Literature Report II

Scalable Enantioselective Total Synthesis of (-)-Goniomitine

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Checker: Zhou-Hao Zhu
Date: 2019-4-15

Xie, J.-H. *et al. Angew. Chem. Int. Ed.* **2019**, *58*, 1174-1177.

CV of Prof. Jian-Hua Xie

Education and Employment:

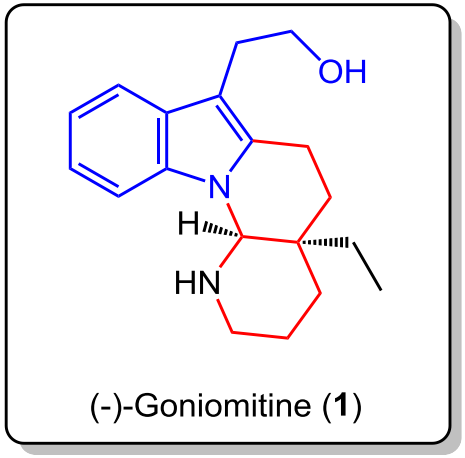
- **1990–1992** B.S., Sichuan Normal College
- **1994–1997** M.S., Nankai University (with Prof. Tian-Lin Liu)
- **2000–2003** Ph.D., Nankai University (with Prof. Qi-Lin Zhou)
- **2003–2005** Assistant Professor, Nankai University
- **2006–2011** Associate Professor, Nankai University
- **2007–2008** Postdoctoral Fellow, University of Maryland (with Prof. Micheal P. Doyle)
- **2011–now** Professor, Nankai University

Research Interests:

- The discovery and development of new catalytic synthetic methods
- The asymmetric total synthesis of various biologically active natural products
- The design and synthesis of new highly efficient chiral ligands and catalysts

Contents

Introduction



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

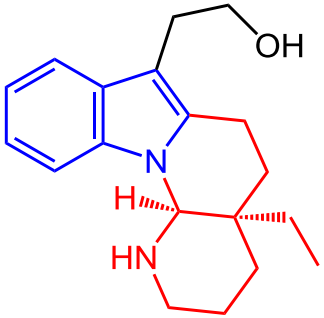
Gonioma Malagasy

- It is an important member of the Aspidosperma family of indole alkaloids, and was isolated from the root bark of *Gonioma Malagasy* by Husson et al in 1987;
- It displays promising antiproliferative activity in several tumor cell lines;
- It has a unique octahydroindolo[1,2-α][1,8]naphthyridine core together with a tryptophol moiety.

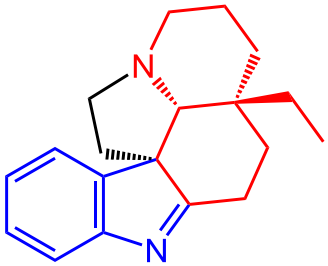
Husson, H.-P. *et al*. *Tetrahedron Lett*. **1987**, *28*, 2123.
Waser, J. *et al*. *Angew. Chem. Int. Ed*. **2010**, *49*, 5767.

Introduction

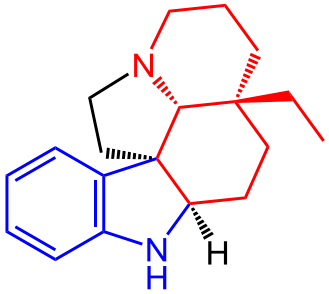
Representative *Aspidosperma*
family monoterpenoid indole alkaloids



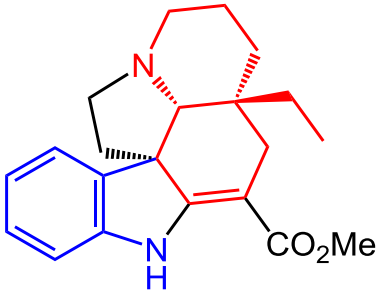
(-)-Goniomitine (**1**)



(+)-1,2-dehydro
aspidospermidine (**2**)

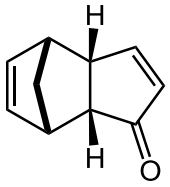
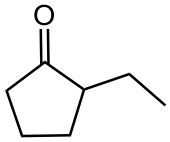
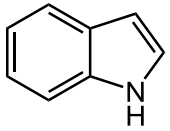
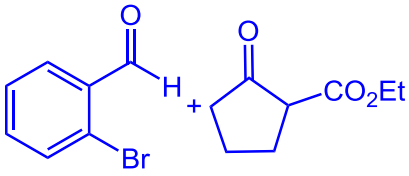


(+)-aspidospermidine (**3**)



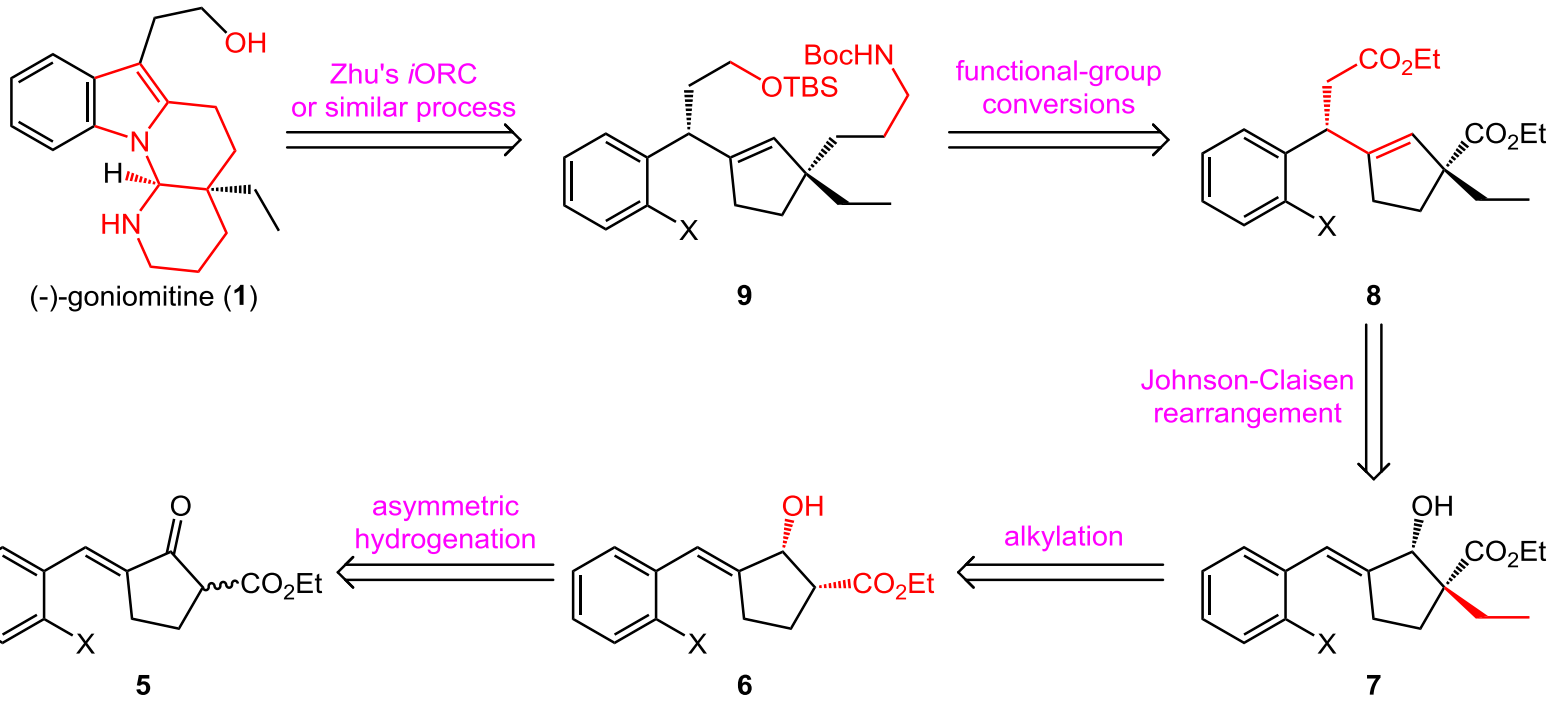
(+)-vincadifformine (**4**)

