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X-ray investigations of bicyclic *α*-methylene-*δ*-valerolactones. V. (4a*S*,7*R*,8a*R*)-7-Isopropenyl-4a-methyl-3-methyleneperhydrochromen-2-one[1]

Jakub Wojciechowski,[a] Henryk Krawczyk,[b] Marcin Śliwiński,[b] Karolina Kafarska[a] and Wojciech M. Wolf[a]*

[a]Institute of General and Ecological Chemistry, Technical University of Łódź, ul. Żeromskiego 116, 90-924 Łódź, Poland, and [b]Institute of Organic Chemistry, Technical University of Łódź, ul. Żeromskiego 116, 90-924 Łódź, Poland
Correspondence e-mail: wmwolf@p.lodz.pl

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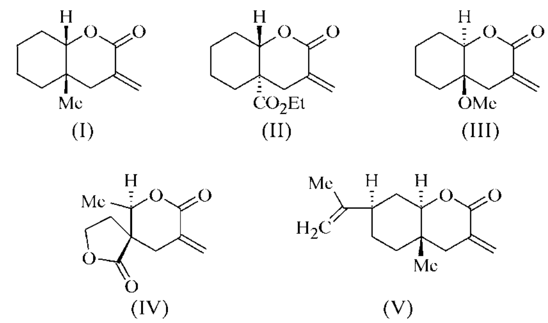
The title compound, $C_{14}H_{20}O_2$, adopts a conformation in which the *δ*-valerolactone and cyclohexane rings are almost coplanar with one another. The *γ*-methyl substituent occupies an axial position with respect to the cyclohexane ring. The *δ*-valerolactone moiety adopts an envelope arrangement, while the cyclohexane ring exists in a chair conformation.

Comment

The *α*-methylene-*δ*-valerolactone moiety is found in a wide range of natural products. Several of them, like vernolepin (Kupchan *et al.*, 1968), teucriumlactone (Nangia *et al.*, 1997) and artemisitene (Liao *et al.*, 2001), have proven antibacterial and antitumour activities. Morever, the *δ*-valerolactones are also useful substrates for the preparation of versatile biodegradable polyesters with good mechanical properties (Lou *et al.*, 2002), which may find biomedical and pharmaceutical applications (Albertsson & Varma, 2003). Enantiomerically pure *α*-methylene-*δ*-valerolactones are interesting chiral building blocks whose use in organic chemistry has been restricted by the limited availability of their synthesis (Suzuki *et al.*, 1991; Krishna *et al.*, 2004) The first synthesis by an asymmetric Michael reaction, leading to the enantioenriched species, has been described recently by us (Krawczyk & Śliwiński, 2003; Krawczyk, Śliwiński *et al.*, 2004; Krawczyk *et al.*, 2006).

The present study is a continuation of our structural investigations of optically active bicyclic *α*-methylene-*δ*-valerolactones. Four crystal structures have been published previously, namely (4a*S*,8a*S*)-4a-methyl-3-methyleneperhydrochromen-2-one, (I) (Krawczyk, Śliwiński & Wolf, 2004), ethyl *trans*-(4a*S*,8a*S*)-3-methylene-2-oxohexahydrochromene-4a-carboxylate, (II) (Krawczyk, Śliwiński *et al.*, 2004), *trans*-(4a*R*,8a*R*)-4a-methoxy-3-methyleneperhydrochromen-2-one, (III) (Wojciechowski *et al.*, 2005), and (5*R*,6*R*)-6-methyl-9-methylene-2,7-dioxa-spiro[4.5]decane-1,8-dione, (IV) (Krawczyk *et al.*, 2006). The title compound, (V), is fifth in the series. In compounds (I), (II), (III) and (V), the *δ*-valerolactone ring is condensed with the cyclohexane ring along the individual $C_\delta - C_\gamma$ single bond. The molecule of (IV) adopts an unusual spiro arrangement, with the *γ*-lactone and *δ*-lactone rings sharing the pivotal C atom and strongly twisted with respect to one another.



