Enantiomerically pure H-Arg(Z)₂-aldehyde diethylacetal: A **Useful Building Block in the Synthesis of Peptide Aldehydes**

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Introduction

 α -Amino and peptide aldehydes are useful synthetic intermediates [1,2], and some of them are potent inhibitors of proteases [3]. Their tendency to racemize during their synthesis, purification and acetalization is a widely known problem since the acidity of the α -proton facilitates the enolization of the aldehyde [4]. In the course of our work, we found only few examples that describe a suitable procedure of protected α -amino aldehydes in high enantiomeric purity [5,6].

In this poster, we present on the one hand a racemization free synthesis of H-Arg(Z)₂-aldehyde diethylacetal (5) starting from commercially available $Fmoc-Arg(Z)_2-OH$ (1) [5], and on the other hand detailed analytical procedures that confirm the high enantiomeric excess of 5.

Synthesis

Starting from the Fmoc- and di-Z-protected arginine 1, the synthesis commenced with the formation of the mixed anhydride, followed by sodium borohydride reduction to argininol 2. Subsequent Parikh-Doering oxidation [7] led to arginine aldehyde 3 whose acetalization under very mild conditions [6] provided $Fmoc-Arg(Z)_2$ -aldehyde diethylacetal **4**. The Fmoccleavage was performed under standard conditions using piperidine in DMF to give 5.



Determination of the Enantiomeric Purity

Verification of the enantiomeric purity of 4 was obtained via two independent methods.

Direct determination of the enantiomeric excess at the stage of Fmoc-Arg(Z)₂-aldehyde diethylacetal was achieved in a chiral HPLC assay, in which less than 0.1% of the D-enantiomer (D-4) were found (Figure 1).



Chiral HPLC, Chiralpak AD 0.46x25cm, 30°C, flow 1.0 ml/min, Hexan/iso-Propanol 60:40, 0.01% TFA, detection 254 nm: (a) Chromatogram of synthesized 4 containing < 0.1% D-enantiomer D-4; (b) 4 spiked with D-enantiomer D-4 (obtained by independent synthesis)

Alternatively, 4 was Fmoc deprotected and coupled with Z-Leu-OH using the mixed anhydride method (Scheme 2) to provide the Z-Leu-Arg(Z)_2-aldehyde diethylacetal (6a). In the same manner, the diastereoisomer 6b was prepared starting from **D-4**. With **6b** as a reference the ratio of the two diastereoisomers 6a and 6b in the crude reaction mixture of 6a could be determined by HPLC





HPLC, Bakerbond WP 300-5, 65°C, flow 1.0 ml/min, TEAP(H₂O)/ACN 20:80 \rightarrow 100:0, detection 220 nm: Chromatogram of dipeptide **6**, containing < 1% (*L*,*D*)-enantiomer 6b.

Conclusion

The presented synthesis in Scheme 1 illustrates the easy access to enantiomeric pure $H-Arg(Z)_2$ -aldehyde diethylacetal (5) that can be used as building block in the synthesis of peptide aldehydes.

The enantiomeric purity was determined in two different ways. The analysis of the enantiomeric purity of diethylacetal 4 on a chiral HPLC column gave a similar result as the analytical experiment on the diastereomeric level. For the latter assay, 5 was coupled with a leucine derivative followed by the separation of the two putative diastereomers 6a and 6b on HPLC.

The synthetic method described in the poster is very versatile and can be applied to a variety of different amino acids, thus representing a general approach for the preparation of amino and peptide aldehydes.

In addition, mild reaction conditions and simple workup procedures in all the steps allow a scale-up towards an industrial scale.

References

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The HPLC chromatogram showed that the (L,L)diastereomer 6a was present in a large excess compared to the corresponding (L,D)-analog 6b (de>98%, Figure 2).

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