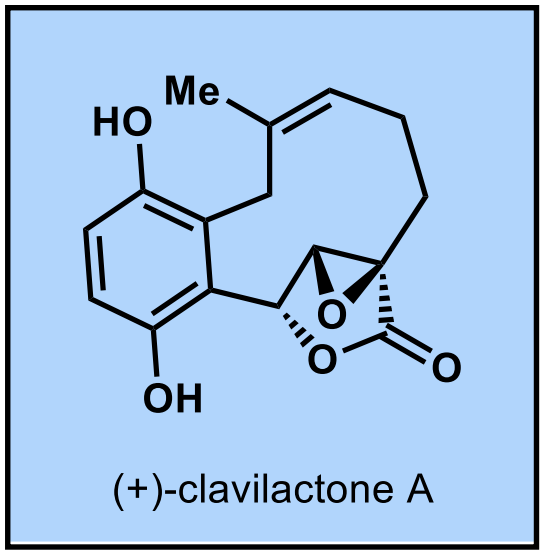
Total Syntheses of Clavilactones



(+)-clavilactone A

Sarah Korb

Literature Presentation

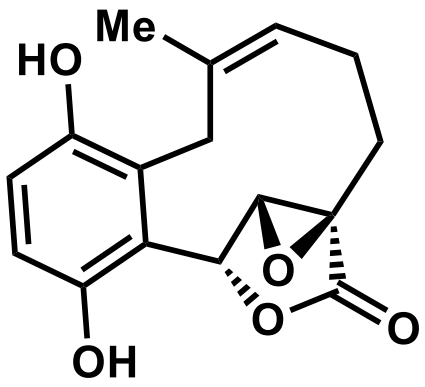
1/24/2025

Clavilactones

Structure and Biological Significance

- isolated from fungi
- meroterpenoids
- benzo or quinone fused 10/5/3 tricyclic nested skeleton
- potent inhibitors of several mammalian cell lines
  - many with IC_{50}< 30 (µM)





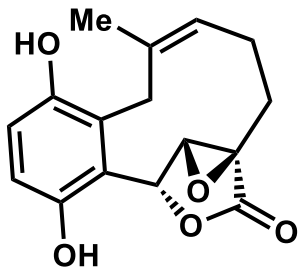
clavilactone core

Compound	IC_{50} (µM)	Cell Line
A	26	EGFR
B	27	EGFR
D	5.5	EGFR
F	18.22± 1.35	A549
H	14.5 ± 1.2	SGC-7901
ent-J	1.9	MCF-7
ent-J quinone	6.5	A431
L	11.76	MGC-083
M	22.8 ± 0.9	Hela
N	19.7 ± 1.1	Hela

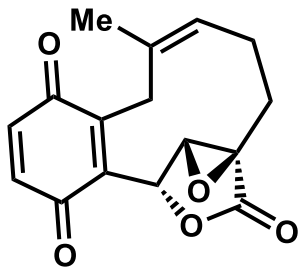
J. Chem. Soc., Perkin Trans. **1994**, 2165.; Phytochemistry 2000, 53, 1039– 1041.; *Org. Chem. Front.* **2019**, *6*, 3759-3765.; *Molecules*. **2019**. *24* (22),4015.; *Fitoterapia* **2022**, *161* (7), 105251.; *J. Nat. Prod.* **2023**, *86* (11), 2580–2584.; *Zhongguo Zhong yao za zhi.***2024**, *49*(11), 2947–2952.; *Molecules* **2023**, *28*(14), 5456.; *Biochem. Pharmacol.* **2000**, *59,* 1539-1547

Clavilactone Family

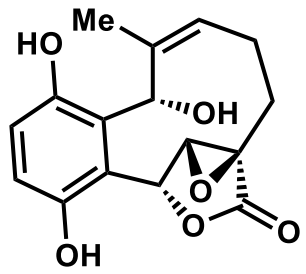
Compounds A-I



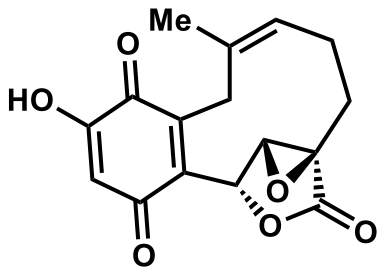
(+)-clavilactone A



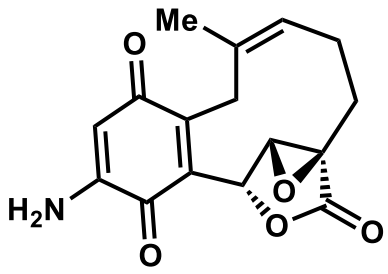
(-)-clavilactone B



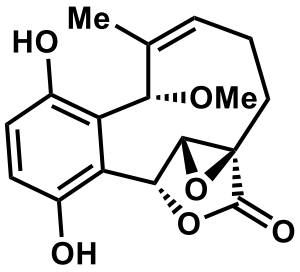
(+)-clavilactone C



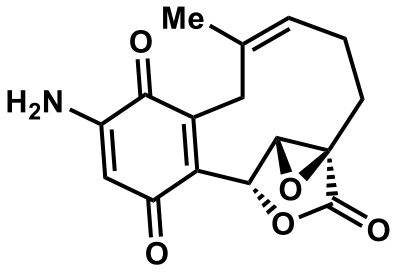
(+)-clavilactone D
(originally proposed structure)



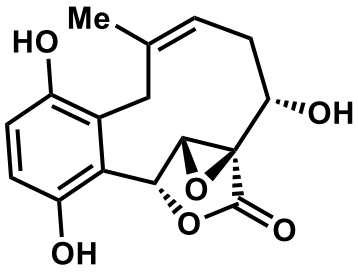
(+)-clavilactone D
(revised structure)



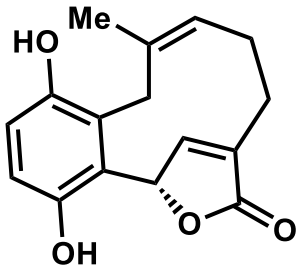
(+)-clavilactone E



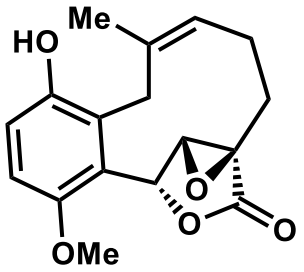
(+)-clavilactone F



(+)-clavilactone G



(-)-clavilactone H

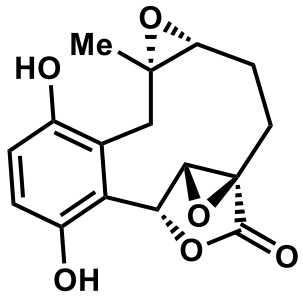


(+)-clavilactone I

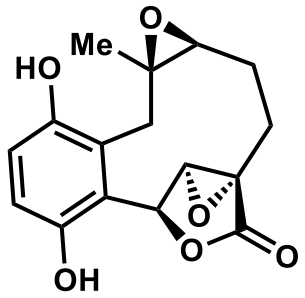
J. Chem. Soc., Perkin Trans. **1994**, 2165.; Phytochemistry 2000, 53, 1039– 1041.; *Org. Chem. Front.* **2019**, *6*, 3759-3765.; *Molecules*. **2019**. *24* (22),4015

Clavilactone Family

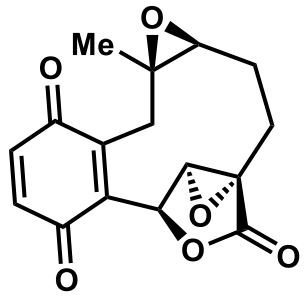
Compounds J-P



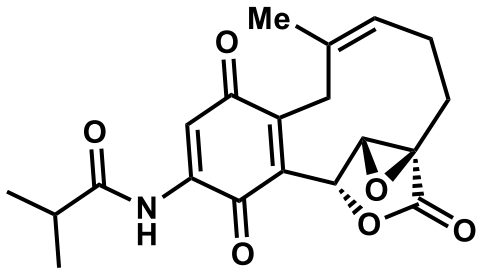
(+)-clavilactone J
(revised structure)



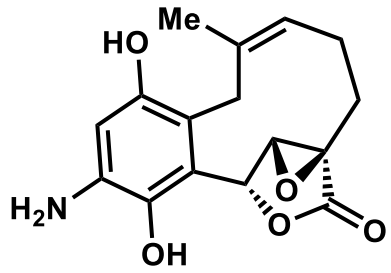
(-)-*ent*-clavilactone J



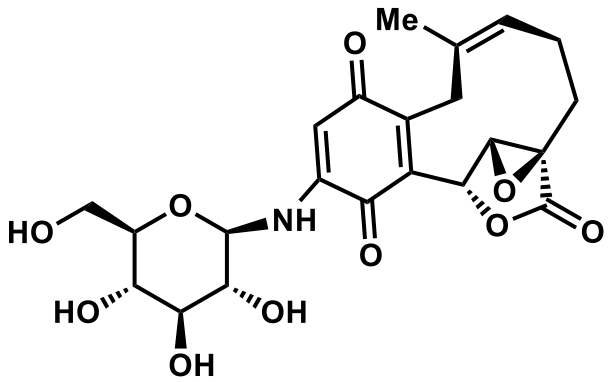
(+)-*ent*-clavilactone
J quinone



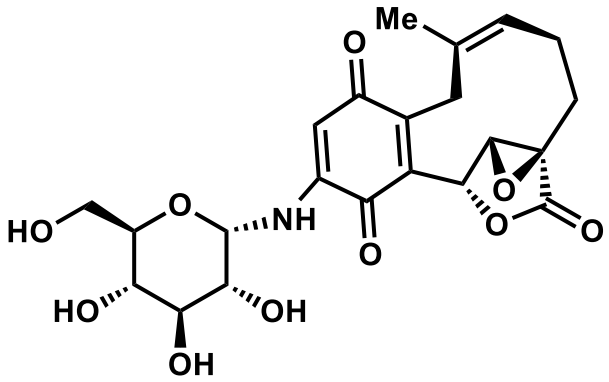
(+)-clavilactone K



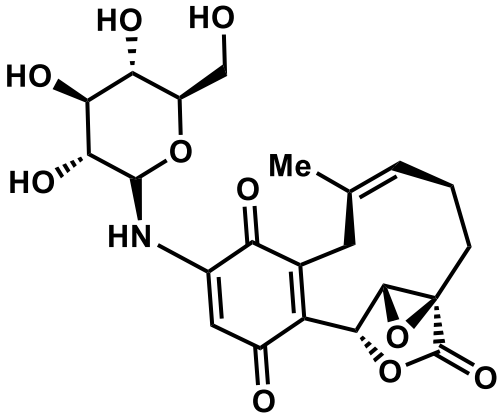
clavilactone L



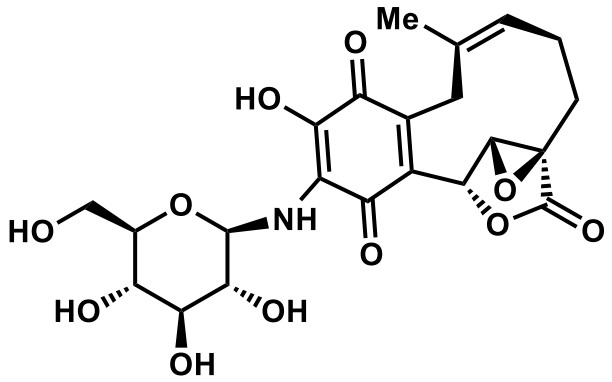
clavilactone M



clavilactone N



clavilactone O

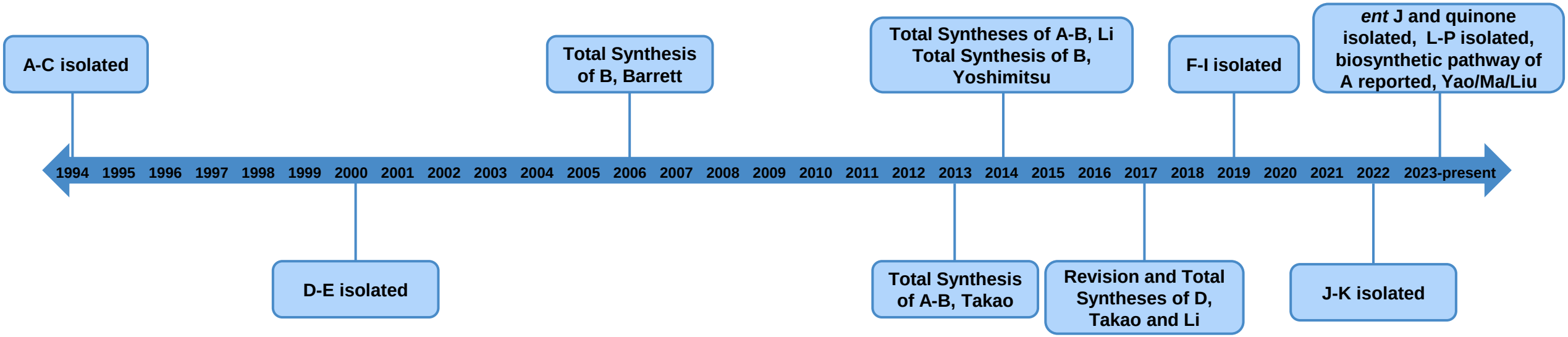


clavilactone P

Fitoterapia **2022**, *161* (7), 105251.; *Nat. Prod. Rep*. **2022**, *39*, 2003-2007; *J. Nat. Prod*. **2023**, *86* (11), 2580–2584.; *Zhongguo Zhong yao za zhi.* **2024**, *49*(11), 2947–2952.; *Molecules* **2023**, *28*(14), 5456

