Total Synthesis of *Akuammiline* Alkaloid (-)-Vincorine via Intramolecular Oxidative Coupling

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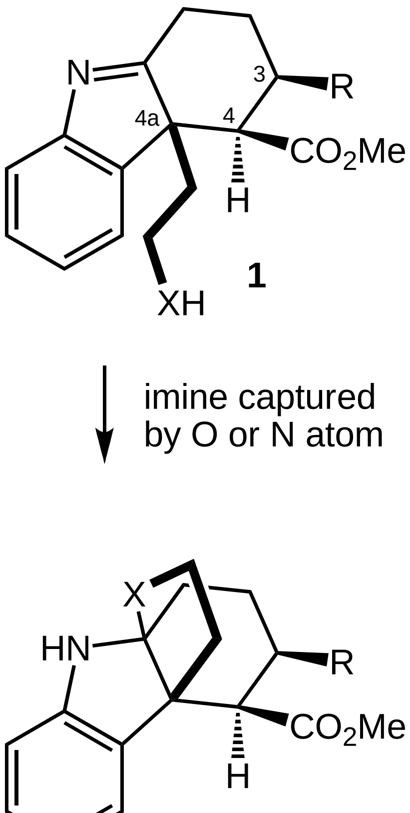
Checker : Ran-Ning Guo

Date: 2012/7/17

Ma, D. et al *J. Am. Chem. Soc.* **2012**, *134*, 9126

目录

1. 简介

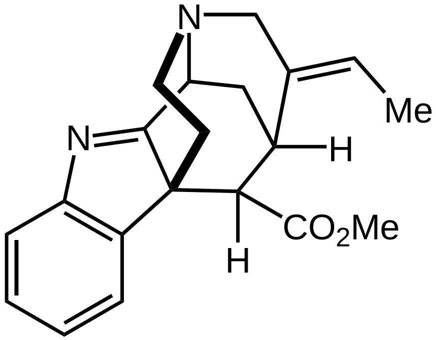


1

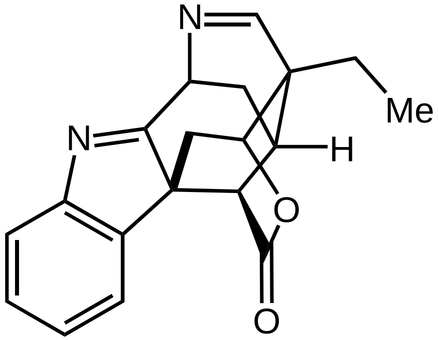
imine captured
by O or N atom

2

R = alkenyl chain
X = NH or O

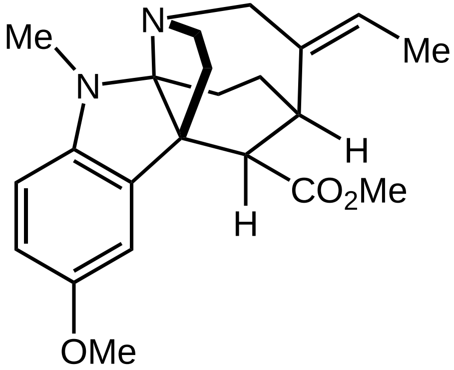


Strictamine (**3**)



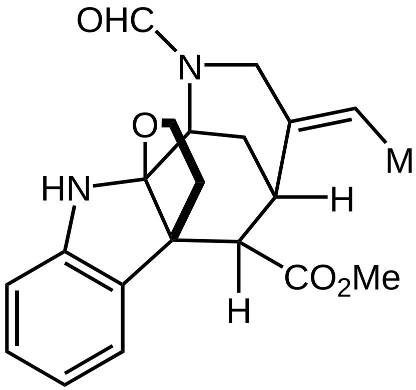
Scholarisine A (**4**)

Smith, A. B. et al *J. Am. Chem. Soc.* **2012**, *134*, 4037



Vincorine (**5**)

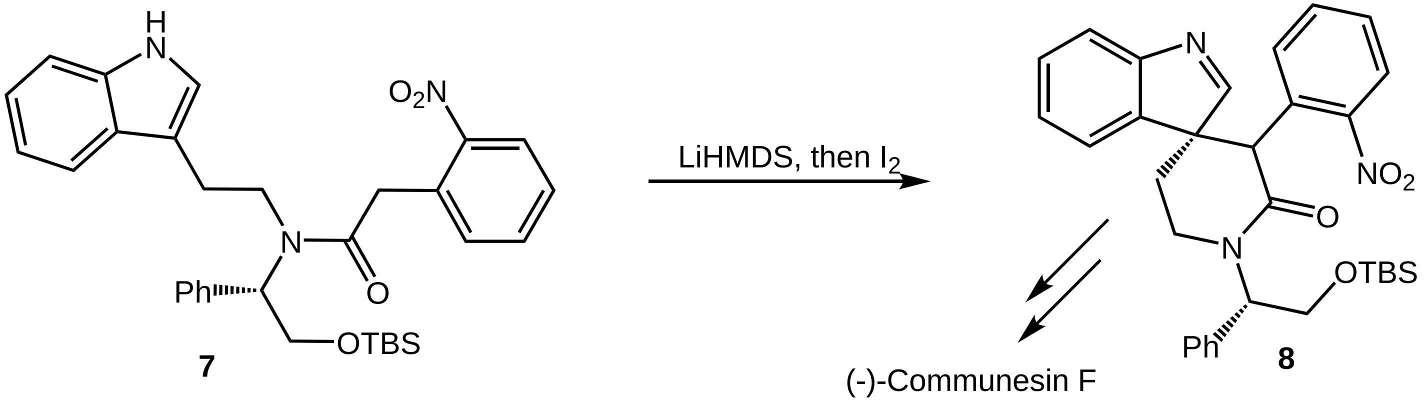
Qin, Y. et al *J. Am. Chem. Soc.* **2009**, *131*, 6013



Aspidophylline A (**6**)

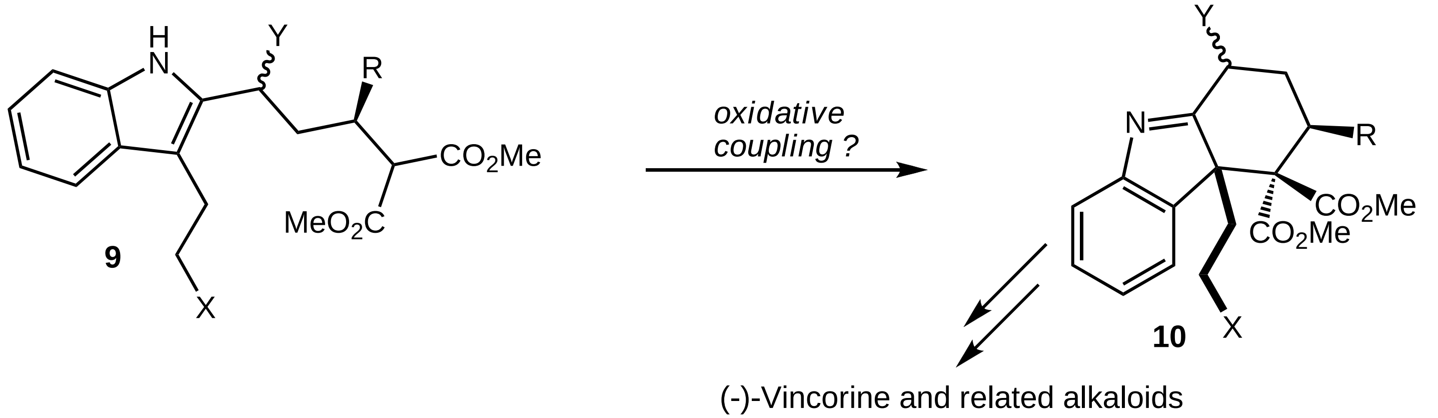
Garg, N. K. et al *J. Am. Chem. Soc.* **2011**, *133*, 8877

Type 1 oxidative coupling (previous work)

