Simeprevir (TMC435): development of a large scale ring closing metathesis (RCM) process

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Simeprevir (TMC435) is the best-in-class Hepatitis C virus NS3 protease inhibitor, commercially launched by Janssen Pharmaceutica in 2013:

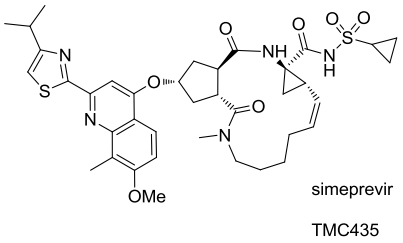

Figure 1. Structure of simeprevir, HCV protease inhibitor.

The key step of the synthesis is the ring closing metathesis (RCM) reaction used to build the 14 membered macrocyclic core. The RCM reaction is an extremely efficient synthetic option since it supplies both the 14-membered macrocycle and the *Z*-double bond (key features of the molecule) in a single catalytic step.

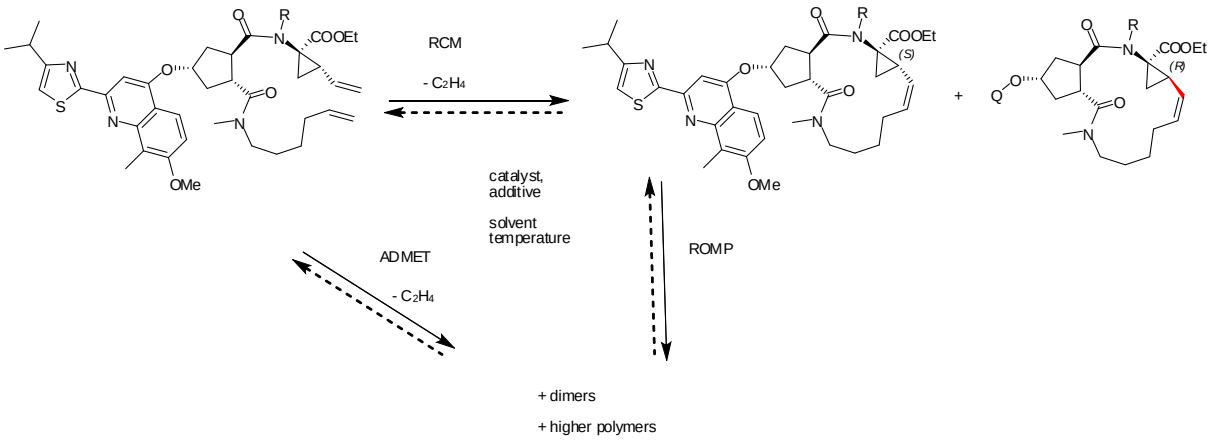

Figure 2. The metathesis manifold for the macrocyclization step in the synthesis of simeprevir..

Development of the RCM step into a process practical for large scale manufacturing will be discussed. The tools and techniques used to develop this macrocyclization reaction, including the role of substrate modifications in increasing the cyclisation efficiency (and consequently, the space-time-yield of the process), will be presented in detail.