The Chemistry of Larry E. Overman

Application in Total Synthesis

Distinguished Professor of Chemistry
University of California, Irvine

http://faculty.sites.uci.edu/overman/

Topic Review

Bern, May, 1st 2014

Julien Pomarole

Index

About Larry E. Overman

- B. A. from Earlham College, Richmond, IND (1965)
- Ph.D from University of Wisconsin, Madison, WI (1969)

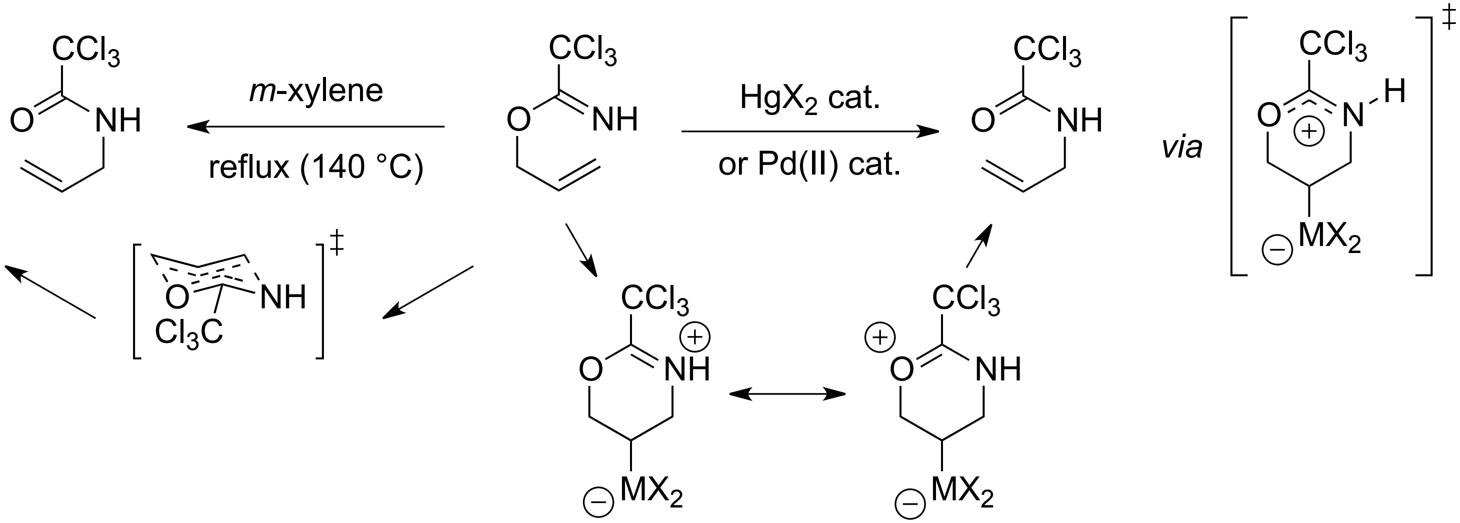
  Under the supervision of Pr Howard H. Whitlock Jr.
- NIH postdoctoral fellowship, Columbia University, New York, NY (1969-1971),

  with Pr Ronald Breslow
- Joined University of California, Irvine, CA (1971)
  - *1971-1974: Assistant Professor*
  - *1974-1994: Full Professor*
  - *1994-currently: Distinguished Professor*

http://faculty.sites.uci.edu/overman/
http://www.scienceblog.com/community/older/2003/C/2003436.html
http://pubs.acs.org/cen/awards/8106/8106awards.html

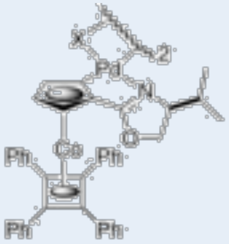
Overman Rearrangement

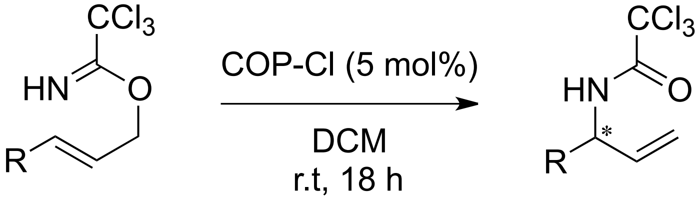
- Allylic imidate rearrangement: Mumm and Möller (1937)
- Overman rearrangement (1974, allylic trichloroacetimidate rearrangement)

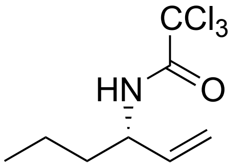


(1) Mumm, O.; Möller, F. *Ber.* **1937**, *11*, 2214–2227.
(2) Overman, L. E. *J. Am. Chem. Soc.* **1974**, *96*, 597–599.
(3) Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901–2910.

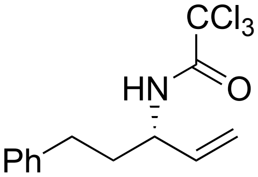
Overman Rearrangement







80%
94% ee



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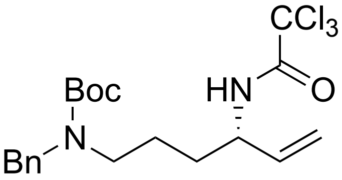
96% ee



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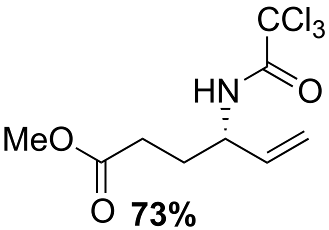
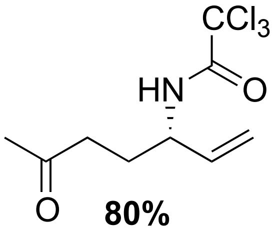
95% ee



73%
95% ee



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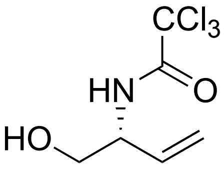
94% ee

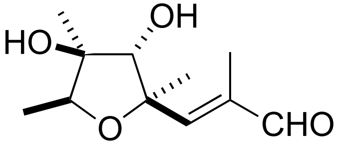


84%
80% ee

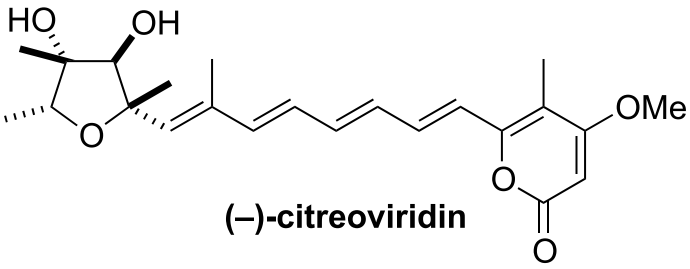
Overman, L. E.; Owen, C. E.; Pavan, M. M.; Richards, C. J. *Org. Lett.* **2003**, *5*, 1809–1812.
Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412–12413.

Prins-Pinacol rearrangement Strategy

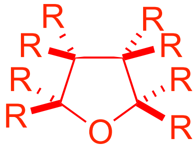
Formation of high substituted tetrahydrofuran

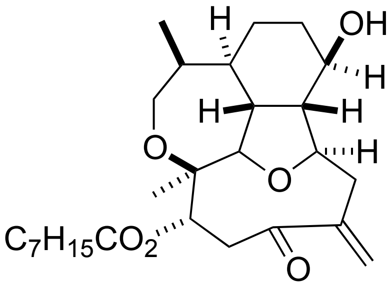


(–)-citreoviral

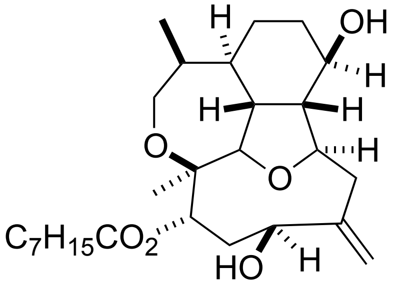


(–)-citreoviridin

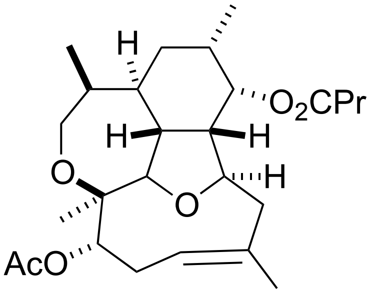




biarellin F



biarellin E

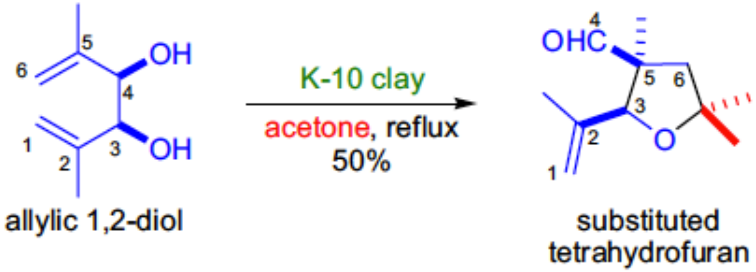


asbestinin-1

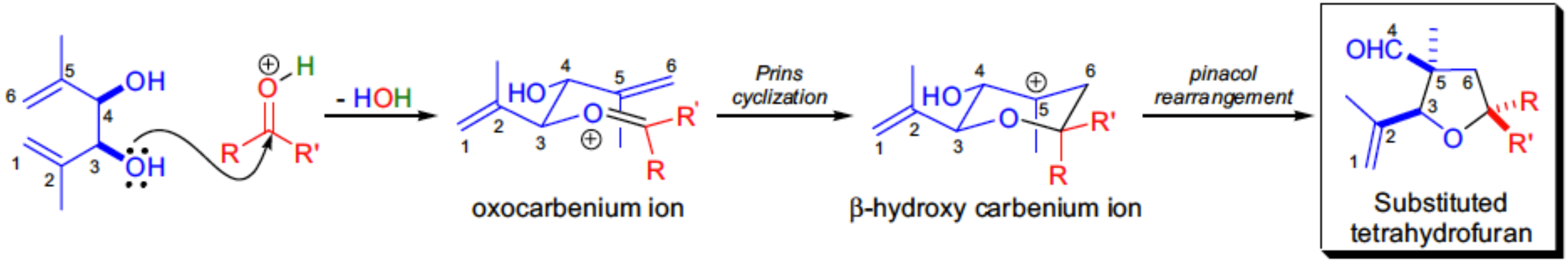
Prins-Pinacol rearrangement Strategy

Prins-Pinacol reaction

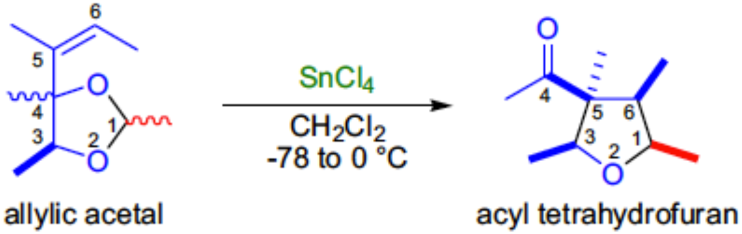
- First example : Mousset and co-worker (1969)



- Mechanism :



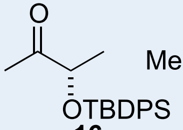
- Overman's condition (1987):



Martinet, P., Mousset, G., Colineau, M. *Acad. Sci. C.* **1969**, 268, 1303-1306.
Hopkins, M. H., Overman, L. E. *J. Am. Chem. Soc.* **1987**, 109, 4748
Overman, L. E., Pennington, L. D. *J. Org. Chem.* **2003**, 68, 7143

Prins-Pinacol rearrangement Strategy

(–)-citreoviral synthesis



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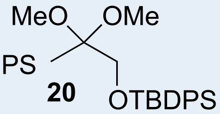

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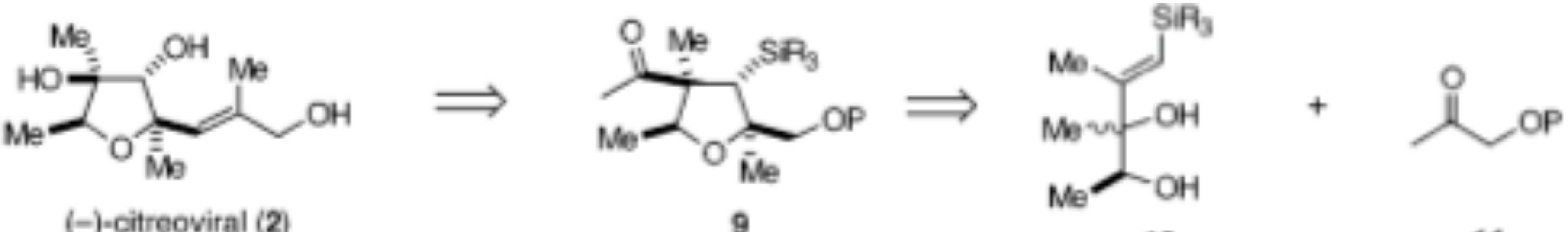
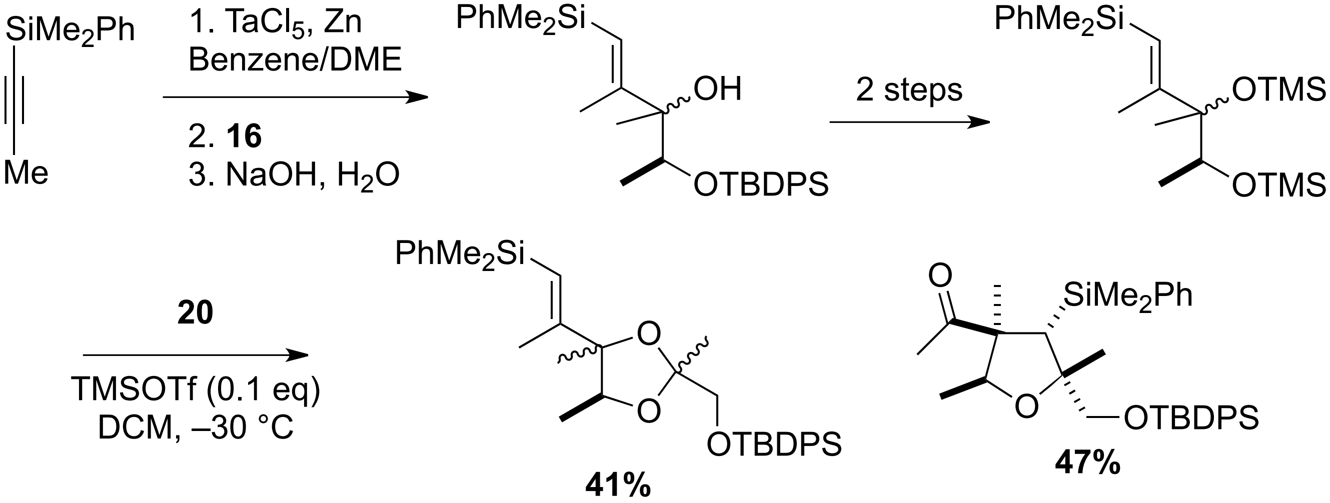


(–)-citreoviral (2)

9

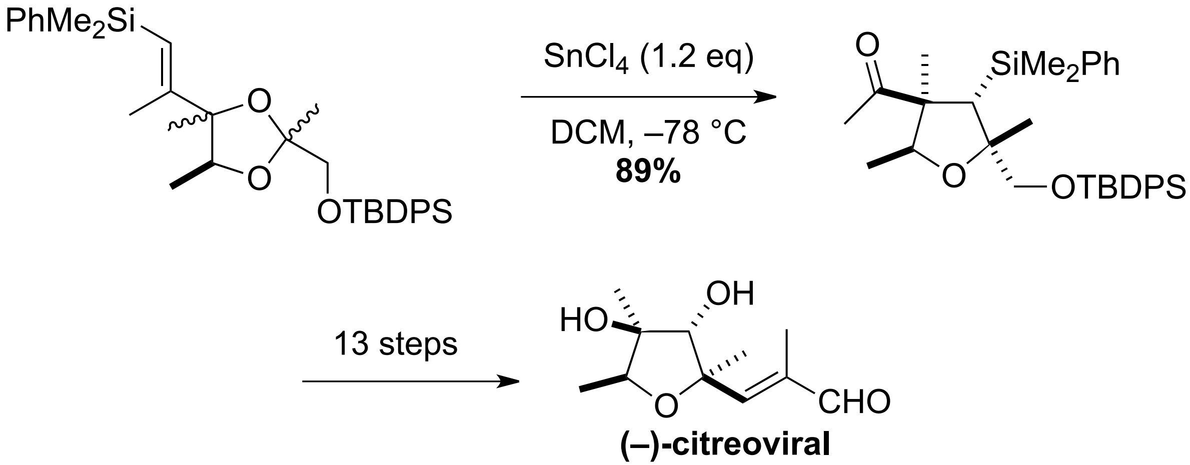
10

11



Hanaki, N.; Link, J. T.; MacMillan, D.; Overman, L. E. *Org. Lett.* **2000**, *2*, 223–226.

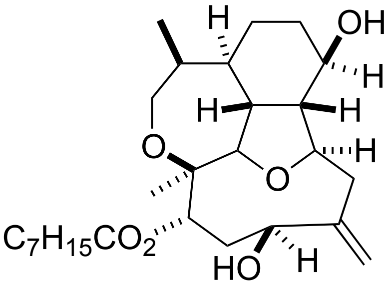
Prins-Pinacol rearrangement Strategy
(–)-citreoviral synthesis



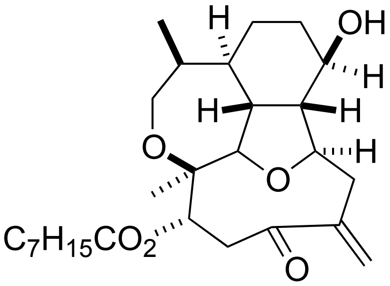
Hanaki, N.; Link, J. T.; MacMillan, D.; Overman, L. E. *Org. Lett.* **2000**, *2*, 223–226.

