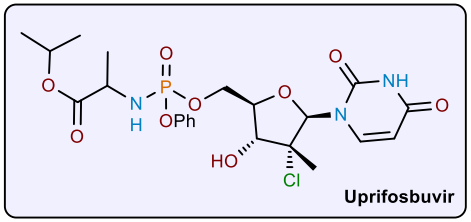
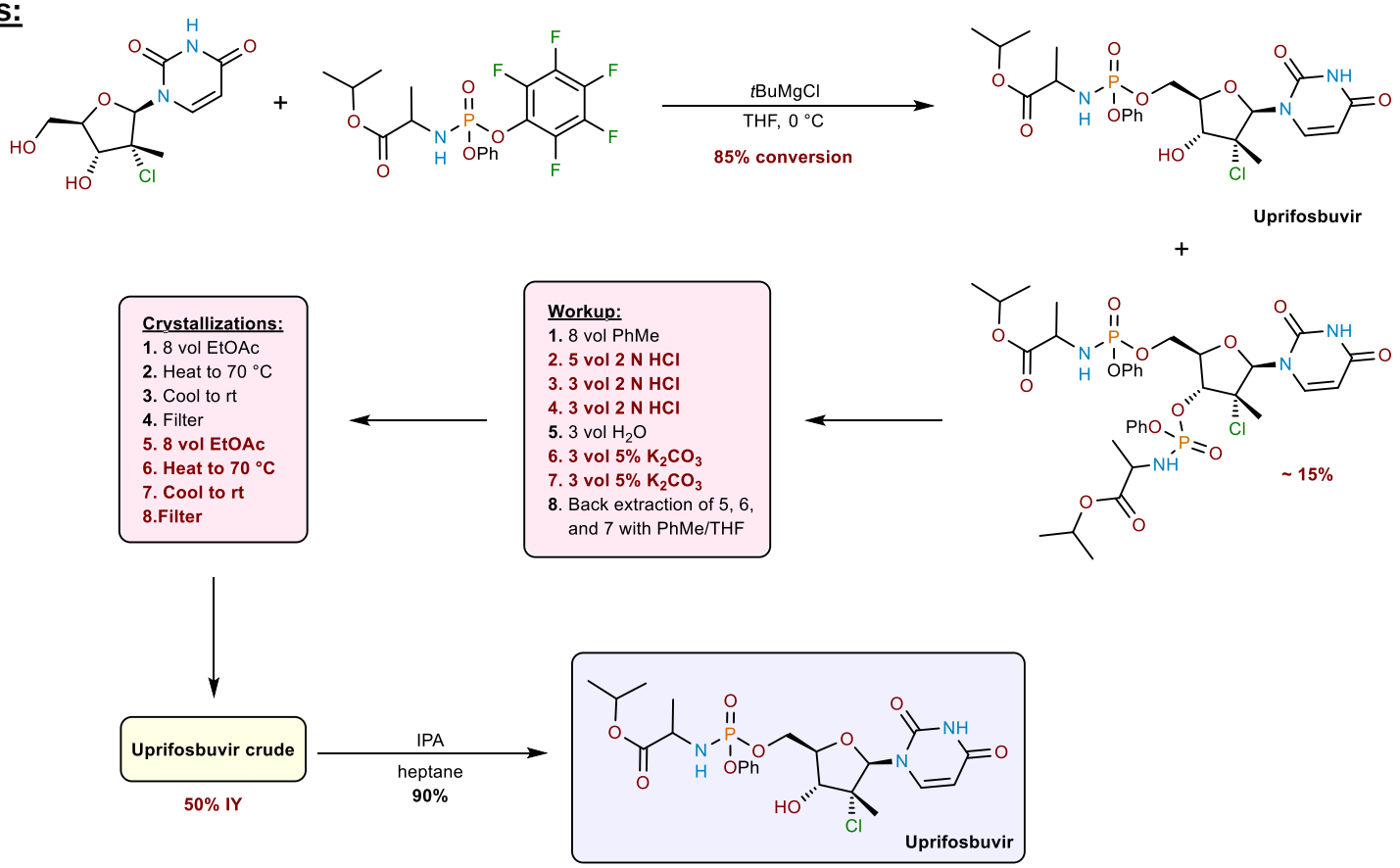
Uprifosbuvir (MK-3682)



