Direct Preparation of [N,C$^{\alpha}$]-Diprotected L-α-Aminoadipic Acid from L-Lysine

Jack E. Baldwin,* Paul Harrison, and John A. Murphy

Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford OX1 3QY, U.K.

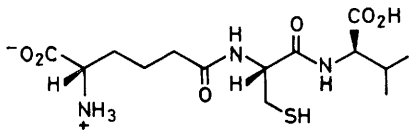
L-Lysine was converted into *N*-benzyloxycarbonyl-L-α-aminoadipic acid 1-benzyl ester by a short route which avoids the intermediacy of L-α-aminoadipic acid.

L-α-Aminoadipic acid is of crucial importance in biosynthetic studies on penicillin since it is a component of the LLD-ACV tripeptide (**1**), which has been shown to be a precursor of penicillin[1] and subsequently the cephalosporins.[2] Consequently there has been a demand for preparative methods for (**1**), and various congeners thereof[3] in relation to these studies. These methods have to date required the synthesis of L-α-aminoadipic acid and its conversion into [N,C$^{\alpha}$]-diprotected material for subsequent condensation at the δ-carboxy-group to form the tripeptide (**1**).

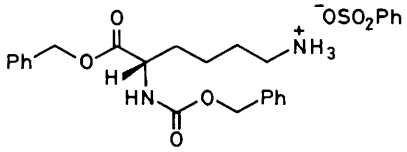
Many groups have sought an efficient method for producing L-α-aminoadipic acid.[4] We have found all the published routes too indirect. Moreover, the subsequent [N,C]-protection is very inefficient providing yields of only 40%.[3]

We now report a direct and efficient conversion of the readily available L-lysine into the required diprotected form of L-α-aminoadipic acid without the intermediacy of the free amino acid. Thus *N*-benzyloxycarbonyl-L-lysine α-benzyl ester benzenesulphonate (**2**), easily prepared from L-lysine,[5] was converted into the free amine by washing with sodium carbonate solution and then reacted with benzenediazonium tetrafluoroborate[6] in dimethylformamide to yield the triazene (**3**) as an orange oil† (83%) {δ ($CDCl_3$) 1.26—1.82 (m, 3CH_2), 3.50 (t, *J* 6.5 Hz, CH_2N), 4.42 (m, CO.CHN), 5.06 (s, ArCH_2), 5.10 (q, *J* 12.3 Hz, ArCH_2), 5.76 (d, *J* 8.7 Hz, NH), 7.05 (br.s, NH–N=N), and 7.27 (15H, m, ArH); ν ($CHCl_3$) 3440(N–H), 1740 (C=O), and 1407 (N=N) cm^{-1}; $[\alpha]_D^{20}$ −10.8° (*c* 1.28, acetone)}. This substance with 98% formic acid at room

† All new compounds reported here also gave satisfactory ^{13}C n.m.r. spectra, and mass spectra. High resolution mass measurement was satisfactory for the molecular ions of all compounds except (**3**). For (**3**) the molecular ion peak was observed but was too transient for high resolution measurement.



(1)



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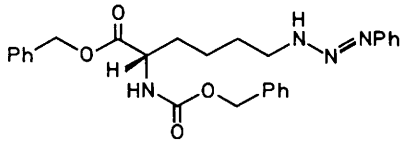
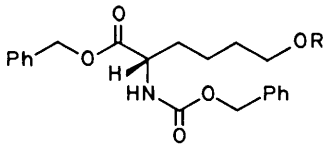
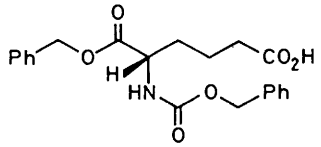


(3)



(4)



(5)

temperature yielded a mixture of the alcohol (**4**; R = H) (31%) {δ ($CDCl_3$) 1.25—1.85 (m, $3CH_2$), 3.55 (t, *J* 6.1 Hz, CH_2OH), 4.42 (m, CO.CHN), 5.09 (s, $ArCH_2$), 5.12 (q, *J* 12.0 Hz, $ArCH_2$), 5.42 (d, *J* 8.4 Hz, NH), and 7.34 (10H, m, ArH); ν ($CHCl_3$) 3620 and 3600—3200 (OH), 3430 (N–H), and 1720 (C=O) cm^{-1}, $[\alpha]_D^{20}$ −3.6° (*c* 2.5, $CHCl_3$)} and its formate ester (**4**; R=CHO) (22%) {δ ($CDCl_3$) 1.25—1.90 (m, $3CH_2$), 4.09 (t, *J* 6.8 Hz, CH_2O), 4.44 (m, CO.CHNH), 5.11(s, $ArCH_2$), 5.17(q, *J* 12.3 Hz, $ArCH_2$), 5.33 (d, *J* 8.2 HzNH), 7.31—7.40 (10H, m, ArH), and 8.00 (s, HCO); ν ($CHCl_3$) 3440 (N–H) and 1720(C=O) cm^{-1}, $[\alpha]_D^{20}$ −2.4° (*c* 2.72, $CHCl_3$)} which were separated by chromatography (silica gel, EtOAc, CH_2Cl_2). The formate was efficiently converted (99%) into the alcohol by reaction with sodium borohydride (methanol, reflux, 2 min) to give an overall yield of 53% of (**4**; R=H) from the triazene (**3**).

Finally, oxidation with potassium permanganate (benzene, water in the presence of tetra-n-butylammonium bisulphate) gave the required substance (**5**) [50% from (**4**; R=H)]. {δ [$(CD_3)_2CO$] 1.69—1.99 (m, $2CH_2$), 2.33 (t, *J* 6.8 Hz, CH_2CO_2H), 4.30 (m, CO.CHN), 5.08 (s, $ArCH_2$), 5.18 (s, $ArCH_2$), 6.78 (br.d, *J* 7.9 Hz, NH), and 7.28—7.39 (10H, m, ArH), ν ($CHCl_3$) 3440(N–H) and 1720 (C=O) cm^{-1}; m.p. 87—89 °C (lit.[3] 90—92 °C); $[\alpha]_D^{20}$ −13.3° (*c* 2, acetone) [lit.[3] −13.3°(*c* 2, acetone)]}.

Since this substance can now be converted into (**1**), or its analogues, in high yield,[3] we have effectively removed a bottleneck which has heretofore made access to such peptides a rather tedious and troublesome process.

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