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Cyclobutane Structures Fused to a 13-Membered Ring

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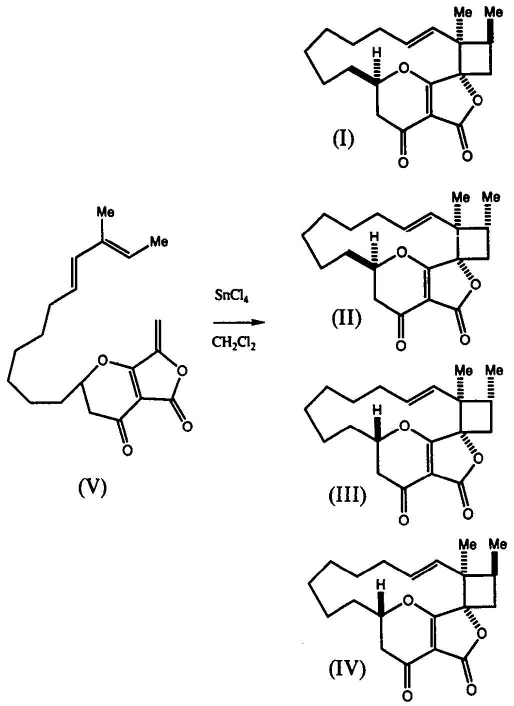
Abstract

The structures of two diastereomers, (1_R_*,6a_S_*,14a_S_*,14b_R_*,13_E_)- and (1_R_*,6a_R_*,14a_R_*,14b_S_*,13_E_)-1,14a-dimethyl-1,2,6,6a,7,8,9,10,11,12-decahydro-4_H_,5_H_,14a_H_-6a,14c-epoxy-3-cyclobuta[1′,2′:1,2]cyclopentadeca[2,3,4-_b_,_c_]furan-4,5-dione, in which a cyclobutane moiety is fused to a 13-membered ring are reported for the first time. The two diastereomers exhibit similar conformations except for the configuration about the methyl carbon (C15).

Comment

In the course of our synthetic studies on the antibiotic okilactomycin, we have found the unexpected formation of intramolecular [2 + 2] cycloadducts (Takeda, Shimotani, Yoshii & Yamaguchi, 1992). This cycloaddition was performed from compound (V), a precursor of okilactomycin. The cycloaddition of (V), carried out at low temperature in CH_2Cl_2 in the presence of $SnCl_4$, afforded four diastereomeric [2 + 2] cycloadducts [(I)–(IV)]. Cyclobutane structures fused to a 13-membered ring, previously unreported, were confirmed by X-ray crystallographic analysis on (I) and (II).



Figs. 1 and 2 show _ORTEP_ (Johnson, 1976) drawings of molecules (I) and (II), with the respective crystallographic numbering systems. The two diastereomers exhibit similar conformations except for the configuration at C15 [_trans_ in (I) and _cis_ in (II) relative to C16]. In the 13-membered ring, the most significant difference found between these two molecules was in the torsion angles C21—C22—C23—C24 and C23—C24—C6—O1 [−165.3 (3) in (I), 59 (1)° in (II) and 49.2 (3) in

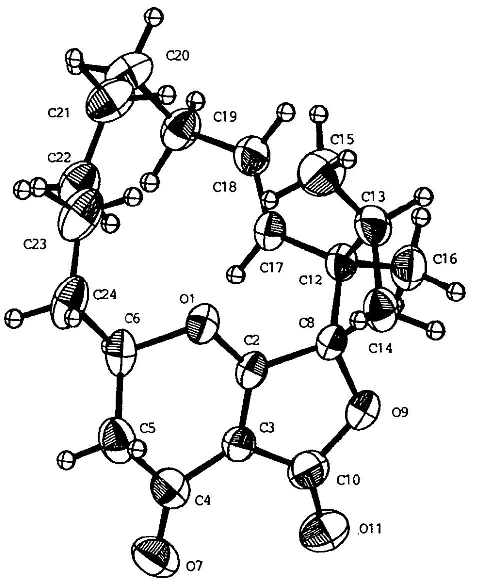


Fig. 1. _ORTEP_ (Johnson, 1976) drawing of (I). Ellipsoids are drawn at the 50% probability level while isotropic H-atom thermal parameters are represented by spheres of arbitrary size.