Prins-Pinacol rearrangement Strategy

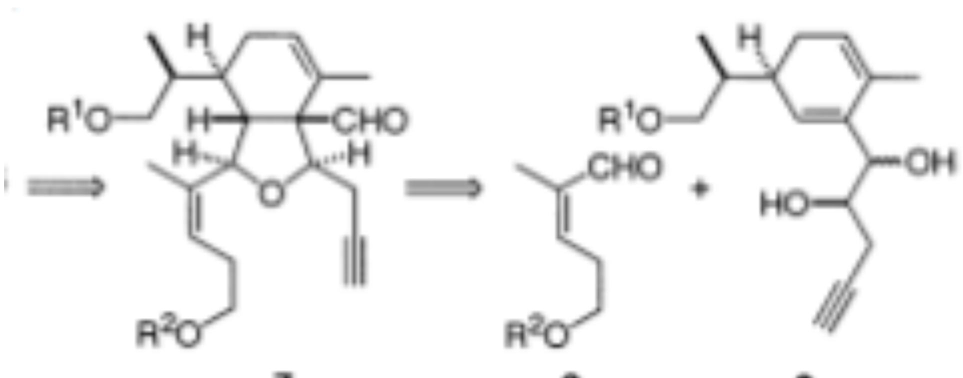
Biarellin E and F syntheses



biarellin E



biarellin F

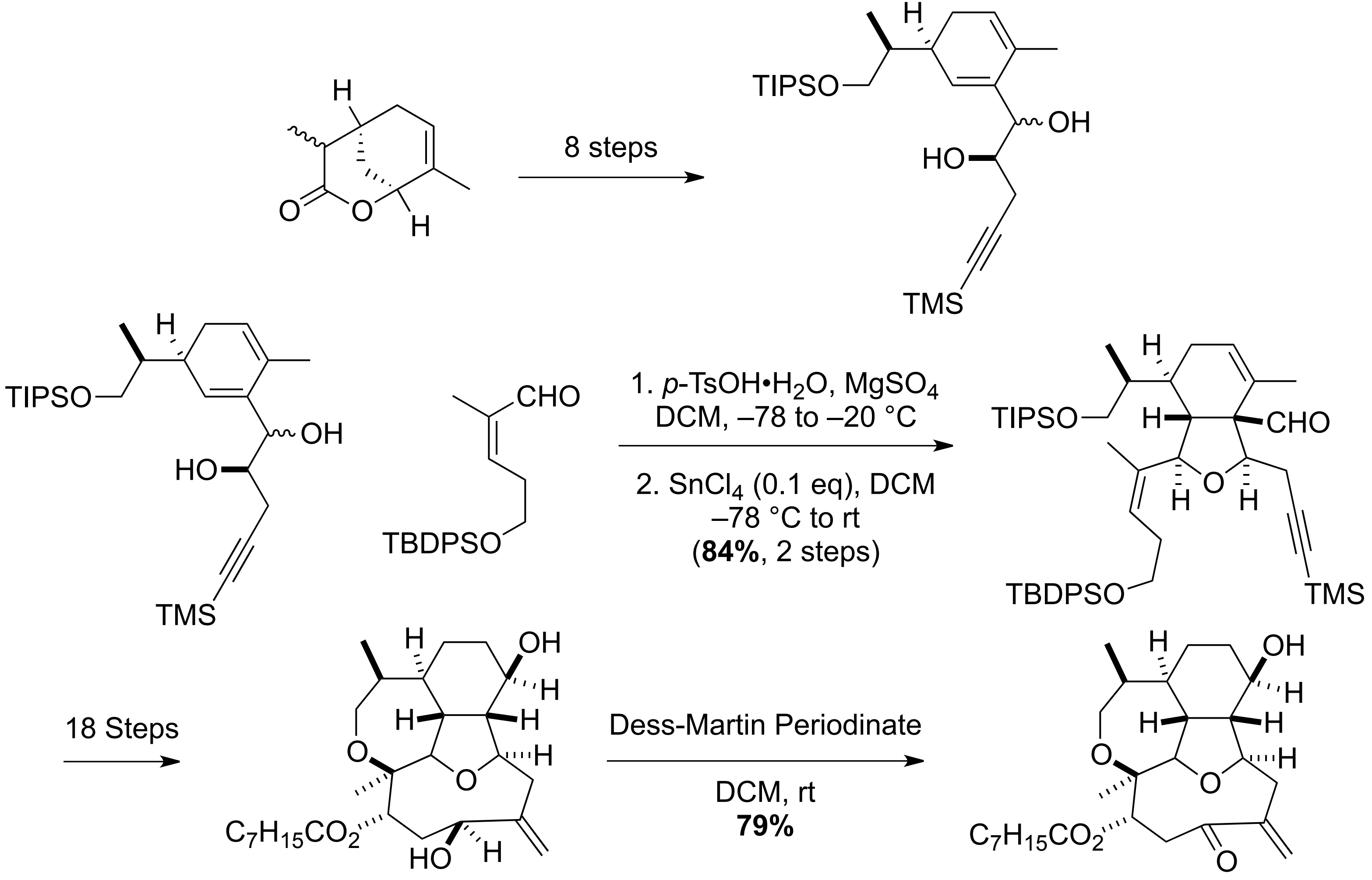


7 **8** **9**

Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2003**, *125*, 6650–6652.

Prins-Pinacol rearrangement Strategy

Biarellin E and F syntheses



8 steps

1. *p*-TsOH•H_2O, $MgSO_4$ DCM, –78 to –20 °C

2. $SnCl_4$ (0.1 eq), DCM –78 °C to rt (**84%**, 2 steps)

18 Steps

Dess-Martin Periodinate

DCM, rt **79%**

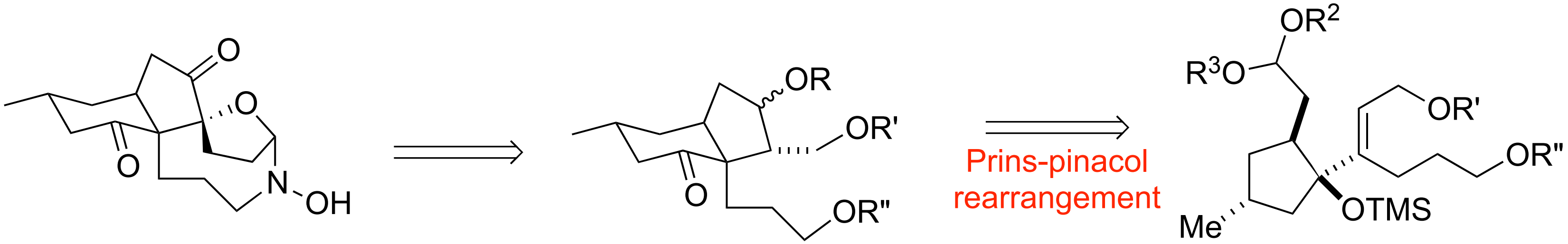
biarellin E

biarellin F

Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2003**, *125*, 6650–6652.

Prins-Pinacol rearrangment Strategy

(+)-Sieboldine A synthesis

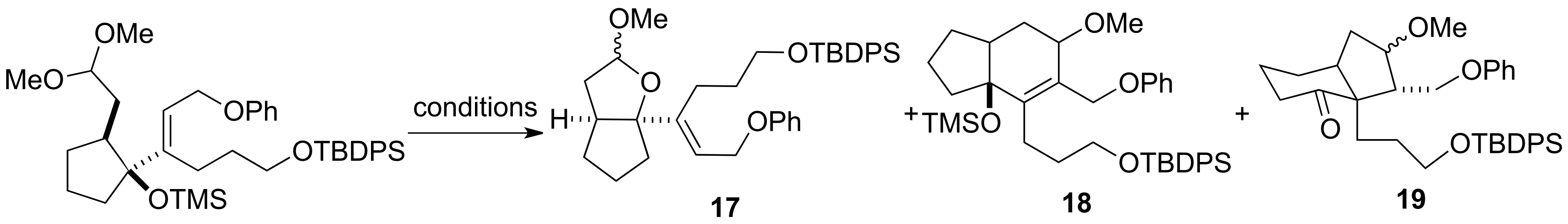


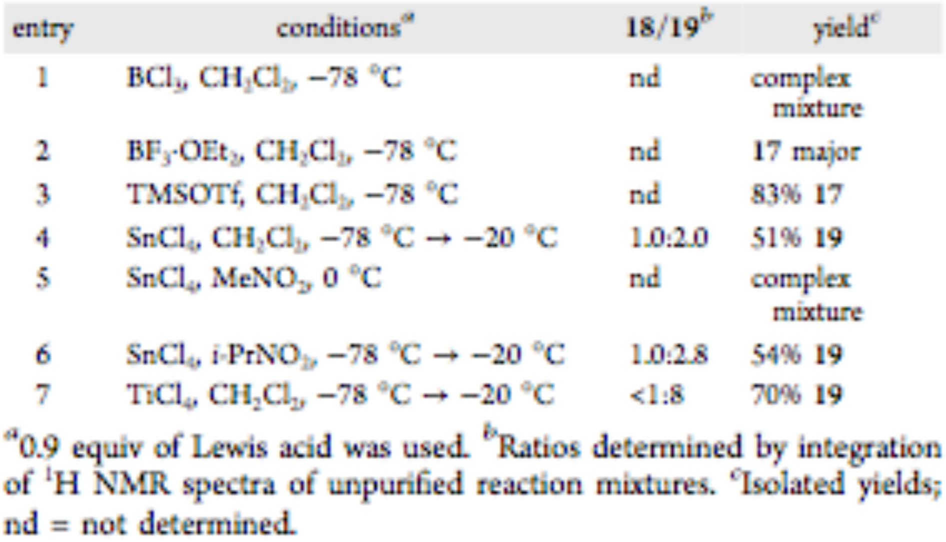
(+)-sieboldine A

Canham, S. M.; France, D. J.; Overman, L. E. *J. Org. Chem.* **2013**, *78*, 9–34.

Prins-Pinacol type Reaction

(+)-Sieboldine A synthesis





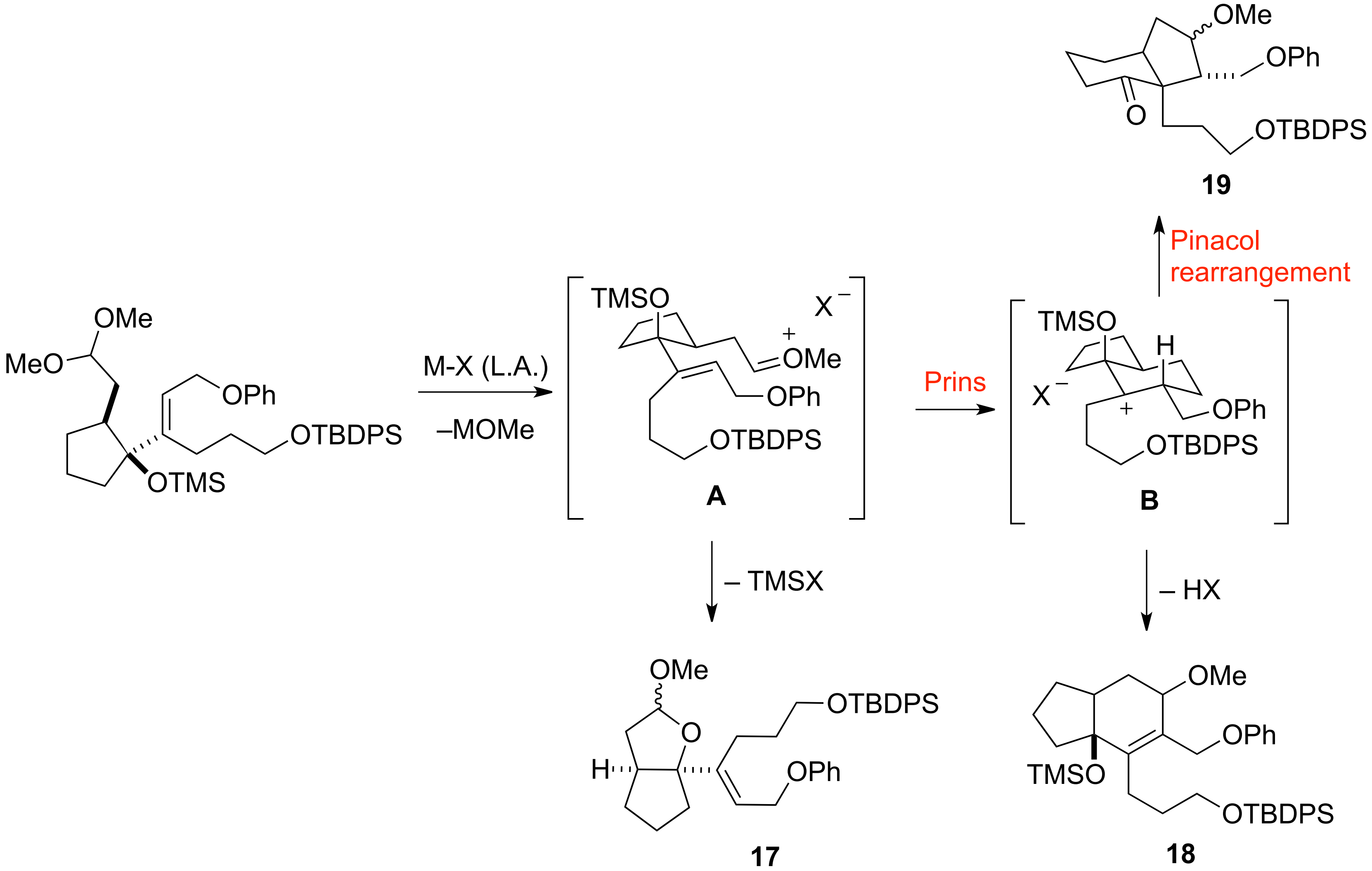
entry	conditions[a]	18/19[b]	yield[c]
1	BCl_3, CH_2Cl_2, −78 °C	nd	complex mixture
2	$BF_3 \cdot OEt_2$, CH_2Cl_2, −78 °C	nd	17 major
3	TMSOTf, CH_2Cl_2, −78 °C	nd	83% 17
4	$SnCl_4$, CH_2Cl_2, −78 °C → −20 °C	1.0:2.0	51% 19
5	$SnCl_4$, $MeNO_2$, 0 °C	nd	complex mixture
6	$SnCl_4$, i-$PrNO_2$, −78 °C → −20 °C	1.0:2.8	54% 19
7	$TiCl_4$, CH_2Cl_2, −78 °C → −20 °C	<1:8	70% 19

[a] 0.9 equiv of Lewis acid was used. [b] Ratios determined by integration of ^1H NMR spectra of unpurified reaction mixtures. [c] Isolated yields; nd = not determined.

Canham, S. M.; France, D. J.; Overman, L. E. *J. Org. Chem.* **2013**, *78*, 9–34.

Prins-Pinacol type Reaction

(+)-Sieboldine A synthesis



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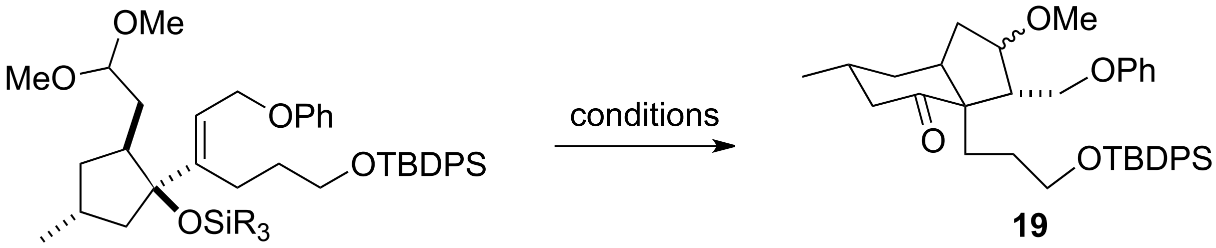
Prins-Pinacol type Reaction
(+)-Sieboldine A synthesis



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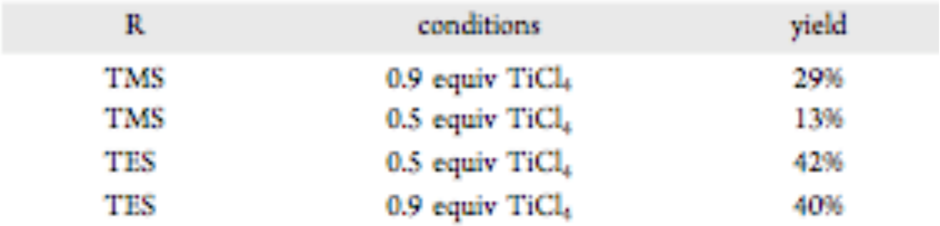
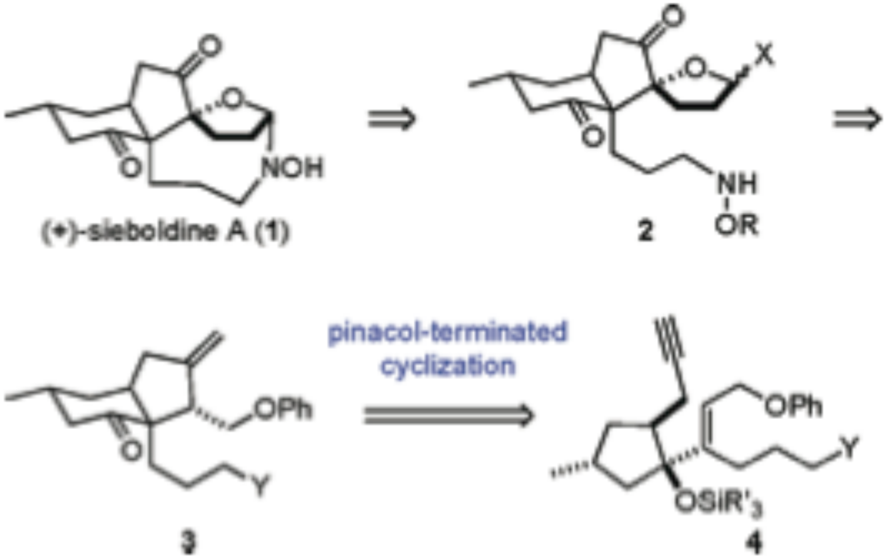


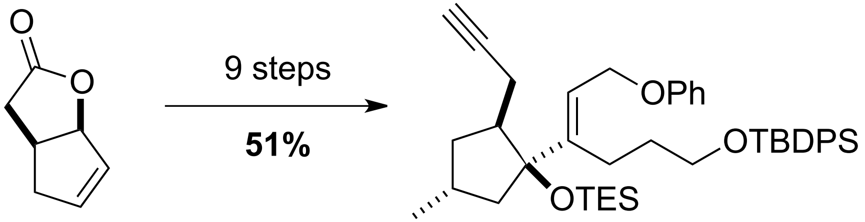
R	conditions	yield
TMS	0.9 equiv $TiCl_4$	29%
TMS	0.5 equiv $TiCl_4$	13%
TES	0.5 equiv $TiCl_4$	42%
TES	0.9 equiv $TiCl_4$	40%

Canham, S. M.; France, D. J.; Overman, L. E. *J. Org. Chem.* **2013**, *78*, 9–34.

