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1,3-Bis(3,4,5-trimethoxyphenyl)-2,3-epoxypropanone: an anticancer chalcone epoxide

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Key indicators

Single-crystal X-ray study
T = 173 K
Mean σ(C–C) = 0.004 Å
R factor = 0.063
wR factor = 0.137
Data-to-parameter ratio = 13.0

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

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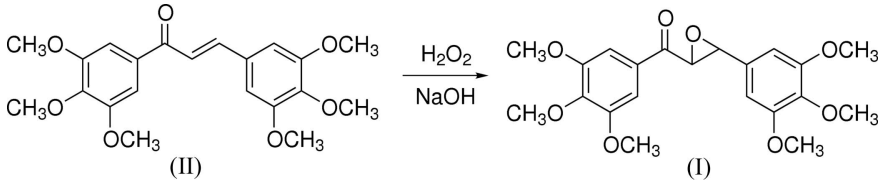
The title compound, $C_{21}H_{24}O_8$, crystallizes as colorless needles composed of a racemic mixture that adopts the packing order of columns of alternating enantiomers, all of whose oxirane rings are essentially aligned. Within each column, the carbonyl groups of adjacent enantiomers are oriented in nearly opposite directions. The structure is stabilized by several C—H···O associations.

Comment

Chalcones are biosynthesized by plants, and an impressive number have been found toxic to cancer cells (Rao *et al.*, 2004; Sabzevari *et al.*, 2004; Kumar *et al.*, 2003; Lopez-Lazaro, 2002; Seguin *et al.*, 2002; Nakamura *et al.*, 2002; Lawrence *et al.*, 2000; Park *et al.*, 1998; De Vincenzo *et al.*, 1995; Yamamoto *et al.*, 1991). Chalcone epoxides have long been suspected as intermediates in the biosynthesis of plant flavonoids (reviewed by Litkei, 1979). Also, facile epoxide ring-opening by nucleophilic groups, such as those in cellular biomolecules, may result in irreversible modification of biomolecules through covalent bond formation (Hinterding *et al.*, 1998; Youssef & El-Sadany, 1983; Morisseau *et al.*, 1998). We have found that the title chalcone epoxide, (I), has anticancer activity in cell culture.



(II) (I)

Very few crystal structures of chalcone epoxides have been reported to date. In one case, the structure of one enantiomer was determined (Baures *et al.*, 1990). In another, the structure of a racemic mixture was determined, and it was found to be monoclinic when crystallized from ethanol and trigonal when crystallized from chloroform–hexane (Stomberg *et al.*, 1994). The trigonal form had a high *R* value, apparently due to solvent-filled channels in the crystals, and may be an inclusion compound (Bardet *et al.*, 1999) or clathrate (Zass *et al.*, 2002). The monoclinic form crystallized in aggregates that were twinned.

Crystals of the title chalcone epoxide from three preparations were examined in an effort to obtain the best possible structure. The structure is stabilized by intermolecular associations between the oxirane O atom and a nearest-neighbor H atom on the oxirane ring, which approximately parallels the crystallographic *b* axis, as well as between several methoxy H

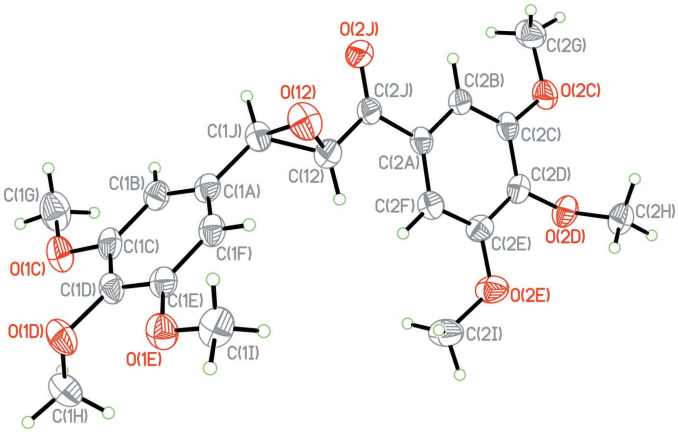


Figure 1
A view of (I), with displacement ellipsoids drawn at the 50% probability level.