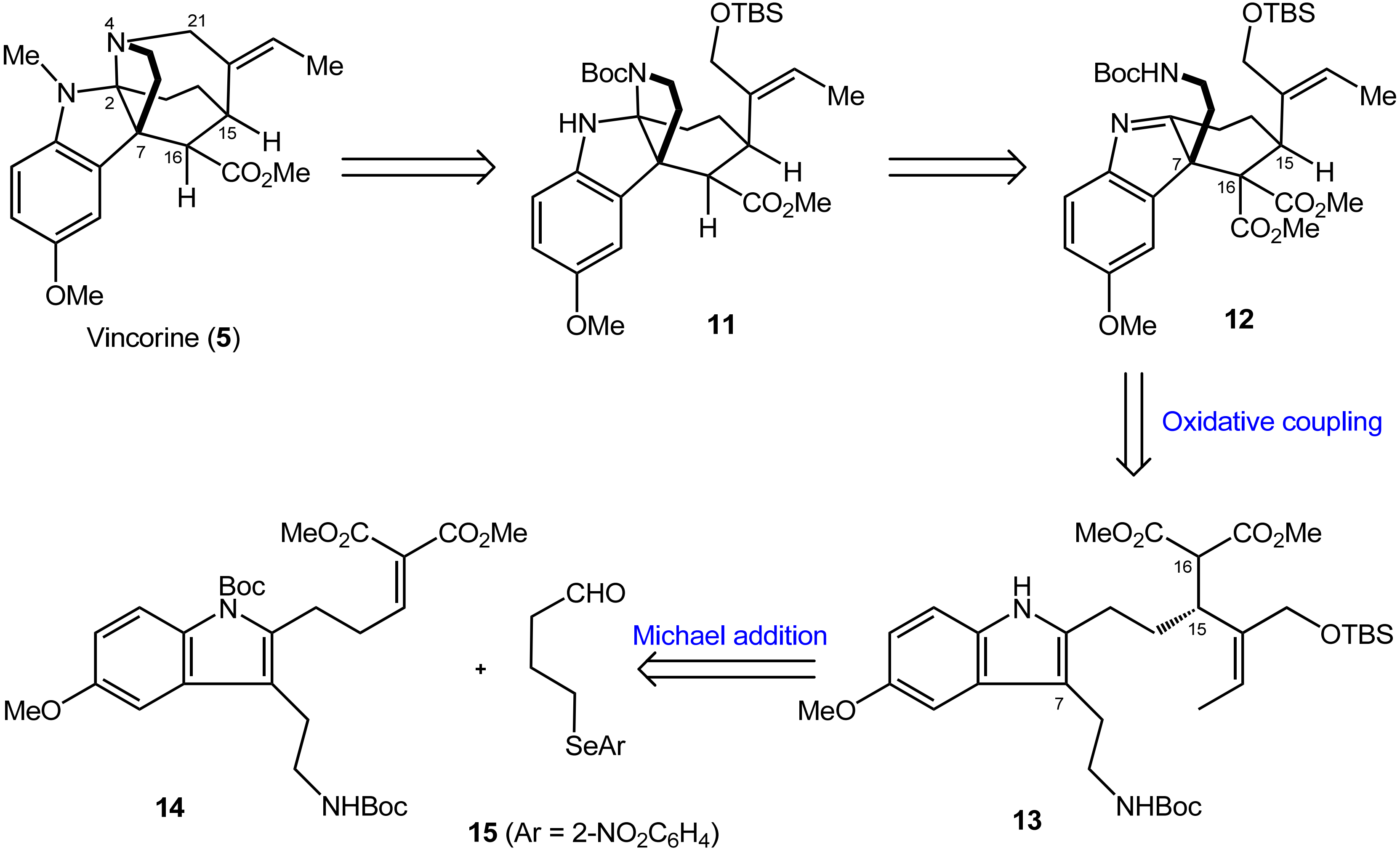


Ma, D. et al *J. Am. Chem. Soc.* **2010**, *132*, 13226
Angew. Chem. Int. Ed. **2011**, *20*, 12008

Type 2 oxidative coupling (this work)



2. 反合成分析



Vincorine (**5**)

