

Background

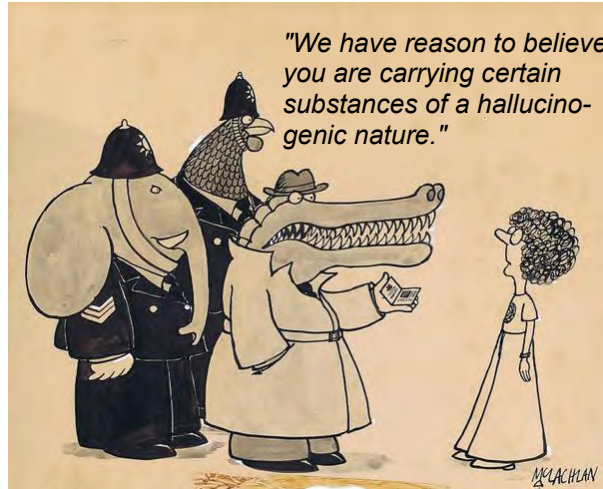
What qualifies as hallucinogenic?

- 1- Single effective dose
- 2- Produce noticeable changes in thought, mood, and perception without memory loss
- 3- Produce neither narcosis nor excessive stimulation
- 4- Produce no severe autonomic side effects
- 5- Are non-addictive

Hollister, L.E. *Chemical Psychoses*, Charles C. Thomas, Springfield, IL, **1968**.

Unlike other psychoactive drugs, like stimulants and opioids [see Morphinans, DJJ], these drugs do not merely amplify familiar states of mind, but rather induce experiences that are qualitatively different from those of ordinary consciousness

- trance
- meditation
- dreams
- insanity
- religious ecstasy
- near-death experiences



Typically broken into three categories: **psychedelics**, **dissociatives**, and **deliriants**

Psychedelics alter cognition & perception, and typically fall into three classes: tryptamines, phenethylamines, and lysergamides

Dissociatives distort perception and produce feelings of detachment from environment and self.

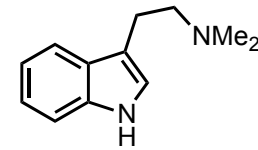
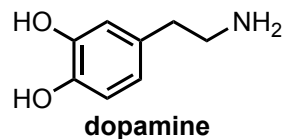
Deliriants induce (you guessed it) delirium, as opposed to the more lucid states of the other two classes.

Psychedelics

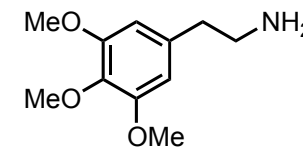
Often referred to as serotonergic or classical hallucinogens

Generally defined by action as an agonist (full or partial) at 5-HT_{2A} receptors

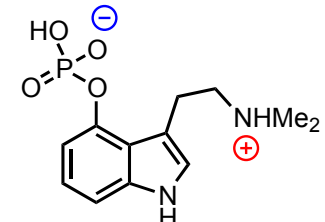
The 5-HT receptors are GPCRs (save one) that act as a receptor for the neurotransmitter serotonin (or 5-HydroxyTryptamine). There are different effects associated with each one, but in general, they regulate cell levels of cAMP (cyclic Adenosine MonoPhosphate)



Dimethyltryptamine (DMT)



Mescaline



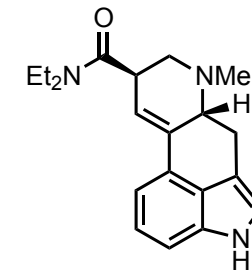
Psilocybin

"Naturally occurring hallucinogenic drugs played a significant role in the development of philosophy and religious thought in many earlier cultures... How many Neolithic hunters, one might wonder, eking out an existence in the wild, were likely to sit before the fire at night contemplating the nature of man and the meaning of life?"

Nichols, D.E. *Pharmacology & Therapeutics* **2004**, 101, 131-181.

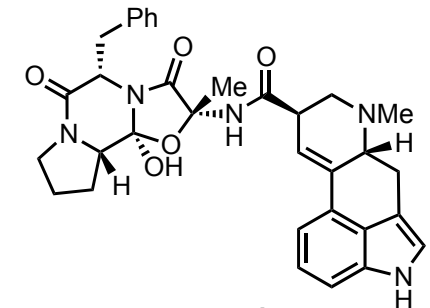
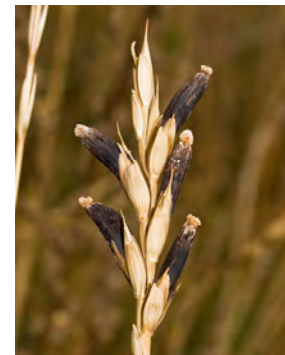
Psilocybin ("magic" mushrooms), mescaline (*peyote* cactus), and dimethyltryptamine (various sources) have been used medicinally and spiritually since before recorded history. The discovery of LSD by Albert Hofmann in 1943 (and likely the popularity of hallucinogens in the ensuing decades) sparked research into the usefulness of these compounds.

- Project MKULTRA
- Problem solving/creativity
- Psychotomimetic
- Adjunct to therapy
- Terminal illness
- Alcoholism
- Antipsychotic drugs



Lysergic Acid Diethylamide (LSD)

"I consider LSD to be a powerful unspecified amplifier or catalyst of biochemical and physiological processes in the brain." Grof, S. *Observations from LSD Research* **1975**, New York: Viking Press.

