Pergamon

Tetrahedron Letters 42 (2001) 2381–2384

TETRAHEDRON LETTERS

Double stereodifferentiation in aldol reactions on protected pyroglutamate esters

Peter B. Hitchcock, Bernard A. Starkmann and Douglas W. Young*

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

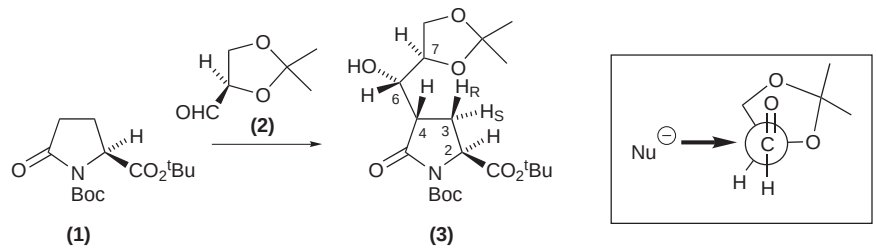
Received 8 December 2000; revised 17 January 2001; accepted 25 January 2001

Abstract—Excellent stereoselectivity is observed at both chiral centres created in the aldol condensation of the matched pairs of (2*S*)-pyroglutamate ester urethane **1** and either (*R*)-glyceraldehyde acetonide **2** or the (*S*)-Garner aldehyde **6**. Stereoselectivity was not so impressive with the mismatched pairs **1**+**4** or **1**+**8** or when the C-2 reduced bromide **12** was used in the corresponding reaction with aldehyde **2**. © 2001 Elsevier Science Ltd. All rights reserved.

The continuing interest in naturally occurring non-proteinogenic amino acids and in unnatural synthetic amino acids has led to an intense effort aimed at discovering new methods for the synthesis of these biologically important compounds. The use of the cyclic amido acid pyroglutamic acid as a template for the stereospecific synthesis of new amino acids has appealed to several groups including our own.[1] Our interest in the stereochemical course of biological reactions led to our use this template in the synthesis of labelled amino acids.[2,3] We have also used it to synthesise a variety of homochiral amino acids,[4,5] and compounds designed as glutamate antagonists[6] and as potential anti-bacterial drugs.[7]

The aldol condensation of aldehydes at C-4 of pyroglutamic ester urethanes has been studied by several groups who obtained undefined mixtures of diastereoisomers at the two centres created in the reaction.[8–10] In 1991, we reported our results on the reaction of imines at C-4 of such esters where we achieved a remarkable degree of stereoselectivity at the two new chiral centres created in the reaction.[11] There was only one configuration at C-4 of the products, due to reaction occurring entirely at the less hindered face of the pyroglutamate moiety. Furthermore, the second chiral centre was created with a very high degree of stereoselectivity. Although it has been shown that 4α-selectivity can be achieved in aldol condensations of pyroglutamates by use of a titanium enolate,[12] the only study of stereoselectivity at the second centre created in such a reaction is our work using imines.[11]

In spite of the fact that our initial studies[11] had given impressive stereoselectivity, the use of protected pyroglutamates in the synthesis of compounds containing multiple chiral centres has been under-exploited. We argued that, if double stereodifferentiation could be exhibited in aldol condensations of pyroglutamates with chiral aldehydes, then a way would be opened to extend the use of this synthon. We therefore reacted the protected pyroglutamate **1**[2] with D-(*R*)-glyceraldehyde acetonide **2**[13] using either LDA or LHMDS in THF/HMPA, as shown in Scheme 1. A single diastereoiso-



Scheme 1.

* Corresponding author.

