Facile Optical Resolution of a Dibenzopyrazinoazepine Derivative and the Nature of Molecular Recognition of Amines by Chiral 2,3-Di-*O*-(arylcarbonyl)tartaric Acids

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A facile optical resolution of recemic 1,2,3,4,10,14b-hexahydrodibenzo[*c*,*f*]pyrazino[1,2-*a*]azepine (**1**) was developed using 2,3-di-*O*-benzoyl-D-(−)-tartaric acid ((+)-DBT) as a resolving agent. The resolution efficiency depends remarkably on the (+)-DBT : **1** ratio. When (+)-DBT and recemic **1** were mixed in methanol–water (9 : 1 v/v) in a 1 : 4 stoichiometry, a crystalline salt consisting of (+)-DBT, (*R*)-**1**, methanol, and water in a 1 : 2 : 2 : 2 ratio crystallized preferentially in a fair yield. X-Ray crystallographic analysis showed its highly ordered supramolecular structure: (+)-DBT molecules self-assemble via hydrogen bonding with the aid of water and methanol to form a puckered layer, and stacking of (*R*)-**1** molecules constructs a column which is sandwiched in between the puckered layers. The X-ray crystallographic data reported for the salts that consist of amines and DBT were reinvestigated to reveal that most of the host frameworks derived from DBT have a layer structure similar to the above puckered one.

Since the optical resolution using fractional crystallization was developed by Louis Pasteur in 1853,[1] this has been widely employed for preparing chiral compounds,[2] and a vast number of useful resolving agents are now available.[2] One of them is chiral 2,3-di-*O*-benzoyltataric acid (DBT). It is commercially available in both enantiomer forms and is useful for resolving not only amines,[3] but also phosphine oxides.[4,5] It should be noted that crystalline salts of DBT and amines have been of current interest in the field of materials science because of their potential utility as an organic nonlinear optical material.[6]

Here we report a practical optical resolution of racemic 1, 2,3,4,10,14b-hexahydrodibenzo[*c*,*f*]pyrazino[1,2-*a*]azepine (**1**), a key synthetic intermediate of biologically active compounds with antiallergic and antihistaminic activities.[7—9] In order to elucidate the driving force for the optical resolution using optically active DBT, the crystal structure of the least-soluble salt consisting of (+)-DBT and (*R*)-**1** was studied by X-ray crystallography. In addition, we reinvestigated the X-ray crystallographic data reported for fifteen amine salts of DBT and closely related 2,3-di-*O*-(*p*-toluoyl)tartaric acid (DTT)[10] to understand why these acids can accommodate numerous amine compounds in co-crystallization with high levels of enantiopreference.

Results and Discussion

Optical Resolution of Racemic 1. Since DBT is well known to form stoichiomerically different salts, normally 1 : 1 and 1 : 2 salts, with an amine,[11] at least two pairs of diastereomeric salts are possible for a combination of (+)-DBT and racemic **1**: (+)-DBT·(*R*)-**1** (hereafter abbreviated to salt $\mathbf{R_{11}}$) and (+)-DBT·(*S*)-**1** (salt $\mathbf{S_{11}}$) as 1 : 1 salts; (+)-DBT·2(*R*)-**1** (salt $\mathbf{R_{12}}$) and (+)-DBT·2(*S*)-**1** (salt $\mathbf{S_{12}}$) as 1 : 2 salts (Chart 1). Prior to the optical resolution, we prepared all of these salts by the use of enantiomerically pure **1** to characterize their physical properties.

When (+)-DBT·H_2O and (*R*)-**1** were mixed in a 1 : 2 ratio in methanol, the 1 : 2 salt ($\mathbf{R_{12}}$) was precipitated as an amorphous solid with mp 187—193 °C (decomp). Under the similar conditions, (*S*)-**1** afforded the 1 : 2 salt ($\mathbf{S_{12}}$) with mp 170—172 °C (decomp), which is gelatinous in methanol. On the other hand, a rapid contact of (*R*)-**1** with 1.2 molar amount of (+)-DBT·H_2O at room temperature deposited the 1 : 1 salt ($\mathbf{R_{11}}$) with mp 160—162 °C. In contrast, when (*S*)-**1** was mixed with an equimolar amount of (+)-DBT·H_2O, the 1 : 1 salt ($\mathbf{S_{11}}$) did not crystallize even after evaporation of the solvent.

The physical properties of these salts are listed in Table 1, which shows a significant difference in their solubility.

Since recrystallization of the 1 : 1 salt ($\mathbf{R_{11}}$) from hot methanol afforded the 1 : 2 salt ($\mathbf{R_{12}}$), it is easily predictable that $\mathbf{R_{12}}$ precipitates preferentially from a 1 : 4 mixture of (+)-DBT and racemic **1** to render (*S*)-**1** free. At a 1 : 1 ratio of (+)-DBT and racemic **1**, the salt $\mathbf{R_{11}}$ is also expected to crystallize dominantly.

With these inferences, the optical resolution of racemic **1** was performed with varying the ratio of (+)-DBT : **1**. To a refluxing solution of racemic **1** (2.5 g, 10 mmol) in methanol

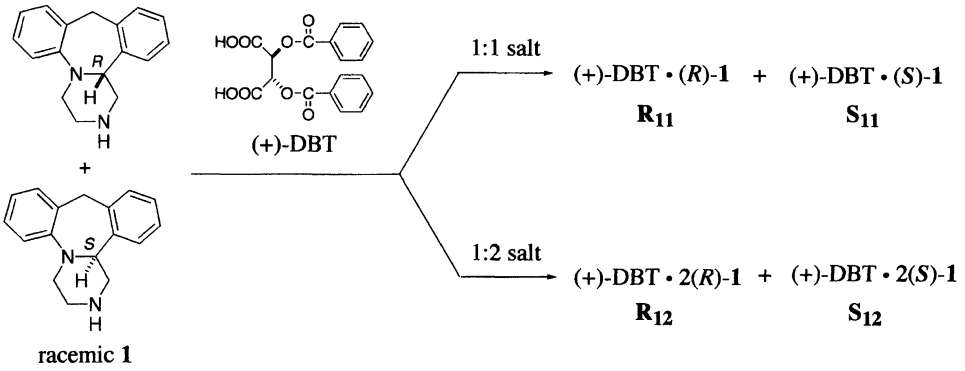

Chart 1.

Table 1. Physical Properties of the Salts $\mathbf{R_{11}}$, $\mathbf{S_{11}}$, $\mathbf{R_{12}}$, and $\mathbf{S_{12}}$

	Salt			
	$\mathbf{R_{11}}$	$\mathbf{S_{11}}$	$\mathbf{R_{12}}$	$\mathbf{S_{12}}$
Mp/°C	160–162	An oil	187–193 (decomp)	170–172 (decomp)
$[\alpha]_D^{22}$(DMF)/°	−191	–[b]	−270	+292
Solubility[a]	7	Freely soluble	4	33

a) In methanol at 25 °C (g dm^{-3}). b) Not measured.

