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Hydrogen-bonding sheets in crystals for chirality recognition: synthesis and application of (2*S*,3*S*)-2,3-dihydroxy- and (2*S*,3*S*)-2,3-dibenzyloxy-1,4-bis(hydroxyamino)butanes

Yuka Kobayashi *, Yasushi Kokubo, Takamitsu Aisaka, Kazuhiko Saigo *

Department of Chemistry and Biotechnology, Graduate School of Engineering, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-8656, Japan

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ABSTRACT

Two enantiopure bis(hydroxyamino) compounds were successfully prepared from dialkyl tartrate by a chiral-pool method and applied as basic resolving agents in the enantioseparation of 2-arylpropanoic acids and arylglycolic acids. (2*S*,3*S*)-2,3-Dihydroxy-1,4-bis(hydroxyamino)butane (2*S*,3*S*)-**1a** could moderately recognize the chirality of the 2-arylpropanoic acids, while (2*S*,3*S*)-2,3-dibenzyloxy-1,4-bis(hydroxyamino)butane (2*S*,3*S*)-**1b** could not due to the low crystallinity of both the corresponding diastereomeric salts. On the other hand, (2*S*,3*S*)-**1b** showed a similar chirality-recognition ability for the arylglycolic acids. The ability of (2*S*,3*S*)-**1b** was different from those generally observed for widely used primary amine-type resolving agents with regard to the relationship between the resolution efficiency and the similarity in the relative molecular length of a resolving agent and a target racemate. The X-ray crystallographic analyses of the less-soluble diastereomeric salts revealed that in the salts (2*S*,3*S*)-**1a** formed a supramolecular sheet, of which the distance was variable to make the resultant dissymmetric space fit to the shape of the target acids, and that (2*S*,3*S*)-**1b** was constructed from a robust supramolecular sheet, consisting of hydrogen-bonding 2_1 columns, with the participation of the hydroxy group of the arylglycolic acids. These X-ray crystallographic analyses also suggested that for the formation of a supramolecular sheet, the coexistence of two hydroxyamino groups is essential.

1. Introduction

The enantioseparation of racemic amines/carboxylic acids via diastereomeric salt formation with an enantiopure carboxylic acid/amine (resolving agent) is an interesting method for obtaining the enantiopure forms of the racemates.[1,2] Among acidic resolving agents, enantiopure monocarboxylic acids and arylglycolic acids generally form a helical hydrogen-bonding column with a twofold screw axis in the center (2_1 column) in less-soluble salt crystals with chiral primary amines.[3–5] In contrast, tartaric acid, a typical diacidic resolving agent, frequently forms a two-dimensional hydrogen-bonding sheet in less-soluble 1:1 salt crystals with chiral primary amines.[6] The sheet is fundamentally constructed by (1) hydrogen bonds between the carboxyl group of a tartaric acid molecule and the carboxylate group of a neighboring tartrate molecule, which forms an ionic pair with an ammonium group derived from a chiral amine, in a head-to-tail manner to afford a one-dimensional chain and 2) those between the carboxyl/carboxylate groups of a chain and the hydroxy groups of a neighboring chain. As a result, there exists a two-dimensional dissymmetric space between the sheets, which can recognize the chirality of the ammonium molecules. Contrary to this, there is no strong intermolecular interaction other than van der Waals interaction between the sheet and the substituents of the ammonium molecules. Therefore, the distance between the sheets is variable to a considerable extent, depending on the molecular shape and/or length of the amine without the deterioration of the chirality-recognition ability of tartaric acid.

In a similar manner, enantiopure primary amines and amino alcohols (basic resolving agents) commonly form a 2_1 column in less-soluble salt crystals with chiral carboxylic acids. In contrast, alkaloids, such as quinine, morphine, and brucine, afford a two-dimensional hydrogen-bonding sheet in less-soluble salt crystals with chiral carboxylic acids to show a wide chirality-recognition ability arising from the variability of the distance between the sheets, although the hydrogen-bonding network is rather complicated. Thus, alkaloids are powerful basic resolving agents. However, they have serious drawbacks as resolving agents that only one of a pair of enantiomers is generally available, some of which are highly toxic. These situations prompted us to develop a new type of basic resolving agent, which can form a hydrogen-bonding sheet and recognize the chirality of a variety of racemic carboxylic acids upon changing the distance between the sheets.

* Corresponding authors. Tel.: +81 3 5841 7266; fax: +81 3 5802 3348 (K.S.).
E-mail addresses: saigo@chiral.t.u-tokyo.ac.jp, saigo@k.u-tokyo.ac.jp (K. Saigo).