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(I), −125.3 (6)° in (II)]. The cyclobutane ring is almost planar, with a maximum displacement out of the least-squares plane of 0.125 (9) Å for C14 in (I) and 0.097 (3) Å for C12 in (II).

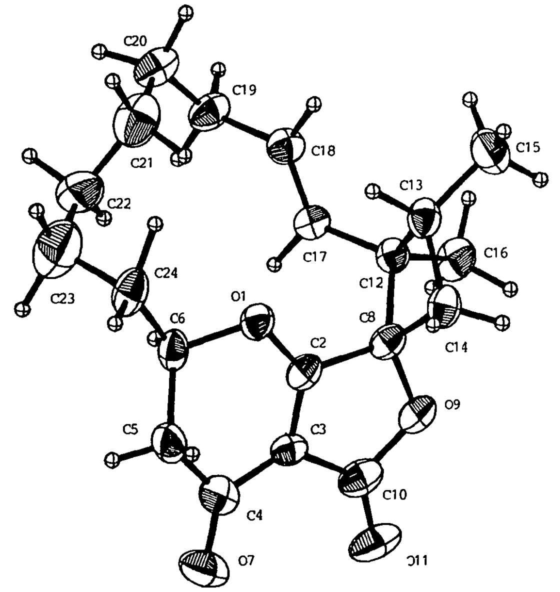

Fig. 2. *ORTEP* (Johnson, 1976) drawing of (II). Ellipsoids are drawn at the 30% probability level while isotropic H-atom thermal parameters are represented by spheres of arbitrary size.

Experimental

Compound (I)

Crystal data

$C_{20}H_{26}O_4$
$M_r = 330.42$
Monoclinic
$P2_1/a$
$a = 15.870$ (1) Å
$b = 8.061$ (1) Å
$c = 14.879$ (1) Å
$\beta = 112.46$ (1)°
$V = 1759.1$ (5) Å^3
$Z = 4$
$D_x = 1.248$ Mg m^{-3}
Cu $K\alpha_1$ radiation
$\lambda = 1.5405$ Å
Cell parameters from 20 reflections
$\theta = 28.5$–$30.5°$
$\mu = 0.653$ mm^{-1}
$T = 297$ K
Needle
0.18 × 0.06 × 0.50 mm
Clear

Data collection

Rigaku AFC-5 diffractometer
2θ scans
Absorption correction: none
2997 measured reflections
2608 independent reflections
1997 observed reflections [$F > 3\sigma(F)$]
$R_{\rm int} = 0.026$
$\theta_{\rm max} = 60°$
$h = -17 \rightarrow 17$
$k = 0 \rightarrow 9$
$l = 0 \rightarrow 16$
3 standard reflections monitored every 200 reflections intensity variation: <3%

Refinement

Refinement on F^2
Final $R(F) = 0.0485$
$wR(F^2) = 0.0478$
$S = 1.493$
1997 reflections
321 parameters
All H-atom parameters refined
Calculated weights $w = 1/[\sigma^2(F) + 0.013F^2]$
$(\Delta/\sigma)_{\rm max} = 0.17$
$\Delta\rho_{\rm max} = 0.188$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.238$ e Å^{-3}
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 1. *Fractional atomic coordinates and equivalent isotropic thermal parameters* (Å^2) *for* (I)

