Preparation and Absolute Configurations of Optical Isomers of Sodium 2-[[4-(3-Methoxypropoxy)-3-methylpyridin-2-yl]methylsulfinyl]-1*H*-benzimidazole (E3810)

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The optical isomers of sodium 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methylsulfinyl]-1*H*-benzimidazole (E3810), a proton pump inhibitor, were separated by HPLC and their absolute configurations were determined by X-ray crystallographic analysis.

Key words proton pump inhibitor; optical isomer; optical resolution; absolute configuration; X-ray crystallographic analysis; E3810

Sodium 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methylsulfinyl]-1*H*-benzimidazole (E3810), a proton pump inhibitor, has a powerful inhibitory effect on gastric acid secretion. Its development as a drug to treat peptic ulcers is in progress, and clinical studies are being conducted.[1–6] E3810 is a racemic compound (Fig. 1), and it is therefore desirable to prepare each optical isomer and to elucidate its physicochemical properties and pharmacological activities. In the present study, we separated the optical isomers of E3810 by chromatographic resolution and determined the absolute configurations of the isomers by X-ray crystallographic analysis.

As shown in Fig. 2, the optical isomers of E3810 could be separated by HPLC on a chiral column, and on a preparative scale, enantiomeric purities of nearly 100% ee were obtained. However, the chemical purities were only 93.7% for (*R*)-isomer and 84.4% for (*S*)-isomer, respectively, because E3810 decomposed during the HPLC and during extraction from the eluates.

We found that E3810 could be stabilized by introducing a protecting group at the N atom located in the first position of benzimidazole. Then, we assessed the feasibility of fractionation of the optical isomers after stabilization with three kinds of protecting groups, the benzyloxymethyl group, the 2-trimethylsilylethoxymethyl group and the methoxymethyl group (Fig. 3). The derivatives of E3810 (**1**—**3**) were subjected to HPLC on a chiral column, and it was found that the optical isomers of all the derivatives could be separated by HPLC. The HPLC conditions and the retention times of the optical isomers are shown in Table 1. Benzyloxymethylated E3810 (**1**) was considered most suitable for separation, because the difference in the retention times of the optical isomers was largest. Thus, the benzyloxymethyl group was selected as a protecting group. The method is summarized in Fig. 4. Deprotection with sulfuric acid was carried out by a modification of the method of Kohl and Senn-Bilfinger.[7] The chemical purities of the (*S*)-isomer and the (*R*)-isomer of E3810 obtained by this method were 99.8% and 99.8%, respectively. The enantiomeric purities were 96.6% ee and 96.7% ee, respectively.

We determined the absolute configurations of the optical isomers of E3810 by X-ray crystallographic analysis of the optical isomers of **1**, which are synthetic intermediates to the optical isomers of E3810, because E3810 itself could hardly be crystallized. Each optical isomer of **1** was crystallized from Et_2O–hexane in a refrigerator. The absolute configurations were determined by the Bijvoet pairs intensity comparison method. The initial structure of each optical isomer was supposed to be (*R*)-configura-

