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1-Deoxy-1-(4-fluorophenyl)-β-D-ribofuranose, its hemihydrate, and 1-deoxy-1-(2,4-difluorophenyl)-β-D-ribofuranose: structural evidence for intermolecular C—H···F—C interactions

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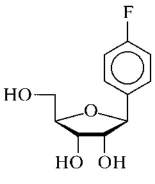
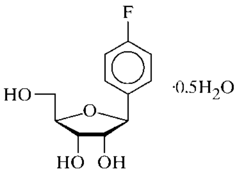
The structures of 1-deoxy-1-(4-fluorophenyl)-β-D-ribofuranose in two crystal forms, (I*a*) and (I*b*) ($C_{11}H_{13}FO_4$), 1-deoxy-1-(4-fluorophenyl)-β-D-ribofuranose hemihydrate, (I*c*) ($C_{11}H_{13}FO_4\cdot 0.5H_2O$) and 1-deoxy-1-(2,4-difluorophenyl)-β-D-ribofuranose, (II) ($C_{11}H_{12}F_2O_4$), show two-dimensional networks of intermolecular hydrogen bonds between the hydroxyl groups. Weak intermolecular C—H···F—C and C—H···$\pi_{\rm arene}$ interactions complete the packing in the third dimension. The ribofuranose ring has a conformation intermediate between a C1′-*exo*,C2′-*endo* twist and a C2′-*endo* envelope for (I*a*) and (I*c*), a conformation intermediate between a C2′-*endo*,C3′-*exo* twist and a C2′-*endo* envelope for (I*b*) and an unsymmetrical C2′-*exo*,C3′-*endo* twist conformation for (II).

Comment

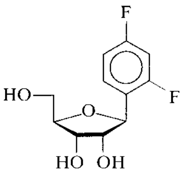
This paper presents the crystal structures of four ribofuranose-based compounds, namely, 1-deoxy-1-(4-fluorophenyl)-β-D-ribofuranose in two crystal forms, (I*a*) and (I*b*), 1-deoxy-1-(4-fluorophenyl)-β-D-ribofuranose hemihydrate, (I*c*), and 1-deoxy-1-(2,4-difluorophenyl)-β-D-ribofuranose, (II).



(I*a*) and (I*b*)



(I*c*)



(II)

The five-membered ribofuranose rings in (I*a*) and (I*c*) (Fig. 1) have rather similar conformations. The ring puckering parameters defined by Cremer & Pople (1975) are $q = 0.375$ Å and $\varphi = 60.2°$ for (I*a*), and $q = 0.421$ Å and $\varphi = 63.4°$ for (I*c*). This corresponds to a conformation intermediate between a C1′-*exo*,C2′-*endo* twist and a C2′-*endo* envelope. The hydroxyl group at C2 and the phenyl group attached to C1 are both in pseudo-equatorial positions, while the hydroxyl group at C3 is in a pseudo-axial position and the methanol group attached to C4 is in a bisecting position with respect to the five-membered ring. No short intramolecular contacts are observed for this conformation.

The five-membered ribofuranose ring in (I*b*) (Fig. 1) is considerably different. It has a conformation intermediate between a C2′-*endo*,C3′-*exo* twist and a C2′-*endo* envelope. The ring puckering parameters are $q = 0.368$ Å and $\varphi = 81.6°$. The hydroxyl group on C2 and the phenyl group attached to C1 are in pseudo-equatorial positions, while the hydroxyl group at C3 and the methanol group attached to C4 are both in pseudo-axial positions with respect to the five-membered ring.

