

# Ergot Alkaloid Syntheses

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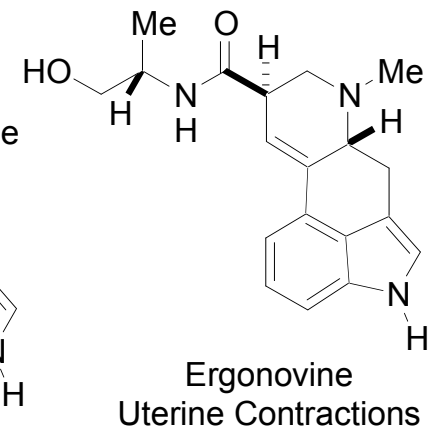
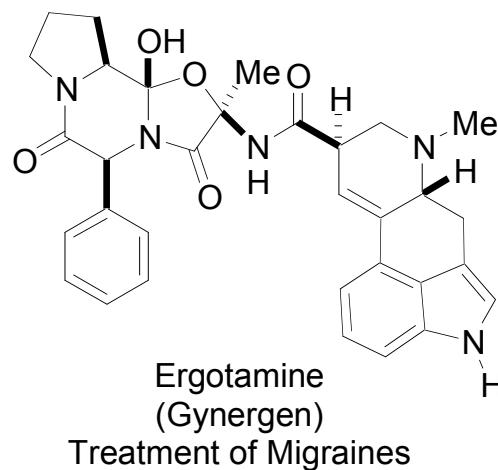
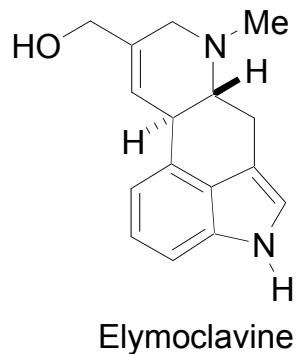
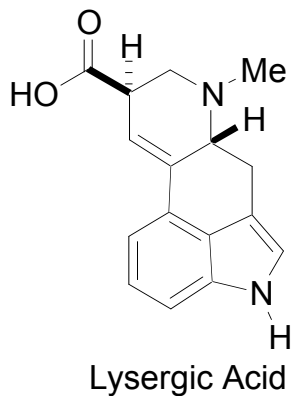
(a.k.a., “crappy hippy”)

2 November 2005

# Ergot Alkaloids

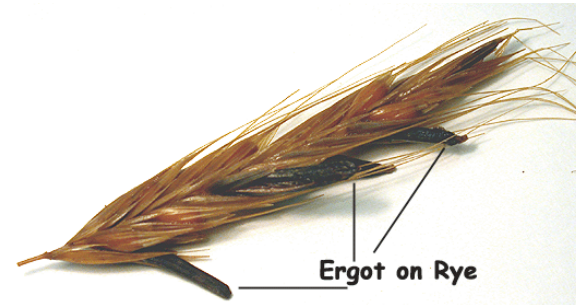
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- Isolated from the dry sclerotium of the fungus *Claviceps purpurea* (ergot), a parasite that grows on grains.
- Modern sources include isolation from field-cultivated ergot, semisynthesis, and fermentation of the fungus *Secale cornutum*.
- Most biologically-active agents are amides or peptides of lysergic acid.
- Methylation of the indole nitrogen increases serotonin-antagonistic effect of the drug.



# History & Ergot Alkaloids

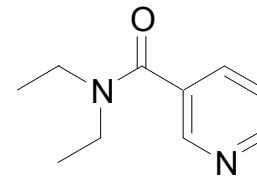
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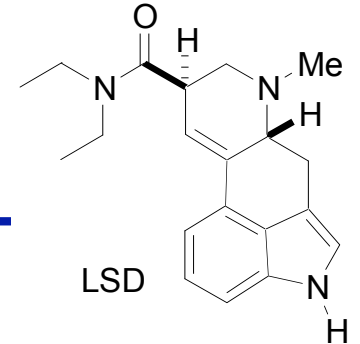
- Many ailments have been linked to ergot alkaloids.
  - St. Anthony’s Fire (a.k.a., “Devil’s curse”, gangrenous ergotism)
  - Convulsive ergotism (delirium, epileptic-type seizures)
- Historically, ergot was thought to be a normal part of rye.
- Wet, rainy weather is particularly conducive to ergot growth.
- Rye was mostly consumed by poor. (ergo, ...)
- True cause of ergotism not discovered until 19<sup>th</sup> century.
- Ergot attributed to witch trials (yes, Salem circa 1691).
- In the middle ages, some instances of the black plague may have actually been ergotism.
- Last great epidemic occurred in 1926-1927, in certain areas of southern Russia.

