SESQUITERPENE LACTONES FROM *ARTEMISIA FRIGIDA*

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ABSTRACT.—1,10α-Epoxy-8α-hydroxyachillin (**1**), anhydrogrossmisin (**2**), canin (**3**), artecanin (**4**), ridentin (**5**) and 8α-hydroxyachillin (**6**) were isolated from *A. frigida*. 1,10α-Epoxy-8α-hydroxyachillin (**1**) was obtained for the first time as a natural product. The stereochemistry of 1,10α-epoxy-8α-hydroxyachillin (**1**) and anhydrogrossmisin (**2**) is discussed on the basis of spectroscopic data. That canin (**3**) is the same as chrysartemin-A was further confirmed and ¹³C-nmr and pmr data are described.

Leaves of *Artemisia frigida* Willd. (Compositae) are not eaten by the grasshopper *Hypochlora alba*, while the leaves of *A. ludoviciana* var. *ludoviciana* Nutt. provide the primary food source for this insect. Since both plant species appear to have similar mats of pubescence and glandular trichomes, these feeding preferences may result from chemical differences. Thus, in connection with establishing the nature of the feeding deterrence of *A. frigida* to *H. alba* (a joint project with Professors H. Knutson and T. Hopkins, Kansas State University) we now report six sesquiterpene lactones from *A. frigida*. Their effects on insects will now be determined. We previously described fourteen flavonoids from this same species [1, 2].

RESULTS AND DISCUSSION

Ground air-dried leaves of *Artemisia frigida* were extracted with aqueous methanol. After removal of the methanol, the resulting aqueous layer was stored in a refrigerator; a precipitate which appeared was filtered off. The aqueous layer was partitioned between hexane, chloroform, and ethyl acetate. Chromatographic separation of the chloroform extract and treatment of the precipitate afforded six sesquiterpene lactones (**1–6**).

