

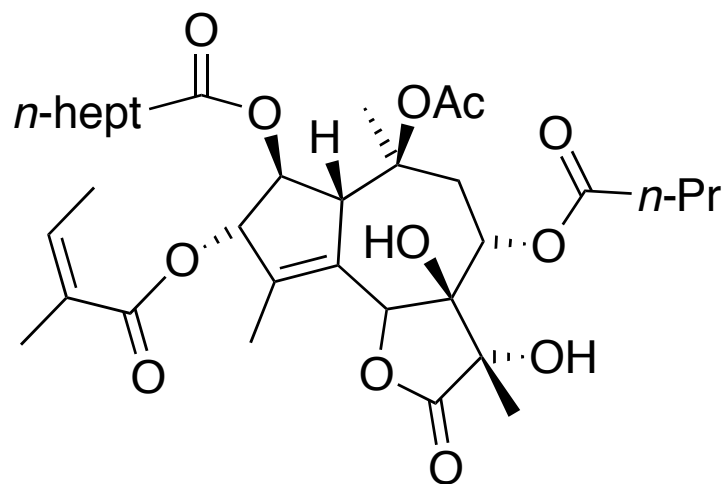
# Journal Club

Nick Tappin  
Renaud Group  
01 June 2017

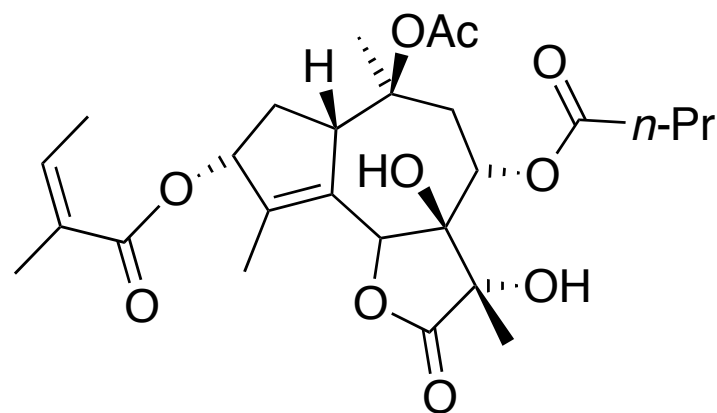
# A Concise, Efficient and Scalable Total Synthesis of Thapsigargin and Nortrilobolide from (*R*)-(-)-Carvone

Chen, D.; Evans, P. A., *J. Am. Chem. Soc.* **2017**, ,  
*139* (17), 6046-6049.

DOI: 10.1021/jacs.7b01734



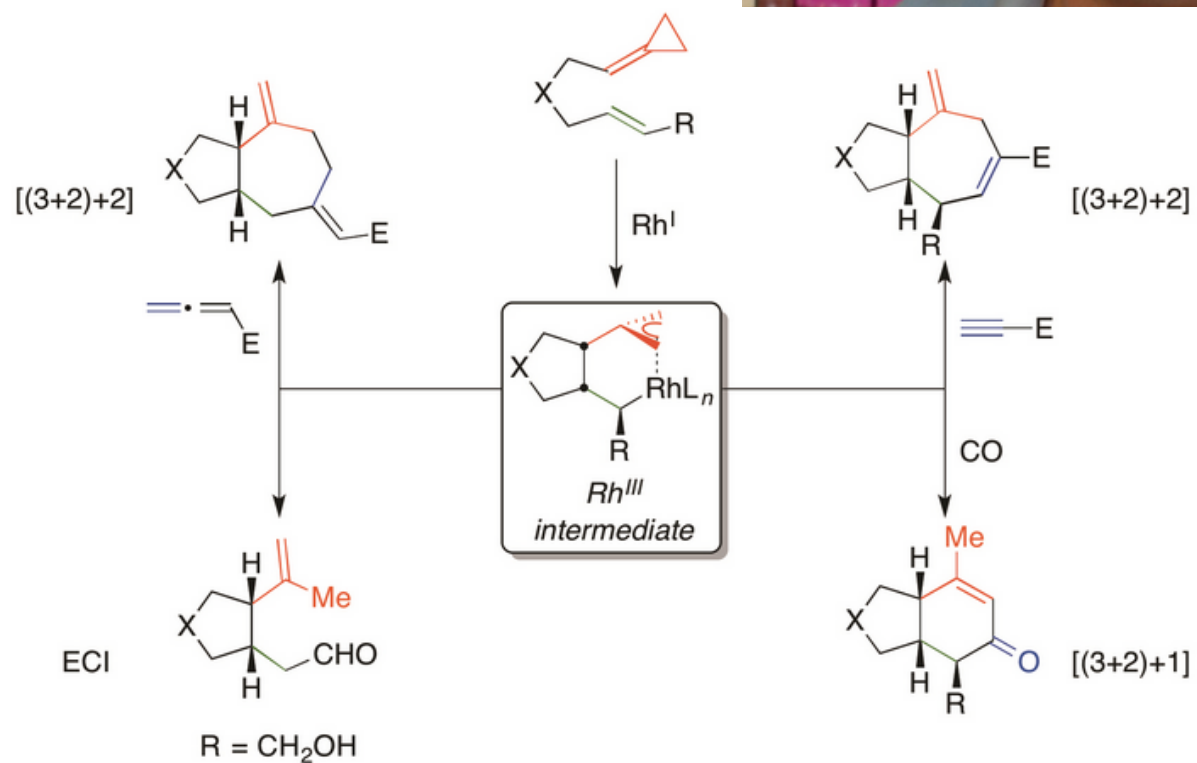
**Thapsigargin**



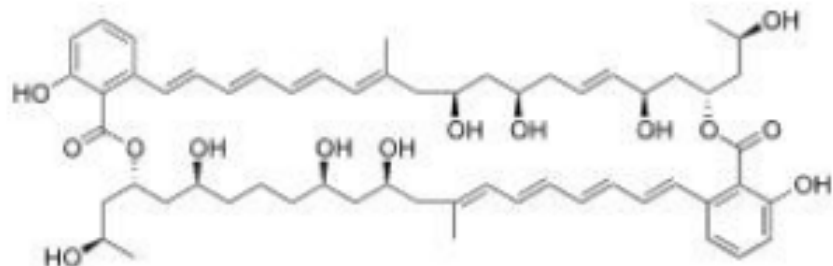
**Nortrilobolide**

# P. Andrew Evans

- Born 1964, Wales
- 1987 B. Sc. Newcastle Poly
- 1990 PhD under Holmes, Cambridge Uni
- 1993 PostDoc under Magnus, UT, Austin
- Various academic posts
- 2006, at Queen's Uni, Ontario
- 2012, A. R. Bader Chair in O Chem

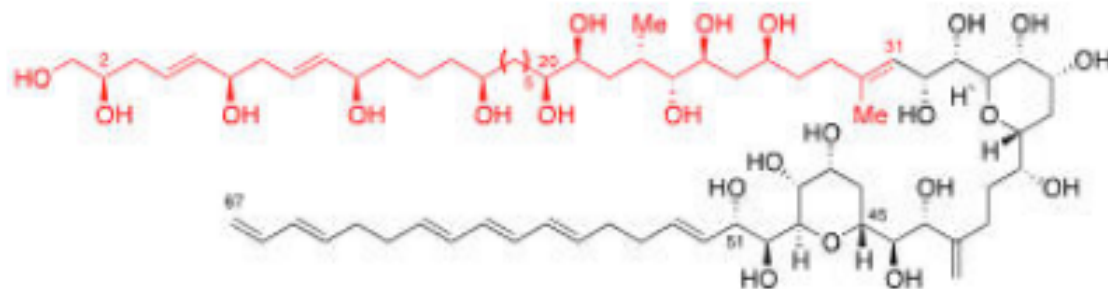


# P. Andrew Evans



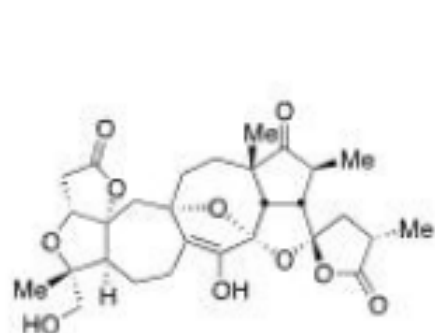
**Marinomycin A - 18 Steps**

(Antibiotic Activity: *Nature Chem.* 2012, 4, 680)