# The LSD Story

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Coramine



LSD

- Discovered by Albert Hofmann (Sandoz Co., Basel, CH).
- Worked under Arthur Stoll, who had interests in foxglove (*Digitalis*), Mediterranean squill (*Scilla maritima*), and ergot of rye (*Claviceps purpurea* or *Secale cornutum*).
- LSD-25 (Lysergsäure-diäthylamid) was first synthesized in 1938.
- “I had planned the synthesis of this compound with the intention of obtaining a circulatory and respiratory stimulant (an analeptic). Such stimulating properties could be expected for lysergic acid diethylamide, because it shows similarity in chemical structure to the analeptic already known at that time, namely nicotinic acid diethylamide (Coramine). During the testing of LSD-25 in the pharmacological department of Sandoz, whose director at the time was Professor Ernst Rothlin, a strong effect on the uterus was established. It amounted to some 70 percent of the activity of ergobasine. The research report also noted, in passing, that the experimental animals became restless during the narcosis. The new substance, however, aroused no special interest in our pharmacologists and physicians; testing was therefore discontinued.”

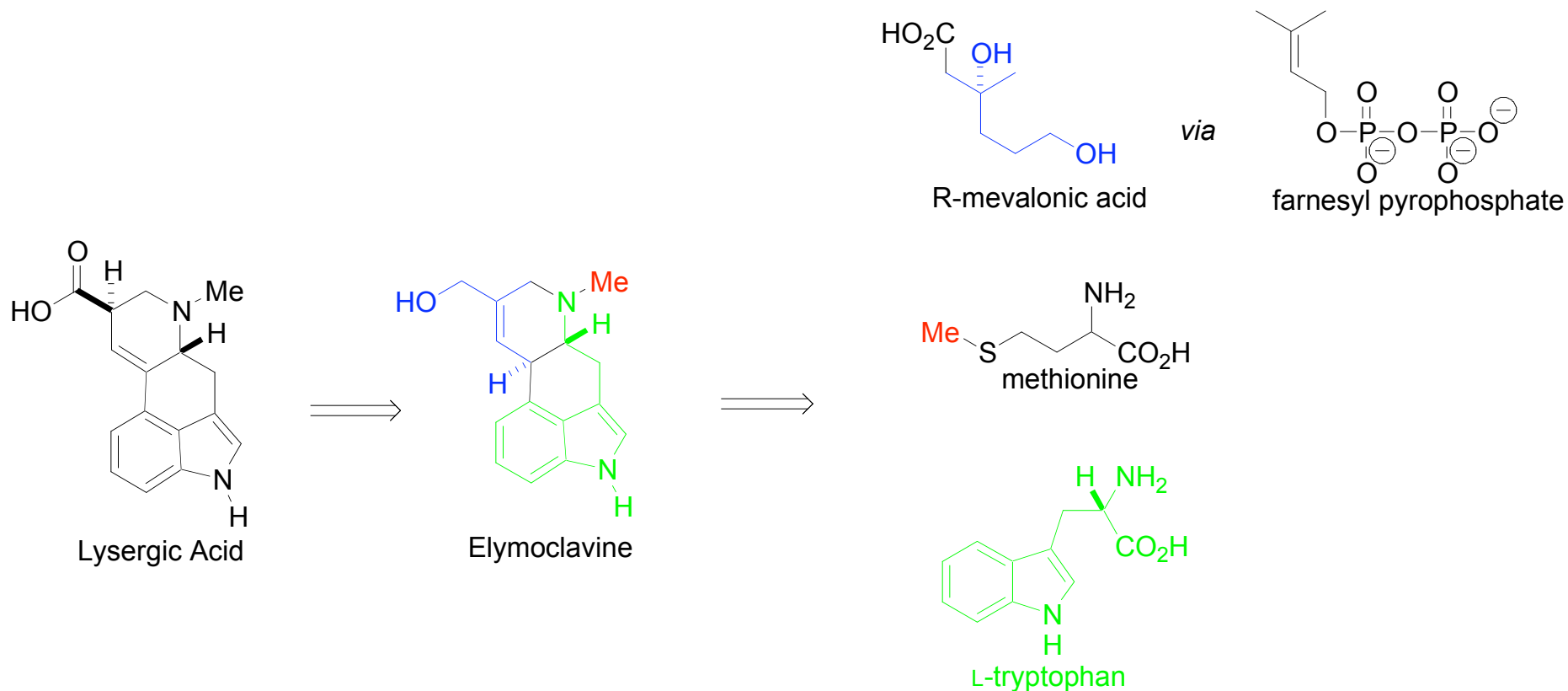
See “LSD: My Problem Child”, by A. Hofmann  
(<http://nepenthes.lycaenum.org/Drugs/LSD/ProbChild/>)

