Synthesis and Chemical Modification of Homoseryl Peptides†

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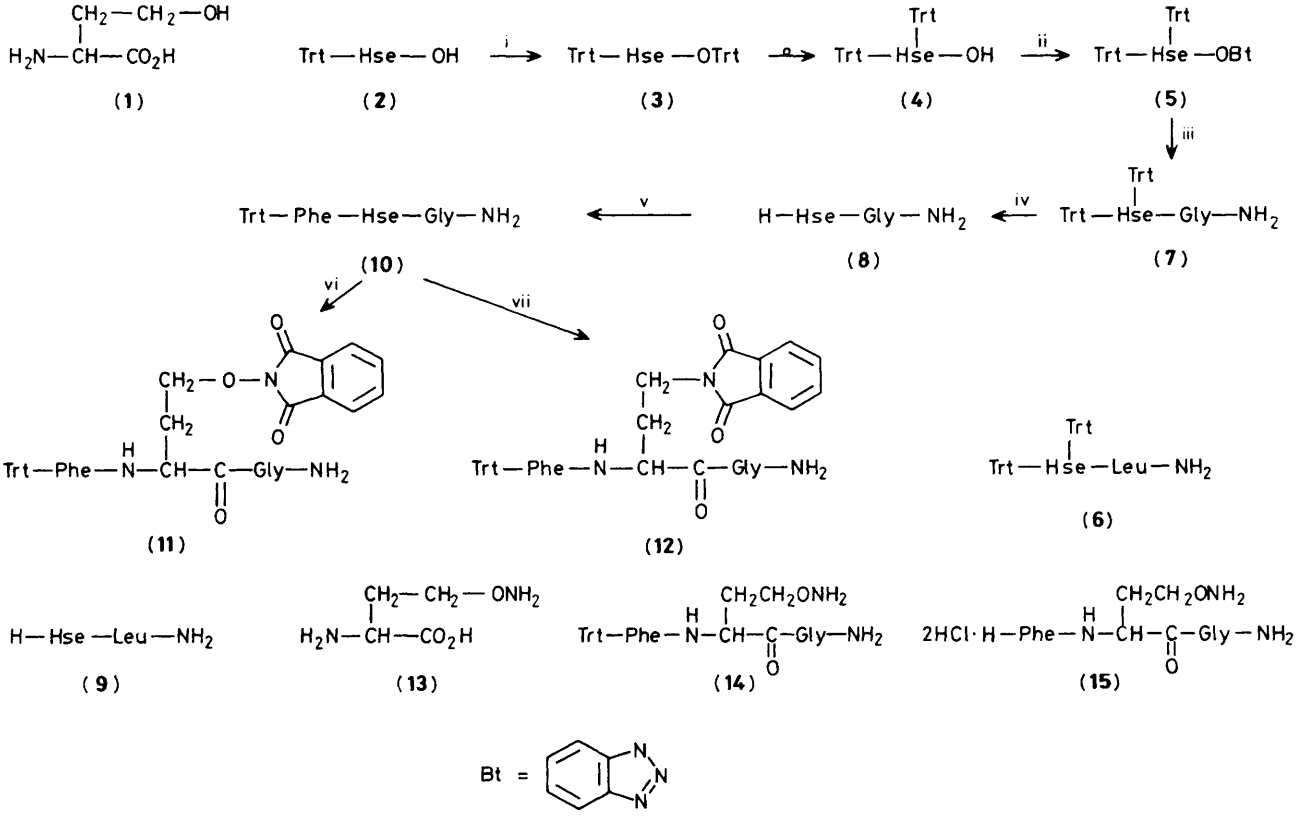
The readily synthesised *N,O*-ditritylhomoserine (**4**) was used for the efficient incorporation of homoserine (**1**) into peptides; the derived homoseryl peptides were transformed into peptides of canaline and 1,4-diaminobutyric acid using the Mitsunobu reaction.

Homoserine, Hse, (**1**) is a naturally occurring amino acid with important biological properties.[1] Because of the strong tendency of its unprotected hydroxy derivatives towards lactonisation,[2] few homoseryl peptides have been synthesised[3] to date. Incorporation of (**1**) into peptides is of interest because its side chain hydroxy function could be transformed into derivative groups, thus providing a number of modified peptides useful in structure–activity related investigations. However realisation of this projected application of (**1**), characterising the so-called pluripotential amino acids,[4] requires derivatives of (**1**) with extremely labile hydroxy protecting groups. We report here on the simple synthesis of one such derivative, namely (**4**), which allows for efficient incorporation of (**1**) into peptides, and provide first examples of the use of (**1**) as a pluripotential amino acid.

