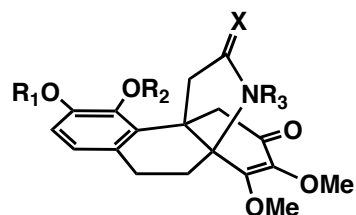
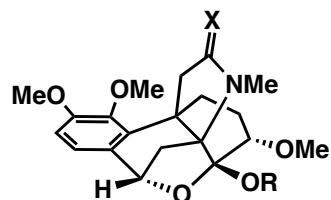
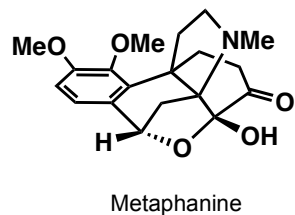
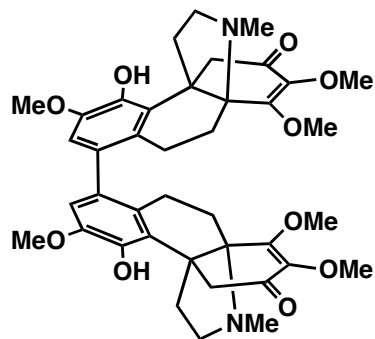
**Hasubanan alkaloids:**

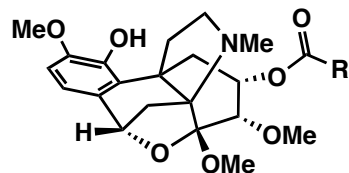
$R_1=R_2=R_3=Me$, $X=H_2$: Hasubanonine
 $R_1=H$, $R_2=R_3=Me$, $X=H_2$: Homostephanoline
 $R_1=R_3=Me$, $R_2=H$, $X=H_2$: Aknadinine
 $R_1, R_2=CH_2$, $R_3=Me$, $X=H_2$: Delavanine
 $R_1=Me$, $R_2=R_3=H$, $X=H_2$: Aknadicine
 $R_1=R_3=Me$, $R_2=H$, $X=O$: Aknadilactam



$R=Me$, $X=H_2$: Stephamiersine
 $R=Me$, $X=O$: Oxostephamiersine
 $R=H$, $X=H_2$: Stephasunoline



Bisaknadinine



$R=Ph$: Stephabenine
 $R=4-OH-3-MeO-Ph$: Stephavanine
 $R=CH=CH-Ar$: Stephisoferuline

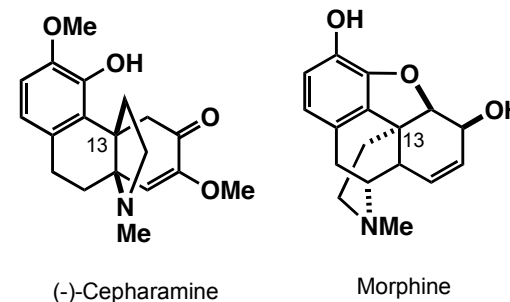
Isolation and/or structure determination:

Cepharamine: Tomita *Tetrahedron Lett.* **1966**, 6229. Hasubanonine: Tomita *Chem. Pharm. Bull.* **1965**, 13, 538. Metaphanine: Tomita *Tetrahedron Lett.* **1964**, 3605. Bisaknadinine: Kunitomo *Heterocycles* **1980**, 14, 175. Stephamiersine: Watanabe *Tetrahedron Lett.* **1973**, 4263. Stephavanine: Kupchan *J. Am. Chem. Soc.* **1970**, 92, 5756. Stephisoferuline: Kupchan *Tetrahedron Lett.* **1970**, 4975. Stephabenine: *Chem. Pharm. Bull.* **1983**, 31, 2547.

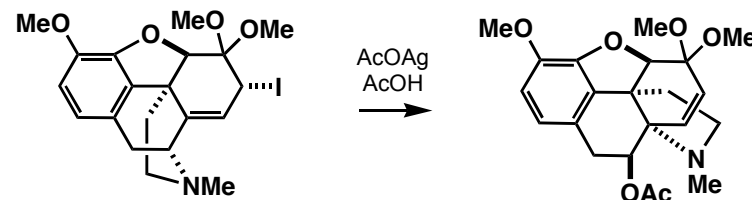
Total syntheses reported:

Racemic: Cepharamine, hasubanonine, aknadilactam, metaphanine.
 Enantioselective: (+)-cepharamine (unnatural).

The structure of hasubanan alkaloids resembles that of morphinan alkaloids, comprising the same phenanthrene-like skeleton, but with the nitrogen of the side aminoethyl chain attached on C-14 (phenanthrene numbering) and without the oxo bridge of morphine. Most important: the stereochemistry at C-13 is the opposite of the morphinan alkaloids and hasubanans do not display analgesic properties.

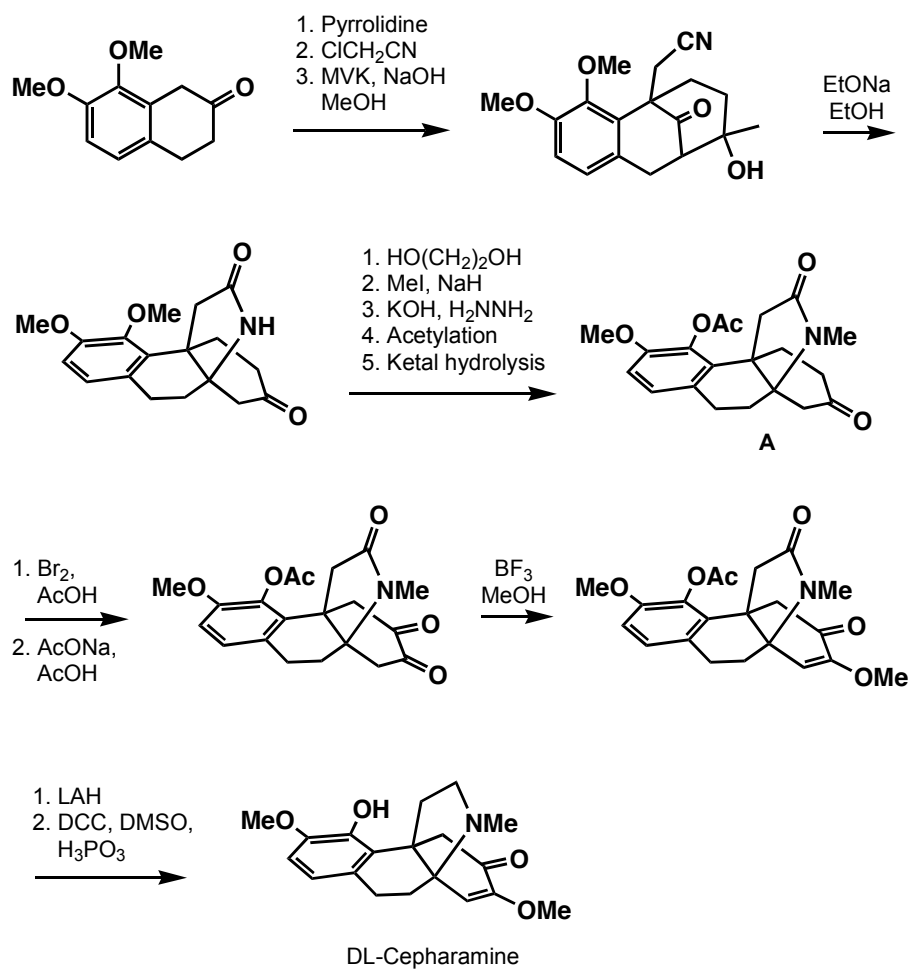


Conversion of morphinan to hasubanan skeleton:



