The Resolution and Absolute Configuration of 2,3-Methanopyroglutamic Acid, 3-Oxo-2-azabicyclo[3,1,0]hexane-1-carboxylic Acid[1)]

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The resolution of racemic 2,3-methanopyroglutamic acid (∇Glp) was accomplished using L- and D-Leu-NH_2 and both isomers were hydrolyzed to give optically active (*Z*)-2,3-methanoglutamic acids[1)] (∇^ZGlu), respectively. The optical rotations of these samples were compared with ∇^ZGlu obtained by hydrolysis of ∇Glp prepared by oxidation of (2*S*,3*R*)- or (2*R*,3*S*)-2,3-methanoproline[1)] (∇Pro), the absolute configurations of which were determined by X-ray diffraction earlier. These experiments showed (−)- and (+)-∇Glp to have the (2*S*,3*S*)- and (2*R*,3*R*)-configurations, respectively.

Conformational constraint of neuropeptides has been used in the past to design receptor-specific and -selective compounds and to elucidate further their structure-activity relationships.[2)] Conformationally constrained 2,3-methanoamino acids (cyclopropane amino acids) have been incorporated into neuropeptides, not only for this purpose, but also to protect from enzymolysis specific peptide linkages known to be involved in enzymatic degradation.[3)] For these reasons, we have previously synthesized[4)] racemic 2,3-methanopyroglutamic acid (∇Glp, (±)-**1**) and a thyrotropin releasing hormone (TRH) analog,[5)] (±)-∇Glp-His-Pro-NH_2, containing it. This analog showed enhanced bioactivity vis a vis native TRH in several in vivo central nervous system assays.[6)] For better understanding of conformation-activity relationships, the TRH analogs containing optically active ∇Glp residues are required. In this paper, we report the resolution of racemic 2,3-methanopyroglutamic acid and the absolute configurations of its enantiomers.

Results and Discussion

Synthesis. Synthesis of the required dehydroamino acid, *N*-benzyloxycarbonyl 2,3-dehydroglutamic acid α-benzyl ester (**2**), by the method of Baldwin et al.[7)] instead of that previously reported by us,[4)] was investigated in this work (Fig. 1), but, due to γ-decarboxylation of **2** during base treatment of the lactone precursor, we found Elrod's[4)] method superior. Not reported in the earlier work was the ease with which the crude ∇^ZGlu derivative cyclizes to ∇Glp in ethyl acetate containing acetic acid.

Resolution. The resolution of ∇Glp, (±)-**1**, was accomplished by crystallization of the diasteromeric salts formed by treatment with the commercially available enantiomers of leucinamide. Two recrystallizations of the more insoluble salt from 2-butanol gave the (−)-L-Leu-NH_2 salt of (−)-∇Glp in 60% yield, $[\alpha]_D$ −68.0°, and the (+)-D-Leu-NH_2 of (+)-∇Glp in 67% yield, $[\alpha]_D$ +68.0°. The diasteromeric salt remaining in either mother liquor could be acidified, the Leu-NH_2 removed, and the opposite Leu-NH_2 enantiomer added: ∇Glp·L-Leu-NH_2, $[\alpha]_D$ −68.5° was obtained in 82% yield this way. The salts were decomposed using Dowex 50 (H^+ form). The rotation values of (+)- and (−)-∇Glp ((+)- and (−)-**1**) were +143.6° and −145.8° from the D- and L-Leu-NH_2 salts, respectively.

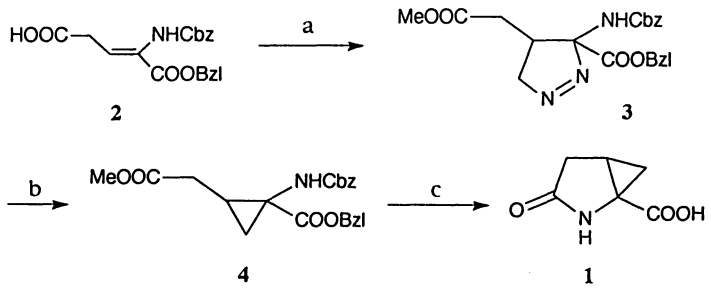

Fig. 1. Synthesis of (±)-2,3-methanopyroglutamic acid.
Reagents; a, CH_2N_2; b, *hν*; c, H_2/Pd-C.

