GILEAD

Creating Possible

Synthetic and Process Strategies for the Successful Scale-Up of Rovafovir Etalafenamide

Rovafovir etalafenamide (GS-9131, **1**) is the phosphonamidate prodrug of a novel nucleotide reverse transcriptase inhibitor under development at Gilead Sciences for the treatment of HIV infection. In order to support pre-clinical and clinical studies, a process was needed to produce **1** on multi-kilogram scale. The novel structure of **1** presented a variety of synthetic challenges in order to retain the desired stereochemistry and integrity of the functional groups over numerous chemical transformations. This presentation will outline the strategies used to develop a robust, operationally-safe, and chromatography-free synthetic route to **1**. Topics to be discussed will include the development of a decarboxylative elimination, the Design of Experiments study of an iodoetherification reaction, the development of an oxidative elimination, and dynamic strategies investigated for improving the synthesis of the phosphonamidate fragment **2**.

References: Standley, E. A., *et. al. Org. Proc. Res. Dev.* **2021**, *25*, 1215-1236. Bringley, D. A., *et. al. Org. Proc. Res. Dev.* **2021**, *25*, 1237-1246. Ambrosi, A., *et. al. Org. Proc. Res. Dev.* **2021**, *25*, 1247-1262. Siler, D. A., *et. al. Org. Proc. Res. Dev.* **2021**, *25*, 1263-1274.