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A Scalable Route for the Regio- and Enantioselective Preparation of a Tetrazole Prodrug: Application to the Multi-Gram-Scale Synthesis of a PCSK9 Inhibitor
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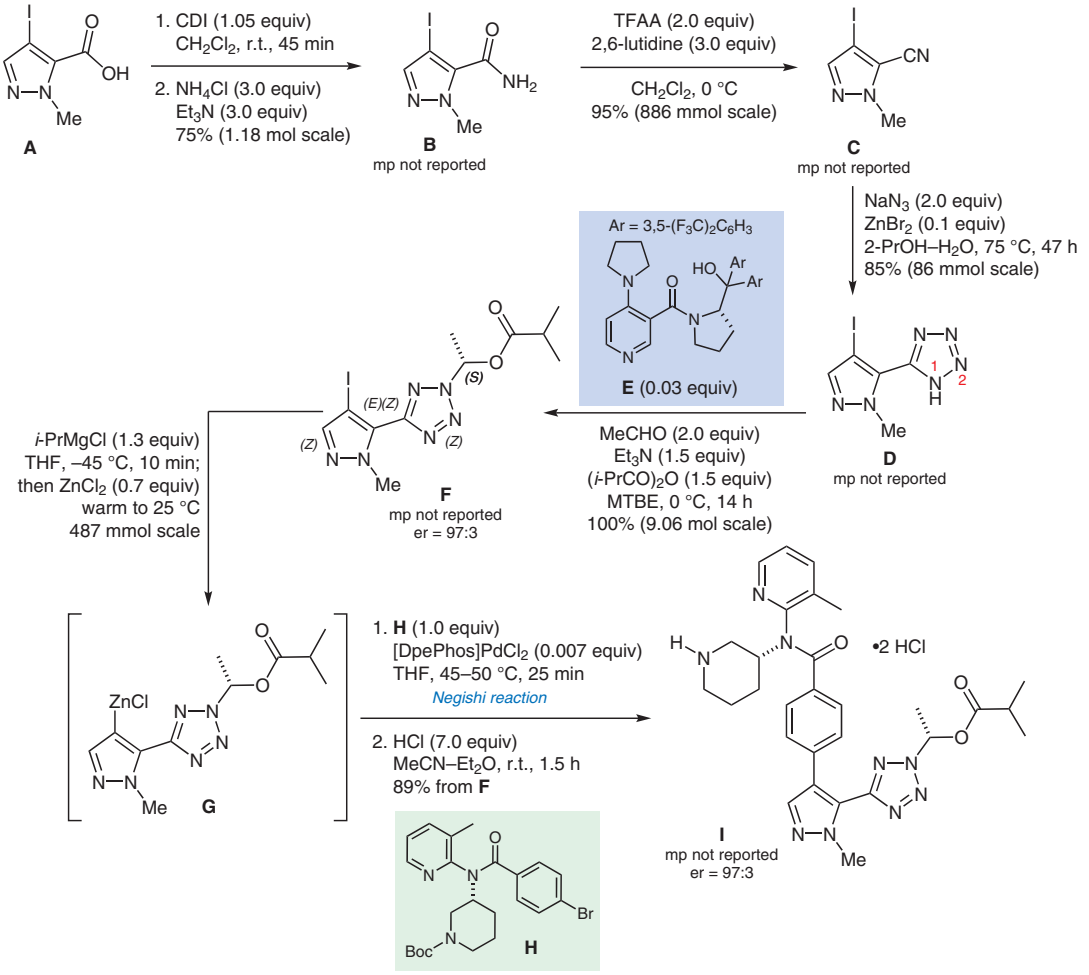
Synthesis of a PCSK9 Inhibitor



Significance: The target molecule **I** is a hemiaminal ester prodrug of an inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9) that is of interest for reducing serum LDL-cholesterol levels. A markworthy step in the synthesis depicted is the three-component dynamic kinetic resolution between tetrazole **D**, acetaldehyde, and isobutyric anhydride catalyzed by the enantiopure DMAP catalyst **E** to afford hemiaminal ester (*S*)-**F** (er = 97:3) in quantitative yield on a multikilogram scale.

Comment: The tetrazole **D** was initially generated by reaction of nitrile **C** with hydrazoic acid generated in situ from sodium azide and ammonium chloride in DMF at >100 °C. This method generates toxic and explosive anhydrous hydrazoic acid (pK_a = 4.6). A safer method shown here for the synthesis of **D** entails reaction of sodium azide (2 equiv) with nitrile **C** using zinc bromide (0.1 equiv) as a catalyst in isopropanol–water (1:1) at 75 °C. Under these conditions only trace amounts of hydrazoic acid are generated. The yield is 85%.

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Synthesis of Natural Products and Potential Drugs

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