

Germacranolides of *Erlangea cordifolia*: Structure and Absolute Stereochemistry of Cordifene and Cordifene 4 β ,15-Oxide by X-Ray and Spectroscopic Methods

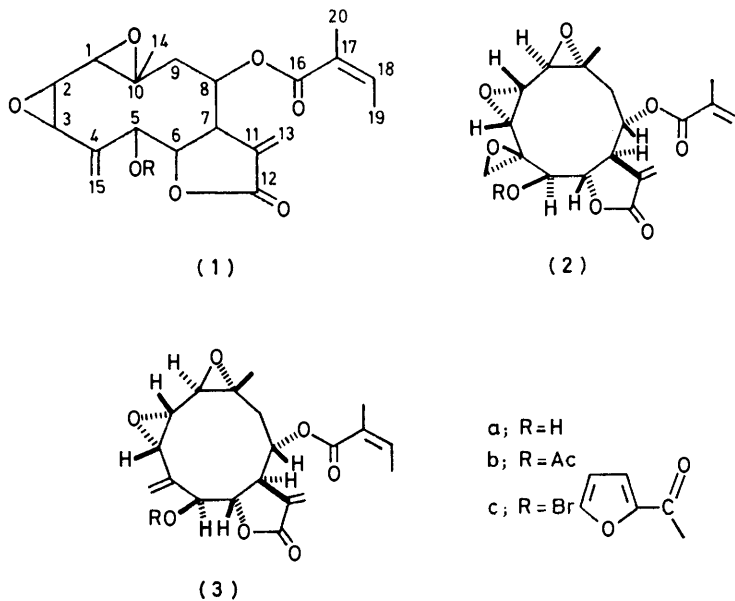
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Cordifene and cordifene 4 β ,15-oxide, extracted from the insect-antifeedant plant *Erlangea cordifolia*, have been examined by spectroscopic and X-ray techniques. Cordifene is shown by X-ray analysis (R 5.49%) as its 5-bromo-2-furoate (3c) to be the 8-angelate ester of a 1*R*,2*S*,3*S*,5*S*,6*S*,7*R*,8*S*,10*R*-6,7-lactonised dihydroxy-germacranolide bis-epoxide (3a). Cordifene 4 β ,15-oxide, having three contiguous epoxide groups and nine chiral centres, is the 4*R*-derivative (2a), as demonstrated by direct X-ray methods (R 3.2%): its absolute configuration is linked to (3a) by c.d. methods. On the basis of Stöcklin's rules, the signature of the $n \rightarrow \pi^*$ c.d. maximum leads to an incorrect absolute configuration for both compounds, but the Beecham-McPhail treatment satisfactorily explains the situation. ^1H N.m.r. data indicate that solution conformations are similar to crystal conformations.

THE plant *Erlangea cordifolia* (S. Moore) (Compositae) is a native drug of Kenya. Extractives of the leaves show antifeedant properties towards the army worm¹ and can be used to protect other plants: they have also been used to induce labour during childbirth.² From a methanolic extract of the leaves, two compounds, cordifene, $\text{C}_{20}\text{H}_{24}\text{O}_7$, m.p. 206 °C, and cordifene oxide, $\text{C}_{20}\text{H}_{24}\text{O}_8$, m.p. 225–227 °C were isolated by reversed-phase

(angelate) ester [δ 1.96 (dq), 1.80 (dq), and 6.11 (qq)] and a methylene lactone [6.32br (s) and 5.69 (d)].^{3,4} One secondary hydroxy-group was present (H-5, δ 4.12 \rightarrow 5.39 on acetylation) together with a second vinyl group (δ 5.31, 5.55) and two ether oxygen atoms. Spin-decoupling, together with esterification shifts and biosynthetic considerations, allowed tentative assemblage of the structure as (1a). The relationship of the hydrogens



preparative h.p.l.c. followed by preparative t.l.c. Both compounds formed crystalline acetates and 5-bromo-2-furoates. Since no botanical provenance was known to the Nottingham authors in the earlier part of the investigation, the structures of the new compounds were explored by spectroscopic methods.

In the i.r. spectrum cordifene absorbed at 3 500 (OH), 1 780 (γ -lactone), and 1 715 (ester) cm^{-1} and in the u.v. spectrum it showed a strong end-absorption at 220 nm. Examination of the ^1H n.m.r. spectrum at once revealed the characteristic signals for a (*Z*)-2-methylbutenoate

of the epoxide-bearing carbon atoms is shown by the decouplings summarised in Table I, and the presence of a low-field quaternary methyl group (δ 1.59) invites a C-10 placing. The vinyl remnant of a methyl group can be placed at C-4 on biogenetic grounds and is connected to H-5 by the shifts (Table I) occurring on esterification of the hydroxy-group carried by the latter: H-5 is connected to H-6 by decoupling and by esterification shifts. Chemical shifts and decoupling (Table I) define the H-7, -8, and -9 sequence and the relationship of the H-7 hydrogen to the C-13 vinylic carbon atom is indicated by

TABLE 1
¹H N.m.r. data for cordifene and cordifene 4 β ,15-oxide and derivatives ^a

