Total Synthesis of Bryostatin 3

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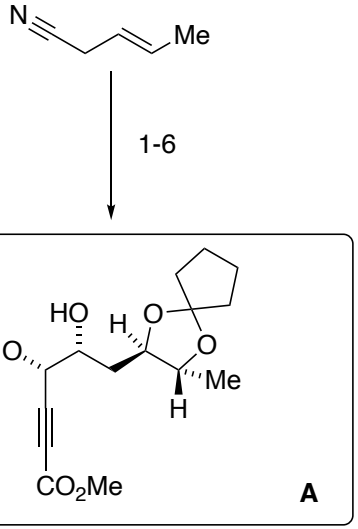

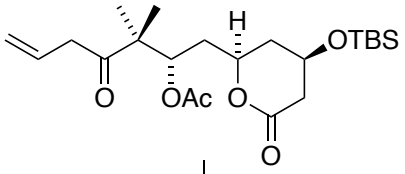

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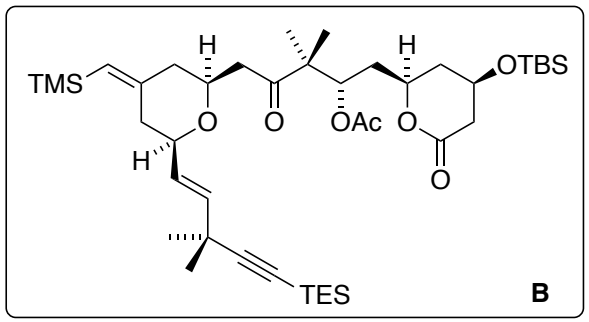
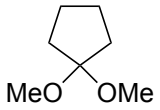


1. $K_2OsO_4(H_2O)_2$ (1 mol%),
   $(DHQD)_2PHAL$ (2 mol%),
   $K_3Fe(CN)_6$, $MeSO_2NH_2$, K_2CO_3, $NaHCO_3$
2. **1**, CSA, DCM
3. DIBAL-H, Et_2O
4. $[Ph_3PCH_2I]I$, NaHMDS
5. methylpropiolate, LDA,
   then $ZnBr_2$, $PdCl_2dppf$ (10 mol%)
6. $K_2OsO_2(OH)_4$ (25 mol%),
   $(DHQ)_2PHAL$ (60 mol%),
   $K_3Fe(CN)_6$, $MeSO_2NH_2$, K_2CO_3, $NaHCO_3$



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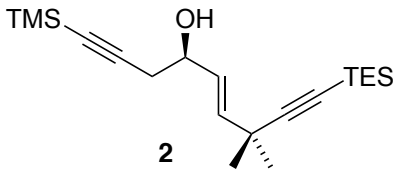
7. **2**, $[CpRu(MeCN)_3]PF_6$ (10 mol%)



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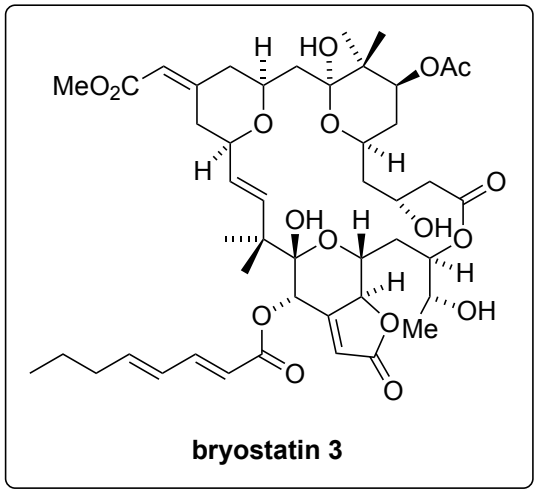
1. Name Reaction and reagent mixture
hint: (*R*,*R*) product obtained
Sharpless asymmetric dihydrogenation
AD-mix β

4. Name Reaction?
Stork-modified Wittig Reaction

6. Name reagent mixture
AD-mix α

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



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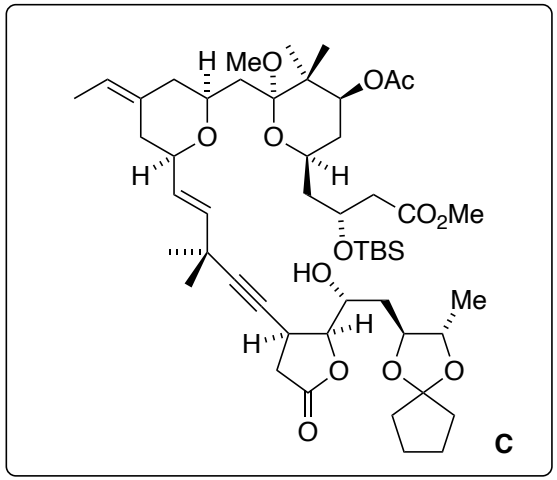