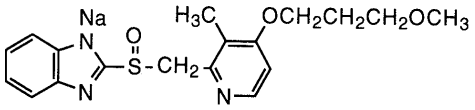

Fig. 1. Chemical Structure of E3810

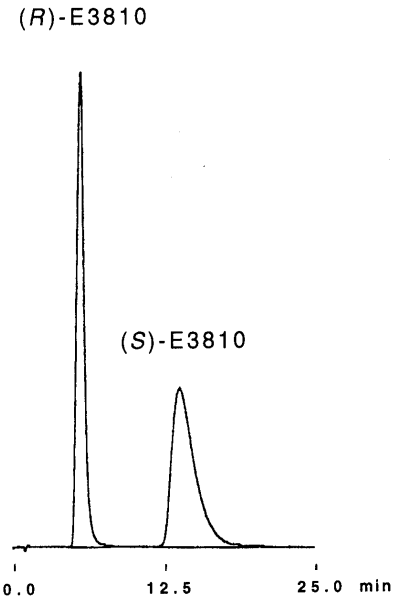

Fig. 2. Chromatogram of Optical Isomers of E3810

HPLC conditions were as follows. Detector, UV absorption photometer (wavelength: 290 nm); column, Resolvosil-BSA-7 4 mm in inside diameter and 15 cm in length (M. Nagel, Düren, Germany); column temperature, 25 °C; mobile phase, mixture of 0.1 M phosphate buffer, pH 8.5 and *n*-PrOH (20 : 1); flow rate, 2.0 ml/min; injection volume, 10 μl; sample solution, E3810 dissolved in 0.01 N NaOH at a concentration of 1 mg/ml.

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tion, and the judgment of the absolute structure was performed by examining whether the D value was positive or negative. The D value is given by the equations:

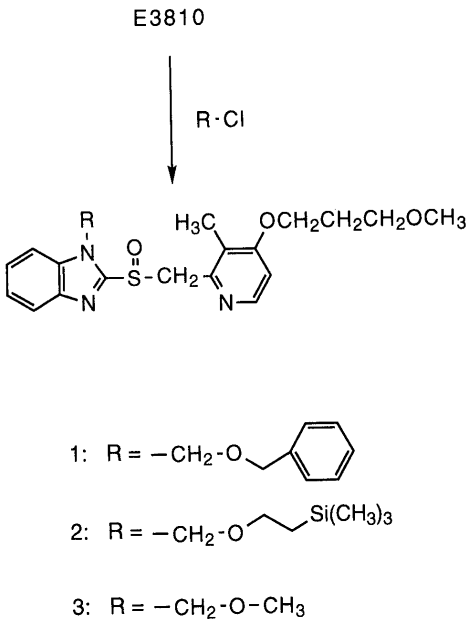

Fig. 3. Protection of E3810

$$D = B_o/B_c$$

$$B_o = [F_o(h,k,l) - F_o(\bar{h},\bar{k},\bar{l})]/[F_o(h,k,l) + F_o(\bar{h},\bar{k},\bar{l})]$$

$$B_c = [F_c(h,k,l) - F_c(\bar{h},\bar{k},\bar{l})]/[F_c(h,k,l) + F_c(\bar{h},\bar{k},\bar{l})]$$

where $F(h,k,l)$ denotes the structure factor for the index (h,k,l), the suffix o denotes that the value is found, and the suffix c denotes that the value is calculated. If the (R)-configuration, which is the initially supposed structure, is consistent with the absolute structure actually observed in the crystal, the D value is theoretically 1, and if the

Table 1. Retention Times of Optical Isomers of E3810 Derivatives

Compd. No.	Retention time (min)
1	140, 290[a]
2	88, 156[b]
3	110, 210[a]

a) HPLC conditions were as follows. Detector, UV absorption photometer (wavelength: 286 nm); column, Chiralcel of 4.6 mm in inside diameter and 25 cm in length (Daicel Chemical Industries, Tokyo, Japan); column temperature, 25 °C; mobile phase, mixture of hexane and iso-PrOH (1 : 1); flow rate, 1.5 ml/min. *b*) HPLC conditions were as follows. Detector, UV absorption photometer (wavelength: 286 nm); column, Chiralcel of 4.6 mm in inside diameter and 25 cm in length; column temperature, 25 °C; mobile phase, mixture of hexane and iso-PrOH (3 : 7); flow rate, 2.0 ml/min.

