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The Discovery of I-BET726 (GSK1324726A), a Potent Tetrahydroquinoline ApoA1 Up-Regulator and Selective BET Bromodomain Inhibitor

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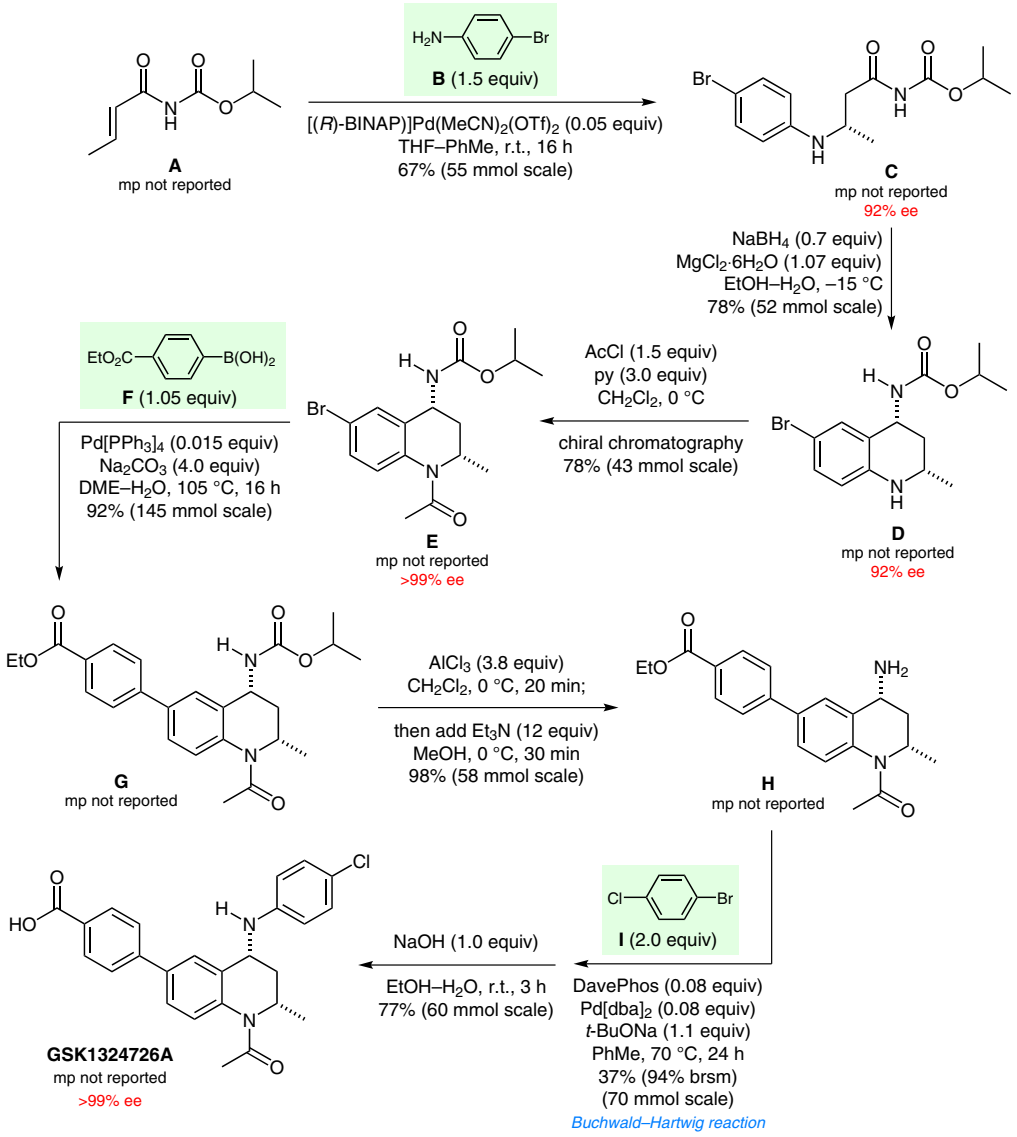
Synthesis of GSK1324726A



Significance: The BET family of bromodomain-containing proteins regulates expression of multiple genes including those involved in tumor cell growth and inflammation. GSK132476A is a BET bromodomain inhibitor that displays significant antiproliferative and anti-inflammatory effects.

Comment: Key steps in the synthesis depicted are (1) the Pd-catalyzed asymmetric aza–Michael addition of 4-bromoaniline to (*E*)-isopropyl but-2-enoyl-carbamate (**A**) and (2) a diastereoselective cyclization of an immonium ion generated by reduction of **C** to generate the tetrahydroisoquinoline **D**.

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