Lactone **1** (mp 252–255°, $[\alpha]^{28}D = +98°$ (MeOH,C=0.46) was isolated as colorless needles. It was soluble in dimethylsulfoxide, hot methanol and ethanol, but only slightly soluble in chloroform, benzene, ethyl acetate, acetone and pyridine. Lactone **1** appeared as a dark purple spot on a silica gel GF 254 plate in uv light; the spot turned blue fluorescent in long wave-length uv light after spraying with 20% H_2SO_4 and heating at 105°. The mass spectrum of **1** showed a molecular ion peak at m/z 278 (48%) corresponding to formula $C_{15}H_{18}O_5$ and base peak at m/z 151. An M–16 fragment appeared at m/z 262 (38%). Lactone **1** showed uv absorption maxima at 234 ($\epsilon = 12,800$) and 206 nm ($\epsilon = 18,300$). The bands at 3430, 1754, 1715 and 1620 cm⁻¹ in the ir spectrum indicated the presence, respectively, of a hydroxyl group, γ-lactone ring, α, β-unsaturated cyclopentenone and a double bond. The pmr spectrum of **1** exhibited a doublet at δ 1.13 (3H, $J=8$ Hz), which was assigned to the C–11 methyl group of the lactone ring; two signals at δ 1.64 (3H) and 2.27 (3H) were attributed to the C–10 and C–4 methyl groups, respectively; a signal at δ 6.27 (1H, $J=1$ Hz) was assigned to an olefinic proton at C–3; and a doublet at δ 3.41 (1H, $J_{5,6}=10.5$ Hz) corresponded to an α-proton at C–5. A triplet at δ4.22 (1H, $J_{5,6}=10.5$, $J_{6,7}=10.5$ Hz) is characteristic for the C–6 proton in guaianolide-type sesquiterpene lactones. A double-quartet appearing at δ2.61 (1H, $J_{7,11}=8$, $J_{11,13}=8$ Hz) was assigned to the proton at C–11. A multiplet appeared centered at δ3.57 (1H) for the proton at C–8, and the C–8 hydroxyl proton gave a doublet at δ4.92. The coupling constants $J_{5,6}=10.5$ Hz and $J_{6,7}=10.5$ Hz suggest a *trans*-axial arrangement for the protons at C–5, 6 and 7. Therefore, if the C_6–H configuration is β, as is
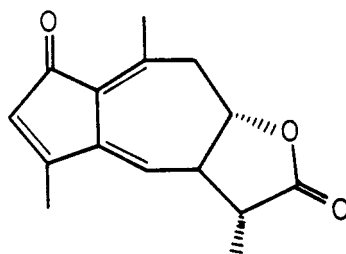
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likely, the proton configurations are then H–5α, H–6β and H–7α. Such configurations have been confirmed for all guaianolides so far isolated from *Artemisia* except one, sieversin, whose configurations at these positions are not settled. If
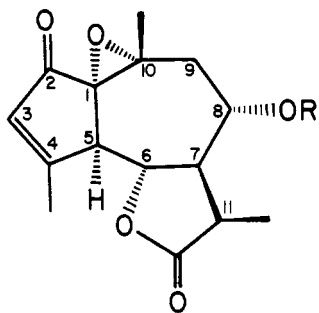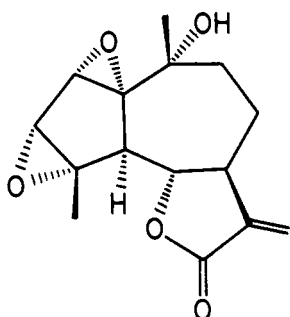
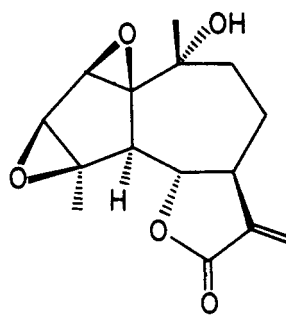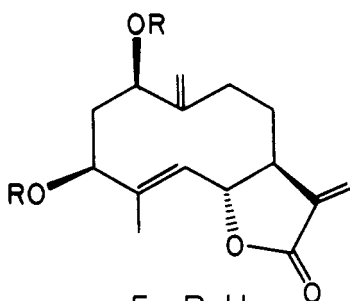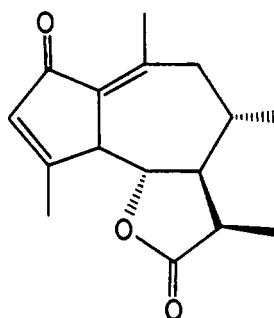<u>1</u> R=H
<u>1a</u> R=Ac

<u>2</u>

<u>3</u>

<u>4</u>

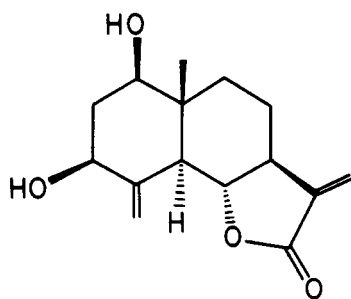<u>5</u> R=H
<u>5a</u> R=TMSi

<u>6</u> R=H
<u>6a</u> R=Ac

<u>7</u>

the fusion of the lactone is *trans*, the observed $J_{7,11}$ of 7.5 Hz requires the C_{11}-methyl group to be β-oriented [3]. Biogenetically, a β-oriented C_{10}-methyl group (and thus an α C_1–C_{10} epoxy group) is favored for 1 since this same stereochemistry has been established for all known guaianolides so far isolated from *Artemisia* including those with a C_1–C_{10} epoxy group. These deductions lead to the stereochemistry as shown in 1. Moreover, the ^{13}C-nmr data (see table 2) support structure 1. The signals for C–1 and C–10 of 1 overlapped at 65.2 ppm, indicating the equivalence of these two carbons as a result of the presence of the 1,10-epoxy group.

