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Crystal structure of the ethyl 2,4-dihydroxy-6-methylbenzoate from *Illicium difengpi* K.I.B et K.I.M.

Huiping Xiong,[a] Shilong Mao,[b] Qianzhou Lv[b] and Ning Zhang[b]*

[a]School of Mathematics and Physics, Shanghai University of Electric Power, Shanghai, 200090, People's Republic of China, and [b]Department of Pharmacy, Xuhui District Central Hospital, Shanghai, 200031, People's Republic of China. *Correspondence e-mail: zhangningpharm@163.com

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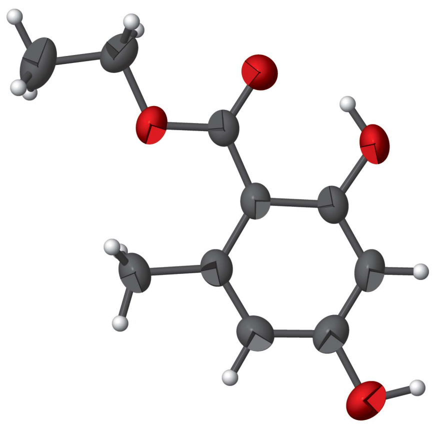
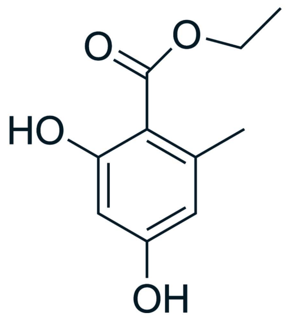
The title compound, $C_{10}H_{12}O_4$, was isolated from *Illicium difengpi* K.I.B et K.I.M. An intramolecular O—H⋯O hydrogen bond stabilizes the molecular conformation. In the crystal, the compound forms offset slanted stacks of alternating inversion-related molecules along the *a* axis direction. Intermolecular O—H⋯O hydrogen bonds link the molecules into double strands parallel to the [101] direction.

3D view



Chemical scheme



Structure description

Illicium difengpi is a small shrub growing in Guangxi province of China, belonging to the family Illiciaceae (He *et al.*, 2014). The stem bark of *I. difengpi* is listed in the Chinese Pharmacopoeia (Pharmacopeia Committee of P. R. of China, 2010). It is an important traditional Chinese medicine and is mainly used as a treatment for rheumatic arthritics (Huang *et al.*, 1996). The alcoholature of the stem bark of *I. difengpi* showed outstanding clinical efficacy and pharmacodynamics potency. Previous studies led to the isolation of phenylpropanoids, lignans, neolignans and triterpenoids from an extract of *I. difengpi* (Kouno *et al.*, 1992,1993; Wang *et al.*, 1994; Huang *et al.*, 1997; Fang *et al.*, 2010, 2011; Chu *et al.*, 2011; Li *et al.*, 2013, 2015*a*,*b*; Pan *et al.*, 2016). An ongoing search for bioactive natural products from folk medicine resulted in the isolation of the title compound, which was previously obtained from *Umbilicaria esculenta* (Miyoshi) Minks (Qiu & Ding, 2001). The isolation of the title compound from the stem bark of *I. difengpi* and its crystal structure are reported here.

The molecular structure of the title compound is shown in Fig. 1. The molecular structure contains a methyl group, two hydroxyl groups, and a carboethoxy group, which

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

D—H$\cdots$$A$	D—H	H$\cdots$$A$	$D$$\cdots$$A$	D—H$\cdots$$A$
O3—H3$\cdots$O1	0.89 (2)	1.72 (3)	2.4868 (18)	143 (3)
O4—H4$\cdots$O3^{i}	0.96 (3)	1.91 (3)	2.853 (2)	169 (3)
C3—H3$A$$\cdots$O4^{ii}	0.93	2.54	3.290 (2)	138

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

are attached to C2, C4, C6 and C7 of the central benzene ring, respectively. An intramolecular O3—H3$\cdots$O1 hydrogen bond (Table 1) stabilizes the molecular conformation.

