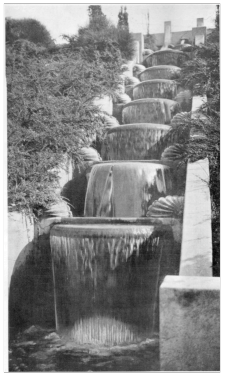
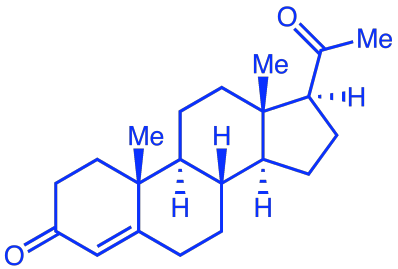
Cascades in Total Synthesis

Domino

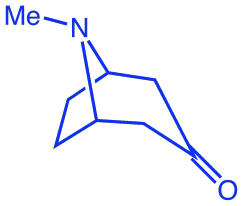


Cascade

Tandem



(±)-*Progesterone*
Johnson, W. S. **1971**

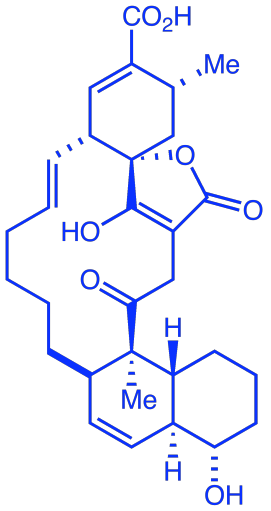


Tropinone
Robinson, B. **1917**

Phong V. Pham

MacMillan Group Meeting

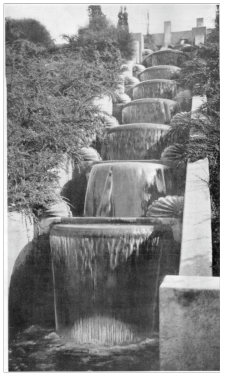
Princeton, July 29, 2009



Chlorothricolide
Roush, W. R. **1998**

What Are Cascade Reactions?

Domino



Cascade

Tandem

Cascade reactions are chemical transformations where two or more bonds are formed in one-pot, in which the latter transformations take place at the functionalities obtained in the former-bond forming process.

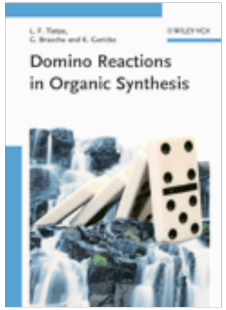
Advantages:

1) Save material, time, labor, energy, resourse and waste management.
2) Beneficial effect on the environment.

Leading references:

1) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*, Wiley–VCH, Weinheim 2006

2) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *ACIE* **2006**, *45*, 7134



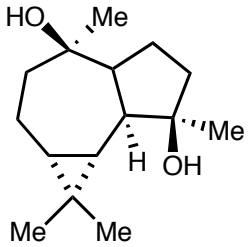
Why Do We Need "Cascades in Total Synthesis"?

The ability to create complex molecules in only a few steps has long been the dream of chemists. Nature has been using cascade approaches for billion of years to efficiently construct compounds with different levels of structural complexity.[1]

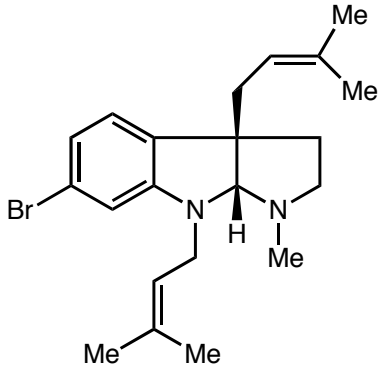
"We need to set a time line, at which any natural products can be synthesized in less than 5 steps..."

Dave MacMillan (Group meeting)

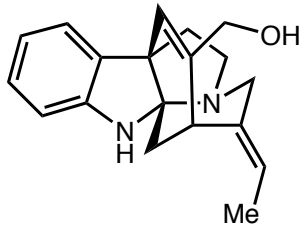
Walji, A. A. and MacMillan, D. W. C. *Synlett* **2007**, 1477



(–)-Aromadendranediol
ACIE **2009**, *48*, 4349.
11 steps, 25.6% overal yield

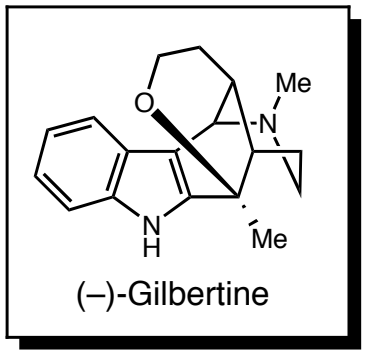


(–)-Flustramine B
PNAS **2004**, *101*, 5482.
7(+) steps,58.1% overal yield



(+)-Minfiensine
JACS **2009**
9 steps, 21% overal yield

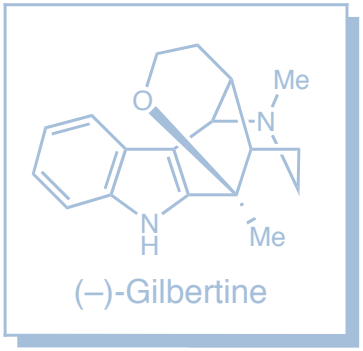
Cationic Cascade: Synthesis of (–)-Gilbertine



(–)-Gilbertine

- Bletchert, S. *TL* **1982**, *23*, 5395 *(isolated)*

Cationic Cascade: Synthesis of (–)-Gilbertine



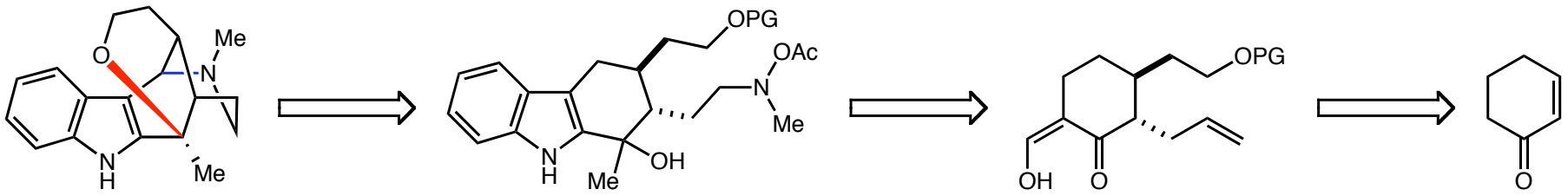
■ Bletchert, S. *TL* **1982**, *23*, 5395 *(isolated)*

■ Blechert, S. *JACS* **2004**, *126*, 3534 *(synthesis)*

Shibashaki–Michael reaction

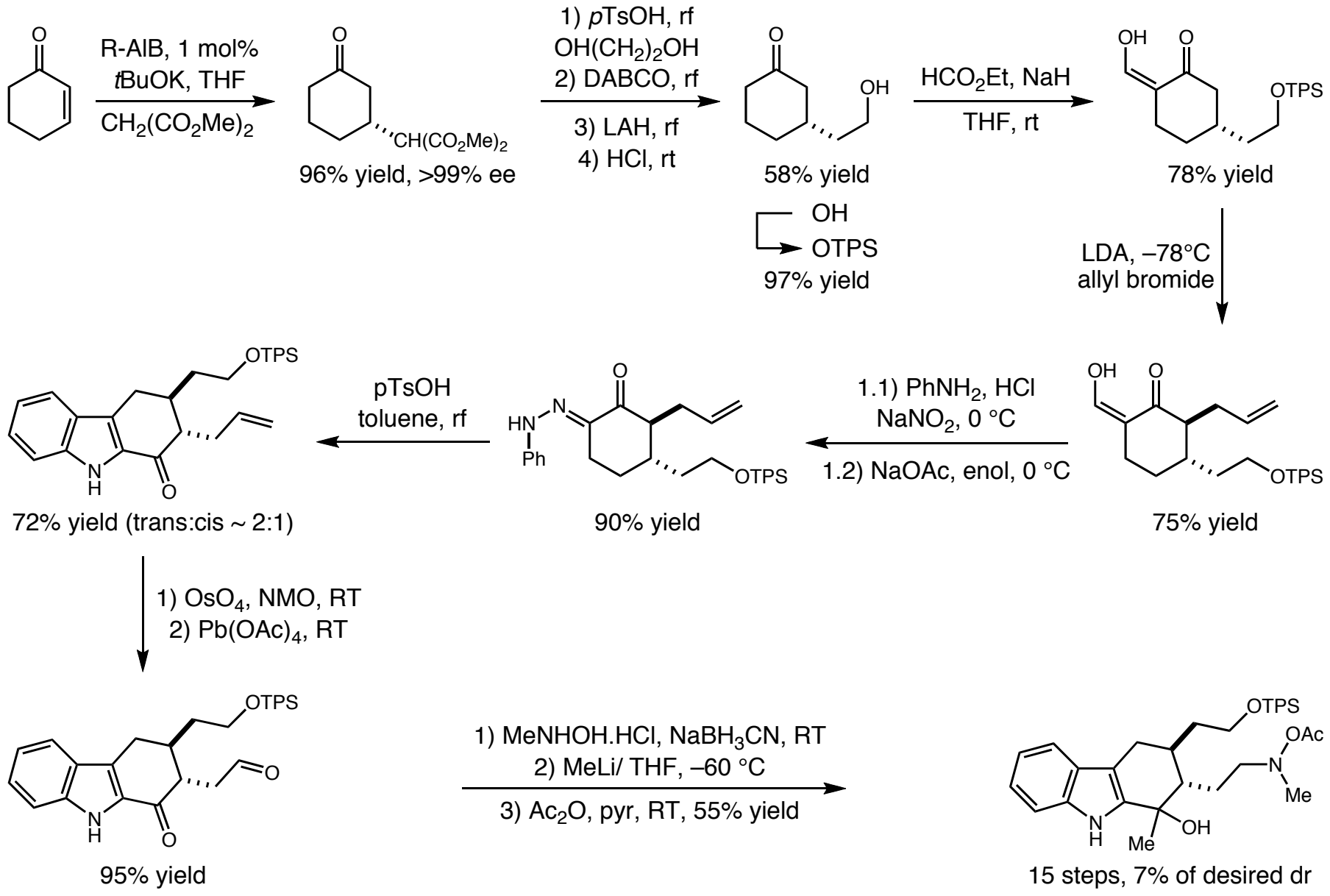
Japp–Klingeman Fisher indol

Cationic cascade

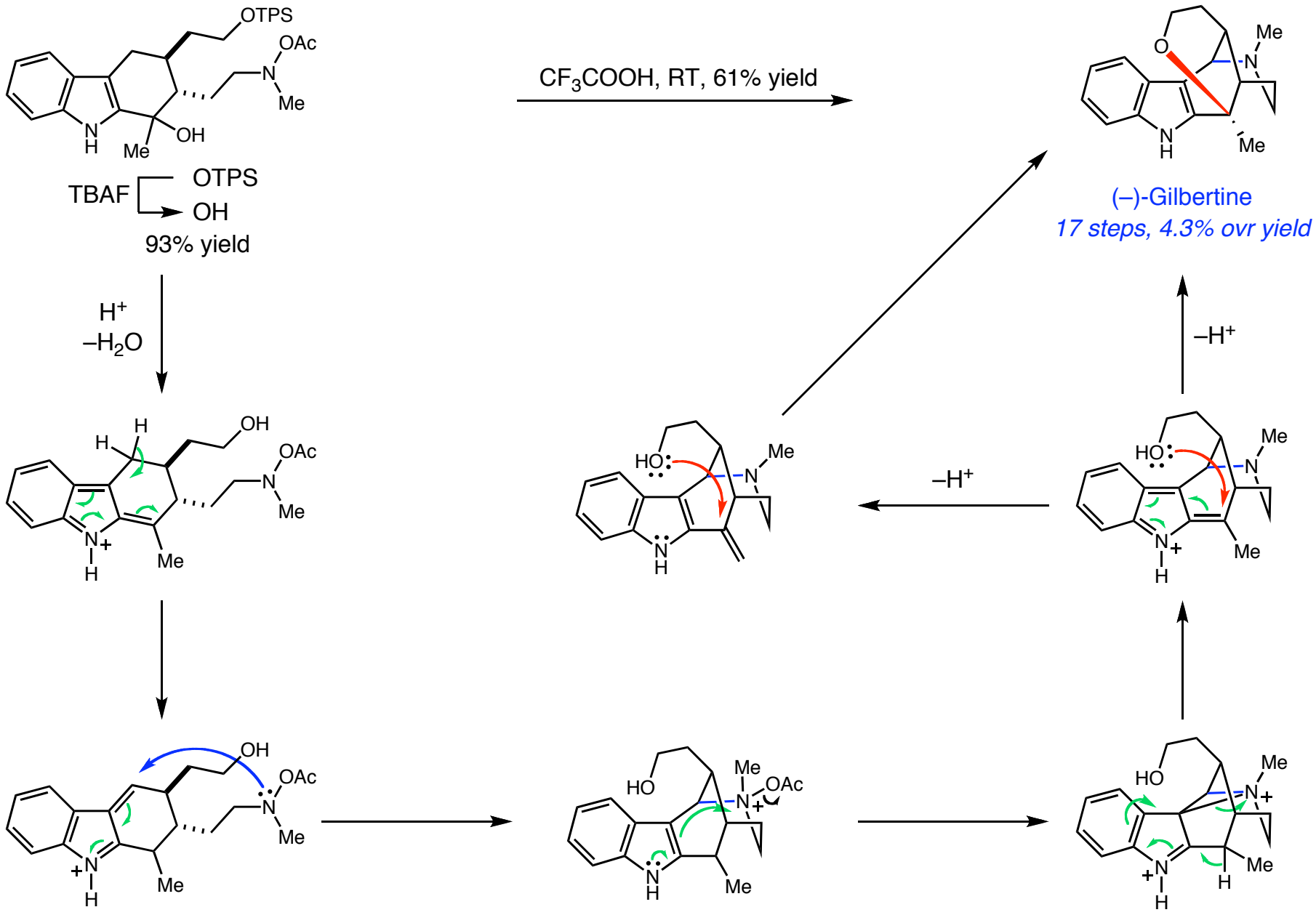


(–)-Gilbertine, **1**

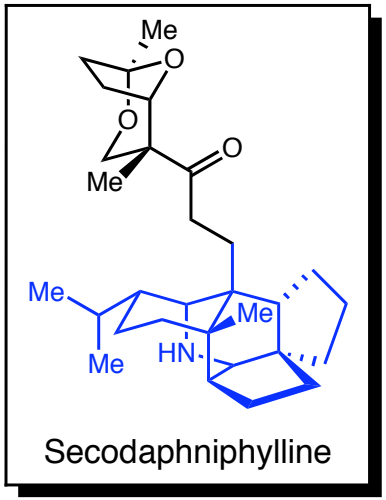
Synthesis of (–)-Gilbertine: Synthesis of the Cascade Precusor



Cationic Cascade: Synthesis of (–)-Gilbertine - end game



Nuclephilic Cascade: Synthesis of (–)-Secodaphniphylline



Secodaphniphylline

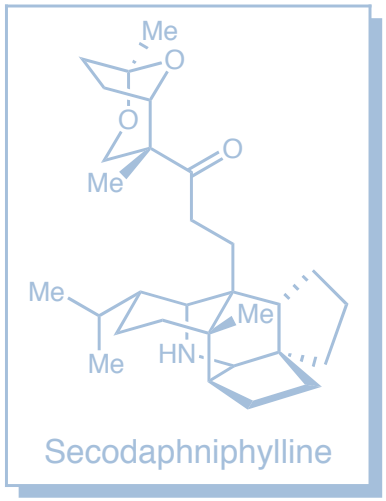
■ Hirata, Y. *TL* **1969**, *10*, 1821 *(isolated)*

Compact pentacyclic system

8 stereocenter

Kobayashi, J. *Nat. Prod. Rep.* **2009**, *26*, 936 (*review*)

Nucleophilic Cascade: Synthesis of (–)-Secodaphniphylline



Secodaphniphylline

■ Hirata, Y. *TL* **1969**, *10*, 1821 *(isolated)*

Compact pentacyclic system

8 stereocenter

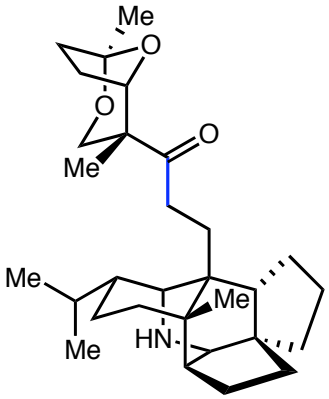
Kobayashi, J. *Nat. Prod. Rep.* **2009**, *26*, 936 (*review*)

■ Heathcock, C.H. *JOC* **1992**, *57*, 2566 *(synthesis)*

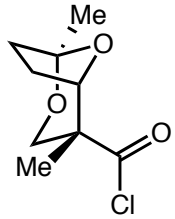
intramolecular hetero-Diels–Alder/pericyclic cascade

