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Development and Scale-Up of a Manufacturing Route for the Non-nucleoside Reverse Transcriptase Inhibitor GSK2248761A (IDX-899): Synthesis of an Advanced Key Chiral Intermediate

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Synthesis of Fosdevirine

Significance: Fosdevirine (GSK2248761A, IDX-899) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that was of interest for the treatment of HIV. It is P-stereogenic with the *S*-enantiomer being 1800-fold less active against the wild type virus and inactive against NNRTI-resistant viruses. The key step in the enantio-specific synthesis of (*R*)-Fosdevirine depicted is the first process-scale example of a palladium-catalyzed *H*-phosphinate coupling to give the entire backbone of Fosdevirine in one telescoped stage in 65% average yield on a 68 kg scale.

Comment: The final step in the synthesis, amidation of carboxylic acid (*R*)-**H**, is described in an accompanying paper (*Org. Process Res. Dev.* **2018**, *22*, 207). The larger scale (41.5 mol) process depicted uses eight equivalents of gaseous ammonia and results in three significant impurities. An investigation of the origin, fate, and control of these impurities led to a simpler optimized process (not shown) which is described on a much smaller scale (48 mmol) and uses aqueous ammonium hydroxide instead of ammonia in the final amidation reaction.

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