

Stereoselective Synthesis of (-)-Cephalotaxine and C-7 Alkylated Analogues

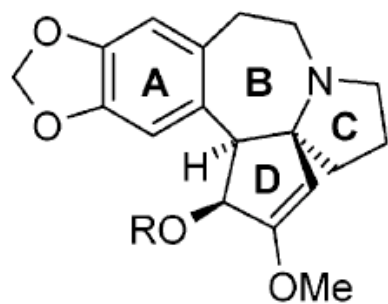
Loic Plannas, Joelle Perard-Viret and Jacques Royer

J. Org. Chem., **2004**, *69*, 3087.

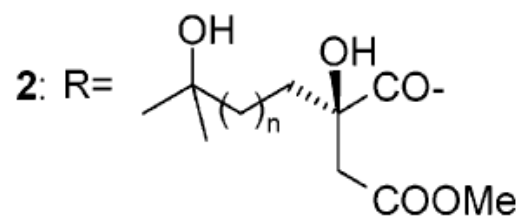


Cephalotaxus drupacea

Japanese Plum-Yew



1: R = H, (-)-cephalotaxine



a n=1: harringtonine

b n=2: homoharringtonine

Biological Activity

Homoharringtonine is effective against chronic Myelogenous Leukaemia
Currently in Phase III clinical trials

