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Platelet-Activating-Factor Antagonist Design. 4. Structure and Intermolecular Crystal Lattice Interactions of *cis*-3,4-Dibenzyl-2-oxo-2,3,4,5-tetrahydrofuran

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Abstract. *cis*-3,4-Dibenzyl-2-oxo-2,3,4,5-tetrahydrofuran, $C_{18}H_{18}O_2$, $M_r = 266{\cdot}3$, monoclinic, $P2_1/c$, $a = 7{\cdot}838$ (4), $b = 27{\cdot}383$ (9), $c = 6{\cdot}858$ (3) Å, $\beta = 95{\cdot}92$ (4)°, $V = 1464$ Å^3, $Z = 4$, $D_x = 1{\cdot}21$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71073 Å, $\mu = 0{\cdot}43$ cm^{-1}, $F(000) = 568$, $T = 293$ K, final $R = 0{\cdot}078$ for 909 observed [$F_o \geq 2{\cdot}5\sigma(F_o)$] reflections. The observed structure confirms a *cis* relationship for the two benzyl substituents. The lactone ring system adopts an envelope conformation. There is no crystallographically imposed symmetry. van der Waals interactions predominate in the crystal lattice of this compound.

Introduction. Platelet-activating-factor (PAF) is a natural phospholipid ether of mammalian systems that elicits a myriad of biological and physiological effects (Venuti, 1985; McManus, 1986; Etienne, Hecquet & Braquet, 1988; Smith, Rubin & Patterson, 1988). The binding of PAF to a specific, cellular membrane receptor site is the first step leading to its biological response (McManus, 1986; Hwang, Lam, Biftu, Beattie & Shen, 1985). New, potent and selective PAF-receptor antagonists are needed to investigate fully the important mediator role that PAF portrays in human disease states (Corey, Chen & Parry, 1988; Grue-Sorensen, Nielsen & Nielsen, 1988). We recently reported some early investigations aimed at the design of such antagonists (Peterson, Smillie & Rogers, 1989; Peterson, Do & Rogers, 1989; Peterson, Horsley, Brozik & Rogers, 1989) that are based upon natural product (Braquet & Godfroid, 1986; Biftu & Stevenson, 1987) and synthetic analogue models (Hwang *et al.*, 1985; Biftu, Gamble, Doebber, Hwang, Shen, Snyder, Springer & Stevenson, 1986; Wu, Biftu & Doebber, 1986; Ponpipom, Hwang, Doebber, Acton, Alberts, Biftu, Brooker, Bugianesi, Chabala, Gamble, Graham, Lam & Wu, 1988). We project the X-ray crystallographic studies of these compounds (Codding & Muir, 1985; Codding, 1988) will afford important and pharmaceutically useful information about the molecular nature of the PAF-receptor site (Braquet & Godfroid, 1986; Godfroid & Braquet, 1986). In conjunction with this effort, the X-ray crystal structure and an analysis of closest intermolecular contacts in the cell lattice of *cis*-3,4-dibenzyl-2-oxo-2,3,4,5-tetrahydrofuran is described herein. The title compound is a synthetic congener of the prestegane family of PAF-antagonistic natural products and provides a biological probe into the effect of *cis* substitution about the γ-lactone ring (Braquet & Godfroid, 1986).

Experimental. The title dihydrofuran was prepared in 77% yield on a 0·58 mmol scale by catalytic hydrogenolysis of 2,4-diphenyl-3,7-dioxabicyclo[3.3.0]oct-1-en-8-one (Horsley, 1989) over 5% palladium on activated carbon in absolute ethanol (20 mL). The reaction mixture was mechanically shaken at ambient temperature for 24 h under a hydrogen atmosphere (40 p.s.i.) before removing the spent catalyst by filtration through a short column of Celite. Concentration of the filtrate afforded an oil that crystallized from chloroform. Recrystallization of this solid yielded colorless, parallelepiped crystals (m.p. 352–353 K) suitable for X-ray analysis. The observed structure was in full agreement with the spectral and analytical data.† D_m was not determined. Crystal 0·10 × 0·10 × 0·13 mm. Enraf–Nonius CAD-4 diffractometer, graphite-mono-

