Electronic Supplementary Information

\( p_{1,n_1} \) Salts: Self assembled supramolecular structures sequestering racemates. Diastereomeric separation and enantiomeric enrichment of \textit{trans}-chrysanthenic acid.

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General Experimental Section

Where not otherwise stated, optical rotations were measured at 20°C. Enantiomeric composition of chrysanthenic acid samples was determined by CSP GC (capillary column Rt-\( \beta \)DEXsm™-RESTEK Corp.; 30 m; 0.32 mmID; 0.25\( \mu \); injector 275 °C; FID detector 300 °C; 80 °C (2 min) then to 125 °C (1.5 °C/min). Differential scanning calorimetric measurements were performed with a TA-Instruments DSC-2920 apparatus adopting a temp. program consisting of one heating ramp starting from r.t. at a heating rate of 4 °C/min under \( \text{N}_2 \).

Preparation of \((+)-n, \,(+)-p \) and \((+)-p_{1,n_1} \) salts: General procedure

A 250 mL round-bottomed flask was fitted with a magnetic stirbar and a reflux condenser. The flask was charged with \((1S,2S)-(+)-\text{DMPP} \) (5.85 g, 30 mmol) and 100 mL of \( \text{iPr}_2\text{O} \). The suspension was heated to reflux until the base was completely dissolved, then the heating was stopped to add 30 mmol \((5.04 \text{ g dissolved in 20 mL of } \text{iPr}_2\text{O})\) of \((-)-\text{trans-ChA}, \,(+)-\text{trans-ChA}, \) or \((\pm)-\text{trans-ChA}\) in one portion to obtain, respectively, the \((+)-n\) salt, the \((+)-p\) salt and the \((+)-p_{1,n_1}\) salt. The addition of \((-)-\text{trans-ChA}\) and \((\pm)-\text{trans-ChA}\) produced the quick precipitation of, respectively the
(+)-n salt and the (+)-p₁,n₁ salt. The mixtures were heated for one more hour, cooled to room temperature and the resulting microcrystalline solids were isolated by filtration, washed with n-hexane and dried in vacuo to give the (+)-n salt (95% yield) or the (+)-p₁,n₁ salt (94% yield). After the addition of (+)-trans-ChA no precipitation of (+)-p salt occurred, the solution was refluxed for one additional hour and then cooled at room temperature. It was necessary to scratch the walls of the flask to start the precipitation of the p salt as a white solid (80% yield).

Characterisation of the salts

((±)-trans-ChA•(1S,2S)-(+) DMPP [(+)p₁,n₁ salt]

¹H NMR (300 MHz, CDCl₃): δ 1.08 p.p.m. (s, 3H); 1.22 (s, 3H); 1.30 (dd, 1H, J₁ = 5.4 Hz, J₂=1.8 Hz); 1.68 (s, 6H); 1.94 (dd, 1H, J₁ = 8.0 Hz, J₂=5.4 Hz); 2.71 (s, 6H); 2.94 (m, 1H); 3.33 (dd, 1H, J₁ = 12.9 Hz, J₂=6.2 Hz); 3.52 (dd, 1H, J₁ = 12.9 Hz, J₂= 2.8 Hz); 4.67 (d, 1H, J₁ = 9.5 Hz); 4.85 (d, 1H, J₁ = 5.2 Hz); 7.34 (m, 5H); 7.41 (bs, 3H). ¹³C-NMR (75 MHz, CDCl₃): δ 19.10; 21.35; 23.06; 26.16; 27.94; 32.31; 32.42; 37.49; 37.63; 42.06; 58.41; 71.51; 71.69; 122.80; 122.85; 127.68; 128.91; 129.27; 134.85; 141.86; 179.60. IR (KBr) ν: 3,151; 2,922; 1,568; 1,421 cm⁻¹. MS (ES⁺, m/z): 196 (M⁺+1); 197 (M⁺+2); (ES⁻, m/z): 167 (M⁻-1); 168 (M⁻). [α]D + 26.8 (c 1.036, CHCl₃); m.p.: 109.7-111.5 °C; DSC: peak: 110.97 °C; ΔHf -146.4 Jg⁻¹.