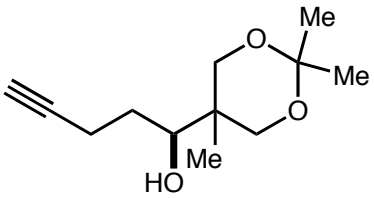
Heathcock, C.H. *PNAS* **1996**, *93*, 14323

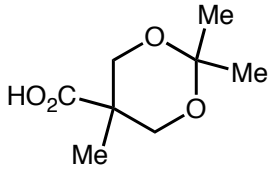
Heathcock, C.H. *JOC* **2001**, *66*, 450

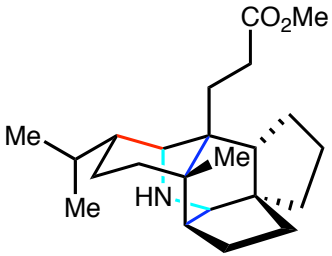


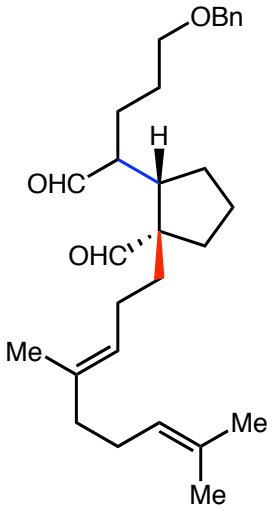
Secodaphniphylline

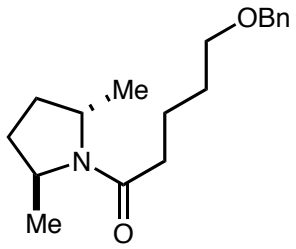




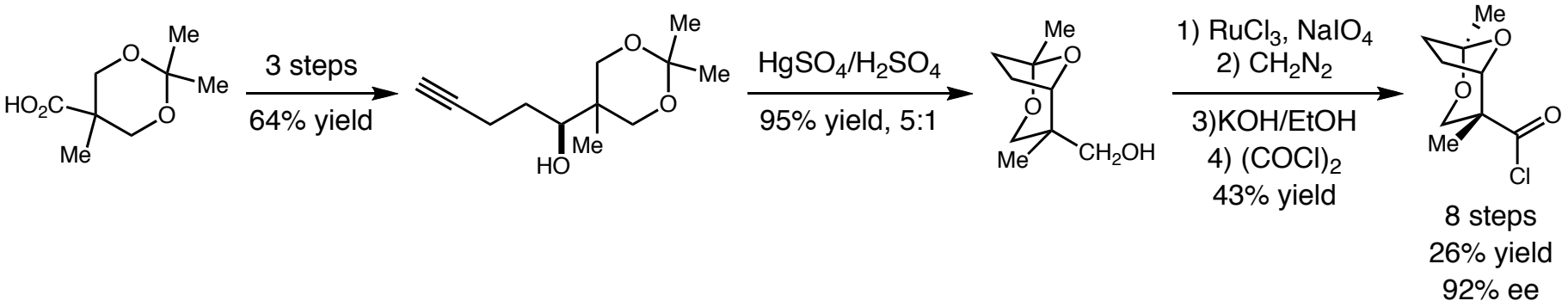




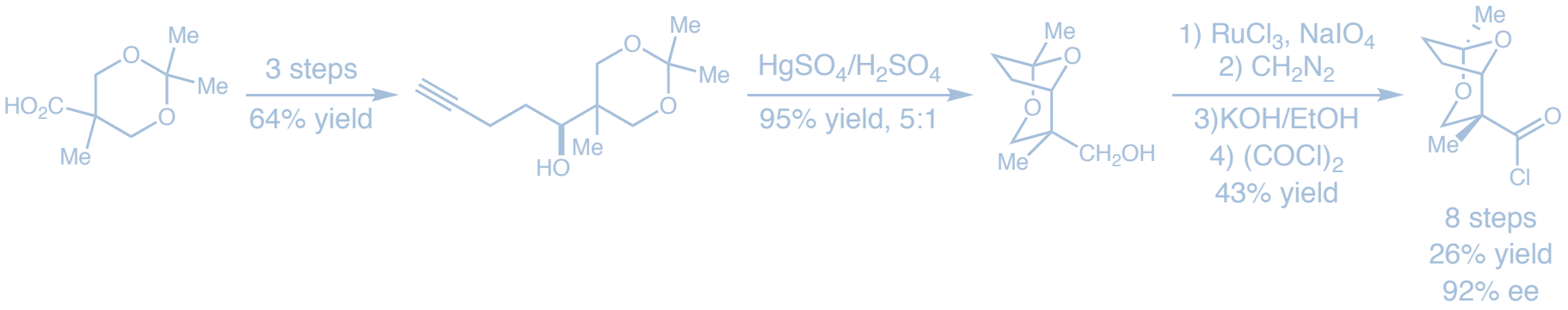


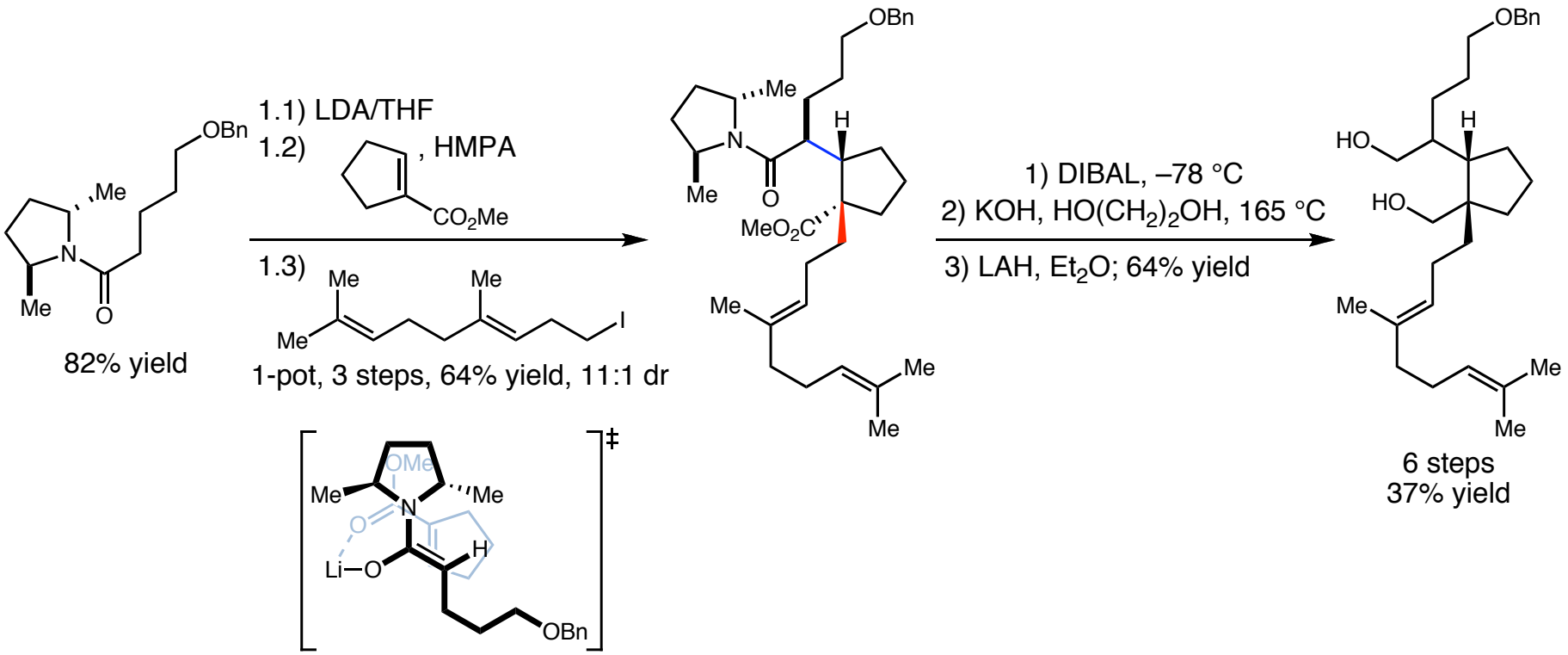


Synthesis of (–)-Secodaphniphylline: Synthesis of the top Fragment

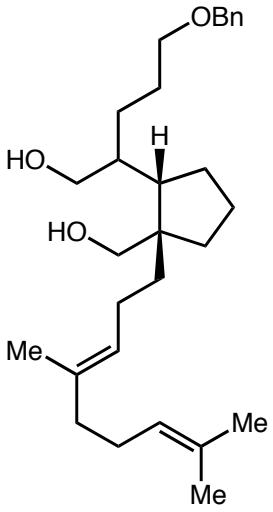


Synthesis of (–)-Secodaphniphylline: Synthesis of the Cascade Precusors



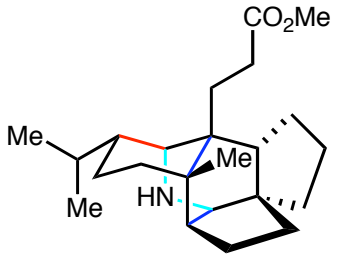


Nucleophilic Cascade: Synthesis of (–)-Secodaphniphylline



1.1) Swern oxidation
1.2) NH_3, 0°C-RT, 40 min
1.3) NH_4OAc, AcOH, 75 °C, 2h

2) H_2/Pd-C, HCl
3) Jones oxidation
4) MeOH, H_2SO_4

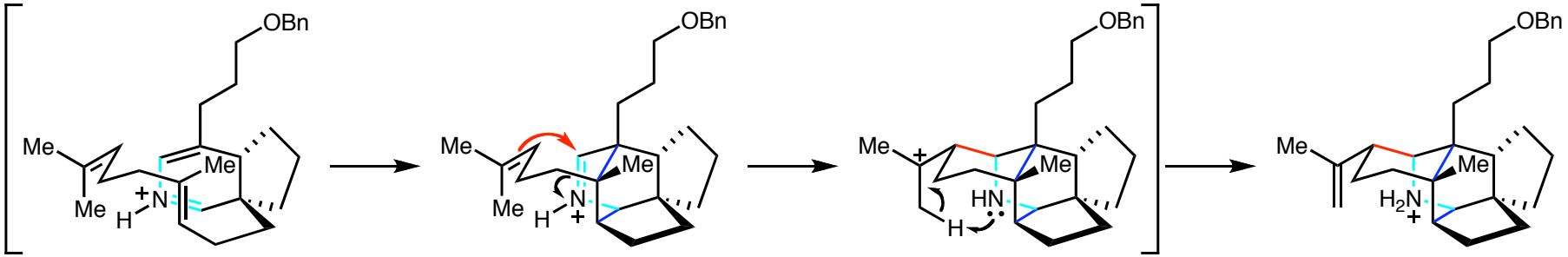


7 steps
60% yield
90% ee

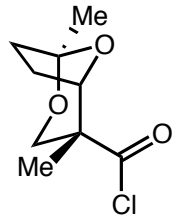
1.1) Swern oxidation
1.2) NH_3, 0°C-RT, 40 min

1.3) NH_4OAc, AcOH, 75 °C, 2h

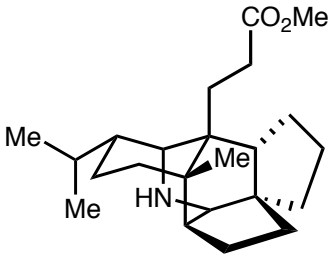
2) H_2/Pd-C, HCl
3) Jones oxidation
4) MeOH, H_2SO_4



Nucleophilic Cascade Cascade: Synthesis of (–)-Secodaphniphylline - Last Steps



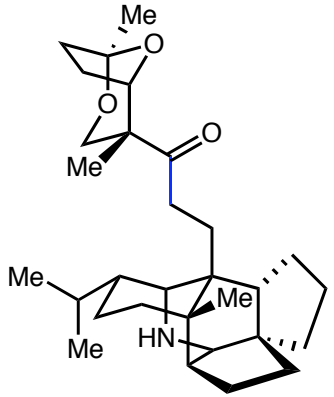
2



3

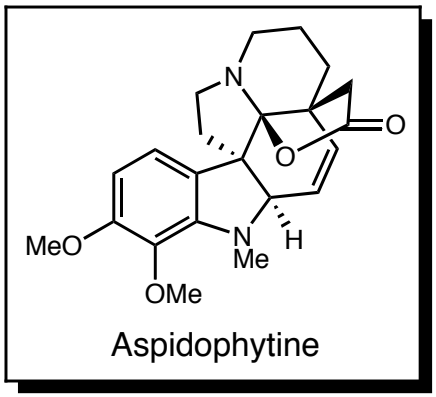
1.1) **3**, LDA, THF, –78 °C
1.2) **2**

2) NaCN, DMSO, 150 °C
43% yield



Secodaphniphylline **1**
18 longest linear steps
6.7% overal yield

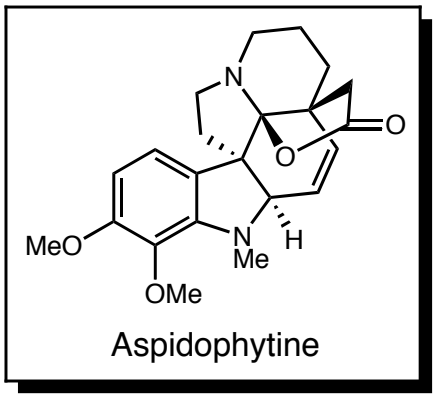
Nucleophilic Cascade: Synthesis of Aspidophytine



Aspidophytine

- Snyder, H. R. *JACS* **1952**, *74*, 1987 *(isolated)*;
  Cave, M. P. and Yates, P. *JACS* **1973**, *95*, 7842 *(structure)*

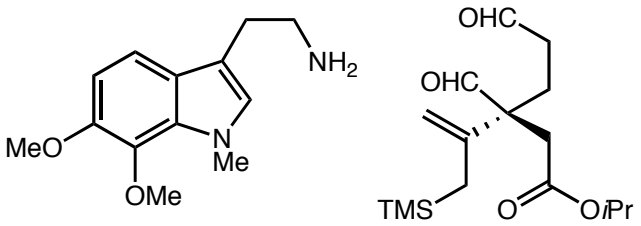
Nucleophilic Cascade: Synthesis of Aspidophytine



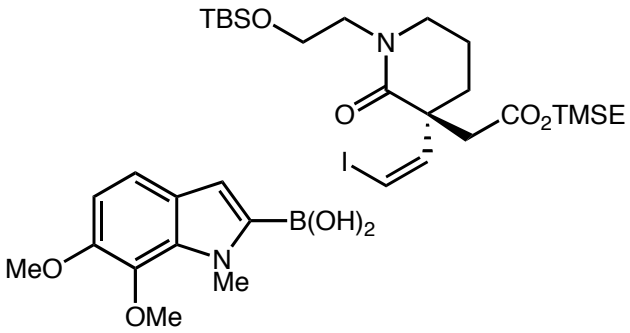
Aspidophytine

■ Snyder, H. R. *JACS* **1952**, *74*, 1987 *(isolated)*;
Cave, M. P. and Yates, P. *JACS* **1973**, *95*, 7842 *(structure)*

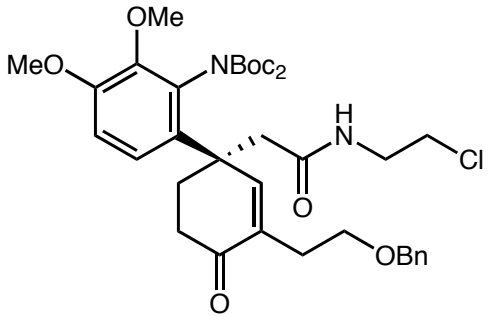
■ Corey E. J. *JACS* **1999**, *121,* 6711
15 steps, 3.44% overal yield



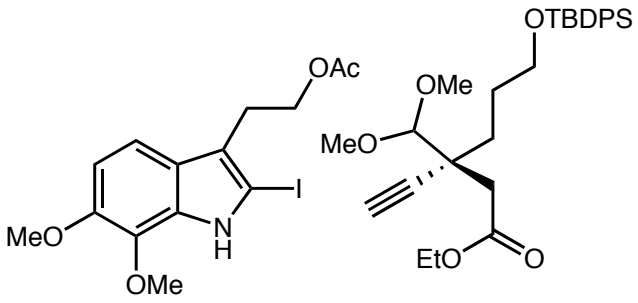
Nicolaou, K. C. *JACS* **2008**, *130,* 14942
13 steps, 3.08% overal yield



