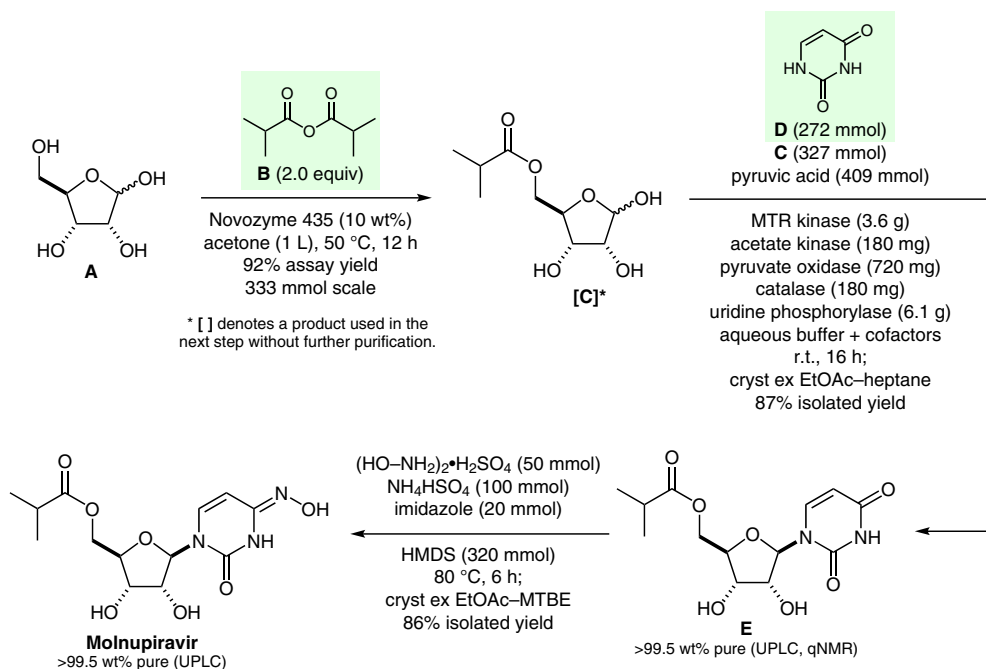


Synthesis of Molnupiravir



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 pH, after which the product crystallized. The synthesis depicted was accomplished in three steps and 69% overall yield from commodity chemicals.

Category

Synthesis of Natural Products and Potential Drugs

Key words

molnupiravir
nucleic acids
COVID-19
enzyme cascade
hexamethyldisilazane
dehydration

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of the
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