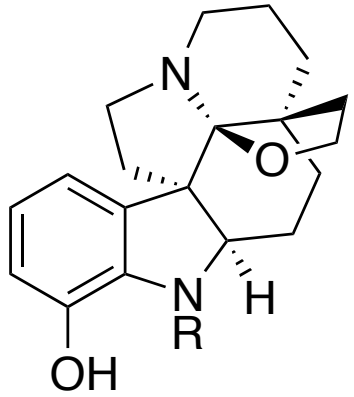
Concise Total Syntheses of (+)-Haplocidine and (+)-Haplocine Via Late-Stage Oxidation of (+)-Fendleridine Derivatives

Kolby L. White, and Mohammad Movassaghi
JACS. **2016**, 11383



(+)-haplocidine, R = COMe
(+)-haplocine, R = COEt

Ruiting Liu

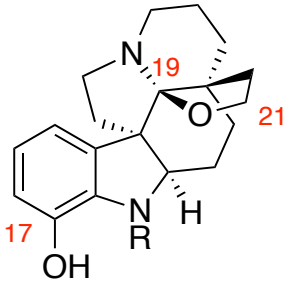
Wipf Group Current Literature

11/19/2016

1

(+)-Haplocidine and (+)-Haplocine

- (+)-Haplocidine and (+)-Haplocine are a subset of Aspidosperma alkaloids isolated from Apocynaceae
- Potent caspase-8 inhibitor
- Hexacyclic C19-hemiaminal ether alkaloid



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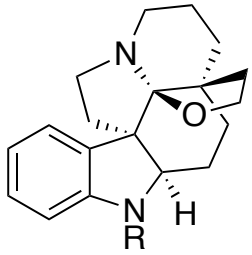
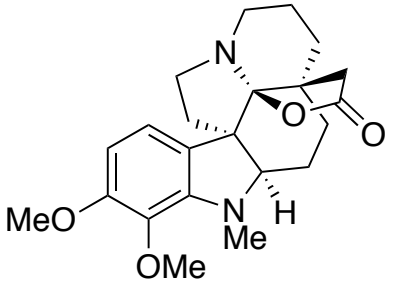


