The Practical Resolution of (2*RS*,3*RS*)-2-Hydroxy-3-(4-methoxyphenyl)-3-(2-nitrophenylthio)propionic Acid, a Key Intermediate for Diltiazem, with L-Lysine

Masaru SENUMA,*[a] Masataka SHIBAZAKI,[a] Shigeru NISHIMOTO,[a] Keijiroh SHIBATA,[a] Kimio OKAMURA,[b] and Tadamasa DATE[b]

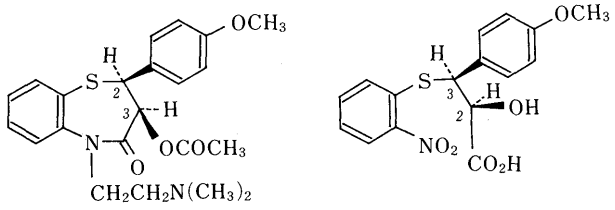
Pharmaceutical Technics Division,[a] Tanabe Seiyaku Co., Ltd., 3-16-89, Kashima, Yodogawa-ku, Osaka 532, Japan and Organic Chemistry Research Laboratory,[b] Tanabe Seiyaku Co., Ltd., Kawagishi, Toda-shi, Saitama 335, Japan. *Received April 13, 1989*

Practical resolution of (2*RS*,3*RS*)-2-hydroxy-3-(4-methoxyphenyl)-3-(2-nitrophenylthio)propionic acid (2) was examined by the use of several basic amino acids. L-Lysine was found to be the most effective resolving agent to obtain (+)-(2*S*,3*S*)-2, a key intermediate for the synthesis of diltiazem (1). This new method should be applicable to the industrial production of 1 in view of the simplicity of the procedure, the ready availability of L-lysine, and the high yield of the desired isomer. The absolute stereochemistry of (+)-2 was determined to be 2*S*,3*S* by X-ray crystallographic analysis.

Keywords 2-hydroxy-3-(4-methoxyphenyl)-3-(2-nitrophenylthio)propionic acid; optical resolution; selective precipitation; absolute configuration; X-ray crystallographic analysis

Diltiazem, (+)-(2*S*, 3*S*)-3-acetoxy-5-[2-(dimethylamino)-ethyl]-2, 3-dihydro-2-(4-methoxyphenyl)-1, 5-benzothiazepin-4(5*H*)-one (**1**), is a potent calcium channel blocker and has been clinically used as an effective antianginal and antihypertensive agent in more than ninety countries.[1] Among the two enantiomers of **1**, the (2*S*, 3*S*) enantiomer selectively exhibits potent activity.[2]

Therefore, a practical synthesis of (+)-(2*S*, 3*S*)-2-hydroxy-3-(4-methoxyphenyl)-3-(2-nitrophenylthio)propionic acid (**2**), the key intermediate for **1**, is required. The highly diastereoselective synthesis of (2*RS*, 3*RS*)-**2** has been achieved by the stereoselective *cis* opening of methyl *trans*-3-(4-methoxyphenyl)glycidate by 2-nitrothiophenol in the presence of tin Lewis acid.[3]



(+)-(2*S*,3*S*)-**1** diltiazem (+)-(2*S*,3*S*)-**2**

Chart 1

Inoue *et al.* reported the optical resolution of (±)-**2** by chinchonidine.[4] The less soluble cinchonidine salt of **2**, however, was the unwanted (2*R*, 3*R*) isomer, and the desired (2*S*, 3*S*) isomer was obtained from the mother liquor. Moreover, a large quantity of expensive cinchonidine is required. These flaws preclude the industrial application of this method. We describe here a highly effective and practical optical resolution of (±)-**2** by the use of L-lysine. The absolute stereochemistry of (±)-**2** determined by X-ray crystallographic analysis is also presented.

