Synthesis and Bioactivity of Ergot Alkaloids

Outline

1. **Introduction**
2. **Biology**
   a. Commercial drugs
   b. Biosynthesis
3. **Classes of Alkaloids**
   a. Ergopeptides
   b. Amides
   c. Clavines
4. **Total Synthesis**
   a. Lysergic acid
   b. Dihydrolysergic acid
   c. Cycloclavine

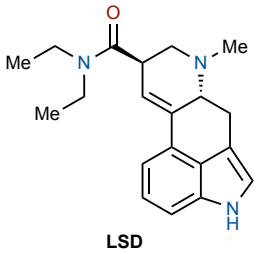
Not covered:

- Non-natural ergot alkaloid derivatives
- This is not a comprehensive review of the field; syntheses chosen to highlight breadth of strategies

Key references:

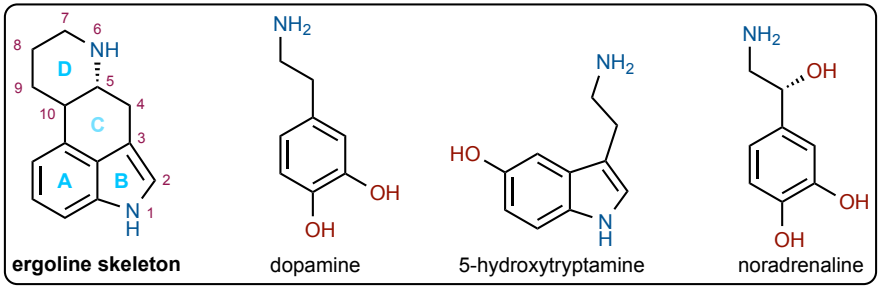
Ergot alkaloid syntheses 2000-2017

The Alkaloids: Chemistry and Biology



LSD

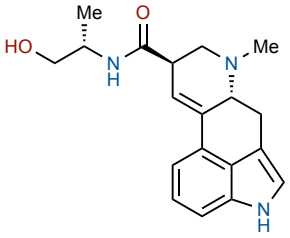
- Ergot alkaloids first isolated from ergot, from the fungus *Claviceps purpurea*
- Over 90 alkaloids have been isolated
- Oldest known producers of mycotoxins
- Cause of several epidemics in the middle ages due to infected grass and grains
- Earliest reports of bioactivity come from ancient Greek and Chinese writings
- Ergot alkaloids have been extensively used for medicinal purposes throughout history
- Many are highly bioactive with diverse pharmacological effects



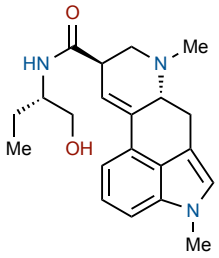
Medicinal Compounds and Biosynthesis

Medicinal Natural and Semi-synthetic Ergot Alkaloids

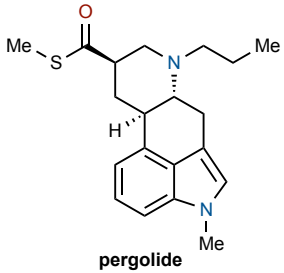
Due to high levels of biological activity, much focus has been placed into development of drug candidates derived from ergots that do not possess hallucenogenic or toxic effects



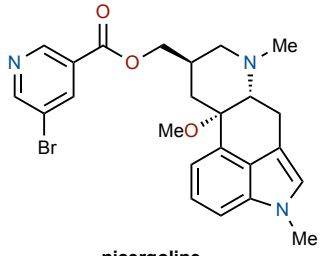
ergometrine
post-partum hemorrhage
natural



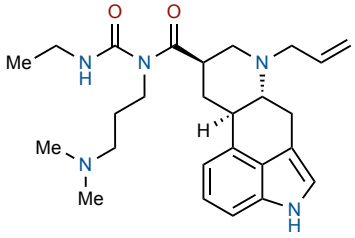
methysergide
migraines
semi-synthetic



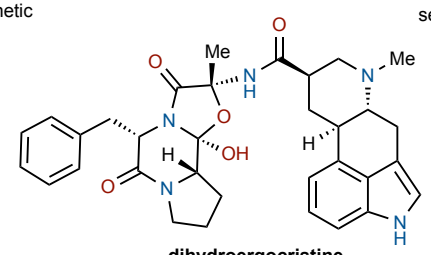
pergolide
Parkinson's disease
semi-synthetic



nicergoline
senile dementia
semi-synthetic



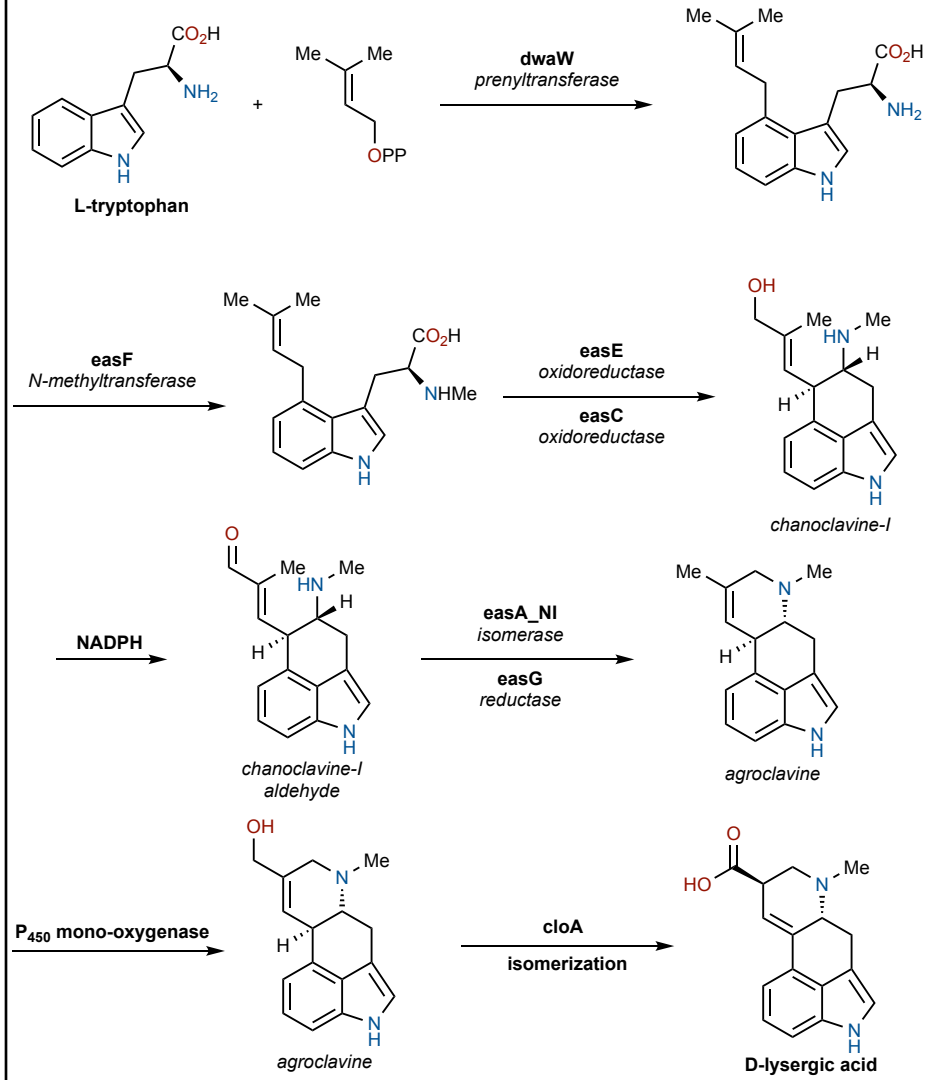
cabergolide
Parkinson's disease
semi-synthetic



dihydroergocristine
Parkinson's disease
semi-synthetic

Toxins., **2022**, 14 Special Issue
Eur. Journal of Medicinal Plants., **2016**, 14, 3, DOI: 10.9734/EJMP/2016/25975

