Systematic study of chiral discrimination upon crystallisation. Part 2.[1] Chiral discrimination of 2-arylalkanoic acids by (1*R*,2*S*)-2-amino-1,2-diphenylethanol

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The resolution of 2-arylalkanoic acids by (1*R*,2*S*)-2-amino-1,2-diphenylethanol has been studied. It has been found that the position of a substituent on the aromatic group of the acids affects resolution efficiency to a considerable extent. Crystal structure analysis of the diastereomeric salts has revealed that a columnar hydrogen-bond network is commonly formed in the diastereomeric salts studied. A detailed analysis of the hydrogen-bond networks formed in the diastereomeric salts has enabled clear elucidation of the correlation between crystal structure and efficiency of resolution; differential stability of the crystals of less- and more-soluble salts, which results in large differences in solubility and subsequently in resolution efficiency, is found to arise from the inclusion of water molecules in the less-soluble salt, reinforcing the columnar hydrogen-bond network by strong hydrogen bonds, and from the absence of such water molecules in the more-soluble salt. On the other hand, when the resolution gave poor efficiency, such a remarkable difference in stability between the pairs of diastereomeric salts is not observed.

The resolution of enantiomers *via* the formation of a pair of diastereomers is the most practical method for obtaining enantiomerically pure compounds on both laboratory and industrial scales.[2] This method was developed by Pasteur in the middle of the nineteenth century,[3] and has been widely applied to the preparation of many optically active compounds up to the present day.[4] However, despite its definite advantages, the method has remained a purely practical one and systematic studies focusing on the mechanism by which chiral discrimination during crystallisation is achieved, have not been carried out until now. Thus, the prediction and design of a suitable resolving agent for a target racemate are still considered to be impossible, and quite laborious trial and error is required during the selection process.

The chiral discrimination mechanism involved in crystallisation is considered to include a number of factors, such as solvent and temperature. Since the solubility of crystals is generally related to their stability,[5] knowledge of the most prominent interaction in the crystals, which stabilises the packing, is important to understanding their solubility. Therefore, the most important factors affecting solubility are the crystal structures of the pair of diastereomeric salts formed, which should directly correlate with differences in solubility, and hence the efficiency of the resolution. From this viewpoint, special attention has been paid to the nature of the hydrogen-bonds formed in diastereomeric salts, since hydrogen bonds are usually the strongest interaction in the diastereomeric salt crystals.[6] However, the target compounds in these cases were not systematically selected. Thus, no prevalent correlation between the crystal structures and the efficiency of the resolution has been found, and hence no widely applicable criterion for the selection of a resolving agent has been proposed.

Taking these current problems into account, we have recently carried out the optical resolution of systematically-selected 1-arylethylamines by mandelic acid and found a correlation between the molecular structure of the target racemate and the efficiency of the resolution.[7] In addition, detailed study of the crystal structures of the resulting diastereomeric salts led to a reasonable explanation of the results; the formation of a crystal, stabilised by both hydrogen-bonding and van der Waals' interactions in one of a pair if the diastereomeric salts, is essential for achieving high resolution efficiency.[1] In the less-soluble salt, the role of the hydroxy group of mandelic acid is distinctive. Through OH···O hydrogen bonds these hydroxy groups interlink the columnar supramolecular assemblies formed by hydrogen bonds between the carboxylate oxygens and the ammonium hydrogens, constructing a tightly hydrogen-bonded supramolecular sheet [Fig. 1(a)]. Moreover, the planar surfaces of the hydrogen-bonded sheet allow their close packing; the realisation of planarity of the surfaces is one of the most effective ways to achieve the close packing. On the basis of these results, we established a criterion for the choice of a resolving agent for 1-arylethylamines, namely that the resolving agent (a hydroxy acid), which has a similar molecular length to that of the target racemate, would show high resolution ability for the racemate. This criterion led us to successfully design a tailored acidic resolving agent which showed excellent resolution ability with a variety of 1-arylalkylamines.[8]

Although we have published these results on acidic resolving agents, such a systematic study has not yet been carried out for resolution by basic resolving agents, and there are no established criteria for the selection of a basic resolving agent. Since most of the known basic resolving agents are naturally occurring compounds having complicated structures and high toxicity,[4] the development of a novel basic resolving agent, of which both enantiomers can be made readily available, is highly desirable.

Thus, we decided to carry out a study on the resolution of chiral acids by basic resolving agents. As basic compounds, amino alcohols were chosen in the expectation that their hydroxy groups would play a similar role to the hydroxy group of mandelic acid in the chiral discrimination during the resolution;[1] it was postulated that the hydroxy groups of the amino alcohol molecules would interlink columnar hydrogen-bond networks formed by the carboxylate oxygens of a target acid and the ammonium hydrogens of the amino alcohol by strong hydrogen bonds, so as to construct a hydrogen-bonded sheet and stabilise the less soluble diastereomeric salt [Fig. 1(b)].

In the present paper, we describe the optical resolution of systematically selected 2-arylalkanoic acids by (1*R*,2*S*)-2-

