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Optical Resolution and Absolute Configuration of *anti* Head-to-Head Umbelliferone Dimer

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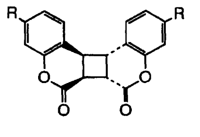
(±)-*anti* Head-to-head umbelliferone dimer was resolved into a pair of optically active forms in good yields with high optical purity by a diastereomeric separation of two diastereomeric diamides obtained by the ring-opening addition reaction with optically pure *erythro*-2-amino-1,2-diphenylethanol or norephedrine, followed by hydrolysis and relactonization. The absolute configuration of the cyclobutane in $(-)_{589}$-*anti* head-to-head umbelliferone dimer was confirmed to be (*S*,*S*,*S*,*S*) by an X-ray crystallographic analysis of the diamide derived from the $(-)_{589}$-form by the ring-opening addition reaction with (*S*)-$(-)_{589}$-1-(1-naphthyl)ethylamine. The absolute configuration of the cyclobutane in $(-)_{589}$-*anti* head-to-head umbelliferone dimer is in agreement with that in $(-)_{589}$-*anti* heat-to-head coumarin dimer.

An optically active diacid compound with C_2 symmetry has been attracting much attention regarding organic and polymer syntheses. For instance, naturally occurring tartaric acid and its derivatives, as well as optically-resolved *trans*-1,2-cyclohexanedicarboxylic acid, 1,1′-binaphthalene-2,2′-dicarboxylic acid, and their derivatives are used as chiral auxiliaries for asymmetric synthesis[1)] and/or chiral components for polymer synthesis.[2)]

We recently reported that optically active *anti* head-to-head coumarin dimer (**1**) could be easily obtained by the optical resolution of (±)-**1**,[3)] and that **1** underwent a ring-opening addition reaction due to its high strain, which accumulates in the course of the photodimerization of coumarin.[4)] As a result, **1** gave diesters and diamides without any condensation reagent,[5)] and optically active **1** could be used as a new type of derivatizing agent[6)] and as a starting material for polymer synthesis.[7)]

On the other hand, *anti* head-to-head umbelliferone (7-hydroxycoumarin) dimer (**2**), which can be easily prepared from umbelliferone, has the same basic skeleton as **1**, showing reactivity as high as **1**.[8)] Therefore, optically active **2** is expected to be a new C_2 symmetric component in organic and polymer syntheses (Chart 1).

In the present paper, we describe the optical resolution of *anti* head-to-head umbelliferone dimer (**2**) as well as its absolute configuration determined on the basis of an X-ray crystallographic analysis.



1: R = H
2: R = OH
3: R = OAc

Chart 1.

Results and Discussion

Optical Resolution of *anti* Head-to-Head Umbelliferone Dimer (2). We have reported that optically active *anti* head-to-head coumarin dimer (**1**) could be easily obtained by a diastereomeric separation of a couple of diastereomeric diamides prepared by the ring-opening addition reaction of (±)-**1** with (*S*)-$(-)_{589}$-1-phenylethylamine, followed by hydrolysis and relactonizaiton.[3)] Therefore, a similar strategy was considered to be effective for the resolution of (±)-*anti* head-to-head umbelliferone dimer (**2**). From a practical point of view, we used (±)-*anti* head-to-head 7-acetoxycoumarin dimer (**3**) as the starting material, since (±)-**3** can be easily obtained in large quantity by the cyclodimerization of 7-acetoxycoumarin.[9)]

Our first trial, resolution by using optically active 1-phenylethylamine, was, unfortunately, unsuccessful, since a pair of diastereomeric diamides had similar polarity and were thus not separable. A pair of diastereomeric diamides derived from (±)-**3** and optically active *erythro*-2-amino-1,2-diphenylethanol (**4**), however, were found to be separable. When (±)-**3** was allowed to react with two molar amounts of (1*R*,2*S*)-$(-)_{589}$-**4** in 1,4-dioxane at room temperature, a white precipitate was deposited. The precipitate comprised only one of a pair of diastereomeric diamides **5a** (72%), which was confirmed on the basis of an HPLC analysis, as well as ^{1}H NMR and IR spectral data. The residue, which was obtained upon concentration of the mother liquor, could be separated into **5a** and the other diastereomer **5b** by silica-gel column chromatography. In total, **5a** and **5b** were obtained in 96% yields, respectively.