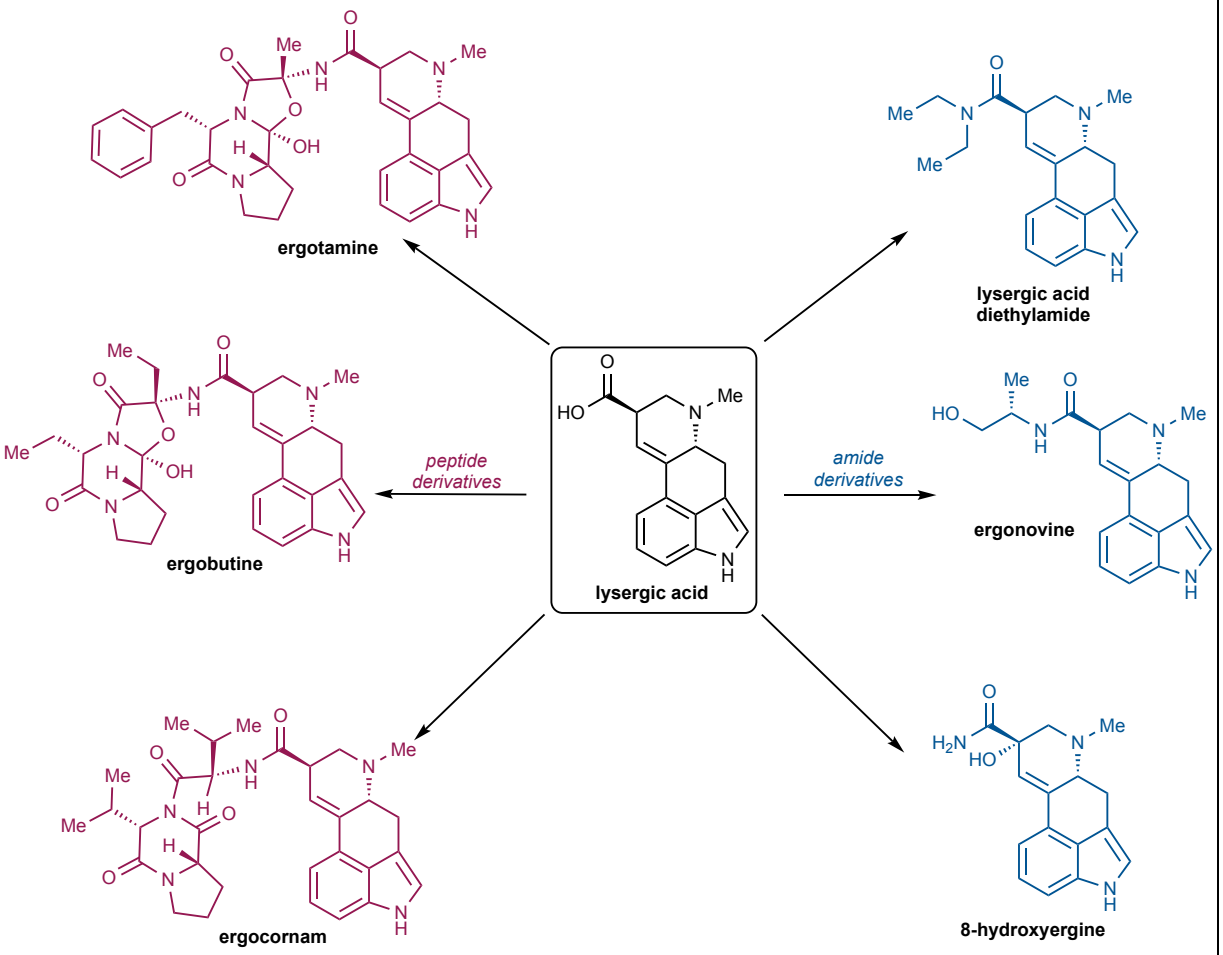
Biosynthetic Route



Nature Comm., **2022**, 13, 712, 1-10 https://doi.org/10.1038/s41467-022-28386-6
Nat. Prod. Rep., **2014**, 31, 1328-1338 DOI: 10.1039/c4np00062e

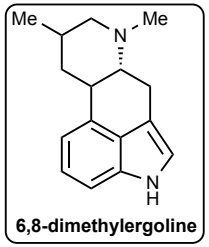
Classes of Ergot Alkaloids

Class I: derivatives of lysergic acid

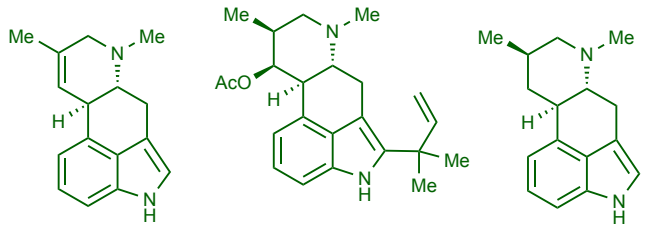


Total synthesis of ergot alkaloids focuses heavily on lysergic acid, with 20 completed total syntheses to date

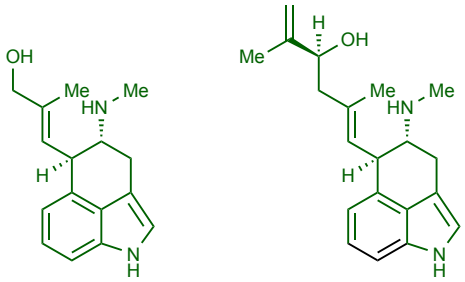
Class II: clavines



tetracyclic clavines:

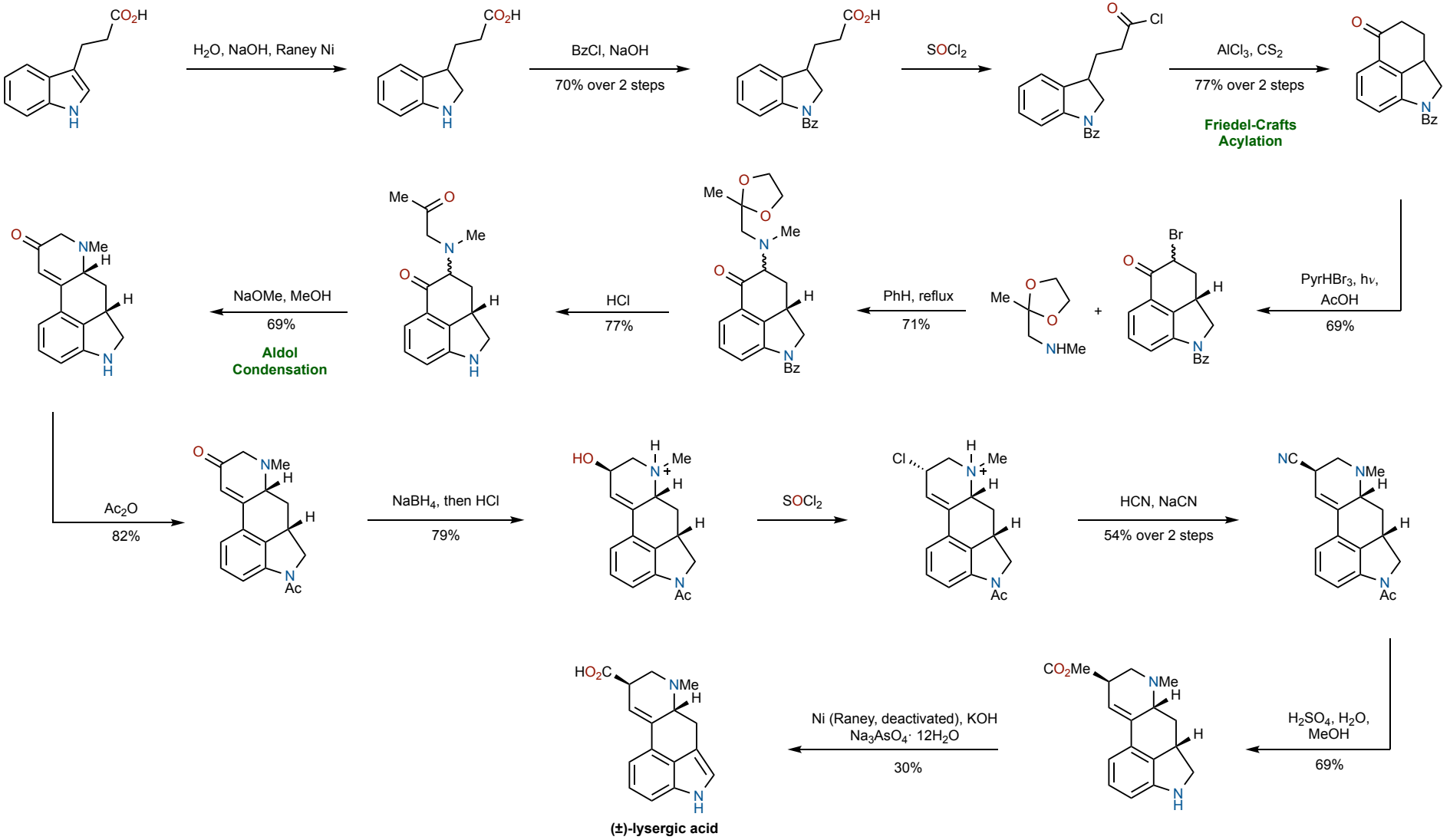


tricyclic clavines:



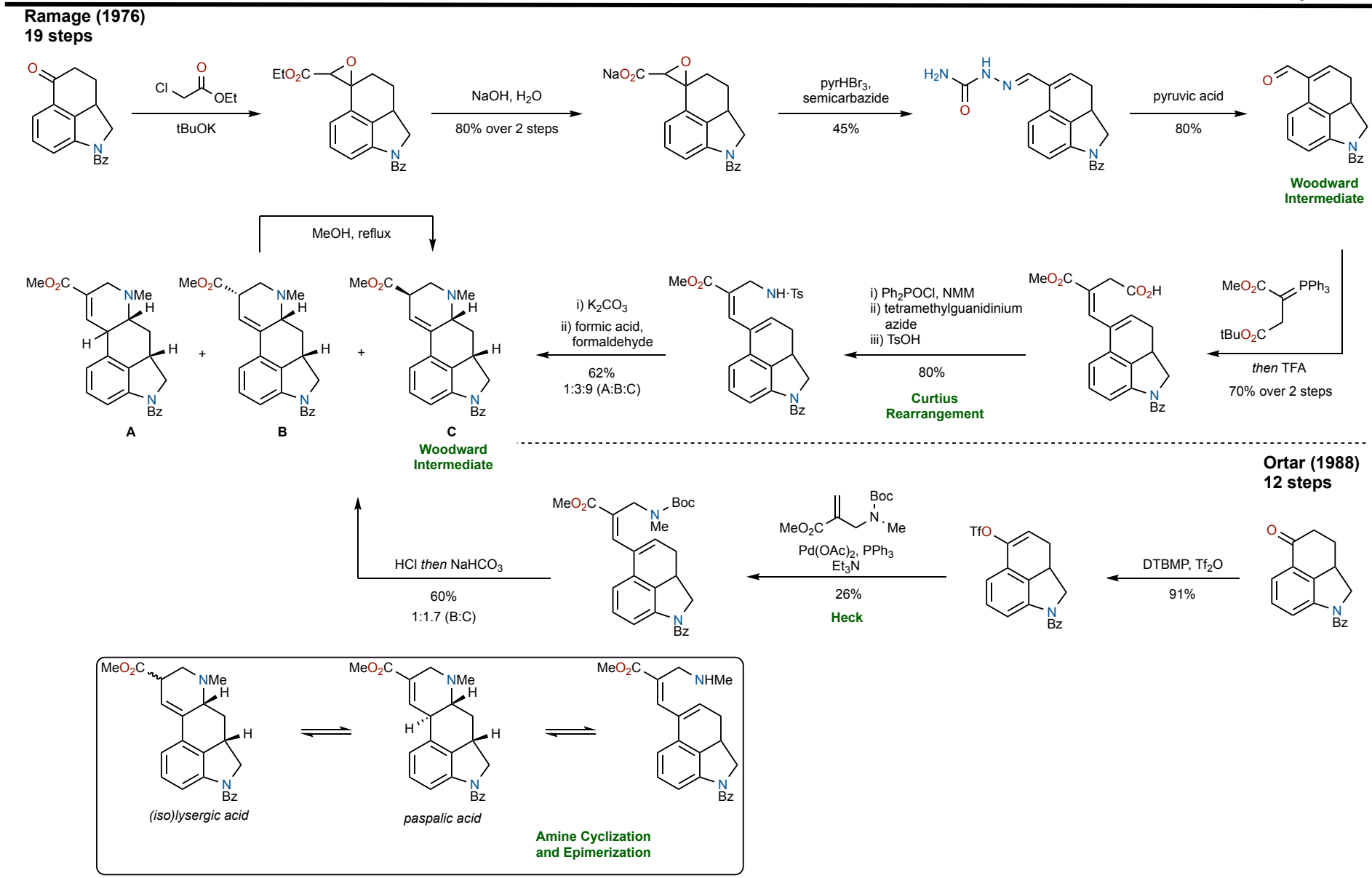
Woodward (1956)

15 steps



J. Am. Chem. Soc. **1956**, 78, 13, 3087–3114 https://pubs.acs.org/doi/10.1021/ja01594a039
J. Am. Chem. Soc. **1954**, 76, 20, 5256−5257 https://pubs.acs.org/doi/10.1021/ja01649a100