Optical resolution of (±)-**2** was examined by the use of several natural basic amino acids such as L-lysine, L-arginine, and L-ornithine, since they are inexpensive and readily available. Preliminary experiments revealed that

TABLE I. Salts Formation of (±)-**2** with Various Molar Ratios of L-Lysine

Molar ratio of L-lysine	Precipitated salt				Degree of optical resolution[c] (%)
	Yield		$[\alpha]_D^{25}$ in 0.1 N NaOH	Optical purity (%)[b]	
	(g)	(%)[a]			
0.15	1.5	100.0	−100.2°	97.1	14.7
0.30	2.6	87.5	−98.6°	95.6	25.1
0.38	3.6	95.6	−99.5°	96.4	35.0
0.50	4.6	92.7	−94.5°	91.6	42.0
0.60	5.3	89.2	−70.2°	69.1	37.0
0.70	6.3	90.8	−41.6°	42.6	27.1
0.85	7.9	93.8	−14.3°	17.3	13.8
1.00	9.1	91.8	−0.2°	4.2	3.9

a) Based on the amount of L-lysine used. *b*) This was calculated from the equation given in Experimental using the $[\alpha]_D$ values of the authentic L-lysine salts of (2*S*, 3*S*)-**2** and (2*R*, 3*R*)-**2**. *c*) Calculated yield of the L-lysine salt of (2*S*, 3*S*)-**2**.

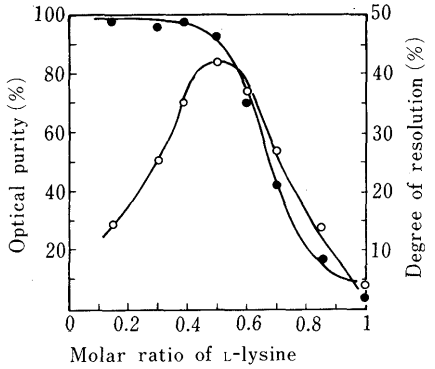


Fig. 1. Effect of the Molar Ratio of L-Lysine on the Optical Purity and Yield

○, degree of resolution (calculated yield of the salt of (2*S*, 3*S*)-**2**); ●, optical purity.

TABLE II. The Solubility of the L-Lysine Salts of (2*S*, 3*S*)-**2** and (2*R*, 3*R*)-**2**

	L-Lysine salt	Solubility (g/100 ml of MeOH)
A[a]	(2*S*, 3*S*)-**2**	0.11
	(2*R*, 3*R*)-**2**	0.45
B[b]	(2*S*, 3*S*)-**2**	0.13
	(2*R*, 3*R*)-**2**	0.31

a) Solubility of each salt alone. *b*) The solubility in the presence of an equimolar For methodology, see Experimental.

L-lysine appears to be a promising resolving agent for (±)-**2**, because the less soluble salt proved to be the salt of the (2*S*, 3*S*) isomer. Optical resolution of (±)-**2** by L-lysine was, therefore, studied in detail.

Addition of a 50% aqueous L-lysine solution to a 6% methanolic solution of (±)-**2** readily caused precipitation of the L-lysine salt. The effect of the amount of L-lysine on the yield and optical purity of the precipitated salt was examined by varying the molar ratio to (±)-**2** (Table I). The optical purity of the salt was determined by comparing its specific rotation with that of the authentic L-lysine salt prepared from pure (2*S*, 3*S*)-**2**.[4,5]

Table I shows that increase in the molar ratio of L-lysine from 0.15 to 1.0 causes a linear increase in the amount of the precipitated salt, and the yield based on the amount of L-lysine used was about 90% in every case. The optical purity of the salt, however, markedly decreases when the molar ratio of L-lysine exceeds 0.5. Therefore, the best result in terms of degree of resolution (the calculated yield of the salt of (2*S*, 3*S*)-**2**) was obtained by the use of 0.5 mol of L-lysine. This indicates that the nearly selective precipitation of the salt of (2*S*, 3*S*)-**2** occurs in the presence of L-lysine in an amount of less than 0.5 mol. Precipitation of the diastereoisomeric salt of (2*R*, 3*R*)-**2** appears to start rapidly, when the molar ratio of L-lysine reaches about 0.5. These results are clearly shown in Fig. 1.

