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Stereospecific Synthesis of 4-Alkylglutamates and 4-Alkylprolines

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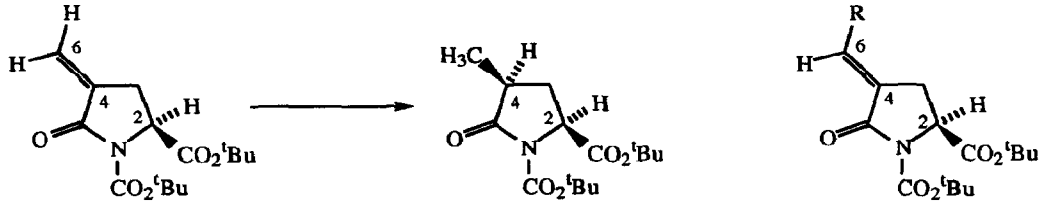
Abstract : Catalytic reduction of the 4-alkylidenepyroglutamate derivatives (3) affords an effective route to (2S,4S)-4-alkylglutamic acids and (2S,4S)-4-alkylprolines. The route has also been used to prepare a 4-alkylpyroglutamic acid derivative which is stereospecifically labelled in the side chain. Synthesis of the (2S,4R)-epimers using cuprate addition has also been investigated.

There has recently been considerable interest in non-proteinogenic naturally occurring amino acids[1,2] and in unnatural synthetic amino acids[3] for their enzyme inhibitory and antimetabolite properties and their ability to impart protease resistance and unique conformational inducing properties when incorporated into proteins. Substituted glutamic acids are of particular interest because of their interaction with glutamate receptors in the CNS and their involvement in many other biological processes. Proline and its analogues are constituent amino acids in antibiotics;[4-7] are of interest for angiotensin converting enzyme inhibitors;[8-10] and provide conformational constraint in proteins.[11] We now report a general and stereospecific synthesis of (2S,4S)-4-alkylglutamic acid and (2S,4S)-4-alkylproline derivatives and a stereoselective route which can afford the (2S,4R)-epimers.

Use of protected pyroglutamic acids is attractive as a potential route to substituted glutamic acids and prolines and reactions of the anion α to the amide carbonyl group of pyroglutamic acid have been investigated as possible routes to 4-substituted derivatives. Variable stereoselectivity in syntheses using highly modified derivatives[8,12,13] and in aldol condensations at C-4 of simple protected pyroglutamates[14,15] have so far made such an approach less useful, although we have achieved stereospecificity at C-4 in a high yielding aldol-type reaction using activated imines as the electrophiles and have also observed considerable stereoselectivity at the second asymmetric centre to be generated in this reaction.[16]

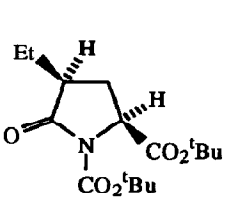


(1) (2) (3)

Direct alkylation of the α–anion of protected pyroglutamate derivatives has proved to be unrewarding as a stereospecific route to non-proteinogenic amino acids except in the case of benzylation.[15] In a recent synthesis of stereospecifically deuteriated leucine we discovered that the enone (1), which is readily accessed from the corresponding protected pyroglutamic acid, could be catalytically hydrogenated from the less hindered side to yield the 4-methylpyroglutamate (2) with *cis*-stereospecificity.[17] Although this contrasted with the reported lack of stereospecificity in reduction of 4-methyleneproline derivatives,[7] we felt that the result indicated that catalytic reduction of 4-alkylidenepyroglutamic acid derivatives would allow a more general synthesis of (2S,4S)-4-

alkylpyroglutamic acids to be developed. Since we have devised a general synthesis of (E)-4-alkylidenepyroglutamates (3)[18] we expected to be able to prepare a series of (2S,4S)-4-alkylpyroglutamate derivatives from which (2S,4S)-4-alkylglutamates and (2S,4S)-4-alkylprolines might be derived. Access to the corresponding (2S,4R)-4-alkylpyroglutamates might be gained by conjugate addition of cuprates to the 4-alkylidenepyroglutamic acid derivatives since the thermodynamically more stable *trans* product at C_4 would be expected. If attack of the cuprate were from the less hindered face, then a second new chiral centre would be generated at C_6.

When the 4-ethylidene derivative (**3, R = Me**) was hydrogenated using 10% Pd-C in ethyl acetate, the product, m.p. 49 - 51 °C, $[\alpha]_D^{21}$ -32° (c 0.2, $CHCl_3$)† obtained in 99% yield, was a single diastereoisomer. Overlap in the ^{1}H-NMR spectra in various solvents, however, precluded easy assignment of stereochemistry. Although the (2S,4S)-product (**4**) was expected from the reaction, this could only be proved when the (2S,4R)-isomer (**5**) was prepared and its stereochemistry assigned unambiguously as described below. The corresponding (2S,4S)-4-propylpyroglutamic acid derivative, m.p. 59 - 61 °C, $[\alpha]_D^{21}$ -35° (c 0.3, $CHCl_3$)† was obtained by this route in 98% yield from the 4-propylidenepyroglutamate (**3, R = Et**).