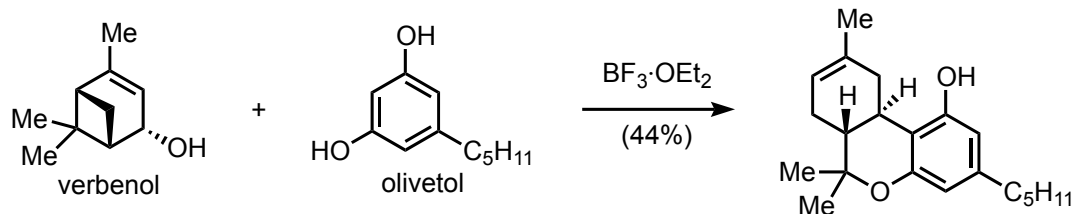


ergotamine

Therapeutic Hallucinogens

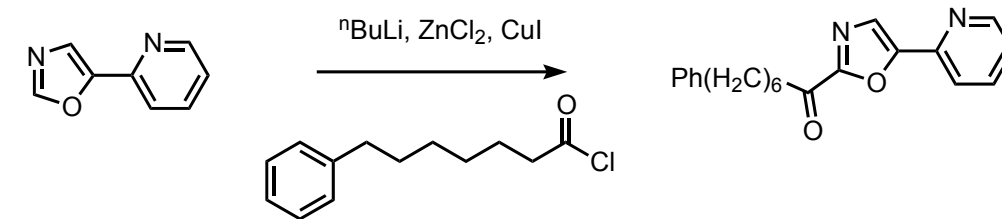
Shenvi Group Meeting
07/24/14

Jeremy Roach

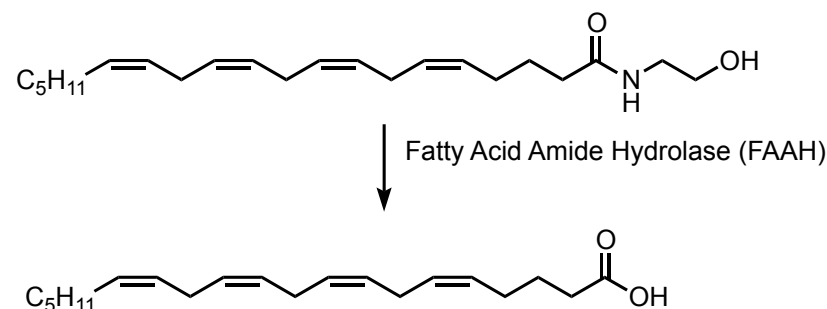


Mechoulam, R.; Braun, P.; Gaoni, Y. *J. Am. Chem. Soc.* **1967**, *89*, 4552.

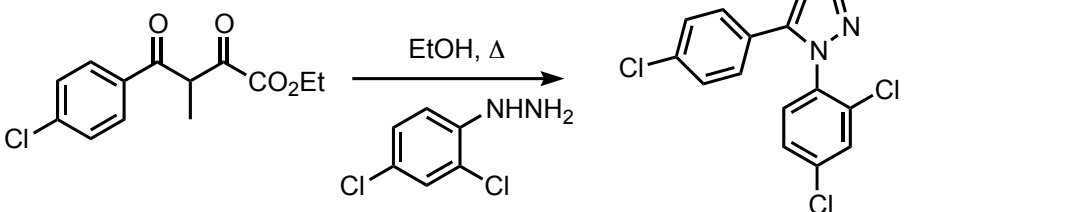
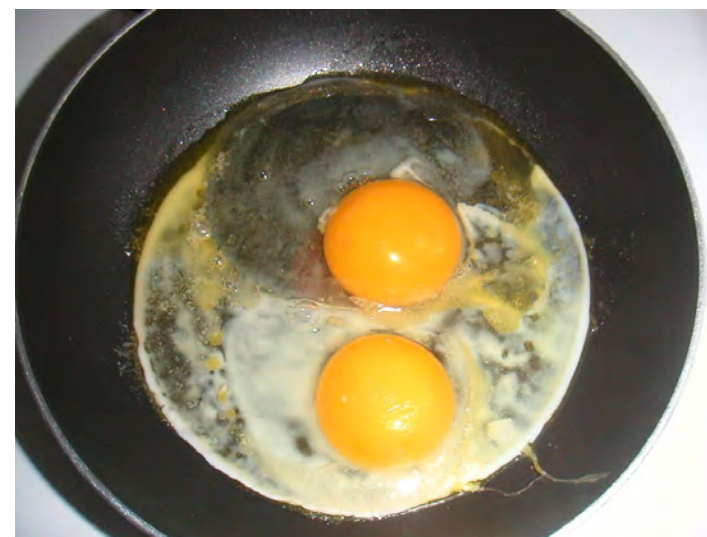
- Synthetic THC is used to treat nausea and vomiting brought on by chemotherapy, as well as an appetite stimulant
- CBD is generally believed to have a wider scope of medical applications, and is "less mind-altering"



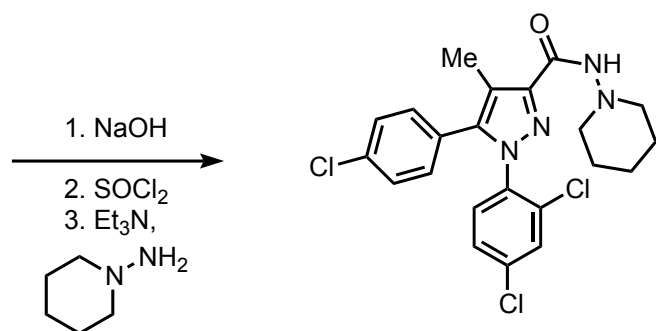
Boger, D.L.; Cravatt, B.F. *et. al. J. Med. Chem.* **2005**, *48*, 1849.



The α -keto heterocycle shown above was found to have a 4.7 nM K_i vs FAAH, and was found to produce analgesia in "multiple nociceptive models"

