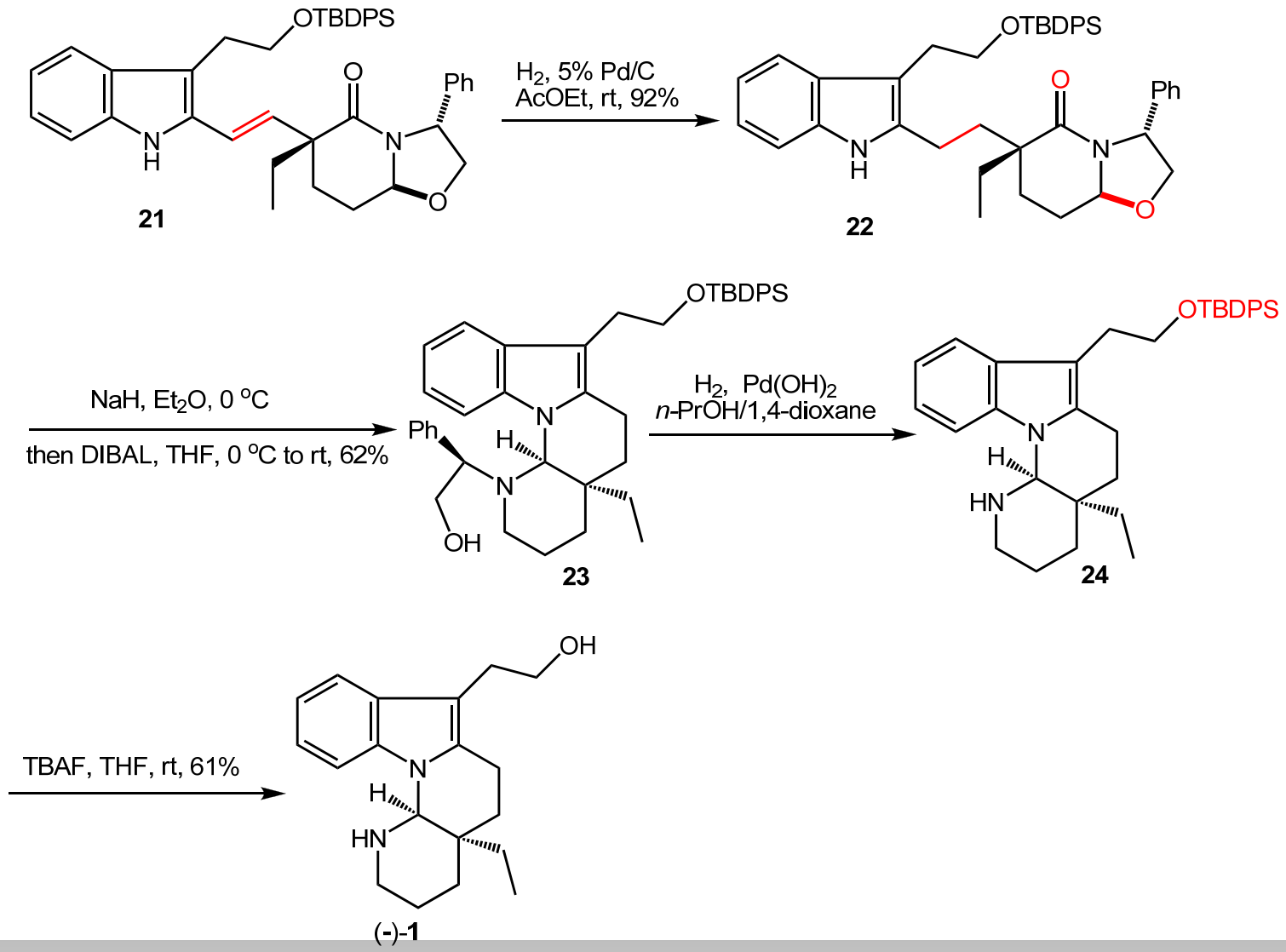
Completion of Total Synthesis of (±)-Goniomitine



