Stereoselective Bulk Synthesis of CCR2 Antagonist BMS-741672: Assembly of an All-cis (S,R,R)-1,2,4-Triaminocyclohexane (TACH) Core via Sequential Heterogeneous Asymmetric Hydrogenations


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. A salient feature of the synthesis depicted is the construction of the all-cis 1,2,4-triaminocyclohexane core. This route delivered 50 kg of the target in 12 steps and in 9% overall yield.

Comment: A platinum-catalyzed reduction of β-enaminoester A using (S)-α-methylbenzylamine as a low-cost chiral template and reductive amination of the 3,4-cis-disubstituted cyclohexanone F with a secondary amine on a sulfided platinum catalyst established the stereochemistry in the trisubstituted cyclohexane G.