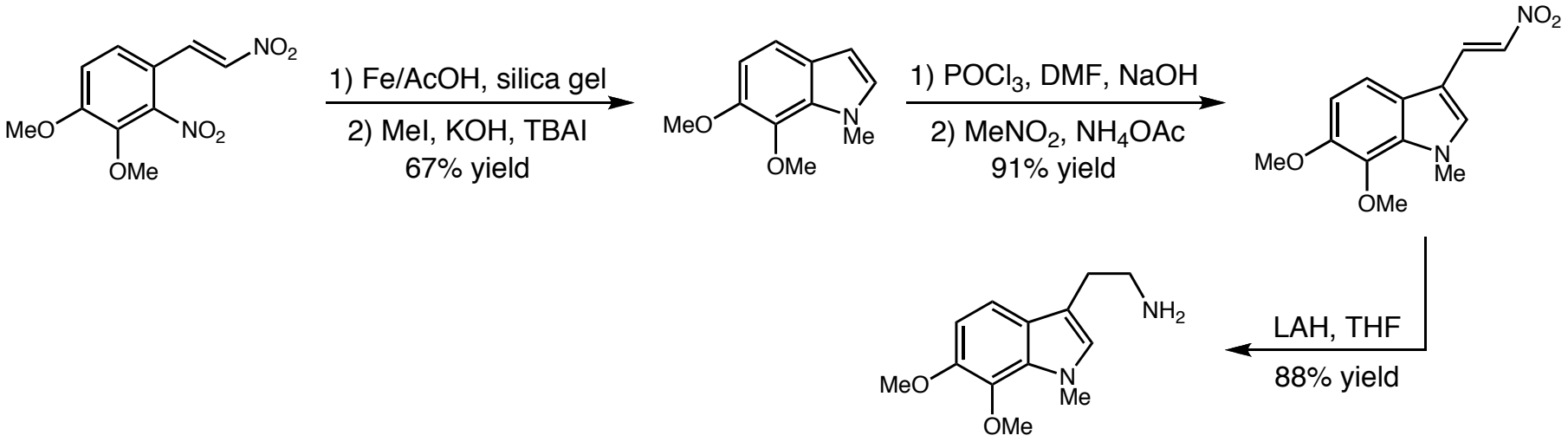
Marino, J. P. *TL* **2006**, *47,* 7711
19 steps, 1.37% overal yield



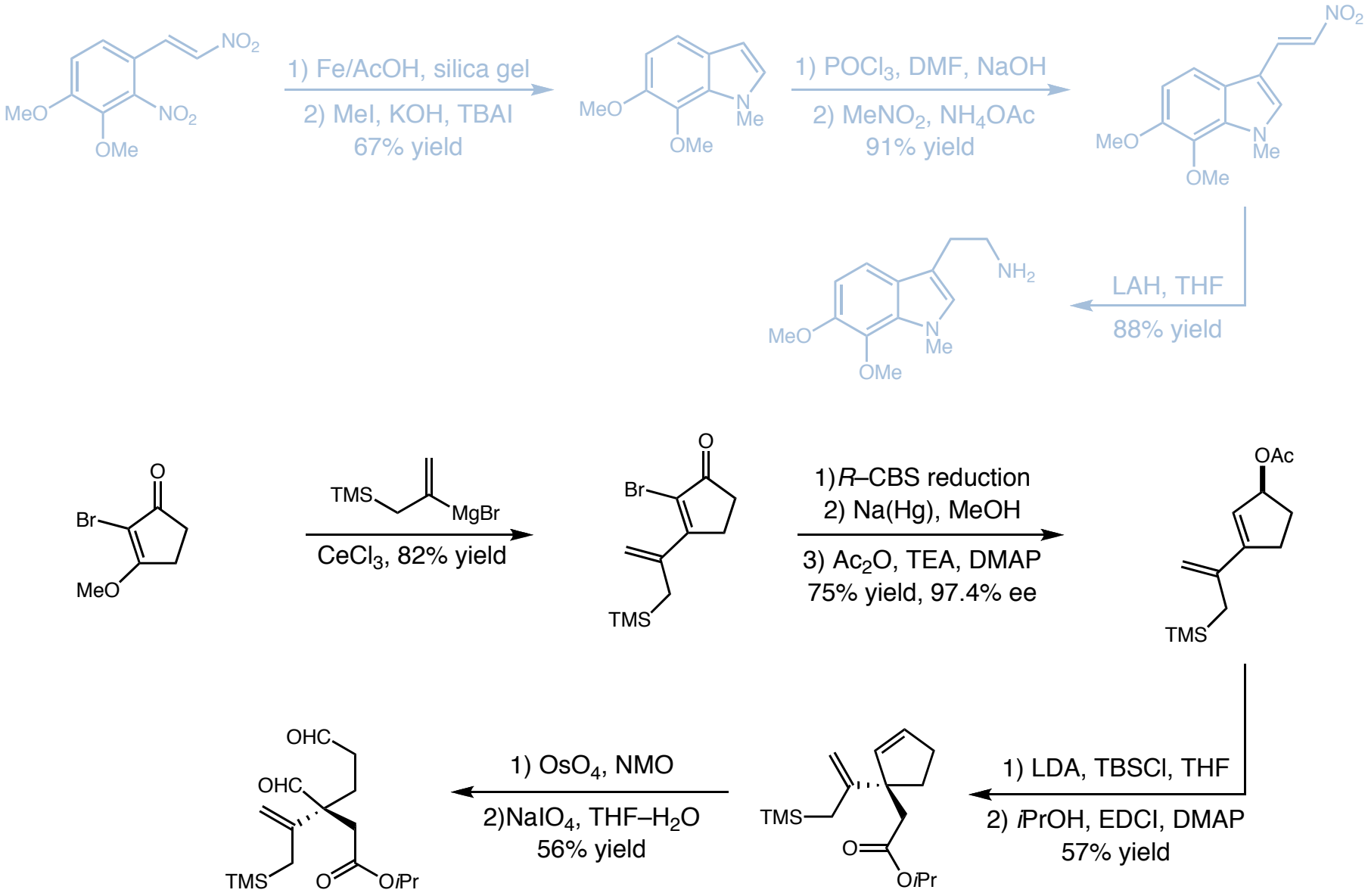
Fukuiyama, T. *OL* **2003**, *5,* 1891
22 steps, 0.88% overal yield



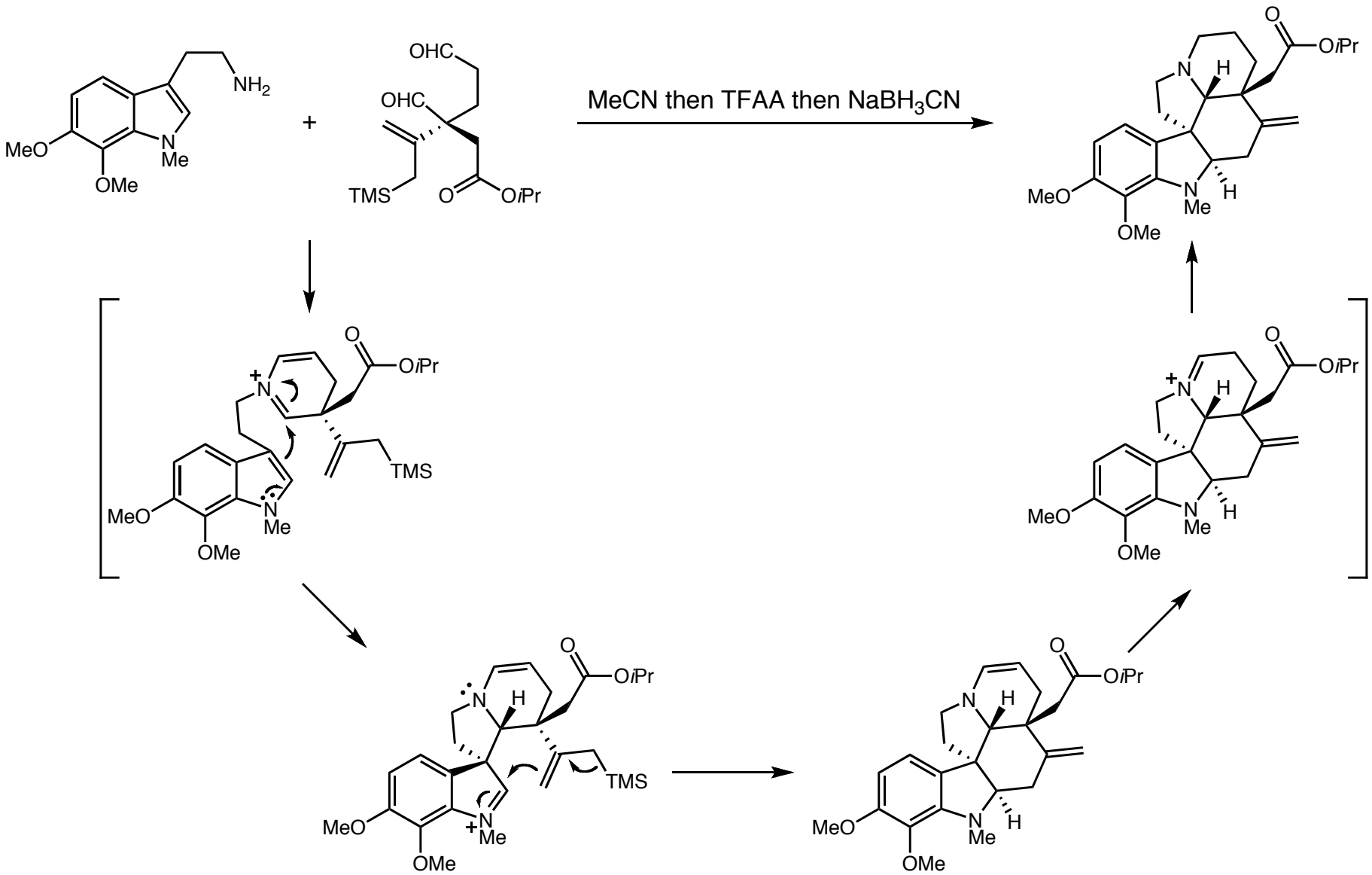
Synthesis of Aspidophytine: Synthesis of Fragments



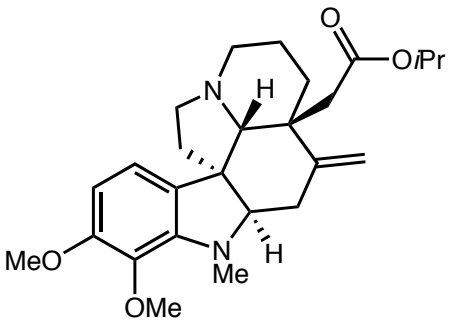
Synthesis of Aspidophytine: Synthesis of Fragments



Nucleophilic Cascade: Synthesis of Aspidophytine

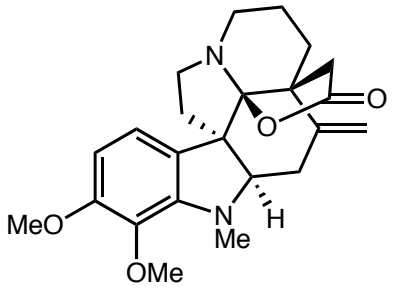


Nucleophilic Cascade: Synthesis of Aspidophytine



1) NaOH, EtOH, 88% yield

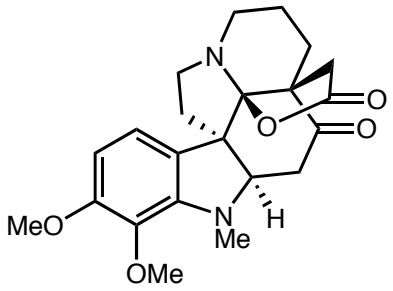
2) $K_3Fe(CN)_6$, $NaHCO_3$, 92% yield



1) OsO_4, DMAP, $NaSO_3$

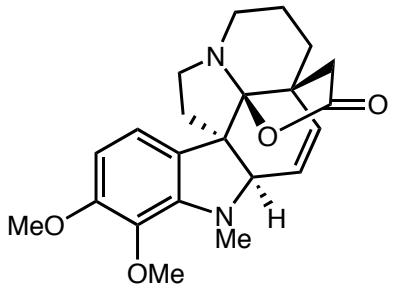
2) $Pb(OAc)_4$, AcOH

71% yield



1) KHMDS, $PhNTf_2$, 54% yield

2) $Pd(PPh_3)_6$, Bu_3SnH, 86% yield

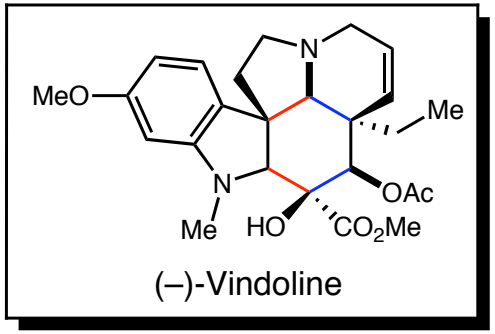


Aspidophytine

15 longest linear steps

3.44% overal yield

Pericyclic Cascade: Synthesis of (–)-Vindoline



(–)-Vindoline

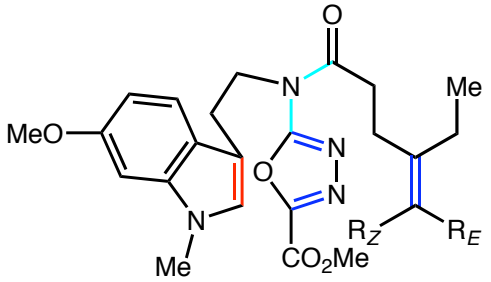
Biemann, K. *JACS* **1962**, *84*, 1058 *(structure)*

■ Boger, D.L. *JACS* **2006**, *128,* 10596

Intramolecular [4+2]/[3+2] cascade

15 steps, 3.71% overal yield for R_Z

18 steps, 1.87% overal yield for R_E



Fukuiyama, T. *Synlett* **2000**, 883

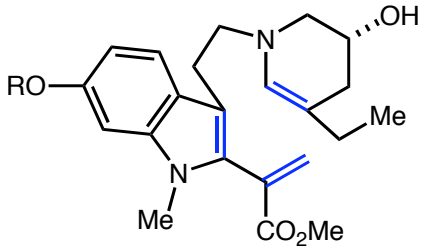
biomimetic, IMDA (R=OMs)

25 steps, 5.59% overal yield

Kuehne, M. E. *JOC* **1987**, *52,* 347

biomimetic, IMDA (R=OMe)