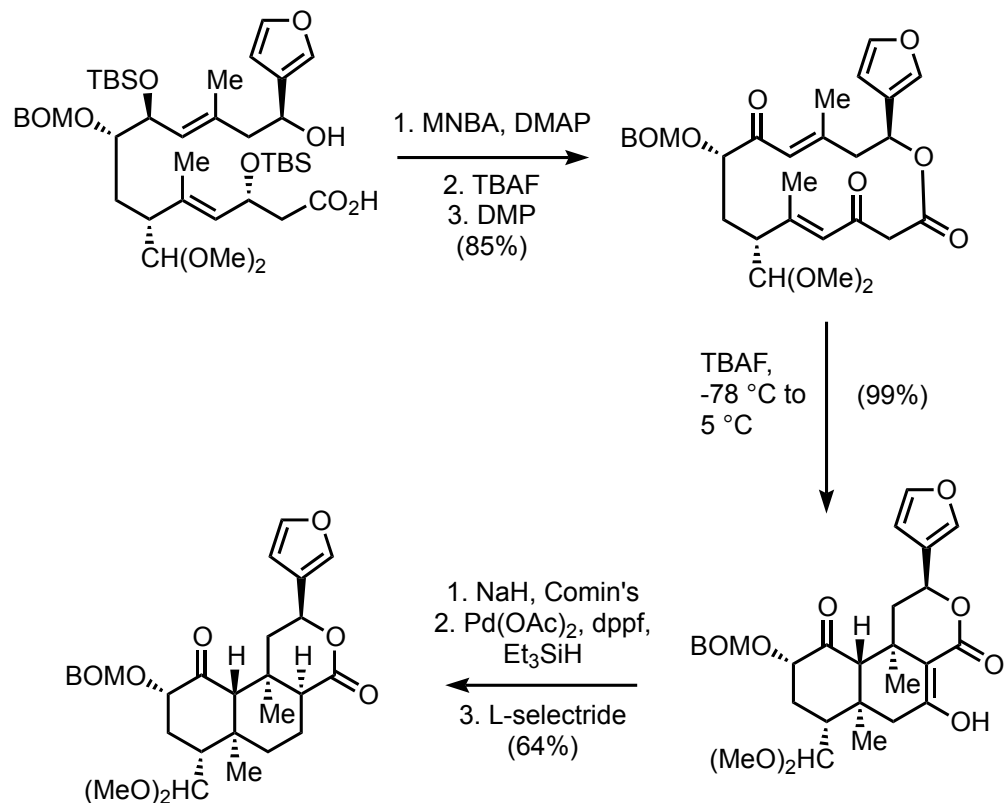


CB1 antagonist **Rimonabant** was explored as an obesity treatment and appetite suppressant. "One European clinical study... found that a daily dose of 20 mg coupled with a reduced calorie diet led to an average sustained weight loss of 7 kg vs. an average sustained weight loss of 2 kg in the placebo group, treated with diet alone." Since, rimonabant has been removed from the market due to risk of severe depression and suicidal thoughts.



Seltzman, H.H.; Carroll, F.I.; Burgess, J.P.; Wyrick, C.D.; Burch, D.F. *J. Chem. Soc., Chem. Comm.* **1995**, *24*, 1549.

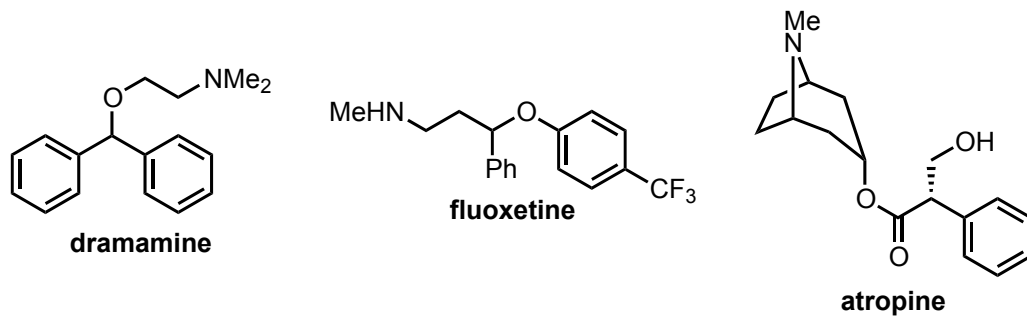
Van Gaal, L.F.; Rissanen, M.; Scheen, A.J.; Ziegler, O.; Rössner, S. *Lancet* **2005**, *365*, 1389.



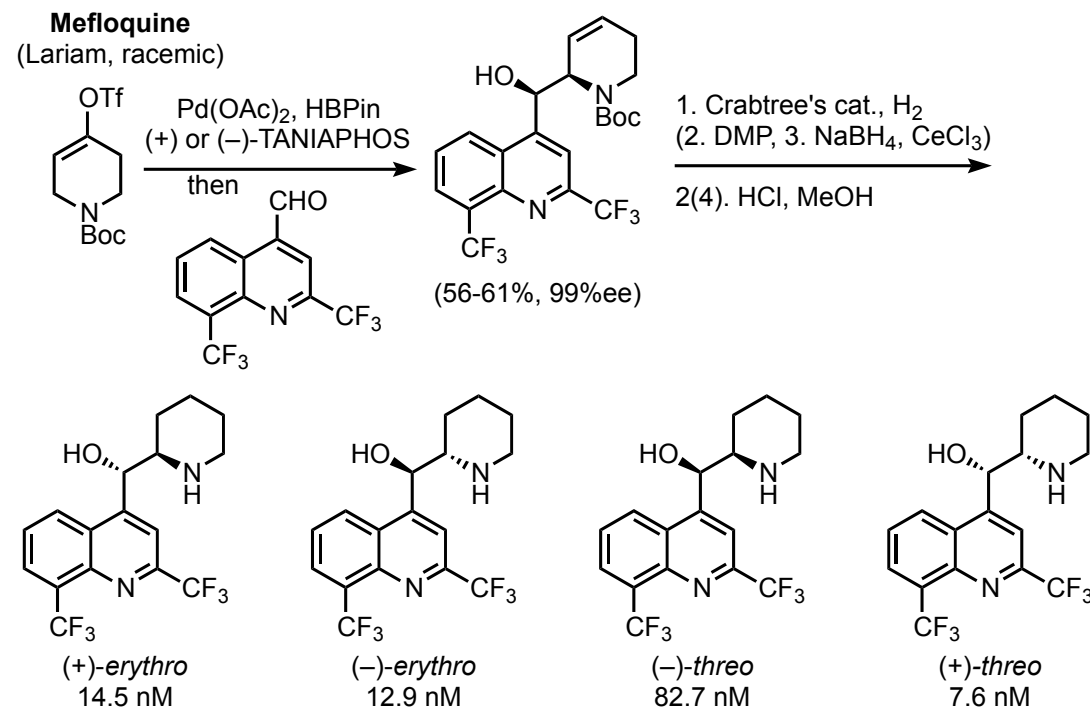
Scheerer, J.R.; Lawrence, J.F.; Wang, G.C.; Evans, D.A. *J. Am. Chem. Soc.* **2007**, *129*, 8968.

Deliriant

Deliriant induce delirium, and generally refer to anticholinergic drugs, which block the neurotransmitter acetylcholine in both the CNS and PNS. Some examples include uncured tobacco (in high enough doses), the tropane alkaloids found in Mandrake & Jimson Weed, and OTC drugs like benadryl and dramamine.