X-Ray crystal structure: orthorhombic, space group P2₁2₁2₁, a = 11.1297(6), b = 13.4914(7), c = 28.0333(14) Å, V = 4209.3(4) Å³, T = 293(2) K, Z = 8, ρc = 1.147 g cm⁻³, F(000) = 1584.0, graphite-monochromated MoKα radiation (λ = 0.71073 Å), μ(MoKα) = 0.078 mm⁻¹, colourless block (0.4 × 0.3 × 0.1 mm³), empirical absorption correction with SADABS (transmission factors: 0.9694 – 0.9922), 2400 frames, exposure time 10 s, θmax = 27.50, hmax = 14, kmax = 17, lmax = 36, 45793 reflections collected, 9681 independent reflections (Rint = 0.045), solution by direct methods (SHELXS97) and subsequent Fourier syntheses, full-matrix least-squares on F₀² (SHELX97),

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Supplementary Material (ESI) for Chemical Communications

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hydrogen atoms refined with a riding model, data / parameters = 9681 / 495, \( S(F^2) = 1.030, R(F) = 0.0605 \) and \( wR(F^2) = 0.1136 \) on all data, \( R(F) = 0.0387 \) and \( wR(F^2) = 0.1187 \) for 1652 reflections with \( I > 2\sigma(I) \), weighting scheme \( w = 1/[\sigma^2(F_o^2) + (0.0567P)^2 + 0.2527P] \) where \( P = (F_o^2 + 2F_c^2)/3 \), largest difference peak and hole 0.144 and –0.177 e Å\(^{-3}\).

a) Sheldrick, G. M. SHELX97; Universität Göttingen, Germany, 1997.

\((-\text{trans-})\text{ChA} \cdot 1S,2S-(-)\text{-DMPP} \ [(\text{+})\text{-n salt}]

\(^1\text{H-NMR}\) (300 MHz, CDCl\(_3\)): \( \delta \) 1.08 p.p.m. (s, 3H); 1.22 (s, 3H); 1.30 (\(dd\), 1H, \(J_1 = 5.4\) Hz, \(J_2 = 1.8\) Hz); 1.69 (s, 6H); 1.94 (\(dd\), 1H, \(J_1 = 7.9\) Hz, \(J_2 = 5.4\) Hz); 2.71 (s, 6H); 2.94 (\(m\), 1H); 3.31 (\(dd\), 1H, \(J_1 = 12.9\) Hz, \(J_2 = 6.2\) Hz); 3.4 (\(dd\), 1H, \(J_1 = 12.9\) Hz, \(J_2 = 2.8\) Hz); 4.68 (\(d\), 1H, \(J_1 = 9.5\) Hz); 4.85 (\(d\), 1H, \(J_1 = 5.2\) Hz); 7.32 (\(m\), 5H); 7.67 (bs, 3H). \(^{13}\text{C-NMR}\) (75 MHz, CDCl\(_3\)): \( \delta \) 18.60; 20.83; 22.57; 25.67; 27.33; 31.77; 37.56; 41.53; 57.83; 71.00; 122.37; 127.20, 128.42, 128.77; 134.32; 141.39; 179.20. \(^\text{IR}\) (KBr) \( \nu \): 3,151; 2,922; 1,568; 1,421 cm\(^{-1}\). \(^\text{MS}\): (ES+, \(m/z\)): 196 (M\(^+\)+1); 197 (M\(^+\)+2); (ES-, \(m/z\)): 167 (M\(^-\)-1); 168 (M\(^-\)). \( [\alpha]_D^\circ + 12.3 \) (c 0.9720, CHCl\(_3\)). \( m.p.\): 132.6-134.0 °C. \(^\text{DSC}\): peak: 131.27 °C; \( \Delta H_f \) -126.7 J g\(^{-1}\).

\(^\text{X-Ray crystal structure}\): orthorhombic, space group P2\(_1\)2\(_1\)2\(_1\), \(a = 7.3883(8)\), \(b = 10.1582(11)\), \(c = 28.935(3)\) Å, \(V = 2171.6(4)\) Å\(^3\), \(T = 293(2)\) K, \(Z = 4\), \(\rho_c = 1.112\) g cm\(^{-3}\), \(F(000) = 792.0\), graphite-monochromated MoK\(_x\) radiation (\(\lambda = 0.71073\) Å), \(\mu(\text{MoK}\alpha) = 0.076\) mm\(^{-1}\), empirical absorption correction with SADABS (transmission factors: 0.9694 – 0.9922), 2400 frames, exposure time 10 s, \(\theta_{\text{max}} = 29.98\), \(h_{\text{max}} = 10\), \(k_{\text{max}} = 14\), \(l_{\text{max}} = 40\), 6299 reflections collected, 3606 independent reflections, solution by direct methods (SHELXS97\(^a\)) and subsequent Fourier syntheses, full-matrix least-squares on \(F_o^2\) (SHELX97\(^a\)), hydrogen atoms refined with a riding model, data / parameters = 3606 / 495, \(S(F^2) = 1.045, R(F) = 0.0560\) and \(wR(F^2) = 0.1441\) on all data, \(R(F) = 0.0387\) and
wR(F²) = 0.1187 for 1652 reflections with I > 2σ(I), weighting scheme w = 1/[σ²(Fo²) + (0.0567P)² + 0.2527P] where P = (Fo² + 2Fc²)/3, largest difference peak and hole 0.144 and –0.177 e Å⁻³.

a) Sheldrick, G. M. SHELB97; Universität Göttingen, Germany, 1997.