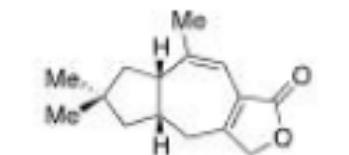
**Amphidinol 3**

(Antifungal : C1-C31 Fragment : *Chem Sci.* 2015, 6, 6407)



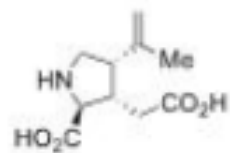
**Lancifodilactone G**

(Anti-HIV)



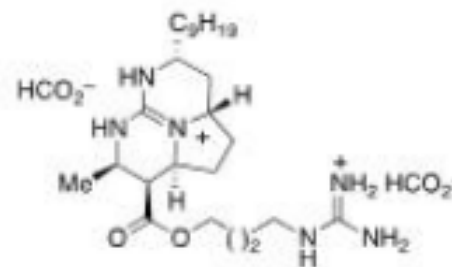
**Pyrovellerolactone - 3 Steps**

(*Org Lett.* 2013, 15, 1798)



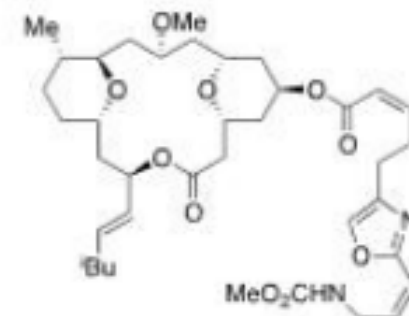
**(-)- $\alpha$ -Kainic Acid - 7 Steps - Aspira Scientific**

(Neuroexcitatory AA: *JACS* 2012, 134, 3635)



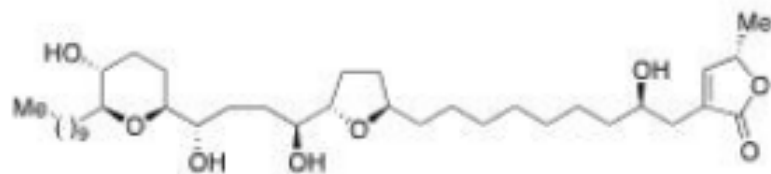
**(-)-Batzelladine D - 14 Steps**

(Anti-HIV: *ACIE* 2007, 46, 7417)



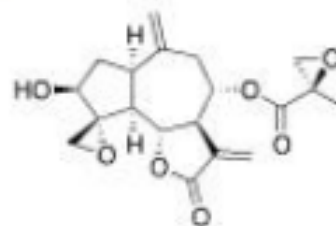
**(+)-Leucascandrolide A - 15 Steps**

(Antitumor Agent: *ACIE* 2008, 47, 5426)



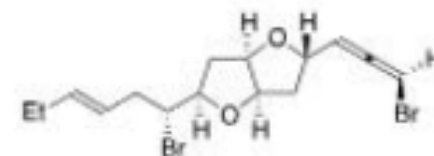
**(-)-Mucocin - 12 Steps**

(Antitumor Agent: *JACS* 2003, 125, 14702)



**Ropin**

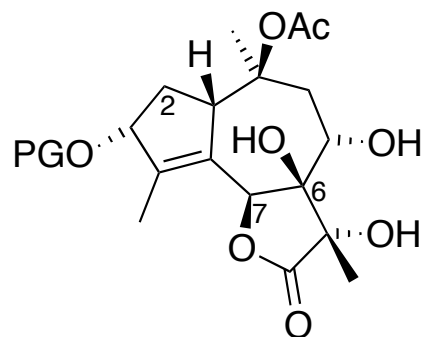
(Antitumor Agent)



**(-)-Kumausallene - 14 Steps**

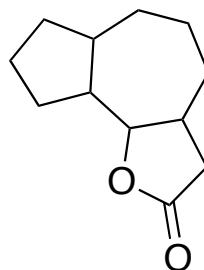
(Antitumor Agent: *ACIE* 1999, 38, 3175)

# Structural features

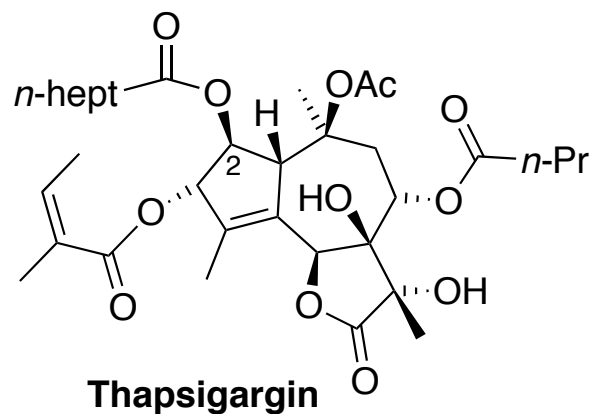
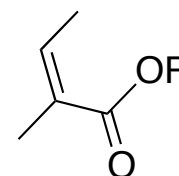


8 stereogenic centres (inc. C-2)

5-7-5 tricyclic guaianolide skeleton

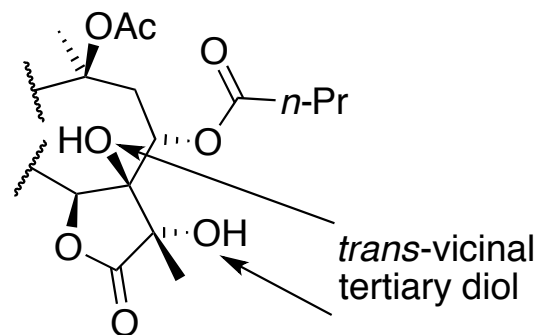


internal tetra-substituted olefin

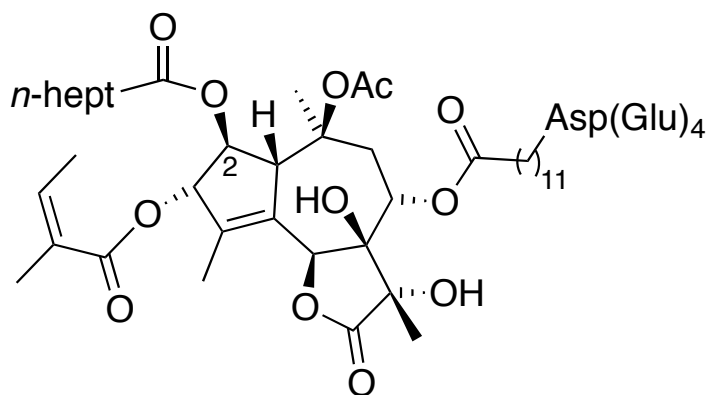
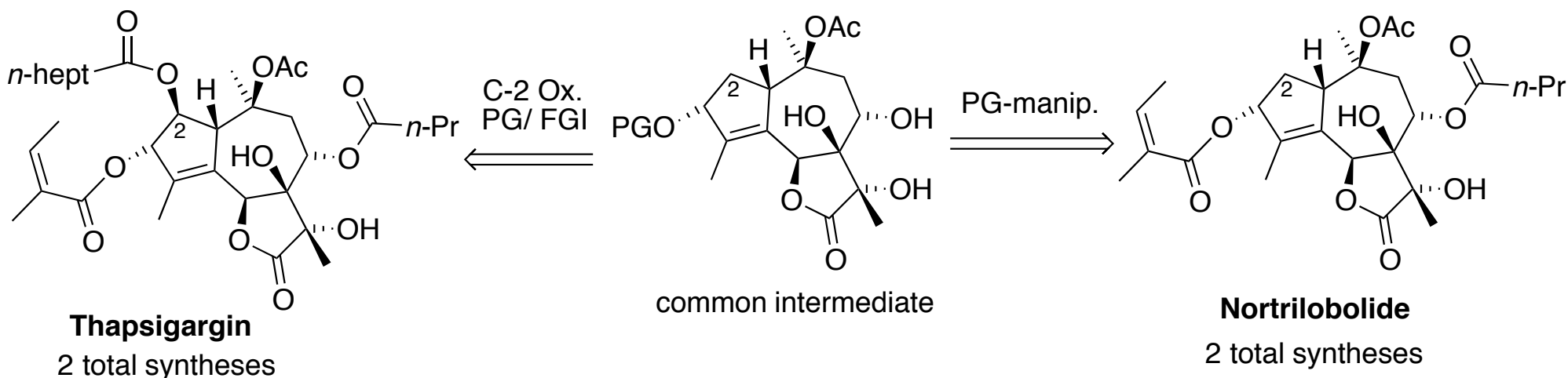