Clavilactones

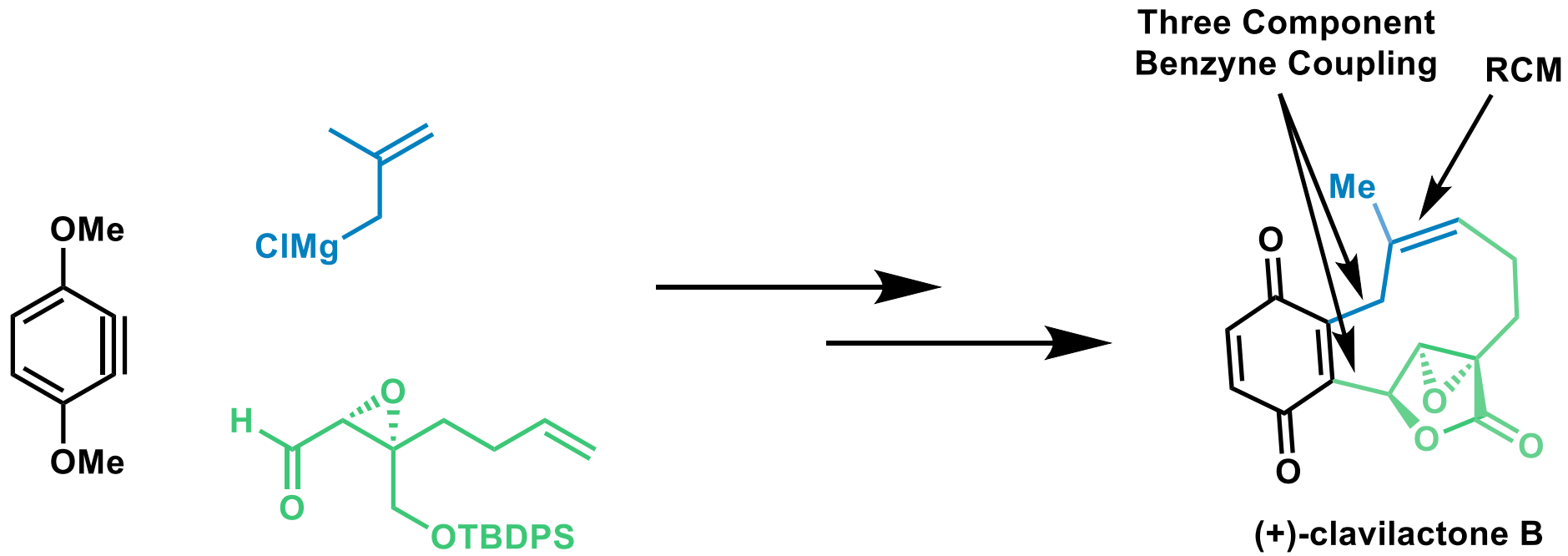
A History



J. Chem. Soc., Perkin Trans. **1994**, 2165.; Phytochemistry 2000, 53, 1039– 1041.; *Org. Chem. Front.* **2019**, *6*, 3759-3765.; *Molecules*. **2019**. *24* (22),4015.; *Fitoterapia* **2022**, *161* (7), 105251.; *J. Nat. Prod*. **2023**, *86* (11), 2580–2584.; *Zhongguo Zhong yao za zhi.***2024**, *49*(11), 2947–2952.; *Molecules* **2023**, *28*(14), 5456.; *Biochem. Pharmacol.* **2000**, *59,* 1539-1547.; *J. Am. Chem. Soc*. **2006**, *128* (43), 14042–14043 .; *Org. Lett.* **2013**, *15* (21), 5582-5585 .; *Chem. Eur. J.* **2017**, *23*, 3828 .; *J. Org. Chem.* **2018**, *83* (13), 7060–7075 .; *Angew. Chem. Int. Ed.* **2014,** *53,* 4164–4167 .; *J. Org. Chem.* **2017,** *82* (10), 5487-5491 .; *Org Lett.* **2015,** *17* (1), 126-129 .; *J. Am. Chem. Soc.* **2024,** *146* (16), 11457-11464

Barrett Lab Synthesis, 2006

Introduction

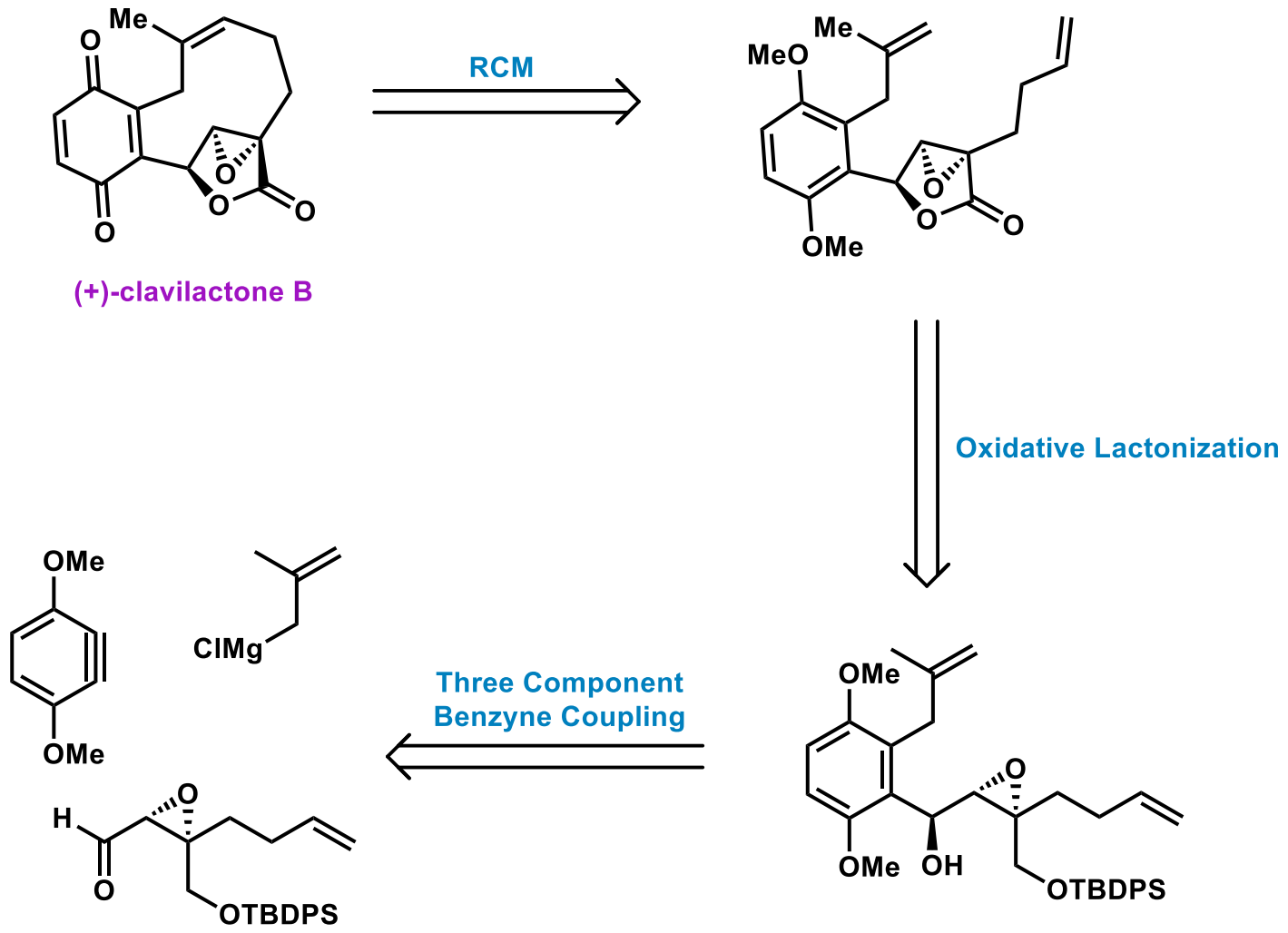


- first asymmetric synthesis of clavilactone B
- established absolute configuration of natural clavilactone family
- 11-12 steps, ~9% overall yield

