A Highly Convergent Total Synthesis of Leustroducsin B

- Isolated from a culture broth of soil bacterium Streptomyces Platensis in 1993
- Antibacterial, antifungal, antitumor activity:
  * Inhibition of protein serine/threonine phosphatase 2A (which regulates cell growth and inhibits metastasis)
  * Produces increased in vivo resistance to E. coli infections.

Shortest prior total synthesis: 37 linear and 64 total steps!!

**Exercise 1: General strategy.** Think like Trost! Identify the two main disconnections, which leads to fragments 2, 3, 4.
(Hint: reason broadly and not stepwise - there are 9 steps between 1 and 2, 3, 4)

2  3  4

**Exercise 2: Synthesis of fragment 2 (Ask Julien for help for red parts)**

2 steps:
Provide conditions
Model for selectivity
Decomposed if concentrated (used as a solution)
Exercise 3: Synthesis of fragment 3 (Ask Julien for help for red parts)

1. (R,R)-Noyori cat. iPrOH
2. TBSCI, imidazole
3. PMB-CH₂Cl, DIPEA
3. AcOH, H₂O, Me₂CO then NaN₃

Exercise 4: Synthesis of fragment 4

1. BnOH tBuOK cat.
2. Cl⁺CO₂Me, TEA
3. 5, (S,S)-Trost Ligand cat.
   (η₃-C₃H₅PdCl)₂ cat.
   NaH, Hex₃NB₃
3. DMP
4. Stork-Zhao olefination
Exercises 5, 6, 7 (based on the remaining time)

Propose a synthetic route for 5

1. DDQ in wet DCM
2. 6, tetrazole then tBuOOH

Leustroducsin B

3. Staudinger, then AllocCl
4. Pd(PPh₃)₄ cat. HCO₂H, TEA

1. PCC
2. TEA +
3. 4, Pd₂dba₃, TBAF, AcOH
4. TESOTf, lutidine then TMSOTf
A Highly Convergent Total Synthesis of Leustroducin B

- Isolated from a culture broth of soil bacterium *Streptomyces Platensis* in 1993
- Antibacterial, antifungal, antitumor activity:
  * Inhibition of protein serine/threonine phosphatase 2A (which regulates cell growth and inhibits metastasis)
  * Produces increased in vivo resistance to *E. coli* infections.

Shortest prior total synthesis: 37 linear and 64 total steps!!

**Exercise 1:** General strategy. Think like Trost! Identify the two main disconnections, which leads to fragments 2, 3, 4.
(Hint: reason broadly and not stepwise - there are 9 steps between 1 and 2, 3, 4)

**Exercise 2:** Synthesis of fragment 2 (Ask Julien for help for red parts)

Decomposed if concentrated
(used as a solution)
Exercise 3: Synthesis of fragment 3 (Ask Julien for help for red parts)

1. (R,R)-Noyori cat.
   iPrOH
2. TBSCI, imidazole
3. PMB-CH₂Cl, DIPEA
3. AcOH, H₂O, Me₂CO
   then NaN₃

Exercise 4: Synthesis of fragment 4

1. BnOH
tBuOK cat.
2. ClCO₂Me, TEA
3. 5. (S,S)-Trost Ligand cat.
   (η₃-C₃H₅PdCl)₂ cat.
   NaH, Hex₃NBr
4. 4. Stork-Zhao olefination

?? → HO₂C₇

1. H₂, Pd/C
2. BH₃•SMe₂
3. DMP

5HO

O
Me
Exercises 5, 6, 7 (based on the remaining time)

Propose a synthetic route for 5

2 → OTBS
THF, -78 °C for 10 min.
then 3 in DCM
-78 °C for 9 hours

1. PCC
2. TEA +
3. 4, Pd$_2$dba$_3$, TBAF, AcOH
4. TESOTf, lutidine
then TMSOTf

1. DDQ in wet DCM
2. 6, tetrazole
then tBuOOH

3. Staudinger, then AllocCl
4. Pd(PPh$_3$)$_4$ cat.
HCO$_2$H, TEA

Leustroducsin B