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Enantioselective Synthesis of a Highly Substituted Tetrahydrofluorene Derivative as a Potent and Selective Estrogen Receptor Beta Agonist

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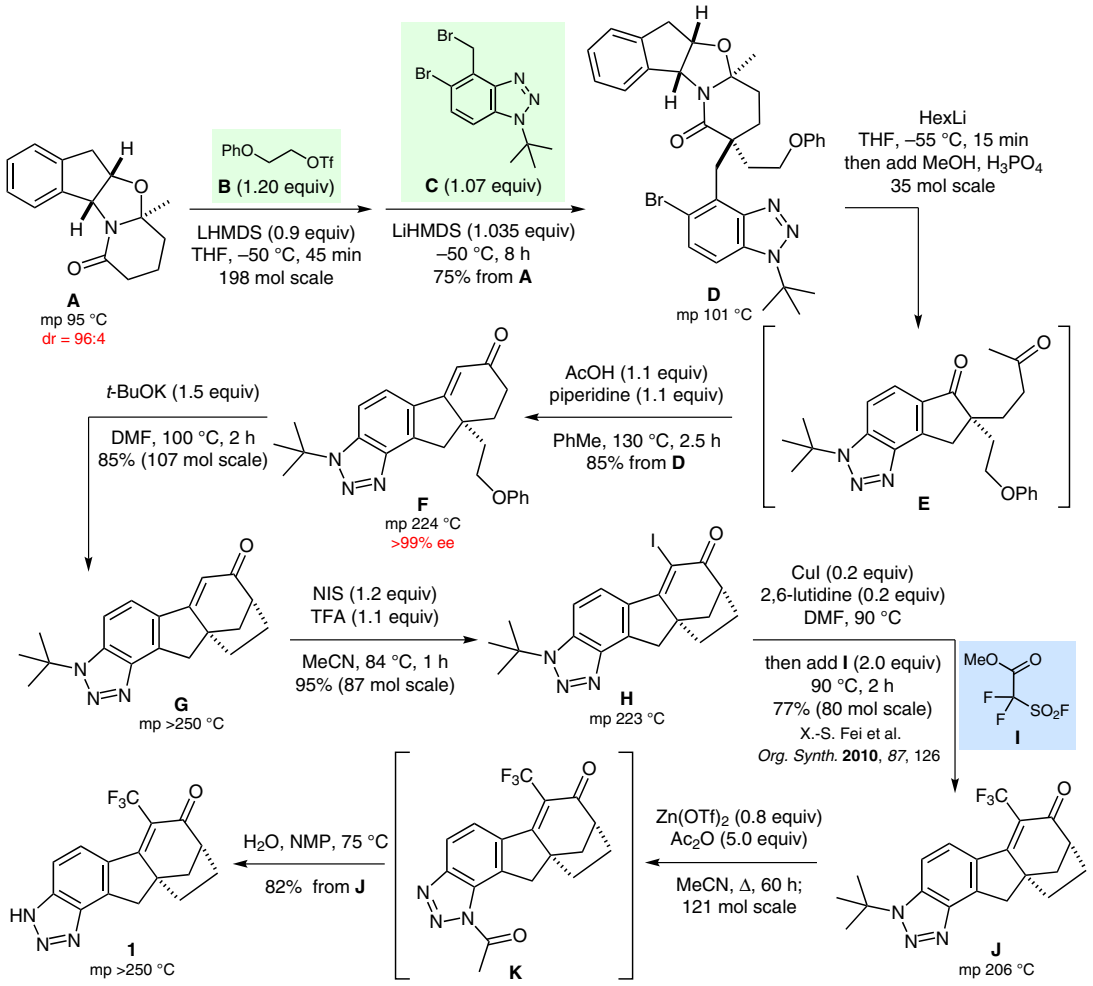
Synthesis of an Estrogen Receptor Beta Agonist



Significance: The target tetrahydrofluorene is an estrogen receptor β agonist that is of interest for the treatment of symptoms associated with reduced estrogen levels in post-menopausal women. The large-scale synthesis depicted features a chiral auxiliary mediated dialkylation to construct the quaternary center in **G** with excellent stereocontrol. Note the intramolecular enolate alkylation **F** → **G** in which phenoxide ion is the leaving group.

Comment: This route delivered more than 30 kg of drug candidate in 21% overall yield through a longest linear sequence of 13 steps and with >99% ee. For syntheses of related tetrahydrofluorenes, see: M. A. Huffman et al. *Tetrahedron* **2007**, *63*, 4459; J. P. Scott et al. *Org. Process Res. Dev.* **2008**, *12*, 723; D. J. Wallace, R. A. Reamer *Tetrahedron Lett.* **2013**, *54*, 4425.

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