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In order to realize the formation of a sheet by basic molecules, we selected a hydroxyamino group as a key functional group, because it is well known that its nitrogen atom is still basic and its hydroxy hydrogen atom is acidic to some extent; achiral 2,3-bis(hydroxyamino)-2,3-dimethylbutane has been reported to form a chain by hydrogen bonds between the hydroxyamino groups.[7] Herein, we report the synthesis and chirality-recognition ability of (2*S*,3*S*)-2,3-dihydroxy-1,4-bis(hydroxyamino)butane and its *O*,*O*′-dibenzylated derivative.

2. Results and discussion

2.1. Synthesis of (2*S*,3*S*)-2,3-dihydroxy- and (2*S*,3*S*)-2,3-dibenzyloxy-1,4-bis(hydroxyamino)butanes (2*S*,3*S*)-1a and -1b

Taking into account of the fact that the C_2 symmetric structure of tartaric acid plays an important role in the realization of its wide chirality-recognition ability and in the formation of a hydrogen-bonding sheet, and with an expectation that the hydroxy and hydroxyamino groups would be attractive as interactive functional groups in a crystal, we selected a C_2 symmetric alkane with two hydroxy groups and two hydroxyamino groups, as a fundamental skeleton. Finally, we designed (2*S*,3*S*)-2,3-dihydroxy-1,4-bis-(hydroxyamino)butane (2*S*,3*S*)-**1a**, because we could expect that both enantiomers of **1a** should be prepared from commercially available tartaric acid derivatives by a chiral-pool method (Fig. 1).

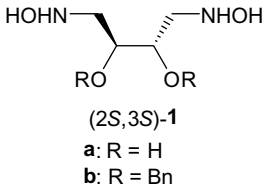


Figure 1. Structures of bis(hydroxyamino) compounds.

The target compound (2*S*,3*S*)-**1a** could be prepared from commercially available dimethyl (*R*,*R*)-tartrate **2a** through five steps involving a Mitsunobu reaction as a key step, as shown in Scheme 1. The reaction of (*R*,*R*)-**2a** with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate in methanol afforded the corresponding acetal **3**, which was reduced with sodium borohydride in methanol to give the dihydroxy acetal **4**. The Mitsunobu reaction of **4** with *N*,*O*-di(*tert*-butoxycarbonyl)hydroxyamine in the presence of triphenylphosphine/diisopropyl azodicarboxylate (DIAD), followed by the deprotection of the *tert*-butoxycarbonyl groups in the product with hydrogen chloride in ethanol, took place very smoothly to give (2*S*,3*S*)-**1a** dihydrochloride. The free form (2*S*,3*S*)-**1a** was so soluble in water that it was very hard to isolate (2*S*,3*S*)-**1a** by extraction with an organic solvent from an aqueous solution; the isolation of (2*S*,3*S*)-**1a** was finally achieved through an ion-exchange process using Diaion WA 30. For the handling of (2*S*,3*S*)-**1a**, special attention should be paid, because (2*S*,3*S*)-**1a** in a solution was rather unstable toward oxidation.

Although **1a** was successfully prepared as shown in Scheme 1, we were concerned about drawbacks in the recovery and re-use of (2*S*,3*S*)-**1a** due to its instability in a solution and high solubility in water. In order to overcome this anxiety, we next designed (2*S*,3*S*)-2,3-dibenzyloxy-1,4-bis(hydroxyamino)butane (2*S*,3*S*)-**1b** as another resolving reagent, although there was concern that the benzyloxy groups in **1b** would prevent the formation of a sheet by hydrogen bond(s) because of a lack of hydrogen-donating ability of the benzyloxy groups.

A procedure similar to that for the synthesis of (2*S*,3*S*)-**1a** was conducted for the preparation of (2*S*,3*S*)-**1b** (Scheme 2), the O,O′-dibenzylation of diethyl (*R*,*R*)-tartrate **2b**, the reduction of the O,O′-dibenzylated diester **5** with lithium aluminum hydride, the Mitsunobu reaction of diol **6**, the deprotection of the condensate **7** with hydrogen chloride in ethanol, and the extraction of (2*S*,3*S*)-**1b** from an aqueous solution of the reaction mixture. As expected, the reactions proceeded smoothly to give (2*S*,3*S*)-**1b**, which was more resistible than (2*S*,3*S*)-**1a** toward oxidation, although it is still unstable in a solution. Moreover, (2*S*,3*S*)-**1a** could be easily extracted from a water solution with ethyl acetate.

2.2. Chirality-recognition ability of (2*S*,3*S*)-1a and -1b

With the 1,4-bis(hydroxyamino)butane derivatives (2*S*,3*S*)-**1a**,**b** in hand, we at first attempted the enantioseparation of racemic 2-arylpropanoic acids **7a,b** and **8** with (2*S*,3*S*)-**1a** in order to demonstrate its chirality-recognition ability. When a 1:1 mixture of the 2-arylpropanoic acid and (2*S*,3*S*)-**1a** in ethanol/2-propanol (1:2, v/v) was refluxed and then slowly cooled down to 30 °C, the corresponding 1:1 salt deposited. The results are summarized in Table 1.

