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A Novel Synthesis of L-Pyroglutamic Acid Derivatives from L-Proline: Utility of *N*-Protecting Groups for Ruthenium Tetroxide Oxidation of Cyclic α-Amino Acids[1)]

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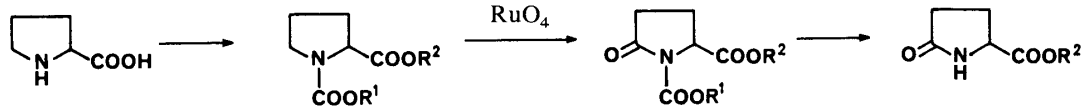
The utility of four urethane type *N*-protecting groups, benzyloxycarbonyl (Z), *p*-nitrobenzyloxycarbonyl [Z(NO$_2$)], trichloroethoxycarbonyl (Troc) and *tert*-butoxycarbonyl (Boc) groups, was tested in the ruthenium tetroxide (RuO_4) oxidation of *N*-protected L-proline esters. Three groups, but not the Z group, which was decomposed by RuO_4, were found to be stable during the oxidation and afforded high yields of the corresponding L-pyroglutamic acid esters. Removal of the protecting groups from the oxidation products was carried out successfully in the usual manner to give *N*-unsubstituted (NH-type) L-pyroglutamic acid derivatives without racemization. The first transformation of L-proline into L-pyroglutamic acid and its derivatives has been accomplished.

Keywords——oxidation; ruthenium tetroxide oxidation; lactam synthesis; L-pyroglutamic acid synthesis; carboxamide *N*-protection; ruthenium tetroxide; L-proline; L-pyroglutamic acid; two-phase method

Ruthenium tetroxide (RuO_4) is a highly effective oxidant for the conversion of *N*-acylated cyclic amines into the corresponding lactams.[2)] However, this reagent as well as other common oxidants can not directly oxidize *N*-unsubstituted cyclic amines to the NH-type lactams,[3)] but gives only an intractable mixture of decomposed products.[4)] In the previous paper,[5)] we described a novel synthesis of L-glutamic acid from L-proline, involving the formation of *N*-acyl-L-pyroglutamic acid esters by RuO_4 oxidation of L-proline esters substituted on nitrogen with acetyl, propionyl and cyclohexanecarbonyl groups. L-Pyroglutamic acid is an important lactam-type amino acid and exists in an *N*-unsubstituted form at the *N*-terminus of some natural biologically active peptides.[6)] Since selective exocyclic deacylation of *N*-acyllactams is generally difficult, *N*-unsubstituted (NH-type) pyroglutamic acid esters have not been prepared from *N*-acyl-L-pyroglutamic acid esters obtained by the above oxidation. As a part of our studies on chemical conversion of L-proline residue in peptides into L-pyroglutamic acid residue or L-glutamic acid residue for producing new types of peptides, we have investigated a new synthetic route to *N*-unsubstituted L-pyroglutamic acid derivatives starting from L-proline by selective exocyclic deacylation, as illustrated in Chart 1.

In order to prepare NH-type lactams from *N*-acylated cyclic amines by the RuO_4 oxidation method, the *N*-acyl group should be stable during the RuO_4 oxidation and should be selectively removable after the oxidation without ring cleavage of the resulting lactams. The methoxyoxalyl (CH_3OCOCO) group was used first by Sheehan and Tulis[2a)] for this purpose to protect simple cyclic amines in the single-phase method of RuO_4 oxidation. However, this group is not favorable in the two-phase procedure, employing an organic solvent-water system, which is economical and convenient. Moreover, sodium methoxide for deprotection can not be applied to our optically active substrates bearing an ester group. In

order to develop a general procedure for the preparation of such NH-lactam type amine acid derivatives by oxidation of cyclic α-amino acid derivatives with RuO_4, we examined urethane-type *N*-protecting groups, which are widely used in amino acid chemistry.[7]



1 **2a—f** **3a—f** **4**: $R^2=CH_3$

5: $R^1=tert$-Bu, $R^2=H$ **6**: $R^2=H$

a: $R^1=C_6H_5CH_2$, $R^2=CH_3$
b: $R^1=p$-$NO_2C_6H_4CH_2$, $R^2=CH_3$
c: $R^1=CCl_3CH_2$, $R^2=CH_3$
d: $R^1=tert$-Bu, $R^2=CH_3$
e: $R^1=tert$-Bu, $R^2=tert$-Bu
f: $R^1=tert$-Bu, $R^2=p$-$NO_2C_6H_4CH_2$