In the crystal, O4—H4$\cdots$O3^{i} and C3—H3$A$$\cdots$O4^{ii} hydrogen bonds link the molecules into double strands parallel to the [101] direction. (Fig. 2, Table 2). In the solid state, the compound also forms offset slanted stacks of alternating inversion-related molecules along the *a*-axis direction. (Fig. 3)

A search of the Cambridge Crystallographic Database (version 5.39 with updates up to May 2018; Groom *et al.*, 2016) indicated that no 2,4-dihydroxy-6-methylbenzoic acid ethyl ester has been structurally characterized. Four structurally similar 2,4-dihydroxy-6-methylbenzoic acid derivatives have been reported, namely (2-ethoxycarbonyl-3,5-dihydroxyphenyl)acetic acid monohydrate (Luck & Mendenhall, 2002), phomozin monohydrate (Mazars *et al.*,1990), 2,3-dimethyl-3-(*O*-orsellinoyl)lactic acid monohydrate (Declercq *et al.*,1991) and 2,3,4,5-tetrahydroxypentyl 4,6-dihydroxy-2,3-dimethylbenzoate (Talontsi *et al.*, 2012).

Synthesis and crystallization

The stem bark of *Illicium difengpi* (5.0 kg), which was purchased from Caitongde Pharmacy, Shanghai, China, was powdered and extracted three times with aqueous ethanol (ethanol/water 8:2) under reflux. The solvent was then evaporated under reduced pressure to obtain a dry residue (150 g). The residue was suspended in water (2 L) and extracted successively with petroleum ether (3 × 2 L), EtOAc (3 × 2 L) and BuOH (3 × 2 L), affording 5 g, 70 g, and 40 g, respectively, of each dried fraction. The EtOAc fraction was subjected to silica gel column chromatography using gradient elution (CH_2Cl_2/CH_3OH, 200:1 to 2:1, *v*/*v*) to give four main fractions (Fr.1-1–Fr.1-4), of which Fr.1-2 was purified by successive silica gel column chromatography (CH_2Cl_2/CH_3OH, 100:1→20:1); 2,4-dihydroxy-6-methylbenzoic acid ethyl ester (30 mg) was obtained from the fraction eluted by CH_2Cl_2/CH_3OH (40:1). Single crystals suitable for X-ray diffraction analysis were obtained by slow evaporation from acetone solution after two weeks at room temperature.

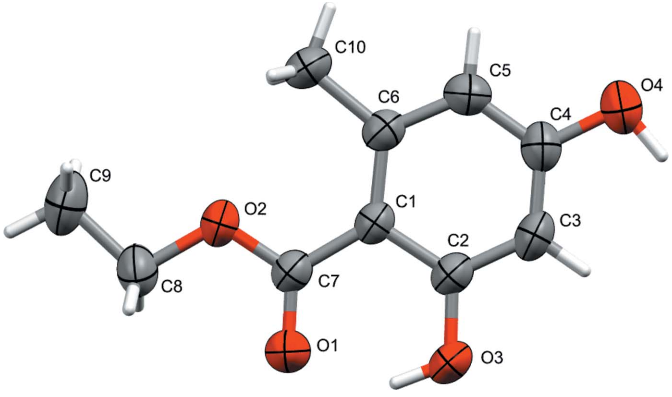

Figure 1
The molecular structure. Displacement ellipsoids are shown at the 50% probability level.

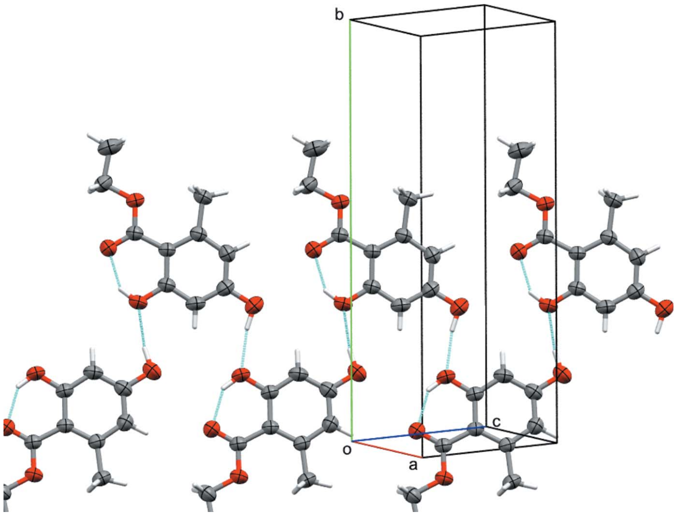

Figure 2
The packing of the title compound viewed along the *a*-axis direction. Dashed lines indicate hydrogen bonds.

