Supplementary Material (ESI) for Chemical Communications

Electronic Supplementary Information

p_1,n_1 Salts: Self assembled supramolecular structures sequestering racemates. Diastereomeric separation and enantiomeric enrichment of *trans*-chrysanthemic acid.

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General Experimental Section

Where not otherwise stated, optical rotations were measured at 20°C. Enantiomeric composition of chrysathemic acid samples was determined by CSP GC (capillary column Rt-βDEXsm™-RESTEK Corp.; 30 m; 0.32 mmID; 0.25μ; 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 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 (1*S*,2*S*)-(+)-DMPP (5.85 g, 30 mmol) and 100 mL of *i*Pr_2O. The suspension was heated to reflux until the base was completely dissolved, then the heating was stopped to add 30 mmol (5.04 g dissolved in 20 mL of *i*Pr_2O) of (–)-*trans*-ChA, (+)-*trans*-ChA, or (±)-*trans*-ChA in one portion to obtain, respectively, the (+)-*n* salt, the (+)-*p* salt and the (+)-p_1,n_1 salt. The addition of (–)-*trans*-ChA and (±)-*trans*-ChA produced the quick precipitation of, respectively the

(+)-*n* salt and the (+)-p_1,n_1 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 (+)-p_1,n_1 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•(1*S*,2*S*)-(+)-DMPP [(+)-p_1,n_1 salt]

^{1}H NMR (300 MHz, $CDCl_3$): δ 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); 1.68 (*s*, 6H); 1.94 (*dd*, 1H, J_1 = 8.0 Hz, J_2 =5.4 Hz); 2.71 (*s*, 6H); 2.94 (*m*, 1H); 3.33 (*dd*, 1H_a, J_1 = 12.9 Hz, J_2 =6.2 Hz); 3.52 (*dd*, 1H_b, J_1 = 12.9 Hz, J_2 = 2.8 Hz); 4.67 (*d*, 1H, J_1 = 9.5 Hz); 4.85 (*d*, 1H, J_1 = 5.2 Hz); 7.34 (*m*, 5H); 7,41 (*bs*, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$): 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^-). **$[\alpha]_D$** + 26.8 (*c* 1.036, $CHCl_3$); **m.p.:** 109.7-111.5 °C; **DSC**: peak: 110.97 °C; ΔH_f -146.4 Jg^{-1}.

X-Ray crystal structure: orthorhombic, space group $P2_12_12_1$, a = 11.1297(6), b = 13.4914(7), c = 28.0333(14) Å, V = 4209.3(4) Å^3, T = 293(2) K, Z = 8, ρ_c = 1.147 g cm^{-3}, F(000) = 1584.0, graphite-monochromated $Mo_{K\alpha}$ radiation (λ = 0.71073 Å), $\mu(Mo_{K\alpha})$ = 0.078 mm^{-1}, colourless block (0.4 × 0.3 × 0.1 mm^3), empirical absorption correction with SADABS (transmission factors: 0.9694 – 0.9922), 2400 frames, exposure time 10 s, θ_{max} = 27.50, h_{max} = 14, k_{max} = 17, l_{max} = 36, 45793 reflections collected, 9681 independent reflections (R_{int} = 0.045), 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 = 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.

(–)-*trans*-ChA•1*S*,2*S*-(+)-DMPP [(+)-*n* salt]

^{1}H-NMR (300 MHz, $CDCl_3$): δ 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$_a$, J_1 = 12.9 Hz, J_2 = 6.2 Hz); 3.4 (*dd*, 1H$_b$, 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}C-NMR** (75 MHz, $CDCl_3$): δ 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. **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^-). **$[\alpha]_D$** + 12.3 (*c* 0.9720, $CHCl_3$); **m.p.:** 132.6-134.0 °C. **DSC**: peak: 131.27 °C; ΔH_f -126.7 Jg^{-1}.

X-Ray crystal structure: orthorhombic, space group $P2_12_12_1$, $a = 7.3883(8)$, $b = 10.1582(11)$, $c = 28.935(3)$ 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 $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), $\mu(Mo_{K\alpha}) = 0.076$ mm^{-1}, empirical absorption correction with SADABS (transmission factors: 0.9694 – 0.9922), 2400 frames, exposure time 10 s, $\theta_{max} = 29.98$, $h_{max} = 10$, $k_{max} = 14$, $l_{max} = 40$, 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

$wR(F^2) = 0.1187$ 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}.

