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 Mel 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.