An Alternative Synthesis of N^5-Acetyl-N^5-hydroxy-L-ornithine from L-Ornithine

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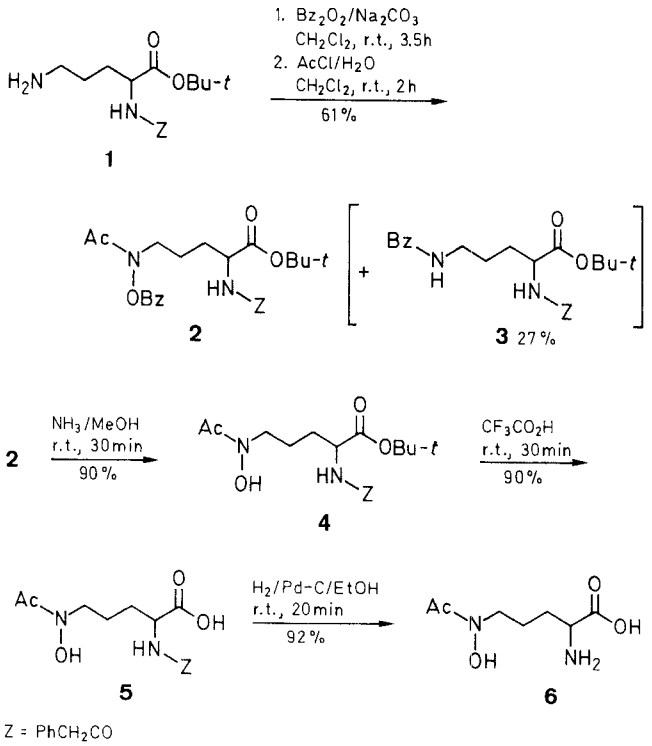
N^5-Acetyl-N^5-hydroxy-L-ornithine is obtained from L-ornithine in 20% overall yield via oxidation of the ω-amino group in N^2-benzyloxycarbonyl-L-ornithine *tert*-butyl ester with dibenzoyl peroxide and subsequent N^5-acetylation.

N^5-Hydroxy-L-ornithine is a naturally occuring ω-hydroxyamino acid, a constituent of some chelating agents of low molecular weight (siderophores):[1,2,3] ferrichromes, fusarinines, pyoverdines, fusigen, and antibiotics such as albomycins,[4] and vanoxonin.[5] In general, N^5-hydroxy-L-ornithine exists as its N^5-acetyl derivative **6**. Several syntheses of the amino acid **6** have been reported, most of them starting from glutamic acid.[2,6-12] All these methods are multi-step procedures which afford the final product in low yields. We now describe, as a new method, the conversion of L-ornithine into compound **6** via the direct oxidation of N^2-benzyloxycarbonyl-L-ornithine *tert*-butyl ester (**1**).



tert-Butyl ester **1** was oxidized with dibenzoyl peroxide in the presence of sodium carbonate. The products were not isolated but *in situ* acetylated with acetyl chloride under Schotten–Baumann conditions. The separation of the undesired side product, benzamide **3**, from the hydroxamic acid *O*-benzoyl derivative **2** was accomplished by chromatography on silica gel. Ester **2** was easily transformed into N^5-acetyl-N^2-benzyloxycarbonyl-N^5-hydroxyornithine *tert*-butyl ester **(4)** by treatment with 10% ammonia in methanol. The two protective groups, i.e., the *tert*-butyl group of the ester and the *N*-benzyloxycarbonyl group, were removed by consecutive acidolysis with trifluoroacetic acid and hydrogenolysis with elemental hydrogen in the presence of Pd-C to give compound **6**; selective deprotection of **4** affords useful synthons for siderophore synthesis.

All reagents were of commercial quality and were taken from freshly opened containers. Benzoyl peroxide was purified by crystalization from $CHCl_3$/MeOH (1:2). Analytical TLC plates (silica gel 60) and silica gel (< 200 mesh, 70–270 mesh) were purchased from Merck. Melting points are uncorrected. Microanalyses were obtained using a Perkin-Elmer 240 element analyser and optical rotations were measured using a Polamat A (Carl-Zeiss Jena) polarimeter. Mass spectra were obtained using a Varian MAT-711 spectrometer with either EI (70 eV) or FD ionization. ^{1}H-NMR spectra were recorded on a Varian 360 (60 MHz) spectrometer or (for the end product) on a Bruker (500 MHz) spectrometer.

