

3 β -Benzyloxy-17 α -hydroxy-5 β ,14 β -isocard-20(22)-enolide*

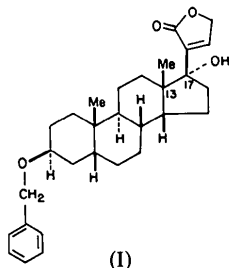
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Abstract. C₃₀H₄₀O₄, triclinic, *P*1, *Z* = 1, *a* = 9.204 (1), *b* = 11.977 (1), *c* = 6.278 (1) Å, α = 102.90 (2), β = 105.43 (2), γ = 101.39 (2)°, *V* = 625.51 Å³, *F*(000) = 252, *D*_c = 1.233, *D*_m = 1.231 Mg m⁻³; *R* = 0.038 and *R*_w = 0.041 for 2376 observed reflexions. The molecular structure confirms the stereospecificity of the novel synthetic procedure through which the compound was obtained. An intramolecular O—H...O hydrogen bond is indicated between the hydroxyl and carbonyl groups with O...O = 2.799 (4) Å.

Introduction. The present cardenolide was synthesized by a short and efficient new method developed by Marini-Bettolo, Tsai, Tsai & Wiesner (1981), who expected the structure to be that shown in (I) but were not certain about the configuration at C(17). The structural study was undertaken to clear this ambiguity and thus verify the important question of the stereospecificity of the new method. The X-ray results have confirmed the expected structure and the validity of the synthetic pathway.



Crystals of this compound, obtained from a mixture of chloroform and diethyl ether, are colourless transparent plates, m.p. 470–471 K; the one used for data collection was of dimensions 0.47 × 0.37 × 0.20 mm and was mounted normal to the large face. The space group was identified unambiguously as *P*1 with *Z* = 1 on the basis of precession photographs and the fact that the compound was known to be optically active. The crystal density was measured by flotation in a mixture of CCl₄ and toluene at 297 K.

The X-ray measurements were carried out on a Nonius CAD-4 diffractometer using Ni-filtered Cu *K* α radiation, $\lambda(K\alpha_1)$ = 1.54050 Å, at a take-off angle of 3.0°. The cell parameters were derived from a least-squares fit to the angular settings of 12 well centred reflexions with 40 < θ < 63°. The intensities were measured by ω -2 θ scans for ω = (0.7 + 0.14 × tan θ)° at a maximum ω speed of 4° min⁻¹ for the

Table 1. Fractional coordinates ($\times 10^4$) and equivalent isotropic thermal parameters (Å²) for non-hydrogen atoms

$$B_{eq} = \frac{1}{3} \pi^2 \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$$

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> _{eq}
C(1)	5181 (3)	12042 (3)	5585 (5)	3.1 (0.1)
C(2)	6338 (4)	11814 (3)	4317 (5)	3.4 (0.1)
C(3)	7602 (3)	11364 (3)	5658 (5)	3.0 (0.1)
C(4)	6850 (3)	10264 (3)	6213 (5)	2.9 (0.1)
C(5)	5748 (3)	10513 (2)	7594 (4)	2.7 (0.1)
C(6)	5105 (4)	9405 (3)	8270 (5)	3.4 (0.1)
C(7)	3949 (3)	8418 (3)	6196 (5)	3.3 (0.1)
C(8)	2610 (3)	8868 (2)	4972 (4)	2.5 (0.1)
C(9)	3215 (3)	9962 (2)	4229 (5)	2.5 (0.1)
C(10)	4420 (3)	10989 (2)	6326 (5)	2.6 (0.1)
C(11)	1829 (3)	10342 (3)	2908 (6)	3.4 (0.1)
C(12)	612 (4)	9313 (3)	906 (5)	3.5 (0.1)
C(13)	-25 (2)	8253 (2)	1711 (5)	2.8 (0.1)
C(14)	1362 (3)	7856 (2)	2995 (5)	2.7 (0.1)
C(15)	1908 (4)	7199 (3)	1067 (6)	3.8 (0.1)
C(16)	437 (4)	6730 (3)	-1111 (6)	4.6 (0.1)
C(17)	-901 (4)	7124 (3)	-423 (5)	3.4 (0.1)
C(18)	-1040 (3)	8581 (3)	3172 (6)	3.6 (0.1)
C(19)	3633 (4)	11510 (3)	8027 (6)	3.8 (0.1)
C(20)	-1859 (4)	6179 (3)	259 (6)	3.8 (0.1)
C(21)	-1452 (4)	5347 (3)	1178 (7)	4.8 (0.1)
C(22)	-2749 (5)	4699 (4)	1763 (8)	6.8 (0.2)
C(23)	-3512 (4)	6082 (4)	86 (7)	5.2 (0.1)
C(24)	10026 (4)	12148 (3)	8721 (6)	4.2 (0.1)
C(25)	10808 (3)	13050 (3)	11068 (6)	3.3 (0.1)
C(26)	12230 (4)	13866 (3)	11555 (6)	3.9 (0.1)
C(27)	12950 (4)	14679 (3)	13738 (7)	5.0 (0.1)
C(28)	12246 (5)	14690 (4)	15416 (7)	5.2 (0.1)
C(29)	10820 (5)	13874 (4)	14931 (7)	4.8 (0.1)
C(30)	10122 (4)	13061 (3)	12787 (7)	4.1 (0.1)
O(1)	-4026 (3)	5196 (3)	945 (6)	6.9 (0.1)
O(2)	-4362 (3)	6642 (3)	-714 (6)	6.8 (0.1)
O(3)	8542 (2)	12318 (2)	7706 (4)	3.2 (0.1)
O(4)	-1895 (3)	7370 (2)	-2352 (4)	4.9 (0.1)