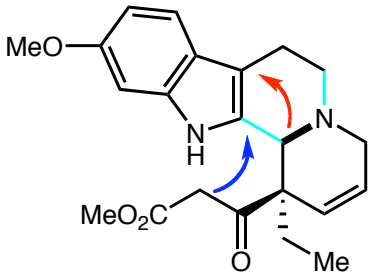
14 steps, 2.08% overal yield



Rapoport, H. *JACS* **1987**, *109,* 1603

Wagner–Meerwein rearrangement

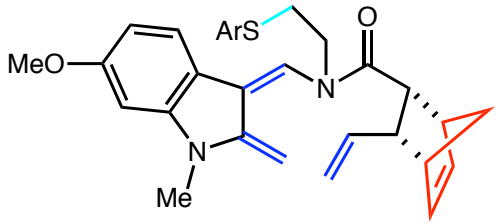
22 steps, 1.79% overal yield



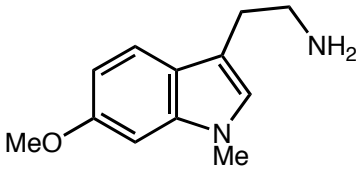
Magnus, P. *JACS* **1988**, *110,* 2242

IMDA, Pummerer, and retro-DA

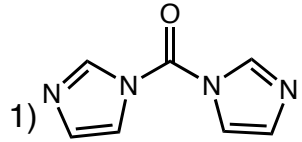
20 steps, 1.85% overal yield



Pericyclic Cascade: Synthesis of (–)-Vindoline



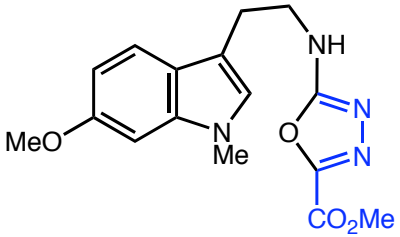
3 steps, 98% yield

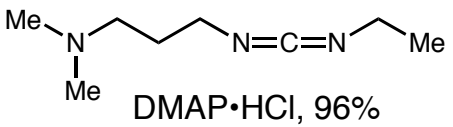


1) (CDI), 90%

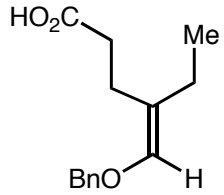
2) $H_2NNHCOCO_2Me$, 79%

3) TsCl, TEA, 81%



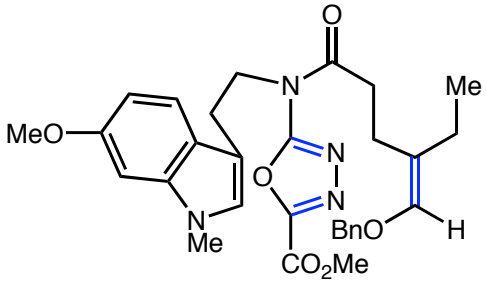


DMAP•HCl, 96%

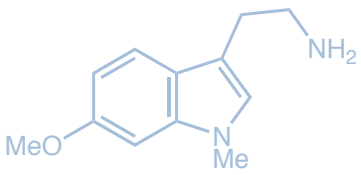


230°C

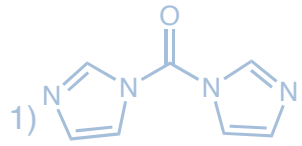
TIPB



Pericyclic Cascade: Synthesis of (–)-Vindoline



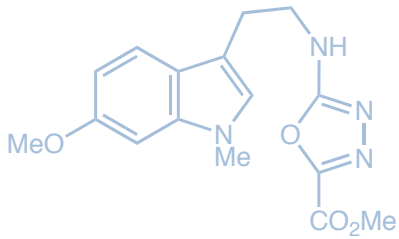
3 steps, 98% yield

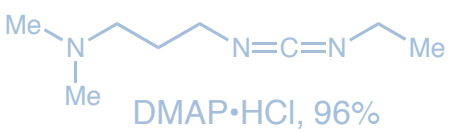


1) (CDI), 90%

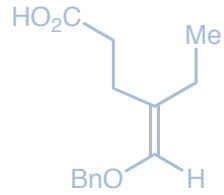
2) $H_2NNHCOCO_2Me$, 79%

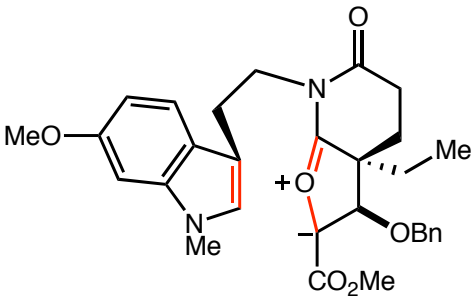
3) TsCl, TEA, 81%



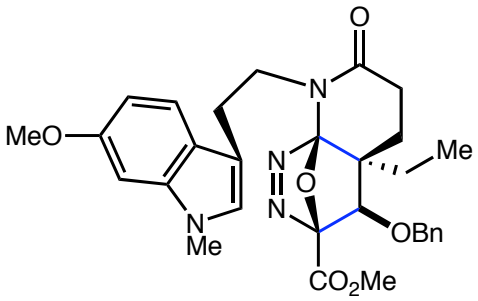


DMAP•HCl, 96%



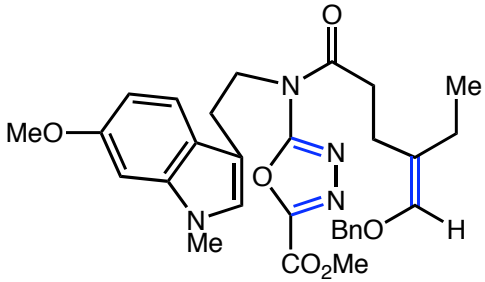


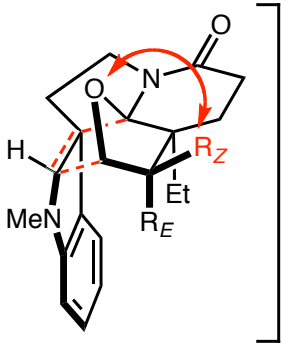
–N_2



230°C

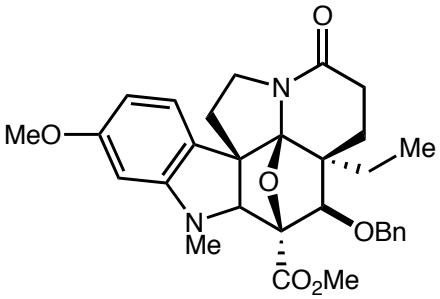
TIPB





53% yield

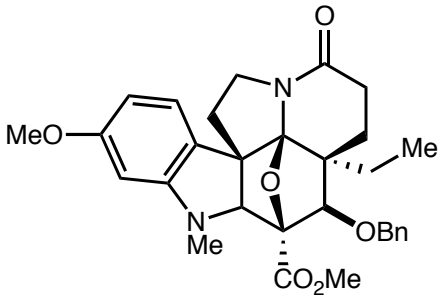
(>95% w *E*)



α-face opposite fused lactam.
endo indole transition state.

E (20 h) faster than *Z* (90 h).
Forms 3 rings, 4 C–C bonds,
6 stereocenters, 4 quat centers.

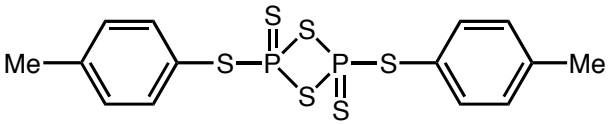
Pericyclic Cascade: Synthesis of (–)-Vindoline

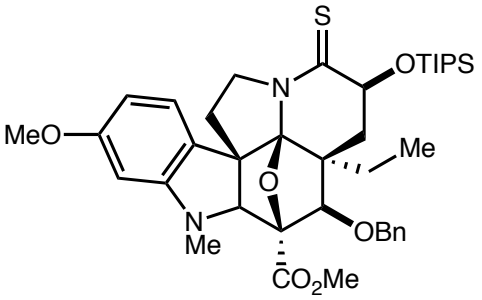


ChiralCel OD resolution

1) LDA, (TMSO)2, TIPSOTf

2) Lawesson reagent

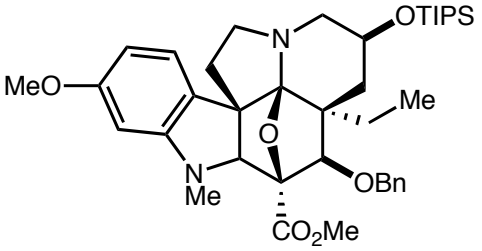




45% yield

Ra–Ni

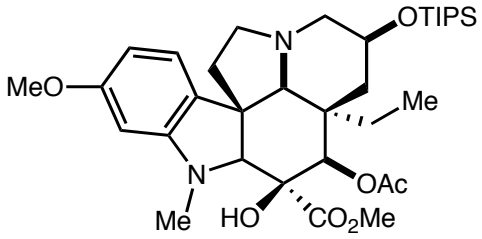
RT, 2h



91% yield

1) H_2/PtO_2

2) Ac_2O



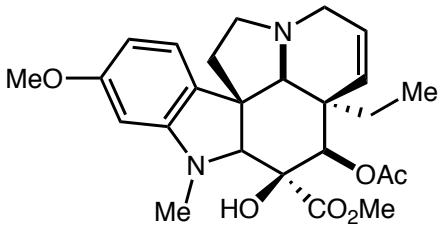
95% yield

1) TBAF

2) Ph_3P

DEAD

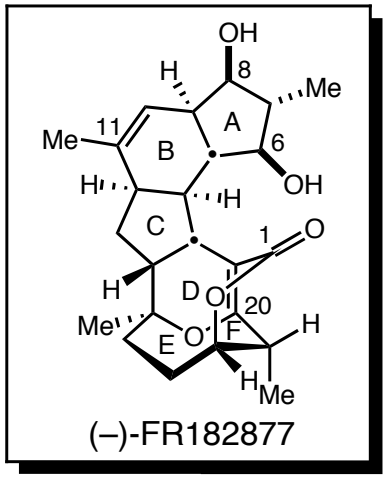
67% yield



(–)-Vindoline

15 steps, 3.71% overal yield

Pericyclic Cascade: Synthesis of (–)-FR182877



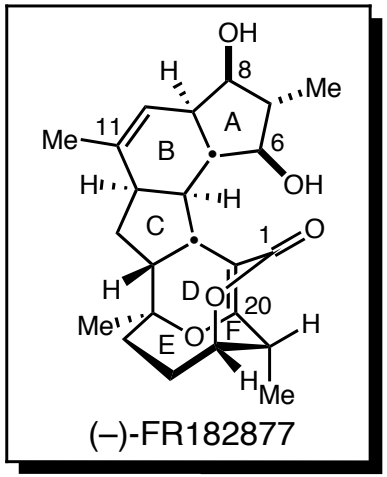
(–)-FR182877

- Reported 1998 by the Sato group (Japan)

Sato, B. *J. Antibiot.* **2000**, *53*, 123, 204, and 615*(structure)*;

Sato, B. *J. Antibiot.* **2002**, *55*, C-1*(enantiomer corected)*

Pericyclic Cascade: Synthesis of (–)-FR182877



(–)-FR182877

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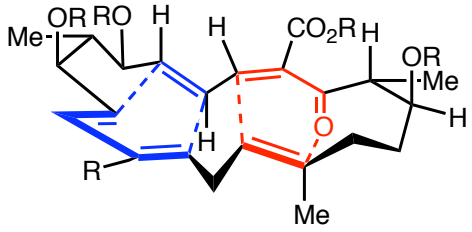
Sato, B. *J. Antibiot.* **2000**, *53*, 123, 204, and 615*(structure)*;

Sato, B. *J. Antibiot.* **2002**, *55*, C-1*(enantiomer corected)*

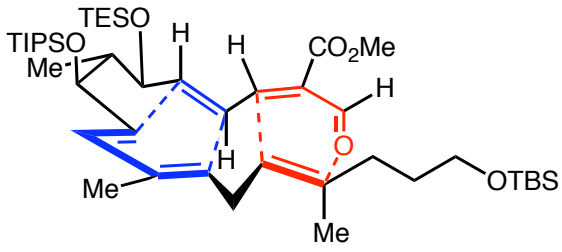
Evans D. A. *JACS* **2003**, *125,* 1531
22 steps, 2.81% overal yield

Sorensen E. J. *JACS* **2003**, *125,* 5393
22 steps, 3.46% overal yield

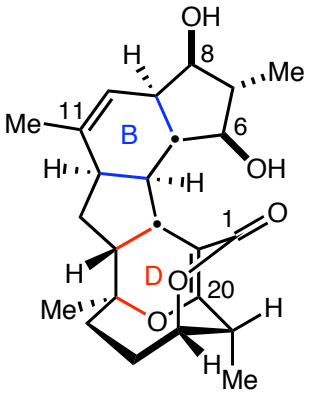
aldol reaction with Evans Auxiliary
transannular IMDA–IMHDA cascade



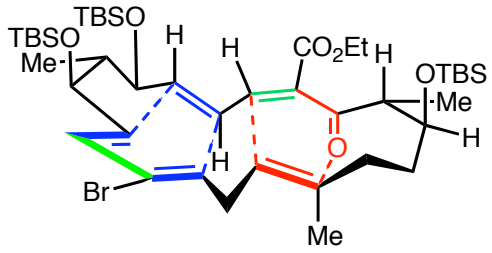
Nakada, M. *ACIE* **2009**, *48,* 2580
aldol reaction with Evans Auxiliary
IMDA–IMHDA cascade
26 steps, 1.52% overal yield

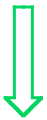


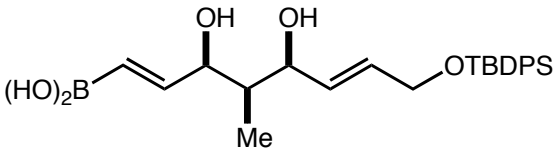
Pericyclic Cascade: Retrosynthetic Plan of (–)-FR182877 by Evans

