# Synthesis of 1-Aminocyclopropaneboronic Acid as an Inhibitor of Hepatitis C Virus NS3 Protease

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## Supporting Information

**General Methods**. Reactions were run under an argon atmosphere in oven dried glassware. Anhydrous solvents over molecular sieves were purchased from Fluka and used without further purification. Preparative liquid chromatography was performed on Merck silica gel 60 (230-400 mesh). Thin layer chromatography was performed on glass plates coated with silica gel 60 (250 μm layer) and visualized with cerium-molybdate or ninhydrin stains. Analytical and preparative reverse phase HPLC were performed on a Rainin Dynamax HPLC System (analytical column: Rainin Dynamax 60Å C18, 25 x 0.46 cm, particle size 8 μm; preparative column: Rainin Dynamax 60Å C18, 30 x 2.1 cm, particle size 8 μm) using a gradient from solvent A (0.1 % trifluoroacetic acid in water) to B (0.1% trifluoroacetic acid in acetonitrile) at a flow rate of 1 mL/min (analytical) or 15 mL/min (preparative). Chromatograms were monitored by UV detection at 220 nm and retention times ($t_R$) are reported in minutes.

**1-Isocyanocyclopropylboronate (+)-pinanediol ester (7).** *n*-Butyllithium (1.9 mL, 3.0 mmol, 1.6 M solution in hexane) was added dropwise to cyclopropyl isocyanide[1] (0.250 mL, 3.06 mmol) in tetrahydrofuran (5 mL) at –78 ºC After 20 min, triisopropyl borate (0.780 ml, 3.38 mmol) was added dropwise to the pale yellow solution. The reaction mixture was allowed to

[1] Schollkopf, U.; Gerhart, F.; Hoppe, I.; Harms, R.; Hantke, K.; Scheunemanne, K.-H.; Eilers, E.; Blume, E. *Liebigs Ann. Chem.* **1976**, 183-202.

slowly warm to room temperature. After 14 hours, sodium hydrogen sulfate (0.43 g, 3 mmol) and water (1 ml) were added. The organic layer was separated and the aqueous layer was washed twice with ether. The solution was dried briefly over magnesium sulfate, and (+)-pinanediol (521 mg, 3.06 mmol) was added. After stirring 5 h, the solution was concentrated and the residue was purified by flash chromatography (silica gel, 20% ethyl acetate/hexanes) to give **7** as a colorless, crystalline solid (0.244 g, 33%). $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 4.36 (1H, dd, J = 8.8, 1.8, OC<u>H</u>), 2.39-2.20 (2H, m), 2.04 (1H, t, J = 5.5), 1.96-1.85 (2H, m), 1.40 (3H, s, C<u>H</u>$_3$), 1.29 (5H, m, C<u>H</u>$_3$, 2 cyclopropyl C<u>H</u>), 1.13-1.11 (3H, m, pinanediol C<u>H</u>, 2 cyclopropyl C<u>H</u>), 0.83 (3H, s, C<u>H</u>$_3$); $^{13}$C NMR($CDCl_3$, 300 MHz) δ 150.7 (<u>C</u>NCH, br) 87.4, 79.1, 51.2, 39.3, 38.2, 35.2, 28.4, 27.0, 26.3, 23.9, 15.9 (cyclopropyl <u>C</u>H$_2$), 15.7 (cyclopropyl <u>C</u>H$_2$); HRMS-CI (m/z): $[M+H]^+$ calcd for $C_{14}H_{21}BNO_2$, 246.1665; found, 246.1668; IR (KBr): 2927 (s) 2872 (w), 2138 (m, isonitrile), 1450 (s), 1413 (s), 1390 (s), 1290 (m), 1167 (s) $cm^{-1}$.

**1-Aminocyclopropylboronate (+)-pinanediol ester hydrochloride (10).** Concentrated hydrochloric acid (0.1 mL) was added to a solution of **7** (15.8 mg, 0.064 mmol) in methanol (2 mL). The reaction mixture was stirred at room temperature for 45 min and then heated at 50 ºC for 5 h. The solvent was evaporated to obtain **10** (16. 8 mg, 96%) as a pale yellow solid. $^{1}$H NMR (DMSO-$d_6$, 300 MHz) δ 8.30 (3H, br s, <u>H</u>$_3$N), 4.41 (1H, d, J = 7.7, OC<u>H</u>), 2.33-2.15 (2H, m), 1.96 (1H, t, J = 5.3), 1.86 (1H, m), 1.73 (1H, m), 1.32 (3H, s, C<u>H</u>$_3$), 1.23 (3H, s, C<u>H</u>$_3$), 1.10-1.04 (3H, m, pinanediol C<u>H</u>, 2 cyclopropyl C<u>H</u>), 0.79 (5H, m, C<u>H</u>$_3$, 2 cyclopropyl C<u>H</u>); $^{13}$C NMR (DMSO-$d_6$, 300 MHz) δ 87.3, 78.3, 51.2, 38.3, 35.2, 28.6, 27.2, 26.4, 24.0, 10.3 (cyclopropyl <u>C</u>H$_2$), 10.1 (cyclopropyl <u>C</u>H$_2$); HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{13}H_{23}BNO_2$, 236.1816; found, 236.1829; IR (KBr): 3453 (m), 2921 (s), 1595 (w), 1431 (s), 1197 (s) $cm^{-1}$.

**Boc-Aspartyl(*O*-*t*-Bu)-Glutamyl(*O*-*t*-Bu)-Valyl-Valyl-Prolyl-1-aminocyclopropylboronate (+)-pinanediol ester (13**). *N*,*N*-Diisopropylethylamine (0.017 mL, 0.099 mmol) was added

dropwise to a solution of Boc-Asp(*O*-*t*-Bu)-Glu(*O*-*t*-Bu)-Val-Val-Pro-OH (36.7 mg, 0.048 mmol) and PyAOP[2] (25 mg, 0.048 mmol) in *N*,*N*-dimethylformamide (1.0 mL). After 7 min, one half of the activated peptide solution was added to a solution of **10** (6.6 mg, 0.024 mmol) in *N*,*N*-dimethylformamide (0.5 mL). After 2 h, the reaction mixture was concentrated under vacuum. The residue was purified by preparative HPLC (70 to 100% B over 30 min) to give **13** as a colorless solid (10.5 mg, 44%). Analytical HPLC (60 to 90% B over 30 min): $t_R$ = 6.3 (free boronic acid), 19.9 (pinanediol ester), purity >98%; HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{50}H_{84}BN_6O_{13}$, 987.6168; found, 987.6194

**H-Aspartyl-Glutamyl-Valyl-Valyl-Prolyl-1-aminocyclopropylboronate (+)-pinanediol ester (16**). Protected peptide **13** (14.9 mg, 0.0151 mmol) was dissolved 1,4-dioxane containing hydrogen chloride (0.7 mL, 2.8 mmol, 4 M solution). After 3 h, the reaction mixture was concentrated. The residue was purified by preparative HPLC (30 to 60% B over 30 min) to give **16** as a colorless glassy solid (5.2 mg, 44%). Analytical HPLC (10 to 70% B over 60 min): $t_R$ = 10.9 (free boronic acid), 33.6 (pinanediol ester), purity 94%; HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{37}H_{60}BN_6O_{11}$, 775.4398; found, 775.4393

[2] Carpino, L. A.; El-Faham, A.; Minor, C. A.; Albericio, F. *J. Chem. Soc., Chem. Commun.* **1994**, 201-203.