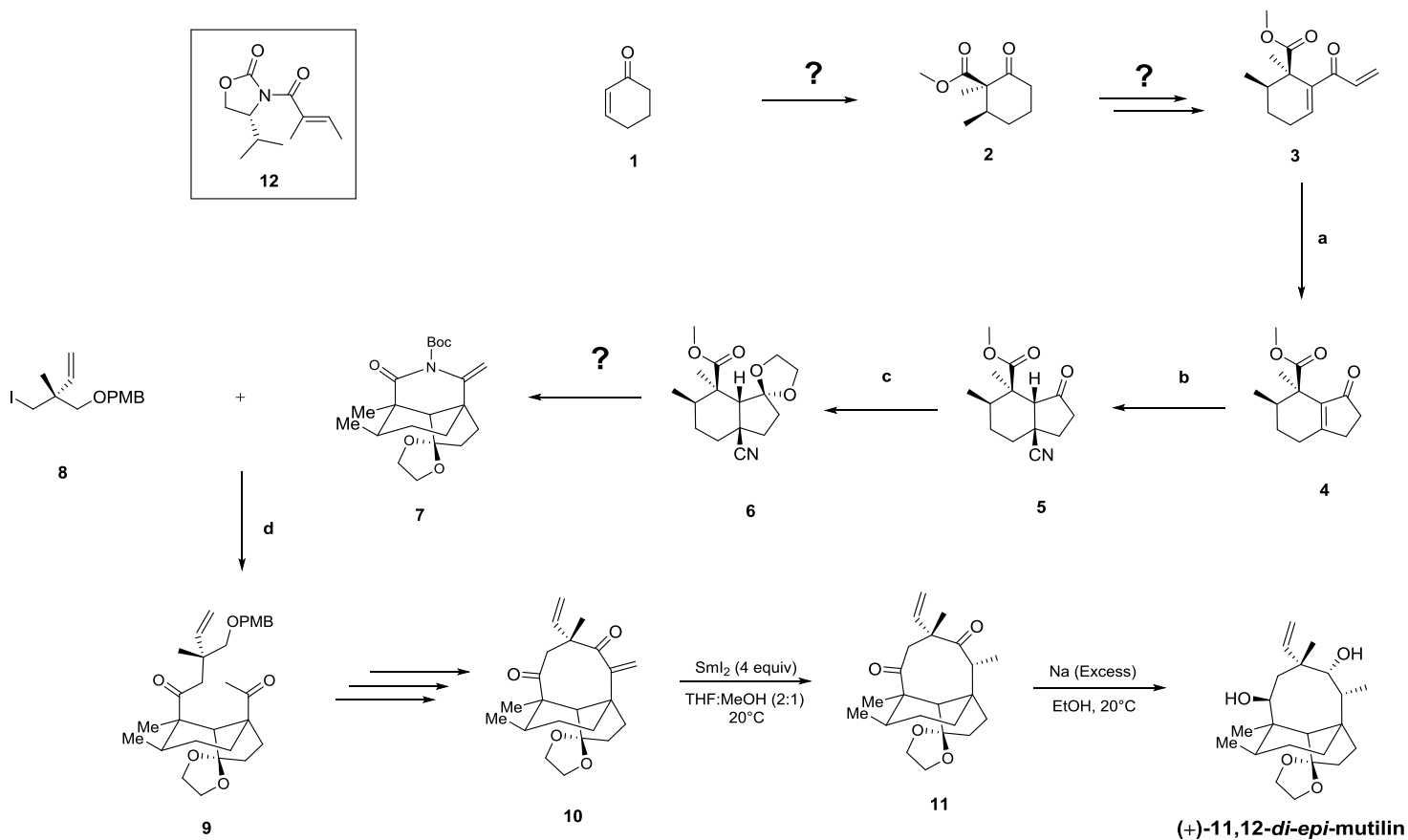


Synthesis of pleuromutilin antibiotics



- a) $\text{Cu}(\text{OTf})_2$ (5 mol%), DCM, 60°C .
 b) Et_2AlCN (3 equiv), 0°C , then DIBAL (3 equiv), THF, -78°C , then 0.01M NaOH MeOH:H₂O (5:1), 0°C .
 c) TMSOTf (2 equiv), $(\text{TMSOCH}_2)_2$ (7 equiv), DCM, 20°C .
 d) $t\text{BuLi}$ (4.4 equiv), **8** (2.4 equiv) Et₂O, -45°C , then **7** (1 equiv) -45°C -**work up**-, then HCl 1M, THF, 0°C .

- How would you synthesize the compound **2** from **1**? (with the relative stereochemistry shown)
- Starting from **2**, provide the synthetic steps needed to obtain **3** (give the corresponding reagents and conditions)
- Explain the stereoselectivity of the hydrocyanation reaction leading to compound **5**. What is the name of this reaction?
- Give the reagents and conditions to perform the transformation of **6** into **7** in one single step. Provide the corresponding reaction mechanism.
- Propose the reaction mechanisms involved in the formation of **9** and **11**.