atoms and neighboring methoxy O, carbonyl O, and oxirane O atoms (Table 1). Such interactions are generally regarded as a weak form of hydrogen bond, and they have been observed to contribute to higher-order structuring (Taylor & Kennard, 1982; Steiner & Saenger, 1992; Jiang & Lai, 2002; Grabowski, 2004).

The two chiral centers occur only as either (2*R*,3*S*) or the enantiomeric (2*S*,3*R*) configurations. This is presumably because the ring closure producing the *trans*-substituted oxirane is more facile than ring closure to the sterically strained *cis* isomer, which would result in the diastereomeric pair of enantiomers with (2*R*,3*R*) and (2*S*,3*S*) configurations.

The precursor chalcone, 1,3-bis(3,4,5-trimethoxyphenyl)propenone, (II), is known and was synthesized by use of a previously published procedure (Herencia *et al.*, 1998). Conversion of (II) into the title chalcone epoxide, (I), was accomplished by treatment of (II) with hydrogen peroxide and sodium hydroxide in ethanol, as used for the bis(dimethoxy) analog (Stomberg *et al.*, 1994). While this manuscript was in preparation, the title compound and other chalcone epoxides were reported as intermediates in the synthesis of substituted pyrazoles (Bhat *et al.*, 2005).

Our observation of the anticancer activity of the title compound against tumor cells grown in culture will be reported elsewhere.

Experimental

A suspension of 1,3-bis(3,4,5-trimethoxyphenyl)propenone [(II), 170 mg, 0.44 mmol] in ethanol (2 ml) was cooled in an ice bath for 5 min. Aqueous NaOH (2 *M*, 0.110 ml) and H_2O_2 (30% in H_2O, 0.070 ml) were added. The mixture was stirred for 18 h as the ice bath was allowed to warm to room temperature. The desired product, (I), was collected by suction filtration, and the white powder was washed with ice-cold ethanol followed by recrystallization from acetone–ethanol (1:1) that was allowed to evaporate for 1 d at room temperature. Clear colorless crystals of (I) were collected by suction filtration on a glass frit, whereupon they were washed with ice-cold ethanol and dried *in vacuo* (153 mg, 86%).

Crystal data

$C_{21}H_{24}O_8$
M_r = 404.40
Orthorhombic, *Pbcn*
a = 18.5563 (11) Å
b = 7.7666 (5) Å
c = 27.4354 (17) Å
V = 3954.0 (4) Å^3
Z = 8
D_x = 1.359 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 6496 reflections
θ = 2.2–27.5°
μ = 0.10 mm^{-1}
T = 173 (2) K
Needle, colorless
0.37 × 0.12 × 0.08 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
ω scans
Absorption correction: none
29894 measured reflections
3490 independent reflections
3038 reflections with $I > 2\sigma(I)$
R_{int} = 0.052
θ_{max} = 25.0°
$h = -22 \rightarrow 22$
$k = -9 \rightarrow 9$
$l = -32 \rightarrow 32$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.063
$wR(F^2)$ = 0.137
S = 1.19
3490 reflections
268 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0446P)^2 + 3.305P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.47 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}

Table 1
C—H···O associations in (I).