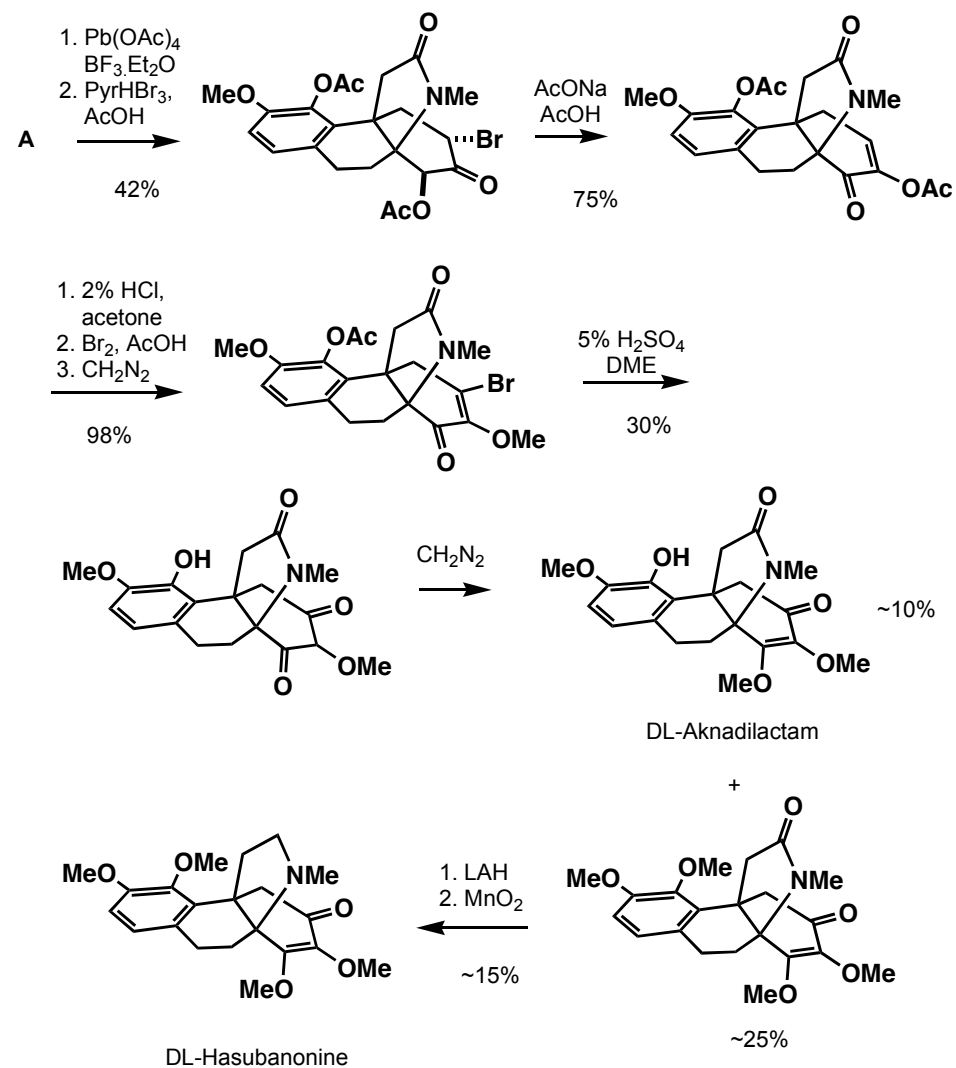
G. W. Kirby. *J. Chem. Soc., Perkin Trans 2* **1973**, 363.

Cepharamine



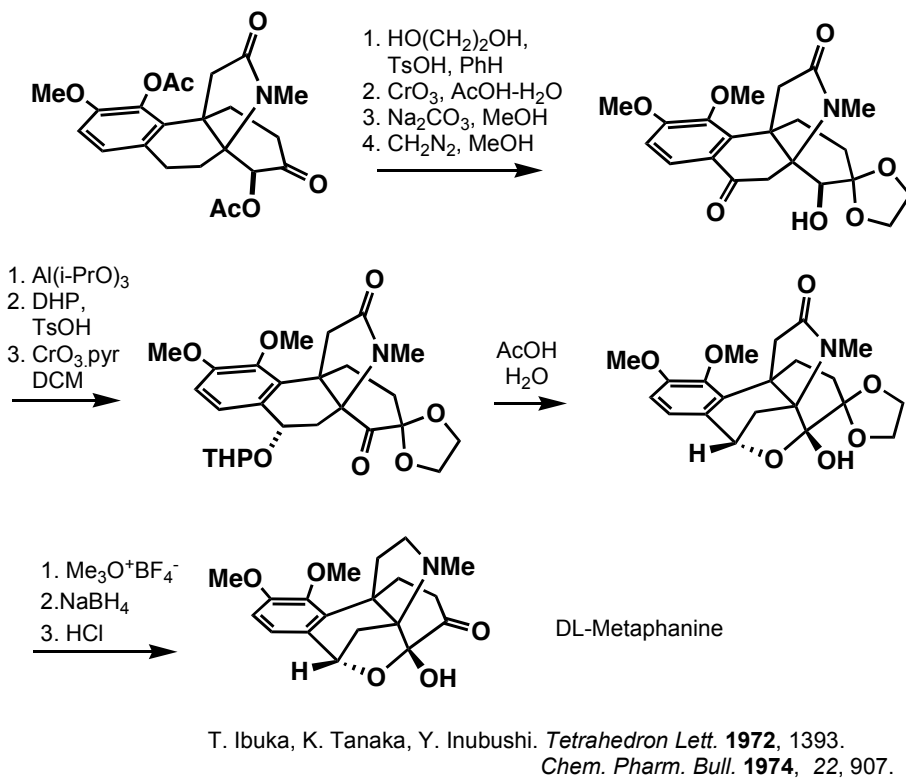
Y. Inubushi, T. Ibuka, M. Kitano. *Tetrahedron Lett.* **1969**, 1611.
Chem. Pharm. Bull. **1971**, 19, 1820.

