Pergamon

Tetrahedron Letters 39 (1998) 2199–2202

TETRAHEDRON LETTERS

Reinvestigation of the Alkylation of Pyroglutamate Ester Urethanes

Jean-Damien Charrier, James E. S. Duffy, Peter B. Hitchcock and Douglas W. Young*

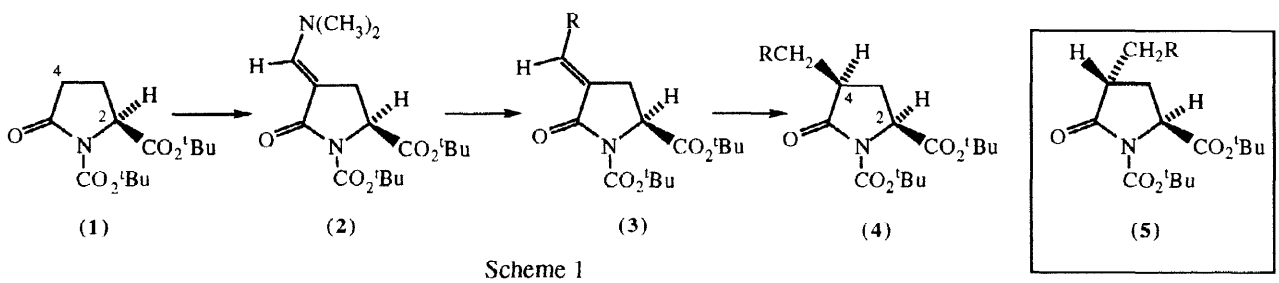
Sussex Centre for Biomolecular Design and Drug Development, CPES, University of Sussex, Falmer, Brighton, BN1 9QJ, U.K.

Received 15 December 1997; revised 12 January 1998; accepted 16 January 1998

Abstract : Previous studies by several groups on the alkylation of pyroglutamic acid derivatives have led to a consensus that the stereoselectivity of alkylation at C-4 is invariably *trans* to the ester group at C-2. We have now discovered that this generalisation is not invariably correct and that, although for S_N1-type electrophiles stereoselectivity is in fact *trans*, S_N2-type electrophiles can give the thermodynamically less stable *cis* products with high diastereoselectivity. Use of the bulky proton source 2,6-di-*tert*-butylphenol to quench these reactions yields *cis* isomers as the only products in good yield, thus making direct alkylation of pyroglutamic acid derivatives a useful starting point for the synthesis of homochiral target compounds.

Protected pyroglutamic acid derivatives have been used as chiral starting materials for the synthesis of a variety of interesting natural products. For reactions involving functionalisation at C-4, derivatives in which the ester at C-2 had been converted to a protected alcohol were traditionally used, presumably due to fears that this centre might prove configurationally unstable under the reaction conditions used. Subsequent work using the esters themselves has shown that these fears are groundless and reactions have been carried out using the anion at C-4 of protected pyroglutamate esters without loss of stereochemical integrity at C-2. Alkylation has been successfully carried out at C-4 but, with the exception of benzylation which gave only the diastereoisomer with the C-4 benzyl group *trans* to the bulky ester at C-2,[1] these reactions proved not to be 100% diastereoselective, although the *trans* isomer has always been reported to be the major one.[2]

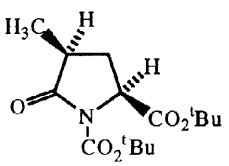
Our interest in assaying for the diastereotopic methyl groups of leucine residues in proteins[3] led us to use the protected pyroglutamic ester (**1**) to develop a synthesis of the amino acid leucine in which one of the diastereotopic methyl groups was labelled with deuterium.[4] The complete diastereoselectivity achieved in this synthesis prompted us to develop the first general, reliable and diastereoselective method for the preparation of 4-alkylpyroglutamic esters (**4**) in which the alkyl group was *cis* to the ester at C-2.[5] This method involved first reacting the protected pyroglutamic acid (**1**) with Bredereck's reagent to yield the enaminone (**2**) which on reaction with DIBALH[4] or Grignard reagents[5] gave a variety of alkylidene derivatives (**3**). Catalytic reduction of these compounds then afforded single diastereoisomers (**4**) from which diastereoisomerically pure (2S,4S)-4-alkylglutamic acids and (2S,4S)-4-alkylprolines were prepared. Cuprate addition to the enone (**3, R = H**), although only 80% diastereoselective,[5] afforded access to the (2S,4R)-epimeric series (**5**).

