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Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the pathogen that causes the disease COVID-19, produces replicase polyproteins 1a and 1ab that contain, respectively, 11 or 16 nonstructural proteins (nsp). Nsp5 is the main protease (M^{pro}) responsible for cleavage at eleven positions along these polyproteins, including at its own N- and C-terminal boundaries, representing essential processing events for subsequent viral assembly and maturation. We have determined X-ray crystallographic structures of this cysteine protease in its wild-type free active site state at 1.8 Å resolution, in its acyl-enzyme intermediate state with the native C-terminal autocleavage sequence at 1.95 Å resolution and in its product

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S. 301-G (306, a . . a . . Y . YaY (Y . a a . . Y
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S6-S1 . a Y Y . . (FY. 1) . T Y
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a . a Y . a Y (Y . Y . 164-166 β-

16 C-
187-191
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1.25⁵; PDB
6YB7), a
P1.
N
M
1.95⁵
OH⁻

SARS-C V-1 P³ 309 (P3')
SARS-C V-2 Va (P3'; FY. 5). W
SARS-C V-1 a⁻² M S3' S
A46S a S 46

