Solutions | Problem Set #1 – Solving Organic Synthesis

🫣 Did I just catch you peeking without thinking *hard* about the problems first?

Just kidding :) Here are the solutions to our first problem set along with some commentary for additional on context or chemistry. Let me know if these exercises are interesting/ instructive and if you have any topics you want to practice or learn about in particular!

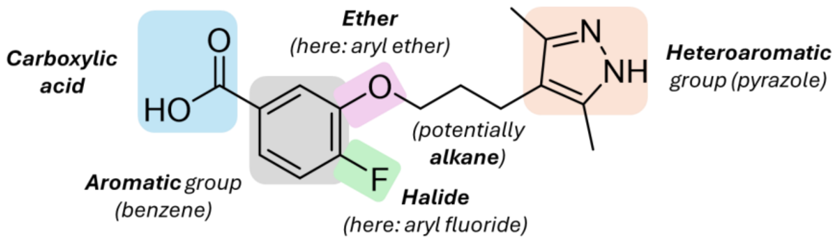
For reference, these are the levels of difficulty. *I might need to tune them down a bit?*

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

Exercise A: Acoramidis

I loved looking at "real" examples of molecules when studying. So, I picked a newly approved pharmaceutical drug that allows us to explore a little bit of biochemistry as well.

① *Q: Identify five functional groups in acoramidis' structure.*



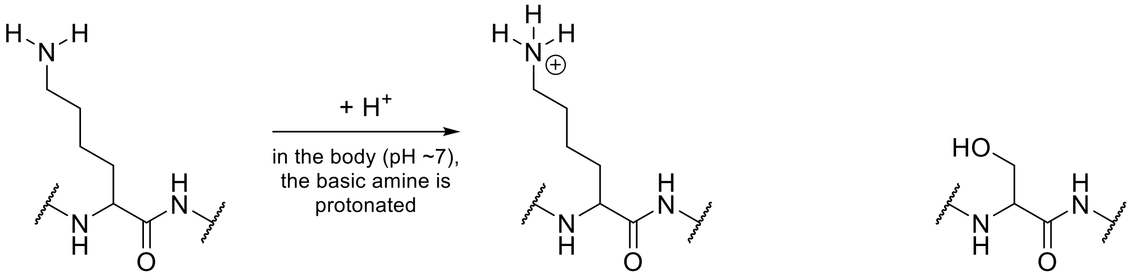
Two comments on this type of question: Your teacher/professor might or might not count alkanes as a functional group. If allowed, this is a free point if you see this in an exams. Or maybe, your teacher is also being sneaky and asking for more FGs than you see at first glance. In that case, you might be allowed to double count, e.g., highlighting an alkene within an aromatic ring as a functional group.

② *Q: 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: NAS 2013, 110, 9992

This question seems simple at first sight, but I included a trick to see who is really paying attention! To understand the question, you need to know about **intermolecular interactions** (hydrogen bonds, salt bridges) and **basicity/acidity of functional groups**.

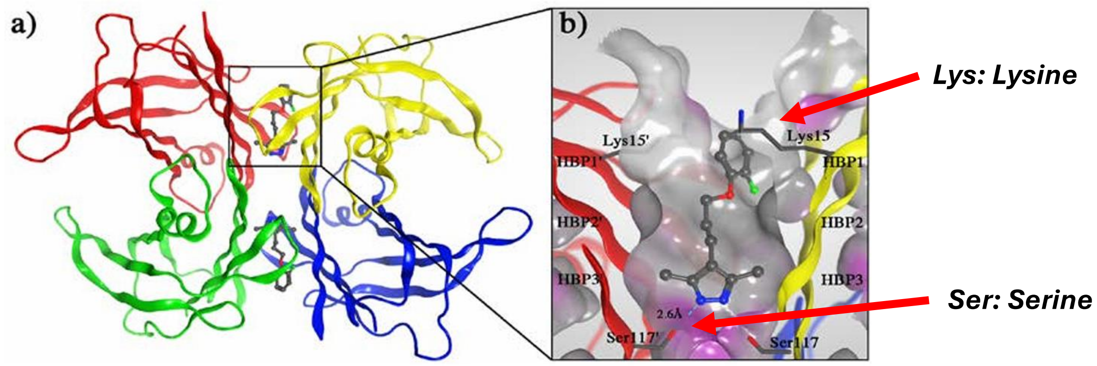
To elicit an effect on their biological target, drugs can literally react with them (covalent inhibition) or simply interact through **non-covalent intermolecular interactions**. Thus, this question requires us to **identify sources of intermolecular attraction between acoramidis and the TTR protein**. Proteins are made of amino acids, and the **only two amino acids** labeled in the figure are **lysine (Lys)** and **serine (Ser)**.

These two amino acids have functional groups as well. Lysine has an **amino group**. This group is **basic** and is protonated at neutral pH which means that in the body, lysine is present in its ionic ammonium form. Serine has a **hydroxyl group** (aka hydroxy aka alcohol).



Lysine ***Serine***

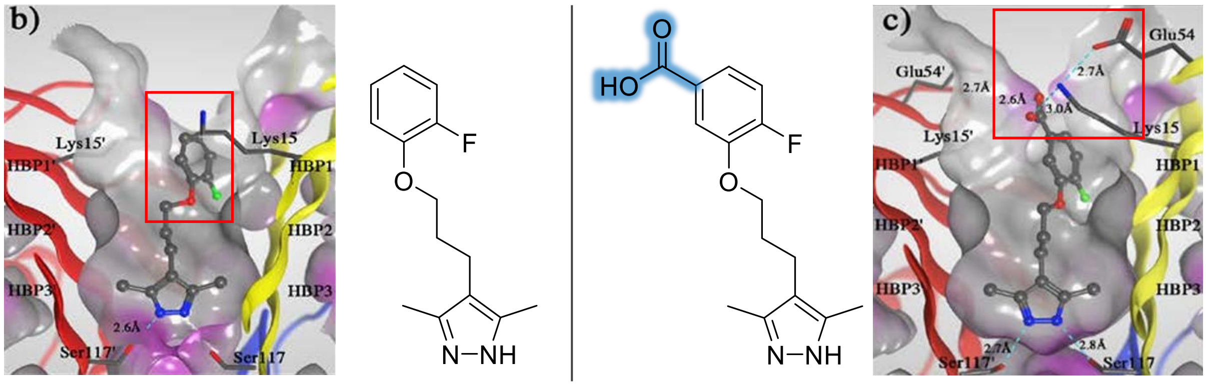
By considering their **location in the crystal structure**, we see that they are close to the respective aromatic rings – Lys is close to the benzene, while Ser is close to the pyrazole.



Without taking a close look, you might conclude that:

1. Lys' positive charge probably **interacts with the deprotonated carboxylic acid** of acoramidis (acids are negatively charged 'carboxylates' at neutral pH) through a **salt bridge** (electrostatic interaction; opposite charges attract).
2. Ser's hydroxyl group interacts with the pyrazole ring through **hydrogen bonding**. This is indicated with the 2.6 Å distance and a dotted bond.