Introduction

Entry	Starting materials	Overall yield (steps, mg)	Authors
1		2.8% (24 steps)	Takano, S.
2		24% (5 steps, 9.2 mg)	Zu, L.
3		8% (11 steps, 33 mg)	Stoltz, B. M.
4		**27% (11 steps, 716 mg)**	**Xie, J.**

Stoltz, B. M. *et al*. *Angew. Chem. Int. Ed*. **2016**, *55*, 13529.
Zu, L. *et al*. *Angew. Chem. Int. Ed*. **2017**, *56*, 2754.
Takano, S. *et al*. *Chem. Commun*. **1991**, 462.

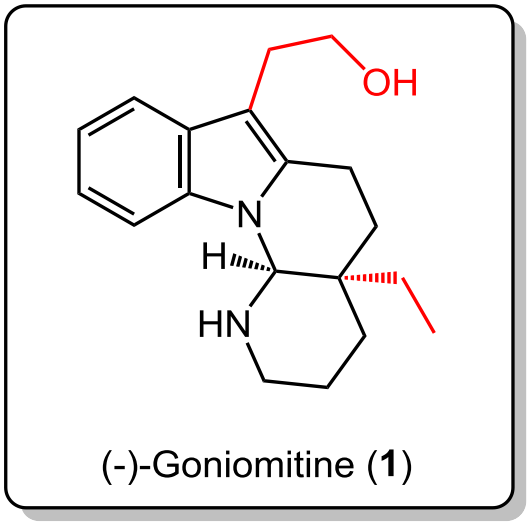
Retrosynthetic analysis



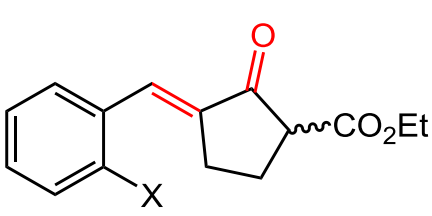
(X = NO_2, NHBoc, Br)

*i*ORC: integrated oxidation/reduction/cyclization

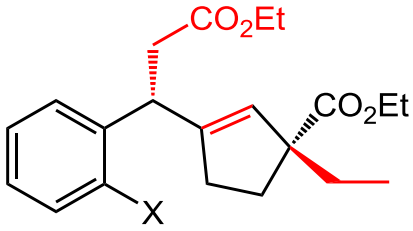
The synthesis of 8



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



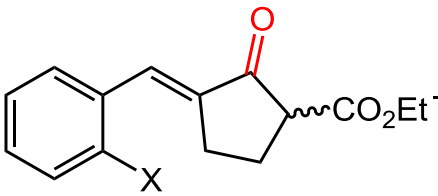
5



8

(X = NO_2, NHBoc, Br)

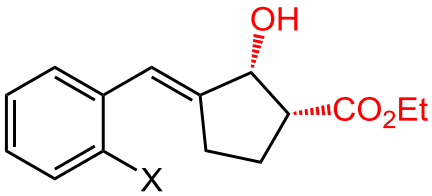
The synthesis of 8



5

5a, X = Br
5b, X = NO_2
5c, X = NHBoc

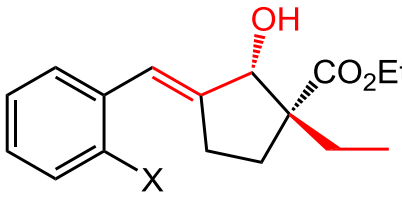
H_2 (10 atm)
(*S*)-**10** (0.2 mol%)
KO*t*Bu (1 mol%)
EtOH, rt



6

6a, (*S*)-**10b**, 95%, 92% ee
6b, (*S*)-**10b**, 98%, 91% ee
6c, (*S*)-**10a**, 87%, 80% ee

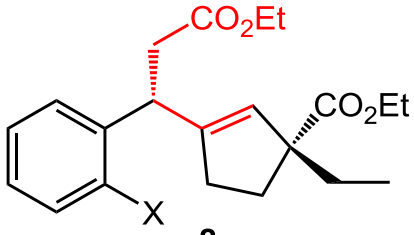
LDA, THF
then, HMPA, EtI



7

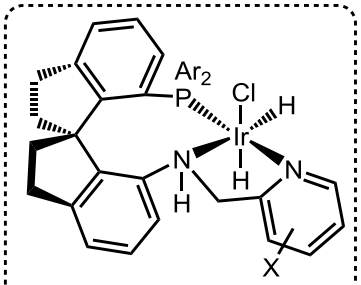
7a, 75%
7b, 30%
7c, 60%

$MeC(OEt)_3$
$EtCO_2H$ (5 mol%)



