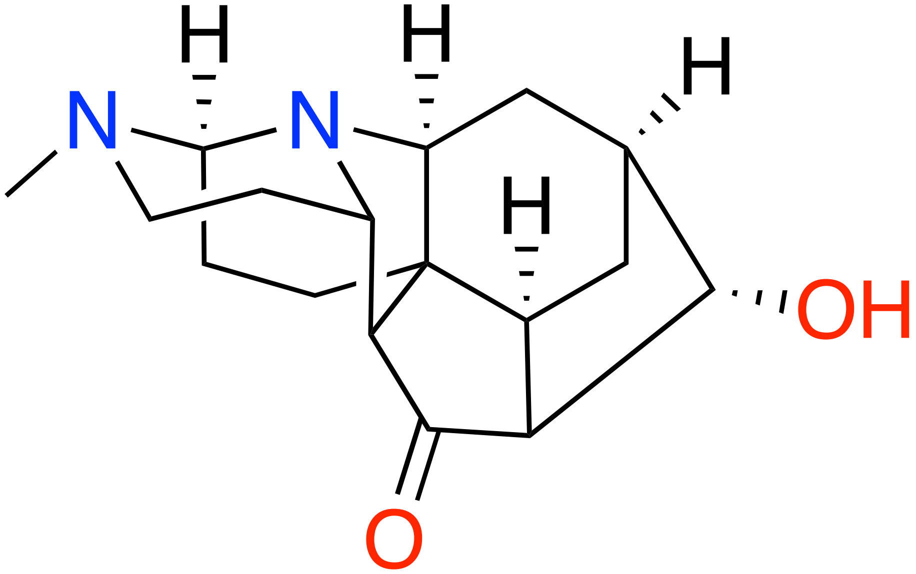
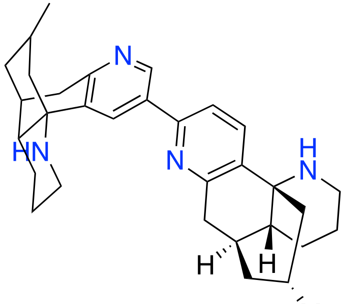
Expedient Synthesis of (+)-Lycopalhine A

Benjamin M. Williams and Dirk Trauner

Angew. Chem. Int. Ed., **2016**, *128*, 2231-2234

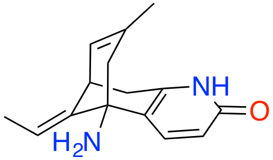


Lycopodium alkaloids



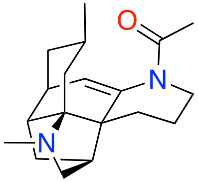
complanadine A

stimulates nerve growth factor (NGF) production in human glial cells

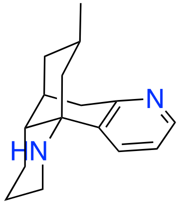


huperzine A

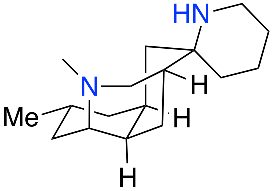
reversible inhibitor of AChe



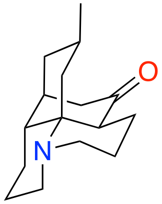
fastigiatine



lycodine-type



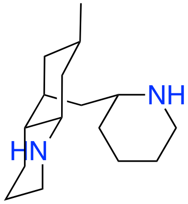
nankakurine A



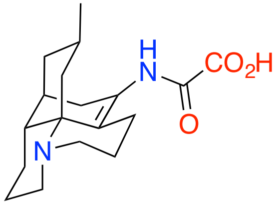
lycopodine-type

Lycopodium alkaloids

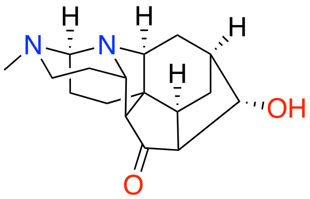
miscellaneous



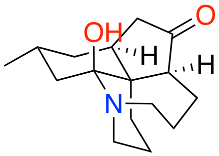
phlegmarine



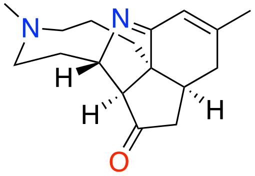
huperzine G



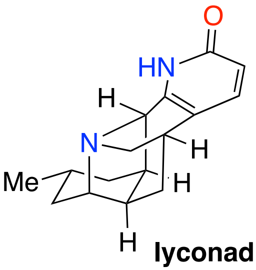
lycopalhine A



Fawcettimine-type



obscurinine



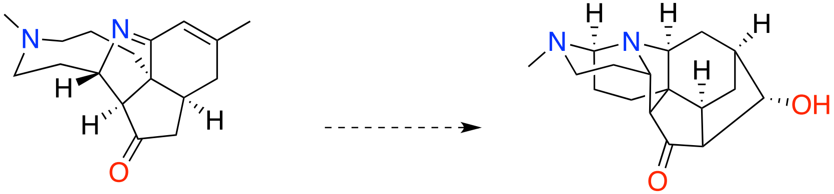
lyconadin A

* cytotoxic to murine lymphoma cells (IC_{50} = 0.46 µg/mL) & human epidermoid carcinoma KB cells (IC_{50} = 1.7 µg/mL)

* stimulates NGF production in human glial cells

Isolation/ Characterization

- Isolated in Guizhou Province, China from *Palhinhaea cernua* along with it's proposed biosynthetic precursor obscurinine



obscurinine
(10 mg)

lycopalhine A
(1.5 mg)

Palhinhaea cernua

Structure & absolute configuration determined through spectroscopic/computational methods