**Thapsigargin**

4-different ester groups (PG)



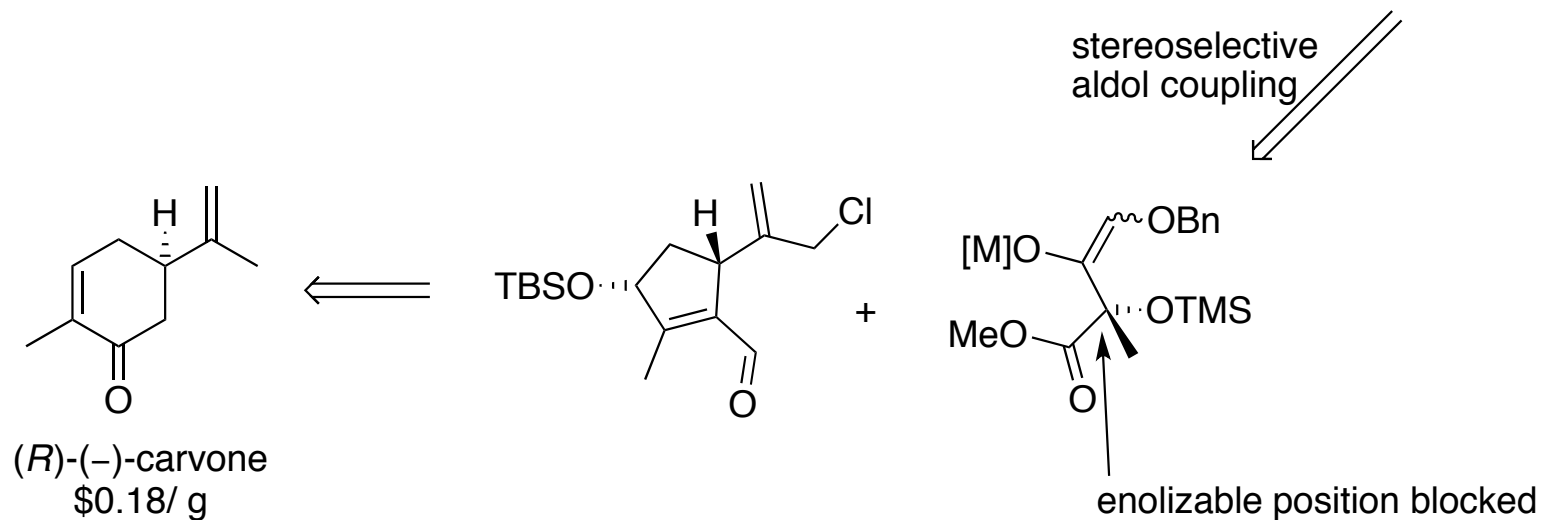
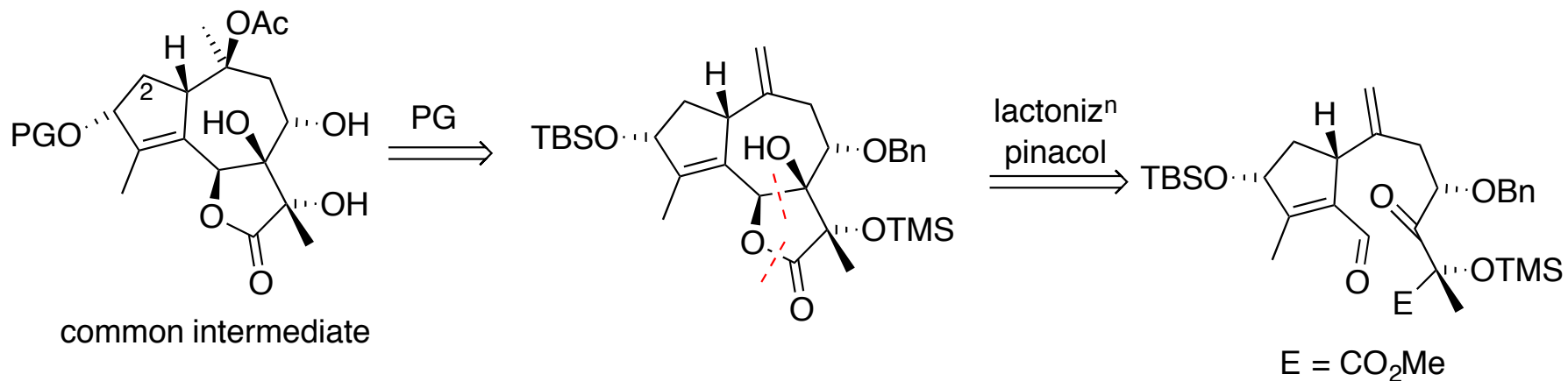
# Retrosynthetic analysis and importance



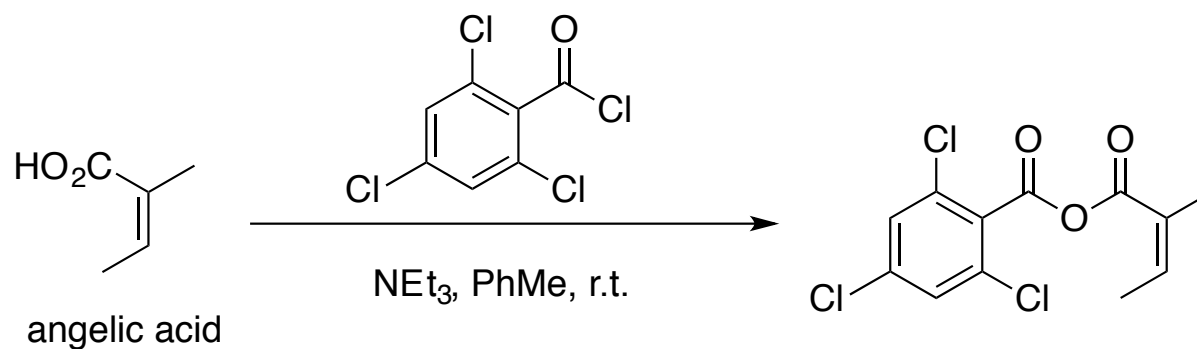
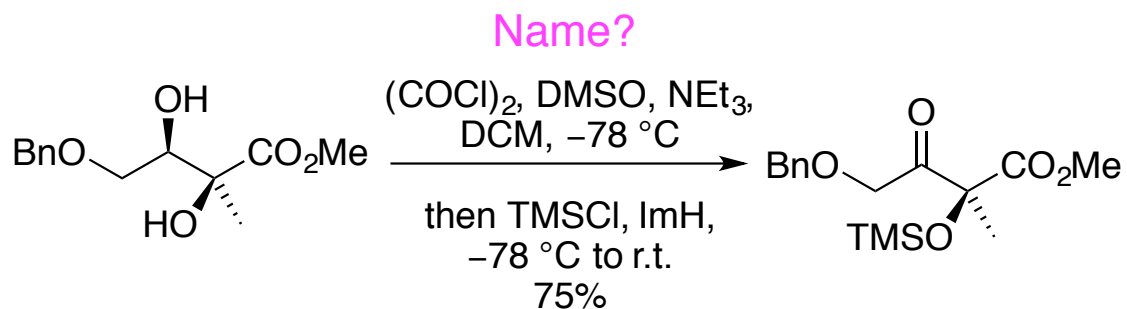
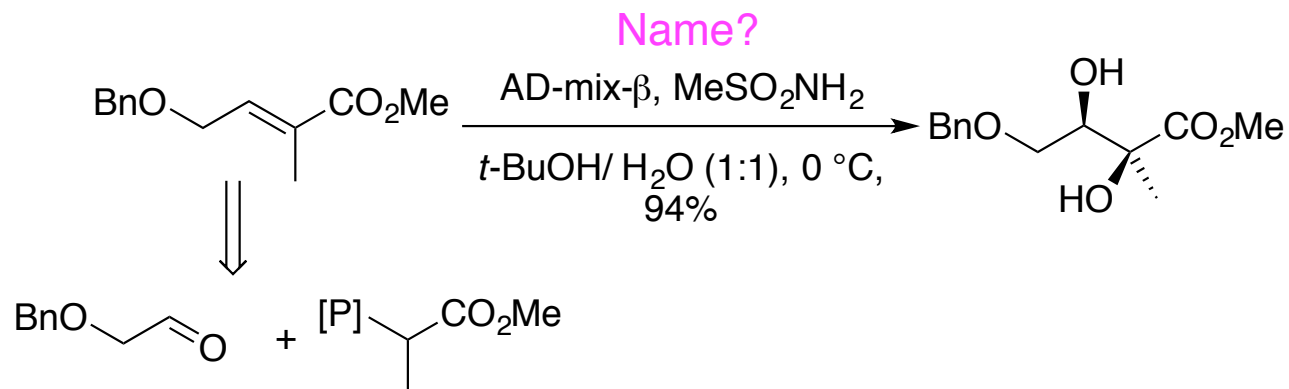
**Mipsagargin**, prodrug, Phase II clinical Trials  
~ tonne/ year anticipated (exceeds natural sources)

For treatment of liver, brain, prostate,  
And kidney cancers. (SERCAs).

