# Total Synthesis of Lysergic Acid

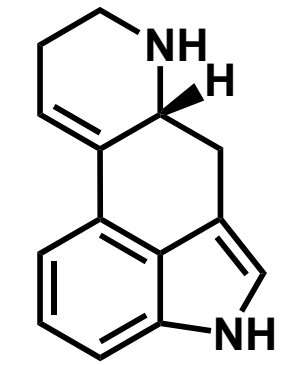



**Krishna P Kaliappan**

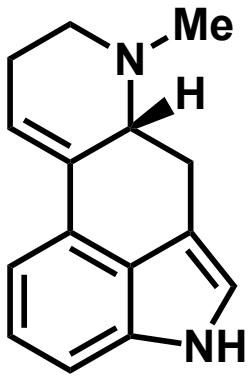
***Professor of Chemistry, IIT Bombay***


**CH-845 Course on Organic Synthesis**

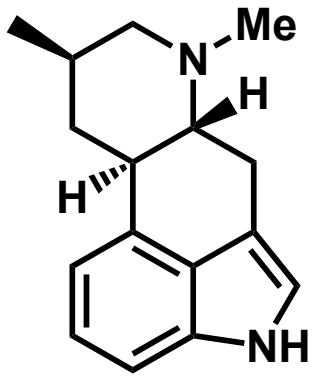
# Lysergic Acid



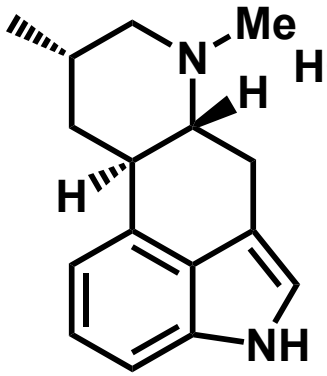

Ergot Alkaloids



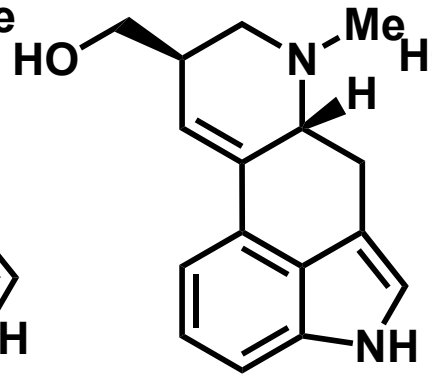

Ergoline



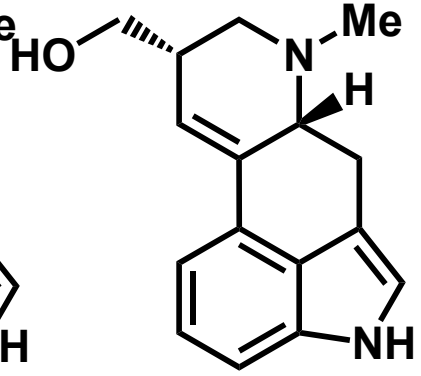

Festuclavine



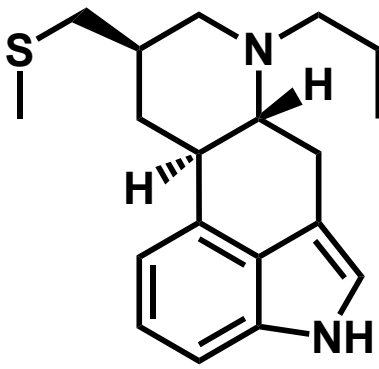

Pyroclavine



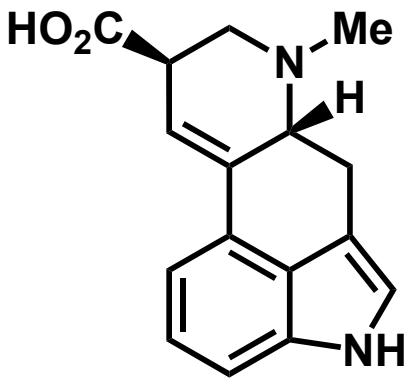

Lysergol




Isolysergol




Pergolide




Lysergic acid

Ergot alkaloids are unique tetracyclic compounds having indole as their core structure

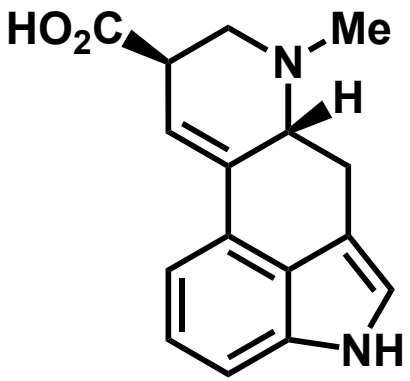
They were among the first used drugs for the treatment of migraine

The tetracyclic core structure is responsible for biological activity

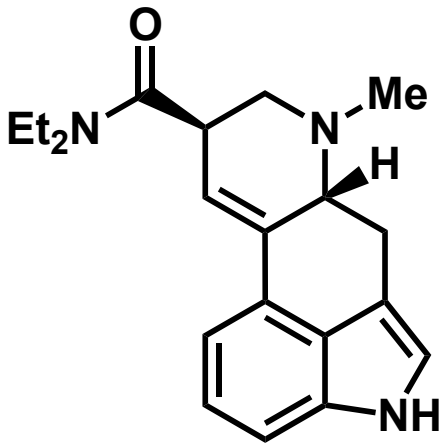
Pergolide is being used for the treatment of Parkinson's disease

Jacobs, W. A., and Craig, L. C. *J. Biol. Chem.* **1934**, *104*, 547–551

# Lysergic Acid




Lysergic acid



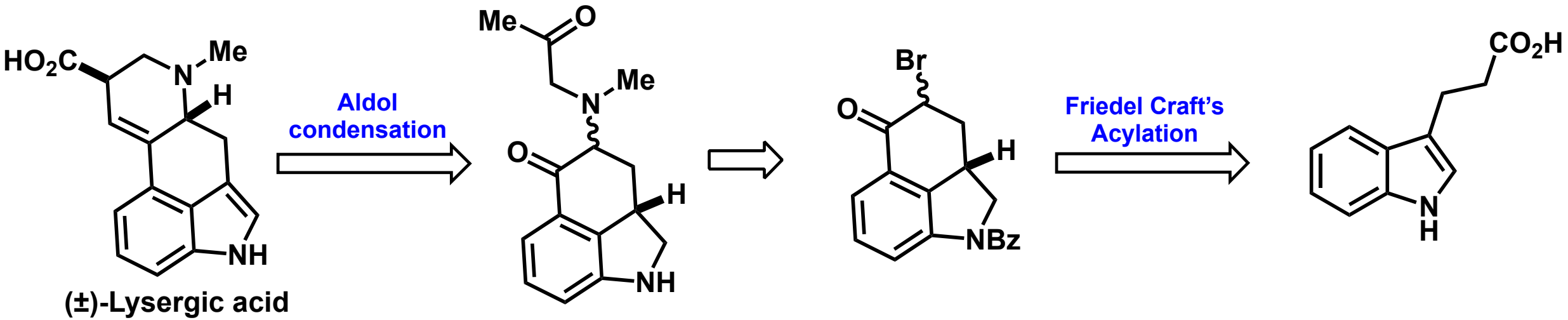

Lysergic Acid Diethylamide (LSD)

- Lysergic acid is a representative natural product of the ergot alkaloid family, which are particularly important because they possess a wide spectrum of biological activities
- LSD is one of the most potent psychoactive agents known

- LSD was accidentally discovered with psychoactive effects in 1943 by scientists from Sandoz.
- LSD was formally placed under controlled substance in 1970
- It was first synthesized by a natural product chemist, Albert Hofmann in 1938.
- During the purification in the final step, he was interrupted by some unusual sensation.
- After that he went home and while laying down, he was dreaming with unbelievable imagination