Acetylation of 1 yielded the monoacetate 1a whose pmr spectrum exhibited an acetyl signal at $\delta 2.09$ (table 1). The mass spectrum of 1a showed a molecular ion peak at m/z 320 corresponding to formula $C_{17}H_{20}O_6$. Thus, the structure of 1 was confirmed as 1,10α-expoxy-8α-hydroxyachillin. Gonzalez and co-workers [4] isolated a mixture of two compounds from *Artemisia lanata* which could be separated only as acetylation products. One of the acetates was described as 1,10-epoxy-8α-acetoxyachillin on the basis of ms and pmr data. However, the stereochemical assignments were not discussed.

Lactone 2 (mp 193–194°) was isolated as colorless crystals. The mass spectrum of 2 showed a molecular ion peak at m/z 244 (100%) corresponding to formula $C_{15}H_{16}O_3$. Compound 2 exhibited absorption maxima at 243 ($\epsilon = 15,800$), 256 ($\epsilon = 15,500$) and 310 nm ($\epsilon = 8,200$) in the uv spectrum and bands at 1770, 1690, 1625, 1605, 990 and 868 cm^{-1} in the ir spectrum, indicating the presence of a γ-lactone ring, a conjugated keto group in a five-membered ring and double bonds. The ^{13}C-nmr spectrum of 2 exhibited two singlets at 194.9 and 177.5 ppm, which could be assigned to the C–2 keto group and C–12 lactone carbonyls, respectively. In the unsaturated carbon region, four singlets appeared at 161.5, 145.9, 140.3 and 127.5 ppm which could be assigned to C–1, C–5, C–4 and C–10, respectively; two doublets at 132.1 and 118.8 ppm were assigned to C–3 and C–6. Three other doublets which appeared at 77.8, 50.3 and 41.5 ppm were assigned to the saturated carbon atoms at positions 8, 7 and 11, respectively. In addition to a triplet at 44.6 ppm for C–9, three methyl carbon quartets appeared at 21.4, 14.1 and 13.1 ppm for the C–13, C–15 and C–14 methyl carbons, respectively (table 2) [5–7]. The pmr spectrum of 2 (table 1) exhibited signals which were in accord with the ^{13}C-nmr data and supported the guaianolide structure 2. Examination of the pmr couplings of 2 ($J_{7,8} = 8$ Hz, $J_{8,9a} = 4$ Hz and $J_{8,9b} = 10$ Hz) indicated a C–7,8 *trans*-fused lactone ring. A *trans*-fused lactone ring was further supported by the coupling constant between H–7 and H–11 ($J_{7,11} = 13$ Hz). On the basis of the benzene-induced shift of the C–11 methyl group ($\Delta = \delta_{CDCl_3} - \delta_{C_6D_6} = 1.37 - 1.06 = 0.31$ ppm) this methyl group must be α-oriented [3].

Three compounds have been reported with the same skeletal structure, namely, ferulin, anhydrogrossmisin and anhydroaustrin; however, no information about their stereochemistry is available [8–9]. Since the melting point of compound 2 isolated here coincides with that of anhydrogrossmisin we use the name anhydrogrossmisin for 2 and define its stereochemistry. Anhydrogrossmisin (2) was previously obtained as a product of chemical transformation [9]; this is the first report of its natural occurrence.

Lactone 3 was identified as canin [10–12] by direct comparison of ir, pmr, uv, ms and other physical constants with those of an authentic specimen. The ^{13}C-nmr spectrum of 3 provided further confirmation of its structure (table 2).

The R_f values, ir and pmr spectra of both lactone 3 and authentic canin were also identical to those of an authentic specimen of chrysartemin-A [13–14], reconfirming the identity of the latter two compounds (table 3).

Lactone 5 [mp 208–211°, $[\alpha]^{28}D = -111°$ (MeOH, C=0.42)] was isolated as colorless needles. The uv, ir and ms of 5 were identical to those of ridentin (reported mp 215–218°) which was reported as a constituent of other species of *Artemisia* [15–16]. The pmr of the trimethylsilyl ether of 5 was also identical

TABLE 1.   Pmr data of sesquiterpene lactones **1-6** from *Artemisia frigida*[a].