	1-H	2-H	3-H	5-H	6-H	7-H	8-H	9- α H	9- β H	13-H
Cordifene (3a)	2.61 (d)	3.01 (dd)	3.99 (dt)	4.12 (d)	4.39 (d)	2.92br (d)	5.12 (ddd)	1.35br (t)	2.58 (dd)	5.69 (d)
	8	4.5, 8	4.5, 1	10	10	10	4, 10, 12	12	4, 12	1
Acetate (3b)	2.59 (d)	3.05 (dd)	3.79 (d)	5.39 (d)	4.46 (d)	2.95br (d)	5.10 (ddd)	1.34br (t)	ca. 2.6 (dd)	5.71 (d)
	8	4.5, 8	4.5	10	10	10	4, 10, 12	12	4, obsc.	1
5-Bromofuroate (3c)	2.63 (d)	3.10 (dd)	3.88 (d)	5.56 (d)	4.59 (d)	3.00br (d)	5.12 (m)	1.36 (t)	2.6 (dd)	5.74 (s) ^b
	8	4.5, 8	4.5	10	10	10	4, obsc.	12	4, obsc.	1
Cordifene 4,15-oxide (2a)	2.65 (d)	3.07 (dd)	3.85 (d)	3.24 (d)	4.53 (d)	2.93br (d)	5.15 (ddd)	1.43br (t)	2.65 (dd)	5.68 (d)
	8.5	4.5, 8.5	4.5	10	10	10	4, 10, 12	12	4, ca. 12	1
Acetate (2b)	2.63 (d)	3.11 (dd)	3.74 (d)	4.64 (d)	4.54 (d)	2.95br (d)	5.11 (ddd)	1.41br (t)	ca. 2.7 (dd)	5.71 (d)
	8.5	4.5, 8.5	4.5	10	10	10	4, 10, 12	12	4, obsc.	1
5-Bromofuroate (2c)	2.68 (d)	3.18 (dd)	3.84 (d)	4.31 (d)	4.67 (d)	3.02br (d)	5.13 (m)	1.44 (t)	ca. 2.7 (dd)	5.75 (s)
	8.5	4.5, 8.5	4.5	10	10	10		12	4, 12	
	13'-H	15-H	15'-H	14-Me	18-H	19-Me	20-Me	OH	Ac-Me	Furoate
Cordifene (3a)	6.32br (s)	5.31 (s)	5.55 (t)	1.59 (s)	6.11 (qq)	1.96 (dq)	1.80 (dq)	ca. 3.0br (s)		
			1.5		1.5, 7	1.5, 7	ca. 1.5			
Acetate (3b)	6.37br (s)	5.45 (s)	5.63 (t)	1.60 (s)	6.08 (qq)	1.93 (dq)	1.79 (m)		2.16 (s)	
			1.5							
5-Bromofuroate (3c)	6.39br (s)	5.52 (s)	5.68 (t) ^b	1.64 (s)	6.11 (qq)	1.96 (m)	1.80 (m)			
Cordifene 4,15-oxide (2a)	6.29br (s)	3.29 (d)	2.74 (dd)	1.64 (s)	6.11 (qq)	1.93 (dq)	1.80 (m)	ca. 3.43br (s)		
		5	5, 1							
Acetate (2b)	6.36br (s)	3.34 (d)	2.84 (dd)	1.64 (s)	6.13 (qq)	1.95 (m)	1.80 (m)		2.21 (s)	
		5	5, 1							
5-Bromofuroate (2c)	6.39br (s)	3.38 (d)	2.90 (d)	1.68 (s)	6.12 (m)	1.95 (m)	1.80 (m)			6.52 (d); 7.23 (d)
		5	5							3.5 3.5

¹H Spin-decoupling for cordifene:



^a CDCl₃, 250 MHz. ^b Assignment may be interchanged.

TABLE 2

¹³C N.m.r. data for cordifene and cordifene 4 β ,15-oxide and acetates ^a

	1-C ^b	2-C ^b	3-C	4-C	5-C	6-C	7-C	8-C	9-C	10-C	11-C
Cordifene (3a)	53.3 (d)	55.1 (d)	62.8 (d)	142.0 (s)	81.6 (d)	78.0 (d)	48.7 (d)	69.0 (d)	45.7 (t)	55.9 (s)	136.2 (s)
											136.4 (s)
Acetate (3b)	53.0 (d)	55.3 (d)	62.4 (d)	137.8 (s)	77.4 (d)	78.3 (d)	48.5 (d)	68.7 (d)	45.5 (dd)	56.0 (s)	136.1 (s)
											135.2 (s)
Cordifene 4,15-oxide (2a)	51.4 (d)	55.5 (d)	61.6 (d)	58.8 (s)	81.0 (d)	78.7 (d)	48.6 (d)	68.9 (d)	45.2 (dd)	56.3 (s)	
Acetate (2b)	51.1 (d)	55.6 (d)	61.2 (d)	57.3 (s)	77.6 (d)	77.8 (d)	48.8 (d)	68.5 (d)	45.1 (dd)	56.4 (s)	
Cordifene (3a)	168.7 (s)	126.1 (t)	17.9 (q)	117.4 (t)	166.6 (s)	128.3 (s)	139.3 (d)	15.8 (q)	20.4 (q)		22-C
Acetate (3b)	169.5 (s)	127.1 (t)	17.8 (q)	121.0 (t)	166.5 (s)	128.2 (s)	139.6 (d)	15.8 (q)	20.3 (q)	168.1 (s)	
Cordifene 4,15-oxide (2a)	168.5 (s)	126.0 (t)	17.7 (q)	50.3 (dd)	166.6 (s)	128.2 (s)	139.4 (d)	15.8 (q)	20.3 (q)		
Acetate (2b)	169.5 (s)	127.0 (t)	17.6 (q)	51.2 (dd)	166.5 (s)	128.1 (s)	139.6 (d)	15.8 (q)	20.3 (q)	167.8 (s)	20.5 (q)

^a Solvent acetone. ^b Assignments may be reversed.

removal of the small coupling on the latter when H-7 is irradiated. The coupling between the hydrogen atoms at C-6 and -7 is near to zero. On the basis of (1a), the ^{13}C spectrum could be readily assigned. The epoxide group of cordifene oxide was clearly seen to be at the 4,15-position from the ^1H chemical shifts at C-15: otherwise the ^1H and ^{13}C n.m.r. data parallel those for cordifene.

This phase of the work is outlined only briefly because at this stage the botanical source, *E. cordifolia*, became available and it was apparent that cordifene was the same as an extractive, m.p. 200–210 °C, described in a recent patent,¹ for which the same planar formula was proposed without discussion: the spectra given, however, leave little doubt of the identity of the two materials. Cordifene oxide was not mentioned. Cordifene has eight chiral centres, and its epoxide nine, and although some progress could be made from the ^1H -coupling data not all the centres are susceptible to such analysis and the conformational flexibility of the ten-membered ring adds indecision and uncertainty. A direct methods X-ray structure of a crystal of the more complex cordifene oxide was therefore undertaken using diffractometer data.

