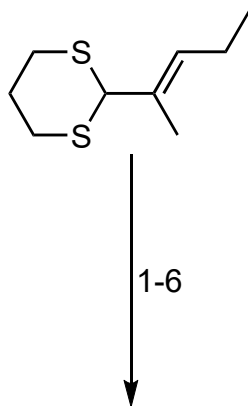
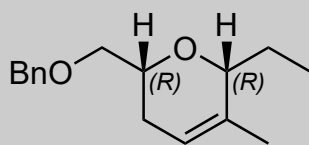


Combining total synthesis and genetic engineering to probe dihydropyran formation in ambruticin biosynthesis

Bowen, J. I.; Zhong, X.; Gao, K.; Reed, B.; Crump, M. P.; Wang, L.; Willis, C. L.,
Chem. Sci. **2024**, 15 (14), 5319–5326

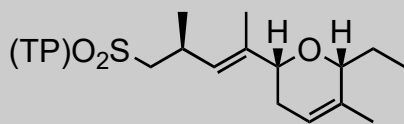


1-6

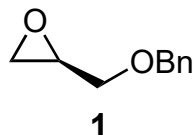


A

7-14

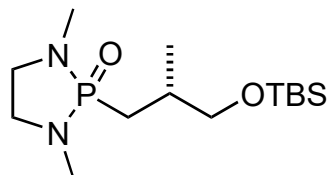


B



1

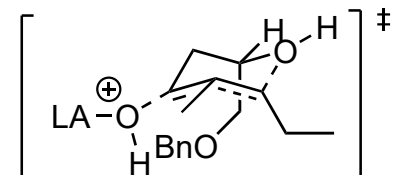
- 1) *n*-BuLi, then **1**, THF, -78°C
- 2) TBSOTf, lutidine, DCM
- 3) (PhSeO)₂O, DCM
- 4) CeCl₃, NaBH₄, MeOH, 0°C
- 5) TBAF, THF
- 6) BF₃OEt₂ (cat.), DCM



2

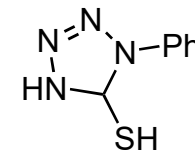
- 7) Na, THF, NH₃, -33°C
- 8) DMSO, (COCl)₂, NEt₃, DCM, -78°C
- 9) MeMgBr, THF, 0°C
- 10) DMSO, (COCl)₂, NEt₃, DCM, -78°C
- 11) **2**, *n*-BuLi, then PDT of step 10, THF, -78°C
- 12) TBAF, THF
- 13) PT-SH, DIAD, PPh₃, THF, 0°C
- 14) Molybdenate, H₂O₂ in EtOH (30%)

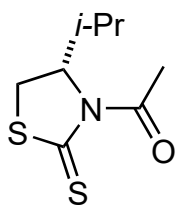
- 1) How might you make reagent **1**?
 Allyl Alcohol, Sharpless epox, protect
- 3) 1668 cm⁻¹ IR signal
- 4) Rxn name? Luche Reduction
 Resultant alcohol has inconsequential stereochemistry
- 6) Draw the transition state.



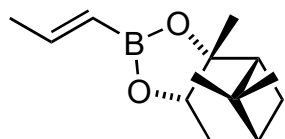
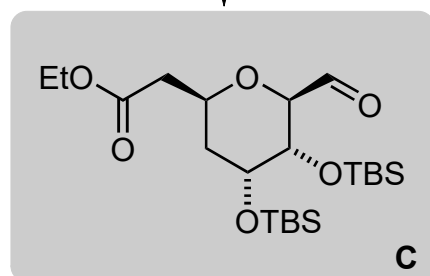
- 8) Rxn name? Swern Oxidation

- 13) Rxn name? Mitsunobu Reaction
 Hint: PT-SH =

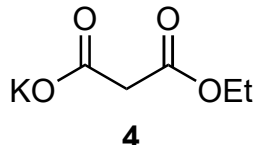
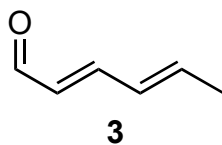
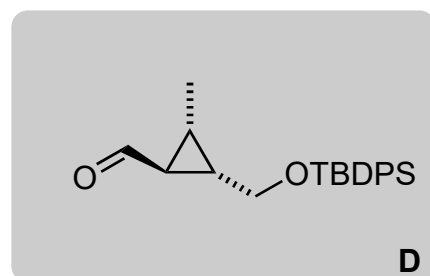




