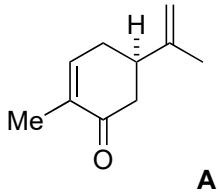
A Concise, Efficient and Scalable Total Synthesis of Thapsigargin and Nortilobide

Dezhi Chen and P. Andrew Evans, *J. Am. Chem. Soc.* **2017**, *139*, 6046 - 6049



A

Name of **A**?

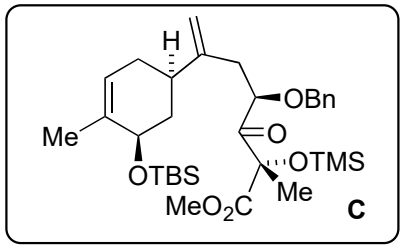
(*R*)-carvone

1-3

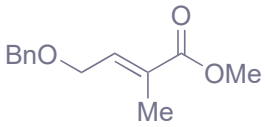
1) *t*BuOCl
2) DIBAL-H *then* TBSCl
3) $Pd_2(dba)_3$•$CHCl_3$, (*S*)-BINAP, LiCl, *then* **B**, LiHMDS

Mechanism of **step 3**?

See Below

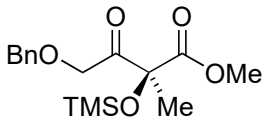


C



1) AD-mix β, $MeSO_2NH_2$
2) Swern, *then* TMSCl

B =



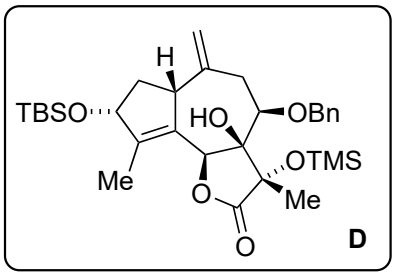
How would you synthesize this ketoester?

4-5

4) O_3, PPh_3, *then* piperidinium acetate
5) $VCl_3(THF)_3$, Zn, HMPA

Mechanism of step **5**? How do you explain the stereoselectivity?

See Below



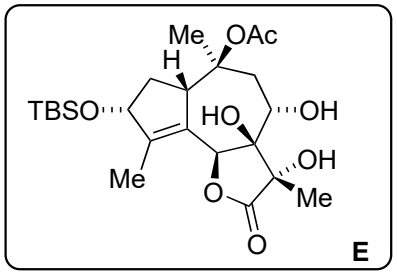
D

6-8

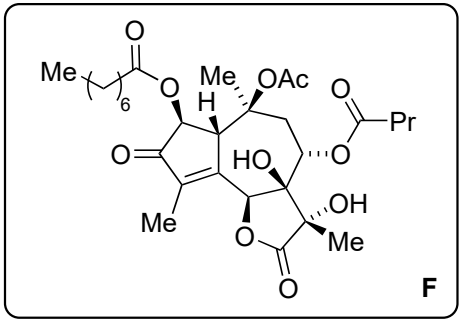
6) $Co(acac)_2$, $PhSiH_3$, O_2
7) Ac_2O, DMAP
8) $Pd(OH)_2/C$, H_2 *then* IBX, *then* $NaBH_4$

Mechanism of step **6**?

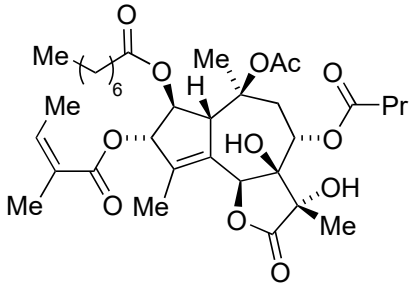
See Below



9-10



11-12



9) $(PrCO)_2O$, DMAP, *then* CrO_3
10) $Mn(OAc)_3$, $C_7H_{15}CO_2H$

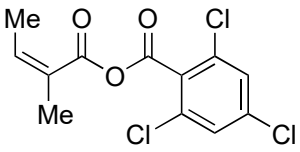
See Below

Mechanism of **step 10**?
What other conditions could accomplish the same transformation?

