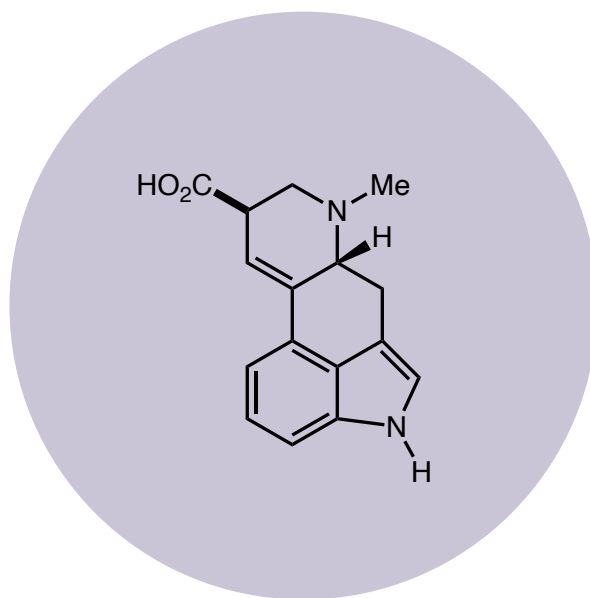


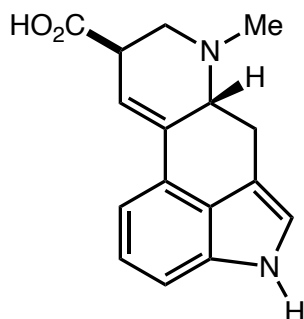
Asymmetric Synthesis of Lysergic Acid via an Intramolecular (3+2) Dipolar Cycloaddition/Ring-Expansion Sequence



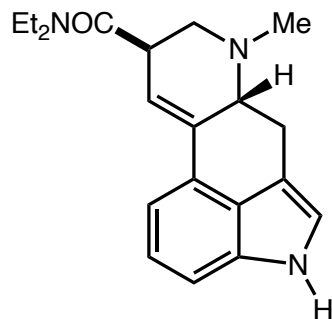
Yu Wang

Literature 10/08/2021

Introduction



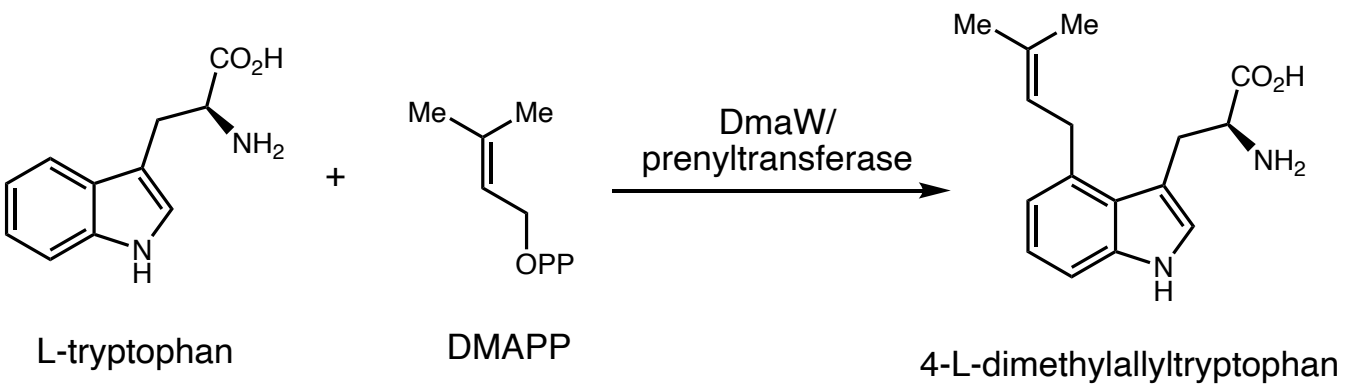
Lysergic Acid



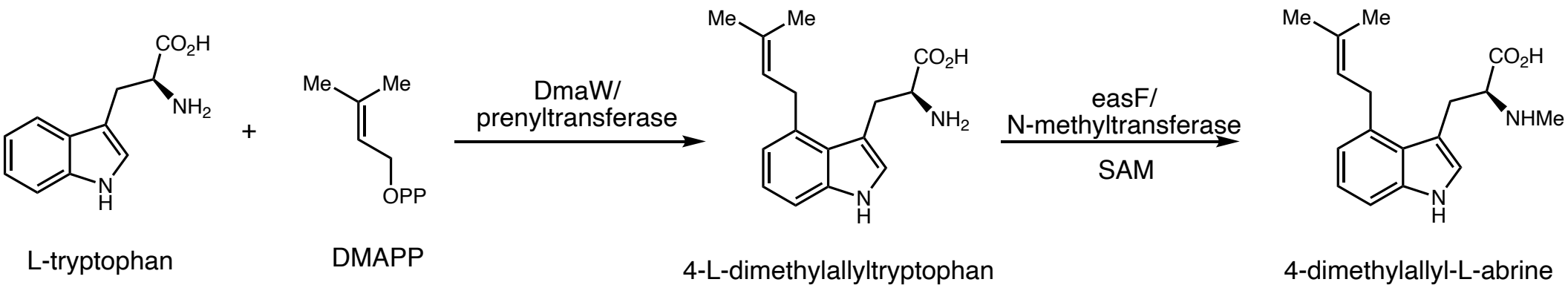
Lysergic Acid Diethylamide

- A precursor for a wide range of ergoline alkaloids that are produced by the ergot fungi
- Industrial scale via hydrolysis of naturally occurring peptidic ergot alkaloids
- First total synthesis reported by Woodward in 1956
- The chiral tetracyclic molecule remains as a popular target

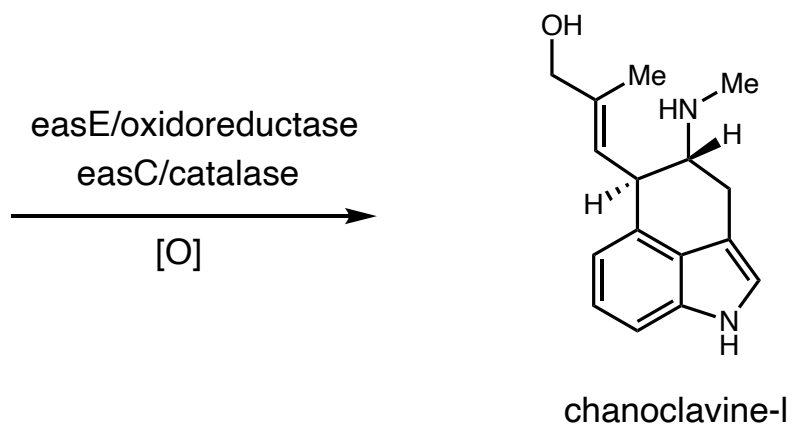
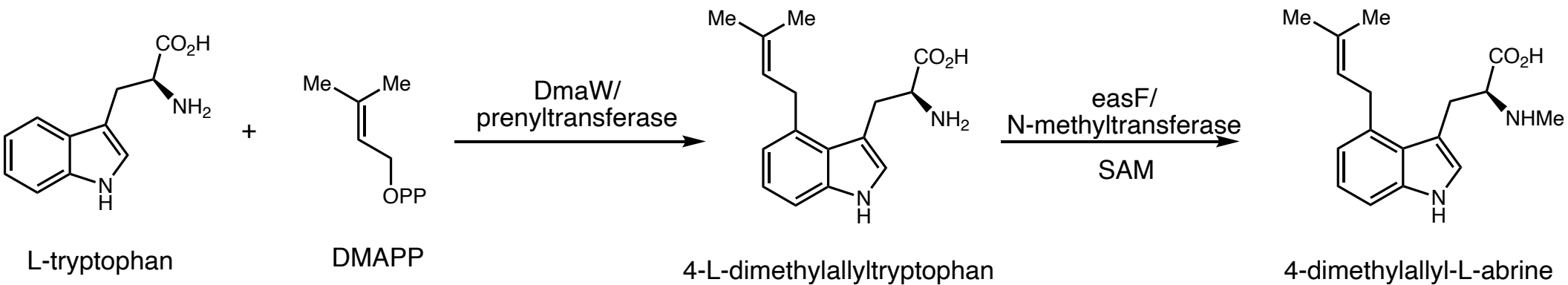
Biosynthesis of Lysergic Acid