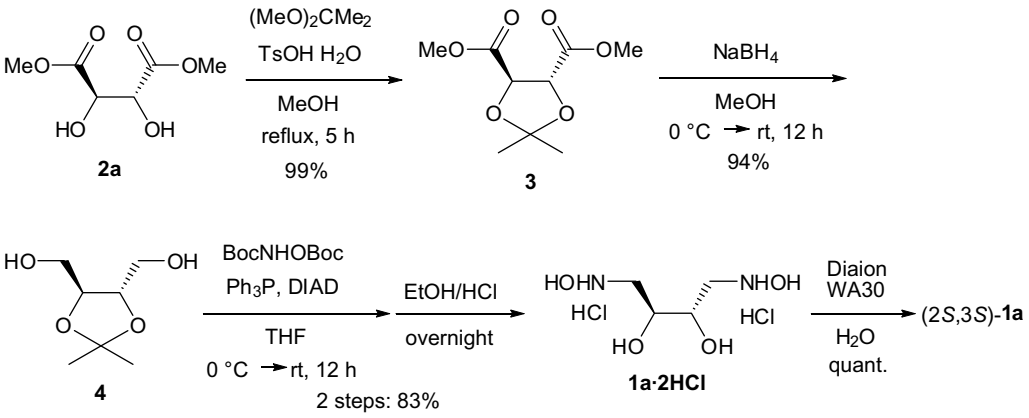
As can be seen from the resolution efficiencies (the yield × the enantiomeric excess), which represent the chirality-recognition ability of (2*S*,3*S*)-**1a** during the diastereomeric salt formation with the acids, (2*S*,3*S*)-**1a** showed a moderate chirality-recognition ability for the 2-arylpropanoic acids. It is noteworthy that (2*S*,3*S*)-**1a** could recognize the chirality of **8** with a relatively long molecular length, compared with (2*S*,3*S*)-**1a**, even though it is known that the chirality-recognition ability of a resolving agent dramatically deserved when increasing the molecular length of a target racemate.[8]

Next, we examined the chirality-recognition ability of (2*S*,3*S*)-**1b**. Contrary to the case of (2*S*,3*S*)-**1a**, the salts of **7** and **8** with (2*S*,3*S*)-**1b** did not crystallize at all. Then, we selected arylglycolic acids **9** and **10** as target racemates with the idea that the hydroxy group in the arylglycolic acids would contribute to the improvement of the crystallinity of the corresponding salts. At first, we attempted the enantioseparation of 2-naphthylglycolic acid **9** with (2*S*,3*S*)-**1b** and observed a peculiar phenomenon; a 2:1, **9**:(2*S*,3*S*)-**1b** salt was obtained even when the salt was allowed to crystallize from a methanol/water solution containing **9** and (2*S*,3*S*)-**1b** in a ratio of 1:1. The enantioseparation with (2*S*,3*S*)-**1b** was then conducted in a molar ratio of 2:1 for the arylglycolic acids and (2*S*,3*S*)-**1b**. The results are listed in Table 2.

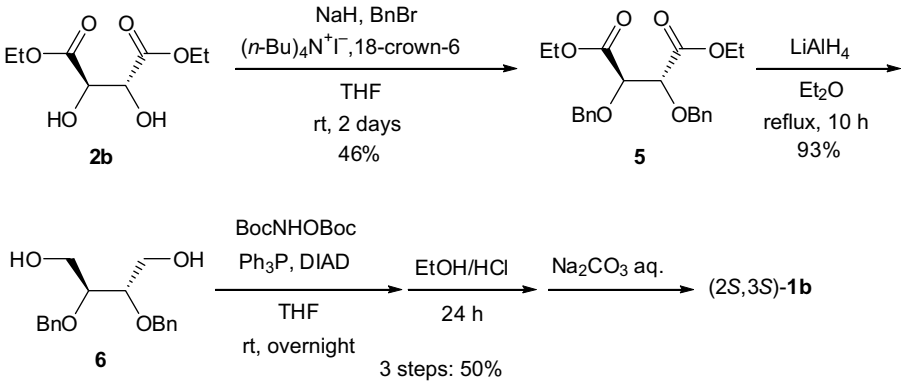
The bis(hydroxyamino) derivative (2*S*,3*S*)-**1b** showed an excellent chirality-recognition ability in the enantioseparation of the unsubstituted, *o*-substituted, and *m*-substituted mandelic acids **10a**-**d**, while the chirality of *p*-substituted mandelic acids **10e**,**f** was recognized less sufficiently by (2*S*,3*S*)-**1b** during the diastereomeric salt formation. Moreover, there was no positive correlation observed between the relative molecular lengths of **9**,**10e**-**g**/(2*S*,3*S*)-**1b** and the resolution efficiency. These results are considerably different from that generally observed in the enantioseparation of racemic carboxylic acids/primary amines with enantiopure primary amine-type/carboxylic acid-type resolving agents; such resolving agents commonly form a 2_1 column with the racemates to show a chirality-recognition ability for *m*-substituted derivatives which is lower than that for the mother compound and *o*-substituted derivatives.[8] The unique ability of (2*S*,3*S*)-**1b** suggests that another ordered structure different from a 2_1 column exists in the present diastereomeric salt crystals.