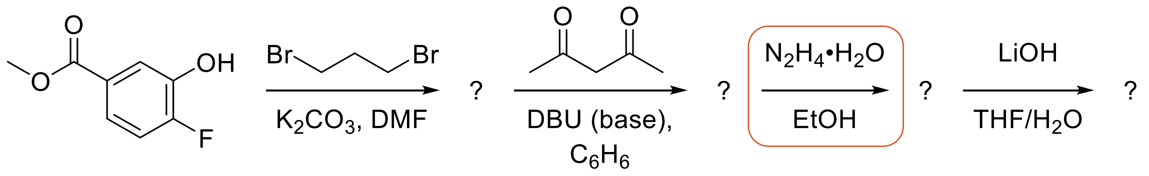
So where is the trick? Well, if we inspect the benzene ring of our ligand more closely, we realize that **this molecule is not acoramidis** because it lacks the carboxylic acid!



Our first crystal structure does not actually show acoramidis – **only the right one does**! There, you can also see the newly marked electrostatic interactions between the carboxylate, our lysine and even another glutamate (Glu) in the protein. Glu is an amino acid with a carboxylic acid. Just like acoramidis, it's deprotonated at neutral pH.

If you didn't notice that the figure lacks the acid, remember to **always inspect data carefully and critically**. As this is not a formal exam, I figured I can be a bit tricky.

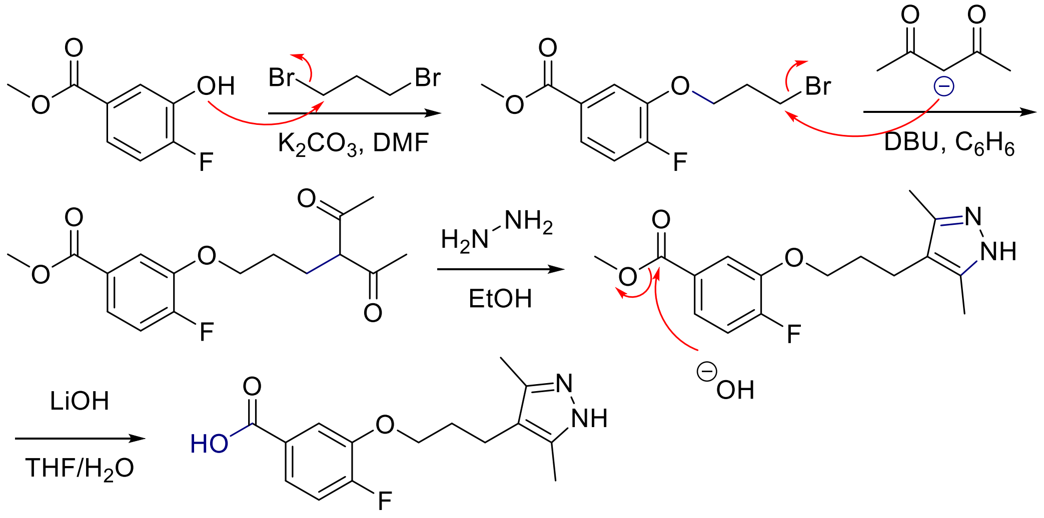
3 *Q: The synthesis of acoramidis features just four steps from this starting material which can be bought. Fill in the gaps, and draw the mechanism for the highlighted step.*



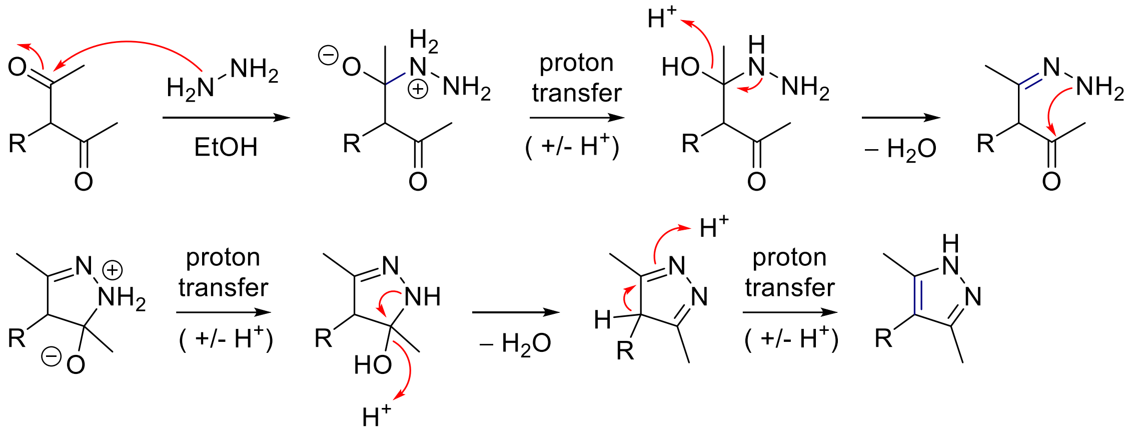
Before we go into the solutions, you should appreciate that such multi-step synthesis schemes can sometimes be **solved forwards OR also partially backwards**! Sometimes we get stuck going forward. Sometimes, we can use backward/retro-logic for hints, or to at least gain a conceptual understanding.

Thinking backwards: Here, we know that the product is acoramidis and we know its structure already (because the exercise says so and this time, it's not a trick). The starting material contains a methyl ester but acoramidis doesn't. Thus, we know that at some point, there is a hydrolysis reaction. Indeed, this is the last reaction in the scheme. The reaction with hydrazine looks less clear, but it's also quite clear that this is a way to synthesize the heteroaromatic **pyrazole** ring. The diketone brings additional the carbon atoms present in our pyrazole ring, and the first reaction obviously attaches the linker to the aromatic ring.

Forward synthesis: I've indicated some electron movements but note that these aren't full mechanisms! The reactions are **ether synthesis** via S_N2 / alkylation, **α-alkylation** of the enolate formed by base, **pyrazole synthesis** and **ester hydrolysis**.



This way of making pyrazoles is called the **KNORR pyrazole synthesis**, named after the same chemist as the (PAAL-) KNORR pyrrole synthesis.

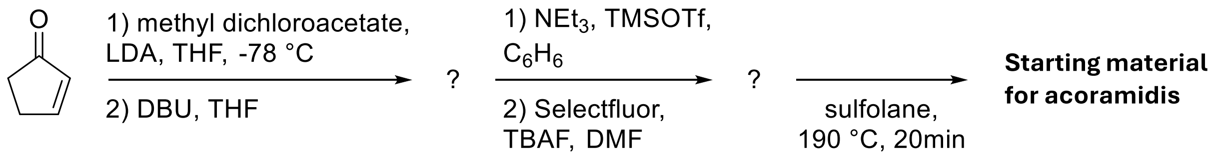


This reaction, like many heteroaromatic syntheses, leverages the nucleophilicity of nitrogen (or other heteroatoms for other types of rings). The mechanism includes two condensation reactions and aromatization to the pyrazole.

