D. MITCHELL* ET AL. (ELI LILLY AND COMPANY, INDIANAPOLIS, USA)

Double Heck Route to a Dibenzoxepine and Convergent Suzuki Cross-Coupling Strategy for the Synthesis of an MR Antagonist

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Category

Synthesis of Natural Products and Potential Drugs

Key words

LY2623091

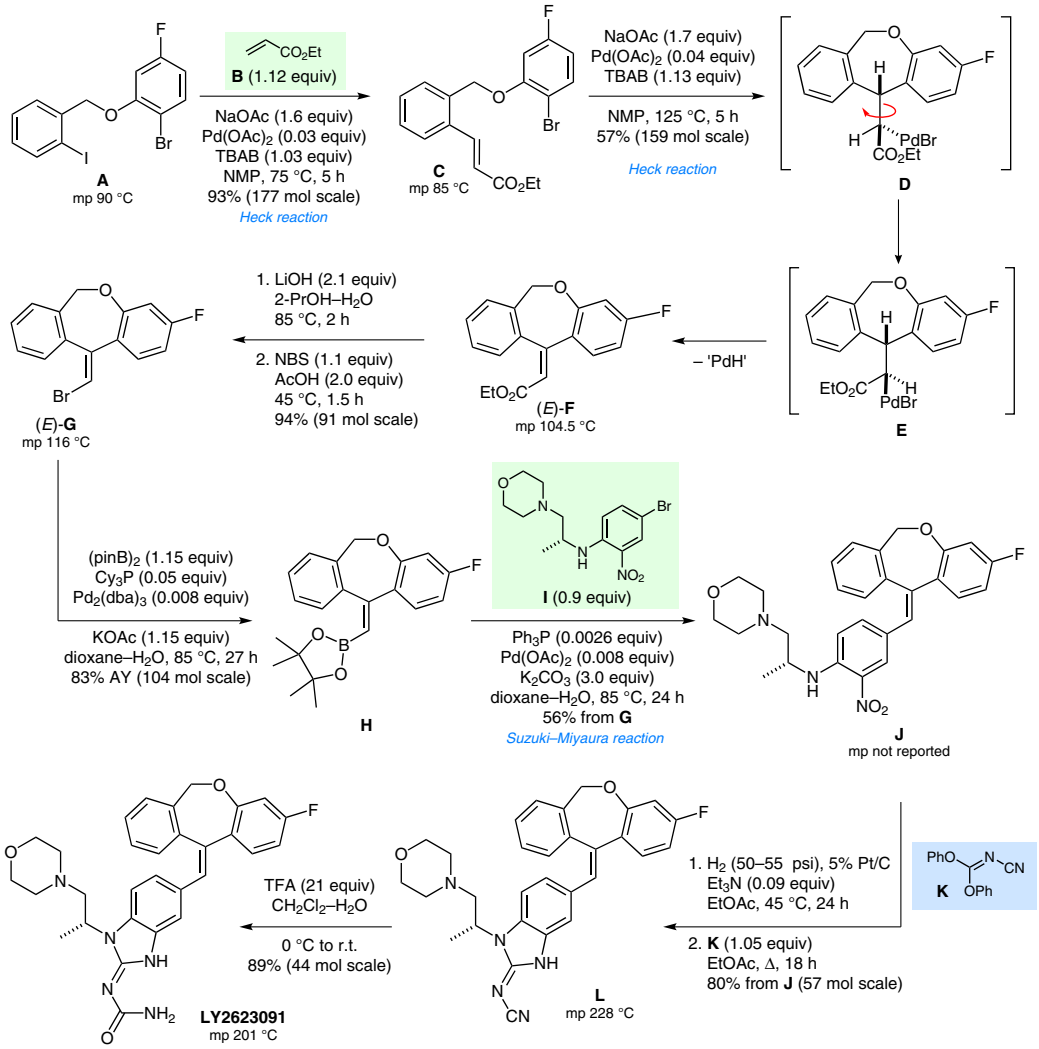
mineralocorticoid receptor antagonist

intramolecular Heck reaction

Suzuki–Miyaura cross-coupling

dibenzoxepine ring formation

Synthesis of LY2623091



Significance: LY2623091 is a mineralocorticoid receptor antagonist that was of interest for the treatment of resistant hypertension. The kilogram-scale synthesis depicted features two sequential Heck reactions to construct the (*E*)-dihydrodibenzo[*b*,*e*]oxepine ring system. Note the clean retention of stereochemistry in the conversion of (*E*)-**F** into bromoalkene (*E*)-**G**.

Comment: An investigation of the conversion of **A** into (*E*)-**F** through a one-pot, double Heck reaction revealed that the first Heck reaction (**A** → **C**) was fast and occurred at 60 °C whereas the second Heck reaction [**C** → (*E*)-**F**] required a much higher temperature (145 °C) owing to iodide acting as a catalyst poison. Better yields and stereoselectivity were obtained in the two-pot process shown.

SYNFACTS Contributors: Philip Kocienski
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