2.3. Crystal structures of the salts with (2*S*,3*S*)-1a or -1b

The single crystals of the less-soluble (2*S*,3*S*)-**1a**·**7a**[9] and **1a**·**7b**[10] salts were obtained with good quality for X-ray crystallographic

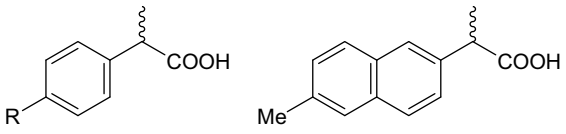


Scheme 1. Synthesis of (2*S*,3*S*)-**1a**.



Scheme 2. Synthesis of (2*S*,3*S*)-**1b**.

Table 1
Chirality-recognition ability of (2*S*,3*S*)-**1a** for 2-arylpropanoic acids[a]

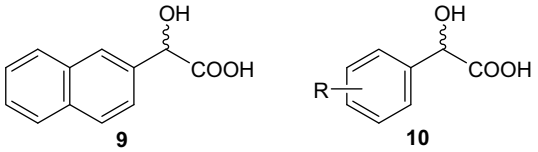


a: R = H **b**: R = Me

Racemic acid	Yield[b] (%)	ee[c] (%)	Resolution efficiency[d]
7a	50	56	0.28
7b	67	53	0.36
8	56	43	0.24

[a] Solvent, ethanol/2-propanol (1 mL/2 mL) normalized for a 1 mmol scale.
[b] Based on a half amount of the racemic acid used.
[c] The enantiomeric excess of the acid liberated from the salt by treatment with HCl aq.
[d] The yield × the ee.

Table 2
Chirality-recognition ability of (2*S*,3*S*)-**1b** for 2-arylglycolic acids[a]



a: R = H
b: R = *o*-Me
c: R = *m*-Me
d: R = *m*-Cl
e: R = *p*-Me
f: R = *p*-MeO
g: R = *p*-CF_3

Racemic acid	Yield[b] (%)	ee[c] (%)	Resolution efficiency[d]
9	81	73	0.59
10a	91	67	0.61
10b	86	65	0.56
10c	63	95	0.60
10d	63	95	0.60
10e	89	18	0.16
10f	86	19	0.16
10g	45	85	0.38

[a] Solvent, ethanol/water (1 mL/1 mL) normalized for a 1 mmol scale.
[b] Based on a half amount of the racemic acid used.
[c] The enantiomeric excess of the acid liberated from the salt by treatment with HCl aq.
[d] The yield × the ee.

analyses and successfully applied to the determination of their crystal structures (Figs. 2 and 3, respectively). Both crystal structures are intrinsically similar to each other in terms of the formation of a supramolecular sheet self-assembled by cooperative hydrogen bonds. Two hydroxyamino groups in a (2*S*,3*S*)-**1a** molecule contribute to the formation of a chain-like hydrogen-bonding network with neighboring molecules along the *a*-axis. Furthermore, two (2*S*,3*S*)-**1a** molecules are located in a face-to-face manner by a O–H···O hydrogen bond between one of the hydroxy groups of a (2*S*,3*S*)-**1a** molecule and that of a neighboring molecule along the *b*-axis. As a consequence, (2*S*,3*S*)-**1a** molecules construct

