
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)

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**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-butyperoxide 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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