Literature Report

A Concise and Versatile Synthesis of Alkaloids from *Kopsia tenuis*: Total Synthesis of (±)-Lundurine A and B

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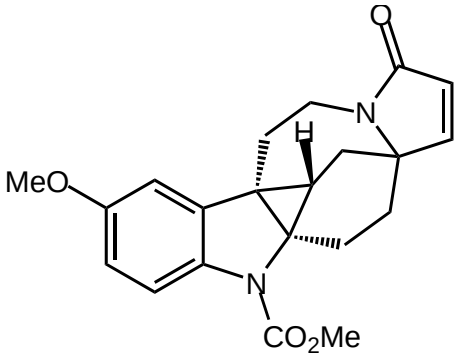
Checker: Zhang-Pei Chen
Date: 2014-06-24

Nishida, A. *et al.*
Angew. Chem. Int. Ed. **2014**, *53*, 5569–5572.

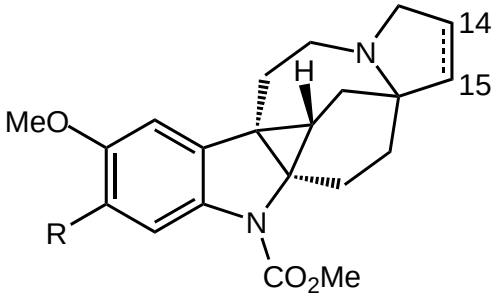
Chiba University

Contents

Kopsia

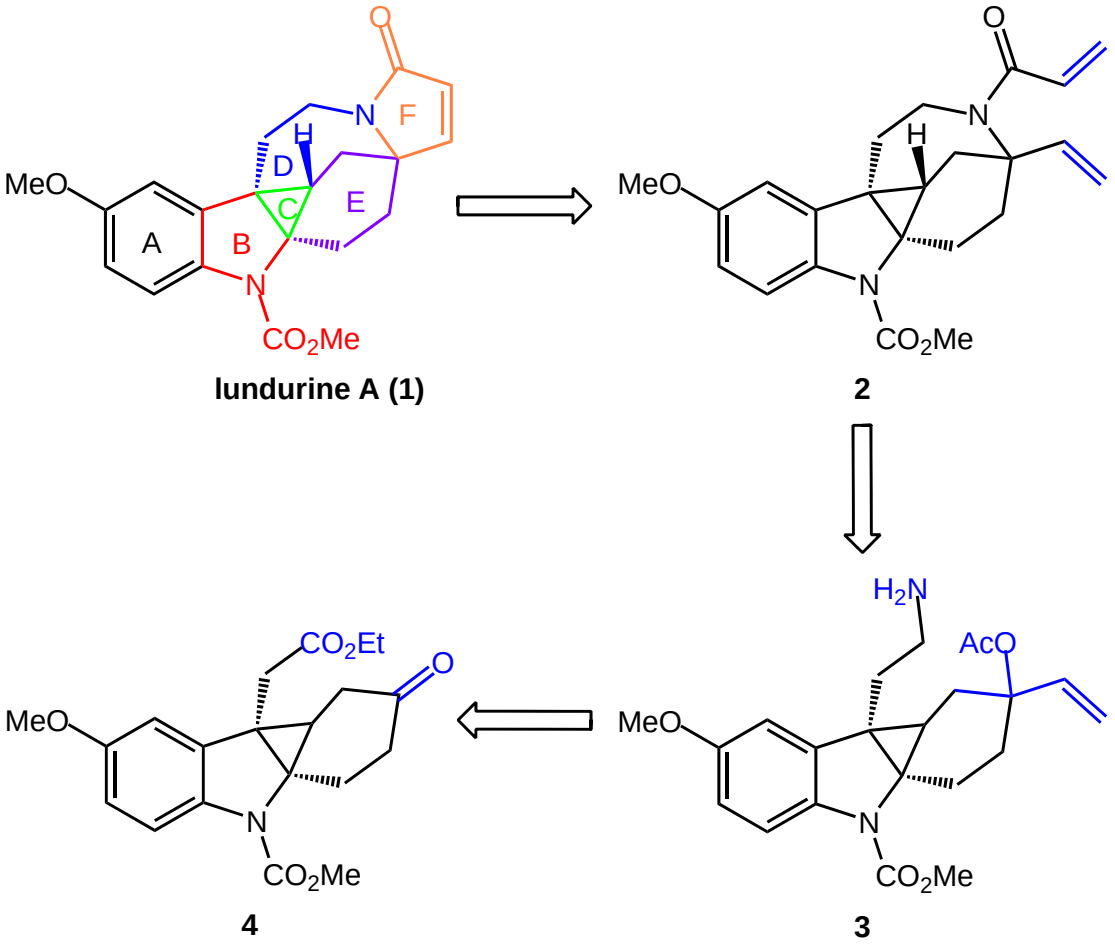


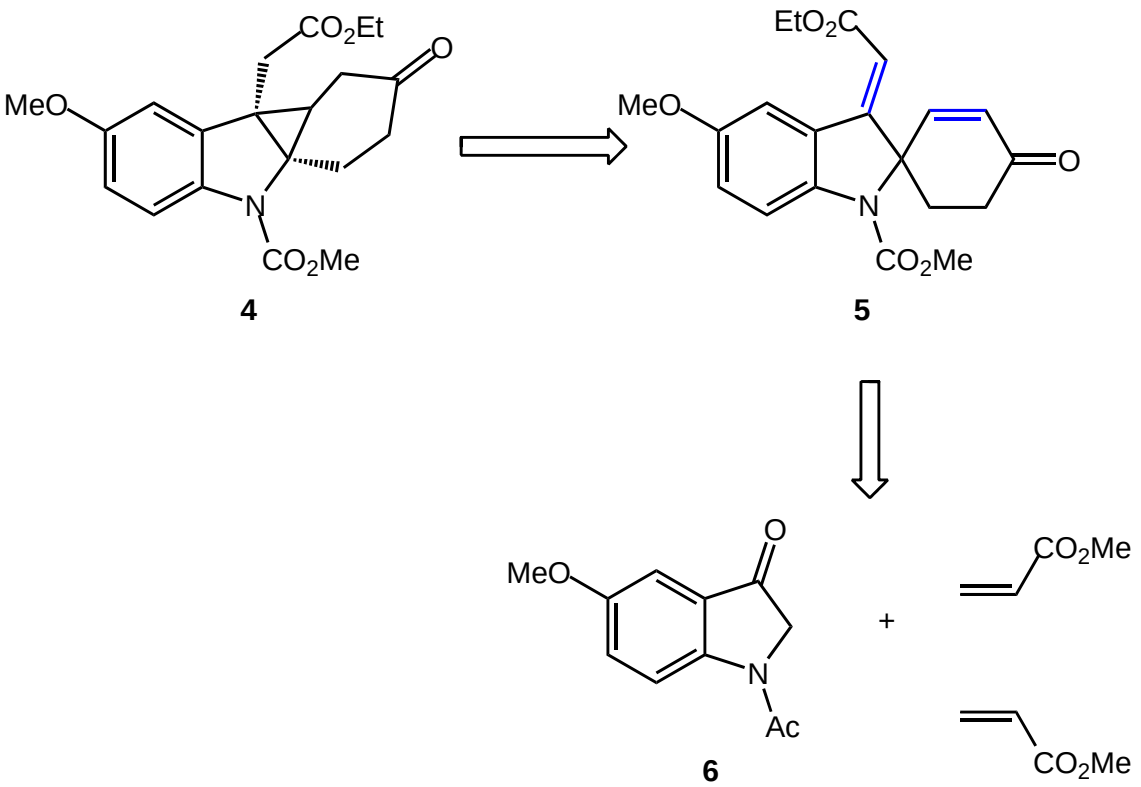
lundurine A



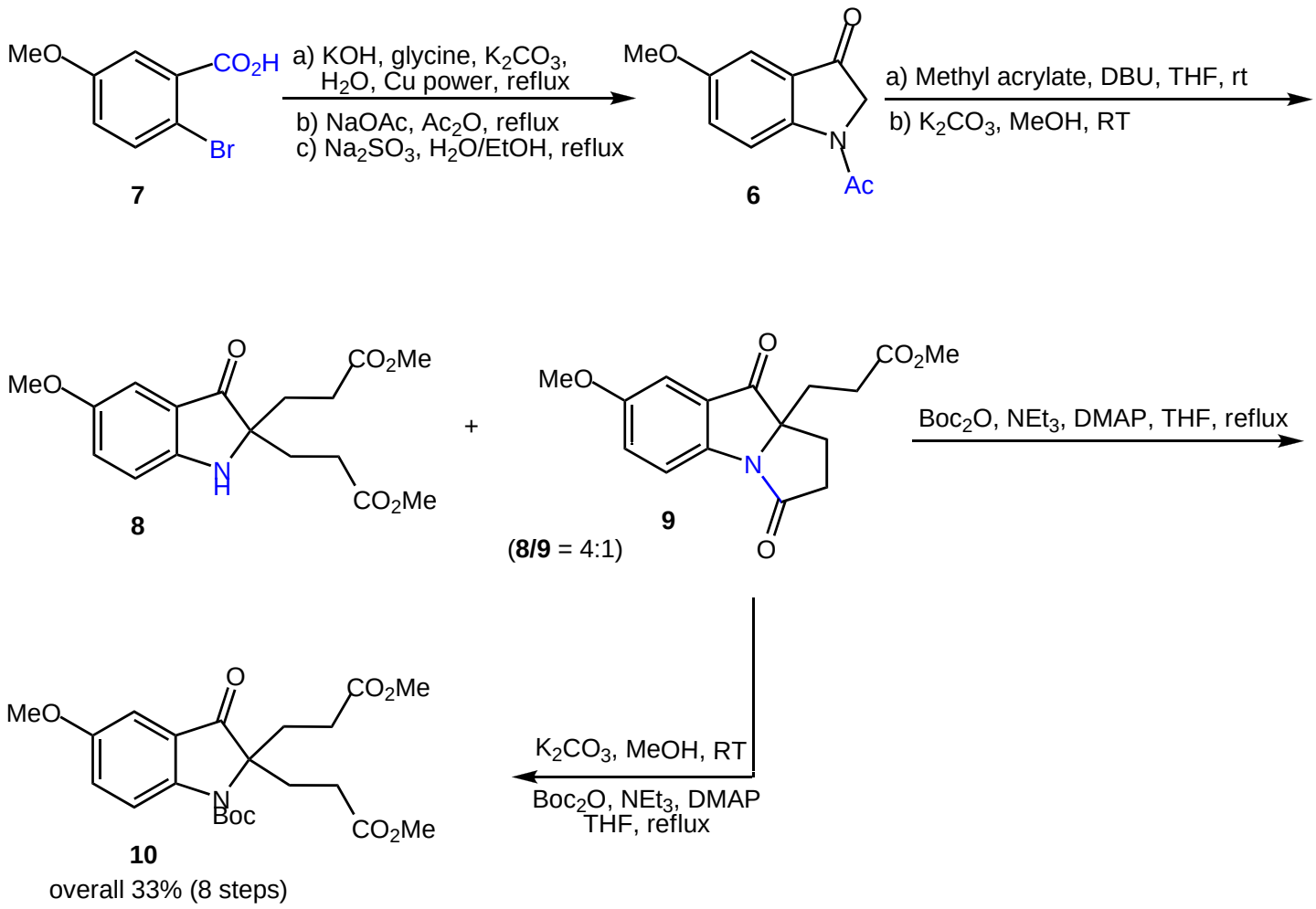
lundurine B, R = H, $\Delta^{14,15}$
lundurine C, R = H,
lundurine D, R = OMe, $\Delta^{14,15}$