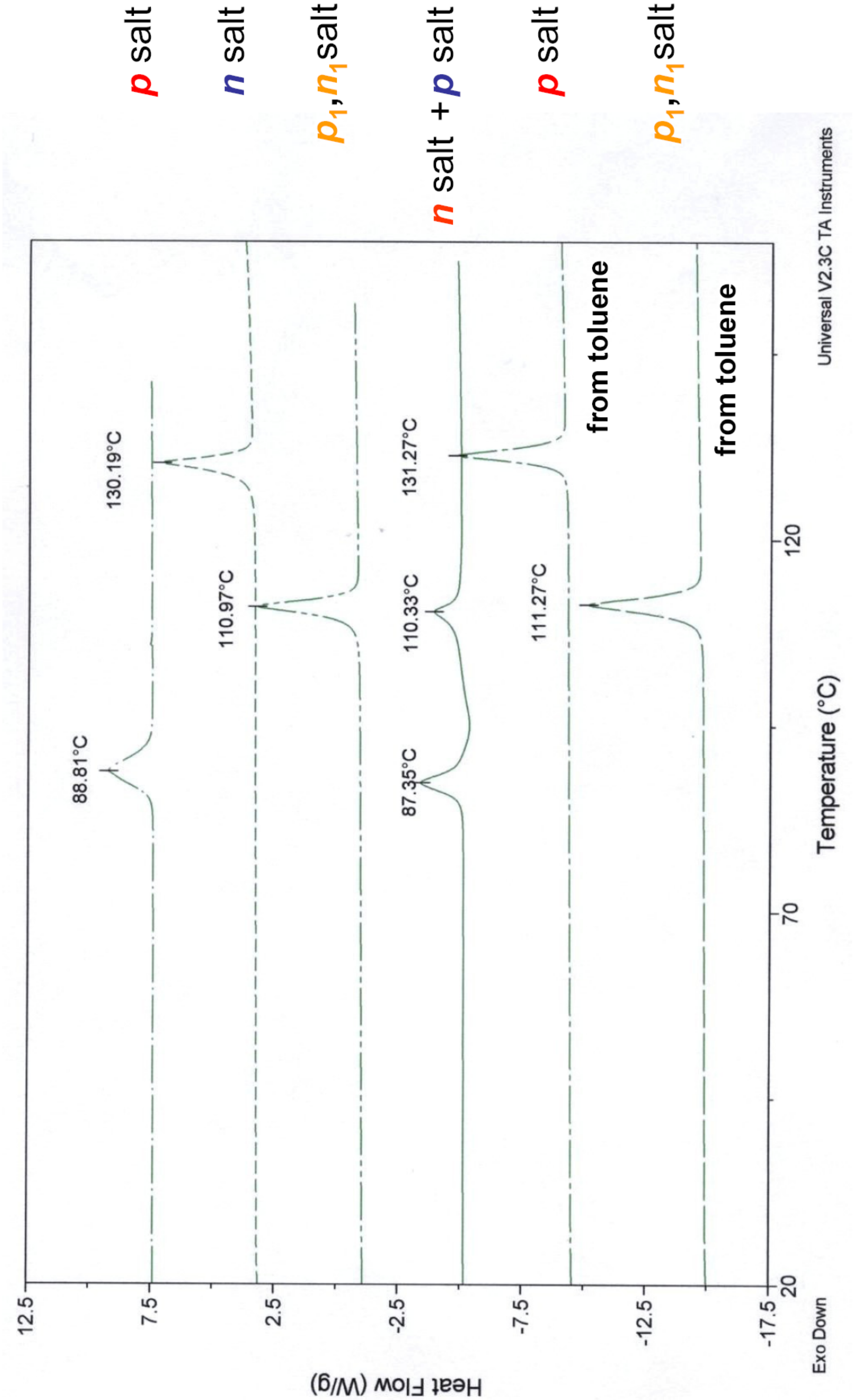
a) Sheldrick, G. M. *SHELX97*; Universität Göttingen, Germany, 1997.

