

Synthesis of Strychnine by R. B. Woodward et al. (1954)

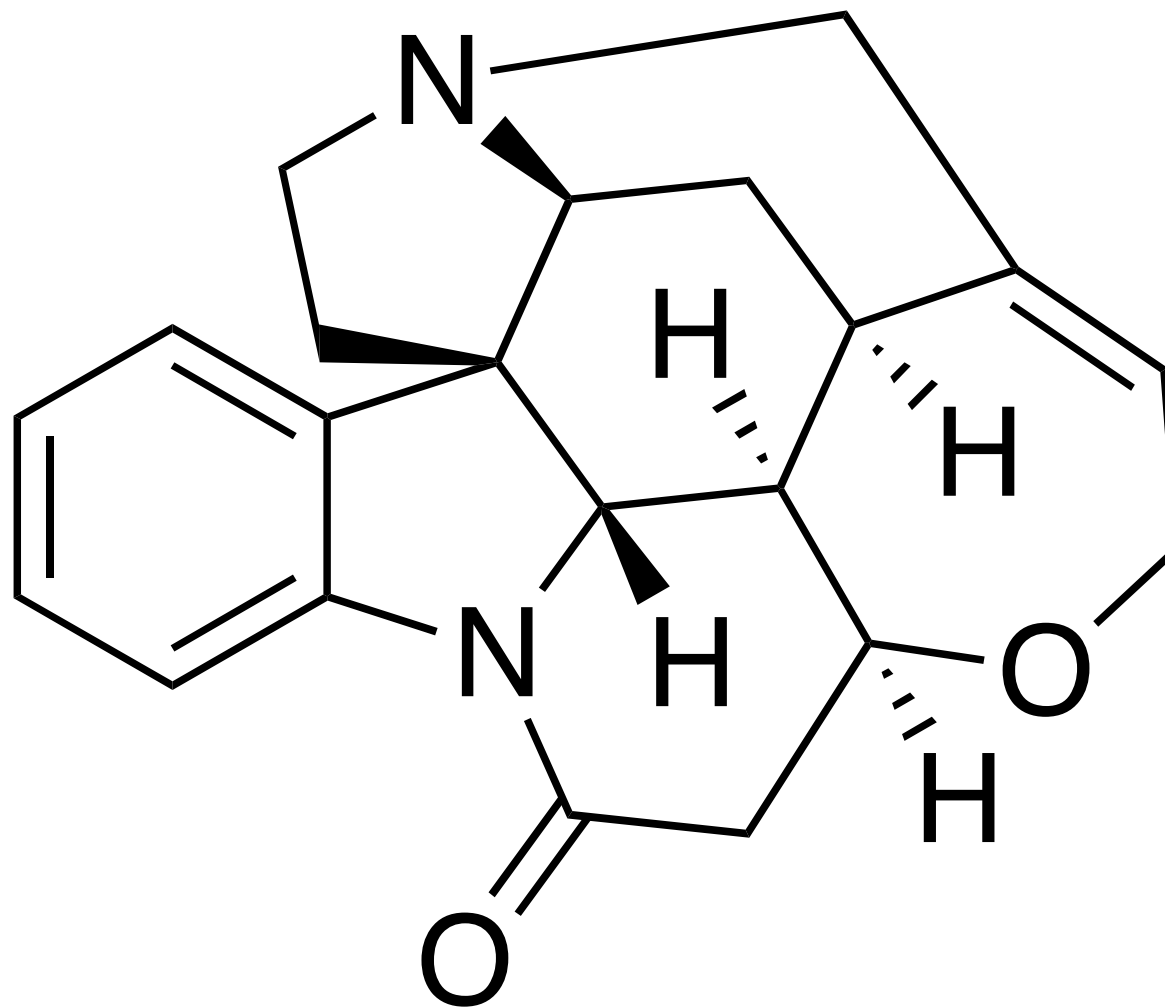
Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K.. *J. Am. Chem. Soc.*, **1954**, *76*, 4749.

Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis, Targets, Strategies, Methods*; Wiley-VCH: New York, 1996; pp 21-40.

Presenter: Kiyoto Tanemura

Strychnine

- Synthetic challenge
 - Seven fused rings
 - Six chiral centers
- Validation of certain step in strychnine biosynthesis



Background

- First isolation of strychnine from *Strychnos ignatii*¹
- *Strychnos* species recognized as poisonous
- Structure of strychnine elucidated
 - chemical degradation²
 - X-ray crystallography³



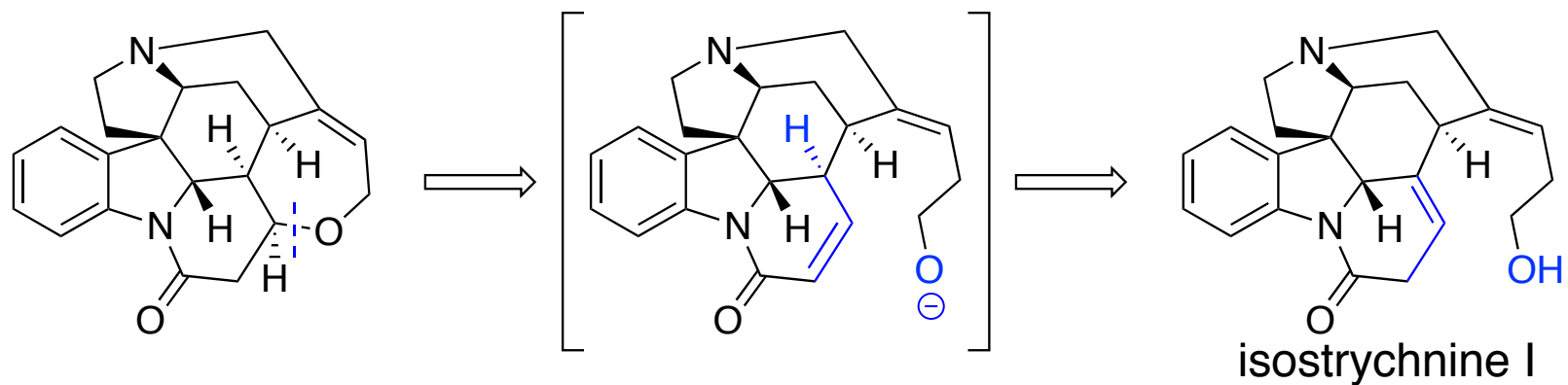
Strychnos ignatii (image from rarebooks.org)

[1] note: Original paper not found. Pelletier, P. J.; Caventou, J. B. *Ann. Chim. Phys.* **1818**, *8*, 323.