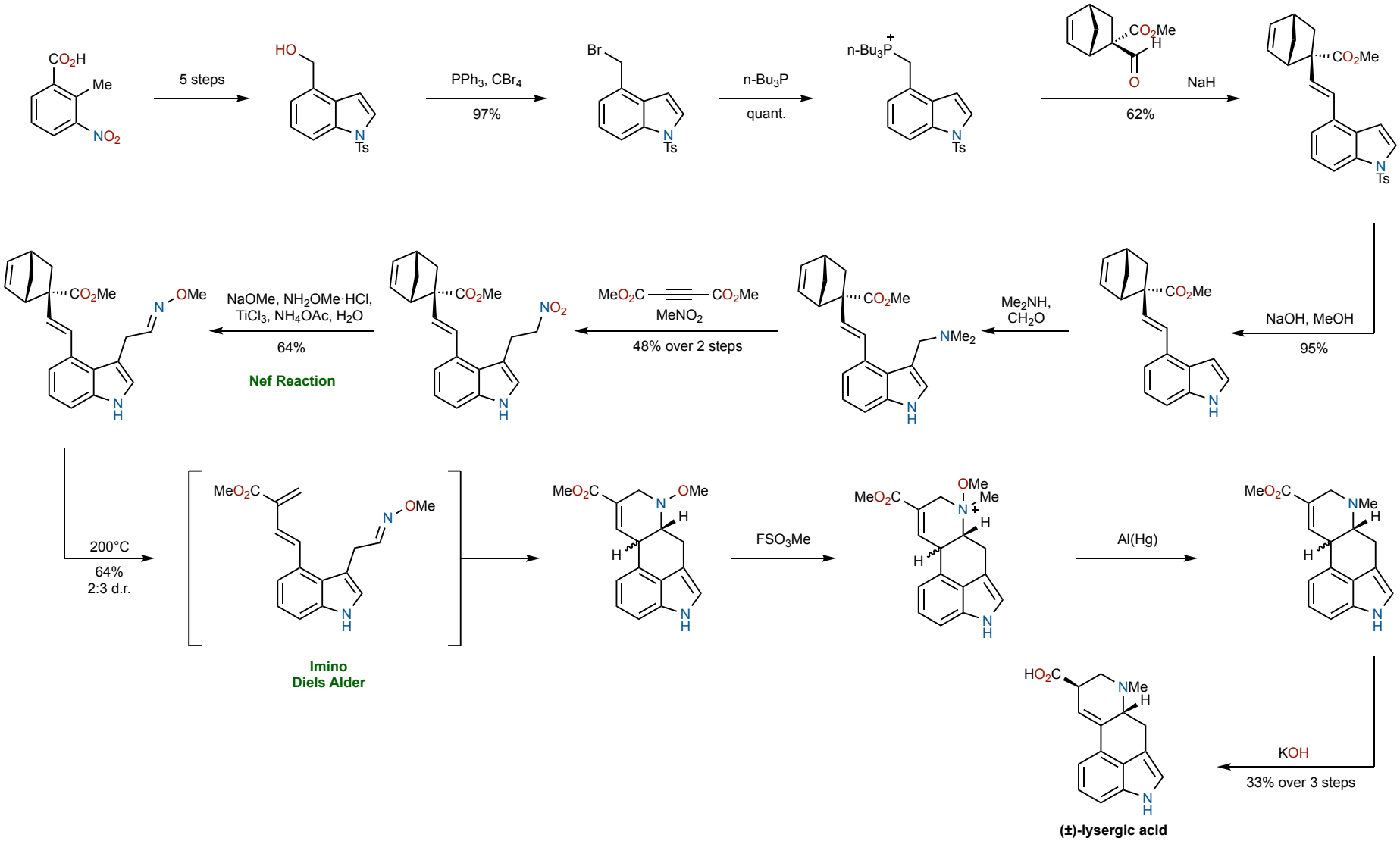
Ramage (1976) and Ortar (1988)



Tetrahedron Lett., **1981**, 37, 157-164 https://www.sciencedirect.com/science/article/pii/004040208185051X
Tetrahedron Lett.,. **1976**, 17, 47, 4311-4314 https://www.sciencedirect.com/science/article/pii/0040403976801037
Tetrahderon Lett., **1988,** 29, 25, 3117-3120 https://www.sciencedirect.com/science/article/pii/0040403988851013

Oppolzer (1981)

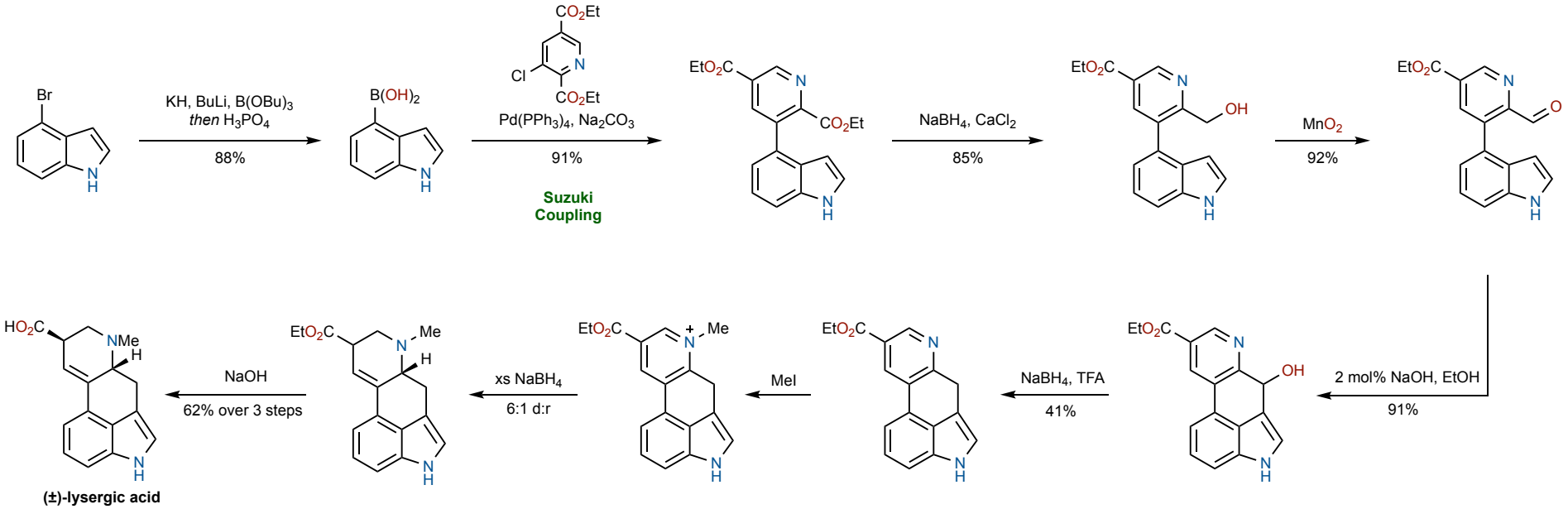
17 steps



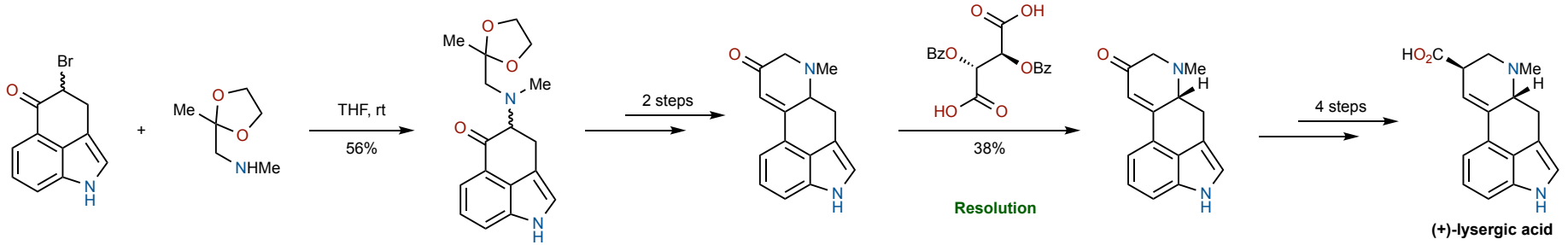
Helv. Chem. Acta. **1981**, 64, 13, 478-481 https://onlinelibrary.wiley.com/doi/10.1002/hlca.19810640212