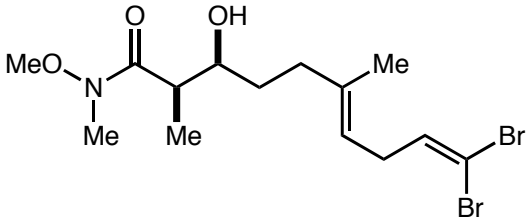


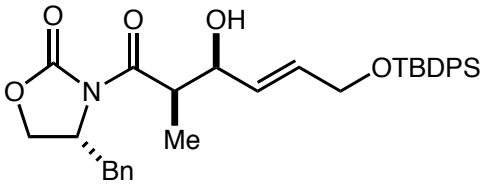
(–)-FR182877

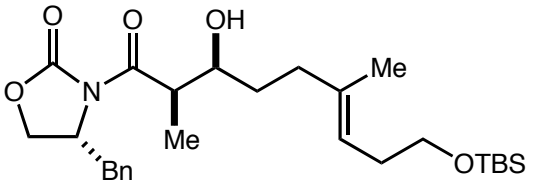


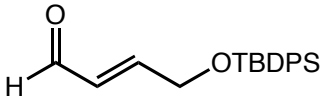


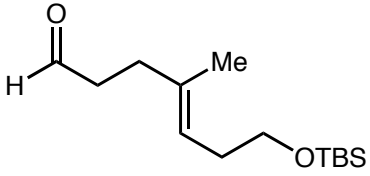




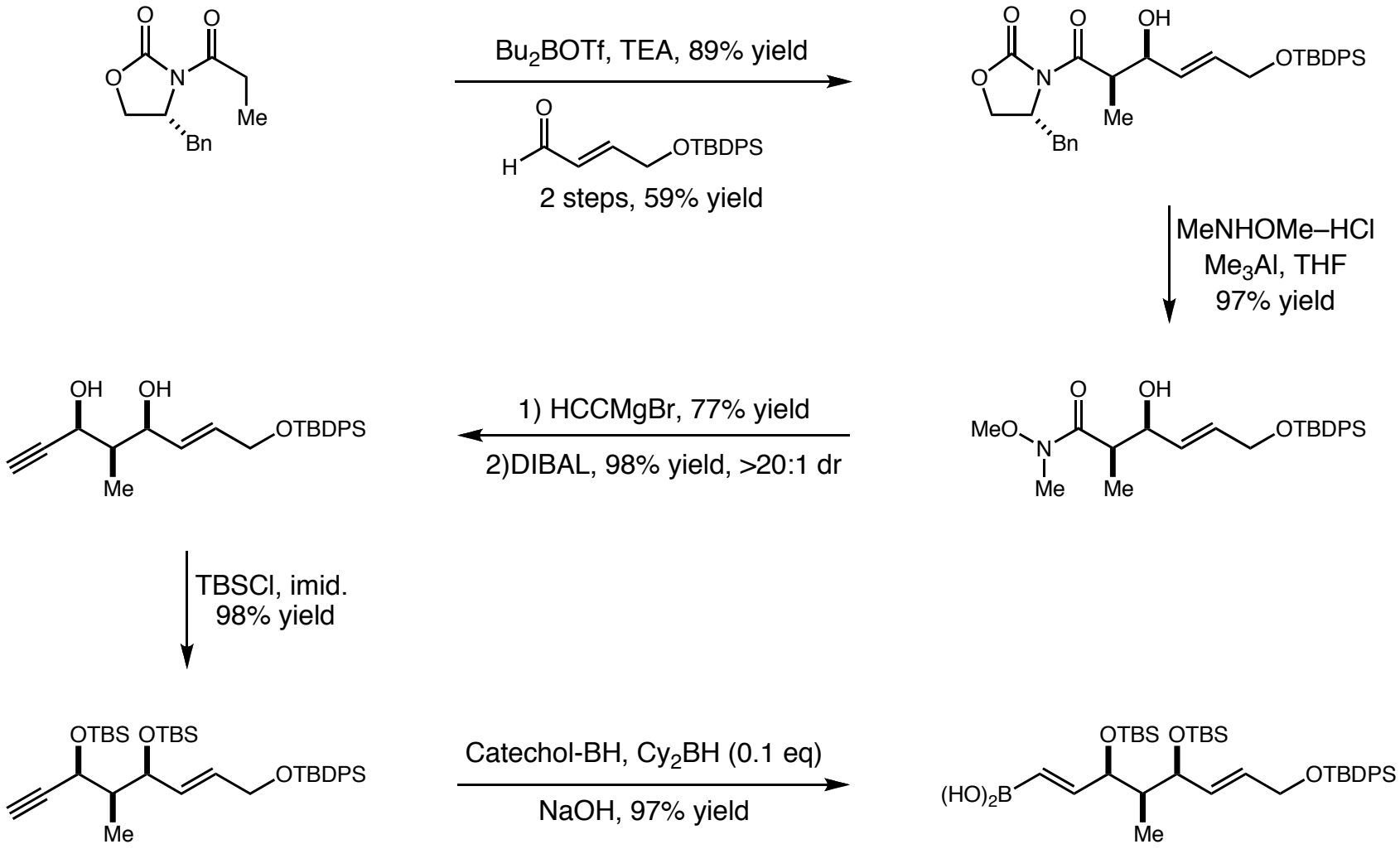




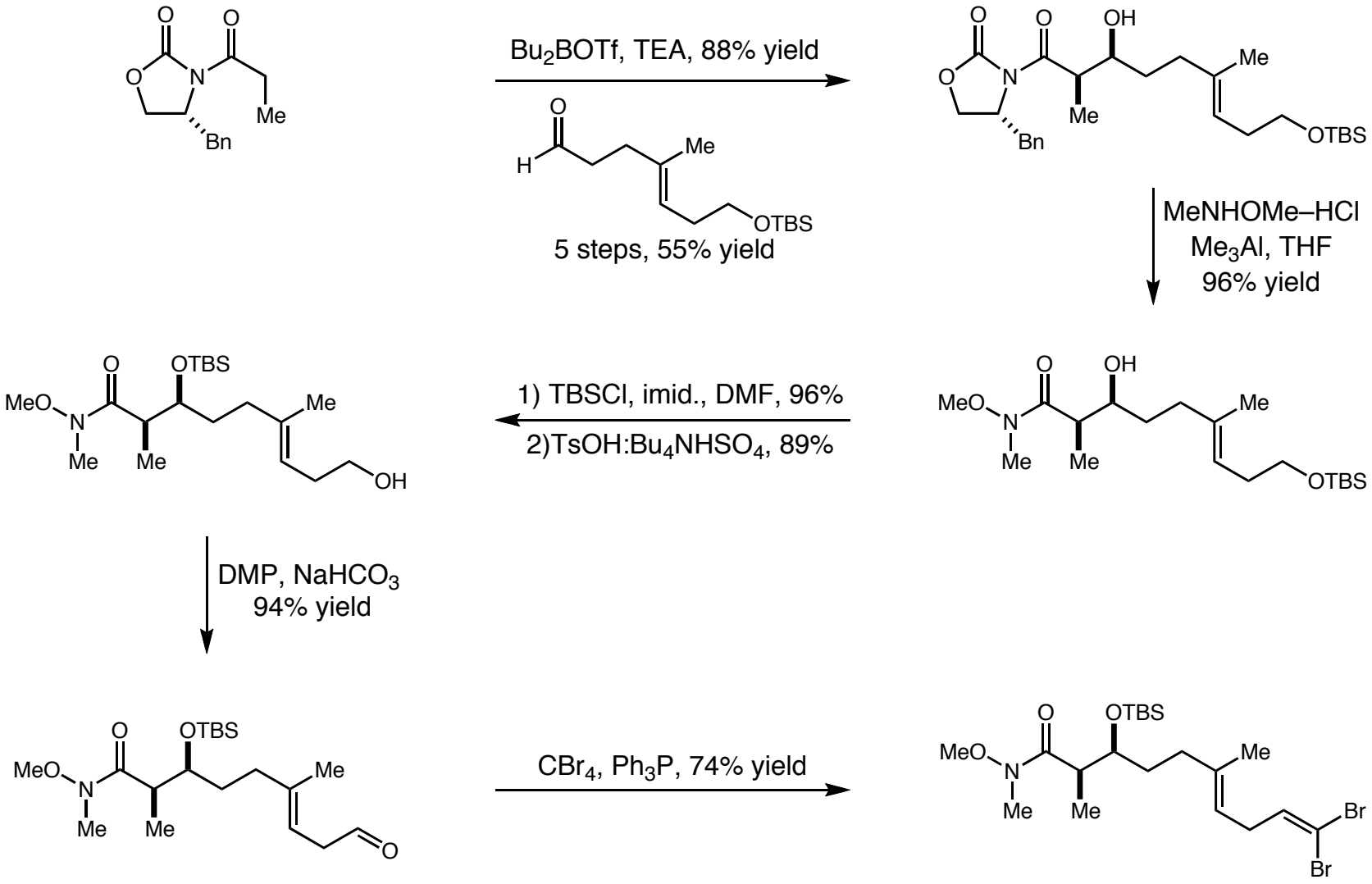




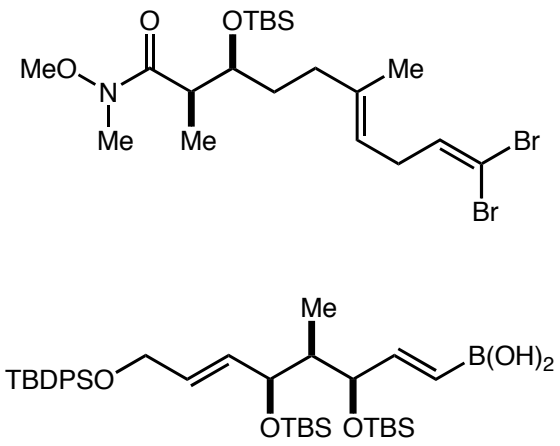
Synthesis of (–)-FR182877: Synthesis of Boronic Acid Fragment



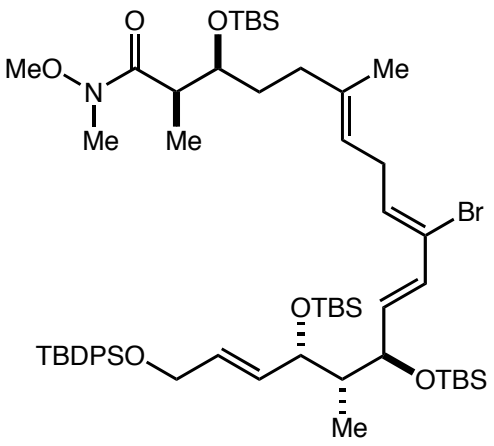
Synthesis of (–)-FR182877: Synthesis of Dibromide Fragment



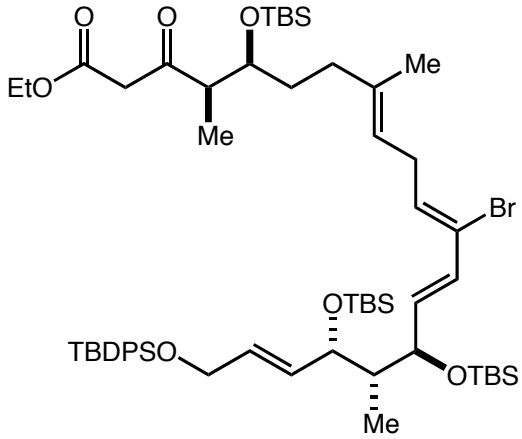
Synthesis of (–)-FR182877: Macrocycle Formation



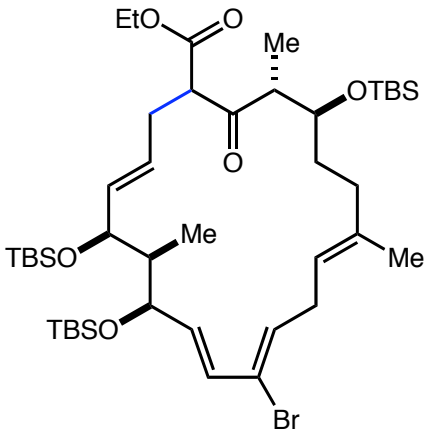
$Pd(Ph_3P)_4$, Tl_2CO_3, 84% yield



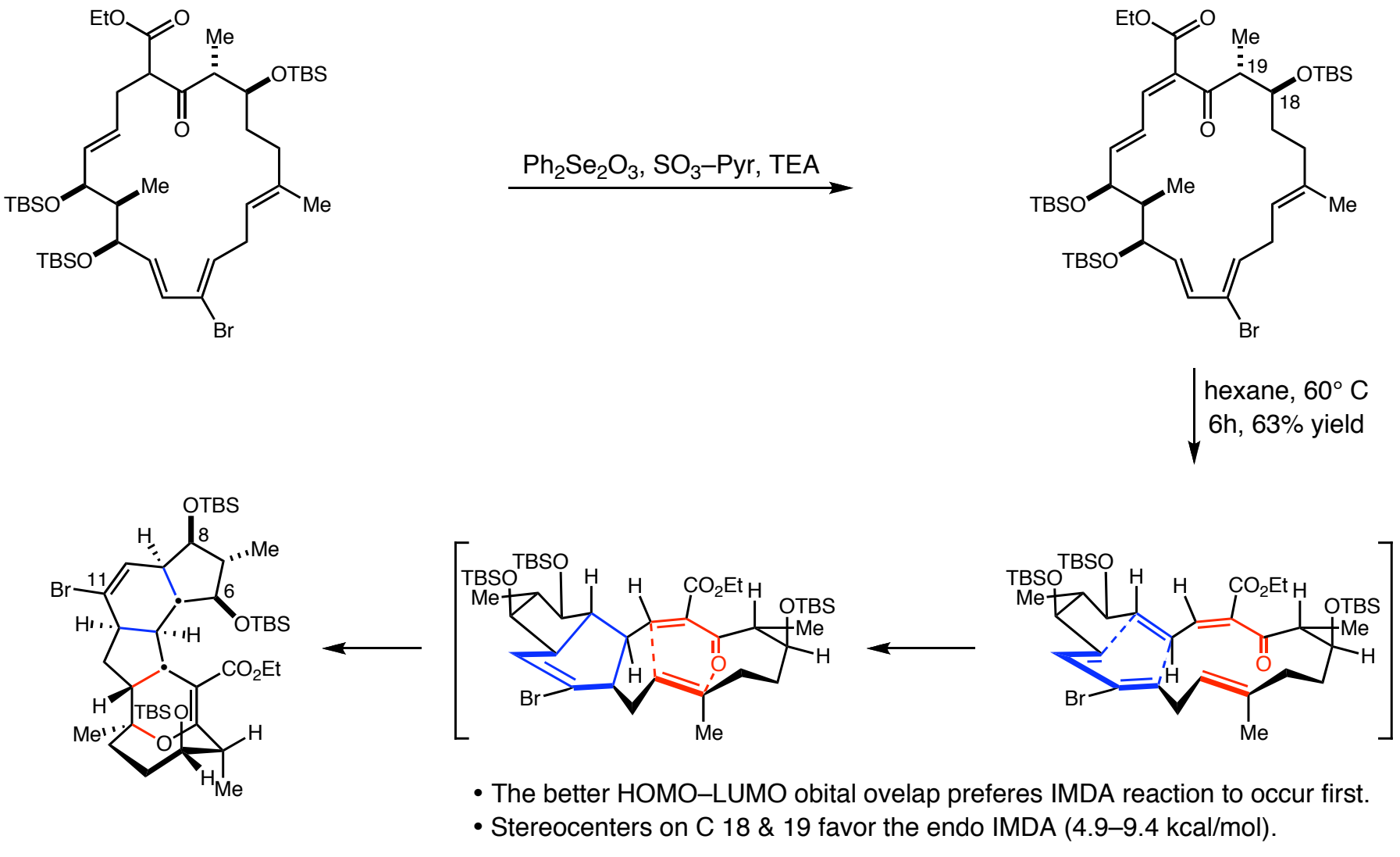
1) DIBAL, –78 °C
2) $EtO_2CCH_2N_2$
$SnCl_2$, 70% yield



1) TBAF, AcOH, DMF, 92%
2) I_2, Ph_3P, DCM
3) Cs_2CO_3, THF, 77% yield

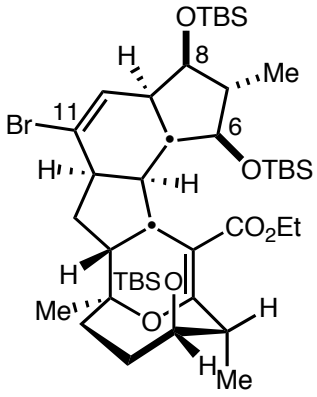


Pericyclic Cascade: Transannular IMDA–IMHDA.



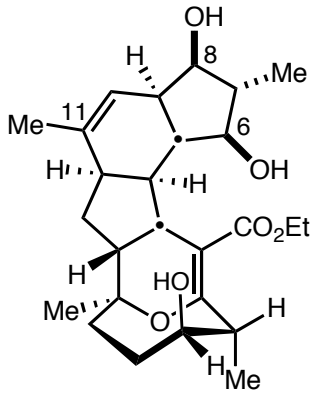
- The better HOMO–LUMO obital ovelap preferes IMDA reaction to occur first.
- Stereocenters on C 18 & 19 favor the endo IMDA (4.9–9.4 kcal/mol).

Pericyclic Cascade: Synthesis of (–)-FR182877

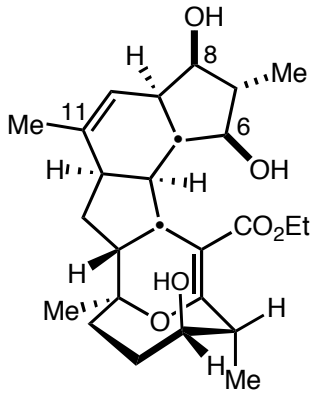


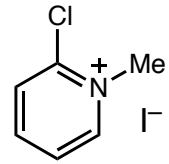
1) HF–MeCN, 89% yield

2) $Me_3B_3O_3$, $Pd(dppf)Cl$, Cs_2CO_3
71% yield

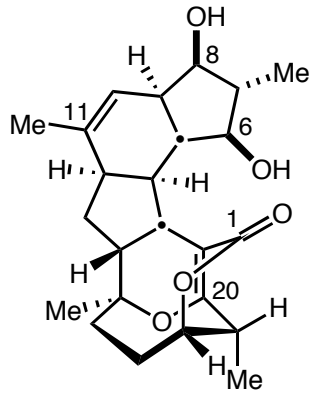


TMSOK
THF



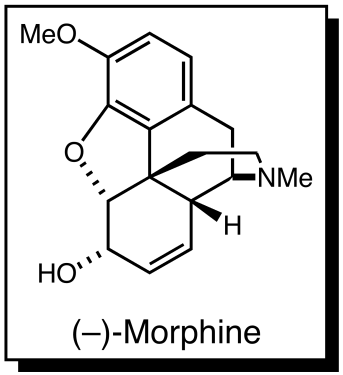


$NaHCO_3$, 62% yield



(–)-FR182877
22 steps, 2.81% overal yield

Radical Cascade: Formal Synthesis of (–)-Morphine



(–)-Morphine

Morphine was discovered as the first active alkaloid extracted from the opium poppy plant in 1804 in Paderborn, Germany by Friedrich Wilhelm Adam Sertürner (1783-1841), an obscure, uneducated, 21-year-old pharmacist's assistant with little equipment but loads of curiosity. Serturner's crystallization of morphine was the first isolation of a natural plant alkaloid. In 1831, Sertürner won a lucrative prize for the discovery.

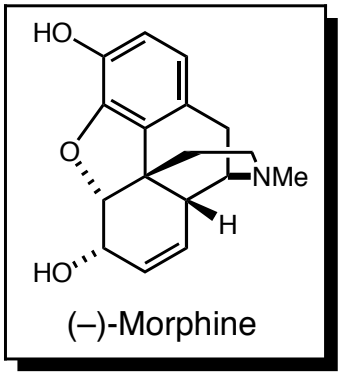
Sertürner wondered about the medicinal properties of opium, which was widely used by 18th-century physicians. In a series of experiments, performed in his spare time and published in 1806, he managed to isolate an organic alkaloid compound from the resinous gum secreted by Papaver somniferum -- the opium poppy.

Friedrich Wilhelm Adam Sertürner
(1783-1841)

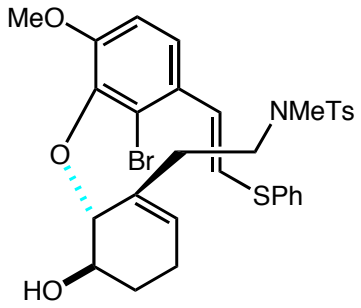
Sertürner found that opium with the alkaloid removed had no effect on animals, but the alkaloid itself had ten times the power of processed opium. He named that substance morphine, after Morpheus, the Greek god of dreams, for its tendency to cause sleep. He spent several years experimenting with morphine, often on himself, learning its therapeutic effects as well as its considerable dangers. Although his work was initially ignored, he recognized its significance. "I flatter myself," he wrote in 1816, that "my observations have explained to a considerable extent the constitution of opium, and that I have enriched chemistry with a new acid (meconic) and with a new alkaline base (morphium), a remarkable substance."