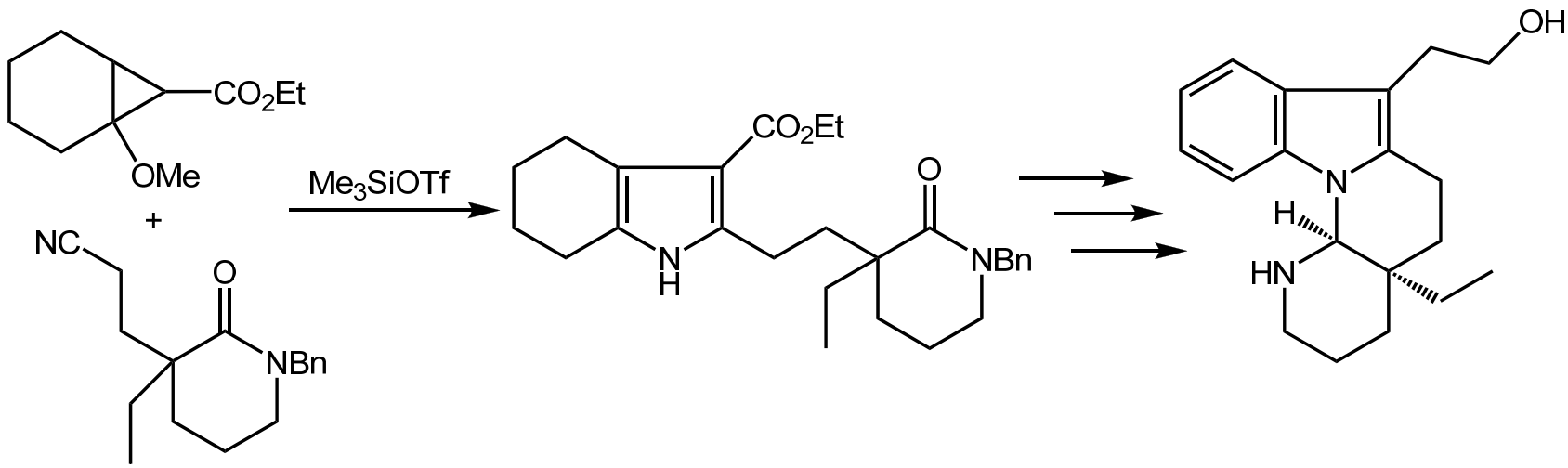
Completion of Total Synthesis of (-)-Goniomitine





