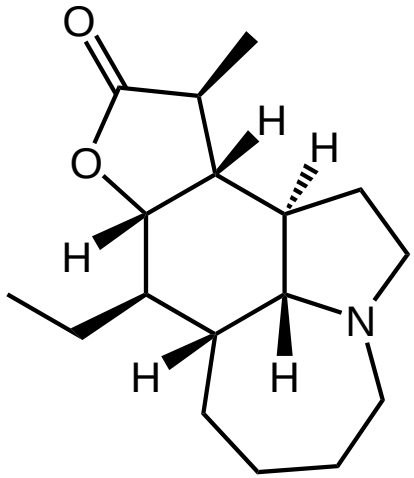
Literature Report

Changbin Yu 2012-02-28　　检查: Kai Gao

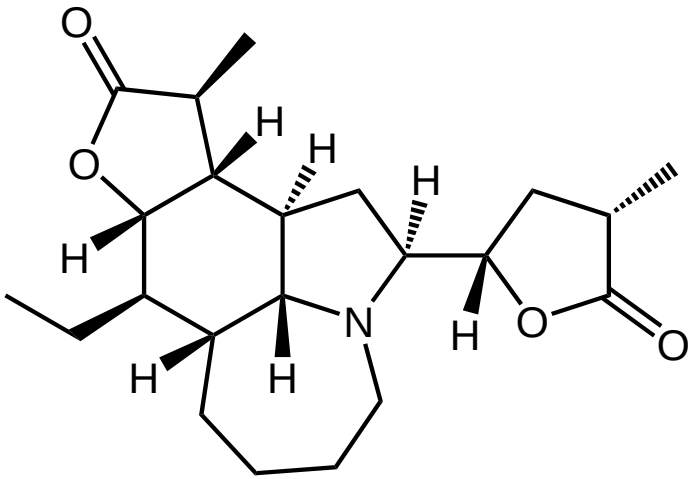
Enantioselective Total Synthesis of (-)-Stenine

Hongbin Zhang* *et al*. *Angew. Chem*. *Int. Ed*. **2012,** *51*, 1024-1027.

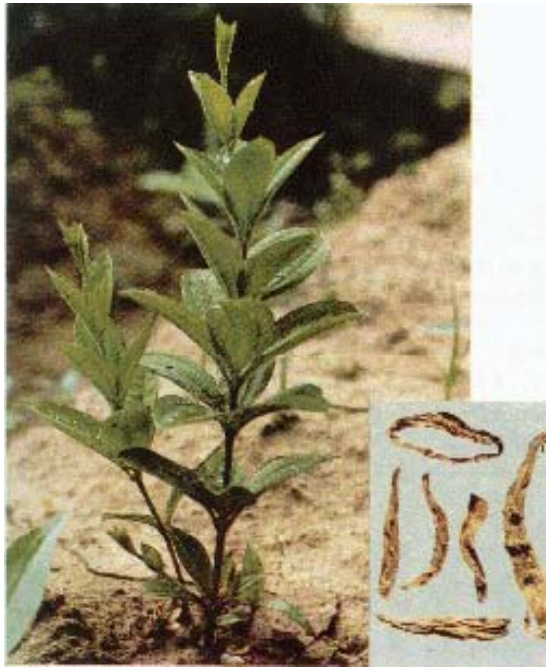
Structures of (-)-Stenine (**1**) and Tuberostemonine (**2**)



(-)-Stenine (**1**)



Tuberostemonine (**2**)