Note that hydrazine is particularly nucleophilic due to the **α-effect**. If you haven't heard of it and you are already in your 1st year of undergrad, better Google it.

4 *Q: Fill in the gaps and draw all mechanisms.*

Source: Angew. Chem Int. Ed., 2015, 54, 11835



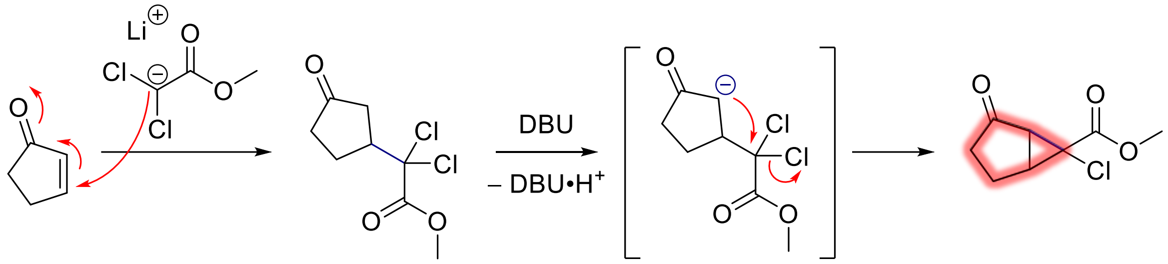
Now this synthesis of acoramidis is more challenging. We again know our final product (the starting material for acoramidis in question 3). However, the last transformation seems very strange so we can't "think backwards" as much as we did before.

But we can still hypothesize a few things based on just looking at the reactions overall:

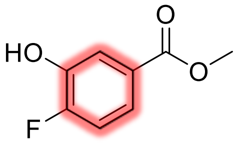
- The conditions of the last step (short time at very high temperatures) might remind you of rearrangement, pyrolysis or extrusion reactions. Our initial starting material is a five-membered ring, and our product contains a benzene ring, so we **clearly need a rearrangement** somewhere to expand the ring.
- The Selectfluor (source of electrophilic fluorine) step will introduce the carbon-fluorine bond which we require in our product.
- The addition of methyl dichloroacetate will introduce the methyl ester.

Note that my mechanisms will again not be completely "written out" (just key steps/ ideas).

The missing carbon (to get from 5- to 6-membered ring) is added through the first step. Here, the LDA base deprotonates α to the acetate reactant, creating an enolate nucleophile that can add in a 1,4-manner to the enone (conjugate addition). The second step is an **intramolecular cyclization** to create a three-membered ring.



Through the intramolecular cyclopropanation, we have completed the linkage of our target benzene ring!

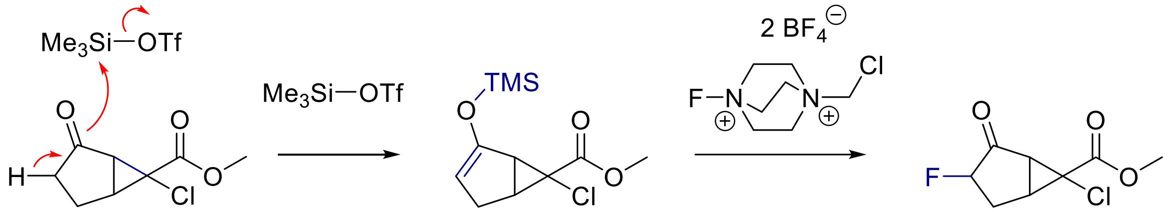


When I saw this, I wondered: if the enolate forms upon conjugate addition anyways, is a separate reaction with DBU necessary? I checked the original procedure that reported this methodology *Tetrahedron 2001, 57, 9423*. They write:

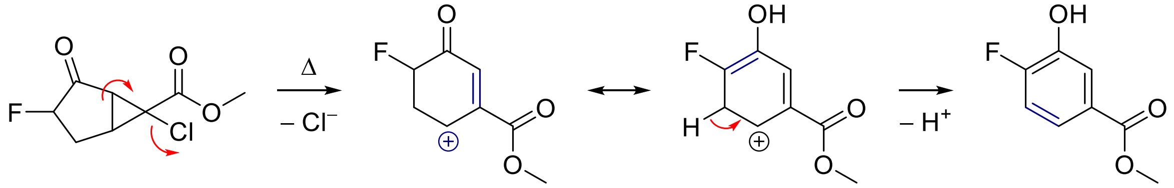
"Although the reaction of cyclopentenone with methyl dichloroacetate anion ***gives rise directly*** *to the corresponding cyclopropane,* ***the other enones examined*** *afforded the 1,4 addition products that required the presence of DBU for subsequent cyclization. Therefore, the cyclopropanation can be considered as the result of a 'tandem process'."*

The publication at hand (*Angew. Chem Int. Ed., 2015, 54, 11835*) opted for the 2-step/tandem process regardless. Maybe this way was more reproducible, or higher yielding in their hands (they got 65% of cyclopropane product vs. 62% reported in the original procedure).

The next two steps are **enol ether formation** and **α-fluorination of the ketone**.