Hendrickson and Szántay (2004)

Hendrickson (2004)
9 steps*

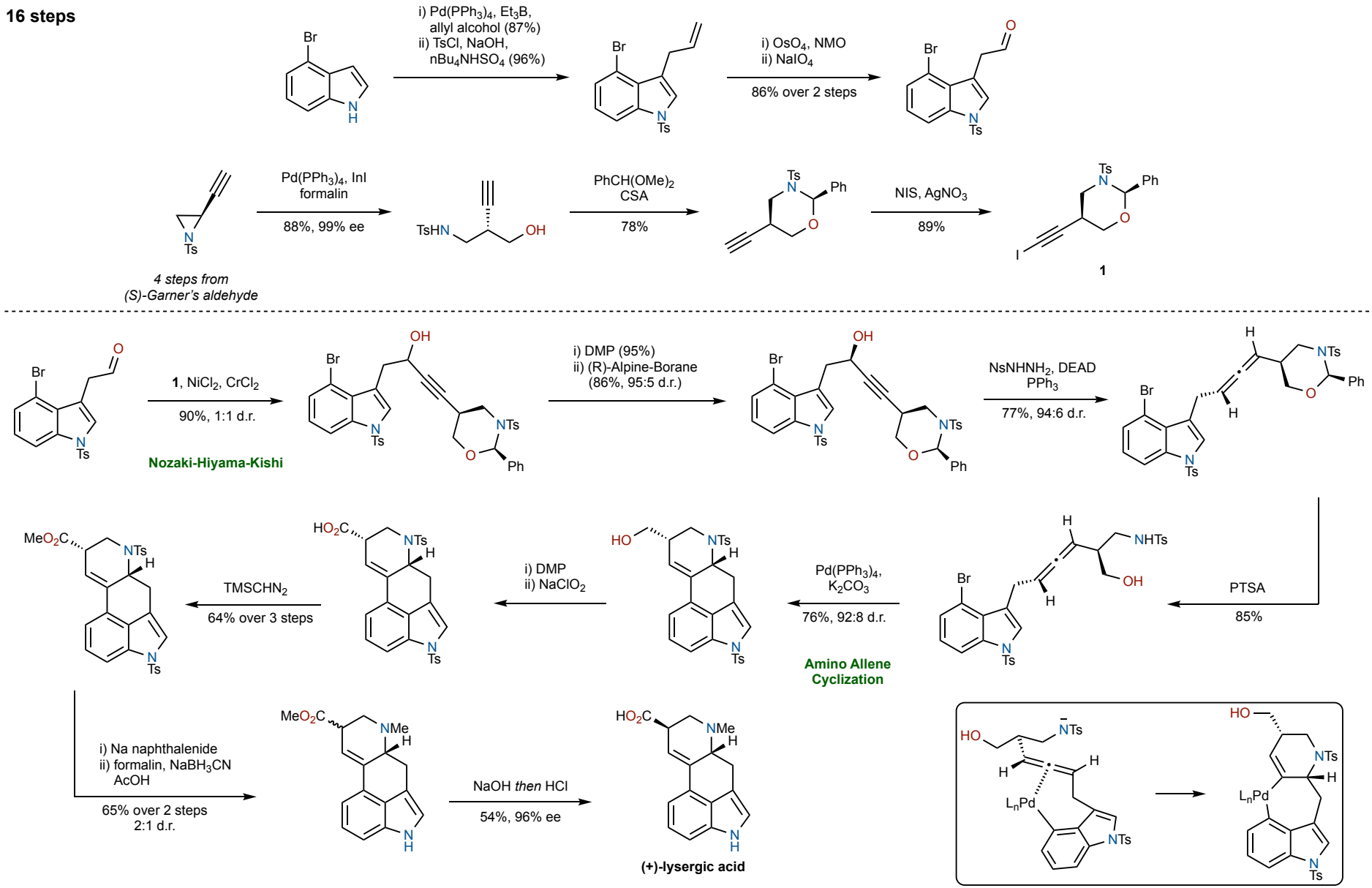


Szántay (2004)
15 steps



Org. Lett., **2004**, 6, 1, 3-5 https://pubs.acs.org/doi/10.1021/ol0354369
J. Org. Chem., **2004**, 69, 18, 5993-6000 https://doi.org/10.1021/jo049209b
Org. Lett., **2011**, 14, 1, 296-298 https://pubs.acs.org/doi/pdf/10.1021/ol203048q

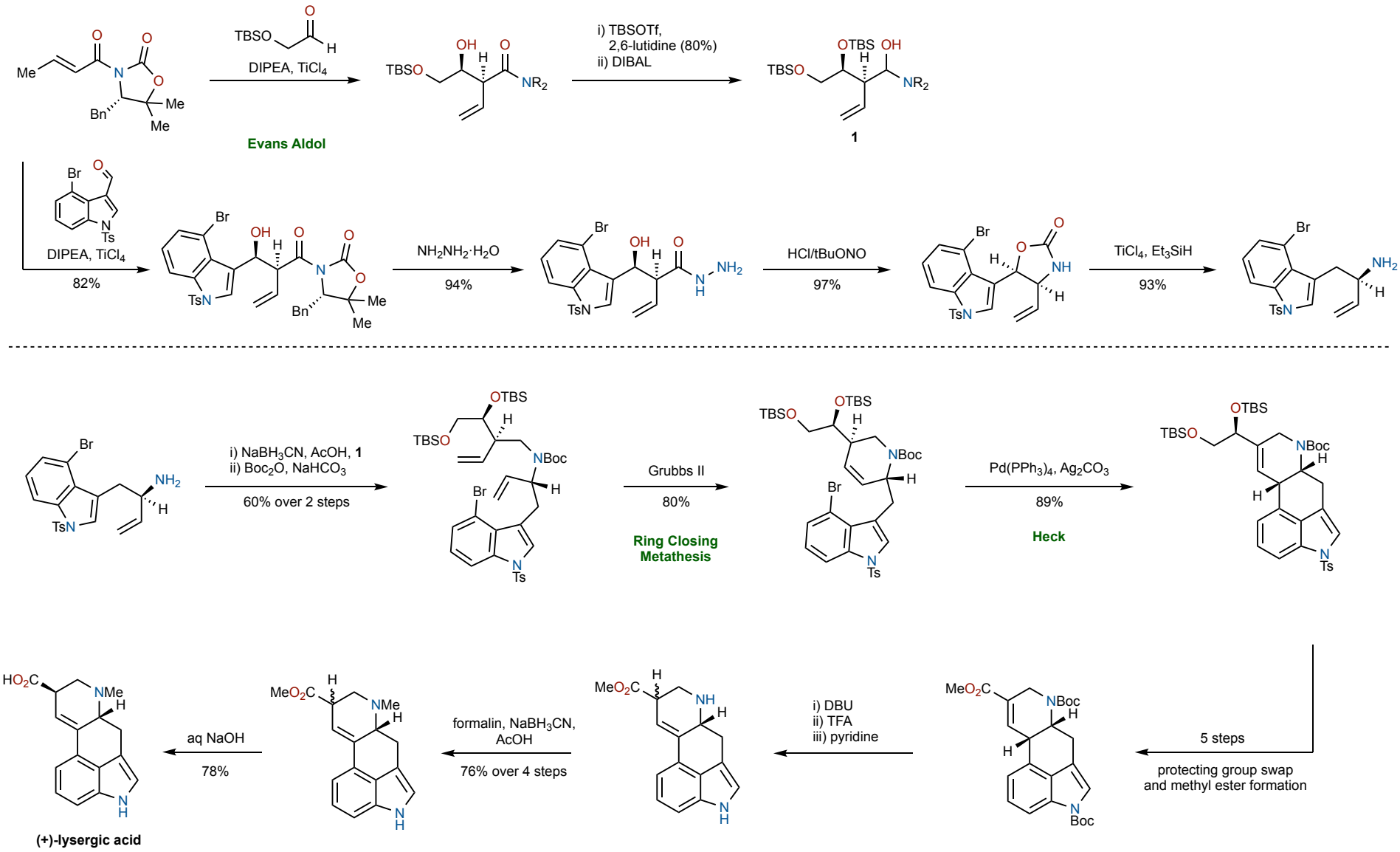
Fujii and Ohno (2011)