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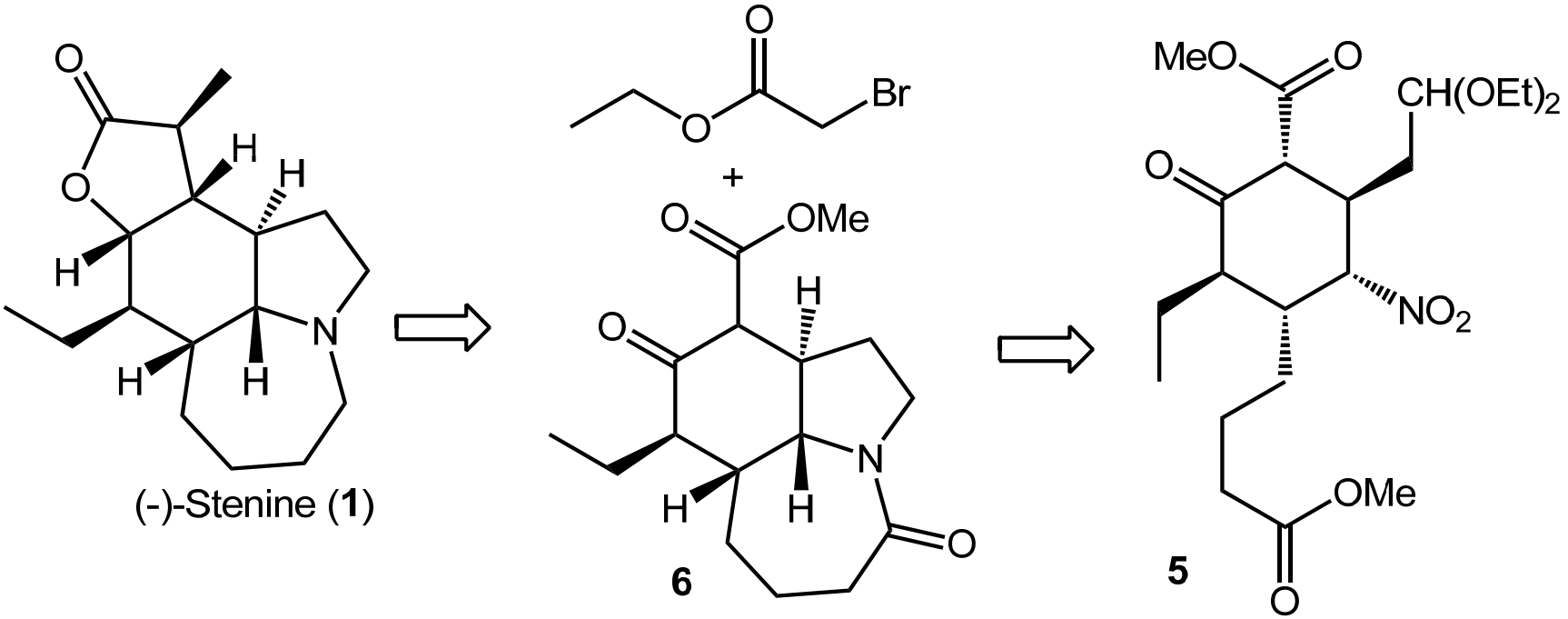
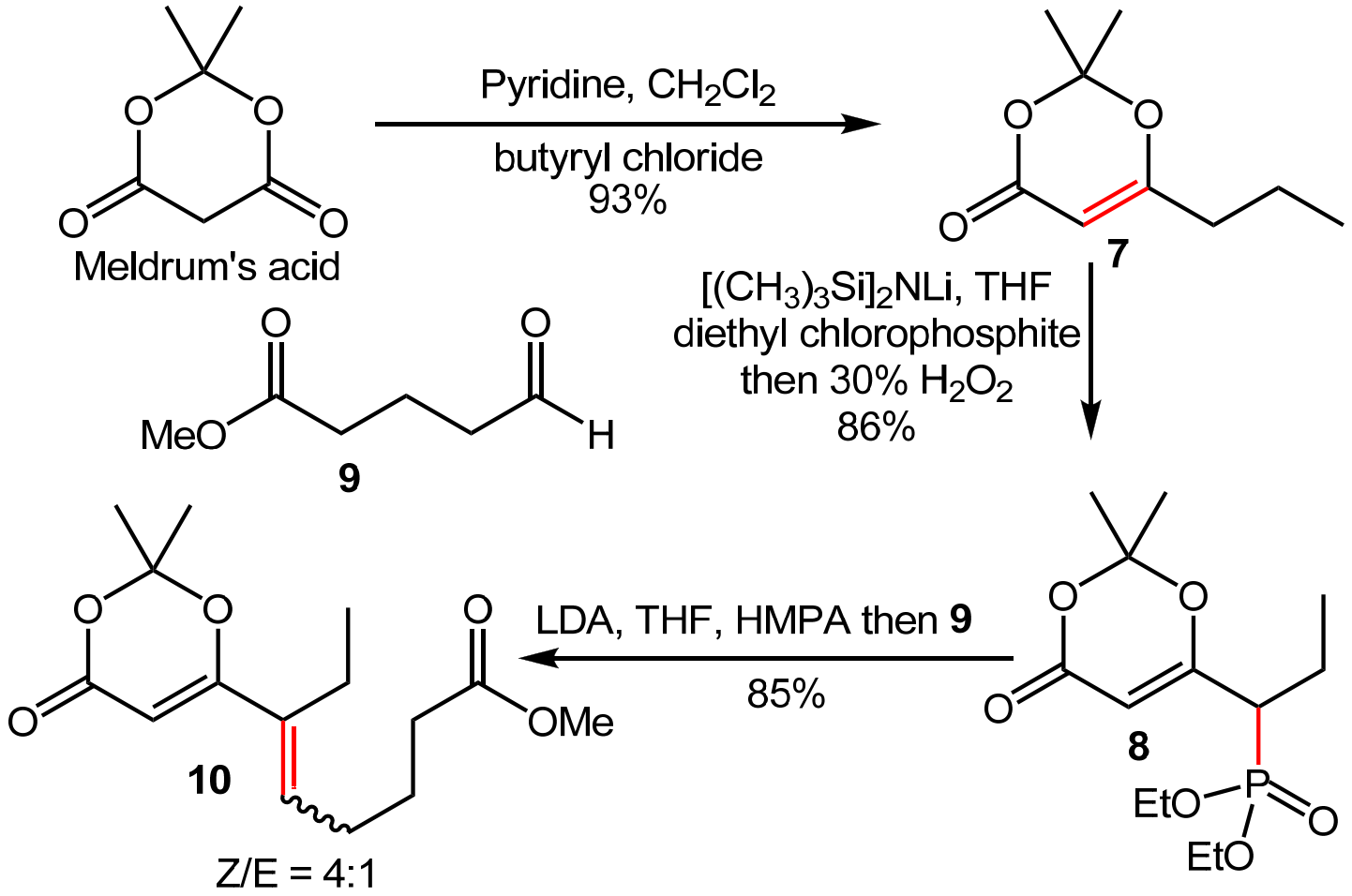
