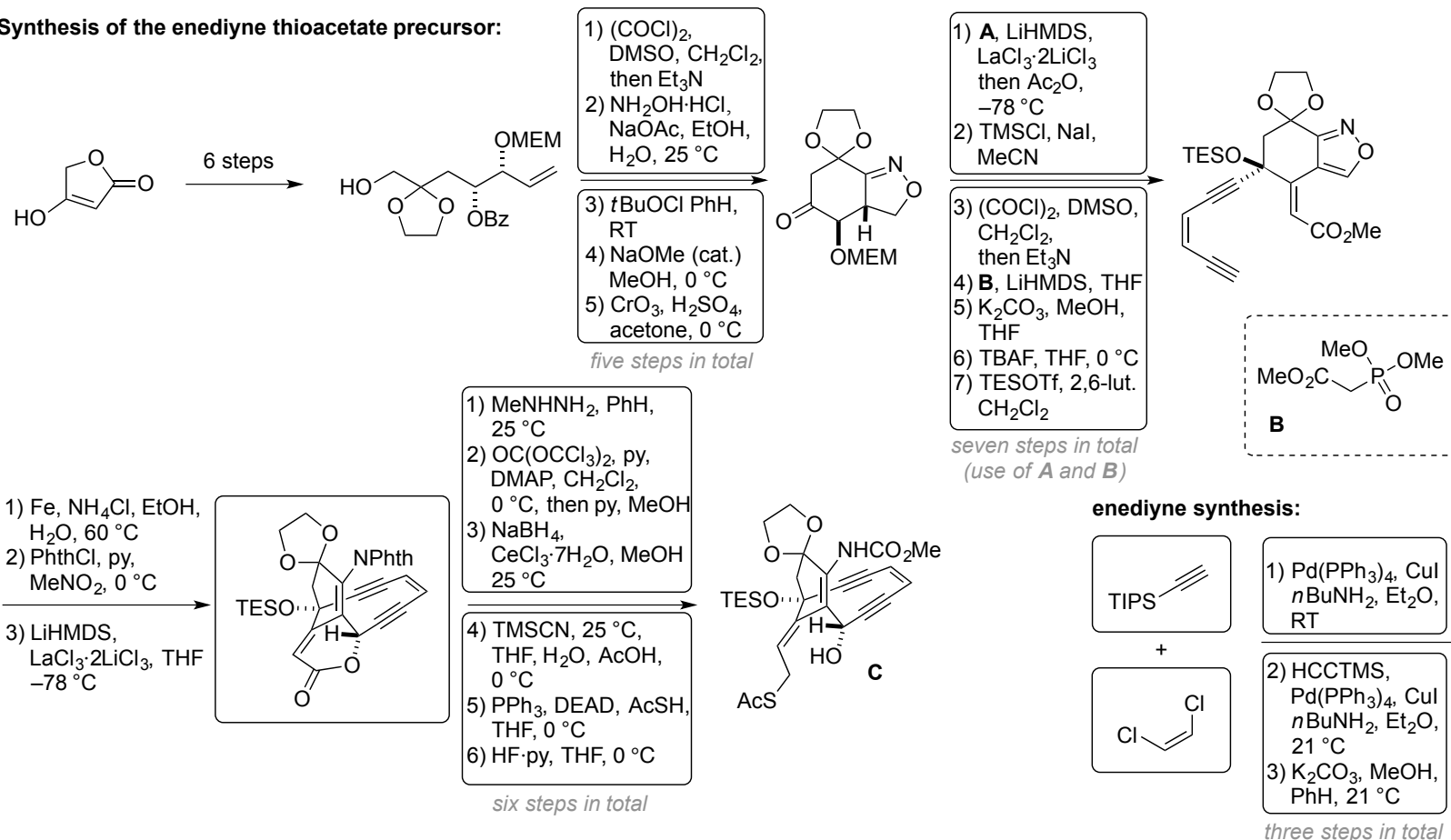


Solution E17: Total Synthesis of Shishijimicin A^[1-4]

Synthesis of the enediyne thioacetate precursor:



- Shishijimicin A is a rare marine natural product with extreme antitumor properties ($\text{IC}_{50} = 0.48 \text{ pM}$ against P388 leukemia cells)
- Similar to calicheamicin γ_1 the mode of action involves a Bergmann-cycloaromatization, enabling cleavage of double-stranded DNA
- Total synthesis should yield enough material to investigate the compound in depth (e.g. for antibody-drug conjugate formation)

[1] K.C. Nicolaou, Z. Lu, R. Li, J. R. Woods, T. Sohn, *J. Am. Chem. Soc.* **2015**, *137*, 8716–8719.