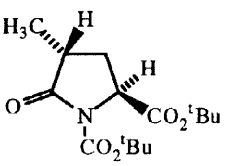


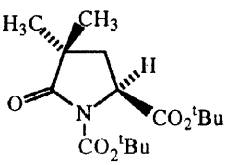
Scheme 1

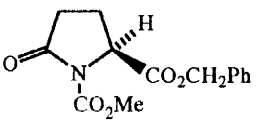
PII: S0040-4039(98)00174-9

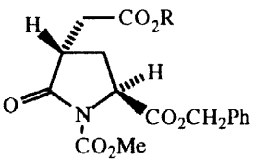
In extending our work to the use of ^{19}F NMR spectroscopy to study protein conformation, we have adapted our general synthesis of 4-alkylpyroglutamate derivatives to provide stereochemically pure 5-fluoroleucine[6,7b] which we have incorporated into a protein for conformational studies.[7] Although useful quantities were obtained, we realised that, if the potential of this fluorinated amino acid were to be exploited to the full in molecular recognition studies, we would need to obtain it in large quantities. This meant that the synthesis would have to be improved and, as methylation involved two steps - reaction of the protected pyroglutamate (**1**) with the costly Bredereck's reagent to obtain the enaminone (**2**) followed by reduction to the *cis*-methyl derivative (**6**) using large quantities of catalyst, we decided to reinvestigate direct alkylation of the protected pyroglutamic ester (**1**) as a way of preparing our key synthetic intermediate (**6**) or its *trans* epimer (**7**). Reports of direct methylation of protected pyroglutamate esters were not promising as Baldwin[1] had no success when a pyroglutamate enolate was reacted with methyl iodide and Ezquerra[2] obtained yields of less than 10% when this electrophile was used. However, when we treated the protected ester (**1**) with lithium hexamethyldisilazide in THF at -78 °C, followed by reaction with methyl iodide, we obtained a 67 % yield of monoalkylated products together with 10 % of the dialkylated compound (**8**)†.


(6)


(7)


(8)


(9)


(10)

The monoalkylated products were present in a diastereoisomeric ratio of 5 : 1 and were separated by chromatography. To our surprise, the major isomer was identical in all respects to the *cis* isomer (**6**)† which we had prepared by the route outlined in Scheme 1. Although we had assigned stereochemistry to this product on the basis of nOe studies, and the coupling constants were in keeping with the considerable number of examples in the literature, the alkylations reported by Ezquerra had all resulted in the *trans* isomer as the major product. We therefore decided to confirm our assignment by single crystal X-ray structure determination, the result of which is shown in Figure 1.[8]