Isolation

Paudler, W. W.; Kerley, G. I.; McKay, J. J. *Org. Chem.*, 1963, 28, 2194

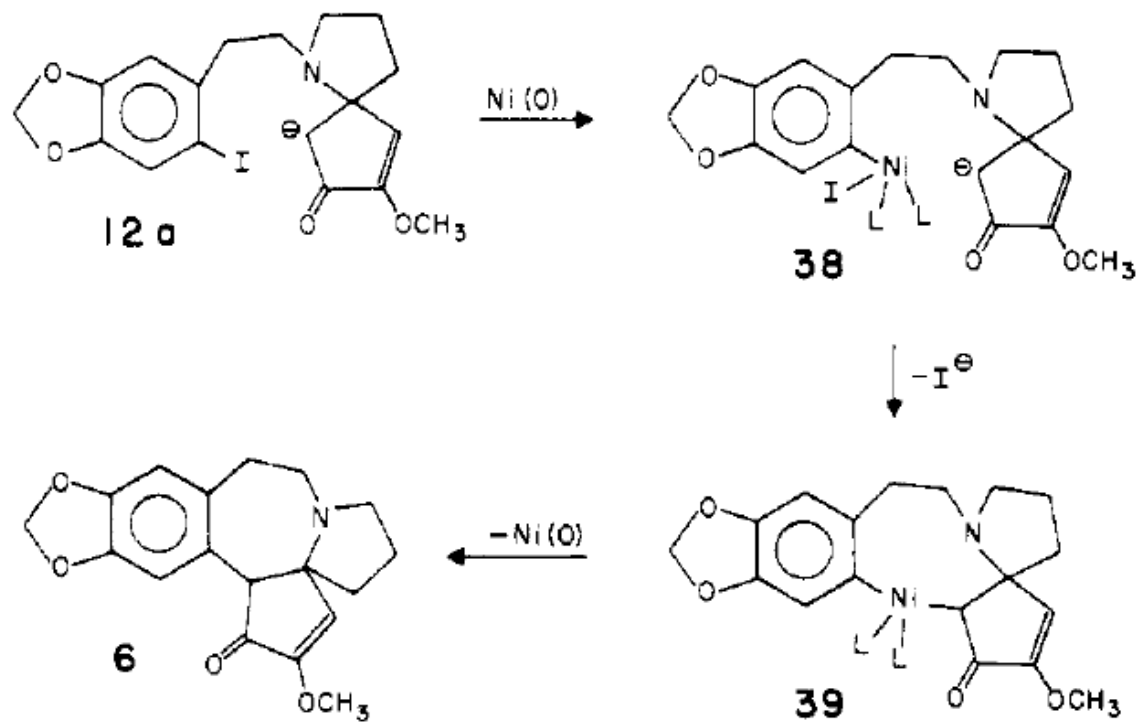
Previous Syntheses

Over a dozen racemic syntheses since 1972

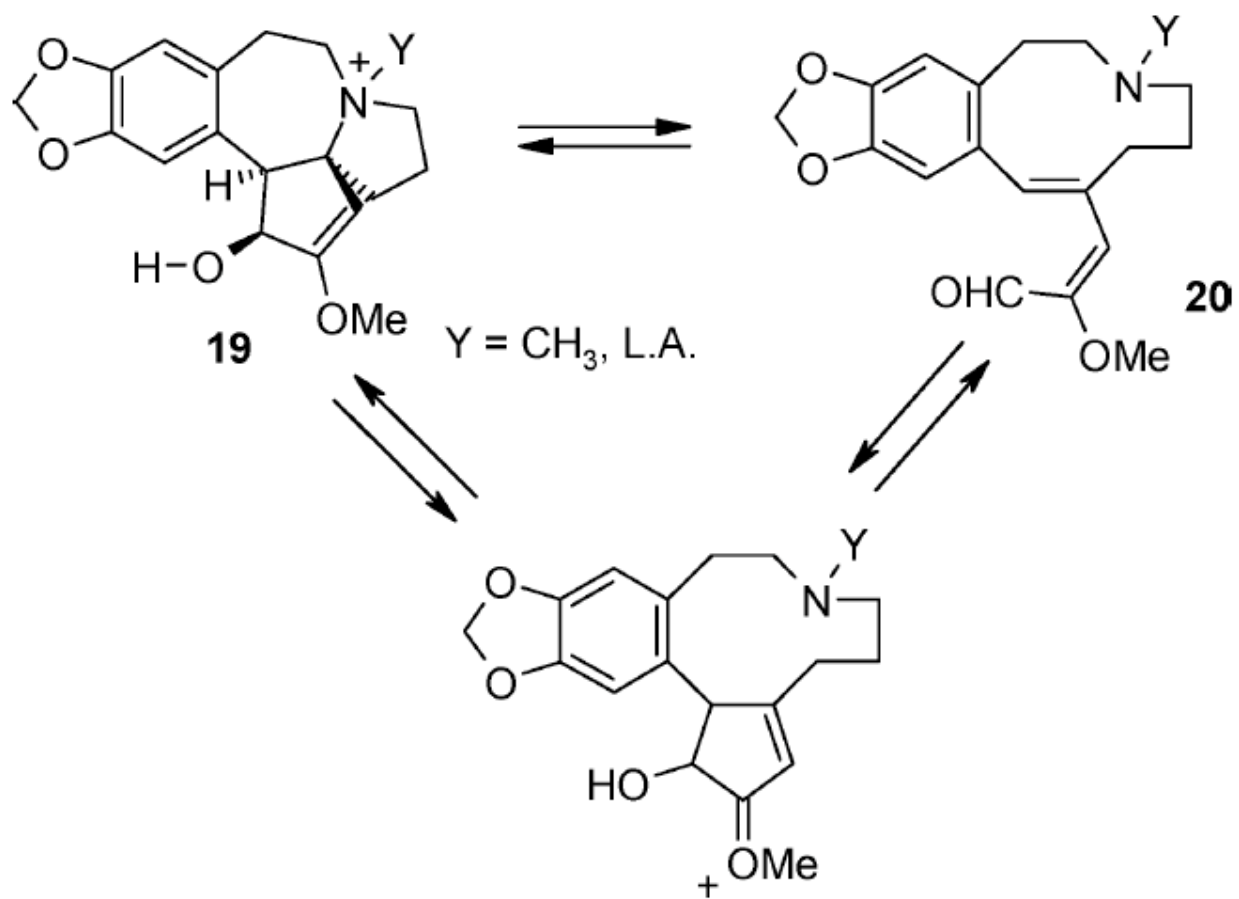
Asymmetric Syntheses

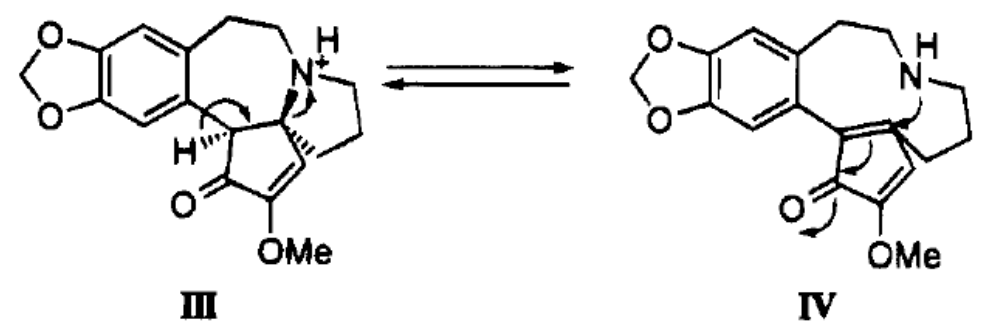
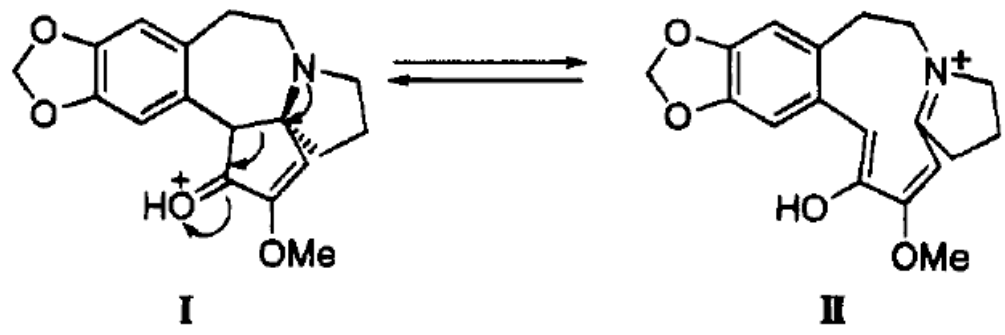
- 1) Mori and Isono, *J. Org. Chem.*, **1995**, 60, 115.
- 2) Nagasaka, Sato and Saeki, *Tetrahedron Asymm.*, **1997**, 8, 191.
- 3) Ikeada, et. al, *Chem. Pharm Bull.*, **1999**, 47, 983.
- 4) Tietze and Schirok, *J. Am. Chem. Soc.*, **1999**, 121, 10264.
- 5) Planas, Perard-Viret and Royer, *J. Org. Chem.*, **2004**, 69, 3087.

