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Stereoselective Lithiation and Carboxylation of Boc-Protected Bicyclopyrrolidine: Synthesis of a Key Building Block for HCV Protease Inhibitor Telaprevir


Synthesis of a Key Building Block for HCV Protease Inhibitor Telaprevir

Significance: The target molecule H is a fragment of the HCV protease inhibitor telaprevir. A large-scale process for the synthesis of H entails a stereoselective lithiation–carboxylation of A to give rac-C followed by a resolution with (S)-1,2,3,4-tetrahydronaphthalen-1-amine (D). Two hundred kilograms of the target molecule H were manufactured in 27% overall yield by this route.

Comment: An enantioselective synthesis of C via asymmetric lithiation–carboxylation using a variety of chiral diamine ligands was also investigated. For example the chiral diamine ligand (−)-cytisine developed by O’Brien and co-workers (J. Am. Chem. Soc. 2002, 124, 11870) provided enantioselective C in 44% yield and er > 99:1 after crystallization. However, this route was not pursued owing to the high cost and uncertain supply of (−)-cytisine.