Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

(*R*)-4-(4-Aminophenyl)-2,2,4-trimethylchroman and (*S*)-4-(4-aminophenyl)-2,2,4-trimethylthiachroman

Christopher S. Frampton,[a]* David D. MacNicol[b] and Derek R. Wilson[b]

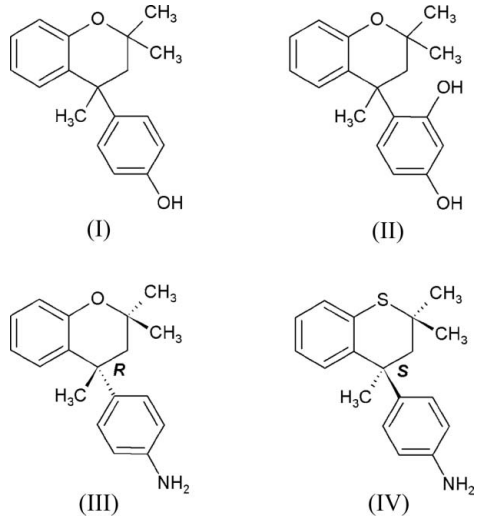
[a]Pharmorphix Solid State Services, A Sigma–Aldrich Company, 250 Cambridge Science Park, Milton Road, Cambridge CB4 0WE, England, and [b]Department of Chemistry, University of Glasgow, Glasgow G12 8QQ, Scotland
Correspondence e-mail: chris.frampton@sial.com

Received 22 March 2011
Accepted 31 March 2011
Online 16 April 2011

The title compounds, $C_{18}H_{21}NO$ and $C_{18}H_{21}NS$, in their enantiomerically pure forms are isostructural with the enantiomerically pure 4-(4-hydroxyphenyl)-2,2,4-trimethylchroman and 4-(2,4-dihydroxyphenyl)-2,2,4-trimethylchroman analogues and form extended linear chains *via* N—H···O or N—H···S hydrogen bonding along the [100] direction. The absolute configuration for both compounds was determined by anomalous dispersion methods with reference to both the Flack parameter and, for the light-atom compound, Bayesian statistics on Bijvoet differences.

Comment

As part of our continuing studies of the structural properties of materials that demonstrate a close relationship with Dianin's compound [4-(4-hydroxyphenyl)-2,2,4-trimethylchroman], (I), we have focused on how small incremental changes to the scaffold of Dianin's compound can affect the crystal engineering properties of this classic host–guest material (Hardy *et al.*, 1977, 1979; Beresford *et al.*, 1999; Frampton *et al.*, 1992) [structural data for (I), together with ellipsoid and packing plots, are available in the *Supplementary material*]. In its racemic form, Dianin's compound and its thia- and selenachroman analogues (Hardy *et al.*, 1979; MacNicol *et al.*, 1969, 1987; MacNicol & Wilson, 1971) form a series of isomorphous and isostructural clathrates having the common space group $R\overline{3}$ with approximate cell paramenters a = 27 Å and c = 11 Å. In contrast, Dianin's compound in its enantiomerically pure form has a packing arrangement that is significantly different from that of the racemate and does not form a clathrate-type structure (Brienne & Jaques, 1975). The crystal structure of Dianin's compound as the enantiomerically pure *S* isomer has been described previously (Lloyd & Bredenkamp, 2005) and crystallizes with one molecule in the asymmetric unit in the orthorhombic space group $P2_12_12_1$. The absolute configuration in this instance was derived from the purification of the (*S*,*S*)-4-(2,2,4-trimethylchroman-4-yl)-phenyl camphonate of known stereochemistry, rather than by anomalous dispersion methods.



The crystal structures of the two title compounds, (III) and (IV), where the 4-hydroxy substituents of 4-(4-hydroxyphenyl)-2,2,4-trimethylchroman and 4-(4-hydroxyphenyl)-2,2,4-trimethylthiachroman are replaced by a 4-amino group, are described here. For comparison purposes, we also report the structure of racemic 'guest-free' Dianin's compound, (I), at 100 K, since the two previously published structures were performed at room temperature (Goldup & Smith, 1971; Imashiro *et al.*, 1998).

