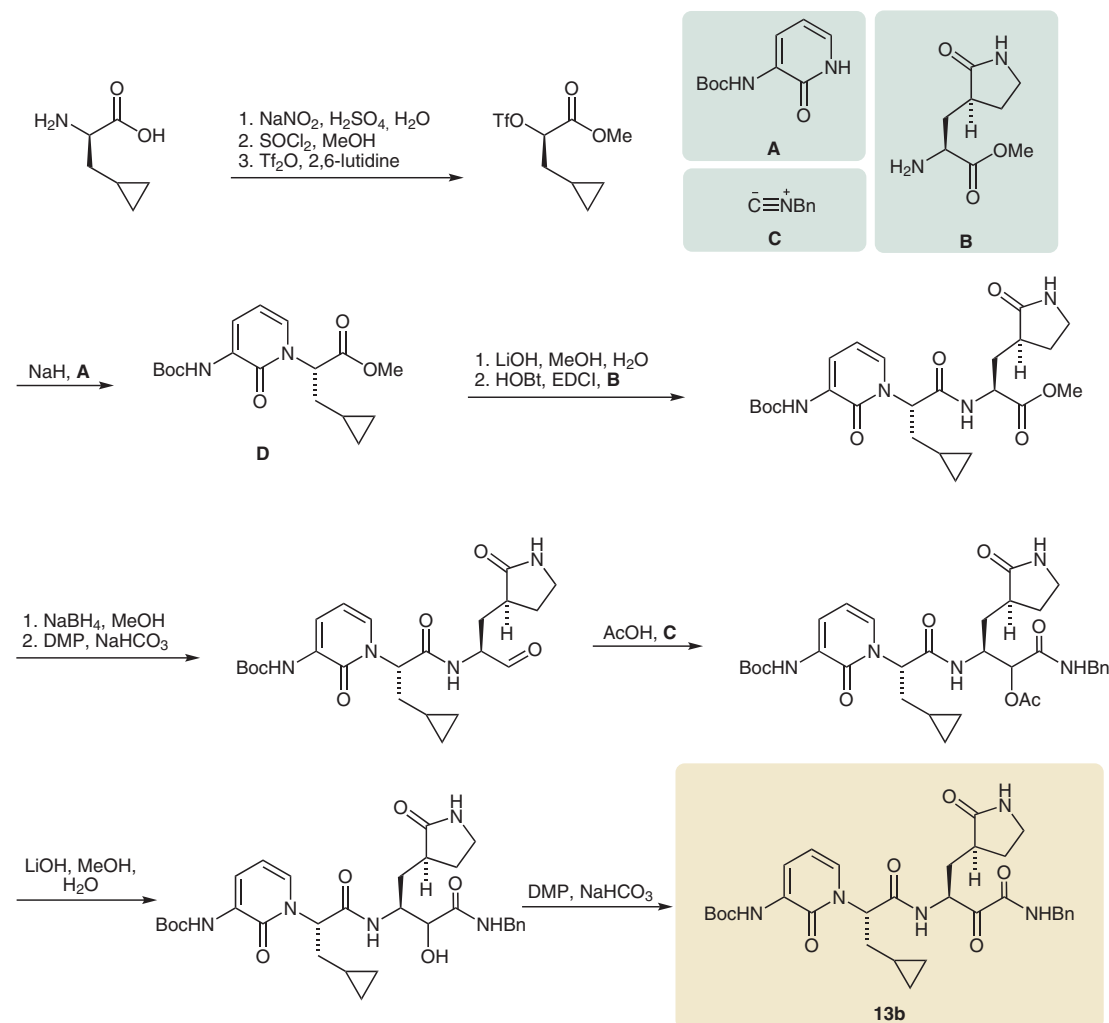


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Crystal Structure of SARS-CoV-2 Main Protease Provides a Basis for Design of Improved α -Ketoamide Inhibitors
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α -Ketoamide Inhibitors of SARS-CoV-2 Main Protease



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 $\text{IC}_{50} = 0.67 \pm 0.18 \mu\text{M}$ and displays promising lung tropism and inhalation tolerance in mice.

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