Synthesis of MK-6096

Significance: The orexins are peptides that act as neurotransmitters in the central nervous system. MK-6096 is a dual orexin receptor antagonist that is a candidate for the treatment of insomnia. A noteworthy feature of the synthesis depicted is the biocatalytic transamination reaction on prochiral substrate A using a three-enzyme cocktail that delivers piperidinone B (>99% ee) on a multikilogram scale.

Comment: The diastereoisomeric ratio of the α-hydroxymethyl lactam (dr = 1.7:1) was improved to >40:1 by reduction of the lactam followed by salt formation using D-(+)-camphorsulfonic acid [D-(+)-CSA]. For the development of transaminase ATA-117 in the manufacture of sitagliptin, see: C. K. Savile et al. *Science* 2010, 329, 305.