Hasubanonine and Aknadilactam

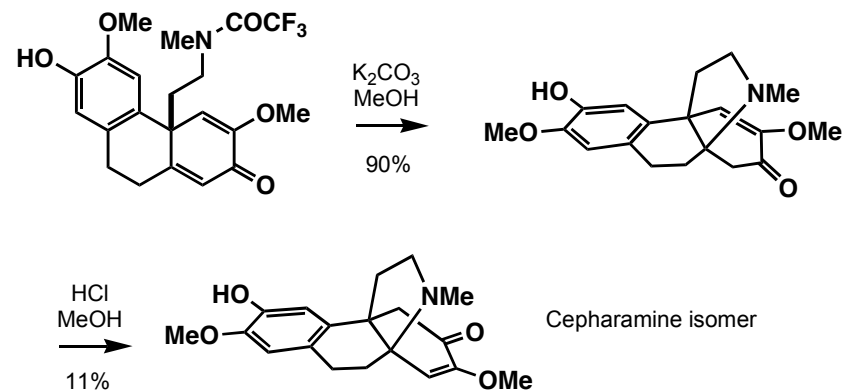
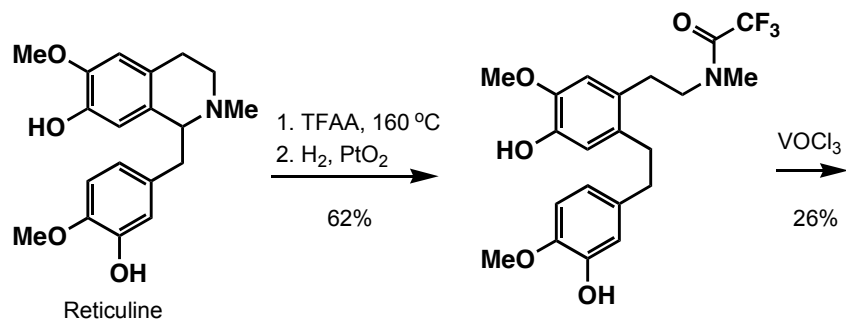


