Solving Organic Synthesis – Problem Set #2

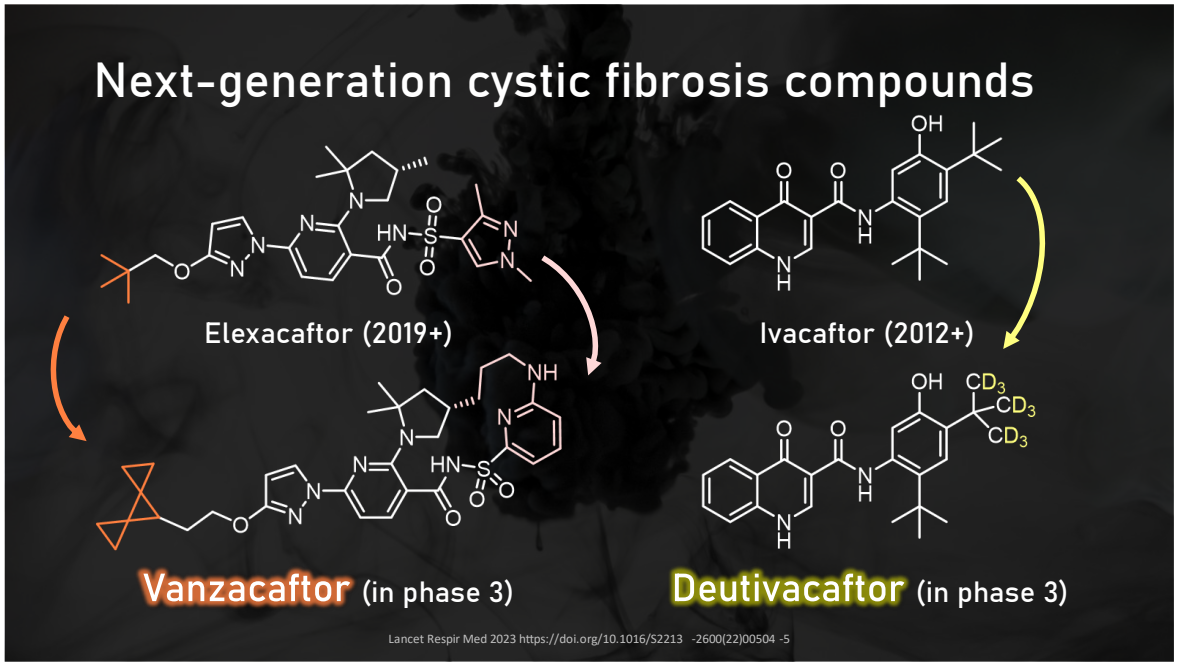
Welcome back! I loved the positive feedback on Problem Set #1 – thank you! In this edition, we keep a good mix of topics, reactions and difficulties (slightly more 'easy' ones).

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

Overview: A) **Putting "the D" into drugs**, B) **Cyclopropyl**^{3}, C) **Grayanotoxin, but oldschool**

Exercise A: **Putting "the D" into drugs**

Many of you indicated that you're interested in medicinal chemistry and pharmaceuticals. We'll keep looking at **new drugs** (and old ones) as they provide relevant real-world examples of chemistry at work. The **final drug approval of 2024** is a **friendly face**!



If our video on deuterium, you will remember that we discussed how ^{2}H / **deuterium** is different from ^{1}H hydrogen, and why it can be found in some pharmaceuticals.
Also, in our video on cubane synthesis, we discussed **cystic fibrosis**, a really crappy disease where abnormal flow of ions and water into/out of cells causes problems in various organs in the body (e.g., lung damage). We mentioned that some compounds – at the time, still in clinical trials – have structural modifications. One of these is **deutivacaftor**!