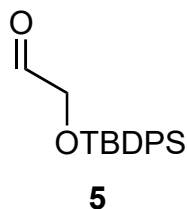
15-20



21-24



- 15) **3** TiCl_4 , DIPEA, DCM, -78°C
 16) **4**, MgCl_2 , imidazole, THF
 17) NaBH_4 , Et_2BOMe , MeOH, THF, -78°C
 18) $t\text{-BuOOH}$, $\text{Ti}(\text{O}i\text{-Pr})_4$, (-)-DIPT, DCM, -20°C
 19) TBSOTf (2 eq.), 2,6-lutidine, DCM
 20) $\text{K}_2\text{OSO}_4 \cdot 2\text{H}_2\text{O}$, acetone, *then* NaIO_4 , THF, H_2O



- 21) $n\text{-BuLi}$, DCM, THF, -100°C
then $\text{TMSCH}_2\text{MgCl}$, -78°C
 22) **5**, BF_3OEt_2 , THF, -78°C
 23) Tf_2O , 2,6-lutidine, DCM, -78°C
 24) $\text{K}_2\text{OSO}_4 \cdot 2\text{H}_2\text{O}$, acetone, *then* NaIO_4 , THF, H_2O

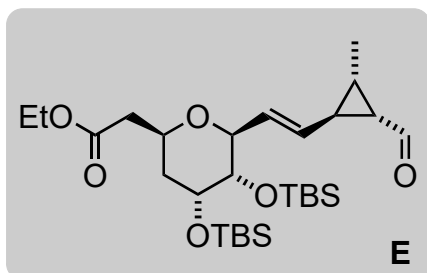
- 15) New stereocenter is R
 16) Rxn name?
 Claisen Condensation
 17) Rxn name?
 Narasaka Prasad Reduction
 18) Hint: 2 events occur.
 Rxn name?
 Sharpless Asymmetric Epoxidation
 20) Rxn name? Lemieux Johnson
 What is the organic byproduct of this reaction? Acetaldehyde

How might you make reagent **5**?
 Monoprotect ethylene glycol, then oxidize

- 21) Hint: DCM plays a critical role
 Rxn name (first part)? Mechanism?
 Matteson Homologation
 22) Hint: Both stereocenters are S
 23) Hint: Special carbocation

D

25-29

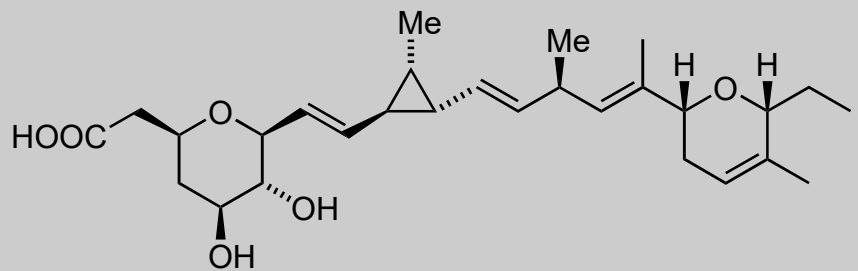


- 25) DIBAL-H, DCM
- 26) PT-SH, DIAD, PPh₃, THF, *then* mCPBA, DCM
- 27) LiHMDS, *then* **C**, DMF/HMPA, -60°C
- 28) TBAF, AcOH, THF
- 29) DMP, DCM

27) Rxn name? Julia Kocienski
Olefination

B

30-34



- 30) KHMDS, *then* **E**, DME, -60°C
- 31) TBAF (2 eq.), THF
- 32) Fétizon's reagent, PhMe, 110°C
- 33) NaBH₄, MeOH
- 34) LiOH, MeOH, THF, H₂O

32) What is Fétizon's reagent?
Ag₂CO₃ on celite