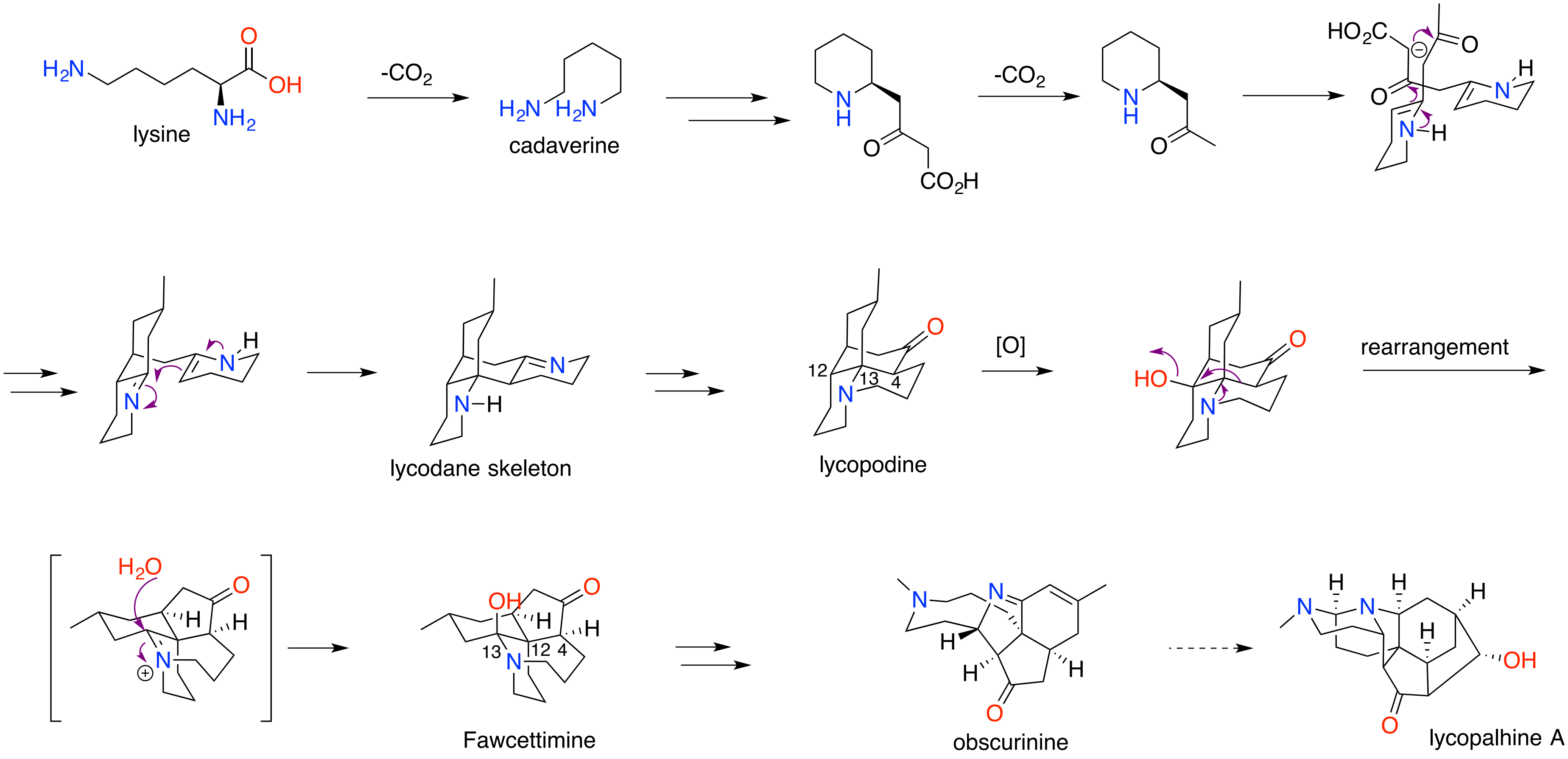
- Complex hexacyclic ring system containing
  - 1x6 + 2x5 membered carbocycles, 1x piperidine ring & 1x hexahydropyrimidine ring on a highly substituted pyrrolidine core
  - Sensitive aminal functionality + strained aldol moiety
  - 9 stereogenic centres, 8 of which are contiguous

- Weak butyrylcholinesterase (BuChe) inhibitory activity
  - (31.4% at 50 μM) compared to Tacrine (87.8% at 33 μM, + control)

