Synthesis of MK-8248

Significance: MK-8248 is a γ-secretase modulator that is of interest for the treatment of Alzheimer’s disease. Key steps in the synthesis depicted are (1) an amino acid dehydrogenase mediated conversion of α-keto carboxylic acid A into 3,4,5-trifluoro-(S)-phenylglycine (B) and (2) a four-step sequence including a dehydrative intramolecular cyclization to form the 1,2,4-oxadiazine ring (C).

Comment: On treating a solution of I with hexamethyldisilazane (HMDS) and catalytic amounts of trimethylsilyl trifluormethanesulfonate (TMSOTf), the desired intramolecular cyclization took place in high yield. This silyl-mediated dehydration provided a milder alternative to Bronsted acids. The target molecule MK-8248 was isolated as its crystalline hemi-fumarate salt.