Org. Lett., **2008**, 10, 22, 5238-5242 https://doi.org/10.1021/ol8022648
J. Org. Chem.,. **2011**, 76, 7, 2072-2083 https://doi.org/10.1021/jo102388e

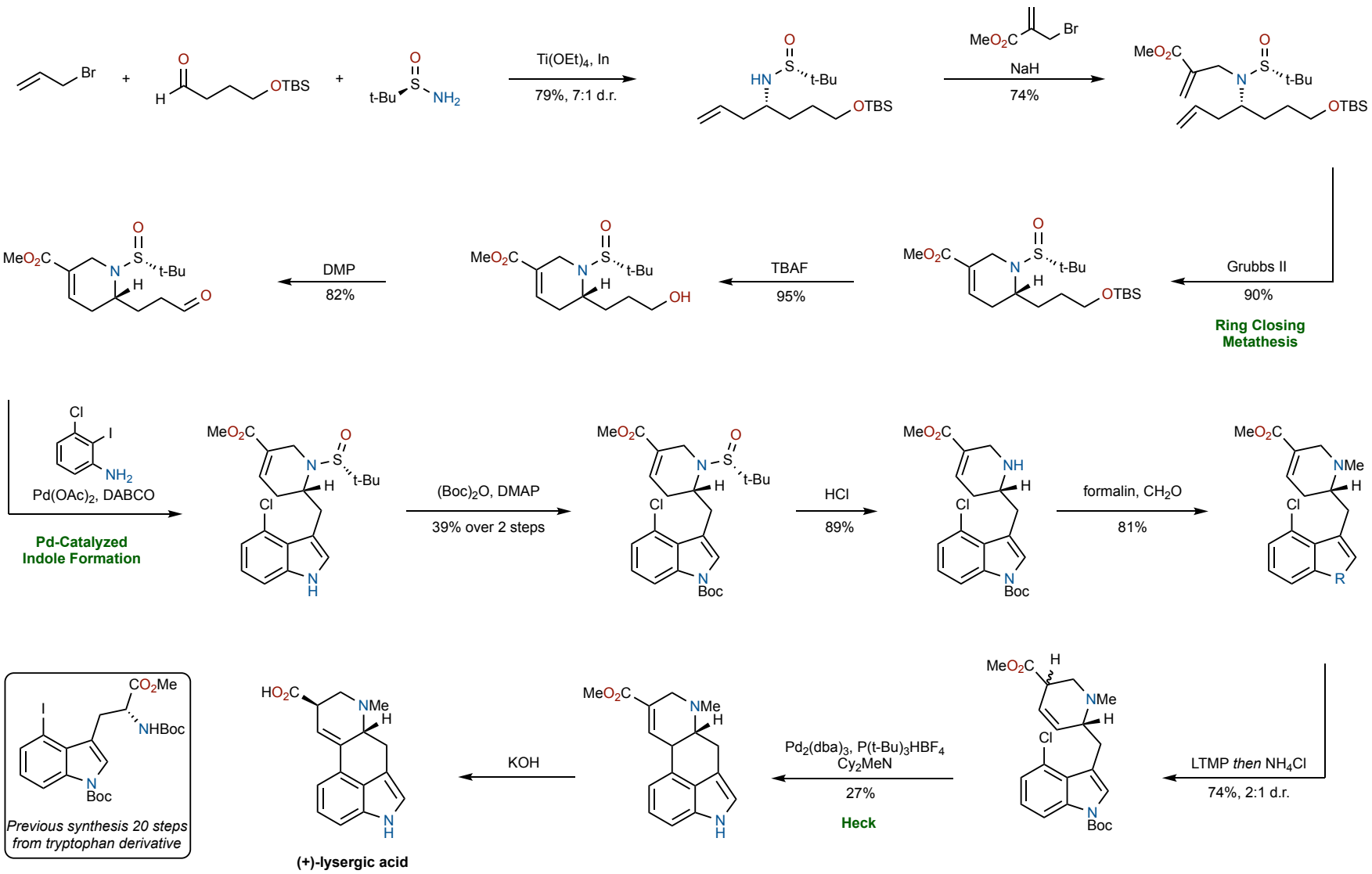
Fukuyama (2011)

19 steps



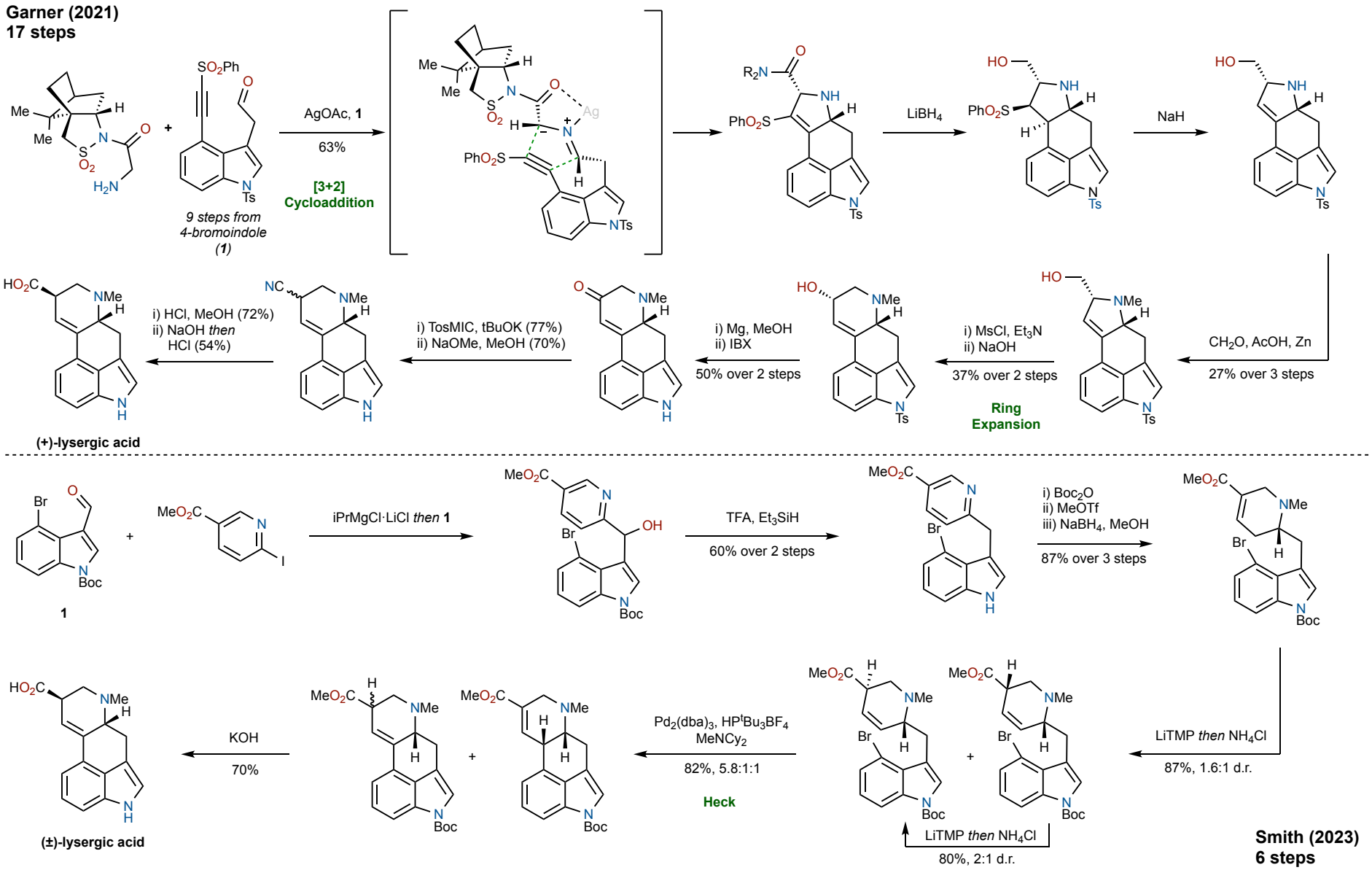
Org. Lett., **2013**, 15, 16, 4230-4233 https://doi.org/10.1021/ol4019562

