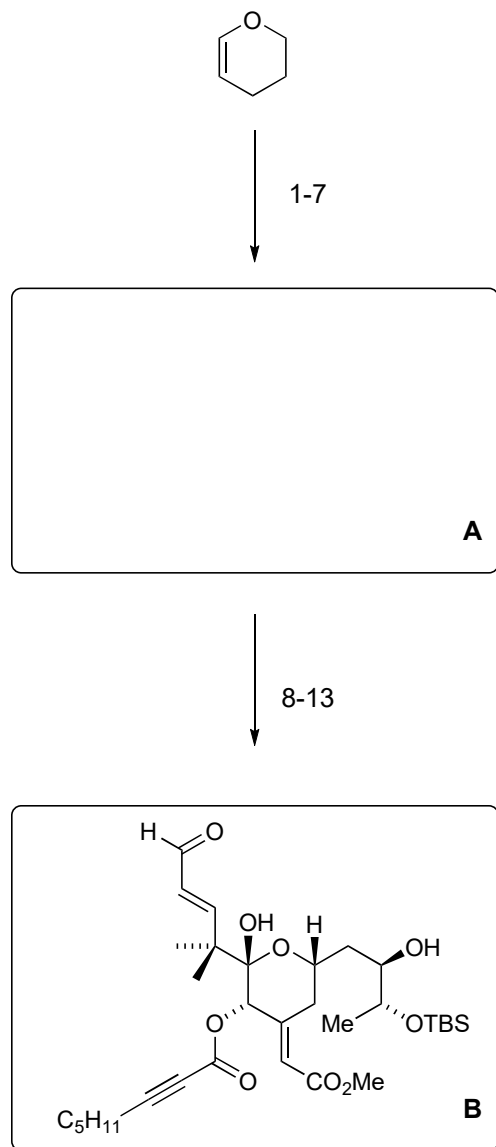


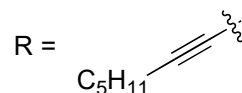
Total Synthesis of Bryostatin 1

Paul A. Wender, Clayton T. Hardman, Stephen Ho, Matthew S. Jeffreys, Jana K. Maclaren, Ryan V. Quiroz, Steven M. Ryckbosch, Akira J. Shimizu, Jack L. Sloane, Matthew C. Stevens

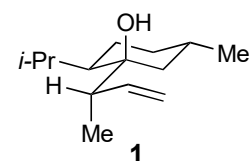
Science **2017**, *358*, 218-223



- 1) aq. NH_4Cl
then Zn powder, prenyl bromide, THF
- 2) $(\text{COCl})_2$, DMSO, CH_2Cl_2 , -78°C
then **substrate**, Et_3N , -78° to -30°C
- 3) **1**, $p\text{-TsOH}\cdot\text{H}_2\text{O}$, CHCl_3
then 4 Å molecular sieves, 70°C
then **2**, NaHCO_3 , MeOH
- 4) DMP, pyridine, CH_2Cl_2 , 0°C
- 5) glyoxylate **3**, K_2CO_3 , THF/MeOH
- 6) $\text{CeCl}_3\cdot 7\text{H}_2\text{O}$, NaBH_4 , MeOH, -50°C
- 7) $(\text{RCO})_2\text{O}$, DMPA, CH_2Cl_2 , -20° to 0°C

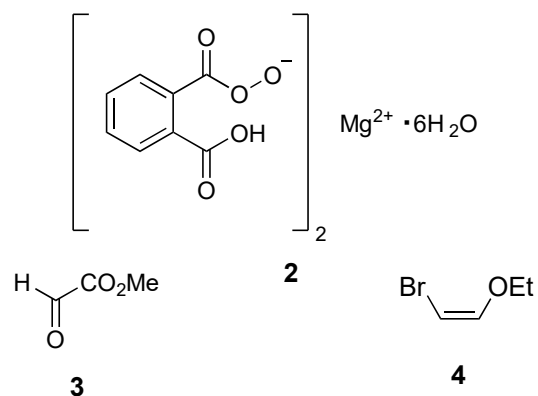


- 8) $\text{K}_2\text{OsO}_2(\text{OH})_4$ (1.0 mol%),
 $(\text{DHQD})_2\text{PHAL}$ (5.0 mol%), $\text{K}_3\text{Fe}(\text{CN})_6$,
 K_2CO_3 , MeSO_2NH_2 , $t\text{-BuOH}/\text{H}_2\text{O}$ (1:1)
- 9) 2,2-dimethoxypropane, PPTS, CH_2Cl_2
- 10) O_3 , CH_2Cl_2 , then thiourea, $i\text{-PrOH}$
- 11) **4**, $t\text{-BuLi}$, Me_2Zn , Et_2O , -78°C
then **substrate**; then aq. 1.0 M HCl
- 12) $p\text{-TsOH}\cdot\text{H}_2\text{O}$, $\text{MeCN}/\text{H}_2\text{O}$ (4:1), r.t. to 45°C
- 13) TBS-Cl, imidazole, DMF

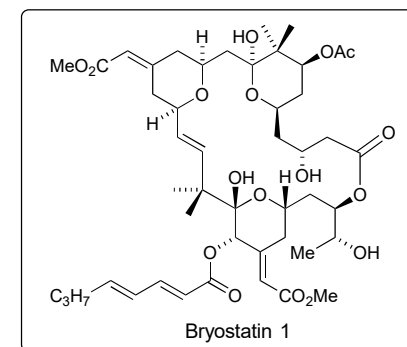


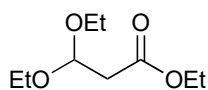
2) Name reaction?