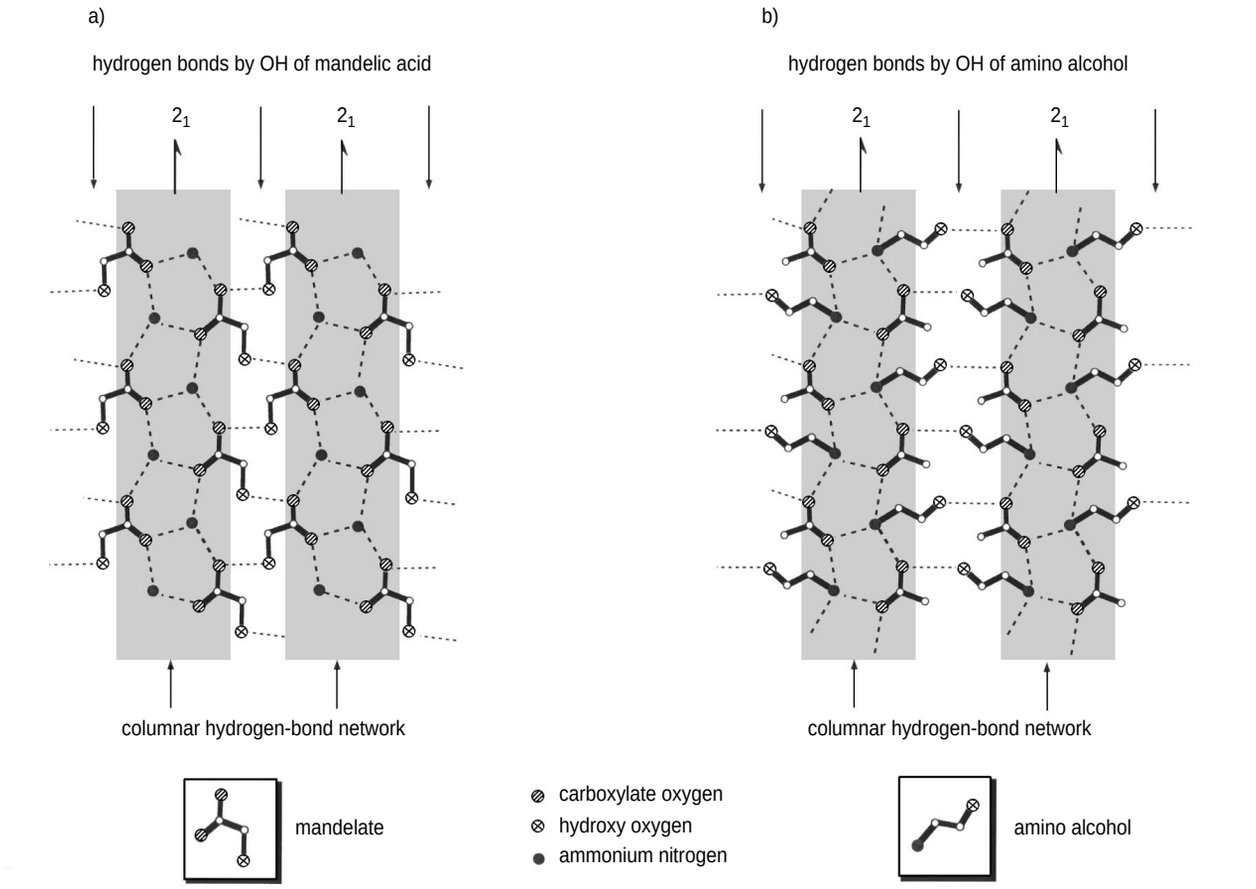


Fig. 1 (a) Schematic representation of the hydrogen-bond network of the less-soluble salts of optically pure mandelic acid with 1-arylethylamines. (b) Schematic image of the hydrogen-bond network of the less-soluble salts of optically pure amino alcohols with carboxylic acids.

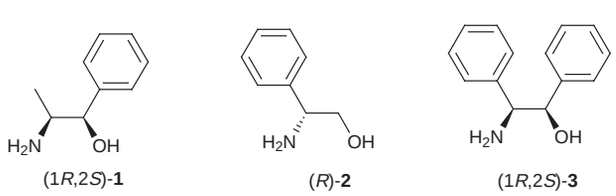
amino-1,2-diphenylethanol and discuss the correlation between the crystal structure of the resulting diastereomeric salts and the efficiency of the resolution, with the particular intention of elucidating the commonly-occurring supramolecular assemblies formed in the diastereomeric salts.

Results and discussion

Optical resolution of 2-arylalkanoic acids by amino alcohols

In order to carry out a systematic study on the resolution of acidic racemates with an amino alcohol, 2-arylalkanoic acids were selected as the target racemates for the present study on the basis that they form a series of structurally simple chiral acids, and that some of them are important intermediates for pharmaceuticals.[9]

At first, resolution of 2-phenylpropionic acid (**4a**), which is structurally the simplest compound in the series of 2-arylalkanoic acids, but requires multi-recrystallisation to obtain it in its enantiomerically pure form by the conventional diasteromeric salt method,[10] was attempted using the readily available enantiomerically pure amino alcohols, (1*R*,2*S*)-norephedrine (**1**)[4,11] and (*R*)-2-phenylglycinol (**2**)[4,12] which are both widely used as resolving agents, and (1*R*,2*S*)-2-amino-1,2-diphenylethanol (**3**), which is easily available through the resolution of its racemic derivative by preferential crystallisation,[13] and can be used as resolving agent in the resolution of some racemic acids.[14] The diastereomeric salt was obtained upon single-crystallisation of an equimolar mixture of racemic 2-phenylpropionic acid and the enantiomerically pure amino alcohol from a protic solvent system, an alcohol or an alcohol–water mixture. The results are summarised in Table 1.



As can be seen from Table 1, of the amino alcohols examined (1*R*,2*S*)-**3** was found to have the highest resolution ability for **4a**. Therefore, we decided to use (1*R*,2*S*)-**3** as resolving agent in the succeeding study; the resolution of a series of racemic 2-arylalkanoic acids was carried out by using (1*R*,2*S*)-**3** as a resolving agent.

In order to make the crystallisation conditions as similar as possible, the resolutions were carried out upon single-crystallisation of an equimolar mixture of the corresponding racemic acid and (1*R*,2*S*)-**3** from an alcohol–water mixture at 30 °C. The amount of the solvent was controlled so that the resulting diastereomeric salt was obtained as close as possible to the range of 70–90% yield (based on a half amount of the racemic acid to be resolved). The ratio of alcohol–water was controlled only to adjust the solubility of the salt, and had essentially little effect on the de of the precipitated salt.

As is shown in Table 2, (1*R*,2*S*)-**3** had moderate to excellent resolution ability for a variety of 2-arylalkanoic acids (**4**–**6**), which could be regarded as derivatives of **4a** having substituent(s) at the β-position and/or on the phenyl ring. The efficiency of the resolution was strongly affected by the presence and position of the substituent on the aromatic group of the 2-arylalkanoic acid. There appeared to be a weak correlation between the position of the substituent and the efficiency of the resolution; non- or *o*-substituted acids were resolved with high

Table 1 Resolution of 2-phenylpropionic acid by (1*R*,2*S*)-**1**, (*R*)-**2** and (1*R*,2*S*)-**3**[a]

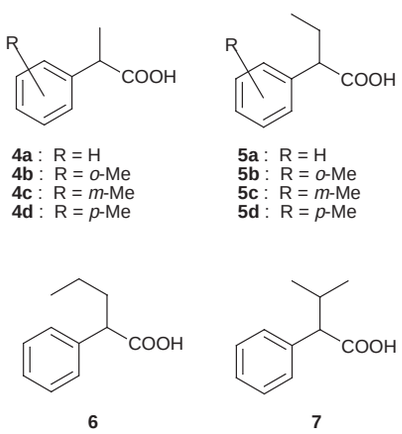
Entry	Resolving agent	Solvent (mass, *m*/g)	Yield (%)[a]	Ee (%)[b]	Resolution efficiency[c]
1	(1*R*,2*S*)-**1**	MeOH (2.90)[d]	72[e]	6	0.04
2	(*R*)-**2**	MeOH (3.35)[d]	94[e]	17	0.16
3	(1*R*,2*S*)-**3**	H_2O–EtOH (0.50/2.30)[f]	89[g]	77	0.69

[a] Yield of the crystallised diastereomeric salt based on a half amount of the racemic acid. [b] Enantiomeric excess (ee) of the liberated acid as determined by HPLC analysis (Daicel Chiralcel OJ-R). [c] Defined as the product of the yield of the diastereomeric salt and the ee. [d] The resolution was carried out on a 6 mmol scale. [e] The diastereomeric salt was crystallised at 0 °C. [f] The resolution was carried out on a 3 mmol scale. [g] The diastereomeric salt was crystallised at 30 °C.