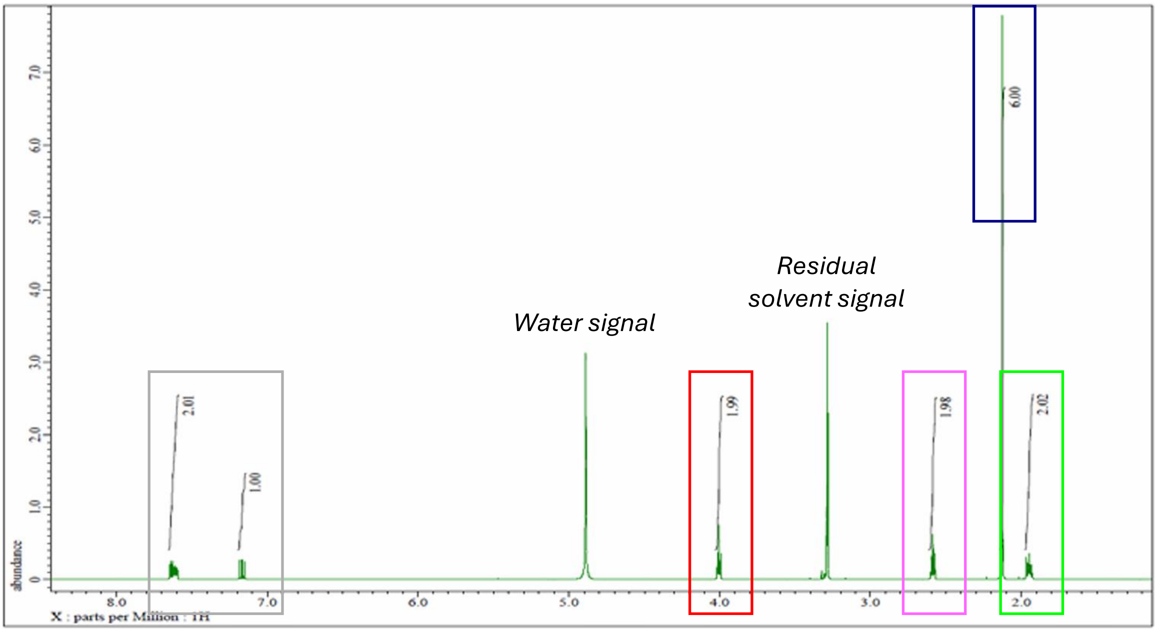


Finally, we need to figure out the mechanism that transforms the cyclopropane into the benzene. Cyclopropanes have significant **ring strain** energy, so when we see high temperature conditions, we might anticipate that this is some sort of **thermal ring opening**.

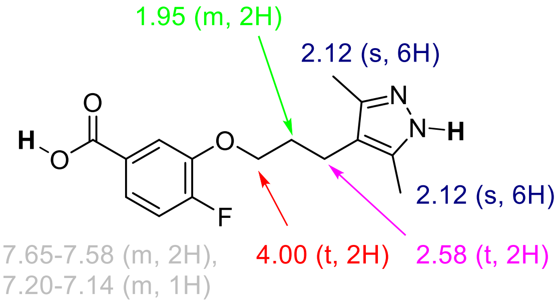


At high temperatures, the cyclopropane can open up to give an **allyl-type cation**. The opening is 2π-electron disrotatory but stereochemistry is not important here. The cation is stabilized by the **enol** form of the ketone. A deprotonation gives the aromatic product.

⑤ *Q: 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?*



First, the spectrum looks very clean which is always good! Next, we should **count the hydrogen integrals** in the ^{1}H NMR and **compare them with our molecule**. The multiplicity and chemical shifts are straight-forward if you've studied ^{1}H NMR structure determination (can't explain it all here!). The **aromatic** signals of the benzene protons are trickier to assign but overall, the number is what we expect. I'd say the most shielded proton is the one ortho the fluorine, while the two protons ortho to the acid are more de-shielded.

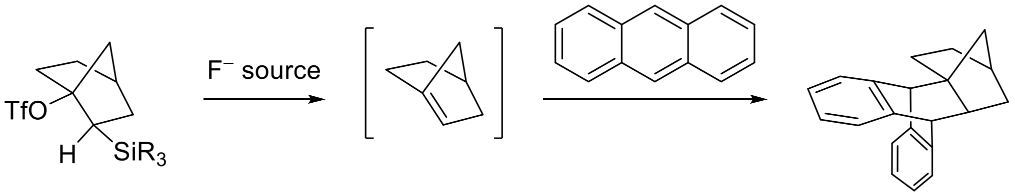


The bolded carboxylic acid O-**H** and pyrazole N-**H** cannot be seen but theoretically we would expect them to show up more downfield (de-shielded, higher chemical shift). These heteroatom-bound hydrogens are **exchangeable**, meaning the protons can spontaneously exchange for deuterium in deuterated NMR solvents. This is where your critical thinking should activate, as we have **not specified our solvent in the exercise yet**! It's **CD_3OD**, so it's not surprising that we can't see them (protic solvent, i.e., can easily exchange D^+ with our analyte). The same phenomenon can occur in standard $CDCl_3$ if the solvent bottle/ ampule is not fresh (formation of trace DCl).

Overall, we're happy with the NMR as excluding the absence of the exchangeable protons, we could match all signals to acoramidis! Indeed, this is the published spectrum of acoramidis *PNAS 2013, 110, 9992*.

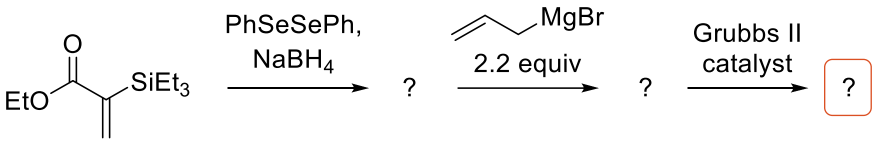
Exercise B:

This exercise is a deeper dive on our recent video on ***anti*-BREDT olefins** (link) with the first two questions drawing on the 2024 publication *Science 2024, 386, eadq3519*.

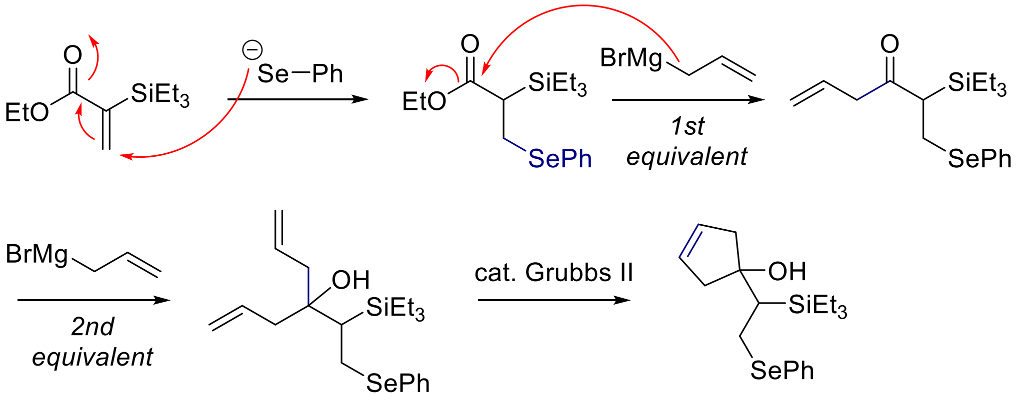


① *Q: In that video we heard that chemists found a way to **create very strained olefins** (which defy Bredt's rule) by using a fluoride-mediated elimination of a [2.2.1] ring precursor.*

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?



