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Enantioselective syntheses of α-substituted glutamic acids and α,γ-disubstituted glutamic acids by an asymmetric Strecker reaction

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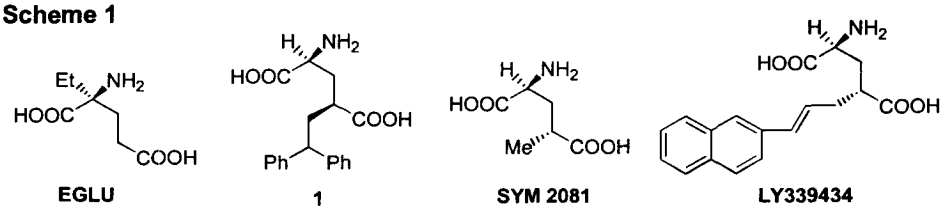
Abstract: The Strecker reaction of the product from the treatment of the sodium salt of γ-keto acids with (*S*)-phenylglycinol followed by heating the products to 200 °C gives the bicyclic lactones **9** and **10**. Alkylation of **9** provides **11** and **12**. Both **9b** and **11a** are converted into the corresponding substituted glutamic acids *via* reductive cleavage and hydrolysis.

L-Glutamate is the major excitatory amino acid (EAA) neurotransmitter in the central nervous system and operates through multiple ionotropic and G-protein-coupled receptors.[1] Recently, it was found that some glutamate analogues with suitable substituents at α or γ-positions could selectively modulate the special glutamate receptor and thus turn out to be useful tools for investigating the specific function of the individual glutamate receptors.[2-5] For example, both (*S*)-2-ethyl glutamic acid (EGLU)[2] and (2*S*,4*S*)-4-(2,2-diphenylethyl) glutamic acid (**1**)[3] were found to be selective antagonists for group II metabotropic glutamate receptors; while (2*S*,4*R*)-4-methyl glutamic acid (SYM2081)[4] and (2*S*,4*R*)-4-(3-naphthyl-2-propenyl) glutamic acid (LY339434)[5] showed selective agonist activity for kinate receptors. To seek further the structure-activity relationship of this class of analogues, a general and efficient synthetic route to these compounds is highly desirable. However, most of the known methods for preparing these compounds including diastereoselective alkylation of α-amino acids or chemical resolution are not efficient.[3,4,6] In connection with our efforts on the studies of selective modulators of metabotropic glutamate receptors,[7] we developed a general protocol for synthesizing α-substituted or α, γ-disubstituted glutamic acids by asymmetric Strecker reaction of γ-keto acids.

Scheme 1



EGLU **1** **SYM 2081** **LY339434**

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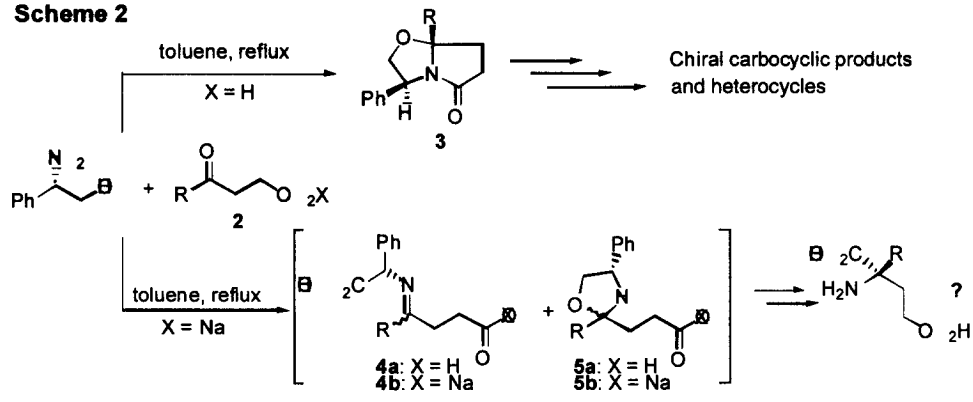
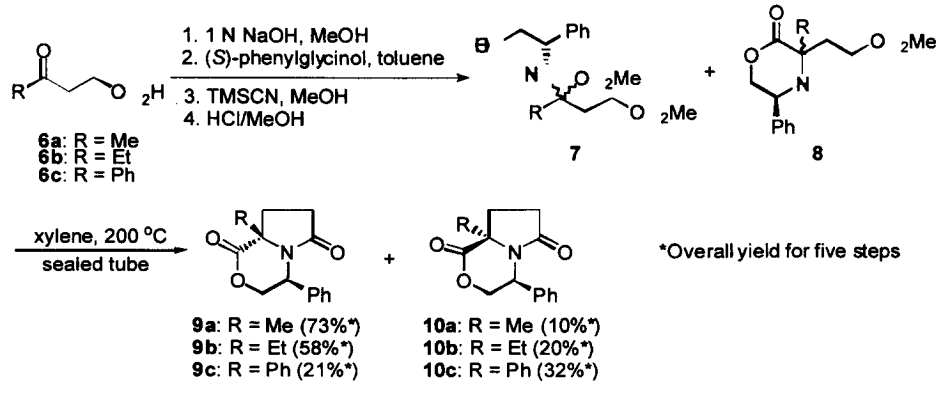
As shown in Scheme 2, we planned to use a similar strategy to that used for preparing α-substituted phenylglycine to set up the skeleton of the α-substituted glutamic acid.[7a] It is impossible to use directly the reaction of a γ-keto acid and phenylglycinol to obtain the desired Schiff's base **4a** or 1,3-oxazolidine **5a** because it is well known that under our reaction conditions[7a] they would be converted into a bicyclic compound **3** quantitatively.[8] Meyers and co-workers have demonstrated the use of **3** as a chiral building block for synthesizing various carbocyclic products and heterocycles.[8] After some experimentation, we found that if a sodium salt of a γ-keto acid was used, the formation of **3** could be inhibited and the desired Schiff's base **4b** and 1,3-oxazolidine **5b** were obtained as a mixture analysed by ^{1}H NMR spectroscopy.

