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Resolution of racemic 1-benzyl-5-oxo-3-pyrrolidinecarboxylic acid with enantiopure (*S*)-phenylalanine *N*-benzylamide via diastereomeric salt formation

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Abstract—The resolution of racemic 1-benzyl-5-oxo-3-pyrrolidinecarboxylic acid **1**, a potent chiral synthon with high pharmacological activity, was investigated with a variety of basic chiral resolving agents via diastereomeric salt formation. The findings in the optimization of resolution conditions aiming at an industrial-scale production revealed that (*S*)-phenylalanine benzylamide (*S*)-**10** and 2-propanol containing ca. 4 mol % of water to (*RS*)-**1** were the best conditions for obtaining enantiopure less-soluble diastereomeric salt, (*S*)-**1**/(*S*)-**10**/0.5H_2O (81%, 98% de, *E* 79%). X-ray crystallographic analysis of the salt clearly revealed that water molecules play a key role in crystallizing the enantiopure salt crystals, while stabilizing the crystal structure via three types of hydrogen-bond network associated with water molecules in addition to usual acid–base hydrogen bond.

1. Introduction

It is well known that a number of pyrrolidinone compounds are useful key intermediates for various types of drugs, such as antidepressants [Rolipram, (*R*)-**2**][1], antihypertensive [Cromakalim, (*S*)-**3**],[2] or muscarinic antagonist [Oxotremorine, **4**].[3] Various researches have been reported which show how to synthesize such functionalized pyrrolidinone compounds[4] and to clarify their SARs (structure–activity relationships).[5] Among them, especially, enantiopure 1-benzyl-5-oxo-3-pyrrolidinecarboxylic acid (*S*)-**1** is the most likely one to exhibit interesting pharmacological activity because the oxo-analog, enantiopure paraconic acid (*S*)-**5**,[6] acts as an inducer of cytodifferentiation in many streptomycetes (Fig. 1).

(*RS*)-**1** is commonly prepared via the Michael reaction of itaconic acid with benzylamine.[5,7] The carboxyl group on the pyrrolidinone ring of **1** can be easily converted into the corresponding ester, amide, or hydroxyl group. For this reason, therefore, compound **1** is considered to be a useful chiral building block in synthetic organic chemistry. Although it is known that (*RS*)-**1** can be produced effectively, only a few methods of producing enantiopure **1** have been reported, such as enzymatic stereoselective hydrolysis of its methyl ester,[5] resolution of its amide by HPLC[8] and diastereomeric resolution of (*RS*)-**1** with cinconine.[9] Unfortunately, these methods are considered difficult to apply to an industrial-scale production from economical and scale-up technical points of view.

To establish an industrial production process for preparing enantiopure **1**, we have investigated the resolution of (*RS*)-**1** with chiral basic resolving agents. As a result, we found that (*S*)-phenylalanine benzylamide (*S*)-**10** is the most preferable resolving agent for the resolution of (*RS*)-**1**, and the water molecule contained in the solvent plays a crucial role in crystallizing the enantiopure less-soluble salt. We herein report a new efficient preparation method of enantiopure **1** by resolution via diastereomeric salt formation suited for the industrial-scale production, and discuss the molecular mechanism of the resolution reaction on the basis of the X-ray crystallographic analysis of less-soluble diastereomeric salt.

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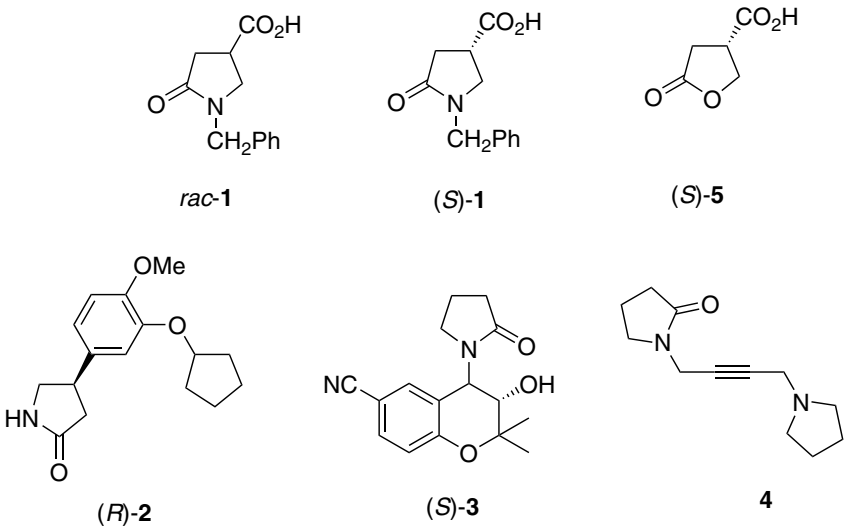

Figure 1.