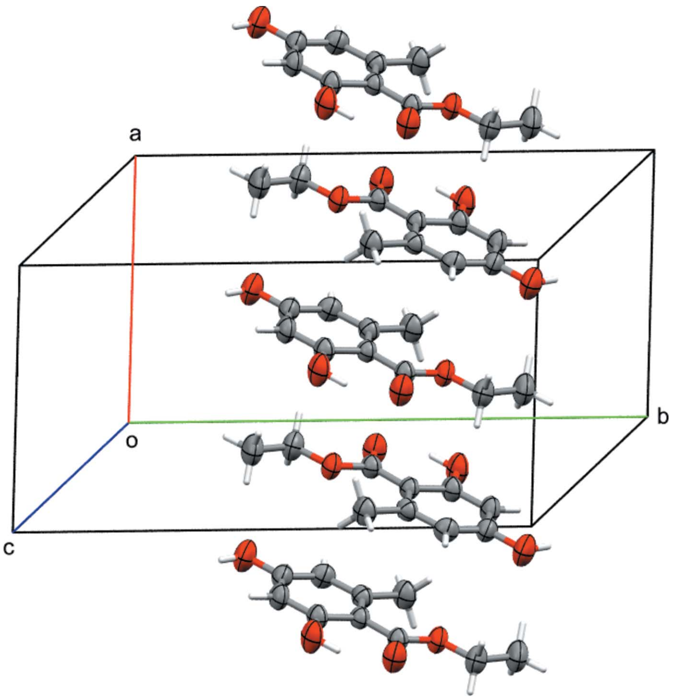

Figure 3
One of the slanted stacks of inversion-related molecules along the *a*-axis direction.

Refinement

Crystal data, data collection and structure refinement details are summarized in Table 2.

Table 2
Experimental details.

Crystal data	
Chemical formula	$C_{10}H_{12}O_4$
M_r	196.20
Crystal system, space group	Monoclinic, $P2_1/n$
Temperature (K)	293
a, b, c (Å)	7.818 (3), 17.017 (6), 8.189 (3)
β (°)	117.459 (4)
V (Å^3)	966.7 (6)
Z	4
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.10
Crystal size (mm)	0.15 × 0.13 × 0.08
Data collection	
Diffractometer	Bruker SMART APEX CCD area-detector
Absorption correction	Multi-scan (*SAINT-Plus*; Bruker, 1999)
T_{min}, T_{max}	0.405, 0.968
No. of measured, independent and observed $[I > 2\sigma(I)]$ reflections	4542, 2097, 1390
R_{int}	0.037
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.649
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.057, 0.172, 1.02
No. of reflections	2097
No. of parameters	135
No. of restraints	2
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.45, −0.23

Computer programs: *SMART* (Bruker, 1997), *SAINT-Plus* (Bruker, 1999), *SHELXS97* and *SHELXTL* (Sheldrick, 2008), *SHELXL2016* (Sheldrick, 2015) and *publCIF* (Westrip, 2010).

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full crystallographic data

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Huiping Xiong, Shilong Mao, Qianzhou Lv and Ning Zhang

Ethyl 2,4-dihydroxy-6-methylbenzoate

Crystal data

$C_{10}H_{12}O_4$
$M_r = 196.20$
Monoclinic, $P2_1/n$
$a = 7.818$ (3) Å
$b = 17.017$ (6) Å
$c = 8.189$ (3) Å
$\beta = 117.459$ (4)°
$V = 966.7$ (6) Å^3
$Z = 4$
$F(000) = 416$
$D_x = 1.348$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 878 reflections
$\theta = 2.4$–26.4°
$\mu = 0.10$ mm^{-1}
$T = 293$ K
Sheet, colorless
0.15 × 0.13 × 0.08 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
phi and ω scans
Absorption correction: multi-scan (SAINT-Plus; Bruker, 1999)
$T_{\min} = 0.405$, $T_{\max} = 0.968$
4542 measured reflections
2097 independent reflections
1390 reflections with $I > 2\sigma(I)$
$R_{\text{int}} = 0.037$
$\theta_{\max} = 27.5°$, $\theta_{\min} = 2.4°$
$h = -5 \rightarrow 10$
$k = -21 \rightarrow 22$
$l = -10 \rightarrow 8$

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.057$
$wR(F^2) = 0.172$
$S = 1.02$
2097 reflections
135 parameters
2 restraints
Primary atom site location: structure-invariant direct methods
Secondary atom site location: difference Fourier map
Hydrogen site location: mixed
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.1019P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} < 0.001$
$\Delta\rho_{\max} = 0.45$ e Å^{-3}
$\Delta\rho_{\min} = -0.23$ e Å^{-3}

