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(5*α*,8*α*,9*β*,11*S*)-5,7,8,9-Tetrahydro-11-(fluoromethyl)-9-(3,4,5-trimethoxyphenyl)-5,8-methano-1,3-dioxolo[4,5-*h*][2]benzoxepin

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean *σ*(C–C) = 0.004 Å
R factor = 0.050
wR factor = 0.143
Data-to-parameter ratio = 9.5

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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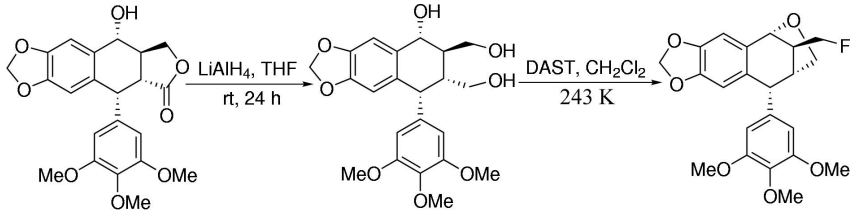
The title compound, $C_{22}H_{23}FO_6$, is an unexpected product of the fluorination of podophyllol. The absolute configuration was determined from the known configuration of the synthetic precursor. Non-classical C—H···O hydrogen bonds link the molecules in the crystal structure into sheets parallel to (001).

Comment

It has been well established over a number of years that the introduction of an F atom into some biomolecules can result in important modifications of their biological properties (Welch & Eswarakrishnan, 1991; Filler *et al.*, 1993). In order to find new compounds with high anticancer activities, we reacted podophyllol, (2), which can be prepared from the naturally occurring podophyllotoxin, (1), according to the published procedure of Drake & Price (1951), with (diethylamino)sulfur trifluoride (DAST), and unexpectedly obtained the title compound, (3), the crystal structure of which we report here.



(1) (2) (3)

The molecular structure of (3) is shown in Fig. 1. Selected molecular parameters and hydrogen-bond geometric characteristics are listed in Tables 1 and 2, respectively. The absolute configuration was assigned according to the known configuration of the starting material, as the chiral centres were not affected by the reaction. Intermolecular O—H···O hydrogen bonds play an important role, resulting in the formation of polymeric sheets parallel to (001).

Experimental

To a stirred suspension of compound (2) (200 mg, 0.48 mmol) in anhydrous CH_2Cl_2 (15 ml), (diethylamino)sulfur trifluoride (DAST) (0.1 ml) was added dropwise at 243 K under nitrogen. The reaction solution was stirred for 30 min at 243 K and then water was added dropwise (0.1 ml) to quench unreacted DAST. The solution was then washed with saturated aqueous $NaHCO_3$ and water. The organic phase was dried over $MgSO_4$. After removal of the solvent *in vacuo*, the solids were crystallized from AcOEt to afford pure (3) as colourless crystals (125 mg, yield 65%; m.p. 481-483 K). ^{1}H NMR (500 MHz, $CDCl_3$, δ, p.p.m.): 6.64 (*s*, 1H), 6.58 (*s*, 1H), 6.37 (*s*, 2H), 5.92 (*dd*, *J* = 0.9 and 15.5 Hz, 2H), 4.69 (*d*, *J* = 4.8 Hz, 1H), 4.61–4.45

(*m*, 2H), 4.37 (*d*, *J* = 3.8 Hz, 1H), 3.97 (*dd*, *J* = 1.8 and 8.9 Hz, 1H), 3.85 (*s*, 3H), 3.80 (*s*, 6H), 3.72 (*dd*, *J* = 5.0 and 8.9 Hz, 1H), 3.0–2.8 (*m*, 1H), 2.70 (*m*, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, δ, p.p.m.): 153.4 (*d*, J_{CF} = 3.6 Hz), 148.1, 146.6, 138.7 (*d*, J_{CF} = 4.4 Hz), 132.0 (*d*, J_{CF} = 6.0 Hz), 129.7, 110.1, 108.2, 107.0, 106.9 (*d*, J_{CF} = 1.4 Hz), 101.3, 82.0 (*d*, J_{CF} = 163.0 Hz), 69.0, 61.1 (*d*, J_{CF} = 3.5 Hz), 56.5 (*d*, J_{CF} = 1.8 Hz), 47.6, 46.1 (*d*, J_{CF} = 21.0 Hz), 46.1, 43.2; HRMS (ESI): *m*/*z*, calculated for $C_{22}H_{23}FO_6^+$: 402.1479; found: 402.1480; IR (KBr): 1591, 1505, 1487, 936.5 cm^{-1}.

