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A concise synthesis of protected (2*S*,4*R*)-4-hydroxyornithine

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Abstract

A short synthesis of the nonproteinogenic amino acid, (2*S*,4*R*)-4-hydroxyornithine is described. Starting from racemic benzyl glycidol, the scaffold of the target compound was constructed in high enantio- and diastereoselectivity using Jacobsen's hydrolytic kinetic resolution (HKR) and regioselective opening of an epoxide as key steps.

Keywords: Hydroxyornithine; Jacobsen's HKR; Epoxide; Grignard reaction; Natural product

4-Hydroxyornithine **1a**–**b** is a nonproteinogenic amino acid found abundantly in nature. It is a 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] macrocyclic antibiotics such as the biphenomycin A and B **2a**–**b**,[5] the β-lactam antibiotic clavalanine **3**[6] and polyoxin M.[7] Related 4-hydroxylated α-amino acid, (2*S*,4*S*,6*R*)-4-hydroxy-5-phenylsulfinyl-norvaline **4** has also been identified as a key component of ustiloxin A and B,[8] a family of cyclic peptides with potent antimitotic activity (Fig. 1).[9]

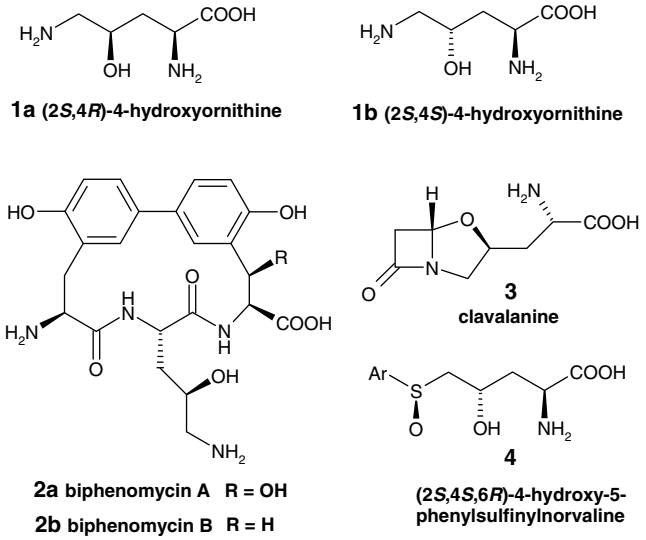

Fig. 1.

Various methods for the synthesis of 4-hydroxyornithine including stereoselective approaches have been reported in the literature.[10] Rudolph et al. described the synthesis of the target compound from a chiral pool starting material, (*S*)-*N*-Boc-aspartic acid *tert*-butyl ester. This approach, which is based on an initial homologation of the acid side chain to form an α-nitroketone and subsequent diastereoselective ketone reduction to the corresponding β-nitro alcohol, involves the use of an excess of starting material (10-fold of nitromethane) and suffers from a low overall yield of the product.[11] In another approach, the scaffold of **1** was constructed by multi-step synthesis starting from (*R*)-1,2-*O*-isopropylideneglycerol.[12] Very recently, Paintner et al. developed a stereoselective approach to **1** based on a bis(oxazoline) copper(II)-complex mediated diastereoselective Henry reaction of nitromethane with the homoserine-derived aldehyde in 11 steps.[13]

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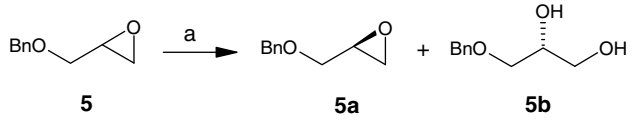
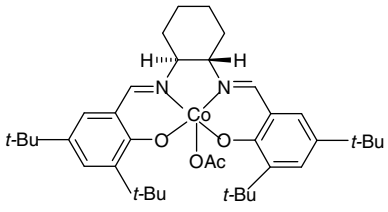


Scheme 1. Reagents and conditions: (a) (*R*,*R*)-Salen-Co^{III}·(OAc) (0.5 mol %), distd H_2O (0.55 equiv), 0 °C, 14 h, (47% for **5a**, 43% for **5b**).

