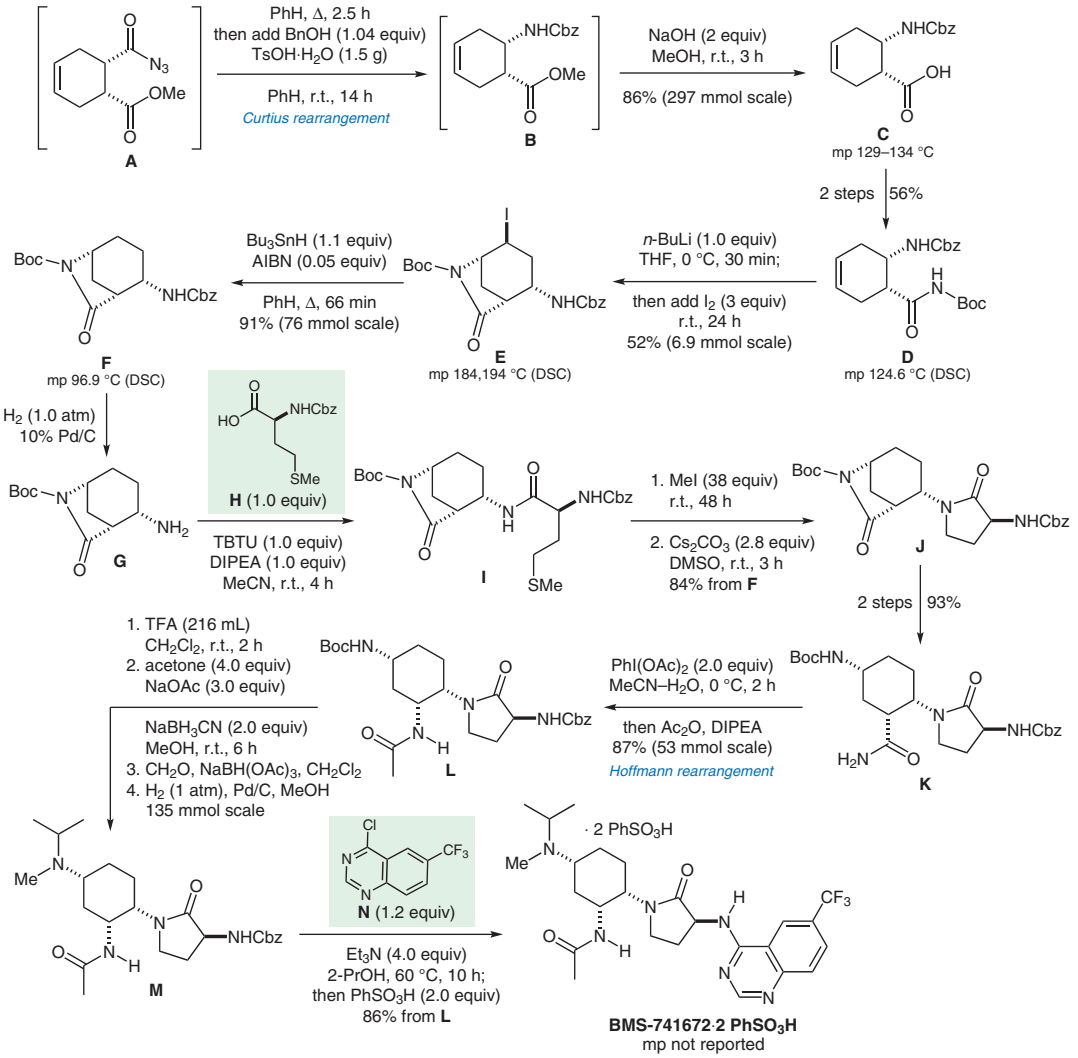
P. H. CARTER* ET AL. (BRISTOL-MYERS SQUIBB COMPANY, PRINCETON, USA)

Use of a Conformational-Switching Mechanism to Modulate Exposed Polarity: Discovery of CCR2 Antagonist BMS-741672
ACS Med. Chem. Lett. **2019**, *10*, 300–305.

Synthesis of BMS-741672



Significance: BMS-741672 is a chemotactic chemokine receptor 2 (CCR2) antagonist that is of interest for the treatment of inflammatory, cardiovascular, and metabolic diseases. The discovery synthesis depicted (>20 steps) is based on construction of the all-*cis* 1,2,4-triaminocyclohexane core using a Curtius rearrangement (**A** → **B**), an iodolactamization (**D** → **E**), and a Hoffman rearrangement (**K** → **L**).

Comment: The synthesis of lactam **G** was previously developed by Bristol-Myers Squibb (C. L. Campbell et al. *J. Org. Chem.* **2009**, *74*, 6368), and a shorter large-scale route to BMS-741672 was subsequently reported that delivered 50 kg of API for clinical evaluation (J. Deerberg et al. *Org. Process Res. Dev.* **2016**, *20*, 1949).

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Synthesis of Natural Products and Potential Drugs

Key words
BMS-741672
Hoffman rearrangement
Curtius rearrangement
iodolactamization
1,2,4-triamino-cyclohexanes

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