Crystal data

$C_{22}H_{23}FO_6$
M_r = 402.4
Orthorhombic, $P2_12_12_1$
a = 7.2253 (1) Å
b = 8.1217 (1) Å
c = 32.7768 (4) Å
V = 1923.40 (4) Å^3
Z = 4
D_x = 1.39 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 22 120 reflections
θ = 1.2–27.5°
μ = 0.11 mm^{-1}
T = 293 (2) K
Prism, colourless
0.38 × 0.22 × 0.21 mm

Data collection

Rigaku RAXIS-RAPID diffractometer
ω scans
Absorption correction: multi-scan (*ABSCOR*; Higashi, 1995)
T_{min} = 0.956, T_{max} = 0.978
14 274 measured reflections
2519 independent reflections
2296 reflections with $I > 2\sigma(I)$
R_{int} = 0.025
θ_{max} = 27.5°
$h = -9 \rightarrow 9$
$k = -10 \rightarrow 10$
$l = -42 \rightarrow 40$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.05
$wR(F^2)$ = 0.143
S = 1.09
2519 reflections
265 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0946P)^2 + 0.3221P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.73 e Å^{-3}
$\Delta\rho_{min}$ = −0.33 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

F1—C5	1.400 (4)	O2—C10	1.409 (5)
O1—C3	1.438 (4)	O4—C16	1.373 (3)
O1—C6	1.447 (4)	O4—C20	1.416 (3)
O2—C9	1.383 (3)		
C3—O1—C6	106.9 (2)	O1—C3—C2	106.9 (2)
C9—O2—C10	105.3 (3)	F1—C5—C4	108.0 (3)
C16—O4—C20	117.2 (2)	O1—C6—C4	102.4 (2)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C10—H10*B*···O1^{i}	0.97	2.45	3.238 (6)	138
C12—H12···O1^{ii}	0.93	2.41	3.315 (3)	166

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

The absolute stereochemistry could not be established from the diffraction experiment, because of the lack of significant anomalous dispersion effects; Friedel pairs in the data set were merged. The absolute configuration was, therefore, chosen on the basis of the known configuration of the synthetic precursor. The methyl H atoms were constrained to an ideal geometry (C—H = 0.96 Å), with U_{iso}(H) = 1.5U_{eq}(C), and were allowed to rotate freely about the C—C bonds.

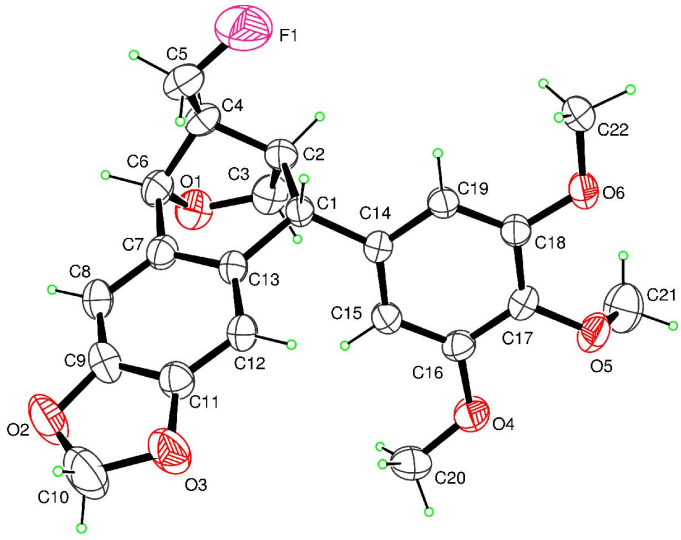


Figure 1
A view of the molecular structure of (3). Displacement ellipsoids are drawn at the 50% probability level.

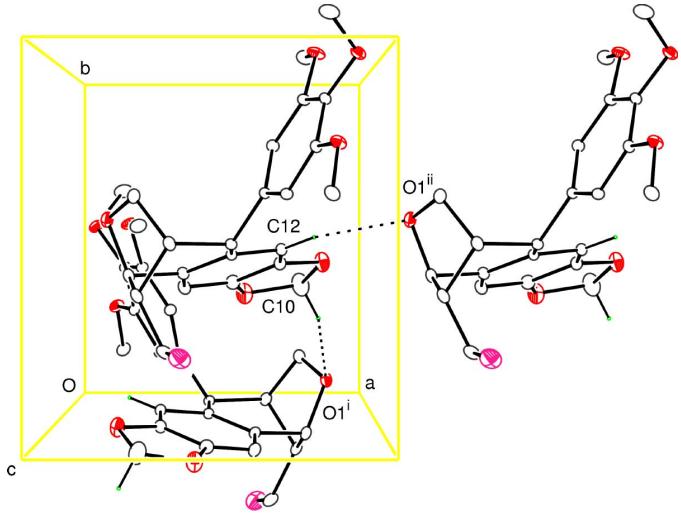


Figure 2
The molecular packing of (3), viewed down the *c* axis. Dashed lines indicate the hydrogen-bonding interactions. H atoms not involved in the hydrogen bonding have been omitted. (see Table 2 for symmetry codes).

The remaining H atoms were placed in calculated positions (C—H = 0.93–0.98 Å), with U_{iso}(H) = 1.2U_{eq} of the carrier atoms, and included in the final cycles of refinement in the riding model approximation.

Data collection: *PROCESS-AUTO* (Rigaku, 1998); cell refinement: *PROCESS-AUTO*; data reduction: *CrystalStructure* (Rigaku/MSC, 2004); program(s) used to solve structure: *SIR97* (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *WinGX* (Farrugia, 1999) and *PLATON* (Spek, 2003).

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