Synthesis of LY2623091

Category

Synthesis of Natural Products and Potential Drugs

Key words

LY2623091

mineralocorticoid receptor antagonist

intramolecular Heck reaction

Suzuki–Miyaura cross-coupling

dibenzoxepine ring formation

Synfact
of the month

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)-dihydrodibenzoxepine 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** $\rightarrow$ **C**) was fast and occurred at 60 °C whereas the second Heck reaction [**C** $\rightarrow$ (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.

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