N^2-Benzyloxycarbonyl-L-ornithine *tert*-Butyl Ester (1):[13]

N^2-Benzyloxycarbonyl-L-ornithine is prepared from L-ornithine (13.4 g, 0.1 mol) analogously to N^2-benzyloxycarbonyl-L-lysine;[14] yield: 18.5 g (70%); mp 206–208°C; $[\alpha]_D^{15}$ −7° (*c* = 2, 5N aqueous HCl) [Lit.[15] mp 209–210°C; $[\alpha]_D^{25}$ −8.5° (*c* = 1, 5N aq HCl)].

N^2-Benzyloxycarbonyl-L-ornithine tert-Butyl Ester **(1)**: A solution of N^2-benzyloxycarbonyl-L-ornithine (2.75 g, 10 mmol), *tert*-butyl acetate (150 mL, 1.25 mol), and 72% aq $HClO_4$ (1.5 mL, 11 mmol) is stirred for 4–5 days at r.t. The mixture is then cooled to 0°C and extracted with 0.5 N aq HCl (4 × 25 mL). The aqueous solution is neutralized with Na_2CO_3 to pH 8 and extracted with Et_2O (3 × 125 mL). The organic extract is dried ($MgSO_4$) and the solvent is removed under reduced pressure to give product **1** as a colorless oil; yield: 1.9 g (59%); $[\alpha]_D^{20}$ −6.5° (*c* = 8, acetone).

$C_{17}H_{26}N_2O_4$	calc.	C 63.35	H 8.07	N 8.70
(322.4)	found	63.11	8.19	8.59

^{1}H-NMR (CCl_4/TMS: δ = 1.4 [s, 9H, $C(CH_3)_3$], 1.4–1.95 (m, 4H, CH_2CH_2), 2.9 (m, 2H, CH_2NH), 3.9–4.1 (m, 1H, CHNH), 5 (s, 2H, CH_2Ph), 6.4 (m, 3H, NH), 7.25 (s, 5H_{arom}).

N^5-Acetyl-N^5-benzoyloxy-N^2-benzyloxycarbonyl-L-ornithine *tert*-Butyl Ester (2) [and N^5-Benzoyl-N^2-benzyloxycarbonyl-L-ornithine *tert*-Butyl Ester (3)]:

A solution of N^2-benzyloxycarbonyl-L-ornithine *tert*-butyl ester (**1**; 770 mg, 2.4 mmol) in CH_2Cl_2 (5 mL) is added dropwise to a vigorously stirred mixture of dibenzoyl peroxide (580 mg, 2.4 mmol) and Na_2CO_3 (760 mg, 7.2 mmol) in CH_2Cl_2 (10 mL) and stirring is continued for 3.5 h at r.t. The mixture is then diluted

with H_2O (10 mL) and CH_2Cl_2 (20 mL), and AcCl (0.15 mL, 2.5 mmol) is added dropwise. After 2 h, the organic layer is separated and washed with H_2O (2 × 15 mL), 1 N citric acid (2 × 20 mL), and H_2O (2 × 15 mL), and dried ($MgSO_4$). The solvent is removed under reduced pressure and the remaining mixture of products **2** and **3** is separated by column chromatography on silica gel (Merck < 200 mesh) using benzene as eluent.

Product **2** is obtained as a colorless oil; yield: 700 mg (61%); $[\alpha]_D^{20}$ + 3° (*c* = 6, CCl_4).

$C_{26}H_{32}N_2O_7$	calc.	C 64.45	H 6.66	N 5.87
(484.5)	found	64.10	6.70	5.89

MS (EI): *m/z* = 428 (0.5%), 384 (1), 306 (10), 190 (18) 105 (100).

MS (FD): *m/z* = 485 (M + 1), 484 (M).

^{1}H-NMR (CCl_4/TMS): δ = 1.35 [s, 9H, $C(CH_3)_3$], 1.45–1.9 (m, 4H, CH_2CH_2), 1.9 (s, 3H, CH_3CO), 3.7 (m, 2H, CH_2NH), 3.9–4.2 (m, 1H, CH), 4.9 (s, 2H, CH_2Ph), 5.5 (d, 1H, NH), 7.2 (s, 5H_{arom}), 7.3–7.6 (m, 2H, PhCO), 7.85–8.1 (m, 3H, PhCO).

Product **3**; yield: 270 mg (27%).

$C_{24}H_{30}N_2O_5$	calc.	C 67.59	H 7.09	N 6.57
(426.5)	found	67.21	6.98	6.72

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.4 [s, 9H, $C(CH_3)_3$], 1.7 (m, 4H, CH_2CH_2), 3.4 (q, 2H, CH_2NH), 4–4.4 (m, 1H, CHCO), 5 (s, 2H, CH_2Ph), 5.5 (d, 1H, NH), 6.7 (m, 1H, NH), 7.3 (s, 5H_{arom}), 7.2–7.5 (m, 2H, PhCO), 7.7–7.9 (m, 3H, PhCO).