2. Results and discussion

2.1. Screening of resolving agents

Racemic **1** was prepared according to the method proposed by Felluga et al.[5] and was used for resolution experiments as a starting material. First, 15 commercially available basic resolving agents classified in seven (7) types of basic structures, such as enantiopure (a) alanine derivatives, (b) phenylalanine derivatives, (c) pyrrolidine derivatives, (d) aminocyclohexanol derivatives, (e) 1-phenylethylamine derivatives, (f) aromatic amines, and (g) aliphatic diamines. The structures of the resolving agents used in the experiments are illustrated in Figure 2. Screening of resolving agents was performed using approximately 2 mmol-scale of (*RS*)-**1**, an equivalent amount of resolving agent, and 1 mL of pure or mixed solvent (water, methanol, or 2-propanol). As a result, 2-propanol was chosen as a universal solvent for the resolution experiments, judging from the solubility and appearance of the obtained salt, whereas no crystal was precipitated due to the excessive solubility of the intended salt in the solvents when methanol or water was used as a solvent. The screening results using 2-propanol as a solvent are summarized in Table 1.

As shown in Table 1, fine salt crystals were precipitated with (*S*)-alanine benzylamide (*S*)-**6** (entry 1), (*S*)-phenylalanine benzamide (*S*)-**9** (entry 4), and (*S*)-phenylalanine benzylamide (*S*)-**10** (entry 5), while no crystal was precipitated or scaled solids were obtained with the other resolving agents. These test results indicate that the 'aromatic' group of the effective resolving agents **6**, **9**, and **10** plays an extremely important role for realizing salt crystallization. Furthermore, these phenomena obviously suggest that the critical parameter of salt crystallization would not be the main backbone with a stereogenic center but the moiety of the aromatic amide such as a benzamide or benzylamide (entries 1, 4, and 5). On the other hand, solid–liquid separability of the salt crystals from mother liquor is also an extremely important factor for industrial-scale production and is affected by the appearances of the salt crystals such as shape, rigidity, and thickness. And it is true that appearances vary remarkably, depending on the resolving agent used. On the basis of this empirical knowledge, the salt crystal with (*S*)-**10** was the best in terms of separability of the salt from mother liquor. Thus, the resolution condition of (*RS*)-**1** with (*S*)-**10** in 2-propanol was optimized in detail.

2.2. Optimization of the solvent for the resolution of (*RS*)-1 with (*S*)-10

Resolution of (*RS*)-**1** with (*S*)-**10** in 2-propanol was optimized to obtain enantiopure **1**. The test results are summarized in Table 2. As shown in the Table 2, the enantiomeric purity of the salt obtained from pure 2-propanol was as low as 29% de [(*S*)-enantiomer rich, entry 1]. We tried to change the solvent property, by adding small amounts of water into 2-propanol.[10] As a result, it was surprisingly found that the enantiomeric purity drastically increased while the resolution efficiency (*E*)[11] remained nearly unchanged in a range of water contents between 0.6 and 3.7 mol %, and large rigid and clear salt crystals containing (*S*)-**1** with higher enantiomeric purity (98% de) were obtained when 3.7 mol % of water was added to (*RS*)-**1** (entry 6). This result clearly indicates that water molecule leads the chiral recognition as observed in our previous studies.[10,12] Resolved (*S*)-**1** in the diastereomeric salt obtained could be easily isolated in the usual manner, where cleavage with alkaline water and extraction with solvent were carried out, followed by acidification and filtration to give enantiopure acid (*S*)-**1** without any deterioration of the enantiomeric purity of the diastereomeric salt. To determine the role of the water molecule, the crystal structure of the less-soluble diastereomeric salt was determined by X-ray crystallographic analysis.