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Absolute Configuration. The crystals obtained from the Leu-NH_2 salts were unacceptable for X-ray analysis as were several other salts prepared from the ∇Glp enantiomers. Consequently, we determined the absolute configurations of (+)- and (−)-2,3-methanopyroglutamic acid by a chemical method. Muramatsu et al.[8] and Yoshifuji et al.[9] reported the oxidation of specific proline derivatives to pyroglutamic acid derivatives using potassium permanganate and ruthenium tetraoxide, respectively. The *N*-propionyl methyl ester (**6**) of each optical isomer[10] of 2,3-methanoproline was prepared and oxidized with ruthenium tetraoxide to give the corresponding active methanopyroglutamic acid derivative (**7**) (Fig. 2). Peculiarly, when either *N*-benzyloxycarbonyl or *N*-ethoxycarbonyl derivatives were used, no pyroglutamic acid derivatives could be isolated.

The optically active derivatives of **7** obtained by oxidation of methanoproline derivatives, and the methanopyroglutamic acid enantiomers (**1**), obtained by resolution, were hydrolyzed and the optical rotations of the methanoglutamic acids (**8**) obtained were compared, as shown in Fig. 3. The (−)-∇Glp enantiomer, obtained by synthesis and resolution was shown to have the (2*S*,3*S*)-configuration by this method. The results indicated that the (−)- and (+)-∇Glp isomers prepared by resolution have (2*S*,3*S*)- and (2*R*,3*R*)-configurations, respectively.

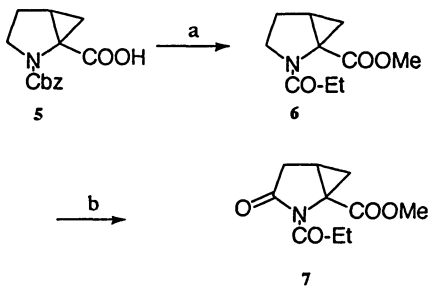

Fig. 2. Syntheses of (+)- and (−)-2,3-methanopyroglutamic acid from (+)- and (−)-2,3-methanoproline. Reagents; a, (i) MeOH/H_2SO_4, (ii) H_2/Pd-C, (iii) EtCO-Cl; b, RuO_4.

Experimental

General. All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter at 25 °C. Elemental analyses were performed by Atlantic Microlab, Atlanta, GA. ^{1}H NMR spectra were recorded on Varian EM-390 and Bruker WM-300 NMR spectrometers operating at frequencies of 90 and 300 MHz, respectively, with tetramethylsilane and HDO as an internal standard. Where necessary, solutions were dried over anhydrous $MgSO_4$ before evaporation; solvents were evaporated in vacuo on a rotating evaporator. Thin-layer chromatography was carried out on Merck silica gel GF_{254} precoated plates with the following solvent systems: (by volume) R_f^1 $CHCl_3$-MeOH (9:1), R_f^2 $CHCl_3$-MeOH-AcOH (95:5:1), R_f^3 $CHCl_3$-MeOH-AcOH (50:10:2), R_f^4 hexane-EtOAc (1:1), R_f^5 hexane-EtOAc (2:1), R_f^6 hexane-EtOAc (1:2), R_f^7 hexane-EtOAc (1:7), and R_f^8 *n*-BuOH-AcOH-H_2O (4:1:2). The plates were visualized with Cl_2-*o*-tolidine or ninhydrin.

4-Methoxycarbonylmethyl-3-benzyloxycarbonylamino-3-benzyloxycarbonyl-1-pyrazoline (3). To a chilled solution of *N*-benzyloxycarbonyl-(*Z*)-dehydroglutamic acid α-benzyl ester (**2**) (12.9 g, 35 mmol) in CH_2Cl_2 (300 mL) was added dropwise a solution of diazomethane generated from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide[11] (Diazald, 45.0 g, 210 mmol) in ether (200 mL). The reaction mixture was stirred 2 h at −20 °C and 12 h at room temperature. Excess CH_2N_2 was quenched by $CaCl_2$, the mixture filtered and the filtrate evaporated: 14.9 g (100%); R_f^2 0.76, R_f^4 0.27. This crude product was used for next reaction without further treatment.