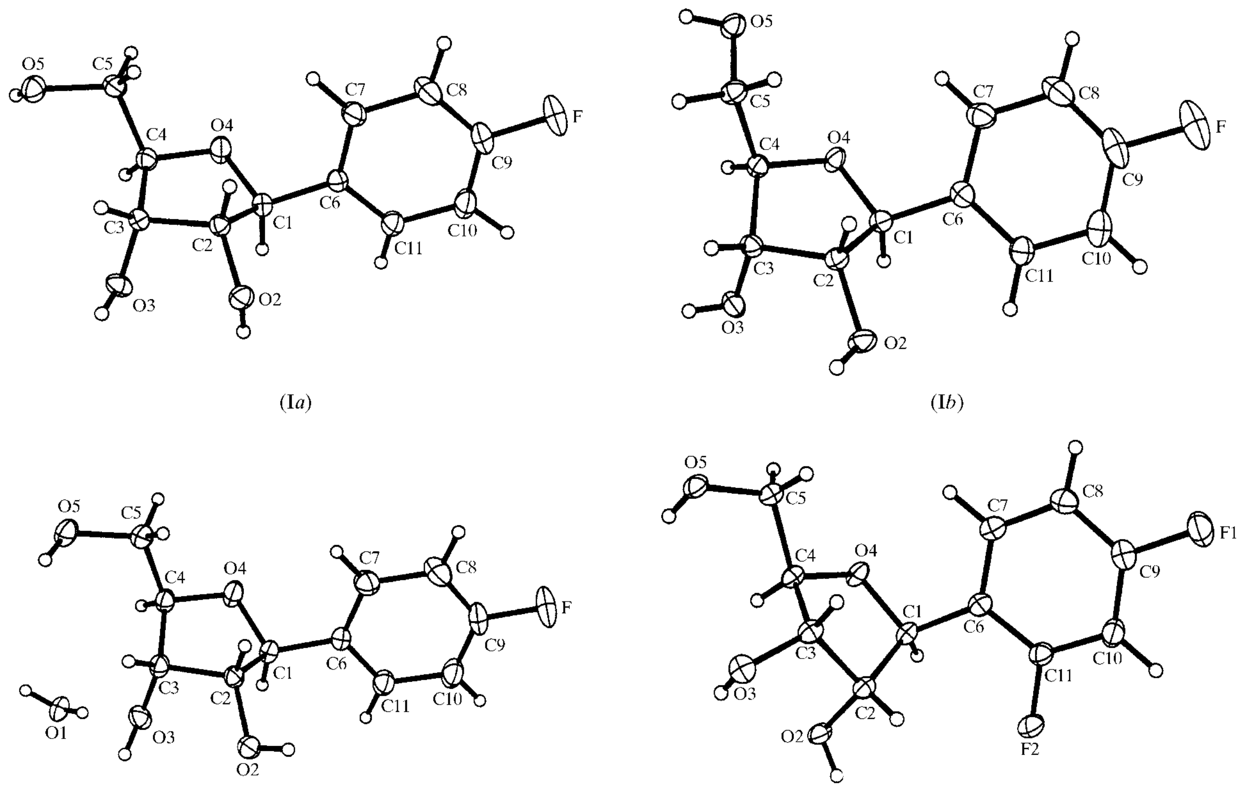
The five-membered ribofuranose ring in (II) (Fig. 1) is different again. It approximately has an unsymmetrical C2′-*exo*,C3′-*endo* twist conformation. The ring puckering parameters are $q = 0.390$ Å and $\varphi = 274.8°$. The hydroxyl group at C2 is in an axial position, the hydroxyl group at C3 is in an equatorial position, the methanol group attached to C4 is in a pseudo-equatorial position and the phenyl group attached to C1 is in a pseudo-axial position with respect to the five-membered ring.

Molecules (I*b*) and (II) show a short intramolecular contact distance of 2.42 (2) for (I*b*) and 2.44 (2) Å for (II) between O4 and H7. This distance is equal to the van der Waals contact distance of 2.4 Å between O and H. Each molecule of (I*a*) and (I*b*) is connected by intermolecular hydrogen bonding (Tables 1 and 2, Figs. 2 and 3) to six neighbouring molecules, leading to a two-dimensional network in the *ab* direction.

For (I*c*), a rather similar two-dimensional network is found in the *bc* direction. In this case, the water molecule is included in the network. Each molecule of (I*c*) is connected by hydrogen bonding (Table 3, Fig. 4) to three neighbouring molecules of (I*c*) and to two different water molecules.

Each molecule of (II) is connected by intermolecular hydrogen bonding (Table 4, Fig. 5) to four different neighbouring molecules, leading to a two-dimensional network in the *ab* direction. Two-dimensional networks of hydrogen bonds have also been observed in the crystal structures of 1-deoxy-1-phenyl-β-D-ribofuranose (Matulic-Adamic *et al.*, 1996), 1-deoxy-1-(2-fluorophenyl)-β-D-ribofuranose (Bats *et al.*, 1999*a*) and 1-deoxy-1-(3-fluorophenyl)-β-D-ribofuranose (Bats *et al.*, 1999*b*).

