Category

Synthesis of Natural Products and Potential Drugs

Key words

telaprevir

stereoselective lithiation

carboxylation

classical resolution

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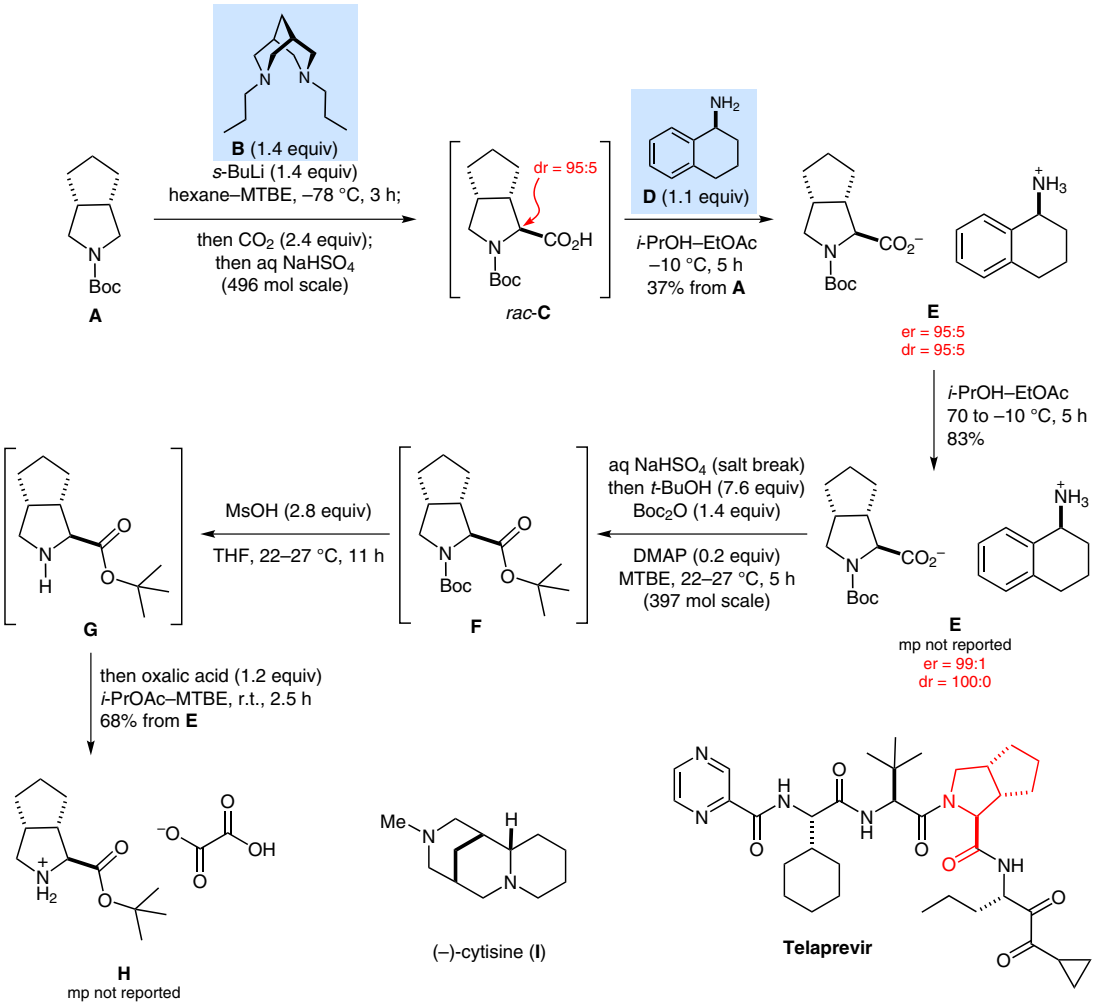
Stereoselective Lithiation and Carboxylation of Boc-Protected Bicyclopyrrolidine: Synthesis of a Key Building Block for HCV Protease Inhibitor Telaprevir

Org. Process Res. Dev. **2014**, *18*, 1234–1244.

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 *ent*-**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.

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Synfacts 2015, 11(1), 0004 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379645; **Reg-No.:** K05914SF

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