

# Synthesis of the Glucocorticoid Agonist BI 653048 BS H<sub>3</sub>PO<sub>4</sub>

Category

Synthesis of Natural Products and Potential Drugs

Key words

BI 65308 BS H<sub>3</sub>PO<sub>4</sub>

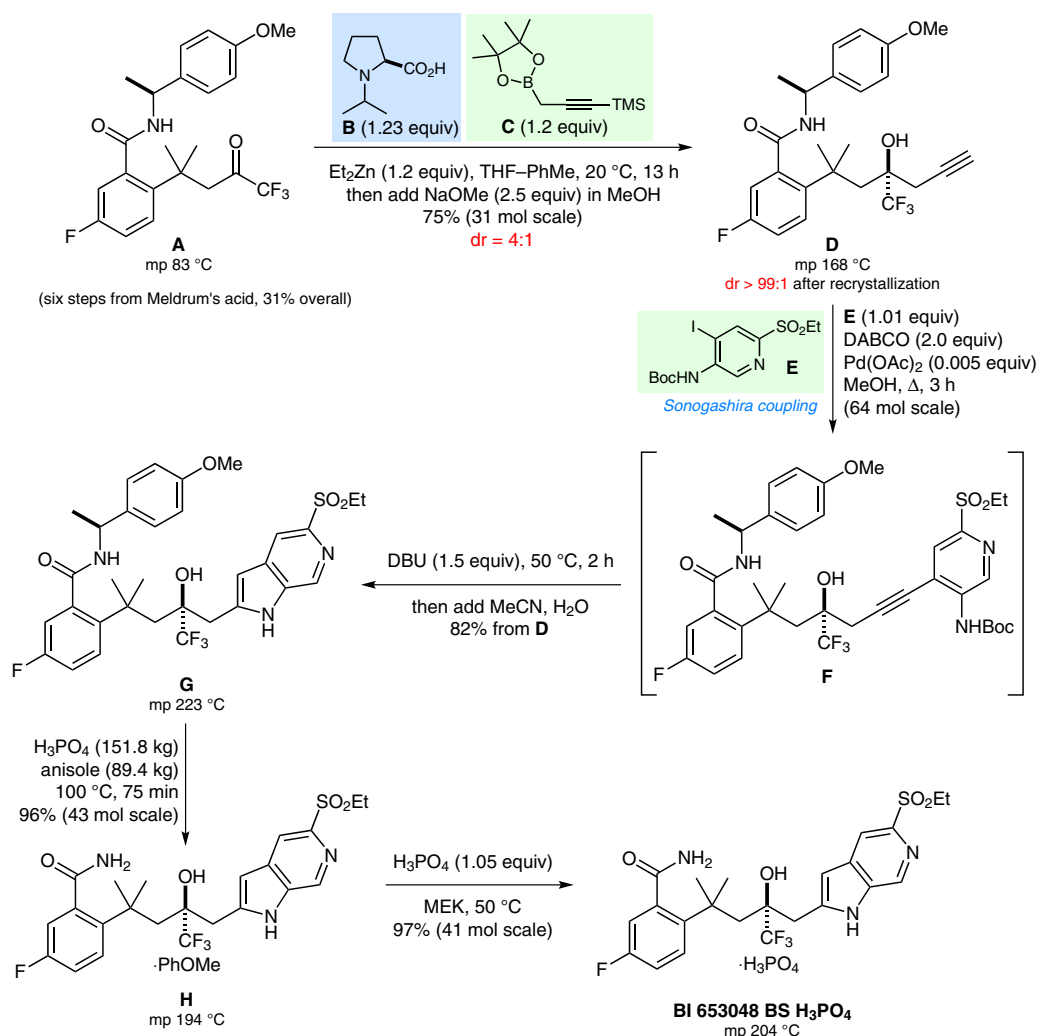
glucocorticoid agonist

asymmetric propargylation

organocatalysis

trifluoromethyl ketones

**SYNFACT**  
*of the month*



**Significance:** BI 653048 BS H<sub>3</sub>PO<sub>4</sub> is a glucocorticoid agonist that is a candidate for the treatment of rheumatoid arthritis. In the synthesis depicted, the key step is the zinc-mediated asymmetric propargylation of trifluoromethyl ketone **A** using propargyl boronate **C** and proline-derived ligand **B**. The synthesis delivered 94 kg of the API in 17.6% overall yield.

**Comment:** A detailed exploration of the mechanism of the zinc-mediated propargylation of the trifluoromethyl ketone **I** is described in an accompanying paper (*J. Org. Chem.* **2013**, *78*, 3592) that includes a zinc-catalyzed variant. In the case of the zinc-catalyzed reaction, water is an essential component. The target molecule is isolated as a 1:1 complex (not a salt) with phosphoric acid.

**SYNFACTS Contributors:** Philip Kocienski  
Synfacts 2013, 9(7), 0689 Published online: 17.06.2013  
DOI: 10.1055/s-0033-1338916; Reg-No.: K03713SF