Table 2 Resolution of 2-arylalkanoic acids **4**–**6** by (1*R*,2*S*)-**3**[a]

Entry	Racemic acid	Solvent (ratio[b])	Yield (%)[c]	Ee (%)[d,e]	Resolution efficiency[f]	Absolute configuration of major isomer
1	**4a**	H_2O–EtOH (0.17:0.76)	89	77[d]	0.69	*R*
2	**5a**	H_2O–MeOH (0.17:0.67)	70	70[d]	0.49	*R*
3	**6**	H_2O–EtOH (0.20:1.03)	75	79[e]	0.59	*R*
4	**7**	H_2O–MeOH (0.17:1.28)	77	9[e]	0.07	—[g]
5	**4b**	H_2O–EtOH (0.33:1.65)	65	37[e,h]	0.24	*R*
6	**4c**	H_2O–MeOH (0.17:0.73)	71	57[e]	0.40	*R*
7	**4d**	H_2O–MeOH (0.17:1.40)	74	6[e]	0.04	—[g]
8	**5b**	H_2O–EtOH (0.30:0.33)	87	49[e]	0.43	*R*
9	**5c**	H_2O–EtOH (0.20:0.74)	72	36[d]	0.26	*R*
10	**5d**	H_2O–MeOH (0.17:0.98)	77	13[e,h]	0.10	*R*

[a] The resolution was carried out on a 1–3 mmol scale. [b] Mass (g) of the solvents was normalized to 1 mmol scale. [c] Yield of the crystallised diastereomeric salt based on half amount of the racemic acid. [d] Enantiomeric excess (ee) of the liberated acid as determined by HPLC analysis (Daicel Chiralcel OJ-R). [e] Ee of the liberated acid as determined by HPLC analysis [Daicel Chiralcel OD (entries 3–6, 8 and 10) and OB (entry 7)] after its conversion to its methyl ester using diazomethane. [f] Defined as the product of the yield of the diastereomeric salt and the ee. [g] The absolute configuration of the major isomer was not determined. [h] The diastereomeric salt was crystallised at 0 °C.



resolution efficiency while *p*-substituted acids were not resolved effectively.

It is noteworthy that each less-soluble salt has in common incorporation of the chiral acid of *R* absolute configuration. This result suggests that the resolution by (1*R*,2*S*)-**3** occurs under a similar chiral discrimination mechanism, namely, the crystal structures of the less-soluble salts should be similar to each other.

Crystal structure of the less-soluble salts

One of the major objects of the present study is the elucidation of the commonly occurring supramolecular assemblies in the diastereomeric salts. To determine the crystal structures of the less-soluble salts, which preferentially crystallised out of the solution with high efficiency, crystallographic analyses were performed. We could determine the crystal structures of five of these [(1*R*,2*S*)-**3**·(*R*)-**4a**·H_2O, (1*R*,2*S*)-**3**·(*R*)-**4c**·H_2O, (1*R*,2*S*)-**3**·(*R*)-**5a**·H_2O, (1*R*,2*S*)-**3**·(*R*)-**5b**·H_2O, and (1*R*,2*S*)-**3**·(*R*)-**6**·H_2O], and a summary of the crystallographic analyses is listed in Table 3.

The crystal structures of these less-soluble salts revealed some common characteristics. A typical crystal structure [(1*R*,2*S*)-**3**·(*R*)-**5a**·H_2O] is shown in Fig. 2. The first characteristic of these crystal structures is that a chiral columnar hydrogen-bond network is formed around a two-fold screw axis by the ammonium hydrogens and the carboxylate oxygens. This hydrogen-bond pattern is commonly found in the salts of primary amines with mono-carboxylic acids,[15] suggesting that the hydrogen-bond network formed in the present less-soluble crystals is general and thus stable.

The second common characteristic is the incorporation of water molecules which form hydrogen bonds with the hydroxy group of (1*R*,2*S*)-**3** and the carboxylate oxygens [Fig. 2(c)]. These hydrogen bonds reinforce the above-mentioned columnar structure to a considerable extent, resulting in a strongly hydrogen-bonded supramolecular column. The strong hydrogen-bonding interaction including water molecules is revealed by the short O···O distances shown in Table 4 (D and E) and also by the DSC-TG analysis of the less-soluble salt, which showed that the water molecules were not released until the temperature reached the melting point, *ca.* 145 °C. These tightly hydrogen-bonded water molecules were found in all of the less-soluble salts in the present study.

At the initial stage of the present study, we had expected that the hydroxy group of (1*R*,2*S*)-**3** would play a similar role to the hydroxy group of mandelic acid in a hydrogen-bond network; *i.e.* that it would interlink hydrogen-bond columns to form a hydrogen-bonded sheet in the less-soluble salts [Fig. 1(b)]. However, in the present cases, the hydroxy group of (1*R*,2*S*)-**3** formed a hydrogen bond with a water molecule to reinforce the hydrogen-bond column. In connection with this phenomenon, the conformation of (1*R*,2*S*)-**3** in these less-soluble salts is noteworthy; in each case, the hydroxy and the ammonium groups are *gauche*, and the two phenyl groups are also *gauche* (the dihedral angle = 54.6–56.0°), which seems to cause steric repulsion. This conformation enables (1*R*,2*S*)-**3** to form strong hydrogen bonds upon incorporation of water molecules.

The third common characteristic of the less-soluble salt is that there is no strong interaction between the hydrogen-bond columns, except for weak hydrophobic interactions, in contrast to the strong hydrogen-bonding and electrostatic interactions within the columns; the whole crystal could be regarded as assemblies of these supramolecular hydrogen-bond columns

