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-metallation, and a Sharpless–Katsuki asymmetric epoxidation.

Comment: The directed ortho-metallation 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-Pr)2NZnEt2Li was used as base, there was no dianion formation and only 4% metalation at C6 was observed.

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