3) Name reaction? Mechanism? Please explain the stereochemical outcome. How would you synthesis **1**?

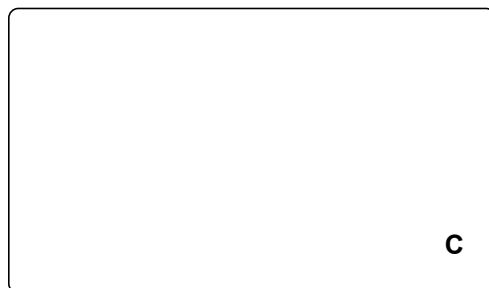


8) Name reaction?

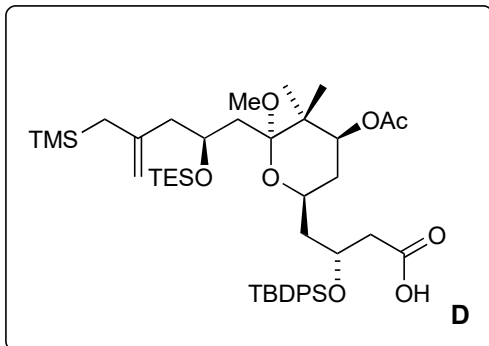




14-20

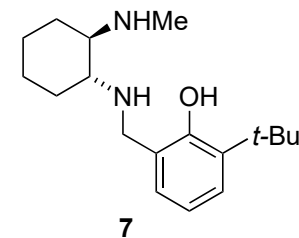
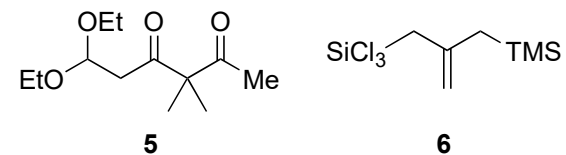


21-23



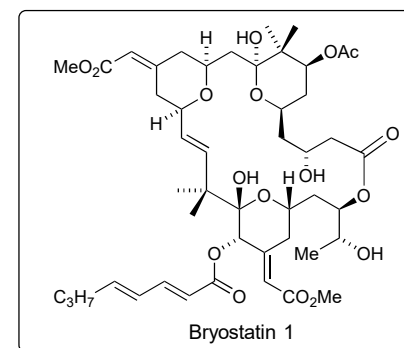
- 14) LDA, MeCO₂*t*-Bu, THF, -78 °C to r.t.
- 15) (*R*)-BINAP-RuCl₂ (0.4 mol%), H₂ (650 psi)
then H₂SO₄ (7.5 mol%), 60 °C
- 16) TBDPS-Cl, imidazole, CH₂Cl₂
then aq. TFA
- 17) **5**, Et₂B-OTf, DIPEA, Et₂O, then **substrate**
- 18) NaBH(OAc)₃, MeCN/acetone/AcOH, 0 °C to r.t.
- 19) PPTS, MeOH/CH(OMe)₃
- 20) Ac₂O, DMAP, 2,4,6-collidine, CH₂Cl₂
then TES-OTf; then H₂O, -40 ° to 0 °C

- 21) Silane **6**, diaminophenol **7**, DBU, CH₂Cl₂
then **substrate**; then TBAF
- 22) TES-Cl, imidazole, CH₂Cl₂, 0 °C
- 23) Me₃Sn-OH, toluene, 85 °C
then Ac₂O, DMAP, 0 °C



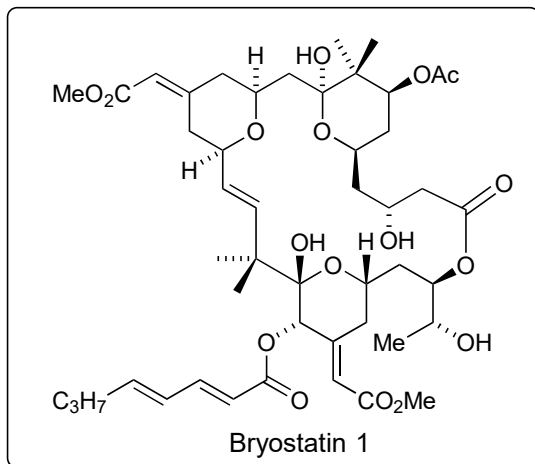
- 15) Catalyst name? Mechanism?
- 18) Name reaction? Mechanism?

- 21) Name reaction?

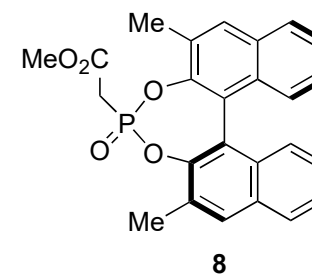


B + D

24-29



- 24) **D**, 2,4,6-trichlorobenzoyl chloride, Et₃N
then **B**, DMAP
- 25) PPTS (30 mol%), MeOH/CH(OMe)₃ (50:1)
- 26) O₃, MeOH/CH₂Cl₂, -78 °C
then Ph₃P, -78 °C to r.t.
- 27) PPh₃, 2,4,6-trimethylphenol, benzene
- 28) Phosphonate **8**, NaHMDS, THF, -78 °C
- 29) HF-pyridine/pyridine/THF (1:2:2), 40 °C
then H₂O, 40 °C



- 24) Name reaction?
- 25) Name reaction?
- 27) Mechanism?