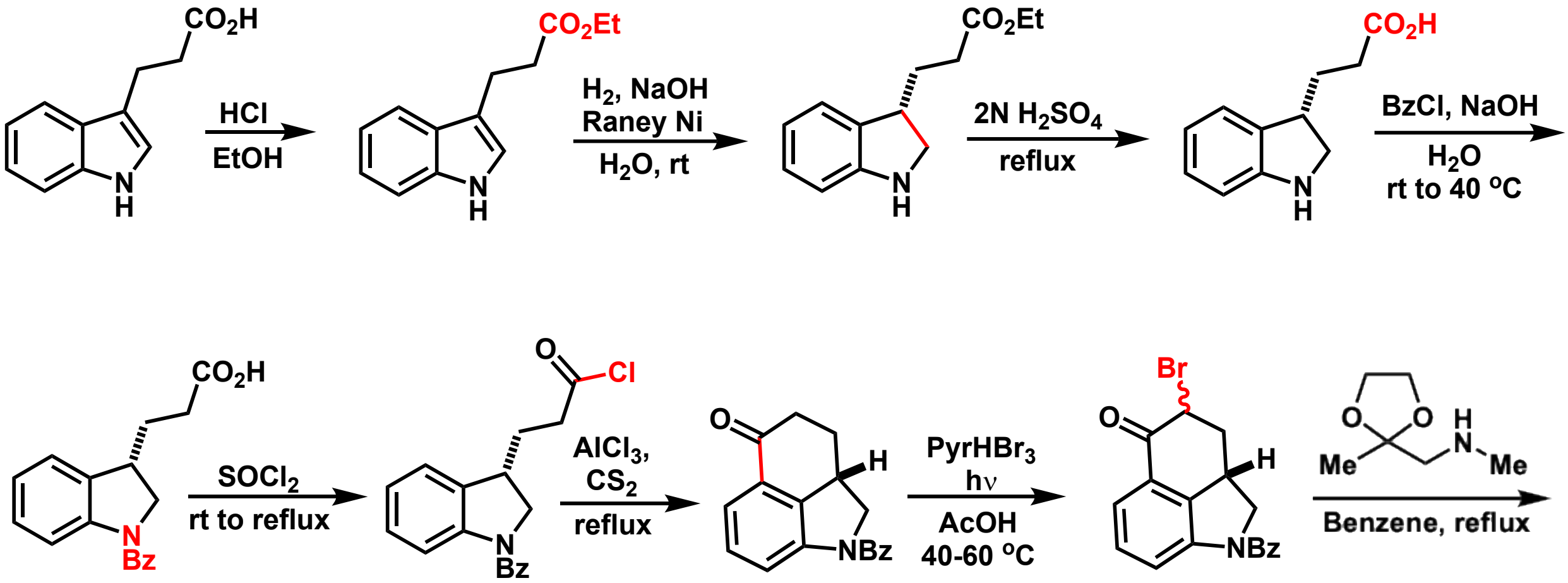
# Woodward's Synthesis of Lysergic Acid

- In 1956, Woodward and co-workers accomplished the first total synthesis of (±)-Lysergic acid
- This basic fragment derived from the ergot alkaloids, has been synthesized beginning with 3-indolepropionic acid
- The key steps in the sequence involves a Friedel Craft's acylation and an aldol condensation reaction



