October 1995 *Chem. Pharm. Bull.* **43**(10) 1617—1620 (1995) 1617

Asymmetric Synthesis of Lycoperdic Acid

Shigeyuki YOSHIFUJI* and Mamoru KANAME

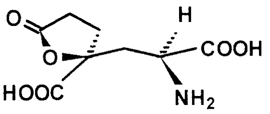
Faculty of Pharmaceutical Sciences of Hokuriku University, Ho-3, Kanagawa-machi, Kanazawa 920–11, Japan.

Received February 13, 1995; accepted June 9, 1995

Lycoperdic acid [(2S,5′S)-2-amino-3-(5′-carboxy-2′-oxo-5′-tetrahydrofuranyl)propanoic acid], isolated from the mushroom *Lycoperdon perlatum*, was synthesized from *trans*-4-hydroxy-L-proline by a six-step route involving samarium diiodide (SmI_2)-mediated formation of the spiro-γ-lactone and ruthenium tetroxide (RuO_4) oxidation of the L-proline ring system to the L-pyroglutamic acid moiety. Lycoperdic acid (1) was found to undergo hydrolysis of the γ-lactone ring in 1 N hydrochloric acid at 23 °C, giving an equilibrated mixture of 1 and the corresponding hydroxy acid.

Key words lycoperdic acid; α-amino acid synthesis; ruthenium tetroxide oxidation; lactam synthesis; samarium diiodide; spirolactonization

Lycoperdic acid, (2S,5′S)-2-amino-3-(5′-carboxy-2′-oxo-5′-tetrahydrofuranyl)propanoic acid (**1**), is a non-proteinogenic α-amino acid isolated from the mushroom *Lycoperdon perlatum* by R-Banga, *et al.* in 1978.[1] The plane structure of **1** and the (S)-configuration at the C2 position were determined by means of chemical and spectral methods,[1a] and the molecular structure was established by an X-ray crystallographic study,[1b] to be as depicted in Fig. 1. This amino acid having a spiro-γ-lactone moiety is a novel analogue of L-glutamic acid, a major neuroexcitatory substance in the mammalian central nervous system. We were interested in synthesizing lycoperdic acid because of its unique structure and potential biological activity. In this paper,[2] we wish to report an efficient synthesis of **1** *via* a six-step route starting from a readily available chiral source.



Lycoperdic Acid (1)

Fig. 1

We chose commercially available *trans*-4-hydroxy-L-proline (**2**) as a starting material since it can be easily transformed into the desired L-glutamic acid system present in the target molecule, and it has a proper functionality at the C4 position for introduction of the spiro-γ-lactone moiety. Therefore, our synthetic access to **1** is based on samarium diiodide (SmI_2)-mediated formation of the spiro-γ-lactone and ruthenium tetroxide (RuO_4) oxidation of the pyrrolidine ring of *trans*-4-hydroxy-L-proline to the L-pyroglutamic acid skeleton.

Following standard procedures,[3] the amino and carboxyl functions of *trans*-4-hydroxy-L-proline (**2**) were first protected in 97% yield with a *tert*-butoxycarbonyl (Boc) and a methyl ester group, respectively. The N,C-protected derivative **3** was subjected to oxidation with RuO_4 to give the N,C-protected 4-keto-L-proline (**4**)[4] in 87% yield. In order to construct the spiro-γ-lactone moiety having (S)-configuration at the C4 position, we initially intended to utilize Grignard-type alkylation to the ketone **4** with a propionic acid equivalent, which is one of several methods[5] reported for spiro-γ-lactone synthesis in other systems. However, we were unable to effect introduction of the phenylethyl side chain at the C4 position using phenylethylmagnesium bromide or phenylethylcerium dichloride in tetrahydrofuran (THF), for conversion to the desired propionic acid by oxidative decomposition under Sharpless conditions.[6] Therefore, as a second choice, SmI_2-mediated spiro-lactonization (reductive cross coupling)[7] was adopted even though no stereoselectivity was expected. Reaction of the ketone **4** with methyl acrylate in the presence of SmI_2 and methanol as a proton source afforded a mixture (78% yield) of two possible diastereoisomeric spiro-γ-lactones (**5a**,**b**), which could not be separated from each other. This coupling reaction in THF proceeded slowly over 12 h at room temperature. However, as reported by Otsubo, *et al.*,[7b] addition of hexamethylphosphoramide (HMPA) to the reaction solution shortened the reaction rate to within 1 h at 0 °C and gave a slightly better yield (81%) of the product.

