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Synthesis of 4-hydroxy-2-methylproline derivatives via pyrrolidine ring assembly: chromatographic resolution and diastereoselective synthesis approaches

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ABSTRACT

4-Hydroxy-2-methylproline diastereomers are successfully prepared without the use of an external chiral auxiliary. Dihydroxylation of the key intermediate **2** resulted in lactone **4** as a mixture of diastereomers in good yield. Mesylation, hydrogenation and concomitant intramolecular cyclization of **4** led to the formation of both (2*R*,4*R*)- and (2*R*,4*S*)-4-hydroxy-2-methylprolines as a mixture of diastereomers. Appropriate protection followed by chromatographic separation resulted in isolation of both *cis*- and *trans*-diastereomers in enantiomerically pure form and in equal quantity. In subsequent experiments, the synthesis of the more challenging diastereomers (2*R*,4*R*)- and (2*S*,4*S*)-4-hydroxy-2-methylproline was achieved by diastereoselective iodolactonization of (*R*)- or (*S*)-allylalanine obtained after hydrolysis of intermediate **2**, followed by pyrrolidine ring closer under mild alkaline conditions. After selective protection and deprotection, Fmoc-(2*R*,4*R*)-α-Me-Hyp(^{t}Bu)-OH **14**, a building block suitable for solid phase peptide synthesis was obtained.

1. Introduction

Modification of native peptides by incorporation of structurally rigid amino acid surrogates into their sequences leads to several beneficial effects such as conformational stability, stability against proteolytic degradation, selectivity and potency.[1] The use of enantiomerically pure quaternary amino acids has gained significant attention due to their unique properties for designing peptides with interesting structural features and biological activity.[2] Quaternary cyclic amino acids, such as proline and hydroxyproline are of special interest due to their exceptional conformational rigidity, which induces helicity upon incorporation into peptides.[3] In spite of their potential advantages, the use of quaternary amino acids is limited as these amino acids are not commercially available. In recent years, efforts were made to develop methodologies for the synthesis of these specialized amino acids for further use. The synthetic procedures for quaternary proline derivatives remain challenging as reported by Calaza and Cativiela.[4]

4-Hydroxy-2-methylprolines are interesting structural variants of cyclic quaternary amino acids but remain underutilized due to limited synthetic methodology. The preparation of 4-hydroxy-2-methylprolines is generally carried out starting from 4-hydroxyproline as a starting material. The stereoselective synthesis reported for 4-hydroxy-2-methylprolines generally yield products with 70–98% ee using chiral auxiliary in one way or the other. It is important to note that the enantiomeric purity of these amino acids is crucial for the biological activity of peptides. Therefore, these interesting monomers can be used for peptide engineering only when a facile synthesis is available to obtain these quaternary amino acids in enantiomerically pure forms. The synthesis of *trans*-4-hydroxy-2-methylprolines by the resolution of racemic or enantioenriched diastereomeric mixtures has already been reported with success starting from *trans*-4-hydroxyproline.[5] However, the other *cis*-diastereomers remain inaccessible by these methods due to the fact that 4-hydroxyproline is readily available only in its *trans*-form while the *cis*-4-hydroxyproline is highly expensive.[6] An interesting stereoselective synthesis of 4-hydroxy-2-methylprolines, that excludes the use of 4-hydroxyproline as a starting material, was reported by Kolaczkowski and Barnes.[7] Starting from (*S*)-alanine, both *cis*- a *trans*-isomers of 4-hydroxy-2-methylprolines were obtained in high yields and enantioselectivity.

Herein we deal with the synthesis of 4-hydroxy-2-methylproline diastereomers via pyrrolidine ring assembly using (2*R*,4*S*)-allyloxazolidinone **2** as a key intermediate. Compound **2** can be easily obtained starting from (2*S*,4*S*)-oxazolidinone **1**, a

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versatile synthon, by enantioretentive allylation.[8] We report the synthesis of enantiopure 4-hydroxy-2-methylprolines starting from alanine via intermediate **1** by a resolution approach using column chromatography. In subsequent experiments, the diastereoselective synthesis of (2*R*,4*R*)- and (2*S*,4*S*)-4-hydroxy-2-methylprolines, the more rare forms, were achieved using **1** as a starting material. In both approaches, diastereomerically pure products were obtained without the use of an external chiral auxiliary.

2. Results and discussion

Quaternary 4-hydroxyprolines are generally prepared from commercially available *trans*-4-hydroxyproline. These procedures are limited to accessing only the (2*S*,4*R*)-configuration starting from *trans* 4-hydroxyproline. The corresponding *cis*-4-hydroxyproline is highly expensive. Therefore, a versatile synthetic route starting from commercially available and cost effective starting material which allows access to both (2*S*,4*R*) and (2*R*,4*R*) is highly desirable. The retrosynthetic analysis for 4-hydroxy-2-methylproline is presented in Figure 1. Our initial strategy was based on the enantioselective dihydroxylation of **2**, obtained by the alkylation of **1** with allyl bromide. Contrary to our expected dihydroxylation product **3**, we isolated lactone **4**. Mesylation of the primary alcohol of **4** resulted in compound **5**, which upon Cbz-deprotection and hydrolysis furnished 4-hydroxy-2-methylproline diastereomers **6** via intramolecular cyclization.

