Solutions | Problem Set #2 – Solving Organic Synthesis

Here are the explanations and comments for the problem set. Again, **let me know** if you like it and if you have any topics you want to practice or learn about in particular!

For reference, these are the levels of difficulty.

- Easy: Elementary Explorer
- Medium: Molecular Manipulator
- Advanced: Atomic Architect

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

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

Here are a few similarities…:

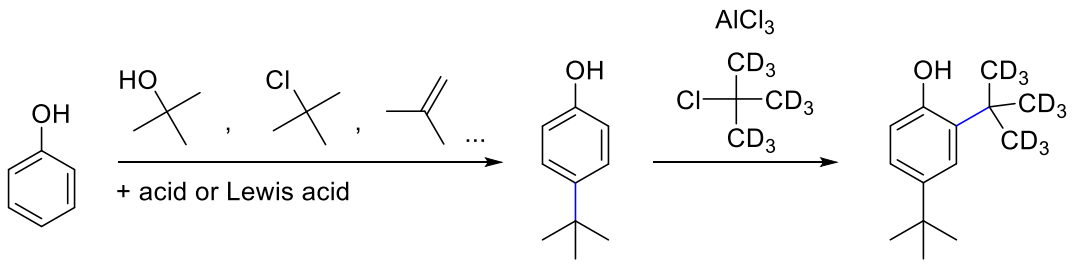
- Both have one proton and one electron
- Both have similar chemistry: they undergo the same reactions and have the same bonding or fundamental reactivity
- Both are non-radioactive (in comparison to tritium / T / ^{3}H)

… and some key differences:

- D has one neutron (whereas ^{1}H hydrogen does not, thus D is an isotope) and thus higher mass (~2x)
- Compared to analogous compounds with hydrogen, compounds with D have different physical properties (e.g., density, boiling point… – typically higher boiling and melting points) and reactivity (kinetic isotope effect, e.g., C-D bond is stronger than C-H)
- D has much lower natural abundance than hydrogen
- *Others* (e.g., D has spin = 1 while ^{1}H has spin = ½)

In medicinal chemistry, the key use of deuteration is to **slow down metabolism** at vulnerable sites ('soft spots'), theoretically extending the half-life of a drug and enabling reduced or less-frequent dosing (because the drug stays around for longer).

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

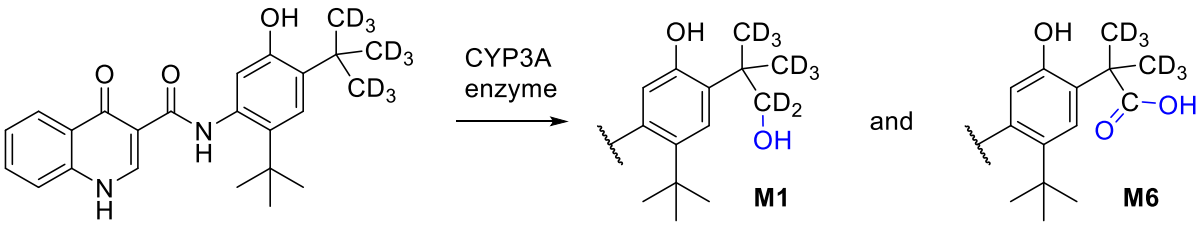


Phenol is an electron-rich aromatic compound, so any type of **electrophilic aromatic substitution reaction** will do. The sequence is key: We need to introduce the normal *t*Bu group **first** as any substitution will occur at the ***para* position prior to *ortho***. For the first step, many different reactions are known, from FRIEDEL-CRAFTS to "brute force" alkylations. They use different electrophiles but achieve the same goal (generation of a *t*Bu cation).

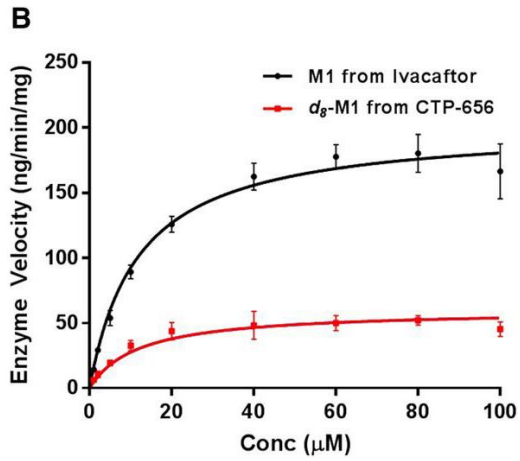
After the first alkylation, the para position is blocked so *ortho* is most reactive. The simplest answer is again a FRIEDEL-CRAFTS alkylation with d9-*t*Bu chloride. This is described in the patent on deutivacaftor. *Source: US9181192B2 patent*