11

12

Oxidative coupling

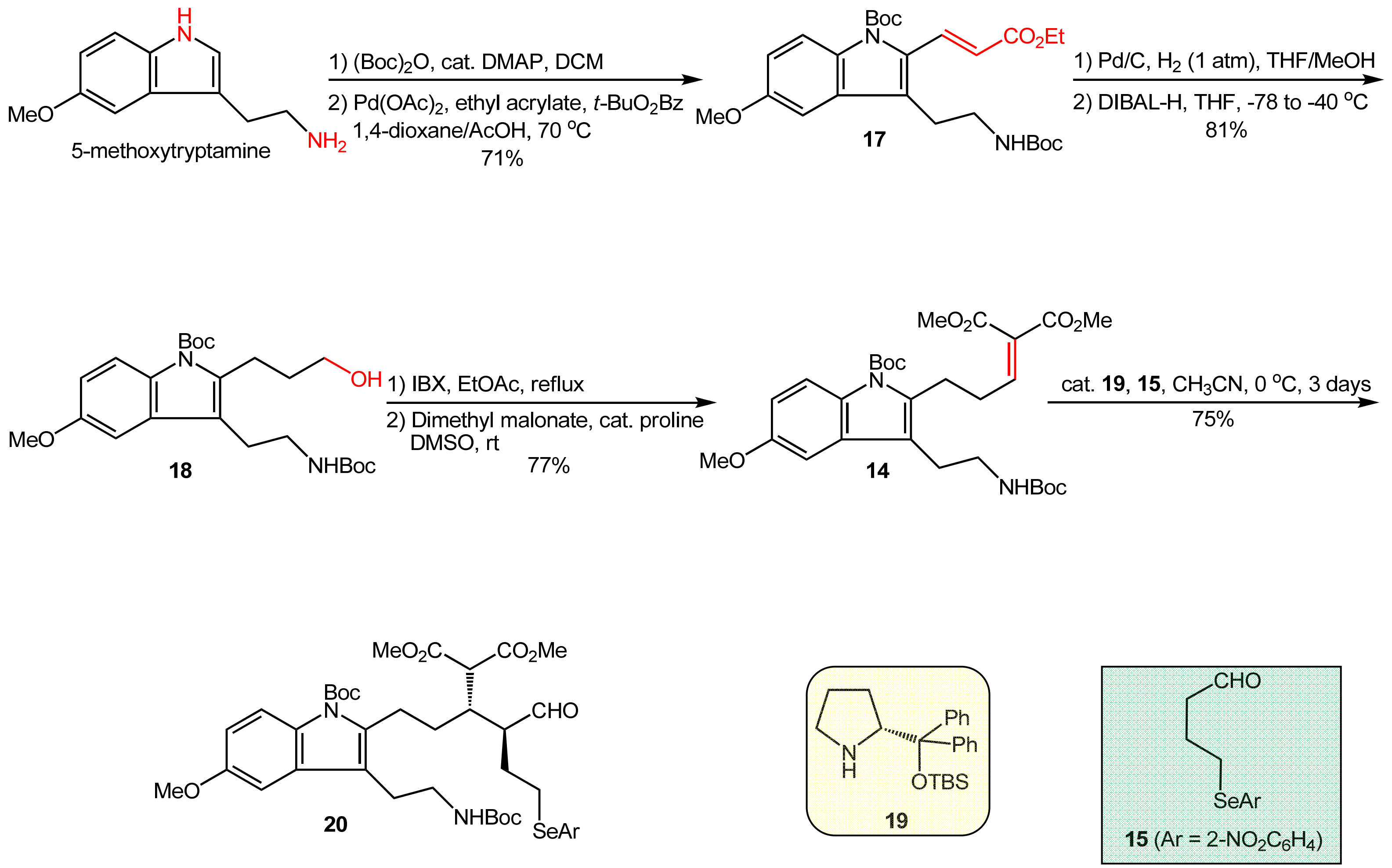
13

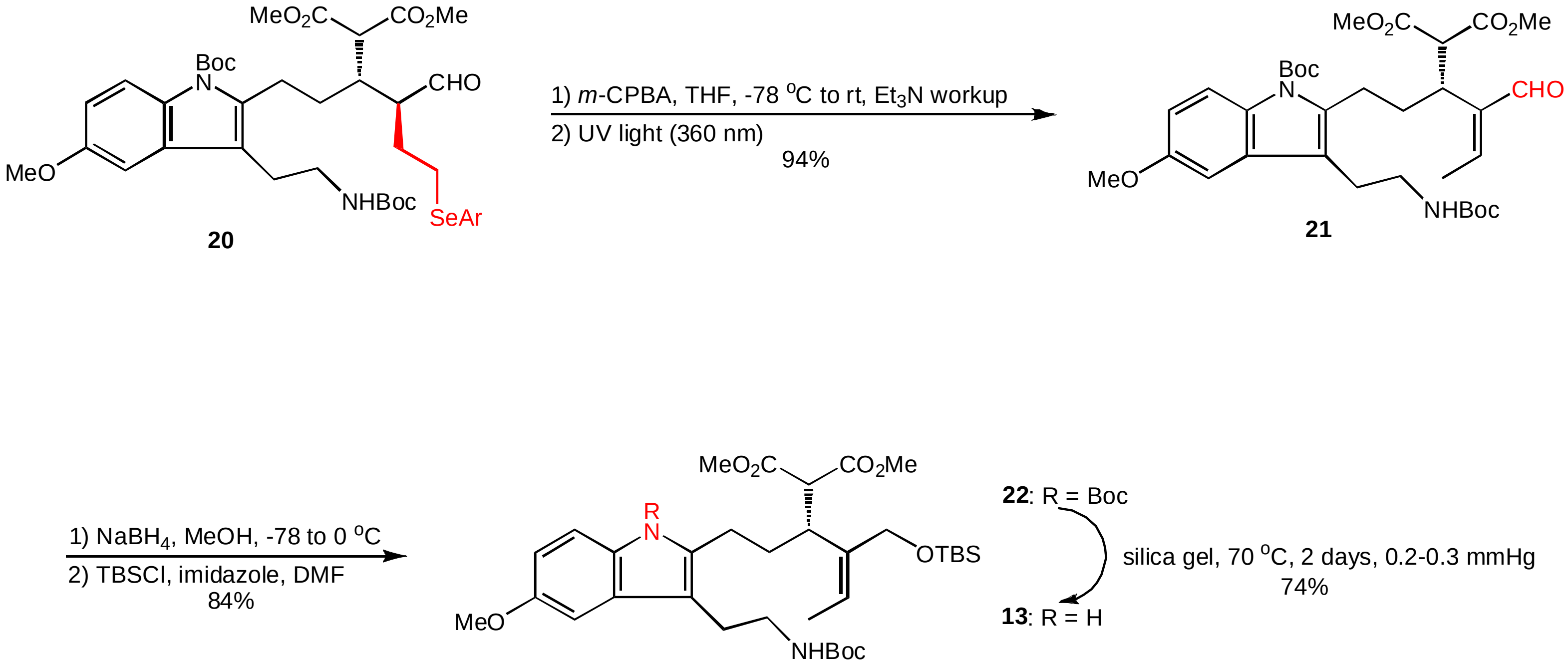
Michael addition

14

15 (Ar = 2-$NO_2C_6H_4$)

3. (-)-Vincorine的合成





20

1) *m*-CPBA, THF, -78 ^{o}C to rt, Et_3N workup

2) UV light (360 nm)