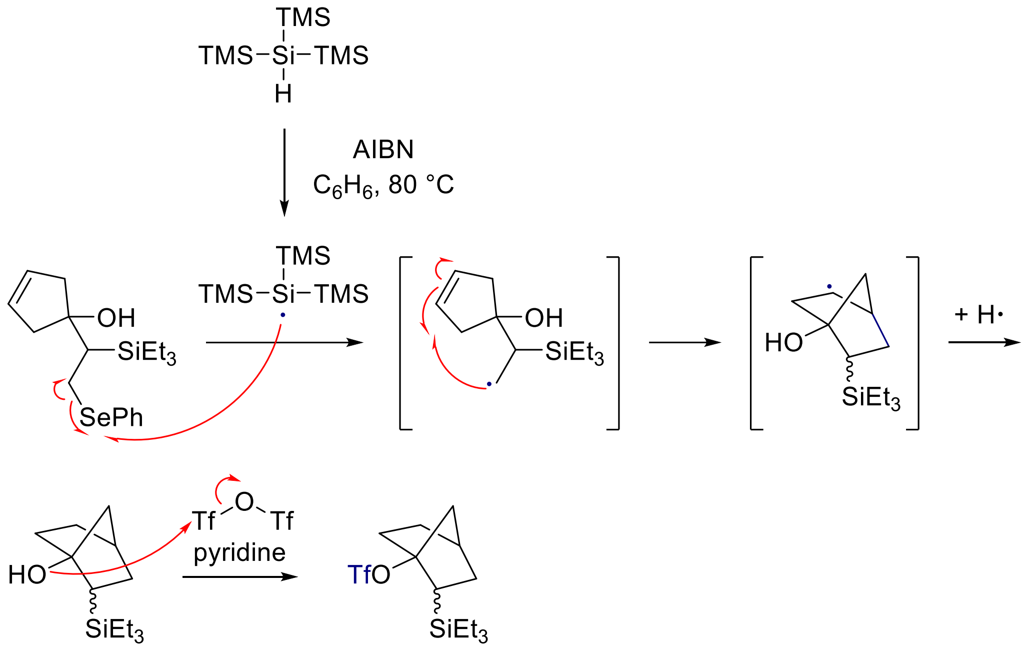
The first step is a **conjugate addition** of a selenide nucleophile formed from reduction of diphenyl diselenide with sodium borohydride. Then, >2 equivalents of allyl GRIGNARD reagent attach **two allyl groups to the carbonyl**. Remember that ketones (products of GRIGNARD reactions with esters) remain nucleophilic so excess reagent will keep adding to them! The GRUBBS catalyst mediates the **ring closing metathesis** of these two olefins to give a cyclopentene. This creates one of the two rings in our final target.



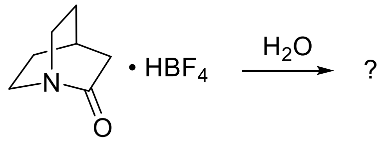
② *Q: Suggest how we could convert the product above into the anti-BREDT precursor.*

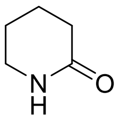
To finalize our *anti*-BREDT precursor, we need to simply **create the bridge** of the [2.2.1] ring system and introduce a triflate group. The cyclization needs to occur between the carbon bound to the selenium and the olefin of the cyclopentene. This can be achieved by **generating a carbon radical**, making use of the weak carbon-selenium bond. After all, we need to practice some radical reactions too!

The authors of this publication used **AIBN** and **TTMSS** as a radical initiation system. AIBN is well known to undergo thermal decomposition, generating free radicals which can react with TTMSS in a radical propagation reaction. TTMSS works like the more commonly seen **tributyltin hydride** (Bu_3SnH) – instead of a weak Sn-H bond, this one has a weak Si-H bond. The generated TTMSS radical cleaves the C-Se bond, creating a reactive carbon-centered radical that can cyclize with the olefin intramolecularly. The conversion into the *anti*-BREDT precursor requires a final triflation of the hydroxyl group.



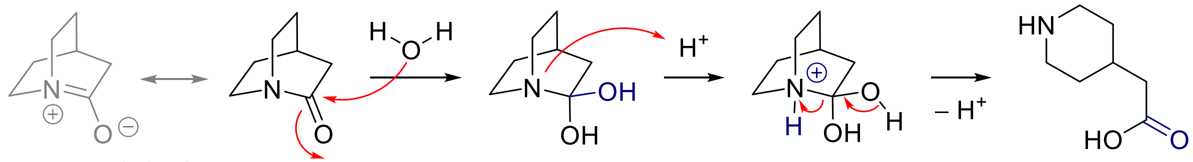
3 *Q: What reaction do you expect to occur in water? How does the reactivity of the 2-quinuclidonium compare to the lactam shown on the right and why?*





Finally, an easier question again! *Nature 2006, 441, 731*

There is no functional group apart from the amide, so the only possible reaction is **hydrolysis** to the acid. But shouldn't amides be resistant to nucleophilic addition of water because of electron donation of the nitrogen's electron pair?



Resonance is irrelevant; thus, amide is electrophilic

The bridged ring is **strained** to begin with, but the typical amide resonance structure also **has no contribution** because it would be an ***anti*-BREDT olefin**. On the other hand, 2-piperidinone is much less reactive and requires harsher hydrolysis conditions.

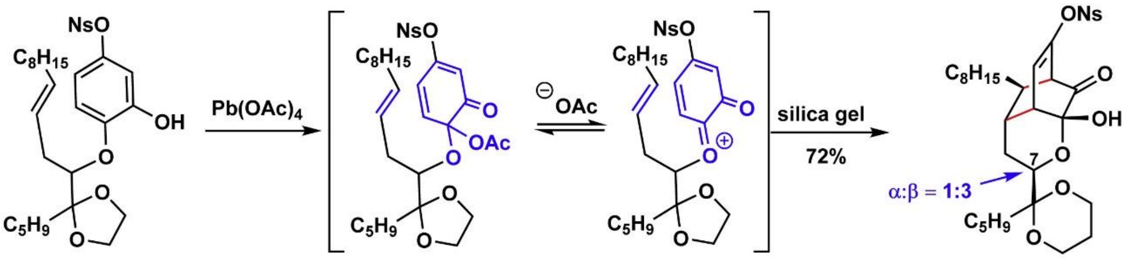
In their 2006 paper, the authors write:

"In the ^1H NMR spectrum acquired ***1 min after dissolving 1·HBF_4 in D_2O****, **only the ring-opened amino acid was observed, corresponding to a $t_{1/2} < 15$ s**. The reaction with 5 equiv. of D_2O in CD_3CN (0.084 M) was slower, with $t_{1/2} = 135$ min. Additionally, 1·HBF_4 is unstable to manipulations in common nucleophilic solvents (DMSO, pyridine, MeOH) aside from CH_3CN and Et_2O. Attempts to observe 1 by free-basing 1·HBF_4 have been unsuccessful, and have resulted largely in polymeric material. These observations illustrate the **propensity for this unusual amide linkage to undergo nucleophile-induced cleavage** and highlight the fragile nature of this interesting molecule."*

4 *Q: Their first key step was the reaction of this intermediate with* ***lead acetate****. What is the product?*

Sources: Chem 2020, 6, 579 (review); Angew. Chem. Int. Ed. 2018, 57, 1723 (total synthesis)

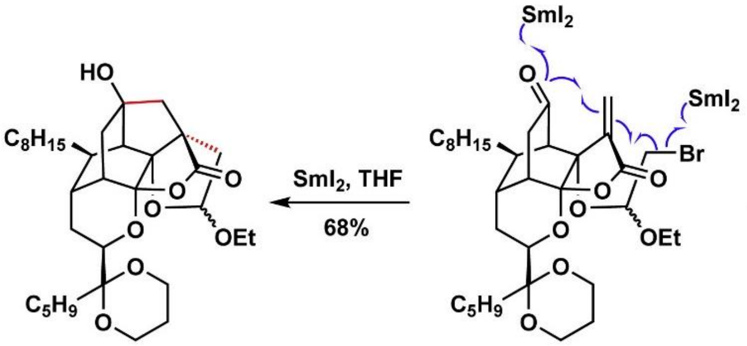
The next three questions are based on a synthesis of **phomoidride D**, a natural product containing a bridgehead olefin. Drawing these structures would be very annoying so I will just paste figures from the papers.



