SYNFACTS

Highlights in Current
Synthetic Organic
Chemistry

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Thieme

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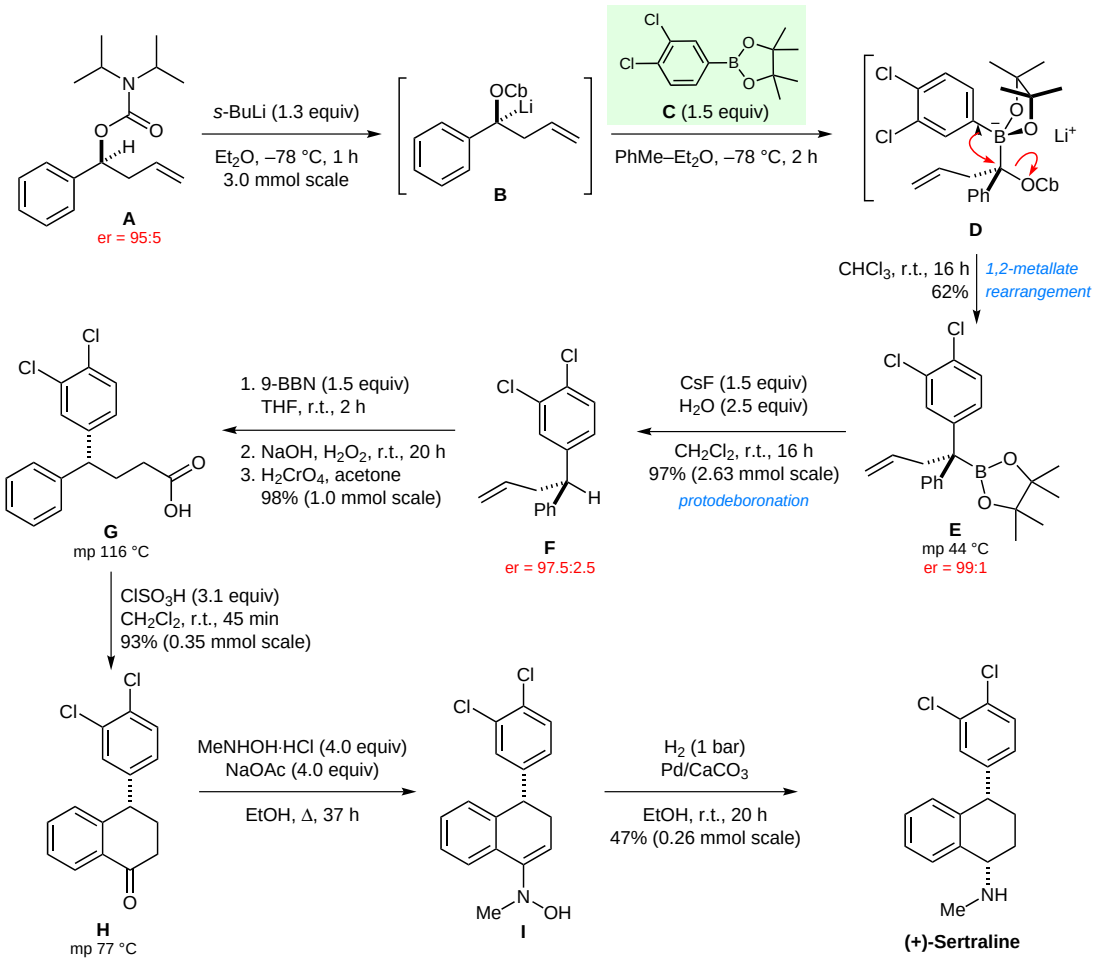
Enantioselective Syntheses of (+)-Sertraline and (+)-Indatraline Using Lithiation/Borylation–Protodeboronation Methodology
Org. Lett. **2011**, *13*, 5740–5743.

Synthesis of (+)-Sertraline



Significance: (+)-Sertraline (Zoloft®) is a competitive selective serotonin reuptake inhibitor (SSRI) that is widely prescribed for the treatment of anxiety. The key steps in the synthesis depicted are (1) a 1,2-metallate rearrangement of the boronate complex **D** with inversion of stereochemistry and (2) a highly stereoselective protodeboronation of the boronic ester **E** (retention) using cesium fluoride and a controlled amount of water. This paper also describes a synthesis of (+)-indatraline from intermediate **F**.

Comment: The boronate complex **D** was remarkably stable and the 1,2-metallate rearrangement required either treatment with 12-crown-4, TMSCl and water (experimental procedure supplied) or a simpler solvent switch to chloroform followed by aging at room temperature for 16 hours. Controlling the amount of water in the protodeboronation step (**E** → **F**) was essential to minimize racemization. Almost complete retention was obtained with 2.5 equivalents of water but further increasing the equivalents of water resulted in diminished yields and enantiomeric ratios.

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Synfacts 2012, 8(1), 0015 Published online: 19.12.2011
DOI: 10.1055/s-0031-1289916; **Reg-No.:** K06911SF

Category

Synthesis of Natural Products and Potential Drugs

Key words

sertraline

indatraline

directed lithiation

1,2-metallate rearrangement

protodeboro-nation