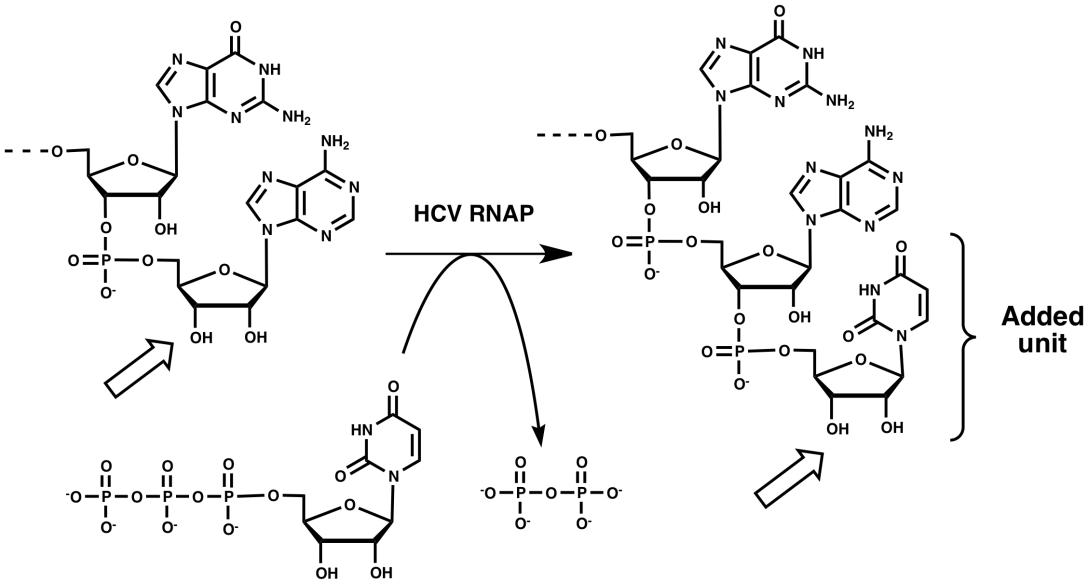
Jobs for professional organic chemists? (Chem 345, Gellman)

Example: Drug development (sofosbuvir)

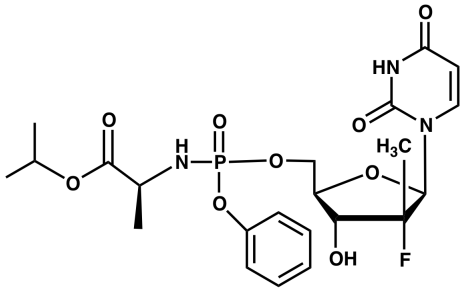
Sofosbuvir is a new drug to treat hepatitis C infections, which afflict as many as 200 million people and can lead to liver failure or liver cancer. This drug is expected to revolutionize medical care for HCV patients, because a complete cure is often achieved after only several weeks of treatment. Other drugs are far less effective and harder to administer, and they cause serious side effects.

The HCV genome is RNA; in contrast, humans store their genome as DNA. A critical aspect of the viral infection/replication cycle is RNA-templated RNA synthesis. Since this process does not occur in humans, inhibitors of the HCV RNA polymerase (HCV RNAP) are expected to be powerful antiviral agents with few toxic side effects for patients.

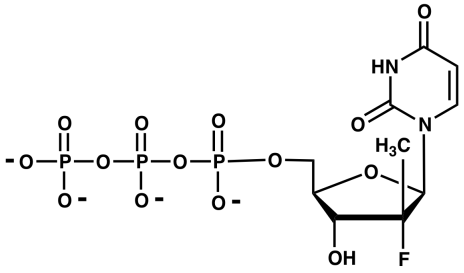
Chemical function of HCV RNAP is illustrated below; the arrow shows the hydroxyl group at which a new unit is added to extend the RNA chain.



Organic chemists led the search for molecules that could mimic the triphosphate substrate of HCV RNAP but not allow further extension of the RNA chain. After synthesis and evaluation of many candidate molecules, sofosbuvir was identified.

