Synthesis of PF-06873600

Significance: The cyclin-dependent kinases (CDKs) are a 21-member family of serine-threonine kinases that are involved in a diverse array of cellular processes. PF-06873600 is a selective cyclin-dependent kinase 2/4/6 inhibitor that advanced to phase I clinical trials in 2018 for the treatment of cancer. The highly efficient (1R,2R)-2-hydroxy-2-methycyclopentyl-1-amine moiety [(1R,2R)-B (US 2018 0044344 A1)] provided a marked improvement in lipophilicity with consequent better potency and metabolic stability.

Comment: A key step in the synthesis of PF-06873600 is a C–H functionalization reaction by which a difluoromethyl radical is generated from a sulfinate precursor (I) and tert-butyl hydroperoxide in the presence of iron or other inorganic counterions (Y. Fujiwara J. Am. Chem. Soc. 2012, 134, 1494; F. O’Hara et al. J. Am. Chem. Soc. 2013, 135, 12122). In this system, the resultant difluoromethyl radical reacts regioselectively at the 6-position of the pyridopyrimidinone core and provides the target molecule in 57% yield.