8

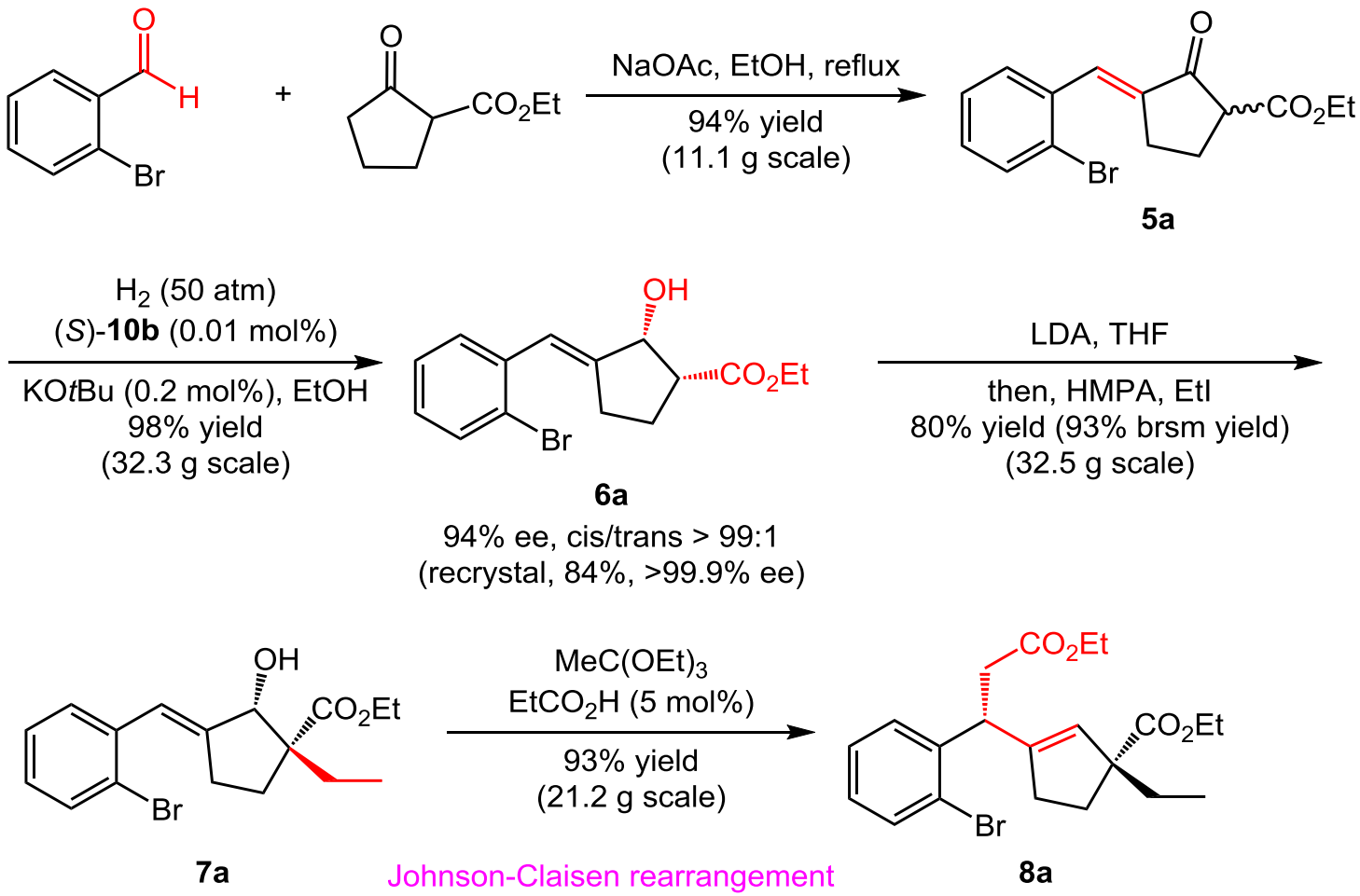
8a, 93%
8b, 71%
8c, 74%



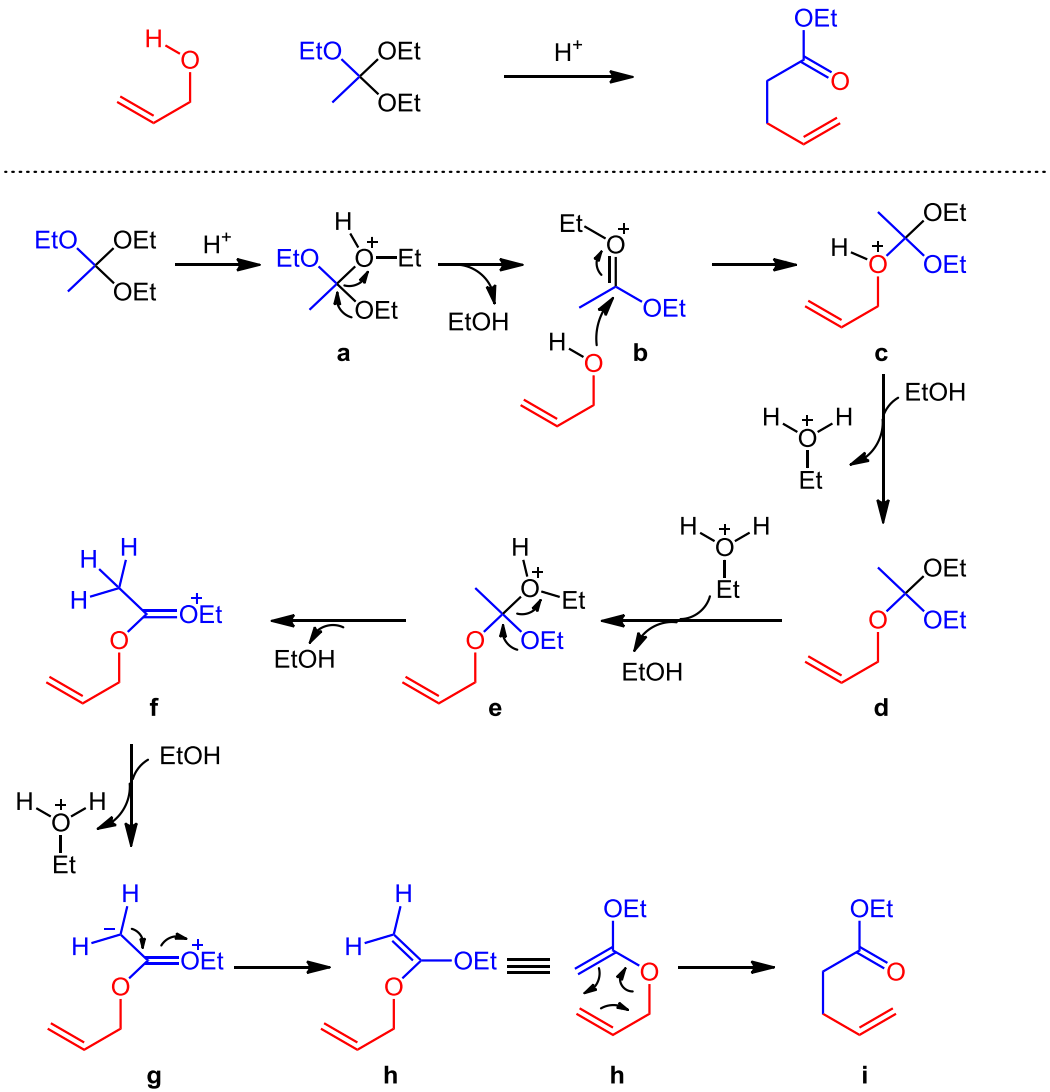
Ar = 3,5-(*t*Bu)$_2$C$_6$H$_3$

(*S*)-**10a**, X = 3-Me
(*S*)-**10b**, X = 4-*t*Bu

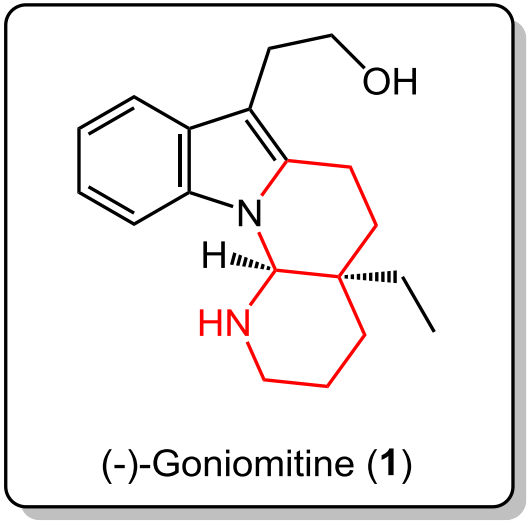
