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Chemical Acylation of an Acquired Serine Suppresses Oncogenic Signaling of K-Ras(G12S)
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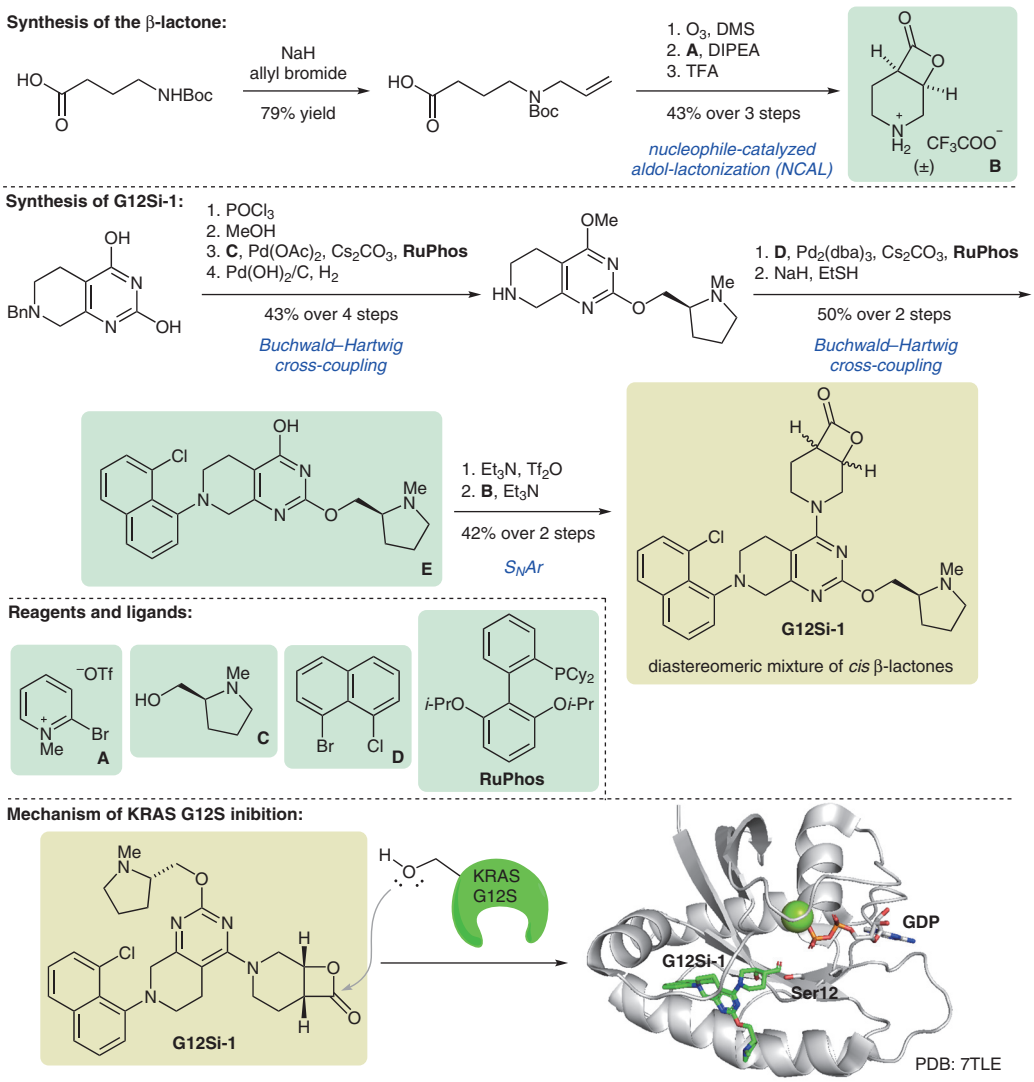
A β-Lactone for Covalent Inhibition of KRAS G12S



Significance: K-Ras is an important kinase that regulates many signaling cascades. Its encoding gene, KRAS, is mutated in approximately 25% of human cancers. The covalent inhibitor sotorasib was recently approved by the FDA and shows promise in treatment of KRAS G12C-mutated tumors. Here, Zhang et al. developed a clever approach to covalently target a different KRAS mutant, G12S, by implementing an electrophilic β-lactone moiety.

Comment: The racemic β-lactone was synthesized from an aldehyde acid precursor by treatment with Mukaiyama-type pyridinium reagent **A**, which initiated an intramolecular, nucleophile-catalyzed, aldol lactonization (NCAL). S_NAr of lactones **B** and triflated tetrahydropyridopyrimidine **E** (US202003191A1) afforded a diastereomeric mixture of inhibitors, **G12Si-1**. Covalent binding with KRAS G12S was confirmed by X-ray crystallography.

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Key words
cancer
covalent inhibition
nucleophile-catalyzed aldol lactonization (NCAL)

Synfact of the Month