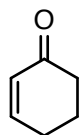
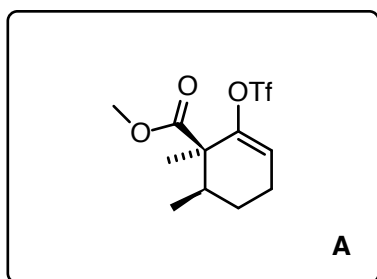


A modular and enantioselective synthesis of the pleuromutilin antibiotics

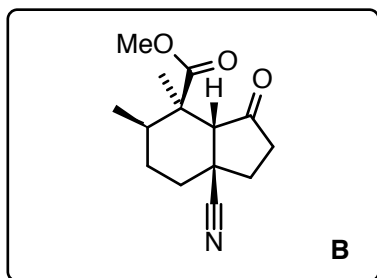
Stephen K. Murphy, Mingshuo Zeng, Seth B. Herzon, *Science* **2017**, *356*, 956–959.



1-3

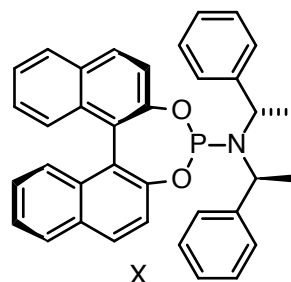


4-6



7, 8

- 1) $\text{Zn}(\text{CH}_3)_2$, 0.5% $\text{Cu}(\text{OTf})_2$, 1% X
then CH_3Li , $\text{CH}_3\text{OC}(\text{O})\text{CN}$
- 2) $t\text{-BuONa}$, CH_3I
- 3) KHMDS , PhNTf_2



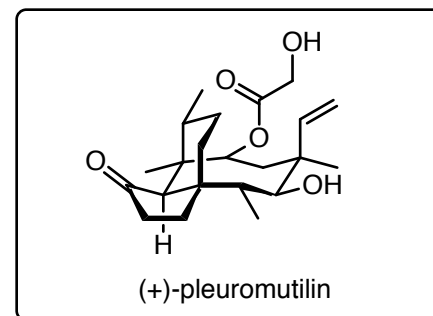
- 4) 5% $\text{Pd}(\text{PPh}_3)_4$, CO , $\text{Sn}(\text{C}_2\text{H}_5)_4$
- 5) 5% $\text{Cu}(\text{OTf})_2$
- 6) Et_2AlCN , then DIBAL-H , then NaOH

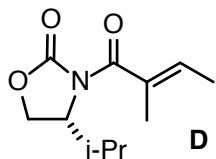
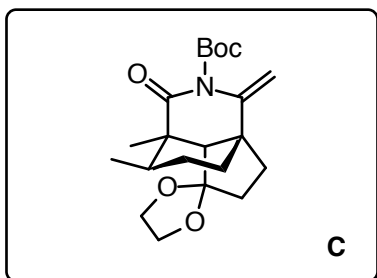
- 7) TMSOTf , $(\text{TMSOCH}_2)_2$
- 8) CH_3Li (3 eq), then Boc_2O

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

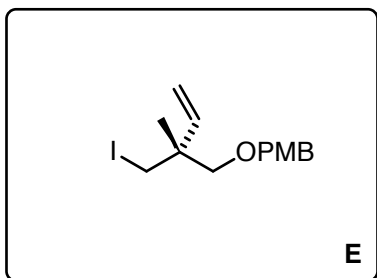
Which named reaction is triggered in step 5?
Cu catalyzed Nazarov cyclization
Name reaction of step 6?
Nagata hydrocyanation
Lit.: Wataru Nagata, Mitsuru Yoshioka, Tadao Terasawa, *J. Am. Chem. Soc.* 1972, *94*, 4672–4683.

Please provide a mechanism for step 8.