[2] A. L. Smith, E. N. Pitsinos, C. K. Hwang, Y. Mizuno, H. Saimoto, G. R. Scarlato, T. Suzuki, K. C. Nicolaou, *J. Am. Chem. Soc.* **1993**, *115*, 7612–7624.

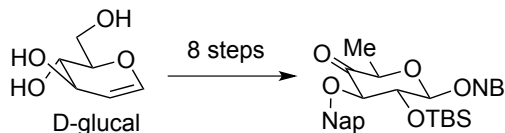
[3] Y.-F. Lu, C. W. Harwig, A. G. Fallis, *Can. J. Chem.* **1995**, *73*, 2253–2262.

[4] Y. Schott, M. Decker, H. Rommelspacher, J. Lehmann, *Bioorg. Chem. Lett.* **2006**, *16*, 5840

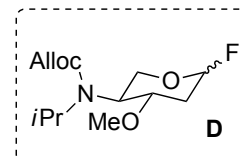
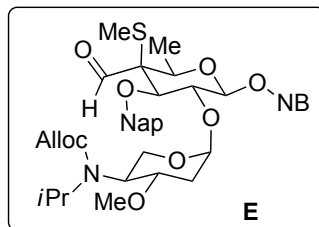


Solution E17: Total Synthesis of Shishijimicin A^[1-4]

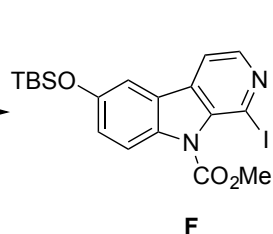
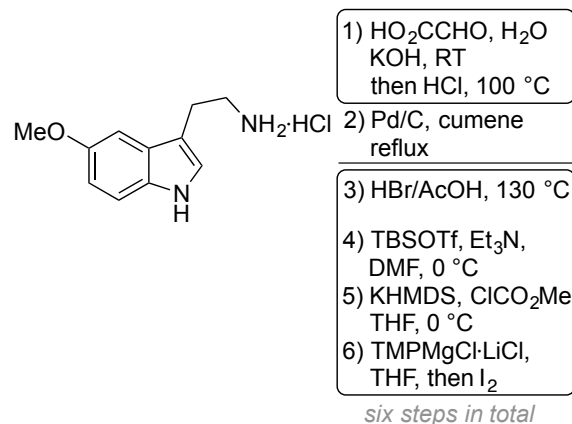
Disaccharide construction:



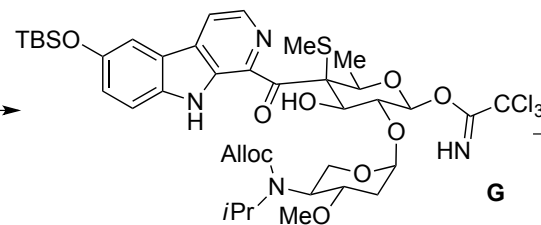
- 1) TMSMe (2.5 equiv), TMSOTf (1.5 equiv.), PhMe
- 2) TMSCN, SnCl₄, CH₂Cl₂, 0 °C (9:1 dr)
- 3) TBAF, NH₄F, THF, 0 °C
- 4) **D**, AgClO₄, SnCl₂, 4 Å MS, THF
- 5) DIBAL-H, CH₂Cl₂, -78 °C



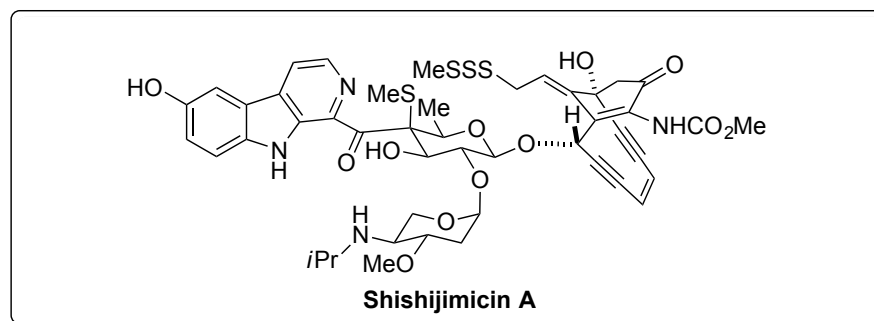
Assembly of the natural product:



6 Steps
using **E**



- 1) **C**, BF₃·Et₂O, 4 Å MS, CH₂Cl₂
- 2) KOH, MeOH, -5 °C, then AcOH
- 3) PhthNSSMe, CH₂Cl₂, 0 °C
- 4) HF·py, THF
- 5) Pd(PPh₃)₄, morpholine, THF, 0 °C
- 6) *p*-TSA, THF, acetone, H₂O



[1] K.C. Nicolaou, Z. Lu, R. Li, J. R. Woods, T. Sohn, *J. Am. Chem. Soc.* **2015**, *137*, 8716–8719.

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