# Chemistry of the Compositae. Part 38.† Structure and Absolute Configuration of Gallicin, a New Germacranolide from *Artemisia*

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Gallicin, a new germacranolide, was isolated from *Artemisia maritima* gallica Willd and assigned structure (3a) on chemical and spectroscopic evidence. Its absolute configuration was determined by the fact that it can be converted to the dihydrosantamarin (5) by a biogenetic cyclization process.

ARTEMIN (1) was earlier isolated from *Artemisia maritima* [1] and now from the same species two more sesquiterpene lactones have been separated. One has been identified by its physical constants and spectral data as 1β-hydroxy-6β,7α,11β*H*-selin-4-en-6,12-olide (2) previously obtained in this laboratory.[2] The second lactone not hitherto reported has been called gallicin (3a).

Gallicin, $C_{15}H_{22}O_3$, *m/e* 232 ($M - 18$), displays hydroxy group, γ-lactone, and C–C double bond i.r. absorptions; its $^1$H n.m.r. spectrum shows a doublet at δ 1.20 ($J$ 7 Hz) due to a secondary methyl (11-Me), a doublet at δ 1.70 ($J$ 2 Hz) assigned to a vinyl methyl (4-Me), a complex signal at δ 3.90 (1-H), a doublet of doublets ($J$ 10 and 9 Hz) at δ 4.40 (6-H), two broad singlets at δ 4.75 and 5.17 (15-H), and a doublet ($J$ 9 Hz) at δ 5.15 (5-H).

Judging from the nature and number of its functional groups and its composition in general, gallicin would seem to have a bicyclic skeleton, which, taken together with its $^1$H n.m.r. spectrum, indicates the germacranolide structure (3a). Further evidence for this structure can be adduced from a double resonance experiment: irradiation at the 5-H frequency changes the signals for 6-H and 4-Me to a doublet ($J$ 10 Hz) and a singlet, respectively, thus confirming allylic coupling between 5-H and 4-Me ($J$ 2 Hz).

The stereochemistry of the lactone ring junction was established as *trans* from the values of the coupling constants $J_{5,6}$ and $J_{6,7}$ (9 and 10 Hz, respectively). The latter figure requires a *trans*-disposition for the 4,5 double bond as a *cis*-relationship would narrow the angle between 6- and 7-H thus reducing the value of $J_{6,7}$ to 2 Hz.[3]

$^{13}$C N.m.r. analysis of gallicin showed absorptions due to 15 carbon atoms, a lactone carbonyl, four olefinic carbons, two carbons joined to oxygen, two methine carbons, four methylene carbons, and two methyl groups. These data agree with the proposed structure (3a). The β-configuration was assigned to C-11 because

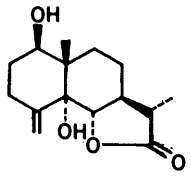
† Part 37, A. G. González, J. M. Arteaga, B. M. Fraga, and M. G. Hernández, *Experientia*.

[1] A. G. González, J. Bermejo, H. Mansilla, G. M. Massanet, I. Cabrera, J. M. Amaro, and A. Galindo. *Phytochemistry*, 1978, **17**, 955.

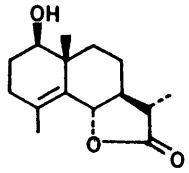
[2] (*a*) A. G. González, J. L. Bretón, and J. Stockel, *Anales de Quim.*, 1974, **70**, 231; (*b*) A. G. González, J. Bermejo, G. M. Massanet, J. M. Amaro, and B. Domínguez, *Phytochemistry*, 1976, **15**, 991.

[3] S. Gnecco, J. P. Poyser, M. Silva, P. G. Sammes, and T. W. Tyler, *Phytochemistry*, 1973, **12**, 2469.

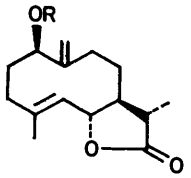
of the chemical shift of C-13 (δ 12.78 p.p.m.); according to Randall *et al.*[4] if the configuration were α, the shift of C-13 would be between δ 9.5 and 10 p.p.m.