It has been assumed that resolution by formation of diastereoisomeric salts can be achieved on the basis of an appreciable difference in solubility.[6] The difference in solubility of the L-lysine salts of (2*S*, 3*S*)-**2** and (2*R*, 3*R*)-**2**

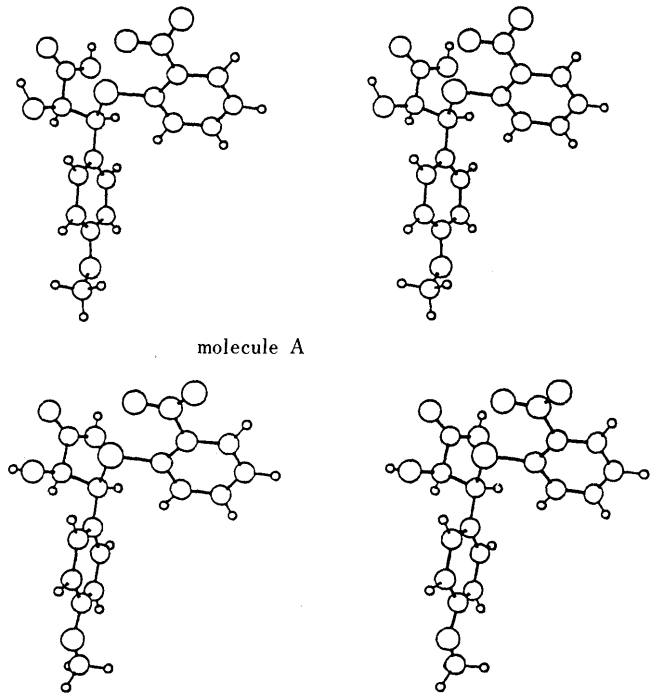


Fig. 2. Stereoscopic View of (2*S*, 3*S*)-**2** with Correct Configuration

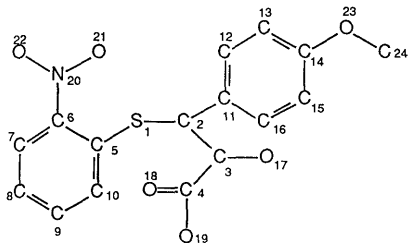


Fig. 3. Numbering of Atoms

TABLE III. Atomic Coordinates (× 10^4) and Equivalent Isotropic Thermal Parameters