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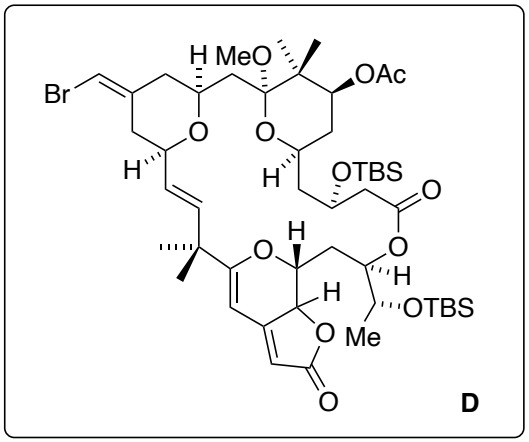


8. NBS, DMF
9. PPTS, MeOH
10. $AgNO_3$, THF/H_2O
11. **A**, $Pd(OAc)_2$ (5 mol%), TDMPP (7.5 mol%) benzene, inert conditions

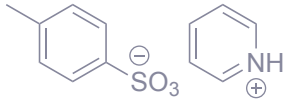
TDMPP = tris(2,6-dimethoxyphenyl)phosphine

12. AuCl(IPr) (10 mol%), $AgSbF_6$ (20 mol%), CH_2Cl_2, r.t.
13. $ZrCl_4$ (2.50 equiv), MeOH
14. TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 15 min
15. Me_3SnOH, DCE
16. 2,4,6-$Cl_3PhCOCl$, Et_3N, THF, *then* slow addition into DMAP, toluene

(intermediates of step 9 shown on page 3)

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

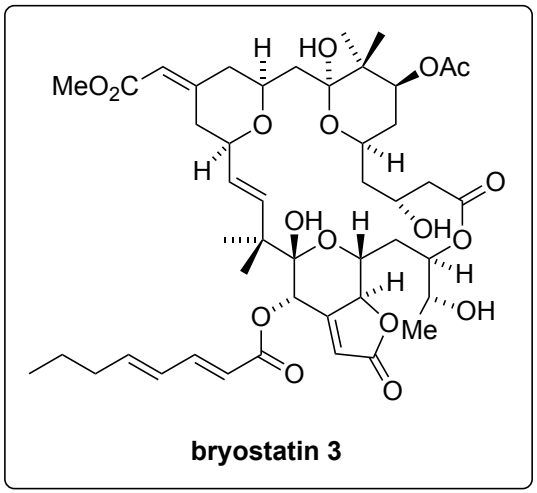
PPTS: pyridinium p-toluenesulfonate



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



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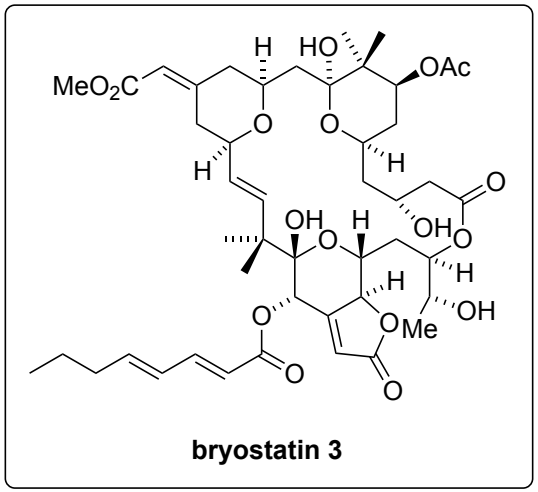

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17. methylrhenium troxide, UHP, 1-methylimidazole, MeOH
18. $ClCH_2CO_2H$, MeOH
19. 2,4-octadienoic anhydride, DMAP
20. $Pd_2(dba)_3CHCl_3$ (20 mol%), Xantphos (60 mol%), CO, *i*-Pr_2NEt DMF, MeOH
21. HF (aq.), MeCN
22. TFA, H_2O, DCM

17. Name the conditions? *Yamazaki conditions*

18) *hint: anti-product favored*

Intermediates in step 9: