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Synthesis of BACE Inhibitor LY2886721. Part II. Isoxazolidines as Precursors to Chiral Aminothiazines, Selective Peptide Coupling, and a Controlled Reactive Crystallization

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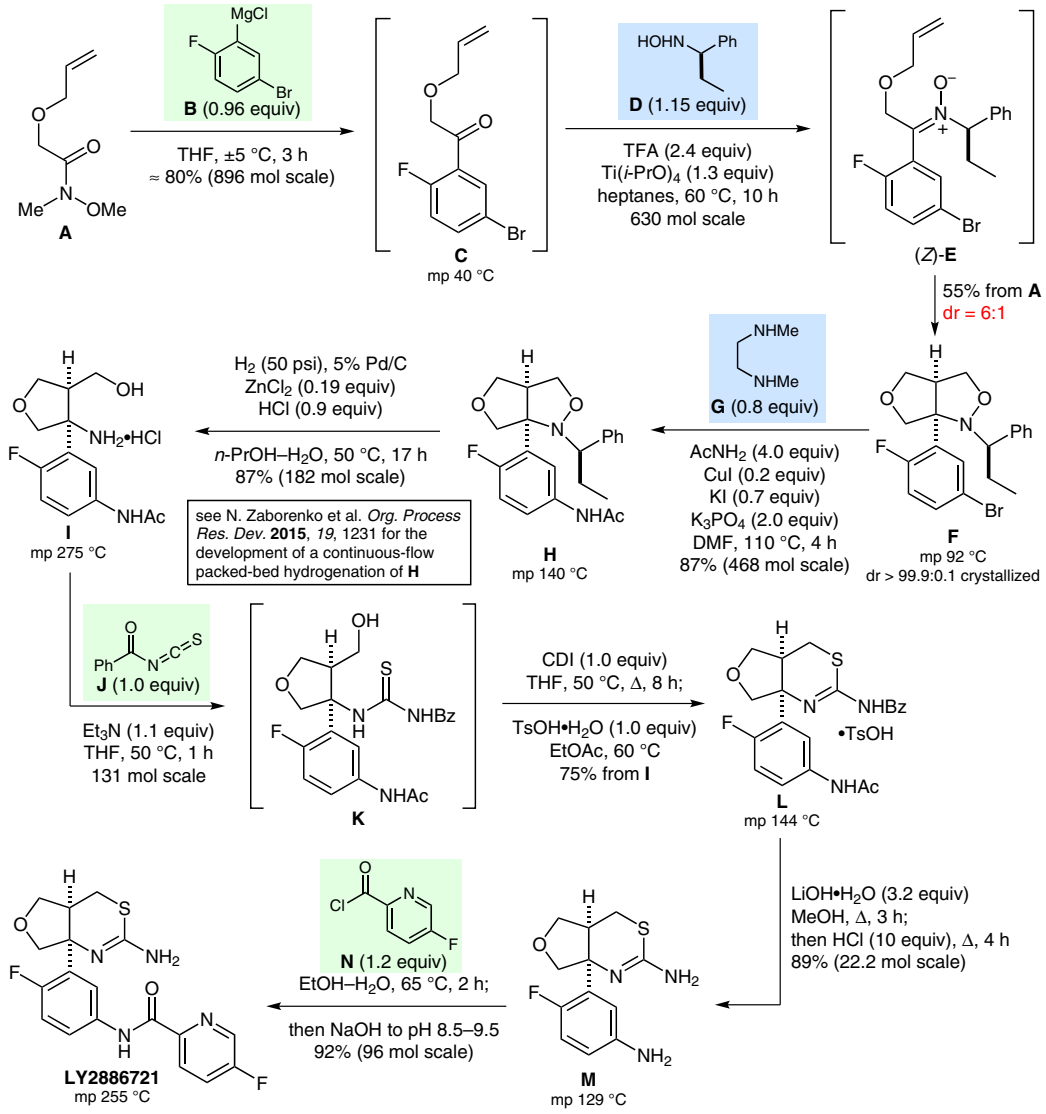
Synthesis of LY2886721



Significance: LY2886721 is a BACE inhibitor that is of interest for the treatment of Alzheimer's disease. In the key intramolecular dipolar cycloaddition, nitrone (*Z*)-**E** underwent kinetic selection to afford a mixture of cycloadducts (dr = 6:1) from which the desired isoxazolidine **F** was isolated in 55% yield by crystallization.

Comment: Minimizing formation of a desfluoro impurity during hydrogenolysis of the isoxazolidine ring and removal of the benzyl chiral auxiliary (**H** → **I**) was a key challenge. The final acylation occurred without competing acylation of the aminothiazine nitrogen to afford LY2886721 in 17% overall yield on a multi-kilogram scale.

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Category

Synthesis of Natural Products and Potential Drugs

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BACE inhibitor

dipolar cycloaddition

nitrone

aminothiazines

ring formation

continuous flow

hydrogenolysis