(+)-acetylaspidoalbidine, R = COMe
(+)-fendleridine, R = H

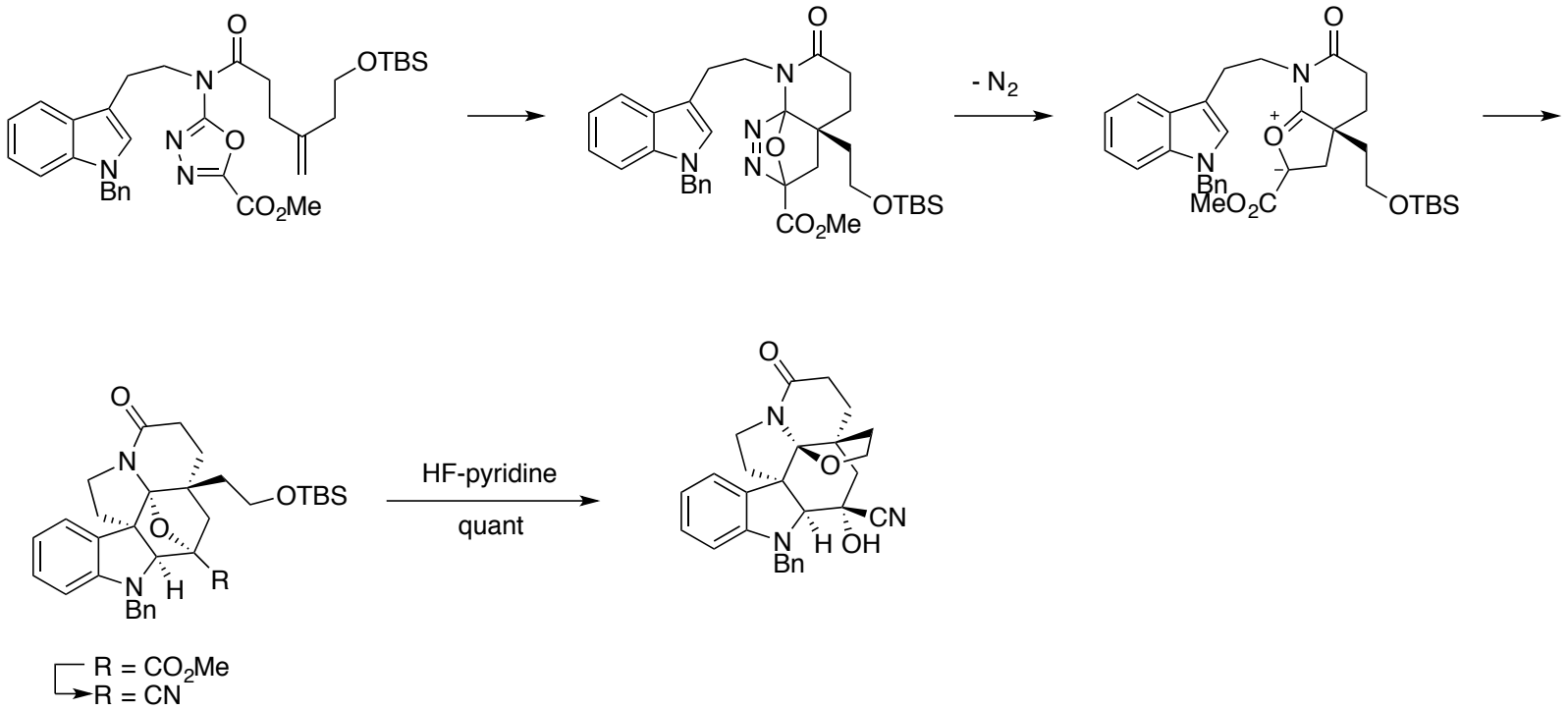


(-)-aspidophytine

Structurally related aspidosperma alkaloids

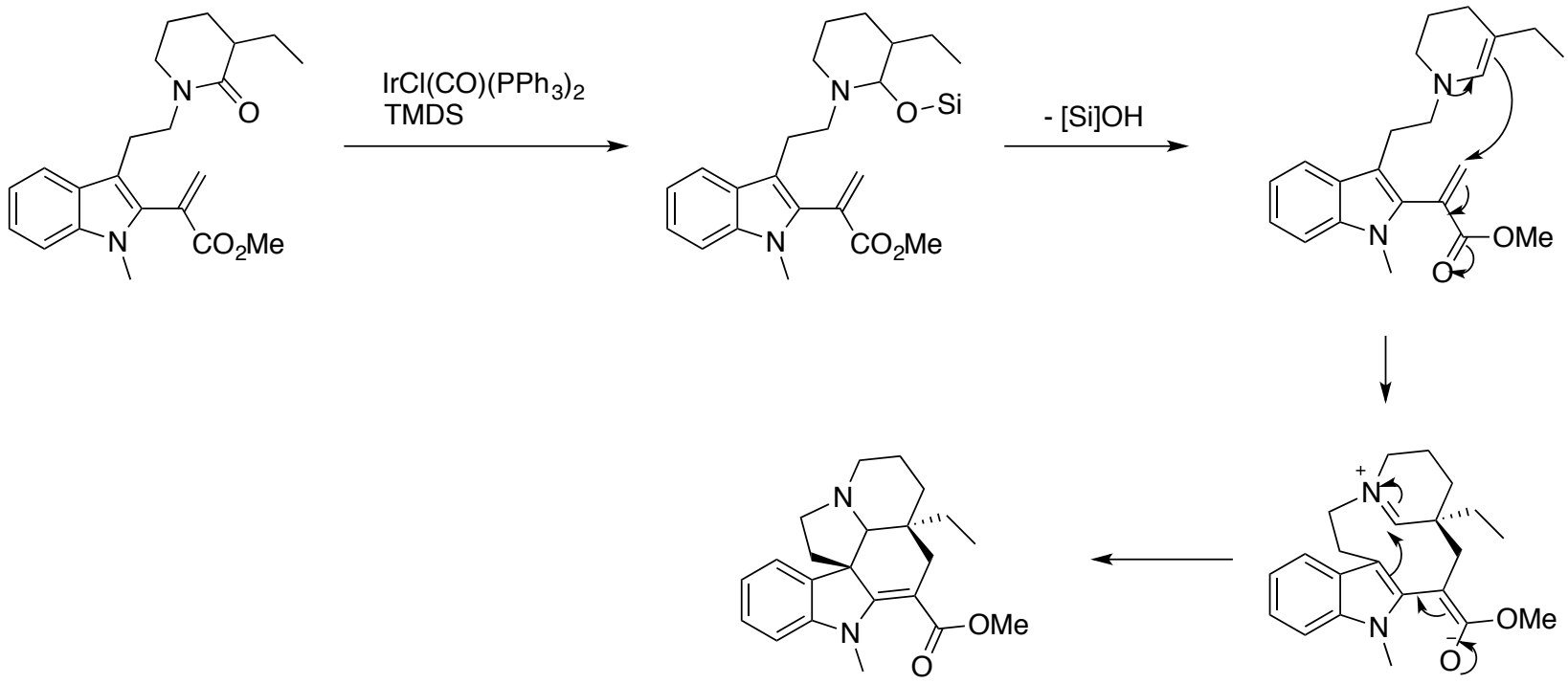
Tetrahedron, **1964**, *20*, 581

Previous Approach to Hemiaminal



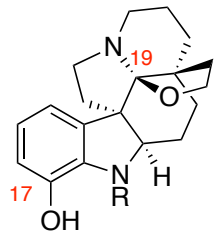
D.L. Boger , *JACS*. **2010**, 3009

Activation of amide



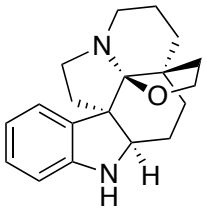
D.J.Dixon, *Angew. Chem. Int. Ed*. **2016**, 13436

Retrosynthesis



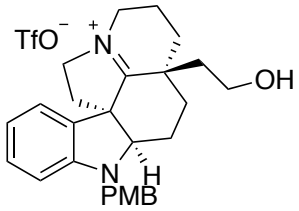
(+)-haplocidine, R = COMe
(+)-haplocine, R = COEt