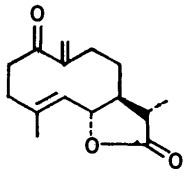
(1)



(2)



(3)
a; R = H
b; R = Ac



(4)

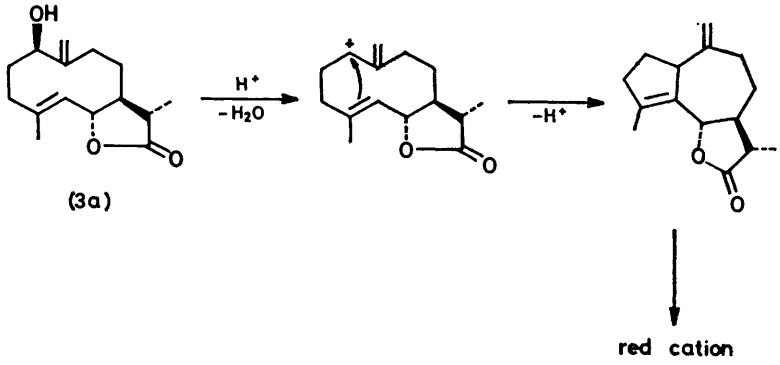
Gallicin must contain one secondary hydroxy group since a monoacetate (3b) can be formed, in the $^1$H n.m.r. spectrum of which one proton undergoes a downfield shift of 1.10 p.p.m. The position of this hydroxy was determined by the following tests. (a) Oxidation by $MnO_2$ of gallicin gave the didehydro derivative (4) in which the carbonyl group is conjugated with the methylene double bond, $\nu_{max.}$ 1 670 cm$^{-1}$, $\lambda_{max.}$ 209 nm (log ε 3.9); there is a marked downfield shift of the 15-H singlets (δ 5.66 and 5.82) in the n.m.r. spectrum. Thus there are two possible positions for the secondary hydroxy group, C-1 and -9. (b) Gallicin when treated with concentrated HCl–EtOH (1 : 1) turns red, $\lambda_{max.}$ 550 nm. According to Geissman [5] guaianolides, xanthanolides, and germacranolides which can be cyclized to form guaianolides give coloured reactions, red or blue, according to the number and types of functional groups present. The cyclization of gallicin to guaianolides is only possible if the hydroxy group is sited at C-1.

The structure and stereochemistry of gallicin was further confirmed by cyclization to a mixture of the eudesmanolides (2) and (5)—(7). Product (2), identical with the natural substance, was obtained in minute quantities and could not be isolated, being identified by g.l.c.–m.s. analysis by comparison with an authentic sample; the other products were isolated and characterized.

The alkene (5) [6] was identified by a comparison of its physical and spectral properties with those of an authentic sample prepared from vulgarin (8) by Zn–AcOH [7] treatment followed by $NaBH_4$ reduction.

The alkene (6) was identified from its spectral data.[6] The fact that (2), (5), and (6) can be obtained definitely established the structure and stereochemistry of gallicin as 1β-hydroxy-6β,7α,11β*H*-germacran-4(5),10(15)-dien-6,12-olide (3a).

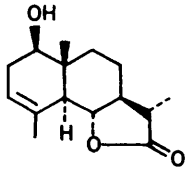
Compound (7), the third cyclization product, $C_{15}H_{22}O_3$, *m/e* 250 ($M^+$), does not possess hydroxy groups so that the third oxygen atom must form part of an epoxide group. This is borne out by the presence in the $^1$H n.m.r. spectrum of a singlet at δ 1.51 attributable to 4-Me and a complex signal centred at δ 4.00 assigned to 1- and 6-H.



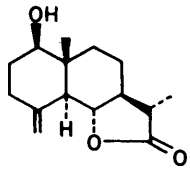

(3a)

SCHEME 1

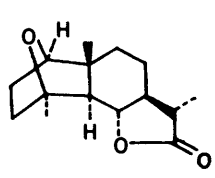
The structure and stereochemistry were determined by its conversion to the alkenes (5) and (6) when subjected



(5)



(6)



(7)

to the same acid treatment as described above. The formation of these products makes it certain that the epoxide group must be on the β face.

A possible cyclization mechanism is shown in Scheme 2. Epoxide (7) may be formed from nucleophilic attack

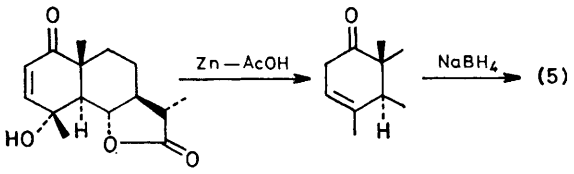
[4] P. S. Pregosin, E. W. Randall, and T. B. H. McMurry, *J.C.S. Perkin I*, 1972, 299. This principle, originally formulated for α-santonin derivatives, has been applied successfully in this laboratory to eudesmanolides and guaianolides.