T. Ibuka, K. Tanaka, Y. Inubushi. *Tetrahedron Lett.* **1970**, 4811.
Chem. Pharm. Bull. **1974**, 22, 782.

Metaphanine

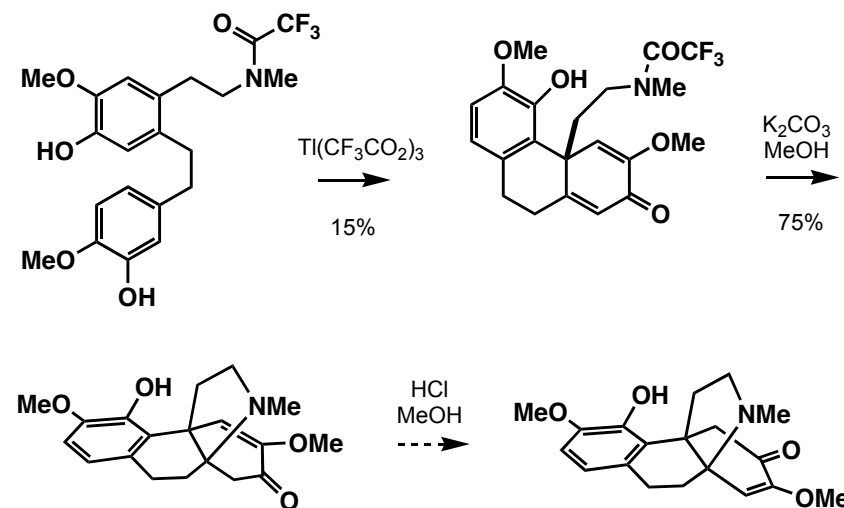


Cepharamine isomer

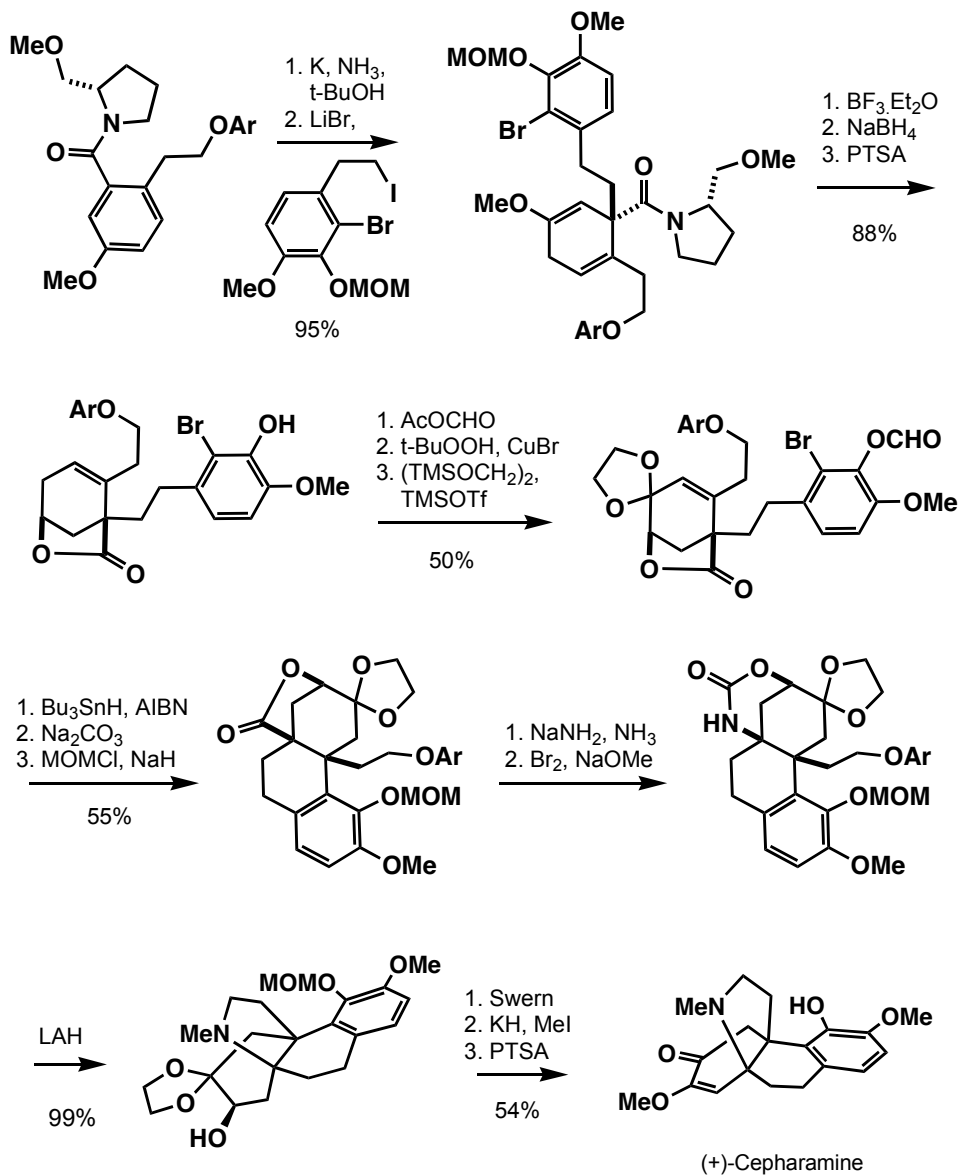


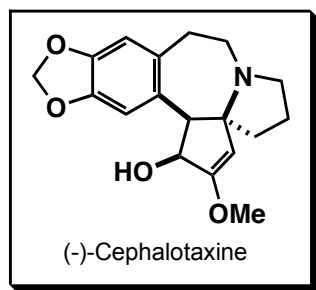
T. Kametani, T. Kobari, K. Fukumoto. *J. Chem. Soc., Chem. Comm.* **1972**, 288.
 T. Kametani, T. Kobari, K. Shishido, K. Fukumoto. *Tetrahedron* **1974**, 30, 1059.

Cepharamine

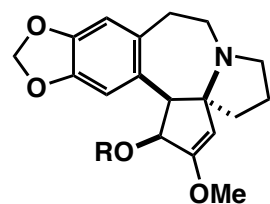


M. A. Schwartz, R. A. Wallace. *Tetrahedron Lett.* **1979**, 35, 3257.

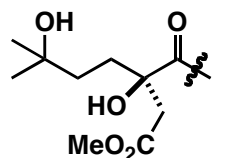
(+)-Cepharamine



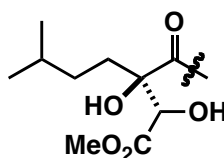
Cephalotaxus harringtonia variety *drupacea*
(Japanese plum yew)



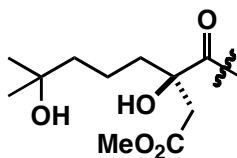
R =



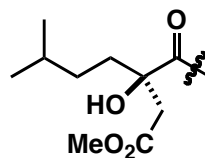
Harringtonine



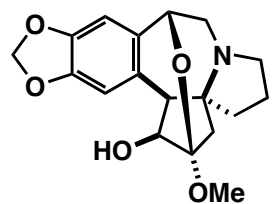
Isoharringtonine



Homoharringtonine



Deoxyharringtonine



Drupacine

Cephalotaxine's natural esters (especially homoharringtonine) display high antileukemic activity.

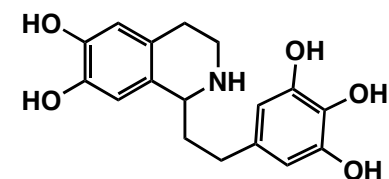
Homoharringtonine currently undergoes phase III clinical trials for the treatment of chronic myelogenous leukemia.

Cephalotaxine shows no activity against tumor cells.

Hemisynthesis of homoharringtonine from (-)-cephalotaxine: *TL* **1999**, *40*, 2931.

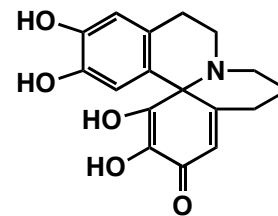
Biosynthesis

Phenylalanine
or tyrosine

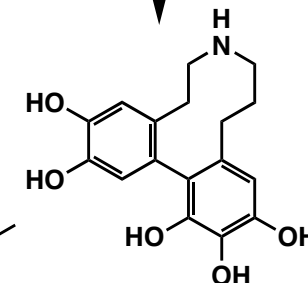


phenethylisoquinoline intermediate

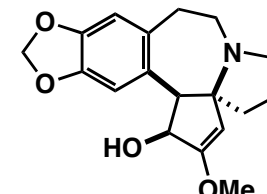
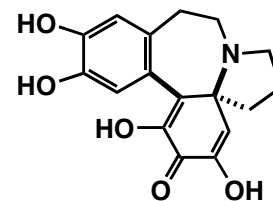
oxidative phenol
coupling



