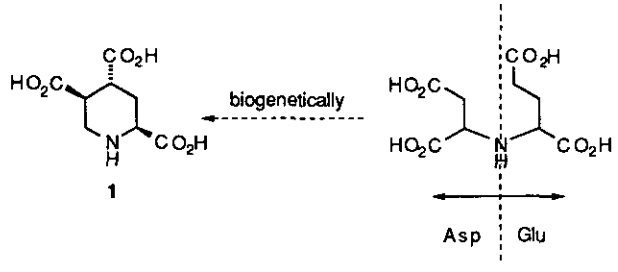
SYNTHESIS OF (2S*,4R*,5S*)-PIPERIDINETRICARBOXYLIC ACID, A NON-PROTEINOGENIC AMINO ACID ISOLATED FROM CLITOCYBE ACROMELALGA†

Kimiko Hashimoto, Shuhei Higashibayashi, and Haruhisa Shirahama*
School of Science, Kwansei Gakuin University, Uegahara, Nishinomiya, 662, Japan

Abstract - (2S*,4R*,5S*)-Piperidinetricarboxylic acid isolated from a poisonous mushroom Clitocybe acromelalga was synthesized along with its stereoisomers and their depolarizing activity was tested.

(2S*,4R*,5S*)-Piperidinetricarboxylic acid (**1**), a non-proteinogenic amino acid, was isolated from a poisonous mushroom Clitocybe acromelalga by our group.[1] From this fungi many non-proteinogenic amino acids have been isolated.[1~3] Most of them are biogenetically composed from two amino acids.[2(a)~(d), 3] For example, acromelic acids, the constituents of the mushroom, should be derived from L-glutamic acid (L-Glu) and DOPA, and the title compound should be arised from glutamic and aspartic acids.[2(i)] L-Glu is an excitatory neurotransmitter in mammalian central nervous systems and the acromelic acids cause marked depolarization, about 300~500 times more potent than L-Glu in the newborn-rat spinal motoneuron, which is probably due to the structural analogy to L-Glu and also to the partially constrained conformation of the L-Glu part.[4] Thus the similar biological action had been expected for the title amino acid, but it had not been tested for its scarecity from nature. The biological interests prompted us to synthesize the amino acid along with its stereoisomers.

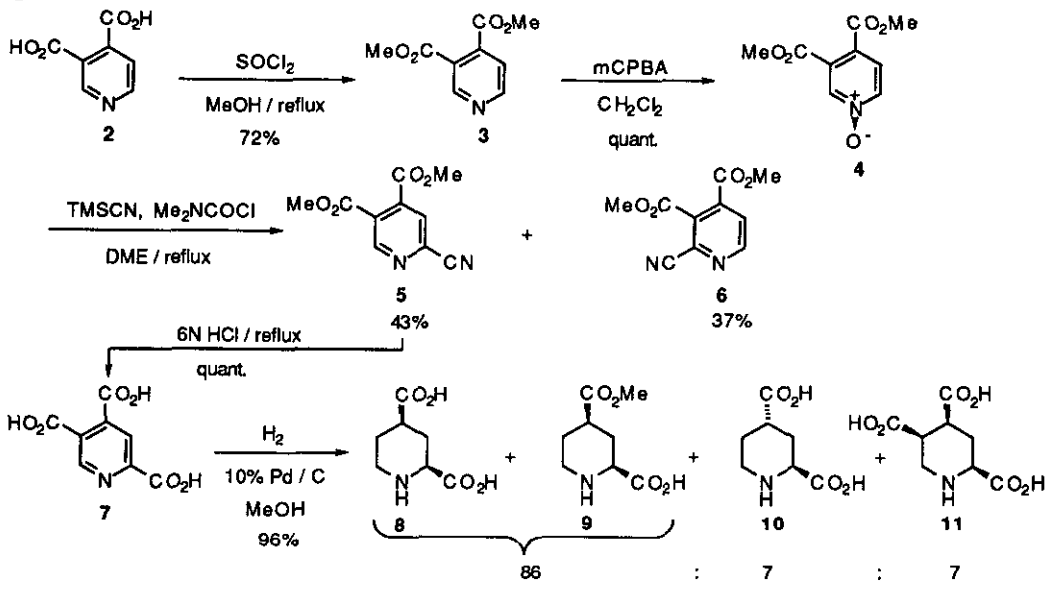


1

For our purpose, the most reasonable method to obtain all isomers of the title amino acid, would be reduction of the corresponding pyridine derivative. We chose commercially available pyridine-3,4-dicarboxylic acid (**2**) as a starting material. **2** was esterified under the Fischer's conditions to give diester (**3**)[5] in 72% yield, and which was then oxidized to N-oxide (**4**)[5] with mCPBA. The Reissert-Henze

