Synthesis of *ent*-Ketorfanol

**Significance:** The synthesis of *ent*-ketorfanol depicted features a rhodium-catalyzed intramolecular C–H alkenylation/6π electrocyclization cascade that provides the fused bicyclic 1,2-dihydropyridine 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 naltrexone. 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.

**SYNFACTS Contributors:** Philip Kocienski

**SYNFACTS 2016, 12(1), 0001 Published online: 16.12.2015
DOI: 10.1055/s-0035-1560992; Reg-No.: K06815SF**