(+)-trans-ChA•15,2S-(+)-DMPP [(+)-p salt]

¹H-NMR (300 MHz, CDCl₃): δ 1.08 p.p.m. (s, 3H); 1.23 (s, 3H); 1.32 (dd, 1H, J₁ = 5.4 Hz, J₂ = 1.78 Hz); 1.69 (s, 6H); 1.94 (dd, 1H, J₁ = 8.0 Hz, J₂ = 5.4 Hz); 2.70 (s, 6H); 2.94 (m, 1H); 3.33 (dd, 1Hₐ, J₁ = 12.9 Hz, J₂ = 6.2 Hz); 3.51 (dd, 1H₉, J₁ = 12.9 Hz, J₂ = 2.9 Hz); 4.65 (d, 1H, J₁ = 9.6 Hz); 4.87 (d, 1H, J₁ = 5.3 Hz); 7.32 (m, 5H); 7.50 (bs, 3H). ¹³C-NMR (75 MHz, CDCl₃): δ 18.41; 20.66; 22.37; 25.48; 27.32; 31.78; 36.76; 41.40; 57.82; 70.86; 71.13; 122.10; 126.98, 128.21, 128.59; 134.25; 141.19; 178.73. IR (KBr) ν: 3,151; 2,922; 1,568; 1,421 cm⁻¹. MS: (ES+, m/z): 196 (M⁺+1); 197 (M⁺+2); (ES-, m/z): 167 (M⁻-1); 168 (M⁻). [α]D + 39.7 (c 0.9320, CHCl₃); m.p.: 93.7-96.6 °C. DSC: peak: 88.81 °C; ΔHₐ -111.2 Jg⁻¹.

The levorotating enantiomers of n-, p- and p₁,n₁ salts were prepared by reacting (1R,2R)-(−)-DMPP and, respectively, (+)-trans-ChA and (−)-trans-ChA and (±)-trans-ChA
DSC profiles

- $p$ salt
- $n$ salt
- $p_1, n_1$ salt
- $n$ salt + $p$ salt
- $p$ salt
- $p_1, n_1$ salt

from toluene

Exo Down

Heat Flow (W/g)

Temperature (°C)
X-ray crystal structure of the $n$ salt

CCDC 287292 contains the supplementary crystallographic data for the $n$ salt. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif
Separation of (±)-trans-ChA from racemic chrysanthemic acid with a trans:cis ratio of 65:35 using (1S,2S)-(+) DMPP.

(1S,2S)-(+) 2-Dimethylamino-1-phenyl-1,3-propanediol [(1S,2S)-(+) DMPP, 40.6 g, 0.21 mol] was added to diisopropyl ether (200 mL). The mixture was heated to reflux (65 °C) and slowly added with a solution of racemic chrysanthemic acid (50.0 g, 0.30 mol) with a trans:cis ratio of 65:35, in diisopropyl ether (100 mL). After the addition was concluded, a white salt started to precipitate. The mixture was kept under stirring at 65 °C for 45 min. Then the mixture was cooled to 10 °C under stirring and the solid was filtrated and washed twice with diisopropyl ether (50 mL). The crude solid was dried in vacuum (71.9 g) and recrystallised from toluene (500 mL), obtaining 59.6 g of the (+)-p1,n1 salt with mp 110.0-111.5 °C; [α]D + 26.8 (c 1.036, CHCl3).

This salt was treated with 1N HCl, and the aqueous layer extracted with con toluene and then set aside. The organic phases were dried and evaporated under vacuum to afford 26.1 g of racemic trans-chrysanthemic acid (80.3% overall yield) with a trans: cis = 99.5 : 0.5. The acidic aqueous layer was treated with solid NaOH until pH 10. The precipitate was collected by decantation, washing with water, and drying under vacuum, obtaining a first crop of the pure base (1S,2S)-(+) DMPP (30.38 g, 75%). The aqueous layer can be further extracted with diisopropyl ether to obtain a second crop of the pure free base (8.71 g).

Separation of (±)-trans-ChA from racemic chrysanthemic acid with a trans:cis ratio of 65:35 using (1R,2R)(−)-DMPP.