(44 ml) was added a solution of (+)-DBT·H_2O (2.5, 5.0, 7.5, or 10 mmol) in methanol (6 ml), and the resulting suspension was gently refluxed for 30 min. After the mixture was gradually cooled to 20 °C, the precipitated salt was collected by filtration and dried in vacuo. The enantiomeric excess of **1** in the salt was determined by HPLC equipped with a chiral stationary phase column after decomposition with aqueous NaOH. Table 2 summarizes the results. Although a 1 : 2 ratio resulted in a low selectivity (27%ee), the 1 : 4 and 3 : 4 ratios dramatically improved the efficiency to furnish the salt $\mathbf{R_{12}}$ with > 99%ee of (*R*)-**1** in 26 and 30% yields, respectively. The latter case may be explained in terms of easy crystallization of insoluble $\mathbf{R_{12}}$ and remaining of soluble $\mathbf{S_{11}}$ in solution. At the 1 : 1 ratio, the salt $\mathbf{R_{11}}$ with 89%ee of (*R*)-**1** was given in a 25% yield. From these results and the economical point of view, the best molar ratio of (+)-DBT to racemic **1** is 1 : 4.

In order to obtain the crystals of good quality for the salt of (+)-DBT and (*R*)-**1**, various solvent systems had been surveyed and, with effort, we selected a mixed solvent of methanol–water (9 : 1 v/v) which afforded a new crystalline salt ($\mathbf{T_{12}}$). A single crystal X-ray analysis of this salt revealed that it consists of (+)-DBT, (*R*)-**1**, methanol, and water in a ratio of 1 : 2 : 2 : 2. These crystals were so unstable as to gradually become opaque in air. After being dried in vacuo at room temperature, the resulting crystals were shown by elemental analysis to release one water and two methanol molecules and become new crystals ($\mathbf{U_{12}}$) that consist of (+)-DBT, (*R*)-**1**, and water in a ratio of 1 : 2 : 1. Regrettably the single crystal suitable for X-ray crystallography has not been obtained for $\mathbf{U_{12}}$. Therefore the crystal structure of $\mathbf{U_{12}}$ was not revealed, but the crystal lattice seems to remain without large change during this transformation, because the powder X-ray diffraction pattern of $\mathbf{U_{12}}$ resembles that of $\mathbf{T_{12}}$ (Fig. 1).

The crystals of $\mathbf{U_{12}}$ exhibit a higher melting point (190—196 °C) and a lower solubility in MeOH (3 g dm^{-3} at 25 °C). These properties are desirable for the fractional crystallization.

In the present optical resolution using (+)-DBT, its essential amount is half as much as that of (*R*)-**1**, no matter how much (*S*)-**1** exists. This allowed a convenient two-step resolution procedure: the removal of (*S*)-**1** with 0.5 molar amount of (−)-DBT (based on (*S*)-**1**) followed by the fractional crystallization of $\mathbf{U_{12}}$ from the resulting (*R*)-enriched **1** with 0.5 molar amount of (+)-DBT (based on (*R*)-**1**). This procedure is efficient and suitable for a large-scale produc-

Table 2. Optical Resolution of Racemic **1** with (+)-DBT[a]

		Salt		
(+)-DBT/mmol	((+)-DBT : **1**)		Yield/%	ee of (*R*)-**1**/%
2.5	(1 : 4)	$\mathbf{R_{12}}$	26	>99
5.0	(1 : 2)	$\mathbf{R_{12}}$+$\mathbf{S_{12}}$	64	27
7.5	(3 : 4)	$\mathbf{R_{12}}$	30	>99
10	(1 : 1)	$\mathbf{R_{11}}$	25	89

a) A solution of racemic **1** (10 mmol) in methanol (50 ml) was used.

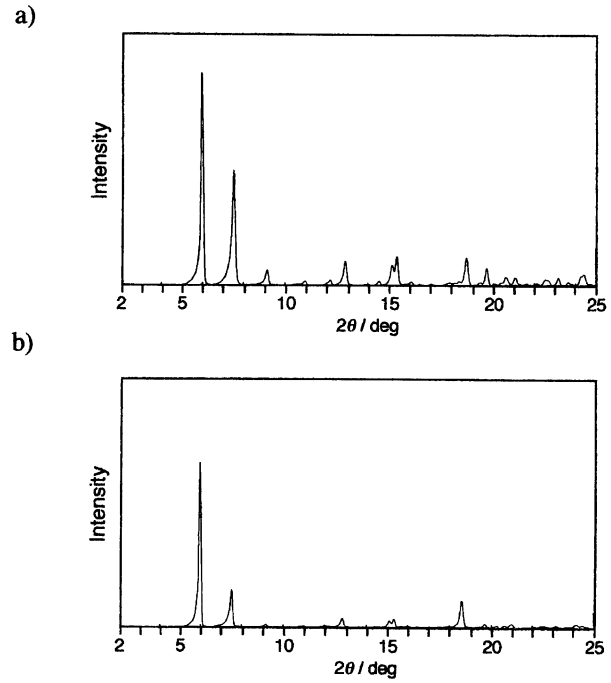

Fig. 1. Powder X-ray diffraction patterns for the salts $\mathbf{T_{12}}$ (a) and $\mathbf{U_{12}}$ (b).

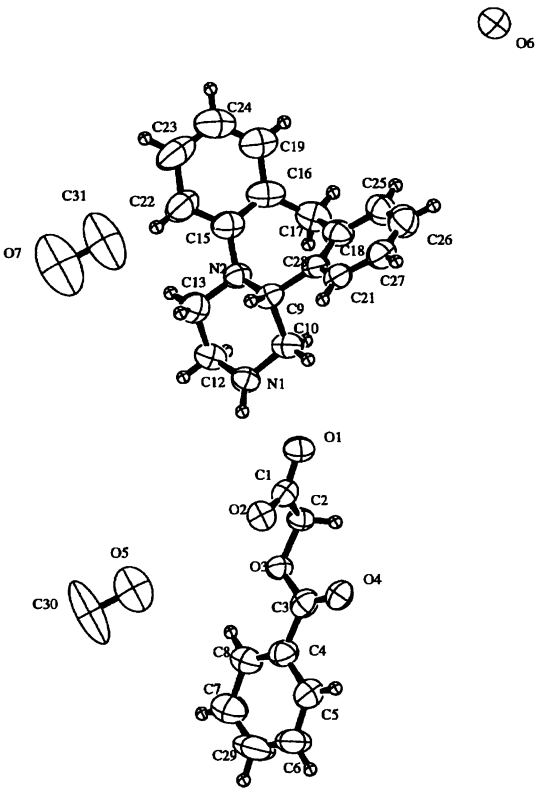

Fig. 2. ORTEP drawing of $\mathbf{T_{12}}$ with atomic numbering scheme. The occupancy factor for O(5), O(7), C(30), and C(31) atoms is 0.5.

tion of (*R*)-**1**. A typical procedure is as follows. Treatment of racemic **1** (100 g, 0.40 mol) with (−)-DBT·H_2O (0.1 mol) in MeOH–water (9 : 1 v/v) gave (−)-DBT·2(*S*)-**1**·H_2O (59.2 g, 34%), the enantiomer of $\mathbf{U_{12}}$, together with (*R*)-enriched **1** (66.4 g, 36%ee) which was recovered from the mother liquor. The latter was treated with (+)-DBT·H_2O (0.1