A view of (V) with the atom-numbering scheme is shown in Fig. 1. The *δ*-valerolactone ring adopts a conformation close to a ^5E envelope (Boeyens, 1978), with atoms O1, C1, C2, C3 and C5 almost coplanar (the average r.m.s. deviation from the mean plane is 0.04 Å) and atom C6 is situated at the flap. The Cremer & Pople (1975) puckering parameters for the ring atom sequence O1/C2/C3/C5/C6/C1 are Q = 0.529 (1) Å, θ = 52.5 (2)° and φ = 251.8 (2)°. The conformation of unsaturated *δ*-valerolactones has been investigated by Brandänge *et al.* (2003). Their *ab initio* HF/6-31G* calculations on isolated molecules showed the high conformational mobility of the ring and indicated that the energy of the envelope conformer is almost 8.5 kJ mol^{-1} higher than the theoretically most stable half-chair arrangement.

The *γ*-methyl substituent occupies an axial position with respect to both the *δ*-valerolactone and the cyclohexane rings. The molecular conformation can be defined as extended, with both rings almost coplanar with one another. A similar

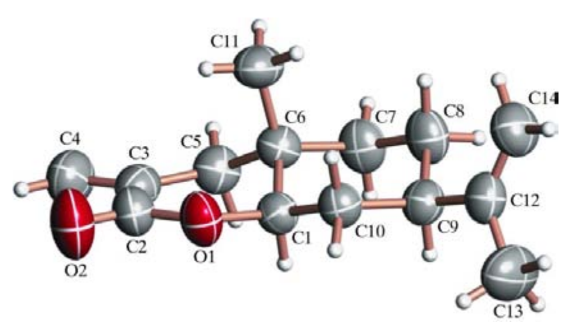


Figure 1
The molecular structure of compound (V), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

[1] Part IV: Krawczyk *et al.* (2006).

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arrangement has been observed in compounds (II) and (III). In (I), both rings are roughly perpendicular to one another, leading to the folded conformation of the molecule. A superposition of (V) on the four structures (I)–(IV), as presented in Fig. 2, clearly shows the high degree of similarity of the δ-valerolactone rings in all five compounds investigated to date.

Bond lengths in (V) are close to those observed in the related compounds (I)–(IV). In particular, two exocyclic double bonds, *viz*. C2═O2 [1.203 (2) Å] and C3═C4 [1.318 (2) Å], are shorter than similar bonds observed in the O═C—C═C group (1.222 and 1.340 Å, respectively; Allen *et al.*, 2004). These bonds are separated by a relatively long C2—C3 bond [1.495 (2) Å; standard value = 1.465 Å] and are quite coplanar, as indicated by a close to zero value of the O2—C2—C3—C4 torsion angle [−0.7 (3)°].

The *syn* conformation of the O2═C2—C3═C4 fragment in all investigated δ-valerolactones, (I)–(V), prompts electronic interactions involving the bonding σ and π orbitals and the antibonding σ^* and π^* orbitals. The most important values (Table 2 and Fig. 3) were computed by the Weinhold natural bond orbitals deletion procedure (Glendening *et al.*, 1992) for wavefunctions calculated using *GAUSSIAN03* (Frisch *et al.*, 2004) at the HF/6-311++G(d,p) level of theory for the X-ray determined coordinates. In particular, the exocyclic C3═C4 bond participates in electron-density transfer towards the carbonyl group in the π–π^* fashion (Giuffreda *et al.*, 2004), while the reverse back-donation is much weaker [60.2 and 13.3 kJ mol^{-1}, respectively, for (V)]. In comparison with the above effect, the energies of mutual *anti* σ–σ^* hyperconjugation (Weinhold, 2001) involving the endocyclic C2—O1 and vinyl C3═C4 bonds are smaller [9.8 and 4.6 kJ mol^{-1}, respectively, for (V)]. The resulting surplus of electron density accumulated on carbonyl atom O2 is back-donated towards atoms C2 and C3 through the $n\pi$(O2)–σ^*(C2—C3) stereoelectronic effect (Graczyk & Mikołajczyk, 1994).

Examination of the crystal packing of (V) indicates that the intermolecular distances are larger than the sums of the respective van der Waals radii (Bondi, 1964).

