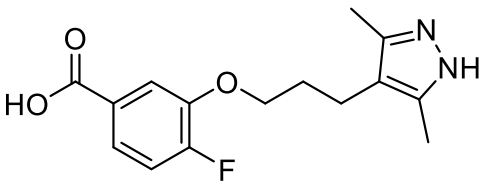
Solving Organic Synthesis – Problem Set #1

SOS – Issues with organic chemistry? Welcome to Solving Organic Synthesis, a set of practice problems to test and refine your understanding of organic chemistry. This first set covers a range of topics, but let me know what topics/ themes you need most help with! To keep it fun for everyone, the exercises will span three levels of difficulty:

- Easy: Elementary Explorer (note: still require organic synthesis knowledge)
- Medium: Molecular Manipulator
- Advanced: Atomic Architect

Exercise A: Acoramidis

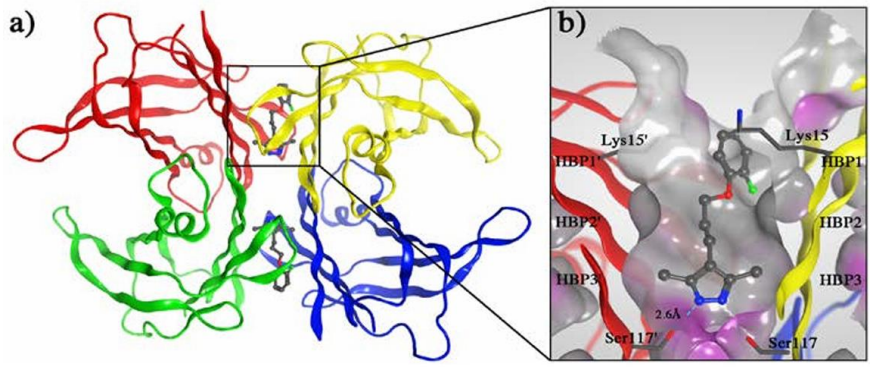
On November 25th, the US Food and Drug Administration (FDA) approved the drug **acoramidis** to treat patients with a rare, serious heart disease called **ATTR-CM** (cardiomyopathy due to transthyretin-mediated amyloidosis). This is a **small molecule drug** made with organic synthesis but beyond, this disease is also seeing broad innovation efforts from pharma/ biotech, including things like RNA silencing or gene editing.



acoramidis (brand name Attruby)

Mechanism: Stabilizes transthyretin proteins to prevent them from forming harmful deposits (these reduce the heart's ability to properly relax and pump blood, i.e., leads to cardiomyopathy)

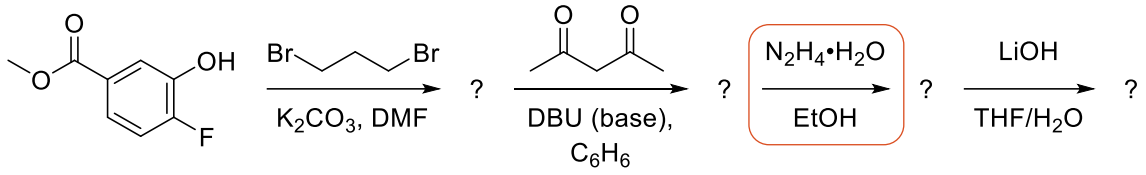
1. Identify **five functional groups** in acoramidis' structure.
2. The figure below shows a ligand complex with the transthyretin protein. Based on the functional groups (FGs) you have identified above, try to find the **two key binding interactions** between acoramidis and the protein.



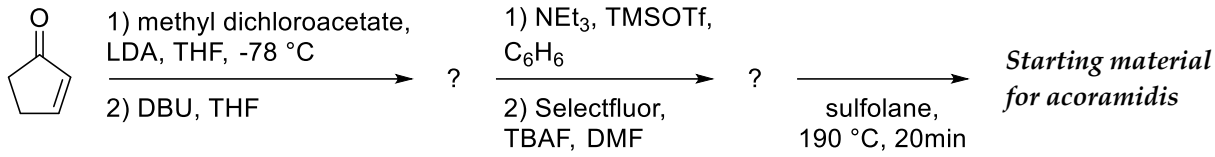
Source: PNAS 2013, 110, 9992 (supporting information)

Hint: Google the structures of the abbreviated amino acids and identify their FGs.