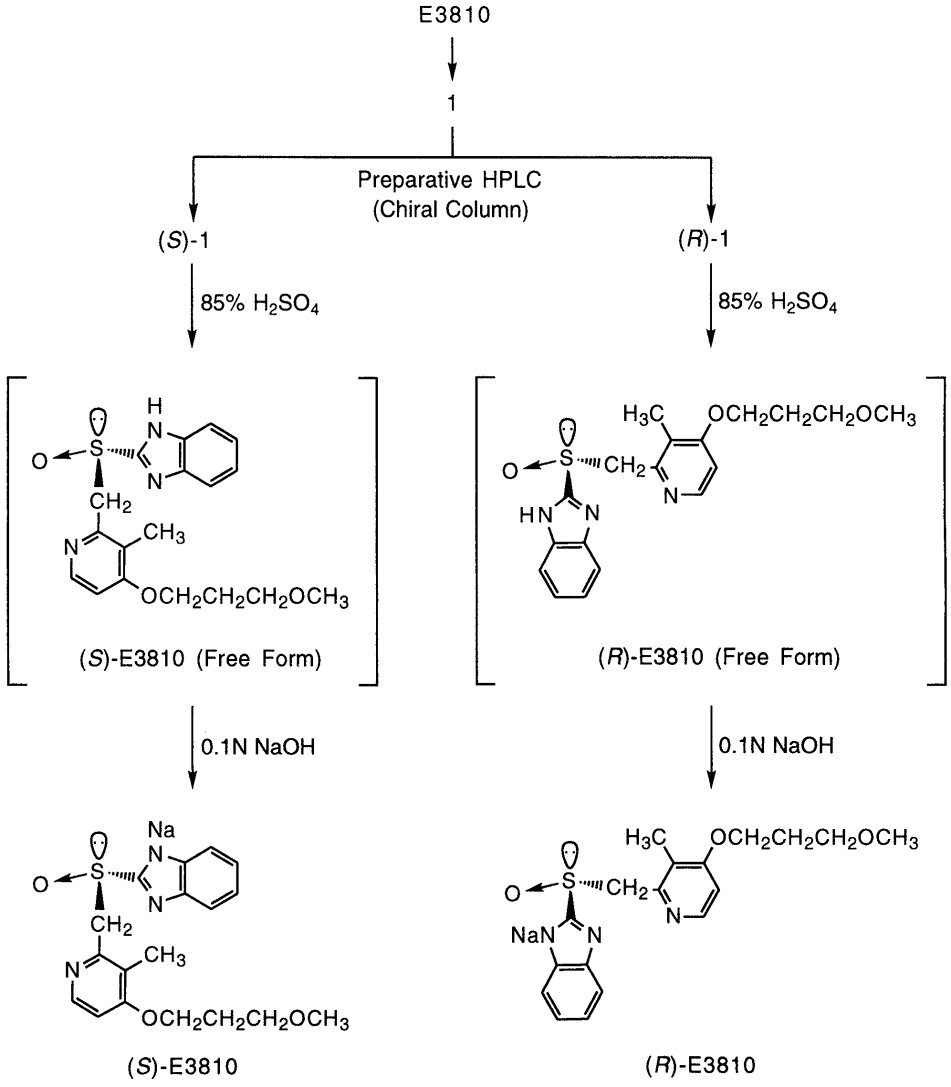

Fig. 4. Preparation of the Optical Isomers of E3810

Table 2. X-Ray Crystallographic Analysis Data of (*R*)-**1** and (*S*)-**1**

Data	(*R*)-**1**	(*S*)-**1**
Molecular formula	$C_{26}H_{29}N_3O_4S$ (479.60)	$C_{26}H_{29}N_3O_4S$ (479.60)
F(000)	1016	1016
Crystal size (mm)	0.36×0.21×0.17	0.26×0.25×0.23
Crystal system (space group)	Monoclinic ($P2_1$)	Monoclinic ($P2_1$)
Lattice unit size *a* (Å)	*a* = 10.132 (2)	*a* = 10.125 (1)
b (Å)	*b* = 18.415 (3)	*b* = 18.422 (2)
c (Å)	*c* = 14.091 (3)	*c* = 14.112 (2)
β (°)	*β* = 107.27 (2)	*β* = 107.23 (1)
V (Å^3)	*V* = 2510.7 (9)	*V* = 2514.1 (5)
Z	4	4
Density: Found	1.270	1.268
: Calcd	1.269	1.267
Linear absorption coefficient (cm^{-1})	14.0	14.0
Measurement method	*ω*–2*θ*	*ω*–2*θ*
$2\theta_{max}$ (°)	130.7	150.0
Measurement range	$-10 \leq h \leq 0$	$-10 \leq h \leq 10$
	$0 \leq k \leq 18$	$-18 \leq k \leq 0$
	$-14 \leq l \leq 14$	$-14 \leq l \leq 0$
Number of independent reflections	4941	5348
Number of observed reflections	1891	3167
Number of parameters for refinement	612	612
Maximum value for final *D* synthesis (*e*/Å^3)	0.369	0.506
R, *Rw*	0.085, 0.101	0.080, 0.100

