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STRUCTURE OF MARITIMIN, A SESQUITERPENE LACTONE FROM *ARTEMISIA MARITIMA GALLICA*

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Key Word Index—*Artemisia maritima gallica*; Compositae; sesquiterpene lactones; 1-keto-6β,7α,11β-H-selin-4(5)-en-6,12-olide; vulgarin; maritimin.

Abstract—1-Keto-6β,7α,11β-H-selin-4(5)-en-6,12-olide, vulgarin and a new eudesmanolide, maritimin, were isolated from *Artemisia maritima gallica*. The structure and stereochemistry of this lactone have been determined by spectral studies and chemical transformations.

INTRODUCTION

Artemin (**1**), gallicin (**2**) and 1β-hydroxy-6β,7α,11β-H-selin-4(5)-6,12-olide (**3**) have been described as constituents of *Artemisia maritima gallica* [1,2]. Their biosynthetic relationships suggest that **2** represents an intermediate stage in the overall synthetic pathway leading to eudesmanolides from gallicin [2]. Re-examination of *A. maritima* has shown that epoxidation is an important route of entrance of oxygen into natural organic compounds.

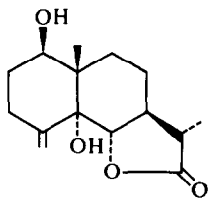
RESULTS AND DISCUSSION

The method described in the Experimental provided 6 sesquiterpene lactones; 5 have been identified by their physical constants and spectral data as artemin (**1**), gallicin (**2**) 1β-hydroxy-6β,7α,11β-H-selin-4(5)-en-6,12-olide (**3**), 1-keto-6β,7α,11β-H-selin-4(5)-en-6,12-olide (**4**) and vulgarin (**5**) previously obtained in this laboratory [1–5]. The sixth compound, hitherto unreported, has been called maritimin (**6**).

Maritimin (**6**), $C_{15}H_{20}O_4$, *m/z* 264 $[M]^+$ had IR bands at 1778 and 1710 cm^{-1} indicative of a γ-lactone and a cyclohexanone; the composition and the absence of hydroxyl group absorptions in the IR spectrum suggested the presence of an epoxy group. Its ^1H NMR spectrum showed a doublet (J = 9 Hz) at δ 4.34 due to the lactonic proton (H-6), a singlet at 1.68 assigned to a methyl attached to the epoxy grouping, a singlet at 1.27 representative of the angular methyl (10-Me) and a doublet (J = 7 Hz) at 1.25 attributable to a secondary methyl (11-Me).

The position of the ketone group at C-1 was determined by the chemical shift of the 10-Me [6] and the stereochemistry of the lactone ring was established as *trans* from the values of the coupling constant $J_{6,7}$ (9 Hz).

Further support for the structure of maritimin was found in the analysis of the ^{13}C NMR spectrum. This spectrum showed absorptions due to 15 carbon atoms, a ketonic group, a lactonic carbonyl, 2 methine carbons, 3 carbons joined to oxygen, 4 methylene carbons, 1 quaternary carbon and 3 methyl groups. These data agree with the proposed structure (**6**).



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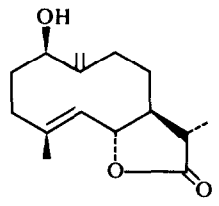

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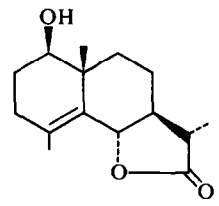

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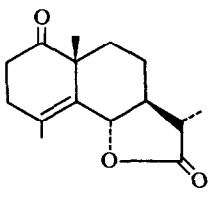

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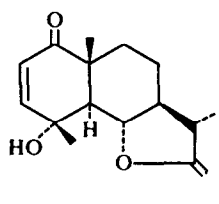

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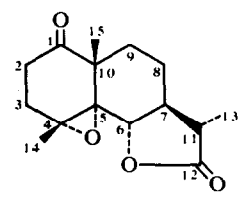

