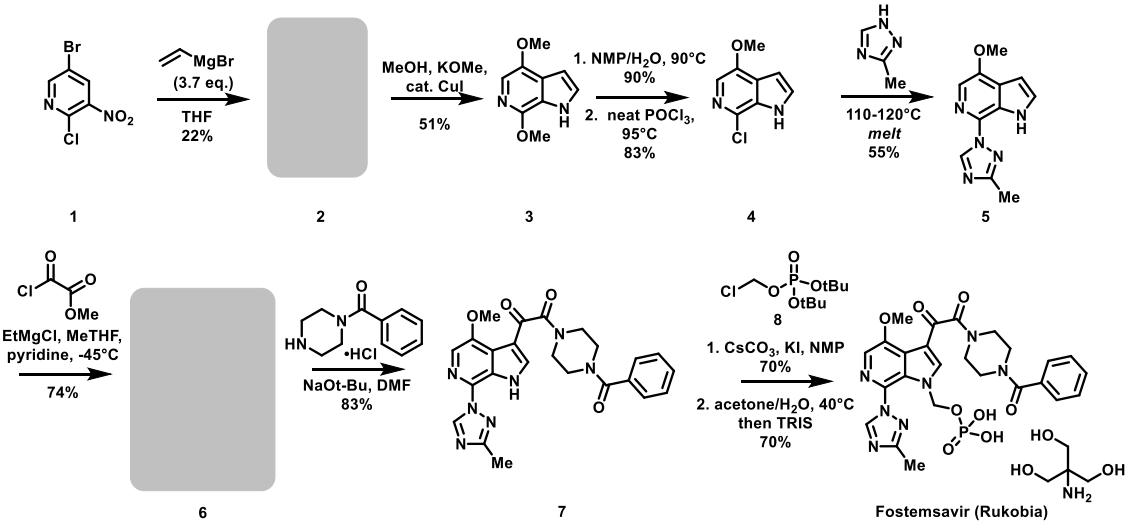
Fostemsavir is a is an antiretroviral medication for the treatment of HIV/AIDS. It was approved for medical use in the US in July 2020, and then in the EU in February 2021. It was discovered by Bristol-Meyers Squibb, and then developed by ViiV Healthcare. Below I have outlined the medicinal chemistry route for its synthesis, followed by a >1000 kg scale route published in 2022.

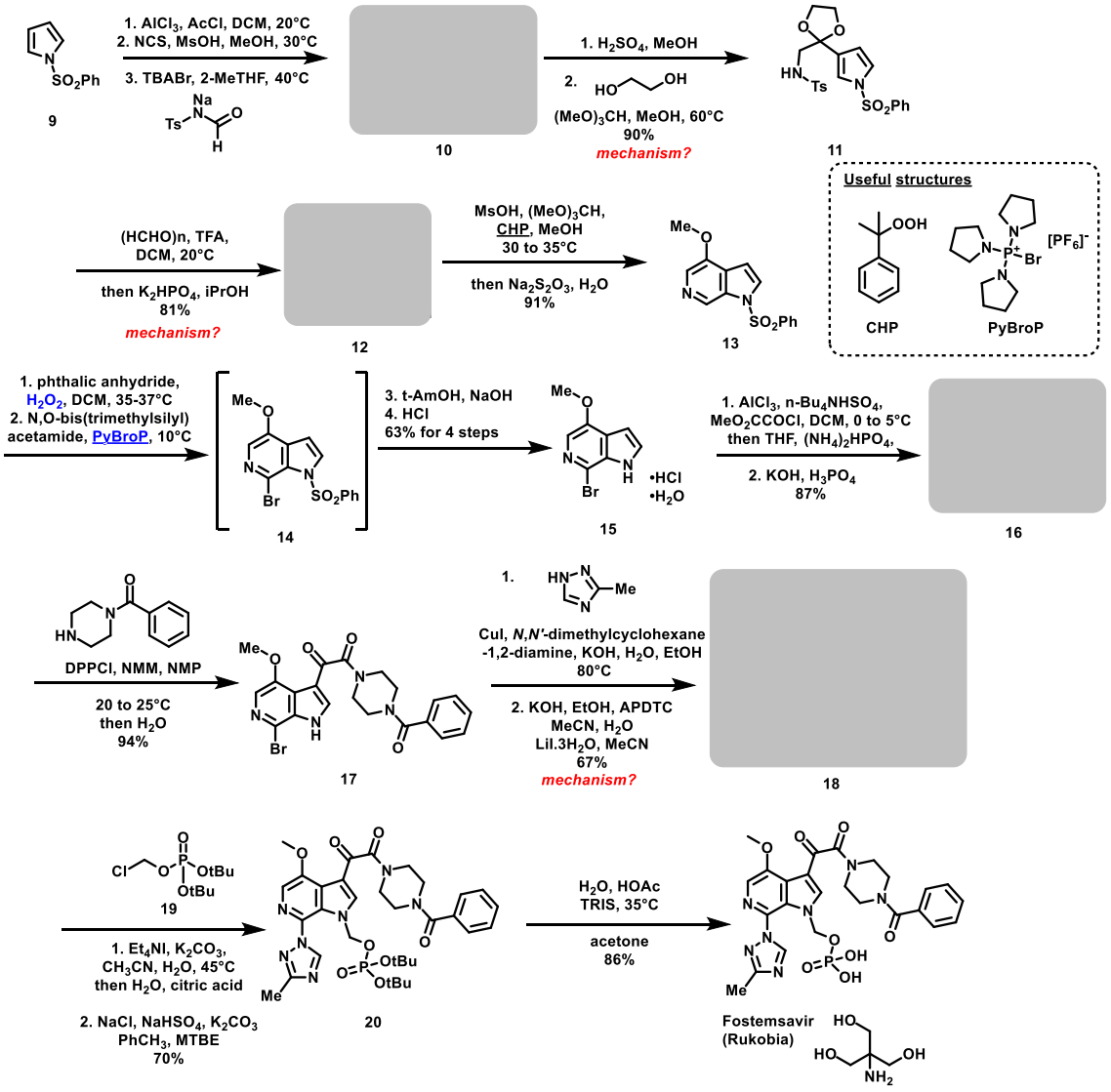
- *Consider the development and process shown below, and think about how they differ. What steps in the first route would be unsuitable for use on an industrial scale?*

Development Route:



1. Suggest a sensible route for the synthesis of compound **1** (consider the reactivity of pyridines).
2. Give the structure of **2**, and provide a mechanism for its formation. Why are 3+ equivalents of Grignard necessary for this transformation? (Hint: named reaction – acidic workup is often needed to get to final product)
3. Explain the chemoselectivity in the formation of **4.**
4. Provide the structure of **6**, and justify the selectivity.

Process Route:



1. Give the structure of **10**. Justify the regioselectivity of the pyrrole substitution.
2. Provide a mechanism for the formation of **11** from **10**.
3. Give the structure of **12**, and provide a mechanism for this transformation (Hint: named reaction).
4. Consider how the bromination step from **13** to **14** proceeds (key reagents in each step are highlighted in blue)
5. In this case, tert-amyl alcohol and NaOH is used to deprotect the benzenesulfonyl group to give **15**. Suggest an alternative method for deprotecting sulfonamide-protected amines.
6. Provide the structure of **16**.
7. Provide a mechanism for step 1 for the formation of **18** (step 2 simply forms the Li salt of **18**).