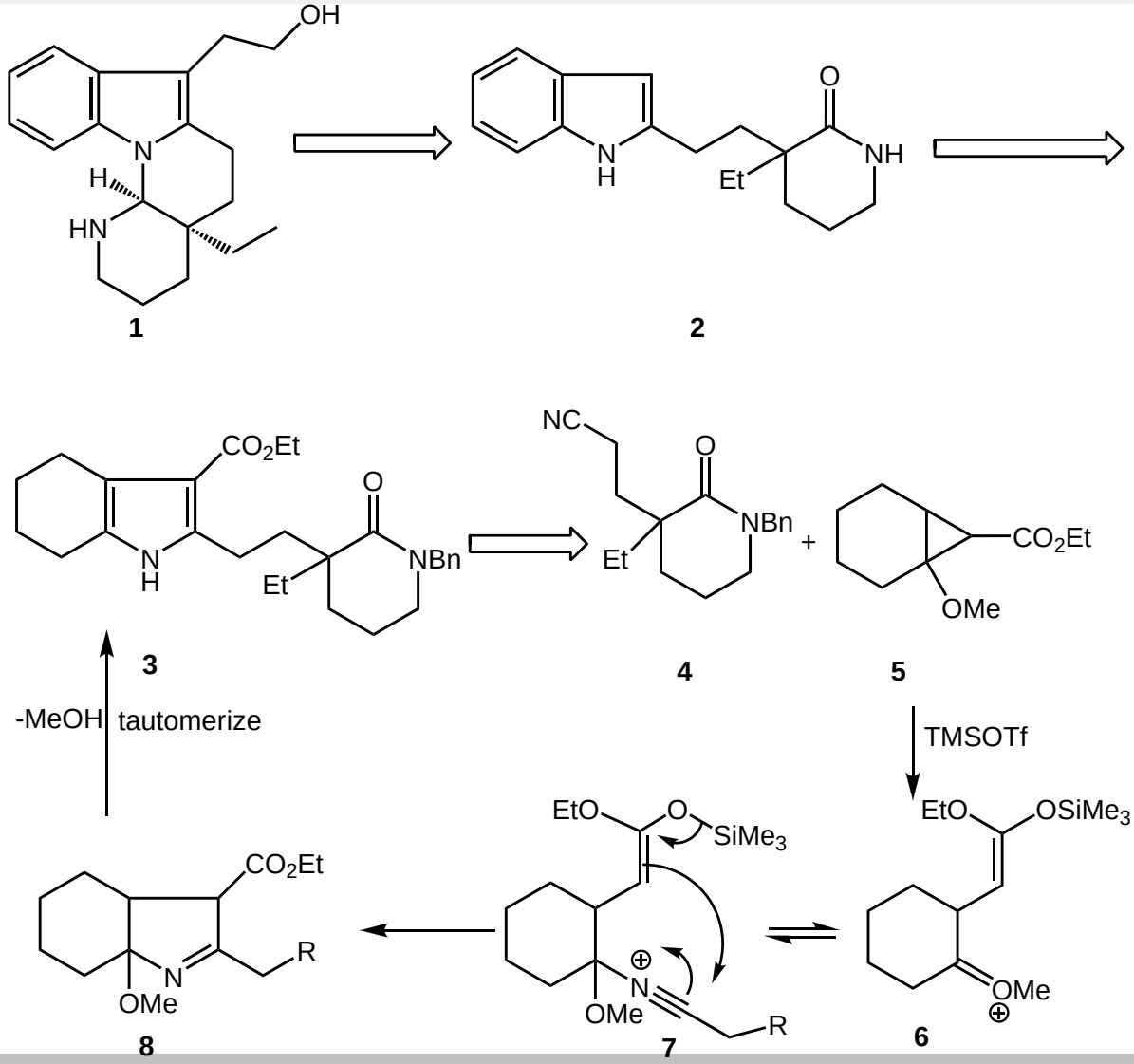

OTBDPS
O
Ph
N
H
N
O
21
H2, 5% Pd/C
AcOEt, rt, 92%
OTBDPS
O
Ph
N
H
N
O
22
NaH, Et2O, 0 °C
then DIBAL, THF, 0 °C to rt, 62%
OTBDPS
Ph
N
H
N
OH
23
H2, Pd(OH)2
n-PrOH/1,4-dioxane
OTBDPS
N
H
HN
24
TBAF, THF, rt, 61%
OH
N
H
HN
(-)-1

Total Synthesis of (±)-Gonimitine via a Formal Nitrile/Donor-Acceptor Cyclopropane [3+2] Cyclization