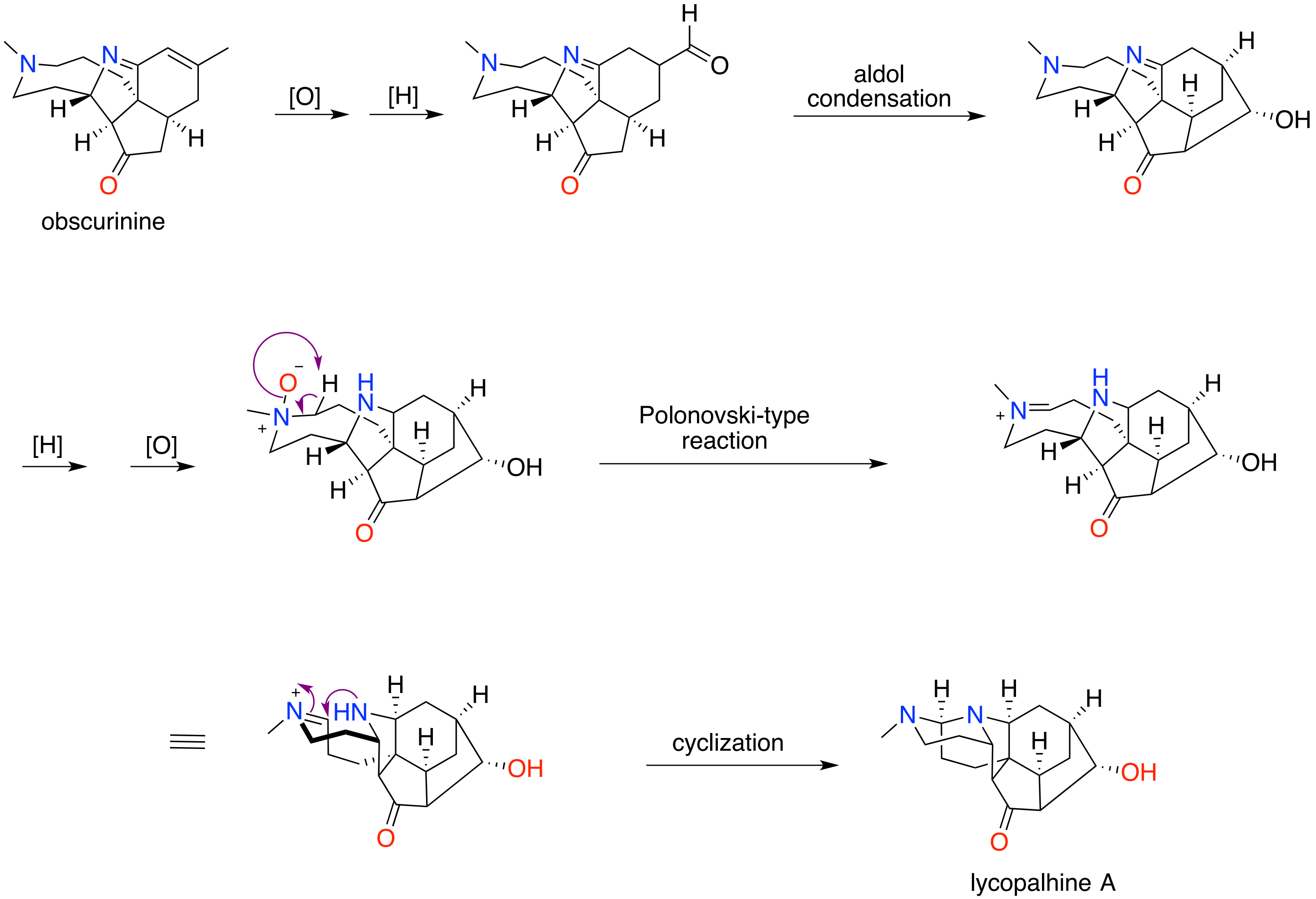
Chem. Commun., **2012**, *48*, 9038

Biosynthesis

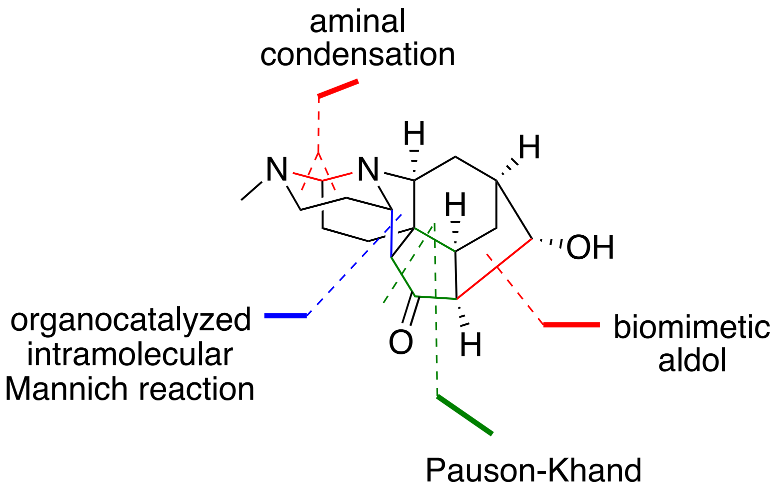
- The biosynthesis of lycopodium alkaloids is not well established due to difficulty cultivating *lycopodium* species in the lab.
- Current insight is largely based on feeding experiments with radiolabeled precursors

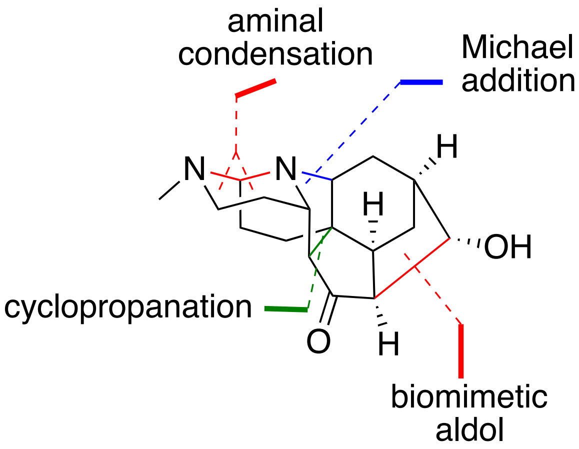


Proposed Biosynthesis



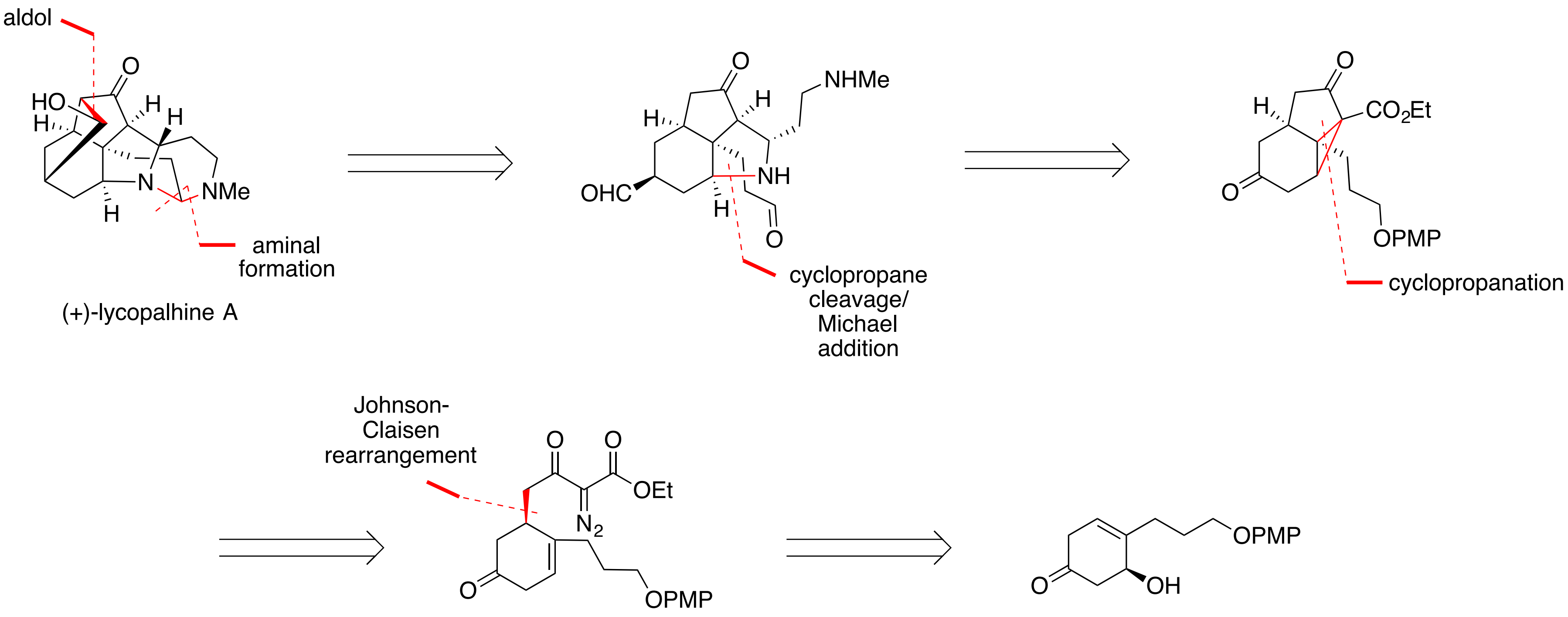
- 2 total syntheses of (+)-Lycopalhine to date:





- Trauner group – published 8th January 2016
- Fukuyama group – 7th March 2016

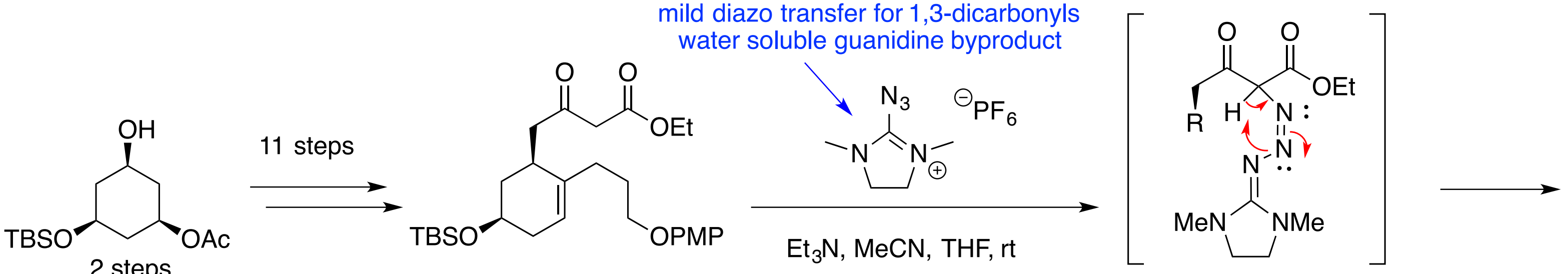
Fukuyama’s Retrosynthesis



(+)-lycopalhine A

Org. Lett., **2016**, *18* (6),1494–1496

Fukuyama’s Approach



11 steps

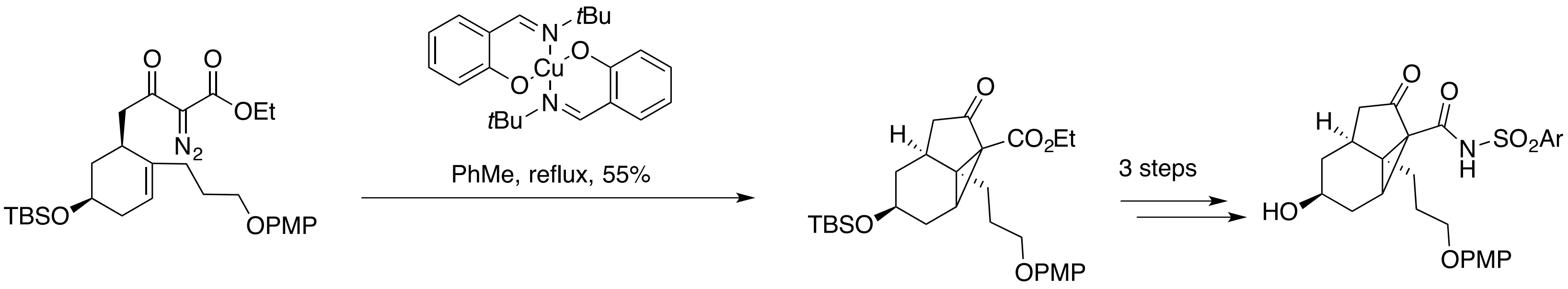
2 steps
(lit. procedure)