# The LSD Story, continued...

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- LSD-25 synthesized again in 1943.
- In the process of recrystallizing the product: “Last Friday, April 16, 1943, I was forced to interrupt my work in the laboratory in the middle of the afternoon and proceed home, being affected by a remarkable restlessness, combined with a slight dizziness. At home I lay down and sank into a not unpleasant intoxicated-like condition, characterized by an extremely stimulated imagination. In a dreamlike state, with eyes closed (I found the daylight to be unpleasantly glaring), I perceived an uninterrupted stream of fantastic pictures, extraordinary shapes with intense, kaleidoscopic play of colors. After some two hours this condition faded away.”
- Then decided to experiment...took 0.25 mg of the tartrate in 10 mL of water. After 40 min., “...difficulty in concentration, visual disturbances, marked by desire to laugh ... great difficulty in speaking coherently, my field of vision swayed before me ... I had the impression of being unable to move from the spot ... all objects appeared in unpleasant, constantly changing colors, the predominant shades being sickly green and blue ... a remarkable feature was the manner in which all acoustic perceptions were transformed into optical effects...”
- And the rest (Timothy Leary, Beatles, etc.) is history...

# Ergot Alkaloid Biosynthetic Precursors



*Tetrahedron* **1976**, 32, 873-912

# Lysergic Acid Total Syntheses (a lot)

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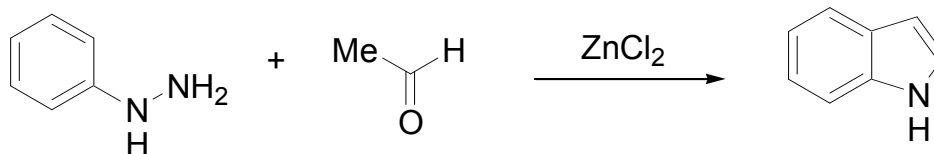
- *J. Am. Chem. Soc.* **1954**, 76, 5256; *J. Am. Chem. Soc.* **1956**, 78, 3087 (Woodward).
- *Tetrahedron Lett.* **1969**, 1569 (Julia).
- *Tetrahedron Lett.* **1976**, 4311; *Tetrahedron Lett.* **1981**, 157 (Armstrong).
- *Helv. Chim. Acta* **1981**, 64, 478 (Oppolzer).
- *Heterocycles* **1982**, 19, 2279 (Kiguchi).
- *Tetrahedron Lett.* **1983**, 24, 859; *J. Am. Chem. Soc.* **1984**, 106, 1813 (Rebek).
- *Chem. Pharm. Bull.* **1986**, 34, 442 (Kurihara).
- *Tetrahedron Lett.* **1988**, 29, 3117 (Ortar).
- *Synlett* **1994**, 487 (Vollhardt).
- *Org. Lett.* **2004**, 6, 3 (Hendrickson).
- *J. Org. Chem.* **2004**, 69, 5993 (Szántay)—essentially the same as Woodward's.
- Also approaches to the skeleton by Padwa (*J. Org. Chem.* **1995**, 60, 2704), Martin (RCM: *Tetrahedron Lett.* **2001**, 1635; VMR: *Acc. Chem. Res.* **2002**, 35, 895), Mann (*Synlett* **1995**, 27), many others.