J. Am. Chem. Soc. **2006**, *128* (43), 14042–14043

Barrett Lab Synthesis, 2006

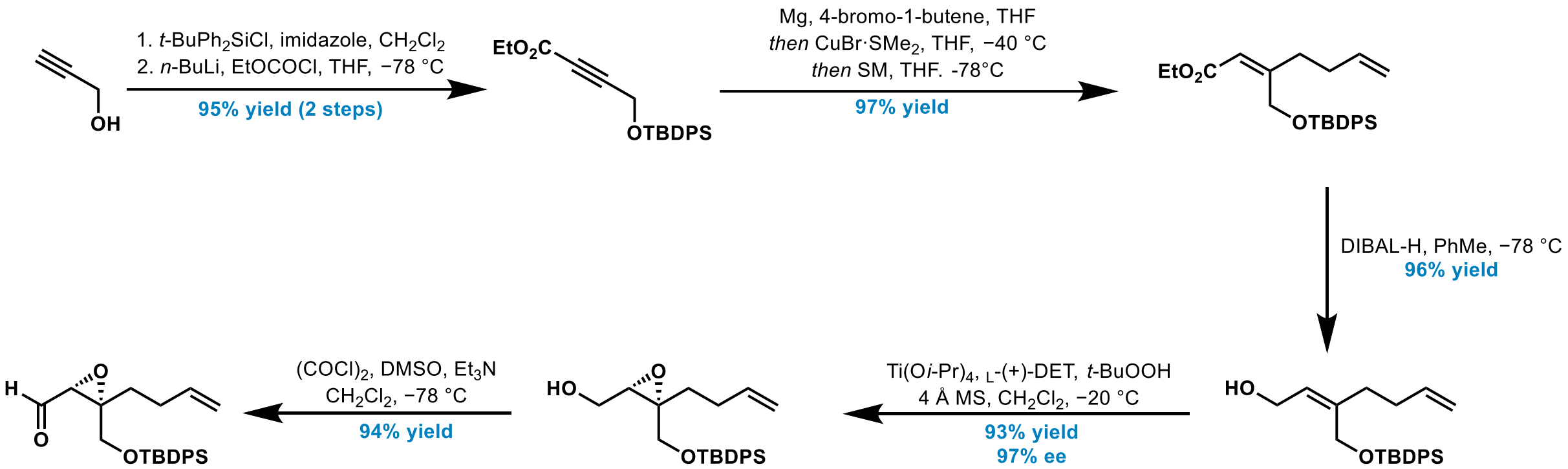
Retrosynthetic Plan



J. Am. Chem. Soc. **2006**, *128* (43), 14042–14043

Barrett Lab Synthesis, 2006

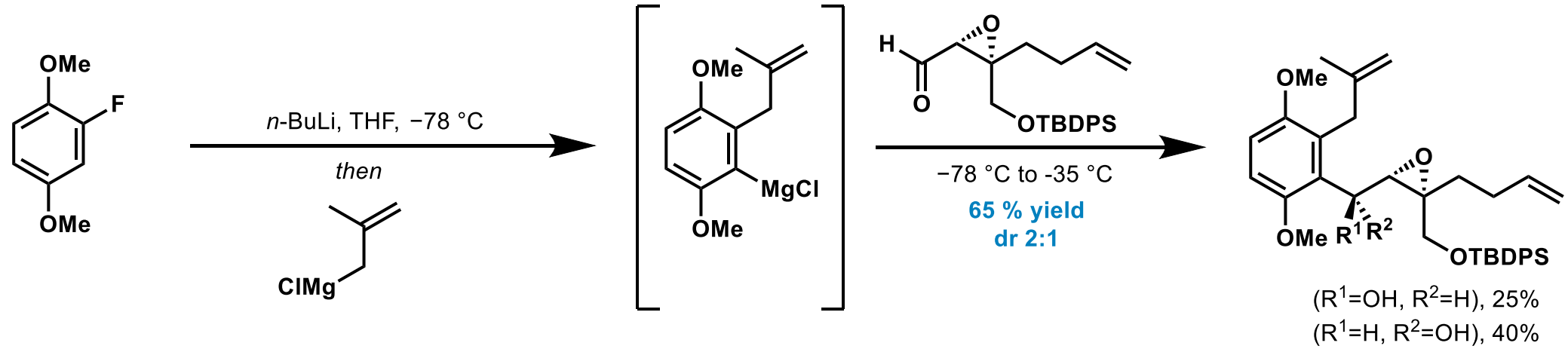
Forward Synthesis: Epoxide Fragment



J. Am. Chem. Soc. **2006**, *128* (43), 14042–14043

Barrett Lab Synthesis, 2006

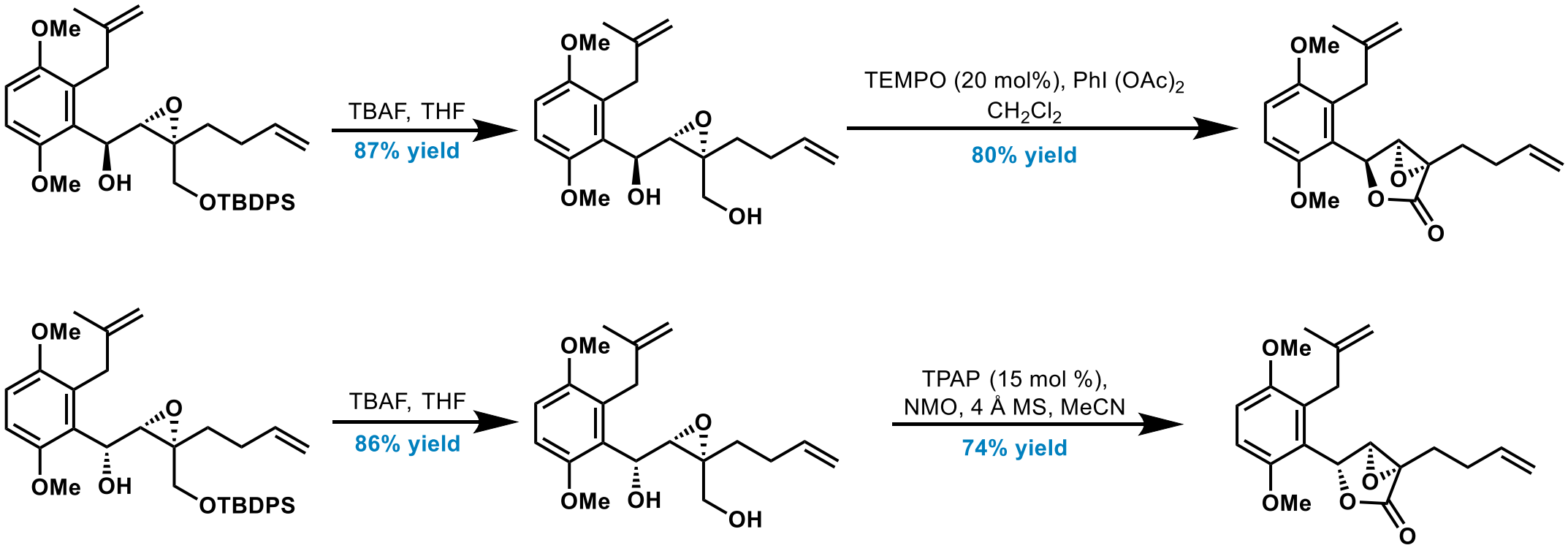
Forward Synthesis: Three Component Benzyne Coupling



J. Am. Chem. Soc. **2006**, *128* (43), 14042–14043

Barrett Lab Synthesis, 2006

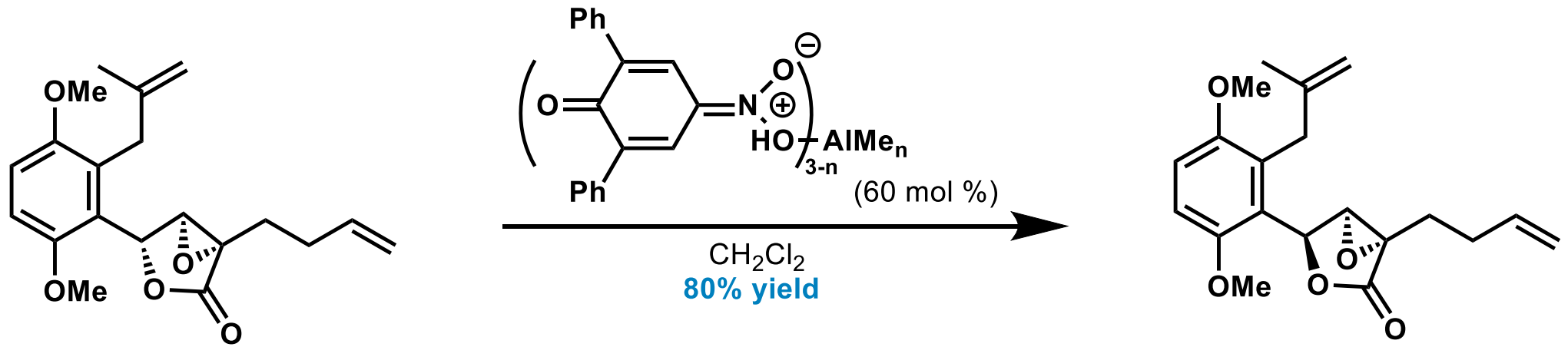
Forward Synthesis



J. Am. Chem. Soc. **2006**, *128* (43), 14042–14043

Barrett Lab Synthesis, 2006

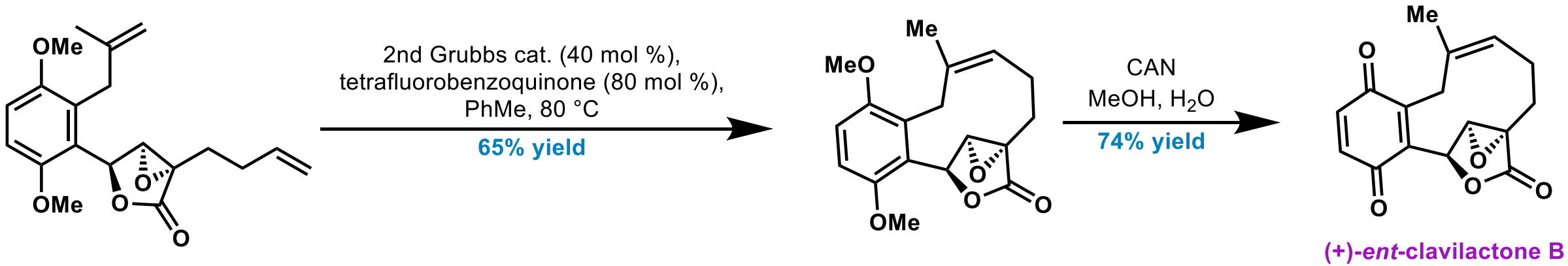
Forward Synthesis: Epimerization



J. Am. Chem. Soc. **2006**, *128* (43), 14042–14043

Barrett Lab Synthesis, 2006

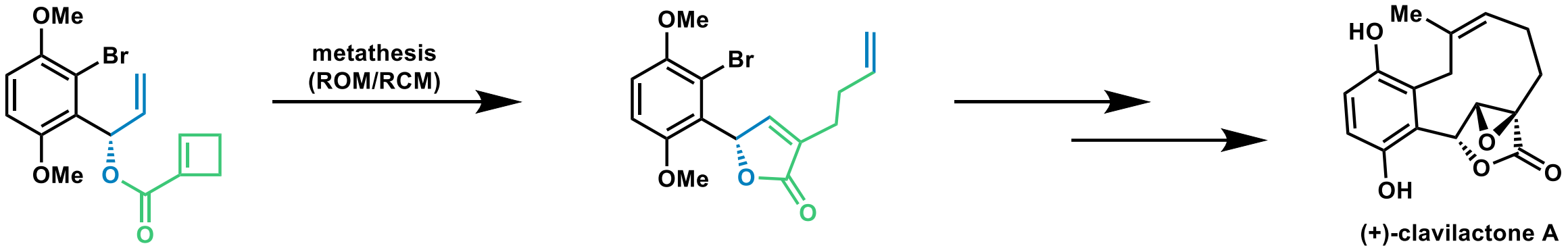
Forward Synthesis: Final Steps



J. Am. Chem. Soc. **2006**, *128* (43), 14042–14043

Takao Lab Synthesis, 2013

Introduction



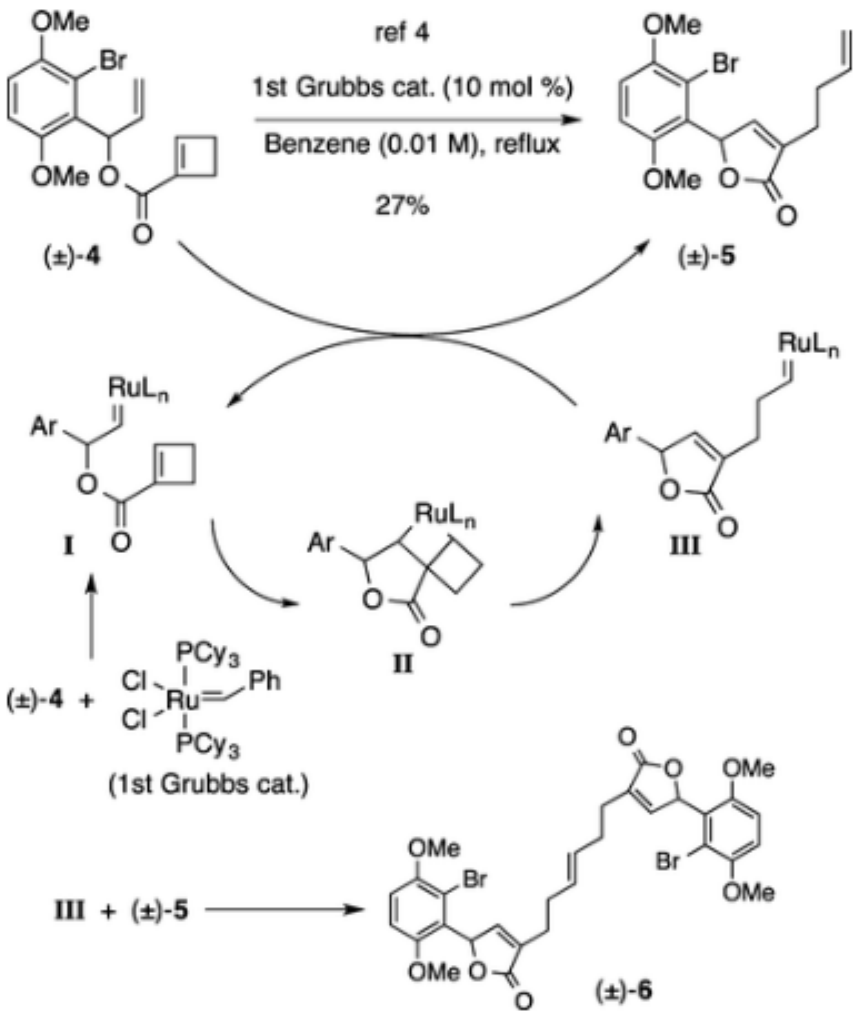
- first asymmetric synthesis of clavilactone A
- second asymmetric synthesis of clavilactone B
- 15 steps to clavilactone A, 1.6% overall yield