Table 3 Summary of the crystal data of the diastereomeric salts

Compound	(1*R*,2*S*)-**3**·(*R*)-**4a**·H_2O (less-soluble)	(1*R*,2*S*)-**3**·(*R*)-**4c**·H_2O (less-soluble)	(1*R*,2*S*)-**3**·(*R*)-**5a**·H_2O (less-soluble)	(1*R*,2*S*)-**3**·(*S*)-**5a**· (more-soluble)	(1*R*,2*S*)-**3**·(*R*)-**5b**·H_2O (less-soluble)	(1*R*,2*S*)-**3**·(*R*)-**5d**	(1*R*,2*S*)-**3**·(*S*)-**5d**·H_2O	(1*R*,2*S*)-**3**·(*R*)-**6**·H_2O (less-soluble)
Formula	$C_{23}H_{27}NO_4$	$C_{24}H_{29}NO_4$	$C_{24}H_{29}NO_4$	$C_{24}H_{27}NO_3$	$C_{25}H_{31}NO_4$	$C_{25}H_{29}NO_3$	$C_{25}H_{31}NO_4$	$C_{25}H_{31}NO_4$
Formula weight	381.5	395.5	395.5	377.5	409.5	391.5	409.5	409.5
Crystal system	Orthorhombic	Monoclinic	Monoclinic	Orthorhombic	Orthorhombic	Orthorhombic	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_1$	$P2_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
a/Å	16.486(3)	15.361(3)	24.774(5)	14.846(2)	16.428(5)	13.813(4)	13.74(1)	16.699(7)
b/Å	20.689(3)	5.943(1)	6.032(2)	21.479(3)	22.083(7)	25.589(7)	26.55(2)	22.174(7)
c/Å	6.264(1)	13.200(2)	14.697(3)	6.572(1)	6.504(7)	6.212(2)	6.497(7)	6.271(3)
α/°	90	90	90	90	90	90	90	90
β/°	90	114.08(1)	94.55(2)	90	90	90	90	90
γ/°	90	90	90	90	90	90	90	90
V/Å^3	2136.7(6)	1100.3(4)	2189.2(8)	2095.7(5)	2359.91(5)	2195.60(1)	2369.9(8)	2322.22(2)
Z	4	2	4	4	4	4	4	4
D_{calcd}/g cm^{-3}	1.183	1.19	1.197	1.207	1.15	1.182	1.146	1.169
Crystal size, mm	2.1 × 0.3 × 0.2	0.65 × 0.15 × 0.1	0.6 × 0.15 × 0.1	4 × 0.2 × 0.15	0.6 × 0.2 × 0.15	0.25 × 0.1 × 0.05	3 × 0.2 × 0.05	2.5 × 0.35 × 0.25
F(000)	776	423	848	808	880	840	880	880
μ/cm^{-1}	5.61	6.14	6.17	5.88	5.86	5.77	5.84	5.96
No. reflections measured	1972	2016	3555	1943	2011	1729	1261	2034
No. reflections observed ($\|F_o\| > 3\sigma\|F_o\|$)	1768	1667	2874	1761	1484	1108	850	1571
No. of parameters	259	264	522	325	265	265	271	277
R	0.068	0.049	0.071	0.054	0.077	0.059	0.090	0.066
R_w	0.089	0.046	0.090	0.050	0.099	0.076	0.085	0.084
Residual electron density/e A^{-3}	0.17, −0.27	0.31, −0.21	0.28, −0.34	0.18, −0.24	−0.22, 0.40	0.22, −0.25	0.28, −0.20	0.23, −0.19

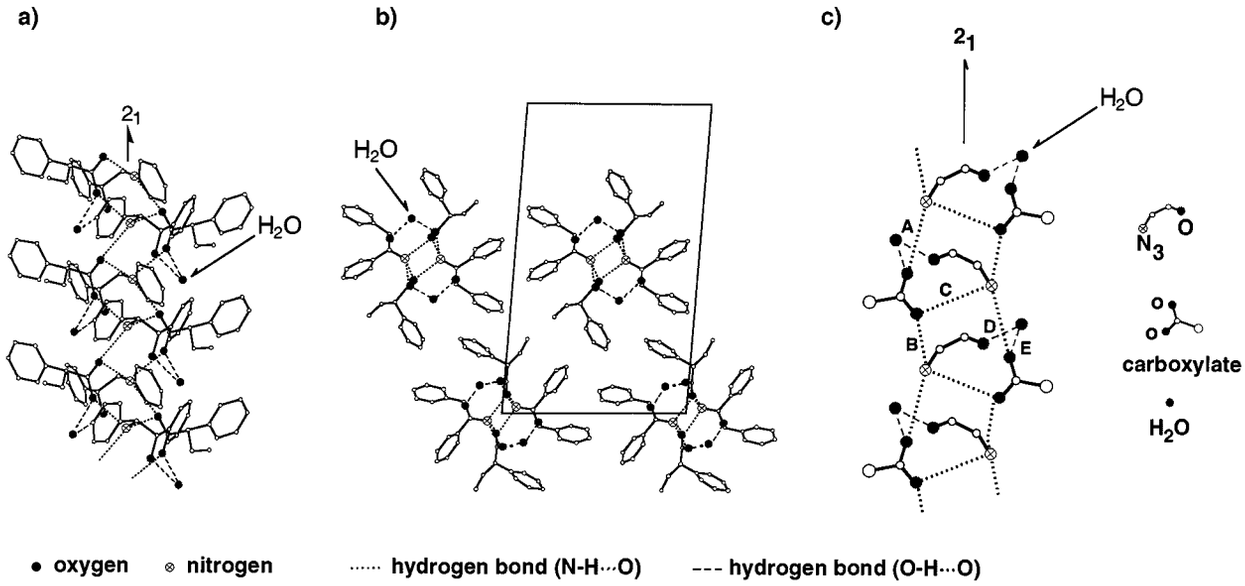


Fig. 2 Crystal structure of less-soluble (1*R*,2*S*)-**3**·(*R*)-**5a**·H_2O. (a) Columnar hydrogen-bond network. (b) Viewed down the 2_1-axis of the hydrogen-bond column (*b*-axis). The solid square shows the unit cell. (c) Schematic representation of the common pattern of the hydrogen-bond network in the less-soluble salts of (1*R*,2*S*)-**3** with 2-arylalkanoic acids.

Table 4 N···O and O···O distances in the diastereomeric salts of (1*R*,2*S*)-**3** with **4**–**6**[a]

	N···O Distances (Å)				O···O Distances (Å)			
Acid part	A	B	C	Average A–C	D	E	F	Average D–F
(*R*)-**5a**	2.732(1)	2.834(1)	2.752(1)	2.773	2.444(2)	2.551(2)	—	2.498
(*S*)-**5a**	2.756(1)	2.758(1)	2.779(1)	2.764	—	—	—	—
(*R*)-**5d**	2.858(1)	2.787(1)	2.758(1)	2.801	—	—	2.784(2)	2.784
(*S*)-**5d**	2.750(1)	2.785(1)	2.765(1)	2.767	2.706(9)	2.630(2)	—	2.668
(*R*)-**4**–**6**[b]	2.771	2.794	2.836	2.800	2.658	2.735		2.699

[a] The definitions of A–F are shown in Figs. 2–5. [b] Average value for five less-soluble salts listed in Table 3.

held together by van der Waals' interactions. This suggests that the most significant interactions, which stabilise the crystal packing, are the hydrogen-bonding and electrostatic interactions.

Crystal structure of a more-soluble salt

In order to find a structural factor responsible for the successful resolution of **5a** by (1*R*,2*S*)-**3**, we determined the crystal structure of the more-soluble (1*R*,2*S*)-**3**·(*S*)-**5a** (Table 2, entry 2), and compared it in detail with that of the corresponding less-soluble (1*R*,2*S*)-**3**·(*R*)-**5a**·H_2O.

