The dependence of donor angle (O—H···O) on O···H bond length provides a semi-quantitative indication of the bond strength. Fig. 3 is a comparison between data obtained from an analysis of water structures in small hydrate crystal structures (Savage & Finney, 1986) and that from this study. The hydrogen-bond lengths tend toward the upper limit of values documented in the Savage & Finney survey. In an apolar environment, the MeBmt-1 side chain has been observed to rotate out of the cleft of the β-sheet and locate proboscis-like in the solvent (Loosli *et al.*, 1985).

No other ordered solvent molecules of significance were found in the final difference Fourier synthesis, where maximum positive and negative residuals were 3·1% of the height of an N-atom peak. All intermolecular distances are in the range of normal van der Waals values.

The *ORTEP*II molecular graphics program (Johnson, 1976) was used to generate the stereoview of the cyclosporin A molecule given in Fig. 4. The water molecule is shown hydrogen bonding the MeBmt-1 side chain to the molecular backbone.

The addition of the geometric parameters for the hydrogen atoms completes the high-resolution structure of cyclosporin A in the single-crystal environment. The geometric parameters of a single bound water molecule has provided evidence for an ordered solvent interaction. What contribution this structural information makes to the understanding of the highly specific pharmacological function of cyclosporin A is under investigation.

The assistance of Sandoz Pharmaceutical Ltd, especially Dr Hans-Peter Weber for access to data before publication and for the supply of a superb single crystal of cyclosporin A mod III, is gratefully acknowledged. The assistance of Dr Don Craig (University of New South Wales) and Dr Mitchell Guss (University of Sydney) with computer graphics is also gratefully acknowledged. Research was carried out, in part, at the Brookhaven National Laboratory under the auspices of the Office of Health and Environmental Research (OHER), US Department of Energy, and with partial support from the National Sciences Foundation.

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Structure and Stereochemistry of an Acetate Derivative of Cacospongionolide, a New Antitumoral Sesterterpenoid from Marine Sponge *Cacospongia mollior*

By Raffaella Puliti and Salvatore De Rosa

Istituto per la Chimica di Molecole di Interesse Biologico CNR, Via Toiano 6, 80072 *Arco Felice, Napoli, Italy*

and Carlo Andrea Mattia and Lelio Mazzarella

Dipartimento di Chimica, Università Federico II, *Via Mezzocannone* 4, 80134 *Napoli, Italy*

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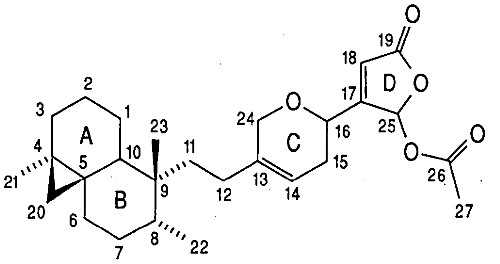
Abstract. 2,5-Dihydro-3-{3,6-dihydro-5-[2-(perhydro-1,2,3-trimethyl-4a,5-methano-1-naphthyl)ethyl]-2*H*-pyran-2-yl}-5-oxo-2-furyl acetate, $C_{27}H_{38}O_5$, $M_r = 442{\cdot}6$, monoclinic, $P2_1$, $a = 9{\cdot}717\ (4)$, $b = 7{\cdot}064\ (3)$, $c = 18{\cdot}751\ (6)$ Å, $\beta = 96{\cdot}94\ (3)°$, $V = 1278\ (2)$ Å^3, $Z = 2$, $D_x = 1{\cdot}150$ Mg m^{-3}, $\lambda(\mathrm{Cu}\ K\alpha) =$

1·5418 Å, $\mu = 0{\cdot}59\ \mathrm{mm}^{-1}$, $F(000) = 480$, room temperature, final $R = 0{\cdot}052$ for 1312 independent observed reflections and 289 variables. The crystallographic analysis confirms the structure previously assigned to cacospongionolide on the basis of spectral data and chemical evidence, including the presence of a cyclopropane ring never found in natural sesterterpenes. In addition it establishes for the title compound, the acetate derivative of the natural product, *S* stereochemistry at C25. Rings *A* and *C* adopt distorted half-boat conformations, ring *B* is in a chair conformation and the γ-lactone ring *D* is planar. In the absence of hydrogen-bonding donors, the crystal packing is governed by van der Waals interactions.