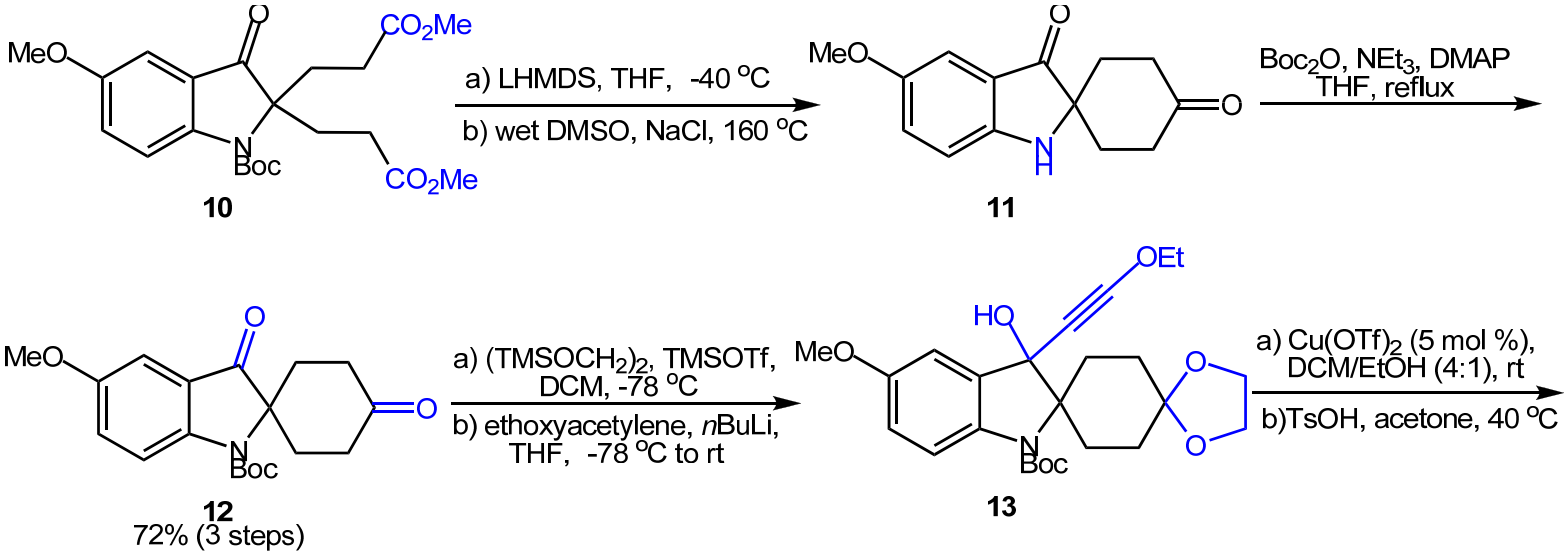
Retrosynthesis of (±)- Lundurine A



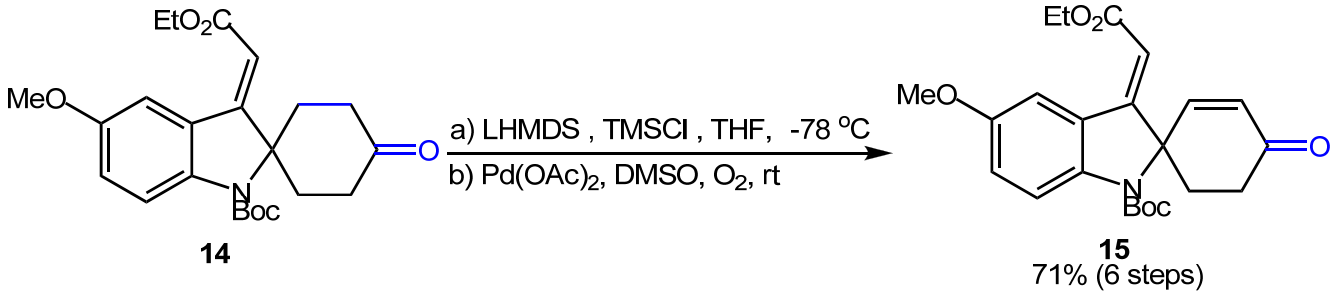

CO2Et
O
MeO
N
CO2Me
4
EtO2C
MeO
O
N
CO2Me
5
O
MeO
N
Ac
6
+
CO2Me
CO2Me

Preparation of 5

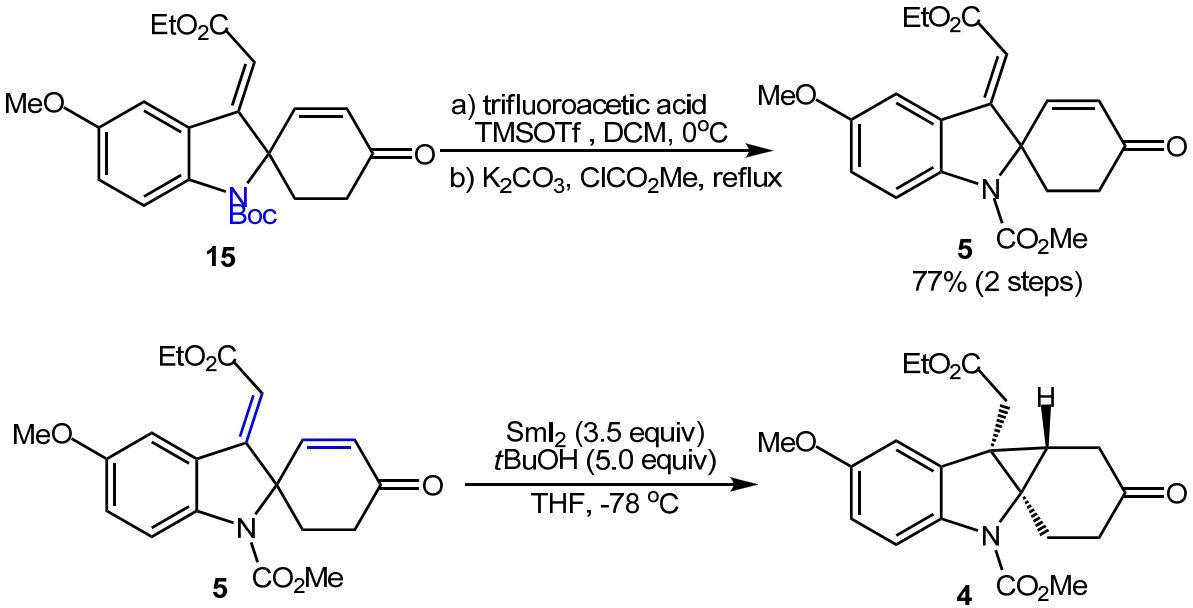




