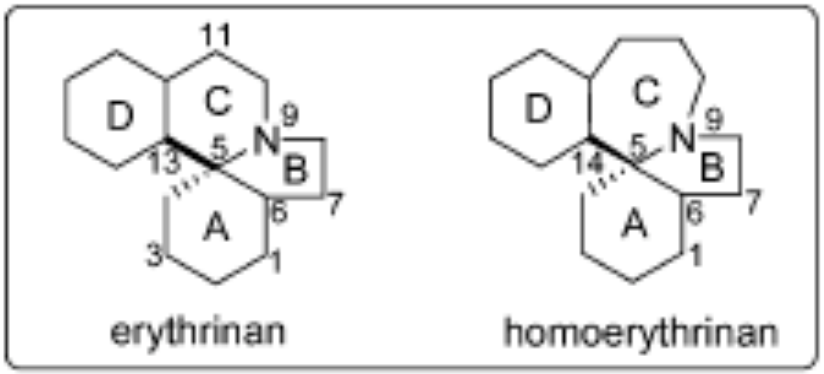
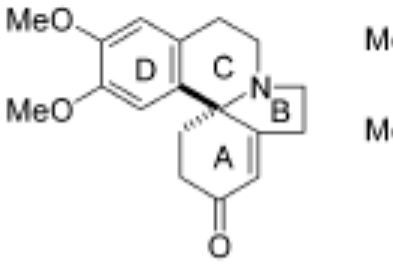
Approach to the Homoerythrina Alkaloids Using a Tandem N-Alkylation/Azomethine Ylide Cycloaddition

Pearson, W. H.; Kropf, J. E.; Choy, A. L.; Lee, I. Y.; Kampf, J. W.
J. Org. Chem.; 2007; 72(11); 4135-4148.

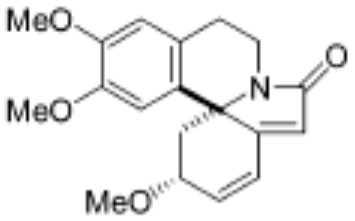
Wipf group Current lit 08-18-07
Akira Nakamura

Background

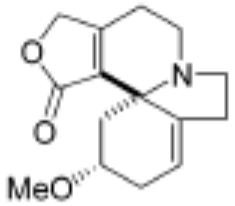




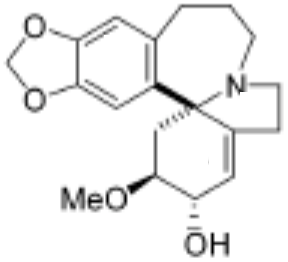
3-demethoxyerythratidinone



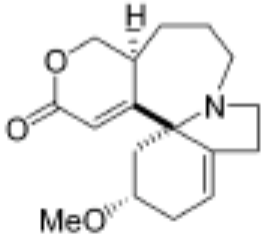
Erysotramidine



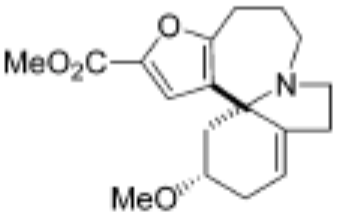
Cocculolidine



Schelhammerine



Phellibiline

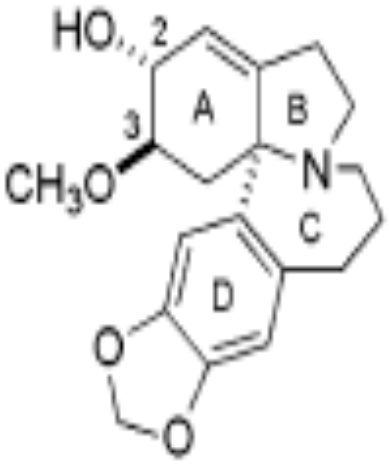


Selaginaidine

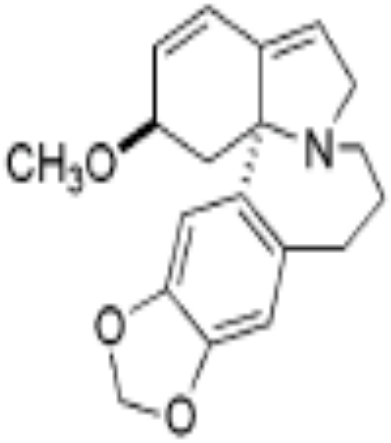
Activities

- Curarelike
- Hypnotic
- Sedative
- Hypotensive
- Neuromuscular blocking
- CNS

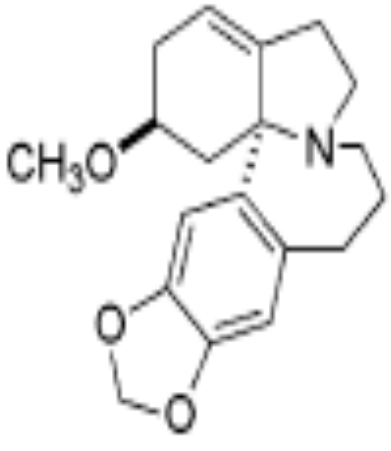
Target Alkaloids



homoerythratine (**1**)



3-*epi*-schelhammeridine (**2**)

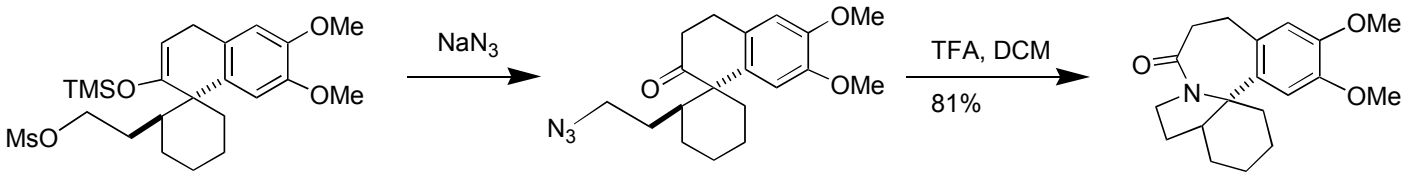


3-*epi*-schelhammericine (**3**)