As part of our research programme aimed at developing enantioselective syntheses of naturally occurring amino-alcohols,[14] we recently developed the asymmetric synthesis of β-hydroxyornithine using Sharpless asymmetric dihydroxylation and cyclic sulfite chemistry.[15] In continuation, we herein report a new and feasible route to 4-hydroxyornithines **1a**–**b** using Jacobsen's hydrolytic kinetic resolution (HKR) as the key step.

As illustrated in Scheme 1, racemic benzyl glycidol **5** was subjected to Jacobsen's HKR[16a] using (*R*,*R*)-Salen-Co^{III}·OAc as the catalyst to give (*S*)-benzyl glycidol **5a** as a single enantiomer {$[\alpha]_D^{25}$ +8.63 (*c* 0.40, EtOH)}, {lit.[16b] $[\alpha]_D^{25}$ +7.82 (*c* 0.40, EtOH)}, which was easily isolated from the more polar diol **5b** by distillation.

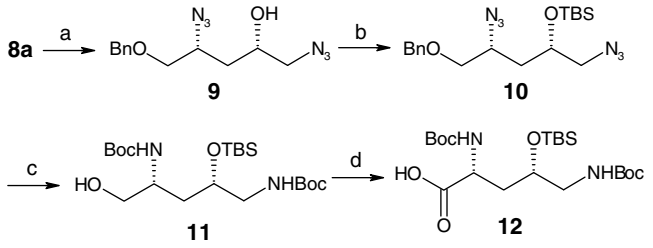
With enantiomerically pure epoxide **5a** in hand our next aim was to construct the *syn*-1,3-amino-alcohol. To establish the second stereogenic centre with the required stereochemistry, it was thought worthwhile to examine stereoselective epoxidation of a homoallylic azide (Scheme 2). Thus, (*S*)-benzyl glycidol **5a** was treated with vinylmagnesium bromide in the presence of CuI to give the homoallylic alcohol **6** in 88% yield. Compound **6** was then converted into its *O*-mesyl derivative, which on treatment with sodium azide in dry DMF furnished azide **7** with the desired inverted stereochemistry. Compound **7** was then subjected to *m*-CPBA epoxidation, and epoxide **8** thus obtained was found to be a mixture of two diastereomers in almost equal amounts (*syn*:*anti*/1:1.18).[17] In order to improve the diastereoselectivity, we attempted the HKR method as depicted in Scheme 2. Thus HKR was performed on **8** with the (*S*,*S*)-Salen Co^{III}·OAc complex (Fig. 2) (0.5 mol %) and water (0.55 equiv) in THF (0.55 equiv) to afford epoxide **8a** as a single diastereoisomer (as determined from ^1H and ^{13}C NMR spectral analyses)[18] in 41% yield and diol **8b** in 43% yield.



(*S*,*S*)-Salen Co(III).OAc complex

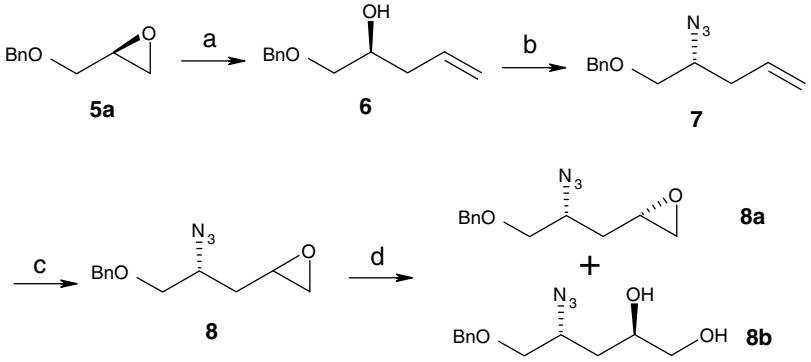
Fig. 2.

The ring opening of epoxide **8a** was carried out with NaN_3 to give the diazido alcohol **9** in 92% yield (Scheme 3). Hydroxyl protection of **9** with *tert*-butyldimethylsilyl chloride and imidazole in the presence of a catalytic amount of DMAP afforded the silyl ether **10** in 97% yield. Concomitant one-pot deprotection of benzyl group, reduction of both the azide groups and Boc protection of the resulting diamine were carried out with $H_2/Pd(OH)_2$, Boc_2O to give alcohol **11** in 86% yield. Finally, amino-alcohol **11** was oxidized with TEMPO/NaOCl/$NaClO_2$ to furnish the desired protected amino acid **12**[19] in excellent yield.