Separation was performed as described above, this time using (1R,2R)(−)-2-dimethylamino-1-phenyl-1,3-propanediol, (1R,2R)(−)-DMPP. This time (−)-p1,n1 salt was obtained, that is (±)-trans-ChA•1R,2R(−)-DMPP with mp 110.0-111.5°C and [α]D ‒26.4 (c 1.032, CHCl3).
dl-ChA (50 g, trans/cis = 4:1) + (1S,2S)-(+) -DMPP (47.6 g, 0.82 eq) were refluxed with iPr$_2$O (470 mL) for 1.5 h and cooled to room temperature. The precipitate (PPT) was filtered off and washed with (iPr$_2$O, 2x50 mL). The mother liquor (ML) was concentrated to 21.0 g.

The precipitate was dissolved in CHCl$_3$ and H$_2$O, followed by the addition of NaOH. The mixture was stirred and then filtered. The filtrate was washed with (iPr$_2$O, 2x50 mL), and the resulting salt was crystallized from toluene. The yield was 74.56 g (86% yield), with dl-trans-ChA purity >98%.

The salt (70.19 g) was dissolved in CHCl$_3$ and H$_2$O, and then concentrated to 14.5 g. The H$_3$O$^+$ was treated with NaOH to precipitate (1S,2S)-(+) -DMPP (36.95 g). The precipitate was filtered, washed with CHCl$_3$, and the salt was crystallized from CHCl$_3$ and H$_2$O. The yield was 31.71 g (81.75% yield).

The stereoisomeric purity was determined by GC.
General procedure for the recovery of the enantiomeric excess of (+)-\textit{trans}-ChA from a scalemic mixture through formation of (+)-p$_1$,n$_1$ salt.

(1S,2S)-(+)\textit{DMPP (2.34 g, 12 mmol) was dissolved in 40 mL of hot iPr$_2$O and to this solution was added a solution of 5.04 g (30 mmol) of a scalemic (+)-\textit{trans}-ChA (ee = 60%) in 20 mL of iPr$_2$O. The mixture was heated at 65 °C under stirring, then cooled to ambient temperature. When a solid started to precipitate heating was protracted for half an hour and then cooled to 0°C under stirring for 15 min. The solid is filtered and washed twice with iPr$_2$O (10 mL).

The salt was dried and afforded 4.05 g (93 % yield) of (+)-p$_1$,n$_1$ salt with mp 110.0-111,5°C and $[\alpha]_D +26.3$ (c 1.026, CHCl$_3$). From this salt, after the acidic/basic treatment described previously, both racemic ±\textit{trans}-ChA and the free base were recovered.

Washing of the mother liquor with an aqueous HCl solution until pH 3.5, drying and evaporation under vacuum (30 °C/24 mbar) afforded 2.66 g of (+)-\textit{trans}-ChA (ee > 95%, 88% yield based on excess of (+)-\textit{trans}-ChA of the starting mixture).

Table. Recovery of the excess of (+)-\textit{trans}-ChA, with (1S,2S)-(+)\textit{DMPP through precipitation of (+)-p$_1$,n$_1$ salt.}

<table>
<thead>
<tr>
<th>(+)-\textit{trans}-ChA</th>
<th>(+)-\textit{DMPP p$_1$,n$_1$ salt</th>
<th>(+)-\textit{trans}-ChA from ML</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+):(-), ee (%)(a)</td>
<td>(eq)</td>
<td>yield(b) (%)</td>
</tr>
<tr>
<td>75:25, 50</td>
<td>0.5</td>
<td>92</td>
</tr>
<tr>
<td>80:20, 60</td>
<td>0.4</td>
<td>93</td>
</tr>
<tr>
<td>85:15, 70</td>
<td>0.3</td>
<td>92</td>
</tr>
<tr>
<td>90:10, 80</td>
<td>0.2</td>
<td>88</td>
</tr>
</tbody>
</table>

(a) Determined by CSP GC. (b) Referred to (±)-\textit{trans}-ChA present in the starting mixture.

(c) Referred to the excess of (+)-\textit{trans}-ChA present in the starting mixture.
Figure. The supramolecular ribbon-like polymers of the two diastereoisomeric $n$ and $p$ tectons in the $p_1,n_1$ salt viewed along $a$, $b$ and $c$ axes. The other components of the unit cell are omitted for clarity and to better show: i. the reciprocal disposition of $n$ and $p$ tectons in the $p_1,n_1$ salt; ii. the H-bonds network of each tecton, iii; the discontinuity in the middle of the cell, and iv. the great structural similarity that the two diastereoisomeric ribbons assume in their disposition in the crystal.