Meyer-Schuster rearrangement

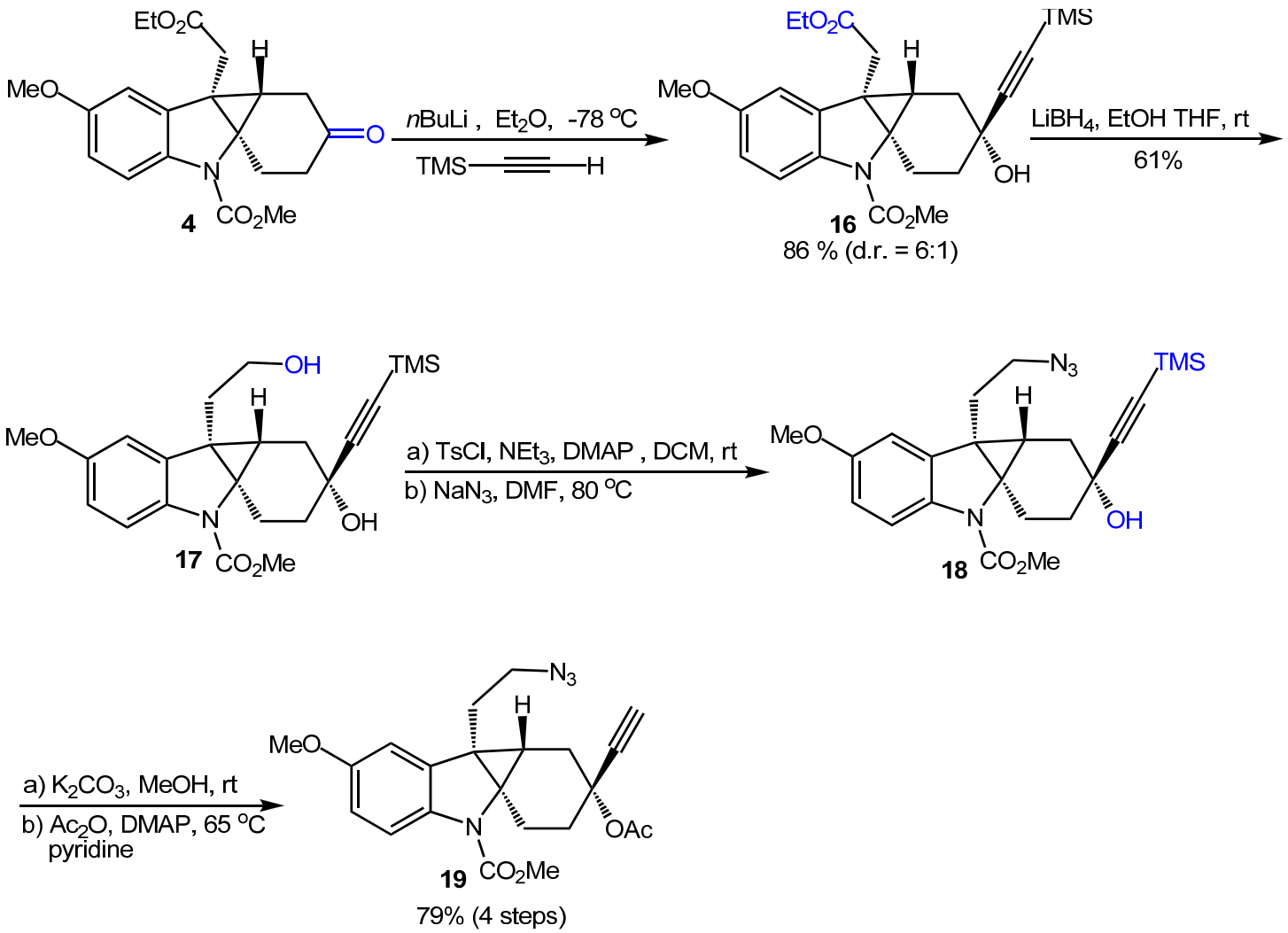


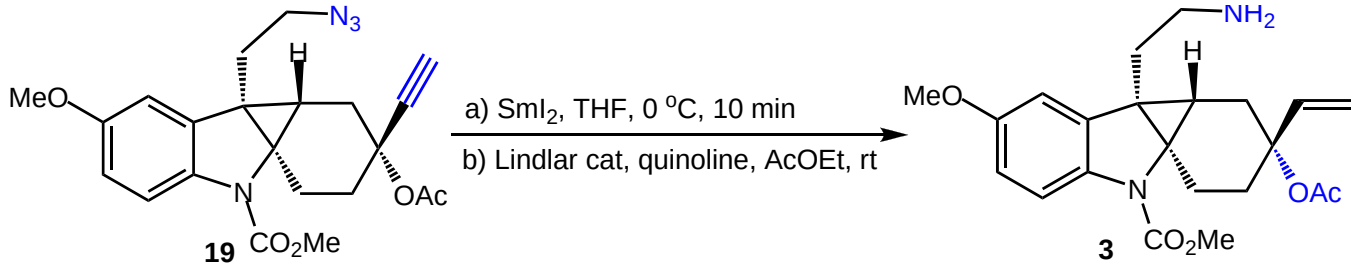
Saegusa-Ito reaction



Entry	Additive (equiv)	T	Yield [%][a]
1	none	3 h	34
2	HMPA (12)	5 min	23
3	LiBr (20)	1 min	42
4	LiCl (20)	1 min	52