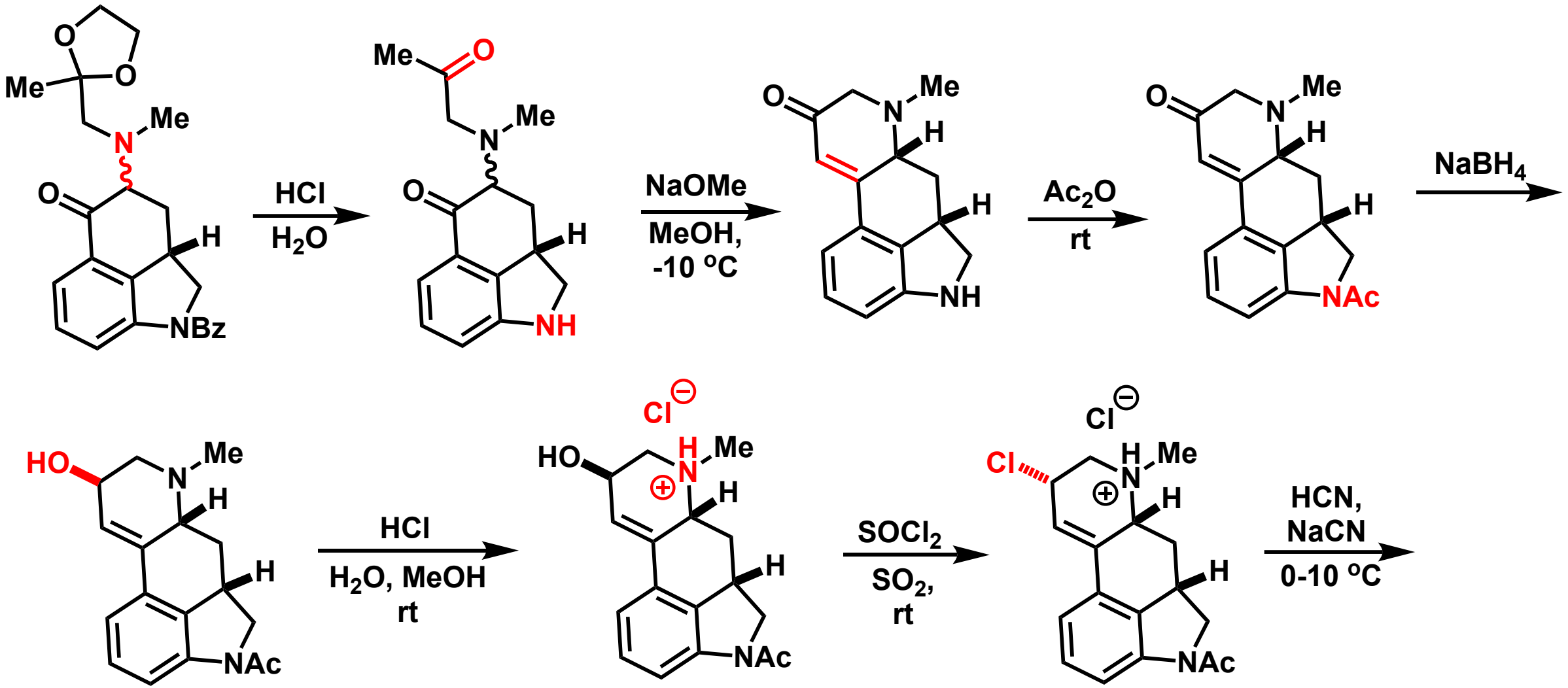

Woodward, R. B., co-workers. *J. Am. Chem. Soc.* **1956**, *78*, 13, 3087–3114

# Woodward's Synthesis of Lysergic Acid

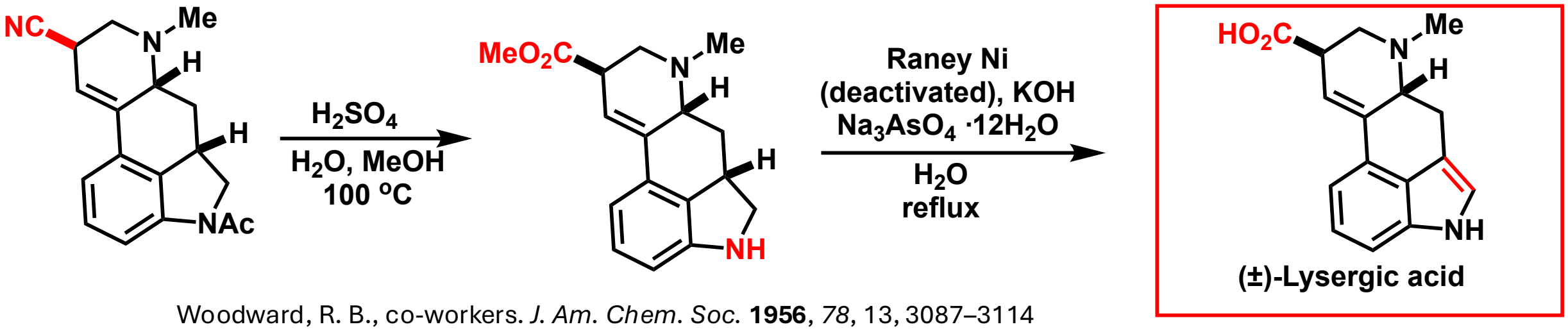



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# Woodward's Synthesis of Lysergic Acid



