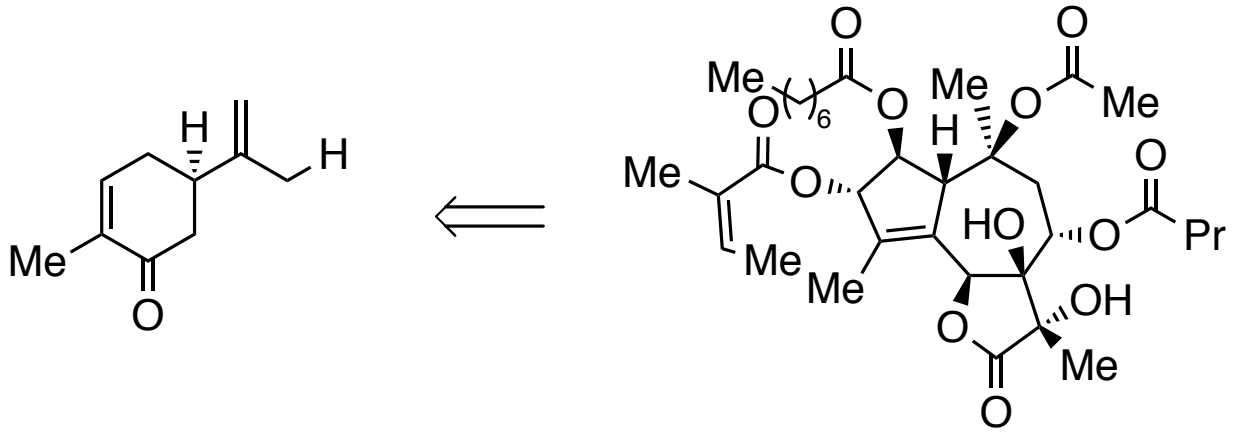
A Concise, Efficient, and Scalable Total Synthesis of Thapsigargin and Nortrilobolide from (R)-(-)-Carvone

Dezhi Chen and P. Andrew Evans

J. Am. Chem. Soc. **2017**, 139, 6046.



(*R*)-(-)-Carvone ⟸ **Thapsigargin**

Evan Carder
Wipf Group Current Literature
June 24, 2017

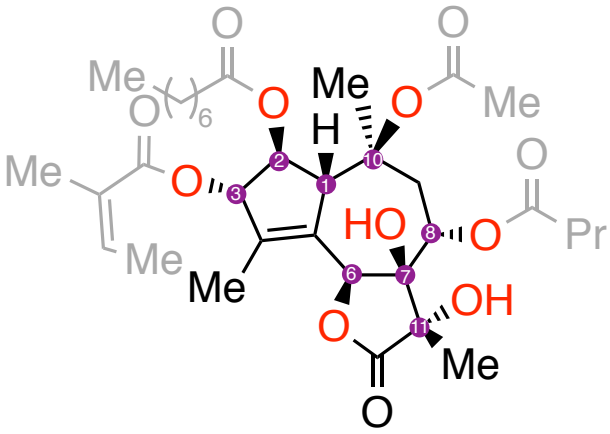
Origins of Thapsigargin

- Associated in folk medicine
- Isolated from the roots of *Thapsia garganica* L. in 1978 by Christensen and coworkers.[1]
- Chemical structure was elucidated by extensive spectroscopic studies and X-ray crystallography.[2,3]
- A member of 17 structurally-related sesquiterpenones, which are collectively known as thapsigargins.

1. *Acta Pharm. Suec.* **1978**, 15, 133.
2. *J. Org. Chem.* **1982**, 47, 649.
3. *Tetrahedron Lett.* **1985**, 26, 107.

Structural Features of Thapsigargin

- 5-7-5 tricyclic core
- Eight stereogenic centers
- Polyoxygenated
- Functionalized with four different ester groups
- Thapsgargins primarily differ in the acyl groups appended to O-2 or O-8.[1]
- Three distinct syntheses have been reported: Steven Ley[2], Phil Baran[3], and P. Andrew Evans[4]

