Practical Asymmetric Synthesis of Efavirenz (DMP 266), an HIV-1 Reverse Transcriptase Inhibitor


Synthesis of Efavirenz via Asymmetric Alkynylation

**Significance:** Efavirenz (Sustiva®) is an HIV-1 reverse transcriptase inhibitor that was approved by the FDA in 1998 for the treatment of HIV/AIDS. The classic DuPont–Merck synthesis depicted incorporates a highly enantioselective addition of lithium acetylide \( K \) (as the tetrameric complex \( F \)) to ketone \( E \) mediated by chiral chaperone \( J \). The synthesis proceeds in 62% overall yield in just seven steps. Since all intermediates were crystalline, no chromatography was required.

**Comment:** For the mechanism of the acetylide addition, see: A. Thompson et al. J. Am. Chem. Soc. 1998, 120, 2028. For further practical refinements in the nucleophilic addition, see: A. Choudhury et al. Org. Process Res. Dev. 2003, 7, 324. A large scale enantioselective alkynylation of ketone \( D \) mediated by chiral chaperone \( J \) gave adduct \( I \) directly in 95% yield (er > 99:1) on a 4.5 mol scale: WO 1998 51676.