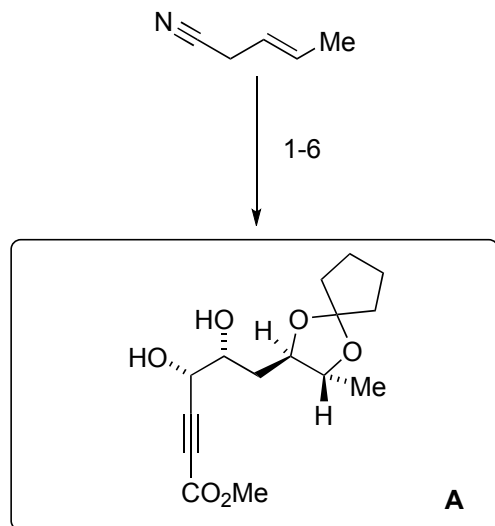


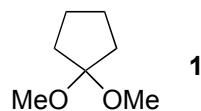
## Total Synthesis of Bryostatin 3

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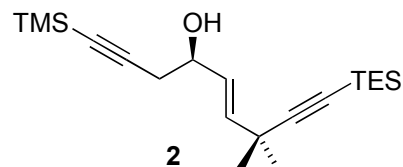


1. K<sub>2</sub>OsO<sub>4</sub>(H<sub>2</sub>O)<sub>2</sub> (1 mol%), (DHQD)<sub>2</sub>PHAL (2 mol%), K<sub>3</sub>Fe(CN)<sub>6</sub>, MeSO<sub>2</sub>NH<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>, NaHCO<sub>3</sub>
2. **1**, CSA, DCM
3. DIBAL-H, Et<sub>2</sub>O
4. [Ph<sub>3</sub>PCH<sub>2</sub>I], NaHMDS
5. methylpropiolate, LDA, then ZnBr<sub>2</sub>, PdCl<sub>2</sub>dppf (10 mol%)
6. K<sub>2</sub>OsO<sub>2</sub>(OH)<sub>4</sub> (25 mol%), (DHQ)<sub>2</sub>PHAL (60 mol%), K<sub>3</sub>Fe(CN)<sub>6</sub>, MeSO<sub>2</sub>NH<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>, NaHCO<sub>3</sub>

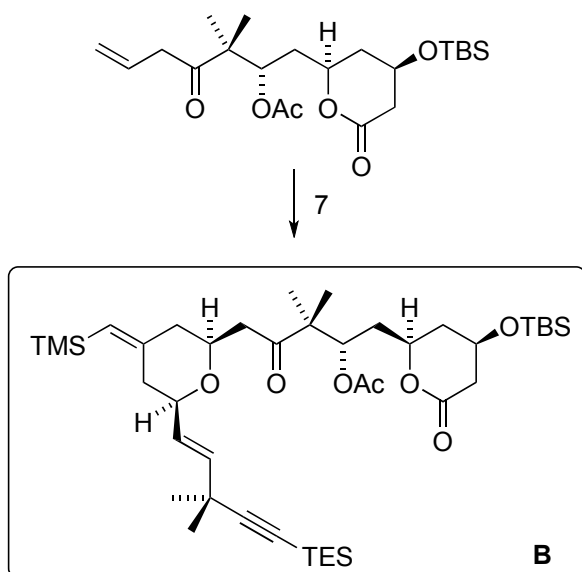


**1**

7. **2**, [CpRu(MeCN)<sub>3</sub>]PF<sub>6</sub> (10 mol%)



**2**



**B**

1. Name Reaction and reagent mixture

*hint: (R,R) product obtained*

*Sharpless asymmetric dihydrogenation*

*AD-mix β*

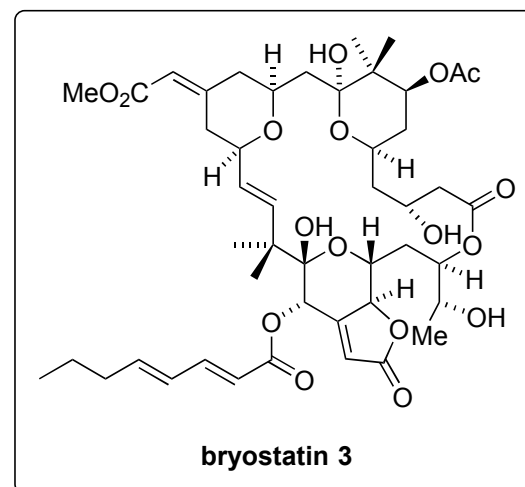
4. Name Reaction?