Chart 1

As urethane-type protecting group, benzyloxycarbonyl (Z), *p*-nitrobenzyloxycarbonyl [Z(NO_2)], trichloroethoxycarbonyl (Troc) and *tert*-butoxycarbonyl (Boc) groups were chosen in this work. The RuO_4 oxidations of the L-proline esters (**2a—f**) protected on nitrogen with these groups were carried out at room temperature according to our standard procedure[5] using a catalytic amount of ruthenium dioxide (RuO_2) hydrate and an excess of 10% aqueous sodium metaperiodate in a two-phase system of ethyl acetate–water. The reactions proceeded smoothly under these conditions and the desired lactam compounds (**3a—f**) were isolated from the organic phase as the sole product except in the case of the *N*-Z derivative (**2a**). The structures of the lactams (**3a—f**) were assigned on the basis of analytical and spectral data. The results with the four *N*-protecting groups are summarized in Table I. The nature of the alkoxy group in **2** affected the reaction rate: a *tert*-butoxy group in the urethane and ester functions accelerated the oxidation reaction.

The oxidation of the *N*-Z derivative (**2a**) was not very satisfactory, giving only a low yield (30%) of the corresponding lactam (**3a**) because of simultaneous oxidative cleavage of a benzene ring,[8] consuming a large excess of sodium metaperiodate which served to generate RuO_4 from RuO_2. This suggests that the Z group may not suitable as an *N*-protecting group in this method of RuO_4 oxidation. The Z(NO_2) group having a deactivated ring with a nitro substituent was more effective, and the oxidation of **2b** proceeded cleanly to afford 87% yield of the lactam (**3b**).

The *N*-protected L-pyroglutamic acid esters (**3a—e**) obtained by the above oxidation were readily converted to the NH-type lactam derivatives by the use of common procedures for removal of protecting groups from *N*-protected amines.[7,9] Thus, the *N*-Z and *N*-Z(NO_2) derivatives (**3a** and **3b**) were easily deprotected under hydrogenolytic conditions (Pd–C/H_2, methanol, room temperature, 1—5 h) to furnish methyl L-pyroglutamate (**4**). The Troc group of **3c** was selectively cleaved with zinc in acetic acid[10] (room temperature, 2 h). The *N*-Boc-lactam (**3d**) was treated with trifluoroacetic acid (TFA) in dichloromethane (room temperature, 1 h). In the same manner, *tert*-butyl *N*-Boc-L-pyroglutamate (**3e**) directly gave L-pyroglutamic acid (**6**). The deprotection yields are included in Table I. The resulting *N*-deprotected product (**4**) was identical with an authentic sample of methyl L-pyroglutamate, prepared by esterification of commercially available L-pyroglutamic acid. *p*-Nitrobenzyl *N*-Boc-L-pyroglutamate (**3f**) was subjected to hydrogenolysis (Pd–C/H_2, methanol, room temperature, 1 h) to produce a 92% yield of *N*-Boc-L-pyroglutamic acid (**5**),[11] which has not previously been directly prepared from L-pyroglutamic acid. Optical activities of all deprotected products (**4**, **5**, **6**) were very satisfactory in comparison with those of these authentic specimens.

TABLE I. RuO_4 Oxidation of **2a**—**f** and Deprotection of **3a**—**e**

N-Protecting group ($COOR^1$)	Substrate R^2	RuO_4 Oxidation Time (h)	RuO_4 Oxidation Yield (%)	Deprotection Method	Deprotection Yield (%)
Z	**2a**: CH_3	5	**3a**: 30	$Pd-C/H_2$	**4**: 80
		57[a]	54		
$Z(NO_2)$	**2b**: CH_3	20	**3b**: 87	$Pd-C/H_2$	**4**: 92
Troc	**2c**: CH_3	17	**3c**: 95	Zn/CH_3COOH	**4**: 82
Boc	**2d**: CH_3	6	**3d**: 98	CF_3COOH	**4**: 91
	2e: *tert*-Bu	2	**3e**: 95	CF_3COOH	**6**: 90
	2f: NBz	8	**3f**: 94		—[b]

Z = benzyloxycarbonyl; $Z(NO_2)$ = *p*-nitrobenzyloxycarbonyl; Troc = trichloroethoxycarbonyl; Boc = *tert*-butoxycarbonyl; NBz = *p*-nitrobenzyl. *a*) The CCl_4–H_2O system was employed. *b*) *N*-Deprotection was not carried out.

