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Versatile assembly of the 2-carboxybenzo[*b*]azepine ring system

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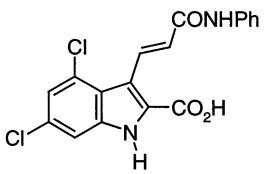
Abstract—A suitable 2-carboxybenzo[*b*]azepine derivative was designed as a potential novel antagonist of the strychnine-insensitive glycine binding site of the NMDA receptor. This compound was synthesized via an *N*-aryl allylglycine, a useful intermediate efficiently prepared from the starting aniline derivative, followed by a short and unusual elaboration of the allyl double bond.

Neurons are highly vulnerable to the very signalling mechanisms that support their ability to receive, process and relay information. Neuronal damage can result from excessive exposure to excitatory amino acids[1] (EAA) and from ingress of abnormally high amounts of Ca^{2+}. Indeed, several pathological conditions of the central nervous system, such as stroke,[2] Huntington's disease,[3] Alzheimer's disease[4] and neurotrauma[5] seem to involve, among other factors, the over-activation of the receptor subtype responding to the exogenous agonist *N*-methyl-D-aspartic acid (NMDA).[6] This receptor, and in particular the modulatory glycine binding site associated with it,[7] is now widely recognized as being a potentially attractive target (Fig. 1).

A sustained effort conducted in our laboratories[8] over the last few years has resulted in the identification of 2-carboxyindole derivatives such as **1**[9] (GV150526) as potent and selective antagonists acting at the glycine binding site associated with the NMDA receptor. During the search for novel classes of ligands of this binding site, the benzoazepine derivative **2** was identified as an alternative template that would additionally enable us to better define the topological requirements of the receptor binding pocket.[10]



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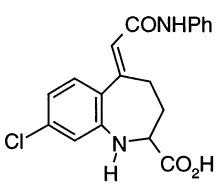

2

Figure 1.

To synthesize this novel class of compounds our plan, as shown in Scheme 1, was to enshrine the whole substitution pattern of the product in a late intermediate **II**, and to effect the cyclization as the last step via a Heck-type reaction. The double bond of **II** would be built via a Horner–Emmons reaction on aldehyde **III**, which derives retrosynthetically from the substituted *N*-phenyl allylglycine **IV**. This intermediate can be derived from **V** through the addition of an allylmetal to a suitable aldimine, a reaction set up in house for the synthesis of tetrahydroquinoline derivatives.[11]

To that end, the reaction of aniline derivative **3** with ethylglyoxal overnight in refluxing toluene, with azeotropic removal of water using a Dean–Stark apparatus, gave the intermediate imine **4** which was, after evaporation of the solvent, dissolved in dry CH_2Cl_2 and treated at −78°C with $TiCl_4$ (1.2 equivalents), followed by the dropwise addition of allyltributyltin (1.2 equivalents). After 1 h the reaction was complete and compound **5** was isolated in 78% overall yield from **3** after purification by flash chromatography. The original synthetic plan, shown in Scheme 1, which called for a hydroboration-oxidation of intermediate **IV**, was rendered impracticable by the failure of any attempt at protecting the poorly nucleophilic secondary amino group. To overcome this issue the alternative route shown in Scheme 2 was envisaged. In this event, the double bond of **5** was oxidized to the corresponding

Keywords: glycine antagonists; synthesis; 2-carboxybenzo[*b*]azepine; allylmetalation reaction.