γ-Methyl *N*-Benzyloxycarbonyl-(*Z*)-2,3-methanoglutamic Acid α-Benzyl Ester; Methyl 2-Benzyloxycarbonyl-2-[(benzyloxycarbonyl)amino]-1-cyclopropaneacetic Acid (4). A solution of **3** (14.89 g, 35 mmol) in CH_2Cl_2 (300 mL) was photolyzed with a medium-pressure mercury lamp for 3 h. The solvent was removed by evaporation and the residue was purified by silica-gel column chromatography (2×40 cm) eluted with hexane-EtOAc (2:1). The fractions containing the desired compound were collected and evaporated giving an oil: 12.30 g (88%); R_f^2 0.66, R_f^5 0.11; ^{1}H NMR ($CDCl_3$) δ=7.34 (s, 10H, 2×*ArH*), 5.70 (br s, 1H, *NH*), 5.16 (s, 2H, ArCH_2), 5.07 (s, 2H, ArCH_2), 3.62 (s, 3H, OCH_3), 2.68 (dd, 1H, H_Y), 2.45 (d, 1H, H_X), 2.06 (m, 1H, H_M), 1.87 (m, 1H, H_B), 1.13 (t, 1H, H_A).

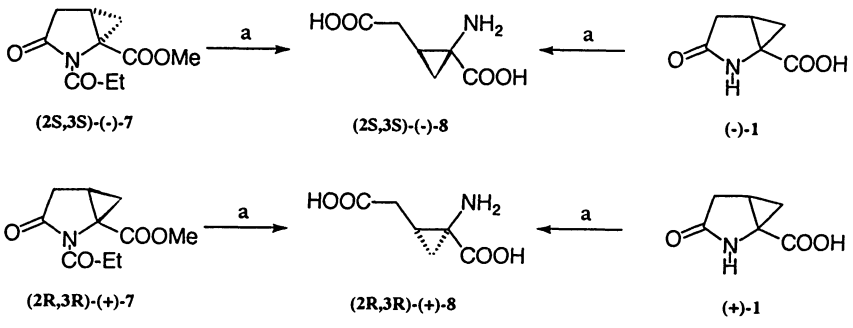

Fig. 3. Syntheses of (+)- and (−)-2,3-methanoglutamic acids and determination of absolute configuration.
Reagent; a, 6 M HCl at 70 °C.

(±)-2,3-Methanopyroglutamic Acid [(±)-∇Glp, 1]. Hydrogen gas was bubbled through a suspension of **4** (6.16 g, 15.5 mmol) and 5% Pd-C (1 g) in MeOH (100 mL) containing AcOH (3 mL) at room temperature and atmospheric pressure for 3 h. The catalyst was removed and the filtrate was evaporated to obtain H-∇^{Z}Glu(OMe)-OH [R_f^8 0.07]. The residue was dissolved in EtOAc (100 mL) containing AcOH (10 mL) and the solution was kept overnight at room temperature. After evaporation, the residue was chromatographed on a column (2×17 cm) of silica gel using $CHCl_3$–MeOH–AcOH (195 : 5 : 1 elutes small amount of ester then change to 95 : 5 : 1) and recrystallized from *i*-PrOH (20 mL) giving 1.20 g (55%); mp 200—201 °C; R_f^3 0.18; ^{1}H NMR (0.5% DCl/D_2O) δ=2.83 (dd, 1H, H_Y), 2.37 (d, 1H, H_X), 2.22 (m, 1H, H_M), 1.81 (dd, 1H, H_B), 1.05 (t, 1H, H_A).

(+)-∇Glp·D-Leu-NH_2 Salt. A solution of racemic ∇Glp, (±)-**1**, (353 mg, 2.5 mmol) and D-Leu-NH_2 (326 mg, 2.5 mmol) in boiling *s*-BuOH (20 mL) and the solution was allowed to stand at room temperature overnight. The precipitate was collected by filtration, washed with 1 mL of cold *s*-BuOH and dried over P_2O_5 in vacuo to give 312 mg (92%) of a mixture enriched in one diastereomeric salt; mp 188—190 °C; $[\alpha]_D$ +32.2° (*c* 1.0, MeOH). Two more recrystallizations of this salt from 5.0 mL of *s*-BuOH, afforded 227 mg (67%) of ∇Glp·D-Leu-NH_2; mp 192—193 °C; $[\alpha]_D$ +68.0° (*c* 1.0, MeOH). Found: C, 53.18; H, 7.81; N, 15.43%. Calcd for $C_{12}H_{21}N_3O_4$: C, 53.12; H, 7.80; N, 15.49%.