The synthesis of 8



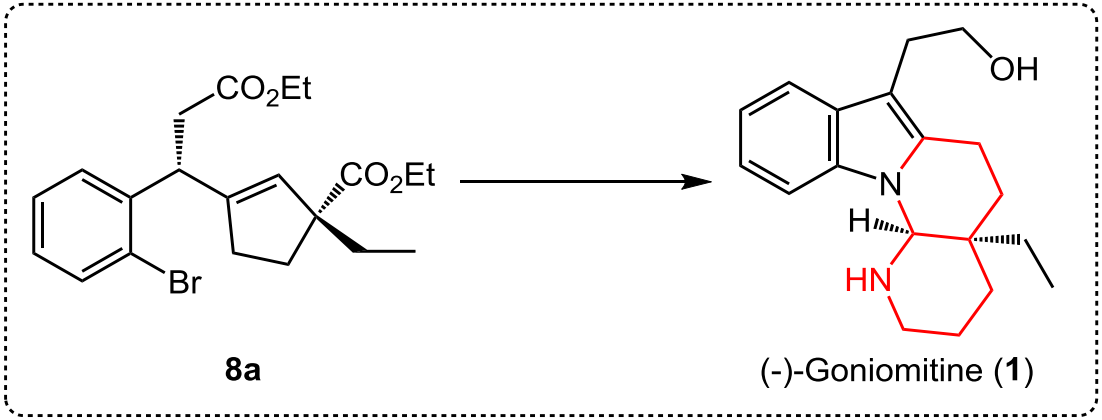
Johnson-Claisen rearrangement



The synthesis of (-)-Goniomitine



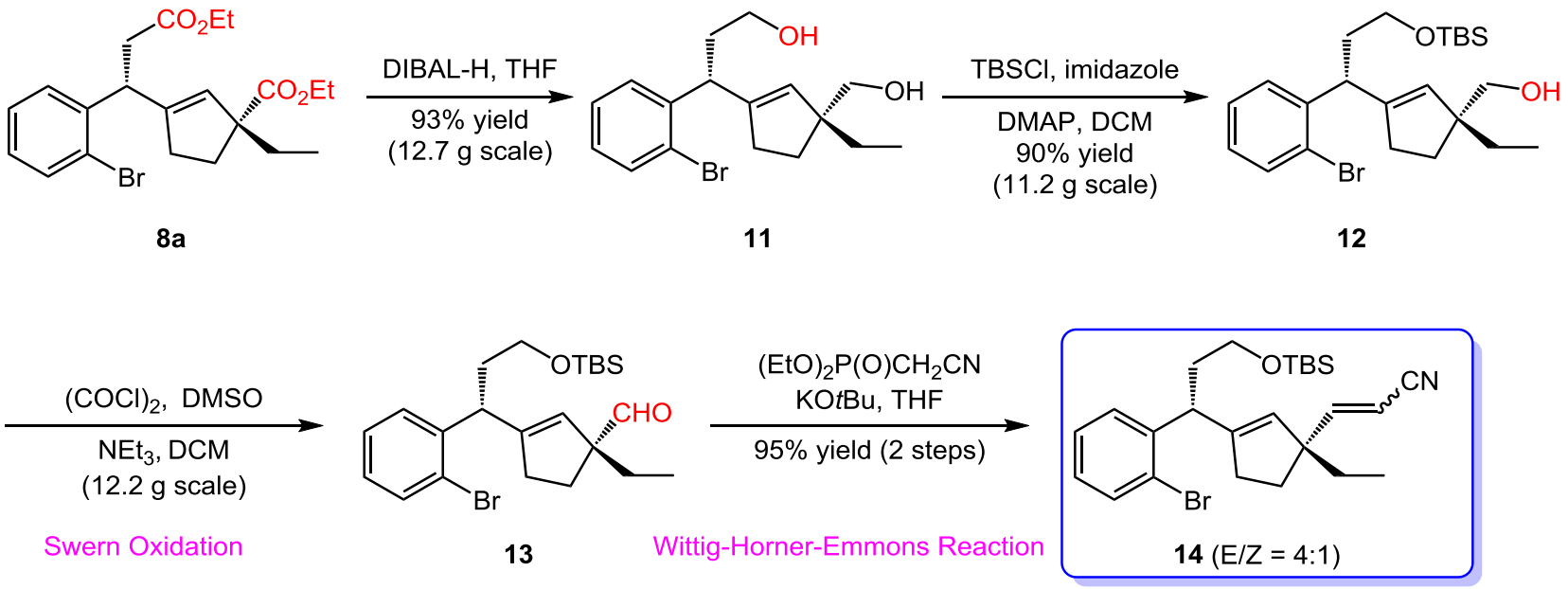
(-)-Goniomitine (**1**)



