Pergamon

Tetrahedron Letters 41 (2000) 10153–10158

TETRAHEDRON LETTERS

Extension of ring switching strategy to the glutamate antagonist 2-(pyrimidin-2,4-dione-5-ylmethyl)-(2*S*)-glycine and related compounds with two chiral centres

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Received 6 September 2000; accepted 11 October 2000

Abstract

2-(Pyrimidin-2,4-dione-5-ylmethyl)-(2*S*)-glycine **8** has been prepared by treatment of the pyroglutamate urea **12** with mild base, followed by deprotection in a modification of our ring switching approach to the synthesis of glutamate antagonists. The product is an isomer of the natural product willardiine **7**. Use of this two step strategy has allowed us to synthesise L-alanine derivatives, which are β-substituted by a reduced pyrimidinedione containing a second chiral centre. There is little difference between the diastereoisomers of one of these compounds as antagonists at metabotropic glutamate receptors.

L-Alanine derivatives substituted at the β-carbon with a heterocyclic ring are of interest because of their potential for interaction with excitatory glutamate receptors in the central nervous system and because of their involvement in many other biological processes. We have recently devised a novel 'ring switching' strategy to allow for the versatile synthesis of homochiral compounds with structures typical of glutamate agonists and antagonists.[1–3] In this synthesis, reaction of a protected 4-formylpyroglutamate ester **3** with a bisnucleophile gave rise, on deprotection, to a variety of homochiral heterocyclic amino acids such as **4**, **5** or **6**, as shown in Scheme 1.

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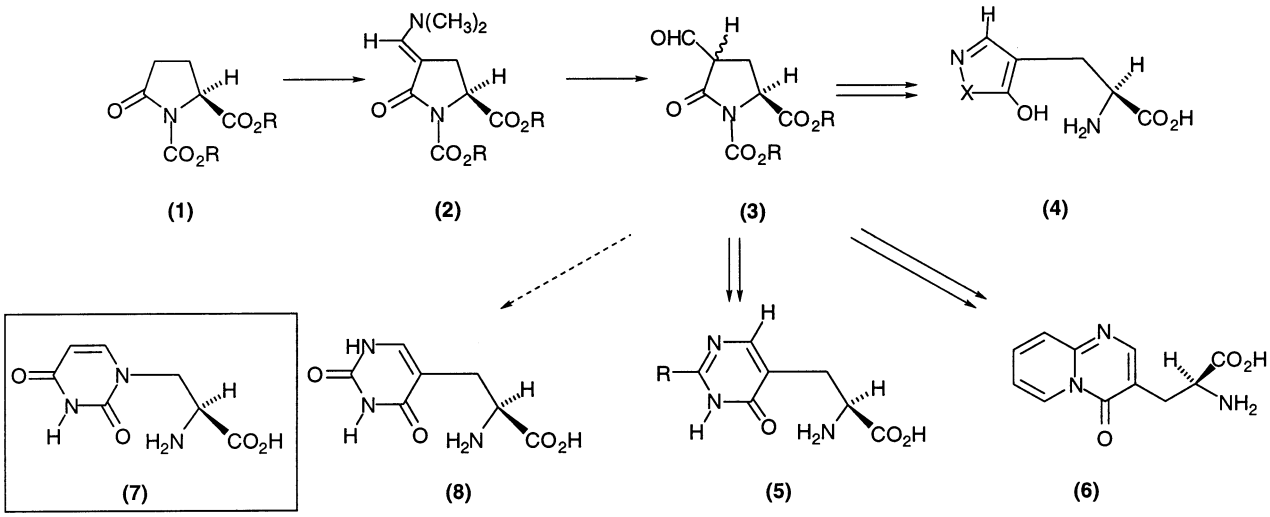
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01800-1



Scheme 1.

