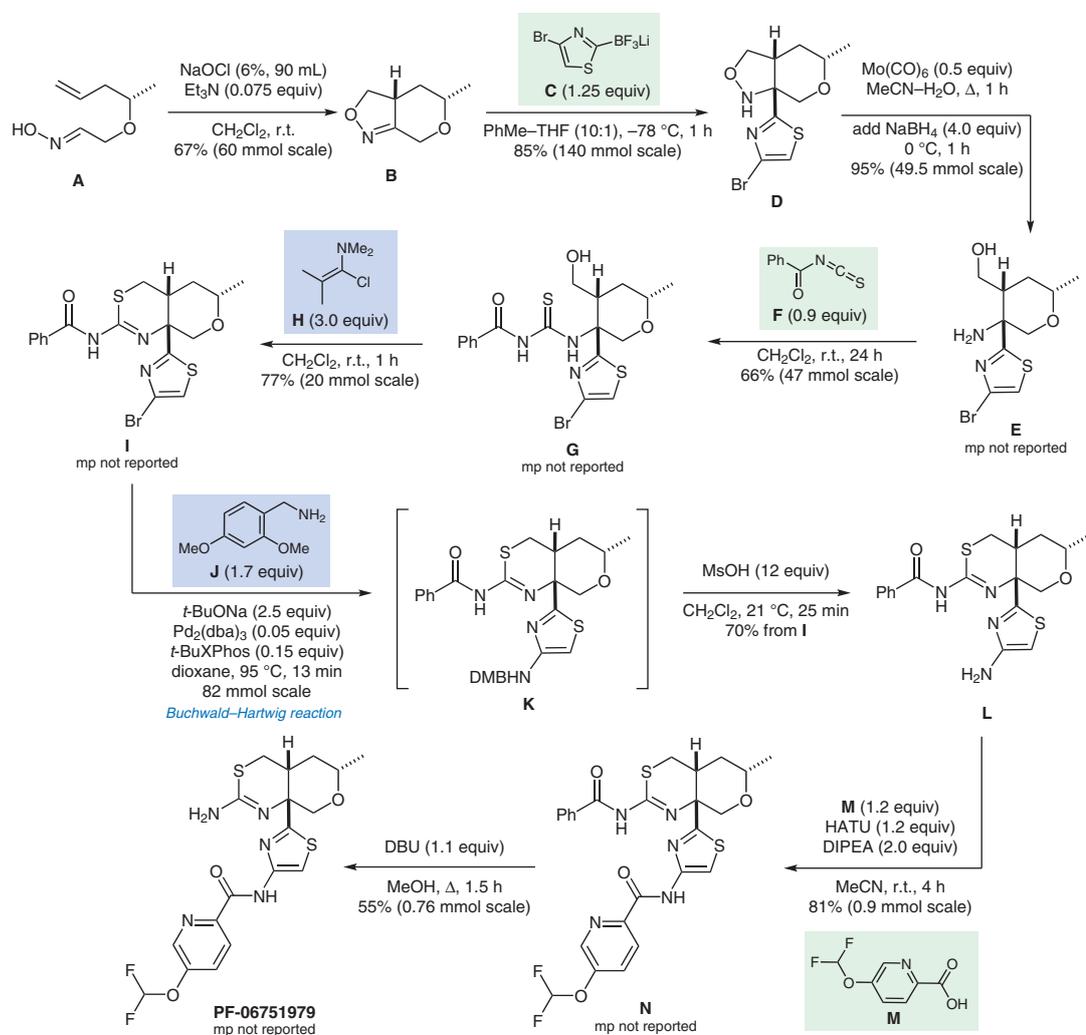


M. BRODNEY* ET AL. (PFIZER, INC., CAMBRIDGE AND GROTON, USA)
 Design and Synthesis of Clinical Candidate PF-06751979: A Potent, Brain Penetrant, β -Site Amyloid Precursor Protein Cleaving Enzyme 1 (BACE1) Inhibitor Lacking Hypopigmentation
J. Med. Chem. **2018**, *61*, 4476–4504.

Synthesis of PF-06751979



Significance: PF-06751979 is a potent brain penetrant β -site amyloid precursor protein cleaving enzyme 1 (BACE1) inhibitor that is of interest for the treatment of Alzheimer's disease. It displays broad selectivity over related aspartyl proteases including BACE2 and cathepsin D. A potential liability of BACE2 inhibition is depigmentation.

Comment: In the key step, the chiral quaternary center in **D** was constructed via diastereoselective addition of the metallated thiazole **C** to the convex face of the bicyclic isoxazoline **B**. The direct conversion of bromothiazole **I** to **N** (61%, 0.11 mmol scale) via a Buchwald–Hartwig coupling with 5-(difluoromethoxy)picolinamide is also reported. See also the synthesis of LY2886721: *Org. Process Res. Dev.* **2015**, *19*, 1214.

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