# Retrosynthetic analysis



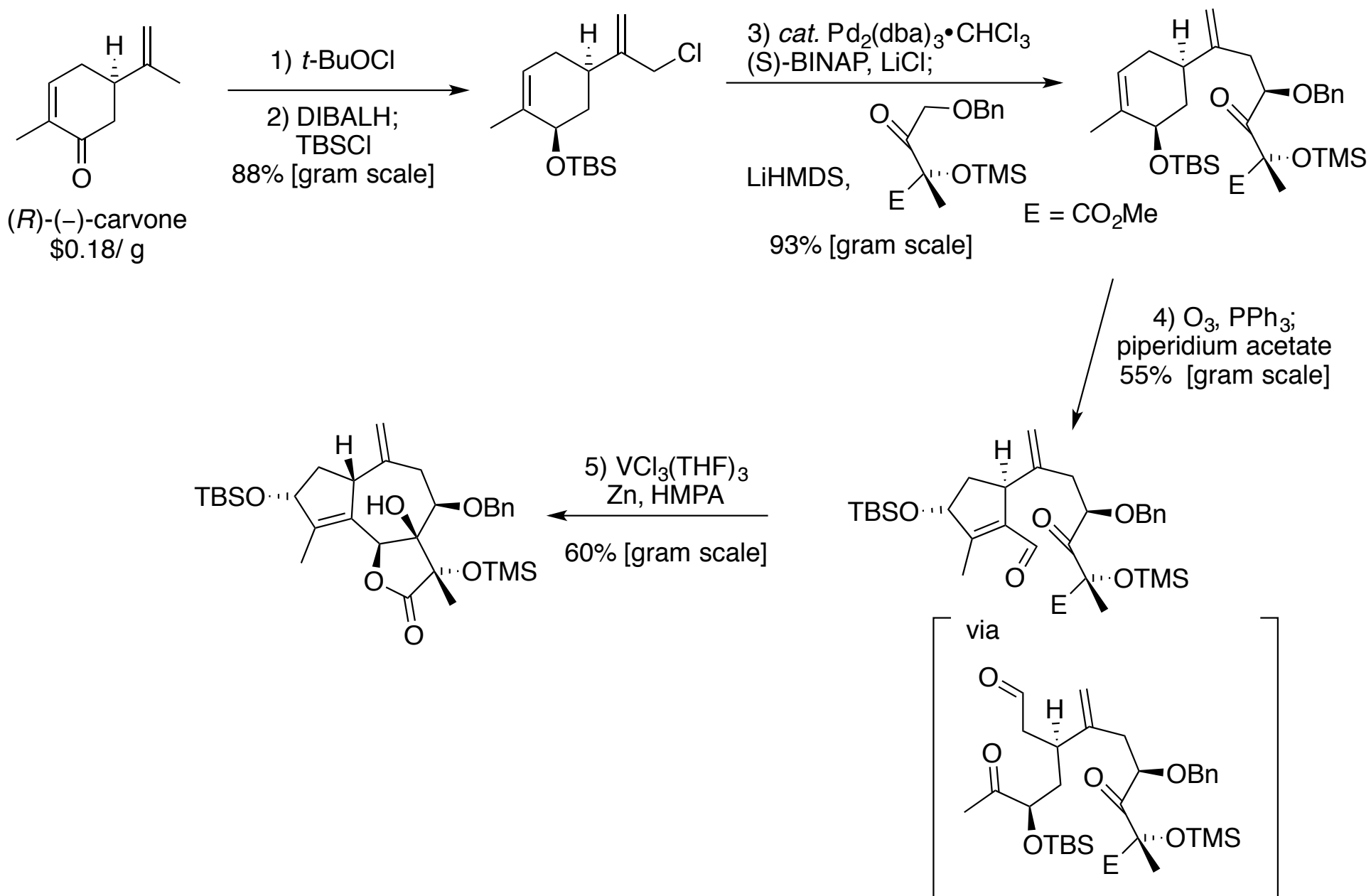
# SM Synthesis



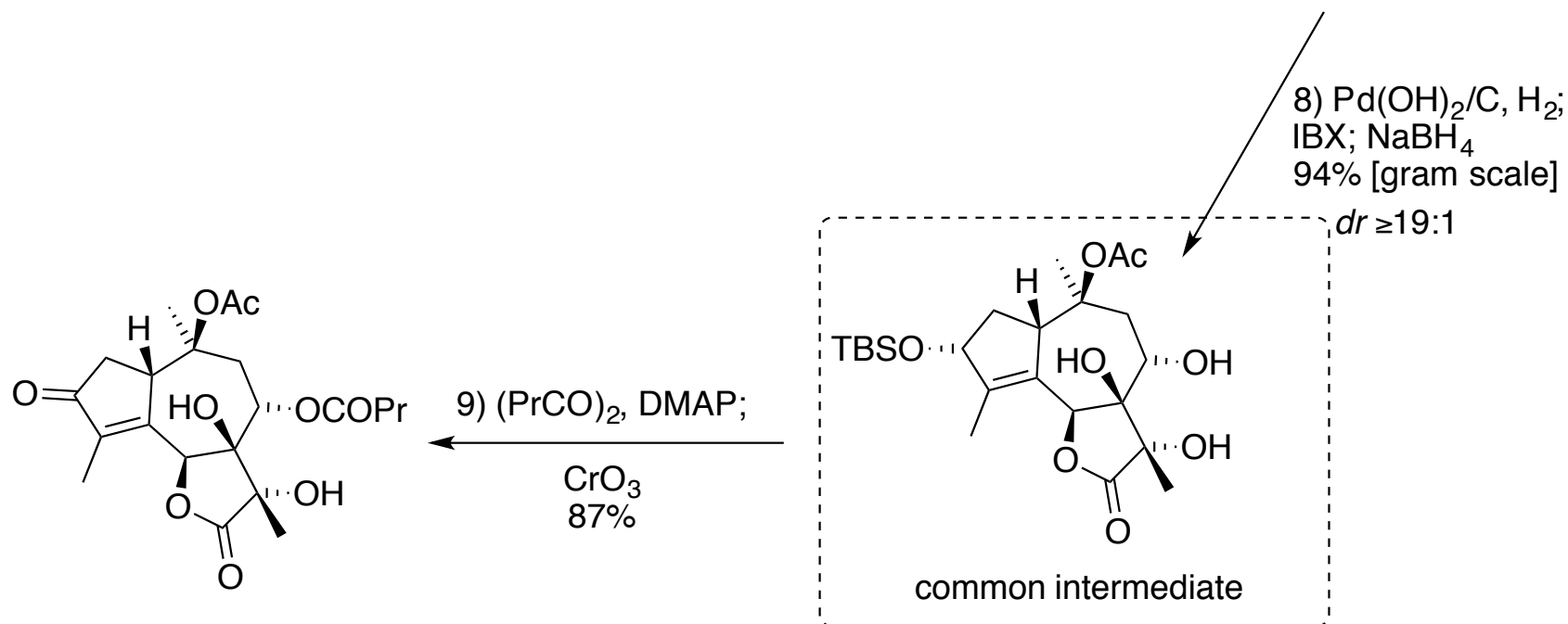
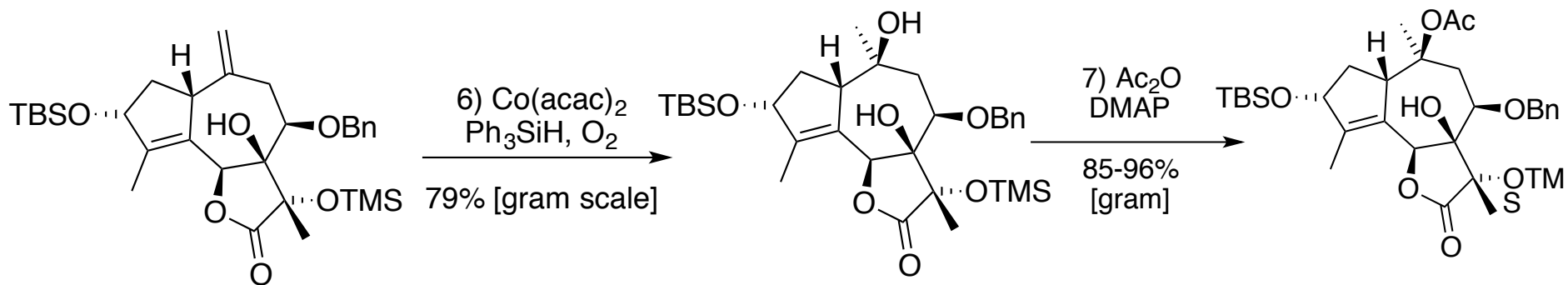
Ley, *Org. Lett.* **2007**, *9*, 663-666.