The reported biological activity of the natural product willardiine **7**[4,5] made the synthesis of isomeric pyrimidinediones of interest. 2-(Pyrimidin-2,4-dione-5-ylmethyl)-(2*S*)-glycine **8** has been erroneously reported in the secondary literature[6] as the structure of a naturally occurring compound present in pea seedlings. We showed[2,3] that reaction of an enol ether of **3** with formamidine, benzamidine, acetamidine and guanidine gave rise, after deprotection, to the pyrimidinones **5** (R = H, Ph, Me and NH_2). The ^1H NMR spectra of these compounds showed unusual conformational isomerism,[3] and a single crystal X-ray structure reported here[7] (Fig. 1(a)) has confirmed the structure of the dihydrochloride hydrate of **5** (R = H). However, all attempts to prepare the pyrimidinedione **8** and related compounds by reacting the poorer nucleophiles urea and thiourea with the pyroglutamate aldehyde **3** have proved ineffective.[2,3]

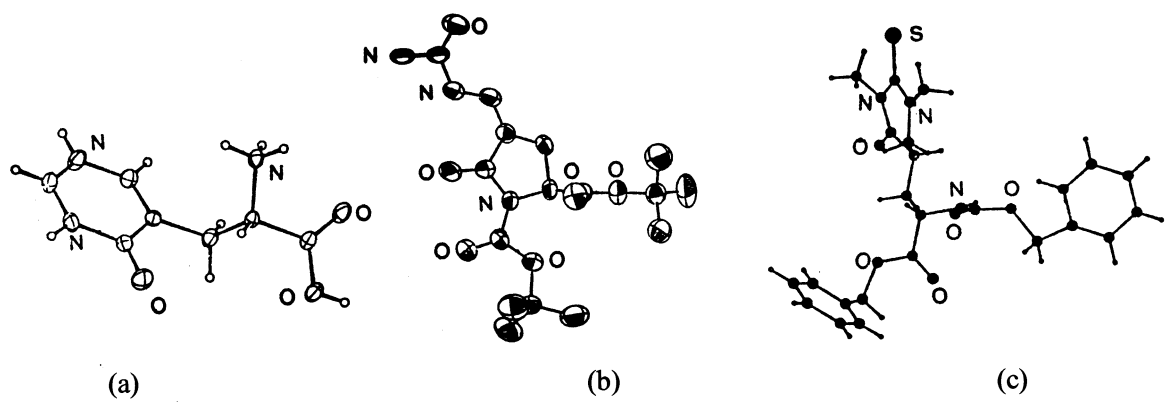
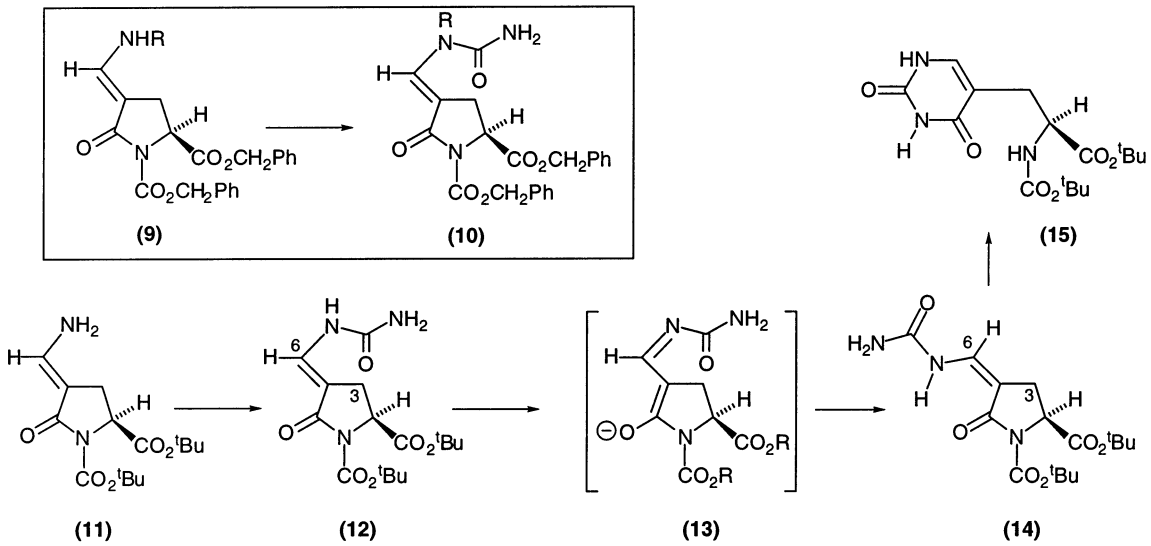