Regioselective
C-17-H Oxidation

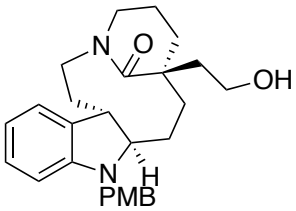


(+)-fendleridine

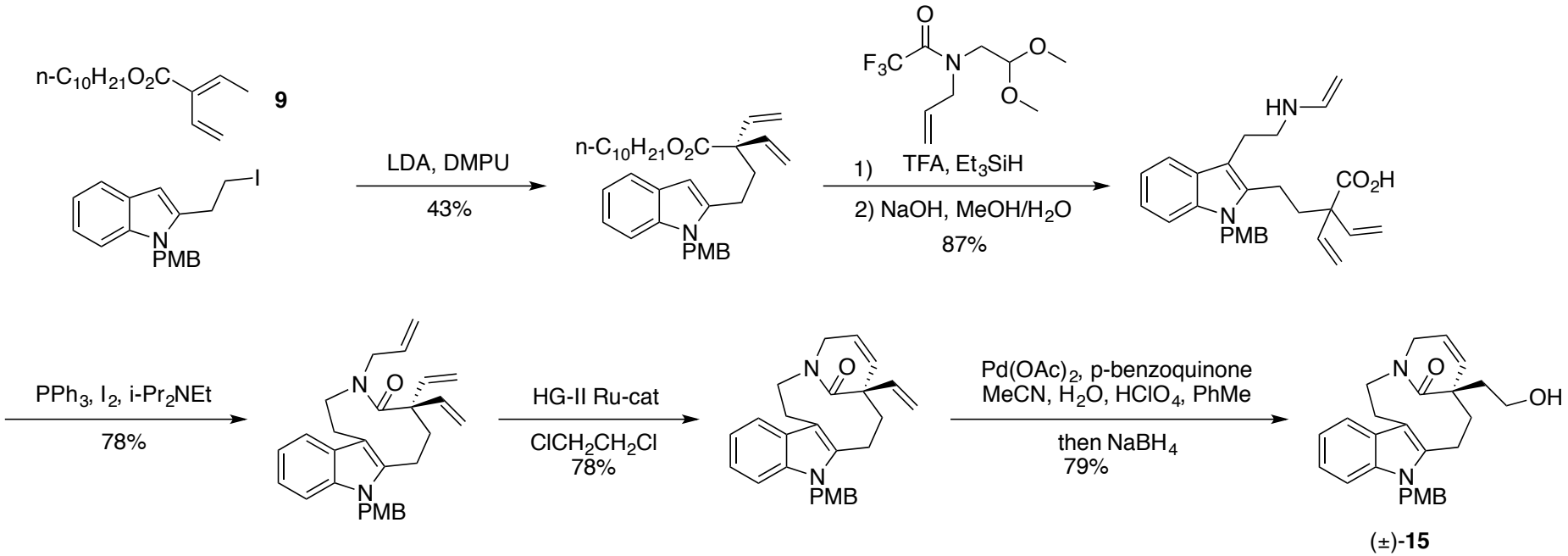
Intramolecular
trapping



Transannular
cyclization

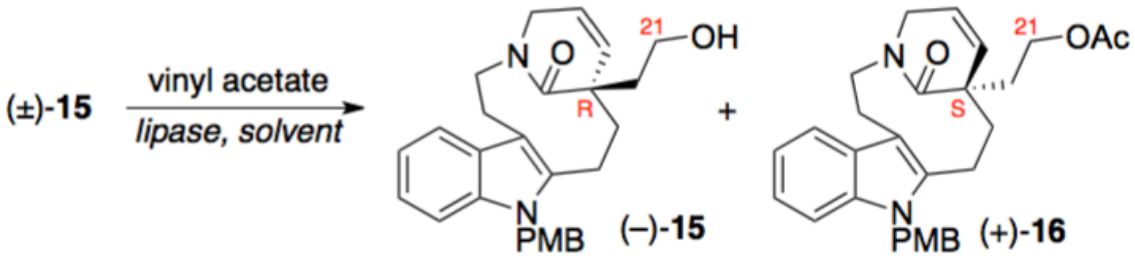


Synthesis of (+)-fendleridine



Resolution of alcohol

Table 1. Enzymatic resolution of alcohol (±)-**15**[a]