Of the four *N*-protecting groups tested above, the Boc group was found to be the most suitable for our purpose in both RuO_4 oxidation and deprotection. *tert*-Butyl and *p*-nitrobenzyl groups proved to be useful for *C*-protection of amino acids against RuO_4 oxidation.

Thus, the first transformation of L-proline into *N*-protected and *N*-unprotected (NH-type) L-pyroglutamic acid derivatives has now been established. This methodology offers a new and useful synthetic strategy for preparing natural and unnatural lactam-type amino acids and peptides[1] containing lactam-type amino acid residues. The use of the urethane-type *N*-protecting groups reported herein has allowed us to develop a general synthesis of NH-lactams by RuO_4 oxidation of *N*-unsubstituted cyclic amines. An application is reported in the following paper.[12]

Experimental

Melting points were taken on a Yanagimoto melting point apparatus. All melting points and boiling points are uncorrected. Infrared (IR) spectra were recorded on a JASCO IRA-2 spectrometer. Mass spectra (MS) were measured on a JEOL JMS D-100 or a JEOL JMS D-300 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained at 23 °C using tetramethylsilane as an internal standard with a JEOL JNM-MH-100 or a JEOL JNM-FX-100 spectrometer. Optical rotations were measured with a JASCO DIP-4 spectrometer.

Starting Materials for the RuO_4 Oxidation——1) *N*-Protected L-Proline Methyl Esters (**2a**—**d**): These substrates were obtained by esterification of commercial L-proline[13] with $SOCl_2$–methanol[14] followed by acylation with Z-Cl or $Z(NO_2)$-Cl or Troc-Cl under basic conditions (triethylamine or K_2CO_3, 0—10 °C) or with *tert*-butyl *S*-4,6-dimethylpyrimid-2-ylthiocarbonate (Boc-S reagent).[15]

2) *N*-Boc-L-proline Esters (**2e**, **f**): These compounds were prepared by esterification of *N*-Boc-L-proline with *tert*-BuOH or 4-nitrobenzyl alcohol in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine.[16]

New compounds were characterized as described below.

Methyl L-1-Benzyloxycarbonylprolinate (2a)——A colorless oil, bp 149 °C (3 mmHg). $[\alpha]_D^{21}$ −57.8° (c = 1.0, EtOH). MS *m/e*: 263 (M^+). IR δ_{max}^{film} cm^{-1}: 1705 (urethane C=O), 1745 (ester C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.70—2.50 (4H, m, C_3-H_2 and C_4-H_2), 3.30—3.80 (2H, m, C_5-H_2), 3.76 (3H, s, CO_2CH_3), 4.28—4.50 (1H, m, C_2-H), 5.02 and 5.20 (2H, a pair of AB-type d's, J = 12 Hz, $C\underline{H}_2C_6H_5$), 7.36 (5H, s, aromatic protons).

Methyl L-1-(4-Nitrobenzyloxycarbonyl) Prolinate (2b)——A pale yellow oil. $[\alpha]_D^{15}$ −39.8° (c = 1.0, EtOH). MS *m/e*: 308 (M^+). IR ν_{max}^{film} cm^{-1}: 1700 (urethane C=O), 1742 (ester C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.41 (4H, m, C_3-H_2 and C_4-H_2), 3.49—3.81 (2H, m, C_5-H_2), 3.74 and 3.80 (3H, each s, rotational isomeric CO_2CH_3), 4.37—4.58 (1H, m, C_2-H), 5.26 and 5.34 (2H, each s, rotational isomeric $C\underline{H}_2C_6H_4$), 7.58—8.33 (4H, m, aromatic protons).

Methyl L-1-Trichloroethoxycarbonylprolinate (2c)——A colorless oil, bp 124 °C (1 mmHg). $[\alpha]_D^{12}$ −52.5° (c = 1.0, EtOH). MS *m/e*: 304 (M^+). IR ν_{max}^{film} cm^{-1}: 1714 (urethane C=O), 1746 (ester C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.68—2.36 (4H, m, C_3-H_2 and C_4-H_2), 3.24—3.80 (2H, m, C_5-H_2), 3.68 and 3.70 (3H, each s, rotational isomeric CO_2CH_3),

4.30—4.48 (1H, m, C_2-H), 4.60 and 4.81 (2H, a pair of AB-type d's, $J=12$ Hz, $CO_2CH_2CCl_3$).