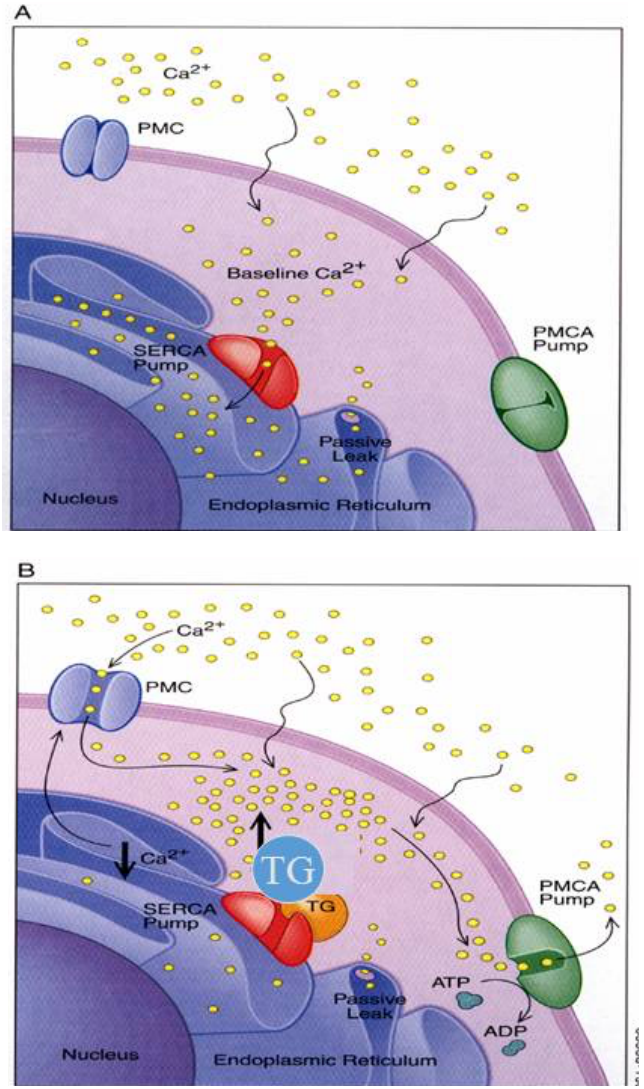


Thapsigargin

1. *Chem. Eur. J.* **2007**, 13, 5688.
2. *Angew. Chem., Int. Ed.* **2003**, 42, 5996.
3. *ACS Cent. Sci.* **2017**, 3, 47.
4. *J. Am. Chem. Soc.* **2017**, 139, 6046.

Biological Relevance of Thapsigargin

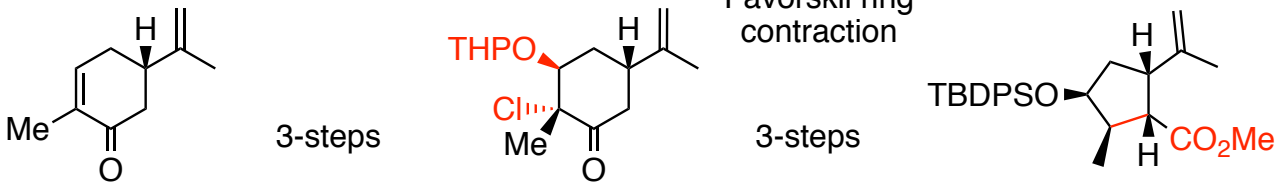
- Extensive biological evaluation
- Selective, sub-nanomolar inhibitor of sarco/endoplasmic reticulum calcium ATPase (SERCA)-dependent pumps.[1,2]
- Binds to SERCA and induces a conformation that deters calcium and ATP binding.[1,2]
- Treatment severely alters cellular calcium concentrations, leading to disrupted cell growth and programmed cell death.[3,4]
- Promising therapeutic potential



1. *J. Biol. Chem.* **1991**, 266, 13503.
2. *J. Biol. Chem.* **1995**, 270, 11731.
3. *J. Biol. Chem.* **1994**, 269, 11927.
4. *Prostate* **1997**, 80, 201.

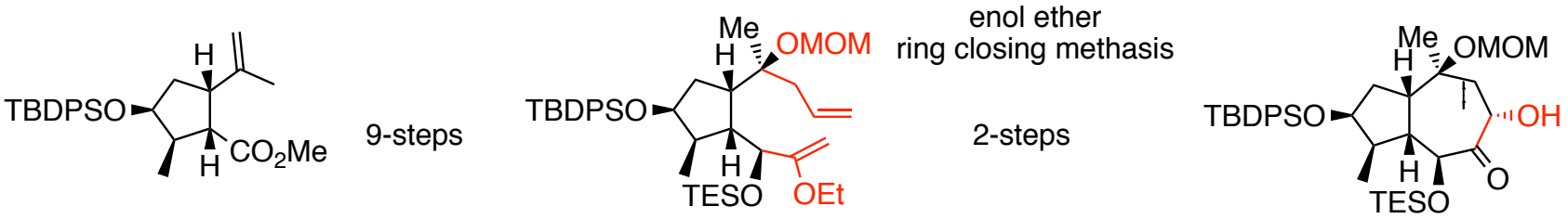
Total Synthesis by the Steven Ley Lab

Angew. Chem., Int. Ed. **2003**, 42, 5996.
Proc. Natl. Acad. Sci. U.S.A. **2004**, 101, 12073.
Chem. Eur. J. **2007**, *13, 5688.*
Org. Lett. **2007**, 8, 2879.

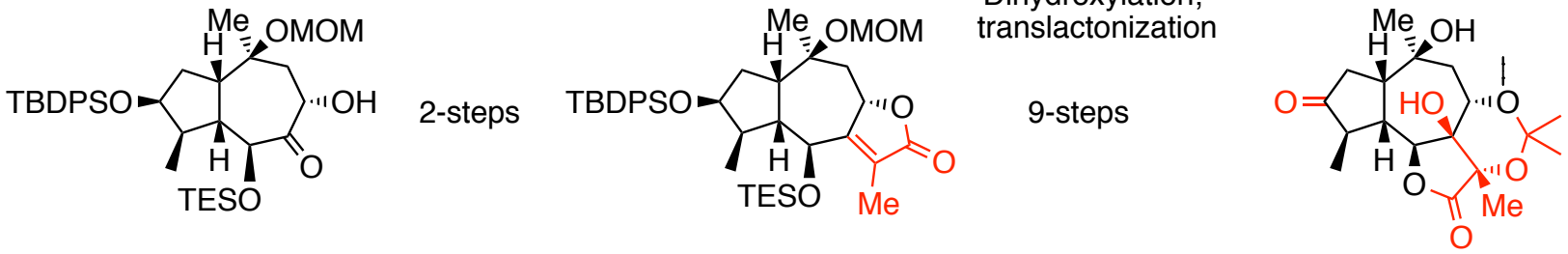


(*S*)-(+)-Carvone

Ley Lab

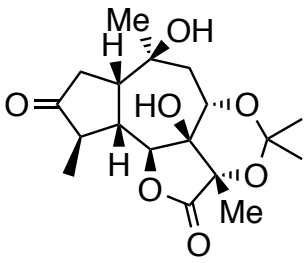

TBDPSO
H
CO_2Me
H
9-steps
Me
H
OMOM
TBDPSO
H
TESO
OEt
enol ether
ring closing methasis
2-steps
Me
H
OMOM
TBDPSO
OH
H
TESO
O