The hydrolysis of each **5** in degassed 2-propanol/4 mol dm^{-3} hydrochloric acid under reflux proceeded smoothly to give a mixture of diacid, monoacid-monoester, and diester within 4 h. Upon heating the residue, obtained by concentrating the reaction mixture, in acetic acid under a nitrogen atmosphere, relac-

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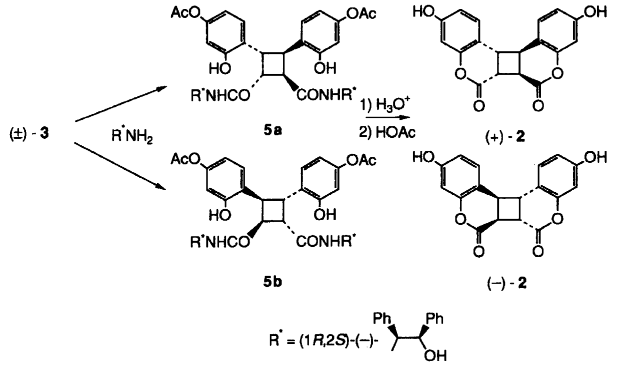
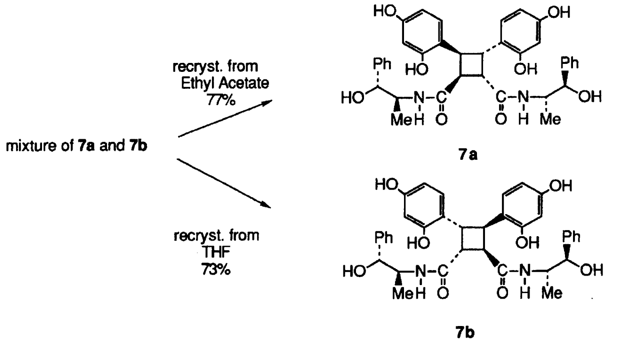
tonization took place to afford optically active **2** in about 95% yield. Recrystallization of the crude product from 2-propanol at a relatively low temperature gave the corresponding optically pure dimer; (+)$_{589}$-**2**·0.5H_2O (48%) from **5a** and (−)$_{589}$-**2**·0.5H_2O (49%) from **5b**. The purification could also be performed by silica-gel short column chromatography to give optically active **2** (90% yield), which was applicable as a starting material for organic and polymer syntheses (Scheme 1).

From the viewpoint of a large-scale synthesis, fractional crystallization is more desirable than chromatographic separation. However, it was hard to fractionally recrystallize not only **5b**, but also the diastereomeric diamides derived from (±)-**3** and optically active amine, such as norephedrine, (+)$_{589}$-*s*-butylamine, or (−)$_{589}$-1-(1-naphthyl)ethylamine. We thus tried to use (±)-**2** as a starting material. As a result, a pair of diastereomeric diamides derived from (±)-**2** and (1*R*,2*S*)-(−)$_{589}$-norephedrine (**6**) were found to be separable by fractional crystallization. One of the diastereomers **7a** was crystallized from ethyl acetate in 77% yield, and the other **7b** was crystallized from tetrahydrofuran (THF) in 73% yield. (Scheme 2); the former comprised (−)-**2** and (−)$_{589}$-**6**, and the latter did (+)-**2** and (−)$_{589}$-**6**, which were determined by comparison of their ^{1}H NMR spectral data with those of authentic samples synthesized independently. Although **7a** and **7b** were separated by crystallization, they were not easily separated on silica-gel thin layer chromatography.



Scheme 1.



Scheme 2.

The crystals of **7a** were found to include two molecules of ethyl acetate in an asymmetric unit on the basis of an X-ray crystal structure analysis.[10] However, the ethyl acetate molecules were completely removed from the crystal upon drying for 24 h at room temperature. This behavior suggests that the ethyl acetate molecules work as "crystallization templates". In contrast, the crystals of **7b** included an equimolar amount of THF, which was confirmed on the basis of the ^{1}H NMR spectrum, differential scanning calorimetry-thermogravimetry (DSC-TG), and elementary analysis. Although the THF molecule could not be removed at room temperature, it was eliminated upon drying in vacuo at 60°C for 24 h, meaning that **7b** formed a chrathlate with THF by a rather strong intermolecular interaction(s).

Absolute Configuration of (−)$_{589}$-2. In order to determine the absolute configuration of optically active **2**, we at first measured the circular dichroism (CD) spectrum of (−)$_{589}$-**2** (Fig. 1). However, no informative Cotton effect was unfortunately observed. We then performed an X-ray crystallographic analysis of the diamides derived from (−)$_{589}$-**2** and an optically active amine, whose absolute configuration was known, such as *erythro*-2-amino-1,2-diphenylethanol, norephedrine, 2-amino-1-propanol, 1-amino-2-propanol, *s*-butylamine, 2-(methoxymethyl)pyrrolidine, methyl 2-phenylglycinate, 1-phenylethylamine, 1-(4-nitrophenyl)ethylamine, 1-(4-chlorophenyl)ethylamine, 1-(4-bromophenyl)ethylamine, or 1-(1-naphthyl)ethylamine. Among the diastereomerically pure diamides that we prepared, diamide **8** derived from (−)$_{589}$-**2** and (*S*)-(−)$_{589}$-1-(1-naphthyl)ethylamine (**9**) gave single crystals which were satisfactory for X-ray crystallographic analysis. The crystals of **8** comprised equimolar amounts of diamide **8**, itself, ethyl acetate, and water, which was confirmed on the basis of the ^{1}H NMR spectrum, DSC-TG, and elementary analysis.