Pinacol-terminated 1,6-enyne cyclization

(+)-Sieboldine A synthesis





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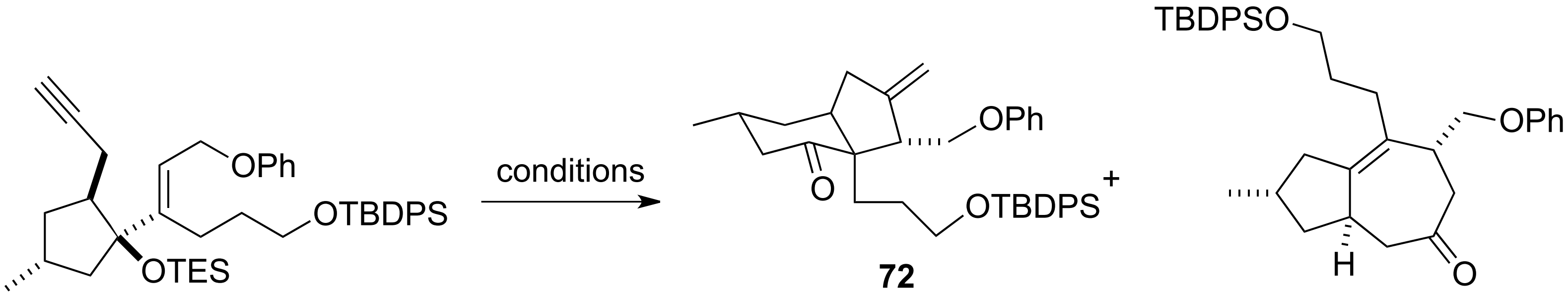
Canham, S. M.; France, D. J.; Overman, L. E. *J. Am. Chem. Soc.* **2010**, *132*, 7876–7877.

Pinacol-terminated 1,6-enyne cyclization

(+)-Sieboldine A synthesis



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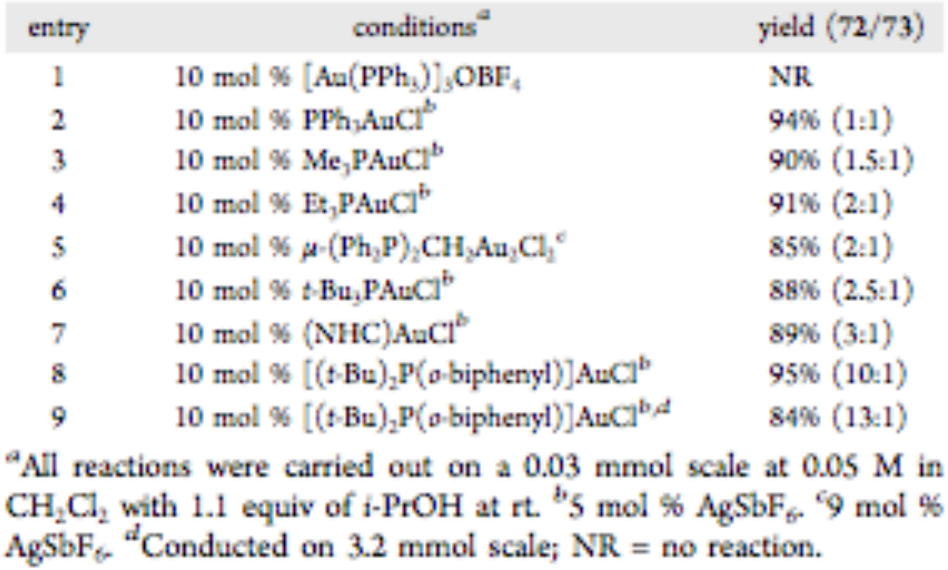
73



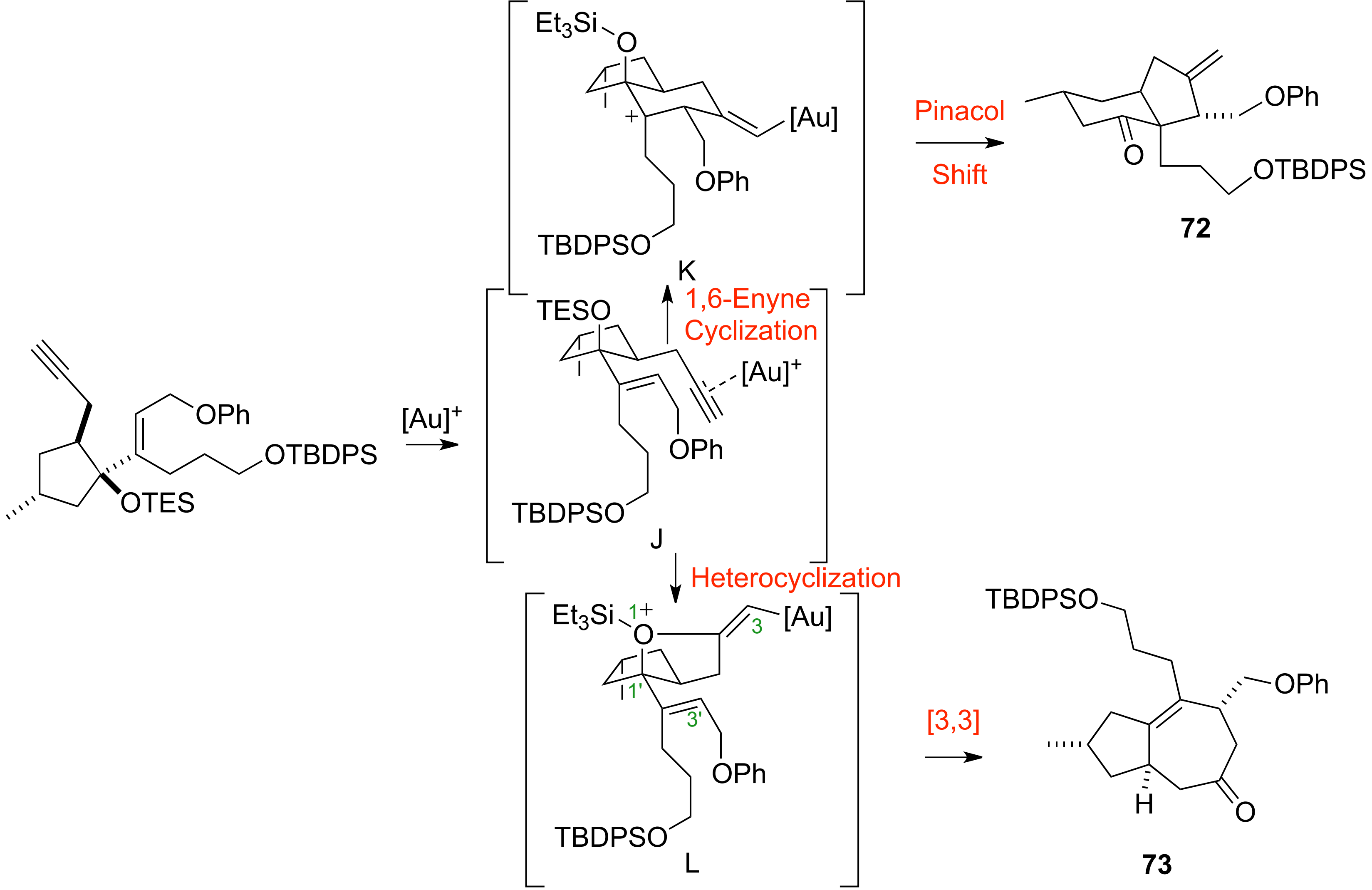
entry	conditions[a]	yield (72/73)
1	10 mol % $[Au(PPh_3)]_3OBF_4$	NR
2	10 mol % PPh_3AuCl[b]	94% (1:1)
3	10 mol % Me_3PAuCl[b]	90% (1.5:1)
4	10 mol % Et_3PAuCl[b]	91% (2:1)
5	10 mol % μ-$(Ph_2P)_2CH_2Au_2Cl_2$[c]	85% (2:1)
6	10 mol % t-Bu_3PAuCl[b]	88% (2.5:1)
7	10 mol % (NHC)AuCl[b]	89% (3:1)
8	10 mol % $[(t\text{-}Bu)_2P(o\text{-biphenyl})]AuCl$[b]	95% (10:1)
9	10 mol % $[(t\text{-}Bu)_2P(o\text{-biphenyl})]AuCl$[b,d]	84% (13:1)

[a] All reactions were carried out on a 0.03 mmol scale at 0.05 M in CH_2Cl_2 with 1.1 equiv of *i*-PrOH at rt. [b] 5 mol % $AgSbF_6$. [c] 9 mol % $AgSbF_6$. [d] Conducted on 3.2 mmol scale; NR = no reaction.

Canham, S. M.; France, D. J.; Overman, L. E. *J. Org. Chem.* **2013**, *78*, 9–34.
Canham, S. M.; France, D. J.; Overman, L. E. *J. Am. Chem. Soc.* **2010**, *132*, 7876–7877.

Pinacol-terminated 1,6-enyne cyclization

(+)-Sieboldine A synthesis



J

K

L

72

73

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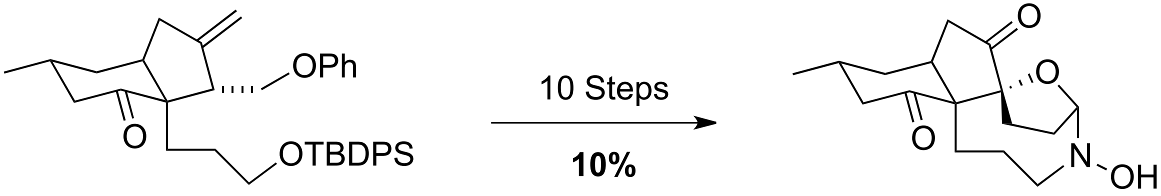
Pinacol-terminated 1,6-enyne cyclization

(+)-Sieboldine A synthesis



10 Steps

10%

72

(+)-sieboldine A

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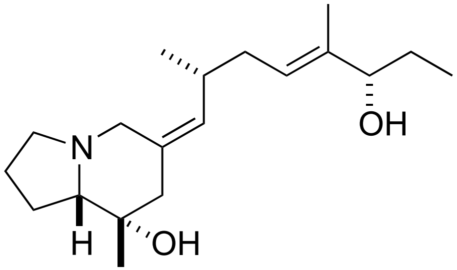
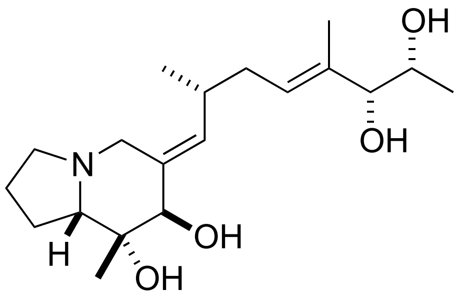
Canham, S. M.; France, D. J.; Overman, L. E. *J. Am. Chem. Soc.* **2010**, *132*, 7876–7877.

Iminium Chemistry

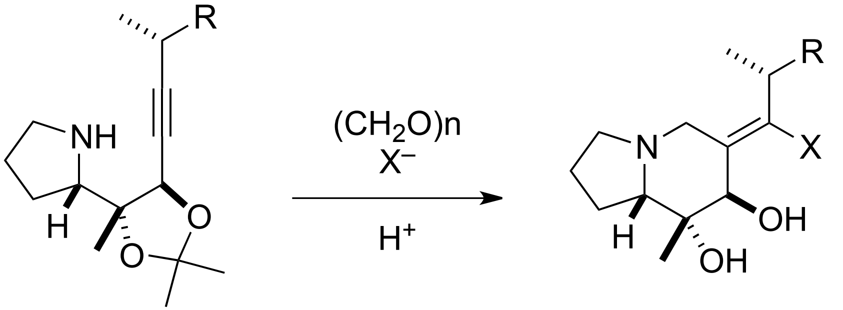
Nucleophile-promoted iminium ion-alkyne cycliztn



(+)-pumilotoxin A



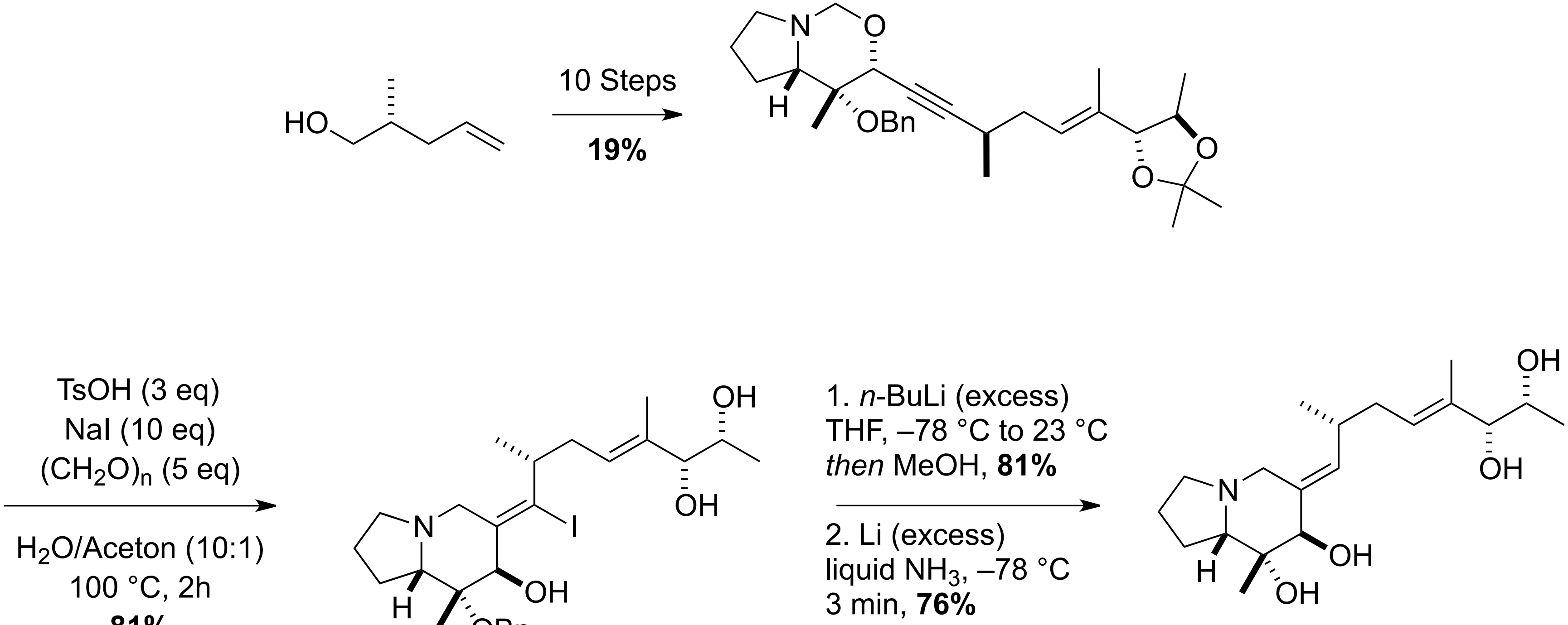
(+)-Allopumiliotoxin 339A



Overman, L. E.; Robinson, L. A. *J. Am. Chem. Soc* **1992**, *114*, 368–369.
Caderas, C.; Lett, R.; Overman, L. E. *J. Am. Chem. Soc* **1996**, *118*, 9073–9082.

Iminium Chemistry

Nucleophile-promoted iminium ion-alkyne cycliztn



10 Steps

19%

TsOH (3 eq)
NaI (10 eq)
$(CH_2O)_n$ (5 eq)

H_2O/Aceton (10:1)
100 °C, 2h
81%

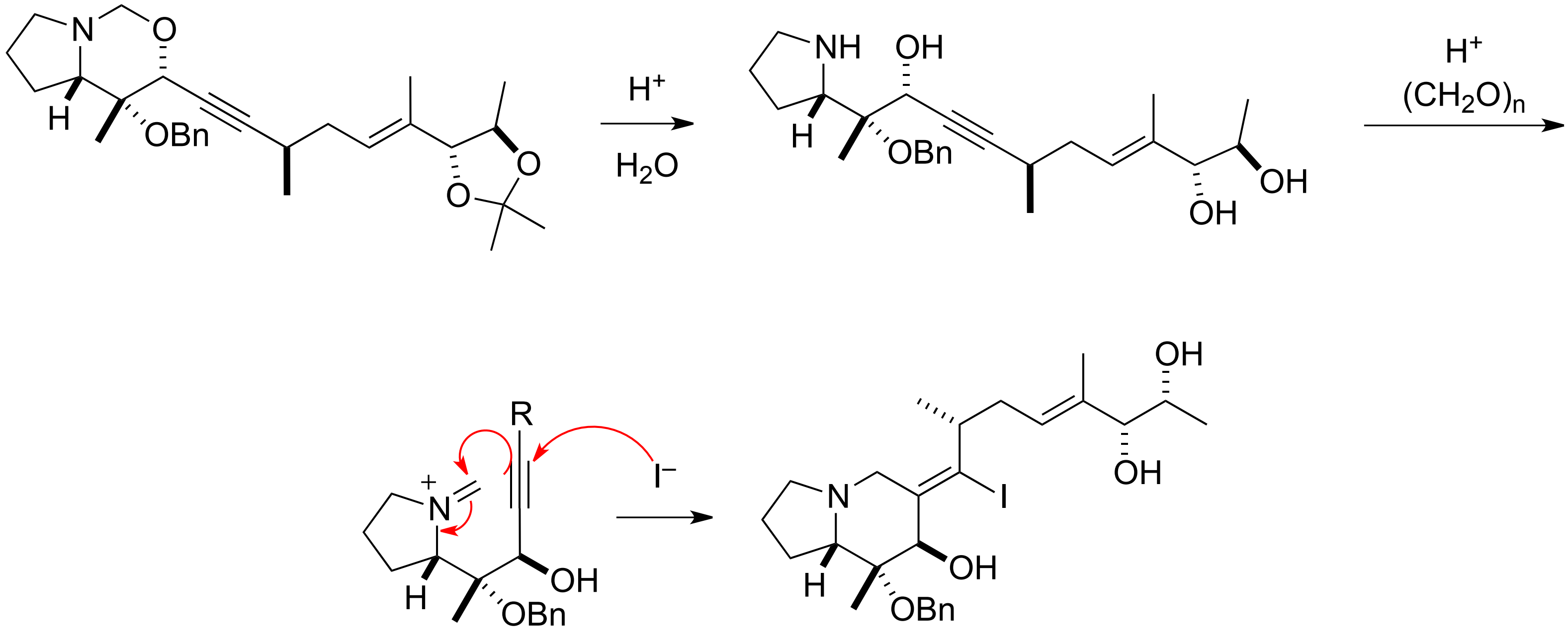
1. *n*-BuLi (excess)
THF, –78 °C to 23 °C
then MeOH, **81%**

2. Li (excess)
liquid NH_3, –78 °C
3 min, **76%**

(+)-Allopumiliotoxin 339A

Overman, L. E.; Robinson, L. A. *J. Am. Chem. Soc* **1992**, *114*, 368–369.