In the next step, conversion of the pyrrolidine ring of the products **5a**,**b** into the L-pyroglutamic acid moiety was conducted smoothly by RuO_4 oxidation[8] as developed in our laboratory. Thus, oxidation of the mixture (**5a**,**b**) was carried out at room temperature for 50 h with a catalytic amount of ruthenium dioxide ($RuO_2 \cdot$hydrate) and an excess of 10% aqueous sodium metaperiodide ($NaIO_4$) in a two-phase system. As the organic solvent of the system, nitromethane was more suitable for the present purpose in terms of reaction rate and product yield than ethyl acetate, which had been exclusively used in the oxidation of amino acid derivatives[8] and other nitrogen-containing compounds.[9] A mixture of two diastereomeric lactams was obtained from the organic phase in 76% total yield and could be easily separated by column chromatography on silica gel to give **6a** (43%) and **6b** (33%) with a ratio of 57 : 43. This ratio is a reflection of the stereoselectivity in the SmI_2-mediated spiro-lactonization. The stereochemistry of the two isomers was determined by means of ^{1}H-NMR spectroscopy including difference nuclear Overhauser effect (NOE) and nuclear Overhauser and exchange spectroscopy (NOESY) experiments. The (5S, 8S)-configuration of **6a** was confirmed by observation

---

* To whom correspondence should be addressed.