The crystal data and the final atomic parameters are

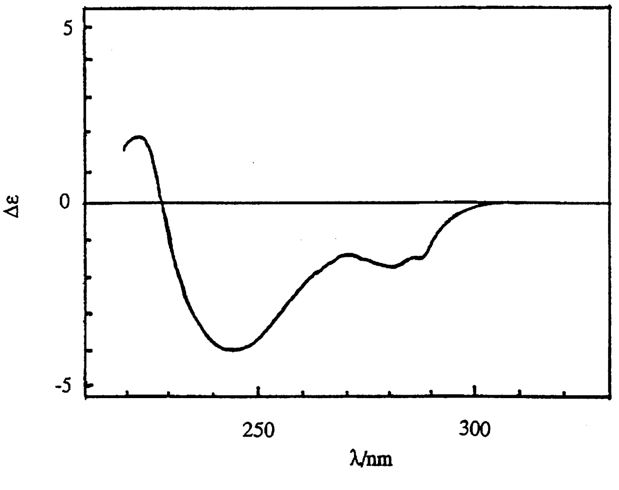


Fig. 1. CD spectrum of (−)-**2**·0.5H_2O in acetonitrile.

listed in Tables 1 and 2, respectively. The finally refined structure of **8** is shown in Fig. 2 with atom numbering. As shown in Fig. 3, the crystal water formed a hydrogen bond with *para*-phenolic hydroxyl O(33) in the same asymmetric unit and also formed a hydrogen bond with amide N(38) in the neighboring asymmetric unit. The ethyl acetate molecule was intercalated between two naphthalene rings of one diamide molecule, and its carbonyl oxygen, O(55) or O(61), hydrogen-bonded with *para*-phenolic hydroxyl O(25) in the neighboring asymmetric unit. As can be seen from Fig. 2, all of the configurations of the cyclobutane carbons of **8** are *S*. Thus, the absolute configuration of $(-)_{589}$-**2** is confirmed to be (1*S*,2*S*,3*S*,4*S*), which is in agreement with that of $(-)_{589}$-**1**.[3)]

Experimental

General. Melting and decomposition points were determined on the basis of DSC curves recorded on a Shimadzu DSC-50 instrument under a nitrogen stream at a heating rate of $10^\circ\mathrm{C\,min^{-1}}$ and are uncorrected. TG curves were recorded on a Shimadzu TGA-50 thermogravimetric analyzer. ^{1}H and ^{13}C NMR spectra were measured at 22—25°C using a JEOL GX-400 spectrometer (399.8 MHz for ^{1}H and 100.5 MHz for ^{13}C). Infrared spectra (KBr pellets) were measured with a JASCO IR-810 infrared spectrophotometer. Specific rotations were measured using a Jasco DIP-360 digital polarimeter at about 15°C in a 1-dm cell at a sample concentration of ca. 1.0—2.0 g $\mathrm{dl^{-1}}$. CD and UV spectra were measured in a 1.0-cm cell at room temperature at a concentration of ca. 10^{-4} $\mathrm{mol\,dm^{-3}}$ on a JASCO-500A spectropolarimeter and on a Shimadzu UV-260 spectrometer, respectively. The measurements were carried out just after the samples were dissolved completely; the CD data are given in $\mathrm{cm^2\,mmol^{-1}}$.

Materials. (±)-*anti* head-to-head umbelliferone dimer (**2**)[8)] and (±)-*anti* head-to-head 7-acetoxycoumarin dimer (**3**)[9)] were prepared by methods described in the literatures.

Table 1. Crystal Data

Compound	**8**·$CH_3COOC_2H_5\cdot H_2O$
Molecular formula	$C_{46}H_{48}N_2O_9$
Formula weight	772.9
Crystal size/mm^3	0.60×0.30×0.10
a/Å	12.178 (3)
b/Å	27.339 (5)
c/Å	11.995 (3)
Volume of unit cell/Å^3	3994 (1)
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Z value	4
$D_{\mathrm{calcd}}/\mathrm{g\,cm^{-3}}$	1.28
Reflections used	3258
No. of variables	698
R; R_{w}	0.049; 0.055
Goodness of fit	0.69
Maximum shift/esd in final cycle	0.06
Max. negative peak in final diff. map/e Å^{-3}	−0.23
Max. positive peak in final diff. map/e Å^{-3}	0.18

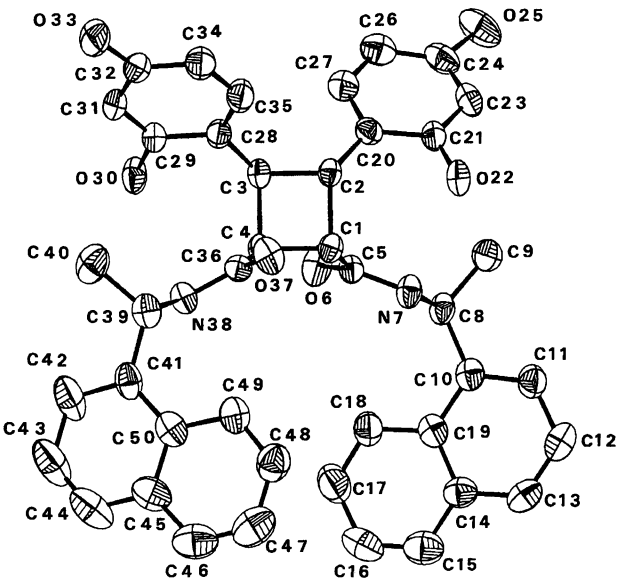


Fig. 2. ORTEP drawing of **8** with atom numbering. Ellipsoids are shown at 50% probability level.

