**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 ZrCl₄ (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.