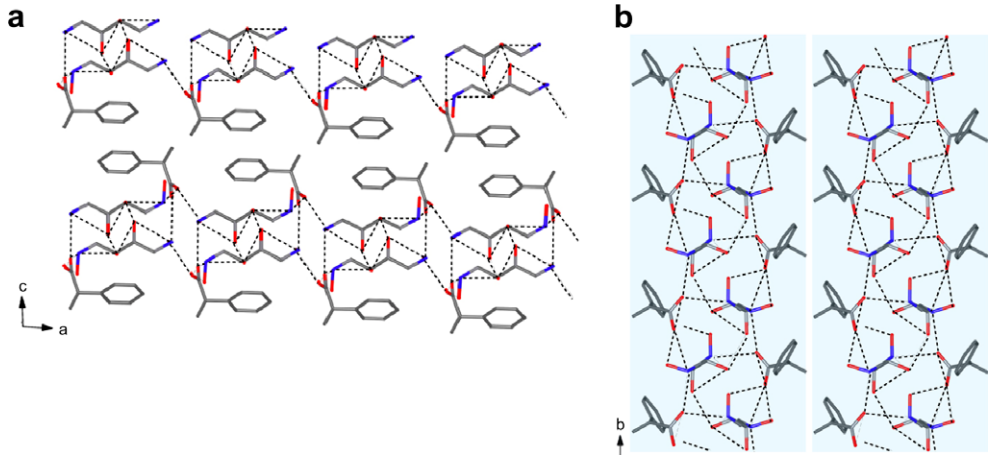


Figure 2. Crystal structure of the less-soluble (2*S*,3*S*)-**1a**·(*R*)-**7a** salt. (a) Viewed down along the *b*-axis. (b) Viewed down along the *a*-axis.

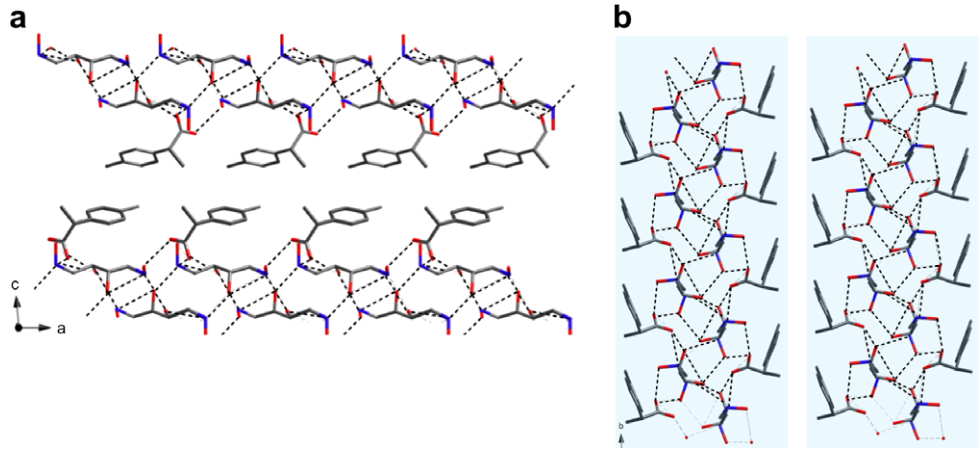


Figure 3. Crystal structure of the less-soluble (2*S*,3*S*)-**1a**·(*R*)-**7b** salt. (a) Viewed down along the *b*-axis. (b) Viewed down along the *a*-axis.

a self-assembled sheet by themselves in a manner very similar to that composed of enantiopure tartaric acid molecules. The target chiral carboxylic acid molecules are fixed between the supramolecular sheets by hydrogen bonds with three (2*S*,3*S*)-**1a** molecules; one is with the hydroxy group, and the others are with the amino parts of the hydroxyamino groups (Figs. 2a and 3a, respectively). These molecular arrangements strongly suggest that the distance between the supramolecular sheets might be able to flexibly

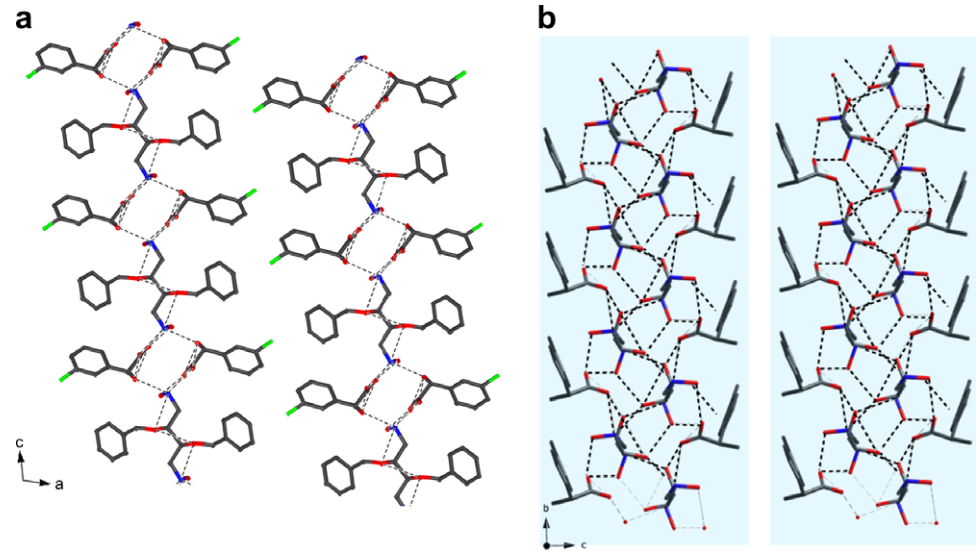


Figure 4. Crystal structure of the less-soluble (2*S*,3*S*)-**1b**·(*R*)-**10d** salt. (a) Viewed down along the *b*-axis. (b) Viewed down along the *a*-axis.

change the cavities between the sheets fit to the shape of the chiral carboxylic acid molecules. The result of the enantioseparation of racemic **8** strongly supports the easy change of the distance, because the resolution efficiency for **8** is at the same level to those for **7a**,**b** despite the fairly long molecular length of **8** compared with those of **7a**,**b**. This flexibility, not observed at all in 2_1 column systems,[8] would be one of the advantages of the present sheet structure, although more sophisticated design is required to realize high crystallinity as well as satisfactory chirality-recognition ability.