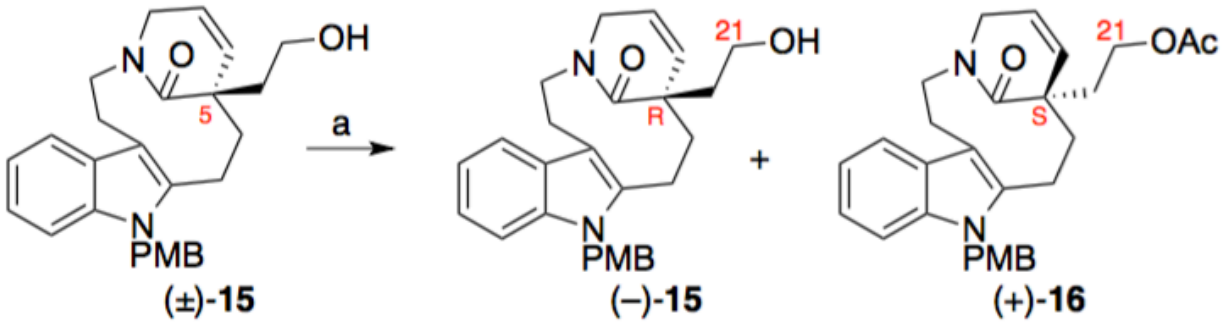


entry	lipase	solvent	conversion	ee of (–)-**15**	ee of (+)-**16**
1	CAL-B	PhMe	–	–	–
2	CCL	PhMe	44%	38%	30%
3	CCL	THF	<15%	8%	49%
4	CCL	PhMe[b]	65%	74%	26%
5	CCL	*t*-BuOMe	55%	60%	42%
6	***Amano PS***	***t-BuOMe***	***55%***	***92%***	***50%***

[a]Reagents and conditions: vinyl acetate (2.0 equiv), 23 °C. Each resolution was monitored for 48 h or until approximately 50% conversion to (+)-**16** (HPLC analysis), whichever occurred first. [b] Triethylamine (1.0 equiv) was utilized as an additive. CAL-B = *Candida antarctica* lipase B, CCL = *Candida rugosa* lipase, Amano PS = *Burkholderia cepacia* lipase.

Optimation

Scheme 3. Preparation of alcohols (–)-**15** and (+)-**15**[a]



50% conversion (7 h): 80% ee 80% ee

- excellent selectivity $E = 22$
- distal, quaternary stereochemistry
- ready access to both enantiomers

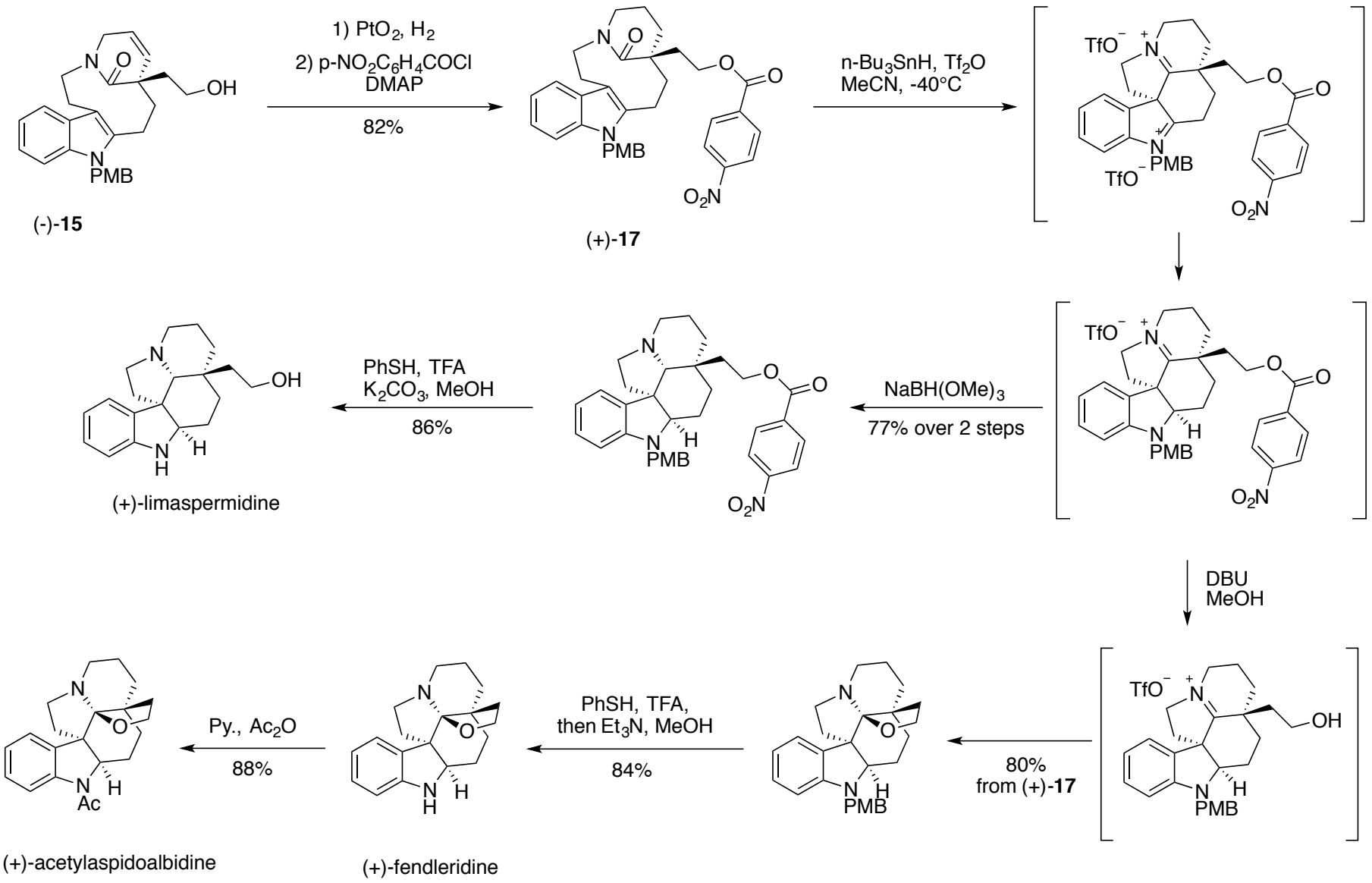
*preparation of alcohol (–)-**15** at 64% conversion (10 h):*