Introduction. As part of a research program (De Rosa, De Stefano, Scarpelli & Zavodnik, 1988, and references therein) on metabolites of northern Adriatic organisms, De Rosa, De Stefano & Zavodnik (1988) have reported the isolation and structural characterization of cacospongionolide, a sesterterpenoid with new carbon skeleton from marine sponge *Cacospongia mollior.* This molecule is a potent antitumoral and ichthyotoxic agent and its gross structure was assigned mainly on the basis of spectral data including 2D NMR spectroscopy. The relative stereochemistry of the rings *A* and *B* was deduced by a NOESY spectrum and NOE difference measurements. In order to confirm the given structure, which is unprecedented in the natural sesterterpenoid class, we have undertaken the crystallographic analysis of the acetyl derivative (I) as the natural product did not give suitable crystals.



(I)

Experimental. The title compound (I) was obtained as the major product of acetylation of cacospongionolide with acetic anhydride in pyridine. The mixture of two diastereoisomers was separated by silica gel chromotagraphy and single crystals of (I) were obtained by careful recrystallization from methanol. Sample of size 0·37 × 0·13 × 0·04 mm was used with Enraf–Nonius CAD-4F diffractometer and monochromated Cu $K\alpha$ radiation. Cell dimensions from 22 reflections ($20 \leq \theta \leq 23°$); ω scan, as suggested by peak-shape analysis; three standard reflections monitored every 4 h (4% max. variation), no significant intensity decay observed; 2368 independent reflections with $\theta \leq 65°$, $0 \leq h \leq 11$, $0 \leq k \leq 8$, $-22 \leq l \leq 22$, 1312 with $I \geq 3\sigma(I)$; Lp correction, absorption ignored. Structure solved by *MULTAN*82 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1982); anisotropic full matrix (on *F*); H atoms generated at the expected positions with C—H distance 1·05 Å, taking into account for methyl groups the indications from ΔF map. H-atom parameters not refined, thermal parameters set equal to B_{eq} of parent atom. Final $R = 0{\cdot}052$, $wR = 0{\cdot}055$, $w^{-1} = [\sigma^2(F_o) + (0{\cdot}02F_o)^2 + 1]$ and σ from counting statistics. Correction for secondary extinction refined [g coefficient = $2{\cdot}6\,(2) \times 10^{-6}$], $S = 0{\cdot}66$; final $(\Delta/\sigma)_{\max} = 0{\cdot}01$; max. and min. heights in final $\Delta\rho$ map 0·16 and $-0{\cdot}19\ \mathrm{e\,Å^{-3}}$. Scattering factors from *International Tables for X-ray Crystallography* (1974), Enraf–Nonius *SDP* software (B. A. Frenz & Associates, Inc., 1985) and MicroVAX computer of the 'Centro di Metodologie Chimico-fisiche dell'Università di Napoli'. Final atomic parameters for the non-H atoms are listed in Table 1.*

Table 1. *Positional parameters* ($\times 10^4$) *and equivalent isotropic thermal parameters* ($\mathrm{Å}^2$) *with e.s.d.'s in parentheses for non-*H *atoms*