Org. Lett. **2013**, *15* (21), 5582-5585

Takao Lab Synthesis, 2013

Mechanism of ROM/RCM

Scheme 1

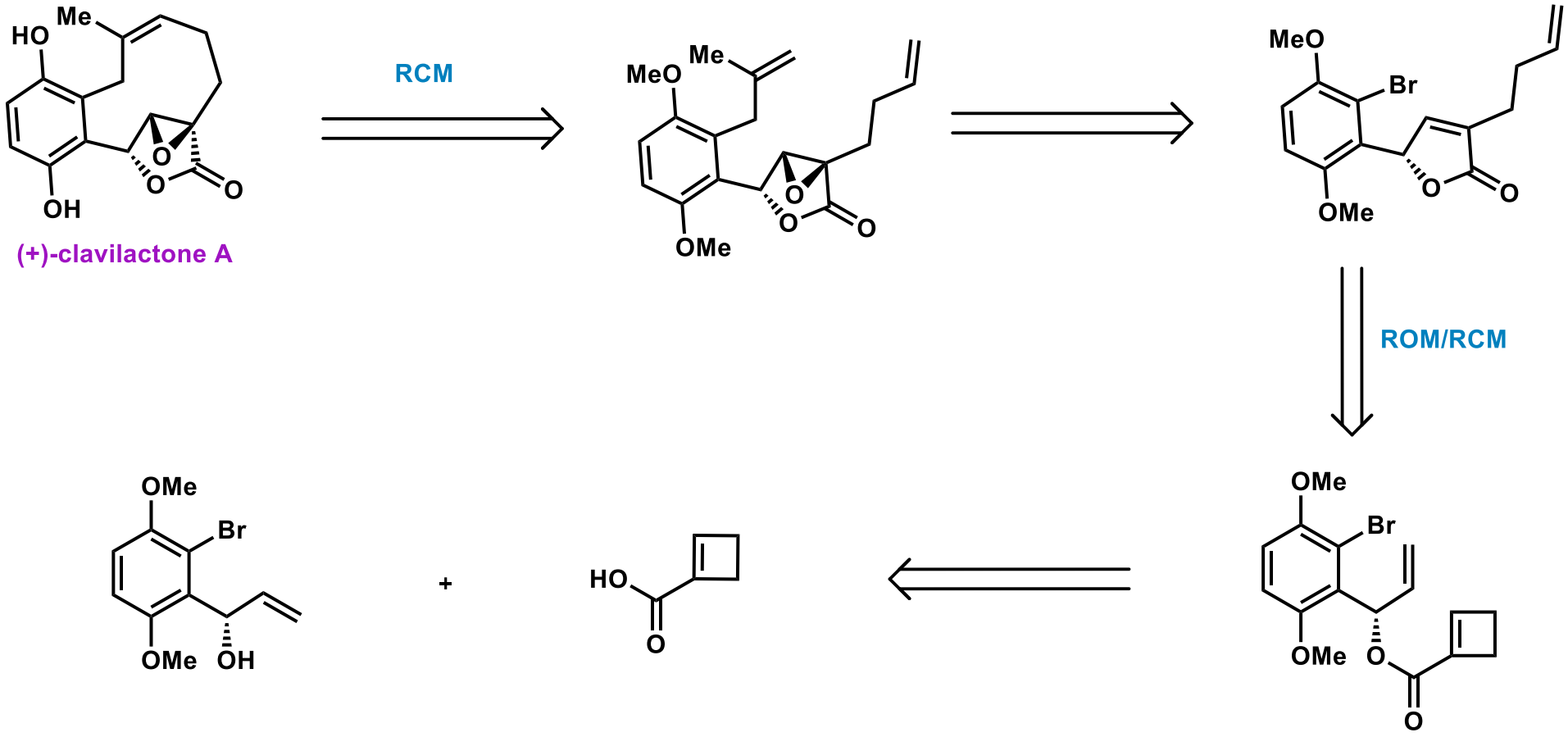


Scheme 1. ROM/RCM of Cyclobutenecarboxylate (±)-**4**

Org. Lett. **2013**, *15* (21), 5582-5585

Takao Lab Synthesis, 2013

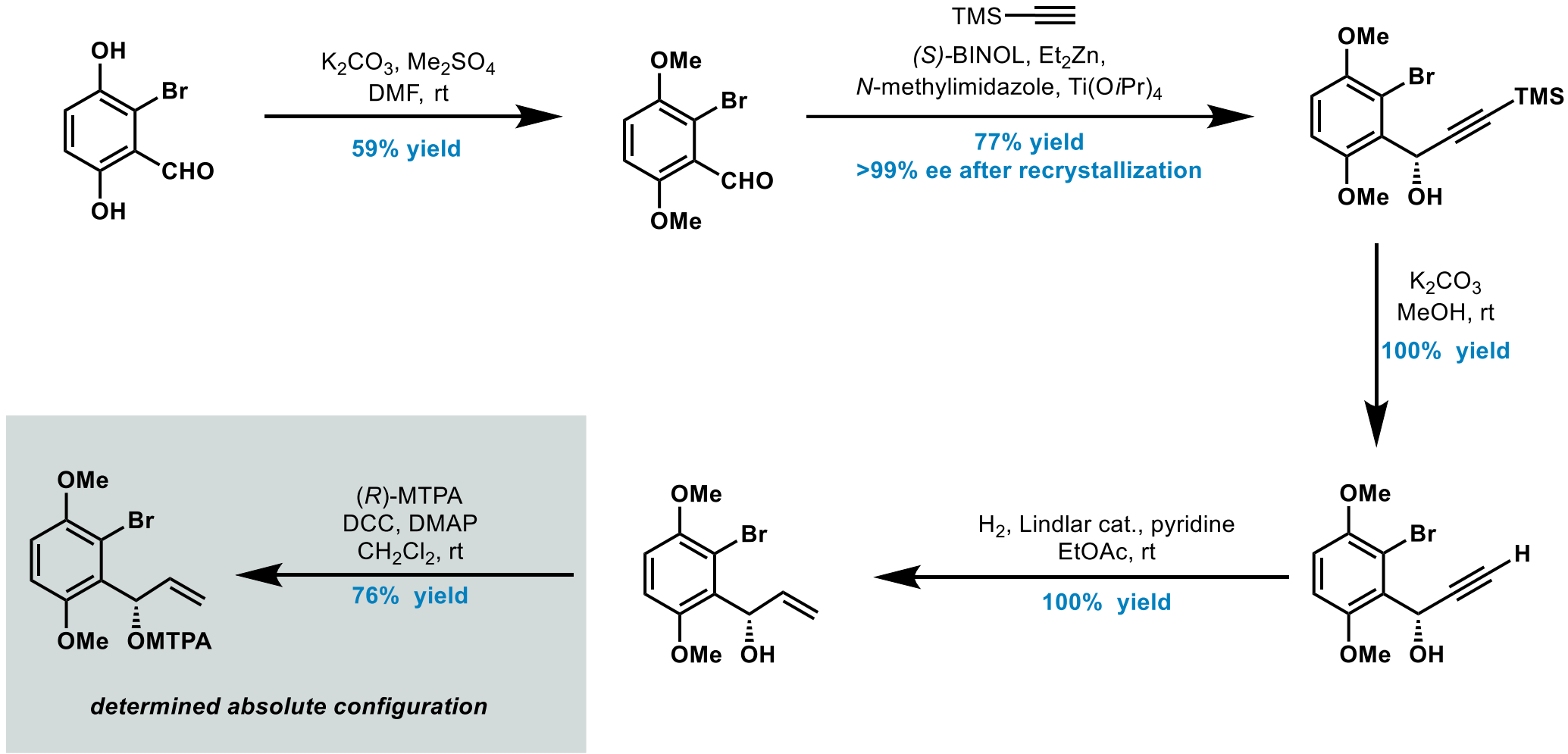
Retrosynthetic Plan



Org. Lett. **2013**, *15* (21), 5582-5585

Takao Lab Synthesis, 2013

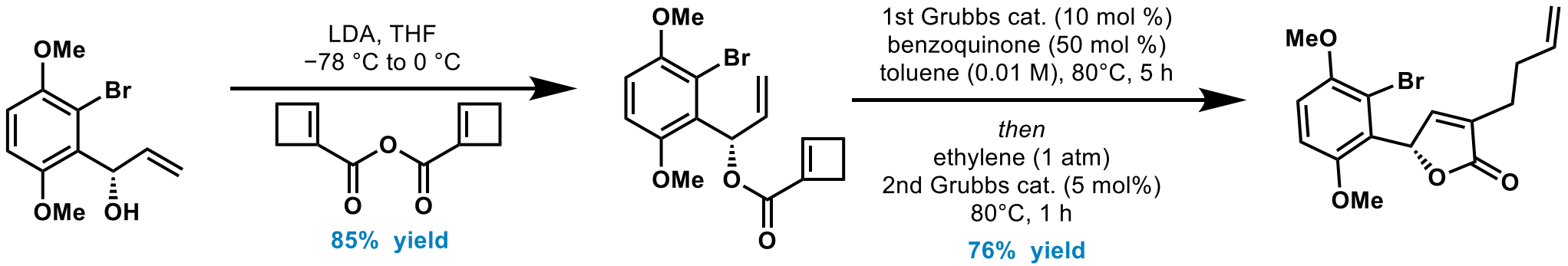
Forward Synthesis: Alcohol Fragment



Org. Lett. **2013**, *15* (21), 5582-5585

Takao Lab Synthesis, 2013

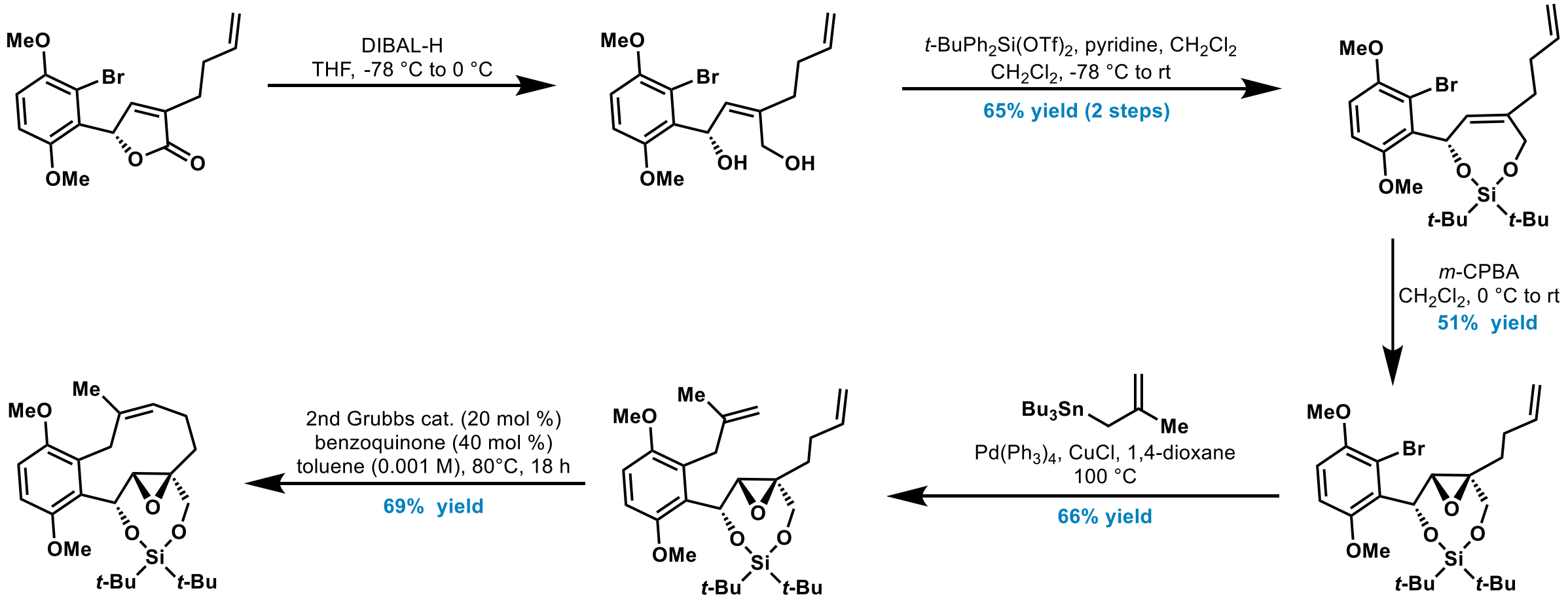
Forward Synthesis: ROM/RCM



Org. Lett. **2013**, *15* (21), 5582-5585

Takao Lab Synthesis, 2013

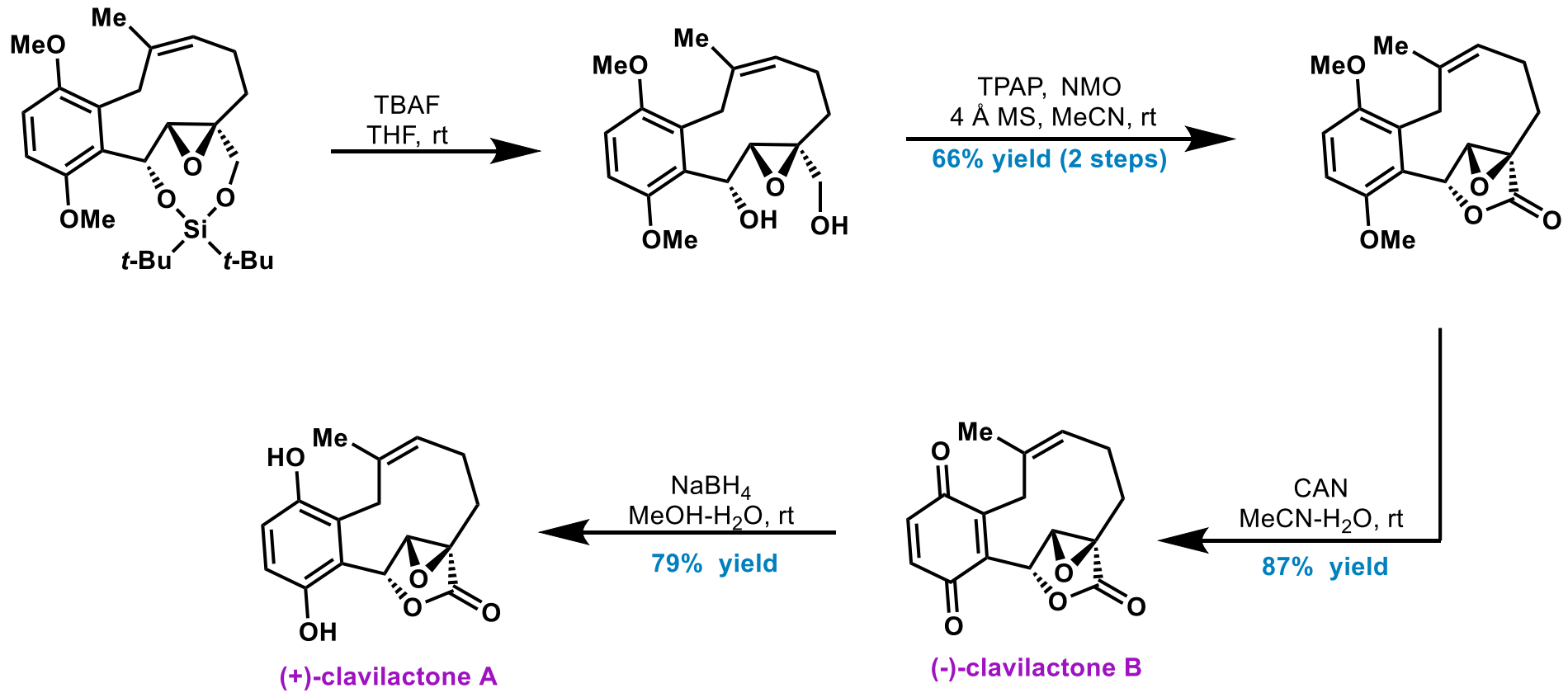
Forward Synthesis



Org. Lett. **2013**, *15* (21), 5582-5585

Takao Lab Synthesis, 2013

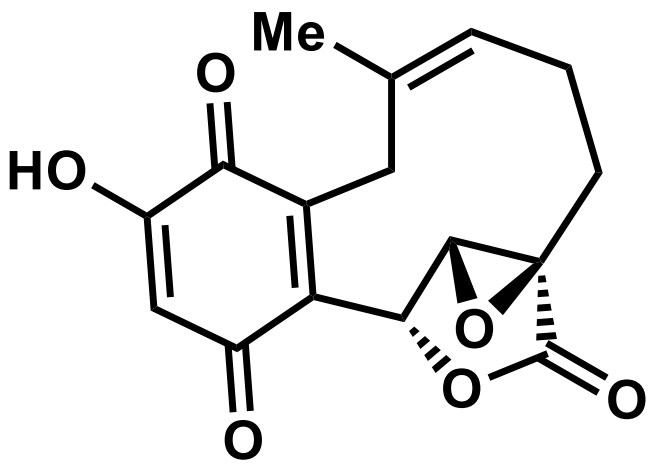
Forward Synthesis: Final Steps



Org. Lett. **2013**, *15* (21), 5582-5585

Takao Lab Synthesis, 2017

Clavilactone D Revisions

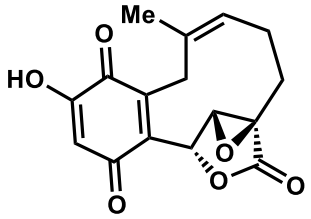


(+)-clavilactone D
(originally proposed structure)

