

Supporting Information

**Chirality Determination from X-ray powder data –
Diastereomeric Co-crystals of Mandelic Acid
and Proline Amide**

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Experimental Section

Materials.

(*R*)-proline amide and (*S*)-proline amide, the co-crystal formers (*R*)-mandelic acid and (*S*)-mandelic acid as well as racemic mandelic acid and the solvent ethanol were commercially available and were used as received without further purification.

Scheme S1. Structural formula of mandelic acid and proline amide.

Solvent drop grinding.

Proline amide mandelic acid co-crystals were produced by grinding an equimolar mixture of the components (total mass of ~100 mg). The compound mixtures were placed into stainless steel grinding beakers (5 mL) and two drops of ethanol were added to the mixture before starting mechanical grinding in a Fritsch mini-mill “pulverisette 23” for 30 min at a frequency of 50Hz, using one stainless steel grinding ball (Ø 10 mm). The external temperature of the grinding jars at the conclusion of the grinding experiments did not exceed circa 35 °C. The solid phases were then characterized by X-ray powder diffraction.

Data collection.

X-Ray diffraction data were collected in transmission geometry at ambient temperature on a STOE STADI P diffractometer equipped with a Ge (111) primary monochromator and a linear position sensitive detector, using Cu-K α_1 radiation ($\lambda=1.54060$ Å) at 40 kV and 40 mA. Samples were prepared by filling the material between two zero scattering foils. Each sample was analyzed between 4°-65° 2θ with a step size of 0.01° 2θ and a total scan time of 14.5 h.

Structure solution and refinement.

Initial indexing of the powder pattern using the program *TOPAS* returned an orthorhombic unit cell (space group $P2_12_12_1$) with lattice parameters $a = 9.4764$ Å, $b = 10.1706$ Å, $c = 14.5367$ Å, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 90^\circ$ and a volume of 1401.05 Å³ for the (*R*)-mandelic acid-

(*R*)-proline amide co-crystal. The Pawley fit using the program *DASH* gave a reasonable fit to the data, with a χ^2 of 1.703.

In the case of (*S*)-mandelic acid-(*R*)-proline amide co-crystal the indexing of the powder pattern using also the program *TOPAS* returned an orthorhombic unit cell (space group $P2_12_12_1$) with lattice parameters $a = 9.3347 \text{ \AA}$, $b = 10.1039 \text{ \AA}$, $c = 14.7107 \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 90^\circ$ and a volume of 1387.78 \AA^3 . The Pawley fit using the program *DASH* gave a reasonable fit to the data, with a χ^2 of 2.379.

Consideration of molecular volumes suggested the presence of four molecules within the unit cell for both co-crystals.

The crystal structures were solved with the programs *DASH* (simulated annealing (SA)) and *TOPAS* (Rietveld refinement). The geometries of the molecules were taken from single-crystal data from the CSD (Version 5.32 (Nov. 2010)). The compounds of one co-crystal system have three flexible torsion angles (see Scheme S1), which combined with six translational (three from each compound) and six orientational degrees (three from each compound) of freedom. This corresponds to 15 degrees of freedom. In order to obtain a better statistic regarding reproducibility the number of SA runs was adjusted to 25 runs. A promising solution with a final χ^2 value of 8.31 for the (*R*)-mandelic acid-(*R*)-proline amide co-crystal and χ^2 value of 6.88 for the (*S*)-mandelic acid-(*R*)-proline amide co-crystal was reached after the SA.

Rietveld refinements were carried out with *TOPAS* using all diffraction data. The *TOPAS* input file was generated automatically by the *DASH*-to-*TOPAS* link available in *DASH*. Suitable chemical restraints were automatically generated by *DASH*. The Rietveld refinement for both co-crystal structures gave good R_{wp} values (3.8 % and 4.7 %) and good fitted curves (Figs. S2,S3 and Table S1).

Table S1. Refinement data

	(<i>R</i>)-mandelic acid-(<i>R</i>)-proline amide	(<i>S</i>)-mandelic acid-(<i>R</i>)-proline amide
Formula	C ₁₃ H ₁₈ N ₂ O ₄	C ₁₃ H ₁₈ N ₂ O ₄
Temperature	ambient	ambient
<i>M</i> _r /g • mol ⁻¹	266.29	266.29
Crystal system	orthorhombic	orthorhombic
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 2 ₁ 2 ₁ 2 ₁
Unit cell dimension		
<i>a</i> /Å	9.47497(16)	9.32239(21)
<i>b</i> /Å	10.17469(14)	10.09939(22)
<i>c</i> /Å	14.53205(25)	14.71604(33)
α/°	90	90
β/°	90	90
γ/°	90	90
<i>V</i> /Å ³	1400.960(39)	1385.522(53)
<i>Z</i>	4	4
2θ Data/°	4.00-64.99	4.00-64.99
<i>R</i> _{wp} Pawley/%	6.2	9.0
<i>R</i> _{wp} Rietveld/% ¹	3.8	4.7
<i>R</i> _{Bragg} /%	0.88	1.06
<i>Gof</i>	1.4	1.4

¹ The *r*_{wp} value is given from the TOPAS output.

