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Atropisomerism by Design: Discovery of a Selective and Stable Phosphoinositide 3-Kinase (PI3K) β Inhibitor
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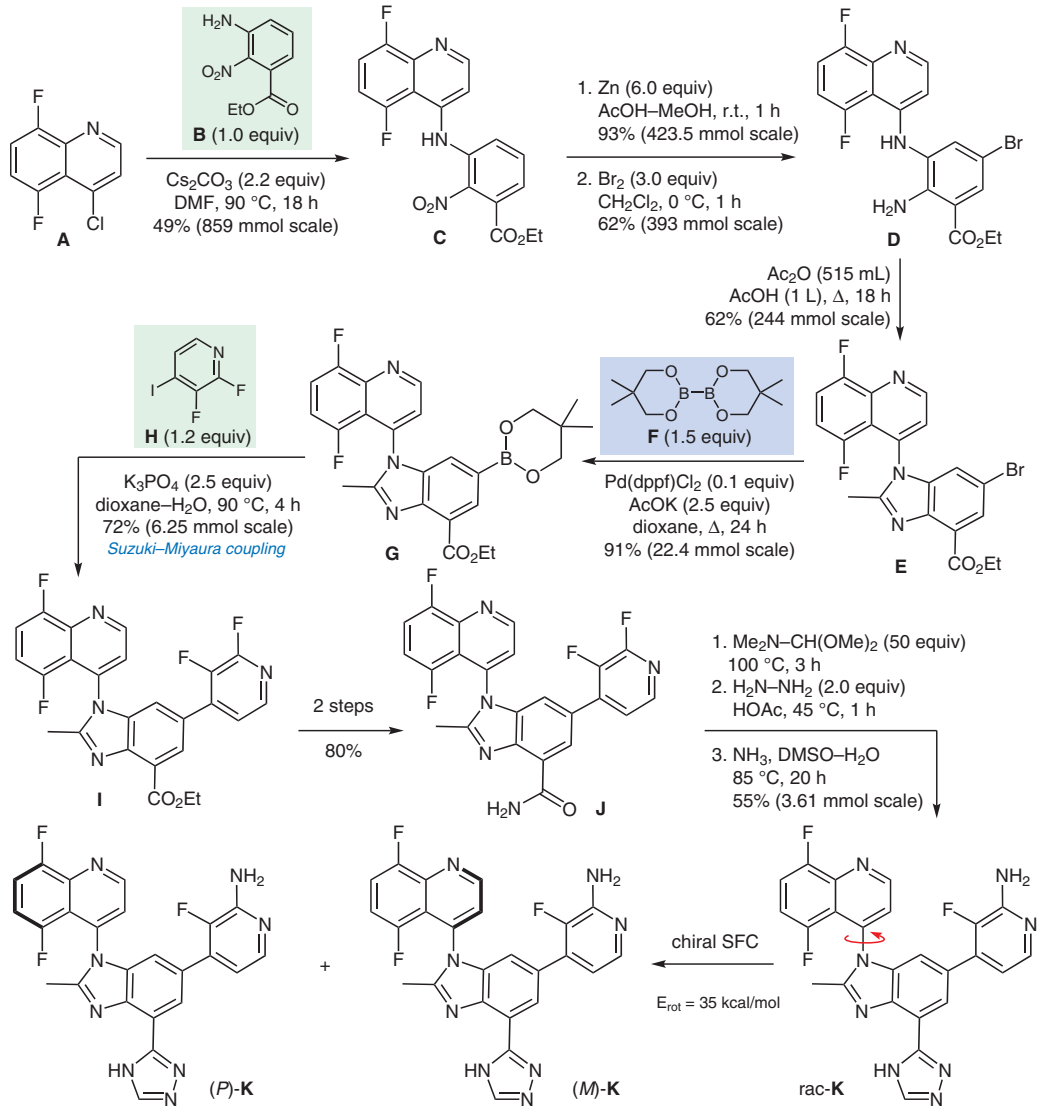
Synthesis of a Phosphoinositide 3-Kinase (PI3K) β Inhibitor



Significance: The target molecule **K** is a phosphoinositide 3-kinase (PI3K) β 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 (ΔE_{rot} = 35 kcal/mol) were separated by preparative chiral SFC chromatography.

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Category

Synthesis of Natural Products and Potential Drugs

Key words

phosphoinositide 3-kinase β inhibitor

aldehyde oxidase

atropisomers

benzimidazole ring formation

1,2,4-triazole ring formation

Suzuki–Miyaura coupling