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An Efficient Asymmetric Synthesis of L-α,ω–Diaminoalkanoic Acids

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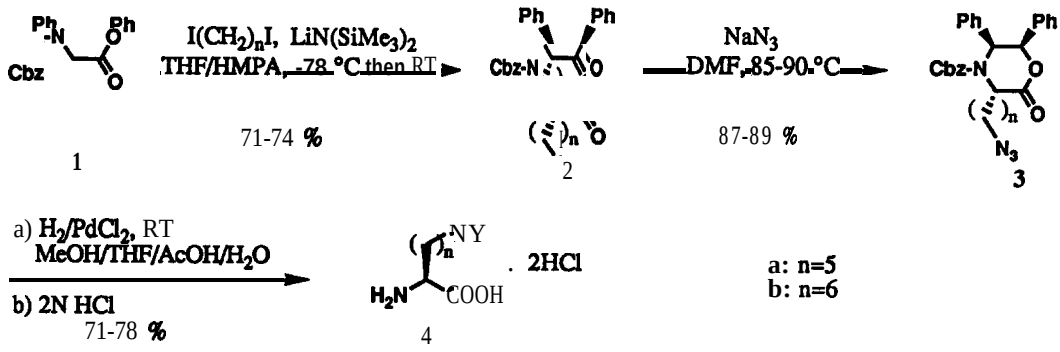
Abstract: Efficient asymmetric syntheses of L-2,7-diaminoheptanoic acid and L-2,8-diaminooctanoic acid are described.

2,7-Diaminoheptanoic acid (homolysine) is a nonproteinogenic amino acid and has been widely used in peptidomimetics and drug design. It has served as a precursor for the syntheses of various lysine derivatives in human renin inhibitors[1] and as a lysine replacement in cyclic enkephalin2 and in vasopressin analogues.3

As part of an ongoing project in this laboratory to develop highly potent and selective substrate analogue inhibitors of human tissue kallikrein,[4] we required optically pure L-homolysine and L-2,8-diaminooctanoic acid. In contrast to the lysine analogues with shorter side chains, the higher homologues am relatively inaccessible, especially in enantiomerically pure form. Almost all the synthetic methods developed in the last several decades produce racemic form of homolysine.5 The procedure yielding D-homolyslne from L-serine is lengthy and inconvenient[6]. In this communication efficient enantioselecdve syntheses of L-homolysine and L-2,8-diaminooctanoic acid are reported, providing a general 3-step approach to various optically pure α,ω-diaminoalkanoic acids.

The protocol is based on the principle advanced by Wiiams, in which the configuration at the a position of an a-amino acid is unambiguously built up by employing a proper diphenyloxazinone as a template.7 As shown in scheme I, the diastereoselective enolate alkylation of the commercially available diphenyloxaxinone 1 with diiodides afforded the alkylated oxaxinone 2 (n=5: m.p.=147-148 °C, n=6: m.p.=151-152 °C) in 71-74 % yield.7 Iodide 2 was then converted into axide 38 (n=5: m.p.=123-124 °C, n=6: m.p.=lOl-102 °C) in 87-89% by treatment with an excess of sodium axide in DMF at 85-90 °C for 15 h. The removal of the chiral-template and the reduction of the axide functional group in axide 3 were accomplished by hydrogenation (50 psi of H2. $PdCl_2$, MeOH/THF/AcOH/H_2O 4:4: 1: 1, RT. 24h). producing the desired L-homolysine 4a[9] and L-1,7-diaminooctanoic acid 4b[10] in 71-78% yield.11

Scheme I



1 2 3 4

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8. n=5: ^{1}H NMR (400 MHz, DMSO-d6, *385* K) δ 1.40-1.60 (6H, m), 2.10-2.16 (2H, dt, J=7.2 Hz, J=7.2 Hz), 3.31 (2H, t, J=6.8 Hz), 4.81 (1H, t, J=7.2 Hz). 4.92-5.08 (2H, m), 5.28 (1H, d, J=2.8 Hz), 6.22 (1H, d, J=3.2 Hz), 6.58 (2H, m), 7.06-7.26 (13H, m).
9. [α]$^{23}_D$=+14.4 (c=0.5, 1N HCl); m.p.=239-242 °C; R_f=0.35 (silica, MeOH/AcOH 20:3, visualizing with ninhydrin); ^{1}H NMR (400 MHz, D_2O) δ 1.31-1.33 (4H, m), 1.55 (2H, m), 1.82 (2H, m). 2.86 (2H, t, J=8.0 Hz), 3.89 (1H, t, J=6.4 Hz); Exact mass calculated for $C_7H_{17}N_2O_2$ (M-2HCl + 1) m/z 161.1290. found 161.1285.
10. [α]$^{23}_D$=+8.4 (c=0.5, 1N HCl); m.p.=252-256 °C (decomposed); R_f=0.39 (silica, MeOH/AcOH 20:3, visualizing with ninhydrin); ^{1}H NMR (400 MHz, D_2O) δ 1.19-1.26 (6H, m). 1.51 (2H, m), 1.78 (2H, m), 2.85 (2H, t, J=7.0 Hz), 3.87 (1H, t, J=4.8 Hz); Exact mass calculated for $C_8H_{19}N_2O_2$ (M - 2HCl + 1) m/z 175.1446, found 175.1447.
11. The purification of 4: a) ion-exchange chromatography on Bio-Rad AG 50W-X8, eluting with water and then 1N NH_4OH; b) treatment with 2N HCl; and c) recrystallization from ethanol/diethyl ether.

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