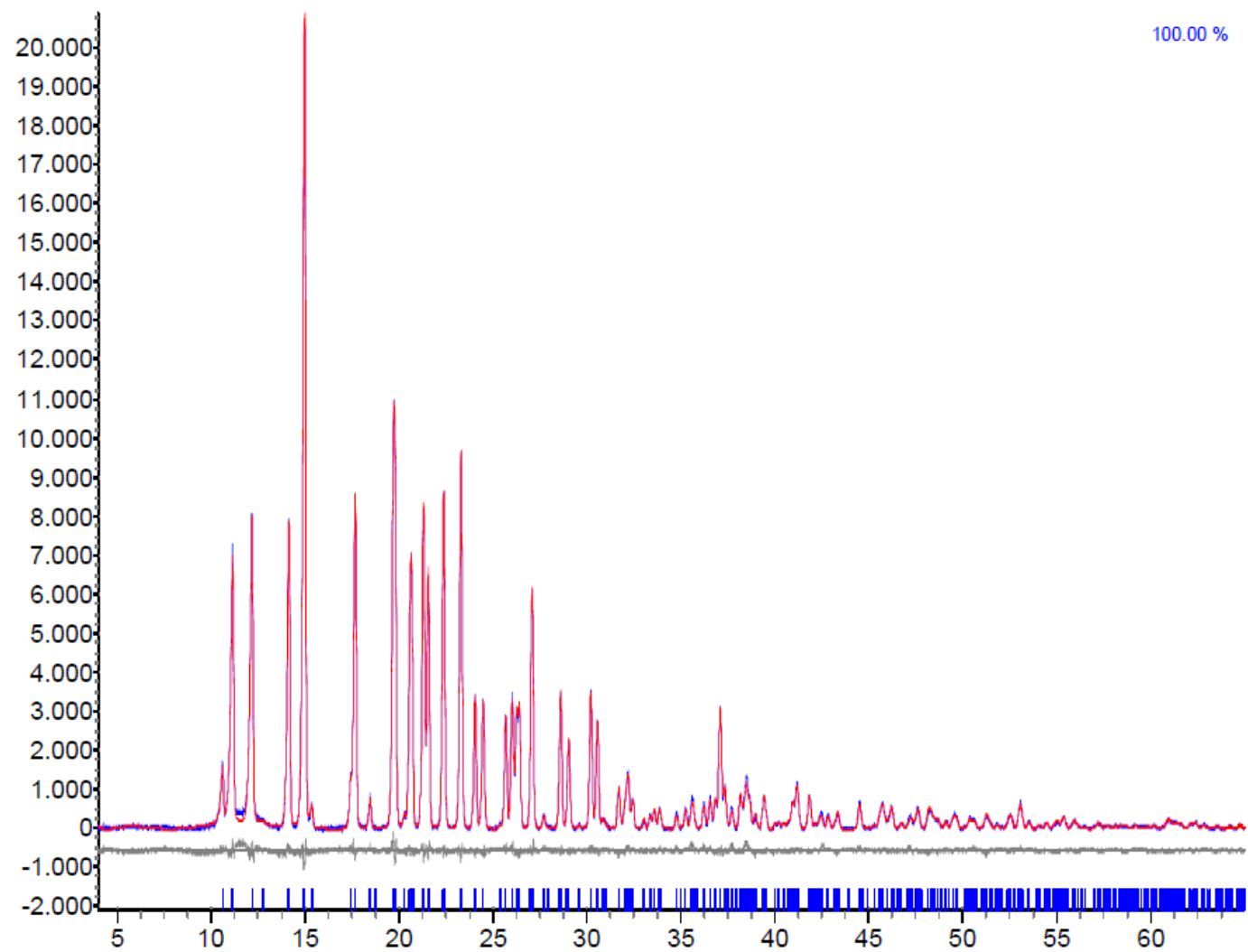


Figure S1. Final X-ray diffraction Rietveld plot for the (*R*)-mandelic acid-(*R*)-proline amide co-crystal.