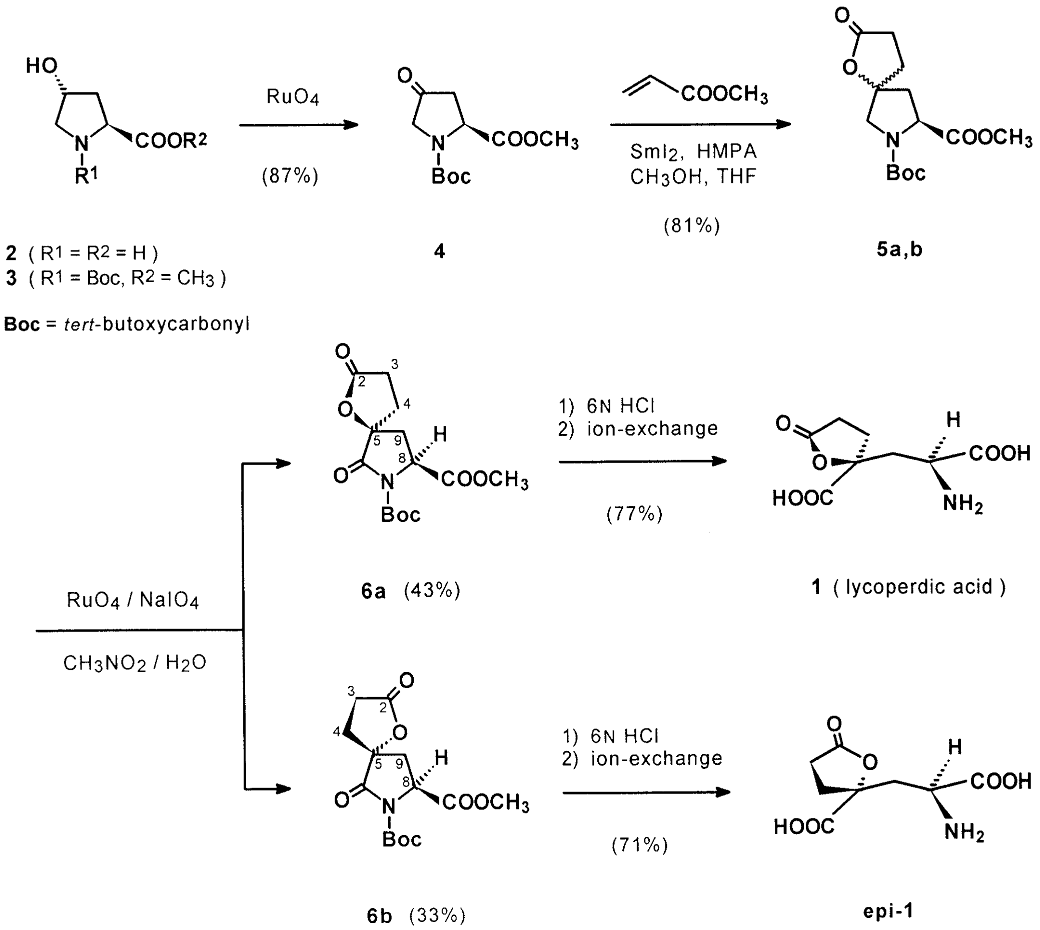


Chart 1

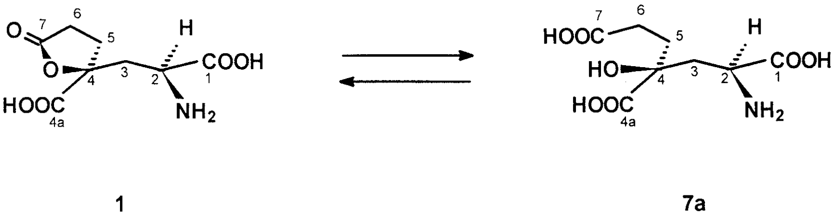


Chart 2. Lycoperdic Acid (**1**) in Acidic Aqueous Solution

of the NOEs between C8-H and C9-α-H, C9-α-H and C4-H, C4-H and C8-H, respectively. For **6b**, NOE was observed between C9-β-H and C4-H, and hence the (5*R*,8*S*)-configuration of **6b** was assigned.

Finally, removal of the Boc group and ester cleavage of **6a** having the requisite stereochemistry were achieved by hydrolysis in refluxing 6 N hydrochloric acid (HCl) followed by ion-exchange chromatography (Dowex 1 × 8, eluted 2 N acetic acid) to furnish the crude product (**1**) in 77% yield in the solid state; it was confirmed by the IR spectrum to have a γ-lactone ring ($\nu_{\max}$ 1772 cm^{-1}), presumably formed by cyclization of the hydroxy acid during the work-up procedure. Recrystallization of the crude amino acid from water gave the desired lycoperdic acid (**1**) in pure form, mp 200—201 °C,[10] $[\alpha]_{\mathrm{D}}^{21}$ $+14.2°$ ($c=0.46$, H_2O) and $[\alpha]_{\mathrm{D}}^{23}$ $+37.2°$ ($c=1.37$, 1 N HCl) [lit.[1a] $[\alpha]_{\mathrm{D}}^{20}$ $+14.9°$ ($c=0.47$, H_2O) and $[\alpha]_{\mathrm{D}}^{20}$ $+36.5°$ ($c=1.37$, 1 N HCl)]. The spectral data [MS, IR, ^{1}H- and ^{13}C-NMR, circular dichroism (CD)] of the synthetic sample were essentially in accord with the reported values for natural lycoperdic acid.[11] The isomeric lactam **6b** was treated in a manner similar to that described above for **6a** to afford a novel amino acid (epi-**1**), 71% yield, mp 176—176.5 °C, $[\alpha]_{\mathrm{D}}^{21}$ $+7.5°$ ($c=1.52$, H_2O) and $[\alpha]_{\mathrm{D}}^{23}$ $+7.7°$ ($c=1.37$, 1 N HCl), which was not identical, from a comparison of spectral data, with natural lycoperdic acid. This was ascertained to be the C5′-epimer of lycoperdic acid.

Lycoperdic acid (**1**) is very stable in the solid state and keeps its structure in a neutral aqueous solution for at least 6 h (by NMR analysis in D_2O). In an acidic solution, however, **1** undergoes hydrolysis of the γ-lactone ring into the corresponding hydroxy acid (structure **7a**, Chart 2).[12] Indeed, it was observed by NMR analysis in 1 N DCl at 23 °C that **1** was gradually hydrolyzed to give an equilibrium mixture of **1** and **7a** (*ca.* 45 : 55, integration ratio of both C2-methine proton signals) after 15 h. Therefore, the optical rotation and CD spectrum of **1** in 1 N HCl must be measured immediately after dissolution of **1**, and

Table 1. ^{13}C-NMR Data for Compounds **1** and **7a** at Equilibrium in 1 N DCl (δ ppm)

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-4a
Lycoperdic acid (**1**)	171.29	50.78	37.55	85.94	33.12	28.15	179.96	174.06
Hydroxy acid (**7a**)	171.71	51.36	38.08	77.24	35.09	28.99	177.96	177.11

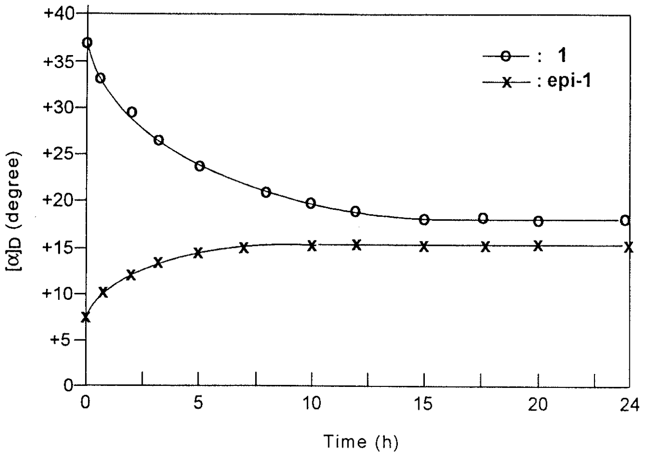


Fig. 2. Time Course of $[\alpha]_D$ (c=1.37, 1 N HCl) of **1** and epi-**1** at 23°C