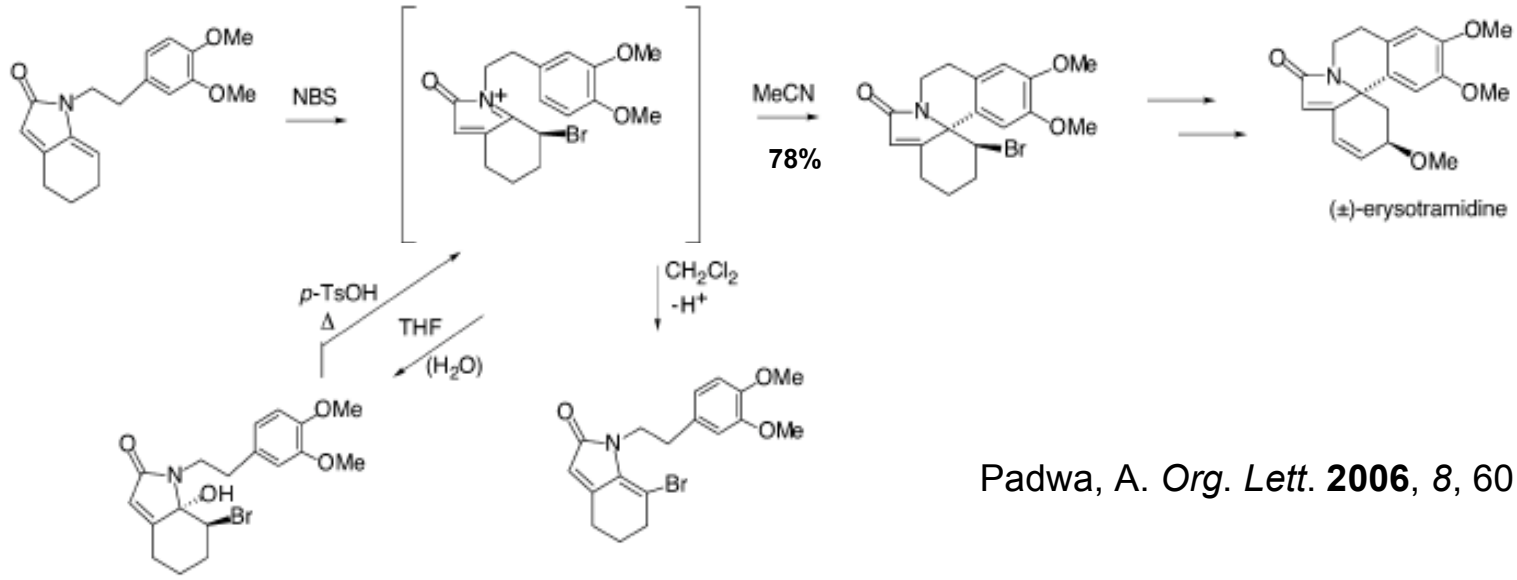
-Isolated from ***D. lenticellare*** Gillespie grown in the Fiji Islands in 1983.
-There are no reports on pharmacological effect either **1** or **2.**
-Isolated alkaloids from *D. lentivellare* which include **3** are shown to have both cardiac effects in rats and molluscicidal activity.

