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Dimethyl 6-methoxy-4aβ-methyl-9-oxo-1,2,3,4,4a,9,10,10aβ-octahydrophenanthrene-1,1-dicarboxylate

Swastik Mondal,[a] Monika Mukherjee,[a]* Arnab Roy[b] and Debabrata Mukherjee[b]

[a]Department of Solid State Physics, Indian Association for the Cultivation of Science, Jadavpur, Calcutta 700 032, India, and [b]Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta 700 032, India
Correspondence e-mail: sspmm@mahendra.iacs.res.in

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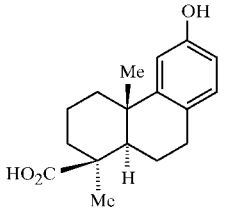
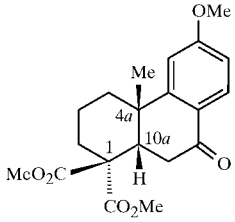
In the title tricyclic keto-diester, $C_{20}H_{24}O_6$, a potential intermediate in the synthesis of bioactive podocarpic acid, the outer cyclohexane ring (in a chair conformation) is *cis* fused to the central cyclohexanone ring (in a half-chair conformation). The conformational analysis of the compound, investigated by semi-empirical quantum mechanical AM1 calculations, shows a good agreement with the X-ray structure, except for the orientation of the methyl, methoxyphenyl and methoxycarbonyl substituents.

Comment

Podocarpic acid, (I), and its derivatives have been successfully used in medicinal chemistry, particularly as inhibitors of plant cell growth (Parish & Miles, 1984), the influenza virus (Staschke *et al.*, 1998), and antileukemic and anti-inflammatory agents (Soderberg *et al.*, 1996). Several diterpenoid



(I)



(II)

quinone taxodiones and maytenoquinones obtained from podocarpic acid also exhibit anticancer activity (Burnell *et al.*, 1988). In order to develop a new stereocontrolled route for the synthesis of (I) using easily accessible 7-methoxy-1-tetralone as the starting material, the title tricyclic keto-diester, (II), has been synthesized. This keto-diester possesses the requisite structural features of a potential intermediate in a total synthesis of (I). To establish the regio- and stereospecificities of the reaction and to build up a hierarchy for such systems, the X-ray structure analysis of (II) was undertaken.

The molecules of (II) consist of three fused six-membered rings (Fig. 1). The cyclohexane ring (ring *A*; atoms C10a/C1–C4/C4a), with puckering parameters (Cremer & Pople, 1975) Q = 0.552 (2) Å, q_2 = 0.022 (2) Å, q_3 = 0.552 (2) Å and θ = 2.3 (2)°, adopts a chair conformation. Due to the C9═O6 double bond and the adjacent essentially planar fused phenyl ring (ring *C*; atoms C4b/C5–C8/C8a), the environment of atom C9 is planar, and hence the cyclohexanone ring (ring *B*; atoms C4a/C4b/C8a/C9/C10/C10a), with puckering parameters Q = 0.485 (2) Å, q_2 = 0.402 (2) Å, q_3 = 0.273 (3) Å and θ = 55.8 (3)°, displays a half-chair conformation. Atom C10a is −0.646 (3) Å from the least-squares plane through the remaining endocyclic atoms of ring *B*. The torsion angle C11—C4a—C10a—H1 is 53.1°, revealing a *cis* geometry at the *A*/*B* ring junction; the dihedral angles between the planar parts of rings *A*/*B* and *B*/*C* are 68.6 (8) and 3.7 (8)°, respectively.

The two methoxycarbonyl groups at atom C1 are in almost antiperiplanar and *gauche* orientations with respect to the C4a—C10a bond [C13—C1—C10a—C4a = −167.7 (2)° and C15—C1—C10a—C4a = 72.7 (2)°]. The extended conformations of the two O═C—O—CH_3 moieties at C1 are established by the torsion angles C14—O3—C13—C1 of 179.3 (2)° and C16—O5—C15—C1 of −178.5 (2)°. The observed bond lengths and angles (Table 1) agree well with the corresponding values reported for related tricyclic structures (Lazar *et al.*, 2002; Stanković *et al.*, 2002; Cambie *et al.*, 1998).

The crystal structure exhibits two intramolecular C—H···O hydrogen bonds (Table 2) which influence the conformations of rings *A* and *B*. A packing diagram, displaying the intermolecular C—H···O contacts, is shown in Fig. 2.