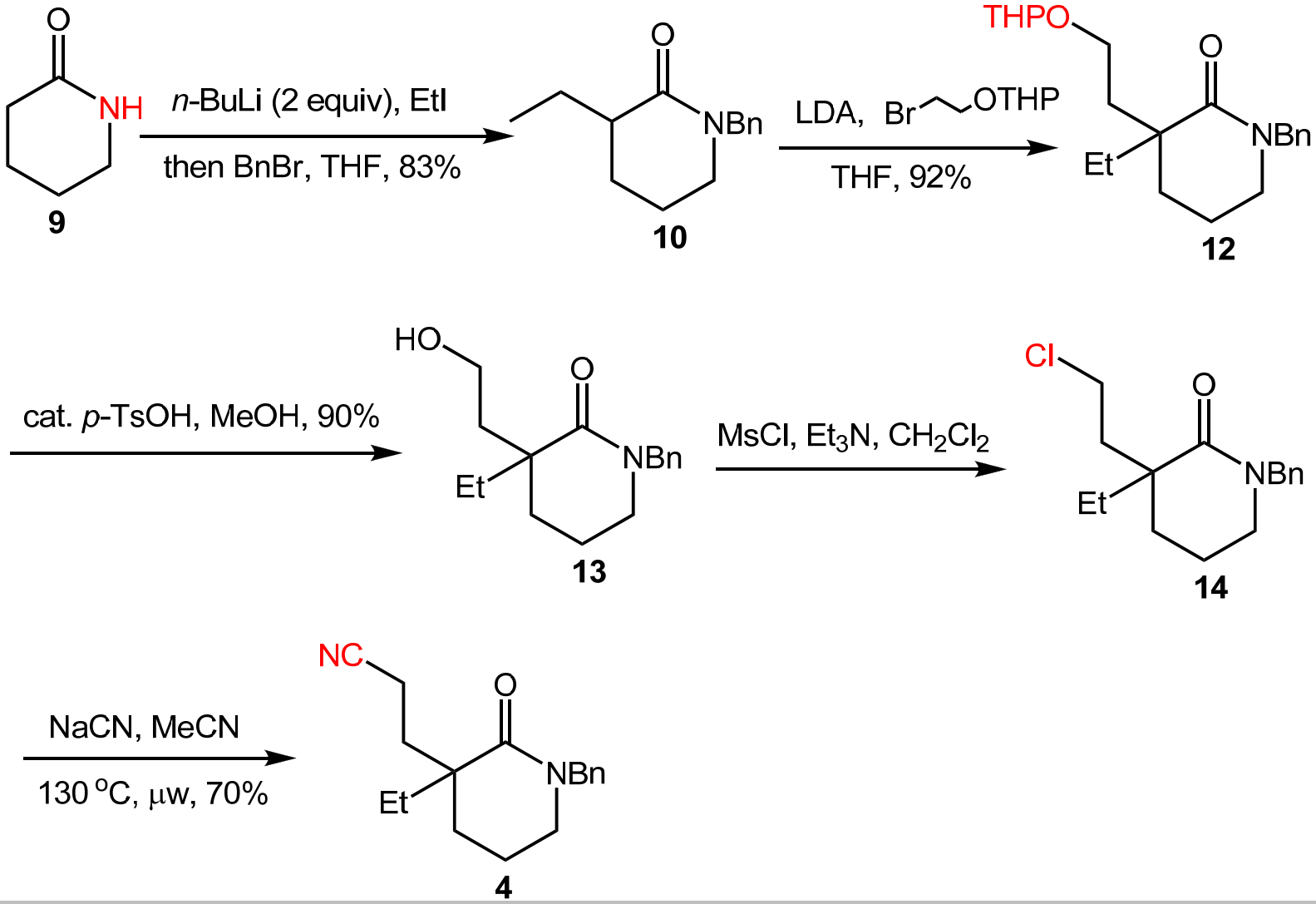


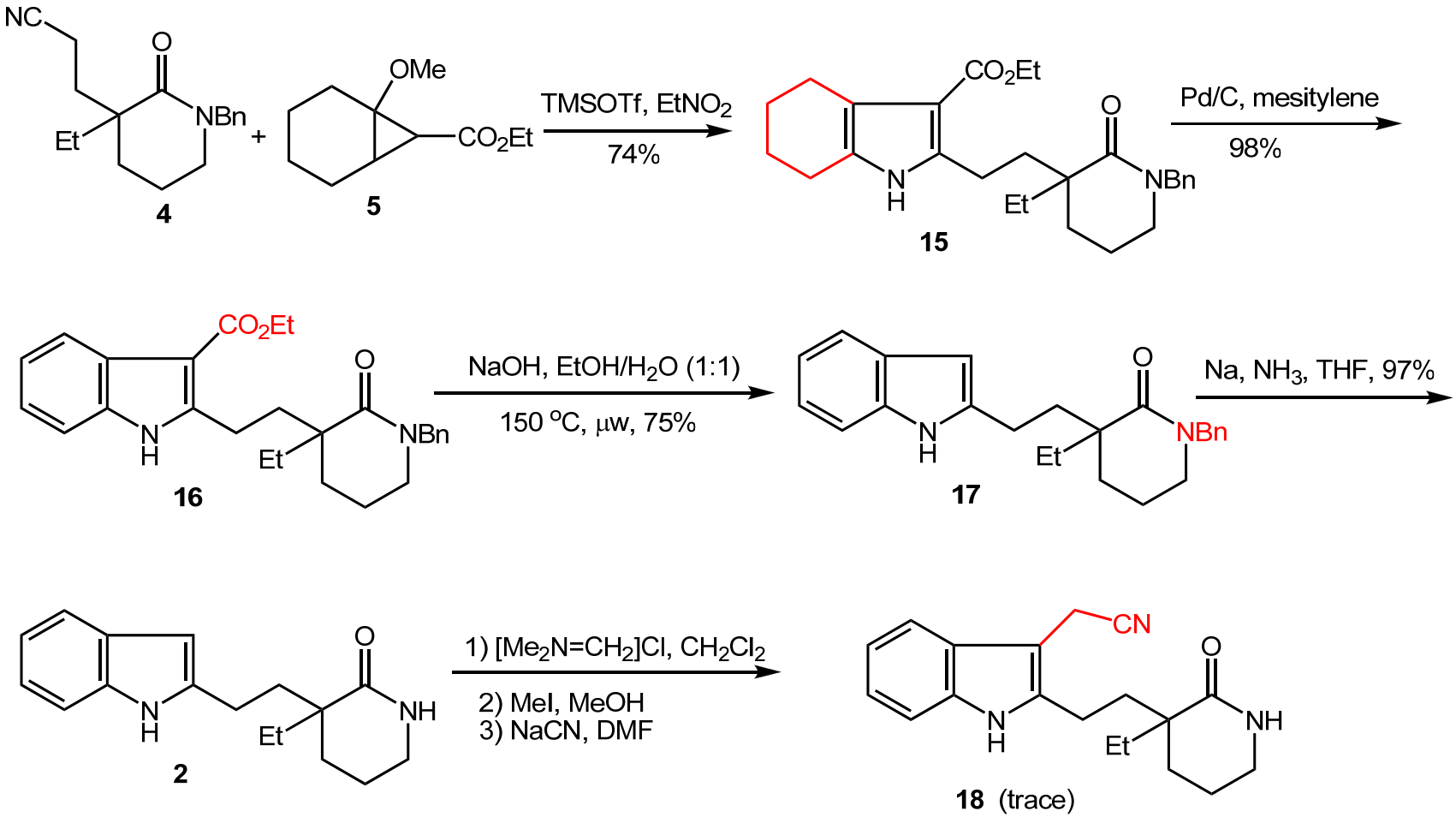
Pagenkopf, B. L.***** *et al* *Org*. *Lett*. **2008**, *10*, 157-159.

