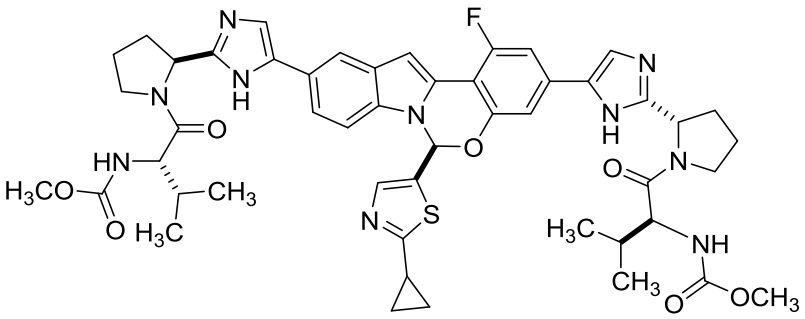
Process Chemistry of HCV NS5A Inhibitor

Department of Process Research & Development
Merck Sharp & Dohme, Rahway, NJ, USA
Tetsuji Itoh

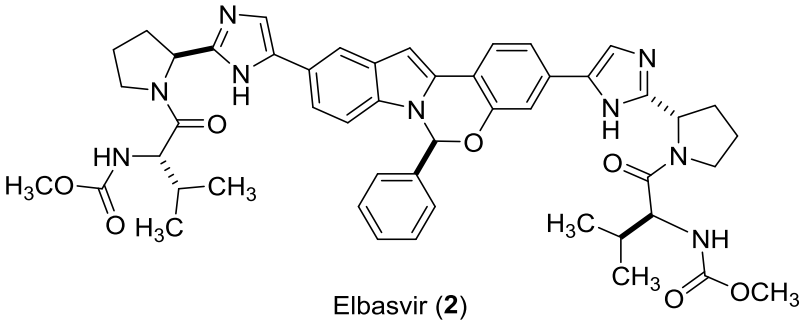
The Department of Process Research & Development (PR&D) at MSD supports all aspects of manufacturing active pharmaceutical ingredients (API). In the early stage of development, we support API supply for non-clinical studies including toxicology and DMPK in addition to providing material for first in human clinical trials. Speed to bulk API supply is of considerable importance in this phase, and we leverage the tools of high-throughput experimentation, rapid process safety screening and efficient kilogram scale operations to meet the necessary demand. As a compound progresses in the clinical study, we engage in the discovery of innovative commercial manufacturing process, where synthetic and environmental efficiency, robustness and process understanding are mandates for the successful filing and launch of the drug to market.

It is estimated that ~170 million individuals worldwide are infected with hepatitis C virus (HCV), and an estimated 700,000 people die each year from hepatitis-C related diseases. Approximately 15-25% of people who contract HCV recover spontaneously within 6 months, while in 75-85% of cases the virus establishes a chronic infection resulting in fibrosis, cirrhosis and hepatocellular carcinoma. In the past decade, various treatment options were brought to market. Recent great advances in the treatment of this chronic disease were achieved with a combination of multiple direct-acting antiviral agents (DAAs), including NS5A RNA replication inhibitors, NS5B RNA polymerase inhibitors and NS3/4A protease inhibitors. Recently approved NS5A inhibitors for the treatment of HCV include daclatasvir (BMS-790052), ledipasvir (GS-5885), ombitasvir (ABT-267), elbasvir (MK-8742, **2**), and velpatasvir (GS-5816).

Ruzasvir (MK-8408, **1**) was discovered at MSD as a potent, pan-genotype HCV NS5A inhibitor, to be used as part of all-oral DAA regimen. Its structure carries a close similarity with one of the components of our market-authorized drug ZEPATIER™, elbasvir (MK-8742, **2**), which is MSD's first-generation HCV NS5A inhibitor.

