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Resolution of (*S*,*S*)-4-(2,2,4-trimethylchroman-4-yl)phenyl camphanate and its 4-chromanyl epimer by crystallization

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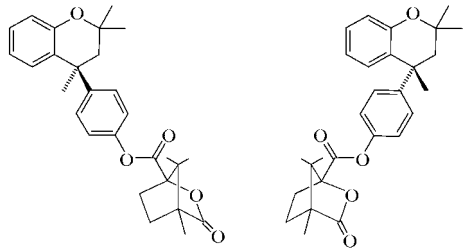
Dianin's compound (4-*p*-hydroxyphenyl-2,2,4-trimethylchroman) has been resolved by crystallization of the (*S*)-(−)-camphanic esters (*S*,*S*)- and (*R*,*S*)-4-(2,2,4-trimethylchroman-4-yl)phenyl 4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate, both $C_{28}H_{32}O_5$, from 2-methoxyethanol, yielding the pure *S*,*S* diastereomer. The relative stereochemistry of both diastereomers has been determined by X-ray crystallography, from which the absolute stereochemistry could be deduced from the known configuration of the camphanate moiety. The crystallographic conformations have been analysed, including the 1:1 disorder of the *R*,*S* diastereomer.

Comment

Dianin's compound is well known for its ability to form clathrates (Finocchiaro & Failla, 1996). Racemates of the compound are required because the 12-membered ring formed by the hydrogen bonding of six phenol OH moieties is comprised of three *R* enantiomers presenting their hydroxy groups from one face of the ring interspersed by three *S* enantiomers doing the same from the opposite face. The ring therefore lies on the plane of symmetry of an S_6 point group. Resolution of Dianin's compound and its derivatives allows for the formation of clathrates composed of complementing enantiomers of different species, thus forming quasi-racemic structures (Brienne & Jacques, 1975; Collet & Jacques, 1976–77). In principle, this can produce a chiral cavity that may show preference for one enantiomer of a guest molecule.

(1*S*)-Camphanic chloride was chosen as chiral adjuvant (Brienne & Jacques, 1975) because of its propensity to produce diastereomeric esters from alcohols which may be separated either by fractional crystallization or chromatography. The diastereomeric mixture obtained from treating Dianin's compound with (1*S*)-camphanic chloride was crystallized from ethanol, yielding a crystalline mixture of both diastereomers. This mixture was further crystallized from 2-methoxyethanol, yielding crystals of the resolved (*S*,*S*)-camphanate, (I), of Dianin's compound. X-ray crystallography of the resolved compound was necessary to deduce the absolute stereochemistry of the Dianin's compound moiety of the ester, as may be obtained from the known stereochemistry of the camphanate moiety. To complement the crystallography of the resolved compound, a suitable crystal of the *R*,*S* isomer, (I*a*), was obtained from the crystalline diastereomeric mixture before resolution, indicating that these diastereomers crystallize separately from ethanol.



(I) (I*a*)

The *S*,*S* isomer of the title compound, (I), along with the numbering scheme, is shown in Fig. 1. The structure of the *R*,*S* isomer, (I*a*), is similar, although exhibiting disorder of the phenyl camphanate moiety, (I*a*′) and (I*a*″), as shown in Fig. 2. The numbering scheme for (I*a*) is identical to that of (I), except that the atoms in the two disordered parts are indicated by the suffixes *A* and *B*, respectively. Despite the disorder, the rigid bicyclic structure of the camphanate moiety ensures that

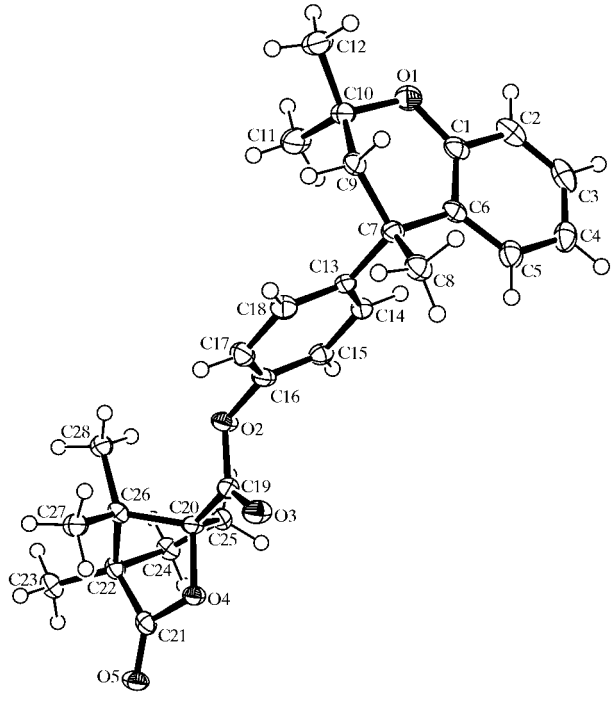


Figure 1
The molecular conformation of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