Ley Lab



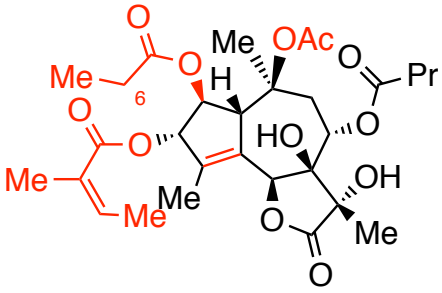
Evan Carder @ Wipf Group

Ley Lab



late-stage *a*-oxidation;
regioselective acylations

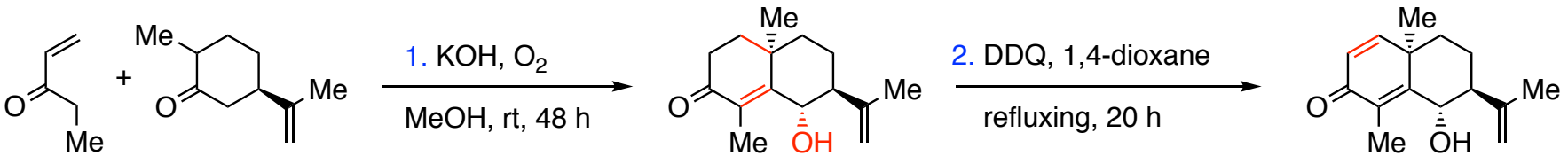
14-steps



Thapsigargin
42-steps, 0.61% overall yield

Toward the Synthesis by the Guillermo Massanet Lab

Org. Lett. **2006**, 8, 2879.



