**Synthesis of ent-Ketorfanol**

**Significance:** The synthesis of ent-ketorfanol depicted features a rhodium-catalyzed intramolecular C–H alkenylation/6π 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 naloxone. 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.

**Category**

- **Synthesis of Natural Products and Potential Drugs**
  - **Key words**
    - ent-ketorfanol
    - C–H alkenylation
    - electrocyclization
    - pinacol rearrangement
    - Friedel–Crafts alkylation
    - rhodium catalysis
    - torquoselective cyclization

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