12 steps



J. Org. Chem., **2013**, 78, 21, 10885-10893 https://doi.org/10.1021/jo4018777
J. Org. Chem.,. **2006**, 71, 20, 7826-7834 https://doi.org/10.1021/jo061471s

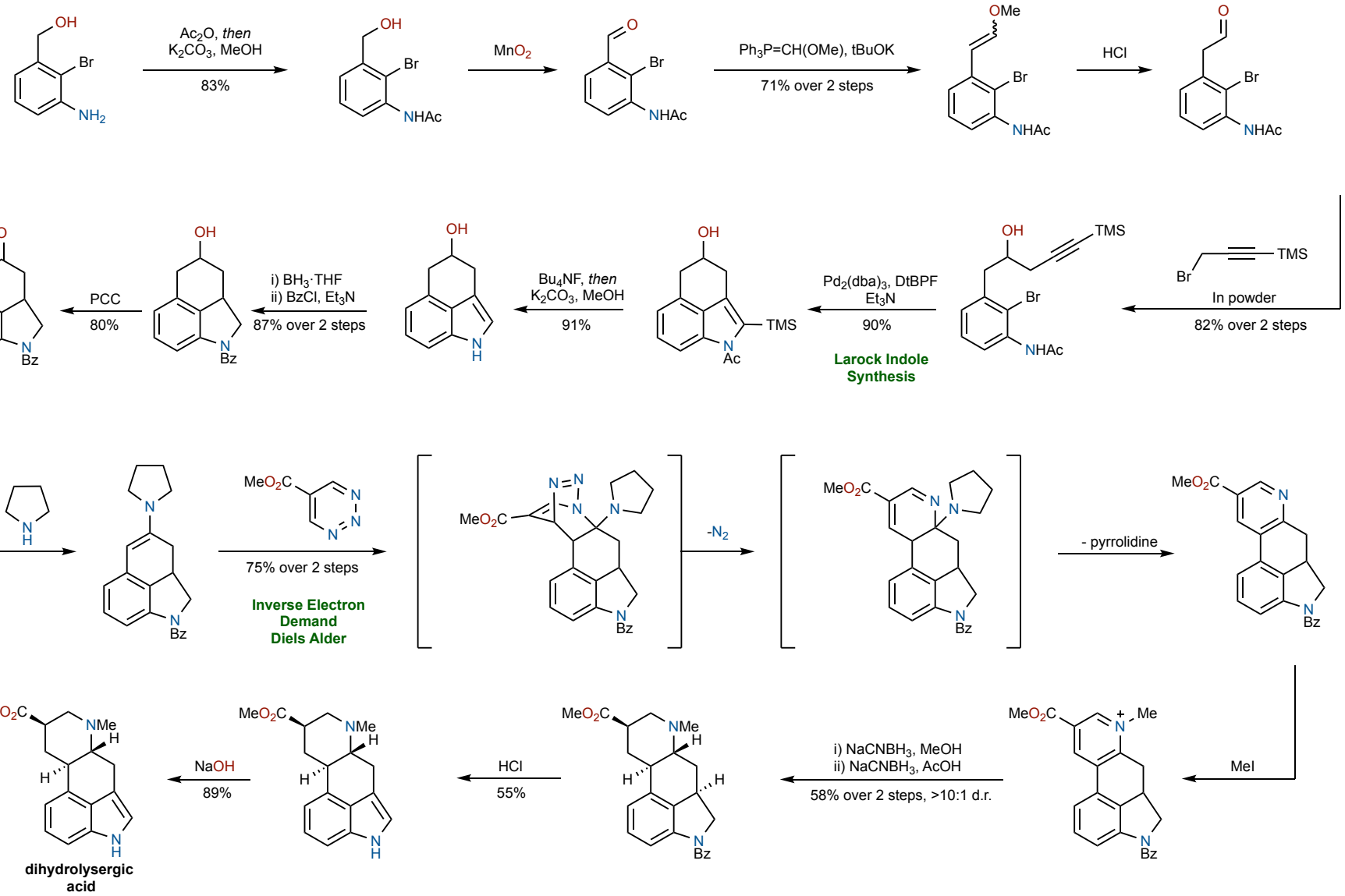
Garner (2021) and Smith (2023)



Org. Lett., **2021**, 23, 17, 6756-6759 https://doi.org/10.1021/acs.orglett.1c02337
J. Org. Chem.,. **2023**, 88, 4, 2158-2165 https://doi.org/10.1021/acs.joc.2c02564