(−)-∇Glp·L-Leu-NH_2 Salt. The combined mother liquor obtained above was evaporated and an aqueous methanolic (95 : 5) solution of the residue was percolated through a column of Dowex-50 resin. The eluent was evaporated and the residue dried over P_2O_5 giving 234 mg (1.66 mmol) of crude (−)-∇Glp. This residue was dissolved in 2-butanol (10 mL) and L-Leu-NH_2 (216 mg, 1.66 mmol) was added. The crude salt, 334 mg (98%); $[\alpha]_D$ −57.2° (*c* 1.0, MeOH) precipitated and was recrystallized from *s*-BuOH (8 mL) giving 279 mg (82%); mp 192—193 °C; $[\alpha]_D$ −68.5° (*c* 1.0, MeOH). Found: C, 53.16; H, 7.85; N, 15.45%. Calcd for $C_{12}H_{21}N_3O_4$: C, 53.12; H, 7.80; N, 15.49%.

(+)-∇Glp ((+)-1). A solution of (+)-∇Glp·D-Leu-NH_2 (162.8 mg, 0.60 mmol) in aqueous MeOH (95 : 5, 0.5 mL) was passed through a column (1.0×6.5 cm) containing 5 mL of Dowex 50×2-100 resin on the H^+ cycle. The fractions containing ∇Glp were evaporated and the residue was crystallized from 2-propanol (1 mL) and ether (5 mL) to give 84.7 mg (100%); mp 165—167 °C; $[\alpha]_D$ +143.6° (*c* 0.5, MeOH); R_f^3 0.27; ^{1}H NMR (0.5% DCl/D_2O) δ=2.83 (dd, 1H, H_Y), 2.37 (d, 1H, H_X), 2.22 (m, 1H, H_M), 1.81 (dd, 1H, H_B), 1.05 (t, 1H, H_A). Found: C, 51.00; H, 4.98; N, 9.83%. Calcd for $C_6H_7NO_3$: C, 51.06; H, 5.00; N, 9.93%.

(−)-∇Glp ((−)-1). (−)-∇Glp·L-Leu-NH_2 (409 mg, 1.51 mmol) afforded 209 mg (98%); mp 160—161 °C; $[\alpha]_D$ −145.8° (*c* 0.5, MeOH), of (−)-**1** according to the above method. R_f value and NMR spectrum were identical to those for (+)-isomer (+)-**1**. Found: C, 51.15; H, 5.02; N, 9.92%. Calcd for $C_6H_7NO_3$: C, 51.06; H, 5.00; N, 9.93%.

(−)-(2*S*,3*R*)-*N*-Benzyloxycarbonyl-2,3-methanoproline Methyl Ester ((−)-5). A mixture of (−)-(2*S*,3*R*)-*N*-benzyloxycarbonyl-2,3-methanoproline, (1.2 g, 4.6 mmol) and concd H_2SO_4 (2 mL) in dry MeOH (30 mL) stood for 20 h at room temperature and was evaporated. The residue was dissolved in EtOAc (25 mL) and the solution washed with sat. NaCl (20 mL), 7% $NaHCO_3$ (20 mL). Evaporation gave (−)-**5** as a colorless oil: 1.15 g (91%); R_f^4 0.62, R_f^5 0.42; $[\alpha]_D$ −49.5° (*c* 1.29, MeOH); ^{1}H NMR ($CDCl_3$) δ=7.23 (s, 5H, *ArH*), 5.07 (dd, *J*=12 Hz, 2H, ArCH_2), 3.59 (s, 3H, OCH_3), 4.01—3.36 (m, 2H, NCH_2), 2.42—1.72 (m, 4H, 2-*H*, Pro δCH_2), 1.03 (br s, 1H, ∇-*H*). Found: C, 65.24; H, 6.28; N, 5.08%. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09%.

(+)-(2*R*,3*S*)-*N*-Benzyloxycarbonyl-2,3-methanoproline Methyl Ester ((+)-5). This compound was prepared from (+)-(2*R*,3*S*)-*N*-benzyloxycarbonyl-2,3-methanoproline, (1.2 g, 4.6 mmol) according to the above method to give 1.17 g (93%); $[\alpha]_D$ +49.6° (*c* 1.37, MeOH); R_f value and NMR spectrum were identical to those for (−)-isomer (−)-**5**. Found: C, 65.29; H, 6.26; N, 5.07%. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09%.