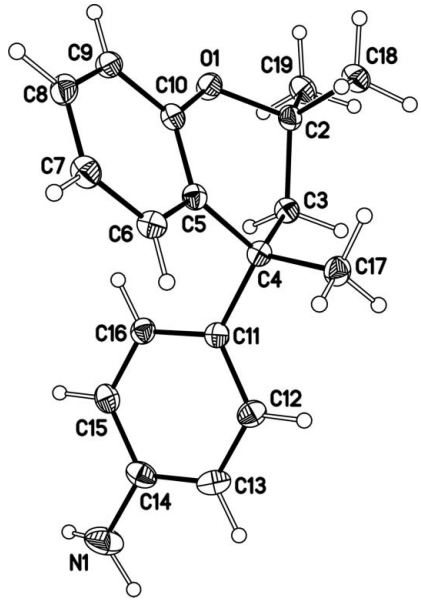


Figure 1
The molecular structure of (III), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level.

  doi:10.1107/S0108270111012157

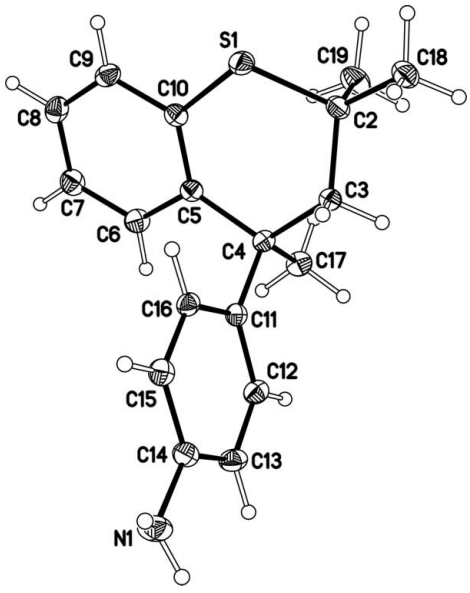


Figure 2
The molecular structure of (IV), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level.

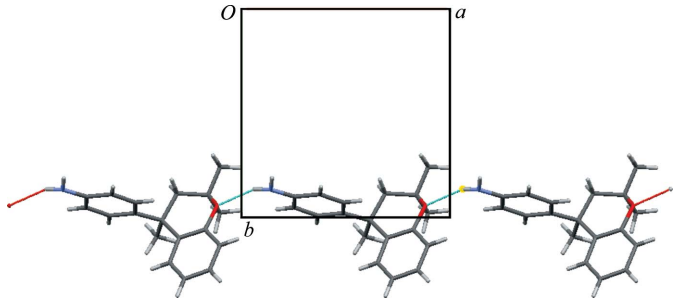


Figure 3
The packing of (III), viewed down the *c* axis, showing the formation of the extended linear N—H···O hydrogen-bonded chain along the [100] direction (thin lines).

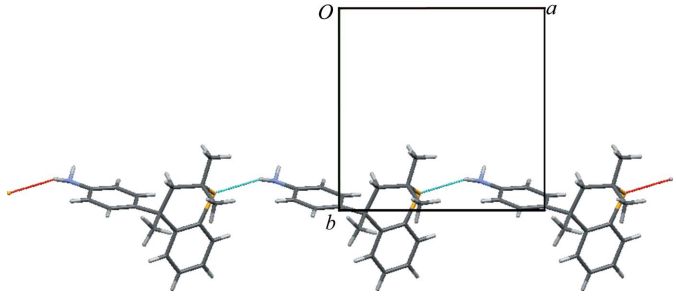


Figure 4
The packing of (IV), viewed down the *c* axis, showing the formation of the extended linear N—H···S hydrogen-bonded chain along the [100] direction (thin lines).