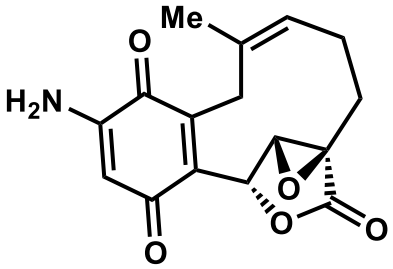
Chem. Eur. J. **2017**, *23*, 3828

Takao Lab Synthesis, 2017

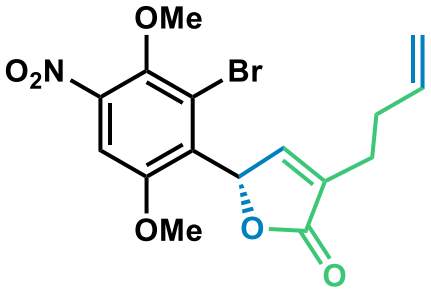
Clavilactone D Revisions

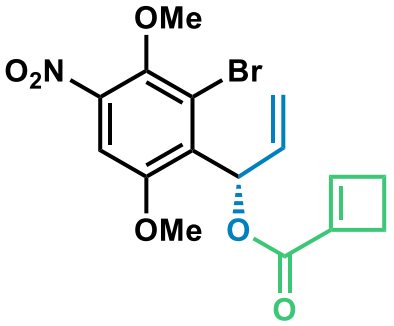


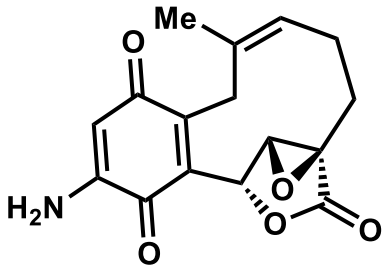
(+)-clavilactone D
(originally proposed structure)



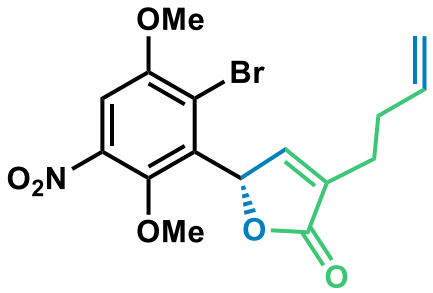
(+)-clavilactone D
structure possibility 1

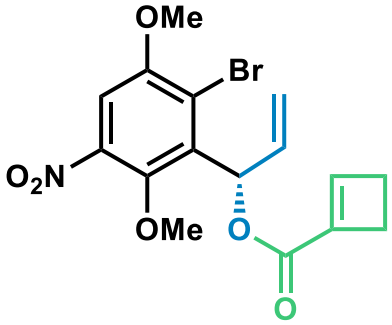






(+)-clavilactone D
structure possibility 2



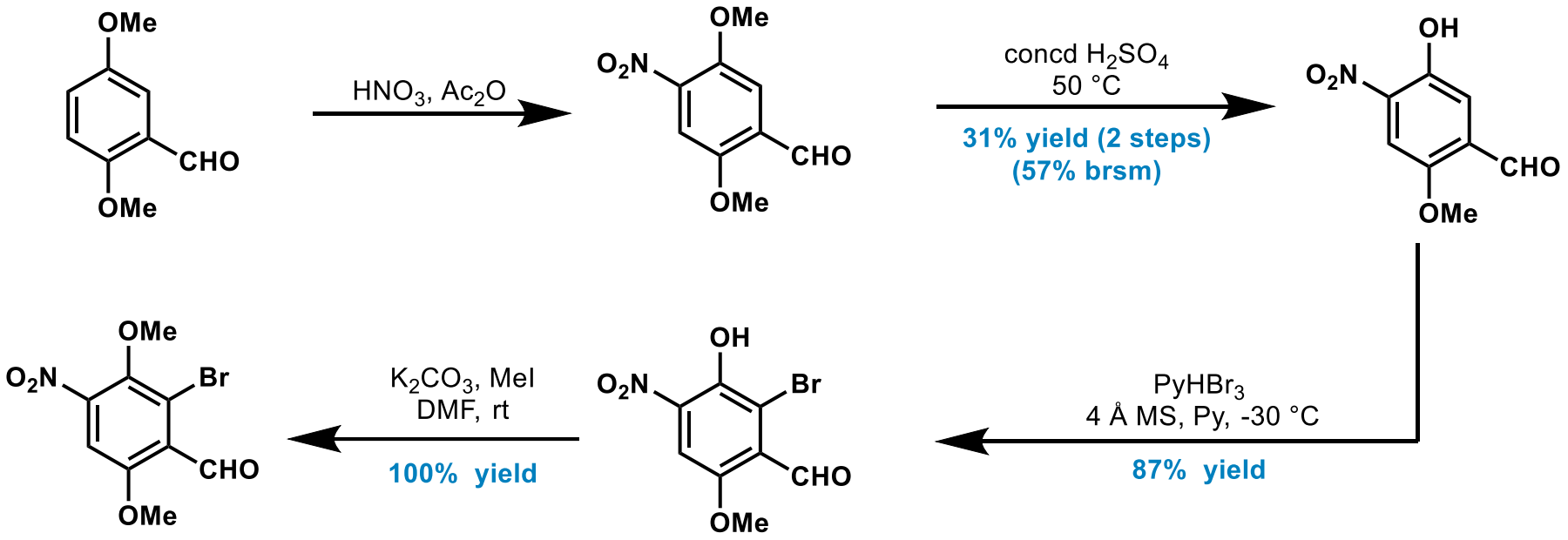


Chem. Eur. J. **2017**, *23*, 3828

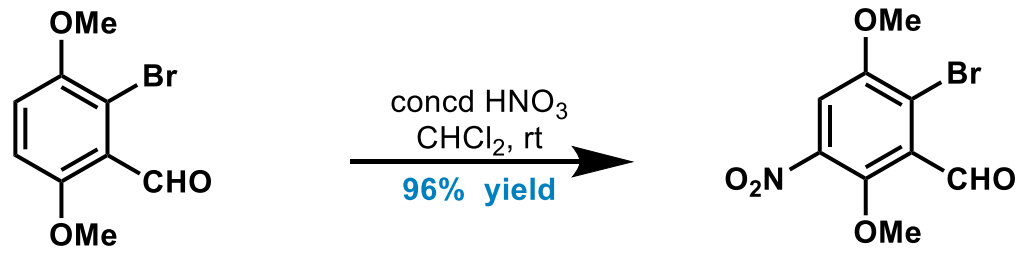
Takao Lab Synthesis, 2017

Clavilactone D Revisions

Towards Structure 1



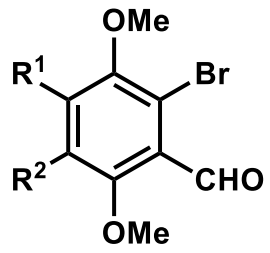
Towards Structure 2



Chem. Eur. J. **2017**, *23*, 3828

Takao Lab Synthesis, 2017

Clavilactone D Revisions

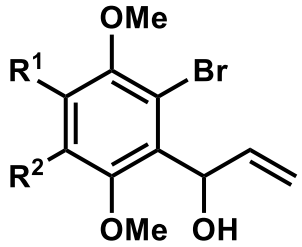


a. R^1=NO_2, R^2=H
b. R^1=H, R^2=NO_2

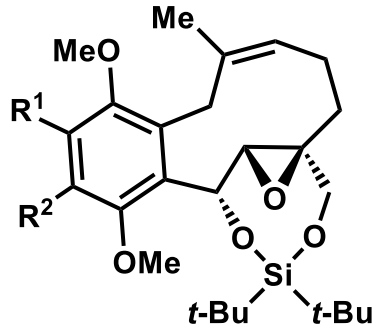
BrMg

THF, -78 °C

a. 73% yield
b. 77% yield



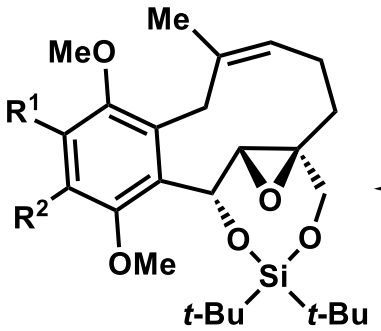
over 7 steps
a. ~14% yield
b. ~12% yield



