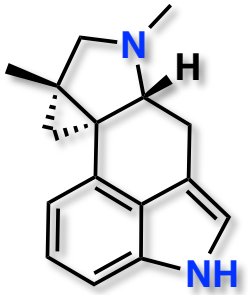
A Second Generation Total Synthesis of (±)-Cycloclavine and Progress Toward an Asymmetric Total Synthesis of (+)-Cycloclavine



Steph McCabe
Research Topic Seminar
30th January 2016

Overview

PART 1:

1.1 Ergot alkaloids

- Classification
- Natural sources/ history
- Biological activity and use as pharmaceuticals

1.2 Clavine Alkaloids

- Classification/ examples
- Biosynthesis of clavine alkaloids
- Summary of recent syntheses of clavine alkaloids based on strategic disconnections
  - Clavicipitic acid
  - Aurantioclavine
  - Rugulovasine A & B
  - Cycloclavine
- Recent syntheses of cycloclavine

PART 2:

Experimental Data

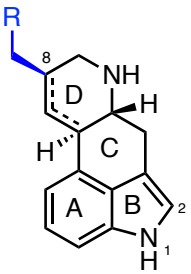
- Retrosynthetic analysis
- Second generation total synthesis of cycloclavine
- Efforts toward an asymmetric synthesis of cycloclavine
- Future directions
- Conclusions

Classification of Ergot Alkaloids

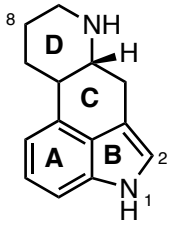
ERGOT ALKALOIDS

Clavines

R = H or OH

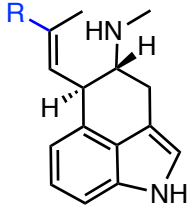


tetracyclic clavines
(ergolines)

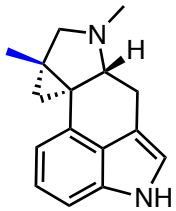


Ergoline Core

R = H, CH_2OH, CHO

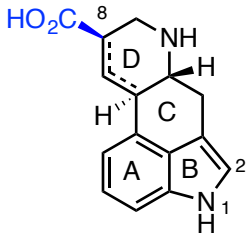


tricyclic clavines
(secoergolines)

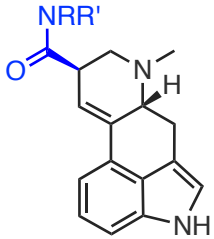


Rearranged clavines

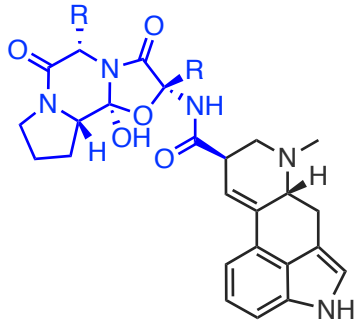
Lysergic Acid



lysergic acid



Lysergic acid amides



ergopeptines

Ergot Alkaloids
Occurrence of Ergot Alkaloids in Nature

- Ergot alkaloids are produced by the *Clavicipitaceae* and *Trichocomaceae* families of filamentous fungi
- These fungi infect cereal grains causing ‘ergot’
- The fungi have a symbiotic relationship with the plant causing no symptoms of infection
  - Ergot alkaloids produced by the fungi help protect the plant from predation and improve growth, while the fungi gain nutrition and shelter from the plant

Ergot on wheat stalks

fruiting *C. purpurea* sclerotia

Nat. Prod. Rep., **2011**, *28*, 496
Nat. Prod. Rep., **2014**, *31*, 1328

History
Ergot & Ergotism

- Consumption of ergot contaminated grains leads to ergotism (St. Anthony's fire), a disease common in central Europe in the middle ages

- Two types of ergotism are recognized:
  - ergotismus convulsivus: characterized by hallucinations, convulsions, confusion and irrational behaviour
  - ergotismus gangrenous: characterized by gangrene of the feet, legs, hands and arms

- Ergotism in humans is now rare due to strict guidelines governing the acceptable concentration of ergot bodies in grain, however ergotism still produces serious epidemics in livestock fed contaminated grain.

- Modern control of ergot is focused on limiting the presence of sclerotia in cereal grains largely through preventative measures or in particularly bad seasons crops can be saved by separating the ergot kernels from cereal grains based on density or colour

Biological Activity of Ergot Alkaloids

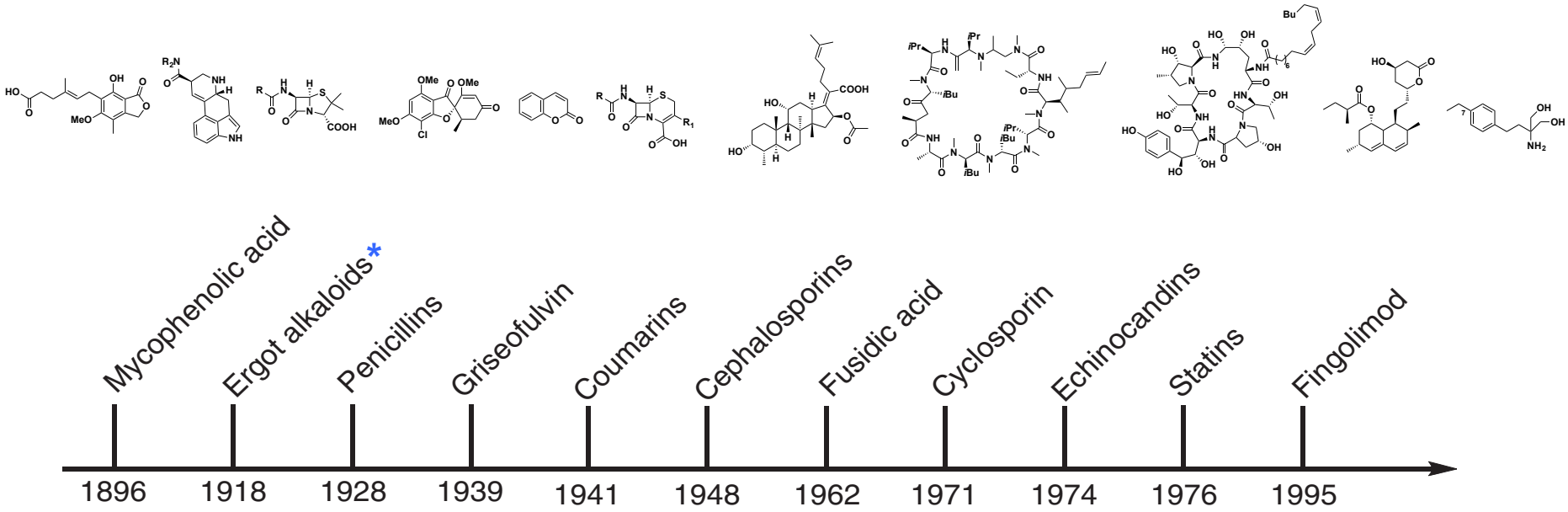


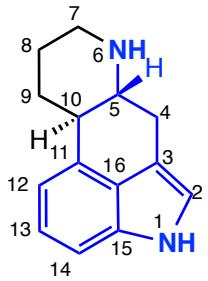
Figure 1. Timeline of the initial discovery of pharmaceutical classes of fungal metabolites

- These classes of fungal metabolites have produced some of the best known/ profitable pharmaceuticals in human medicine
  - Anti-cholesterol statins e.g. rosuvastatin (*crestor*), atorvastatin (*lipitor*), antibiotic penicillin and immunosuppressant cyclosporin A
- Ergot alkaloids possess the widest spectrum of biological activity
  - Ranging from anti-migraine to anti-Parkinson agents

