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CONFORMATION OF GALLICIN, A TEN-MEMBERED-RING SESQUITERPENE LACTONE[1]

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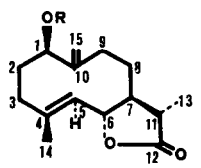
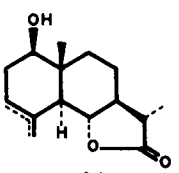
SUMMARY Conformation 8 was assigned to gallicin on the basis of NOE effect, variable-temperature ^{1}H-NMR, LIS and chemical data interpretation.

The structure determination and absolute configuration of gallicin (1a), a germacranolide from *Artemisia maritima gallica* Willd ssp have already been reported[2].

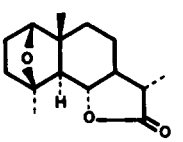
It has been suggested[3] that germacran-1,5-dienes are the biogenetic precursors of eudesmano and guayano sesquiterpenes and are converted to selinane-type derivatives by the antiparallel addition of electrophyls to the double bonds. Considerable experimental work confirms this theory[4] showing that the E,E-cyclodeca-1,5-dienes and derivatives are cyclized due to the action of numerous electrophilic agents. It has also been postulated that this process is carried out by a concerted mechanism via a preferred reacting conformation thus explaining the high stereoselectivity of these reactions[5].



1a R=H
1b R=Ac



2 $\Delta^{3,4}$
3 $\Delta^{4(14)}$
4 $\Delta^{4(5)}$



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Gallicin undergoes a biogenetic-type cyclization to a mixture of the eudesmanolides 2, 3, 4 and 5 when treated with protic acids. This reaction is fully stereoselective and gives rise to purely *trans*-derivatives.

A conformational study of 1a in solution was made using the NOE effect, variable-temperature ^{1}H-NMR and LIS.

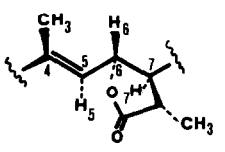
The ^{1}H-NMR (100 MHz, $CDCl_3$) was taken at ordinary probe temperature (+35°) as none of the spectral features changed significantly at temperatures from -60° to +60°. The 1-H, 5-H, 6-H, 15-H, 4-Me and 11-Me signals were quite clear and in some cases have been confirmed by double resonance experiments.

TABLE 1: NMR PARAMETERS

PRODUCT	1-H	5-H	6-H	13-H(11-Me)	14-H(4-Me)	15-H
1a	3•90	5•15 d (10)	4•40 dd (9,10)	1•22 d (7)	1•70 d (2)	4•75 bs 5•17 bs
1b	4•97	5•25 d (10)	4•40 dd (9,10)	1•24 d (7)	1•70 d (2)	4•97 bs 5•25 bs

δ in ppm. The numbers in brackets are J values in Hz; d = doublet; bs = broad singlet; dd = doublet of doublets. Irradiation of 5•15 ppm converts the dd at 4•40 ppm to a doublet, J=10Hz, and the doublet at 1•70 ppm to a singlet.

Double irradiation saturation of 4-Me produced a 12% intensity increase of the 6-H integral indicating that 4-Me and 6-H are *syn*-related. Since 5H is *anti* to 6β-H $J_{5,6} \simeq 10Hz$)[6] the configuration E can be deduced for the double bond $\Delta^{4,5}$ with a relative disposition such as 6 for the carbon fragment C-4, C-5, C-6, C-7, C-11 and C-12. An enantiomeric disposition (7) could not be adopted because the *trans*-γ-lactone ring between C-6 and C-7 prevents them from rotating.



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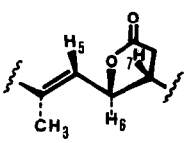

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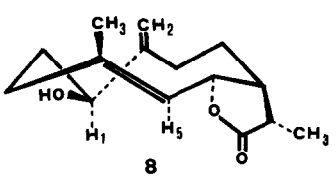
A Dreiding model projection of conformations for gallicin shows four possible solutions: 8, 9, 10 and 11. In two, 8 and 10, the 1β-OH is equatorial and in the others, axial.

In ^{1}H-NMR, the 1-H signal (15-16Hz) is fairly broad suggesting an axial-axial coupling between 1-H and one of the 2-H. This is only possible if the 1β-OH is equatorial. If the 1β-OH were axial, a 4-Me upfield chemical shift, which does not appear, should be seen in the spectrum of 1b (Table 1).