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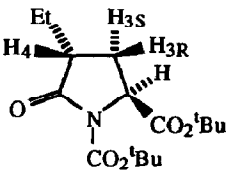

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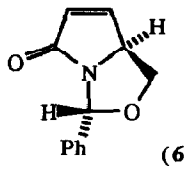

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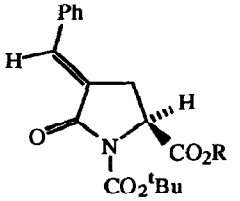
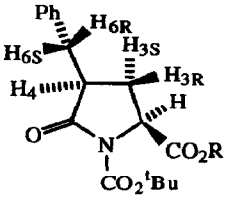


(7)

In an attempt to achieve stereospecific synthesis of the epimeric compound, *tert*-butyl (2S,4R)-N-*tert*-butoxycarbonyl-4-ethylpyroglutamate (**5**), the enone (**1**) was reacted with lithium dimethyl cuprate in diethyl ether at -78 °C. Although excellent control of stereochemistry had been reported in 3-alkylation of endocyclic enones such as (**6**) with alkyl cuprates,[13,19,20] we obtained a mixture of two diastereoisomers in 84% yield from the reaction of the exocyclic enone (**1**). The mixture consisted of 20% of the (2S,4S)-isomer (**4**), identical in ^{1}H-NMR spectrum with the product from hydrogenation of the enone (**3, R = Me**), and 80% of the (2S,4R)-isomer (**5**). The epimers were difficult to purify by flash chromatography but a pure sample of the (2S,4R)-isomer (**5**), m.p. 78 - 79 °C,† was obtained, and its ^{1}H-NMR spectrum in [$^2H_6$]-benzene was well resolved. An nOe was observed between the protons H_{3R} and H_4 and between the protons H_{3S} and H_2 of this compound, confirming its stereochemistry. Thus, while synthesis of the *cis*-isomer (**4**) was completely stereospecific, synthesis of the *trans*-isomer (**5**) was stereoselective to the extent of 4:1 in favour of the (2S,4R)-isomer.



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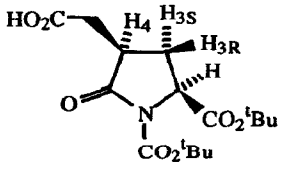

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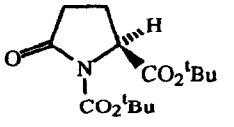

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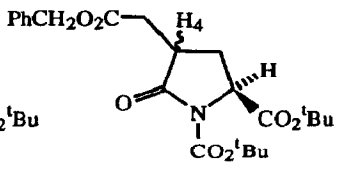
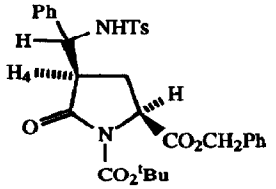


(11)

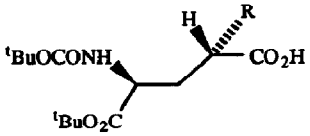
Hydrogenation of the (E)-benzylidene derivative (**7, R = ^{t}Bu**) using 10% Pd-C gave a 63% yield of a single diastereoisomer, the (2S,4S)-benzyl derivative (**8, R = ^{t}Bu**), m.p. 130 - 131 °C, $[\alpha]_D^{22}$ +66° (c 0.2, $CHCl_3$)† which exhibited a clear nOe between H_{3R} and one of the protons H_6 and between H_2 and H_{3S}. This compound had possibilities for developing functionality on the side chain, and, when it was treated with ruthenium(III) chloride and sodium periodate, the acid (**9**), m.p. 125 - 127 °C, was obtained in 54% yield. The stereochemistry of this product was confirmed as (2S,4S) by the observation of an nOe between H_{3S} and H_4 and between H_2 and H_{3S}. In connection with studies related to the synthesis of glutamate antagonists, we have

alkylated *tert*-butyl N-*tert*-butoxycarbonylpyroglutamate (**10**) using benzyl bromoacetate and LHMDS in THF.[21] As was subsequently confirmed on related compounds by other workers,[22,23] the reaction was non-stereospecific and led to a mixture of stereoisomers (**11**). Separation and hydrogenation of the *cis* isomer gave a sample of the acid (**9**), identical spectroscopically with the compound prepared by oxidation of (**8, R = tBu**).