[2] (a) Robinson, R. *Experientia* **1946**, *2*, 28. (b) Briggs, L. H.; Openshaw, H. T.; Robinson, R. *J. Chem. Soc.*, **1946**, 903.

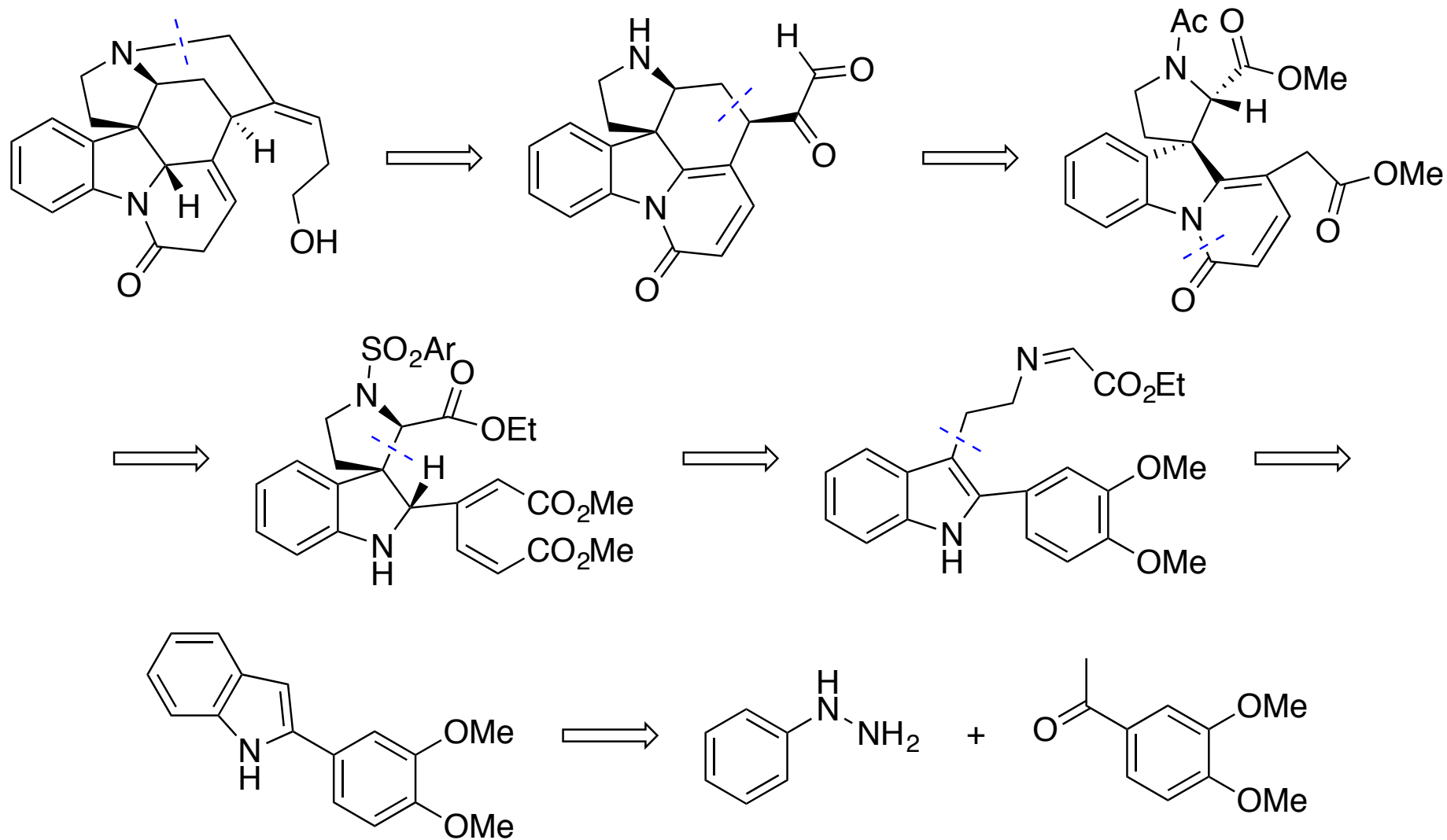
[3] Peerdeman, A. F. *Acta Cryst.*, **1956**, *9*, 824.

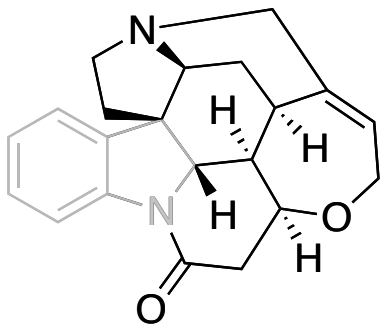
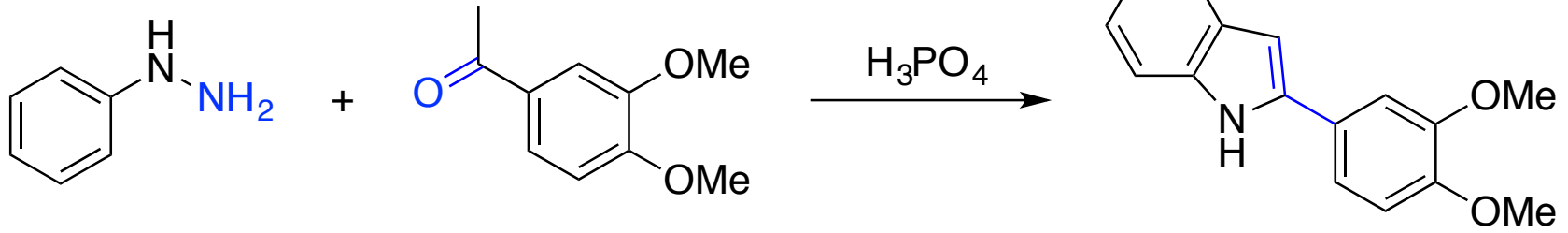
Retrosynthetic analysis



