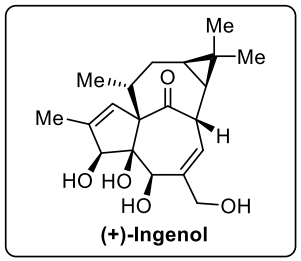
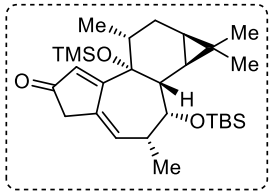
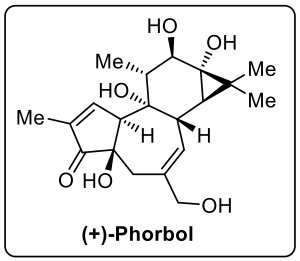


(+)-Ingenol

14-Step Synthesis of (+)-Ingenol
Lars Jørgensen, L.; McKerrall, S. J.; Kuttruff, C. A.; Ungeheuer, F.; Felding, J.; Baran, P. S.
Science **2013,** *341,* 878-882

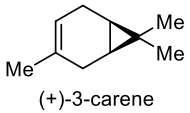


19-Step Total Synthesis of (+)-Phorbol
Kawamura, S.; Chu, H.; Felding, J.; Baran, P. S.
Nature **2016,** *532,* 90-93



(+)-Phorbol

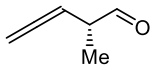
Synthesis of common intermediate:



(+)-3-carene

1. NCS, DMAP
2. O_3, thiourea

3. LiNap, HMPA, MeI, then
LiHMDS,

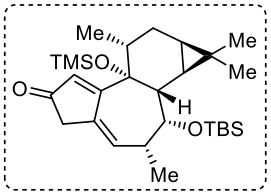


4.

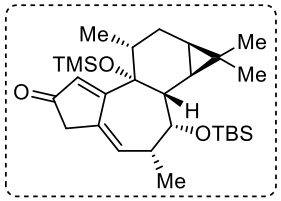
5. TBSOTf,
then TMSOTf

6. $[RhCl(CO)_2]_2$, CO

Name



Synthesis of Ingenol:



7. MeMgBr

8. OsO_4

9. CDI

10. $BF_3.Et_2O$

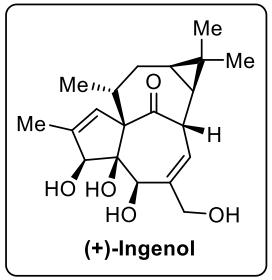
Name
Mechanism

11. SeO_2, then Ac_2O

12. HF

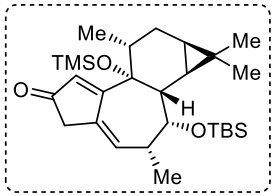
13. Martin's sulfurane then NaOH

14. SeO_2, HCO_2H



(+)-Ingenol

Synthesis of Phorbol:



7. $Mn(acac)_2$, O_2, $PhSiH_3$
then TMSOTf

Name

8. TFDO then
MgI_2, ZnI_2

Oxidation of a methylene carbon

9. $Mn(acac)_2$, O_2,
$PhSiH_3$, PPh_3

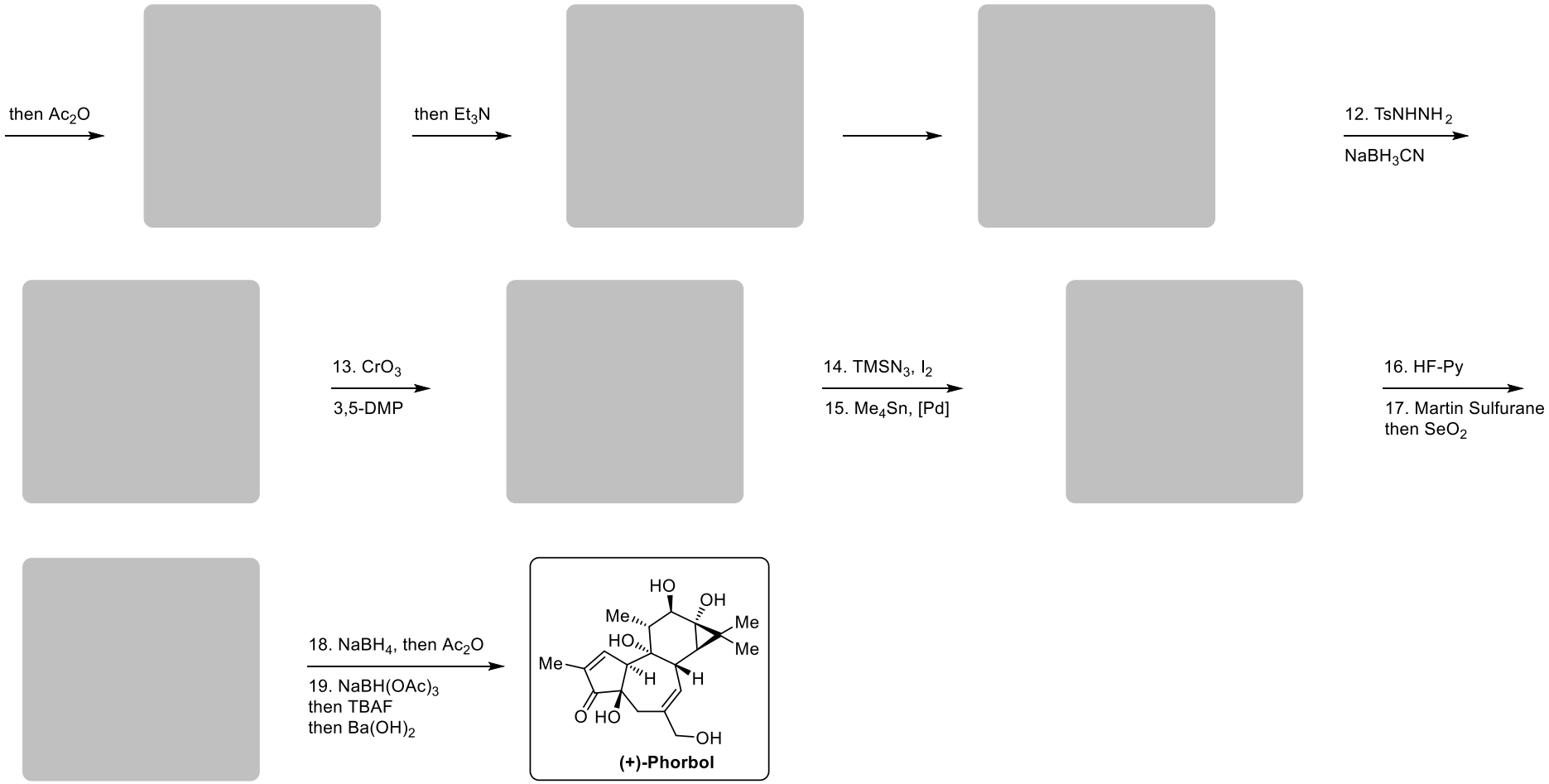
10. $RuCl_3$,
$NaBrO_3$

11. TFAA
then Zn

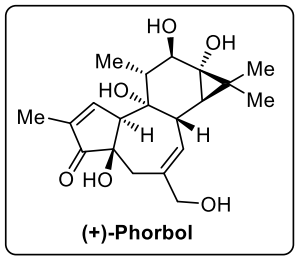
Unexpected C-C bond

$Sc(OTf)_3$

Undesired cyclobutanone

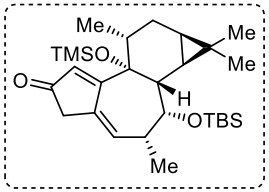

then Ac_2O
then Et_3N
12. $TsNHNH_2$
$NaBH_3CN$
13. CrO_3
3,5-DMP
14. $TMSN_3$, I_2
15. Me_4Sn, [Pd]
16. HF-Py
17. Martin Sulfurane
then SeO_2
18. $NaBH_4$, then Ac_2O
19. $NaBH(OAc)_3$
then TBAF
then $Ba(OH)_2$
HO
OH
Me
Me
HO
Me
Me
H
H
O HO
OH
(+)-Phorbol

Solutions

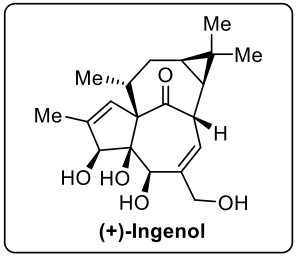


(+)-Phorbol

19-Step Total Synthesis of (+)-Phorbol
Kawamura, S.; Chu, H.; Felding, J.; Baran, P. S.
Nature **2016,** *532,* 90-93

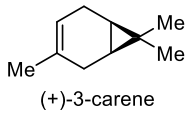


14-Step Synthesis of (+)-Ingenol
Lars Jørgensen, L.; McKerrall, S. J.; Kuttruff, C. A.; Ungeheuer, F.; Felding, J.; Baran, P. S.
Science **2013,** *341,* 878-882