- Clinical candidate for the treatment of hepatitis C from Merck
  - Nucleoside-based prodrug
- Novel application of the synthesis of pronucleotide (ProTide) 5′-phosphoramidate monoesters promoted by aluminum-based Lewis acids
- Key developments are purity control and handling of pyrophoric reagent on scale
- Methodology provides high diastereoselectivity

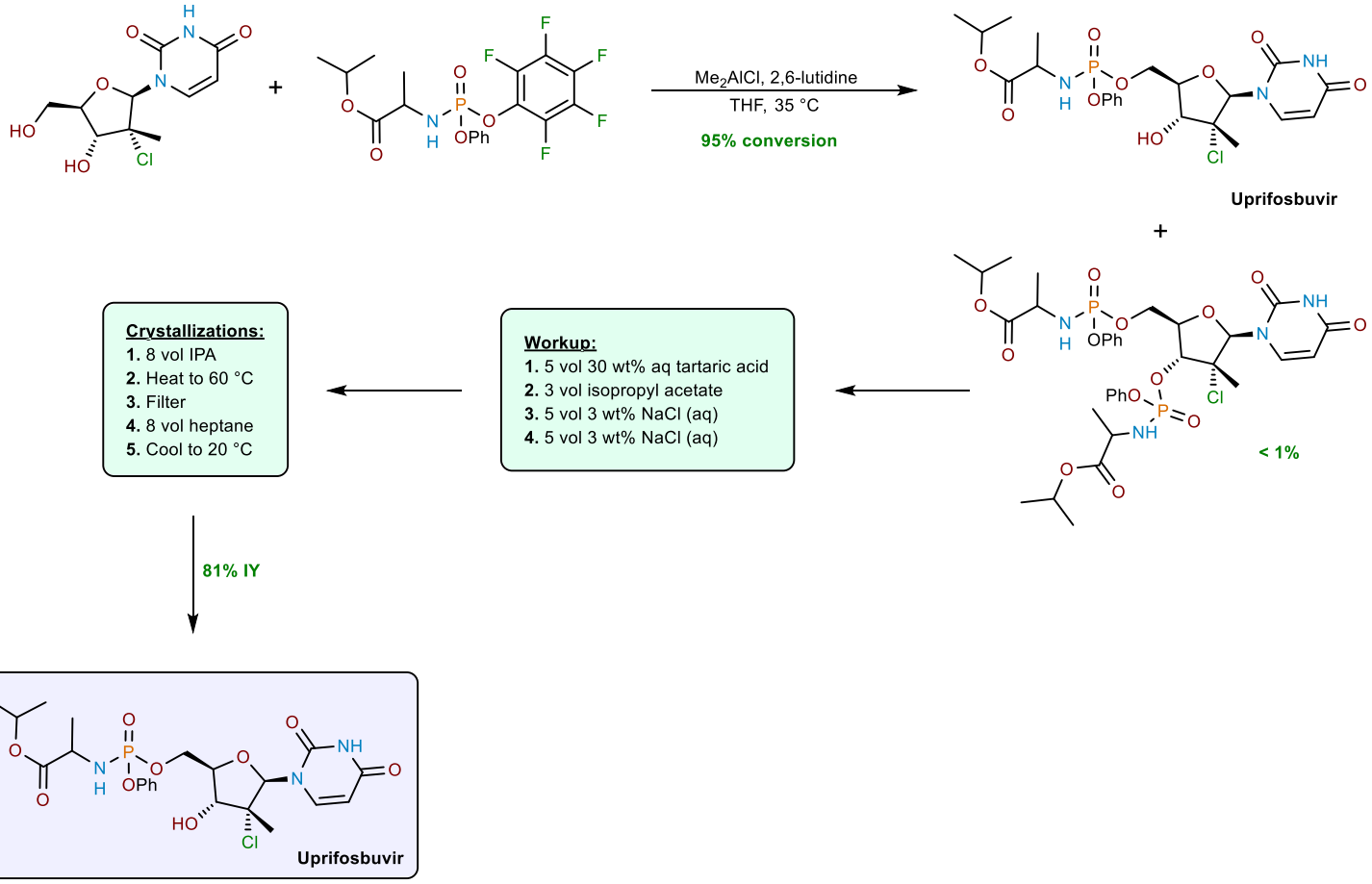
Original Process:



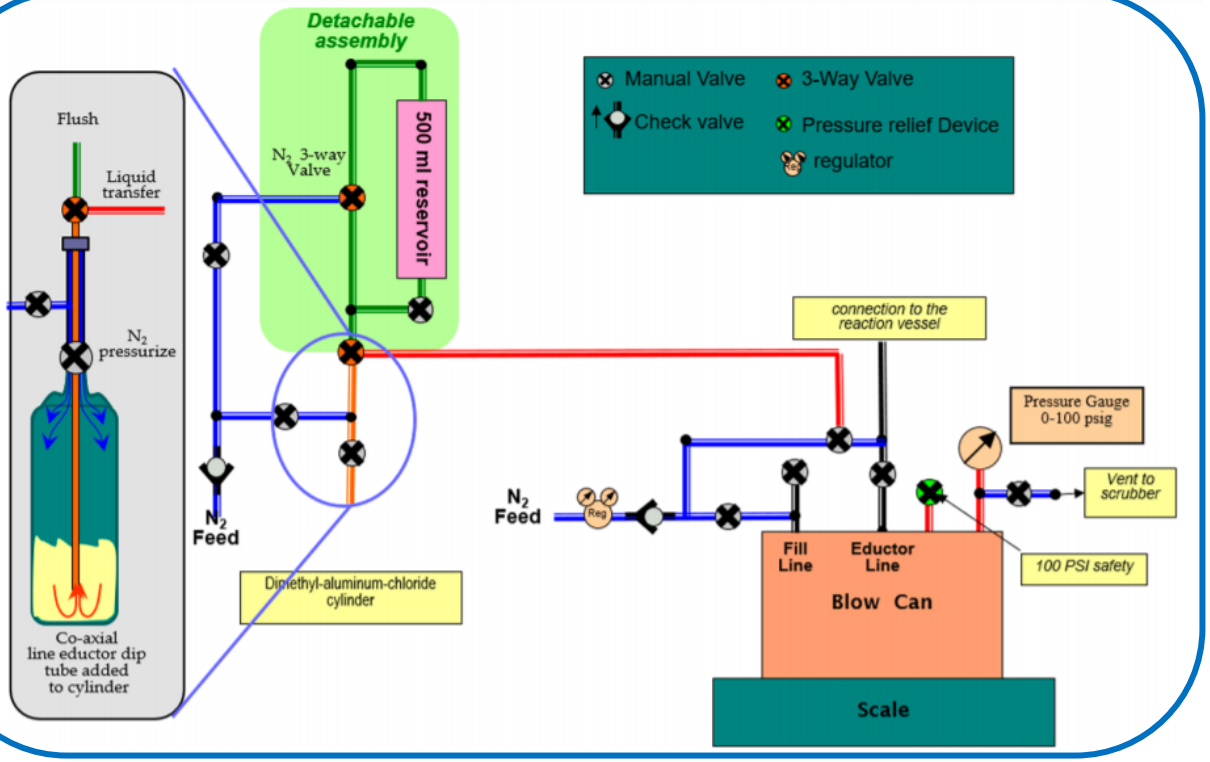
Liu, Z. and Silverman, S. M. *Org. Process Res. Dev.*. **2020**,. DOI: 10.1021/acs.oprd.0c00487. https://doi.org/10.1021/acs.oprd.0c00487

Uprifosbuvir (MK-3682)

Improved Process:



Uprifosbuvir (MK-3682)



- Neat Me_2AlCl transferred from a cylinder into a blow can containing the desired amount of heptane to reduce its interaction with air and moisture
- Slow charging to the reactor containing a THF solution of the other reaction components under moderate pressure at 0 °C followed by line flushing with heptane to prevent any buildup of Me_2AlCl
- Aging rt 12 h before heating to 50 °C for 3 h substantially improved overall conversion and maintained high diastereoselectivity
- Tartaric acid workup eliminates need for second crystallization
- Increase in reaction temperature lead to a significant increase in impurity formation