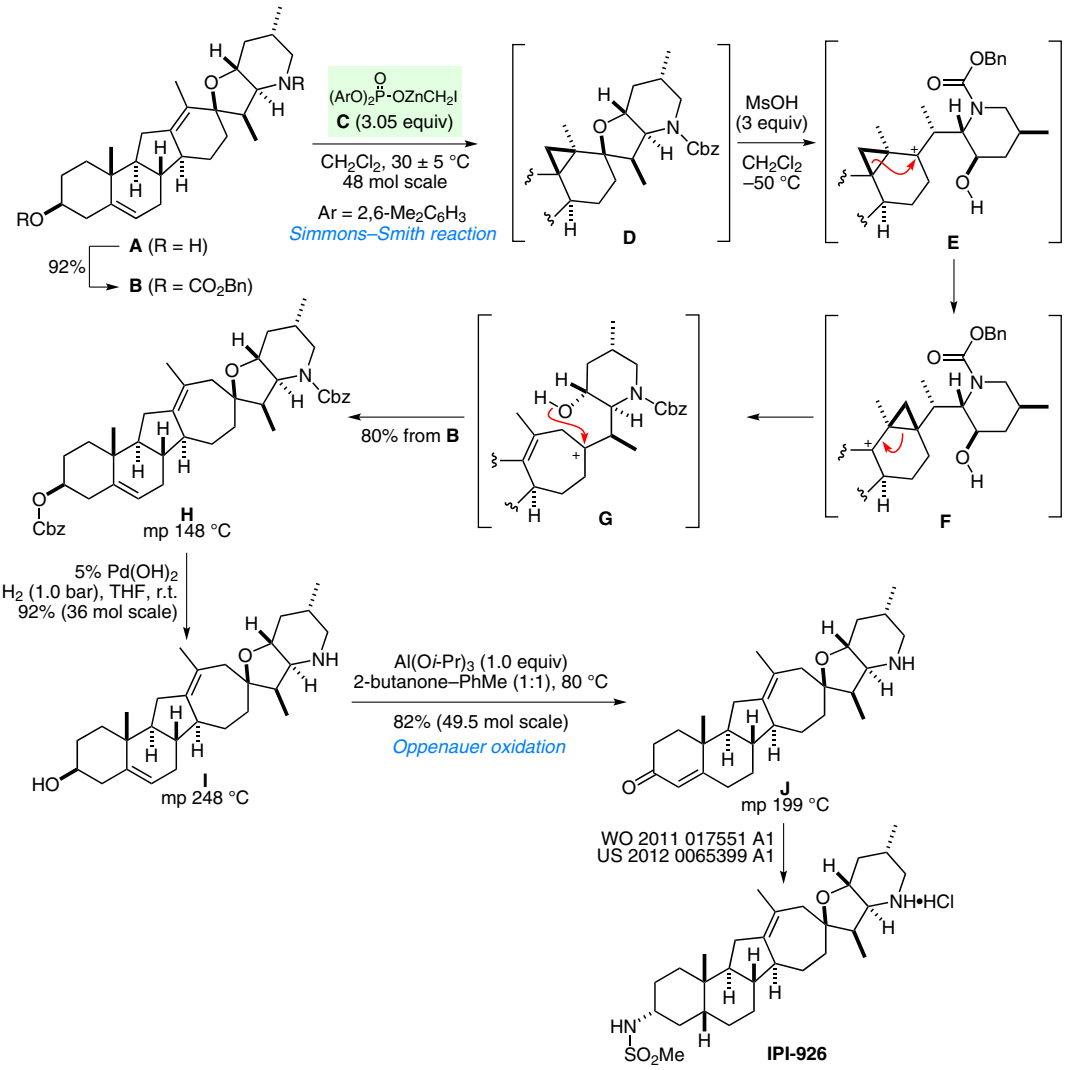
M. R. TREMBLAY* ET AL. (INFINITY PHARMACEUTICALS, CAMBRIDGE AND JOHNSON MATTHEY PHARMA SERVICES, DEVENS, USA; UNIVERSITY OF MONTREAL, CANADA)

Development of a Multi Kilogram-Scale, Tandem Cyclopropanation Ring-Expansion Reaction en Route to Hedgehog Antagonist IPI-926

Org. Process Res. Dev. **2016**, *20*, 786–798.

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 iodomethylzinc 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**).

SYNFACTS Contributors: Philip Kocienski
Synfacts 2016, 12(07), 0657 Published online: 17.06.2016
DOI: 10.1055/s-0035-1562250; **Reg-No.:** K03316SF