

Crystal Structure of Cordialin A Acetate, an Unusual Dammarane Triterpene Hemiacetal

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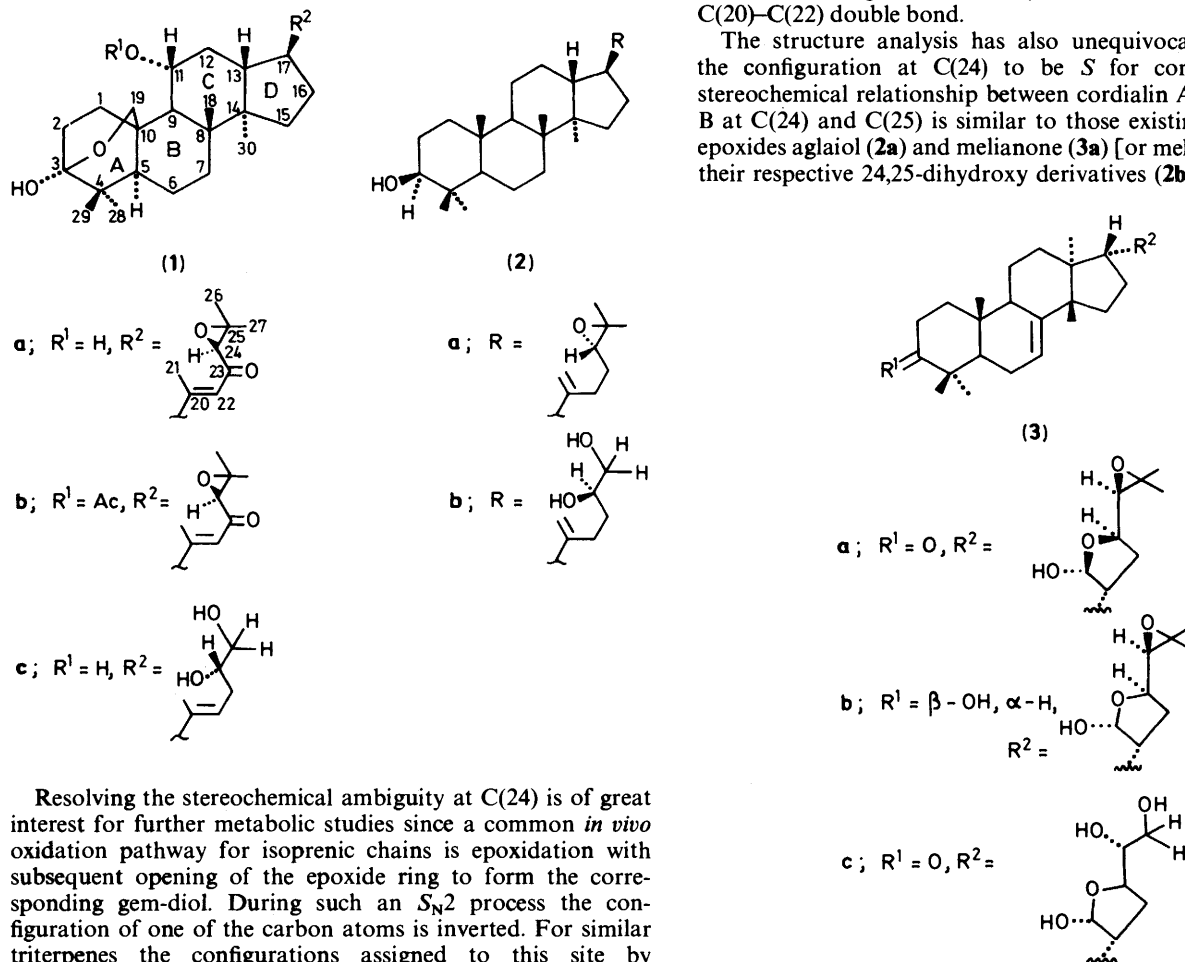
The structure of cordialin A has unambiguously been determined to be (24*S*)-24,25-epoxy-11 α -hydroxydammar-20(22)*en*-23-one 3,19-hemiacetal by an *X*-ray analysis of its C(11) acetate. Crystals are orthorhombic, space group *P*2₁2₁2₁, *a* = 6.431(4), *b* = 20.530(5), *c* = 21.777(8) Å, *Z* = 4. The ring conformations adopted are: for A, a very distorted boat; for B, a flattened chair; for C, a puckered chair; and for D, a distorted envelope.