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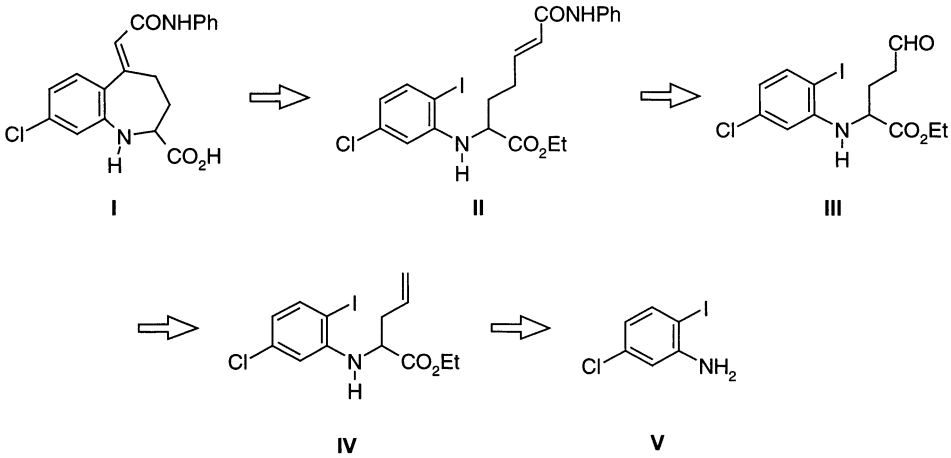
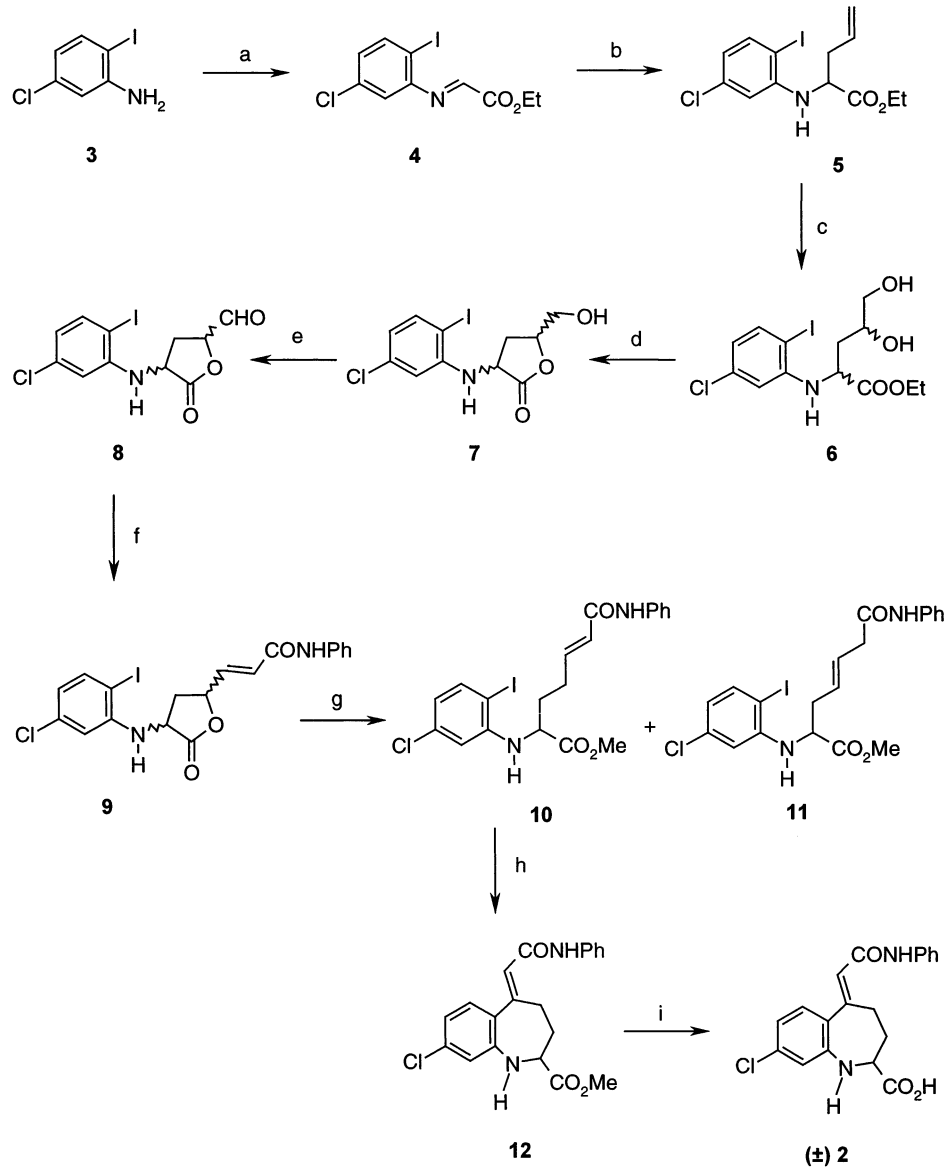


I II III IV V

Scheme 1.