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The *S*-configuration (β-H) is assigned to C-11 because of the chemical shift of C-13 (δ 12.32); according to Pregosin *et al.* [7] if the configuration were *R* the shift of C-13 in *trans*-lactones would be between δ 9.5 and 10. We propose the configuration α for the epoxy group on the basis of the chemical shift of C-7; according to Kori *et al.* [8] the variation in chemical shift of the homoallylic carbon (γ from oxygen) bearing an axial hydrogen atom is strongly dependent upon the configuration of the epoxide ring. If the epoxide oxygen and the axial hydrogen in the γ-position (C-7 in maritimin) are *cis* to one another, the carbon atom bearing the hydrogen is always strongly shielded (3.5–6 ppm). However, in the case of a *trans* relationship, the chemical shift at the γ carbon is only slightly affected. The chemical shift of C-7 in **4** was 53.03, in accordance with the reported values for similar compounds [7] (Table 1). However, the chemical shift of C-7 in maritimin (**6**) was 48.46 ($\Delta\delta = -4.57$); this value suggests a *cis* relation of H-7 and the epoxy group.

Maritimin (**6**) was converted by warming with THF–HCl into the chlorohidrin (**7**). The exceptionally low field at the 10-Me (δ 1.58) is probably due to its proximity to the ketonic group (C-1) and to the chlorine atom (C-4) which is disposed axially (4β). Exposure of **7** to bases resulted in dehydrochlorination to **6**. The treatment of **6** with BF_3-etherate led to ketone (**8**) and dienone **9**, compounds previously reported [4, 9].

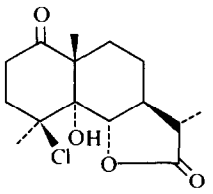
Table 1. ^{13}C NMR spectral data for compounds **4**, **5** and **6***

Carbon	4	5	6
1	212.50	201.2	210.68
2	35.03[a] *t*	125.38 *d*	31.00[b] *t*
3	35.88[a]	152.03 *d*	33.44[b] *t*
4	130.18	69.97	65.97[c]
5	126.58	54.58 *d*	63.59[c]
6	81.54 *d*†	79.48 *d*	76.59 *d*
7	53.03 *d*	52.34 *d*	48.46 *d*
8	23.81 *t*	22.64 *t*	22.88 *t*
9	32.95 *t*	34.22 *t*	27.89 *t*
10	48.82	46.29	49.19
11	40.76 *d*	40.47 *d*	40.41 *d*
12	177.84	178.27	177.96
13	12.25 *q*	12.40 *q*	12.32 *q*
14	19.65 *q*	19.72 *q*	19.41 *q*
15	23.31 *q*	23.66 *q*	20.65 *q*

* Signals were assigned by means of off-resonance decoupled spectra.

† Indicates multiplicity on off-resonance partially decoupled spectra, signal without indication appeared as singlets.

a, b, c: Assignments may be interchanged.



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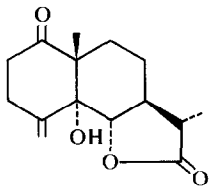

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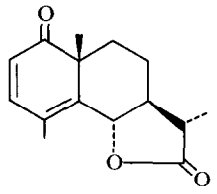

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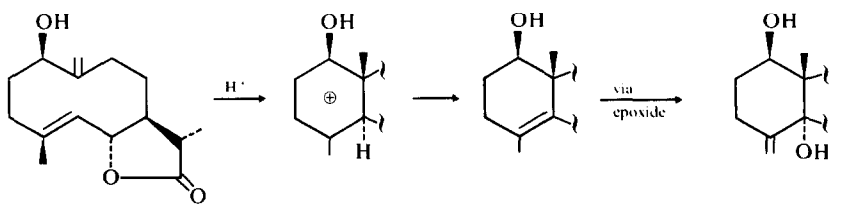
It can be deduced from the foregoing data that maritimin is 1-keto-4α,5α-epoxy-6β,7α,11β-H-selin-6,12-olide (**6**). The structure and stereochemistry of maritimin was further confirmed by treatment of **4** with *m*-chloroperbenzoic acid; the oxide thus obtained is identical with the natural product. Peracid oxidation of **4** takes place on the less hindered side forming the α-epoxide stereoselectively.