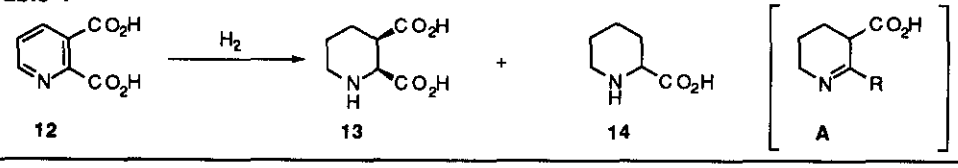
†Dedicated to the memory of the late Professor Shun-ichi Yamada.

Figure 1



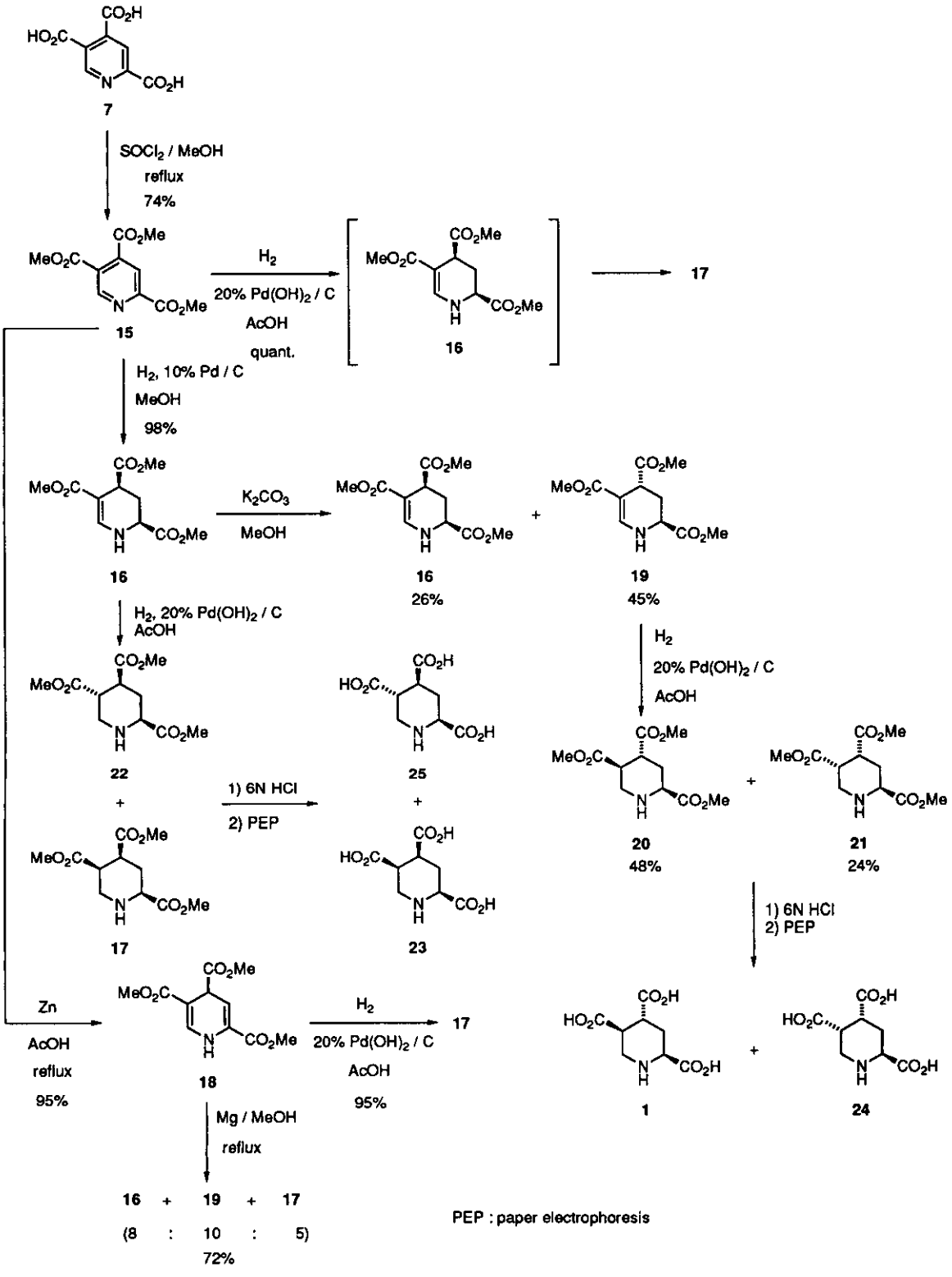
reaction was applied to **4** using TMSCN and N,N-dimethylcarbamoyl chloride[6] to give **5** and **6** in 43% and 37% yields, respectively. Cyanide (**5**) was hydrolyzed to tricarboxylic acid (**7**)[7] by treatment with 6N HCl under reflux conditions. **7** was then exposed to hydrogenation to give piperidinetricarboxylic acid (**11**) only in 7% yield along with decarboxylated compounds (**8**, **9** and **10**). Optimization of the hydrogenation conditions using quinolinic acid as a model compound was examined (Table 1). Slightly