(−)-(2*S*,3*R*)-2,3-Methanoproline Methyl Ester. Hydrogen gas was bubbled into a stirred mixture of (−)-**5** (1.1 g, 4.0 mmol) and 5% Pd/C (0.5 g) in EtOAc (30 mL) under atmospheric pressure at room temperature for 0.5 h. The catalyst was filtered and the filtrate evaporated to afford the crude ester as a pale yellow oil: 390 mg (69%); R_f^7 0.05; $[\alpha]_D$ −63.8° (*c* 0.54, MeOH); ^{1}H NMR ($CDCl_3$) δ=3.66 (s, 3H, OCH_3), 3.30—2.76 (m, 1H, N*CH*), 2.81—2.47 (m, 1H, N*CH*), 2.03 (s, 1H, *NH*), 2.12—1.03 (m, 3H, -*H*, Pro δCH_2). This product was converted into the *N*-propionyl derivative (**6**) without further purification.

(+)-(2*R*,3*S*)-2,3-Methanoproline Methyl Ester. This compound was prepared from (+)-**5** (1.1 g, 4.0 mmol) according to the above method: 370 mg (66%); $[\alpha]_D$ +66.4° (*c* 0.69, MeOH). R_f value and ^{1}H NMR spectrum were identical to those for the (−)-ester. This product was converted into the *N*-propionyl derivative (**6**) without further purification.

(−)-(2*S*,3*R*)-*N*-Propionyl-2,3-methanoproline Methyl Ester ((−)-6). To a solution of the (−)-2,3-methanoproline methyl ester (390 mg, 2.8 mmol) in dry pyridine (0.49 mL, 6.0 mmol) and CH_2Cl_2 (15 mL) propionyl chloride (510 mg, 5.5 mmol) was added dropwise at room temperature. After 2 h, *N,N*-diethylethylenediamine (0.5 mL, 35 mmol) was added and stirring continued for an additional hour. The solution was diluted with CH_2Cl_2 (150 mL), washed with 10% citric acid (2×50 mL) and 7% $NaHCO_3$ (2×50 mL). After evaporation, the residue was chromatographed on a silica-gel column eluted with hexane–EtOAc (1 : 2). Fractions containing the desired compound were combined and evaporated giving (−)-**6** as an oil: 330 mg (61%); $[\alpha]_D$ −85.0° (*c* 0.84, MeOH); R_f^6 0.41; ^{1}H NMR ($CDCl_3$) δ=3.67 (s, 3H, OCH_3), 4.15—3.21 (m, 2H, NCH_2), 2.24 (q, *J*=8 Hz, 2H, CH_2CH_3), 1.10 (t, *J*=8 Hz, 3H, CH_2CH_3), 1.18—0.82 (1H, overlapped, ∇-*H*).

(+)-(2*R*,3*S*)-*N*-Propionyl-2,3-methanoproline Methyl Ester ((+)-6). This compound was prepared from (+)-isomer of the ester (270 mg, 1.9 mmol) according to the above method: 256 mg (68%); $[\alpha]_D$ +85.5° (*c* 0.81, MeOH). The R_f value and ^{1}H NMR spectrum were identical to those for (−)-isomer (−)-**6**.

(−)-(2*S*,3*S*)-*N*-Propionyl-2,3-methanopyroglutamic Acid Methyl Ester ((−)-7). To a solution of compound (−)-**6** (250 mg, 1.27 mmol) in EtOAc (25 mL) was added $RuO_2 \cdot xH_2O$ (150 mg) and 10% aqueous $NaIO_4$ (5O mL), and the mixture was vigorously stirred at room temperature. After 15 h, the layers were separated and the aqueous layer extracted with EtOAc (3×25 mL) and the combined EtOAc extract was washed with water. After evaporation, the residue was purified by chromatography on a silica-gel column eluted with hexane–EtOAc (1 : 2). Fractions containing the desired

compound were combined and concentrated under reduced pressure to provide pure (−)-**7** as a colorless oil: 94 mg (35%); $[\alpha]_D$ −144.4° (*c* 0.63, MeOH); ^{1}H NMR ($CDCl_3$) δ=3.73 (s, 3H, OCH_3), 3.09 (dd, 7Hz, 1H, H_Y), 2.88 (m, 2H, CH_2CH_3), 2.64 (d, *J*=18.9 Hz, 1H, H_X), 2.11 (dd, *J*=6.2 and 8.8 Hz, 1H, H_B), 1.91 (m, *J*=7.4 Hz, 1H, H_M), 1.17 (t, *J*=7.31 Hz, 3H, CH_2CH_3), 0.94 (t, *J*=6.1 Hz, 1H, H_A). Found: C, 56.77; H, 6.22; N, 6.57%. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63%.