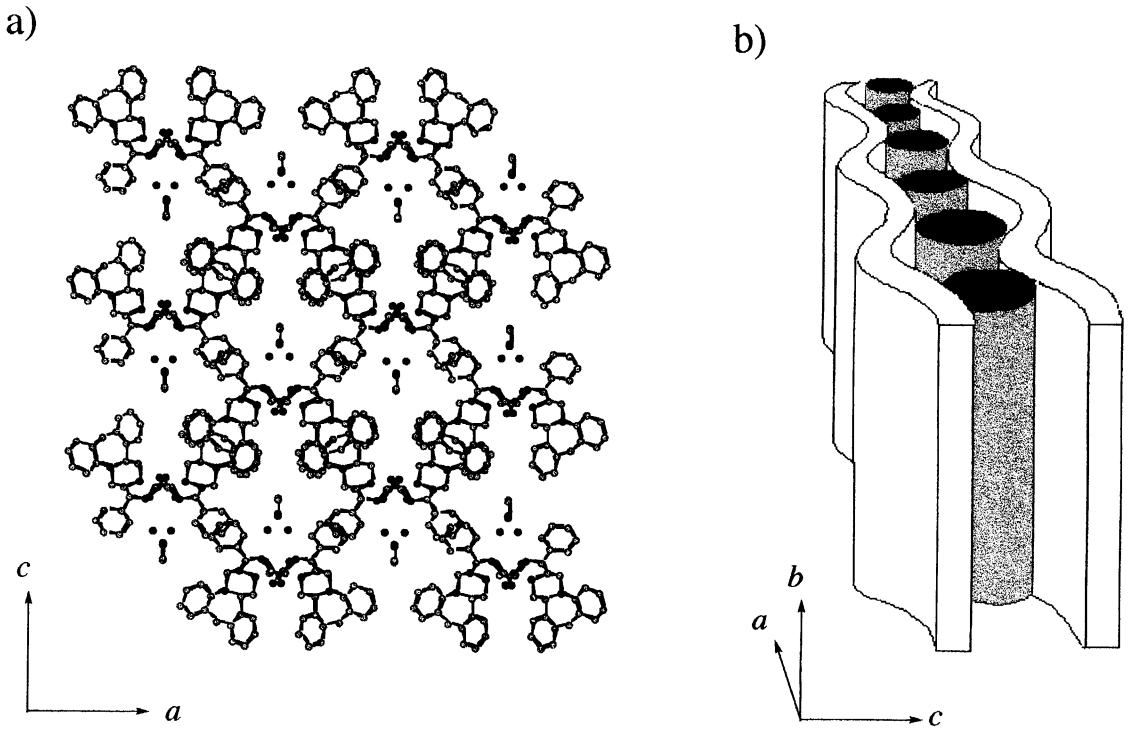

Fig. 3. (a) X-Ray crystal structure of $\mathbf{T_{12}}$ (down the *b* axis). All hydrogen atoms are omitted for clarity, unless otherwise noted. (b) Schematic representation of the crystal structure.

Table 3. Crystal Data and Details of Data Collection of $\mathbf{T_{12}}$

Empirical formula	$C_{28}H_{31}N_2O_6$
Formula weight	479.55
Crystal system	Orthorhombic
Space group	$P2_12_12$ (#18)
Lattice parameters	
a/Å	19.22(1)
b/Å	9.211(1)
c/Å	14.522(3)
$\alpha=\beta=\gamma$/°	90
V_{calcd}/Å^3	2570(3)
Z	4
D_{calcd}/g cm^{-3}	1.239
Crystal size/mm^3	$0.48\times0.30\times0.18$
$F(0\,0\,0)$	958
Diffractometer	Rigaku Raxis II
Radiation	Mo $K\alpha$
μ/cm^{-1}	0.88
T/K	173(1)
No. of collected reflections	1650
Structure solution	SHELXS 86[a]
Refinement	Full-matrix least-squares
Least-squares weigh	$[\sigma_c^2(F_o)+(p^2/4)F_o^2]^{-1}$
p-factor	0.01
No. of observations[b]	1360
No. of variables	414
Residuals R;R_w	0.068;0.067
Goodness of fit indicator	2.87
Max Shift/Error	2.24
$\Delta\rho_{max};\Delta\rho_{min}$/e$^-$Å^{-3}	0.29;−0.40

a) Direct method, see Ref. 22. b) $I>4.00\sigma(I)$.

mol) in MeOH–water (9 : 1 v/v) to give $\mathbf{U_{12}}$ (75.2 g, 43%). Decomposition with aqueous $NaHCO_3$ followed by recrystallization from toluene–isopropyl ether (1 : 3 v/v) afforded enantiomerically pure (*R*)-**1** (40.3 g) in 40% overall yield from racemic **1**.

Crystal Structure of the 1 : 2 : 2 : 2 Salt ($\mathbf{T_{12}}$) of (+)-DBT, (*R*)-1, Methanol, and Water. The single crystal of $\mathbf{T_{12}}$ suitable for X-ray crystallography was obtained by the recrystallization of $\mathbf{U_{12}}$ from methanol–water (9 : 1 v/v). It was mounted in a glass capillary and measured at −100 °C. Crystal data and details of data collection are summarized in Table 3. Table 4 lists atomic coordinates and equivalent isotropic thermal parameters (B_{eq}).[12] Selected nonbonded intermolecular contacts are given in Table 5. An ORTEP[13] drawing of the crystal with atom numbering scheme is shown in Fig. 2.

Figure 3 depicts the X-ray crystal structure of $\mathbf{T_{12}}$ (along the *b* axis), exhibiting an aesthetically beautiful, highly-organized supramolecular structure: (+)-DBT molecules self-assemble to construct a unique, puckered sheet; (*R*)-**1** molecules stack over each other to form a column structure which is sandwiched in between the puckered sheets of (+)-DBT molecules as illustrated in Fig. 3b. The top view (a), the side view (b), and the front view (c) of the (+)-DBT sheet are given in Fig. 4.

Like the most stable conformation of tartaric acid diacyl derivatives,[14] two carboxylate groups in (+)-DBT point in opposite directions (*anti* conformation) and two benzoyloxy groups are located in *gauche* conformation.[15] The carboxylate O(2) atom forms a hydrogen bond with water (O(2)····O-

Table 4. Atomic Coordinates and Equivalent Isotropic Thermal Parameters (B_{eq}) with esd's in Parentheses

