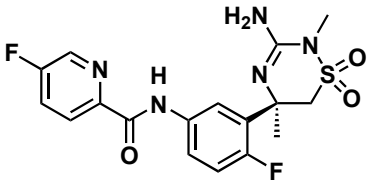
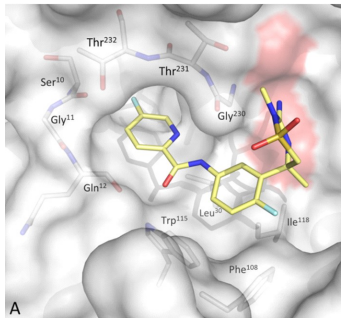
Drug of the Week: Verubecestat (MK-8931)





Drug Background:

-MK-8931, Verubecestat, was a phase III drug candidate for the treatment of Alzheimer's disease.

-The candidate acts as an inhibitor of β-site amyloid precursor protein cleaving enzyme 1 (BACE 1), an enzyme believed to be involved in the initiation of toxic β-amyloid peptide aggregates responsible for disruption of neuron function.

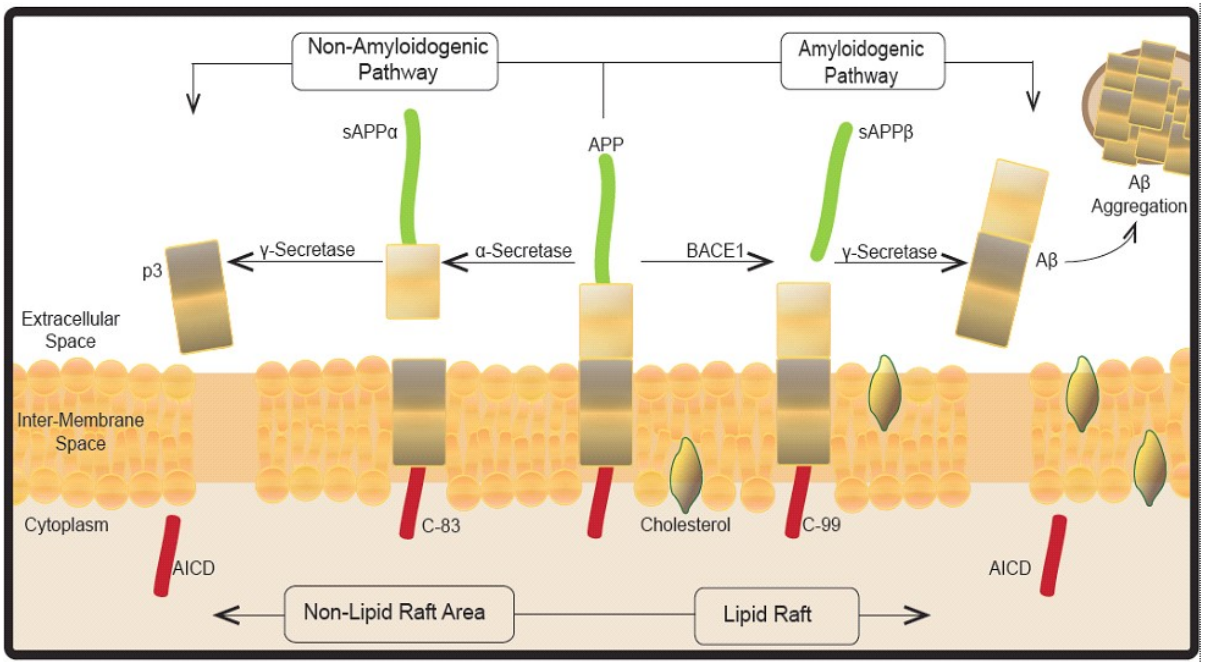
-Until the past several years, it was theorized that sustained inhibition of BACE 1 could ameliorate the formation of amyloid plaques.

-On screening for $BACE_1$ inhibitors, a thiourea-containing hit was optimized to arrive at the final structure of Verubecestat (binding shown above).

-The compound exhibited an IC_{50} of 13 nM in reduction of Aβ40 in animal models, and exhibited no adverse effects in phase I trials.

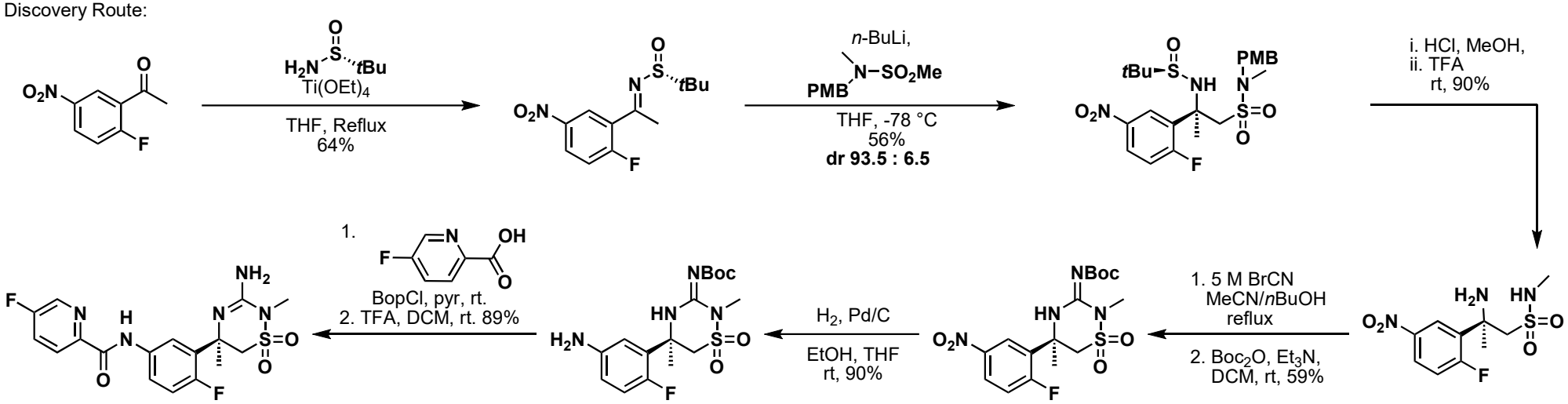
-Following a lack of efficacy in phase III clinical trials, research towards the drug was halted, and most targets have shifted from BACE1 inhibition.