N^5-Acetyl-N^2-benzyloxycarbonyl-N^5-hydroxy-L-ornithine *tert*-Butyl Ester (4):

Compound **2** (600 mg, 1.24 mmol) is added to a 10% solution of NH_3 in MeOH (3 mL). After 30 min, the solvent is removed under reduced pressure. The yellow oily product **4** is purified by column chromatography on silica gel, (Merck, 70–270 mesh) using $CHCl_3$ as eluent; yield: 440 mg (90%); $[\alpha]_D^{22}$ + 12.5° (*c* = 2.5, $CHCl_3$).

$C_{19}H_{28}N_2O_6$	calc.	C 59.99	H 7.42	N 7.36
(380.4)	found	59.81	7.56	7.56

MS (EI): *m/z* = 306 (8%), 190 (15), 105 (92), 91 (100).

^{1}H-NMR ($CDCl_3$): δ = 1.4 [s, 9H, $C(CH_3)_3$], 1.65 (m, 4H, CH_2CH_2), 2 (s, 3H, CH_3CO), 3.55 (m, 2H, CH_2NH), 4.1 (m, 1H, CHN), 5 (s, 2H, CHPh), 5.6 (d, 1H, NH), 7.2 (s, 5H_{arom}).

N^5-Acetyl-N^2-benzyloxycarbonyl-N^5-hydroxy-L-ornithine (5):

A solution of ester **4** (230 mg, 0.6 mmol) in CF_3CO_2H (1 mL) is stirred for 30 min. The solvent is then removed under reduced pressure and the oily product **5** is washed with cold Et_2O (2 × 2 mL); yield: 170 mg (90%).

$C_{15}H_{20}N_2O_6$	calc.	C 55.56	H 6.21	N 8.64
(324.3)	found	55.71	6.30	8.52

MS (EI): *m/z* = 280 (12.1%), 204 (3.3), 128 (3.5), 107 (3), 91 (100).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.4–1.85 (m, 4H, CH_2CH_2), 2 (s, 3H, CH_3CO), 3.4–3.7 (m, 2H, CH_2N), 4.1–4.3 (m, 1H, CHNH), 5 (s, 2H, CH_2Ph), 6–6.2 (m, 1H, NH), 6.6 (m, OH), 7.2 (s, 5H_{arom}).

N^5-Acetyl-N^5-hydroxy-L-ornithine (6):

Hydrogen is passed through a mixture of compound **5** (130 mg, 0.4 mmol) and 5% Pd-C (50 mg) in EtOH (10 mL) at r.t. After 20 min, the catalyst is filtered off and the solvent is removed under reduced pressure. The dried compound is crystallized from H_2O/EtOH to afford the pure product **6**, which gives positive ninhydrin and ferric chloride tests; yield: 74 mg (92%); mp 198–199°C (dec); $[\alpha]_D^{22}$ + 1.03° (*c* = 5.2, H_2O); $[\alpha]_D^{22}$ + 20.8° (*c* = 0.5, 1 N aqueous HCl) [Lit.[11] mp 204°C (EtOH/Et_2O), Lit.[16] mp 194–197°C (H_2O/EtOH); Lit.[11] $[\alpha]_D^{20}$ + 21.26° (*c* = 0.5, 1 N aqueous HCl)]; TLC data: R_F 0.56 (Py:H_2O = 8:2); R_F 0.3 (BuOH:AcOH:H_2O:Py = 15:3:12:10); R_F 0.3 (BuOH:AcOH:H_2O = 4:1:1).

$C_7H_{14}N_2O_4$	calc.	c 44.20	H 7.42	N 14.73
(190.2)	found	44.48	7.35	14.68

MS (FD): *m/z* = 191 (M + 1).

^{1}H-NMR (500 MHz, D_2O/TMS_{ext}): δ = 1.53–1.67 (m, 4H, CH_2CH_2), 2.00 (s, 3H, CH_3CO), 3.20 (m, 1H, CHN), 3.53 (m, 2H, CH_2N). [Lit.[11] ^{1}H-NMR (250 MHz, D_2O/TMS_{ext}): δ = 1.61–1.93 (m, 4H, CH_2CH_2), 2.12 (s, 3H, CH_3CO), 3.65 (m, 2H, CH_2N), 3.73 (m, 1H, CHN)].

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