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A Highly Diastereoselective Chloride-Mediated Dynamic Kinetic Resolution at Phosphorus On-Route To A Key Intermediate In the Synthesis Of GSK2248761A


Synthesis of Fosdevirine

Significance: Fosdevirine (GSK2248761A) is a non-nucleoside reverse transcriptase inhibitor that was of interest for the treatment of HIV. A recent process-scale synthesis of the (R)-enantiomer was achieved by a late-stage classical resolution of racemic phosphinate (1) using cinchonidine as the resolving agent (Org. Process Res. Dev. 2018, 22, 200). A new route to key intermediate (R)-G in the synthesis of (R)-fosdevirine features a highly diastereoselective dynamic kinetic resolution in the reaction of the phosphinyl chloride (R)-C with methyl (S)-phenylglycinate (D).

Comment: The key step in the dynamic kinetic resolution is the rapid racemization of phosphinyl chloride (R)-C by nucleophilic attack at the phosphorus atom by chloride ions followed by diastereoselective reaction of one of the phosphinyl chloride enantiomers with the methyl (S)-phenylglycinate. Fifteen chiral amines were screened in the DKR reaction with best results (dr = 21:1) being obtained with methyl (S)-phenylglycinate. The overall yield of (R)-G from (R)-Fosdevirine was 50% (10 g scale).