Treatment of the readily available *N*-tritylhomoserine (**2**)[5] with a slight excess of trityl chloride and triethylamine in $CHCl_3$ gave (**4**), *via* an intramolecular trityl group migration which occurs rapidly on the initially formed *N*-tritylhomoserine trityl ester (**3**). Compound (**4**), isolated as its corresponding diethylammonium salt {m.p. 172—174 °C, $[\alpha]_D^{25}$ +18.6 (*c* 2, MeOH)} in 74% yield, was further treated with dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt)[6] to provide the active ester (**5**) {oil, $[\alpha]_D^{25}$ +47.5 (*c* 3, $CHCl_3$)} in 93% yield. Coupling[7] of (**5**) with leucinamide and glycinamide yielded the dipeptides (**6**) {m.p. 211—212 °C, $[\alpha]_D^{25}$ −15.7 (*c* 1, $CHCl_3$)} and (**7**) {m.p. 194—196 °C, $[\alpha]_D^{25}$ −39.7 (*c* 1, $CHCl_3$)} in 75% and 87% yield respectively.

Treatment of (**6**) or (**7**) with 25% CF_3CO_2H in CH_2Cl_2 for 5

† All optically active amino acids and derivatives referred to in this communication are of the L configuration. New compounds gave analytical and spectral data in agreement with the proposed structures.



Scheme 1. *Reagents:* i, TrtCl, NEt_3; ii, HOBt, DCC; iii, Gly–NH_2, NEt_3; iv, 1.5% CF_3CO_2H in EtOH–$CHCl_3$ (75:25); v, Trt–Phe–OBt, NEt_3; vi, PPh_3, diethylazodicarboxylate, *N*-hydroxyphthalimide; vii, PPh_3, diethylazodicarboxylate, phthalimide.

min at 0 °C, in an attempt to remove both trityl groups, resulted in fragmentation of the dipeptides to homoserine lactone and the corresponding amino acid amides. In contrast, complete deprotection without fragmentation occurs when (**6**) or (**7**) is treated with 1.5% CF_3CO_2H in EtOH–$CHCl_3$ (75:25) for 5 h at room temperature, and the reaction mixture is concentrated *in vacuo*. The trifluoroacetate salts of (**8**) {powder, m.p. 72 °C (decomp.), $[\alpha]_D^{25}$ +11.4 (*c* 0.6, MeOH)} and (**9**) {powder, $[\alpha]_D^{25}$ −2.1 (*c* 1, MeOH)} were thus isolated in 93% and 85% yield respectively.

Coupling of (**8**) with *N*-tritylphenylalanine 1-hydroxybenzotriazolyl ester[6] gave the homoseryl tripeptide (**10**) {m.p. 112 °C (decomp.), $[\alpha]_D^{25}$ −6.9 (*c* 1, MeOH)} in 72% yield. Condensation of (**10**) with *N*-hydroxyphthalimide[8] or phthalimide[9] using triphenylphosphine and diethylazodicarboxylate[10] gave the protected canalyl tripeptide (**11**) {m.p. 175—177 °C, $[\alpha]_D^{25}$ −11.8 (*c* 1, $CHCl_3$)} and the 1,4-diaminobutyryl peptide (**12**) {m.p. 125 °C, $[\alpha]_D^{25}$ + 10.5 (*c*2, $CHCl_3$)}, in 40% and 58% yield respectively after silica gel column chromatography. Canaline (**13**) is a structural analogue of ornithine with interesting biological properties.[11] Using a similar procedure to that described herein, derivatives of (**13**), suitably protected for peptide synthesis, have also been prepared.[12] Selective removal of the phthalyl-protected group can be readily achieved on treating (**11**) with a mixture of acetic acid and hydrazine hydrate (1:1) in methanol at 45 °C for 4 h. The side chain-unprotected tripeptide (**14**) thus obtained in 68% yield {m.p. 198—199 °C, $[\alpha]_D^{25}$ −4.5 (*c* 1, MeOH)} can be further detritylated with a 5 molar excess of HCl in diethyl ether to afford the dihydrochloride of the canaline containing tripeptide (**15**) {m.p. 190 °C (decomp.), $[\alpha]_D^{25}$ −0.7 (*c* 0.8, MeOH)} in 72% yield. To our knowledge, (**15**) represents the first synthetic peptide of canaline, (**13**), reported to date.

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