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.