Least-squares refinement of the atomic parameters of cordifene oxide converged to R 3.62% over 1 818 independent observed reflections. The structure and stereochemistry are as shown in (2a) whilst Figure 1 shows the conformation of the molecule. It is the expected 7,6-lactonised germacranolide but neither it, nor cordifene itself, can be assigned to one or other of the germacrolide or heliangolide sub-groups⁴ because the biogenetic origin of the functionalities carried on C-4, -5, and -15 is obscure. In view of the high oxygen content of cordifene oxide, attempts were made to determine its absolute configuration by including the anomalous dispersion of oxygen atoms in the structure without any further refinement. Values of R of 3.717 and 3.735% were obtained for the two enantiomers which are significantly different (at the 99.5% level)⁵ but which we later found were indicating an incorrect absolute con-

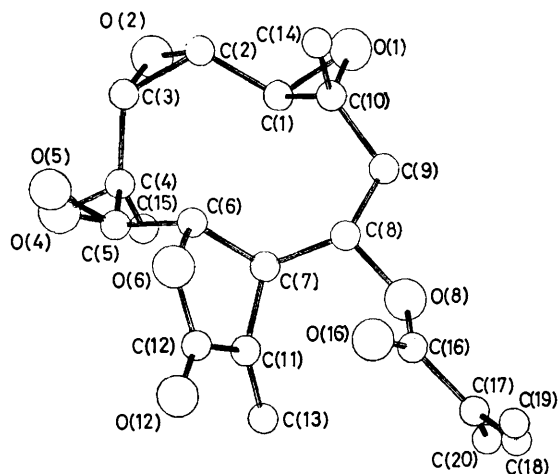


FIGURE 1 X-Ray structure of cordifene 4 β ,15-oxide (2a)

figuration. On the other hand, when weighted R -values were compared, the reverse (and correct) absolute configuration was indicated, although the difference between the values of R_w of 4.040 and 4.044 was considered too small to be significant. It was clear that utilisation of the anomalous dispersion of oxygen was giving unreliable and indecisive results.

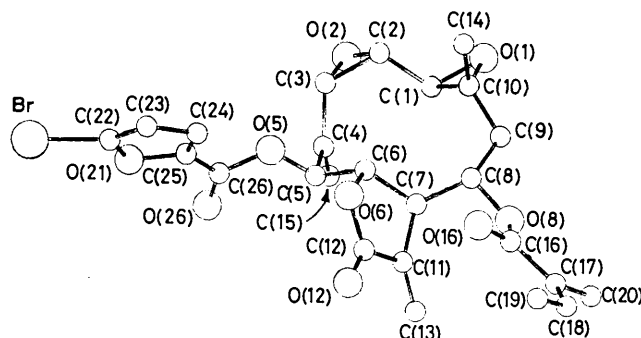


FIGURE 2 X-Ray structure of cordifene 5-bromo-2-furoate (3c)

The absolute configuration was therefore, determined by using the very much larger anomalous dispersion of bromine. This was incorporated as the 5-bromo-2-furoate ester (3c) and cordifene itself was selected in order to enlarge the structural information. The crystal structure was determined using Patterson and Fourier methods on diffractometer data. Least-squares refinement converged to R 5.82% over 1 204 independent observed reflections. When the anomalous dispersion of the bromine atom was included in the calculation without further refinement, values of R of 5.49 and 7.01% were obtained for the two enantiomers (R_w 5.48 and 6.94), which are significantly different way beyond the 99.5% level. This very clear result shows that cordifene 5-bromo-2-furoate is (3c). Figure 2 shows the conformation and correct absolute configuration: its absolute configuration at the C-7 reference centre is 'normal' for natural germacranolides.⁴

Bond lengths for the two germacranolides are compared and listed in Table 3: these are unexceptional and essentially identical for the two structures having regard for the larger standard deviations of the bromo-derivative. Bond angles are similarly listed in Table 4. The angles at C-4 are comparatively unaffected by the presence or absence of the epoxide: on the other hand, the angles at C-5 are significantly modified by the presence of the bromofuroate ester residue. Both structures show a large bond angle at C-18, presumably for steric reasons, and are otherwise identical. Some selected torsion angles about the 10- and 5-membered rings are shown in Table 5: again there is remarkably close agreement between the two structures. Such a situation is of course reflected in the ^1H n.m.r. data of Table 1, and comparison of the ^1H dihedral angles estimated from the Dreiding models for (2a) and (3a), based on Figures 1 and 2, gives a set of coupling constants from the Karplus curve, where applicable, which agree well with those of

TABLE 3
Bond lengths

	Cordifene 4,15-oxide	Cordifene 5-bromofuroate
C(1)-C(2)	1.491(4)	1.497(22)
C(1)-C(10)	1.465(4)	1.450(23)
C(1)-O(1)	1.432(3)	1.448(16)
C(2)-C(3)	1.464(5)	1.486(21)
C(2)-O(2)	1.446(4)	1.432(18)
C(3)-C(4)	1.503(4)	1.531(21)
C(3)-O(2)	1.436(3)	1.443(18)
C(4)-C(5)	1.506(4)	1.542(20)
C(4)-C(15)	1.463(4)	1.290(20)
C(4)-O(4)	1.449(3)	
C(5)-C(6)	1.532(4)	1.496(19)
C(5)-O(5)	1.424(4)	1.463(15)
C(6)-C(7)	1.540(4)	1.541(18)
C(6)-O(6)	1.461(3)	1.502(15)
C(7)-C(8)	1.557(4)	1.587(20)
C(7)-C(11)	1.502(4)	1.526(19)
C(8)-C(9)	1.525(4)	1.555(19)
C(8)-O(8)	1.454(3)	1.410(16)
C(9)-C(10)	1.514(4)	1.476(22)
C(10)-C(14)	1.509(4)	1.494(23)
C(10)-O(1)	1.454(3)	1.448(19)
C(11)-C(12)	1.481(4)	1.496(19)
C(11)-C(13)	1.322(4)	1.283(19)
C(12)-O(6)	1.376(4)	1.343(18)
C(12)-O(12)	1.196(4)	1.212(18)
C(15)-O(4)	1.449(4)	
C(16)-C(17)	1.494(4)	1.478(25)
C(16)-O(8)	1.352(3)	1.346(18)
C(16)-O(16)	1.204(4)	1.211(18)
C(17)-C(18)	1.331(5)	1.313(24)
C(17)-C(20)	1.497(6)	1.482(25)
C(18)-C(19)	1.456(7)	1.460(25)
O(21)-C(22)		1.391(19)
O(21)-C(25)		1.394(19)
C(22)-Br(1)		1.908(15)
C(22)-C(23)		1.264(22)
C(23)-C(24)		1.390(24)
C(24)-C(25)		1.322(21)
C(25)-C(26)		1.433(22)
C(26)-O(5)		1.363(16)
C(26)-O(26)		1.163(17)