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. The positions of hydroxyl H atoms attached to O3 and O4 were refined. All other H atoms were positioned geometrically and treated as riding atoms: C—H = 0.93–0.97 Å. $U_{\rm iso}$(H) were set to $1.5U_{\rm eq}$(C/O) for CH_3 and OH, and to $1.2U_{\rm eq}$(C) for CH_2 and aromatic C—H.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	y	z	$U_{\rm iso}$*/$U_{\rm eq}$
O1	−0.0021 (2)	0.46363 (7)	−0.27773 (18)	0.0663 (5)
O2	0.11562 (18)	0.57656 (6)	−0.13811 (16)	0.0529 (4)
O3	0.1367 (2)	0.33529 (7)	−0.13142 (19)	0.0679 (5)
H3	0.050 (4)	0.3664 (16)	−0.216 (3)	0.102*
O4	0.6778 (2)	0.32885 (8)	0.44828 (18)	0.0718 (5)
H4	0.648 (4)	0.2753 (16)	0.410 (4)	0.108*
C1	0.2660 (2)	0.45967 (8)	0.0181 (2)	0.0420 (4)
C2	0.2682 (2)	0.37634 (9)	0.0131 (2)	0.0484 (4)
C3	0.4047 (3)	0.33288 (9)	0.1552 (3)	0.0551 (5)
H3A	0.403637	0.278312	0.148712	0.066*
C4	0.5412 (3)	0.37051 (10)	0.3052 (2)	0.0524 (5)
C5	0.5453 (3)	0.45134 (10)	0.3168 (2)	0.0525 (5)
H5	0.640522	0.475644	0.420632	0.063*
C6	0.4098 (2)	0.49723 (9)	0.1763 (2)	0.0450 (4)
C7	0.1165 (2)	0.49885 (9)	−0.1435 (2)	0.0450 (4)
C8	−0.0274 (3)	0.61634 (11)	−0.3005 (3)	0.0612 (5)
H8A	−0.156271	0.600967	−0.324130	0.073*
H8B	−0.010341	0.602890	−0.407205	0.073*
C9	0.0009 (4)	0.70282 (12)	−0.2630 (3)	0.0802 (7)
H9A	−0.015784	0.715282	−0.156911	0.120*
H9B	−0.091898	0.731300	−0.367576	0.120*
H9C	0.128638	0.717279	−0.240524	0.120*
C10	0.4251 (3)	0.58478 (9)	0.2029 (3)	0.0592 (5)
H10A	0.535726	0.597063	0.317280	0.089*
H10B	0.310970	0.604287	0.205170	0.089*
H10C	0.438365	0.608915	0.103419	0.089*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0702 (9)	0.0471 (7)	0.0545 (8)	−0.0021 (6)	0.0056 (7)	−0.0024 (5)
O2	0.0591 (8)	0.0349 (6)	0.0567 (8)	0.0057 (5)	0.0198 (6)	0.0033 (5)
O3	0.0783 (10)	0.0327 (6)	0.0659 (9)	−0.0050 (6)	0.0105 (7)	−0.0064 (5)
O4	0.0743 (10)	0.0545 (8)	0.0646 (9)	0.0156 (7)	0.0131 (8)	0.0103 (6)
C1	0.0470 (9)	0.0329 (8)	0.0473 (9)	−0.0001 (6)	0.0228 (8)	−0.0009 (6)
C2	0.0547 (10)	0.0351 (8)	0.0517 (10)	−0.0036 (7)	0.0214 (8)	−0.0036 (7)
C3	0.0657 (12)	0.0326 (8)	0.0659 (11)	0.0043 (8)	0.0294 (10)	0.0027 (8)
C4	0.0542 (10)	0.0455 (9)	0.0558 (10)	0.0095 (8)	0.0238 (9)	0.0080 (8)
C5	0.0501 (10)	0.0517 (10)	0.0479 (10)	−0.0036 (7)	0.0159 (8)	−0.0053 (7)
C6	0.0497 (9)	0.0377 (8)	0.0484 (9)	−0.0032 (7)	0.0234 (8)	−0.0029 (7)
C7	0.0496 (9)	0.0357 (8)	0.0485 (9)	−0.0018 (7)	0.0217 (8)	−0.0015 (7)

