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Synthesis of Non-Proteinogenic Amino Acids with Three Chiral Centres

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Key Words: Pyroglutamate; imine; amino acid; non-proteinogenic; diastereoselective.

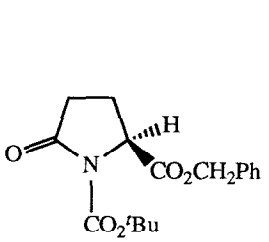
Abstract: Reaction of activated imines with the lactam enolate of the protected pyroglutamic ester (**1**) has been used to prepare optically pure derivatives of amino acids containing three chiral centres.

Non-proteinogenic amino acids are of considerable importance because of their intrinsic biological activity and because, when incorporated into medicinally important peptides, they can modify biological activity in useful ways. L-Pyroglutamic acid is a synthetic precursor of L-proline, substituted derivatives of which provide simple conformational constraints for peptides. It is also a precursor of L-glutamic acid, derivatives of which have a wide range of therapeutic properties. Synthesis of stereospecifically substituted derivatives of L-pyroglutamic acid will, therefore, afford access to a wide variety of useful amino acids.

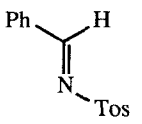
The usefulness of protected L-pyroglutamic acid in the synthesis of natural products has been realised for some time, although, in most cases, use has been made of compounds in which the C-2 ester has been reduced in order to protect the asymmetric centre from racemisation. The nucleophilic nature of C-4 in unreduced derivatives has been used to good effect in a few cases[1-3], one being a recent report[3] that reaction of lactam enolates with aldehydes results in variable yields of C-4 hydroxyalkylated products as mixtures of diastereoisomers at the two new chiral centres. In view of our interest in novel, non-proteinogenic amino acids, we have reacted lactam enolates of the L-pyroglutamic acid derivative (**1**) with electrophilic imines and find that the reaction proceeds in good yield with complete stereospecificity at C-4 and impressive stereoselectivity at the third asymmetric centre.

Protected L-pyroglutamic acid derivatives have usually been prepared from L-glutamic acid[4] or L-proline[5], but we have developed a more direct method of synthesis from L-pyroglutamic acid itself by esterification followed by urethane formation[6]. In this way, the protected derivative (**1**) was prepared in an overall yield of 70%. This was converted to the lactam enolate using lithium hexamethyldisilazide in tetrahydrofuran and the enolate was reacted with the activated imine (**2**) at -78°C for one hour. Flash chromatography on silica gel gave a product, m.pt 143-151°C, in 67% yield. This combusted as the desired adduct, but ^{1}H-nmr spectroscopy showed it to be a mixture of two diastereoisomers in a ratio of 4:1. The major isomer (**3**)†, m.pt 168-170°C, $[\alpha]_D^{29}$ +19.5° (*c* 0.4,$CHCl_3$) was obtained in an overall yield of 45% by recrystallisation from ethyl acetate and hexane. The relative stereochemistry at C-2 and C-4 was shown to be *trans* from the ^{1}H-nmr spectrum in C^2HCl_3, since n.O.es were exhibited between H_2 (δ 4.46) and H_{3S} (δ 2.04) and between H_4 (δ 3.02) and H_{3R} (δ 1.77).

Although the minor isomer (**4**) could not be obtained pure, it was possible to observe n.O.es between H_2 (δ 4.17) and H_{3S} (δ 1.9) and between H_4 (δ 3.20) and H_{3R} (δ 2.05). The asymmetric centre at C-4 had therefore the same stereochemistry in *both* isomers and was that expected if attack were to occur *entirely* from the less hindered face of the protected pyroglutamate derivative.



(**1**)



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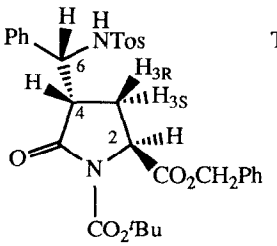
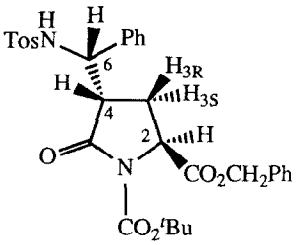


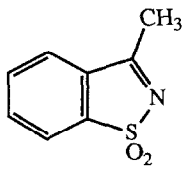
(**3**)



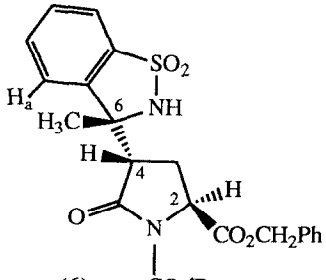
(**4**)

The absolute stereochemistry at C-6 could not be deduced by nmr spectroscopic methods, but an X-ray crystal structure[7] of the major isomer showed the stereochemistry to be 6R (see Figure 2a). The major isomer had, therefore, the stereochemistry represented in (**3**) and the minor isomer the stereochemistry represented in (**4**).