homoerythrina alkaloid
intermediate



benzilic acid
rearrangement



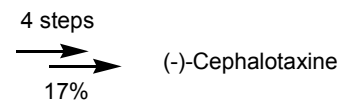
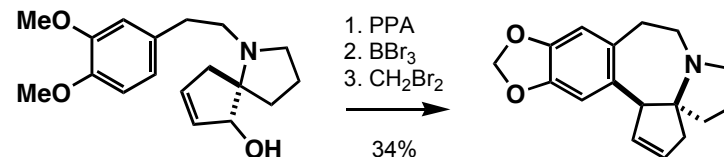
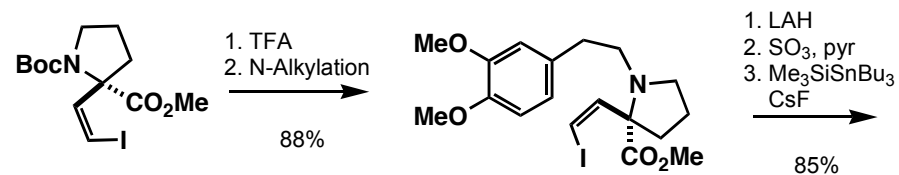
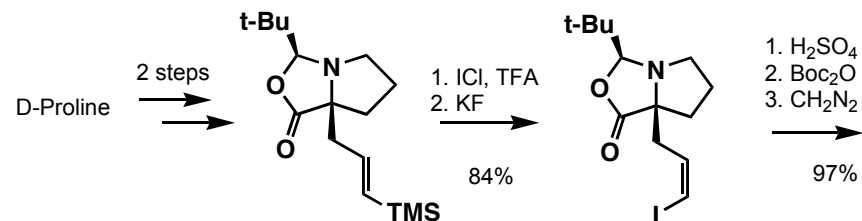
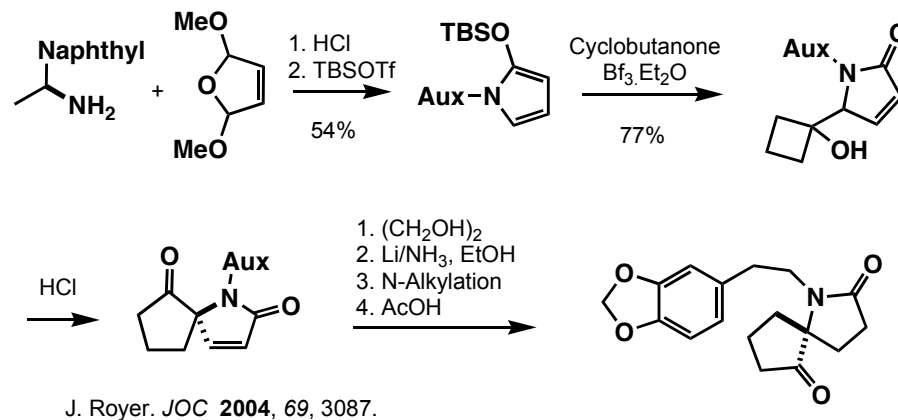
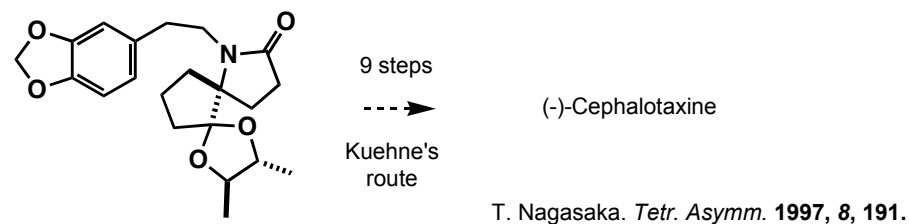
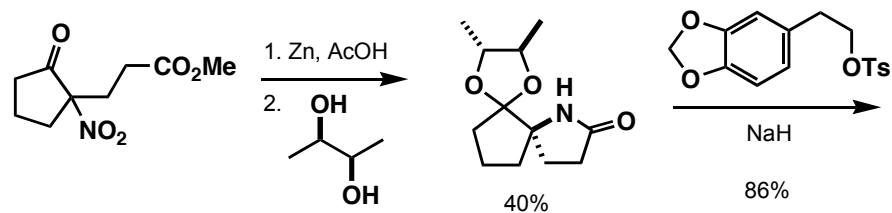
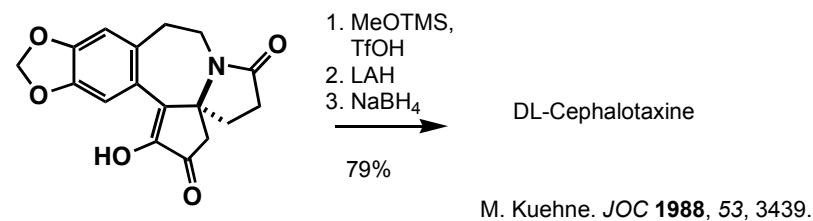
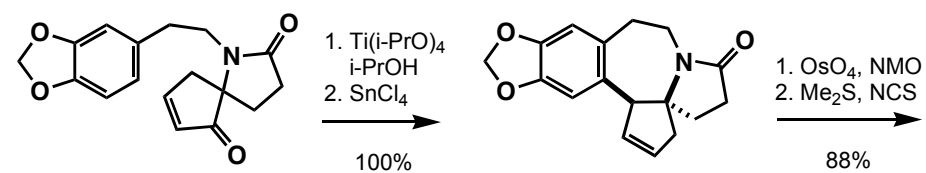
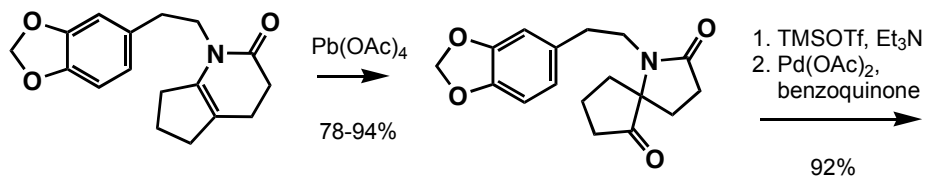
Cephalotaxine

R. J. Parry. *JACS* **1980**, *102*, 1099.

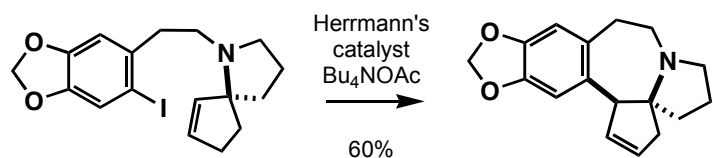
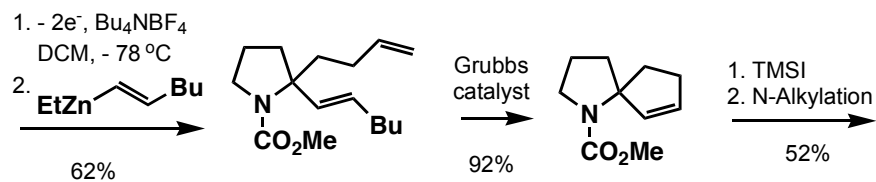
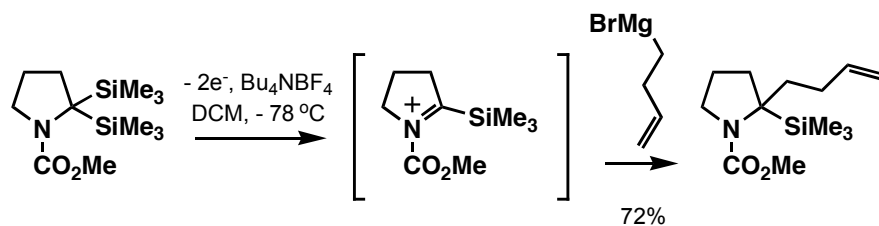
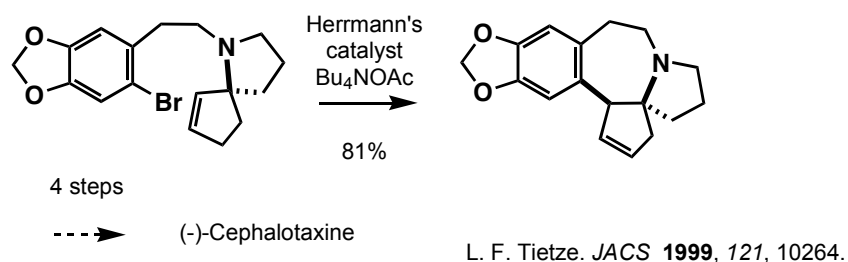
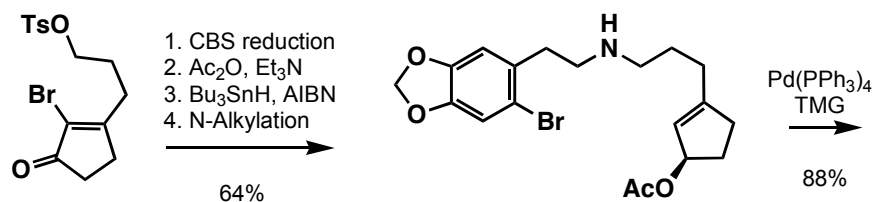
Total syntheses reported:

