X-ray investigations of bicyclic α-methylene-δ-valerolactones. II. (4aS,8aS)-4a-Methyl-3-methylene-perhydrochromen-2-one[1]

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The title compound, $C_{11}H_{16}O_2$, adopts a semifolded conformation with the δ-lactone and cyclohexane rings almost perpendicular to one another. The β-methyl substituent occupies an axial position with respect to the cyclohexane ring. The δ-lactone moiety adopts a slightly distorted half-chair arrangement, while the cyclohexane ring exists in an almost ideal chair conformation.

Comment

Recently, we have employed a highly stereoselective Michael reaction for the synthesis of the optically active α-methylene-δ-valerolactones (Krawczyk & Śliwiński, 2003), and we have described the crystal structure of the first compound in the series, *viz.* 3-methylene-2-oxohexahydrochromene-4a-carboxylic acid ethyl ester, (I) (Krawczyk *et al.*, 2004). In the present paper, we report the structure of the *S,S* enantiomorph of 4a-methyl-3-methyleneperhydrochromen-2-one, (II).
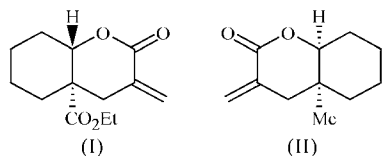
The α-methylene-δ-valerolactone moiety is present in various biologically active natural compounds. Several, such as vernolepin and vernomenin (Kupchan *et al.*, 1968), pentalenolactone E (Cane & Rossi, 1979), teucriumlactone (Nangia *et al.*, 1997), artemisitene (Liao *et al.*, 2001), and crassin (Weinheimer *et al.*, 1979; McMurry & Dushin, 1990), have been isolated and identified. These compounds have been reported to exhibit antibacterial, antifungal and, in some cases,

antitumor activities (Ekthawatchai *et al.*, 2001; Avery *et al.*, 2002). However, work on isolation and synthesis of new α-methylene-δ-valerolactones has not led to a significant number of crystal structure investigations. A search of the Cambridge Structural Database (Version 5.25, March 2004 update; Allen, 2002) shows that high-quality single-crystal X-ray structure determinations are restricted to six naturally occurring compounds. In only three structures is the cyclic δ-valerolactone moiety fused with the cycloxexane ring, *i.e.* juniperine, (III) (Maldonado *et al.*, 1985), zaluzanin B, (IV) (Toscano *et al.*, 1997), and aciculatalactone, (V) (Takaoka *et al.*, 1993). However, the system in which the δ-valerolactone ring is condensed with the cyclohexane moiety along the $C_\delta—C_\gamma$ single bond [as in (I) and (II)] is unique among crystal structures examined to date.

A view of (II), with the atom-numbering scheme, is shown in Fig. 1. The overall molecular conformation can be defined as semifolded, with the δ-lactone and cyclohexane rings almost perpendicular to one another. The β-methyl substituent occupies an axial position with respect to the cyclohexane ring. The δ-lactone ring adopts a slightly distorted half-chair arrangement, while the cyclohexane ring exists in an almost ideal chair conformation. The upper flap of the latter ring points away from the δ-lactone ring. The resulting molecular conformation is stabilized by two weak intramolecular interactions (Desiraju & Steiner, 1999) between axial H atoms at atoms C8 and C10, and atoms O1 and C4, which bear substantial negative charges (−0.64 e and −0.32 e); the respective interatomic distances are 2.60 (2) and 2.65 (2) Å. Atomic charges derived from electrostatic potentials were calculated using *GAUSSIAN*03 (Frisch *et al.*, 2003) at the MP2/6-31+G(*d,p*) level for the X-ray determined coordinates. Grid points were selected according to the *CHELPG* procedure of Breneman & Wiberg (1990).

The X-ray determined structures in which the α-methylene-δ-valerolactone moiety is condensed with the cyclohexane ring, as in (III), (IV) and (V), adopt a fully folded conformation, with the cyclohexane flap pointing towards the δ-lactone ring. The only compound existing in the extended conformation is (I). The superimposition of the title structure, (II), on to the structure of (I), as presented in Fig. 2, clearly
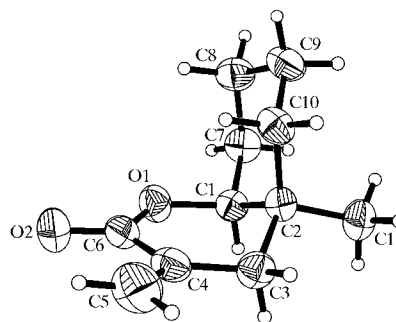
(I)   (II)

Figure 1
The molecular structure of (II). Displacement ellipsoids are drawn at the 50% probability level.