$KMnO_4$, $C_7H_{15}CO_2H$, $(C_7H_{15}CO)_2O$

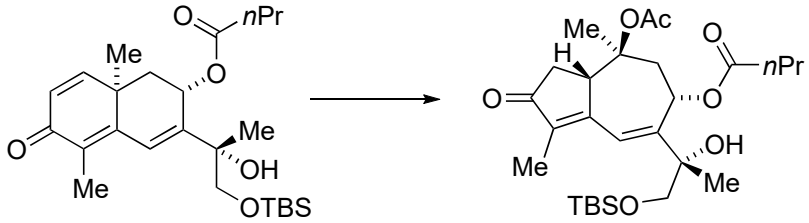
11) $Zn(BH_4)_2$
12) **G**, $NaHCO_3$

G =

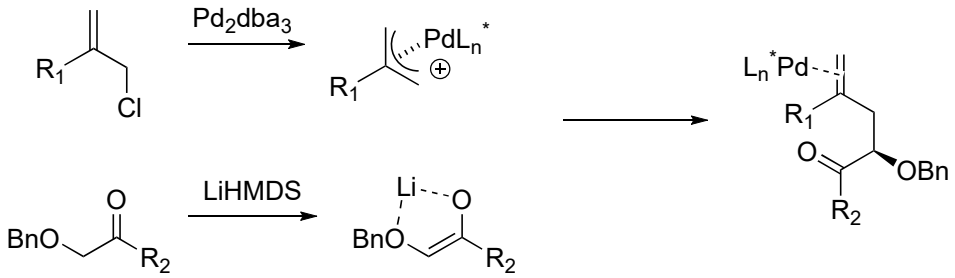


Bonus question - 'Thapsigargin Wars' Edition:
Some great chemistry from Baran and Massanet is featured in a competing short, scalable synthesis of (–)-thapsigargin (*ACS Cent. Sci.* **2017**, *3*, 47-51). What are the conditions and mechanism?