Protons	1 (DMSO-d6)	1a (CDCl3)[b]	2 (CDCl3)	3 (DMSO-d6)[b]	3 (Py-d6)	4 (Py-d6)	5 (Py-d6)	5a (CDCl3)	6 (DMSO-d6)[b]	6a (CDCl3)
H-2				3.28 d, $J=1$	3.38 d, $J=1$	3.28 d, $J=1$	4.33 m[c]	4.01 dd, $J=11$; 5(H-1)	5.15 d (-OH)	
H-3	6.27 d, $J=1$	6.24 d, $J=1$	6.11 d, $J=1$	3.37 d, $J=1$	3.57 d, $J=1$	3.72 d, $J=1$	4.58 t[c]	4.08 dd, $J=11$; 4	6.17 brs	6.18 brs, $J=1$
H-5	3.41 d, $J=10.5$	3.08 d, $J=11$		2.26 d, $J=11$	2.78 d, $J=11$	3.23 d, $J=11$	5.48 d, $J=10$	5.29 d, $J=10$	3.58 d, $J=10$	3.42 dd, $J=9.5$; 1.5
H-6	4.22 t, $J=10.5$	4.34 t, $J=11$	5.86 d, $J=2.5$	4.50 dd, $J=11$; 9.5	4.51 dd, $J=11$; 9.5	4.38 t, $J=10$	4.64 t, $J=10$	4.46 t, $J=10$	3.95 t, $J=10$	3.90 t, $J=10$
H-7	3.35 m				2.48 m		2.85 m	2.86 brt		
H-8	3.57 m	5.02 dt, $J=11.5$; 3.5	2.79 ddd, $J=2.5$; 13; 8 4.37 ddd, $J=8$; 4; 10							4.77 dt, $J=10$; 2
H-9a			2.88 dd, $J=4$; 18							
H-9b			3.10 dd, $J=10$; 18							2.83 m
H-11	2.61 dq, $J=8$	2.72 dq, $J=8$	2.62 dq, $J=13$; 6							
H-13a				5.52 d, $J=3$	5.43 d, $J=3$	5.35 d, $J=3$	5.42 d, $J=3$	5.45 d, $J=3$		
H-13b				5.98 d, $J=3$	6.19 d, $J=3$	6.20 d, $J=3$	6.27 d, $J=3$	6.30 d, $J=3$		
C-4Me	2.27 d, $J=1$	2.39 d, $J=1$	2.16 d, $J=1$	1.40 s	1.65 s	1.48 s	1.97 s	1.75 s	2.22 s[c]	2.28 brs[c]
C-10Me	1.64 s	1.79 s	2.46 s	0.95 s	1.24 s	1.26 s			2.34 s[c]	2.47 brs[c]
C-11Me	1.13 d, $J=8$	1.13 d, $J=8$	1.38 d, $J=6$						1.14 d, $J=7.5$	1.12 d, $J=8$
H-15a		2.09 s (-OAc)					4.95 brs, $J=1$	4.87 brs, $J=1$		2.09 s (-OAc)
H-15b							5.35 brs, $J=1$	5.19 brs, $J=1$		

[a] Recorded on a 200 MHz instrument unless otherwise noted; TMS as internal reference and J in Hz.

[b] Run on a 90 MHz instrument.

[c] Assignments may be interchanged.