Iminium Chemistry
Nucleophile-promoted iminium ion-alkyne cycliztn



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Iminium Chemistry

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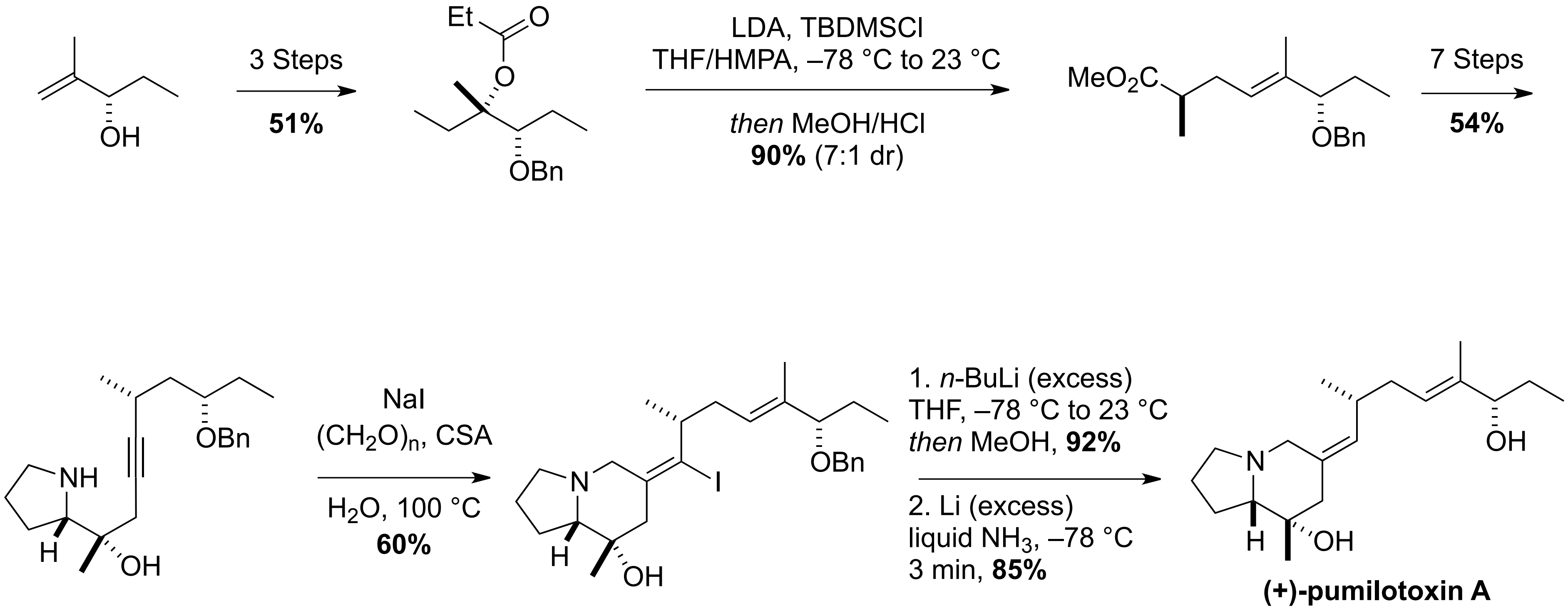


3 Steps

51%

LDA, TBDMSCl

THF/HMPA, –78 °C to 23 °C

then MeOH/HCl

90% (7:1 dr)

7 Steps

54%

NaI

$(CH_2O)_n$, CSA

H_2O, 100 °C

60%

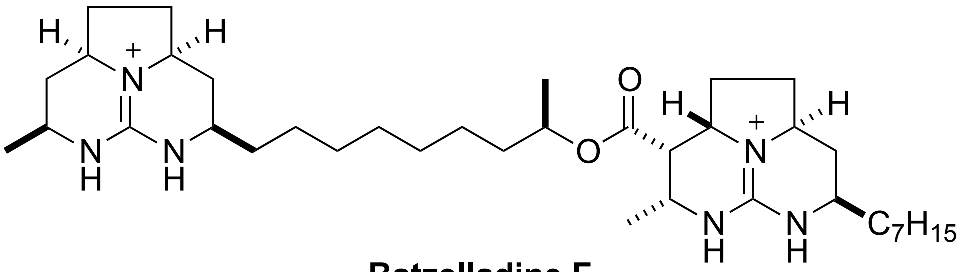
1. *n*-BuLi (excess)
THF, –78 °C to 23 °C
then MeOH, **92%**

2. Li (excess)
liquid NH_3, –78 °C
3 min, **85%**

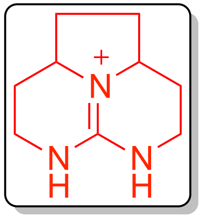
(+)-pumilotoxin A

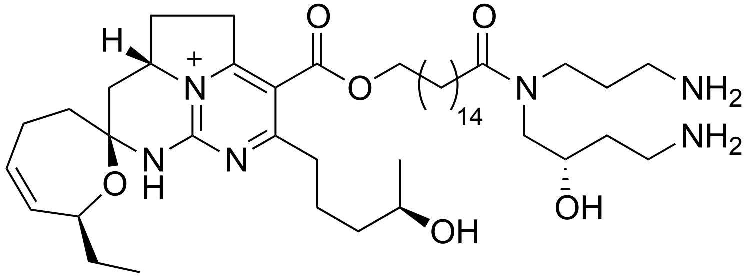
Caderas, C.; Lett, R.; Overman, L. E. *J. Am. Chem. Soc* **1996**, *118*, 9073–9082.

Iminium Chemistry
Biginelli condensation

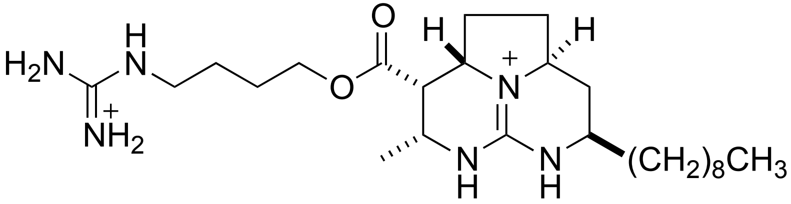


Batzelladine F





(–)-Crambidine



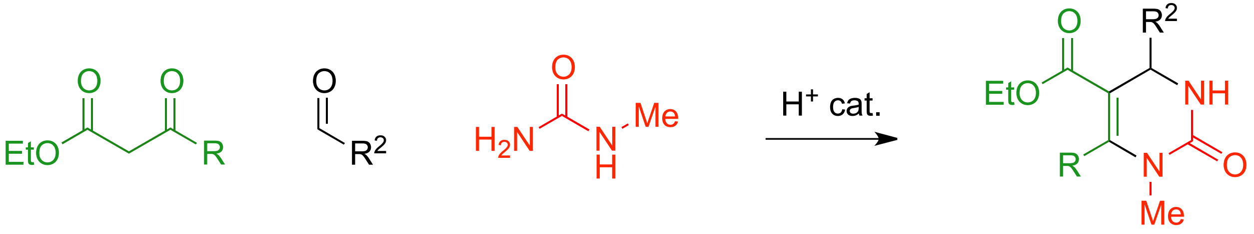
Batzelladine D

McDonald, A. I.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 1520–1528.
Cohen, F.; Overman, L. E. *J. Am. Chem. Soc.* **2001**, *123*, 10782–10783.
Overman, L. E.; Rhee, Y. H. *J. Am. Chem. Soc.* **2005**, *127*, 15652–15658.

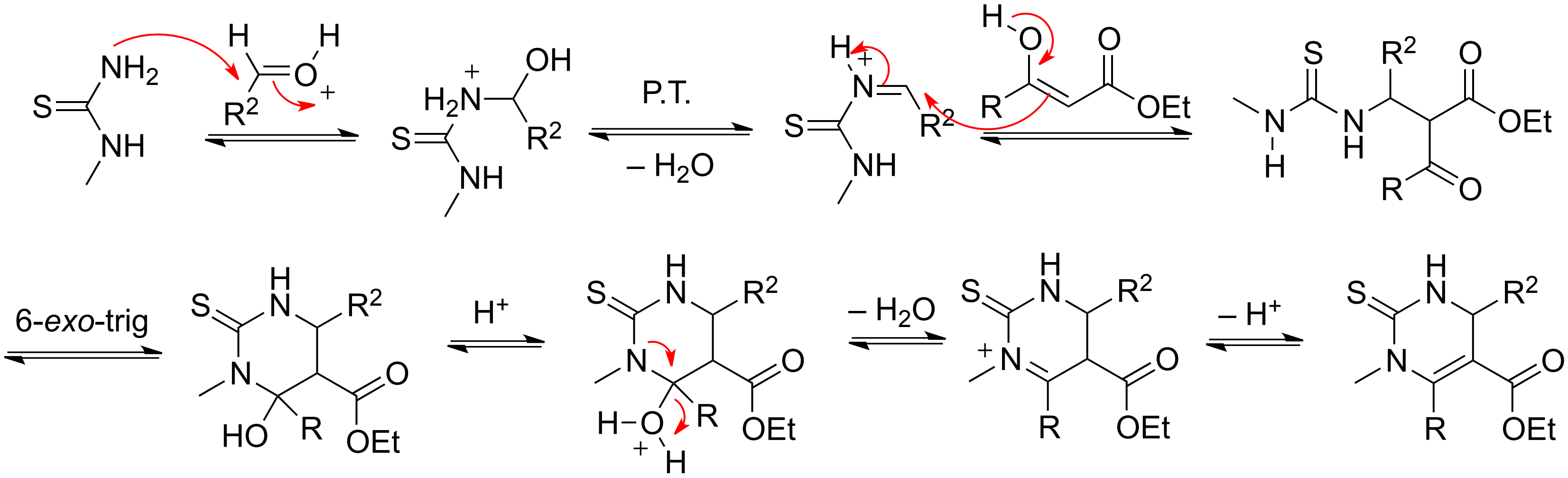
Iminium Chemistry

Biginelli condensation

- Disocvery by Pietro Biginelli in 1891:



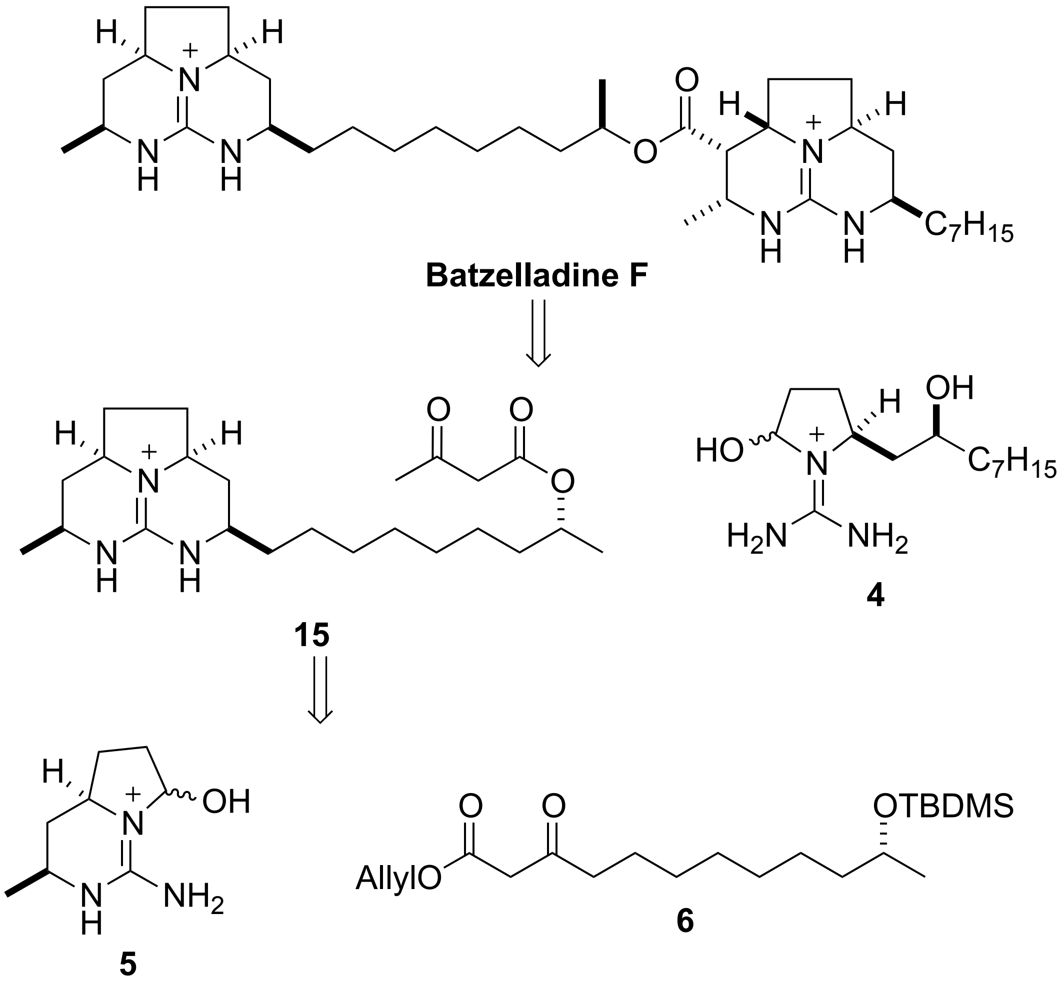
- Mechanism :



Biginelli, P. *Ber.* **1891**, *24*, 2962–2967.
Kappe, C. O. *J. Org. Chem.* **1997**, *62*, 7201–7204.
Hu, E. H.; Sidler, D. R.; Dolling, U. H. *J. Org. Chem.* **1998**, *63*, 3454–3457.

Iminium Chemistry

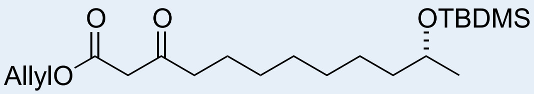
Biginelli condensation



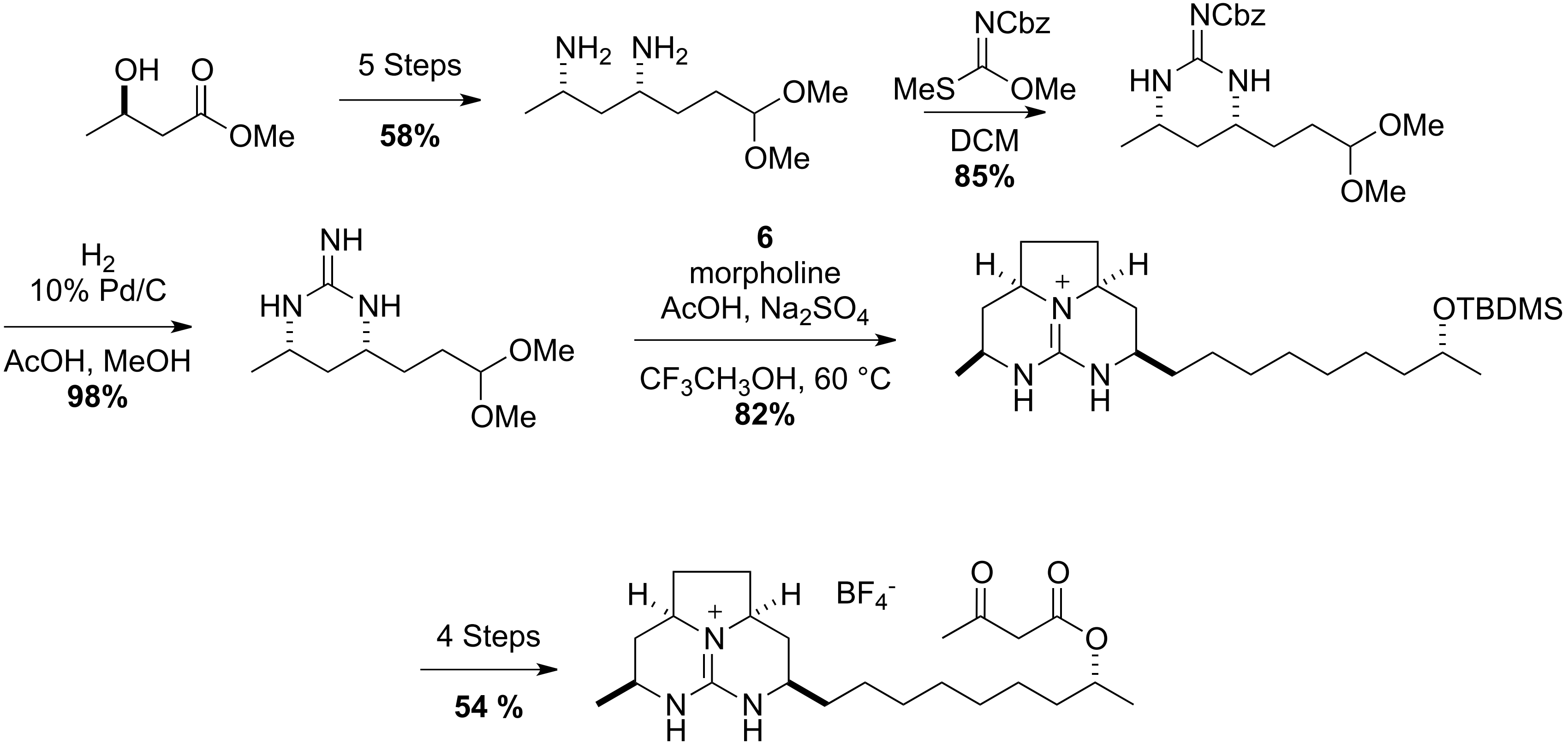
Cohen, F.; Overman, L. E. *J. Am. Chem. Soc.* **2001**, *123*, 10782–10783.