† Physical data: IR (KBr) 3060, 3030, 2920, 2860, 1770, 1600, 1495, 1455, 1375, 1200, 1180, 1145, 1090, 1050, 990, 740, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7·50–7·15 (*m*, 8 H), 7·15–6·95 (*m* 2 H), 4·12–3·92 (*m*, 2 H), 3·34 (*dd*, $J = 14{\cdot}63$, 4·30 Hz, 1 H), 3·20–3·05 (*m*, 2 H), 2·99 (*dd*, $J = 13{\cdot}41$, 3·51 Hz, 1 H), 2·85 (*dd*, $J = 14{\cdot}63$, 10·63 Hz, 1 H), 2·5–2·3 (*m*, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 177·83, 138·61, 138·49, 128·91, 128·78 128·73, 128·57, 128·39, 126·68, 69·39, 45·22, 39·92, 32·93, 30·88: Analysis calculated for $C_{18}H_{18}O_2$: C81·17, H6·81; found C80·99, H6·82%.

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Table 1. *Final fractional coordinates and equivalent isotropic thermal parameters for* $C_{18}H_{18}O_2$

	x	y	z	B_{eq} (Å^2)*
O(1)	0·4116 (7)	0·0046 (2)	0·7248 (8)	4·60
O(2)	0·1765 (8)	−0·0346 (2)	0·7944 (9)	5·60
C(1)	0·248 (1)	0·0035 (3)	0·776 (1)	4·12
C(2)	0·184 (1)	0·0542 (2)	0·797 (1)	3·46
C(3)	0·2989 (8)	0·0838 (3)	0·6742 (9)	3·04
C(4)	0·464 (1)	0·0550 (3)	0·708 (1)	4·11
C(5)	−0·0090 (9)	0·0592 (3)	0·756 (1)	3·80
C(6)	−0·0705 (9)	0·1112 (3)	0·764 (1)	3·24
C(7)	−0·179 (1)	0·1304 (3)	0·614 (1)	4·04
C(8)	−0·236 (1)	0·1772 (4)	0·616 (1)	4·93
C(9)	−0·185 (1)	0·2076 (3)	0·770 (1)	4·55
C(10)	−0·076 (1)	0·1892 (3)	0·917 (1)	4·75
C(11)	−0·018 (1)	0·1417 (4)	0·919 (1)	4·36
C(12)	0·2302 (9)	0·0864 (3)	0·456 (1)	3·74
C(13)	0·3157 (9)	0·1258 (3)	0·346 (1)	3·07
C(14)	0·444 (1)	0·1162 (3)	0·229 (1)	3·55
C(15)	0·513 (1)	0·1527 (4)	0·125 (1)	4·58
C(16)	0·456 (1)	0·1995 (4)	0·136 (2)	5·21
C(17)	0·329 (1)	0·2099 (3)	0·251 (1)	4·95
C(18)	0·260 (1)	0·1736 (3)	0·358 (1)	3·85

*$B_{eq} = \frac{4}{3}(a^2b_{11} + b^2b_{22} + c^2b_{33} + ab\cos\gamma b_{12} + ac\cos\beta b_{13} + bc\cos\alpha b_{23})$.

Table 2. *Bond distances* (Å) *and angles* (°) *for* $C_{18}H_{18}O_2$

O(1)—C(1)	1·360 (8)	O(1)—C(4)	1·448 (8)
O(2)—C(1)	1·199 (9)	C(1)—C(2)	1·49 (1)
C(2)—C(3)	1·531 (8)	C(2)—C(5)	1·514 (9)
C(3)—C(4)	1·515 (9)	C(3)—C(12)	1·537 (8)
C(5)—C(6)	1·51 (1)	C(6)—C(7)	1·37 (1)
C(6)—C(11)	1·38 (1)	C(7)—C(8)	1·36 (1)
C(8)—C(9)	1·37 (1)	C(9)—C(10)	1·35 (1)
C(10)—C(11)	1·38 (1)	C(12)—C(13)	1·512 (9)
C(13)—C(14)	1·373 (9)	C(13) C(18)	1·39 (1)
C(14)—C(15)	1·37 (1)	C(15)—C(16)	1·36 (1)
C(16)—C(17)	1·36 (1)	C(17)—C(18)	1·38 (1)
C(1)—O(1)—C(4)	109·0 (6)	O(1)—C(1)—O(2)	120·8 (8)
O(1)—C(1)—C(2)	110·1 (8)	O(2)—C(1)—C(2)	129·1 (8)
C(1)—C(2)—C(3)	102·1 (6)	C(1)—C(2)—C(5)	114·1 (6)
C(3)—C(2)—C(5)	118·9 (6)	C(2)—C(3)—C(4)	100·7 (6)
C(2)—C(3)—C(12)	113·2 (6)	C(4)—C(3)—C(12)	112·4 (6)
O(1)—C(4)—C(3)	105·1 (6)	C(2)—C(5)—C(6)	113·3 (6)
C(5)—C(6)—C(7)	120·8 (8)	C(5)—C(6)—C(11)	121·8 (8)
C(7)—C(6)—C(11)	117·3 (8)	C(6)—C(7)—C(8)	122·2 (9)
C(7)—C(8)—C(9)	120·9 (9)	C(8)—C(9)—C(10)	117·3 (8)
C(9)—C(10)—C(11)	123·0 (9)	C(6)—C(11)—C(10)	119·3 (8)
C(3)—C(12)—C(13)	113·0 (6)	C(12)—C(13)—C(14)	123·0 (7)
C(12)—C(13)—C(18)	119·2 (8)	C(14)—C(13)—C(18)	117·8 (7)
C(13)—C(14)—C(15)	121·2 (8)	C(14)—C(15)—C(16)	120·3 (9)
C(15)—C(16)—C(17)	120 (1)	C(16)—C(17)—C(18)	120·5 (9)
C(13)—C(18)—C(17)	120·7 (8)		