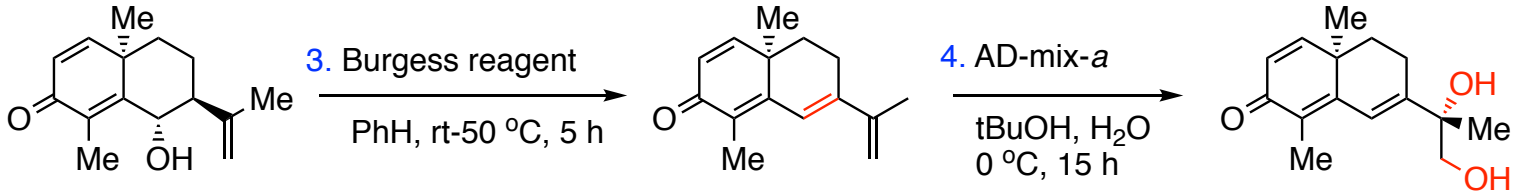
(+)-Dihydrocarvone

Robinson Annulation

70%

85%

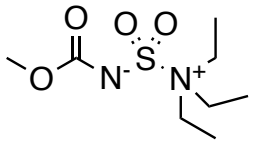
Massanet Lab



98% **76%**

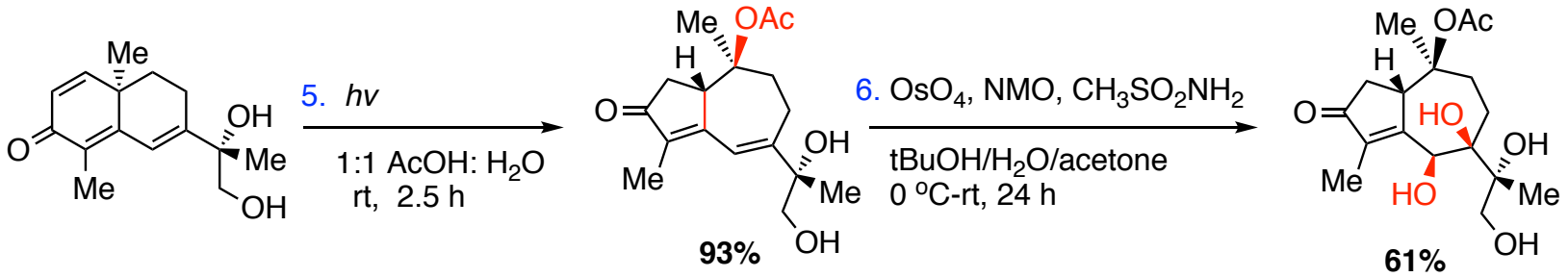
Sharpless assymetric dihydroxylation

Burgess Reagent

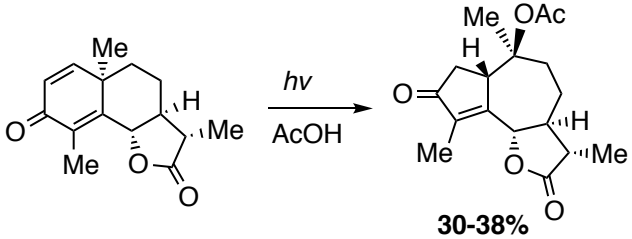


AD-mix-a

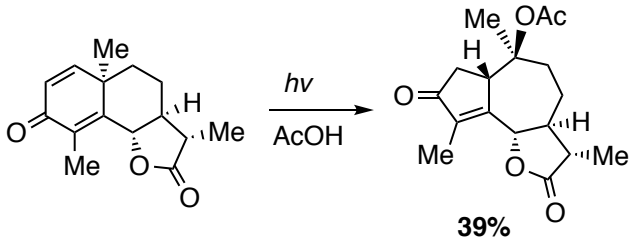
- $K_2OsO_4\ 2H_2O$
- $K_3Fe(CN)_4$
- K_2CO_3
- $(DHQ)_2PHAL$



Precedence:

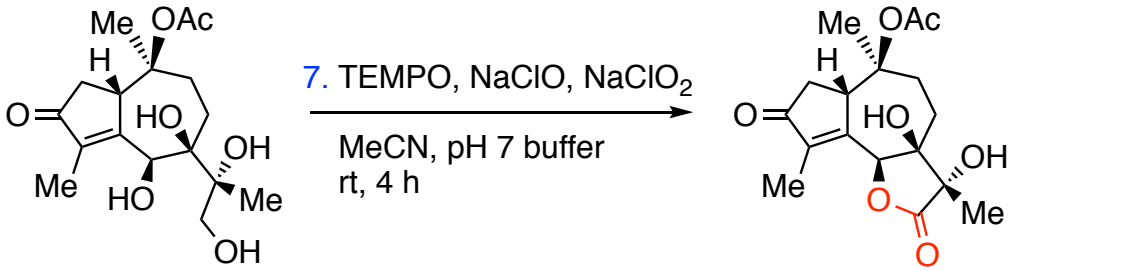


J. Chem. Soc. **1957**, 929.



J. Chem. Soc. **2005**, 127, 18.

Massanet Lab

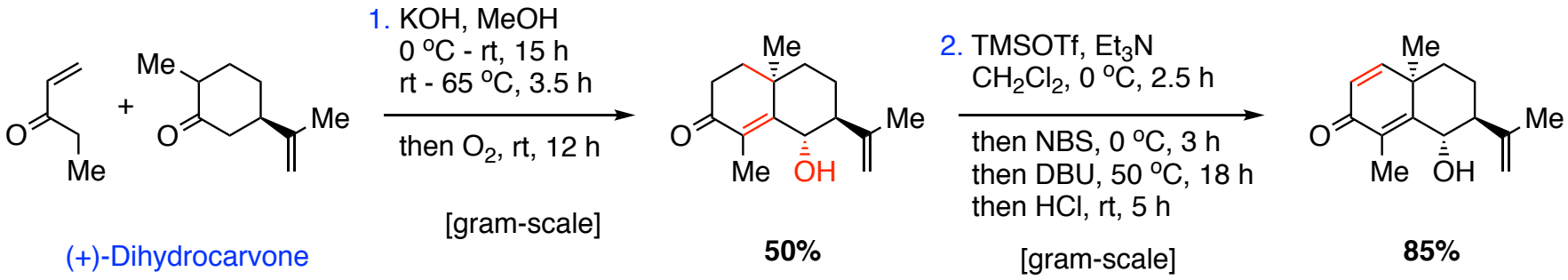


98%

7,11-Dihydoxyguaianolide

Total Synthesis by the Phil Baran Lab

ACS Cent. Sci. **2017**, 3, 47.