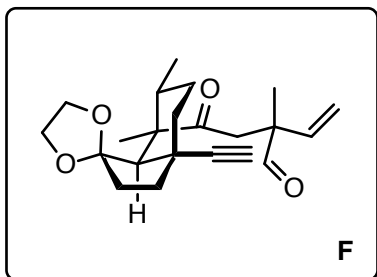




9-11



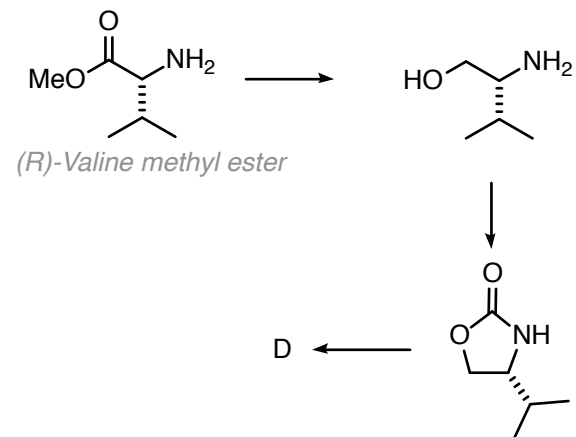
12-15



9) NaHMDS, PMBOCH₂Cl
 10) LAH
 11) PPh₃, I₂, imidazole

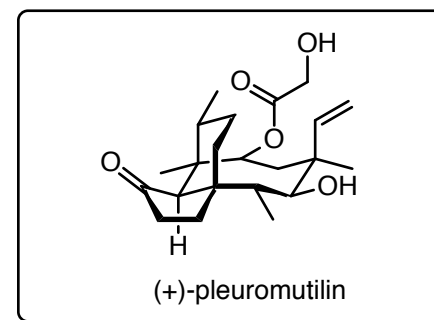
12) *t*-BuLi (4 eq), then **E** (2 eq), then **C**, then HCl
 13) KHMDS (3 eq), Comins' reagent
 14) DDQ
 15) DMP

How could you prepare D?

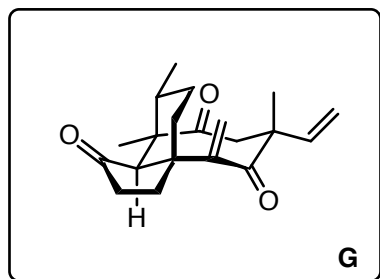


Please rationalize the diastereoselectivity of step 9 by providing a reasonable transition state.

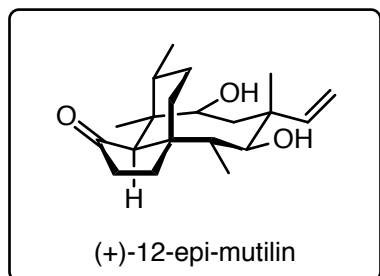
Please explain the used stoichiometry by presenting a mechanism of step 12.
 two-fold neopentyllic fragment coupling



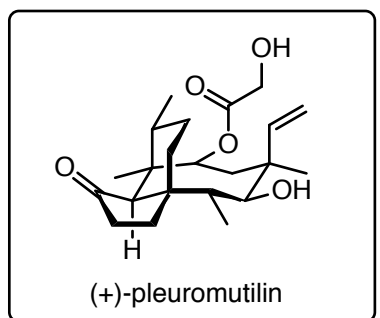
16, 17



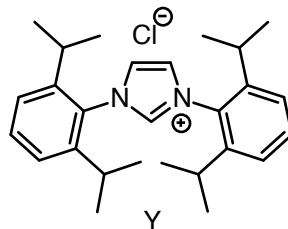
18, 19



20-22



16) Ni(COD)₂, Y, Et₃SiH, *then* TBAF
17) DMP



18) Sml₂
19) Na, EtOH, *then* HCl

20) 1-(trifluoroacetyl)imidazole
21) *O*-tritylglycolic acid, EDC, DMAP
then CH₃OH, NaHCO₃
22) Et₂Zn, *then* HCl

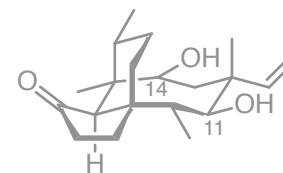
Please provide a mechanism for step 16.

What is the role of Y?