(+)-*trans*-ChA•1*S*,2*S*-(+)-DMPP [(+)-*p* salt]

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.08 p.p.m. (*s*, 3H); 1.23 (*s*, 3H); 1.32 (*dd*, 1H, J_1 = 5.4 Hz, J_2 = 1.78 Hz); 1.69 (*s*, 6H); 1.94 (*dd*, 1H, J_1 = 8,0 Hz, J_2 =5.4 Hz); 2.70 (*s*, 6H); 2.94 (*m*, 1H); 3.33 (*dd*, $1H_a$, J_1 = 12.9 Hz, J_2 = 6.2 Hz); 3.51 (*dd*, $1H_b$, J_1 = 12.9 Hz, J_2 = 2.9 Hz); 4.65 (*d*, 1H, J_1 = 9.6 Hz); 4.87 (*d*, 1H, J_1 = 5.3 Hz); 7.32 (*m*, 5H); 7.50 (*bs*, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$): 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, $CHCl_3$); **m.p.:** 93.7-96.6 °C. **DSC**: peak: 88.81 °C; ΔH_f -111.2 Jg^{-1}.

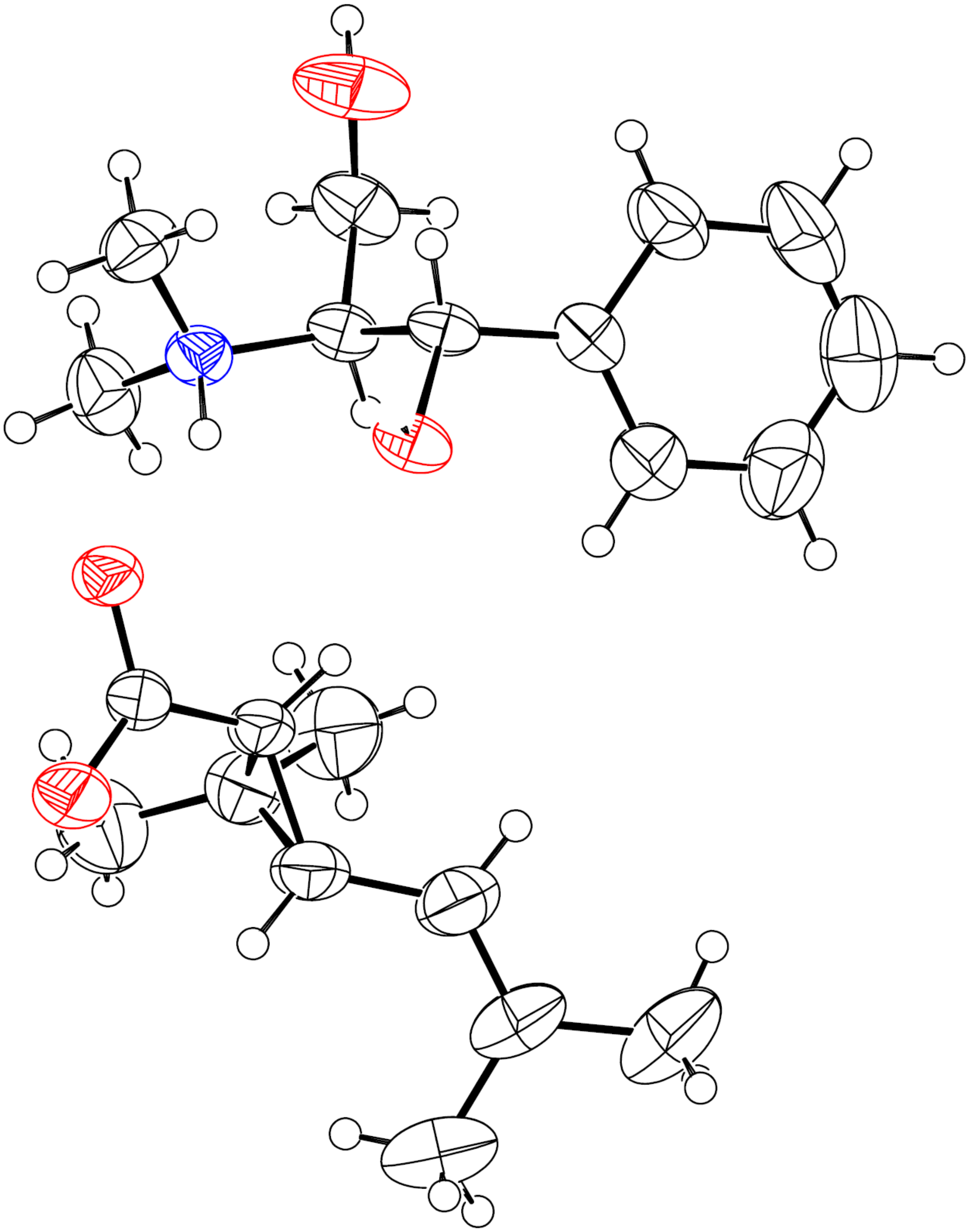
The levorotating enantiomers of *n*-, *p*- and p_1,n_1 salts were prepared by reacting (1*R*,2*R*)-(–)-DMPP and, respectively, (+)-*trans*-ChA *and* (–)-*trans*-ChA and (±)-*trans*-ChA