3 4 5 6 7 8 9 10 11 12 (±) 2

Scheme 2. (a) $HCOCO_2Et$ (1.1 equiv.), toluene, reflux, overnight; (b) $TiCl_4$ (1.2 equiv.), allyltributyltin (1.2 equiv.), CH_2Cl_2, −78°C; (c) OsO_4 (0.1 equiv.), NMO (2 equiv.), THF/H_2O (9:1), rt, 5 h; (d) (i) LiOH (2 equiv.), $EtOH/H_2O$ (4:1), rt, 2 h; (ii) HCl (1N), THF, 24 h; (e) $(COCl)_2$ (1.5 equiv.), DMSO (3 equiv.), TEA (3.5 equiv.), CH_2Cl_2, −78°C, 1 h; (f) $(Ph_3PCHCONHPh)^+Br^-$ (1.2 equiv.), DBU (1.2 equiv.), CH_3CN, rt, 1 h; (g) (i) Bu_3SnH (1.7 equiv.), $Pd(PPh_3)_4$ (0.03 equiv.), THF, rt, 4 h; (ii) $TMSCHN_2$, $CH_2Cl_2/MeOH$ (4:1), rt, 30 min; (h) $Pd(PPh_3)_4$ (0.05 equiv.), TEA (2 equiv.), DMF, 80°C, 1 h; (i) LiOH (2 equiv.), $EtOH/H_2O$ (4:1) rt, 1 h.

diol **6** to give, as expected, a 1:1 mixture of *syn* and *anti* diastereoisomers, which were in turn cyclized to γ-lactone **7** in 77% overall yield. Oxidation of the primary alcohol was carried out following the Swern procedure, and the aldehyde derivative **8** was used crude in the next step. Under Horner–Emmons conditions, this intermediate was coupled to the requisite phosphonate affording the α,β-unsaturated carbamoyl derivative **9** in 50% yield (over two steps) as a 8:2 mixture of *syn* and *anti* diasteroisomers, in which the stereochemistry of the double bond was partially controlled ($E/Z=84:16$). From here, the route to the product proceeded through the reductive opening of the γ-lactone ring, a reaction in which the allylic C–O bond is chemoselectively cleaved, leaving the aromatic C–I bond unscathed. This reaction was successfully accomplished by reacting **9** with Bu_3SnH in the presence of a catalytic amount of $Pd(PPh_3)_4$ in THF.[12] The following treatment with $TMSCHN_2$ in CH_2Cl_2/MeOH gave a 1:1 mixture of desired product **10** and the corresponding isomer **11**, where the double bond had migrated to the β,γ-position, in 70% total yield after purification by flash chromatography. The last hurdle having been overcome, we set out to complete the synthesis by ring-closing via a Heck-type reaction. When **10** was treated with $Pd(PPh_3)_4$ and triethylamine in DMF, the benzazepine derivative **12** was isolated, in which, as expected, the *E* stereochemistry of the double bond was completely controlled.[13] The final deprotection of the methyl ester afforded the desired product **2** in 60% yield, over the last two steps.[14]

In conclusion, an efficient synthesis of a novel 2-carboxybenzo[*b*]azepine derivative was set up avoiding the drawbacks associated with the need for protecting the poorly reactive secondary aromatic amino group.

The pharmacological profile of this novel glycine antagonist will be reported in due course.

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14. ^{1}H NMR (400 MHz, acetone-d_6) δ 7.76 (m, 2H), 7.32 (m, 2H), 7.22 (m, 1H), 7.10 (m, 1H), 7.06 (m, 1H), 6.75 (m, 1H), 6.40 (s, 1H), 4.17 (dd, $J=12.4$ Hz, 4.8 Hz, 1H), 4.06 (m, 1H), 2.67 (m, 1H), 2.52 (m, 1H), 2.18 (m, 1H); IR (Nujol) ν_{max} (cm^{-1}) 3383, 1736, 1647; MS (FAB) *m*/*z* 357 [M+H]$^+$.