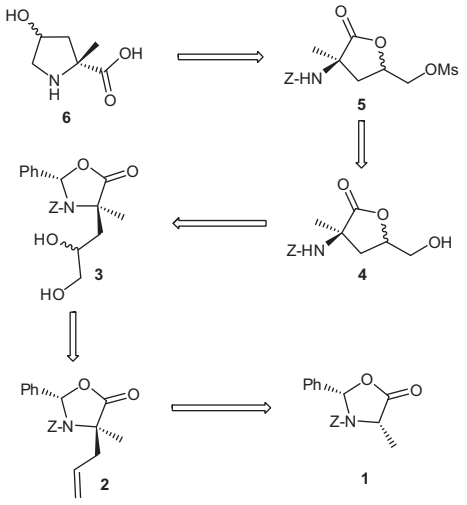


Figure 1. Retrosynthetic analysis of 4-hydroxy 2-methylprolines.

Based on the retrosynthesis, the preparation of 4-hydroxy-2-methylprolines by chromatographic resolution approach is shown in Scheme 1. Compound **1** (Karady oxazolidinone) was prepared by $BF_3{\cdot}Et_2O$ catalysed oxazolidinone formation with Cbz-L-alanine and benzaldehyde dimethyl acetal. Enantioretentive alkylation of **1** using LiHMDS and allyl bromide was optimized at this stage to improve the yield of allyloxazolidinone **2.** It was found that the slow addition of 1.2 equiv of LiHMDS in a pre-cooled mixture of oxazolidinone **1** and 1.2 equiv of allyl bromide gave compound **2** in 75–80% yield. The terminal dihydroxylation of compound **2** was attempted using $K_2OsO_4{\cdot}2H_2O$ according to the literature.[9] We did not obtain the expected dihydroxylated product **3**, instead compound **4** was isolated as nearly a 1:1 mixture of diastereomers as evident from NMR-spectroscopy. The reaction product after the usual work-up showed two spots on TLC, where one spot was characterized as lactone **4** and the other was characterized as benzaldehyde. Interestingly, the formation of benzaldehyde indicated in situ lactonization via intermediate **3** (Fig. 2).[10]

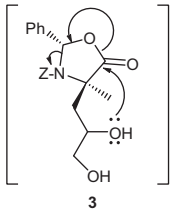
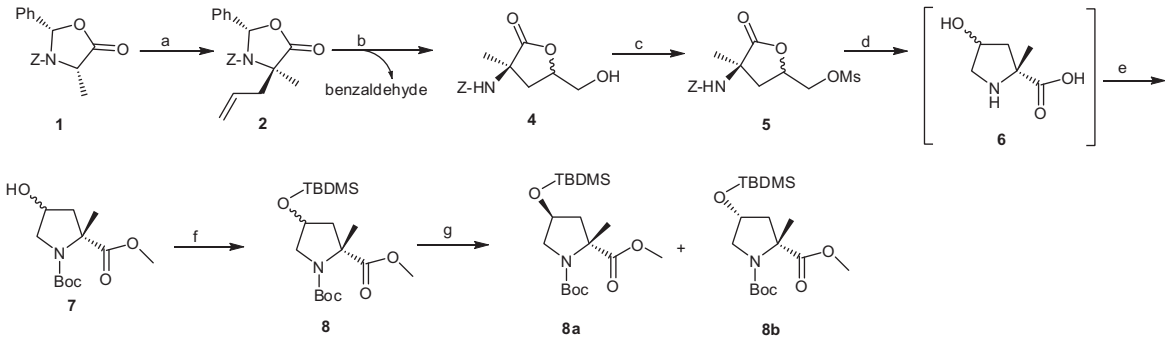


Figure 2. Mechanism for in situ lactonization.

We made several attempts for asymmetric dihydroxylation of the compound **2** with AD mix-α and AD mix-β in order to improve the stereoselectivity but were unsuccessful. Compound **4** was treated with mesyl chloride in the presence of triethylamine to obtain the corresponding methylsulfonate ester **5**. Compound **5** was subjected to catalytic hydrogenation in methanol and 2 equiv of DIEA for 3 h. The crude amino lactones obtained were readily converted into 4-hydroxy-2-methylprolines **6** by treatment with LiOH at room temperature. We did not isolate the free amino acid and the crude product was treated with di-*tert*-butyl-dicarbonate followed by treatment with diazomethane to give the corresponding *N*-Boc protected 4-hydroxy-2-methylproline methylester **7**, which was characterized as mixture of diastereomers (2*R*,4*S*)- and (2*R*,4*R*)-4-hydroxy-2-methylproline. We speculated that after the lactone was opened by LiOH, a successive ring-closure reaction would have occurred immediately resulting in **6**. The diastereomeric mixture of **7** was not resolvable on TLC. Therefore, hydroxyl group was masked with TBDMS-Cl/imidazole to form **8** as a mixture of diastereomers which were very well separated on TLC. Thus the



Scheme 1. Synthesis of protected diastereomers of 4-hydroxy-2-methylproline. Reagents and conditions: (a) LiHMDS, allyl bromide, THF, −78 °C, 3 h, 75–80%; (b) NMO, $K_2OsO_4{\cdot}2H_2O$, acetone, 18 h, 85%; (c) MsCl, Et_3N, THF, 0 °C, 1/2 h, 85%; (d) (i) H_2, Pd/C, DIEA, methanol, 3 h, (ii) LiOH, methanol/water 9:1 (v/v), 2 h; (e) (i) $(Boc)_2O$, dioxane/water 1:1, 0 °C to rt, 3 h (ii) CH_2N_2, diethyl ether, 0 °C to rt, 3 h, (75% over four steps) (f) TBDMS-Cl, imidazole, DMF, rt, 12 h; (g) Chromatography.