$$U_{\rm eq} = \tfrac{1}{3}\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$U_{\rm eq}$
O1	0.6799 (1)	0.3531 (2)	0.1806 (1)	0.044 (1)
C2	0.6943 (1)	0.4650 (3)	0.1229 (1)	0.039 (1)
C3	0.6471 (1)	0.4833 (3)	0.0273 (1)	0.040 (1)
C4	0.5806 (1)	0.3616 (3)	−0.0294 (2)	0.048 (1)
C5	0.5736 (2)	0.2190 (4)	0.0333 (2)	0.056 (1)
C6	0.5882 (1)	0.2754 (3)	0.1349 (2)	0.048 (1)
O7	0.5374 (1)	0.3671 (2)	−0.1169 (1)	0.064 (1)
C8	0.7686 (1)	0.5915 (3)	0.1616 (1)	0.041 (1)
O9	0.7573 (1)	0.6846 (2)	0.0749 (1)	0.054 (1)
C10	0.6854 (1)	0.6246 (4)	−0.0041 (2)	0.053 (1)
O11	0.6653 (1)	0.6893 (2)	−0.0823 (1)	0.080 (1)
C12	0.7733 (1)	0.6977 (3)	0.2517 (1)	0.041 (1)
C13	0.8604 (1)	0.5965 (4)	0.3147 (2)	0.050 (1)
C14	0.8654 (1)	0.5295 (4)	0.2197 (2)	0.051 (1)
C15	0.8010 (2)	0.8771 (4)	0.2402 (2)	0.059 (1)
C16	0.8533 (2)	0.4633 (5)	0.3826 (2)	0.067 (1)
C17	0.6881 (1)	0.6977 (3)	0.2737 (2)	0.041 (1)
C18	0.6833 (1)	0.7125 (3)	0.3596 (2)	0.049 (1)
C19	0.5944 (2)	0.7158 (4)	0.3748 (2)	0.055 (1)
C20	0.5872 (2)	0.5844 (4)	0.4461 (2)	0.067 (1)
C21	0.6116 (2)	0.4099 (4)	0.4275 (2)	0.069 (1)
C22	0.5633 (2)	0.3456 (4)	0.3246 (2)	0.063 (1)
C23	0.6077 (2)	0.1897 (4)	0.3061 (2)	0.073 (1)
C24	0.5805 (2)	0.1402 (4)	0.2010 (2)	0.068 (1)

Table 2. *Geometric parameters* (Å, °) *for* (I)

O1—C2	1.323 (3)	C10—O11	1.201 (3)
O1—C6	1.489 (3)	C12—C17	1.508 (4)
C2—C3	1.339 (3)	C12—C15	1.540 (4)
C2—C8	1.498 (3)	C12—C13	1.569 (3)
C3—C10	1.449 (4)	C13—C16	1.507 (5)
C3—C4	1.452 (3)	C13—C14	1.543 (4)
C4—O7	1.218 (3)	C17—C18	1.314 (4)
C4—C5	1.510 (4)	C18—C19	1.512 (5)
C5—C6	1.511 (4)	C19—C20	1.533 (5)
C6—C24	1.502 (5)	C20—C21	1.511 (5)
C8—O9	1.442 (3)	C21—C22	1.518 (4)
C8—C14	1.531 (3)	C22—C23	1.516 (5)
C8—C12	1.568 (4)	C23—C24	1.510 (5)
O9—C10	1.377 (3)		
C2—O1—C6	111.8 (1)	O11—C10—O9	120.2 (2)
O1—C2—C3	126.8 (2)	O11—C10—C3	131.6 (2)
O1—C2—C8	121.3 (2)	O9—C10—C3	108.2 (2)
C3—C2—C8	111.9 (2)	C17—C12—C15	110.0 (2)
C2—C3—C10	107.2 (2)	C17—C12—C8	115.5 (2)
C2—C3—C4	122.1 (2)	C17—C12—C13	121.9 (2)
C10—C3—C4	130.1 (2)	C15—C12—C8	109.9 (2)
O7—C4—C3	125.7 (2)	C15—C12—C13	109.3 (2)
O7—C4—C5	122.9 (2)	C8—C12—C13	88.4 (2)
C3—C4—C5	111.3 (2)	C16—C13—C14	114.1 (2)
C4—C5—C6	111.7 (2)	C16—C13—C12	119.8 (2)
O1—C6—C24	108.4 (2)	C14—C13—C12	88.6 (2)
O1—C6—C5	109.5 (2)	C8—C14—C13	90.7 (2)
C24—C6—C5	114.6 (2)	C18—C17—C12	126.9 (2)
O9—C8—C2	101.5 (1)	C17—C18—C19	123.4 (2)
O9—C8—C14	115.5 (2)	C18—C19—C20	114.3 (2)

