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Stereoselective Amination of Chiral Benzylic Ethers Using Chlorosulfonyl Isocyanate: Total Synthesis of (+)-Sertraline

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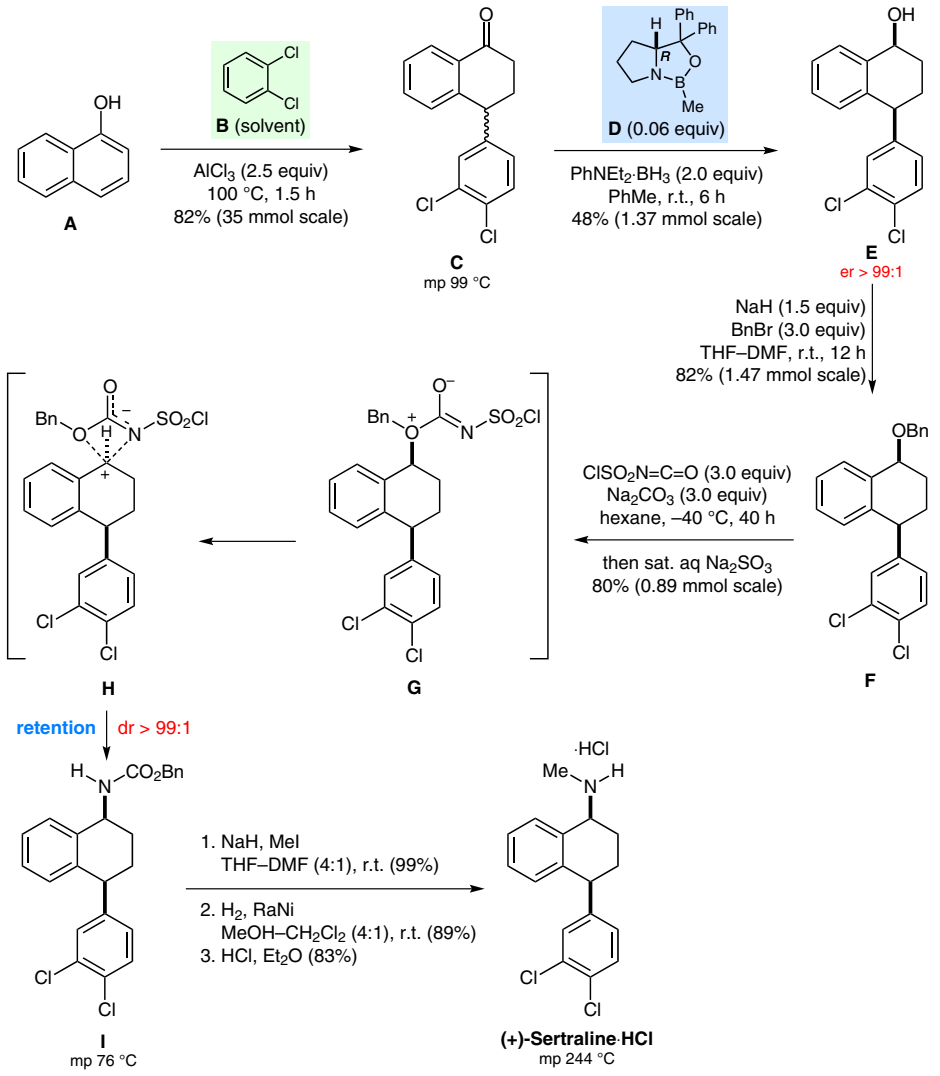
Synthesis of (+)-Sertraline



Significance: Key steps in this small-scale, six-step synthesis of (+)-sertraline (19% overall yield) are (1) the kinetic resolution of the racemic ketone **E** using the (*R*)-(+)-2-methyl-CBS-oxazaborolidine catalyst **D** and *N*,*N*-diethylaniline borane as reducing agent, and (2) the reaction of benzyl ether **F** with chlorosulfonyl isocyanate to give carbamate **I**.

Comment: The retention of configuration observed in the latter reaction arises from the formation of the tight ion pair **H** that allows front-side attack by an S_Ni mechanism involving a four-center transition state. A further 11 examples of the reaction are reported all proceeding with good yield (70–89%) and high ee (88 to >99%). Benzylic methyl ethers give the corresponding methyl carbamates.

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Category

Synthesis of Natural Products and Potential Drugs

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SYNFACT of the month