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Stereoselective Synthesis of (S)-(+)-αM4CPG, a Selective Antagonist of Metabotropic Glutamate Receptors

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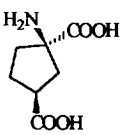
Abstract: The synthesis, from (R)-4-hydroxyphenylglycine, of (+)-α-methyl-4-carboxyphenylglycine ((+)-αM4CPG), a new and selective antagonist of metabotropic glutamate receptor, and assignment of its absolute configuration, are described.

Glutamate receptors play an important role in neuronal plasticity and neurotoxicity in the CNS. Based on electrophysiological, pharmacological, and molecular studies, they have been classified into two distinct groups termed iontropic glutamate receptors and metabotropic glutamate receptors[1-4]. The specific agents for these receptors are not only powerful research tools for understanding the synaptic functions of these receptors, but also might have potential therapeutic applications in the treatment of neurological disorders[1-4]. For the studies of metabotropic glutamate receptors, the cyclic glutamate analogue (1S,3R)-ACPD **1** has found widespread use because of its high specificity for metanotropic relative to ionotropic glutamate receptors[1-4]. However, for a long time, only a selective but very weak antagonist, L-AP3 **2**, was available, which was a limiting factor for biological studies, especially *in vivo* studies in this area[1-4]. Furthermore, molecular cloning studies have revealed the existence of at lest eight metabotropic glutamate receptor subtypes. Those antagonists with isotype-selectivity would obviously be useful tools for identifying the different synaptic functions for different subtypes.



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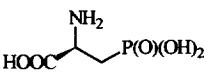

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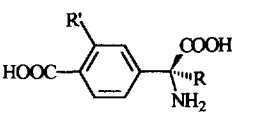
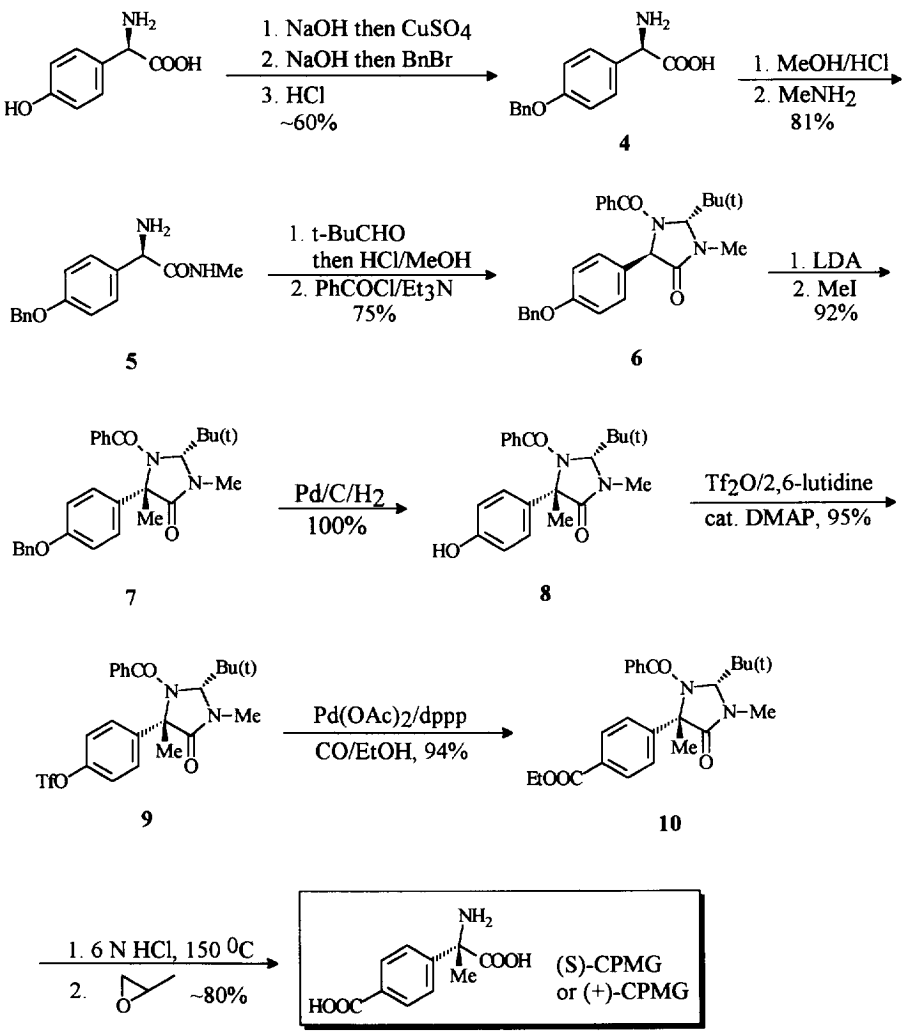


3

Scheme 1

Just two years ago, by biological screening Watkins and coworkers[5, 6] found that some phenylglycine derivatives **3** were a new class of selective ligands for metabotropic glutamate receptors. Among of them, (+)-αM4CPG (**3**, R = Me, R' = H) was recognized as a selective and relatively potent antagonist. Preliminary studies have shown that this compound also has some isotype-selectivity. Although it is still not as potent, this compound has found very immediate applications in investigating the functions of metabotropic glutamate receptors in synaptic activity[7-12].



