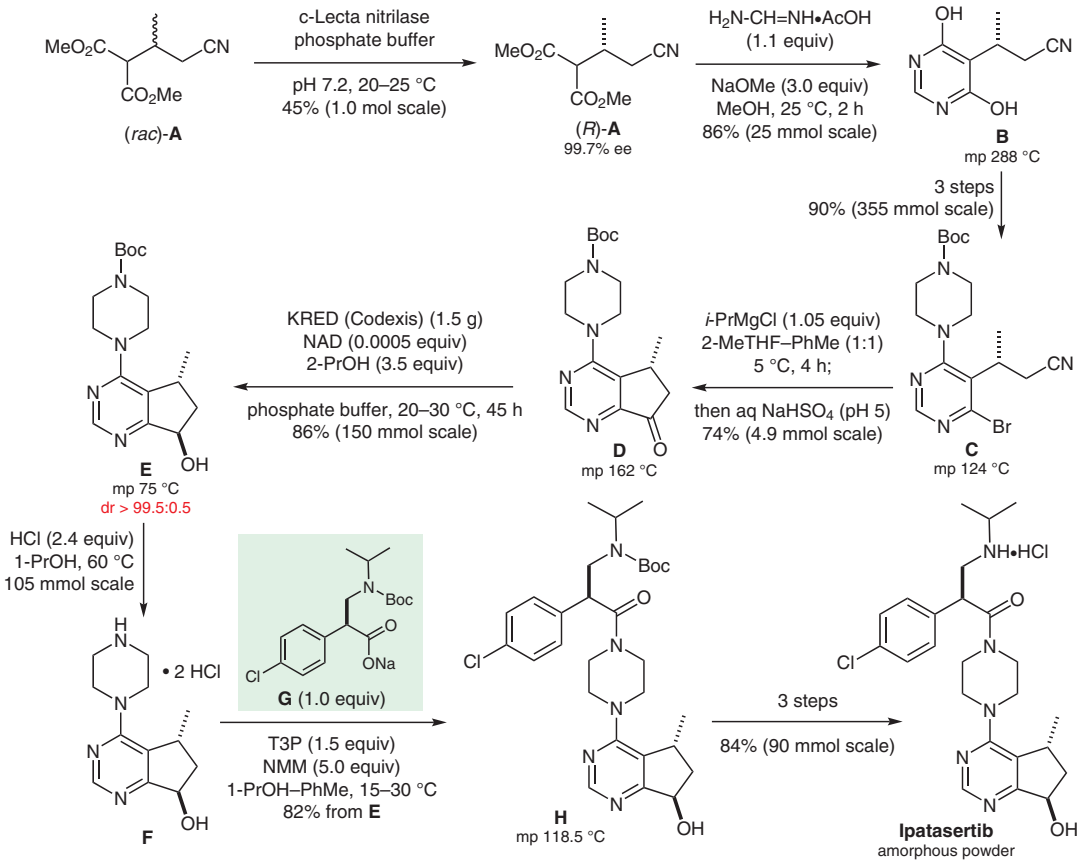
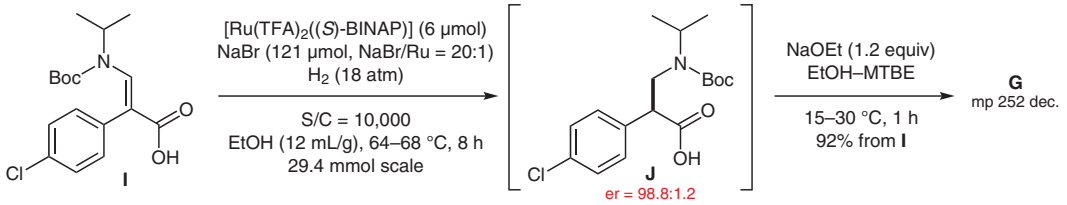
F. GOSSELIN* ET AL. (GENENTECH, INC., SOUTH SAN FRANCISCO, USA AND F. HOFFMANN-LA ROCHE AG, BASEL, SWITZERLAND)
Asymmetric Synthesis of Akt Kinase Inhibitor Ipatasertib
Org. Lett. **2017**, *19*, 4806–4809.

Asymmetric Synthesis of Ipatasertib



Synthesis of fragment G:



Significance: Ipatasertib (GDC-0068) is an Akt kinase inhibitor that that is of interest for the treatment of cancer. The stereogenic centers in fragment **F** were installed using a nitrilase-catalyzed resolution of nitrile (*rac*)-**A** and a ketoreductase-catalyzed reduction of ketone **D**. For a related large-scale synthesis of Ipatasertib, see: T. Remarchuk et al. *Org. Process Res. Dev.* **2014**, *18*, 1652.

Comment: The stereogenic center in fragment **L** was installed by asymmetric hydrogenation. Using [Ru(TFA)$_2$((*S*)-BINAP)] with catalyst activation by NaBr as an additive, allowed for S/C = 10,000. The optimal ratio to ensure reaction robustness was Ru/NaBr = 1:20 and thus afforded >99% conversion and 98.8:1.2 er.

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Category

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Key words

Ipatasertib
Akt kinase inhibitor
biotransformation
nitrilase-catalyzed resolution
ketoreductase reduction
asymmetric hydrogenation

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