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

During metabolism, enzymes in the body **modify a small molecule drug to increase its polarity, allowing easier excretion**. This can take several steps, but the most common initial reaction is the **oxidation of a C-H bond** performed by a "CYP" enzyme (cytochrome P450 monooxygenase).
It's obvious from our question that this is what happens here, because the drug developers have replaced the C-H bonds at the *t*Bu group with C-D bonds.



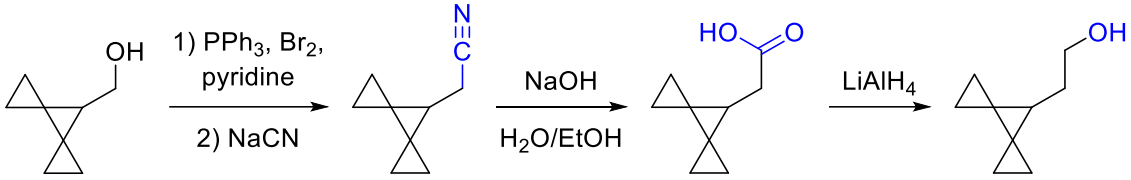
In the case of deutivacaftor, this leads to the formation of metabolite M1 and to a lesser degree, M6.



In this figure, an experiment with human liver microsomes indicates the **rate of formation of metabolite M1** at different concentrations of normal ivacaftor and deutivacaftor. This nicely shows the **slowed metabolization** because C-D bonds are harder to break and oxidize than C-H bonds. Deutivacaftor has a 47% longer half-life *in vitro* (so not measured in a living organism but fair enough) compared to ivacaftor.

Source: Journal of Pharmacology and Experimental Therapeutics 2017, 362, 359

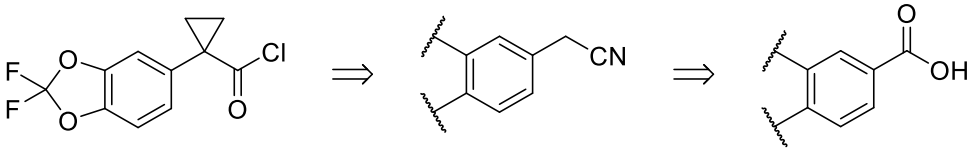
4 It's not terribly efficient, but a sequence of standard reactions leads to an overall extension by one carbon: **Appel reaction**, **substitution with cyanide**, **hydrolysis** and **reduction** back to the primary alcohol. It's important to realize that the carbon in cyanide is at the same oxidation state as carboxylic acids.



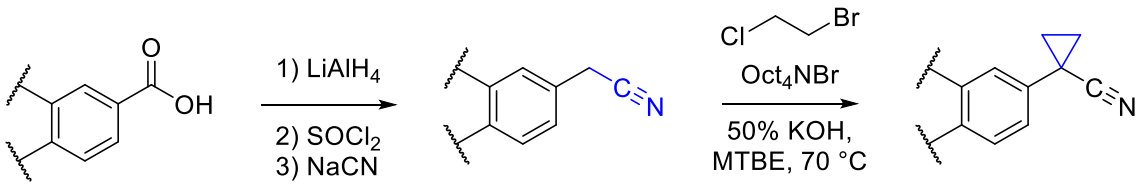
Cyanide is often used to introduce carbons into molecules. It's handy because it's nucleophilic but additional reduction steps might be needed, and hydrolysis conditions can be **aggressive**. This reaction proceeds with ~10 equivalents of NaOH and 70 °C overnight, so you can imagine that if we were in a more complex molecule, not every functional group would like this or survive! *Source: US11873300B2 patent*

I hope you agree the "dispiro[2.0.2.1]" group looks cool. *Today I learned:* series of spiro-linked cyclopropane rings are called **triangulanes**. So, this one is a [3]triangulane.
The discovery work behind these compounds is not disclosed (that's why I had to fish the info out of the patents). I would be really interested in how this ring differed from others during optimization and how the hell they even thought about introducing it! I'm not aware of any other compounds featuring this triangulane.

