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CONSTITUENTS OF MICROBIAL IRON CHELATORS. THE SYNTHESIS OF OPTICALLY ACTIVE DERIVATIVES OF δ-N-HYDROXY-L-ORNITHINE.

by

Byung Hyun Lee and Marvin J. Miller*‡
Department of Chemistry
University of Notre Dame
Notre Dame, IN 46556

δ-N-Hydroxy-L-ornithine derivatives were synthesized from L-glutamic acid by reduction of the γ-acid chloride to the aldehyde, formation of the substituted oxime, and reductive acylation.

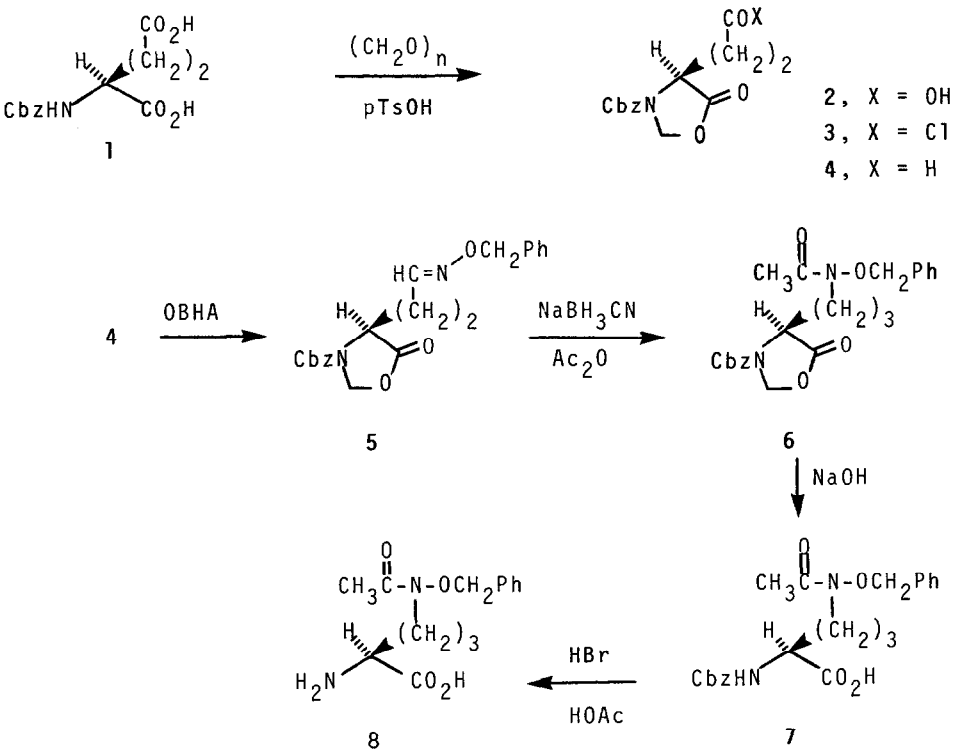
The development of essential roles of iron in physiological systems has required the microbial evolution of efficient iron chelators. Many of these siderophores utilize hydroxamate containing amino acids and peptides for ferric ion chelation.[1] The most common hydroxamates are derived from ω-N-acetyl-ω-N-hydroxy ornithine and lysine. Although several syntheses of these modified amino acids have been reported,[2] most approaches are either low yielding or require a resolution to obtain the desired L-amino acids. One of our goals has been to prepare chiral derivatives of δ-N-hydroxyornithine and ε-N-hydroxylysine from other readily available, optically pure amino acids. Without homologation, the only two common amino acids which are logical precursors of δ-N-hydroxy-ornithine are L-glutamic acid and ornithine itself. This paper describes the synthesis of several derivatives of δ-N-acetyl-δ-N-hydroxy-L-ornithine from L-glutamic acid (Scheme 1).

The α-amino and carboxyl groups of L-glutamic acid were first protected by reaction of L-Cbz-glutamic acid **1**[3] with paraformaldehyde and a catalytic amount of pTsOH in toluene with azeotropic removal of H_2O to provide 2 in 85% yield.[4,5] Refluxing acid **2** with excess $SOCl_2$ for 20 min provided the acid chloride **3**[5,6] in 78% yield after recrystallization from ethyl acetate - hexanes. The aldehyde **4**[5] was obtained in 55-85% yield by reduction of 3 with either $(nBu)_3SnH$[7] (ethyl acetate, room temperature, 24 h) or with $Li(O^tBu)_3AlH$[8] (THF, -78°C, 1h, then warmed to room temperature over 1 h, followed by an ice water quench and extractive workup). The latter procedure was preferred since it required no chromatographic purification. Reaction of **4** with O-benzylhydroxylamine[3] in CH_3OH - H_2O (7:3) at pH 5 for 1h provided the oxime **5**[5] in 82% yield. The oxime was reduced with $NaBH_3CN$[9] (100 mole %) in acetic acid containing acetic anhydride (200 mole %) at room temperature for 1 h to provide the desired δ-N-acetyl-δ-N-benzyloxy-L-

ornithine 6[5] in 70% yield.[10] Saponification of derivative 6 with 1N NaOH in THF for 20 min at room temperature gave the acid 7[5] in 92% yield. Removal of the Cbz group in the presence of the O-benzylhydroxamate was accomplished by reaction of 7 with HBr in acetic acid[11] (2h, room temperature), followed by solvent evaporation and liberation of the free acid 8[5] from the HBr salt by chromatography on Dowex X-8 (H^+) with H_2O, 2% pyridine, 2% NH_3, successively. The optical rotation of 8 was identical to that reported earlier.[12] This indicates that compound 8 and its precursors 2-7 were prepared without racemization.