The representation already indicates that the olefin and the arene might react given their proximity. Lead tetraacetate is an **oxidant** and the phenol ring is very electron-rich – it's a perfect match! The resulting diene can undergo a **cycloaddition** with the olefin. Such de-aromatization/DIELS-ALDER sequences are common in natural product synthesis.

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

Samarium(II) is a **one-electron transfer reagent**. The combination of Sm(II) and a carbonyl **screams ketyl radical generation**! If we believe the scheme below, the radical undergoes two cyclizations (5-*exo*-trig, then 5-*exo*-tet) though they are definitely not concerted.

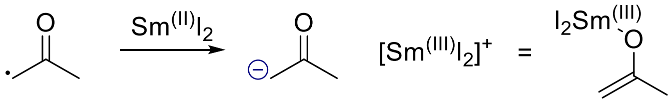


Remember how I tricked you in question A.2 to highlight the importance of **thinking critically** and analyzing data or figures carefully? I wasn't planning on highlighting this topic again this fast, but here we are. **Published literature can contain wrong, inaccurate or misrepresented content!** To explain this, we need to take a slight detour…

So, radical reactions with single-electron transfers reagents can proceed:

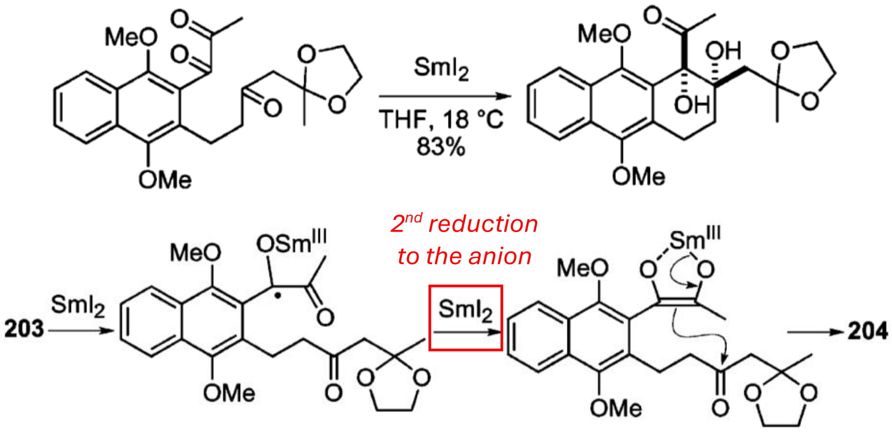
i) Through a "**fully radical**" mechanism. This is what we see in the scheme above, all the arrows are single electron movements.

ii) Through a **"radical, then polar"** mechanism. This is commonly seen for Sm(II)-initiated cascade reactions that feature **enol radicals** as intermediates. Why do these often switch to a polar mechanism? Radicals **α to electron-withdrawing groups are readily reduced** as they can accommodate an additional electron very well through mesomeric stabilization (here, forming the Sm(III)-enolate).



SmI_2 reactions typically use an **excess** of reagent, so there is more than enough single electron transfer in the reaction. By the way, the rate of this 2nd reduction depends on the concentration of SmI_2 – if the concentration is very low, then the radical might react faster in another way. For a complicated cascade reaction, it can be quite the wizardry to get the experimentals just right in the lab.

In the figure above, we started with the α-keto radical for simplicity. Here is a real sequence to exemplify the point (*Chem. Rev.* 2004, *104*, 3371). After ketyl radical generation, a **2nd SmI_2** reduces the system to the **enolate**. This is really a perfect example because it also shows that Sm(III) can chelate / coordinate to multiple oxygens (important for future exercises).