5 This question is a slightly more complex version of the previous one. We again use cyanide to introduce the additional carbon but this time, we also make use of an additional key property of cyanide: its **electron-withdrawing effect** and **acidification** at the α-carbon.

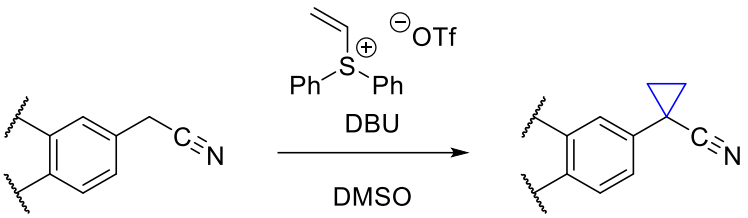


This means that **prior to nitrile hydrolysis** and acyl chloride generation, we should introduce the **cyclopropane through alkylation**. This requires a "1,2-electrophile" and some base (this specific reaction was done in a mixture of aqueous KOH and organic solvent MTBE with a phase-transfer catalyst). *Source: US10071979B2 patent*

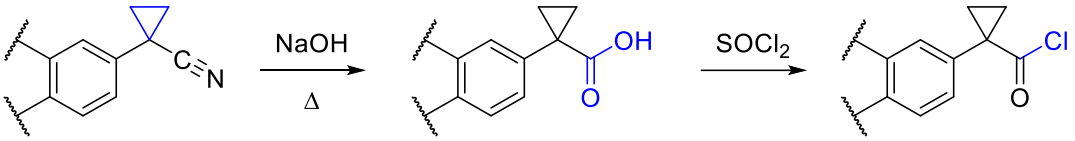


You might be wondering why the dihalide is mixed? You wouldn't do this by default on paper, but the patent says: *"It has been found that a mixed bromo and chloro dihalide works best on an economic scale as it is believed that the thermodynamics of the reaction are more favourable."* (what this actually means, I don't know lol).

That dihalide is also surely **carcinogenic** so the manufacturing will have controls to ensure that no concerning levels are carried into the final product over the next steps/ purifications.



Alternatively, other 1,2-electrophiles have been published in the literature for this specific reaction, e.g., the vinyl sulfonium salt here. *Source: Tetrahedron Letters 2018, 59, 1443*

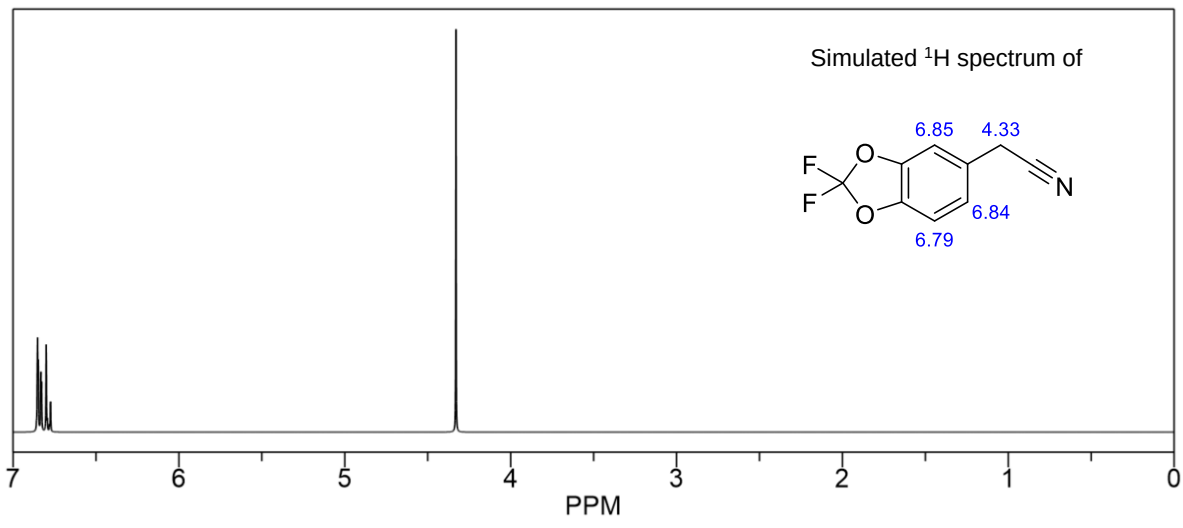


Finally, the nitrile is hydrolyzed, and the carboxylic acid is chlorinated. (Because the free acid does not undergo clean α-alkylation, you couldn't hydrolyze prior to cyclopropane-alkylation – unless you want to convert the nitrile to the **ester** first, which would need at least one additional step).