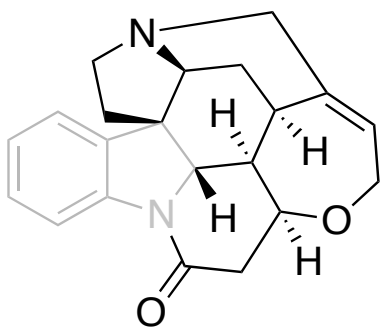
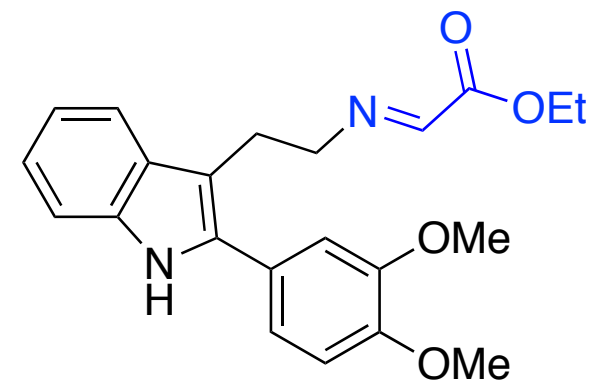
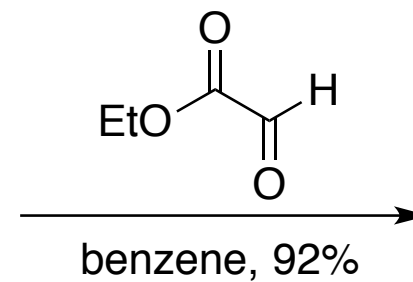
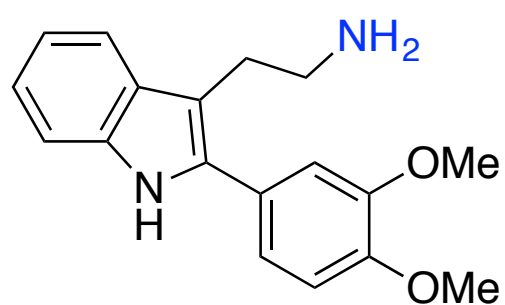
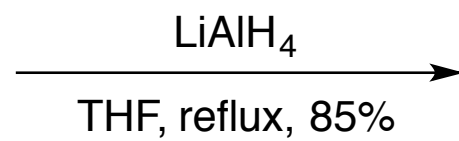
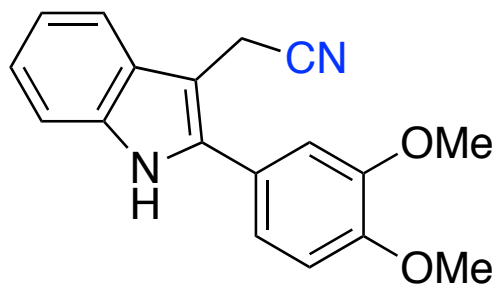
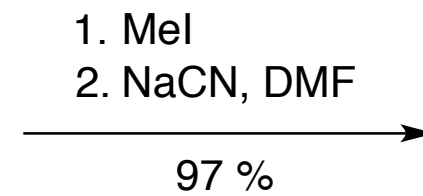
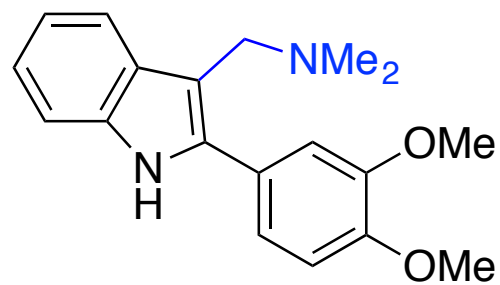
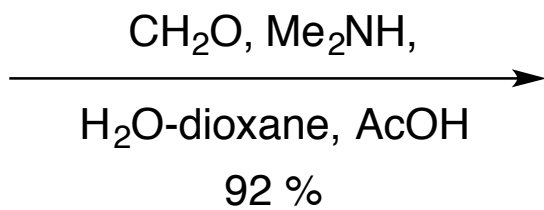
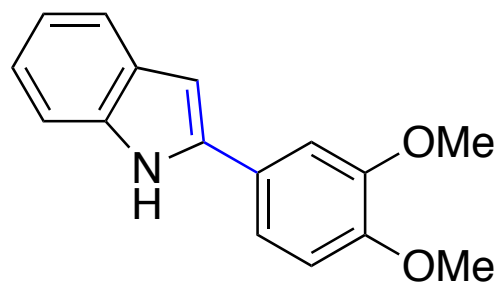
Prelog, V.; Battegay, J.; Taylor, W. I. *Helv. Chim. Acta* **1948**, *31*, 2244.

Retrosynthetic analysis

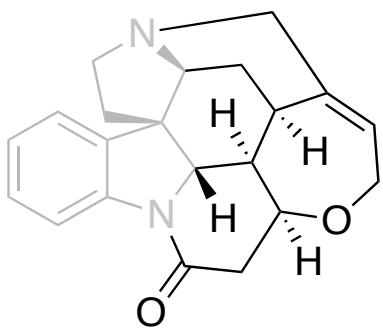
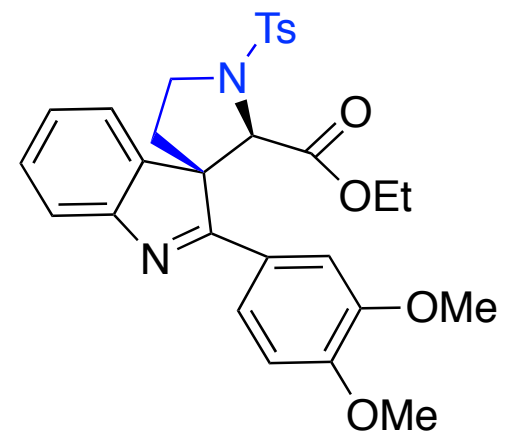
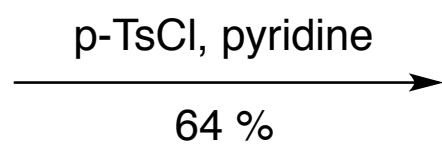
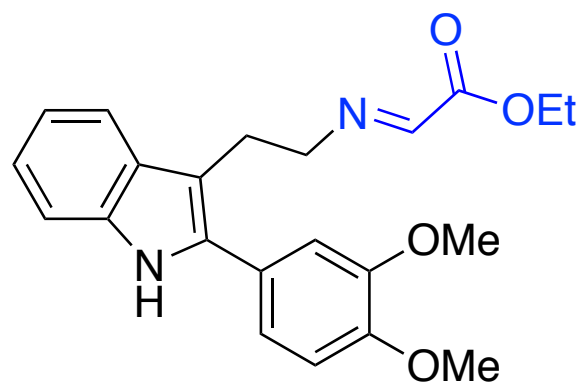