J. Nat. Prod. **1987**, *50*, 1041., *Phytochemistry* **1988**, *27*, 3789.

Construction of the erythrinan ring system

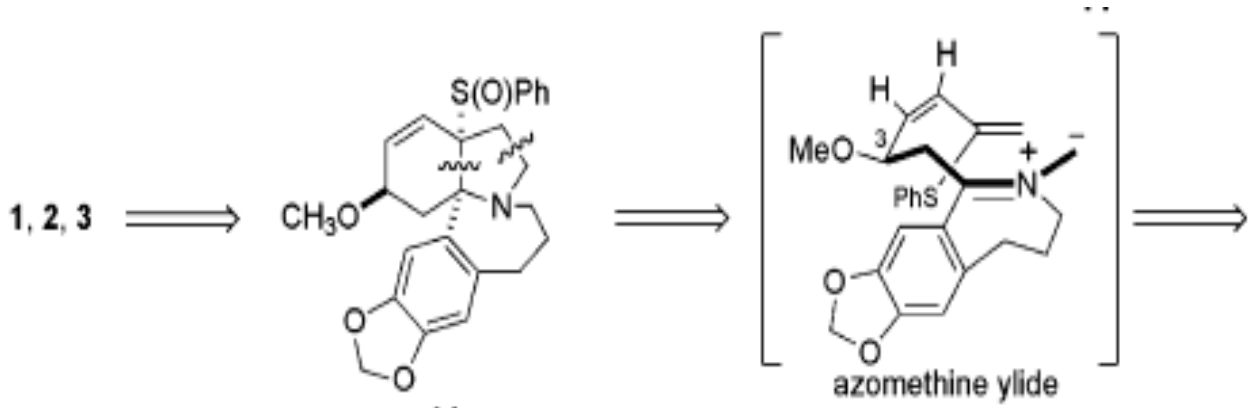


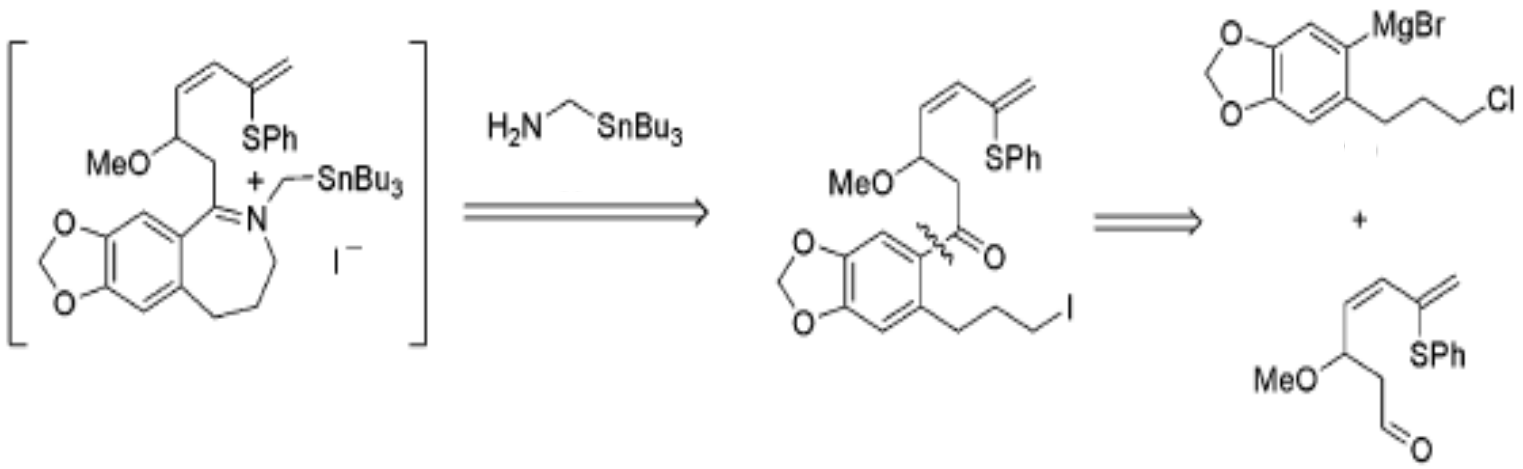
J.d'Angelo, J. *J. Org. Chem.* **1993**, *58*, 2933



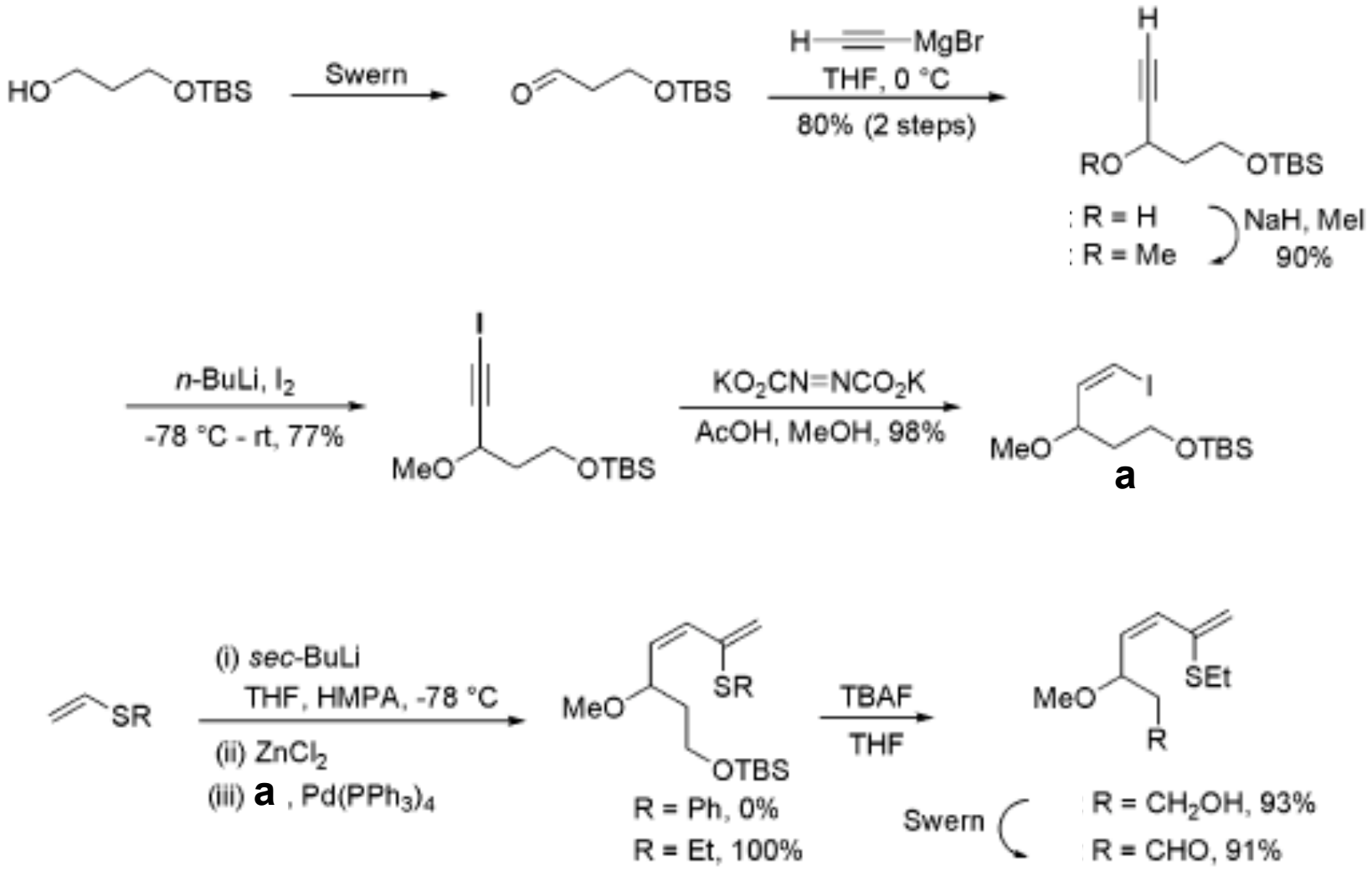
Padwa, A. *Org. Lett.* **2006**, *8*, 601.