chromated Mo $K\alpha$. Cell constants from setting angles of 25 reflections ($\theta > 10°$). Correction for Lorentz–polarization effect. $\theta_{max} = 50°$; h −9 to 9, k −32 to 0, l 0 to 8. Standard reflections 200, 060, 004 observed every 3600 s of data collection time; variation = 1·2%. 3166 reflections measured, 909 independent observed reflections [$F_o \geq 2{\cdot}5\sigma(F_o)$]. Structure solved utilizing *MULTAN* (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980) direct-methods program. Least-squares refinement with isotropic thermal parameters led to $R = 0{\cdot}122$. The geometrically constrained hydrogen atoms were placed in calculated positions 0·95 Å from the bonded carbon atom and allowed to ride on that atom with B fixed at 5·5 Å^2. Scattering factors and anomalous-dispersion corrections were from *International Tables for X-ray Crystallography* (1974); structure refined with *SHELX76* (Sheldrick, 1976). $\sum w(|F_o| - |F_c|)^2$ minimized, weights = $[\sigma(F_o)^2 + 0{\cdot}0016F_o^2]^{-1}$, 181 parameters varied. $R = 0{\cdot}078$, $wR = 0{\cdot}078$ (high values result from the large number of weak reflections), $S = 0{\cdot}77$. Δ/σ in final least-squares refinement cycle $< 0{\cdot}01$, $\Delta\rho < 0{\cdot}03$ e Å^{-3} in final difference map.

Discussion. Fractional coordinates and B_{eq} values are given in Table 1,* bond distances and angles in Table 2, and an *ORTEP* drawing (Johnson, 1976) in Fig. 1. A cell plot is provided in Fig. 2.

* Lists of structure factors, anisotropic thermal parameters, least-squares-planes results, torsion angles and final fractional coordinates for H atoms have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52533 (7 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

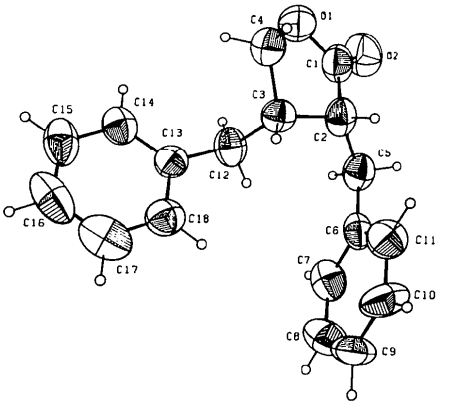

Fig. 1. Thermal-ellipsoid plot of the title tetrahydrofuran illustrating the atom-numbering scheme. The hydrogen atom radii are arbitrarily reduced.

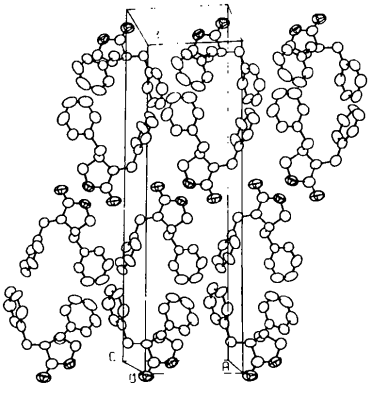

Fig. 2. Cell plot of the title compound.

