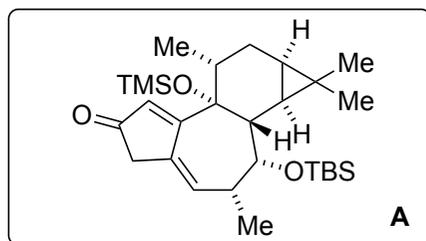
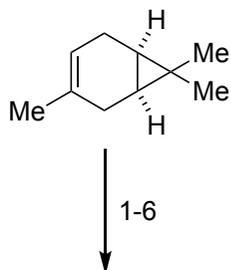


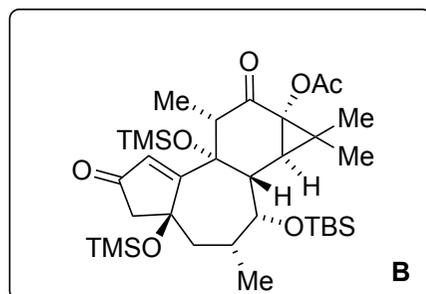
# Nineteen-Step Total Synthesis of (+)-Phorbol

Shuheï Kawamura, Hang Chu, Jakob Felding, Phil S. Baran

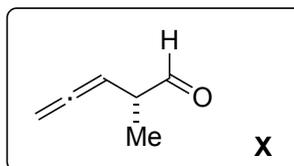
*Nature* **2016**, *532*, 90–93



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- 1) NCS, DMAP
- 2) O<sub>3</sub> then thiourea
- 3) LiNap then HMPA, MeI then LiHMDS, **X**
- 4) Ethynylmagnesium bromide
- 5) TBSOTf, Et<sub>3</sub>N then TMSOTf, Et<sub>3</sub>N
- 6) [RhCl(CO)<sub>2</sub>]<sub>2</sub>, CO



- 7) Mn(acac)<sub>2</sub>, O<sub>2</sub>, PhSiH<sub>3</sub>, PPh<sub>3</sub> then TMSOTf
- 8) TFDO then ZnI<sub>2</sub>, MgI<sub>2</sub>
- 9) Mn(acac)<sub>2</sub>, O<sub>2</sub>, PhSiH<sub>3</sub>, PPh<sub>3</sub>
- 10) RuCl<sub>3</sub>, NaBrO<sub>3</sub>
- 11) TFAA, DMAP then Zn, AcOH then Ac<sub>2</sub>O, DMAP then Et<sub>3</sub>N

What is the name of the starting material and how would you classify it?

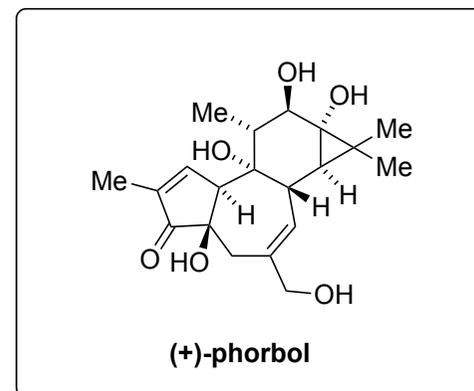
*(+)-3-Carene, a bicyclic monoterpene*

7) Name and mechanism of the reaction?

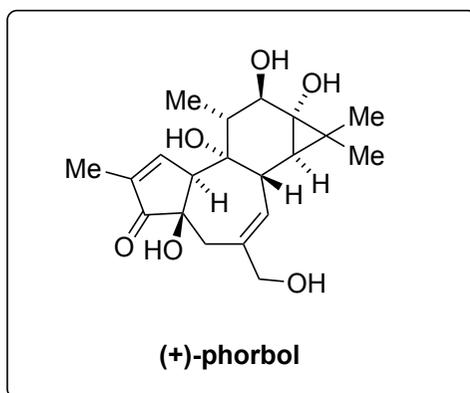
*Mukaiyama hydration (see below)*

8) Hint: TFDO oxidation of a methylene carbon

11) Hint: multistep reaction - after addition of Ac<sub>2</sub>O two new rings have formed - after Et<sub>3</sub>N cyclopropane ring formed again