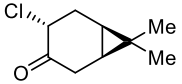
(+)-Ingenol

Synthesis of common intermediate:

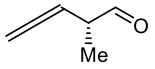


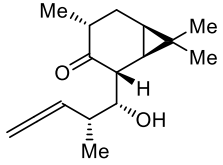
(+)-3-carene

1. NCS, DMAP
2. O_3, thiourea



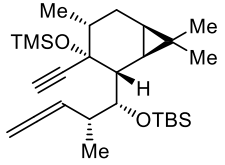
3. LiNap, HMPA, MeI, then LiHMDS,





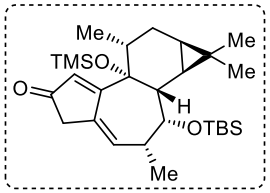
4.

5. TBSOTf, then TMSOTf

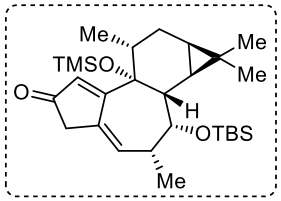


6. $[RhCl(CO)_2]_2$, CO

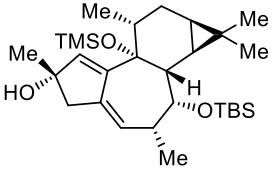
Name
Mechanism



Synthesis of Ingenol:

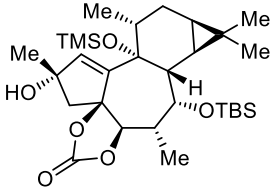


7. MeMgBr

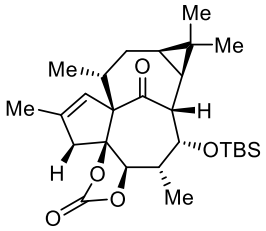


8. OsO_4

9. CDI



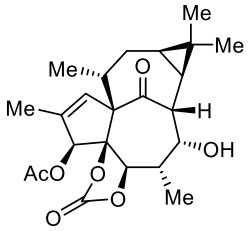
10. $BF_3.Et_2O$



Name
Mechanism

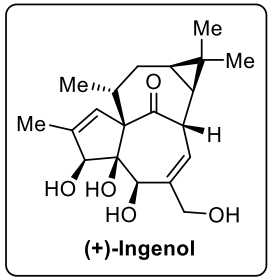
11. SeO_2, then Ac_2O

12. HF

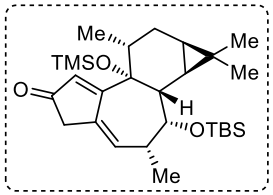


13. Martin's sulfurane then NaOH

14. SeO_2, HCO_2H



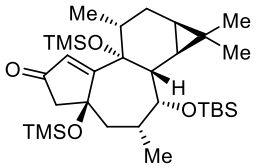
Synthesis of Phorbol:



Name
Mechanism

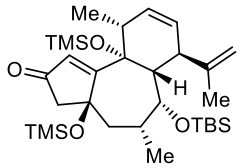
7. [Mn], O_2, $PhSiH_3$

then TMSOTf



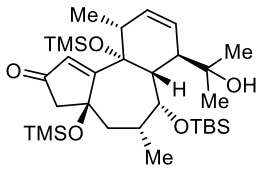
8. TFDO then

MgI_2, ZnI_2



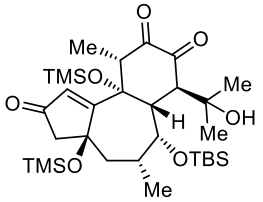
9. [Mn], O_2,

$PhSiH_3$, PPh_3



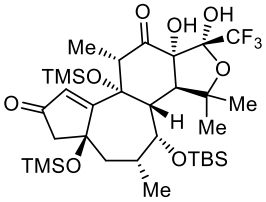
10. $RuCl_3$,

$NaBrO_3$



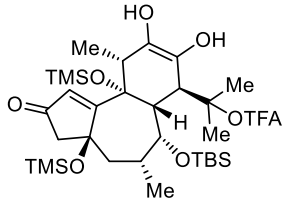
11. TFAA

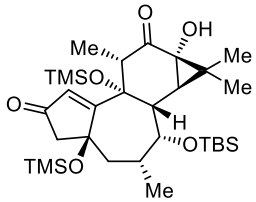
then Zn

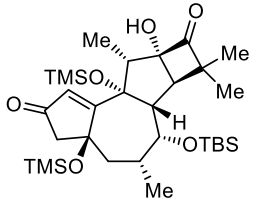


Hint: multistep reaction - after addition of Ac2O two new rings have formed - after Et3N cyclopropane ring formed again

