Synthesis of an HIV-1 Integrase Allosteric Site Inhibitor

Significance: Tetrahydro-1,6-naphthyridine \(Q\) inhibits HIV-1 integrase, one of the three enzymes encoded in the HIV-1 genome required for viral replication. A markworthy step in the small-scale synthesis depicted is the Bode homologation of carboxylic acid \(G\) to \(\alpha\)-keto ester \(J\) via sulfur ylide \(I\) (L. Ju, A. R. Lippert, J. W. Bode, J. Am. Chem. Soc. 2008, 130, 4253).

Comment: Corey–Itsuno asymmetric reduction of \(\alpha\)-keto ester \(J\) gave a 1:1 mixture of diastereoisomers from which the desired atropisomer \(L\) was isolated in 45% yield by column chromatography and crystallization. Tetrahydro-1,6-naphthyridine \(F\) was constructed in four steps in 20% overall yield using a Hantzsch pyridine synthesis.