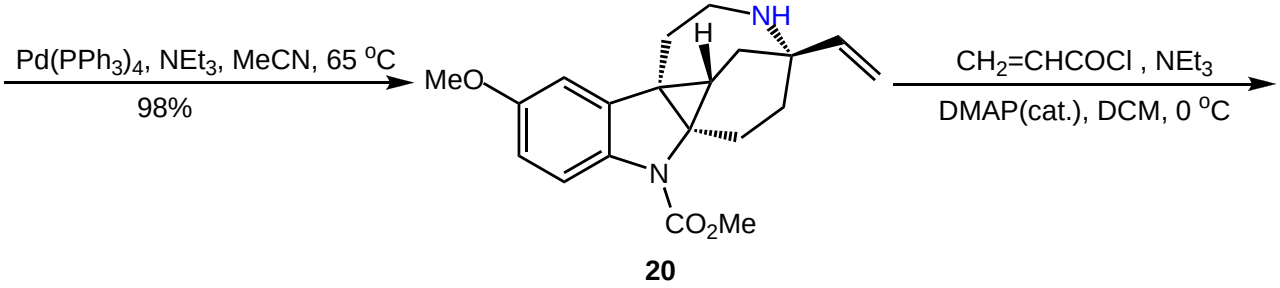
[a] Yield of isolated product, except entry 2 in which yield was estimated by ^{1}H NMR spectroscopy.


EtO2C
H
MeO
O
N
CO2Me
4
nBuLi , Et2O, -78 °C
TMS
H
EtO2C
TMS
H
MeO
OH
N
CO2Me
16
86 % (d.r. = 6:1)
LiBH4, EtOH THF, rt
61%
OH
TMS
H
MeO
OH
N
17
CO2Me
a) TsCl, NEt3, DMAP , DCM, rt
b) NaN3, DMF, 80 °C
N3
TMS
H
MeO
OH
N
18
CO2Me
a) K2CO3, MeOH, rt
b) Ac2O, DMAP, 65 °C
pyridine
N3
H
MeO
OAc
N
19
CO2Me
79% (4 steps)

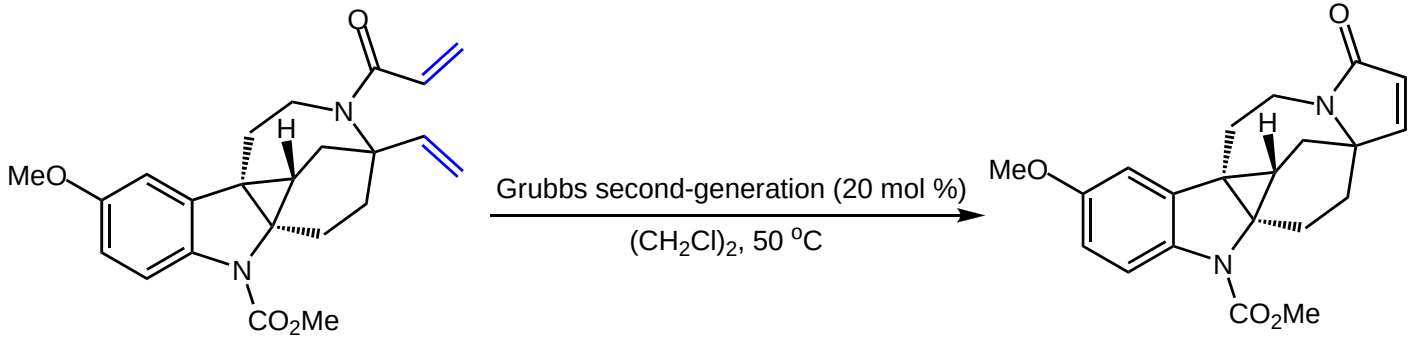


19 **3**

73% (2 steps)

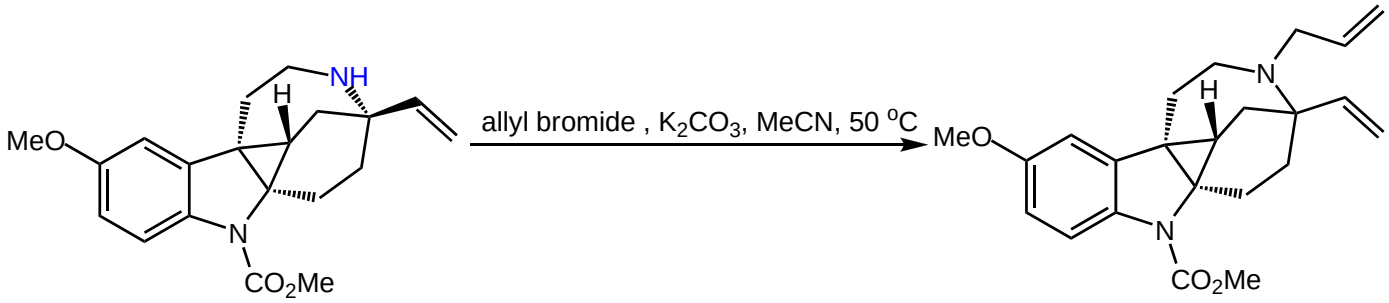


20

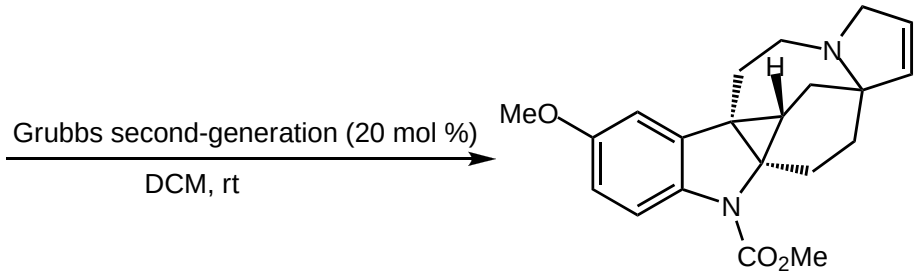


2 **1a**

70% (2 steps)