Semi-empirical AM1 molecular-orbital calculations on (II) with the energy profile as a function of the torsion angle C4—C4a—C10a—C10 show the heat of formation energy to be −226.23 kcal mol^{-1} (1 kcal mol^{-1} = 4.184 kJ mol^{-1}). A

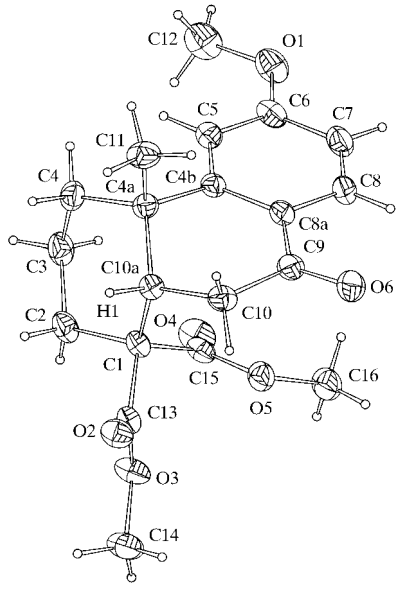


Figure 1
A view of the molecule of (II), with displacement ellipsoids at the 30% probability level. H atoms are shown as small spheres of arbitrary radii.

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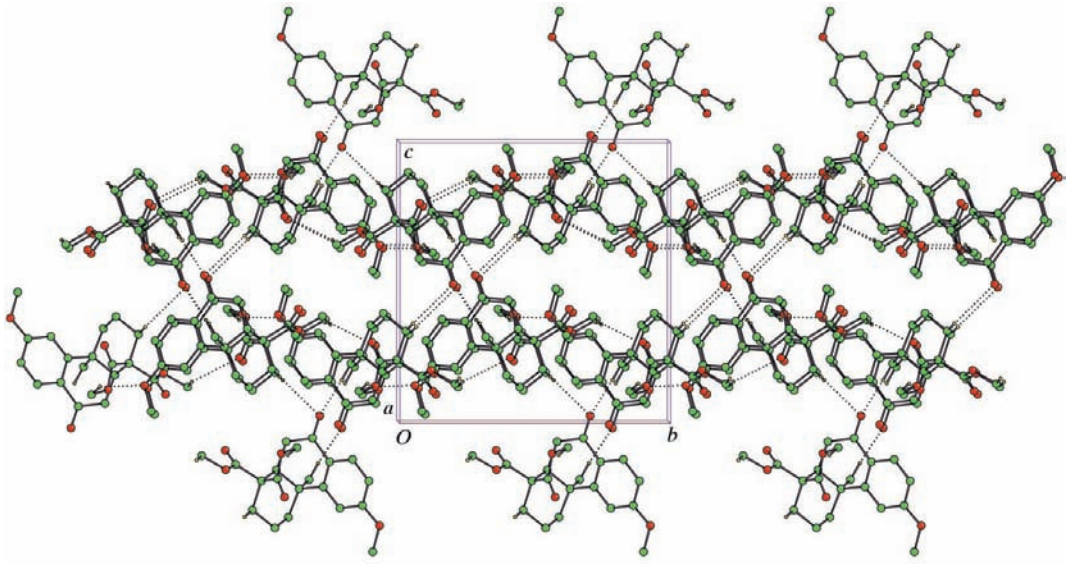

Figure 2
Packing diagram for (II), viewed down the *a* axis. Intermolecular C—H···O contacts are indicated by dotted lines. H atoms not participating in the hydrogen bonding have been omitted for clarity.

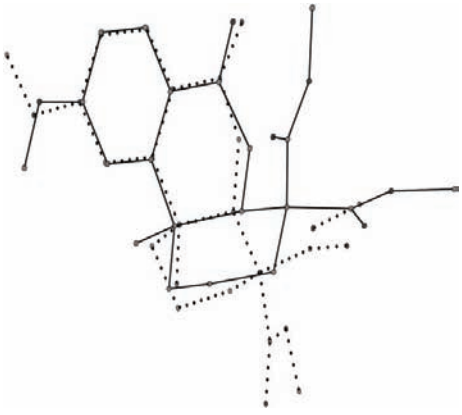

Figure 3
Comparison of the AM1-optimized (dotted lines) and X-ray stuctures for (II).

comparison of the molecular conformations of the AM1-optimized and X-ray structures (Fig. 3) reveals a fairly good agreement between the two in respect of the tricyclic skeleton of the molecule. For the substituents at atoms C1, C4a and C6, however, the solid-state conformations differ noticeably from the AM1-calculated conformations. The methyl group at the *A*/*B* ring junction, C4a, is antiperiplanar with respect to the C1—C10a bond in (II) [C11—C4a—C10a—C1 = 168.5 (2)°] and *gauche* in the AM1-optimized structure (corresponding torsion angle = −73.4°). Compared to the crystallographic study, the methoxy moiety at C6 is rotated about the C6—O1 bond by 173.7° in the AM1-calculated structure. Similarly, the orientations of the C13—O2 and C15—O4 carbonyl groups with respect to the C1—C10a bond are markedly different in the AM1-calculated structure than those in the solid state. The differences in the molecular conformations between the X-ray and energy-minimized structures for compound (II) are presumably due to intermolecular forces involving the side-chain atoms, which influence the packing of the molecules in the crystalline state.