the rotation value ($[\alpha]_D^{23}$ +37.2°) fell gradually with time to +18.2° (at the equilibrium stage, Fig. 2). Although the hydroxy acid (**7a**) could not be isolated from the HCl solution due to partial transformation into the lactone (**1**) and another product upon concentration of the solution, its structure was assigned by ^{13}C-NMR analysis in 1 N DCl using correlation spectroscopy (COSY) (^{1}H–^{1}H, ^{1}H–^{13}C and ^{1}H–^{13}C long range). The C4 quaternary carbon of **7a** showed a large upfield shift of 8.7 ppm compared with that of lycoperdic acid **1** (Table 1), indicating the existence of the non-acylated tertiary alcoholic OH group.[13] From the equilibrated mixture of **1** and **7a** in HCl solution, **1** was recovered in 78% yield without loss of optical purity by ion-exchange chromatography followed by solidification. These findings suggested that lycoperdic acid in the mushroom might be in a mixture of at least two forms, **1** and **7a**.

In summary, the first chemical synthesis of lycoperdic acid (**1**) has been accomplished, confirming the structure proposed by R-Banga, *et al.*[1]

Experimental

All melting points were taken on a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. CD spectra were measured on a JASCO J-20 spectrometer. MS were obtained on a JEOL JMS-DX300 spectrometer. IR spectra were recorded on a Hitachi 270-30 spectrophotometer. ^{1}H-NMR spectra were obtained at 23 °C on a JEOL PMX-60-SI or JNM-EX90A or JNM-GSX-400 spectrometer using tetramethylsilane (TMS, δ 0 ppm) or dioxane (δ 3.70 ppm from TMS) as an internal standard. ^{13}C-NMR spectra were measured on a JEOL JNM-GSX-400 spectrometer using TMS or dioxane (δ 67.4 ppm from TMS) as an internal standard. The following abbreviations are used: m=multiplet, q=quartet, t=triplet, d=doublet, s=singlet, and br=broad. Column chromatography was carried out on silica gel (Kieselgel 60, 70—230 mesh, Merck).

Methyl (2*S*,4*R*)-1-*tert*-Butoxycarbonyl-4-hydroxy-2-pyrrolidinecarboxylate (3) Compound **3** was prepared from commercial *trans*-4-hydroxy-L-proline (**2**) according to the literature[3] [by esterification with thionyl chloride–methanol, followed by *N*-protection with di-*tert*-butyl dicarbonate (Boc_2O) (triethylamine, dichloromethane, 20 °C, 4 h)]. Yield 97%. Colorless prisms, mp 92—93 °C (benzene–hexane) (lit.[3] mp 92—93 °C).

Methyl (2*S*)-1-*tert*-Butoxycarbonyl-4-oxo-2-pyrrolidinecarboxylate (4) The previously reported procedure[4] was slightly modified in the amount of ruthenium dioxide (RuO_2) used. Thus, the alcohol **3** (12.3 g, 50 mmol) was oxidized using a catalytic amount of $RuO_2 \cdot xH_2O$ (168 mg, 10% of the reported amount[4]) to give the corresponding ketone **4** (10.6 g, 87%) as a colorless oil. $[\alpha]_D^{22}$ −23.0° (c=1.24, methanol). (lit.[4] $[\alpha]_D^{26}$ −21.7° (c=1.24, methanol)).

Methyl (5*S*,8*S*)- and (5*R*,8*S*)-7-*tert*-Butoxycarbonyl-2-oxo-1-oxa-7-azaspiro[4.4]nonane-8-carboxylate (5a,b) A THF solution of SmI_2 (0.1 M) (1000 ml, 0.1 mol) was added dropwise to a stirred mixture of the ketone **4** (8.10 g, 33.3 mmol), methyl acrylate (5.74 g, 66.7 mmol) and methanol (1.60 g, 50.0 mmol) over a period of 1 h at −20 °C in an atmosphere of argon. Then, HMPA (30 ml) was added, and the whole was stirred at 0 °C for 1 h. A 5% HCl solution (150 ml) was added to the reaction solution and the whole was extracted with ether (450 ml, and 200 ml × 2). The ether extracts were combined, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave a pale brown oil. Purification of the oil by column chromatography (AcOEt–hexane, 1 : 1, v/v) afforded **5a,b** (8.18 g, 81%) as a colorless oil, which was presumed to be a mixture of the two possible diastereoisomeric spirolactones (see below), although the oil showed a single spot on TLC analysis (silica-gel, AcOEt–hexane system). This mixture was used directly in the next oxidation step without separation. MS m/z: 299 (M^+). IR ν_{max}^{neat} cm^{-1}: 1782, 1756, 1704.

