Synthesis of Omarigliptin

Significance: Omarigliptin (MK-3102) is a dipeptidyl peptidase-4 (DPP-4) inhibitor that has received marketing authorization in Japan for the once-weekly treatment of type 2 diabetes. The synthesis of pyranone H depicted features three ruthenium-catalyzed reactions: (1) a DKR reduction of rac-α-aminoketone C to set the two contiguous stereogenic centers, (2) a cycloisomerization of alkyne E to dihydropyran F, and (3) a ruthenium-catalyzed oxidation of pyranol G to the desired pyranone H.

Comment: The Takasago tethered ruthenium(II) catalyst D is a highly efficient asymmetric transfer hydrogenation catalyst. The catalyst loading was reduced to 0.1 mol% without sacrificing selectivity and reaction kinetics. It was critical to apply efficient N2 sparging during the reaction to remove CO2; otherwise, the reaction could stall if this was allowed to accumulate. For the discovery synthesis of omarigliptin, see: T. Biftu et al. J. Med. Chem. 2014, 57, 3205.