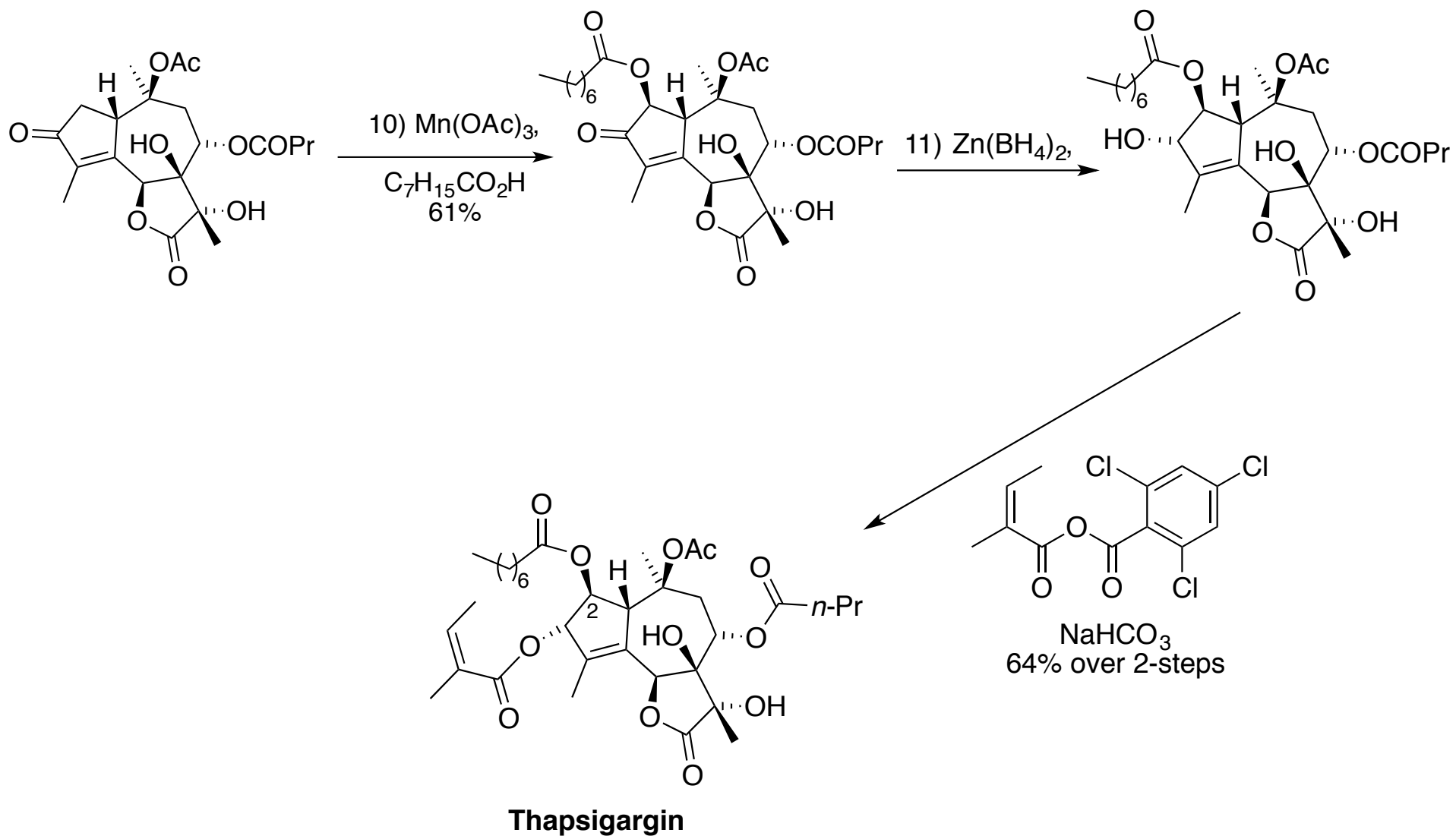
# Forward Synthesis



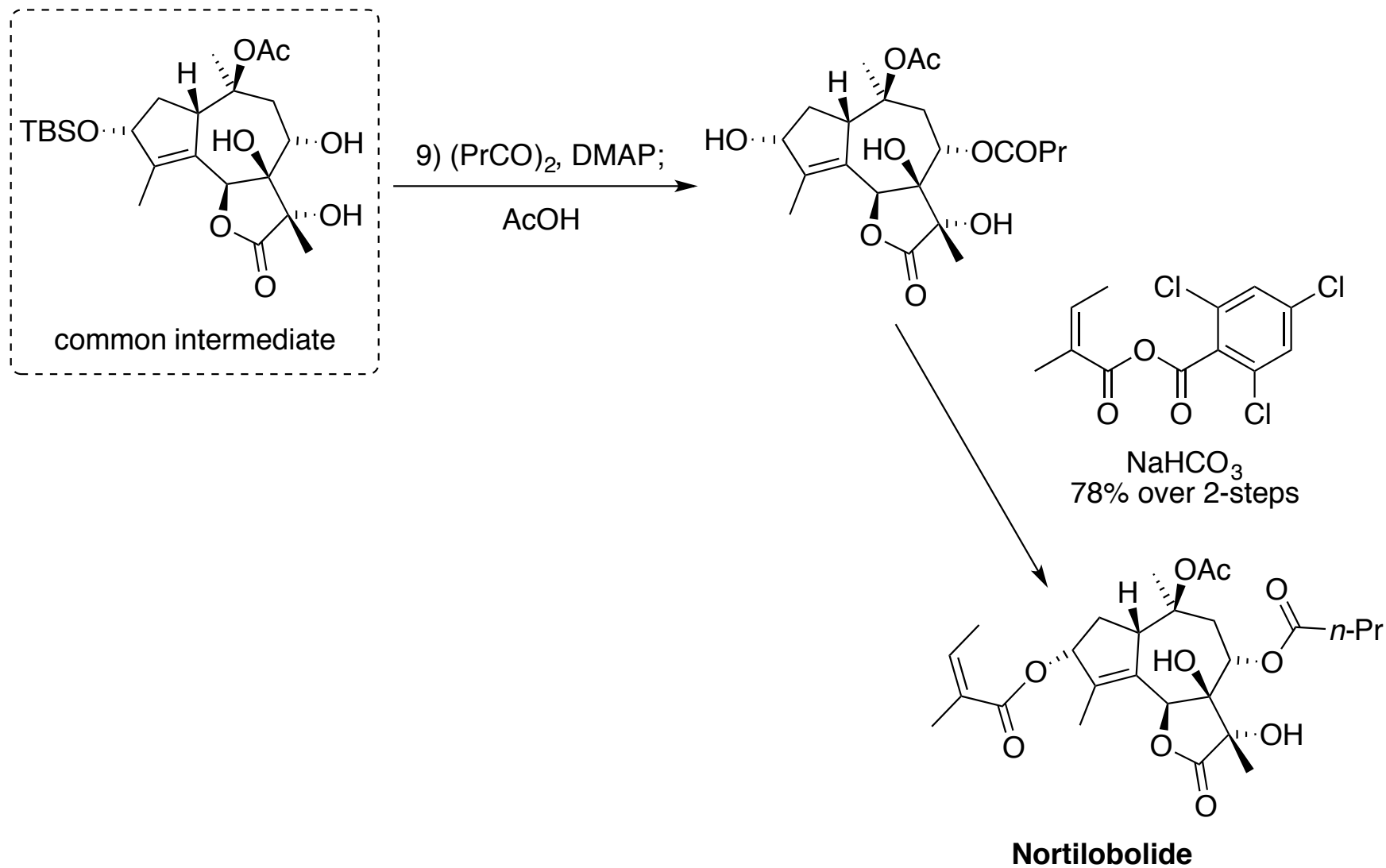
# Forward Synthesis



# Forward Synthesis

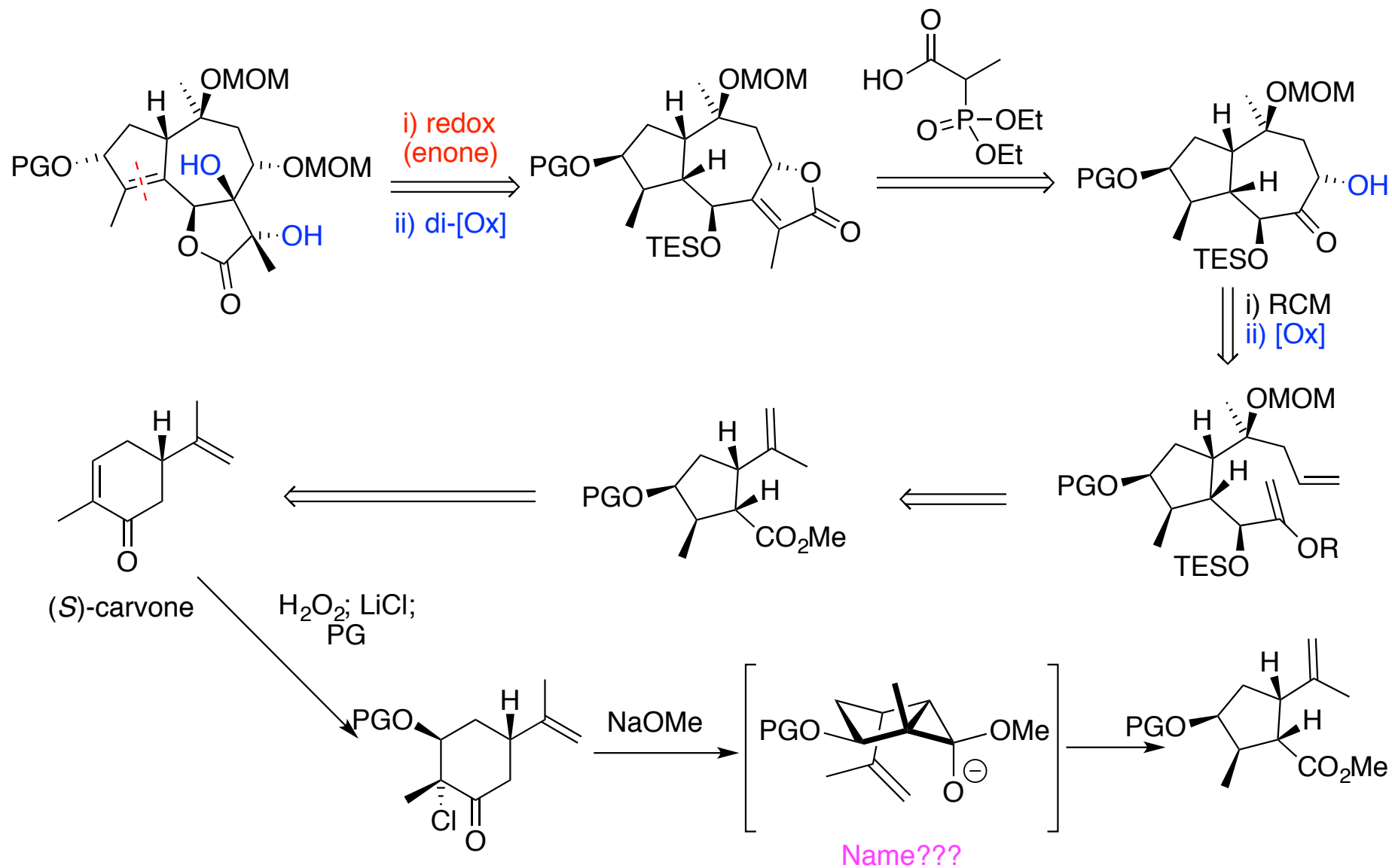


# Forward Synthesis



# Comparison to others

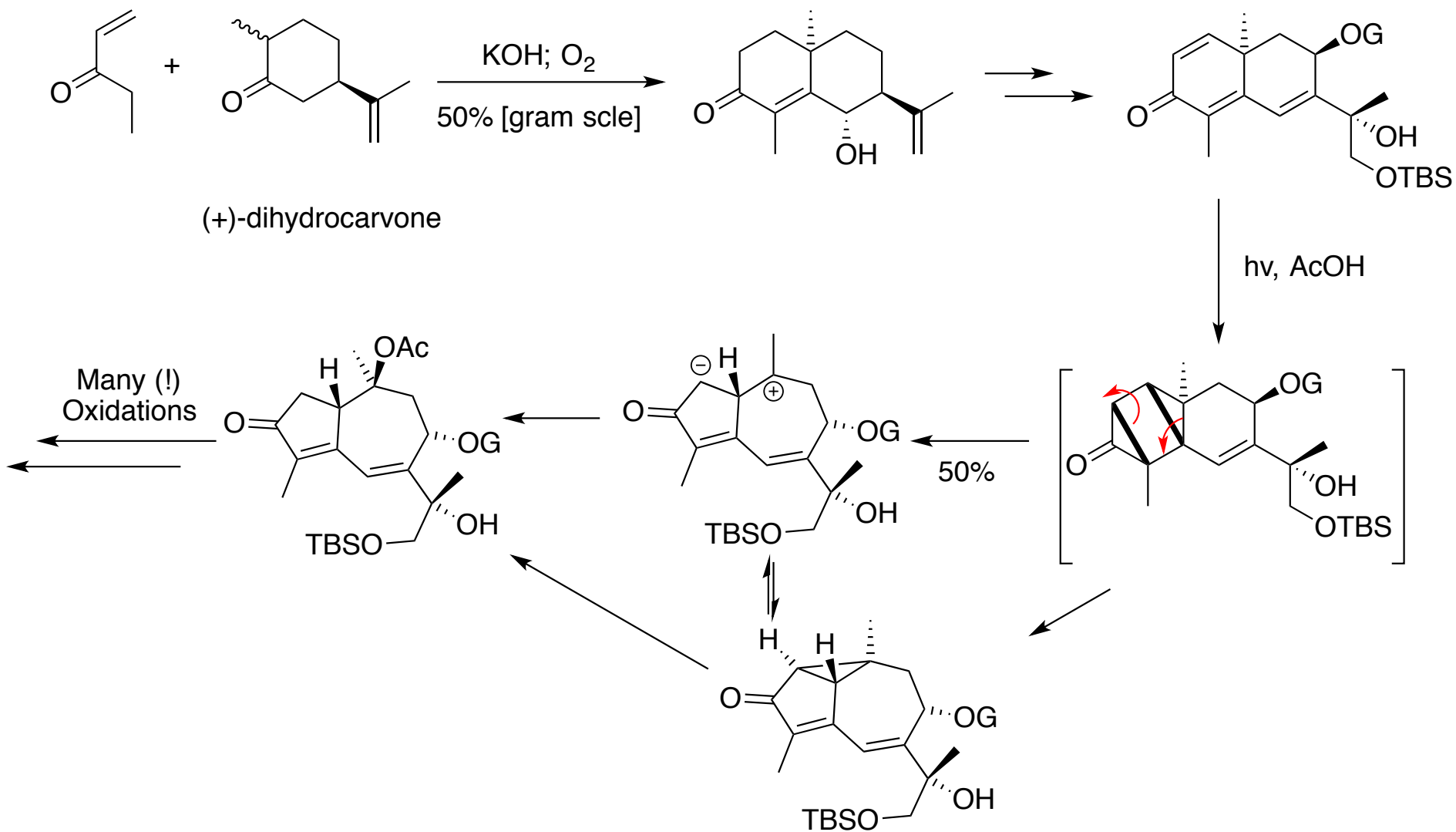
Key Disconnections for Ley's Synthesis (non-divergent, multiple redox)



Ley et al., *Angew. Chem. Int. Ed.* **2003**, 42, 5996-6000; *Org. Lett.* **2007**, 9, 663-666;  
*Chem. Eur. J.* **2007**, 13, 5688-5712.

