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(*E*)-1-(2-Hydroxy-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene

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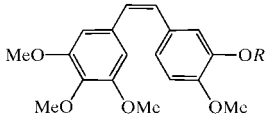
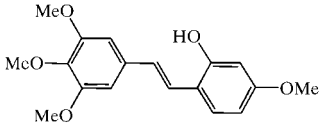
In the crystal structure of the title compound, $C_{18}H_{20}O_5$, all geometric parameters fall within experimental error of the expected values. Analysis of the molecular-packing plots reveals an infinite one-dimensional linear array running parallel to the *c* axis, formed by an O—H···O intermolecular hydrogen-bonding interaction. The stilbene framework and most of the substituents are approximately coplanar.

Comment

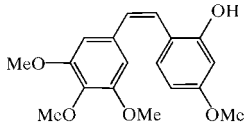
The microtubule system of eukaryotic cells is an important target for the development of anticancer agents. Novel drugs have been developed that bind to tubulin, disrupting cellular microtubule structure and function, thus resulting in mitotic arrest. The combretastatins are tubulin polymerization inhibitors isolated from the bark of the South African tree *Combretum caffrum* (Pettit *et al.*, 1982, 1989). The most potent of these is combretastatin A-4 (CA-4), (I), which is a potent cytotoxic agent and which strongly inhibits the polymerization of tubulin by binding to the colchicine site (Hamel & Lin, 1983).



(I) (CA-4) R=H
(II) (CA-4P) R=PO_3Na_2



(III)



(IV)

CA-4 shows potent cytotoxicity against a wide range of human cancers, including multi-drug-resistant cell lines (El-Zayat *et al.*, 1993), and is thus an attractive lead compound for the development of anticancer drugs. However, CA-4 has a demonstrated lack of efficacy *in vivo*, presumably because of poor pharmacokinetics that arise from its high lipophilicity and limited aqueous solubility. A phosphate prodrug of CA-4, *viz.* CA-4P or (II) (Pettit & Rhodes, 1998), has been synthesized in order to improve the aqueous solubility and pharmacokinetics.

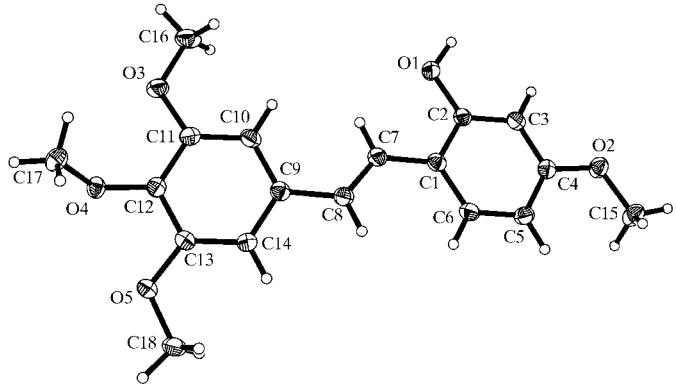


Figure 1
SHELXTL (Sheldrick, 1994) plot of (III), showing displacement ellipsoids at the 35% probability level for non-H atoms. H atoms are shown as circles of arbitrary size.

To obtain compounds with pharmaceutically acceptable properties and improved antitumor activities, we have designed and synthesized a number of CA-4 analogs and their corresponding sodium phosphate prodrugs. Compounds (III) and (IV) are two isomeric derivatives that we have prepared recently. In order to unequivocally confirm the molecular structure, and to gather information for our molecular recognition studies, we have determined the crystal structure of (III). Fig. 1 shows the crystallographically determined molecular structure of (III), while selected parameters are presented in Table 1. All internuclear distances and angles fall within the range of expected values, and the stilbene system exhibits only minor deviations from ideal planarity, as evidenced by the torsion angles (Table 1). Each methoxy substituent is approximately coplanar with the aromatic rings, with the exception of the O4 methoxy group, which is twisted

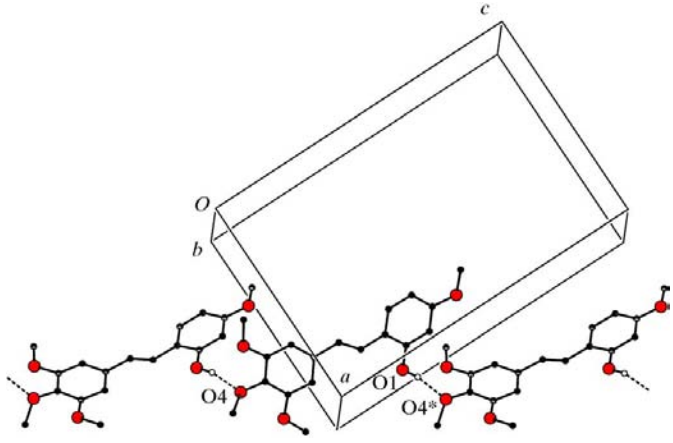


Figure 2
The crystal packing in (III), viewed along the *b* axis, showing the intermolecular hydrogen bonding (dashed lines). [Symmetry code: (*) $-\frac{1}{2}+x, -\frac{1}{2}-y, -\frac{1}{2}+z$.]