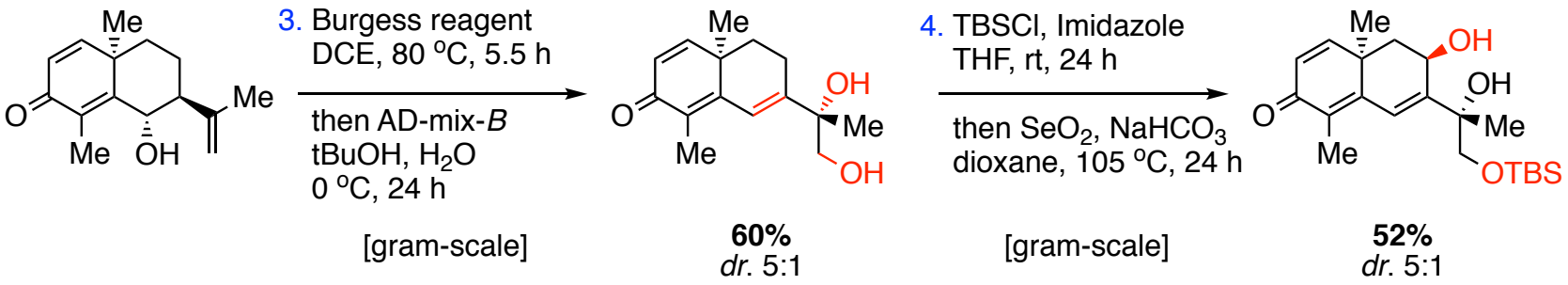


(+)-Dihydrocarvone

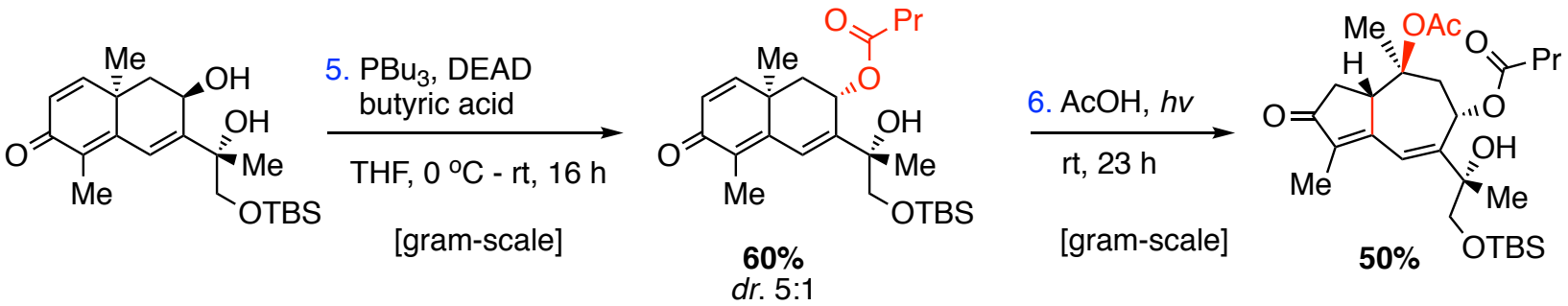
50%

85%

Robinson Annulation

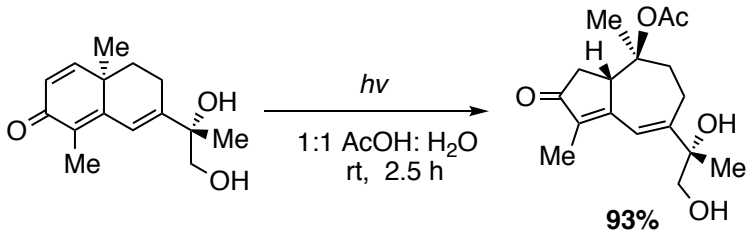


Sharpless assymetric dihydroxylation

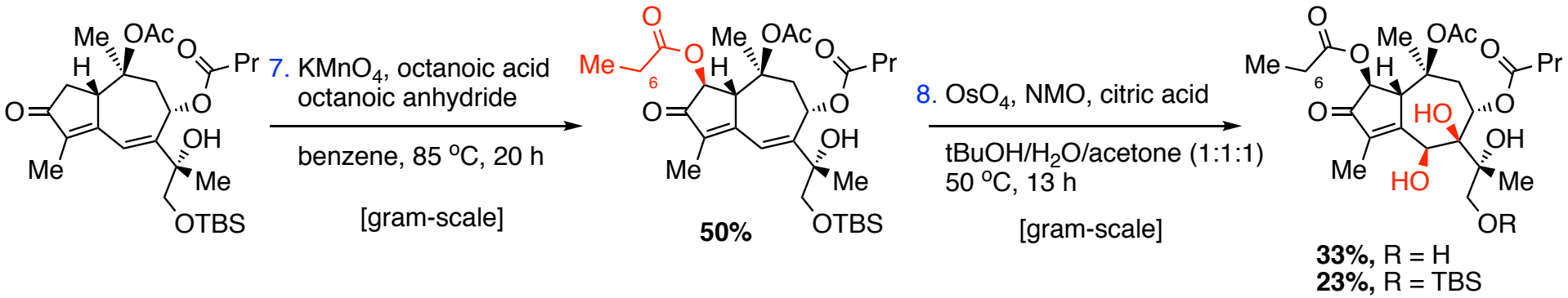


Mitsunobu Reaction

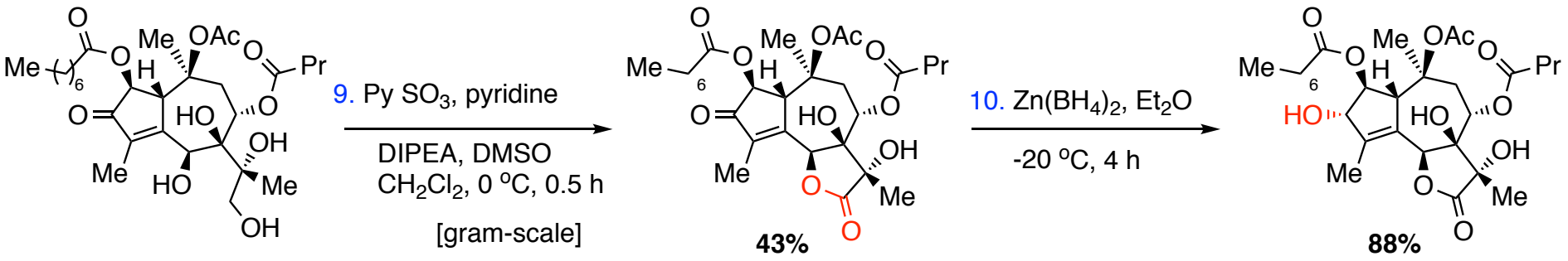
Precedence:



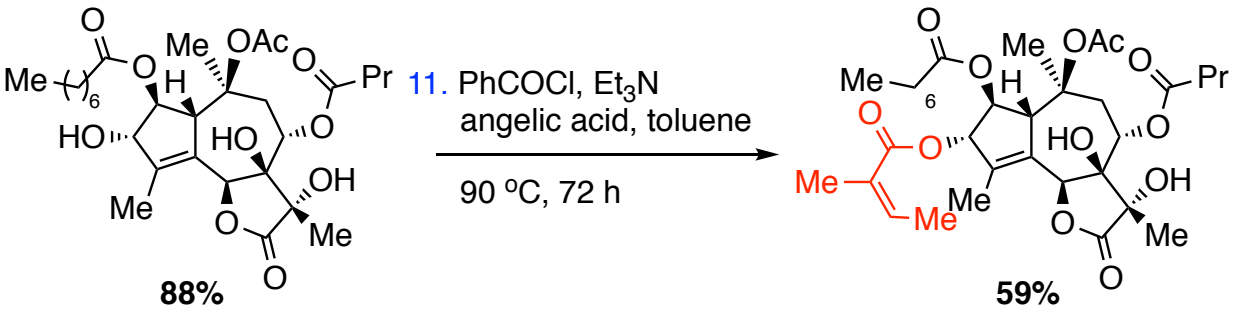
Org. Lett. **2006**, 8, 2879.