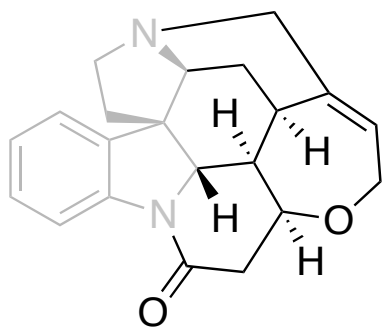
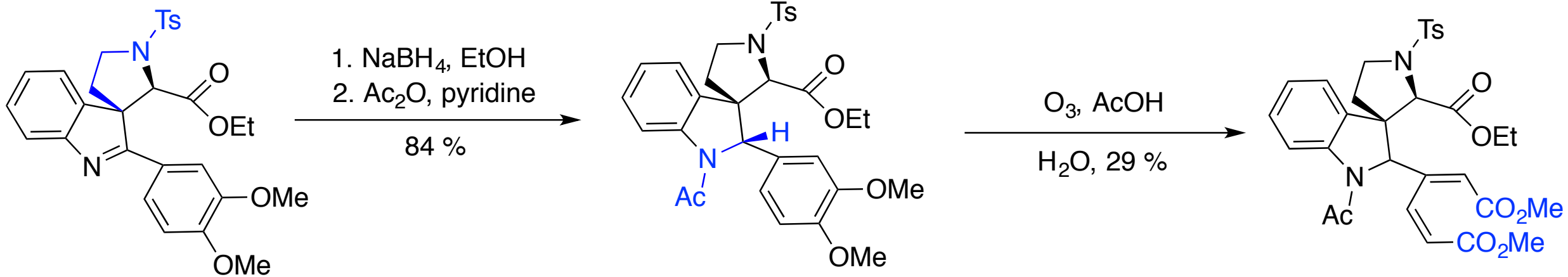
100 %



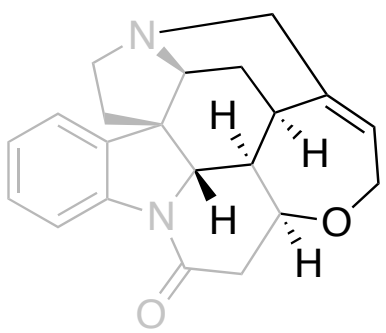
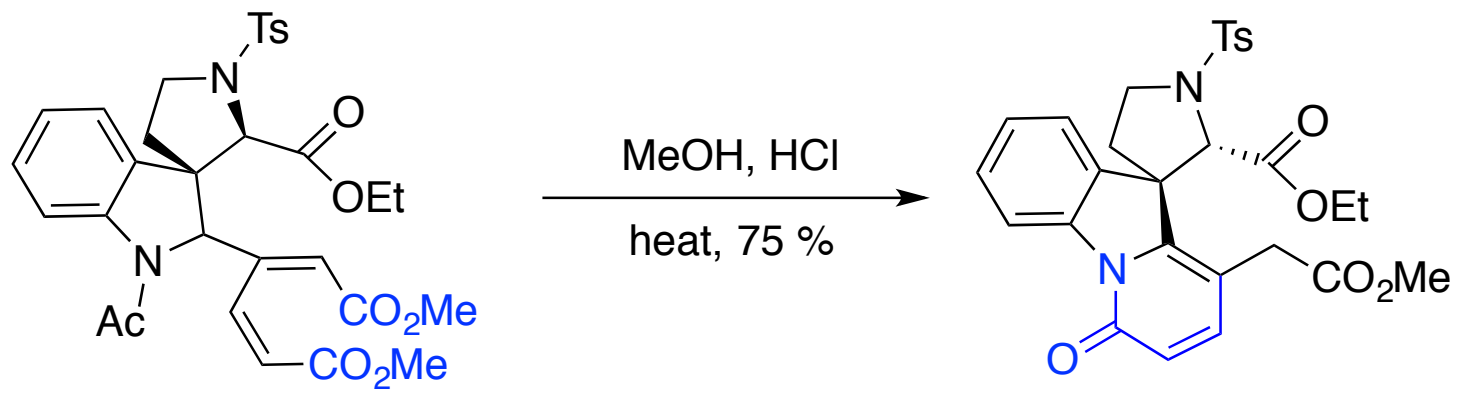
70. %

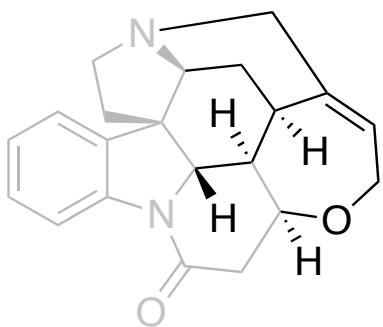
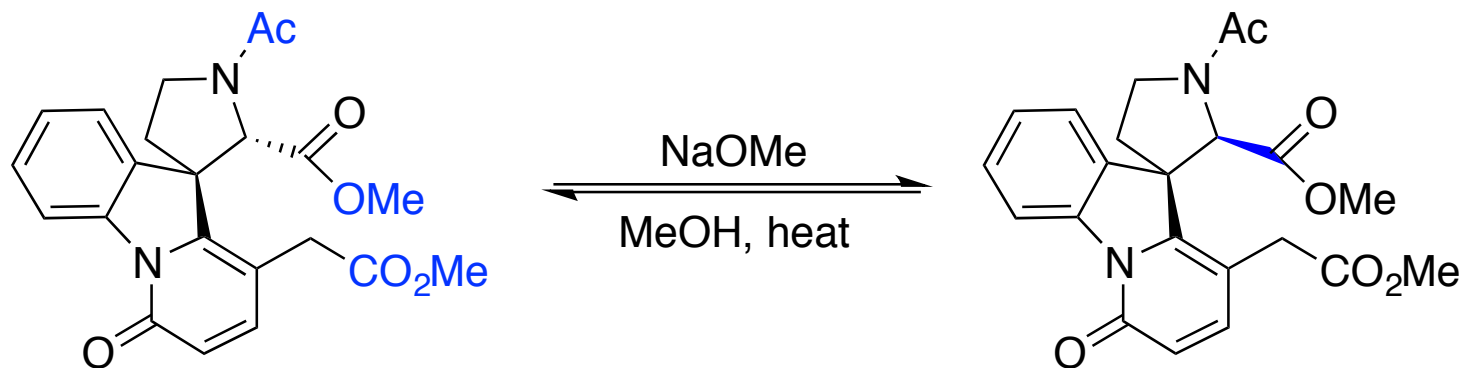
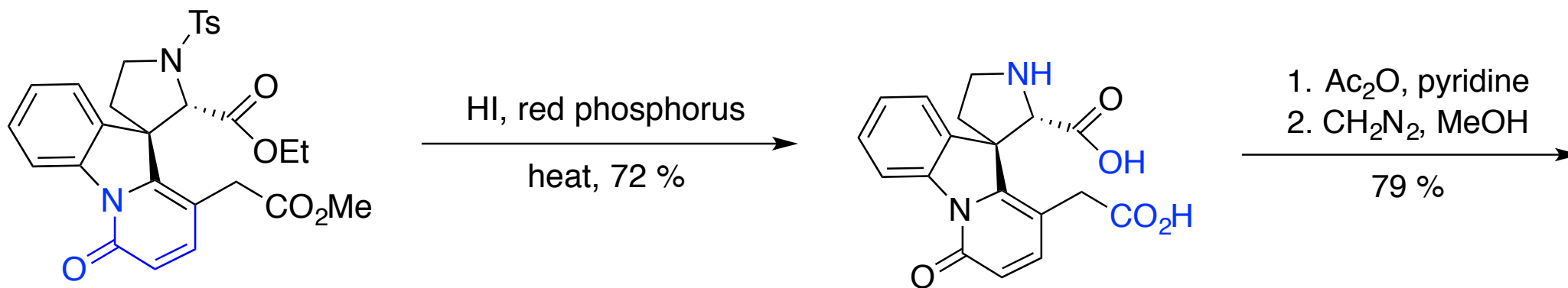


