A. IRONMONGER*, M. SHIPTON, F. SLATER, P. SZETO, M. G. UNTHANK, F.-R. ALEXANDRE, C. CAILLET, C. B. DOUSSON (GLAXOSMITHKLINE MEDICINES RESEARCH CENTRE, STEVENAGE AND NORTHUMBRIA UNIVERSITY, NEWCASTLE UPON TYNE, UK; MERCK & CO., INC., RAHWAY, USA)

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

Category

Synthesis of Natural Products and Potential Drugs

Key words

Fosdevirine

GSK2248761A

non-nucleoside reverse transcriptase inhibitor

dynamic kinetic resolution

phosphinate esters

Synfact
of the month

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**).

SYNFACTS Contributors: Philip Kocienski
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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 *rac*-**A** was 50% (10 g scale).