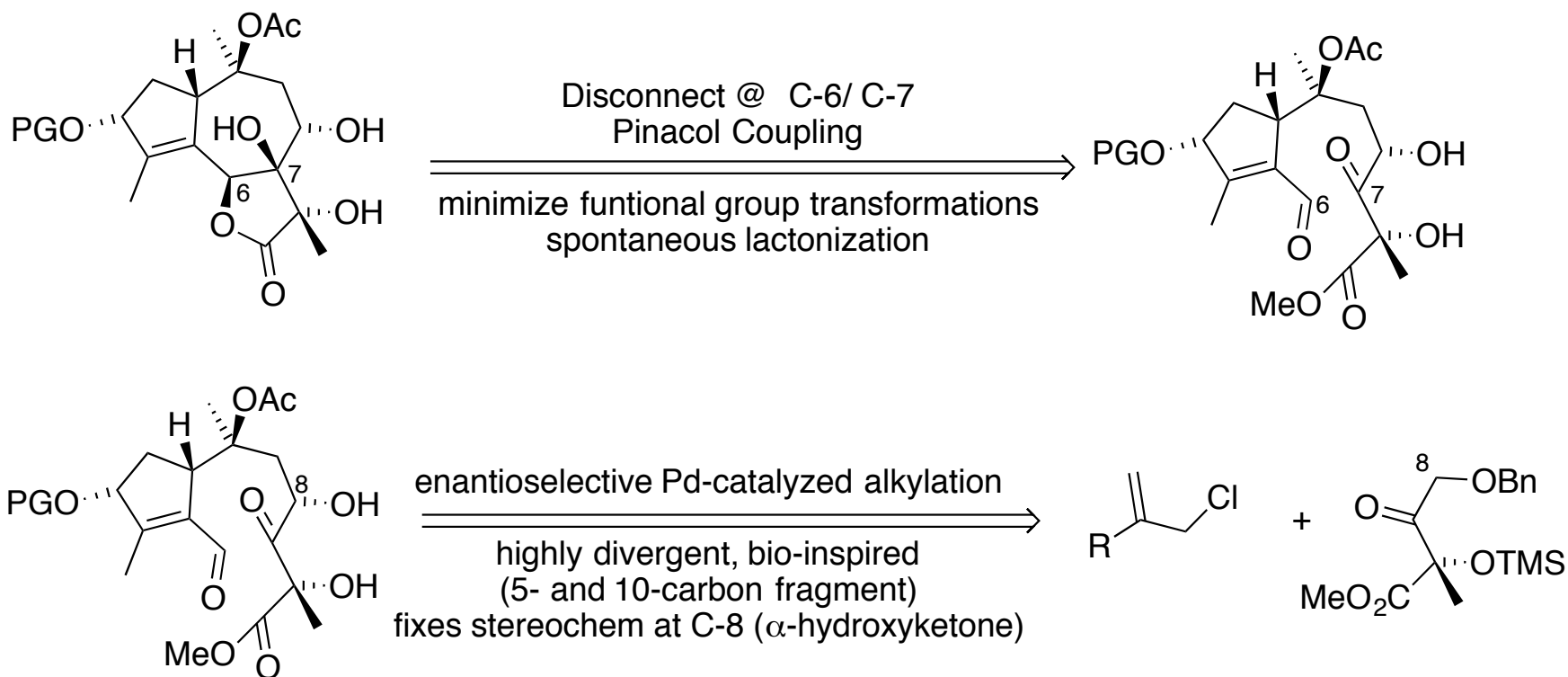
# Comparison to others

## Outline for Baran's Synthesis (non-divergent, multiple ox)

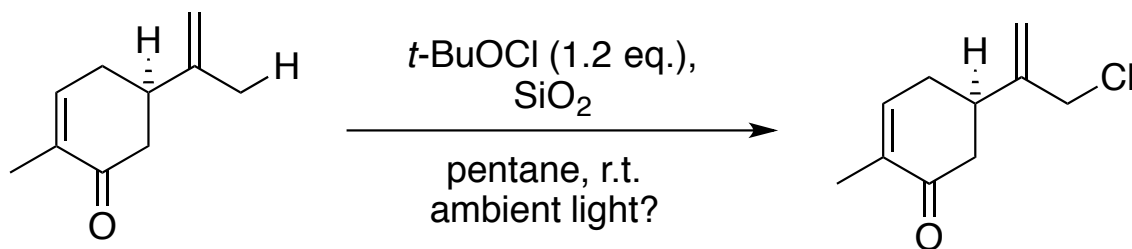


# Comparison to others and summary

## Key Disconnections for Evans' Synthesis



# Explanations

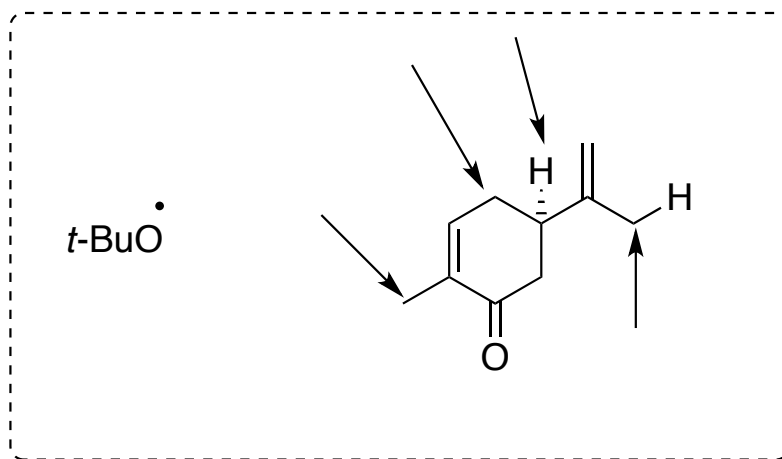


other important examples:

*J. Braz. Chem. Soc.* **2006**, *17*, 321-327.

Paterson, *Org. Lett.* **2012**, *14*, 5492-5495.

*Tetrahedron Lett.* **1980**, *21*, 441-444.

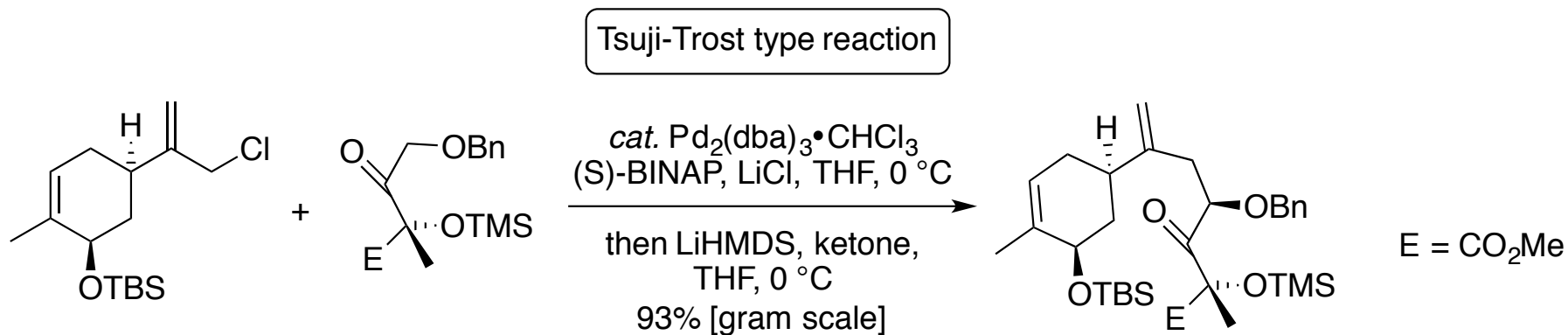


partial explanation and review

Simpkins, N. S.; Cha, J. K., t-Butyl Hypochlorite. In *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, Ltd: 2001.