6 Apart from performing the cleanest isolation any chemist has ever seen, there is a big problem with the spectrum, and we don't need any integrals to spot it. Apart from the aromatic signals we have what looks like a sharp singlet at a relatively high chemical shift. **This is not what our alkyl CH_2 group should look like: we would expect a multiplet at a much lower chemical shift ($\delta < 2$ ppm)**.

The general answer is that you messed up somehow, and the specific answer following our synthesis is that you mixed up your samples, measuring the un-alkylated cyanide intermediate

Always label and track your samples!



7 Blockbusters are pharmaceutical drugs generating **>$1 billion** in annual sales. There were 152 of these in 2023 across the globe!
Alyftrek is expected to make the cut easily, with analysts estimating **$8 billion in peak sales**. This might be surprising given the combo only increases administration convenience and does not offer superior efficacy, but discussing this would go well beyond our problem set :)

So, you see, deuterium isn't a niche application. I think it's pretty insane that kinetic isotope effects – which sounds rather boring (it's related to physical chemistry after all) and seems to be mostly used in elucidation of mechanisms – can lead to such mega-blockbusters. As mentioned in our video, there are very sensible public concerns about drug pricing, equitable access and durability of intellectual property related to such therapies.

Exercise B: **Cyclopropyl**[3]

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

Normal cubane is stable and forms crystals. This was documented by EATON in his landmark cubane synthesis in 1964 already.

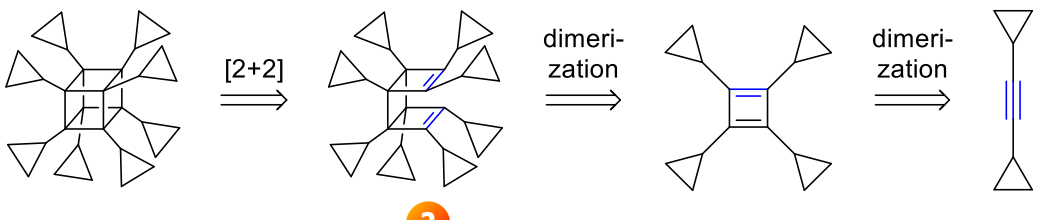
"Cubane is produced by thermal decomposition at 150° of the t-butyl perester of cubane carboxylic acid in diisopropyl benzene. The hydrocarbon is removed from the solvent as it is formed entrained in a nitrogen stream and then captured in an ice trap. Crystallization from methanol and sublimation just above room temperature at atmospheric pressure gives pure material as glistening rhombs, m.p. (sealed capillary) 130-131°." *Source: J. Am. Chem. Soc. 1964, 86, 3157*

You obviously couldn't know this, but based on the decoration with cyclopropyl groups, **you should expect this molecule to be more stable than the unsubstituted cubane.** The cubane core is obviously what's unstable, so by shielding it with relatively unreactive cyclopropyl groups, we increase the kinetic stability of the cubane core. These groups are like bodyguards protecting a "highly reactive celebrity" :)

Indeed, the chemists that made this compound found much higher stability:

*"Octacyclopropylcubane 3 has a **half-life of ≈3 h at 250 °C**. […] **Compared to cubane itself, which has a half-life of 24 min at 250 °C**, 3 experiences remarkable kinetic stabilization, and this must be a consequence of the steric encumbrance exerted on the core by the eight surrounding cyclopropyl groups. …* *Source: Angew. Chem. Int. Ed. 2007, 46, 4574*

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



?

Extra question: Suggest a name for this structure?

The obvious disconnection is taking apart one of the cyclobutanes (obviously it doesn't matter which side) through a **[2+2] cycloaddition**. We are left with "octacyclopropyl-*syn(/endo)*-**tricyclo[4.2.0.0^{2,5}]octa-3,7-diene**".

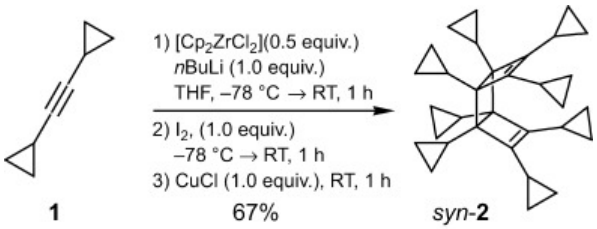
This structure is still symmetrical, so separating it through the middle is logical. A dimerization of a **cyclobutadiene** would achieve this. (Note that retrosynthetically it doesn't matter if the dimerization occurs with a [2+2] or [4+2] logic because both products are the same). The cyclobutadiene is **antiaromatic** and thus unstable, so we would need to form it *in situ* and hope that it dimerizes.

