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Synthesis of Captopril starting from an Optically Active β-Hydroxy Acid

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A synthesis of *N*-(3-mercapto-2-D-methylpropanoyl)-L-proline (**1**, Captopril) is described in which the key intermediate, optically active 3-chloro-2-D-methylpropanoyl chloride (**3b**), was prepared by treating microbiologically derived optically active 3-hydroxy-2-D-methylpropanoic acid (**2**) with thionyl chloride. The compound **3b** was coupled with L-proline to afford the chloride (**4**) which was directly converted into Captopril by reaction with hydrosulfide or trithiocarbonate ion in hot water with retention of the stereochemistry. The preparation of another useful intermediate, 3-acetylthio-2-D-methylpropanoic acid (**9a**), is also described.

Keywords——Captopril; antihypertensive agents; 3-hydroxy-2-D-methylpropanoic acid; 3-chloro-2-D-methylpropanoyl chloride; hydrosulfide ion; trithiocarbonate ion; thiosulfate ion; 3-mercapto-2-D-methylpropanoic acid; 3-acetylthio-2-D-methylpropanoic acid

We have reported a stereoselective conversion of isobutyric acid or methacrylic acid to an optically active 3-hydroxy-2-methylpropanoic acid by microorganisms,[1] and we suggested the versatility of the hydroxy acid possessing a chiral, secondary methyl center for the synthesis of useful natural or unnatural compounds. Cohen *et al.*[2] have developed the utilization of microbiologically derived 3-hydroxy-2-L-methylpropanoic acid as a starting compound for the synthesis of key optically active side chain synthons in their synthetic studies on (2*R*, 4′*R*, 8′*R*)-α-tocopherol.

Recently an orally active antihypertensive agent having a unique inhibitory action on angiotensin-converting enzyme, *i.e.*, *N*-(3-mercapto-2-D-methylpropanoyl)-L-proline (**1**) (Captopril), was reported.[3] Ondetti *et al.*[4] showed that the potency of *N*-(3-mercapto-2-methylpropanoyl)-L-propline as an inhibitor of the enzyme depends critically on the configuration of the mercaptoalkanoyl side chain, and the compound with D-configuration is about 100 times more active than the corresponding L-enantiomer. Captopril **1** has thus far been prepared by coupling 3-acetylthio or 3-benzoylthio-2-D-methylpropanoic acid or the acyl chloride of either compound with L-proline followed by deacylation of the product. The optically active 3-acylthio-2-methylpropanoic acid has hitherto been obtained only by chemical optical resolution of a racemic mixture using an optically active organic amine such as 1,2-diphenylethylamine or 2-amino-1-butanol,[5] and there is no report on the synthesis of optically active 3-acylthio-2-methylpropanoic acid without chemical optical resolution. This prompted us to synthesize optically active *N*-(3-mercapto-2-methylpropanoyl) amino acids such as Captopril **1** using optically active 3-hydroxy-2-D-methylpropanoic acid (**2**) as a side chain synthon, since compound **2** possesses the same absolute configuration and four-carbon unit as in the mercaptoalkanoyl side chain of **1**.

This is the first report of a facile synthesis of **1** without optical resolution or protection of the thiol group, starting from a microbiologically derived, optically active compound **2** (Chart 1). This paper also presents a facile preparation of optically active 3-mercapto-2-D-methylpropanoic acid (**8**) from which optically active 3-acylthio-2-methylpropanoic acid (**9**) can be derived by a conventional acylation; compound **9** in turn can be readily led to **1** (Chart 2).

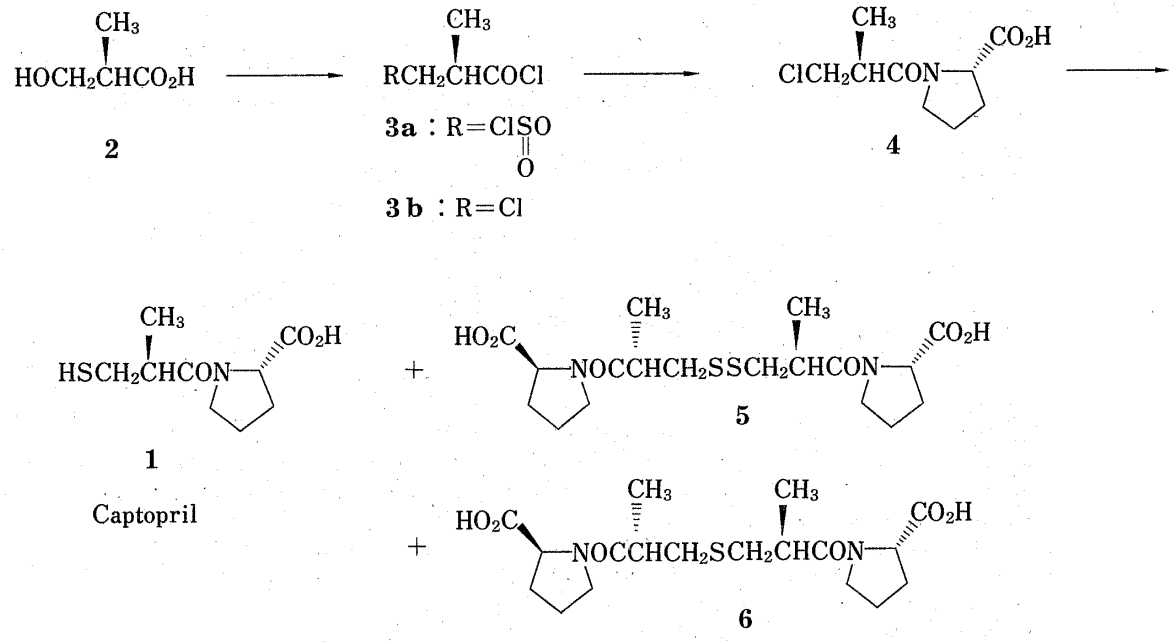

Chart 1

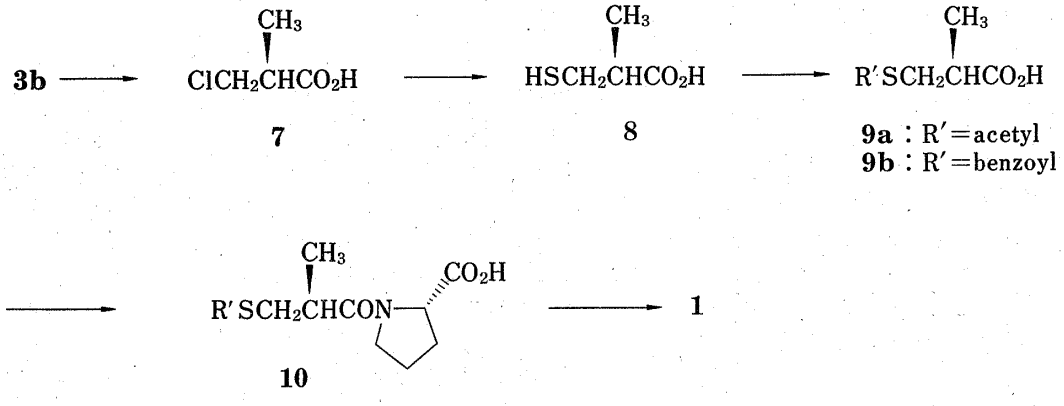

Chart 2

Our strategy to synthesize **1** was to 1) convert the hydroxy acid **2** into a chloroacid chloride (**3b**), 2) couple **3b** with L-proline to afford a chloride (**4**), and 3) substitute the chlorine atom of **4** by a thiol group directly at the final step in the synthetic process, with optical integrity of all the compounds during chemical manipulations.

Chlorination of the optically Active Hydroxy Acid 2

A useful key intermediate, 3-chloro-2-D-methylpropanoyl chloride (**3b**) was prepared by reacting **2** with thionyl chloride with or without a solvent in the presence of an organic base as a catalyst (Table I). The action of thionyl chloride on lactic acid or 2-hydroxy-2-methylpropanoic acid is reported to produce anhydrosulfite instead of the corresponding chloroalkanoyl chloride.[6] In another report,[7] an optically active α-chlorophenylacetic acid was produced from mandelic acid by a two-step process in which the carboxyl group is first protected by esterification with ethanol and then the hydroxyl group is chlorinated with thionyl chloride. The desired free acid is finally obtained by hydrolysis of the ester group. In contrast with these known chlorinations of hydroxy acid, it is noteworthy that optically active **2** is chlorinated on both the hydroxyl and the carboxyl group in one step with retention of the configuration. The chlorination proceeded well in the presence of a catalytic amount of

Table I. Chlorination of **2** with Thionyl Chloride

Run No.	Reactants: Add	Reactants: to	$SOCl_2/2$[a]	Catalyst (mol%)	Solvents	Product[b] (%)
1	$SOCl_2$	**2**	2.4	None	None	14
2	$SOCl_2$	**2**	3.3	DMF(7)	None	54
3	$SOCl_2$	**2**	2.4	DMF(11)	None	60
4	$SOCl_2$	**2**	3.0	Pyridine(5)	None	66
5	$SOCl_2$	**2**	3.0	NEt_3(5)	None	59
6	$SOCl_2$	**2**	3.0	DMA[c](5)	None	35
7	$SOCl_2$	**2**	3.0	Imidazole (0.5)	None	80
8	$SOCl_2$	**2**	3.0	Imidazole (0.5)	Et_2O	84
9	$SOCl_2$	**2**	3.0	Imidazole (0.5)	CH_2Cl_2	86
10	$SOCl_2$	**2**	2.5	Imidazole (0.5)	CH_2Cl_2	88[d]
11	**2**	$SOCl_2$	2.5	Imidazole (0.5)	CH_2Cl_2	84[d]
12	$SOCl_2$	**2**	2.5	Imidazole (0.5)	CH_2Cl_2	83[d]
13	$SOCl_2$	**2**	2.5	Pyridine (2.5)	CH_2Cl_2	80[d]

a) Molar ratios.
b) Isolated yield after distillation except where otherwise noted.
c) *N,N*-Dimethylaniline.
d) Determined by gas chromatography using a Hitachi gas chromatograph, Model 163, equipped with a Hitachi Chromato-Processor, Model 834-30. A glass column (1 m × 3 mmϕ) packed with Shimadzu FAL-M 10%/Shimalite TPA (30—60 mesh) was used under the following conditions: injection temp, 150°C; column temp, 100°C; N_2 carrier gas, 0.4 kg/cm^2. A sample was analyzed as a 1% ethanol solution and a single peak of ethyl 3-chloro-2-D-methylpropionate was seen with a retention time of 5.5—6.0 min.

organic base, and imidazole was found to be most effective in terms of providing a high yield of **3b**.

The rate-determining step of the chlorination was suggested to be decomposition of a nonisolable, unstable intermediate, 2-D-chloroformylpropyl chlorosulfite (**3a**), whose formation and decomposition were confirmed by observing the ^1H nuclear magnetic resonance (^1H NMR) spectrum of the reaction mixture. Compound **3a** readily decomposed, liberating sulfur dioxide on being warmed to provide **3b**, while the chemical shift of 3-CH_2 in the ^1H NMR spectrum drifted from δ 4.54 ppm (**3a**) to δ 3.73 ppm (**3b**) in deuterated chloroform. The time course of the thermal decomposition of **3a** is shown in Table II. Changing the order of addition of the reactants produced no significant change in product composition or yield.

Table II. Thermal Decomposition of the Intermediate Chlorosulfite **3a**

Reaction conditions	**3a**	:	**3b**[a]
40°C 1 h	100	:	0
60°C 4 h	50	:	50
70°C 3 h	5	:	95
85°C 2 h	0	:	100

a) The relative ratio was determined by integration of the 3-CH_2 signals of **3a** and **3b** on the ^1H NMR spectra.

Compound **2** could be chlorinated in the absence of a solvent, but the use of an inert organic solvent such as diethyl ether, methylene chloride or toluene made the reaction controllable. The temperature control was important to avoid intermolecular esterification or thermal decomposition of **3b** with loss of hydrogen chloride to afford methacrylic acid, which may recombine with hydrogen chloride, giving a racemic mixture of 3-chloro-2-methylpropanoyl chloride. Therefore **2** and thionyl chloride were mixed at less than 25 °C. Compound **2**

was completely converted to **3a** by stirring the reaction mixture until the evolution of gaseous hydrogen chloride and sulfur dioxide subsided. The complete conversion of **3a** to **3b** was achieved by heating the reaction mixture to more than 60 °C after completion of mixing of the reactants, as shown in Table II. Pure **3b** was obtained by distillation under reduced pressure as a colorless liquid, $[\alpha]_D^{25}$ −5.53° (c=2.0, CH_2Cl_2).

Coupling of **3b** with L-proline was carried out by means of the Schotten-Baumann reaction using two equivalents of sodium hydroxide to afford **4**, $[\alpha]_D^{25}$ −103.6° (c=2.0, EtOH), in almost quantitative yield.

Direct Substitution of the Chlorine Atom by a Thiol Group

The substitution of a halogen atom by a thiol group using hydrosulfide ion as a strong nucleophile is a general method to prepare a mercaptan.[8] However, there are no previous examples of the application of such reagents to an optically active compound.[9] The reagent, sodium or ammonium hydrosulfide, is strongly alkaline in solution, and it has not been applied to optically active compounds because racemization is expected to take place readily under such conditions.

Nevertheless if such direct substitution could be conducted with retention of the stereochemistry of the optically active starting compound, the preparation of **1** would be greatly simplified, since there is no need for protection of the thiol group and the subsequent deprotection thereof, which are required in existing methods to prepare **1**.

The direct substitution of the chlorine atom of **4** by the thiol group was achieved with retention of the stereochemistry in *N*,*N*-dimethylformamide (DMF), dimethyl sxlfoxide (DMSO) and, remarkably, in water using hydrosulfide or trithiocarbonate ion[10] as a nucleophilic reagent. There were two problems in this reaction; one was the the sensitivity of the desired product **1** to oxidative coupling to afford disulfide (**5**), and the second was the inevitable formation of a symmetric monosulfide (**6**) as a by-product. In this respect DMF and DMSO were not good solvents. The reaction in water using ammonium hydrosulfide was

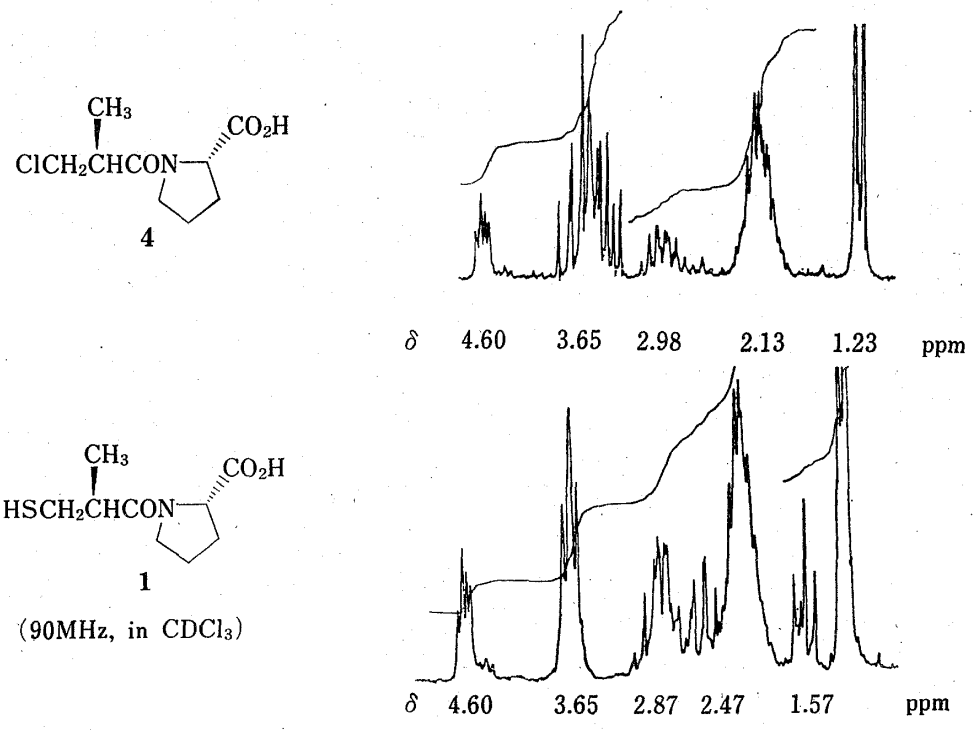

Fig. 1. ^1H NMR Spectra of the Chloride (**4**) and Captopil (**1**)

somewhat preferable, minimizing the formation of both by-products **5** and **6**. The best reagent was the trithiocarbonate ion, which afforded only a trace of the monosulfide (**6**). Production of the disulfide (**5**) was also diminished as well as when ammonium hydrosulfide was used as the reagent. It was a remarkable fact that compound **4** underwent no racemization in such a strongly alkaline solution as sodium or ammonium hydrosulfide or sodium trithiocarbonate in water. The use of high temperature (80—100 °C) was effective to accelerate the reaction and the time course of the conversion was followed by observing the ^{1}H NMR spectrum and by high performance liquid chromatography (HPLC) at intervals. The consumption of **4** was confirmed by the disappearance of sharp multiplet signals of 3-CH_2 in the side chain of **4** at δ 3.3 to 3.9 ppm in the ^{1}H NMR spectrum (Fig. 1). Three products were detected on a thin layer chromatogram (*Rf* 0.31, 0.91 and 0.14) developed twice with benzene–acetic acid (3: 1, by vol.). They were all isolated by silica gel column chromatography eluting with a linear gradient of 0—80% methanol in ethyl acetate in the same order of mobility as on the thin layer chromatogram. Compound **1**, $[\alpha]_D^{25}$ −129.8° (*c*=2.0, EtOH), was eluted first, followed by the disulfide **5**, $[\alpha]_D^{25}$ −187° (*c*=1.0, EtOH), and the monosulfide **6**, $[\alpha]_D^{25}$ −118.3° (*c*=2.0, EtOH), in that order.

A more lengthy approach to the compound **1** was also somewhat somplified by using the optically active key compound **3b** without a troublesome optical resolution. Compound **7**, $[\alpha]_D^{25}$ −13.2° (*c*=2.0, MeOH), was easily prepared by hydrolysis of **3b** with water. Subsequent treatment of **7** with the hydrosulfide, thiosulfate or trithiocarbonate ion provided optically active 3-mercapto-2-D-methylpropanoic acid (**8**), $[\alpha]_D^{25}$ −27.4° (*c*=2.0, MeOH). Compound **8** was readily acylated by a conventional method, giving the thioacetate (**9a**) or thiobenzoate (**9b**). The desired product **1** was then obtained by reacting **9a** or **9b** with L-proline followed by deacylation in ammoniacal methanol.[5] It is a noteworthy feature of the process that the compound **8** can be prepared in a one-pot reaction from the starting compound **2** without isolation of the intermediates (**3b** and **7**).

To the best of our knowledge this is the first description of the synthesis of optically active **7** and **8**. A racemic mixture of **7** was prepared by the addition of hydrogen chloride to methacrylic acid, but optically active enantiomer was not isolated.[11] A small amount of 3-mercapto-2-methylpropanoic acid is found in nature as a flavor component in asparagus but the stereochemistry is not known. A racemic mixture of **8** has been prepared by adding hydrogen sulfide to methyl methacrylate followed by hydrolysis of the ester.[12]

Noteworthy features of the present methodology include the following: (1) optical activity of the starting compound is retained throughout the process; (2) no protection on the thiol group is necessary and the process is very straightforward.

Experimental

Melting points were determined in open capillary tubes with a Yamato melting point apparatus, Model 21, and are uncorrected. Boiling points are also uncorrected. Optical rotations were measured on a Union Giken PM-101 automatic digital polarimeter. A Varian EM-390 spectrometer was used to obtain the ^{1}H NMR spectra. Chemical shifts are reported relative to tetramethylsilane as an internal standard. Infrared (IR) spectra were recorded on a Hitachi infrared spectrophotometer, Model 260-30. Refractive index was measured with an Abbe apparatus. The pK_a values of compounds **1** and **4** were determined from titration curves observed on a Kyoto Denshi Kogyo AT 107 automatic titrator according to the method of Park and Davis.[13] The progress of the reaction was monitored by thin layer chromatography (TLC) and HPLC. TLC was performed on Merck silica gel 60 F_{254} plates which were developed with one of the following mobile phase solvent systems: A, ethyl acetate–ethanol–water (5: 1: 1, by vol.); B, benzene–acetic acid (3: 1, by vol.); C, toluene–*n*-heptane–acetic acid (9: 9: 2, by vol.). Spots were detected with UV light (254 nm), iodine vapor, or by spraying a 0.1% ethanolic solution of sodium 2,6-dichlorophenolindophenol or TTC blue reagent.[14] HPLC was done on a Jasco TRI ROTAR-II instrument using a pre-packed column of Jasco Finepak SIL C_{18} (4.6 mmϕ × 250 mm). Detection of each component was carried out with a UV detector (210 nm). As a mobile phase, 0.02 M KH_2PO_4–MeOH (55: 45, v/v) was used.

3-Chloro-2-D-methylpropanoyl Chloride (**3b**)——Method A. Addition of Thionyl Chloride to **2**: Thionyl

chloride (30 g, 0.25 mol) was added dropwise to a solution of **2** (10.4 g, 0.1 mol) in methylene chloride (10 ml) containing imidazole (0.5 g, 7.35 mol) as a catalyst with stirring at 0—15°C over a period of 30 minutes. The reaction mixture was then warmed to 80°C. Stirring was continued until gaseous evolution of hydrogen chloride and sulfur dioxide subsided. After removal of the solvent and excess thionyl chloride on a rotary evaporator at 40°C, 3-chloro-2-D-methylpropanoyl chloride **3b** was obtained as a colorless liquid by distillation under reduced pressure (11.7 g, 83%). bp 54—55°C/22 mmHg. $[\alpha]_D^{25}$ −5.60° (c=2.0, CH_2Cl_2). n_D^{20} 1.4534. ^{1}H NMR ($CDCl_3$, 90 MHz) δ ppm: 1.42 (3H, d, J=7.2 Hz, CH_3), 3.26 (1H, m, CH), 3.73 (2H, m, CH_2).

^{1}H NMR of **3a** δ ppm: 1.45 (3H, d, J=7.2 Hz, CH_3), 3.37 (1H, m, CH), 4.54 (2H, m, CH_2).

Method B. Addition of **2** to Thionyl Chloride: Compound **2** (10 g, 0.1 mol) was added dropwise to a mixture of thionyl chloride (30 g, 0.25 mol) and imidazole (0.5 g, 7.35 mmol) at 0—20°C with stirring during 15 min. The resulting mixture was then warmed to 80°C and stirring was continued at this temperature for 3 h. Pure **3b** was obtained by distillation directly from the reaction mixture under reduced pressure (Yield, 12.1 g, 86%). bp 54—55°C/22 mmHg.

***N*-(3-Chloro-2-D-methylpropanoyl)-L-proline (4)**——Compound **3b** (5.0 g, 35.5 mmol) was added in one portion to a cold solution of L-proline (4.1 g, 35.6 mmol) in 2 N NaOH (36 ml) at 0°C, and the resulting mixture was stirred at the same temperature for 1 h then allowed to warm to ambient temperature in the course of 1 h. Only one product was detected on TLC (system A, Rf=0.56). The reaction mixture was then adjusted to pH 1 with 6 N HCl and the desired product **4** was extracted with ethyl acetate (30 ml×2). The organic extract was washed with saturated aqueous NaCl, and dried over anhydrous $MgSO_4$. The solvent was removed on a rotary evaporator to yield a crude syrup (7.5 g). Analytically pure crystalline **4** was obtained by crystallization from ethyl acetate and n-hexane (*ca.* 1: 1, by vol.). Yield 7.0 g (90%). mp 129—130°C. $[\alpha]_D^{25}$ −103.6° (c=2.0, EtOH). IR(KBr) cm^{-1}: 1730, 1600, 1470, 1445, 1180. ^{1}H NMR ($CDCl_3$, 90 MHz) δ ppm: 1.23 (3H, d, CH_3), 2.17 (4H, m, 3,4-CH_2CH_2 in proline), 3.00 (1H, m, CH in the side chain), 3.67 (4H, m, $ClCH_2$ and 2-CH_2 in the proline), 4.60 (1H, m, 5-CH in the proline), 11.4 (1H, s, COOH). pK_a: 4.2 (COOH). *Anal.* Calcd for $C_9H_{14}ClNO_3$: C, 49.21; H, 6.42; N, 6.38; O, 21.85; Found: C, 49.52; H, 6.54; N, 6.43; O, 21.34.

***N*-(3-Mercapto-2-D-methylpropanoyl)-L-proline (1)**——Method A: A mixture of **4** (2.19 g, 10 mmol) and sodium hydrosulfide dihydrate (2.3 g, 3 eq) in DMF (20 ml) was stirred for 4 h at 50°C under nitrogen, then cooled and diluted with water (80 ml). The mixture was adjusted to pH 1 with 6 N HCl and the product **1** was extracted with ethyl acetate (100 ml+50 ml). The extract was washed with water, and dried over anhydrous $MgSO_4$, then the solvent was removed on a rotary evaporator to provide 2.1 g of crude syrup. TLC (system B, developed twice) showed three components with Rf values of 0.31 (**1**), 0.19 (**5**) and 0.14 (**6**). They were all isolated by silica gel column chromatography (Wakogel C200, supplied by Wako Pure Chemical Ind., Co., Ltd., 30 g, L/D=900 mm/10 mmϕ). Elution with a linear gradient of 0—80% methanol in ethyl acetate gave **1** (1.19 g, 55%), **5** (518 mg, 12%), and **6** (200 mg, 5%), in the order. Their physical constants are as follows:

Compound **1**: mp 105—106°C. $[\alpha]_D^{25}$ −129.8° (c=2.0, EtOH); −136.1° (c=2.0, MeOH). IR(KBr) cm^{-1}: 2560, 1740, 1585, 1470. ^{1}H NMR ($CDCl_3$, 90 MHz) δ ppm: 1.22 (3H, d, CH_3), 1.57 (1H, t, SH), 2.17 (4H, m, 3,4-CH_2CH_2 in proline), 2.47 (1H, m, CH in the side chain), 2.87 (2H, m, $HSCH_2$), 3.65 (2H, t, 2-CH_2 in the proline), 4.60 (1H, m, 4-CH in the proline), 11.3 (1H, s, COOH). pK_a: 4.1 (COOH), 10.5 (SH). *Anal.* Calcd for $C_9H_{15}NO_3S$: C, 49.75; H, 6.96; N, 6.45; Found: C, 49.66; H, 6.92; N, 6.40.

Compound **5**: mp 217—219°C. $[\alpha]_D^{25}$ −187° (c=1.0, EtOH). IR(KBr) cm^{-1}: 1740, 1720, 1600, 1475, 1445, 1195. ^{1}H NMR (CD_3OD, 90 MHz) δ ppm: 1.20 (6H, d, CH_3), 2.07 (8H, m, 3,4- and 3′,4′-CH_2CH_2 in the proline), 2.6—3.2 (6H, m, SCH_2CH), 3.70 (4H, t, 2- and 2′-CH_2 in the proline), 4.42 (2H, m, 4- and 4′-CH in the proline).

Compound **6**: mp 143.5—145.0°C. $[\alpha]_D^{25}$ −118.3° (c=2.0, EtOH). IR(KBr) cm^{-1}: 1730, 1620, 1450. ^{1}H NMR ($CDCl_3$, 90 MHz) δ ppm: 1.22 (6H, d, CH_3), 2.09 (8H, m, 3,4- and 3′,4′-CH_2CH_2 in the proline), 2.50 (2H, m, CH in the side chain), 2.87 (4H, m, SCH_2), 3.63 (4H, m, 2- and 2′-CH_2 in the proline), 4.53 (2H, m, 4- and 4′-CH in the proline), 9.73 (2H, s, COOH).

Method B: A solution of the chloride **4** (0.5 g, 2.28 mmol) and sodium hydrosulfide dihydrate (0.84 g, 9.13 mmol) in water (12 ml) was warmed with stirring at 80°C for 4 h under a nitrogen atmosphere; the starting halide was no longer detectable on TLC (system A, Rf of **4**=0.56 and Rf of **1**=0.58). The reaction mixture was diluted with cold water (10 ml), adjusted to pH 1 with sulfuric acid, and treated with zinc powder (0.5 g) as a reducing agent by stirring at room temperature for 4 h under nitrogen. The by-product disulfide **5** (*ca.* 20 mol % by HPLC) was thus reduced to **1**. Insoluble materials were filtered off from the reaction mixture and washed with fresh water. The combined filtrate and washing were extracted with ethyl acetate (50 ml×3). The organic extract was washed with a saturated aqueous solution of NaCl and dried over anhydrous $MgSO_4$. Removal of the solvent from the extract left a colorless syrup (0.47 g), which was crystallized from ethyl acetate–n-hexane (2 ml–2 ml) to give white crystals of **1** (0.35 g, 71%). $[\alpha]_D^{25}$ −128.5° (c=2.0, EtOH). mp 84—85°C.

Method C: The chloride **4** (2.2 g, 10 mmol) was added at room temperature to a solution of ammonium hydrosulfide prepared by dissolving hydrogen sulfide (1.02 g, 30 mmol) in a 0.3 M aqueous ammonium hydroxide solution (100 ml). The resulting mixture was warmed with stirring at 90°C for 16 h under nitrogen. The conversion of the chloride into the thiol compound **1** was followed by HPLC at intervals. The reaction

mixture was then concentrated to about 20 ml, and adjusted to pH 1 with 6 N HCl. The products were extracted with ethyl acetate (50 ml × 3). The organic extract was treated in the same manner as in the preceding experiment and the resulting colorless syrup (1.1 g) was chromatographed on a long column (L/D = 80) of silica gel (Wakogel C200, 30 g) eluting with a linear gradient of 0—80% methanol in ethyl acetate. Fractions containing the desired product **1** were pooled and concentrated to dryness under reduced pressure. Crystallization of the resulting residue from ethyl acetate–cyclohexane (4 ml–2 ml) afforded pure **1** (0.84 g, 85%). From other fractions, the disulfide **5** (38 mg, 3.9%) and the monosulfide **6** (59 mg, 3.9%) were isolated.

Method D: An aqueous solution of sodium trithiocarbonate (32 ml, prepared as described below with 100 ml of water at 45°C for 4 h) was added to a solution of the chloride (3.8 g, 17 mmol) and sodium carbonate (1.1 g, 34 mmol) in water (10 ml), and the resulting mixture was stirred at 85°C for 5 h. The reaction mixture was acidified to pH 1 with conc. HCl and heated at 45°C until gaseous evolution of H_2S and CS_2 subsided. The crude **1** was extracted with ethyl acetate and a syrup (4.4 g) was obtained. HPLC showed the presence of three products as follows: compound **1** (74%), disulfide (1.5%) and the monosulfide (0.5%).

Sodium Trithiocarbonate——An aqueous solution of this reagent was prepared by the following modification of the method of Martin and Greco:[10] Carbon disulfide (11.6 g, 0.152 mol) was added all at once to an aqueous solution of disodium sulfide ($Na_2S \cdot 9H_2O$, 33.0 g, 0.137 mol in 100—150 ml of water), and the reaction mixture was warmed at 40—45°C for 4—6 h in a vessel fitted with a reflux condenser. The excess CS_2 was recovered by distillation after the reaction and the resulting aqueous solution was used portion-wise for substitution of a chlorine atom by a thiol group. The solution could be kept at room temperature for a week.

3-Chloro-2-D-methylpropanoic Acid (7)——Compound **3b** (5.35 g, 37.9 mmol) was added in one portion to water (80 ml) and the mixture was stirred at ambient temperature for 4 h; the temperature of the reaction mixture rose to about 40°C in the early stage and then gradually fell to room temperature. A clear homogenous solution was formed, and TLC showed only one product (system A, $Rf = 0.66$). The reaction mixture was then adjusted to pH 1 with 6 N HCl and the product was extracted with ethyl acetate (100 ml + 50 ml). The extract was washed successively with aqueous NaCl and water, then dried over anhydrous $MgSO_4$. Removal of the organic solvent left **7** as a syrup (4.46 g, 96%). An analytical sample was obtained by distillation under reduced pressure. bp 91—92°C/9 mmHg. $[\alpha]_D^{25}$ −13.9° ($c = 2.0$, MeOH). n_D^{20} 1.4450. IR(neat) cm^{-1}: 1710, 1460, 1220. ^1H NMR ($CDCl_3$, 90 MHz) δ ppm: 1.33 (3H, d, $J = 6.9$ MHz, CH_3), 2.90 (1H, seq., CH), 3.67 (2H, oct., CH_2), 10.8 (1H, s, COOH).

3-Mercapto-2-D-methylpropanoic Acid (8)——A mixture of **7** (15 g, 0.122 mol) and sodium hydrosulfide dihydrate (4 g, 0.60 mol) in water (150 ml) was heated at 80°C for 1 h under nitrogen. After cooling to room temperature, the reaction mixture was adjusted to pH 2 with phosphoric acid and the product was extracted with ethyl acetate (total 300 ml, twice). The extract was washed with saturated aqueous NaCl and dried over anhydrous Na_2SO_4. Removal of the solvent from the extract left a pale yellow oil (14 g). The oil was then dissolved in 1 N H_2SO_4 (100 ml) and treated with zinc powder (5 g) under nitrogen by stirring at room temperature for 5 h, whereby the by-product disulfide (*ca.* 10 mol % as determined by HPLC) was reduced to the desired product **8**. Insoluble materials were filtered off and washed with fresh ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (100 ml × 3). The extract was washed with saturated aqueous NaCl and dried over anhydrous $MgSO_4$. Removal of the solvent afforded **8** as a colorless syrup (11.3 g, 77%). An analytical sample was obtained by distillation under reduced pressure. bp 62—63°C/1 mmHg. $[\alpha]_D^{25}$ −27.5° ($c = 2.0$, MeOH). n_D^{20} 1.4837. IR(neat) cm^{-1}: 2580, 1710, 1465, 1425, 1254. ^1H NMR ($CDCl_3$, 90 MHz) δ ppm: 1.28 (3H, d, CH_3), 1.55 (1H, t, SH), 2.73 (3H, m, CH and CH_2), 11.1 (1H, s, COOH). This compound migrated on TLC (system A) with an *Rf* value of 0.70.

3-Mercapto-2-D-methylpropanoic Acid (8)——Sodium thiosulfate ($Na_2S_2O_3 \cdot 5H_2O$, 26 g, 0.105 mol) was added to a solution of the chloride **7** (12.0 g, 0.098 mol) and $NaHCO_3$ (8.9 g, 0.106 mol) in water (120 ml), and the resulting mixture was heated at 100°C for 1 h under nitrogen, then cooled. Conc. HCl (40 ml) was added and the resulting mixture was heated at 100°C for 1 h, then cooled. The products were extracted with ethyl acetate (150 ml × 2) and treated as usual to afford a crude syrup (10.2 g), which was found by HPLC to consist of **8** (76 wt%) and the disulfide (5 wt%). The monosulfide was not produced in the reaction.

3-Acetylthio-2-D-methylpropanoic Acid (9a)——Acetic anhydride (9.45 ml, 0.1 mol) was added dropwise to a solution of **8** (6.0 g, 0.05 mol) in 1 N NaOH (150 ml, 0.15 mol) with stirring and cooling in an ice-water bath during one hour. After additional stirring for an hour, the starting **8** was no longer observed on TLC (system A, **8**: $Rf = 0.67$; **9a**: $Rf = 0.74$). The reaction mixture was acidified (pH 2) with 6 N HCl and extracted with ethyl acetate (150 ml × 3). The extract was treated as usual, giving crude **9a** (8.0 g). Analytically pure **9a** was obtained by vacuum distillation. bp 115°C/0.9 mmHg. $[\alpha]_D^{22}$ −48.55° ($c = 1.0$, 95% EtOH). n_D^{20} 1.4902. IR(neat) cm^{-1}: 1750, 1720. ^1H NMR ($CDCl_3$, 90 MHz) δ ppm: 1.27 (3H, d, CH_3), 2.32 (3H, s, CH_3CO), 2.75 (1H, m, CH), 3.08 (2H, m, CH_2), 10.8 (1H, s, COOH). This compound moved on TLC with *Rf* values of 0.74 (system A) and 0.28 (system C).

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