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Development and Implementation of an Aluminum-Promoted Phosphorylation in the Uprifosbuvir Manufacturing Route
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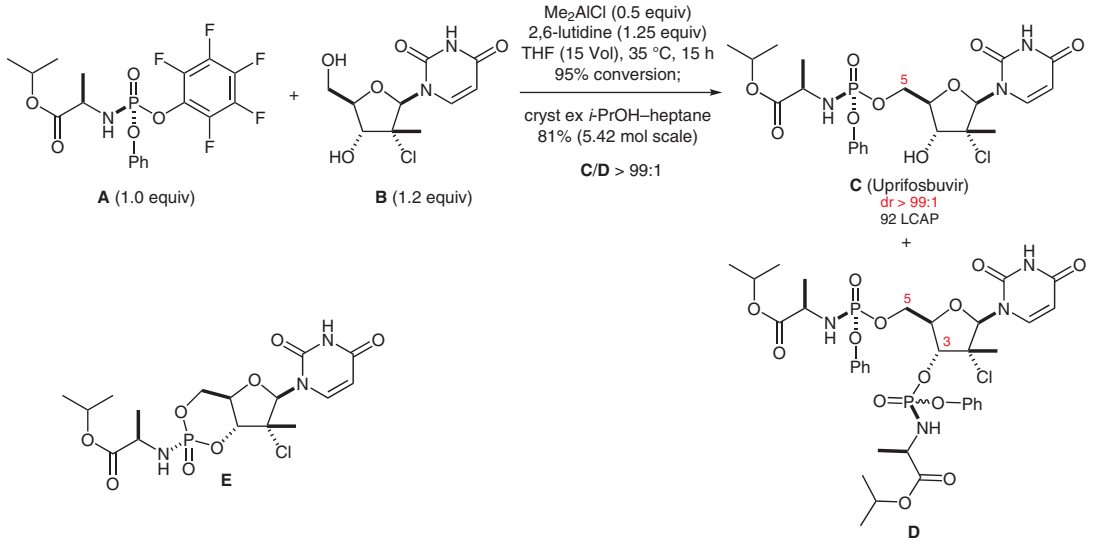
A Refined ProTide Route to Uprifosbuvir



Significance: The hepatitis C virus (HCV) has infected 170 million people worldwide. Over 70 million have succumbed to chronic hepatitis C that can lead to a spectrum of conditions affecting the liver, ranging from inflammation to cirrhosis and cancer. Uprifosbuvir (MK-3682) is an NS5B RNA polymerase inhibitor that was of interest as a combination therapy for the treatment of HCV infections. It is a nucleoside-based prodrug that utilizes the 5′-aryloxyphosphoramidate or ProTide moiety **A** to enhance cellular permeability and phosphorylation rates. Over 20 forms of uprifosbuvir have been identified, some showing dramatically reduced bioavailability.

Comment: A major improvement in the multikilogram-scale synthesis of **C** entailed the reaction of phosphoramidate **A** (1.0 equiv) with nucleoside **B** (1.2 equiv) promoted by dimethylaluminum chloride (0.5 equiv) and 2,6-lutidine (1.25 equiv) in THF at 35 °C. Under these precisely defined conditions, uprifosbuvir was isolated in 81% yield with >100:1 diastereoselectivity at the phosphorus stereocenter and >100:1 selectivity for the 5′-mono phosphorylation product **C** over the undesired bisphosphorylation side products **D**. A small increase in the reaction temperature led to a significant increase in the formation of cyclic phosphoramidate impurity **E**. Techniques and apparatus are described to safely handle neat pyrophoric dimethylaluminum chloride.

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Category

Synthesis of Natural Products and Potential Drugs

Key words

uprifosbuvir
hepatitis C
MK-3682
phosphorylation
prodrug
nucleotides

Synfact of the Month