Iminium Chemistry

Biginelli condensation



6

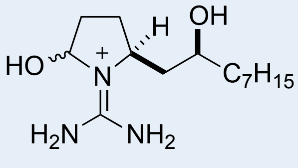


15

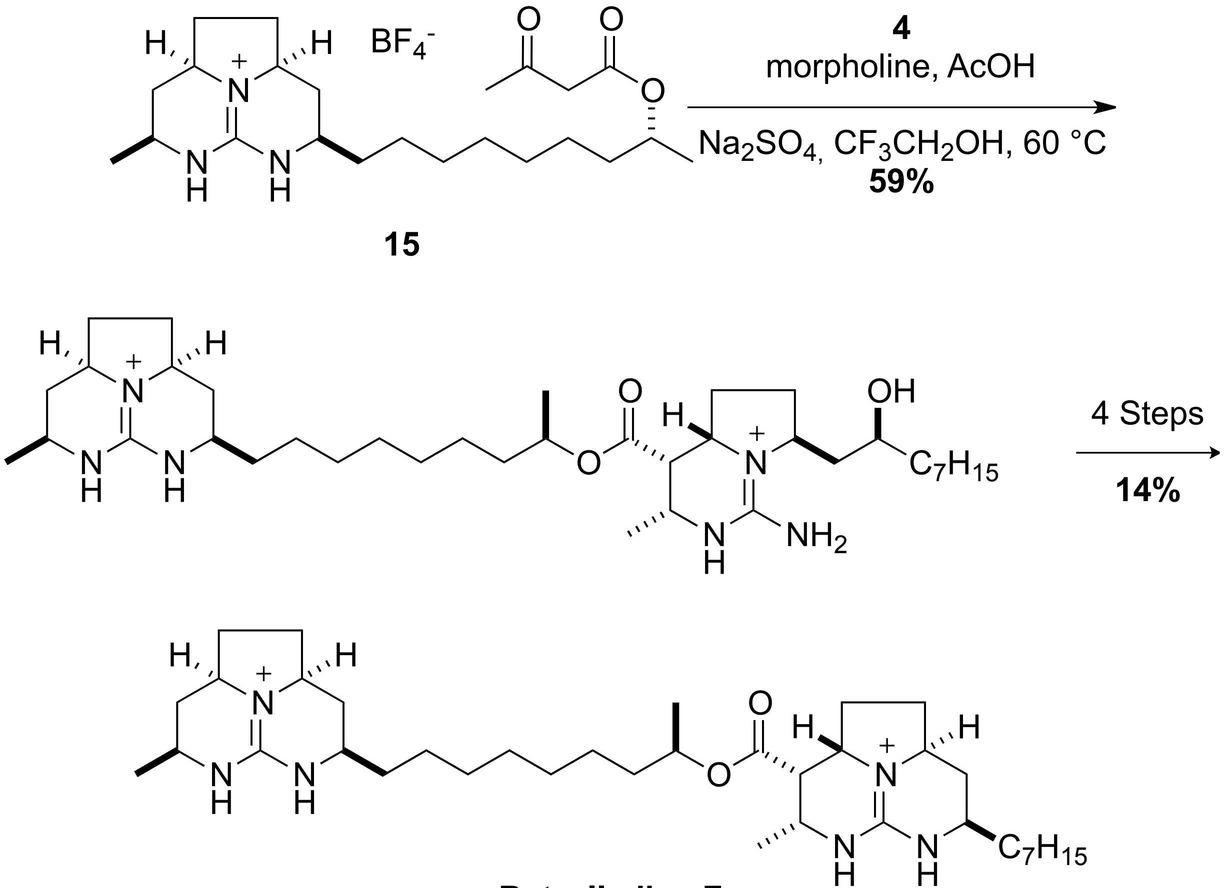
Cohen, F.; Overman, L. E. *J. Am. Chem. Soc.* **2001**, *123*, 10782–10783.

Iminium Chemistry

Biginelli condensation



4



15

4
morpholine, AcOH
Na_2SO_4, CF_3CH_2OH, 60 °C
59%

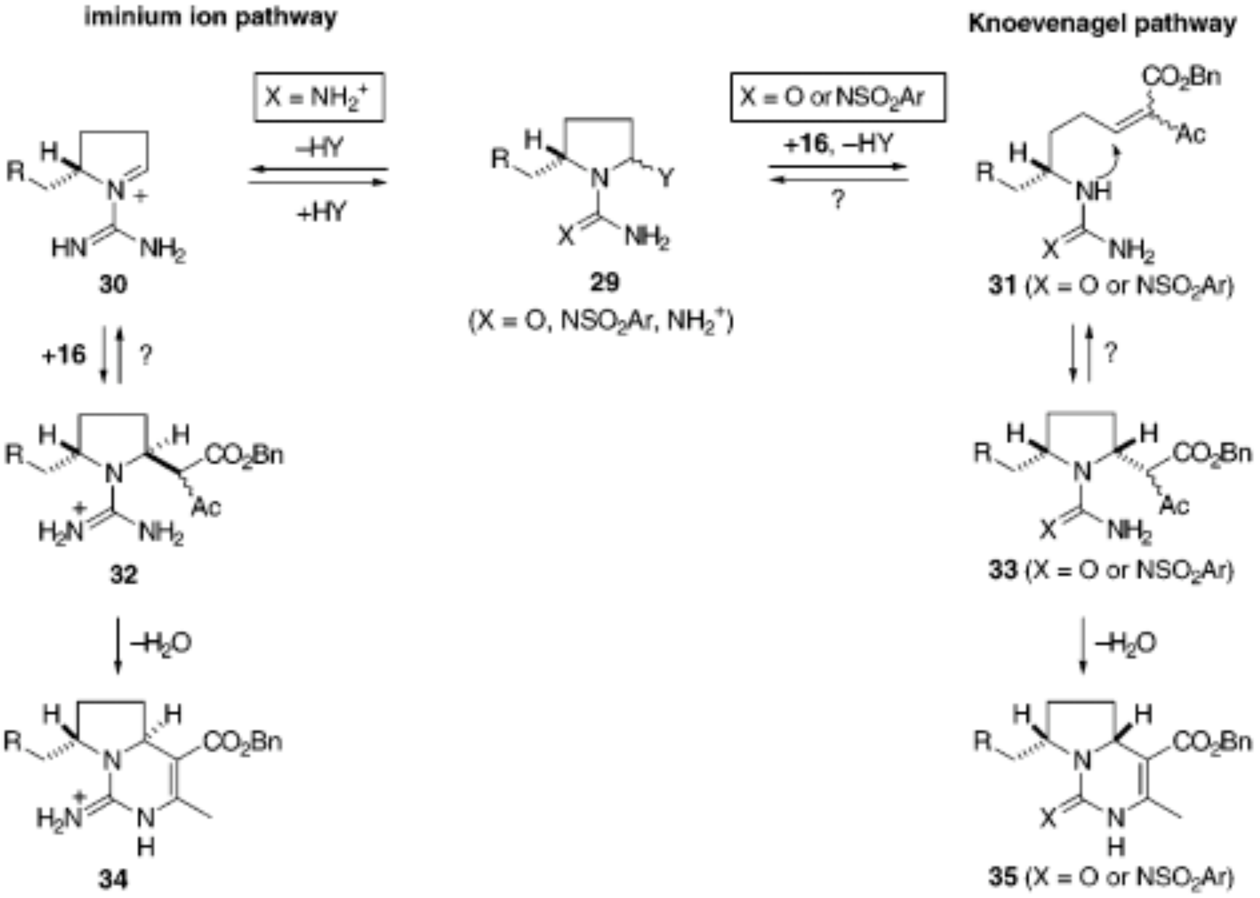
4 Steps
14%

Batzelladine F

Cohen, F.; Overman, L. E. *J. Am. Chem. Soc.* **2001**, *123*, 10782–10783.

Iminium Chemistry

Biginelli condensation

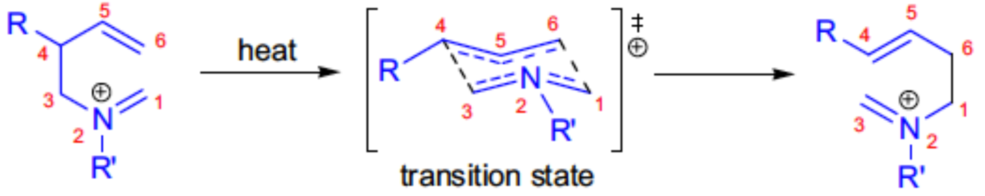


Kappe, C. O. *J. Org. Chem.* **1997**, *62*, 7201–7204.
McDonald, A. I.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 1520–1528.

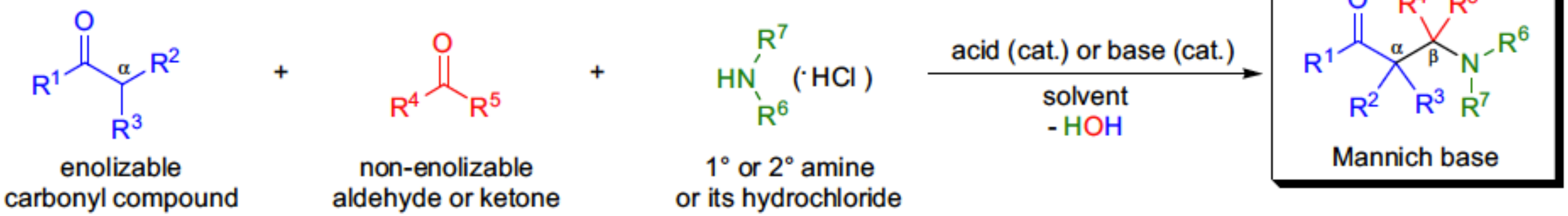
Iminium Chemistry

Aza-Cope/Mannich rearrangement

Aza-Cope rearrangement :



Mannich reaction:

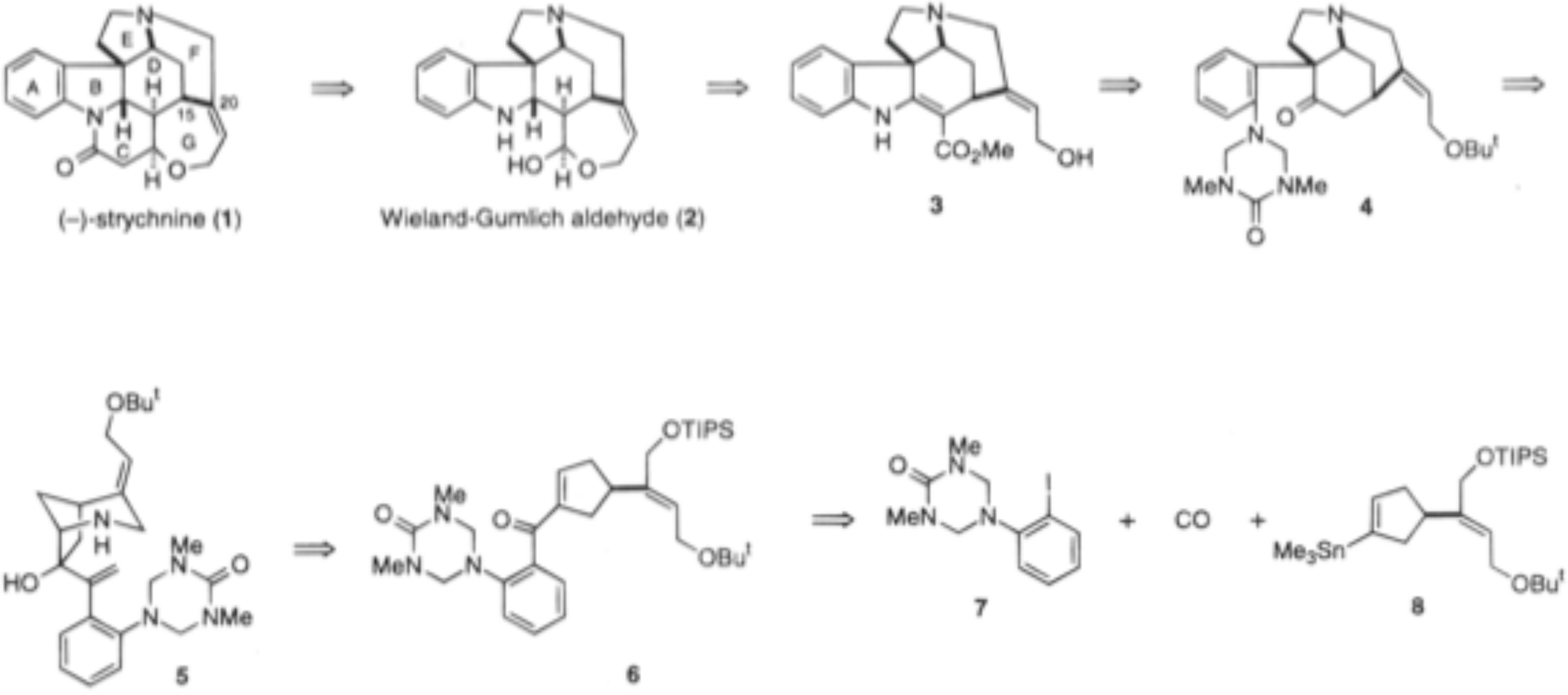


R^1 = H, alkyl, aryl, OR; $R^{2\text{-}3}$ = H, alkyl, aryl; $R^{4\text{-}5}$ = H, alkyl, aryl; R^6 = H, alkyl, OH, NH_2; R^7 = H, alkyl; solvent = ROH, H_2O, AcOH

Jacobsen, E. J.; Levin, J.; Overman, L. E. *J. Am. Chem. Soc* **1988**, *110*, 4329–4336.

Iminium Chemistry

Aza-Cope/Mannich rearrangement



(–)-strychnine (**1**)

Wieland-Gumlich aldehyde (**2**)

3

4

5

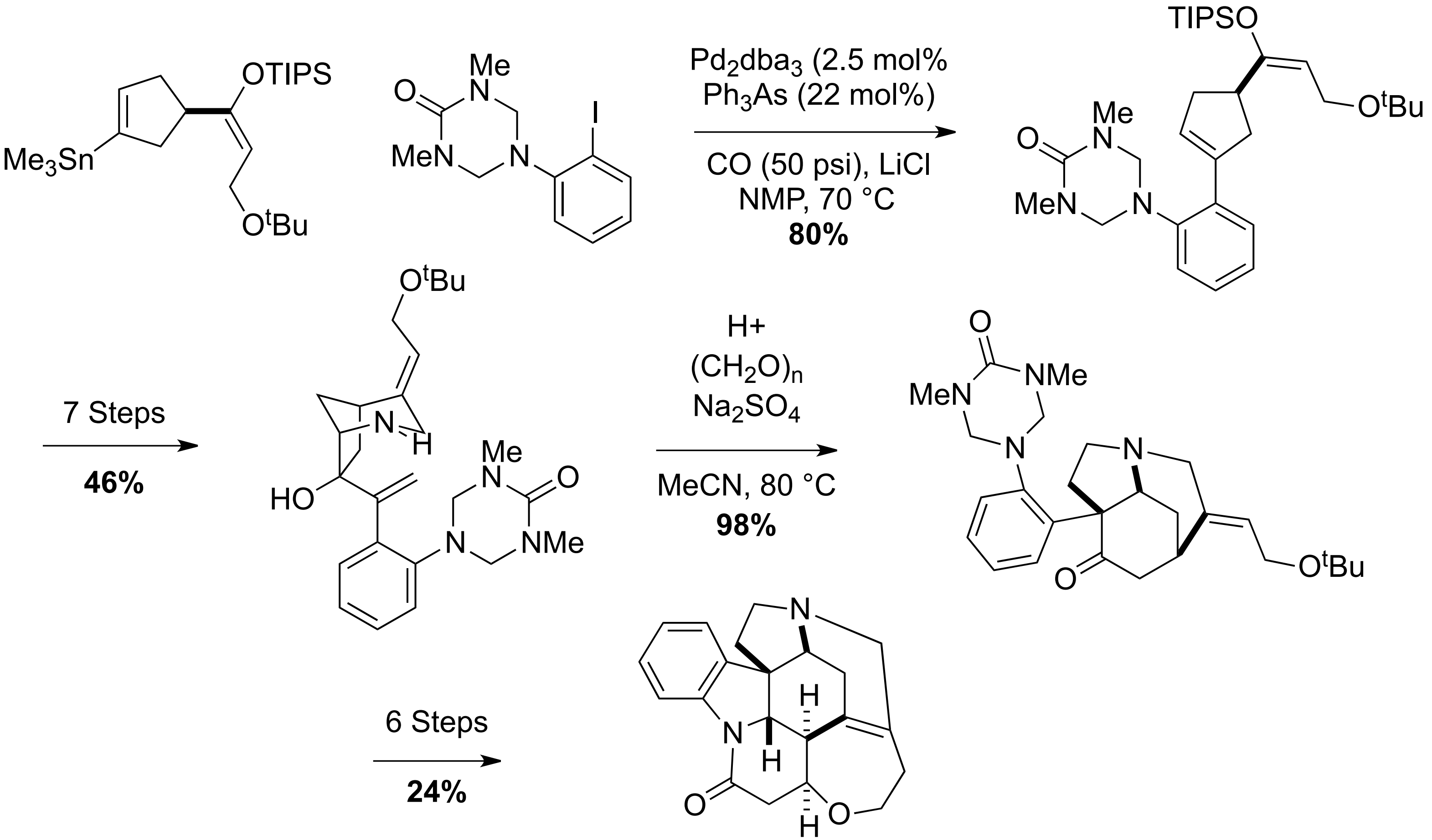
6

7

8

Knight, S. D.; Overman, L. E. *J. Am. Chem. Soc* **1995**, *117*, 5776–5788.

Iminium Chemistry
Aza-Cope/Mannich rearrangement



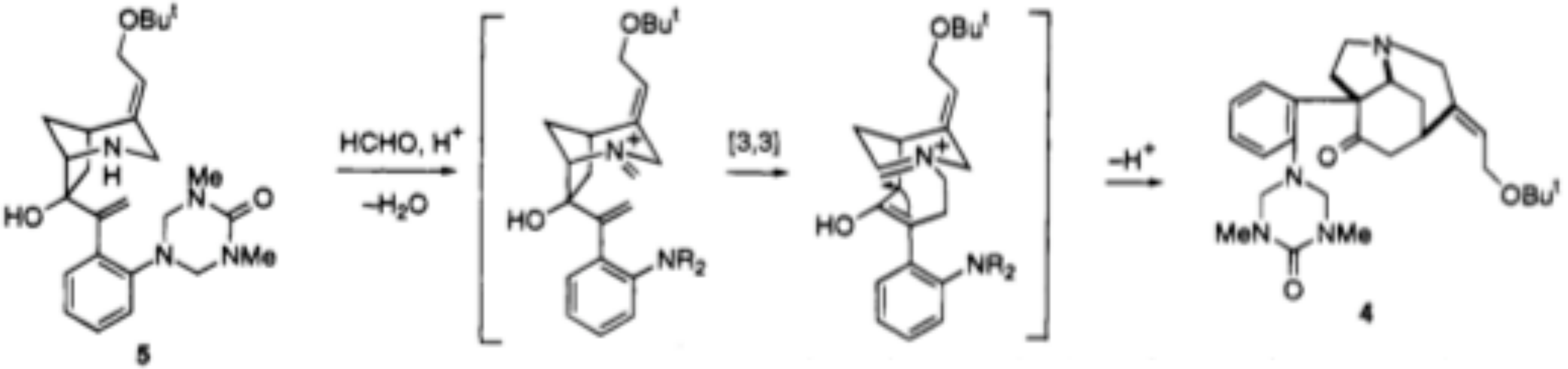
(–)-strchnine

$[a]_D^{25} = –139$ (c =1.0, $CHCl_3$)

Knight, S. D.; Overman, L. E. *J. Am. Chem. Soc* **1995**, *117*, 5776–5788.