absolute structure is opposite to that initially supposed, the *D* value is −1. The results obtained by the X-ray crystallographic analysis are shown in Table 2.

Both optical isomers were found to contain two molecules having different conformations in an asymmetric crystal unit. The structural refinement was performed with an *R*-factor of 8.0% for (*S*)-**1** and of 8.5% for (*R*)-**1**. With regard to (*S*)-**1**, the D value obtained after analysis of the Bijvoet pairs was -0.921 ± 0.438, demonstrating that the absolute structure was the opposite of the (*R*)-configuration initially supposed. The *D* value of (*R*)-**1** was 0.842 ± 0.543, demonstrating that the absolute structure was (*R*)-configuration. The crystal structures are represented schematically in Fig. 5.

E3810 is considered to modify the SH groups of H^+, K^+-ATPase, leading to inhibition of gastric acid secretion.[5] The IC_{50} values of the enzyme inhibition with (*S*)-E3810 and (*R*)-E3810 were 0.30 μM.[8] These results suggest that the reaction is not stereospecific. This is consistent with our previous finding that the metabolism of E3810 mainly proceeded *via* the sulfenic acid, a reactive intermediate which lacks chirality.[9]

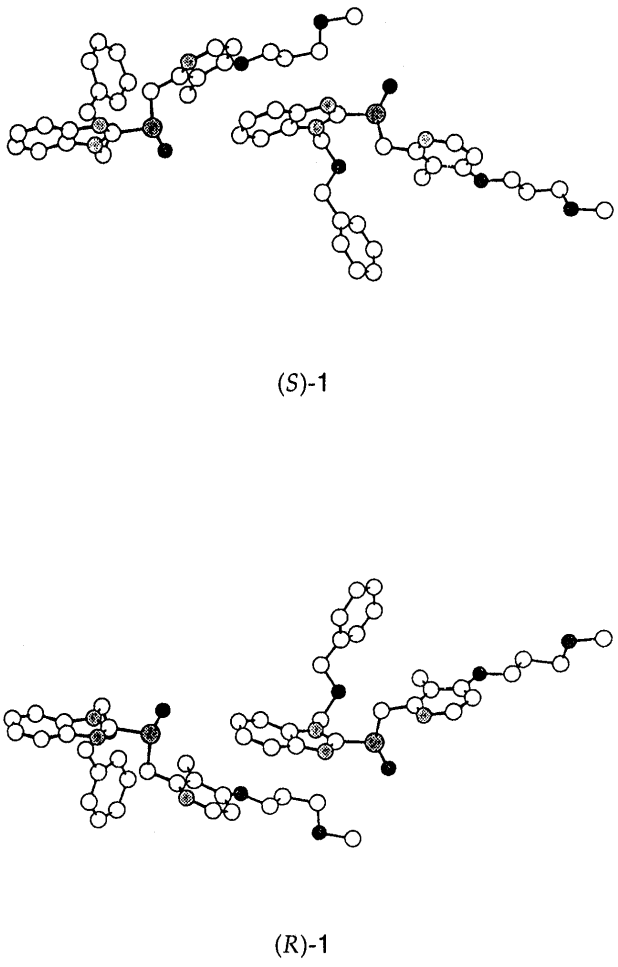

Fig. 5. Crystal Structures of (*S*)-**1** and (*R*)-**1**

Experimental

E3810 was prepared according to the patented method[10] at Eisai Chemical Co., Ltd. Benzyl chloromethyl ether, chloromethyl 2-trimethylsilylethyl ether and chloromethyl methyl ether were purchased from Tokyo Kasei Kogyo Co., Ltd. Melting points were determined on a Yanagimoto melting point apparatus without correction. IR spectra were obtained on a Nicolet 730FT-IR spectrometer. NMR spectra were obtained on a Varian Unity 400 (400 MHz) spectrometer. Abbreviations are: s, singlet; d, doublet; t, triplet; quint, quintet; m, multiplet. MS were recorded on a JEOL JMS-HX100 or JMS-SX102A mass spectrometer. Optical rotations were measured with a Jasco DIP-360 digital polarimeter. HPLC apparatus for analytical HPLC: pump, Tosoh CCPM; pump controller, Tosoh PX-8010; sample injector, Waters 712 WISP; detector, Jasco 875-UV; integrator, SIC Chromatocorder 12. HPLC apparatus for preparative HPLC: pump, Tosoh CCP-8070; pump controller, Tosoh SC-8070; sample injector, Tosoh SV-8070; detector, Tosoh UV-8070; recorder, Pantos Unicorder U-228.