Retrosynthetic sequence

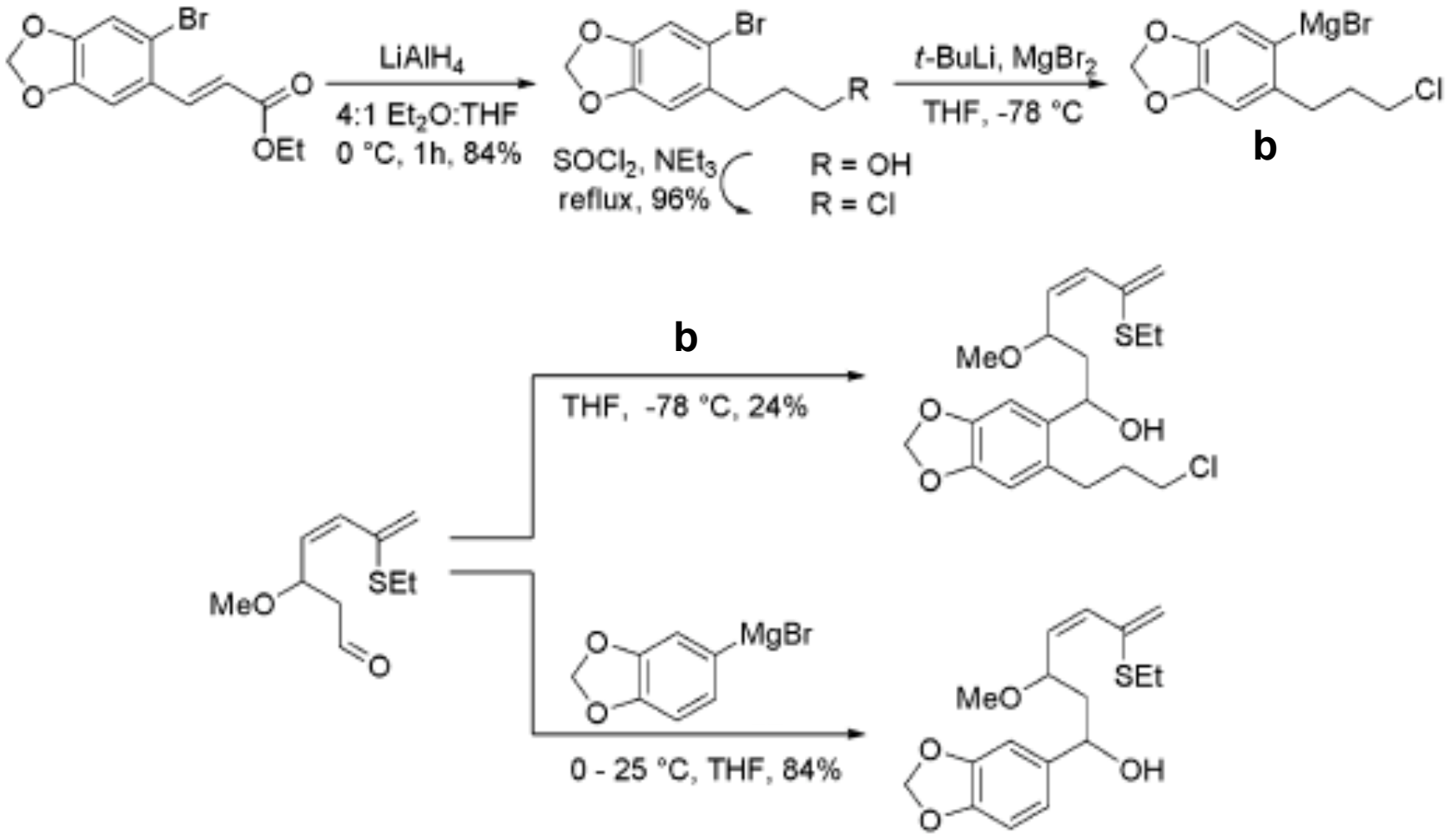




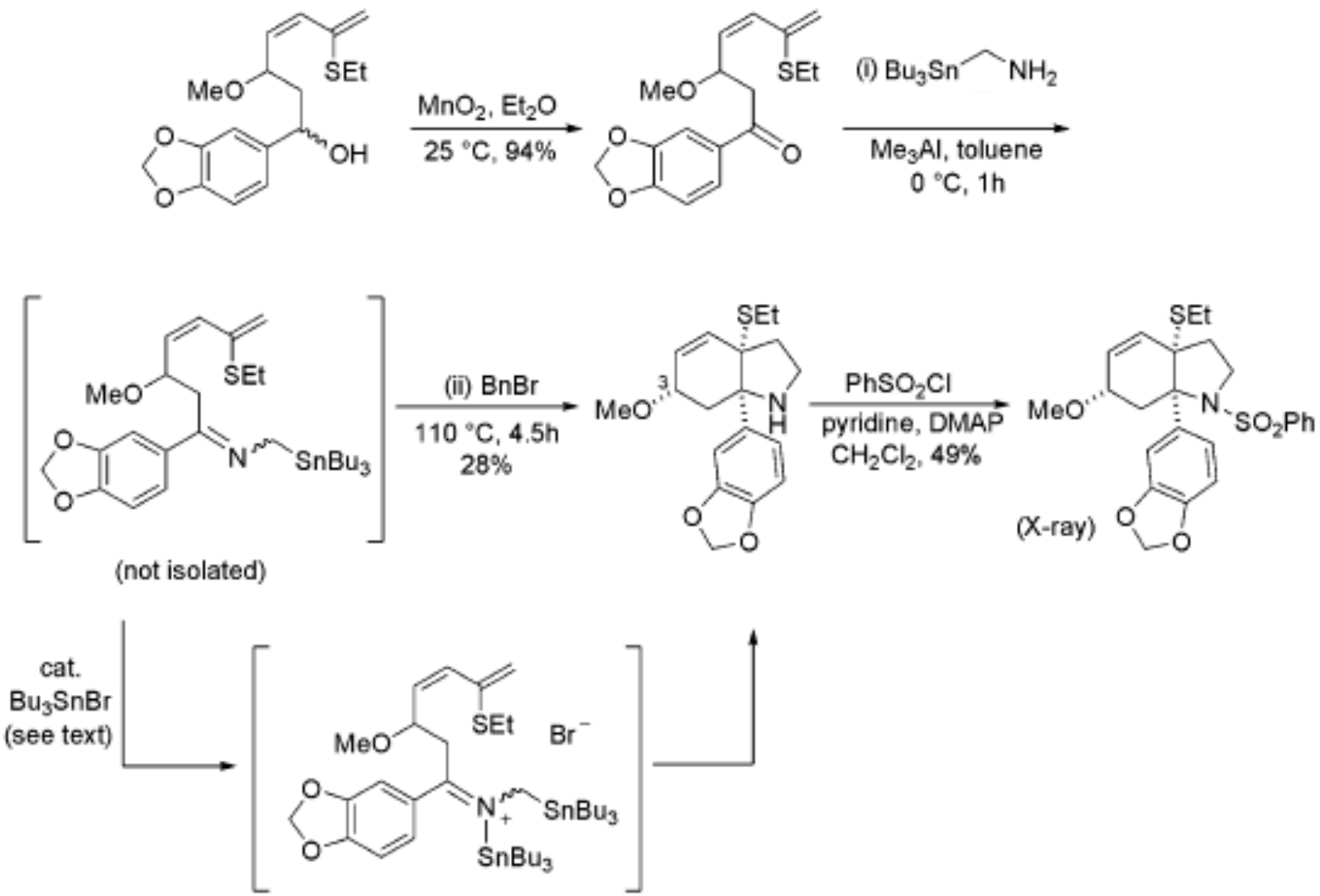
Starting material synthesis



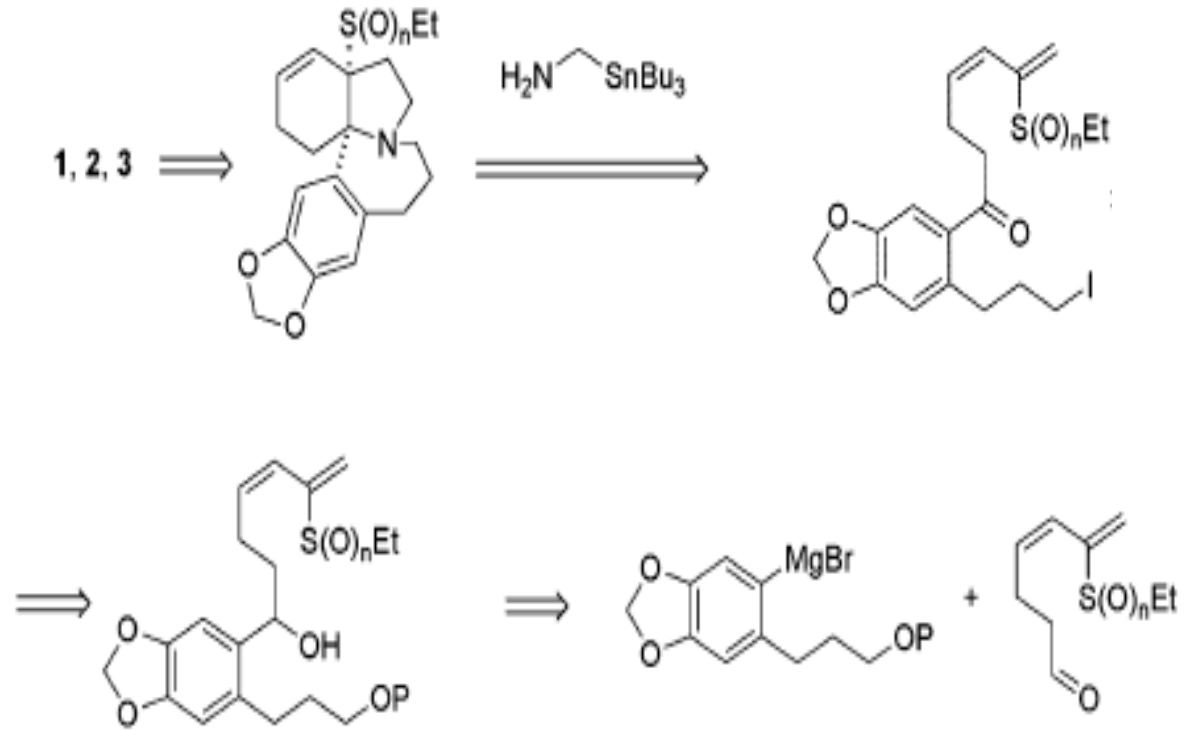
Synthesis


Br
O
O
O
OEt
LiAlH4
4:1 Et2O:THF
0 °C, 1h, 84%
Br
O
O
R
SOCl2, NEt3
reflux, 96%
R = OH
R = Cl
t-BuLi, MgBr2
THF, -78 °C
MgBr
O
O
Cl
b
b
THF, -78 °C, 24%
MeO
SEt
OH
Cl
MeO
SEt
O
MgBr
0 - 25 °C, THF, 84%
MeO
SEt
OH