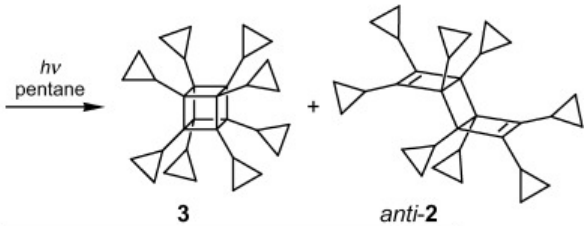
Because our cyclobutadiene is still symmetric (notice the pattern), we can simply propose another dimerization reaction. Obviously, there's a big question around what conditions would activate the dicyclopropyl**acetylene** to achieve this double-dimerization, but the retrosynthetic logic is simple.

The first and only investigation of this cubane achieved this first step through a protocol using **zirconium**.

Source: Angew. Chem. Int. Ed. 2007, 46, 4574

? Looking at the figure on the right, how do steps 1), 2) and 3) work?

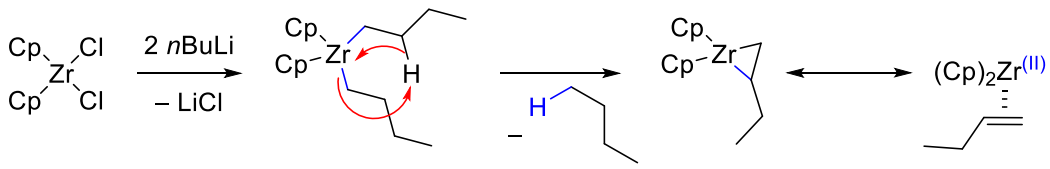




Temp. [°C]	3 (%)	anti-2 (%)
20	48	0
–30	17	10
–50	29	47

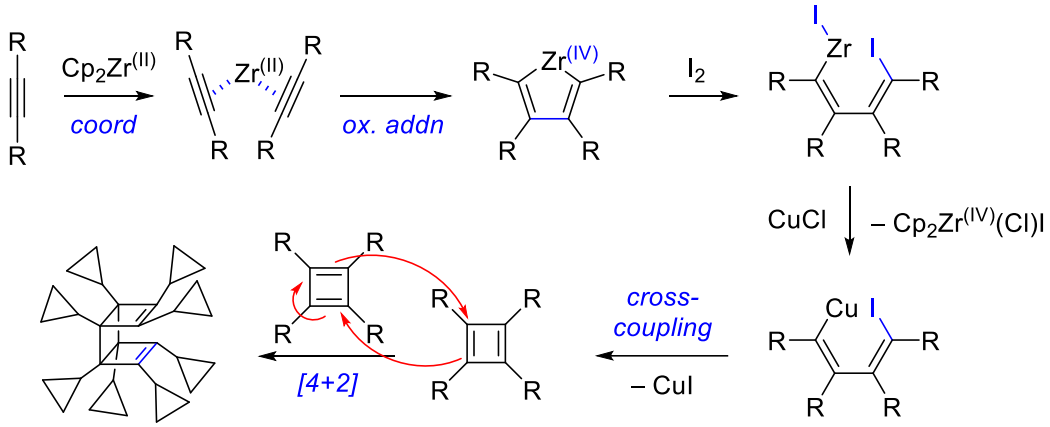
If you have seen prior zirconium magic, you might know that it often involves **Cp$_2$Zr(II) species**. We'll get to know why. But first, **how do we generate Zr(II)** for this first step?

We start with Zr(IV), so it needs to be **reduced** in some way. Our other reactant is *n*-BuLi, so it must be the reductant. In a first step, the highly nucleophilic butyl groups can **replace the chloride ligands**. Then, a **β-hydrogen abstraction** releases butane. The resulting complex can be present as a zirconacyclopropene or the **reduced [Cp$_2$Zr(II)]**. This combination/mixture is also known as NEGISHI reagent. *Acc. Chem. Res. 1994, 27, 124*



What happens next? The zirconium obviously helps to connect alkynes so evidently, we need to go through some Zr-C and C-C bond formations.