Experimental

A solution of 1-(4,4-dimethoxycarbonylbutyl)-7-methoxy-1-methyl-1,4-dihydronaphthalen-4-one (0.5 g, 1.39 mmol; prepared from 7-methoxy-1-tetralone) in dry *tert*-butanol (5 ml) was added dropwise, under a nitrogen atmosphere at 283 K, to a stirred solution of potassium *tert*-butoxide [prepared from potassium (0.027 g, 0.69 mmol)] in *tert*-butanol (5 ml). After stirring at room temperature for 16 h, the reaction mixture was diluted with water (20 ml) and extracted with ether (3 × 25 ml). The ether extract was washed with water, dried and concentrated. The residue was crystallized from a mixture of methyl acetate and light petroleum (1:1) to furnish the title keto-diester, (II) (yield: 0.389 g, 76%; m.p. 431 K). Elemental analysis for $C_{20}H_{24}O_6$: C 66.65, H 6.71%; found: C 66.47, H 6.83%.

Crystal data

$C_{20}H_{24}O_6$
M_r = 360.39
Orthorhombic, $P2_12_12_1$
a = 9.491 (4) Å
b = 13.541 (5) Å
c = 14.051 (6) Å
V = 1805.8 (12) Å^3
Z = 4
D_x = 1.326 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 4990 reflections
θ = 2.4–24.9°
μ = 0.10 mm^{-1}
T = 293 (2) K
Block, colourless
0.40 × 0.30 × 0.25 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
14 200 measured reflections
2041 independent reflections
1913 reflections with $I > 2\sigma(I)$
R_{int} = 0.016
θ_{max} = 26.0°
$h = -11 \rightarrow 11$
$k = -16 \rightarrow 16$
$l = -17 \rightarrow 17$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0633P)^2 + 0.1483P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.035$	$(\Delta/\sigma)_{max} = 0.024$
$wR(F^2) = 0.096$	$\Delta\rho_{max} = 0.31$ e Å^{-3}
$S = 1.10$	$\Delta\rho_{min} = -0.15$ e Å^{-3}
2041 reflections	
239 parameters	
H-atom parameters constrained	

Table 1
Selected geometric parameters (Å, °).

O2—C13	1.194 (2)	C3—C4	1.511 (4)
O4—C15	1.189 (3)	C4—C4a	1.536 (3)
O6—C9	1.213 (3)	C4a—C4b	1.527 (3)
C1—C2	1.547 (3)	C4a—C10a	1.555 (3)
C1—C10a	1.558 (3)	C9—C10	1.508 (3)
C2—C3	1.511 (3)	C10—C10a	1.527 (3)
C2—C1—C10a	109.87 (17)	O6—C9—C10	120.2 (2)
C4b—C4a—C10a	109.79 (15)	C8a—C9—C10	118.17 (17)
C4—C4a—C10a	108.71 (15)	C10—C10a—C4a	110.10 (15)
O6—C9—C8a	121.6 (2)	C4a—C10a—C1	114.18 (15)
C11—C4a—C10a—C10	−60.7 (2)	C15—C1—C10a—C4a	72.7 (2)
C11—C4a—C10a—C1	168.49 (17)	C14—O3—C13—C1	179.35 (18)
C13—C1—C10a—C4a	−167.70 (15)	C16—O5—C15—C1	−178.45 (16)

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

D—H···A	D—H	H···A	D···A	D—H···A
C3—H3B···O4	0.97	2.52	3.102 (3)	118
C10—H10B···O2	0.97	2.56	3.128 (3)	117

Theoritical calculations for the energy-minimized structure of (II) were carried out with the *MOPAC* program package (Stewart, 1988), which included the AM1 Hamiltonian (Dewar, 1985). The inital molecular geometries were adopted from standard data incorporated in the package and subsequently fully optimized using an energy gradient method. The refined value of the Flack (1983) parameter [0.1 (8)] was inconclusive (Flack & Bernardinelli, 2000), hence the Friedel equivalents were merged prior to the final refinement. H atoms of the methyl groups, the benzene ring and the secondary CH_2 groups were placed geometrically and treated as riding. The H atom on C10a was found in a difference map. The methyl H atoms were constrained using the HFIX 137 instruction in *SHELXL*97 (Sheldrick, 1997), with the C—H distance fixed at 0.96 Å and the H—C—H angle tetrahedral. Other H atoms were treated as riding, with C—H distances in the range 0.93–0.97 Å.

Data collection: *SMART* (Bruker, 1998); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 1998); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *WinGX* (Farrugia, 1999) and *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *SHELXL*97 and *PARST* (Nardelli, 1995).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1615). Services for accessing these data are described at the back of the journal.

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