[5] T. A. Geissman and T. S. Griffin, *Phytochemistry*, 1971, **10**, 2475.

[6] F. Shafizadeh, N. R. Bhadane, M. S. Morris, R. G. Kelsey, and S. N. Khanna, *Phytochemistry*, 1971, **10**, 2746.

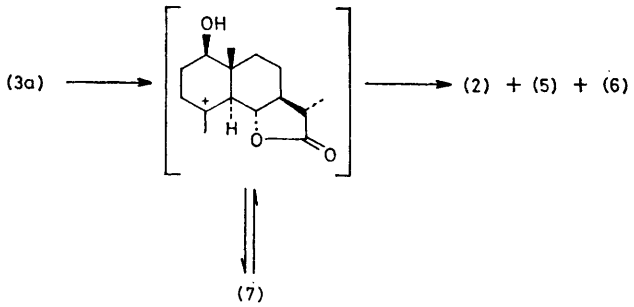
[7] T. A. Geissman and G. A. Ellestad, *J. Org. Chem.*, 1962, **27**, 1855.

of the hydroxy group on the cation centre C-4 followed by the elimination of a proton. Geissman has proposed



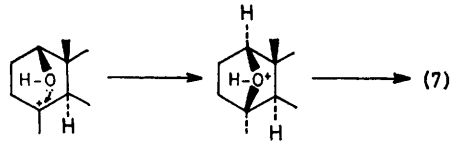

(8)

a similar biogenetic cyclization for germacranolides [8] to explain the formation of several products isolated from the genus *Artemisia* and his hypothesis is here confirmed by such a transformation being carried out *in vitro*. In

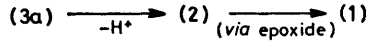



SCHEME 2

accordance with Geissman's theory, Scheme 4 shows the biogenetic relationships between gallicin, (2), and artemin.




SCHEME 3




SCHEME 4

## EXPERIMENTAL

General experimental details have been described previously.[1] M.p.s were determined with a Kofler hot-plate apparatus. I.r. spectra were taken for solutions of $CHCl_3$, u.v. spectra for EtOH, 90 MHz $^1H$ and 20 MHz $^{13}C$ n.m.r. for $CDCl_3$ (tetramethylsilane as internal reference). Optical rotations were measured for solutions in $CHCl_3$. Unless otherwise stated, column chromatography was carried out with Merck silica gel (0.05—0.2 mm) or Merck natural alumina (II—III activity). G.l.c.–m.s. analysis was carried out on a Hewlett–Packard 5710A instrument using 3 m × $\frac{1}{8}$ in steel column packed with 5% OV-17 or Gas-Chrom Q (100–120 mesh).

1β-*Hydroxy*-6β,7α,11βH-*selin*-4-*en*-6,12-*olide* (2).—General chromatography product (2g) was chromatographed on silica gel. From elution with 1 : 1 $C_6H_6$–EtOAc compound (2) (130 mg, 0.02%) was obtained. Recrystallization from $C_6H_6$–n-hexane gave needles, m.p. 172—174°; $[\alpha]_D$ +60.7° (*c* 0.42); $\nu_{max.}$ 3 600 (OH), 1 770 (γ-lactone), and 1 605 $cm^{-1}$ (C=C); *m/e* 250 ($M^+$) and 232 ($M^+ - 18$); δ 1.05 (s, 10-Me), 1.17 (d, *J* 7 Hz, 11-Me), 1.78 (s, 4-Me), 3.46 (dd, *J* 8 Hz, 1-H), and 4.53 (d, *J* 9 Hz, 6-H).