*Stork-modified Wittig Reaction*

6. Name reagent mixture

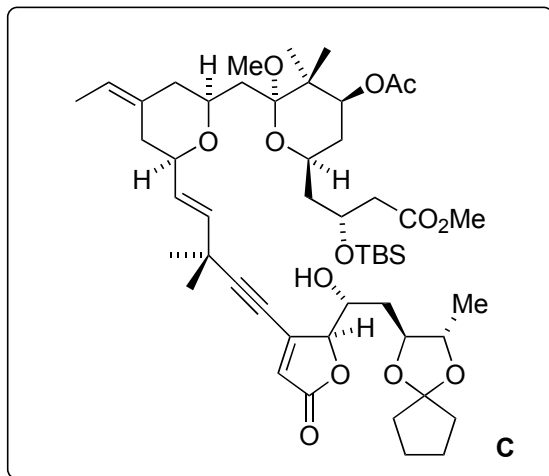
*AD-mix α*

7. *hint: ring formation; syn-addition favored*

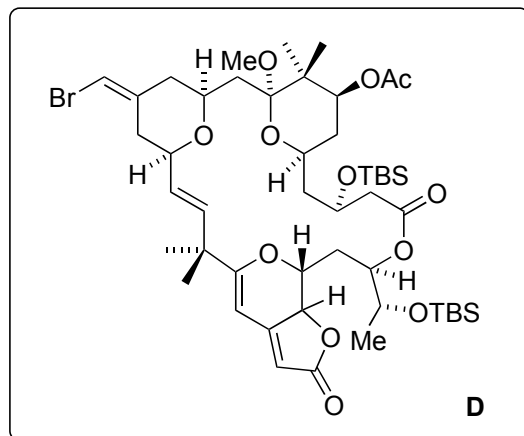


**bryostatin 3**

8-11



12-16



8. NBS, DMF
9. PPTS, MeOH
10. AgNO<sub>3</sub>, THF/H<sub>2</sub>O
11. **A**, Pd(OAc)<sub>2</sub> (5 mol%), TDMPP (7.5 mol%)  
benzene, inert conditions

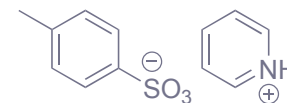
TDMPP = tris(2,6-dimethoxyphenyl)phosphine

12. AuCl(IPr) (10 mol%),  
AgSbF<sub>6</sub> (20 mol%), CH<sub>2</sub>Cl<sub>2</sub>, r.t.
13. ZrCl<sub>4</sub> (2.50 equiv), MeOH
14. TBSOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>,  
-78 °C, 15 min
15. Me<sub>3</sub>SnOH, DCE
16. 2,4,6-Cl<sub>3</sub>PhCOCl, Et<sub>3</sub>N, THF,  
then slow addition into DMAP, toluene

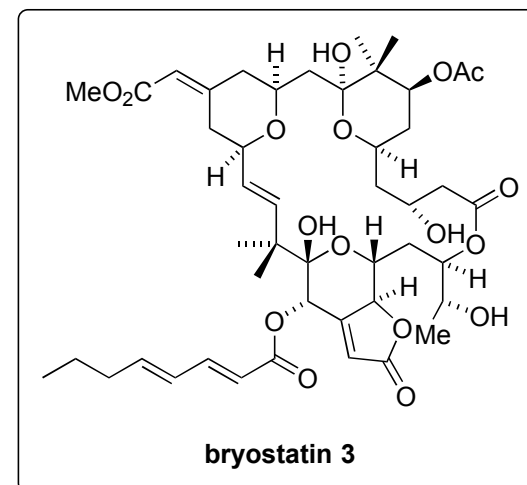
9. Structure of PPTS?
10. *hint: desilylation*
11. *hint: ring formation*

(intermediates of step 9  
shown on page 3)

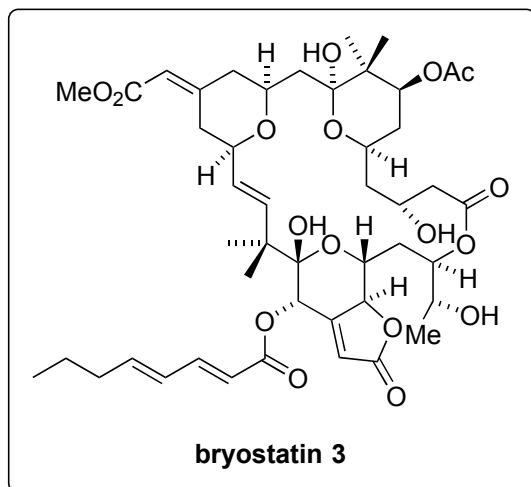
PPTS: pyridinium *p*-toluenesulfonate



12. Classify the cyclization with Baldwin's rules  
*6-endo-dig cyclization*
14. *hint: bis-silylated product obtained*
15. Who developed this chemistry?  
*K. C. Nicolaou*
16. Name Reaction?  
*Yamaguchi macrolactonization*



17-22



17. methylrhenum trioxide, UHP, 1-methylimidazole, MeOH
18. ClCH<sub>2</sub>CO<sub>2</sub>H, MeOH
19. 2,4-octadienoic anhydride, DMAP
20. Pd<sub>2</sub>(dba)<sub>3</sub>CHCl<sub>3</sub> (20 mol%), Xantphos (60 mol%), CO, *i*-Pr<sub>2</sub>NEt, DMF, MeOH
21. HF (aq.), MeCN
22. TFA, H<sub>2</sub>O, DCM

17. Name the conditions? *Yamazaki conditions*

18) *hint: anti-product favored*

*Intermediates in step 9:*

