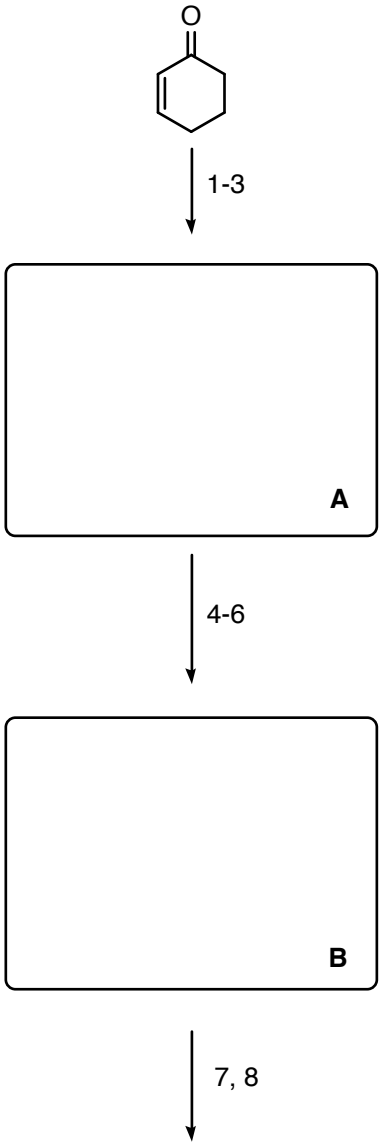
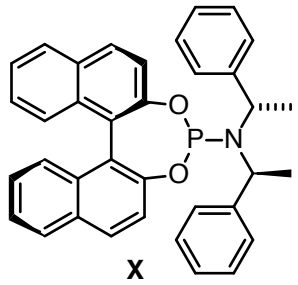
A modular and enantioselective synthesis of the pleuromutilin antibiotics

Stephen K. Murphy, Mingshuo Zeng, Seth B. Herzon, *Science* **2017**, *356*, 956–959.



1) $Zn(CH_3)_2$, 0.5% $Cu(OTf)_2$, 1% **X**
then CH_3Li, $CH_3OC(O)CN$
2) *t*-BuONa, CH_3I
3) KHMDS, $PhNTf_2$



X

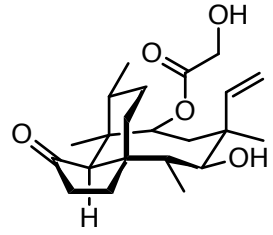
4) 5% $Pd(PPh_3)_4$, CO, $Sn(C_2H_3)_4$
5) 5% $Cu(OTf)_2$
6) Et_2AlCN, *then* DIBAL-H, *then* NaOH

7) TMSOTf, $(TMSOCH_2)_2$
8) CH_3Li (3 eq), *then* Boc_2O

Hint: The first stereocenter being formed has (*R*)-chirality.
(97:3 er, >20:1 dr over two steps)

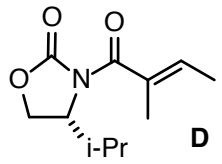
Which named reaction is triggered in step 5?
Name reaction of step 6?

Please provide a mechanism for step 8.



(+)-pleuromutilin

C



D

How could you prepare **D**?

9-11

9) NaHMDS, $PMBOCH_2Cl$
10) LAH
11) PPh_3, I_2, imidazole

Please rationalize the diastereoselectivity of step 9 by providing a reasonable transition state.

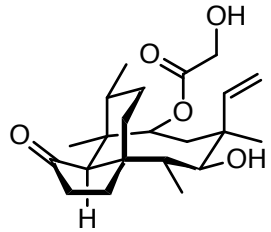
E

12-15

12) *t*-BuLi (4 eq), *then* **E** (2 eq), *then* **C**, *then* HCl
13) KHMDS (3 eq), Comins' reagent
14) DDQ
15) DMP

Please explain the used stoichiometry by presenting a mechanism of step 12.

F



(+)-pleuromutilin

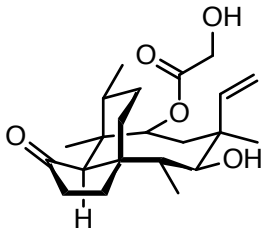
16, 17

G

18, 19

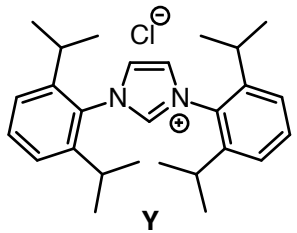
(+)-12-epi-mutilin

20-22



(+)-pleuromutilin

16) $Ni(COD)_2$, **Y**, Et_3SiH, *then* TBAF
17) DMP



Y

18) SmI_2
19) Na, EtOH, *then* HCl

20) 1-(trifluoroacetyl)imidazole
21) *O*-tritylglycolic acid, EDC, DMAP
then CH_3OH, $NaHCO_3$
22) Et_2Zn, *then* HCl

Please provide a mechanism for step 16.
What is the role of Y?

Please explain step 22 with a mechanism.