Atoms	x	y	z	B_{eq}[a]
O1	0.5150(3)	0.2522(5)	0.3056(4)	4.8(1)
O2	0.4455(3)	0.2771(5)	0.1832(4)	4.6(1)
O3	0.4264(2)	−0.0144(5)	0.1709(3)	3.9(1)
O4	0.3297(3)	0.0504(6)	0.2446(4)	5.4(2)
O5	0.5000	0.0000	−0.0886(8)	9.4(3)[b]
O6	0.9586(3)	0.2510(8)	1.0063(4)	6.9(2)
O7	1.0000	0.0000	0.081(1)	15.0(6)[b]
N1	0.5985(3)	0.4795(7)	0.2770(5)	4.4(2)
N2	0.7263(3)	0.5770(6)	0.3548(4)	4.3(2)
C1	0.4757(4)	0.2055(8)	0.2435(7)	4.1(2)
C2	0.4654(3)	0.0391(7)	0.2482(6)	3.7(2)
C3	0.3573(4)	−0.0074(9)	0.1803(7)	4.7(2)
C4	0.3213(4)	−0.0840(8)	0.1036(7)	4.8(2)
C5	0.2478(5)	−0.084(1)	0.1096(7)	6.2(3)
C6	0.2114(6)	−0.159(1)	0.0428(9)	7.1(3)
C7	0.3177(7)	−0.224(1)	−0.0326(8)	8.2(3)
C8	0.3539(7)	−0.151(1)	0.0370(7)	6.1(3)
C9	0.6610(4)	0.6380(8)	0.3883(6)	4.0(2)
C10	0.6055(5)	0.524(1)	0.3760(7)	4.7(2)
C12	0.6672(5)	0.4314(10)	0.2402(9)	5.1(3)
C13	0.7192(5)	0.553(1)	0.2547(7)	5.5(3)
C15	0.7889(4)	0.6433(9)	0.3832(7)	5.3(2)
C16	0.8104(4)	0.6120(9)	0.4733(8)	5.7(3)
C17	0.7640(5)	0.5285(10)	0.5330(7)	5.7(3)
C18	0.7021(4)	0.6212(8)	0.5582(7)	5.1(2)
C19	0.8730(5)	0.666(1)	0.5054(9)	6.3(3)
C21	0.6075(4)	0.7749(9)	0.5164(7)	4.6(2)
C22	0.8299(5)	0.726(1)	0.3230(10)	6.8(3)
C23	0.8951(6)	0.776(1)	0.359(1)	8.4(4)
C24	0.9137(6)	0.746(1)	0.450(1)	7.7(4)
C25	0.6929(5)	0.6636(10)	0.6495(8)	5.7(3)
C26	0.6409(5)	0.756(1)	0.6743(7)	6.4(3)
C27	0.5974(5)	0.8157(9)	0.6079(8)	5.3(2)
C28	0.6590(4)	0.6797(8)	0.4905(6)	4.2(2)
C29	0.2471(8)	−0.226(1)	−0.027(1)	8.7(4)
C30	0.5000	0.0000	−0.181(1)	14.2(8)[b]
C31	1.0000	0.0000	0.175(2)	13.8(8)[b]
H2	0.16(1)	−0.16(2)	0.05(1)	21(1)
H17	0.617(3)	0.441(6)	0.412(4)	1(1)

a) $B_{eq}=(4/3)\sum_i\sum_j\beta_{ij}\boldsymbol{a}_i\cdot\boldsymbol{a}_j$. b) Occupancy factor for these atoms is 0.5.

Table 5. Selected Nonbonded Intermolecular Contacts in $\mathbf{T_{12}}$ (esd's, where given, are in parentheses)

Atoms	Symmetry	Distance/Å
O(1)···N(1)	x,y,z	2.670(8)
O(2)···N(1)	$1-x,\ 1-y,z$	2.756(8)
O(2)···O(6)	$-1/2+x,\ 1/2-y,\ 1-z$	2.775(9)
O(5)···O(6)	$3/2-x,-1/2+y,1-z$	2.706(9)
O(6)···O(7)	$x,y,\ 1+z$	2.674(10)
O(6)···H(2)–C(6)	$1-x,\ -y,\ 1+z$	2.51
C(10)–H(17)···C(24)	$3/2-x,\ -1/2+y,\ 1-z$	2.76

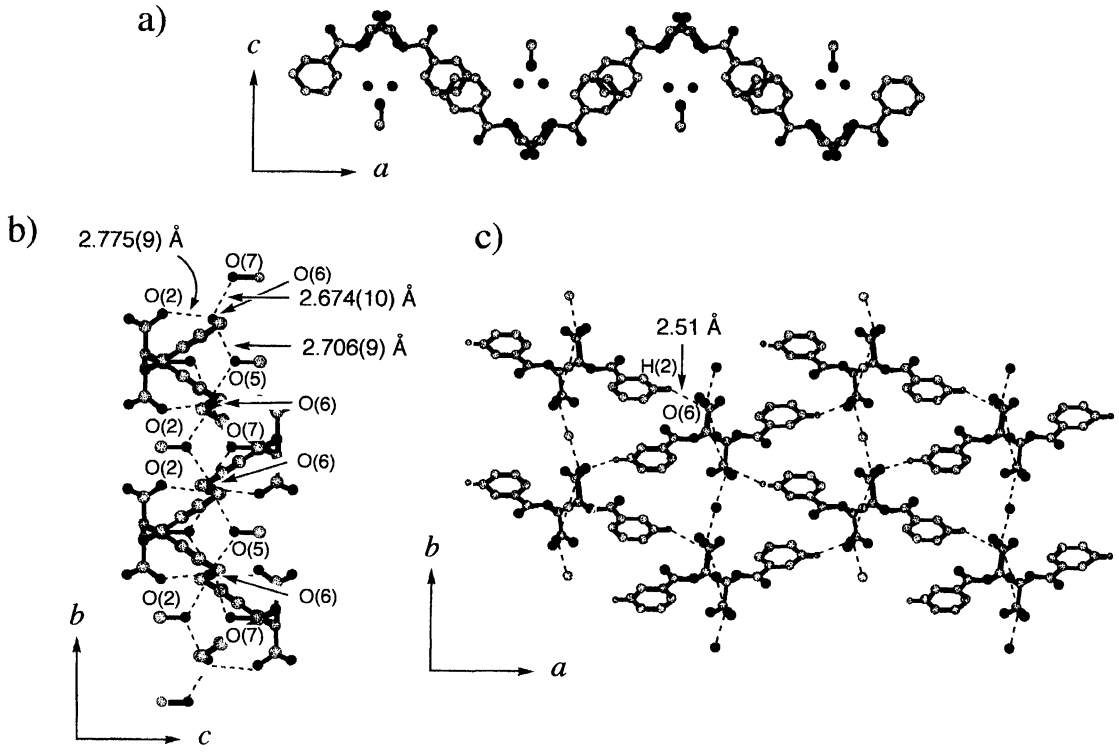

Fig. 4. Sheet structure of (+)-DBT·2MeOH·2H_2O. (a) Top view down the *b* axis. (b) Side view down the *a* axis. (c) Front view down the *c* axis (only H(2) atoms are shown).

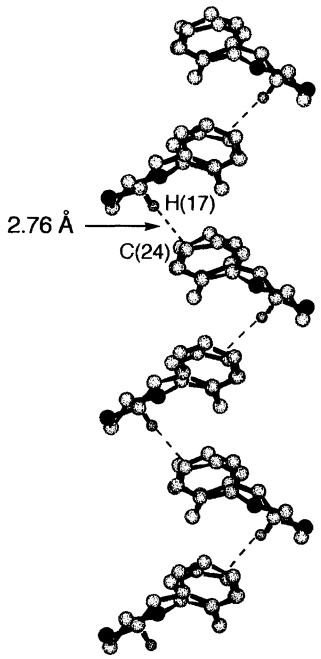

Fig. 5. Column structure of (*R*)-**1** molecules. Dotted lines refer to CH-π interactions (only H(17) atoms are shown).