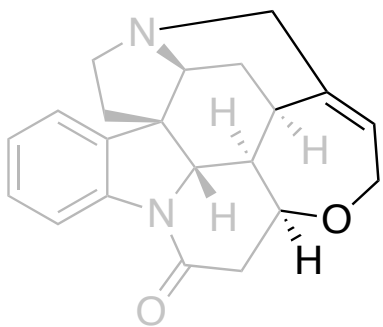
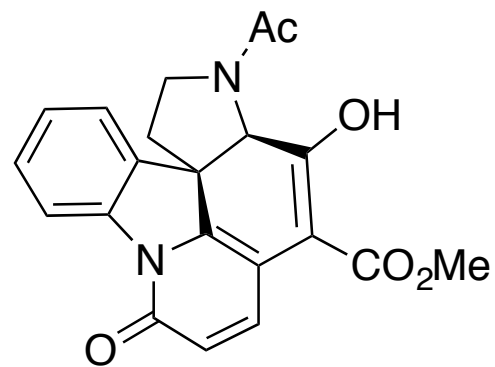
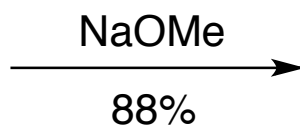
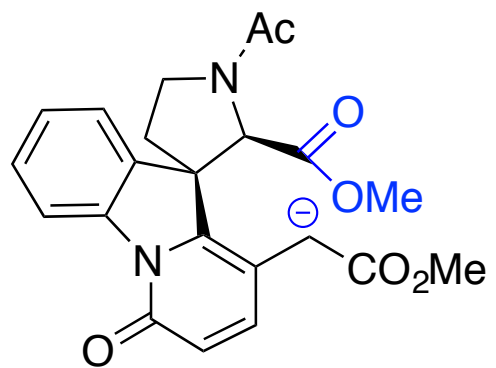
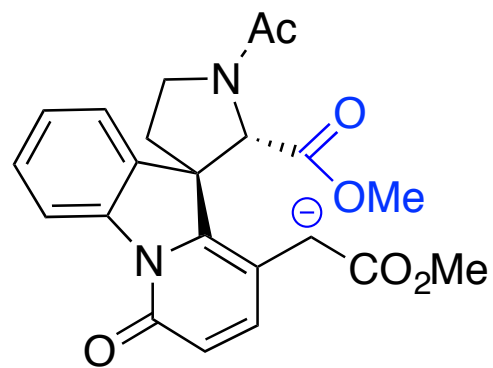
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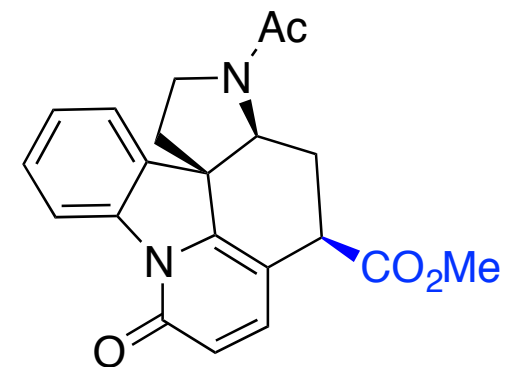
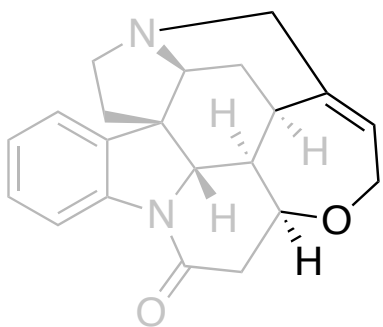
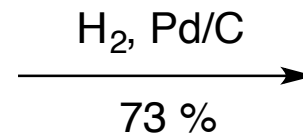
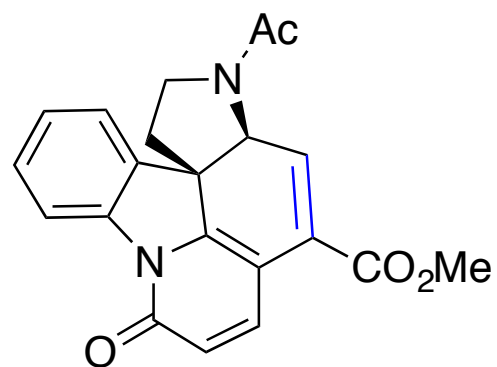
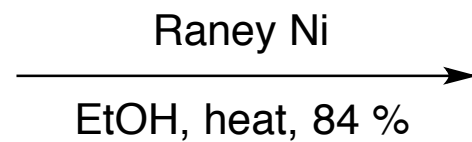
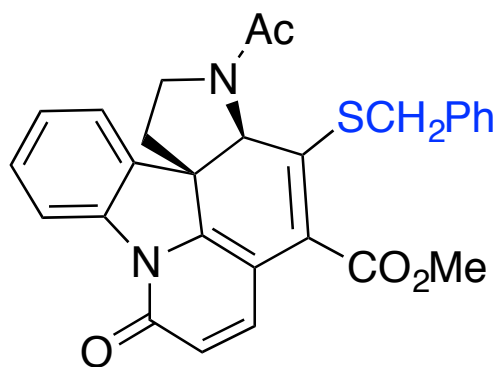
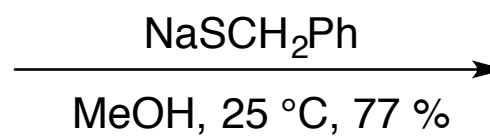
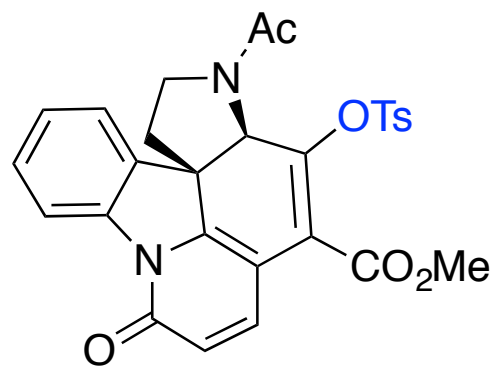
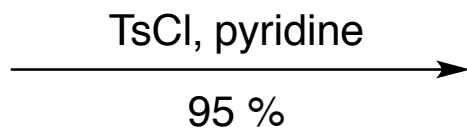
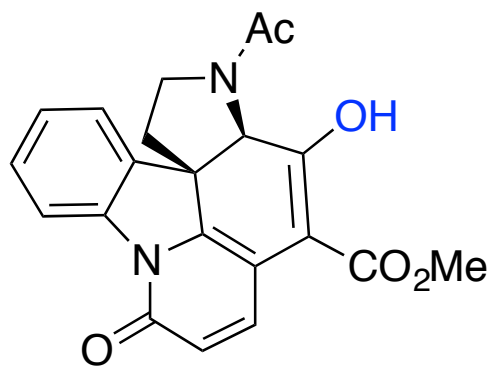