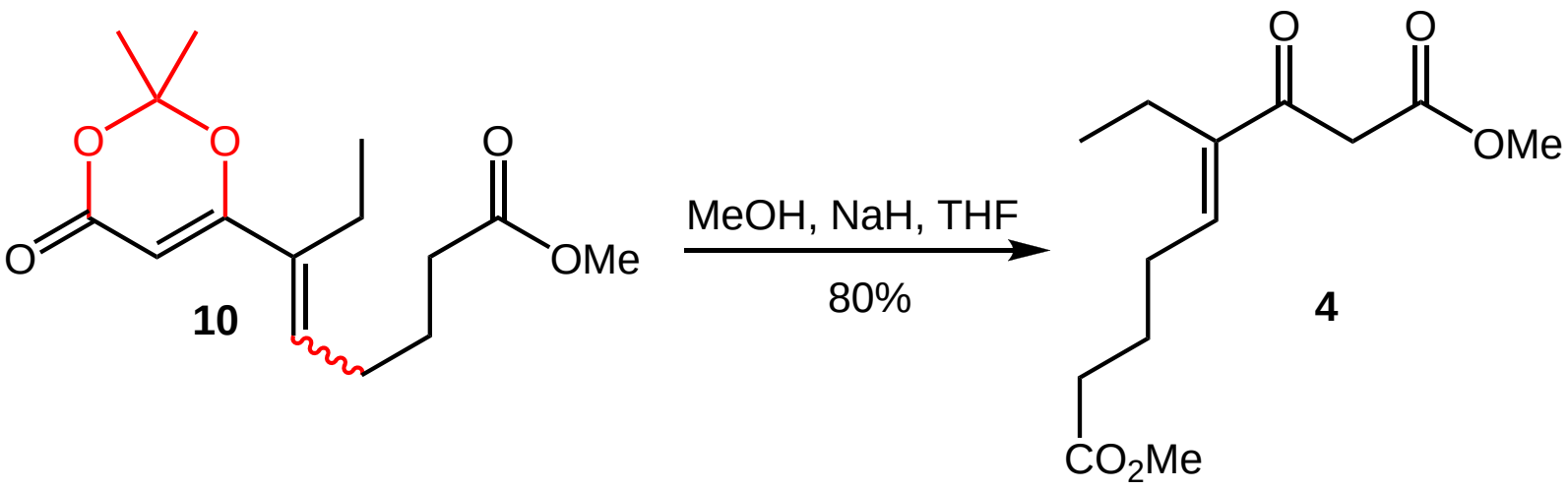
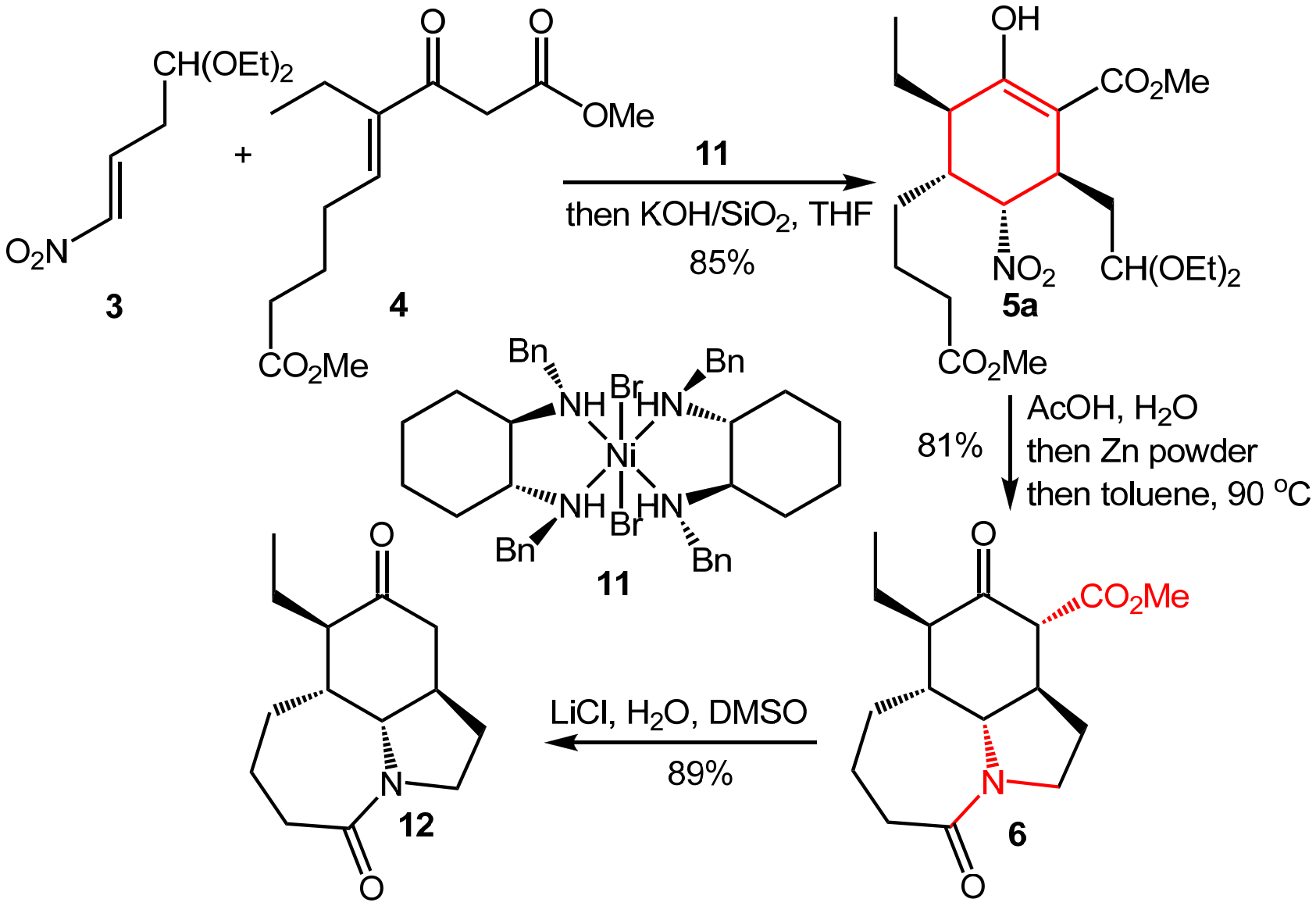
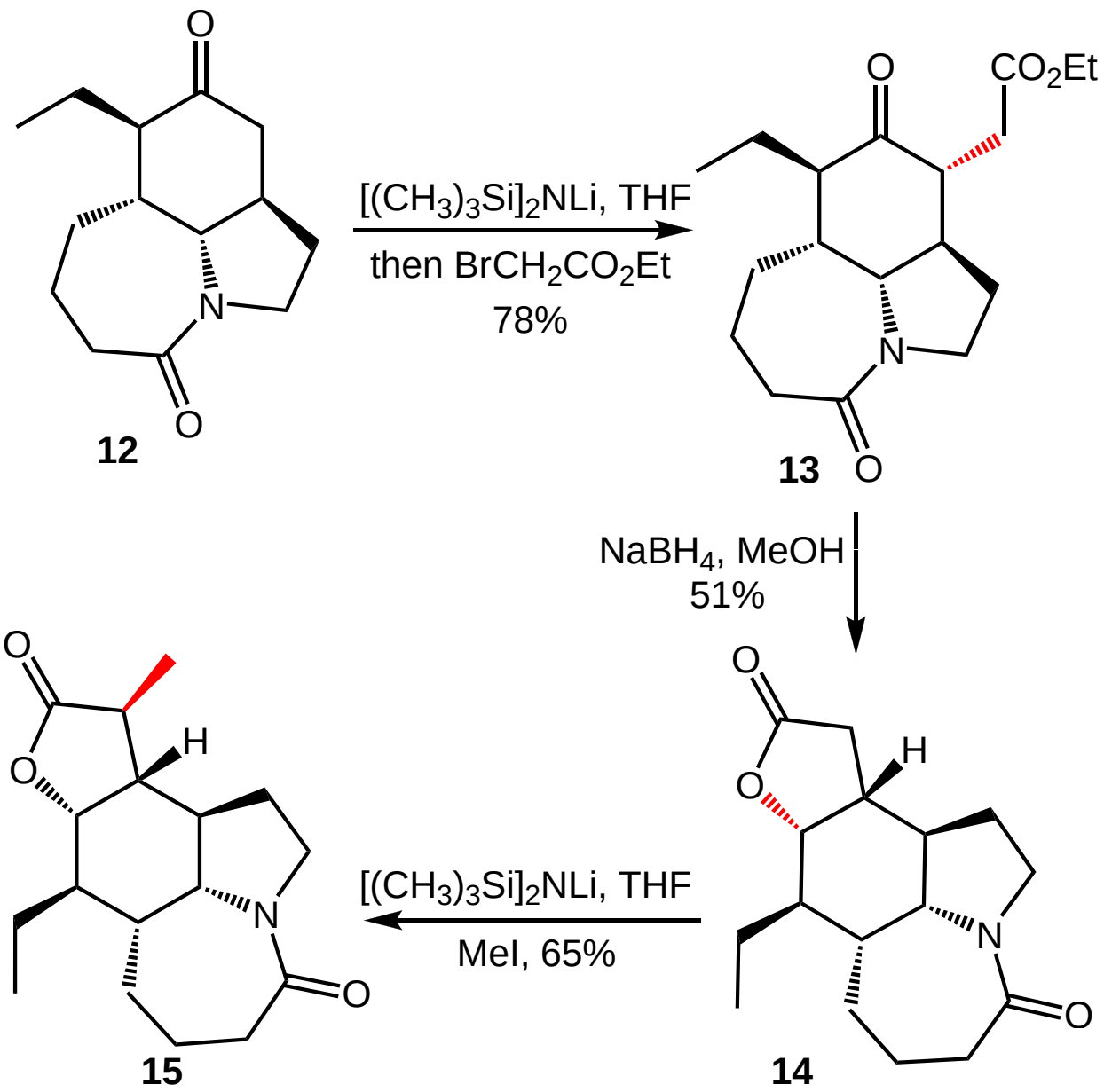
Retrosynthetic analysis of (-)-Stenine (**1**)

