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First Michael Addition Reaction of α-Substituted N-Diphenylmethyleneglycinate with Ethyl Propiolate. Synthesis of α-Substituted (E)-3,4-Dehydroglutamic Acids

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Abstract: (E)-α-substituted 3,4-dehydro glutamic acids **4**, were prepared from ethyl N-diphenylmethyleneglycinate **5** by alkylation with a suitable alkyl halide followed by a Michael type addition reaction with ethyl propiolate, giving rise to a mixture of E/Z adducts **7/8**. Sequential hydrolysis of the substituted glycine synthons **7/8** afforded the titled compounds **4** as single diastereomers.

Excitatory amino acid (EAA) receptors are generally accepted as the main transmitter receptors mediating synaptic excitation in the mammalian central nervous system (CNS),[1] being implicated in the pathogenesis of many CNS disorders.[2] Ionotropic glutamate receptors are named after the agonists NMDA, Kainate and AMPA, whereas the G-protein coupled metabotropic receptors are selectively activated by (1S,3R)-ACPD (**1**)[3] (Figure 1). Another selective agonist for the metabotropic receptors is L-CCG-1 (**2**).[4] The receptor selectivity of these conformationally constrained glutamic acids may be determined by the fixed distance between the amino and distal carboxyl groups and a pharmacophore model of a metabotropic glutamate receptor based on the superimposition of (**1**) and (**2**) has been proposed.[5] More recently it has been shown that α-methylation of L-CCG-1 (**2**), to give MCCG (**3**) converts it into an antagonist for the metabotropic receptors.[6]

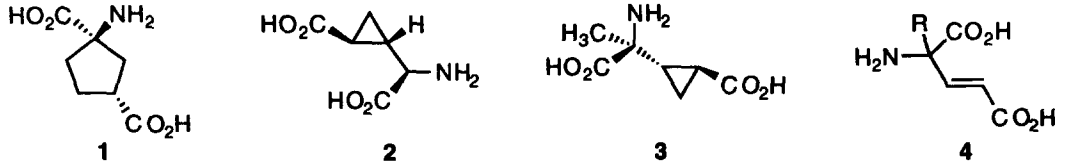
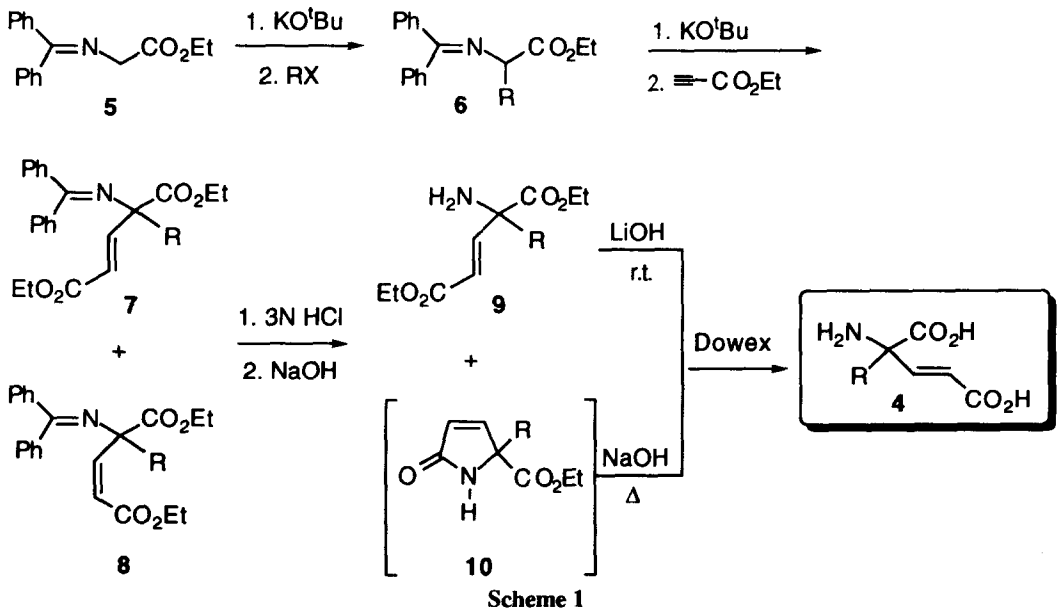


Figure 1

Considering these structural requirements we decided to undertake the synthesis of α-substituted (E)-3,4-dehydroglutamic acids[7] **4**, where the (E)-double bond would restrict the glutamate backbone conformation to resemble L-CCG-1.

It is known that the non-commercially available aldimines (benzaldehyde and *p*-chlorobenzaldehyde) derived from glycine esters[8] undergo mono and double alkylation[9] or Michael addition reactions[8,10] yielding the corresponding α-monosubstituted or α,α-disubstituted α-amino acids. However, there are few precedents in the literature where the Michael addition reaction is done with an α-substituted aldimine.[11] We have recently shown[12] that the more stable and commercially available N-diphenylmethyleneglycinate **5** can be dialkylated, under phase transfer catalysis, to give the α,α-disubstituted α-amino acid. Our approach for the synthesis of compounds **4** is based on the Michael addition of α-substituted N-diphenylmethyleneglycinate **6** to ethyl propiolate, a Michael acceptor that has not been used before with any glycine anion synthon.

The synthesis of compounds **4** has been done following the reaction sequence depicted in Scheme 1 and the yields are described in Table 1.