Compounds (III) and (IV) (Figs. 1 and 2) are isostructural not only with each other but also, suprisingly, with the enantiomerically pure forms of the 4-(4-hydroxyphenyl)-, (I) (Lloyd & Bredenkamp, 2005), and 4-(2,4-dihydroxyphenyl)-2,2,4-trimethylchroman, (II) (Beresford *et al.*, 1999), analogues. Crystals of both (III) and (IV) were obtained by spontaneous resolution on crystallization, yielding a 50:50 mixture of the pure enantiomers. The heterocyclic chroman ring in both compounds adopts an envelope conformation or *E* form, with atom C2 displaced from the mean plane defined by atoms O1(S1)/C10/C5/C4/C3 by 0.641 (1) and 0.809 (2) Å, respectively, which are directly comparable with the displacements of −0.649 and −0.647 Å found for atom C2 for the 4-hydroxyphenyl and 2,4-dihydroxyphenyl analogues, respectively. In marked contrast, the conformation of the heterocyclic chroman ring in the racemic forms of (I) and (II) (Beresford *et al.*, 1999) is best described as a half-chair or *H* form, with atoms C2 and C3 displaced from the mean plane defined by atoms O1/C10/C5/C4 by 0.331 (2) and −0.352 (2) Å for (I), and 0.384 (3) and −0.317 (3) Å for (II). A change in the magnitude of the C2—C3—C4—C11 torsion angle from *ca* 80° in the racemic forms of (I) and (II) to *ca* 150° in the pure enantiomers leads to very short intramolecular contacts between the *syn*-related methyl groups, C17 and C18, of 3.287, 3.325 (3), 3.314 (2) and 3.419 (2) Å for (I)–(IV), respectively, which are all less than the sum of the van der Waals radii of 4 Å (Chang, 2000). The corresponding C17···C18 distance in the racemic forms is 4.9066 (15) Å for (I) and 4.925 (4) Å for (II).

The absolute configurations of (III) and (IV), respectively *R* and *S* at the chiral centre C4, were determined by anomalous-dispersion methods (Flack, 1983). The determination of the absolute configuration of (III) was challenging, given that the molecule contains only a single N and a single O atom. To maximize the likelihood of success, a full sphere of data was collected at 100 K using Cu *Kα* radiation to a maximum resolution of 0.80 Å. A total of 25 124 reflections were collected, yielding a Flack parameter *x* and standard uncertainty *u* for this structure of −0.07 (18). The value of *u* is beyond the limit of enantiopure sufficient distinguishing power (Flack & Bernardinelli, 2000), and for further confirmation of the absolute configuration a determination using Bayesian statistics on Bijvoet differences (Hooft *et al.*, 2008), as implemented in the program *PLATON* (Spek, 2009), was performed. This gave probability values *P*3(true), *P*3(twin) and *P*3(wrong) of 1.000, 0.000 and 0.000, respectively. The calculation was based on 14 290 Bijvoet pairs. The determination of the absolute configuration of (IV) was less challenging, owing to the presence of the heavy S atom, and in this case the Flack parameter was determined as 0.016 (11).

The crystal packing arrangements for the 4-aminophenyl analogues (III) and (IV) are very similar to those found in both the enantiopure 4-hydroxyphenyl and 2,4-dihydroxyphenyl analogues, (I) and (II), with the formation of an extended linear N—H···O or N—H···S hydrogen-bonded chain along the [100] direction (Figs. 3–6, and Tables 1 and 2). However, in the case of the amino compounds, only one of the two available N—H bonds of the amino group is utilized in the hydrogen-bonding arrangement, thereby breaking Etter's first rule of hydrogen bonding for organic compounds which states that all good proton donors and acceptors are used in

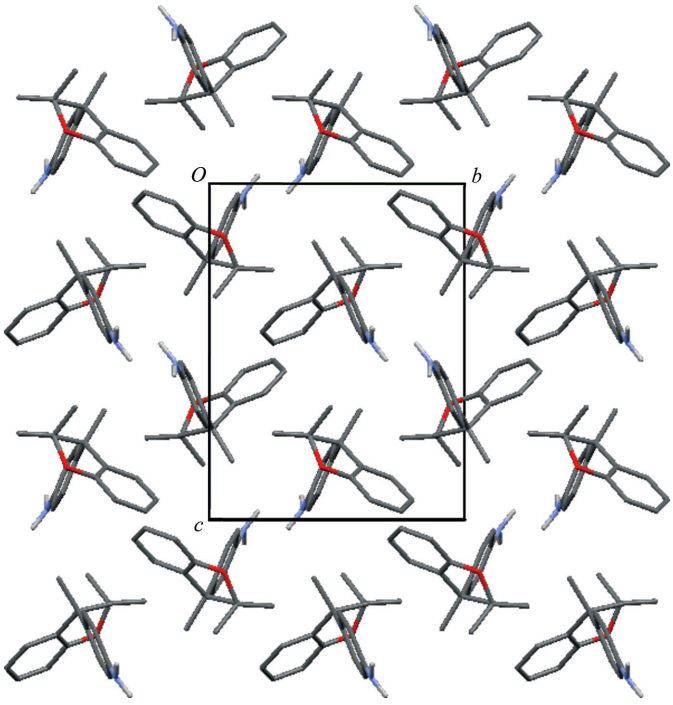


Figure 5
The packing of (III), viewed down the *a* axis. Only amine H atoms are shown.