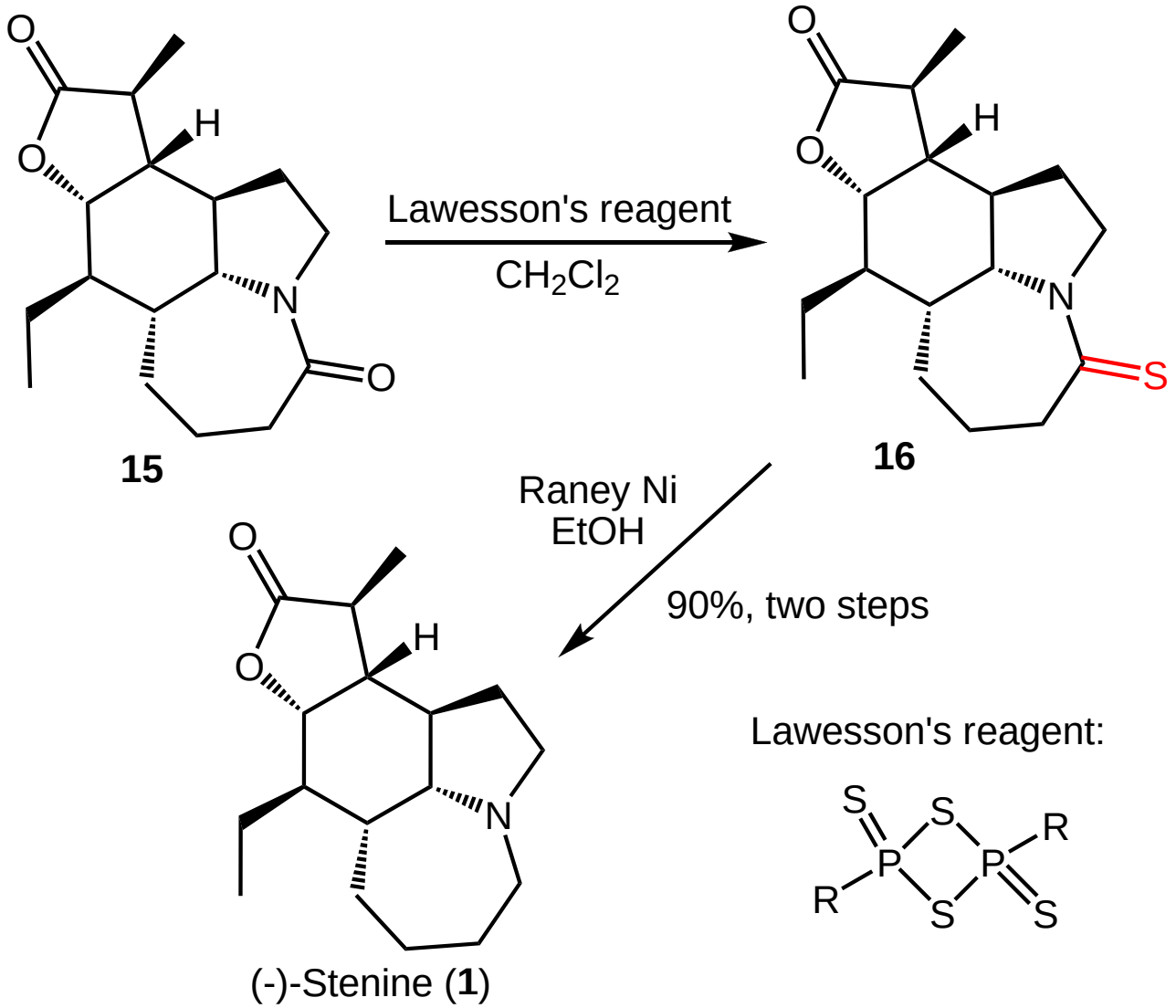



Pyridine, CH2Cl2
butyryl chloride
93%
Meldrum's acid
7
[(CH3)3Si]2NLi, THF
diethyl chlorophosphite
then 30% H2O2
86%
9
LDA, THF, HMPA then 9
85%
8
10
Z/E = 4:1

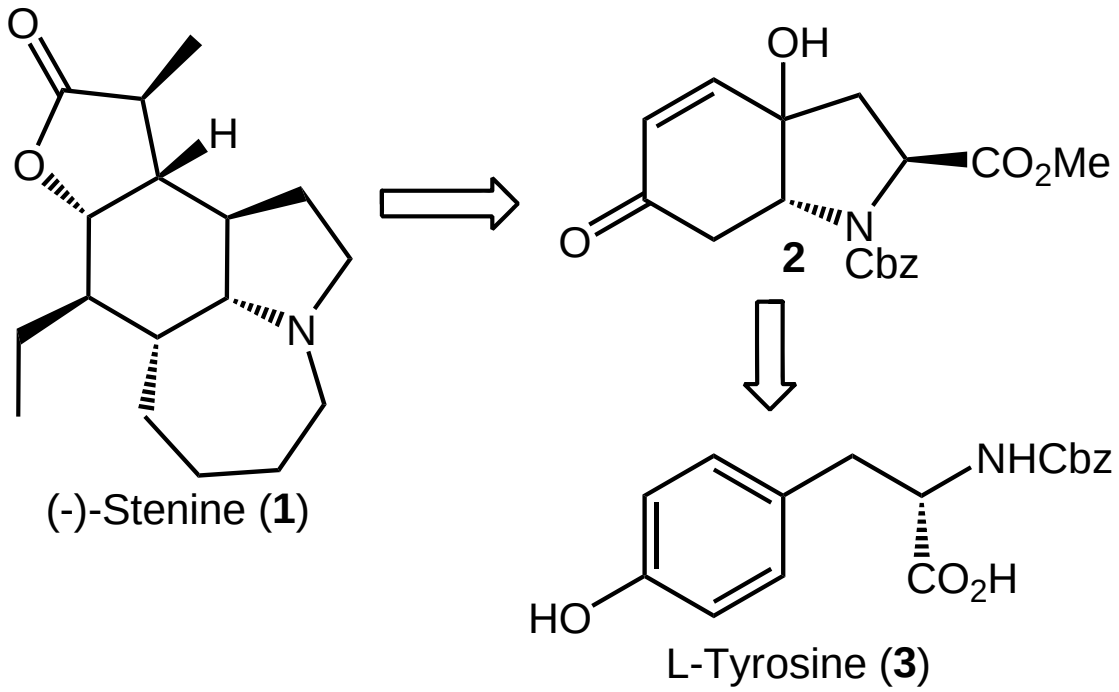

O
O
O
O
OMe
10
MeOH, NaH, THF
80%
O
O
OMe
4
CO2Me


CH(OEt)2
O2N
3
+
O
O
OMe
CO2Me
4
11
then KOH/SiO2, THF
85%
OH
CO2Me
NO2
CH(OEt)2
5a
CO2Me
Bn
NH
Br
HN
Bn
Ni
NH
Br
HN
Bn
Bn
11
81%
AcOH, H2O
then Zn powder
then toluene, 90 °C
O
CO2Me
N
6
O
LiCl, H2O, DMSO
89%
O
N
12
O

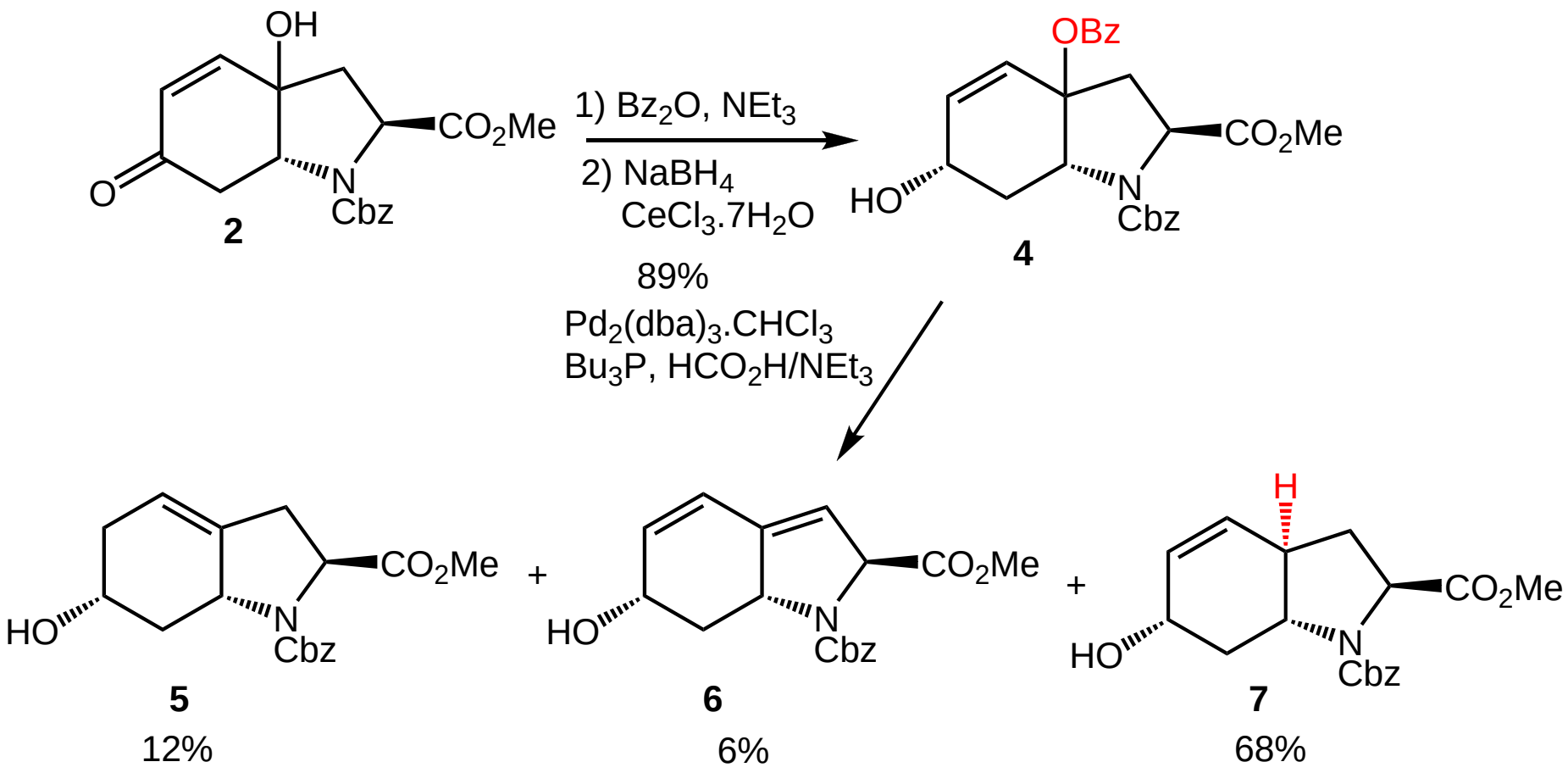

O
N
O
12
[(CH3)3Si]2NLi, THF
then BrCH2CO2Et
78%
O
CO2Et
N
O
13
NaBH4, MeOH
51%
O
H
O
N
O
14
[(CH3)3Si]2NLi, THF
MeI, 65%
O
H
O
N
O
15