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it is almost identical in (I) and both conformations of (I*a*), with comparable bond lengths and angles.

The orientation of the carboxyl group (atoms O2, C19 and O3) relative to the bicyclic structure of the camphanic moiety is, however, different in (I) and the two conformations of (I*a*). In (I), the plane through atoms O2, C19 and O3 is only slightly twisted with respect to the plane through atoms O4, C21 and O5 [dihedral angle = 17.6 (2)°], with the O4—C20—C19—O2 torsion angle being −177.7 (2)°. One of the conformations in (I*a*) [(I*a*′)] is similarly only slightly twisted [dihedral angle = 16.0 (7)° and O4—C20—C19—O2 torsion angle −167.5 (6)], whereas in the other conformation, (I*a*″), it is substantially twisted away from the plane through atoms O4, C21 and O5 [dihedral angle = 55.9 (3)° and O4—C20—C19—O2 torsion angle = −47 (1)°]. The phenyl ring is twisted away from the O2/C19/O3 plane by 75.6 (1)° for (I), and by 54.4 (4) and 55.9 (3)° for conformations (I*a*′) and (I*a*″), respectively. The phenyl ring in turn is twisted away from the plane through atoms C13, C7 and C8 in the trimethylchroman moiety by 61.8 (1)° for (I), and by 55.2 (4) and 57.1 (4)° for (I*a*′) and (I*a*″), respectively, such that for (I) and (I*a*′), atoms O1, C7, C8, C13, C16, O2, O3, C19, C20, O4, O5 and C21 are almost coplanar. In the case of (I*a*″), these same atoms form an anticlockwise spiral rather than a plane.

The packing of the stereoisomers is also different. In (I), face-to-edge π–π interactions between neighbouring trimethylchroman moieties in a herring-bone pattern lead to broad flat bands of interacting molecules (Fig. 3). In (I*a*), the orientations of the 0.50:0.50 disordered molecules require alternation of (I*a*′) and (I*a*″), leading to off-set stepwise stacks (Fig. 4). The reason for the twisting of (I*a*″) relative to (I*a*′) or (I) is clear from Fig. 4; the twisted orientation of the camphanic moiety allows C—H···O interactions between methyl and carbonyl groups on neighbouring molecules.

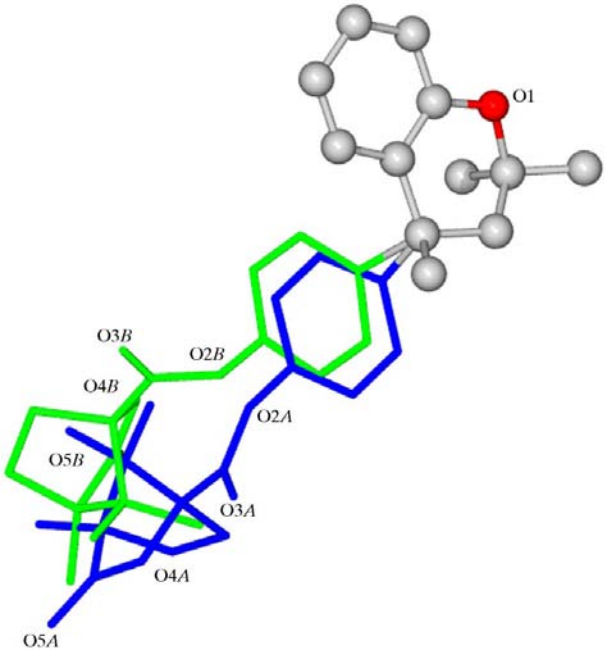

Figure 2
The molecular conformation of (I*a*), showing the disorder. The numbering scheme is identical to that for (I), except that the atoms in the two disordered parts are indicated by the suffixes *A* and *B*. H atoms have been omitted for clarity.