C8	0.0674 (12)	0.0505 (10)	0.0580 (11)	0.0125 (9)	0.0223 (10)	0.0125 (8)
C9	0.0965 (17)	0.0464 (11)	0.0998 (17)	0.0137 (10)	0.0471 (14)	0.0177 (10)
C10	0.0657 (12)	0.0390 (9)	0.0612 (11)	−0.0087 (8)	0.0192 (10)	−0.0093 (8)

Geometric parameters (Å, º)

O1—C7	1.220 (2)	C4—C5	1.378 (3)
O2—C7	1.323 (2)	C5—C6	1.390 (2)
O2—C8	1.451 (2)	C5—H5	0.9300
O3—C2	1.3502 (19)	C6—C10	1.502 (2)
O3—H3	0.89 (2)	C8—C9	1.499 (3)
O4—C4	1.365 (2)	C8—H8A	0.9700
O4—H4	0.96 (3)	C8—H8B	0.9700
C1—C6	1.417 (2)	C9—H9A	0.9600
C1—C2	1.419 (2)	C9—H9B	0.9600
C1—C7	1.461 (2)	C9—H9C	0.9600
C2—C3	1.377 (2)	C10—H10A	0.9600
C3—C4	1.359 (2)	C10—H10B	0.9600
C3—H3A	0.9300	C10—H10C	0.9600

C7—O2—C8	116.70 (13)	O1—C7—O2	120.51 (15)
C2—O3—H3	112.1 (18)	O1—C7—C1	123.39 (15)
C4—O4—H4	103.7 (17)	O2—C7—C1	116.10 (13)
C6—C1—C2	117.54 (14)	O2—C8—C9	106.95 (15)
C6—C1—C7	126.02 (14)	O2—C8—H8A	110.3
C2—C1—C7	116.42 (14)	C9—C8—H8A	110.3
O3—C2—C3	116.31 (14)	O2—C8—H8B	110.3
O3—C2—C1	121.87 (14)	C9—C8—H8B	110.3
C3—C2—C1	121.82 (15)	H8A—C8—H8B	108.6
C4—C3—C2	119.36 (15)	C8—C9—H9A	109.5
C4—C3—H3A	120.3	C8—C9—H9B	109.5
C2—C3—H3A	120.3	H9A—C9—H9B	109.5
C3—C4—O4	120.56 (15)	C8—C9—H9C	109.5
C3—C4—C5	121.07 (15)	H9A—C9—H9C	109.5
O4—C4—C5	118.36 (16)	H9B—C9—H9C	109.5
C4—C5—C6	121.27 (16)	C6—C10—H10A	109.5
C4—C5—H5	119.4	C6—C10—H10B	109.5
C6—C5—H5	119.4	H10A—C10—H10B	109.5
C5—C6—C1	118.93 (15)	C6—C10—H10C	109.5
C5—C6—C10	117.23 (15)	H10A—C10—H10C	109.5
C1—C6—C10	123.84 (14)	H10B—C10—H10C	109.5

C6—C1—C2—O3	179.79 (15)	C2—C1—C6—C5	0.4 (2)
C7—C1—C2—O3	−1.4 (2)	C7—C1—C6—C5	−178.29 (16)
C6—C1—C2—C3	−0.3 (2)	C2—C1—C6—C10	−179.25 (15)
C7—C1—C2—C3	178.47 (16)	C7—C1—C6—C10	2.1 (3)
O3—C2—C3—C4	−179.87 (17)	C8—O2—C7—O1	−2.1 (2)
C1—C2—C3—C4	0.3 (3)	C8—O2—C7—C1	177.74 (14)

C2—C3—C4—O4	179.75 (17)	C6—C1—C7—O1	178.68 (16)
C2—C3—C4—C5	−0.2 (3)	C2—C1—C7—O1	0.0 (2)
C3—C4—C5—C6	0.3 (3)	C6—C1—C7—O2	−1.1 (2)
O4—C4—C5—C6	−179.68 (16)	C2—C1—C7—O2	−179.83 (14)
C4—C5—C6—C1	−0.4 (2)	C7—O2—C8—C9	−179.38 (14)
C4—C5—C6—C10	179.29 (16)		

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O3—H3···O1	0.89 (2)	1.72 (3)	2.4868 (18)	143 (3)
O4—H4···O3^{i}	0.96 (3)	1.91 (3)	2.853 (2)	169 (3)
C3—H3*A*···O4^{ii}	0.93	2.54	3.290 (2)	138

Symmetry codes: (i) *x*+1/2, −*y*+1/2, *z*+1/2; (ii) *x*−1/2, −*y*+1/2, *z*−1/2.