The above reaction without HMPA required a long reaction time of 12 h and afforded a 78% yield of the product.

N-Deprotection of **5a,b**: The mixture (**5a,b**) (30 mg, 0.1 mmol) was treated with trifluoroacetic acid (TFA) (0.05 ml) in CH_2Cl_2 (3 ml) at room temperature for 8 h to give the *N*-deprotected TFA salt (31 mg, 100%). ^{1}H-NMR ($CDCl_3$) δ: 2.30—2.81 (6H, m, C9-H_2, C3-H_2, C4-H_2), 3.60—3.90 (2H, m, C6-H_2), 3.82 and 3.89 [total 3H (integration ratio 4 : 5), each s, diastereoisomeric CH_3's], 4.68 and 4.79 [total 1H (integration ratio 4 : 5), each dd, J=7.0, 11.7 Hz and J=2.6, 8.8 Hz, diastereoisomeric C8-H's].

RuO_4 Oxidation of 5a,b [Preparation of Methyl (5*S*,8*S*)-7-*tert*-Butoxycarbonyl-2,6-dioxo-1-oxa-7-azaspiro[4.4]nonane-8-carboxylate (6a) and Methyl (5*R*,8*S*)-7-*tert*-Butoxycarbonyl-2,6-dioxo-1-oxa-7-azaspiro[4.4]nonane-8-carboxylate (6b)] A solution of **5a,b** (6.88 g, 23 mmol) in nitromethane (77 ml) was added to a mixture of $RuO_2 \cdot xH_2O$ (575 mg) and 10% aqueous $NaIO_4$ (230 ml). The mixture was vigorously stirred at room temperature for 50 h in a sealed flask. The two layers were separated and the aqueous layer was extracted with AcOEt (200 ml × 3). The combined organic solution was treated with isopropyl alcohol (10 ml) for 2 h in order to decompose the oxidant (RuO_4), and the black precipitate (RuO_2) was filtered off. The filtrate was washed with 5% aqueous $Na_2S_2O_3$ (50 ml) and H_2O (50 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to leave a yellowish solid (6.90 g), which was separated by column chromatography (AcOEt–hexane, 1 : 1, v/v) to give **6b** (2.37 g, 33% from the first fractions) and **6a** (3.08 g, 43% from the second fractions).

When AcOEt was used as the organic phase in RuO_4 oxidation, the reaction proceeded slowly (72 h), and **6a** (30%) and **6b** (25%) were obtained after column chromatographic separation.

6a: Colorless needles, mp 143—145 °C (benzene–hexane). $[\alpha]_D^{21}$ −68.2° (c=1.1, $CHCl_3$). MS m/z: 314 (M^++1). IR ν_{max}^{KBr} cm^{-1}: 1802, 1752. ^{1}H-NMR ($CDCl_3$) δ: 1.52 (9H, s, *tert*-butyl protons), 2.16 (1H, ddd, J=10.1, 10.5, 14.0 Hz, C4-H), 2.51 (1H, dd, J=8.1, 14.7 Hz, C9-β-H), 2.56 (1H, dd, J=4.8, 14.7 Hz, C9-α-H), 2.57—2.63 (2H, m, C3-H and C4-H), 2.98 (1H, m, C3-H), 3.81 (3H, s, OCH_3), 4.64 (1H, dd, J=4.8, 8.1 Hz, C8-H). ^{13}C-NMR ($CDCl_3$) δ: 27.82 (q), 28.26 (t), 30.14 (t), 34.18 (t), 52.95 (q), 55.64 (d), 84.27 (s), 84.78 (s), 148.90 (s), 169.89 (s), 170.08 (s), 174.91 (s). *Anal.* Calcd for $C_{14}H_{19}NO_7$: C, 53.67; H, 6.11; N, 4.47.

Found: C, 53.95; H, 6.13; N, 4.59. The stereochemistry of **6a** was clarified by means of difference NOE and NOESY experiments.