94%

21

1) $NaBH_4$, MeOH, -78 to 0 ^{o}C

2) TBSCl, imidazole, DMF

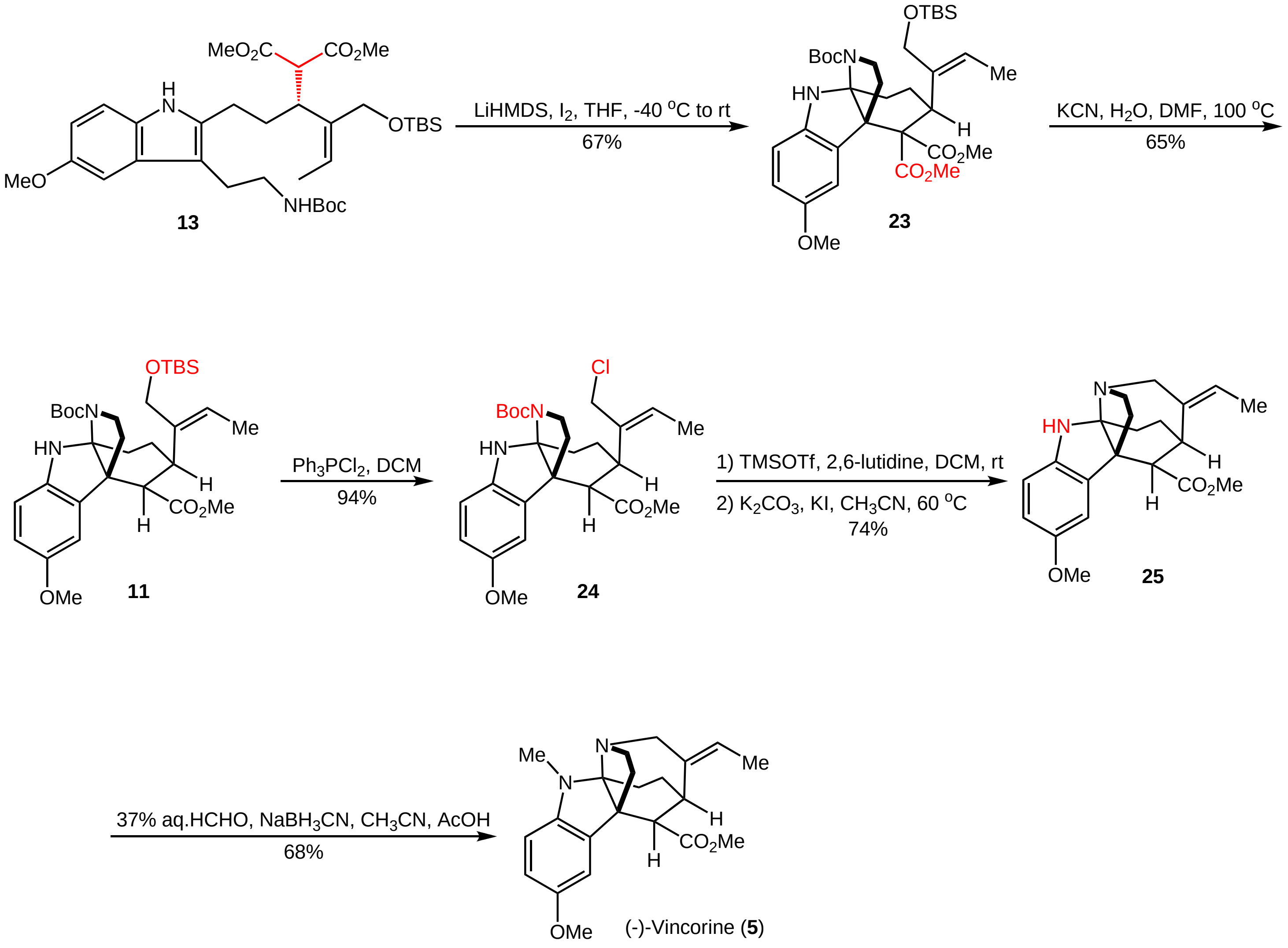
84%

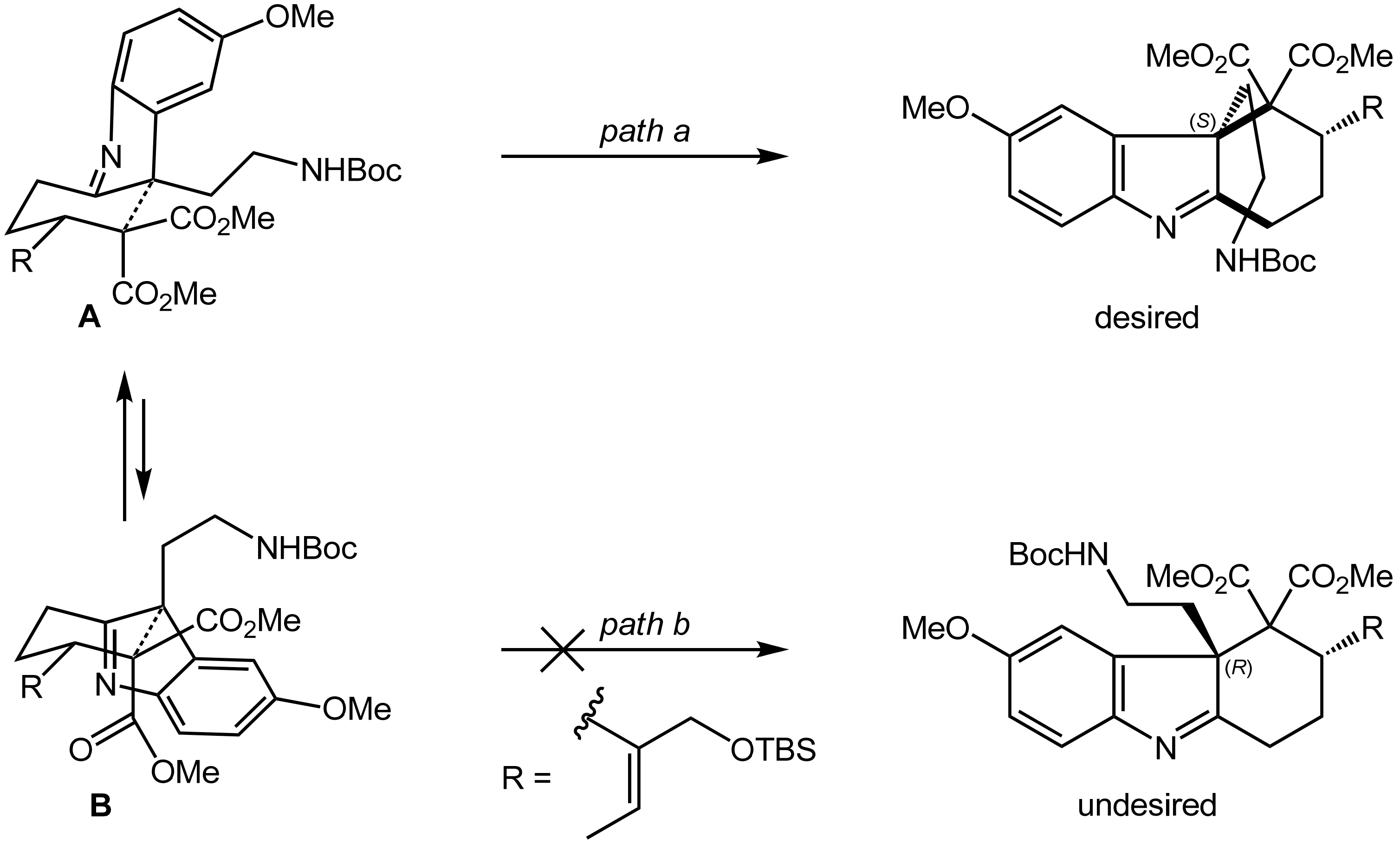
22: R = Boc

silica gel, 70 ^{o}C, 2 days, 0.2-0.3 mmHg

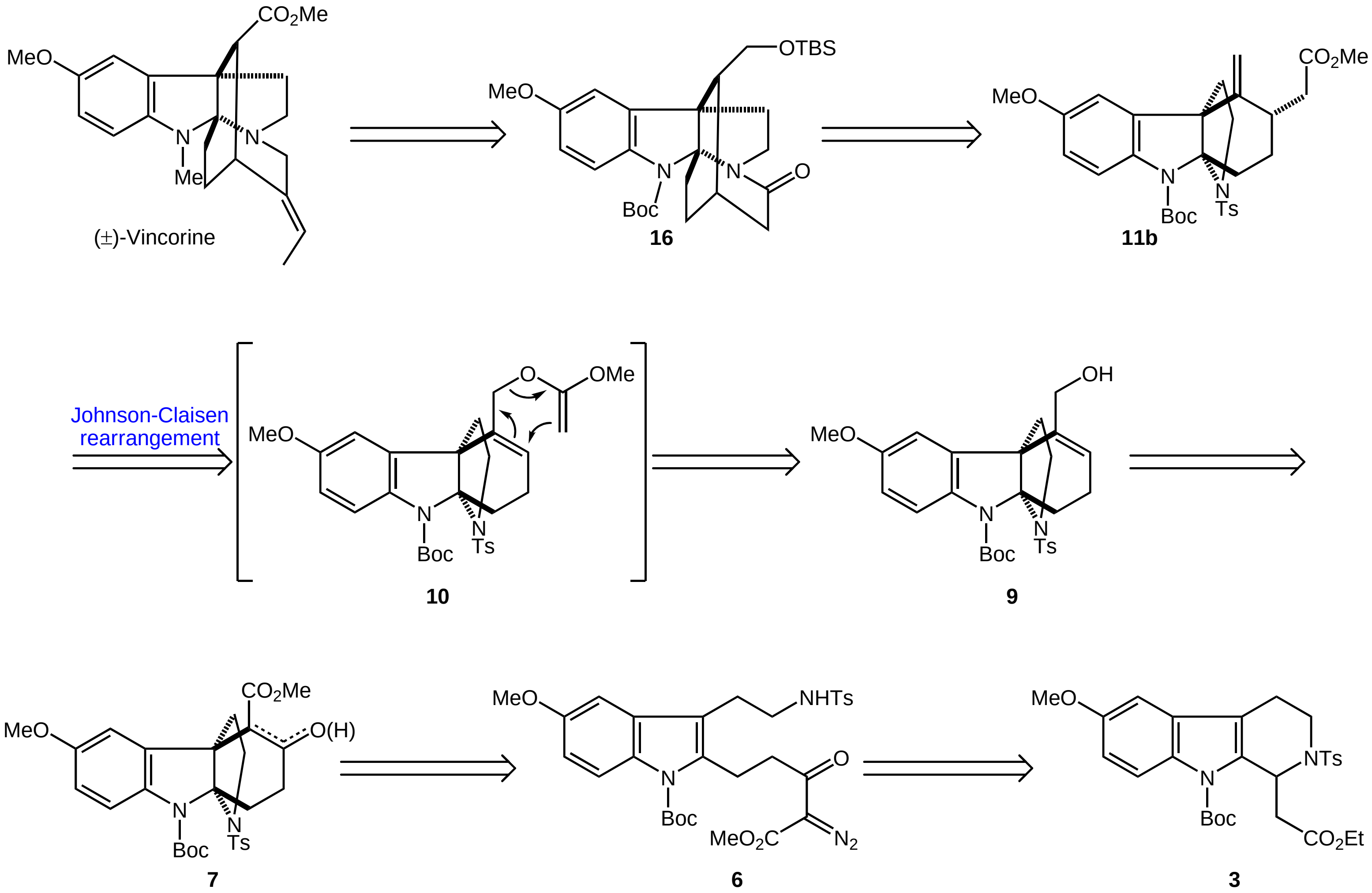
74%

13: R = H


13
LiHMDS, I_2, THF, -40 °C to rt
67%
23
KCN, H_2O, DMF, 100 °C
65%
11
Ph_3PCl_2, DCM
94%
24
1) TMSOTf, 2,6-lutidine, DCM, rt
2) K_2CO_3, KI, CH_3CN, 60 °C
74%
25
37% aq.HCHO, $NaBH_3CN$, CH_3CN, AcOH
68%
(-)-Vincorine (5)

