Phytochemistry, 1980, Vol. 19, pp. 849–856. © Pergamon Press Ltd. Printed in England. 0031-9422/80/0501-0849 $02.00/0

NEW GERMACROLIDE- AND HELIANGOLIDE-TYPE SESQUITERPENE LACTONES FROM *MELAMPODIUM LINEARILOBUM*

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(*Received* 23 *July* 1979)

Key Word Index—*Melampodium linearilobum*; Heliantheae; Compositae; sesquiterpene lactones; germacrolides; heliangolides.

Abstract—Chemical analysis of *Melampodium linearilobum* yielded, besides coumarin, seven germacrolide-type sesquiterpene lactones, linearilobin A to G and two heliangolides, linearilobin H and I. All new sesquiterpene lactones are oxygenated at C-14 and C-15 and differ by the number and types of ester moieties at C-8, C-14 and C-15. *M. linearilobum* represents the first species within the genus known to produce germacrolides and heliangolides instead of the more common melampolides.

INTRODUCTION

In connection with our biochemical systematic study of the subtribe Melampodiinae and our search for antineoplastic constituents within the family Compositae we have analysed *Melampodium linearilobum* of the subtribe Melampodiinae. In contrast to other *Melampodium* species, which typically produce melampolides [1], *M. linearilobum* from Mexico contains germacrolides and heliangolides. The aerial parts of three populations provided nine new sesquiterpene lactones which we named linearilobin A to I. Their structures were established by spectroscopic methods (NMR, MS and CD) and chemical transformations.

RESULTS AND DISCUSSION

Linearilobin A and B

Linearilobin A (**1a**), $C_{21}H_{28}O_7$ (HRMS, CI), mp 144–145°, showed sharp doublets at δ 5.62 (H-13a) and 6.38 (H-13b) and a multiplet at 2.79 (H-7) typical of α,β-unsaturated γ-lactones. A three-proton singlet at 2.12 and two methyl doublets at 1.18 and 1.19 suggested an acetate and isobutyrate, respectively. Prominent MS peaks at *m/e* 333 ($M-C_2H_3O_2$) and 43 (C_2H_3O, base peak) as well as 305 ($M-C_4H_7O_2$) and 71 (C_4H_7O) verified the above ^{1}H NMR assignments. The molecular ion at *m/e* 392 and a strong peak at *m/e* 244 ($M-C_4H_8O_2-C_2H_4O_2$) indicated that after the loss of the two ester side chains a $C_{15}H_{16}O_3$ MS-fragment remained, thus indicating a third oxygen function in addition to the lactone oxygens within the basic ring structure in **1a**; this was verified by a strong IR absorption at 3520 cm^{-1} (hydroxyl) and the formation of an acetate (**1b**).

Extensive spin-decoupling experiments were performed on the acetate **1b**. Irradiation at δ 2.92 (H-7) collapsed the two doublets at 5.62 and 6.38 (H-13a and H-13b) to singlets, reduced the doublet of doublets at 5.11 (H-6, $J_{5,6}=10.0$, $J_{6,7}=8.5$ Hz) to a doublet and sharpened the multiplet at 5.76 (H-8). Since the signal at 5.76 in **1b** resulted from a downfield shift of the multiplet at 4.62 in **1a**, when acetylated, the hydroxyl group in **1a** must be attached to C-8. Irradiation at 5.76 (H-8) caused the multiplet at 2.92 (H-7) to collapse to a broadened triplet of a doublet ($J_{6,7}=$ 8.5, $J_{7,13a}=3.0$, $J_{7,13b}=3.5$ Hz) and the doublet of doublets at 3.19 (H-9b, $J_{8,9}=ca$ 6.0, $J_{9a,9b}=15.0$ Hz) simplified to a broadened doublet. This broadening of H-9b was attributed to long-range coupling with H-14. Irradiation at 3.19 (H-9b) sharpened the multiplet at 5.76 (H-8) to a broadened singlet and collapsed the broad doublet at 2.20 (H-9a) to a broad singlet. The splitting of the H-1 singlet (5.21, *dd*, $J=12.0$ and 5.0 Hz) indicated that C-2 represents a methylene group. When H-1 at 5.21 was irradiated, the multiplets at 1.63 (H-2a) and 2.40 (H-2b) were affected.

The decoupling experiments indicated that new compound belonged to the germacranolide series containing C-14 and C-15 oxygen functions. Similar medium ring compounds with both C-14 and C-15 being oxygenated had previously been reported from *Jurinea* species [2, 3]. The chemical shifts of the two pairs of geminally coupled doublets, each pair integrating for two protons, indicated that C-14 and C-15 represent acyloxy-containing methylenes. In **1a**, a pair of doublets at 4.56 ($J_{15a,b}=13.0$ Hz) and 4.73 were assigned to the two H-15. The pair of doublets at 4.51 ($J_{14a,b}=12.5$ Hz) and 4.63 were ascribed to H-14 based on correlations of chemical shift data of **1a** and **1b** with linearilobin C (**3a**) and the acetate (**3b**). In **3a** the H-14 and H-15 absorptions had been unambiguously assigned by oxidative conversion of the C-14 hydroxyl group to the aldehyde **3d**. The sterochemistry and conformation of **1a** were assigned on NMR and CD spectral grounds. Based on the biogenetic assumption that H-7 adopts an α-configuration [4] H-6 should be β-oriented since the coupling constants $J_{6,7}$ (8.5 Hz) suggested an antiperiplanar orientation of H-7 and H-6. Furthermore, a large $J_{5,6}$ (10 Hz) indicated that H-5 and H-6 also have an antiperiplanar

arrangement typical of germacrolides and melampolides [4]. Furthermore, the allylic coupling $J_{7,13a}$ (3.0 Hz) and $J_{7,13b}$ (3.5 Hz) support the above arguments suggesting a *trans*-fused lactone group and a *trans*-4,5-double bond [5]. The CD spectrum of **1a** exhibited two strong bands of opposite sign, a positive band at 244 nm and a negative absorption near 205 nm. CD spectra exhibited by **1a** are typical for germacrolides with 7,6-*trans*-lactone ring closure in which the two homoconjugated double bonds have a chiral arrangement with both, C-14 and C-15, being placed above the plane of the medium ring [2, 4, 6].

The configuration of the C-8 hydroxyl group was derived from the $J_{7,8}$ values. Based on model considerations, the small coupling ($J_{7,8}$ = 1–2 Hz) required that the C-8 hydroxyl group be β-oriented. This was further verified by the following observations. Upon acetylation of **1a** one of the protons at the β-oriented C-14 (H-14a) is exposed to the shielding sphere of the newly introduced acetate carbonyl at C-8 causing a substantial upfield shift of H-14a from 4.56 in **1a** to 4.17 in **1b** whereas H-14b is essentially unaffected.