Determination of Chemical Purity of E3810 Chemical purity of E3810 was determined by HPLC under the following conditions: detector, UV absorption photometer (wavelength: 290 nm); column, Nucleosil $5C_{18}$ 4.6 mm in inside diameter and 15 cm in length (M. Nagel, Düren, Germany); column temperature, 25 °C; mobile phase, mixture of MeOH and 0.05 M phosphate buffer, pH 7.0 (3 : 2); flow rate, 1.0 ml/min.

Determination of Enantiomeric Purity of E3810 Enantiomeric purity of E3810 was determined by HPLC under the following conditions: detector, UV absorption photometer (wavelength: 290 nm); column, Resolvosil-BSA-7 4.0 mm in inside diameter and 15 cm in length (M. Nagel, Düren, Germany); column temperature, 25 °C; mobile phase, mixture of 0.1 M phosphate buffer, pH 8.5 and *n*-PrOH (20 : 1); flow rate, 2.0 ml/min.

Optical Resolution of E3810 by Preparative HPLC E3810 was dissolved in 0.1 N NaOH at a concentration of 30 mg/ml, and injected into the HPLC column under the following conditions: detector, UV absorption photometer (wavelength: 290 nm); column, Resolvosil-BSA-7 10 mm in inside diameter and 25 cm in length (M. Nagel, Düren, Germany); column temperature, 25 °C; mobile phase, mixture of 0.1 M phosphate buffer, pH 8.5 and *n*-PrOH (20 : 1); flow rate, 9.0 ml/min; injection volume, 50 μl. After 10 cycles of chromatography, about 200 and 700 ml of (*R*)-E3810 and (*S*)-E3810 fraction eluates were obtained, respectively. Each eluate was evaporated at 35 °C on a water bath *in vacuo*. The residues were shaken vigorously in $CHCl_3$ (100 ml) for 5 min and insoluble materials were filtered off. The filtrates were washed with H_2O and dried over Na_2SO_4. The solvent was evaporated at 35 °C on a water bath *in vacuo*. The residue was dried under reduced pressure in

a desiccator to afford 4.67 mg of (*R*)-E3810 (free form, 66%) as a brownish oil and 4.57 mg of (*S*)-E3810 (free form, 65%) as a dark brownish oil. The chemical purities of (*R*)-E3810 and (*S*)-E3810 were 93.7% and 84.4%, and the enantiomeric purities were 100.0% ee and 97.7% ee, respectively.

