Synthesis of (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid and its enantiomer: a non-proteinogenic amino acid segment of the linear pentapeptide microginin

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Abstract

A directed manipulation of the functional groups at C3 and C4 of D-glucose was demonstrated to synthesize naturally occurring (2*S*,3*R*)-α-hydroxy-β-aminodecanoic acid (AHDA, **2a**) and its enantiomer **2b**. The enantiomer of **2a** is the N-terminal part of the natural linear pentapeptide microginin, which is used as an antihypertensive agent.

Introduction

Microginin **1** (Figure 1), isolated from the cyanobacterium *Microcystis aeruginosa,* is a linear pentapeptide consisting of L-Tyr-L-*N*-Me-Tyr-L-Val-L-Ala and (2*S*,3*R*)-α-hydroxy-β-aminodecanoic acid ((2*S*,3*R*)-AHDA, **2a**) [1]. Microginin is used as a hypertensive agent based on its biological activity against angiotensin converting enzyme, which is responsible for the vasoconstriction of blood vessels [2-4]. Amongst different amino acids present in microginin, (2*S*,3*R*)-AHDA (**2a**) is a non-proteinogenic natural amino acid attached at the N-terminal part of the peptide chain. The α-hydroxy-β-amino acid fragment in AHDA **2a** is also present in linear peptides such as bestatin and valinoctin [5-8], which are isolated from the same species. In addition, the chiral α-hydroxy-β-amino acid constituent is an important component of protein kinase inhibitor compounds like balanol and the anticancer drug taxol [9].
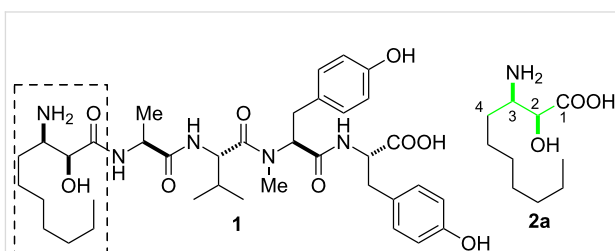

**Figure 1:** Microginin (**1**) and (2*S*,3*R*)-AHDA (**2a**).

Due to the biological importance of (2*S*,3*R*)-AHDA, the enantioselective synthesis of its chiral core is a challenge task. This fact led to several approaches for the stereoselective synthesis of (2*S*,3*R*)-AHDA including (i) the enantioselective introduction of amino- and hydroxy-groups to olefinic acid by either asymmetric epoxidation, dihydroxylation or aminohydroxylation [10-15], (ii) the asymmetric synthesis of β-lactams by a Staudinger reaction between ketene and imine to give the corresponding amino acids [16], and (iii) the Lewis acid catalyzed multicomponent condensation reactions of aldehyde, an amine and ketene silyl acetal derivatives to get the vicinal hydroxylamino acids [17]. In addition, a few strategies employ a chiral pool approach. For example, Wee et al. utilized the zinc-silver-mediated reductive elimination of α-D-lyxofuranosyl phenylsulfone to get (4*S*,5*S*)-4-formyl-5-vinyl-2-oxazolidone, which was converted into **2a** [18]. Merrer and co-workers used D-isoascorbic acid, which was transformed via (2*R*)-amino-1,3,4-triol to **2a** [19]. Bergmeier et al. synthesized a chiral allyl alcohol from D-mannitol, which is converted to the azidoformate and thermally cyclized to a bicyclic aziridine. The opening of the aziridine with organocuprate led to a corresponding chiral hydroxylated amino acid core [20]. Although a number of chiron approaches are known [21], there is no report from D-glucose towards the synthesis of (2*S*,3*R*)-AHDA (**2a**) and its enantiomer (2*R*,3*S*)-AHDA (**2b**). As a part of our continuous interest in the synthesis of chiral amino acids [22,23] and their utility in the synthesis of iminosugars [24-29], we report here an efficient and practical approach for the synthesis of both enantiomers of AHDA (**2a** and **2b**) from the same precursor D-glucose by simple manipulation of the functional groups.

We visualized that the structural and the stereochemical symmetry of both enantiomers (**2a**/**2b**) is present in D-glucose. The C1-carboxyl carbon atom of **2a** is present at the C2 of the D-glucose, and the C4 carbon atom with an alkyl chain in **2a** could be built on C5 of the D-glucose (Scheme 1). The required relative stereochemistry of the vicinal hydroxyamino function-

ality in **2a** at C2 and C3 is embedded at the C3 and C4 of D-glucose, respectively, and needs to be manipulated by usual functional group transformations. Thus, for the synthesis of enantiomers **2a** and **2b** the corresponding sugar precursors were found to be suitably protected β-L-arabino-pentodialdo-1,4-furanose **3a** [30,31] and α-D-ribo-pentodialdo-1,4-furanose **3b** [32]. There exists a distinct possibility to synthesize these chiron synthons **3a** and **3b** from the easily available and cheap starting material D-glucose. Our results of the synthesis of both enantiomers **2a** and **2b** are described herein.