2.3. Role of water in resolution: crystal structure of the less-soluble diastereomeric salt

X-ray crystallographic analysis of the less-soluble salt revealed that molar ratios of substrate, resolving agent,

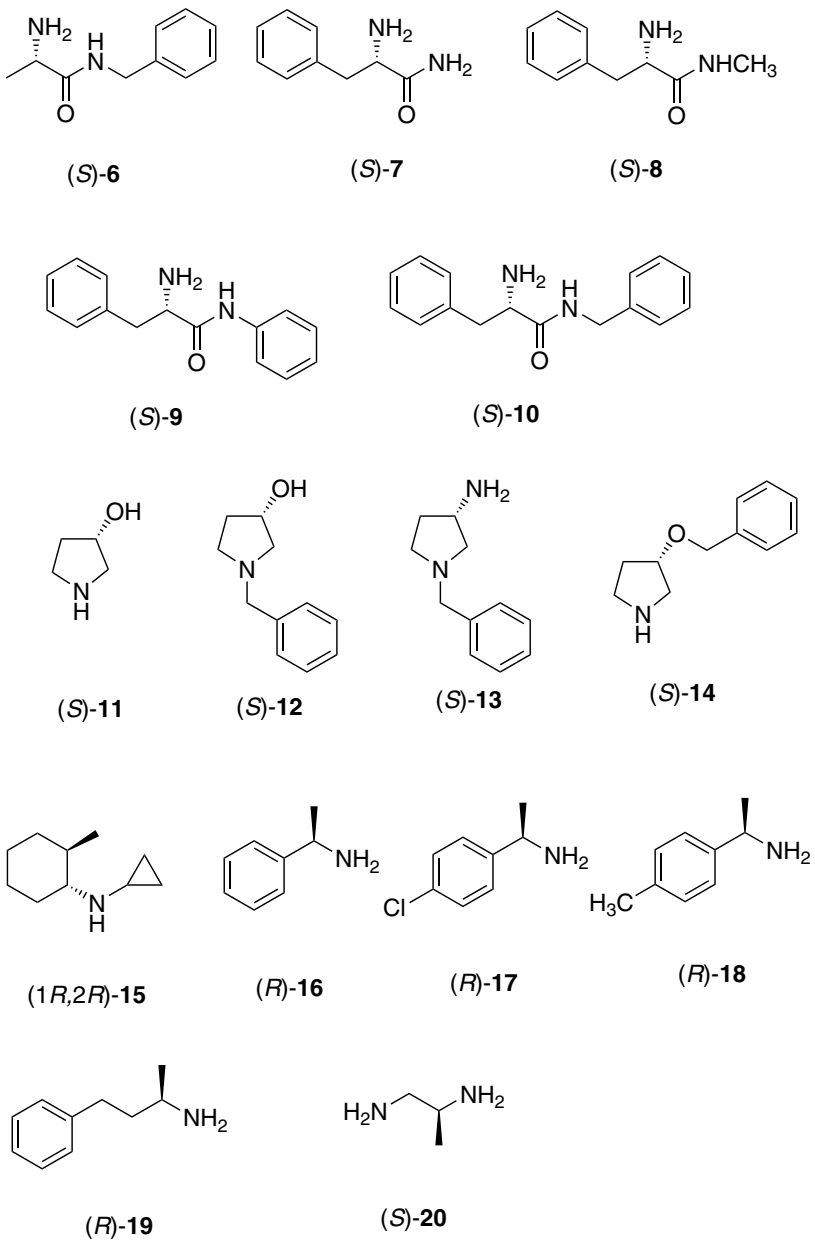

Figure 2. Resolving agents.

and water were 1:1:0.5 [(*S*)-**1**/(*S*)-**10**/0.5H_2O]. This result was also supported by the elemental analysis of the salt. The crystal data and structure of the less-soluble salt are shown in Table 3 and Figure 3, respectively.

Figure 3, as seen from the *a*-axis, demonstrates that the less-soluble salt crystallizes in space group *P*1, crystal system 'triclinic' with $Z = 1$. The unit lattice consists of four molecules of (*S*)-**10** (resolving agent), four molecules of (*S*)-**1**, and two molecules of water. All the phenyl rings of (*S*)-**1** and (*S*)-**10** located on the [0 0 1] and [0 0 2] planes form hydrophobic space which stabilizes the outer surface along + and − sides of the *c* axis. Although we did not measure the interaction lengths between all of the atoms in detail, there is no doubt that the crystal consists of not only hydrogen bonds between some functional groups, but also a variety of interactions, such as π–π intramolecular interaction between two types of phenyl rings in one (*S*)-**10** molecule, and CH–CH intermolecular interaction between two phenyl rings of adjacent (*S*)-**10** molecules, CH–π intermolecular interaction between phenyl ring of (*S*)-**1** molecule and the phenyl ring of (*S*)-**10** molecules, CH–CH intermolecular interaction between benzylic methylene of (*S*)-**1** molecule and phenyl ring of (*S*)-**10** molecules. Furthermore, it is thought that the van der Waals interactions were closely related to the stability of the crystal formation.