synthesized 26.1 g scale

mild diazo transfer for 1,3-dicarbonyls
water soluble guanidine byproduct

Et_3N, MeCN, THF, rt

Synlett, **2009**, *2009*, 2943
Synthesis, **2011**, *7*, 1037

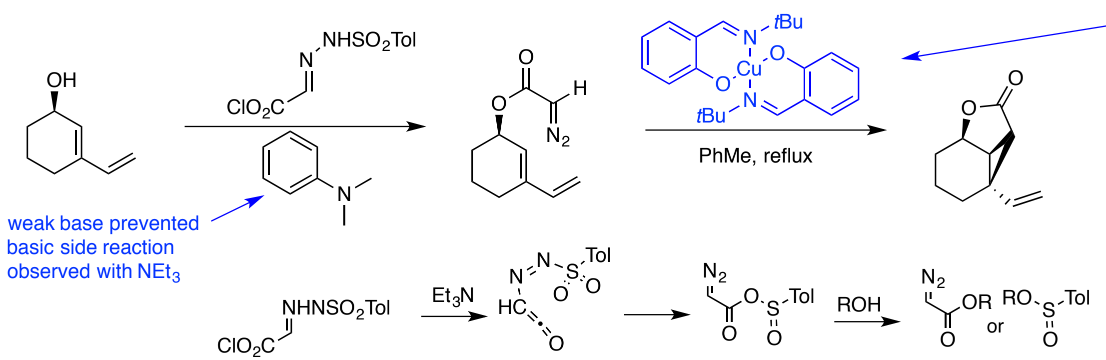


PhMe, reflux, 55%

3 steps

Ar = C_6H_4-*p*-CF_3

E. J. Corey and Andrew G. Myers *Tetrahedron Lett.*, **1984**, *25*, 3559

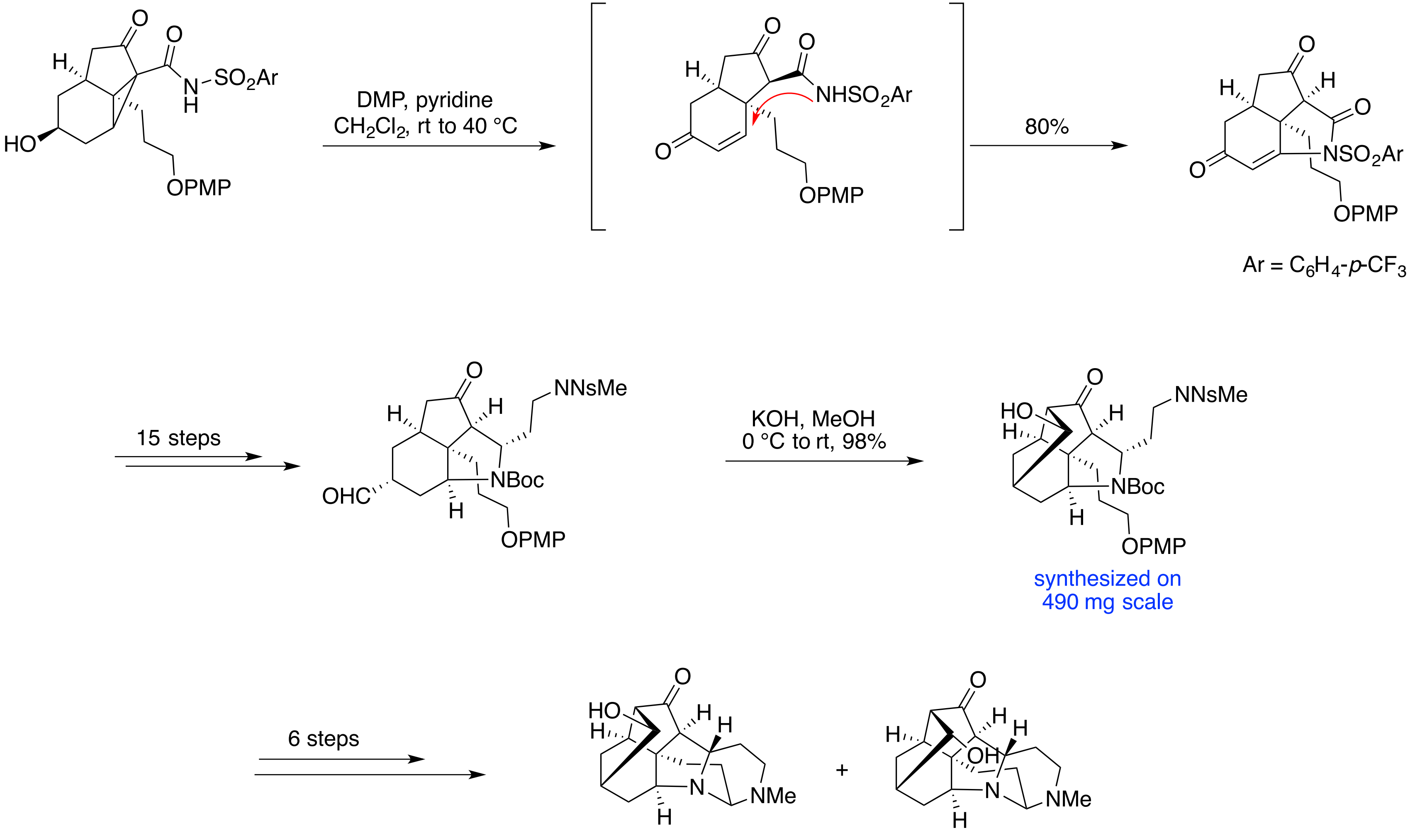


PhMe, reflux

weak base prevented
basic side reaction
observed with NEt_3

bis-(*N*-*t*-butylsalicylaldiminato)
copper (II) catalyst
- soluble catalyst --> higher yields
on scale compared to
heterogenous Cu powder