Racemic: 8. Enantioselective: 3. Enantioselective formal: 2

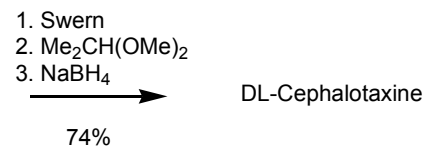
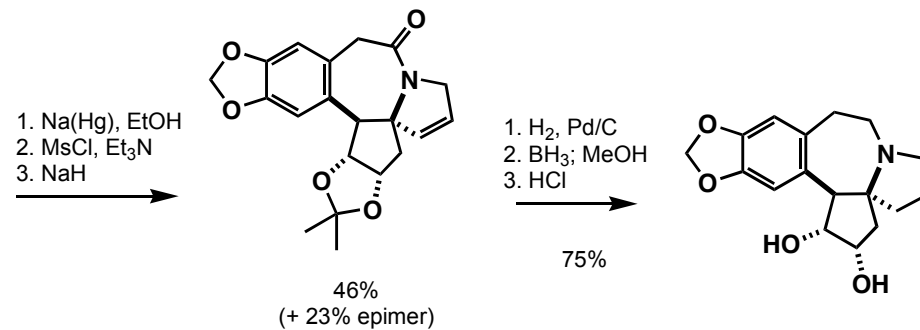
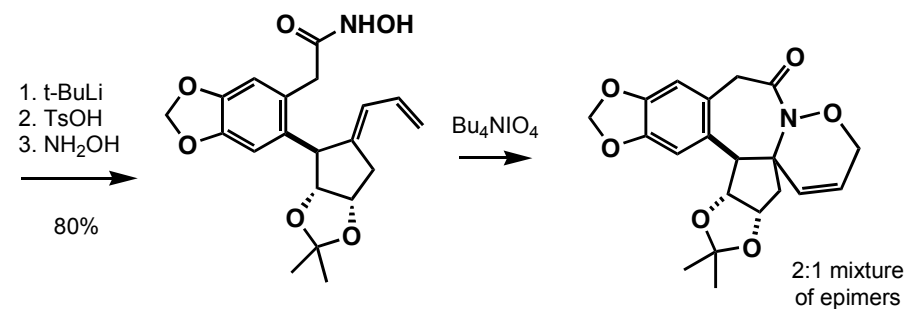
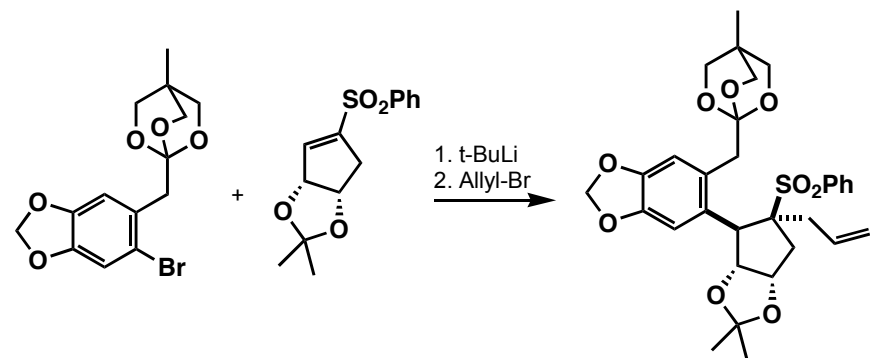
Allyl cation cyclizations



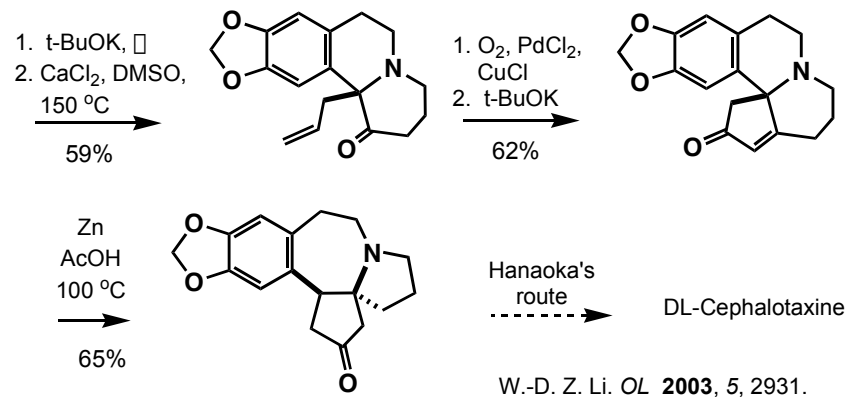
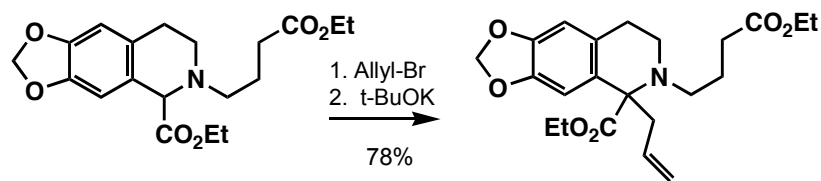
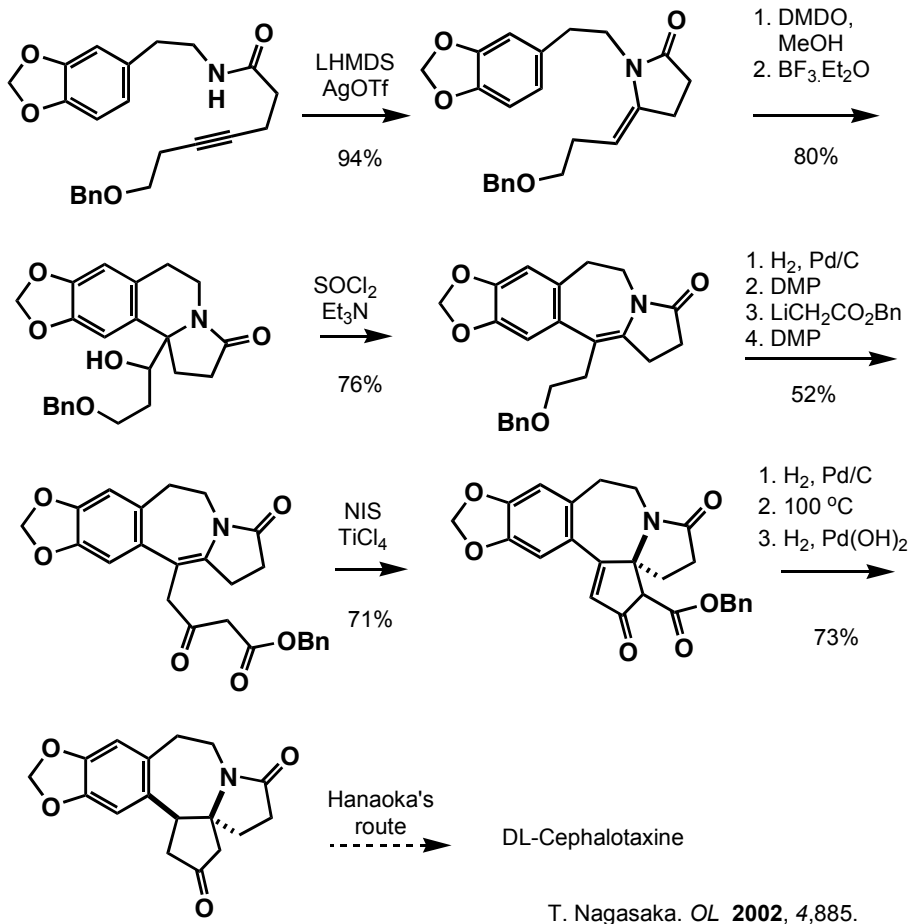
Heck cyclizations