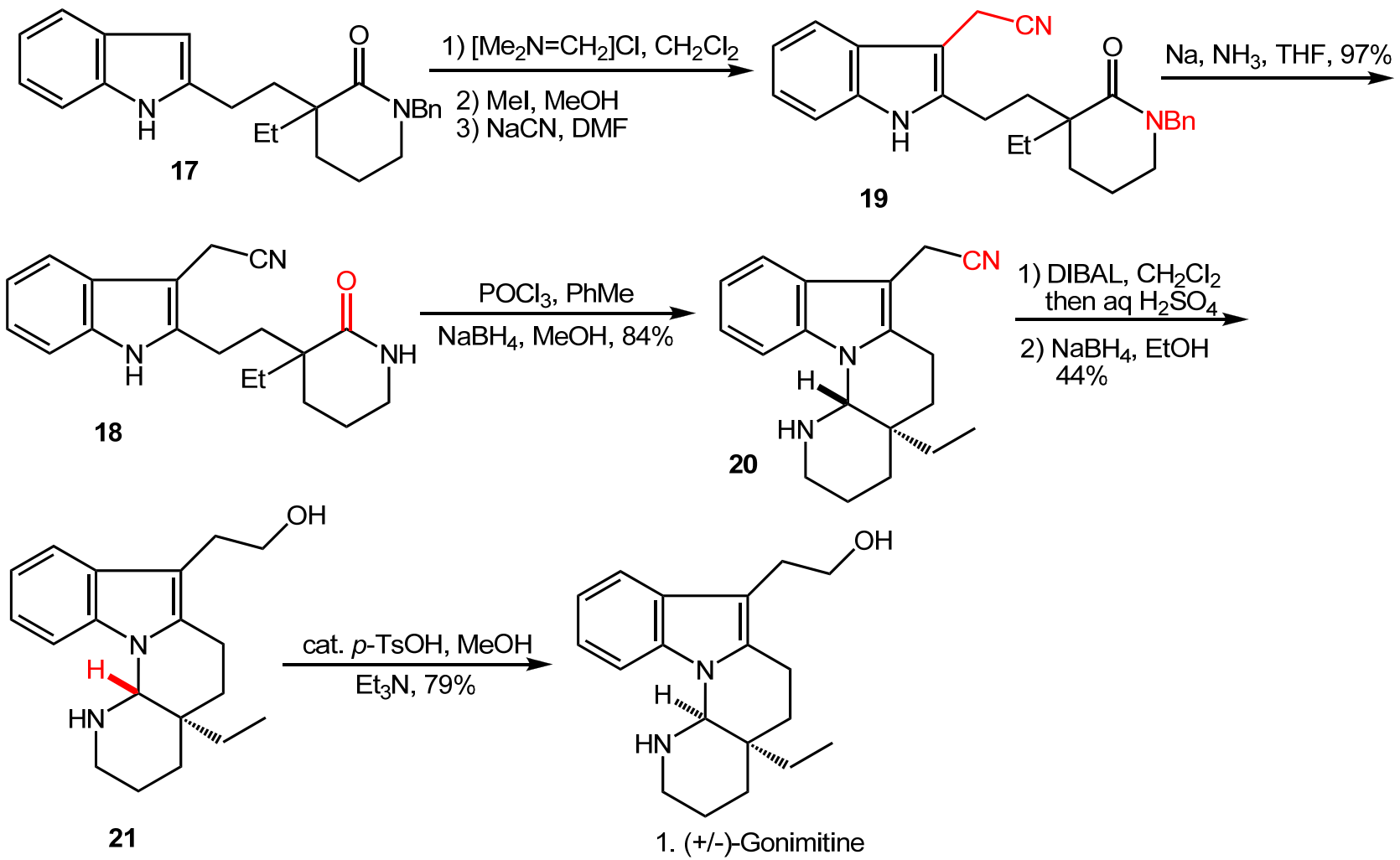
Retrosynthetic Analysis



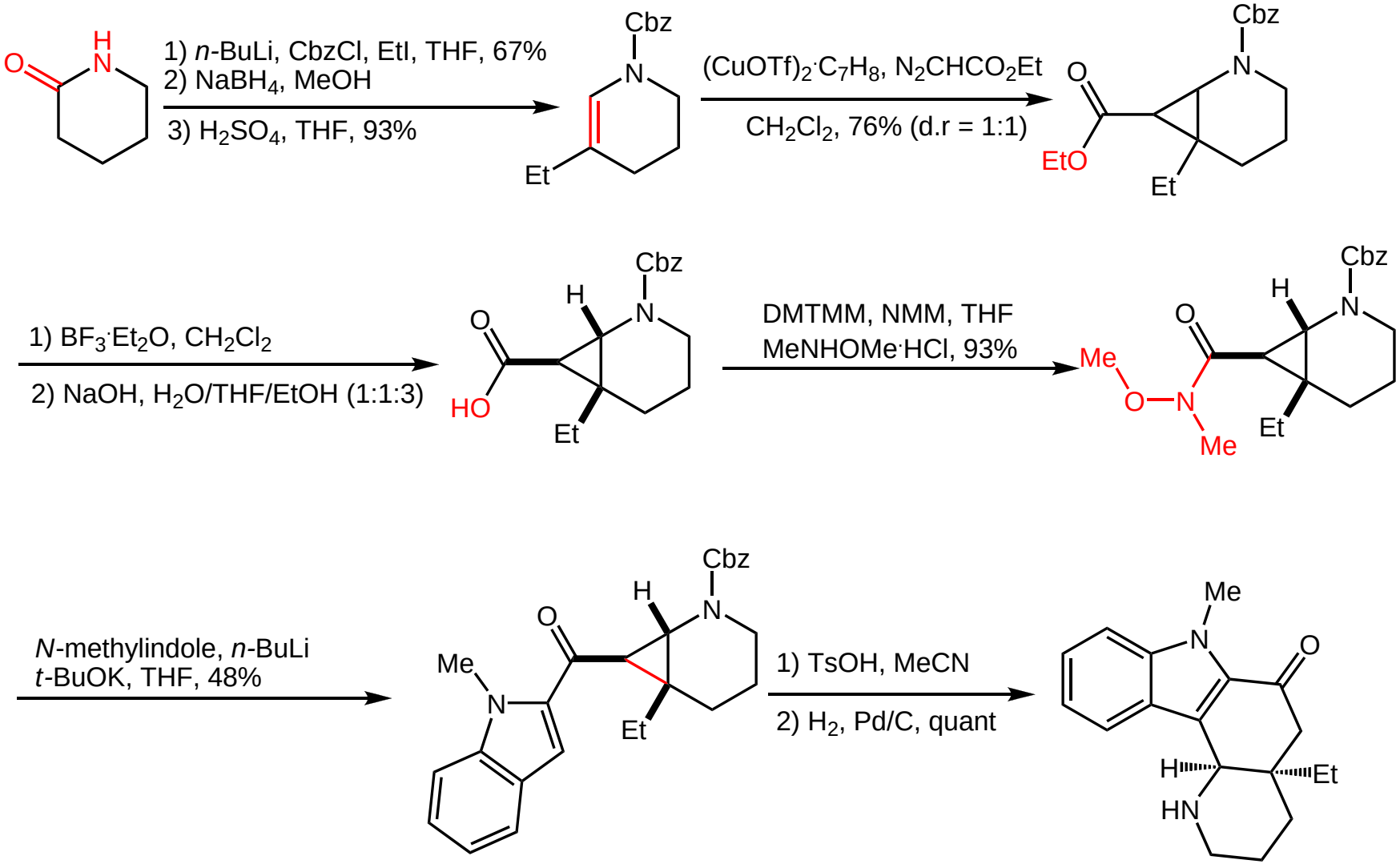
Synthesis of Nitrile **4**



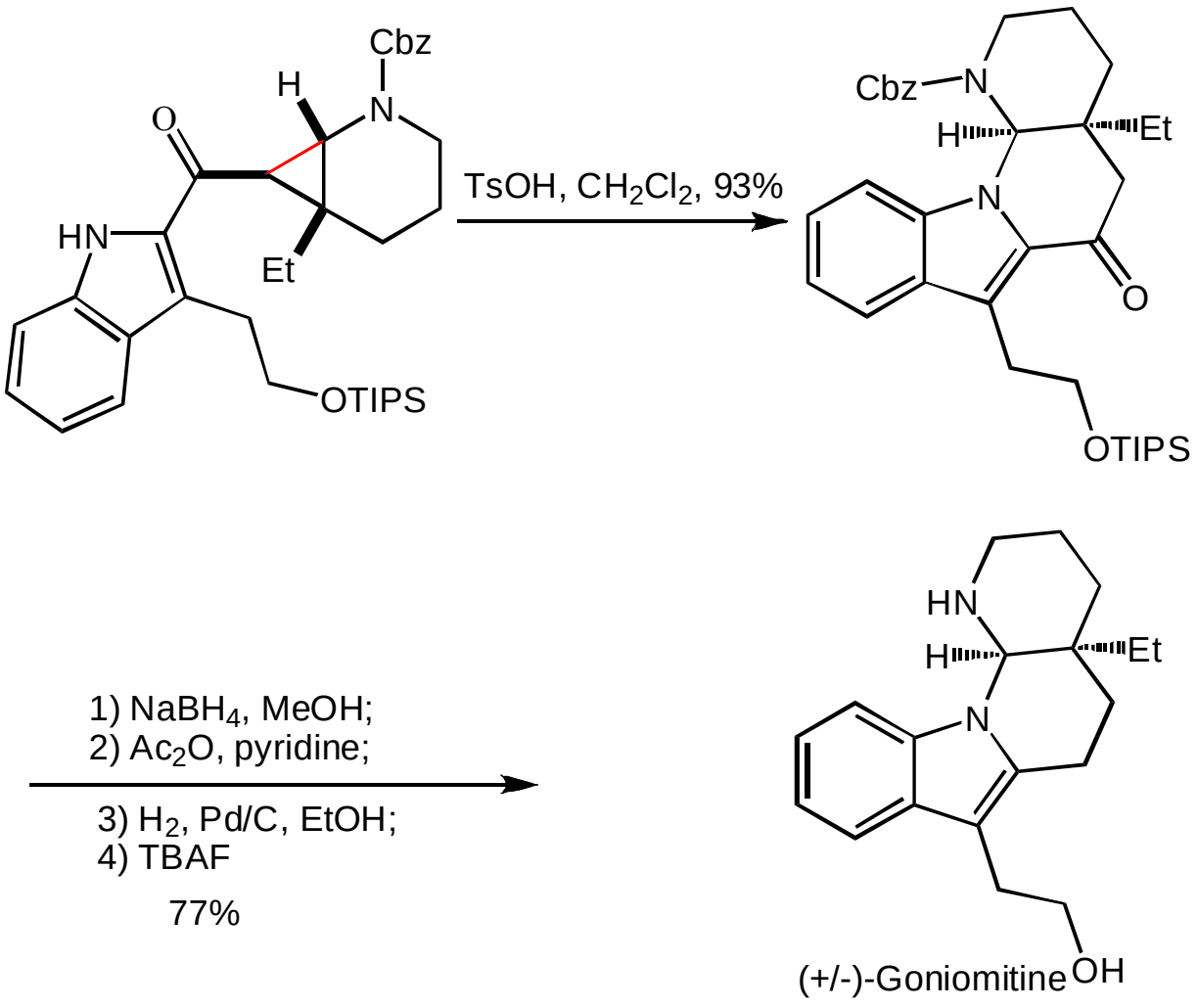

NC
O
NBn
Et
4
+
OMe
CO2Et
5
TMSOTf, EtNO2
74%
CO2Et
O
N
H
NBn
Et
15
Pd/C, mesitylene
98%
CO2Et
O
N
H
NBn
Et
16
NaOH, EtOH/H2O (1:1)
150 °C, μw, 75%
O
N
H
NBn
Et
17
Na, NH3, THF, 97%
O
N
H
NH
Et
2
1) [Me2N=CH2]Cl, CH2Cl2
2) MeI, MeOH
3) NaCN, DMF
CN
O
N
H
NH
Et
18 (trace)


1) [Me2N=CH2]Cl, CH2Cl2
2) MeI, MeOH
3) NaCN, DMF
Na, NH3, THF, 97%
17
19
18
POCl3, PhMe
NaBH4, MeOH, 84%
20
1) DIBAL, CH2Cl2
then aq H2SO4
2) NaBH4, EtOH
44%
21
cat. p-TsOH, MeOH
Et3N, 79%
1. (+/-)-Gonimitine