# Primer on Indole Syntheses

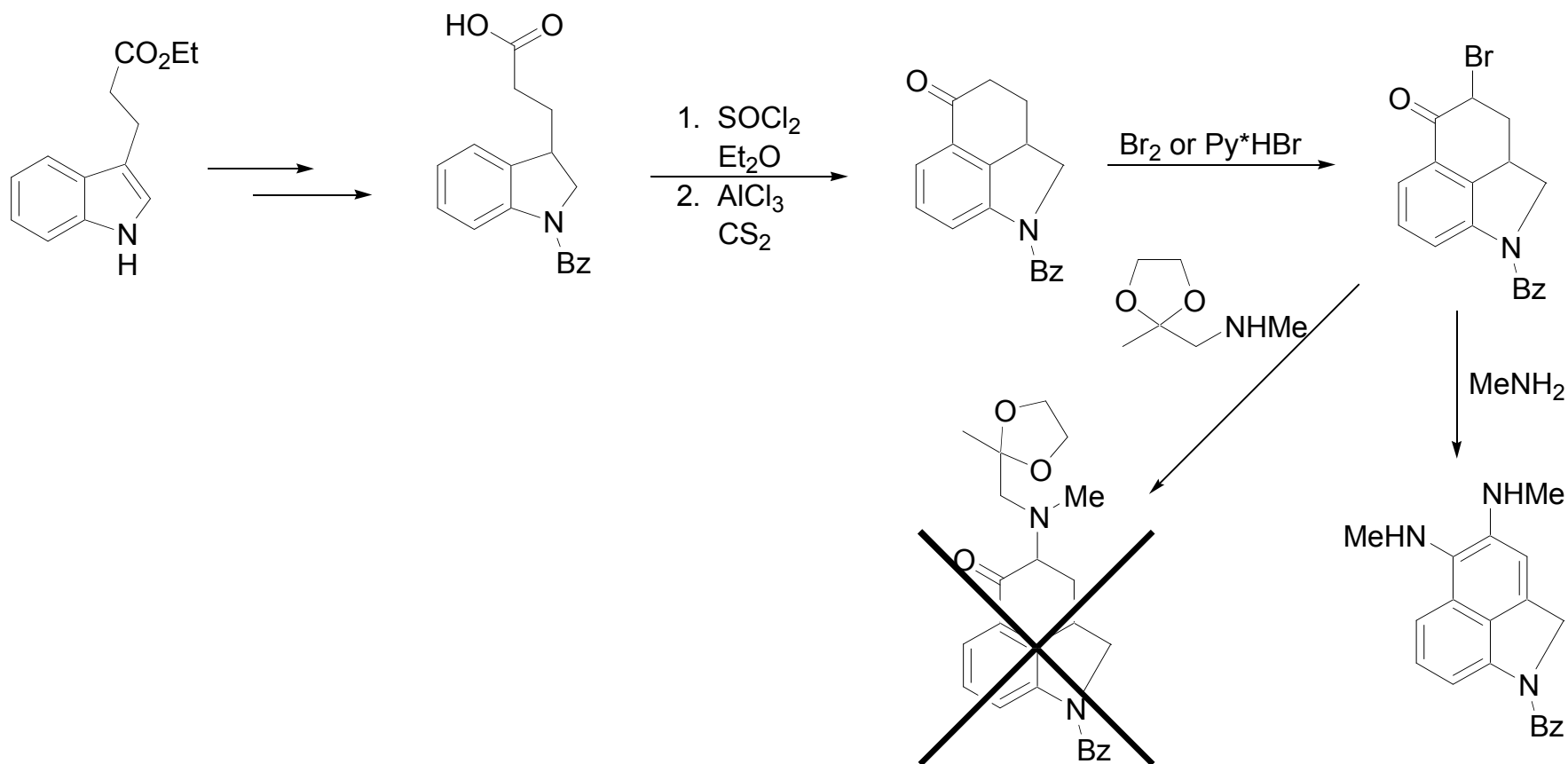
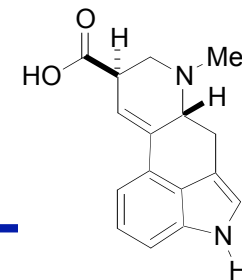
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There are many ways to generate indoles. But among my favorites (and most famous) is:

- Fisher Indole Synthesis (Borsche-Drechsel Cyclization):

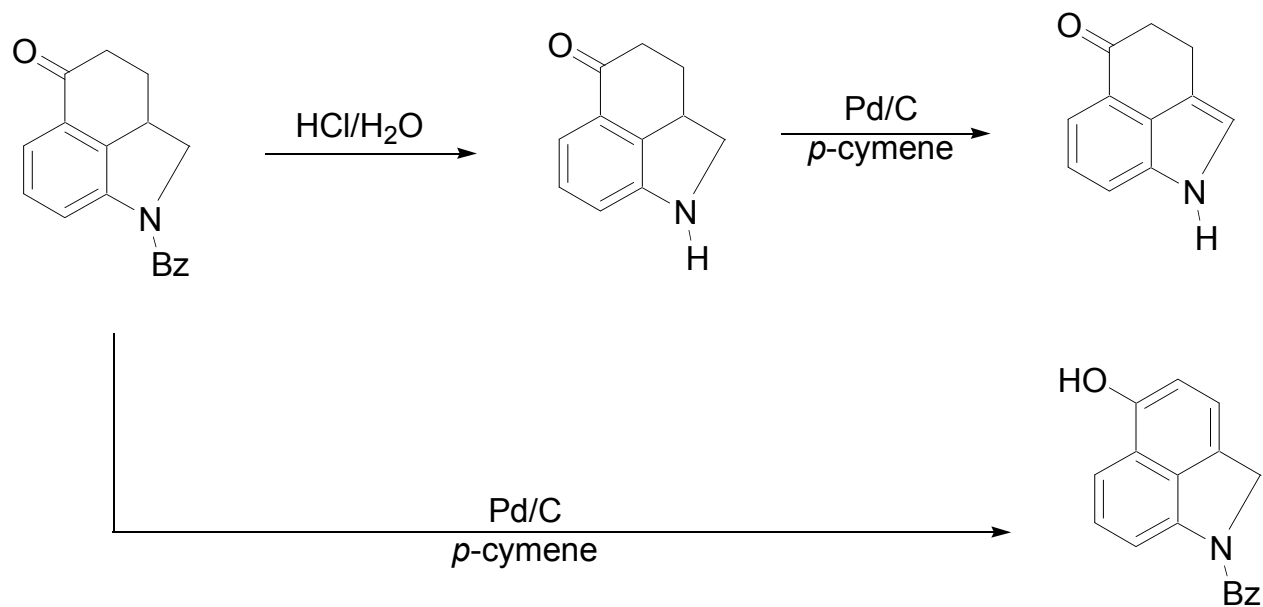
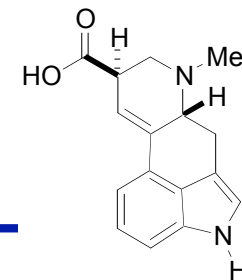