J. Yoshida. *JACS* **2002**, *124*, 14824.

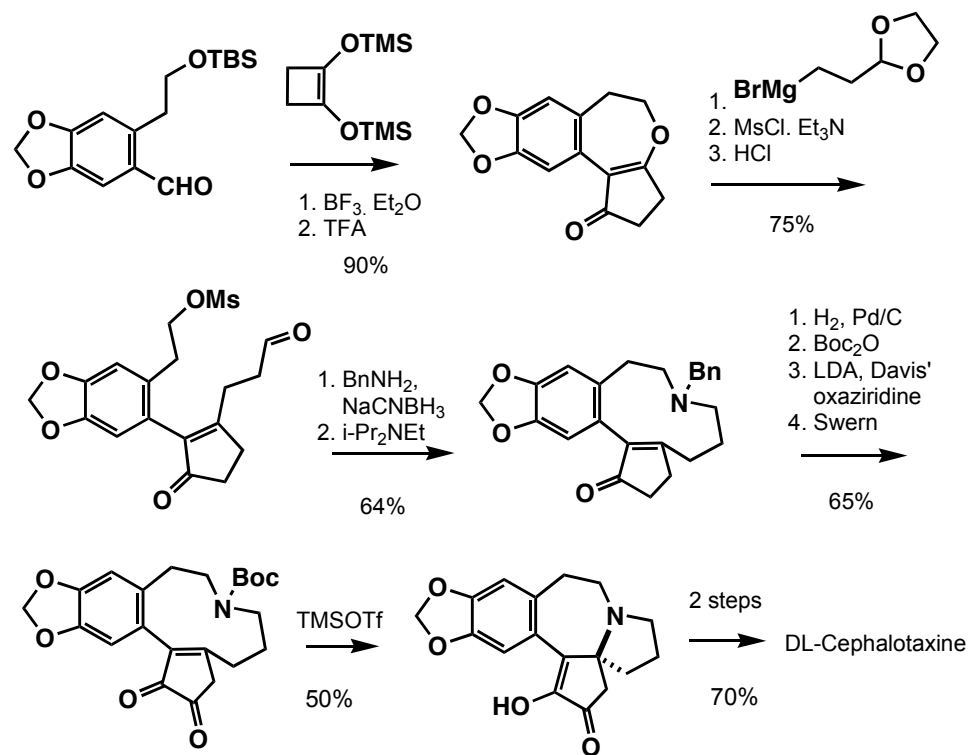
[4+2] Cycloaddition

P. L. Fuchs. *JACS* **1988**, *110*, 2341;
JACS **1990**, *112*, 9601.

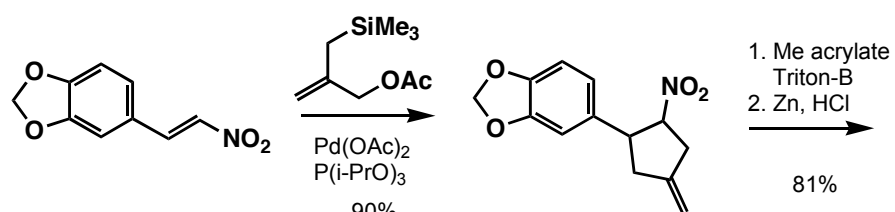
Ring expansion



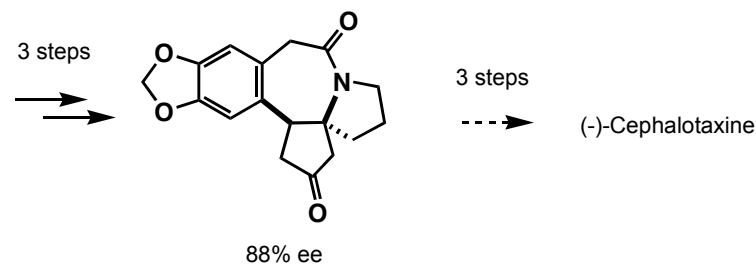
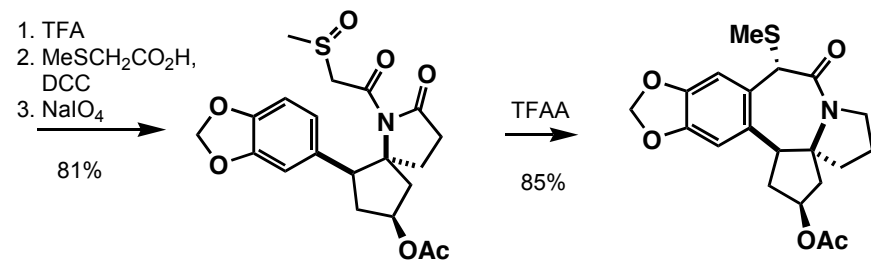
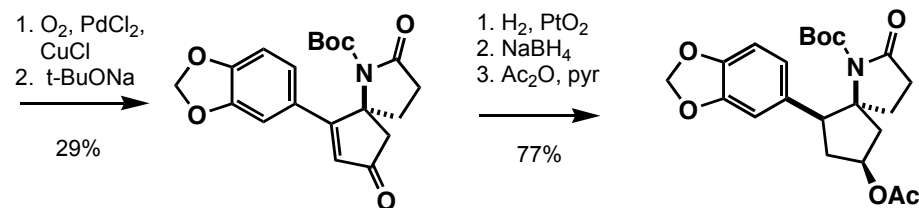
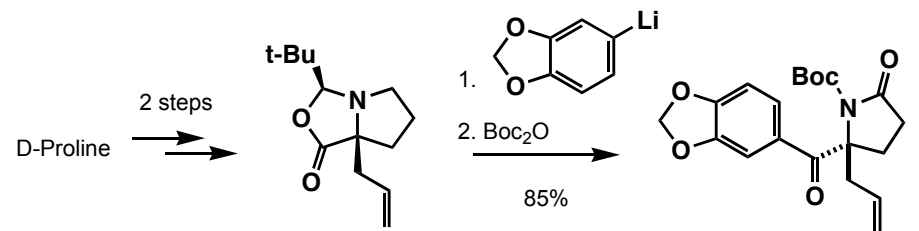
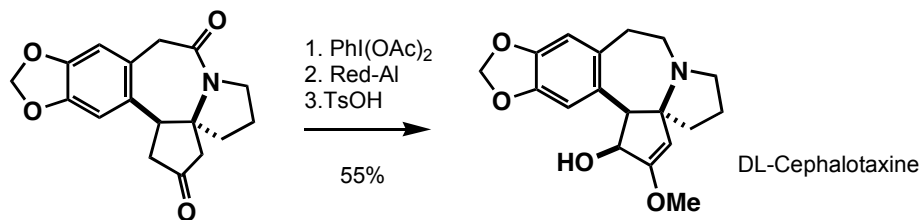