6b: Colorless needles, mp 153—154 °C (benzene–hexane). $[\alpha]_D^{21}$ +59.4° (c=0.9, $CHCl_3$). MS m/z: 314 (M^++1). IR ν_{max}^{KBr} cm^{-1}: 1808, 1786, 1754. ^{1}H-NMR ($CDCl_3$) δ: 1.52 (9H, s, *tert*-butyl protons), 2.13 (1H, ddd, J=10.1, 13.2, 13.3 Hz, C4-H), 2.23 (1H, dd, J=3.7, 14.3 Hz, C9-β-H), 2.58 (1H, ddd, J=3.3, 9.5, 17.6 Hz, C3-H), 2.66 (1H, ddd, J=3.3, 9.8, 13.1 Hz, C4-H), 2.82 (1H, dd, J=9.5, 13.9 Hz, C9-α-H), 2.95 (1H, ddd, J=10.0, 10.0, 17.5 Hz, C3-H), 3.82 (3H, s, OCH_3), 4.69 (1H, dd, J=3.7, 9.5 Hz, C8-H). ^{13}C-NMR ($CDCl_3$) δ: 27.80 (q), 28.20 (t), 31.35 (t), 33.98 (t), 52.94 (q), 55.10 (d), 84.20 (s), 84.87 (s), 148.76 (s), 170.21 (s), 171.22 (s), 175.10 (s). *Anal.* Calcd for $C_{14}H_{19}NO_7$: C, 53.67; H, 6.11; N, 4.47. Found: C, 53.85; H, 5.99; N, 4.20. The stereochemistry of **6b** was established in a similar way to that of **6a**.

Lycoperdic Acid (1) [(2*S*,5′*S*)-2-Amino-3-(5′-carboxy-2′-oxo-5′-tetrahydrofuranyl)propanoic Acid] A solution of **6a** (1.57 g, 5 mmol) in 6 N HCl (40 ml) was refluxed in an oil bath for 12 h. The reaction solution was concentrated under reduced pressure and the residue was dissolved in a small amount of H_2O. The aqueous solution was applied to a column of Dowex 1 × 8 (200—400 mesh, 300 ml, CH_3COO^- form), and eluted with 2 N acetic acid. Concentration of the eluate to dryness afforded the crude amino acid (**1**) (840 mg, 77%) as a white solid, which was identical (IR, ^{1}H- and ^{13}C-NMR spectra) with the purified sample. Recrystallization of the solid from H_2O furnished the desired lycoperdic acid (**1**). Colorless needles, mp 200—201 °C (H_2O).10) $[\alpha]_D^{21}$ +14.2° (c=0.46, H_2O) (lit.1a) $[\alpha]_D^{20}$ +14.9° (c=0.47, H_2O)), $[\alpha]_D^{23}$ +37.2° (c=1.37, 1 N HCl) (lit.1a) $[\alpha]_D^{20}$ +36.5° (c=1.37, 1 N HCl)). CD (0.063 M, 1 N HCl) $[\theta]^{23}$ (nm): 0 (260), −342 (233), 0 (224), +1075 (208), +803 (203). [or λ_{max} 208 nm, $\Delta\varepsilon$= +0.33] (lit.1a) λ_{max} 210 nm, $\Delta\varepsilon$= +0.14 (0.063 M, 1 N HCl)). MS m/z: 218 (M^++1), 199 (M^+-H_2O). IR ν_{max}^{KBr} cm^{-1}: 3440, 3248, 2944, 2916, 2836, 2780, 2648, 2596, 2504, 2064, 1772, 1734, 1636, 1532, 1210, 1100. ^{1}H-NMR (D_2O) δ: 2.22—2.32 (2H, m, C4′-H, C3-H), 2.54 (1H, m, C4′-H), 2.63—2.67 (2H, m, C3′-H_2), 2.84 (1H, dd, J=3.3, 15.8 Hz, C3-H), 3.93 (1H, dd, J=3.3, 10.3 Hz, C2-H). ^{13}C-NMR (D_2O) δ: 28.52 (t, C3′), 33.13 (t, C4′), 38.56 (t, C3), 52.41 (d, C2), 88.65 (s, C5′), 172.88 (s, C1), 176.24 (s, C5′-$\underline{C}$OOH), 180.60 (s, C2′). The spectrum in D_2O did not change within 6 h. ^{1}H-NMR (CF_3COOD) δ: 2.19 (1H, m, C4′-H), 2.38 (1H, dd, J=10.4, 15.9 Hz, C3-H), 2.52—2.71 (3H, m, C4′-H, C3′-H_2), 3.02 (1H, d, J=15.9 Hz, C3-H), 4.37 (1H, d, J=10.4 Hz, C2-H). ^{13}C-NMR (CF_3COOD) δ: 27.80 (t, C3′), 33.03 (t, C4′), 37.32 (t, C3), 52.70 (d, C2), 87.25 (s, C5′), 171.99 (s, C1), 175.00 (s, C5′-$\underline{C}$OOH), 180.66 (s, C2′). *Anal.* Calcd for $C_8H_{11}NO_6$: C, 44.24; H, 5.10; N, 6.45. Found: C, 44.50; H, 5.18; N, 6.26.