5 %

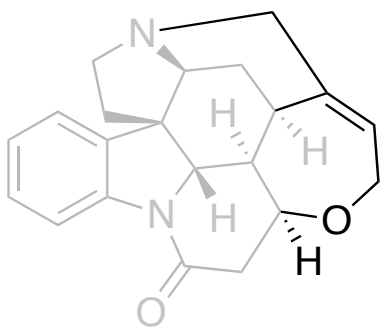
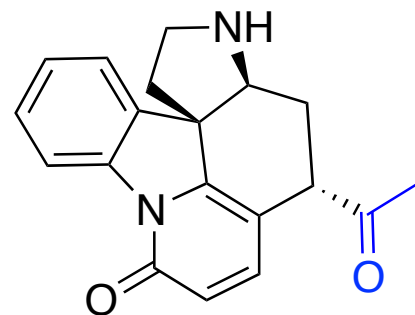
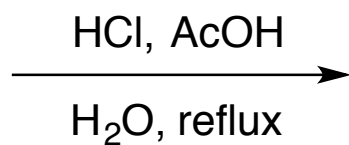
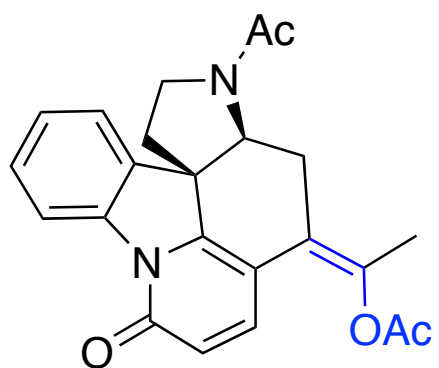
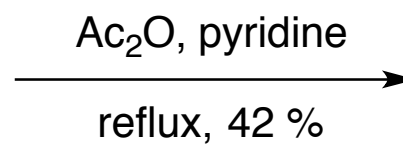
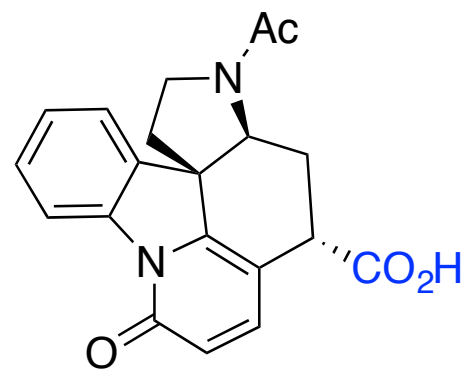
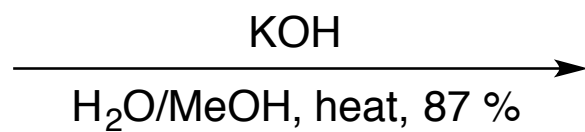
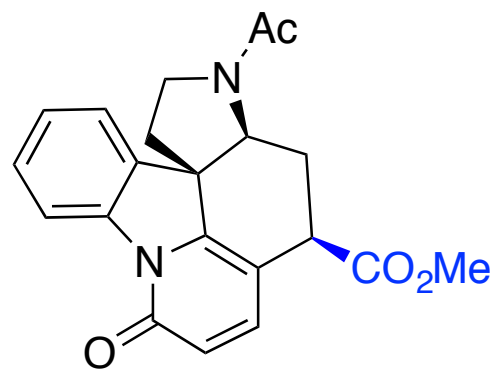




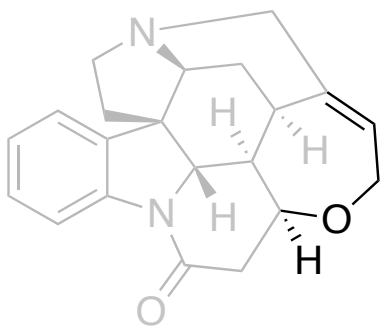
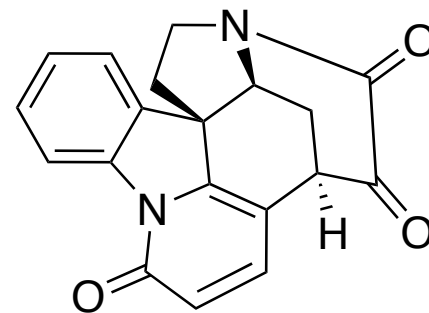
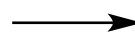
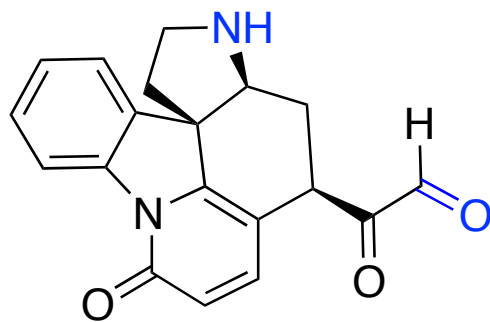
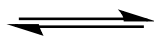
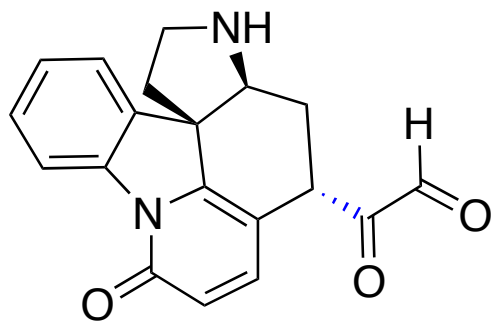
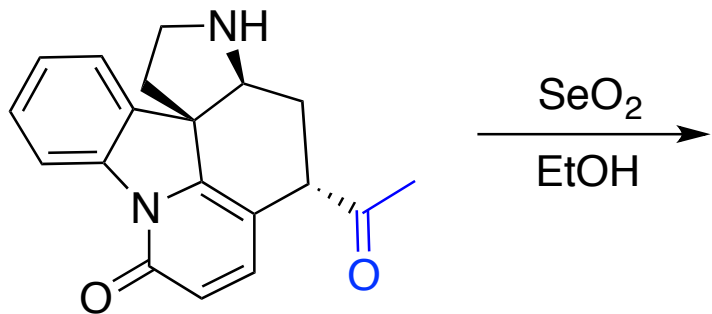