C—H···O	C···O (Å)	Symmetry code
C1*I*—H1*IA*···O2*J*	3.491 (4)	$x+\frac{1}{2}, -y+\frac{5}{2}, -z+1$
C1*J*—H1*J*···O12	3.000 (4)	$-x+\frac{1}{2}, y-\frac{1}{2}, z$
C2*G*—H2*GB*···O2*E*	3.503 (4)	$-x+\frac{1}{2}, y+\frac{1}{2}, z$
C2*I*—H2*IA*···O2*E*	3.224 (4)	$-x+1, y, -z+\frac{1}{2}$
C2*I*—H2*IC*···O1*D*	3.419 (4)	$-x+1, -y-2, -z+1$
C2*I*—H2*IC*···O1*E*	3.271 (4)	$-x+1, -y-2, -z+1$
C12—H12···O1*E*	3.556 (4)	$-x+1, -y-2, -z+1$

Methyl and benzyl H atoms were positioned using geometric considerations. The H atoms on the oxirane ring, however, were found in difference electron density maps and allowed to refine as independent isotropic atoms, with the constraints U_{iso}(H1*J*) = U_{eq}(C1*J*), and U_{iso}(H12) = 1.2U_{eq}(C12). The refined H-atom positions result in a torsion angle of −150 (3)° for H12—C12—C1*J*—H1*J*, which is significantly less than the torsion angles observed in the monoclinic and trigonal forms [169 (5) and 157 (15)°, respectively] of a very similar epoxy ketone (Stomberg *et al.*, 1994). The torsion angle of 154.6 (3)° for C1*A*—C1*J*—C12—C2*J*, however, is comparable with the torsion angles observed in the monoclinic form [151.0 (6)°; Stomberg *et al.*, 1994) and the trigonal forms [149 (1)° (Stomberg *et al.*, 1994) and 150.7 (2)° (Bardet *et al.*, 1999)].

Data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 2001); software used to prepare material for publication: *SHELXTL*.

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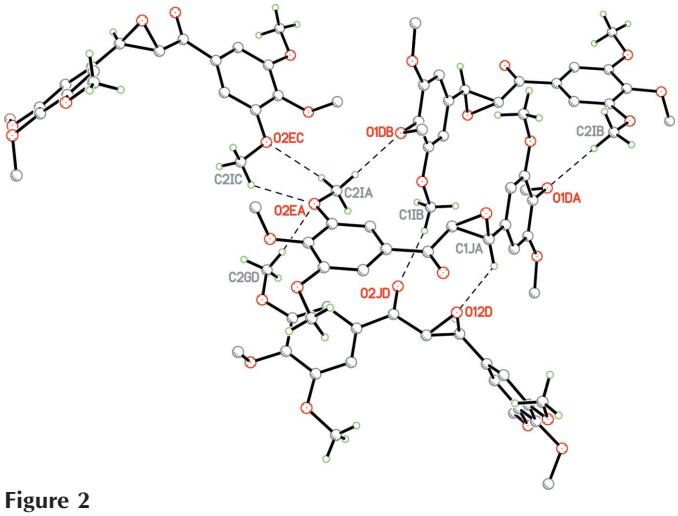

Figure 2
The molecular associations within the solid that stabilize the structure of (I). The central molecule at (x, y, z) is involved with molecule A [atoms with the suffix A, at ($x+\frac{1}{2}$, $-y+\frac{5}{2}$, $-z+1$)], molecule B [atoms with the suffix B, at ($-x+\frac{1}{2}$, $y-\frac{1}{2}$, z)], molecule C [atoms with the suffix C, at ($-x+1$, y, $-z+\frac{1}{2}$)] and molecule D [atoms with the suffix D, at ($-x+1$, $-y+2$, $-z+1$)]. Only the H atoms in associations involving the central molecule, with C—H···O associations up to a C···O distance of 3.5 Å, are shown.

References

Bardet, M., Foray, M. F., Li, S., Lundquist, K. & Stomberg, R. (1999). *J. Chem. Crystallogr.* **29**, 1023–1029.

Baures, P. W., Eggleston, D. S., Flisak, J. R., Gombatz, K., Lantos, I., Mendelson, W. & Remich, J. J. (1990). *Tetrahedron Lett.* **31**, 6501–6504.