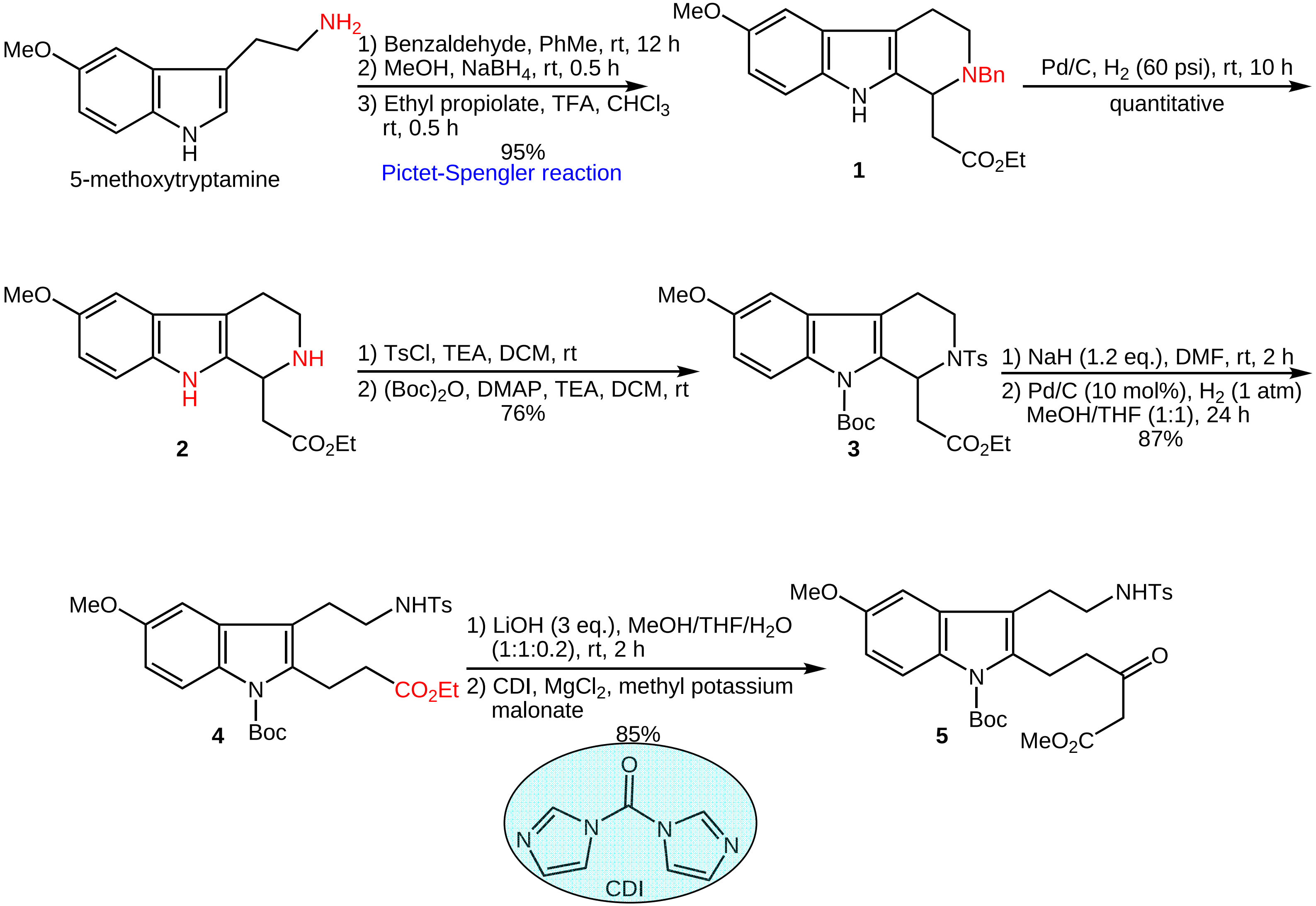

OMe
NHBoc
N
CO2Me
R
CO2Me
A
path a
MeO
MeO2C
CO2Me
(S)
R
N
NHBoc
desired
NHBoc
CO2Me
R
N
OMe
O
OMe
B
path b
R =
OTBS
BocHN
MeO2C
CO2Me
MeO
R
(R)
N
undesired

