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The Synthesis of [2.2.2]Bicyclooctane and [3.1.1]Bicycloheptane Based Amino Acids as Constrained Glutamate Analogues.

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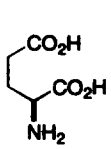
Abstract

A novel [2.2.2]bicyclooctane analogue of glutamic acid was synthesised using a modification of the Corey-Link amino acid synthesis. A related [3.1.1]bicycloheptane was prepared by cyclising a symmetrical 4,4-disubstituted cyclohexanone.

Keywords: amino acids; bicyclic aliphatic compounds; cyclisation

The amino acid glutamate **1** is the major neurotransmitter in the mammalian central nervous system and acts at two classes of receptors. Ionotropic receptors are ligand gated ion channels, while metabotropic glutamate receptors (mGluRs) are a family of G-protein coupled receptors. To date, eight distinct metabotropic glutamate receptor proteins (mGluR1-8) have been identified and divided into three subgroups according to sequence homology, signal transduction mechanism and pharmacology[1,2]. Group I receptors (mGluR1 and mGluR5) activate phospholipase C which results in the release of intracellular calcium stores *via* the second messenger inositol triphosphate. Groups II and III (comprising mGluR2 and 3 and mGluR4, 6, 7 and 8 respectively) are negatively coupled to adenylate cyclase and their activation leads to decreased intracellular cyclic AMP levels. There is at present considerable interest in the discovery of subgroup selective ligands for mGluRs with the aim of developing pharmacological probes and drug candidates for the treatment of neurological disorders as diverse as pain, ischaemia, epilepsy and various chronic neurodegenerative diseases.



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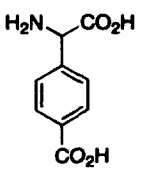

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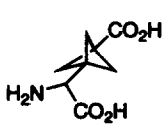

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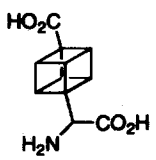

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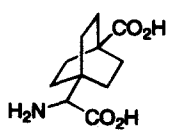

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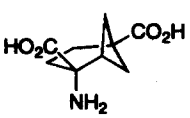

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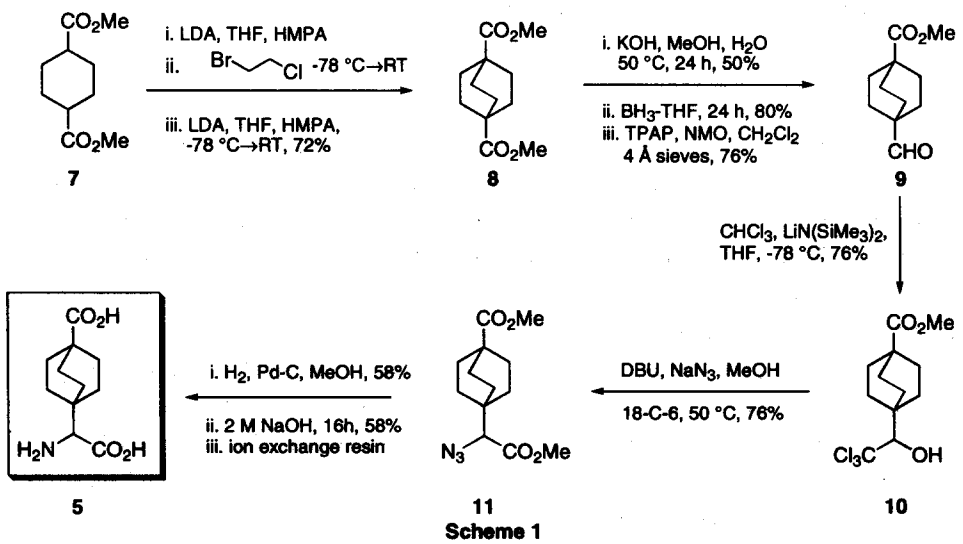
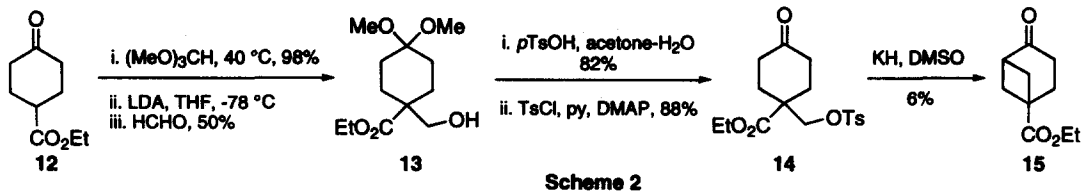
With this incentive we have sought to find new ligands for Group I receptors. Current ligands include 4-carboxyphenylglycine **2**[3] and the [1.1.1]bicyclopentane **3**[4]. In both of these compounds the bond linking the distal carboxylic acid to the rest of the molecule bisects the glycine dihedral angle, a feature also present in **4**[5] and the novel amino acids **5** and **6.**

