Synthesis of \textit{ent}-Ketorfanol

\textbf{Significance:} The synthesis of \textit{ent}-ketorfanol depicted features a rhodium-catalyzed intramolecular C–H alkenylation/6π electrocyclization cascade (E $\rightarrow$ G $\rightarrow$ H) that provides the fused bicyclic 1,2-dihydropyridine H as a key intermediate. The torqueselectivity 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 $\rightarrow$ J).

\textbf{Comment:} Ketorfanol is a semisynthetic opioid that was previously derived from morphine or naloxone. It was never marketed. Because both enantiomers of diol B are readily available by Sharpless asymmetric dihydroxylation, both ketorfanol and \textit{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.

\textbf{Key words:} \textit{ent}-ketorfanol C–H alkenylation electrocyclization pinacol rearrangement Friedel–Crafts alkylation rhodium catalysis torquoselective cyclization

\textbf{Category:} Synthesis of Natural Products and Potential Drugs