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

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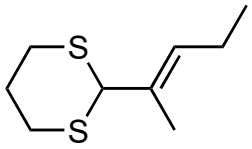
Chem. Sci. **2024**, 15 (14), 5319–5326

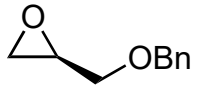


1-6

A

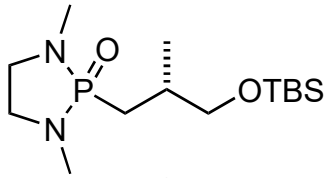
7-14

B



1

1) *n*-BuLi, *then* **1,** THF, -78°C
2) TBSOTf, lutidine, DCM
3) $(PhSeO)_2O$, DCM
4) $CeCl_3$, $NaBH_4$, MeOH, 0°C
5) TBAF, THF
6) BF_3OEt_2 (cat.), DCM



2

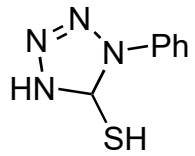
7) Na, THF, NH_3, -33°C
8) DMSO, $(COCl)_2$, NEt_3, DCM, -78°C
9) MeMgBr, THF, 0°C
10) DMSO, $(COCl)_2$, NEt_3, DCM, -78°C
11) **2**, *n*-BuLi, *then* PDT of step 10**,** THF, -78°C
12) TBAF, THF
13) PT-SH, DIAD, PPh_3, THF, 0°C
14) Molybdenate, H_2O_2 in EtOH (30%)

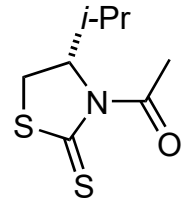
1) How might you make reagent **1**?

3) 1668 cm^{-1} IR signal
4) Rxn name?
   Resultant alcohol has inconsequential stereochemistry
6) Draw the transition state.

8) Rxn name?

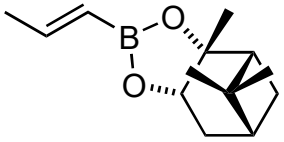
13) Rxn name?
Hint: PT-SH =





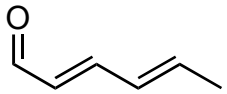
15-20

C

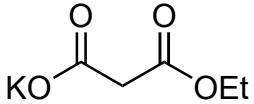


21-24

D

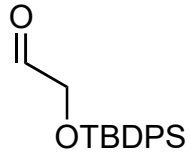


3



4

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*-BuOOH, $Ti(Oi\text{-}Pr)_4$, (-)-DIPT, DCM, -20°C
19) TBSOTf (2 eq.), 2,6-lutidine, DCM
20) $K_2OSO_4 \cdot 2H_2O$, acetone, *then* $NaIO_4$, THF, H_2O



5

21) *n*-BuLi, DCM, THF, -100°C
then $TMSCH_2MgCl$, -78°C
22) **5**, BF_3OEt_2, THF, -78°C
23) Tf_2O, 2,6-lutidine, DCM, -78°C
24) $K_2OSO_4 \cdot 2H_2O$, acetone, *then* $NaIO_4$, THF, H_2O

15) New stereocenter is R
16) Rxn name?
17) Rxn name?
18) Hint: 2 events occur.
Rxn name?
20) Rxn name?
What is the organic byproduct of this reaction?

How might you make reagent **5**?

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

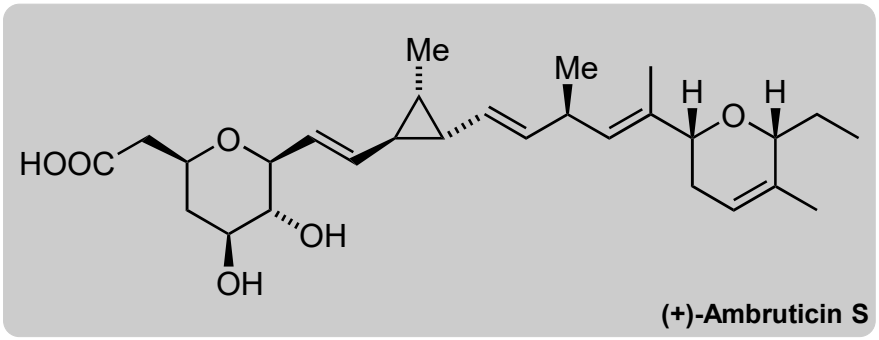
D

25-29

E

B

30-34



(+)-Ambruticin S

25) DIBAL-H, DCM
26) PT-SH, DIAD, PPh_3, THF, *then* mCPBA, DCM
27) LiHMDS, *then* **C**, DMF/HMPA, -60°C
28) TBAF, AcOH, THF
29) DMP, DCM

27) Rxn name?

30) KHMDS, *then* **E,** DME, -60°C
31) TBAF (2 eq.), THF
32) Fétizon's reagent, PhMe, 110°C
33) $NaBH_4$, MeOH
34) LiOH, MeOH, THF, H_2O

32) What is Fétizon's reagent?