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Synthesis of Rovafovir Etalafenamide (Part I): Active Pharmaceutical Ingredient Process Development, Scale-Up, and Impurity Control Strategy

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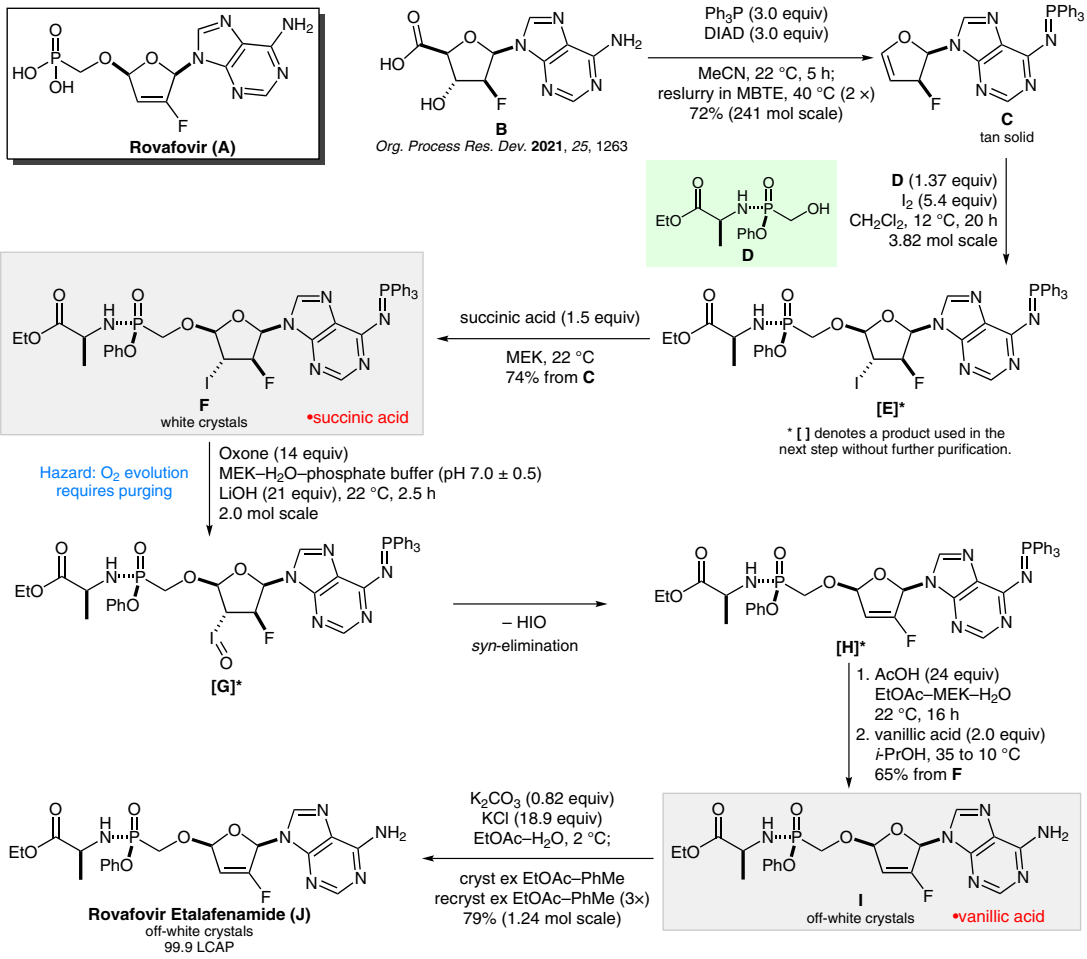
Synthesis of Rovafovir Etalafenamide



Significance: Rovafovir etalafenamide (**J**) is a phosphonamidate prodrug of the nucleotide reverse transcriptase inhibitor rovofovir (**A**) that is under investigation for the treatment of HIV-1 infection. Workers at Gilead describe the development of a manufacturing route to **J** in four parts. Part I (*Org. Process Res. Dev.* **2021**, *25*, 1215) deals with the closing stages depicted in which nucleoside **B** is converted to the final product **J**. The key step entails oxidation of the iodo derivative **F** to the iodoso compound **G** that syn-eliminates hypoiodous acid to give the desired fluoroalkene **H** in 65% yield.

Comment: Part II (*Org. Process Res. Dev.* **2021**, *25*, 1237) gives further details of the key oxidative elimination of iodo derivative **F** to fluoroalkene **H**. Part III (*Org. Process Res. Dev.* **2021**, *25*, 1247; *Synfacts* **2021**, *17*, 844) focuses on the synthesis of phosphonate **D** and part IV (*Org. Process Res. Dev.* **2021**, *25*, 1263; *Synfacts* **2021**, *17*, 845) describes the synthesis of nucleoside **B**. In the final step a highly efficient iterative crystallization process was used to purge the product of the *des*-fluoro analogue of **J** (not shown), a mitochondrial toxin, together with other process impurities.

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Category

Synthesis of Natural Products and Potential Drugs

Key words

rovafovir

oxidative elimination

decarboxylative elimination

glycosylation

phosphonamidate prodrug

dimethyldioxirane

Synfact of the Month