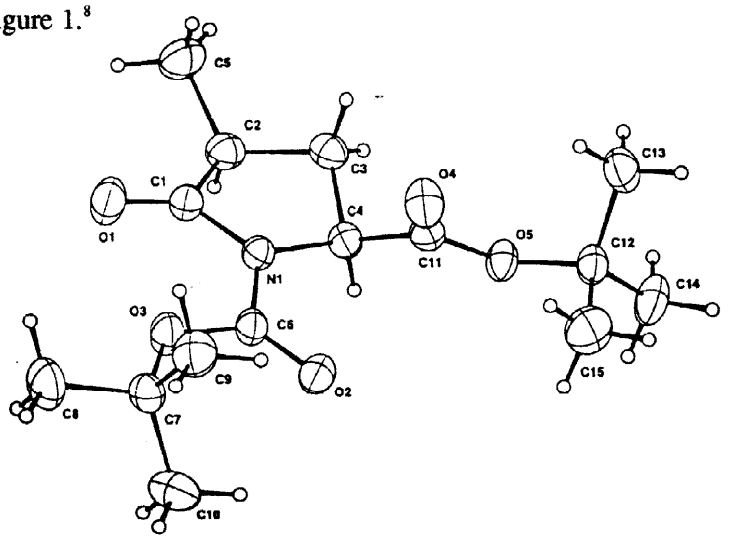
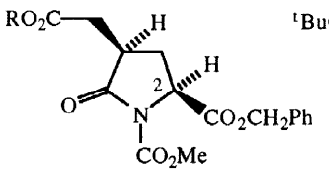


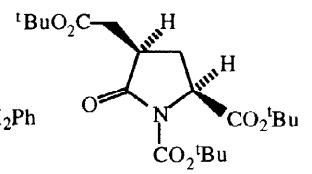
Figure 1 : X-ray crystal structure of the major product (6) from reaction of the anion of the protected pyroglutamate (1) with methyl iodide.

On careful re-examination of the literature, we noted a report by Langlois and Rojas[9] indicating that treatment of the protected pyroglutamate (**9**) with LHMDS followed by reaction with methyl or *tert*-butyl bromoacetate, had given mixtures, the major product of which they assigned as the *trans* isomer (**10**). Assignment of stereochemistry was based on incomplete nOe experiments and indeed the spectral characteristics of these compounds were more in keeping with those of a *cis*-alkylated compound (**11**). Ezquerra investigated a very similar reaction[2] and found a 2 : 1 ratio in favour of the *trans* isomer, and comparison of his spectral data

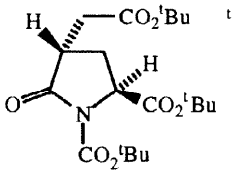
and those of Langlois make it likely that Langlois had obtained *cis* stereoselectivity in her reaction although not to such an impressive extent as we had found for the methylation reaction.



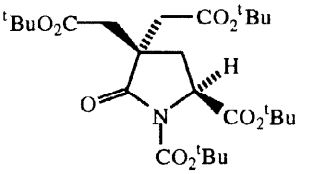
(11)



(12)



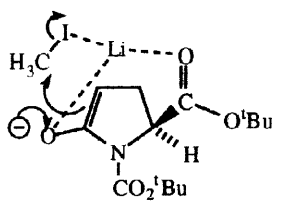
(13)



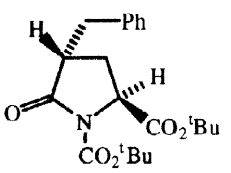
(14)

We therefore investigated reaction of our protected pyroglutamic acid derivative (**1**) with 1.5 equivalents of LHMDS at -78 °C followed by addition of 1.2 equivalents of *tert*-butyl bromoacetate at the same temperature and obtained a 70 % yield of a mixture of diastereomeric monoalkylated products with a *cis* (**12**)† : *trans* (**13**)† ratio of 4 : 1[10] together with a 16% yield of the 4,4-dialkyl derivative (**14**)†.

