Enantiomerically pure H-Arg(Z)$_2$-aldehyde diethylacetal: A Useful Building Block in the Synthesis of Peptide Aldehydes

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Introduction

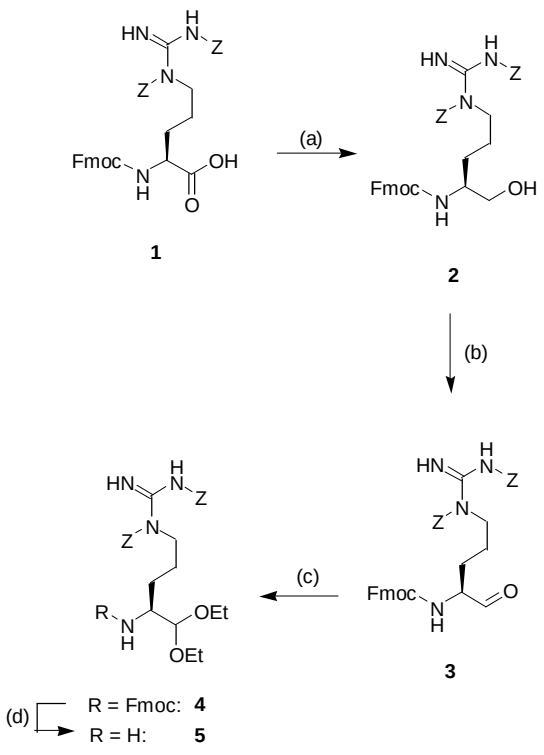
α-Amino and peptide aldehydes are useful synthetic intermediates [1,2], and some of them are potent inhibitors of proteases [3]. Their tendency to racemize during their synthesis, purification and acetalization is a widely known problem since the acidity of the α-proton facilitates the enolization of 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 Fmoc-cleavage was perfomed under standard conditions using piperidine in DMF to give **5**.

Scheme 1

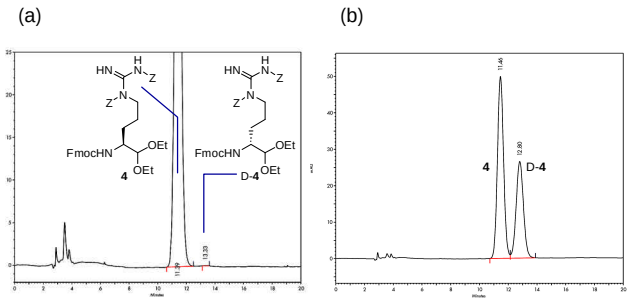


Reagents and conditions: (a) (i) mixed anhydride, NMM, DME, (ii) $NaBH_4$, H_2O, 75%; (b) SO_3-pyridine, Et_3N, DMSO, THF, 85%; (c) triethyl orthoformate, THF, EtOH abs., p-TsOH, 65%; (d) piperidine, DMF, 70%.

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).

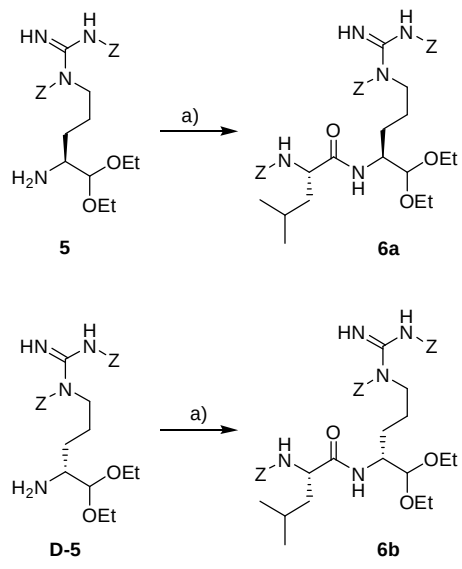
Figure 1



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.

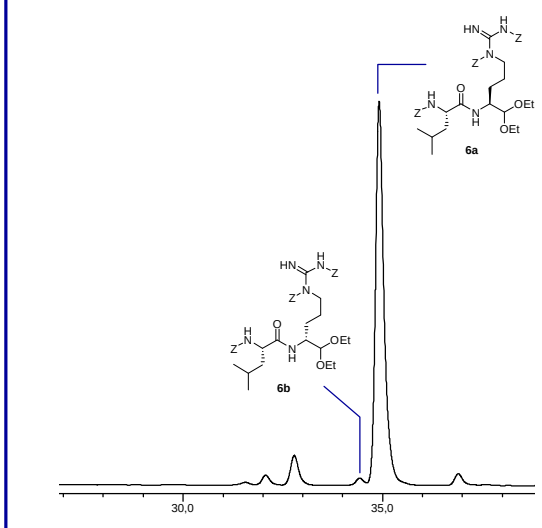
Scheme 2



Reagents and conditions: a) mixed anhydride, NMM, EtOAc/DMF, 94% (oil)

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).

Figure 2



HPLC, Bakerbond WP 300-5, 65°C, flow 1.0 ml/min, TEAP(H_2O)/ACN 20:80 → 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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