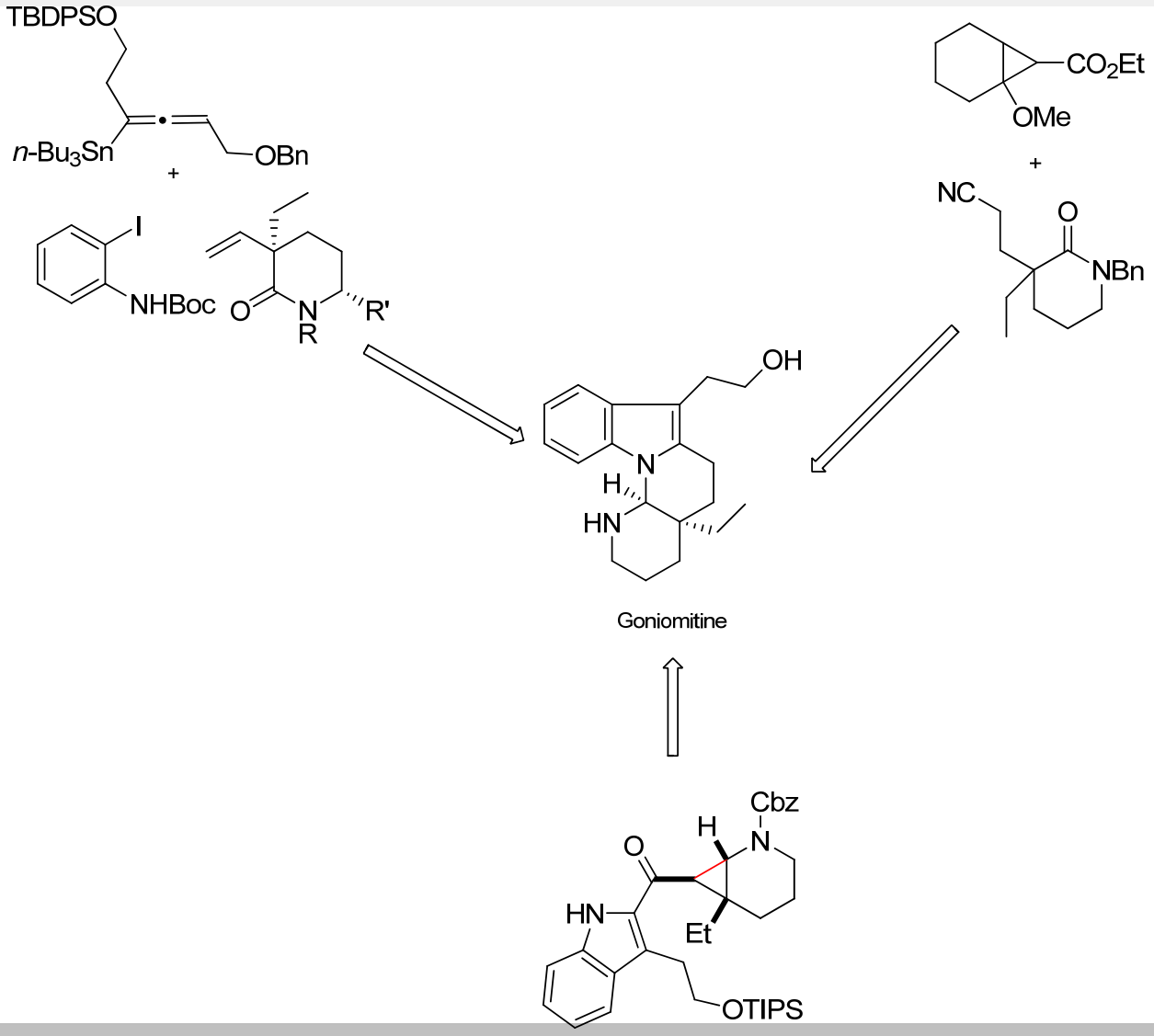
Catalytic Selective Cyclizations of Aminocyclopropanes: Formal Synthesis of Aspidospermidine and Total Synthesis of Goniomitine



Waser, J. * *et al* *Angew.Chem. Int. Ed*. **2010**, *49*, 5767-5770.


Cbz
H
N
O
HN
Et
OTIPS
TsOH, CH_2Cl_2, 93%
Cbz
N
H
Et
N
O
OTIPS
1) $NaBH_4$, MeOH;
2) Ac_2O, pyridine;
3) H_2, Pd/C, EtOH;
4) TBAF
77%
HN
H
Et
N
(+/-)-Goniomitine
OH

summarize


TBDPSO
n-Bu3Sn
OBn
+
I
NHBoc
O
N
R
R'
CO2Et
OMe
+
NC
O
NBn
OH
N
H
HN
Goniomitine
Cbz
H
N
O
HN
Et
OTIPS

(-)-Goniomitine (1), isolated from the root bark of *Gonioma malagasy* in 1987, is a significantly unique member of the Aspidosperma indole alkaloid family. In 1991, Takano and Ogasawara reported the first total synthesis of this intriguing alkaloid in an optically active form from dicyclopentadiene in 28 steps. The recent independent records from Pagenkopf's and Waser's laboratories showed two additional efficient total syntheses of goniomitine in a racemic form: Pagenkopf's synthesis involved the formal [3 + 2] cycloaddition between the nitrile and cyclopropane derivatives as the crucial step, whereas Waser and co-workers successfully took advantage of the selective cyclization of amino-cyclopropane.

In summary, the total syntheses of the natural (-)-goniomitine and unnatural (+)-goniomitine were attained (in 10 steps from the commercially available 3-butyn-1-ol or 13 steps from the commercially available δ-valerolactone) in a highly stereoselective manner by taking advantage of our procedure for the preparation of 2-vinylindole, followed by its cross-metathesis with the chiral oxazolopiperidone derivative. Furthermore, natural (-)-goniomitine was found to have stronger antiproliferative activity in Mock and MDCK/MDR1 cells than its enantiomer.