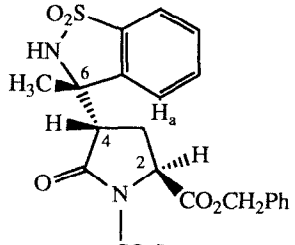
The high degree of stereoselectivity at C-6 in this reaction was extremely interesting, and, since the activated imine (**2**) would be expected to have the (*E*)-geometry shown[8], we decided to examine the fate of an analogous (*Z*)-imine in the reaction. The cyclic imine (**5**) was therefore reacted with the lactam enolate of the protected pyroglutamate (**1**) at -78°C in THF to yield a 5:2 mixture of two diastereoisomeric adducts in 95% yield. These were separated by flash chromatography on silica gel to yield gums. The major isomer, $[\alpha]_D^{23}$ +4.7° (*c* 0.87, $CHCl_3$)†, was obtained in 45% overall yield and the minor isomer, $[\alpha]_D^{23}$ -50.9° (*c* 0.33,$CHCl_3$)†, was obtained in 17% overall yield. The ^{1}H-nmr spectra ($C_6{}^2H_6$) of both compounds had n.O.es between H_4 and H_{3R} and between H_2 and H_{3S} which again clearly indicated that the reaction had occurred *entirely* from the less hindered side of the pyroglutamate moiety, C-2 and C-4 having a *trans* relationship in *both* isomers.



(**5**)



(**6**)



(**7**)

It was also possible to define the stereochemistry at C-6 in these products using ^{1}H-nmr spectroscopy since each isomer was shown to exist in one major conformation in $C_6{}^2H_6$ (see Figure 1). In the major isomer, n.O.es between H_4 (δ 3.10) and *both* the NH (δ 5.25) and methyl (δ 1.39) groups attached to C-6 indicated a conformation such as (**6a**), whereas in the minor isomer, an n.O.e. between H_4 (δ 2.91)

and the C-6 methyl group (δ 1.68) indicated a conformation such as (**7a**). The fact that an n.O.e. was observed between the aromatic doublet for H_a (δ 6.33) and *both* H_{3R} (δ 1.23) and H_4 (δ 2.91) in the ^{1}H-nmr spectrum of the minor isomer and no such effect was observed in the spectrum of the major isomer indicated that the minor isomer had the stereochemistry shown in structure (**7a**).

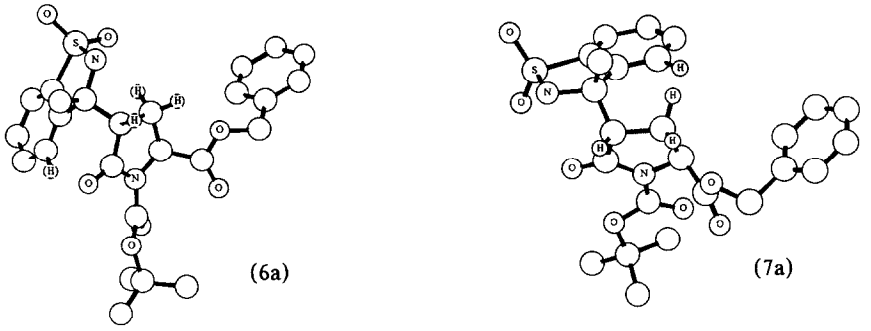


Figure 1. Conformations adopted by the major (**6a**) and minor (**7a**) isomers obtained from reaction of the protected pyroglutamate (**1**) with the activated imine (**5**), as deduced from n.O.e experiments.

The major isomer was therefore the (2S,4S,6R) isomer (**6a**) and this was confirmed by hydrogenolysis to the free acid, an X-ray crystal structure[7] of the dicyclohexylamine salt of which is shown, in part, in Figure 2b. The conformation adopted by this salt in the solid state has the C_6-methyl and C_4-hydrogen in a *transoid* relationship, whereas they are nearly *cisoid* in the ester (**6a**) in $C_6{}^2H_6$ solution.