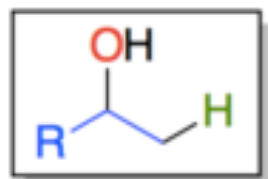
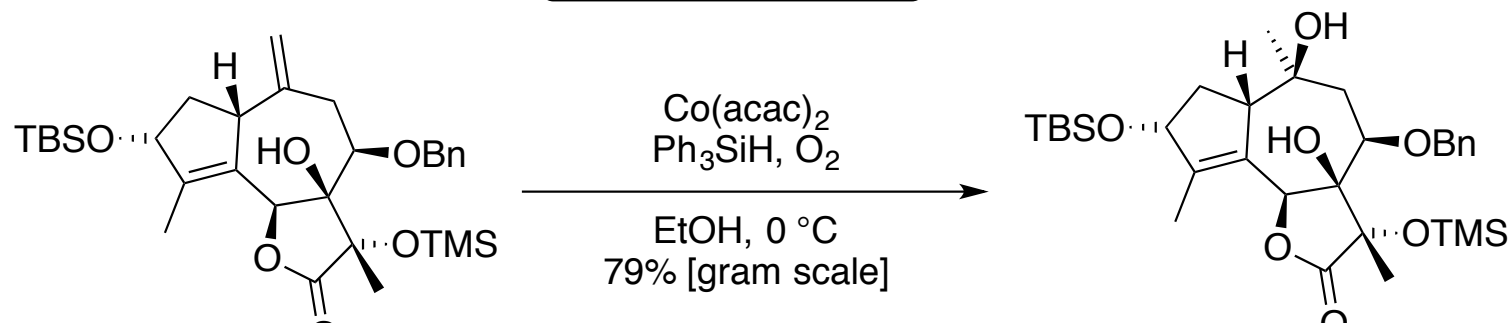
# Explanations



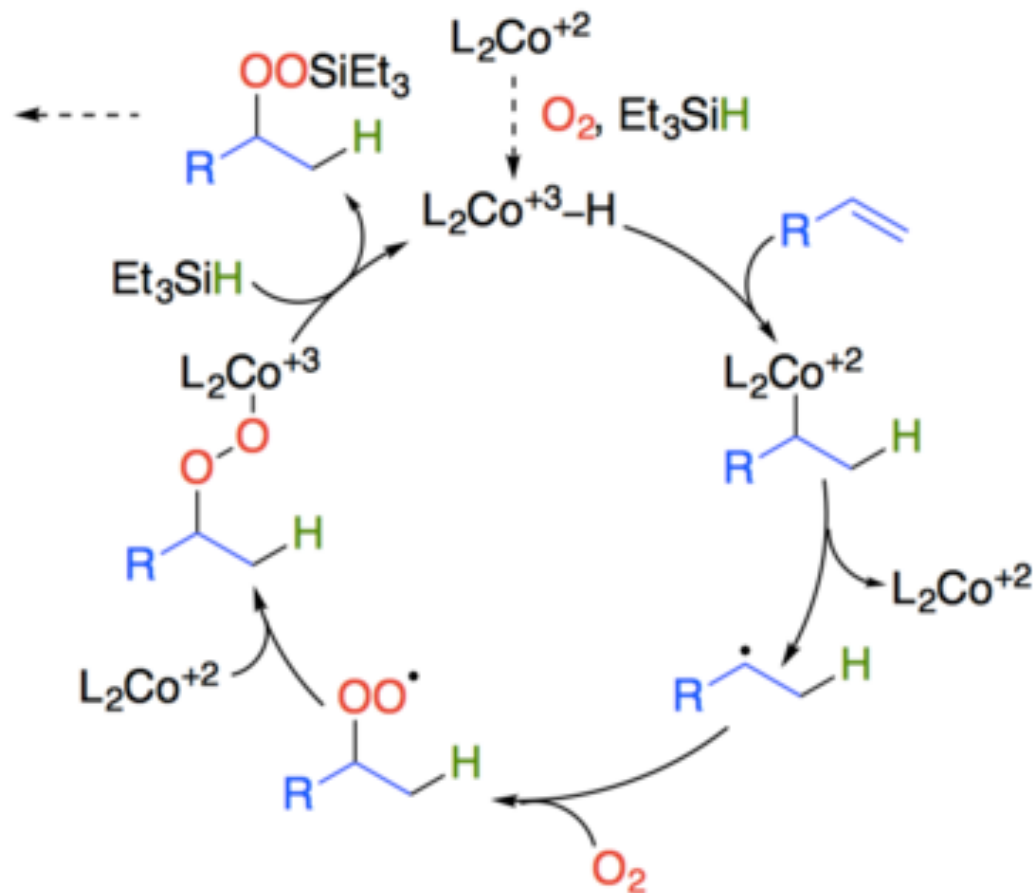
Braun, M.; Meier, T.; Laicher, F.; Meletis, P.; Fidan, M., *Adv. Synth. Catal.* **2008**, *350*, 303-314.

# Explanations

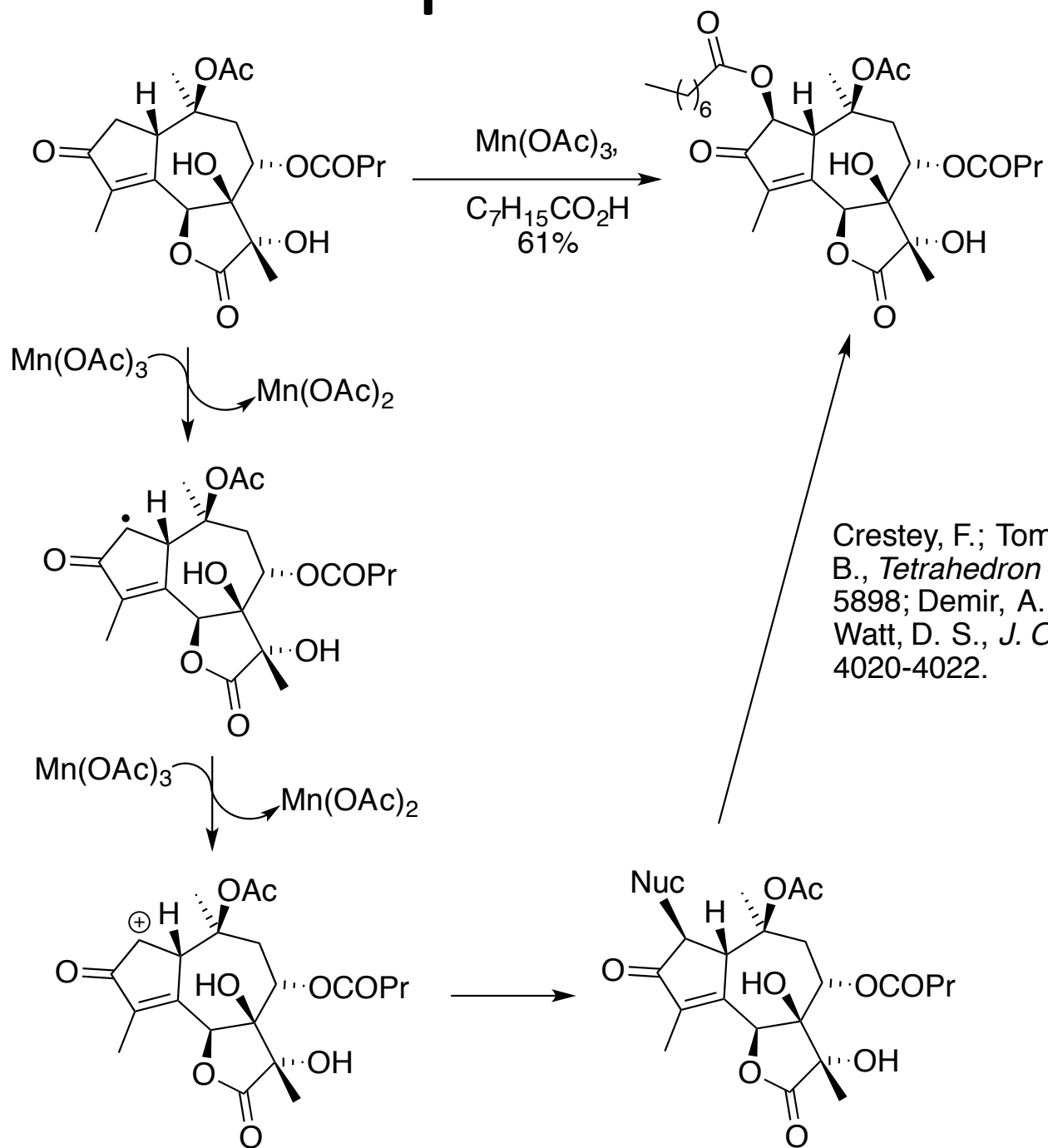
Mukaiyama hydration



Markovnikov alcohol product



# Explanations



Crestey, F.; Toma, M.; Christensen, S. B., *Tetrahedron Lett.* **2015**, *56*, 5896-5898; Demir, A. S.; Jeganathan, A.; Watt, D. S., *J. Org. Chem.* **1989**, *54*, 4020-4022.

Thanks for attention!

And

any questions?