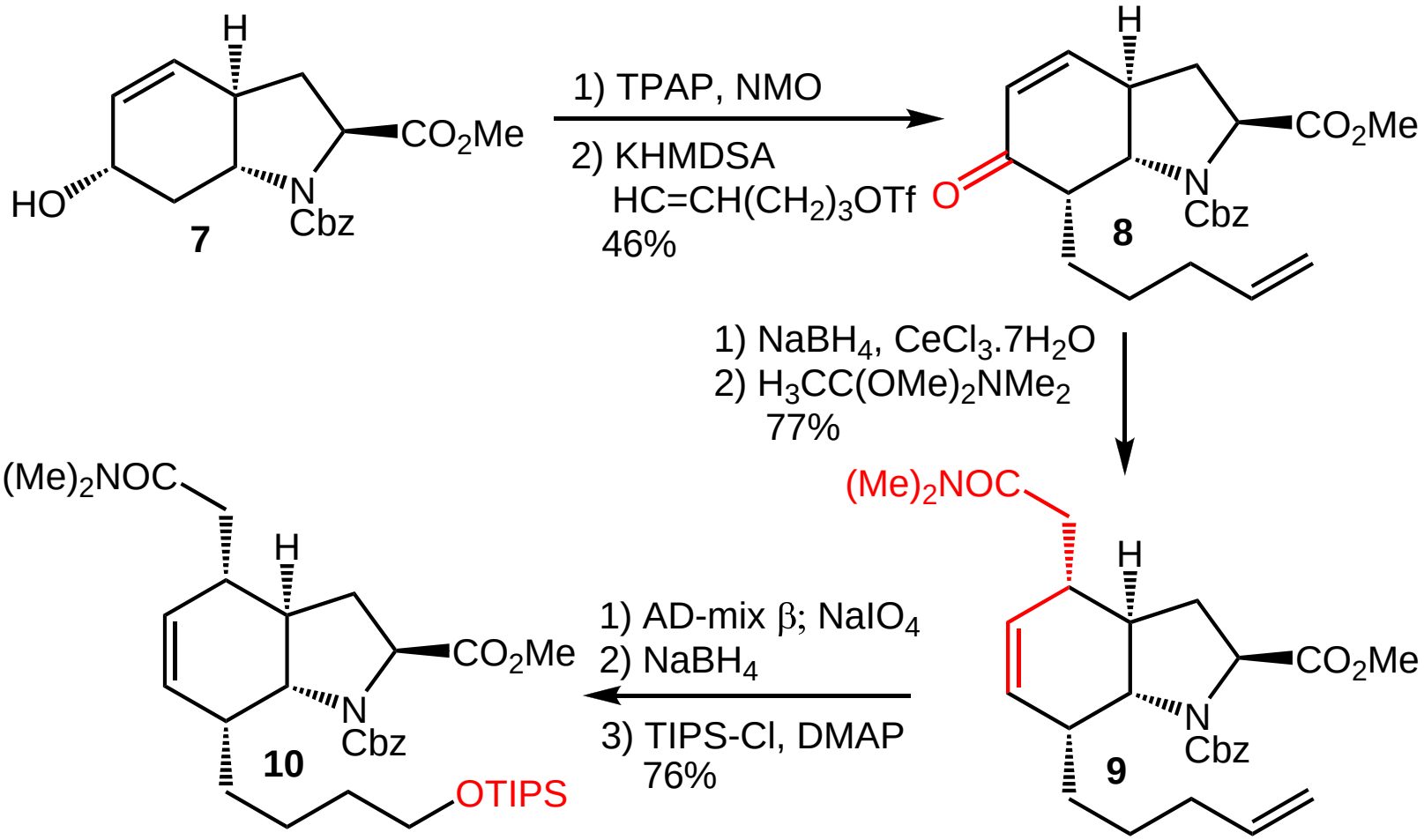

O
O
H
N
O
15
Lawesson's reagent
CH_2Cl_2
O
O
H
N
S
16
Raney Ni
EtOH
90%, two steps
O
O
H
N
(-)-Stenine (**1**)
Lawesson's reagent:
S
S
R
P
P
R
S
S

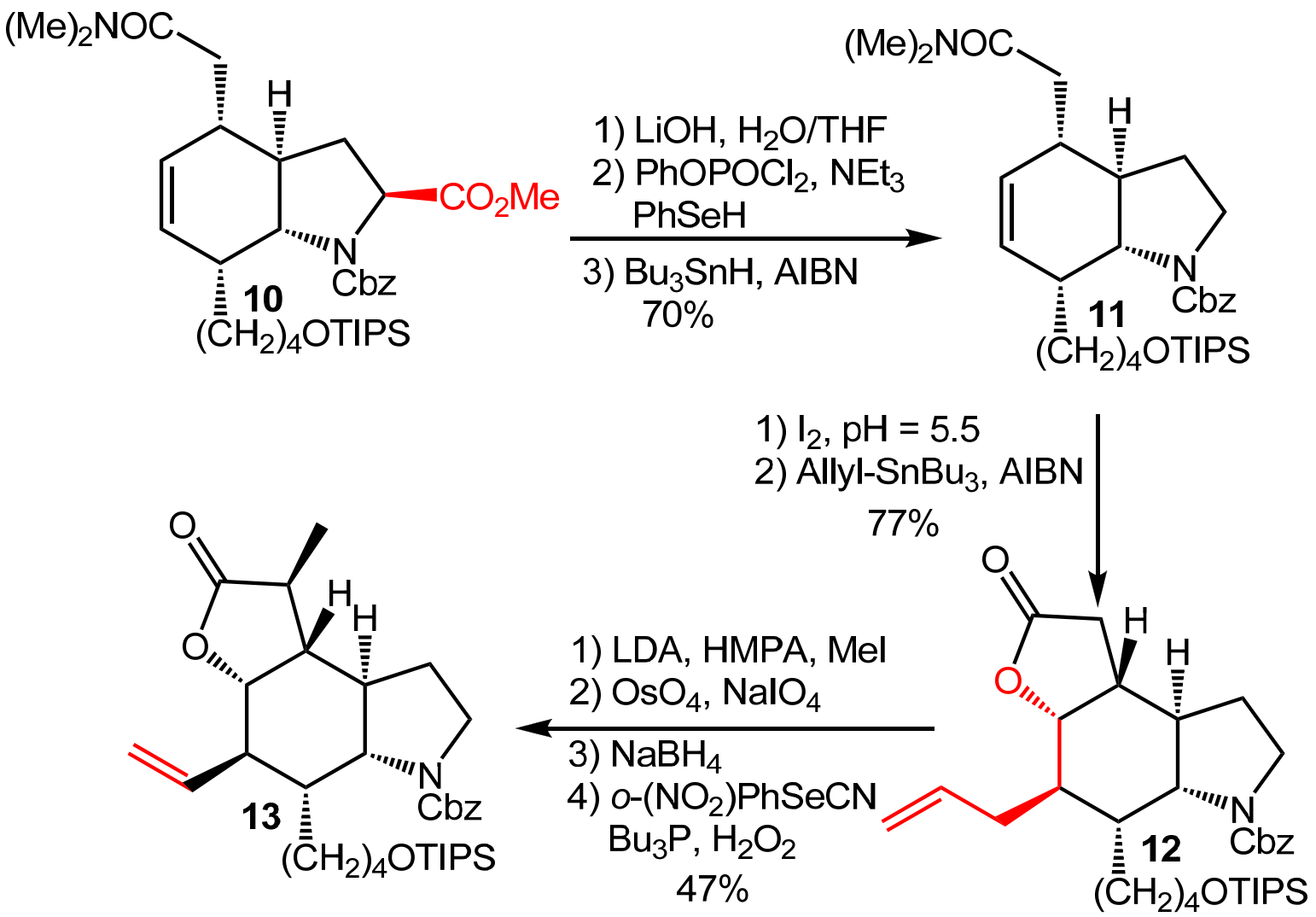
Retrosynthetic analysis of (-)-Stenine (**1**)

