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Enantioselective synthesis of (2*R*,3*R*)- and (2*S*,3*S*)-β-hydroxyornithine☆

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Abstract—An efficient and short synthesis of (2*R*,3*R*)- and (2*S*,3*S*)-β-hydroxyornithine **1a**–**b** is described using Sharpless asymmetric dihydroxylation and regioselective nucleophilic opening of a cyclic sulfite as the key steps.

β-Hydroxyornithines **1a**–**b** serve as intermediates in the synthesis of important natural products like β-lactams and amino polyols[1] and as biosynthetic precursors to both the β-lactamase inhibitor clavulanic acid **2** and the anticancer agent, acivicin **3**.[2] Proclavaminic acid **4** has been recognized as the biosynthetic precursor of clavulanic acid **2**, a potent inhibitor of bacterial β-lactamase (Fig. 1). Various methods for the synthesis of β-hydroxyornithine in its different stereoisomeric forms, mainly based on auxiliary supported or chiral pool approaches, have been documented in the literature.[3]

Very recently, Williams et al. reported the asymmetric synthesis of β-hydroxyornithines **1a**–**b** via an aldol reaction with a chiral oxazinone.[4]

As part of our research program aimed at developing enantioselective syntheses of naturally occurring amino alcohols and lactones,[5] the Sharpless asymmetric dihydroxylation and subsequent transformation of the diol formed via a cyclic sulfite/sulfate were envisioned as powerful tools offering considerable opportunities for synthetic manipulations. Herein, we report a new

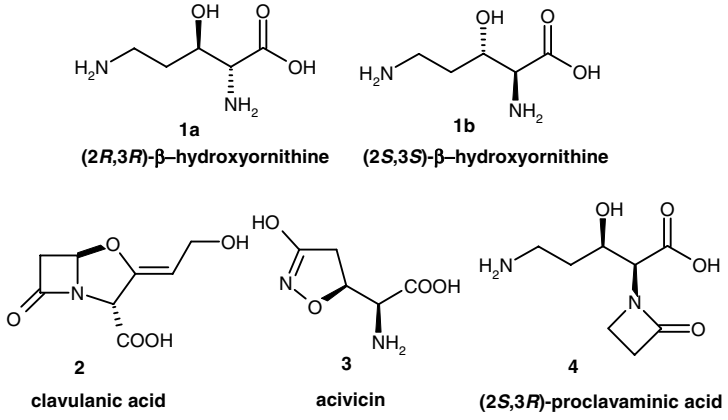

Figure 1.

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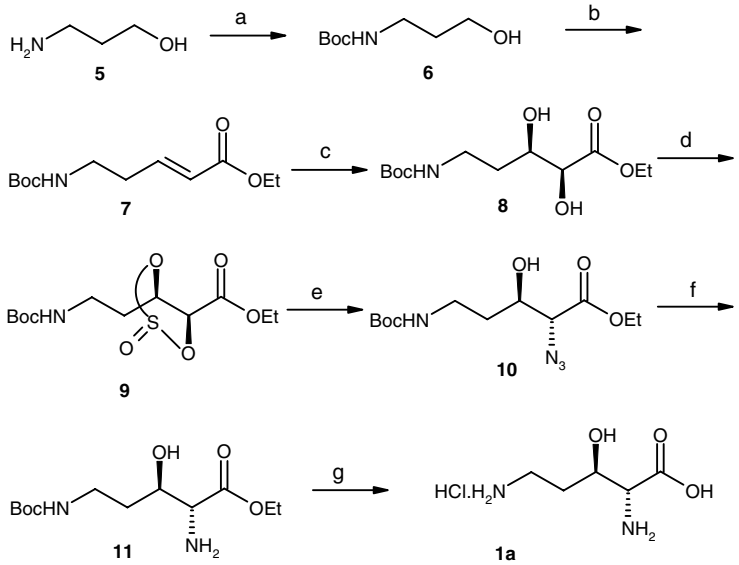

Scheme 1. Reagents and conditions: (a) Boc_2O, NaOH, 1,4-dioxane, H_2O, 0 °C–rt; then $KHSO_4$, 3 h, 94%; (b) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to −60 °C, 2 h; (ii) $Ph_3P{=}CHCOOEt$, dry THF, rt, 24 h, 88%; (c) $(DHQD)_2PHAL$, OsO_4, $CH_3SO_2NH_2$, K_3FeCN_6, K_2CO_3, *t*-BuOH–H_2O (1:1), 24 h, 0 °C, 95%; (d) $SOCl_2$, Et_3N, 30 min, 97%; (e) NaN_3, dry DMF, 60 °C, 20 h, 93%; (f) 10% Pd–C, H_2, EtOAc, rt, 98%; (g) 6 N HCl, reflux, 6 h, 88%.

and short synthesis of β-hydroxyornithines **1a**–**b** by employing cyclic sulfite methodology and Sharpless asymmetric dihydroxylation as the source of chirality.