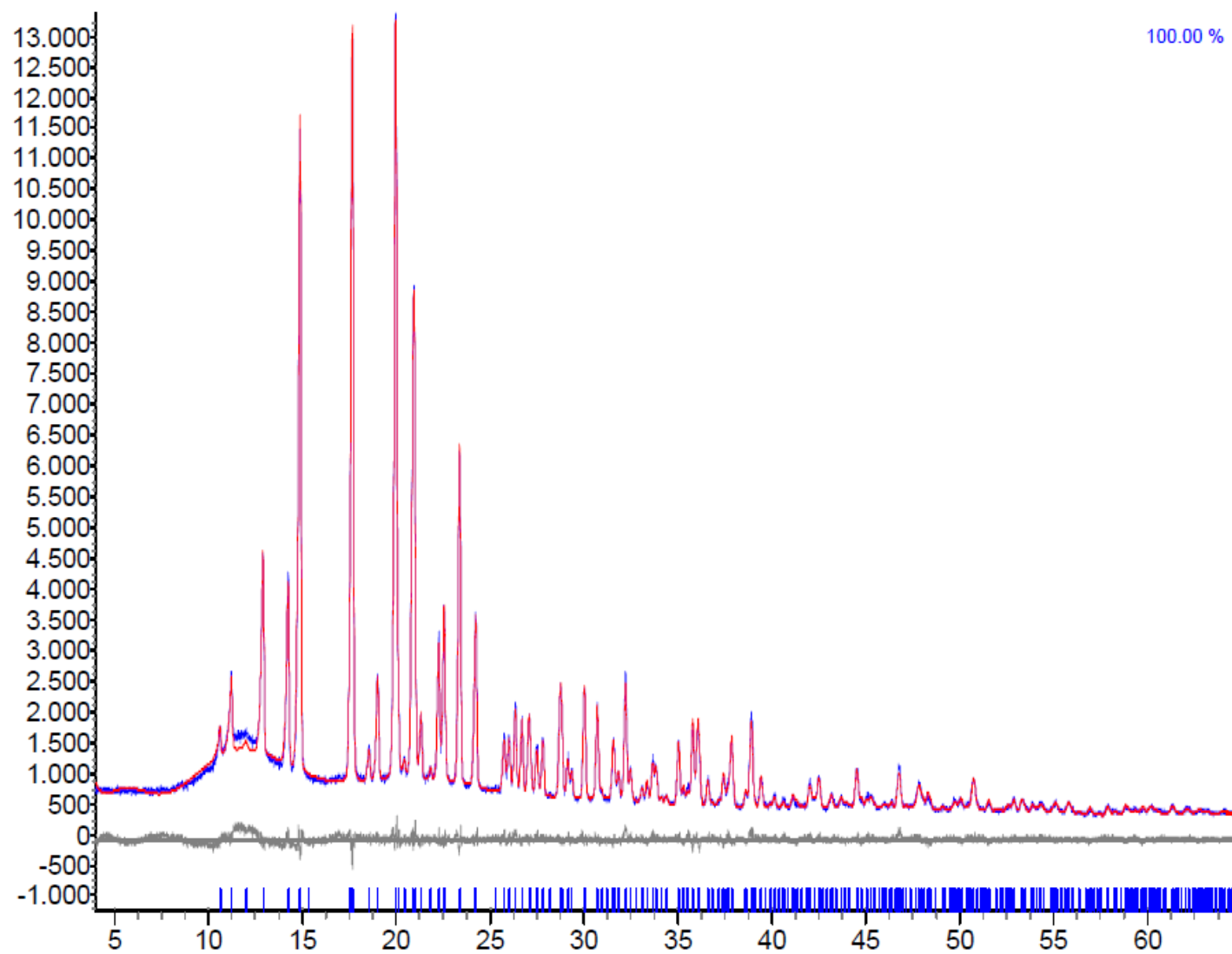


Figure S2. Final X-ray diffraction Rietveld plot for the (S)-mandelic acid-(R)-proline amide co-crystal.

Table S2. Hydrogen bonds with H...A < r(A) + 2.000 Angstroms and Angle DHA > 110 deg.