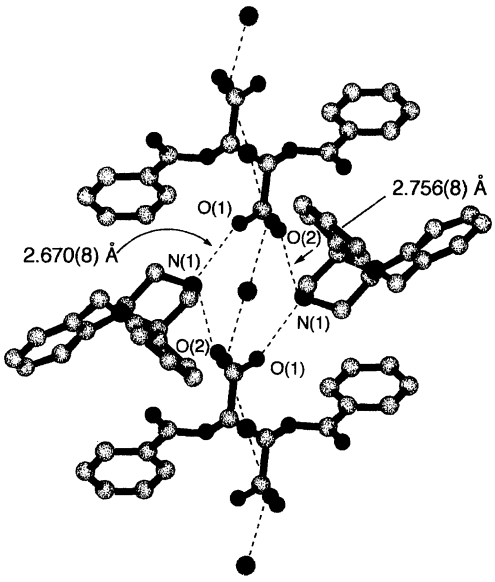

Fig. 6. Salt-type hydrogen bonds (dotted lines) between (+)-DBT and (*R*)-**1**.

(6) = 2.775(9) Å). The water further interacts with upper and lower methanols (O(6)····O(5) = 2.706(9) Å and O(6)····O-(7) = 2.674(10) Å), that is (+)-DBT molecules stand in a row along the *b* axis by the aid of water and methanol molecules (Fig. 4b). The *meta* hydrogen [H(2)] of the benzene ring in (+)-DBT is very close to the proximal O(6) of water to form a C–H····O hydrogen bond[16] (H(2)····O(6) = 2.51 Å, ∠C(6)–H(2)····O(6) = 152°), which contributes to the entire stability of the sheet structure (Fig. 4c).

Figure 5 shows the column structure of (*R*)-**1** molecules which stack along the *b* axis. A distinct feature of the stacking is that H(17) on C(10) approaches the neighboring aromatic ring probably due to CH-π interaction.[17] Indeed the H(17)····C(24) distance is 2.76 Å, which is apparently shorter

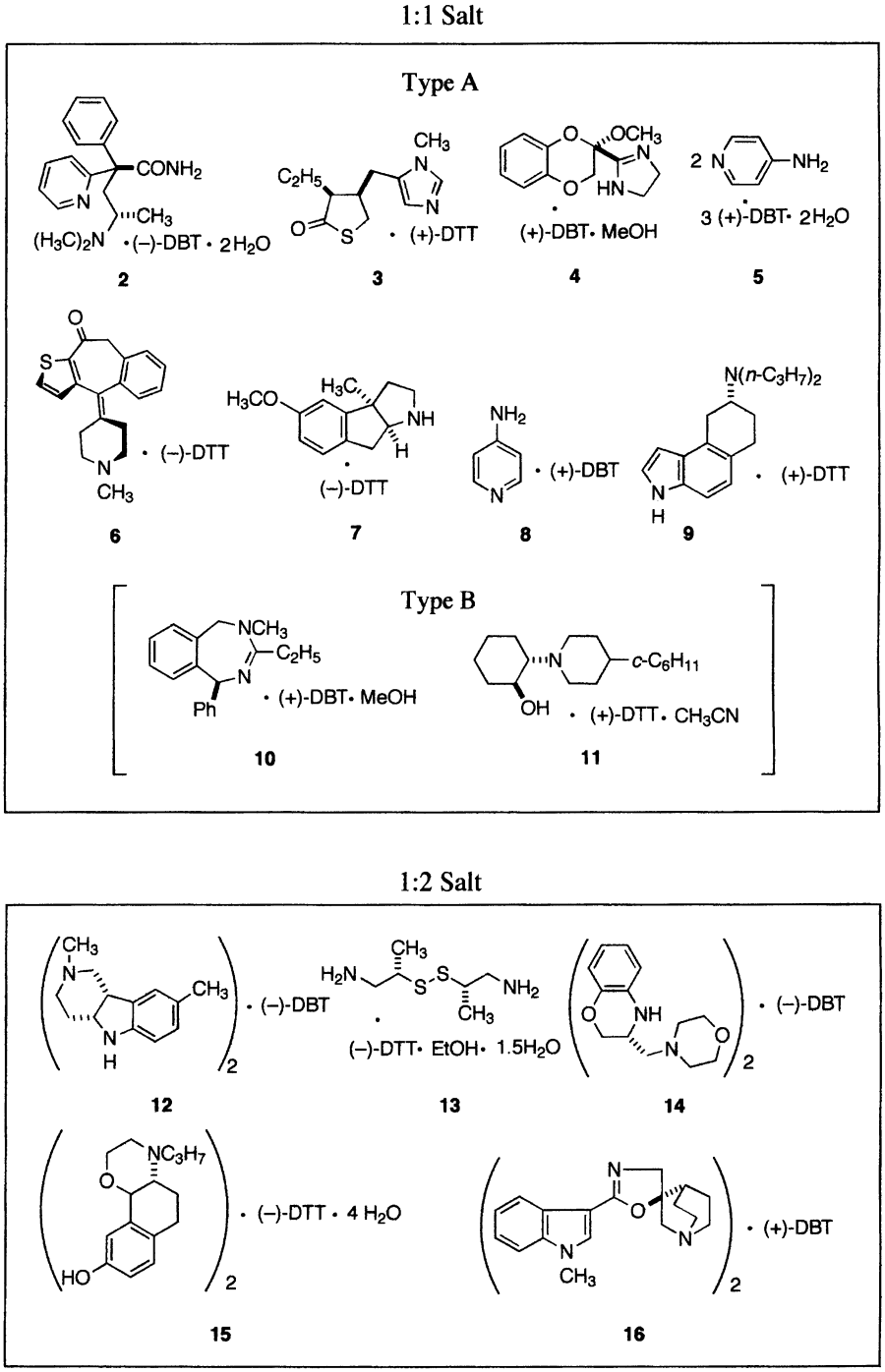

Chart 2.

than the sum of the van der Waals radii[18] of H atom (1.2 Å) and the aromatic C atom (1.77 Å).[18] This phenomenon is consistent with the finding that the C–H group adjacent to a positively changed nitrogen atom (N(1) in this case) has a potent donor ability for hydrogen bond.[16a] It is noteworthy that the (+)-DBT sheets sandwich the azepine column through two kinds of hydrogen bonds: The H atoms on N(1) bond to the carboxylate O(1) and O(2) atoms (N(1)····O(1)=2.670(8) Å and N(1)····O(2) = 2.756(8) Å) (Fig. 6).

Generality of the Crystal Structure Observed in the T_{12} Crystals. As mentioned above, the T_{12} crystal consist of the puckered sheet of (+)-DBT molecules and the column of (*R*)-**1** molecules with good steric complementarity. We were interested in the generality of the sheet structure constructed by the self-assembly of (+)-DBT molecules. Although a number of X-ray crystallographic data have been reported, their three-dimensional structures have not been well defined. We reinvestigated the X-ray data reported for the salts of amines and DBT (or DTT), most of which were collected from the Cambridge Structural Database.[19] Eleven salts (**2**—**4**, **6**, **7**, **9**—**11**, and **14**—**16** in Chart 2) and four published crystal structures (**5**, **8**, **12**, and **13**) were system-

