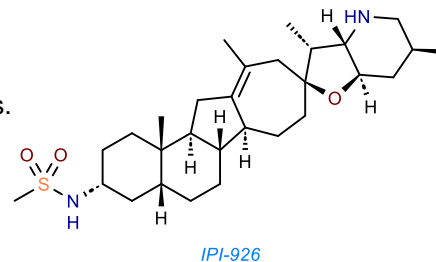


IPI-926

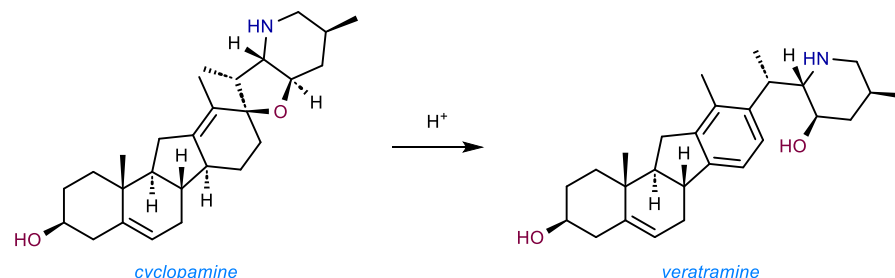
- Analog of cyclopamine, which is a known antagonist of the hedgehog signaling pathway.
- The hedgehog signaling pathway is a potential target for cancer therapeutics.
- Was taken to phase II clinical trials.
- Failed due to lower rate of survival in patients with untreated metastatic pancreatic cancer. Paired with gemcitabine (approximately six months) vs. placebo with gemcitabine (over six months).



<https://www.sec.gov/Archives/edgar/data/1113148/000119312512026049/d290658dex991.htm>

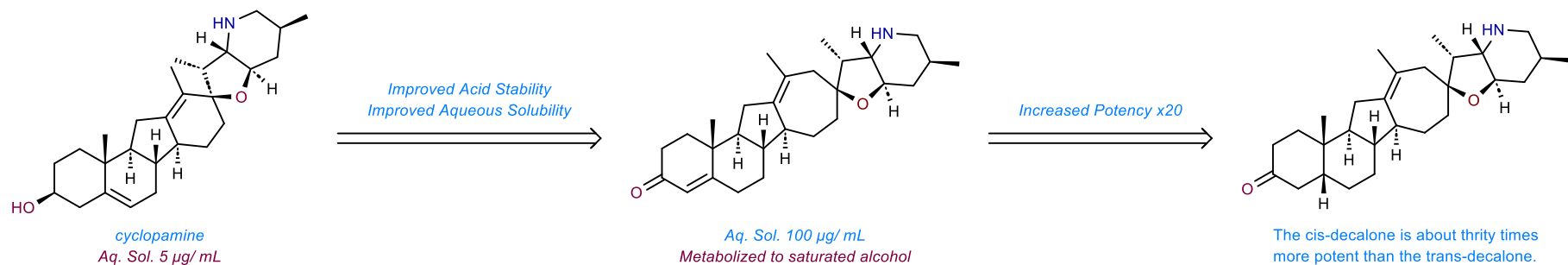
Cyclopamine

- Steroidal alkaloid that is isolated ~1.3 g per kg of *Veratrum californicum* roots
- Unstable to acidic conditions as the D ring aromatizes forming veratramine which causes hemolysis.
- In addition, cyclopamine has low aqueous solubility.