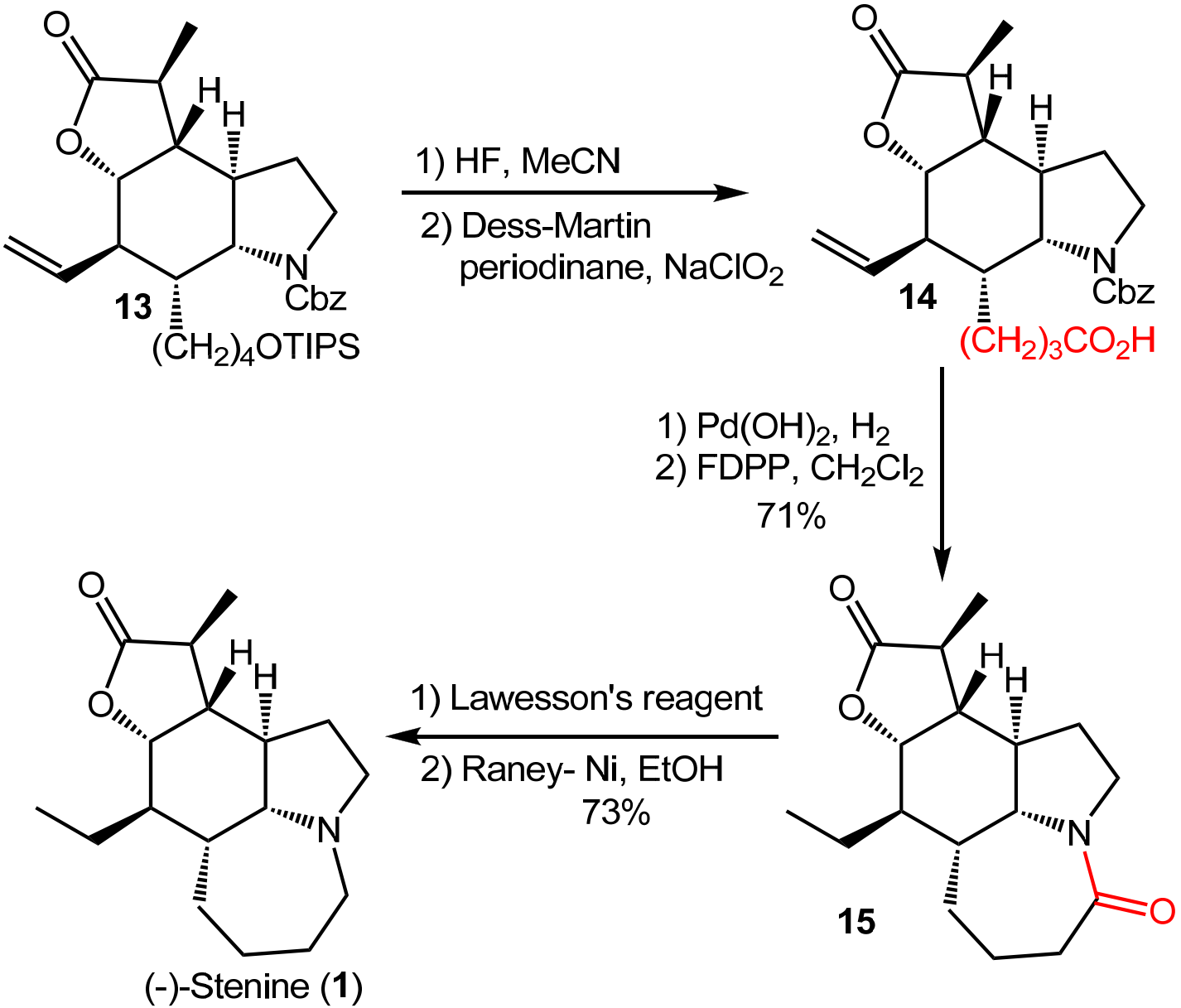


Peter Wipf *et al*. *J. Am. Chem. Soc*. **1995**, *117*, 11106-11112.