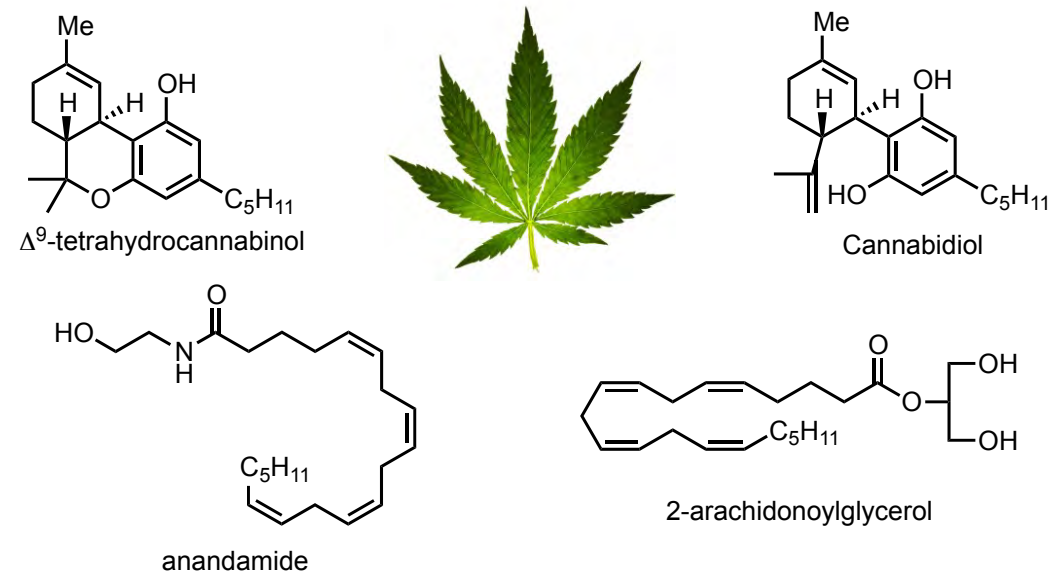


Misc.: Psychotic antimalarial

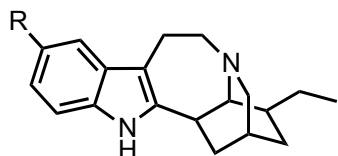


Ding, J.; Hall, D.G. *Angew. Chem. Int. Ed.* **2013**, *52*, 8069.

Cannabinoids

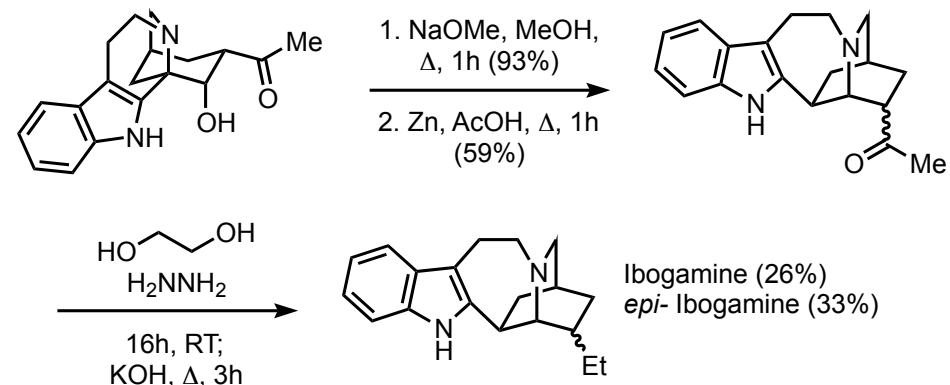
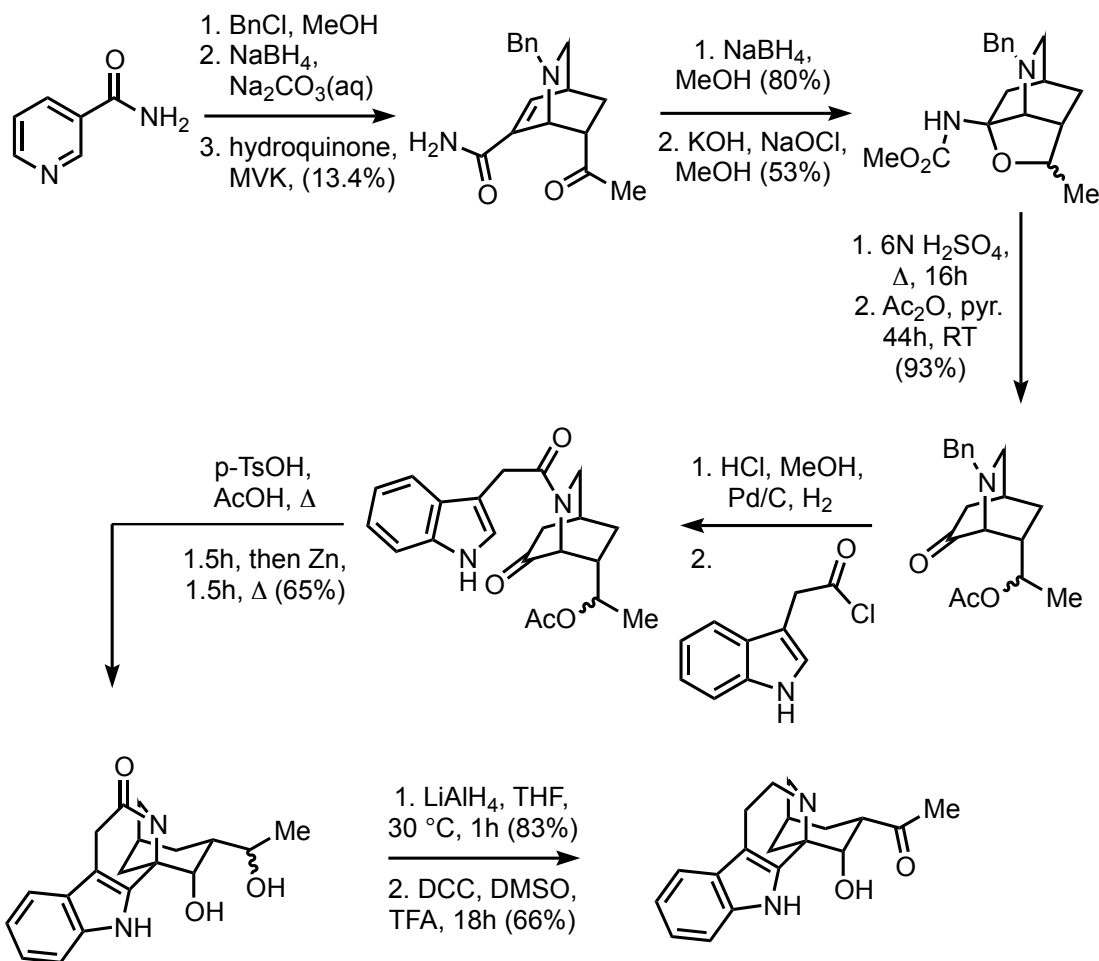