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by approximately 75° relative to the plane of the aromatic ring. This twist minimizes steric interactions with the neighboring O3 and O5 methoxy groups.

The crystal packing of (III) (Fig. 2) consists of corrugated ribbons formed by an infinite linear array of molecules related by an *n*-glide operation and linked by an intermolecular O1—H···O4 hydrogen-bonding interaction (Table 2).

Experimental

To a dimethylformamide (7 ml) solution containing an isomeric mixture of the silyl-protected precursor to (III) and (IV) [3:1 (*Z*):(*E*)-1-(2-*tert*-butyldimethylsiloxy-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethane] (1.12 g, 2.6 mmol) were added KF (150 mg, 2.6 mmol) and HBr (462 mg, 0.3 ml, 2.5 mmol). Additional HBr (0.3 ml) was added after 12 h. The reaction mixture was stirred for a total of 2 d, and then water (15 ml) was added to the solution and the resulting suspension extracted with ethyl acetate (3 × 15 ml). The combined organic extracts were washed with water, dried over sodium sulfate and evaporated to dryness. The residue was applied to a silica-gel column and eluted with hexane/ethyl acetate (75:25). Compound (III) was obtained as a white powder, which was crystallized from methanol to afford pure (III) as white crystals (210 mg, 0.49 mmol; yield 18%).

Crystal data

$C_{18}H_{20}O_5$
M_r = 316.34
Monoclinic, $P2_1/n$
a = 11.6693 (15) Å
b = 7.9790 (8) Å
c = 17.5818 (13) Å
β = 90.673 (9)°
V = 1636.9 (3) Å^3
Z = 4
D_x = 1.284 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 12.5–21.3°
μ = 0.09 mm^{-1}
T = 293 (2) K
Block, colorless
0.54 × 0.47 × 0.41 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
ω scans
3369 measured reflections
2867 independent reflections
2420 reflections with $I > 2\sigma(I)$
R_{int} = 0.016
θ_{max} = 24.9°
$h = -1 \rightarrow 13$
$k = 0 \rightarrow 9$
$l = -20 \rightarrow 20$
3 standard reflections
every 600 reflections
intensity decay: 2.1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.050
$wR(F^2)$ = 0.128
S = 1.16
2867 reflections
209 parameters
H atom refined by a mixture of constrained and independent refinement
$w = 1/[\sigma^2(F_o^2) + (0.0813P)^2 + 0.3079P]$ where $P = (F_o^2+2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.74 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}
Extinction correction: *SHELXL*93
Extinction coefficient: 0.164 (8)

Systematic conditions suggested the unambiguous space group $P2_1/n$. The space group was confirmed by successful convergence of the full-matrix least-squares refinement on F^2 (Sheldrick, 1993). The highest peaks in the final difference Fourier map were in the vicinity of atom C16, and the final map had no other significant features. All H atoms bonded to C atoms were allowed for as riding atoms, with C—H distances of 0.93 and 0.96 Å; the hydroxy atom H1 was located from a difference map and its coordinates freely refined.

Table 1
Selected geometric parameters (Å, °).

O1—C2	1.3623 (19)	O4—C12	1.3778 (19)
O2—C4	1.374 (2)	O4—C17	1.4405 (19)
O2—C15	1.428 (2)	O5—C13	1.3671 (19)
O3—C11	1.365 (2)	O5—C18	1.425 (2)
O3—C16	1.421 (2)		
C4—O2—C15	117.49 (13)	O2—C4—C5	124.79 (15)
C11—O3—C16	117.98 (14)	O3—C11—C10	125.30 (15)
C12—O4—C17	115.69 (12)	O3—C11—C12	114.69 (15)
C13—O5—C18	117.40 (12)	O4—C12—C13	119.21 (14)
O1—C2—C3	122.02 (14)	O4—C12—C11	120.78 (14)
O1—C2—C1	116.79 (14)	O5—C13—C14	125.21 (14)
O2—C4—C3	115.13 (14)	O5—C13—C12	114.49 (13)
C18—O5—C13—C14	−2.6 (2)	O4—C12—C11—O3	5.4 (2)
O5—C13—C14—C9	177.77 (14)	C12—C11—O3—C16	−172.68 (15)
C17—O4—C12—C13	107.59 (16)	C16—O3—C11—C10	6.6 (2)
C18—O5—C13—C12	175.59 (14)	C15—O2—C4—C5	−2.7 (2)
C17—O4—C12—C11	−77.41 (19)	C15—O2—C4—C3	177.12 (15)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O1—H1···O4^{i}	0.89 (3)	1.85 (3)	2.7052 (16)	161 (2)

Symmetry code: (i) $x-\frac{1}{2}, -\frac{1}{2}-y, z-\frac{1}{2}$.

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Software*; data reduction: *XCAD*4 (Harms, 1993); Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993); molecular graphics: *SHELXTL*/*PC* (Sheldrick, 1994); software used to prepare material for publication: *SHELXTL*/*PC*

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SQ1018). Services for accessing these data are described at the back of the journal.

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