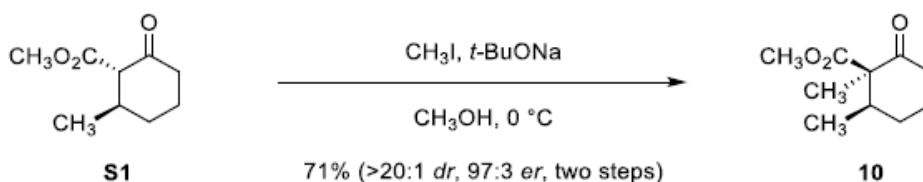
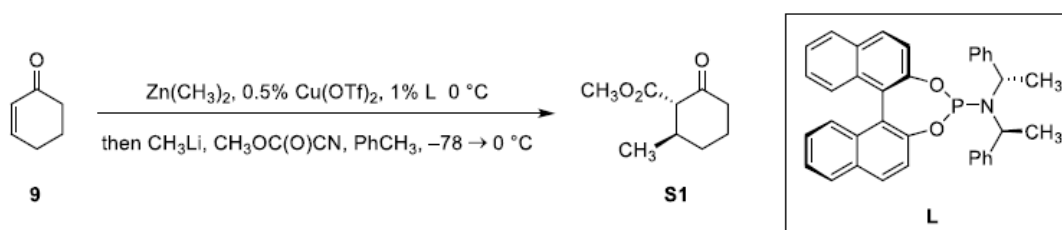
Bonus: How would you prepare the iodide **8** from the chiral precursor **12**?

Synthesis of pleuromutilin antibiotics

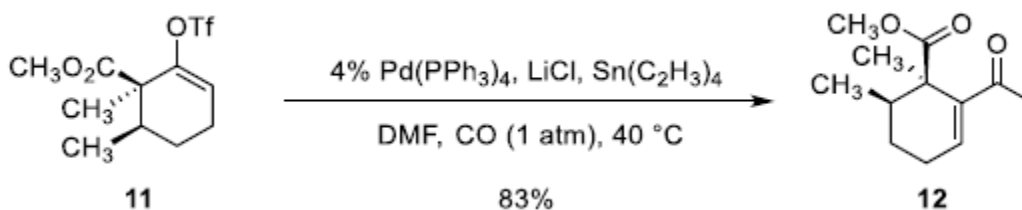
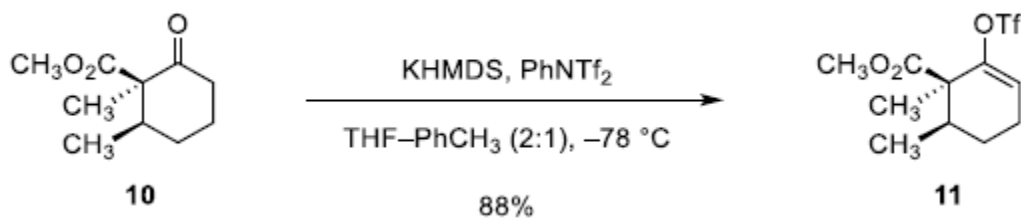
Submitted by Camilo M.

Solution

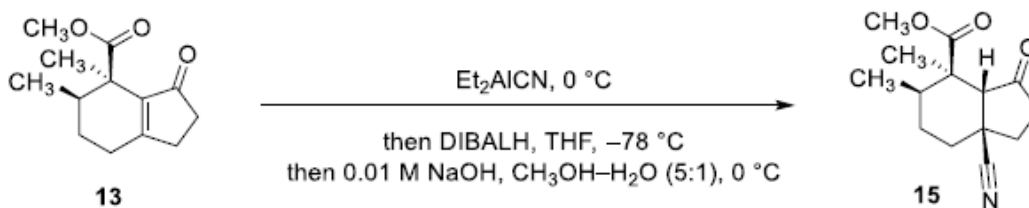
1. How would you synthesize the compound 2 from 1? (with the relative stereochemistry shown)



2. Starting from 2, provide the synthetic steps needed to obtain 3 (give the corresponding reagents and conditions)

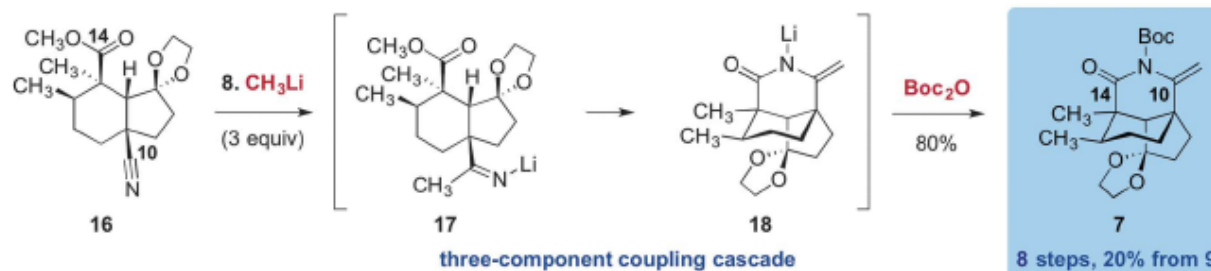


3. Explain the stereoselectivity of the hydrocyanation reaction leading to compound 5. What is the name of this reaction?