Dissociatives- KOR agonists

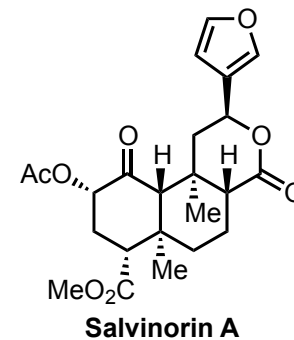


R= OMe **Ibogaine**
R= H **Ibogamine**

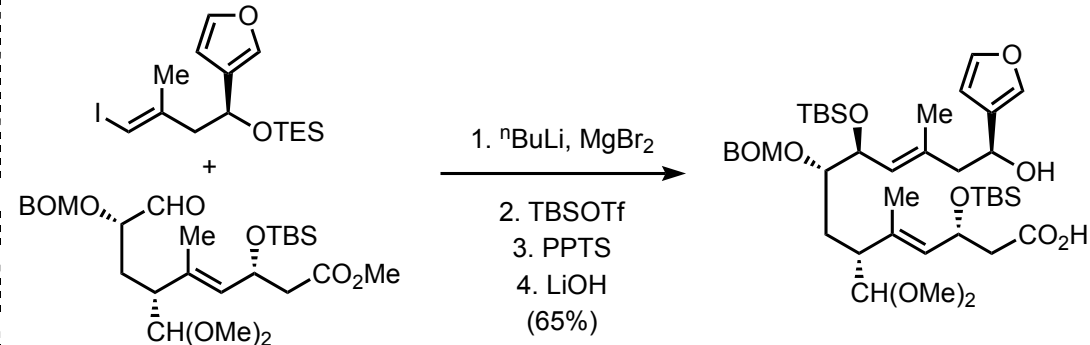
- Nonselective- 5HT, KOR, D, M, A, N
- Used to treat fatigue, hunger, and thirst
- opiate addicts reported they lost the desire to use
- studies in cocaine self-administrating rats corroborate



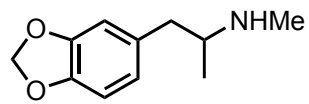
Büchi, G.; Coffen, D.L.; Kocsis, K.; Sonnet, P.E.; Ziegler, F.E. *J. Am. Chem. Soc.* **1966**, *88*, 3099.



- Salvia divinorum*
- religious sacrament
- analgesia & addiction treatment



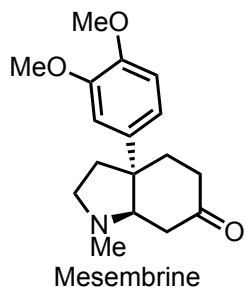
Serotonin Releasers

3,4-methylenedioxyamphetamine
(MDMA)

- Empathogen
- Neither a psychedelic nor a stimulant
- Empathy, love, and closeness to others



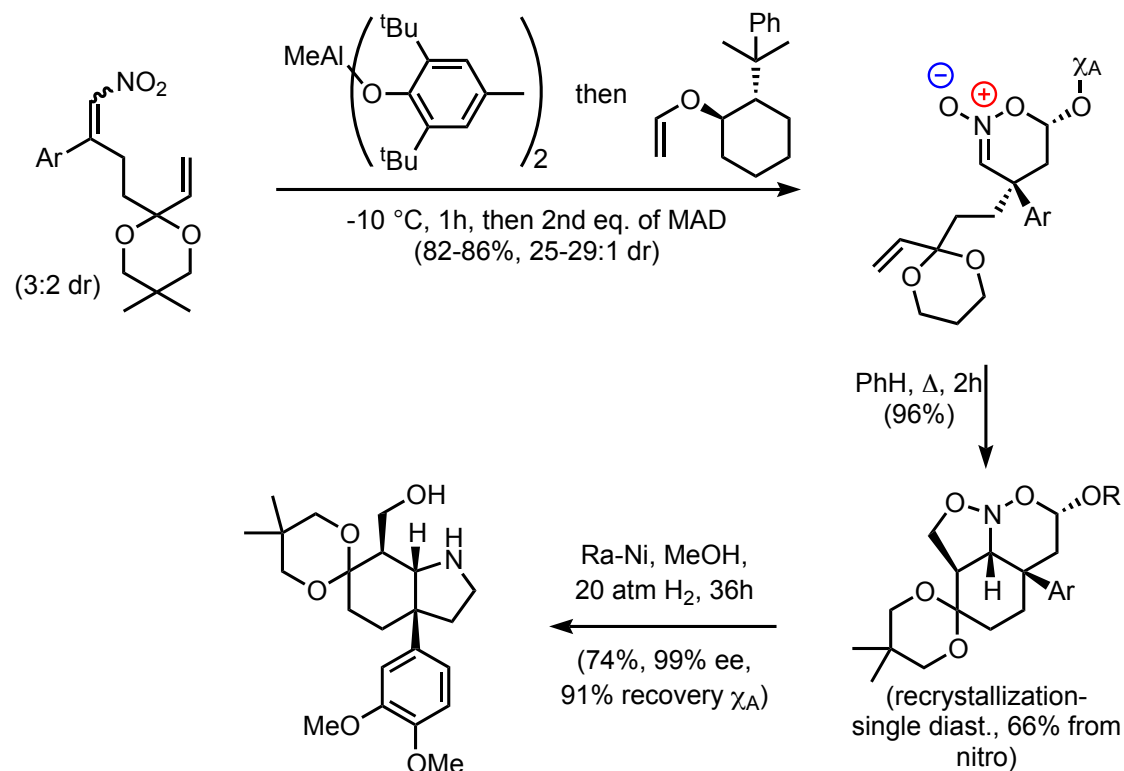
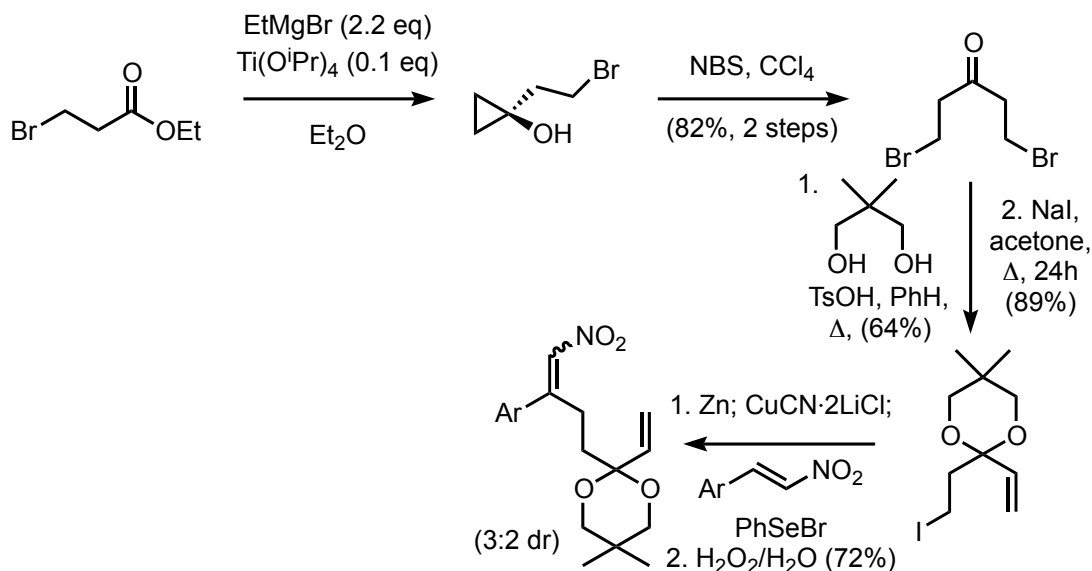
"In a double-blind placebo controlled pilot study investigating the efficacy of MDMA in the treatment of PTSD, 20 individuals diagnosed with PTSD took part in 2 drug administration sessions and 11 psychotherapy sessions. The MDMA group showed 83% clinical response to treatment compared to 25% in the placebo control group at two month follow-up."



