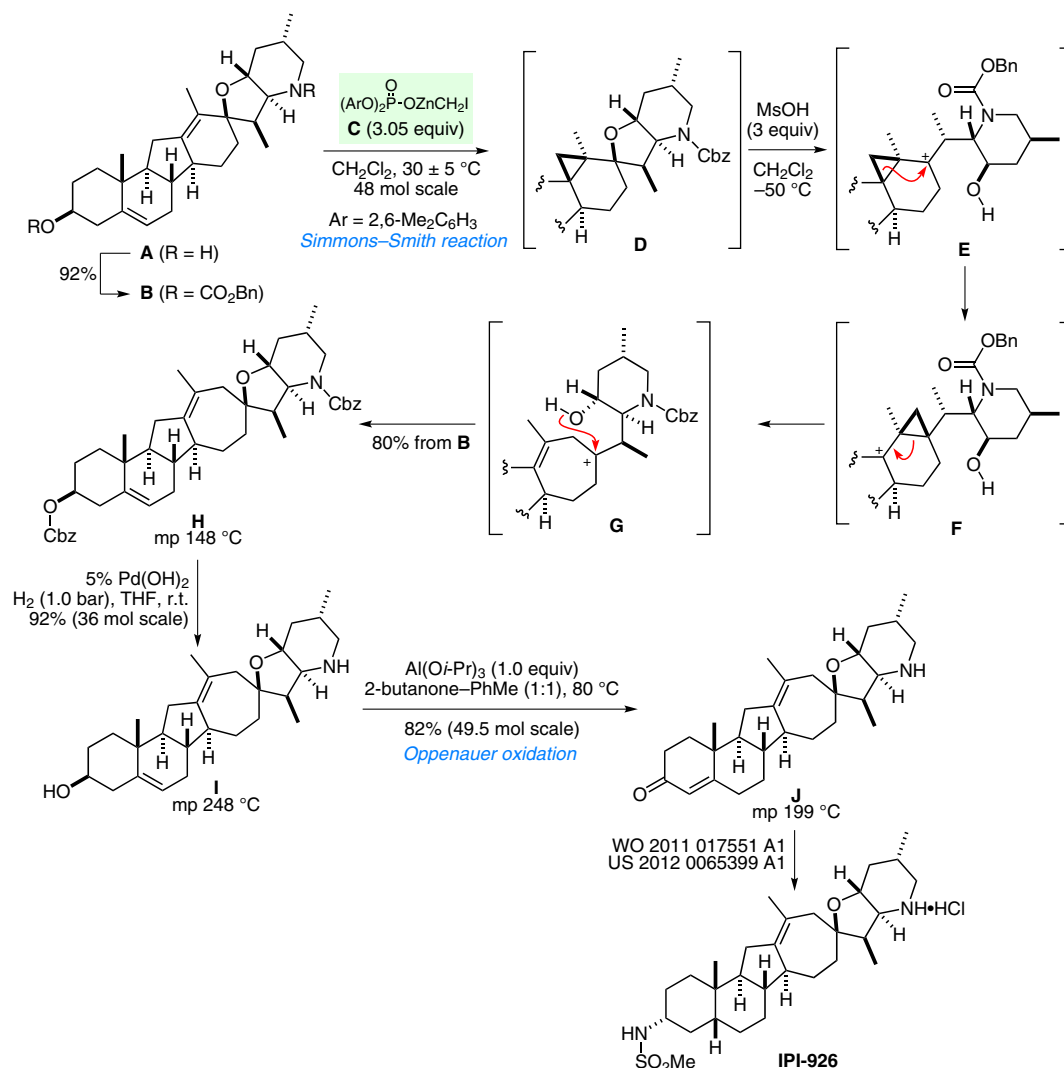


M. R. TREMBLAY* ET AL. (INFINITY PHARMACEUTICALS, CAMBRIDGE AND JOHNSON MATTHEY PHARMA SERVICES, DEVENS, USA; UNIVERSITY OF MONTREAL, CANADA)
Development of a Multi Kilogram-Scale, Tandem Cyclopropanation Ring-Expansion Reaction en Route to Hedgehog Antagonist IPI-926
Org. Process Res. Dev. **2016**, 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 iodo-methylzinc 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
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