Linearilobin B (**2a**), $C_{22}H_{30}O_7$ (MS, CI), mp 151–152°, displayed ^{1}H NMR signals that were nearly identical with the absorptions of **1a** with the exception that the isobutyrate signals were replaced by those characteristic of α-methyl-*n*-butyrate (Table 1). The low resolution MS supported the ^{1}H NMR assign-

Table 1. ^{1}H NMR parameters of

	1a	**2a**	**1b**	**2b**	**3a**†	**3b**	**3d**
H-1	5.18 *dd* (12.5, 5.0)	5.17 *dd* (12.5, 5.0)	5.21 *t* (8.5)	5.21 *t* (8.5)	5.21 *t* (9.0)	5.23 *m*	6.43 *dd* (13.0, 4.0)
H-2a	1.63 *m*	1.63 *m*	1.63 *m*	1.63 *m*	1.5–2.7	—	—
H-2b	2.40 *m*	2.40 *m*	2.40 *m*	2.40	1.5–2.7	—	—
H-3a	2.40 *m*	2.40 *m*	2.40 *m*	2.40 *m*	1.5–2.7	—	—
H-3b	2.64 *m*	2.60 *m*	2.64 *m*	2.64 *m*	1.5–2.7	2.61	—
H-5	5.04 *brd* (10.5)	5.04 *brd* (10.5)	4.99 *brd* (10.5)	4.99 *brd* (10.5)	5.03 *d* (12.0)	4.99 *d* (10.5)	5.30‡ *brd* (10.0)
H-6	5.27 *dd* (10.5, 8.5)	5.27 *dd* (10.5, 8.5)	5.11 *dd* (10.0, 9.0)	5.11 *dd* (10.0, 9.0)	5.14 *dd* (10.0, 9.0)	5.16 *m*	5.14 *m*‡
H-7	2.79 *m*	2.79 *m*	2.92 *m*	2.92 *m*	2.97 *m*	2.96 *m*	2.95 *m*
H-8	4.62 *m*	4.62 *m*	5.76 *m*	5.76 *m*	5.81 *m*	5.83 *m*	5.78 *m*
H-9a	2.22 *m*	2.22 *m*	2.21 *m*	2.21 *m*		—	—
H-9b	2.96 *dd* (15.0, *ca* 6.0)	2.98 *dd* (15.0, *ca* 6.0)	3.19 *m*	3.19 *m*	3.30 *dd* (15.0, 6.0)	3.3 *dd* (15.0, 6.0)	3.60 *m*
H-13a	5.62 *d* (3.0)	5.62 *d* (3.0)	5.62 *d* (3.0)	5.62 *d* (3.0)	5.65 *d* (3.0)	5.61 *d* (3.0)	5.64 *d* (3.0)
H-13b	6.38 *d* (3.5)	6.37 *d* (3.5)	6.34 *d* (3.5)	6.34 *d* (3.5)	6.33 *d* (3.5)	6.31 *d* (3.5)	6.32 *d* (3.5)
H-14a	4.56 *d* (12.5)	4.56 *d* (12.5)	4.17 *brd* (12.5)	4.17 *d* (12.5)	3.76 *d* (12.5)	4.03 *d* (12.5)	9.89 *s* [-CHO]
H14b	4.73 *d* (12.5)	4.74 *d* (12.5)	4.74 *d* (12.5)	4.72 *d* (12.5)	4.16 *d* (12.5)	4.71 *d* (12.5)	
H-15a	4.51 *d* (13.0)	4.51 (13.0)	4.59 *d* (13.0)	4.58 *d* (13.0)	4.57 *d* (13.0)	4.56§ [2H]	4.51§ [2H]
H-15b	4.63 *d* (13.0)	4.74 (13.0)	4.67 *d* (13.0)	4.67 *d* (13.0)	4.70 *d* (13.0)	—	
H-2′	2.58 *m*	2.39 *sext.* (7.0)	2.51 *m*	2.39 *m*	—	—	—
H-3′	—	*a.* 1.48 *p* (7.0) *b.* 1.69 *p* (7.0)	—	*a.* 1.46 *p* (7.0) *b.* 1.63 *p* (7.0)	6.74 *tq* (1.0, 6.0)	6.64 *tq* (1.0, 6.0)	5.66 *dq* (1.5, 7.0)
H-4′	—	0.91 *t* (7.0) [3H]	—	0.89 *t* (7.0) [3H]	4.28‡ [2H]	4.71‡ [2H]	10.15 *d* (7.0) [-CHO]
C2′-C<u>H</u>$_3$	1.18 *d* (7.0) 1.19 *d* (7.0)	1.15 *d* (7.0)	1.15 *d* (7.0) 1.15 *d* (7.0)	1.12 *d* (7.0)	1.80 *brs* (1.0)	1.84 *brs* (1.0)	2.28 *m*
Acetates	2.12 [C-15]	2.13 [C-15]	2.15 [C-15] 2.05 [C-8]	2.15 [C-15] 2.05 [C-8]	2.14 [C-15]	2.14 [C-15] 2.08 [C-4′] 1.91 [C-14]	2.08 [C-15]
COOC<u>H</u>$_3$							

*Spectra of **1a** through **3b** were run in $CDCl_3$ at 270 MHz and TMS was used as internal standard; spectra of **3d** through **8b** were run at 100 MHz. Values are recorded in ppm relative to TMS. Multiplets are given by the usual symbols. Figures in parentheses are coupling constants or line separations in hertz. Data in brackets indicate assignments or number of protons.

†^{1}H NMR parameters of compound **3c** are like **3a** except H-3′: 5.66 *tq* (1.5;7.0); C-3′ aldehydes: 10.15 *d* (7.0); C-2′-Me: 2.28 *m*.

ments. Besides the parent peak at *m/e* 406, compound **2a** exhibited significant peaks at *m/e* 346 ($M-C_2H_4O_2$), 304 ($M-C_5H_{10}O_2$), and 244 ($M-C_5H_{10}O_2-C_2H_4O_2$) which must be due to the loss of the respective side chains, acetic acid and α-methylbutyric acid, from the basic ring skeleton by a McLafferty rearrangement. Further peaks at *m/e* 85 (C_5H_9O) and 57 (C_4H_7) support the presence of moiety **B** in **2a**. Arguments for the sites of attachments of the ester functions in **1a** and **2a** will be presented later.