DSC profiles



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



A. L. Spek (2005) PLATON, A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands.

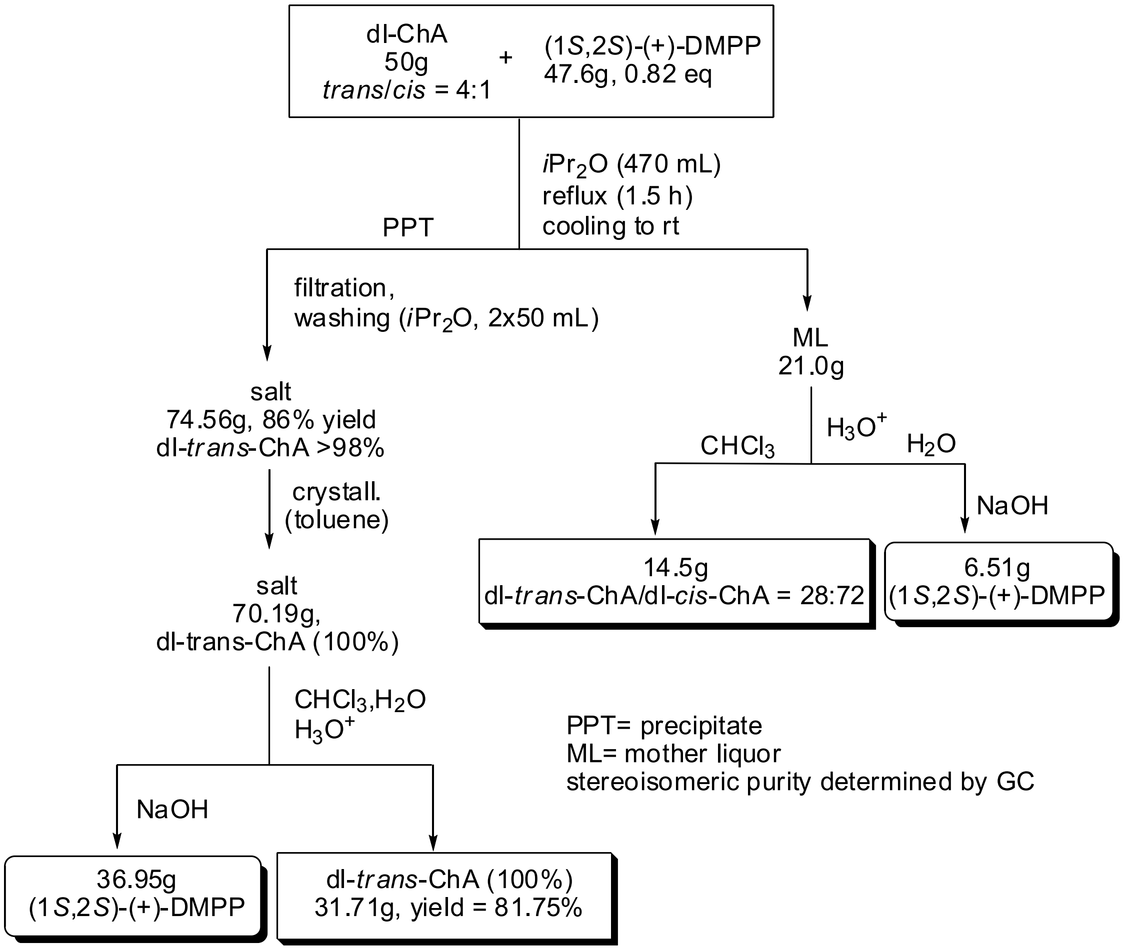
Separation of (±)-*trans*-ChA from racemic chrysanthemic acid with a *trans*:*cis* ratio of 65:35 using (1S,2S)-(+)-DMPP.

