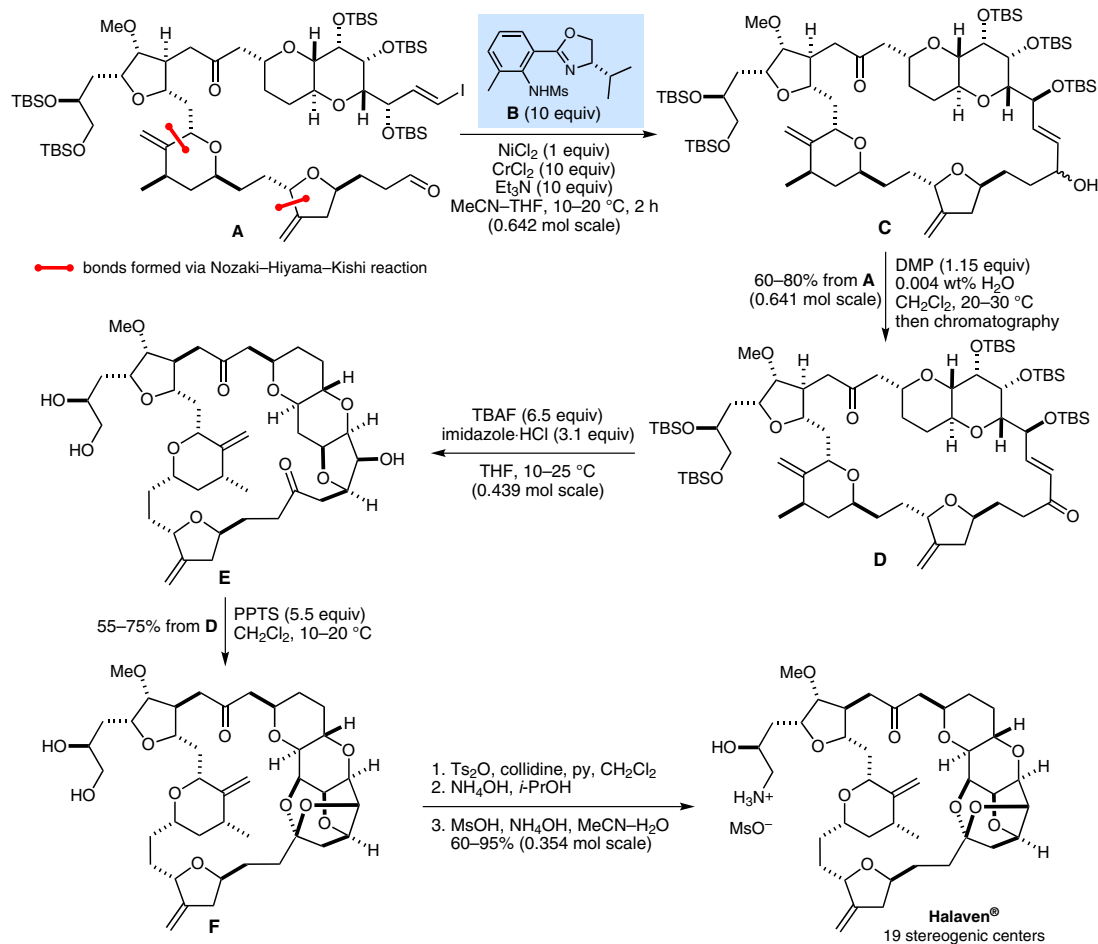


Commercial Manufacture of Halaven®



Significance: Eribulin mesylate (Halaven®) was approved by the FDA in 2010 for the treatment of metastatic breast cancer. It triggers apoptosis in cancer cells following prolonged and irreversible mitotic blockade. Workers at the Eisai company report a multigram-scale synthesis of eribulin that is a tour de force of synthetic strategy and tactics. The closing stages are shown in the scheme. Two accompanying papers describe the synthesis of the key fragments from D-(–)-gulono-1,4-lactone (B. M. Lewis et al. *Synlett* 2013, 24, 323) and D-glucurono-3,6-lactone (C. E. Chase et al. *Synlett* 2013, 24, 327).

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Comment: The Eisai synthesis of eribulin underscores the power of the Nozaki–Hiyama–Kishi (NHK) reaction in the construction of complex frail molecules. It was twice deployed in the construction of the bonds indicated in structure **A**; however, the most spectacular achievement was the forging of the macrocycle **C** under high dilution conditions using a ligand-accelerated asymmetric variant of the NHK reaction – a process that has been implemented on kilogram scale.