(–)-**15**, **>98% ee**, 36% (+)-**16**, 56% ee, 60%

*preparation of alcohol (+)-**15** from acetate (+)-**16**:*

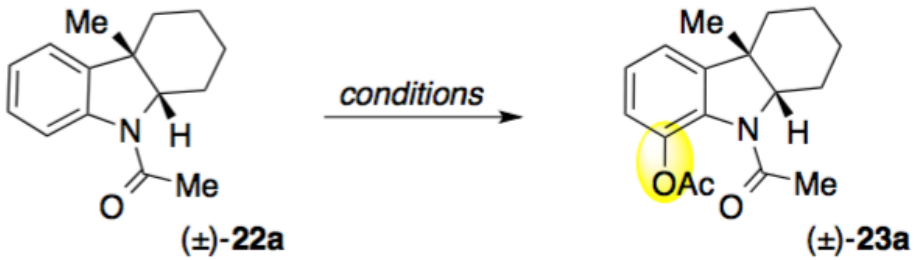
(+)-**16**, 71% ee $\xrightarrow{b}$ (+)-**15**, **90% ee**, 46%

[a]Reagents and conditions: (a) Amano PS Lipase (>500 U/g), vinyl acetate (4.50 equiv), *t*-BuOMe, CH_2Cl_2, 28 °C. (b) CCL, H_2O, Et_3N, *t*-BuOMe, 21 h, 28 °C.


1) PtO2, H2
2) p-NO2C6H4COCl
DMAP
82%
n-Bu3SnH, Tf2O
MeCN, -40°C
NaBH(OMe)3
77% over 2 steps
DBU
MeOH
80%
from (+)-17
PhSH, TFA,
then Et3N, MeOH
84%
Py., Ac2O
88%
PhSH, TFA
K2CO3, MeOH
86%
(-)-15
(+)-17
(+)-limaspermidine
(+)-fendleridine
(+)-acetylaspidoalbidine

Oxidation of C17-H

Table 2. Directed C–H oxidation of indoline (±)-**22a** [a]