Bhat, B. A., Dhar, K. L., Puri, S. C., Saxena, A. K., Shanmugavel, M. & Qazi, G. N. (2005). *Bioorg. Med. Chem. Lett.* **15**, 3177–3180.

Bruker (2001). *SHELXTL* (Version 6.12), *SAINT* (Version 6.45a) and *SMART* (Version 5.630). Bruker AXS Inc., Madison, Wisconsin, USA.

De Vincenzo, R., Scambia, G., Panici, P., Benedetti, E., Ranelletti, F. O., Bonanno, G., Ercoli, A., Delle Monache, F., Ferrari, F., Piantelli, M. & Mancuso, S. (1995). *Anti-Cancer Drug Des.* **10**, 481–90.

Grabowski, S. J. (2004). *J. Phys. Org. Chem.* **17**, 18–31.

Herencia, F., Ferrandiz, M. L., Ubeda, A., Dominguez, J. N., Charris, J. E., Lobo, G. M. & Alcaraz, M. J. (1998). *Bioorg. Med. Chem. Lett.* **8**, 1169–1174.

Hinterding, K., Knebel, A., Herrlich, P. & Waldmann, H. (1998). *Bioorg. Med. Chem.* **6**, 1153–1162.

Jiang, L. & Lai, L. (2002). *J. Biol. Chem.* **277**, 37732–37740.

Kumar, S. K., Hager, E., Pettit, C., Gurulingappa, H., Davidson, N. E. & Khan, S. R. (2003). *J. Med. Chem.* **46**, 2813–2815.

Lawrence, N. J., McGown, A. T., Ducki, S. & Hadfield, J. A. (2000). *Anti-Cancer Drug Des.* **15**, 135–141.

Litkei, G. (1979). *Recent Dev. Chem. Nat. Carbon Compd.* **9**, 293–408.

Lopez-Lazaro, M. (2002). *Curr. Med. Chem. Anti-Cancer Agents*, **2**, 691–714.

Morisseau, C., Du, G., Newman, J. W. & Hammock, B. D. (1998). *Arch. Biochem. Biophys.* **356**, 214–228.

Nakamura, C., Kawasaki, N., Miyataka, H., Jayachandran, E., Kim, I. H., Kirk, K. L., Taguchi, T., Takeuchi, Y., Hori, H. & Satoh, T. (2002). *Bioorg. Med. Chem.* **10**, 699–706.

Park, E. J., Park, H. R., Lee, J. S. & Kim, J. (1998). *Planta Med.* **64**, 464–466.

Rao, Y. K., Fang, S.-H. & Tzeng, Y.-M. (2004). *Bioorg. Med. Chem.* **12**, 2679–2686.

Sabzevari, O., Galati, G., Moridani, M. Y., Siraki, A. & O'Brien, P. J. (2004). *Chem. Biol. Interact.* **148**, 57–67.

Seguin, E., Elomri, A., Magiatis, P., Skaltsounis, A.-L., Chao, L. R. & Tillequin, F. (2002). *Nat. Prod. Lett.* **16**, 187–193.

Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.

Steiner, T. & Saenger, W. (1992). *J. Am. Chem. Soc.* **114**, 10146–10154.

Stomberg, R., Li, S. & Lundquist, K. (1994). *J. Chem. Crystallogr.* **24**, 407-413.

Taylor, R. & Kennard, O. (1982). *J. Am. Chem. Soc.* **104**, 5063–5070.

Yamamoto, S., Aizu, E., Jian, H., Nakadate, T., Kiyoto, I., Wang, J. C. & Kato, R. (1991). *Carcinogenesis*, **12**, 317–323.

Youssef, A. H. & El-Sadany, S. K. (1983). *Indian J. Chem. Sect B*, **22**, 601–604.

Zass, E., Plattner, D. A., Beck, A. K. & Neuburger, M. (2002). *Helv. Chim. Acta*, **85**, 4012–4045.