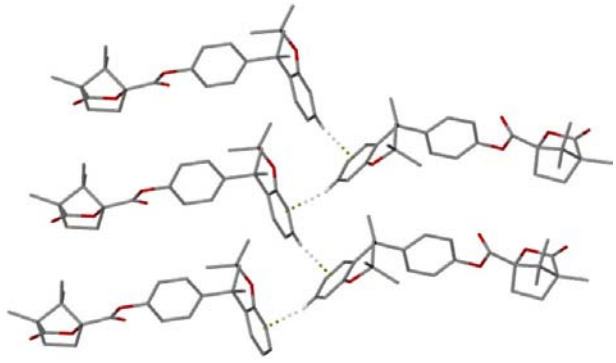

Figure 3
The packing of (I), showing the herring-bone pattern of face-to-edge π–π interactions (dotted lines).

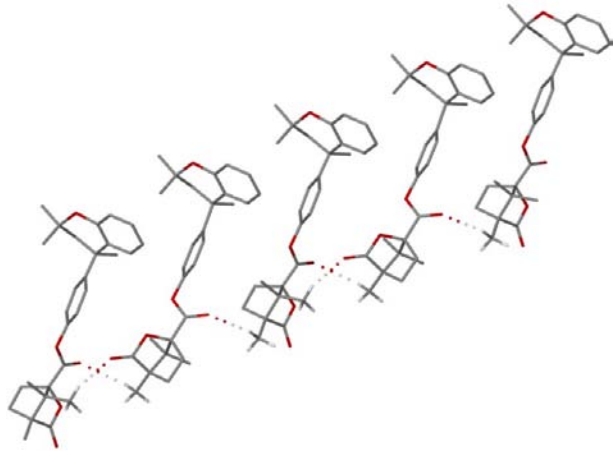

Figure 4
The packing of (I*a*), showing the alternating pattern of (I*a*′) and (I*a*″) connected by C—H···O interactions (dotted lines).

Experimental

The benzene clathrate of Dianin's compound (1:6) (Baker *et al.*, 1956; 1.00 g, 3.34 mmol), 4-(dimethylamino)pyridine (DMAP, 48 mg, 393 µmol) and triethylamine (1.08 g, 10.7 mmol) were dissolved/suspended in dichloromethane (15 ml), and camphanic chloride (932 mg, 4.30 mmol) was added. The mixture was stirred at ambient temperature for 30 h and ice (*ca* 20 ml) was added to quench the reaction. The aqueous phase was extracted with dichloromethane (15 ml), the combined organic phases were washed with water (25 ml) and dried over anhydrous magnesium sulfate, and the solvents were removed under reduced pressure. On exposing the residue to a minimum of ethanol, white crystals formed, which were filtered off, washed with cold ethanol and dried under vacuum (yield 1.367 g, 91%). The compound was pure by NMR. The only indication of the presence of diastereomers in either the ^{1}H or ^{13}C NMR spectra was the doubling of the signal at δ_C = 127.63 and 127.66 ($CDCl_3$, 75 MHz; Varian VXR 300). In an unoptimized effort at resolving the diastereomers, a small quantity (1.15 g, 2.56 mmol) was dissolved in a minimum of 2-methoxyethanol (Brienne & Jacques, 1975) at 333 K

and allowed to crystallize on cooling to ambient temperature. Pure (*S*,*S*)-4-(*p*-camphanyloxyphenyl)-2,2,4-trimethylchroman (276 mg, 615 µmol) was obtained [m.p. 451 K; literature value 450 K (Brienne & Jacques, 1975)]. ^{1}H NMR (300 MHz, $CDCl_3$, $CHCl_3$ used as reference at δ = 7.24): δ 0.87 (3*H*, *s*), 1.03 (3*H*, *s*), 1.08 (3*H*, *s*), 1.10 (3*H*, *s*), 1.30 (3*H*, *s*), 1.66 (3*H*, *s*), 1.70 (1*H*, *ddd*, *J* = 13.4, 9.3 and 4.3 Hz), 1.93 (1*H*, *ddd*, *J* = 13.2, 10.8 and 4.5 Hz), 2.05 (1*H*, *d*, *J* = 14.2 Hz), 2.13 (1*H*, *ddd*, J = 13.5, 9.5 and 4.7 Hz), 2.32 (1*H*, *d*, *J* = 14.2 Hz), 2.50 (1*H*, *ddd*, *J* = 13.6, 10.7 and 4.3 Hz), 6.86 (1*H*, *d*, *J* = 8.3 Hz), 6.91 (1*H*, *t*, *J* = 7.5 Hz), 6.99 (2*H*, *d*, *J* = 8.8 Hz), 7.14–7.19 (2*H*, *m*), 7.21 (2*H*, *d*, *J* = 8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$ used as reference at δ = 77.00): δ 9.48, 16.62, 27.28, 28.78, 29.76, 30.56, 32.27, 39.04, 50.19, 54.55, 54.78, 74.48, 90.85, 118.32, 120.33, 120.81, 127.63, 128.09, 128.28, 129.50, 148.05, 148.58, 153.81, 166.38, 178.12.