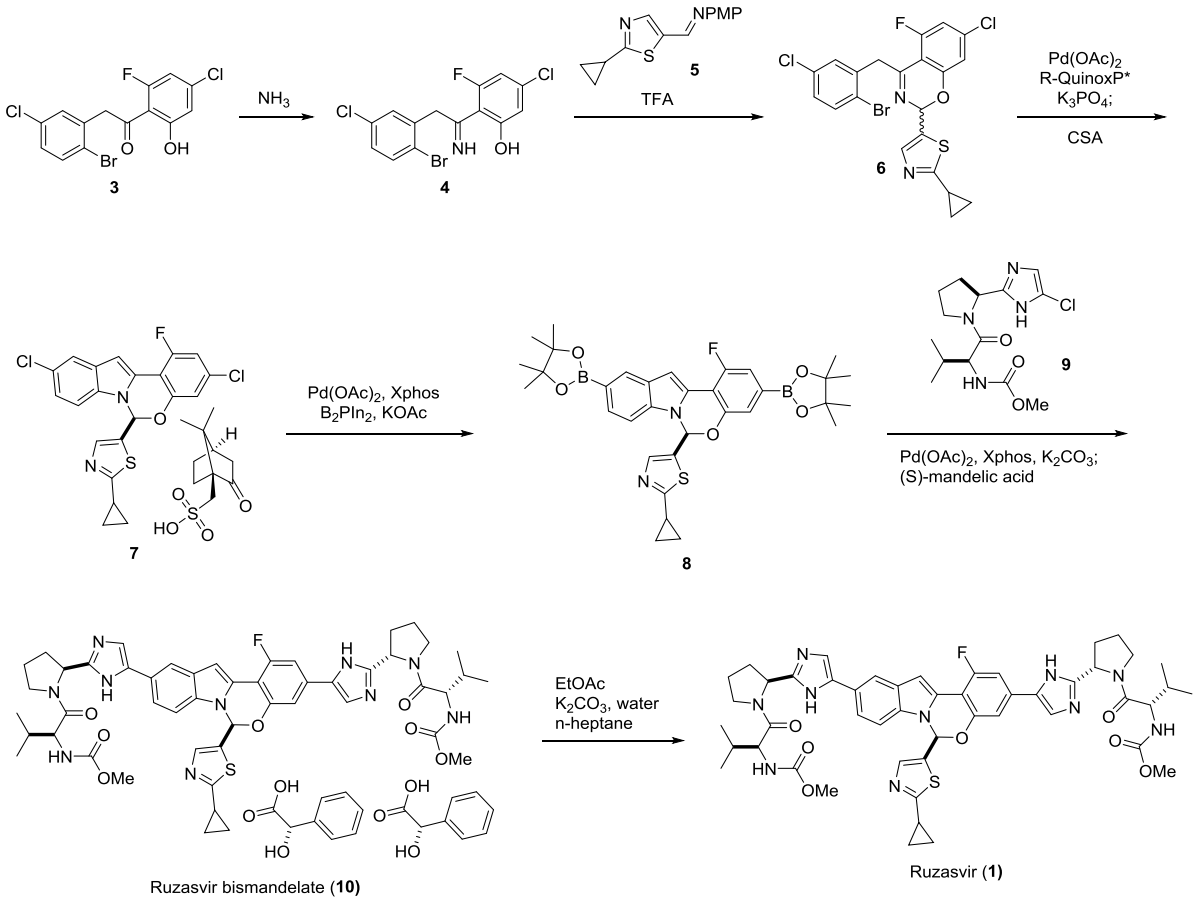


Ruzasvir (MK-8408, **1**)



Elbasvir (**2**)

The manufacturing route of Ruzasvir (**1**) is shown in the scheme below. Aryl-ketone (**3**) is advanced to racemic hemiaminal (**6**) in a two-step sequence. Hemiaminal (**6**) undergoes Pd-catalyzed C-N bond formation which simultaneously establishes the benzylic hemiaminal stereocenter in Indole (**7**). This novel transformation utilizes a P-chiral phosphine ligand discovered and developed by Prof. Imamoto. Subsequently Miyaura-Borylation reaction (from **7** to **8**) and Suzuki-Miyaura coupling reaction (from **8** and **9** to **10**) are utilized to construct Ruzasvir molecule. This presentation will describe the discovery and development of the commercial manufacturing process to Ruzasvir (**1**).



References

'Thiazolyl-substituted tetracyclic compounds and methods of use thereof for treatment of viral diseases', WO2014/110687 A1

'Discovery of Ruzasvir (MK-8408): A Potent, Pan-Genotype HCV NS5A Inhibitor with Optimized Activity against Common Resistance-Associated Polymorphism', *Journal of Medicinal Chemistry*, **2017**, *60*, 290-306

'Process for making tetracyclic heterocycle compounds', WO 2016/004899 A1

'Process for preparing substituted tetracyclic compounds', WO 2016/196932 A1

'Enantioselective Synthesis of Hemiaminals via Pd-Catalyzed C-N Coupling with Chiral Biphosphine Mono-oxides', *Journal of the American Chemical Society*, **2015**, *137*, 13728-13731

'An Air-Stable P-Chiral phosphine Ligand for Highly Enantioselective Transition-Metal-Catalyzed Reactions', T. Imamoto et al., *Journal of the American Chemical Society*, **2005**, *127*, 11934-11935