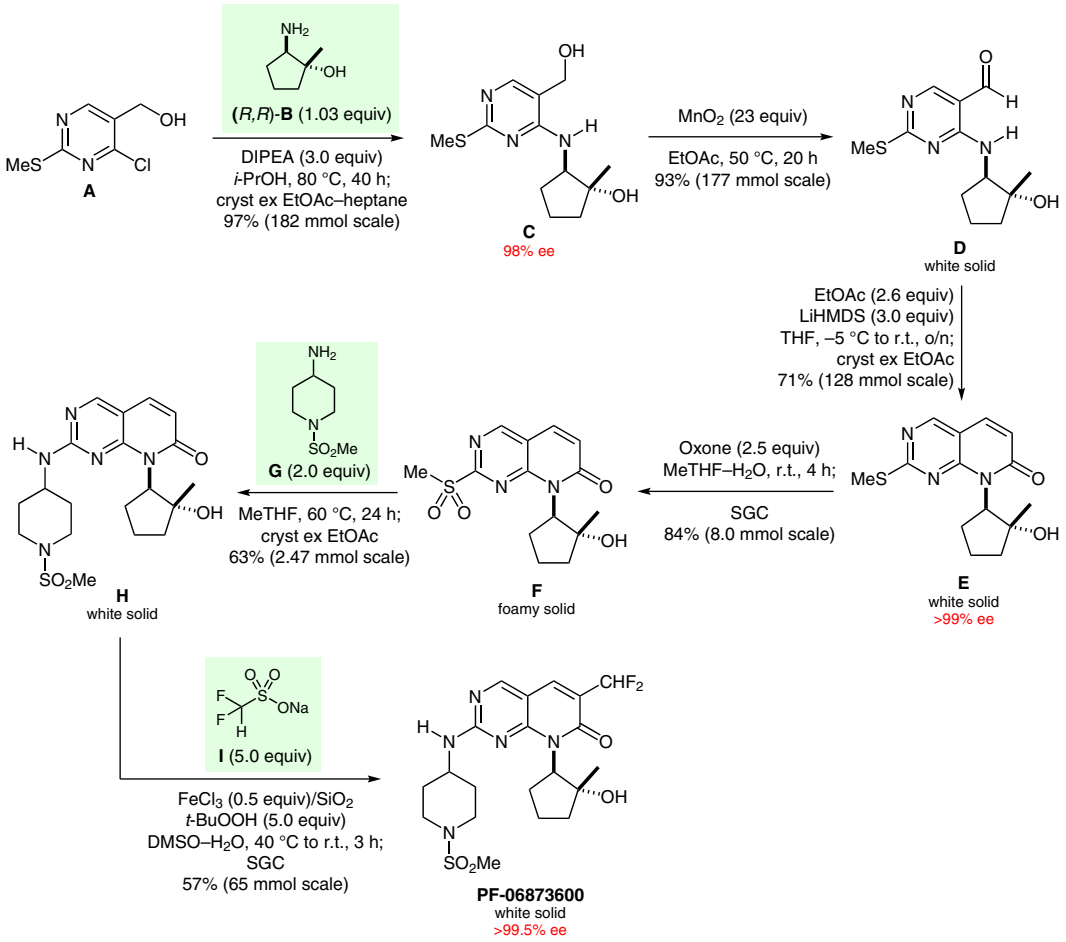
K. D. FREEMAN-COOK* ET AL. (PFIZER GLOBAL RESEARCH & DEVELOPMENT, LA JOLLA, USA)

Discovery of PF-06873600, a CDK2/4/6 Inhibitor for the Treatment of Cancer
J. Med. Chem. **2021**, *64*, 9056–9077, DOI: 10.1021/acs.jmedchem.1c00159.

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-methycyclopentyl-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.

SYNFACTS Contributors: Philip Kocienski
Synfacts 2021, 17(09), 0961 Published online: 18.08.2021
DOI: 10.1055/s-0040-1720754; **Reg-No.:** K04921SF