From http://www.wikipedia.org and
http://www.sciencebase.com/structure_of_morphine.html

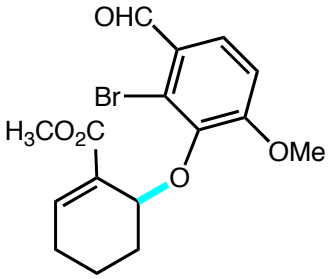
Radical Cascade: Formal Synthesis of (–)-Morphine



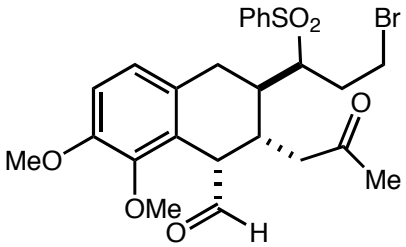
Parker K. A. *JOC* **2006**, *71,* 449 (enantioselective)
Parker K. A. *JACS* **1992**, *114,* 9688 (racemix)
21 steps, ~1.64% overal yield



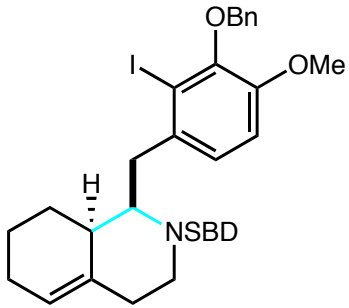
Trost, B. M. *JACS* **2005**, *127,* 14785
17 steps, 3.43% overal yield



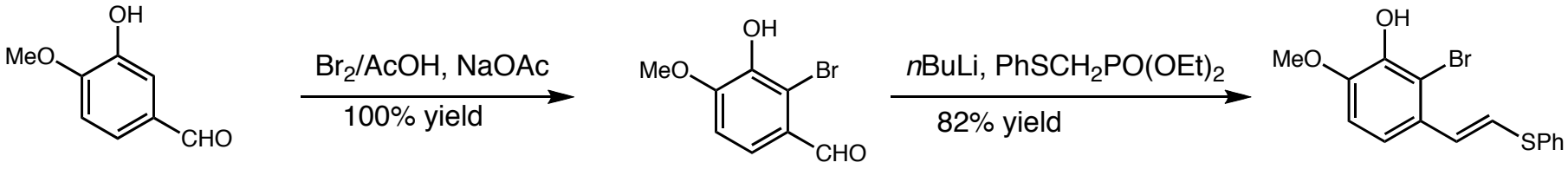
Taber, D. F. *JASC* **2002**, *124,* 12416
28 steps, 0.60% overal yield



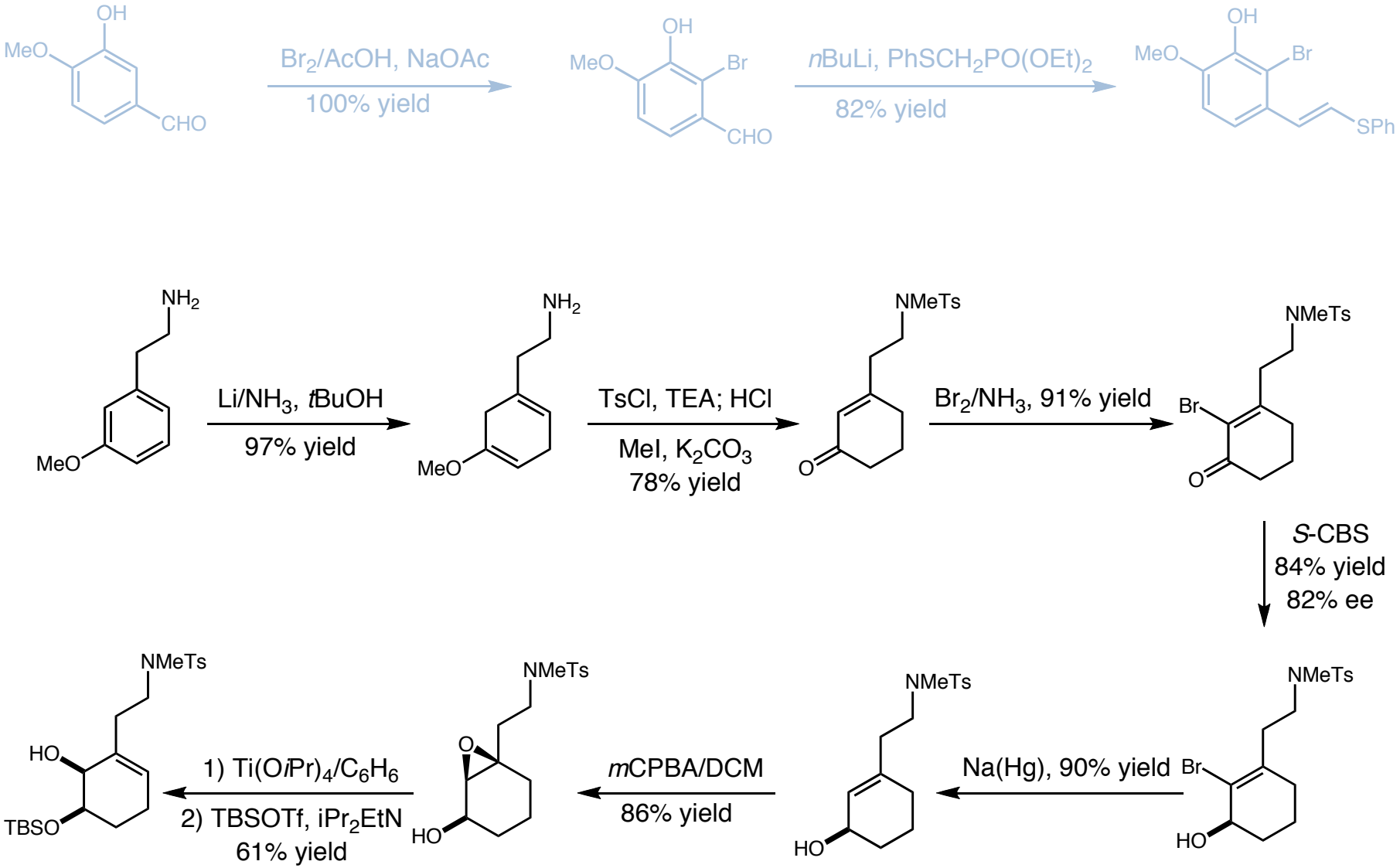
Overman, L. E. *JACS* **1993**, *115,* 11028
19 steps, 3.01 overal yield



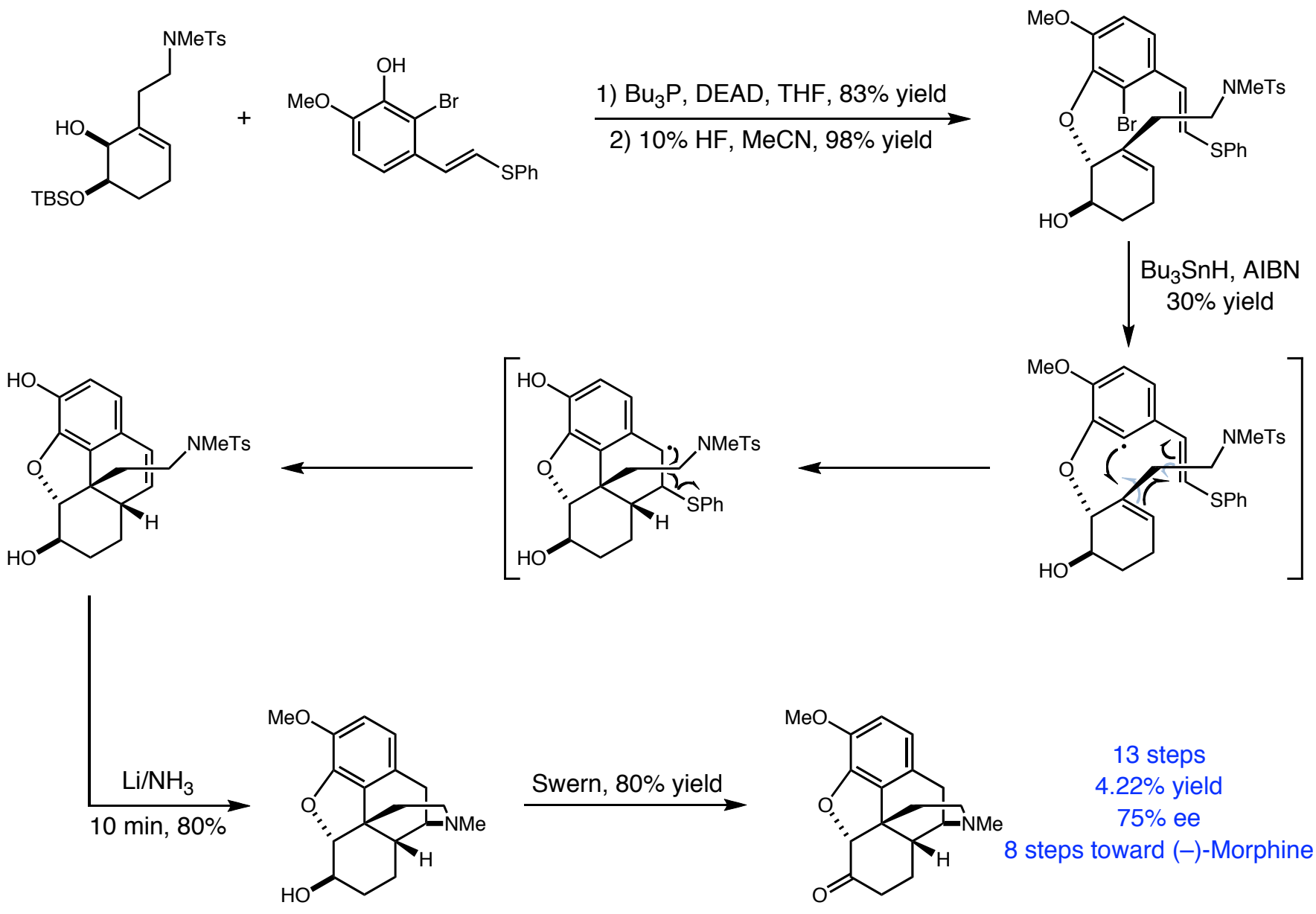
Formal Synthesis of (–)-Morphine: Synthesis of Fragments



Formal Synthesis of (–)-Morphine: Synthesis of Fragments

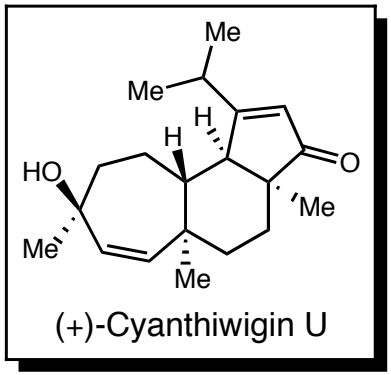


Radical Cascade: Formal Synthesis of (–)-Morphine



13 steps
4.22% yield
75% ee
8 steps toward (–)-Morphine

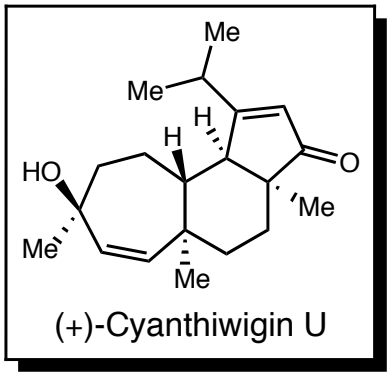
ROM/RCM Cascade: Synthesis of (+)-Cyanthiwigin U



(+)-Cyanthiwigin U

- Hamann, M. T. *Tet.* **2002**, *58,* 7809

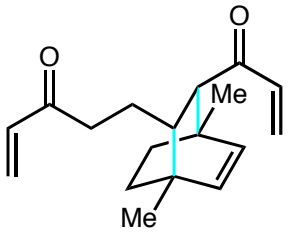
ROM/RCM Cascade: Synthesis of (+)-Cyanthiwigin U



(+)-Cyanthiwigin U

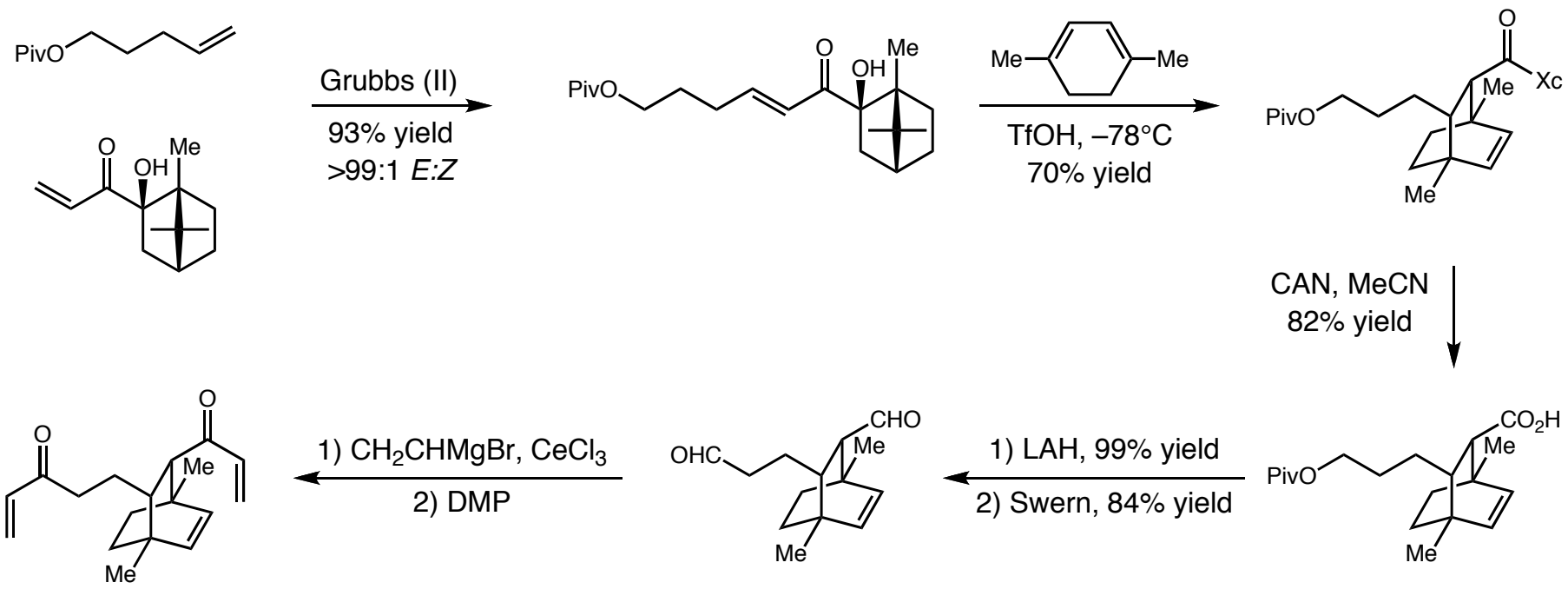
Hamann, M. T. *Tet.* **2002**, *58,* 7809

Phillips, A. J. *JACS* **2005**, *127,* 15284
14 steps, 11.85% overal yield

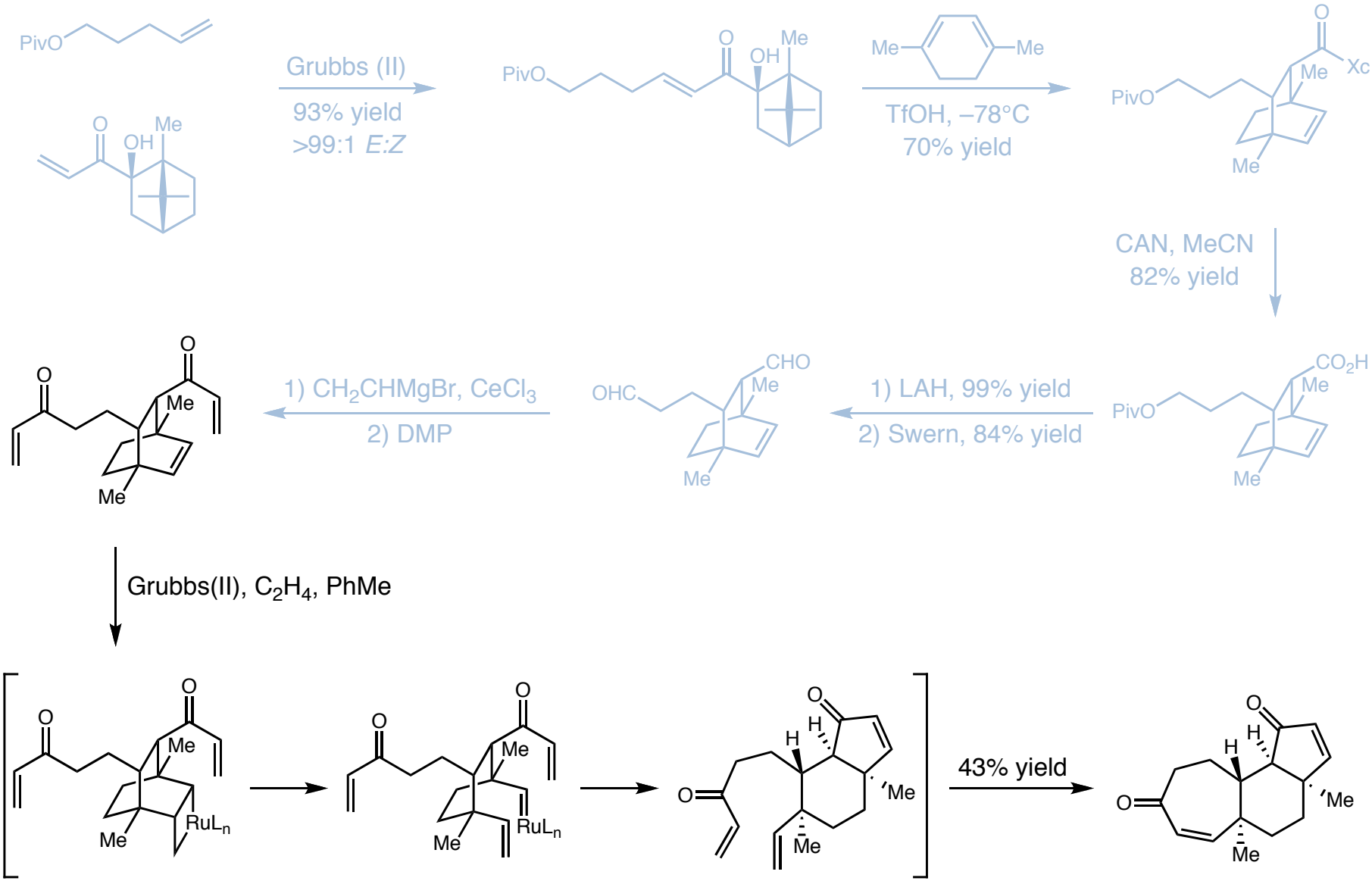


For related studies, see:
1) Stoltz, B. M. *Nature* **2008**, *453*, 1228 (Cyanthiwigin F)
2) Sarpong, R. *ACIE* **2009**, *48*, 2398 (Parallel kinetic resolution-Cyclopropanation/Cope rearraggement approach)