In more-soluble (1*R*,2*S*)-**3**·(*S*)-**5a**, there is a columnar hydrogen-bond network formed by the ammonium hydrogens and the carboxylate oxygens [Fig. 3(a)] similar to that in the corresponding less-soluble (1*R*,2*S*)-**3**·(*R*)-**5a**·H_2O. The N···O distances in these salts (A–C, in Table 4) are similar to each other. However, there is a remarkable difference between the crystal structures of more-soluble (1*R*,2*S*)-**3**·(*S*)-**5a** and less-soluble (1*R*,2*S*)-**3**·(*R*)-**5a**·H_2O, in that water molecules are not incorporated in the columnar hydrogen-bond network of the former [Fig. 3(c)]. In addition, the hydroxy group of (1*R*,2*S*)-**3** is free and forms no hydrogen bond in the more-soluble salt. However, the whole crystal of more-soluble (1*R*,2*S*)-**3**·(*S*)-**5a** can also be regarded as an assembly of hydrogen-bond columns, in which there exist only weak hydrophobic interactions between the hydrogen-bond columns [Fig. 3(b)]; from this point of view, the crystal structures of more-soluble (1*R*,2*S*)-**3**·(*S*)-**5a** and less-soluble (1*R*,2*S*)-**3**·(*R*)-**5a**·H_2O are similar to each other.

On the basis of these observations, the difference in stability between less-soluble (1*R*,2*S*)-**3**·(*R*)-**5a**·H_2O and more-soluble (1*R*,2*S*)-**3**·(*S*)-**5a** can be clearly elucidated: in less-soluble (1*R*,2*S*)-**3**·(*R*)-**5a**·H_2O, the columnar structure consisting of hydrogen-bonds [Fig. 3(b); A, B and C] is reinforced by strong hydrogen-bonds formed by water molecules and the hydroxy group of (1*R*,2*S*)-**3** [Fig. 2(c); D and E], while no hydrogen bonds other than A, B and C exist in the corresponding more-soluble salt [(1*R*,2*S*)-**3**·(*S*)-**5a**, Fig. 3(c)]. Thus, the incorporation of water molecules in the less-soluble salt plays an important role in increasing the difference in stability between the less- and more-soluble salts and achieving high resolution efficiency.

Crystal structures of a pair of poorly resolved diastereomeric salts

In the next stage, we studied and compared the crystal structures of a pair of diastereomeric salts, (1*R*,2*S*)-**3** with (*R*)-**5d** and (*S*)-**5d**, the combination of which gave an unsatisfactory result for resolution upon crystallisation (Table 2, entry 10, and Figs. 4 and 5).

In the case of the water-containing less-soluble salts discussed above, the common absolute configuration of the acid part was *R* when (1*R*,2*S*)-**3** was used as resolving agent. Contrary to our observations for these compounds, in the case of (1*R*,2*S*)-**3**·(*R*)-**5d** water molecules were not incorporated in the columns, although a columnar hydrogen-bond network was formed by the ammonium hydrogens and the carboxylate oxygens (Fig. 4). Instead of the incorporation of water molecules, direct hydrogen bonding of the hydroxy group of (1*R*,2*S*)-**3** to the carboxylate oxygen of (*R*)-**5d** so as to reinforce the columnar hydrogen-bond network [Fig. 4(c), hydrogen-bond F] was observed. However, the O···O distance in this crystal (Table 4,

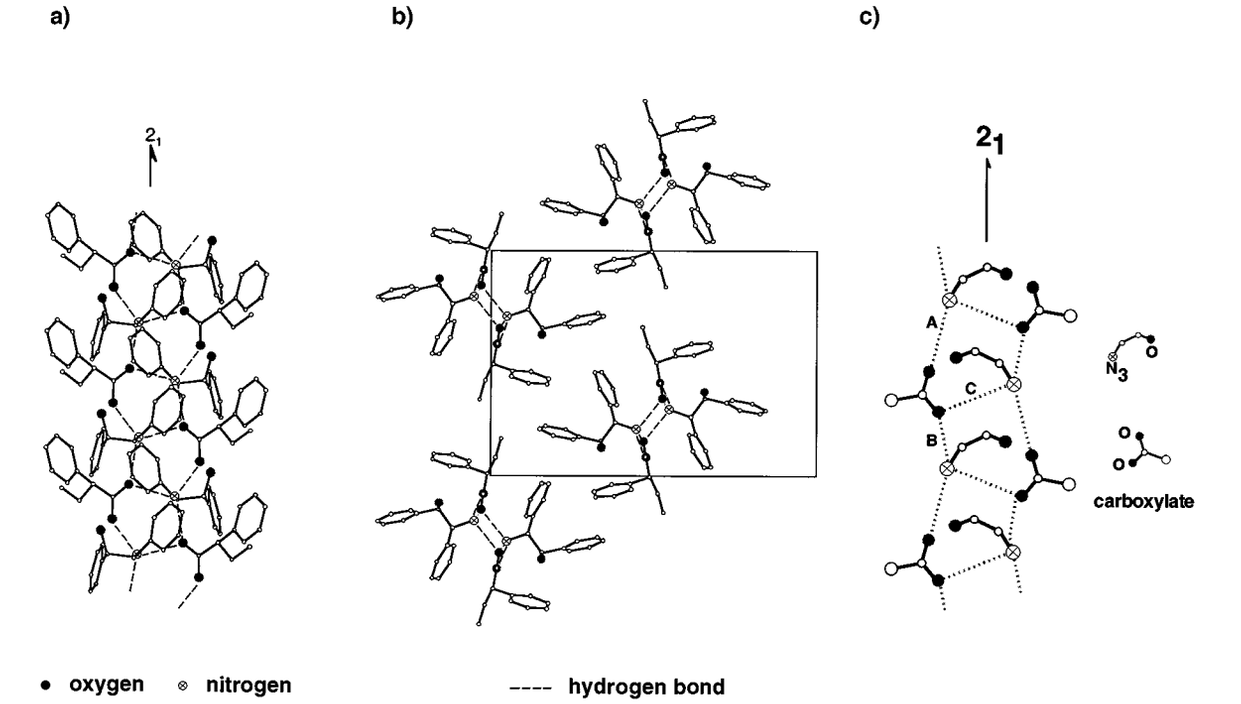


Fig. 3 Crystal structure of more-soluble (1*R*,2*S*)-**3**·(*S*)-**5a**. (a) Hydrogen-bond network. (b) Viewed down the 2_1-axis of the hydrogen-bond column (*c*-axis). The solid square shows the unit cell. (c) Schematic representation of the hydrogen-bond network.

