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(Chloromethyl)dimethylchlorosilane–KF: A Two-Step Solution to the Selectivity Problem in the Methylation of a Pyrimidone Intermediate en Route to Raltegravir

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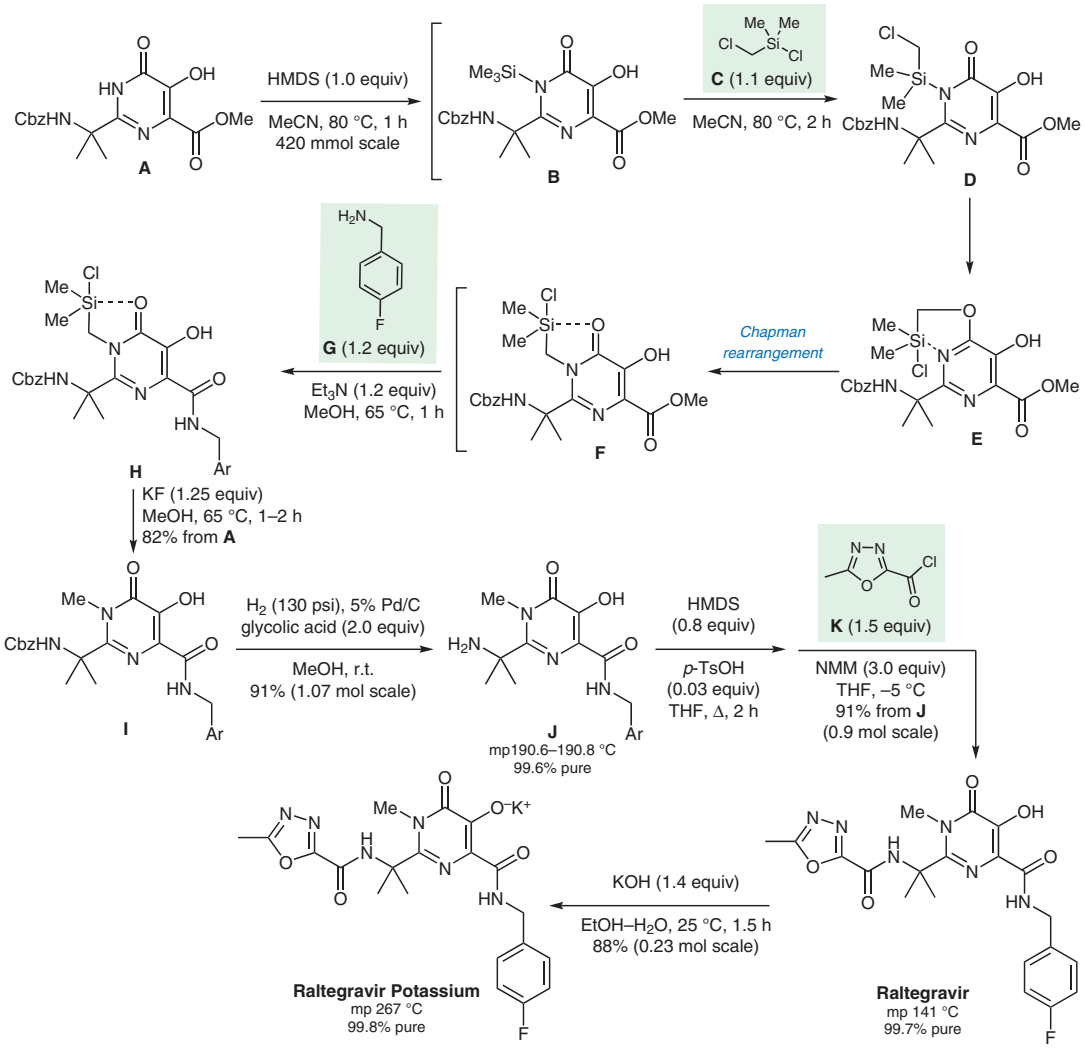
Synthesis of Raltegravir



Significance: Raltegravir potassium (Isentress®) is an HIV integrase inhibitor manufactured by Merck & Co. (G. R. Humphrey et al. *Org. Process Res. Dev.* **2011**, *15*, 73). A major challenge in the synthesis of raltegravir is the selective N-methylation of the pyrimidone intermediate **A**. Conventional methylating agents such as MeI produced mixtures of N- and O-methylated pyrimidones that were difficult to separate.

Comment: Highly selective N-methylation of **A** was achieved by the three-step sequence developed by workers at Pharmathen involving (1) N-alkylation of **B** with **C** to give **F**, (2) amidation of **F** with amine **G**, and (3) desilylation of **H** with potassium fluoride in methanol. By this procedure, the desired *N*-methylpyrimidone **I** was obtained in 82% overall yield on a 420 mmol scale. For a mechanism for the formation of **I**, see: V. A. Pestunovich and co-workers *J. Organomet. Chem.* **1989**, *361*, 147.

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Category

Synthesis of Natural Products and Potential Drugs

Key words

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N-methylation

Chapman rearrangement