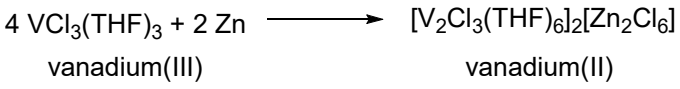
See Below

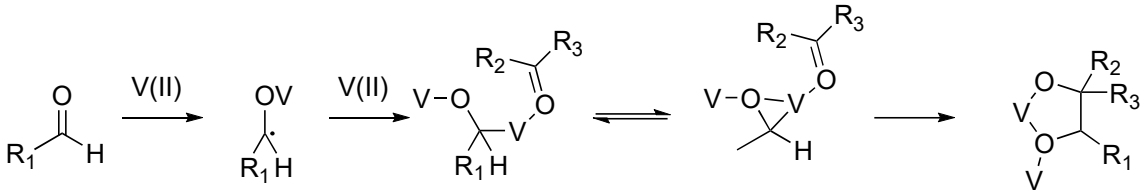


Mechanism of **step 3**



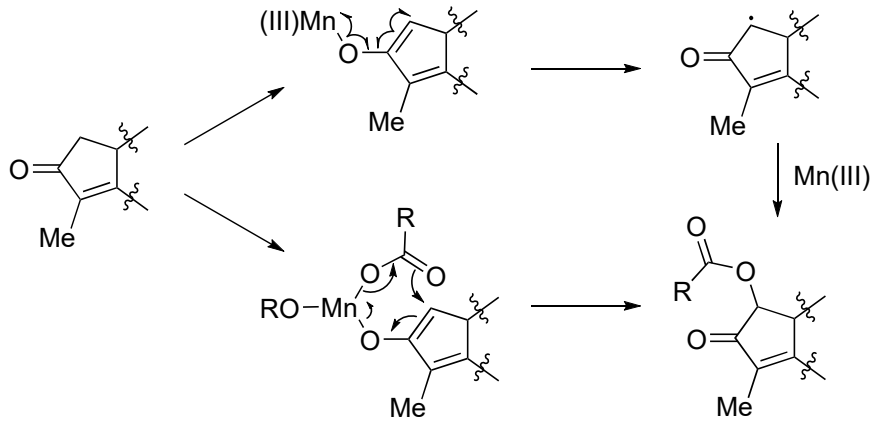
Mechanism of **step 5**



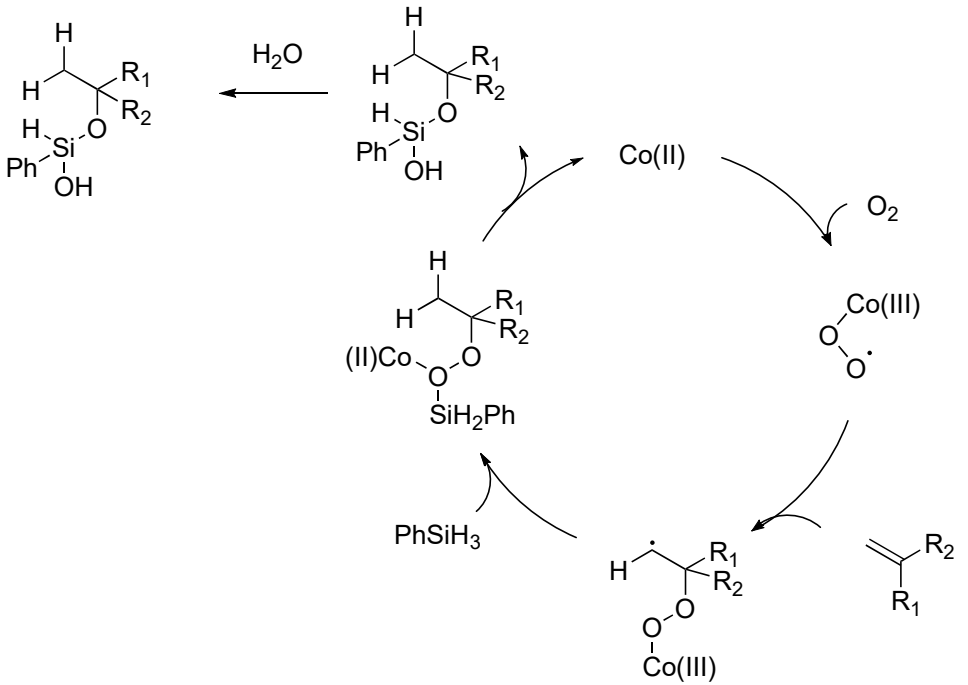


J. Am. Chem. Soc. **1989**, *111*, 8016-8018

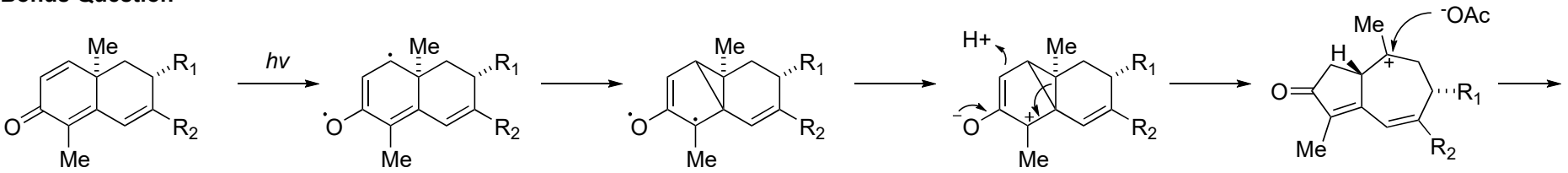
Mechanism of **step 10**



Mechanism of **step 6**



Bonus Question



JACS, **1967**, *89*, 906
J. Org. Chem. **1973**, *38*, 967