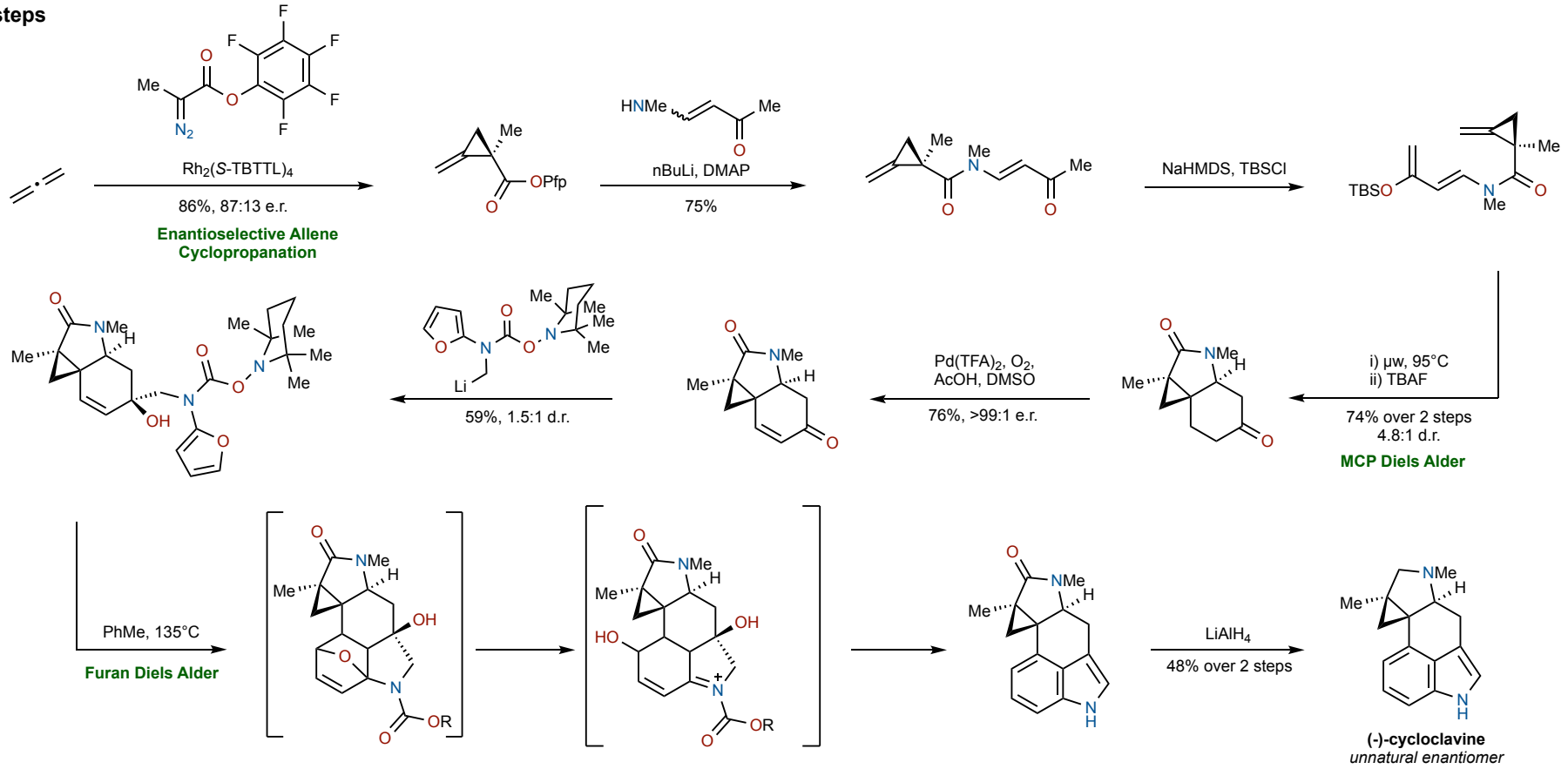
Boger (2015)

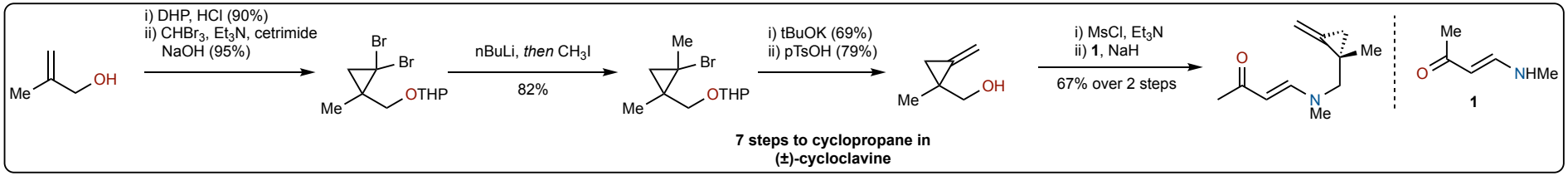
dihydrolysergic acid
18 steps



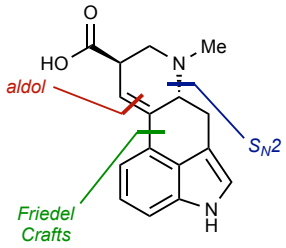
Tetrahedron, **2015**, 71, 5897-5905 https://doi.org/10.1016/j.tet.2015.05.093

cycloclavine
8 steps

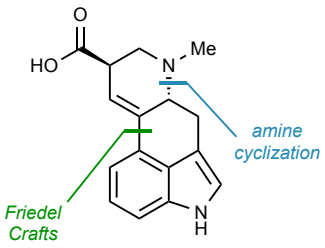




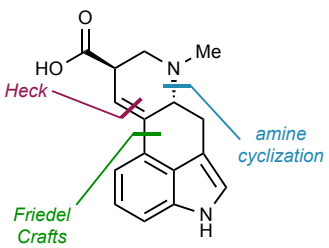
Summary



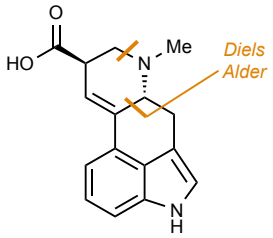
Woodward



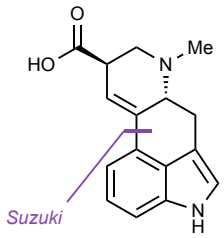
Ramage



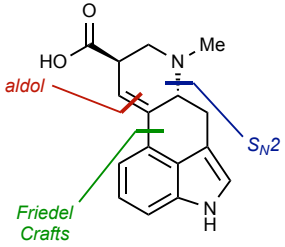
Ortar



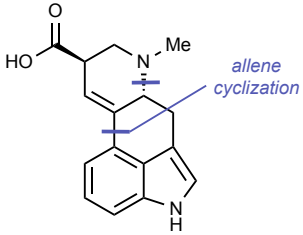
Oppolzer



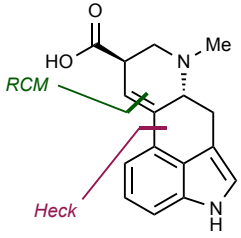
Hendrickson



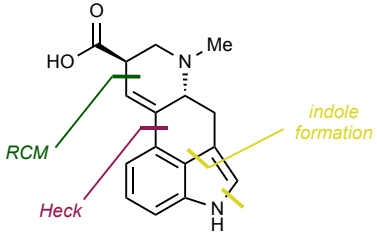
Szántay



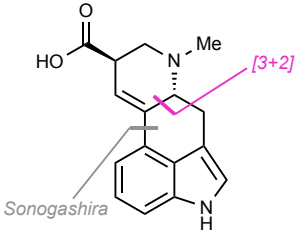
Fujii and Ohno



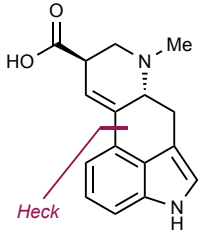
Fukuyama



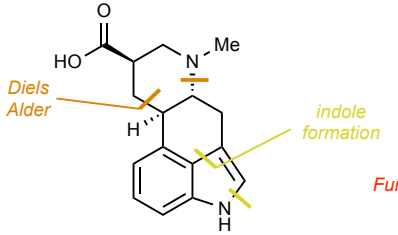
Jia



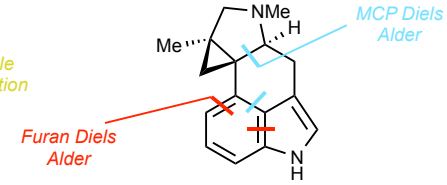
Garner



Smith



Boger



Wipf

- Modern methods allow for enantioselective construction
- Basic bond disconnections remain similar to Woodward's initial approach
- Indole synthesis permits unique disconnections
- Prevalence of Uhle and Kornfeld's ketones as key intermediates decreased over time