This result supports the previously suggested hypothesis [2] regarding the biogenetic relationships between gallicin (**2**), 1β-hydroxy-6β,7α,11β-H-selin-4(5)-en-6,12-olide (**3**) and artemin (**1**) (Scheme 1).

EXPERIMENTAL

General experimental details for extraction have been described previously [1]. Mps were determined with a Kofler hot-plate apparatus and were uncorr. IR spectra were taken with solns in $CHCl_3$, UV spectra used EtOH, 90 MHz ^1H NMR and 20 MHz ^{13}C NMR were in $CDCl_3$ (TMS as int. reference). Optical rotations were measured with solns in $CHCl_3$. CC was carried out with Merck Sil gel (0.05–0.2 mm) or Merck neutral Al_2O_3 (activity IV).

1-Keto-6β,7α,11β-H-selin-4(5)-en-6,12-olide (**4**). The extract was chromatographed on Si gel. Elution with petrol–EtOAc



2 10 3 1

Scheme 1.

(8:2) gave compound **4** (4.5 g, 0.04%). Recrystallization from EtOAc–*n*-hexane gave needles, mp 116–118°; $[\alpha]_D$ −115° (*c*, 0.2%); IR ν_{max} cm^{-1}: 1780 (γ-lactone) 1710 (ketone); MS: M^+ at *m/z* 248; ^1H NMR: δ 1.23 (3 H, *d*, *J* = 7 Hz, 11 − Me), 1.33 (3 H, *s*, 10 − Me), 1.98 (3 H, *s*, 4 − Me), 4.62 (1 H, *d*, *J* = 9 Hz, H − 6). (Found: C 72.41; H 8.02. Calc. for $C_{15}H_{20}O_3$: C 72.55; H 8.12%).

Vulgarin (**5**). Elution with petrol–EtOAc (1:1) gave compound **5** (25 mg, 0.0002%). Recrystallization from Me_2CO–*n*-hexane gave needles mp 176–177° $[\alpha]_D$ +39° (*c*, 0.3%); IR ν_{max} cm^{-1}: 3520 (OH) 1780 (γ-lactone) 1675 (ketone α,β-unsaturated) UV λ_{max} nm: 215; ^1H NMR: δ 1.23 (3 H, *s*, 10 − Me), 1.28 (3 H, *d*, *J* = 7 Hz, 11 − Me), 1.55 (3 H, *s*, 4 − Me), 2.36 (1 H, *d*, *J* = 10 Hz, H − 5), 4.25 (1 H, *dd*, *J* = 9, 10 Hz, H − 6), 5.90 (1 H, *d*, *J* = 10 Hz, H − 2), 6.61 (1 H, *d*, *J* = 10 Hz, H − 3). (Found: C 68.36; H 7.75. Calc. for $C_{15}H_{20}O_4$: C 68.16; H 7.63%).

Maritimin (**6**). Fractions 63–80 from the chromatography was repeatedly chromatographed on Si gel. Elution with C_6H_6–EtOAc (1:1) gave compound **6** (400 mg, 0.003%). Recrystallization from petrol–EtOAc gave needles, mp 176–178°, $[\alpha]_D$ −42° (*c*, 0.3%); IR ν_{max} cm^{-1}: 1778 (γ-lactone) 1710 (ketone); MS: M^+ at *m/z* 264. ^1H NMR: δ 1.25 (3 H, *d*, *J* = 7 Hz, 11 − Me), 1.27 (3 H, *s*, 10 − Me), 1.68 (3 H, *s*, 4 − Me), 4.34 (1 H, *d*, *J* = 9 Hz, H − 6). (Found: C 67.85; H 7.53. Calc. for $C_{15}H_{20}O_4$: C 68.16; H 7.63%).

