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(5a*R*,8a*R*,9*R*)-9-(3,4,5-Trimethoxyphenyl)-5a,6,8a,9-tetrahydrofuro[3′,4′:6,7]naphtho-[2,3-*d*][1,3]dioxole-5,8-dione

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.004 Å
R factor = 0.033
wR factor = 0.112
Data-to-parameter ratio = 9.6

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

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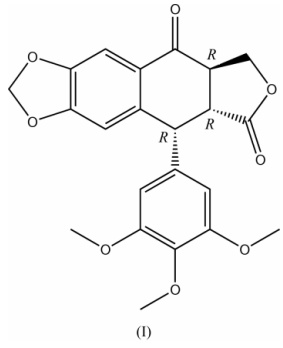
The title compound, $C_{22}H_{20}O_8$, a product of oxidation of podophyllotoxin, a lignan of the phenyltetralin type, represents a synthon for potential antitumour agents. It has the same configuration of three chiral centres as the starting material, podophyllotoxin, and, as well as the latter, contains a γ-lactone ring *trans*-fused to the tricylic system. Non-classical C—H···O hydrogen bonds link the molecules in the crystal structure into infinite chains along the *a* axis.

Comment

Podophyllotoxin is a lignan of the phenyltetralin type, which is widespread in higher plants. The discovery of the antitumour activity of etoposide (VP-16) and teniposide (VM-26), semi-synthetic analogues of the naturally occurring podophyllotoxin, has stirred up renewed interest in this field in recent years (Damayanthi & Lown, 1998; Silverberg *et al.*, 2000; Van Vliet *et al.*, 2001). In a continuation of our previous work (Xu *et al.*, 2002; Ma *et al.*, 2000; Cao *et al.*, 1999), we have synthesized potential antitumour agents having the structure of 4-heterocyclespiropodophyllotoxins, using the title compound, podophyllotoxone, (I), as a starting material. Here we report the crystal structure of (I).



(I)

The molecular structure of (I) is shown in Fig. 1. Selected molecular parameters and hydrogen-bond geometric characteristics are listed in Tables 1 and 2, respectively. The relative configuration of the chiral centres at atoms C5a, C8a and C9 is the same as in the starting compound, podophyllotoxin; this was not unexpected, as the chiral centres were not affected by the reaction. The absolute configuration was chosen in accordance with the known configuration of podophyllotoxin (Gordaliza *et al.*, 2001). Atom H8*A* in (I) is *cis* relative to H9 and *trans* relative to H5*A*. The observed *trans*-fusion of the γ-lactone has been proved to be essential to the bioactivity of podophyllotoxin derivatives (Brewer *et al.*, 1979). The loss of activity of picropodophyllotoxin, which contains a *cis*-fused γ-lactone, has been attributed to differences in the conformation (Gensler *et al.*, 1977).

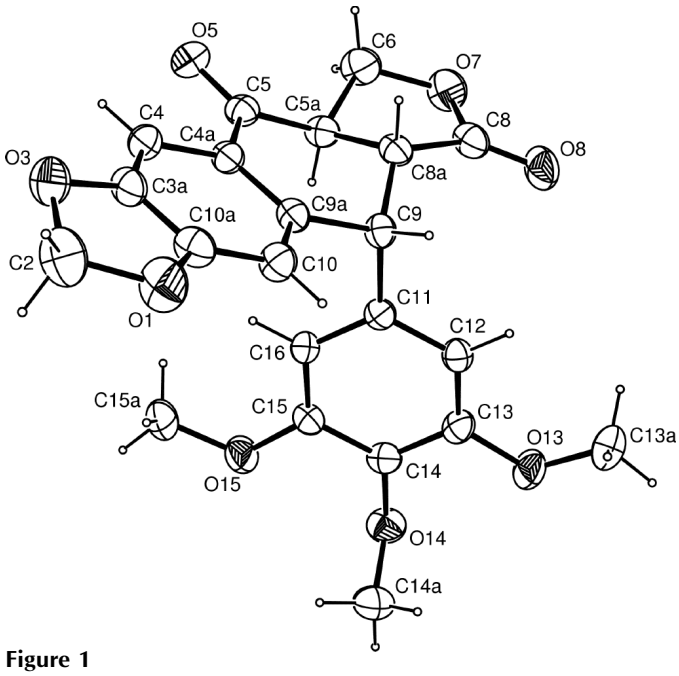


Figure 1
The molecular structure of podophyllotoxone, (I). Displacement ellipsoids are drawn at the 30% probability level.

