

Synthesis of novel conformationally restricted L-glutamate analogues

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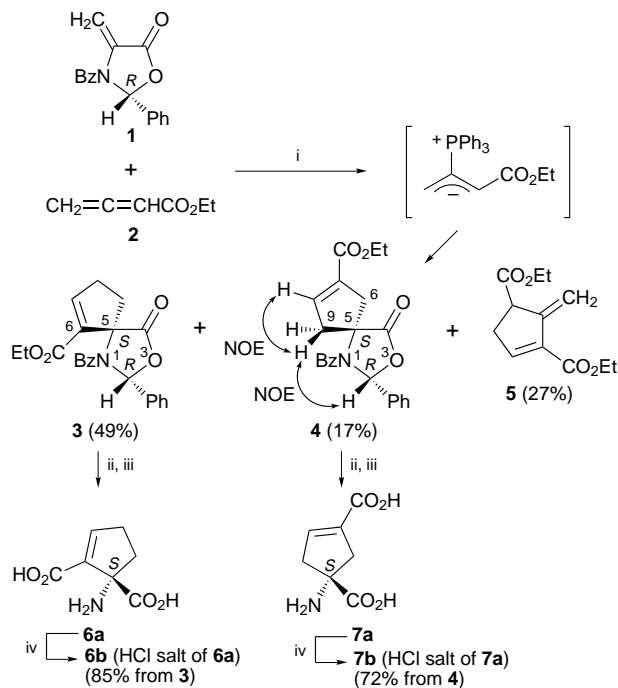
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The novel, optically active and conformationally restricted L-glutamate analogues **6**, **7** and **11** have been prepared via the PPh₃ catalysed cycloaddition of the allenes **2** and **9** with the chiral oxazolidinone **1**.

L-Glutamate is an excitatory neurotransmitter in the mammalian central nervous system (CNS). This amino acid activates both the metabotropic and the ionotropic group of glutamate receptors. The latter group includes the *N*-methyl-D-aspartic acid (NMDA), α -amino-3-hydroxy-5-methylisoxazole-4-propionate and kainate receptor subclasses. These receptors form ligand-gated ion channels and mediate excitatory neurotransmission. The former receptor group are coupled to G-proteins and activate or inhibit intracellular signals. Elevated glutamate concentrations can lead to excitotoxicity which has been implicated in the pathogenesis of neurological disorders, including epilepsy and chronic neurodegenerative diseases.^{1,2} Excitatory amino acid transporters (EAATs) in the CNS maintain extracellular glutamate concentrations below excitotoxic levels.³ Selective agonists and antagonists for glutamate receptor subtypes¹ and selective blockers for EAATs are invaluable tools in understanding neuronal biochemistry. Furthermore, such compounds allow an understanding of the structural features of these receptor subtypes and the future design of new therapeutics for the treatment of neurodegenerative diseases.¹ One such compound is the conformationally restricted glutamate analogue, (1*S*,3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid (ACPD), which selectively activates metabotropic glutamate

receptors and differentiates them from the ionotropic type.⁴ Here we describe a novel synthesis of some dehydro derivatives of ACPDA via the cycloaddition reactions of the chiral oxazolidinone **1**⁵ and allenic esters **2** and **9** and report some preliminary results on the pharmacological activities of these compounds.

Treatment of a benzene solution of the oxazolidinone **1** (1 equiv.) and ethyl buta-2,3-dienoate **2**⁶ (5 equiv.) with PPh₃⁷ (0.1 equiv.) at room temperature for 5 h gave, after purification by column chromatography, the major cycloadduct **3**[†] (49%), the minor cycloadduct **4**[†] (17%) and the dimer **5**^{7a} (27%) (Scheme 1). The diastereoisomeric ratio of **3** and **4** was estimated to be 77:23 from ¹H NMR analysis of the crude reaction mixture. The stereochemistry of **3** was revealed by a single crystal X-ray structural analysis, as shown in Fig. 1.[‡] This analysis showed that the major cycloadduct had the 5*S* stereochemistry at the newly created stereogenic centre, consistent with the known tendency of **1** in [3 + 2] cycloaddition reactions to give products that arise from attack of the three-atom component *anti* to the C(2) phenyl substituent.⁸ The minor cycloadduct **4** was a regioisomer of **3** and also had the 5*S* stereochemistry as shown by NOESY experiments which revealed cross-peaks between the signal for H-2 and that for one H-9 proton, as indicated in structure **4** (Scheme 1). Interestingly, the regiochemistry of the major cycloadduct **3** was different to that of the major cycloadduct formed from the reaction of ethyl acrylate or methyl methacrylate with 2-PPh₃.^{7a} The enantiomeric purity of **3** was determined to be 88% from ¹H NMR analysis of its



Scheme 1 Reagents and conditions: i, PPh₃ (10 mol%); ii, 6 M HCl, reflux, 16 h; iii, ion-exchange; iv, HCl