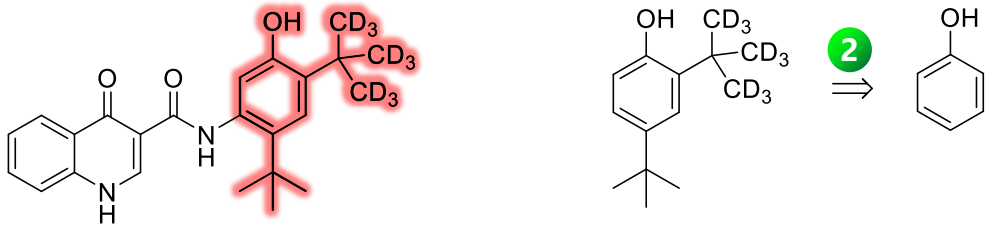
Well, **triple-combination therapy** with deutivacaftor, vanzacaftor and tezacaftor *(not shown above)*, was approved by the US FDA on December 20th, 2024 (brand name Alyftrek). Previous therapy included an **evening dose of ivacaftor** on top of a morning dose of another triple combo. The new combo is taken **once daily**, so it's more convenient for patients.

Mutations in the CFTR ion channel hinder its ability to traffic several different ions as intended. Drugs aim to (partially) restore its function. Vanzacaftor and tezacaftor are **correctors**, helping the channel **take on the right shape** and to **traffic to the cell surface** while deutivacaftor is a **potentiator**, helping **hold CFTR open** at the cell surface. There are **hundreds of CFTR mutations** known and unfortunately, not all of them can be treated.

1 What are two similarities and two differences **between deuterium and hydrogen**?

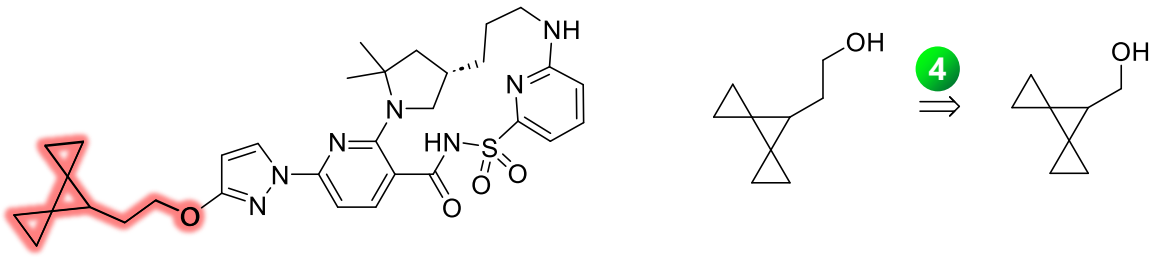
Let's get started with some basic synthesis questions on the three constituents of Alyftrek.

2 *Deutivacaftor*: How would you incorporate the **d$_9$-*tert*-butyl group** into the aromatic building block starting from phenol?

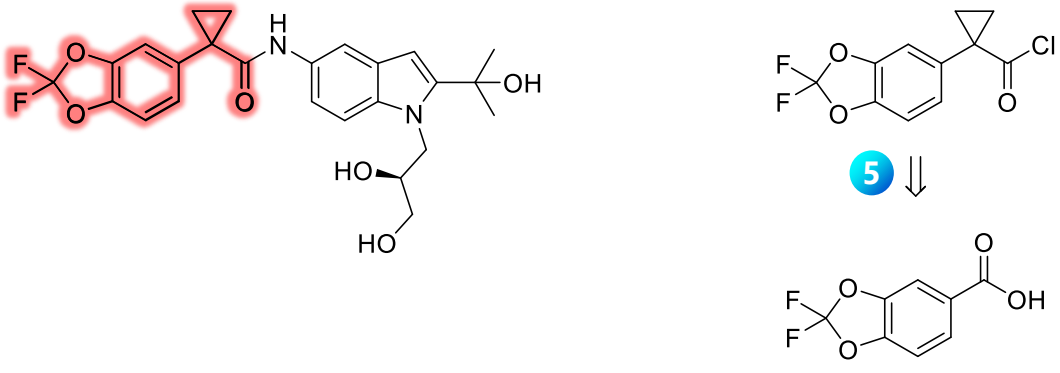


3 *Deutivacaftor*: Based on the location of the deuterium atoms, what product(s) do you think deutivacaftor is **metabolized** to?

