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Engineered Ribosyl-1-kinase Enables Concise Synthesis of Molnupiravir, an Antiviral for COVID-19
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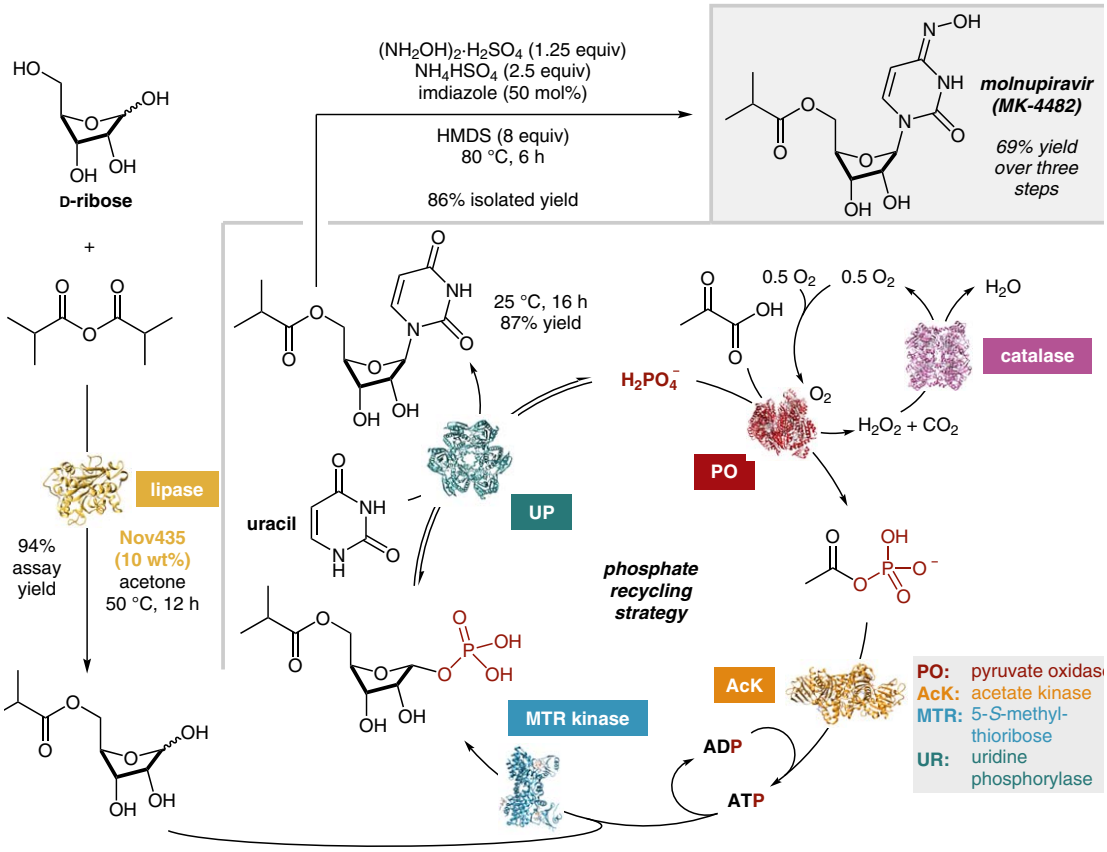
Efficient Synthesis of Molnupiravir by a Biocatalytic Cascade Involving a Phosphate-Recycling Strategy



Significance: Fier, McIntosh, and co-workers disclose a highly efficient enzymatic cascade approach to the experimental COVID-19 antiviral agent molnupiravir (Lagevrio; MK-4482). The route features an unprecedented biocatalytic nucleoside synthesis with a 5-esterified sugar and a novel phosphate-recycling strategy that obviates the need for a stoichiometric phosphoryl donor and separate removal of inorganic phosphate. Conversion of the amidic carbonyl into the required oxime proceeds efficiently in neat hexamethyldisilazane (HMDS) as a mild dehydrating agent to furnish molnupiravir in 69% yield over three steps.

Comment: The developed three-step synthesis of molnupiravir represents a vast improvement on the initial ten-step route which gave less than 10% overall yield. Key to the success of the biocatalytic cascade approach was the use of specifically evolved ribosyl-1-kinase and uridine phosphorylase enzymes in conjunction with an efficient phosphate-recycling strategy. A practical benefit of the in situ silylation in the last step is the convenient removal of inorganic salts. The new biocatalytic approach is expected to serve as a general tool for the rapid synthesis of nucleosides.

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