Mesembrine is found in the herb kanna, used by South African hunter-gatherers as a mood-altering, empathogenic substance. It is generally believed to be a selective serotonin reuptake inhibitor. Kanna has been used to decrease anxiety and treat depression.



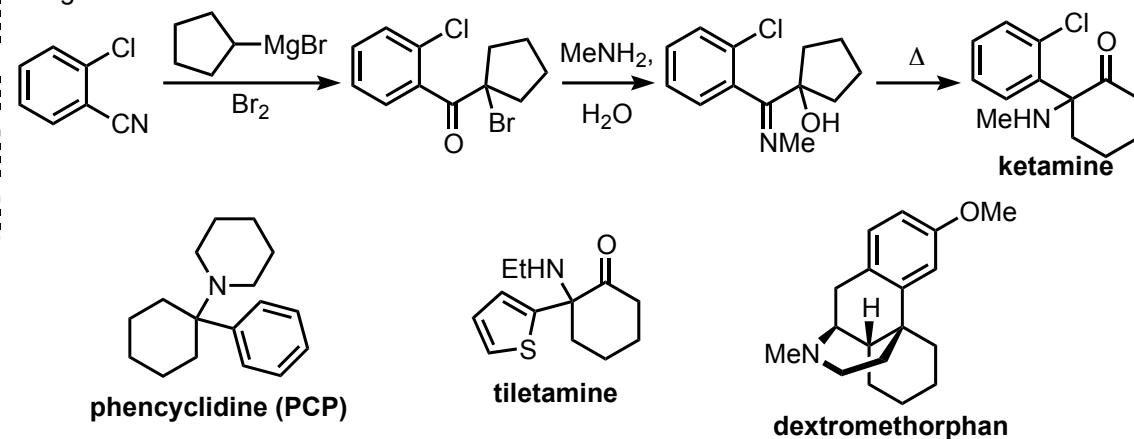
Photo by DC Williams © Erowid.org



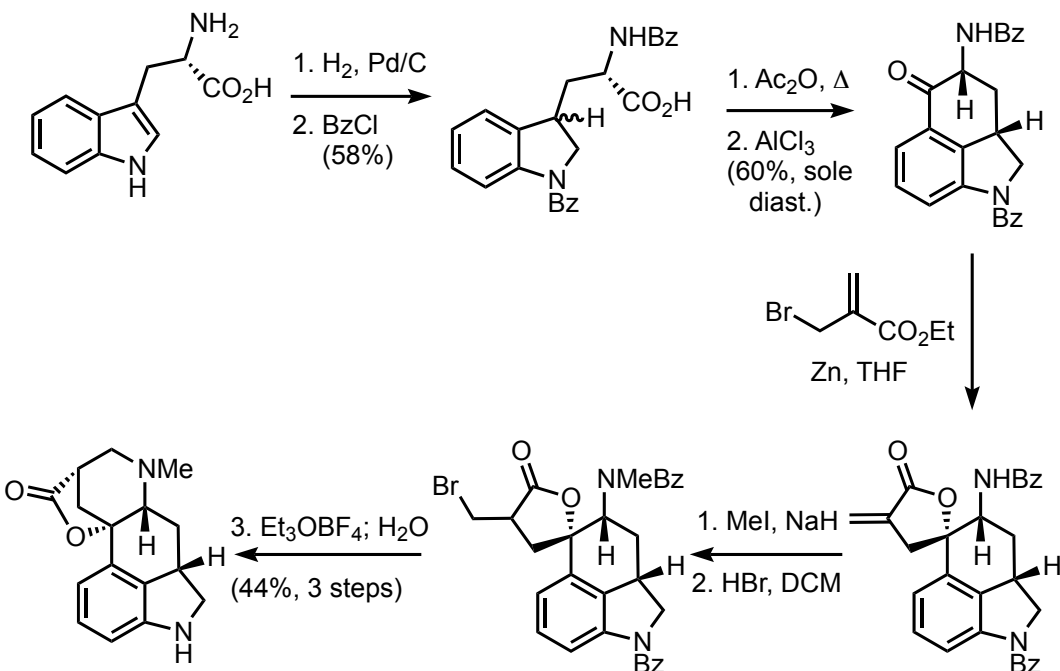
Denmark, S.E.; Marcin, L.R. *J. Org. Chem.* **1997**, *62*, 1675.

Dissociatives

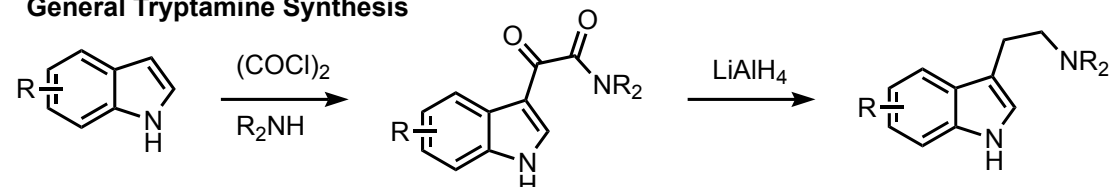
Dissociatives produce a feeling of detachment from the environment and self. They block signals to the conscious mind from other parts of the brain, and often cause sensory deprivation. Some may induce euphoria, and they are generally associated with depressant effects. Two classes are NMDA (N-methyl-D-aspartate) antagonists and κ -opioid receptor agonists.