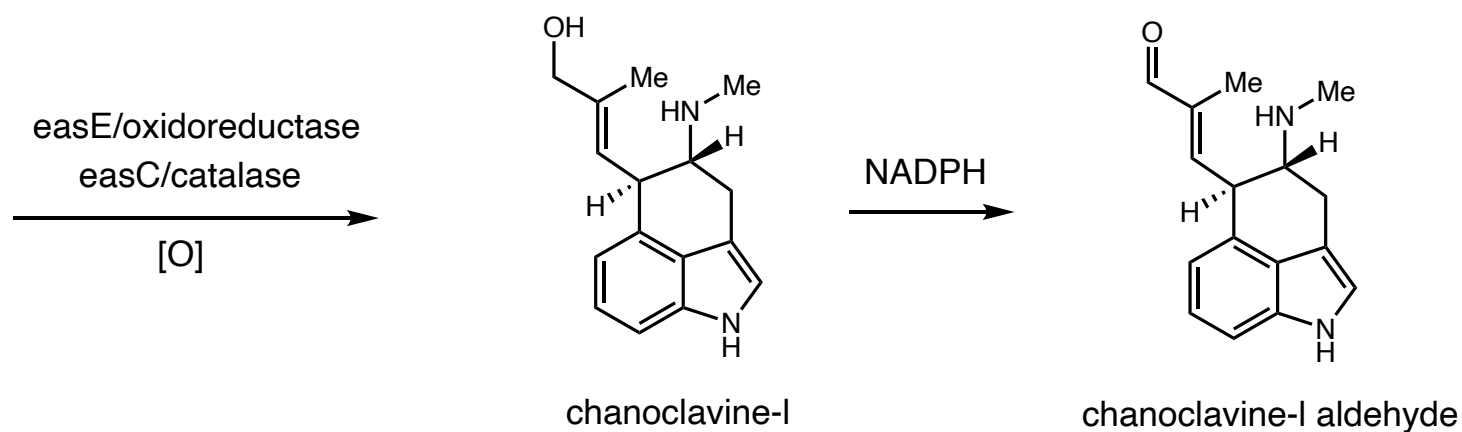
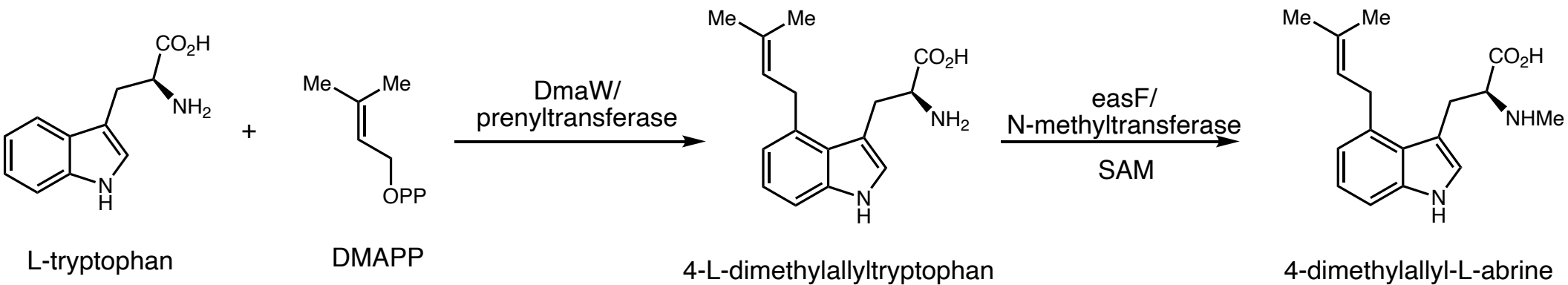
Biosynthesis of Lysergic Acid



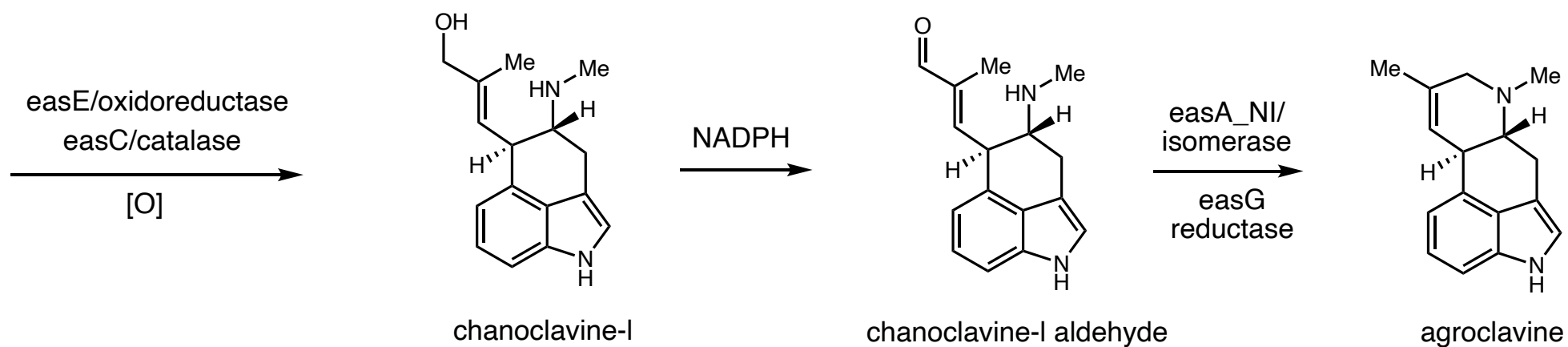
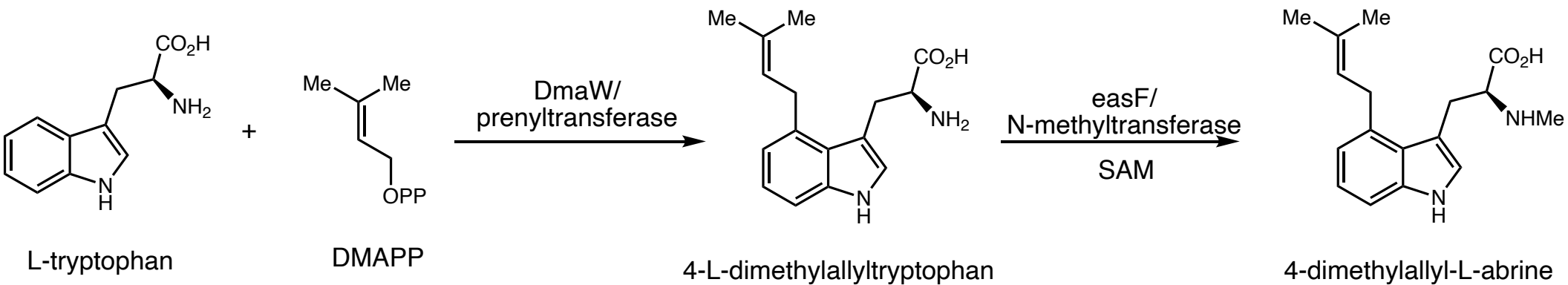
Biosynthesis of Lysergic Acid