The X-ray crystal structure analysis reveals that the carboxyl group of (*S*)-**1** strongly bonds to the amino group of the resolving agent based on a common acid–base interaction, NH–O hydrogen bond. In addition, the crystal contains three types of hydrogen bonds associated with water molecules, (a) O(water)–HN(**10**), (b) OH(water)–O=C(**10**), and (c) OH(water)–O=C(**1**). It is clear that these

Table 1. Screening results of resolving agents in 2-propanol

Entry	Main structure	Resolving agent for (*RS*)-**1**	Solubility	Crystallization
1	Alanine	(*S*)-Alanine *N*-benzylamide **6**	A	a
2	Phenylalanine	(*S*)-Phenylalanine amide **7**	B	NA
3		(*S*)-Phenylalanine *N*-methylamide **8**	A	c
4		(*S*)-Phenylalanine *N*-benzamide **9**	A	a
5		(*S*)-Phenylalanine *N*-benzylamide **10**	A	a
6	Pyrrolidine	(*S*)-3-Hydroxypyrrolidine **11**	A	c
7		(*S*)-1-Benzyl-3-hydroxypyrrolidine **12**	A	c
8		(*S*)-1-Benzyl-3-aminopyrrolidine **13**	A	b
9		(*R*)-3-Benzyloxypyrrolidine **14**	A	c
10	Aminocyclohexanol	(1*R*,2*R*)-2-Cyclopropylaminocyclohexanol **15**	A	c
11	1-Phenylethylamine	(*R*)-1-Phenylethylamine **16**	A	b
12		(*R*)-1-(4-Chlorophenyl)ethylamine **17**	A	b
13		(*R*)-1-(4-Methylphenyl)ethylamine **18**	A	b
14	Aromatic amine	(*R*)-1-Phenyl-3-butylamine **19**	A	c
15	Aliphatic diamine	(*S*)-1,2-Diaminopropane **20**	A	c

Solubility = A: dissolved at less than 65 °C, B: not dissolved. Crystallization = a: crystallized, b: scaled, c: not crystallized, NA: not applicable.

Table 2. Resolution of (*RS*)-**1** with (*S*)-**10** in 2-propanol with or without water

Entry	Water/**1** (mol %)	Yield (%)	Diastereomeric excess (% de)	Resolution efficiency[a] (*E*, %)
1	0.0	96	29	28
2	0.6	107	69	74
3	1.0	95	80	76
4	1.4	95	84	80
5	1.8	81	95	77
6	3.7	80	98	78
7	5.9	6	86	5

[a] Resolution efficiency (*E*, %) = yield (%) × diastereomeric excess (% de) × 2/100.

interactions contribute critically to the formation of three-dimensional networks in the hydrophilic layer and stabilize the crystal structure. Accordingly, it was concluded that the crystal structure of the less-soluble salt is stabilized by the supraspace formed between the [0 0 1] and [0 0 2] planes, composed of the four types of hydrogen bonds, the acid–base interaction based on NH–O hydrogen bond between the carboxyl group of (*S*)-**1** and the amino group of (*S*)-**10**, and three hydrogen bonds via water molecules as mentioned above.

3. Conclusion

The resolution of racemic 1-benzyl-2-oxo-3-pyrrolidine carboxylic acid (*RS*)-**1** via diastereomeric salt formation was investigated aiming at an industrial production. The findings in the optimization of the resolution parameters for obtaining (*S*)-**1** were that (*S*)-phenylalanine benzylamide (*S*)-**10** and 2-propanol containing water (ca. 4 mol %) are the most suitable combination of resolving agent and solvent, respectively. The X-ray crystallographic analysis of the less-soluble salt revealed that water molecules play a key role in forming stable rigid salt crystals with high enantiomeric purity. The three types of hydrogen bonds associated with water molecules and the usual acid–base hydrogen bond between molecules **1** and **10** form three-dimensional hydrophilic supraspace.

