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Development of a Kilogram-Scale Asymmetric Synthesis of a Potent DP Receptor Antagonist

Synthesis of Prostaglandin D₂ Receptor Antagonist

Significance: An efficient kilogram-scale synthesis of the target prostaglandin D₂ receptor antagonist features a Friedel–Crafts cyclization of an iminopyrrole to generate the azaindole core in D.

Key steps are (1) a very efficient asymmetric hydrogenation to install the single stereogenic center (G → H) and (2) a mild sulfonylation using the shelf-stable N-arylhithiophthalimide I.

Comment: The high er of the hydrogenation was surprisingly insensitive to solvent, but it was sensitive to the E/Z ratio. Thus, batches of G that contained 9% of the Z-isomer afforded H in only 81% ee, whereas batches of G containing 1% of the Z-isomer gave H in 96% ee. The E/Z ratio of the Horner–Wadsworth–Emmons reaction (14:1) could be upgraded to 1000:1 by crystallizing the phosphate salt of G.