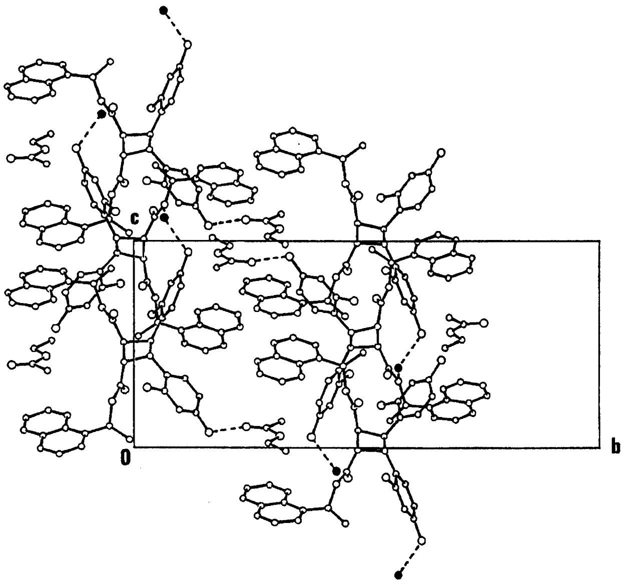


Fig. 3. Crystal structure of **8**·$CH_3COOC_2H_5\cdot H_2O$ projected along the *a* axis. C57, C58, O59, C60, O61, and C62, which are attributable to the disordered ethyl acetate molecule, are omitted for clarity.

Table 2. Final Atomic Coordinates and Equivalent Isotropic Thermal Parameter $B_{eq}=4/3\Sigma\Sigma B_{ij}\boldsymbol{a}_i\cdot\boldsymbol{a}_j$ for Non-H Atoms

Atom	x	y	z	B_{eq}	Atom	x	y	z	B_{eq}
C1	−0.0420(2)	0.0209(1)	0.9135(2)	2.60(6)	C2	−0.0673(2)	−0.0344(1)	0.9422(2)	2.39(6)
C3	0.0385(2)	−0.0360(1)	1.0142(2)	2.62(6)	C4	0.0442(2)	0.0217(1)	1.0095(2)	2.52(6)
C5	0.0070(2)	0.0285(1)	0.7997(3)	2.60(7)	O6	0.1035(2)	0.0190(1)	0.7795(2)	4.19(7)
N7	−0.0627(2)	0.0458(1)	0.7234(2)	3.10(6)	C8	−0.0386(3)	0.0513(1)	0.6038(3)	3.14(8)
C9	−0.0930(4)	0.0096(1)	0.5392(3)	4.14(9)	C10	−0.0710(3)	0.1022(1)	0.5661(3)	3.21(8)
C11	−0.1627(3)	0.1096(1)	0.5036(3)	3.69(8)	C12	−0.1954(4)	0.1562(2)	0.4680(4)	4.4(1)
C13	−0.1329(4)	0.1958(2)	0.4940(4)	4.3(1)	C14	−0.0353(4)	0.1907(1)	0.5569(3)	3.74(9)
C15	0.0325(4)	0.2312(2)	0.5826(4)	4.9(1)	C16	0.1242(4)	0.2263(2)	0.6421(4)	5.5(1)
C17	0.1576(4)	0.1790(2)	0.6790(4)	5.3(1)	C18	0.0964(3)	0.1391(2)	0.6551(3)	4.03(9)
C19	−0.0035(3)	0.1432(1)	0.5934(3)	3.37(8)	C20	−0.0817(2)	−0.0707(1)	0.8495(3)	2.80(7)
C21	−0.1684(2)	−0.0660(1)	0.7733(3)	2.75(6)	O22	−0.2409(2)	−0.0285(1)	0.7908(2)	3.50(6)
C23	−0.1790(3)	−0.0979(1)	0.6839(3)	3.45(8)	C24	−0.1036(4)	−0.1349(1)	0.6697(3)	4.11(9)
O25	−0.1147(3)	−0.1631(1)	0.5744(3)	5.52(9)	C26	−0.0208(3)	−0.1425(1)	0.7481(4)	4.2(1)
C27	−0.0117(3)	−0.1104(1)	0.8348(3)	3.73(9)	C28	0.0383(3)	−0.0609(1)	1.1252(3)	2.78(7)
C29	0.1347(3)	−0.0600(1)	1.1898(3)	3.10(7)	O30	0.2233(2)	−0.0383(1)	1.1415(2)	3.75(6)
C31	0.1377(3)	−0.0801(1)	1.2942(3)	3.44(8)	C32	0.0442(3)	−0.1007(1)	1.3403(3)	3.59(8)
O33	0.0528(3)	−0.1186(1)	1.4469(2)	5.02(8)	C34	−0.0528(3)	−0.1018(1)	1.2799(3)	4.05(8)
C35	−0.0545(3)	−0.0822(1)	1.1738(3)	3.81(9)	C36	0.0062(2)	0.0447(1)	1.1156(3)	2.60(7)
O37	−0.0916(2)	0.0423(1)	1.1452(2)	3.73(6)	N38	0.0838(2)	0.0666(1)	1.1753(2)	2.87(6)
C39	0.0741(3)	0.0835(1)	1.2907(3)	3.44(8)	C40	0.1372(4)	0.0474(2)	1.3652(3)	4.8(1)
C41	0.1105(3)	0.1364(1)	1.3019(3)	3.65(8)	C42	0.2098(4)	0.1467(2)	1.3507(4)	5.7(1)
C43	0.2460(4)	0.1950(2)	1.3622(5)	6.6(2)	C44	0.1820(4)	0.2324(2)	1.3290(5)	6.4(2)
C45	0.0796(4)	0.2242(2)	1.2804(4)	4.6(1)	C46	0.0090(5)	0.2632(2)	1.2452(5)	6.0(1)
C47	−0.0879(5)	0.2546(2)	1.1962(5)	6.3(2)	C48	−0.1238(4)	0.2061(2)	1.1797(4)	4.9(1)
C49	−0.0610(3)	0.1678(2)	1.2132(3)	3.96(9)	C50	0.0431(3)	0.1754(1)	1.2645(3)	3.63(8)
C51	0.2188(5)	0.1720(2)	1.0165(6)	6.7(4)	C52	0.1329(5)	0.2092(2)	0.9773(6)	5.0(3)
O53	0.0373(5)	0.1840(2)	0.9412(6)	5.4(2)	C54	−0.0465(5)	0.2123(2)	0.9030(6)	6.2(4)
O55	−0.0450(5)	0.2565(2)	0.8972(6)	6.3(2)	C56	−0.1440(5)	0.1808(2)	0.8710(6)	8.1(6)
C57	0.8143(8)	0.1635(3)	0.8597(9)	11.0(7)	C58	0.9072(8)	0.2006(3)	0.8766(9)	8.1(6)
O59	0.9998(8)	0.1764(3)	0.9227(9)	7.1(3)	C60	1.0870(8)	0.2052(3)	0.9494(9)	7.8(6)
O61	1.0941(8)	0.2484(3)	0.9287(9)	11.1(4)	C62	1.1796(8)	0.1746(3)	0.9969(9)	9.1(6)
O63	0.1822(3)	−0.0661(2)	1.6127(4)	7.3(1)					