Semmelhack, et. Al., *J. Am. Chem. Soc.*, **1975**, 97, 2507

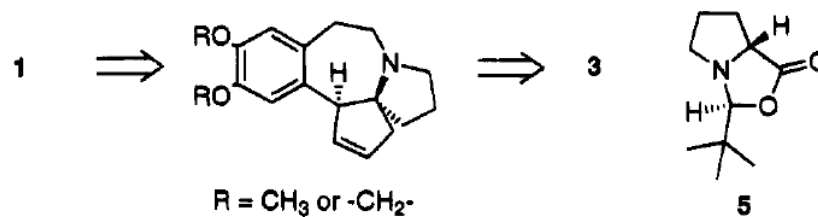
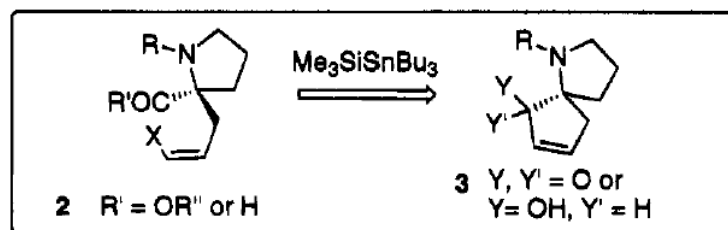