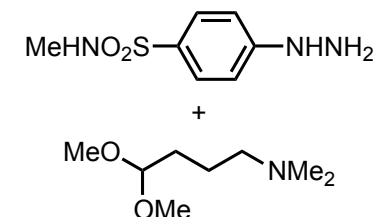
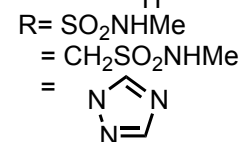
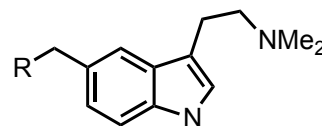
Syntheses of Lysergic Acid

Rebek, J.; Tai, D.F.; Shue, Y.-K. *J. Am. Chem. Soc.* **1984**, *106*, 1813.

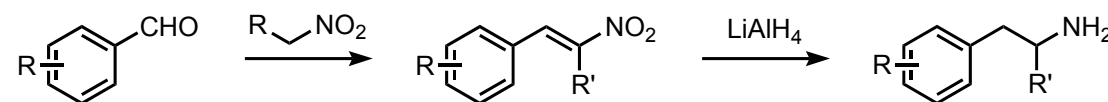
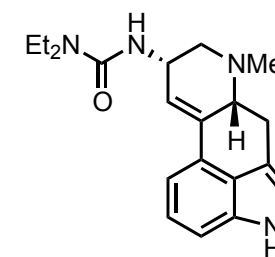
General Tryptamine Synthesis



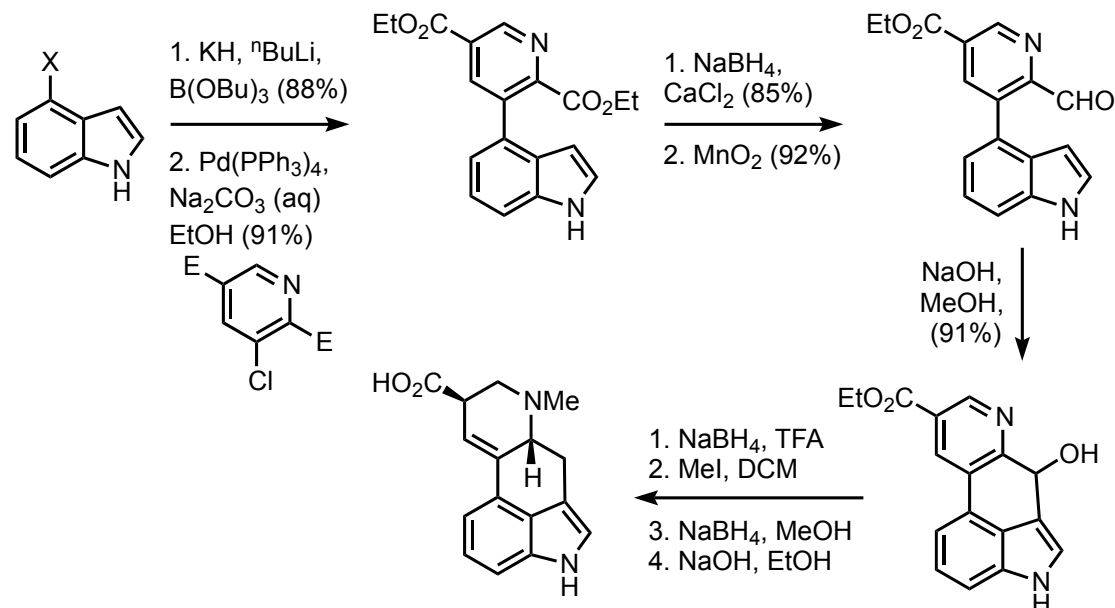
Triptans are used as migraine treatments (not preventative) first introduced in the 1990s

"Obsessive thoughts would be worse for 1 hour followed by total remission for 4-5 hours" in an OCD patient using psilocybin. Leonard & Rappoport *Am. J. Psychiatry* **1987**, *144*, 1239.