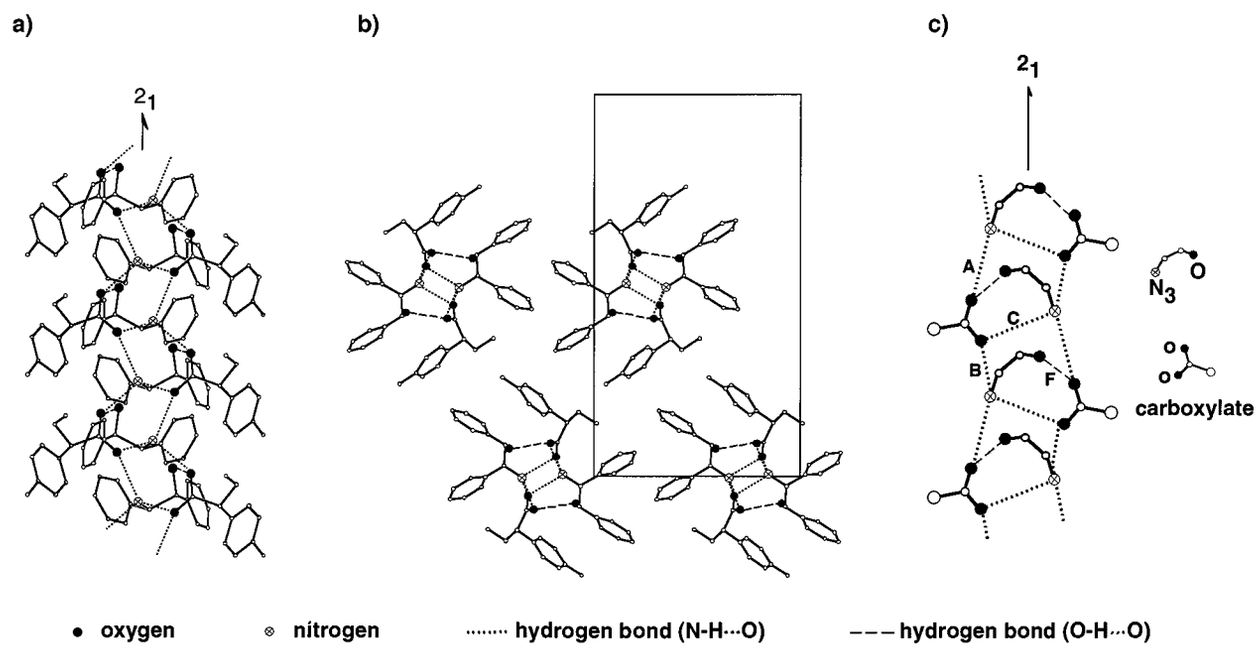


Fig. 4 Crystal structure of (1*R*,2*S*)-**3**·(*R*)-**5d**. (a) Hydrogen-bond network. (b) Viewed down the 2_1-axis of the hydrogen-bond column (*c*-axis). The solid square shows the unit cell. (c) Schematic representation of the hydrogen-bond network.

F) is much longer than those in (1*R*,2*S*)-**3**·(*R*)-**5a**·H_2O (hydrogen bonds D and E), indicating that hydrogen bond F is weaker than D and E. In addition, the conformation of (1*R*,2*S*)-**3** was slightly different from that in (1*R*,2*S*)-**3**·(*R*)-**5a**·H_2O; the dihedral angle between two phenyl groups (51.0°) is smaller than that in (1*R*,2*S*)-**3**·(*R*)-**5a**·H_2O (55.4°), suggesting that there is more severe steric repulsion between the two phenyl groups of (1*R*,2*S*)-**3** in this crystal than in (1*R*,2*S*)-**3**·(*R*)-**5a**·H_2O.

On the other hand, in the case of the salt of (1*R*,2*S*)-**3** with (*S*)-**5d**, water molecules are incorporated, just as in the case of (1*R*,2*S*)-**3**·(*R*)-**5a**·H_2O (Fig. 5). A columnar hydrogen-bond network formed by the ammonium hydrogens and the carboxylate oxygens exists, and the water molecules formed hydrogen bonds within this column with the hydroxy group of (1*R*,2*S*)-**3** and the carboxylate oxygens of (*S*)-**5d**. However, the bond lengths of the hydrogen-bonds involving the water molecule are longer than in (1*R*,2*S*)-**3**·(*R*)-**5a**·H_2O, suggesting weaker hydrogen-bonding interactions of the water molecules in the hydrogen-bond columns. The DSC-TG analysis of (1*R*,2*S*)-**3**·(*S*)-**5d**·H_2O, showing that water molecules were released in the range 50–80 °C at a much lower temperature than for (1*R*,2*S*)-**3**·(*R*)-**5a**·H_2O (*ca.* 145 °C), also supports the contention that the OH · · · O hydrogen bonds are weak in this crystal. Concerning the conformation of (1*R*,2*S*)-**3**, the

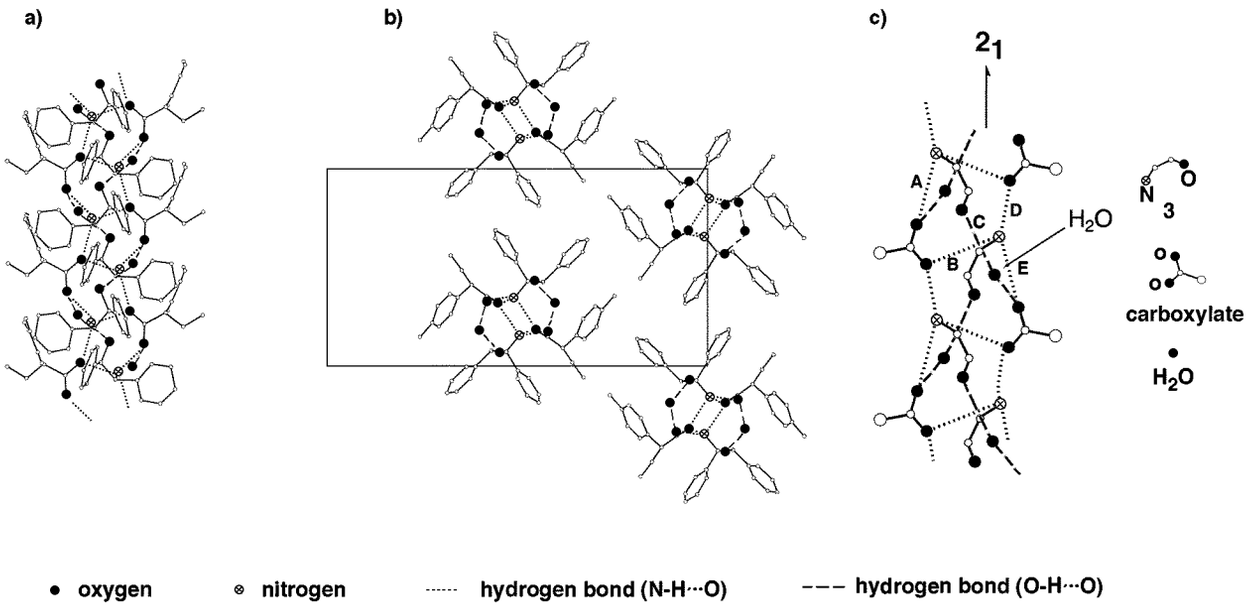


Fig. 5 Crystal structure of (1*R*,2*S*)-**3**·(*S*)-**5d**·H_2O. (a) Hydrogen-bond network. (b) Viewed down the 2_1-axis of the hydrogen-bond column (*c*-axis). The solid square shows the unit cell. (c) Schematic representation of the hydrogen-bond network.

dihedral angle between two phenyl groups (59.7°) is larger than that in (1*R*,2*S*)-**3**·(*R*)-**5a**·H_2O (55.4°). In this crystal, steric repulsion between the two phenyl groups of (1*R*,2*S*)-**3** is not so severe as in (1*R*,2*S*)-**3**·(*R*)-**5d**.