# Woodward's Synthesis of Lysergic Acid



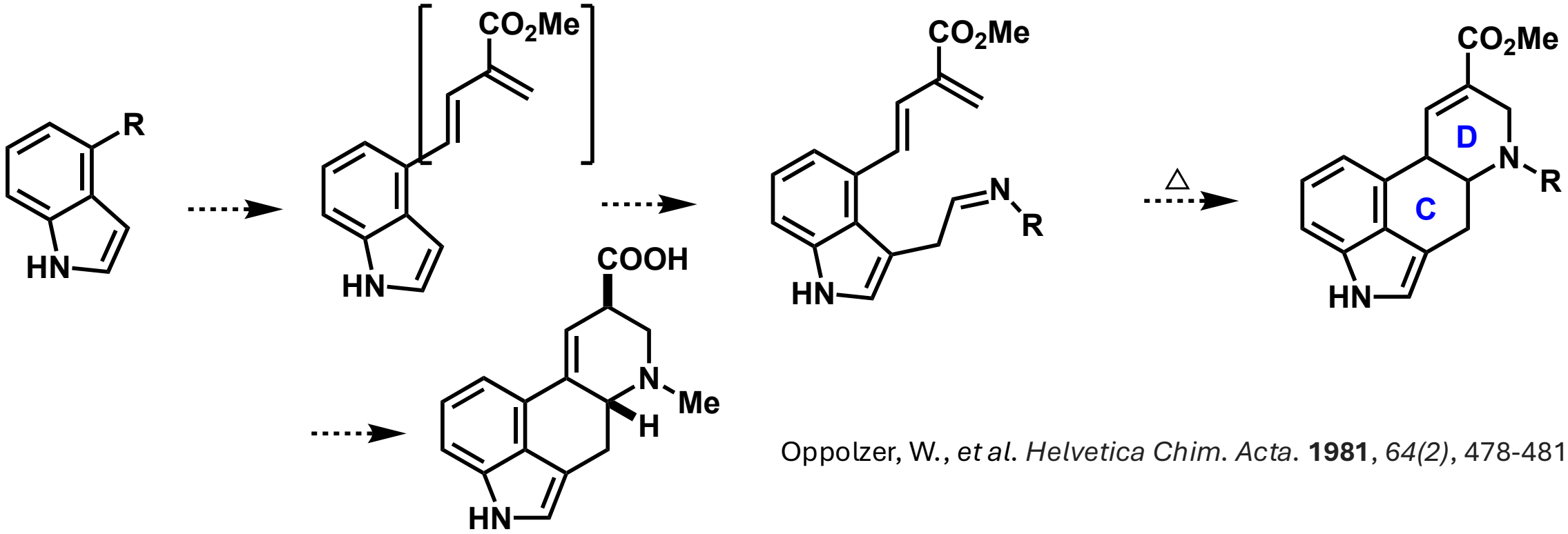

Woodward, R. B., co-workers. *J. Am. Chem. Soc.* **1956**, *78*, 13, 3087–3114

- In 1956, Woodward and co-workers accomplished the first total synthesis of (±)-Lysergic acid
- This basic fragment derived from the ergot alkaloids, has been synthesized beginning with 3-Indolepropionic acid
- The key steps in the sequence involves a Friedel Craft's acylation and an aldol condensation reaction