Iminium Chemistry

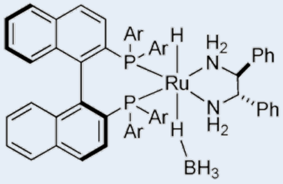
Aza-Cope/Mannich rearrangement



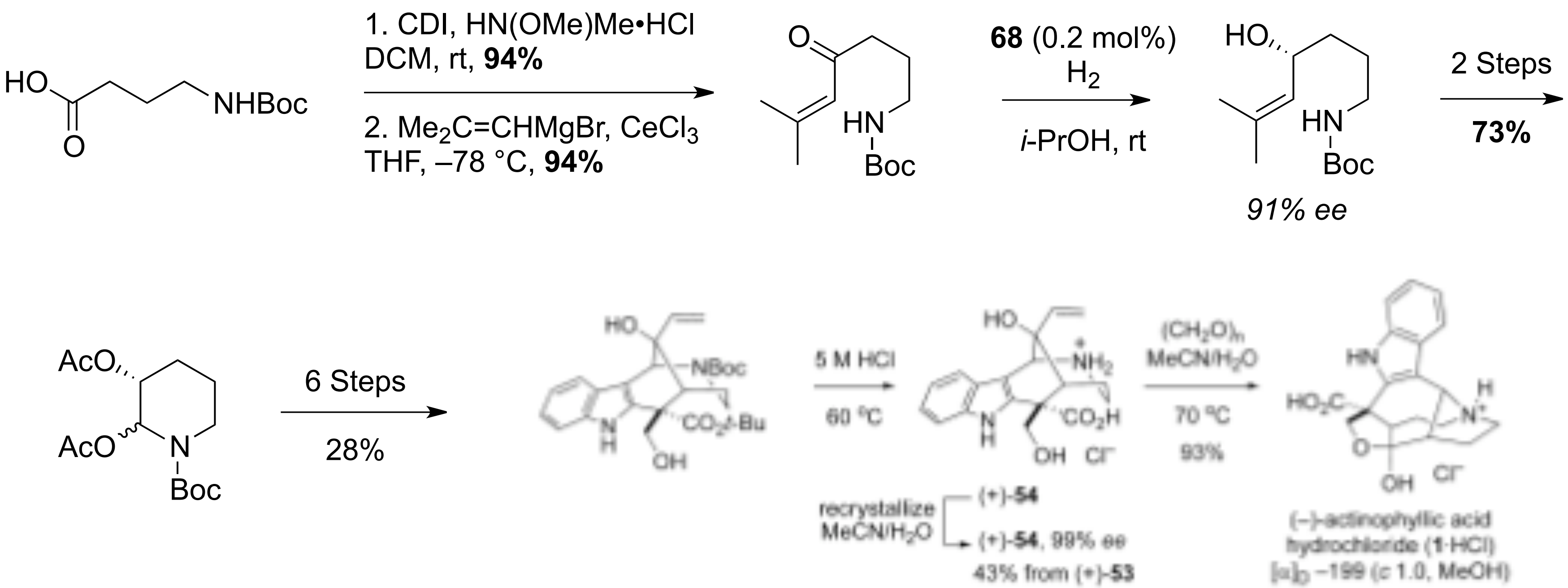
Knight, S. D.; Overman, L. E. *J. Am. Chem. Soc* **1995**, *117*, 5776–5788.

Iminium Chemistry

Aza-Cope/Mannich rearrangement



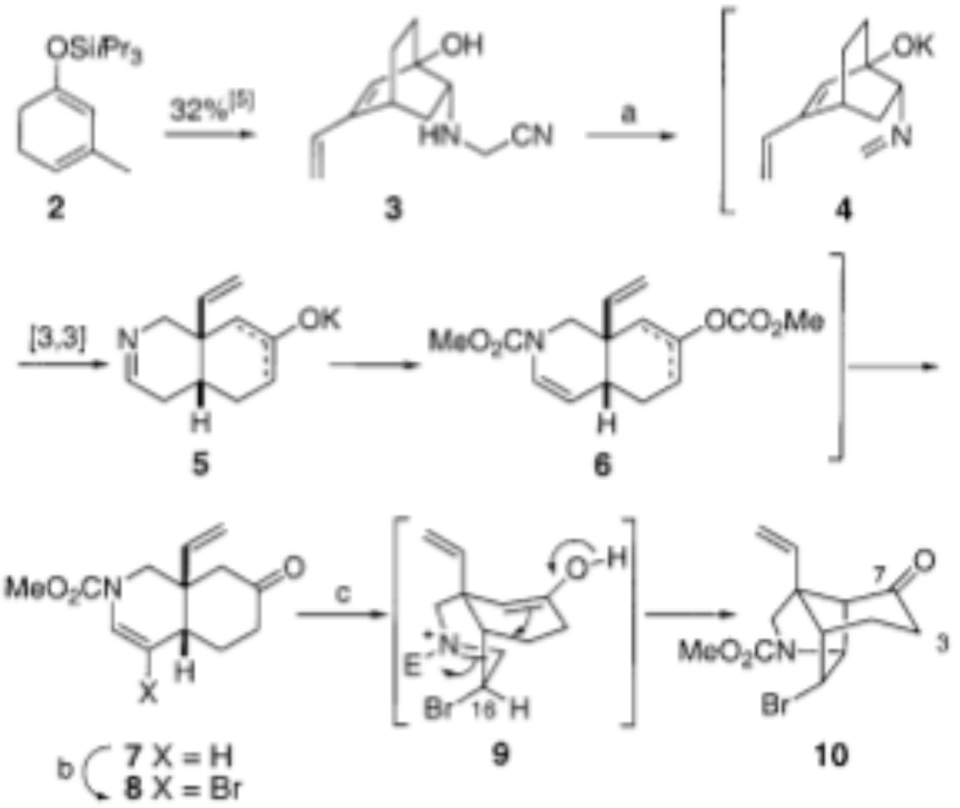
68: Ar = 3,5-$Me_2C_6H_3$



Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 4894–4906.

Iminium Chemistry

Aza-Cope/Mannich rearrangement

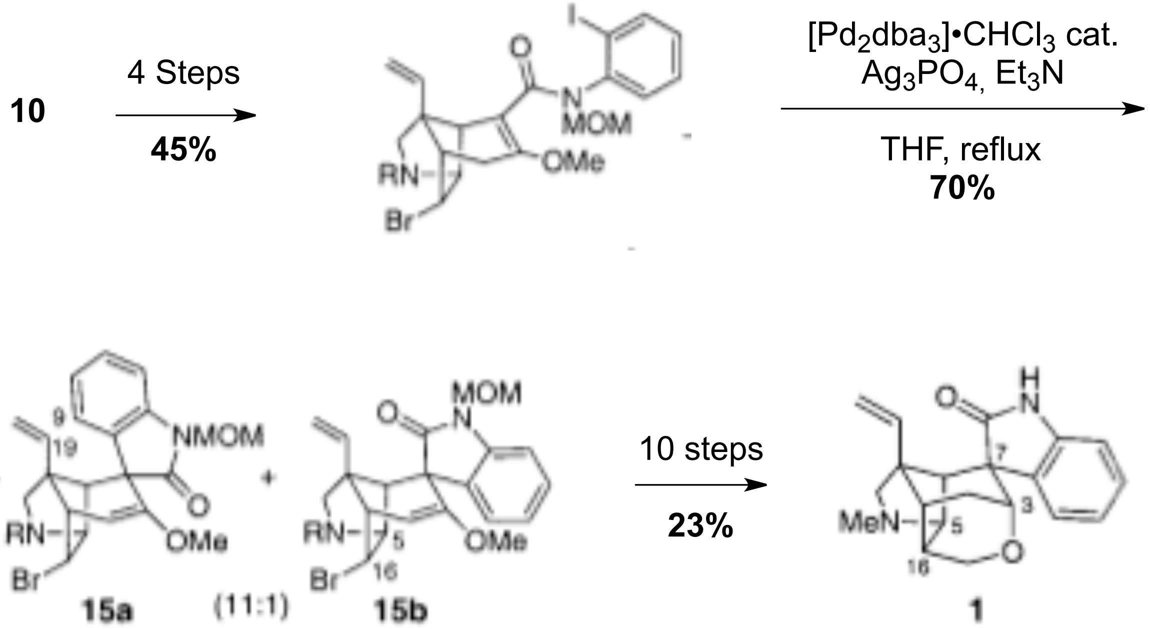


Scheme 1. Reaction conditions: a) KH, [18]crown-6, THF, rt; ClCO$_2$Me, DTBMP, −78°C→rt; KOH, MeOH, H$_2$O, rt, 81%; b) Br$_2$, 1,2,2,6,6-pentamethylpiperidine, CH$_2$Cl$_2$, −78°C; c) TFA, reflux, 67% over 2 steps. DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W. *Angew. Chem. Int. Ed.* **1999**, *38*, 2934–2936.

Iminium Chemistry

Aza-Cope/Mannich rearrangement



10

4 Steps

45%

$[Pd_2dba_3] \cdot CHCl_3$ cat.

Ag_3PO_4, Et_3N

THF, reflux

70%

15a (11:1) **15b**

10 steps

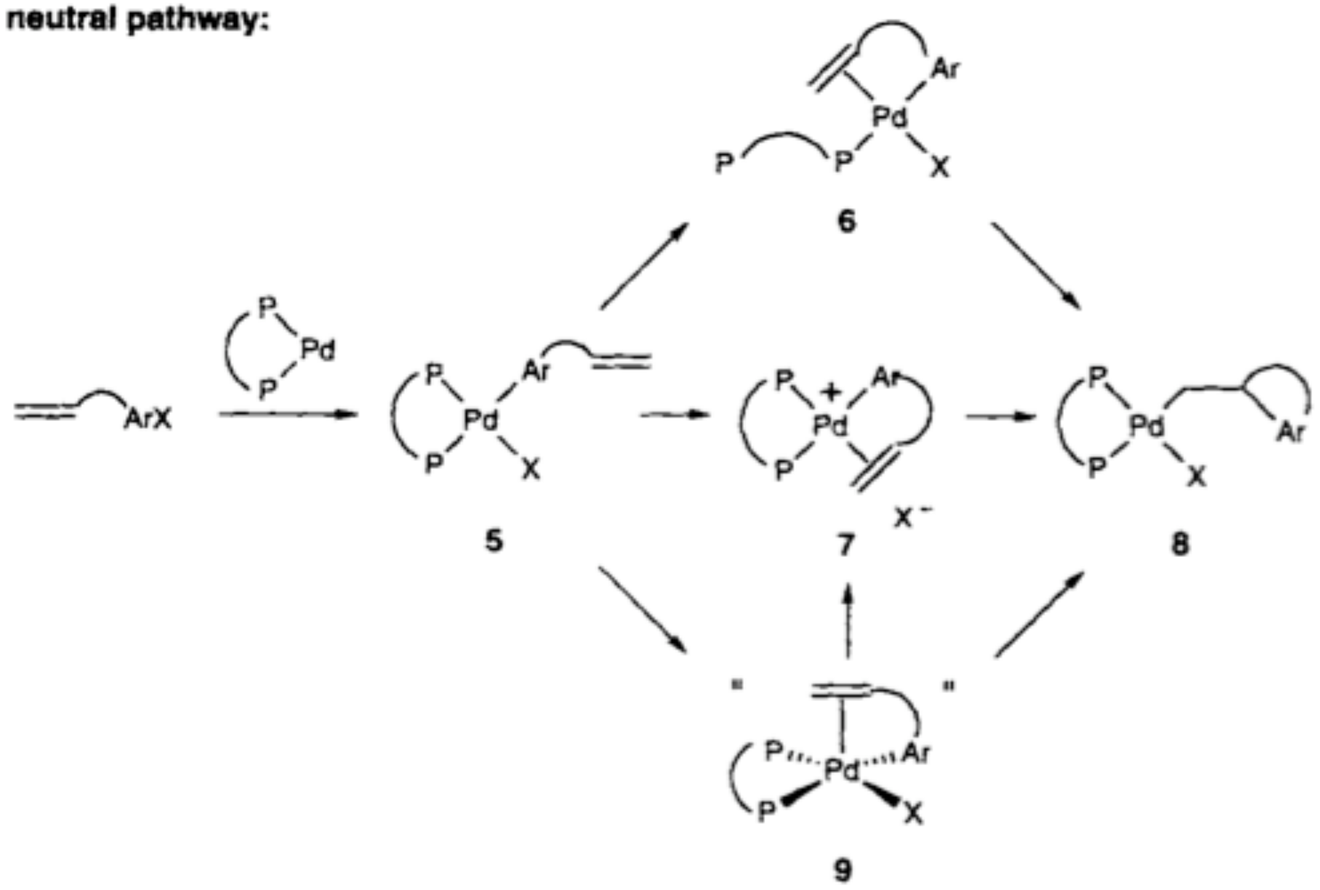
23%

1

Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W. *Angew. Chem. Int. Ed.* **1999**, *38*, 2934–2936.

Quaternary Carbon-center formation

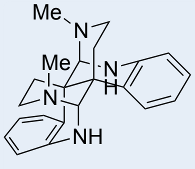
Heck-type cyclization



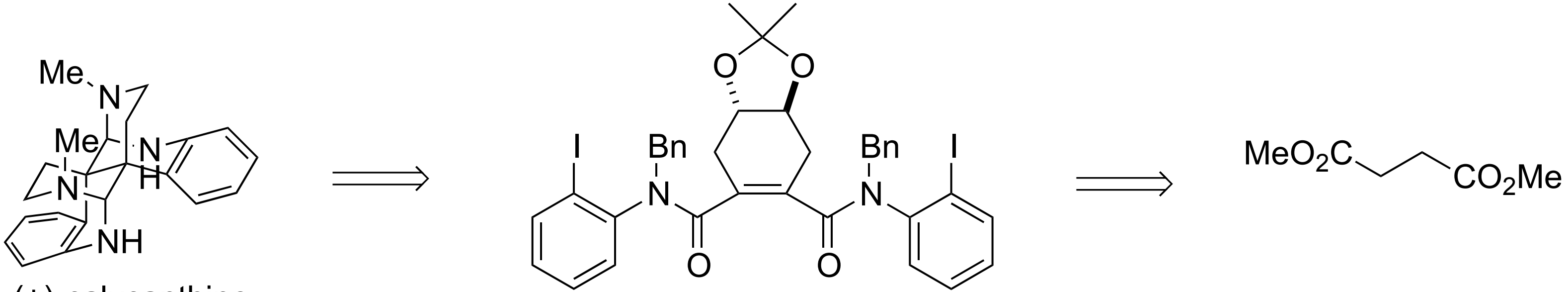
Overman, L. E.; Poon, D. J. *Angew. Chem. Int. Ed.* **1997**, *36*, 518–521.

Quaternary Carbon-center formation

Heck-type cyclization



(+)-calycanthine

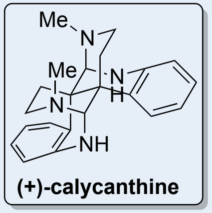


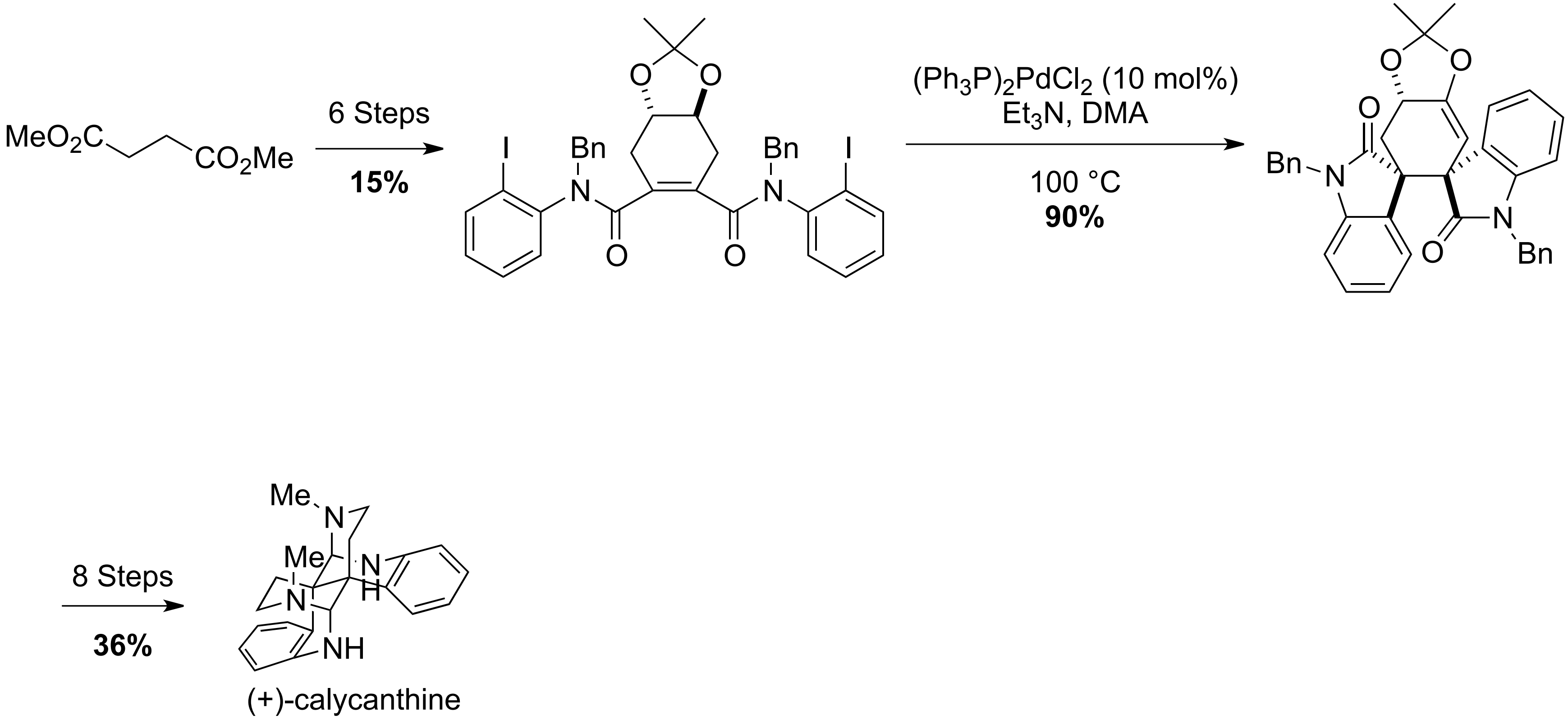
(+)-calycanthine

Overman, L. E.; Paone, D. V.; Stearns, B. A. *J. Am. Chem. Soc* **1999**, *121*, 7702–7703.

