

## Synthesis of a Phosphoinositide 3-Kinase (PI3K) $\beta$ Inhibitor

Category

Synthesis of Natural Products and Potential Drugs

Key words

phosphoinositide 3-kinase  $\beta$  inhibitor

aldehyde oxidase

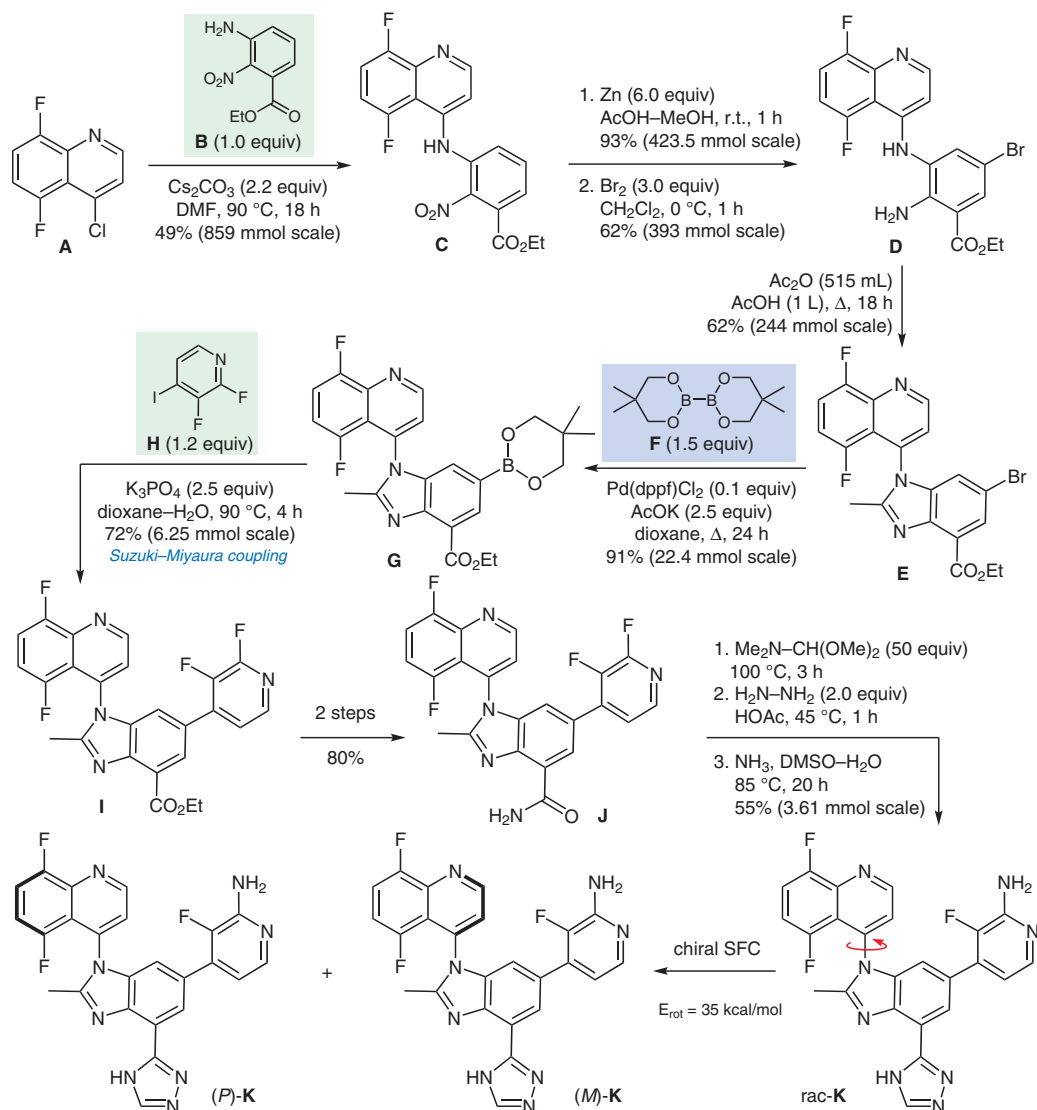
atropisomers

benzimidazole ring formation

1,2,4-triazole ring formation

Suzuki–Miyaura coupling

Synfact  
of the month



**Significance:** The target molecule **K** is a phosphoinositide 3-kinase (PI3K)  $\beta$  Inhibitor that is of interest for the treatment of various cancers. The restricted axis of rotation around a carbon–nitrogen bond of **rac-K** generated atropisomeric compounds **(P)-K** and **(M)-K** with significantly different pharmacological and pharmacokinetic profiles.

**Comment:** The metabolism of the inactive atropisomer **(M)-K** is the result of the action of the enzyme aldehyde oxidase (AO) whereas the active atropisomer **(P)-K** has lower affinity for AO resulting in better metabolic stability. The atropisomers ( $\Delta E_{\text{rot}} = 35 \text{ kcal/mol}$ ) were separated by preparative chiral SFC chromatography.

**SYNFACTS Contributors:** Philip Kocienski  
Synfacts 2018, 14(10), 0999 Published online: 17.09.2018  
**DOI:** 10.1055/s-0037-1610902; **Reg-No.:** K05518SF