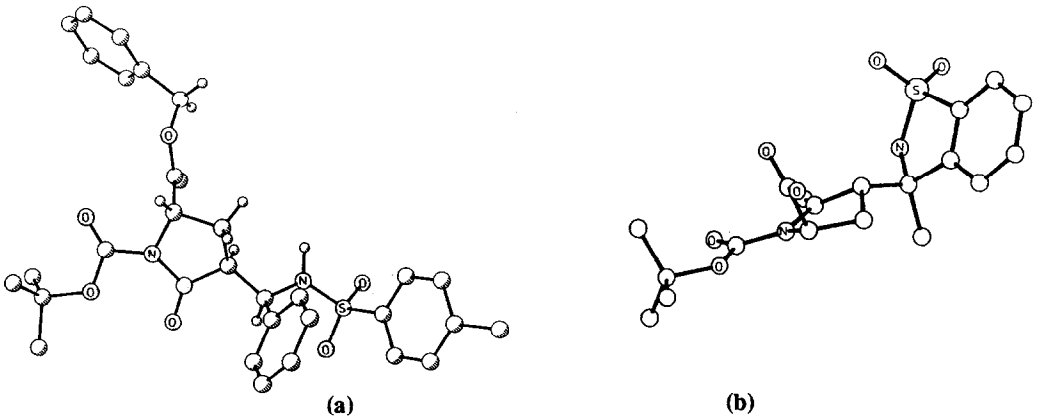
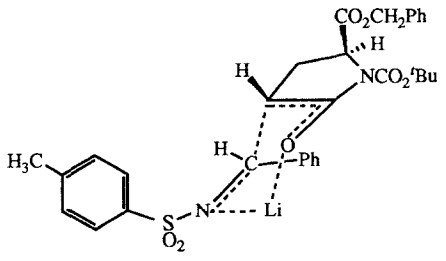
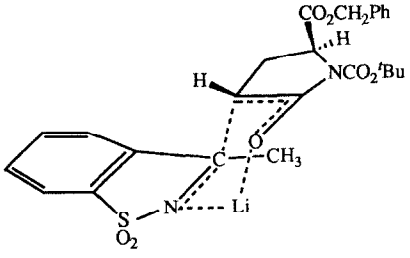


Figure 2. X-ray crystal structure of (**a**) the major isomer (**3**) from reaction of the activated imine (**2**); and (**b**) the anion of the dicyclohexylamine salt (**8**) derived from the major isomer (**6**) from reaction of the activated imine (**5**)

Although it is evident that the stereospecificity of addition of the imines (**2**) and (**5**) at C-4 of (**1**) is the expected result of steric control from C-2 of the pyroglutamic acid moiety, the stereoselectivity at C-6 in the products is less immediately apparent. If chair-like transition states (**9**) and (**10**) are assumed for the two reactions[8], then the kinetically favoured product from the reaction of the (*E*)-imine (**2**) would be the 6S isomer (**4**). Given the bulk of the phenyl group in (**9**), however, the product of thermodynamic control would be the 6R isomer (**3**), which is in fact the major product found in the reaction. The 6R isomer (**6**) would be expected from the reaction of the (*Z*)-imine (**5**) for either kinetic or thermodynamic control.



(**9**)



(**10**)

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References and Notes

† The compounds had satisfactory analytical and spectroscopic data.

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7. The atomic coordinates and e.s.d.s for both structures are available on request from The Director, Cambridge Crystallography Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Structure solution by direct methods and refinement by least squares analysis.
   Crystals of (**3**)[Rigaku AFC5R diffractometer with graphite monochromated Cu Kα radiation and a 12kW rotating anode generator] are monoclinic, $P2_1$ (No.4), a= 14.242 (4), b=6.179 (2), c=17.080 (4) Å, β=98.47 (2)°, Z=2, Dc=1.29 gcm^{-3}, F(000) =612, R=0.084, wR=0.082 ($w=4Fo^2/\sigma^2(Fo^2)$) for 996 observed reflections ($I>3\sigma(I)$).
   Crystals of (**8**) [Enraf-Nonius CAD4 diffractometer with Mo-Kα radiation] are monoclinic, $P2_1$ (No4), a=11.945(4), b=10.442 (3), c=13.244 (2) Å, β=108.69 (2)°, Z=2, Dc=1.26gcm^{-3}, F(000)= 636, R=0.065, wR= 0.050 ($w=1/\sigma(F)$), for 2027 reflections ($I>\sigma(I)$)
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