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Improvements to Enable the Large Scale Synthesis of 1-[[[(2S,3S,4S)-3-Ethyl-4-fluoro-5-oxopyrrolidin-2-yl]methoxy]-7-methoxyisoquinoline-6-carboxamide (PF-06650833)
Org. Process Res. Dev. **2018**, 22, 1835–1845.

Synthesis of PF-06650833

Significance: PF-06650833 is an interleukin-4 receptor associated kinase (IRAK-4) inhibitor that is of interest for the treatment of inflammatory disorders such as rheumatoid arthritis. A significant challenge in the large-scale synthesis of PF-06650833 was the construction of lactam **I** with its three contiguous stereogenic centers.

Comment: The preparation of lactam **I** from **E** was achieved by the highly diastereoselective oxidation of enolate **E** to **F** with lithium *tert*-butylperoxide in a flow process (*Org. Process Res. Dev.* **2018**, 22, 707, see also *Synfacts* **2019**, 15, 328, this issue). Thereafter activation of **F** by reaction with nonafluorobutanesulfonyl fluoride allowed S_N2 displacement by fluoride ion in a single step, without need for the isolation of the intermediate sulfonate ester **G**. This route provided PF-06650833 in batches of greater than 30 kg at a time.

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