As mentioned above, the crystallinity of the salts of (2*S*,3*S*)-**1b** with the 1-arylpropionic acids **7** and **8** is very low, resulting in no deposition of the salts despite great effort in the examination of solvent systems and crystallization conditions. In contrast, the salts of (2*S*,3*S*)-**1b** with the 1-arylglycolic acids **9** and **10** exhibit good crystallinity and moderate/good resolution efficiency, most likely owing to the additional hydroxy group of **9** and **10**. The crystal structures of (2*S*,3*S*)-**1b**·**10d**[11] are shown in Figure 4. The mechanism for the chirality recogntion with (2*S*,3*S*)-**1b** would be fundamentally the same as that with (2*S*,3*S*)-**1a** in the respect that a supramolecular sheet is constructed in the less-soluble salt. However, the hydrogen-bonding pattern and molecular array are largely different from those of (2*S*,3*S*)-**1a**. The hydroxyamino group of (2*S*,3*S*)-**1b** and the carboxylate and hydroxy groups of **10d** construct a columnar hydrogen-bonding network with a twofold screw axis in the center, and this network runs in the supramolecular sheet along the *b*-axis; the hydroxy group of **10d** plays an important role to form the robust supramolecular sheet consisting of the columnar hydrogen-bonding networks to dramatically improve the crystallinity of the less-soluble diastereomeric salt. Moreover, the distance between the supramolecular sheets seems to be variable to some extent, depending on the shape of the acid incorporated, as those in the less-soluble salts of (2*S*,3*S*)-**1a** with 1-arylpropanoic acids. The robust intercolumnar hydrogen-bonding network would stabilize the less-soluble salt and contribute to the realization of the moderate/good chirality-recogniton ability of (2*S*,3*S*)-**1b**.

3. Conclusion

The new basic resolving agents (2*S*,3*S*)-**1a** and -**1b** have been successfully synthesized, and were found to show a chirality-recognition ability for some racemic 2-arylpropanoic acids and 2-arylglycolic acids. The crystal structures of the less-soluble salts of (2*S*,3*S*)-**1a** or -**1b** showed that two-dimensional supramolecular sheets, which are constructed by hydrogen-bonded hydroxyamino groups, included target molecules and are stacked in a three-dimensional manner. The chirality recognition between the sheets occurred upon changing the distance between the sheets to a considerable extent, in dependence of the shape and/or size of the target molecules.

4. Experimental

4.1. General

Melting points were determined on a Yamato MP-21. IR spectra were recorded on a Jasco model FT/IR-480 Plus. ^{1}H NMR spectra were recorded on a Varian Mercury 300 instrument operating at 300 MHz. Angles of rotations were measured on a Jasco DIP-360 polarimeter. X-ray data were collected on a Mac Science DIP-2000 with graphite monochromated Mo Kα irradiation. High performance liquid chromatographic analyses were carried out on a Chiralcel or Chiralpak column (Daicel) using a Jasco PU-2080 Plus or PU-2080i Plus pump equipped with a Jasco 2075 Plus UV detector and a Hitachi D-2500 Chromato-Integrator.

4.2. Synthesis of dimethyl (*R*,*R*)-*O*,*O*′-isopropylidenetartrate 3

To a solution of dimethyl (*R*,*R*)-tartrate (40.0 g, 225 mmol) in dry methanol (18 mL) were successively added 2,2-dimethoxypropane (60 mL, 488 mmol) and *p*-toluenesulfonic acid monohydrate (0.36 g, 2 mmol) under an argon atmosphere, and the solution was heated at 77 °C (bath temperature) for 1 h; during the period, the color of the solution turned to a reddish black. After dry cyclohexane (85 mL) was added to the reaction mixture, methanol and acetone were removed by using a Vigreux column under gentle reflux. Next, 2,2-dimethoxypropane (10 mL, 81 mmol) and dry cyclohexane (15 mL) were added to the mixture, and the solution was refluxed for 1 h. Upon cooling the solution to room temperature, K_2CO_3 (2.0 g) was added, and the reddish black color faded. The insoluble mass in the solution was filtered off, and the filtrate was concentrated under reduced pressure. The residual oil which remained was roughly purified by short silica gel column chromatography (eluent: hexane/ethyl acetate = 2:1, v/v). Distillation (96–98 °C, 3 mmHg) of the oil gave pure **3** (48.4 g, 222 mmol, 99%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 6H), 3.83 (s, 6H), 4.82 (s, 2H).