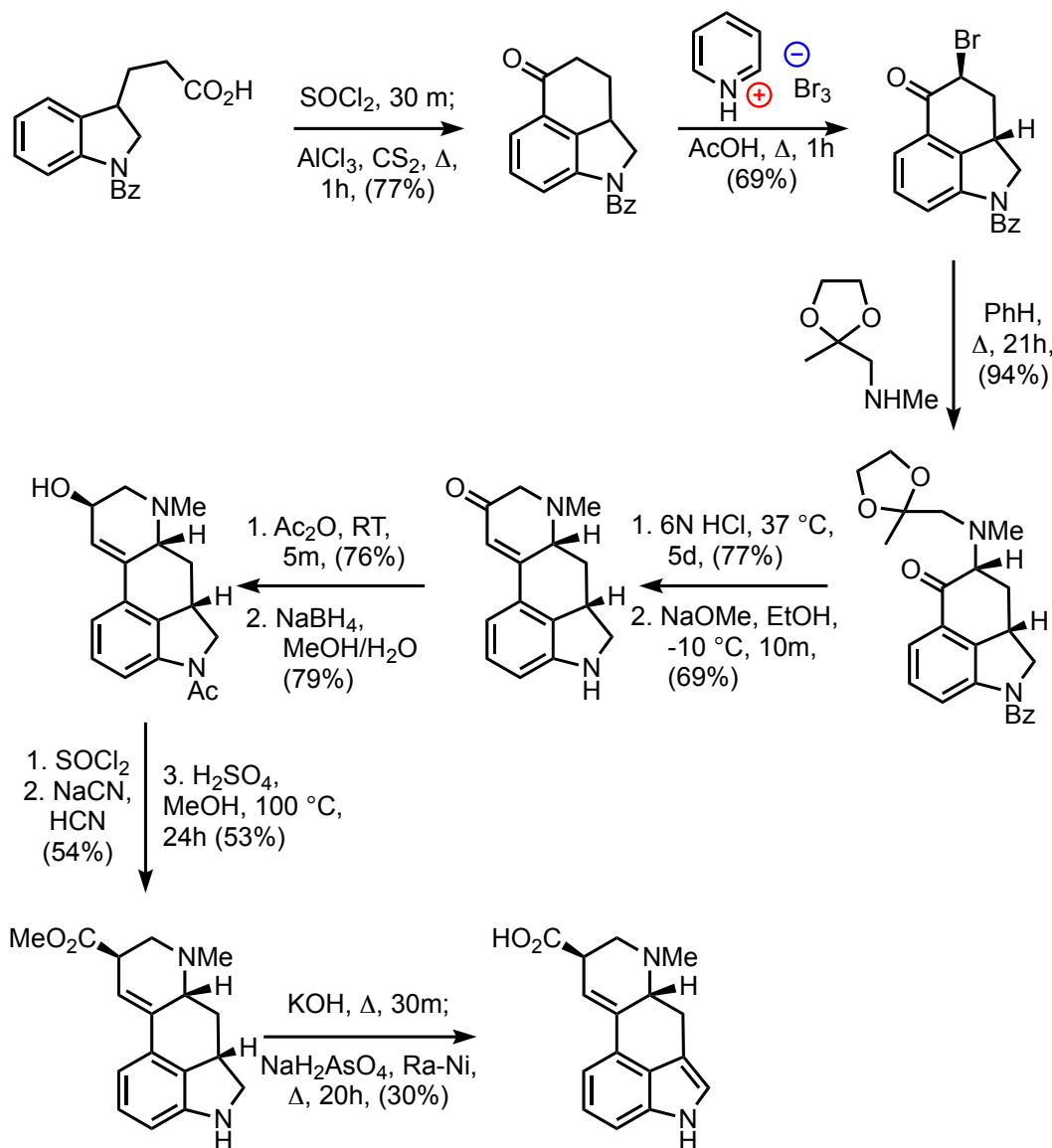
General Phenethylamine Synthesis

"Mescaline... produces symptoms almost identical with schizophrenia." Osmond & Smythies *J. Ment. Sci.* **1952**, *98*, 309.

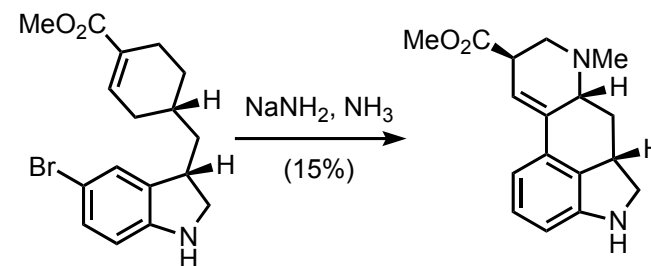
Lisuride, an antiparkinson agent available in several EU countries and China is nonhallucinogenic in humans. It is also used to treat migraines in low doses.

Hendrickson, J.B.; Wang, J. *Org. Lett.* **2004**, *6*, 3.

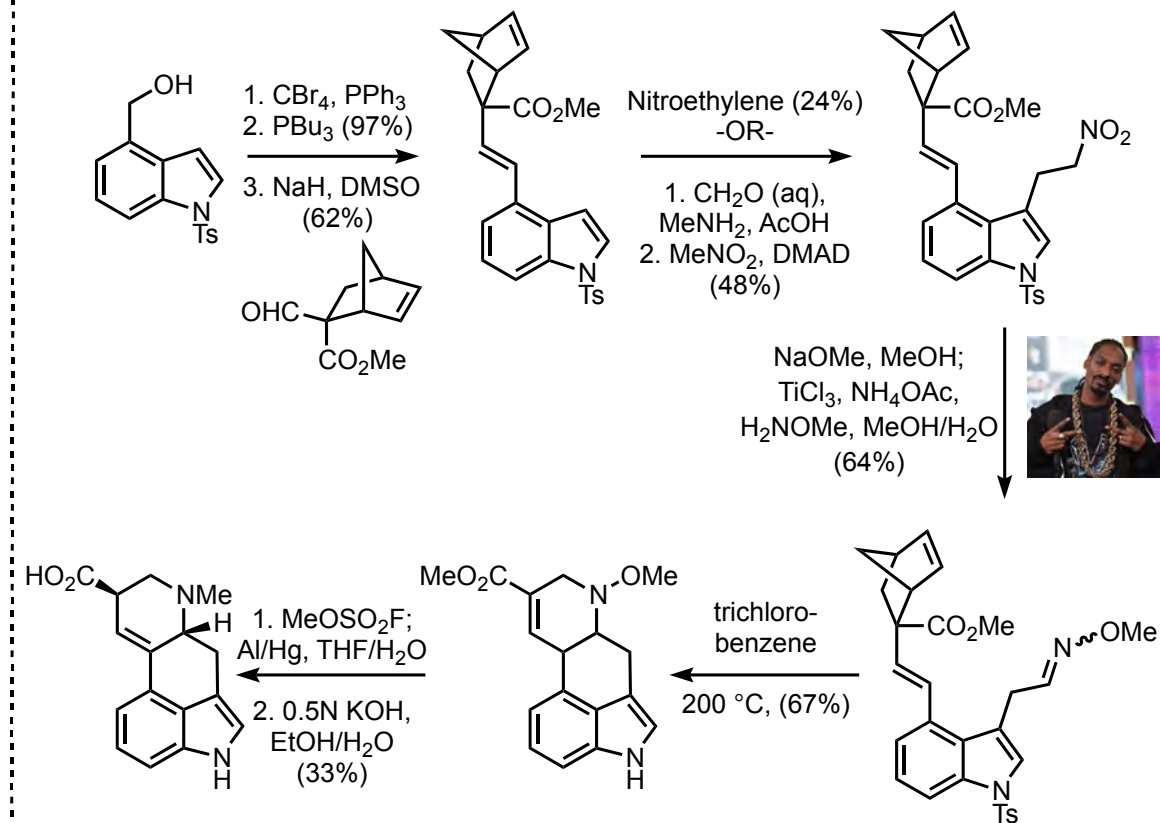
Syntheses of Lysergic Acid



Kornfeld, E.C.; Fornefeld, E.J.; Kline, G.B.; Mann, M.J.; Morrison, D.E.; Jones, R.G.; Woodward, R.B. *J. Am. Chem. Soc.* **1956**, *78*, 3087.



Julia, M.; LeGoffic, F.; Igolen, J.; Baillarge, M. *Tet. Lett.* **1969**, *20*, 1569.



Oppolzer, W.; Francotte, E.; Bättig, K. *Helv. Chim. Acta* **1981**, *64*, 478.