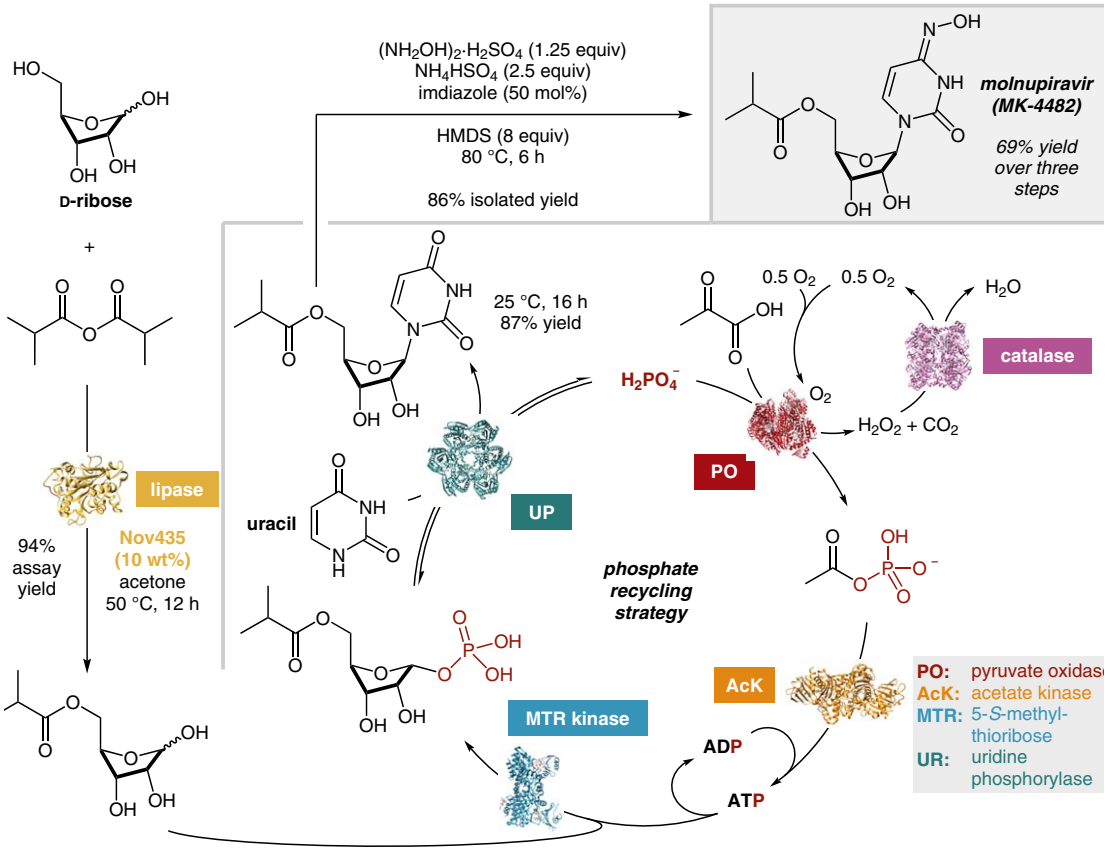
J. A. MCINTOSH*, T. BENKOVICS, S. M. SILVERMAN, M. A. HUFFMAN, J. KONG, P. E. MALIGRES, T. ITOH, H. YANG, D. VERMA, W. PAN, H. HO, J. VROOM, A. M. KNIGHT, J. A. HURTAK, A. KLAPARS, A. FRYSZKOWSKA, W. J. MORRIS, N. A. STROTMAN, G. S. MURPHY, K. M. MALONEY, P. S. FIER* (MERCK & CO., INC., RAHAWAY, USA)
Engineered Ribosyl-1-kinase Enables Concise Synthesis of Molnupiravir, an Antiviral for COVID-19
ACS Cent. Sci. **2021**, DOI: 10.1021/acscentsci.1c00608.

Category
Organo- and Biocatalysis

Key words
molnupiravir
enzymatic cascade
ribosyl kinase
phosphate recycling
medicinal chemistry
antivirals

Synfact of the Month

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 monupiravir (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.

SYNFACTS Contributors: Benjamin List, Mathias Turberg
Synfacts 2022, 18(01), 0075 Published online: 17.12.2021
DOI: 10.1055/0041-1737191; **Reg-No.:** B10621SF

© 2022. Thieme. All rights reserved.
Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.