Table 1. This suggests that there is little conformational change when the molecules in the crystals are dissolved in CDCl_3 . The five-membered ring adopts the expected envelope conformation with C-6 out of the plane of the other atoms: its chirality is discussed later. The furoate ring is essentially planar. One significant dif-

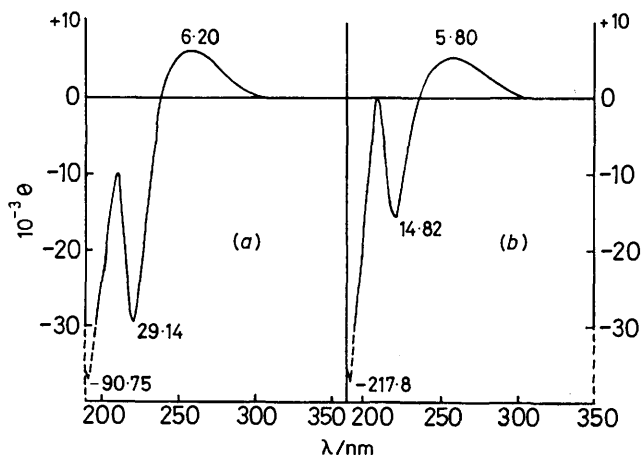


FIGURE 3 C.d. spectra for (a) cordifene (3a) and (b) cordifene 4 β ,15-oxide (2a)

ference between the conformations of the two structures is in the angelate side-chain where there are different torsion angles about the C-16-C-17 bond. Underiv-ated cordifene oxide showed an intramolecular hydrogen bond, O-5 to O-4 of 2.78 Å.

The c.d. curves (Figure 3) link the absolute configur-

TABLE 4
Bond angles

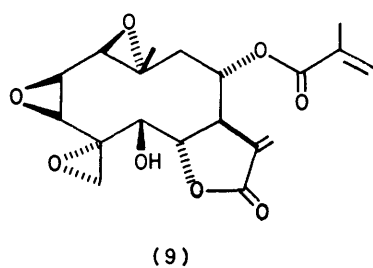
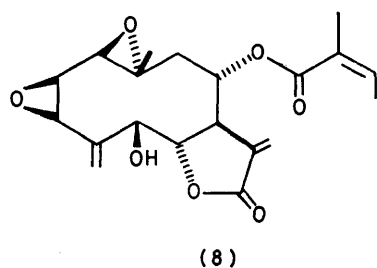
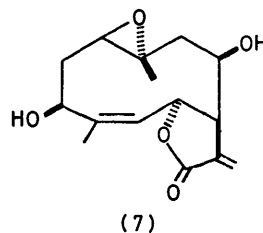
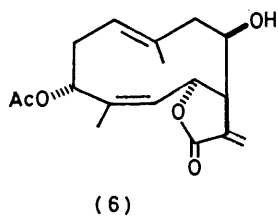
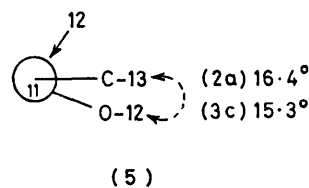
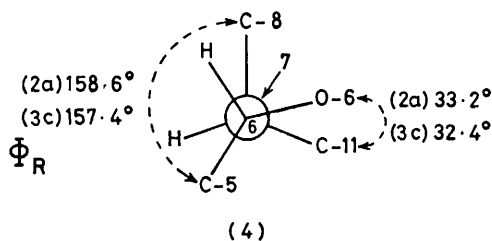
	Cordifene 4,15-oxide	Cordifene 5-bromofuroate
C(2)-C(1)-C(10)	121.7(3)	120.7(14)
C(2)-C(1)-O(1)	117.9(2)	118.6(13)
C(10)-C(1)-O(1)	60.2(2)	60.0(10)
C(1)-C(2)-C(3)	120.2(2)	118.4(14)
C(1)-C(2)-O(2)	116.1(3)	115.6(14)
C(3)-C(2)-O(2)	59.1(2)	59.2(9)
C(2)-C(3)-C(4)	122.4(3)	120.2(13)
C(2)-C(3)-O(2)	59.8(2)	58.5(9)
C(4)-C(3)-O(2)	115.9(3)	113.6(14)
C(3)-C(4)-C(5)	117.0(3)	113.6(14)
C(3)-C(4)-C(15)	121.3(3)	124.8(16)
C(3)-C(4)-O(4)	111.9(2)	
C(5)-C(4)-C(15)	119.3(3)	121.6(15)
C(5)-C(4)-O(4)	112.0(2)	
C(15)-C(4)-O(4)	59.7(2)	
C(4)-C(5)-C(6)	115.6(2)	112.9(11)
C(4)-C(5)-O(5)	106.3(2)	112.3(11)
C(6)-C(5)-O(5)	110.2(2)	103.4(11)
C(5)-C(6)-C(7)	115.2(2)	115.6(11)
C(5)-C(6)-O(6)	105.7(2)	106.1(10)
C(7)-C(6)-O(6)	104.5(2)	103.0(11)
C(6)-C(7)-C(8)	111.6(2)	110.6(11)
C(6)-C(7)-C(11)	99.7(2)	101.6(10)
C(8)-C(7)-C(11)	112.5(2)	112.6(11)
C(7)-C(8)-C(9)	114.1(2)	112.8(12)
C(7)-C(8)-O(8)	109.1(2)	109.9(11)
C(9)-C(8)-O(8)	103.4(2)	106.0(12)
C(8)-C(9)-C(10)	115.2(2)	114.4(12)
C(1)-C(10)-C(9)	117.2(2)	117.2(13)
C(1)-C(10)-C(14)	122.9(3)	123.3(16)
C(1)-C(10)-O(1)	58.7(1)	59.9(10)
C(9)-C(10)-C(14)	116.6(3)	116.3(17)
C(9)-C(10)-O(1)	113.7(2)	114.5(13)
C(14)-C(10)-O(1)	112.7(2)	111.4(15)
C(7)-C(11)-C(12)	107.4(2)	104.9(13)
C(7)-C(11)-C(13)	128.3(3)	130.4(14)
C(12)-C(11)-C(13)	124.1(3)	124.3(14)
C(11)-C(12)-O(6)	108.0(2)	110.7(14)
C(11)-C(12)-O(12)	130.6(3)	127.1(17)
O(6)-C(12)-O(12)	121.4(3)	122.2(16)
C(4)-C(15)-O(4)	59.7(2)	
C(17)-C(16)-O(8)	111.2(3)	110.1(15)
C(17)-C(16)-O(16)	125.4(3)	127.3(18)
O(8)-C(16)-O(16)	123.4(3)	122.6(17)
C(16)-C(17)-C(18)	120.7(4)	120.6(18)
C(16)-C(17)-C(20)	117.7(3)	118.7(17)
C(18)-C(17)-C(20)	121.7(4)	120.4(19)
C(17)-C(18)-C(19)	131.3(4)	129.3(18)
C(1)-O(1)-C(10)	61.0(2)	60.1(10)
C(2)-O(2)-C(3)	61.0(2)	62.2(9)
C(4)-O(4)-C(15)	60.7(2)	
C(5)-O(5)-C(26)		117.3(12)
C(6)-O(6)-C(12)	108.9(2)	108.8(11)
C(8)-O(8)-C(16)	117.1(2)	116.7(12)
C(22)-O(21)-C(25)		100.1(12)
O(21)-C(22)-C(23)		115.4(14)
O(21)-C(22)-Br(1)		109.1(14)
C(23)-C(22)-Br(1)		135.4(17)
C(22)-C(23)-C(24)		105.6(17)
C(23)-C(24)-C(25)		107.7(16)
O(21)-C(25)-C(24)		111.0(14)
O(21)-C(25)-C(26)		114.9(16)
C(24)-C(25)-C(26)		113.9(18)
C(25)-C(26)-O(5)		108.1(14)
C(25)-C(26)-O(26)		127.9(15)
O(5)-C(26)-O(26)		123.8(15)

