

Synthesis of MK-8248

Category

Synthesis of Natural
Products and
Potential Drugs

Key words

MK-8248

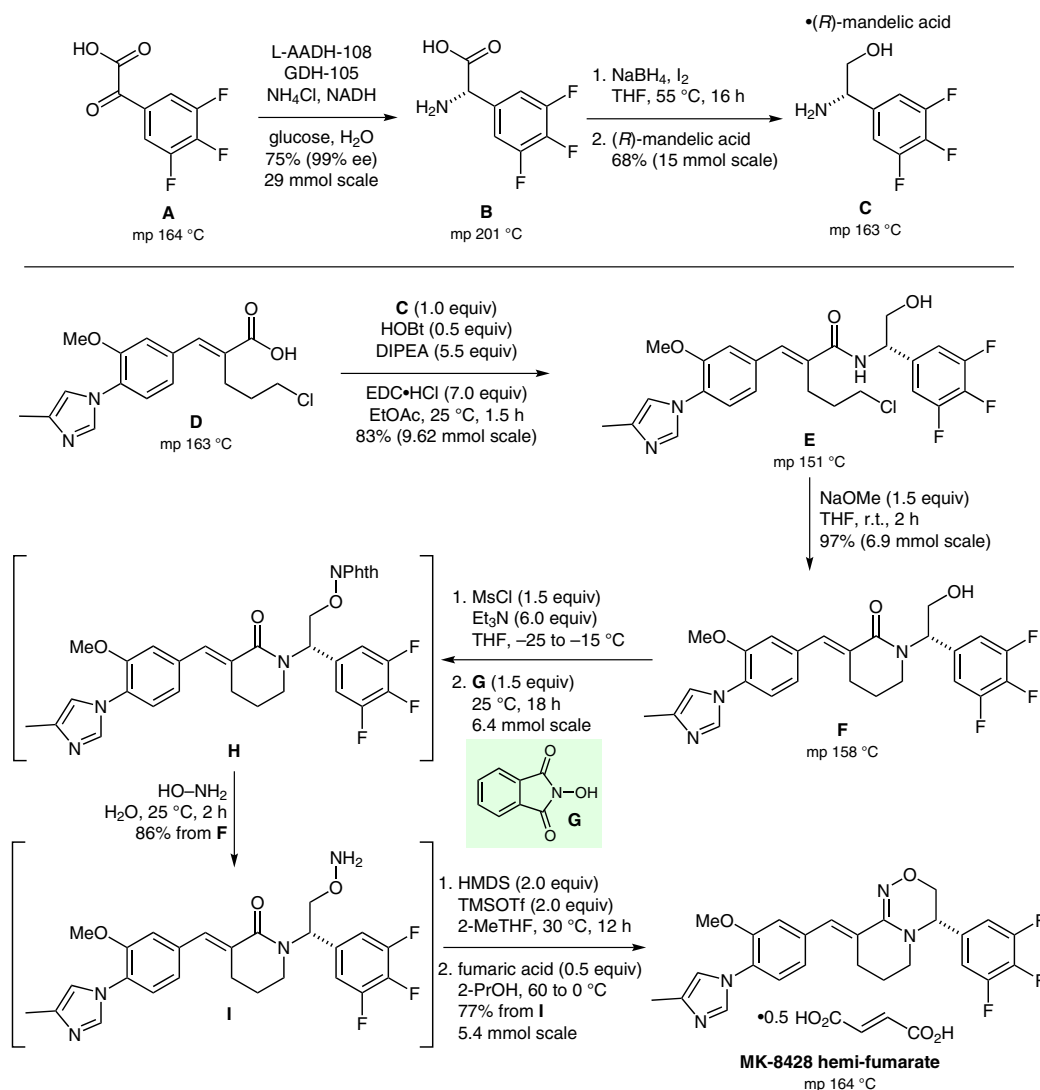
γ -secretase
modulator

amino acid
dehydrogenase

1,2,4-oxadiazine
ring formation

reductive amination

Synfact
of the month



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 oxadiazine ring.

Comment: On treating a solution of **I** with hexamethyldisilazane (HMDS) and catalytic amounts of trimethylsilyl trifluoromethanesulfonate (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-8248 was isolated as its crystalline hemi-fumarate salt.