The packing in the direction of the long dimension of the unit cell consists entirely of intermolecular interactions between the fluorophenyl groups. Rather short intermolecular C—H···F—C contacts are observed in (I*a*), (I*b*) and (I*c*). The intermolecular H10···F distance is 2.30 (2) in (I*a*), 2.42 (2) in (I*b*) and 2.38 (2) Å in (I*c*). These distances are comparable to the van der Waals contact distance between F and H [2.35 Å according to Pauling (1960) or 2.47 Å according to Bondi (1964)]. Each 4-fluorophenyl group is involved in two of these contacts, resulting in zigzag chains of molecules (Fig. 6). In addition to these C—H···F—C interactions, the crystal



(I*a*) (I*b*)

(I*c*) (II)

Figure 1
The molecules of (I*a*), (I*b*), (I*c*) and (II) with 50% probability displacement ellipsoids. H atoms are shown as spheres of arbitrary radii.

packing of (I*a*), (I*b*) and (I*c*) also shows intermolecular C—H···$\pi_{\rm arene}$ interactions. The H8···*Cg* distance is 2.82 in (I*a*), 2.84 in (I*b*) and 2.82 Å in (I*c*) (*Cg* is the centroid of the phenyl ring). Intermolecular C—H···$\pi_{\rm arene}$ interactions play a significant role in crystal structures (Brady *et al.*, 1998; Gallagher *et al.*, 1998). Koch & Egert (1995) have shown these interactions to be of an electrostatic nature.

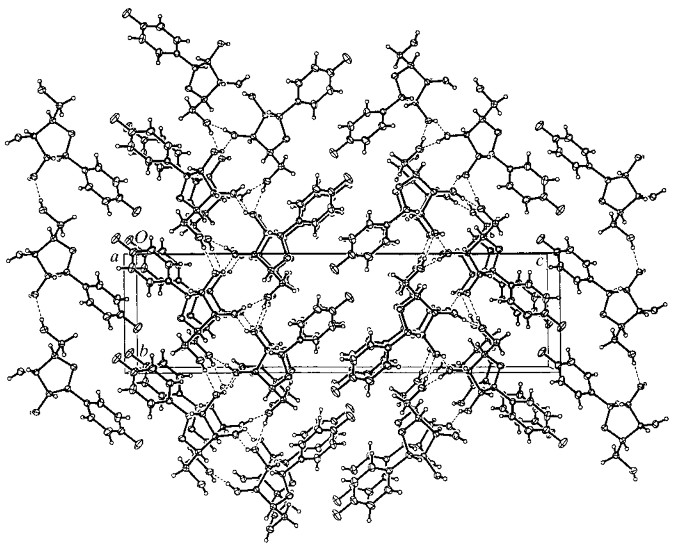


Figure 2
The crystal packing of (I*a*) shown down the *a* axis.

The crystal structure of (II) shows pairs of molecules related by a twofold axis, with intermolecular distances of 2.57 (2) Å between F1 and H10($-x$, y, $-z$) (Fig. 7). These distances are longer than the van der Waals contact distance. No other intermolecular interactions between the phenyl groups are