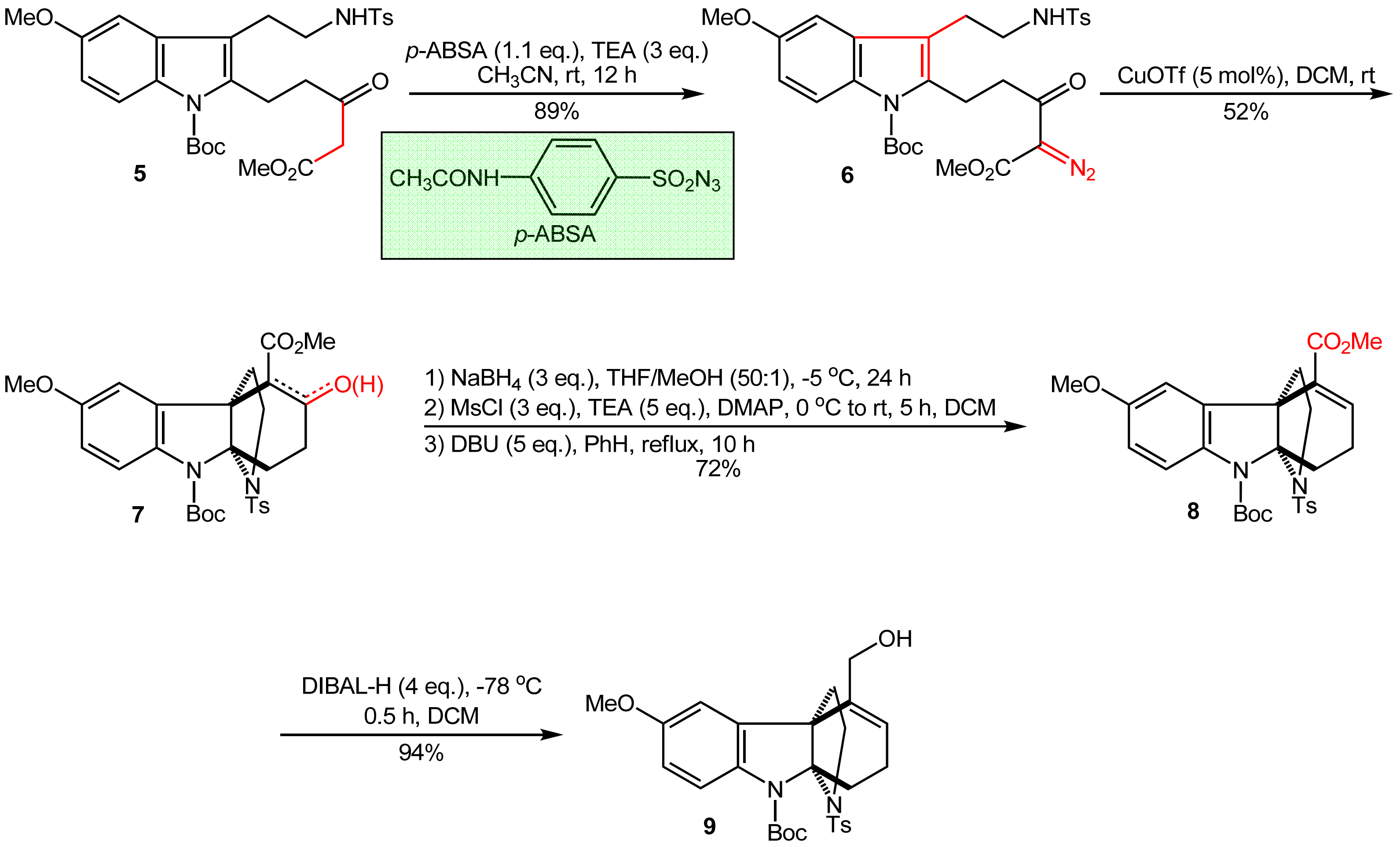
4. (±)-Vincorine 的反合成分析



Qin, Y. et al *J. Am. Chem. Soc.* **2009**, *131*, 6013

5. (±)-Vincorine 的合成





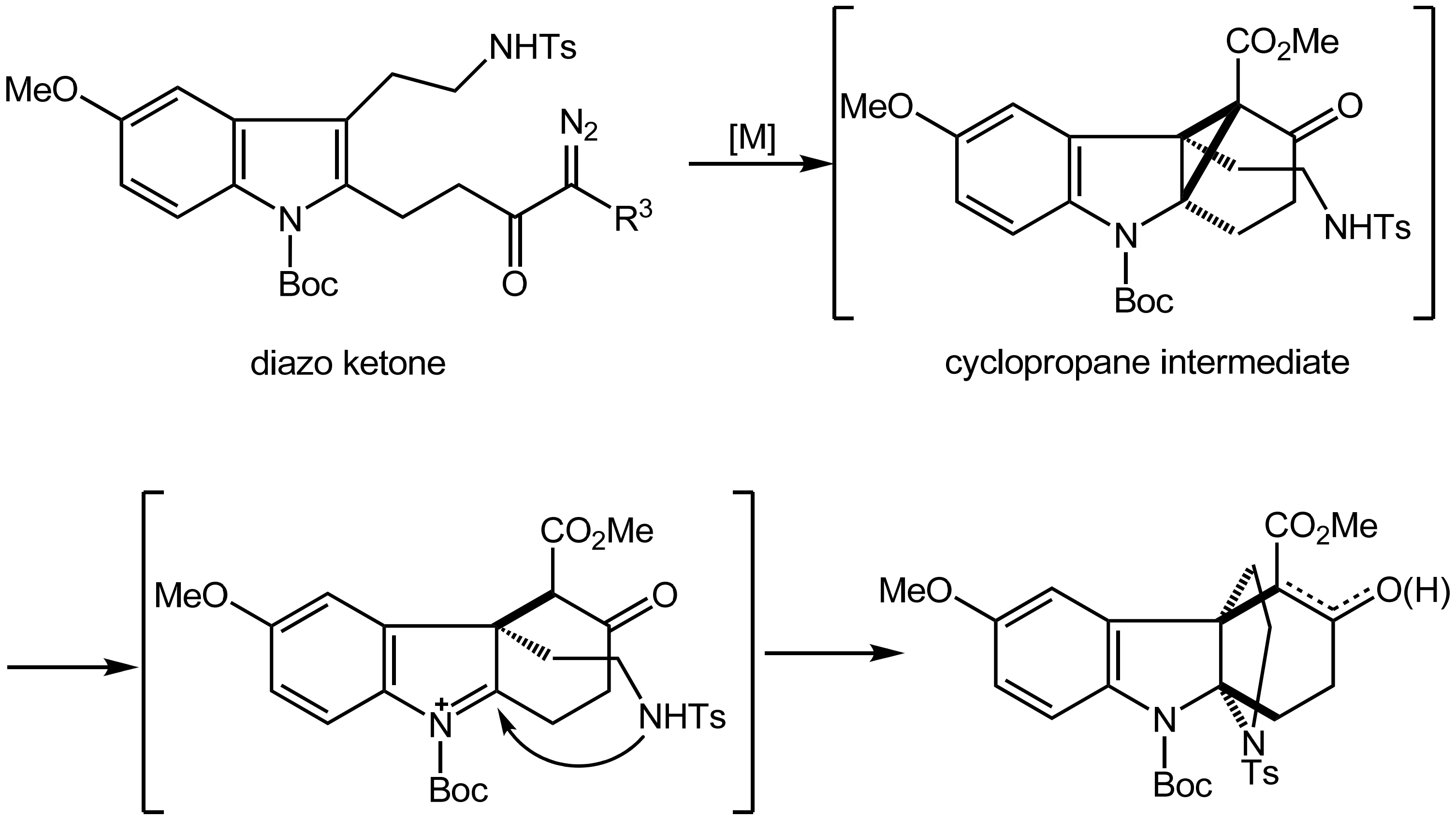
p-ABSA (1.1 eq.), TEA (3 eq.)
CH_3CN, rt, 12 h
89%

CuOTf (5 mol%), DCM, rt
52%

1) $NaBH_4$ (3 eq.), THF/MeOH (50:1), -5 °C, 24 h
2) MsCl (3 eq.), TEA (5 eq.), DMAP, 0 °C to rt, 5 h, DCM
3) DBU (5 eq.), PhH, reflux, 10 h
72%

DIBAL-H (4 eq.), -78 °C
0.5 h, DCM
94%

Three-step one-pot cascade reaction for the assembly of tetracyclic skeleton



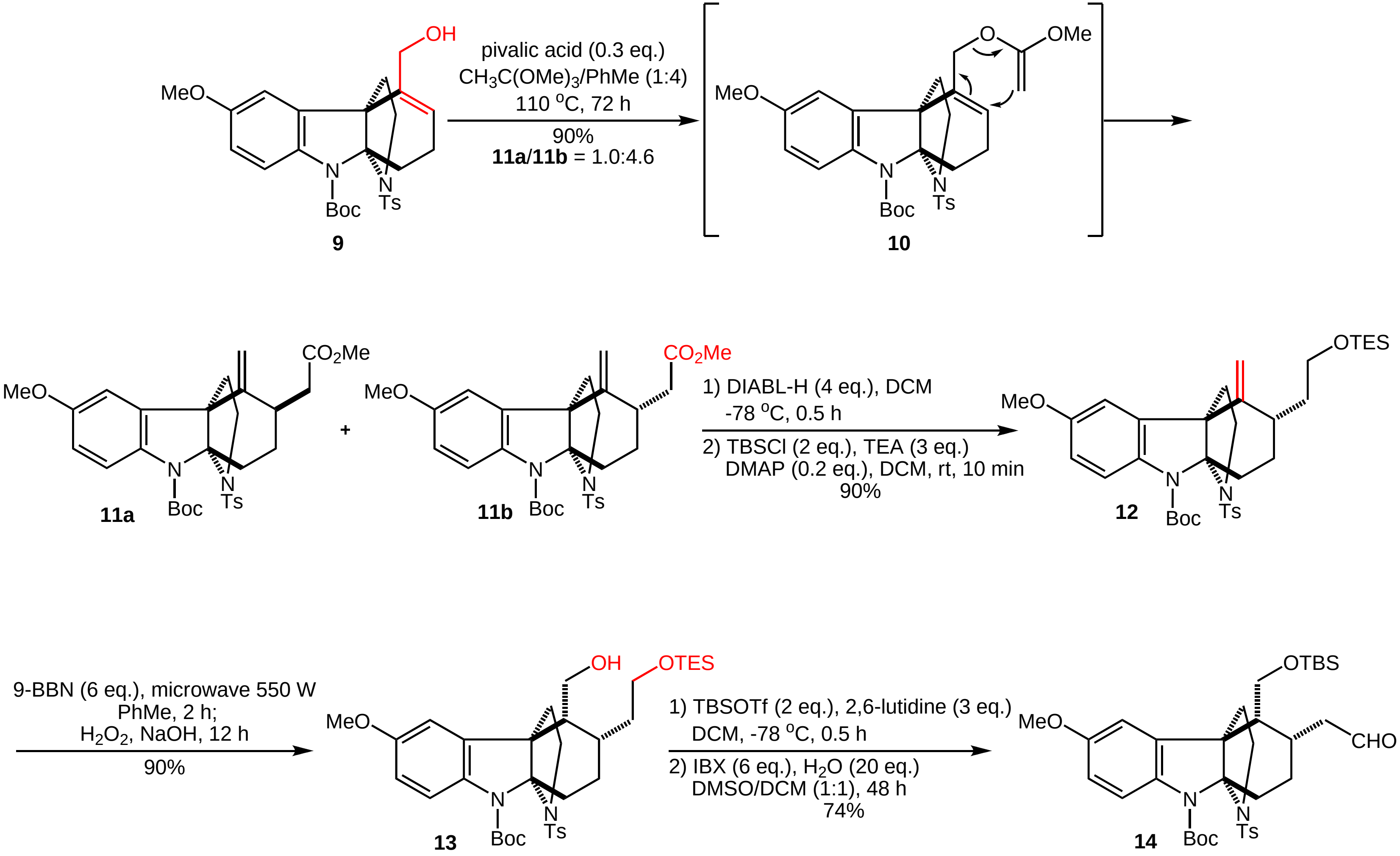
diazo ketone

cyclopropane intermediate

indolenium cation

substituted tetracyclic

Qin, Y. et al *Angew. Chem. Int. Ed.* **2008**, *47*, 3618



pivalic acid (0.3 eq.)
$CH_3C(OMe)_3$/PhMe (1:4)
110 ^oC, 72 h
90%
11a/11b = 1.0:4.6

9

10

11a

11b

1) DIABL-H (4 eq.), DCM
-78 ^oC, 0.5 h
2) TBSCl (2 eq.), TEA (3 eq.)
DMAP (0.2 eq.), DCM, rt, 10 min
90%