So, this is what I think it looks like *(I exclude the Cp ligands because they do not change)*: After coordination of the alkynes, an **oxidative cyclization** creates a zirconacyclopentadiene (it's like a (2+2+1) addition). Here we see why it's important that we start with Zr(II) and not Zr(IV). Zr has an electron-configuration of [Kr] $4d^2$ $5s^2$ so there's no way it would form an analogous Zr(**VI**) species.



These cyclopentadiene intermediates can be intercepted with different reagents but in step 2) of our cubane example, iodine can add across the Zr-C bond. Step 3) adds copper which suggests that there is a **transmetalation**. This creates a copper intermediate which can **cross-couple** our two loose ends together (oxidative addition to Cu(III) followed by reductive elimination). The result is a reactive cyclobutadiene which dimerizes in a thermal [4+2] fashion. Pretty wild that this all occurs with **67% yield**!

Interestingly, the final photochemical [2+2] gave a better yield at higher temperatures. At low temperatures, they saw higher degrees of isomerization to the *anti* ring instead.

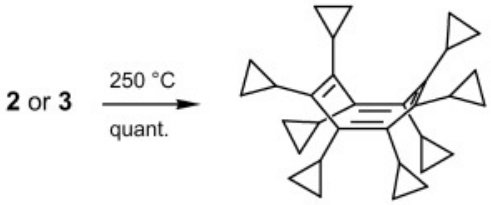
Last comment, because it's always good to look at the experimentals. Because the [2+2] is an intramolecular reaction, you would want to run it under **high-dilution conditions** (at low concentrations, molecules are less likely to run into each other intermolecularly so any intramolecular reactions will become faster). The experimentals read:

*"A solution of syn-2 (**117 mg**) in **50 mL** of pentane was irradiated in a 50-mL photochemical reactor with a quartz cooling sleeve with a 450-W medium-pressure mercury lamp and external and internal cooling at 20 °C for 3 h. After evaporation of the solvent and column chromatography on silica gel (10 g, Rf=0.67) 56 mg (48 %) of 3 was isolated as colorless crystals, m.p. >300 °C (decomp.)."*

This is a bit lazy writing because quantities in mol are missing. Doing the calculations ourselves, we can see that the concentration was **5 mmol/L** which is indeed very low.

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

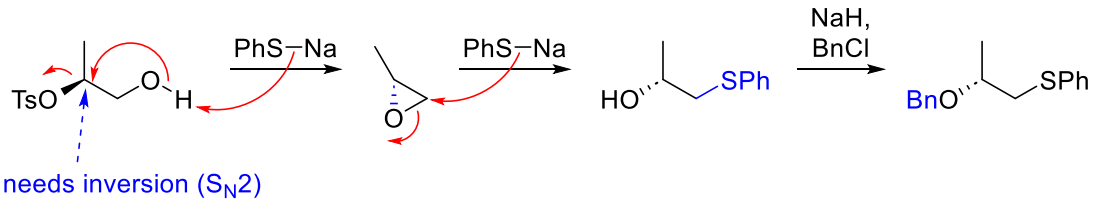
At high temperatures, the exceptional stability of the cubane becomes irrelevant as it will have enough activation energy available to get rid of its strain. Every cyclobutane cycloreverses to ultimately give a **cyclooctatetraene**.



Exercise C: **Grayanotoxin, but oldschool**

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

We have three objectives over the sequence: i) invert the configuration at the C-O bond, ii) introduce the phenyl sulfide group and iii) get a benzyl protecting group in there. It's key to realize that we have a **1,2 relationship of a nucleophile and a leaving group**. This means that in the presence of base, the free hydroxyl group will intramolecularly **form the epoxide with inversion**.

