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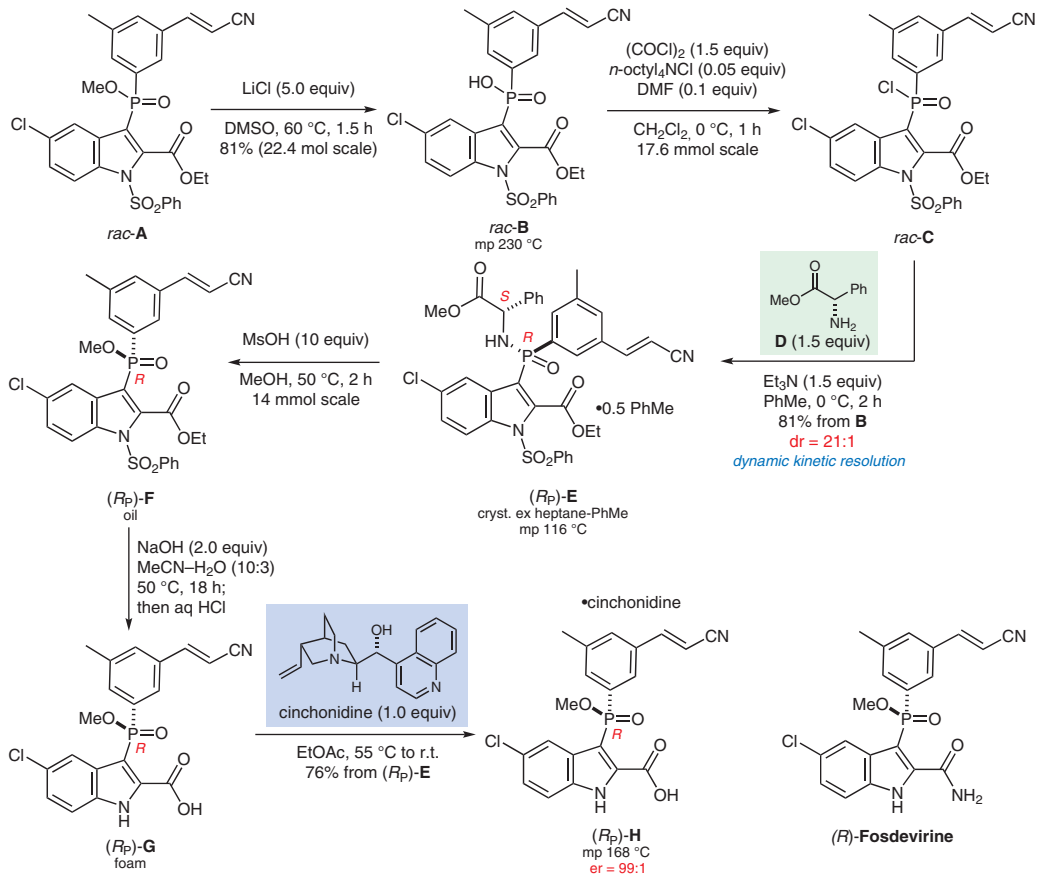
A Highly Diastereoselective Chloride-Mediated Dynamic Kinetic Resolution at Phosphorus On-Route To A Key Intermediate In the Synthesis Of GSK2248761A

*Tetrahedron Lett.* **2018**, *59*, 2154–2156.

# 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 **G** using cinchonidine as the resolving agent (*Org. Process Res. Dev.* **2018**, *22*, 200). A new route to key intermediate ($R_P$)-**G** in the synthesis of (*R*)-fosdevirine features a highly diastereoselective dynamic kinetic resolution in the reaction of the phosphinyl chloride *rac*-**C** with methyl (*S*)-phenylglycinate (**D**).

**Comment:** The key step in the dynamic kinetic resolution is the rapid racemization of phosphinyl chloride *rac*-**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 ($R_P$)-**H** from **A** was 50% (10 g scale).

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**Category**

**Synthesis of Natural Products and Potential Drugs**

**Key words**

**Fosdevirine**

**GSK2248761A**

**non-nucleoside reverse transcriptase inhibitor**

**dynamic kinetic resolution**

**phosphinate esters**