Linearilobin C, D and E

Linearilobin C (**3a**), $C_{22}H_{28}O_8$ (MS) differs from **1a** and **2a** by the presence of a five-carbon ester group at C-8 or C-15 and a hydroxy function at C-14, which was established by detailed ^1H NMR double-resonance experiments. In addition to the NMR signals typical of the medium ring skeleton, (assignments are given in Table 1), the ^1H NMR spectrum contained a broad vinyl methyl absorption at δ 1.80 ($J \approx 1.0$ Hz), a two-proton doublet at 4.28 and a one-proton quartet of a triplet at 6.74 ($J = 6.0$, 1.0 Hz). Irradiation at 6.74 (H-3′) collapsed the doublet at 4.28 (H-4′a and b). In return, when the signal at 4.28 was irradiated, the absorption at 6.74 simplified to a narrowly split quartet ($J \approx 1$ Hz). Saturation of the methyl absorption at 1.80 (C-2′-Me) caused the signal at 6.74 (H-3′) to simplify to a triplet ($J_{3,4} = 6.0$ Hz).

linearilobin A–H and derivatives*

4a	**5**	**6a**	**6b**	**7a**	**7c**	**8a**	**8b**
5.15 *m*	5.18 *m*	5.17 *m*	5.18 *dd* (11.5, 6.0)	5.23 *dd* (12.0, 6.0)	5.23 *dd* (12.0, 6.0)	5.32 *m*	5.32 *m*
—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—
5.04 *d*‡ (11.0)	5.03 *brd* (10.5)	4.91 *d* (10.0)	5.97‡	5.75‡	5.75‡	5.50 *brd*‡ (11.0)	6.32 *d* (10.5)
5.12‡	5.26 *dd*	5.40 *dd* (9.0, 10.0)	5.90	5.75	5.75‡	5.28 *dd*‡ (11.0, 2.5)	5.44 *dd* (10.5, 2.5)
3.00 *m*	2.79 *m*	2.74 *m*	2.86 *m*	2.89 *m*	2.89 *m*	2.99 *m*	3.14 *m*
5.78 *m*	4.60 *m*	4.58 *m*	4.64 *m*	5.80 *m*	5.80 *m*	5.26 *ddd* (1.0, 2.0 4.0)	5.31 *m*
—	—	2.18 *m*	2.18 *m*	—	—	2.31 *dd* (2;15)	—
3.34 *dd* (15.0,6.0)	—	3.09 *m*	3.09 *m*	—	—	3.03 *m*	—
5.62 *d* (3.0)	5.59 *d* (3.0)	5.58 *d* (2.5)	5.99 *d* (3.0)	5.64 *d* (3.0)	5.64 *d* (3.0)	5.74 *d* (2.0)	5.90 *d* (2.0)
6.25 *d* (3.5)	6.32 *d* (3.5)	6.30 *d* (3.0)	6.43 *d* (3.5)	6.32 *d* (3.5)	6.32 *d* (3.5)	6.31 *d* (2.5)	6.47 *d* (2.0)
3.72 *d* (12.5)	4.65§ [2H]	4.52 *d* (12.5)	10.00 [-CHO]	4.03 *d* (12.5)	3.92 *d* (12.5)	4.5 *d* (12.5)	4.54 *brd* (13.0)
4.17 *d* (12.5)	—	4.69 *d* (12.5)	—	4.72 (12.5)	4.56 (12.5)	4.82 *d* (12.5)	4.87 *brd* (13.0)
4.59§ [2H]	4.65§ [2H]	4.01 *d* (13.0)	4.16 *d* (12.5)	8.72 [-COOH]	—	4.08§ (9.5‖,1.5) [2H]	9.46 *s* [-CHO]
—	—	4.24 *d* (13.0)	4.58 *d* (12.5)	—	—	—	—
—	—	2.38 *m*	2.38 *m*	2.34 *sext* (7.0)	—	—	—
a. 6.01 *brs*	6.08 *brs*		1.51 *p* (7.0)	1.40 *p*	—	5.61 *brs*	5.64 *brs*
b. 5.56 *brs*	5.56 *brs*		1.70 *p* (7.0)	1.64 *p*		6.04 *brs*	6.07 *brs*
—	—	0.87 *t* (7.0) [3H]	0.87 *t* (7.0) [3H]	0.89 *t* (7.0)	—	—	—
1.92 *brs*	1.93 *brs*	1.12 *d* (7.0)	1.12 *d* (7.0)	1.10 *d* (7.0)	—	—	1.87 *brs*
2.15 [C-15]	2.11 [C-15]	—	—	1.97 [C-8]	1.99 [C-8]	1.96 [C-8]	2.07 [C-8]

3.82

‡ Overlapping signals.
§ Center of two proton AB patterns.
‖ Center of two proton ABX patterns.

MS peaks at *m/e* 420 (M^+), 305 ($M-C_5H_7O_3$) and 99 ($C_5H_7O_2$) [2] together with the above ^1H NMR assignments suggested a five-carbon ester function represented by **C**. Further evidence for the presence of the side chain **C** in **3a** was provided by acetylation to yield **3b** and MnO_2 oxidation to give the aldehyde derivatives **3c** and **3d**. Upon acetylation, the two-proton AB pattern due to C-4′ at 4.28 in **3a** shifted to 4.71 in **3b** and the pair of doublets due to two C-14 protons changed from 3.76 and 4.16 to 4.03 and 4.71, respectively. Prominent MS peaks at *m/e* 305 ($M-C_2H_2O-C_7H_9O_4$) and 227 ($M-C_7H_9O_4-2C_2H_4O_2$) indicated the loss of acetic acid and a 7-carbon side chain ($C_7H_9O_4$) from the parent ion *m/e* 504 (M^+) of **3b**. Ion signals at *m/e* 141 ($C_7H_9O_3$) and 99 ($C_5H_7O_2$), assigned to the seven- and five-carbon acylium ions, substantiated the above assignments. Short-time oxidation of **3a** with activated MnO_2 converted the allylic C-4′ hydroxyl group to an aldehyde function (**3c**) with an aldehydic proton doublet at 10.15 ($J_{3,4}=7.0$ Hz). Extended MnO_2 oxidation resulted in the aldehyde **3d** *m/e* 416 (M^+) and 387 ($M-CHO$), which exhibited a broadened singlet at 9.89 due to the aldehydic H-14. In addition, the H-1 signal had shifted from 5.21 in **3a** to 6.43 in **3d**. Furthermore, comparison of the ^1H NMR shifts of **3d** with data of melampolides of similar oxidation pattern [7] together with the application of Herz's rule [8] for the aldehydic H-14 chemical shift and for H-1 in **3d** disagreed with a melampolide skeleton and favored a 1(10)-*trans*-double bond and confirmed that the hydroxyl group in **3a** had to be attached to C-14 and not C-15.

