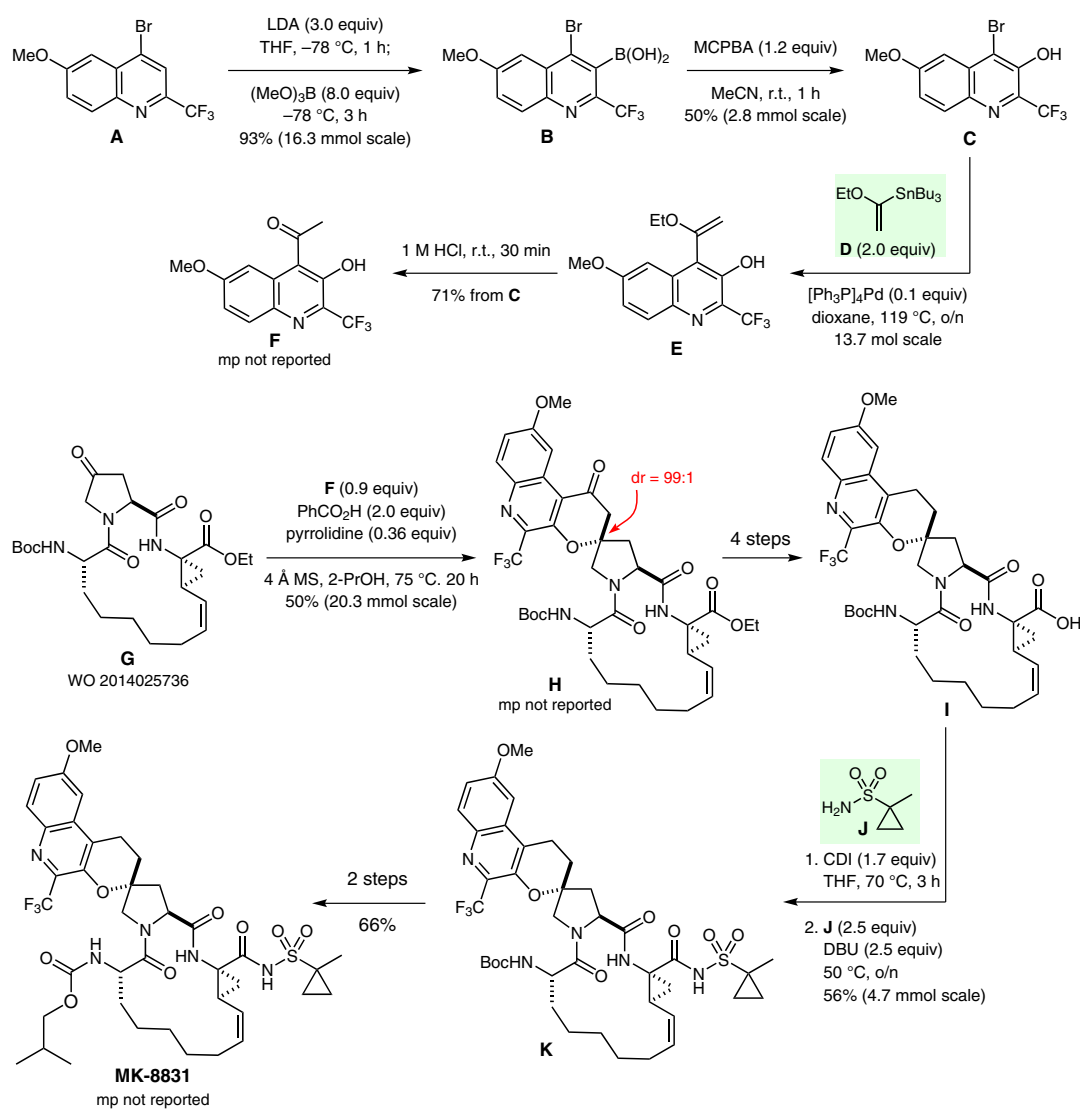


Synthesis of MK-8831



Significance: A Merck team has devised a route to HCV NS3/4a protease inhibitors containing a spirocyclic proline core. Optimization of the structure–activity relationships resulted in the identification of the clinical candidate MK-8831 with excellent pan-genotypic activity and safety profile.

Comment: Ketone **F** was cyclized with the previously reported macrocyclic prolinone **G** employing benzoic acid and pyrrolidine. Initial conditions gave very poor yields, but the optimized methods gave spirocycle **H** in 50% yield and high levels of diastereoselectivity (dr = 99:1).