TABLE 5
Selected torsion angles

	Cordifene 4,15-oxide	Cordifene 5-bromofuroate
C(10)-C(1)-C(2)-C(3)	-110.7	-114.6
C(1)-C(2)-C(3)-C(4)	-0.9	-3.6
C(2)-C(3)-C(4)-C(5)	92.4	99.1
C(3)-C(4)-C(5)-C(6)	-70.4	-69.2
C(4)-C(5)-C(6)-C(7)	-64.8	-71.6
C(5)-C(6)-C(7)-C(8)	158.6	157.4
C(6)-C(7)-C(8)-C(9)	-91.7	-93.7
C(7)-C(8)-C(9)-C(10)	56.5	66.4
C(8)-C(9)-C(10)-C(1)	-87.6	-89.9
C(9)-C(10)-C(1)-C(2)	151.2	148.6
O(6)-C(6)-C(7)-C(11)	33.2	32.4
C(6)-C(7)-C(11)-C(12)	-26.9	-25.6
C(7)-C(11)-C(12)-O(6)	11.0	9.0
C(11)-C(12)-O(6)-C(6)	11.5	12.7
C(12)-O(6)-C(6)-C(7)	-28.9	-28.9
O(16)-C(16)-C(17)-C(18)	-30.8	-4.6

ation determined for cordifene with its 4,15-oxide and the extra centre in the latter is β . Cordifene is $1R,2S,3S,5S,6S,7R,8S,10R$ and its epoxide has one further $4R$ -centre.* However, the c.d. curves are also of interest in

analysis⁸ of the c.d. of lactones. Beecham has shown that the right-handed chirality of the C=C-C=O system in a *cisoid* α -methylene- γ -lactone corresponds to a positive $n \rightarrow \pi^*$ Cotton effect (the inverse is true of a *transoid* case), whilst McPhail has demonstrated that in the germacranolides the C=C-C=O torsion angle of an exocyclic α -methylene- γ -lactone is paired with that of the endocyclic torsion angle about the C-6-C-7 bond. A change in magnitude of this angle in the ten-membered ring can be reflected in the torsion angle of the C=C-C=O system, changing the sign of the Cotton effect. Where the C-6-C-7 ring-torsion angles Φ_R are significantly $<120^\circ$, the Cotton effect is negative: for those significantly $>120^\circ$ [e.g. heliangolides such as eupafornonin (6) or helianginol (7)] it is positive. In the case of cordifene 5-bromofuroate the torsion angle Φ_R for C(5)-C(6)-C(7)-C(8) is 157.4° and in the case of cordifene 4,15-oxide it is 158.6° , clearly in accord with McPhail's analysis. The twist in the methylene lactones can also be measured directly from the X-ray analyses (5). The very small *trans*-6-H-7-H coupling in the ^1H n.m.r. data noted



another connection. According to the Stöcklin-Waddell-Geissman rules⁶ the positive signature of the $n \rightarrow \pi^*$ transition near 255 nm in the c.d. spectrum of a *trans*-fused C-6 lactone should give the C-7 centre in cordifene a $7S$ -assignment. The limitations of the Stöcklin rules have been discussed by McPhail⁷ in terms of Beecham's

above, and the small couplings between the 7-H and 13-H also became understandable in terms of the large values for Φ_R .^{4,9}

Very recently Bohlmann *et al.*¹⁰ have also isolated cordifene and a gummy epoxide which apparently has the same gross structure as our crystalline material. Based mainly on n.m.r. data they have proposed (8) as the stereochemistry of cordifene and (9) as the stereochemistry of the 3,15-epoxide. Both stereochemical

* Note that this changes other descriptors for cordifene 4 β ,15-oxide which are $1R,2R,3R,4R,5R,6S,7R,8S,9R$ although the stereochemistry remained unchanged.

proposals are at variance with the conclusions arrived at in this work.