Upjohn dihydroxylation



Parikh-Doering Oxidation

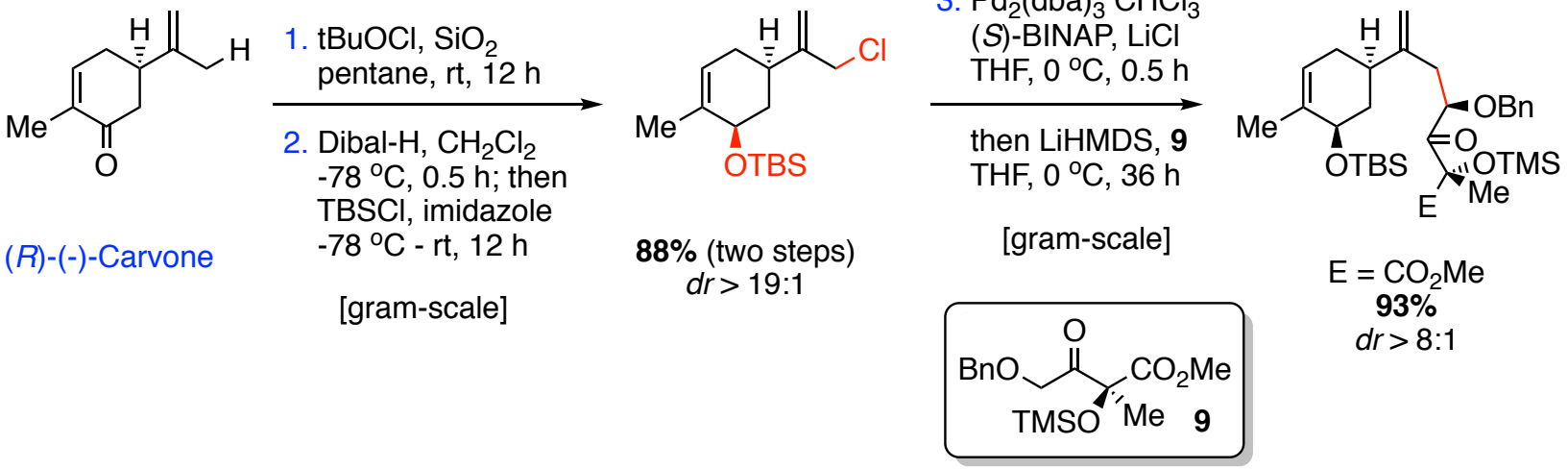


Thapsigargin

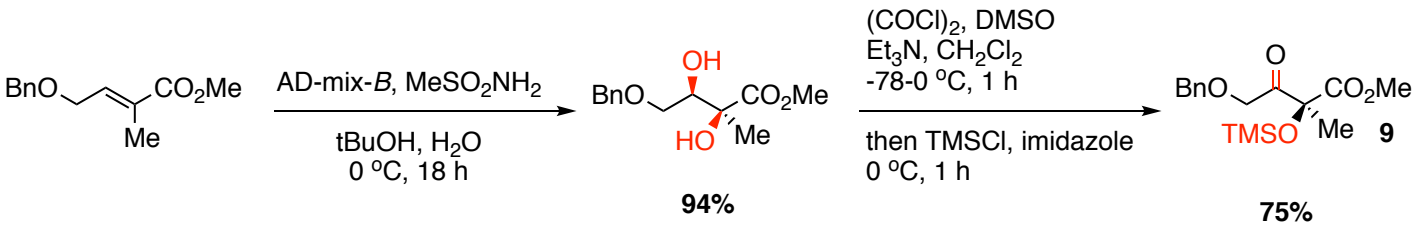
11-steps, 0.137% overall yield

Current work: P. Andrew Evans Lab

J. Am. Chem. Soc. **2017**, 139, 6046.

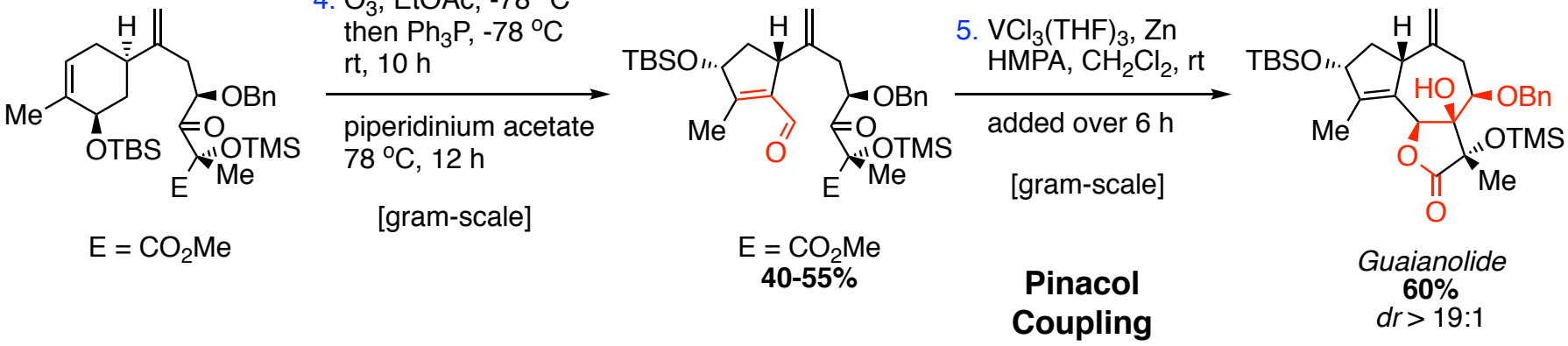


Synthesis of **9**:

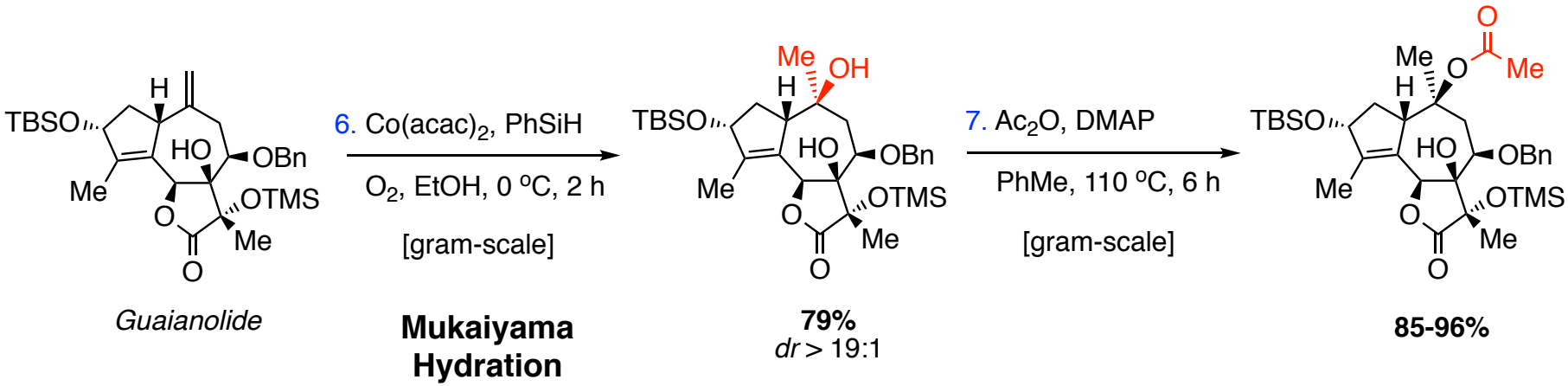


Evan Carder @ Wipf Group

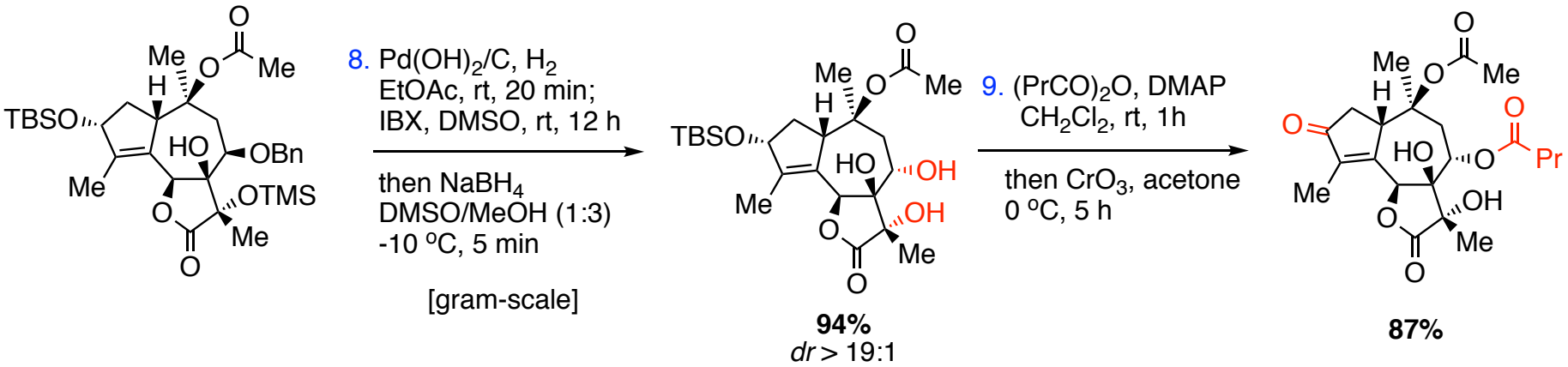
Evans Lab


H
Me
OBn
O
OTBS
OTMS
E
Me
E = CO2Me
4. O3, EtOAc, -78 °C
then Ph3P, -78 °C
rt, 10 h
piperidinium acetate
78 °C, 12 h
[gram-scale]
TBSO
H
OBn
Me
O
O
OTMS
E
Me
E = CO2Me
40-55%
5. VCl3(THF)3, Zn
HMPA, CH2Cl2, rt
added over 6 h
[gram-scale]
Pinacol
Coupling
TBSO
H
HO
OBn
Me
O
OTMS
Me
O
Guaianolide
60%
dr > 19:1