a. R^1=NO_2, R^2=H
b. R^1=H, R^2=NO_2

1. Pd/C, 1,4 cyclohexadiene
EtOH, 70 °C
2. $(Boc)_2O$, Et_3N, 1,4-dioxane, 85 °C

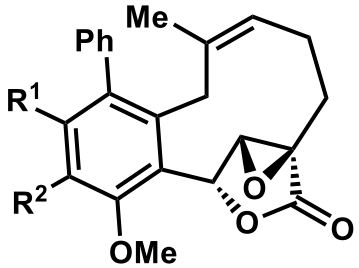
a. 86% yield
b. 99% yield



a. R^1=NHBoc, R^2=H
b. R^1=H, R^2=NHBoc

1. TBAF, THF, rt
2. TPAP, NMO, 4 Å MS, MeCN, rt

a. 74% yield
b. 87% yield



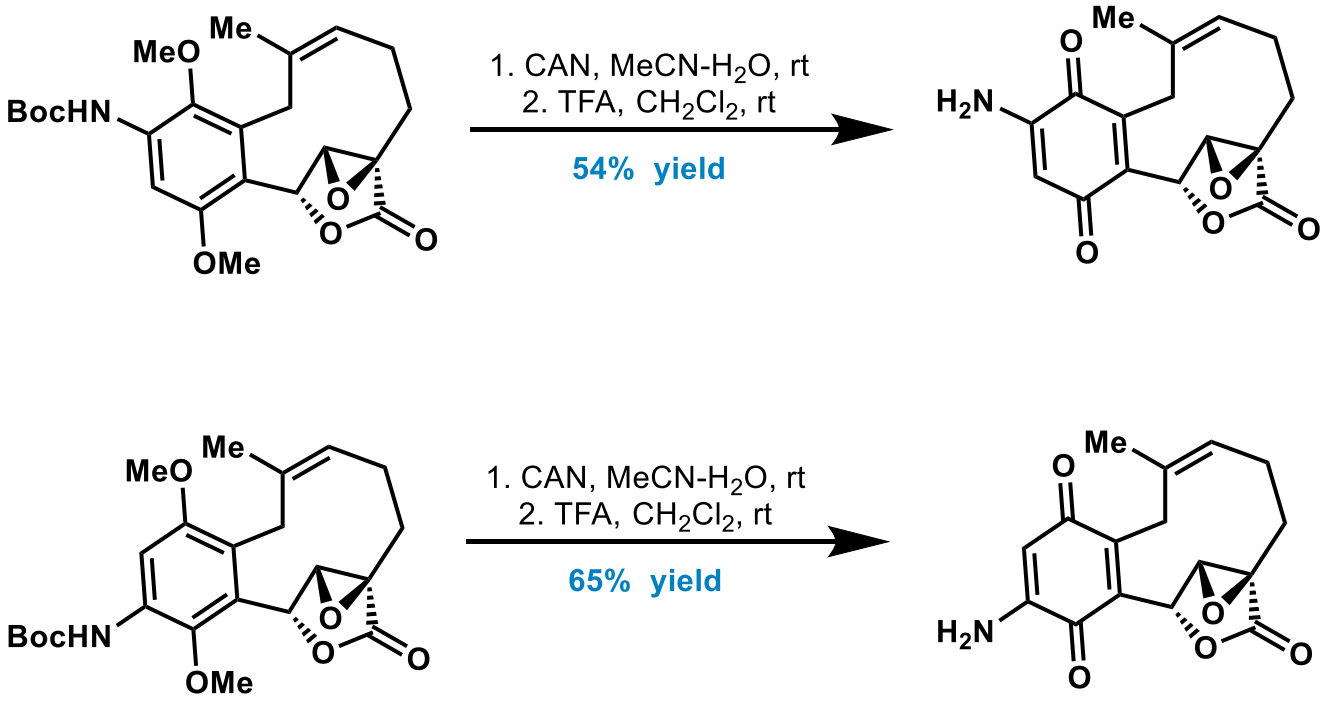
a. R^1=NHBoc, R^2=H
b. R^1=H, R^2=NHBoc



Chem. Eur. J. **2017**, *23*, 3828

Takao Lab Synthesis, 2017

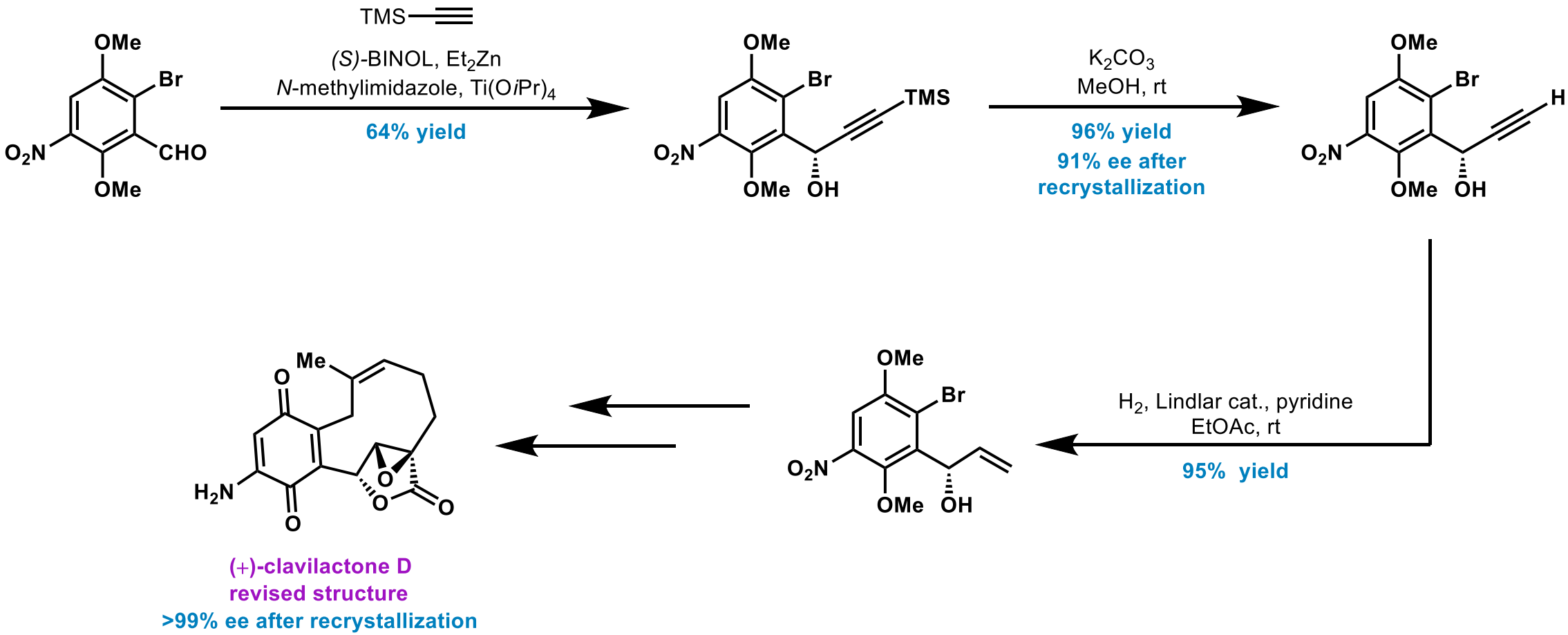
Clavilactone D Revisions



Chem. Eur. J. **2017**, *23*, 3828; *Org. Chem. Front.* **2019**, *6*, 3759-3765

Takao Lab Synthesis, 2018

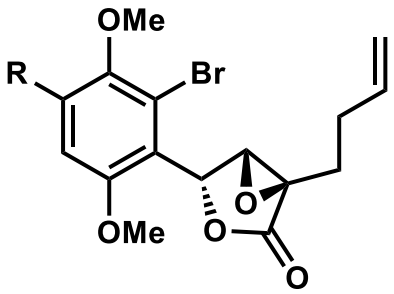
Clavilactone D Revisions



J. Org. Chem. **2018**, *83* (13), 7060–7075

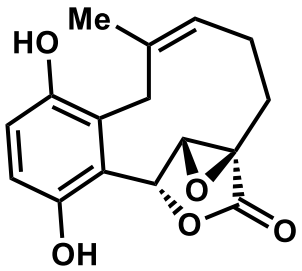
Li Lab Synthesis, 2014

Introduction

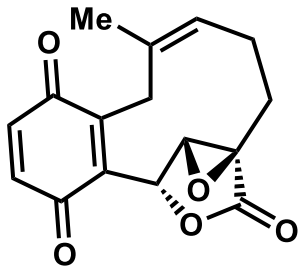


single diastereomer

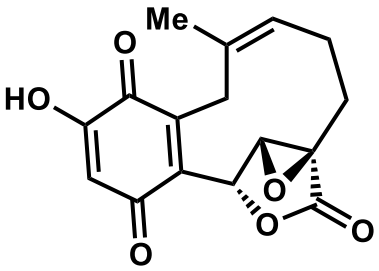
3-4 steps



(±)-clavilactone A

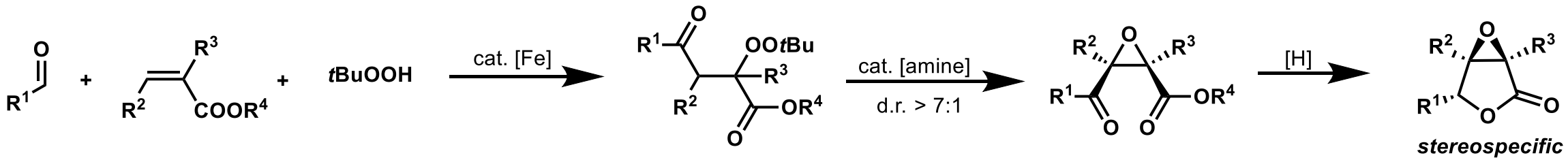


(±)-clavilactone B



(±)-clavilactone D
(originally proposed structure)

key methodology



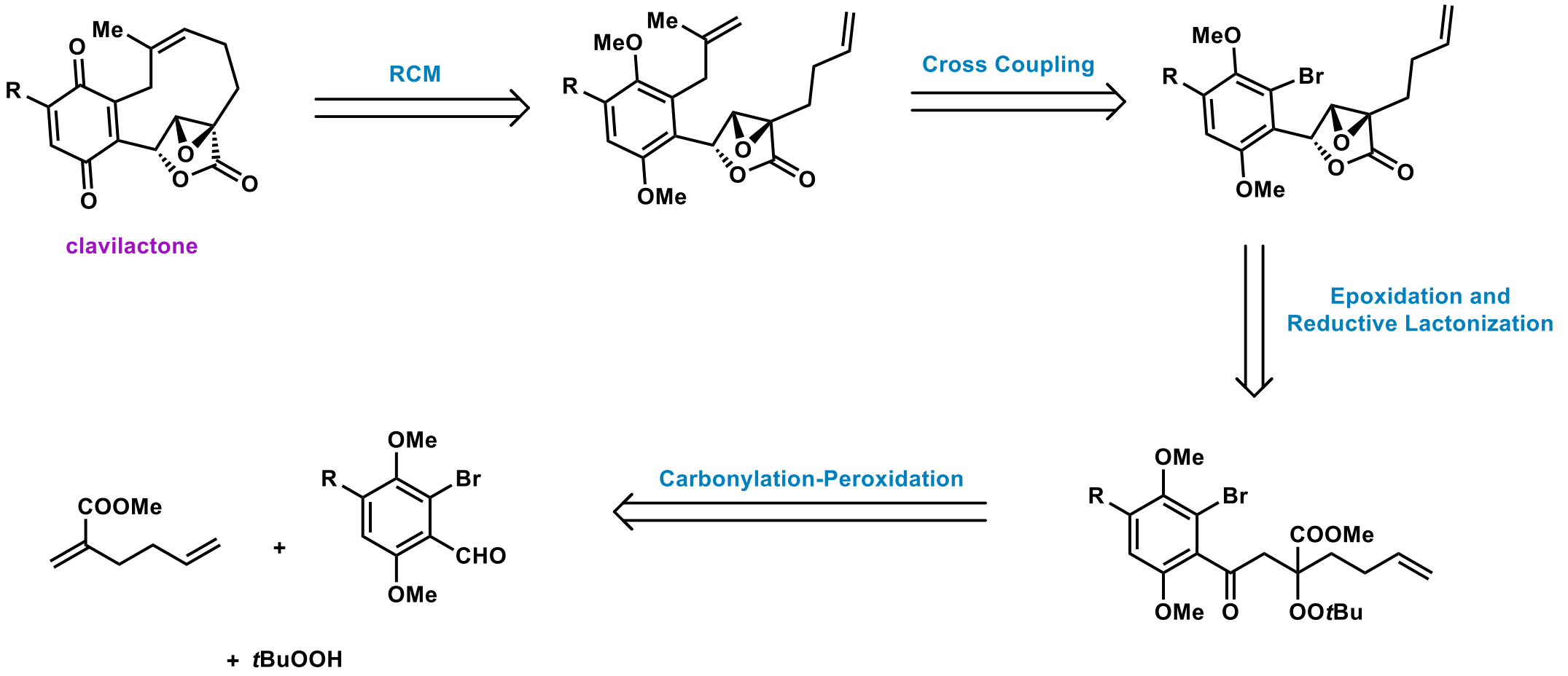
- iron catalyzed carbonylation-peroxidation
- amine-catalyzed epoxidation and reductive lactonization
- synthesis of (±) clavilactone A in 7 steps, 14.9 % overall yield
- synthesis of (±) clavilactone B in 6 steps, 15.1 % overall yield
- synthesis of (±) proposed clavilactone D in 7 steps, 15.5 % overall yield