TABLE 2. ^{13}C-nmr of sesquiterpene lactones 1-6 from *Artemisia frigida*.[a]

Carbon Nos.	1 (DMSO-d$_6$)	2 (CDCl$_3$)	3 (DMSO-d$_6$)	4 (DMSO-d$_6$)	5 (DMSO-d$_6$)	6 (DMSO-d$_6$)
1.............	65.2 s	161.5 s	79.6 s	77.7 s	73.6 d	132.3 s
2.............	201.1 s	194.9 s	78.4 d	82.3 d	41.4 t	195.1 s
3.............	132.3 d	132.1 d	57.7 d	57.0 d	74.0 d	134.7 d
4.............	177.7 s	140.3 s	72.6 s	70.4 s	140.3 s	170.6 s
5.............	56.4 d	145.9 s	42.5 d	44.0 s	120.8 d	50.8 d
6.............	77.0 d	118.8 d	57.4 d	56.0 d	79.7 d	80.8 d
7.............	47.4 d	50.3 d	49.5 d	42.5 d	47.5 d	56.8 d
8.............	62.4 d	77.8 d	23.5 t	22.2 t	31.1 t^b	63.7 d
9.............	43.7 t	44.6 t	33.0 t	36.9 t	25.9 t^b	47.6 t
10.............	65.2 s	127.5 s	71.5 s	70.2 s	147.8 s^b	146.3 s
11.............	37.5 d	41.5 d	140.9 s	139.6 s	150.0 s^b	37.6 d
12.............	178.5 s	177.5 s	169.3 s	169.6 s	170.0 s	178.2 s
13.............	8.8 q	21.4 q	118.9 t	118.7 t	118.4 t	8.8 q
14.............	20.3 q^b	13.1 q^b	19.2 q	19.5 q	11.6 q	20.9 q^b
15.............	18.5 q^b	14.1 q^b	27.0 q	26.9 q	110.0 t	19.2 q^b

[a]Run on a 22.6 MHz instrument in deuterium solvents with TMS as internal standard. Signals were assigned by means of off-resonance decoupled spectra.
[b]Assignments may be interchanged.

to the spectrum of the TMSi ether of ridentin [17]. That 5 differed from ridentin-B (7) (an isomeric sesquiterpene lactone of ridentin [18]) was evident from the ^{13}C-nmr spectrum of 5 (table 2). One singlet at 140.3 and a doublet at 120.8 ppm indicated the olefinic character of C-4 and C-5 in 5. Moreover, a one-proton doublet at δ5.48 in the pmr spectrum suggested the presence of an olefinic proton at C-5 in 5; 7 does not have a C-5 olefinic proton. Therefore, 5 is identical with ridentin.

Lactones 4 and 6 were identified as artecanin and 8α-hydroxyachillin, respectively, on the basis of pmr, ^{13}C-nmr, ms, uv, ir and comparison with authentic samples.

TABLE 3. Chromatographic data of lactone 3 and 4.[a]

Solvent Systems	Lactone 3	Canin	Chrysarte-min-A	Lactone 4	Artecanin	Chrysarte-min-B
Benzene-ethyl acetate-methanol (4:6:1).........	0.59	0.59	0.59	0.67	0.67	0.67
Ethyl-acetate..............	0.45	0.45	0.45	0.53	0.53	0.53
Chloroform-acetone (1:1)...	0.67	0.67	0.67	0.74	0.74	0.74
Benzene-ethyl acetate (1:4).	0.36	0.36	0.36	0.42	0.42	0.42
Toluene-ethanol (5:6)^b......	0.17	0.17	0.17	0.20	0.20	0.20
Chloroform-methanol (15:1).....................	0.48	0.48	0.48	0.46	0.46	0.46

[a]Developed on silica gel GF-254 plates; visualization was realized by spraying with 20% H$_2$SO$_4$.
[b]Twice developed.

EXPERIMENTAL

PLANT MATERIAL.—The aerial parts of *A. frigida* were collected by Dr. Greg Mulkem, near Fargo, North Dakota, August 18, 1979. Voucher specimen G. M. R. K. No. 1 is deposited in the Lundell Herbarium, The University of Texas at Austin.

GENERAL TECHNIQUES.—Mps were determined on a Fisher-Johns mp block and are uncorrected. Column chromatography employed Polyclar AT (GAF Corp.). Si gel 60 GF-254 (E. Merck) was used for tlc. Visualization of the sesquiterpene lactones on tlc plates was realized by uv light (254 and 366 nm) before and after spraying with 20% H$_2$SO$_4$ and heating at 105°.