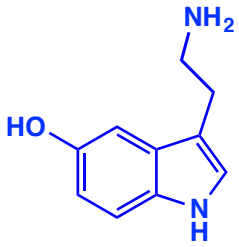
Aus. J. Chem., **2014**, *67*, 827

Biological Activity of Ergot Alkaloids

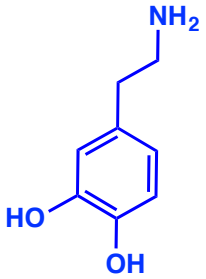
- The broad spectrum of bioactivity exhibited by ergot alkaloids is due to their structural similarity to natural neurotransmitters



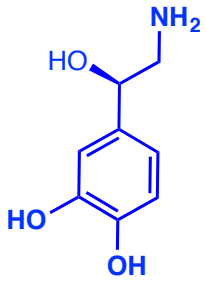
Ergoline



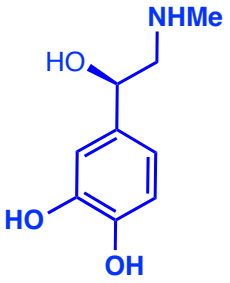
serotonin (5-HT)



dopamine (DA)



norepinephrine (noradrenalin)

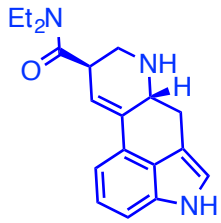


epinephrine (adrenalin)

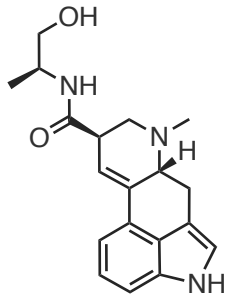
- Ergot alkaloid drugs generally act by mimicking (agonist) or blocking (antagonist) the binding of natural neurotransmitters to their receptors

Ergot Alkaloid Pharmaceuticals

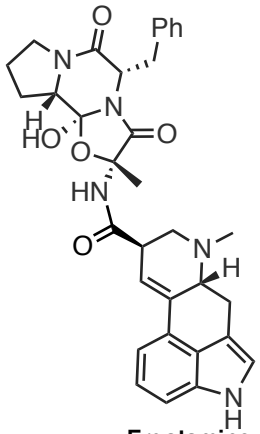
- The majority of ergot alkaloid pharmaceuticals are semi-synthetically prepared from lysergic acid derivatives



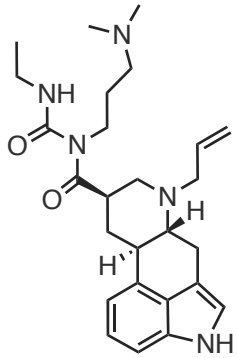
Lysergic acid diethylamide (LSD)



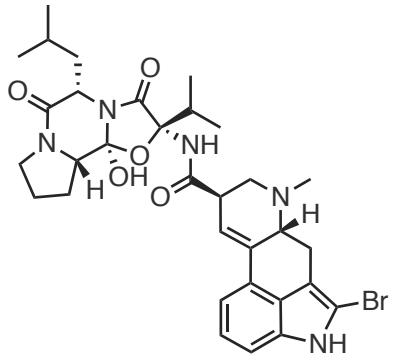
Ergometrine
prevents post partum haemorrhage
MOA: a-1A adrenergic agonist
5-HT_2 agonist



Ergotamine
migraine treatment
MOA: 5-HT_{1B} agonist



Cabergoline
Parkinson's disease
MOA: D_2 agonist



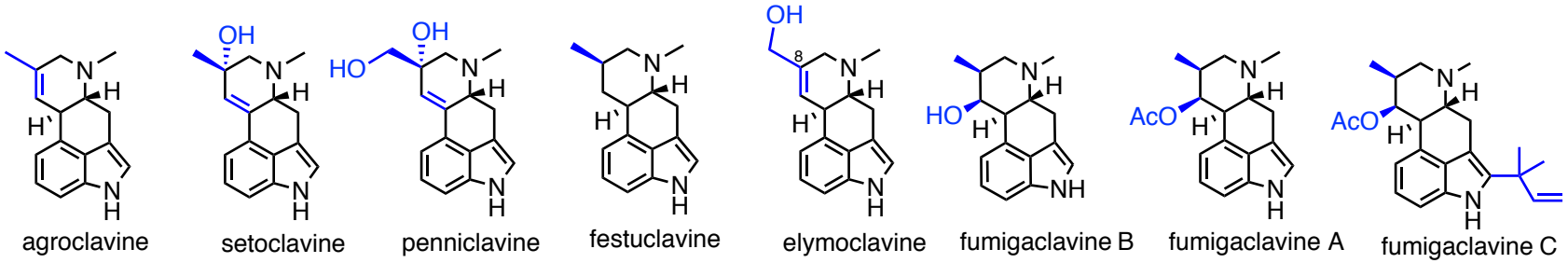
Bromocriptine
Parkinson's disease
Type 2 diabetes
MOA: D_2 agonist

Clavine Alkaloids

1.2 Clavine Alkaloids

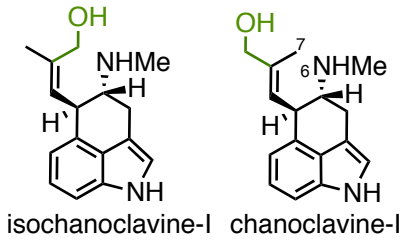
- Classification/ examples
- Biosynthesis of clavine alkaloids
- Summary of recent syntheses of clavine alkaloids based on strategic disconnections
  - Clavicipitic acid
  - Aurantioclavine
  - Rugulovasine A & B
  - Cycloclavine
- Recent syntheses of cycloclavine