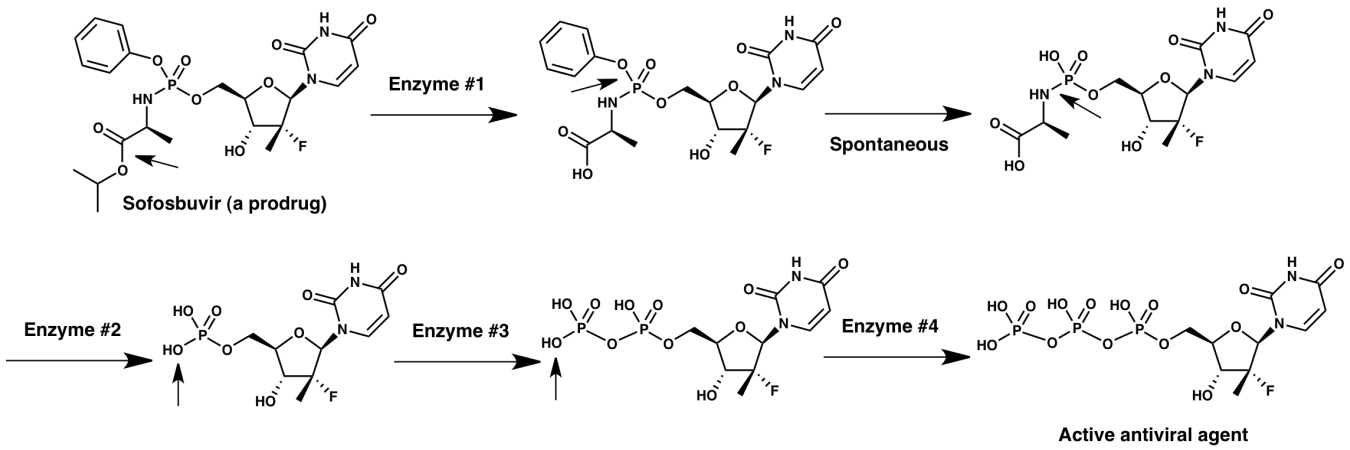


Sofosbuvir (a prodrug)



Active antiviral agent

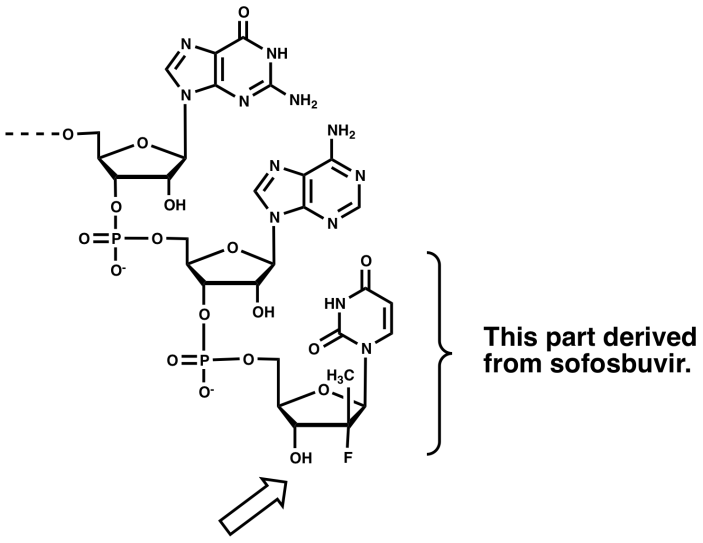
Sofosbuvir is not the active antiviral agent. Instead, sofosbuvir is converted into the active agent, shown above on the right, via several enzymatic transformations in the human body. Thus, sofosbuvir is referred to as a "prodrug". The transformation process is indicated below (note the different style of drawing these compounds below vs. above).



In the reaction scheme above, the arrows on the upper structures show the bond that is broken in the next reaction, while the arrows on the lower structures show the atom to which a new phosphate group is added.

Why not simply use the active compound as the drug? The answer to this question lies in physical and biological properties. Sofosbuvir is "orally bioavailable", which means that a patient can take a pill orally, and the molecule will make its way through the GI tract and into the bloodstream. In contrast, the active agent is <u>not</u> orally bioavailable. This compound could be delivered intravenously, but this mode of administration is *vastly* less appealing to patients, and therefore vastly less effective from a health perspective.

The active agent will bind to HCV RNAP and be incorporated at the end of the growing RNA chain, as shown below. At this point HCV is unable to add another unit at the hydroxyl indicated by the arrow below, because of the unnatural methyl group on the adjacent carbon, which apparently has unfavorable steric interactions with HCV RNAP. Thus, viral RNA replication is halted.



Teams of organic and analytical chemists, biochemists, biologists, chemical engineers and other highly trained professionals worked together to develop this valuable new antiviral drug.