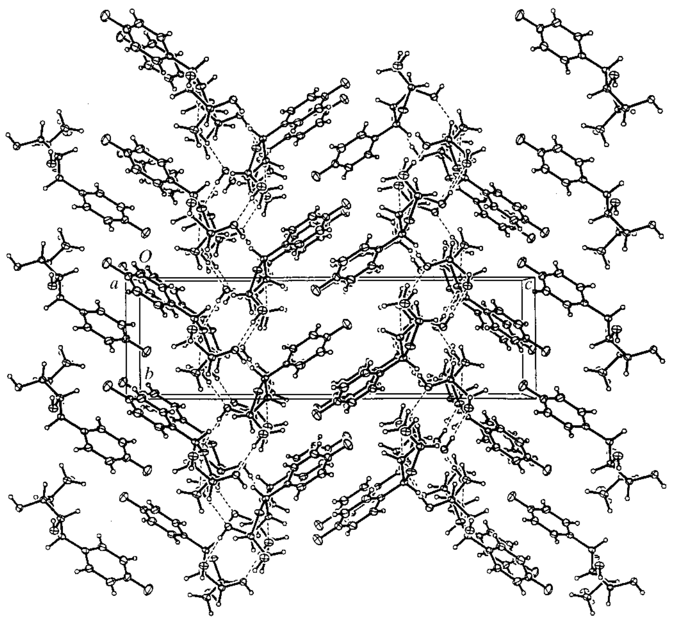


Figure 3
The crystal packing of (I*b*) shown down the *a* axis.

found in this case, which can explain the crystal packing in the *c* direction. Intermolecular F···H contacts have also been reported for other crystal structures (Karipides *et al.*, 1988; Bruno *et al.*, 1997; Antolić *et al.*, 1996; Vij *et al.*, 1996; Shimoni *et al.*, 1994; Weiss *et al.*, 1997). A search of the Spring 1999 release of the Cambridge Structural Database (Allen & Kennard, 1993) for structures containing fluorophenyl groups, with H-atom coordinates included and no disorder reported, revealed 1144 crystal structures. Among these structures, 1596 different C—H···F—C contacts were found with H···F distances shorter than 2.6 Å (652 shorter than 2.5, 182 shorter than 2.4 and 37 shorter than 2.3 Å). About one third of these interactions were C_{phenyl}—H···F—C_{phenyl} contacts. The number of dimeric structures as found for (II) is rather small. Only 35 dimers were found with both C—H···F—C contacts shorter than 2.6 Å. Larsen & Marthi (1994) and Kubota & Ohba (1992) have shown the F atom in fluorophenyl groups to bear a small negative charge of about −0.1 e $Å^{-3}$. Thus, the C—F bond is a likely candidate for electrostatic interactions with electropositive C—H bonds.

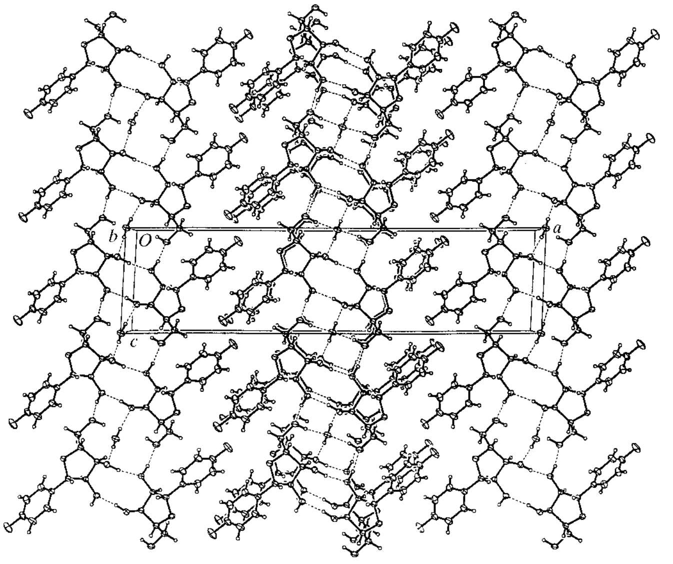


Figure 4
The crystal packing of (I*c*) shown down the *b* axis.

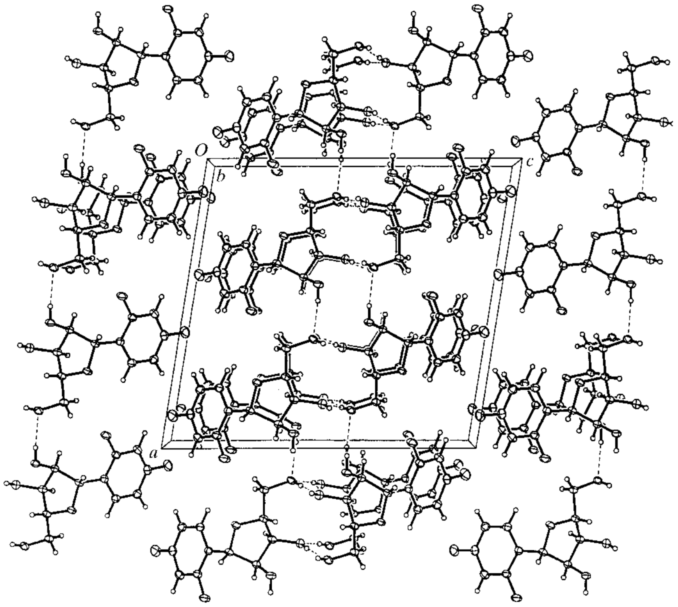


Figure 5
The crystal packing of (II) shown down the *b* axis.