Figure 1. X-Ray structures of (a) **5** (R = H)·2HCl·H_2O; (b) **14** and (c) **19** (R = R^1 = Me, X = S)

An alternative synthetic approach to pyrimidinedione analogues of willardiine was required. Arguing that, if a bond could be made between the carbon atom of the aldehyde and a nitrogen atom from the poor nucleophile, then the subsequent 'ring switching' process might be possible, we prepared the secondary enaminone **9** (R = CH_3), λ_{max} 315 nm, by treating aldehyde **3** (R = CH_2Ph) with excess methylamine at room temperature for 15 min. The enaminone was entirely the *E*-isomer **9** (R = Me) in the crystalline state but formed a mixture of *E*- and *Z*-isomers on standing in solution. The signal for the NH proton at δ ca. 7.8 ppm for the *Z*-isomer was over 3 ppm downfield from the corresponding proton (δ 4.42 ppm) in the *E*-isomer, consistent with the hydrogen bonding expected in the former isomer. The enaminone **9** (R = Me) reacted with chlorosulfonyl isocyanate to afford the urea **10** (R = CH_3) as a glass, $[\alpha]_D$ +11 (*c* 0.6, $CHCl_3$), λ_{max} 274 nm[§] in 88% yield. Attempts to cause this compound to undergo 'ring switching' by thermolysis failed completely and heating to reflux in K_2CO_3/EtOH seemed merely to remove the protecting groups (Scheme 2).



Scheme 2.

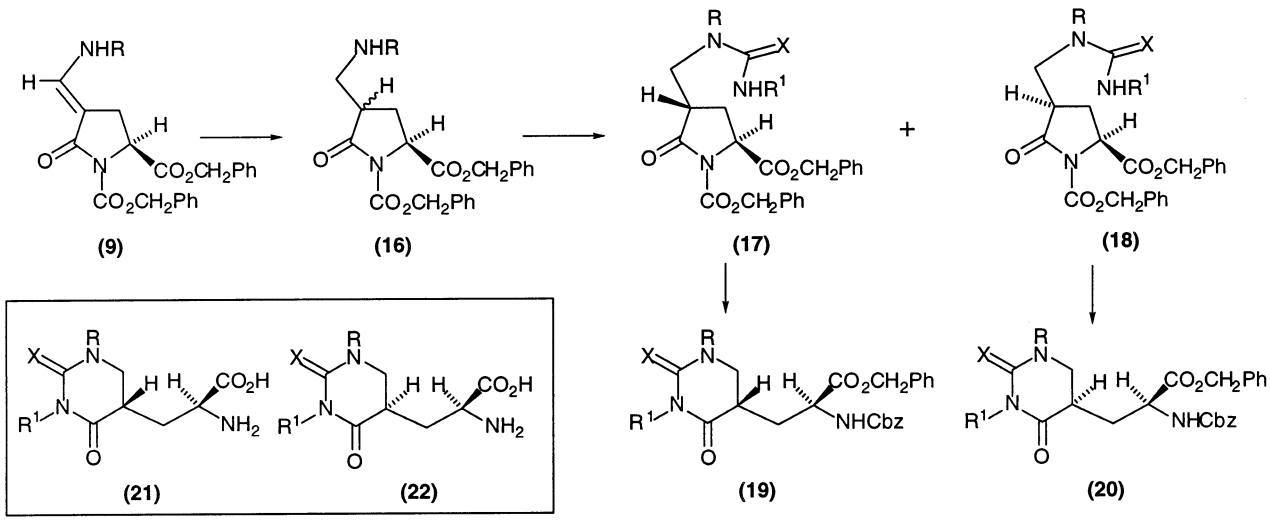
Because failure of the urea **10** (R = CH_3) to undergo 'ring switching' might be due to it being fixed as the *E*-isomer, the corresponding urea **10** (R = H) was prepared from the primary enaminone **9** (R = H). On treatment with base, this should be capable of yielding the *Z*-isomer required for cyclisation. The primary enaminone **9** (R = H), mp 82–85°C, $[\alpha]_D$ −33 (*c* 1, $CHCl_3$),[§] was prepared in 68% yield by reacting the unstable aldehyde **3** (R = CH_2Ph) with NH_4OAc/AcOH in the presence of 3 Å molecular sieves. The ^1H NMR spectrum at room temperature showed the olefinic proton at δ 6.67 ppm, coupled to the NH_2 protons, which were not apparent in the spectrum at this temperature but were evident at 60°C as a broad signal at δ 6.16 ppm, and at −50°C as individual absorptions due to the NH protons of the *Z*-isomer. Reaction of the enaminone **9** (R = H) with chlorosulfonyl isocyanate gave the urea **10** (R = H), mp 199–200°C, $[\alpha]_D$ +17 (*c* 0.8, $CHCl_3$)[§] in 67% yield. This was heated to reflux in K_2CO_3/EtOH, but again deprotection appeared to be the only reaction.