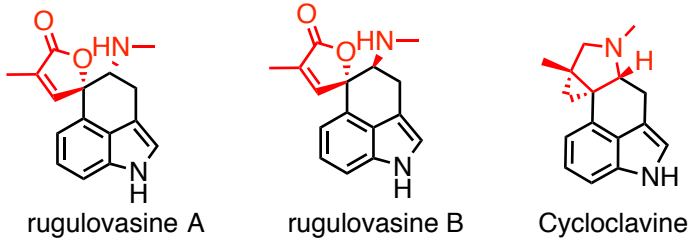
Clavine Alkaloids

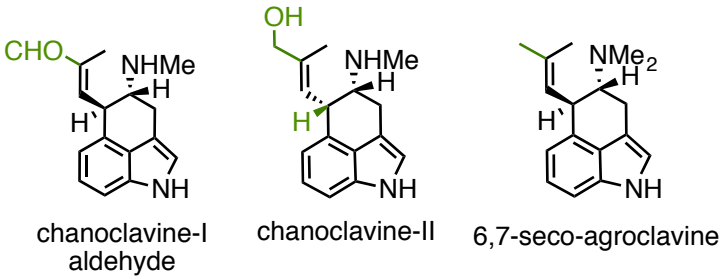


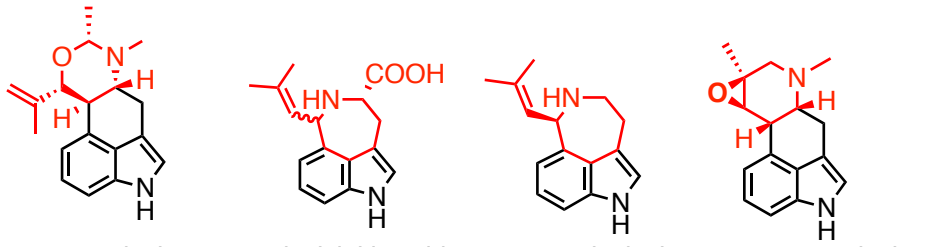
tetracyclic clavines

tricyclic clavines ← **Clavine Alkaloids** → **Rearranged clavines**



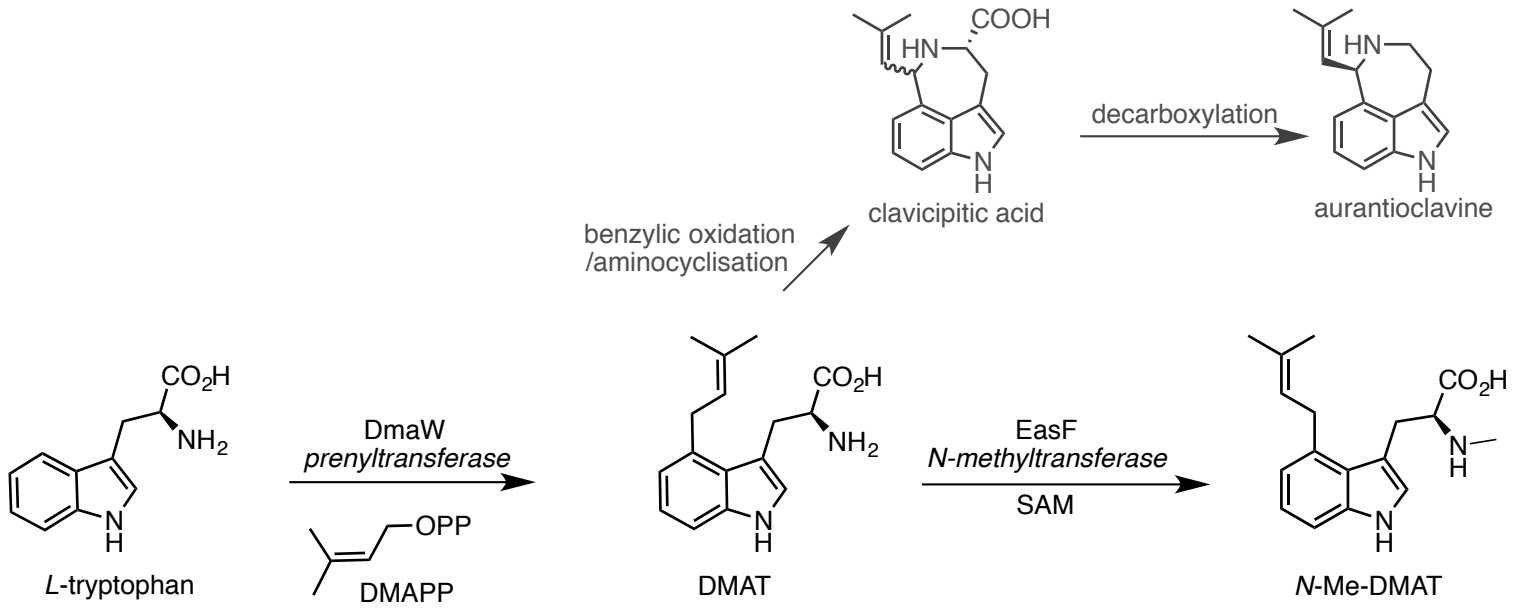






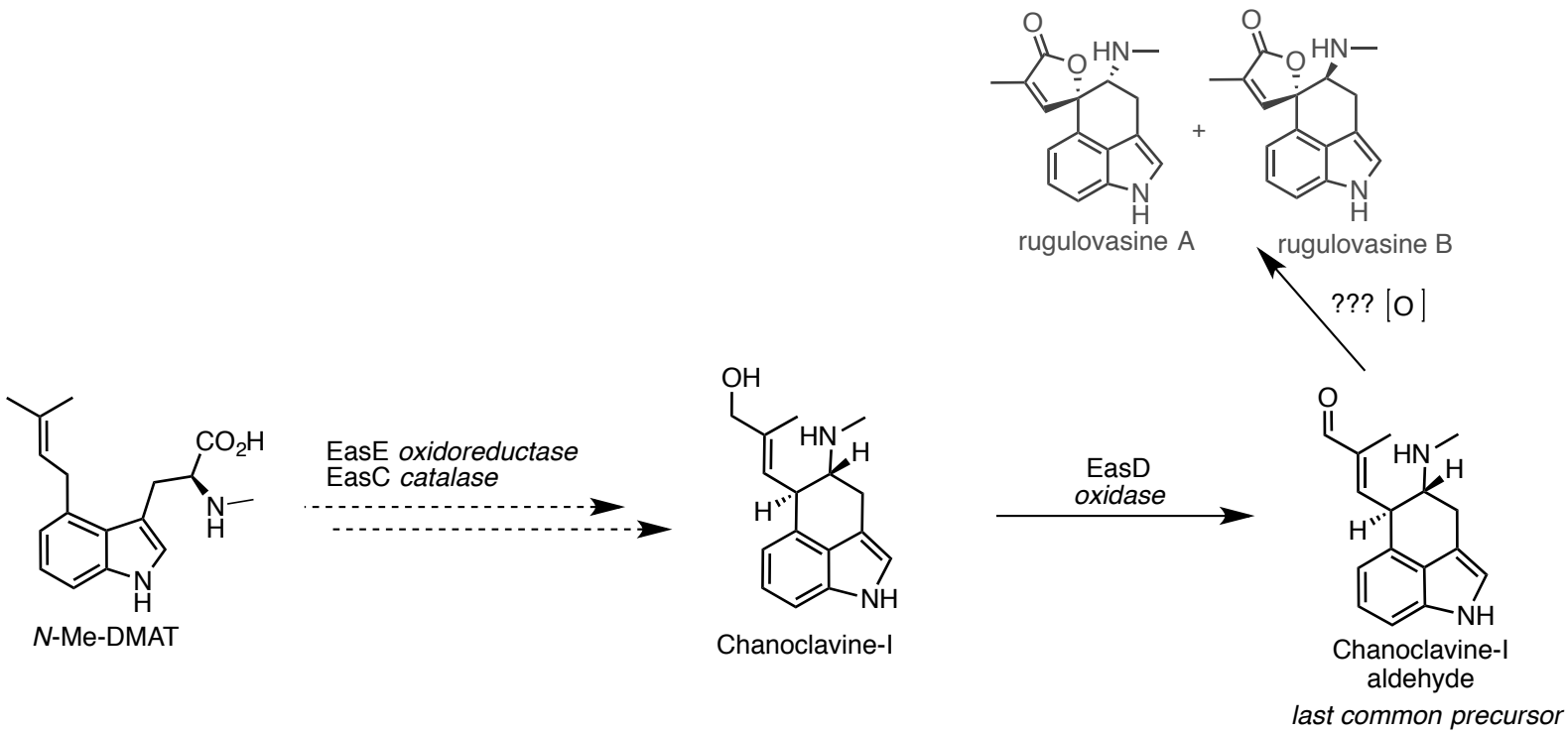
Biosynthesis of Clavine Alkaloids

- The first 5 steps in the biosynthetic pathway are common to all *ergot* alkaloids and are responsible for the formation of the core ergoline scaffold
    - Most diversification occurs late stage *via* functionalization of ergoline core however, in some fungi diversification can occur early on *via* short diverted pathways