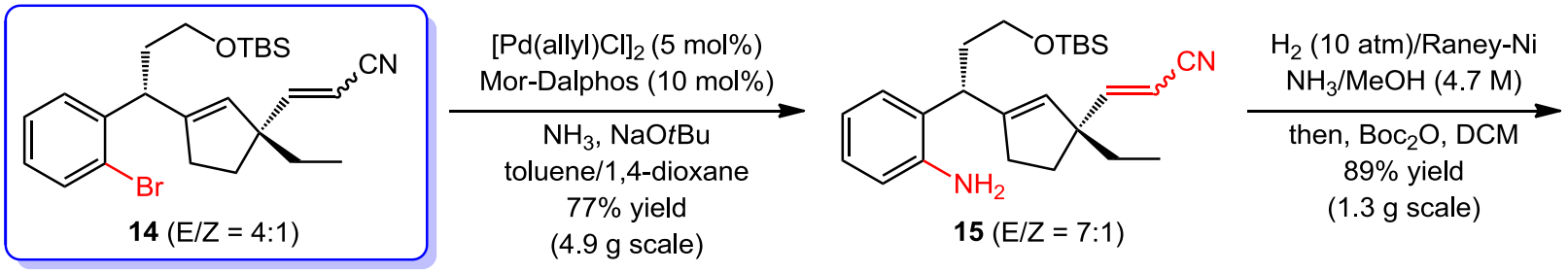
8a

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

The synthesis of 14



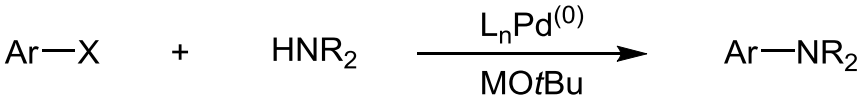
The synthesis of (-)-Goniomitine

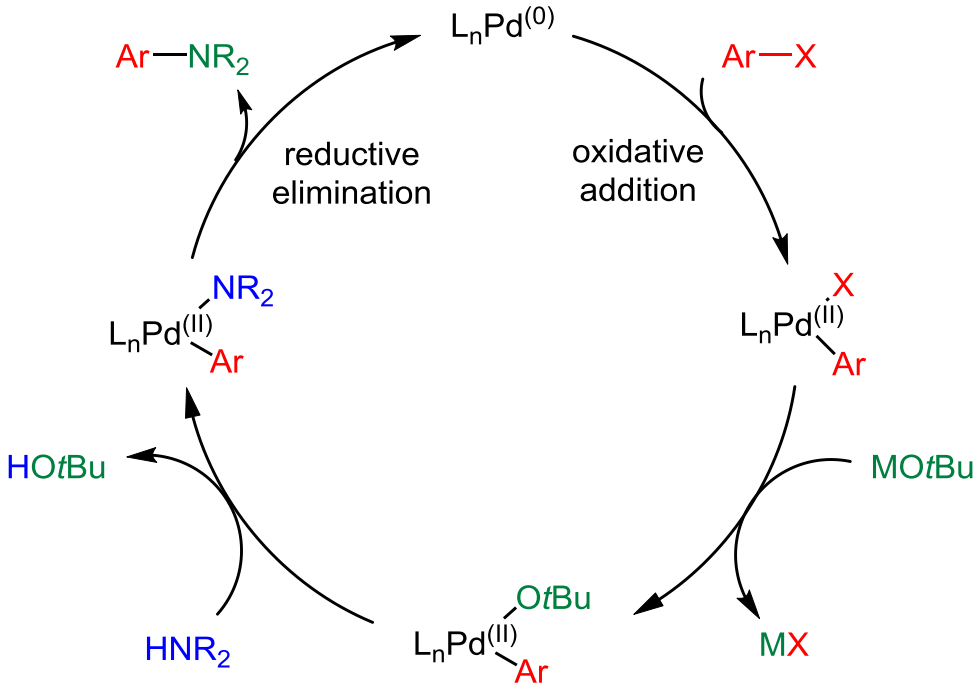


Buchwald-Hartwig Cross Coupling Reaction

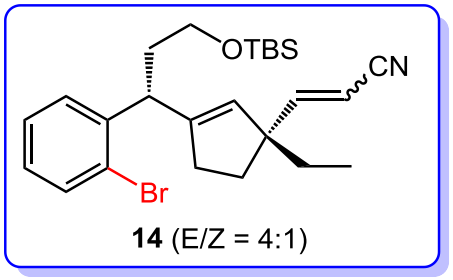
Zhu's *i*ORC

Buchwald-Hartwig cross coupling reaction





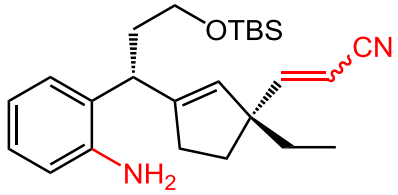
The synthesis of (-)-Goniomitine



14 (E/Z = 4:1)

$[Pd(allyl)Cl]_2$ (5 mol%)
Mor-Dalphos (10 mol%)

NH_3, NaO*t*Bu
toluene/1,4-dioxane
77% yield
(4.9 g scale)

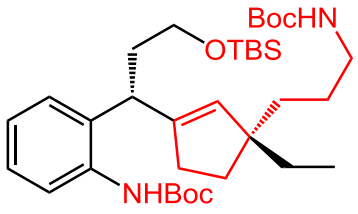


15 (E/Z = 7:1)

H_2 (10 atm)/Raney-Ni
NH_3/MeOH (4.7 M)

then, Boc_2O, DCM
89% yield
(1.3 g scale)

Buchwald-Hartwig Cross Coupling Reaction

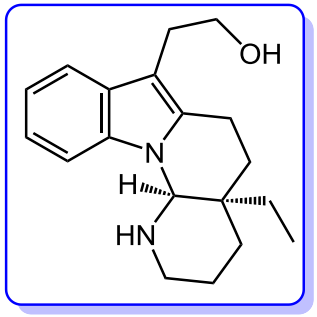


9

O_3, DCM, Me_2S

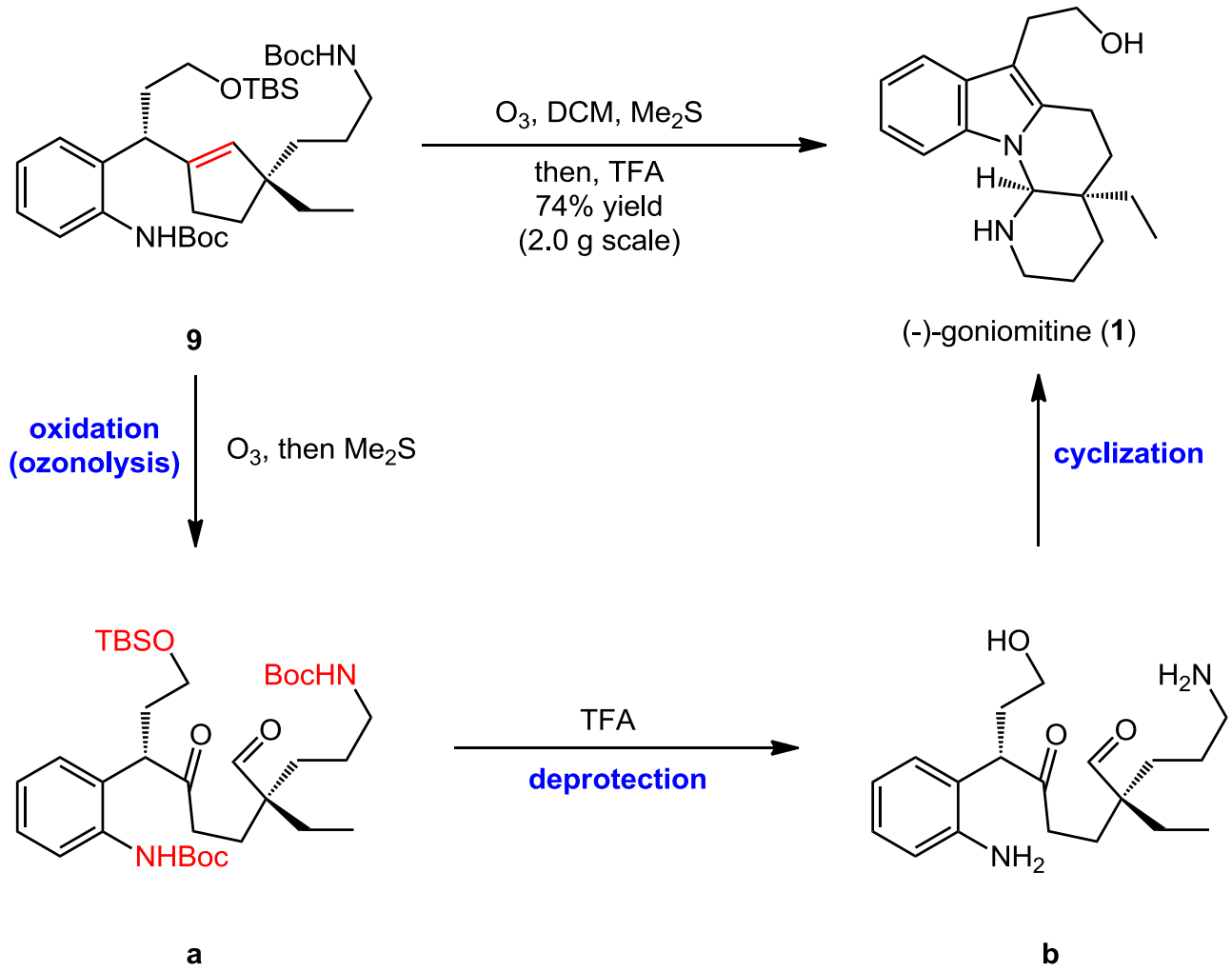
then, TFA
74% yield
(2.0 g scale)