Crude **3** was purified by recrystallization from degassed acetic acid. All of the optically active amines were of commercial origin (*erythro*-2-amino-1,2-diphenylethanol (**4**) from Yamakawa Chemical Industrial Co., Ltd., norephedrine (**6**) and 1-(1-naphthyl)ethylamine (**9**) from Aldrich Chemical Company, Inc.) and were used without further purification. 1,4-Dioxane was dried with 4A molecular sieves.

Synthesis and Separation of Diastereomeric Diamides 5. A mixture of finely powdered (±)-**3** (2.86 g, 7.00 mmol) and $(-)_{589}$-**4** (2.99 g, 14.00 mmol) in 1,4-dioxane (23 ml) was stirred at room temperature. Upon being stirred for 5 min, the mixture became clear, and then a white precipitate gradually appeared. After being stirred for 24 h, the precipitate was collected by filtration and dried over P_2O_5 in vacuo at 50°C for 12 h to afford colorless needle **5a** (2.09 g, 72%). The filtrate was concentrated to dryness under reduced pressure. Separation of the residue by silica-gel column chromatography (eluent: dichloromethane/methanol =60/1 v/v at first, and then 20/1 v/v), followed by drying over P_2O_5 in vacuo at 50°C for 12 h, gave **5a** (0.71 g, 24%) and **5b** (2.80 g, 96%). In total, **5a** and **5b** were obtained in 96% yields, respectively.

Diastereomeric Diamide 5a (less polar diastereomer): Mp 228.8°C; $[\alpha]_D^{23}$ +49.5° (*c* 2.00, CH_2Cl_2); ^1HNMR (DMSO-d_6) $\delta=2.21$ (6H, s), 3.59 (2H, d, $J=9$ Hz), 4.32 (2H, t, $J=4$ Hz), 4.56 (2H, dd, $J=4$ and 8 Hz), 4.65 (2H, d, $J=9$ Hz), 5.04 (2H, d, $J=4$ Hz), 6.54 (2H, dd, $J=2$ and 8 Hz), 6.60 (2H, d, $J=2$ Hz), 6.78—6.83 (8H, m), 7.02—7.14 (14H, m), 7.86 (2H, d, $J=8$ Hz), and 9.85 (2H, s); ^{13}CNMR (DMSO-d_6) $\delta=24.86$, 42.29, 47.92, 63.13, 78.73, 112.18, 115.60, 127.79, 130.16, 130.32, 130.71, 130.82, 131.34, 131.96, 132.48, 142.63, 146.05, 153.62, 159.67, 173.02, and 174.33; IR (KBr) 3650—3000, 1635, 1510, 1420, 1365, 1210, 1150, 970, and 700 cm^{-1}.

