S. F. NEELAMKAVIL\* ET AL. (MERCK RESEARCH LABORATORIES, KENILWORTH, USA) Discovery of MK-8831, A Novel Spiro-Proline Macrocycle as a Pan-Genotypic HCV-NS3/4a Protease Inhibitor *ACS Med. Chem. Lett.* **2016**, *7*, 111–116.

## 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).

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Synthesis of Natural Products and Potential Drugs

**Key words** 

MK-8831

HCV NS3/4a protease inhibitors

spirocycles

macrocycles