1-Benzyloxymethyl-2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulfinyl]-1*H*-benzimidazole (1) Benzyl chloromethyl ether (4.93 g, 31.5 mmol) was added dropwise to a solution of E3810 (10.0 g, 26.2 mmol) and *N*,*N*-diisopropylethylamine (10 ml, 57.4 mmol) in anhydrous tetrahydrofuran (THF) (10 ml) under a nitrogen stream with ice-cooling. The solution was stirred for 17 h at room temperature, and the solvent was evaporated *in vacuo*. The residue was taken up in H_2O (300 ml) and the whole was extracted with AcOEt. The extract was washed with H_2O, saturated aqueous $NaHCO_3$, saturated aqueous NH_4Cl and finally brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (YMC SIL-120-S50, hexane–Et_2O–MeOH 5:4:1), and the product was recrystallized from MeOH—Et_2O to give **1** (8.01 g, 64%) as colorless prisms, mp 86.5—87.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.05 (2H, quint, J=6.0 Hz), 2.21 (3H, s), 3.34 (3H, s), 3.53 (2H, t, J=6.0 Hz), 4.05 (2H, t, J=6.0 Hz), 4.55 (1H, d, J=11.6 Hz), 4.60 (1H, d, J=11.6 Hz), 4.95 (1H, d, J=13.8 Hz), 5.04 (1H, d, J=13.8 Hz), 5.89 (1H, d, J=11.0 Hz), 5.94 (1H, d, J=11.0 Hz), 6.64 (1H, d, J=5.8 Hz), 7.28 (5H, m), 7.36 (1H, m), 7.40 (1H, m), 7.55 (1H, m), 7.84 (1H, m), 8.15 (1H, d, J=5.8 Hz). Positive FAB-MS (NBA) *m/z*: 480 $(M+H)^+$. High-resolution FAB-MS (NBA) *m/z*: 480.1953 $(M+H)^+$ (Calcd for $C_{26}H_{30}N_3O_4S$: 480.1957).

2-[[4-(3-Methoxypropoxy)-3-methylpyridin-2-yl]methylsulfinyl]-1-(2-trimethylsilylethoxy)methyl-1*H*-benzimidazole (2) Chloromethyl 2-trimethylsilylethyl ether (0.393 g, 2.36 mmol) was added to a solution of E3810 (0.500 g, 1.31 mmol) and *N*,*N*-diisopropylethylamine (0.27 ml, 1.55 mmol) in *N*,*N*-dimethylformamide (DMF) (10 ml) under a nitrogen stream and the solution was stirred for 20 h at room temperature. Saturated aqueous NH_4Cl (100 ml) was added and the mixture was extracted with AcOEt. The organic solution was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography (YMC SIL-120-S50, hexane–AcOEt, 1:9) to give **2** (0.465 g, 72%) as a pale yellowish oil. ^{1}H-NMR ($CDCl_3$) δ: 0.00 (9H, s), 0.98 (2H, m), 2.12 (2H, quint, J=6.0 Hz), 2.28 (3H, s), 3.40 (3H, s), 3.61 (2H, t, J=6.0 Hz), 3.69 (2H, m), 4.13 (2H, t, J=6.0 Hz), 5.03 (2H, s), 5.85 (1H, d, J=11.0 Hz), 5.91 (1H, d, J=11.0 Hz), 6.72 (1H, d, J=5.8 Hz), 7.40 (1H, m), 7.45 (1H, m), 7.63 (1H, br d, J=7.6 Hz), 7.89 (1H, br d, J=7.6 Hz), 8.24 (1H, d, J=5.8 Hz). Positive FAB-MS (NBA) *m/z*: 490 $(M+H)^+$. High-resolution FAB-MS (NBA) *m/z*: 490.2196 $(M+H)^+$ (Calcd for $C_{24}H_{36}N_3O_4SSi$: 490.2196).