Atom	*x*	*y*	*z*	B_{eq}	Atom	*x*	*y*	*z*	B_{eq}
Molecule A					Molecule B				
S1A	3374 (2)	327 (1)	5453 (2)	4.43	S1B	7593 (2)	4904 (1)	1268 (2)	4.84
C2A	3533 (6)	−507 (4)	3516 (7)	3.59	C2B	7766 (8)	5784 (5)	574 (8)	4.73
C3A	3616 (6)	−1557 (4)	4009 (8)	4.09	C3B	7473 (7)	6814 (4)	−26 (8)	4.15
C4A	2064 (7)	−1704 (4)	4915 (8)	4.26	C4B	5746 (7)	7004 (4)	−750 (8)	4.19
C5A	2441 (8)	1434 (4)	4807 (8)	4.49	C5B	7046 (8)	3849 (4)	−441 (8)	4.43
C6A	1831 (9)	2218 (5)	5951 (9)	5.71	C6B	6678 (8)	3037 (5)	−1435 (9)	5.35
C7A	994 (1)	3091 (6)	5483 (11)	7.89	C7B	6162 (12)	2213 (5)	−850 (11)	7.63
C8A	898 (13)	3201 (6)	3822 (12)	8.50	C8B	6090 (12)	2216 (6)	849 (11)	7.71
C9A	1505 (14)	2424 (6)	2645 (10)	8.36	C9B	6501 (13)	3000 (6)	1877 (10)	8.14
C10A	2283 (11)	1564 (5)	3130 (9)	6.71	C10B	6895 (13)	3815 (5)	1276 (9)	7.34
C11A	4908 (7)	−433 (4)	2340 (4)	4.03	C11B	9293 (9)	5661 (5)	1557 (9)	5.77
C12A	4624 (8)	−549 (5)	606 (8)	4.79	C12B	10824 (10)	5323 (7)	781 (12)	7.90
C13A	5818 (8)	−509 (5)	−554 (8)	4.96	C13B	12248 (10)	5271 (8)	1688 (17)	10.52
C14A	7326 (8)	−366 (5)	18 (8)	4.84	C14B	12185 (14)	5541 (7)	3350 (16)	12.46
C15A	7733 (8)	−222 (6)	1666 (10)	6.02	C15B	10731 (16)	5862 (7)	4154 (15)	12.21
C16A	6437 (9)	−253 (6)	2884 (9)	5.63	C16B	9297 (12)	5925 (6)	3245 (11)	8.12
O17A	4965 (4)	−1737 (3)	5042 (6)	5.01	O17B	8654 (12)	6893 (3)	−1210 (6)	5.87
O18A	2093 (5)	−1946 (4)	6281 (5)	5.44	O18B	5572 (5)	7248 (3)	−2127 (5)	4.84
O19A	742 (5)	−1539 (4)	4007 (6)	5.60	O19B	4622 (5)	6887 (4)	302 (5)	5.38
N20A	1863 (11)	2167 (6)	7738 (8)	9.12	N20B	6714 (11)	2997 (5)	−3284 (8)	9.37
O21A	2630 (6)	1492 (4)	8296 (6)	6.55	O21B	7110 (8)	3648 (4)	−3916 (6)	7.74
O22A	1102 (21)	2782 (9)	8644 (9)	26.40[a]	O22B	6576 (26)	2222 (9)	−4055 (11)	27.70[a]
O23A	8473 (6)	−322 (4)	−1268 (7)	7.24	O23B	13682 (13)	5423 (8)	4121 (17)	21.25
C24A	9972 (10)	30 (7)	−820 (14)	8.45	C24B	14000 (23)	5456 (10)	5497 (28)	22.00
					O w1	8256 (5)	8240 (4)	5902 (6)	5.68
					O w2	1737 (6)	7554 (7)	9406 (7)	7.75

a) The temperature factor of the O atom of *ortho*-substituted nitrobenzenes is known to be large. See reference 11.

TABLE IV. Bond Angles (°)

Bond	Mol. A angle	Mol. B angle	Bond	Mol. A angle	Mol. B angle
C2–S1–C5	102.5 (3)	103.6 (3)	C7–C8–C9	119.1 (8)	119.7 (8)
S1–C2–C3	106.5 (4)	105.9 (4)	C8–C9–C10	120.9 (8)	121.6 (8)
S1–C2–C11	117.4 (4)	117.1 (4)	C5–C10–C9	121.5 (6)	121.5 (7)
C3–C2–C11	110.7 (4)	112.1 (5)	C2–C11–C12	119.0 (5)	121.9 (7)
C2–C3–C4	111.4 (5)	111.5 (5)	C2–C11–C16	122.6 (6)	121.6 (7)
C2–C3–O17	110.1 (5)	109.6 (4)	C12–C11–C16	118.3 (6)	116.5 (8)
C4–C3–O17	109.2 (5)	110.5 (5)	C11–C12–C13	122.8 (6)	121.6 (9)
C3–C4–O18	121.8 (5)	120.3 (5)	C12–C13–C14	117.5 (6)	119.6 (9)
C3–C4–O19	112.0 (5)	111.7 (5)	C13–C14–C15	124.9 (6)	120.9 (11)
O18–C4–O19	126.2 (6)	128.0 (6)	C13–C14–O23	113.5 (6)	114.0 (10)
S1–C5–C6	121.4 (5)	122.3 (5)	C15–C14–O23	121.5 (6)	125.1 (12)
S1–C5–C10	122.3 (5)	122.5 (5)	C14–C15–C16	116.8 (6)	119.8 (11)
C6–C5–C10	116.4 (6)	115.1 (6)	C11–C16–C15	119.7 (6)	121.8 (9)
C5–C6–C7	123.0 (7)	124.5 (7)	C6–N20–O21	120.9 (6)	121.0 (7)
C5–C6–N20	121.9 (6)	120.5 (7)	C6–N20–O22	119.5 (8)	116.0 (8)
C7–C6–N20	114.8 (6)	114.9 (7)	O21–N20–O22	119.6 (8)	122.0 (8)
C6–C7–C8	118.8 (7)	117.4 (7)	C14–O23–C24	118.4 (6)	130.6 (15)