(+)-(2*R*,3*R*)-*N*-Propionyl-2,3-methanopyroglutamic Acid Methyl Ester ((+)-7). This compound was prepared from (+)-**6** (250 mg, 1.27 mmol) according to the above method: 65 mg (24%); $[\alpha]_D$ +143.9° (*c* 0.61, MeOH). R_f value and ^{1}H NMR spectrum were identical to those for (−)-isomer (−)-**7**. Found: C, 56.76; H, 6.22; N, 6.55%. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63%.

(−)-(2*S*,3*S*)-2,3-Methanoglutamic Acid ((−)-8). From (−)-∇Glp ((−)-1): A solution of compound (−)-**1** (31 mg, 0.22 mmol) in 6 M (1 M=1 mol dm^{-3}) HCl (2 mL) was heated at 70 °C for 3 h and evaporated in vacuo. The crude (−)-**8** was dried over KOH and washed with ether (3×1 mL): 43 mg (100%); mp 202—203 °C; $[\alpha]_D$ −10.4° (*c* 0.5, 5M HCl); R_f[8] 0.25; ^{1}H NMR (0.5% DCl/D_2O) δ=2.72 (dd, 1H, *J*=7.3 and 17.5 Hz, H_Y), 2.57 (dd, 1H, *J*=7.8 and 17.5 Hz, H_X), 2.10 (m, 1H, H_M), 1.77 (dd, 1H, H_B), 1.26 (dd, 1H, H_A). Found: C, 36.67; H, 5.14; N, 7.06%. Calcd for $C_6H_{10}NO_4Cl$: C, 36.84; H, 5.15; N, 7.16%.

From (−)-(2*S*,3*S*)-*N*-Propionyl-∇Glp-OMe ((−)-7): (−)-**7** (9.0 mg) was hydrolyzed in 6 M HCl (2 mL) at 70 °C for 3 h giving (2*S*,3*S*)-2,3-methanoglutamic acid, (−)-**8**, 8.0 mg, (96%); mp 199—202 °C; $[\alpha]_D$ −11.6° (*c* 0.5, 5 M HCl). R_f value and ^{1}H NMR spectrum were identical to those for product, (−)-**8** from (−)-**1**.

(+)-(2*R*,3*R*)-2,3-Methanoglutamic Acid ((+)-8). From (+)-∇Glp ((+)-1): (+)-**1** (31.2 mg, 0.22 mmol) was hydrolyzed in 6 M HCl (2 mL) at 70 °C for 3 h, and evaporated in vacuo. The crude (+)-**8** was dried over KOH and washed with ether: 43 mg (100%); mp 202—204 °C; $[\alpha]_D$ +9.7° (*c* 0.7, 5 M HCl); R_f[8] 0.25; ^{1}H NMR (0.5% DCl/D_2O) δ=2.72 (dd, 1H, *J*=7.3 and 17.5 Hz, H_Y), 2.57 (dd, 1H, *J*=7.8 and 17.5 Hz, H_X), 2.10 (m, 1H, H_M), 1.77 (dd, 1H, H_B), 1.26 (dd, 1H, H_A). Found: C, 36.65; H, 5.10; N, 7.06%. Calcd for $C_6H_{10}NO_4Cl$: C, 36.84; H, 5.15; N, 7.16%.

From (+)-(2*R*,3*R*)-*N*-propionyl-∇Glp-OMe ((+)-7): (+)-**7** (9.0 mg) was hydrolyzed in 6 M HCl (2 mL) at 70 °C for 3 h giving (2*R*,3*R*)-2.3-methanoglutamic acid, (+)-**8**, 7.9 mg, (95%); mp 201—203 °C; $[\alpha]_D$ +10.1° (*c* 0.5, 5 M HCl). R_f value and ^{1}H NMR spectrum were identical to those for product, (+)-**8** from (+)-**1**.

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1) Symbols and abbreviations used are according to IUPAC-IUB Commissions, *Eur. J. Biochem.*, **138**, 9 (1984). In this paper, the title compounds were named as modified amino acids. The amino acids referred to as 2,3-methanoamino acids. The symbol ∇ prefixed to the abbreviation for an amino acid residue, as in ∇^ZGlu means the *Z*-diastereomer of 2,3-methano or cyclopropane-glutamic acid; 2,3-methanopyroglutamic acid (∇Glp), 3-oxo-2-azabicyclo[3,1,0]hexane-1-carboxylic acid; 2,3-methanoglutamic acid (∇Glu), 2-amino-2-carboxy-1-cyclopropaneacetic acid; 2,3-methanoproline (∇Pro), 2-azabicyclo[3,1,0]hexane-1-carboxylic acid.

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