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 \( (G \rightarrow H) \) and (2) a mild sulfenylation using the shelf-stable N-arylsulfonylhydrazine 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 \( G \).