Compound (I)

Crystal data

$C_{28}H_{32}O_5$	Mo $K\alpha$ radiation
M_r = 448.54	Cell parameters from 4712 reflections
Orthorhombic, $P2_12_12_1$	θ = 2.5–26°
a = 7.398 (2) Å	μ = 0.08 mm^{-1}
b = 8.413 (2) Å	T = 100 (2) K
c = 38.628 (11) Å	Prism, colourless
V = 2404.3 (12) Å^3	0.27 × 0.24 × 0.19 mm
Z = 4	
D_x = 1.239 Mg m^{-3}	

Data collection

Bruker SMART APEX CCD area-detector diffractometer	2743 independent reflections
	2258 reflections with $I > 2\sigma(I)$
ω scans	R_{int} = 0.055
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2002)	θ_{max} = 26.0°
	$h = -9 \rightarrow 8$
T_{min} = 0.97, T_{max} = 0.98	$k = -10 \rightarrow 7$
13 603 measured reflections	$l = -47 \rightarrow 43$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0356P)^2 + 0.0289P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.039	
$wR(F^2)$ = 0.082	
S = 1.12	$(\Delta/\sigma)_{max}$ = 0.001
2743 reflections	$\Delta\rho_{max}$ = 0.20 e Å^{-3}
304 parameters	$\Delta\rho_{min}$ = −0.20 e Å^{-3}
H-atom parameters constrained	

Compound (I*a*)

Crystal data

$C_{28}H_{32}O_5$	Mo $K\alpha$ radiation
M_r = 448.54	Cell parameters from 5449 reflections
Orthorhombic, $P2_12_12_1$	θ = 2.5–28°
a = 7.0710 (5) Å	μ = 0.09 mm^{-1}
b = 6.8500 (4) Å	T = 100 (2) K
c = 48.717 (4) Å	Prism, colourless
V = 2359.7 (3) Å^3	0.22 × 0.21 × 0.17 mm
Z = 4	
D_x = 1.263 Mg m^{-3}	

Data collection

Bruker SMART APEX CCD area-detector diffractometer	2734 independent reflections
	2282 reflections with $I > 2\sigma(I)$
ω scans	R_{int} = 0.064
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2002)	θ_{max} = 26.0°
	$h = -8 \rightarrow 7$
T_{min} = 0.98, T_{max} = 0.99	$k = -8 \rightarrow 7$
13 513 measured reflections	$l = -56 \rightarrow 60$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0295P)^2 + 0.4167P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.067	
$wR(F^2)$ = 0.131	
S = 1.19	$(\Delta/\sigma)_{max}$ = 0.023
2734 reflections	$\Delta\rho_{max}$ = 0.20 e Å^{-3}
489 parameters	$\Delta\rho_{min}$ = −0.15 e Å^{-3}
H-atom parameters constrained	

The positions of the disordered atoms in (I*a*) were identified from a difference Fourier map. Atoms from the different disorder groups were refined anisotropically [with appropriate restraints using SIMU and ISOR in *SHELXL*97 (Sheldrick, 1997)] with common site occupancies; refinement showed the disorder to be exactly 50:50%. H atoms were positioned geometrically and constrained to ride on their attached atoms, with U_{iso}(H) = 1.2 or 1.5 (for methyl groups) times U_{eq}(C). Friedel pairs were merged [1969 for (I) and 1889 for (I*a*)] before the final refinement in both cases.

For both isomers, data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2002); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *XSEED* (Barbour, 2001); software used to prepare material for publication: *XSEED*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: HJ1032). Services for accessing these data are described at the back of the journal.

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