Synthesis of a Glucagon Receptor Antagonist

Significance: The target glucagon receptor antagonist is a candidate for the treatment of type 2 diabetes. Key steps in the synthesis of the sterically congested 1,1,2-triarylalkane core are (1) the asymmetric Noyori hydrogenation of ketone involving a dynamic kinetic resolution and (2) the anti-selective Friedel–Crafts alkylation of the fluoroindole by chiral benzylic carbocation.

Comment: Optimal Friedel–Crafts diastereoselectivity and yield were achieved with nosyl-protected indole using TFA as solvent and catalytic MsOH. A highly efficient, large-scale Larock-type synthesis of fluoroindole from 2-bromoaniline was also developed. For the stereochemistry of the anti-selective Friedel–Crafts alkylation, see: J. Y. L. Chung et al. Org. Lett. 2008, 10, 3037.