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Synthesis of *ent*-Ketorfanol via a C–H Alkenylation/Torquoselective 6 π Electrocyclization Cascade
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Synthesis of *ent*-Ketorfanol

Significance: The synthesis of *ent*-ketorfanol depicted features a rhodium-catalyzed intramolecular C–H alkenylation/6 π electrocyclization cascade (**E** → **G** → **H**) that provides the fused bicyclic 1,2-dihydropyridine **H** as a key intermediate. The torquoselectivity of the electrocyclization is a consequence of remote asymmetric induction provided by the isopropylidene-protected diol. Another noteworthy facet is the acid-catalyzed pinacol rearrangement/Friedel–Crafts alkylation (**I** → **J**).

Comment: Ketorfanol is a semisynthetic opioid that was previously derived from morphine or nal-trexone. It was never marketed. Because both enantiomers of diol **B** are readily available by Sharpless asymmetric dihydroxylation, both ketorfanol and *ent*-ketorfanol can be prepared in eleven steps and 9% overall yield without recourse to opiate modification. Note the use of the chlorine substituent in **I** to direct the regioselectivity of the Friedel–Crafts cyclization.

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