Scheme 3. Reagents and conditions: (a) NaN_3, NH_4Cl, DMF, 50 °C, 14 h, 92%; (b) TBS–Cl (TBS = *tert*-butyldimethylsilyl), imidazole, DMAP, CH_2Cl_2, 0 °C–rt, 4 h, 97%; (c) 20% $Pd(OH)_2/C$, H_2, Boc_2O, EtOAc, 12 h, 86%; (d) TEMPO, NaOCl, $NaClO_2$, CH_3CN, 82%.

In conclusion, we have developed a short approach to protected (2*S*,4*R*)-4-hydroxyornithine in high enantio-



Scheme 2. Reagents and conditions: (a) vinylmagnesium bromide, CuI, THF, −20 °C, 12 h, 88%; (b) (i) MsCl, Et_3N, DMAP, 0 °C–rt, 1.5 h; (ii) NaN_3, DMF, 70 °C, 9 h, 91%; (c) *m*-CPBA, CH_2Cl_2, 0 °C–rt, 10 h, 96%, ds, *syn*:*anti*/1:1.18; (d) (*S*,*S*)-Salen Co^{III}·OAc (0.5 mol %), distd H_2O (0.55 equiv), THF, 0 °C, 14 h (41% for **9a**, 43% for **9b**).

and diastereomeric excess using Jacobsen's HKR as the key step. The *syn*- and *anti*-configuration of the 1,3-amino-alcohol moiety can be manipulated simply by changing the Jacobsen's catalyst in the hydrolytic kinetic resolution step. The target compound **12** has been synthesized from **5** in 9 steps and in 9.3% overall yield. The synthetic strategy described here has significant potential for stereochemical variations and further extension to other stereoisomers, and analogues, for example (2*S*,4*S*,6*R*)-4-hydroxy-5-phenylsulfinyl-norvaline **4**. Currently, studies are in progress in this direction.

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17. The diastereoselectivity was determined from ^{1}H and ^{13}C NMR spectral data.
18. Spectral data of compound **8a**: Pale yellow liquid, $[\alpha]_D^{25}$ +49 (*c* 1.00, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu} = 2922, 2115, 1601, 1453, 1272\ cm^{-1}$. ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.48–1.61 (m, 1H), 1.75–1.89 (m, 1H), 2.53 (dd, $J = 2.78, 5.05$ Hz, 1H), 2.84 (t, $J = 4.04$ Hz, 1H), 3.02–3.11 (m, 1H), 3.53 (dd, $J = 7.07, 9.85$ Hz, 1H), 3.66 (dd, $J = 3.91, 6.31$ Hz, 1H), 3.75–3.88 (m, 1H), 4.59 (s, 2H), 7.30–7.38 (m, 5H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 34.3, 47.2, 49.2, 59.4, 72.6, 73.2, 127.4, 127.7, 128.3, 137.6 ppm. Anal. Calcd for $C_{12}H_{15}N_3O_2$: C, 61.7; H, 6.48; N, 18.01. Found: C, 61.58; H, 6.67; N, 17.69.
19. Spectral data of compound **12**: $[\alpha]_D^{25}$ +38 (*c* 0.50, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu} = 3346, 2910, 1716, 1453\ cm^{-1}$. ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 0.08 (s, 6H), 0.88 (s, 9H), 1.45 (s, 18H), 1.75–1.82 (m, 2H), 2.62–2.89 (m, 1H), 3.61–3.81 (m, 1H), 3.98–4.38 (m, 2H), 4.31–4.62 (m, 1H), 5.49–5.74 (m, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ_C −5.1, −4.7 14.1, 18.0, 22.7, 28.3, 31.9, 42.5, 65.2, 66.3, 80.4, 163.3 ppm. Anal. Calcd for $C_{21}H_{42}N_2O_7Si$: C, 54.52; H, 9.15; N, 6.05%. Found: C, 54.25; H, 9.37; N, 5.75%.