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strong reflexions and at lower speeds for the weaker ones. Each scan was extended by 25% at each end of the scan for measurement of the background. Three standard reflexions, monitored every 50 min of exposure time, showed only random variations within $\pm 4\%$ of their mean values. Data collection was limited to $2\theta < 155.9^\circ$; 2636 independent reflexions were measured and, of these, 2376 (90%) with $I > 2\sigma(I)$ were considered observed. The net intensities were corrected for Lorentz and polarization effects but not for absorption ($\mu = 0.595 \text{ mm}^{-1}$).

The structure was determined from a combination of direct and Fourier methods. An E map evaluated with 299 reflexions whose $|E| \geq 1.50$ and $R_K = 0.16$ contained 15 peaks with the expected geometry for rings A , B , C and atom $O(3)$, as well as several other peaks. However, the rest of the molecule could not be identified unambiguously and had to be constructed in stages from Fourier maps. The correct model with all

34 C and O atoms gave an R index of 0.29. After refinement to $R = 0.09$ the H atoms, except that of the OH group, were located in a difference map. Refinement by block-diagonal least squares was then continued with isotropic thermal parameters for the 39 H atoms until the mean and maximum parameter shifts were reduced to 0.14σ and 0.62σ , respectively. The quantity minimized was $\sum w(|F_o| - |F_c|)^2$, with $w = \{1 + [(|F_o| - 5)/20]^2\}^{-1}$ where the constants were chosen to make $\sum w(F_o - F_c)^2$ independent of $|F_o|$. In the final cycle, $R = 0.038$ for the observed reflexions and $R_w = 0.041$. The final difference map was featureless and within -0.15 and $0.12 \text{ e } \text{Å}^{-3}$. All calculations were carried out with the NRC system of programs (Ahmed, Hall, Pippy & Huber, 1973). The scattering-factor curves were those of Hanson, Herman, Lea & Skillman (1964) for C and O, and of Stewart, Davidson & Simpson (1965) for H. The refined atomic parameters are listed in Tables 1 and 2.*

Table 2. Fractional coordinates ($\times 10^3$) and isotropic B values (Å^2) for H atoms