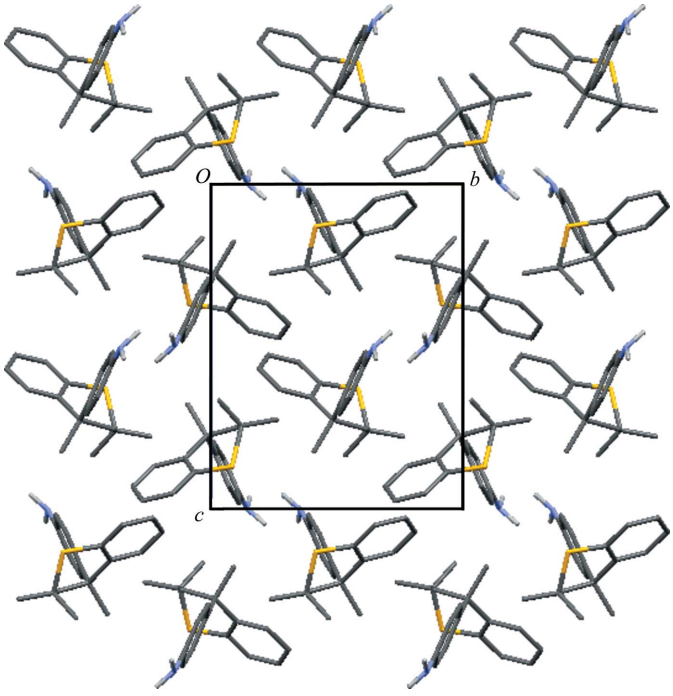


Figure 6
The packing of (IV), viewed down the *a* axis. Only amine H atoms are shown.

hydrogen bonding (Etter, 1990). Further work is currently in progress on racemic and quasi-racemic analogues of Dianin's compound.

Experimental

For the preparation of 4-(4-aminophenyl)-2,2,4-trimethylchroman, (III), 2-phenyl-3-[4-(2,2,4-trimethylchroman-4-yl)phenyl]quinazolin-4(3*H*)-one (Gilmore *et al.*, 1977) (4.5 g, 9.5 mmol) was heated (Scherrer & Beatty, 1972) at 423 K for 22 h in ethylene glycol (100 ml) with KOH pellets (6.5 g) under pure nitrogen with magnetic stirring. After ether extraction (3 × 100 ml), washing with brine and removal of the solvent, the amine (2.37 g, 93%) was recrystallized from ethanol or CCl_4 to give prisms [m.p. 409–410 K (sealed tube)]. Analysis for $C_{18}H_{21}NO$ requires (found): C 80.86 (80.59), H 7.92 (7.62), N 5.24% (5.51%). MS *m*/*z*: 267.16204, calc. 267.162306. ^{1}H NMR (100 MHz, $CDCl_3$): δ 0.97 (*s*, 3H), 1.37 (*s*, 3H), 1.68 (*s*, 3H), 2.19 (*q*, 2H, δ_{AB} = 0.29 p.p.m., J_{AB} = 14 Hz), 3.8–3.3 (*br s*, 2H), 7.4–6.4 (aromatic, 8H); FT–IR (ν_{max}, ATR, cm^{-1}): 3467, 3369 [ν(N—H)].

