Synthesis of IPI-926

Significance: Cyclopamine (A) is a teratogenic alkaloid isolated from the corn lily (Veratrum californicum). IPI-926 is a Hedgehog signalling pathway antagonist derived from cyclopamine that was evaluated for the treatment of cancer. The key step in the synthesis depicted is the robust and scalable Simmons–Smith cyclopropanation of B followed by an acid-catalyzed carbocation rearrangement.

Comment: For the large-scale Simmons–Smith reaction, a series of new safe and soluble iodoalkylmethylzinc bis(aryl)phosphate reagents (e.g., C) were prepared under mild conditions that were stable during the course of the reaction. Note the rare application of an Oppenauer oxidation (I → J).