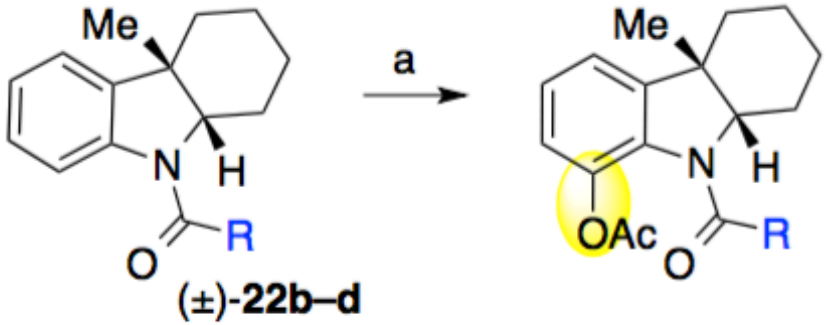


(±)-**22a** (±)-**23a**

entry	$Pd(OAc)_2$	$PhI(OAc)_2$	time	temperature	solvent	yield
1	20 mol%	4 equiv	24 h	70 °C	HFIP	38%
2	100 mol%	2 equiv	24 h	55 °C	HFIP	61%
3	20 mol%	2 equiv	24 h	100 °C	AcOH	23%
4	100 mol%	2.5 equiv	12 h	100 °C	AcOH[b]	87%
5	***15 mol%***	***2.5 equiv***	***9 h***	***100 °C***	***AcOH[b]***	***84%***
6	5 mol%	2.5 equiv	12 h	100 °C	AcOH[b]	67%
7	—	2.5 equiv	12 h	100 °C	AcOH[b]	0%
8	20 mol%	2.5 equiv	13 h	100 °C	AcOH[b,c]	74%

[a]Reactions conducted in *solvent* and Ac_2O mixture (10:1, v/v). [b]Reaction conducted under O_2 atmosphere. [c]Reaction conducted without Ac_2O.