Cephalotaxine can racemize

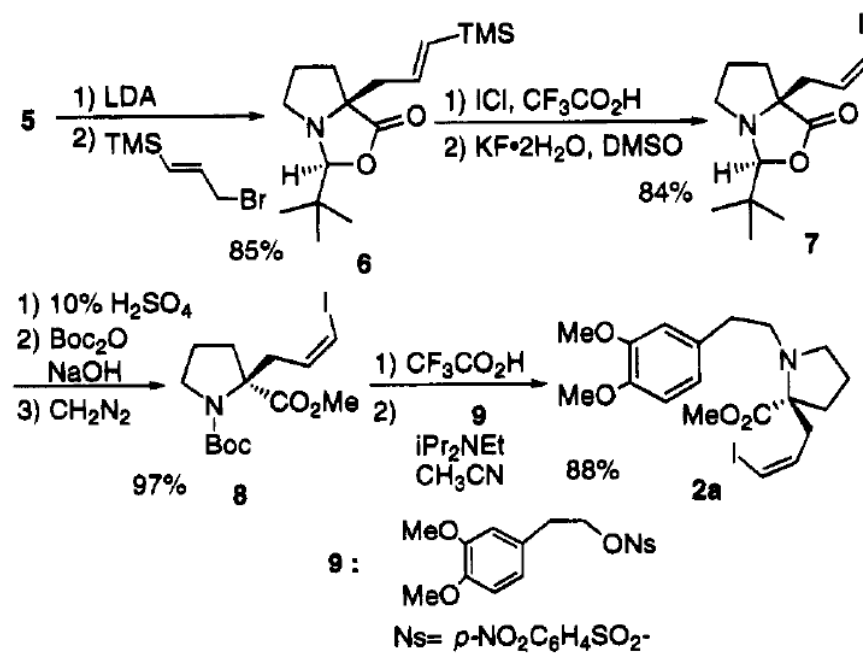


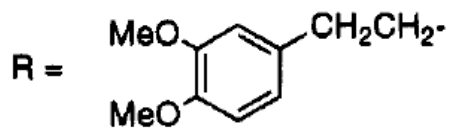
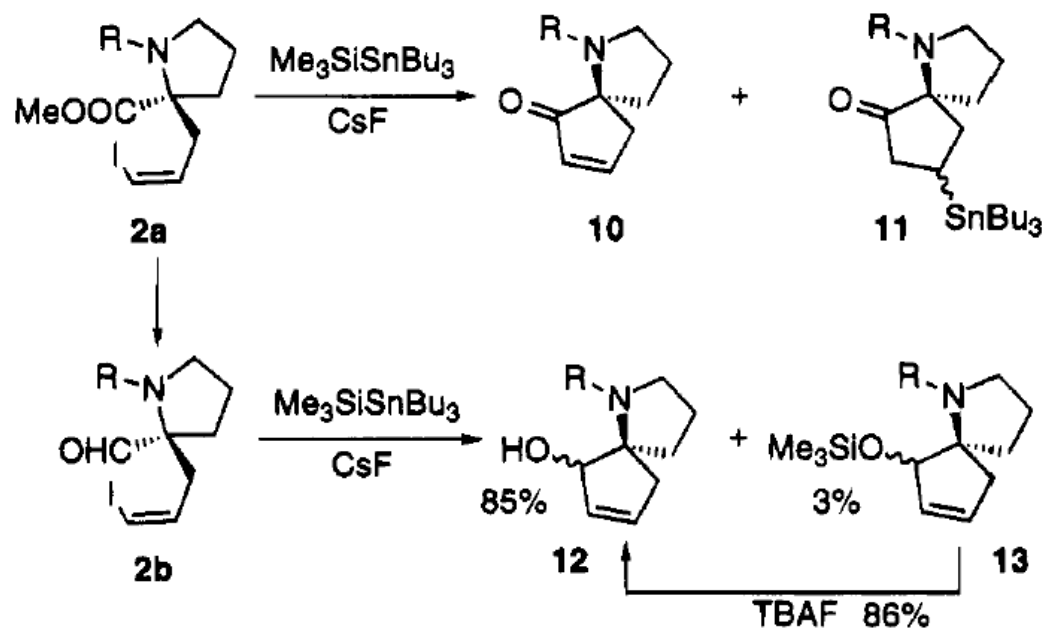


Mori and Isono, *J. Org. Chem.*, **1995**, *60*, 115.

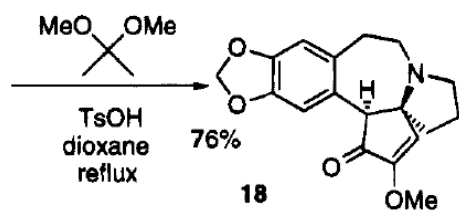
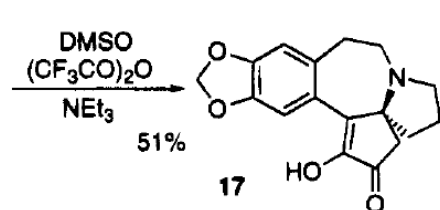
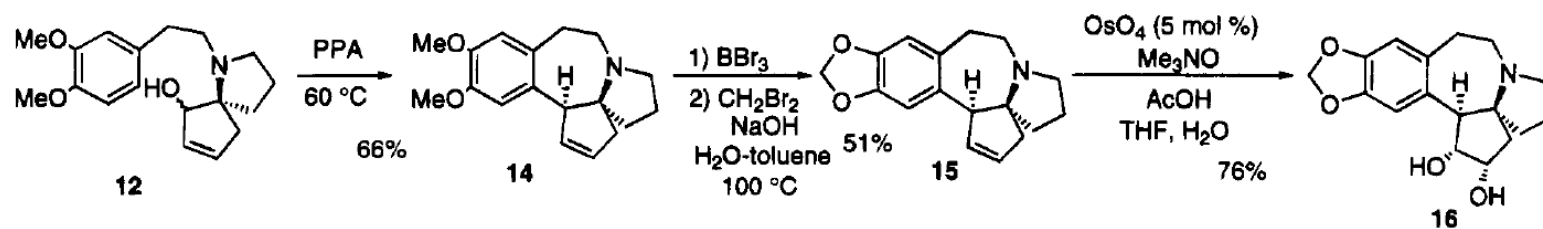


Scheme 2

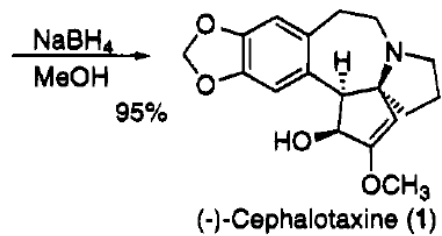
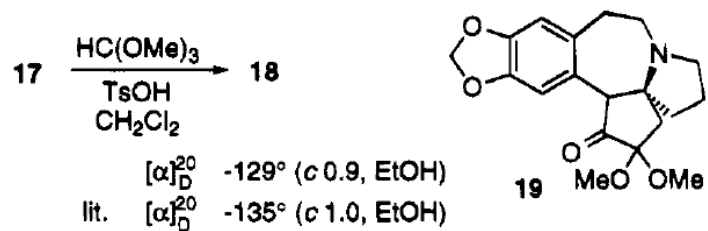