Results and Discussion

As reported earlier, D-glucose was converted to the 3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-arabino-pentodialdo-1,4-furanose (**3a**) in 72% yield (Scheme 2) [30]. While targeting the synthesis of **2a**, the Wittig olefination of **3a** with *n*-hexyltriphenylphosphonium bromide and *t*-BuOK gave olefin **4a** as a diasteromeric mixture of *Z* and *E*-isomers in the ratio 9.5:0.5 as shown by ^{1}H NMR of the crude product. The catalytic hydrogenation of alkene **4a** with 10% Pd/C in methanol:ethyl acetate (3:2) at balloon pressure gave 4-heptyl-L-threose derivative **5a** as a viscous oil in 99% yield [33]. Removal of the 1,2-acetonide group with TFA–water in **5a** provided an anomeric mixture of the hemiacetal, which was directly subjected to oxidative cleavage by using sodium metaperiodate in acetone–water (to cleave the anomeric carbon) followed by a treatment with sodium borohydride to give triol **6a** as a viscous oil in 78% overall yield in three steps [34]. The primary hydroxy group of triol **6a** was selectively monosilylated with *t*-butyldiphenylsilyl chloride to give **7a**. Subsequently, the secondary hydroxy group in **7a** was converted to azido derivative **8a** with an inversion of the configuration by using diphenylphosphoryl azide in the presence of DBU in 88% yield [35]. Cleavage of the silyl functionality in **8a** with *n*-tetrabutylammonium fluoride offered azido alcohol **9a** as a viscous oil. The azido alcohol **9a** was oxidized to the corresponding acid by using RuCl$_3$·3H$_2$O/NaIO$_4$ to give **10a** [36].
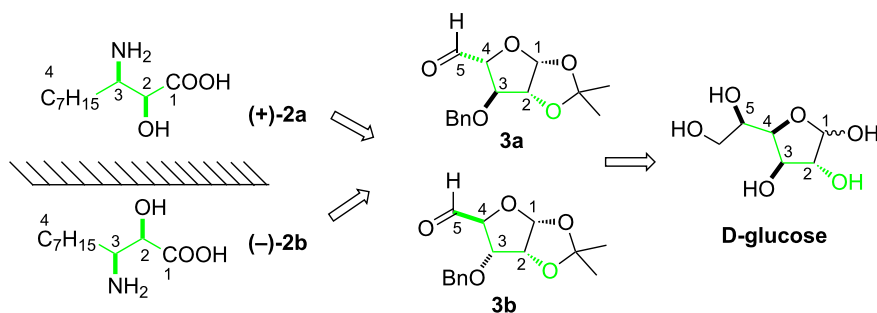
Scheme 1: Retrosynthetic analysis of AHDA.
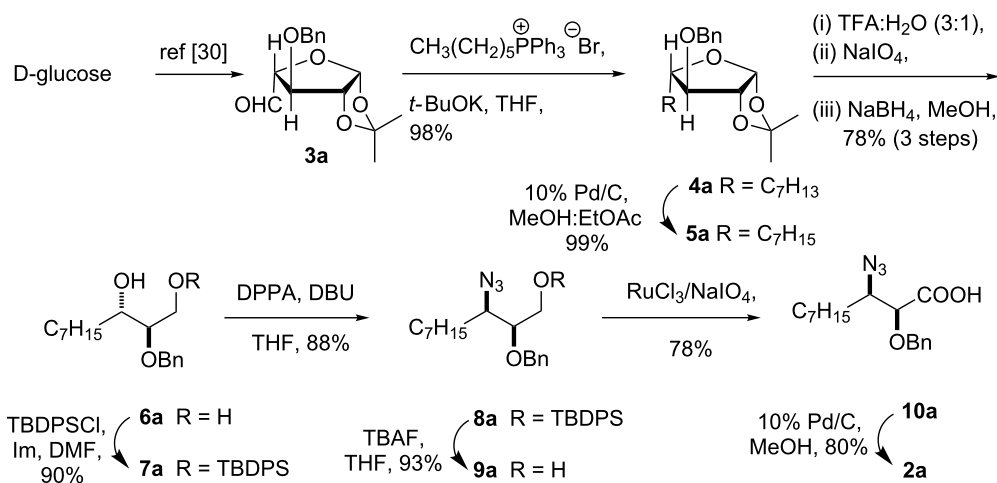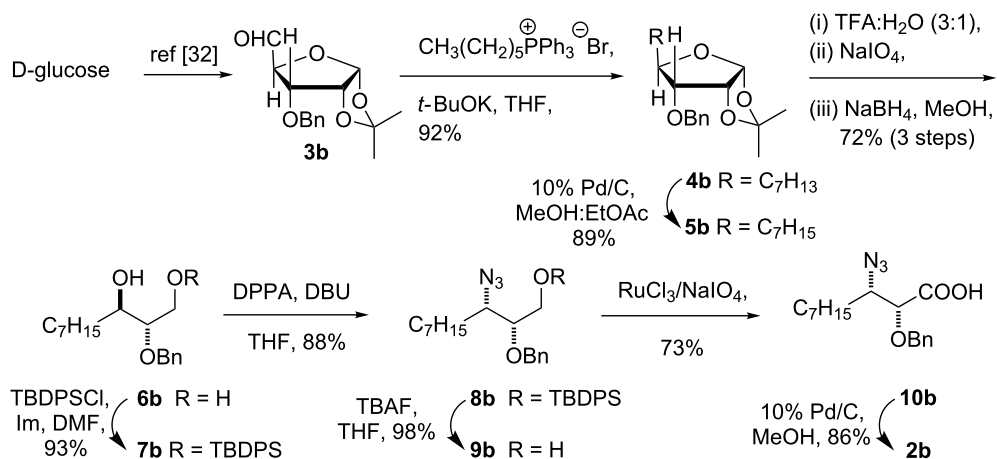
Scheme 2: Synthesis of AHDA **2a**.