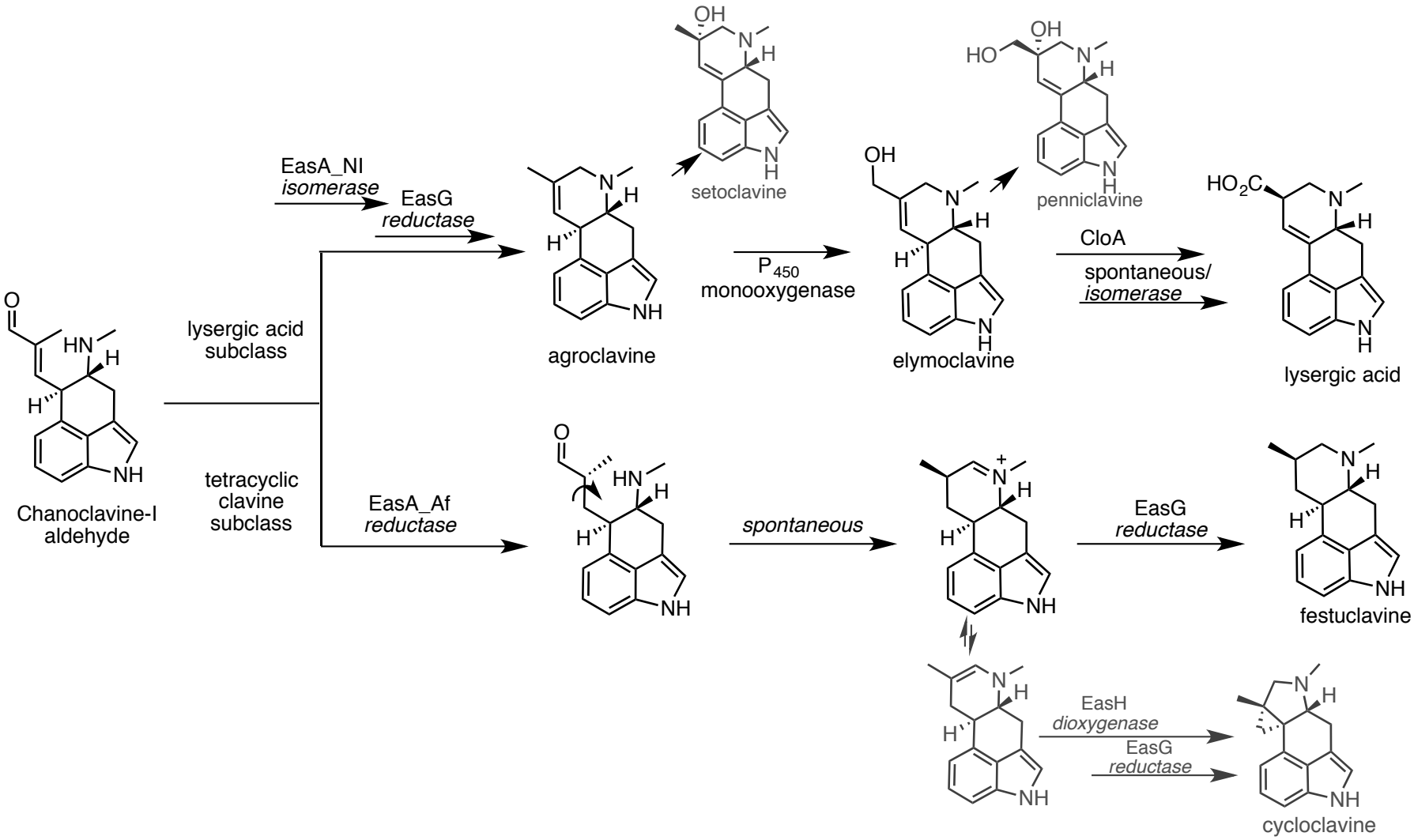


ACIE, **2015**, *54,* 3004-3007 (aurantioclavine)
J. Org. Chem., **1980**, *45*, 1117 (clavicipitic acid)
Nat. Prod. Rep., **2011**, *28*, 496
Toxins, **2014**, *6*, 3281
Nat. Prod. Rep., **2014**, *31*, 1328

