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Asymmetric Synthesis of a Glucagon Receptor Antagonist via Friedel–Crafts Alkylation of an Indole with Chiral α-Phenyl Benzyl Cation

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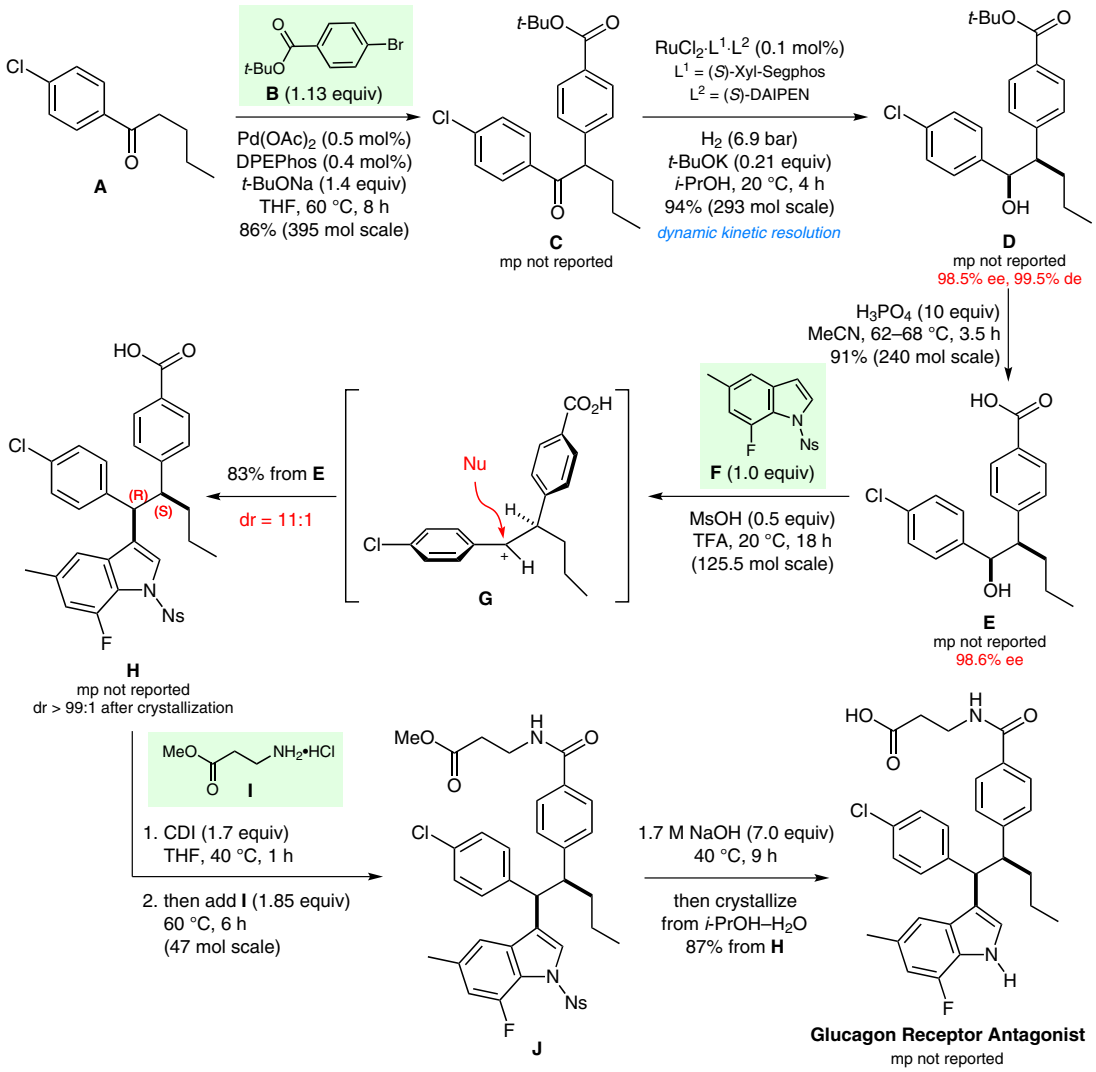
Synthesis of a Glucagon Receptor Antagonist



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 **C** involving a dynamic kinetic resolution and (2) the *anti*-selective Friedel–Crafts alkylation of the fluoroindole **F** by chiral benzylic carbocation **G**.

Comment: Optimal Friedel–Crafts diastereoselectivity and yield were achieved with nosyl-protected indole **F** using TFA as solvent and catalytic MsOH. A highly efficient, large-scale Larock-type synthesis of fluoroindole **F** 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.

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Category

Synthesis of Natural Products and Potential Drugs

Key words

glucagon receptor antagonists

Friedel–Crafts alkylation

palladium-catalyzed enolate arylation

Noyori asymmetric hydrogenation

dynamic kinetic resolution

SYNFACT of the month

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