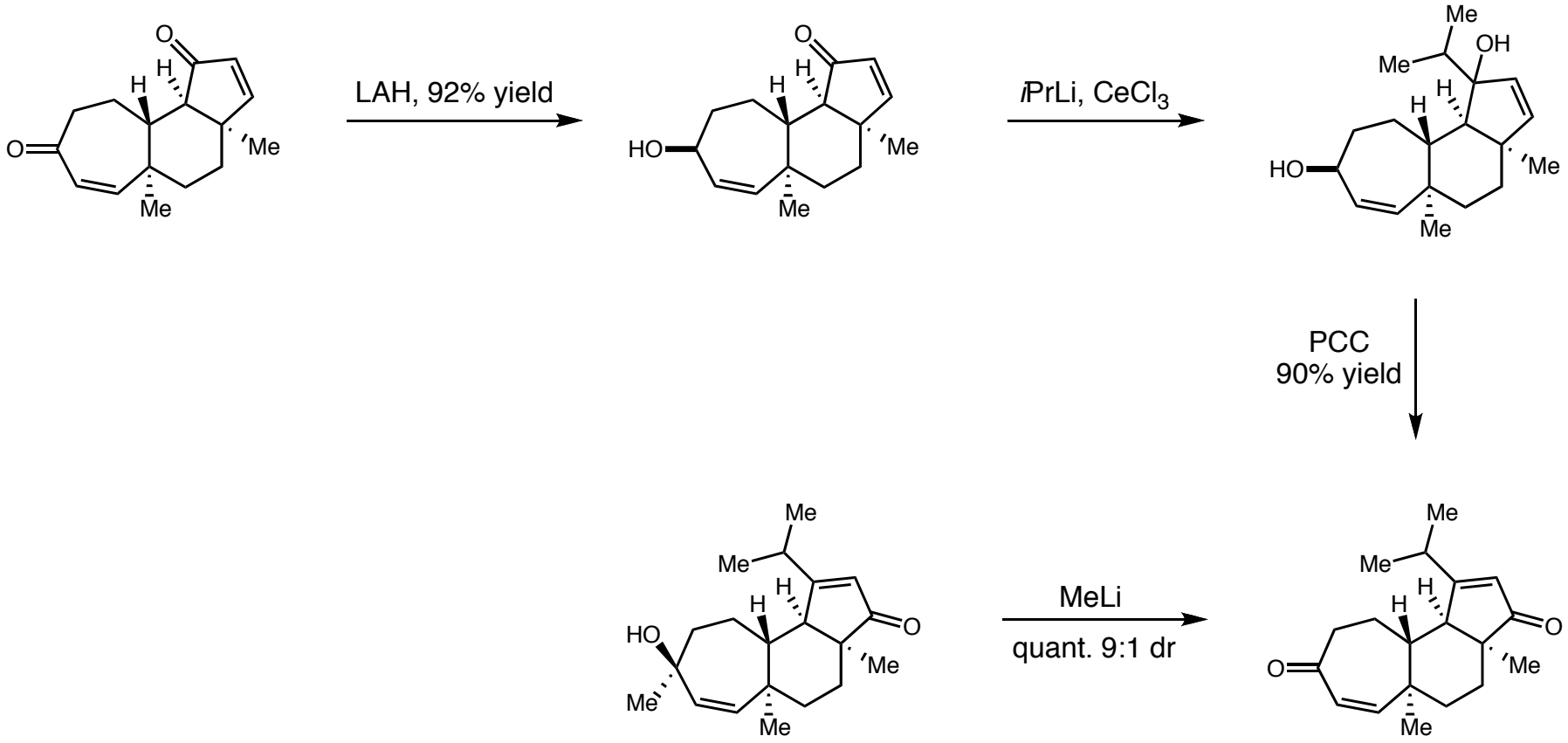
ROM/RCM Cascade: Synthesis of (+)-Cyanthiwigin U



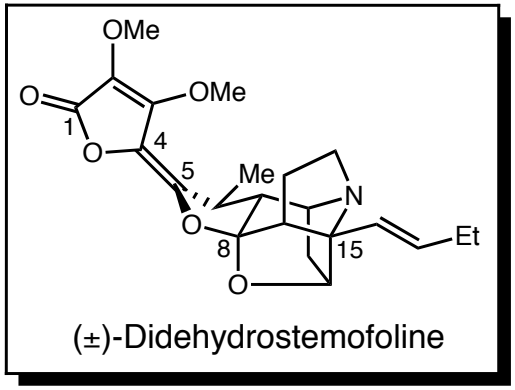
ROM/RCM Cascade: Synthesis of (+)-Cyanthiwigin U



ROM/RCM Cascade: Synthesis of (+)-Cyanthiwigin U



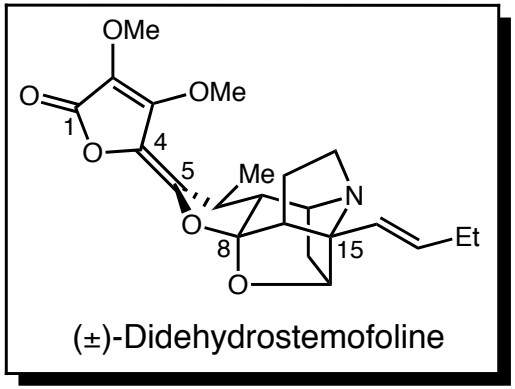
Pericyclic Cascade: Synthesis of (±)-Didehydrostemofoline (Asparagaemine A)



(±)-Didehydrostemofoline

- Sekine, T. *Chem. Pharm. Bull.* **1994**, *42,* 1360

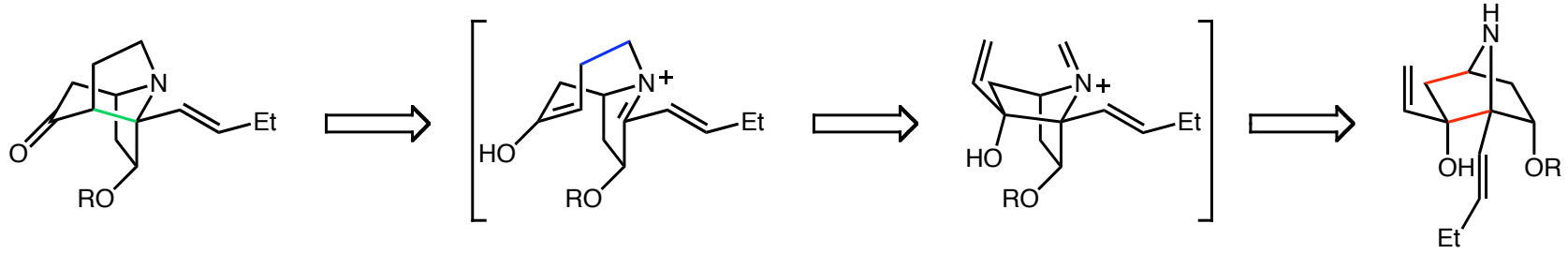
Pericyclic Cascade: Synthesis of (±)-Didehydrostemofoline (Asparagaemine A)



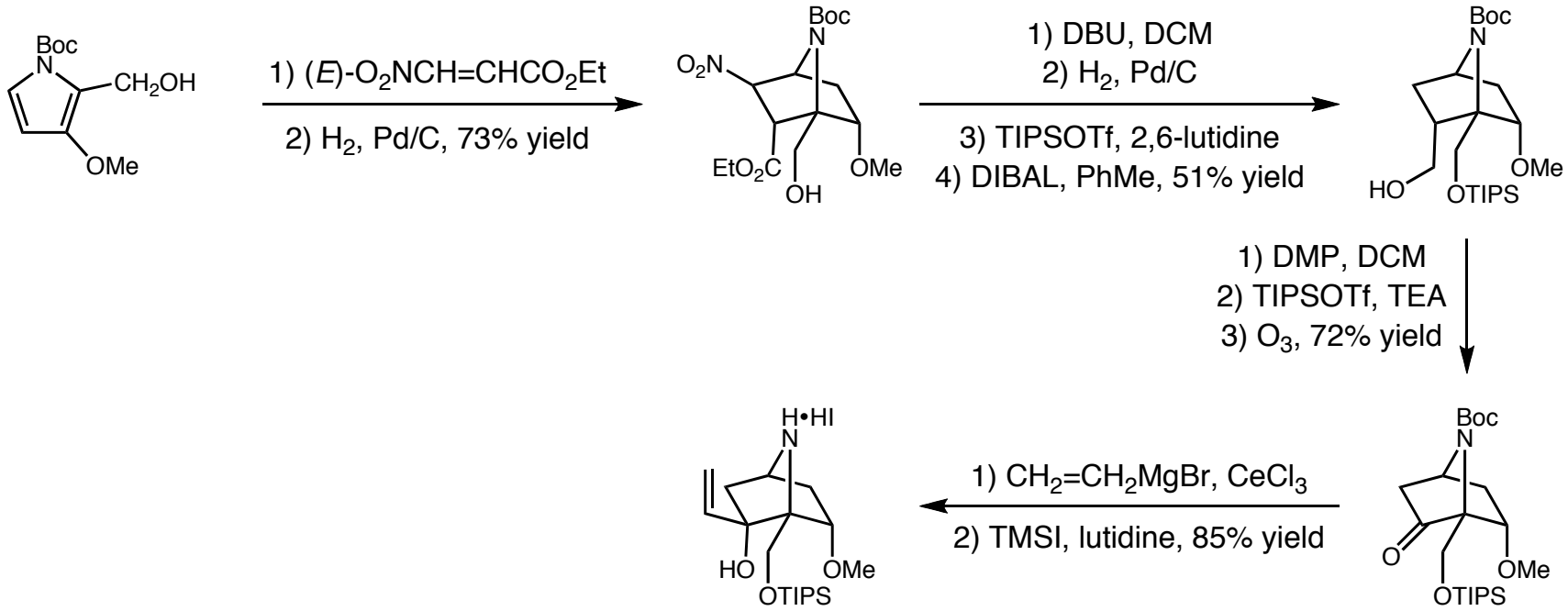
(±)-Didehydrostemofoline

Sekine, T. *Chem. Pharm. Bull.* **1994**, *42,* 1360

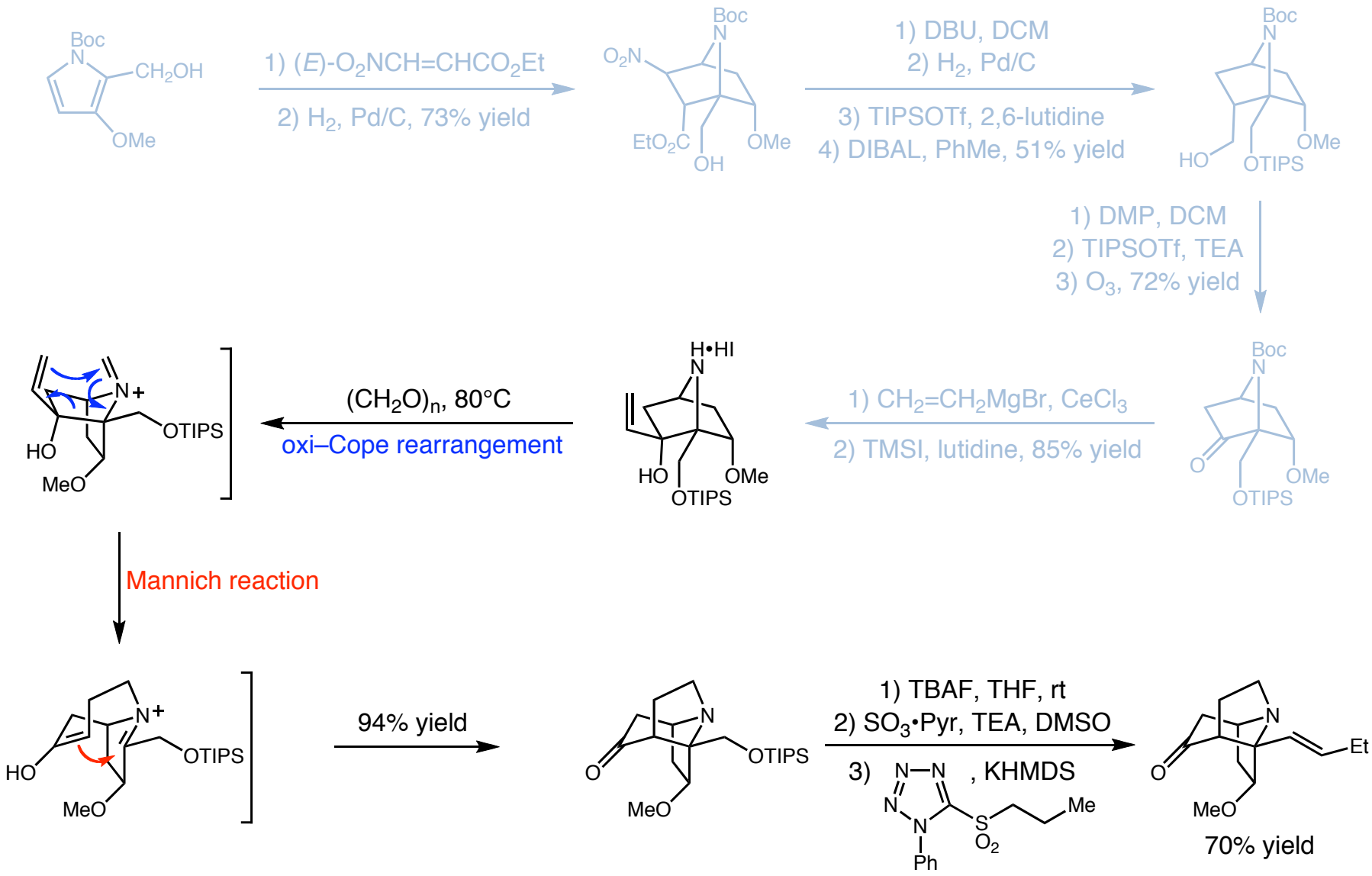
Overman, L. E. *JACS* **2003**, *125,* 15284
27 steps, 0.51% overal yield



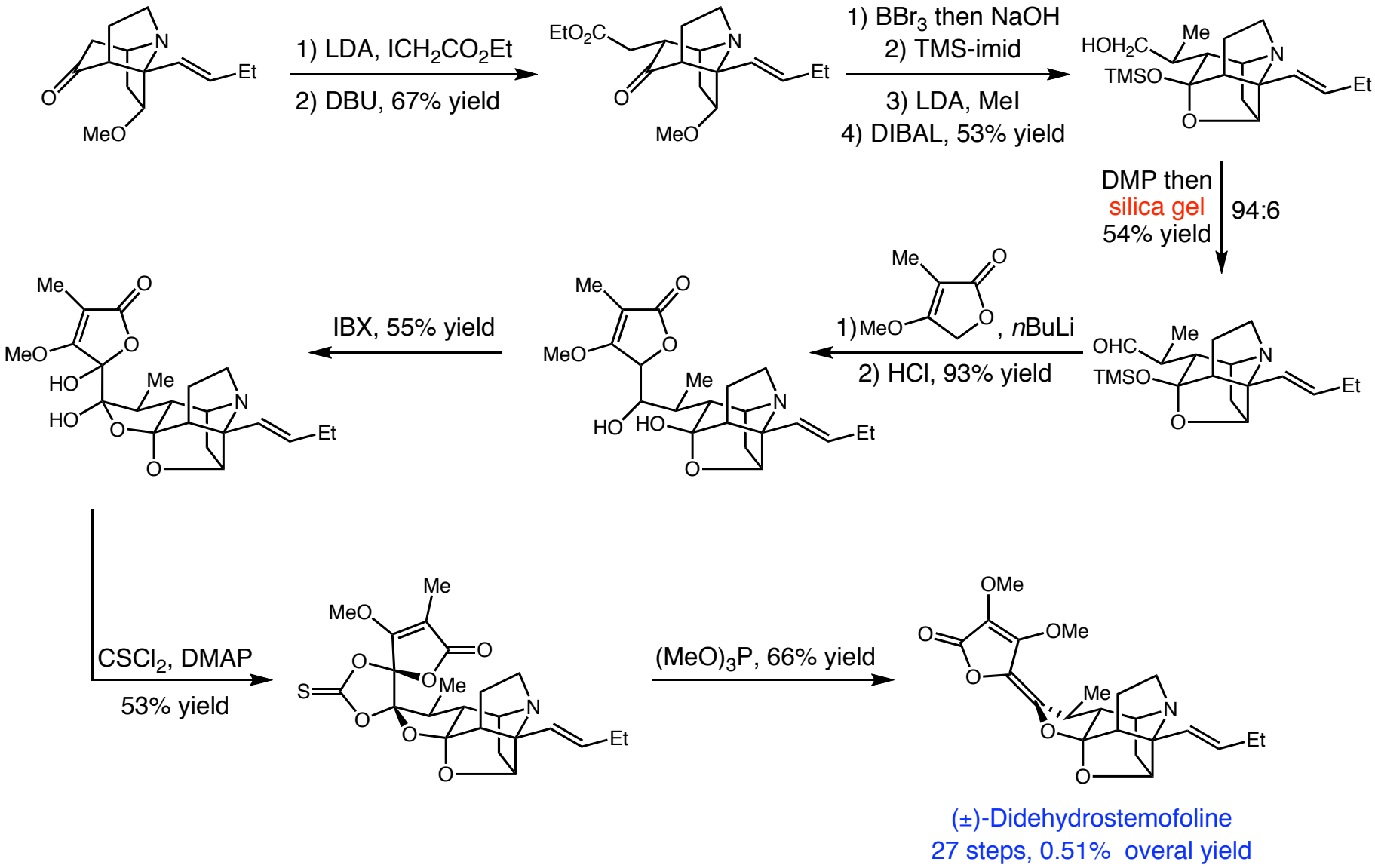
Pericyclic Cascade: Synthesis of (±)-Didehydrostemofoline (Asparagaemine A)



