Synthesis of PDE4 Inhibitors

Significance: The target phosphodiesterase type 4 (PDE4) inhibitor \( \text{I} \) is of interest for the treatment of chronic obstructive pulmonary disease. The multikilogram-scale synthesis depicted features a highly regioselective Dieckmann condensation \( \text{A} \rightarrow \text{B} \) required for the construction of the dihydrothieno[3,2-d]pyrimidine \( \text{D} \) and the asymmetric sulfoxidation of intermediate \( \text{G} \) using the conditions of Uemura and co-workers (J. Org. Chem. 1993, 58, 4529).

Comment: The transformation \( \text{E} \rightarrow \text{G} \) was accompanied by 15% of the product resulting from displacement of the chlorine at C2. Investigation of alternative bases and solvents failed to improve the regioselectivity; however, the undesired regioisomer was significantly more soluble than \( \text{H} \) and was completely removed from the product during the isolation by filtration.