Simple Syntheses of (*S*)-2- and 4-Amino-5-hydroxypentanoic Acids†

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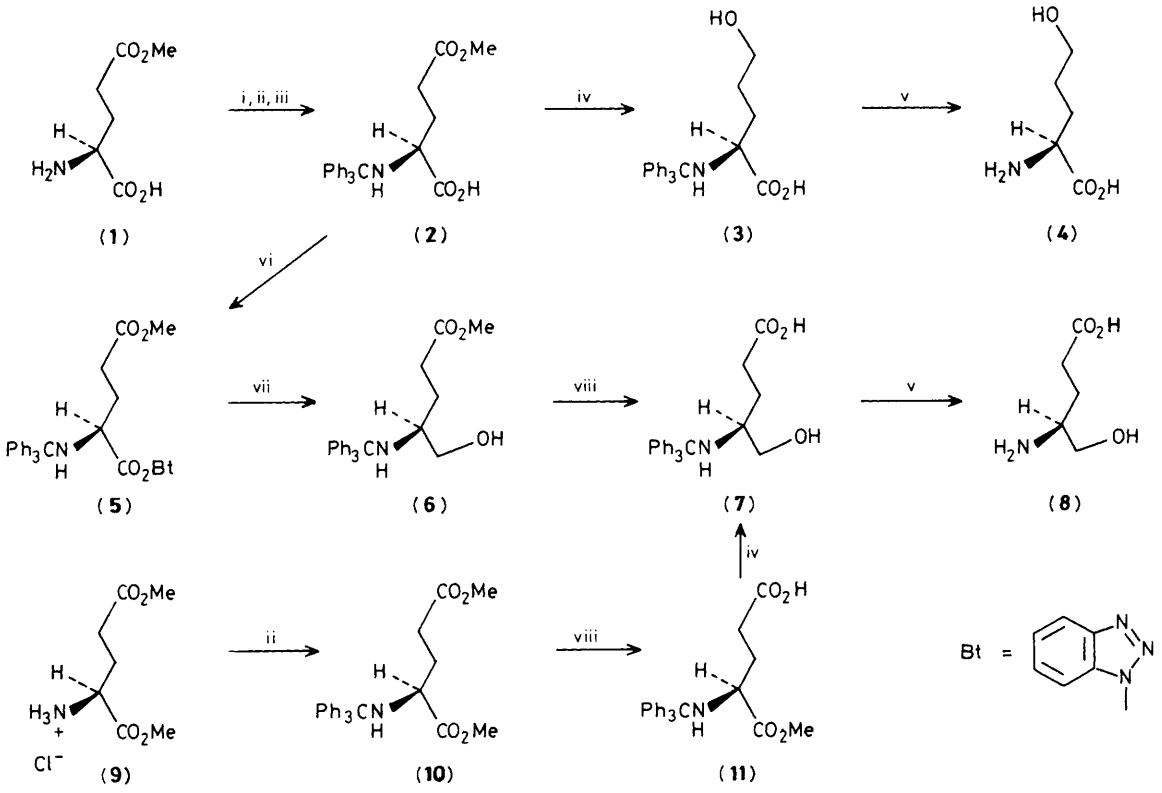
The title compounds were efficiently prepared by selective reductions of α- and γ-methyl (*S*)-*N*-tritylglutamates with $LiAlH_4$

(*S*)-2-Amino-5-hydroxypentanoic acid (L-δ-hydroxynorvaline) (**4**), the next higher homologue of homoserine, and (*S*)-4-amino-5-hydroxypentanoic acid (**8**) are competitive inhibitors of γ-cystathionase[1] and γ-aminobutyric acid aminotransferase,[2] respectively. Furthermore, the amino acid (**4**) acts as the biological precursor of the polyoxins (nucleoside peptide antibiotics), in which its whole carbon skeleton is found intact,[3] and it is also incorporated into the oxazolidine segment of clavulanic acid,[4] a potent inhibitor of bacterial β-lactamases.