Howard *et al.* (1996) calculated the C—H···F—C interaction energy of a complex between CH_3F and H_4C to be approximately −0.2 kcal mol^{-1} (1 cal = 4.184 J), which is an order of magnitude smaller than the corresponding value for a complex between CH_3F and H_2O. They termed the C—H···F—C interaction as a van der Waals interaction rather than a hydrogen bond. Thalladi *et al.* (1998) showed the packing in fluorobenzenes containing no other elements than C, H and F to be dominated by C—H···F—C interactions. They also showed the C—H···F interactions to have similar characteristics to those of weak C—H···O and C—H···N hydrogen bonds. These interactions are rather weak and thus are easily overridden by stronger intermolecular interactions. In the crystal structures reported here, however, stronger interactions are missing in one direction. Thus, weaker C—H···F—C and C—H···π interactions dominate the crystal packing in this direction.

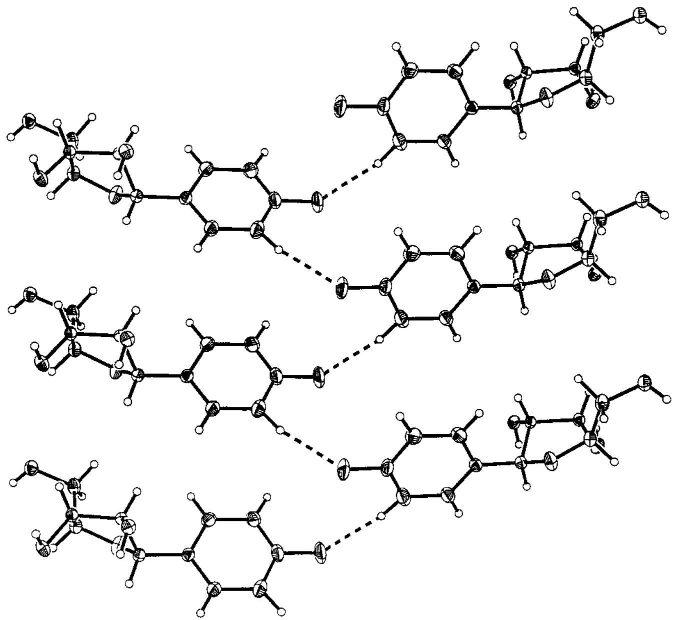


Figure 6
Zigzag chains of molecules connected by C—H···F interactions in (I*a*). Similar chains occur in (I*b*) and (I*c*).

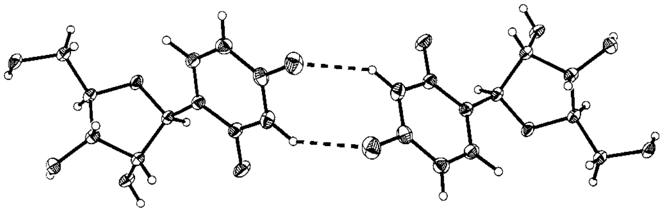


Figure 7
Dimers of molecules of (II) connected by C—H···F interactions.

Experimental

The title compounds were prepared according to Krohn *et al.* (1992). Thus, 1-bromo-4-fluorobenzene [for (I)] or 1-bromo-2,4-difluorobenzene [for (II)] was lithiated and added to 2′,3′,5′-tri-*O*-benzyl-D-ribono-1,4-lactone (Barker & Fletcher, 1961; Timpe *et al.*, 1975). The resulting intermediate lactol was directly dehydroxylated to yield a sterically uniform β-*C*-riboside. Debenzylation of the hydroxyl groups resulted in the unprotected *C*-nucleoside. Compound (I) was recrystallized from methanol, resulting in two different crystalline modifications, (I*a*) and (I*b*), while recrystallization from water yielded the hemihydrate (I*c*). Compound (II) was also recrystallized from water.

