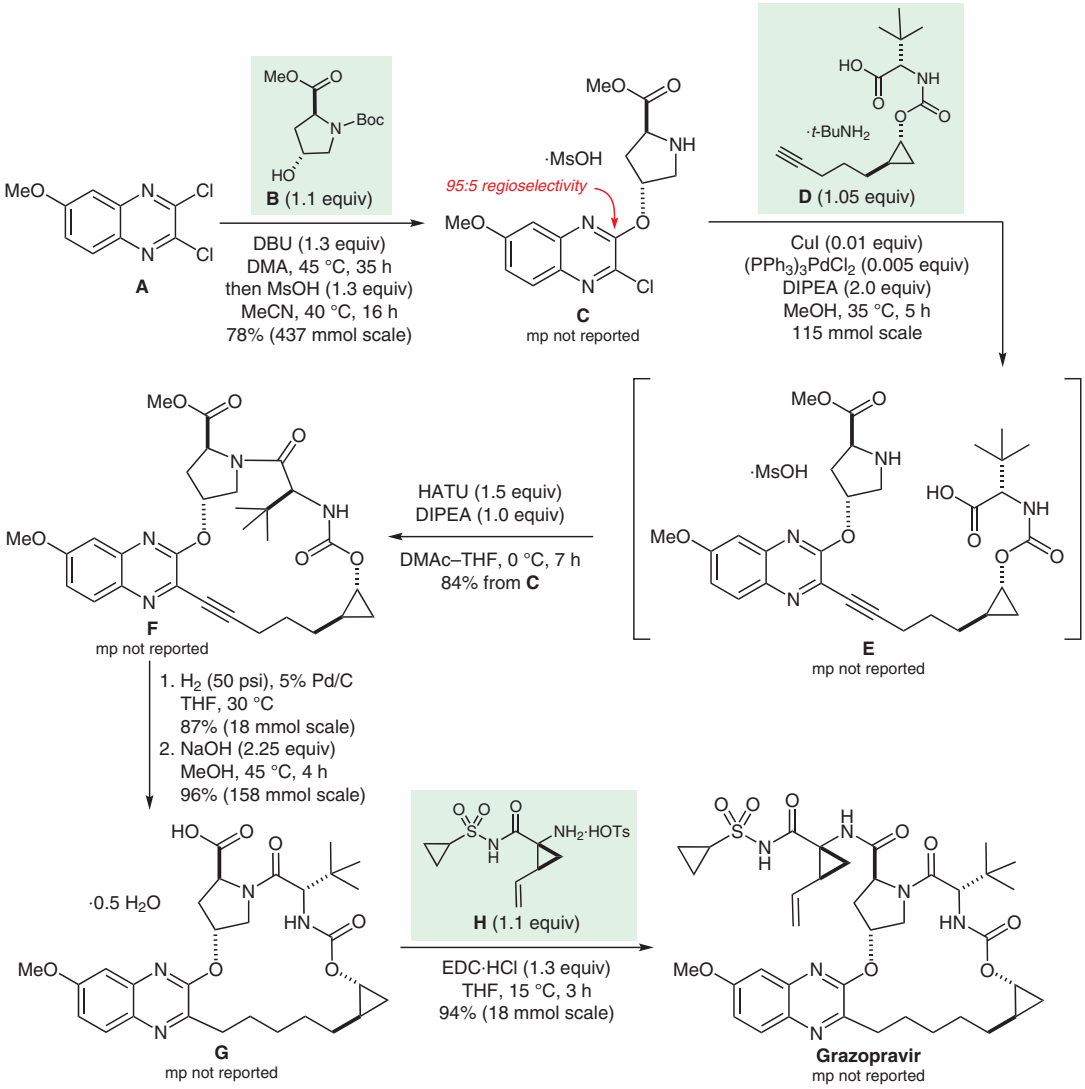
F. XU*, J. KIM, J. WALDMAN, T. WANG, P. DEVINE (MERCK & CO., INC., RAHWAY, USA)
Synthesis of Grazoprevir, a Potent NS3/4a Protease Inhibitor for the Treatment of Hepatitis C Virus
Org. Lett. **2018**, *20*, 7261–7265.

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.

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Category

Synthesis of Natural Products and Potential Drugs

Key words

grazoprevir

NS3/4a protease inhibitor

macrolactamization

Sonogashira reaction