EXPERIMENTAL

Isolation of Cordifene and Cordifene 4β,15-Oxide.—Dried leaves of *Erlangea cordifolia* (1 kg) were blended in methanol and the extract was evaporated, the product being defatted by washing with light petroleum (b.p. 60–80 °C). The defatted residue was redissolved in methanol, decolourised with charcoal, and evaporated to 30 ml; a crude mixture of cordifene and the 4β,15-oxide (0.75 g) crystallised within 2 days. The crude mixture (4.2 g) in methanol (20 ml) was purified by preparative h.p.l.c. (Waters cartridge instrument, C₁₈-reversed phase) eluting with methanol–water (2:1 v/v) at 100 ml min⁻¹. The cordifene oxide was eluted after 6–11 min, the front edge of the peak being collected, and cordifene after 15–20 min, the back edge of the peak being collected. Material not collected was recycled, the front and back edges being collected. In this way semi-purified cordifene (1.89 g) and the epoxide (0.72 g) were isolated.

Cordifene (3a).—The semi-purified material (above) was further purified by preparative t.l.c. on five 40 × 40 cm HF254 silica G plates, eluting with chloroform–methanol (20:1 v/v). Recrystallisation of the main band from ether gave *cordifene* (1.34 g) which crystallised from methylene chloride–ether in needles, m.p. 206 °C (decomp.) (prior to melting, fine needles grew whilst the original crystals decreased in size: the fine needles had m.p. 208 °C) (lit.,¹ 200–210; lit.,¹⁰ 183 °C) (Found: C, 63.9; H, 6.6%; *M*⁺, 376.1534. C₂₀H₂₄O₇ requires C, 63.8; H, 6.45%; *M*, 376.1522), [α]₅₈₉²⁶ –106°, [α]₅₄₆²⁶ –127° (*c*, 0.46 in CHCl₃), *v*_{max.} (KBr) *ca.* 3 500 (OH), 1 780 (γ-lactone), and 1 715 (ester) cm⁻¹, u.v. end absorption to 220 nm.

Acetylation with pyridine–acetic anhydride at 20 °C gave *cordifene 5-acetate* (3b) as needles, m.p. 223–224 °C (from ether–methylene chloride) (lit.,¹⁰ oil) (*M*⁺, 418.1631. C₂₂H₂₆O₈ requires *M*, 418.1628), *v*_{max.} (KBr) 1 775, 1 750, 1 715, and 1 225 cm⁻¹. *Cordifene 5-bromofuroate* was prepared by stirring cordifene (93 mg), 5-bromofuroic acid (62 mg), 4-dimethylaminopyridine (2.2 mg) and dicyclohexylcarbodi-imide (62 mg) in dry methylene chloride (0.5 ml) at 0 °C for 15 min and then at 20 °C for 4 h. Work-up and preparative t.l.c. on three 20 × 20 on silica GHF₂₅₄ plates, eluting with 4% v/v methanol–chloroform, followed by crystallisation from methanol, gave the *5-bromo-2-furoate*, m.p. 182–183 °C (Found: C, 54.9; H, 4.7. C₂₅H₂₅BrO₉ requires C, 54.6; H, 4.6%), *M*⁺ 548 (weak) and 550 (weak). This material was used for the X-ray analysis.

Cordifene 4β,15-Oxide (2a).—Semi-purified material (above) was purified and crystallised as described for cordifene. The *epoxide (2a)* formed needles, m.p. 225–227 °C (decomp.) (from MeOH) (during the determination fine spicules formed from about 170 °C and these melted sharply at 213–214 °C before the larger crystals) (lit.,¹⁰ gum) (Found: C, 60.75; H, 6.25%; *M*⁺, 392.1448. C₂₀H₂₄O₈ requires C, 61.2; H, 6.15%; *M*, 392.1471, *v*_{max.} (KBr) *ca.* 3 450, 1 785, and 1 720 cm⁻¹, u.v. end absorption to 220 nm.

The *acetate (2b)* prepared as above crystallised from ether–chloroform in needles, m.p. 243–244 °C (Found: C, 60.65; H, 5.95%; *M*⁺, 434.1562. C₂₂H₂₆O₉ requires C, 60.8; H, 6.05; *M*, 434.1577), *v*_{max.} (KBr) 1 780, 1 745, 1 715, and 1 225 cm⁻¹. The *5-bromofuroate (2c)* (*M*⁺, 564 and 566 weak) formed needles, m.p. 245–246 °C.

X-Ray Crystallography

Crystallographic Analyses of Cordifene 4β,15-Oxide (2a) and Cordifene 5-Bromo-2-furoate (3c).—The space group and preliminary cell parameters were determined photographically. For intensity measurement of (2a) a crystal of approximate dimensions 0.5 × 0.5 × 0.1 mm³ was mounted on a CAD-4 diffractometer. Accurate lattice parameters were obtained by least-squares refinement of 25 reflections measured on the diffractometer. Intensity data were collected with Cu-K_α radiation using an ω-4/30 scan for 1° ≤ θ ≤ 66°. A total of 1 955 independent reflections was measured of which 1 818 had *I* ≥ 3σ(*I*) and were considered observed and used in the subsequent refinement. For (3c) a crystal of approximate dimensions 0.7 × 0.15 × 0.05 mm³ was mounted on a Hilger Y290 diffractometer. 22 Reflections were used to determine accurate lattice parameters by least-squares. The intensity data were collected with Mo-K_α radiation using an ω-2θ scan for 1° ≤ θ ≤ 22°. A total of 1 825 independent reflections was measured of which 1 221 had *I* ≥ 3σ(*I*) and were considered observed. For each structure the data were corrected for Lorentz and polarisation factors, but no absorption corrections were applied. Data reduction and subsequent crystallographic calculations were performed using the CRYSTALS system of programs.

