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Highly Efficient Chiral-Pool Synthesis of (2*S*,4*R*)-4-Hydroxyornithine

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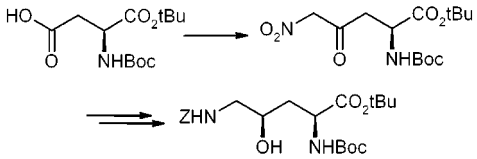
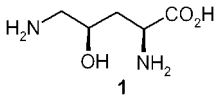
ABSTRACT



A concise synthesis of the amino acid (2*S*,4*R*)-4-hydroxyornithine is described. Starting from diprotected L-aspartic acid, the scaffold of the target compound is constructed in a three-step approach: an efficient α-nitroketone formation through acylation of nitromethane is followed by a diastereoselective reduction of the resulting ketone. In the last step, the nitro group is reduced to furnish the (2*S*,4*R*)-4-hydroxyornithine scaffold. This new approach to the title compound offers advantages to the synthetic pathways previously described.

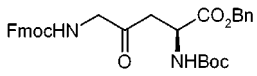
(2*S*,4*R*)-4-Hydroxyornithine (**1**) is a nonproteinogenic amino acid that is widely found in nature. For example, it is a



1

component of marine organism[1] and plants,[2] as well as a constituent of a number of peptide natural products, such as the antifungal lipopeptides echinocandin and pneumocandin,[3] the K 582 type antibiotics,[4] and the biphenomycin antibiotics.[5] The interest in (2*S*,4*R*)-4-hydroxyornithine (**1**) is documented in a variety of synthetic approaches previously described in the literature. Apart from procedures that do not proceed stereoselectively,[6−10] two recent selective synthetic pathways to prepare the (2*S*,4*R*)-4-hydroxyornithine structure have been described. Schmidt et al. synthesized the scaffold of **1** starting from (*R*)-isopropylideneglyceraldehyde. This sequence involves about 10 steps and proceeds nondiastereoselectively, i.e., an asymmetric catalytic hydrogenation step is needed for stereoselective introduction of the second stereogenic center.[11]

A very concise approach using L-serine as starting material is described by Jackson. The key step is a palladium-catalyzed coupling of a serine-derived zinc compound with an acid chloride to form ketone **2**, which is later reduced in



2

a diastereoselective fashion. The elegance of this approach

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however is hampered by the low yield (<30%) of the C−C coupling step.[12]

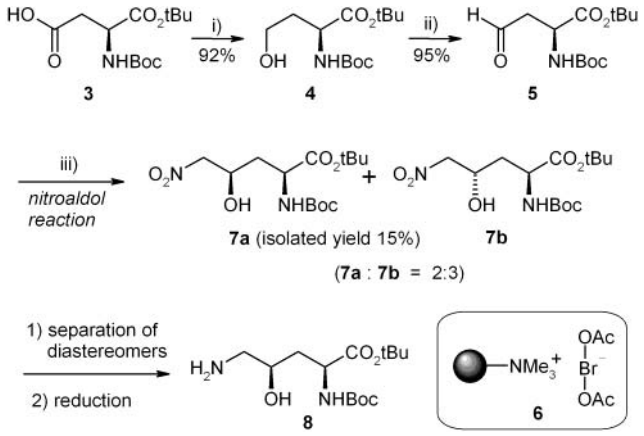
Overall, access to (2*S*,4*R*)-4-hydroxyornithine (**1**) remained problematic since either complicated purification procedures, numerous steps, or unsatisfactory reactions were involved.

As we were interested in a more efficient access to (2*S*,4*R*)-4-hydroxyornithine (**1**), we envisioned a strategy starting from L-aspartic acid and adding a nucleophilic C−N unit to the carboxylic acid function of its side chain.

We began our investigations with a nitroaldol reaction approach[13] using the semialdehyde of diprotected L-aspartic acid[14] and nitromethane, as shown in Scheme 1. As starting material for the synthesis of the aspartic acid semialdehyde, we chose commercially available (*S*)-*N*-Boc-aspartic acid *tert*-butyl ester **3**. The *tert*-butyl ester group of γ-hydroxy amino acids is known to be stable toward lactonization which we preferred to avoid. (*S*)-*N*-Boc aspartic acid *tert*-butyl ester **3** was reduced to the corresponding homoserine derivative **4**,[15] which was subsequently oxidized to the semialdehyde **5**. The method of choice for oxidizing the alcohol function of **4** was found to be the polymer-bound bromite(I) complex **6** as recently described by Kirschning et al.[16] This method gave very high yields and was found to be superior to the Dess−Martin reagent. We then performed the Henry reaction using nitromethane and 5% sodium ethoxide in ethanol which proved to be the best conditions with respect to substrate conversion. However, selectivity of this reaction was found to be unfavorable, namely, the undesired (2*S*,4*S*)-diastereomer (*threo*) (**7b**) was formed in a 3:2 ratio with regard to the desired (2*S*,4*R*)-diastereomer (*erythro*) (**7a**) as determined by ^{1}H NMR analysis (stereochemistry assigned via X-ray analysis of the isolated threo-isomer **7b**). Following this approach, we were able to isolate only 15% of the nitro alcohol **7a**. Attempts to improve the selectivity were unsuccessful.[17]