# Woodward Synthesis of Lysergic Acid

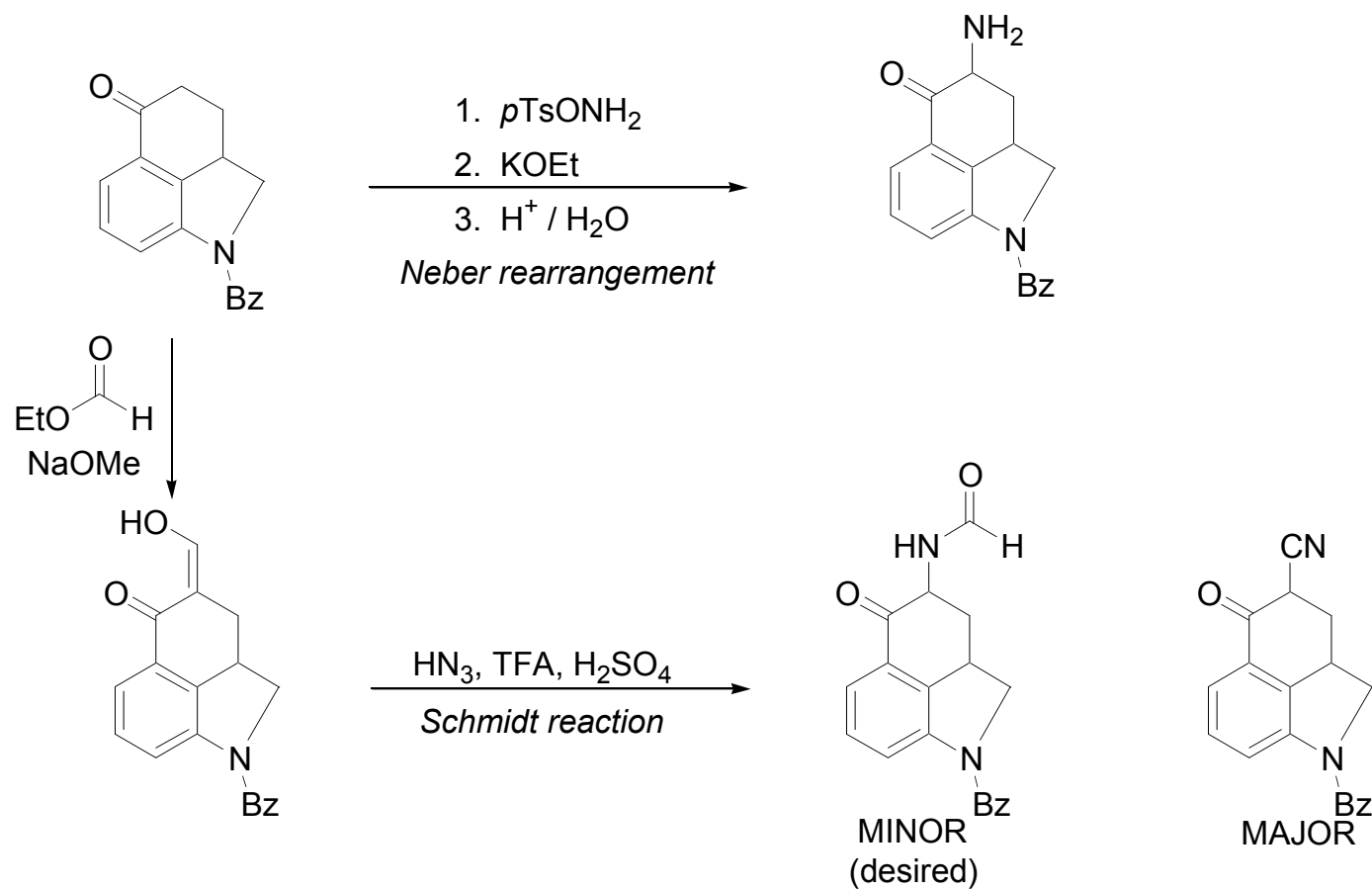
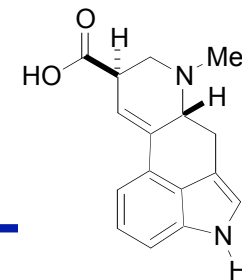