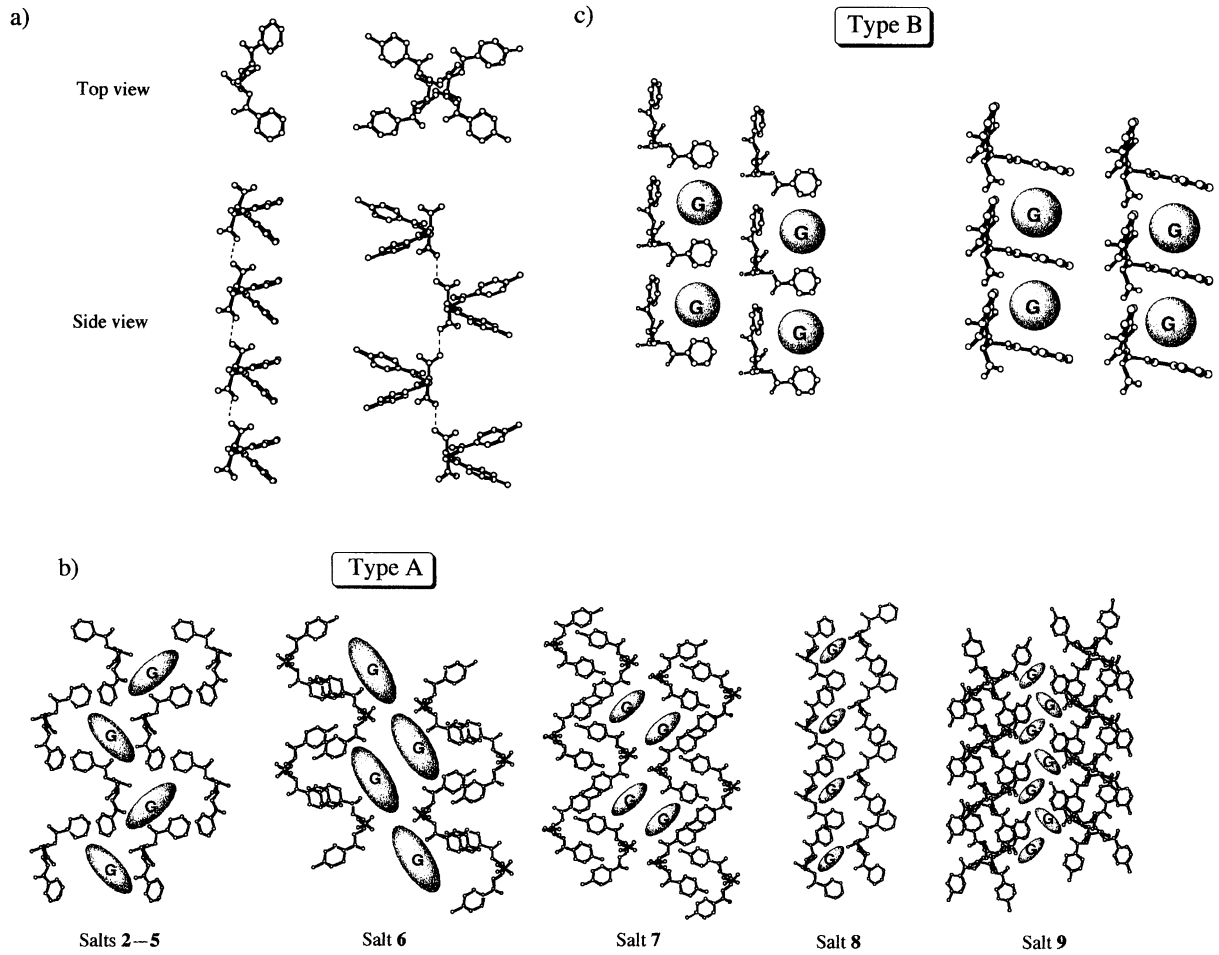

Fig. 7. (a) Ribbon structures of the host molecules in the 1 : 1 salts. A representative ribbon structure for the salts **2**—**8**, **10**, and **11** (left) and that of **9** (right). (b) Top views of the host frameworks in Type A. (c) A typical framework belonging to Type B. Top view (left) and side view (right).

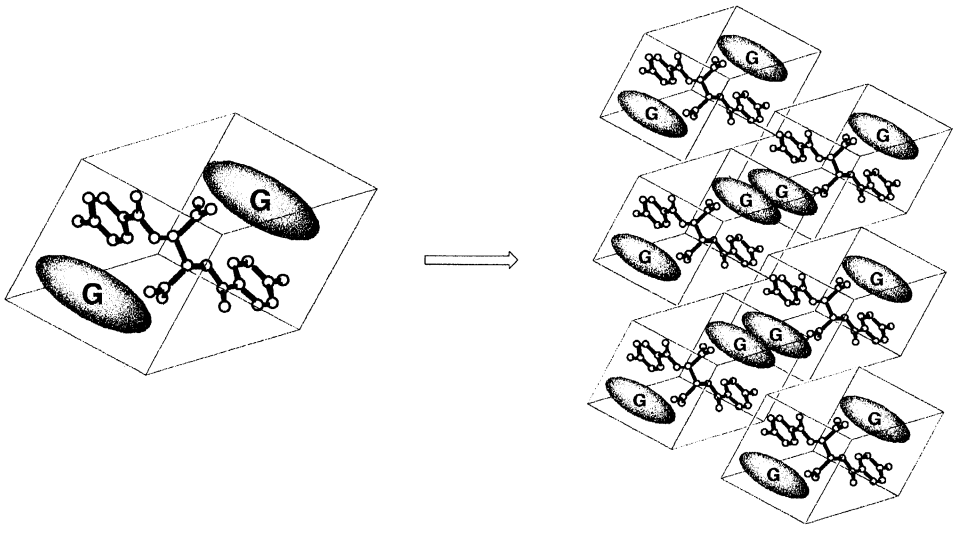

Fig. 8. A representative crystal structure in the 1 : 2 salts.

atically studied to understand their inherent features for the optical resolution of amines.[20]

In cases of the 1 : 1 salts (**2**—**11**), $P2_12_12_1$ and $P2_1$ space groups appear most frequently in their crystals. The host molecules are interlinked by $COO^-\cdots HOOC$ hydrogen bonds to make ribbon structures (Fig. 7a) which further assemble to form a puckered sheet in a manner similar to that of $\mathbf{T_{12}}$, except for two salts (**10** and **11**).[21] The puckered

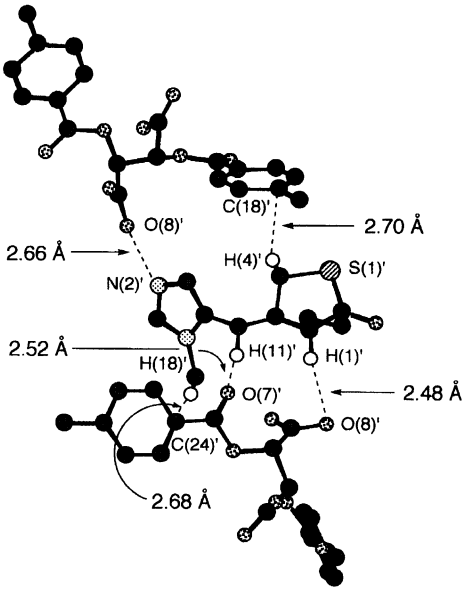

Fig. 9. Intermolecular interactions (dotted lines) in the solid state of **3**. All hydrogen atoms participating in intermolecular contacts are shown.

sheet seems to change its form according to the shape and size of the amine, as summarized in Fig. 7b. In crystals of **10** and **11** with $P1$ space group, no intermolecular interaction works between the ribbons, which point to the same direction and align so as to create appropriate cavities for the guest (Fig. 7c).