[§] These compounds had the expected analytical and spectroscopic properties.

Since instability of the protecting groups seemed to be a problem, we prepared the *tert*-butoxycarbonyl *tert*-butyl ester **11**[§] in 40% overall yield, by first reacting the corresponding unfunctionalised diprotected pyroglutamate[8] with lithium hexamethyldisilazide, followed by treatment with methyl formate to yield the intermediate aldehyde as an oil and then reacting this with NH_4OAc/AcOH and 3 Å molecular sieves. The primary enaminone **11**[§] had similar spectroscopic properties at room temperature, 60 and −50°C to those exhibited by **10** (R = H). Reaction with chlorosulfonylisocyanate and flash chromatography of the product on silica gel gave the *Z*-isomer **14**,[§] mp 183–185°C, $[\alpha]_D$ −31.6 (*c* 0.6, MeOH) in 18% yield, and the *E*-isomer **12**,[§] mp 175–177°C, $[\alpha]_D$ +13 (*c* 0.5, MeOH) in 22% yield. The stereochemistry and structure of the isomers was indicated by NOE experiments. Irradiation of the olefinic proton, H-6, at 7.24 ppm in the spectrum of the *Z*-isomer **14** caused a 1.98% NOE in one of the absorptions due to H-3, whereas irradiation at the exchangeable NH signal at δ 8.99 ppm in the spectrum of the *E*-isomer **12** caused small enhancements in both protons H-3. The NH signal in the *Z*-isomer **14** was 0.7 ppm downfield from that in the *E*-isomer **12**, indicating hydrogen bonding in **14**. The stereochemistry was confirmed by single-crystal X-ray structure analysis of the *Z*-isomer **14**,[9] shown in Fig. 1(b), where the distance between the lactam carbonyl group and NH was 1.98 Å.

When the *E*-urea **12** was heated at reflux in ethanol containing 1 equiv. of K_2CO_3, 'ring switching' was finally accomplished and the protected pyrimidin-2,4-dione **15**[§] was obtained in 57% yield. Deprotection of the pyrimidine-2,4-dione using hydrochloric acid gave the amino acid **8**[§] in quantitative yield, mp 245°C (decomp.), $[\alpha]_D$ −11.6 (*c* 1.2, H_2O).

All of the compounds which we have prepared to date with potential for interaction with glutamate receptors have been in the L-series and have contained but one asymmetric centre. It was of interest to see whether compounds containing a second asymmetric centre in the heterocyclic ring might be biologically active and whether biological activity might be related to stereochemistry. We therefore reduced the secondary enaminone **9** (R = Me) with sodium cyanoborohydride in methanol at pH 3–4.6 using screened methyl orange and 1 M HCl to maintain pH as shown in Scheme 3. The diastereoisomeric amines **16** (R = Me) were obtained as an inseparable mixture. Reaction with phenylisocyanate gave the corresponding ureas **17** (R = Me, R^1 = Ph, X = O) and **18** (R = Me, R^1 = Ph, X = O) in 90% yield and these could be



Scheme 3.