Compound	D-H...A	d(D-H)/Å	d(H...A) /Å	d(D...A) /Å	Angle DHA/°	symm
(R/R)	N8-H8A...O9	1.008	1.604	2.603	170.25	[1-x,-1/2+y,1.5-z]
	N1-H1B...O9	1.009	1.827	2.834	175.67	[1.5-x,-y,-1/2+z]
	O13-H13A...O3	0.830	2.268	2.826	124.84	[1/2-x,-y,1/2+z]
	N1-H1A...O13	1.009	2.022	3.002	163.07	[1-x,1/2+y,1.5-z]
	N8-H8B...O10	0.999	2.000	2.890	147.15	[1/2-x,-y,-1/2+z]
(S/R)	N8-H8A...O9	1.011	1.694	2.681	164.01	[1.5-x,1-y,-1/2+z]
	N1-H1A...O9	1.009	1.879	2.885	173.74	[-1/2+x,1/2-y,-1-z]
	O13-H13A...O3	0.983	1.870	2.801	157.00	[2-x,-1/2+y,1.5-z]
	N1-H1B...O13	1.009	1.990	2.909	150.17	[x,y,z]
	N8-H8B...O10	1.000	1.884	2.791	149.30	[2-x,1/2+y,1.5-z]

O44 H44 O33 2_674 0.990(10)

1.99(3) 2.842(6) 143(2)

O33 H33b O2 4_467 0.970(10)

1.820(10)

2.715(7) 152.0(10)