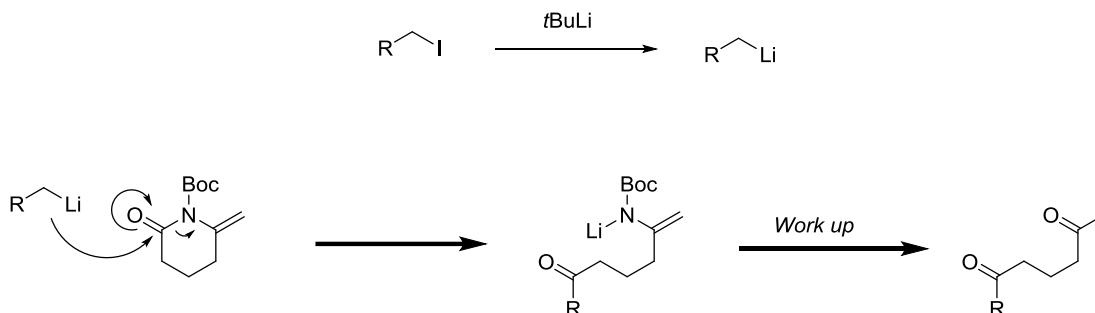
Nagata hydrocyanation: Coordination of aluminum with the ester moiety directs the nucleophilic attack of CN^- . Once the conjugated addition takes place, the so generated enolate can coordinate with aluminum as well. By doing this, steric hindrance favors the protonation *anti* to the CN group, leading to a *trans* connectivity of the two rings. Nevertheless, the corresponding epimer formed (selectivity 3:1) is selectively reduced by DIBAL and separated from the original mixture. At the end, by adding base, the product isomerizes to the *cis* product.

4. Give the reagents and conditions to perform the transformation of 6 into 7 in one single step. Provide the corresponding reaction mechanism

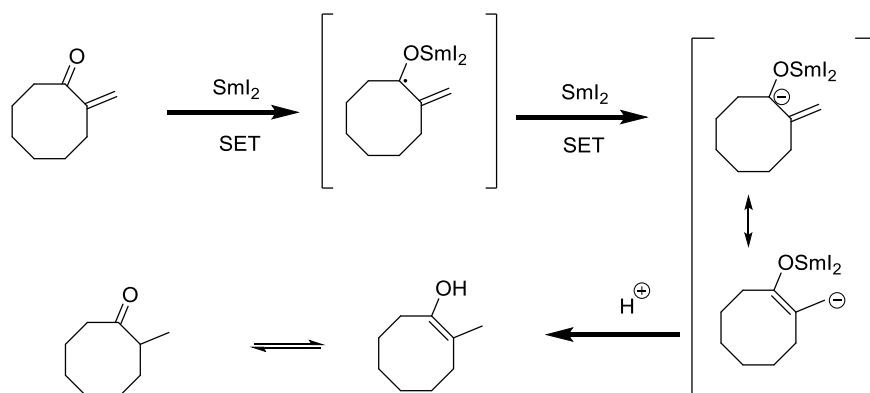


5. Propose the reaction mechanisms involved in the formation of 9 and 11.

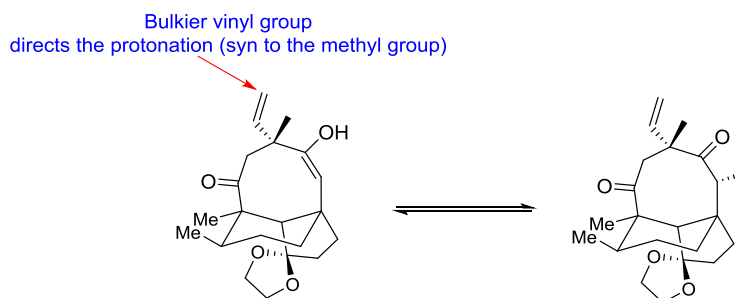
FOR 9



FOR 11



In terms of stereoselectivity, the protonation taking place during the keto-enol tautomerism is directed by the bulkier vinyl group (relative to the methyl substituent)



Bonus: How would you prepare the iodide **8** from the chiral precursor **12**?