0040-4039/01/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(01)00150-2

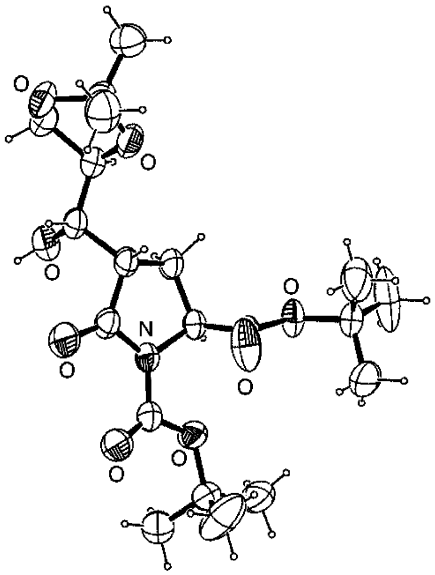


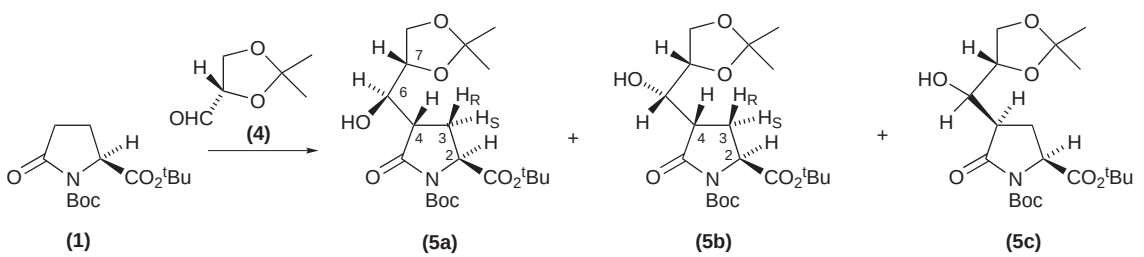
Figure 1. X-Ray crystal structure of compound **3**.

mer **3**, mp 136–138°C, $[\alpha]_D^{19}$ −43.1 (*c* 1, $CHCl_3$),† was obtained from these reactions in 74 and 76% yields, respectively. NOE experiments defined the centre at C-4 as (4*S*), with irradiation of H-2 at 4.45 ppm causing NOE to H-3*S* at 2.5 ppm and irradiation of H-4 causing NOE to H-3*R* at 2.0 ppm. Reaction had therefore occurred from the less hindered side of the molecule, a fact that was confirmed by an X-ray crystal structure (Fig. 1).[14a] This showed that the other chiral centre created in the reaction had (6*S*) stereochemistry and that there was an intermolecular hydrogen bond in the crystal lattice between the 6-OH of one molecule and the β-oxygen of the dioxolidine ring in another. When HMPA was omitted from the reaction, a crystalline product was obtained in 67% yield, the NMR spectra of which indicated it to be a mixture containing product **3** and a minor diastereoisomer in a ratio of ca. 12.5:1. The signals due to the minor isomer in the NMR spectrum were not well enough resolved for us to speculate on its stereochemistry.

When L-(*S*)-glyceraldehyde **4**[15] was used in the aldol condensation with the protected pyroglutamic acid **1** using LHMDS in THF/HMPA, the product **5**, proved to be a mixture of three diastereoisomers as shown in

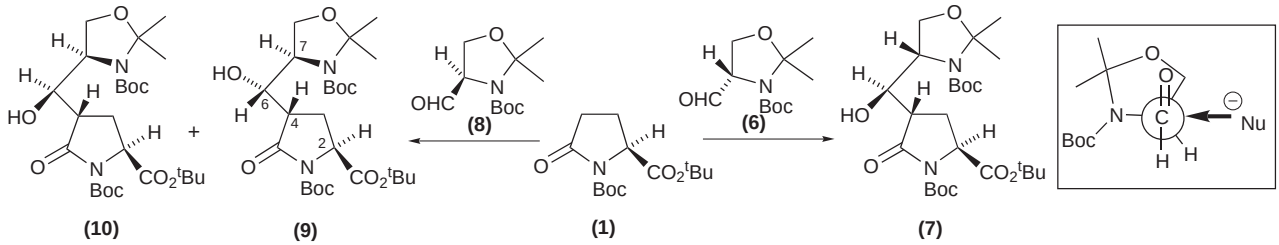
Figure 2. X-Ray crystal structure of compound **5a**.