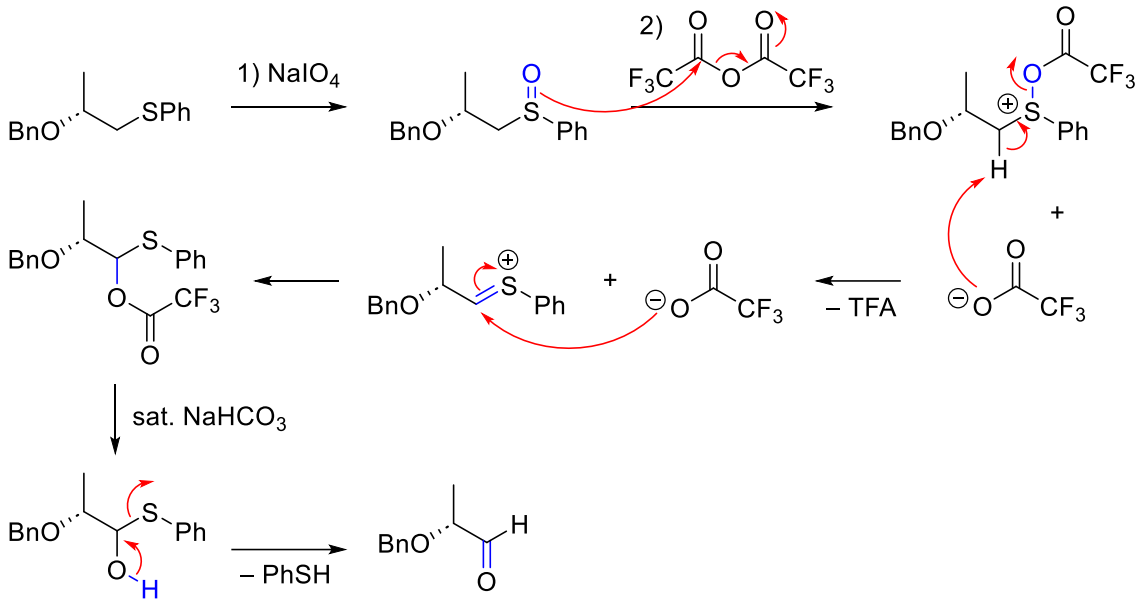


The reference synthesis found that by adding excess NaSPh, the epoxide forms in situ and gets re-opened by the nucleophile at the less hindered position. This achieves two objectives i) and ii) in one step. *J. Org. Chem. 1994, 59, 5532*

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

The first step oxidizes the sulfide to the sulfoxide. By the way, the exact mechanism for this might be quite complicated. *J. Org. Chem. 2012, 77, 1, 351*

More importantly, the subsequent addition of anhydride triggers a PUMMERER rearrangement (more common is Ac_2O, this here is the TFA-anhydride). Basic hydrolysis cleaves the ester and the unstable S,O-hemiacetal converts to the aldehyde. Overall, this process leads to oxidation of the carbon atom through reduction of the sulfur atom.

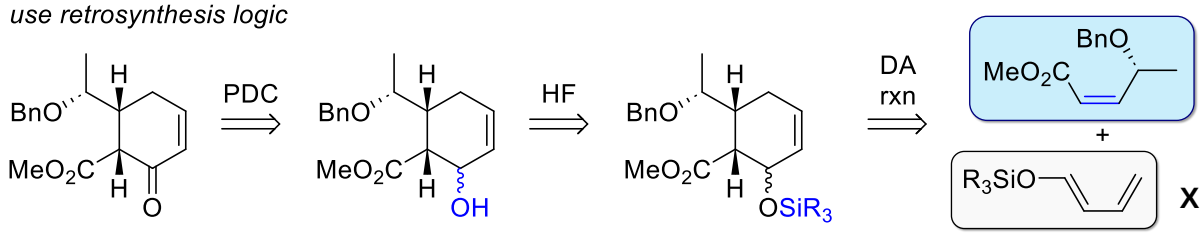


3 *Based on the aldehyde you just made, look at the full synthetic scheme (in combination with the next Q). Figure out what initial intermediate you need and how you would make it.*

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

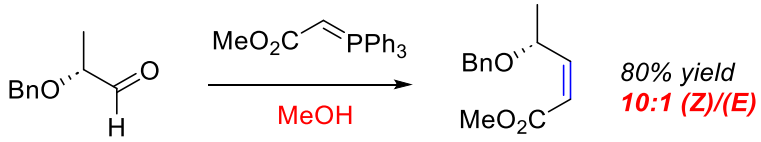
Let's solve these questions together. The final product is a 6-membered ring with a double bond, so it screams DIELS-ALDER reaction. The indicated steps likely suggest 2) removal of a silyl group with HF and 3) oxidation of a hydroxyl group to the ketone with PDC.

use retrosynthesis logic



Based on this, our **reactant X** should be a diene with a silyl-protected alcohol. This would be an electron-rich diene, so let's get an **electron-poor dienophile**. Deconstructing the DIELS-ALDER means we need a ***(Z)***-olefin (because substituents on the cyclohexane are *syn*). We can make that from our aldehyde through an olefination reaction.