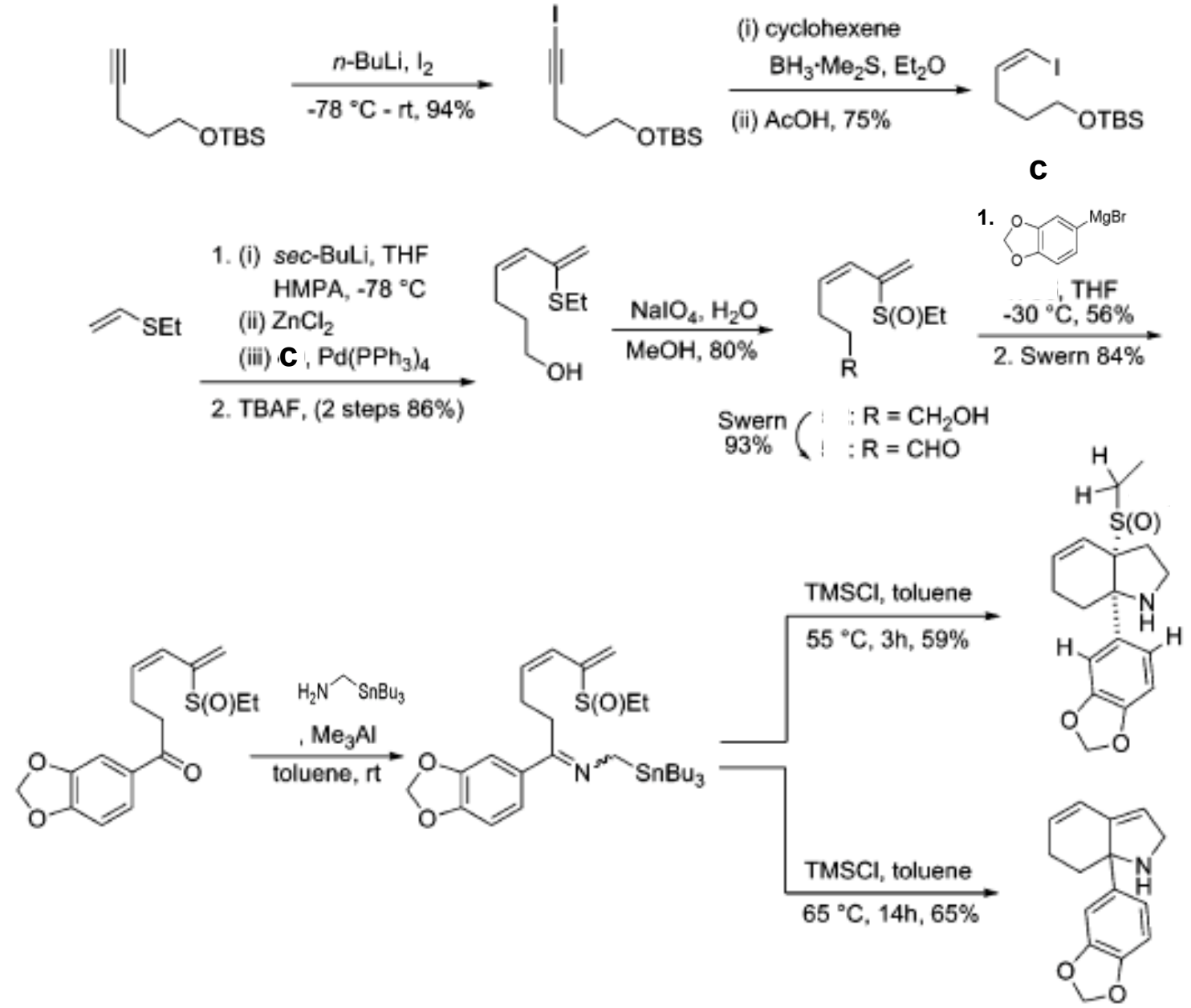
Key cycloaddition test



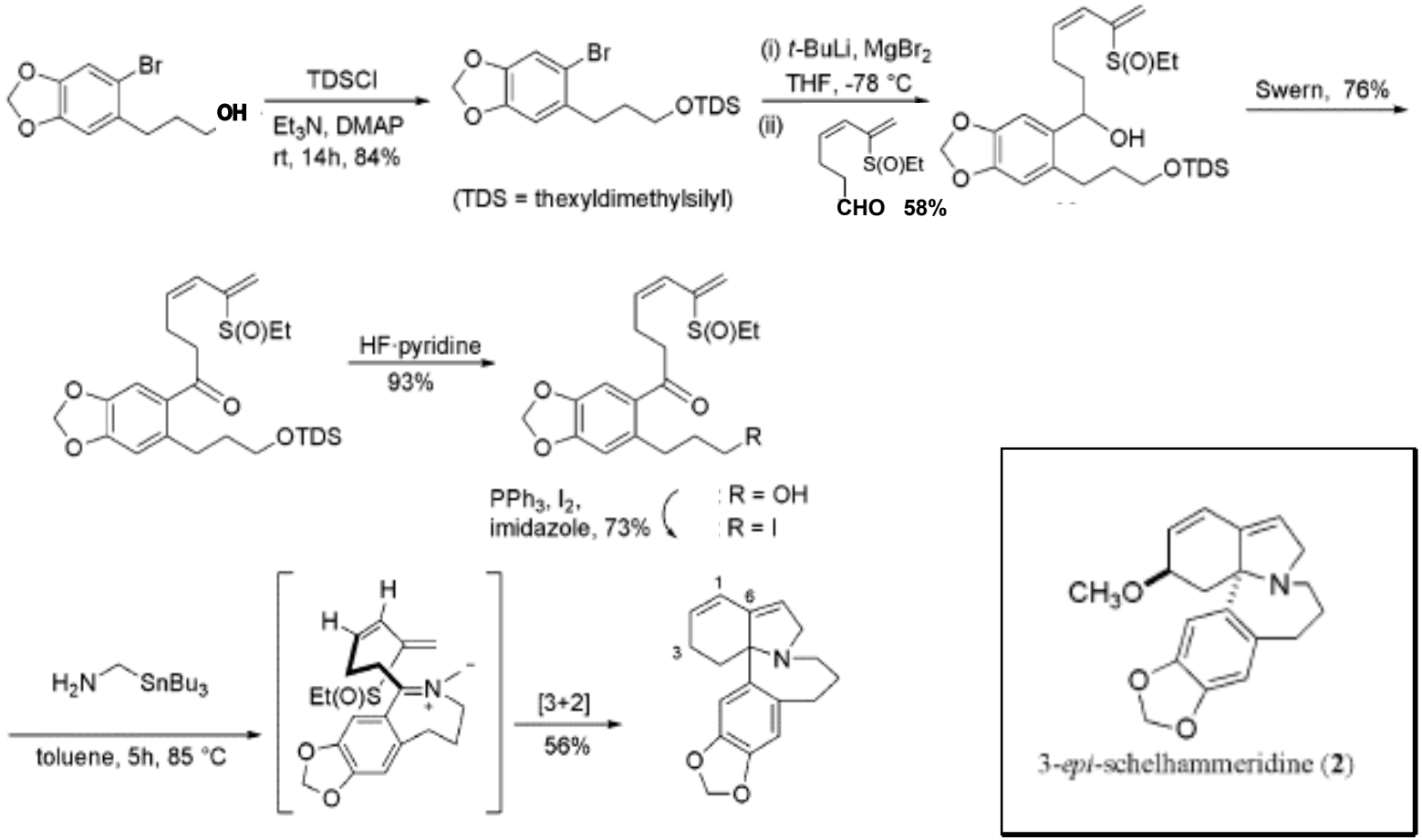
2nd Retrosynthetic sequence



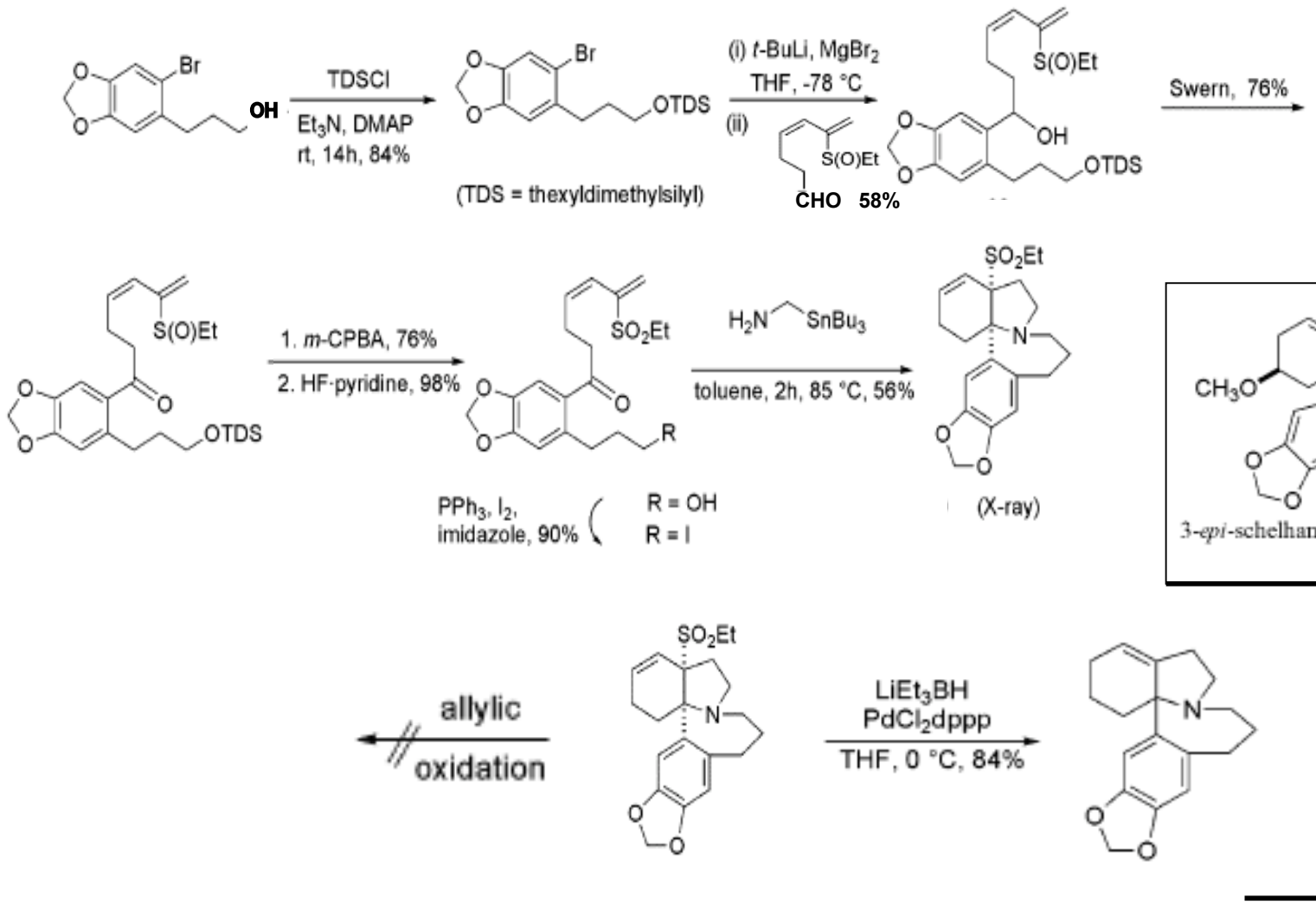
2nd Key cycloaddition test



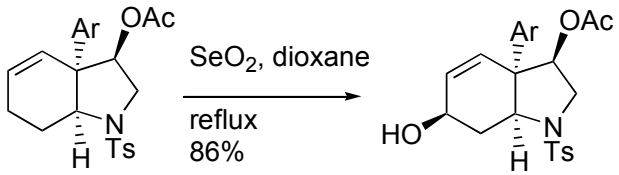
Synthesis


Br
OH
TDSCl
Et3N, DMAP
rt, 14h, 84%
Br
OTDS
(TDS = thexyldimethylsilyl)
(i) t-BuLi, MgBr2
THF, -78 °C
(ii)
S(O)Et
CHO 58%
S(O)Et
OH
OTDS
Swern, 76%
S(O)Et
OTDS
HF·pyridine
93%
S(O)Et
R
PPh3, I2,
imidazole, 73%
R = OH
R = I
H2N
SnBu3
toluene, 5h, 85 °C
H
H
Et(O)S
N
[3+2]
56%
1
6
3
N
CH3O
N
3-epi-schelhammeridine (2)