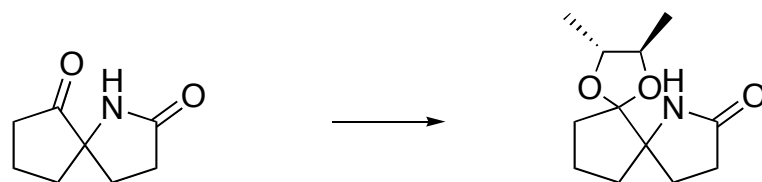
$\text{Me}_3\text{SiSnBu}_3$	10	11
1.2 eq	51%	3%
4.0 eq	-	63%



$[\alpha]_D^{19} -8.2^\circ$ (*c* 0.4, EtOH)
 lit. $[\alpha]_D^{20} -135^\circ$ (*c* 1.0, EtOH)



Nagasaka, Sato and Saeki, *Tetrahedron Asymm*, **1997**, 8, 191.



Ikeada, et. al, *Chem. Pharm Bull.*, 1999, 47, 983.

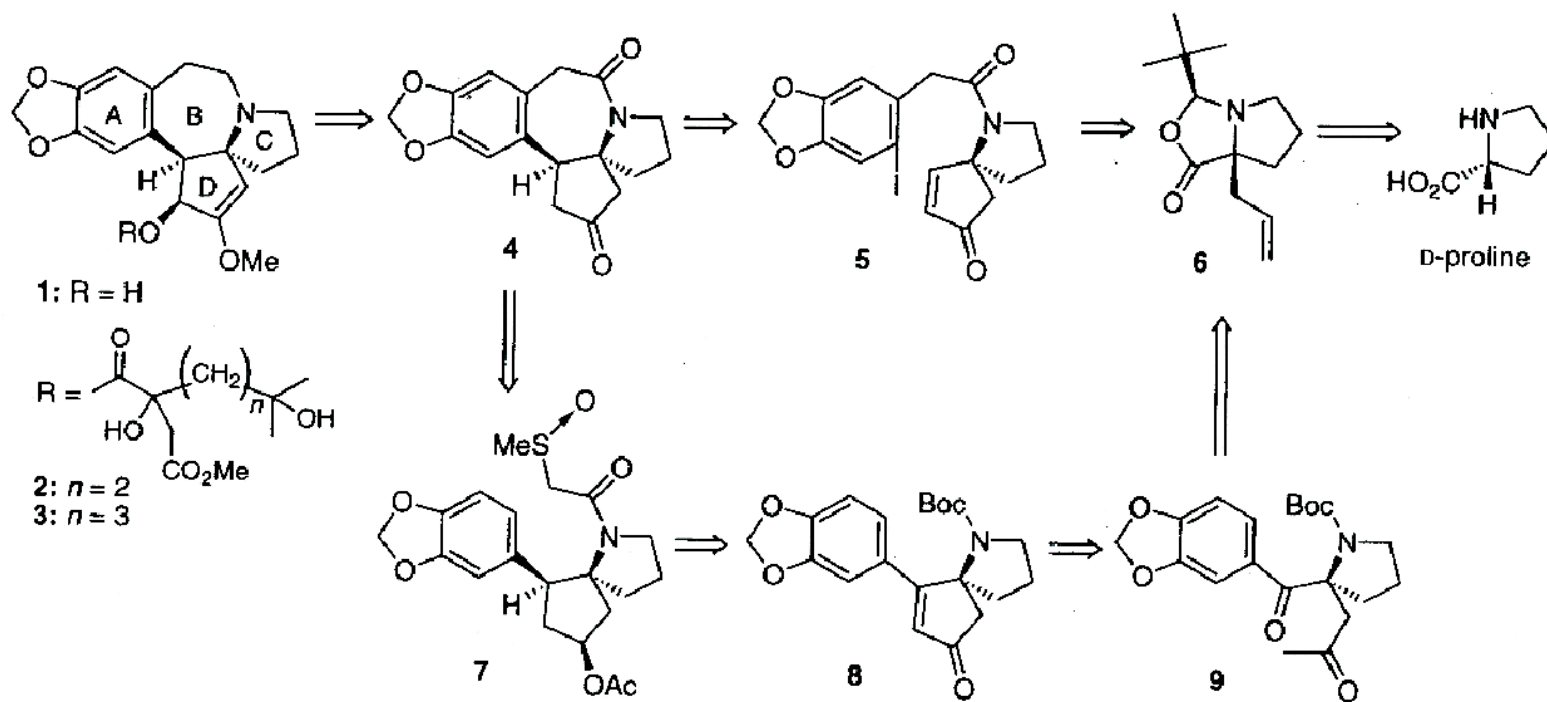
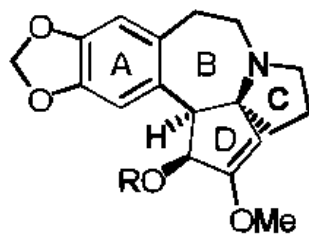
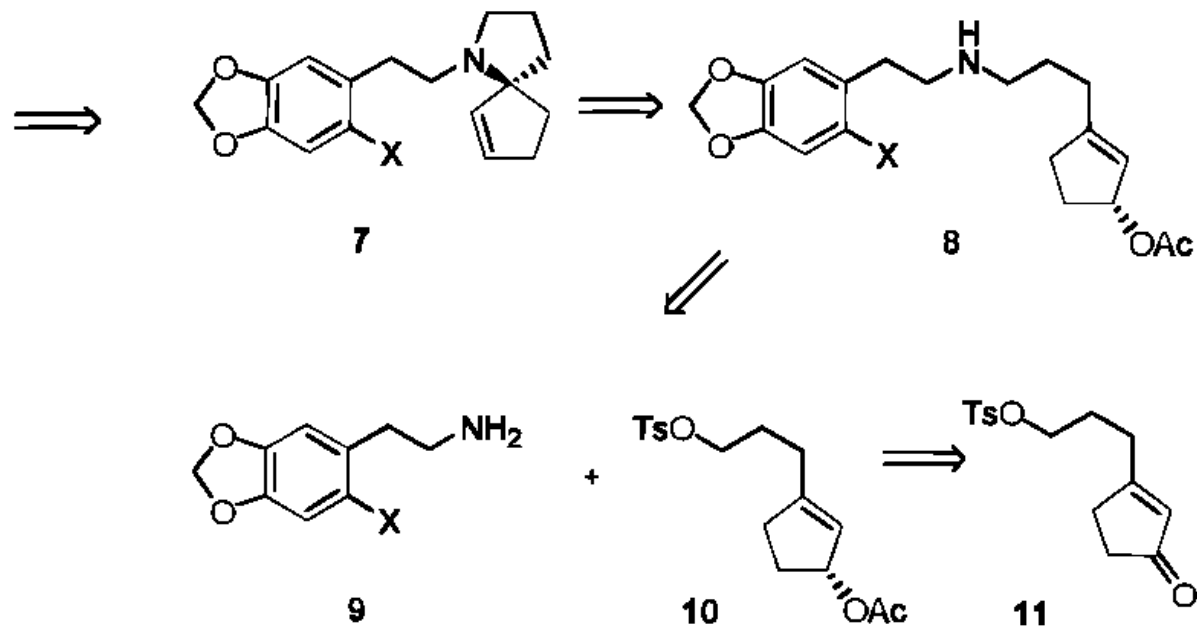
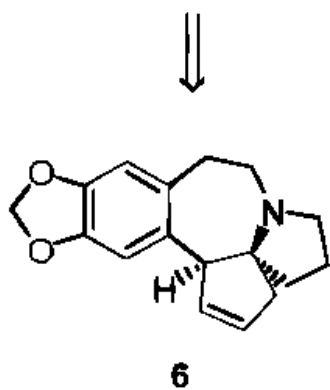


