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Short, Stereoselective Syntheses of 4,5,6-Trihydroxylated Norleucines: An Approach to the Synthesis of (+)-Bulgecinine

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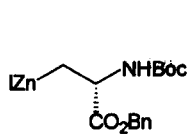
Abstract: Reaction of the *L*-serine derived zinc reagent **1** with *D*-isopropylideneglyceryl chloride gave the 4-oxo amino acid **5**, which was reduced with high diastereoselectivity to give the *trans*-lactone **7**. Analogous reaction of the *D*-serine derived zinc reagent gave the the 4-oxo amino acid **6**, which was reduced with high diastereoselectivity to give the *cis*-lactone **8**. Conversion of **8** to **11**, the enantiomer of the Boc-protected analogue **10** of an intermediate in Fleet's synthesis of (-)-bulgecinine, was achieved in two steps.

We have recently demonstrated that 4-oxo-α-amino acids **2** can be prepared in enantiomerically pure form by reaction of the serine-derived organozinc reagent **1** with acid chlorides under palladium catalysis.[1] In this letter, we report applications of this transformation to the stereoselective synthesis of 4,5,6-trihydroxynorleucines **3**[2] in an extremely rapid and convergent manner, which allows for control of stereochemistry by use of enantiomerically pure starting materials. We also demonstrate the viability of this approach for the synthesis of (+)-bulgecinine **4**, the enantiomer of the naturally occurring constituent of the bulgecin glycopepetides, which have been the subject of significant recent synthetic interest.[3]



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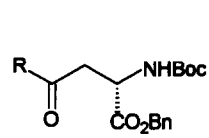

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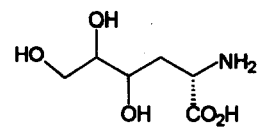

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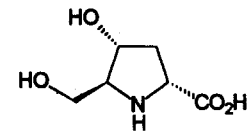
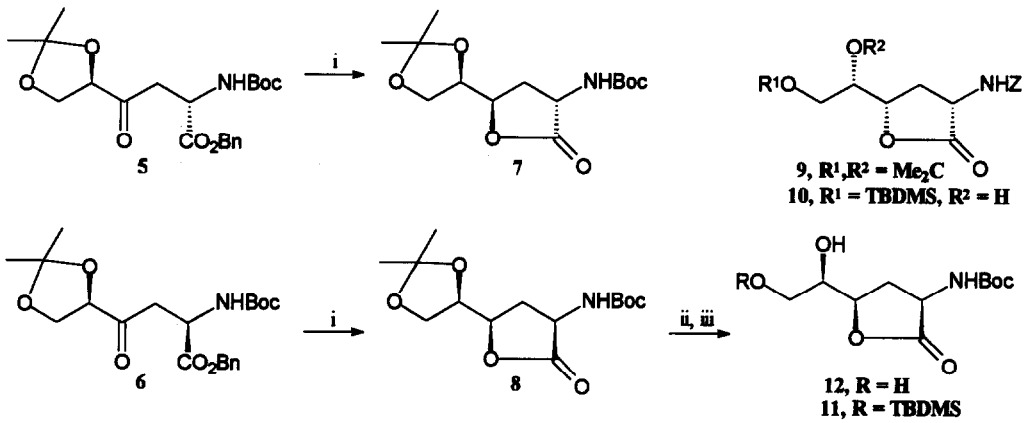


4, (+)-Bulgecinine

(*R*)-isopropylideneglyceryl chloride,[4] prepared from (*R*)-isopropylideneglyceric acid calcium salt, was coupled with the *L*-serine derived zinc reagent **1** under palladium catalysis to give in a single step the protected 5,6-dihydroxy-4-oxonorleucine derivative **5** (51 %). Reaction of the *D*-serine derived zinc reagent under the same conditions gave the 5,6-dihydroxy-4-oxonorleucine derivative **6** (45 %), without any detectable contamination by the diastereoisomeric compound **5**, as determined by ^{1}H NMR. This confirmed that no loss of stereochemical integrity had occurred either at the α-centre, consistent with our previous observations,[1] or at the stereogenic centre of the isopropylideneglyceryl moiety. In order to complete the synthesis of the 4,5,6-trihydroxynorleucines **4**, we investigated the reduction of the ketones **5** and **6**. Previous observations suggested that L-selectride® would be the reagent of choice for these reductions,[5] and a survey of simple hydride reducing agents confirmed this. Thus reduction of the ketone **5** with L-selectride gave the *trans*-lactone **7** (69 %), with no trace of the diastereoisomeric lactone. In an analogous manner, reduction of the ketone **6** with L-selectride® gave the *cis*-lactone **8** (64 %), again with no detectable amount of the corresponding *trans* lactone. Our overall conclusion is that the steric course of the reduction is controlled by the adjacent stereocentre, with the α-centre having a very minor influence, and that the products are of *syn*-relative configuration.[6]



Reagents and conditions: i, L-Selectride®, THF, - 78 °C, 3 h; ii, I_2 in MeOH (1 %), room temp., 48 h; iii, TBDMSCl, NEt_3, DMAP, CH_2Cl_2/DMF.

The stereochemical assignments for the lactones **7** and **8** are based on analysis of their ^{1}H NMR spectra, by methods previously described.[5] Corroboration of the stereochemical assignment for the lactone **8** was provided by comparison of its ^{1}H NMR spectrum with that of the corresponding enantiomeric Z-protected lactone **9**.[7] The spectra were identical, apart from those signals attributable to the protecting group. Conversion of lactone **8** to lactone **11**, the enantiomer of the Boc-protected analogue of a late intermediate **10** in Fleet's synthesis of (-)-bulgecinine,[8] was carried out using a two stage deprotection/reprotection sequence. Removal of the isopropylidene acetal to give the diol **12** was achieved in good yield (72 %) using iodine in methanol,[9] and selective protection of the primary hydroxyl group was carried out under standard conditions to give the silyl ether **11** (52 %). We are at present investigating methods for reduction of the ketones **5** and **6** to give an *anti* relationship at positions 4 and 5, and our results will be reported in due course.

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