M. TUDGE,* C. G. SAVARIN, K. DIFELICE, P. MALIGRES, G. HUMPHREY, B. REAMER, D. M. TELLERS, D. HUGHES (MERCK & CO., RAHWAY, USA)

Development of a Kilogram-Scale Asymmetric Synthesis of a Potent DP Receptor Antagonist
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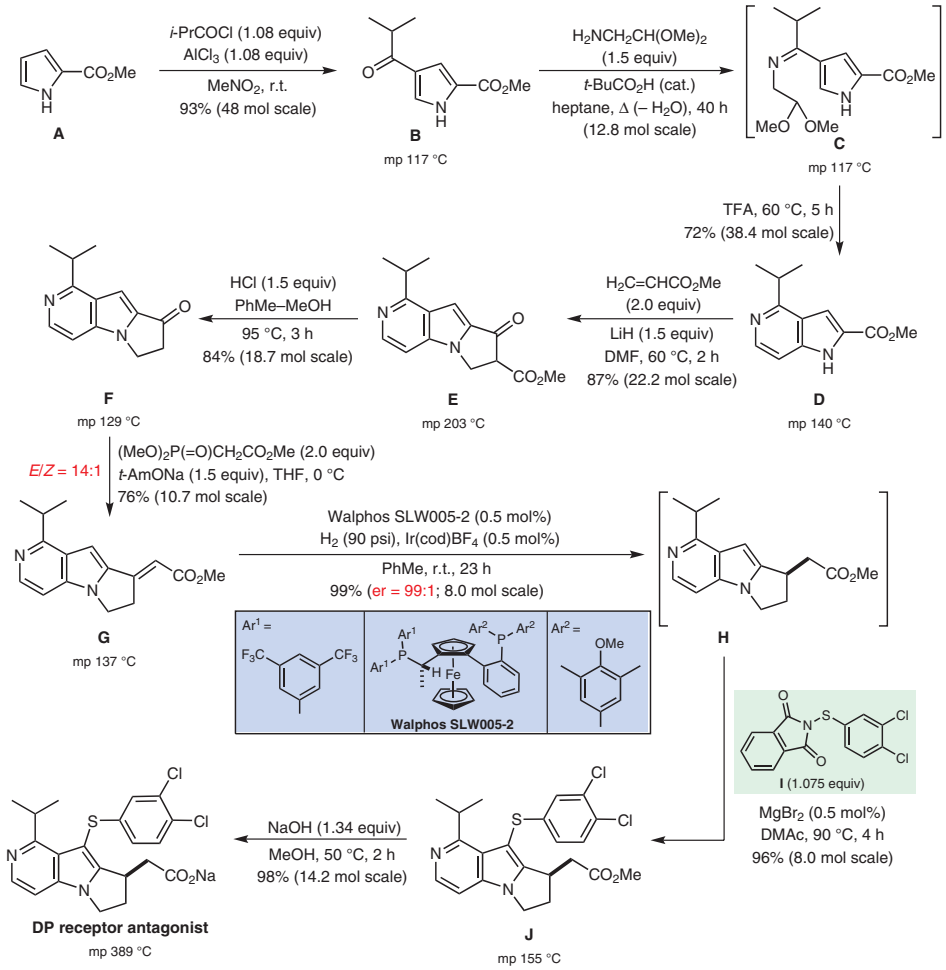
Synthesis of Prostaglandin D_2 Receptor Antagonist



Significance: An efficient kilogram-scale synthesis of the target prostaglandin D_2 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 sulfenylation using the shelf-stable *N*-arylthiophthalimide **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**.

SYNFACTS Contributors: Philip Kocienski
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Category
Synthesis of Natural Products and Potential Drugs

Key words
prostaglandin D_2 receptor antagonists
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azaindoles
sulfenylation
asymmetric hydrogenation

SYNFACT of the month

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