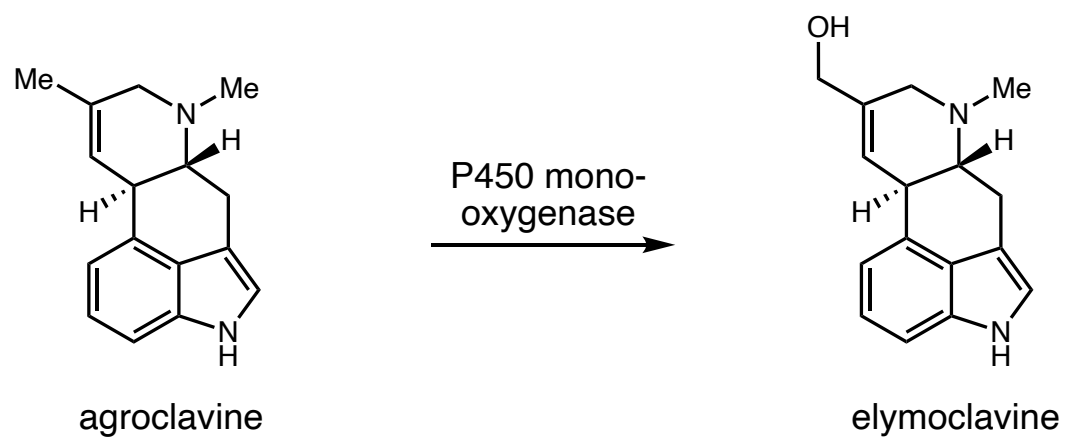
Biosynthesis of Lysergic Acid



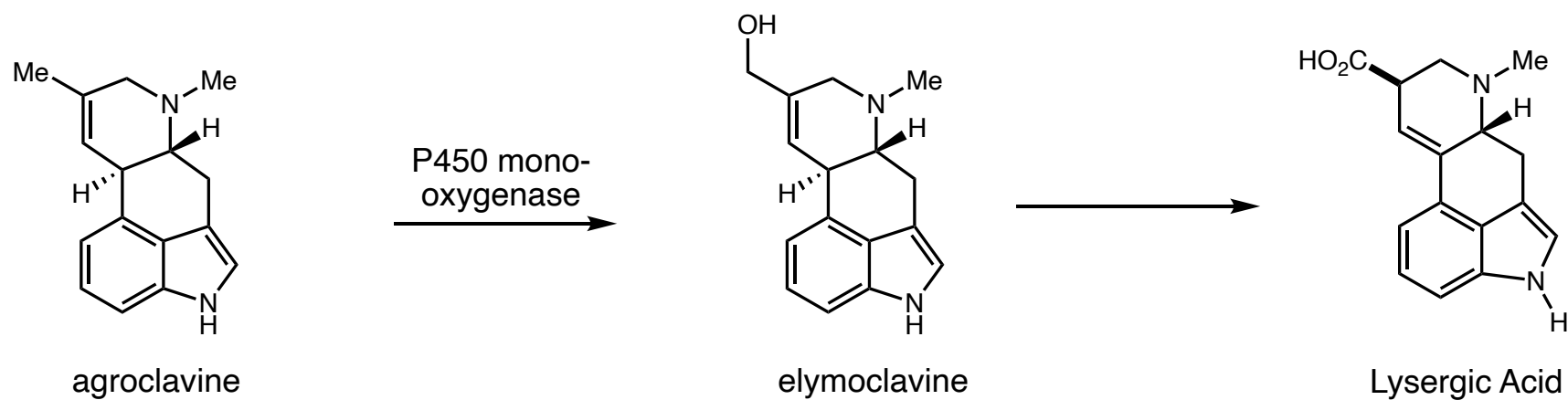
Biosynthesis of Lysergic Acid



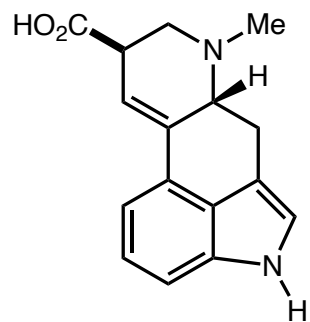
Biosynthesis of Lysergic Acid



Biosynthesis of Lysergic Acid

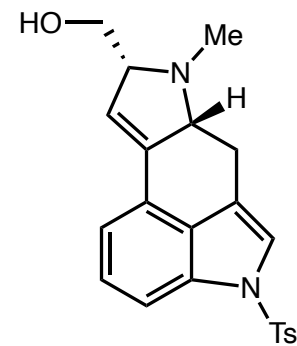
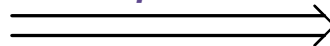


Synthetic Plan

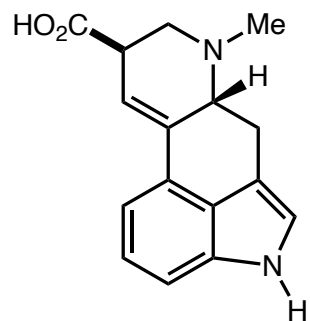


Lysergic Acid

*ring-expansion
sequence*

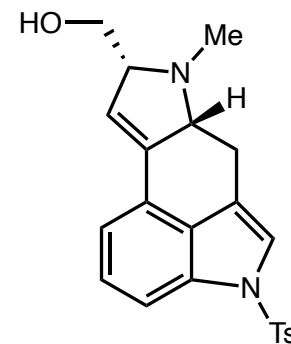


Synthetic Plan

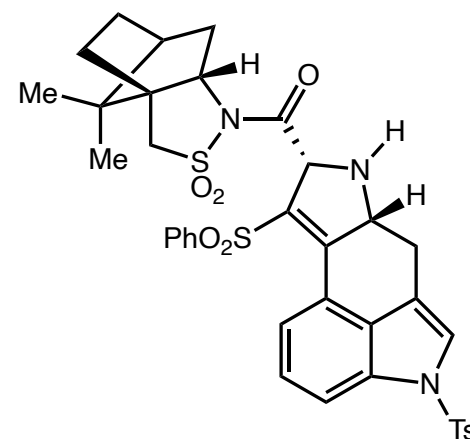


Lysergic Acid

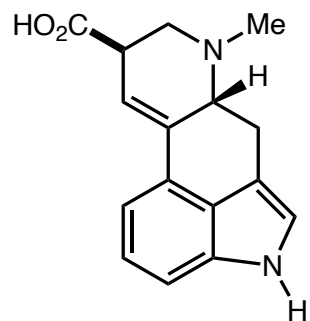
*ring-expansion
sequence*



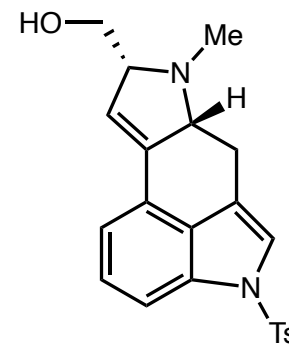
*functional group
manipulation*



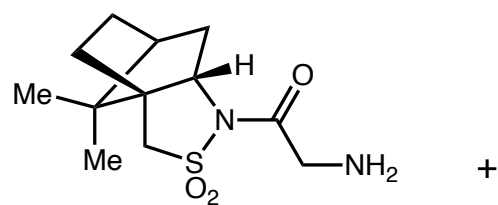
Synthetic Plan



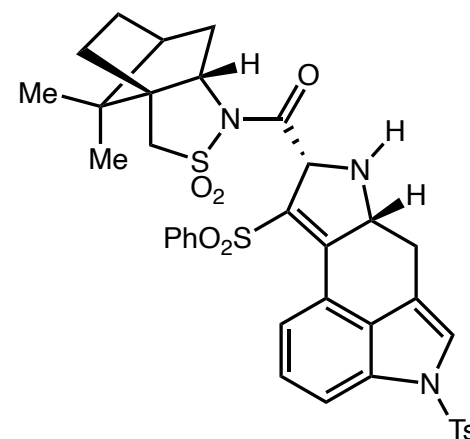
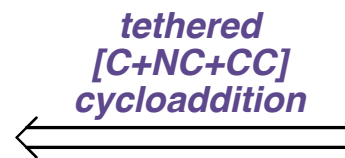
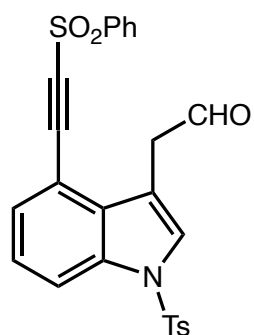
Lysergic Acid