Recently two new dammarane-type triterpenes, cordialin A (**1a**) and cordialin B (**1c**), have been identified and reported with structures assigned *via* spectral interpretation.¹ The molecules are particularly interesting because they were reported to possess both a C(11) hydroxy group and a C(3), C(19) hemiacetal bridge. Neither of these features is frequently encountered in triterpenes and, to our knowledge, they have never before been observed in the same molecule. A double bond was reported at C(20)–C(22) and the configuration at C(24) was not assigned.

interpretation of spectral data and by chemical interconversions have been a subject of controversy.² For these reasons a single crystal *X*-ray analysis of cordialin A acetate (**1b**) was undertaken. This is one of only five dammarane-type triterpenes to be studied crystallographically.^{3–5}

The relative configuration and solid-state conformation of cordialin A acetate is shown in the Figure; the absolute configuration follows from the known configuration of all other dammarane triterpenes. The molecule does indeed possess an α -oriented oxygen function at C(11), a C(3), C(19) hemiacetal bridge across the β -face of the A ring, and a C(20)–C(22) double bond.

The structure analysis has also unequivocally established the configuration at C(24) to be *S* for cordialin A. The stereochemical relationship between cordialin A and cordialin B at C(24) and C(25) is similar to those existing between the epoxides aglaiol (**2a**) and melianone (**3a**) [or melianol (**3b**)] and their respective 24,25-dihydroxy derivatives (**2b**)⁶ and (**3c**).^{2a,7}



Resolving the stereochemical ambiguity at C(24) is of great interest for further metabolic studies since a common *in vivo* oxidation pathway for isoprenic chains is epoxidation with subsequent opening of the epoxide ring to form the corresponding gem-diol. During such an *S_N2* process the configuration of one of the carbon atoms is inverted. For similar triterpenes the configurations assigned to this site by

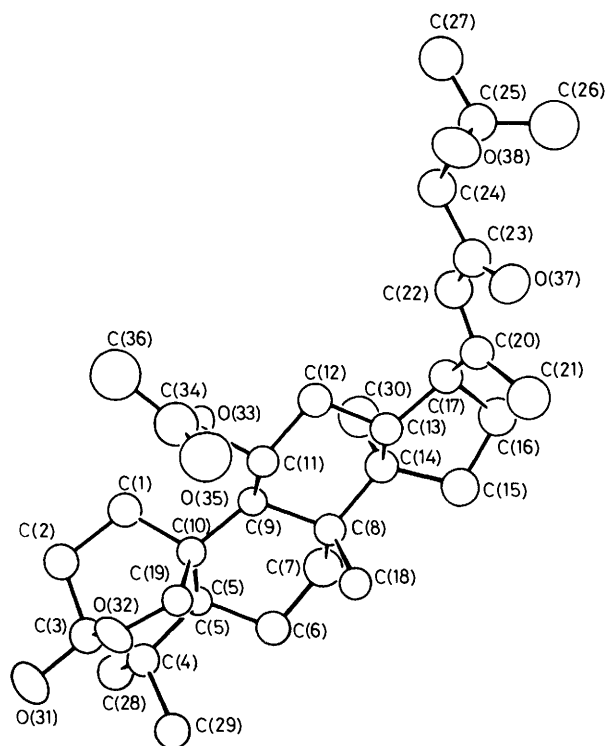


Figure. Perspective view of cordialin A acetate with the numbering scheme; hydrogen atoms have been omitted for clarity.

