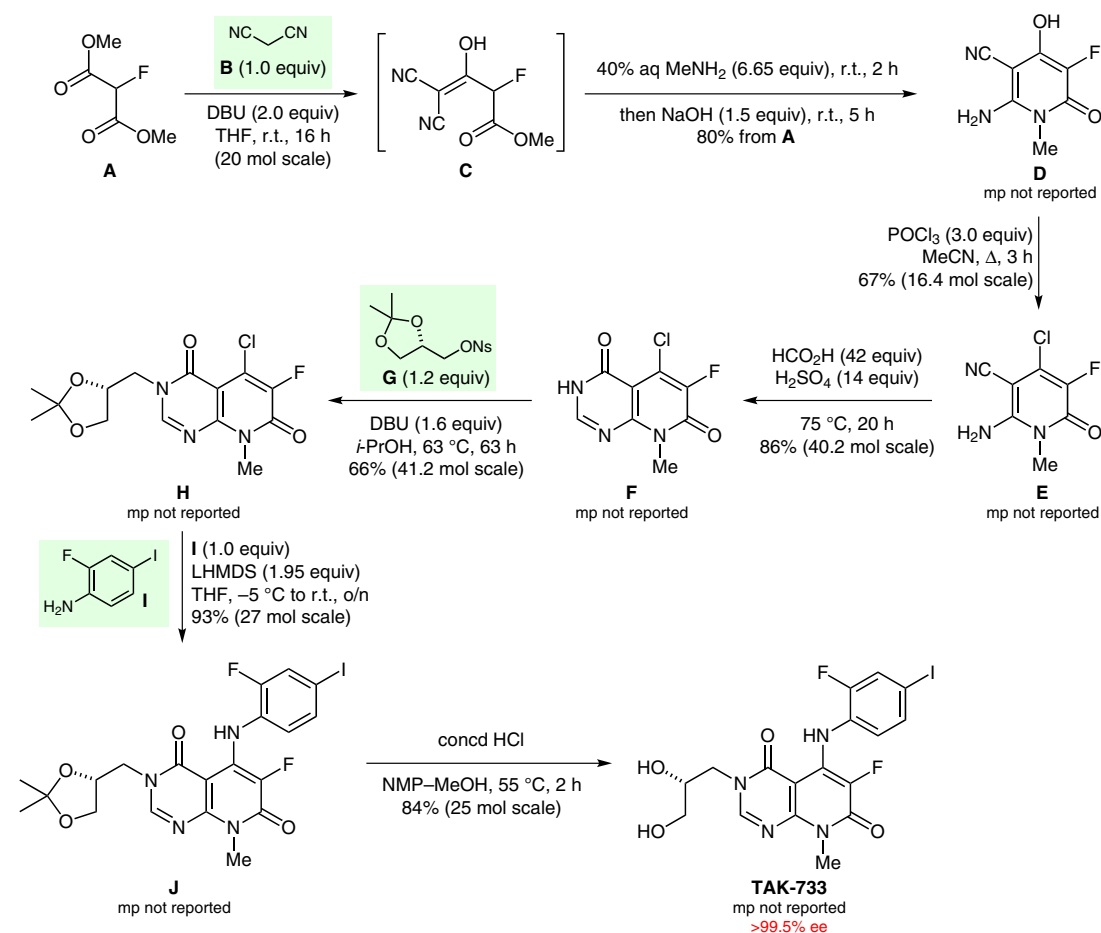


Synthesis of TAK-733



Significance: MEK kinases regulate the pathway that mediates proliferative and anti-apoptotic signaling factors that promote tumor growth and metastasis. TAK-733 is an MEK kinase inhibitor that entered phase I clinical trials for the treatment of cancer. A noteworthy feature of this short synthesis (25% yield overall) is the one-pot, three-step synthesis of the fluoropyridone **D**, in which the fluorine atom is present at the outset.

Comment: The reaction of **F** with the nosylate **G** gave a mixture of N- and O-alkylation products (8:1) from which the desired N-alkylation product was isolated by crystallization. The mixture of N-methyl pyrrolidine (NMP) and methanol used in the final deprotection step, helped to ensure formation of the desired polymorph. The nine-step discovery synthesis (3% overall yield) is also presented.