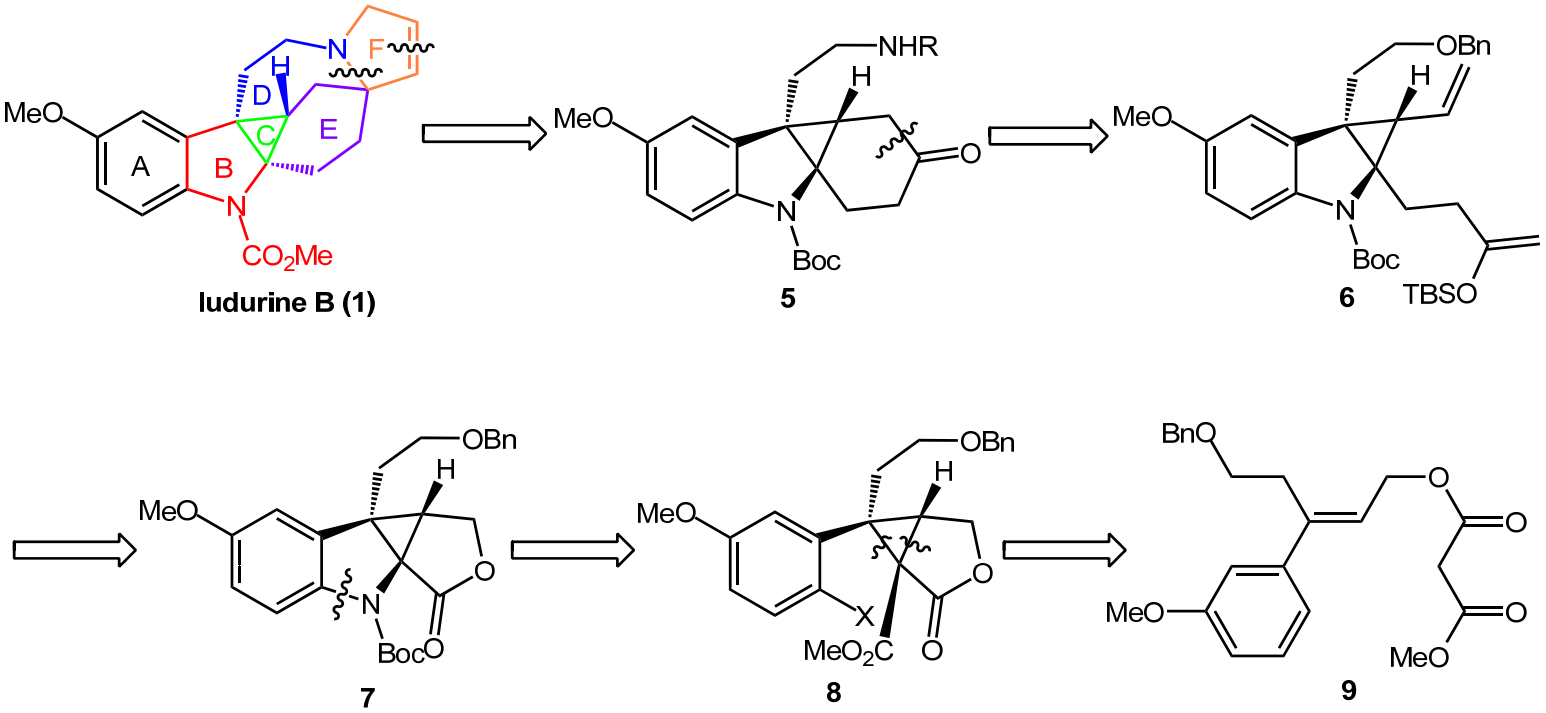


20 **21**



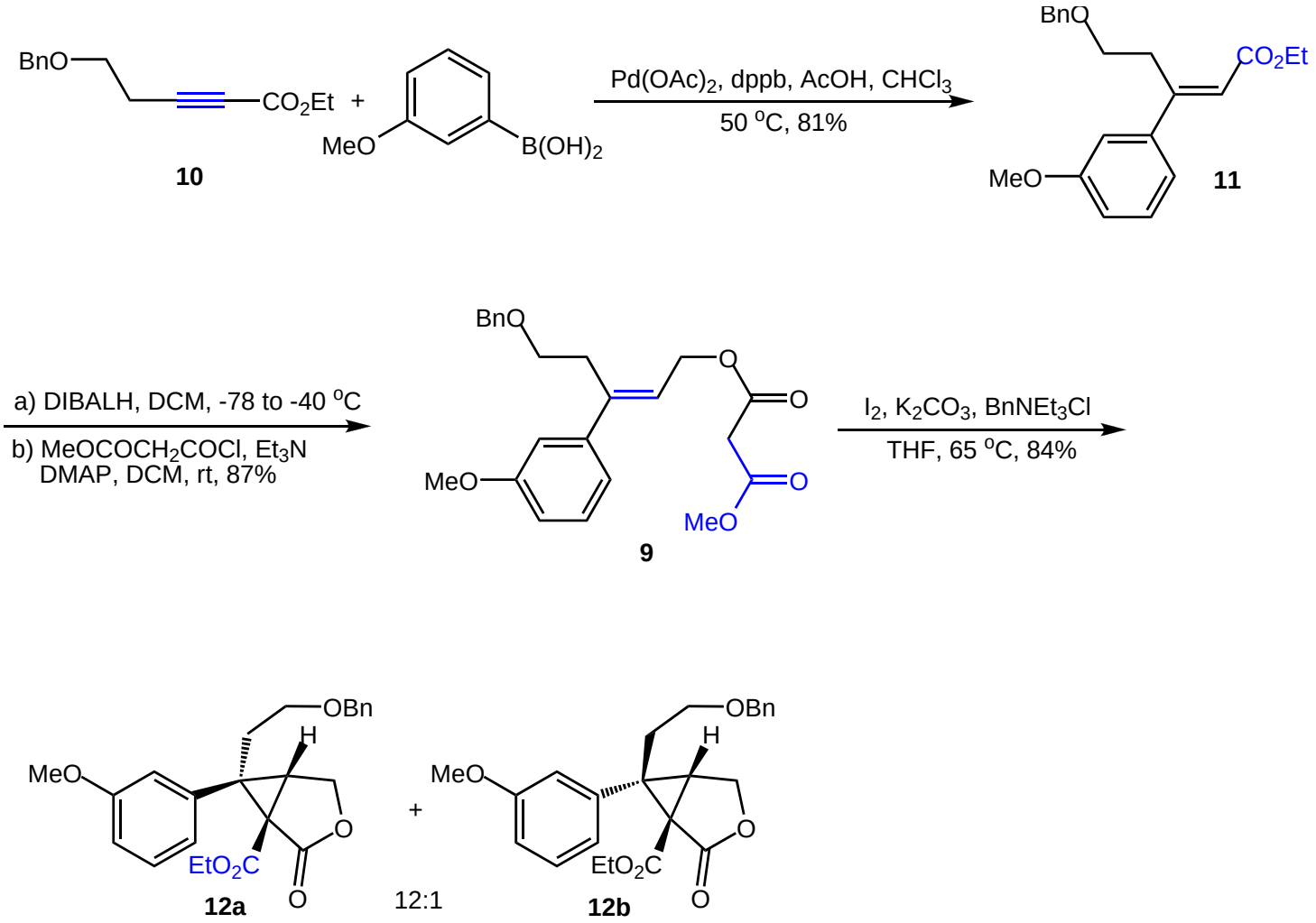
1b
85% (2 steps)

