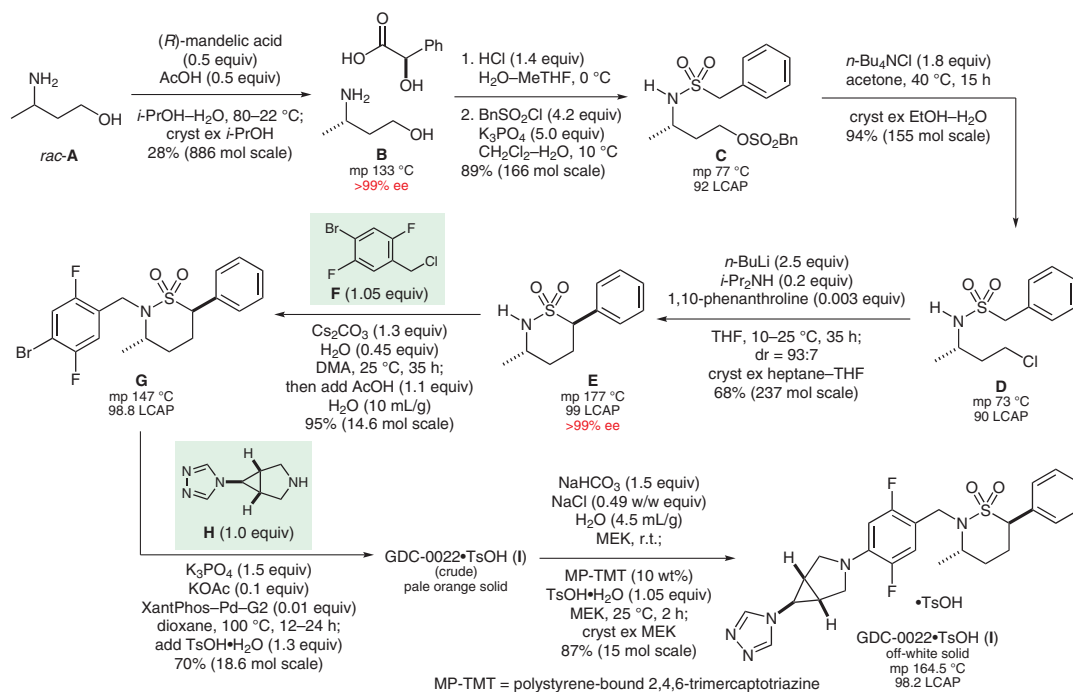
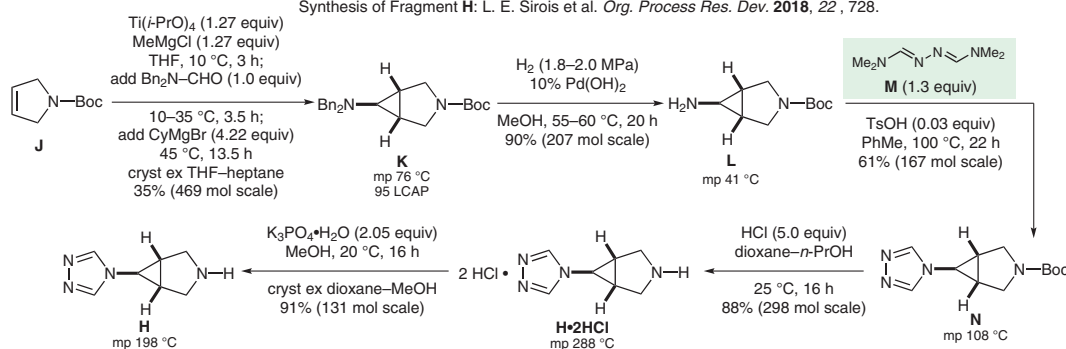


Synthesis of GDC-0022



Synthesis of Fragment H: L. E. Sirois et al. Org. Process Res. Dev. 2018, 22, 728.



Significance: Retinoid-related orphan receptor γ (RORc) is a transcription factor and nuclear receptor implicated in proinflammatory cytokine production. GDC-0022 is a RORc inhibitor. The key step in the synthesis depicted was the Buchwald–Hartwig coupling of bromoarene **G** with pyrrolidine **H** on an 8.0 kg scale using just 1 mol% of catalyst.

Comment: For a multikilogram-scale synthesis of pyrrolidine **H**, see: L. E. Sirois et al. Org. Process Res. Dev. 2018, 22, 728. Cyclization of **D** using *n*-BuLi (2.5 equiv) and diisopropylamine (0.2 equiv) gave sultam **E** as a mixture of diastereoisomers that slowly equilibrated to the desired *trans*-sultam **E** (dr = 93:7).