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 Synthesis of Bis-Macrocyclic HCV Protease Inhibitor MK-6325 via Intramolecular  $sp^2$ – $sp^3$  Suzuki–Miyaura Coupling and Ring Closing Metathesis  
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## Synthesis of HCV Protease Inhibitor MK-6325

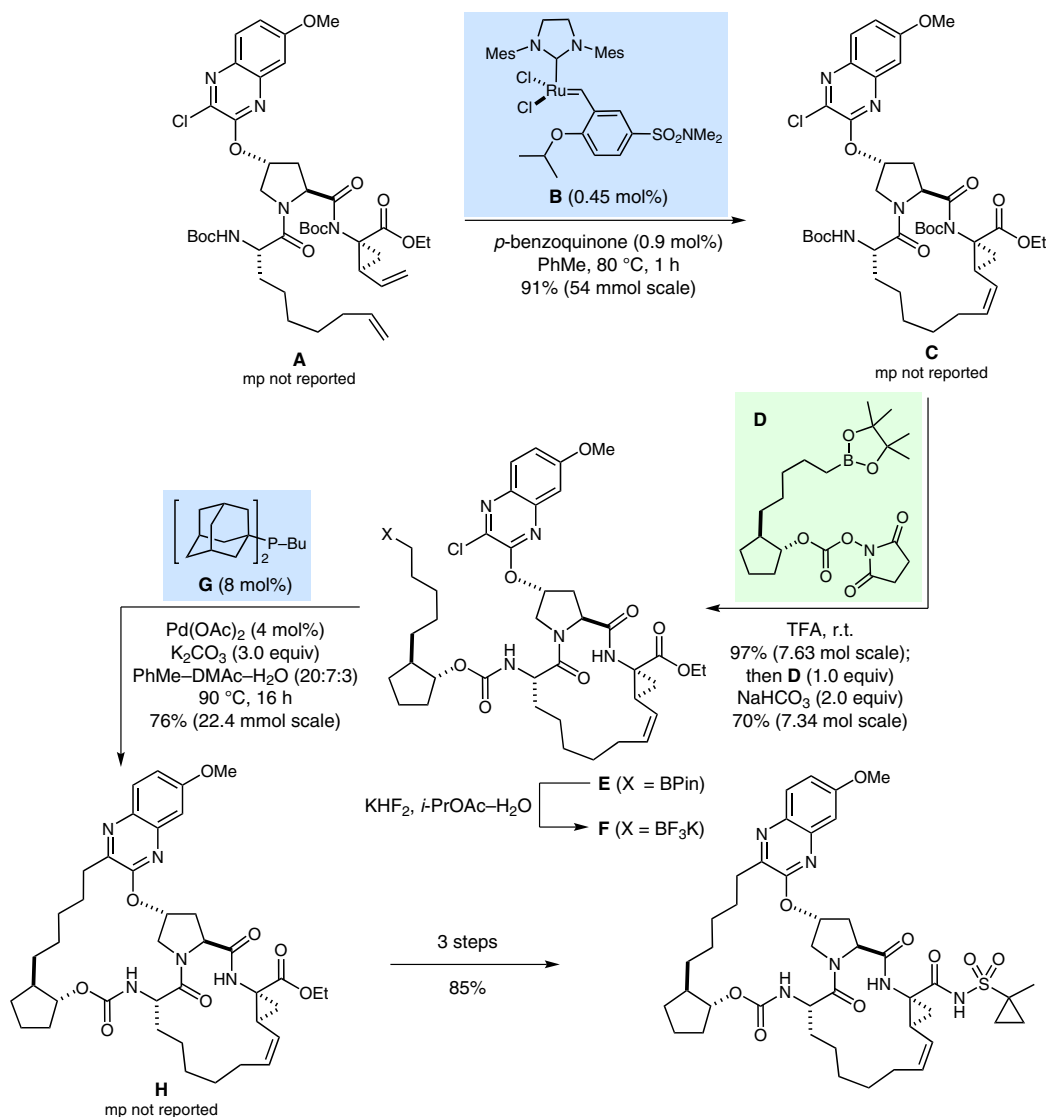
Category

Synthesis of Natural Products and Potential Drugs

Key words

MK-6325  
 HCV NS3/4A protease inhibitors  
 ring-closing metathesis  
 Suzuki–Miyaura coupling  
 macrocyclization

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**Significance:** MK-6325 is a potent HCV NS3/4A protease inhibitor. The construction of the daunting bis-macrocyclic structure was accomplished by a ring-closing metathesis (RCM) to forge the 15-membered macrocycle followed by an intramolecular Suzuki–Miyaura cross-coupling to append the 18-membered macrocycle.

**Comment:** The route depicted delivered multikilogram quantities of the MK-6325. Construction of fragment **D** was achieved using (1) a Novozyme 435 resolution with succinic anhydride and (2) an iridium-catalyzed hydroboration. CataCXium A (**G**) was superior to all other ligands evaluated for the Suzuki–Miyaura reaction.

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