Spectral Data of **1** in 1 N HCl (and 1 N DCl for NMR Measurements) at 23 °C: The $[\alpha]_D^{23}$ value (+37.2°, c=1.37, 3 min after dissolving) of **1** in 1 N HCl changed to +18.2° after 15 h (at equilibrium) [see Fig. 2]. The CD spectrum (λ_{max} 209 nm, $\Delta\varepsilon$= +0.33, 10 min after dissolving) in 1 N HCl changed to λ_{max} 209 nm, $\Delta\varepsilon$= +1.25 (after 20 h). ^{1}H-NMR (1 N DCl) δ (15 h after dissolving): 4.24 (0.45H, d, C2-H for **1**), 4.09 (0.55H, d, C2-H for the hydroxy acid, **7a**). ^{13}C-NMR (1 N DCl): Table 1 in Chart 2.

Recovery of **1** from 1 N HCl Solution: A solution of a mixture of **1** and **7a** in 1 N HCl used for spectral measurements ($[\alpha]_D$ and CD) was concentrated under reduced pressure and the residue was desalted in a manner similar to that described above to afford **1** as a crude solid (78%), mp 195—199 °C, $[\alpha]_D^{21}$ +36.1° (c=0.45, 1 N HCl). Recrystallization of the solid from H_2O provided pure **1**, colorless needles, mp 200—201 °C.

(2*S*,5′*R*)-2-Amino-3-(5′-carboxy-2′-oxo-5′-tetrahydrofuranyl)propanoic Acid (epi-1) A solution of **6b** (627 mg, 2 mmol) in 6 N HCl (15 ml) was refluxed in an oil bath for 12 h. The reaction solution was concentrated under reduced pressure and the residue was desalted by ion-exchange chromatography on an Amberlite IR-120B (40 ml, H^+ form) column with 1 N pyridine. Concentration of the eluate afforded a residue containing pyridine, which was dissolved in a little H_2O and applied again to a column of IR-120B, eluting with H_2O. The eluate was concentrated to dryness under reduced pressure to furnish a crude amino acid as a white solid. Recrystallization of the solid from 70% aqueous dioxane gave pure epi-**1** (309 mg, 71%). Colorless needles, mp 176—176.5 °C (dioxane–H_2O). $[\alpha]_D^{21}$ +7.5° (c=1.52, H_2O), $[\alpha]_D^{23}$ +7.7° (c=1.37, 1 N HCl). CD (0.063 M, 1 N HCl) $[\theta]^{23}$ (nm): 0 (260), +10732 (209), +9779 (203). [or λ_{max} 209 nm, $\Delta\varepsilon$= +3.25]. MS m/z: 218 (M^++1), 199 (M^+-H_2O). IR ν_{max}^{KBr} cm^{-1}: 3448, 3232, 2900, 2668, 1770, 1729, 1624, 1570, 1194, 1080. ^{1}H-NMR (D_2O) δ: 2.26—2.35 (1H, m, C4′-H), 2.46—2.71 (5H, m, C3-H_2, C3′-H_2 and C4′-H), 4.03 (1H, dd, J=5.1, 5.9 Hz, C2-H). ^{13}C-NMR (D_2O) δ: 28.83 (t, C3′), 32.69 (t, C4′), 37.64 (t, C3), 51.39 (d, C2), 87.67 (s, C5′), 172.91 (s, C1), 176.54 (s, C5′-$\underline{C}$OOH), 180.94 (s, C2′). ^{1}H-NMR (CF_3COOD) δ: 2.21—2.29 (1H, m, C4′-H), 2.51 (1H, dd, J=9.2, 15.9 Hz, C4′-H), 2.57—2.74 (3H, m, C3-H, C3′-H_2), 2.81 (1H, dd, J=7.3, 16.5 Hz, C3-H), 4.41 (1H, br, C2-H). ^{13}C-NMR (CF_3COOD) δ: 28.27 (t, C3′), 32.55 (t, C4′), 36.27 (t, C3), 51.58 (d, C2), 86.37 (s, C5′), 172.49 (s, C1), 175.79 (s, C5′-$\underline{C}$OOH), 181.22 (s, C2′). *Anal.* Calcd for $C_8H_{11}NO_6$: C, 44.24; H, 5.10; N, 6.45. Found: C, 44.07; H, 4.88; N, 6.32.