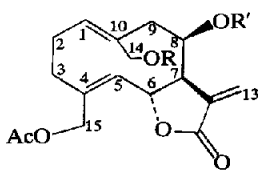
Linearilobin D (**4a**), $C_{21}H_{26}O_7$ (MS, 390) exhibited ^1H NMR spectral patterns very similar to **3a**, except for the ester side chain signals. A pair of broadened singlets at δ 6.01 (H-3a′) and 5.56 (H-3b′) and a broadened three-proton singlet at 1.92 (**D**, C-2′ methyl) together with MS peaks at *m/e* 304 ($M-C_4H_6O_2$) and 69 [$CH_2=C(Me)CO^+$] were diagnostic of the methacrylate moiety (**D**).

The attachment of the acetoxy group to C-15 instead of C-8 was favoured on the basis of the strong MS peak at *m/e* 331 ($M^+-MeCOO^\cdot$), the M-59 peak being generally observed for acetates attached to allylic carbons.

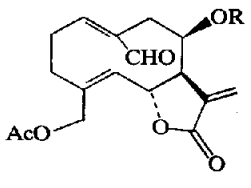
Linearilobin E (**5**), $C_{21}H_{26}O_7$, exhibited ^1H NMR and MS spectral parameters very similar to those of linearilobin A (**1a**) and B (**2a**). ^1H NMR signals characteristic of the methacrylate moiety (Table 1) indicated the presence of this ester function either at C-14 or C-15 with an acetate group at the remaining carbon. MS peaks at *m/e* 390 (M^+), 305 ($M-C_4H_5O_2$), 262 ($M-C_4H_6O_2-C_2H_2O$), 244 ($M-C_4H_6O_2-C_2H_4O_2$) and 69 (C_4H_5O) verified the ^1H NMR assignments. It is of interest to note that the intensity of the peak at *m/e* 244, which must be due to the loss of the two ester functions (acetate, methacrylate) by a McLafferty rearrangement, was relatively strong (22.9%) in **4a** and of low intensity (1.9%) in **5**. Instead, compound **5** exhibited a prominent peak at *m/e* 305 [$M-CH_2=C(Me)-COO^\cdot$] and no *m/e* 304, indicating the attachment of the methacrylate moiety to an allylic carbon in **5** and a nonallylic position (C-8) in **4a**. Based on the acetate chemical shift at 2.11 in **5** which is similar to the shifts in **1a** and **2a**, we tentatively assign structure **5** to linearilobin E using the same arguments that follow for linearilobin A–D.

The sites of attachment of the various ester moieties in **1a** to **4a** and their derivatives were tentatively assigned on the basis of chemical shift data of the acetate methyl absorptions in the different compounds. In compounds **1a** and **2a** the ^1H NMR acetate signals appear at δ 2.12 and 2.13 (C-14 or C-15), respectively. Acetylation of the C-8 hydroxyl group in the two compounds yielded **1b** and **2b** both having acetate signals at 2.05 and 2.15. If acetylation of the C-8 hydroxyl had not strongly affected the chemical shift of the acetate methyl at C-14 or C-15, the signals at 2.15 in **1b** and **2b** could be assigned to the acetoxy methyls at C-14 or C-15 and the absorption at 2.05 to the C-8 acetoxy methyl. Furthermore, linearilobin D (**4a**) with a C-14 hydroxyl group exhibited an acetate ^1H NMR absorption at 2.15 (C-8 or C-15) and gave upon acetylation acetate signals at 1.92 and 2.15. It is most reasonable to assign the signal at 1.92 to the newly introduced acetate at C-14. Therefore, by analogy to **1b** and **2b**, the signal at 2.15 could be assigned to the C-15 acetate signal. Based on the above chemical shift considerations of the acetate absorptions of the four linearilobins and their derivatives, we tentatively assign structures **1a–5** to linearilobin A–E, respectively.

The CD spectra of **1a–5** exhibited two strong exiton bands of opposite sign. Positive bands near 220 nm and negative bands at *ca* 205 nm, which were observed in all five compounds, are typical for germacrolides in which the homoconjugated 1(10)- and 4,5-*trans*-double bonds have a chiral arrangement. In this conformation, both C-14 and C-15 are oriented above the plane of the medium ring [2, 6]. A weak negative band near 260 nm in **1a–5** was assigned the $n \rightarrow \pi^*$ α-methylene-γ-lactone transition, which by the application of Geissman's rule [9] indicated *trans*-lactones in all five linearilobins and their derivatives. On the



		R	R′
Linearilobin A	(**1a**)	**A**	H
	(**1b**)	**A**	Ac
Linearilobin B	(**2a**)	**B**	H
	(**2b**)	**B**	Ac
Linearilobin C	(**3a**)	H	**C**
	(**3b**)	Ac	C-4′OAc
	(**3c**)	H	**E**
Linearilobin D	(**4a**)	H	**D**
	(**4b**)	Ac	**D**
Linearilobin E	(**5**)	**D**	H



3d R = **E**

basis of the CD data and the ^{1}H NMR parameters we suggest configurations **1a–5** for linearilobins A–E, respectively and conformations with a crown arrangement of the medium ring most typical for 7,6-*trans*-lactonic germacrolides [10].

Linearilobin F and G

Linearilobin F (**6a**), $C_{20}H_{28}O_6$ (MS), was a gum which on the basis of inspection of ^{1}H NMR parameters must represent the desacetoxy derivative of linearilobin B (**2a**). Oxidation of **6a** with activated MnO_2 provided further evidence for the above spectral results. The ^{1}H NMR signals centered at δ 4.04 assigned to the C-15 methylene in **6a** disappeared upon oxidation and a singlet at 10.0 appeared in **6b**. In addition, H-5 and H-6 shifted from 4.91 and 5.40 in **6a** to 5.97 and 5.90, respectively in **6b**. The downfield shift of H-6 by 0.5 ppm must be due to the deshielding effect of the newly introduced C-15 aldehyde carbonyl. This lends support to a β-oriented C-15, since the $J_{5,6}$, $J_{6,7}$ and $J_{7,13a,b}$ indicate a *trans*-lactone with H-6 adopting a β-configuration [4, 5]. Application of Herz's rule [8] for H-15 (10.0 ppm) and the chemical shift of H-5 (5.90) in **6b** suggest the presence of a 4,5-*trans*-double bond which is in agreement with the CD data of the acetate of **6b**, in which a positive band at 268 nm and a negative band at 202 nm indicated a germacrolide skeleton [6].