Because we need *(Z)* and we introduced an electron-withdrawing group (i.e., "stabilized" ylide reagent), you would suggest using the **STILL-GENNARI modification** of the HORNER–WADSWORTH–EMMONS. **The reference synthesis used a WITTIG reaction…**



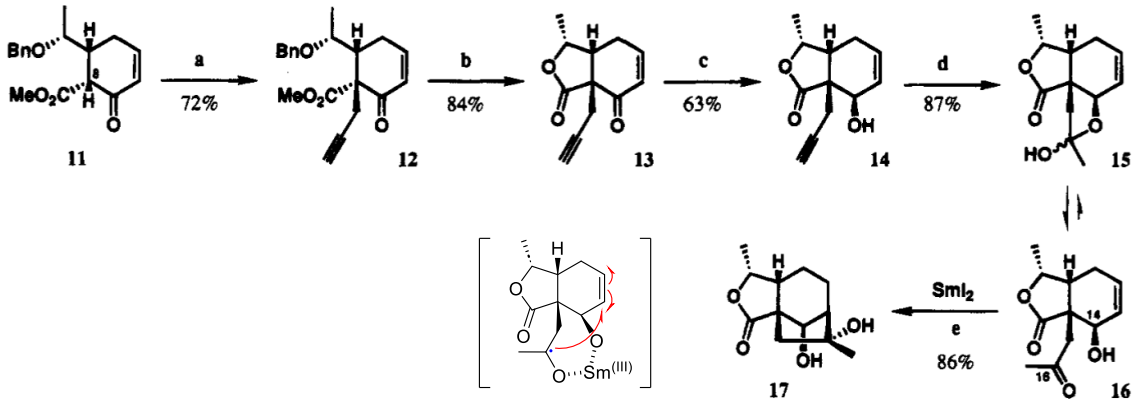
… but why would their reaction be *(Z)*-selective?!

Another key lesson here: **Never forget about the solvent**. For the WITTIG reaction, it's documented that alcoholic solvents like methanol **can** favor the *(Z)* isomer, even for stabilized ylides. The explanation doesn't seem obvious *(hydrogen-bonding that stabilizes TS/int. leading to (Z)?)* and there are also examples where methanol does not do this. This is more a reminder that there are exceptions all rules.

"It is well-known that the use of a stabilized WITTIG reagent in a nonpolar solvent leads to the (E) olefinic product. The corresponding (Z) isomer, however, very often constitutes the major product if the reaction is carried out in a hydroxylic solvent such as methanol.

Source: J. Org. Chem. 1982, 47, 1373 | Fun fact: the early K. B. Sharpless is on this paper (2x Nobel laureate)

5 *Suggest reactants for all steps and identify the missing product, incl. stereochemistry.*



[a] Key: (a) (1) NaH, DMF, 0 °C; (2) HC≡CCH$_2$Br, 0 °C; (b) FeCl$_3$, CH$_2$Cl$_2$, rt; (c) NaBH$_4$, CeCl$_3$·7H$_2$O, MeOH, −78 °C → rt; (d) NaAuCl$_4$·H$_2$O, H$_2$O−THF, 60 °C; (e) SmI$_2$, HMPA−THF, −78 → 0 °C;

Source: J. Org. Chem. 1994, 59, 5532

Quick rundown of the steps:

(a) **Alkylation with propargyl bromide** (diastereoselectivity driven by steric shielding of the other face by the β-substituent)

(b) Some form of LEWIS-acid mediated **benzyl ether cleavage**, the hydroxyl group closes to the lactone (hydrogenation conditions could impact the double bond)

(c) **LUCHE reduction** to the allylic alcohol, avoiding 1,4-reduction with $CeCl_3$. Presence of the α-substituent favors addition from the face opposite to it

(d) Some type of metal **catalyzed cyclization**. Au(III) used here but any suggestion like Hg(II) or Pd(II) works

(e) **Intramolecular cyclization** of a ketyl-radical with the olefin. Formation of the **five-membered ring is faster** than the six-membered one (if you didn't know this, this is a generally correct rule of thumb). Given a free hydroxyl group is present, we can assume there is **chelation** (again, see Problem Set #1).
"Obviously, the observed stereochemistry of 17 is established by chelation between the C-14 hydroxyl group and the resulting Sm(III) cation generated after single electron transfer from SmI_2 to the C-16 ketone functionality of 16.

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

As always, thank you for your interest and your **feedback**.

Total Synthesis

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