Table 1



catalyst	molar amount of catalyst	solvent	13	14	others	yield (%)	recovery of 12 (%)
10% Pd / C	0.2	MeOH	41	54	5	20	57
10% Pd / C	0.4	MeOH	46	54	-	28	69
10% Pd / C	1.0	MeOH	28	72	-	39	13
10% Pd / C	0.2	0.01N NaOH aq.	47	48	5	75	25
10% Pd / C	0.4	0.01N NaOH aq.	42	55	3	82	7
10% Pd / C	0.6	0.01N NaOH aq.	39	60	1	80	0
10% Pd / C	0.2	H_2O	69	27	4	61	28
10% Pd / C	0.4	H_2O	56	39	5	64	27
10% Pd / C	0.6	H_2O	48	49	3	100	0
10% Pd / C	0.2	0.01N HCl aq.	70	24	6	68	32
10% Pd / C	0.4	0.01N HCl aq.	67	27	6	78	25
10% Pd / C	1.0	0.01N HCl aq.	54	44	2	100	0
20% $Pd(OH)_2$ / C	0.2	MeOH	55	44	1	64	25
20% $Pd(OH)_2$ / C	0.4	MeOH	55	42	3	88	12
20% $Pd(OH)_2$ / C	0.6	MeOH	53	48	-	60	0
20% $Pd(OH)_2$ / C	0.2	H_2O	61	32	7	100	0
20% $Pd(OH)_2$ / C	0.2	0.01N NaOH aq.	51	43	6	100	0
20% $Pd(OH)_2$ / C	0.2	0.01N HCl aq.	63	30	7	100	0

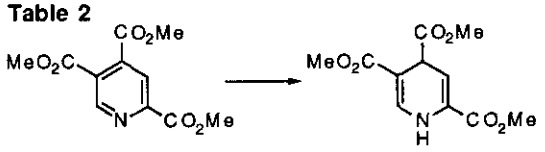
Figure 2


7
SOCl2 / MeOH
reflux
74%
15
H2
20% Pd(OH)2 / C
AcOH
quant.
16
17
H2, 10% Pd / C
MeOH
98%
K2CO3
MeOH
16
26%
19
45%
H2, 20% Pd(OH)2 / C
AcOH
22
+
17
1) 6N HCl
2) PEP
25
+
23
H2
20% Pd(OH)2 / C
AcOH
20
48%
21
24%
1) 6N HCl
2) PEP
Zn
AcOH
reflux
95%
18
H2
20% Pd(OH)2 / C
AcOH
95%
17
Mg / MeOH
reflux
16 + 19 + 17
(8 : 10 : 5)
72%
1
24
PEP : paper electrophoresis

acidic conditions without organic solvent gave better results. Although a few reports were appeared on the decarboxylation of pyridinecarboxylic acids under hydrogenation conditions,[8] mechanism of the decarboxylation has been unclear. From the fact that only the C3- or C5-carboxyl group is decarboxylated under these conditions, dihydropyridine derivative (**A**), a disguised form of β-keto acid, was proposed as the precursor.[8(a), (b)]