Fukuyama's Approach



DMP, pyridine
CH_2Cl_2, rt to 40 °C

80%

Ar = C_6H_4-*p*-CF_3

15 steps

KOH, MeOH
0 °C to rt, 98%

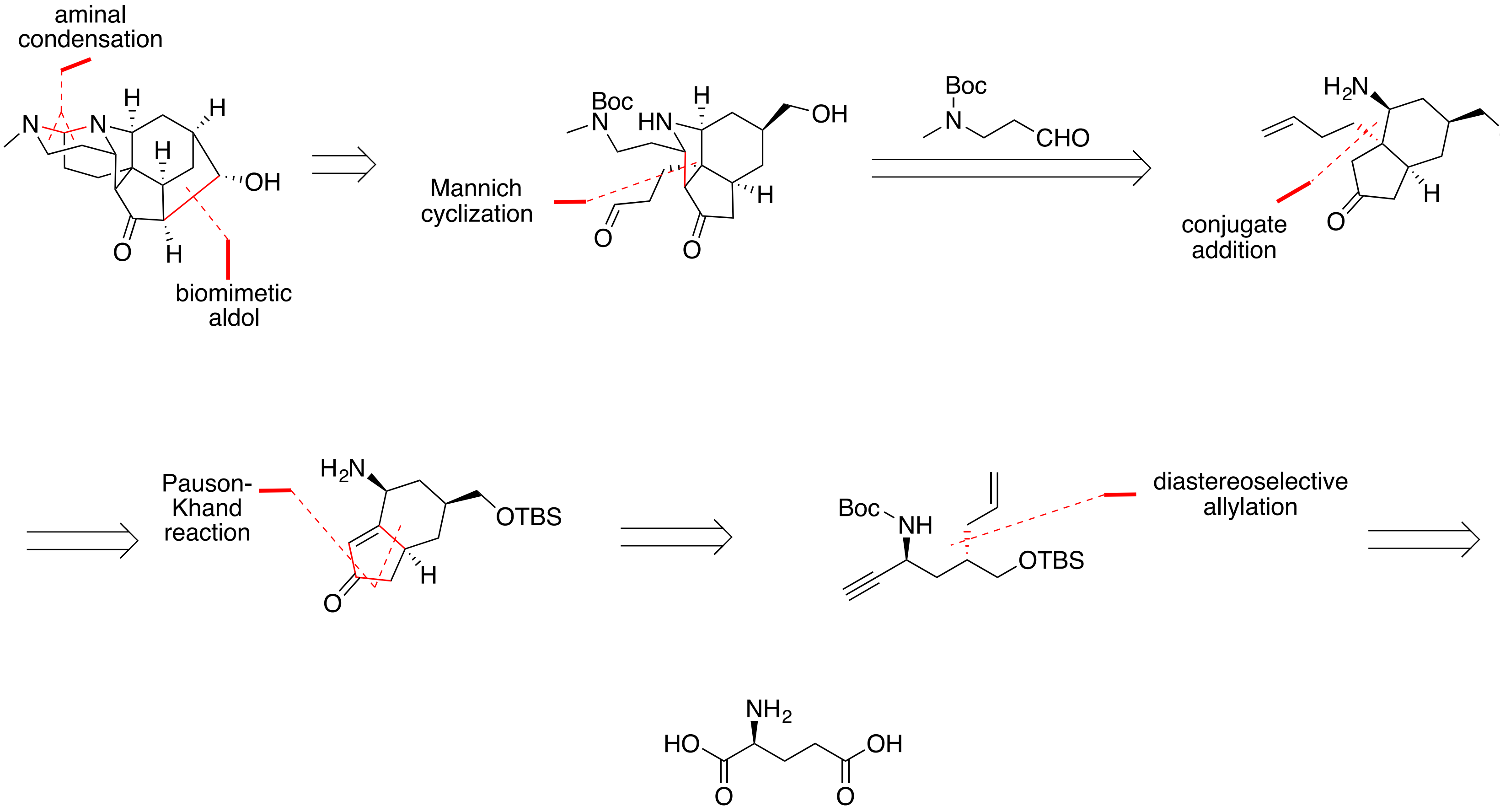
synthesized on
490 mg scale

6 steps

lycopalhine A

epi-lycopalhine A

Retrosynthesis



aminal condensation

biomimetic aldol

Mannich cyclization

conjugate addition

Pauson-Khand reaction

diastereoselective allylation

L-glutamic acid

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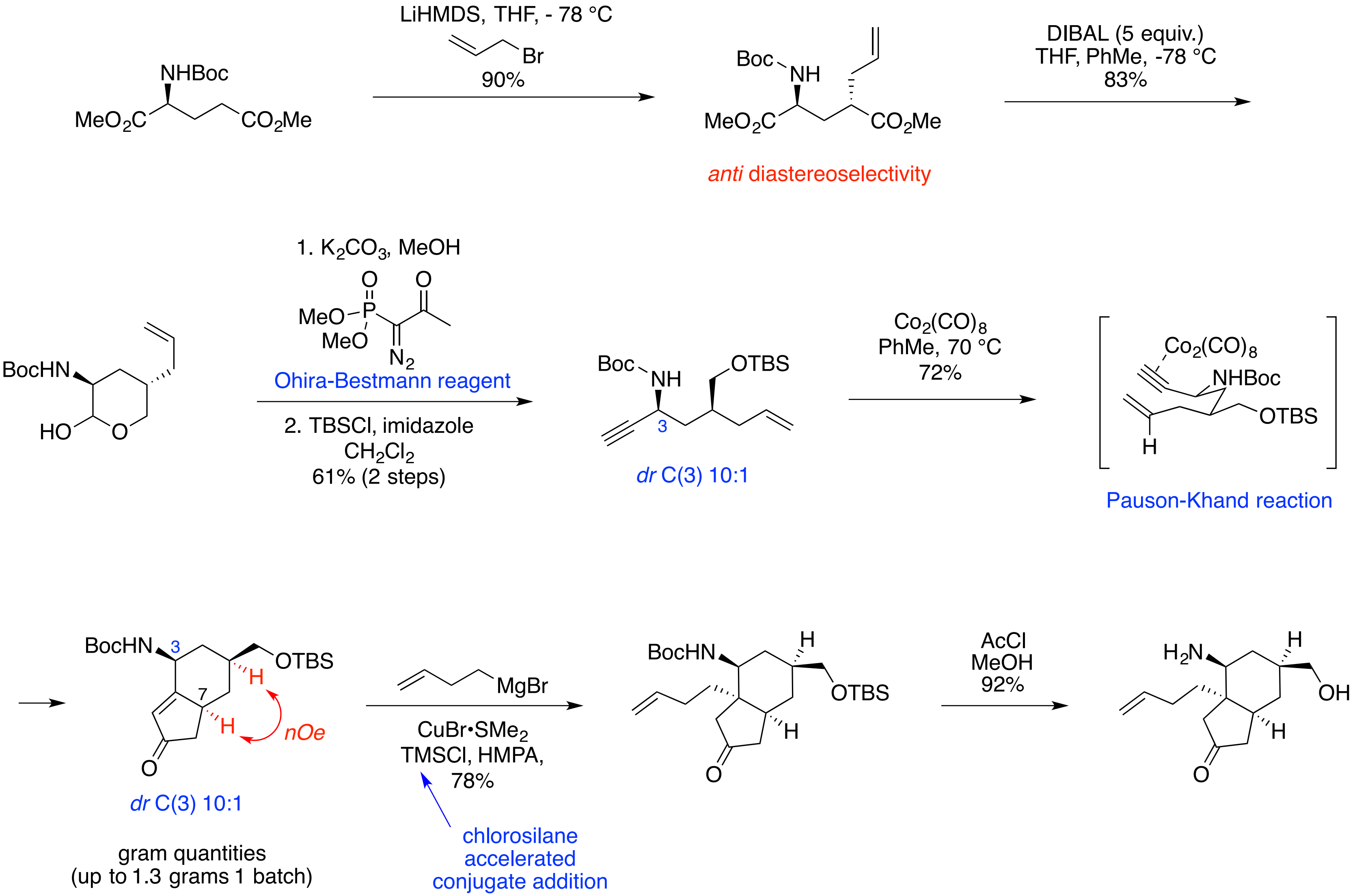
Synthesis of Core Bicycle



LiHMDS, THF, - 78 °C

90%

anti diastereoselectivity

DIBAL (5 equiv.)
THF, PhMe, -78 °C
83%

1. K_2CO_3, MeOH

Ohira-Bestmann reagent

2. TBSCl, imidazole
CH_2Cl_2
61% (2 steps)

dr C(3) 10:1

$Co_2(CO)_8$
PhMe, 70 °C
72%

Pauson-Khand reaction

nOe

dr C(3) 10:1

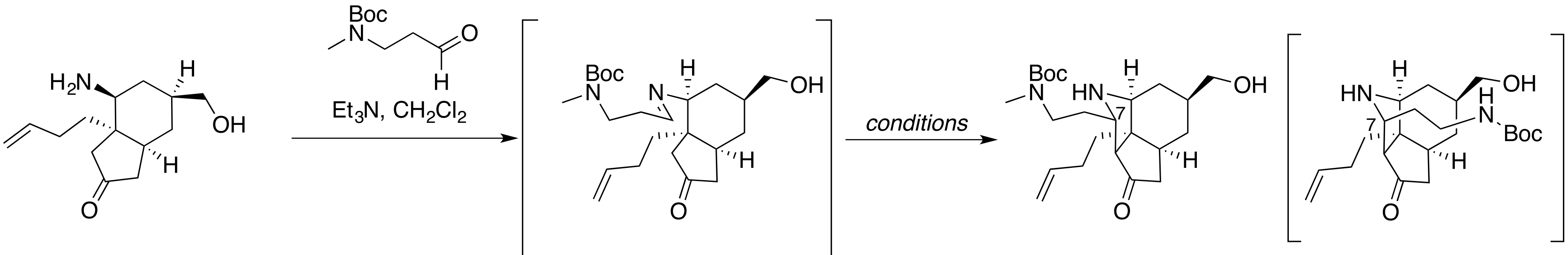
gram quantities
(up to 1.3 grams 1 batch)