Scheme 2. Asymmetric route to (S)-αM4CPG

Originally, (+)-αM4CPG was prepared by a Strecker reaction of the corresponding ketone followed by chemical resolution. Watkins and coworkers could not assign its absolute configuration by using chiral HPLC techniques[5, 6]. This route is very limited for further modification of this lead compound, which is very important for developing more potent and selective antagonists for metabotropic glutamate receptors[13, 14]. To solve these problems, we decided to develop an asymmetric synthesis of this compound.

As shown in Scheme 2, we started our total synthesis from commercially available (R)-4-hydroxyphenylglycine. To avoid the problems from the hydroxyl group in the following steps, we needed a suitable protecting group. We found that a similar method as used for protection of tyrosine[15] could be extended to this case successfully. Thus, (R)-4-hydroxyphenylglycine was treated with one equivalent of NaOH and resulting salt was mixed with $CuSO_4$ to form an amino acid-copper complex. This complex, was treated with another equivalent of NaOH followed by the reaction with benzyl bromide, and then grounded with concentrated hydrochloric acid to release the free benzyl-protected (R)-4-hydroxyphenylglycine **4**. This operation could be carried out in one-pot and gave about 60% overall yield. We then used Seebach's strategy[16] to introduce a methyl group at the α position of this amino acid. Therefore, **4** was converted to the corresponding methyl ester and then treated with methylamine to get amide **5** ($[\alpha]_D^{25}$ = - 22.3 (CH_3Cl, c = 0.22)) in 81% yield. The amide **5** was reacted with *tert*-butylaldehyde, and then treated with gaseous HCl saturated methanol followed by the reaction with benzoyl chloride to afford **6** ($[\alpha]_D^{25}$ = -137.5 (CH_3Cl, c = 1.02)). in about 75% overall yield. The trans isomer is the major product and only small amount of cis-isomer was separated by silica gel chromatography. The trans isomer was treated with LDA and the resulting anion was trapped with methyl iodide to produce **7** ($[\alpha]_D^{25}$ = + 141.3 (CH_3Cl, c = 1.33)). The configuration of the new stereogenic center should be S and ^1H NMR showed that only one isomer was formed. It is worth noting that the present methodology should permit the preparation of a wide variety of analogous compounds for biological tests just by employing different electrophilies. The benzyl protecting group was removed by Pd/C catalyzed hydrogenation and free hydroxyl group of **8**[17] was transferred to the triflate **9** by the reaction with trifluoromethanesulfonic anhydride[18]. At this stage we could employ a palladium-catalyzed carbonylation[18, 19] to generate the desired ester **10** ($[\alpha]_D^{25}$ = + 147.5 ($CHCl_3$, c = 1.48)). It was found that the reaction did not occur using triphenylphosphine to replace 1,3-bis(diphenylphosphino)propane (dppp). Heating a solution of the ester **10** in 6 N HCl at 150 ^{0}C removed all the protecting groups. The resulting hydrochloride salt of the amino acid was treated with propylene oxide to release the free (S)-αM4CPG. The specific rotation of this compound is $[\alpha]_D^{25}$ = + 90 (6 N HCl, c = 0.51) that is close to that reported ($[\alpha]_D^{18}$ = + 93 (6 N HCl, c = 0.53)). Thus, through this synthesis we can assign the absolute configuration of (+)-αM4CPG to be (S).

In conclusion, we have developed an asymmetric and practical route to (+)-αM4CPG. By using this route we have prepared multi-gram quantities of (+)-αM4CPG for biological tests. Further studies using this

protocol to synthesize the analogues of (S)-αM4CPG in order to find more potent and selective antagonists of metabotropic glutamate receptors are underway.

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17. Selected data for **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (m, 1H), 7.43-7.09 (m, 6H), 6.70 (m, 2H), 5.59 (br s, 1H), 5.41 (s, 1H), 3.02 (s, 3H), 1.72 (s, 3H), 0.81 (s, 9H). The cis-configuration was confirmed by NOESY spectrum, which revealed an NOE between t-Bu and HOC_6H_4 group.
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