Quaternary Carbon-center formation

Heck-type cyclization

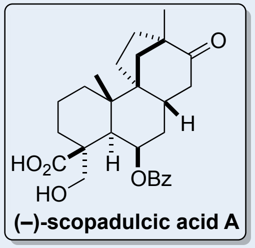


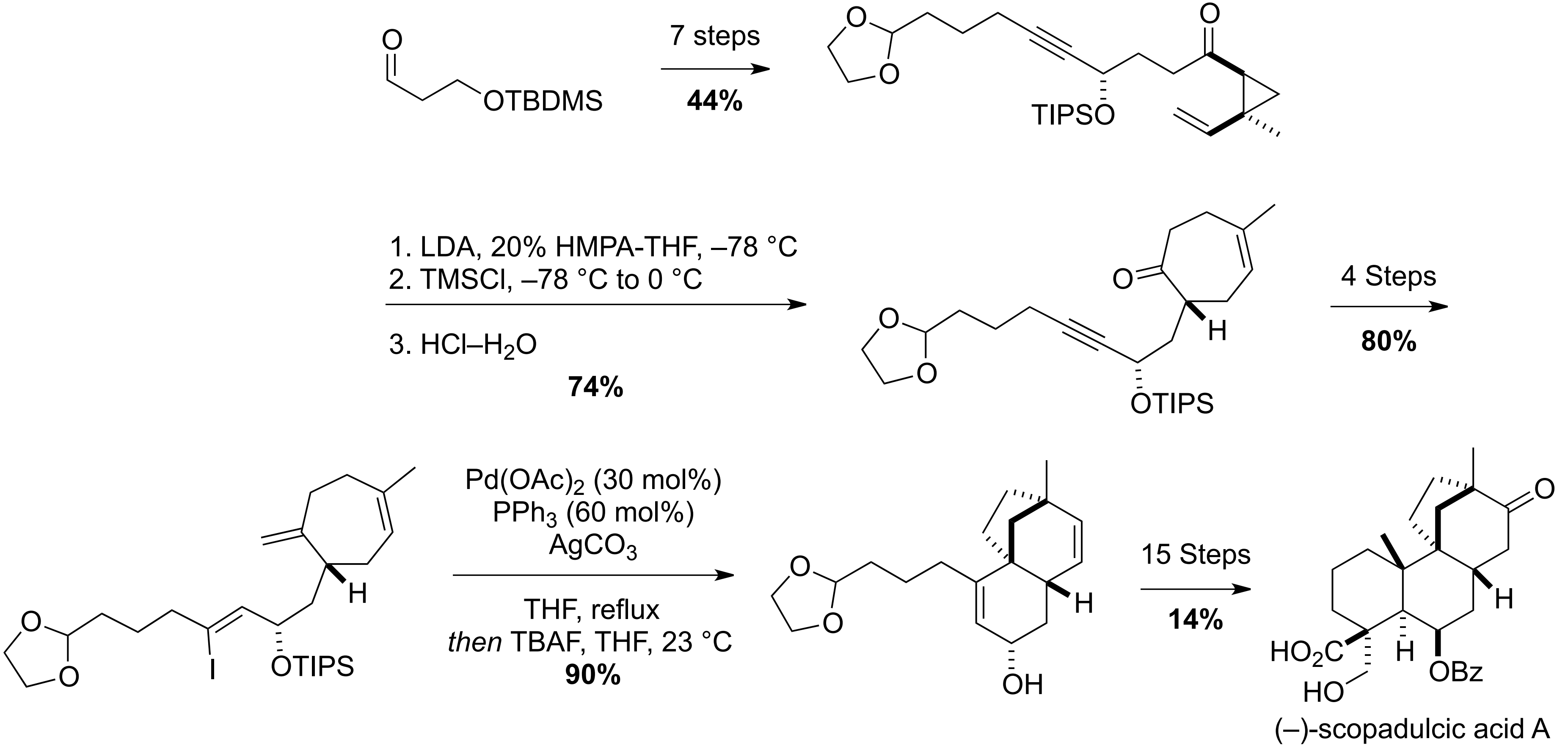


Overman, L. E.; Paone, D. V.; Stearns, B. A. *J. Am. Chem. Soc* **1999**, *121*, 7702–7703.

Quaternary Carbon-center formation

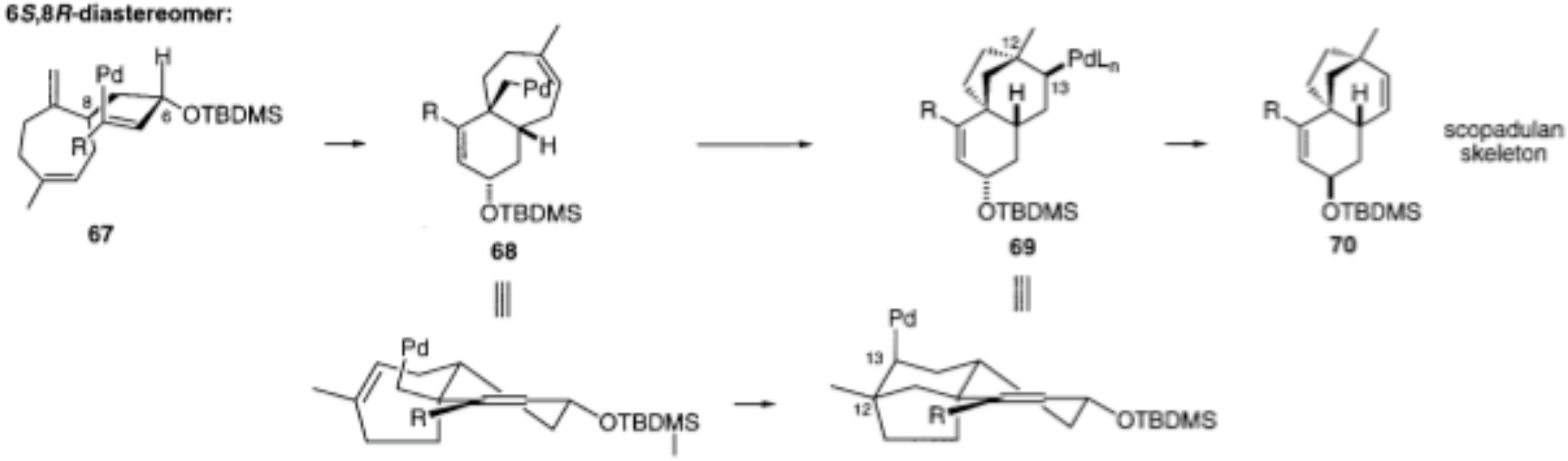
Heck-type cyclization





Fox, M. E.; Li, C.; Marino, J. P. *J. Am. Chem. Soc* **1999**, *121*, 5467–5480.

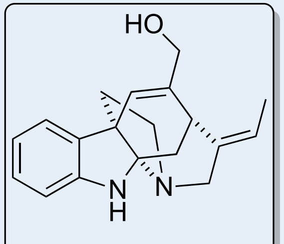
Quaternary Carbon-center formation
Heck-type cyclization



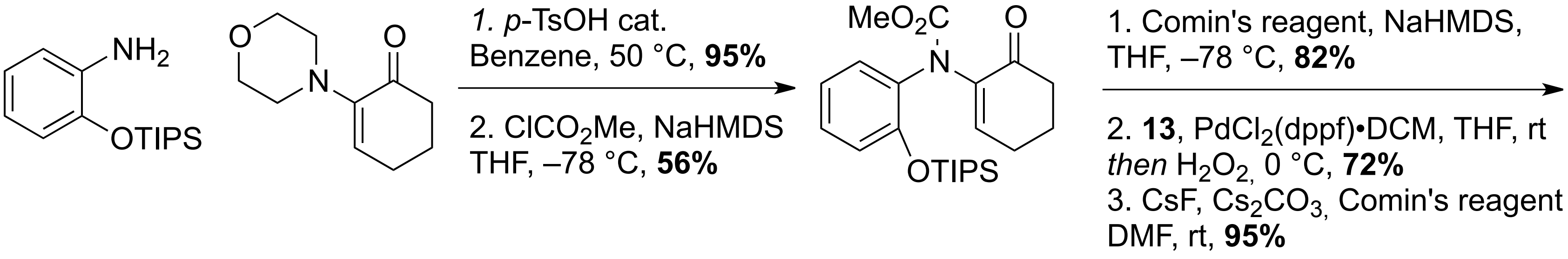
Fox, M. E.; Li, C.; Marino, J. P. *J. Am. Chem. Soc* **1999**, *121*, 5467–5480.

Quaternary Carbon-center formation

Heck-Iminium Ion Cyclization



minfiensine

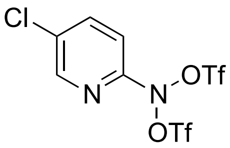


1. p-TsOH cat.
Benzene, 50 °C, **95%**

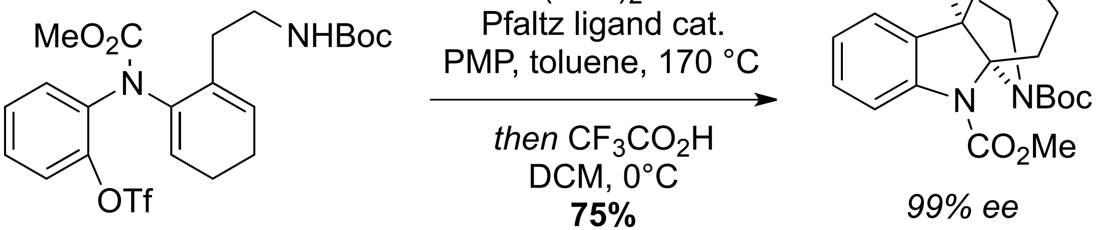
2. $ClCO_2Me$, NaHMDS
THF, –78 °C, **56%**

1. Comin's reagent, NaHMDS,
THF, –78 °C, **82%**

2. **13**, $PdCl_2(dppf)$•DCM, THF, rt
then H_2O_2, 0 °C, **72%**
3. CsF, Cs_2CO_3, Comin's reagent
DMF, rt, **95%**



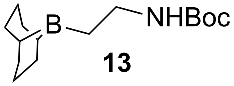
Comin's reagent



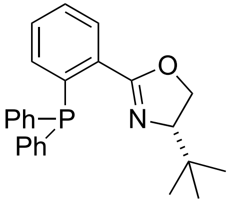
$Pd(OAc)_2$ cat.
Pfaltz ligand cat.
PMP, toluene, 170 °C

then CF_3CO_2H
DCM, 0°C
75%

99% ee



13

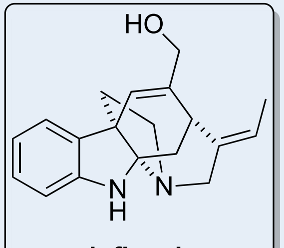


Pfaltz ligand

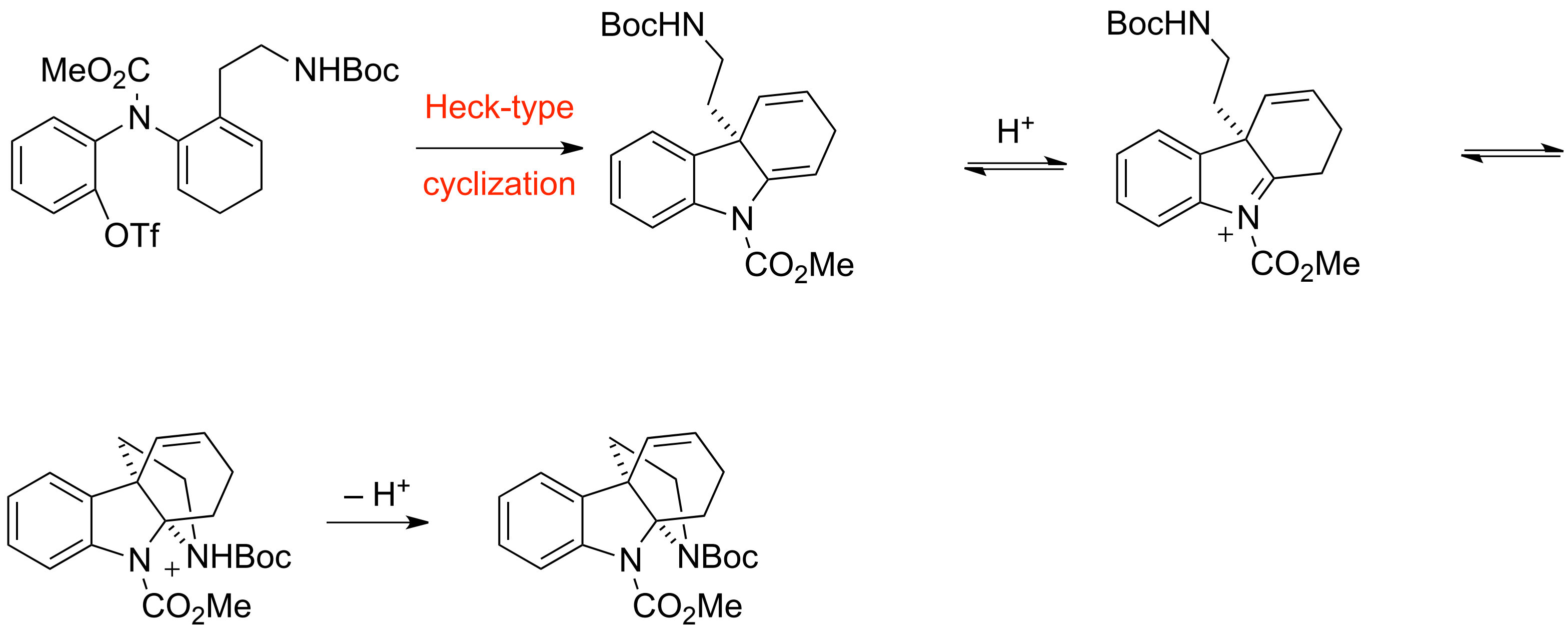
Dounay, A. B.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2005**, *127*, 10186–10187.

Quaternary Carbon-center formation

Heck-Iminium Ion Cyclization



minfiensine



Heck-type

cyclization

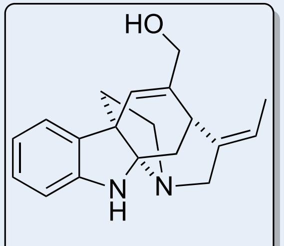
H^+

$-\ H^+$

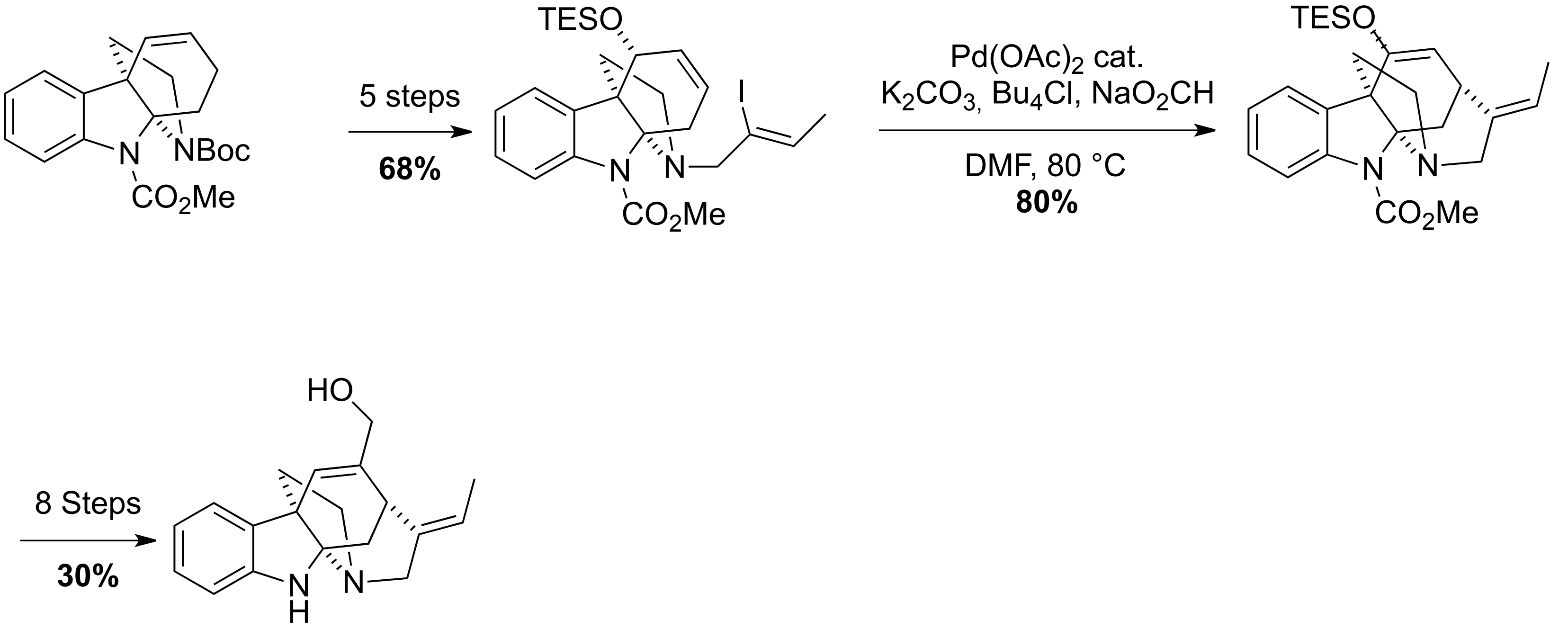
Dounay, A. B.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2005**, *127*, 10186–10187.

Quaternary Carbon-center formation

Heck-Iminium Ion Cyclization



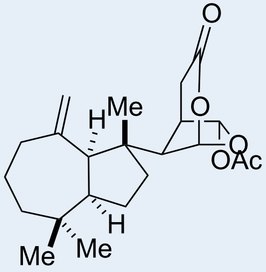
minfiensine



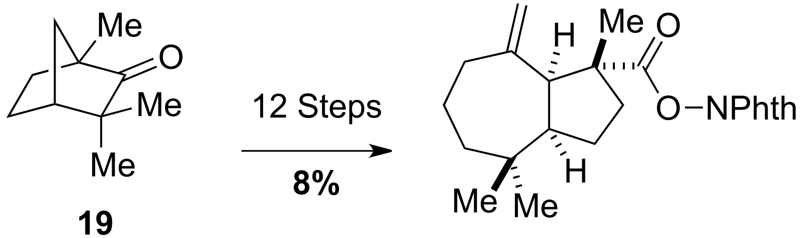
minfiensine

Dounay, A. B.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2005**, *127*, 10186–10187.