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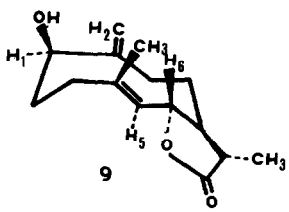

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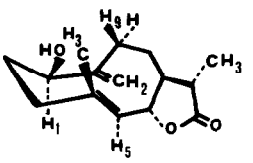

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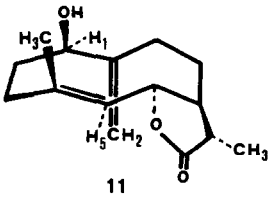

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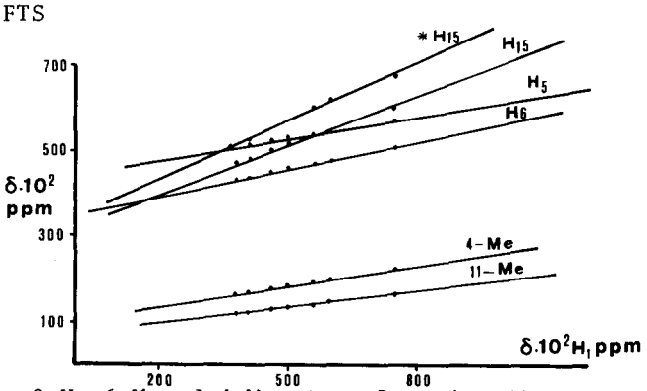
The addition of $Eu(fod)_3$ caused the chemical shifts shown below. Those affecting 15-H are the most important. The changes undergone by 6-H and 11-Me suggest two points of complexation between gallicin and Europium salt, 1β-OH and the lactone carbonyl[7].

The slight shift of the 4-Me in gallicin is not compatible with the axial conformation of 1β-OH in 9 and 11 where these two groups stay relatively close and the Europium influence should be stronger. An axial disposition for 1β-OH should keep the Europium away from 15-H and this does not explain the marked shift shown for these protons.

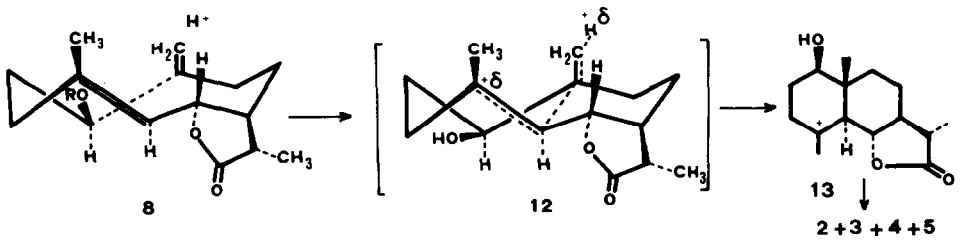
TABLE 2: $EU(FOD)_3$-INDUCED CHEMICAL SHIFTS

PROTON	SLOPE STRAIGHT LINES
11-Me	0 12
4-Me	0 16
5-H	0 17
6-H	0 21
15-H	0 33
15-H*	0 48
1-H	1 00

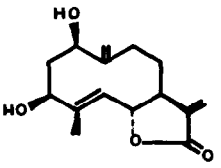


Of the equatorial alternatives 8 and 10, 9-H, 6-H and 4-Me stay close together in 10 giving rise to a Van der Waals tension which is absent from 8 which therefore seems the likelier conformation.

Gallicin is converted to a eudesmanolide by acid action and this may be due to the CC conformation of 8. The cyclization takes place via a cyclohexane chair-chair transition state as shown below in the proposed concerted mechanism. The CC conformation of 8 has a β-axial methylene group at C-10 and an α-axial H-5 and so the resulting *trans*-eudesmanolide has the 10β-Me, 5α-H configuration associated with naturally-occurring eudesmanolides.



The results reached are consistent with Geissman *et al*'s hypothesis accounting for the conformation of ridentine (14) on the basis of ^{1}H-NMR data[8].



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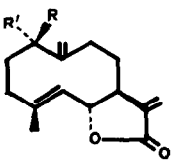
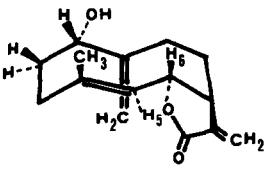


15 R=H, R'=OH
16 R=OH, R'=H



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The germacranolide artemorin (16) only differs from gallicin (1a) in having a methylene double bond at C-11 instead of a methyl. Geissman originally[9] suggested structure 15 for this compound and, using ^{1}H-NMR analysis, assigned it conformation 17. Later El-Feraly *et al*[10] modified the structure of artemorin, establishing it as 16. If the reasoning Geissman applied to ridentine were to be applied to artemorin (16) the result would be a conformation virtually the same as 8 which is proposed here for gallicin.

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