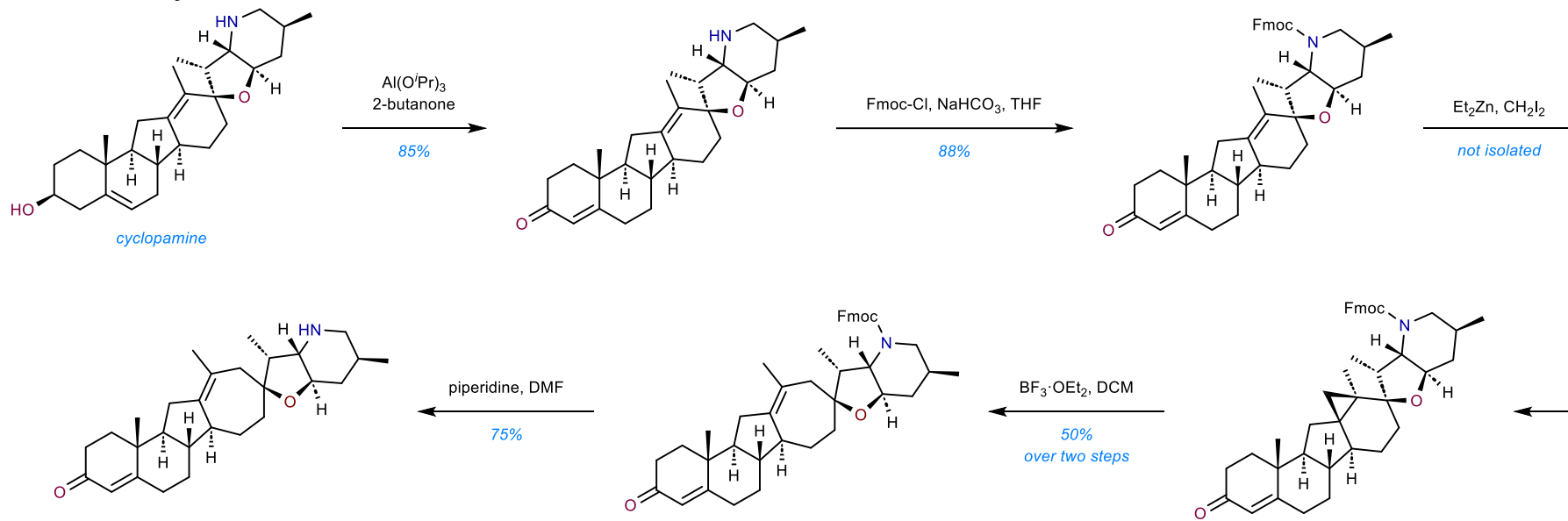
Chem, Gen. J. **2008**, 2, 12 <https://doi.org/10.1186/1752-153X-2-12>
J. Med. Chem. **2008**, 51, 6646–6649 <https://doi.org/10.1021/jm8008508>

Initial scaffold optimization

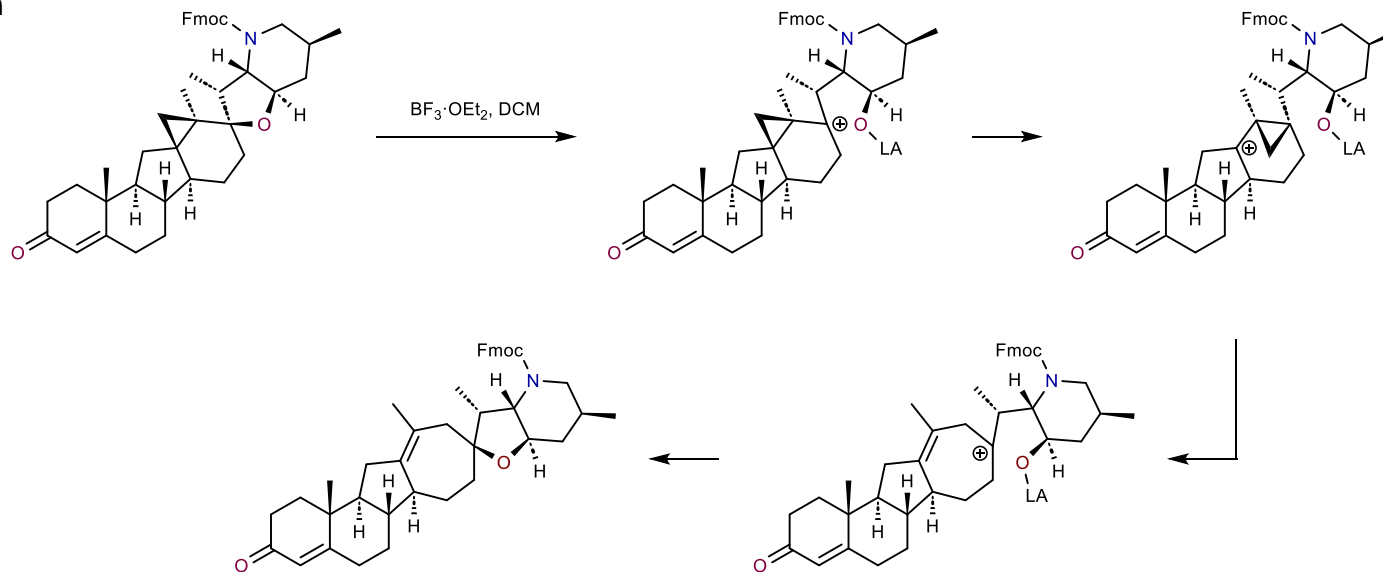


J. Med. Chem. **2009**, 52, 4400–4418 <https://doi.org/10.1021/jm900305z>

Synthesis of key enone



Ring expansion



Completion of IPI-926