1-Methoxymethyl-2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulfinyl]-1*H*-benzimidazole (3) A solution of E3810 (4.00 g, 10.5 mmol) and triethylamine (8 ml, 57.4 mmol) in DMF (160 ml) was treated with chloromethyl methyl ether (1.01 g, 12.6 mmol) under a nitrogen stream and the solution was stirred for 24 h at room temperature. Water (100 ml) was added and the mixture was extracted with AcOEt. The organic solution was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography (YMC SIL-120-S50, AcOEt) to give **3** (3.37 g, 78%) as a pale yellowish oil. ^{1}H-NMR ($CDCl_3$) δ: 2.06 (2H, quint, J=6.0 Hz), 2.23 (3H, s), 3.35 (3H, s), 3.38 (3H, s), 3.54 (2H, t, J=6.0 Hz), 4.07 (2H, t, J=6.0 Hz), 4.96 (1H, d, J=13.6 Hz), 5.17 (1H, d, J=13.6 Hz), 5.78 (1H, d, J=11.0 Hz), 5.84 (1H, d, J=11.0 Hz), 6.67 (1H, d, J=5.6 Hz), 7.36 (1H, m), 7.41 (1H, m), 7.57 (1H, m), 7.84 (1H, m), 8.17 (1H, d, J=5.6 Hz). Positive FAB-MS (NBA) *m/z*: 404 $(M+H)^+$. High-resolution FAB-MS (NBA) *m/z*: 404.1653 $(M+H)^+$ (Calcd for $C_{20}H_{26}N_3O_4S$: 404.1644).

Optical Resolution of 1 by Preparative HPLC A solution of **1** (2.00 g, 4.17 mmol) in iso-PrOH (50 ml) was mixed with 50 ml of hexane. This solution was subjected to HPLC under the following conditions: detector, UV absorption photometer (wavelength: 290 nm); column, Chiralcel of 5 cm in inside diameter and 50 cm in length (Daicel Chemical Industries, Tokyo, Japan); column temperature, 30 °C; mobile phase, mixture of hexane and iso-PrOH (1:1); flow rate, 145 ml/min. The eluates containing (*S*)-**1** and (*R*)-**1** were concentrated at 40 °C on a water bath *in vacuo* to give 0.80 g each of (*S*)-**1** and (*R*)-**1**, each as a pale yellowish oil (80%).

Sodium (*S*)-2-[[4-(3-Methoxypropoxy)-3-methylpyridin-2-yl]methylsulfinyl]-1*H*-benzimidazole (*S*)-E3810 A solution of (*S*)-**1** (5.80 g, 12.1 mmol) in CH_2Cl_2 (15 ml) was added dropwise to a mixture of 85% (w/w) sulfuric acid (43.5 ml) and CH_2Cl_2 (15 ml) under a nitrogen stream with ice-cooling while the temperature of the solution was kept between 0 °C and 5 °C. The solution was stirred for 35 min under a nitrogen stream with ice-cooling, then added dropwise to 870 ml of 2 N NaOH under ice-cooling. Stirring was continued for 45 min under ice-cooling, then the solution was washed with CH_2Cl_2 and Et_2O, and NH_4Cl (167 g) was added. The mixture was extracted with CH_2Cl_2 which had previously been washed with saturated aqueous K_2CO_3. The extract was washed with H_2O and dried over $MgSO_4$. This solution was combined with the solution obtained from (*S*)-**1** (6.10 g, 12.7 mmol) by the same method and was evaporated at 30 °C on a water bath *in vacuo* to give 6.29 g of (*S*)-E3810 (free form). The amount of CH_2Cl_2 retained in the (*S*)-E3810 (free form) was determined by GLC (Hewlett Packard 5890 Series II) under the following conditions: detector, hydrogen flame ionization detector; column, PEG-20M Bonded 0.53 mm in inside diameter and 25 m in length (GL Sciences Inc., Tokyo, Japan); column temperature, 40 °C; injection port temperature, 230 °C; detector temperature, 230 °C; carrier gas, helium with a linear velocity of about 35 cm/s. The amount of (*S*)-E3810 (free form) excluding CH_2Cl_2 was calculated and the equivalent amount of 0.1 N NaOH was added. The solution was washed with Et_2O, and filtered, then the filtrate was lyophilized to give (*S*)-E3810 (6.13 g, 65%) as a colorless powder. The chemical and enantiomeric purities were 99.8% and 96.6% ee, respectively. $[\alpha]_D^{20}$ −9° (c=0.020, 0.01 N NaOH). IR (KBr): 2930, 1580, 1300, 1095 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.91 (2H, quint, J=6.2 Hz), 2.09 (3H, s), 3.18 (3H, s), 3.41 (2H, t, J=6.2 Hz), 4.03 (2H, t, J=6.2 Hz), 4.38 (1H, d, J=13.0 Hz), 4.60 (1H, d, J=13.0 Hz), 6.82 (2H, m), 6.86 (1H, d, J=5.7 Hz), 7.40 (2H, m), 8.21 (1H, d, J=5.7 Hz). Positive FAB-MS (NBA) *m/z*: 382 $(M+H)^+$. High-resolution FAB-MS (NBA) *m/z*: 382.1212 $(M+H)^+$ (Calcd for $C_{18}H_{21}N_3NaO_3S$: 382.1201).

