Synthesis of novel conformationally restricted L-glutamate analogues

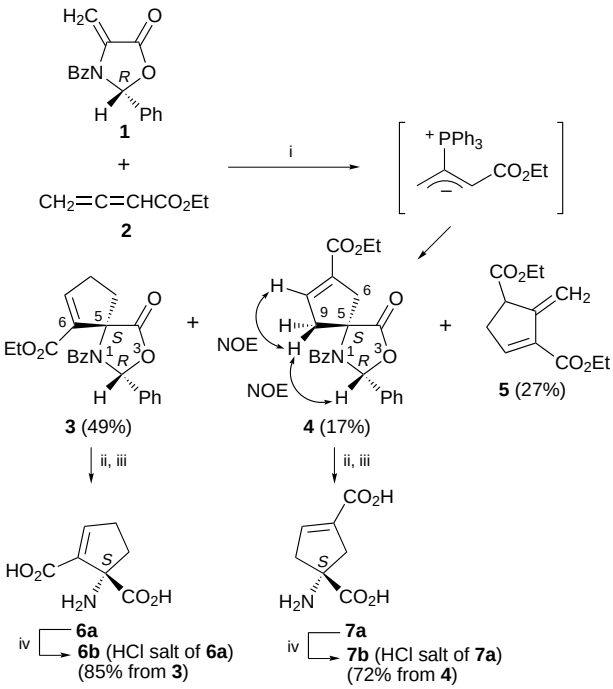
Stephen G. Pyne,*[a] Karl Schafer,[a] Brian W. Skelton[b] and Allan H. White[b]

[a] *Department of Chemistry, University of Wollongong, Wollongong, New South Wales, 2522, Australia*
[b] *Department of Chemistry, University of Western Australia, Nedlands, Western Australia, 6907, Australia*

The novel, optically active and conformationally restricted L-glutamate analogues 6, 7 and 11 have been prepared *via* the PPh_3 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 excitoxicity 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 subtypes[1] 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 (ACPDA), 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 PPh_3[7] (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 ^{1}H 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**–PPh_3.[7a] The enantiomeric purity of **3** was determined to be 88% from ^{1}H NMR analysis of its



Scheme 1 *Reagents and conditions*: i, PPh_3 (10 mol%); ii, 6 M HCl, reflux, 16 h; iii, ion-exchange; iv, HCl

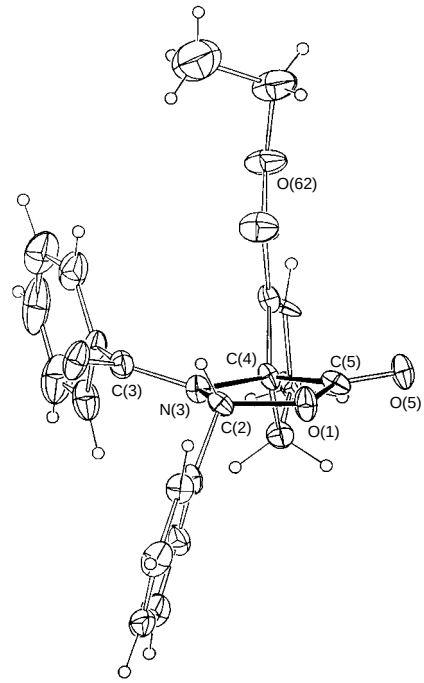
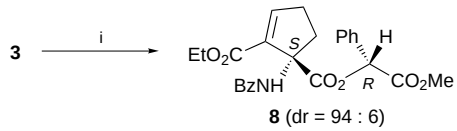


Fig. 1 Projection of **3** through the heterocyclic ring plane (20% thermal ellipsoids are shown for C, N, O, H having arbitrary radii of 0.1 Å)



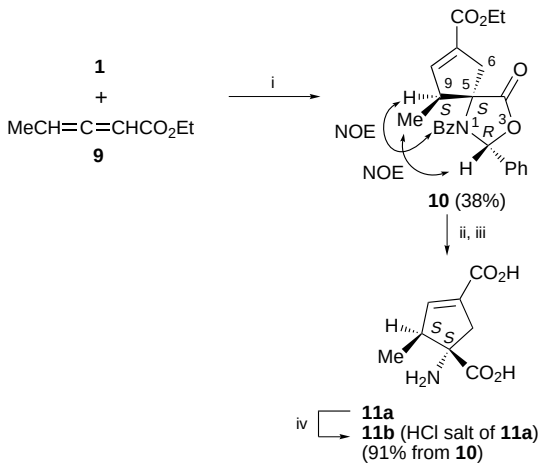
Scheme 2 *Reagents and conditions*: i, (*R*)-methyl mandelate, Et_3N, CH_2Cl_2, 7 days, 63%