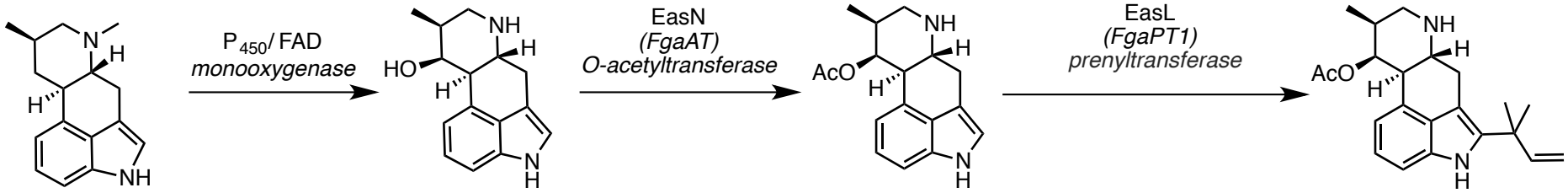
Biosynthesis of Clavine Alkaloids



Biosynthesis of Clavine Alkaloids

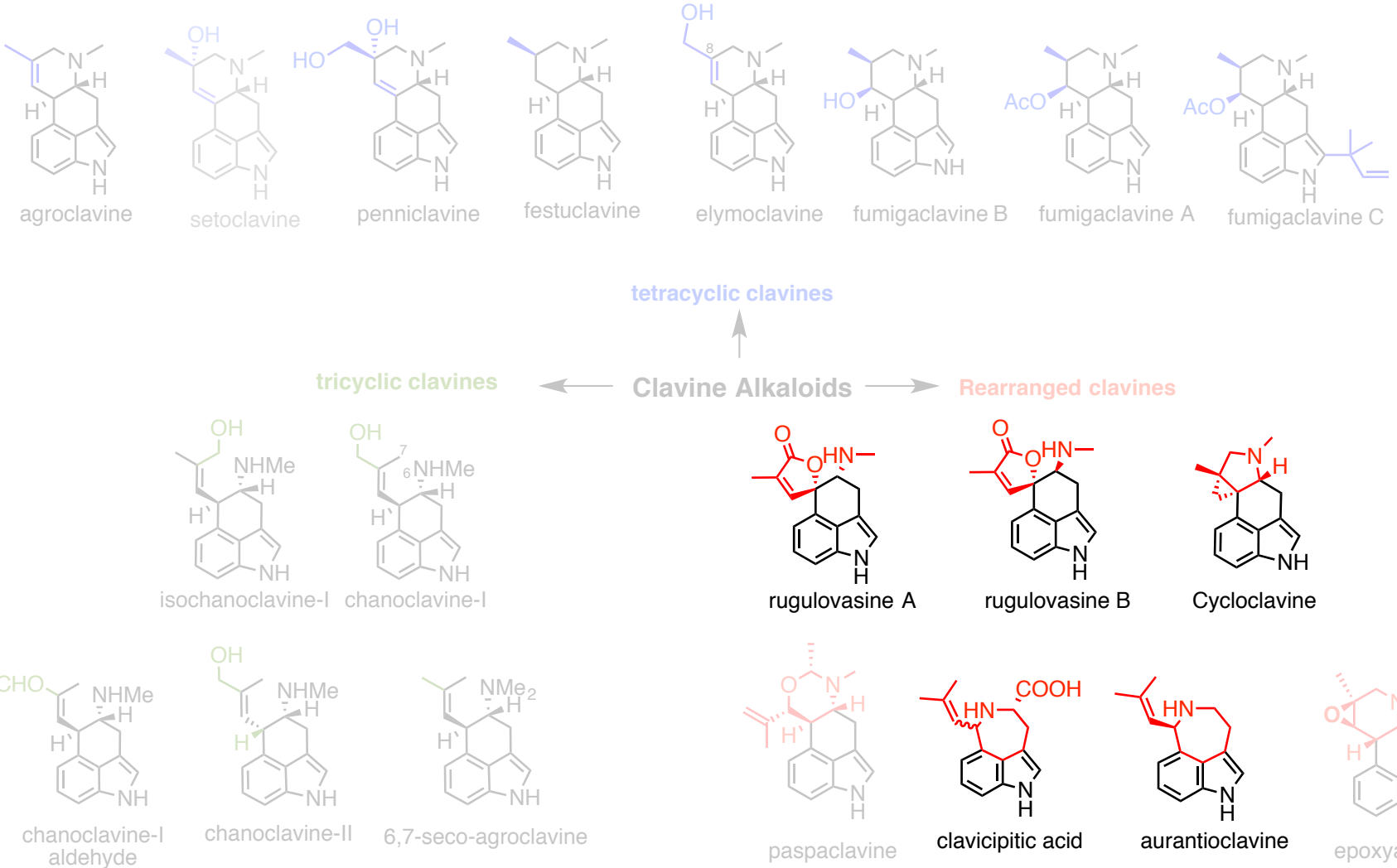


Biosynthesis of Clavine Alkaloids

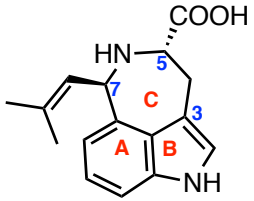


festuclavine | fumigaclavine B | fumigaclavine A | fumigaclavine C

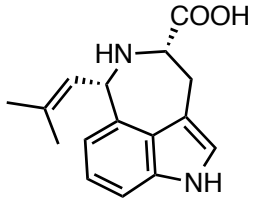
Recent Synthetic Approaches to *Clavine* Alkaloids



Recent Synthetic Approaches to *Clavine* Alkaloids
Clavicipitic Acid



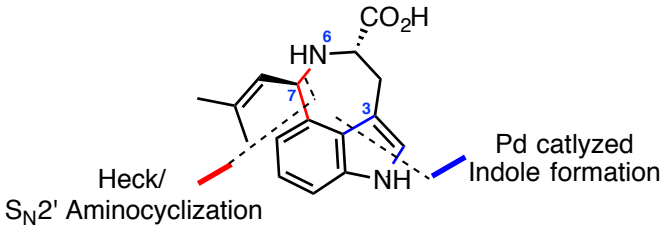
(-)-*trans* clavicipitic acid



(-)-*cis* clavicipitic acid

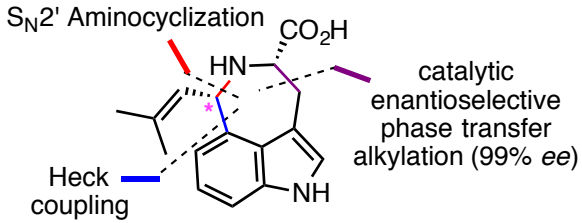
- Clavicipitic acid is a rearranged clavine alkaloid that was isolated as a mixture of naturally occurring *cis* and *trans* diastereomers from *Claviceps* species of fungi. (*fusiformis* and *claviceps* SD 58)
- Unusual azepinoindole core bearing two stereocentres presents an interesting synthetic challenge

JIA (2010)



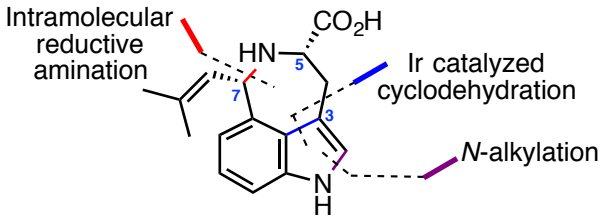
7 steps, 34% overall yield *trans*
7 steps, 7% overall yield *cis*

PARK (2007)



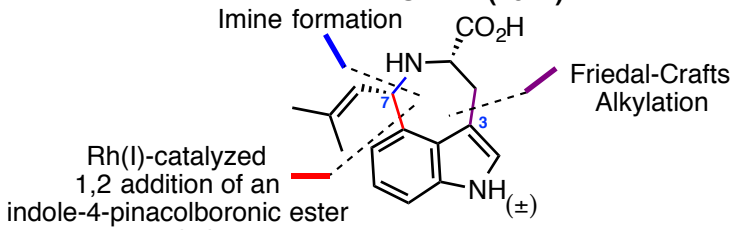
11 steps, ~20 % overall yield

SHIBATA (2015)



9 steps (to CO_2Me)
15% overall yield (" ")

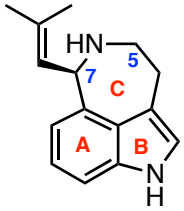
PIERSANTI (2014)



4 steps, 34% overall yield

JOC, **2014**, *79*, 3255; *JOC*, **2010**, *75*, 7626; *JOC*, **2007**, *72*, 8115; *Eur. J. Org. Chem.*, **2004**, 1244; *Chem. Eur. J.*, **2015**, 11340

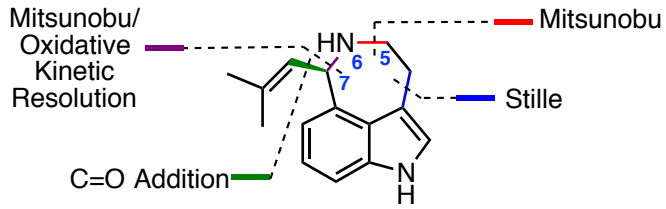
Recent Synthetic Approaches to *Clavine* Alkaloids
Aurantioclavine



(-)-Aurantioclavine

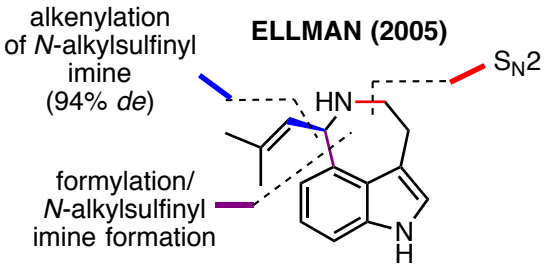
- Same azepinoindole core as Clavicipitic acid
- Isolated in 1981 from the fungus *penicillium aurantiovirens*
- Absolute Stereochemistry was determined to be 7R by Stoltz (based on X-ray analysis of an advanced intermediate)

STOLTZ (2008)



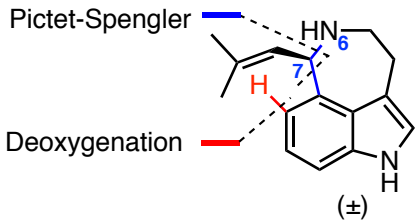
13 steps, <1% overall yield

ELLMAN (2005)



6 steps, 27% overall yield

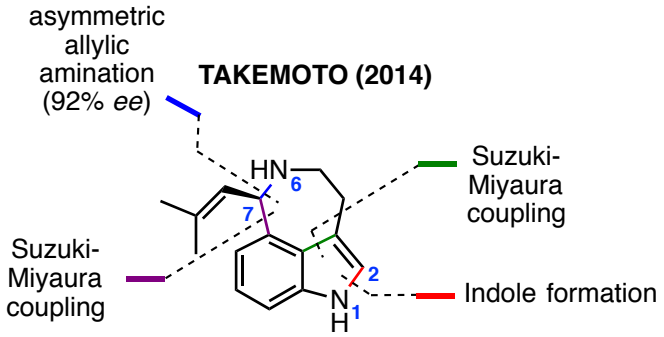
ISHIKURA (2009)