Sodium (*R*)-2-[[4-(3-Methoxypropoxy)-3-methylpyridin-2-yl]methylsulfinyl]-1*H*-benzimidazole [(*R*)-E3810] From (*R*)-**1** (8.98 g, 18.7 mmol), (*R*)-E3810 (4.52 g, 63%) was obtained as a pale yellowish powder by the same method as used to prepare (*S*)-E3810. The chemical and enantiomeric purities were 99.8% and 96.7% ee, respectively. $[\delta]_D^{20}$ +9° (c=0.019, 0.01 N NaOH). IR (KBr): 2930, 1580, 1300, 1095 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.91 (2H, quint, J=6.2 Hz), 2.09 (3H, s), 3.18 (3H, s), 3.41 (2H, t, J=6.2 Hz), 4.03 (2H, t, J=6.2 Hz), 4.40 (1H, d, J=13.0 Hz), 4.62 (1H, d, J=13.0 Hz), 6.84 (2H, m), 6.86 (1H, d, J=5.6 Hz), 7.42 (2H, m), 8.20 (1H, d, J=5.6 Hz). Positive FAB-MS (NBA) *m/z*: 382 $(M+H)^+$. High-resolution FAB-MS (NBA) *m/z*: 382.1997 $(M+H)^+$ (Calcd for $C_{18}H_{21}N_3NaO_3S$: 382.1201).

X-Ray Crystallographic Analysis of (*S*)-1 and (*R*)-1 (*S*)-**1** and (*R*)-**1** were each crystallized from Et_2O–hexane at 4 °C in the dark. (*S*)-**1** was obtained as colorless prisms, mp 61—62 °C, high-resolution FAB-MS (NBA) *m/z*: 480.2007 $(M+H)^+$ (Calcd for $C_{26}H_{30}N_3O_4S$: 480.1957). (*R*)-**1** was obtained as colorless prisms, mp 61—62 °C, high-resolution FAB-MS (NBA) *m/z*: 480.1949 $(M+H)^+$ (Calcd for $C_{26}H_{30}N_3O_4S$: 480.1957). The X-ray crystallographic analyses were conducted with crystals thus obtained. Intensity data of reflections were collected with an Enraf-Nonius CAD4 diffractometer using Cu$K\alpha$ radiation (λ=1.54184 Å, 20 mA × 40 kV), and measurements were conducted on one component of Bijvoet pairs at 26—27 °C in the dark using the CAD4-Express program for measurements.[11] Structural analysis was conducted on a DEC VAX-11/750 computer with the MOLEN program.[12] The initial structure of each optical isomer was supposed to be (*R*)-configuration, based on the SIR method.[13] Refinement of the structure was conducted by a least-squares method ignoring the anomalous scattering term of the atomic scattering factor, $\Delta f''$. Then, 40 of the Bijvoet pairs having large intensity and high measurement accuracy were selected, and subjected to measurement of reflection intensities. The criteria for selection of the Bijvoet pairs was based on the S value obtained from the equation:

$$S=[F_c(h,k,l)-F_c(\bar{h},\bar{k},\bar{l})]/\sigma[F_o(h,k,l)]$$

where $\sigma[F_o(h,k,l)]$ is the standard deviation of the found data of the structure factor, $F_o(h,k,l)$. Measurements of the Bijvoet pairs were conducted four times with each reflection, and their mean values were used in the analysis of the absolute structure. The densities of the crystals were determined as the specific gravity of a potassium iodide solution with the same specific gravity as that of the crystals, using a hydrometer.

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