$CuBr{\bullet}SMe_2$
TMSCl, HMPA,
78%

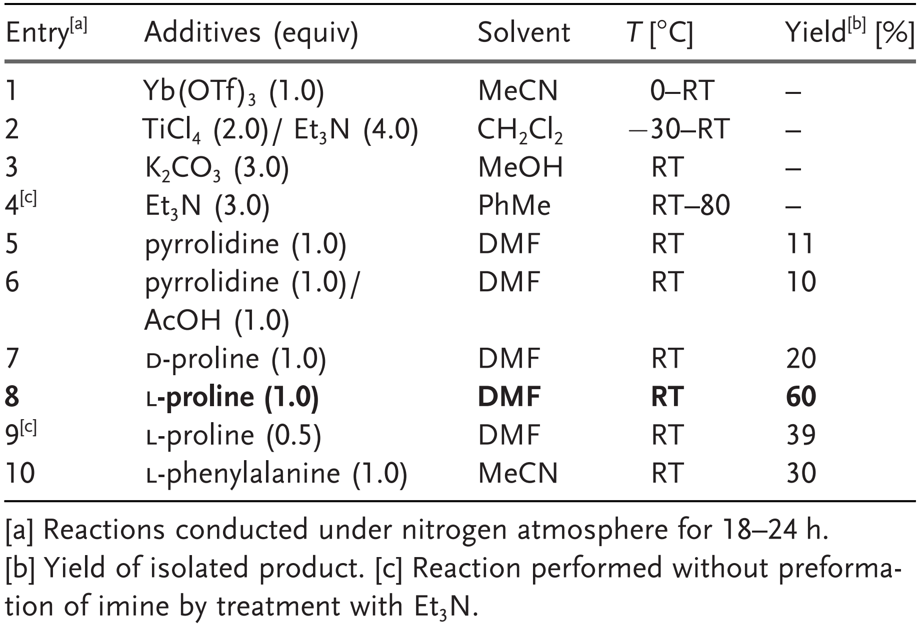
chlorosilane
accelerated
conjugate addition

AcCl
MeOH
92%

5-*endo*-trig Mannich reaction



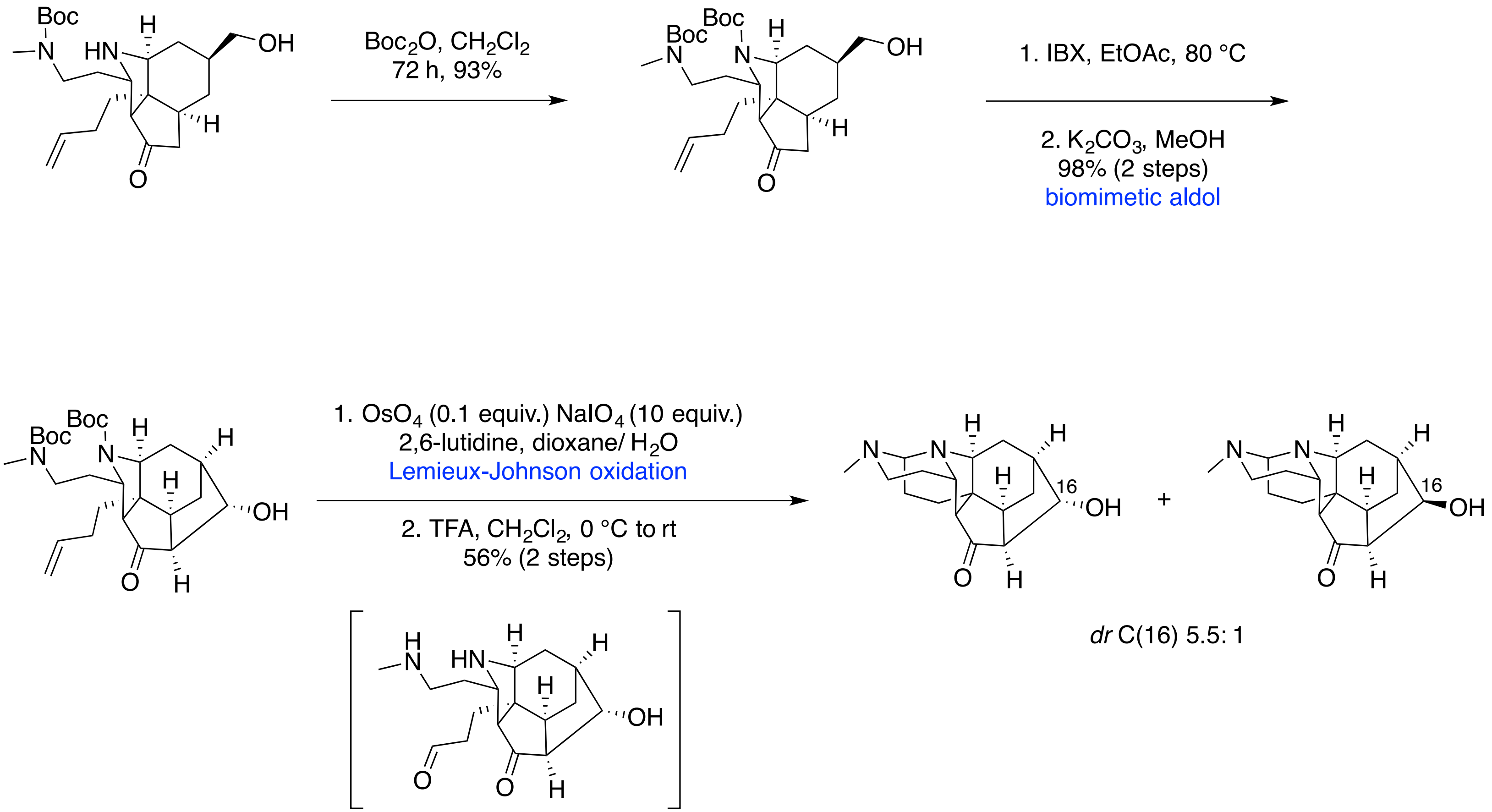
(not observed)



Entry[a]	Additives (equiv)	Solvent	*T* [°C]	Yield[b] [%]
1	$Yb(OTf)_3$ (1.0)	MeCN	0–RT	–
2	$TiCl_4$ (2.0)/ Et_3N (4.0)	CH_2Cl_2	-30–RT	–
3	K_2CO_3 (3.0)	MeOH	RT	–
4[c]	Et_3N (3.0)	PhMe	RT–80	–
5	pyrrolidine (1.0)	DMF	RT	11
6	pyrrolidine (1.0)/ AcOH (1.0)	DMF	RT	10
7	D-proline (1.0)	DMF	RT	20
8	**L-proline (1.0)**	**DMF**	**RT**	**60**
9[c]	L-proline (0.5)	DMF	RT	39
10	L-phenylalanine (1.0)	MeCN	RT	30

[a] Reactions conducted under nitrogen atmosphere for 18–24 h.
[b] Yield of isolated product. [c] Reaction performed without preformation of imine by treatment with Et_3N.