separated chromatographically and assigned stereochemistry using NOE experiments. The ratio of *trans* **17** to *cis* **18** isomers was 7:3. Although treatment of the major isomer **17** (R = Me, R^1 = Ph, X = O) with sodium hydride in THF caused 'ring switching' in 40% yield, this was accompanied by epimerisation to give a mixture of **19** (R = Me, R^1 = Ph, X = O) and **20** (R = Me, R^1 = Ph, X = O) which could be separated chromatographically. Thermal rearrangement could be achieved without epimerisation, albeit in only 20% yield, but this allowed the stereochemistry of the products to be assigned. Deprotection by hydrogenolysis gave the free amino acids **21** (R = Me, R^1 = Ph, X = O) and **22** (R = Me, R^1 = Ph, X = O) and these were found to be equally weakly antagonistic to the action of the metabotropic agonist *trans*-aminocyclopentanedicarboxylic acid (ACDP) in Purkinje rat cells.[10]

Reaction of the amines **16** (R = Me) with KCNO/HOAc gave the ureas **17** (R = Me, R^1 = H, X = O) and **18** (R = Me, R^1 = H, X = O) in 86% yield as a pure mixture of diastereoisomers, which could be rearranged to the protected heterocyclic amino acids **19** (R = Me, R^1 = H, X = O) and **20** (R = Me, R^1 = H, X = O) using NaH in 90% yield. These could be deprotected by hydrogenolysis, giving the amino acids **21** (R = Me, R^1 = H, X = O) and **22** (R = Me, R^1 = H, X = O) in 90% yield. Reaction of the amines **16** (R = Me) with methylisothiocyanate in CH_2Cl_2 gave an inseparable 7:3 mixture of the diastereoisomeric thioureas (**17**, R = R^1 = Me, X = S) and **18** (R = R^1 = Me, X = S) in 72% yield. Thermal rearrangement gave the 'ring switched' products **19** (R = R^1 = Me, X = S) and **20** (R = R^1 = Me, X = S) in 75% yield in unchanged ratio, and these were separated chromatographically. Single-crystal X-ray structural analysis (Fig. 1(c))[11] confirmed that the major isomer was the (2*S*,4*S*)-isomer **19** (R = R^1 = Me, X = S). All attempts to deprotect the thiopyrimidones to obtain the corresponding amino acids were unsuccessful.

Reduction of the primary enaminone **11**, reaction with KCNO/HOAc, ring switching and deprotection has also allowed us to access **21** (R = R^1 = H, X = O) and **22** (R = R^1 = H, X = O).

Acknowledgements

We thank the E.P.S.R.C. and GlaxoWellcome for a CASE studentship (to A.D.).

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7. **Crystal data for 5 (R = H)·2HCl·H_2O**: $C_7H_{13}Cl_2N_3O_4$, orthorhombic, $P2_12_12_1$ (No. 19), a = 5.9010(10), b = 11.953(2), c = 16.801(6) Å, Z = 4, R_1 = 0.033 for 1498 reflections with $I > 2\sigma(I)$. The atomic coordinates are available on request from The Director, Cambridge Crystallography Data Centre (CCDC), University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.
8. August, R. A.; Khan, J. A.; Moody, C. M.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 507–514.
9. **Crystal data for 14**: $C_{16}H_{25}N_3O_6$, orthorhombic, $P2_12_12_1$ (No. 19), a = 9.644(3), b = 18.766(4), c = 21.049 (5) Å, Z = 8, R_1 = 0.086 for 2664 reflections with $I > 2\sigma(I)$. The atomic coordinates are available on request from The Director, Cambridge Crystallography Data Centre (address, Ref. 6).

10. The assay of East, S. J.; Garthwaite, J. *Eur. J. Pharmacol.* **1992**, *219*, 395–400 was performed by Dr. A. Batchelor of the Wellcome foundation. 100 μm of compound **21** (R = Ph, X = O) elicited 85% diminution in the response of 50 μm ACDP, whereas 100 μm of compound **22** (R = Ph, X = O) elicited 76% diminution in this response.
11. **Crystal data for 19** (**R** = **Me**, **X** = **S**): $C_{24}H_{27}N_3O_5S$, orthorhombic, $P2_12_12_1$ (No. 19), $a = 11.315(3)$, $b = 10.348(4)$, $c = 23.186(6)$ Å, $Z = 4$, $R_1 = 0.130$ for 3371 reflections with $I > 2\sigma(I)$. The atomic coordinates are available from The Director, Cambridge Crystallography Data Centre (address, Ref. 6).