The observed *cis* orientation of the C(2) and C(3) benzyl substituents is in accordance with the addition of hydrogen proceeding from the convex face of 2,4-diphenyl-3,7-dioxabicyclo[3.3.0]oct-1-ene-8-one. The torsion angles C(5)—C(2)—C(3)—C(12) of −39·6 and H(1)C(2)—C(2)—C(3)—H(1)C(3) of −32·6° support this observation. The lactone ring exists in an envelope conformation with ring atoms O(1), C(1), C(2) and C(4) describing a plane to within 0·003 Å. Ring atom C(3) deviates from this plane by 0·556 Å and carbonyl oxygen atom O(2) by 0·025 Å. The deviation of C(3) from the O(1), C(1), C(2) and C(4) plane results in a −33·0° torsion angle about C(1)—C(2)—C(3)—C(4) and a torsion angle of 34·1° about C(2)—C(3)—C(4)—O(1). Similar conformational effects have been observed in related molecules. The same ring atoms in methyl *trans*-5-(3,4-dimethoxyphenyl)-2,3,4,5-tetrahydro-2-oxo-4-furancarboxylate, $C_{14}H_{16}O_6$ (Peterson, Smillie & Rogers, 1989), define a plane to within 0·016 Å, while ring atom C(3) deviates from this plane by 0·516 Å and carbonyl oxygen atom O(2) by 0·040 Å. Likewise, ring atom C(3) deviates by 0·473 Å from the O(1), C(1), C(2) and C(4) plane of dimethyl 2,3,4,5-tetrahydro-5β-(3,4-methylenedioxyphenyl)-2-oxo-3β-(3,4,5-trimethoxyphenyl)-3α,4α-furandicarboxylate (Peterson, Do & Rogers, 1989).

Both phenyl rings of the title compound describe planes with atoms C(6) through C(11) and atoms C(13) through C(18) within 0·006 and 0·007 Å, respectively, of planarity. Interestingly, the phenyl ring of the quasiequatorial C(2) benzyl group intersects the lactone ring plane at the nearly perpendicular angle of 76·3°, while the C(3) quasiaxial aromatic plane lies more coplanar to the O(1), C(1), C(2) and C(4) plane with a 25·4° angle of intersection. Phenyl ring plane C(6) through C(11) intersects that of atoms C(13) through C(18) by 101·6°. Such features* may be characteristic of the prestegnane family of PAF antagonists as the crystallographic structure of enterolactone, $C_{18}H_{18}O_4$, revealed a similar spatial disposition of the aromatic rings (Cooley, Farrant, Kirk, Patel, Wynn, Buckingham, Hawkes, Hursthouse, Galas, Lawson & Setchell, 1984).

The internal bond angles of the lactone ring of the title compound are significantly less than the values normally associated with sp^2 and sp^3 hybridized carbon centers. This internal bond-angle compression about atoms C(1) through C(4) in turn induces a broadening of the external bond angles. Related molecules were found to exhibit similar geometrical trends, and Table 3 provides a comparison of the lactone ring bond angles for the title compound with those of $C_{14}H_{16}O_6$ (Peterson, Smillie & Rogers, 1989) and $C_{18}H_{18}O_4$ (Cooley *et al.*, 1984). Bond distances about atoms C(1) through C(4) are unaffected by ring geometry in these compounds, however.

Table 3. *Lactone ring bond-angle comparison of* $C_{18}H_{18}O_2$, $C_{14}H_{16}O_6$ *and* $C_{18}H_{18}O_4$

	$C_{18}H_{18}O_2$	$C_{14}H_{16}O_6$[a]	$C_{18}H_{18}O_4$[b]
O(1)—C(1)—C(2)	110·1 (8)	109·4 (3)	111·6 (1)
C(1)—C(2)—C(3)	102·1 (6)	102·8 (2)	103·6 (1)
C(2)—C(3)—C(4)	100·7 (6)	102·4 (2)	102·4 (1)
O(1)—C(4)—C(3)	105·1 (6)	103·4 (2)	105·8 (1)
O(2)—C(1)—C(2)	129·1 (8)	129·3 (3)	129·0 (1)
C(1)—C(2)—C(5)	114·1 (6)	—	112·2 (1)
C(3)—C(2)—C(5)	118·9 (6)	—	117·7 (1)
C(2)—C(3)—C(12)	113·2 (6)	116·4 (2)	115·2 (1)
C(4)—C(3)—C(12)	112·4 (6)	112·9 (3)	112·3 (1)

Notes: (*a*) Peterson, Smillie & Rogers (1989); (*b*) Cooley, Farrant, Kirk, Patel, Wynn, Buckingham, Hawkes, Hursthouse, Galas, Lawson & Setchell (1984).