Scheme 1

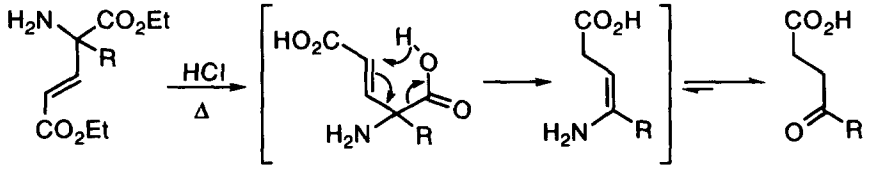
Ethyl N-diphenylmethyleneglycinate **5** was deprotonated[8] with KO^{t}Bu at room temperature and alkylated with a suitable alkyl halide giving rise to the α-substituted N-diphenylmethyleneglycinate **6** in good yields. Reaction of **6** with ethyl propiolate at -78°C in THF and in the presence of KO^{t}Bu gave, after 5 minutes, a mixture of E/Z Michael adducts **7/8**[13] in high yield. Longer reaction times resulted in product decomposition. No attempt was made to separate the **7/8** E/Z mixtures since during the deprotection step, the Z-olefin formed the 3,4-dehydro pyroglutamate **10**,[14] which was easily separated during the reaction work-up. Thus, the **7/8** mixtures were treated with 3N-HCl for 3 hours, the benzophenone was removed by extraction with ethyl ether and the aqueous solution was basified to pH=12 with NaOH solution. The diethyl α-alkyl 3,4-dehydro glutamate **9** was isolated by extraction with methylene chloride. Finally, compound **9** was hydrolysed with LiOH at room temperature yielding the free amino acid **4**[15] which was isolated as its zwitterion by ion exchange chromatography (Dowex 50x8-100). It was found that, when the pH=12 solution of the pyroglutamate **10** was heated under reflux for 1 hour, the glutamic acid **4** was obtained in the same yields, after ion exchange chromatography, as those obtained from **9**.

Table 1

Entry	R-X	**6** (% yield)[a]	**7/8** (% yield)[a]	**9** (% yield)[b]	**4** (% yield)[c]
a	CH_3I	90	72 (1/1)	39	40
b	$C_6H_5CH_2CH_2I$	86	77 (1.3/1)	42	78
c	$C_6H_5CH_2CH_2CH_2I$	72	80 (2.2/1)	36	52
d	$(CH_3)_2CHCH_2I$	91	77 (3.3/1)	61	64

[a] In brackets E/Z diastereoisomeric ratio. [b] Yields obtained from the **7/8** mixtures. [c] Yields obtained from **9**.

The acid hydrolysis (6N-HCl/reflux) of the diester **9** produced the keto acid **11** (Scheme 2) through a decarboxylation process .



9 **I** **II** **11**

Scheme 2

In summary, a novel, facile and straightforward route for the synthesis of α-substituted 3,4-dehydro glutamic acids has been achieved with a Michael addition reaction of α-substituted N-diphenylmethyleneglycinate **6** with ethyl propiolate. This is the first time that this process has been conducted using this substrate. The reaction highlights the usefulness of the commercially available N-diphenylmethyleneglycinate **5** for the synthesis of α,α-disubstituted α-amino acids compared with the non-commercially available and less stable glycine aldimines.

Further applications of this Michael addition reaction with other Michael acceptors are currently under investigation and will be reported in due course.

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13 The assignment of the E/Z configurations was made based on the coupling constants of the olefinic protons: J_{3-4} (E) = 15.9 Hz and J_{3-4} (Z) = 12.7 Hz.

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15 Satisfactory spectroscopic data (^{1}H NMR, ^{13}C NMR and MS) have been obtained for all compounds reported in this communication. The following are the spectroscopic data and physical constants for the final amino acids: **4a**: mp 113°C (dec). ^{1}H NMR (MeOH-d^4) δ 6.87 (d, J = 15.8 Hz, 1H), 5.93 (d, J = 15.8 Hz, 1H), 1.40 (s, 3H); ^{13}C NMR (MeOH-d^4) 182.1, 175.7, 149.3, 125.8, 61.4, 27.0; MS (CI) m/e 116 (M^++1). **4b**: mp 147°C. ^{1}H NMR (D_2O-Pyr-d^4) δ 7.60-7.40 (m, 5H), 7.35 (d, J = 16.3 Hz, 1H), 6.63 (d, J = 16.3 Hz, 1H), 3.20-2.90 (m, 2H), 2.80-2.40 (m, 2H); ^{13}C NMR (D_2O-Pyr-d^4) δ 175.3, 174.9, 142.5, 141.4, 130.6, 130.4, 129.6, 128.2, 67.0, 40.7, 31.8; MS (CI) m/e 206 (M^++1). **4c**: mp 138-40°C. ^{1}H NMR (MeOH-d^4) δ 7.35-7.00 (m, 5H), 6.92 (d, J = 15.9 Hz, 1H), 5.91 (d, J = 15.9 Hz, 1H), 2.60 (t, J = 7 Hz, 2H), 2.0-1.50 (m, 4H); ^{13}C NMR (MeOH-d^4) δ 180.8, 175.7, 148.9, 143.9, 129.4, 129.2, 126.9, 125.5, 64.4, 41.1, 37.3, 27.5; MS (CI) m/e 220 (M^++1), 202 (M^++1-H_2O). **4d**: mp 123-4°C. ^{1}H NMR (D_2O-Pyr-d^4) δ 7.00 (d, J = 16.2 Hz, 1H), 6.24 (d, J = 16.3 Hz, 1H), 2.30-1.90(m, 3H), 1.21 (d, 6.4 Hz, 3H), 1.19 (d, 6.4 Hz, 3H); ^{13}C NMR (D_2O-Pyr-d^4) δ 175.71, 175.67, 142.5, 128.5, 66.6, 46.6, 25.8, 25.6, 24.3; MS (CI) m/e 206 (M^++1).

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