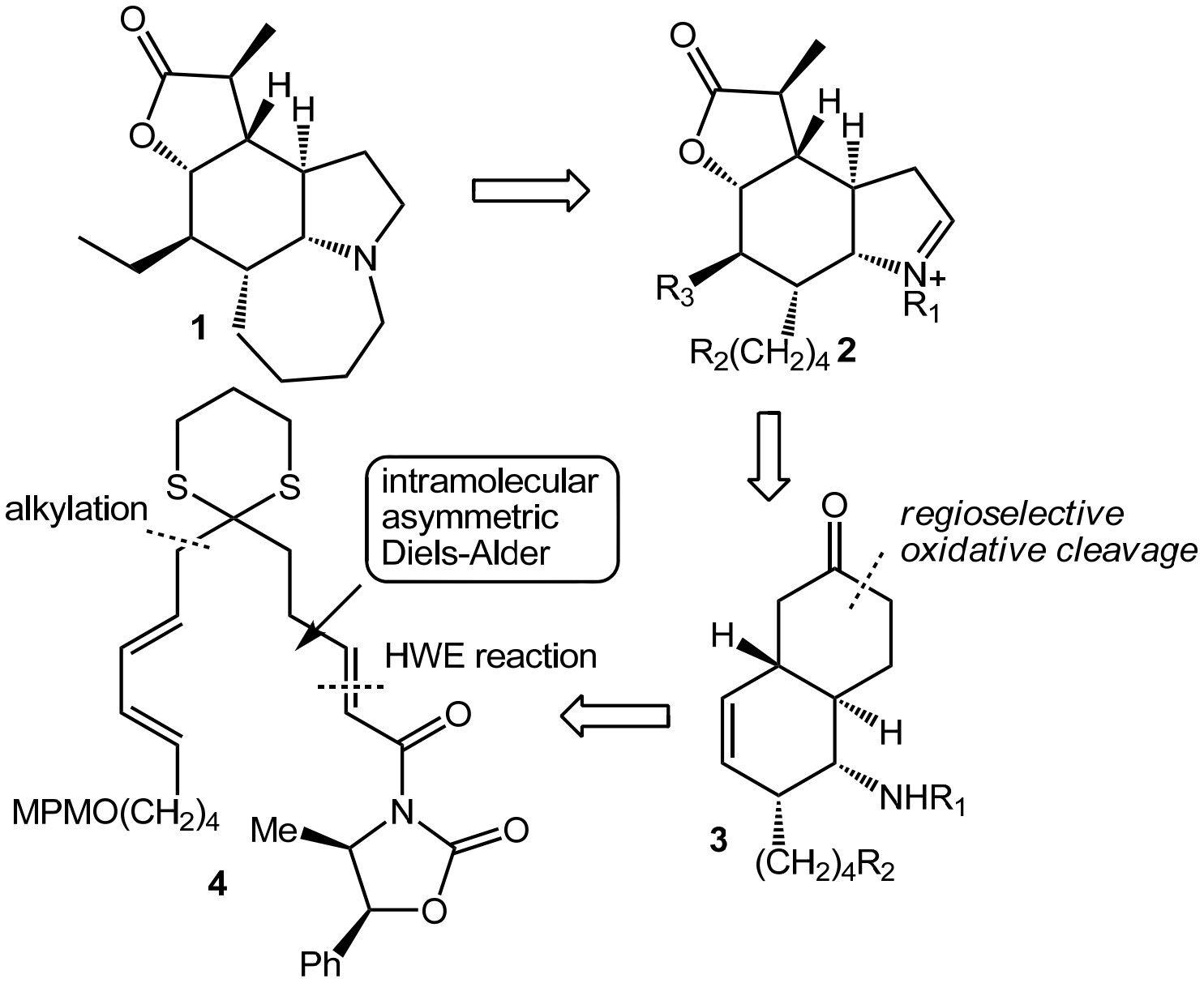

OH
O
CO2Me
N
Cbz
2
1) Bz2O, NEt3
2) NaBH4
CeCl3.7H2O
89%
OBz
HO
CO2Me
N
Cbz
4
Pd2(dba)3.CHCl3
Bu3P, HCO2H/NEt3
HO
CO2Me
N
Cbz
5
12%
+
HO
CO2Me
N
Cbz
6
6%
+
H
HO
CO2Me
N
Cbz
7
68%


H
HO
CO2Me
N
Cbz
7
1) TPAP, NMO
2) KHMDSA
HC=CH(CH2)3OTf
46%
O
8
1) NaBH4, CeCl3.7H2O
2) H3CC(OMe)2NMe2
77%
(Me)2NOC
9
1) AD-mix β; NaIO4
2) NaBH4
3) TIPS-Cl, DMAP
76%
10
OTIPS


(Me)2NOC
H
CO2Me
N
Cbz
10
(CH2)4OTIPS
1) LiOH, H2O/THF
2) PhOPOCl2, NEt3
PhSeH
3) Bu3SnH, AIBN
70%
(Me)2NOC
H
N
Cbz
11
(CH2)4OTIPS
1) I2, pH = 5.5
2) Allyl-SnBu3, AIBN
77%
O
H
H
O
O
N
Cbz
12
(CH2)4OTIPS
1) LDA, HMPA, MeI
2) OsO4, NaIO4
3) NaBH4
4) o-(NO2)PhSeCN
Bu3P, H2O2
47%
O
H
H
O
N
Cbz
13
(CH2)4OTIPS

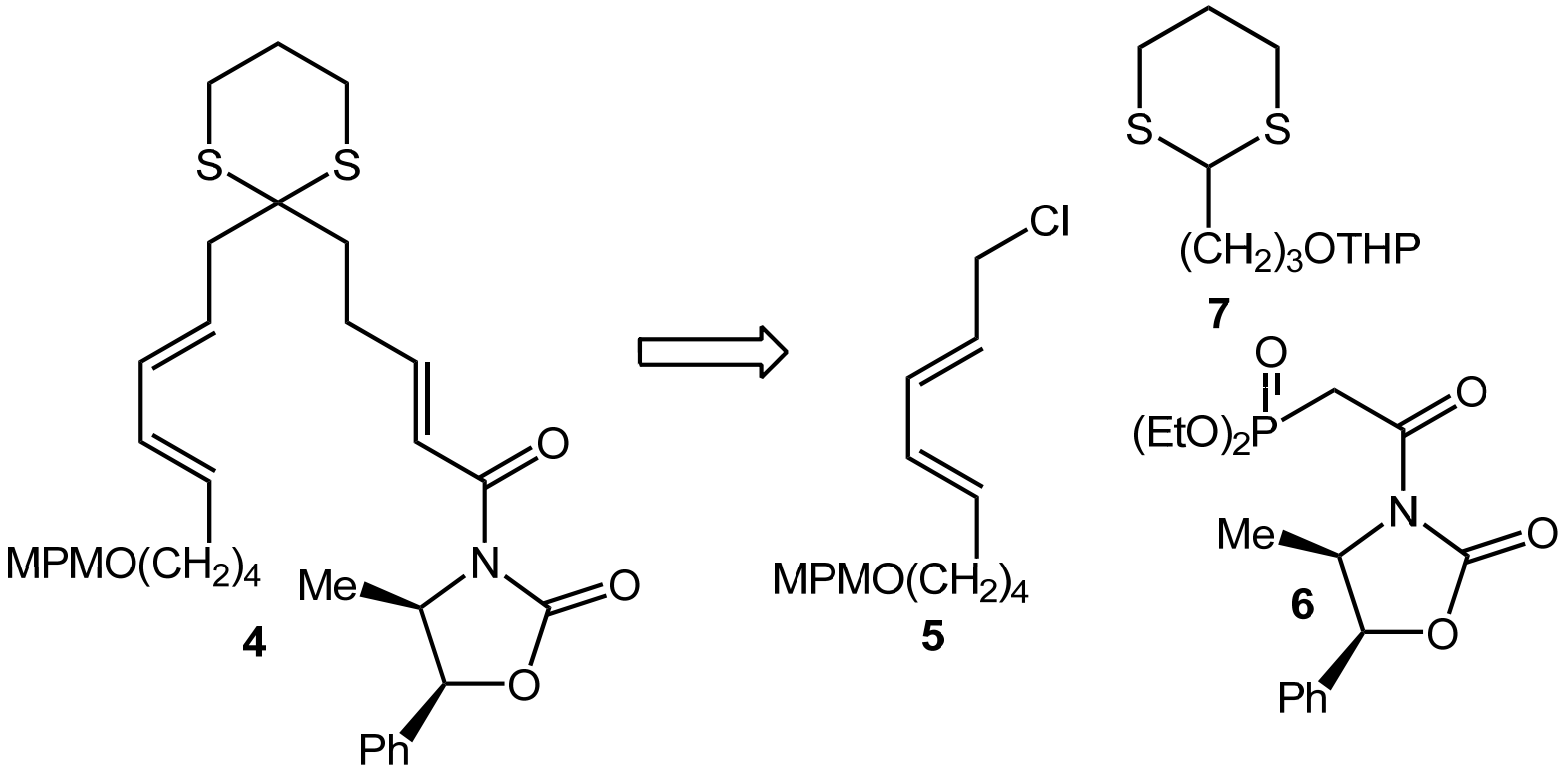

1) HF, MeCN
2) Dess-Martin periodinane, NaClO2
13
(CH2)4OTIPS
14
(CH2)3CO2H
Cbz
1) Pd(OH)2, H2
2) FDPP, CH2Cl2
71%
15
1) Lawesson's reagent
2) Raney- Ni, EtOH
73%
(-)-Stenine (1)

Retrosynthetic analysis of (-)-Stenine **1**



Yoshiki Morimoto *et al*. *Chem. Eur. J*. **2001**, *7*, 4107-4116.