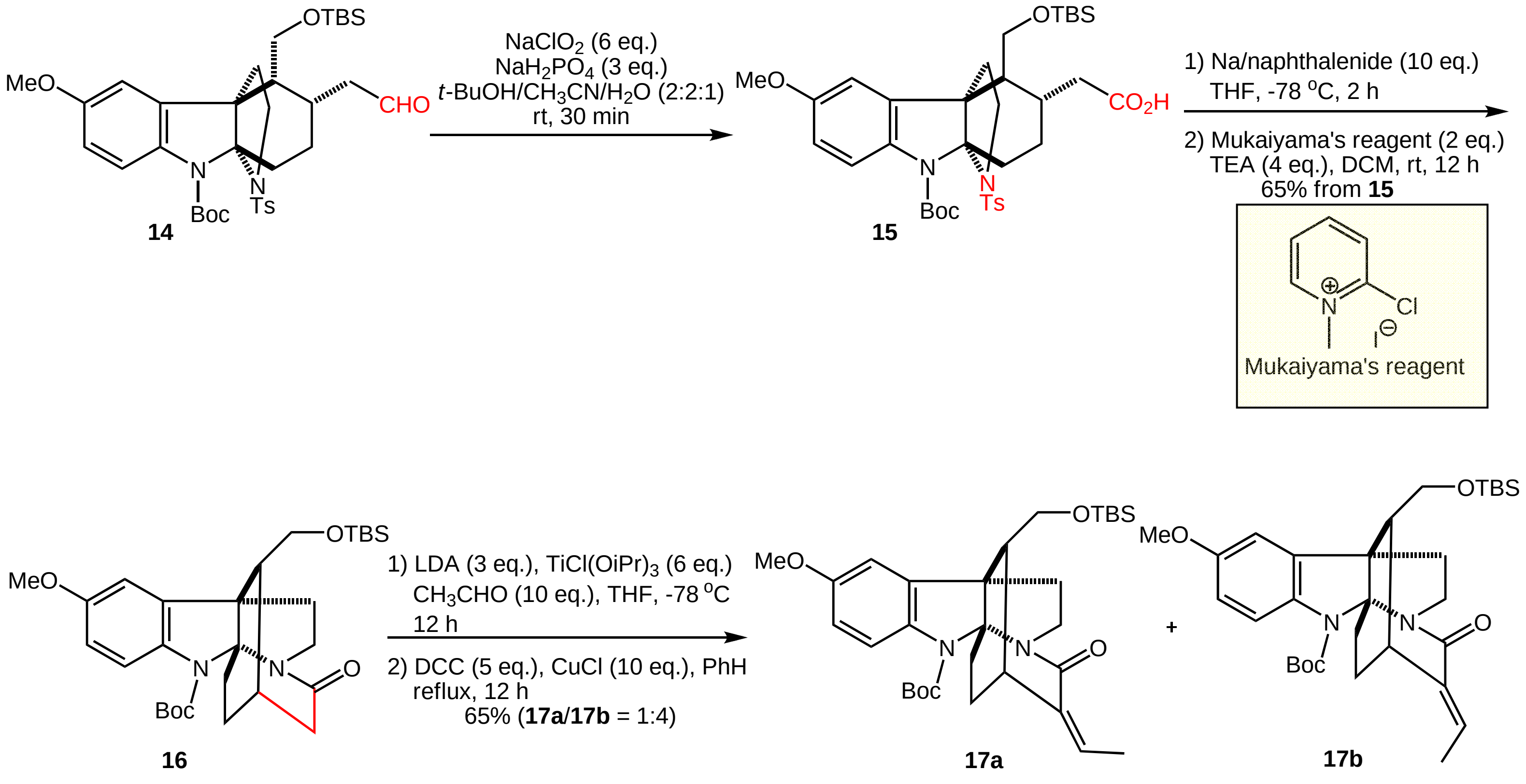
12

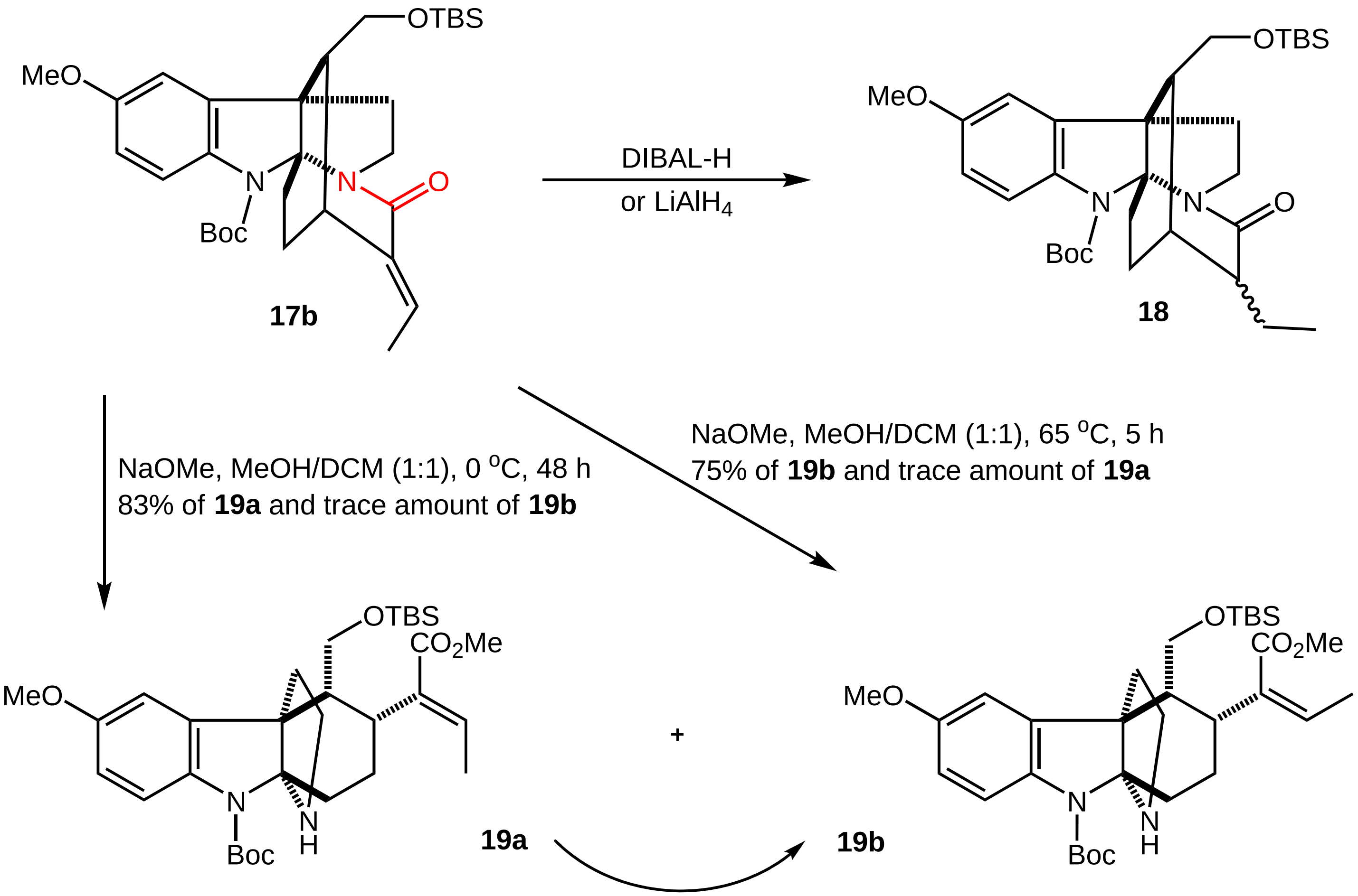
9-BBN (6 eq.), microwave 550 W
PhMe, 2 h;
H_2O_2, NaOH, 12 h
90%

13

1) TBSOTf (2 eq.), 2,6-lutidine (3 eq.)
DCM, -78 ^oC, 0.5 h
2) IBX (6 eq.), H_2O (20 eq.)
DMSO/DCM (1:1), 48 h
74%

14


MeO
OTBS
CHO
N
Boc
N
Ts
14
NaClO$_2$ (6 eq.)
NaH$_2$PO$_4$ (3 eq.)
t-BuOH/CH$_3$CN/H$_2$O (2:2:1)
rt, 30 min
MeO
OTBS
CO$_2$H
N
Boc
N
Ts
15
1) Na/naphthalenide (10 eq.)
THF, -78 ^oC, 2 h
2) Mukaiyama's reagent (2 eq.)
TEA (4 eq.), DCM, rt, 12 h
65% from **15**
N
Cl
I
Mukaiyama's reagent
MeO
OTBS
N
Boc
N
O
16
1) LDA (3 eq.), TiCl(OiPr)$_3$ (6 eq.)
CH$_3$CHO (10 eq.), THF, -78 ^oC
12 h
2) DCC (5 eq.), CuCl (10 eq.), PhH
reflux, 12 h
65% (**17a**/**17b** = 1:4)
MeO
OTBS
N
Boc
N
O
17a
+
MeO
OTBS
N
Boc
N
O
17b