In cases of the 1 : 2 salts (**12**—**16**), their crystal (the space group: $C2$ for **12**—**15** and $P2_1$ for **16**) is constructed by the closest packing of the identical unit that comprises one host and two amine molecules (Fig. 8). It should be noted that the host framework of $\mathbf{T_{12}}$ ($P2_12_12$) resembles to those of the 1 : 1 salts. In the $\mathbf{T_{12}}$ crystal, the host molecules are linked to each other through the solvent molecules to form the hydrogen-bond network [Fig. 4b: O(2)····O(6)····O(7)····O(6)····O(2)] that makes it possible to construct the sheet structure.

Thus DBT and DTT have proven to possess outstanding ability for various weak intermolecular interactions such as hydrogen bonding, CH-π interaction, and aromatic–aromatic interactions. As a typical example, the intermolecular interactions observed in **3** are shown in Fig. 9: The toluoyl carbonyl O(7)′ atom contacts with the H(11)′ atom through C–H····O hydrogen bonding (C(7)′–H(11)′····O(7)′ = 2.52 Å; ∠C(7)′–H(11)′····O(7)′ = 131°) and two aromatic rings of DTT interact with the C–H group adjacent to the electron-withdrowing group (C(18)′····H(4)′ = 2.70 Å and C(24)′····H(18)′ = 2.68 Å). This ability gives an answer to the question why DBT and DTT recognize a wide range of amine compounds with a high enantiopreference.

Conclusion

In summary, a practical optical resolution of racemic **1** was developed by the use of 0.25 molar amounts of (−)-DBT and (+)-DBT, which gave enantiomerically pure (*R*)-**1** in 40% overall yield based on racemic **1**. X-Ray structural analysis of the salt $\mathbf{T_{12}}$, which consists of (+)-DBT, (*R*)-**1**, methanol, and water in a 1 : 2 : 2 : 2 ratio, elucidated its highly ordered superstructure of (+)-DBT molecules. In the solid state of $\mathbf{T_{12}}$, (+)-DBT molecules self-assemble by the aid of water and methanol to construct the sheet structure, in which (*R*)-**1** molecules are incorporated as guests. A comprehensive study on the crystal structures of the related salts revealed the important driving forces for the chiral recognition of amines by DBT and DTT. The host frameworks in the 1 : 1 salts can be classfied by two types, and most crystal structures of 1 : 2 salts were shown to exhibit a striking similarity. This work will shed some light on the mechanism for the recognition of amines by DBT and DTT.

Experimental

Melting points were determined with a Yamato MP-21 melting point apparatus or a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were determined with a Horiba SEPA-300 or JASCO DIP-370 polarimeter. ^{1}H NMR spectra were recorded on a JEOL JNM-GSX 400 (400 MHz) spectrometer, and chemical shifts were reported in ppm relative to tetramethylsilane as an internal standard. Infrared spectra were run on a JASCO FT/IR-8900 spectrometer. Enantiomeric excess of **1** was determined by chiral HPLC: Column, Daicel Chiralcel OJ (ϕ 4.6×250 mm); eluent, 2-propanol/hexane (2 : 1); flow rate, 0.7 ml min^{-1}; t_R of (*R*)-**1** = 6.7 min, t_R of (*S*)-**1** = 7.8 min. Powder X-ray diffraction patterns were measured with an MXP system (MAC Science Co.) using Cu $K\alpha$ radiation. Compound **1** was prepared according to the literature procedure.[7)]

Preparation of (*R*)- or (*S*)-1,2,3,4,10,14b-Hexahydrodibenzo-[*c*,*f*]pyrazino[1,2-*a*]azepinium Hydrogen 2,3-Di-*O*-benzoyl-D-(−)-tartrate ($\mathbf{R_{11}}$ or $\mathbf{S_{11}}$). A solution of (+)-DBT·H_2O (2.26 g, 6.01 mmol) in methanol (6 ml) was added to a stirred solution of (*R*)-**1** (1.25 g, 4.99 mmol) in methanol (44 ml) at room temperture. After 5 min, the precipitate was filtered off and dried in vacuo to afford the 1 : 1 salt $\mathbf{R_{11}}$ (1.80 g, 59%) as a colorless solid. The mp, specific rotation, and solubility of this salt are shown in Table 1. ^{1}H NMR (CD_3OD) signals due to (*R*)-**1**: δ = 3.26—3.55 (m, 6H, $(CH_2)_2NCH_2$), 3.38 (d, J=12.7 Hz, 1H, ArCH*H*Ar), 4.23 (dd, J=3.7 and 10.1 Hz, 1H, ArNC*H*Ar), 4.76 (d, J = 12.7 Hz, 1H, ArCH*H*Ar), 6.89—7.23 (m, 8H, Ar*H*); signals due to (+)-DBT: δ = 5.92 (s, 2H, 2×C*H*OBzl), 7.44 (t-like, J = 8 Hz, 4 H, Ar*H*), 7.56—7.60 (m, 2H, Ar*H*), 8.11—8.13 (m, 4H, Ar*H*). IR (KBr) 3428, 1725, 1631, 1602, 1493, 1452, 1265, 1114, 715 cm^{-1}. Found: C, 68.62; H, 5.66; N, 4.65%. Calcd for $C_{35}H_{32}N_2O_8 \cdot 0.7H_2O$: C, 68.36; H, 5.36; N, 4.56%.

When (*S*)-**1** was treated with equimolar amount of (+)-DBT, no crystalline salt was formed before or after concentration of the reaction mixture.

Preparation of Bis((*R*)- or (*S*)-1,2,3,4,10,14b-hexahydrodibenzo[*c*,*f*]pyrazino[1,2-*a*]azepinium)2,3-Di-*O*-benzoyl-D-(−)-tartrate ($\mathbf{R_{12}}$ or $\mathbf{S_{12}}$). To a stirred solution of (*R*)-**1** (1.25 g, 4.99 mmol) in methanol (44 ml) was added a solution of (+)-DBT·H_2O (0.94 g, 2.5 mmol) in methanol (6 ml) at room temperature. After 30 min, the solid was collected by filtration and dried in vacuo to afford the 1 : 2 salt $\mathbf{R_{12}}$ (1.71 g, 77%) as a colorless solid. The mp, specific rotation, and solubility of $\mathbf{R_{12}}$ are listed in Table 1. ^{1}H NMR (CD_3OD) signals due to (*R*)-**1**: δ = 3.20—3.51 (m, 12H, 2×$(CH_2)_2NCH_2$), 3.36 (d, J = 12.8 Hz, 2H, 2×ArCH*H*Ar), 4.19 (dd, J = 3.3 and 10.2 Hz, 2H, 2×ArNC*H*Ar), 4.76 (d, J = 12.7 Hz, 2H, 2×ArCH*H*Ar), 6.87—7.20 (m, 16H, 2×Ar*H*); signals due to

(+)-DBT: δ = 5.93 (s, 2H, 2×C*H*OBzl), 7.39 (t-like, J = 7.6 Hz, 4H, Ar*H*), 7.52 (t-like, J = 7.6 Hz, 2H, Ar*H*), 8.14 (t-like, J = 7.6 Hz, 4H, Ar*H*). IR (KBr) 3414, 1717, 1634, 1601, 1492, 1452, 1266, 1115, 758, 718 cm^{-1}. Found: C, 70.69; H, 5.84; N, 6.39%. Calcd for $C_{52}H_{50}N_4O_8 \cdot 1.4H_2O$: C, 70.64; H, 6.02; N, 6.34%.