$$B_{\text{eq}} = (4/3)\textstyle\sum_i\sum_j\beta_{ij}\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	B_{eq}
O1	2320 (3)	5000	7732 (1)	5·90 (7)
O2	5776 (3)	7809 (5)	9329 (2)	6·19 (7)
O3	5243 (3)	10690 (5)	8905 (2)	7·81 (9)
O4	6313 (3)	4843 (5)	8909 (1)	5·44 (7)
O5	7188 (4)	4017 (6)	10027 (2)	8·8 (1)
C1	−3902 (4)	−391 (7)	7023 (3)	6·4 (1)
C2	−5328 (4)	42 (7)	6605 (3)	7·7 (1)
C3	−6121 (4)	−1775 (8)	6377 (3)	6·9 (1)
C4	−5239 (4)	−3353 (7)	6124 (2)	6·0 (1)
C5	−3664 (4)	−3222 (6)	6222 (2)	4·91 (9)
C6	−2856 (5)	−4083 (8)	5682 (3)	6·8 (1)
C7	−1341 (5)	−4490 (7)	6017 (3)	6·9 (1)
C8	−638 (4)	−2645 (6)	6327 (2)	5·3 (1)
C9	−1468 (4)	−1746 (6)	6893 (2)	4·57 (9)
C10	−2983 (4)	−1381 (6)	6543 (2)	4·77 (9)
C11	−800 (4)	194 (6)	7154 (2)	5·4 (1)
C12	755 (4)	29 (7)	7435 (3)	6·8 (1)
C13	1368 (4)	1792 (7)	7821 (2)	5·7 (1)
C14	1681 (5)	1864 (7)	8521 (2)	6·3 (1)
C15	2496 (4)	3498 (7)	8883 (2)	5·8 (1)
C16	3266 (4)	4430 (6)	8331 (2)	5·0 (1)
C17	4061 (4)	6141 (6)	8611 (2)	4·50 (9)
C18	3935 (4)	7953 (7)	8433 (2)	5·7 (1)
C19	4995 (4)	9036 (7)	8882 (2)	5·9 (1)
C20	−4392 (5)	−4513 (6)	6696 (3)	6·4 (1)
C21	−5987 (5)	−4381 (8)	5487 (3)	8·1 (1)
C22	−332 (5)	−1380 (8)	5714 (2)	7·2 (1)
C23	−1443 (4)	−3033 (7)	7551 (2)	5·8 (1)
C24	1731 (5)	3372 (7)	7338 (2)	6·6 (1)
C25	5258 (4)	5902 (7)	9191 (2)	5·1 (1)
C26	7232 (5)	3948 (8)	9403 (2)	6·5 (1)
C27	8244 (5)	2880 (9)	9029 (3)	8·5 (2)

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* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52722 (12 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Discussion. Fig. 1 shows a view of the molecule together with the atomic labelling scheme. In the absence of atoms with strong anomalous scattering, the absolute configuration of this molecule could not be determined and the chosen configuration corresponds to that of the cacospongionolide skeleton given by De Rosa, De Stefano & Zavodnik (1988). On this basis, the crystallographic analysis fixes for the acetyl derivative the *S* configuration at the chiral centre C25.

The molecule presents a pentacyclic skeleton characterized by a system of two *trans*-connected six-carbon rings (*A* and *B*), which has a cyclopropyl methylene group joining 4,5 positions and two axial methyl substituents at C8 (α-oriented) and at C9 (β-oriented). This moiety is linked to a 5,6-dihydro-2*H*-pyran ring (*C*), through a C9 equatorial ethylene bridge. Ring *C* is further connected to a γ-acetoxy-α,β-unsaturated-γ-lactone (ring *D*). The formation of a cyclopropane ring, involving the axial methyl at C4, has been found in some di- and triterpenoid systems (Connolly, Freer, Anjaneyulu, Ravi & Sambasivarao, 1986, and references therein), but it is unprecedented in natural sesterterpenes.

Geometrical parameters involving non-H atoms are given in Table 2. On average the molecular dimensions agree with the values found for similar compounds (Giordano & Puliti, 1987; Cimino, Gavagnin, Sodano, Puliti, Mattia & Mazzarella, 1988). Average values for distances are C(sp^3)—C(sp^3) 1·529 (6), C(sp^3)—C(sp^2) 1·504 (7), C=C 1·318 (6), C(sp^3)—O 1·435 (5), C(sp^2)—O 1·366 (5), C=O 1·185 (6) Å. Excluding the cyclopropane and lactone rings, the valency angles involving tetrahedral and trigonal C atoms have mean values of 111·2 (4) and 120·3 (4)°, respectively.

Ring *A* is restrained by the cyclopropane ring on the 4,5 positions and adopts a distorted half-boat conformation as shown by the puckering parameters (Cremer & Pople, 1975): Q = 0·516 (7), q_2 = 0·389 (7), q_3 = 0·340 (8) Å, φ_2 = 72 (2)°. θ = 48·8 (9)° for the sequence C10, C1, C2, C3, C4, C5. In this ring, C1 and C2 atoms are respectively 0·579 (8) Å on one side and 0·177 (9) Å on the other with respect to the best plane defined by the remaining atoms. Ring *B* exhibits a chair conformation with C7 and C10

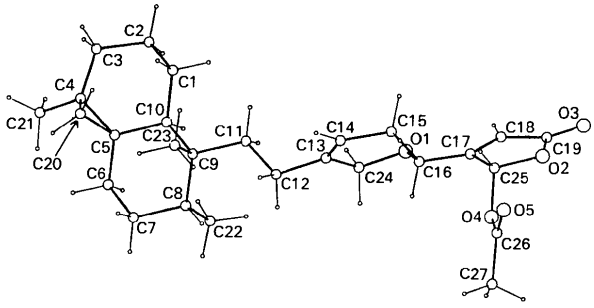

Fig. 1. Drawing of the molecule (labels for H atoms have been omitted for clarity).