The synthesis of β-hydroxyornithine **1a** started from the commercially available 3-aminopropanol **5**, as illustrated in Scheme 1. Amino group protection of **5** with $(Boc)_2O$ led to compound **6** in 94% yield, which was oxidized to the aldehyde under Swern conditions[6] and subsequently treated with (ethoxycarbonylmethylene)triphenylphosphorane in dry THF to furnish the Wittig product **7** in 88% yield. Subsequent treatment of olefin **7** with osmium tetroxide and potassium ferricyanide as co-oxidant, in the presence of $(DHQD)_2PHAL$ under Sharpless asymmetric conditions,[7] gave diol **8** in 95% yield with 98% ee.[8] Diol **8** was then treated with thionyl chloride and Et_3N to give the cyclic sulfite **9** in 97% yield. The synthetic strategy shown in Scheme 1 was based on the presumption that the nucleophilic opening of cyclic sulfite **9** would occur in a regiospecific manner at the α-carbon atom. Indeed, the cyclic sulfite reacted with NaN_3 with apparent complete selectivity for attack at C-2 to furnish azido alcohol **10**[9] in 93% yield. The carbonyl group must be responsible for the increased reactivity of the α-position.[10] Hydrogenation of azido alcohol **10** with 10% Pd–C led to amino alcohol **11** in 98% yield. Finally, concomitant deprotection of the Boc group and ester hydrolysis were carried out with 6 N HCl to furnish **1a** in excellent yield; $[\alpha]_D^{25}$ −21.32 (*c* 0.47, 6 N HCl), {lit.[4] $[\alpha]_D^{25}$ −20.20 (*c* 0.47, 6 N HCl)}. The physical and spectroscopic data were in full agreement with the literature.[4]

In a similar way, (2*S*,3*S*)-β-hydroxyornithine **1b** was synthesized using $(DHQ)_2PHAL$ in the Sharpless asymmetric dihydroxylation step and following a series of reactions analogous to those shown in Scheme 1.

In conclusion, a practical, short and highly enantioselective synthesis of (2*R*,3*R*)- and (2*S*,3*S*)-β-hydroxyornithine has been achieved by employing Sharpless asymmetric dihydroxylation and cyclic sulfite methodology as the key steps. The merits of this synthesis are high enantioselectivity with high yielding reaction steps. The synthetic strategy described has significant potential for further extension to other stereoisomers via double inversion at the α-carbon. Currently, work is in progress in this direction.

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8. For the measurement of the enantiomeric excess, diol **8** was converted into its dibenzoate. The enantiomeric purity of the dibenzoate was estimated to be 98% by chiral HPLC analysis using Cyclobond I beta 25 cm, 4.6 mm, HPLC-Cartridge (R.R.-Whelk-01), MeOH–H_2O, wavelength 254 nm, 1.0 mL/min. Spectral data of compound **8**: white solid, mp 178 °C, $[\alpha]_D^{25}$ +15.89 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3340, 2972, 1751, 1681, 1524, 1214 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, $J = 7.1$ Hz, 3H), 1.45 (s, 9H), 1.59–1.95 (m, 2H), 2.92 (br s, 2H), 3.11–3.27 (m, 1H), 3.37–3.51 (m, 1H), 4.01 (dt, $J = 10.1$, 3.5 Hz, 1H), 4.07 (d, $J = 2.4$ Hz, 1H) 4.29 (q, $J = 7.2$ Hz, 2H), 4.83 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 28.2, 33.8, 37.1, 61.7, 69.8, 73.7, 79.4, 156.8, 173.1, Anal. Calcd for $C_{12}H_{23}NO_6$ (277.31): C, 51.97; H, 8.36; N, 5.05. Found: C, 51.89; H, 8.33; N, 5.08.
9. Spectral data of compound **10**: $[\alpha]_D^{25}$ +8.27 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3389, 2980, 2109, 1689, 1520, 1253 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.33 (t, $J = 7.2$ Hz, 3H), 1.44 (s, 9H), 1.59–1.85 (m, 2H), 3.10–3.24 (m, 1H), 3.46 (br s, 1H), 3.77 (d, $J = 3.1$ Hz, 1H), 3.95–4.06 (m, 1H), 4.15 (dt, $J = 10.4$, 3.2 Hz, 1H), 4.28 (q, $J = 7.2$ Hz, 2H), 4.86 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 28.1, 34.3, 36.6, 61.8, 65.8, 69.4, 79.5, 156.9, 169.1, Anal. Calcd for $C_{12}H_{22}N_4O_5$ (302.33): C, 47.67; H, 7.33; N, 18.53. Found: 47.70; H, 7.35; N, 18.51.
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