- The total synthesis was accomplished in a sequence of 15 linear steps with an overall yield of 0.78%

# Oppolzer's Synthesis of Lysergic Acid

- In 1981, Oppolzer *et al* accomplished the total synthesis of (±)-Lysergic acid by an Intramolecular Imino-Diels-Alder Reaction

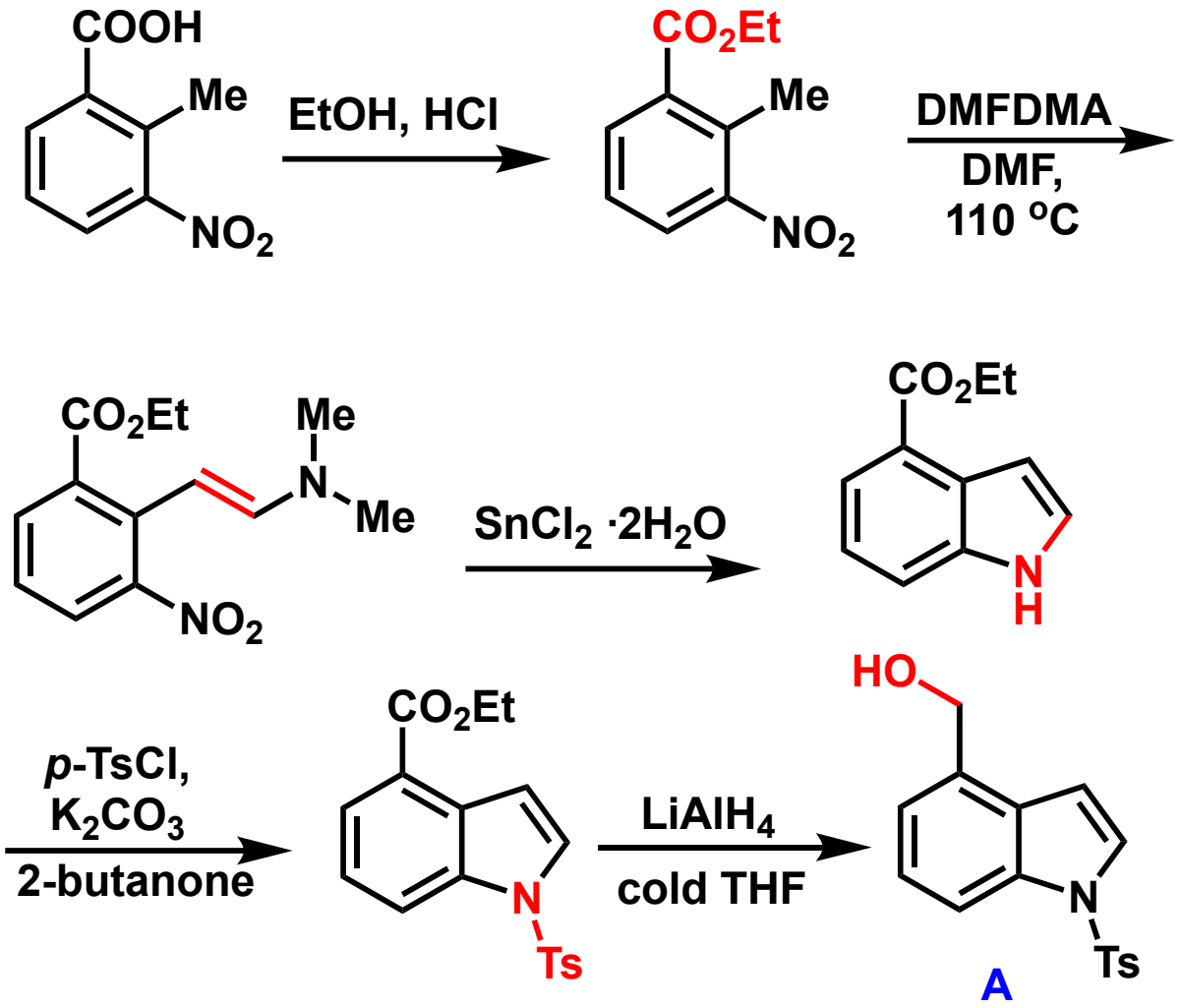
- (±)-Lysergic acid has been synthesized from 4-hydroxymethyl-1–tosylindole by a sequence of 9 steps