	x	y	z	B
H(1,1)	443 (4)	1234 (3)	461 (6)	4.3 (0.7)
H(1,2)	569 (4)	1268 (3)	697 (6)	3.9 (0.7)
H(2,1)	577 (4)	1119 (3)	276 (6)	4.0 (0.8)
H(2,2)	674 (4)	1249 (3)	391 (6)	4.4 (0.8)
H(3)	828 (3)	1116 (2)	475 (4)	1.9 (0.5)
H(4,1)	766 (4)	993 (3)	705 (5)	3.5 (0.7)
H(4,2)	618 (3)	961 (3)	466 (5)	2.4 (0.6)
H(5)	643 (3)	1112 (3)	909 (5)	2.9 (0.7)
H(6,1)	604 (4)	915 (3)	907 (6)	4.0 (0.7)
H(6,2)	451 (4)	962 (3)	937 (6)	3.8 (0.7)
H(7,1)	352 (4)	778 (3)	674 (6)	4.5 (0.8)
H(7,2)	458 (3)	814 (3)	514 (5)	2.6 (0.6)
H(8)	211 (3)	911 (3)	616 (5)	2.7 (0.6)
H(9)	381 (3)	973 (3)	308 (5)	2.3 (0.6)
H(11,1)	135 (4)	1072 (3)	405 (6)	4.0 (0.8)
H(11,2)	218 (4)	1095 (3)	223 (5)	3.4 (0.7)
H(12,1)	108 (4)	907 (3)	-28 (6)	3.6 (0.7)
H(12,2)	-32 (4)	964 (3)	20 (6)	4.9 (0.8)
H(14)	91 (3)	725 (2)	365 (5)	2.3 (0.5)
H(15,1)	224 (4)	647 (3)	143 (6)	4.9 (0.8)
H(15,2)	271 (4)	776 (3)	78 (6)	4.7 (0.8)
H(16,1)	16 (5)	584 (4)	-182 (7)	6.7 (1.1)
H(16,2)	71 (4)	708 (3)	-243 (6)	4.9 (0.9)
H(18,1)	-136 (4)	799 (3)	394 (6)	4.3 (0.8)
H(18,2)	-213 (5)	864 (4)	201 (7)	5.6 (1.0)
H(18,3)	-58 (5)	936 (4)	450 (7)	6.6 (1.0)
H(19,1)	295 (4)	1088 (3)	849 (6)	4.0 (0.8)
H(19,2)	301 (3)	1201 (3)	750 (5)	3.7 (0.6)
H(19,3)	446 (4)	1199 (3)	962 (6)	4.3 (0.8)
H(21)	-35 (5)	521 (4)	158 (7)	7.6 (1.2)
H(22,1)	-305 (5)	385 (4)	105 (8)	8.0 (1.2)
H(22,2)	-249 (5)	486 (4)	351 (7)	7.0 (1.1)
H(24,1)	997 (5)	1136 (4)	897 (7)	6.9 (1.0)
H(24,2)	1074 (5)	1231 (4)	762 (8)	6.7 (1.2)
H(26)	1272 (4)	1390 (3)	1036 (6)	5.4 (0.9)
H(27)	1399 (5)	1530 (4)	1417 (7)	6.3 (1.0)
H(28)	1275 (4)	1525 (3)	1697 (6)	5.1 (0.9)
H(29)	1025 (4)	1388 (3)	1611 (6)	4.4 (0.8)
H(30)	910 (5)	1243 (3)	1241 (7)	5.5 (0.9)

Discussion. A perspective view of the molecular structure, drawn in the absolute configuration of the natural product, is presented in Fig. 1. As expected, the lactone ring, the two methyl groups $C(18)$ and $C(19)$, and atom $O(3)$ are β , thus confirming the stereospecificity of the new synthetic procedure.

The bond lengths and angles, not corrected for thermal vibration, are shown in Fig. 2. The 22 $C(sp^3)$ - $C(sp^3)$ bonds occur in the range 1.511 (5)–1.568 (4) Å and have a mean value of 1.536 Å. The two longest, $C(13)$ - $C(17)$ 1.568 (4) and $C(9)$ - $C(10)$ 1.561 (4) Å, are associated with highly substituted atoms. The two $C(sp^3)$ - $C(sp^2)$ bonds of the lactone ring are comparable in length [1.469 (7) and 1.475 (6) Å] but considerably shorter than the two exocyclic bonds $C(17)$ - $C(20)$ 1.505 (5) and $C(24)$ - $C(25)$ 1.508 (5) Å. The aromatic C-C bonds of ring F are of normal lengths 1.371 (6)–1.390 (6) Å.

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36564 (13 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

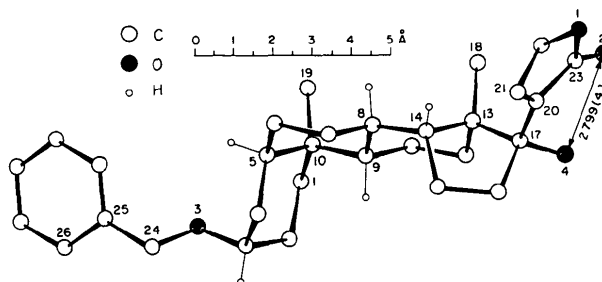


Fig. 1. Perspective view of the molecular structure.