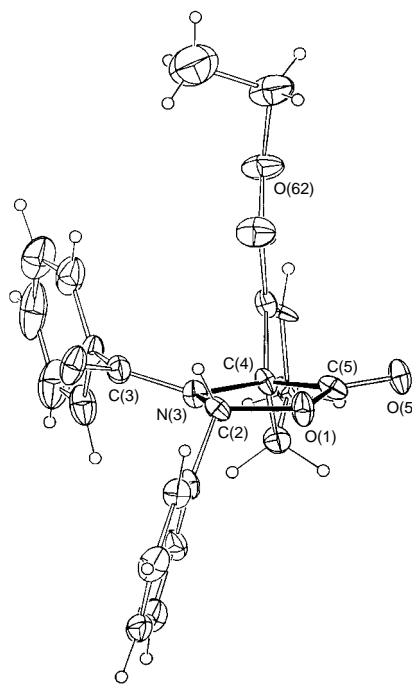
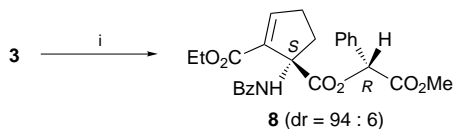


Fig. 1 Projection of **3** through the heterocyclic ring plane (20% thermal ellipsoids are shown for C, N, O, H having arbitrary radii of 0.1 Å)



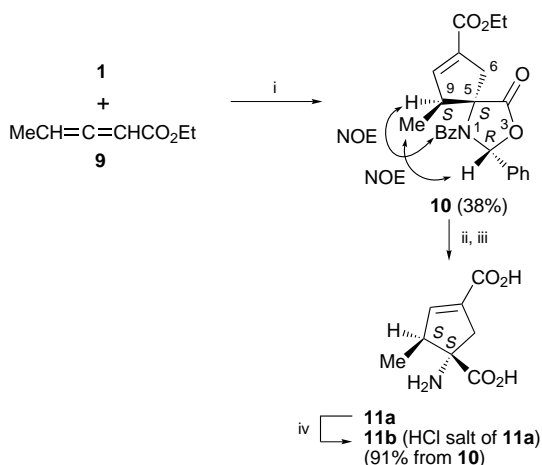
Scheme 2 Reagents and conditions: i, (*R*)-methyl mandelate, Et₃N, CH₂Cl₂, 7 days, 63%

(*R*)-methyl mandelate derivative **8**, which was a 94 : 6 mixture of diastereoisomers [major: $\delta_{\text{H}}(\text{CDCl}_3)$ 5.99 (s), minor 5.98 (s)] (Scheme 2). Acid hydrolysis of **3** and **4** followed by purification *via* ion-exchange chromatography gave diastereoisomerically pure amino acids **6a** and **7a**, respectively, which were characterized as their respective hydrochloride salts, **6b**[†] and **7b**.[†] Amino acid **7a** has been reported recently, however this product was racemic and was obtained as a mixture of two isomers from which racemic **7a** could be obtained in 1.75% yield after selective crystallization.⁹

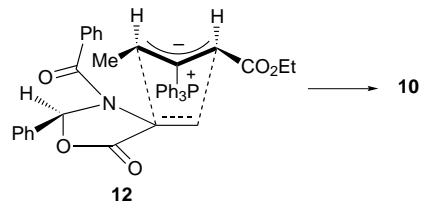
Treatment of a benzene solution of **1** and ethyl penta-2,3-dienoate **9**⁶ (5 equiv.) with PPh₃ (0.1 equiv.) at room temperature for 5 h gave a single cycloadduct **10**[†] in 38% isolated yield after purification by column chromatography on silica gel. No other stereoisomer of **10** could be detected by ¹H NMR analysis of, or was isolated from, the crude reaction mixture. The 5*S*,9*S* stereochemistry of **10** was evident from NOESY experiments, which showed cross-peaks between H-2 and the C(9) methyl group and between H-9 and the *ortho* protons of the benzamido group, as shown in Scheme 3. Acid hydrolysis of **10** gave the amino acid **11a**, which was characterized as its hydrochloride salt **11b**.[†]

Thus the PPh₃ catalysed reactions of **2** and **9** with oxazolidinone **1** proceed in a different regiochemical sense. It is not clear if these reactions occur *via* a four step reaction sequence that involves initially a Michael addition reaction, then cyclization followed by proton transfer and then elimination of PPh₃,^{7b} or *via* a three step mechanism *via* an initial 'concerted' 2,3-cycloaddition reaction.^{7a} In the latter case, the transition state structure **12**, in which steric interactions between the substituents on the zwitterionic species formed between **9** and PPh₃ and the benzamido group on **1** are minimized, is consistent with the observed stereochemical outcome in **10** (Scheme 4). Attempts to obtain cycloadducts from the (2*S*)-*tert*-butyl analogue⁵ of **1** and allene **2** gave only the dimer **5**.