Thus, while a difference in stability can be deduced from comparison of the crystal structures of (1*R*,2*S*)-**3**·(*R*)-**5a**·H_2O and (1*R*,2*S*)-**3**·(*S*)-**5a**, which could be efficiently discriminated upon crystallisation, in contrast, comparison of the crystal structures of (1*R*,2*S*)-**3**·(*R*)-**5d** and (1*R*,2*S*)-**3**·(*S*)-**5d**·H_2O revealed that the difference in stability should be small, since the common hydrogen-bond columns, reinforced by additional hydrogen bonds including the hydroxy group of (1*R*,2*S*)-**3**, in both salts should be similar in stability from the point of view of the balance of attractive hydrogen-bonding and repulsive steric interactions, resulting in the low resolution efficiency. In addition, considering the strength of hydrogen bonds formed by the hydroxy group of (1*R*,2*S*)-**3**, which reinforce the columnar hydrogen-bond network, and the conformation of (1*R*,2*S*)-**3**, both (1*R*,2*S*)-**3**·(*R*)-**5d** and (1*R*,2*S*)-**3**·(*S*)-**5d**·H_2O seem less stable than (1*R*,2*S*)-**3**·(*R*)-**5a**·H_2O (and other less-soluble salts). The failure in realisation of the ideal less-soluble crystal structure in both (1*R*,2*S*)-**3**·(*R*)-**5d** and (1*R*,2*S*)-**3**·(*S*)-**5d**·H_2O might be a subsidiary reason for the low resolution efficiency for **5d**.

Conclusions

The common features of the diastereomeric salts of (1*R*,2*S*)-**3** with 2-arylalkanoic acids in the present study can be summarised as follows: (1) there is a columnar hydrogen-bond network formed by the ammonium hydrogens and the carboxylate oxygens and (2) the whole crystal can be regarded as supramolecular assemblies of the hydrogen-bond columns, in which there are only weak van der Waals' interactions between the columns.

High resolution efficiency is achieved when quite a stable hydrogen bond column is formed in the less-soluble salts, which is reinforced by strong hydrogen bonds between the hydroxy group and water molecules, while in the corresponding more-soluble salts, the hydroxy group is not involved in hydrogen bonding. In contrast, the resolution results in low efficiency when the hydroxy group participates moderately in the formation of hydrogen-bonds in each of a pair of diastereomeric salts. Note that the conformation of (1*R*,2*S*)-**3** varies according to the mode of the hydrogen bonds; the flexibility of (1*R*,2*S*)-**3** plays a role in the participation of the hydroxy group in the hydrogen-bond network.

Experimental

General

The IR spectra were recorded on a Jasco IR-810 spectrophotometer, and the ^1H and ^{13}C NMR spectra were measured on a JEOL PMX-60SI or Varian Mercury-300 instrument using tetramethylsilane as an internal standard. Analytical HPLC was performed using Daicel Chiralcel OJ, OB, OD (eluent: hexane–propan-2-ol), or OJ-R [eluent: 0.5 M H_3PO_4–KH_2PO_4 buffer (pH 2)–CH_3CN] columns with the detector wavelength at 254 nm. The chromatograms were recorded on a HITACHI D02500 chromato-integrator. DSC-TG thermograms were measured on Shimadzu DSC-50 and TG-50 instruments, using an aluminum pellet as a standard, at a scan rate of 5.0 °C min^{-1}.

(1*R*,2*S*)-**1**, (*R*-**2**, (1*R*,2*S*)-**3**, **4a** and **5a** were commercially available. All solvents were distilled before use.

Preparation of 2-arylalkanoic acids

Racemic acids **4**–**6** were prepared by the alkylation of the corresponding 2-arylacetic acids according to the reported procedure.[16] A typical procedure is shown for the synthesis of **5b**.

To a solution of *o*-tolylacetic acid (9.01 g, 0.06 mol) in THF (90 cm^3) was added dropwise Bu^{n}Li (81 cm^3, 0.13 mol, as 1.6 M hexane solution) at 0 °C under argon. Then, the white suspension formed was treated with, *N*,*N*′-hexamethylphosphoric triamide (12 cm^3 0.066 mol) to afford a homogeneous solution. After the reaction mixture had been stirred for 1 h at room temperature, ethyl iodide (4.97 cm^3, 0.072 mol) was added dropwise, and the mixture was stirred for a further 2 h. The reaction was quenched by the addition of 10% hydrochloric acid (220 cm^3). The liberated oil was extracted with diethyl ether (100 cm^3), and the organic layer was dried over anhydrous magnesium sulfate. Upon removal of the solvent under reduced pressure, the crude acid was obtained as a white solid, which was purified by recrystallisation from light petroleum (bp 30–70 °C) (150 cm^3) to afford **5b** (7.5 g, 63% yield) as white crystals. **5b**: ν_{max}/cm^{-1} 2840, 1700, 1225 and 920; δ_H(60 MHz; $CDCl_3$;

Me_4Si) 1.0 (3 H, t, *J* 7, Me), 2.0 (3 H, m, CH_2), 2.5 (3 H, s, *o*-*Me*Ph), 3.8 (1 H, t, *J* 7, CH), 7.3 (4 H, m, C_6H_4). Found: C, 74.04; H, 8.08. $C_{11}H_{14}O_2$ requires C, 74.13; H, 7.92%.

(*RS*)-2-(*o*-Tolyl)propionic acid (**4b**): ν_{max}/cm^{-1} 3000, 1700, 1240 and 760; δ_H(60 MHz; $CDCl_3$; Me_4Si) 1.5 (3 H, d, *J* 7, Me), 2.3 (3 H, s, *o*-*Me*Ph), 4.0 (1 H, q, *J* 7, CH), 7.2 (4 H, m, C_6H_4).

(*RS*)-2-(*m*-Tolyl)propionic acid (**4c**): ν_{max}/cm^{-1} 2950, 1710, 1610 and 480; δ_H(60 MHz; $CDCl_3$; Me_4Si) 1.5 (3 H, d, *J* 7, Me), 2.3 (3 H, s, *m*-*Me*Ph), 3.7 (1 H, q, *J* 7, CH), 7.2 (4 H, m, C_6H_4).

(*RS*)-2-(*p*-Tolyl)propionic acid (**4d**): ν_{max}/cm^{-1} 2950, 1710, 1515 and 480; δ_H(60 MHz; $CDCl_3$; Me_4Si) 1.4 (3 H, d, *J* 7, Me), 2.2 (3 H, s, *p*-*Me*Ph), 3.6 (1 H, q, *J* 7, CH), 7.1 (4 H, m, C_6H_4).

(*RS*)-2-(*m*-Tolyl)butyric acid (**5c**): ν_{max}/cm^{-1} 2840, 1700, 1225 and 920; δ_H(60 MHz; $CDCl_3$; Me_4Si) 1.0 (3 H, t, *J* 7, Me), 2.0 (3 H, m, CH_2), 2.5 (3 H, s, *m*-*Me*Ph), 3.8 (1 H, t, *J* 7, CH), 7.3 (4 H, m, C_6H_4). Found: C, 74.33; H, 7.90. $C_{11}H_{14}O_2$ requires C, 74.13; H, 7.92%.