12-19

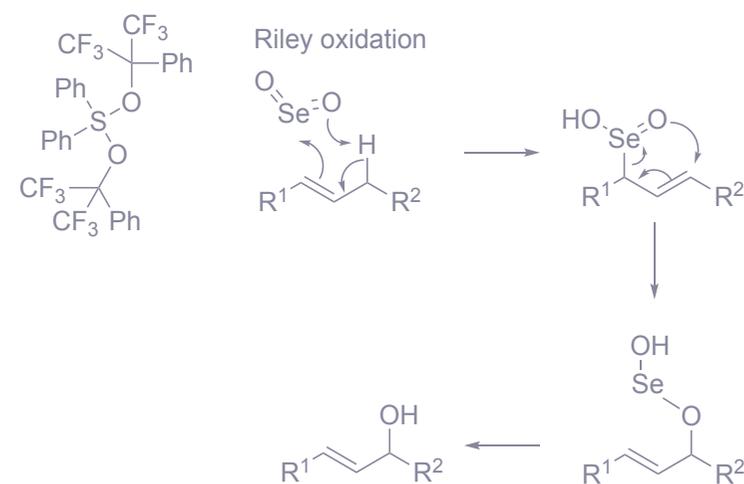


- 12)  $\text{TsNHNH}_2$  then  $\text{NaBH}_3\text{CN}$
- 13)  $\text{CrO}_3$ , 3,5-dimethylpyrazole
- 14)  $\text{TMSN}_3$  then  $\text{I}_2$ , pyridine
- 15)  $\text{Me}_4\text{Sn}$ ,  $\text{AsPh}_3$ ,  $\text{PdCl}_2(\text{PhCN})_2$ ,  $\text{CuI}$
- 16)  $\text{HF-Py}$
- 17) Martin sulfurane then  $\text{SeO}_2$
- 18)  $\text{NaBH}_4$  then  $\text{Ac}_2\text{O}$ , DMAP
- 19)  $\text{NaBH}(\text{OAc})_3$  then TBAF then  $\text{Ba}(\text{OH})_2$

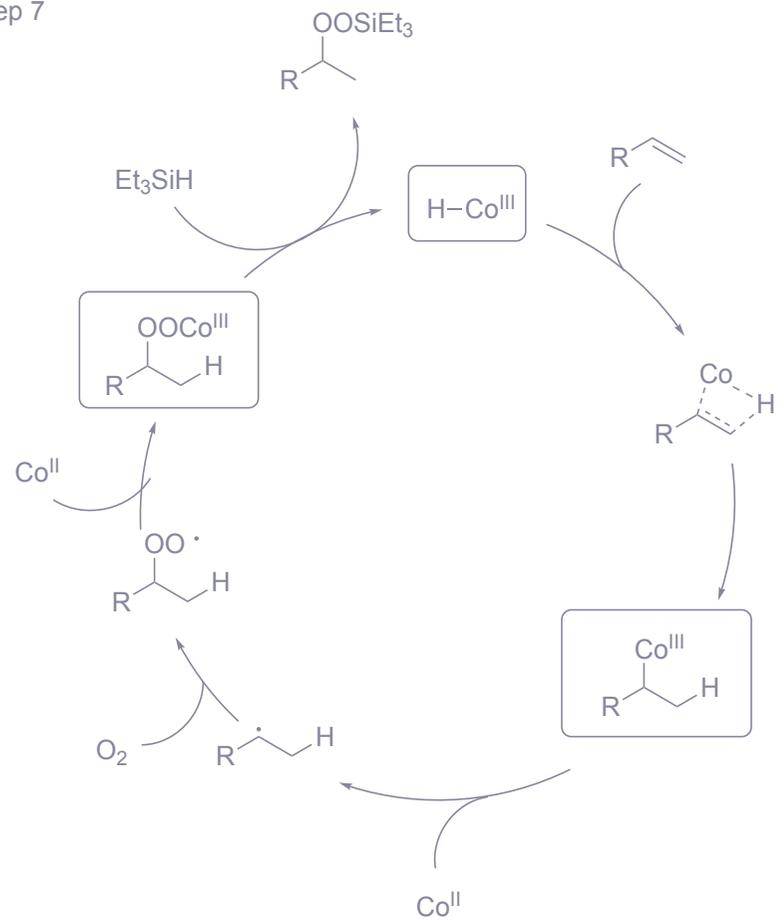
13) What is the role of 3,5-dimethylpyrazole?

*Complexation of  $\text{CrO}_3$  and abstraction of an allylic hydrogen atom*

17) Structure of Martin sulfurane? What name reaction is taking place in this step and what is the mechanism?



Step 7



*Org. Lett.* **2002**, 4, 21, 3595–3598