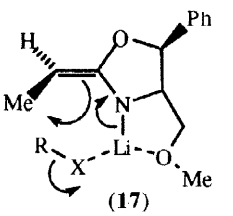
As improving the yield and diastereoselectivity of the methylation reaction had been our first objective, we now used methyl triflate as the electrophile in the reaction. This resulted in monoalkylation in increased yield (75%) and no dialkylation was observed. The *cis* : *trans* ratio of 5 : 1 was unaltered. A possible explanation of the unusual *cis* stereoselectivity might be formation of a lithium complex (**15**) involving the methyl iodide as shown. This would hold the electrophile preferentially on the same face as the ester at C-2. Such an explanation would imply an S_N2 mechanism and might not apply to electrophiles which are more likely to operate in an S_N1 manner. Indeed, when we used benzyl bromide in the reaction, the sole product observed was the *trans* product (**16**)†, obtained in 72 % yield. This result is in keeping with that observed by Baldwin.[1] When the methylation reaction using LHMDS and methyl triflate was repeated in toluene as solvent, a 73% yield of the monoalkylated product was obtained with a *cis* : *trans* ratio of 17 : 1. Chelation as in (**15**) below therefore seems a reasonable explanation and, although Meyers[11] has recently shown that, in the absence of chelating groups, alkylation of 1,5-dimethyl-γ-lactams proceeds preferentially to give *anti*-alkylated products, attack of an electrophile on an oxazoline containing a suitably placed chelating group has been shown to occur suprafacially,[12] presumably *via* a chelate such as (**17**). The nitrogen N1 in our X-ray structure of the pyroglutamate derivative (**6**) is nearly planar but involvement of its lone pair in the complex cannot be ruled out as nitrogen is known to be highly pyrimidalised in amide enolates.[13] Unusual *endo* selectivity has also been observed in methylation of bicyclic enolates which however are benzylated with *exo* selectivity and this was ascribed to the steric demand of the electrophile.[14] The suprafacial result for the bromoacetates in our study, however, is more in keeping with a chelation controlled result, although, on changing the counter-ion by using KHMDS in THF in the methylation reaction, the *cis* : *trans* ratio was again 5 : 1. Further, the ratio was not affected by the lithium ion effect noted by Seebach[15] when LiCl was added to a methylation reaction.



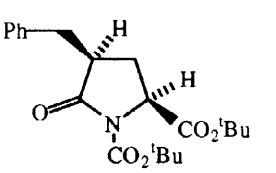
(15)



(16)



(17)



(18)

We have thus shown that alkylation of pyroglutamate urethanes at C-4 is not as simple a process as had been previously thought and it is evident from the variation between our results and those of Ezquerra, that subtle changes in reaction conditions can alter diastereomeric ratios considerably. However, although we had improved *cis* diastereoselectivity by using solvents of low dielectric constant, we had yet to achieve complete diastereoselectivity in these reactions except in the case of the *trans* specificity previously discovered by Baldwin for the benzylation reaction.[1] We were finally able to achieve total *cis* diastereoselectivity by recourse to the hindered proton source 2,6-di-*tert*-butylphenol.[16,17] When the *trans*-methylpyroglutamate (**7**)† was reacted with LHMDS at -78 °C and quenched with 2,6-di-*tert*-butylphenol, then the sole product was the *cis* epimer (**6**) in

89% yield. Amending the conditions of the *trans*-specific benzylation reaction was now investigated and the pyroglutamate **(1)** was treated with 1.15 equivalents of LHMDS and 1.2 equivalents of benzyl bromide followed by addition of a further 1.3 equivalents of LHMDS. 2,6-Di-*tert*-butylphenol was finally added and the sole monoalkylated product of the reaction, obtained in 63 % yield was now the *cis* product **(18)** accompanied by *ca.* 9 % of dialkylation.

Acknowledgements

We thank the BBSRC/EPSRC for a fellowship (to J-D. C.); the EPSRC for a studentship (to J. E. S. D.); and Gaelle Yvert for technical assistance.