Amide group preference

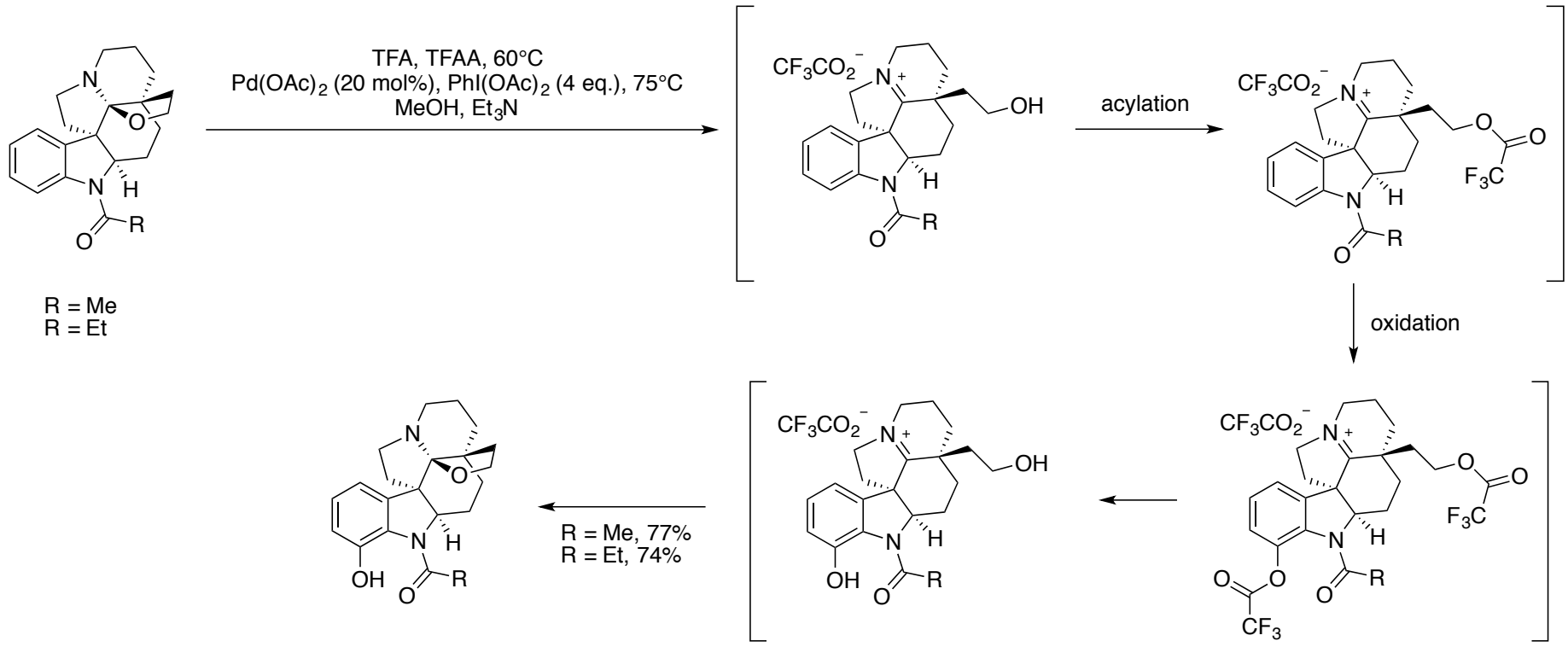


(±)-**23b**, R=C(O)*t*-Bu, 86%
(±)-**23c**, R=C(O)Et, 82%
(±)-**23d**, R=C(O)Ph, 59%

[a]Reagents and conditions: (a) $Pd(OAc)_2$ (15 mol%), $PhI(OAc)_2$ (2.5 equiv), AcOH, Ac_2O, 100 °C, O_2.

-- (±)-**23b**, the *s*-cis conformer, was calculated to be 1.52 kcal/mol lower in energy than the corresponding *s*-trans conformer
-- The *s*-cis conformer for amide (±)-**23d** was only 0.13 kcal/mol.

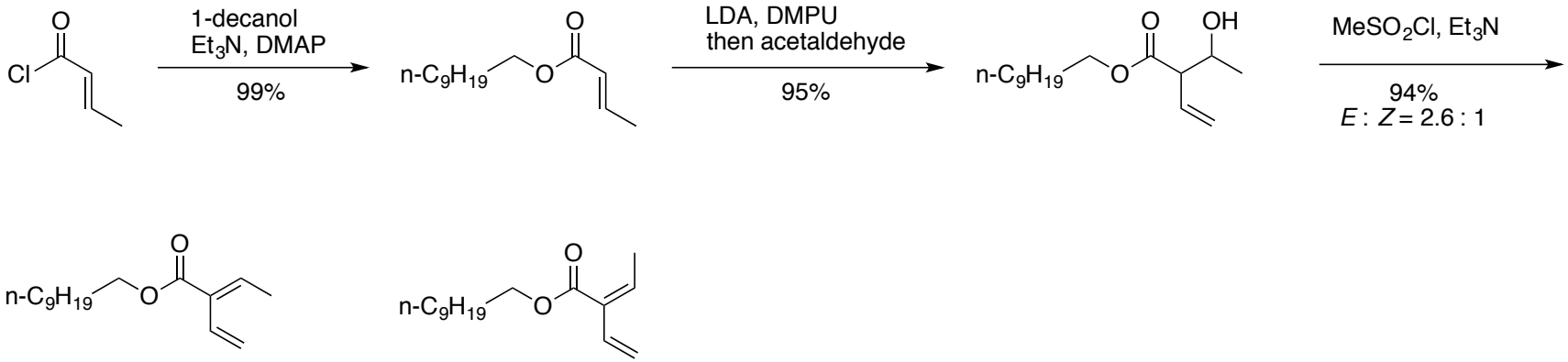
Synthesis of (+)-Haplocidine and (+)-Haplocine



Reverse hemiaminal opening needed to deactivate the amine lone pair

Conclusion

- First total synthesis of (+)-Haplocidine and (+)-Haplocine via a unified strategy
- Highly stereoselective synthesis of versatile iminium ion
- Directed C-H oxidation


1-decanol
Et3N, DMAP
99%
LDA, DMPU
then acetaldehyde
95%
MeSO2Cl, Et3N
94%
E : Z = 2.6 : 1

(E) **- 9**