Electronic Supplementary Information

Solid state grinding as a tool to aid enantiomeric resolution by cocrystallisation

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Experimental Section

Chemicals were purchased from SigmaAldrich and used as received.

X-ray powder diffraction analysis was performed on a Philips X’Pert Diffractometer with Cu Kα radiation at a wavelength of 1.5406 Å and data collected between 3 and 50 °20 at ambient temperature.

Differential scanning calorimetry thermograms were recorded in a nitrogen atmosphere using a Mettler Toledo STARRe DSC822e/700 calorimeter. The heating rate was 10 °C.min⁻¹ and endotherms are plotted as downward peaks.

Single crystal X-ray structure data were collected at 180 K on a Nonius Kappa CCD diffractometer equipped with an Oxford Cryosystems cooling device using MoKα radiation.

For crystal structure determination from powder X-ray diffraction data, indexing was performed in the program DICVOL06. The most probable space group was determined by analysing the individual diffracted intensities extracted using the Pawley refinement procedure implemented in the program DASH 3.3. Structure solution and Rietveld refinement were performed in the software TOPAS Academic. Molecular geometries were defined by rigid bodies and constraints were used to specify bond lengths, bond angles and most of the torsion angles. Torsion angles corresponding to the flexible degrees of freedom, however, were allowed to refine. Standard uncertainties on atom coordinates were calculated using the bootstrap method.

Ball milling was performed in a Retsch MM200 grinder for 30 minute periods at a frequency of 30 Hz using a metal vial with two 7 mm diameter metal balls. For liquid assisted grinding 20 µl of liquid was also added. Typically, experiments were performed on a 300 mg scale.
DSC analysis of cocrystal forms of malic acid and tartaric acid

Fig. S1 Differential scanning calorimetry thermograms of: (top) L-ma:D-ta, (middle) Form II of L-ma:L-ta and (bottom) Form I of L-ma:L-ta. Endothermic events are plotted in a downward direction. The trace of L-ma:D-ta shows a melt endotherm with onset at 130 °C. The traces of both Form I and Form II of L-ma:L-ta show a small endotherm, at 134 °C and 140 °C respectively, which corresponds to conversion to a third polymorph of the L-ma:L-ta cocrystal. This polymorph (Form III) then melts at 163 °C.
PXRD analysis of three polymorphs of the L-malic acid:L-tartaric acid cocrystal

Fig. S2 Powder X-ray diffractograms of (a) Form I, (b) Form II and (c) Form III of the 1:1 L-malic acid:L-tartaric acid cocrystal.
**Crystal structure of Form III of the L-malic acid:L-tartaric acid cocrystal**

Form III of the L-malic acid:L-tartaric acid cocrystal crystallises as a monoclinic $P2_1$ structure with unit cell dimensions at ambient temperature of $a = 12.4497(2)$ Å, $b = 8.8886(2)$ Å, $c = 5.0103(1)$ Å, $\beta = 96.758(1)^\circ$ (a crystallographic information file is included with the supplementary data).

**Fig. S3.** The crystal structure of Form III of the L-malic acid:L-tartaric acid cocrystal. (a) View down the b-axis. (b) View down the a-axis. Malic acid and tartaric acid molecules form ribbons through $R_2^2(8)$ hydrogen bonding interactions. Hydrogen bonds to hydroxyl groups of adjacent chains give an overall 3D hydrogen bonded network.