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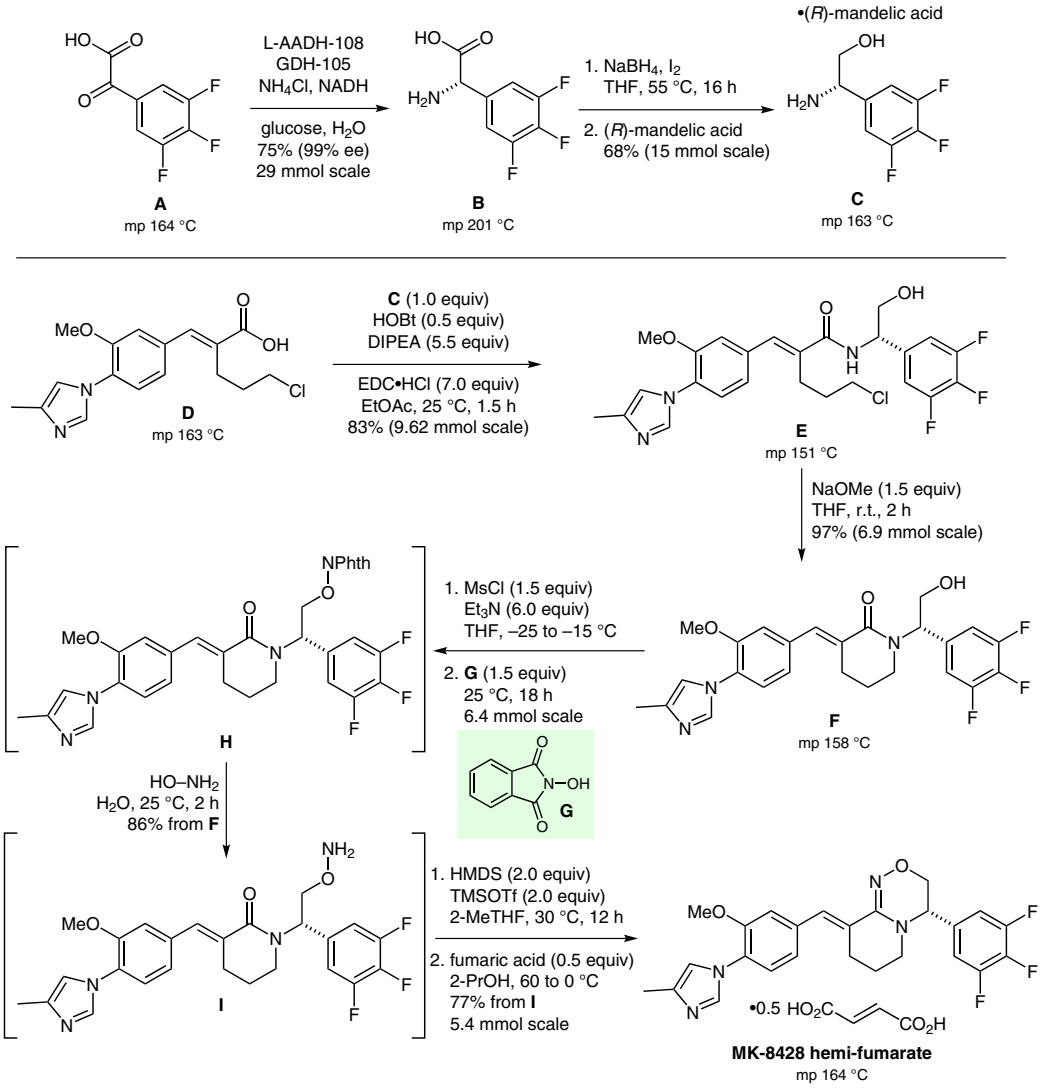
Synthesis of the γ-Secretase Modulator MK-8428
J. Org. Chem. **2017**, *82*, 2957–2964.

Synthesis of MK-8248



Significance: MK-8428 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 oxadiazine ring.

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 Brønsted acids. The target molecule MK-8428 was isolated as its crystalline hemi-fumarate salt.

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Synfacts 2017, 13(06), 0563 Published online: 16.05.2017
DOI: 10.1055/s-0036-1590388; **Reg-No.:** K02017SF

Category

Synthesis of Natural Products and Potential Drugs

Key words

MK-8248

γ-secretase modulator

amino acid dehydrogenase

1,2,4-oxadiazine ring formation

reductive amination