(1*S*,2*S*)-(+)-2-Dimethylamino-1-phenyl-1,3-propanediol [(1*S*,2*S*)-(+)-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 (+)- p_1,n_1 salt with mp 110.0-111.5 °C; $[\alpha]_D$ + 26.8 (*c* 1.036, $CHCl_3$).

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 *p*H 10. The precipitate was collected by decantation, washing with water, and drying under vacuum, obtaining a first crop of the pure base (1*S*,2*S*)-(+)-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 (1*R*,2*R*)-(–)-2-dimethylamino-1-phenyl-1,3-propanediol, (1*R*,2*R*)-(–)-DMPP. This time (–)-p_1,n_1 salt was obtained, that is (±)-*trans*-ChA•1*R*,2*R*-(–)-DMPP with mp 110.0-111.5°C and $[\alpha]_D$–26.4 (*c* 1.032, $CHCl_3$).


dl-ChA
50g
trans/*cis* = 4:1
+
(1*S*,2*S*)-(+)-DMPP
47.6g, 0.82 eq
*i*Pr$_2$O (470 mL)
reflux (1.5 h)
cooling to rt
PPT
filtration,
washing (*i*Pr$_2$O, 2x50 mL)
ML
21.0g
salt
74.56g, 86% yield
dl-*trans*-ChA >98%
H_3O^+
CHCl$_3$
H_2O
crystall.
(toluene)
NaOH
14.5g
dl-*trans*-ChA/dl-*cis*-ChA = 28:72
6.51g
(1*S*,2*S*)-(+)-DMPP
salt
70.19g,
dl-trans-ChA (100%)
CHCl$_3$,H_2O
H_3O^+
PPT= precipitate
ML= mother liquor
stereoisomeric purity determined by GC
NaOH
36.95g
(1*S*,2*S*)-(+)-DMPP
dl-*trans*-ChA (100%)
31.71g, yield = 81.75%

General procedure for the recovery of the enantiomeric excess of (+)-*trans*-ChA from a scalemic mixture through formation of (+)-p_1,n_1 salt.

(1*S*,2*S*)-(+)-DMPP (2.34 g, 12 mmol) was dissolved in 40 mL of hot *i*Pr_2O and to this solution was added a solution of 5.04 g (30 mmol) of a scalemic (+)-*trans*-ChA (ee = 60%) in 20 mL of *i*Pr_2O. 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 *i*Pr_2O (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 ±-*trans*-ChA and the free base were recovered.

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

Table. Recovery of the excess of (+)-*trans*-ChA, with (1*S*,2*S*)-(+)-DMPP through precipitation of (+)-p_1,n_1 salt.

(+)-*trans*-ChA	(+)-DMPP	p_1,n_1 salt	(+)-*trans*-ChA from ML	
(+):(–), ee (%)[(a)]	(eq)	yield[(b)] (%)	ee (%)[(a)]	yield[(c)] (%)
75:25, 50	0.5	92	94	92
80:20, 60	0.4	93	96	94
85:15, 70	0.3	92	96	93
90:10, 80	0.2	88	94	90

(a) Determined by CSP GC. (b) Referred to (±)-*trans*-ChA present in the starting mixture. (c) Referred to the excess of (+)-*trans*-ChA present in the starting mixture.