EXTRACTION AND PARTITIONING OF EXTRACT RESIDUE.—Ground, dried leaves and stems (1.58 kg.) were extracted with 85% aq. methanol (10 liters x 3) and 50% aq. methanol (10 liters x 2). The extracts were combined and evaporated under reduced pressure until only water remained. The precipitate (63.2 g) obtained after the concentrate was allowed to stand

in the refrigerator for 2 days was filtered off.   The aqueous layer was partitioned with *n*-hexane (1.5 liters x 4), chloroform (1.2 liters x 8) and ethyl acetate (1.2 liters x 15).

ISOLATION OF SESQUITERPENE LACTONES.—The chloroform extract concentrate (25 g) was chromatographed over a Polyclar column, which was eluted with a mixture of benzene-methanol with a gradual increase in the ratio of methanol.   Fractions of 500 ml each were collected. Fractions 5–7 contained lactone **3**; 9 gave lactone **6**; 10 contained lactone **1**; 13 yielded lactone **4** ; and 21 gave lactone **5**.

The precipitate (63.2 g) noted above was treated with 5% aq. Na₂CO₃ (150 ml).   After filtering, the filtrate was acidified with conc. HCl.   A yellow-green precipitate (5.6 g) which formed was filtered and washed with deionized water and then separated over a Polyclar column.   The column was eluted with benzene-methanol (9:1).   Fractions of 100 ml each were collected.   The first two fractions contained lactone **2**, which was further purified on a column of silica gel (30 g).   When this latter column was eluted with toluene-ethyl acetate (5:5), the second 50 ml fraction gave pure lactone **2**.

1,10α-EPOXY-8α-HYDROXYACHILLIN (LACTONE **1**).—Compound **1** was crystallized from methanol and recrystallized from ethanol (yield 77 mg).   It exhibited the following spectral properties, ir, ν max (Nujol) 3430, 1754, 1715, 1620, 1450, 1353, and 845 cm⁻¹: ms, m/z M⁺ 278 (49%), 262 (38), 244 (3), 229 (2), 216 (4), 201 (4), 189 (10), 171 (10), 159 (9), 151 (100), 147 (13), 136 (11), 122 (15) and 109 (42): pmr and ¹³C-nmr see tables 1 and 2.   **1** (15 mg) was treated overnight with acetic anhydride-pyridine (3:2, 1 ml).   Following removal of excess reagents under high vacuum and crystallization from ethanol, the acetylation product (**1a**, 11 mg), mp 268–271°, exhibited the following spectral properties: ir, ν max (Nujol) 1775 (γ-lactone), 1735 (acetyl), 1695 (α,β-unsaturated carbonyl) and 1605 cm⁻¹; ms, m/z M⁻ 320 (40%), 304 (4), 278 (13), 260 (21), 244 (3), 232 (10), 217 (7), 204 (11), 189 (8), 176 (9), 161 (10), 151 (72), 135 (11), 122 (35), 109 (45) and 43 (100): uv, λ max (EtOH), 236 nm (ϵ=14800): for pmr, see table 1.

ANHYDROGROSSMISIN (LACTONE **2**).—Compound **2** was crystallized from methanol and recrystallized from propanol-isopropyl ether (yield 71 mg; an additional 28 mg was obtained from the mother liquor).   It exhibited the following spectral properties: ms m/z M⁻ 244 (100%), 229 (3), 216 (7), 201 (10), 188 (21), 173 (34), 171 (31), 159 (42), 145 (44), 129 (26) and 115 (35): for pmr and ¹³C-nmr, see tables 1 and 2.