Chart 1

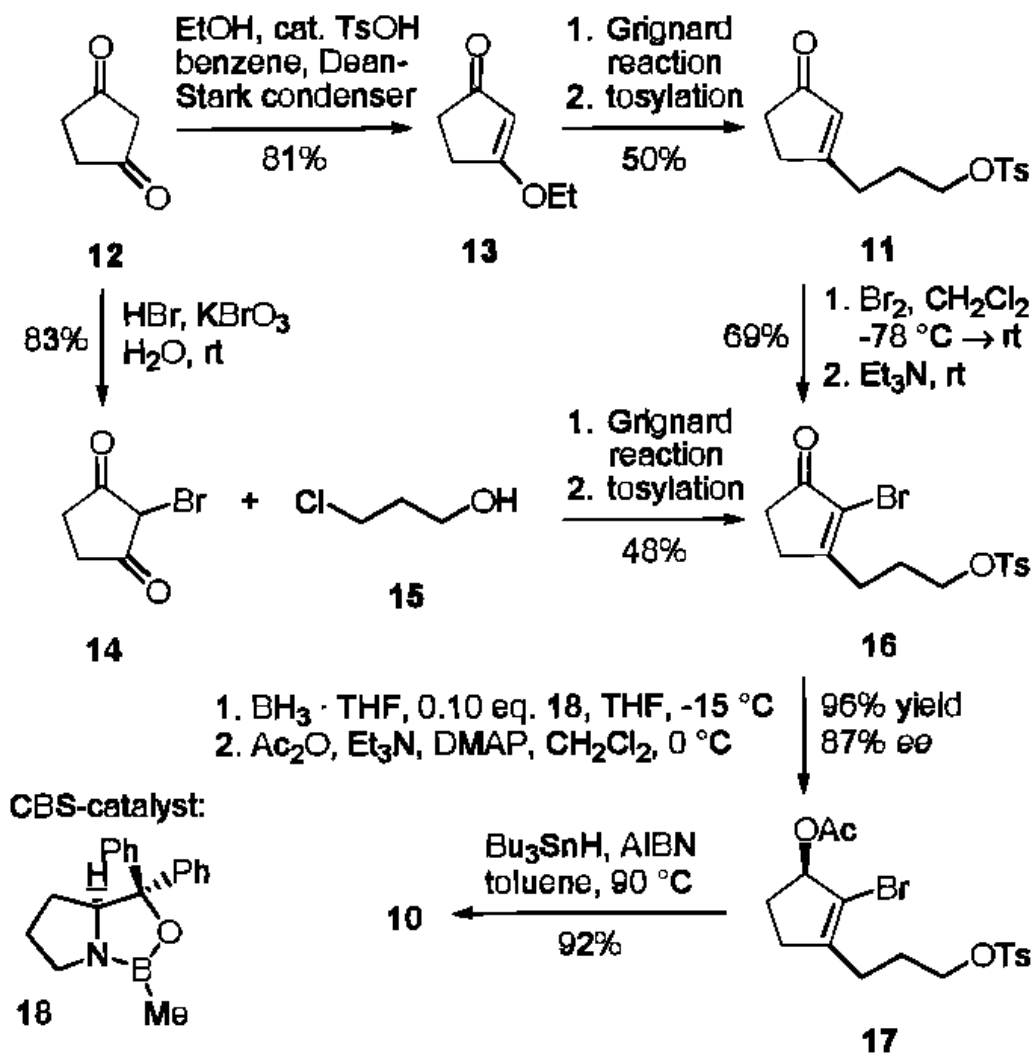


1 : R = H, (-)-Cephalotaxine

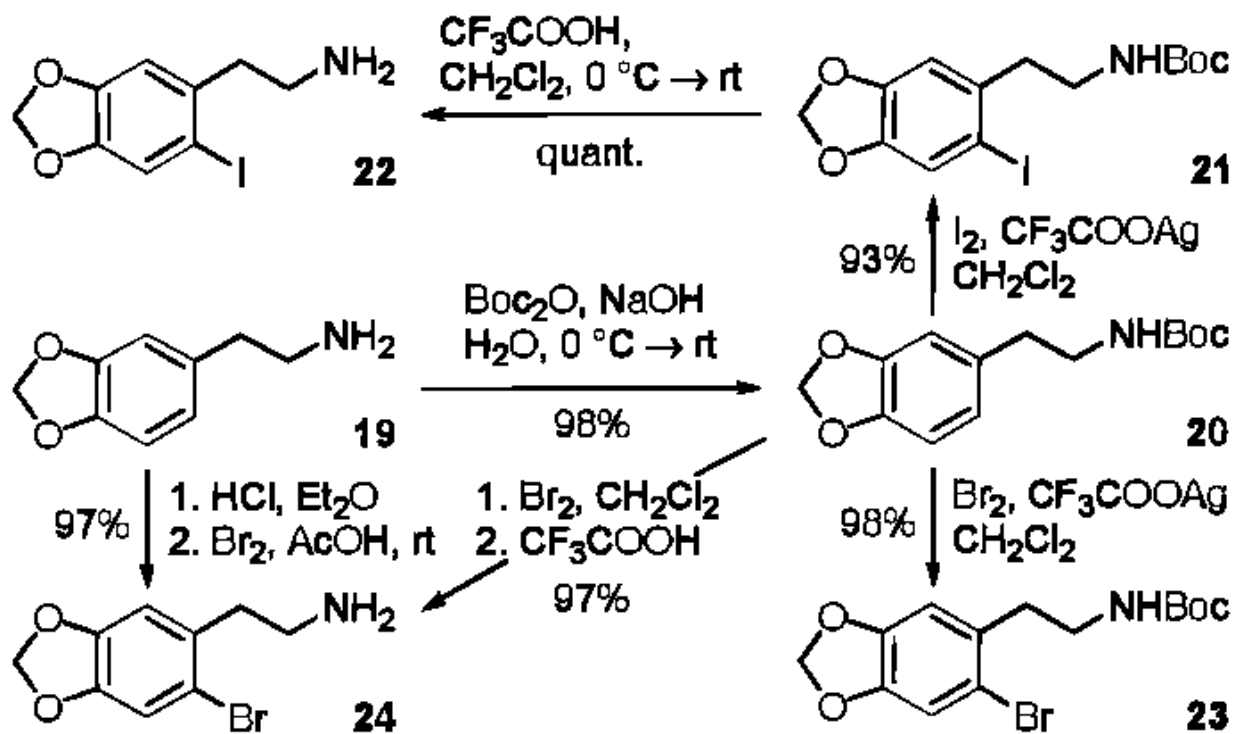


Tietze and Schirok, *J. Am. Chem. Soc.*, **1999**, *121*, 10264.