Amyloid Plaque Formation: Proposed Pathway



Read, J. S., Cenk (2012). "Dropping the BACE: Beta Secretase ($BACE_1$) as an Alzheimer's Disease Intervention Target."

Discovery Route:



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Merck Newsroom (2017) *www.mrknewsroom.com/news-release/research-and-development-news/*

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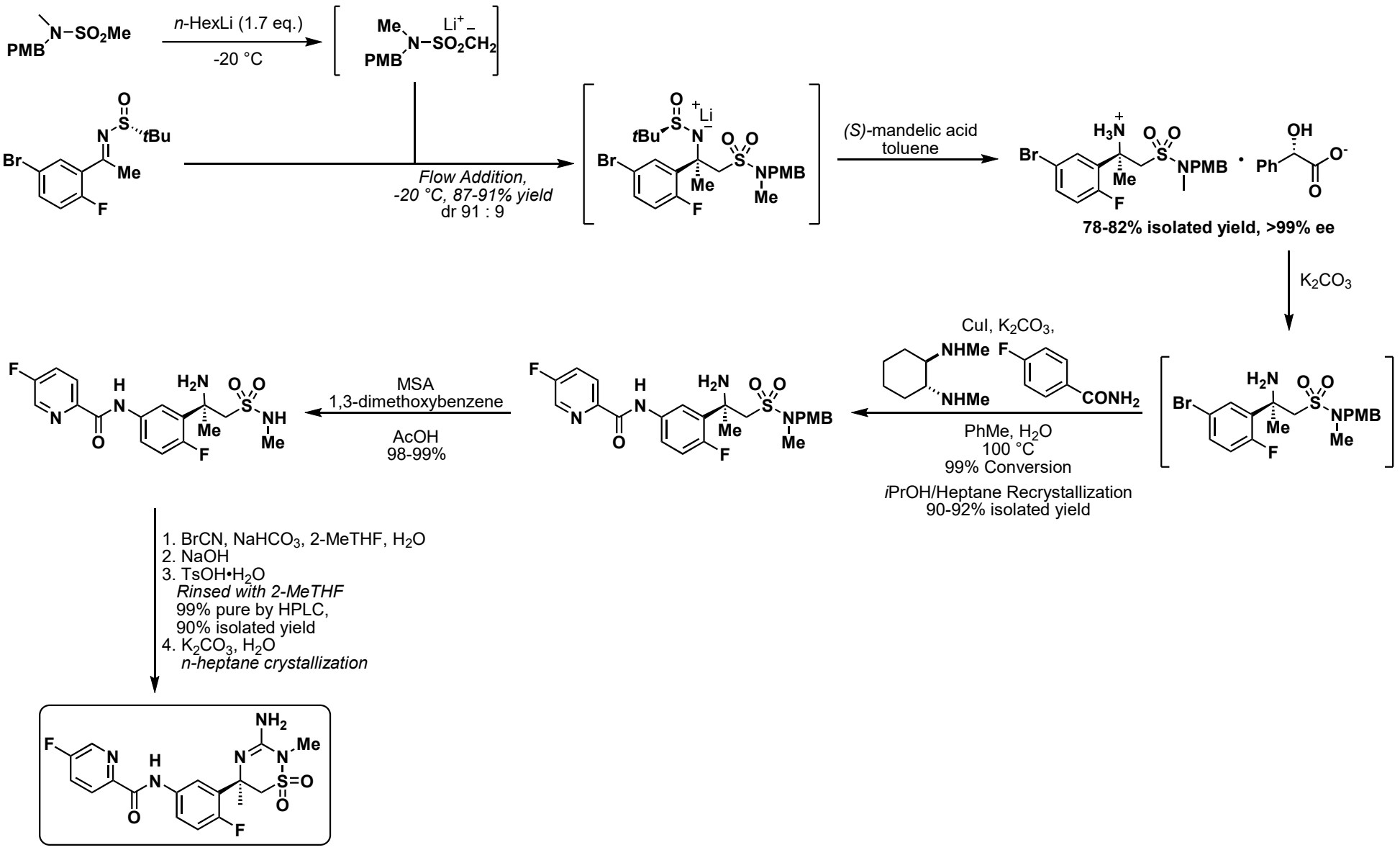
Commercial Synthesis:



Org Lett. **2018**, 20, 1568.