(*RS*)-2-(*p*-Tolyl)butyric acid (**5d**): ν_{max}/cm^{-1} 2840, 1700, 1225 and 920; δ_H(60 MHz; $CDCl_3$; Me_4Si) 0.9 (3 H, t, *J* 7, Me), 2.0 (3 H, m, CH_2), 2.3 (3 H, s, *p*-*Me*Ph), 3.4 (1 H, t, *J* 7, CH), 7.2 (4 H, m, C_6H_4).

(*RS*)-2-Phenylpentanoic acid (**6**): ν_{max}/cm^{-1} 2810, 1700, 1220 and 700; δ_H(60 MHz; $CDCl_3$; Me_4Si) 1.0 (3 H, t, *J* 7, Me), 1.3 (2 H, m, CH_2), 1.9 (2 H, m, CH_2), 3.6 (1 H, t, *J* 7, CH), 7.4 (5 H, m, Ph).

(*RS*)-3-Methyl-2-phenylbutyric acid (**7**): ν_{max}/cm^{-1} 2890, 1710, 1220 and 710; δ_H(60 MHz; $CDCl_3$; Me_4Si) 0.7 (3 H, d, *J* 7, Me), 1.1 (3 H, d, *J* 7, Me), 2.4 (1 H, m, β-CH), 3.2 (1 H, d, *J* 7, α-CH), 7.4 (5 H, m, Ph).

Optical resolution of 2-arylalkanoic acids by (1*R*,2*S*)-3

Equimolar amounts of 2-arylalkanoic acid (**4**–**7**) (1–3 mmol) and (1*R*,2*S*)-**3** (1–3 mmol) were placed in a 5–10 cm^3 sample tube and suspended in an alcohol–water mixture (the quantities are listed in Table 2). The sample tube was heated on a hot-plate until the suspension turned to a clear solution. The heating was continued for an additional 10 min, and then the sample tube was moved to a water bath kept at 30 °C and allowed to stand for 12 h. The crystals precipitated were collected by filtration and dried *in vacuo* for a few hours. After the crystals had been treated with 1 M hydrochloric acid, the liberated acid was extracted with diethyl ether (10 cm^3), and then the ethereal solution was dried over magnesium sulfate. Removal of the solvent under vacuum gave the acid, the enantiomeric excess of which was determined by HPLC analysis. If necessary, the acid was converted to the corresponding methyl ester by treatment with diazomethane before HPLC analysis. The details for the selection of the HPLC-column and the eluent are available as supplementary material (SUPPL. NO. 57405, 1 pp.). For details of the Supplementary Publications Scheme see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, available *via* the RSC Web page (http://www.rsc.org/authors). The supplementary data is also available on the RSC's web server (http://www.rsc.org/suppdata/perkin2/1998/1767).

Crystal-structure determination and refinement

Preparation of single crystals. The single crystals of the less-soluble salts [(1*R*,2*S*)-**3**·(*R*)-**4a**·H_2O, (1*R*,2*S*)-**3**·(*R*)-**4c**·H_2O, (1*R*,2*S*)-**3**·(*R*)-**5a**·H_2O, (1*R*,2*S*)-**3**·(*R*)-**5b**·H_2O and (1*R*,2*S*)-**3**·(*R*)-**6**·H_2O] were directly prepared during the optical resolution experiments described above. Single crystals of (1*R*,2*S*)-**3**·(*S*)-**5a**, (1*R*,2*S*)-**3**·(*R*)-**5d** and (1*R*,2*S*)-**3**·(*S*)-**5d**·H_2O were prepared from an equimolar mixture of (1*R*,2*S*)-**3** and the corresponding enantiomerically pure acid upon slow evaporation of the solvent from an aqueous alcohol solution.

(1*R*,2*S*)-**3**·(*R*)-**4a**·H_2O.—mp 156.0–158.0 °C; ν_{max}/cm^{-1} 3360, 2150, 1960, 1890, 1820, 1590, 1530, 1500 and 1400.

(1*R*,2*S*)-**3**·(*R*)-**4c**·H_2O.—mp 144.0–145.0 °C; ν_{max}/cm^{-1} 3400, 2140, 1950, 1880, 1600, 1560, 1520 and 1400.

(1*R*,2*S*)-**3**·(*R*)-**5a**·H_2O.—mp 142.0–145.0 °C; ν_{max}/cm^{-1} 3400, 2150, 1960, 1880, 1810, 1630, 1520 and 1400.

(1*R*,2*S*)-**3**·(*S*)-**5a**.—mp 145.0–146.0 °C; ν_{max}/cm^{-1} 3450, 2150, 1960, 1880, 1810, 1600, 1560, 1520 and 1390.

(1*R*,2*S*)-**3**·(*R*)-**5b**·H_2O.—mp 96.0–97.0 °C; ν_{max}/cm^{-1} 3300, 2150, 1960, 1880, 1800, 1610, 1570, 1500 and 1390.

(1*R*,2*S*)-**3**·(*R*)-**5d**.—mp 154.0–154.5 °C; ν_{max}/cm^{-1} 3430, 2150, 1950, 1880, 1810, 1600, 1520, 1500 and 1390.

(1*R*,2*S*)-**3**·(*S*)-**5d**·H_2O.—mp 129.0–130.0 °C; ν_{max}/cm^{-1} 3600, 3300, 2150, 1960, 1890, 1820, 1560, 1520 and 1400.

(1*R*,2*S*)-**3**·(*R*)-**6**·H_2O.—mp 149.0–150.0 °C; ν_{max}/cm^{-1} 3360, 2150, 1960, 1890, 1820, 1620, 1560, 1520 and 1400.

Data collection and processing

The X-ray intensities were measured up to $2\theta = 130°$ with graphite-monochromated Cu-Kα radiation ($\lambda = 1.5418$ Å) on a Mac Science MXC18 four-circle diffractometer by a 2θ-ω scan. All of the data were collected at 293 K. The cell dimensions were obtained by the least-square analyses of the setting angles of 20 reflections ($50° < 2\theta < 60°$). The intensities and orientation of the crystals were checked by three standard reflections every 100 reflections.

Structure analysis and refinement

The structures were solved and refined by applying the CRYSTAN-GM package;[17] the direct method (SIR92[18]) followed by normal heavy-atom procedures, full-matrix least-squares refinement with all non-hydrogen atoms anisotropic and hydrogens in calculated positions with thermal parameters equal to those of the atom to which they were bonded. Final *R* and R_w values are given in Table 3. Atomic coordinates, thermal parameters, bond lengths and angles for all diastereomeric salts have been deposited at the Cambridge Crystallographic Data Centre. For details of the deposition scheme, see 'Instruction for Authors', *J. Chem. Soc.*, *Perkin Trans. 2*, available *via* the RSC Web page (http://chemistry.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 188/130.

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