*functional group
manipulation*

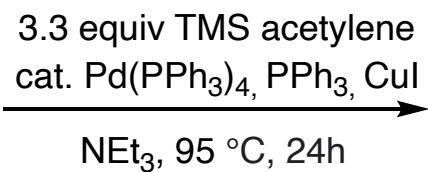
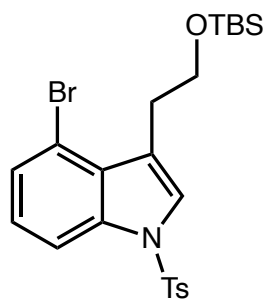


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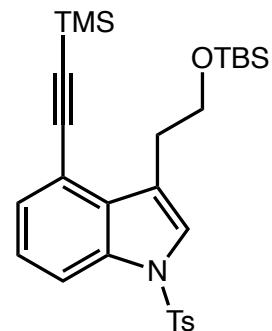


Synthesis of Lysergic Acid

Forward Synthesis-Indole Component



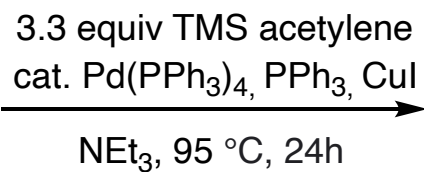
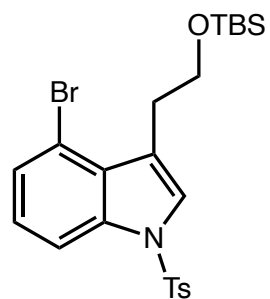
98% yield



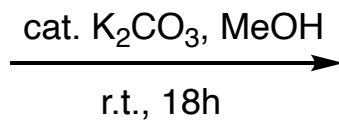
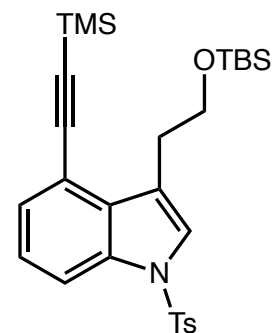
5 steps from 4-bromoindole

Synthesis of Lysergic Acid

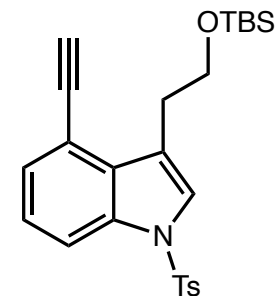
Forward Synthesis-Indole Component



98% yield



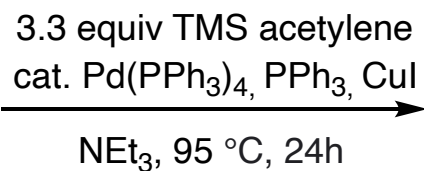
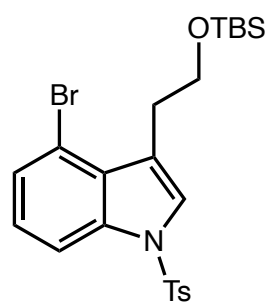
97% yield



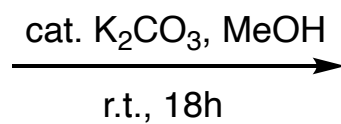
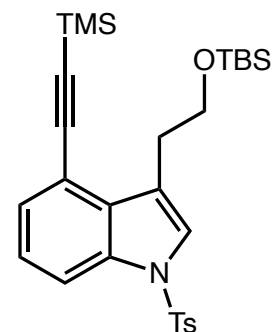
5 steps from 4-bromoindole

Synthesis of Lysergic Acid

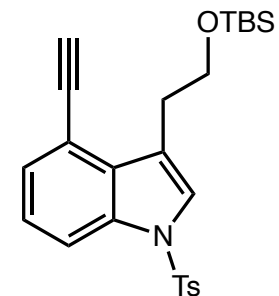
Forward Synthesis-Indole Component



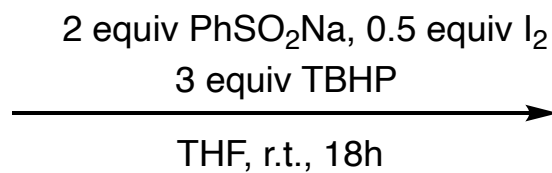
98% yield



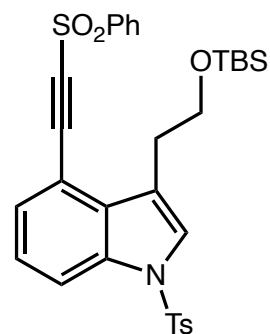
97% yield



5 steps from 4-bromoindole

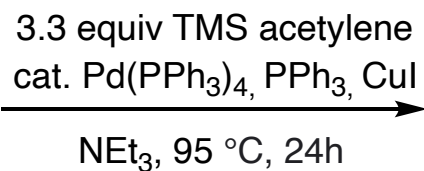
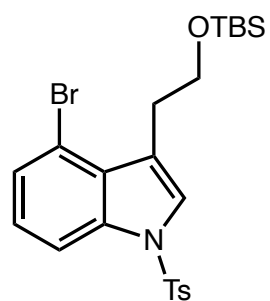


70% yield

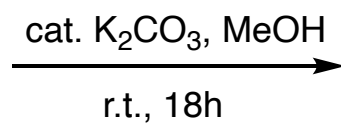
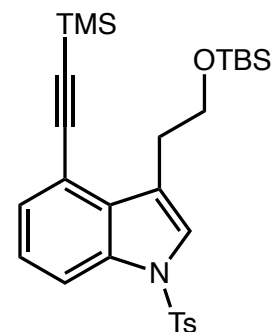


Synthesis of Lysergic Acid

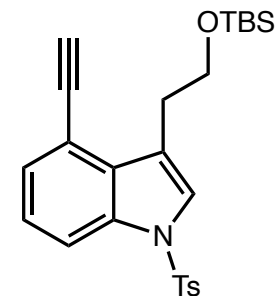
Forward Synthesis-Indole Component



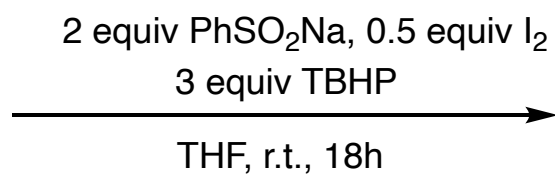
98% yield



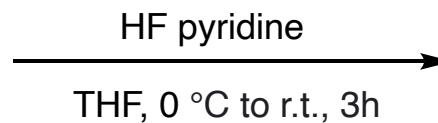
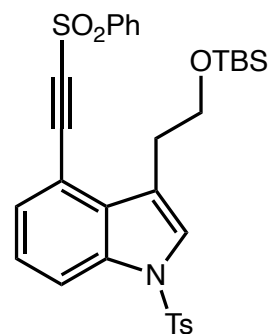
97% yield



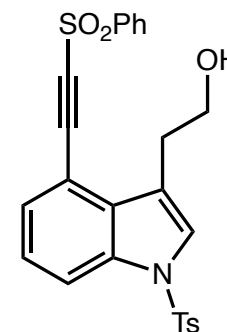
5 steps from 4-bromoindole



70% yield

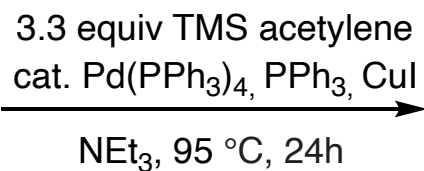
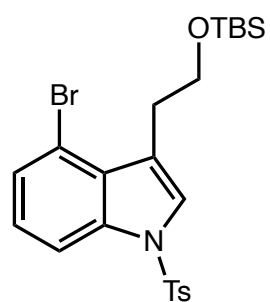