Retrosynthesis of (±)- Lundurine B

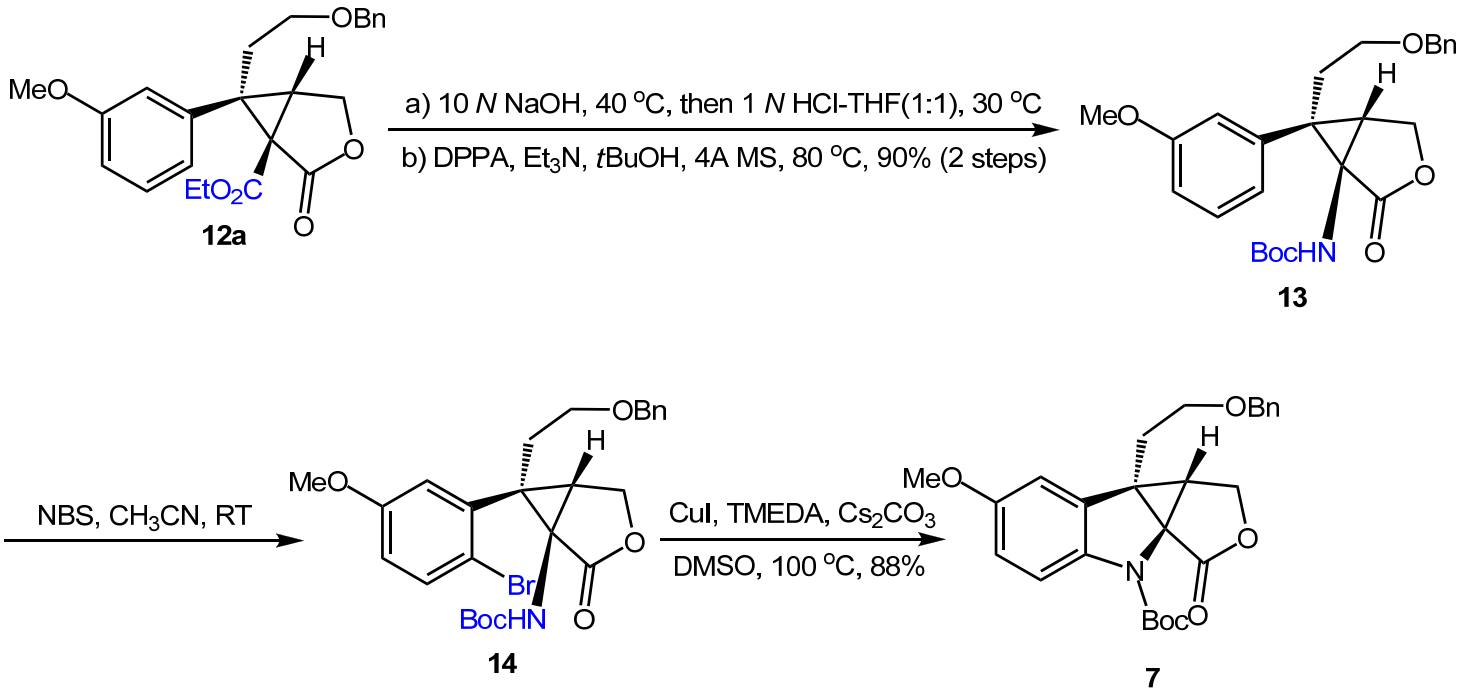


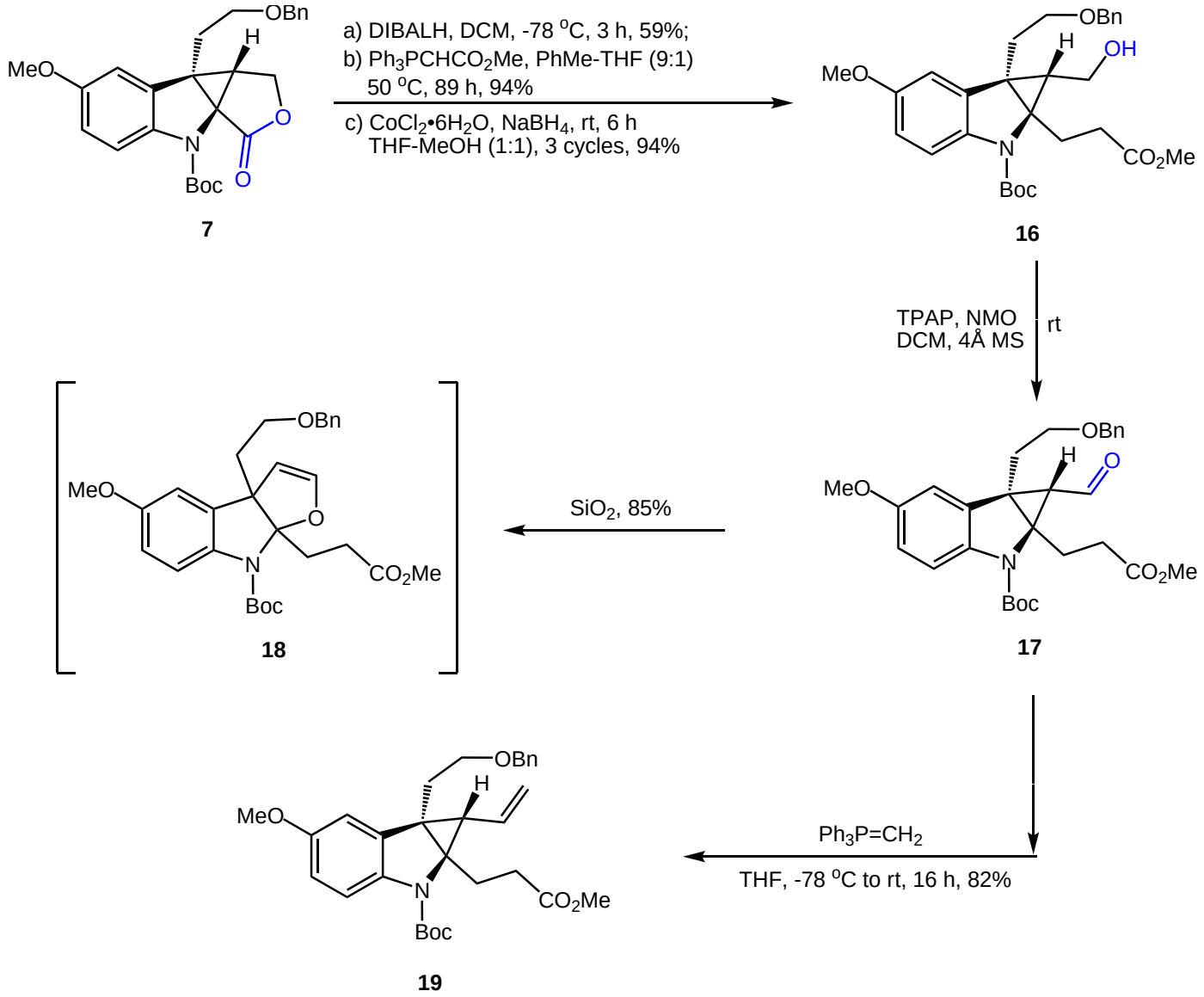
Org. Lett. **2014**, *16*, 768-771.

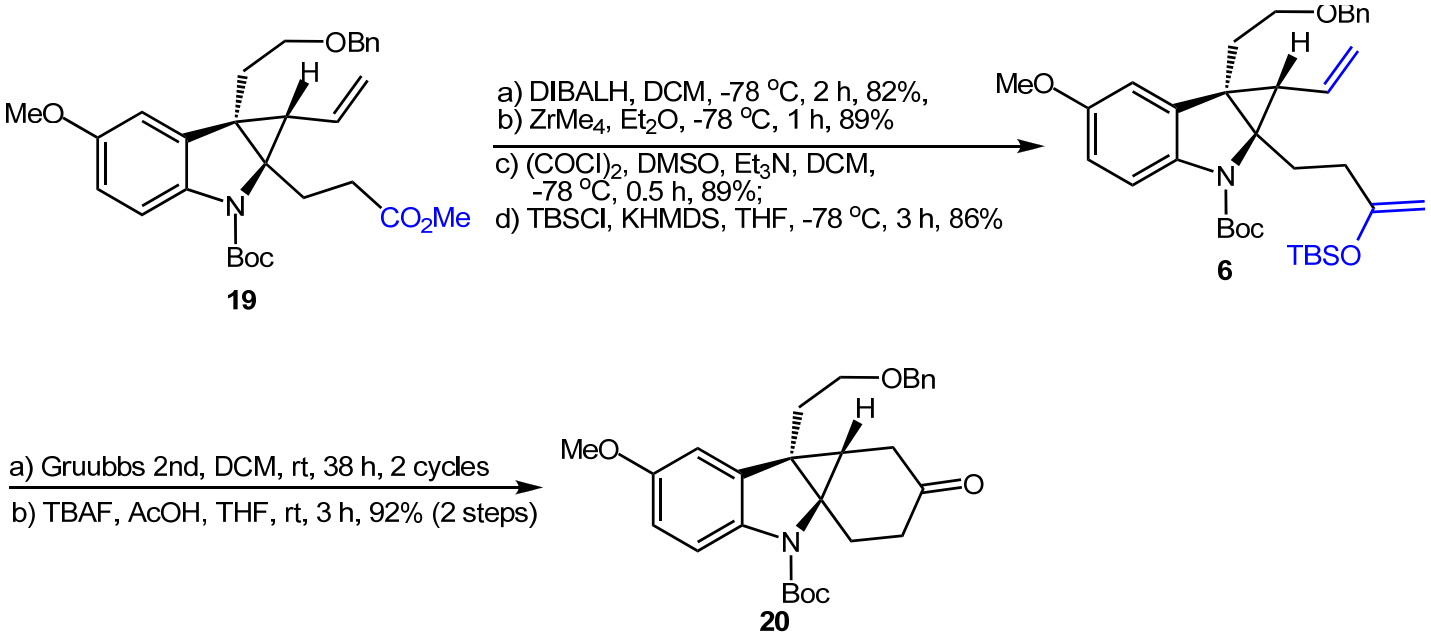
Synthesis of Cyclopropane-Fused Indoline 7