Table 2. *Bond lengths* (Å), *bond angles* (°) *and some torsion angles* (°) *with e.s.d.'s in parentheses*

O1—C16	1·421 (4)	C6—C7	1·556 (6)
O1—C24	1·446 (5)	C7—C8	1·551 (6)
O2—C19	1·369 (5)	C8—C9	1·545 (6)
O2—C25	1·450 (5)	C8—C22	1·514 (7)
O3—C19	1·193 (6)	C9—C10	1·559 (5)
O4—C25	1·422 (5)	C9—C11	1·569 (6)
O4—C26	1·363 (5)	C9—C23	1·530 (6)
O5—C26	1·177 (6)	C11—C12	1·543 (6)
C1—C2	1·538 (6)	C12—C13	1·526 (6)
C1—C10	1·514 (6)	C13—C14	1·311 (6)
C2—C3	1·531 (7)	C13—C24	1·506 (7)
C3—C4	1·517 (7)	C14—C15	1·514 (7)
C4—C5	1·522 (6)	C15—C16	1·501 (6)
C4—C20	1·512 (6)	C16—C17	1·495 (6)
C4—C21	1·507 (7)	C17—C18	1·325 (6)
C5—C6	1·483 (7)	C17—C25	1·503 (5)
C5—C10	1·548 (6)	C18—C19	1·465 (6)
C5—C20	1·508 (6)	C26—C27	1·482 (8)

C16—O1—C24	110·9 (3)	C1—C10—C5	111·4 (3)
C19—O2—C25	108·9 (3)	C1—C10—C9	114·9 (3)
C25—O4—C26	115·7 (6)	C5—C10—C9	111·2 (3)
C2—C1—C10	110·3 (4)	C9—C11—C12	113·1 (3)
C1—C2—C3	111·5 (4)	C11—C12—C13	114·3 (4)
C2—C3—C4	114·8 (4)	C12—C13—C14	122·5 (4)
C3—C4—C5	121·0 (4)	C12—C13—C24	115·2 (4)
C3—C4—C20	117·1 (4)	C14—C13—C24	122·0 (4)
C3—C4—C21	111·4 (4)	C13—C14—C15	121·6 (4)
C5—C4—C20	59·6 (3)	C14—C15—C16	107·6 (4)
C5—C4—C21	120·5 (4)	O1—C16—C15	109·9 (3)
C20—C4—C21	118·0 (4)	O1—C16—C17	107·9 (3)
C4—C5—C6	120·0 (4)	C15—C16—C17	113·0 (3)
C4—C5—C10	118·3 (4)	C16—C17—C18	131·6 (3)
C4—C5—C20	59·9 (3)	C16—C17—C25	119·1 (4)
C6—C5—C10	111·9 (4)	C18—C17—C25	109·3 (4)
C6—C5—C20	118·6 (4)	C17—C18—C19	108·8 (4)
C10—C5—C20	119·2 (3)	O2—C19—O3	120·2 (4)
C5—C6—C7	110·7 (4)	O2—C19—C18	108·7 (4)
C6—C7—C8	110·4 (4)	O3—C19—C18	131·1 (4)
C7—C8—C9	111·1 (3)	C4—C20—C5	60·5 (3)
C7—C8—C22	109·2 (4)	O1—C24—C13	112·9 (3)
C9—C8—C22	116·5 (4)	O2—C25—O4	107·7 (3)
C8—C9—C10	108·9 (3)	O2—C25—C17	104·3 (3)
C8—C9—C11	110·0 (3)	O4—C25—C17	108·6 (3)
C8—C9—C23	110·5 (3)	O4—C26—O5	123·9 (4)
C10—C9—C11	108·7 (3)	O4—C26—C27	109·4 (4)
C10—C9—C23	111·1 (3)	O5—C26—C27	126·7 (5)
C11—C9—C23	107·6 (3)		