90% yield

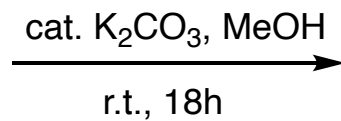
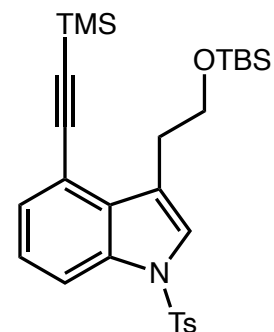


Synthesis of Lysergic Acid

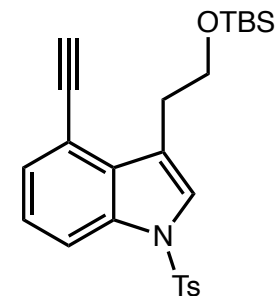
Forward Synthesis-Indole Component



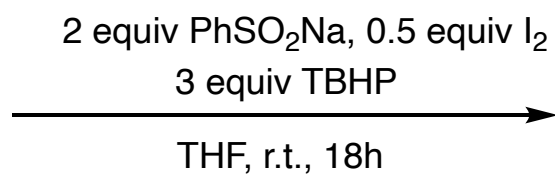
98% yield



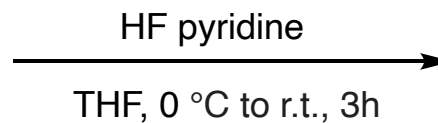
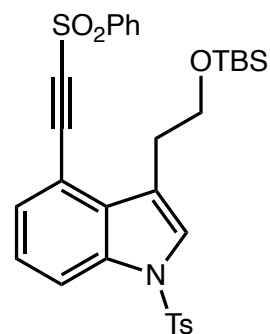
97% yield



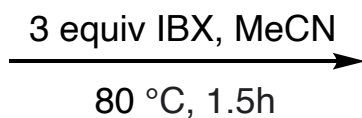
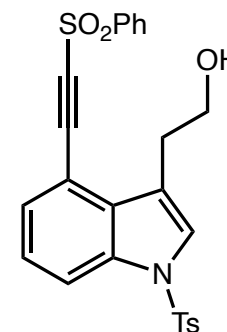
5 steps from 4-bromoindole



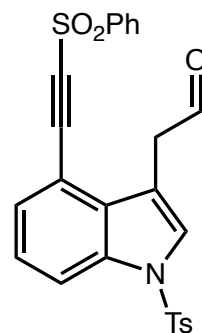
70% yield



90% yield

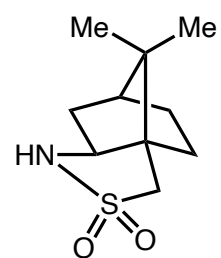


quant. yield



Synthesis of Lysergic Acid

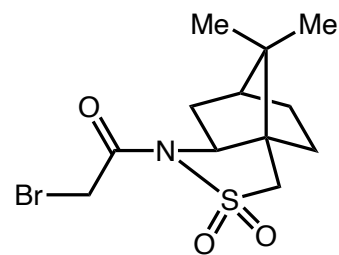
Forward Synthesis-NC Component



(2S)-bornane-2,10-sultam

1. 1.1 equiv n-BuLi
THF, -78 °C, 1h

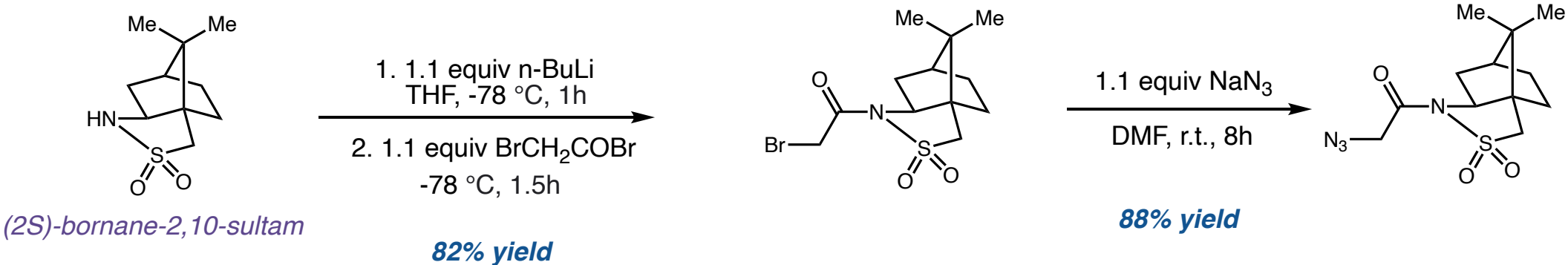
2. 1.1 equiv BrCH₂COBr
-78 °C, 1.5h



82% yield

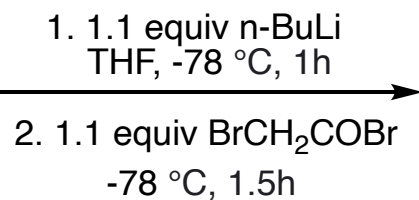
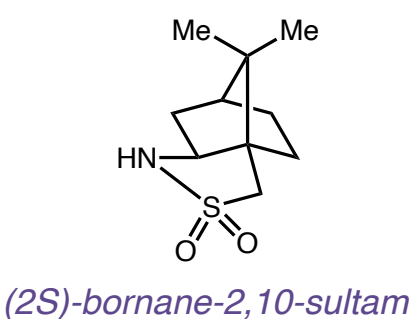
Synthesis of Lysergic Acid

Forward Synthesis-NC Component

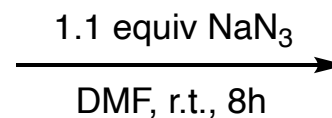
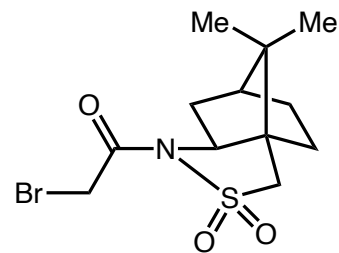


Synthesis of Lysergic Acid

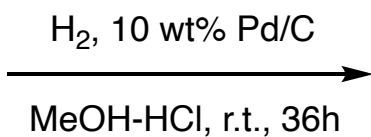
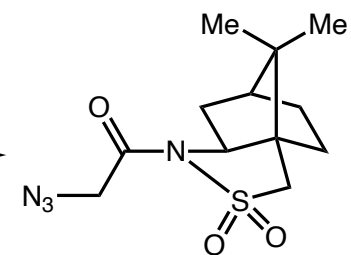
Forward Synthesis-NC Component