For the preparation of 4-(4-aminophenyl)-2,2,4-trimethylthiachroman, (IV), 2-phenyl-3-[4-(2,2,4-trimethylthiachroman-4-yl)phenyl]-quinazolin-4(3*H*)-one (6.7 g, 13.7 mmol) was heated at 423 K for 22 h in ethylene glycol (120 ml) with KOH pellets (13 g) under pure nitrogen with magnetic stirring. After ether extraction (3 × 250 ml), washing with brine and removal of the solvent, the amine (3.6 g, 92.5%) was recrystallized from ethanol after decolorizing with powdered animal charcoal to give colourless needles [m.p. 410–411 K (sealed tube)]. Analysis for $C_{18}H_{21}NS$ requires (found): C 76.30 (76.14), H 7.47 (7.46), N 4.94 (4.65), S 11.31% (11.67%). MS *m*/*z*: 283, calc. 283. ^{1}H NMR (100 MHz, $CDCl_3$): δ 1.1 (*s*, 3H), 1.39 (*s*, 3H), 1.73 (*s*, 3H), 2.27 (*q*, 2H, δ_{AB} = 0.32 p.p.m., J_{AB} = 14Hz), 3.51 (*br s*, 2H), 7.3–6.6 (aromatic, 8H); FT–IR (ν_{max}, ATR, cm^{-1}): 3442, 3353 [ν(N—H)].

'Guest-free' racemic 4-(4-hydroxyphenyl)-2,2,4-trimethylchroman, (I), was prepared as follows. Racemic (I) was prepared and desolvated as described by Baker *et al.* (1956). Clear colourless prisms of the guest-free form of (I) suitable for X-ray analysis were obtained by sublimation of desolvated material *in vacuo* (at *ca* 10^{-3} mm Hg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (*s*, 3H), 1.36 (*s*, 3H), 1.69 (*s*, 3H), 2.07 (*d*, 1H, J_{AB} = 14 Hz), 2.36 (*d*, 1H, J_{AB} = 14 Hz), 4.61 (*br s*, 1H), 6.68–6.73 (*m*, 2H), 6.86–6.90 (*m*, 1H), 6.91–6.96 (*m*, 1H), 7.04–7.09 (*m*, 2H), 7.15–7.23 (*m*, 2H); FT–IR (ν_{max}, ATR, cm^{-1}): 3285 (*br*) [ν(O—H)].

Compound (III)

Crystal data

$C_{18}H_{21}NO$
M_r = 267.36
Orthorhombic, $P2_12_12_1$
a = 10.23394 (11) Å
b = 10.25106 (10) Å
c = 13.47563 (13) Å
V = 1413.71 (2) Å^3
Z = 4
Cu *K*α radiation
μ = 0.60 mm^{-1}
T = 100 K
0.50 × 0.45 × 0.20 mm

Data collection

Agilent SuperNova dual source diffractometer with an Atlas detector
Absorption correction: multi-scan (*CrysAlis PRO*; Agilent Technologies, 2010)
T_{min} = 0.697, T_{max} = 1.000
25124 measured reflections
2876 independent reflections
2864 reflections with $I > 2\sigma(I)$
R_{int} = 0.024

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.026
$wR(F^2)$ = 0.072
S = 1.00
2876 reflections
193 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.21 e Å^{-3}
$\Delta\rho_{min}$ = −0.14 e Å^{-3}
Absolute structure: Flack (1983), with 1221 Friedel pairs; Hooft *et al.* (2008)
Flack parameter: −0.07 (18)

Table 1
Hydrogen-bond geometry (Å, °) for (III).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1A···O1^{i}	0.956 (19)	2.323 (19)	3.2295 (14)	157.9 (15)

Symmetry code: (i) $x-1, y, z$.

Table 2
Hydrogen-bond geometry (Å, °) for (IV).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1A···S1^{i}	0.88 (2)	2.82 (2)	3.6562 (14)	158.3 (16)

Symmetry code: (i) $x-1, y, z$.

Compound (IV)

Crystal data

$C_{18}H_{21}NS$
M_r = 283.42
Orthorhombic, $P2_12_12_1$
a = 10.6043 (6) Å
b = 10.4104 (5) Å
c = 13.4126 (6) Å
V = 1480.68 (13) Å^3
Z = 4
Cu $K\alpha$ radiation
μ = 1.83 mm^{-1}
T = 100 K
0.50 × 0.45 × 0.20 mm

Data collection

Agilent SuperNova dual source diffractometer with an Atlas detector
Absorption correction: multi-scan (*CrysAlis PRO*; Agilent Technologies, 2010)
T_{min} = 0.654, T_{max} = 1.000
6825 measured reflections
3015 independent reflections
2976 reflections with $I > 2\sigma(I)$
R_{int} = 0.019

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.027
$wR(F^2)$ = 0.070
S = 1.00
3015 reflections
193 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.23 e Å^{-3}
$\Delta\rho_{min}$ = −0.26 e Å^{-3}
Absolute structure: Flack (1983), with 1281 Friedel pairs
Flack parameter: 0.016 (11)

The nonstandard unit cell for (IV), with $a > b < c$, was necessary to preserve the isostructural element of the four structures under comparison. H atoms bonded to N atoms were located in a difference map and refined freely. Other H atoms were positioned geometrically and refined using a riding model (including free rotation about the methyl C—C bond), with C—H = 0.95–0.99 Å and with U_{iso}(H) = 1.5U_{eq}(C) for methyl groups and 1.2U_{eq}(C) otherwise.