Methyl L-1-*tert*-Butoxycarbonylprolinate (2d)——A colorless oil. $[\alpha]_D^{25}$ −69.4° ($c=1.0$, EtOH). MS *m/e*: 229 (M^+). IR ν_{max}^{film} cm^{-1}: 1694 (urethane C=O), 1745 (ester C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.40 and 1.45 (9H, each s, rotational isomeric $CO_2C(CH_3)_3$), 1.71—2.47 (4H, m, C_3-H_2 and C_4-H_2), 3.31—3.67 (2H, m, C_5-H_2), 3.72 (3H, s, CO_2CH_3), 4.15—4.47 (1H, m, C_2H).

***tert*-Butyl L-1-*tert*-Butoxycarbonylprolinate (2e)**——A colorless oil. $[\alpha]_D^{22}$ −35.5° ($c=0.9$, $CHCl_3$). MS *m/e*: 271 (M^+). IR ν_{max}^{film} cm^{-1}: 1700 (urethane C=O), 1740 (ester C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.44 (18H, s, 2×$CO_2C(CH_3)_3$), 1.72—2.12 (4H, m, C_3-H_2 and C_4-H_2), 3.28—3.60 (2H, m, C_5-H_2), 4.04—4.24 (1H, m, C_2-H).

4-Nitrobenzyl L-1-*tert*-Butoxycarbonylprolinate (2f)——A colorless oil. $[\alpha]_D^{12}$ −45.1° ($c=1.24$, $CHCl_3$). MS *m/e*: 249 ($M^+ - CO_2C(CH_3)_3$). IR ν_{max}^{film} cm^{-1}: 1692 (urethane C=O), 1752 (ester C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.36 and 1.47 (9H, each s, rotational isomeric $CO_2C(CH_3)_3$), 1.77—2.49 (4H, m, C_3-H_2 and C_4-H_2), 3.03—3.69 (2H, m, C_5-H_2), 4.25—4.49 (1H, m, C_2-H), 5.24 and 5.29 (2H, each s, rotational isomeric $CH_2C_6H_4$), 7.50 and 8.19 (4H, each d, $J=10$ Hz, aromatic protons).

Standard Procedure for the RuO_4 Oxidation in a Two-Phase System——A solution of a substrate (12 mmol) to be oxidized in AcOEt (40 ml) was added to a mixture of RuO_2 hydrate [Aldrich Chemical Co.] (240 mg) and 10% aqueous $NaIO_4$ (120 ml). The mixture was vigorously stirred using a mechanical stirrer with a glass blade at room temperature. After the starting material had disappeared as determined by thin layer chromatography (TLC), the layers were separated. The aqueous layer was extracted with three 40-ml portions of AcOEt. The combined organic solution was treated with isopropyl alcohol (2 ml) for 2—3 h to decompose the RuO_4 oxidant and filtered. The filtrate was washed with H_2O (40 ml) and dried over anhydrous Na_2SO_4. The solution was evaporated *in vacuo* to leave a residue, which was purified by column chromatography on silica-gel using AcOEt–hexane (1 : 2—2 : 1, v/v) as the eluent, and/or by vacuum distillation for oily substances or by recrystallization for solid products.

In the case of the *N*-Z derivative (**2a**), the oxidation was initiated under the conditions described above, but after 2 h, $NaIO_4$ (20 g) was added.

The results are summarized in Table I. The characteristics of the products were as follows.

Methyl L-1-Benzyloxycarbonylpyroglutamate (3a)——A colorless oil. $[\alpha]_D^{21}$ −41.3° ($c=1.0$, EtOH). MS *m/e*: 277 (M^+). IR ν_{max}^{film} cm^{-1}: 1720, 1750, 1800 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.80 (4H, m, C_3-H_2 and C_4-H_2), 3.64 (3H, s, CO_2CH_3), 4.63 (1H, dd, $J=9$, 3 Hz, C_2-H), 5.20 (2H, m, $NCO_2CH_2C_6H_5$), 7.30 (5H, s, aromatic protons).

Methyl L-1-(4-Nitrobenzyloxycarbonyl)pyroglutamate (3b)——A pale yellow oil. $[\alpha]_D^{15}$ −32.8° ($c=1.0$, EtOH). MS *m/e*: 322 (M^+). IR ν_{max}^{film} cm^{-1}: 1730, 1744, 1790 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.09—2.89 (4H, m, C_3-H_2 and C_4-H_2), 3.92 (3H, s, CO_2CH_3), 4.85—5.05 (1H, m, C_2-H), 5.61 (2H, s, $NCO_2CH_2C_6H_4$), 7.91 and 8.56 (2H×2, each d, $J=10$ Hz, aromatic protons).