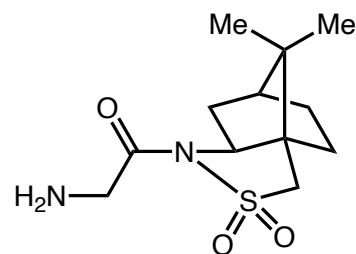
82% yield



88% yield

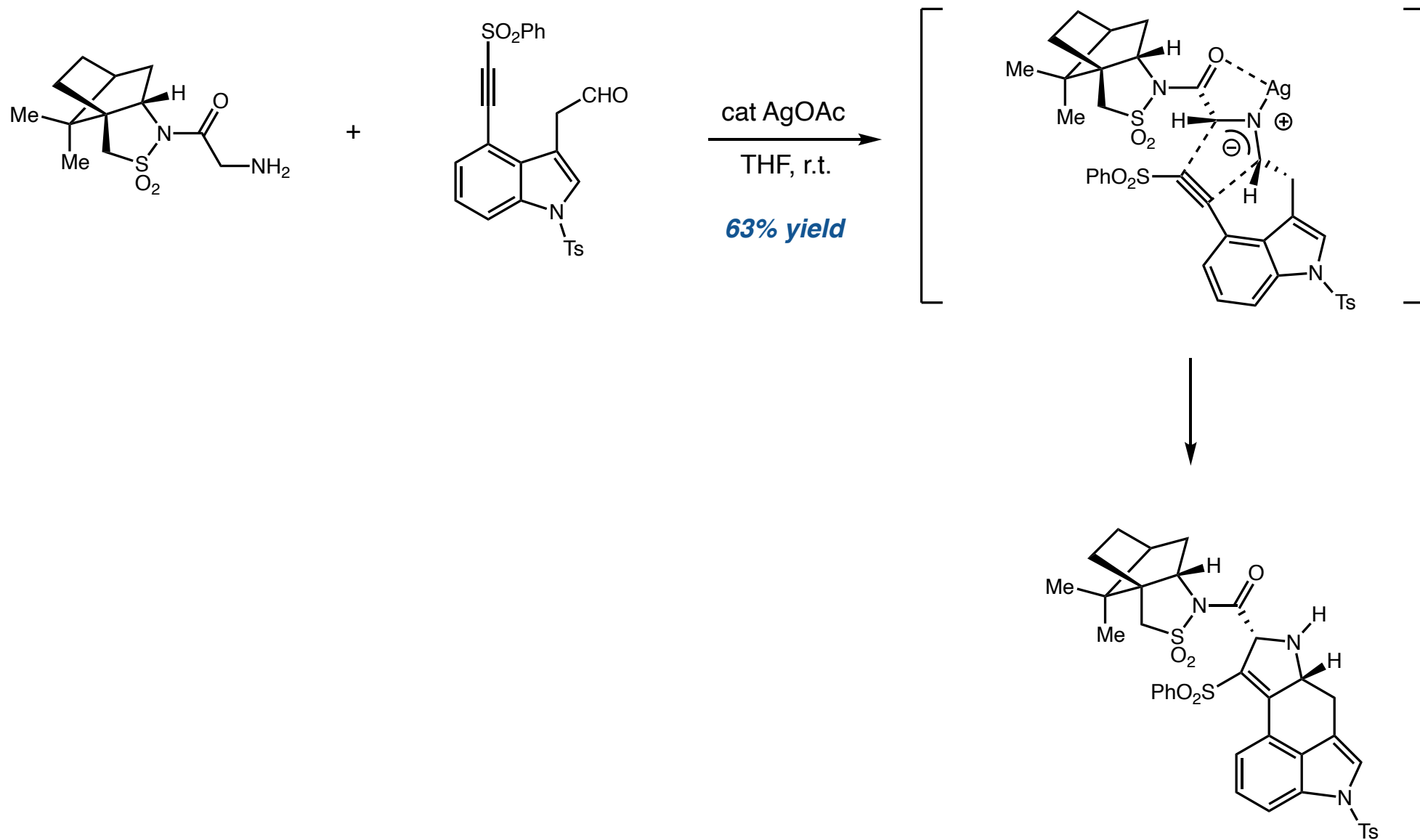


91% yield



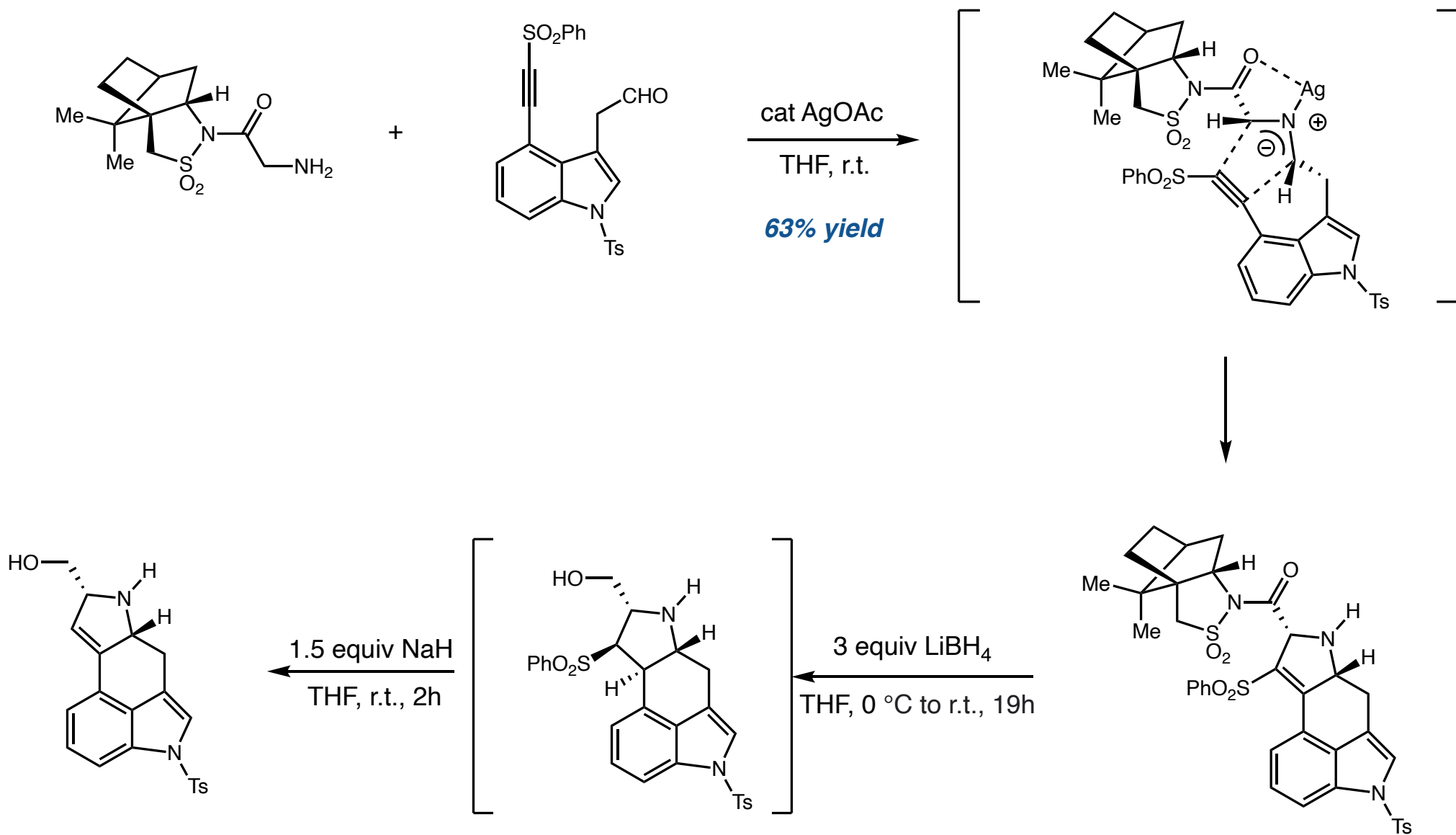
Synthesis of Lysergic Acid

Forward Synthesis-Assembly Key Step



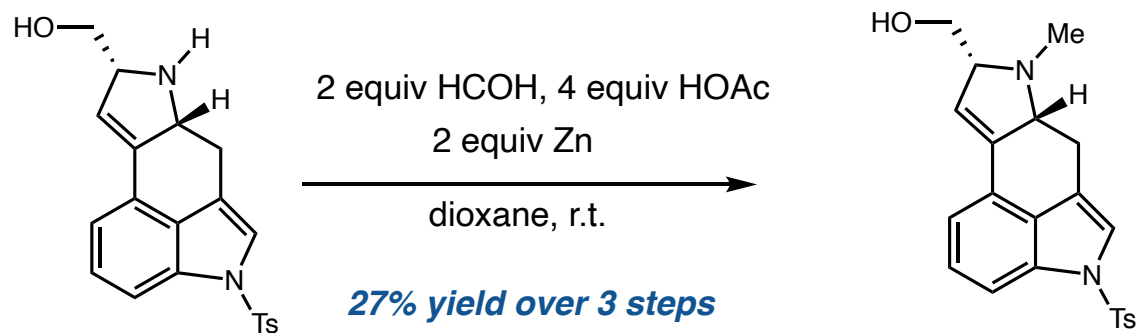
Synthesis of Lysergic Acid

Forward Synthesis-Assembly Key Step



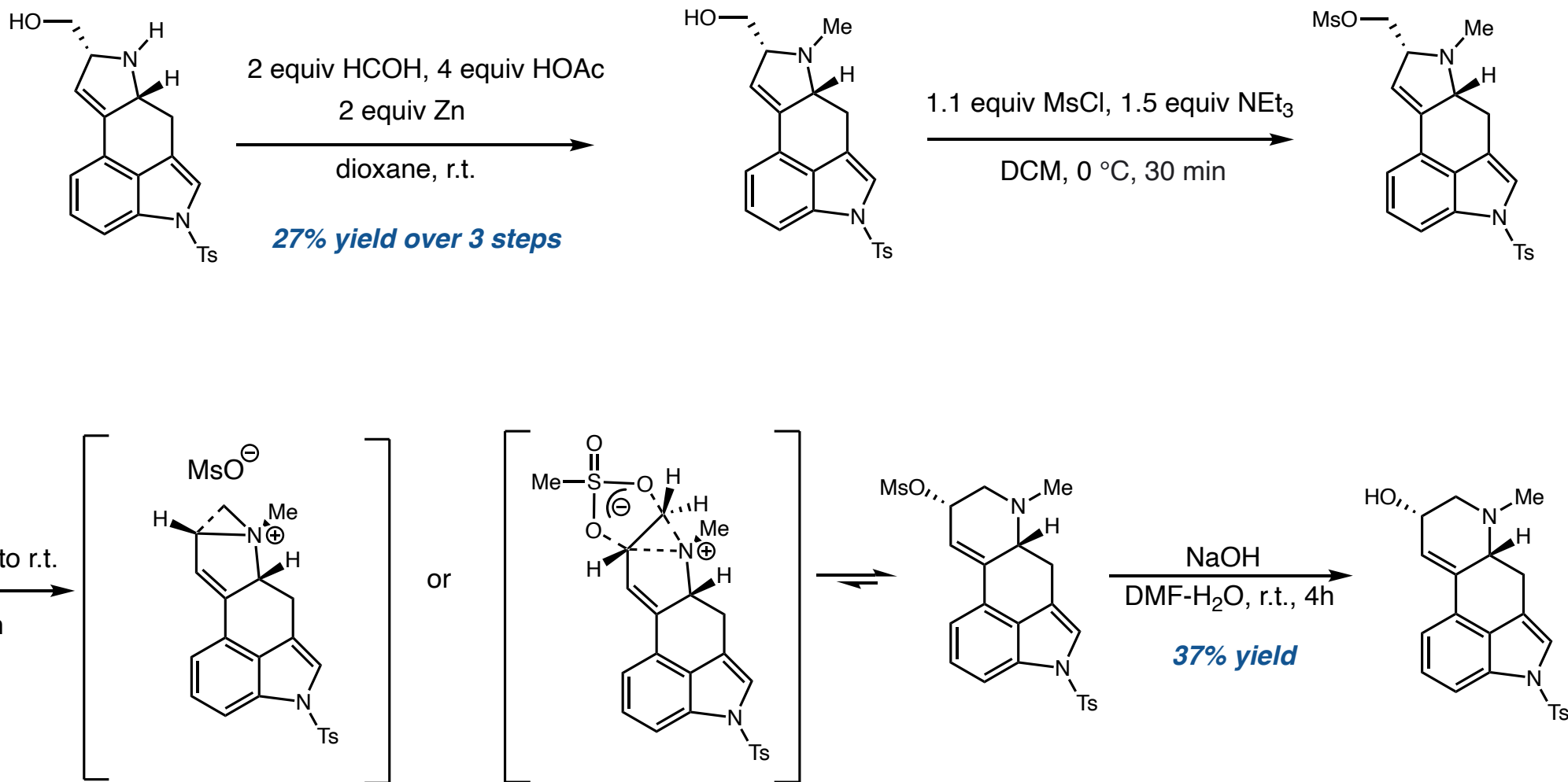
Synthesis of Lysergic Acid