In both of the last mentioned cases the configuration at C(24) for the dihydroxy derivatives has been reported as opposite to that for the epoxides. On the basis of similar deductions, and since the two cordialins, A and B, have been isolated from the same plant, one can assume that the latter (**1c**) is the product of an epoxide opening and therefore the configuration at C(24) should be opposite to that in (**1a**). However, because (**1a**) possesses a C(23) carbonyl function and (**1c**) does not, the assignment at C(24) for (**1c**) must be *S*.

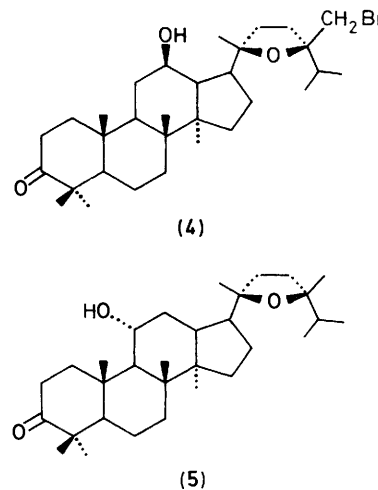
With regard to melianone and related compounds, it is felt that the absolute configuration of the side chain has yet to be confirmed unequivocally.

The A ring of cordialin A acetate, as well as the other two rings formed by the hemiacetal bridge, adopts a very distorted boat conformation. Instead of the ideal zero degree torsion angles about the C(1)–C(2) and C(4)–C(5) bonds, the A ring displays angles of 9.8 and 20.2°, respectively. Benulin⁸ and rhuslactone⁹ are triterpenes each of which possesses an A ring hemiacetal bridge across the β -face and neither of which possesses a C(11) substituent. Both exhibit a significantly less distorted boat conformation for ring A than is found for (**1b**). For example, in benulin the twist from an eclipsed conformation about the C(4)–C(5) bond is only *ca.* 15° while in (**1b**) it is *ca.* 28°. This distortion is probably attributable to the proximity of C(1) and the C(11) substituent in (**1b**).

With respect to this, it is instructive to compare the A ring conformations of 31-bromo-20,24-epoxy-12-hydroxy-24-methyl-dammaran-3-one⁴ (**4**) and 20,24-epoxy-11-hydroxy-24-methyl-dammaran-3-one³ (**5**) (alnuserol), unbridged dammaranes which have been previously studied crystallographically. The only essential difference between molecules of (**4**) and (**5**) is that (**4**) has a C(12) β -hydroxy group and (**5**) has a C(11) α -hydroxy group, yet they adopt radically different A ring conformations. In (**4**) the A ring is in a symmetrical chair form which suffers only minor flattening at C(4) to relieve the steric interaction between C(19) and C(29). In (**5**), however, the A ring is in a very distorted twist-boat form with a small

Table 1. Fractional atomic co-ordinates ($\times 10^4$) for the non-hydrogen atoms, with estimated standard deviations in parentheses.