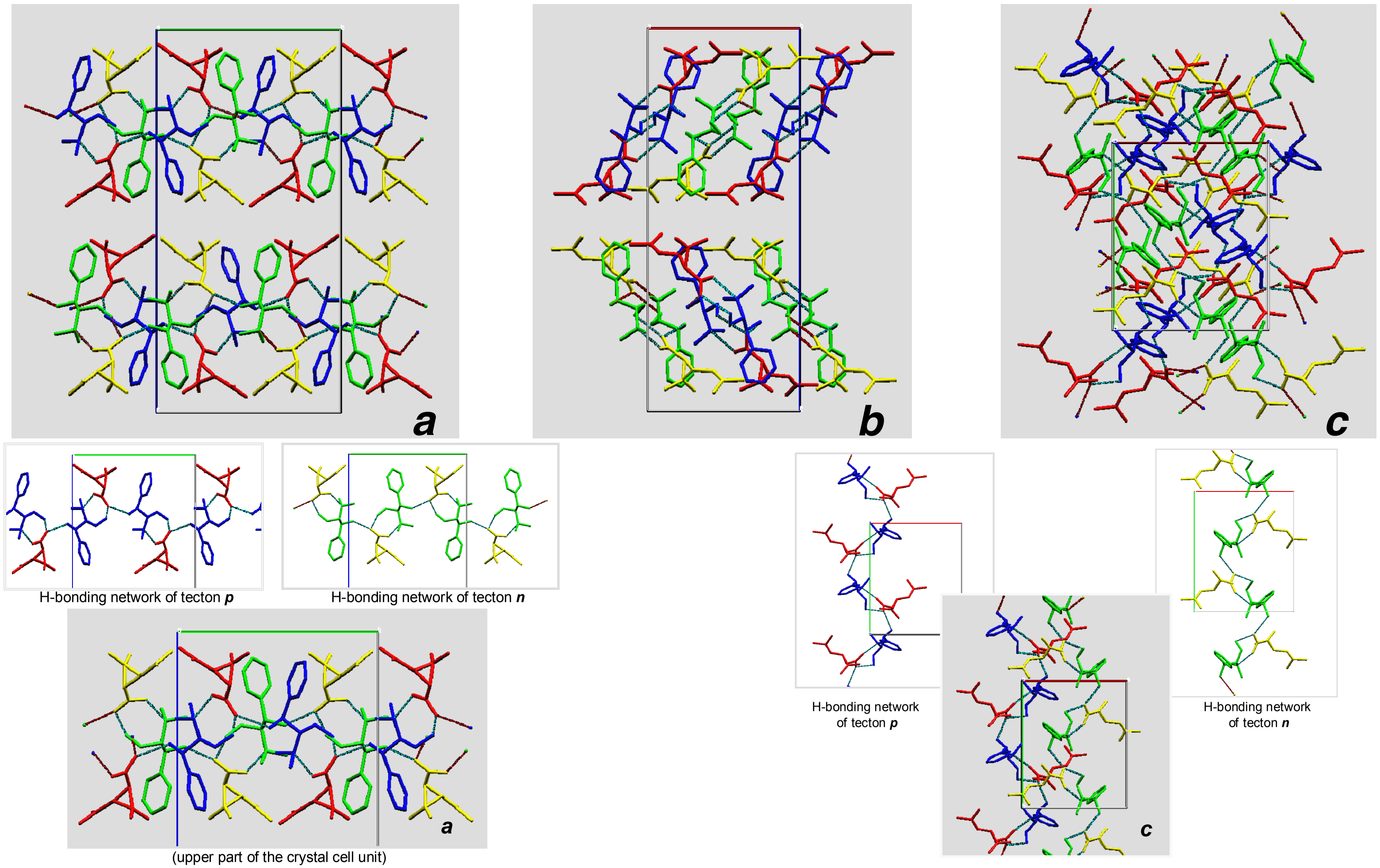


Figure. The supramolecular ribbon-like polymers of the two diastereoisomeric ***n*** and ***p*** tectons in the $\boldsymbol{p_1,n_1}$ salt viewed along *a*, *b* and *c* axes. The other components of the unit cell are omitted for clarity and to better show: i. the reciprocal disposition of ***n*** and ***p*** tectons in the $\boldsymbol{p_1,n_1}$ 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.