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Synthesis of Protected 4-Oxopipecolic Acid and 4-Oxolysine using a Palladium-catalysed Coupling Process

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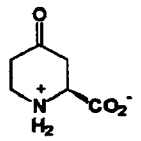
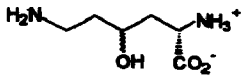
Abstract: **Reaction of the *L*-serine derived zinc reagent 3 with acryloyl chloride gave the 4-oxo amino acid 4, with no evidence of products arising from conjugate addition. Treatment of the adduct 4 with benzylamine gave protected 4-oxolysine 5 directly. Reduction of the ketone proceeded without significant stereoselectivity to give the 4-hydroxylysine derivatives 6 as a diastereoisomeric mixture. Treatment of the adduct 4 with HCl/ether gave 4-oxopipecolic acid benzyl ester hydrochloride 7 in quantitative yield. Evidence for initial formation of the HCl adduct 8 was obtained.**

There has been much recent interest in the synthesis of enantiomerically pure functionalised pipecolic acid derivatives, and although there have been several successful approaches to the synthesis of 5-oxo derivatives,[1] the corresponding 4-oxo derivative **1**, a constituent of the virginiamycin family of cyclic peptides,[2] has only been prepared from *cis*-4-hydroxypipecolic acid.[3] This latter compound has been prepared from 4-hydroxylysine **2**,[4] itself derived from lysine using a photochemical chlorination procedure.[5] We have recently demonstrated that 4-oxo-α-amino acids can be prepared in enantiomerically pure form by reaction of the serine-derived organozinc reagent **3** with acid chlorides under palladium catalysis.[6] In this letter, we report applications of this transformation to the stereoselective synthesis of protected 4-oxygenated lysine derivatives, and also 4-oxopipecolic acid benzyl ester.[7]

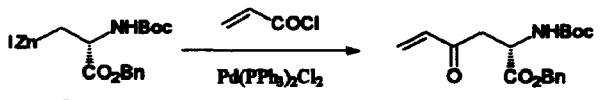


1



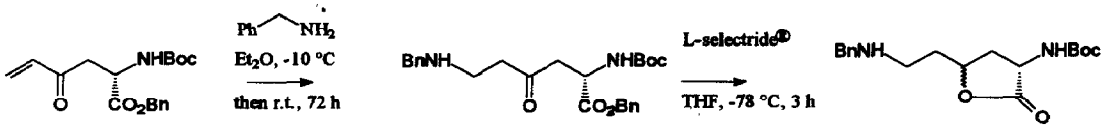
2

Our synthetic plan relies on the preparation of the adduct **4**[8] derived from palladium catalysed coupling of the serine-derived organozinc reagent **3** with acryloyl chloride. Although precedent for the coupling of acryloyl chloride with alkylzinc halides exists,[9] we were concerned that this process might not proceed efficiently. In the event, reaction of the zinc reagent **3**, generated by ultrasonication in benzene/dimethylacetamide, with acryloyl chloride in the presence of *bis*(triphenylphosphine)palladium dichloride, gave the desired enone **4**, with no trace of any products arising from conjugate addition. Reaction with 3-bromopropionyl chloride also gave the enone **4**, although less efficiently.



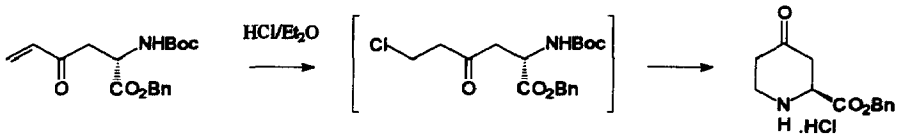
3 **4**

Treatment of the enone **4** with benzylamine gave the 4-oxolysine derivative **5** (72 %). This reaction must be conducted at relatively low concentration (0.06 *M*) to ensure a satisfactory yield. We have previously reported that stereoselective reduction of functionalised 4-oxo amino acids can best be achieved using L-selectride® in THF.[10] However, reduction of **5** under these conditions gave the corresponding lactones **6** as a 1:1 mixture of diastereoisomers (75 %), as judged by ^{1}H NMR.[10]



4 **5** **6**

Preparation of 4-oxopipecolic acid merely requires an intramolecular Michael addition, for which excellent precedent in the racemic series was available.[7] Treatment of enone **4** with 1*M* hydrogen chloride in ether for 48 h gave 4-oxopipecolic acid benzyl ester as the hydrochloride salt **7** (100 %). Of some interest is that, although t.l.c. analysis indicated a rather slow conversion to the product, work-up of the reaction after 24 h resulted in the isolation of the β-chloroenone **8**. It is very likely that this *in situ* protection of the sensitive enone functionality,[11] during the relatively slow deprotection process, is the origin of the unique effectiveness of hydrogen chloride; other methods for the cleavage of the *t*-butoxycarbonyl group (*e.g.* trifluoroacetic acid) did not permit the isolation of any product.



4 **8** **7**

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