Zhu's *i*ORC

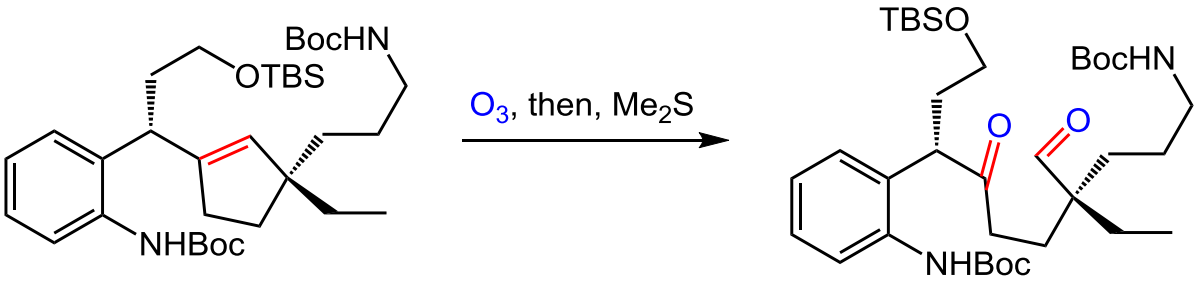


(-)-goniomitine (**1**)
716 mg, 11 steps
27% overall yield

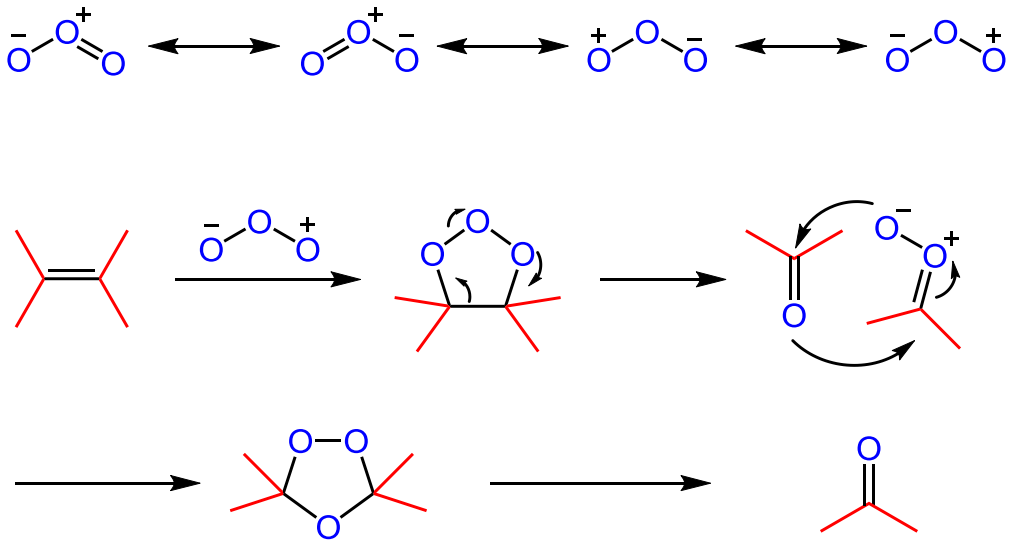
Zhu's *i*ORC


BocHN
OTBS
NHBoc
9
O_3, DCM, Me_2S
then, TFA
74% yield
(2.0 g scale)
OH
N
H
HN
(-)-goniomitine (1)
oxidation
(ozonolysis)
O_3, then Me_2S
cyclization
TBSO
BocHN
O
O
NHBoc
a
TFA
deprotection
HO
H_2N
O
O
NH_2
b