4.3. Synthesis of (2*S*,3*S*)-2,3-isopropylidenedioxy-1,4-butanediol 4

To a solution of dimethyl (*R*,*R*)-*O*,*O*′-isopropylidenetartrate **3** (10.0 g, 46 mmol) in dry methanol (165 mL), cooled with an ice bath, was added sodium borohydride (8.8 g, 229 mmol) in small portions under an argon atmosphere, and the mixture was stirred at the same temperature for 1 h and then at room temperature for 3 h, after which it was concentrated under reduced pressure. Water (300 mL) was added to the remaining residue, and the aqueous mixture was extracted with ethyl acetate (4 × 250 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give crude **4** with an acceptable purity (6.97 g, 43 mmol, 94%) as an yellowish oil. The crude **4** thus obtained was used for the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 6H), 2.31 (br s, 2H), 3.69–3.73 (m, 2H), 3.79–3.83 (m, 2H), 4.00–4.02 (m, 2H).

4.4. Synthesis of (2*S*,3*S*)-2,3-dihydroxy-1,4-bis(hydroxyamino)butane dihydrochloride 1a·2HCl

To a solution of (2*S*,3*S*)-2,3-isopropylidenedioxy-1,4-butanediol **4** (1.24 g, 7.7 mmol), triphenylphosphine (6.02 g, 33 mmol), and *N*,*O*-bis(*t*-butoxycarbonyl)hydroxyamine (5.35 g, 33 mmol) in dry tetrahydrofuran (70 mL) was added dropwise diisopropyl azodicarboxylate (3.63 g, 18 mmol) using a syringe at 0 °C under an argon atmosphere. The mixture was stirred at the same temperature for 2 h and then at room temperature overnight, after which it was concentrated under reduced pressure. An ethanol solution saturated with HCl (30 mL) was added to the remaining residue at 0 °C, and the solution was stirred overnight at room temperature and concentrated under reduced pressure. The suspension of the remaining solid in chloroform (200 mL) was ultrasonicated for 3 min, and the powdery solid mass was collected by filtration and dried under reduced pressure to give **1a·2HCl** (1.42 g, 6.3 mmol, 83%) as a white powdery solid. IR (KBr) 3532, 3404, 2942 (br), 1575, 1513, 1448, 1402, 1312, 1244, 1147, 1042, 1003 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 3.32–3.41 (m, 8H), 4.05–4.10 (m, 4H).

4.5. Liberation of (2*S*,3*S*)-2,3-dihydroxy-1,4-bis(hydroxyamino)butane 1a

A solution of (2*S*,3*S*)-2,3-dihydroxy-1,4-bis(hydroxyamino)butane dihydrochloride **1a**·**2HCl** (1.27 g, 5.6 mmol) in water (1 mL) was charged on a column filled with a weakly basic ion exchange resin (Diaion WA 30, 20 equiv), and the product was eluted with water (5 mL). The elution was collected, concentrated under reduced pressure, and dried thoroughly under reduced pressure to give **1a** (0.85 g, 5.6 mmol, quant.) as a white solid. $[\alpha]_D^{23.5} = +54.3$ (*c* 1.44, H_2O); IR (KBr) 3195, 3094 (br), 1436, 1167, 1080, 1039 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.69–2.73 (m, 2H), 2.80–2.84 (m, 2H), 3.35 (s, 2H), 3.61 (s, 2H), 5.50 (br s, 2H), 7.19 (s, 2H). HRMS (ESI) calcd for [M ($C_4H_{12}N_2O_4$)+H]$^+$ 153.0875, found 153.0868.

4.6. Synthesis of diethyl (2*R*,3*R*)-2,3-dibenzyloxysuccinate 5

Sodium hydride (50% in a mineral oil, 10.2 g, 233 mmol) washed with hexane (3 × 200 mL) was suspended in dry tetrahydrofuran (120 mL) under an argon atmosphere, and a solution of diethyl (*R*,*R*)-tartrate (25.1 g, 122 mmol) in dry tetrahydrofuran (85 mL) was added dropwise to the suspension at 0 °C over a period of 1.5 h. The reaction mixture was stirred at 0 °C for 4 h and then at room temperature overnight. To the mixture was successively added tetrabutylammonium iodide (9.0 g, 24 mmol) and 18-crown-6 (200 mg, 0.8 mmol). Finally, benzyl bromide (27.7 mL, 233 mmol) was added dropwise to the mixture at 0 °C over a period of 30 min. The reaction mixture was stirred at room temperature, after which the reaction was quenched by adding 1 M HCl aq (300 mL). The resulting reaction mixture was extracted with ether (3 × 200 mL), and the combined extracts were successively washed with satd $NaHCO_3$ (200 mL) and brine (200 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The remaining residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 10:1 to 2:1, v/v) to give pure **5** (20.4 g, 53 mmol, 46%) as a colorless oil. ^1H NMR (300 MHz, CD_3OD) δ 1.18 (t, *J* = 15 Hz, 6H), 3.9–4.3 (m, 4H), 4.39 (s, 2H), 4.45 (d, *J* = 12 Hz, 2H), 4.87 (d, *J* = 12 Hz, 2H), 7.25–7.40 (m, 10H).