Found: C, 70.31; H, 5.48; N, 3.31%. Calcd for $C_{50}H_{46}N_2O_{10}\cdot H_2O$: C, 70.41; H, 5.67; N, 3.28%.

Diastereomeric Diamide 5b (more polar diastereomer): Mp 217.7°C; $[\alpha]_D^{23}$ −78.7° (*c* 2.00, CH_2Cl_2); ^1HNMR (DMSO-d_6) $\delta=2.20$ (6H, s), 3.41 (2H, dd, $J=2$ and 7 Hz), 4.33 (2H, dd, $J=2$ and 7 Hz), 4.41 (4H, m), 5.46 (2H, d, $J=4$ Hz), 6.16 (2H, dd, $J=2$ and 8 Hz), 6.43 (2H, d, $J=2$ Hz), 6.63 (6H, dd, $J=8$ and 14 Hz), 6.95—7.05 (6H, m), 7.14—7.25 (10H, m), 7.44 (2H, d, $J=8$ Hz) and 9.86 (2H, s); ^{13}CNMR (DMSO-d_6) $\delta=24.86$, 42.32, 47.97, 62.54, 78.83, 112.12, 115.46, 127.32, 129.93, 130.52, 130.85, 130.95, 131.47, 131.82, 143.16, 146.54, 153.46, 159.30, 172.82, and 174.07; IR (KBr) 3650—3000, 1735, 1635, 1510, 1425, 1370, 1210, 1150, 1075, 970, and 700 cm^{-1}.

Found: C, 71.63; H, 5.79; N, 3.39%. Calcd for $C_{50}H_{46}N_2O_{10}$: C, 71.93, H, 5.55; N, 3.36%.

Synthesis of Optically Pure 2. A suspension of **5a** (6.68 g, 8.00 mmol) in a mixture of 2-propanol (250 ml) and 4 mol dm^{-3} hydrochloric acid (250 ml) was refluxed for 4 h under a nitrogen atmosphere to give a clear solution. After concentration, saturated aqueous sodium hydrogencarbonate (350 ml) was added to the residue, and the aqueous solution was extracted with dichloromethane (3×300 ml) in order to remove $(-)_{589}$-**4**. The aqueous layer was carefully neutralized with concentrated hydrochloric acid and extracted with ethyl acetate (3×300 ml). The extracts were combined, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. To the remaining solid mass were added acetic acid (40 ml) and benzene (40 ml); the solution was then refluxed under a nitrogen stream for 30 h. Evaporation of the solvents to dryness gave 2.41 g of solid mass. Recrystallization of the crude product (300 mg) from 2-propanol at ca. −20°C gave a colorless needle, which was found to be $(+)_{589}$-**2**$\cdot 0.5H_2O$ on the basis of its elementary analysis (144 mg, 48%).

In a similar manner, $(-)_{589}$-**2**$\cdot 0.5H_2O$ (49%) was obtained from **5b**.

Optically pure $(+)_{589}$-**2** and $(-)_{589}$-**2** were also obtained by short silica-gel column chromatography (eluent: degassed ethyl acetate) in 90% yields, respectively.

$(+)_{589}$-2·0.5H$_2$O: Decomp. temp ca. 250°C; $[\alpha]_D^{20}$ +35.0° (*c* 1.00, CH_3CN); ^{1}H NMR (DMSO-d_6) δ=3.63 (2H, d, J=8 Hz)), 3.83 (2H, d, J=8 Hz), 6.46 (2H, d, J=2 Hz), 6.63 (2H, dd, J=2 and 8 Hz), 7.14 (2H, d, J=8 Hz), and 9.83 (2H, s); ^{13}C NMR (DMSO-d_6) δ=38.82, 42.40, 103.39, 111.78, 112.69, 129.37, 151.29, 157.95, and 166.03; IR (KBr) 3650—3000, 1760, 1625, 1560, 1510, 1455, 1300, 1280, 1155, 1115, 840, 830, 810, and 795 cm^{-1}.

Found: C, 64.73; H, 3.78%. Calcd for $C_{18}H_{12}O_6\cdot 0.5H_2O$: C, 64.87, H, 3.93%.

$(-)_{589}$-2·0.5H$_2$O: Decomp. temp ca. 250°C; $[\alpha]_D^{27}$ −33.1° (*c* 1.00, CH_3CN); ^{1}H NMR (DMSO-d_6) δ=3.63 (2H, d, J=8 Hz)), 3.83 (2H, d, J=8 Hz), 6.46 (2H, d, J=2 Hz), 6.63 (2H, dd, J=2 and 8 Hz), 7.14 (2H, d, J=8 Hz), and 9.83 (2H, s); ^{13}C NMR (DMSO-d_6) δ=38.82, 42.40, 103.39, 111.78, 112.69, 129.37, 151.29, 157.95, and 166.03; IR (KBr) 3650—3000, 1760, 1625, 1560, 1510, 1455, 1300, 1280, 1155, 1115, 840, 830, 810, and 795 cm^{-1}.