Acid treatment of maritimin (**6**). (a) Compound **6** (100 mg) was dissolved in THF (10 ml) and THF (10 ml) was added, through which HCl gas was bubbled for 1 min. The mixture was stirred at room temp. for 17 hr, poured into H_2O, extrd with $CHCl_3$, washed with NaCl saturated, dried, concd *in vacuo* and chromatographed on Si gel, yielding compound **7** (34%) and small quantities of the ketone **8** and dienone **9**. Recrystallization from Me_2CO–*n*-hexane gave needles mp 202–204°; $[\alpha]_D$ +67.8° (*c*, 0.2%); IR ν_{max}^{KBr} cm^{-1}: 3480 (OH) 1770 (γ-lactone) 1725 (ketone): MS *m/z*: 300 $[M]^+$, 264 $[M - HCl]^+$; ^1H NMR: δ 1.25 (3 H, *d*, *J* = 7 Hz, 11 − Me), 1.58 (3 H, *s*, 10 − Me), 1.86 (3 H, *s*, 4 − Me), 4.68 (1 H, *d*, *J* = 8 Hz, H − 6). (Found: C 59.98; H 6.85; Cl 11.94. Calc. for $C_{15}H_{21}O_4Cl$: C 60.00; H 7.0; Cl 11.66%).

(b) Compound **6** (266 mg) was dissolved in C_6H_6 (10 ml) and BF_3 etherate (1 ml), freshly distilled, was added. The mixture was stirred at room temp. for 2 hr, poured into a cold satd soln of $NaCO_3H$, extrd with $CHCl_3$, dried, concd *in vacuo* and chromatographed successively on neutral Al_2O_3 (activity IV) (*n*-hexane–EtOAc, 7:3) and Si gel (*n*-hexane–EtOAc, 1:1). Repeated recrystallization from CH_2Cl_2–*n*-hexane gave needles of compound **9** (10%) mp 258–261°; $[\alpha]_D$ +206.5° (c, 0.2%); IR ν_{max} cm^{-1}: 1775 (γ-lactone) 1710 (ketone) 1650 (double bond); ^1H NMR δ 1.16 (3 H, *s*, 10 − Me), 1.23 (*d*, *J* = 7 Hz, 11 − Me), 4.31 (1 H, *d*, *J* = 10 Hz, H − 6), 5.25 (2 H, *bs*, C_4=CH_2). (Found: C 68.53; H 7.64. Calc. for $C_{15}H_{20}O_4$: C 68.16; H 7.63%).

Recrystallization of the mother liquor from CH_2Cl_2–*n*-hexane gave needles (40%), mp 137–140°; $[\alpha]_D$ −118° (*c*, 0.2%); IR ν_{max} cm^{-1}: 1775 (γ-lactone) 1665, 1630 (αβ-unsaturated ketone); UV λ_{max} nm: 325 (log ε = 3.6); MS: M^+ at *m/z* 246; ^1H NMR: δ 1.24 (3 H, *d*, *J* = 7 Hz, 11 − Me), 1.34 (3 H, *s*, 10 − Me), 2.18 (3 H, *d*, *J* = 2 Hz, 4 − Me), 4.73 (1 H, *d*, *J* = 10 Hz, H − 6), 6.04 (1 H, *d*, *J* = 10 Hz, H − 2), 6.85 (1 H, *d*, *J* = 10 Hz, H − 3).

Alcalin treatment of **7**. Compound **7** (50 mg) was dissolved in MeOH (15 ml) and Na_2CO_3 (90 mg) was added. The mixture was stirred at room temp. for 24 hr, poured into H_2O, extrd with $CHCl_3$, dried and concd *in vacuo*, yielding maritimin (**6**) quantitatively.

Epoxidation of **4**. Compound 4 (60 mg) was dissolved in $CHCl_3$ (15 ml) and 3 mequiv. of *m*-chloroperbenzoic acid was added. The mixture was stirred at room temp. for 6 hr, poured into dil. Na_2SO_3 soln, washed with satd $NaCO_3H$ soln, extrd with $CHCl_3$, dried and concd *in vacuo*. Crystallization from Me_2CO–*n*-hexane gave needles (90%) of maritimin (**6**).

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