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A concise synthesis of (2*S*,4*R*)- and (2*S*,4*S*)-4-methylglutamic acid

Zi-Qiang Gu[a] and Min Li[b,*]

[a]*Laboratory of Medicinal Chemistry, NIDDK, National Institutes of Health, Bethesda, MD 20892, USA*
[b]*Sunmack Science Inc, PO Box 7002, Gaithersburg, MD 20898, USA*

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Abstract—A concise, multi-gram scale method for producing the bioactive and enantiomerically pure epimers, (2*S*,4*R*)- and (2*S*,4*S*)-glutamic acids, in a single synthetic scheme is described.

Analogs of glutamic acid have been found to be useful probes for studying a number of biological systems including various enzymes[1–3] and receptors.[4–7] In particular, two isomers of 4-methyl-L-glutamic acid, i.e. (2*S*,4*R*)- and (2*S*,4*S*)-4-methylglutamic acids (**7** and **8**, Scheme 1), deserve special attention, as the (2*S*,4*R*) isomer is a highly selective and potent agonist for kainate receptors,[5,6] while the (2*S*,4*S*) one is a potent agonist for metabotropic receptors.[7] The two isomers may be prepared in enantiomerically pure forms by procedures that have been reported in the literature, which include asymmetric syntheses using enzymes[8,9] or chiral auxiliaries,[10] and alkylation of protected glutamates[11] or pyroglutamates[12] and related compounds.[13] One of the latter procedures, reported by Coudert et al., produced the two isomers (63:37 molar ratio) in a single reaction sequence, which was followed by two steps of ion-exchange chromatography to yield the two enantiomerically pure epimers.[12] In this paper, we report a simpler preparation of the two enantiomerically pure epimers in a single reaction sequence which involves less synthetic steps and requires only one silica gel column chromatography.

The preparation (Scheme 1) can start from either one of the commercially available starting materials, (*S*)-pyroglutamic acid or its ethyl ester (both are available from Fluka). In the former case, (*S*)-pyroglutamic acid was converted to its methyl ester (**1**) by addition of thionyl chloride into an ice-water cooled solution of (*S*)-pyroglutamic acid in methanol.[14] The NH group of the methyl or ethyl ester (**2**) was further protected with the BOC group by using a standard procedure.[15] In a typical alkylation procedure, the fully protected pyroglutamate (**3b**, R = Et, 20 g scale) was enolized at the 4-position by using 1.03 equiv. $LiN(SiMe_3)_2$ in THF at −78°C, and the enolate formed was then reacted with 2.5 equiv. methyl iodide. After workup, a mixture of *trans* (**4b**), *cis* (**5b**), and disubstituted (**6b**) pyroglutamate derivatives was obtained; separation of the mixture was readily achieved on a silica gel column chromatography to give **4b** (7.8 g, 37% based on **3b**), **5b** (6.0 g, 28%) and **6b** (2.5 g, 11%), respectively.[16] Each of these compounds was subsequently deprotected via a two-step procedure,[13] in which the ester functionality was taken off with an aqueous lithium hydroxide solution in THF and the BOC group removed by TFA in methylene chloride. The (2*S*,4*R*)- and (2*S*,4*S*)-glutamic acids (**7** and **8**, respectively) thus obtained displayed the same spectroscopic properties as reported previously.[11,13] The overall yield for the two isomers (**7** and **8**) combined was around 42% starting from compound **3b** (similar yields were achieved by starting from the methyl ester **3a**).

In summary, a concise method for preparing the biologically active and enantiomerically pure epimers, (2*S*,4*R*)- and (2*S*,4*S*)-4-methylglutamic acids, in a single synthetic scheme has been described. It provides an efficient and practical way of making the two isomers or the corresponding diastereomers, (2*R*,4*S*)- and (2*R*,4*R*)-4-methylglutamic acids, if the synthesis starts with (*R*)-pyroglutamic acid. The overall procedure is readily scaled up beyond the multi-gram level.

Keywords: 4-methylglutamic acid; synthesis; enantiomerically pure.
* Corresponding author.

