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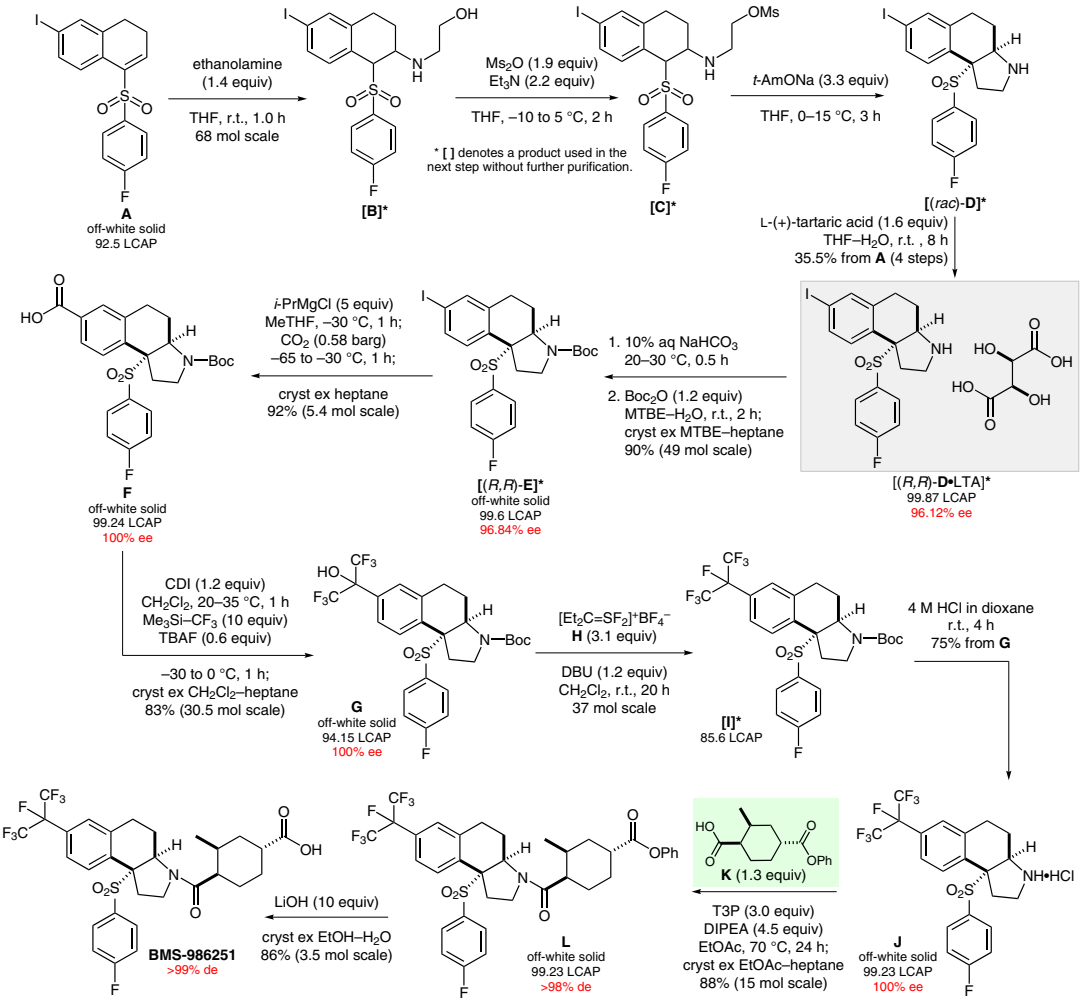
Development of a Scalable Synthetic Route to BMS-986251, Part 2: Synthesis of the Tricyclic Core and the API
Org. Process Res. Dev. **2021**, *25*, 1556–1572, DOI: 10.1021/acs.oprd.1c00125.

Synthesis of the Tricyclic Core of BMS-986251



Significance: RORγt is a nuclear receptor that regulates the production of proinflammatory cytokines, such as IL-17 and IL-22. BMS-986251 is a RORγt inverse agonist that is of interest for the treatment of immunological disorders. For syntheses of related analogues, see: D. Marcoux et al. *J. Med. Chem.* **2019**, *62*, 9931; A. Karmakar et al. *Org. Process Res. Dev.* **2021**, *25*, 1001.

Comment: Highlights of the synthesis of BMS-986251 depicted are (1) a high-yielding four-step aza-Michael addition/mesylation/annulation sequence to form the tricyclic core, and (2) installation of the heptafluoroisopropyl moiety through a three-step carboxylation–bistrifluoromethylation–deoxyfluorination sequence.

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Category
Synthesis of Natural Products and Potential Drugs

Key words
BMS-986251
halogen–metal exchange
deoxyfluorination
annulation

Synfact of the Month