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A Formal Synthesis of (±)-Morphine

Significance: In 1982, Evans and Mitch disclosed an elegant route to access the core of morphine alkaloids. Their synthetic route provides access to an intermediate from Gates' seminal morphine synthesis (J. Am. Chem. Soc. 1956, 78, 1380). Evans' formal synthesis, which features an unusual Kornblum oxidation as its centerpiece, accesses known tetracycle I, which can be transformed into the natural product in nine additional steps.

Comment: Metalation and double alkylation of C affords enamine E which is, under kinetic conditions, transformed into the cis-configured iminium F. A subsequent aziridination and Kornblum oxidation sequence gives rise to α -amino aldehyde **H**. A Friedel-Crafts-type reaction of **H** affords tetracycle I, which is then elaborated into known intermediate I, thereby completing the formal synthesis of (±)-morphine.

Synthesis of Natural Products

Key words

morphine opioids

kinetic protonation

iminium aziridination

Kornblum oxidation

Lemieux-Johnson reaction



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