In this paper we report the synthesis of these two novel amino acids **5** and **6** which form part of the general family described above. The synthesis of the [2.2.2]bicyclooctane based amino acid is outlined in Scheme 1. The [2.2.2]bicyclooctane diester **8** was prepared from a mixture of *cis* and *trans* dimethylhexahydroterephthalate **7** in a two step sequence[6]. Basic hydrolysis provided the corresponding half acid[7] in up to 50% yield together with 25% recovered starting material. Selective reduction of the acid was achieved with borane-THF complex[8] over a 24 h period and the resulting primary alcohol oxidised with TPAP[9] to furnish the aldehyde **9**. Surprisingly, this aldehyde failed to react under both Bucherer Berg and ultrasound promoted Strecker[10] conditions. As an alternative we employed a novel modification of the Corey-Link amino acid synthesis[11] in which *chloroform anion was added to the carbonyl component* to afford **10**. This approach offers a more general access to the β-trichloromethyl alcohol intermediate and can be applied to ketones as well as aldehydes, offering a new synthesis of α,α-disubstituted amino acids[12]. Treatment of **10** with sodium azide, employing methanol as the solvent and diazabicyclo[5.4.0]undec-7-ene (DBU) as the base rather than sodium hydroxide furnished the azido ester **11**, instead of the corresponding acid, presumably by way of the generally accepted pathway[11]. This new procedure has the advantage of permitting the amino acid precursor to be purified readily by chromatography. Reduction of the azide **11** followed by basic hydrolysis provided the amino acid **5**.[1]



Scheme 1

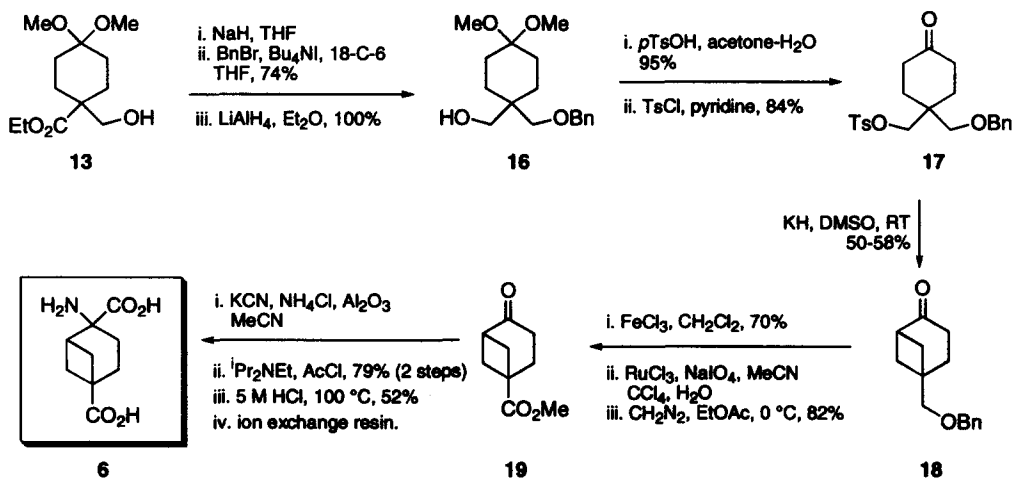
The synthesis of the structurally more challenging [3.1.1]bicycloheptane amino acid **6** commenced with the keto ester **12** (Scheme 2). Protection of the ketone as the corresponding dimethyl acetal was achieved with trimethyl orthoformate. Sequential treatment with lithium diisopropyl amide (LDA) and formaldehyde, obtained by heating paraformaldehyde to >150 °C, provided the primary alcohol **13**.