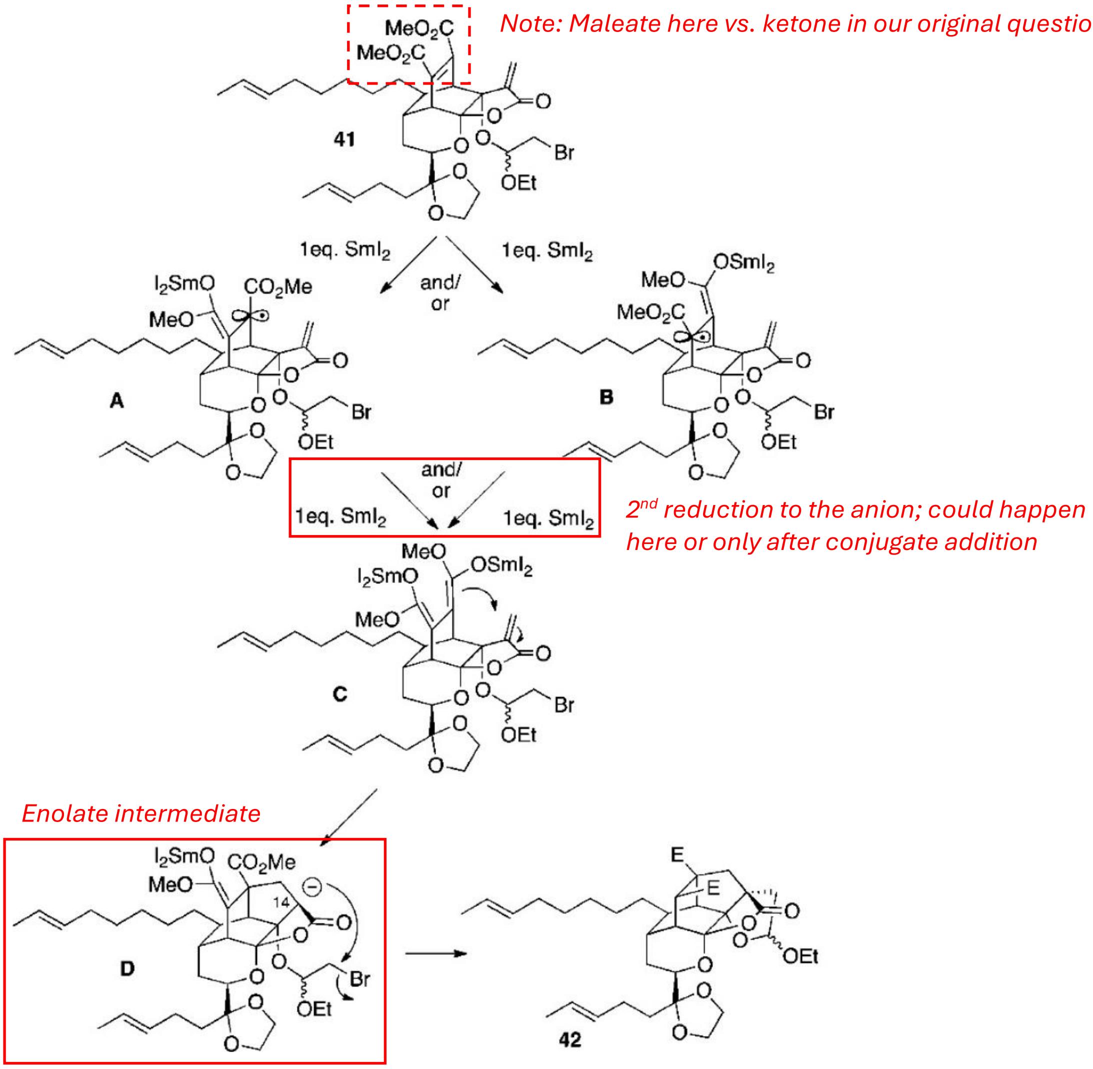


The key realization is that in our question ⑤, our first conjugate addition would form an α-keto radical. It would make more sense if this mechanism were also **"radical, then polar"**: Instead of a continued radical cascade, we have a **second single electron reduction** followed by polar enolate alkylation (S_N2 at the alkyl bromide).

Going into a reference (*J. Org. Chem.* 2013, *78*, 477) of the original total synthesis of pleuromutilin (*Angew. Chem. Int. Ed.* 2018, *57*, 1723), we can find that the **original authors do suggest such a "radical, then polar" mechanism** for a slightly different system.

They write:

"Reduction of the maleate double bond in ***41*** *delivers vinylogous ketyls* ***A*** *and* ***B*** *that, upon a second electron transfer, furnish bis-enolate* ***C****. Reaction of* ***C*** *via a 5-endo-trig Michael addition into the pendent exo-methylene lactone produces an intermediate enolate (****D****) that is poised to undergo a 5-exo-tet displacement of bromide to complete the cyclization and produce* ***42****."*



Note: Maleate here vs. ketone in our original question

2nd reduction to the anion; could happen here or only after conjugate addition

Enolate intermediate

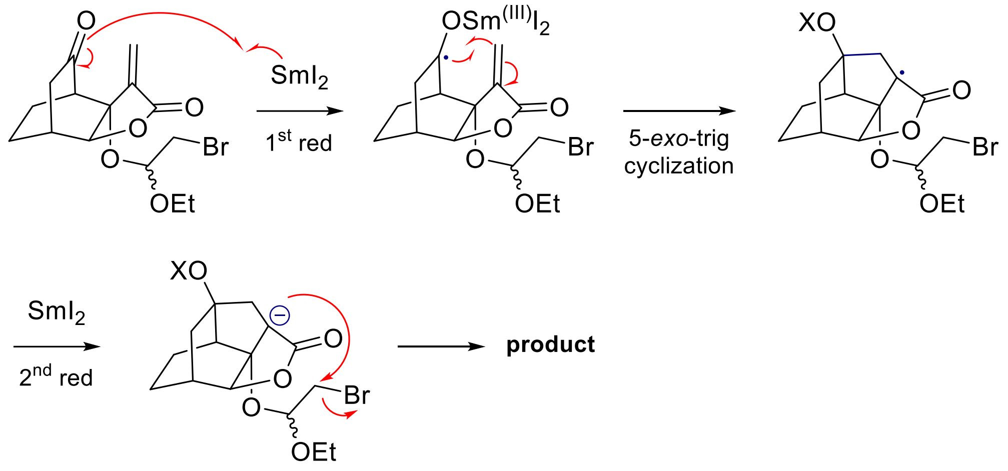
Regarding the sequence of the 2nd single electron transfer, the authors add in a footnote:

"It is possible that the ***initial cyclization is a radical event****, in which case the resultant C(14) radical would be reduced to the enolate D prior to the second cyclization".*

This sequence is exactly what I would expect to happen in our original question. Because we only have a ketone, our ketyl radical is more reactive towards immediate intramolecular cyclization. You can remember that **unstabilized ketyl radicals usually react directly** while as discussed, stabilized radicals α to electron-withdrawing groups could get reduced first.

The scheme on the next page shows a more likely mechanism (I omitted the parts of the molecule that don't react).

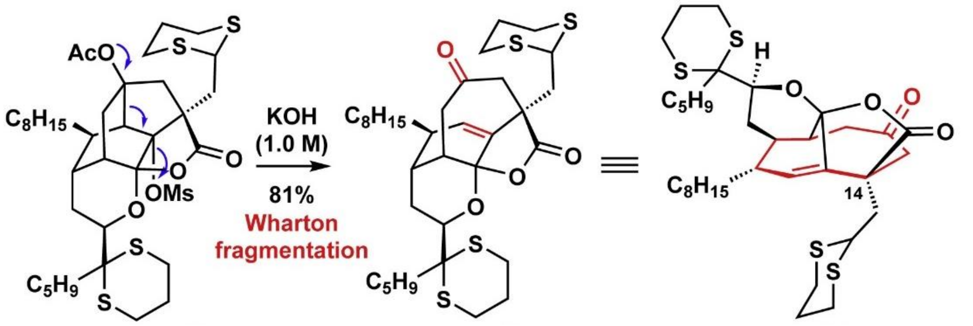
Always pay attention and keep your brain on! Inaccuracies can be present in all journals or research, regardless of "prestige" or impact factor.



⑥ *Q: 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?*

This one is tricky. The question itself has a little bit of a hint as it implies that the ring system changes its structure somehow. But where is the reaction? Notably, we now have a leaving group (-OMs). You might look for ester hydrolysis or an elimination reaction. We kinda have both!

For a normal elimination, you would need a hydrogen α to the mesylate. However, we can kick out leaving groups without hydrogens, assuming we have another bond that can break (instead of C-H). If we want to use more nerd speak, the mesylate is the nucleofuge while the C-C bond acts as the electrofuge. Here, the **C-C bond *anti* to the C-O**(Ms) bond is well positioned (*anti* key for orbital orientation) and activated upon cleavage of the acetyl group.



This is an awesome application of an uncommon reaction (Grob-Wharton fragmentation), creating the bridgehead olefin and finalizing the target ring system in one step.

