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 M$_3$ 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 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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\begin{align*}
A & \xrightarrow{\text{K$_2$CO$_3$ (1.2 equiv), EICN, 80 °C, 18 h}} B (1.2 \text{ equiv}) \\
B & \xrightarrow{\text{H$_2$ (4 bar), 20% Pd(OH)$_2$/C}} C \\
C & \xrightarrow{\text{then add oxalic acid (0.5 equiv)}} D
\end{align*}
$$

$$
\begin{align*}
E & \xrightarrow{\text{ZrCl$_4$ (2.3 equiv), MeMgBr (9.0 equiv), THF, –5 °C, 4 h}} G \\
G & \xrightarrow{\text{DL-methionine (3.0 equiv), MeOH, 30 °C, 72 h}} F
\end{align*}
$$

$$
\begin{align*}
F & \xrightarrow{\text{KOH (18.5 equiv), t-AmOH, 99 °C, 24 h, then HCl (1.05 equiv)}} H \\
H & \xrightarrow{\text{MTBE, r.t., 19 h recrystallize from MEK–H$_2$O}} \text{PF-3635659 Hydrochloride}
\end{align*}
$$