Atom	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>
C(1)	5 089(16)	4 472(4)	8 461(4)
C(2)	4 809(16)	4 992(5)	8 953(4)
C(3)	6 119(15)	4 790(5)	9 521(4)
C(4)	5 280(14)	4 182(4)	9 830(4)
C(5)	4 862(13)	3 669(4)	9 305(4)
C(6)	5 142(15)	2 978(4)	9 528(4)
C(7)	4 624(16)	2 487(5)	9 011(4)
C(8)	6 204(14)	2 569(4)	8 473(4)
C(9)	6 111(13)	3 293(4)	8 229(4)
C(10)	6 134(13)	3 853(4)	8 722(4)
C(11)	7 663(13)	3 352(4)	7 679(4)
C(12)	7 233(15)	2 857(5)	7 165(4)
C(13)	7 208(13)	2 170(4)	7 415(4)
C(14)	5 668(15)	2 094(4)	7 949(4)
C(15)	5 879(16)	1 363(5)	8 076(4)
C(16)	5 956(16)	1 052(5)	7 427(4)
C(17)	6 698(16)	1 599(5)	6 974(4)
C(18)	8 402(15)	2 421(4)	8 737(4)
C(19)	8 316(15)	4 083(5)	8 922(4)
C(20)	8 390(15)	1 442(5)	6 540(4)
C(21)	10 174(19)	1 030(6)	6 774(5)
C(22)	8 404(16)	1 704(5)	5 974(4)
C(23)	9 948(18)	1 638(5)	5 493(5)
C(24)	9 343(16)	1 975(5)	4 919(5)
C(25)	8 709(17)	1 612(5)	4 367(5)
C(26)	8 784(21)	879(6)	4 355(6)
C(27)	7 239(20)	1 923(6)	3 929(6)
C(28)	3 240(15)	4 315(4)	10 166(4)
C(29)	6 820(15)	3 955(4)	10 314(4)
C(30)	3 382(16)	2 191(5)	7 726(5)
O(31)	6 305(11)	5 285(3)	9 953(3)
O(32)	8 182(10)	4 660(3)	9 283(3)
O(33)	7 444(11)	3 987(3)	7 393(3)
C(34)	9 210(17)	4 273(5)	7 185(5)
O(35)	10 898(13)	4 075(4)	7 307(4)
C(36)	8 677(22)	4 852(6)	6 798(6)
O(37)	11 630(12)	1 371(4)	5 552(3)
O(38)	10 730(12)	1 918(4)	4 401(3)



C(10)–C(1)–C(2)–C(3) torsion angle (9.7°), again implicating the steric intervention of the C(11) substituent. Interestingly, the twist about the C(4)–C(5) bond in this unbridged system is only 33°, very similar to that found in (**1b**).

While rings B and C both adopt chair conformations, ring B is overall flattened (mean endocyclic dihedral angle 51.9°) and ring C is substantially puckered (mean endocyclic dihedral angle

Table 2. Selected interatomic distances (Å) and valency angles (°), with estimated standard deviations in parentheses.

(a) Bond lengths			
C(1)–C(2)	1.524(13)	C(9)–C(11)	1.564(12)
C(1)–C(10)	1.546(12)	C(10)–C(19)	1.544(13)
C(2)–C(3)	1.553(13)	C(11)–C(12)	1.537(12)
C(3)–C(4)	1.517(13)	C(12)–C(13)	1.512(12)
C(3)–O(32)	1.450(12)	C(13)–C(14)	1.535(12)
C(4)–C(5)	1.577(12)	C(13)–C(17)	1.549(12)
C(5)–C(6)	1.510(12)	C(14)–C(15)	1.532(13)
C(5)–C(10)	1.556(11)	C(15)–C(16)	1.551(13)
C(6)–C(7)	1.549(13)	C(16)–C(17)	1.569(13)
C(7)–C(8)	1.559(13)	C(19)–O(32)	1.424(11)
C(8)–C(9)	1.580(12)	C(24)–C(25)	1.473(14)
C(8)–C(14)	1.542(12)	C(24)–O(38)	1.443(12)
C(9)–C(10)	1.574(11)	C(25)–O(38)	1.446(13)
(b) Valency angles			
C(2)–C(1)–C(10)	111.6(7)	C(3)–O(32)–C(19)	114.0(7)
C(1)–C(2)–C(3)	108.0(8)	C(23)–C(24)–C(25)	121.7(9)
C(2)–C(3)–C(4)	112.3(8)	C(23)–C(24)–O(38)	117.3(8)
C(2)–C(3)–O(32)	105.3(7)	C(25)–C(24)–O(38)	59.4(6)
C(4)–C(3)–O(32)	109.0(7)	C(24)–C(25)–C(26)	120.7(9)
C(3)–C(4)–C(5)	106.8(7)	C(24)–C(25)–C(27)	118.8(9)
C(4)–C(5)–C(10)	109.9(7)	C(24)–C(25)–O(38)	59.2(6)
C(1)–C(10)–C(5)	105.7(7)	C(26)–C(25)–C(27)	116.0(9)
C(1)–C(10)–C(19)	104.3(7)	C(26)–C(25)–O(38)	114.0(9)
C(5)–C(10)–C(19)	108.8(6)	C(27)–C(25)–O(38)	114.7(9)
C(10)–C(19)–O(32)	111.1(7)	C(24)–O(38)–C(25)	61.3(6)