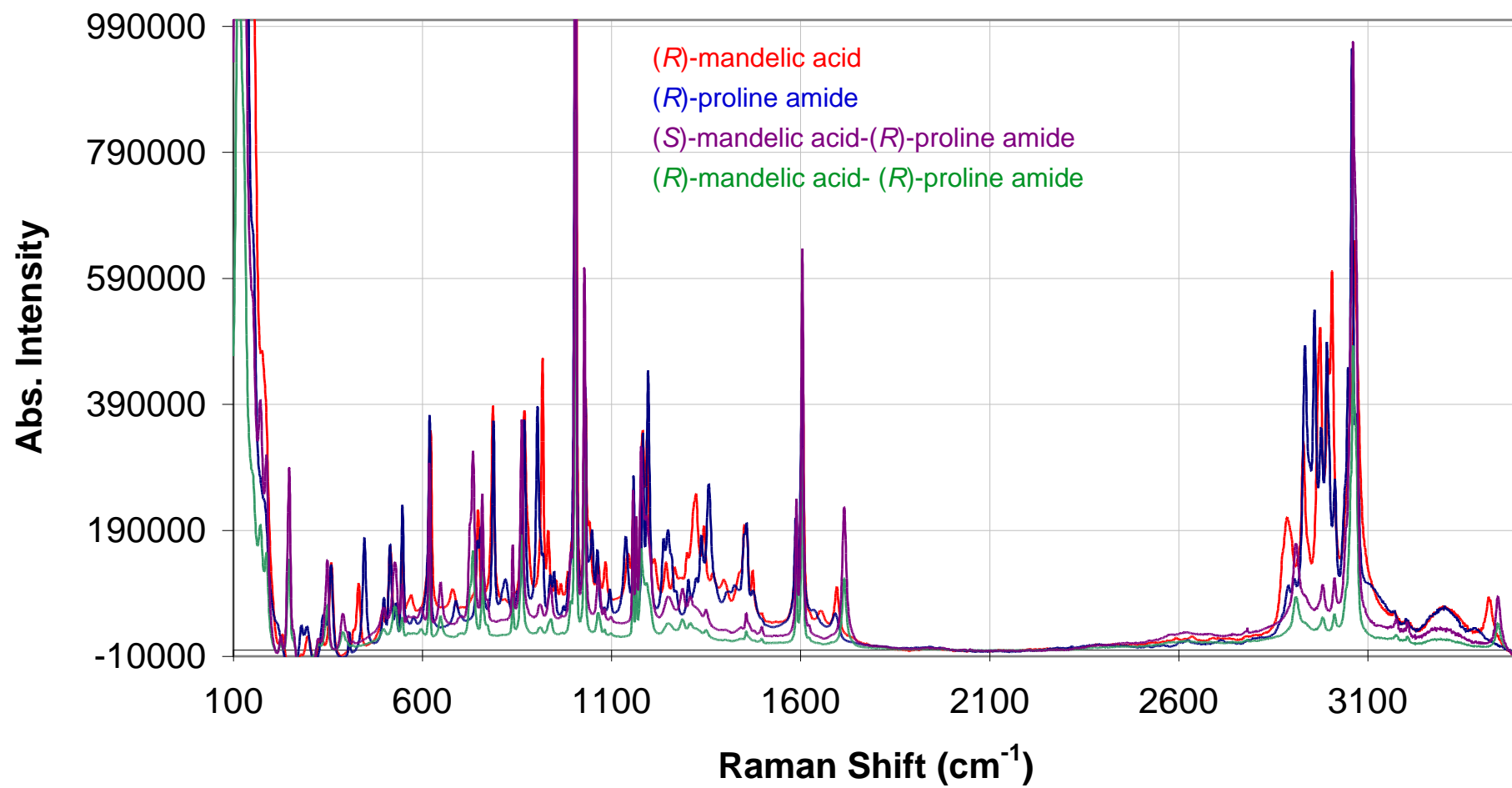


Figure S3. Comparison of Raman-spectra

Structure solution and refinement with the wrong diastereomer

With regard to the initial intention of using the method to determine the absolute configuration of one of the two components in the co-crystal while the other is known, the following calculation was performed. The co-crystal powder diffractogram of (*R*)-mandelic acid together with (*R*)-proline amide was used in the structure solution but the atomic coordinates were those of (*R*)-mandelic acid and (*S*)-proline amide; the other diastereomer. The resulting best χ^2 value after the simulated annealing run was 13.8 compared to 8.3 for the correct assignment. The same test was also performed for the other diastereomer. The wrong combination afforded a χ^2 value of 9.4 compared to 6.9 for the correct one. This difference in χ^2 values is sufficiently large to reliably select the correct diastereomer, moreover validation of the resulting hydrogen bonding (see Fig. S4) supports the rejection of the wrong diastereomer.

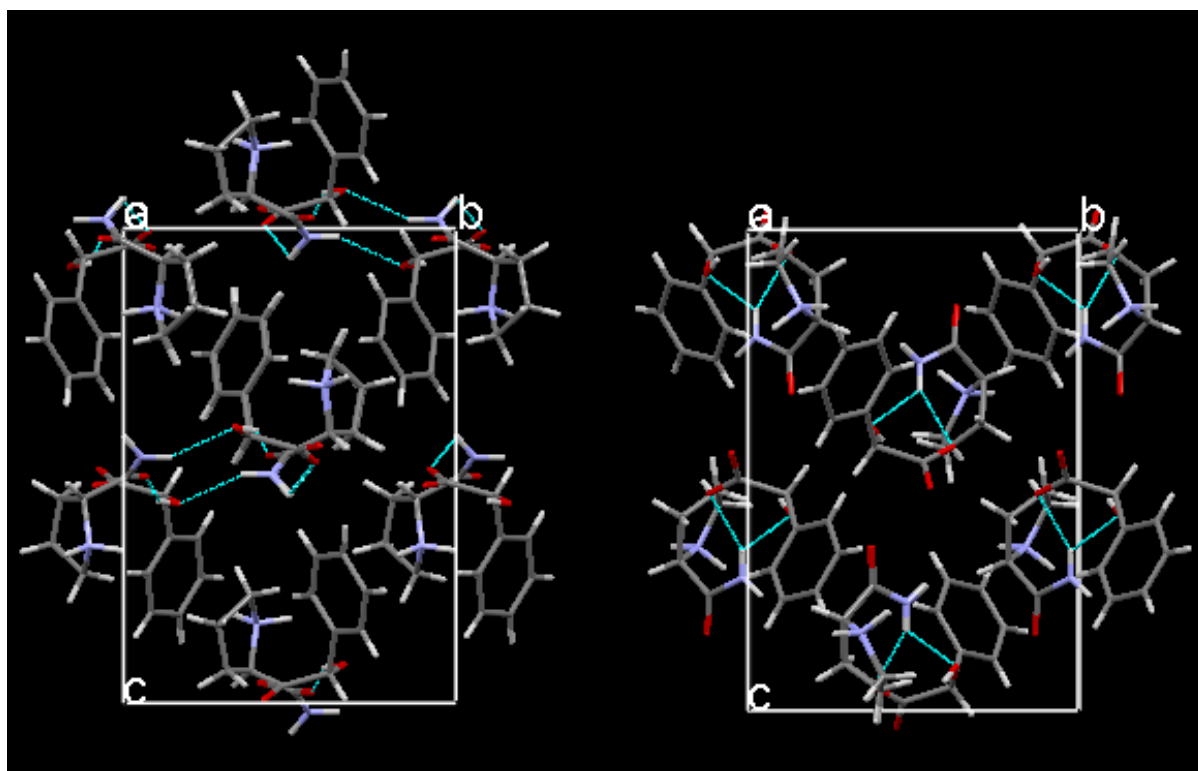


Figure S4. The crystal packing of the (*R*)-mandelic acid-(*R*)-proline amide co-crystal (left) and the (*S*)-mandelic acid-(*R*)-proline amide co-crystal (right) viewed down the *a* axis of the unit cell with the wrong diastereomer