*Gallicin* (3a).—General chromatography product (13 g) was repeatedly chromatographed with neutral alumina and silica gel impregnated with $AgNO_3$ (20%) and then eluted with 6 : 4 $C_6H_6$–EtOAc to give *gallicin* [1β-*hydroxy*-6β,7α,11βH-*germacran*-4(5),10(15)-*dien*-6,12-*olide*] (3a) (980 mg, 0.15%) which was recrystallized with EtOAc–hexane, m.p. 114—116°; $[\alpha]_D$ +121° (*c* 0.28); $\nu_{max.}$ 3 600 (OH), 1 765 (γ-lactone), 1 670, 1 640, and 1 600 $cm^{-1}$ (C=C); *m/e* 232 ($M^+ - 18$); $\delta_H$ 1.22 (d, *J* 7 Hz, 11-Me), 1.70 (d, *J* 2 Hz, 4-Me), 3.90 (m, 1-H), 4.40 (dd, *J* 9 and 10 Hz, 6-H), 4.75br (s, 15-H), 5.15 (d, *J* 9 Hz, 5-H), and 5.17br (s, 15-H); $\delta_C$ 12.78 (C-13), 17.86 (C-14), 27.20 (C-8), 31.16 and 32.84 (C-2 and -9), 36.30 (C-3), 42.01 (C-11), 52.30 (C-7), 78.15 (C-6), 80.46 (C-1), 110.37 (C-15), 122.88 (C-5), 144.68 (C-4), 151.59 (C-10), and 178.69 p.p.m. (C-12) (Found: C, 71.7; H, 9.1. $C_{15}H_{22}O_3$ requires C, 71.95; H, 8.85%).

Gallicin, when treated with acetic anhydride–pyridine, formed the *monoacetate* (3b) which crystallized with EtOAc–hexane, m.p. 113—115°; $[\alpha]_D$ +222.7° (*c* 0.24); $\nu_{max.}$ 1 765 (γ-lactone), 1 720 (acetate), 1 670, 1 645, and 1 600 $cm^{-1}$ (C=C); *m/e* 292 ($M^+$) and 250 ($M^+ - 42$); δ 1.24 (d, *J* 7 Hz, 11-Me), 1.70 (d, *J* 2 Hz, 4-Me), 2.10 (s, OAc), 4.40 (dd, *J* 9 and 10 Hz), 4.97 (m, 1- and 15-H), and 5.25 (m, 5- and 15-H) (Found: C, 69.9; H, 8.0. $C_{17}H_{24}O_4$ requires C, 69.85; H, 8.25%).

*Colour Reaction Procedure.*—Gallicin (3a) (*ca.* 1 mg) was dissolved in 1 : 1 (v/v) concentrated HCl–EtOH (10 ml). The u.v.–visible spectrum was taken after 1 h at room temperature, $\lambda_{max.}$ 550 nm (log ε 2.4).

*Oxidation of Gallicin with* $MnO_2$.—Active $MnO_2$, freshly prepared (1.5 g), was added to a solution of gallicin (107 mg) in $CH_2Cl_2$ (6 ml) and the mixture was stirred for 1 h. It was then filtered through Celite and concentrated *in vacuo*. Upon recrystallizing with EtOAc–hexane, the 1-*oxo derivative* (4) (87 mg, 92%) of gallicin was obtained, m.p. 128—130°; $[\alpha]_D$ +169.6° (*c* 0.39); $\nu_{max.}$ 1 765 (γ-lactone) and 1 670 $cm^{-1}$ (αβ-unsaturated ketone); $\lambda_{max.}$ 209 nm (log ε 3.9); *m/e* 248 ($M^+$); $\delta_H$ 1.24 (d, *J* 7 Hz, 11-Me), 1.75 (d, *J* 2 Hz, 4-Me), 4.35 (dd, *J* 10 and 9 Hz, 6-H), 5.02 (d, *J* 10 Hz, 5-H), 5.66, and 5.82 (s, 10-$CH_2$) (Found: C, 72.3; H, 7.85. $C_{15}H_{20}O_3$ requires, C, 72.55; H, 8.1%).

*Cyclization of Gallicin.*—Gallicin (200 mg) was dissolved in $CHCl_3$ (10 ml) and $CHCl_3$ (2 ml) was added, through which HCl gas was bubbled for 1 min. The mixture was stirred at room temperature for 6 h, diluted with $CHCl_3$, washed with $NaCO_3H$ (1%), then $H_2O$, dried ($MgSO_4$), concentrated *in vacuo*, and chromatographed on silica gel impregnated with 20% $AgNO_3$, yielding four products (2) and (5)—(7).