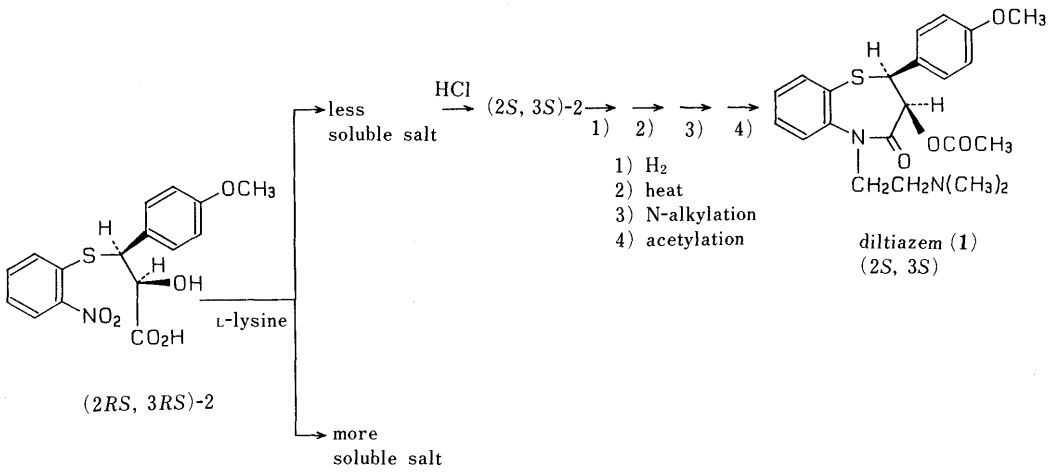


Chart 2

TABLE V. Bond Lengths (Å)

Bond	Mol. A	Mol. B	Bond	Mol. A	Mol. B
S1–C2	1.812 (6)	1.809 (6)	C8–C9	1.385 (11)	1.351 (12)
S1–C5	1.769 (6)	1.781 (7)	C9–C10	1.385 (12)	1.353 (12)
C2–C3	1.547 (9)	1.553 (9)	C11–C12	1.408 (9)	1.411 (11)
C2–C11	1.500 (8)	1.489 (10)	C11–C16	1.372 (9)	1.363 (11)
C3–C4	1.521 (8)	1.543 (8)	C12–C13	1.370 (10)	1.380 (14)
C3–O17	1.405 (7)	1.388 (8)	C13–C14	1.350 (10)	1.343 (18)
C4–O18	1.191 (8)	1.204 (8)	C14–C15	1.364 (10)	1.363 (17)
C4–O19	1.326 (7)	1.296 (8)	C14–O23	1.417 (9)	1.381 (17)
C5–C6	1.377 (9)	1.356 (9)	C15–C16	1.460 (10)	1.387 (16)
C5–C10	1.390 (10)	1.398 (10)	N20–O21	1.200 (9)	1.167 (10)
C6–C7	1.412 (11)	1.394 (12)	N20–O22	1.169 (13)	1.184 (14)
C6–N20	1.452 (10)	1.484 (10)	O23–C24	1.407 (10)	1.136 (26)
C7–C8	1.368 (13)	1.371 (13)			