Angew. Chem. Int. Ed. **2014,** *53,* 4164–4167

Li Lab Synthesis, 2014

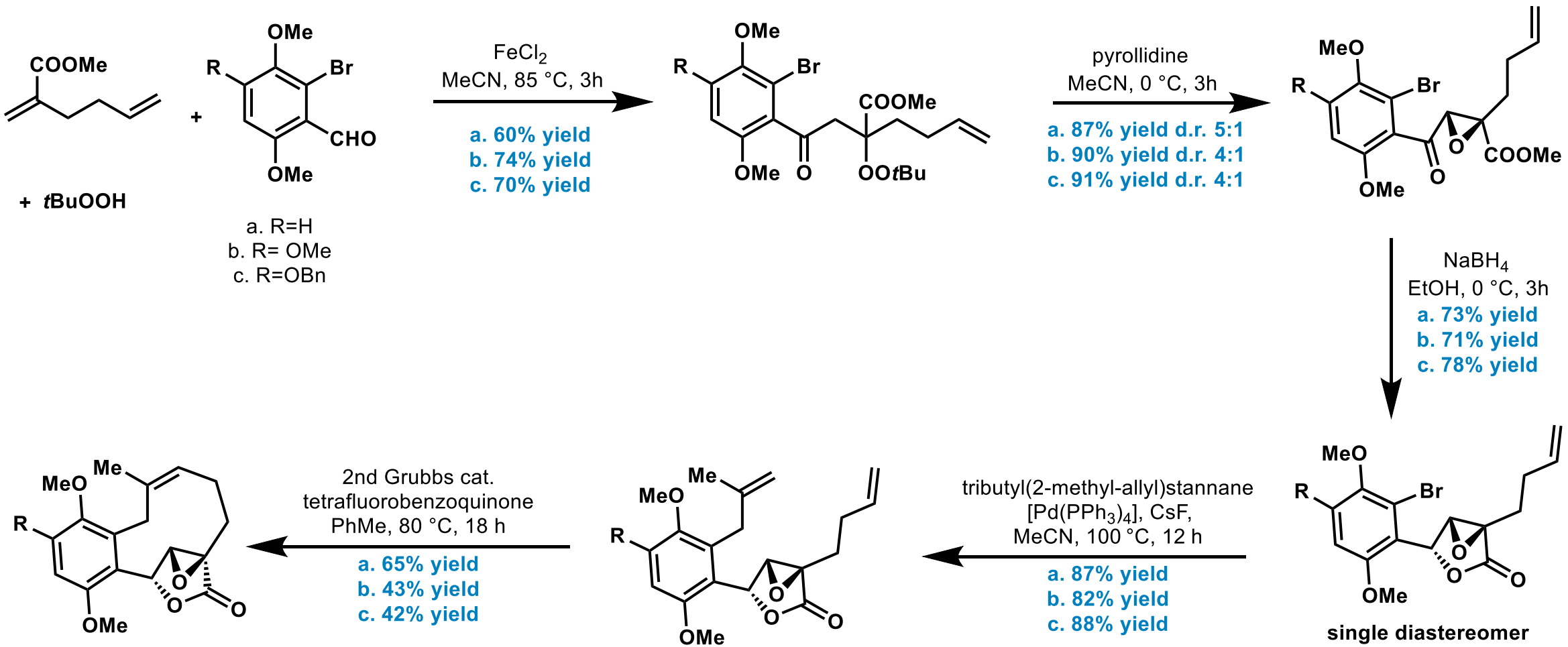
Retrosynthetic Plan



Angew. Chem. Int. Ed. **2014,** *53,* 4164–4167

Li Lab Synthesis, 2014

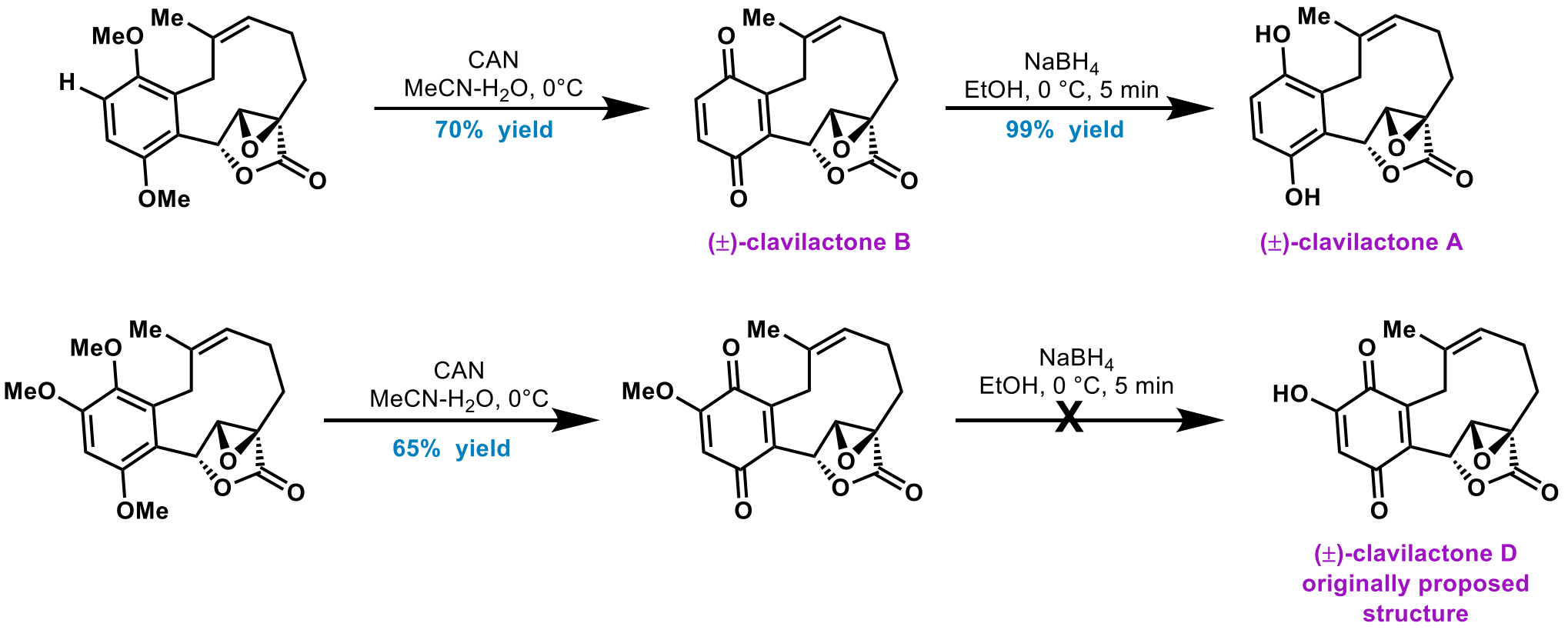
Forward Synthesis



Angew. Chem. Int. Ed. **2014,** *53,* 4164–4167

Li Lab Synthesis, 2014

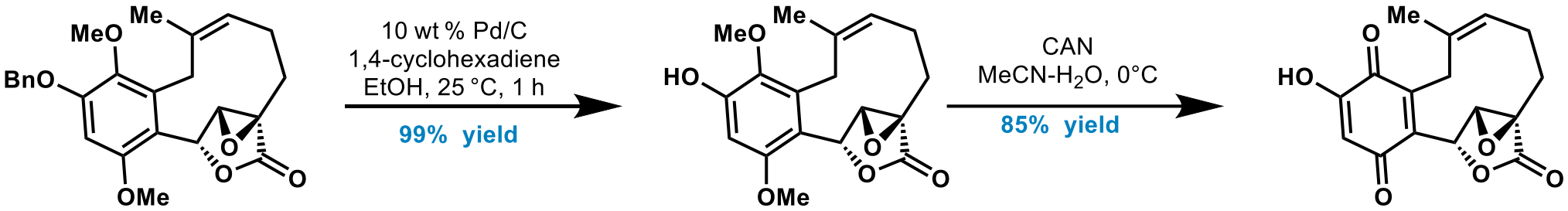
Forward Synthesis: Final Steps



Angew. Chem. Int. Ed. **2014,** *53,* 4164–4167

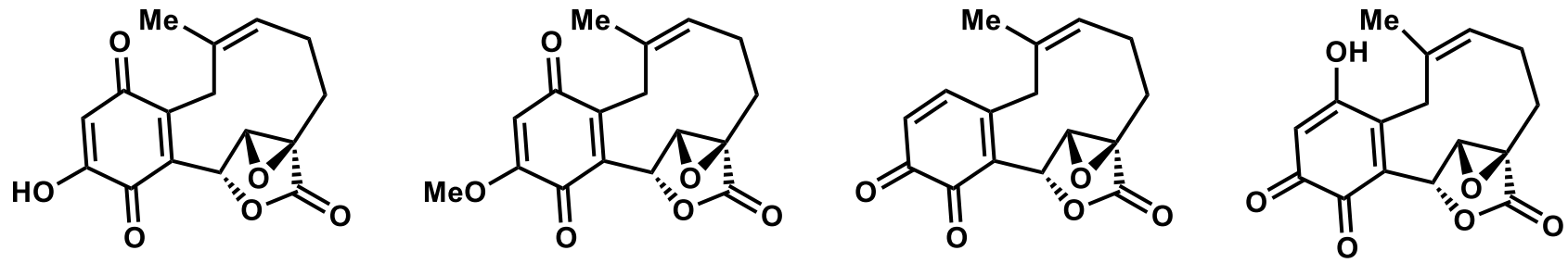
Li Lab Synthesis, 2014

Forward Synthesis: Final Steps



(±)-clavilactone D
originally proposed structure

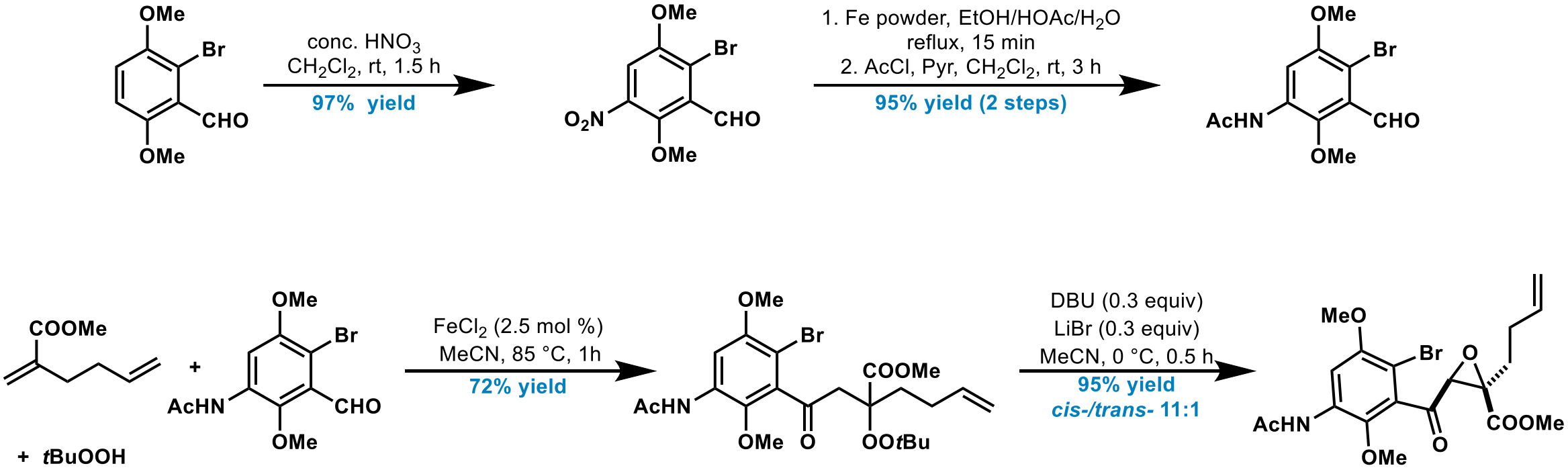
other derivatives made



Angew. Chem. Int. Ed. **2014,** *53,* 4164–4167

Li Lab Synthesis, 2017

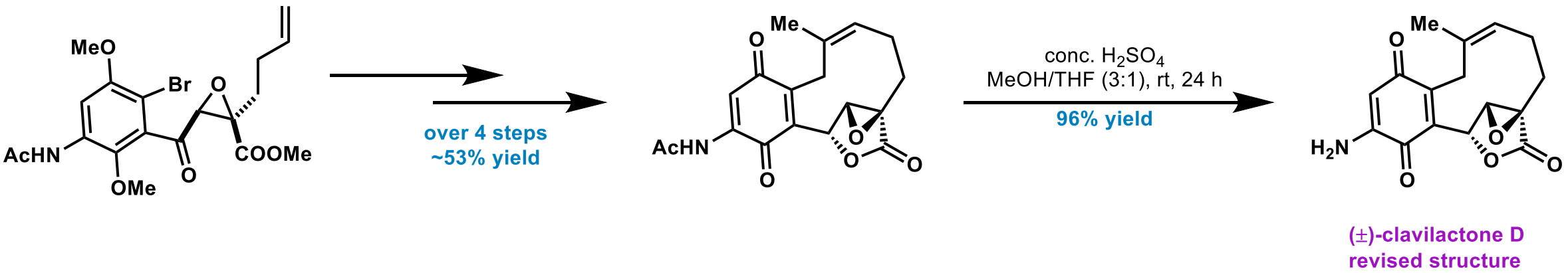
Clavilactone D Revisions



J. Org. Chem. **2017,** *82* (10), 5487-5491

Li Lab Synthesis, 2017

Clavilactone D Revisions

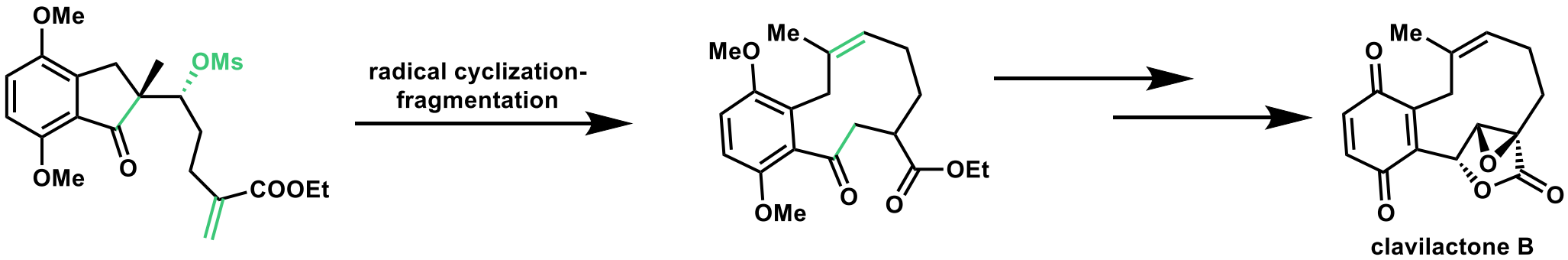


(±)-clavilactone D revised structure

J. Org. Chem. **2017,** *82* (10), 5487-5491

Yoshimitsu Lab Synthesis, 2014

Introduction

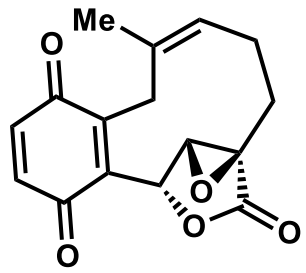


- SmI_2-mediated radical cyclization, alternative to RCM
  - 8 steps to clavilactone B, ~9% overall yield