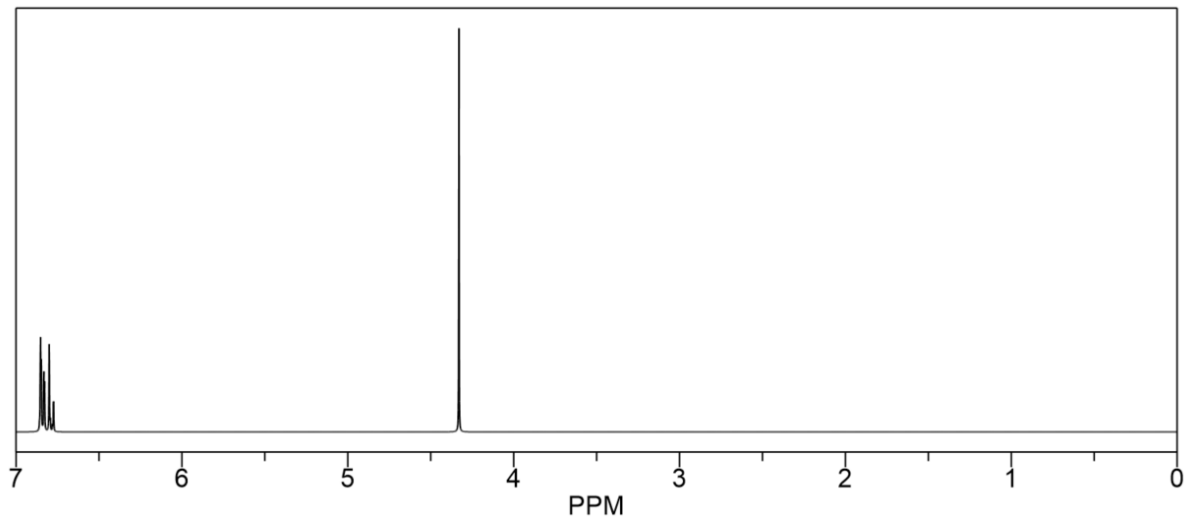
4 *Vanzacaftor:* How would you make the **extended** building block from the shorter starting material?



5 *Tezacaftor:* The final partner in crime also needs a **one-carbon extension** in its synthesis. In contrast to vanzacaftor, it has just one **cyclopropane** but this time we need to make this ring ourselves! Can you help with a clever synthetic route?



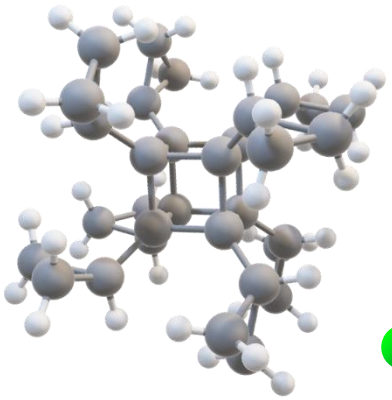
6 *Tezacaftor:* You've just completed your final reaction and measured a **^{1}H NMR** of your product for the question above, giving the following spectrum. What do you think?



7 This question is not science-related – thus, the cool grayscale format.

At what level of annual sales are pharmaceuticals called **blockbusters**? What do you guess, how high are the estimated peak sales of **Alyftrek**?

Exercise B: **Cyclopropyl**[3]



Because I linked one of my cubane videos in exercise A, I'm thinking about cubanes…

Also, we have seen several cyclopropyl rings just now…

And many of you also indicated that you like to practice your **retrosynthesis**…

Let's combine these and look at **octacyclopropylcubane**!

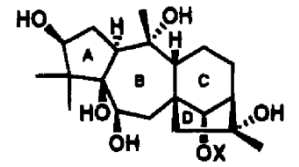
1 Do you expect octacyclopropylcubane to be **more stable or less stable** compared to **unsubstituted cubane**?

2 Propose a **retrosynthesis** of this cubane to a starting material with **8 carbons or less**.

! **Additional advanced questions** are included in **the solutions** (separate file).
As they would be a "spoiler" for your retrosynthesis, they are not shown here.

3 When **heated at 250 °C**, the cubane **rearranges** to a much less strained product. What is it?

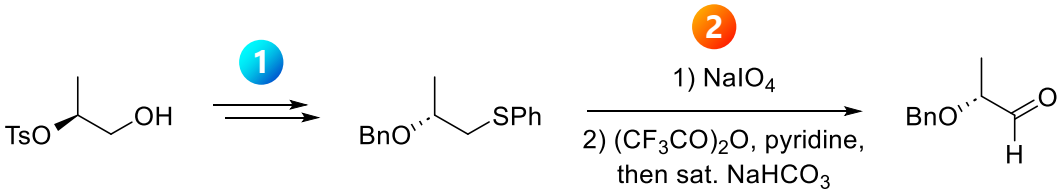
Exercise C: **Grayanotoxin, but oldschool**



Grayanotoxin I (1) X=Ac
Grayanotoxin III (3) X=H

In our recent video on "mad honey", we discussed the structures and chemistry of kalmanol and grayanotoxin. These natural products are produced by certain plants in nature and can end up in honey, rendering it toxic and slightly hallucinogenic.