Table 3. Crystal data and structure refinement for (*S*)-**1**/(*S*)-**10**/0.5H_2O

Empirical formula	$4(C_{16}H_{18}N_2O)\cdot4(C_{12}H_{13}NO_3)\cdot2H_2O$
Formula weight	1930.26
Temperature	93 K
Wavelength (Å)	1.54187
Crystal system	Triclinic
Space group	*P* 1
Unit cell dimensions	$a = 11.486\ (8)$ Å, $\alpha = 108.65\ (5)°$ $b = 14.015\ (10)$ Å, $\beta = 90.72\ (5)°$ $c = 18.328\ (13)$ Å, $\gamma = 114.06\ (4)°$
Volume	2517(3) Å^3
Z	1
Density (calculated) (g/cm^3)	1.273
Absorption coefficient (mm^{-1})	0.703
F(000)	1028
Crystal size (mm^3)	0.10 × 0.05 × 0.05
Theta range for data collection (°)	3.68–67.50
Index ranges	$-13 \leqslant h \leqslant 13$, $-16 \leqslant k \leqslant 16$, $-21 \leqslant l \leqslant 21$
Reflections collected	15,128
Independent reflections	15,128 [*R*(int) = 0.0000]
Completeness to theta = 67.50° (%)	93.4
Absorption correction	Empirical
Max. and min. transmission	0.9657 and 0.9330
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	15,128/9/1280
Goodness-of-fit on F^2	0.888
Final *R* indices [$I > 2$sigma(I)]	$R_1 = 0.1189$, $wR_2 = 0.2616$
R indices (all data)	$R_1 = 0.2200$, $wR_2 = 0.3291$
Largest diff. peak and hole (e Å^{-3})	0.003 and −0.003

4. Experimental

4.1. General

Racemic 1-benzyl-2-oxo-3-pyrrolidine carboxylic acid (*RS*)-**1** (CP > 99% by HPLC) was prepared according to the conventional method[5] using the Michael reaction of itaconic acid with benzylamine. All the basic resolving agents

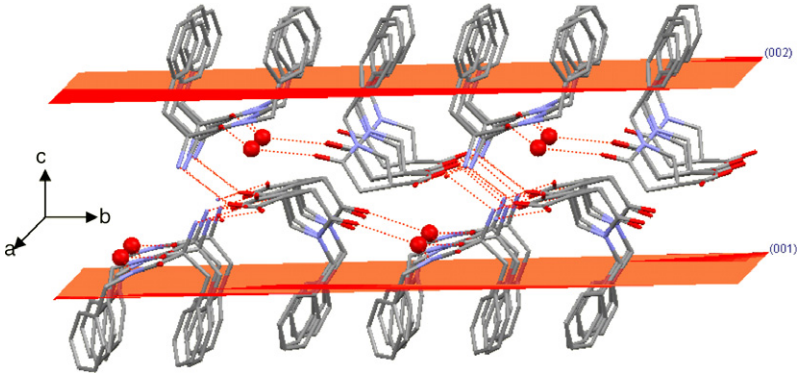

Figure 3. Crystal structure of (*S*)-**1**/(*S*)-**10**/0.5H_2O viewed along the *a*-axis. Red balls and dotted lines indicate water molecules and hydrogen bonds, respectively.

used were prepared according to the methods disclosed in the patents[13] and had high enantiomeric purities with over 99% ee or 99% de.

X-ray crystallographic analysis was performed on a Rigaku *R*-axis Rapid diffractometer with Cu Kα radiation ($\lambda = 1.54187$ Å) at 93 K. Optical rotations were measured with a JASCO DIP-140 polarimeter. Melting points were obtained on a YAMATO apparatus MODEL MP-21. IR spectrum was measured on a PERKIN ELMER SYSTEM 2000 spectrometer in KBr pellet. ^{1}H NMR spectrum was recorded on a JEOL JNM-AL400 spectrometer (400 MHz for a proton), using $CDCl_3$ as solvent and tetramethylsilane as the internal reference. Elemental analysis was run on Perkin Elmer CHNS/O 2400II Analyzer. Enantiomeric purity (diastereomeric excess, de %) of the salt was directly determined by HPLC using a CHIRALPAK AD-RH (ID 4.6 mm × 150 mm, DAICEL). Analytical conditions for the HPLC were as follows; mobile phase; aqueous phosphoric acid (pH 2)/acetonitrile = 84/16 (v/v), detector: UV (220 nm), column temperature: 40 °C, elution rate: 0.5 (mL/min.). Retention times; (*R*)-enantiomer 15.2 min, (*S*)-enantiomer 16.8 min.