Forward Synthesis



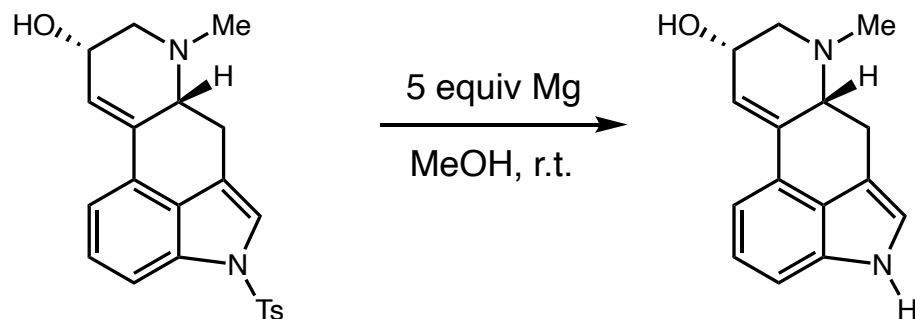
Synthesis of Lysergic Acid

Forward Synthesis



Synthesis of Lysergic Acid

Endgame

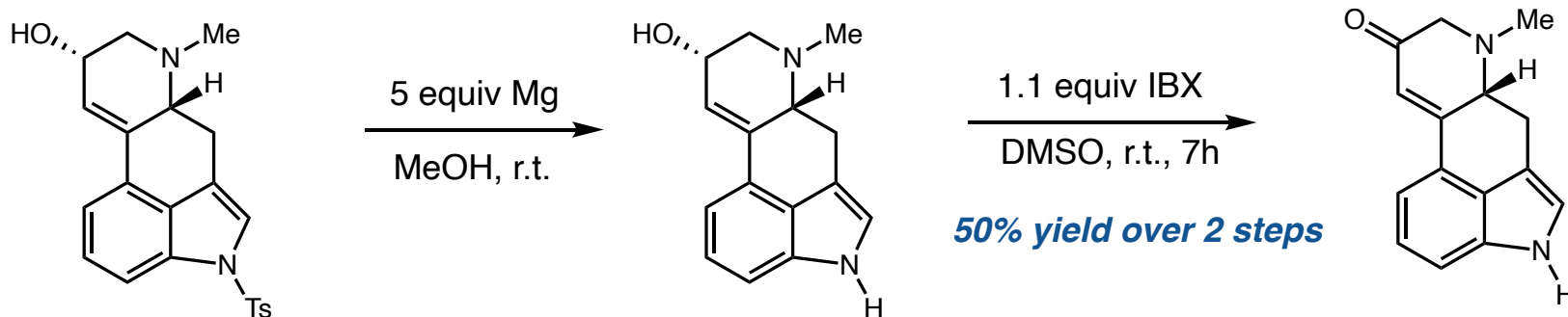


Rathnayake. U, Garner. P, *Org. Lett.* **2021**, 23, 17, 6756-6759;

Moldvai. I, Temesvari-Major. E, Incze. M, Szentirmay. E, Gacs-Baitz. E, Szantay. C, *J. Org. Chem.* **2004**, 69, 5993-6000

