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Asymmetric Synthesis of Salvinorin A, A Potent κ Opioid Receptor Agonist
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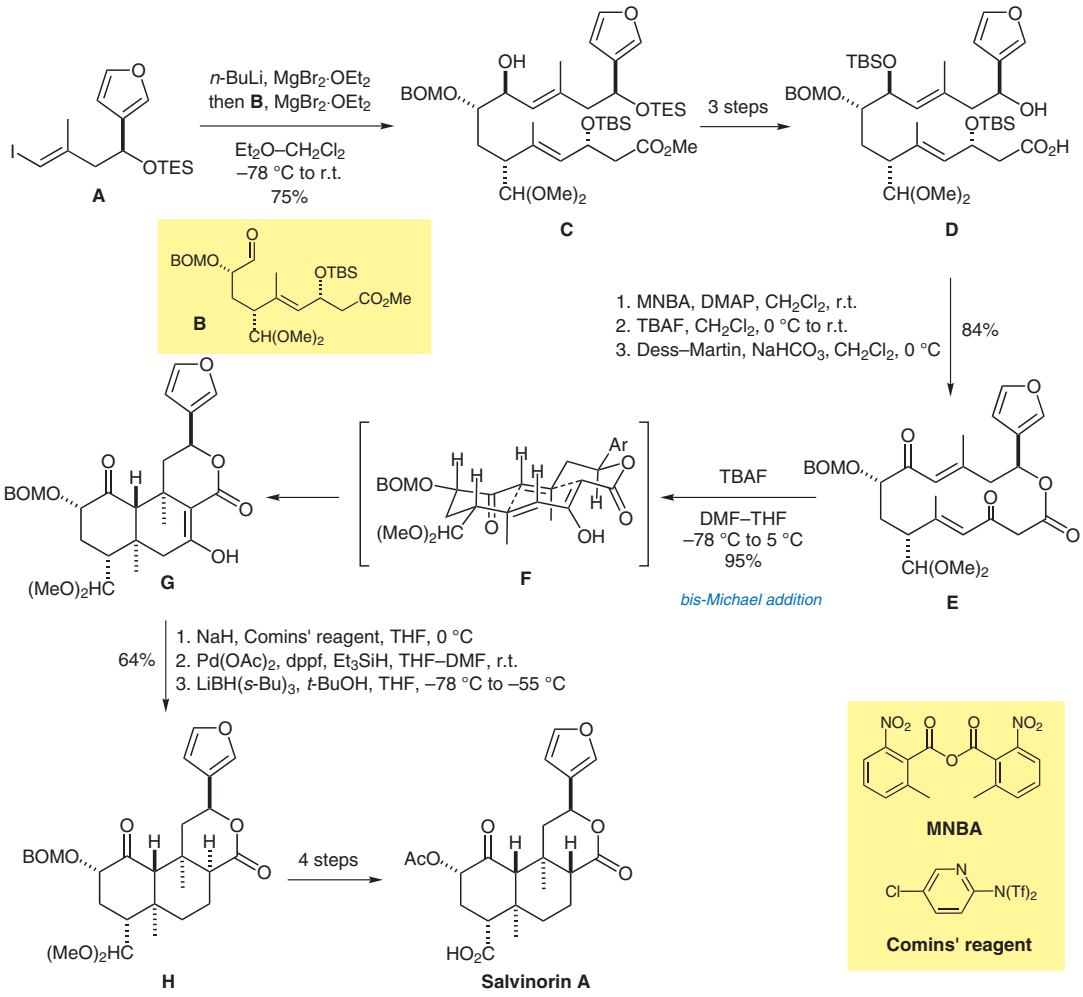
Synthesis of Salvinorin A



Significance: Salvinorin A is a neoclerodane diterpene isolated from *Salvia divinorum*. As a potent agonist of the κ opioid receptor, it is the only non-alkaloid psychoactive substance and the most potent naturally occuring hallucinogen. The synthesis of salvinorin exploits a bis-Michael addition of macrocylce **E** to create the tricyclic core. A rich array of innovative chemistry was used to synthesise fragment **B**.

Comment: The 14-membered macrolactone **E** was produced at very low concentrations (0.0015 M) using MNBA to produce a mixed anhydride which cyclized in very good yield (96%). The transannular bis-Michael addition of **E** promoted by TBAF was proposed to go via the transition state **F** to give the correct stereochemistry in **G**. It was also suggested that a concerted *exo*-selective Diels–Alder reaction would result in the correct product.

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