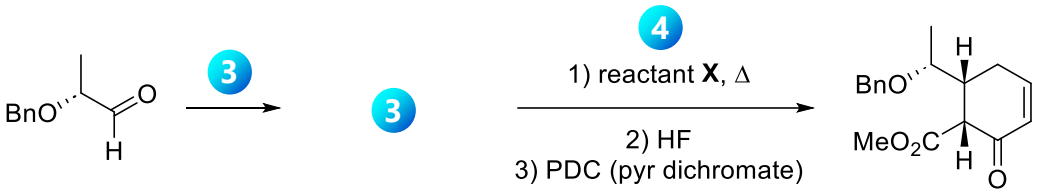
Let's check out a few steps here.



1 How would you convert the starting material to the **sulfide intermediate**?

2 What is the **mechanism of step 2)**? Does it remind you of a name reaction?

Let's look at this next synthetic scheme with the aldehyde we've just made.



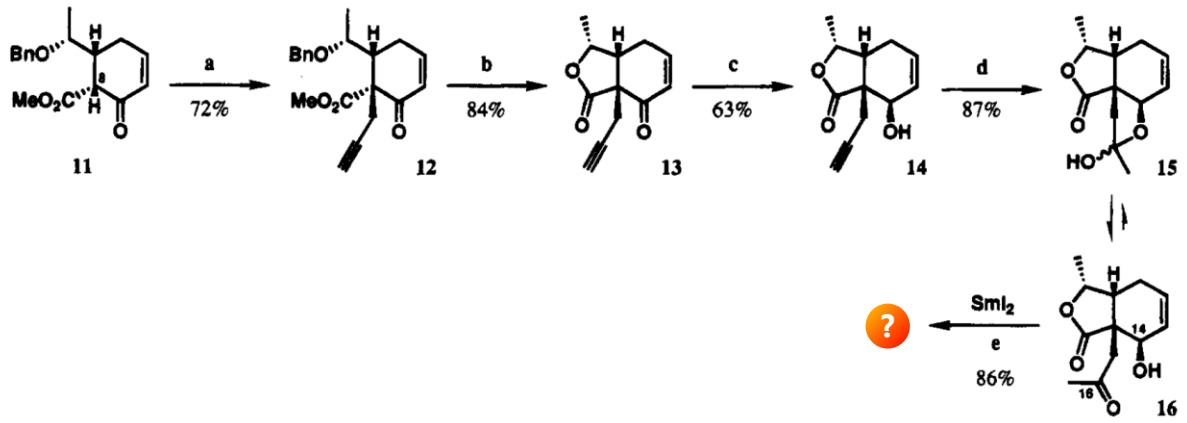
3 Figure out what initial **intermediate** you need and how you would make it.

4 Identify **reactant X** and explain the individual reactions and **selectivities** to form the product shown.

Because this is an early synthesis and grayanotoxin is complex, you can imagine the full synthesis is quite long. On the next page, there are some of the subsequent steps. They are nicely finished off by a **SmI_2** reaction (remember what you learned in Problem Set #1).

5 Look at the synthetic scheme on the next page.
Suggest reactants for all steps and identify the missing product, incl. stereochemistry.

Do NOT cross-check grayanotoxin's structure on this page, unless you need a hint.



To not overload the problem set, we will stop here. We will get back to this family of natural products in future.

If you're still looking for more content, you may want to read the discovery paper (open access) for ivacaftor, the predecessor of deutivacaftor discussed in exercise A:
J. Med. Chem. 2014, 57, 23, 9776; link

It's a great medicinal chemistry publication with interesting observations on the structure of the drug (e.g., relevance of tautomers) and synthetic chemistry.

That's it for this edition. I hope you enjoyed it!

As always, thank you for your interest!

Total Synthesis

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