Compound (I*a*)

Crystal data

$C_{11}H_{13}FO_4$
M_r = 228.21
Orthorhombic, $P2_12_12_1$
a = 5.4741 (9) Å
b = 7.3018 (7) Å
c = 26.791 (3) Å
V = 1070.9 (2) Å^3
Z = 4
D_x = 1.416 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 279 reflections
θ = 3–23°
μ = 0.118 mm^{-1}
T = 134 (2) K
Plate, colourless
1.30 × 0.64 × 0.15 mm

Data collection

Siemens SMART diffractometer
ω scans
18 913 measured reflections
3431 independent reflections
3273 reflections with $I > 2\sigma(I)$
$R_{\rm int}$ = 0.084
$\theta_{\max}$ = 31.3°
$h = -7 \rightarrow 8$
$k = -10 \rightarrow 10$
$l = -38 \rightarrow 35$
369 standard reflections
frequency: 540 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.037$
$wR(F^2)$ = 0.111
S = 1.393
3431 reflections
197 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.06P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max}$ = 0.002
$\Delta\rho_{\max}$ = 0.36 e Å^{-3}
$\Delta\rho_{\min}$ = −0.20 e Å^{-3}

Table 1
Hydrogen-bonding geometry (Å, °) for (I*a*).

D—H···A	D—H	H···A	D···A	D—H···A
O2—HO2···O3$^{\rm i}$	0.85 (2)	1.96 (2)	2.729 (1)	151 (2)
O3—HO3···O5$^{\rm ii}$	0.88 (2)	1.91 (2)	2.774 (1)	169 (2)
O5—HO5···O2$^{\rm iii}$	0.80 (2)	1.89 (2)	2.682 (1)	172 (2)

Symmetry codes: (i) $1 - x, \frac{1}{2} + y, \frac{3}{2} - z$; (ii) $2 - x, \frac{1}{2} + y, \frac{3}{2} - z$; (iii) $x, y - 1, z$.

Compound (I*b*)

Crystal data

$C_{11}H_{13}FO_4$
M_r = 228.21
Orthorhombic, $P2_12_12_1$
a = 6.7109 (14) Å
b = 6.7653 (7) Å
c = 22.846 (3) Å
V = 1037.2 (3) Å^3
Z = 4
D_x = 1.461 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 161 reflections
θ = 3–23°
μ = 0.122 mm^{-1}
T = 135 (2) K
Rod, colourless
0.66 × 0.45 × 0.28 mm

Data collection

Siemens SMART diffractometer
ω scans
Absorption correction: numerical (*SHELXTL*; Sheldrick, 1996)
$T_{\min}$ = 0.932, $T_{\max}$ = 0.968
19 895 measured reflections
3512 independent reflections
2944 reflections with $I > 2\sigma(I)$
$R_{\rm int}$ = 0.058
$\theta_{\max}$ = 31.9°
$h = -9 \rightarrow 9$
$k = -10 \rightarrow 10$
$l = -34 \rightarrow 31$
275 standard reflections
frequency: 540 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.039$
$wR(F^2)$ = 0.090
S = 1.114
3512 reflections
198 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.05P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$\Delta\rho_{\max}$ = 0.30 e Å^{-3}
$\Delta\rho_{\min}$ = −0.20 e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.010 (3)

Table 2
Hydrogen-bonding geometry (Å, °) for (I*b*).

D—H···A	D—H	H···A	D···A	D—H···A
O2—HO2···O5$^{\rm i}$	0.83 (2)	1.91 (2)	2.706 (1)	160 (1)
O3—HO3···O2$^{\rm ii}$	0.79 (2)	1.94 (2)	2.721 (1)	170 (1)
O5—HO5···O3$^{\rm iii}$	0.88 (2)	1.91 (2)	2.782 (1)	174 (1)

Symmetry codes: (i) $x - 1, y, z$; (ii) $-x, y - \frac{1}{2}, \frac{3}{2} - z$; (iii) $1 - x, y - \frac{1}{2}, \frac{3}{2} - z$.