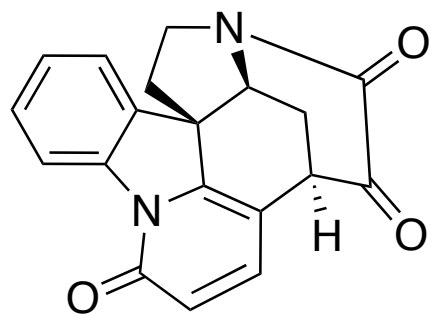


1 %

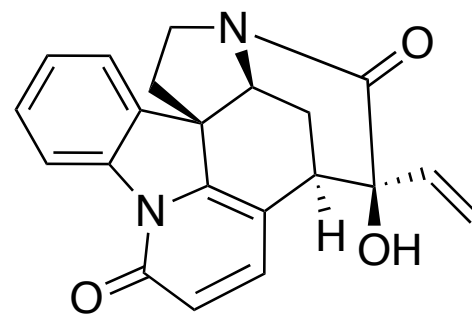


0.3 %

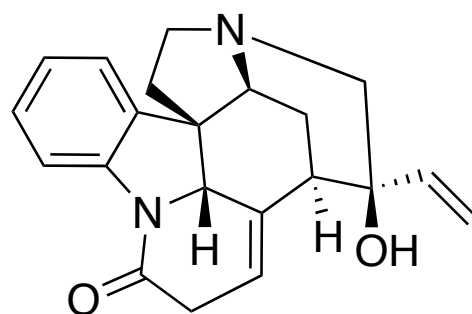




1. NaCCH, THF, 53 %
2. H₂, Lindlar, 86 %

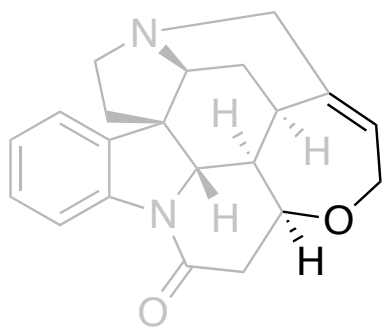
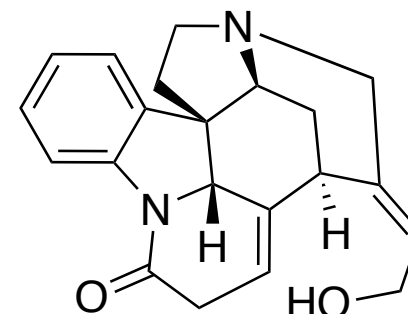


LiAlH₄
Et₂O, reflux, 30 %

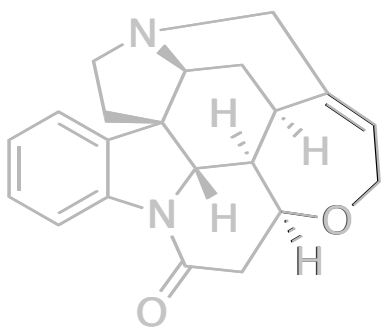
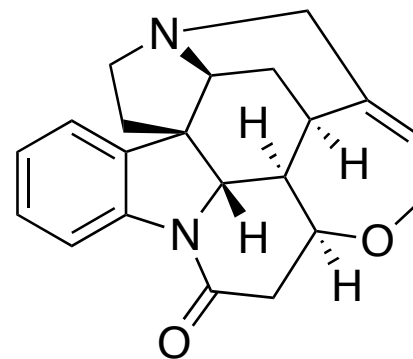
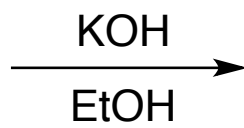
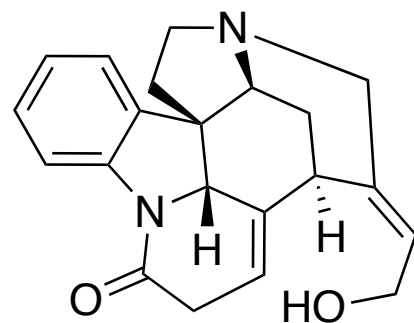