For all compounds, data collection: *CrysAlis PRO* (Agilent Technologies, 2010); cell refinement: *CrysAlis PRO*; data reduction: *CrysAlis PRO*; program(s) used to solve structure: *SHELXTL* (Sheldrick, 2008); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL* and *Mercury* (Version 2.4; Macrae *et al.*, 2008); software used to prepare material for publication: *SHELXTL* and *Mercury*.

The authors thank the EPSRC for financial support (to DRW).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM3104). Services for accessing these data are described at the back of the journal.

References

Agilent Technologies (2010). *CrysAlis PRO*. Version 1.171.34.46. Agilent Technologies, Yarnton, Oxfordshire, England.
Baker, W., Floyd, A. J., McOmie, J. F. W., Pope, G., Weaving, A. S. & Wild, J. H. (1956). *J. Chem. Soc.* pp. 2010–2017.
Beresford, T. W., Frampton, C. S., Gall, J. H. & MacNicol, D. D. (1999). *Zh. Strukt. Khim.* **40**, 872–882.
Brienne, M. J. & Jaques, J. (1975). *Tetrahedron Lett.* **28**, 2349–2352.
Chang, R. (2000). *Physical Chemistry for the Chemical and Biological Sciences*, p. 681. Herndon, VA: University Science Books.
Etter, M. C. (1990). *Acc. Chem. Res.* **23**, 120–126.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Flack, H. D. & Bernardinelli, G. (2000). *J. Appl. Cryst.* **33**, 1143–1148.
Frampton, C. S., MacNicol, D. D., Mallinson, P. R. & White, J. D. (1992). *J. Crystallogr. Spectrosc. Res.* **22**, 551–555.
Gilmore, C. J., Hardy, A. D. U., MacNicol, D. D. & Wilson, D. R. (1977). *J. Chem. Soc. Perkin Trans. 2*, pp. 1427–1434.
Goldup, A. & Smith, G. W. (1971). *Sep. Sci.* **6**, 791–817.
Hardy, A. D. U., McKendrick, J. J. & MacNicol, D. D. (1977). *J. Chem. Soc. Perkin Trans. 2*, pp. 1145–1147.
Hardy, A. D. U., McKendrick, J. J. & MacNicol, D. D. (1979). *J. Chem. Soc. Perkin Trans. 2*, pp. 1072–1077.
Hooft, R. W. W., Straver, L. H. & Spek, A. L. (2008). *J. Appl. Cryst.* **41**, 96–103.
Imashiro, F., Yoshimura, M. & Fujiwara, T. (1998). *Acta Cryst.* C**54**, 1357–1360.
Lloyd, G. O. & Bredenkamp, M. W. (2005). *Acta Cryst.* E**61**, o1512–o1514.
MacNicol, D. D., Mallinson, P. R., Keates, R. A. B. & Wilson, F. B. (1987). *J. Inclusion Phenom. Mol. Recognit. Chem.* **5**, 373–377.
MacNicol, D. D., Mills, H. H. & Wilson, F. B. (1969). *J. Chem. Soc. D*, pp. 1332–1333.
MacNicol, D. D. & Wilson, F. B. (1971). *J. Chem. Soc. D*, pp. 786–787.
Macrae, C. F., Bruno, I. J., Chisholm, J. A., Edgington, P. R., McCabe, P., Pidcock, E., Rodriguez-Monge, L., Taylor, R., van de Streek, J. & Wood, P. A. (2008). *J. Appl. Cryst.* **41**, 466–470.
Scherrer, R. A. & Beatty, H. R. (1972). *J. Org. Chem.* **37**, 1681–1686.
Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.
Spek, A. L. (2009). *Acta Cryst.* D**65**, 148–155.