O9—C8—C12	115.5 (2)	C21—C20—C19	115.1 (3)
C2—C8—C14	117.9 (2)	C20—C21—C22	115.8 (2)
C2—C8—C12	118.3 (2)	C23—C22—C21	112.0 (2)
C14—C8—C12	89.1 (1)	C24—C23—C22	116.0 (2)
C10—O9—C8	111.2 (2)	C6—C24—C23	115.1 (2)

Compound (II)

Crystal data

$C_{20}H_{26}O_4$
$M_r = 330.42$
Monoclinic
$A2/a$
$a = 28.875\ (4)$ Å
$b = 6.820\ (2)$ Å
$c = 19.572\ (2)$ Å
$\beta = 108.56\ (1)°$
$V = 3653\ (1)$ Å^3
$Z = 8$
$D_x = 1.201$ Mg m^{-3}
Cu $K\alpha_1$ radiation
$\lambda = 1.5405$ Å
Cell parameters from 20 reflections
$\theta = 28.5–30.5°$
$\mu = 0.629$ mm^{-1}
$T = 297$ K
Needle
$0.08 \times 0.08 \times 0.40$ mm
Clear

Data collection

Rigaku AFC-5 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
3155 measured reflections
2724 independent reflections
1643 observed reflections $[F > 3\sigma(F)]$
$R_{\rm int} = 0.050$
$\theta_{\rm max} = 60°$
$h = -32 \rightarrow 32$
$k = 0 \rightarrow 7$
$l = 0 \rightarrow 22$
3 standard reflections monitored every 200 reflections intensity variation: <3%

Refinement

Refinement on F^2
Final $R(F) = 0.0683$
$wR(F^2) = 0.0610$
$S = 1.995$
1643 reflections
321 parameters
All H-atom parameters refined
Calculated weights $w = 1/[\sigma^2(F)+0.005F^2]$
$(\Delta/\sigma)_{\rm max} = 0.36$
$\Delta\rho_{\rm max} = 0.112$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.109$ e Å^{-3}
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 3. *Fractional atomic coordinates and equivalent isotropic thermal parameters* (Å^2) *for* (II)

$$U_{\rm eq} = \tfrac{1}{3}\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$U_{\rm eq}$
O1	0.3894 (1)	0.4916 (4)	0.2523 (1)	0.059 (1)
C2	0.4334 (1)	0.4658 (6)	0.3004 (2)	0.054 (2)
C3	0.4764 (1)	0.4680 (7)	0.2890 (2)	0.059 (2)
C4	0.4809 (2)	0.5268 (8)	0.2202 (3)	0.077 (2)
C5	0.4318 (2)	0.5780 (10)	0.1662 (3)	0.080 (2)
C6	0.3903 (2)	0.4615 (9)	0.1775 (2)	0.066 (2)
O7	0.5191 (1)	0.5443 (6)	0.2073 (2)	0.107 (2)
C8	0.4382 (1)	0.4290 (7)	0.3774 (2)	0.056 (2)
O9	0.4906 (1)	0.4094 (5)	0.4093 (1)	0.068 (1)
C10	0.5135 (2)	0.4308 (8)	0.3581 (3)	0.071 (2)
O11	0.5573 (1)	0.4176 (6)	0.3749 (2)	0.094 (1)
C12	0.4065 (1)	0.2605 (7)	0.3941 (2)	0.053 (1)
C13	0.3724 (1)	0.4250 (8)	0.4061 (2)	0.065 (2)
C14	0.4133 (2)	0.5756 (9)	0.4144 (3)	0.067 (2)
C15	0.4358 (2)	0.1523 (10)	0.4631 (3)	0.078 (3)
C16	0.3499 (3)	0.4070 (15)	0.4671 (4)	0.099 (3)
C17	0.3852 (1)	0.1153 (7)	0.3344 (2)	0.054 (2)
C18	0.3396 (1)	0.0577 (8)	0.3122 (2)	0.064 (2)
C19	0.3185 (2)	−0.0906 (9)	0.2543 (3)	0.074 (2)
C20	0.2716 (2)	−0.0243 (11)	0.1964 (4)	0.085 (3)
C21	0.2764 (2)	0.1716 (14)	0.1617 (4)	0.108 (4)
C22	0.3085 (2)	0.1569 (13)	0.1143 (4)	0.106 (4)
C23	0.3159 (3)	0.3496 (16)	0.0779 (5)	0.137 (5)
C24	0.3389 (2)	0.5186 (10)	0.1295 (3)	0.077 (2)