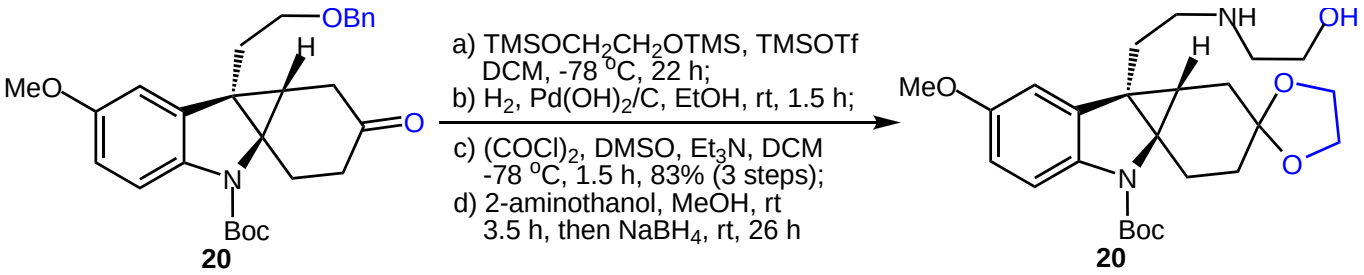


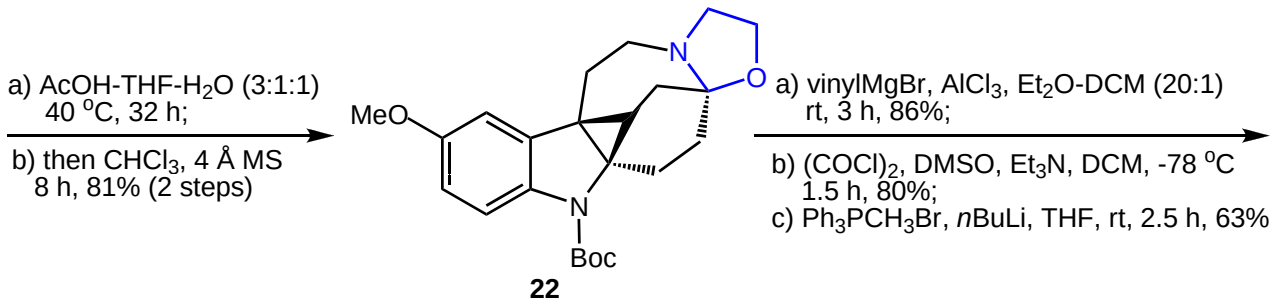
Synthesis of Cyclopropane-Fused Indoline 7

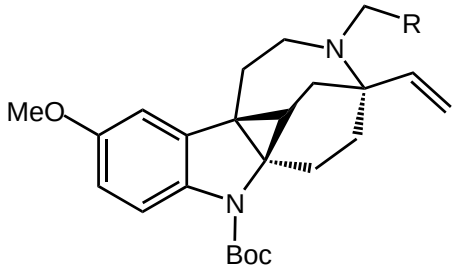



OBn
H
MeO
O
N
Boc
O
7
a) DIBALH, DCM, -78 °C, 3 h, 59%;
b) Ph3PCHCO2Me, PhMe-THF (9:1)
50 °C, 89 h, 94%
c) CoCl2•6H2O, NaBH4, rt, 6 h
THF-MeOH (1:1), 3 cycles, 94%
OH
CO2Me
16
TPAP, NMO
DCM, 4Å MS
rt
17
SiO2, 85%
18
Ph3P=CH2
THF, -78 °C to rt, 16 h, 82%
19

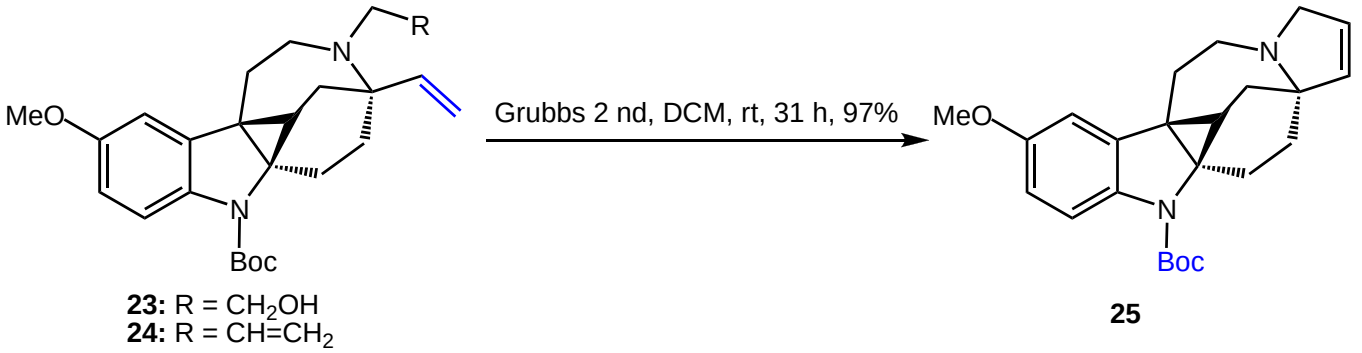

OBn
H
MeO
N
Boc
CO2Me
19
a) DIBALH, DCM, -78 °C, 2 h, 82%,
b) ZrMe4, Et2O, -78 °C, 1 h, 89%
c) (COCl)2, DMSO, Et3N, DCM,
-78 °C, 0.5 h, 89%;
d) TBSCl, KHMDS, THF, -78 °C, 3 h, 86%
OBn
H
MeO
N
Boc
TBSO
6
a) Gruubbs 2nd, DCM, rt, 38 h, 2 cycles
b) TBAF, AcOH, THF, rt, 3 h, 92% (2 steps)
OBn
H
MeO
O
N
Boc
20