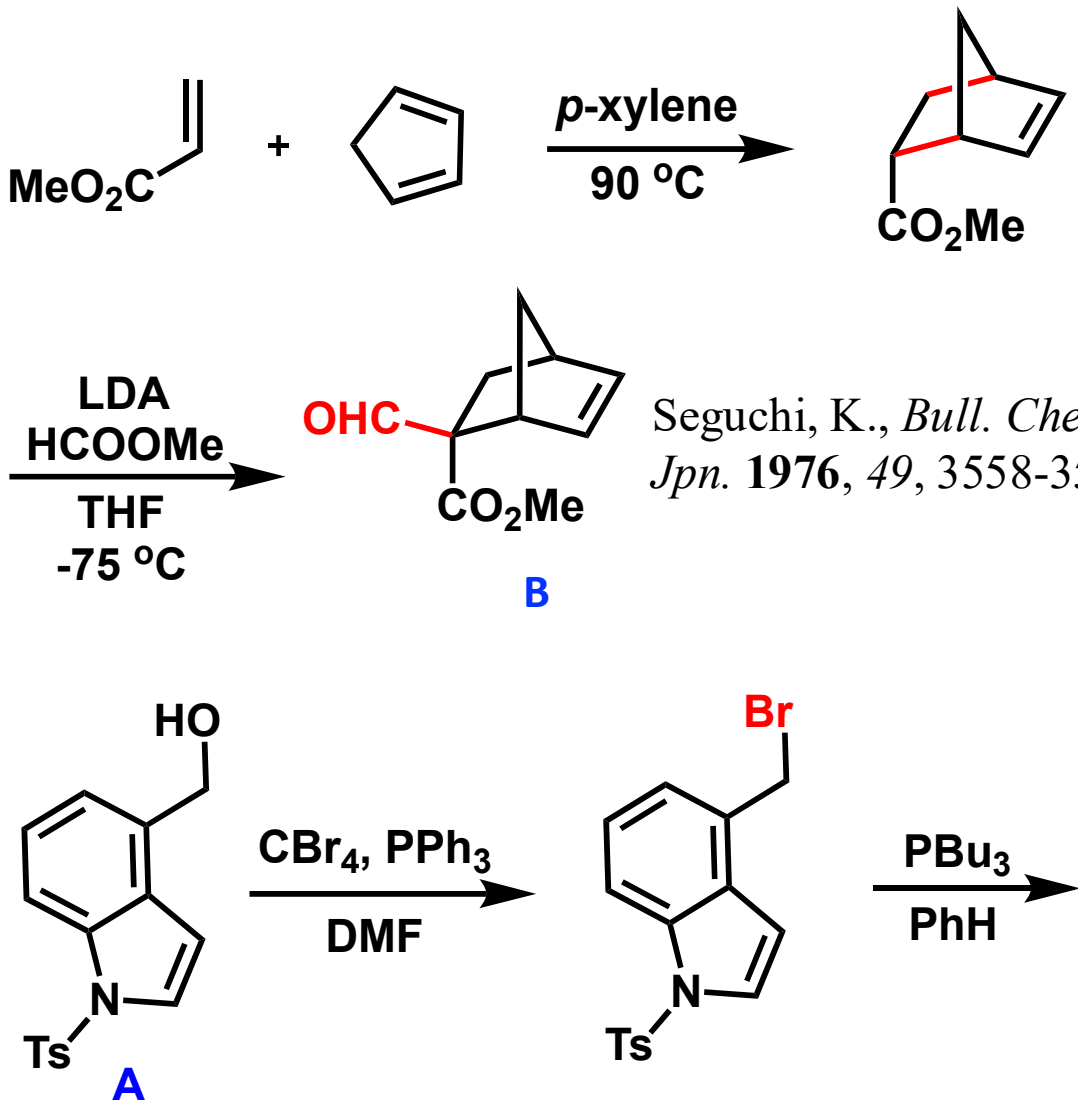

Lysergic Acid

Oppolzer, W., *et al*. *Helvetica Chim. Acta*. **1981**, *64(2)*, 478-481

# Oppolzer's Synthesis of Lysergic Acid

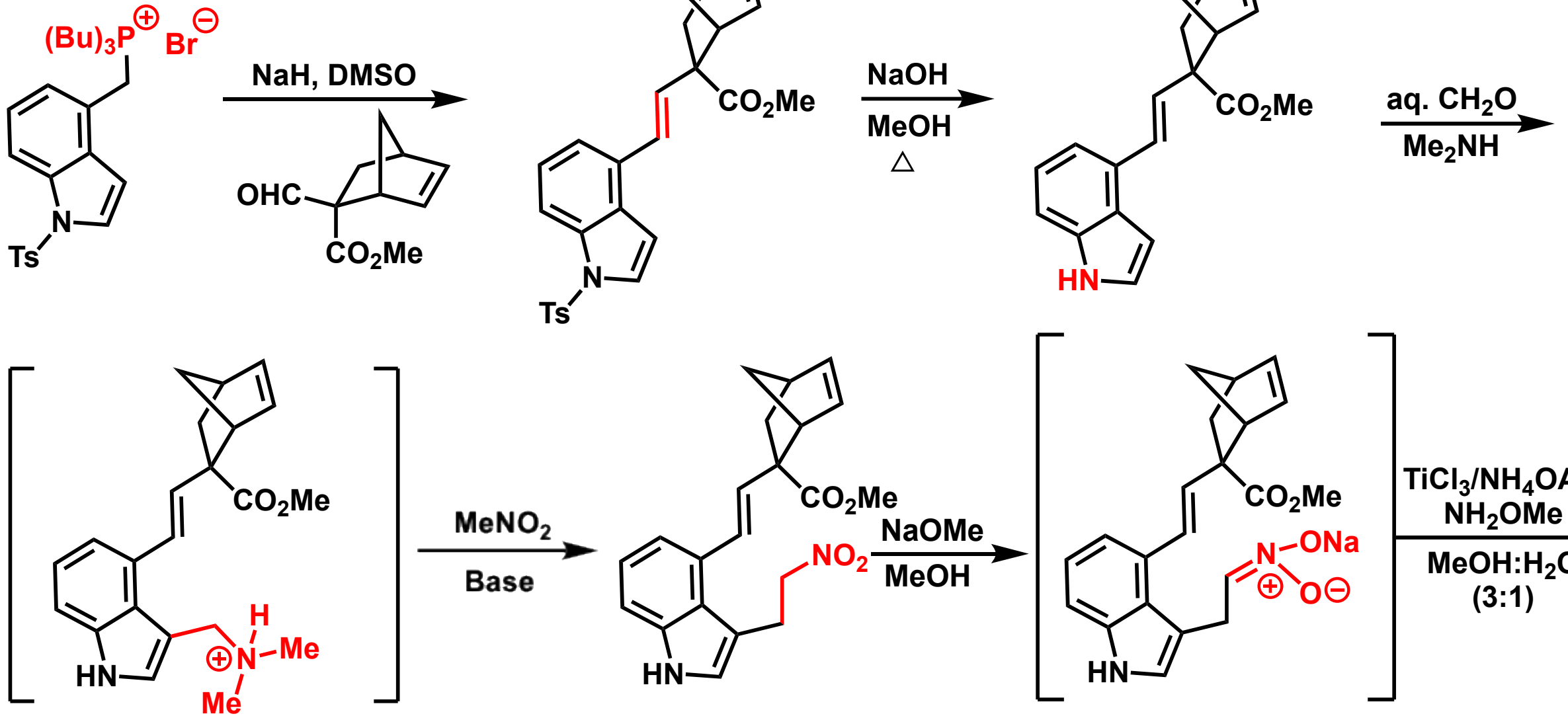



Ponticello, G.S., *et al. J. Org. Chem.* **1979**, *44*, 4003-4005