(±)

3 steps, 26% overall yield

TAKEMOTO (2014)

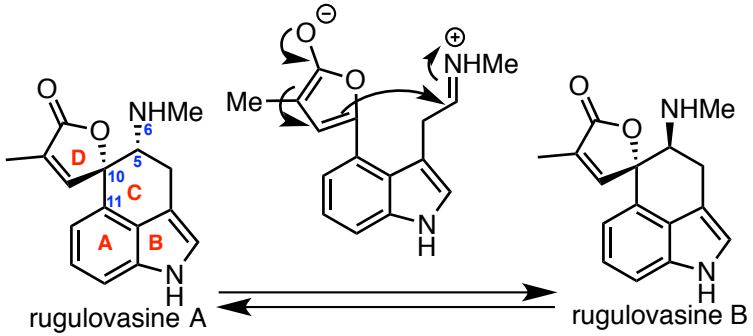


16 steps, 13% overall yield

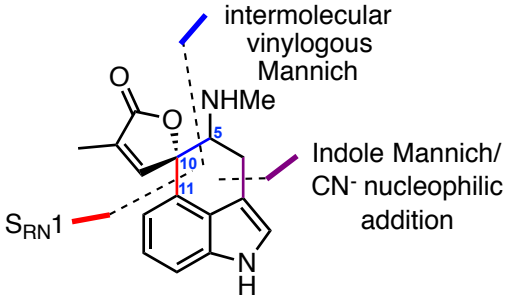
JACS, **2008**, *130*, 13745; *OL*, **2014**, *16*, 996; *OL*, **2010**, *12*, 2004; *Eur. J. Org. Chem.*, **2009**, 5752
Early racemic synthesis *Chem. Pharm. Bull.*, **1985**, *33*, 2162; *JOC*, **1987**, *52*, 3319

Recent Synthetic Approaches to *Clavine* Alkaloids
Rugulovasine A & B

- Rugulovasine A and B are modified clavine alkaloids containing a spirolactone moiety
- They were isolated as a mixture of naturally occurring diastereomers from the fungus *penicillium concavo-rugulosum*
- Both Rugulovasine A and B were isolated in racemic form and interconverted at room temperature
- Interconversion is proposed to occur *via* a vinylogous Mannich reaction that proceeds through an achiral 2-alkoxyfuran intermediate

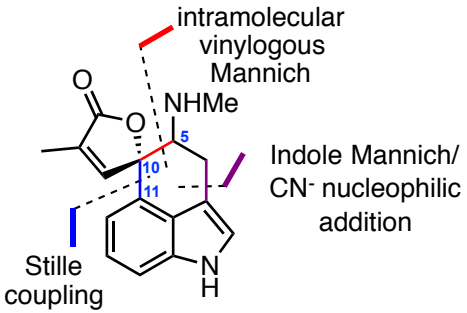


MARTIN (2001)



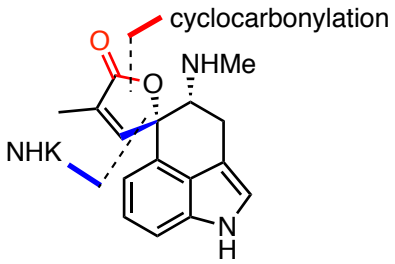
8 steps
11% overall yield

MARTIN (2001)



8 steps
30% overall yield

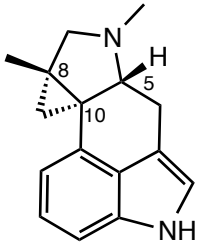
JIA (2013)



5 steps
20% overall yield

JACS, **2001**, *123*, 5918; *OL*, **2013**, *15*, 3662

Isolation of Ergot Alkaloid Cycloclavine



(+)-Cycloclavine

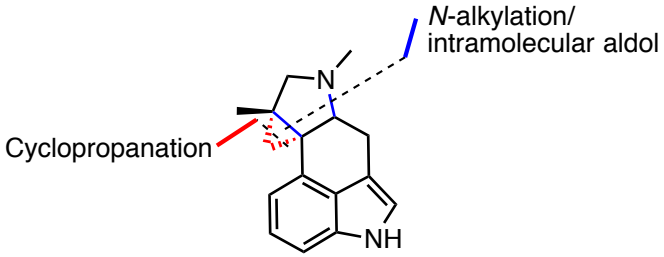
Ipomea hildebrandtii

- First isolated in 1969 from the seeds of the African morning glory (*Ipomea hildebrandtii*)
- Structure elucidation, including relative and absolute stereochemistry (5R, 8S, 10S) was determined by X-ray crystallographic analysis of the methobromide salt
  - Optical rotation $[\alpha]^{20}_{D}$ = + 39 (pyr)
- Therapeutic potential of cycloclavine remains underexplored (1 patent describes pesticidal properties)
  - "Cycloclavine and derivatives thereof for controlling invertebrate pests" (BASF, 2013)

Tetrahedron, **1969,** *25*, 5879
PCT Int. Appl. WO2014096238 A1, 2013

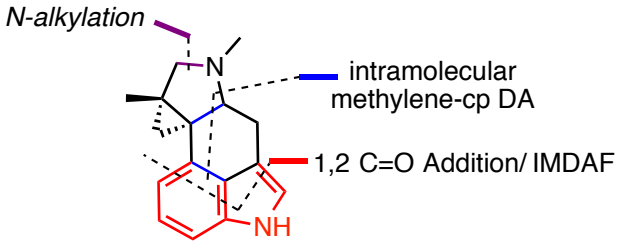
Recent Synthetic Approaches to *Clavine* Alkaloids
Cycloclavine

SZANTAY (2008)

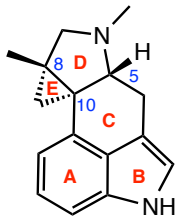


7 steps, 1% overall yield
from Uhle's ketone derivative

WIPF (2011)

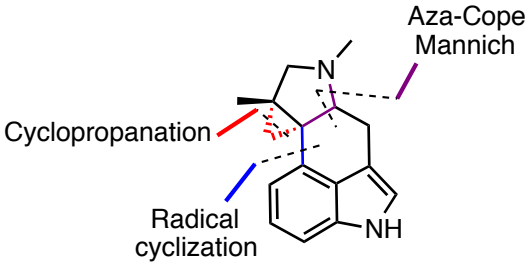


14 steps, 1.2% overall yield



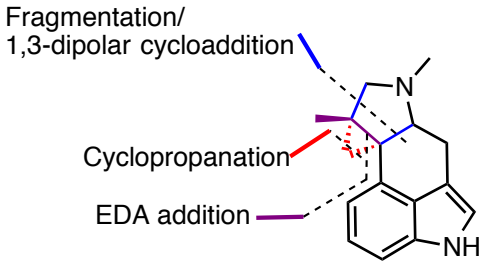
(+)-Cycloclavine

CAO (2014)