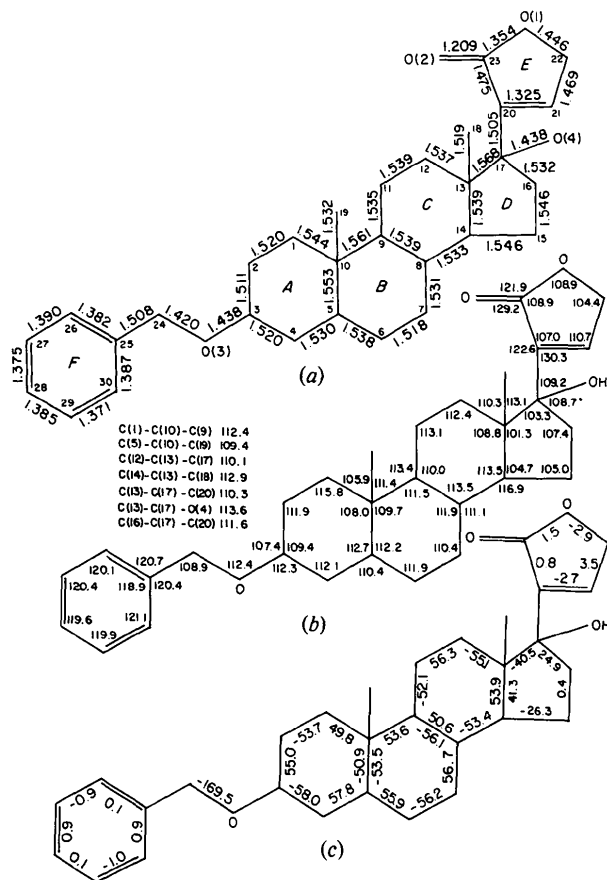


Fig. 2. (a) Bond lengths (Å), (b) valence angles (°) and (c) torsion angles (°). The ranges of their estimated standard deviations are 0.004–0.006 Å, 0.2–0.4° and 0.6–0.8°, respectively.

Four of the C–O single bonds have lengths 1.420 (4), 1.438 (4), 1.438 (4) and 1.446 (6) Å, comparable to the mean value of 1.43 (1) Å for a paraffinic C–O (*Molecular Structures and Dimensions*, 1972), while C(23)–O(1) which is adjacent to the carbonyl group is considerably shorter [1.354 (6) Å]. The 39 C–H bonds range from 0.95 to 1.10 ($\sigma = 0.03$ –0.05) Å.

Rings *A*, *B* and *C* have the chair conformation, as indicated by the torsion angles in Fig. 2(c). While slight distortions of ring *C* were reported for (20*R*)-3-hydroxy-22-methylene-5 β -card-14-enolide where C(14)–C(15) was a double bond (Rohrer, Duax & Fullerton, 1976), and for 5 β -hydroxygitoxigenin which contained an OH substituent at C(14) (Przybylska & Ahmed, 1979), there is no such distortion in ring *C* of the present structure. The maximum asymmetry parameters (Duax, Weeks & Rohrer, 1976) for the *A*, *B* and *C* rings are $\Delta C_2[C(2)–C(3)] = 6.4$, $\Delta C_2[C(5)–C(6)] = 2.9$ and $\Delta C_2[C(9)–C(11)] = 4.1^\circ$, respectively. The *D* ring has an envelope conformation, $\Delta C_s[C(13)] = 1.1^\circ$, with atoms C(14), C(15), C(16) and C(17) forming a plane, $\chi^2 = 1.28$, while C(13) is 0.652 (3) Å from that plane. The four atoms C(21),

C(20), C(23) and O(1) of the lactone ring also are coplanar, $\chi^2 = 3.03$, while C(22) of the ring and O(2) lie slightly off the plane at distances of -0.049 (5) and 0.043 (4) Å respectively. The C atoms of the benzene ring are coplanar with $\chi^2 = 8.0$.

The ring junctions are *A/B cis*, *B/C trans* and *C/D cis* (Fig. 1) as observed for cardenolides (Karle & Karle, 1969; Gilardi & Flippen, 1973; Przybylska & Ahmed, 1979). The dihedral angles between the mean planes of the rings are *A–B* = 62.5, *B–C* = 2.8, *C–D* = 69.9, *D–E* = 92.4 and *A–F* = 91.2 ($\sigma = 0.6$)°.

The only possible hydrogen bonding in the structure would involve the H atom of the hydroxyl group but that atom has not been located. However, O(4) is >3.5 Å away from any other O atom except O(2) of the same molecule where O(4)···O(2) = 2.799 (4) Å, which is indicative of a possible intramolecular hydrogen bond. A very weak peak (H) of $0.11 e \text{ \AA}^{-3}$ is present in the final difference map with O(4)–H 1.02, H···O(2) 1.86 Å, and C(17)–O(4)–H 98 and O(4)–H···O(2) 157°, giving acceptable geometry for a hydrogen bond. Also, H is only 0.23 Å from the O(4)O(2)C(23) plane and 0.16 Å from the O(2)O(4)C(17) plane.

The molecule is oriented with its length approximately along the [101] diagonal and extends beyond one unit cell. Its shortest intermolecular contacts are 2.33 (6) for H···H, 2.66 (4) for O···H and 2.79 (4) Å for C···H which are reasonable van der Waals distances.

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