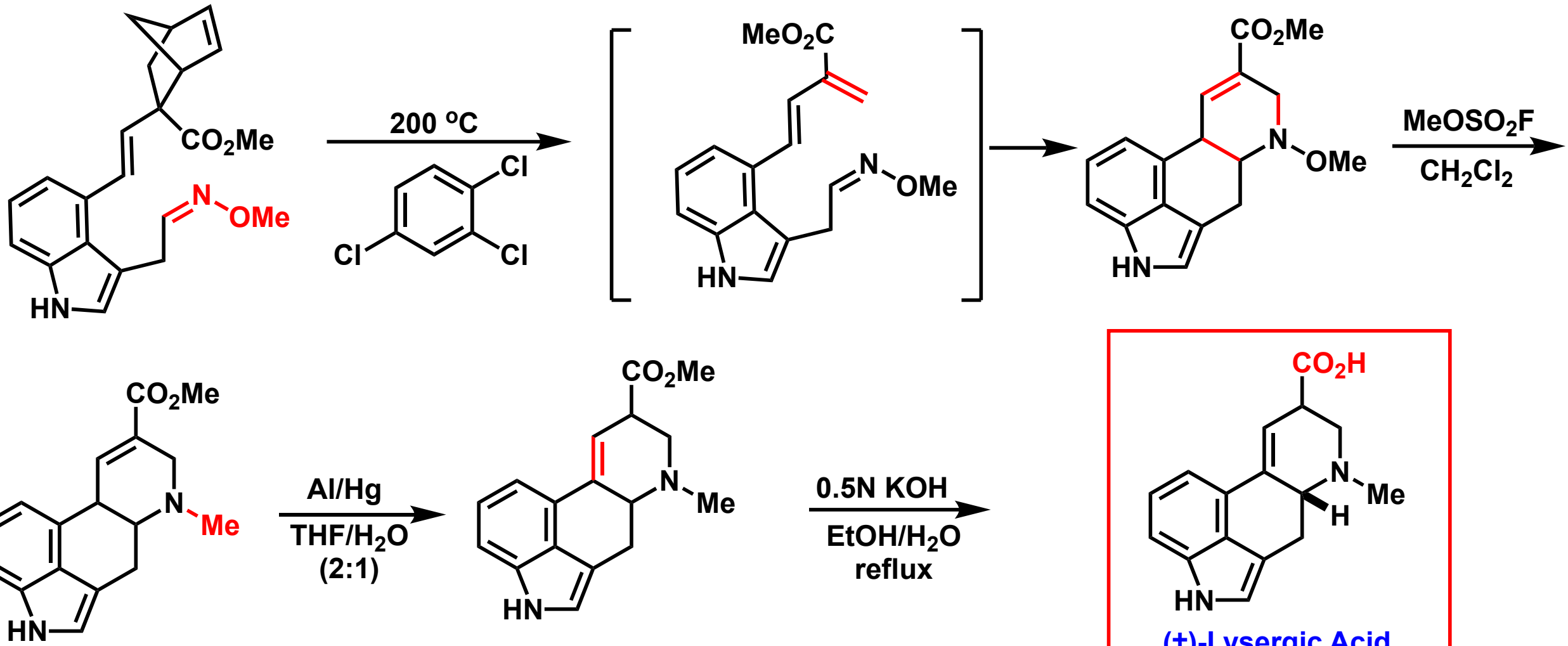



Seguchi, K., *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3558-3563

# Oppolzer's Synthesis of Lysergic Acid



# Oppolzer's Synthesis of Lysergic Acid




- The total synthesis was accomplished with an overall yield of 3.88%