Quaternary Carbon-center formation
Tertiary Radical pathway



Aplyviolene

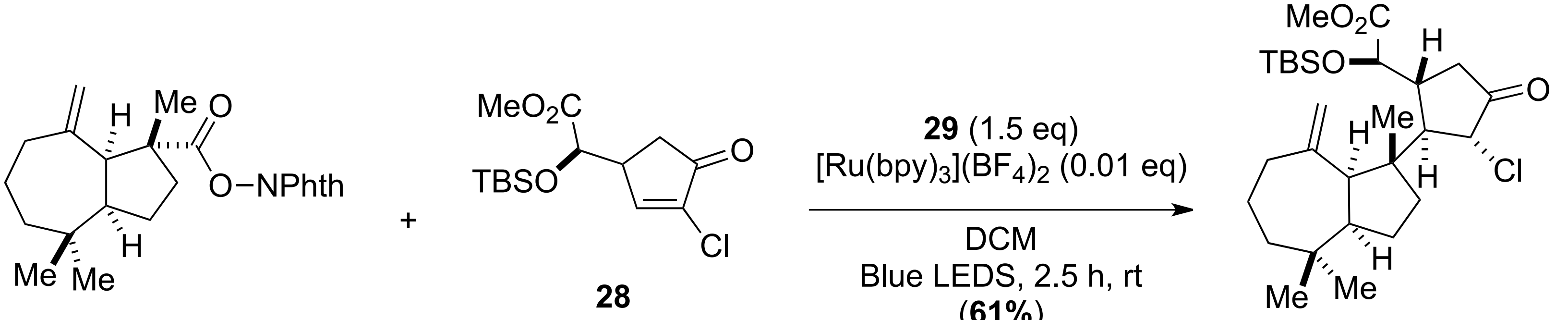


12 Steps

8%

19
(+)-fenchone

27



27

28
(1.5 eq)

29 (1.5 eq)
[Ru(bpy)$_3$](BF$_4$)$_2$ (0.01 eq)

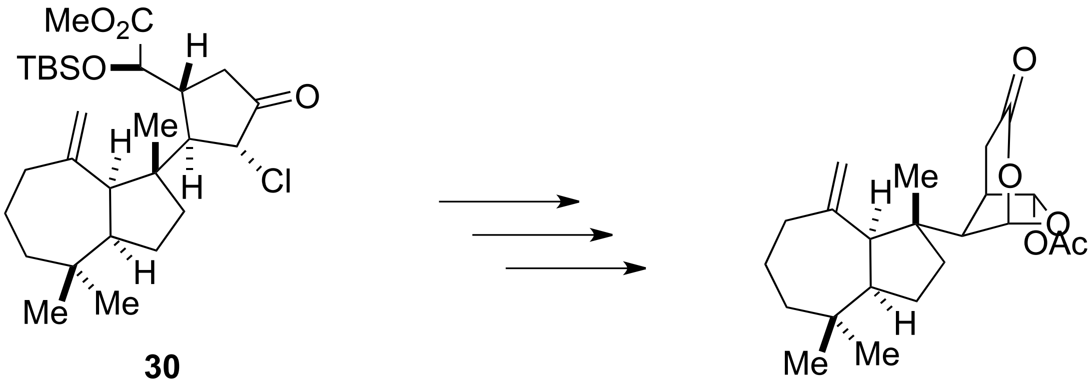
DCM
Blue LEDS, 2.5 h, rt
(**61%**)

30
single
diastereoisomere

Schnermann, M. J.; Overman, L. E. *Angew. Chem.Int. Ed.* **2012**, *51*, 9576–9580.

Quaternary Carbon-center formation

Tertiary Radical pathway

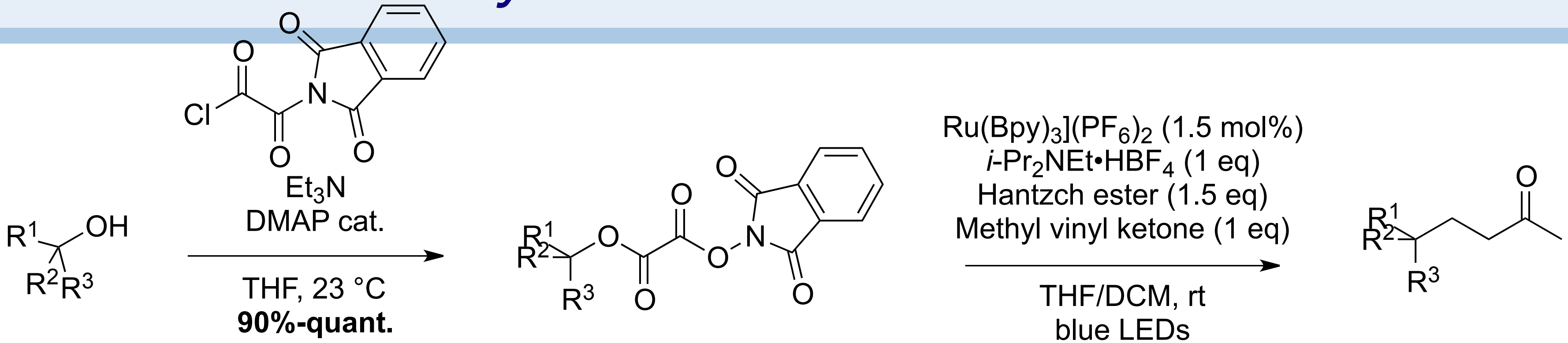


30
single
diastereoisomere

Aplyviolene

Schnermann, M. J.; Overman, L. E. *Angew. Chem.Int. Ed.* **2012**, *51*, 9576–9580.

Quaternary Carbon-center formation
Radical Pathway

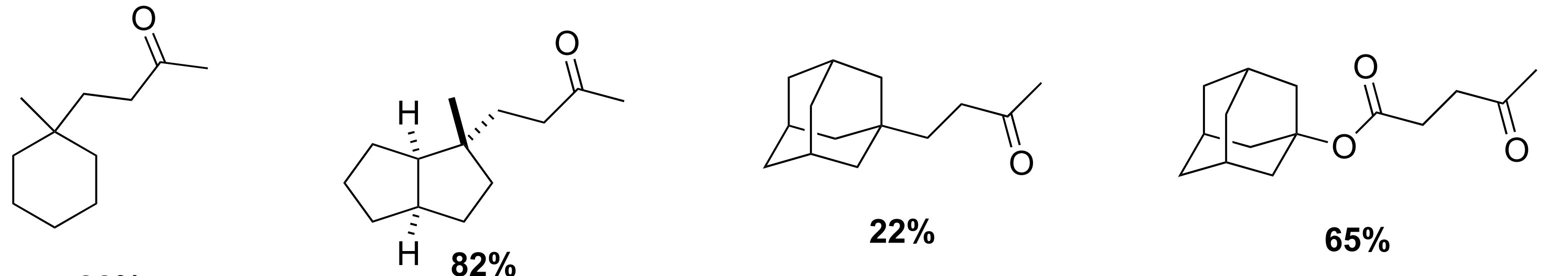


Et$_3$N
DMAP cat.

THF, 23 °C
90%-quant.

Ru(Bpy)$_3$](PF$_6$)$_2$ (1.5 mol%)
i-Pr$_2$NEt•HBF$_4$ (1 eq)
Hantzch ester (1.5 eq)
Methyl vinyl ketone (1 eq)

THF/DCM, rt
blue LEDs



82% **82%** **22%** **65%**

Ru(Bpy)$_3$](PF$_6$)$_2$ (1.5 mol%)
i-Pr$_2$NEt•HBF$_4$ (1 eq)
Hantzch ester (1.5 eq)
Methyl vinyl ketone (1 eq)

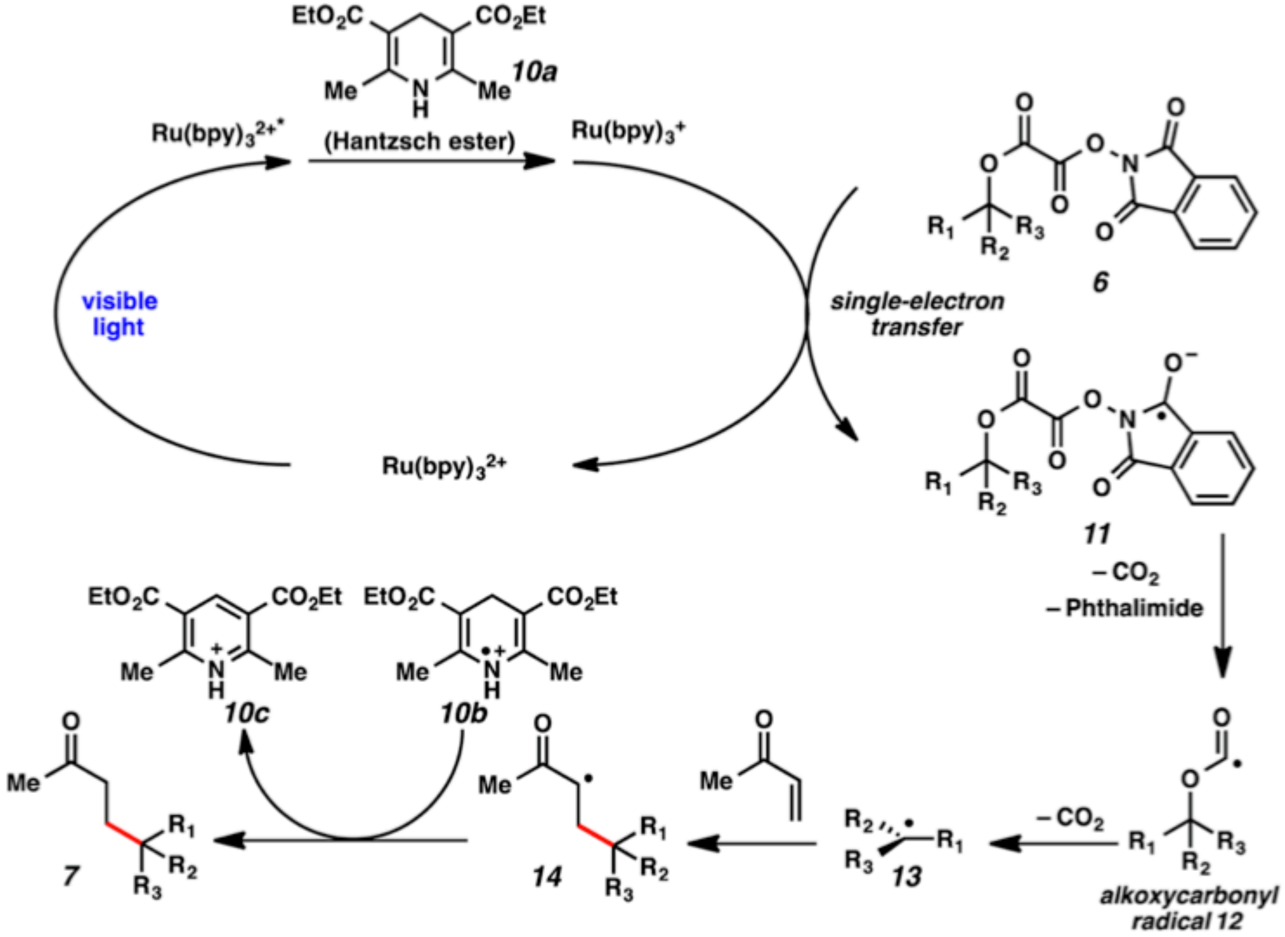
THF/DCM, rt
blue LEDs

43%

Lackner, G. L.; Quasdorf, K. W.; Overman, L. E. *J. Am. Chem. Soc.* **2013**, *135*, 15342–15345.

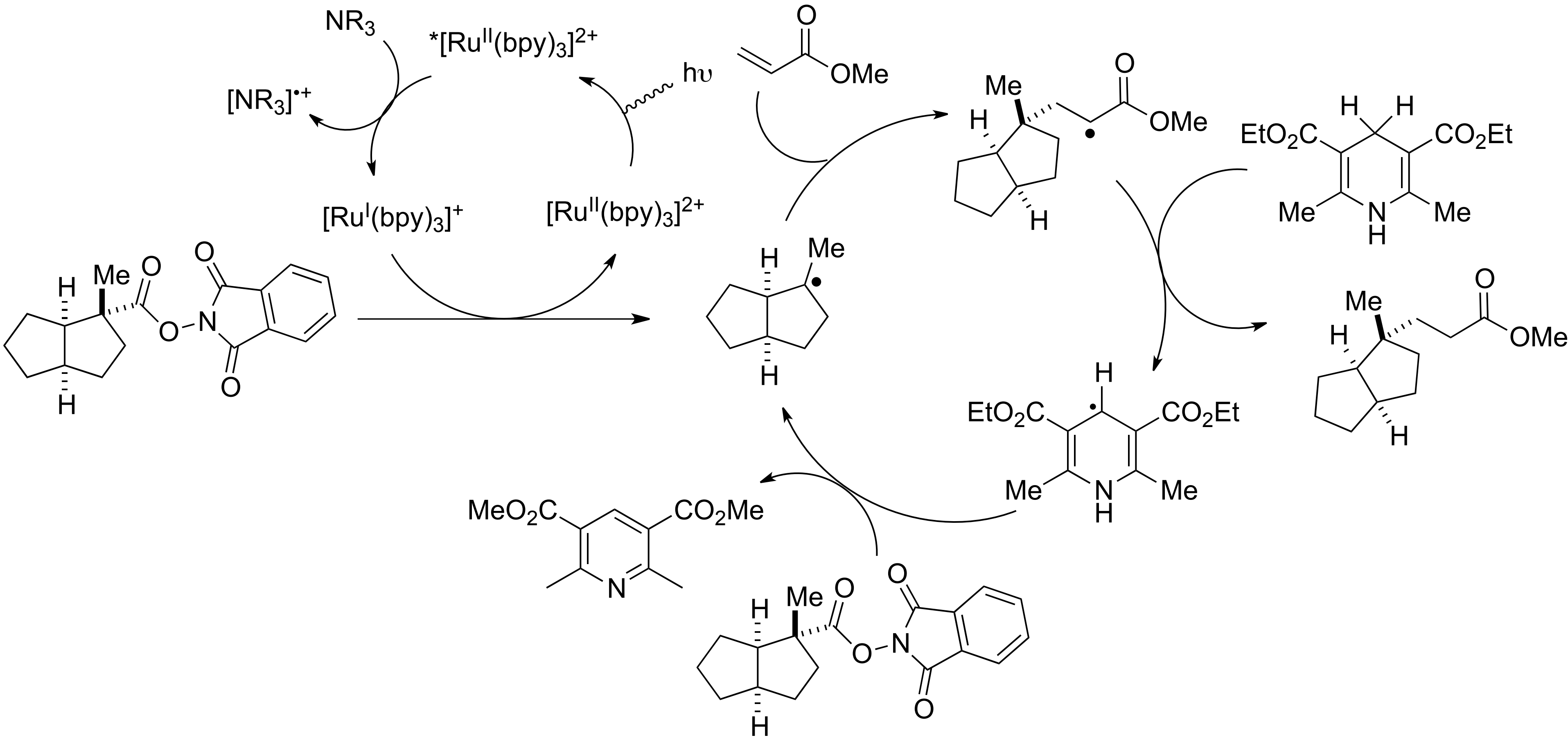
Quaternary Carbon-center formation

Tertiary Radical pathway



Lackner, G. L.; Quasdorf, K. W.; Overman, L. E. *J. Am. Chem. Soc.* **2013**, *135*, 15342–15345.

Quaternary Carbon-center formation
Tertiary Radical pathway

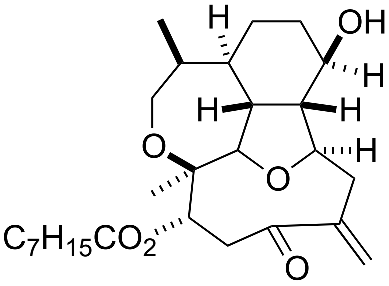


Okada, K.; Okamoto, K.; Morita, N.; Okubo, K.; Oda, M. *J. Am. Chem. Soc.* **1991**, *113*, 9401–9402.
Andrews, R. S.; Becker, J. J.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2010**, *49*, 7274–7276.
Andrews, R. S.; Becker, J. J.; Gagné, M. R. *Org. Lett.* **2011**, *13*, 2406–2409.
Lackner, G. L.; Quasdorf, K. W.; Overman, L. E. *J. Am. Chem. Soc.* **2013**, *135*, 15342–15345.

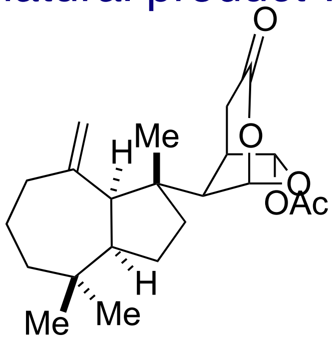
Conclusion

- Differents strategies with highly stereo-control:
  - Prins-Pinacol rearrangement.
  - Aza-Cope/Mannich rearrangement.
  - Biginelli condensation
  - Heck-type cyclization

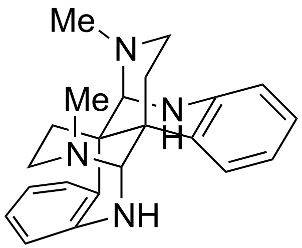
- Amazing variety of natural product were synthetized in his lab.



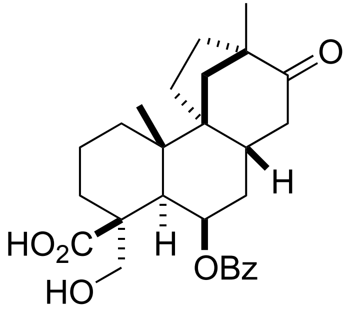
biarellin F



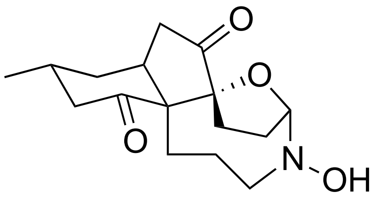
Aplyviolene



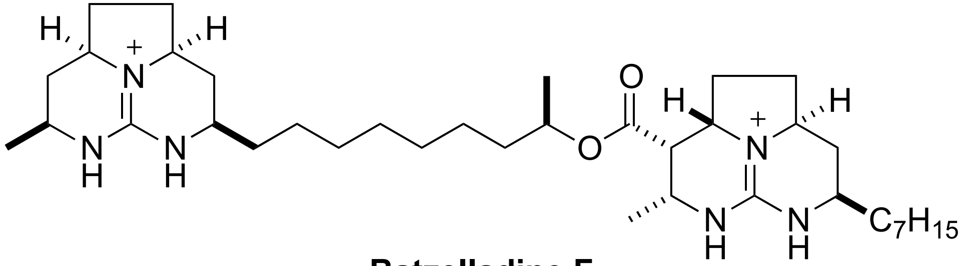
(+)-calycanthine



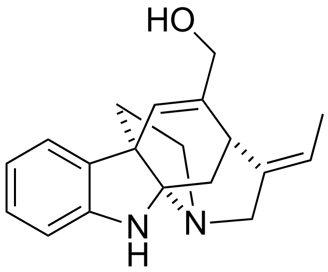
(–)-scopadulcic acid A



(+)-sieboldine A



Batzelladine F



minfiensine

http://faculty.sites.uci.edu/overman/

Conclusion on Larry E. Overman

- Overman’s Lab has completed synthesis of more of 80 complex natural products and close to of 364 publication in major journal.

- 2003 : ACS Arthur C. Cope Award

  - "I hated chemistry in high school.” (Overman, 2003)

  - “I had absolutely no interest in chemistry until I was inspired by a great teacher in college. What ultimately intrigued me was not only the idea of studying the natural world but also creating things that didn't exist before.” (Overman, 2003)

http://faculty.sites.uci.edu/overman/
http://www.scienceblog.com/community/older/2003/C/2003436.html
http://pubs.acs.org/cen/awards/8106/8106awards.html

END