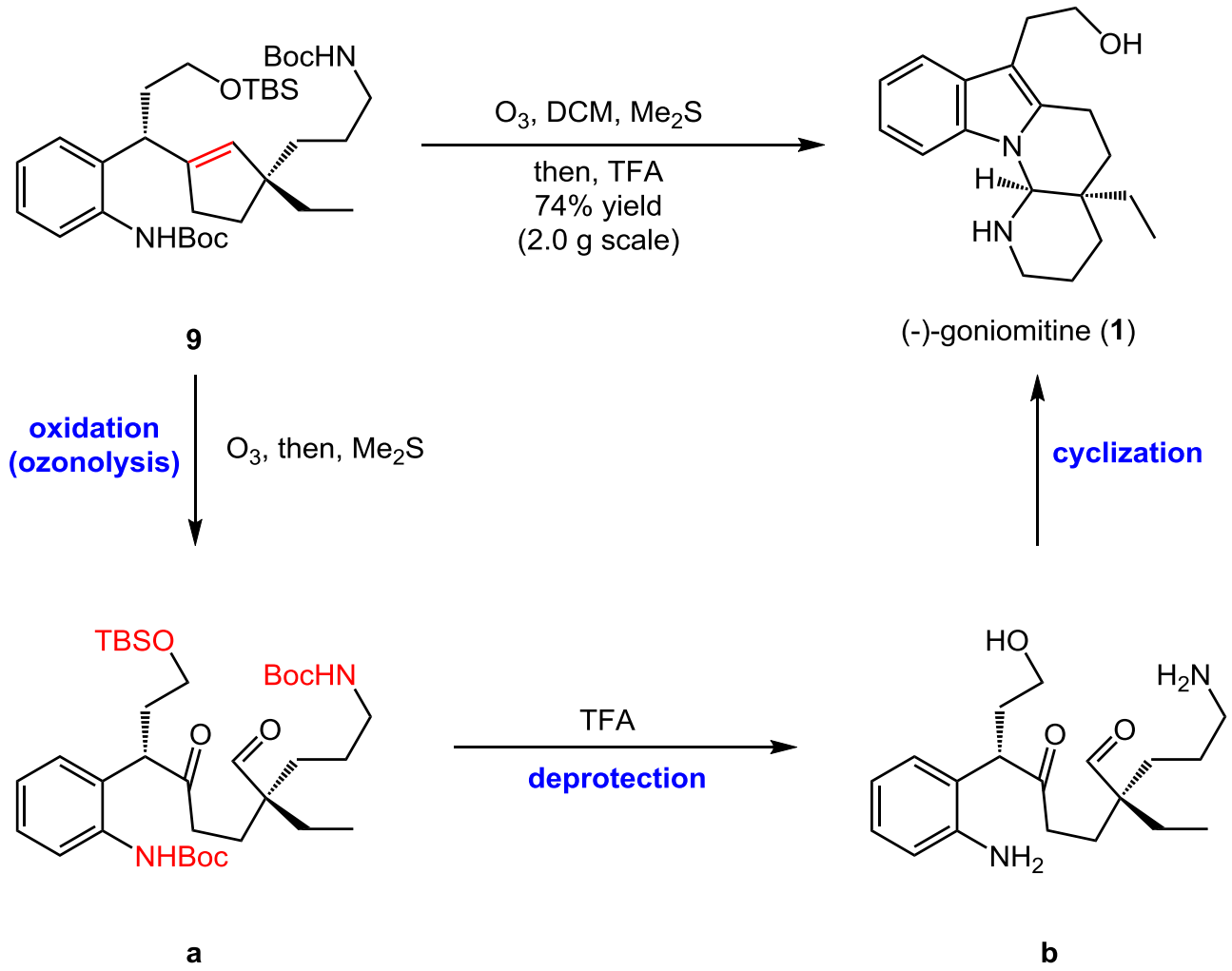
Ozonolysis



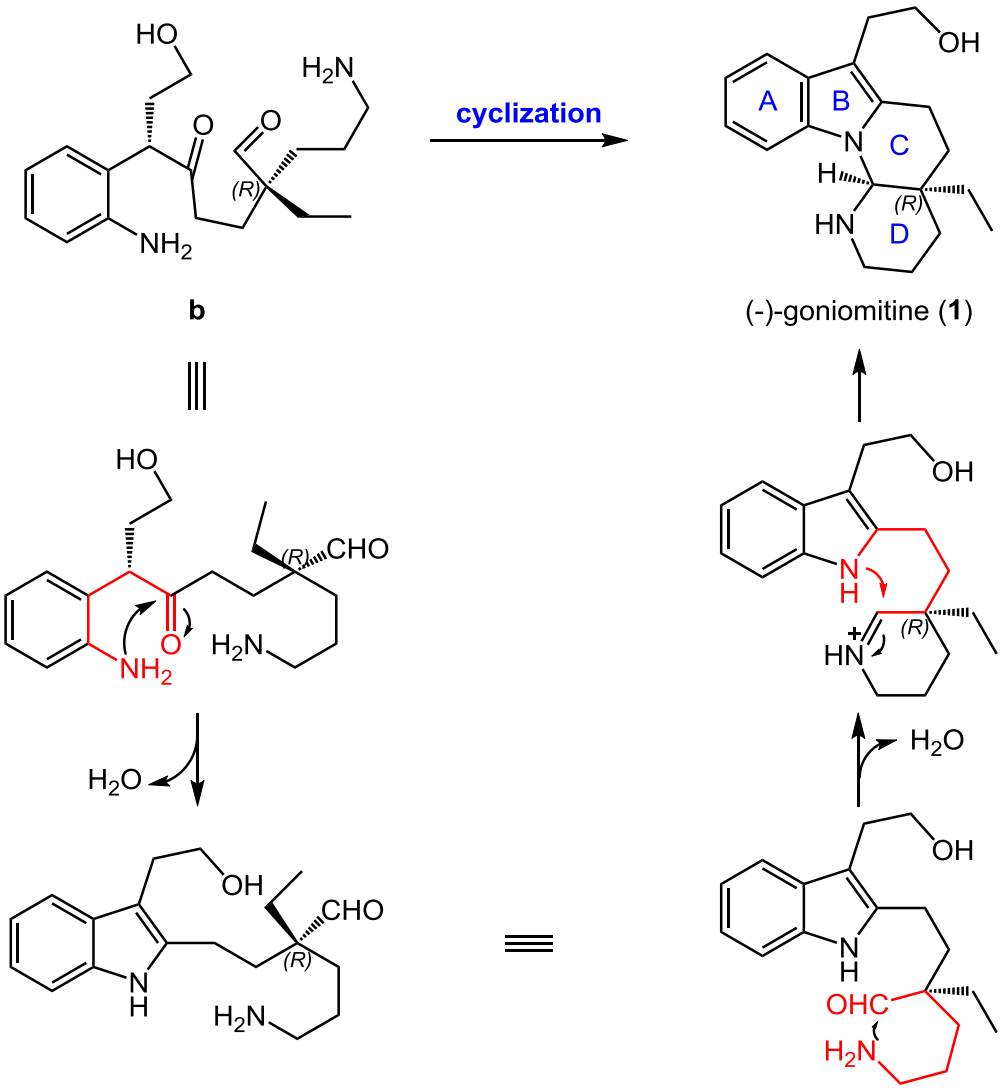
9 **a**



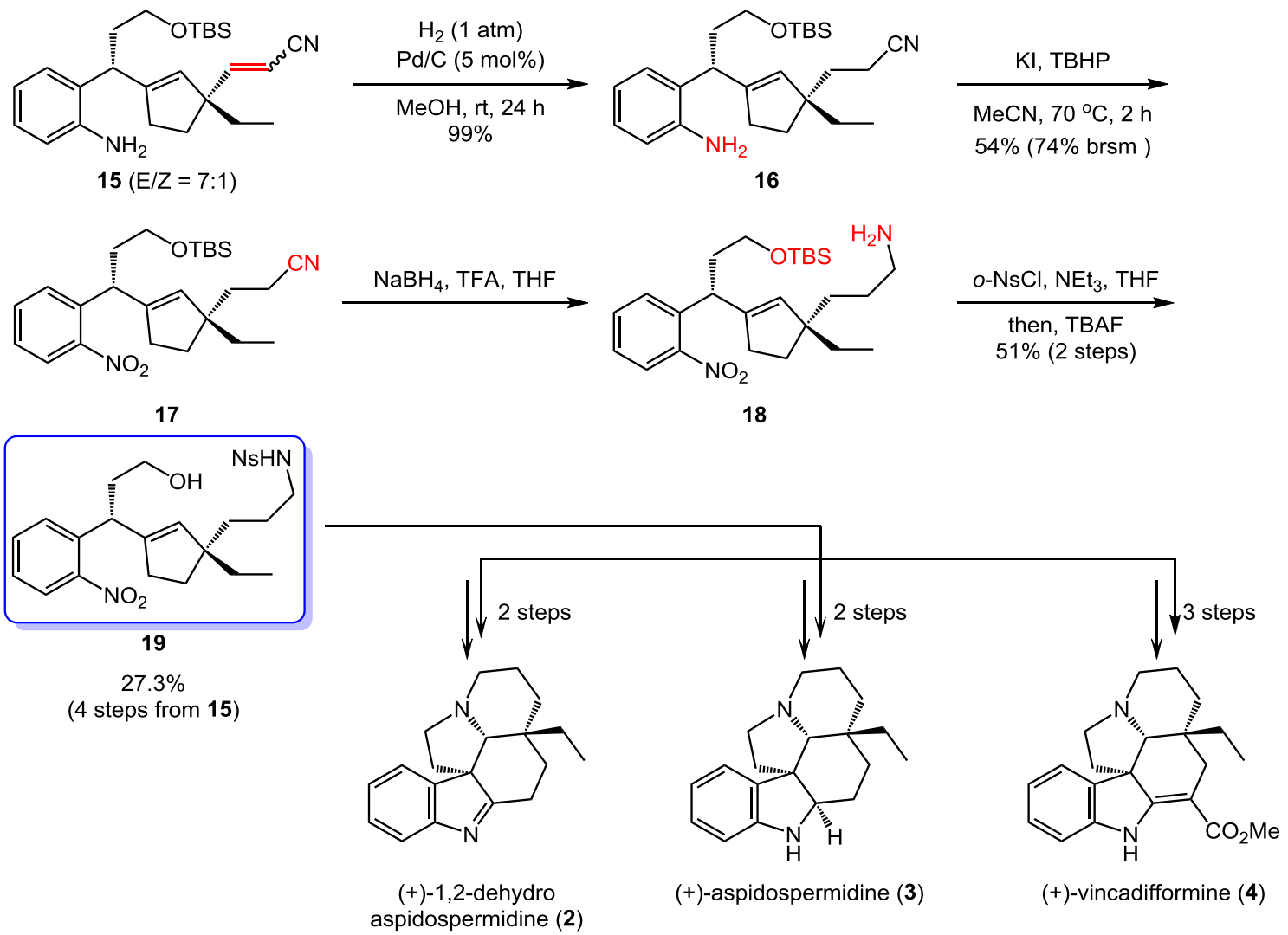
Zhu's *i*ORC


BocHN
OTBS
NHBoc
9
O_3, DCM, Me_2S
then, TFA
74% yield
(2.0 g scale)
OH
N
H
HN
(-)-goniomitine (1)
oxidation
(ozonolysis)
O_3, then, Me_2S
cyclization
TBSO
BocHN
O
O
NHBoc
a
TFA
deprotection
HO
H_2N
O
O
NH_2
b

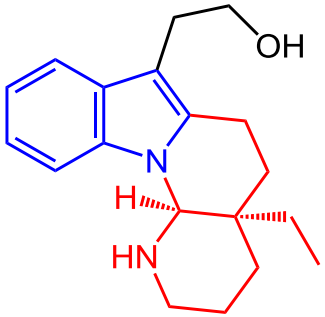
Cyclization



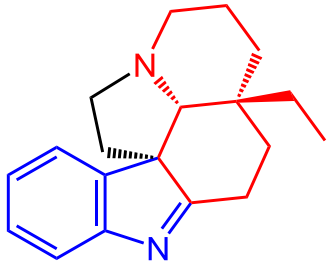
Formal synthesis of Aspidosperma family



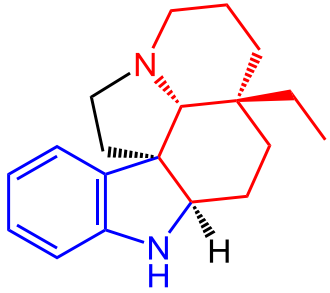
Summary



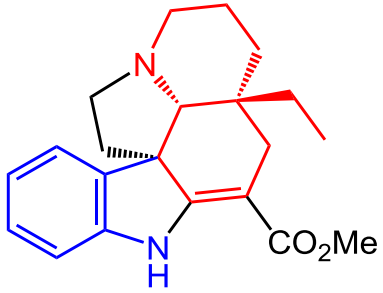
(-)-Goniomitine (**1**)



(+)-1,2-dehydro aspidospermidine (**2**)



(+)-aspidospermidine (**3**)



(+)-vincadifformine (**4**)

- Scalable total synthesis of (-)-goniomitine (1): 11 steps, 27% yield;
- Iridium-catalyzed asymmetric hydrogenation;
- Johnson–Claisen rearrangement;
- Integrated oxidation/deprotection/cyclization process;
- Formal synthesis of (+)-1,2-dehydroaspidospermidine (2), (+)-aspidospermidine (3), and (+)-vincadifformine (4).

The first paragraph

Natural products constitute a main source for drug discovery. Because most of the pharmacologically active natural products are optically pure compounds, the development of enantioselective synthetic methods for their synthesis, especially catalytic asymmetric synthetic methods for scalable production, has been a long-term challenge for synthetic chemists and the pharmaceutical industry. Monoterpene indole alkaloids represent an important class of natural products that possess significant biological activities, and