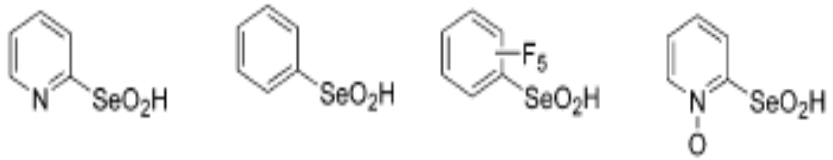
Synthesis


TDSCl
Et3N, DMAP
rt, 14h, 84%
(TDS = thexyldimethylsilyl)
(i) t-BuLi, MgBr2
THF, -78 °C
(ii)
CHO 58%
Swern, 76%
1. m-CPBA, 76%
2. HF·pyridine, 98%
PPh3, I2,
imidazole, 90%
R = OH
R = I
toluene, 2h, 85 °C, 56%
(X-ray)
3-epi-schelhammericine (3)
allylic
oxidation
LiEt3BH
PdCl2dppp
THF, 0 °C, 84%

Allilic oxidation

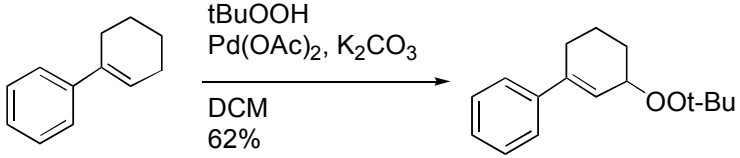


Mori, M. *J. Org. Chem.* **1998**, *63*, 7586-7587.



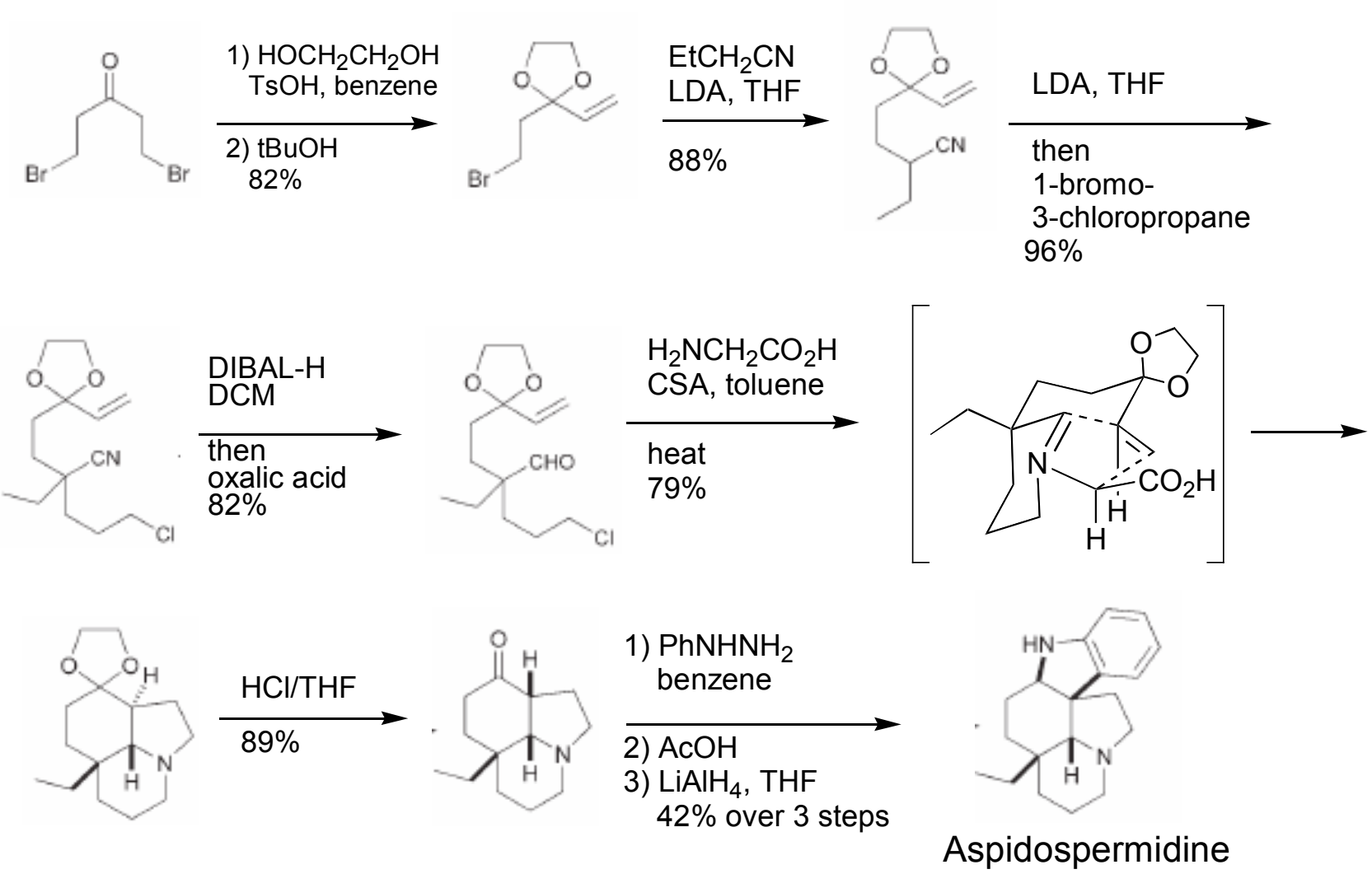
(1) (2) (3) (4)

(1) Andrus, M. B.; Lashley, J. C. *Tetrahedron* **2002**, *58*, 845.
(2) Corey, E. J. *J. Am. Chem. Soc*. **2003**, *125*, 3232.
(3) Hoekstra, W. J. In *EROS*; Paquette, L. A., Ed.: Wiley: Chicester,UK, 1995; Vol. 6, p 4437.
(4) Sharpless, K. B. *J. Am. Chem. Soc*. **1977**, *99*, 5526.



Corey, E. J. *Org. Lett.* **2002**, *4*, 2727-2730.

Successful example of [3 + 2] Cycloaddition



Iain. Coldham, *Angew. Chem.*, **2007**, *119*, 6271

Conclusion

- A tandem N-alkylation/azomethine ylide [3 + 2] cycloaddition provides a rapid access to tricyclic amines from acyclic precursors.

-Two separate model systems guided to improve yields of the key step.

- Allilic oxidation was unsuccessful.