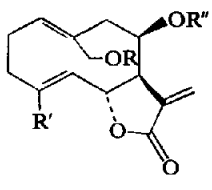
Linearilobin G (**7a**), $C_{20}H_{26}O_7$, an impure gum, was separated from other constituents by conversion to the acetate **7b**. Identification of **7a** was mainly performed on its acetate **7b** and the acetate–methylester **7c**. The ^{1}H NMR parameters of **7b** were assigned by inspection and detailed decoupling experiments (Table 1). The ^{1}H NMR spectral pattern of **7b** differed from that of **2b** and related compounds in that H-5 and H-6 appeared near δ 5.75, that is considerably more downfield than in the previously discussed linearilobins which show absorptions near 5.2. This fact, together with the presence of a proton signal at 8.72, which disappeared upon addition of D_2O, suggested the presence of a carboxyl group at C-4. Methylation of **7b** with diazomethane yielded the methylester **7c** which differed from **7a** by the presence of a methoxy signal at 3.82 and an upfield shift of H-14a to 3.92 and H-14b to 4.56, typical for C-8- and C-14-acyloxy-substituted medium rings. In contrast to the H-6 signals in **1a** to **6a**, the appearance of H-6 in **7a** and **7b** at lower field near 5.75 must be due to the deshielding effect by the C-4 carboxyl group for the same reasons previously discussed for compound **6b**. The MS data of **7a** verified the ^{1}H NMR assignments, in particular, those of the α-methylbutyrate side chain. Besides the typical ^{1}H NMR absorptions a MS peak at *m/e* 318 ($M-C_5H_{10}O_2$) together with the diagnostic peaks at *m/e* 85 (C_5H_9O) and 57 (C_4H_9) indicated the presence of an α-methylbutyrate in **7a** and **7b**. Since in **7b** the shielding influence of the C-8β-acyloxy carbonyl upon the C-14 protons was observed together with the deshielding effect of the C-4 carboxyl group upon the β-oriented H-6, the conformation of **7b** and therefore of **7a** can in this instance be derived from the ^{1}H NMR parameters alone. The above data require that both C-14 and C-15 are situated above the medium ring as expected for 7,6-lactonic germacrolides [4,10].

Linearilobin H and I

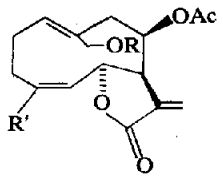
Linearilobin H (**8a**), $C_{21}H_{26}O_7$ (MS) and linearilobin I (**9a**), $C_{22}H_{28}O_7$, resembled the sesquiterpene lactones **1a–6a** in the oxidation of C-14 and C-15 as well as the substitution patterns around the medium ring. However the 100 MHz ^{1}H NMR spectrum displayed signals with chemical shifts and couplings distinctly different from the spectral features of the germacrolides **1a–6a**. Specifically, the relatively downfield chemical shifts of H-5 (5.40) and H-6 (5.30), the small coupling constant between H-6 and H-7, $J_{6,7}=2.5$ Hz, a large coupling between H-5 and H-6, $J_{5,6}=10.5$ Hz, and small $J_{7,13}$ values near 2.0 Hz were observed.

The basic skeleton as well as the types and sites of attachments of the side chains, acetate and methacrylate in **8a** or tiglate in **9a**, were determined by inspection of the ^{1}H NMR spectrum and detailed decoupling experiments and verified by diagnostic MS peaks. The ^{1}H NMR results are summarized in Table 1. The downfield shift of the two H-14 proton signals suggested that an ester function be present at C-14. Their considerable differences in chemical shifts, δ 4.50 (H-14a) and 4.88 (H-14b), resembled earlier instances (**1a** and **2a**) where acetylation at C-8 resulted in the deshielding of only one H-14 proton which was accompanied with an upfield shift of H-14b relative to the other H-14 signal.

The pair of doublets corresponding to the two H-15 protons displayed a chemical shift of the center of an AB system at δ 4.08 indicative of an allylic hydroxy-containing methylene group. Oxidation of a mixture of **8a** and **9a** with activated MnO_2 yielded the aldehyde mixture **8b** and **9b** which exhibited the following diagnostic ^{1}H NMR parameters: (1) the replacement of the AB system at 4.08 in **8a–9a** by an aldehyde singlet at 9.46; (2) downfield shift of H-5 from 5.50 to 6.32 and (3) a lesser downfield shift of H-6 from 5.28 to 5.44. Application of Herz's rule [8] suggested that the C-15 aldehyde proton at 9.46 and H-5 are a part of a α,β-unsaturated carbonyl system with a *cis*-4,5-double bond in the medium ring, results which are in good agreement with the formulation of a heliangolide skeleton for **8a** and **9a**. Further arguments for the presence of a heliangolide skeleton in **8a** and **9a** were



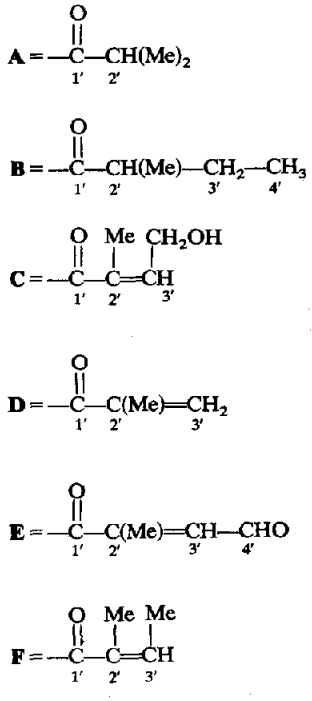
		R	R'	R''
Linearilobin F	(**6a**)	β	CH_2OH	H
	(**6b**)	β	CHO	H
	(**6c**)	β	CHO	Ac
Linearilobin G	(**7a**)	β	COOH	H
	(**7b**)	β	COOH	Ac
	(**7c**)	β	$COOCH_3$	Ac



		R	R′
Linearilobin H	(**8a**)	D	CH_2OH
	(**8b**)	D	CHO
Linearilobin I	(**9a**)	F	CH_2OH

based on the following data. The comparison of the chemical shifts and coupling constants of H-6, H-7, H-8, H-9 and the two H-13 with those of the diagnostic ^1H NMR signals of known heliangolides [4, 5] revealed great similarities. The attachments of the ester side chains were tentatively assigned exclusively on the basis of a relatively intense M-59 peak in **8a** indicating the attachment of the acetate moiety at an allylic position, that is C-14. Selected hydrolysis experiments could not be carried out due to lack of material.