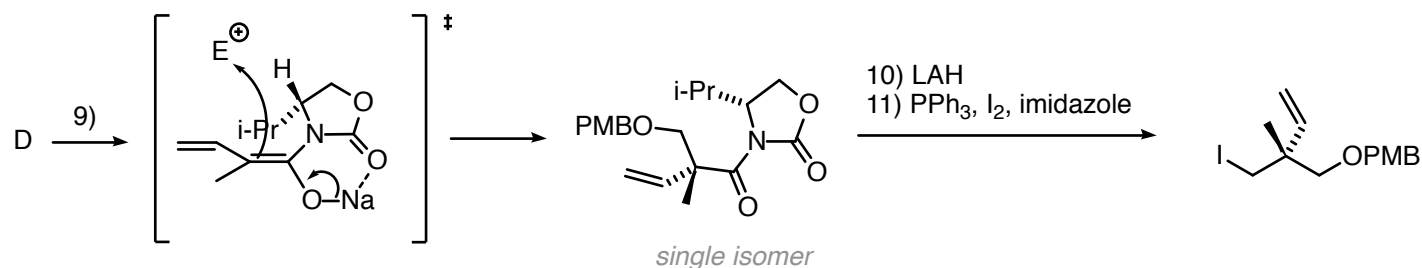
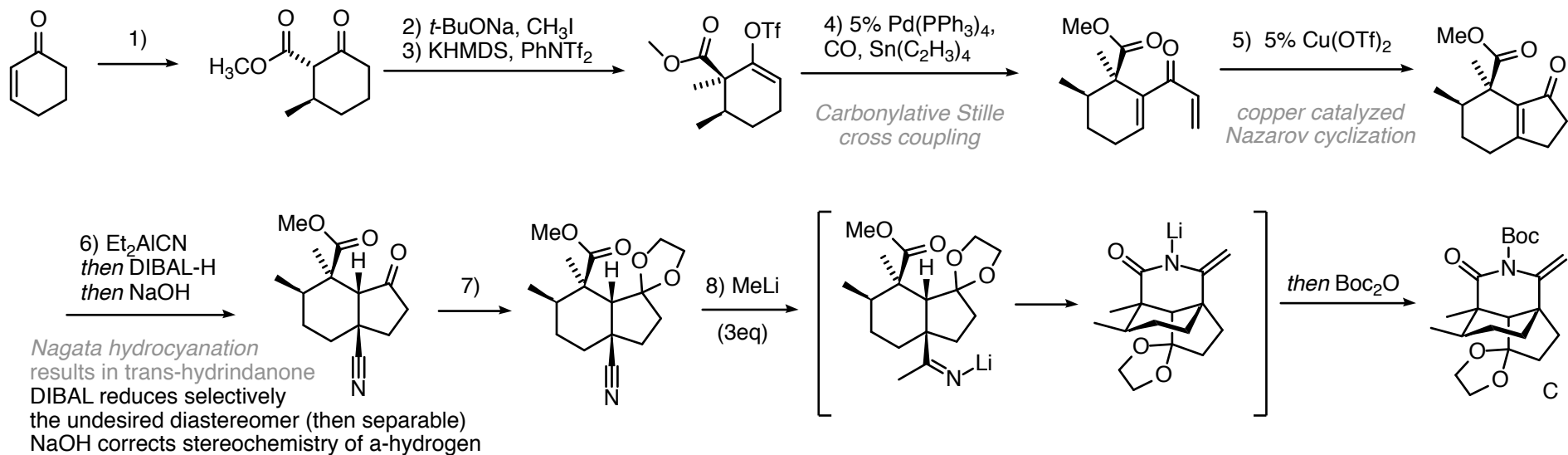
Large NHC-ligands favor the formation of the exo-methylene cyclization product

Reference: Evan P. Jackson, Hasnain A. Malik, Grant J. Sormunen, Ryan D. Baxter, Peng Liu, Hengbin Wang, Abdur-Rafay Shareef, John Montgomery, *Acc Chem Res.* **2015**, *48*, 1736–1745.

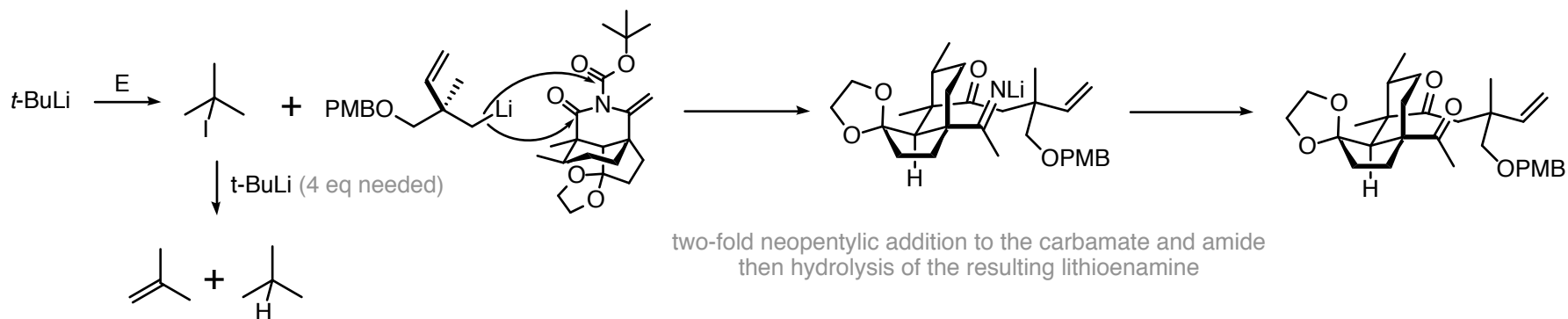
18) >20:1 dr
19) C14 >20:1 dr, C11 3:1 dr