60.6°). These distortions can be viewed as the result of severe transannular interactions, particularly those involving C(18). Because the hydrogen atoms on C(19) are not free to rotate the H(18)···H(19) interactions must be relieved by a flattening of the C(10) end of ring b (dihedral angles *ca.* 41°). The puckered conformation of the c ring is the result of the establishing of an energetic balance among three major factors: β -side interactions involving the C(18) methyl group, α -side interactions involving the C(30) methyl group, and the proximity of H(1 β) to O(33). The D ring adopts a distorted envelope (C_s) conformation with C(14) as the flap atom.

Much of the C(17) β -oriented side chain lies in a plane; the C(21)–C(20)–C(22)–C(23), C(20)–C(22)–C(23)–O(37) and O(37)–C(23)–C(24)–O(38) torsion angles are -1 , -4 and 7° , respectively. Atom C(21) is oriented over the D ring and closer to C(16) than to C(13) [C(16)–C(17)–C(20)–C(21) -41° , C(13)–C(17)–C(20)–C(21) 79°].

The molecules pack in a herringbone pattern, held together in the *y* direction by head-to-tail hydrogen bonds [O(31)···O(37) 2.80 Å, C(3)–O(31)···O(37) 110.9°]. Other molecular separations <3.6 Å correspond to normal van der Waals interactions.

Experimental

Cordialin A acetate was ultimately crystallized by allowing a solution of (1b) in ethanol and methylene chloride to evaporate slowly under an atmosphere saturated with heptane.

Crystal Data.— $C_{32}H_{48}O_6$, $M = 528.7$, Orthorhombic, $a = 6.431(4)$, $b = 20.530(5)$, $c = 21.777(8)$ Å, $U = 2.875(1)$ Å³, $Z = 4$, $D_c = 1.221$ g cm⁻³, $F(000) = 1152$. Mo- K_α radiation ($\lambda = 0.7107$ Å), $\mu = 0.9$ cm⁻¹. Space group $P2_12_12_1$ (D_2^4) by systematic absences: $h00$ when $h \neq 2n$, $0k0$ when $k \neq 2n$, $00l$ when $l \neq 2n$. Specimen: $0.10 \times 0.10 \times 0.15$ mm.

Crystallographic Measurements.—Cordialin A acetate (1b) was initially studied using a Syntex $P2_1$ automated diffractometer with Cu- K_α radiation ($\lambda = 1.5418$ Å). Cell dimensions

were determined by least-squares refinement of 15 reflections well separated in reciprocal space with $49 \leq 2\theta \leq 73^\circ$. Data collection using copper radiation caused significant, non-linear diminution in intensity. Scaling together partial data sets from several crystals did not provide a data set which allowed structure solution. Data were then collected with Mo- K_α radiation ($\lambda = 0.7107$ Å). An octant of data was measured with $3 \leq 2\theta \leq 40^\circ$ using a Nicolet R3m/E automated diffractometer in the $\theta/2\theta$ scanning mode. The scans were variable speed scans with a minimum speed of $4^\circ/\text{min}$. Two reflections measured periodically showed approximately 10% diminution in intensity. Of the 1625 reflections collected, the 1284 with $I \geq 2\sigma(I)$ were corrected for Lorentz and polarization effects.