Scheme 2



Our detailed synthesis is outlined in Scheme 3. After levulinic acid **6a** was treated with 1 equiv. of sodium hydroxide, the generated salt was dried *in vacuo* and reacted with (*R*)-phenylglycinol to give a mixture of the Schiff's base and the 1,3-oxazolidine. Reaction of this mixture with trimethylsilyl cyanide followed by treatment with HCl-saturated methanol afforded a mixture of **7** and **8**, which were heated at 200 °C in a sealed tube to provide the two separable bicyclic products **9a** and **10a**. The overall yields from **6a** for **9a** and **10a** were 73% and 10% respectively. Thus, we concluded that the diastereoselectivity for the Strecker step was about 7/1.

Scheme 3



In a similar manner, ethyl ketone **6b** and phenyl ketone **6c** were tested. They were converted into bicyclic products **9**[9] and **10** in high yield but the diastereoselectivity was only 2.9/1 and 1.5/1 respectively, which implied that bigger R groups decrease the diastereoselectivity. The configuration of each bicyclic product was assigned by a combination of X-ray analysis (Figure 1) and ^{1}H NMR experiments.

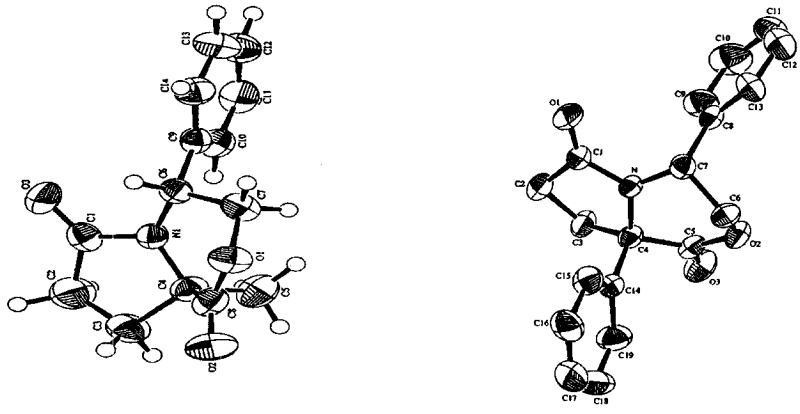
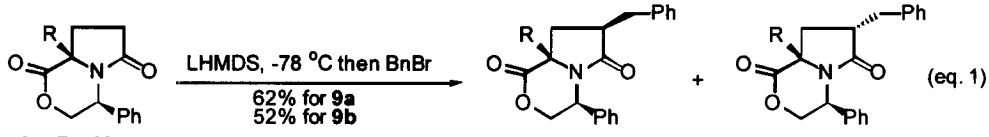


Figure1. X-ray crystal structures of **9a** (left) and **10 c** (right).