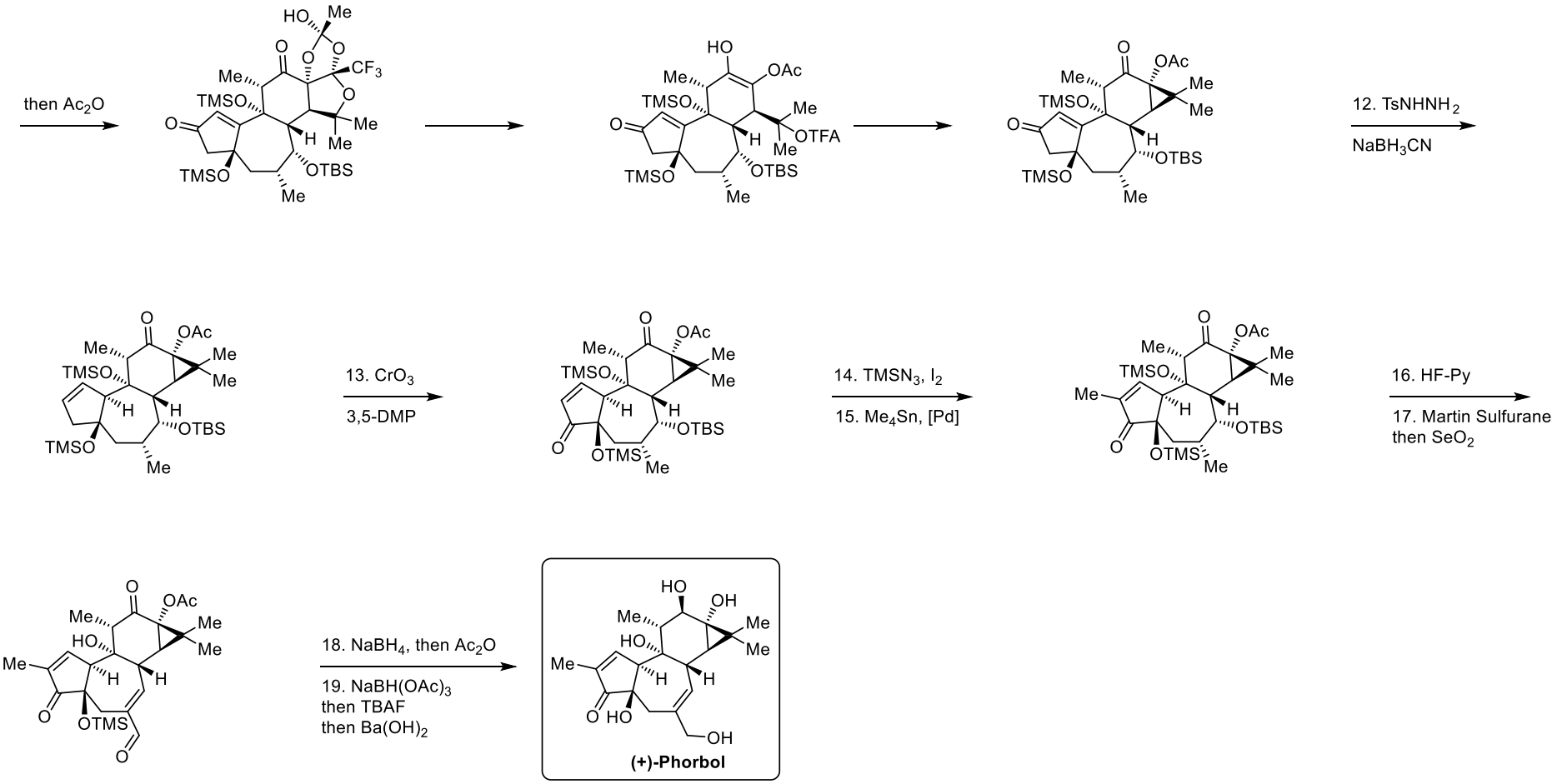
$Sc(OTf)_3$







Undesired cyclobutanone


then Ac_2O
12. $TsNHNH_2$
$NaBH_3CN$
13. CrO_3
3,5-DMP
14. $TMSN_3$, I_2
15. Me_4Sn, [Pd]
16. HF-Py
17. Martin Sulfurane
then SeO_2
18. $NaBH_4$, then Ac_2O
19. $NaBH(OAc)_3$
then TBAF
then $Ba(OH)_2$
(+)-Phorbol