4.2. Resolution of (*RS*)-1 with (*S*)-10

A typical resolution procedure is as follows. To a 100 mL-flask were added 5.02 g of (*RS*)-**1** (22.9 mmol), 5.80 g of (*S*)-**10** (22.8 mmol), 32.7 g of 2-propanol, and 1.5 g of water (3.7 mol % to (*RS*)-**1**) followed by heating to obtain a homogeneous solution at 65 °C. After cooling, the precipitated diastereomeric salt was filtrated and washed with 2-propanol (80.6% on the basis of (*S*)-enantiomer contained in the fed (*RS*)-**1**, 98% de, $E = 79\%$). Analytical data for the recrystallized salt is as follows: (*S*)-**1**/(*S*)-**10**/0.5H_2O: $[\alpha]_D^{25} = +20.9$ (*c* 10.0, MeOH); >99% de; mp 102–105 °C; IR (KBr) cm^{-1}: 3512, 3424, 3323, 3248, 3088, 3064, 3030, 2940, 2158, 1683, 1669, 1560, 1496, 1457, 1395, 1271, 1225, 1199, 1078, 951, 918, 853, 732, 697, 601; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.60–7.20 (m, 15H), 4.71–4.37 (m, 4H), 3.73 (dd, $J = 4.4$ Hz, 9.2 Hz, 1H), 3.51–3.43 (m, 2H), 3.27 (dd, $J = 14.0$ Hz, 4.4 Hz, 1H), 3.19 (dddd, $J = 8.0$ Hz, 8.0 Hz, 8.0 Hz, 8.0 Hz, 1H), 2.68–2.82 (m, 3H); Anal. Calcd for $C_{28}H_{31}N_3O_4 \cdot 0.5H_2O$: C, 69.69; H, 6.68; N, 8.71. Found: C, 69.68; H, 6.66; N, 8.70.

The less-soluble salt obtained was recrystallized from 2-propanol containing 3.7 mol % of water to the amine component of the salt. The filtrated crystal was treated with toluene and aqueous sodium hydroxide. The resulting aqueous layer was separated and extracted with tetrahydrofuran under acidic conditions with sulfuric acid. The upper layer (oil) was separated and concentrated to give the crystalline (*S*)-**1** with 99% ee.

(*S*)-**1**: $[\alpha]_D^{25} = +15.5$ (*c* 0.5, EtOH); 99% ee; mp 100 °C (lit.[5a] 99–100 °C); IR (KBr) cm^{-1}:3409, 2923, 2882, 2800, 2495, 1907, 1709, 1632, 1497, 1465, 1455, 1438, 1426, 1359, 1332, 1263, 1202, 1177, 1110, 1070, 1040, 1005, 975, 931, 917, 888, 852, 820, 805, 759, 703, 677, 612; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.60–7.20 (m, 5H), 4.53 (d, $J = 14.4$ Hz, 1H), 4.40 (d, $J = 14.4$ Hz, 1H), 3.45–3.60 (m, 2H), 3.15–3.30 (m, 1H), 2.79 (dddd, $J = 8.0$ Hz, 8.0 Hz, 8.0 Hz, 8.0 Hz, 2H).

4.3. X-ray crystallographic structure analysis (Fig. 4 and Table 3)

Single crystals of (*S*)-**1**/(*S*)-**10**/0.5H_2O [4($C_{16}H_{18}N_2O$)·4($C_{12}H_{13}NO_3$)·2(H_2O), MW = 1930.26] suitable for X-ray analysis were grown by slowly cooling a hot 2-propanol/water (0.89 g/0.07 g) solution of (*S*)-**1**/(*S*)-**10**/0.5H_2O (100 mg) to ambient temperature, and a single colorless crystal with dimensions 0.10 × 0.05 × 0.05 mm was selected for intensity measurements. The unit cell was triclinic with the space group *P*1 with $Z = 1$. Crystal data and structure refinement for (*S*)-**1**/(*S*)-**10**/0.5H_2O are summarized in Table 3. Crystallographic data for (*S*)-**1**/(*S*)-**10**/0.5H_2O have been deposited with Cambridge Crystallographic Data Centre as supplementary publication number CCDC 666198. The ORTEP drawing is shown in Figure 4.