[1] Part I: Krawczyk, Śliwiński & Wolf (2004). *Synlett*, pp. 1995–1999.
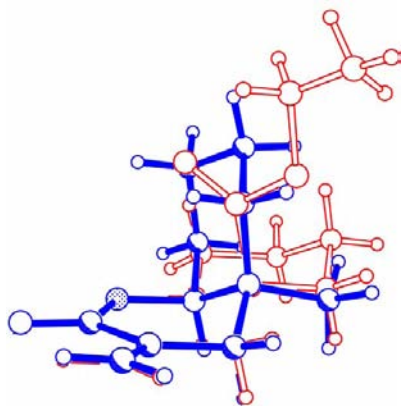
organic compounds

Figure 2
A superimposition of the structures of (I) and (II). Compound (II) is plotted with filled bonds.

shows the similarity of their δ-lactone rings and the substantial difference between the positions of the cyclohexane rings. The least-squares fit was based on all common non-H atoms of the α-methylene-δ-valerolactone fragment; the r.m.s. deviation was 0.87 Å.

The bond lengths in (II) (Table 1) are close to those observed in the related compounds (I) and (III)–(V). In particular, the two exocyclic double bonds [C6=O2 = 1.2083 (15) Å and C4=C5 = 1.3153 (19) Å] are shorter than similar bonds observed in the C=O—C=C moiety [1.222 and 1.340 Å, respectively; Allen *et al.*, 1992]. Those bonds are separated by a relatively long C4—C6 bond [1.4919 (18) Å; the standard value is 1.465 Å] and are not strictly coplanar, as indicated by the non-zero value of the O2=C6—C4=C5 torsion angle [−7.8 (2)°]. These results suggest that the highly polar character of the carbonyl group hinders π electron density delocalization within the O2=C6—C4=C5 moiety.

In the crystal structure, the endocyclic O1 and exocyclic O2 atoms are involved in close contacts with the surrounding H atoms of the cyclohexane ring and the methyl group, respectively. According to the definition of Desiraju and Steiner (Steiner, 1997; Steiner & Desiraju, 1998), these contacts could be classified as weak C—H···O hydrogen bonds. Details are summarized in Table 2.

Experimental

The synthesis of enantiomerically pure compound (II) was achieved by employing a highly stereoselective Michael reaction of the chiral imine derived from (*R*)-1-phenylethylamine and 2-methylcyclohexanone 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 (II) as higher than 0.99 was confirmed by GC analysis on a chiral column. Details of the synthesis procedure have been described elsewhere (Krawczyk & Śliwiński, 2003; Krawczyk *et al.*, 2004). Colourless crystals (m.p. 344 K) were grown over 8 d by slow evaporation from a 1:1 mixture of methanol and ethyl acetate.

Table 1
Selected geometric parameters (Å, °).

O1—C6	1.3319 (15)	C2—C10	1.5361 (14)
O1—C1	1.4698 (13)	C3—C4	1.4939 (16)
O2—C6	1.2083 (15)	C4—C5	1.3153 (19)
C1—C7	1.5162 (15)	C4—C6	1.4919 (18)
C1—C2	1.5222 (13)	C7—C8	1.5225 (18)
C2—C3	1.5294 (15)	C8—C9	1.515 (2)
C2—C11	1.5324 (15)	C9—C10	1.5314 (17)
C5—C4—C6	118.43 (14)	O2—C6—O1	117.70 (12)
C5—C4—C3	123.44 (14)	O2—C6—C4	124.01 (12)
C6—C4—C3	118.11 (9)	O1—C6—C4	118.26 (9)
O1—C1—C2—C3	53.59 (11)	C10—C9—C8—C7	−55.17 (15)
C1—C2—C3—C4	−56.38 (12)	C9—C8—C7—C1	55.34 (15)
C2—C1—O1—C6	−30.29 (14)	C8—C7—C1—C2	−54.31 (14)
C3—C4—C6—O1	−8.15 (15)	C7—C1—C2—C10	51.54 (12)
C4—C6—O1—C1	5.71 (15)	O2—C6—C4—C5	−7.8 (2)
C6—C4—C3—C2	35.04 (14)	C9—C10—C2—C11	69.64 (13)
C1—C2—C10—C9	−51.39 (13)	C7—C1—C2—C11	−70.85 (12)
C2—C10—C9—C8	54.14 (14)		

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
C11—H113···O2^i	0.97 (2)	2.69 (2)	3.599 (2)	157 (2)
C9—H91···O1^{ii}	1.00 (2)	2.68 (2)	3.677 (2)	175 (2)

Symmetry codes: (i) $\frac{1}{2} + x, \frac{1}{2} - y, 2 - z$; (ii) $\frac{3}{2} - x, 1 - y, \frac{1}{2} + z$.

All H atoms were located on a difference Fourier map calculated after three cycles of anisotropic refinement. The H-atom positional and isotropic displacement parameters were allowed to refine freely [C—H = 0.94 (3)–1.04 (2) Å]. Refinement of the Flack (1983) para-

meter is in agreement with the absolute configuration as assigned from the mechanism of the highly stereoselective Michael reaction (Krawczyk & Śliwiński, 2003). An attempt to refine the inverted structure led to a Flack parameter of 1.0 (2).

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*.

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