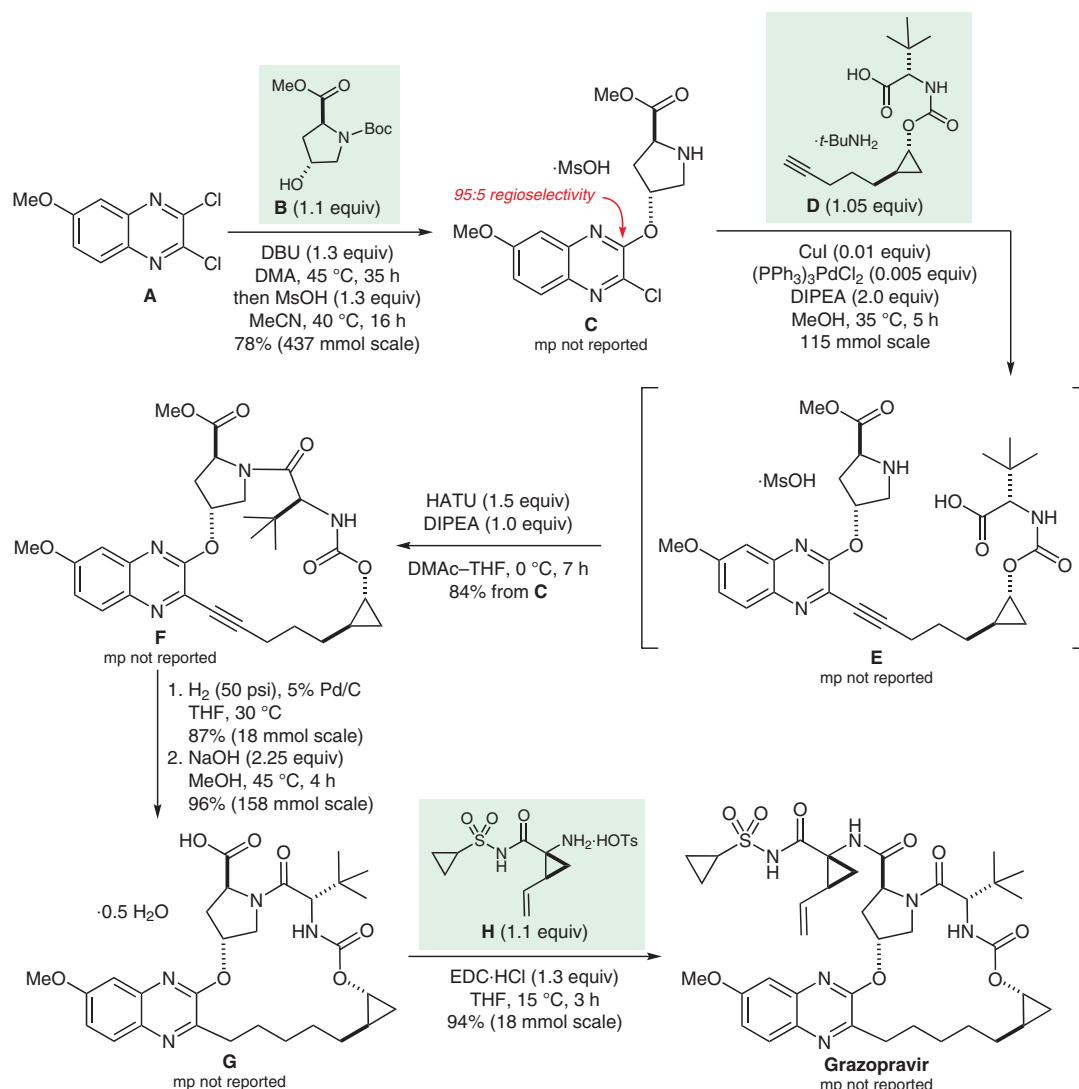


## Synthesis of Grazoprevir



**Significance:** Grazoprevir is an NS3/4a protease inhibitor. It was approved by the FDA in 2016 as a combination drug with elbasvir (Zepatier®) for the treatment of hepatitis C viral infections. The scheme depicts the chemistry developed to conjoin the fragments **A**, **B**, **D**, and **H** on large scale (>100 kg) in 51% overall yield and >99.8% purity.

**Comment:** The thermal instability of the free base of alkyne **D** was a challenge in the Sonogashira reaction. By using methanol as solvent, catalyst stability and reactivity was improved as evinced by increased catalytic turnover at milder temperatures (35 °C). The free base of sulfonamide **H** was unstable at ambient temperature. Therefore, the EDC coupling was conducted at 0 °C by adding pyridine to a slurry of the acid **G** and the PTSA salt **H** in THF.