# Woodward

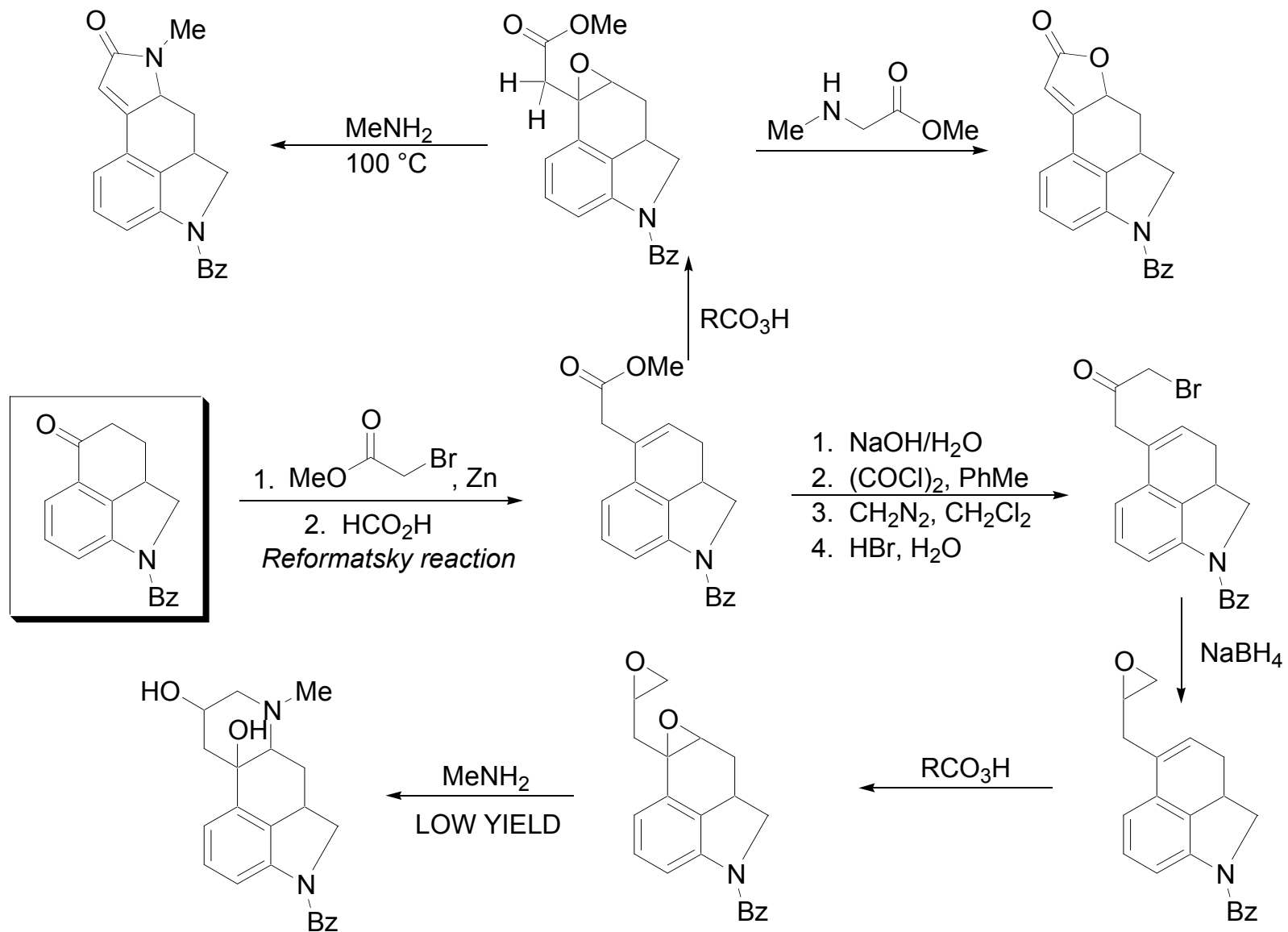
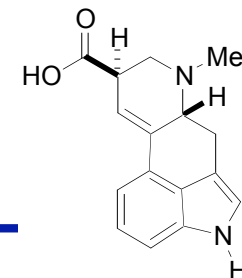
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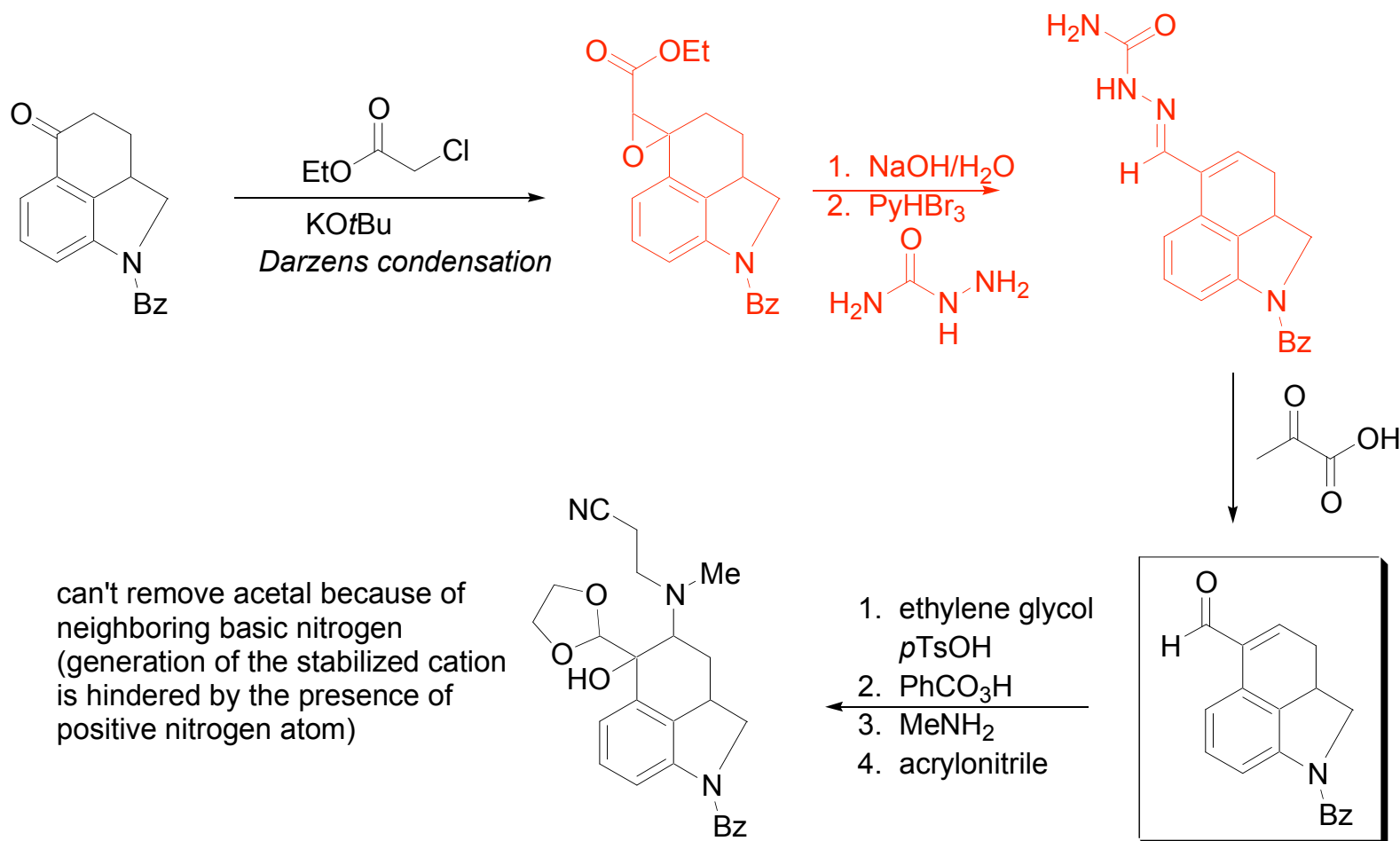
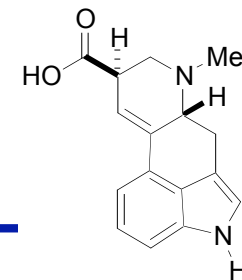
# Woodward



