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 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.

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**SYNFACTS of the month**

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**Key words:**
- PF-3635659
- muscarinic M₃ antagonists
- Bouveault reaction
- gem-dimethylation
- zirconium tetrachloride

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**Category:** Synthesis of Natural Products and Potential Drugs