J. A. MCINTOSH*, P. S. FIER* ET AL. (MERCK & CO., INC., RAHWAY, USA)
Engineered Ribosyl-1-Kinase Enables Concise Synthesis of Molnupiravir, an Antiviral for COVID-19
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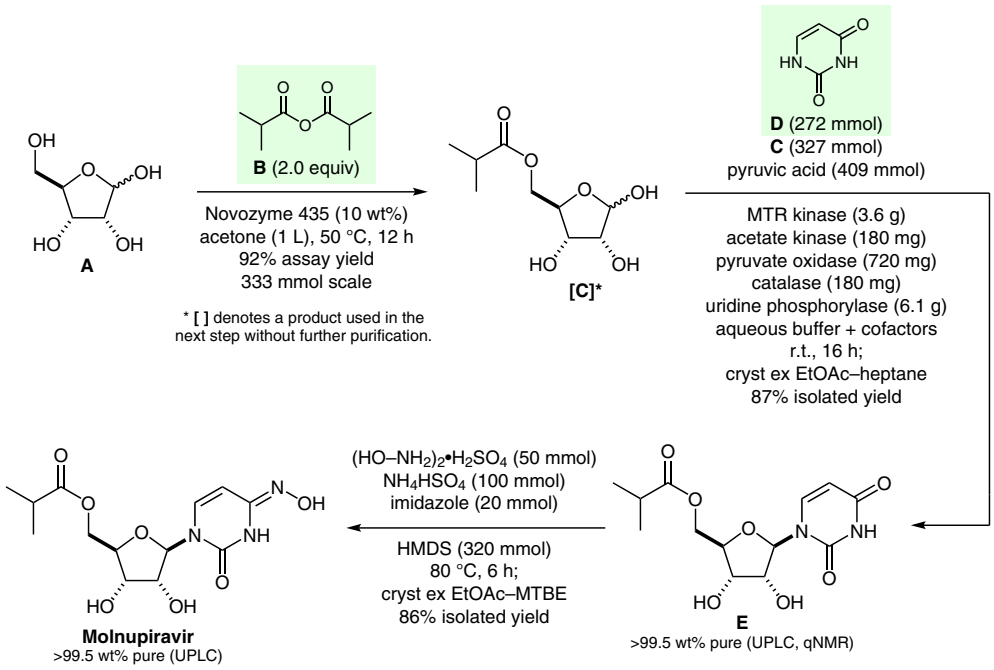
Synthesis of Molnupiravir



Significance: Molnupiravir (MK-4482) is an orally available antiviral agent that reduces the risk of hospitalization or death from COVID-19 by 30% compared with placebo. The highly innovative enzymatic cascade that converts **C** to **E** comprises pyruvate oxidase and acetate kinase for ATP regeneration, MTR kinase (engineered) for the phosphorylation of **C**, uridine phosphorylase (engineered) for uracil incorporation, and catalase to decompose hydrogen peroxide formed by pyruvate oxidase. This cascade can be run at high concentrations (>80 g/L) of **C**, forms the product in quantitative yield, and allows for easy isolation of crystalline **E** in >99.5 wt% purity.

Comment: The conversion of **E** to molnupiravir occurs in nearly quantitative yield in neat HMDS. The initial product of the reaction is the bis-TMS derivative (not shown) that allowed easy removal of inorganic salts and byproducts via aqueous washes. Molnupiravir itself is highly water-soluble, and the removal of inorganic salts would be difficult without transient masking of the alcohols as TMS ethers. The TMS groups were easily cleaved by adjusting the *p*H, after which the product crystallized. The synthesis depicted was accomplished in three steps and 69% overall yield from commodity chemicals.

SYNFACTS Contributors: Philip Kocienski
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Category
Synthesis of Natural Products and Potential Drugs

Key words
molnupiravir
nucleic acids
COVID-19
enzyme cascade
hexamethyldisilazane
dehydration

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