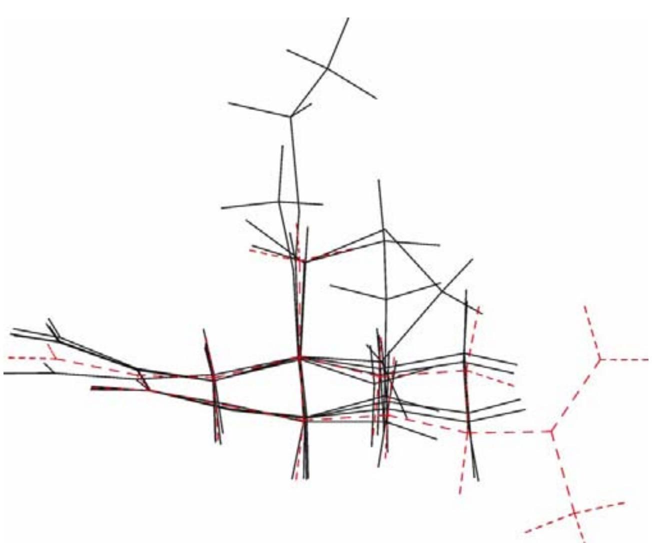

Figure 2
A superposition of structures (I)–(IV) on the title compound, (V); the latter is indicated by dashed lines. The least-squares fit is based on all common non-H atoms of the α-methylene-δ-valerolactone fragment. The largest r.m.s. deviation is 0.94 Å.

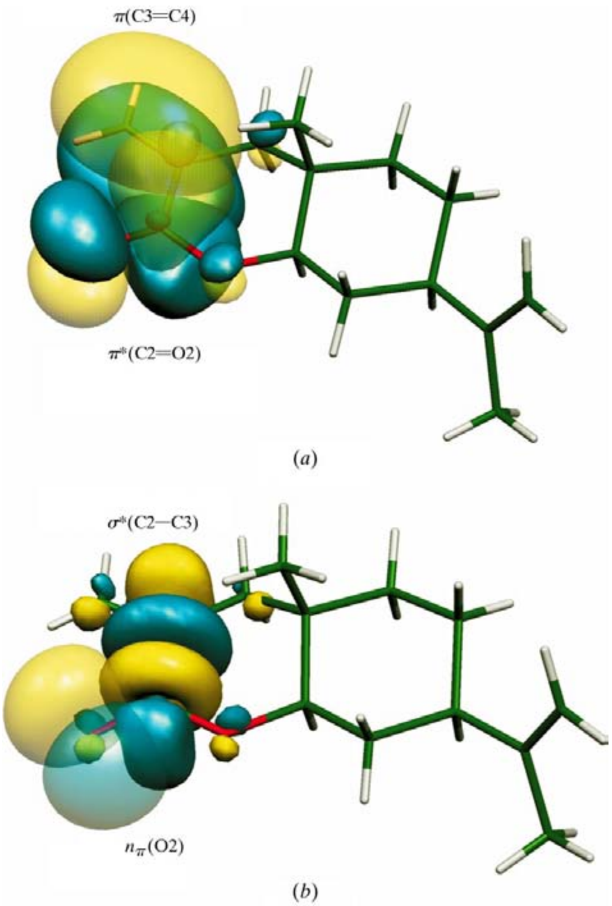

Figure 3
(*a*) Natural bond orbitals in compound (V) involved in electron-density transfer from the exocyclic C3═C4 to the C2═O2 carbonyl group. (*b*) The back-donation from the O2 n_π lone pair towards the endocyclic C2—C3 bond.

Experimental

The synthesis of enantiomerically pure α-methylene-δ-valerolactone (V) was based on a highly stereoselective Michael reaction of the chiral enamine derived from (*R*)-1-phenylethylamine and (*R*)-dihydrocarvone with dicyclohexylammonium 2-(diethoxyphosphoryl)-acrylate. Subsequent reduction of the carbonyl group in the adduct with KBH_4 was followed by lactonization of the resulting 2-(diethoxyphosphoryl)-5-hydroxyalkanoic acid. The final step in the synthesis pathway was the Horner–Wadsworth–Emmons olefination of the obtained α-phosphono-δ-valerolactone with formaldehyde. The enantiomeric purity of (V) was confirmed as higher than 0.99 by gas chromatographic analysis on a chiral column. Details of the procedure have been described elsewhere (Krawczyk & Śliwiński, 2003; Krawczyk, Śliwiński *et al.*, 2004; Krawczyk *et al.*, 2006). Colourless crystals of (V) (m.p. 397 K) were grown within 4 d by slow evaporation of a solution in a 1:1 mixture of methanol and ethyl acetate.

