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


**Synthesis of GSK1324726A**

- **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.**

**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.