CANIN (LACTONE **3**).—Compound **3** was crystallized from methanol and recrystallized from ethanol (yield 116 mg) as colorless prisms, mp 243–246° [lit. (10) 244–246°; (11) 245–246°)]. It exhibited the following spectral properties: uv (EtOH) λ max 211 nm (ϵ=8320); ir, ν max (Nujol) 3480 (–OH), 1765 and 1660 cm⁻¹ (γ-lactone conjugated with an exocyclic methylene group); ms, m/z M⁺ 278 (1%), 260 (5), 231 (4), 217 (4), 203 (4), 189 (40), 175 (6), 161 (7), 151 (18), 135 (8), 123 (10) and 111 (100): for pmr and ¹³C-nmr, see tables 1 and 2.

ARTECANIN (LACTONE **4**).—Lactone **4** was crystallized from methanol and recrystallized from ethanol (yield 62 mg) as colorless prisms, mp 249–251° [lit. (10) 244°; (11) 244–245°; (12) 253–254°; (13) 262–263°; (14) 234–237°].   It exhibited the following spectral properties: uv, (EtOH) λ max 209 nm (ϵ=8270); ir ν max (Nujol) 3400 (–OH), 1740 (γ–lactone) and 1156 cm⁻¹: ms, m/z M⁺ 278 (1%), 260 (3), 249 (2), 217 (2), 203 (3), 189 (3), 175 (5), 161 (5), 161 (5), 151 (12), 137 (7), 123 (10) and 111 (100): for pmr and ¹³C-nmr, see tables 1 and 2; for co-chromatographic data, see table 3.

RIDENTIN (LACTONE **5**).—Lactone **5** was crystallized from methanol and recrystallized from ethanol (yield 56 mg) as colorless needles, mp 208–211° [lit. (16) 215–218°].   It exhibited the following spectral properties: ir, ν max (Nujol) 3300 (–OH), 1760, 1645 (γ-lactone conjugated with an exocyclic methylene grouping) and 1670 cm⁻¹ (double bond); uv, (EtOH) λ max 209 nm (ϵ=12,500); ms, m/z M⁻ 264 (3%), 246 (9), 236 (2), 228 (8), 219 (18), 217 (18), 213 (6), 203 (14), 189 (19), 185 (11), 175 (42), 157 (17), 149 (66), 133 (27), 121 (43), 105 (51), 91 (83), 79 (64), 71 (60), 53 (86) and 43 (100); for pmr and ¹³C-nmr, see tables 1 and 2.   Compound **5** (12 mg) was trimethylsilylated with hexamethyldisilazane and trimethylchlorosilane in pyridine (yield 15 mg).   The trimethylsilylation product **5a**, which was readily soluble in chloroform and carbon tetrachloride, was used for a decoupling experiment; for see pmr, table 1).

8α-HYDROXYACHILLIN (LACTONE **6**).—Lactone **6** was crystallized from methanol and recrystallized from ethanol (yield 991 mg) as colorless prisms, mp 125–128°, [α]²⁵D = +104° (MeOH, C=0.64).   It exhibited the following spectral properties: ir, ν max (Nujol) 3450 (–OH), 1750 (γ-lactone), 1675 (α,β-unsaturated carbonyl), 1645 and 1615 cm⁻¹ (double bonds); uv, (EtOH) λ max 255 nm (=14,100); ms, m/z M⁺ 262 (100%), 244 (5), 229 (8), 216 (20), 201 (19), 189 (40), 183 (9), 171 (40), 159 (27), 147 (37), 136 (30), 115 (12) and 105 (20); for pmr and ¹³C-nmr, see tables 1 and 2.   Compound **6** (20 mg) was acetylated with acetic anhydride-pyridine.   The acetylation product **6a** was crystallized from ethanol as colorless needles (yield 18 mg) mp 186–189°; ms, m/z M⁺ 304 (100%), 262 (17), 244 (63), 229 (19), 216 (27), 201 (29), 188 (31), 171 (49), 159 (55) and 151 (30); ir, ν max 1780 (γ-lactone), 1735 (acetyl), 1680 (α,β-unsaturated carbonyl), 1635 and 1615 cm⁻¹ (double bonds); for pmr, see table 1.

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