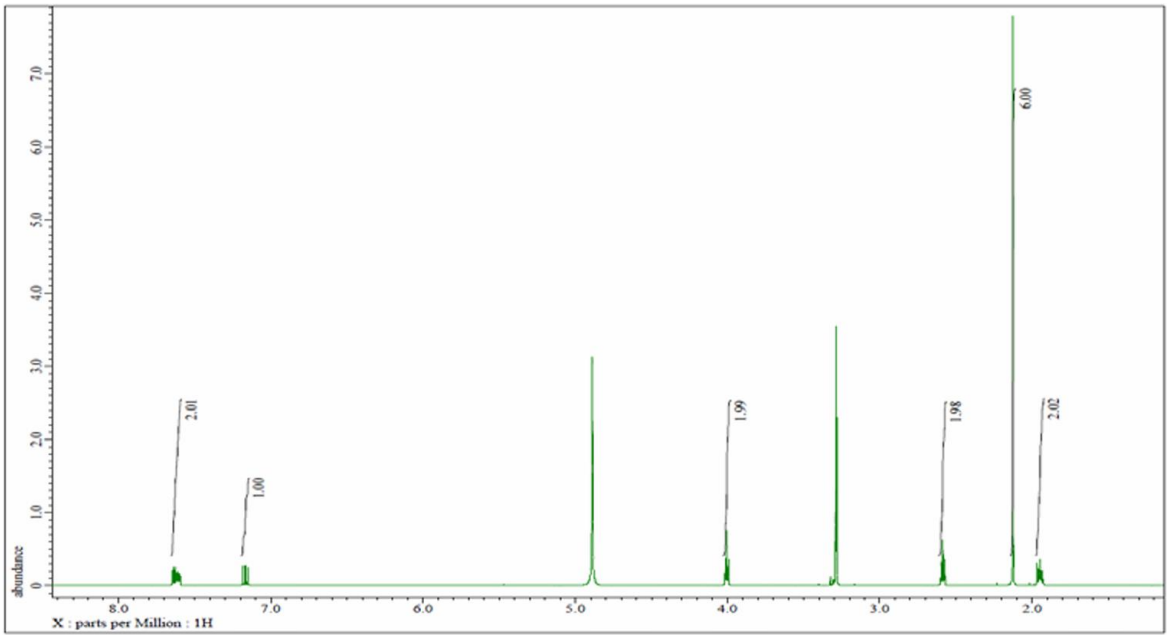
3 The **synthesis** of acoramidis features just four steps from this starting material which can be bought. **Fill in the gaps**, and **draw the mechanism** for the highlighted step.



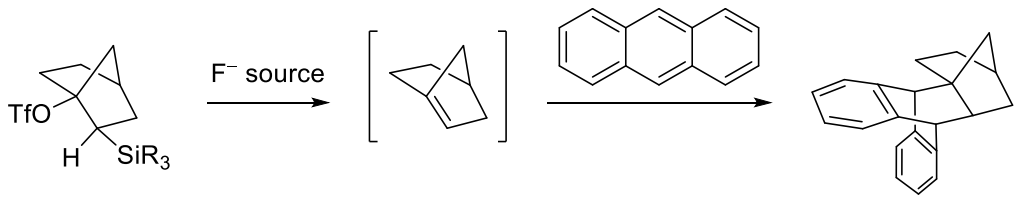
4 *"OH NO!", you shriek.* You find out that none of your chemicals suppliers have the starting material in stock, but **you need to synthesize acoramidis as soon as possible**. You also find any in your university's chemical storage rooms either – the bad smell of the air in the storage room also makes you think that you lost a year of your lifespan... After complaining about this to your professor, **he smiles cheekily** and suggests you run the following experiment. **Fill in the gaps** and **draw all mechanisms**.



5 After several productive days in the lab, you've finally completed your synthesis of acoramidis. You measure the following **^{1}H NMR spectrum – should you be satisfied**?

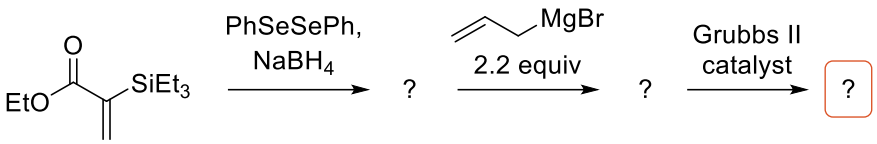


Exercise B: Remember our recent video on so-called **anti-BREDT olefins** (link)?



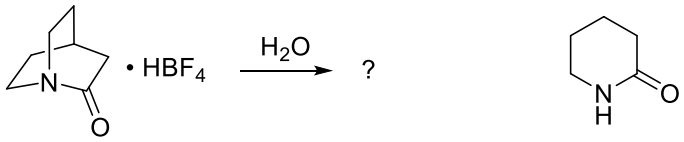
In that video we heard that chemists found a way to **create very strained olefins** (which defy Bredt's rule) by using a fluoride-mediated elimination of a [2.2.1] ring precursor.

1 **How do we make that functionalized precursor though**? The reactions below play a part in that synthesis. Fill in the gaps! **What is the product** that we arrive at?

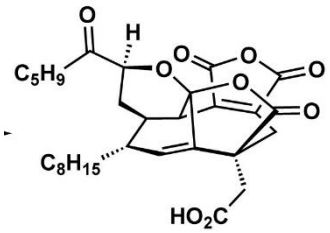


2 Suggest how we could convert the product above into the **anti-Bredt precursor**.

3 In 2006, STOLTZ and TANI synthesized and isolated **2-quinuclidonium tetrafluoroborate**, an interesting molecule with a 1-azabicyclo[2.2.2]octane skeleton. What reaction do you expect to occur in water? How does the reactivity of the 2-quinuclidonium compare to the lactam shown on the right and why?