Completion of the Synthesis via a biomimetic aldol reaction



Boc_2O, CH_2Cl_2
72 h, 93%

1. IBX, EtOAc, 80 °C

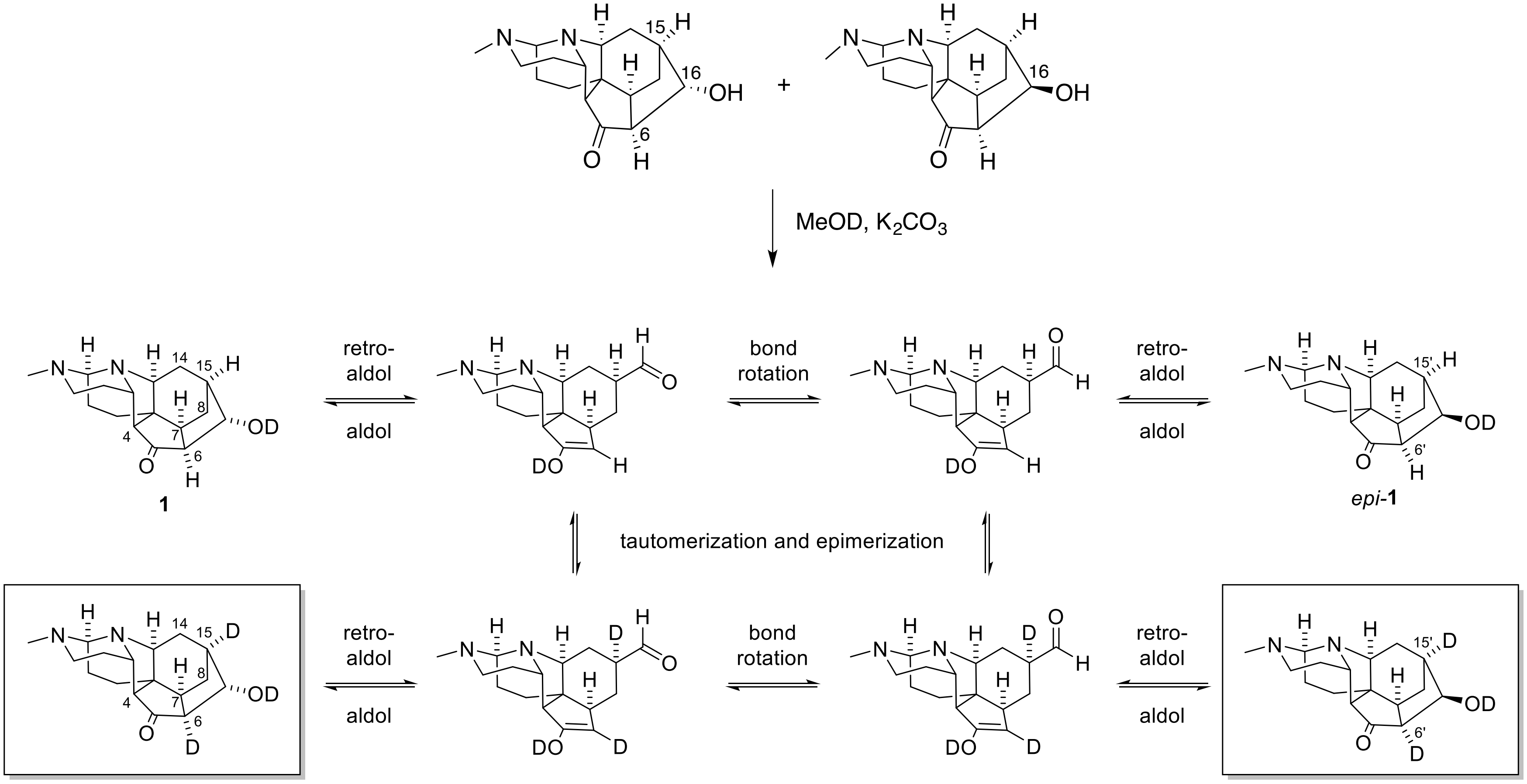
2. K_2CO_3, MeOH
98% (2 steps)
biomimetic aldol

1. OsO_4 (0.1 equiv.) $NaIO_4$ (10 equiv.)
2,6-lutidine, dioxane/ H_2O
Lemieux-Johnson oxidation

2. TFA, CH_2Cl_2, 0 °C to rt
56% (2 steps)

dr C(16) 5.5: 1

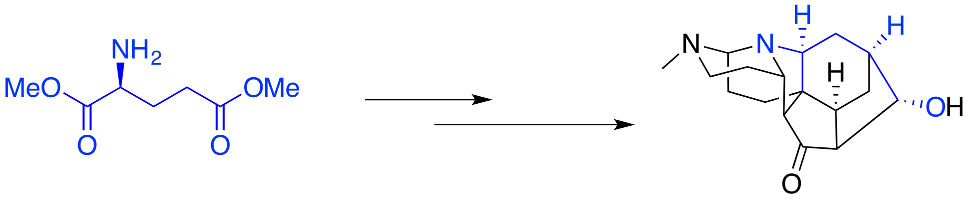
Deuterium Study



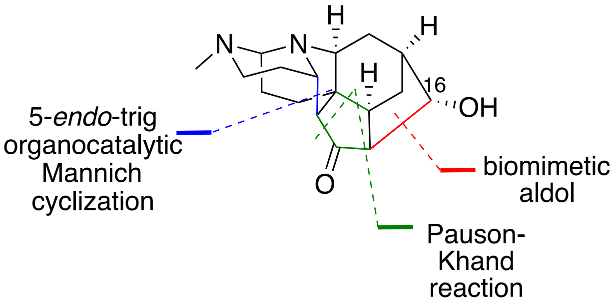
- Deuterium exchange between C_6/C_{15} under basic conditions + the existence of both epimers in the experimental and isolated samples suggests equilibration with a thermodynamic preference for closed aldol product.

Conclusions

- First total synthesis of lycopalhine A
- First asymmetric synthesis utilizing a chiral pool approach



- Key steps:



5-*endo*-trig organocatalytic Mannich cyclization

biomimetic aldol

Pauson-Khand reaction

- Comparison of synthetic routes
  :

Synthesis	Steps	Overall Yield (mixture of C(16) epimers)	Quantity
Fukuyama	41	~2%	13.0 mg
Trauner	13	~5.7%	4.0 mg

- Application of P-K/ organocatalytic Mannich approach to other lycopodium alkaloids