**Synthesis of Dual Orexin Receptor Antagonist MK-6096**

**Significance:** Orexins-A and -B are neuropeptides that regulate arousal and sleep–wake cycles by hypothalamic signaling through the orexin-1 and -2 receptors. MK-6096 is a dual orexin receptor antagonist that is of interest for the treatment of insomnia. In the asymmetric synthesis depicted (7 steps, 37% overall), the key stereogenic steps are (1) a biocatalytic transamination \((A \rightarrow B)\) and (2) a highly diastereoselective Mukaiyama directed aldol reaction \((C \rightarrow D, \text{dr} > 99:1)\).

**Comment:** During a previous kg-scale synthesis of MK-6096 (M. Girardin et al. *Org. Process Res. Dev.* 2013, 17, 61) the challenging amidation of fragments \(I\) and \(J\) required 3.4 equivalents of expensive T3P (1-propylphosphonic anhydride). In the current route the same amidation was accomplished using only 0.05 equivalents of T3P together with stoichiometric amounts of pivaloyl chloride as the dehydrating agent. A mechanism for this unusual transformation is presented that implicates participation by the pyrimidine ring.

**Key words**
- MK-6096
- orexin antagonists
- amide bond formation
- 1-propylphosphonic anhydride
- enzymatic transamination
- Mukaiyama directed aldol reaction