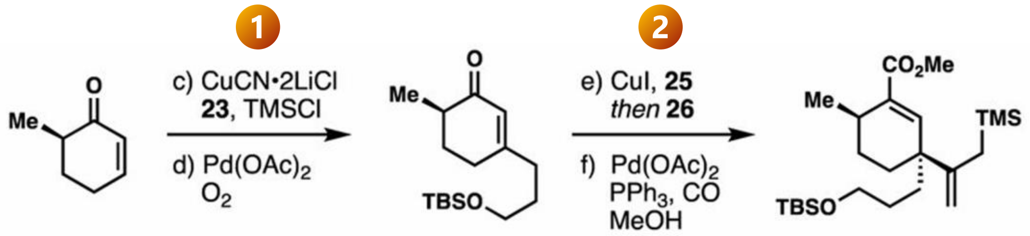
⑦ *Q: You will have seen that between the structures in question 5 and question 6, the protecting group on the lower side chain of the molecule has changed. How are these new protecting groups called, and what are similarities vs. differences compared to the initial group?*

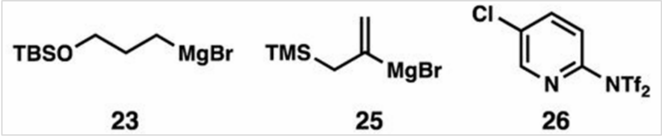
The oxygen-based **acetal** protecting group (1,3-dioxane) was exchanged for sulfur-based **thioacetal** (1,3-dithiane).

- Similarities: Same oxidation state, similar mechanism of formation, both types of cyclic acetals are more stable than their acyclic counterparts; …
- Differences: **Thioacetals are more stable towards acidic hydrolysis than acetals**, thioacetals are less stable to reductive methods than acetals (e.g., RANEY nickel/H_2), thioacetals are particularly labile to heavy metal salts like mercury (or some other LEWIS acids), thioacetals can be converted to nucleophiles through **Umpolung** chemistry…

Exercise C: *Sources: Chem. Eur. J. 2013, 19, 6718; Nat Prod Rep. 2018, 35, 174*

Because some of you said you are interested in radical mechanism, this exercise will culminate in more radical fun. It's from a synthesis of **(+)-pleuromutilin**. This natural product inhibits the protein synthesis of bacteria, finding some use as an antibiotic in veterinary medicine and even humans (lefamulin, a derivative of pleuromutilin, is used to treat pneumonia)





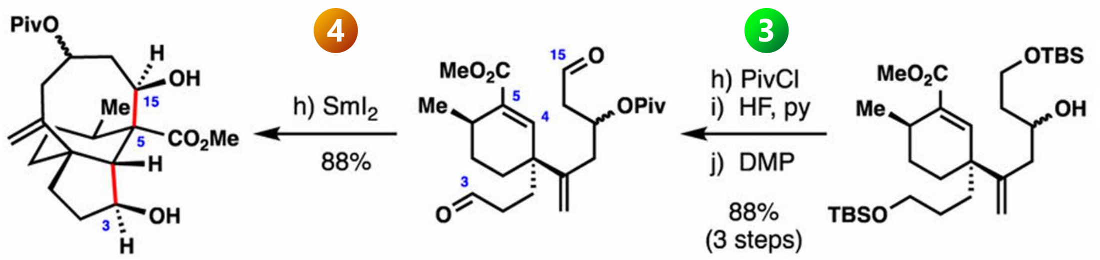
23 **25** **26**

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

Conjugate addition of an **alkyl nucleophile equivalent** followed by **regeneration of the enone** through desaturation. The synthesis here is particularly efficient as the enolate formed by the conjugate addition of the GRIGNARD reagent **23** is trapped as the silyl enol ether to set up the SAEGUSA-ITO oxidation.

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

Conjugate addition of an **alkenyl nucleophile** followed by **methoxycarbonylation**. We have the same efficient concept here: after addition of **25**, the enolate intermediate is immediately triflated with COMINS' reagent **26** to avoid an addition experimental step.



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

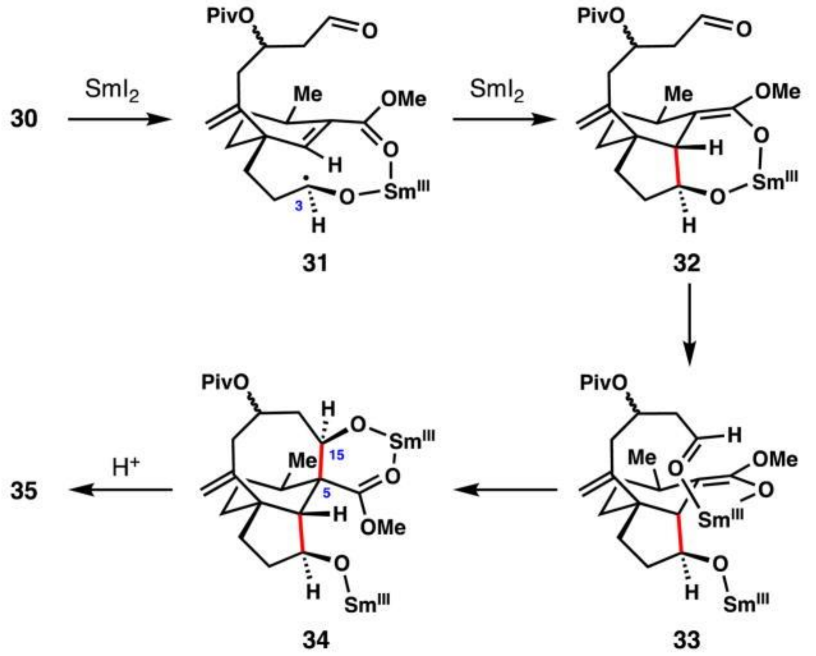
For a clean sequence, the free secondary hydroxyl group should be protected prior to TBS deprotection and oxidation of the primary hydroxyls. There was a good reason to choose the pivalate as the protecting group. The authors write:

"The protecting group for the secondary hydroxyl in 4b proved significant: dialdehyde 4b was ***more stable and easier to isolate than the analogous substrate*** *bearing an* ***acetate*** *protecting group."*

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

In no shock to anyone, this is another case of **samarium(II) + carbonyls = radical fun**. It also follows the "radical, then polar" mechanism that we've seen in exercise B.5.

There are four key steps: 1) **ketyl radical generation** through single-electron transfer; 2) radical **cyclization** (5-*exo*-trig), 3) a **second single-electron reduction** to the enolate *(exercise B.5!)*, and 4) an intramolecular **aldol reaction** to form the eight-membered ring.



The samarium controls the mechanism through **chelating effects** which we've already mentioned. It encourages selective formation of the **(Z)**-Sm(III) enolate (this is needed for it to keep binding to both oxygens), and it subsequently controls the diastereoselectivity of the aldol addition as well.

Was this problem set a difficult start to the series? I'd like everyone – from beginners to advanced students – to learn something which is why I kept it mixed, but one idea could be to create problem sets limited to a certain level (e.g., 1st year undergrad).

Your **feedback** and support is encouraged.

Thank you,

Total Synthesis

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