Structure Analysis.—Structure solution was ultimately achieved *via* direct phasing methods using MULTAN 80.¹⁰ Structure solution was simultaneously effected using RANT.¹¹ The non-hydrogen atoms were refined using full-matrix least squares. The number of atoms compared with the number of observations suggested that the carbon atoms be refined isotropically and only oxygen atoms be refined anisotropically. Hydrogen atoms, except for those on C(21) and C(26), were included at calculated positions. Convergence was reached at $R = 0.074$. Atomic scattering factors for oxygen and carbon were taken from ref. 12, those for hydrogen were from ref. 13.

In the least-squares refinement the function minimized was $\Sigma w\Delta^2$ and the weights were defined by $w^{\frac{1}{2}} = 1$ for $|F_o| \leq 19.0$ and $w^{\frac{1}{2}} = 19.0/|F_o|$ for $|F_o| > 19.0$. All calculations, except RANT, were carried out on a VAX 11/780 computer. The full-matrix least-squares program used was FMLS by P. L. Ganzel, R. A. Sparks, and K. N. Trueblood, modified by A. T. McPhail and the crystallographic illustration was drawn using ORTEP.¹⁴ Atomic positional parameters for the non-hydrogen atoms appear in Table 1, selected interatomic bond lengths and angles are in Table 2 and selected torsion angles are in Table 3. Hydrogen atom and thermal parameters, a complete table of interatomic bond lengths and valency angles, a complete table of torsion angles, intermolecular separations <3.6 Å, and a packing diagram may be found in a Supplementary Publication

Table 3. Selected torsion angles ($^{\circ}$), with estimated standard deviation in parentheses

Ring A		Ring c	
C(10)–C(1)–C(2)–C(3)	9.8(9)	C(14)–C(8)–C(9)–C(11)	–61.1(8)
C(2)–C(1)–C(10)–C(5)	53.4(8)	C(8)–C(9)–C(11)–C(12)	60.8(9)
C(1)–C(2)–C(3)–C(4)	–67.4(10)	C(9)–C(11)–C(12)–C(13)	–59.4(8)
C(2)–C(3)–C(4)–C(5)	49.4(9)	C(11)–C(12)–C(13)–C(14)	57.3(9)
C(2)–C(3)–O(32)–C(19)	–73.1(9)	C(12)–C(13)–C(14)–C(8)	–61.9(9)
C(4)–C(3)–O(32)–C(19)	48.7(9)	C(13)–C(14)–C(8)–C(9)	63.2(8)
C(3)–C(4)–C(5)–C(10)	20.2(9)		
C(4)–C(5)–C(10)–C(1)	–72.9(8)	Ring d	
C(1)–C(10)–C(19)–O(32)	45.9(9)	C(17)–C(13)–C(14)–C(15)	50.4(9)
C(5)–C(10)–C(19)–O(32)	–64.2(8)	C(13)–C(14)–C(15)–C(16)	–45.8(9)
C(10)–C(19)–O(32)–C(3)	19.0(8)	C(14)–C(15)–C(16)–C(17)	26.4(9)
		C(15)–C(16)–C(17)–C(13)	3.6(9)
Ring B		C(16)–C(17)–C(13)–C(14)	–33.0(9)
C(10)–C(5)–C(6)–C(7)	–53.1(9)	Other	
C(5)–C(6)–C(7)–C(8)	64.1(9)	C(11)–C(9)–C(10)–C(1)	79.6(8)
C(6)–C(7)–C(8)–C(9)	–61.6(8)	C(11)–C(9)–C(10)–C(19)	–42.1(9)
C(7)–C(8)–C(9)–C(10)	50.2(9)	C(10)–C(9)–C(11)–O(33)	–56.0(8)
C(8)–C(9)–C(10)–C(5)	–40.8(8)		
C(9)–C(10)–C(5)–C(6)	41.5(9)		

(SUP No. 56116, 15 pages). * Observed and calculated structure amplitudes are available from the Editorial office on request.

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* For details of the Supplementary Publications scheme, see Instructions to Authors (1985), *J. Chem. Soc., Perkin Trans. 1*, 1985, Issue 1.

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