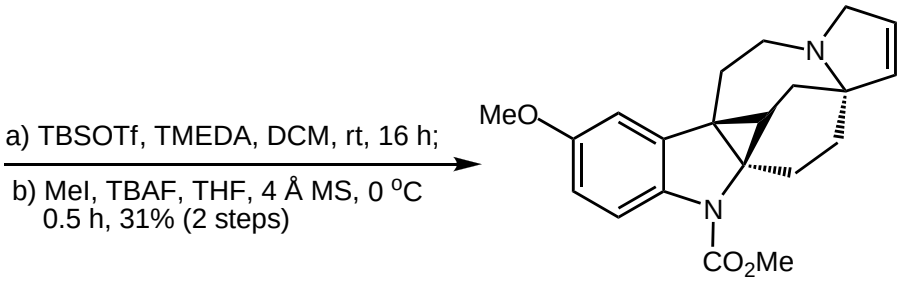


23: R = CH_2OH
24: R = $CH{=}CH_2$

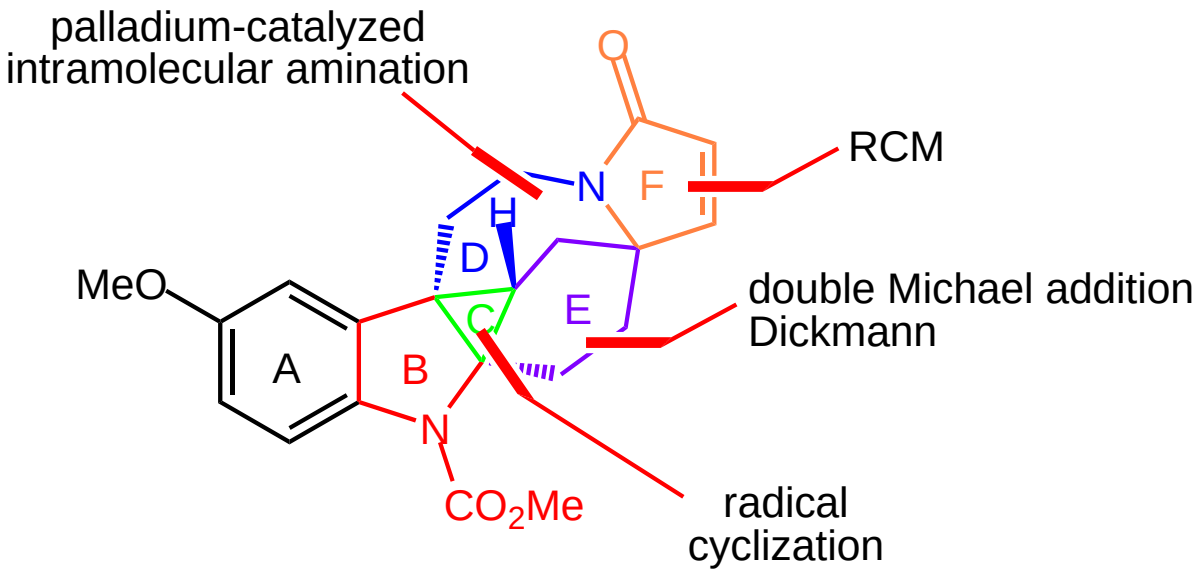


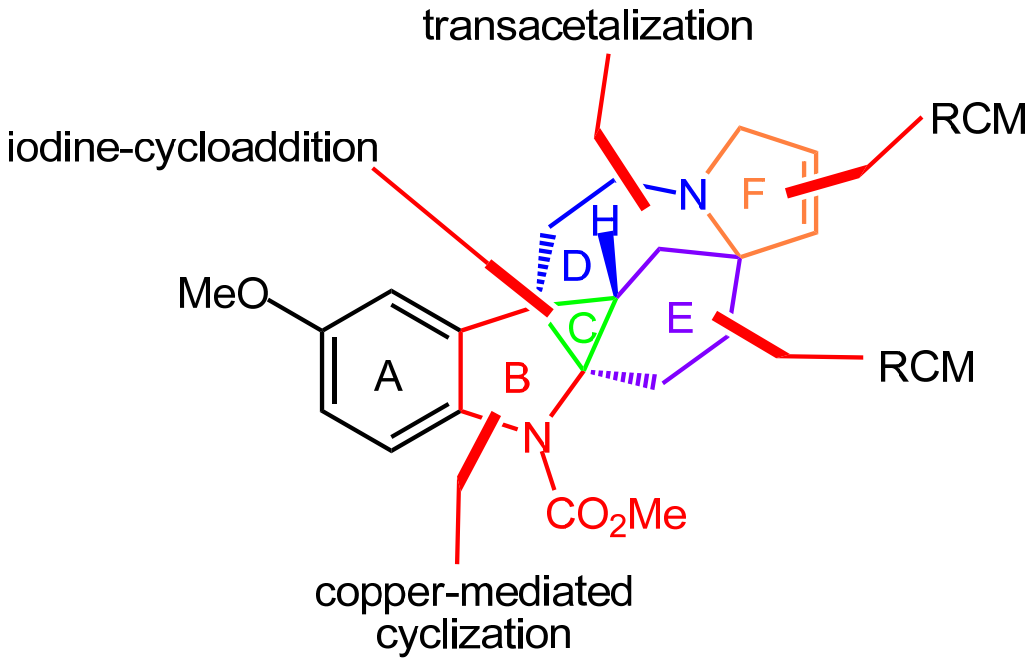
23: R = CH_2OH
24: R = $CH{=}CH_2$

25



(±)-1


palladium-catalyzed
intramolecular amination
RCM
double Michael addition
Dickmann
radical
cyclization
MeO
A
B
C
D
E
F
N
H
O
N
CO2Me

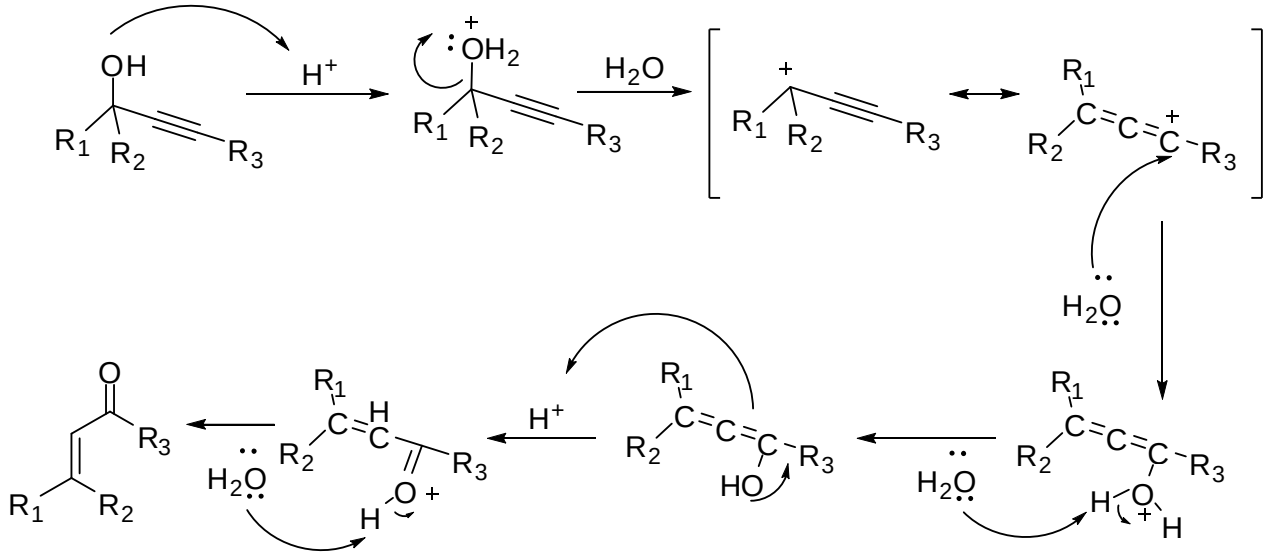

transacetalization
iodine-cycloaddition
RCM
N
F
H
D
MeO
C
E
A
B
RCM
N
CO_2Me
copper-mediated
cyclization

Kopsia alkaloids are interesting molecules because of their biological activities and their unique polycyclic skeletons. For their synthesis or scalable preparation, facile access to the spiroindoline core, shown in red, should lead to a unified total synthesis of all of the related alkaloids shown. .

The kopsia alkaloids called lundurines have been particularly attractive compounds for synthetic chemists because they are the only natural products which have an indoline cyclopropane structure and most of the stereogenic centers, including two quaternary carbon atoms, which are part of the cyclopropane ring. However, while their biological effects, such as the high toxicities of lundurines B and D toward B16 melanoma cells and reverse multidrug resistance in vincristine-resistant KB cells, are also interesting, their limited availability and scalable preparation has constrained their application as a biological tool. Since their discovery by Kam and co-workers in 1995, the total synthesis of these natural products has been a challenging issue. However, only two synthetic approaches have been reported to date.

In summary, we have succeeded in the total synthesis of (±)-lundurine A and B by using a new radical cyclization protocol to join the unsaturated ester and ketone. A key cyclopropanation mediated by SmI_2 is quite suitable for the synthesis of a highly functionalized cyclopropane core because of 1) perfect stereoselectivity and 2) efficacy of transformation of both oxygen functionalities to achieve elegant construction of the C, D, and F rings at a late stage in the synthesis. The spiroindoline intermediate 5 is expected to be a versatile intermediate for the unified total synthesis of the Kopsia alkaloid family and further studies are currently underway.

Meyer-Schuster rearrangement



Saegusa-Ito reaction