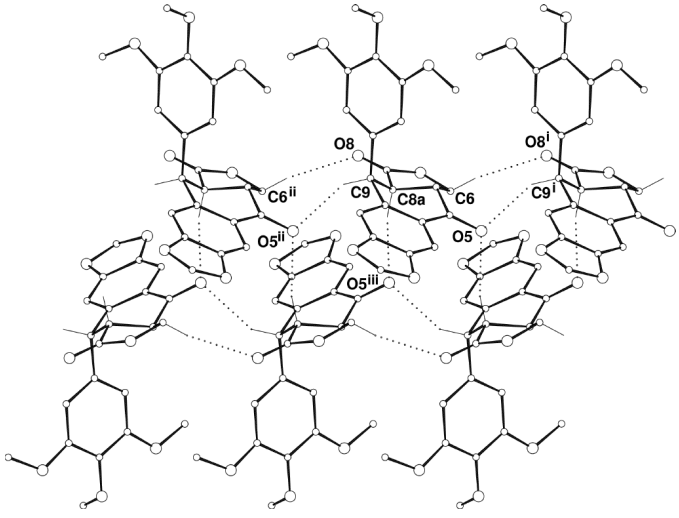


Figure 2
Polymeric chains formed due to the C—H···O hydrogen bonds in the crystal packing of the title compound (see Table 2 for symmetry codes).

In the crystal structure, non-classical C—H···O hydrogen bonds play an important role, resulting in the formation of polymeric chains running along the crystallographic *a* axis.

Experimental

Pyridinium dichromate (PDC; 0.89 g, 2.40 mmol) was added to a solution of podophyllotoxin (0.69 g, 1.65 mmol) in dry dichloromethane (20 ml) and stirred at room temperature for 4 h. The excess of PDC was removed by filtration, followed by column chromatography of the residue on silica gel to give 520 mg (78%) of podophyllotoxone (Gordaliza *et al.*, 2001). Colorless crystals were obtained from an ethyl acetate solution after it was left to stand for 4 d. C and H were analysed using a Carlo–Erba 1160 instrument. Analysis calculated for $C_{22}H_{20}O_8$: C 64.07, H 4.89%; found: C 63.83, H 4.92%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.55 (*s*, 1H), 6.71 (*s*, 1H), 6.39 (*s*, 2H), 6.10 (*ss*, 2H), 4.85 (*d*, 1H), 4.55 and 4.36 (*dd*, 2H), 3.82 (*s*, 3H), 3.75 (*s*, 6H), 3.51 (*m*, 1H), 3.27 (*dd*, 1H).

Crystal data

$C_{22}H_{20}O_8$
M_r = 412.38
Orthorhombic, $P2_12_12_1$
a = 6.4927 (9) Å
b = 12.1940 (11) Å
c = 24.9681 (18) Å
V = 1976.8 (4) Å^3
Z = 4
D_x = 1.386 Mg m^{-3}
D_m = 1.379 Mg m^{-3}
D_m measured by flotation in a mixture of hexane and carbon tetrachloride
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 3.0–26.5°
μ = 0.11 mm^{-1}
T = 293 (2) K
Prism, colorless
0.45 × 0.30 × 0.25 mm

Data collection

Rigaku R-AXIS RAPID diffractometer
$\omega/2\theta$ scans
Absorption correction: multi-scan (*ABSCOR*; Higashi, 1995)
T_{min} = 0.963, T_{max} = 0.974
4509 measured reflections
2610 independent reflections
1817 reflections with $I > 2\sigma(I)$
R_{int} = 0.015
θ_{max} = 27.5°
$h = -8 \rightarrow 8$
$k = -15 \rightarrow 15$
$l = -32 \rightarrow 32$
3 standard reflections
every 100 reflections
intensity decay: 0.2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.033
$wR(F^2)$ = 0.112
S = 0.98
2610 reflections
272 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0667P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.23 e Å^{-3}
$\Delta\rho_{min}$ = −0.25 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0133 (17)

Table 1
Selected geometric parameters (°).

C6—C5*A*—C8*A*—C8	−34.8 (3)	C5—C5A—C8A—C9	63.8 (3)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C6—H6*A*···O8^{i}	0.97	2.57	3.531 (5)	169
C9—H9···O5^{ii}	0.98	2.37	3.254 (3)	150
C8*A*—H8*A*···O5^{iii}	0.98	2.26	3.220 (3)	167

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

Friedel pairs were merged and the refinement of the Flack parameter (Flack & Schwarzenbach, 1988) was suppressed, as the lack of anomalous scatterers did not allow the absolute configuration to be determined from the X-ray measurements. The absolute configuration was, therefore, chosen on the basis of the known configuration of the synthetic precursor. The H atoms of the methyl, methylene, methine groups and of the aromatic ring were placed in calculated positions, with C—H distances of 0.96, 0.97, 0.98 and 0.93 Å, respectively, and were included in the final cycles of least-squares refinement as riding on the carrier atoms, with $U_{iso}(H) = 1.2U_{eq}$ of the corresponding carrier atoms ($1.5U_{eq}$ in the case of methyl H atoms).

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure corporation, 1992); cell refinement: *MSC/AFC*

Diffractometer Control Software; data reduction: *TEXSAN* (Molecular Structure Corporation, 1993); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1993); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 *for Windows* (Farrugia, 1997) and *CAMERON* (Watkin, 1993); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

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