1. HBr, AcOH, 120 °C
2. H₂SO₄, H₂O, reflux

13 %



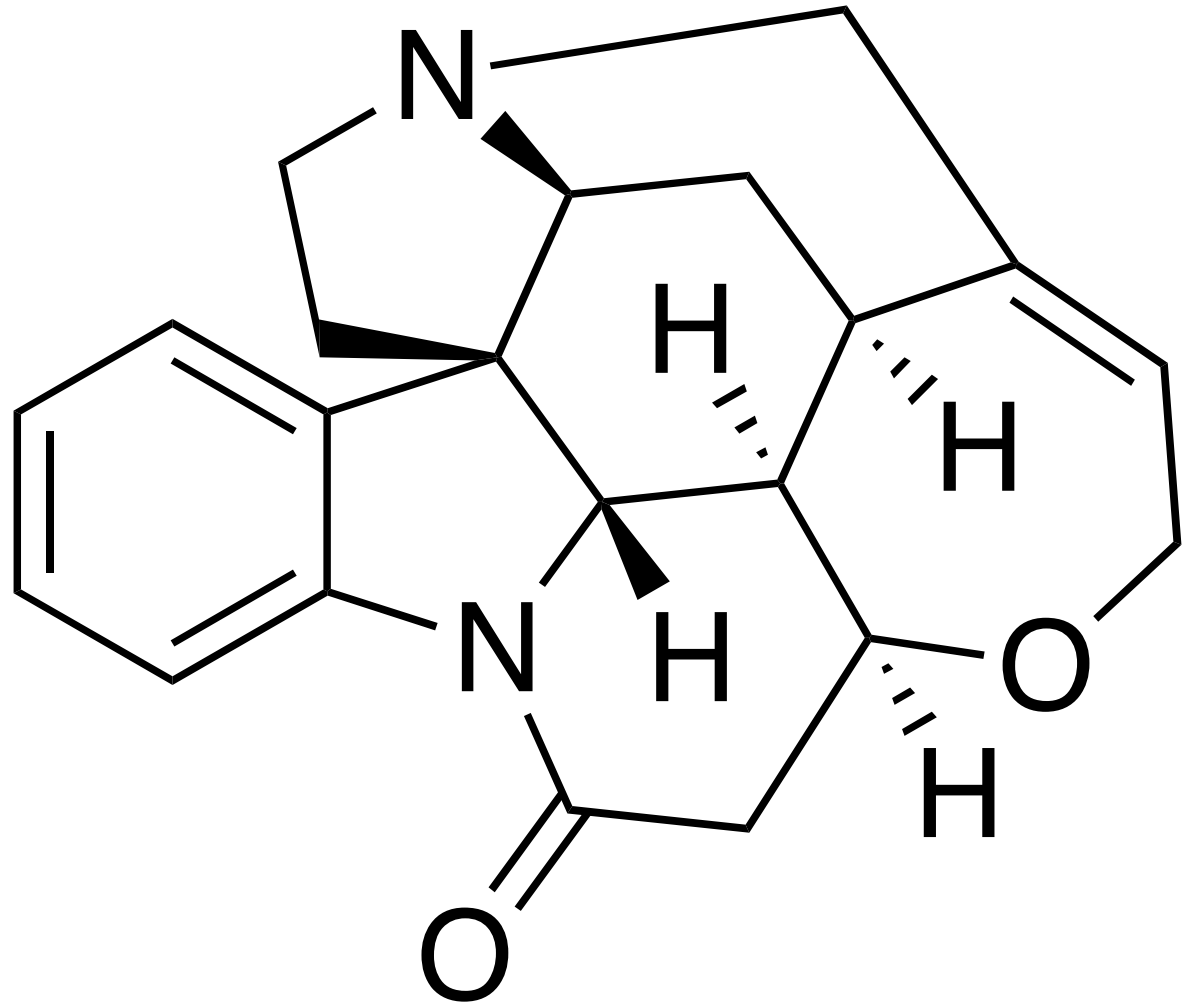
0.006 %



0.006 %

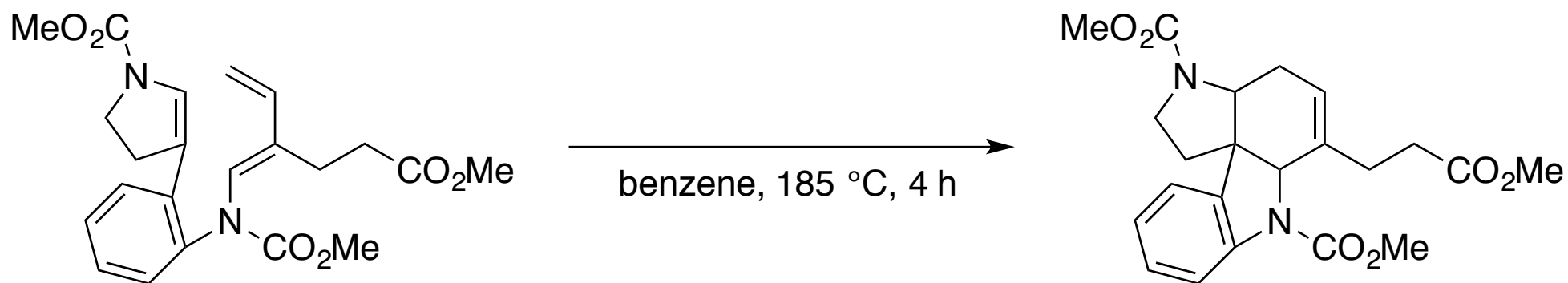
Strychnine

- 30 steps
- 0.006 % total yield



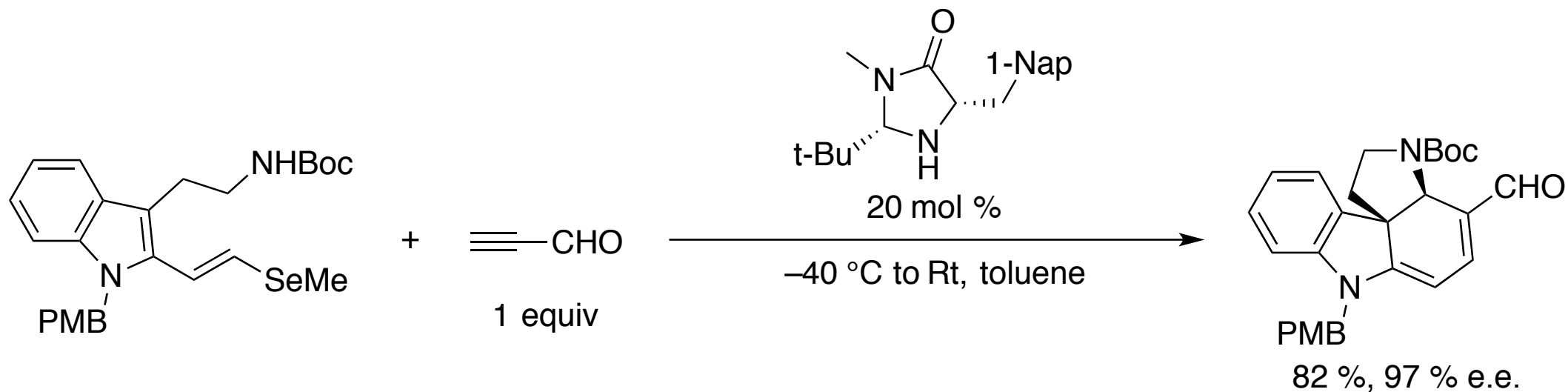
Later Syntheses: Diels-Alder route

3 % yield, 12 steps



Later Syntheses: Collective total synthesis/organocascade catalysis

- 6 % yield, 12 steps



Strychnine

- 30 steps
- 0.006 % total yield