# Woodward

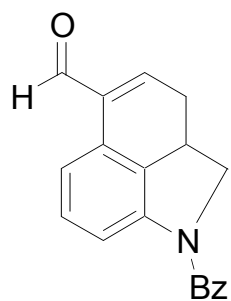
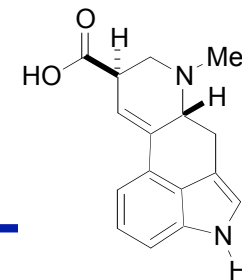


# Woodward

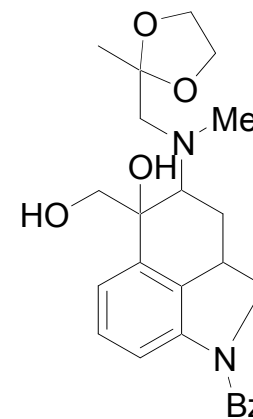
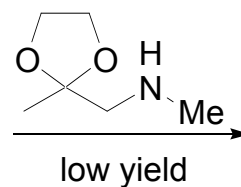
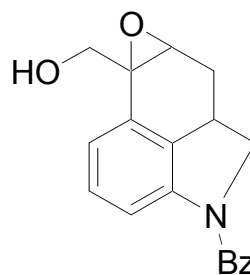


"... brutal means led only to deep-seated changes of no utility"