Compound (I*c*)

Crystal data

$C_{11}H_{13}FO_4 \cdot 0.5H_2O$
M_r = 237.22
Monoclinic, $C2$
a = 29.356 (6) Å
b = 5.3068 (7) Å
c = 7.3530 (11) Å
β = 93.215 (10)°
V = 1143.7 (3) Å^3
Z = 4
D_x = 1.378 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 185 reflections
θ = 3–23°
μ = 0.116 mm^{-1}
T = 154 (2) K
Block, colourless
0.45 × 0.44 × 0.40 mm

Data collection

Siemens SMART diffractometer
ω scans
5566 measured reflections
2827 independent reflections
2746 reflections with $I > 2\sigma(I)$
$R_{\rm int}$ = 0.041
$\theta_{\max}$ = 29.0°
$h = -40 \rightarrow 37$
$k = -7 \rightarrow 6$
$l = -9 \rightarrow 10$
207 standard reflections
frequency: 540 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.034$
$wR(F^2)$ = 0.100
S = 1.486
2827 reflections
207 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.05P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$\Delta\rho_{\max}$ = 0.35 e Å^{-3}
$\Delta\rho_{\min}$ = −0.17 e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.006 (2)

Table 3
Hydrogen-bonding geometry (Å, °) for (I*c*).

D—H···A	D—H	H···A	D···A	D—H···A
O1—HO1···O3$^{\rm i}$	0.84 (2)	1.86 (2)	2.701 (1)	176 (2)
O2—HO2···O5$^{\rm ii}$	0.88 (2)	1.79 (2)	2.661 (1)	167 (2)
O3—HO3···O2$^{\rm iii}$	0.92 (2)	1.77 (2)	2.669 (1)	168 (2)
O5—HO5···O1$^{\rm iv}$	0.93 (2)	1.85 (2)	2.777 (1)	172 (2)

Symmetry codes: (i) $1 - x, y, -z$; (ii) $x, y, 1 + z$; (iii) $1 - x, y, 1 - z$; (iv) $x, y - 1, z$.

Compound (II)

Crystal data

$C_{11}H_{12}F_2O_4$
$M_r = 246.21$
Monoclinic, $C2$
$a = 14.684\ (2)$ Å
$b = 4.6609\ (6)$ Å
$c = 15.772\ (2)$ Å
$\beta = 99.476\ (11)^\circ$
$V = 1064.7\ (2)$ Å^3
$Z = 4$

$D_x = 1.536$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 217 reflections
$\theta = 3$–23°
$\mu = 0.138$ mm^{-1}
$T = 134\ (2)$ K
Thick plate, colourless
0.75 × 0.70 × 0.20 mm

Data collection

Siemens SMART diffractometer
ω scans
9578 measured reflections
3048 independent reflections
2794 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.068$
$\theta_{\rm max} = 30.6^\circ$

$h = -20 \rightarrow 21$
$k = -6 \rightarrow 6$
$l = -22 \rightarrow 21$
183 standard reflections
frequency: 540 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.046$
$wR(F^2) = 0.122$
$S = 1.400$
3048 reflections
202 parameters

All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.06P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$\Delta\rho_{\rm max} = 0.37$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.25$ e Å^{-3}

For all compounds, data collection: *SMART* (Siemens, 1995); cell refinement: *SMART*; data reduction: *SAINT* (Siemens, 1995); program(s) used to solve structure: *SHELXTL* (Sheldrick, 1996); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *XP* in *SHELXTL*; software used to prepare material for publication: *CIF* in *SHELXL*97.

Table 4
Hydrogen-bonding geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
O2—HO2···O5$^{\rm i}$	0.82 (2)	1.97 (2)	2.780 (1)	171 (2)
O3—HO3···O5$^{\rm ii}$	0.76 (2)	2.07 (2)	2.827 (1)	174 (2)
O5—HO5···O3$^{\rm ii}$	0.81 (2)	1.92 (2)	2.724 (1)	171 (2)

Symmetry codes: (i) $\frac{1}{2} + x, y - \frac{1}{2}, z$; (ii) $-\frac{1}{2} - x, y - \frac{1}{2}, 1 - z$.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: KA1343). Services for accessing these data are described at the back of the journal.

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