The absolute configuration was determined from the known configuration of (*S*)-**10**. All calculations were performed using the CrystalStructure crystallographic

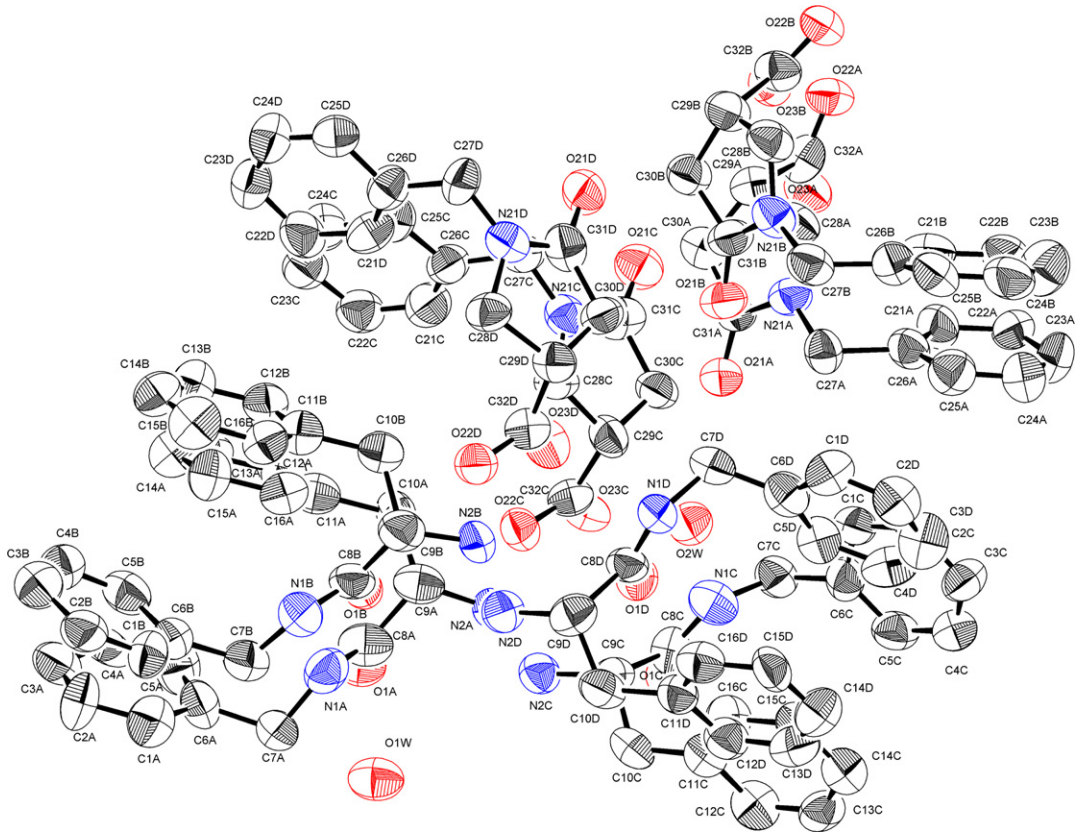

Figure 4. ORTEP drawing of (*S*)-**1**/(*S*)-**10**/0.5H_2O.

software package.[14] The structure was solved by direct methods using the program SHELXS-97[15] and refined by full-matrix least squares methods on F^2 using SHELXL-97.[16] All non-hydrogen atoms were refined anisotropically.

The very small crystal size and weak diffraction led to a low $2\theta_{max}$ for the data used in the refinement. The positions of all the hydrogen atoms were calculated geometrically and refined as a riding model. The hydrogen atoms of the water molecules and the amino groups which could not be located from difference Fourier maps. Since the number of possible hydrogen moieties that could be involved was quite large, no attempt was made to place the hydrogen atoms at calculated positions.

Crystals of (*S*)-**1**/(*S*)-**10**/0.5H_2O indicated twinning. Combined data with complete or no overlap were used for refinement, and the twinning prevented the merging of equivalent reflections before refinement. The partially overlapped reflections were rejected, resulting in a low data completeness value of 93.4%. The TwinRotMat procedure in PLATON[17] was used to generate a HKLF5 file containing 15,128 reflections.

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