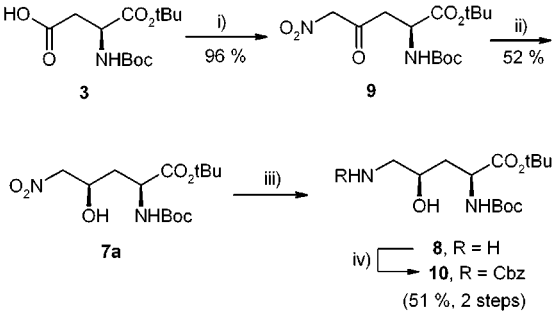
Because of the unfavorable diastereoselectivity and yield of the nitroaldol reaction, we turned to a different strategy for C−C-coupling which would involve the generation of an α-nitroketone. It is known that α-nitroketones can be formed by reaction of acylimidazoles with deprotonated nitromethane.[18,19] On the basis of this method, we developed a versatile procedure which proved to be superior for our purposes compared to the original one (Scheme 2): (*S*)-*N*-Boc-aspartic acid *tert*-butyl ester **3** was activated with carbonyl diimidazole and transformed to the nitroketone **9** by treatment with excess nitromethane in the presence of *t*-BuOK in a very clean reaction (96% yield). It was found to be particularly important to use an excess of nitromethane (10-fold) and an equimolar amount of *t*-BuOK. After the successful implementation of the scaffold of hydroxyornithine, we wanted to first reduce the keto group of **9** to an alcohol function in a diastereoselective manner and

Scheme 1. Synthetic Pathway to (2*S*,4*R*)-4-Hydroxyornithine via Henry Reaction[a]



[a] (i) NMM, ClCOOEt, THF; $NaBH_4$, H_2O; (ii) polymer-bound bromite(I) complex **6**, catalytic TEMPO; (iii) CH_3NO_2, NaOEt (5%), EtOH.

Scheme 2. Synthesis of the Hydroxyornithine Derivative **10** via Acylation of Nitromethane as the Key Step[a]



[a] (i) CDI (1.05 equiv), THF, rt; CH_3NO_2 (10 equiv), *t*-BuOK (1.1 equiv), rt; (ii) L-Selectride, THF, −78 °C; (iii) catalytic Pd/C, $NH_4^+HCOO^-$, −10 °C; (iv) Z-OSu, DIPEA, DMF, rt.

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(18) Baker, D. C.; Putt, S. R. *Synthesis* **1978**, 478−479. According to the authors, the high preference of C-acylation over O-acylation for the ambidently nucleophilic methanenitronate anion is assigned to the unique reactivity of the acylimidazole which behaves differently from other activated acyl species.

(19) For a recent application, see: Yuasa, Y.; Yuasa, Y.; Tsuruta, H. *Synth. Commun.* **1998**, *28*, 395−401.

subsequently reduce the nitro group to an amino function. As is known from detailed studies on the reduction of 4-keto δ-amino acids by Jackson,[12] the α-center of such compounds exerts moderate stereochemical control and use of the reducing agent L-Selectride[20] gives the highest levels of stereoselectivity in favor of the *erythro*-diastereoisomer.

Accordingly, we found that using L-Selectride gave rise to a 85:15 mixture in favor of the desired *erythro* compound **7a** (= (2*S*,4*R*)-diastereomer). We were able to separate the diastereomers via silica gel chromatography. In the last step of the sequence, the nitro group was reduced to furnish the vicinal amino alcohol function of the *tert*-butyl (2*S*,4*R*)-*N*-Boc-4-hydroxyornithinate **8**. Surprisingly, hydrogen reduction using different catalysts under a variety of reaction conditions (different pressures, temperatures) was unsuccessful. Instead, hydrogen transfer, i.e., ammonium formate in methanol in the presence of palladium on carbon, proved to be the method of choice for this transformation.[21] The resulting amino alcohol **8** was found to be unstable and was therefore further transformed to the corresponding N^{δ}-Z-protected hydroxyornithine derivative **10**.

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In summary, a practical and concise synthesis of the nonproteinogenic amino acid (2*S*,4*R*)-4-hydroxyornithine has been developed starting from commercially available diprotected L-aspartic acid. The synthesis involves an efficient homologization of the acid side chain to form an α-nitroketone in the first step and subsequent generation of the second stereogenic center through diastereoselective ketone reduction. We find that this approach allows a very direct access to (2*S*,4*R*)-4-hydroxyornithine derivatives that offers some advantages over the syntheses previously described. In addition, the described two-step approach to nitro alcohols is a useful and general alternative to the classical Henry reaction.

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Supporting Information Available: Description of all experimental procedures and product characterization. Crystal structure data for compound **7b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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