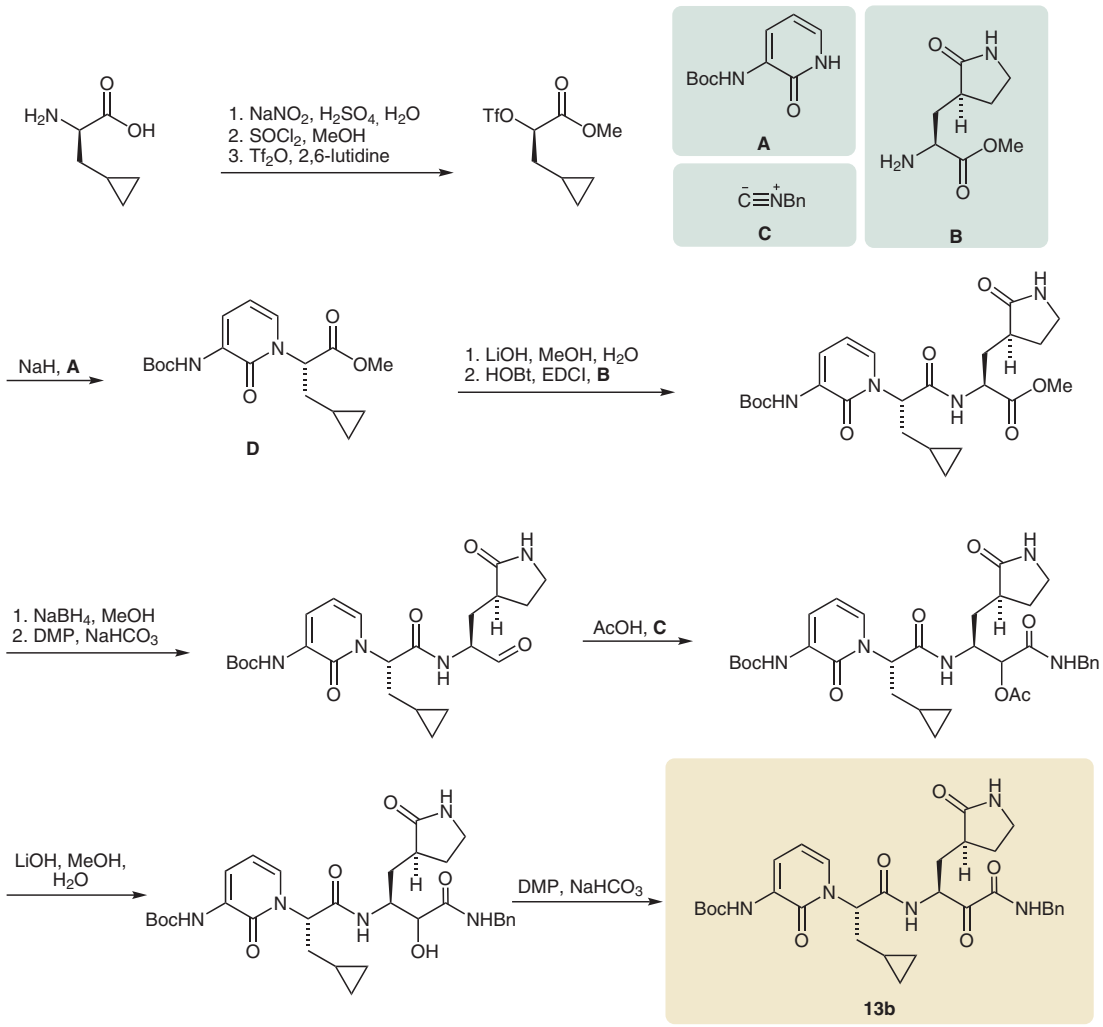
L. ZHANG, D. LIN, X. SUN, U. CURTH, C. DROSTEN, L. SAUERHERING, S. BECKER, K. ROX, R. HILGENFELD* (UNIVERSITY OF LÜBECK, GERMANY)

Crystal Structure of SARS-CoV-2 Main Protease Provides a Basis for Design of Improved α-Ketoamide Inhibitors
Science **2020**, *368*, 409–412.

α-Ketoamide Inhibitors of SARS-CoV-2 Main Protease



Significance: SARS-CoV-2 is the virus responsible for the coronavirus disease 2019 (COVID-19) pandemic. Potent, broad-spectrum α-ketoamide inhibitors of the main protease (M^{pro}) of betacoronaviruses and alphacoronaviruses were recently reported by Hilgenfeld and co-workers (*J. Med. Chem.* **2020**, DOI: 10.1021/acs.jmedchem.9b01828). X-ray crystallography and structure-based design led to the discovery of submicromolar α-ketoamide inhibitor **13b**, which has now been developed specifically against SARS-CoV-2 M^{pro} to shut down the processing of polyproteins translated from viral RNA.

Comment: Starting from commercially available (*R*)-2-amino-3-cyclopropylpropanoic acid, Boc-protected pyridone **D** is synthesized in four steps. γ-Lactam **B**, a proxy for glutamine, is made using an asymmetric dianionic cyanomethylation of *N*-Boc-L-(+)-glutamic acid dimethyl ester (Q. Tian et al. *Tetrahedron Lett.* **2001**, *42*, 6807) and is coupled to the hydrolysis product of **D**. Five additional transformations yield **13b**, which inhibits SARS-CoV-2 M^{pro} with IC_{50} = 0.67±0.18 μM and displays promising lung tropism and inhalation tolerance in mice.

SYNFACTS Contributors: Dirk Trauner, Christopher J. Arp
Synfacts 2020, 16(06), 0713 Published online: 15.05.2020
DOI: 10.1055/s-0040-1706957; **Reg-No.:** T04720SF

Category
Chemistry in Medicine and Biology

Key words
SARS-CoV-2
COVID-19
α-ketoamides
main protease (M^{pro})

Synfact of the Month