12 steps (formal synthesis)
6% overall yield

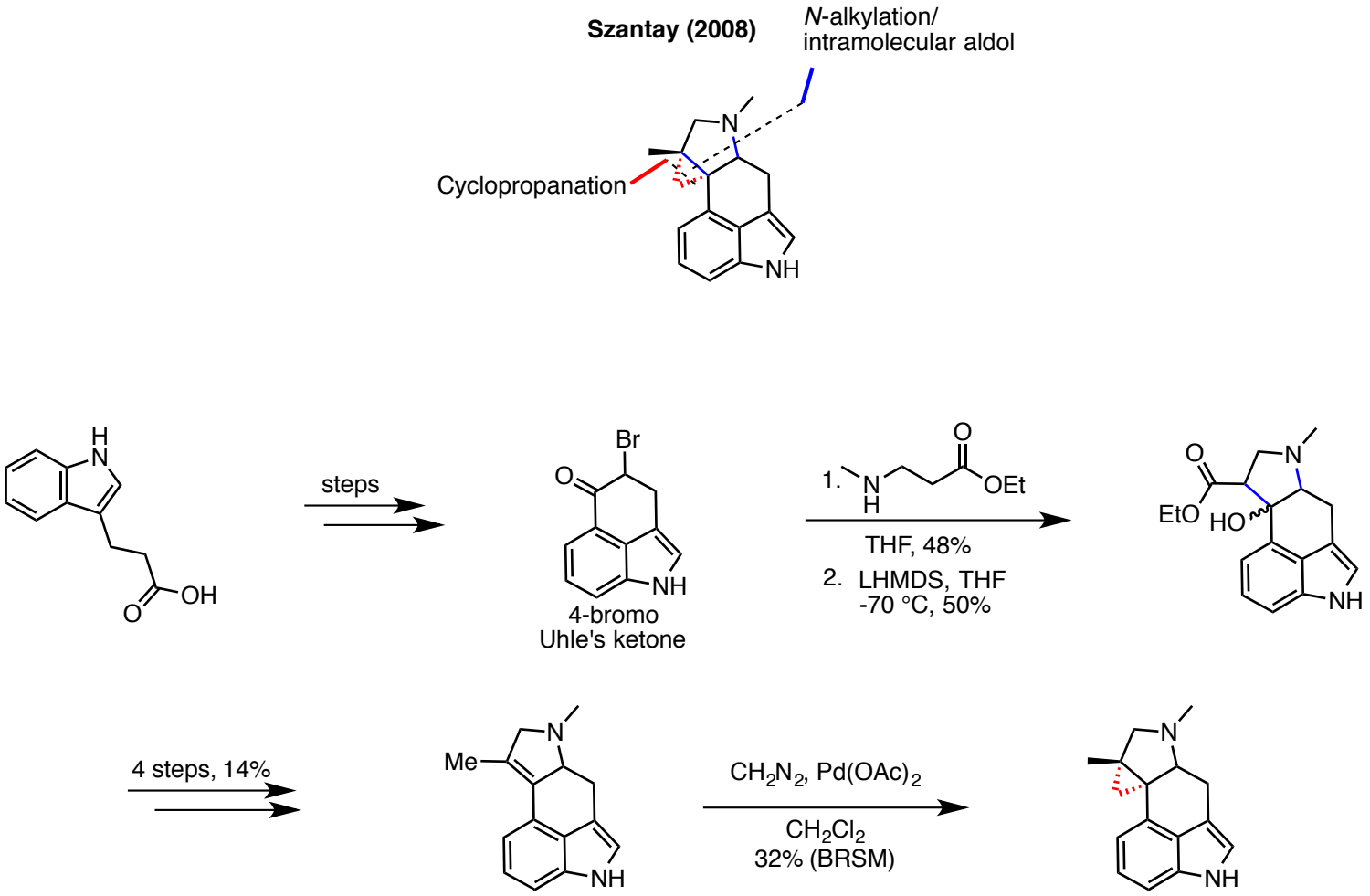
BREWER (2014)



8 steps, 7% overall yield (formal synth.)
14 steps, <1 % overall yield (total synth.)

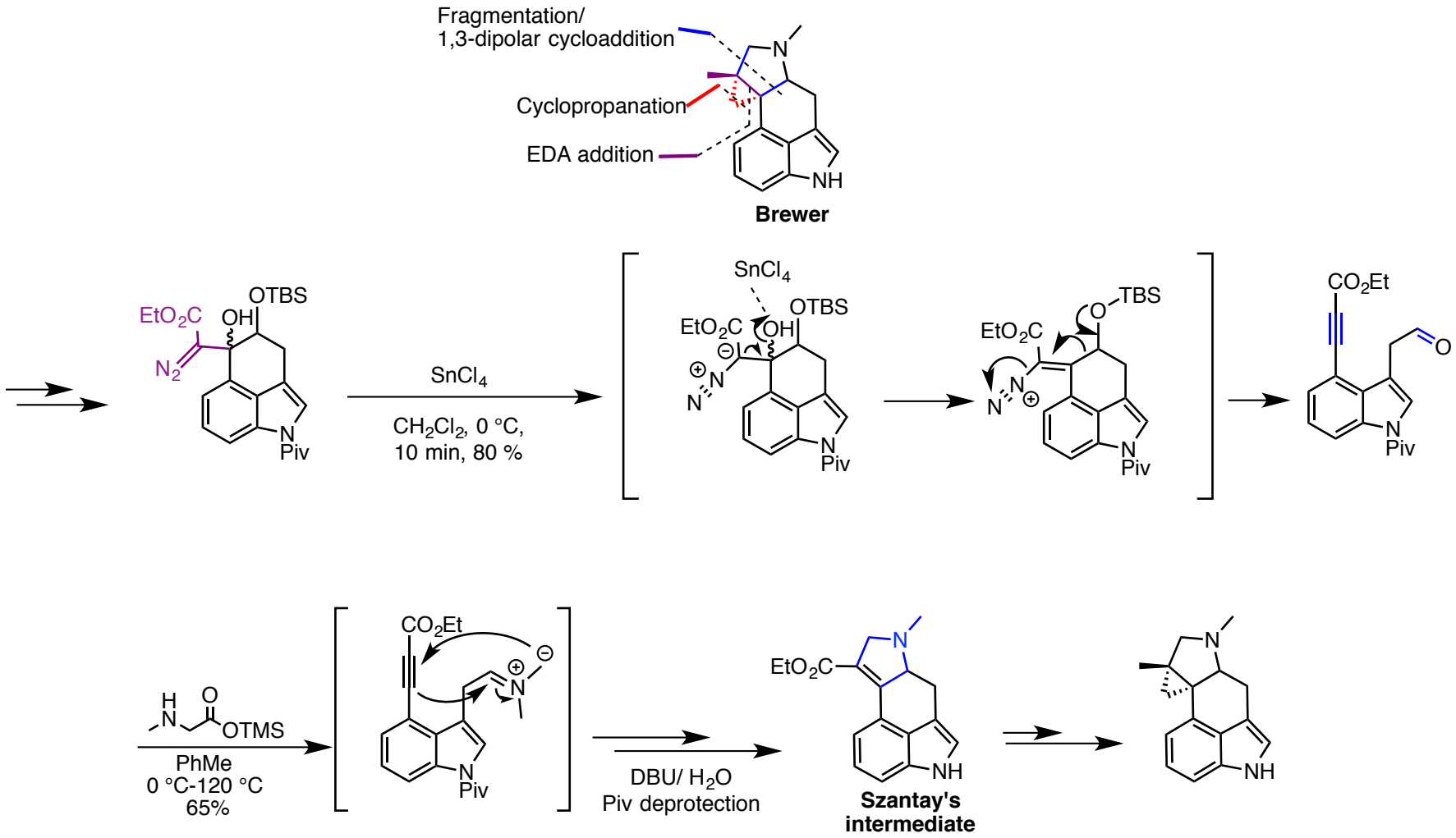
Tetrahedron, **2008**, *64*, 2924; *Tetradhedron Lett*,, **2014**, *56*, 197; *JOC*, **2014**, *79*, 122; *JACS*, **2011**, *133*, 7704