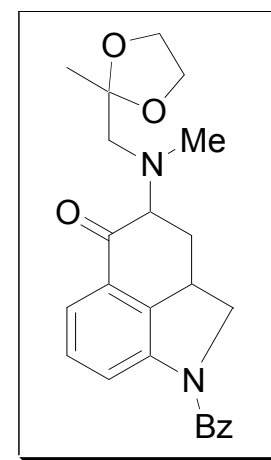
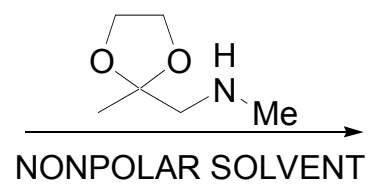
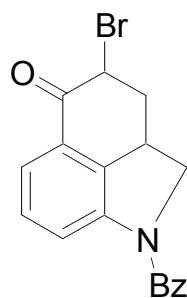
# Woodward



1.  $\text{H}_2\text{O}_2$   
2.  $\text{NaBH}_4$

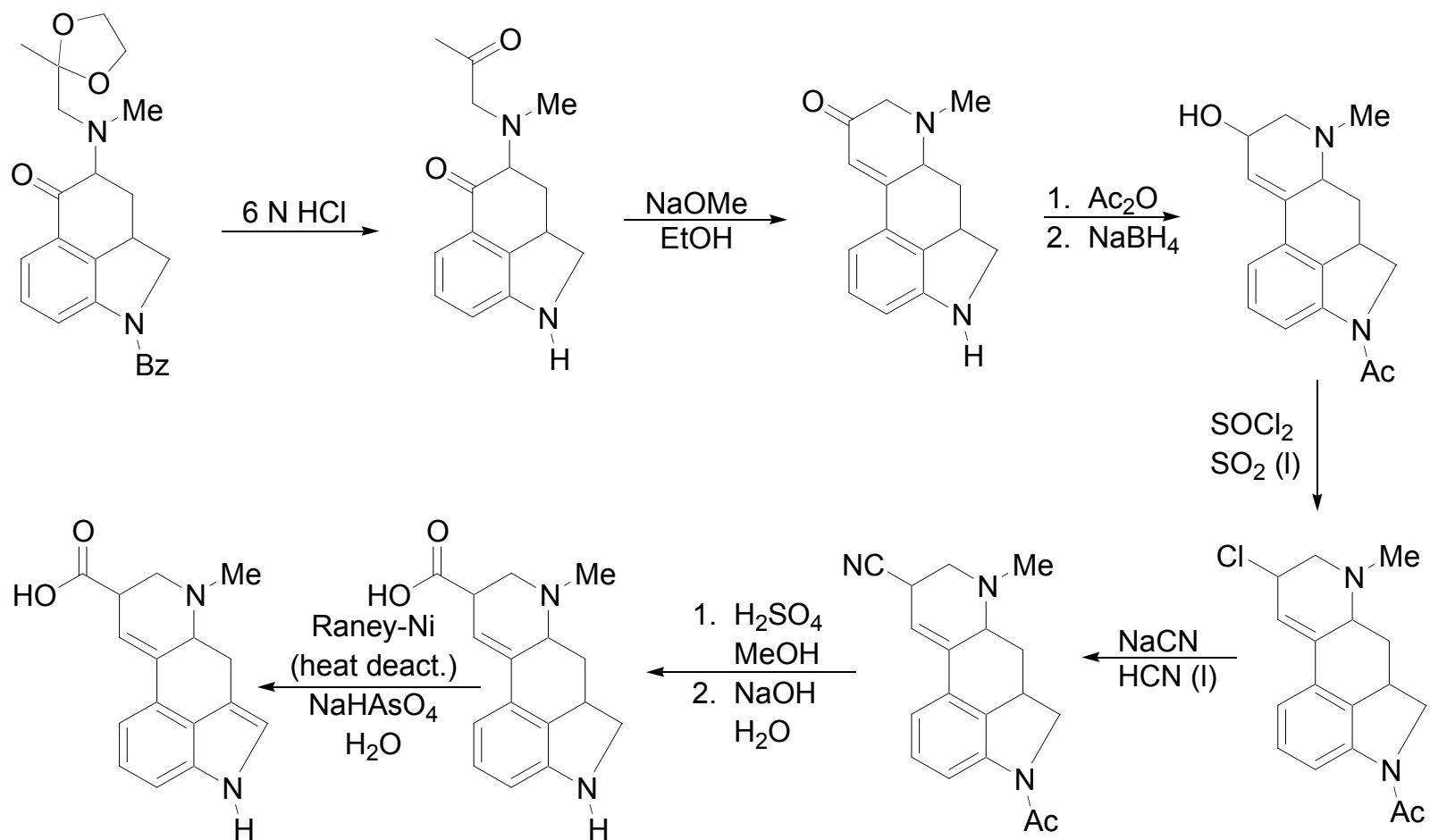
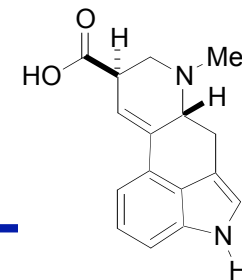


$\text{NaIO}_4$   
 $\text{H}^+$



11 steps from original ketone

# Woodward Endgame





# Padwa Approach