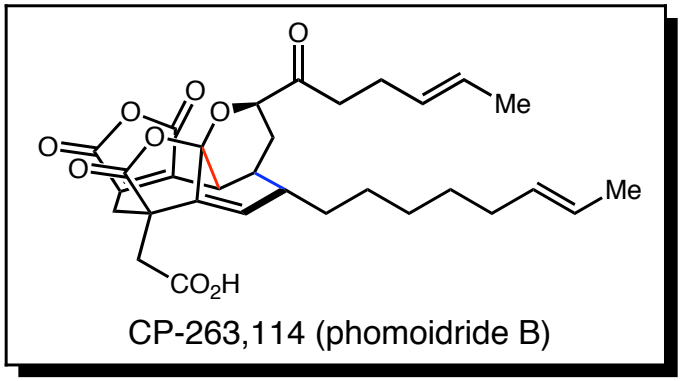
Pericyclic Cascade: Synthesis of (±)-Didehydrostemofoline (Asparagaemine A)



Pericyclic Cascade: Synthesis of (±)-Didehydrostemofoline (Asparagaemine A)



Anionic/Pericyclic Cascade: Synthesis of CP-263,114



CP-263,114 (phomoidride B)

- Stinson, S. *Chem. Eng. News* **1995**, *73*, 29 *(reported???)*

Kaneko, T. *J. Antibiot.* **1997**, *50*, 1 *(isolated)*

5+6+7+9-membered rings

highly oxygenated and sensitive functional groups

- Nicolaou, K. C. in Classics in Total Synthesis II, chap. 13

(synthesis review)

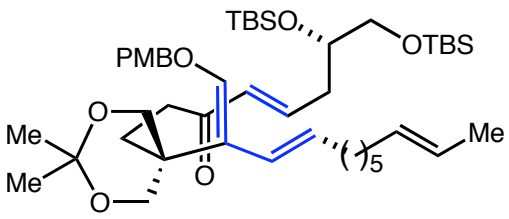
Nicolaou, Fukuiyama, Danishefsky, Shair

Shair, M. D. *JACS* **2000**, *122,* 7424

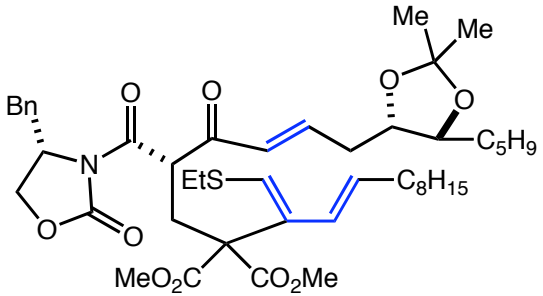
Grinard add./oxi-Cope/Dieckmann-type cyclization cascade

17 (or 21) longest linear steps, 0.14% overal yield (0.21%)

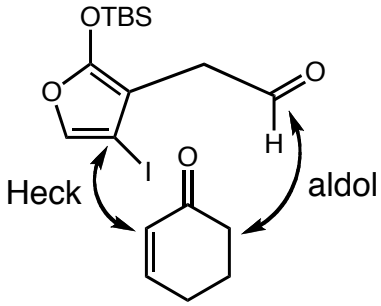
Nicolaou, 2000-2002
IMDA
46 longest linear steps
0.01% overal yield



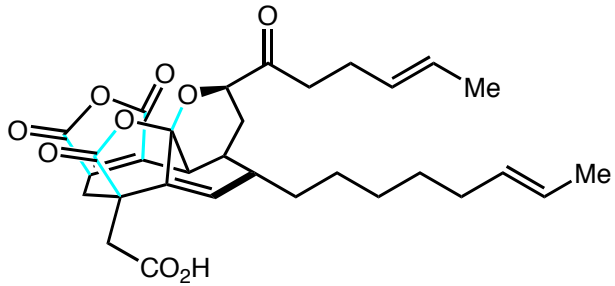
Fukuiyama
IMDA
JACS **2000**, *122*, 7825
22 linear steps
1.57% overal yield



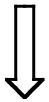
Danishefsky, 2000
Aldol–Heck reaction
≥ 30 steps

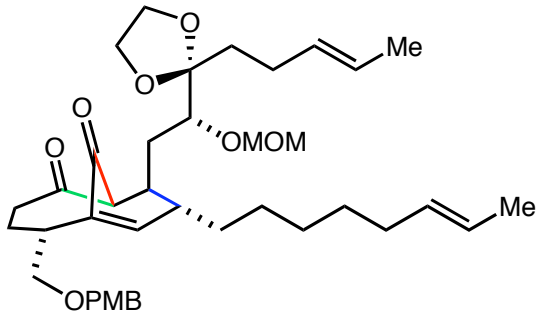


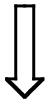
Anionic/Pericyclic Cascade: Retro Synthesis of CP-263,114

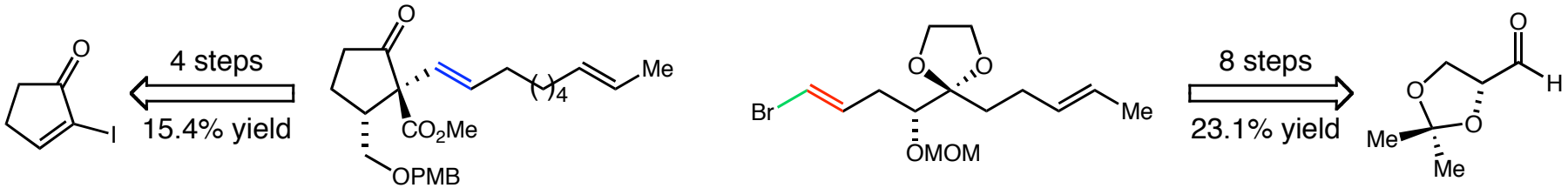


CP-263,114 (phomoidride B)

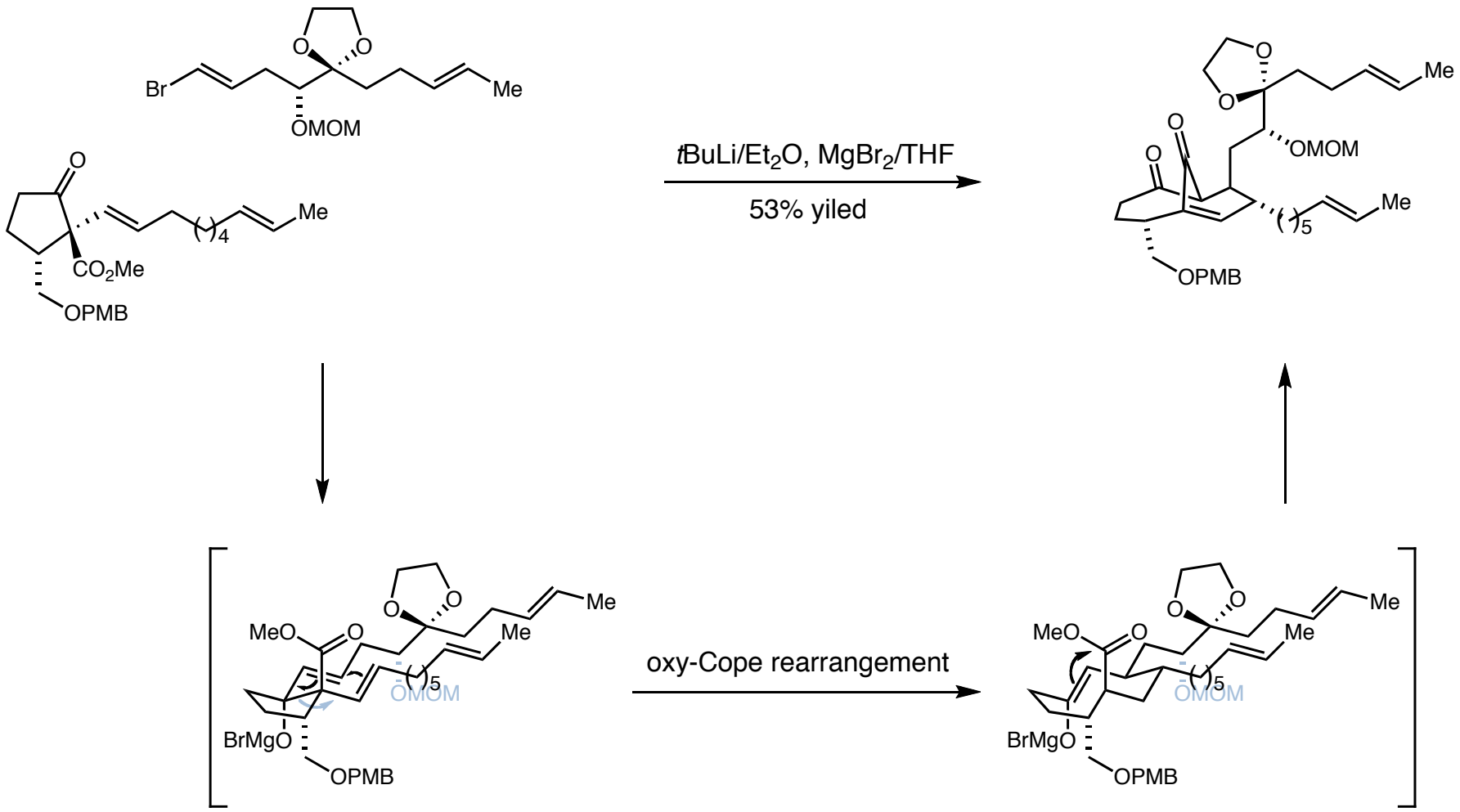




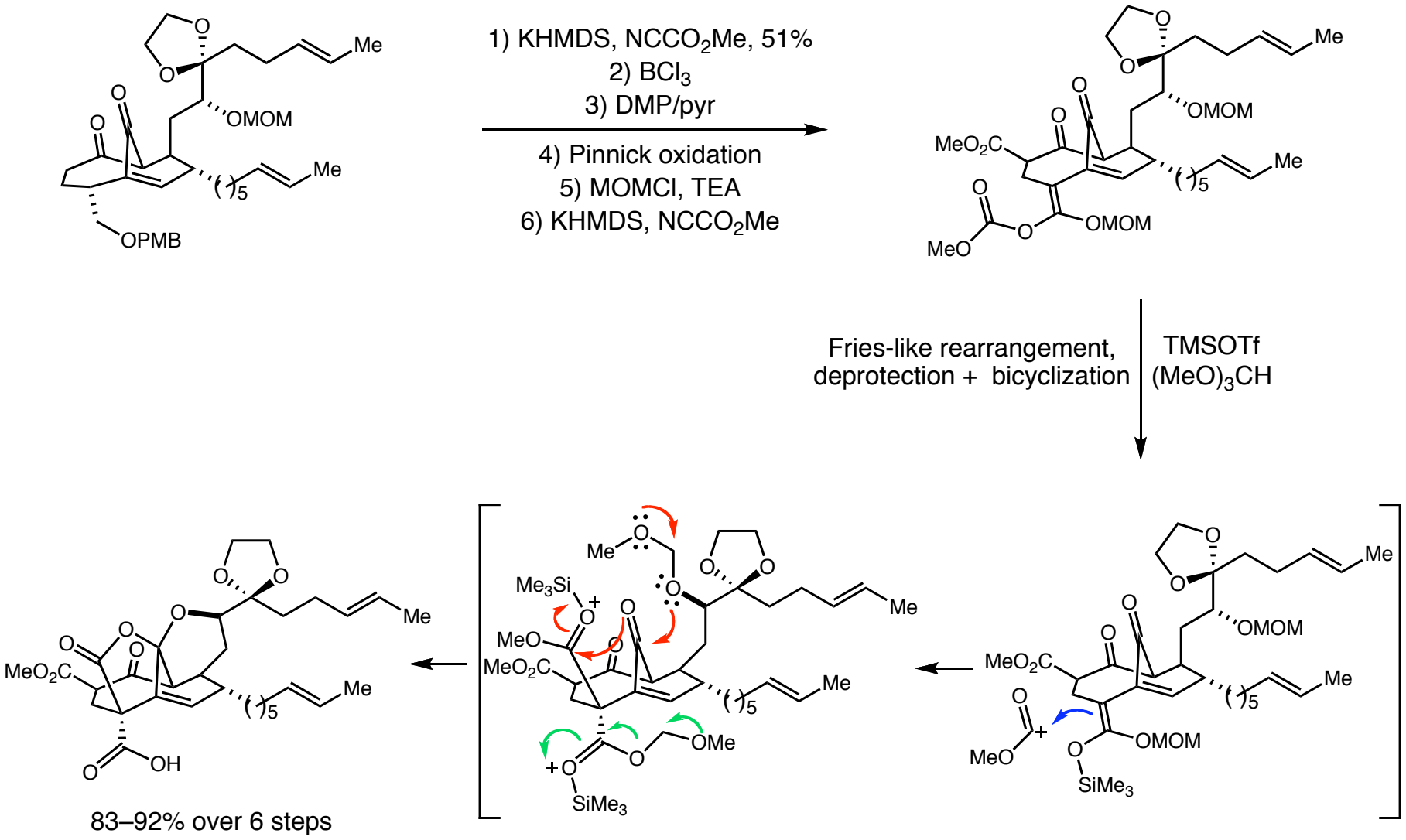




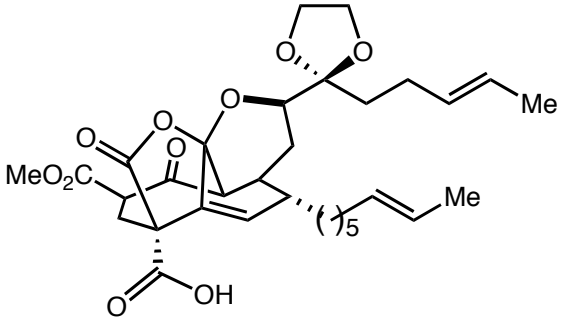
Anionic/Pericyclic Cascade: Synthesis of CP-263,114 Core



Anionic/Pericyclic Cascade: Synthesis of CP-263,114

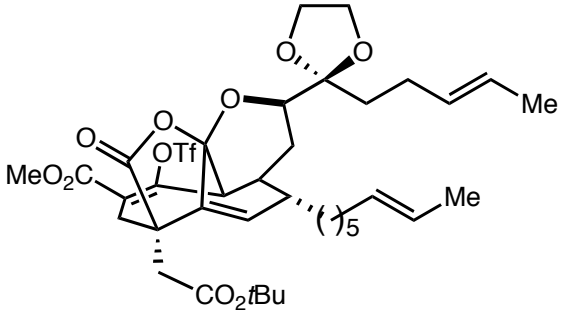


Anionic/Pericyclic Cascade: Synthesis of CP-263,114



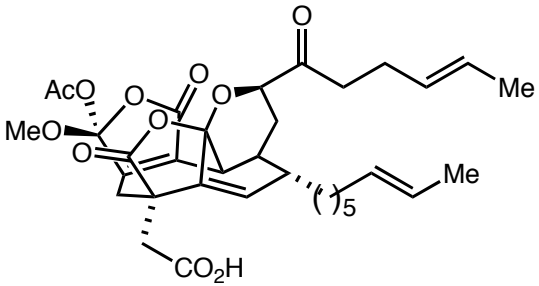
1) MsCl, TEA, CH_2N_2
2) hν, *t*BuOH-Et_2O, 12% yield

3)KDA, Tf_2O, 55% yield

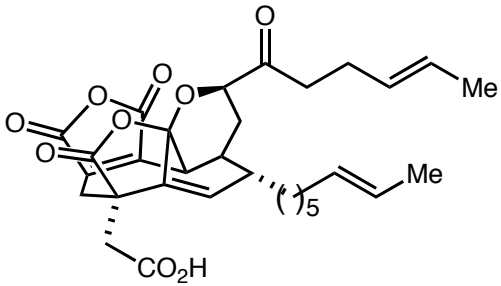


$Pd(OAc)_2$, $P(OMe)_3$
CO (500 psi)

THF–MeCN
70% yield



HCO_2H, 79% yield



CP-263,114 (phomoidride B)
21 longest linear steps
0.21% overal yield