Finally, cleavage of the 2-*O*-benzyl ether and reduction of the 3-azido group to the corresponding amine in one step with 10% Pd/C in methanol provided (−)-α-hydroxy-β-aminodecanoic acid (AHDA, **2a**) in 80% yield as a white solid. The spectral and analytical data of **2a** was found to be in good agreement with published data ([α]$_D^{25}$ +5.6 (*c* 0.51, 1 M HCl). [α]$_D^{22}$ +7.3 (*c* 0.37, 1 M HCl)) [18].

The synthesis of AHDA enantiomer **2b** was accomplished starting from 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-ribo-pento-dialdo-1,4-furanose (**3b**) which was obtained from D-glucose in good yield as reported earlier [33]. Thus, the Wittig reaction of **3b** followed by hydrogenation (10% Pd/C) gave 4-heptyl-D-threose derivative **5b** (Scheme 3). Hydrolysis of 1,2-*O*-isopropylidene (TFA:H$_2$O) followed by oxidative cleavage of the hemiacetal with NaIO$_4$ and reduction with NaBH$_4$ gave triol

6b, which was monosilylated with TBDPSCl to give **7b**. Conversion of the secondary hydroxy group in **7b** to azide **8b** according to the Mitsunobu protocol, and deprotection followed by oxidation of the primary hydroxy group gave azido acid **10b**. Finally, hydrogenolysis of the benzyl group and reduction of the azido group by using 10% Pd/C, in one pot, gave **2b** in 30.1% overall yield from **3b**. The spectral and analytical data was found to be in good agreement with reported data ([α]$_D^{30}$ −5.1(*c* 0.51, 1 M HCl). [α]$_D^{30}$ −6.2 (*c* 0.4, 1 M HCl)) [21].

Conclusion

In conclusion, we demonstrated a practical approach for the synthesis of both enantiomers of AHDA (**2a** and **2b**) to obtain the stereochemistry required for the α-hydroxy-β-amino acid. Our method starts from D-glucose by an easy manipulation of

Scheme 3: Synthesis of *ent*-AHDA **2b**.

its functional groups at C3 and C4. In addition, the chiral core (α-hydroxy-β-amino acid) in **2a** is present in several biologically active compounds such as taxol, balanol and bestatin. Therefore, this methodology could be potentially exploited for the synthesis of the chiral segment of these compounds.

Supporting Information

Supporting Information File 1
Experimental procedures.
[http://www.beilstein-journals.org/bjoc/content/
supplementary/1860-5397-10-59-S1.pdf]

Supporting Information File 2
Copies of NMR spectra.
[http://www.beilstein-journals.org/bjoc/content/
supplementary/1860-5397-10-59-S2.pdf]

Acknowledgements

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