Table 4. *Geometric parameters* (Å, °) *for* (II)

O1—C2	1.330 (5)	C10—O11	1.204 (6)
O1—C6	1.488 (6)	C12—C17	1.506 (6)
C2—C3	1.330 (8)	C12—C15	1.536 (7)
C2—C8	1.492 (7)	C12—C13	1.559 (8)
C3—C4	1.448 (9)	C13—C14	1.534 (8)
C3—C10	1.456 (7)	C13—C16	1.536 (11)
C4—O7	1.214 (8)	C17—C18	1.309 (7)
C4—C5	1.513 (8)	C18—C19	1.497 (8)
C5—C6	1.511 (10)	C19—C20	1.533 (8)
C6—C24	1.534 (8)	C20—C21	1.525 (12)
C8—O9	1.446 (5)	C21—C22	1.508 (14)
C8—C14	1.540 (8)	C22—C23	1.541 (14)
C8—C12	1.567 (7)	C23—C24	1.537 (12)
O9—C10	1.374 (8)		
C2—O1—C6	111.4 (4)	O11—C10—O9	120.1 (5)
O1—C2—C3	127.8 (5)	O11—C10—C3	131.7 (6)
O1—C2—C8	119.9 (4)	O9—C10—C3	108.2 (4)
C3—C2—C8	112.3 (4)	C17—C12—C15	110.0 (4)
C2—C3—C4	121.5 (4)	C17—C12—C13	117.9 (3)
C2—C3—C10	107.0 (5)	C17—C12—C8	116.3 (4)
C4—C3—C10	130.9 (5)	C15—C12—C13	114.2 (5)
O7—C4—C3	125.2 (5)	C15—C12—C8	109.8 (4)
O7—C4—C5	122.8 (6)	C13—C12—C8	86.7 (4)
C3—C4—C5	111.9 (5)	C14—C13—C16	118.2 (5)
C6—C5—C4	112.7 (5)	C14—C13—C12	89.8 (4)
O1—C6—C5	109.5 (4)	C16—C13—C12	120.2 (5)
O1—C6—C24	104.5 (5)	C13—C14—C8	88.5 (4)
C5—C6—C24	115.9 (5)	C18—C17—C12	125.1 (5)
O9—C8—C2	101.5 (4)	C17—C18—C19	125.2 (5)
O9—C8—C14	115.9 (3)	C18—C19—C20	114.2 (5)
O9—C8—C12	116.3 (3)	C21—C20—C19	113.7 (5)
C2—C8—C14	117.3 (4)	C22—C21—C20	112.2 (7)
C2—C8—C12	117.4 (3)	C21—C22—C23	115.4 (8)
C14—C8—C12	89.3 (4)	C24—C23—C22	115.5 (7)
C10—O9—C8	111.0 (3)	C6—C24—C23	110.1 (6)

Data collection: *AFD* (Rigaku Corporation, 1985*a*). Data reduction: *FASE* (Yamaguchi, 1993). Program(s) used to solve structure: *SAPI*85 (Yao, Zheng, Qian, Han, Gu & Fan, 1985). Program(s) used to refine structure: *RCRYSTAN* (Rigaku Corporation, 1985*b*). Molecular graphics: *ACV* (Stardent Computer Inc., 1990). Software used to prepare material for publication: *XPACK* (Yamaguchi, 1987). Initial structure analysis was performed by a continuous process related to the data collection and using the fully automatic procedure *FASE* (Yamaguchi, 1993). The structures were solved by direct methods, included in *FASE*. Further refinement was by full-matrix least squares.

Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and complete geometry have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 71202 (27 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: AS1054]

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Non-Natural 14-Hydroxy Steroids. III. (+)-Methyl 17β-Benzoyloxy-14β-hydroxy-3β-isopropenyl-1,7-dioxo-5β-androstan-19-oate

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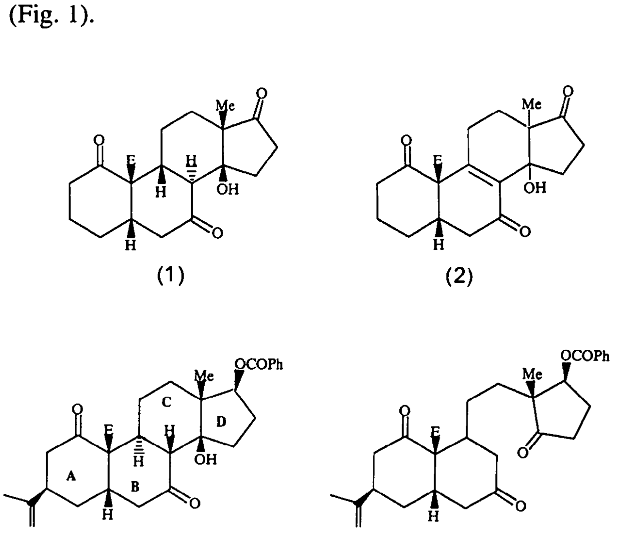
Abstract

This non-natural steroid compound bears an isopropenyl substituent at C3, a methoxycarbonyl group at C10 and a benzoyloxy group at C17. The relative stereochemistry is *cis* for the *A*/*B* ring junction, *anti* between MeO$_2$C—C10 and H—C9, *trans* for the *B*/*C* ring junction, *syn* between H—C8 and HO—C14 and *cis* for the *C*/*D* ring junction, and a chair-boat-chair conformation is adopted.

Comment

We have reported previously the crystallographic analyses of non-natural 14β-hydroxy steroid compounds (1) (Michel, Ruel & Michel-Dewez, 1989) and (2) (Drouin, Ruel & Michel, 1991). Relative to non-natural 14β-hydroxy steroids, racemic compound (1) has an opposite (β) H—C9 stereochemistry and a C8=C9 double bond characterizes the racemic compound (2). Compound (3) has all of the eight asymmetric carbon centers with the stereochemistry normally found in natural cardiotonic steroids (Lociuro, Tsai & Wiesner, 1988). Furthermore, the C3 and C17 substituents mimic the natural alkoxy and pyrone groups and will potentially allow the synthesis of many more steroid derivatives. This new steroid compound (3) was synthesized from the caesium carbonate-catalyzed aldol reaction on a triketone (4) in 32% yield (Ruel & Deslongchamps, 1992) and, importantly, is enantiomerically pure $\{[\alpha]_D\ +61.5^\circ\ (c\,1,\ \mathrm{CHCl_3})\}$. The present crystallographic analysis was undertaken to confirm the structure of this new steroid (3) (Fig. 1).



(1) (2)

(3) (4)

Fig. 1. Molecular formulae (E = COOCH$_3$).

The crystal structure shows that ring *A* has a chair conformation with the C3-isopropenyl substituent equatorial, while ring *B* adopts a boat conformation. Ring *C* has a chair conformation and ring *D* forms an α-envelope. The *A*/*B* and *C*/*D* ring junctions are *cis*, the *B*/*C* junction is *trans*, the H9 proton being *anti* to the methoxycarbonyl substituent at C10. According to stereoelectronic control (Deslongchamps, 1983), the aldolic condensation must proceed through a conformation where ring *B* in compound (4) adopts a boat conformation (Lavallée & Deslongchamps, 1988). Consequently, the product (3) obtained under such conditions was expected to adopt the conformation confirmed by the crystal structure: ring *B* adopts the boat conformation (Fig. 2). This molecular arrangement allows the C3-isopropenyl substituent to be equatorial, avoiding the unfavorable 1,3-diaxial interaction with H—C5. The overall conformation is very similar to the previously reported non-natural steroid (1). The *A* ring is oriented such as to give a global conformation more extended than the usual globular shape of cardenolides (Kálmán, Argay, Scharfenberg-Pfeiffer, Höhne & Ribár, 1991, and references therein), where *A*/*B* and *C*/*D* ring junctions are also *cis*. The benzoate fragment is relatively planar; the torsion angle O5—C24—C25—C26 is −7.8 (6)° and the average aromatic bond distance is 1.388 (16) Å. Best-plane calculations on ring *D* show that C14 is 0.54 (1) Å outside the plane defined by C13, C15,