In some preliminary studies, amino acids **6**, **7** and **11** showed no activity against NMDA-induced depolarizations in the rat neocortex at 500 μM concentrations.¹⁰ Compound **11**, however, selectively blocks glutamate transport by EAAT2 expressed in



Scheme 3 Reagents and conditions: i, PPh₃ (10 mol%); ii, 6 M HCl, reflux, 16 h; iii, ion-exchange; iv, HCl



Scheme 4

oocytes ($K_i = 62 \mu\text{M}$) but is inactive on EAAT1.¹¹ Further biological studies are in progress and these will be reported in a future paper.

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Footnotes and References

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[†] Selected data for **3**: colourless crystals, mp 144–146 °C, $[\alpha]_{\text{D}}^{21} +155$ (c 0.60, CHCl₃); $\delta_{\text{H}}(\text{CDCl}_3)$ 1.35 (t, *J* 7.2, 3 H), 2.75–3.19 (m, 4 H, H-8 α , H-8 β , H-9 α and H-9 β), 4.28 (q, *J* 7.2, 2 H), 6.77 (br s, 1 H, H-2), 6.97 (br s, 1 H, H-7), 7.02 (d, *J* 6.9, 2 H), 7.25 (d, *J* 6.9, 2 H), 7.29–7.39 (m, 6 H). For **4**: white solid, mp 70–73 °C, $[\alpha]_{\text{D}}^{23} +202$ (c 0.10, CHCl₃); $\delta_{\text{H}}(\text{CDCl}_3)$ 1.32 (t, *J* 7.2, 3 H), 3.20–3.26 (m, 1 H, H-9 α), 3.32–3.39 (m, 2 H, H-6 α and H-9 β), 3.60–3.66 (m, 1 H, H-6 β), 4.23 (q, *J* 7.2, 2 H), 6.67 (br s, 1 H, H-2), 6.72 (br s, 1 H, H-8), 6.91 (d, *J* 7.5, 2 H), 7.12 (d, *J* 7.2, 2 H), 7.20–7.35 (m, 6 H). For **10**: pale yellow gum, $[\alpha]_{\text{D}}^{21} +90$ (c 0.30, CHCl₃); $\delta_{\text{H}}(\text{CDCl}_3)$ 1.33 (t, *J* 7.2, 3 H), 1.38 (d, *J* 7.5, 3 H), 3.45–3.51 (m, 1 H, H-6 α), 3.65–3.71 (m, 1 H, H-6 β), 3.74–3.79 (m, 1 H, H-6 β), 4.24 (q, *J* 7.2, 2 H), 6.57 (s, 1 H, H-2), 6.68 (br s, 1 H, H-8), 6.81, d, *J* 6.9, 2 H), 7.02 (d, *J* 6.9, 2 H), 7.1–7.33 (m, 6 H). For **6b**: white solid, mp >250 °C, $[\alpha]_{\text{D}}^{22} +15$ (c 0.20, 6 M HCl); $\delta_{\text{H}}(\text{D}_2\text{O})$ 2.78–2.84 (app br d, *J* 16.2, 2 H, H-2 α and H-5 α), 3.22–3.27 (app br d, *J* 16.8, 2 H, H-2 β and H-5 β), 6.66 (br s, 1 H, H-4). For **7b**: white hygroscopic solid, mp >250 °C, $[\alpha]_{\text{D}}^{22} +11$ (c 0.40, 6 M HCl); $\delta_{\text{H}}(\text{D}_2\text{O})$ 2.09–2.18 (m, 1 H, H-5 α), 2.39–2.48 (m, 1 H, H-5 β), 2.57–2.68 (m, 2 H, H-4 α and H-4 β), 6.82 (br s, 1 H, H-3). For **11b**: white hygroscopic solid, mp >250, $[\alpha]_{\text{D}}^{22} +10$ (c 0.10, 6 M HCl); $\delta_{\text{H}}(\text{D}_2\text{O})$ 1.13 (d, *J* 7.5, 3 H), 3.30 (app t, *J* 1.8, 1 H, H-2 α), 3.36 (app t, *J* 2.1, 1 H, H-2 β), 3.55–3.65 (m, 1 H, H-5), 6.64 (s, 1 H, H-4).

[‡] Selected X-ray data for **3**: C₂₃H₂₁NO₅, *M* = 391.4; orthorhombic, *P*2₁2₁2₁, *a* = 21.13(1), *b* = 11.22(1), *c* = 8.474(7) Å, *V* = 2009 Å³, *D*_c (*Z* = 4) = 1.29 g cm⁻³, 795 'observed' [*I* > 3 σ (*I*)] diffractometer reflections out of 2032 independent to 2 θ_{max} = 50° (monochromatic Mo-K α radiation, λ = 0.7107 Å, no absorption correction) yielding conventional *R*, *R*_w |*F*| = 0.054, 0.046 (statistical weights). Anisotropic C, N, O thermal parameter refinement (*x*, *y*, *z*, *U*_{iso})_H constrained at estimates *T* = 295 K. Chirality was assigned from the chemistry. CCDC 182/630.

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