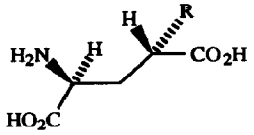
Since our 4-alkylidene derivatives had well-defined side chain geometry, stereospecific development of two chiral centres was possible. Hydrogenation of the benzyl ester (**7, R = PhCH$_2$**), derived[24] from the adduct (**12**)[16] by base catalysed elimination, gave the acid (**8, R = H**).[25] When this reaction was repeated using deuterium,[25] one single stereospecifically labelled acid was obtained. The ^{1}H-NMR spectrum of this compound indicated that only one deuteriated isomer had been obtained and, since the geometry of the starting benzylidene derivative (**7, R = PhCH$_2$**) was known to be (E)[18,24] and hydrogenation was expected to occur with *cis* stereospecificity, it was concluded that the product was (2S,4S,6S)-[4,6-^{2}H$_2$]-N-*tert*-butoxycarbonyl-4-benzylpyroglutamic acid (**8, R = H, H$_{6S}$ = H$_4$ =^{2}H**).



(**12**)



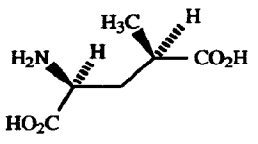
(**13**)



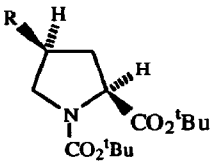
(**14**)

To demonstrate that the synthetic *cis*-4-alkylpyroglutamic acid derivatives could be converted to the corresponding (2S,4S)-4-alkylglutamic acids, the methyl and ethyl derivatives (**2**) and (**4**) were reacted with aqueous LiOH in THF when hydrolysis of the ring imide gave the acids (**13, R = Me**), m.p. 74 - 76 °C, $[\alpha]_D^{24}$ +3.5° (c 2, $CHCl_3$)† and (**13, R = Et**), m.p. 90 - 92 °C, $[\alpha]_D^{21}$ -0.9° (c 0.23, $CHCl_3$)† respectively as single diastereoisomers in 94% and 68% yields respectively. These were then treated with 6N HCl to yield the hydrochlorides of (2S,4S)-4-methylglutamic acid (**14, R = Me**), m.p. 148 - 153 °C, $[\alpha]_D^{21}$ +25.3° (c 1, 1N HCl)† in 100% yield and (2S,4S)-4-ethylglutamic acid (**14, R = Et**), m.p. 135 - 138 °C, $[\alpha]_D^{24}$ +3.2° (c 1.0, 3N HCl),† in 85% yield respectively. The sample of (**14, R = Me**) was different from an authentic sample of the natural product isolated by Kasai *et al.* from a variety of plant sources and designated (2S,4R)-4-methylglutamic acid (**15**) by them.[26,27] The synthesis thus confirmed this assignment.

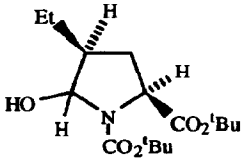
The 4-alkylpyroglutamic acid derivatives were converted to the corresponding protected (2S,4S)-4-alkylprolines using borane-dimethyl sulphide in THF. Thus the methyl derivative (**16, R = Me**), $[\alpha]_D^{25}$ -5.5° (c 1.0, $CHCl_3$)† was obtained in 65% yield, the ethyl derivative (**16, R = Et**), $[\alpha]_D^{22}$ -49° (c 1.0, $CHCl_3$)† in 53% yield, and the 4-propyl derivative (**16, R = Pr**), $[\alpha]_D^{25}$ -52° (c 1.1, $CHCl_3$)† in 66% yield. The carbinolamine (**17**) was obtained as a single diastereoisomer when the 4-ethylpyroglutamate derivative (**4**) was reduced for a short time. This would be the (2S, 4S, 5S)- isomer if, as expected, attack of the borane were from the less hindered side, but the complication of the ^{1}H-NMR spectrum due to the conformational isomerism did not allow this to be verified. ^{1}H- and ^{13}C-NMR spectra of the protected prolines (**16**) were complicated by conformational isomerism, although the ^{1}H NMR spectrum could be simplified by use of variable temperature techniques. Deprotection of the derivatives (**16**) in 6N HCl gave the desired (2S,4S)-4-alkylprolines (**18, R = Me**), m.p. 165 - 166 °C, $[\alpha]_D^{24}$ -19° (c 0.1, 3N HCl)† and (**18, R = Pr**),† in 94% and 89% yields respectively as the hydrochlorides.



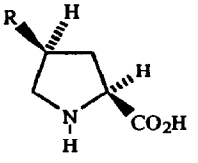
(**15**)



(**16**)



(**17**)



(**18**)

cis-4-Methylproline (**18**, R = Me) has been isolated from natural sources but the reported[28] $[\alpha]_D$ (-43° in 3N HCl) differed from that found for our synthetic product. The analytical and spectroscopic data were, however, in keeping with our structure, and an nOe between H_2 and H_{3S} and between the methyl and H_{3R} confirmed the *cis* stereochemistry.

Acknowledgements
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† These compounds had the expected analytical and spectroscopic properties.

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