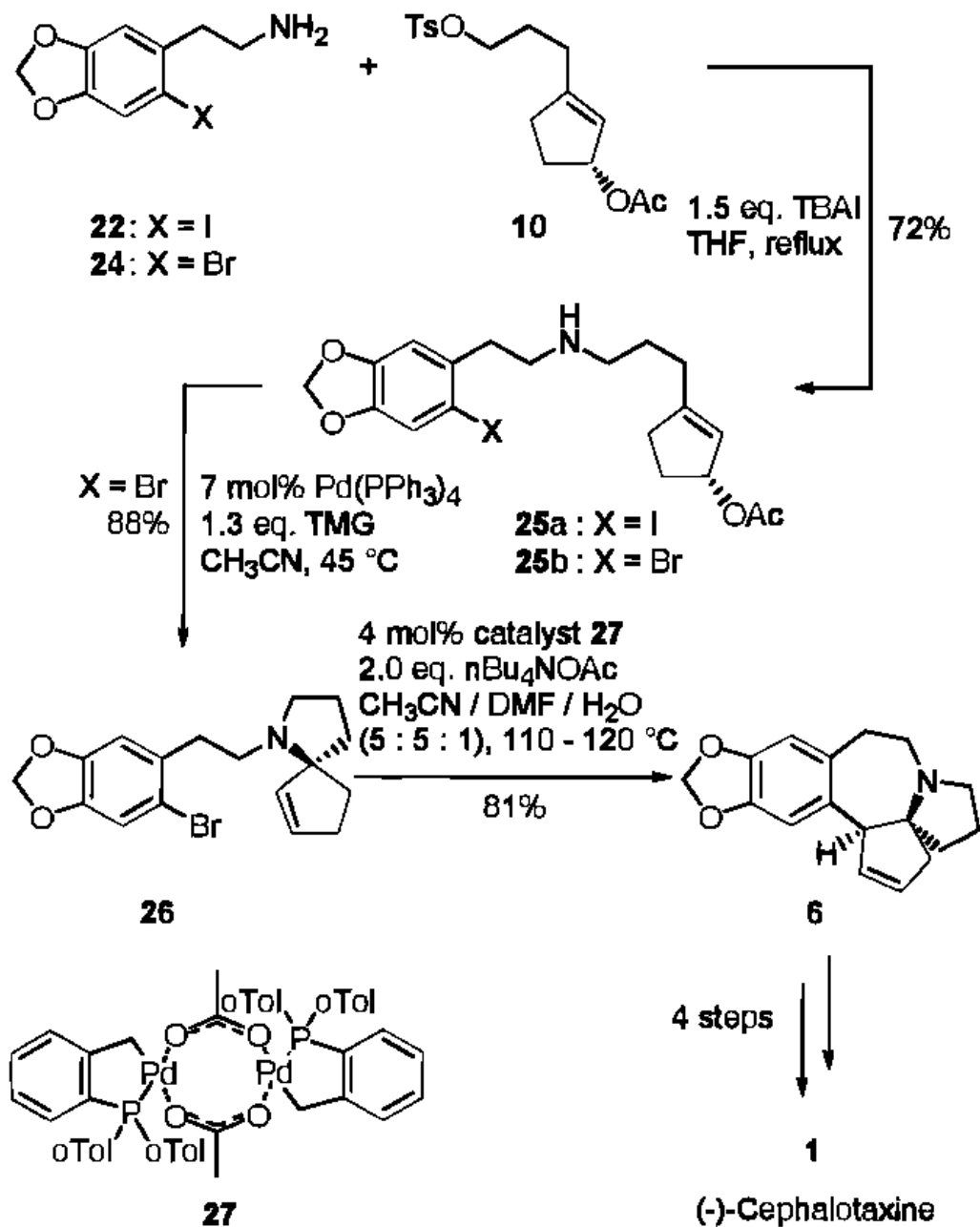
Scheme 2. Enantioselective Preparation of Allylic Acetate
10



Scheme 3. Halogenation of Phenylethylamines



Scheme 4. Synthesis of (-)-Cephalotaxine Precursor **6**



Planas, Perard-Viret and Royer, *J. Org. Chem.*, **2004**, *69*, 3087.

