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Development of a Scalable Synthesis of a Geminal Dimethyl Tertiary Amine as an Inhaled Muscarinic Antagonist for the Treatment of COPD
Org. Process Res. Dev. **2012**, *16*, 195–203.

Synthesis of PF-3635659

Significance: Chronic obstructive pulmonary disease (COPD) is projected to become the third leading cause of death worldwide by 2020. PF-3635659 is a once-daily, inhaled muscarinic M₃ antagonist that has entered phase II clinical trials for the treatment of COPD. The synthesis depicted delivered 2.6 kg of the hydrochloride salt and benefited from crystalline intermediates at every stage.

Comment: A noteworthy feature of the synthesis is the reaction of amide **F** with MeMgBr in the presence of $ZrCl_4$ (a variant of the classical Bouveault reaction) to give the sterically encumbered *gem*-dimethyl amine **G** in 74% yield on an 8.2 mol scale. Late-stage demethylation of the phenol methyl ether **G** using methionine in methanesulfonic acid avoided the genetic toxicity problems of the more commonly used boron tribromide.

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Synfacts 2012, 8(5), 0467 Published online: 18.04.2012
DOI: 10.1055/s-0031-1290833; Reg-No.: K02112SF