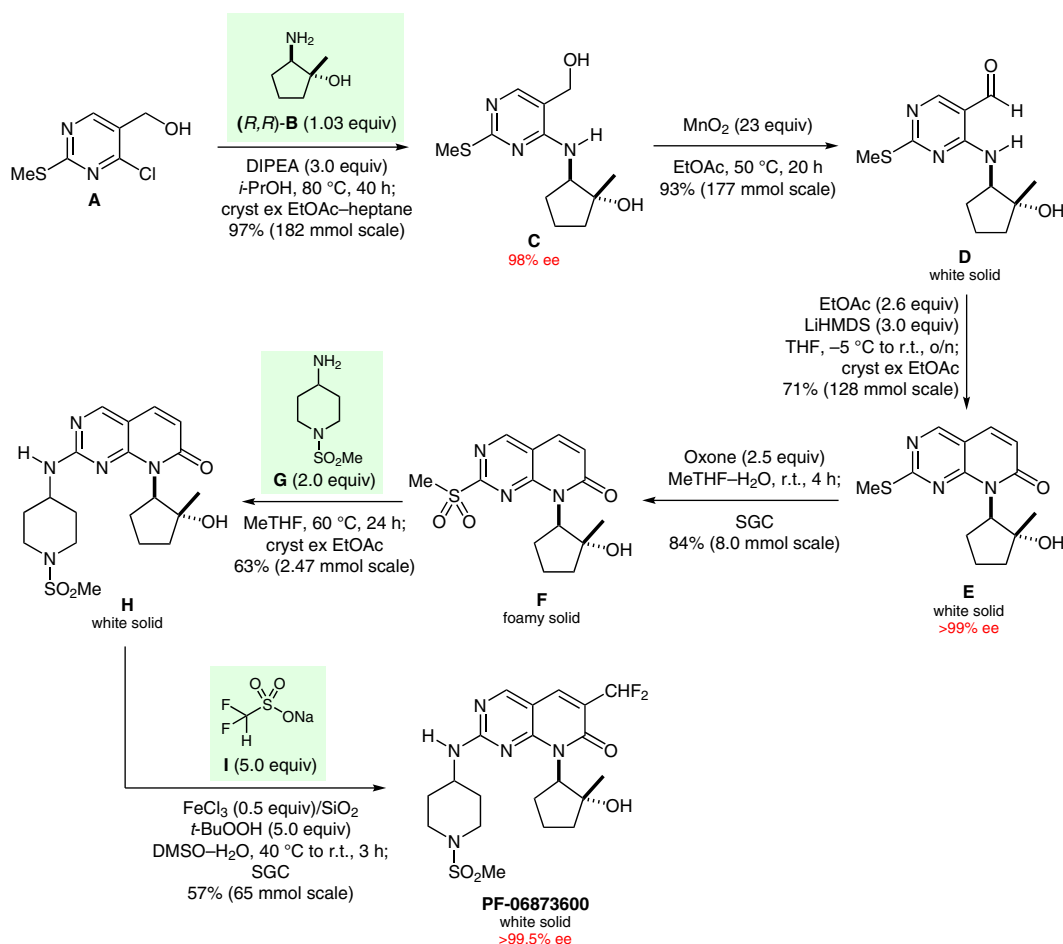


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Discovery of PF-06873600, a CDK2/4/6 Inhibitor for the Treatment of Cancer

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## 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 (1*R*,2*R*)-2-hydroxy-2-methylcyclopentyl-1-amine moiety [(1*R*,2*R*)-**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.

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Synthesis of Natural Products and Potential Drugs

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