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Unusual Pyrimidine Participation: Efficient Stereoselective Synthesis of Potent Dual Orexin Receptor Antagonist MK-6096

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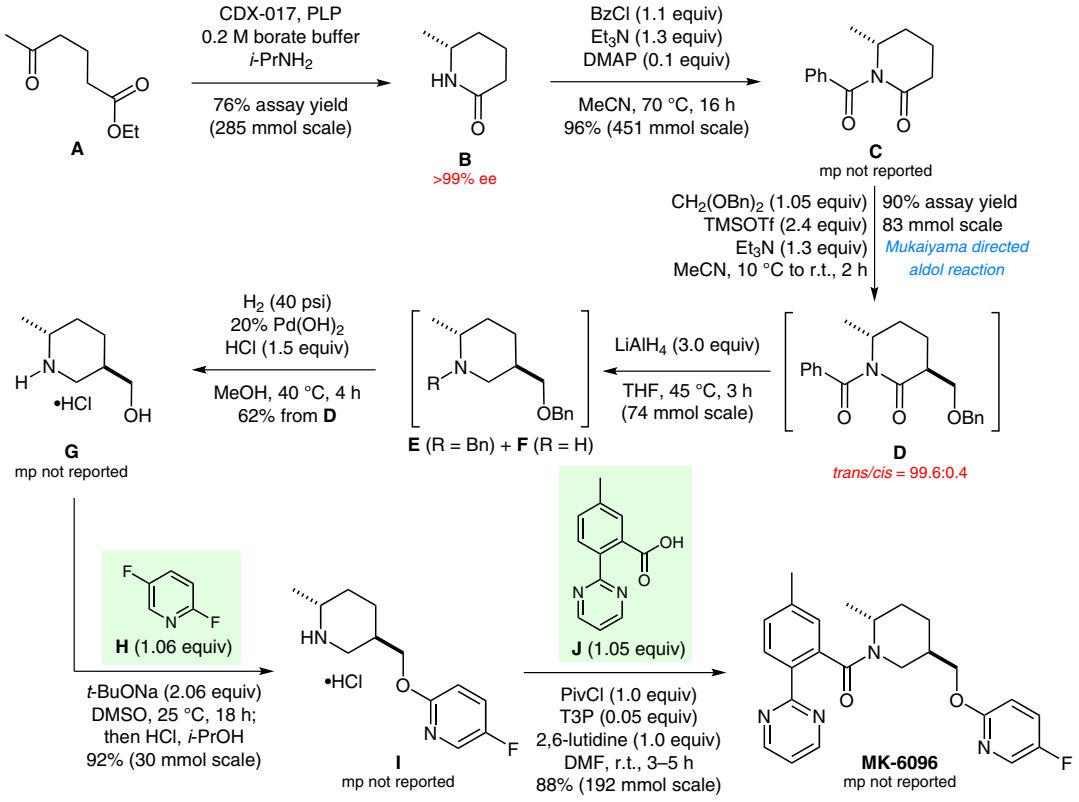
Synthesis of Dual Orexin Receptor Antagonist MK-6096



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**→**B**) and (2) a highly diastereoselective Mukaiyama directed aldol reaction (**C**→**D**, 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 choride as the dehydrating agent. A mechanism for this unusual transformation is presented that implicates participation by the pyrimidine ring.

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