References and Notes

1. Baldwin, J. E.; Miranda, T.; Moloney, M.; Hokelek, T., *Tetrahedron*, **1989**, 45, 7459 - 7468.
2. Ezquerra, J.; Pedregal, C.; Rubio, A.; Yruretagoyena, B.; Escribano, A.; Sanchez-Ferrando, F., *Tetrahedron*, **1993**, 49, 8665 - 8678.
3. Ostler, G.; Soteriou, A.; Moody, C. M.; Khan, J. A.; Birdsall, B.; Carr, M. D.; Young, D. W.; Feeney, J., *FEBS. Lett.*, **1993**, 318, 177 - 180.
4. (a) August, R. A.; Khan, J. A.; Moody, C. M.; Young, D. W., *Tetrahedron Lett.*, **1992**, 33, 4617 - 4620; (b) *ibid., J. Chem. Soc., Perkin Trans. 1*, **1996**, 507 - 514.
5. (a) Moody, C. M.; Young, D. W., *Tetrahedron Lett.*, **1993**, 34, 4667 - 4670; (b) *ibid., Tetrahedron Lett.*, **1994**, 35, 7277 - 7280; (c) *ibid, J. Chem. Soc., Perkin Trans. 1*, **1997**, 3519 - 3530.
6. Moody, C. M.;. Starkmann, B. A.; Young, D. W., *Tetrahedron Lett.*, **1994**, 35, 5485 - 5488.
7. (a) Feeney, J.; McCormick, J. E.; Bauer, C. J.; Birdsall, B.; Moody, C. M.; Starkmann, B. A.; Young, D. W.; Francis, P.; Havlin, R. H.; Arnold, W. D.; Oldfield, E., *J. Am. Chem. Soc.*, **1996**, 118, 8700 - 8706; (b) *ibid, idem*, supplementary material.
8. **Crystal data** : $C_{15}H_{25}NO_5$, M = 299.4, orthorhombic, space group $P2_12_12_1$, a = 8.776 (3), b = 11.131 (3), c = 17.188 (6) Å, V = 1679 (1) Å^2, Z = 4, D_{calc}= 1.18 gcm^{-3}, F(000) = 648, μ (Mo-Kα) = 0.09 mm^{-1}, T = 293 K. 1706 independent reflections collected on Enruf-Nonius CAD4 diffractometer using Mo-Kα radiation (λ = 0.71073Å) for 2<θ<25°. Structure solution by direct methods (SHELXS) and refinement on F^2 using SHELXL-93 with non-H atoms anisotropic and H atoms in riding mode. Final residuals were R1 = 0.049 (for 1171 reflections with I>2σ(I)) and wR2 = 0.125 (for all reflections). The atomic coordinates are available on request from The Director, Cambridge Crystallography Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW.
9. Langlois, N.; Rojas, A., *Tetrahedron Lett.*, **1993**, 34, 2477 - 2480.
10. The stereochemistry of all 4-alkylated products was confirmed by nOe enhancement studies, the hydrogens H-2 and H-4 causing enhancement to a common H-3 hydrogen in the *cis* isomer and to different H-3 hydrogens in the *trans* isomer. The coupling constants were also in keeping with the general rules outlined by Ezquerra.[2]
11. Meyers, A. I.; Seefeld, M. A.; Lefker, B. A.; Blake, J. F., *J. Amer. Chem. Soc.*, **1997**, 119, 4565 - 4566.
12. Meyers, A. I., *Accounts of Chem. Res.*, **1978**, 11, 375 - 381.
13. Laube, T.; Dunitz, J. D.; Seebach, D., *Helv. Chim. Acta*, **1985**, 68, 1373 - 1393.
14. Armstrong, R. W.; DeMattei, J. A., *Tetrahedron Lett.*, **1991**, 32, 5749 - 5752.
15. Seebach, D., *Angew. Chem., Int. Ed. Engl.*, **1988**, 27, 1624 - 1654.
16. Davies, S. G.; Garrido, N. M.; Ichihara, O.; Walters, I. A. S., *J. Chem. Soc., Chem. Commun.*, **1993**, 1153 - 1155.
17. Hanessian, S.; Reinhold, U.; Gentile, G., *Angew. Chem., Int. Edn. Engl.*, **1997**, 36, 1881 - 1884.

† These compounds had the expected analytical and spectroscopic properties and an acceptable specific rotation. Where appropriate, they had comparable properties to those reported in the literature.