Stereospecific Amino Acid Synthesis; Preparation of the γ-Anion derived from Glutamic Acid

Jack E. Baldwin,* Michael North, Anthony Flinn, and Mark G. Moloney

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

Reaction of α-t-butyl γ-methyl *N*-trityl-L-glutamate (**7**) with lithium isopropylcyclohexylamide in hexane leads to the specific formation of the γ-ester enolate, a potential synthetic equivalent to the γ-anion synthon for stereospecific α-amino acid synthesis.

The non-proteinogenic α-amino acids represent an important group of natural and unnatural products.[1] Their biological properties,[2] and use in the investigation of enzyme mechanisms,[2,3] has prompted many stereospecific syntheses.[4—6] Amongst these the bis-lactim ether method of Schollkopf,[6] *via* an α-anion synthon, has already found applicability in the synthesis of a wide range of amino acids.

We report here a convenient and short synthesis of a synthetic equivalent to the γ-anion synthon (**1**) for stereospecific α-amino acid synthesis.

Literature precedent[7] suggested dibenzyl *N*-trityl-L-glutamate (**2**) as a suitable precursor for the synthon (**1**), since it was reported that treatment of (**2**) with lithium di-isopropylamide (LDA) followed by benzyl chloroformate gave, after deprotection, γ-carboxyglutamic acid (**3**) with no detectable racemisation at the α-position. However our attempts to bring about reactions of the glutamate (**2**) with LDA followed by other electrophiles (alkyl halides and carbonyl compounds) did not yield any of the desired γ-substituted glutamic acid derivatives. α-t-Butyl γ-methyl *N*-trityl-L-glutamate (**7**) was chosen as an alternative to glutamate (**2**), since the γ-methyl ester of (**7**) and its derivatives could be selectively saponified,[8] the *N*-trityl group would prevent racemisation at the α-position,[7,9] and the bulky t-butyl ester group would minimise intramolecular cyclisation of the ester enolate once formed.

The γ-methyl ester (**5**), prepared by treatment of L-glutamic acid with methanolic hydrogen chloride,[10] was converted into the t-butyl ester (**6**) (isobutene/concentrated sulphuric acid)[11] and thence into the *N*-trityl derivative (**7**)† (trityl chloride/triethylamine)[12] in 35% overall yield (Scheme 1). In view of the low cost of L-glutamic acid and the suitability of this synthesis for large-scale reactions, their yield was considered suitable for our needs.

† All new compounds gave satisfactory analytical and spectroscopic data.

Treatment of the glutamate (**7**) with LDA, followed by propanal, in tetrahydrofuran (THF) as solvent, did not lead to the isolation of the desired hydroxy ester (**8**). However when the γ-ester enolate was generated with lithium isopropylcyclohexylamide (LICA) and quenched with various carbonyl compounds, the corresponding hydroxy esters (**8**)—(**13**) were obtained in moderate yield (see Table 1).

When hexane was used as solvent, the hydroxy esters (**8**)—(**13**) were obtained in moderate to high yield (30—95%) as mixtures of diastereoisomers at the two new chiral centres.

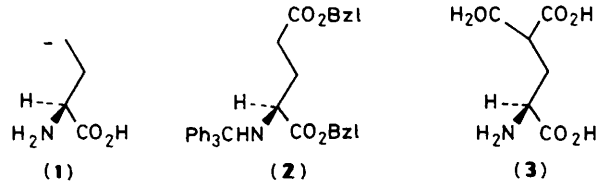
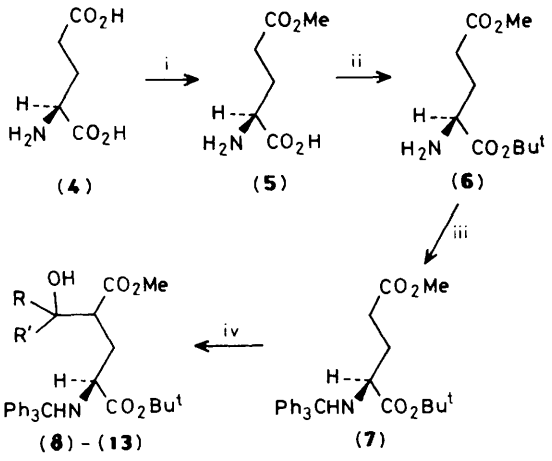


Table 1. Products and yields from the reactions of the glutamate (**7**) with electrophiles.

Electrophile	Product	Solvent	Yield (%)
EtCHO	(**8**; R = Et, R′ = H)	THF	68
		Hexane	68
PhCHO	(**9**; R = Ph, R′ = H)	THF	10
		Hexane	35
MeCOMe	(**10**; R = Me, R′ = Me)	THF	20
		Hexane	40
H_2CO	(**11**; R = H, R′ = H)	THF	17
		Hexane	30
Me_2CHCHO	(**12**; R = Me_2CH, R′ = H)	THF	25
		Hexane	50
p-$NO_2C_6H_4$ CHO	(**13**; R = *p*-$NO_2C_6H_4$, R′ = H)	Hexane	95



Scheme 1. *Reagents and conditions:* i, MeOH/HCl; ii CH_2=CMe_2/H_2SO_4; iii, Ph_3CCl/Et_3N; iv, (a) LICA/hexane, −78 °C, (b) RCOR'.

The optical integrity of C-2 in the hydroxyalkylated products (**8**)—(**13**) was proven by using the chiral shift reagent tris-[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]-europium(III) [Eu(tfc)$_3$].[13] The racemic hydroxy ester (**9**) was synthesised from DL-glutamic acid as described for the L-isomer. When its 500 MHz ^{1}H n.m.r. spectrum was obtained in the presence of Eu(tfc)$_3$, the methyl ester signals were split, showing that the Eu(tfc)$_3$ resolved the enantiomers. When this process was repeated with the hydroxy ester (**9**) derived from L-glutamic acid, no splitting of the methyl ester signals occurred, demonstrating that the products were enantiomerically pure within the detection limits of 500 MHz n.m.r. (the minimum enantiomeric excess was calculated as 99% based on the observed signal-to-noise ratio).

The use of the glutamate (**7**) in the synthesis of non-proteinogenic α-amino acids is being investigated.

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