Scheme 2

Conversion to the keto tosylate **14** proceeded in good yield to give the cyclisation precursor. Cyclisation of the corresponding system lacking the C-4 ester group is known[13]. However, in this instance, treatment of **14** with a range of bases provided at best only a trace of the required compound **15** with a poor overall mass recovery. The bases examined for the cyclisation included sodium hexamethyldisilazide[14], sodium hydride[15] and dimsyl sodium[16], although they were found to be uniformly poor. It seemed likely that the electrophilic ester was responsible for this failure so the corresponding cyclisation precursor in which the ester had been reduced and protected was prepared (Scheme 3). Protection of the primary alcohol **13** as the corresponding benzyl ether[17] followed by reduction of the ester with lithium aluminium hydride gave the alcohol **16**. Subjecting this to similar conditions as before gave the primary tosylate **17** in good overall yield. Gratifyingly, slow addition of this keto-tosylate to a solution of dimsyl potassium in DMSO at room temperature induced cyclisation to the [3.1.1]bicycloheptane **18**, enolization at either carbon giving rise to a single product by virtue of its symmetry.

The removal of the benzyl protecting group proved problematical but was accomplished with iron trichloride[18] and oxidation/esterification afforded the keto-ester **19**. Of those conditions attempted for the latter conversion, catalytic ruthenium trichloride with sodium periodate as co-oxidant[19], followed by treatment of the crude acid with diazomethane proved the most efficient. Strecker reaction promoted by ultrasound[10], followed by acetylation of the crude amino nitrile and then acidic hydrolysis gave the amino acid **6**.[1]



Scheme 3

Both compounds were tested on functional responses of human metabotropic glutamate receptor subtypes mGluR1α and mGluR5a expressed in AV-12 cells, designed to measure the degree of suppression of quisqualate induced PI hydrolysis[20]. Unfortunately, both compounds were inactive in this assay. In the case of **5** this may be a result of the increased steric bulk due to the three additional methylene groups when compared to **3**, while for the amino acid **6** the inactivity may stem from the fixed conformation of the glycine moiety, which fails to match the active site of the receptor.

In conclusion, two new amino acids have been prepared, one employing a novel modification of the Corey-Link synthesis. Both amino acids were designed to incorporate particular structural features with regard to the disposition of the glycine moiety and the distal acid group. Both compounds were inactive on a PI hydrolysis assay. Further studies in this area are ongoing.

[†]The amino acids **5** and **6** were isolated by ion exchange chromatography on DOWEX® 50WX8-100 resin. Selected spectroscopic data for **5**: δ_H(300 MHz; D_2O, KOD) 3.00 (1H, s), 1.55 (6H, m), 1.70 (6H, m); δ_C(75 MHz; D_2O, KOD) 190.8, 182.4, 66.7, 42.8, 36.2, 31.4, 29.9. Data for **6**: δ_H(300 MHz; D_2O, KOD) 2.35 (1H, m), 2.20-2.07 (2H, m), 1.95 (1H, m), 1.95-1.80 (3H, m), 1.64 (1H, dt, *J*, 14.3, 9.1), 1.46 (1H, t, *J* 9.1); δ_C(75 MHz; D_2O, KOD) 189.7, 186.9, 63.8, 51.1, 41.2, 38.6, 33.3, 32.1, 30.6.

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