The bicyclic compounds **9** and **10** could be further functionalized. For example, alkylation of **9a** with benzyl bromide gave the two isomers **11a** and **12a** in a ratio of 3.3/1, which were separable via column chromatography. In a similar manner, **11b**[10] and **12b** were obtained in a ratio of 1.6/1.

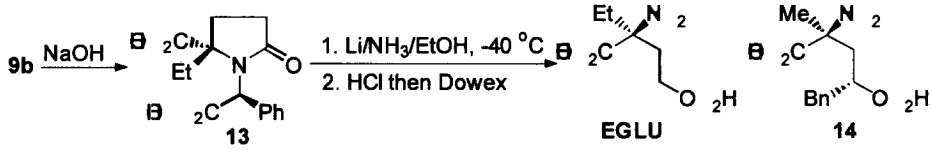


9a: R = Me
9b: R = Et

11a: R = Me
11b: R = Et

12a: R = Me
12b: R = Et

With these bicyclic products in hand, we could easily transform them to the corresponding α-substituted glutamic acids. For example, EGLU[11] was obtained as its ammonium salt from **9b** in 83% overall yield by the following steps: 1) treatment of **9b** with NaOH to open the lactone ring; 2) reductive cleavage of the *N*-benzylic bond with lithium/liquid ammonia;[12] 3) hydrolysis with 6 N HCl followed by purification with Dowex eluting with 1% aqueous ammonia. Following the same procedure except for carrying out the reductive cleavage at -78 °C, α,γ-disubstituted glutamic acid **14**[13] was prepared from **11a** in 54% overall yield.



13

EGLU

14

In conclusion, we have demonstrated a workable protocol for preparing α-substituted and α,γ-disubstituted glutamic acids. Synthesis of other glutamate analogues using this procedure and their biological evaluation are in hand.

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9. Selected data for **9b**: $[\alpha]^{18}_{D}$ +22.7 (*c* 19.2 $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 7.42-7.31 (m, 5H), 5.17 (dd, *J* = 10.8, 6.6 Hz, 1H), 4.62 (dd, *J* = 12.5, 6.7 Hz, 1H), 4.50 (dd, *J* = 12.4, 11.0 Hz, 1H), 2.71-2.52 (m, 2H), 2.44-2.26 (m, 2H), 2.08 (m, 1H), 1.94 (m, 1H), 1.05 (t, *J* = 7.3 Hz, 3H).
10. Selected data for **11b**: $[\alpha]^{20}_{D}$ -25.8 (*c* 5.2 $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 7.39-7.28 (m, 6H), 7.20-7.18 (m, 4H), 5.27 (dd, *J* = 11.4, 7.8 Hz, 1H), 4.70 (dd, *J* = 12.0, 7.8 Hz, 1H), 4.43 (dd, *J* = 12.6, 12.0 Hz, 1H), 3.08 (dd, *J* = 13.8, 4.2 Hz, 1H), 3.00 (dd, *J* = 13.2, 7.8 Hz, 1H), 2.98 (dd, *J* = 14.4, 11.4 Hz, 1H), 2.89-2.84 (m, 1H), 1.90 (m, 1H), 1.83 (dd, *J* = 13.5, 7.5 Hz, 1H), 1.32 (m, 1H), 0.83 (t, *J* = 7.2 Hz, 3H).
11. Selected data for EGLU: $[\alpha]^{18}_{D}$ +47.3 (*c* 6.9 H_2O); ^1H NMR (300 MHz, D_2O) δ 2.39-2.31 (m, 2H), 2.09 (t, *J* = 7.6 Hz, 2H), 1.98 (dt, *J* = 14.7, 7.5 Hz, 1H), 1.88 (dt, *J* = 14.7, 7.3 Hz, 1H), 0.98 (t, *J* = 7.5 Hz, 3H).
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13. Selected data for **14**: $[\alpha]^{18}_{D}$ -113.3 (*c* 7.0 H_2O); ^1H NMR (300 MHz, D_2O) δ 7.33-7.25 (m, 2H), 7.23-7.20 (m, 3H), 2.84-2.67 (m, 2H), 2.53 (m, 1H), 1.96 (dd, *J* = 14.8, 9.1 Hz, 1H), 1.84 (dd, *J* = 14.8, 3.2 Hz, 1H), 1.31 (s, 3H).