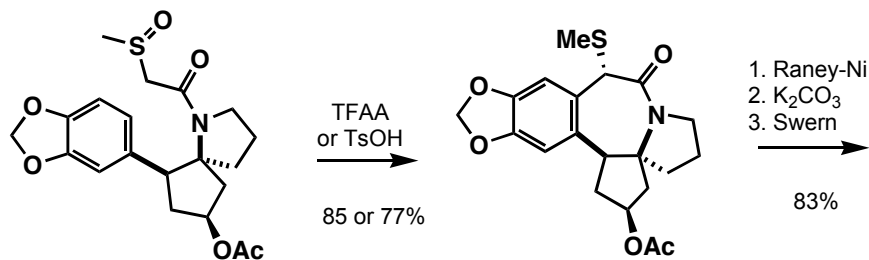
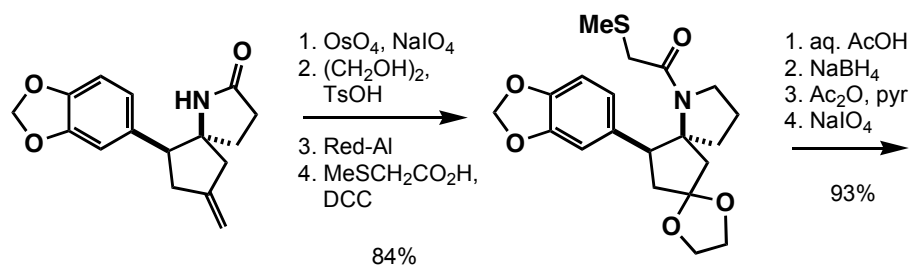
Transannular cyclization



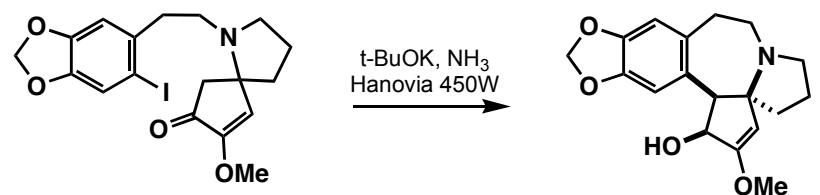
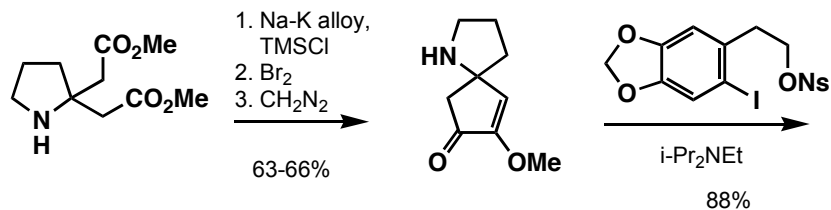
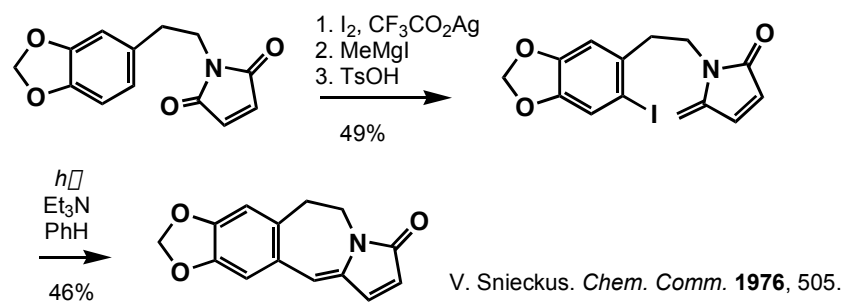
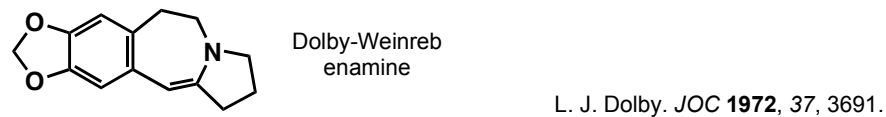
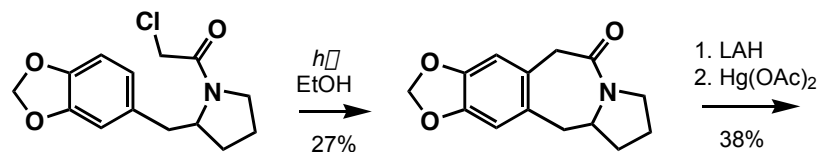
Pummerer cyclizations



mixture of diastereomers



Photoinduced cyclizations

M. F. Semmelhack. *JACS* **1975**, *97*, 2507.

Radical cyclization