Crystal data

$C_{14}H_{20}O_2$	$V = 1260.53$ (3) Å^3
$M_r = 220.30$	$Z = 4$
Orthorhombic, $P2_12_12_1$	Cu $K\alpha$ radiation
$a = 6.44510$ (10) Å	$\mu = 0.60$ mm^{-1}
$b = 13.9619$ (2) Å	$T = 293$ (2) K
$c = 14.0081$ (2) Å	0.35 × 0.20 × 0.10 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer	14510 measured reflections
Absorption correction: multi-scan (*SHELXTL*; Bruker, 2003) $T_{min} = 0.876$, $T_{max} = 0.943$	2404 independent reflections
	2362 reflections with $I > 2\sigma(I)$
	$R_{int} = 0.019$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.034$	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2) = 0.097$	$\Delta\rho_{max} = 0.14$ e Å^{-3}
$S = 1.05$	$\Delta\rho_{min} = -0.14$ e Å^{-3}
2404 reflections	
211 parameters	

Table 1
Selected geometric parameters (Å, °).

O1—C2	1.3439 (17)	C2—C3	1.495 (2)
O1—C1	1.4588 (14)	C9—C12	1.5115 (19)
O2—C2	1.203 (2)	C12—C14	1.337 (2)
C3—C4	1.318 (2)	C12—C13	1.473 (2)
C3—C5	1.501 (2)		
C2—O1—C1	120.56 (10)	C4—C3—C2	117.12 (16)
O2—C2—O1	117.68 (14)	C4—C3—C5	123.34 (16)
O2—C2—C3	123.64 (14)	C2—C3—C5	119.54 (13)
O1—C2—C3	118.68 (13)		
O2—C2—C3—C4	−0.7 (3)	C3—C2—O1—C1	−7.7 (2)
O1—C2—C3—C4	−179.70 (15)	C2—O1—C1—C6	41.39 (16)
C1—C6—C5—C3	54.19 (14)	C8—C9—C12—C14	31.9 (2)
C6—C5—C3—C2	−24.85 (18)	C10—C9—C12—C14	−93.00 (17)
C5—C3—C2—O1	−0.5 (2)		

Table 2
Energy of the selected electronic interactions calculated using natural bond orbital theory.

Stabilization energies were calculated using *GAUSSIAN03* (Frisch *et al.*, 2004) at the HF/6-311++G(d,p) level of theory for X-ray determined coordinates. The standard *NBO* deletion procedure (Glendening *et al.*, 1992) was applied.

Type of interaction	Stabilization energy (kJ mol^{-1}) (I)	(II)	(III)	(IV)	(V)
σ(C3=C4)–σ*(C2—O1)	7.8	8.6	8.9	9.2	9.8
σ(C2—O1)–σ*(C3=C4)	5.3	4.7	4.8	5.0	4.6
π(C3=C4)–π*(C2=O2)	57.8	57.2	56.8	62.0	60.2
π(C2=O2)–π*(C3=C4)	13.3	13.1	13.1	14.0	13.3
n_π(O2)–σ*(C2—C3)	66.3	66.9	66.1	64.8	67.3

All H atoms, except those of the methyl groups, were located in a difference Fourier map calculated after three cycles of anisotropic refinement. Their positional and isotropic displacement parameters were allowed to refine freely [C—H = 0.945 (18)–1.029 (17) Å]. The methyl H atoms were placed in calculated positions [C—H = 0.96 (2) Å] and refined as riding. The absolute configuration was known from the method of synthesis and refinement of the Flack (1983) parameter led to a value of 0.0 (2) (Flack & Bernardinelli, 2000).

Data collection: *SMART* (Bruker, 2003); cell refinement: *SMART*; data reduction: *SAINT-Plus* (Bruker, 2003); program(s) used to solve structure: *SHELXTL* (Bruker, 2003); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

Natural bond orbital analysis was calculated at the ACK CYFRONET Kraków, Poland; support through computational grant Nos. 055/1999 and 056/1999 is gratefully acknowledged.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: AV3076). Services for accessing these data are described at the back of the journal.

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