Methyl L-1-Trichloroethoxycarbonylpyroglutamate (3c)——Recrystallized from hexane as colorless needles, mp 90—91 °C; $[\alpha]_D^{12}$ −52.8° ($c=1.0$, EtOH). MS *m/e*: 318 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1803 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.86—2.76 (4H, m, C_3-H_2 and C_4-H_2), 3.77 (3H, s, CO_2CH_3), 4.66—5.00 (3H, m, C_2-H and CO_2CH_2). *Anal.* Calcd for $C_9H_{10}Cl_3NO_5$: C, 33.94; H, 3.16; N, 4.40. Found: C, 33.86; H, 3.20; N, 4.33.

Methyl L-1-*tert*-Butoxycarbonylpyroglutamate (3d)——Recrystallized from hexane as colorless prisms, mp 72—72.5 °C; $[\alpha]_D^{25}$ −44.3° ($c=1.0$, EtOH). MS *m/e*: 142 ($M^+ - CO_2C(CH_3)_3$). IR ν_{max}^{KBr} cm^{-1}: 1690, 1732 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.48 (9H, s, $C(CH_3)_3$), 1.91—2.76 (4H, m, C_3-H_2 and C_4-H_2), 3.78 (3H, s, CO_2CH_3), 4.65 (1H, dd, $J=9$, 3 Hz, C_2-H). *Anal.* Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.21; H, 7.15; N, 5.69.

***tert*-Butyl L-1-*tert*-Butoxycarbonylpyroglutamate (3e)**——A pale yellow oil. $[\alpha]_D^{22}$ −35.1° ($c=0.9$, $CHCl_3$). MS *m/e*: 212 ($M^+ - OC(CH_3)_3$), 184 ($M^+ - CO_2C(CH_3)_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1792 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.47 (18H, s, 2×$C(CH_3)_3$), 1.82—2.68 (4H, m, C_3-H_2 and C_4-H_2), 4.48 (1H, dd, $J=9$, 3 Hz, C_2-H). *Anal.* Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 58.76; H, 8.02; N, 5.14.

4-Nitrobenzyl L-1-*tert*-Butoxycarbonylpyroglutamate (3f)——A colorless viscous oil. $[\alpha]_D^{12}$ −193.0° ($c=1.0$, $CHCl_3$). MS *m/e*: 264 ($M^+ - CO_2C(CH_3)_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1716, 1755, 1796 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s, $CO_2C(CH_3)_3$), 1.76—2.76 (4H, m, C_3-H_2 and C_4-H_2), 4.61—4.74 (1H, m, C_2-H), 5.30 (2H, s, $CH_2C_6H_4$), 7.50 and 8.18 (4H, each d, $J=10$ Hz, aromatic protons). *Anal.* Calcd for $C_{17}H_{20}N_2O_7$: C, 56.04; H, 5.53; N, 7.69. Found: C, 55.93; H, 5.66; N, 7.74.

Methyl L-Pyroglutamate (4)——1) Authentic Sample: L-Pyroglutamic acid was converted to the methyl ester (**4**) by esterification with diazomethane (ether–methanol, 0 °C, 30 min). The crude product was distilled under reduced pressure to give an authentic sample, colorless oil, bp 133 °C (3 mmHg). $[\alpha]_D^{20}$ −5.9° ($c=1.0$, H_2O) [lit.[17] $[\alpha]_D$ −5.6° ($c=2.8$, H_2O)]. MS *m/e*: 143 (M^+). IR ν_{max}^{film} cm^{-1}: 3250 (NH), 1700, 1740 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.20—2.52 (4H, m, C_3-H_2 and C_4-H_2), 3.77 (3H, s, CO_2CH_3), 4.18—4.36 (1H, m, C_2-H), 7.12 (1H, brs, NH).

2) From **3a**: A solution of **3a** (555 mg, 2.0 mmol) in methanol (20 ml) was hydrogenated over 10% palladium-on-charcoal (100 mg) at room temperature for 5 h. The catalyst was removed by filtration and washed with a little methanol. The filtrate and washings were combined and evaporated *in vacuo*. The resulting oil was distilled under reduced pressure to give **4** (230 mg, 80%) as a pale yellowish oil, bp 145—150 °C (1 mmHg). $[\alpha]_D^{21}$ −5.6° ($c=1.0$, H_2O). The IR and NMR spectra of **4** were identical with those of an authentic sample.