The homologous ω-N-hydroxy-lysine derivatives should be able to be prepared in the same manner starting with L-α-amino adipic acid. These compounds, as well as 6, 7, and 8, are useful intermediates for synthesis of peptide based microbial iron chelators[1] and analogs of potential utility for iron chelation therapy. Incorporation of these amino acids in such syntheses will be described subsequently.

Scheme 1



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5. A partial list of characterization data for compounds **2-8** includes: **2**, colorless oil; ^{1}HNMR ($CDCl_3$/acetone-d_6, 90 MHz) δ 2.1-2.6 (m, 4H), 4.2-4.5 (m, 1H), 5.10 (m, 3H), 5.50 (d, 1H), 7.37 (s, 5H), 8.9 (br s, CO_2H); IR (neat) 1810, 1730-1680 cm^{-1}; ms (EI) m/e 293 (M^+); $[\alpha]_D^{25}$ = +73° (C=2.35, CH_3OH). **3**, mp 76-78°C; ^{1}HNMR ($CDCl_3$) δ 2.1-2.4 (m, 2H), 3.07 (t, 2H), 4.33 (t, 1H), 5.20 (m, 3H), 5.53 (d, 1H), 7.43 (s, 5H); IR (KBr) 1800, 1720, 1700 cm^{-1}; $[\alpha]_D^{25}$ = +93° (c=1.56, $CHCl_3$). **4** colorless oil; ^{1}HNMR ($CDCl_3$) δ 2.0-2.8 (m, 4H), 4.38 (t, 1H), 5.20 (m, 3H), 5.52 (d, 1H), 7.40 (s, 5H) 9.75 (s, 1H); IR (neat) 1800, 1700-1715 cm^{-1}. **5** colorless oil; ^{1}HNMR ($CDCl_3$) δ 2.0-2.6 (m, 4H), 4.2-4.4 (m, 1H), 5.0-5.2 (m, 5H), 5.47 (d, 1H), 5.0 and 6.67 (each tr, total 1H) 7.40 (d, 10H); IR (neat) 1800, 1715 cm^{-1}; ms (EI), m/e 291 (M-91); $[\alpha]_D^{25}$ = +85° (C=1.95, CH_3OH). **6** colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.3-2.1 (m, 4H), 2.03 (s, 3H), 3.65 (t, 2H), 4.3 (t, 1H), 4.78 (s, 2H), 5.15 (s, 2H), 5.18 (d, 1H), 5.50 (d, 1H), 7.38 (s, 10H); IR (neat) 1800, 1710, 1650 cm^{-1}; ms (EI), m/e 383 (M-CH_3CO); $[\alpha]_D^{25}$ = +58° (C=2.35, CH_3OH). **7** colorless oil; ^{1}HNMR ($CDCl_3$) δ 1.4-2.0 (m, 4H), 2.05 (s, 3H), 3.65 (t, 2H), 4.2-4.5 (m, 1H), 4.75 (s, 2H), 5.07 (s, 2H), 5.78 (d, NH), 7.35 (s, 5H), 7.40 (s, 5H),

10.47 (CO_2H). The dicyclohexylammonium salt of 7 was recrystallized from $CHCl_3$-hexanes: mp 131-133°C; IR ($CHCl_3$) 1700, 1620-1660 cm^{-1}; $[\alpha]_D$ = +8.4° (C=2.8, CH_3OH). Anal. Calcd. for $C_{34}H_{49}N_3O_6$: C, 68.54; H, 8.29, N, 7.05. Found: C, 68.29; H, 8.46; N, 6.80. 8, mp 159-161°C (lit.[12] 161-163°C); $[\alpha]_D^{25}$ = +13.7° (C=1, 1N HCl, lit.[12], $[\alpha]_D^{23}$ = +13.9°); ^{1}HNMR (DMSO-d_6) δ 1.6 (m, 4H), 2.0 (s, 3H), 3.05 (m, 1H), 3.60 (m, 2H), 4.85 (s, 2H), 7.40 (m, 5H); IR (KBr) 1650 cm^{-1}.

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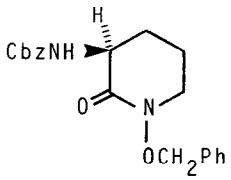
10. When this reaction was performed without acetic anhydride, the free O-benzylhydroxylamine was not obtained. Instead, apparently the lactam 9 formed by intramolecular acylation. Similar results were observed during attempted reduction of acid **10** → **11** with $NaBH_4$. In this case, only the lactone **12** was isolated.



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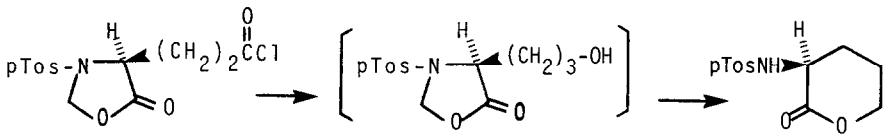

10 **11** **12**

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