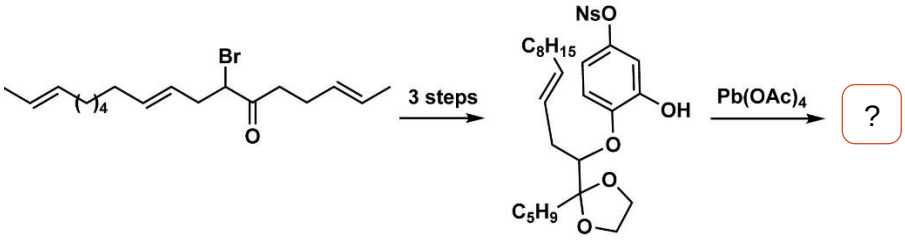


4 After 22 years of research (!!), WOOD, STOLTZ and co-workers reported a synthesis of **phomoidride D** in 2017. As you might remember, it belongs to a family of compounds with bridgehead olefins (CP molecules). Despite the small size of the bridged ring (S = # of atoms in the bridges = 8), the anti-BREDT double bond is stable.

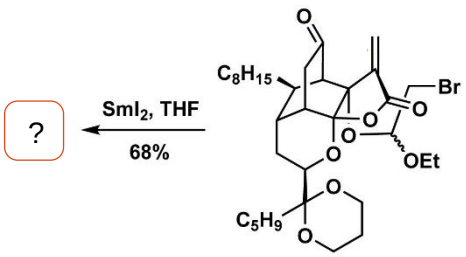


(±)-phomoidride D (25)

After some preparatory steps, their first key step was the reaction of this intermediate with **lead acetate**. What is the product?

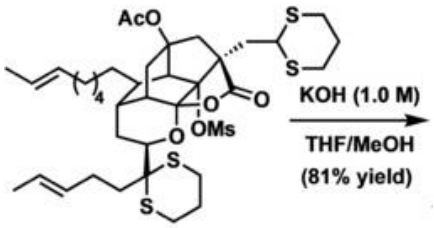


5 Six additional steps (which we will not discuss) gave this more complex intermediate. What reaction do you expect to occur with **samarium(II) iodide**?



Hint: If you can't find it, look at the next question for an indirect structural hint.

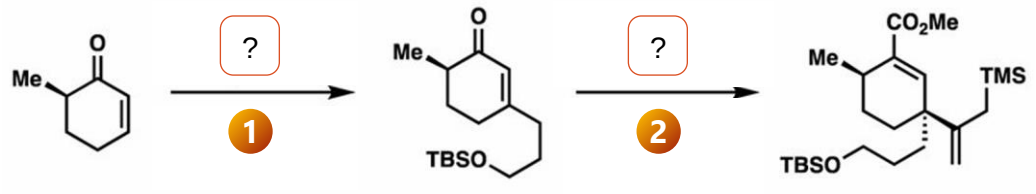
6 Four more steps gave an even more complicated intermediate (this is how it goes in total synthesis) with a mighty ring structure. This is not the ring structure of phomoidride D, but some **potassium hydroxide** can help. How?



7 You will have seen that between the structure in question 5 and question 6, **the protecting group on the lower side chain of the molecule has changed**. How are these new protecting groups called, and what are similarities vs. differences compared to the initial group?

Exercise C: Another total synthesis

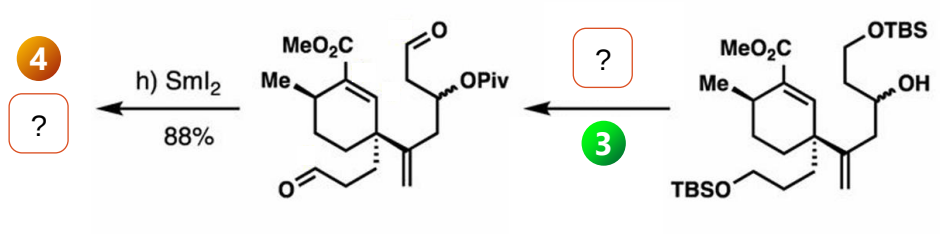
This exercise has less backstory and lets you get **more "reps" in**. We will look at two schemes from the **total synthesis of a terpenoid natural product**. I will not show you the full target structure to avoid spoilers (you'll see them in the answers), but rest assured that it's pretty cool and somewhat useful, as it's used as an antibiotic in veterinary medicine.



1 How would you convert the chiral starting material into the first intermediate?

2 Along the same lines, how could we progress to the next intermediate?

After additional manipulations, we end up with the compound on the right in the second scheme below.



3 Provide plausible steps to convert the far-right compound into the **intermediate**.

4 Treatment with **samarium(II) iodide** provides a product featuring a new 8-membered ring. What is the product and how is it formed?