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# A NEW SYNTHETIC EQUIVALENT OF THE GLUTAMIC ACID γ-ANION AND ITS APPLICATION TO THE SYNTHESIS OF S-(+)-γ-CARBOXYGLUTAMIC ACID.

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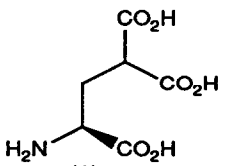
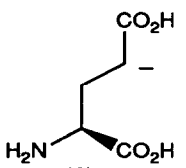
**Summary:** Protected S-pyroglutamic acid can be deprotonated specifically at the γ-position. The resulting enolate can be converted into γ-carboxyglutamic acid in optically pure form.

The naturally occurring aminoacid γ-carboxyglutamic acid (1; Gla) is a constituent of prothrombin and other proteins.[1] The natural enantiomer of this aminoacid has been prepared both by resolution[2,3] and by elaboration of S-glutamic acid (S-Glu) derivatives involving anion formation at the γ-position with retention of configuration at the α-centre.[4,5] The γ-anion synthon (2) is also of interest for the generation of other derivatives of glutamic acid but current methodology has limited applicability.[6,7] We now report a practical synthetic equivalent which has been converted to S-Gla via a differentially protected derivative, and which offers attractive new scope for synthesis of non-proteinogenic α-aminoacids.[8]

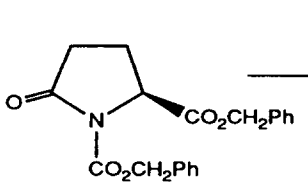


(1)



(2)

Danishefsky and coworkers[4] had noted that benzyl N-(benzyloxycarbonyl)-pyroglutamate (3) reacts with tert-butoxy-bis-(dimethylamino)-methane[9] to give adduct (4) without racemisation, a reaction considered to proceed through the enolate anion.[10] Drawing on this precedent, we hoped to elaborate the pyroglutamate derivative (5) by anion formation using strong base without racemisation. This approach immediately differentiates between the two carboxylic acids of Glu, protecting the γ-carboxylic acid as the lactam amide. Protection of the α-carboxylic acid as the tert-butyl ester minimised its chance of interference in the reaction sequence, while protection of the lactam -NH as the tert-butoxycarbonyl derivative was chosen to allow eventual easy opening of the lactam ring.[4,11]



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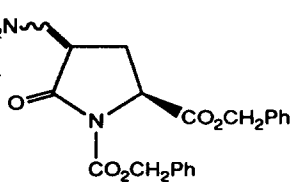
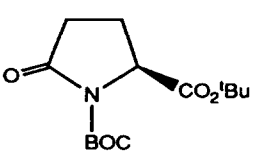
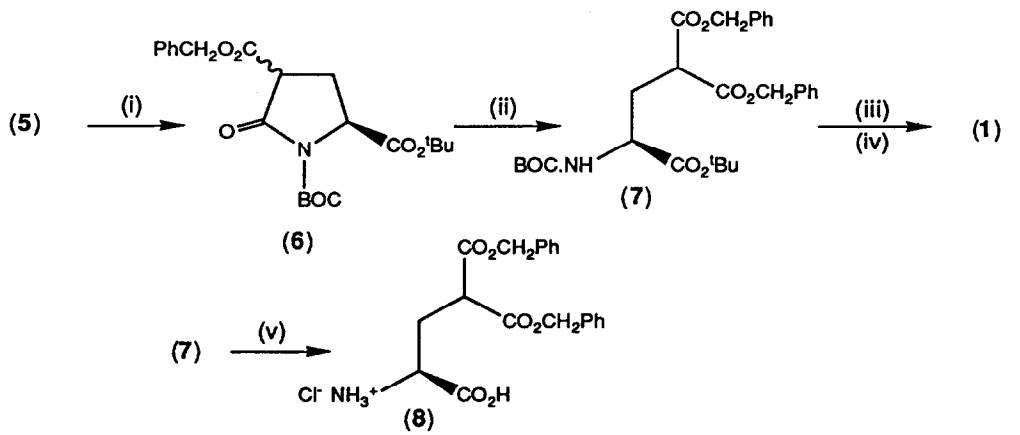


(4)



(5)

Treatment of S-pyroglutamic acid with isobutene and sulphuric acid in dioxan,[12] followed by N-protection with di-t-butyl dicarbonate and 4-dimethylaminopyridine in dichloromethane[11] afforded (5) straightforwardly (40% overall, m.p. 56-57°; $[\alpha]_D$ = -51.6°, c=1, $CH_3OH$). Addition of (5) to lithium diisopropylamide (1.1 equivalents) in tetrahydrofuran followed by reaction with benzyl chloroformate gave crystalline diester (6) of uncertain stereochemistry (52%), the ring of which opened smoothly with benzyl alcohol containing a trace of sodium benzoxide to yield the fully protected Gla derivative (7) (64%). Deprotection (palladium-carbon/ hydrogen then trifluoroacetic acid) afforded S-(+)-Gla in 48% yield, m.p.168-169° (dec.), lit.[2] 167-167.5° (dec.); $[\alpha]_D$ = +40.4° (c=1, 6M HCl), lit.[2] +35.3° (cf. -37.5° for enantiomer). The enantiomeric purity of synthetic S-Gla has been confirmed by previous workers[2] by decarboxylation and comparison of optical rotation with that of authentic S-Glu . We have also shown that diester (8) is optically pure to the limit of detection (>98%) by thin layer chromatography on chirally doped silica plates[13] which resolve racemic (8), prepared for comparison from racemic pyroglutamic acid. Transformation of (6) into a wide range of novel γ-substituted derivatives of glutamic acid will be described in a full paper.




**Reagents:** (i) LDA (1.1 eq.) / THF / $PhCH_2OCOCl$, -78° to +20° (ii) $NaOCH_2Ph$ (cat) / $PhCH_2OH$
(iii) Pd / $H_2$ / i-PrOH (iv) TFA (v) HCl / EtOAc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