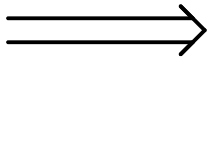
Org Lett. **2015,** *17* (1), 126-129

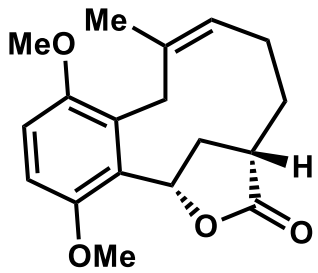
Yoshimitsu Lab Synthesis, 2014

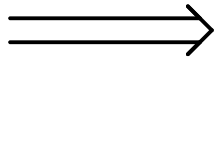
Retrosynthetic Plan

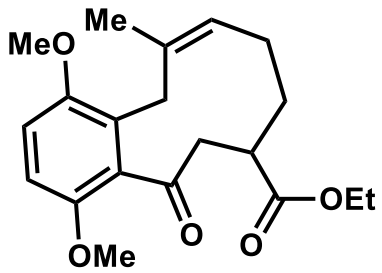


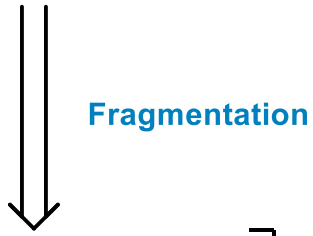
clavilactone B

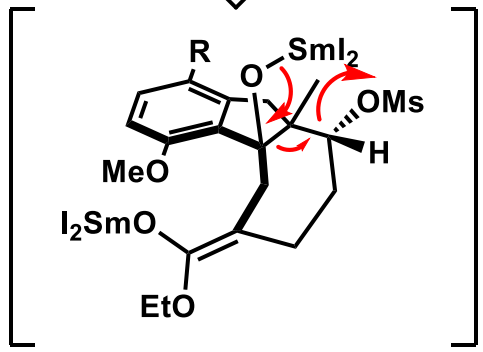


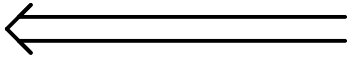


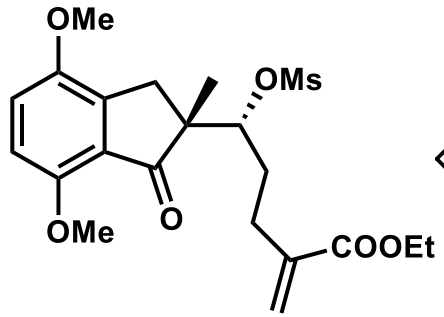


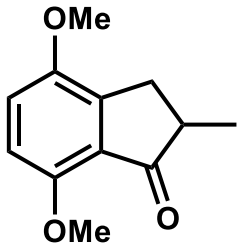










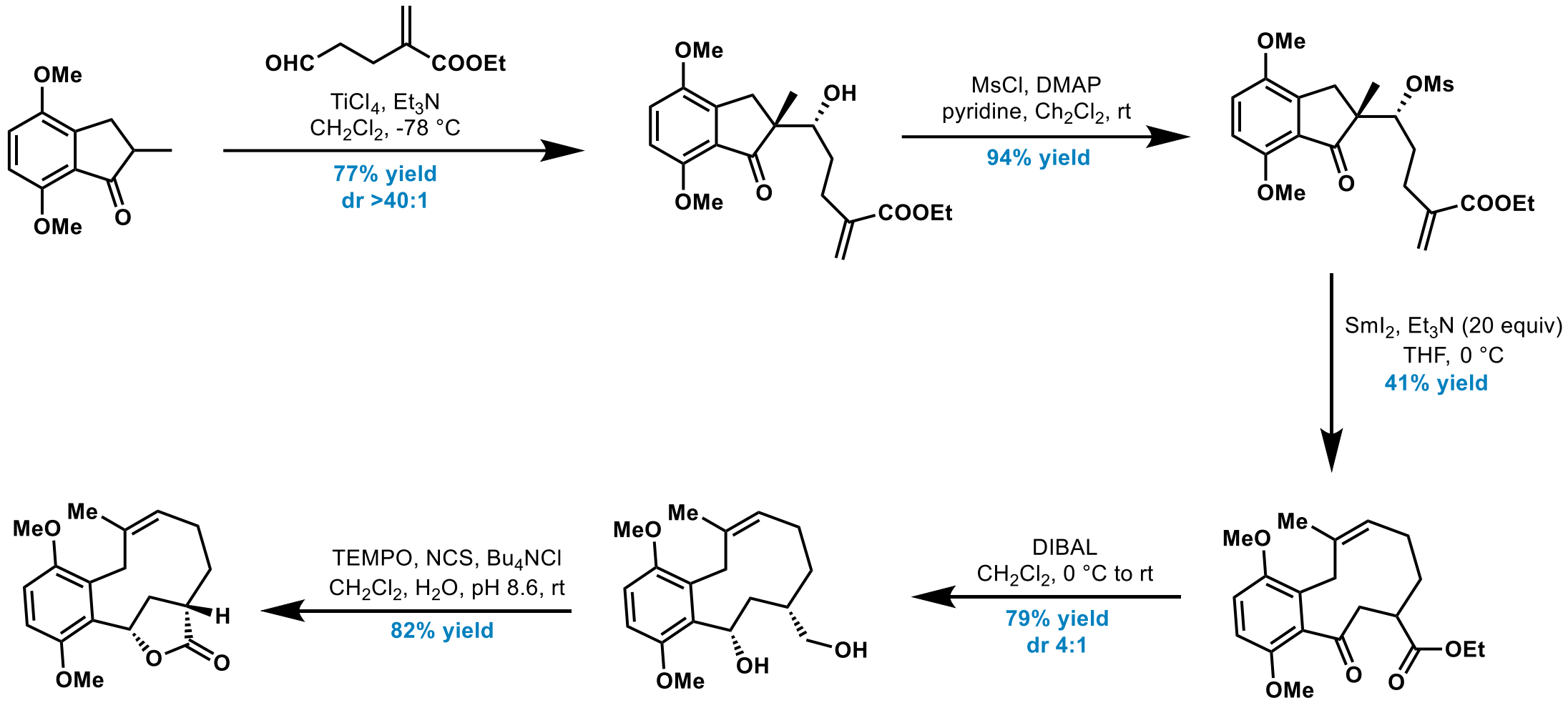




Org Lett. **2015,** *17* (1), 126-129

Yoshimitsu Lab Synthesis, 2014

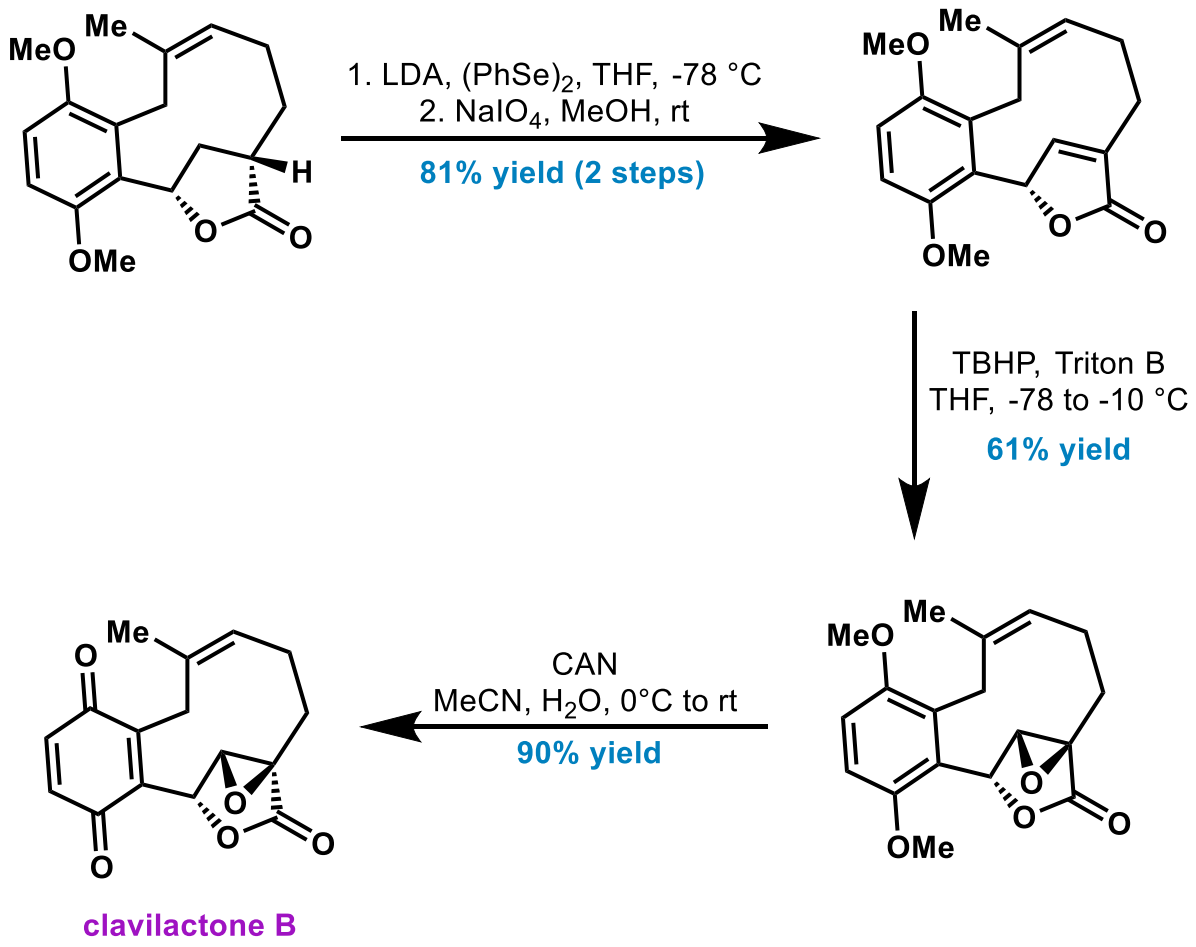
Forward Synthesis



Org Lett. **2015,** *17* (1), 126-129

Yoshimitsu Lab Synthesis, 2014

Forward Synthesis: Final Steps

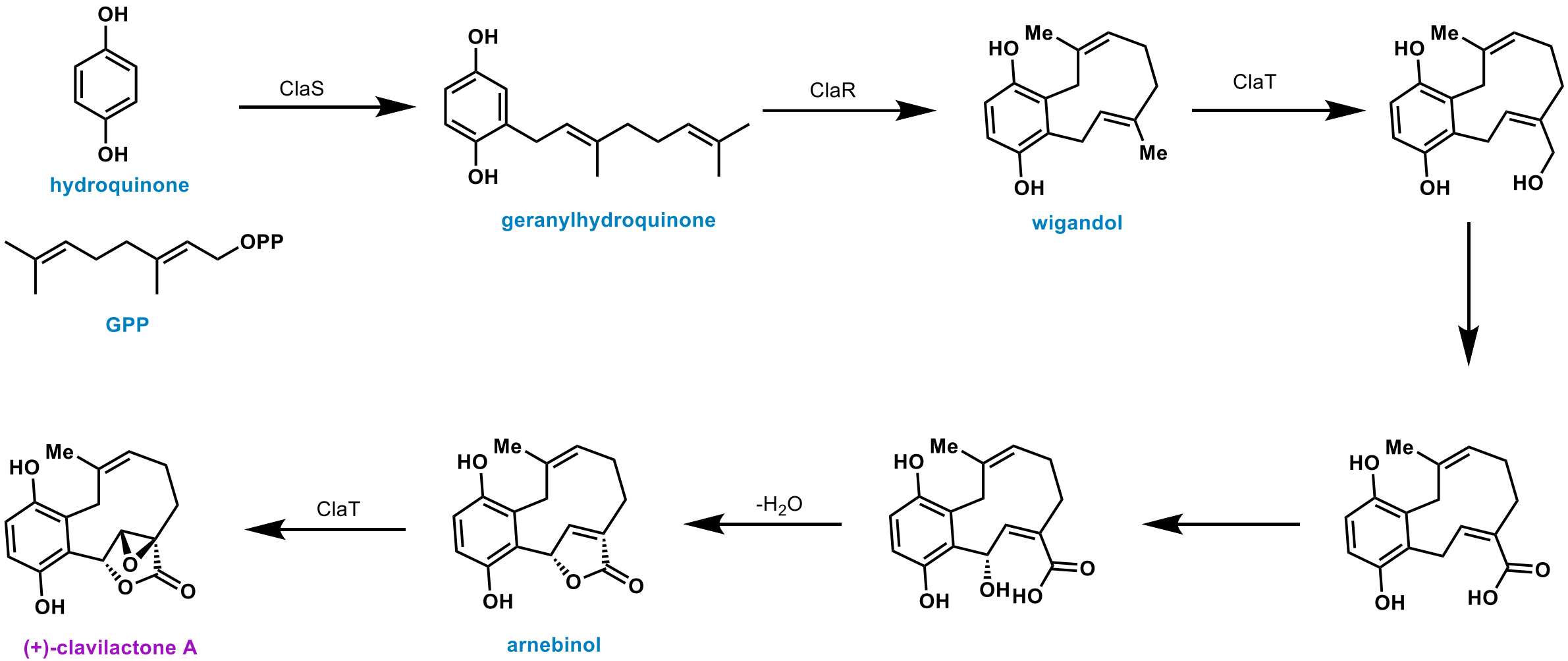


clavilactone B

Org Lett. **2015,** *17* (1), 126-129

Biosynthetic Pathway, 2024

Yao, Ma, and Liu



J. Am. Chem. Soc. **2024,** *146* (16), 11457-11464