Synthesis and Separation of Diastereomeric Diamides 7. A mixture of finely powdered (±)-**2** (2.00 g, 6.17 mmol) and $(-)_{589}$-**6** (1.87 g, 12.34 mmol) in 1,4-dioxane (400 ml) was heated for 10 min to give a clear solution; the solution was quickly cooled to room temperature and stirred at that temperature for 24 h. Then, silica gel (10.00 g) was added to the solution, and the suspension was concentrated to dryness under reduced pressure and washed with ethyl acetate (5×300 ml) on a glass filter. The filtrate was concentrated to about 500 ml to give a precipitate. Collection by filtration, followed by air-drying at room temperature for 0.5 h, afforded **7a**$\cdot 0.5CH_3COOEt\cdot 0.5H_2O$ (confirmed on the basis of the elementary analysis and ^{1}H NMR spectrum). Further drying at room temperature for 24 h gave **7a** (1.43 g, 77%) (confirmed on the basis of the ^{1}H NMR). The filtrate for crystallization of **7a**$\cdot 0.5CH_3COOEt\cdot 0.5H_2O$ was concentrated to dryness under reduced pressure. Recrystallization of the residue from THF, followed by air-drying at room temperature for 24 h, gave **7b**·THF·$2H_2O$ (confirmed on the basis of the elementary analysis and ^{1}H NMR spectrum). Further drying in vacuo at 60°C for 24 h gave **7b** (1.35 g, 73%) (confirmed on the basis of the ^{1}H NMR).

Diastereomeric Diamide 7a·0.5CH$_3$COOEt·0.5H$_2$O (consisting of $(-)_{589}$-2 and $(-)_{589}$-6): DSC-TG 59.3°C (*endo*) with 5.6% weight loss, 100.0°C (*endo*), 175.4°C (*endo*), and 202.9°C (*endo*); $[\alpha]_D^{26}$ −92.3° (*c* 1.00, C_2H_5OH); ^{1}H NMR (DMSO-d_6) δ=0.38 (6H, d, J=7 Hz), 3.46 (2H, pseudo d, J=7 Hz), 3.68—3.71 (2H, m), 4.33 (2H, pseudo d, J=7 Hz), 4.48 (2H, s), 5.33 (2H, d, J=4 Hz), 6.03 (2H, dd, J=2 and 9 Hz), 6.27 (2H, d, J=2 Hz), 6.64 (2H, d, J=9 Hz), 6.73 (2H, d, J=9 Hz), 7.18—7.31 (10H, m), 8.93 (2H, s), and 9.42 (2H, s); ^{13}C NMR (DMSO-d_6) δ=13.26, 38.29, 43.24, 49.93, 74.32, 102.15, 105.63, 116.90, 126.00, 126.70, 127.82, 143.26, 155.78, 156.65, and 170.56. IR (KBr) 3650—3000, 2975, 1620, 1520, 1450, 1300, 1160, 970, 840, 755, and 700 cm^{-1}.

Found: C, 66.96; H, 6.40; N, 4.42%. Calcd for $C_{36}H_{38}N_2O_8\cdot 0.5C_4H_8O_2\cdot 0.5H_2O$: C, 67.14; H, 6.38; N, 4.12%.

Diastereomeric Diamide 7b·THF·2H$_2$O (consisting of $(+)_{589}$-2 and $(-)_{589}$-6): DSC-TG 120.4°C (*endo*) with 13.7% weight loss, 163.8°C (*endo*), 180.7°C (*exo*), and 250.4°C (*endo*); $[\alpha]_D^{25}$ +115.7° (*c* 1.00, C_2H_5OH); ^{1}H NMR (DMSO-d_6) δ=0.70 (6H, d, J=7 Hz), 3.49 (2H, pseudo d, J=7 Hz), 3.62 (2H, m), 4.13 (2H, s), 4.54 (2H, pseudo d, J=7 Hz), 4.69 (2H, d, J=4 Hz). 6.13 (2H, d, J=8 Hz), 6.28 (2H, d, J=8 Hz), 6.88 (2H, d, J=8 Hz), 7.11 (4H, d, J=8 Hz), 7.17—7.20 (4H, m), 7.28 (4H, t, J=8 Hz), 8.94 (2H, s), and 9.25 (2H, s); ^{13}C NMR (DMSO-d_6) δ=12.61, 38.10, 43.93, 50.87, 74.44, 101.92, 105.54, 117.08, 125.77, 126.57, 127.79, 128.35, 142.81, 155.85, 156.67, and 171.35; IR (KBr) 3650—3000, 2970, 1620, 1605, 1520, 1450, 1130, 970, 825, 745, and 700 cm^{-1}.