Melampodium linearilobum is the first species within the genus to produce germacrolides and heliangolides instead of the commonly occurring melampolides [1, 11]. This completes the detection of all four possible types of germacranolides [1, 4] within the genus *Melampodium* since recently *cis,cis*-germacradienolides were isolated from *M. leucanthum* [12]. These findings again raise the question whether the biogenesis of the four different types of cyclodecadienes follow separate pathways in the formation of the geometrically isomeric medium rings or double bond isomerizations of the *trans,trans*-cyclodecadiene skeleton takes place after the cyclization step. The presently available data within the *Melampodium* complex suggest that in this genus double bond isomerizations of the germacrolide skeleton leading to melampolides, heliangolides and *cis,cis*-germacranolides seem to be connected to the oxidative biomodifications of C-14 and/or C-15 and could occur simultaneously or proceed after oxidation of these activated allylic sites.



EXPERIMENTAL

Melampodium linearilobum DC. (Hartman–Funk No. 4204; voucher deposited as OS: *Mexico*: Guerrero: Hwy 200, 79 miles NM of Pinotepa Nacional, August 1976). Stems and leaves (550 g) were extracted in 3 l. $CHCl_3$ and worked up according to a standard procedure [11] to yield 4.8 g of crude syrup. The syrup was chromatographed over 220 g Si gel taking 20 ml fractions. $CHCl_3$ was used as an eluant followed by $CHCl_3$–Me_2CO mixtures (95:5, 90:10, 80:20, etc.). Fractions 2–6 gave 0.3 g of coumarin. Fractions 33–38 contained 0.4 of a mixture of **1a** and **2a** which could be separated by rechromatography. Fractions 48–63 provided crude **3a** which upon rechromatography yielded 40 mg of pure **3a** as a gum. Later fractions (124–142) contained 0.6 g of **4a**.

A collection of *M. linearilobum* (580 g dried stems and leaves) from Oaxaca, Mexico (Hartman–Funk No. 4200; voucher deposited at OS; *Mexico*: Oaxaca: Hwy 131, 50 miles SW of Oaxaca, August 1976), yielded 8.0 g of crude syrup which was dissolved in warm IsOH to give, after cooling, 2.3 g of a crystalline mixture of **1a** and **2a**. The mother liquor was chromatographed over 250 g Si gel using the elution procedure described above. Fractions 6-9 yielded pure **1a** while fractions 16–17 contained pure **2a**. Fractions 40–41 provided 50 mg of **6a** and fractions 42-43 gave a crude mixture containing **7a**. The crude mixture was acetylated and chromatographed over Si gel (30 g) with $CHCl_3$ taking 15 ml fractions. Fractions 9–10 contained 50 mg pure **7b**. A collection of 650 g *M. linearilobum* (Hartman–Funk No. 4173; voucher deposited at OS; *Mexico*: Oaxaca: Hwy 190, 56 miles ENE of Tehuantepec, August 1976) provided 8.0 g of crude syrup which was chromatographed over Si gel (250 g). Fractions 8–11 gave 25 mg **5**, fractions 16–20 contained **4a** and fractions 29–31 provided 160 mg of a mixture of **8a** and **9a** which could not be completely separated.

Linearilobin A (**1a**). Mp 144–145°; UV, strong end absorption; CD (3.88×10^{-5}, MeOH) $[\theta]_{205}-8.38\times10^4$, $[\theta]_{223}$ 1.06×10^5, $[\theta]_{260}-1.3\times10^3$; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3490 (OH), 1755 (γ-lactone), 1730, 1715 (esters), 1685, 1660 (double bonds); MS (70 eV) *m/e* (rel. int.): 392 (0.1) M^+, 374 (0.1, $M-H_2O$), 350 (0.1, $M-C_2H_2O$), 333 (1.8, $M-C_2H_3O_2$), 305 (16.5, $M-C_4H_7O_2$), 292 (1.2, $M-H_2O-C_4H_7O_2$), 263 (3.9, $M-C_2H_2O-C_4H_7O_2$), 262 (3.6, $M-C_2H_8O_2-C_2H_2O$), 245 (8.6, $M-C_2H_4O_2-C_4H_7O_2$), 244 (5.8, $M-C_2H_4O_2-C_4H_8O_2$), 226 (6.4, $M-C_2H_4O_2-C_4H_8O_2-H_2O$), 71 (32.2, C_4H_7O), 43 (100, C_2H_3O or C_3H_7); MS CI (*iso*-butane, 35 eV): 393 (MH^+). (Calc. for $C_{19}H_{25}O_5$: 333.1707. Found: (MS) 333.1697). Acetylation of 34 mg of **1a** in 1 ml Py and 1 ml Ac_2O for 24 hr followed by the usual work-up gave 35 mg **1b** as a gum; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770 (γ-lactone), 1735, 1720, 1715 (esters); MS *m/e* (rel. int.): 434 (not observed) M^+, 347 (72.9, $M-C_4H_7O_2$), 305 (16.7, $M-C_2H_2O-C_4H_7O_2$), 245 (35.4, $M-C_2H_2O-C_4H_7O_2-C_2H_4O_2$), 227 (45.8, $M-C_2H_2O-C_4H_8O_2-H_2O-C_2H_3O_2$), 226 (31.2, $M-C_2H_2O-C_4H_8O_2-H_2O-$

$C_2H_4O_2$), 213 (20.8, $M-C_2H_2O-C_4H_8O_2$–MeOH–$C_2H_3O_2$), 71 (60.4, C_4H_7O), 43 (100, C_2H_3O or C_3H_7).

Linearilobin B (**2a**). Mp 151–152°; UV, strong end absorption; CD (4.93×10^{-5}, MeOH) $[\theta]_{205}-1.0\times10^5$; $[\theta]_{223}$ 8.7×10^4; $[\theta]_{260}-4.1\times10^3$; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520 (OH), 1755 (γ-lactone), 1725, 1720 (esters), 1690, 1665 (double bonds); MS (70 eV) *m/e* (rel. int.): 406 (0.5, M^+), 405 (1.3, M−1), 388 (0.8, $M-H_2O$), 364 (0.7, $M-C_2H_2O$), 347 (1.9, $M-C_2H_3O_2$), 346 (4.9, $M-C_2H_4O_2$), 304 (100, $M-C_5H_{10}O_2$), 262 (17.1, $M-C_5H_{10}O_2-C_2H_2O$), 244 (40.0, $M-C_5H_{10}O_2-C_2H_4O_2$), 226 (34.3, $M-C_5H_{10}O_2-C_2H_4O_2-H_2O$), 85 (36.2, C_5H_9O), 57 (37.1, C_4H_9), 43 (0.71, C_2H_3O); CI (*iso*-butane, 35 eV): 407 (MH^+); [Calc. for $C_{20}H_{27}O_5$: 347.1858. Found: (MS) 347.1862].