TABLE VI. Determination of the Absolute Configuration

h	k	l	$\lvert F_O(+)\rvert/\lvert F_O(-)\rvert$	$\lvert F_C(+)\rvert/\lvert F_C(-)\rvert$
5	3	1	1.267	1.053
5	1	1	0.925	0.872
4	2	1	0.962	0.948
3	7	1	0.911	0.883
3	6	2	0.953	0.957
3	5	2	1.077	1.073
3	1	4	1.045	1.048
3	1	3	1.030	1.040
3	1	2	0.963	0.951
3	1	1	1.071	1.070
2	8	1	0.967	0.955
2	7	2	0.946	0.955
2	5	2	0.963	0.971
2	4	4	0.917	0.949
2	3	3	0.947	0.971
2	2	1	0.964	0.969
1	7	1	0.905	0.876
1	6	3	0.882	0.896
1	2	2	0.937	0.964

in methanol was relatively small (Table II). The salt of the (2*S*, 3*S*) isomer is about four times less soluble than that of the (2*R*, 3*R*) isomer. When measured in the presence of equimolar amounts of the diastereoisomers, the difference in solubility was only 2.4.

In recent years, several attempts have been made to provide an insight into the mechanism of optical resolution *via* diastereoisomeric salt formation on the basis of X-ray crystallography.[7] The difference in the crystallographic structures of the L-lysine salts of (2*S*, 3*S*)-**2** and (2*R*, 3*R*)-**2** would allow a greater insight into the mechanism of the highly effective resolution of (±)-**2** by L-lysine. Unfortunately, to date we have been unable to prepare crys-

tals of the salts suitable for X-ray analysis.

L-Ornithine, the nor analogue of L-lysine, proved to be an ineffective resolving agent for (±)-**2**, the optical purity of the precipitated salt being 38% at best. No optical resolution was observed with L-arginine.

On the basis of the above observations, the effective resolution of (±)-**2** on a preparative scale was achieved by the use of 0.5 eq of L-lysine. Simple digestion of the precipitated salt with boiling methanol gave the optically pure L-lysine salt of (2*S*, 3*S*)-**2** in 44% yield. Treatment of the salt with aqueous HCl readily regenerated (2*S*, 3*S*)-**2** in 95% yield. The optical purity of (2*S*, 3*S*)-**2** thus obtained was determined to be 99.7% by high-performance liquid chromatography (HPLC) using a CHIRALPAK column (Daicel Co., Ltd.). The absolute stereochemistry of (2*S*, 3*S*)-**2** was confirmed by X-ray crystallographic analysis. There are two crystallographically independent molecules in a unit cell, which are named molecule A and molecule B (Fig. 2).

The present method provided a practical optical resolution of (±)-**2** in view of the simplicity of the procedure, the ready availability of inexpensive L-lysine, and the high yield of the desired isomer. The carboxylic acid [(2*S*, 3*S*)-**2**] has already been converted to diltiazem (**1**) by the sequence of reactions shown in Chart 2 without any isomerization.[4] This improved resolution of (±)-**2** should be applicable to the industrial production of diltiazem.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were obtained on a Shimadzu IR-420 infrared spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Hitachi R-90H spectrometer with tetramethylsilane reference. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Optical rotations were determined for solutions in chloroform or 0.1 N NaOH on a Perkin-Elmer 243 polarimeter. Optical purity was measured by HPLC with a Shimadzu LC-6A liquid chromatograph and ultraviolet photometer, using a CHIRALPAC WM column.