Table 4. *Intermolecular contact distances* (Å) *for* $C_{18}H_{18}O_2$

O(1)···H(1)C(14^{i})	2·57	O(1)···H(2)C(4^{i})	2·90
O(1)···C(14^{i})	3·50 (1)	O(1)···C(4^{i})	3·61 (1)
O(2)···H(1)C(5^{ii})	2·69	O(2)···C(5^{ii})	3·54 (1)
H(1)C(15)···H(1)C(4^{iii})	2·69	H(1)C(14)···H(1)C(4^{iii})	2·82
C(13)···H(1)C(11^{iii})	2·83	C(18)···H(1)C(11^{iii})	2·90
H(1)C(9)···H(1)C(16^{iv})	2·62	H(1)C(8)···H(1)C(16^{iv})	2·78
H(1)C(8)···H(1)C(9^{v})	2·67	H(1)C(16)···H(1)C(17^{v})	2·72
H(1)C(9)···H(1)C(10^{v})	2·73		
H(1)C(7)···H(2)C(4^{vi})	2·60	C(7)···C(4^{vi})	3·59 (1)
C(10)···H(1)C(15^{vii})	3·01	C(9)···H(1)C(15^{vii})	3·14
C(11)···H(1)C(15^{vii})	3·19	C(9)···H(1)C(16^{vii})	3·36
C(8)···H(1)C(15^{vii})	3·42	C(6)···H(1)C(15^{vii})	3·50
C(7)···H(1)C(15^{vii})	3·59		

Atoms related to those in Table 1 by (i) $1-x,-y,1-z$; (ii) $-x,-y,2-z$; (iii) $x,y,z-1$; (iv) $x-1$, $\frac{1}{2}-y,\frac{1}{2}+z$; (v) $x,\frac{1}{2}-y,z-\frac{1}{2}$; (vi) $x-1,y,z$; (vii) $x-1,y,z+1$.

An analysis of the closest intermolecular contact distances reveals that van der Waals interactions predominate in the crystal lattice of this compound. Several interactions were noted to occur with neighboring molecules and the most prominent are described in Table 4. The shortest intermolecular contact of 2·57 Å exists between atoms O(1) and H(1)C(14) on a molecule at $1-x,-y,1-z$. At closest contact, the lactone ring planes are separated by 3·61 (1) Å between atoms O(1) and C(4) for the same molecules with a corresponding non-hydrogen O(1) to hydrogen H(2)C(14) separation of 2·90 Å. The C(6) through C(11) phenyl ring of one molecule weakly stacks with the C(13) through C(18) ring of an adjacent molecule at $x-1,y,z+1$. The non-hydrogen to hydrogen separations between these rings range from 3·01 Å for C(10)—H(1)C(15) to 3·59 Å for C(7)—H(1)C(15).

Van der Waals contacts and ring geometrical and conformational preferences such as those described for the title compound could prove to be important for the binding of furanoid lignans to the PAF–membrane receptor site. Additional investigations of several natural and synthetic lignans are now in

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progress in our laboratory to determine the utility of this X-ray crystallographic approach to the design of potent and specific PAF antagonists and an improved drug–receptor site binding model.

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Abstract. [3a*R*-(3aα,4aβ,8aα,9α,10aα)]-Octahydro-4a,9-dimethyl-3-methylenefuro[2′,3′:5,6]cyclohepta-[1,2-*c*]pyran-2,7(3*H*,4*H*)-dione, $C_{15}H_{20}O_4$, M_r = 264·31, monoclinic, $P2_1$, a = 10·001 (3), b = 10·327 (2), c = 13·388 (4) Å, β = 93·12 (2)°, V = 1380·6 (6) Å^3, Z = 4, D_x = 1·272, D_m = 1·29 (2) g cm^{-3}, Cu $K\alpha$, λ = 1·5418 Å, μ = 7·08 cm^{-1}, $F(000)$ = 586, T = 298 K, R = 0·0444 for 1720 unique observed data. The six-membered ring is in the half-chair form, the central seven-membered ring is in the boat form, and the five-membered ring is planar. The angle between the plane of the five-

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