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Target-Directed Synthesis of Antibacterial Drug Candidate GSK966587

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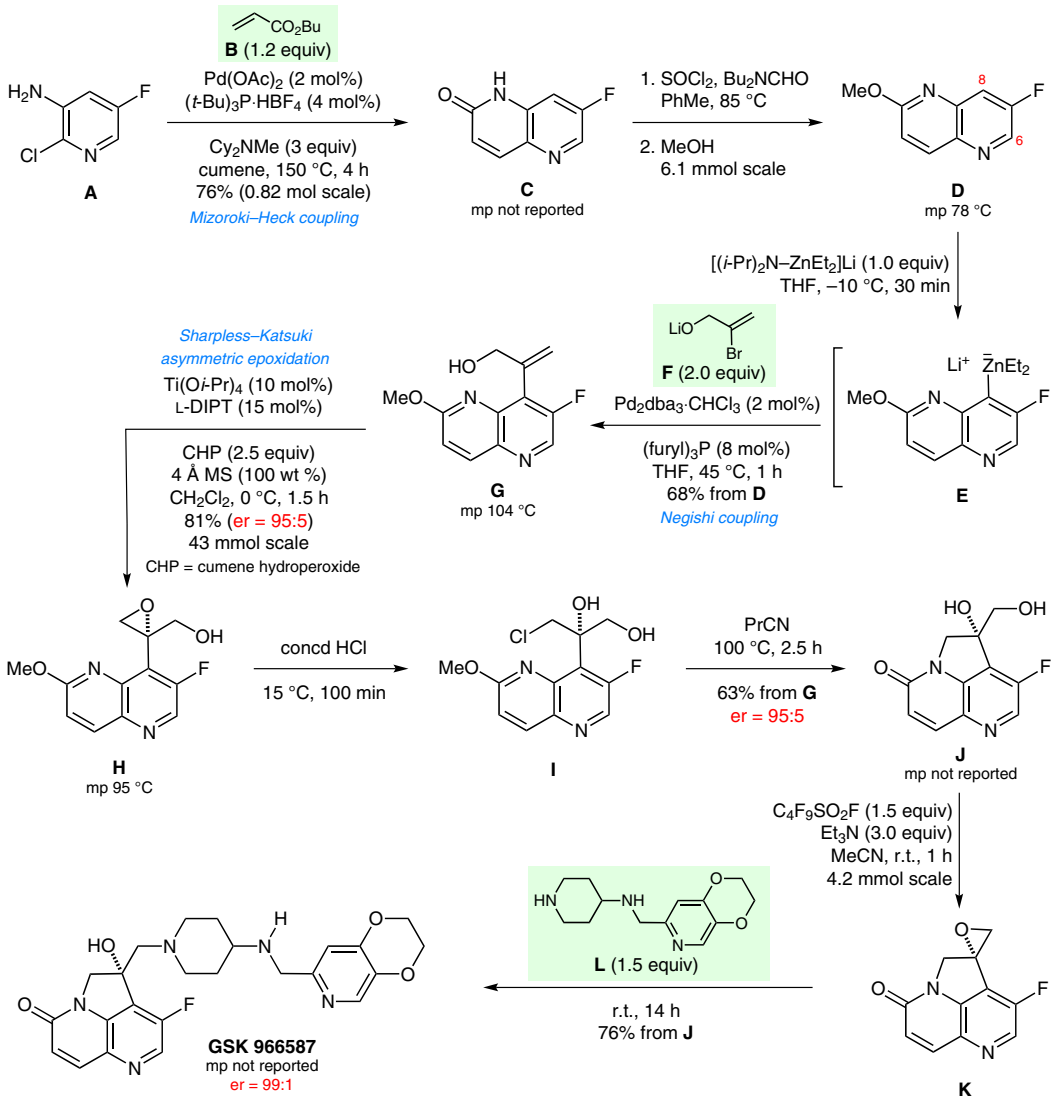
Synthesis of GSK966587



Significance: The eight-step synthesis of antibacterial agent GSK966587 (25% overall yield) required no protecting groups and involved only three isolated intermediates (**C**, **G** and **J**). Key steps were a Mizoroki–Heck reaction, a Negishi coupling, a directed *ortho*-metalation, and a Sharpless–Katsuki asymmetric epoxidation.

Comment: The directed *ortho*-metalation of naphthyridine **D** was strongly base-dependent. Problems included dianion formation, competing metalation at C6 as well as nucleophilic substitution of the fluorine atom. However, when $(i\text{-Pr})_2NZnEt_2Li$ was used as base, there was no dianion formation and only 4% metalation at C6 was observed.

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Category

Synthesis of Natural Products and Potential Drugs

Key words

GSK966587

Heck reaction

Negishi cross-coupling

directed *ortho*-metalation

zincate