C5—C10—C9—C11	175·6 (5)	O1—C16—C17—C18	5·9 (9)
C10—C9—C11—C12	−173·7 (6)	C16—C17—C25—O4	65·3 (7)
C9—C11—C12—C13	−168·9 (6)	C17—C25—O4—C26	−158·1 (6)
C11—C12—C13—C14	106·4 (8)	C25—O4—C26—C27	178·9 (6)

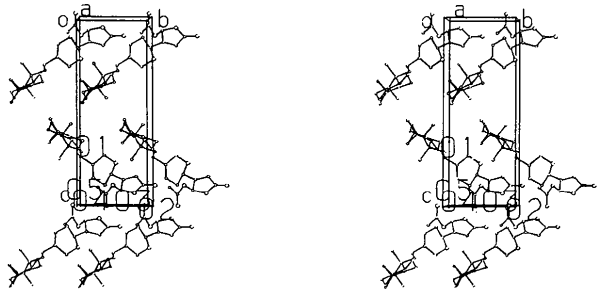

Fig. 2. Stereographic packing plot. H atoms omitted.

displaced 0·696 (8) and 0·686 (7) Å respectively from the best plane through C5, C6, C8 and C9. The absolute value of the intracycle torsion angles is on average 56·8 (6)°. The dihydropyran ring *C*, which has a double bond in positions 13,14, approximates a half-boat conformation with apex at C16 and total puckering amplitude Q = 0·521 (8) Å; the atom O1 is only 0·189 (4) Å out of the plane formed by the remaining four atoms. The lactone system is planar within the e.s.d. and makes a dihedral angle of 106·8 (3)° with the acetoxy group. The torsion angle O1—C16—C17—C18 is 6 (1)° with O1 *cis* to C18 and C15 *gauche* to C25. The molecule has the most extended conformation with the central ethylene group in a nearly *trans* conformation.

The molecular arrangement, shown in Fig. 2, is governed by van der Waals interactions and the shortest intermolecular contacts (> 3·0 Å) involve the lactone ring *D* and the acetyl group.

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Structures of 2-(2-Methoxyphenyl)-4*H*-1-benzopyran-4-one (1) and 5,7-Dimethoxy-2-(2,4-dimethoxyphenyl)-4*H*-1-benzopyran-4-one (2) (2′-Methoxyflavone and 2′,4′,5,7-Tetramethoxyflavone)

By Jean-Claude Wallet* and Emile M. Gaydou

Laboratoire de Phytochimie, Ecole Supérieure de Chimie de Marseille, Faculté des Sciences et Techniques de Saint-Jérôme, Avenue Escadrille Normandie-Niemen, 13397 Marseille CEDEX 13, France

Joël Jaud

CNRS, Laboratoire de Chimie de Coordination, 205, Route de Narbonne, 31077 Toulouse CEDEX, France

and André Baldy

CNRS UA126, Faculté des Sciences, Centre de Saint-Jérôme, 13397 Marseille CEDEX 13, France

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Abstract. Compound (1): $C_{16}H_{12}O_3$, M_r = 252·27, triclinic, $P\bar{1}$, a = 7·245 (10), b = 8·305 (12), c = 10·800 (14) Å, α = 97·7 (1), β = 93·1 (1), γ = 111·2 (1)°, V = 597 (2) Å^3, Z = 2, D_m = 1·4, D_x = 1·404 g cm^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, μ = 0·904 cm^{-1}, F(000) = 264, T = 223 K. R = 0·053 for 2180 reflections. 2′-Methoxyflavone is a predominantly flat molecule (the γ-benzopyrone portion makes an angle of 3° with the phenyl ring). Two intramolecular hydrogen bonds may contribute to the marked planarity of the molecule. Compound (2): $C_{19}H_{18}O_6$, M_r = 342·35, monoclinic, $P2_1/n$, a = 7·205 (7), b = 12·769 (4), c = 17·567 (8) Å, β = 93·27 (2)°, V = 1613 (2) Å^3, Z = 4, D_x = 1·412 g cm^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, μ = 0·986 cm^{-1}, F(000) = 720, T = 223 K. R = 0·041 for 3621 reflections. The dihedral angle between the planar phenyl ring and the slightly puckered γ-benzopyrone portion is 24°. No intramolecular H bonds.

Introduction. Flavonoids are used in the treatment of diabetes, cancers, allergies and viral infections. From the structure–activity data in the literature it is clear

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* Author to whom correspondence should be addressed.