Crystal Data.—*Cordifene 4β,15-oxide (2a)*, C₂₀H₂₄O₈, *M* = 392.4. Orthorhombic, *a* = 8.8727(6), *b* = 9.8116(7), *c* = 22.2617(17) Å, *U* = 1938.0 Å³, *Z* = 4, *D*_c = 1.34 g cm⁻³, *F*(000) = 912. Space group *P*2₁2₁2₁ uniquely from systematic absences. Cu-K_α radiation λ = 1.541 78 Å, μ(Cu-K_α) = 8.86 cm⁻¹.

Cordifene 5-bromofuroate (3c), C₂₅H₂₅O₉Br, *M* = 549.4. Orthorhombic, *a* = 11.908(1), *b* = 13.105(1), *c* = 16.273(2) Å, *U* = 2 539.5 Å³, *Z* = 4, *D*_c = 1.44 g cm⁻³, *F*(000) = 1 128. Space group *P*2₁2₁2₁ uniquely from systematic absences. Mo-K_α radiation, λ = 0.710 69 Å, μ(Mo-K_α) = 17.7 cm⁻¹.

Structure Solution and Refinement.—Structure (2a) was solved by direct methods using the MULTAN program. 250 Reflections with *E* > 1.46 were used. The *E* map based on the best set of phases revealed the positions of all 28 non-hydrogen atoms among the largest peaks in the map. Full-matrix isotropic least-squares refinement of these positions gave a value for *R* of 10.53%.

Structure (3c) was solved by the heavy-atom method. A Patterson synthesis clearly revealed the position of the bromine atom. An initial difference map following a structure-factor calculation revealed the positions of a further 22 atoms. However, four further series of difference maps following structure-factor calculations on an ever-improving model were required before all 35 non-hydrogen atoms were finally successfully located. Full-matrix isotropic least-squares refinement of these positions gave a value for *R* of only 21.2; however, this was rapidly lowered to 9.44% when the bromine atom was allowed to vibrate anisotropically.

For both structures refinement was continued with anisotropic thermal parameters for all non-hydrogen atoms. Difference maps were next calculated to determine the positions of the hydrogen atoms. For structure (2a) the hydrogen atom positions were all clearly revealed and the positions were taken from the peaks in the map. For structure (3c) the peaks indicated only approximate hydrogen positions and these were then calculated accurately from geometric considerations. For both structures the

TABLE 6

Fractional atomic co-ordinates with standard deviations in parentheses for cordifene 4,15-oxide

Atom	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>
C(1)	0.476 7(3)	-0.055 9(3)	0.018 9(1)
C(2)	0.627 5(4)	-0.104 6(3)	-0.001 4(1)
C(3)	0.759 1(4)	-0.015 3(3)	0.003 1(1)
C(4)	0.749 1(3)	0.127 6(3)	0.027 1(1)
C(5)	0.777 5(3)	0.146 7(3)	0.093 3(1)
C(6)	0.655 0(3)	0.091 0(3)	0.135 1(1)
C(7)	0.500 7(3)	0.161 9(3)	0.130 1(1)
C(8)	0.371 4(3)	0.069 7(3)	0.154 4(1)
C(9)	0.297 2(3)	-0.019 3(3)	0.106 6(1)
C(10)	0.403 4(3)	-0.112 1(3)	0.072 5(1)
C(11)	0.529 0(3)	0.283 6(3)	0.169 5(1)
C(12)	0.646 0(4)	0.244 6(3)	0.213 7(1)
C(13)	0.471 5(4)	0.407 5(3)	0.164 7(2)
C(14)	0.464 0(4)	-0.233 8(3)	0.106 2(2)
C(15)	0.672 5(4)	0.235 3(4)	-0.006 6(2)
C(16)	0.248 8(4)	0.190 3(3)	0.234 0(1)
C(17)	0.119 0(4)	0.281 4(4)	0.248 7(2)
C(18)	0.058 1(4)	0.280 8(5)	0.303 3(2)
C(19)	0.094 4(6)	0.202 1(6)	0.356 8(2)
C(20)	0.061 9(5)	0.373 4(4)	0.200 1(2)
O(1)	0.351 3(2)	-0.146 5(2)	0.012 45(9)
O(2)	0.688 7(3)	-0.038 4(3)	-0.054 09(9)
O(4)	0.835 1(2)	0.222 8(3)	-0.009 0(1)
O(5)	0.918 0(2)	0.082 3(3)	0.105 6(1)
O(6)	0.706 2(2)	0.121 7(2)	0.196 05(8)
O(8)	0.248 6(2)	0.155 5(2)	0.175 27(8)
O(12)	0.687 8(3)	0.300 9(3)	0.258 3(1)
O(16)	0.344 1(3)	0.153 7(3)	0.268 99(9)
H(1)	0.4566	0.0424	0.0077
H(2)	0.6474	-0.2063	0.0013
H(3)	0.8610	-0.0552	0.0092
H(5)	0.7725	0.2501	0.1003
H(6)	0.6446	-0.0106	0.1301
H(7)	0.4832	0.1956	0.0862
H(8)	0.4055	0.0199	0.1925
H(9A)	0.2460	0.0418	0.0799
H(9B)	0.2203	-0.0795	0.1216
H(13A)	0.5030	0.4781	0.1977
H(13B)	0.3963	0.4290	0.1275
H(14A)	0.5101	-0.2158	0.1416
H(14B)	0.3692	-0.2966	0.1238
H(14C)	0.5352	-0.2934	0.0788
H(15A)	0.6341	0.3116	0.0185
H(15B)	0.6197	0.2203	-0.0423
H(18)	-0.0327	0.3568	0.3077
H(19A)	-0.0012	0.1630	0.3769
H(19B)	0.1087	0.2803	0.4003
H(19C)	0.1587	0.1301	0.3628
H(20A)	0.0333	0.3208	0.1624
H(20B)	0.1633	0.4514	0.1877
H(20C)	-0.0080	0.4469	0.2066
H(50)	0.9174	0.0891	0.1419

