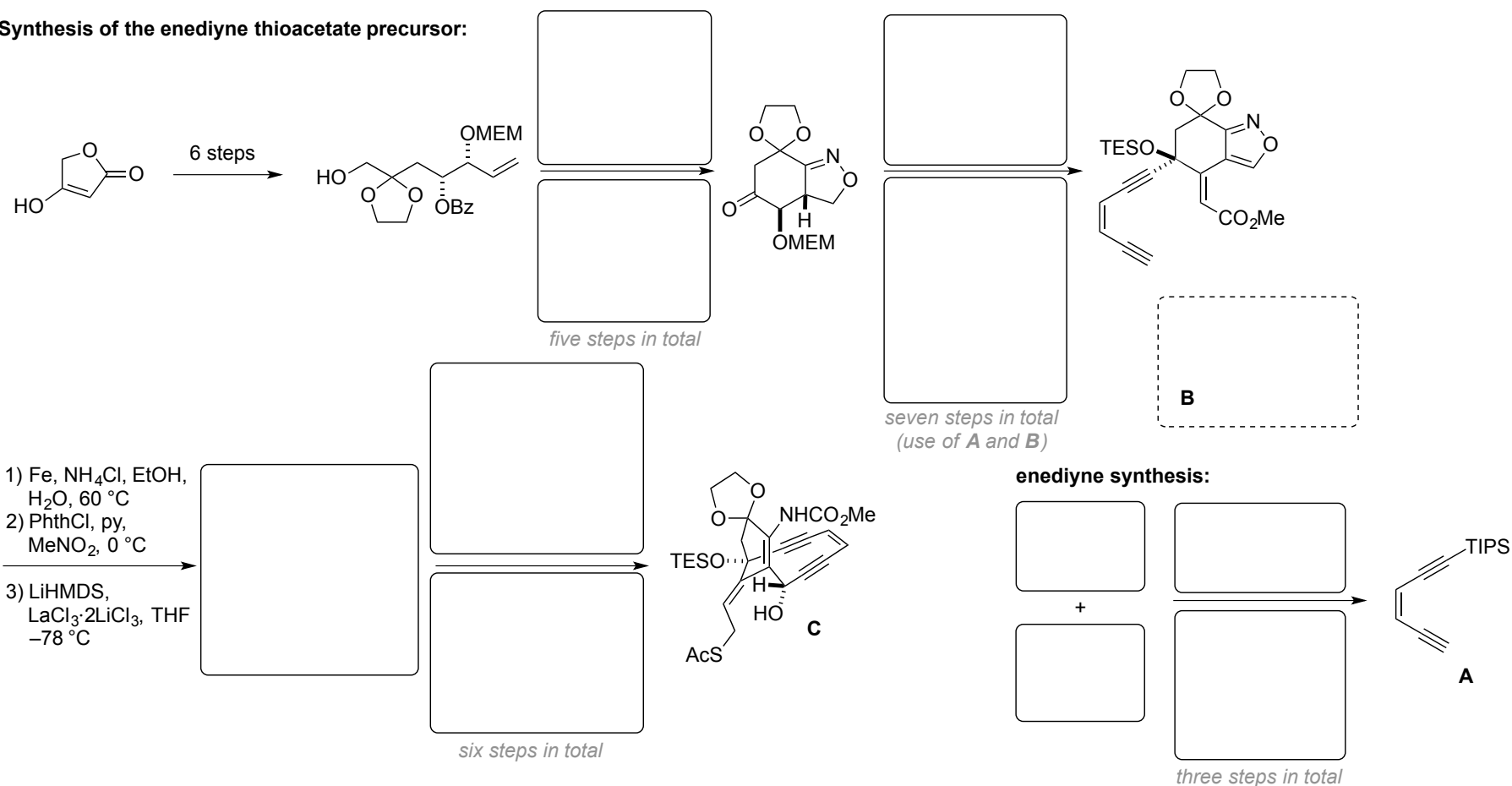


# E17: Total Synthesis of Shishijimicin A<sup>[1-4]</sup>

## Synthesis of the enediyne thioacetate precursor:



- Shishijimicin A is a rare marine natural product with extreme antitumor properties (IC<sub>50</sub> = 0.48 pM against P388 leukemia cells)
- Similar to calicheamicin  $\gamma_1$  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.

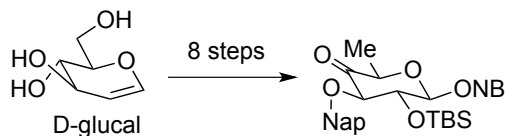
[2] A. L. Smith, E. N. Pitsinos, C. K. Hwang, Y. Mizuno, H. Saimoto, G. R. Scarlato, T. Suzuki, K. C. Nicolaou, *J. Am. Chem. Soc.* **1993**, *115*, 7612–7624.

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

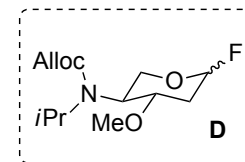
[4] Y. Schott, M. Decker, H. Rommelspacher, J. Lehmann, *Bioorg. Chem. Lett.* **2006**, *16*, 5840

# E17: Total Synthesis of Shishijimicin A<sup>[1-4]</sup>

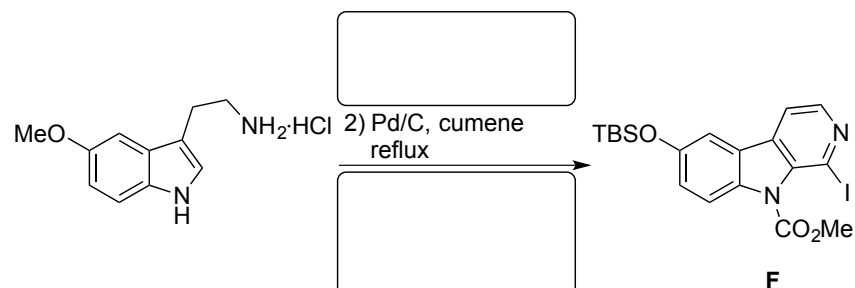
## Disaccharide construction:



- 1) TMSSMe (2.5 equiv), TMSOTf (1.5 equiv.), PhMe
- 2) TMSCN, SnCl<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C (9:1 dr)
- 3) TBAF, NH<sub>4</sub>F, THF, 0 °C
- 4) **D**, AgClO<sub>4</sub>, SnCl<sub>2</sub>, 4 Å MS, THF
- 5) DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C

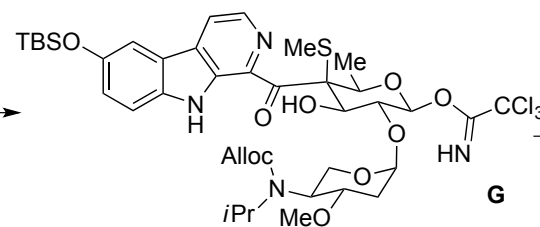


## Assembly of the natural product:



six steps in total

6 Steps  
using **E**



- 1) **C**, BF<sub>3</sub>·Et<sub>2</sub>O, 4 Å MS, CH<sub>2</sub>Cl<sub>2</sub>
- 2) KOH, MeOH, -5 °C, then AcOH
- 3) PhthNSSMe, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C
- 4) HF·py, THF
- 5) Pd(PPh<sub>3</sub>)<sub>4</sub>, morpholine, THF, 0 °C
- 6) *p*-TSA, THF, acetone, H<sub>2</sub>O

**Shishijimicin A**

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

<sup>[2]</sup> 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.

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

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