The L-Lysine Salt of (2*S*, 3*S*)-2-Hydroxy-3-(4-methoxyphenyl)-3-(2-nitrophenylthio)propionic Acid (2) A solution of L-lysine (5.8 g, 0.04 mol) in H_2O (5.8 ml) was added to a solution of (2*S*, 3*S*)-**2**[4] (14 g, 0.04 mol) in MeOH (280 ml) at 30 °C. Stirring was continued for 30 min at the same temperature, then the yellow precipitates formed were collected and recrystallized from aqueous MeOH to give, after drying, 17.1 g, (86.5%) of the L-lysine salt of (2*S*, 3*S*)-**2** as needles, mp 222—223.5 °C. $[\alpha]_D^{25}$ −103.4° (*c* = 1, 0.1 N NaOH). IR ν_{max}^{Nujol} cm^{-1}: 3275, 1590, 1510, 1075. *Anal.* Calcd for $C_{22}H_{29}N_3O_8S$: C, 53.32; H, 5.90; N, 8.48; S, 6.47. Found; C, 53.36; H, 5.83; N, 8.44; S, 6.53. ^{1}H-NMR (D_2O) δ: 1.30—2.00 (6H, m), 3.02 (2H, t, *J* = 4 Hz), 3.70 (3H, s), 3.75 (1H, t, *J* = 3 Hz), 4.35 (1H, d, *J* = 2 Hz), 4.89 (1H, d, *J* = 2 Hz), 6.74—7.96 (8H, m).

In a similar manner, the L-lysine salt of (2*R*, 3*R*)-**2** was obtained as yellow needles in 88% yield, mp 217.5—220 °C. $[\alpha]_D^{25}$ +112.0° (*c* = 1, 0.1 N NaOH). IR ν_{max}^{Nujol} cm^{-1}: 3276, 1590, 1510, 1075. *Anal.* Calcd for $C_{22}H_{29}N_3O_8S$: C, 53.32; H, 5.90; N, 8.48; S, 6.47. Found; C, 53.35; H, 5.85; N, 8.45; S, 6.45.

Reaction of (±)-2 with Various Amounts of L-Lysine In a typical procedure, a solution of L-lysine (1.1 g, 0.0076 mol) in H_2O (1.1 ml) was added to a solution of (±)-**2** (7.0 g, 0.02 mol) in MeOH (105 ml). The mixture was stirred at 30 °C for 30 min, filtered, and washed with MeOH (10 ml) to give, after drying, 3.6 g (95.6% based on the L-lysine) of the crude L-lysine salt of (2*S*, 3*S*)-**2**. $[\alpha]_D^{25}$ −99.5° (*c* = 1, 0.1 N NaOH). The optical purity of this sample was 96.4%, which was calculated from the following equation on the basis of the $[\alpha]_D$ values of the authentic L-lysine salts of (2*S*, 3*S*)-**2** and (2*R*, 3*R*)-**2** described above.

$$\frac{-99.5-\left|\frac{-103.4+112.0}{2}\right|}{103.4+\left|\frac{-103.4+112.0}{2}\right|}\times 100$$

Accordingly, the calculated yield of the L-lysine salt of (2*S*, 3*S*)-**2** in this run was 35.0%. Similar experiments were performed by the use of various molar ratios of L-lysine and the results are summarized in Table I and Fig. 1.

Optical Resolution of (±)-2 by L-Lysine A solution of L-lysine (14.6 g, 0.1 mol) in H_2O (14.6 ml) was added to a stirred solution of (±)-**2** (69.8 g, 0.2 mol) in MeOH (700 ml). The mixture was stirred at room temperature for 1 h and filtered to give 45.5 g of a yellow solid which had $[\alpha]_D^{25}$ −98° (*c* = 1, 0.1 N NaOH). The crude salt was refluxed with MeOH (645 ml) for 30 min. The mixture was cooled to room temperature, filtered, and washed with MeOH to give 43.2 g (44%) of the optically pure L-lysine salt of (2*S*, 3*S*)-**2**. $[\alpha]_D^{25}$ −103° (*c* = 1, 0.1 N NaOH). This salt was dissolved in hot water (1200 ml), and the mixture was made acidic (pH 2.1) with aqueous HCl. The separated solid was collected, washed with H_2O, and dried *in vacuo* at 60 °C to give 29 g (41.8% from (±)-**2**) of (2*S*, 3*S*)-**2**. mp 111 °C (lit.[4] mp 106—109 °C). $[\alpha]_D^{25}$ +121° (*c* = 1, $CHCl_3$) (lit.[4] $[\alpha]_D^{22}$ +119.5° (*c* = 1, $CHCl_3$)). The optical purity of this material was determined to be 99.7% by HPLC (HPLC conditions in this case were the same as in the determination of solubilities described below).