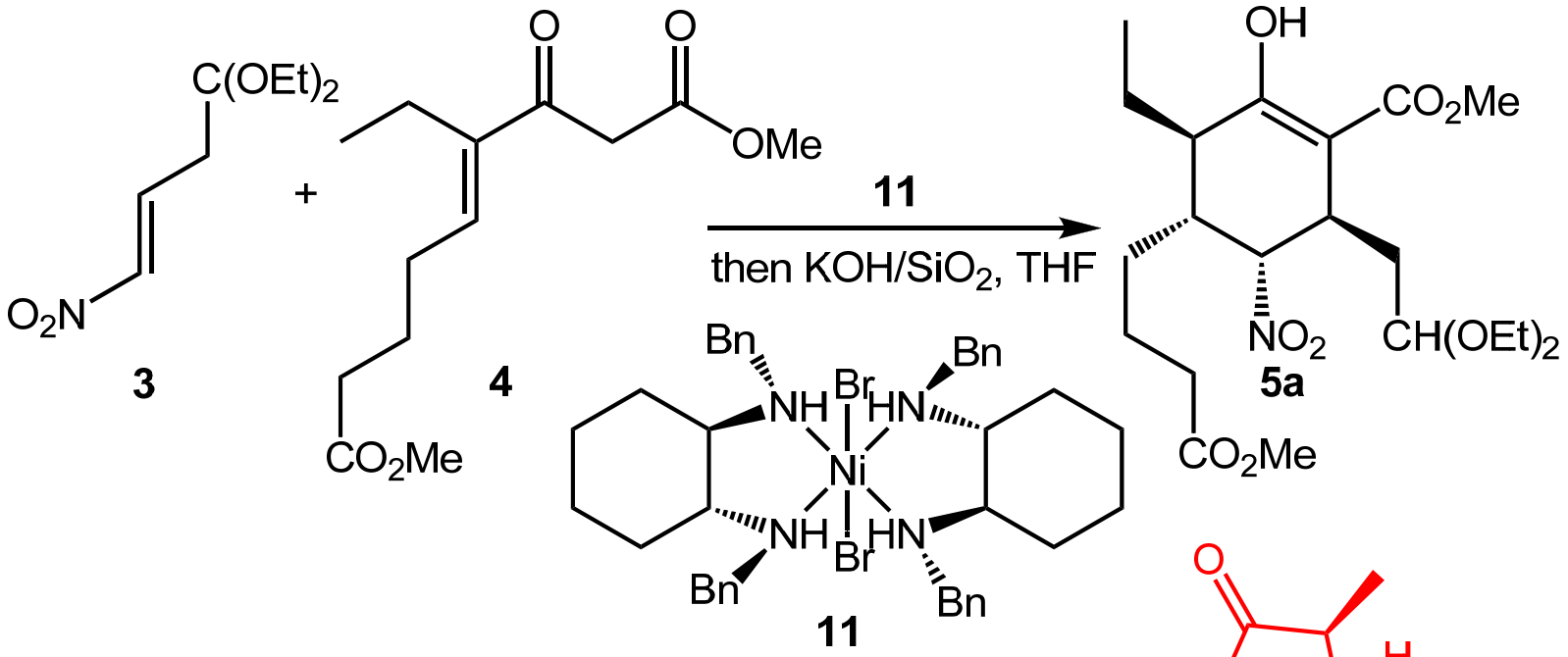
Retrosynthetic analysis of (-)-Stenine **1**

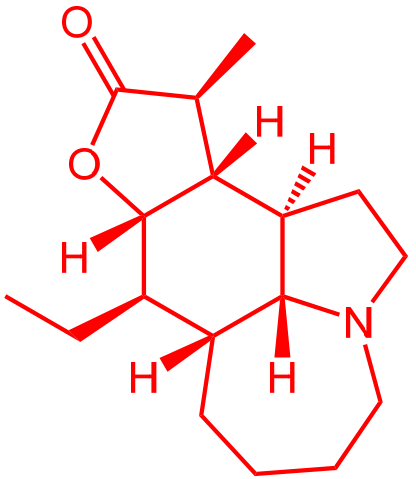


Yoshiki Morimoto *et al*. *Chem. Eur. J*. **2001**, *7*, 4107-4116.

Zhang's group

key step：





(-)-Stenine (**1**)

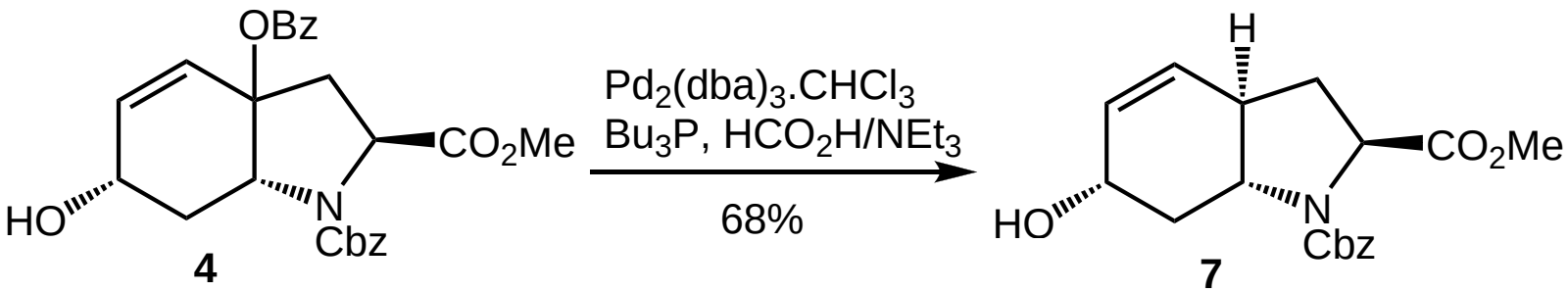
Reactions:

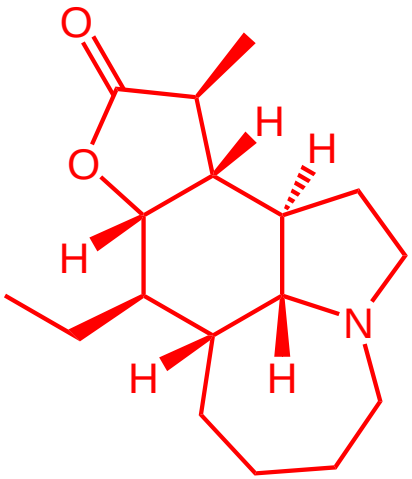
Michael addition, Reductive amination, Horner-Wadsworth-Emmons reaction

Lawesson's reagent.

Peter Wipf's group

key step：





(-)-Stenine (**1**)

Reactions:

π-allylpalladium, Luche reduction, AD-mix-β dihrdyoxylation, Dess-Martin Eschenmoser-Claisen rearrangement, Johnson-Lemieux oxidation Grieco-elimination, Lawesson's reagent.

The roots of Stemonaceae plants are used in traditional Chinese medicines for the treatment of various respiratory ailments. The structure of (-)-stenine (**1**), an alkaloid that is isolated from the roots of Stemona species, is unique among Stemona alkaloids; it has a pyrrolo[*1,2*-α]azepine nucleus and a highly substituted perhydroindole ring system. The polycyclic system and the seven contiguous stereogenic centers in (-)-stenine as well as (-)-tuberostemonine (**2**) present a challenge for asymmetric organic synthesis. Previous efforts to synthesize (-)-stenine have resulted in a number of elegant total syntheses. However, only two asymmetric syntheses have been reported; these involve 25 and 30 synthetic steps. Most of the synthetic strategies rely on a Diels–Alder reaction as the key step in assembling the core cyclohexane ring. Herein, we report an alternative, efficient approach for the enantioselective synthesis of (-)-stenine.

In summary, we have developed a catalytic, enantioselective strategy for the synthesis of (-)-stenine. This route, which features a highly stereocontrolled, one-pot cyclization to establish the required stereogenic centers, gives (-)-stenine in 14 steps from commercially available materials (11 steps from known starting materials) in an overall yield of 5.9%. This strategy is flexible and could be used for the synthesis of stenine analogues, which are of interest in medicinal chemistry. The application of this method to the catalytic asymmetric synthesis of (-)-tuberostemonine (**2**), which is a more complex target, is currently under investigation.