Found: C, 65.02; H, 6.64; N, 3.89%. Calcd for $C_{36}H_{38}N_2O_6\cdot THF\cdot 2H_2O$: C, 65.37; H, 6.85; N, 3.81%.

Synthesis of Diastereomeric Diamide 8. To a solution of (−)-**2**$\cdot 0.5H_2O$ (100 mg, 0.30 mmol) in THF (15 ml) was added (*S*)-(−)-**9** (123 mg, 0.72 mmol). After being stirred for 3 h at room temperature under an argon atmosphere, the reaction mixture was added drop by drop to hexane (500 ml). The precipitate which appeared was collected by filtration and purified by silica-gel column chromatography (eluent: ethyl acetate). Recrystallization of the crude product from ethyl acetate, followed by air-drying at room temperature for 24 h, afforded **8**$\cdot CH_3COOC_2H_5\cdot H_2O$ (144 mg, 63%).

DSC-TG 142.0°C (*endo*) with 7.8% weight loss, and 166.6°C (*endo*). $[\alpha]_D^{24}$ −113.0° (*c* 1.00, C_2H_5OH); ^{1}H NMR (DMSO-d_6) δ=0.99 (6H, d, J=7 Hz), 1.17 (3H, t, J=7 Hz, ethyl acetate), 1.99 (3H, s, ethyl acetate), 3.56 (2H, pseudo dd, J=1 and 8 Hz), 4.02 (2H, q, J=7 Hz, ethyl acetate), 4.49 (2H, pseudo dd, J=1 and 8 Hz), 5.42 (2H, t, J=7 Hz), 6.16 (2H, dd, J=2 and 8 Hz), 6.32 (2H, d, J=2 Hz), 6.84 (4H, d, J=8 Hz), 7.42 (4H, m), 7.49 (4H, t, J=7 Hz), 7.57 (2H, d, J=8 Hz), 7.76 (2H, dd, J=1 and 7 Hz), 7.89 (2H, dd, J=1 and 7 Hz), 8.00 (2H, d, J=8 Hz), 9.03 (2H, s) and 9.41 (2H, s); ^{13}C NMR (DMSO-d_6) δ=14.10 (ethyl acetate), 20.78 (ethyl acetate), 21.25, 38.47, 43.39, 43.81, 59.79 (ethyl acetate), 102.09, 105.74, 117.17, 122.56, 123.07, 125.50, 125.52, 126.12, 127.11, 128.28, 128.62, 130.25, 133.29, 140.23, 155.92, 156.72, 170.38 (ethyl acetate), and 170.64; IR (KBr) 3650—3000, 2950, 1710, 1630, 1610, 1525, 1455, 1380, 1305, 1160, 1130, 970, 845, 800, and 770 cm^{-1}. Found: C, 71.04; H, 6.35; N, 3.64%. Calcd for $C_{42}H_{38}N_2O_6 \cdot C_4H_8O_2 \cdot H_2O$: C, 71.49; H, 6.26; N, 3.62%.

X-Ray Crystal Structure Determination. Colorless plate-shaped crystals of **8** were grown from an ethyl-acetate solution by slow evaporation at room temperature. The crystal data are listed in Table 1. The specimen used for the X-ray crystallographic analysis was a fragment of a plate (0.60×0.30×0.10 mm) of $\mathbf{8} \cdot C_4H_8O_2 \cdot H_2O$. The precise lattice constants and intensity data were derived from measurements on a Mac Science MXC18 diffractometer with graphitemonochromated CuKα radiation. All reflections within the range of $2\theta<130°$ were collected at room temperature using the ω–2θ scan mode with a constant scan rate of 12° min^{-1}, of which 3258 were greater than $3\sigma(|F_o|)$ and were used for the structure determination. No correction was made for absorption. The intensity of three standard reflections, (−4 −3 6), (4 15 0), and (4 −15 0), recorded every 100-measurement, showed no significant variation.

The structure was solved by the direct method[11)] and was refined by the full-matrix least-squares method.[12)] All of the non-hydrogen atoms were refined anisotropically. All of the hydrogen atoms were located in the calculated positions and were refined isotropically (U_{iso} of H(9C), H(34), H(43), H(44), H(51A), H(51C), H(52B), H(56A), H(56B), H(56C), H(57A), H(57B), H(57C), H(58B), H(62A), H(62B), H(62C), H(63A), and H(63B) were fixed at U_{iso} of the attached non-hydrogen atoms). There appeared to be two regions in an asymmetric unit which were occupied by water and disordered ethyl acetate. The ethyl acetate molecule was treated as being a rigid group, and the occupancy factors were fixed at 0.5 : 0.5. Final $R=0.049$; $R_w=0.055$, $w=1/(\sigma^2(F)+0.008863|F_o|^2)$. The highest and lowest peaks in the final ΔF map were 0.18 and −0.23 e Å^{-3}, respectively. The atomic scattering factors were taken from Internationl Tables for X-Ray Crystallography (1974). The final atomic coordinates for **8** are given in Table 2. Absolute configuration of 1-(1-naphthyl)ethylamine is known.[13)]

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