The $[\alpha]_D^{23}$ value (+7.7°, 3 min after dissolving) of epi-**1** in 1 N HCl changed to +15.2° after 15 h (at equilibrium) (see Fig. 2).

In the desalting process described above, use of Dowex 1 × 8 instead of Amberlite IR-120B failed to afford pure epi-**1**; the product did not completely solidify.

References and Notes

1) *a*) R-Banga N., Welter A., Jadot J., Casimir J., *Phytochemistry*, **18**, 482 (1979); *b*) Lamotte J., Oleksyn B., Dupont L., Dideberg O., Campsteyn H., Vermeire M., R-Banga N., *Acta Crystallogr.*, **B34**, 3635 (1978).

2) A part of this work was reported in a preliminary form; Kaname M., Yoshifuji S., *Tetrahedron Lett.*, **33**, 8103 (1992).

3) Rosen T., Chu D. T. W., Lico I. M., Fernandes P. B., Marsh K., Shen L., Cepa V. G., Pernet A. G., *J. Med. Chem.*, **31**, 1598 (1988).

4) Dormoy J.-R., Castro B., *Synthesis*, **1986**, 81.

5) *a*) Eaton P. E., Cooper G. F., Johnson R. C., Mueller R. H., *J. Org. Chem.*, **37**, 1947 (1972); *b*) Trost B. M., Bogdanowicz M. J., *J. Am. Chem. Soc.*, **95**, 5321 (1973); *c*) Buchmann B., Marschall-Weyerstahl H., Weyerstahl P., *Tetrahedron*, **40**, 393 (1984); *d*) Schlect M. F., Kim H. J., *Tetrahedron Lett.*, **26**, 127 (1985); *e*) Delay F., Giersch W. K., Ohloff G., Eur. Patent. EP 200.890, 17, Dec. 1986 [*Chem. Abstr.*, **106**, 72735*y* (1987)]; *f*) Buchwald S. L., Fang Q., King S. M., *Tetrahedron Lett.*, **33**, 3445 (1988); *g*) Alonso D., Font J., Ortuno R. M., *J. Org. Chem.*, **56**, 5567 (1991).

6) Carlsen P. H. J., Katsuki K., Martin V. S., Sharpless K. B., *J. Org. Chem.*, **46**, 3936 (1981).

7) *a*) Fukuzawa S., Nakanishi A., Fujinami T., Sakai S., *J. Chem. Soc. Chem. Comm.*, **1986**, 624; *b*) Otsubo K., Inanaga J., Yamaguchi M., *Tetrahedron Lett.*, **27**, 5763 (1986).

8) *a*) Yoshifuji S., Tanaka K., Kawai T., Nitta Y., *Chem. Pharm. Bull.*, **33**, 5515 (1985); *b*) Tanaka K., Yoshifuji S., Nitta Y., *Heterocycles*, **24**, 2539 (1986); *c*) Yoshifuji S., Tanaka K., Kawai T., Nitta Y., *Chem. Pharm. Bull.*, **34**, 3873 (1986); *d*) Tanaka K., Yoshifuji S., Nitta Y., *ibid.*, **34**, 3879 (1986); *e*) Yoshifuji S., Tanaka K., Nitta Y., *ibid.*, **35**, 2994 (1987).

9) *a*) Yoshifuji S., Arakawa Y., Nitta Y., *Chem. Pharm. Bull.*, **33**, 5042 (1985); *b*) Yoshifuji S., Arakawa Y., Nitta Y., *ibid.*, **35**, 357 (1987); *c*) Fujii T., Ohba M., Shimohata K., Yoshifuji S., *Heterocycles*, **26**, 2949 (1987); *d*) Tanaka K., Yoshifuji S., Nitta Y., *Chem. Pharm. Bull.*, **36**, 3125 (1988); *e*) Yoshifuji S., Arakawa Y., *ibid.*, **37**, 3380 (1989).

10) The melting point of natural lycoperdic acid has not been reported (ref. 1).

11) We could not obtain a sample of natural lycoperdic acid or the original records of its spectral data from the authors, Prof. R-Banga, *et al.* (ref. 1) because their address was not known.

12) Hydrolysis of lycoperdic acid in 3 N NaOH and in TFA–D_2O was observed by R-Banga, *et al.* (ref. 1*a*), but isolation and structure assignment of the hydrolyzed product (hydroxy acid) were not done.

13) Kalinowski H.-O., Berger S., Braun S., "Carbon-13 NMR Spectroscopy," John Wiley & Sons, New York, 1988, p. 215.