Determination of the Solubilities of the L-Lysine Salts of (2*S*, 3*S*)-2 and (2*R*, 3*R*)-2 A mixture of MeOH (50 ml) and the L-lysine salt of (2*S*, 3*S*)-**2** (5 g) was stirred at 30 °C for 5 h. The supersaturated solution thus obtained was filtered. A small sample (5 ml) of the mother liquor was dried to constant weight at 50 °C. From the weight of the residue (5.5 mg), the solubility of the L-lysine salt of (2*S*, 3*S*)-**2** was calculated to be 0.11 g in MeOH (100 ml) at 30 °C. In a similar manner, the solubility of the L-lysine salt of (2*R*, 3*R*)-**2** was determined to be 0.45 g in MeOH (100 ml) at 30 °C. On the other hand, the solubility of each L-lysine salt in the presence of the other diastereomer was determined as follows. The supersaturated solution obtained from L-lysine salts of (2*S*, 3*S*)-**2** (5 g) and (2*R*, 3*R*)-**2** (5 g) in MeOH (100 ml) after stirring for 5 h at 30 °C was filtered and a small sample of the mother liquor was analyzed by HPLC under the following conditions: column, CHIRALPAK WM (Daicel Co., Ltd.) (4.6 × 250 mm); column temperature, 50 °C; mobile phase, a mixed solution of 0.5 M copper(II) sulfate solution and acetonitrile (8 : 2); the pressure or flow rate was adjusted so that retention time of the (2*S*, 3*S*)-**2** peak was about 19 min. The solubilities of the L-lysine salts thus obtained are listed in Table II.

X-Ray Analysis A transparent yellow crystal of (2*S*, 3*S*)-**2** with dimensions of 0.4 × 0.3 × 0.2 mm was chosen for the diffraction experiments. The cystal data are as follows: $C_{16}H_{15}O_6$ NS·H_2O, MW = 367.38, *a* = 8.235(1), *b* = 13.809(2), *c* = 8.062(1) Å, α = 97.39(1), β = 90.19(1), γ = 83.35(1), *U* = 903.0(2) Å, space group: *P*1, *Z* = 2, D_x = 1.351 g/cm^2, μ(Cu K_α) = 18.908 cm^{-1}. The intensity data were measured on a four-circle diffractometer (AFC5, Rigaku). Of 3082 unique reflections, 2841 with $|F_O| \geqq 2.67\sigma(F_O)$ were judged significant. The structure was solved by the direct methods using SIR85[8] and refined by block-diagonal matrix least-squares methods with anisotropic thermal factors for the non-hydrogen atoms and with isotropic ones for all hydrogen atoms. The final *R* value was 0.064, and R_w was 0.064, where $w = 1/\sigma^2(F)$ was used, $\Delta\rho\max = 0.3$ and $\Delta\rho\min = -0.3$ e/Å^3. The atomic scattering factors were taken from "International Tables for X-Ray Crystallography".[9] The final atomic parameters are given in Table III. The bond angles and lengths are listed in Tables IV and V, respectively.

Absolute Configuration The absolute configuration was determined by the Bijvoet pairs method.[10] The structure factors were calculated including anomalous scattering factors of S and O atoms for Cu K_α radiation. The intensity data of the Bijvoet pairs, (*h*, *k*, *l*) and (−*h*, −*k*, −*l*) were measured precisely, in a right-handed set of coordinate axes. The results are shown in Table VI. Figure 2 shows the stereoscopic molecular structures drawn in the right-handed set of coordinate axes, which shows the correct absolute configuration of the molecule as C2(S) and C3(S). (The nomenclature of atoms is shown in Fig. 3.)

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