Szántay's Approach (2008)



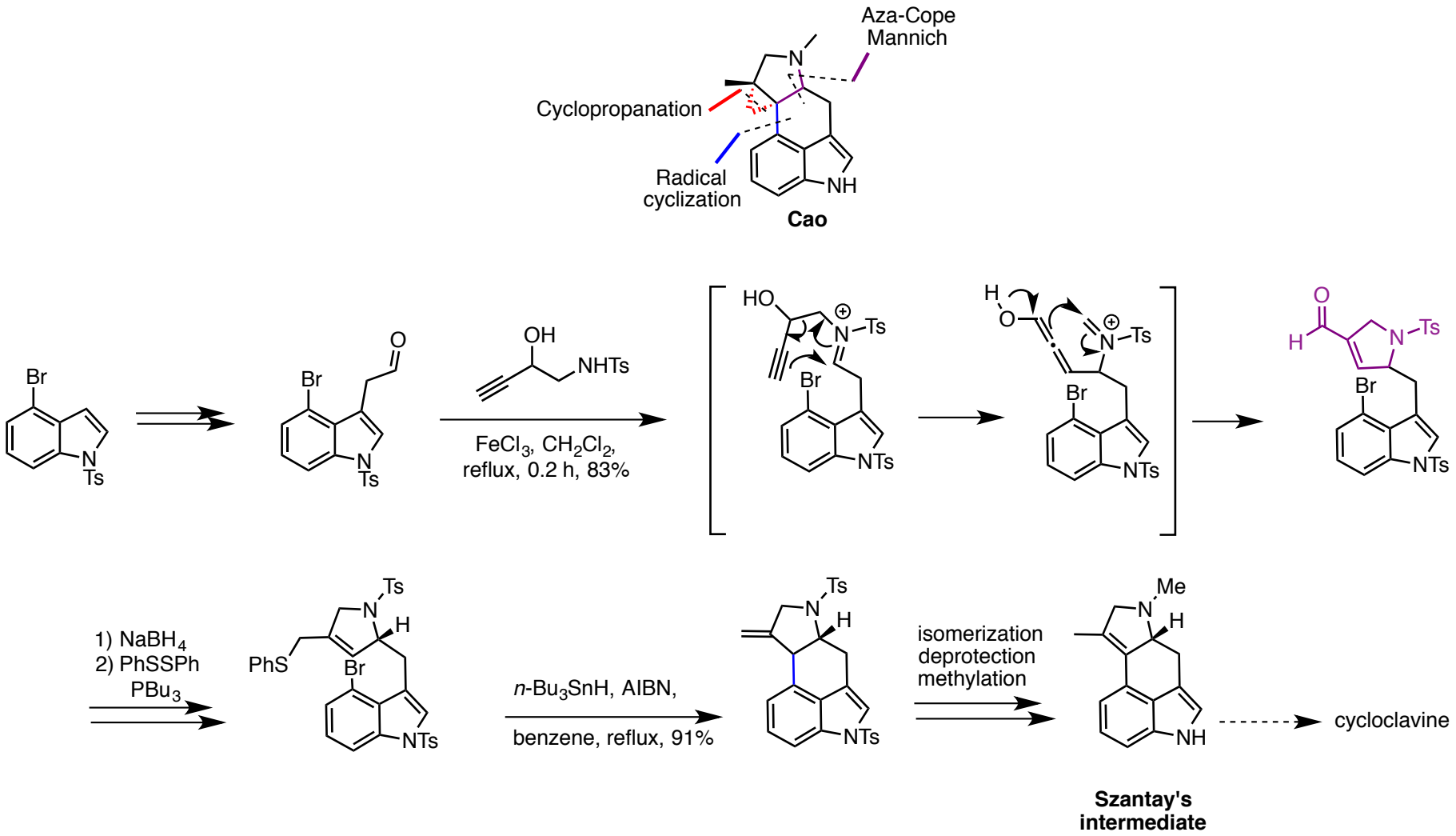
Tetrahedron, **2008**, *64*, 2924

Brewer's Approach (2014)



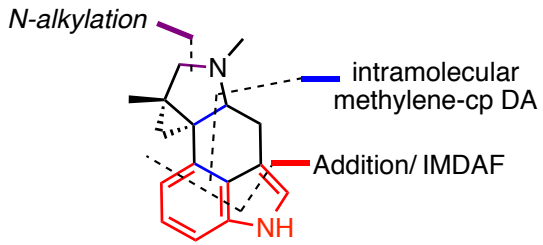
Tetradhedron Lett,, **2014**, *56*, 197

Cao's Approach (2014)

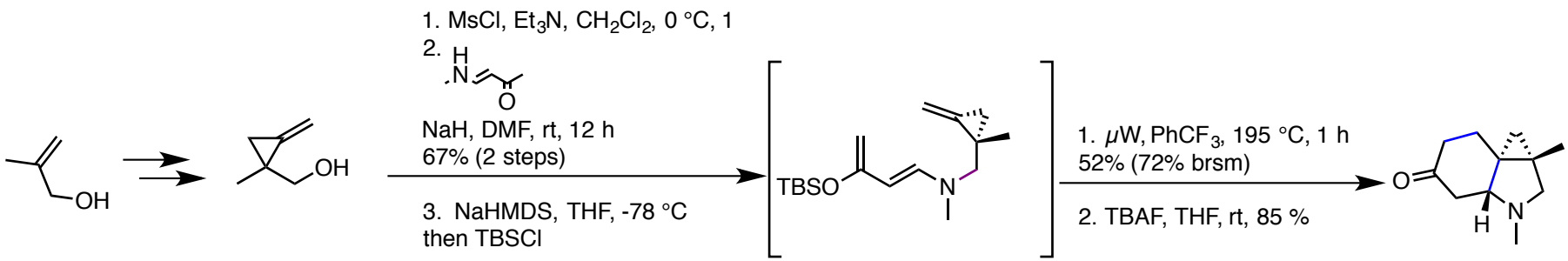


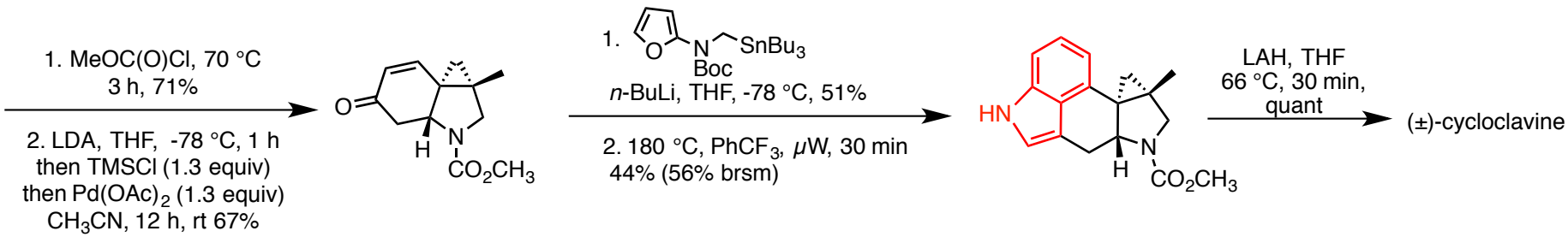
JOC, **2014**, *79*, 122

Wipf's Approach (2011)



Wipf





Dr Filip Petronijevic
JACS, **2011**, *133*, 7704

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