17b

DIBAL-H
or $LiAlH_4$

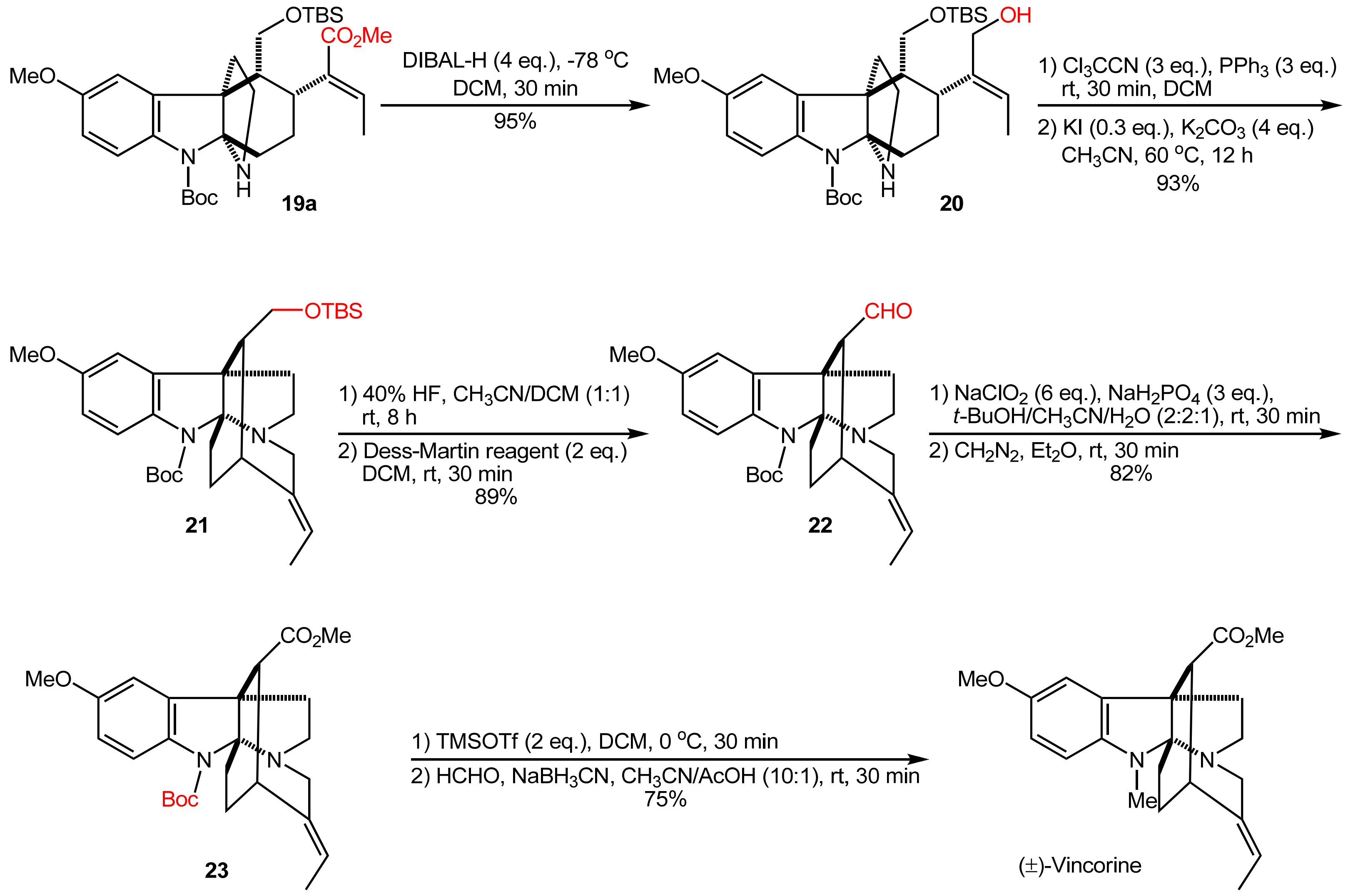
18

NaOMe, MeOH/DCM (1:1), 0 °C, 48 h
83% of **19a** and trace amount of **19b**

NaOMe, MeOH/DCM (1:1), 65 °C, 5 h
75% of **19b** and trace amount of **19a**

19a + **19b**

NaOMe, MeOH/DCM (1:1), 65 °C, 5 h



19a

DIBAL-H (4 eq.), -78 °C
DCM, 30 min
95%

20

1) Cl_3CCN (3 eq.), PPh_3 (3 eq.)
rt, 30 min, DCM
2) KI (0.3 eq.), K_2CO_3 (4 eq.)
CH_3CN, 60 °C, 12 h
93%

21

1) 40% HF, CH_3CN/DCM (1:1)
rt, 8 h
2) Dess-Martin reagent (2 eq.)
DCM, rt, 30 min
89%

22

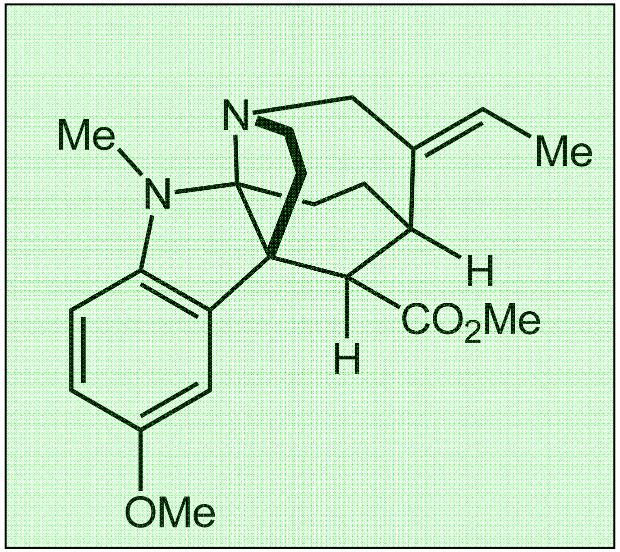
1) $NaClO_2$ (6 eq.), NaH_2PO_4 (3 eq.),
t-BuOH/CH_3CN/H_2O (2:2:1), rt, 30 min
2) CH_2N_2, Et_2O, rt, 30 min
82%

23

1) TMSOTf (2 eq.), DCM, 0 °C, 30 min
2) HCHO, $NaBH_3CN$, CH_3CN/AcOH (10:1), rt, 30 min
75%

(±)-Vincorine

6. 总结与讨论



1. 18 steps, 5% overall yield;
2. Pd-catalyzed direct C–H functionalization of indole derivatives;
3. Organocatalyzed asymmetric Michael addition of aldehydes to alkylidene malonates;
4. Intramolecular oxidative coupling between indole and malonate moieties.

1. 31 steps, 1% overall yield from **3**;
2. Concisely assembling the key tetracyclic core structure through three-step one-pot cascade reaction consisting of intermolecular cyclopropanation, ring-opening, and ring closure.

3,4a-Disubstituted-2,3,4,4a-tetrahydro-1*H*-carbazole-4-carboxylic acid methyl ester (**1**) and its heteroatom-captured form **2** are highly congested polycyclic ring systems that are common skeletons for *Akuammiline*-type alkaloids such as strictamine (**3**), scholarisine A (**4**), vincorine (**5**), and aspidophylline A (**6**). Because of their interesting biological activity and inspiring architecture, these alkaloids have garnered considerable interest in the synthetic community. In 2009, the Qin group completed the first total synthesis of (±)-vincorine, in which they employed an intramolecular cyclopropanation and subsequent ring-opening strategy to elaborate a key tricyclic intermediate. Quite recently, Garg and co-workers reported a total synthesis of (±)-aspidophylline A utilizing the interrupted Fischer indolization reaction as a key step, and the Smith group disclosed an elegant synthesis of (+)-scholarisine A featuring a reductive cyclization cascade to form the cage-shaped tricyclic intermediate.

In conclusion, we have developed an efficient approach for the synthesis of (-)-vincorine. This protocol allows the assembly of the target molecule in 18 steps from commercially available 5-methoxytryptamine in an overall yield of 5%. The key elements in this synthesis include the use of two newly developed reactions, namely, a Pd-catalyzed direct C–H functionalization of indole derivatives and an organocatalyzed asymmetric Michael addition of aldehydes to alkylidene malonates, as well as an intramolecular oxidative coupling between indole and malonate moieties. The completion of the (-)-vincorine synthesis also demonstrates the versatility of these new methodologies in natural product synthesis. Obviously, such a synthetic strategy is also promising for assembling other *Akuammiline*-type alkaloids. Investigations to prove this hypothesis are being actively pursued, and the results will be reported in due course.