To prevent the decarboxylation, then, the carboxyl groups of **7** were esterified to give triester (**15**)[9] which was exposed to hydrogenation using 20% $Pd(OH)_2/C$ as a catalyst in acetic acid to give all-cis-piperidine triester (**17**) in quantitative yield. To obtain other stereoisomers, stepwise reduction was tried on the triester (**15**) (Table 2). Reduction of the pyridine nucleus using sodium borohydride or sodium cyano-

Table 2



15 **18**

reagents	e.q.	solvents	temp.	**18**
$NaBH_4$	3.0	MeOH	rt	-
$NaBH_3CN$	3.0	EtOH	reflux	trace
$NaBH_3CN$	3.0	H_2O	reflux	-
$NaBH_3CN$	3.0	MeOH	rt	-
$NaBH_3CN$	3.0	MeOH	reflux	trace
$NaBH_3CN$	3.0	MeOH	60°C	6%
Zn	3.9	AcOH	rt	95%

borohydride[10] resulted in almost no reaction, only Zn in acetic acid[10] gave the desired 1,4-dihydropyridine derivative (**18**). **18** was then reduced with Mg in refluxing MeOH to give tetrahydro derivatives (**16**) and (**19**), and further reduced piperidine derivative (**17**) in totally 72% yield in 8:10:5 ratio, respectively. On the other hand, triester (**15**) was exposed to hydrogenation using 10% Pd/C as a catalyst in MeOH to give cis-tetrahydro derivative (**16**) as a sole product in 98% yield. **16** was then isomerized to trans-isomer (**19**) on treatment with K_2CO_3 in MeOH at room temperature for 3 h to give trans-isomer (**19**) in 45% yield with recovery of the cis-isomer (**16**) (26%). The resulting trans-isomer (**19**) was then exposed to hydrogenation using 20% $Pd(OH)_2/C$ in acetic acid to give 2,4-trans-4,5-trans-isomer (**20**) and 2,4-trans-4,5-cis-isomer (**21**) in 48% and 24% yields (judged from ^{1}HNMR), respectively, as an inseparable mixture. The mixture was exposed to hydrolysis under acidic conditions and then the resulting salts were desalted and separated by repeating paper electrophoresis (PEP) to give **1** and **24** in 10 and 11% yields, respectively. Other stereoisomers were synthesized from **16** following the same sequence of reaction (1) H_2, 20% $Pd(OH)_2/C$, AcOH 2) 6N HCl, reflux 3) PEP to give **25** and **23** in 4.1% and 27% yield, respectively. Depolarizing effect for these four amino acids were performed using the new-born rat spinal motoneurons. **1**, **24**, **25** showed the biological activity, but the potency was very weak relative to L-Glu (1/50) and **23** showed almost no activity. The order of the potency is as follows, **1**>**25**>**24**>**23**.

EXPERIMENTAL

IR spectra were recorded on a JASCO FT/IR-8000 spectrophotometer. ^{1}HNMR were recorded on a Varian

UNITY plus 300 (300 MHz). Chemical shifts are expressed in ppm relative to TMS (tetramethylsilane) in $CDCl_3$ as an internal standard or relative to HOD (4.65 ppm) in D_2O. EI and HRMS spectra were obtained on a JEOL SX-102A. Elemental analyses were performed on a Perkin Elmer Series II CHNS/O Analyzer 2400. Silica gel (Merk 60) and flash silica gel (Fuji silysia BW-200) was used for column chromatography. Paper electrophoresis was performed on Whatman 3MM filterpaper (190 x 460 mm) using a model 20-TR apparatus (MS-kiki Co.Ltd.) and separations were effected at pH 3.0, pyridine-formic acid-water (2:6:992 by volume), 600V, 4-5 hours.

Dimethyl pyridine-3,4-dicarboxylate (3)

Thionyl chloride (10 mL, 52 mmol) was added to dry methanol (100 mL) dropwise at 0°C under argon and the solution was stirred for 15 min. To the solution were added pyridine-3,4-dicarboxylic acid (5.0 g, 30 mmol) and 2,2-dimethoxypropane (10 mL, 113 mmol) and the mixture was refluxed with a Dean-Stark condenser for 24 h. After removal of the solvent by evaporation in vacuo, the residue was dissolved in methanol and then neutralized with diethylamine. The resulting precipitate was removed by filtration and the filtrate was evaporated in vacuo. The residue was chromatographed on silica gel (70% ether-hexane) to afford ester (**3**) (4.2 g, 72%) as an oil. ^{1}HNMR ($CDCl_3$) δ 3.95 (3H, s), 3.96 (1H, s), 7.50 (1H, dd, J=0.8, 5.0 Hz), 8.84 (1H, d, J=5.0 Hz), 9.08 (1H, d, J=0.8 Hz); IR (cm^{-1}, neat) 1730, 1300.

Dimethyl pyridine-3,4-dicarboxylate 1-oxide (4)

To a solution of ester (**3**) (13.6 g, 69.7 mmol) in CH_2Cl_2 (60 mL) was added 3-chloroperbenzoic acid (18.1 g, 105 mmol) in CH_2Cl_2 (150 mL) at 0°C and the mixture was stirred for 15 h. To the solution was added an etherial diazomethane and then the solvent was evaporated in vacuo. The residue was chromatographed on silica gel (3% methanol-chloroform) to give N-oxide (**4**) (14.7 g, quant.) as colorless crystals, which were recrystallized from chloroform-hexane. mp 110°C; ^{1}HNMR ($CDCl_3$) δ 3.93 (3H, s), 3.96 (3H, s), 7.69 (1H, d, J=6.7 Hz), 8.24 (1H, dd, J=1.8, 6.7 Hz), 8.34 (1H, d, J=1.8 Hz); IR (cm^{-1}, KBr) 1740, 1720, 1320, 1300, 1250.

Dimethyl 2-cyano-pyridine-4,5-dicarboxylate (5)

To a solution of N-oxide (**4**) (17.2 g, 81.5 mmol) in 1,2-dimethoxyethane (170 mL) was added 95% trimethylsilyl cyanide (17.1 mL, 122 mmol) at rt. After stirring for 15 min, to the mixture was added dimethylcarbamoyl chloride (11.2 mL, 122 mmol) and the mixture was refluxed for 23 h. The mixture was quenched with saturated aqueous sodium hydrocarbonate at 0°C and extracted with ethyl acetate (100 mL x 3). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered through Celite and evaporated. The residue was chromatographed on flash silica gel (50% ether-hexane) to afford cyanides (**5**) (7.7 g, 43%) and (**6**) (6.6 g, 37%). **5** was further purified by recrystallization from chloroform-hexane. mp 76-77°C; ^{1}HNMR ($CDCl_3$) δ 3.989 (3H, s), 3.991 (3H, s), 7.93 (1H, d, J=0.9 Hz), 9.10 (1H, d, J=0.9 Hz); IR (cm^{-1}, KBr) 1750, 1730, 1300, 1280; EI-HRMS, m/z 220.0485 (M^+), calcd for $C_{10}H_8O_4N_2$ 220.0484 ; Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.55 ; H, 3.66 ; N, 12.72, Found: C , 54.47 ; H , 3.53 ; N , 12.69.

Dimethyl 2-cyanopyridine-3,4-dicarboxylate (6)

mp 77-78 °C; ^{1}HNMR ($CDCl_3$) δ 3.98 (3H, s), 4.06 (3H, s), 7.97 (1H, d, J=5.1 Hz), 8.91(1H, d, J=5.1 Hz); IR (cm^{-1}, KBr) 1740, 1290; EI-HRMS, m/z 220.0484 (M^+), calcd for $C_{10}H_8N_2O_4$ 220.0484; Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.55 ; H, 3.66 ; N, 12.72, Found: C , 54.56 ; H , 3.52 ; N , 12.71.

Trimethyl pyridine-2,4,5-tricarboxylate (15)

A solution of cyanide (**5**) (8.5 g, 39 mmol) in 6N hydrochloric acid (250 mL) was refluxed for 5 h. The solvent was evaporated in vacuo to afford crude tricarboxylic acid (**7**). The crude product was used for the next esterification without further purification.

Thionyl chloride (15 mL, 77 mmol) was added to dry methanol (150 mL) dropwise at 0°C under argon and the solution was stirred for 15 min. To the solution was added the tricarboxylic acid (**7**) and the mixture was refluxed with a Dean-Stark condenser for 24 h. After removal of the solvent by evaporation in vacuo, the residue was dissolved in methanol and then neutralized with diethylamine. The resulting precipitate was removed by filtration and the filtrate was evaporated in vacuo. The residue was chromatographed on silica gel (40% ethyl acetate-hexane) to afford ester (**15**) (7.2 g, 74%) as an oil. ^{1}HNMR ($CDCl_3$) δ 3.98 (6H, s), 4.06 (3H, s), 8.35 (1H, d, J=0.6 Hz), 9.12 (1H, d, J=0.6 Hz); IR (cm^{-1}, neat) 1730, 1440, 1300, 1260, 1130; EI-HRMS, m/z 253.0585 (M^+), calcd for $C_{11}H_{11}NO_6$ 253.0586.

(2S*,4S*)-Trimethyl 1,2,3,4-tetrahydropyridine-2,4,5-tricarboxylate (16)

To a round-bottomed flask containing10% palladium on carbon (918 mg) was added ester (**15**) (435 mg, 3.57 mmol) in methanol (8 mL) under argon. After replacement of argon to hydrogen, the mixture was stirred under hydrogen atmosphere for 1 h. The suspension was filtered and the filtrate was evaporated. The residue was chromatographed on silica gel (60% ethyl acetate-hexane and then 7% methanol-chloroform) to give tetrahydropyridine (**16**) (433 mg, 98%) as an oil. ^{1}HNMR ($CDCl_3$) δ 2.33 (1H, ddd, J=5.0, 6.6, 13.5 Hz), 2.39 (1H, ddd, J=6.6, 6.7, 13.5 Hz), 3.57 (1H, dd, J=6.6, 6.7 Hz), 3.66 (3H, s), 3.68 (3H, s), 3.75 (3H, s), 3.99 (1H, ddd, J=2.2, 5.0, 6.6 Hz), 5.07 (1H, dd, J=2.2, 6.0 Hz), 7.60 (1H, d, J=6.0 Hz); IR (cm^{-1}, neat) 1740, 1680, 1630, 1440, 1220, 1190; EI-HRMS, m/z 257.0899 (M^+), calcd for $C_{11}H_{15}NO_6$ 257.0899.

(2S*,4S*,5S*)-Piperidinetricarboxylic acid (23) and (2S*,4S*,5R*)-Piperidine-tricarboxylic acid (25)

To a suspension of 20% palladium hydroxide on carbon (166 mg, 0.312 mmol) in acetic acid (3.0 mL) was added tetrahydropyridine (**16**) (40.2 mg, 0.156 mmol) in acetic acid (0.4 mL) under argon atmosphere. After replacement of argon to hydrogen, the mixture was stirred under hydrogen atmosphere for 12 h. The suspension was filtered and the filtrate was evaporated in vacuo to afford a mixture of acetates, (2S*,4S*,5S*)-trimethyl piperidinetricarboxylate (**17**) and (2S*,4S*,5R*)-trimethyl piperidinetricarboxylate (**22**), as an inseparable mixture.

The mixture in 6N aqueous hydrochloric acid (20 mL) was refluxed for 10 h. Then the solvent was

evaporated in vacuo to give a mixture of hydrochlorides of (2S*,4S*,5S*)-piperidinetricarboxylic acid (**23**) and (2S*,4S*,5R*)-piperidinetricarboxylic acid (**25**). The mixture was desalted and purified by repeating paper electrophoresis to give **23** (9.1 mg, 27%) and **25** (1.4 mg, 4.1%). **23**; ^{1}HNMR (D_2O, pH=2.8, HOD=4.65 ppm) δ 1.97 (1H, ddd, J=11.6, 11.8, 14.5 Hz), 2.42 (1H, ddd, J=3.7, 3.9, 14.5 Hz), 2.98 (1H, ddd, J=3.9, 4.1, 11.6 Hz), 3.24 (1H, dd, J=4.4, 13.4 Hz), 3.32 (1H, ddd, J=2.9, 4.1, 4.4 Hz), 3.70 (1H, dd, J=3.7, 11.8 Hz), 3.77 (1H, dd, J=2.9, 13.4 Hz); EI-HRMS, m/z 217.0588 (M^+), calcd for $C_8H_{11}O_6N$ 217.0587. **25**; ^{1}HNMR (D_2O, pH=2.9, HOD=4.65 ppm) δ 1.69(1H, ddd, J=11.3, 12.9, 14.4 Hz), 2.53(1H, ddd, J=3.3, 3.5, 14.4 Hz), 2.82(1H, ddd, J=3.5, 10.7, 11.3 Hz), 2.87(1H, ddd, 3.2, 10.7, 11.8 Hz), 3.00(1H, dd, J=11.8, 12.5 Hz), 3.63(1H, dd, J=3.3, 12.9 Hz), 3.64(1H, 1H, J=3.2, 12.5 Hz); EI-HRMS, m/z 199.0481 (M^+-H_2O), calcd for $C_8H_9NO_5$ 199.0480.

(2S*,4R*)-Trimethyl 1,2,3,4-tetrahydropyridine-2,4,5-tricarboxylate (19)

To a solution of potassium carbonate (120 mg, 0.86 mmol) in methanol (40 mL) was added tetrahydropyridine (**16**) (4.4 g, 17.1 mmol) in methanol (10 mL). The mixture was stirred at rt for 3 h. The mixture was poured into water and extracted with ether (50 mL x 3). The combined extracts were washed with brine, dried over sodium sulfate, filtered through Celite and evaporated. The residue was chromatographed on silica gel (60% ether-hexane and then 40% ethyl acetate-hexane) to give tetrahydropyridine (**19**) (2.0 g, 45%) and the starting material (**16**) (1.14 g, 26%) was recovered. Tetrahydropyridine (**19**) was recrystallized from chloroform-hexane. mp 77-78 °C; ^{1}HNMR ($CDCl_3$) δ 1.73(1H, ddd, J=5.8, 11.9, 13.4 Hz), 2.52(1H, dddd, J=1.4, 2.2, 3.7, 13.4 Hz), 3.67(1H, dd, J=2.2, 5.8 Hz), 3.68(3H, s), 3.71(3H, s), 3.81(3H, s), 4.11(1H, dd, J=3.7, 11.9 Hz), 5.24(1H, dd, J=1.4, 6.3 Hz), 7.59(1H, d, J=6.3 Hz); EI-HRMS, m/z 257.0900 (M^+), calcd for $C_{11}H_{15}NO_6$ 257.0899; Anal. Calcd for $C_{11}H_{15}NO_6$: C, 51.36 ; H, 5.88 ; N, 5.44, Found: C , 51.37 ; H , 5.84 ; N , 5.43.

(2S*,4R*,5S*)-Piperidinetricarboxylic acid (1) and (2S*,4R*,5R*)-Piperidine-tricarboxylic acid (24)

To a suspension of 20% palladium hydroxide on carbon (463 mg, 0.87 mmol) in acetic acid (10 mL) was added tetrahydropyridine (**19**) (745 mg, 0.29 mmol) in acetic acid (0.8 mL) under argon atmosphere. The mixture was stirred under hydrogen atmosphere for 12 h. The suspension was filtered and the filtrate was evaporated in vacuo. To the residue was added aqueous sodium hydrogen carbonate to be basic and the mixture was extracted with ethyl acetate (2.0 mL x 3). The combined extracts were dried over anhydrous sodium sulfate, filtered through Celite and evaporated in vacuo. The residue was chromatographed on flash silica gel (10% acetone-chloroform) to afford a mixture of (2S*,4R*,5S*)-trimethyl piperidinetricarboxylate (**20**) and (2S*,4R*,5R*)-trimethyl piperidinetricarboxylate (**21**).

The mixture of **20** and **21** in 6N aqueous hydrochloric acid (10 mL) was refluxed for 10 h. The solvent was evaporated in vacuo to give a mixture of hydrochlorides, (2S*,4R*,5S*)-piperidinetricarboxylic acid (**1**) and (2S*,4R*,5R*)-piperidinetricarboxylic acid (**24**). The mixture was desalted and purified using repeating paper electrophoresis to give **1** (6.5 mg, 10%) and **24** (6.7 mg, 11%). **1**; ^{1}HNMR (D_2O, pH=2.9, HOD=4.65 ppm) δ 2.15 (1H, ddd, J=4.7, 8.0, 14.9 Hz), 2.24 (1H, ddd, J=4.8, 6.9, 14.9 Hz),

2.86 (1H, ddd, J=4.8, 7.7, 8.0 Hz), 3.00 (1H, ddd, J=4.7, 7.7, 7.8 Hz), 3.33 (1H, dd, J=4.7, 13.2 Hz), 3.40 (1H, dd, J=7.8, 13.2 Hz), 3.89 (1H, dd, J=4.7, 6.9 Hz); EI-HRMS, m/z 217.0585 (M^+), calcd for $C_8H_{11}O_6N$ 217.0587. **24**; ^{1}HNMR (D_2O, pH=2.5, HOD=4.65 ppm) δ 1.98 (1H, ddd, J=4.7, 12.0, 15.1 Hz), 2.53 (1H, ddd, J=3.4, 3.5, 15.1 Hz), 2.95 (1H, ddd, J=4.7, 4.8, 11.6 Hz), 3.32 (1H, dt, J=3.5, 4.7 Hz), 3.35 (1H, dd, J=11.6, 12.9 Hz), 3.55 (1H, dd, J=4.8, 12.9 Hz), 3.59 (1H, dd, J=3.4, 12.0 Hz); EI-HRMS, m/z 199.0479 (M^+-H_2O), calcd for $C_8H_9NO_5$ 199.0480.

ACKNOWLEDGMENT

We are grateful to Drs. H.Shinozaki and M. Ishida (Tokyo Metropolitan Institute for Medical Science) for the biological test.

REFERENCES

1. K. Yamano and H. Shirahama, *Z. Naturforsch.*, 1994, **49C**, 707.
2. (a) K. Yamano and H. Shirahama, *Z. Naturforsch.*, 1994, **49C**, 157. (b) K. Yamano and H. Shirahama, *Tetrahedron*, 1993, **49**, 2427. (c) K. Yamano, K. Konno, and H. Shirahama, *Heterocycles*, 1993, **35**, 125. (d) K. Yamano and H. Shirahama, *Chem. Lett.*, 1993, 21. (e) K. Yamano, K. Hashimoto, and H. Shirahama, *Heterocycles*, 1992, **34**, 445. (f) K. Yamano and H. Shirahama, *Tetrahedron*, 1992, **48**, 1457. (g) K. Yamano, K. Konno, and H. Shirahama, *Chem. Lett.*, 1991, 1541. (h) F. Hirayama, K. Konno, H. Shirahama, and T. Matsumoto, *Phytochemistry*, 1989, **28**, 1133. (i) K. Konno, K. Hashimoto, Y. Ohfune, H. Shirahama, and T. Matsumoto, *J. Am. Chem. Soc.*, 1988, **110**, 4807. (j) K. Konno, H. Shirahama, and T. Matsumoto, *Phytochemistry*, 1984, **23**, 1003. (k) K. Konno, H. Shirahama, and T. Matsumoto, *Tetrahedron Lett.*, 1983, **24**, 939.
3. S. Fushiya, M. Matsuda, S. Yamada, and S. Nozoe, *Tetrahedron* , 1996, **52**, 877.
4. M. Ishida and H. Shinozaki, *Br. J. Pharmacol.*, 1991, **104**, 873.
5. A. Nuvole and G. Paglietti, *J. Chem. Soc., Perkin Trans. I*, 1989, 1007.
6. (a) W. K. Fife, *J. Org. Chem.*, 1983, **48**, 1375. (b) W. K. Fife and B. D. Boyer, *Heterocycles*, 1984, **22**, 1121.
7. (a) J. R. Hadfield, J. S. E. Holker, and D. N. Stanway, *J. Chem. Soc., Section C*, 1967, 751. (b) R. M. Acheson and G. A. Taylor, *J. Chem. Soc.*, 1959, 4140.
8. (a) E. Wenkert, *Acc. Chem. Res.*, 1968, **1**, 78. (b) F. Sorm, *Coll. Czech. Chem. Commun.*, 1948, **13**, 57. (c) M. Freifelder, *J. Org. Chem.*, 1963, **28**, 1135. (d) M. Freifelder, R. M. Robinson, and G. R. Stone, *J. Org. Chem.*, 1962, **27**, 284. (e) M. Freifelder and G. R. Stone, *J. Org. Chem.*, 1961, **26**, 3805.
9. M. Luigi, F. Ernesto, C. Guido, De S. Salvatore, and N. A. Rodolfo, *Gazz. Chim. Ital.*, 1969, **99**, 431.
10. U. Eisner and J. Kuthan, *Chem. Rev.*, 1972, **72**, 1.

Received, 12th May, 1997