3) From **3b**: A solution of **3b** (485 mg, 1.5 mmol) in methanol (20 ml) was hydrogenated over 10% palladium-on-

charcoal (100 mg) at room temperature for 1 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to a small volume. The residue was acidified with 5% hydrochloric acid under cooling and extracted with $CHCl_3$ (3 × 15 ml). The extracts were combined, washed with brine, and dried over anhydrous Na_2SO_4. Evaporation of the $CHCl_3$ solution to dryness *in vacuo* gave **4** (198 mg, 92%) as a colorless oil, which was identical with an authentic sample. $[\alpha]_D^{15}$ −5.1° (c = 1.0, H_2O).

4) From **3c**: Zinc powder (1.0 g) was added to a solution of **3c** (510 mg, 1.6 mmol) in acetic acid (10 ml). The suspension was stirred at room temperature for 2 h and then filtered. The zinc powder was washed with a little acetic acid. The filtrate and the washings were combined and concentrated *in vacuo* to a small volume. Saturated aqueous $NaHCO_3$ was added to the residue and extracted with three 10-ml portions of chloroform. The extracts were dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to dryness, leaving a pale yellowish oil which was distilled to give **4** (184 mg, 82%) as a pale yellowish oil, bp 155 °C (2 mmHg, bath temperature). This sample was identical (in terms of IR and NMR spectra) with the authentic specimen. $[\alpha]_D^{20}$ −5.9° (c = 1.0, H_2O).

5) From **3d**: Compound **3d** (500 mg, 1.6 mmol) was treated with TFA (2 ml) in dichloromethane (2 ml) at room temperature for 1 h. Excess TFA was removed *in vacuo*, and the residue was neutralized with saturated aqueous $NaHCO_3$. The solution was extracted with three 10-ml portions of $CHCl_3$. The combined extracts were washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated *in vacuo* to provide **4** (267 mg, 91%) as a pale yellowish oil, identical (in terms of IR and NMR spectra) with the sample obtained by method (1). The crude product was distilled for measurement of the optical rotation, bp 150 °C (2 mmHg, bath temperature). $[\alpha]_D^{18}$ −5.2° (c = 1.0, H_2O).

Deprotection of 3e [Preparation of L-Pyroglutamic Acid (6)]——A solution of **3e** (700 mg, 2.45 mmol) in dichloromethane (3 ml) was treated with TFA (3 ml). After being stirred at room temperature for 20 min, the solution was evaporated *in vacuo* and the residue was triturated with EtOH–petroleum ether to precipitate fine crystals, which were collected by filtration and washed with EtOH–pertoleum ether to give **6** (290 mg, 90%), mp 183—185 °C. $[\alpha]_D^{12}$ −13.0° (c = 1.20, H_2O). This sample was identical (in terms of IR and NMR spectra) with authentic commercial L-pyroglutamic acid (Sigma Chemical Co.; $[\alpha]_D^{15}$ −11.9° (c = 1.5, H_2O); lit.[18] $[\alpha]_D^{25}$ −13.3° (c = 1.5, H_2O)).

Deprotection of 3f [Preparation of L-1-*tert*-Butoxycarbonylpyroglutamic Acid (5)]——A solution of **3f** (960 mg, 2.6 mmol) in methanol (20 ml) was hydrogenated over 10% palladium-on-charcoal (200 mg) at room temperature. The reaction was completed within 1 h and the catalyst was removed by filtration. The filtrate was concentrated *in vacuo*, and 5% hydrochloric acid (15 ml) was added to the resulting residue under cooling. The whole was extracted with AcOEt (3 × 20 ml). The extract was washed with water, dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to give **5** (495 mg, 83%) as a solid. Recrystallization of **5** from ethanol afforded colorless needles, mp 113—115 °C; $[\alpha]_D^{12}$ −34.8° (c = 1.2, AcOH) [lit.[11] mp 115—116 °C. $[\alpha]_D^{25}$ −35.3° (c = 1, AcOH)]. IR ν_{max}^{KBr} cm^{-1}: 3400, 1770. ^1H-NMR ($CDCl_3$) δ: 1.47 (9H, s, $C(CH_3)_3$), 1.98—2.75 (4H, m, C_3-H_2 and C_4-H_2), 4.42—4.62 (1H, dd, J = 9, 3 Hz, C_2-H), 9.54 (1H, br s, COOH). *Anal.* Calcd for $C_{10}H_{15}NO_5$: C, 52.39; H, 6.60; N, 6.11. Found: C, 52.12; H, 6.45; N, 6.01.

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References and Notes

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