(*R*)-methyl mandelate derivative **8**, which was a 94 : 6 mixture of diastereoisomers [major: $\delta_H(CDCl_3)$ 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]

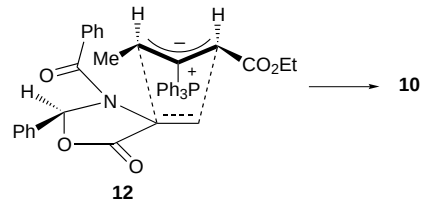
Treatment of a benzene solution of **1** and ethyl penta-2,3-dienoate **9**[6] (5 equiv.) with PPh_3 (0.1 equiv.) at room temperature for 5 h gave a single cycloadduct **10**† in 38% isolated yield after purification by column chromatography on silica gel. No other stereoisomer of **10** could be detected 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 PPh_3 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 PPh_3,[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 PPh_3 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 analogue[5] 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, PPh_3 (10 mol%); ii, 6 M HCl, reflux, 16 h; iii, ion-exchange; iv, HCl



Scheme 4

oocytes (K_i = 62 μM) 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

* E-mail: s.pyne@uow.edu.au

† *Selected data* for **3**: colourless crystals, mp 144–146 °C, $[\alpha]_D^{21}$ +155 (*c* 0.60, $CHCl_3$); $\delta_H(CDCl_3)$ 1.35 (t, *J* 7.2, 3 H), 2.75–3.19 (m, 4 H, H-8α, H-8β, H-9α and H-9β), 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, $[\alpha]_D^{23}$ +202 (*c* 0.10, $CHCl_3$); $\delta_H(CDCl_3)$ 1.32 (t, *J* 7.2, 3 H), 3.20–3.26 (m, 1 H, H-9α), 3.32–3.39 (m, 2 H, H-6α and H-9β), 3.60–3.66 (m, 1 H, H-6β), 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, $[\alpha]_D^{21}$ +90 (*c* 0.30, $CHCl_3$); $\delta_H(CDCl_3)$ 1.33 (t, *J* 7.2, 3 H), 1.38 (d, *J* 7.5, 3 H), 3.45–3.51 (m, 1 H, H-6α), 3.65–3.71 (m, 1 H, H-6β), 3.74–3.79 (m, 1 H, H-6β), 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, $[\alpha]_D^{22}$ +15 (*c* 0.20, 6 M HCl); $\delta_H(D_2O)$ 2.78–2.84 (app br d, *J* 16.2, 2 H, H-2α and H-5α), 3.22–3.27 (app br d, *J* 16.8, 2 H, H-2β and H-5β), 6.66 (br s, 1 H, H-4). For **7b**: white hygroscopic solid, mp > 250 °C, $[\alpha]_D^{22}$ +11 (*c* 0.40, 6 M HCl); $\delta_H(D_2O)$ 2.09–2.18 (m, 1 H, H-5α), 2.39–2.48 (m, 1 H, H-5β), 2.57–2.68 (m, 2 H, H-4α and H-4β), 6.82 (br s, 1 H, H-3). For **11b**: white hygroscopic solid, mp > 250, $[\alpha]_D^{22}$ +10 (*c* 0.10, 6 M HCl); $\delta_H(D_2O)$ 1.13 (d, *J* 7.5, 3 H), 3.30 (app t, *J* 1.8, 1 H, H-2α), 3.36 (app t, *J* 2.1, 1 H, H-2β), 3.55–3.65 (m, 1 H, H-5), 6.64 (s, 1 H, H-4).

‡ *Selected X-ray data* for **3**: $C_{23}H_{21}NO_5$, *M* = 391.4; orthorhombic, $P2_12_12_1$, *a* = 21.13(1), *b* = 11.22(1), *c* = 8.474(7) Å, *V* = 2009 Å^3, D_c (*Z* = 4) = 1.29 g cm^{-3}, 795 'observed' [$I > 3\sigma(I)$] diffractometer reflections out of 2032 independent to $2\theta_{max}$ = 50° (monochromatic Mo-Kα 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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