hydrogen atoms were then included in the calculations but without refinement. Analysis of the agreement between F_o and F_c suggested the adoption of a weighting scheme based on a Chebyshev polynomial for structure (2a) but that unit weights were satisfactory for structure (3c). Refinement finally converged with the largest parameter shifts 0.02σ (2a) and 0.1σ (3c) giving final R values of 3.62% (2a) and 5.82% (3a) after totals of 16 (2a) and 23 (3c) cycles of least-squares refinement. Final difference maps were calculated which both showed no peaks or depressions $>0.2 \text{ e}\text{\AA}^{-3}$ other than in the immediate neighbourhood of the heavy bromine atom. Finally, structure-factor calculations were performed including anomalous dispersion to obtain indications of absolute configuration. For structure (2a) with anomalous dispersion of oxygen atoms values of $R(+)$ 3.735 and $R(-)$ 3.717 (ratio $R = 0.995$) were obtained together with $R_w(+)$ 4.040 and $R_w(-)$ 4.044 (ratio $R_w = 1.001$), with weights w redefined in terms of the variances of the observations $w =$

$1/\sigma^2$. If the anomalous dispersion of both oxygen and carbon atoms was included the values are ($R(+)$ 3.775, $R(-)$ 3.764 ($R = 0.997$) and $R_w(+)$ 4.170, $R_w(-)$ 4.172 ($R = 1.005$). In each case the indications from R and R_w are contradictory and the differences between the unweighted R values are more significant. For structure (3c) with the larger anomalous dispersion of bromine the corresponding values are $R(+)$ 5.49, $R(-)$ 7.01 ($R = 1.277$) and $R_w(+)$ 5.48, $R_w(-)$ 6.94 ($R_w = 1.266$), a highly significant difference. In each case the + sign refers to the listed co-ordinates corresponding to the absolute configuration

TABLE 7

Fractional atomic co-ordinates with standard deviations in parentheses for cordifene 5-bromofuroate

Atom	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>
C(1)	0.751(1)	0.240(1)	0.370(1)
C(2)	0.699(1)	0.156(1)	0.320(1)
C(3)	0.584(1)	0.121(1)	0.343(1)
C(4)	0.525(1)	0.165(1)	0.419(1)
C(5)	0.439(1)	0.250(1)	0.397 7(9)
C(6)	0.494(1)	0.345(1)	0.367 7(9)
C(7)	0.557(1)	0.407 8(9)	0.433 1(9)
C(8)	0.649(1)	0.479(1)	0.391 4(9)
C(9)	0.767(1)	0.429(1)	0.388(1)
C(10)	0.774(1)	0.339(1)	0.334(1)
C(11)	0.462(1)	0.468(1)	0.472(1)
C(12)	0.374(1)	0.475(1)	0.407(1)
C(13)	0.449(1)	0.500(1)	0.547(1)
C(14)	0.767(2)	0.359(1)	0.243(1)
C(15)	0.543(1)	0.137(1)	0.493(1)
C(16)	0.602(1)	0.651(1)	0.413(1)
C(17)	0.629(2)	0.740(2)	0.465(1)
C(18)	0.586(2)	0.830(2)	0.449(1)
C(19)	0.505(2)	0.859(1)	0.386(1)
C(20)	0.713(2)	0.728(2)	0.532(1)
O(1)	0.865 2(8)	0.270(1)	0.352 6(7)
O(2)	0.682 7(9)	0.061 6(9)	0.362 6(7)
O(5)	0.365 3(7)	0.220 8(8)	0.329 9(6)
O(6)	0.400 0(8)	0.415 5(8)	0.343 1(6)
O(8)	0.661 8(8)	0.569 3(9)	0.437 7(6)
O(12)	0.289(1)	0.527(1)	0.409(1)
O(16)	0.537(1)	0.647 7(9)	0.356 2(8)
Br(1)	-0.075 9(1)	0.053 3(2)	0.190 6(1)
O(21)	0.103 2(7)	0.113 3(9)	0.280 7(7)
C(22)	0.050(1)	0.140(1)	0.208(1)
C(23)	0.095(2)	0.214(2)	0.169(1)
C(24)	0.191(1)	0.239(1)	0.213(1)
C(25)	0.194(1)	0.181(1)	0.279(1)
C(26)	0.266(1)	0.175(1)	0.350(1)
O(26)	0.244 3(9)	0.146(1)	0.415 2(8)
H(1)	0.7092	0.2139	0.4205
H(2)	0.7375	0.1797	0.2681
H(3)	0.5107	0.1090	0.3123
H(5)	0.3951	0.2625	0.4510
H(6)	0.4927	0.3779	0.3102
H(7)	0.5998	0.3644	0.4761
H(8)	0.6200	0.4984	0.3349
H(9A)	0.7882	0.4063	0.4466
H(9B)	0.8246	0.4819	0.3715
H(13A)	0.3763	0.5323	0.5657
H(13B)	0.5113	0.4932	0.5895
H(14A)	0.7689	0.2946	0.2107
H(14B)	0.6911	0.3948	0.2282
H(14C)	0.8274	0.4063	0.2226
H(15A)	0.5036	0.1690	0.5421
H(15B)	0.6012	0.0808	0.5077
H(18)	0.6115	0.8922	0.4840
H(19A)	0.4869	0.9360	0.3872
H(19B)	0.4318	0.8222	0.3940
H(19C)	0.5344	0.8436	0.3296
H(20A)	0.7376	0.6557	0.5355
H(20B)	0.6855	0.7522	0.5863
H(20C)	0.7841	0.7709	0.5182
H(23)	0.0687	0.2477	0.1138
H(24)	0.2493	0.2967	0.1989

derived from the bromo-derivative. Final atomic coordinates are listed in Tables 6 and 7, temperature factors and observed and calculated structure factors are listed in Supplementary Publication No. SUP 23109 (42 pp.).*

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