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 G.

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 SN_i 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.