Similarly, (*S*)-**1** (1.25 g, 4.99 mmol) was treated with (+)-DBT·H_2O (0.94 g, 2.5 mmol) to give the 1 : 2 salt $\mathbf{S_{12}}$ (1.38 g, 62%) as a colorless solid. The mp, specific rotation, and solubility of $\mathbf{S_{12}}$ are shown in Table 1. ^{1}H NMR (CD_3OD) signals due to (*S*)-**1**: δ = 3.20—3.51 (m, 12H, 2×(CH_2)$_2$NCH_2), 3.32 (d, J = 12.6 Hz, 2H, 2×ArCH*H*Ar), 4.19 (dd, J = 3.1 and 10.5 Hz, 2H, 2×ArNC*H*Ar), 4.75 (d, J = 12.6 Hz, 2H, 2×ArCH*H*Ar), 6.88—7.20 (m, 16H, 2×Ar*H*); signals due to (+)-DBT: δ = 5.93 (s, 2H, C*H*OBzl), 7.40 (t-like, J = 7.6 Hz, 4H, Ar*H*), 7.53 (t-like, J = 7.6 Hz, 2H, Ar*H*), 8.15 (t-like, J=7.6Hz, 4H, Ar*H*). IR (KBr) 3409, 1716, 1634, 1601, 1493, 1451, 1268, 1116, 759, 719, cm^{-1}. Found: C, 69.71; H, 5.96; N, 6.25%. Calcd for $C_{52}H_{50}N_4O_8 \cdot 2H_2O$: C, 69.78; H, 6.08; N, 6.26%.

Optical Resolution of Racemic 1 with 0.25 Molar Amount of (+)-DBT Using Methanol as Solvent. To a refluxing solution of racemic **1** (2.50 g, 9.99 mmol) in methanol (44 ml) was added a solution of (+)-DBT·H_2O (0.94 g, 2.5 mmol) in methanol (6 ml), and the resulting mixture was gently refluxed for 30 min with stirring. After the mixture was cooled gradually to 20 °C, the precipitated salt was isolated by filtration, washed with methanol (7.5 ml), and dried in vacuo to give 1.15 g of $\mathbf{R_{12}}$. A part of the salt was decomposed upon treatment with aqueous 1 M (1 M = 1 mol dm^{-3}) NaOH to afford free (*R*)-**1**.

In a similar manner, optical resolution of racemic **1** was carried out using 0.5, 0.75, and 1.0 molar amounts of (+)-DBT. The yield of the salt and the enantiomeric excess of (*R*)-**1** are summarized in Table 2.

Optimal Resolution Procedure. To a refluxing solution of **1** (100 g, 400 mmol) in methanol–water (9 : 1 v/v, 1200 ml) was dropwise added a solution of (−)-DBT·H_2O (37.6 g, 99.9 mmol) in methanol–water (9 : 1 v/v, 300 ml), and the resulting suspension was gently refluxed for 30 min with stirring. After the mixture was cooled gradually to 20 °C over 1 h, the precipitate was collected by filtration, washed with a small amount of methanol–water (9 : 1 v/v), and dried in vacuo to give 59.2 g (34%) of (−)-DBT·2(*S*)-**1**·H_2O. The filtrate and the washing were evaporated in vacuo, and toluene (1500 ml) and aqueous 0.2 M $NaHCO_3$ (300 ml) were added to the residue. After the mixture was vigorously stirred at 70 °C for 30 min, the organic layer was separated and concentrated in vacuo to afford 66.4 g of (*R*)-**1** with 36%ee. A solution of (+)-DBT·H_2O (37.6 g, 99.9 mmol) in methanol–water (9 : 1 v/v, 200 ml) was dropwise added to the refluxing solution of the recovered **1** in methanol–water (9 : 1 v/v, 400 ml), and the mixture was gently refluxed for 30 min. After the mixture was cooled gradually to 20 °C over 1 h, the precipitate was collected by filtration, washed with a small amount of methanol–water (9 : 1 v/v), and dried in vacuo to give 75.2 g (43%) of (+)-DBT·2(*R*)-**1**·H_2O ($\mathbf{U_{12}}$) as colorless crystals: Mp 190—196 (decomp); $[\alpha]_D^{20}$ −272° (*c* 0.20, DMF); IR (KBr) 3429, 1719, 1630, 1602, 1493, 1452, 1267, 1116, 758, 718 cm^{-1}. Found: C, 71.27; H, 5.89; N, 6.41%. Calcd for $C_{52}H_{50}N_4O_8 \cdot H_2O$: C, 71.21; H, 5.98; N, 6.35%. The ^{1}H NMR spectrum of this salt was identical with that of $\mathbf{R_{12}}$. The powder X-ray diffraction pattern of this salt is shown in Fig. 1.

To the above salt $\mathbf{U_{12}}$ (75.2 g, 85.7 mmol) were added toluene (340 ml), $NaHCO_3$ (15.1 g, 180 mmol), and water (340 ml) and the resulting mixture was vigorously stirred at 70 °C for 30 min. The toluene layer was separated and the aqueous layer was extracted with toluene (170 ml). The organic layers were combined, washed with water (3×20 ml), and evaporated to afford crude (*R*)-**1** quantitatively, which was recrystallized from toluene–IPE (1 : 3 v/v) to give 40.3 g (40 % overall yield from racemic **1**) of (*R*)-**1** with 100%ee as colorless crystals: Mp 130—130.5 °C; $[\alpha]_D^{23}$ −497° (*c* 1.00, methanol) (lit,[7] $[\alpha]_D^{25}$ −486° (*c* 1.00, methanol); ^{1}H NMR ($CDCl_3$) δ=1.73 (br, 1H, N*H*), 3.0—3.3 (m, 6H, (CH_2)$_2$NCH_2), 3.29 (d, J = 12.6 Hz, 1H, ArCH*H*Ar), 3.94 (dd, J = 2.9 and 9.9 Hz, 1H, ArNC*H*Ar), 4.86 (d, J = 12.6 Hz, 1H, ArCH*H*Ar), 6.85—7.19 (m, 8H, Ar*H*); IR (KBr) 3433, 3203, 1491, 1238, 1133, 754 cm^{-1}.

X-Ray Crystallographic Analysis of $\mathbf{T_{12}}$. All measurements were made on a Rigaku RAXIS II imaging plate area detector with graphite monochromated Mo $K\alpha$ radiation. The data were collected at −100 °C to a maximum 2θ value of 44.1°. A total of 1650 reflections was collected and corrected for Lorentz and polarization effects. The structure was solved by direct methods (SHELXS 86)[22] and expanded using Fourier techniques (DIRDIF 94).[23] The non-hydrogen atoms were refined anisotropically. All hydrogen atoms of the crystal solvents and the two hydrogen atoms due to the carboxyl moieties of (+)-DBT were disordered. Some hydrogen atoms were refined isotropically, and the rest were included in fixed positions. The final cycle of full-matrix least-squares refinement was based on 1360 observed reflections ($I > 4.00\sigma(I)$) and 414 variable parameters and converged with R = 0.068 and R_W = 0.067. All calculations were performed using the teXsan[24] crystallographic software package of Molecular Structure Co. The crystal data and the details of the data collection and structure refinement are presented in Table 4.

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