4.7. Synthesis of (2*S*,3*S*)-2,3-dibenzyloxy-1,4-butanediol 6

To a suspension of lithium aluminum hydride (3.1 g, 81 mmol) in dry ether (45 mL) was added dropwise a solution of diethyl (2*R*,3*R*)-2,3-dibenzyloxysuccinate **5** (14.8 g, 38 mmol) in dry ether (30 mL) at 0 °C under an argon atmosphere, and the mixture was stirred for 1 h at room temperature, for 7 h at reflux, and overnight at room temperature. The remaining lithium aluminum hydride derivatives were quenched by adding H_2O (10 mL) and 6 M HCl aq (10 mL) successively, and reaction mixture was extracted with ether (3 × 50 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The remaining residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 5:1, v/v) to give pure **6** (10.8 g, 36 mmol, 93%) as a colorless oil. ^1H NMR (300 MHz, CD_3OD): δ 2.36 (s, 2H), 3.68–3.83 (m, 6H), 4.65 (s, 4H), 7.25–7.38 (m, 10H).

4.8. Synthesis of (2*S*,3*S*)-2,3-dibenzyloxy-1,4-bis(hydroxyamino)butane 1b

To a solution of (2*S*,3*S*)-2,3-dibenzyloxy-1,4-butanediol **6** (5.29 g, 18 mmol), triphenylphosphine (13.77 g, 53 mmol), and *N*,*O*-bis(*t*-butoxycarbonyl)hydroxyamine (12.25 g, 53 mmol) in dry tetrahydrofuran (175 mL) was dropwise added diisopropyl azodicarboxylate (11.0 mL, 53 mmol) at 0 °C under an argon atmosphere. The mixture was stirred at the same temperature for 3 h and then at room temperature overnight, after which it was concentrated under reduced pressure, and thoroughly dried under reduced pressure. An ethanol solution saturated with HCl (3 mL) was added to the residue at room temperature, and the solution was stirred overnight at room temperature, after which it was concentrated under reduced pressure and thoroughly dried under reduced pressure. The remaining solid was suspended in chloroform (100 mL), and the powdery solid mass was collected by filtration and dried under reduced pressure. To a solution of the remaining powder in water (200 mL) was added Na_2CO_3 until the pH reached 7, and the aqueous solution was extracted with ethyl acetate (3 × 100 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The remaining solid mass was recrystallized from hexane/ethyl acetate to give **1b** (2.91 g, 8.8 mmol, 50%). Mp 72–73 °C; $[\alpha]_D^{23.5} = -36.0$ (*c* 1.03, MeOH); IR (KBr): 3186, 2922, 1455, 1361, 1218, 1089, 1047, 750, 696 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ 2.92 (dd, *J* = 4 and 13 Hz, 2H), 3.13 (dd, *J* = 6 and 13 Hz, 2H), 3.90–3.92 (m, 2H), 4.64 (d, *J* = 11 Hz, 2H), 4.70 (d, *J* = 11 Hz, 2H), 7.26–7.36 (m, 10H). Anal. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N; 8.43. Found: C, 65.08; H, 7.20; N; 8.31.

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10. Crystal data for (2*S*,3S)-**1a**·(S)-**7b**: $C_{14}H_{24}N_2O_6$, *M* = 316.35, monoclinic, space group $P2_1$, *a* = 8.448(5) Å, *b* = 6.542(4) Å, *c* = 14.618(12) Å, *V* = 805.1(10) Å^3, *Z* = 2, D_c = 1.305 Mg m^{-3}, *R* = 0.0480, R_w = 0.0540. CCDC 694657 contains the supplementary crystallographic data for this paper.[12]
11. Crystal data for (2*S*,3S)-**1b**·(R)-**10d**: $C_{34}H_{38}Cl_2N_2O_{10}$, *M* = 705.59, monoclinic, space group *C*2, *a* = 33.105(6) Å, *b* = 4.9790(8) Å, *c* = 10.995(3) Å, *V* = 1752.4(6) Å^3, *Z* = 2, D_c = 1.337 Mg m^{-3}, *R* = 0.0570, R_w = 0.0610. CCDC 694658 contains the supplementary crystallographic data for this paper.[12]
12. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).