Both compounds (**4**) and (**8**) have been prepared previously in low overall yields by rather lengthy and tedious or wasteful synthetic routes.[2a,5] We now report exceptionally simple syntheses which provide (**4**) and (**8**) in good overall yields and excellent purity from commercially available γ-methyl (*S*)-glutamate (**1**) or dimethyl (*S*)-glutamate hydrochloride (**9**). In all the synthetic transformations the bulky triphenylmethyl (trityl) group was chosen for α-amino protection for the following reasons: (a) it is easily introduced, and removed by mild acid treatment in excellent yields,[6] (b) it completely suppresses reduction of the α-carboxy function of amino acids by $LiAlH_4$,[7b] (c) it offers excellent racemisation resistance even in the case of strongly activated chiral amino acid derivatives,[8] and (d) in contrast to protecting groups of the urethane type,[7a] it is compatible with complex metal hydrides.[7b]

Our synthetic route to (**4**) initially involves the tritylation of (**1**) by the trimethylsilyl ester procedure.[6a] The product (**2**) obtained as the diethylammonium (DEA) salt {m.p. 155—156 °C, $[\alpha]_D^{25}$ +13.7° (*c* 1, MeOH)} in 95% yield, was further reduced as such with $LiAlH_4$ in tetrahydrofuran at 0 °C to afford *N*-trityl-δ-hydroxynorvaline (**3**), also isolated as the corresponding DEA salt {m.p. 134—135 °C, $[\alpha]_D^{25}$ −14.3° (*c* 2, MeOH)}, in 87% yield. The reduction proceeds absolutely selectively at the ester function as evidenced by the total

† All optically active amino acid derivatives referred to in this communication are of the *S*-configuration. New compounds gave analytical and spectroscopic data in agreement with the proposed structures.



Scheme 1. *Reagents:* i, Me_3SiCl/Et_3N; ii, Ph_3CCl/Et_3N; iii, MeOH; iv, $LiAlH_4/THF$; v, $AcOH–H_2O$; vi, 1-HOBt, dicyclohexylcarbodiimide; vii, $NaBH_4/(MeO[CH_2]_2)_2O$, 0 °C; viii, 2M NaOH/MeOH, room temp.

absence of by-products shown by h.p.l.c. Finally, detritylation with aqueous 95% acetic acid at ambient temperature gave, after recrystallisation from aqueous ethanol, the product (**4**) {m.p. 231.5 °C, $[\alpha]_D^{25}$ +22.6° (*c* 2, 0.5M HCl) (lit.[5a] m.p. 220—220.5 °C), $[\alpha]_D^{25}$ +28.2 (*c* 1.9, 6M HCl)} in 82% yield.

The 4-amino isomer (**8**) {m.p. 167—168 °C, $[\alpha]_D^{25}$ +24.2° (*c* 2, H_2O) (lit., [2a] m.p. 147—148 °C, no figure for $[\alpha]_D^{25}$)} was prepared, in 72% overall yield based on (**9**), in an analogous manner by reduction of α-methyl (*S*)-*N*-tritylglutamate (**11**) followed by detritylation. As depicted in Scheme 1, (**11**) was prepared by tritylation of (**9**) followed by selective saponification. Alternatively, the reduction product (**7**) was obtained in 77% overall yield based on (**2**) by converting[9] (**2**) into the corresponding oily benzotriazolyl derivative (**5**), followed by selective reduction with $NaBH_4$ and saponification of the resulting methyl 4-tritylamino-5-hydroxypentanoate (**6**). Neither of the reductions leading to (**7**) was as selective as that of (**3**), as evidenced by minor less polar by-products (h.p.l.c.) accompanying its formation. However these by-products are easily separated during crystallisation of the corresponding DEA salt of (**7**) {m.p. 122 °C, $[\alpha]_D^{25}$ +42.7° (*c* 1, MeOH)}.

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