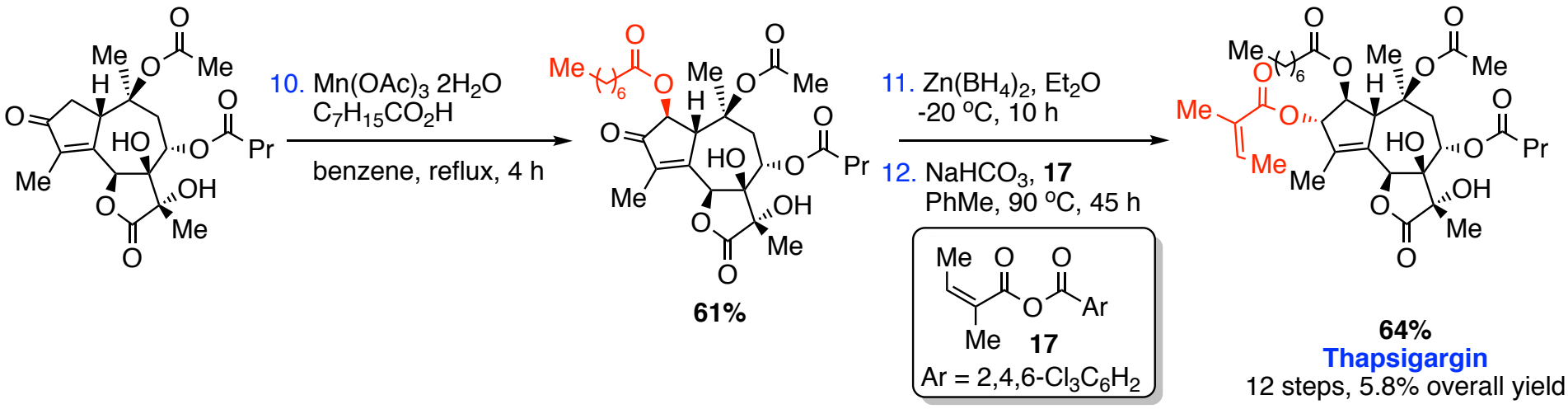
Evans Lab


TBSO
H
HO
OBn
Me
OTMS
O
Me
O
Guaianolide
6. Co(acac)2, PhSiH
O2, EtOH, 0 °C, 2 h
[gram-scale]
Mukaiyama Hydration
Me
OH
79%
dr > 19:1
7. Ac2O, DMAP
PhMe, 110 °C, 6 h
[gram-scale]
85-96%

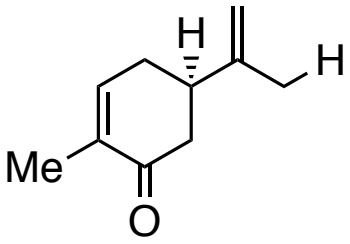
Evans Lab

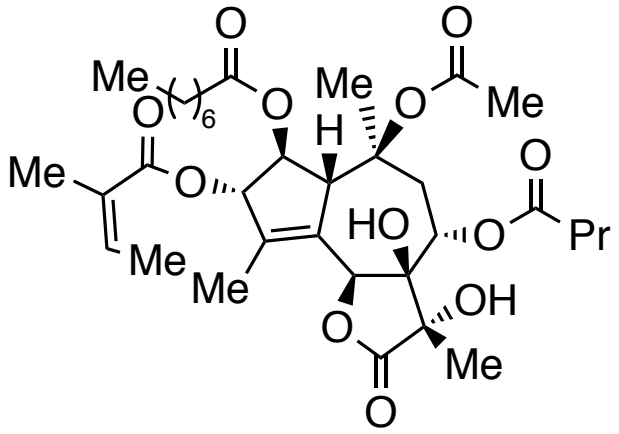

8. Pd(OH)2/C, H2
EtOAc, rt, 20 min;
IBX, DMSO, rt, 12 h
then NaBH4
DMSO/MeOH (1:3)
-10 °C, 5 min
[gram-scale]
94%
dr > 19:1
9. (PrCO)2O, DMAP
CH2Cl2, rt, 1h
then CrO3, acetone
0 °C, 5 h
87%

Evans Lab


10. Mn(OAc)3 2H2O
C7H15CO2H
benzene, reflux, 4 h
61%
11. Zn(BH4)2, Et2O
-20 °C, 10 h
12. NaHCO3, 17
PhMe, 90 °C, 45 h
17
Ar = 2,4,6-Cl3C6H2
64%
Thapsigargin
12 steps, 5.8% overall yield

Summary





(*R*)-(-)-Carvone **Thapsigargin**

Total Synthesis:	**Creighton Lab**	**Baran Lab**		**Evans Lab**
Key step(s)	Favorskii Rearrangement, Ring-closing metathesis	Photochemical ring contraction		Asymmetric allyl alkylation, Pinacol coupling
Linear Steps	42	11		12
Overall yield	0.61%	0.14%	**42x**	5.8%