they have drawn considerable attention from the field of synthetic chemistry during the past years. However, due to their high structural diversity and complexity, monoterpene indole alkaloids are challenging targets for testing new synthetic strategies.

The first paragraph

(-)-Goniomitine (1) is an important member of the Aspidosperma family of indole alkaloids, and was isolated from the root bark of Gonioma Malagasy by Husson et al in 1987. The bioassay indicated that this monoterpene indole alkaloid, which has a unique octahydroindolo[1,2-a][1,8]naphthyridine core together with a tryptophol moiety, displays promising antiproliferative activity in several tumor cell lines. Consequently, a number of total syntheses of this molecule, including enantioselective ones, have been reported. However, the scalable enantioselective total synthesis of 1 or its enantiomer remains a difficult issue.

The last paragraph

In conclusion, we have developed a scalable enantioselective total synthesis of (-)-goniomitine (1) using an iridium-catalyzed asymmetric hydrogenation of exocyclic enone ester to control the configuration, an alkylation and a Johnson–Claisen rearrangement to construct the substituted cyclopentene and the side chain of tryptophol moiety, and an integrated oxidation/deprotection/cyclization process to synthesize the tetracyclic ring. This concise and efficient asymmetric synthetic strategy was also successfully applied to the formal synthesis of (+)-1,2-dehydroaspidospermidine (2), (+)-aspidospermidine (3), and (+)-vincadifformine (4).

Thanks
for your attention