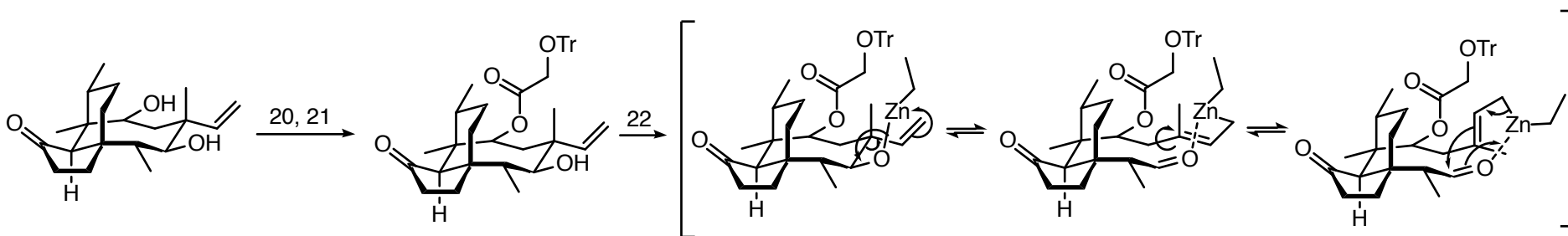
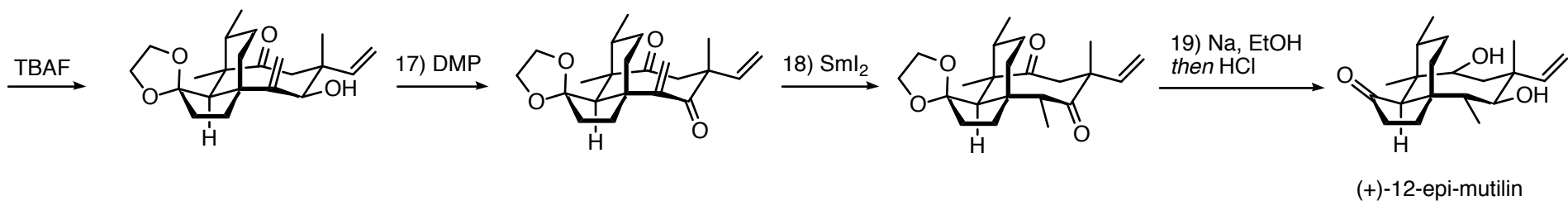
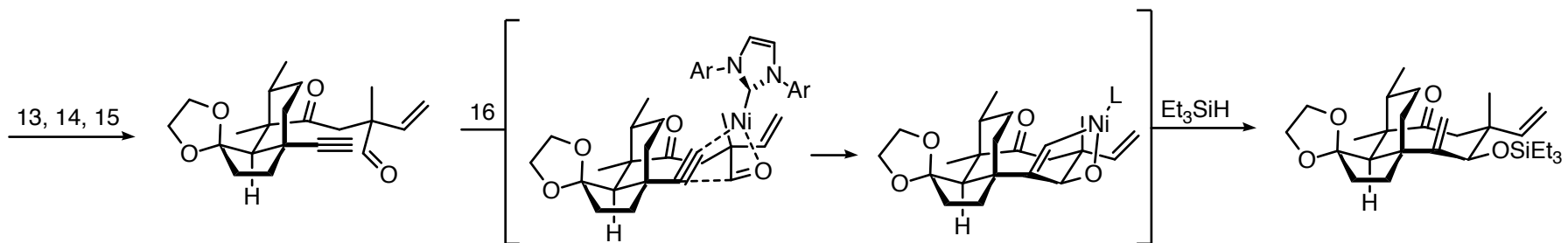


Please explain step 22 with a mechanism.



Reference: Seijiro Hosokawa, Kazuhiko Sekiguchi, Manabu Enemoto, Susumu Kobayashi, *Tetrahedron Lett.*, 2000, 41, 6429–6433.





retroallylation-allylation

Reference: Heinz Berner, Hermann Vypel, Gerhard Schulz, Helmut Schneider, *Monatsh. Chem.* 1986 117, 1073–1080.