Scheme 2. These were separated chromatographically into a major fraction (66%) containing two diastereoisomers **5a** and **b** in a 1:1 ratio together with a minor fraction **5c**. The major fractions were separated by crystallisation. The X-ray crystal structure (Fig. 2)[14b] of the major isomer **5a**, mp 170–171.5°C, $[\alpha]_D^{20}$ +3.4 (*c* 1, $CHCl_3$),† indicated that it was the (2*S*,4*S*,6*R*,7*S*) isomer and showed intermolecular hydrogen bonding in the crystal lattice between the 6-OH of one molecule and the C-5 carbonyl group of another. The relevant coupling constants in the second major isomer **5b**, mp 160–163°C, $[\alpha]_D^{28}$ −24.9 (*c* 1, $CHCl_3$)† indicated that it also had a *trans* relationship between the substituents at C-2 and C-4. This was confirmed by NOE data, since irradiation of H-2 at 4.1 ppm caused enhancement of H-3*S* at 2.5 ppm, and irradiation of H-3*R* at 2.0 ppm caused an NOE to H-4 at 2.7 ppm. The second major isomer was therefore the (2*S*,4*S*,6*S*,7*S*) isomer **5b**. The minor isomer had coupling constants in keeping with it being one of the *cis* diastereoisomers **5c**. In an attempt to improve the diastereoselectivity in this reaction, the pyroglutamate **1** was reacted with $TiCl_4$ and diisopropylethylamine in CH_2Cl_2 at −78°C followed by addition of the aldehyde **4**. The product, obtained in 88% yield, was predominantly a 1:1 mixture of the two *trans* isomers **5a** and **b** containing a very small amount of the *cis* diastereoisomer **5c**. Use of $ZnBr_2$ in the reaction failed to give better stereoselectivity.



Scheme 2.

† These compounds had the expected analytical and spectroscopic properties.



Scheme 3.

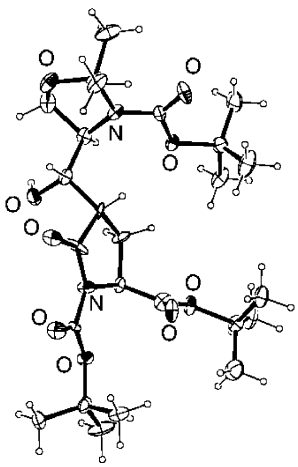


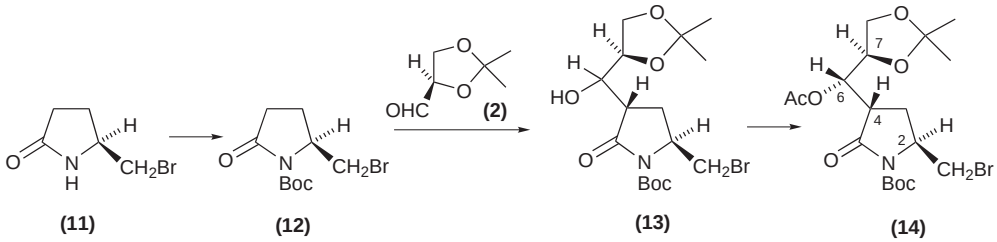
Figure 3. X-Ray crystal structure of compound **9**.

The reaction of the protected pyroglutamate **1** with the D-(*R*)-aldehyde **2** is evidently a good example of double stereodifferentiation[16] in which the enolate of **1** and the aldehyde **2** are a matched pair, leading to the formation of the observed single diastereoisomer **3**. This is not the case for reaction of the enolate of the pyroglutamate (**1**) with the enantiomeric aldehyde **4** where evidently we have a mismatched pair. The stereochemistry in **3** is that expected of Felkin–Ahn control (inset in Scheme 1).

Our interest in analogues of L,L-diaminopimelic acid as potential antibacterial drugs[7] made the reaction of the protected pyroglutamate **1** with the (*S*)-'Garner' aldehyde **6**[17] of interest. This was carried out in THF/HMPA in the presence of LHMDS. The ^{1}H NMR spectrum of the product was complicated by rotational isomerism but variable temperature NMR spectroscopy showed that the reaction had predominantly given one diastereoisomer **7**† together with a minor isomer in a ratio of 19:1. The coupling constants in the ^{1}H NMR spectrum indicated that both isomers had *trans* stereochemistry with respect to the centres C-2 and C-4 of the pyroglutamate ring and the fact that $J_{4,6}$ was 9.2 Hz in the major isomer suggested an *anti* relationship between these protons in a hydrogen bonded model. Thus the predominant product appeared to have the (2*S*,4*S*,6*R*,7*S*) stereochemistry of compound **7**. This is the product expected from the Felkin–Ahn model (inset in Scheme 3).