Acetate **2b**. Gum; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770 (γ-lactone), 1735, 1720, 1715 (esters); MS (70 eV) *m/e* (rel. int.): 448 (not observed, M^+), 389 (8.3, $M-C_2H_3O$), 347 (72.9, $M-C_4H_7O_2$ or $M-C_2H_2O-C_2H_3O_2$), 305 (16.7, $M-C_2H_2O-C_4H_7O_2$), 245 (35.4, $M-C_2H_2O_4-C_5H_9O_2-C_2H_4O_2$), 227 (45.8, $M-C_2H_2O-C_5H_{10}O_2-H_2O-C_2H_3O_2$), 226 (31.2, $M-C_2H_2O-C_5H_{10}O_2-H_2O-C_2H_4O_2$), 213 (20.8, $M-C_2H_2O-C_5H_{10}O_2$–MeOH–$C_2H_3O_2$), 85 (77.1, C_5H_9O), 57 (39.6, C_4H_9), 43 (100, C_2H_3O).

Linearilobin D **4a**. Gum; UV λ_{max}^{MeOH} nm: 205 (ε 1.8×10^4); CD (c 4.8×10^{-4}, MeOH), $[\theta]_{201}-3.1\times10^4$, $[\theta]_{233}$ 4.7×10^4; $[\theta]_{263}-5.0\times10^2$; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH), 1760 (γ-lactone), 1745, 1735 (esters) 1650 (double bonds); MS (70 eV) *m/e* (rel. int.): 390 (1.7), 331 (27.1, $M-C_2H_3O_2$), 317 (18.2, M–MeOH–C_3H_5), 305 (3.4, $M-C_4H_5O_2$), 304 (3.4, $M-C_4H_60_2$), 262 (5.9, $M-C_2H_2O-C_4H_5O_2$), 244 (22.9, $M-C_2H_4O_2-C_4H_6O_2$), 226 (22.5, $M-C_2H_4O_2-C_4H_6O_2-H_2O$), 213 (25.8, $M-C_2H_4O_2-CH_3OH-C_4H_5O_2$), 69 (57.2, C_4H_5O), 41 (12.7, C_3H_5).

Acetate **4b**. was obtained in the usual manner.

Linearilobin C (**3a**). Gum; MS (70 eV) *m/e* (rel. int.): 420 (0.1, M^+), 403 (0.1), 402 (0.1, $M-H_2O$), 360 (1.9, $M-C_2H_4O_2$), 305 (1.9, $M-C_5H_7O_3$), 263 (1.3, $M-C_2H_2O-C_5H_7O_3$), 262 (1.9, $M-C_2H_2O-C_5H_8O_3$), 245 (3.5, $M-C_2H_4O_2-C_5H_7O_3$), 244 (5.4, $M-C_2H_4O_2-C_5H_8O_3$), 226 (4.4, $M-C_5H_8O_3-C_2H_4O_2-H_2O$), 214 (13.3, $M-C_5H_8O_3-C_2H_4O_2-CH_2O$), 99 (100, $C_5H_7O_2$), 71 (55.8, C_4H_7O), 43 (46.2, C_2H_3O).

Acetate **3b**. Gum; UV λ_{max}^{MeOH} nm: 208 (ε 2.2×10^4); CD (c 1.79×10^{-4}) $[\theta]_{202}-2.07\times10^4$, $[\theta]_{223}$ 2.24×10^4; $[\theta]_{265}-2.8\times10^2$; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765 (γ-lactone), 1745, 1740, 1735, 1720 (esters), 1655 (double bond); MS (70 eV) of **3b** showed significant peaks at *m/e* (rel. int.): 504 (0.3, M^+), 445 (9.7, $M-C_2H_3O_2$), 403 (1.8, $M-C_2H_2O-C_2H_3O_2$), 385 (0.8, $M-C_2H_4O_2-C_2H_3O_2$), 347 (1.7, $M-C_7H_9O_4$), 305 (3.5, $M-C_2H_2O$), 245 (13.3, $M-C_2H_2O-C_2H_4O_2-C_7H_9O_4$), 244 (6.0, $M-C_2H_2O-C_2H_4O_2-C_7H_{10}O_4$), 227 (25.5, $M-C_2H_4O_2-C_2H_4O_2-C_7H_9O_4$), 226 (15.7, $M-C_2H_4O_2-C_2H_4O_2-C_7H_{10}O_4$), 141 (8.2, $C_7H_9O_3$), 99 (100, $C_5H_7O_2$), 43 (95.7, C_2H_3O). Oxidation of **3a** with activated MnO_2 in $CHCl_3$ for 24 hr yielded **3d** (gum); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765 (γ-lactone), 1740, 1725 (esters), 1675 (double bonds); MS (70 eV) *m/e* (rel. int.): 416 (13.4, M^+), 401 (4.7, M–Me), 387 (2.6, M–CHO), 356 (25.0, $M-C_2H_4O_2$), 303 (2.0, $M-C_5H_5O_3$), 302 (1.6, $M-C_5H_6O_3$), 260 (9.1, $M-C_5H_6O_3-C_2H_2O$), 242 (43.2, $M-C_5H_6O_3-C_2H_4O_2$), 213 (52.5, $M-C_5H_6O_3-C_2H_4O_2-CHO$), 97 (100, $C_5H_5O_2$), 69 (90.2, C_4H_5O), and 43 (62.6, C_2H_3O).

Linearilobin E (**5**). Gum; UV λ_{max}^{MeOH} nm: 204 (ε 1.8×10^4); CD (c $2.3-10^{-4}$, MeOH), $[\theta]_{204}-2.77\times10^4$, $[\theta]_{223}+2.69\times10^4$; $[\theta]_{258}-1.7\times10^3$; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH), 1765 (γ-lactone), 1725, 1715 (esters), 1665, 1635 (double bonds); MS *m/e* (rel. int.): 390 (1.2, M^+) 331 (1.7, $M-C_2H_3O_2$), 330 (1.7, $M-C_2H_4O_2$), 305 (7.8, $M-C_4H_5O_2$), 262 (2.7, $M-C_4H_6O_2-C_2H_2O$), 244 (1.9, $M-C_4H_6O_2-C_2H_4O_2$), 226 (1.9, $M-C_4H_6O_2-C_2H_4O_2$ 69 (12.9, C_4H_5O), 43 (100, C_2H_3O), 41 (26.8, C_3H_5). (Calc. for $C_{17}H_{21}O_5$: 305.1389. Found: (MS) 305.1400).