Synthesis of Lysergic Acid

Endgame

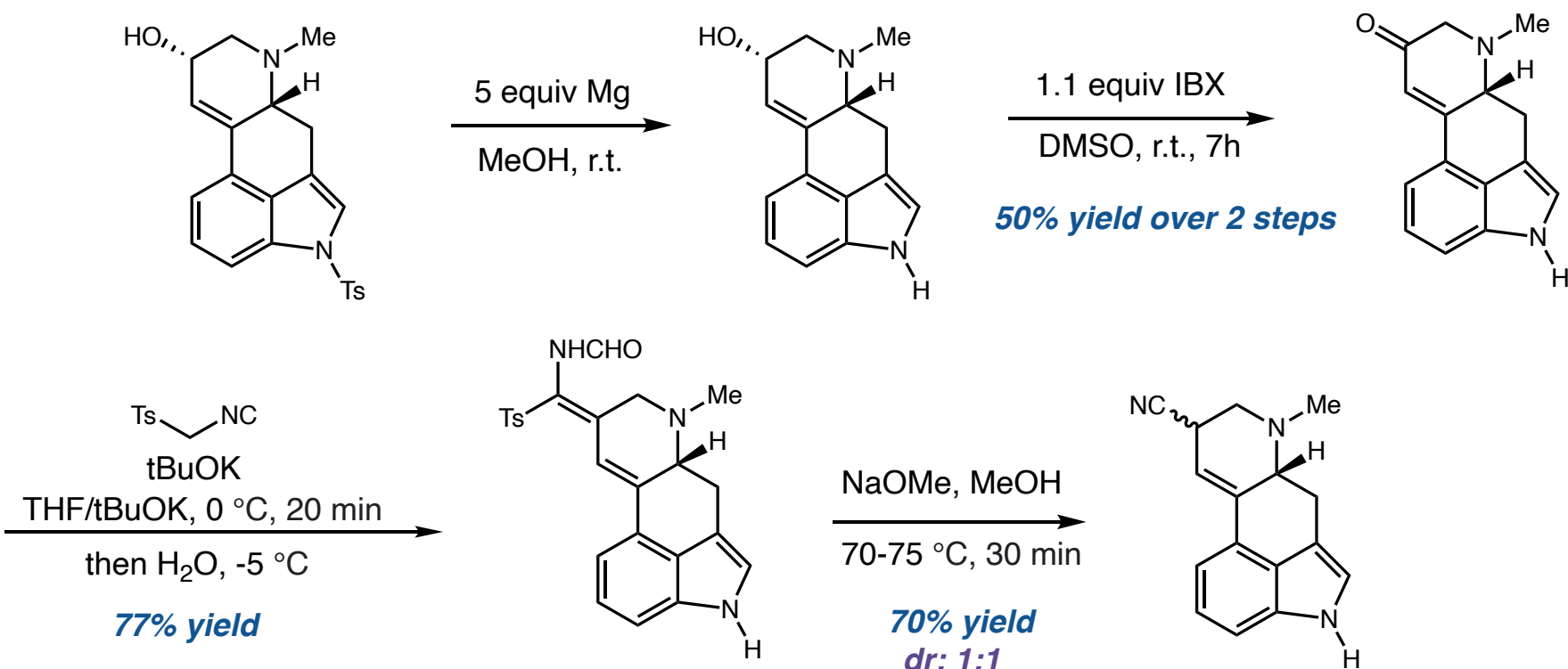


Rathnayake. U, Garner. P, *Org. Lett.* **2021**, 23, 17, 6756-6759;

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Synthesis of Lysergic Acid

Endgame

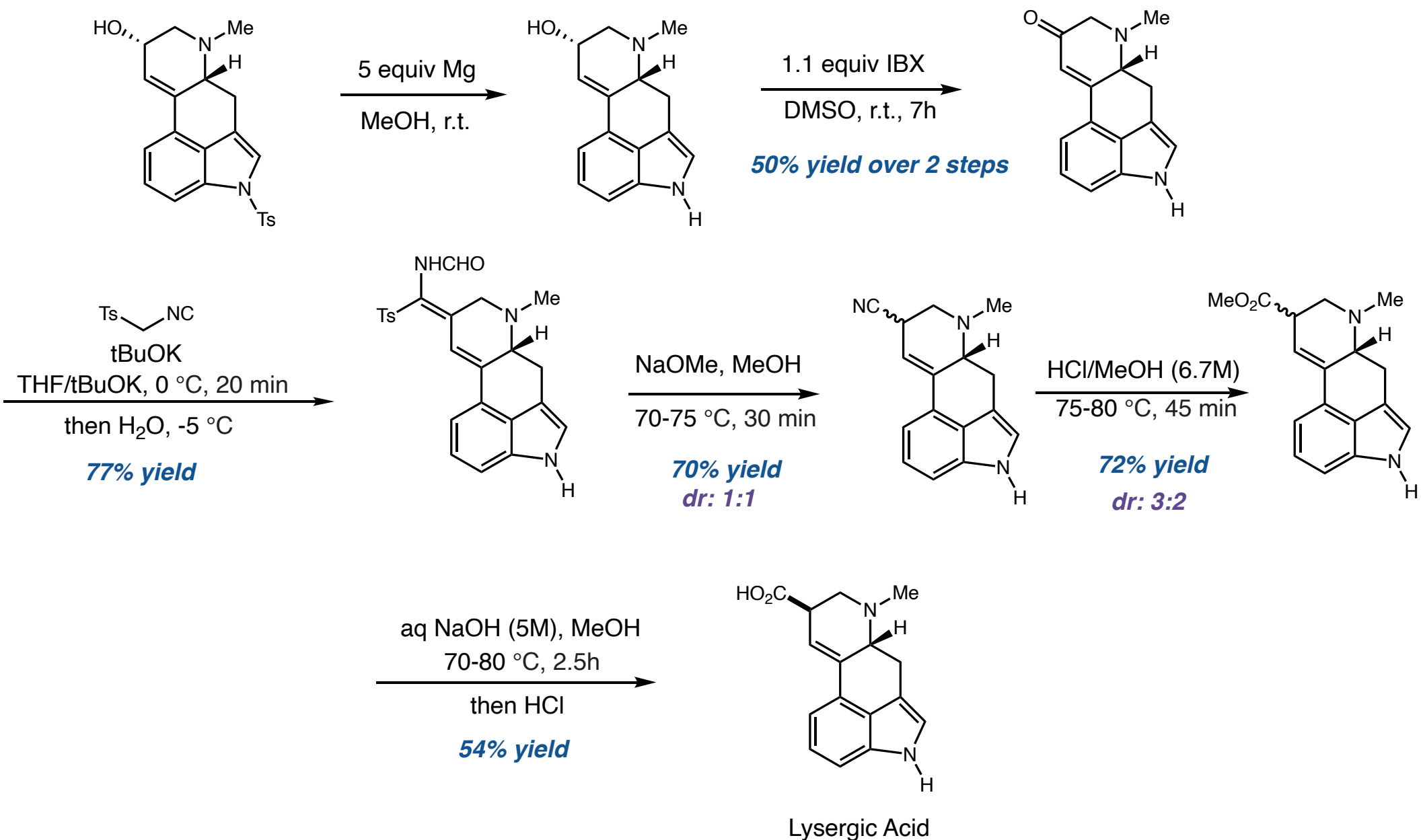


Rathnayake. U, Garner. P, *Org. Lett.* **2021**, 23, 17, 6756-6759;

Moldvai. I, Temesvari-Major. E, Incze. M, Szentirmay. E, Gacs-Baitz. E, Szantay. C, *J. Org. Chem.* **2004**, 69, 5993-6000

Synthesis of Lysergic Acid

Endgame



Rathnayake. U, Garner. P, *Org. Lett.* **2021**, 23, 17, 6756-6759;

Moldvai. I, Temesvari-Major. E, Incze. M, Szentirmay. E, Gacs-Baitz. E, Szantay. C, *J. Org. Chem.* **2004**, 69, 5993-6000