When the (*R*)-Garner aldehyde **8**[18] was subjected to this reaction, the major isomer **9**, mp 170–171°C, $[\alpha]_D^{27}$ −16.7 (*c* 1, $CHCl_3$)† was obtained in 64% yield together with a 21% yield of a minor isomer **10**, mp 164–165°C, $[\alpha]_D^{27}$ +16.2 (*c* 1, $CHCl_3$).† The ^{1}H NMR spectra of these compounds were not complicated by rotational isomerism as had been the case with compound **7** and NOE experiments and coupling in the NMR spectra suggested that both isomers had *trans* stereochemistry with respect to the substituents on the pyroglutamate ring. The coupling constant $J_{4,6}$ for the minor isomer was 9.4 Hz, suggesting an *anti* relationship between H-4 and H-6 in a hydrogen bonded model and $J_{4,6}$ for the major isomer was 2.2 Hz suggesting a *gauche* relationship between these hydrogens. X-Ray crystal structure analysis (Fig. 3)[14c] confirmed that the major isomer had (2*S*,4*S*,6*S*,7*R*) stereochemistry as shown in **9**. This was again in keeping with a Felkin–Ahn model and it seemed that reaction of the enolate of **1** with the (*S*)-aldehyde **6** represented reaction of a matched pair whereas reaction of this enolate with (**8**) represented reaction of a mismatched pair.

Derivatives of pyroglutamic acid modified at C-2 have been used in synthesis, and so it was of interest to see if the excellent stereoselectivity obtained for the matched pairs above might apply to the protected bromide **12**, which we prepared from bromide **11**[19] (Scheme 4). When this was reacted with the aldehyde **2**



Scheme 4.

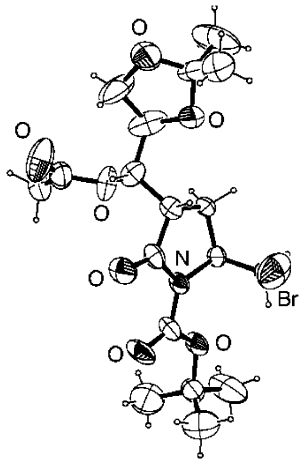


Figure 4. X-Ray crystal structure of compound **14**.

using LHMDS/THF/HMPA, a mixture of stereoisomers **13** was obtained which were derivatised as the acetates. The ratio of diastereoisomeric acetates was 1.4:1 and the major isomer **14**, mp 130–131.5°C, $[\alpha]_D^{29}$ −52.3 (*c* 1, $CHCl_3$),† was shown by X-ray crystallography (Fig. 4) to be the (2*S*,4*S*,6*S*,7*R*) isomer. The stereochemistry of the new centres in this isomer was the same as was found for the sole product **3** from the corresponding reaction with the protected pyroglutamic acid derivative **1** but the degree of stereoselectivity was of a very different order.

Acknowledgements

The authors would like to thank the EPSRC for a studentship (to B.A.S.)