Linearilobin F (**6a**), gum, was identified as aldehyde **6b**. 40 mg of **6a** were dissolved in 10 ml $CHCl_3$ and stirred with 300 mg of MnO_2. The reaction was monitored by TLC until the starting material was oxidized to give 25 mg **6b**. MS *m/e* (rel. int.): 362 (0.8, M^+), 333 (3.8, M–CHO), 260 (3.8, $M-C_5H_{10}O_2$), 242 (2.1, $M-C_5H_{10}O_2-H_2O$), 85 (41.0, C_5H_9O), 57 (100, C_4H_9). (Calc. for $C_{19}H_{25}O_5$: 333.1707. Found: (MS) 333.1702). Compound **6b** (25 mg) was acetylated to give 20 mg of **6c**. UV λ_{max}^{MeOH} nm: 203 (ε 8.8×10^3); CD (c 1.6×10^{-4}, MeOH), $[\theta]_{202}-1.14\times10^4$; $[\theta]_{268}$ 2.8×10^3; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770 (γ-lactone), 1740, 1730 (esters); MS *m/e* (rel. int.): 404 (3.4, M^+), 344 (1.4, $M-C_2H_4O_2$), 302 (5.1, $M-C_5H_{10}O_2$), 260 (11.9, $M-C_5H_{10}O_2-C_2H_2O$), 243 (7.2, $M-C_2H_4O_2-C_5H_9O_2$), 242 (17.1, $M-C_2H_4O_2-C_5H_{10}O_2$), 213 (15.4, $M-C_2H_4O_2-C_5H_{10}O_2-CHO$), 85 (100, C_5H_9O), 57 (92.2, C_4H_9), 43 (81.9, C_2H_3O).

Linearilobin G (**7a**), gum, was identified as the acetate **7b** and ester **7c**. Acetylation of 50 mg of **7a** provided 50 mg **7b**. CD (c 1.7×10^{-4}, MeOH), $[\theta]_{206}-4.0\times10^4$, $[\theta]_{243}+2.4\times10^4$; MS *m/e* (rel. int.): 420 (4.6, M^+), 361 (1.8, $M-C_2H_3O_2$),360 (1.4, $M-C_2H_4O_2$), 318 (5.1, $M-C_5H_{10}O_2$), 300 (5.1, $M-C_5H_{10}O_2-H_2O$), 276 (30.4, $M-C_5H_{10}O_2-C_2H_2O$), 258 (82.0, $M-C_5H_{10}O_2-C_2H_4O_2$), 212 (4.3, $M-C_5H_{10}O_2-C_2H_4O_2-CH_2O_2$), 85 (95.9, C_5H_9O), 57 (100, C_4H_9), 43 (53.0, C_2H_3O). Methylation of **7b** with CH_2N_2 gave **7c**, gum. UV λ_{max}^{MeOH} nm: 203 (ε 1.1×10^4); CD (c 2.1×10^{-4}, MeOH), $[\theta]_{217}-4.0\times10^4$, $[\theta]_{248}+2.4\times10^4$; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770 (γ-lactone), 1735, 1720 (esters), 1680, 1645 (double bonds); MS *m/e* (rel. int.): 434 (20.0, M^+), 403 (1.7, M–MeO), 392 (2.7, $M-C_2H_2O$), 375 (2.7, $M-C_2H_3O_2$), 374 (2.7, $M-C_2H_4O_2$), 361 (4.7, $M-C_2H_2O$–MeO), 332 (9.5, $M-C_5H_{10}O_2$), 300 (5.0 $M-C_5H_{10}O_2$–MeOH), 290 (18.3, $M-C_2H_2O-C_5H_{10}O_2$), 272 (51.7, $M-C_5H_{10}O_2-C_2H_4O_2$), 258 (21.7, $M-C_5H_{10}O_2-C_2H_2O$–MeOH), 240 (33.3, $M-C_5H_{10}O_2-C_2H_4O_2$–MeOH), 85 (95.0, C_5H_9O), 57 (100, C_4H_9), 43 (100, C_2H_3O). (Calc. for $C_{18}H_{20}O_6$: 332.1260. Found: (MS) 332.1258).

Linearilobin H (**8a**) *and I* (**9a**), gum which could not be completely separated; UV λ_{max}^{MeOH} nm: 202 (ε 2.1×10^4); CD (c 1.5×10^4, MeOH). $[\theta]_{210}-7.7\times10^4$, $[\theta]_{247}+3.4\times10^3$; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460 (OH), 1760 (γ-lactone), 1735, 1720 (esters), 1650 (double bonds); **8a**: MS *m/e* (rel. int.): 390 (0.4, M^+), 331 (1.9, $M-C_2H_3O_2$), 330 (1.8, $M-C_2H_4O_2$), 304 (1.2, $M-C_4H_6O_2$), 262 (3.9, $M-C_4H_6O_2-C_2H_2O$), 244 (17.1, $M-C_4H_6O_2-C_2H_4O_2$), 226 (21.8, $M-C_4H_6O_2-C_2H_4O_2-H_2O$), 213 (20.8, $M-C_4H_6O_2-C_2H_4O_2$–MeO), 69 (42.7, C_4H_5O), 43 (23.3, C_2H_3O), 41 (15.1, C_3H_5). **9a**: MS *m/e* (rel. int.): 404 (2.4, M^+), 344 (6.8, $M-C_2H_4O_2$), 83 (100, C_5H_7O), 55 (30.9, C_4H_7), 43 (23.3, C_2H_3O). 45 mg of a mixture of **8a** and **9a** in $CHCl_3$ were treated with activated MnO_2 for 2 hr to give the aldehyde mixture **8b–9b**; CD (c 5.1×10^{-5}, MeOH), $[\theta]_{215}-13.0\times10^4$, $[\theta]_{245}+3.9\times10^3$. Aldehyde **8b**: MS *m/e* (rel. int.): 388 (0.7, M^+), 328 (1.2, $M-C_2H_4O_2$), 302 (3.0, $M-C_4H_6O_2$), 260 (5.4, $M-C_4H_6O_2-C_2H_2O$), 242 (11.7, $M-C_4H_6O_2-C_2H_4O_2$), 213 (10.0, $M-C_4H_6O_2-C_2H_4O_2-CHO$), 69 (100, C_4H_5O), 43 (44.6, C_2H_3O), 41 (34.6, C_3H_5). (Calc. for $C_{21}H_{24}O_7$: 388.1520. Found: (MS) 388.1484).

Aldehyde **9b**. MS *m/e* (rel. int.): 402 (0.7, M^+), 83 (60.7, C_5H_7O), 55 (28.7, C_4H_7), 43 (44.6, C_2H_3O). (Calc. for $C_{22}H_{26}O_7$: 402.1677. Found: (MS) 402.1672).

Acknowledgements—The authors wish to thank Dr. R. Hartman and V. Funk for plant collecting, and Professor F. Bohlmann, Berlin for ^1H NMR data. The work was supported by a grant from the National Science Foundation (DEB 76-20585) and by Grant Number 1-RO1- CA 19800, awarded by the National Cancer Institute, DHEW.

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