Product (2) was separated by g.l.c.–m.s. and proved identical with an authentic sample.

1β-*Hydroxy*-6β,7α,11βH-*selin*-3-*en*-6,12-*olide* (5) (49 mg, 24.5%) was recrystallized from $Et_2O$–hexane, m.p. 130—132°; $[\alpha]_D$ +62° (*c* 0.28); $\nu_{max.}$ 3 600 (OH), 1 770 (γ-lactone), 1 630, and 1 600 $cm^{-1}$ (C=C); *m/e* 250 ($M^+$); $\delta_H$ 0.88 (s, 10-Me), 1.21 (d, *J* 7 Hz, 11-Me), 1.81br (s, 4-Me), 3.65 (dd, *J* 10 Hz, 1-H), 3.95 (t, *J* 10 Hz, 6-H), and 5.35br (s, 3-H) (Found: C, 72.15; H, 9.1. $C_{15}H_{22}O_3$ requires C, 71.95; H, 8.85%).

Alkene (6) (13 mg, 6.5%) could not be crystallized, $\nu_{max.}$ 3 600 (OH), 1 770 (γ-lactone), 1 650, and 1 600 $cm^{-1}$ (C=C); *m/e* 250 ($M^+$); $\delta_H$ 0.82 (s, 10-Me), 1.20 (d, *J* 7 Hz, 11-Me), 3.48 (dd, *J* 10 Hz, 1-H), 4.05 (t, *J* 11 Hz, 6-H), 4.85, and 4.97 (s, 4-$CH_2$).

[8] K. H. Lee, S. Matsueda, and T. A. Geissman, *Phytochemistry*, 1971, **10**, 405.

1β,4β-*Epoxy*-6β,7α,11βH-*selinan*-6,12-*olide* (7) (91 mg, 45.5%) was recrystallized from $Pr^i_2O$, m.p. 159—161°; $[\alpha]_D$ −14.4° (*c* 0.38); $\nu_{max.}$ 1 765 $cm^{-1}$ (γ-lactone); *m/e* 250 ($M^+$); $\delta_H$ 1.12 (s, 10-Me), 1.20 (d, *J* 7 Hz, 11-Me), 1.52 (s, 4-Me), and 4.02 (m, 1- and 6-H) (Found: C, 72.1; H, 8.95. $C_{15}H_{22}O_3$ requires C, 71.95; H, 8.85%).

*Alkene* (5) *obtained from Vulgarin.*—Vulgarin (1 g) was dissolved in boiling glacial acetic acid (20 ml) and zinc powder (2.50 g) was added in small quantities for 45 min. It was poured into water, extracted with EtOAc, washed with a saturated $NaHCO_3$ solution, dried ($Na_2SO_4$), concentrated *in vacuo* and chromatographed on silica gel with $C_6H_6$–EtOAc (1 : 1), yielding deoxyvulgarin (496 mg, 49.6%) which recrystallized with EtOAc–light petroleum, m.p. 136—138°; $[\alpha]_D$ +72.6° (*c* 1.2); $\nu_{max.}$ 1 775 (γ-lactone), 1 715 (C=O), and 1 600 $cm^{-1}$ (C=C); *m/e* 248 ($M^+$); $\delta_H$ 1.12 (s, 10-Me), 1.23 (d, *J* 7 Hz, 11-Me), 1.94br (s, 4-Me), 4.02 (t, *J* 9 Hz, 6-H), and 5.60br (s, 3-H).

Deoxyvulgarin (400 mg) was dissolved in EtOH (10 ml) and $NaBH_4$ (330 mg) dissolved in EtOH (10 ml) was added. After 1 h at room temperature the mixture was poured into water, acidified with dilute $H_2SO_4$, extracted with ethyl acetate and chromatographed on silica gel with $C_6H_6$–EtOAc (7 : 3) giving alkene (5) (320 mg, 78%), m.p. 130—131° (from $Et_2O$–hexane); $[\alpha]_D$ +66° (*c* 0.32); the alkene thus obtained is identical with that from cyclization of gallicin (mixed m.p., i.r., n.m.r., and chromatography results).

*Acid Treatment of Compound* (7).—Compound (7) dissolved in $CHCl_3$ was treated in the same way as for the cyclization of (3a). Alkenes (5) and (6) were obtained.

[7/1775 *Received*, 10*th October*, 1977]