References

1. Nàjera, C.; Yus, C. *Tetrahedron: Asymmetry* **1999**, *10*, 2245–2303.
2. August, R. A.; Khan, J. A.; Moody, C. M.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 507–514.
3. Durand, X.; Hudhomme, P.; Khan, J. A.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1131–1139.
4. (a) Moody, C. M.; Young, D. W. *Tetrahedron Lett*. **1993**, *34*, 4667–4670; (b) Moody, C. M.; Young, D. W. *Tetrahedron Lett*. **1994**, *35*, 7277–7280; (c) Moody, C. M.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3519–3530.
5. (a) Moody, C. M.; Starkmann, B. A.; Young, D. W. *Tetrahedron Lett*. **1994**, *35*, 5485–5488; (b) 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.
6. (a) Bowler, A. N.; Doyle, P. M.; Young, D. W. *J. Chem. Soc., Chem. Commun*. **1991**, 314–316; (b) Dinsmore, A.; Doyle, P. M.; Young, D. W. *Tetrahedron Lett*. **1995**, *36*, 7503–7506; (c) Bowler, A. N.; Dinsmore, A.; Doyle, P. M.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1297–1306; (d) Dinsmore, A.; Doyle, P. M.; Hitchcock, P. B.; Young, D. W. *Tetrahedron Lett*. **2000**, *41*, 10153–10158.
7. Steger, M.; Young, D. W. *Tetrahedron* **1999**, *55*, 7935–7956.
8. Baldwin, J. E.; Miranda, T.; Moloney, M.; Hokelek, T. *Tetrahedron* **1989**, *45*, 7459–7468.
9. Dikshit, D. K.; Panday, S. K. *J. Org. Chem*. **1992**, *57*, 1920–1924.
10. Ezquerra, J.; Pedregal, C.; Yruretagoyena, B.; Rubio, A.; Carreño, M. C.; Escribano, A.; Ruano, J. L. G. *J. Org. Chem*. **1995**, *60*, 2925–2930.
11. (a) Bowler, A. N.; Doyle, P. M.; Hitchcock, P. B.; Young, D. W. *Tetrahedron Lett*. **1991**, *32*, 2679–2682; (b) Bowler, A. N.; Doyle, P. M.; Hitchcock, P. B.; Young, D. W. *Tetrahedron* **1997**, *53*, 10545–10554.
12. Dikshit, D. K.; Bajpai, S. N. *Tetrahedron Lett*. **1995**, *36*, 3231–3232.
13. Jackson, D. Y. *Synth. Commun*. **1988**, *18*, 337–341.
14. **Crystal data**: **(a) Compound 3**: $C_{20}H_{33}NO_8$, $M=415.47$, orthorhombic, space group $P2_12_12_1$ (No. 19), $a=10.147(3)$, $b=10.217(2)$, $c=22.043(5)$ Å, $V=228.2(10)$ Å^3, $Z=4$, $D_{calcd}=1.21$ mg/m^3, μ (Mo Kα) 0.09 mm^{-1}, $T=293(2)$ K, 3729 independent reflections, 2318 with $I>2\sigma(I)$, final residuals were $R_1=0.059$, $wR_2=0.163$; **(b) Compound 5a**: $C_{20}H_{33}NO_8$, $M=415.47$, orthorhombic, space group $P2_12_12_1$ (No. 19), $a=5.911(2)$, $b=10.784(3)$, $c=36.187(12)$ Å, $V=2306.7(13)$ Å^3, $Z=4$, $D_{calcd}=1.20$ mg/m^3, μ (Mo Kα) 0.09 mm^{-1}, $T=293(2)$ K, 2365 independent reflections, 1539 with $I>2\sigma(I)$, final residuals were $R_1=0.054$, $wR_2=0.134$; **(c) Compound 9**: $C_{25}H_{41}N_2O_9$, $M=513.60$, monoclinic, space group $P2_1$ (No. 4), $a=6.058(2)$, $b=25.265(5)$, $c=9.561(3)$ Å, $\beta=106.60(2)°$, $Z=2$, $V=1402.4$ (7) Å^3, $Z=2$, $D_{calcd}=1.22$ mg/m^3, μ (Mo Kα) 0.09 mm^{-1}, $T=293(2)$ K, 2001 independent reflections, 999 with $I>2\sigma(I)$, final residuals were $R_1=0.105$, $wR_2=0.294$; **(d) Compound 14**: $C_{18}H_{28}BrNO_7$, $M=450.32$, monoclinic, space group $P2_1$ (No. 4), $a=13.757(5)$, $b=12.245(5)$, $c=14.373(5)$ Å, $\beta=116.82(3)°$, $V=2132.5(14)$ Å^3, $Z=4$, $D_{calcd}=1.40$ mg/m^3, μ (Mo Kα) 1.96 mm^{-1}, $T=293(2)$ K, 6469 independent reflections, 2168 with $I>2\sigma(I)$, final residuals were $R_1=0.090$, $wR_2=0.242$. In all cases, data collection was carried out using a Nonius CAD4 diffractometer, structure analysis using program package WinGX, and refinement using SHELXL-97. The atomic coordinates for all structures are available on request from: The Director, Cambridge Crystallography Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.
15. (a) Hubschwerlen, C. *Synthesis* **1986**, 962–964; (b) Hubschwerlen, C.; Specklin, J.-L.; Higelin, J. *Org. Synth*. **1995**, *72*, 1–5.
16. Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Eng*. **1985**, *24*, 1–30.
17. McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synthesis* **1994**, 31–33.
18. Prepared using the method of Ref. 17 but with D-serine as starting material.
19. Silverman, R. B.; Levy, M. A. *J. Org. Chem*. **1980**, *45*, 815–818.