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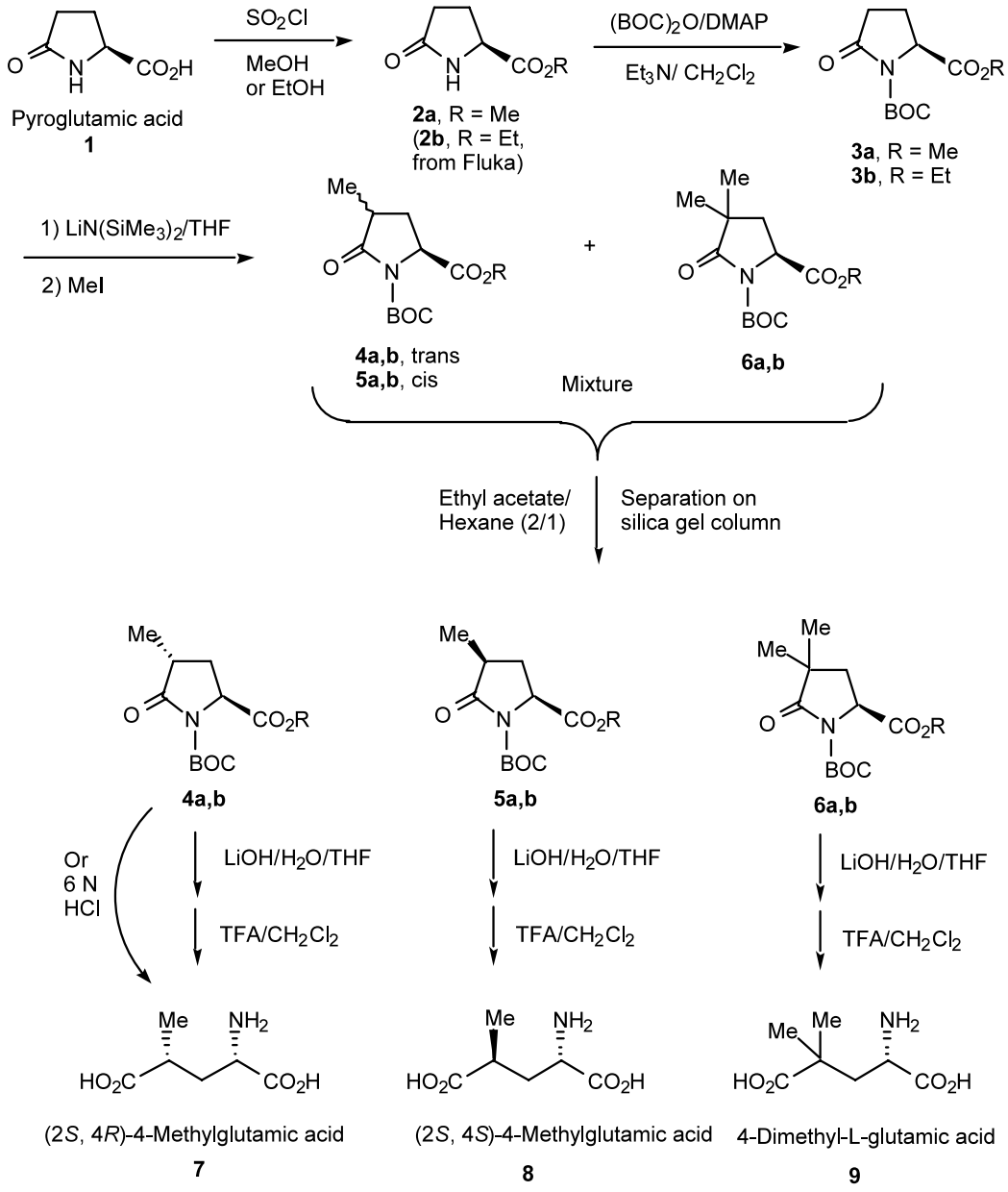

Scheme 1.

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using procedure described in Ref. 11. The drawback of this approach, however, is that slight epimerization occurred at the C-4 position.

14. Preparation procedures: to an ice-water cooled solution of **1** (25.8 g, 200 mmoL) in 180 mL of methanol was added slowly 15 mL of thionyl chloride (200 mmoL). The resulting solution was stirred at 0°C for 30 min and then allowed to warm to room temperature. After stirring at room temperature for 3 h, the reaction mixture was concentrated in vacuo. The residue was loaded onto a pad of silica gel and eluted with a mixture of ethyl acetate/methanol (4/1, v/v). The filtrate was evaporated to yield 20 g of oily product (70%), which showed a single spot at $R_f \sim 0.5$ on silica gel TLC with a mixture of ethyl acetate and methanol (4/1, v/v) as the mobile phase.
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16. Detailed procedures for the alkylation: a solution of compound **3b** (20 g, 77.8 mmoL) in 200 mL of THF was cooled to −78°C, followed by slow addition of 80 mL of 1.0 M $LiN(SiMe_3)_2$ solution in THF. After the addition, the solution was stirred for 45 min and methyl iodide (12 mL, 195 mmoL) was added in one portion. The resulting mixture was continuously stirred at −78°C for another 2 h and then was allowed to gradually warm to room temperature overnight under nitrogen. After the reaction mixture was quenched with 2 equiv. acetic acid and 30 mL of water, it was concentrated in vacuo. The concentrated residue was diluted with water and then extracted with ethyl acetate. The organic extracts were combined and washed with water and brine, respectively. After the washed solution was dried over anhydrous magnesium sulfate, it was evaporated in vacuo to produce an oily residue. The residue was loaded onto a silica gel column and eluted with a mixture of ethyl acetate/hexane (1/2, v/v). Eluted first was the 4,4-dimethyl compound (**6b**, 2.5 g, 11%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.50 (m, 1H), 4.20 (q, 2H, $J=7.2$ Hz), 2.19 (m, 1H), 1.88 (m, 1H), 1.47 (s, 9H), 1.40 (s, 3H), 1.34–1.14 (m, 6H). The *trans*-isomer (**4b**) came out next (7.8 g, 37%). ^{1}H NMR ($CDCl_3$): δ 4.53 (m, 1H), 4.22 (q, 2H, $J=7.1$ Hz), 2.66 (m, 1H), 2.25 (m, 1H), 1.92 (m, 1H), 1.50 (s, 9H), 1.35–1.15 (m, 6H). The *cis*-isomer (**5b**) was collected in the end (6.0 g, 28%). ^{1}H NMR ($CDCl_3$): δ 4.46 (m, 1H), 4.21 (q, 2H, $J=7.2$ Hz), 2.59 (m, 2H), 1.61 (m, 1H), 1.50 (s, 9H), 1.35–1.15 (m, 6H).